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DISSERTATION

CYCLIC ANHYDRIDES AS ELECTROPHILIC PARTNERS IN TRANSITION METAL-CATALYZED CROSS-COUPLING REACTIONS: REACTION DEVELOPMENT AND SYNTHETIC APPLICATIONS

Submitted by

Eric Allen Bercot

Department of Chemistry

Advisor Professor Tomislav Rovis

In partial fulfillment of the requirements

for the Degree of Doctor of Philosophy

Colorado State University

Fort Collins, Colorado

Spring 2005

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WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY ERIC ALLEN BERCOT ENTITLED CYCLIC ANHYDRIDES AS ELECTROPHILIC PARTNERS IN TRANSITION METAL-CATALYZED CROSS COUPLING REACTIONS: REACTION DEVELOPMENT AND SYNTHETIC APPLICATIONS BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS OF THE DEGREE OF DOCTOR OF PHILOSOPHY.

Committee on Graduate Work

Professor Elliot R. Bernstein

Professor Richard G. Finke

Professor Alan J. Kennan

Professor Robert W. Woody

Advisor Professor Tomislav Rovis

Department Head Professor Anthony K. Rappe

ABRSTRACT OF DISSERTATION

CYCLIC ANHYDRIDES AS ELECTROPHILIC PARTNERS IN TRANSITION METAL-CATALYZED CROSS COUPLING REACTIONS: REACTION DEVELOPMENT AND SYNTHETIC APPLICATIONS

A nickel mediated decarbonylative cross coupling of cyclic anhydrides and diorganozinc reagents has been developed. The process involves the oxidative addition of a low-valent nickel catalyst to a cyclic anhydride coupling partner which, upon decarbonylation, furnishes nickelalactone intermediates that are intercepted by organozinc coupling partners supplying cross coupled carboxylic acid products. Cyclic anhydrides bearing substituted backbones participate in the reaction constituting one of the first examples of the introduction of stereochemical information via an electrophilic coupling partner in a transition metal mediated C-C bond forming reaction.

A nickel-catalyzed alkylation of succinic and glutaric anhydrides with diorganozinc reagents has been realized. The reaction scope is remarkably broad with respect to both electrophilic and nucleophilic coupling partners providing ready access to highly functionalized 1,4- and 1,5-keto acid derivatives. The addition of styrene promoters has been shown to effect dramatic rate enhancements. The enantioselective variant of the reaction has also been investigated with limited success.

The asymmetric alkylative desymmetrization of meso succinic anhydrides with dialkyl- and diarylzinc reagents in the presence of catalytic amounts of a chiral palladium complex has been developed. The reaction proceeds at room temperature in many cases supplying the product keto acids containing up to four stereocenters in high yield and enantiomeric excess.

The synthetic utility of the keto acid products derived from the transition metal catalyzed cross-coupling reactions has been briefly investigated. An efficient complementary diastereoselective reduction of 1,4-keto acids bearing cyclic backbones has been discovered. Reduction of keto acids in the presence of two different reducing agents provides ready access to each diastereomer of the product trisubstituted γ-lactone derivatives. In addition, the nickel catalyzed alkylation of succinic anhydrides has been applied to the synthesis natural products, culminating in the efficient preparation of five members of the lignan family of natural products.

Eric Allen Bercot

Department of Chemistry

Colorado State University

Fort Collins, CO 80523

Spring 2005

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Last but certainly not least, I would like to thank my Mom and Dad for their unwavering support throughout my life, without you none of this would have been possible. Thanks to Chris, Susan, and Ben Kandra for everything over the past years, there are too many things to mention. Thanks to all of my friends outside of CSU, you all mean a lot to me and have helped me get through graduate school in your own ways. My wife Shelly, I cannot put into words what she has meant to me over this time in my life. An explanation of her contributions in this endeavor would fill this dissertation several times over. She is the only reason that I made it through graduate school. She is my rock, my love, my soul mate, my life.

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LIST OF ABREVATIONS

AcOH	acetic acid
9-BBN	9-borabicyclo[3.3.1]nonane
bpy	2,2'-bypyridyl
m-CPBA	*meta*-chloroperbenzoic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCPE	1,2-bis(dicyclohexylphosphino)ethane
DIBAL-H	di-*iso*-butylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
1,3-DNB	1,3-dinitrobenzene
DPPB	1,4-bis(diphenylphosphino)butane
DPPE	1,2-bis(diphenylphosphino)ethane
DPPF	1,1'-bis(diphenylphosphino)ferrocene
HOBt	1-hydroxybenzotiazole hydrate
KHMDS	potassium bis(tremethylsilyl)amide
MOMCl	chloromethyl methyl ether
NBS	N-bromosuccinimide
$Ni(COD)_2$	bis(1,5-cyclootadiene)nickel(0)
$Ni(acac)_2$	nickel(II)acetylacetonate
NIS	N-iodosuccinimide
NMP	1-methyl-2-pyrrolidinone
PCy_3	tricyclohexylphosphine

$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium (0)
PDC	pyridinium dichromate
$Pd(PPh_3)_4$	tetrkis(triphenylphosphine)palladium (0)
$P(Fu)_3$	trifurylphosphine
$P(o\text{-tol})_3$	tri-*ortho*-tolylphosphine
PyBOP	benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate
Pyr	pyridine
Super-Hydride	lithium triethylborohydride
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBSCl	*tert*-butyldimethylsilyl chloride
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TMEDA	*N,N,N'N'*-tetramethylenediamine
$TMSCHN_2$	(trimethylsilyl)diazomethane
TMSCl	trimethylsilyl chloride
TsOH	*para*-toluenesulfonic acid

Chapter 1

Cross-Coupling of Metallactones: Introduction of Stereochemistry via the Electrophilic Coupling Partner in Transition Metal Mediated C-C Bond Forming Reactions

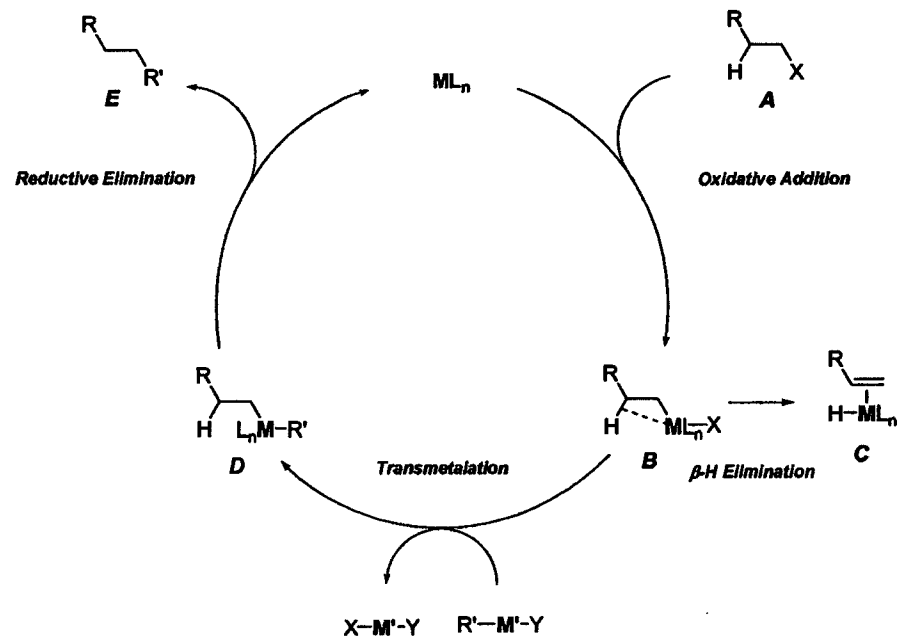
1.1 Introduction

Carbon-carbon bond forming reactions are ubiquitous in organic synthesis yet still represent a significant challenge to organic chemists. Increased target complexity motivates the need for regio- and stereoselective carbon-carbon bond forming reactions. Transition metal-catalyzed carbon-carbon bond forming reactions represent a powerful tool in organic synthesis.[1] Reaction conditions are generally mild and tolerant of otherwise reactive functional groups, making new transition metal mediated reaction manifolds an area of intense investigation.[2] Although extremely useful, transition metal mediated cross-coupling reactions generally do not form stereocenters since the coupling partners are traditionally limited to sp and sp^2 hybridized carbons. Therefore, a general method for coupling two chiral carbon centers would represent an extraordinarily powerful strategy in the concise assembly of stereochemically complex target molecules.

Application of transition metal catalysis to the formation of Csp^3-Csp^3 bonds, once thought improbable, has undergone a revolution in the past few years.[3] The catalytic cycle for transition metal catalyzed cross-coupling, when put in the context of aliphatic coupling partners, is fraught with potential pitfalls (Scheme 1). The initial step of the catalytic cycle involves oxidative addition of a low-valent transition metal catalyst (namely Pd or Ni) into the carbon-halogen bond of the electrophilic coupling partner (**A**). In Csp^2-Csp^2 cross-coupling, oxidative addition is facile for several reasons including the electron deficient nature of the C-X bond (as compared to an aliphatic carbon-halogen bond), potential pre-coordination of the catalyst to the π-system of the electrophilic coupling partner, or a conjugative stabilization of the organometallic intermediates.[4] In contrast, oxidative addition of palladium to alkyl halides is slow and thought to occur through an S_N2 reaction manifold which has been shown,[5] in some cases, to limit the applicability of these transformations to primary electrophiles.[6] Once oxidative addition is achieved, the alkyl-metal intermediate (**B**) can undergo β-hydride elimination resulting in undesired olefinic by-products (**C**). The β-hydride elimination process is thought to occur through an initial coordination, or agostic interaction, between the metal center and the C-H bond that results in the thermodynamically favored elimination reaction.[7] If intermediate **B** is long lived, interception with a main-group organometallic coupling partner results in the dialkyl-metal intermediate (**D**) which can suffer reductive elimination resulting in product formation, or can β-hydride eliminate to again afford undesired by-products. Dialkyl-metal intermediates are quite stable due to the electron-rich nature of the aliphatic substituents on the metal-center which effectively renders reductive elimination slow compared with traditional systems.[8] However, if reductive

elimination is faster than the competing reaction pathways, the desired cross-coupled product **E** is produced with simultaneous regeneration of the low-valent metal catalyst completing the catalytic cycle.

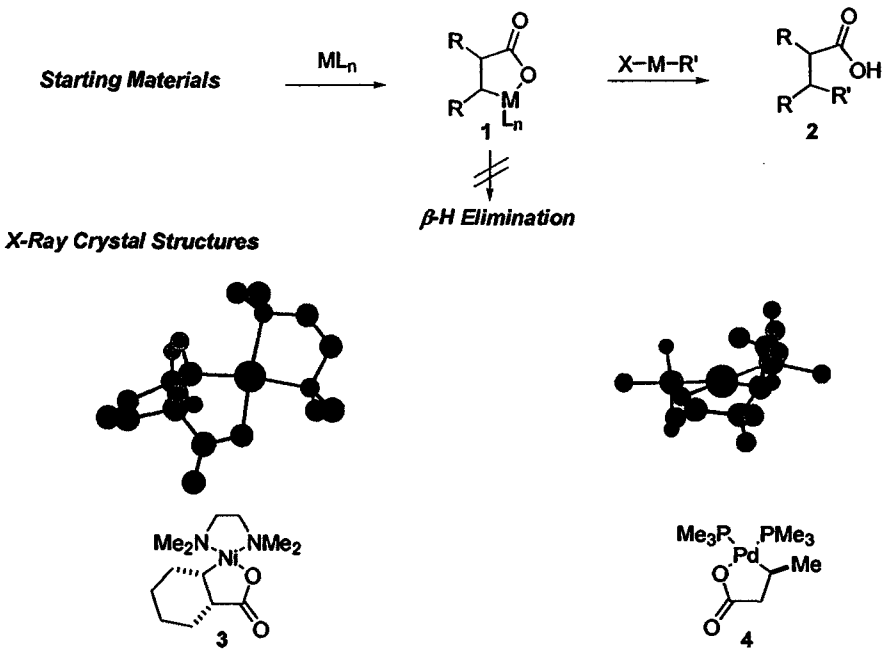
Scheme 1.



We envisioned addressing two of the shortcomings of traditional Csp^3-Csp^3 cross-coupling by exploiting metallacyclic intermediates (Scheme 2). First, by avoiding the use of alkyl halides as electrophilic coupling partners the sluggish oxidative addition could potentially be overcome. Furthermore, the production of a secondary alkyl-metal bond containing stereochemical information could be accessed which was not known in the context of alkyl halide coupling.[9] Second, the geometric constraint imparted by the ring in metallacycles of type **1** should prevent β-hydride elimination. The agostic interaction thought to be required for elimination necessitates a syn co-planar relationship between the β-hydrogen-carbon bond and the metal-carbon bond. Incorporation of the metal center into a ring system should effectively disfavor this required relationship rendering

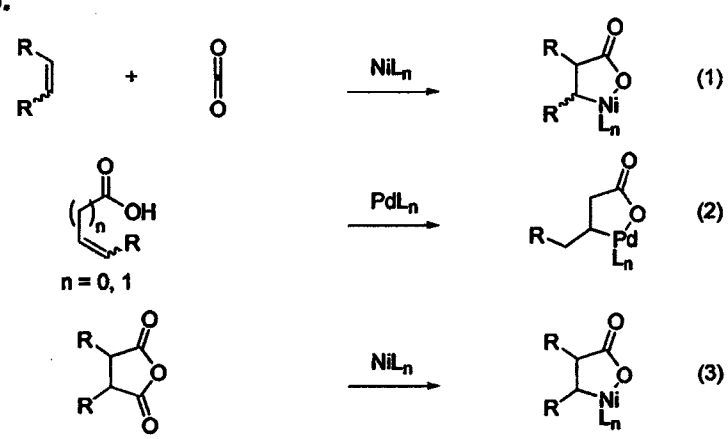
the metallalactone **1** stable to elimination. Several metallalactones have been characterized by x-ray crystallography including structures **3**[10] and **4** which bear *exo*-cyclic β-hydrogens. Although the nature of this stabilization is not completely understood, it seems that the metallacycle is in effect a thermodynamic sink.[11] Interception of **1** with a main-group organometallic coupling partner followed by reductive elimination will provide carboxylic acids of type **2**. The overall process would represent an efficient incorporation of a stereocenter arising from the electrophilic coupling partner in a cross-coupling reaction manifold,[12] an unknown transformation at the time.

Scheme 2.



Although metallalactone intermediates represent an interesting class of electrophilic coupling partners, their preparation needs to be amenable to incorporation into a cross-coupling reaction manifold. Several methods for their synthesis were known in the literature at the time our work commenced (Scheme 3).[13] Approaches to metallactones containing a Csp^3-metal bond are relatively diverse and all three of the following routes could potentially be applied in the context of a cross-coupling manifold. First, the [2 + 2 +1] cycloaddition of an olefin, a low-valent nickel complex, and carbon dioxide results in the formation of the desired metallalactone type intermediates (Scheme 3, eq. 1). Second, treatment of α,β- or β,γ-unsaturated carboxylic acids with low-valent palladium catalysts results in the formation of palladalactones (Scheme 3, eq. 2). Finally, treatment of cyclic anhydrides with low-valent nickel adducts results in the formation of nickelalactones via an oxidative addition-decarbonylation sequence (Scheme 3, eq. 3).

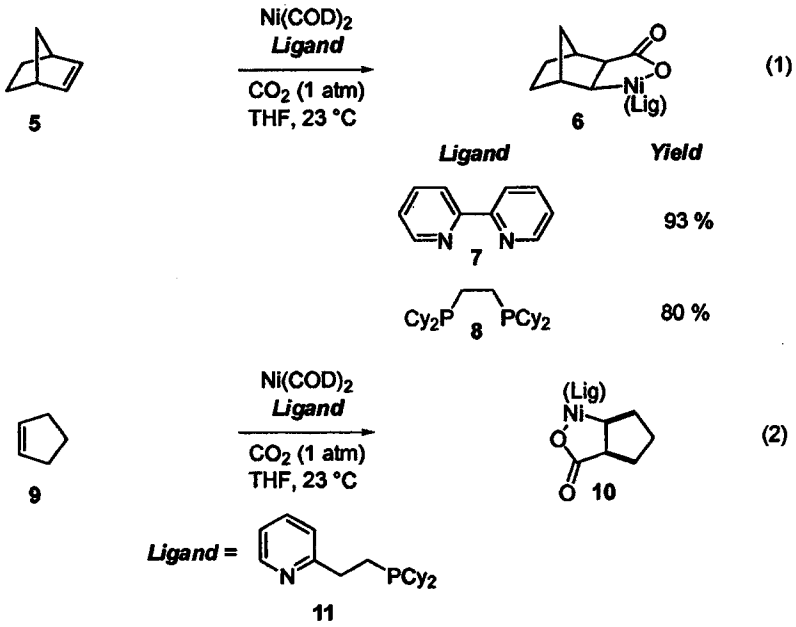
Scheme 3.



The cycloaddition of an olefin, carbon dioxide, and a low-valent metal complex represents a powerful approach to the metallalactone motif. The fixation of carbon dioxide is an attractive tactic in light of its ready availability. Transition metal complexes have long been known to activate this traditionally inert reagent.[14] The preparation of

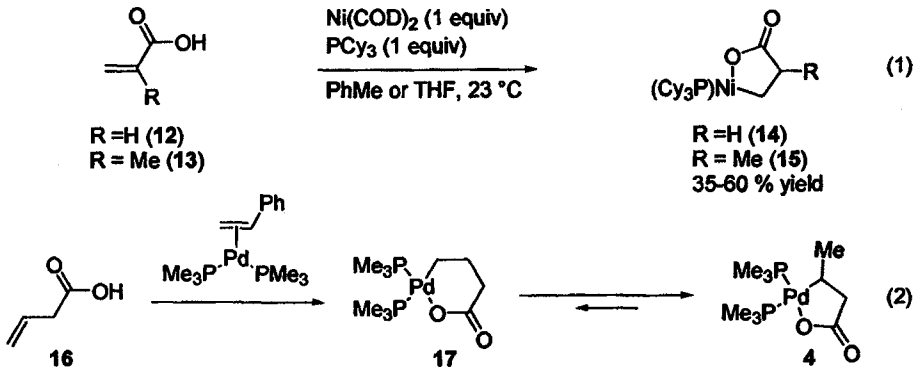
metallactones by this formal oxidative cyclization has been investigated in context of several transition metals including iron[15] and rhodium;[16] however, the bulk of the attention has been focused on nickel.[17] Although conditions for the synthesis of metallactones vary greatly, several nickel complexes are particularly active.[18] The 2,2'-bipyridyl (**7**) derived nickel complex efficiently provides norbornane metallalactone **6** in excellent yield at room temperature under one atmosphere of carbon dioxide (Scheme 4, eq. 1). Likewise the nickel complex prepared from the reaction of $Ni(COD)_2$ and 1 equiv. of bis(dicyclohexylphosphino)ethane (**8**) affords metallalactone **6** in good yield under identical reaction conditions. The phosphino-pyridine ligand **11** has also been found to be extremely effective providing cyclopentene-derived metallalactone **10** in excellent yield, again under mild conditions (Scheme 4, eq. 2).[19] The cycloaddition of alkenes is relatively general and has been applied to formation of metallalactams by the use of isocyanates as reaction partners.[20]

Scheme 4.



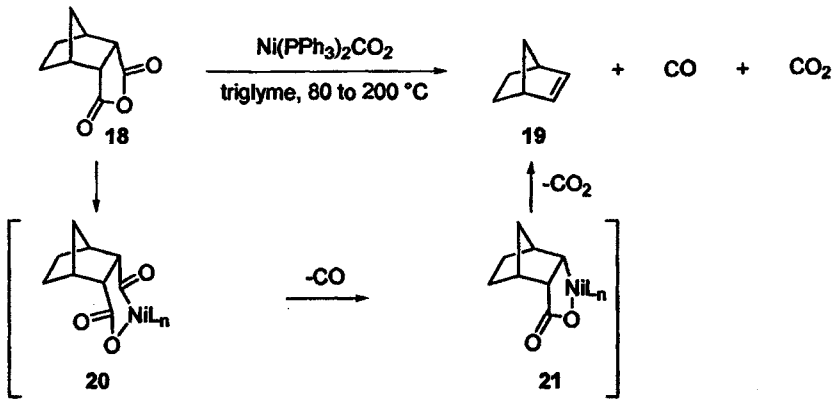
The reaction of low-valent palladium and nickel complexes with unsaturated carboxylic acid derivatives also leads to the formation of metallacyclic products. The reaction of α,β-unsaturated carboxylic acids, namely acrylic acid derivatives (**12** and **13**), with $Ni(COD)_2$ and PCy_3 results in the formation of nickelacycles **14** and **15** in moderate yield (Scheme 5, eq. 1).[21] Analogously β,γ-unsaturated carboxylic acids also afford metallacyclic products when treated with transition metal complexes. For instance, treatment of carboxylic acid **16** with a coordinatively unsaturated palladium complex initially provides the six membered metallacycle **17** which undergoes facile skeletal rearrangement to provide palladacycle **4** containing a secondary carbon-metal bond in a greater than 95:5 ratio (Scheme 5, eq. 2).[22] Metallalactams can also be synthesized by a similar route by simply treating the corresponding carboxamides with metal complexes.

Scheme 5.



The oxidative addition of transition metals to activated acyl derivatives, namely acid chlorides, is well known.[23] Anhydrides are also known to oxidatively add low-valent transition metal complexes. Examples of nucleophilic metal complexes adding to acyclic anhydrides are known;[24] however, much of the attention has been focused on the use of cyclic anhydride derivatives.[25] Depending on the reaction conditions and nature of the substrates employed the initial oxidative addition event may be followed by

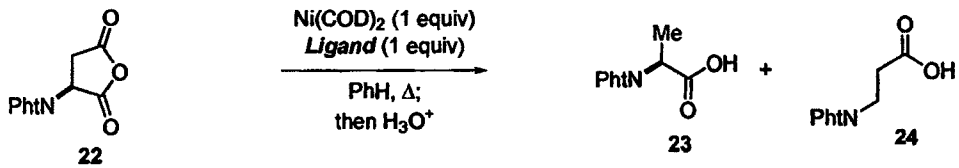
Scheme 6.



decarbonylation providing access to metallactone complexes. Treatment of *endo*-bicyclo[2.2.1]heptane-2,3-dicarboxylic andhyride (**18**) with stoichiometric amounts of a nickel phosphine complex produces the norbornene **19** (Scheme 6, eq. 1).[26] The reaction

is thought to proceed through an initial oxidative addition of the nucleophilic nickel complex to the electron deficient C-O bond providing metallacycle **20** which then undergoes decarbonylation resulting in the formation of metallalactone **21**. Although nickelacycles of type **21** are known to be stable, under the forcing reaction conditions **21** suffers β-elimination of carbon dioxide forming the corresponding olefin. More recently, Echavarren and co-workers have examined a regioselective insertion-decarbonylation sequence in the context of aspartic anhydrides to provide either α-, or β-amino acids (Scheme 7).[27] Treatment of N-protected aspartic anhydride **22** with stoichiometric nickel complexes followed by hydrolysis provides the corresponding regioisomeric amino acid derivatives **23** and **24** respectively. Regioselectivity was found to depend not only on the Ni-ligand complex employed but also on the nature of the protecting group resident on the proximal nitrogen atom.

Scheme 7.

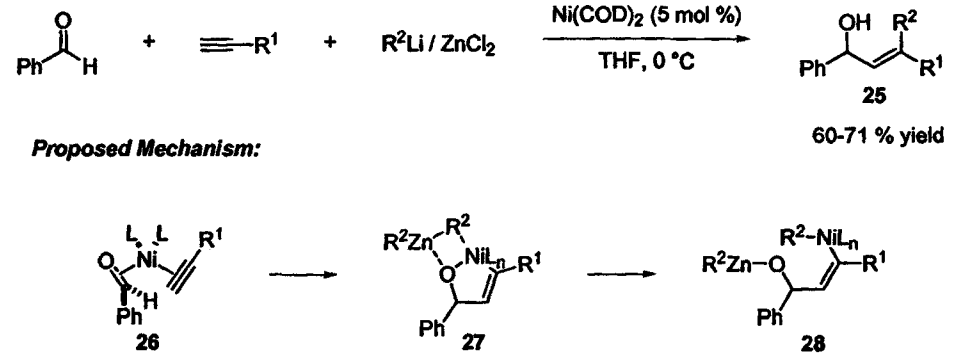


Ligand	*Ratio (23 : 24)*	*Yield*
PPh_3	4 : 1	80
PCy_3	1 : 28	91

Although a relatively large body of work had been compiled on the synthesis and characterization of metallalactone and -lactam complexes, transmetallation of these intermediates was not known. Similar metallacyclic intermediates have been used as electrophilic cross-coupling partners. The intermolecular nickel-catalyzed reductive coupling of aldehydes and alkynes in the presence of trialkylborane or dialkylzinc reagents provides the product allylic alcohols of type **25** in good yield and selectivity

(Scheme 8).[28] The reaction is thought to proceed through the initial coordination of the terminal alkyne[29] and aldehyde[30] coupling partners to the nickel catalyst (**26**) followed by oxidative cyclization affording oxametallacycle **27**.[31] Transmetallation of **27** with diorganozinc reagents presumably proceeds via initial coordination of the Lewis acidic zinc center to the Lewis basic oxygen followed by a σ-bond metathesis-type alkyl group transfer resulting in the formation of the vinyl nickel intermediate **28**. Reductive elimination of **28** results in the formation of the desired product and regeneration of the active nickel catalyst. Although metallalactones bear a less Lewis basic oxygen atom in the ring, it is not unreasonable to conclude that the same type of transmetallation should be operative.

Scheme 8.



1.2 Studies Toward the Decarbonylative Cross Coupling of Anhydrides

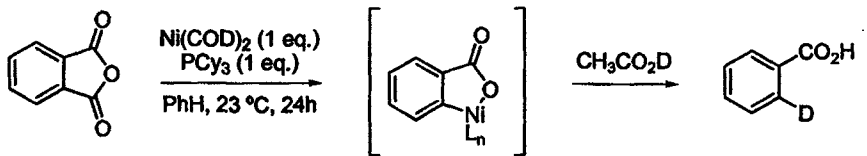
1.2.1 Metallacycle Formation and Transmetalation

Cyclic anhydrides were chosen to generate the desired intermediate metallalactones for several reasons. One, anhydrides are readily available from the corresponding diacid precursors or Diels-Alder chemistry. Two, the cyclization of unsaturated acids and amides was unattractive due to the presence of acidic protons in the starting materials that could potentially react with more basic nucleophilic cross-coupling

partners. Finally, although metallalactone formation from the oxidative cyclization of an olefin and carbon dioxide represented an attractive tactic, preliminary experiments met with very little success.[32]

We chose to first examine metallalactone formation and the unprecedented transmetallation of these intermediates.[33] Although the eventual goal of the project was the coupling of sp^3-hybrizidized electrophilic coupling partners, phthalic anhydride (**29**) was chosen as a model substrate in order to identify metal catalysts capable of undergoing insertion, decarbonylation, and transmetallation sequentially. We hoped that success with phthalic anhydride would translate to more synthetically interesting alkyl anhydrides.

Scheme 9.



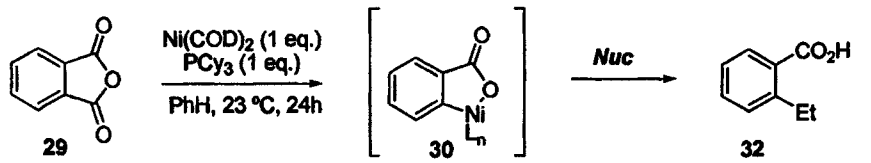
29 **30** **31**

70 % yield

Our investigation began with probing initial metallacycle formation. Phthalic anhydride was subjected to stoichiometric amounts of the nickel complex derived from admixing 1 equiv of $Ni(COD)_2$ and 1 equiv of tricyclohexyl phosphine (PCy_3) in benzene followed by quenching with deutero-acetic acid (CH_3CO_2D) (Scheme 9). We reasoned that if metallacycle **30** was being formed the reaction should provide *o*-deutero-benzoic acid **31** as the major product. To our gratification, subjection of phthalic anhydride to the aforementioned reaction conditions provided **31** in 70 % isolated yield suggesting that the desired metallalactone **30** was being efficiently generated.

With the realization of metallalactone formation, our attention turned to the discovery of a competent main group organometallic coupling partner. Treatment of metallacycle **30** with stoichiometric amounts of diethylzinc (Et_2Zn) afforded the desired cross-coupled product **32** in a modest 30 % yield at room temperature (Scheme 10). Triethylaluminum was also found to be a competent coupling partner providing acid **32** in similar yields; however, due to their ease of synthesis and functional group tolerance zinc reagents[34] were chosen as the nucleophile in subsequent investigations.[35]

Scheme 10.

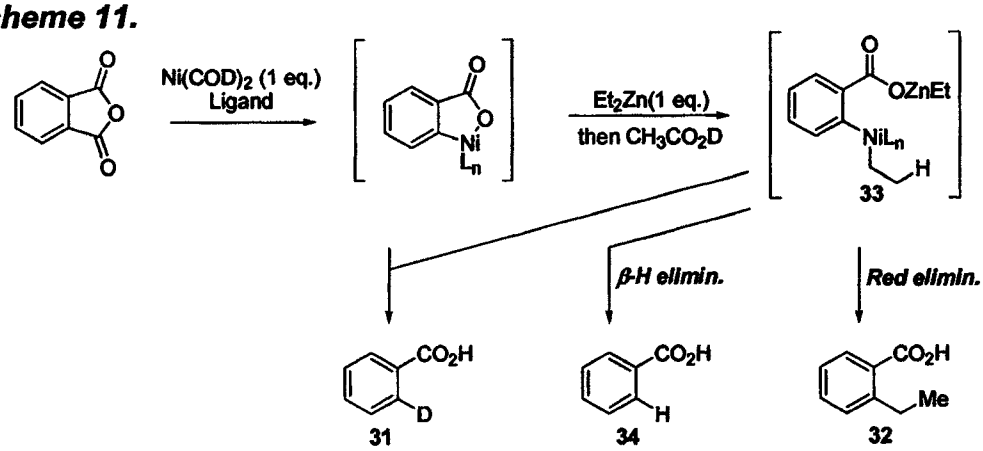


Nuc	Yield (%)
Et_2Zn	30
Et_3Al	~30

Although the present coupling reaction is carried out with an sp^2-hydridized electrophilic coupling partner, thus ruling out the possibility of β-hydride elimination, the use of the Csp^3 ethyl nucleophile could lead to the formation of benzoic acid via the decomposition of the alkyl-aryl nickel intermediate. In order to address the issue of the formation of two different products as well the potential for incomplete reaction of metallacycle, we chose to quench the reaction with a deuterated acid as a probe (Scheme 11). Depending on the efficiency of a certain reaction, three possible products could arise under the devised experimental protocol. The desired product **32** would arise from alkyl group transfer followed by reductive elimination. Proto-benzoic acid (**34**) would appear from the β-hydride elimination of the alkyl-aryl nickel intermediate **33**, giving us information as to which reaction conditions are most effective at suppressing this

unwanted shunt pathway. Finally, deutero-benzoic acid (**31**) would evolve from either quenching of the intermediate metallacycle or the alkyl nickel intermediate **33**. We felt this experimental protocol would provide the most relevant information during our attempts to optimize reaction conditions.

Scheme 11.

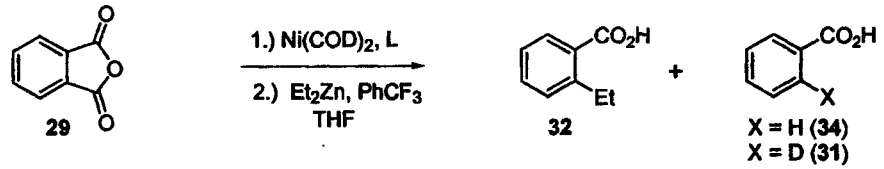


Having identified a competent nucleophilic coupling partner we sought to further improve the present transmetalation manifold. Echavarren had reported the use of either THF or benzene as viable solvents in the context of metallalactone formation. Although our initial results were obtained using benzene as a solvent we felt THF may be a better choice in light of higher anhydride solubility. We quickly found THF to be a viable solvent and subsequent studies were carried out using these conditions.

Reductive elimination of dialkyl-metal intermediates is known to be slow due to the electron-rich nature of the alkyl substituents.[36] It has been shown that addition of electron deficient aromatic and styrenyl moieties facilitates reductive elimination by a proposed π-backbonding interaction in which the filled d-orbitals on the metal donate into the LUMO of the promoter rendering reductive elimination more facile.[37] We reasoned that addition of these promoters may promote reductive elimination of the aryl-

alkyl nickel intermediate and effectively suppress β-hydride elimination and thus adopted their use in our studies.

Table 1.



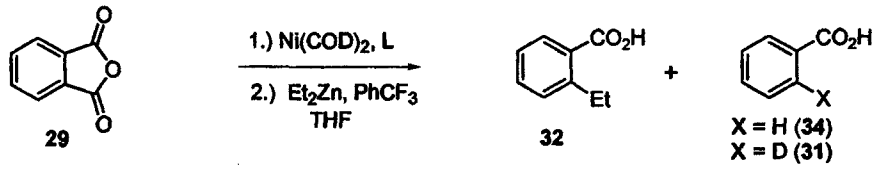
[a]Entry	Ligand	Yield (%)	32 : 34 : 31
1	PCy_3 (1eq)	43	64 : 22 : 14
2	PCy_3 (2eq)	37	40 : 41 : 19
3	PPh_3 (1eq)	60	85 : 10 : 5
4	PPh_3 (2eq)	59	75 : 20 : 5
5	$P(o\text{-}tol)_3$ (2eq)	55	65 : 15 : 20
6	$PMe(Ph)_2$ (2eq)	59	85 : 10 : 5
7	$P(Fu)_3$ (2eq)	34	46 : 54 : 0
8	$As(Ph)_3$ (2eq)	47	73 : 15 :12
9	$P(Bu)_3$ (1eq)	59	62 : 25 : 13

[a]All reactions were carried out at an anhydride concentration of 0.035M. The anhydride was treated with the nickel complex for 2h before addition of $PhCF_3$ (1.4eq.) and Et_2Zn (1.75eq.). After an additional 5h, reactions were quenched with CH_3CO_2D. All yields and product ratios were determined by NMR.

Our initial optimization efforts focused on the nature of the nickel complex, namely identification of a more effective ligand for the conversion of phthalic anhydride to *o*-ethylbenzoic acid. Since tricyclohexylphosphine (PCy_3) was relatively effective we chose to focus our initial ligand screen on monodentate phosphine ligands (Table 1). Use of 1 equiv of PCy_3 to nickel under our modified conditions provided a 43 % overall yield of products, but selectivity was poor (entry 1). Use of 2 equiv of PCy_3 to nickel failed to improve yield or product ratio (entry 2). Triphenylphosphine (PPh_3) proved to be a very competent ligand (entries 3 and 4). The complex derived from 1 equiv of PPh_3 to nickel provided the desired cross-coupled product in good yield and selectivity while the use of 2 equiv of PPh_3 to nickel gave ethyl benzoic acid in nearly identical yield and slightly lower selectivity. Increasing the cone angle of the aromatic phosphine ligand

failed to improve reaction selectivity with P(*o*-tol)$_3$ providing almost the same selectivity as PCy_3 (entry 5). The slightly more electron-rich $PMe(Ph)_2$ provided the desired product in nearly identical yield and selectivity as the complex derived from 1 equiv of PPh_3 (entry 6). Trifurylphosphine failed to improve the reaction providing a nearly 1 : 1 mixture of desired product to β-hydride elimination product in poor yield (entry 7). Triarylarsines are competent ligands in this system, providing products in modest yield and selectivity (entry 8). Finally, the electron-rich tributylphosphine proved efficient but failed to provide an increase in selectivity (entry 9). These results suggest that aromatic phosphines, namely triphenyl phosphine, provide the proper balance of electronic and steric properties to facilitate not only oxidative insertion and subsequent decarbonylation but also transmetallation and reductive elimination.

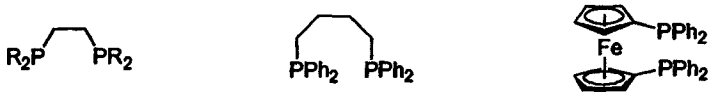
Table 2.



29 32 X = H (34) X = D (31)

[a]Entry	Ligand	Yield (%)	32 : 34 : 31
1	DPPE (35)	31	60 : 33 : 7
2	DPPB (36)	69	77 : 22 : 11
3	DPPF (37)	31	60 : 33 : 7
4	DCPE (8)	41	100 : 0 : 0

[a]All reactions were carried out at an anhydride concentration of 0.035M. The anhydride was treated with the nickel complex (1 equiv of ligand to metal) for 2h before addition of $PhCF_3$ (1.4eq.) and Et_2Zn (1.75eq.). After an additional 5h, reactions were quenched with CH_3CO_2D. All yields and product ratios were determined by NMR.



35 R = Ph
8 R = Cy

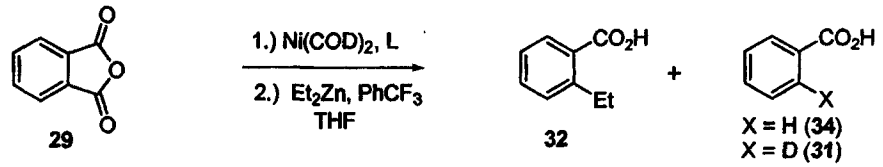
36

37

With monodentate phosphine ligands providing good results we expanded our investigation to include bidentate phosphines (Table 2). The reaction is highly dependent on backbone structure. Bis(diphenylphosphino)ethane (**35**) provides the products in modest yield and poor selectivity (entry 1). Increasing the tether length by two methylene units has a dramatic effect. Bis(diphenylphosphino)butane (**36**) provides the products in 69 % yield in a 77 : 22 : 11 ratio (entry 2). Since an increase in bite angle seems to coincide with an increase in both yield and selectivity we next looked at a ligand possessing a ferrocenyl backbone. Unfortunately ligand **39** failed to improve the reaction providing results identical with DPPE (entry 3). Interestingly, the more basic bis(dicyclohexylphosphino)ethane (**8**) provides only the desired cross-coupled product **32** in 41 % yield (entry 4). Although aromatic phosphines are preferred when monodentate ligands are used, it seems that more basic trialkylphosphines bearing a large cone angle are preferred in the context of bidentate bis-phosphine ligands.

Having thoroughly investigated phosphine ligands in the reaction manifold, we turned our attention to nitrogen-containing ligands. Nitrogen ligands have been extensively investigated in the context of metallalactone formation and several of these intermediates have been characterized by crystallography (*vide supra*). Our screen focused on ligand-metal complexes that had been previously shown to participate in either the oxidative cyclization of carbon dioxide and olefins or the oxidative addition/decarbonylation of anhydrides (Table 3). The nickel complex derived from $Ni(COD)_2$ and 2 equiv of pyridine facilitated the reaction providing a relatively good chemical yield; however, selectivity for the desired cross-coupled product was poor with nearly equal amounts of protio-benzoic acid being formed (entry 1). Use of the more basic DBU again resulted in moderate chemical yield but in this case β-hydride elimination is the preferred reaction pathway providing protio-benzoic acid as the major reaction product (entry 2). Bidentate amine ligands slightly improved reaction selectivity with TMEDA providing ethyl benzoic acid as the major product in modest yield (entry 3). The aromatic ligand 2,2'-bipyridyl (7) provides the best reaction selectivity with respect to product formation but a relatively large amount of deutero-benzoic acid was obtained suggesting that transmetallation of the intermediate metallacycle may be slow compared to other complexes investigated (entry 4).

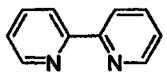
Table 3.



29 32

[a]Entry	Ligand	Yield (%)	32 : 34 : 31
1	pyr	56	42 : 46 : 12
2	DBU	57	14 : 74 : 12
3	TMEDA	59	53 : 33 : 13
4	bpy (7)	43	57 : 15 : 28

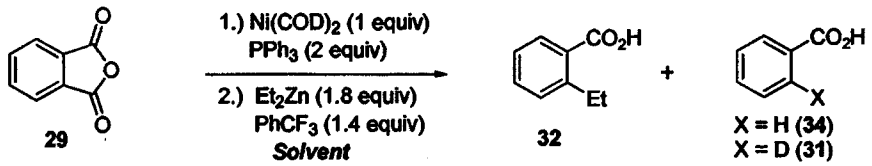
[a]All reactions were carried out at an anhydride concentration of 0.035M. The anhydride was treated with the nickel complex (1 equiv of ligand to metal) for 2h before addition of $PhCF_3$ (1.4eq.) and Et_2Zn (1.75eq.). After an additional 5h, reactions were quenched with CH_3CO_2D. All yields and product ratios were determined by NMR.



7

With the identification of three efficient ligands for the desired transformation, namely PPh_3, DCPE, and bpy, we continued our optimization efforts by investigating solvent effects (Scheme 12). We chose to use the PPh_3 for the investigation since it provided the best combination of selectivity and efficiency. Use of a less polar solvent such as toluene provides a relatively good chemical yield, but the ratio of the desired cross-coupling to by-products was slightly lower than in THF. Increasing the polarity of the reaction medium using a 2:1 mixture of THF and NMP fails to improve the reaction providing products in diminished yield and low selectivity with unwanted β-hydride elimination being the major product. Increasing the concentration of the electron deficient aromatic promoter was also explored. Carrying out the reaction in a 1:1 mixture of $PhCF_3$ and THF results in a yield and selectivity almost identical to the original reaction conditions. Running the reaction in $PhCF_3$ provides a product mixture containing more β-hydride elimination product.

Scheme 12.

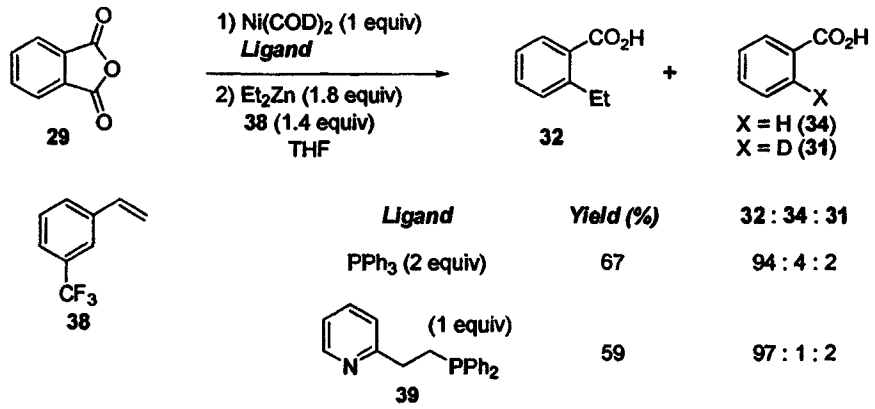


Solvent	*Yield (%)*	32 : 34 : 31
PhMe	55	76 : 18 : 6
THF/NMP (2 : 1)	47	40 : 54 : 6
THF/$PhCF_3$ (1 : 1)	58	83 : 10 : 7
$PhCF_3$	52	68 : 22 : 10

The solvent study revealed THF to be the optimal solvent; however, trifluorotoluene may not be the optimal reductive elimination promoter. Knochel had shown that while trifluorotoluene was an effective promoter, electron-deficient styrenes, particularly trifluoromethyl styrenes, were more efficient providing higher product yields in shorter reaction times.[38] We chose to investigate the use of styrenyl-based promoters in the context of our system with the hope that a faster reductive elimination step would suppress β-hydride elimination thereby increasing selectivity of the reaction in favor of the desired cross-coupled product. To our gratification, replacing trifluorotoluene with *m*-trifluoromethyl styrene (**38**) in the PPh_3 system leads to significantly increased yields (67% vs. 56 %) and a dramatic increase in selectivity (Scheme 13). Using our newly

optimized conditions, we explored the competence of pyridyl-phosphine ligand **39** (pyphos).[39] Hoberg and co-workers had used a similar ligand architecture bearing a dicyclohexylphosphine moiety instead of the diphenylphosphine portion present in **39**. Literature precedent aside, pyphos represents an interesting hybrid of triphenylphosphine and bpy, two ligands that were shown to be successful in our reaction manifold. Subjection of the pyphos-nickel adduct to the optimized reaction conditions provided a 59 % isolated yield of a 97:3 mixture of the desired cross-coupled product **32** to benzoic acid derivatives **34** and **31**. With a relatively efficient stoichiometric process in hand, we changed our focus slightly and started exploring the possibility of rendering the process catalytic in nickel.

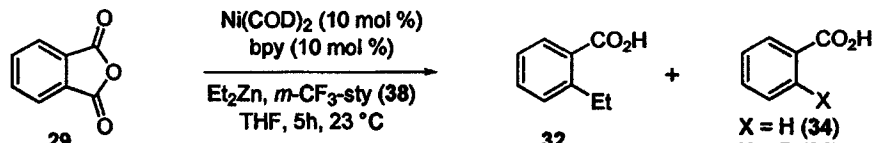
Scheme 13.



At the outset of our work in this area we realized the use of anhydrides to access metallalactone intermediates came with one disadvantage: the extrusion of carbon monoxide in the overall process. Carbon monoxide is known to be a good ligand for electron rich nickel complexes and this ligation could potentially sequester the active metal species retarding the catalytic cycle.[40] During the course of the ligand study it was noticed that when the bpy derived complex was utilized, the deep purple color of the

original nickel species was retained at the end of the reaction. Based on this observation, we reasoned that the active catalyst may be present in the reaction mixture and the opportunity for rendering the process catalytic may exist. Subjection of phthalic anhydride **29** to catalytic amounts of nickel-bpy complex in the presence of 1.4 equiv of nucleophile and promoter, a mixture of three products was isolated in 22% yield favoring the desired cross-coupled product **32** in a 90:10 ratio (Scheme 14). With these promising results in hand several other conditions were examined. Addition of diphenylphosphoryl azide **40**, a compound known to decarbonylate rhodium-CO complexes,[41] to the reaction mixture resulted in a slight increase in yield and the complete suppression of by-product formation. Use of the electron-rich nickel complex derived from the reaction of $Ni(COD)_2$ and DCPE failed to improve the reaction. Encouraged by the indication that catalyst was turning over at least once and that the addition of DPPA seemed to slightly improve the reaction we chose to investigate the effects of other compounds known to facilitate the decarbonylation of CO-ligated metal complexes.

Scheme 14.

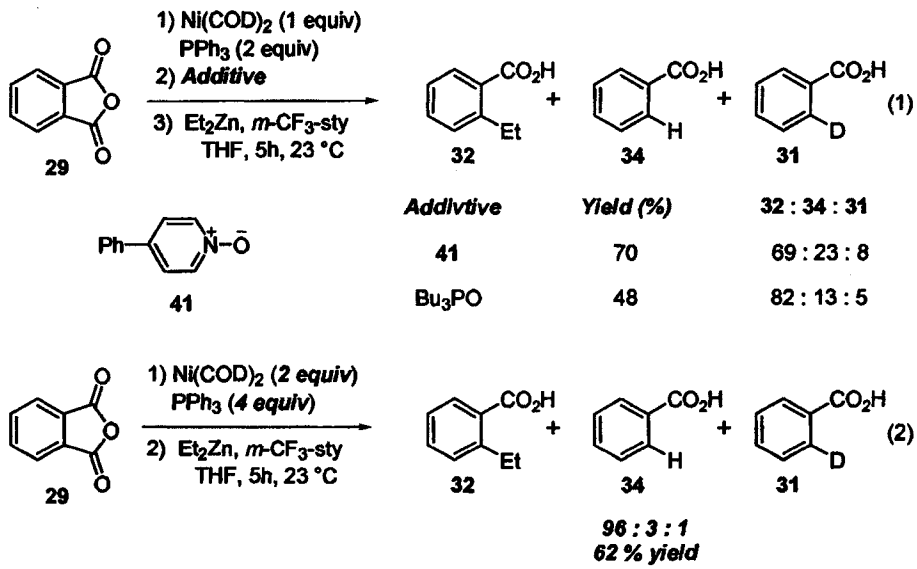


Ligand	*Yield (%)*	32 : 34 : 31
bpy	22	90 : 4 : 6
bpy/40 (1 equiv)	26	100 : 0 : 0
DCPE	6	41 : 50 : 9

Amine and phosphine oxides are known to decarbonylate metal complexes. Amine oxides react at the carbon atom of ligated CO to afford an addition product that decomposes with rupture of the relatively weak N-O bond, forming carbon dioxide and

the corresponding amine.[42] Phosphine oxides react in a similar manner, but due to the P-O bond strength bond breakage does not result. Therefore, phosphine oxides can be used in catalytic amounts with the caveat that CO is released into solution instead of being converted to benign CO_2.[43] Using the stoichiometric nickel-PPh_3 system, we examined the effect of the aforementioned additives looking for a corresponding increase in reaction efficiency as compared with the same reaction performed in the absence of such promoters (Scheme 15). Metallacycle formation under the standard protocol then stepwise treatment with 1 equiv of 4-phenylpyridine N-oxide (**41**) and finally addition of styrenic promoter and nucleophile resulted in a 70 % isolated yield of product (Scheme 15, eq. 1). Unfortunately, the product ratio was greatly diminished favoring the desired product in a modest 69:31 ratio. The addition of **41** of seems to facilitate β-hydride elimination as opposed to the productive pathway and does not significantly increase chemical yields. Performing the reaction in the presence of 30 mol % tributylphosphine oxide failed to increase chemical yields and provided a poor product ratio, again providing increased amounts of proto benzoic acid (Scheme 15, eq. 1). In light of the failure of decarbonylation promoters, we attempted running the reaction in the presence of super stoichiometric amounts of nickel, reasoning that the excess nickel complex should sequester CO leading to better yields. In practice, the reaction was carried out in the presence of 2 equiv of the nickel-phosphine complex under standard reaction conditions. The reaction provided a nearly identical yield and selectivity compared to the same reaction using 1 equiv of the nickel adduct (Scheme 15, eq. 2).

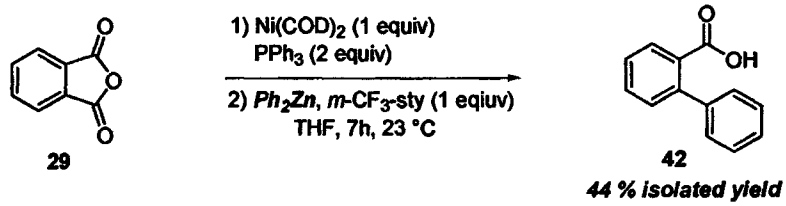
Scheme 15.



1.2.2 Use of Alkyl Anhydride Coupling Partners

The phthalic anhydride model system served as an effective probe for the transmetallation reaction and resulted in the discovery of several nickel-ligand complexes that were competent mediators of the cross-coupling process. Armed with this information, we changed our focus to anhydride coupling partners bearing Csp^3 hybridized backbones with the hope of relaying stereochemical information from the electrophilic coupling partner to the product. In the context of using an sp^3 hybridized electrophilic coupling partner, we chose to focus our efforts on the use of more traditional nucleophilic reagents, namely aromatic zinc reagents, to obviate the potential problems associated with Csp^3-Csp^3 cross-coupling (*vide supra*). To this end, we investigated the competence of diphenylzinc as a nucleophilic coupling partner in the phthalic anhydride model system (Scheme 16). To our gratification, treatment of phthalic anhydride (**29**) with the nickel-complex at room temperature for 2 h followed by the addition of diphenylzinc and promoter and stirring an additional 5 h provided *o*-phenyl benzoic acid (**42**) in 44 % isolated yield.

Scheme 16.

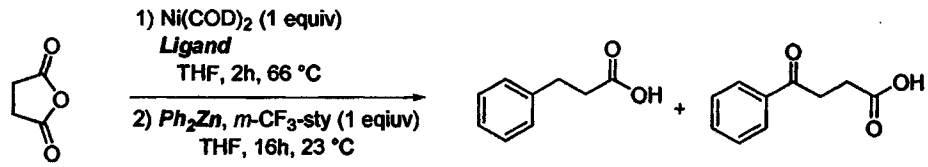


29 42

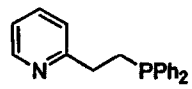
44 % isolated yield

With the successful implementation of aromatic zinc reagents as nucleophilic coupling partners in the model system we began experiments directed toward the use of aliphatic anhydrides in the reaction manifold. Our preliminary efforts focused on the cross-coupling of succinic anhydride (43). Based on our preliminary observations as well

Scheme 17.



43 44 45

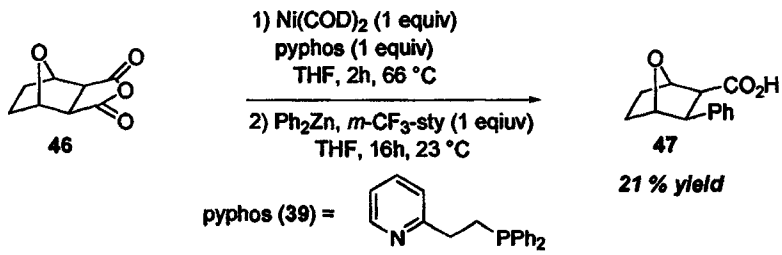
pyphos (39) = 

Ligand	*Yield (%)*	44 : 45
PPh_3 (2 equiv)	~20	65 : 35
bpy (1 equiv)	27	65 : 35
pyphos (1 equiv)	***65***	***82 : 18***

as literature precedent,[44] the initial metallacycle formation was executed at elevated temperatures followed by treatment with nucleophile and reductive elimination promoter at ambient temperature. We focused our efforts on three of the most successful metal-complexes based on our model system (Scheme 17). The bis(triphenylphosphine) nickel adduct proved to be an inefficient complex for the reaction providing a 2:1 mixture of the desired cross-coupled product **44** and keto acid **45**, arising from direct addition of the nucleophile to the anhydride, in low yield. The nickel-bpy complex afforded the same ratio of products in a slightly increased yield. To our delight, use of the pyphos derived

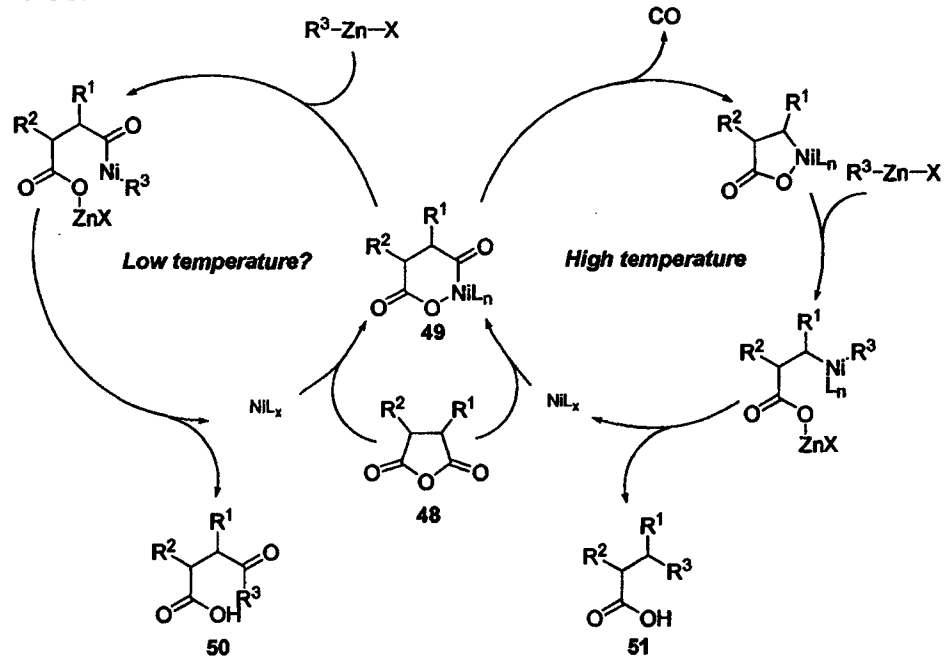
nickel adduct resulted in dramatically improved results, supplying **44** and **45** in a 82:18 ratio in 65% combined yield.

Scheme 18.



With promising results in hand we shifted our focus to an electrophilic coupling partner bearing backbone substitution. Subjection of *meso*-tricyclic anhydride **46** to the reaction conditions provided the desired cross-coupled acid **47** in 21 % isolated yield with no sign of the corresponding direct addition product (Scheme 18). This result represented the first example of cross-coupling a secondary electrophile in the context of a transition metal mediated reaction manifold.[45] With these initial results providing good proof of concept, extensive optimization studies were undertaken resulting in a relatively general decarbonylative cross-coupling of cyclic anhydrides with arylzinc reagents in the presence of stoichiometric amounts of nickel complex.[46]

Scheme 19.



1.3 Conclusion

It is interesting to note that the direct addition product was never observed in any of the reactions performed on phthalic anhydride and only appeared when aliphatic anhydrides were used. We attributed this fact to a slow decarbonylation step in the metal-mediated process and a presumed interception of the initial oxidative addition intermediate **49** (Scheme 19). If **49** could be directly intercepted before decarbonylation by carrying out the reaction at lower temperature, perhaps the direct addition product **50** could be produced in preference to the decarbonylated cross-coupled product **51** constituting a mild alkylation of anhydrides. Another advantage of the direct addition manifold is manifested in the fact that carbon monoxide is not extruded during the process, thus the problem of catalyst poisoning could potentially avoided. Our subsequent efforts focused on the realization of this goal.

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[27] (a) Castaño, A. M.; Echavarren, A. M. *Tetrahedron Lett.* **1990**, *31*, 4783-4786; (b) Castaño, A. M.; Echavarren, A. M. *Tetrahedron Lett.* **1993**, *34*, 4361-4362.

[28] (a) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065-9066; (b) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467-473; (c) Montgomery, J. *Angew. Chem. Int. Ed.* **2004**, *43*, 3890-3908.

[29] For the reductive coupling of internal alkynes, see: (a) Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221-4223; (b) Colby, E. A.; Jamison, T. F. *J. Org. Chem.* **2003**, *68*, 156-166; (c) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442-3443.

[30] For the reductive coupling of alkynes and imines, see: (a) Patel, S. J.; Jamision, T. F. *Angew. Chem. Int. Ed.* **2003**, *42*, 1364-1367; (b) Patel, S. J.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2004**, *43*, 3941-3944.

[31] Similar metallacycles have been characterized by x-ray crystallography and provide coupled product when subjected to the aforementioned reaction conditions, see: Amarasinghe, K. K. D.; Chowdhury, S. K.; Heeg, M.-J.; Montgomery, J. *Organometallics* **2001**, *20*, 370-372.

[32] The problems associated with our efforts toward exploiting this approach may be attributed to our use of CO_2 contaminated with trace oxygen.

[33] Metallalactone intermediates have been coupled with alkyl halides in the presence of manganese metal which presumably involves radical intermediates, see: Ref. 25(d).

[34] Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117-2188.

[35] Other classes of main group coupling partners were also examined including trialkyl boranes, silanes, and stananes all providing little or no product.

[36] Giovannini, R.; Studemann, T.; Devasagayaraj, A.; Dussin, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 3544-3553.

[37] (a) Yamamoto, T.; Yamamoto, A.; Ikeda, S. *J. Am. Chem. Soc.* **1971**, *93*, 3350-3359. (b) Giovannini, R.; Knochel, P. *J. Am. Chem. Soc.* **1998**, *120*, 11186-11187. (c) Piber, M.; Eeg Jensen, A.; Rottlander, M.; Knochel, P. *Org. Lett.* **1999**, *1*, 1323-1326. (d) Yamamoto, T.; Abla, M.; Murakami, Y. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1997-2009.

[38] Knochel has observed dramatic rate differences between promoters in the context of nickel catalyzed Csp^3-Csp^3 cross-coupling reactions; see: reference 36.

[39] Pyphos (**39**) is available in 1 step from the reaction of 2-vinylpyridine and diphenylphosphine, see: Toto, S. D.; Doi, J. T. *J. Org. Chem.* **1987**, *52*, 4999-5003.

[40] The Ni-CO bond strength has been estimated to be on the order of 28.3-47.1 kcal/mol; see: (a) Sunderlin, L. S.; Wang, D.; Squires, R. R. *J. Am. Chem. Soc.* **1992**, *114*, 2788-2796; (b) Ziegler, T.; Tschinke, V.; Ursenback, C. *J. Am. Chem. Soc.* **1987**, *109*, 4825-4837; (c) Li, J.; Schreckenbach, G. Ziegler, T. *J. Am. Chem. Soc.* **1995**, *117*, 486-494.

[41] O'Conner, J. M.; Ma, J. *J. Org. Chem.* **1992**, *57*, 5075-5077.

[42] Albers, M. O.; Coville, N. J. *Coord. Chem. Rev.* **1984**, *53*, 227-259.

[43] Darensbourg, D. J.; Walker, N.; Darensbourg, M. *J. Am. Chem. Soc.* **1980**, *102*, 1213-1214.

[44] Echavarren and co-workers had observed that in most cases metallacycle formation in THF needed to be carried out at elevated temperatures; see: Ref. 27.

[45] After the publication of our results, Fu and co-workers have reported several examples of nickel-catalyzed cross-couplings of secondary alkyl halides; see: (a) Zhou, J. R.; Fu. G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726-14727; (b) Zhou, J. R.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340-1341; (c) Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788-7789.

[46] Optimization and expansion of the substrate scope were undertaken by Erin M. O'Brien; see: O'Brien, E. M.; Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2003**, *125*, 10498-10499.

Chapter 2

Development of an Asymmetric Transition Metal-Catalyzed Anhydride Alkylation

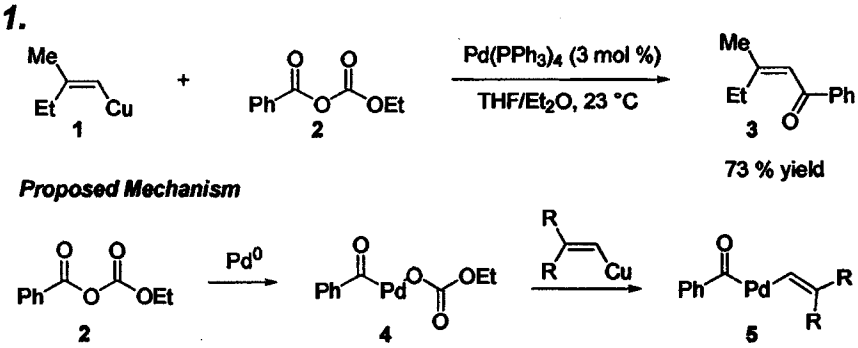
2.1 Introduction

Transition metal-catalyzed carbon-carbon bond forming reactions have become a lynchpin in modern synthetic organic chemistry.[1] Due to the mild nature of reaction conditions employed, a variety of functional groups are well tolerated making transition metal-catalyzed reactions invaluable in the context of complex molecule synthesis. In light of the ever expanding application of these reaction manifolds, the exploitation of new electrophilic and nucleophilic coupling partners continues to be of interest.[2] New methods for the synthesis of ketones through the use of novel electrophilic coupling partners have been of particular interest,[3] providing the desired products without the use of harsh reaction conditions.[4]

A variety of activated acyl species have seen extensive application in transition metal-catalyzed synthesis of ketones. The palladium-catalyzed acylation of organostannanes using acid chlorides,[5] first reported by Migita[6] and later extensively developed by Stille,[7] represented the first example of the utilization of acid halides as electrophilic coupling partners. Following Migita and Stille's pioneering work, a multitude of metal-catalyzed methods have been developed employing activated esters including thioesters[8] and aryltrifluoroacetates.[9]

Anhydrides have only recently garnered attention as competent acylating agents in metal-mediated reaction manifolds. One of the first examples of a transition metal-catalyzed cross-coupling of an anhydride and a main group organometallic was reported by Alexakis and co-workers (Scheme 1).[10] Treatment of mixed carbonic anhydride **2** with catalytic amounts of tetrakis(triphenylphosphine) palladium in the presence of vinyl cuprate **1** provides the desired α,β-unsaturated aromatic ketone **3** in good yield. The mechanism proceeds via oxidative addition of palladium(0) to the electron deficient acyl-oxygen bond of mixed anhydride **2** providing oxo-acyl intermediate **4**. Vinyl group transfer from the copper center to palladium provides vinyl-acyl palladium intermediate **5**, which upon reductive elimination provides the desired addition product.

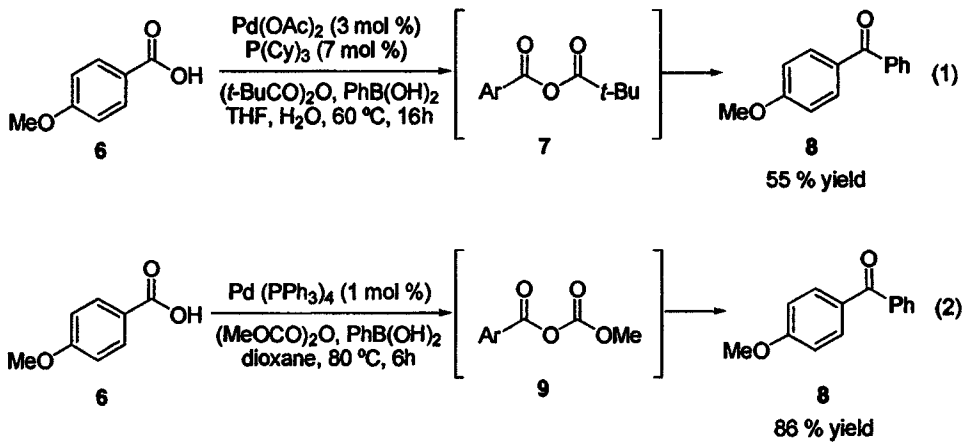
Scheme 1.



Goossen[11] and Yamamoto[12] each independently reported the cross-coupling of acyclic anhydrides with boronic acid coupling partners in the presence of palladium catalysts. Each group took advantage of generating the anhydride *in situ*, which effectively represents a direct conversion of a carboxylic acid to a ketone under extremely mild conditions. Goossen and co-workers take advantage of a steric bias in the intermediate mixed anhydride (**7**), generated by the reaction of the starting carboxylic acid **6** and pivalic anhydride, to direct oxidative addition to the proper C-O bond (Scheme 2, eq. 1). Yamamoto and co-workers exploit an electronic bias by forming the reactive

anhydride coupling partner **9** from the corresponding acid **6** with dimethyl dicarbonate. Each method affords the cross-coupled product **8** in good yields, although these reaction manifolds seem to be generally restricted to the use of aryl boronic acid coupling partners. More recently acyclic anhydrides have been exploited as electrophilic coupling partners in other systems employing different catalysts and main group nucleophiles.[13]

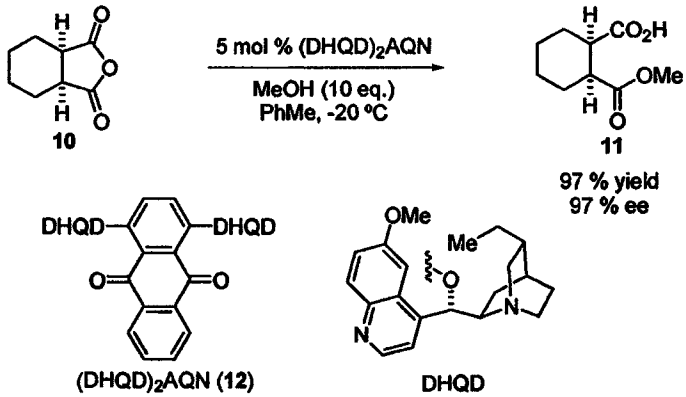
Scheme 2.



Although the aforementioned methods represent powerful approaches to the ketone functionality, they inherently lack the ability to incorporate stereochemical information during the carbon-carbon bond forming event. The use of succinic or glutaric anhydride derivatives as electrophilic coupling partners would provide access to γ- and δ-keto acid derivatives possessing stereochemically defined backbones. Furthermore, alkylation of meso cyclic anhydrides opens the opportunity to render the process asymmetric. The realization of this approach would represent a very efficient entry into 1,4- and 1,5-dicarbonyl systems, intriguing synthons with a demonstrated importance as intermediates in the synthesis of a variety of heterocyclic systems.[14]

The addition of heteroatom nucleophiles to meso anhydrides has been thoroughly investigated. Early work focused on the diastereoselective addition of chiral alcohols to prochiral anhydrides providing the corresponding 1,4- and 1,5-ester acids in good yields and high diastereoselectivity.[15] The current state of the art in the field involves the enantioselective addition of alcohols catalyzed by cinchona alkaloid derivatives (Scheme 3).[16] Deng and co-workers found that cinchona alkaloid-based ligands such as **12** efficiently catalyzed the addition of methanol to meso anhydride **10**, affording hemiester **11** in high yield and excellent enantioselectivtiy.[17] The reaction has been shown to be very versatile with respect to meso succinic and glutaric anhydrides, providing the product half esters in generally good yields and high enantiomeric excess.

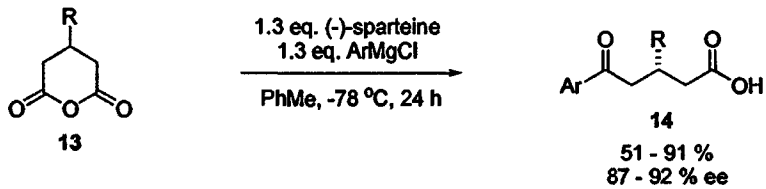
Scheme 3.



In contrast to the addition of heteroatom nucleophiles to cyclic anhydrides, relatively little attention has been paid to the corresponding reaction manifold utilizing carbon-based nucleophiles. The Friedel-Crafts acylation of anhydrides is well known, but is inherently limited to the use of electron-rich aromatic nucleophiles and provides access to ketones bearing limited substitution patterns.[18] Addition of strongly nucleophilic species such as Grignard reagents to meso cyclic anhydrides may lead to

mixtures of products including Meerwein-Ponndorf-Verley reduction, over alkylation, and epimerization.[19] Fu and Shintani recently reported the enantioselective addition of aryl Grignard reagents to glutaric anhydrides at low temperatures in the presence of stoichiometric amounts of (-)-sparteine (Scheme 4).[20] Glutaric anhydrides of type **13** smoothly afford keto acids **14** in relatively good yields and high selectivities. Although this represents a fairly general enantioselective alkylative anhydride desymmetrization, several disadvantages exist: the requirement of stoichiometric chirality, the use of Grignard reagents which are not highly functional group tolerant, and the fact that succinic anhydrides are beyond the current scope.

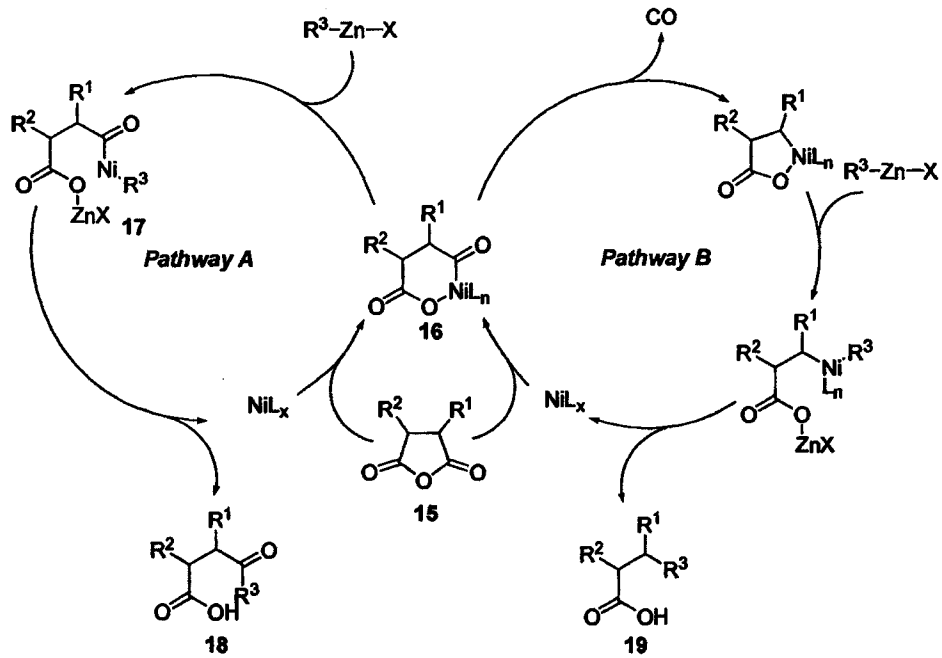
Scheme 4.



We felt the combination of a transition metal-catalyzed carbon-carbon bond forming process with concurrent desymmetrization of a meso compound would represent a powerful method for the synthesis of keto acid derivatives. Furthermore, the use of a chiral metal catalyst could conceivably provide access to enantioenriched keto acids under mild conditions in presence of sub-stoichiometric amounts of chirality. We envisioned two coupled catalytic cycles in the context of the reaction of a nickel catalyst, an anhydride, and a main group organometallic (Scheme 5). As described in Chapter 1, reaction of a cyclic anhydride and stoichiometric amounts of a nickel complex in refluxing THF provides access to nickelalactone intermediates, which upon stepwise treatment with a diorgaozinc reagent provides the cross-coupled products of type **19** in

moderate yields (Pathway B). During the course of our studies on the exploitation of anhydrides bearing aliphatic backbones, we observed minor amounts of the product arising from the direct addition of the nucleophile to the anhydride (**18**). We reasoned that this product could be manifested by direct interception of the initial oxidative addition adduct **16** via transmetalation and reductive elimination (Pathway A). If this is the case, then Pathway A should be favored at lower reaction temperatures. Armed with several effective nickel-ligand complexes for the decarbonylative cross-coupling manifold, we explored their competence in the proposed direct addition reaction.

Scheme 5.



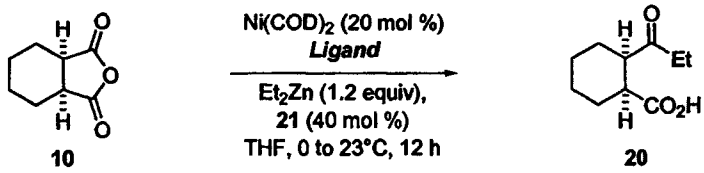
2.2 Achiral Nickel-Catalyzed Anhydride Alkylation

2.2.1 Initial Ligand Screen

Our initial survey began with the known insertion of low-valent nickel complexes into cyclic anhydrides.[21] We envisioned that in the presence of a suitable nucleophilic coupling partner the initial oxidative addition adduct could be intercepted, providing the

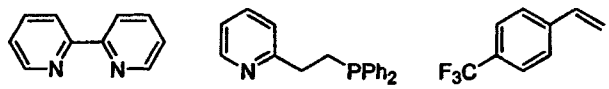
desired keto acid under mild conditions. Organozinc reagents were chosen for several reasons: alkyl zinc reagents are known to transmetalate cyclic nickel alkoxide intermediates,[22] alkyl zinc reagents are easily prepared and functional group tolerant,[23] and control experiments revealed that diethylzinc does not add to cyclohexanedicarboxylic anhydride (THF, 23 °C, 6 h).[24] Cyclohexanedicarboxylic anhydride **10** was subjected to a catalytic amount of a variety of nickel-ligand complexes in the presence of diethylzinc in THF at 0 °C. For instances in which the reaction was slow as indicated by TLC, it was allowed to warm to ambient temperature. Catalytic amounts of electron-deficient styrene **21** were added to accelerate reductive elimination in lieu of potential β-hydride elimination from the presumed acyl-alkyl nickel intermediate (*vide infra*), following the precedent of Knochel.[25]

Table 1.



10 20

Entry	*Ligand*	Metal : Ligand	Yield (%)
1	none	–	76
2	PPh_3	1 : 1	50-60
3	PPh_3	1 : 2	< 5
4	PCy_3	1 : 1	< 5
5	PCy_3	1 : 2	< 5
6	DPPE	1 : 1.2	78
7	DPPB	1 : 1.2	20
8	bpy	1 : 1.2	92
9	pyphos	1 : 1.2	80



bpy pyphos 21

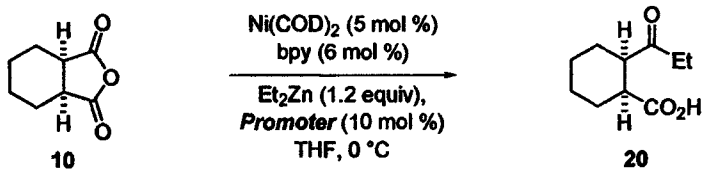
The efficiency of the reaction is highly dependent on the ligand employed (Table 1). In the absence of ligand, the reaction proceeds smoothly to provide the desired keto acid **20** in relatively good yield although reaction times of 20 h are required (entry 1). Trialkyl and triaryl monodentate phosphines proved rather ineffective under the prescribed reaction conditions (entries 2-5). Bidentate phosphine complexes are more efficient than adducts derived from monodentate phosphine ligands and also exhibit a dependence on bite angle. Bis(diphenylphosphino)ethane (DPPE) furnishes the desired product in good yield while bis(diphenylphosphino)butane (DPPB) is less effective (entries 6 and 7). The most competent ligands are 2,2'-bipyridyl (bpy) and (2-diphenylphosphino)ethylpyridine (pyphos)[26] each efficiently supplying the desired addition product **20** in less than 3 h at 0 °C (entries 8 and 9). Each of these ligand-metal complexes deliver analytically pure material upon acid-base workup.

2.2.2 Promoter Study

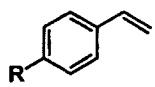
Our working hypothesis regarding the reaction mechanism involved the initial oxidative addition of the low-valent nickel catalyst to the electron-deficient C-O bond of the anhydride followed by a transmetalation event providing an acyl-alkyl nickel intermediate which upon reductive elimination provides the desired alkylation product (*vide supra*). Electron-deficient olefins have been shown to facilitate the reductive elimination of dialkyl nickel intermediates.[27] The acceleration of reductive elimination is thought to proceed through initial coordination of the olefin to the metal center resulting in a π-back bonding interaction leading to weakening of the carbon-metal σ-bonds (Table 2, see figure).[28] Knochel and co-workers have exploited the use of catalytic amounts of electron-deficient olefins in the context of Csp^3-Csp^3 cross-coupling, resulting in dramatic enhancements of reaction rate and efficiency.[29] We had noted the benefit of these olefinic additives in our reaction manifold and sought to quantify this effect; therefore, a systematic study of the reductive elimination promoter was undertaken to probe its effect on reaction rate and efficiency.

The nature of the promoter has a dramatic effect on reaction rate and conversion (Table 2).[30] The reaction proceeds smoothly in the absence of promoter at 0 °C to provide a good yield of addition product **20** although the reaction requires 21 h to proceed to completion (entry 1). The addition of 10 mol % (2 equiv to catalyst) of 4-trifluoromethyl styrene (**22**) results in a dramatic rate acceleration, providing the product acid **20** in 80 % isolated yield in less than 5 minutes (entry 2). Variation of the electronic properties of the styrene-based promoter has little effect on the efficiency of the transformation, but a small effect on the reaction rate was observed. Styrene (**22**)

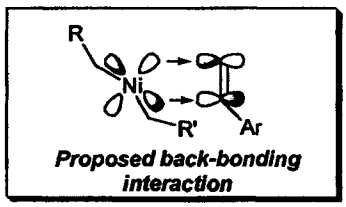
Table 2.



10 20

Entry[a]	*Promoter*	Time (min.)	Yield (%)
1	none	1260	76
			
2	R = CF_3 (22)	< 5	82
3	R = H (23)	25	68
4	R = F (24)	30	80
5	acrylonitrile	2880	< 10
6	$PhCF_3$	2880	~ 50

[a]All reactions run in the presence of $Ni(COD)_2$ (5 mol %), bpy (6 mol %), and Et_2Zn (1.2 eq.) at 0 °C for indicated time.



Proposed back-bonding interaction

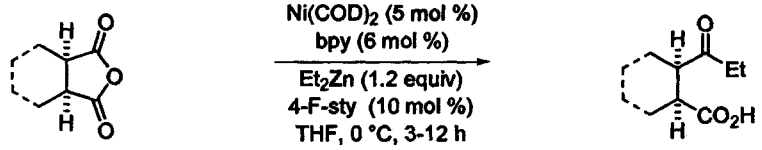
provides the product keto acid in 68 % yield in 25 min. while the more electron deficient 4-fluorostyrene (**24**) provides **20** in 80 % yield in 30 min. (entries 4 and 5). The use of trifluorotoluene or acrylonitrile seems to suppress reactivity providing poor yields of **20** contaminated with by-products[31] even after extended reaction times (entries 5 and 6).

2.2.3 Substrate Scope

A variety of succinic anhydride derivatives undergo alkylation. Succinic anhydrides bearing a fused cyclohexane skeleton provide the desired products in good yields (Table 3). Both *cis*- and *trans*-cyclohexanedicarboxylic anhydride provide the desired products **20** and **26** with no loss of stereochemical integrity (entries 1 and 2). Substrates bearing olefinic backbones are compatible with the prescribed reaction

conditions. Cyclohexenyl succinic anhydride **27** affords the desired acid **28** in excellent yield (entry 3). Likewise, anhydride **29** bearing a tetrasutituted olefin and benzofused substrate **31**, supply addition products **30** and **32** in 90 % isolated yield in each case (entries 4 and 5). Substituents at the β-position of the anhydride are well tolerated, as typified by anhydride **33**, the Diels-Alder adduct of 2,4-hexadiene and maleic anhydride,

Table 3.

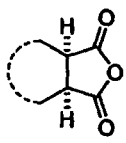


Entry[a]	Anhydride	Product	Yield (%)
1	**10** (*cis*)	**20** (*cis*)	95[b,c]
2	**25** (*trans*)	**26** (*trans*)	87
3	**27** (R =H)	**28** (R =H)	95[b,c]
4	**29** (R = Me)	**30** (R = Me)	90
5	**31**	**32**	90[d]
6	**33**	**34**	61[d]
7	**35**	**36**	61[d]

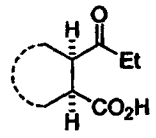
[a]Reactions conducted in the presence of $Ni(COD)_2$ (5 mol %),bpy (6 mol %), 4-F-sty (10 mol %), and 1.2 equiv of Et_2Zn at 0 °C in THF unless otherwise stated. [b]Reaction conducted using $Ni(COD)_2$ (10 mol %), bpy (12 mol %), and 4-F-sty (20 mol %). [c]4-CF_3-sty used as promoter. [d]Isolated as the corresponding methyl ester.

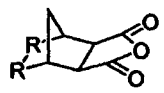
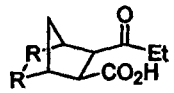
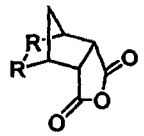
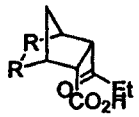
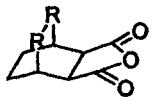
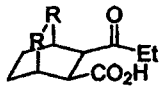
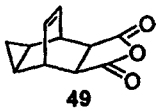
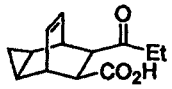
which upon alkylation provides acid **34** containing 4 contiguous stereocenters (entry 6). The reaction is tolerant of potentially labile functionality present in the anhydride backbone as illustrated by anhydride **35**, which upon subjection to the reaction conditions provides the stereochemically defined 1,2,5,6-tetrasubstituted keto acid **36** in moderate yield (entry 7).

Table 4.



$Ni(COD)_2$ (5 mol %)
bpy (6 mol %)
Et_2Zn (1.2 equiv)
4-F-sty (10 mol %)
THF, 0 °C, 3-12 h



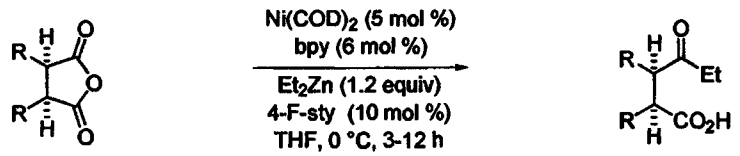
Entry[a]	Anhydride	Product	Yield (%)
			
1	**37** (R = CH_2)	**38** (R = CH_2)	79[b,c,d]
2	**39** (R = CH)	**40** (R = CH)	91[b,c]
			
3	**41** (R = CH_2)	**42** (R = CH_2)	88[b,c]
4	**43** (R = CH)	**44** (R = CH)	96[b,c]
			
5	**45** (R = CH_2)	**46** (R = CH_2)	91
6	**47** (R = CH)	**48** (R = CH)	84
7			68[b,d]
	49	**50**	

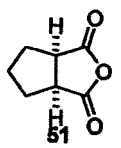
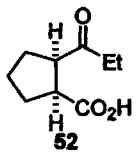
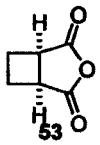
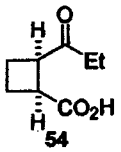
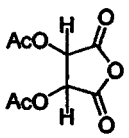
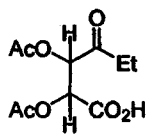
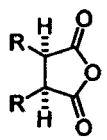
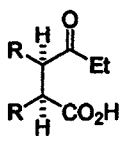
[a]Reactions conducted in the presence of $Ni(COD)_2$ (5 mol %),bpy (6 mol %), 4-F-sty (10 mol %), and 1.2 equiv of Et_2Zn at 0 °C in THF unless otherwise stated. [b]Reaction conducted using $Ni(COD)_2$ (10 mol %), bpy (12 mol %), and 4-F-sty (20 mol %). [c]4-CF_3-sty used as promoter. [d]Isolated as the corresponding methyl ester.

Tricyclic anhydride adducts efficiently participate in this reaction manifold providing ready access to *endo*- and *exo*-bicyclic keto acids (Table 4). Saturated *exo*-anhydride **37** and unsaturated *exo*-[2.2.1] anhydride **39** smoothly provide the corresponding *exo*-acids **38** and **40** in good yield (entries 1 and 2). Isomeric *endo*-[2.2.1] adducts **41** and **43** each efficiently furnish the *endo*-keto acids **42** and **44** with no evidence of epimerization (entries 3 and 4). Not surprisingly, [2.2.2] anhydrides **45** and **47** also supply product acids **46** and **48** in high yields (entries 5 and 6). Anhydride **49**, readily available in one step from cycloheptatriene and maleic anhydride,[32] provides the

desymmetrized product **50**, giving access in two steps to a stereochemically defined hexasubstituted cyclohexane core (entry 7).

Table 5.



Entry[a]	Anhydride	Product	Yield (%)
1	 **51**	 **52**	71[d]
2	 **53**	 **54**	61[b,c]
3	 **55** (*cis*)	 **56** (*cis*)	74
4	**57** (*trans*)	**58** (*trans*)	88[b,c]
5	 **59** (R = Me)	 **60** (R = Me)	93[b,c]
6	**61** (R = $(CH_2)_3CO_2Et$)	**62** (R = $(CH_2)_3CO_2Et$)	75

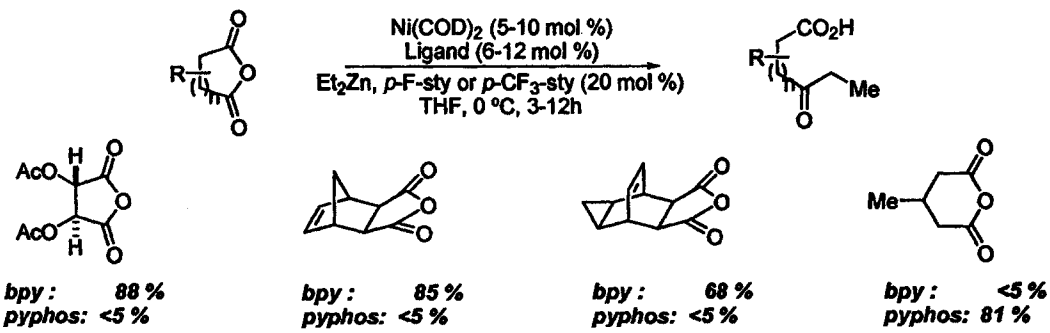
[a]Reactions conducted in the presence of $Ni(COD)_2$ (5 mol %),bpy (6 mol %), 4-F-sty (10 mol %), and 1.2 equiv of Et_2Zn at 0 °C in THF unless otherwise stated. [b]Reaction conducted using $Ni(COD)_2$ (10 mol %), bpy (12 mol %), and 4-F-sty (20 mol %). [c]4-CF_3-sty used as promoter. [d]Isolated as the corresponding methyl ester.

Bicyclic anhydrides bearing smaller ring sizes as well as monocyclic succinic anhydrides are also competent substrates in the reaction (Table 5). Fused cyclopentane and cyclobutane succinic anhydrides **51** and **53**, offer products **52** and **54** in 71 and 61 % yield respectively (entries 1 and 2). Tartaric acid derived anhydrides **55** and **57** efficiently afford the corresponding acyclic keto acids **56** and **58** with no evidence of

elimination or hydrolysis of the potentially labile acetoxy groups (entries 3 and 4). *meso*-Dimethylsuccinic anhydride **59** as well as the homologated ester-containing derivative **61** each furnish the corresponding 1,4-dicarbonyl compounds **60** and **62** (entries 5 and 6).

With the catalytic alkylation applied to succinic anhydride derivatives, we sought to further expand the scope of the current method to glutaric anhydrides. In our initial investigations we used the bpy and pyhpos-derived catalysts interchangeably; however, as work on the substrate scope continued we soon realized a relationship between substrate class and catalyst (Scheme 6). Subjecting succinic anhydride substrates to the reaction conditions using the bpy catalyst uniformly provides product in good yields (*vide supra*). Interestingly, use of the pyphos catalyst in the context of succinic anhydride alkylation fails to provide high yields of products in most cases although some exceptions do exist.[33] Likewise, glutaric anhydrides fail to provide product in the presence of the bpy catalyst, but the use of the pyphos catalyst provides the desired products in good yield.

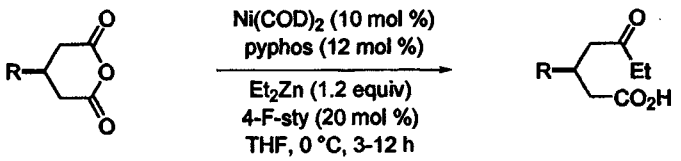
Scheme 6.



The pyphos-derived catalyst is effective for the desymmetrization of a variety of glutaric anhydride derivatives (Table 6). Glutaric anhydrides bearing a variety of substitution at the 4-position participate in this transformation. Methyl glutaric anhydride

63 as well phenyl glutaric anhydride **65** each afford good yields of the corresponding ethyl ketones **64** and **66** (entries 1 and 2). Heteroatom substituents at the 4-position are also well tolerated providing β-benzyloxy acid **68** and N-protected β-amino acid derivative **70** in modest yields (entries 3 and 4). The HMGA-derived anhydride **71**, bearing a potentially labile β-acetate group, efficiently provides keto acid **72** in 75 % yield (entry 5). Substitution at the α-position of the anhydride does not adversely affect the reaction with anhydride **73**, smoothly providing acyclic keto acid **74** containing a skipped 1,3-syn-dimethyl relationship in the backbone (entry 6). Bridged bicyclic glutaric anhydrides **75** and **77** afford 1,3-syn-cyclopentane **76** and 1,3-syn-cyclohexane **78** in 90 and 88 % yield respectively as single diastereomers (entries 7 and 8). Alkylation of polyoxygenated bicyclic anhydride **79** proceeds uneventfully to provide the pentasubstituted cyclopentane **80**, containing several labile elements, in 88 % yield (entry 9).

Table 6.



Entry[a]	Anhydride	Product	Yield (%)	Entry[a]	Anhydride	Product	Yield (%)
1	**63** (R = Me)	**64** (R = Me)	81[c]	7	**75**	**76**	90[b]
2	**65** (R = Ph)	**66** (R = Ph)	77				
3	**67** (R = OBn)	**68** (R = OBn)	52	8	**77**	**78**	88[b]
4	**69** (R = NHTs)	**70** (R = NHTs)	57[b]				
5	**71**	**72**	75	9	**79**	**80**	88
6	**73**	**74**	85				

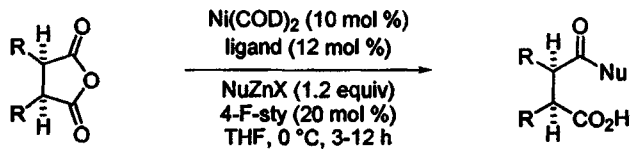
[a]Reactions conducted in the presence of $Ni(COD)_2$ (10 mol %), pyphos (12 mol %), and Et_2Zn (1.2 equiv) at 0 °C unless otherwise stated. [b]Reaction conducted using $Ni(COD)_2$ (5 mol %), pyphos (6 mol %), and 4-F-sty (10 mol %). [c]4-CF_3-sty used as promoter.

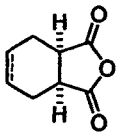
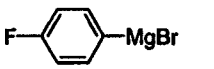
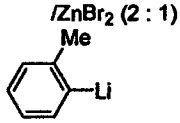
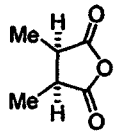
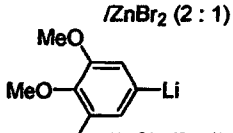
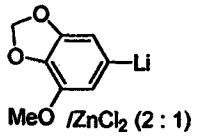
2.2.4 Nucleophile Scope

The reaction is not limited to the use of diethyl zinc as the nucleophilic coupling partner (Table 7). Subjection of anhydride **10** to the reaction conditions using Me_2Zn and Ph_2Zn provides the corresponding methyl and phenyl ketones in excellent yields (entries 1 and 2). The secondary diorganozinc reagent, diisopropyl zinc, smoothly provides the isopropyl ketone with no signs of *iso*-propyl to *n*-propyl isomerization (entry 3). Alkylzinc halides are also competent coupling partners. Although the bpy-derived catalyst system is less efficient, providing the cross-coupled product in 66 % yield using 20 mol % catalyst loading, we found that changing the ligand to the bidentate phosphine DPPE resulted in a more effective catalyst for alkylzinc halide coupling (entries 4 and 5).

Functionalized zinc reagents were also found to be compatible with this reaction manifold, allowing for incorporation of reactive functionality in both coupling partners (entry 6). Diaryl and dialkyl zinc reagents[34] formed *in situ* from the corresponding lithium or Grignard reagents also participate in the reaction demonstrating that by-product lithium and magnesium salts are benign (entries 7-12). It is noteworthy that the aryl lithium reagents (entries 10-12) were generated from the aryl bromide by treatment with *n*-butyllithium, producing butyl bromide as a by-product which does not seem to affect the outcome of the reaction.[35]

Table 7.

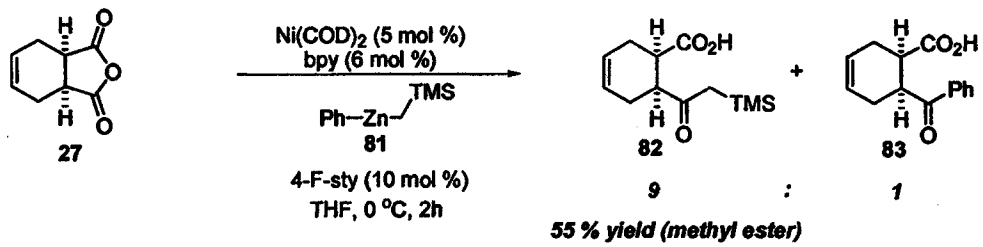


Entry[a]	Anhydride	NuZnX	Ligand	Yield (%)	Entry[a]	Anhydride	NuZnX	Ligand	Yield (%)
					9	27	 /$ZnBr_2$ (2 : 1)	bpy	68[b,e]
1	10	Me_2Zn	bpy	86[d]	10	10	 /$ZnBr_2$ (2 : 1)	bpy	63[b,e]
2	10	Ph_2Zn	bpy	88[d]					
3	27	*i*-Pr_2Zn	bpy	77[b]					
4	10	BuZnBr	bpy	66[c,d,e]	11	 59	 /$ZnCl_2$ (2 : 1)	bpy	90[b]
5	10	BuZnBr	dppe	67[d,e]					
6	10	$BrZnCH_2CH_2CO_2Et$	dppe	53[d,e]					
7	27	2-fur-Li/$ZnCl_2$ (2:1)	bpy	65[b,e]					
8	27	*n*-prop-MgCl/$ZnCl_2$ (2:1)	bpy	61[b,e]	12	59	 /$ZnCl_2$ (2 : 1)	bpy	96[b]

[a]All reactions conducted in the presence of $Ni(COD)_2$ (10 mol %), indicated ligand (12 mol %), and RZnX (1.2 eq.) at 0 °C unless otherwise stated. [b]Reaction conducted using $Ni(COD)_2$ (5 mol %), bpy (6 mol %), and 4-F-sty (10 mol %). [c]Reaction conducted using $Ni(COD)_2$ (20 mol %), bpy (22 mol %), and 4-F-sty (40 mol %). [d]4-CF_3-sty used as promoter. [e]Isolated as the corresponding methyl ester

Although alkylzinc halides are competent nucleophiles in the desymmetrization reaction, generally longer reaction times are required, coupled with lower yields in comparison to the corresponding dialkyl- and diarylzinc reagents. The main draw back of diorganozinc reagents is manifested in the fact that only one alkyl or aryl group is transferred in the transmetalation event.[36] The use of a non-transferable group, or dummy ligand, on the zinc center has been shown to obviate this problem in the context of the conjugate addition of zinc reagents to α,β-unsaturated carbonyl compounds.[37] The requisite zinc reagent **81** was prepared from the reaction of phenylzinc bromide with 1 equiv of trimethylsilylmethyl lithium (Scheme 7). When subjected to standard reaction conditions, the transfer of the dummy ligand predominated, providing a 9:1 mixture of trimethylsilylmethyl keto acid **82** and phenyl keto acid **83** in moderate yield. Although this unexpected result does not provide a solution to the stated problem, it does provide an efficient route to trimethylsilylmethyl ketones which can be considered latent enolate equivalents.

Scheme 7.

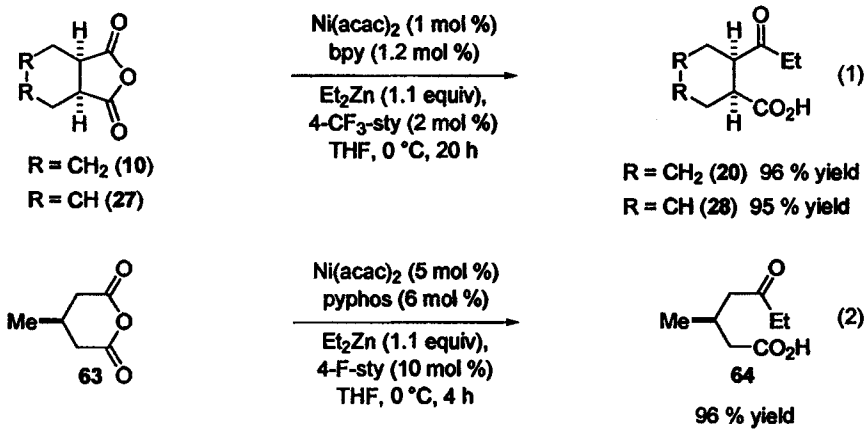


2.2.5 Application of an Air-Stable Precatalyst.

The nickel (0) pre-catalyst, $Ni(COD)_2$, although commercially available, is extremely air-sensitive, requiring the use of an inert atmosphere glove box. In the interest of making the reaction protocol more amenable in a practical sense, we sought the development of an air-stable catalyst precursor thereby obviating the need for glove

box manipulation.[38] Anhydrous nickel (II) acetylacetonate ($Ni(acac)_2$) was used as a catalyst precursor affording an active nickel (0) catalyst upon *in situ* reduction by diethyl zinc. Taking advantage of the most active reductive elimination promoter, 4-trifluoromethyl styrene, catalyst loading was reduced to 1 mol % in the case of cyclohexylsuccinic anhydrides **10** and **27** providing the desired keto acid products **20** and **28** in excellent yield with a longer reaction time (Scheme 8, eq. 1). Each reaction was executed on multi-gram scale (15 mmol) and upon completion, simple acid-base work-up provided analytically pure material circumventing the need for chromatographic separation. The nickel (II) pre-catalyst can also be applied to glutaric anhydrides. Methylglutaric anhydride **63** undergoes smooth alkylation in the presence of 5 mol % pyphos derived catalyst providing the desired δ-keto acid **64** in excellent yield (Scheme 8, eq. 2).

Scheme 8.

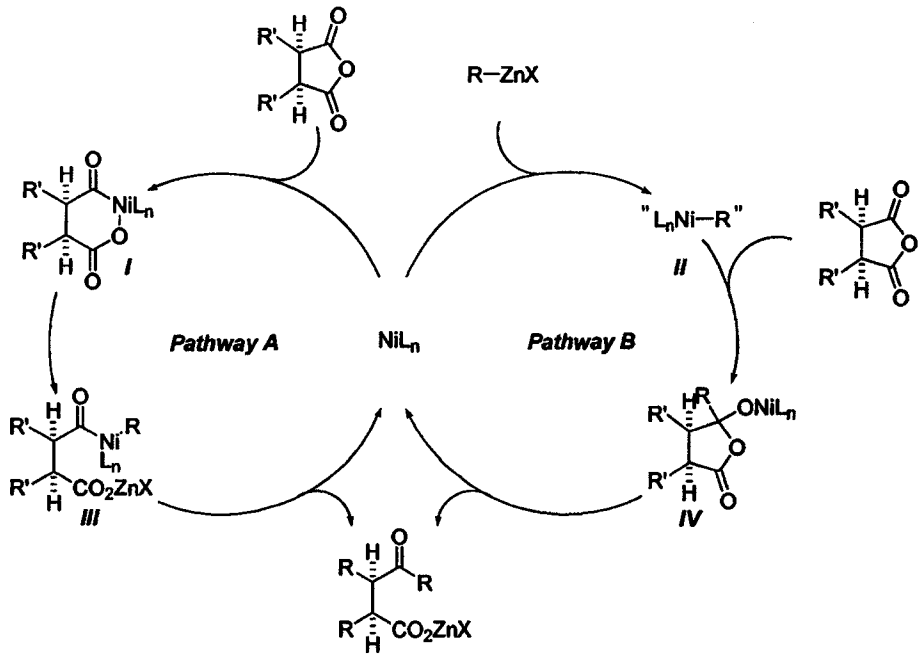


2.2.6 Mechanistic Considerations

Two potential mechanistic pathways for this reaction are depicted in Scheme 9. Pathway A involves oxidative addition of the low-valent nickel complex to the electron-deficient C-O bond of the cyclic anhydride to yield the cyclic acyl-nickel carboxylate **I**.

Transmetalation of **I** provides acyl-alkyl nickel species **III** which could then undergo reductive elimination to provide the desired product along with regeneration of the active catalyst. Another potential route, depicted as pathway B, involves the initial formation of an alkyl nickel intermediate **II** from direct alkyl group transfer from the zinc reagent to the catalyst.[39] Intermediate **II** can then react with the starting anhydride through addition of the alkyl group to the anhydride directly providing tetrahedral intermediate **IV** which upon collapse would provide product. In our previous work on the decarbonylative cross-coupling of cyclic anhydrides[40] we observed the corresponding direct addition product in minor amounts in some reactions, suggesting that the alkylation product in the present reaction manifold may arise from a similar mechanistic pathway, namely a discrete oxidative addition of the low-valent nickel catalyst (Pathway A). Furthermore, a wealth of precedent exists for the stoichiometric interaction of electron-rich nickel complexes and cyclic anhydrides indicating that oxidative addition clearly occurs when the two are admixed.[41] In one instance, this intermediate has been characterized by crystallography.[42] Nevertheless, the slight difference in our optimized reaction conditions compounded with the caveat that stoichiometrically generated species are not always intermediates in catalytic cycles spurred us to investigate the mechanism of this reaction in some detail.

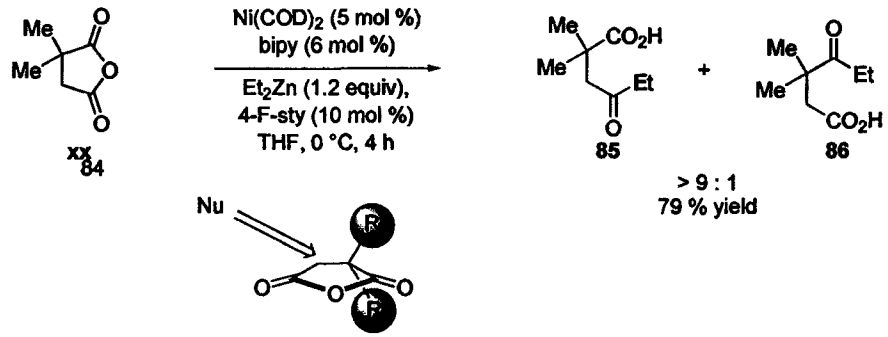
Scheme 9.



We reasoned the use of an unsymmetrical anhydride might provide information regarding the active mechanistic pathway based on the regioisomer obtained. The regioselective alkylation[43] and reduction[44] of unsymmetrical succinic anhydrides is well known. Reaction principally takes place at the carbonyl group adjacent to the more highly substituted carbon atom. This observation has been attributed to a more favored nucleophilic attack trajectory[45] that proceeds over the least sterically hindered α-carbon thereby delivering the nucleophile to the carbonyl neighboring the more substituted α-carbon (Scheme 10).[46] In the event, subjection of 2,2-dimethylsuccinic anhydride **84** to the standard reaction conditions provides a > 9 : 1 regioisomeric mixture of acids **85** and **86** favoring addition at the carbonyl adjacent to the least substituted α-carbon (Scheme 10). This observation suggests that the anhydride is activated by the oxidative addition of the low-valent nickel catalyst as depicted in pathway A. The regiochemical outcome can be rationalized by the steric encumbrance imparted by the geminal dimethyl substituents

effectively shielding the adjacent carbonyl thus favoring precoordination and subsequent oxidative addition of the catalyst to the more accessible C-O bond.

Scheme 10.

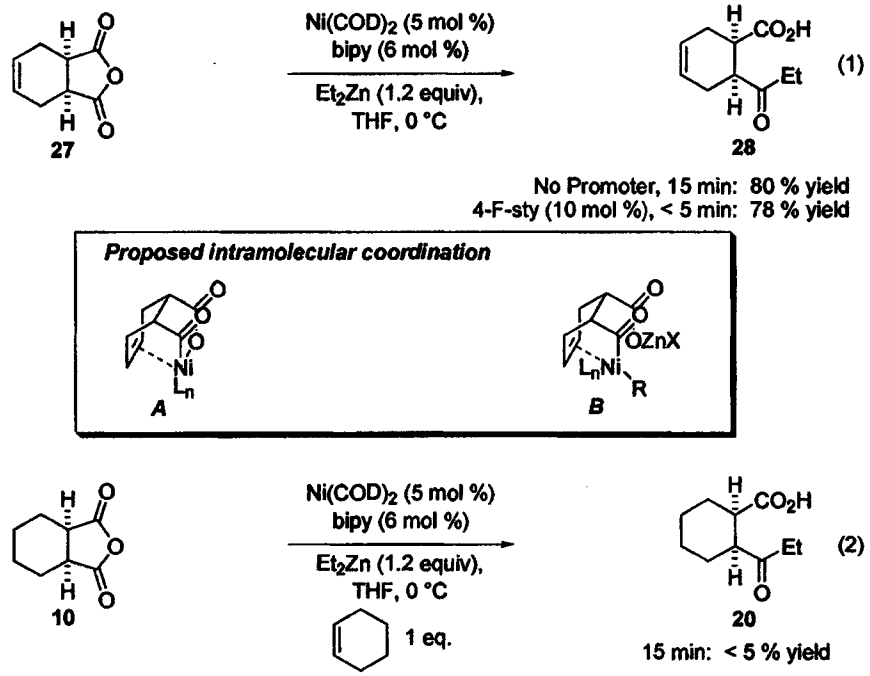


Preferred nucleophilic tragectory

During the course of our olefinic promoter studies we noted that subjection of anhydride **27** to standard reaction conditions using 4-fluorostyrene as the promoter provided the desired product **28** in less than 5 minutes. To our surprise, when the same reaction was carried out in the absence of styrenic additive, the product keto acid **28** was isolated in excellent yield in 15 minutes constituting a striking rate enhancement when compared to the corresponding saturated anhydride derivative (Scheme 11, eq. 1). We attributed the observed acceleration of reaction rate to the ability of the olefinic backbone to stabilize the oxidative addition intermediate by an intramolecular coordination event (**A**) or to facilitate the subsequent reductive elimination of the proposed acyl-alkyl nickel intermediate (**B**).[47] However, we could not rule out the possibility of an intermolecular promotion of the reaction by interaction of the olefinic backone of the starting material or product with reaction intermediates. To establish whether the proposed interaction was intra- or intermolecular in nature, cyclohexanedicarboxylic anhydride **10** was subjected to standard reaction conditions in the presence of 1 equiv of cyclohexene (Scheme 11, eq. 2). After a 15 minute reaction time, less than 5 % of the desired alkylation product was

observed, suggesting that the rate enhancement is a consequence of an intramolecular coordination event.

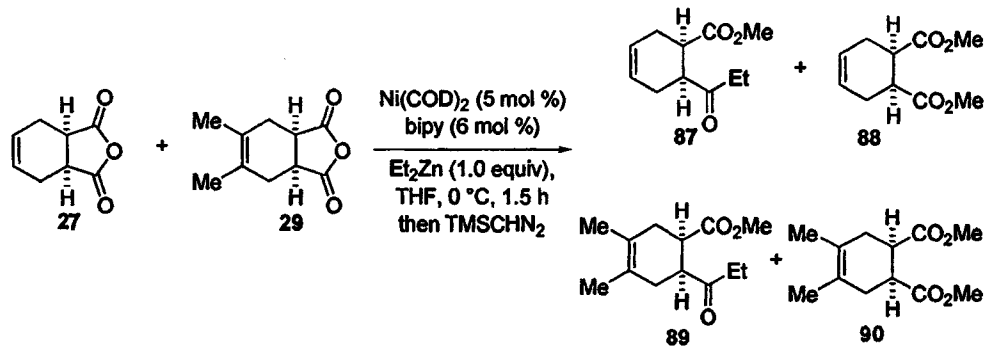
Scheme 11.



With evidence of olefinic backbone acceleration arising from an intramolecular coordination event we still could not rule out the possibility that the cyclohexenyl anhydride was more reactive due to geometric rigidity imparted by unsaturation in the backbone. We reasoned that if the rate difference is a consequence of geometric constraint, substitution of the olefin should not affect the reaction rate; similarly, if the rate enhancement is a product of an intramolecular coordination event, differences in olefin structure should have a sizable impact on the course of the reaction. To probe this question, a competition experiment was performed in which a 1:1 mixture of cyclohexenyl anhydride **27** and dimethylcyclohexenyl anhydride **29** was subjected to standard reaction conditions in the presence of 1 equiv of nucleophile (Scheme 12). After 1.5 h, the reaction was quenched and the unpurified reaction mixture was esterified

and analyzed by gas chromatography to obtain ratios of all four possible reaction components. In the absence of styrenic promoter, virtually complete consumption of anhydride **27** in preference to anhydride **29** is observed. Even in the presence of 4-fluorostyrene anhydride **27** is preferentially consumed, although keto ester **89** is observed in minor amounts compared to ester **87**. These observations suggest that intramolecular coordination is the contributing factor to the increase in reaction rate when unsaturation is present in the anhydride backbone. The efficiency of coordination is influenced by the nature of the olefin with tetrasubstituted derivatives being far less effective than their disubstituted counterparts.

Scheme 12.

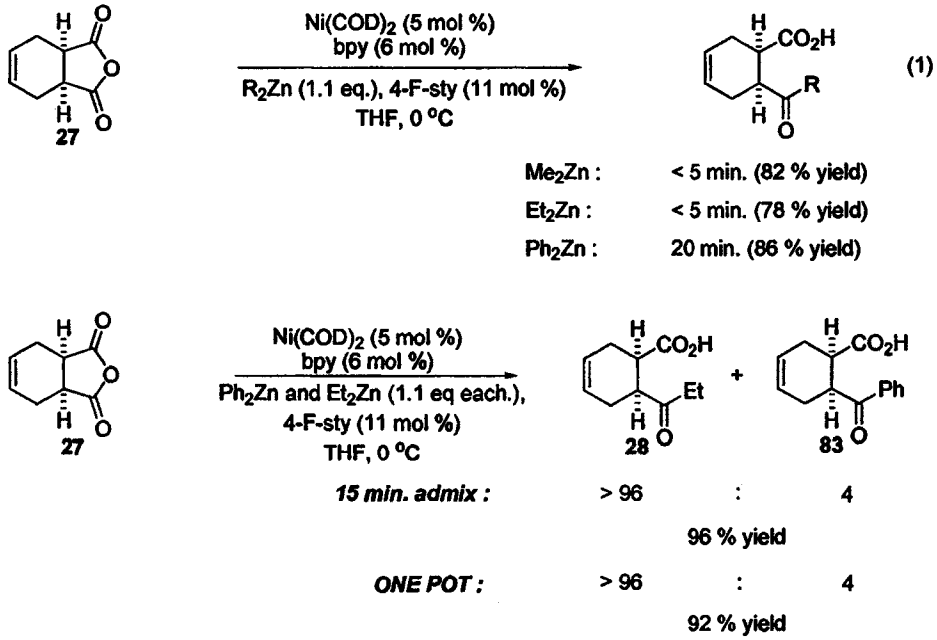


Additive	Product Ratio (87 : 88 : 89 : 90)
None	50 : < 0.5 : < 0.5 : 49
4-F-sty (10 mol %)	51 : < 0.5 : 12 : 36

During the course of our work on expansion of the nucleophile scope, we made the observation that the reaction rate had some dependence on the nature of the diorganozinc reagent (Scheme 13, eq. 1). When the alkylation of anhydride **27** was carried out using either Me_2Zn or Et_2Zn reaction times were observed to be less than 5 minutes with both proceeding in good yield; however, using Ph_2Zn as the nucleophile in the reaction lead to slightly longer reaction times. These results were surprising since

aryl group transfer is usually faster in cross-coupling manifolds and may indicate that the reaction is very sensitive to steric factors. In light of the dramatic difference in observed rates, we examined the effects of mixed diorganozinc reagents. Bolm and co-workers have shown that mixtures of Et_2Zn and Ph_2Zn transfer only the phenyl group to aldehydes in the presence of a chiral ligand.[48] When Et_2Zn and Ph_2Zn are mixed, a disproportionation presumably occurs providing a new mixed diorganozinc, Et(Ph)Zn, which is in equilibrium with other zinc species.[49] In order to probe the competence of the mixed alkyl-arylzinc reagent in our reaction we ran two experiments: one in which 1 equiv of Et_2Zn and Ph_2Zn were admixed at ambient temperature for 15 min. prior to the reaction, and the second in which both nucleophiles were added at the same time to the reaction (Scheme 13, eq. 2). To our delight, when anhydride **27** was subjected to the prescribed reaction conditions almost exclusive phenyl transfer was observed despite the differences in nucleophile preparation. These results suggest that the disproportionation process is faster than either ethyl or phenyl group transfer from Et_2Zn or Ph_2Zn; furthermore, it indicates that the mixed diorganozinc reagent is more kinetically competent than either of the parent zinc nucleophiles. The transmetalation process may be a discrete alkyl/aryl group transfer to the nickel center since aryl group migration is preferred when the mixed zinc reagent is used in the cross-coupling reaction.

Scheme 13.



In light of our mechanistic investigations and based on previously described literature precedent, we propose that the present reaction proceeds through a manifold which involves discrete oxidative addition of the low-valent nickel catalyst followed by alkyl-group transfer and catalyst turnover as illustrated in pathway A (Scheme 9). The intermediacy of an alkyl-nickel intermediate that directly adds to the anhydride coupling partner is unlikely based on our observations involving the cross-coupling of a geminally disubstituted succinic anhydride derivative. Furthermore, the rate acceleration imparted by unsaturation in the anhydride backbone is easiest to rationalize by invoking an intramolecular coordination event, with the presence of the olefin-stabilizing intermediates and/or transition states in the catalytic cycle.

2.3 Enantioselective Nickel-Catalyzed Desymmetrization

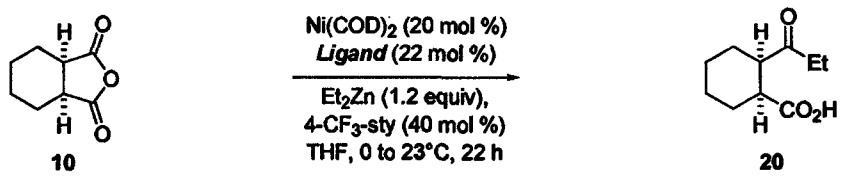
The true power of the transition metal-catalyzed anhydride alkylation lies in the enantioselective variant of the reaction. The desymmetrization of meso compounds is a powerful tool in organic synthesis since the starting materials are generally easy to

prepare and the products commonly contain stereochemical relationships that are not easily accessible by other methods.[50] Immediately following our initial success in the nickel-catalyzed direct addition manifold we initiated studies, in conjunction with expansion of the substrate and nucleophile scope, aimed at the goal of rendering the process asymmetric via the use of nickel complexes bearing chiral ligands.

2.3.1 Enantioselective Alkylation of Succinic Anhydrides

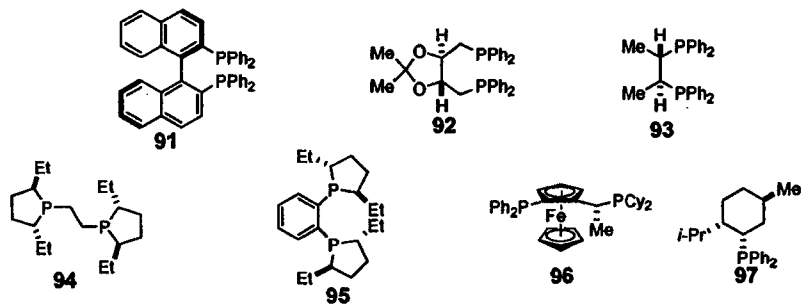
Initial studies were directed at a relatively broad screen of commercially available chiral ligands using cyclohexylsuccinic anhydride **10** as substrate. The bulk of commercially available ligands are bidentate phosphines, which we reasoned may be competent in the context of our chemistry since DPPE was a relatively efficient ligand in the achiral reaction. A variety of chiral phosphines were screened using Et_2Zn as the nucleophile (Table 8). Unfortunately, most of the ligands examined failed to provide product under the reaction conditions. The one exception was CHIRAPHOS (**93**), a close DPPE mimic, which provided the desired product in low yield but high selectivity. We reasoned that the use of an alkylzinc halide nucleophilic coupling partner, which had been shown to be effective using the DPPE-derived nickel catalyst, may increase the yield while preserving the selectivity.

Table 8.



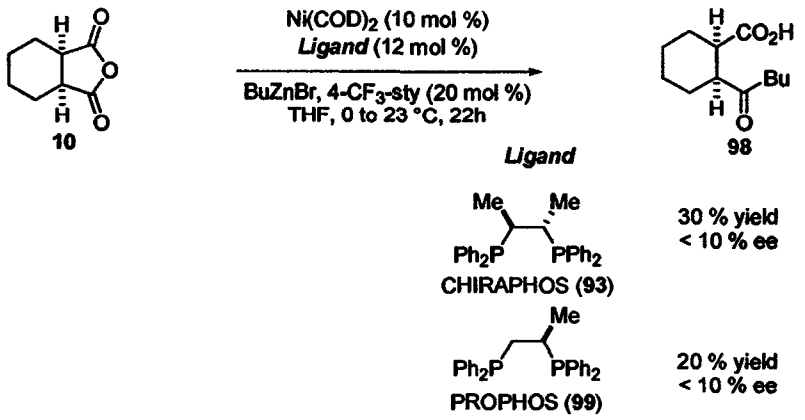
Entry[a]	*Ligand*	Yield (%)	ee[b] (%)
1	BINAP (91)	--	--
2	DIOP (92)	--	--
3	CHIRAPHOS (93)	~10	88
4	Et-BPE (94)	--	--
5	Et-DUPHOS (95)	--	--
6	JOSIPHOS (96)	--	--
7	NMDPP (97)	~50[c]	11

[a]Reactions conducted in the presence of $Ni(COD)_2$ (20 mol %), ligand (22 mol %), 4-CF_3-sty (40 mol %), and 1.2 equiv of Et_2Zn at 0 °C in THF for 2h then warmed to ambient temperature for an additional 20h. [b]Enantiomeric excess determined by HPLC analysis of the corresponding benzyl ester. [c]Reaction conducted inthe presence of $Ni(COD)_2$, (10 mol %), NMDDPP (20 mol %), and 4-F-sty (20 mol %)



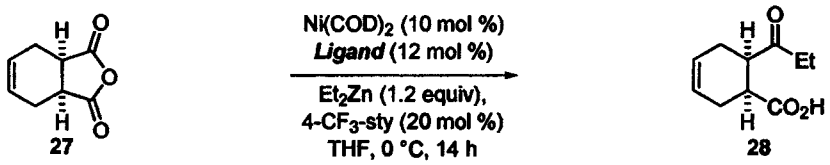
Using standard reaction conditions, we examined the efficacy of two nickel-ligand complexes in the context of alkylzinc halide coupling (Scheme 14).

Scheme 14.



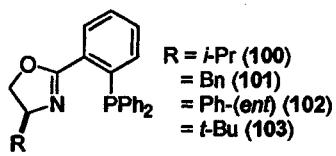
Unfortunately, both chiral DPPE mimics **93** and **99** failed to provide the desired products in good chemical yields or selectivity. With a variety of electronically and sterically dissimilar bisphosphine ligands failing to provide a good combination of selectivity and efficiency, we expanded our ligand screen to include P,N-ligands which had been shown to provide catalytically active complexes in the achiral reaction manifold.

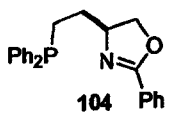
Table 9.



Entry[a]	*Ligand*	Yield (%)	ee[b] (%)
1	*i*-PrPHOX (**100**)	74	71
2	BnPHOX (**101**)	60	56
3	Ph-(*ent*)-PHOX (**102**)	91	69
4	t-BuPHOX (**103**)	–	–
5	JM-PHOS (**104**)	< 20	–

[a]Reactions conducted in the presence of $Ni(COD)_2$ (10 mol %), ligand 12 mol %), 4-CF_3-sty (20 mol %), and 1.2 equiv of Et_2Zn at 0 °C in THF for 14h. [b]Enantiomeric excess determined by HPLC analysis of the corresponding benzyl ester.





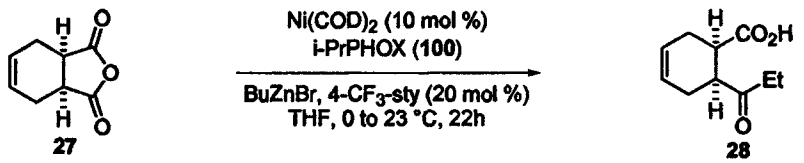
104

Phosphinooxazoline ligands have seen wide application as chiral ligands in a variety of transition metal-catalyzed processes[51] and are easily synthesized from the corresponding amino alcohols.[52] We reasoned that the phosphinooxazoline class of ligands may represent a chiral pyphos equivalent. In the event, anhydride **27** was subjected to a variety of P,N-ligand nickel complexes under standard reaction conditions (Table 9). To our gratification, several of the PHOX-type ligands worked well, providing good yields of product in relatively good selectivity (entries 1-3). The reaction seems to be sensitive to sterics, in that ligand **103** bearing a large *tert*-butyl group fails to provide

product (entry 4). Ligand **104**, developed by Burgess[53] for enantioselective hydrogenation chemistry, failed to give good results. Further optimization of the reaction conditions was undertaken using ligand **100** since it provided the product in the highest selectivity and is an easily handled bench-stable solid, whereas ligands **101** and **102** are viscous oils.

Although phosphinooxazolines are bidentate ligands, there is a possibility that the active catalyst is comprised of two ligands on one metal center. We also reasoned that the selectivity of the reaction could potentially be eroded by unligated metal. In order to probe this possibility we varied the metal to ligand ratio while keeping catalyst loading at 10 mol % (Scheme 15). To our surprise, carrying out the reaction in substoichiometric amounts of ligand to metal (0.75 equiv of ligand to metal) results in an efficient reaction with very little decrease in selectivity representing an example of ligand-accelerated catalysis.[54] The fact that the reaction operates under ligand-accelerated catalysis suggests that the active catalyst bears one ligand on the metal center and that the precatalyst

Scheme 15.



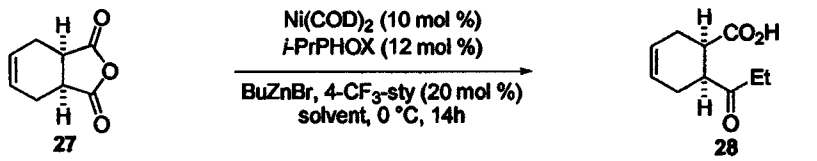
Ligand : Metal	Yield (%)	ee (%)
0.75 : 1	85	68
1.0 : 1	84	71
1.2 : 1	74	71
1.5 : 1	94	71
2.0 : 1	85	70

($Ni(COD_2)$) does not kinetically compete with the ligated complex. Increasing the amount of ligand relative to metal resulted in slightly increased yields and the same selectivities observed using our original reaction conditions. Although increasing the amount of

ligand with respect to metal leads to increased yields, we adopted our original conditions for further studies in order to conserve the relatively valuable ligand.

The optimal solvent for the achiral anhydride alkylation was THF, but we could not rule out the possibility that a different solvent could potentially increase selectivity while preserving reactivity. The nature of the solvent has a dramatic influence on the course of the reaction (Scheme 16). Performing the reaction in a more polar medium, such as MeCN, leads to decreased yields and selectivity. The less polar aromatic solvent toluene (PhMe) also failed to improve the reaction. Diethyl ether provides almost identical results to MeCN, providing the product in 58 % yield and 58 % enantiomeric excess.

Scheme 16.



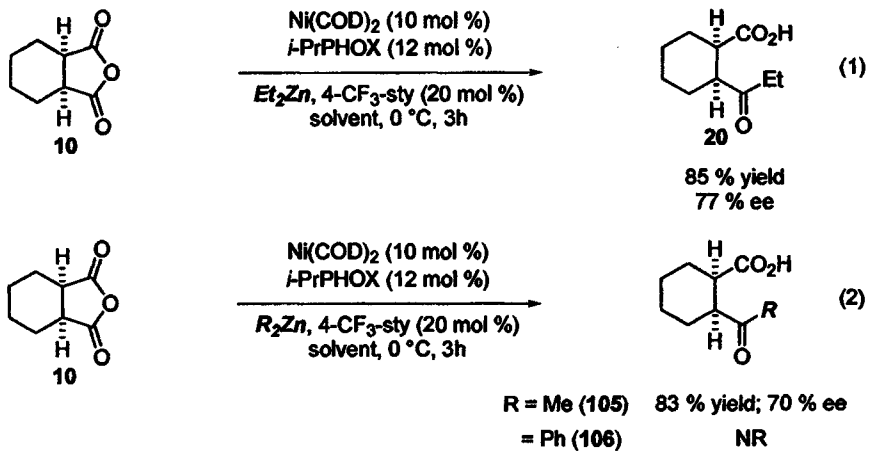
MeCN	60 % yield; 59 % ee
PhMe	40 % yield; 49 % ee
Et_2O	58 % yield; 58 % ee

At the outset of our study we used cyclohexenyl anhydride **27** and cyclohexyl anhydride **10** almost interchangeably. Having developed relatively efficient reaction conditions for anhydride **27**, we explored the competence of anhydride **10** and the role the nucleophile plays in the reaction. Not surprisingly, cyclohexyl anhydride **10** participates in the enantioselective reaction using diethylzinc as the nucleophile, affording ethyl ketone **28** in 85 % yield and 77 % ee (Scheme 17, eq. 1). The nature of the nucleophilic coupling partner has a dramatic effect on the course of the reaction. The slightly smaller aliphatic nucleophile, dimethylzinc, smoothly supplies the corresponding

methyl ketone **105** in good yield and 70 % ee, slightly lower than diethylzinc (Scheme 17, eq. 2). Unexpectedly, when diphenylzinc was employed as the nucleophilic coupling partner, the reaction failed to provide **106** (Scheme 17, eq. 2). We attribute this result to the increased steric bulk associated with Ph_2Zn as opposed to Et_2Zn, although arylzinc reagents are more nucleophilic than dialkylzinc reagents.

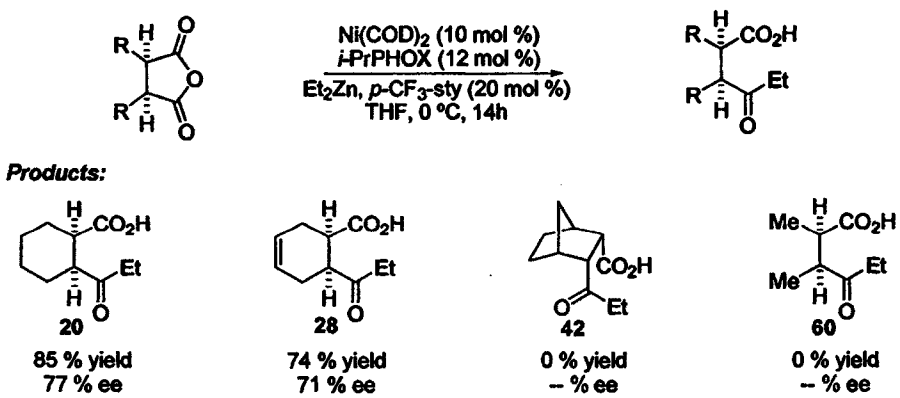
Having optimized several reaction parameters we shifted our focus to expansion

Scheme 17.



of the substrate scope with respect to the anhydride coupling partner (Scheme 18). As

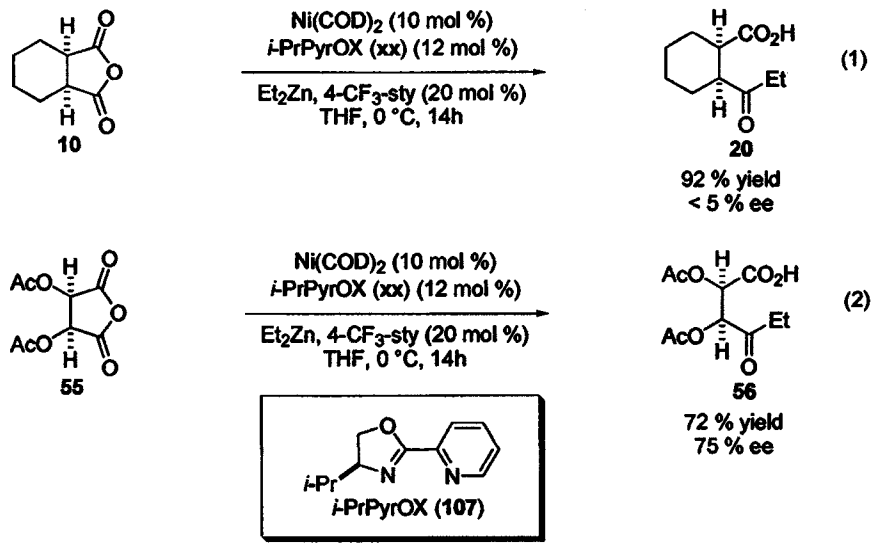
Scheme 18.



described earlier, cyclohexyl and cyclohexenyl anhydrides **10** and **27** participate

smoothly when subjected to the reaction conditions providing ethyl keto acids **20** and **28** in good yield and moderate selectivity. To our disappointment, other anhydrides failed to participate in the alkylation reaction using optimized conditions. We reasoned that the inability of *endo*-tricyclic anhydride to provide keto acid **42** when subjected to the reaction was perhaps a consequence of the steric encumbrance imparted by the backbone of the anhydride. This explanation fits the data from the aspect that more bulky nucleophiles and ligands fail to provide product (*vide supra*). The failure of dimethylsuccinic anhydride to supply the product acid **60** did not fit this explanation, since the substrate is very sterically similar to cyclohexyl anhydride **10.**

Scheme 19.

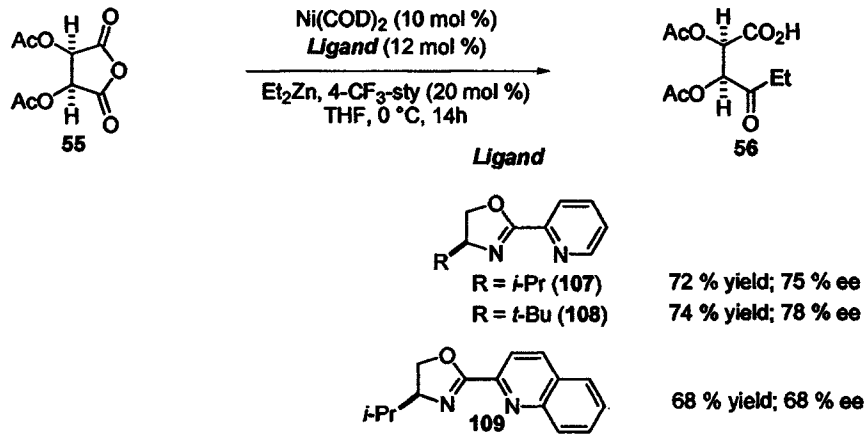


Although we attributed the failure of the aforementioned substrates to steric factors, we could not discount the possibility of electronic effects imparted by the ligand resident on the metal center. Since the N,N-ligand bpy had been extremely successful in the achiral reaction manifold, we set out to examine chiral nitrogen ligands with an emphasis on expansion of the anhydride substrate scope. We envisioned that pyridyloxazoline ligands such as **107** may be effective in the reaction (Scheme 19).

Alkylation of anhydride **10** under standard conditions using pyridyloxazoline **107** as ligand smoothly provided keto acid **20** in 92 % yield but selectivity was poor (Scheme 19, eq. 1). Anhydride **55**, bearing two potentially labile acetoxy groups, failed to provide product using phosphinooxazoline ligands. To our gratification, submission of anhydride **55** to the reaction conditions using ligand **107** provided polyoxygented keto acid **56** in 72 % yield and 75 % enantiomeric excess.

Encouraged by the application of PyrOX ligands to the alkylation of diacetoxy anhydride **55**, despite their failure in the context of alkyl substituted anhydrides, we examined the effects of structural changes in the ligand on reaction selectivity (Scheme 20). Increasing the steric demand of the ligand in the form of *tert*-butyl analog **108** results in a slight increase in selectivity with no decrease in yield. Ligand **109**, bearing an elaborated aromatic portion, failed to increase selectivity or yield.

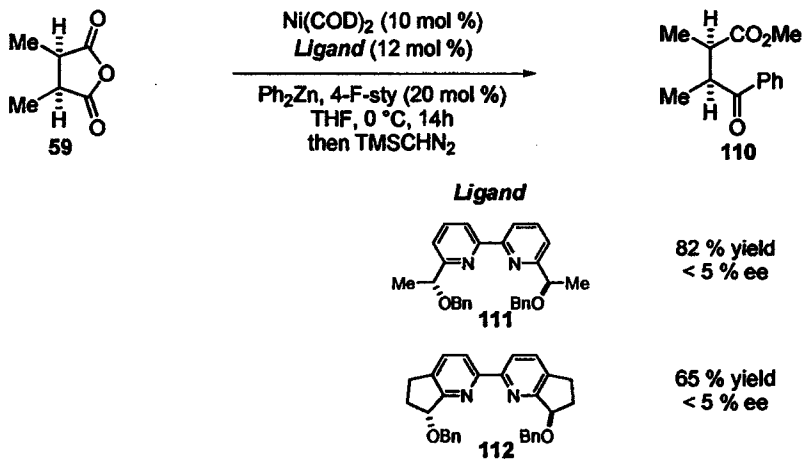
Scheme 20.



Chiral bipyridyl ligands have been shown to be effective in a variety of transition metal-mediated processes.[55] Encouraged by the reactivity of bpy-derived nickel catalysts in the archiral reaction manifold and the results obtained using pyridyloxazoline ligands we examined the efficacy of two chiral bipyridyl ligands (Scheme 21). Dimethylsuccinic

anhydride **59** was subjected to the prescribed reaction conditions using Ph_2Zn as the nucleophile. Chiral bipyridyl ligand **111**, reported by Bolm and co-workers,[56] provided the desired phenyl ketone **110** in good yield but poor selectivity. We thought the poor selectivity could be due the potential for free rotation of the chiral benzylic center on the ligand. In order to probe this possibility, ligand **112**[57] was prepared in which the chiral information is constrained in a fused ring system. In the event, the desired product **110** was obtained in moderate yield and low selectivity.

Scheme 21.



Examination of a variety of chiral nickel-ligand complexes under a variety of conditions had failed to provide a general enantioselective variant of our anhydride alkylation reaction; however, important information about the reaction was gathered during the course of our studies. The reaction is sensitive to both the electronic and steric nature of the ligand employed. The structure of the nucleophile also has an impact on the course of the reaction with diphenylzinc failing to provide product using the most successful phosphinooxazoline ligand in the reaction. Furthermore, N,N-ligands tend to be more reactive in the context of succinic anhydride alkylation, which is in accord with our observations in the achiral system, but fail to provide products in high selectivity.

Taking these observations into consideration, we shifted our focus to the investigation of glutaric anhydrides as electrophilic coupling partners.

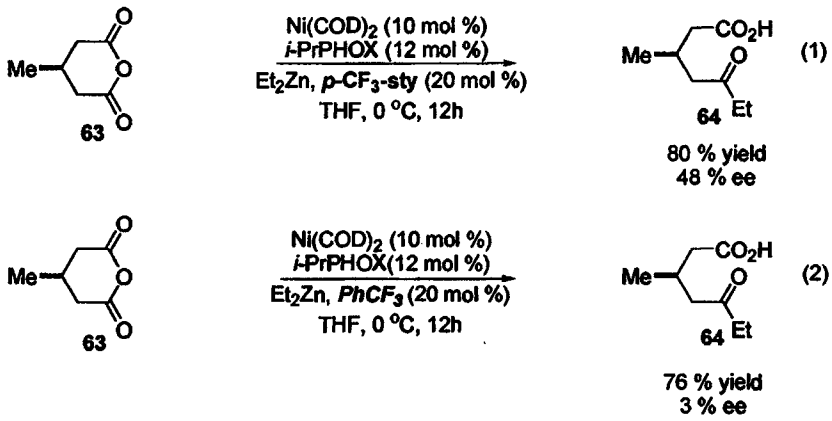
2.3.2 Enantioselective Alkylation of Glutaric Anhydrides

Based on the results garnered in the course of the achiral reaction manifold, in which P,N-ligands seem to be matched to glutaric anhydride substrates coupled with chiral P,N-ligands (phosphinooxazolines) providing superior results in the asymmetric manifold, we reasoned our reaction conditions may be amenable to glutaric anhydride desymmetrization. Additionally, 3-substituted glutaric anhydrides possess more sterically accessible C-O bonds, which we reasoned may facilitate reactivity in this substrate class with the caveat that the chiral control element is further removed from the reaction site, potentially complicating our efforts to render the process highly selective. Initial studies were initiated using reaction conditions optimized in the course of our succinic anhydride investigations.

Glutaric anhydrides are competent electrophilic coupling partners in the presence of chiral metal complexes, but an intriguing olefin effect was observed (Scheme 22). Submission of 3-methylglutaric anhydride **63** to standard reaction conditions using Et_2Zn as the nucleophilic coupling partner provides the product keto acid **64** in 80 % isolated yield and 48 % ee at 0 °C (Scheme 22, eq. 1). Unexpectedly, when the reaction was carried out under identical conditions with the exception of the reductive elimination promoter strange results were obtained. Subjection of anhydride **63** to the reaction using 20 mol % $PhCF_3$ as the promoter in place of *p*-trifluoromethyl styrene the keto acid was obtained in 70 % yield but was nearly racemic (Scheme 22, eq. 2). The fact that the reductive elimination promoter seems to be involved in the enantiodifferentiating step

(oxidative addition) was an unforeseen outcome. We felt this result may not only provide mechanistic insight, but may also as serve as another opportunity to improve reaction selectivity.

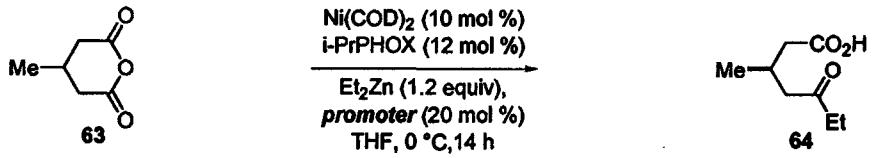
Scheme 22.

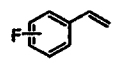
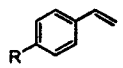
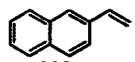


Our preliminary optimization efforts focused on the nature of the olefinic promoter and the possible effect substitution present on the styrene may have on the course of the reaction (Table 10). Substituted fluorostyrenes are effective promoters for the reaction with the position of the fluorine atom having a large impact on selectivity (entries 1-3). *ortho*-Fluorostyrene (**113**) and *meta*-fluorostyrene (**114**) provide the desired keto acid in 44 and 56 % ee respectively, while *para*-fluorostyrene (**24**) furnishes the product **64** in 61 % ee. Substitution at the 4-position with a variety of electron withdrawing and releasing substituents has very little impact on selectivity. Parent styrene **23** affords the product in 65 % ee and 80 % yield (entry 4). Electron rich styrene **115** efficiently mediates the reaction, providing the product in good yield and moderate selectivity (entry 5). Styrene **116**, bearing an electron releasing aryl ring at the *para* position is an effective promoter, supplying product in moderate selectivity (entry 6). The nitro-substituted promoter **117** failed to effectively promote the reaction, giving the product in depressed yield and selectivity (entry 7). Finally, styrene **118**, bearing a

naphthyl ring system, also provides product in approximately the same yield and selectivity as most of the other 4-substituted styrene based promoters (entry 8). The promoter can be isolated unchanged at the end of the reaction. With several effective promoters in hand, we further investigated the effects of promoter structure on reaction outcome.

Table 10.



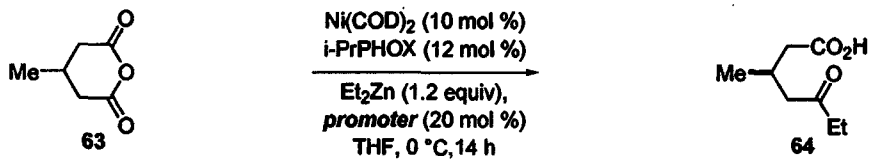
Entry[a]	*Promoter*	Yield (%)	ee[b] (%)
			
1	*o*-F (113)	80	44
2	*m*-F (114)	86	56
3	*p*-F (24)	78	61
			
4	R = H (23)	80	65
5	R = OMe (115)	79	62
6	R = Ph (116)	84	61
7	R = NO_2 (117)	50	55
8	 118	82	60

[a]Reactions conducted in the presence of $Ni(COD)_2$ (10mol %), i-PrPHOX (12 mol %), promoter (20 mol %), and 1.2 equiv of Et_2Zn at 0 °C in THF for 14h. [b]Enantiomeric excess determined by HPLC analysis of the corresponding benzyl ester.

The electronic nature of the styrene promoter seems to be less important than the structural features presented, with *para* substitution patterns uniformly providing the highest selectivities. The unsubstituted styrenic motif seems to be essential to retain a combination of selectivity and efficiency (Table 11). Dihydronapthalene **119** is an effective promoter for the reaction, providing the desired product in 70 % isolated yield albeit in 18 % ee, indicating that substitution of the styrenic double bond is not well tolerated (entry 1). *trans*-Stilbene **120** and the 1,3-diene **121** failed to facilitate the

reaction, affording low yields of the product in nearly racemic form (entries 2 and 3). Terminal olefins do not effectively facilitate the reaction with vinyl cyclohexane **122** supplying the product in low yield and selectivity (entry 4).

Table 11.

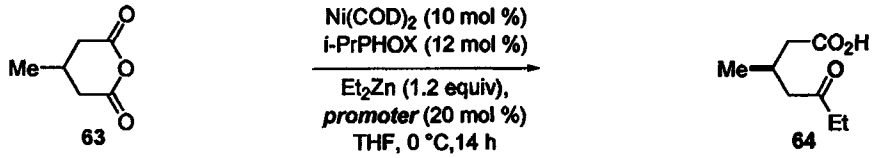


Entry[a]	*Promoter*	Yield (%)	ee[b] (%)
1	 **119**	70	18
2	 **120**	< 20	< 10
3	 **121**	< 20	< 5
4	 **122**	40	< 10

[a]Reactions conducted in the presence of $Ni(COD)_2$ (10mol %), i-PrPHOX (12 mol %), promoter (20 mol %), and 1.2 equiv of Et_2Zn at 0 °C in THF for 14h. [b]Enantiomeric excess determined by HPLC analysis of the corresponding benzyl ester.

Although all of our experimental evidence suggests that styrene-based promoters bearing a terminal olefin are the most effective promoters in the reaction manifold providing the best combination of activity and selectivity, we expanded our olefin study to include moieties that were unrelated to styrenes (Table 12). Simple olefins **123**, **124**, and **125** proved to be ineffective promoters, providing very low yields of the desired product coupled with uniformly poor selectivity (entries 1-3). Protected allyl alcohol derivatives **126** and **127** deliver the addition product in good yield but poor selectivity (entries 4 and 5). Performing the reaction in the presence of 1,4-diene **128** leads to an 88 % yield of the desired product, in elevated selectivity albeit lower than most styrene analogues (entry 6).

Table 12.



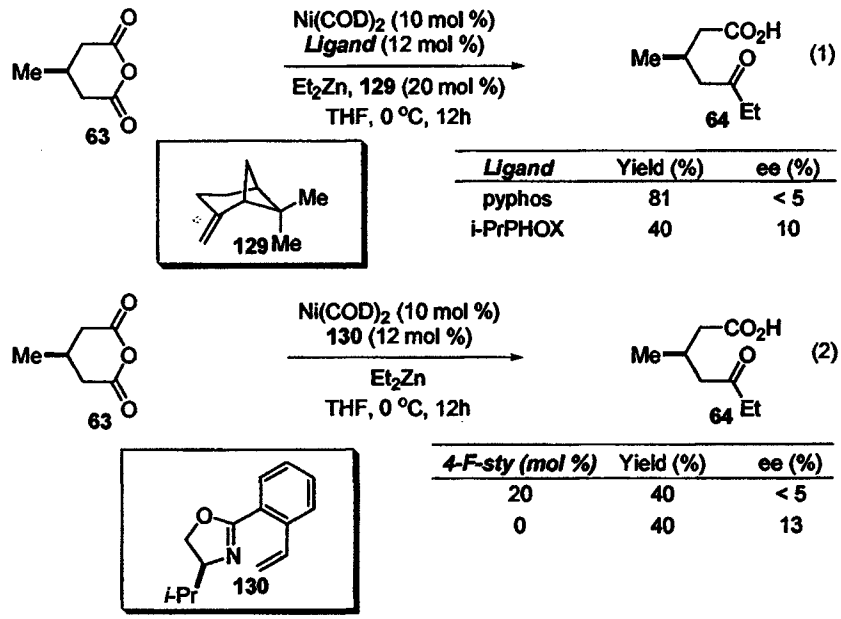
Entry[a]	*Promoter*	Yield (%)	ee[b] (%)
1	 **123**	–	10
2	 **124**	–	< 5
3	 **125**	–	9
4	 R = TMS (**126**)	75	< 5
5	R = Ac (**127**)	72	< 5
6	 **128**	88	42

[a]Reactions conducted in the presence of $Ni(COD)_2$ (10mol %), i-PrPHOX (12 mol %), promoter (20 mol %), and 1.2 equiv of Et_2Zn at 0 °C in THF for 14h. [b]Enantiomeric excess determined by HPLC analysis of the corresponding benzyl ester.

With the olefinic promoter being intimately involved in the enantiodifferentiating step, we were intrigued by the possibility of rendering the reaction asymmetric by the use of a chiral olefinic promoter. In the event, the reaction was performed in the presence of catalytic amounts of β-pinene **129** using the achiral pyphos-derived nickel catalyst (Scheme 23, eq. 1). Unfortunately, the product was isolated in nearly racemic form. The use of a chiral nickel complex in the presence of **129** resulted in a slight increase in selectivity with a simultaneous loss in reaction efficiency. Obviously β-pinene **129** may not be the optimal choice for a chiral promoter since it is not a terminal styrenic olefin; however, incorporation of the promoter into the chiral ligand framework may lead to better results. In order to probe this possibility, styrenyl oxazoline **130** was synthesized

and subjected to the reaction conditions (Scheme 23, eq. 2).[58] When the reaction is conducted in the presence of 20 mol % 4-fluorostyrene the desired product is isolated in moderate yield in < 5 % enantiomeric excess. Interestingly, when the reaction is conducted in the absence of an external promoter, the product is isolated in 40 % yield and slightly increased 13 % ee. Although the use of ligand **130** did not provide product in synthetically useful selectivity, the idea of incorporating of the promoter into the ligand backbone is an interesting concept (*vide infra*).

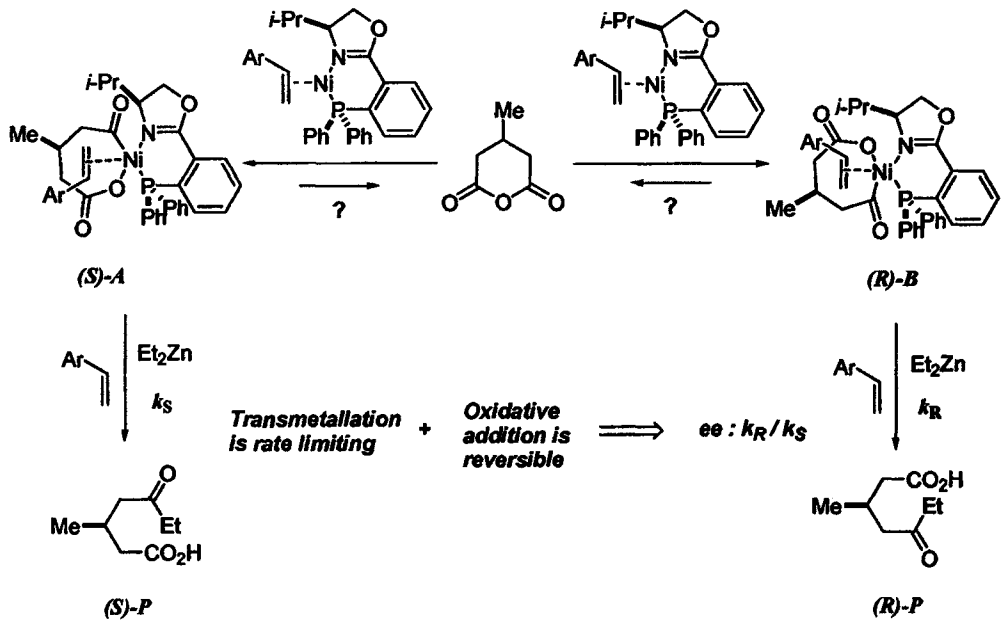
Scheme 23.



In light of our extensive investigation of olefinic promoters, we were able to determine that *para*-substituted styrene moieties were by far the most effective in the asymmetric alkylation of glutaric anhydrides. By modification of the *para*-substituent we were able to increase the selectivity of the reaction from 48 to 61 % ee (*p*-CF_3-sty vs. *p*-F-sty) without changing the nature of the chiral ligand. Although the manifestation of the reductive elimination promoter having an impact on the enantioselectivity of glutaric

anhydride alkylation was a completely unexpected phenomenon, we reasoned we may be able to glean some mechanistic information from these observations.

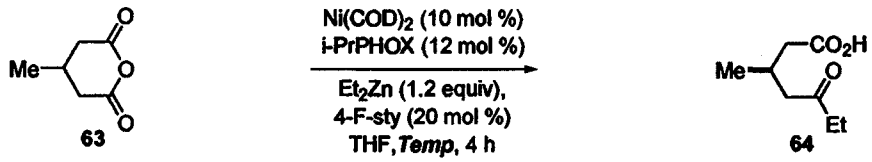
Scheme 24.



Some observations during the course of olefin optimization lead us to propose a mechanistic hypothesis. *The structure of the styrene promoter has no impact on reaction selectivity when succinic anhydrides are used as electrophilic coupling partners.* This may be a consequence of intermediate metallacycle structure, that is, succinic anhydrides proceed through 6-membered metallacyclic intermediates that may be inherently more stable than the corresponding 7-membered oxidative addition adduct that glutaric anhydride substrates proceed through. *Furthermore, the reaction of 3-methyl glutaric anhydride (63) in the absence of promoter under standard conditions provides nearly racemic material, suggesting that the initial oxidative addition of the chiral nickel complex is unselective.* These observations lead us to propose the mechanism depicted in Scheme 24. Based on the experimental observations, we reasoned that the initial oxidative addition may be a reversible process in the presence of the styrenic promoter.

If a fast, reversible, oxidative addition is coupled with the assumption that transmetalation is the rate determining step, then selectivity should be proportional to the rate of transmetalation of each respective diastereomeric insertion adduct **(S)-A** and **(R)-B**. We reasoned that if the proposed mechanism is correct, then reaction parameters such as temperature and relative concentration of reactants may have an effect on selectivity, which may support or refute our hypothesis.

Table 13.



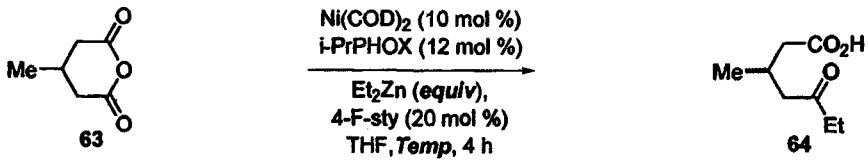
Entry[a]	*Temperature (°C)*	Yield (%)	ee[b] (%)
1	-40	40	85
2	-20	74	72
3	0	78	61
4	23	70	49
5	66	30	37

[a]Reactions conducted in the presence of $Ni(COD)_2$ (10 mol %), ligand (12 mol %), 4-4-F-sty (20 mol %), and 1.2 equiv of Et_2Zn at the indicated temperature in THF for 4h. [b]Enantiomeric excess determined by HPLC analysis of the corresponding benzyl ester.

The first parameter examined was reaction selectivity as a function of temperature. A temperature range of 100 °C was examined with the idea of potentially observing a discontinuity in reaction selectivity which would indicate a change in rate determining step which may reflect the equilibrium constant of the initial oxidative addition (Table 13). Anhydride **63** was subjected to the optimized reaction conditions using Et_2Zn as the nucleophile and 20 mol % 4-F-sty as the olefinic promoter. As can be seen, the reaction exhibits a traditional temperature profile with higher selectivity obtained at lower temperatures, with no obvious discontinuity observed. Although the absence of a discontinuity makes the set of reactions ambiguous with respect to reaction

mechanism, performing the reaction at lower temperatures leads to dramatic increases in selectivity. Another surprising aspect is that the reaction proceeds at -40 °C which is rare for transition metal-mediated C-C bonding forming reactions, providing the keto acid **64** in a synthetically useful 85 % ee.

Table 14.

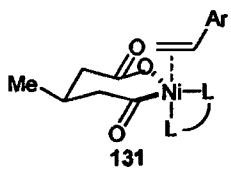


Entry[a]	*Temperature (°C)*	*Equiv (Et_2Zn)*	Yield (%)	ee[b] (%)
1	-20	1.4	74	72
2	-20	5.0	78	73
3	0	1.4	79	64
4	0	5.0	83	64

[a]Reactions conducted in the presence of $Ni(COD)_2$ (10 mol %), ligand (12 mol %), 4-4-F-sty (20 mol %), and indicated amount of Et_2Zn (neat) at the indicated temperature in THF for 4h. [b]Enantiomeric excess determined by HPLC analysis of the corresponding benzyl ester.

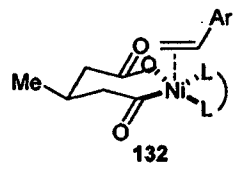
If transmetalation is the rate-determining step in the proposed reaction mechanism, then the concentration of the nucleophilic coupling partner should have an effect on reaction rate and therefore may exert an influence on reaction selectivity. A series of experiments were carried out at two different temperatures using different concentrations of nucleophilic coupling partner (Table 14). As can be seen the concentration of the nucleophilic coupling partner has an indiscernible effect on reaction outcome. When the reaction is carried out at -20 °C in the presence of 1.4 equiv or 5 equiv of Et_2Zn, nearly identical results are obtained (entries 1 and 2). Likewise, the selectivity of the reaction at 0 °C appears to be independent of nucleophile concentration (entries 3 and 4).

Figure 1.



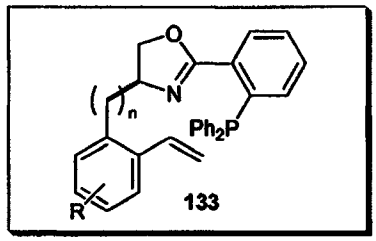
131

Trigonal bipyramidal



132

Square pyramidal



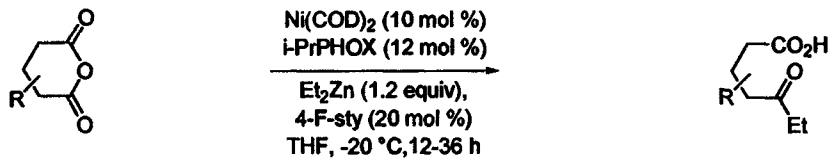
133

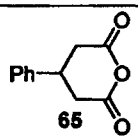
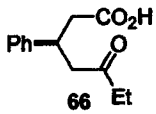
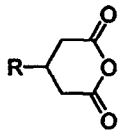
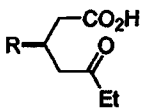
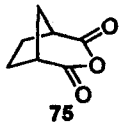
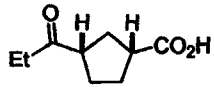
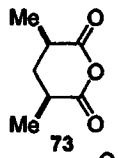
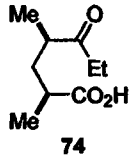
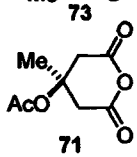
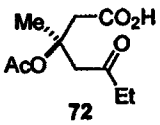
Although the aforementioned studies failed to provide discrete evidence for the proposed mechanistic pathway, the fundamental question of the difference in the structure of the metallacyclic intermediates remains. If the proposed mechanism is operative, there must be a fundamental difference in each insertion adduct. Our working theory at this point is that there may be fundamental differences in metal-center geometry that may affect the outcome of the reaction (Figure 1). Assuming the olefinic promoter is coordinated to the insertion adduct, perhaps the metallacyclic intermediate can adopt two discrete metal-center geometries, namely trigonal bipyramidal intermediate **131** or square pyramidal metallacycle **132**. If the fundamental difference in the diastereomeric insertion adducts lies in the geometric conformation adopted by the metal center and one of these conformations is more kinetically competent in the transmetalation event, then perhaps the use of a tridentate ligand of type **133** could favor one of the insertion adducts. Studies are currently underway exploring the synthesis and application of this class of olefin containing tridentate ligands.

With attempts to probe the mechanism of the reaction failing to provide conclusive evidence supporting or refuting our hypothesis, we turned our attention to the main goal of a general asymmetric alkylation of glutaric anhydrides. A variety of glutaric anhydride derivatives were subjected to optimized reaction conditions (Table 15). Increasing the steric bulk at the 3-position failed to increase the selectivity of the reaction. Subjection of 3-phenylglutaric anhydride **65** to optimized reaction conditions provided phenyl keto acid **66** in good yield but low selectivity (entry 1). Temperature has almost no affect on the selectivity of the alkylation of substrate **65** with higher temperatures providing **66** in almost identical selectivity (entries 2 and 3). Likewise, the nature of the promoter exerts an infinitesimal influence on selectivity (entry 4). We attribute this effect to an internal promotion from the internal aromatic group depressing selectivity. The steric bulk of the substituent at the 3-position of the anhydride exerts a strong influence on the selectivity of the reaction (entries 5-9). The air-stable catalyst precursor $Ni(acac)_2$ can be used in place of $Ni(COD)_2$ with no observed difference in yield or selectivity (entry 5). Reaction selectivity decreases as the size of the substituent increases, with anhydride **134** bearing a methoxy group at the 3-position providing product **135** in the highest selectivity, while 3-*tert*-butylglutaric anhydride **138** supplies keto acid **139** in lower enantiomeric excess. Bicyclic anhydride **75** is a good substrate for the reaction affording acid **76** in moderate yield and high selectivity (entry 10). Anhydride **73**, bearing α-substituents, provides the product **74** in good yield in nearly racemic form (entry 11). Finally, HMGA-derived anhydride **71** undergoes alkylation furnishing acid **72** in 56 % yield and 53 % ee (entry 12). Anhydride **71** is particularly

noteworthy in that the two substituents resident at the 3-position are not extremely different in size, but the catalyst is able to provide moderately enriched product.

Table 15.



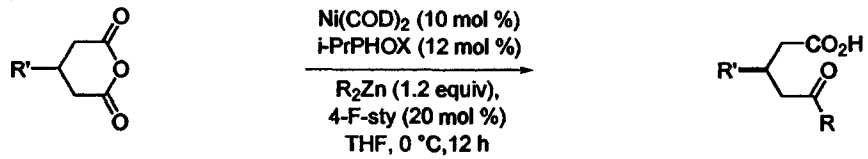
Entry[a]	Substrate	Product	Yield (%)	ee[b] (%)
1	 65	 66	86	19
2			84[c]	14
3			76[d]	16
4			86[e]	13
				
5	63 (R = Me)	64 (R = Me)	73[c,f]	60
6	134 (R = OMe)	135 (R = OMe)	53	57
7	136 (R = i-Pr)	137 (R = i-Pr)	85	29
8	138 (R = t-Bu)	139 (R = t-Bu)	70	34
9	140 (R = OTBS)	141 (R = OTBS)	54	33
10	 75	 76	61	80
11	 73	 74	80	< 5
12	 71	 72	56	53

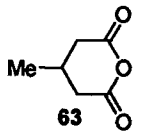
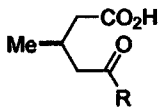
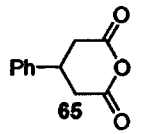
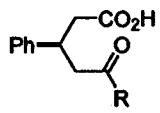
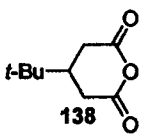
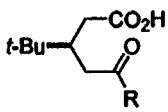
[a]Reactions conducted in the presence of $Ni(COD)_2$ (10mol %), i-PrPHOX (12 mol %), promoter (20 mol %), and 1.2 equiv of Et_2Zn at -20 °C in THF. [b]Enantiomeric excess determined by HPLC analysis of the corresponding benzyl ester. [c]Reaction at 0 °C. [d]Reaction run at ambient temperature. [e]4-CF_3-sty (20 mol %) used as promoter. [f]$Ni(acac)_2$ (10 mol %) used as catalyst precusor.

Having examined the substrate scope with respect to the electrophilic coupling partner, we explored the influence of the nucleophilic coupling partner on the outcome of the reaction. The selectivity of the nickel-catalyzed enantioselective alkylation of

succinic anhydrides showed very little dependence on the nature of the nucleophile. Likewise, glutaric anhydride selectivity displays very little reliance on the nucleophile (Table 16). Anhydride **63** successfully couples with Me_2Zn, Et_2Zn, and Ph_2Zn providing each product in moderate to good yields with less sterically demanding nucleophilic coupling partners providing keto acids in slightly higher selectivity (entries 1-3). Subjection of anhydride **65** to the prescribed conditions using Et_2Zn and Ph_2Zn supplies products **66** and **144** in nearly identical yield and selectivity (entries 4 and 5). Alkylation of **138** with each nucleophile again provides the keto acids **139** and **145** in low selectivity and moderate to low yields (entries 6 and 7).

Table 16.



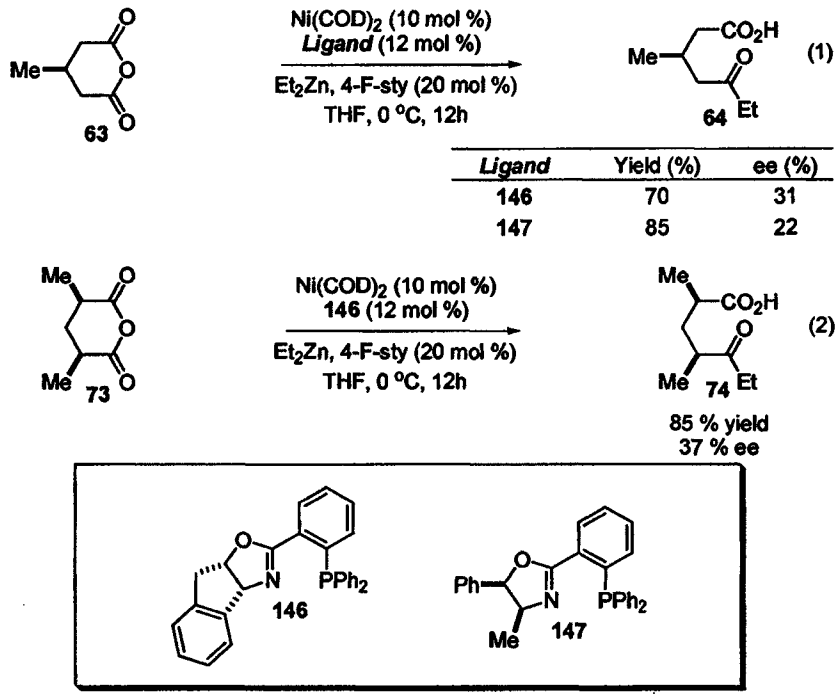
Entry[a]	Substrate	Nucleophile	Product	Yield (%)	ee[b] (%)
					
1		Me_2Zn	**142** (R = Me)	64	65
2		Et_2Zn	**64** (R = Et)	78	61
3		Ph_2Zn	**143** (R = Ph)	50	57
					
4		Et_2Zn	**66** (R = Et)	80	13
5		Ph_2Zn	**144** (R = Ph)	80	19
					
6		Et_2Zn	**139** (R = Et)	60	34
7		Ph_2Zn	**145** (R = Ph)	< 30	27

[a]Reactions conducted in the presence of $Ni(COD)_2$ (10mol %), i-PrPHOX (12 mol %), 4-F-sty (20 mol %), and 1.2 equiv of Et_2Zn at 0°C in THF. [b]Enantiomeric excess determined by HPLC analysis of the corresponding benzyl ester.

All of the data gathered in the context of asymmetric glutaric anhydride suggests that this class of substrates is less sensitive to steric factors than succinic anhydrides (i.e. the fact that Ph_2Zn as nucleophile leads to product using glutaric anhydrides but not with succinic anhydrides). We reasoned that phosphinooxazoline ligands bearing larger groups could potentially increase selectivity while preserving reactivity. Desymmetrization of 3-methylglutaric anhydride **63** under standard conditions using the aminoindanol-derived ligand **146** provided the keto acid **64** in 70 % yield and 31 % ee. Ephedrine-based ligand **147**[59] failed to substantially increase reaction selectivity, providing **64** in 85 % yield and 22 % ee (Scheme 25, eq. 1). Anhydride **73**, bearing α-

methyl substituents was alkylated using ligand **146** resulting in the isolation of acid **74** in good yield and low selectivity (Scheme 25, eq. 2).

Scheme 25.



Extensive optimization of the enantioselective nickel-catalyzed alkylation of meso succinic and glutaric anhydrides had lead to a limited substrate scope, providing enantioenriched 1,4- and 1,5-keto acids in only select cases. Further studies entailed the preparation of relatively elaborate ligands that may or may not serve to extend the utility of the present transformation. The failure of chiral bis-phosphine nickel complexes to facilitate the reaction was a drawback, in that most commercially available ligands reside in this category. We reasoned that perhaps the use of another d^{10} metal, namely palladium, may offer a solution to the problems associated with the nickel-mediated transformation.

2.4 Enantioselective Palladium-Catalyzed Desymmetrization

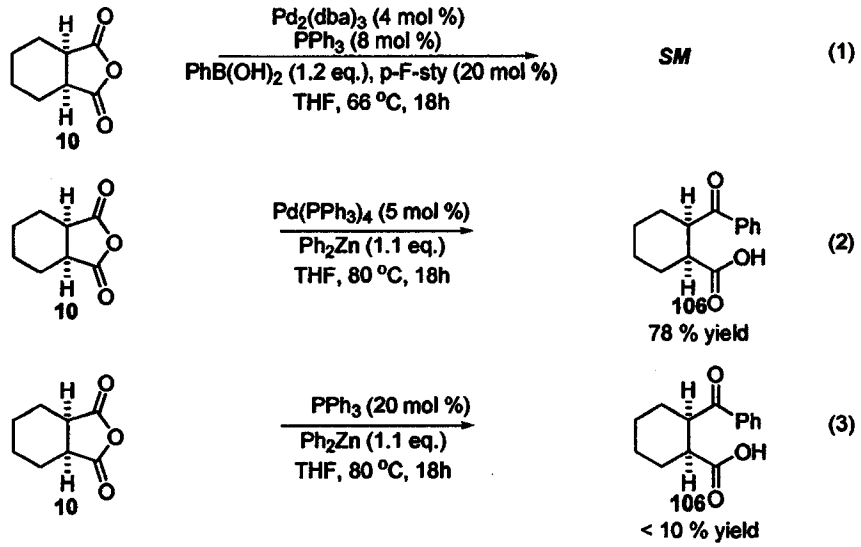
The palladium catalyzed cross-coupling of acyclic anhydrides is known in the context of acyclic anhydride derivatives (*vide supra*); however, cyclic anhydrides have not been used as electrophilic coupling partners. Cyclic anhydrides are more reactive than their acyclic counterparts and should be suitable substrates under the proper conditions. We envisioned that treatment of a cyclic anhydride with a suitable nucleophilic coupling partner in the presence of catalytic amounts of a palladium complex would provide the corresponding keto acid via a mechanistic pathway similar to that of the nickel-mediated reaction (Scheme 5, pathway A).

2.4.1 Reaction Discovery and Optimization

Our preliminary investigations focused on the use of an achiral palladium catalyst to affect the desired alkylation of a succinic anhydride substrate. Based on the precedent of Goossen and Yamamoto, we chose to examine the competence of aryl boronic acids as nucleophilic coupling partners. In the event, cyclohexyldicarboxylic anhydride **10** was treated with 1.2 equiv of phenyl boronic acid in the presence of catalytic amounts of $Pd_2(dba)_3$ and PPh_3 in THF at 66 °C (Scheme 26, eq. 1). Unfortunately, the only product isolated was hydrolyzed starting material. We reasoned that under the anhydrous reaction conditions, phenyl boronic acid potentially self-condenses, forming the corresponding boroxine and extrudes 3 equiv of water which in turn may be hydrolyzing **10**. In light of the success of organozinc reagents in the nickel-catalyzed reaction manifold, we chose to investigate their competence in the present reaction. To our delight, treatment of anhydride **10** with catalytic amounts of $Pd(PPh_3)_4$ and 1.1 equiv of Ph_2Zn in THF at 80 °C provided the desired phenyl addition product **106** in 78 % isolated yield (Scheme 26, eq. 2). Considering the relatively vigorous reaction conditions, we

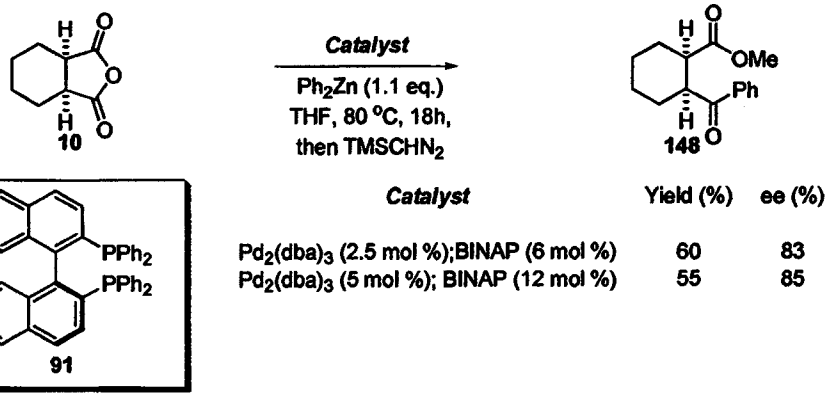
could not rule out the uncatalyzed addition of diphenylzinc to the anhydride or a phosphine-mediated direct addition process. When the reaction is carried out in the presence of 20 mol % PPh_3 and 1.1 equiv of Ph_2Zn the phenyl ketone **106** is isolated, albeit in less than 10 % yield (Scheme 26, eq. 3).

Scheme 26.



With promising results obtained using $Pd(PPh_3)_4$ as the catalyst, we began investigations aimed at rendering the process asymmetric. Since phosphines were successful as ligands, we started the chiral ligand screen with BINAP (**91**). To our gratification, anhydride **10** undergoes smooth arylation with diphenylzinc in the presence of 5 mol % chiral palladium catalyst supplying the desired keto ester **148** in 60 % yield and 83% ee (Scheme 27). As shown by the control reaction, the uncatalyzed addition does occur in low yield. We reasoned that if reaction selectivity is significantly increased when catalyst loading is increased, then the background reaction is eroding selectivity. When catalyst loading was increased to 10 mol % nearly identical results were obtained, suggesting that the uncatalyzed background reaction does not proceed at significant rates under these conditions.

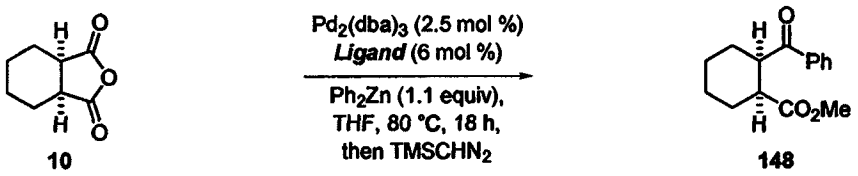
Scheme 27.



Catalyst	Yield (%)	ee (%)
$Pd_2(dba)_3$ (2.5 mol %);BINAP (6 mol %)	60	83
$Pd_2(dba)_3$ (5 mol %); BINAP (12 mol %)	55	85

The initial attempts using a chiral bis-phosphine ligand in the palladium reaction provided outstanding selectivity and moderate yields representing a marked improvement over the nickel-catalyzed reaction. Although reaction selectivity was very good, it had still not surpassed the 90 % ee benchmark. We felt that a relatively focused ligand screen, generally limiting our efforts to chiral bis-phoshpine ligands, may provide a more effective chiral ligand for the reaction. Several bidentate phosphine ligands were submitted to the reaction conditions with varied results (Table 17). *tol*-BINAP **149** provides the desired product in almost identical yield and selectivity to BINAP **91** (entries 1 and 2). Use of ligand **92** leads to dramatically decreased reaction efficiency with a simultaneous drop in selectivity (entry 3). The palladium complex derived from PhanePhos **150** provides the desired product in moderate yield but low selectivity (entry 4). Other chiral bidentate phosphines screened provided product in low to moderate yield in nearly racemic form (entries 5-7).

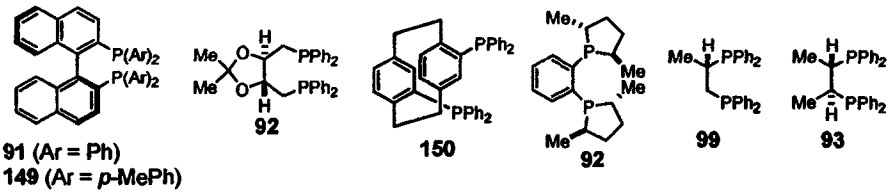
Table 17.



10 148

Entry[a]	*Ligand*	Yield (%)	ee[b] (%)
1	BINAP (91)	60	83
2	*tol*-BINAP (149)	60	81
3	DIOP (92)	32	15
4	PhanePhos (150)	< 5	48
5	Me-DUPHOS (95)	17	14
6	PROPHOS (99)	< 5	46
7	CHIRAPHOS (93)	< 5	44

[a]Reactions conducted in the presence of $Pd_2(dba)_3$ (2.5 mol %), ligand (6 mol %) and 1.1 equiv of Ph_2Zn at 80 °C in THF for 18h. [b]Enantiomeric excess determined by HPLC analysis.

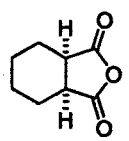


91 (Ar = Ph)
149 (Ar = *p*-MePh)

92 150 92 99 93

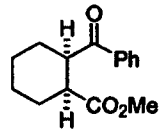
Although the initial screen failed to identify a ligand superior to BINAP, we broadened our investigation to encompass a family of chiral phosphinoferrocene ligands provided to us by Solvias in the form of a ligand screening kit (Table 18). Ligand **96**, known as JOSIPHOS, proved to be a very effective ligand providing the desired product in 61 % yield and 85 % ee (entry 1). Increasing the steric bulk of the alkyl phosphine portion of JOSIPHOS in the form of ligand **151** provides a poor yield of the product but favoring the opposite enantiomer (entry 2). Analogs **152** and **153**, bearing sterically and electronically dissimilar phosphines failed to improve the reaction (entries 3 and 4). Likewise, ligands **154** and **155** did not effectively facilitate the reaction (entries 5 and 6). WALPHOS ligands **156-159** proved ineffective under the standard reaction conditions providing product **148** in uniformly poor selectivity (entries 7-10).

Table 18.

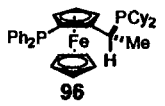
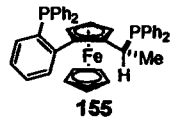
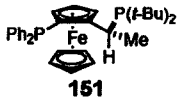
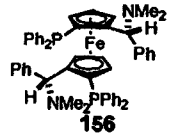
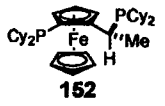
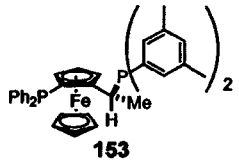
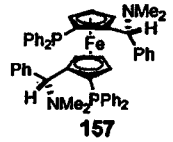
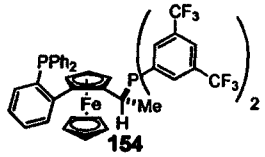
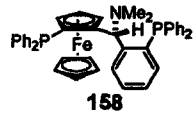


10

$Pd_2(dba)_3$ (2.5 mol %)
Ligand (6 mol %)
Ph_2Zn (1.1 equiv),
THF, 80 °C, 18 h,
then $TMSCHN_2$



148

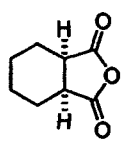
Entry[a]	Ligand	Yield (%)	ee[b] (%)	Entry[a]	Ligand	Yield (%)	ee[b] (%)
1	 96	61	85	6	 155	15	-14
2	 151	10	-40	7	 156	61	-6
3	 152	43	76				
4	 153	64	22	8	 157	38	22
5	 154	15	-8	9	 158	23	10
				10	 159	18	-2

[a]Reactions conducted in the presence of $Pd_2(dba)_3$ (2.5 mol %), ligand (6 mol %) and 1.1 equiv of Ph_2Zn at 80 °C in THF for 18h. [b]Enantiomeric excess determined by HPLC analysis.

Having identified two ligands that facilitate the asymmetric desymmetrization reaction in good selectivity, we shifted our focus to increasing the chemical yields of the process. We reasoned that the nature of the palladium catalyst may lead to a more efficient reaction. With $Pd_2(dba)_3$ providing a catalytically active complex, several palladium precatalysts were examined in the reaction using BINAP as the ligand (Table 19). The use of allyl palladium chloride dimer provides the desired product in slightly lower yield and selectivity (entry 2). The acetonitrile complex of $PdCl_2$ failed to improve the reaction affording the product in low yield and moderate selectivity (entry 3). To our gratification, the use of $Pd(OAc)_2$ provided a more effective catalyst than $Pd_2(dba)_3$,

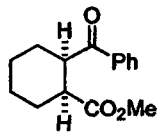
supplying **148** in 87 % ee and 66 % yield (entry 4). Upon completion of the reaction using $Pd(OAc)_2$ as the precatalyst, palladium metal was observed. We reasoned that the yields may be improved by increasing the amount of ligand used, thereby subverting a potential catalyst decomposition pathway. Unfortunately, the use of 7.5 mol % and 10 mol % BINAP to 5 mol % $Pd(OAc)_2$ did not lead to an increase in yield or selectivity (entries 4-6).

Table 19.



10

Pd Source (5 mol %)
BINAP
Ph_2Zn (1.1 equiv),
THF, 80 °C, *18 h*,
then $TMSCHN_2$



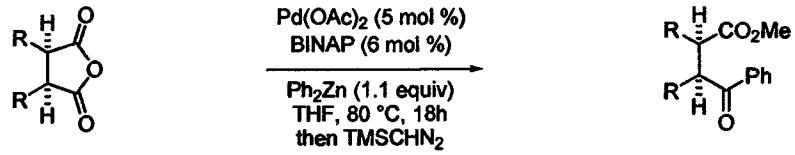
148

Entry[a]	*Pd Source*	BINAP (mol %)	Yield (%)	ee[b] (%)
1	$Pd_2(dba)_3$	6	60	83
2	$[Pd(allyl)Cl]_2$	6	55	75
3	$PdCl_2(MeCN)_2$	6	31	62
4	$Pd(OAc)_2$	6	66	87
5	$Pd(OAc)_2$	7.5	55	85
6	$Pd(OAc)_2$	10	56	81

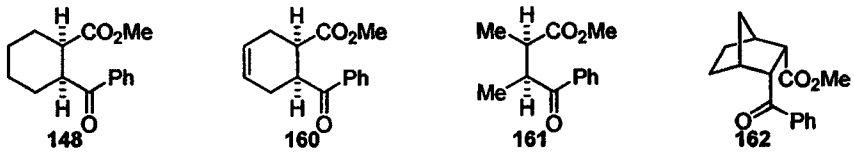
[a]Reactions conducted in the presence of "Pd" (5 mol %), BINAP, and 1.1 equiv of Ph_2Zn at 80 °C in THF for 18h. [b]Enantiomeric excess determined by HPLC analysis.

With the successful initial optimization of the reaction realized we turned our attention to expansion of the substrate scope using the $Pd(OAc)_2$/BINAP system (Scheme 28). Unfortunately, introduction of unsaturation in the cyclohexyl backbone leads to decreased selectivity, providing keto ester **160** in 70 % yield and 77 % ee. Acyclic anhydrides are not exceptional substrates under these conditions with product **161** supplied in a modest yield and selectivity. Tricyclic anhydrides fail to provide product under the prescribed reaction conditions. The current ligand/pre-catalyst fails to provide products in high selectivity in our limited substrate scope study.

Scheme 28.



Products:



148
66 % yield
87 % ee

160
70 % yield
77 % ee

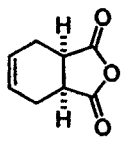
161
49 % yield[a]
75 % ee

162
0 % yield
-- % ee

[a]2.5 mol % $Pd_2(dba)_3$ used.

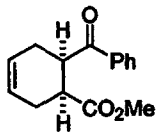
In light of the $Pd(OAc)_2$/BINAP proving less effective when applied to other substrates, we initiated a ligand screen focused on the arylation of cyclohexenyl anhydride **27** (Table 20). The chiral biphenyl ligand **163** provided the desired product in 63 % isolated yield and a slightly improved 80 % ee as compared to BINAP (entries 1 and 2). To our delight, use of JOSIPHOS **96** under optimized conditions afforded the desired product **160** in 67 % yield and 90 % ee, the first example of our anhydride alkylation reaction proceeding in synthetically useful selectivity (entry 3). Manipulation of the electronic and steric properties of the aromatic phosphine portion of the ligand in the form of electron-deficient analog **164** and electron-rich analog **165**, failed to improve reaction selectivity although the yields of **160** were slightly increased (entries 4 and 5). With the identification of a highly effective palladium ligand system providing good yields of the desired product in high selectivity, we sought to further optimize the process by manipulation of solvent and temperature.

Table 20.



27

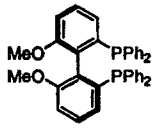
$Pd(OAc)_2$ (5 mol %)
Ligand (6 mol %)
Ph_2Zn (1.1 equiv),
THF, 80 °C, 18 h,
then $TMSCHN_2$



160

Entry[a]	*Ligand*	Yield (%)	ee[b] (%)
1	(*S*)-BINAP (**91**)	67	-77
2	(*S*)-MeOBIPHEP (**163**)	63	-80
3	(*R, S*)-JOSIPHOS (**96**)	67	90
4	(R, S)-**164**	70	77
5	(R, S)-**165**	71	80

[a]Reactions conducted in the presence of $Pd_2(dba)_3$ (2.5 mol %), ligand (6 mol %) and 1.1 equiv of Ph_2Zn at 80 °C in THF for 18h. [b]Enantiomeric excess determined by HPLC analysis.

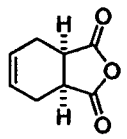


(*S*)-MeOBIPHEP (**163**)

Ar = Ph (**96**)
3,5-CF_3-Ph (**164**)
(3,5-Me)-4-OMe-Ph (**165**)

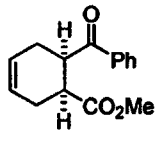
Solvent and temperature have a large impact on the reaction (Table 21). Carrying the reaction out in CH_2Cl_2 at 80 °C in a sealed tube provided the desired keto ester **160** in poor yield and selectivity (entry 1). Likewise, the use of Et_2O as solvent did not lead to an improvement in the reaction, furnishing **160** in 47 % yield and 30 % ee (entry 2). With THF identified as the preferred solvent we examined the effect of temperature on the reaction. The process proceeds at 40 °C over 18 h in THF to supply **160** in almost identical selectivity and slightly improved yield as compared to performing the reaction at 80 °C (entries 3 and 4). To our surprise, the reaction proceeds well even at room temperature to afford the desired product in good yield and selectivity (entry 5). Generally, performing the reaction at lower temperature provides slightly cleaner product.

Table 21.



27

$Pd(OAc)_2$ (5 mol %)
(*R, S*) JOSIPHOS (6 mol %)
Ph_2Zn (1.1 equiv),
Solvent, Temp, 18 h,
then $TMSCHN_2$



160

Entry[a]	*Solvent*	*Temperature (°C)*	Yield (%)	ee[b] (%)
1	CH_2Cl_2	80	26	37
2	Et_2O	80	47	38
3	THF	80	67	90
4	THF	40	75	90
5	THF	23	69	91

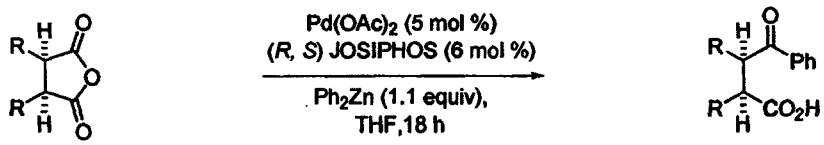
[a]Reactions conducted in the presence of $Pd(OAc)_2$ (5 mol %), (*R,S*) JOSIPHOS (6 mol %), and 1.1 equiv of Ph_2Zn at the indicated temperature and in the indicated solvent for 18h. [b]Enantiomeric excess determined by HPLC analysis.

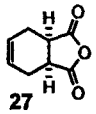
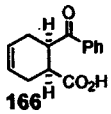
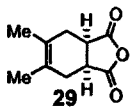
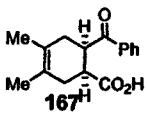
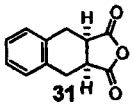
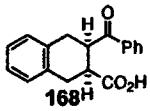
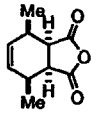
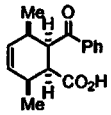
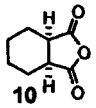
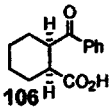
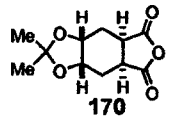
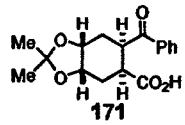
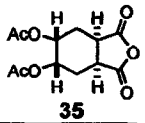
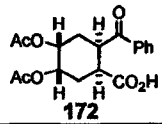
2.4.2 Substrate Scope

Armed with an optimized reaction system that provides the desired arylation products in good yield and selectivity at room temperature we turned our attention to exploration and expansion of the substrate scope. A variety of cyclohexyl fused succinic anhydrides undergo successful arylation (Table 22). The catalyst loading can be reduced to 2.5 mol % without loss of efficiency or selectivity (entry 1). Substitution of the backbone is well tolerated with anhydrides **29** and **31** smoothly affording products **167** and **168** in good yields and high enantiomeric excess (entries 2 and 3). Unfortunately, substitution at the β-position of the anhydride, such as **33**, leads to no reaction presumably due to the increased steric demand of the substrate (entry 4). Cyclohexyl anhydride **10** undergoes smooth arylation providing product **106** in 95 % yield and 84 % ee (entry 5). An interesting concentration effect was observed in the reaction. When the arylation of **10** was performed at high dilution, the product **106** was obtained in 89 % yield and 94 % ee (entry 6). We attribute this effect to Ph_2Zn acting as a Lewis acid which may facilitate non-selective oxidative addition of palladium to the anhydride.

Anhydride **170** supplied the corresponding phenyl ketone **171** in good yield and very high selectivity (entry 7). The nature of backbone substituents in this class of substrates plays a crucial role in the reaction with bisacetoxy anhydride **35** affording the product **172** in moderate yield but low selectivity (entry 8).

Table 22.



Entry[a]	Substrate	Product	Temp. (°C)	Yield (%)	ee[b] (%)
1	 27	 166	23	77[c]	91
2	 29	 167	23	87	90
3	 31	 168	23	84	95
4	 33	 169	23	NR	–
5	 10	 106	23	95	84
6			23	89[d]	94
7	 170	 171	23	83[e]	97
8	 35	 172	23	63[e]	18

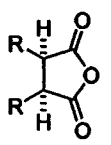
[a]Reactions conducted in the presence of $Pd(OAc)_2$ (5 mol %), (*R,S*) JOSIPHOS (6 mol %), and 1.1 equiv of Ph_2Zn at indicated temperature in THF (0.15 M in sub) for 18h. [b]Enantiomeric excess determined by chiral HPLC of the methyl ester. [c]2.5 mol % $Pd(OAc)_2$ and 3 mol % (*R,S*) JOSIPHOS. [d]Reaction run at 0.034 M in substrate. [e]Isolated as the corresponding methyl ester.

Having thoroughly examined the substrate scope with respect to cyclohexyl fused succinic anhydrides we broadened our screen to include a variety of other succinic

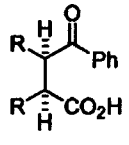
anhydrides (Table 23). Cyclopropylsuccinic anhydride **173** failed to provide product when subjected to the prescribed reaction conditions (entry 1). Anhydride **53** provided phenyl ketone **175** as a 1:1 diastereomeric mixture of *cis* and *trans* isomers each of which was nearly racemic (entry 2). Cyclopentylsuccinic anhydride **51** is a good substrate for the reaction providing the desired product **176** in 74 % yield and 89 % ee at 40 °C (entry 3). Anhydride **177**, bearing β-substituents, failed to supply the corresponding arylation product **178** (entry 4). Likewise, anhydride **179** did not provide the corresponding product **180** in good yield (entry 5). Acyclic anhydrides **59** and **61** were competent substrates for the reaction affording products **181** and **182** in good yield and high selectivity, although elevated temperatures were required (entries 6 and 7). Oxygenated derivatives **55** and **184** did not provide product upon subjection to the reaction conditions (entries 8 and 9). It should also be mentioned that all tricyclic succinic anhydrides failed to give any of the corresponding arylation product under the reaction conditions at a variety of temperatures.

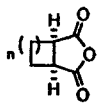
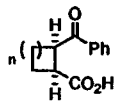
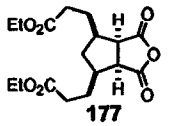
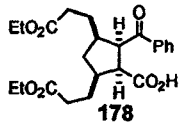
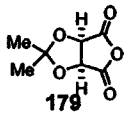
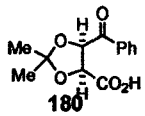
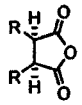
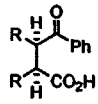
Several general observations concerning the arylation of succinic anhydrides deserve mentioning. First, temperature plays a crucial role in the success of the reaction with cyclcohexyl fused substrates proceeding at room temperature while monocyclic anhydrides must be heated to at least 66 °C in order for good yields to be obtained. Second, substrates bearing substitution at the β-position, or more accurately β-branching, are not well tolerated and lead to no observable product. Finally, it seems as if oxygenation in the backbone has a dramatic influence on the course of the reaction and seems to be substrate specific with some anhydrides providing no product and some other proceeding smoothly.

Table 23.



$Pd(OAc)_2$ (5 mol %)
(*R, S*) JOSIPHOS (6 mol %)
Ph_2Zn (1.1 equiv),
THF,18 h



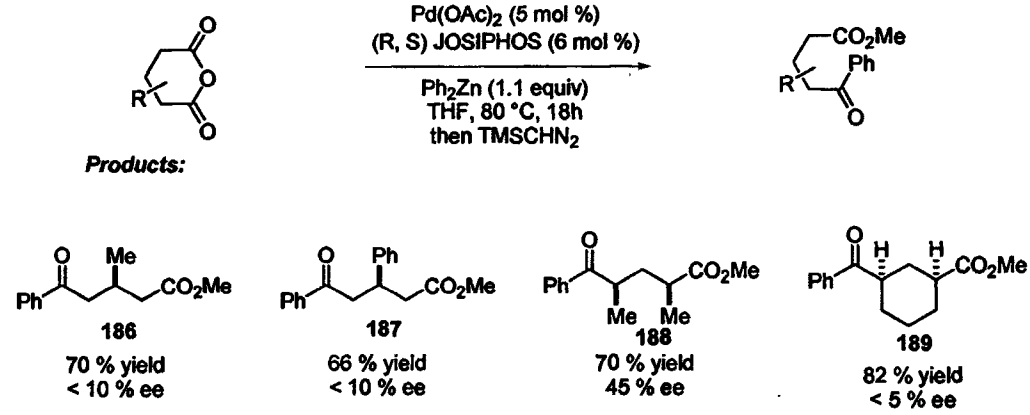
Entry[a]	Substrate	Product	Temp. (°C)	Yield (%)	ee[b] (%)
					
1	n = 0 (**173**)	n = 0 (**174**)	80	NR	--
2	n = 1 (**53**)	n = 1 (**175**)	40	63[c]	< 10
3	n = 2 (**51**)	n = 2 (**176**)	40	74[d]	89
4	 **177**	 **178**	40	NR	--
5	 **179**	 **180**	40	< 10	--
					
6	R = Me (**59**)	R = Me (**181**)	80	72	92
7	R = $(CH_2)_3CO_2Et$ (**61**)	R = $(CH_2)_3CO_2Et$ (**182**)	80	61	89
8	R = OAc (**55**)	R = OAc (**183**)	80	NR	--
9	R = OMe (**184**)	R = OMe (**185**)	40	NR	--

[a]Reactions conducted in the presence of $Pd(OAc)_2$ (5 mol %), (*R,S*) JOSIPHOS (6 mol %), and 1.1 equiv of Ph_2Zn at indicated temperature in THF (0.15 M in sub) for 18h. [b]Enantiomeric excess determined by chiral HPLC of the methyl ester. [c]Isolated as a 1:1 mixture of cis and trans isomers. [d]Isolated as the corresponding methyl ester.

With a well-defined succinic anhydride substrate scope in hand, we investigated the competence of glutaric anhydrides in the reaction manifold (Scheme 29). Although glutaric anhydrides are competent substrates for the reaction, they generally gave poor selectivity. Glutaric anhydrides bearing substituents at the 3-position proved to be poor substrates for the reaction, providing products **186** and **187** in moderate yield but < 10 % ee in each case. We thought that glutaric anhydrides bearing substituents at the 2-position may be more effective in light of the steric control element being closer to the site of reaction. Unfortunately, this theory proved incorrect with product **188** being

supplied in good yield and 45 % ee and the keto ester **189**, arising from arylation of the corresponding bicyclic anhydride isolated as a racemate.

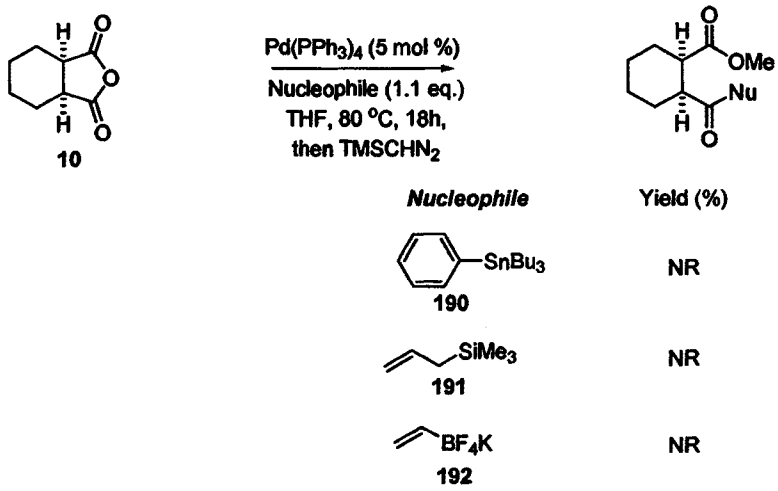
Scheme 29.



2.4.3 Nucleophile Scope

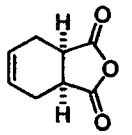
Having delineated the substrate scope with respect to the electrophilic anhydride coupling partner, we turned our attention to the expansion of the scope of the nucleophilic coupling partner. Although the main group organometallic coupling partner in the nickel catalyzed reaction manifold was strictly limited to the use of organozinc reagents, we reasoned that the palladium-catalyzed reaction may be amenable to the use of a more diverse group of nucleophilic reaction partners. Several classes of main group organometallics known to participate in transmetalation with organopalladium intermediates were examined (Scheme 30). Aryltin reagent Bu_3SnPh **190** failed to provide any addition product in the presence of catalytic $Pd(PPh_3)_4$. Likewise, allyl silane **191** and tetrafluoroborate salt **192** did not supply either of the corresponding products.

Scheme 30.



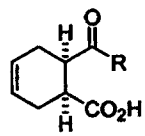
In light of the failure of other main group organometallics to provide product under our initial achiral conditions, the bulk of our work on the nucleophile scope focused on diorganozinc reagents. Dialkylzinc reagents were very effective nucleophilic coupling partners in the nickel mediated reaction and would represent a valuable extension in the context of the palladium chemistry. Dialkylzinc reagents are competent nucleophiles in the palladium-mediated reaction manifold (Scheme 31). When the reaction is performed with Me_2Zn as the nucleophile the desired methyl ketone **193** is obtained in 74 % yield and 64 % ee. Likewise, the use of Et_2Zn supplies the corresponding ethyl ketone **28** in 62 % yield and 62 % ee at elevated reaction temperatures. Interestingly, when alkyl nucleophiles were further examined it was realized that the reaction results were very hard to reproduce. Optimization efforts were undertaken with Me_2Zn as the nucleophile since it lacks β-hydrogens that could potentially lead to by-products by β-hydride elimination of the intermediate acyl-alkyl palladium species.

Scheme 31.



27

$Pd(OAc)_2$ (5 mol %)
(R,S) JOSIPHOS (6 mol %)
R_2Zn (1.1 equiv),
THF, 18 h

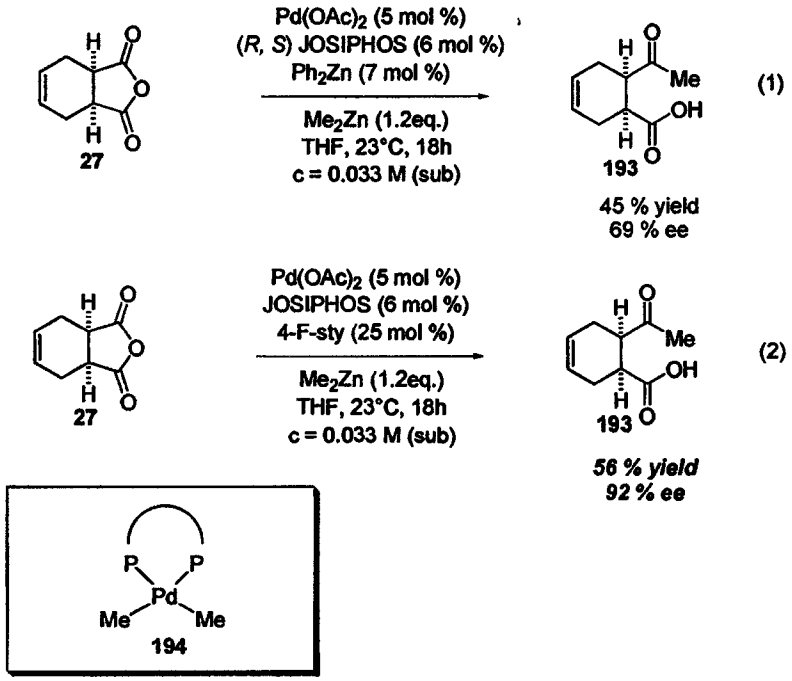


R = Me (193)
R = Et (28)

R_2Zn	Temp (°C)	Yield (%)	ee (%)
Me_2Zn	23	74	64
Et_2Zn	80	62	62

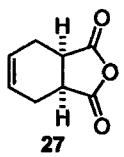
We attribute the irreproducibility to the formation of the active catalytic species. It was thought that perhaps the reduction of palladium (II) to palladium (0) was slow potentially due to a slow decomposition of the presumed dialkyl palladium intermediate **194** (Scheme 32). We reasoned that either pre-reduction of $Pd(OAc)_2$ in the presence of the chiral ligand or addition of an electron deficient olefin, to facilitate decomposition of the dialkyl palladium intermediate (*vide supra*), may be two potential solutions to the problem. The first experiment involved reduction of $Pd(OAc)_2$ with Ph_2Zn in the presence of the ligand followed by addition of Me_2Zn and substrate (Scheme 32, eq. 1). This tactic provided the desired product **193** in slightly lower yield and moderate selectivity but seemed to have little effect on reaction reproducibility. The use of catalytic amounts of 4-fluorostyrene had a *dramatic influence on reaction selectivity* affording **193** in 56 % yield and 92 % ee (Scheme 32, eq. 2). Although the addition of the styrenic additive had a profound and not well understood effect on reaction selectivity, it failed to render the transformation reproducible.

Scheme 32.



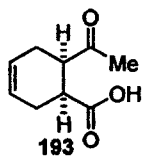
Upon careful analysis of all the reactions that were successful, we realized that the ligand to metal ratio was nearly 1:1 or less, simply due to small variations in the weighing of material during reaction setup. A systematic study exploring the influence of the ligand to metal ratio on the outcome of the reaction was undertaken (Table 24). The reaction becomes reproducible if exactly 1 equiv of ligand to metal is used and under these conditions the styrene additive still exerts an influence on the selectivity of the reaction (entries 1 and 2). If an excess of ligand is used, the reaction fails to provide product (entry 3). Less than 1 equiv of ligand to palladium can be used, with 0.8 equiv proving to be optimal for reliable reproducibility, an example of ligand-accelerated catalysis (entries 4 and 5). Unfortunately, the application of these reaction conditions to other dialkylzinc nucleophiles, namely Et_2Zn and *i*-Pr_2Zn, has failed to provide acceptable yields of the desired alkylation products.

Table 24.



27

$Pd(OAc)_2$ (5 mol %)
(*R, S*) JOSIPHOS
Me_2Zn, 4-F-sty (10 mol %)
THF, 22 h



193

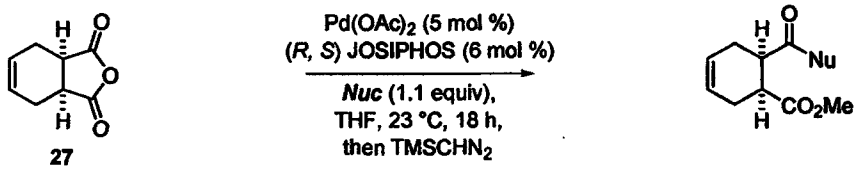
Entry[a]	*Pd : Lig*	4-F-sty (mol %)	Yield (%)	ee[b] (%)
1	1 : 1.0	–	78	64
2	1 : 1.0	25	80	91
3	1 : 1.2	25	NR	–
4	1 : 0.8	25	80	90
5	1 : 0.5	25	<25	84

[a]All reactions conducted in the prescence of $Pd(OAc)_2$ (5 mol %), JOISPHOS, Me_2Zn (1.1 equiv) in THF (0.033 M in sub) at ambient temperature. [b]Enantiomeric excess determined by HPLC of the corresponding benzyl ester.

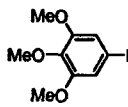
The application of functionalized aromatic nucleophiles was also of interest in light of our efforts directed at the synthesis of natural products (See Chapter 3). We reasoned that diarylzinc reagents generated from the corresponding aryl lithium or aryl Grignard reagents should provide access to aromatic ketones as in the nickel-catalyzed reaction manifold. Additionally, we were interested in exploring the use of arylzinc halides which may be more compatible with the palladium-mediated reaction in light of their extensive use in the cross-coupling of thioesters. A variety of arylzinc halides and diarylzinc reagents were investigated (Table 25). Difurylzinc, generated from the reaction of 2 equiv of furyl lithium and 1 equiv of $ZnCl_2$, was a competent nucleophile in the reaction providing the corresponding furyl ketone in 42 % yield and 77 % ee (entry 1). Furylzinc chloride is also a compatible nucleophile, supplying the addition product in slightly increased yield and 71 % ee (entry 2). Encouraged by these initial results, we examined the competency of the di(trimethoxy)arylzinc reagent generated from the corresponding aryl lithium and zinc salts (entries 3 and 4). Although the reaction in both cases provided the product, albeit in low yields, the selectivity was extremely low.

Phenylzinc bromide is not an efficient coupling partner, affording the aryl addition product in very low yield and in nearly racemic form (entry 5).

Table 25.



27

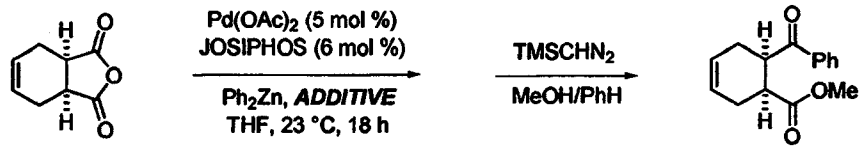
Entry[a]	Nuc	Yield (%)	ee[b] (%)
1	 /$ZnCl_2$ (0.5 equiv)	42	77
2	 /$ZnCl_2$ (1 equiv)	50	71
3	 /$ZnCl_2$ (0.5 equiv)	36	< 10
4		40[c,d]	< 10
5		19[c]	< 10

[a]Reactions conducted in the presence of $Pd(OAc)_2$ (5 mol %), (*R,S*) JOSIPHOS (6 mol %) and 1.1 equiv of Nuc at 23 °C in THF for 18h. [b]Enantiomeric excess determined by HPLC analysis. [c]Reaction conducted at 80 °C. [d]$ZnBr_2$ used in the place of $ZnCl_2$.

With disappointing results obtained with aromatic nucleophiles we reasoned that perhaps some of the by-products produced in the generation of the arylzinc species may be interfering with the reaction. A number of control experiments were performed in order to ascertain what effect each component has on reaction efficiency and selectivity (Scheme 33). Hexanes are present in the arylzinc species since the alkyl lithium reagent used for lithium-halogen exchange is available as a solution in hexanes. When the standard reaction is performed in a 4:1 mixture of THF/hexanes there are no adverse effects on the reaction. Another potential problem is the presence of butylbromide, the by-product resulting from the use of *n*-butyllithium in the lithium-halogen exchange with the aromatic bromide. Under standard conditions at room temperature, butylbromide has no effect on the reaction. The last by-product investigated was the lithium salt generated

from the reaction of the organolithium compound and the zinc halide. Performing the reaction in the presence of LiBr leads to a pronounced decrease in reaction efficiency with simultaneous loss of selectivity.[60] It should be mentioned that the generation of arylzinc reagents from the corresponding Grignard reagents (producing magnesium halide by-products) also failed under the prescribed reaction conditions.

Scheme 33.

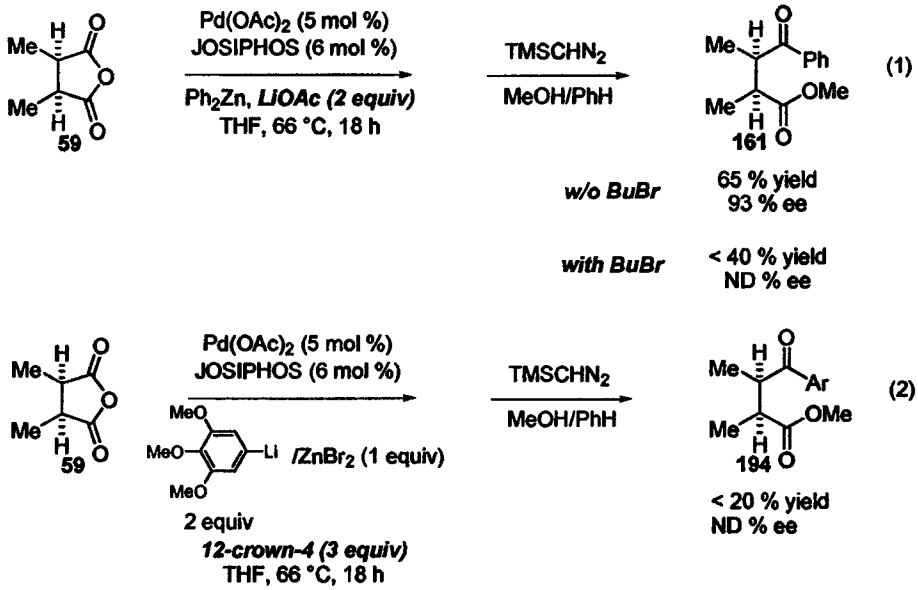


ADDITIVE	Yield	ee
Hexanes (rxn run in 4:1 THF/Hex)	65 %	91 %
butylbromide (1 eq.)	63 %	92 %
LiBr (2 eq.)	<50%	48 %

With the demonstration of deleterious effects imparted by the presence of lithium salt, we still could not determine if the anion (halide) or the cation (lithium) was responsible. In order to probe this question two reactions were carried out: one in the presence of lithium acetate and one in the presence of a crown ether known to ligate lithium cation (Scheme 34). The reaction proceeds smoothly in the presence of 2 equiv of LiOAc to provide the phenyl ketone **161** in 65 % yield and 93 % ee, results almost identical to the reaction performed in the absence of salt (Scheme 34, eq. 1). When the same reaction is performed in the presence of LiOAc and BuBr, the desired product is isolated in low yield and contaminated by unidentified by-products. Using the electron rich trimethoxyarylzinc reagent in the presence of 12-crown-4 failed to provide the desired product in appreciable amounts (Scheme 34, eq. 2). Although the reaction proceeds uneventfully in the presence of LiOAc, we still cannot discern whether the adverse effect of lithium halides is a consequence of the anion or cation. The fact that

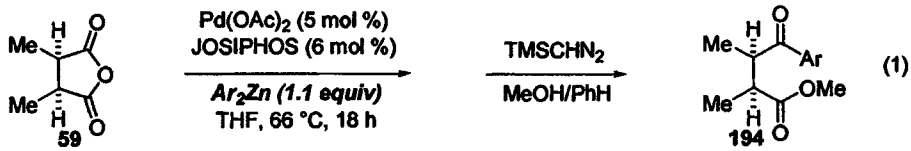
LiOAc does not effect the reaction could be due to the difference in the pKa of the conjugate acid of the anion. Likewise, one could argue that due to the increased basicity of the anion that the lithium cation is a less effective Lewis acid.

Scheme 34.



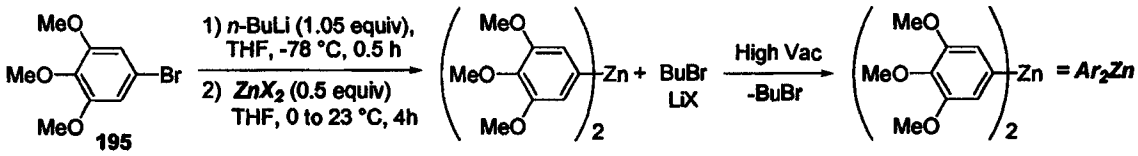
Based on the observation that LiOAc has little effect on the reaction, we investigated two tactics to generate competent arylzinc coupling partners in the context of the desymmetrization of anhydride **59**. We investigated generating the diarylzinc species from zinc salts bearing more basic anions (Scheme 35). The arylzinc species was generated from the reaction of aryl bromide **195** with *n*-BuLi to afford the corresponding aryl lithium which was quenched with each zinc salt. The reaction solvent along with the by-product BuBr was removed under high vacuum and the zinc species taken up in THF and subjected to the reaction conditions. Unfortunately all of the zinc salts examined failed to improve the reaction. One of the main experimental shortcomings of this method is the fact that all of the zinc salts are poorly soluble in THF which could lead to poor yields in the arylation of the zinc center.

Scheme 35.



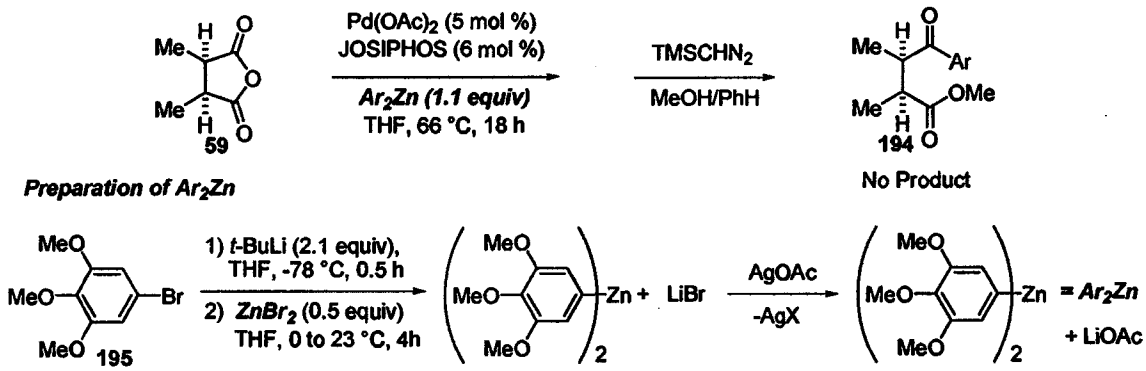
ZnX_2	Yield (%)	ee (%)
$Zn(OTf)_2$	< 20	< 10
$Zn(OAc)_2$	--	--
ZnF_2	< 10	< 10

Preparation of Ar_2Zn



Since we knew that LiOAc did not adversely effect the reaction and that zinc reagent generation from the nucleophilic displacement using $Zn(OAc)_2$ failed to provide the desired product, we turned to an anion exchange reaction (Scheme 36). Aryl bromide **195** was treated with 2.1 equiv of *t*-BuLi (in order to avoid the generation of BuBr) to form the intermediate aryl lithium reagent that was then quenched with 0.5 equiv of $ZnBr_2$. The reaction mixture was then transferred to a suspension of AgOAc in THF with the hope that the insoluble AgBr would precipitate from the reaction medium, effectively exchanging LiBr for the innocuous LiOAc. After stirring the reaction for 1h, the precipitate was removed by Schlenk filtration and the solution of aryl zinc reagent was used in the reaction. The reaction provided none of the arylated product.

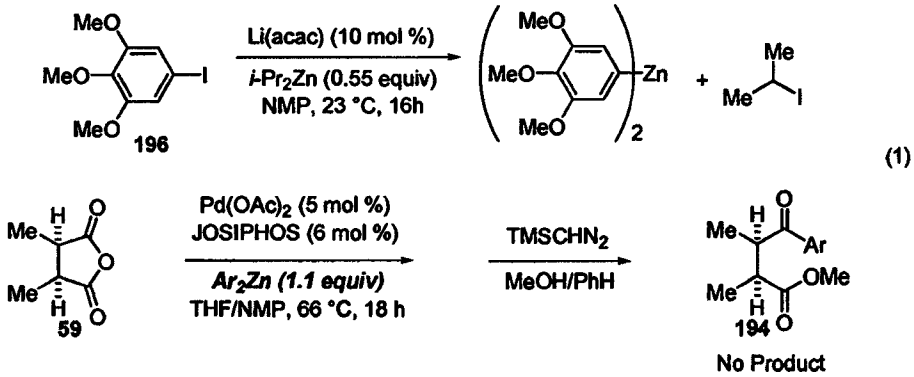
Scheme 36.



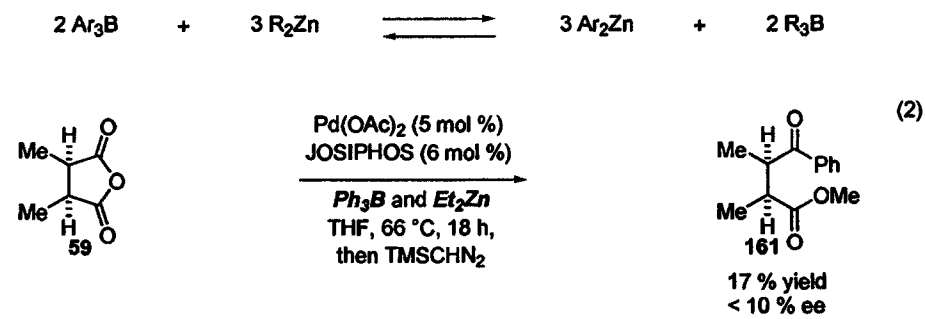
There are very few methods for the preparation of salt-free organozinc reagents in the literature. One recent method reported by Knochel and co-workers involves the generation of diarylzinc species from the reaction of an aryl iodide and *i*-Pr_2Zn in NMP.[61] We examined this method in the context of our system (Scheme 37, eq. 1). Aryl iodide **196** was treated with 0.55 equiv of *i*-Pr_2Zn in the presence of catalytic Li(acac) in NMP for 16h at ambient temperature. Although we have shown that alkyl halides have an adverse effect on the reaction, we reasoned that the presence of a secondary alkyl halide should have little impact since the oxidative addition of palladium complexes to these species is known to be slow.[62] Subjection of the salt-free diarylzinc reagent to the standard reaction conditions failed to provide any product. Aryl group transfer from boron to zinc is known and has been used to prepare salt free zinc reagents.[63] We envisioned in situ generation of the diarylzinc (Ph_2Zn as a probe) reagent from reaction of Ph_3B and Et_2Zn under our reaction conditions (Scheme 37, eq. 2). In the event, a mixture of Ph_3B and Et_2Zn were subjected to the reaction conditions, and to our gratification the desired product **161** was isolated albeit in 17 % yield. Unfortunately, HPLC analysis revealed that the product was nearly racemic.

Scheme 37.

Knochel's method for arylzinc generation



Boron-zinc exchange



Although we have not successfully expanded the nucleophile scope to encompass diarylzinc reagents generated from the corresponding aryl halides we have learned what factors control the reaction outcome. Lithium and magnesium halides are not well tolerated, leading to little or no product formation and extremely poor reaction selectivity. Primary alkyl halides are by-standers when the reaction is carried out at ambient temperature but seem to have a negative impact when the reaction is carried out at elevated temperatures, potentially due to the fact that oxidative addition of the catalyst is not occurring at room temperature but upon heating this pathway is activated.

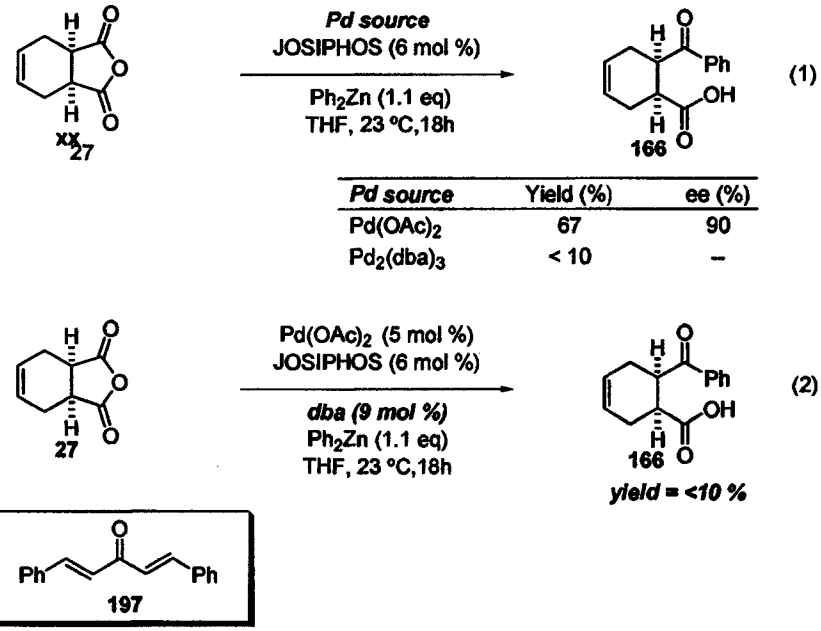
2.4.4 Stereochemistry and Mechanism

At the outset of our studies in the palladium-mediated reaction manifold, we felt the mechanism of the reaction would likely proceed via the same pathway delineated for

the nickel-catalyzed alkylation based on all of our observations, coupled with literature precedent; however, we could not rule out other mechanistic possibilities. One of the main questions was the nature of the active catalyst, or more accurately, the oxidation state of the active catalyst. In light of our initial results in the achiral manifold using $Pd(PPh_3)_4$ as the catalyst, palladium(0) seems most likely to be the active species, but since the optimized asymmetric conditions make use of a $Pd(OAc)_2$ as the pre-catalyst we could not rule out the intermediacy of a Pd(II) species. Some of the observations made over the course of our investigations may provide evidence for Pd(0) being the catalytically active species.

Initial studies in the asymmetric reaction manifold were carried out using $Pd_2(dba)_3$ as the palladium source once again suggesting low-valent metal is the active catalyst. Interestingly, when the reaction is performed at ambient temperature using a catalyst derived from $Pd_2(dba)_3$ and JOSIPHOS, no product is formed (Scheme 38, eq. 1). A control experiment was performed in which the catalyst was generated from $Pd(OAc)_2$ under standard reaction conditions at ambient temperature then 9 mol % dba **197** was added along with substrate (Scheme 38, eq. 2). Addition of dba **197** suppresses the reaction providing the same results as the reaction run using $Pd_2(dba)_3$ as the pre-catalyst. Our hypothesis is that dba coordinates the low-valent catalyst well enough to suppress the reaction at ambient temperature (*the reaction proceeds in the presence of dba at elevated temperatures*).[64]

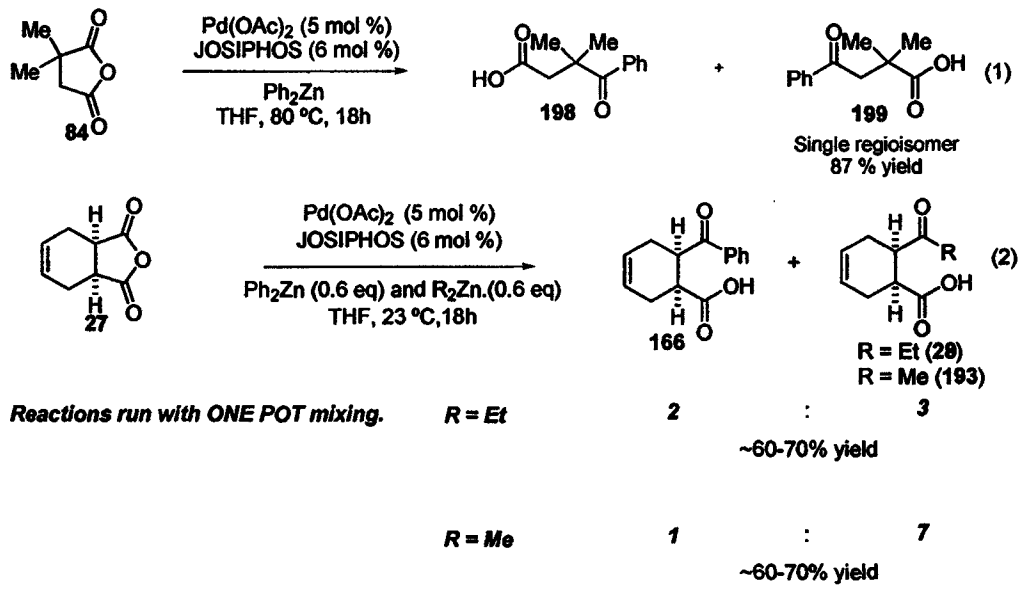
Scheme 38.



In order to garner further information regarding the mechanistic course of the reaction we applied some of the same probes used in the course of studies into the nickel chemistry. The intermediacy of nucleophilic alkyl-palladium species has been invoked in the context of reductive ring-opening reactions[65] and we could not rule out this possibility in the present reaction manifold. We envisioned that the use of an unsymmetrical anhydride in the palladium catalyzed reaction may serve as an effective mechanistic probe much as it had in the context of the nickel-mediated reaction (see Scheme 10). When anhydride **84** was subjected to standard reaction conditions using the $Pd(OAc)_2$/JOSIPHOS catalyst, the arylation product **199** was obtained in high yield as a single regioisomer (Scheme 39, eq. 1). This result is in agreement with the nickel-mediated reaction manifold and suggests the palladium-catalyzed reaction also proceeds via a discrete oxidative addition/transmetalation reaction pathway (*vide supra*). As a possible probe for the transmetalation event, we examined the competence of mixed diorganozinc reagents (Scheme 39, eq. 2). Subjection of anhydride **27** to the

$Pd(OAc)_2$/JOSIPHOS conditions in the presence of a 1:1 mixture of Et_2Zn and Ph_2Zn at ambient temperature resulted in the isolation of nearly a statistical mixture of products **166** and **28** resulting from aryl and alkyl group transfer respectively. Interestingly, when the same reaction was carried out using Me_2Zn as the dialkylzinc coupling partner, selective methyl group transfer was observed, affording a 7:1 mixture of **193** and **166.** We can not completely rule out the possibility of alkyl/aryl palladium intermediates as the active species in the reaction; although, it seems unlikely based on the results obtained in the context of the arylation of anhydride **84.** Furthermore, in light of the mechanistic information gathered in the context of the nickel reaction, coupled with literature precedent, we feel that our mechanistic proposal is not unreasonable.

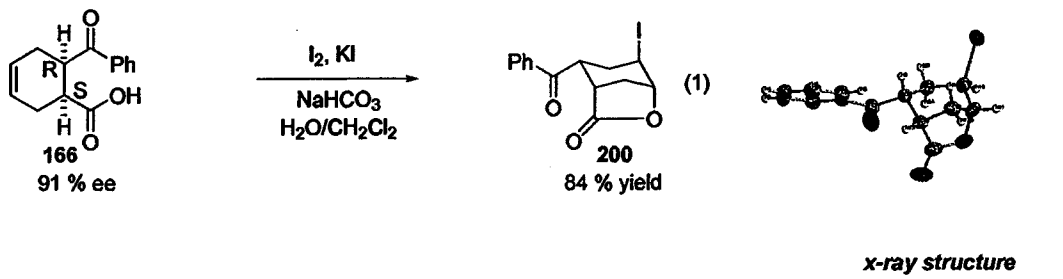
Scheme 39.

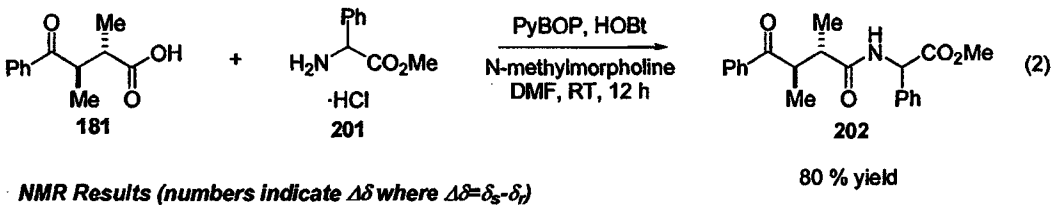


Having realized a highly enantioselective anhydride arylation protocol, we commenced studies aimed at the elucidation of the absolute stereochemistry of the product keto acids. Keto acid **166** was subjected to iodolactonization conditions to provide the highly crystalline bicyclic lactone **200** (Scheme 40, eq. 1). Crystallographic

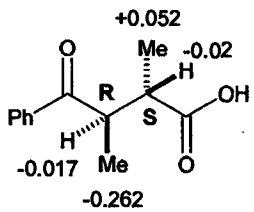
analysis of **200** revealed the absolute configuration as shown. The iodolactonization of **166** is also a demonstration of the synthetic utility of the present method; in two steps from a readily avalaible starting material, iodolactone **200** containing 4 stereocenters set in a relative and absolute sense is easily accessible. In order to be internally consistent, we also elucidated the absolute configuration of keto acid **181** using an NMR technique reported by Nagai and Kusumi.[66] The enantioenriched acid **181** was coupled with each antipode of phenyl glycine **201** (Scheme 40, eq. 2). Each respective diastereomeric amide **202** was then analyzed by NMR and by the difference in chemical shifts of each resonance the absolute configuration was determined to be internally consistent with the results obtained from crystallographic determination of keto acid **166**.

Scheme 40.





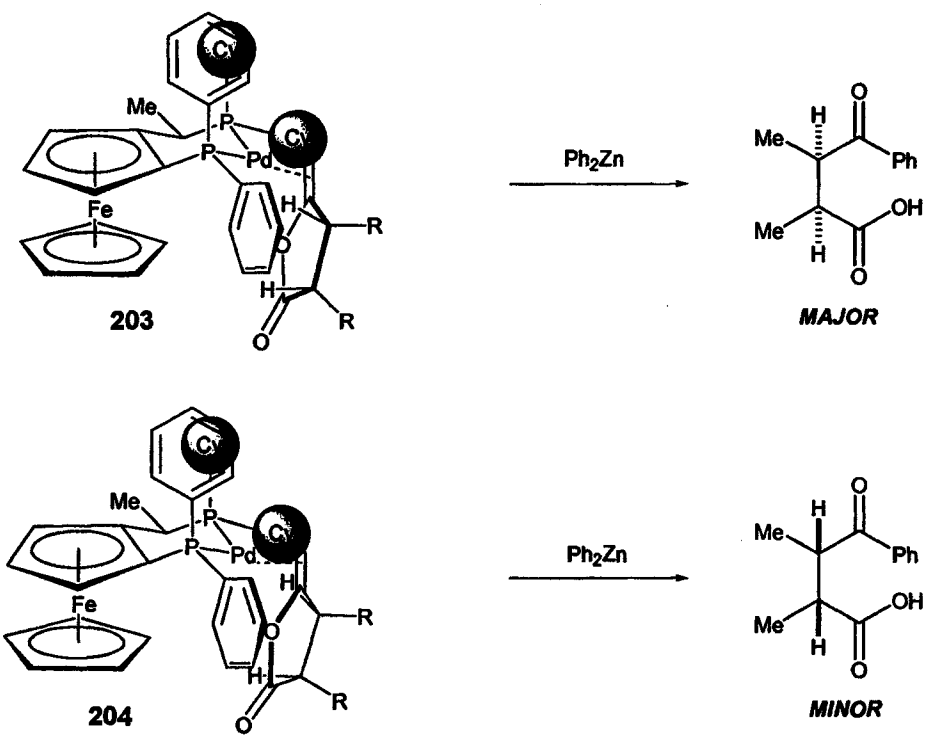
NMR Results (numbers indicate $\Delta\delta$ where $\Delta\delta=\delta_S-\delta_I$)



Having determined the absolute sense of enantioinduction, we propose the following stereochemical model to explain the outcome of the reaction, operating under the assumption that the reaction takes place via a discrete oxidative addition/transmetalation process (Figure 2). The palladium/JOSIPHOS most likely adopts the pseudo-chair conformation as depicted in **203** and **204** with the benzylic methyl group residing in a pseudo-equatorial orientation and the ferrocenyl ring adopting a position anti to the pseudo-axial phosphine substituents.[67] The anhydride most likely coordinates the Pd-center on the π-face *anti* to the backbone substituents due to unfavorable steric interactions of the anhydride backbone and the groups resident on each phosphorous atom. Furthermore, the anhydride most likely occupies a pseudo-equatorial position in order to preserve the preferred metal-center geometry, leading us to propose

the two diastereomeric coordination complexes **203** and **204**. The steric difference between the cyclohexyl and phenyl phosphorus substituents should favor complex **203**, in which the anhydride backbone is closer to the more sterically accommodating diphenylphosphine, leading to the observed enantiomer as the major product.

Figure 2.



2.5 Conclusion

We have developed two new transition metal-catalyzed cross-coupling protocols using cyclic anhydride starting materials providing ready access to stereochemically defined 1,4- and 1,5-keto acid derivatives. The nickel-catalyzed process has an extremely broad substrate scope with respect to both the electrophilic and nucleophilic coupling partners. We have also been able to garner insight with respect to the mechanism of the process, suggesting the reaction proceeds via a discrete oxidative

addition/transmetalation manifold. Furthermore, a dramatic rate enhancement has been observed by the addition of electron-deficient styrene moieties.

The enantioselective variant of the nickel-catalyzed reaction has been thoroughly investigated and chiral nickel-P,N-ligand complexes have been found to provide enantioenriched products in poor to good selectivity. Unexpectedly, the olefinic promoter was shown to have a dramatic influence on selectivity in the context of the asymmetric desymmetrization of glutaric anhydrides, potentially leading to the design of and implementation of a new class of chiral P,N-ligands.

A highly efficient, room temperature palladium-catalyzed cross-coupling of meso anhydrides and diarylzinc reagents was also discovered. The reaction provides ready access to enantioenriched keto acids in good yield and high selectivity. The reaction was applied to a variety of cyclic meso anhydrides and both aromatic and aliphatic nucleophilic coupling partners.

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[31] Reactions that are sluggish often result in the formation of ester by-products presumably arising from the slow oxidation of the alkyl zinc reagent by adventitious oxygen; for a similar example, see: Katritzky, A. R.; Luo, Z. *Heterocycles* **2001**, *55*, 1467-1474.

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[35] It should be noted that generation of aryl lithium reagents from aryl iodides by treatment with *n*-butyllithium leads to no observed product.

[36] The use of 0.5 equiv of dialkylzinc reagent in the reaction manifold does not result in both organic fragments being transferred.

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[59] Ligand **147** was prepared by Amanda Schmisseur (REU undergraduate student Summer 2003).

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[63] See reference 23.

[64] See the electron deffcient alkene results in the context of the nickel catalyzed reaction

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Chapter 3

Synthetic Application of the Transition Metal-Catalyzed Anhydride Alkylation

3.1 Introduction

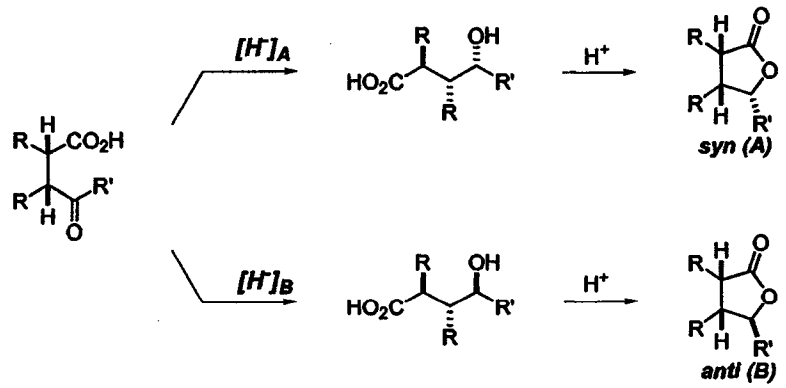
The impetus to pursue the development of new synthetic methodology is two-fold. First, the fundamental understanding of new reactivity or the application of known reactivity to unknown systems supplies answers to fundamental questions and serves to advance basic science. Second, the expedient assembly of complex natural product targets continues to be an intense area of investigation due to their importance in medicine and as fundamental probes in biochemical investigations. Therefore, the discovery and implementation of new synthetic methods continues to be a centerpiece of organic chemistry.

The development of new synthetic methods is intimately coupled with its application to existing problems. As part of our program directed toward the development of new methodology and its relevance with respect to the synthesis of stereochemical relationships that are difficult to access, we sought to investigate the synthetic utility of our anhydride alkylation. We have investigated two discrete areas in pursuit of this goal: the complementary diastereoselective reduction of keto acids as an expedient approach to tri-substituted γ-lactones and the total synthesis of a family of related lignan natural products.

3.2 Complementary Diastereoselective Reduction of Keto Acids

New methods for the synthesis of the lactone moiety continue to be an area of intense investigation due to its synthetic utility and its prevalence in biologically significant natural products.[1] In particular, γ-butyrolactones represent an equivalent to 4-hydroxycarbonyl compounds, also known as homoaldol products.[2] Among the multitude of approaches devised for the synthesis of γ-lactones,[3,4] the synthesis of trisubstituted derivatives still represents a formidable challenge.[5] We have recently developed complementary approaches to γ-keto acid derivatives[6] using alkylative anhydride desymmetrization as well as asymmetric Stetter reactions.[7] We reasoned that the complementary diastereoselective reduction of γ-keto acids bearing a cyclic backbone would provide ready access to trisubstituted γ-lactones. We envisioned that treatment of the 4-oxocarboxylic acids with a particular reducing agent ($[H^-]_A$) would potentially provide the *syn* lactone **A**, while treatment of the starting material with a separate hydride source ($[H^-]_B$) may supply the paired *anti* lactone **B** (Scheme 1).

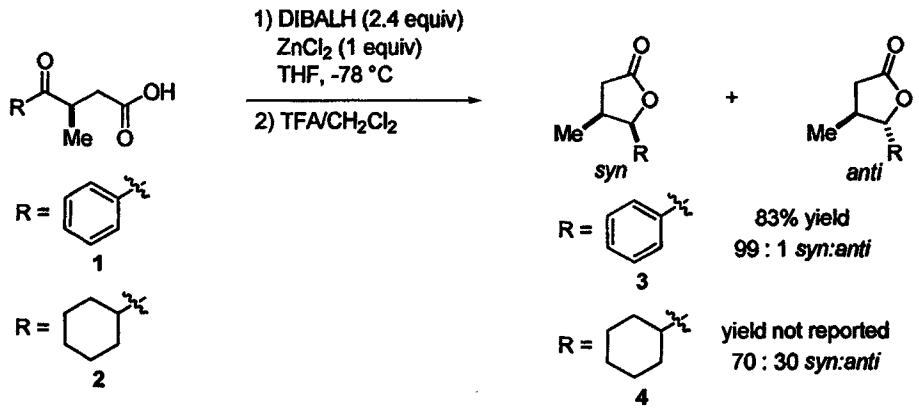
Scheme 1.



Substrate-directed reactions represent a powerful method for the introduction of new stereochemical elements into molecules containing preexisting stereocenters.[8]

Although reductions of β-hydroxyacids are well developed, relatively few examples applying this concept to the reduction of γ-keto acids have appeared.[9] Frenette and co-workers[10] reported a highly diastereoselective reduction of γ-keto acids (Scheme 2). Treatment of keto acid **1** with 2.4 equiv of DIBAL-H in the presence of stoichiometric amounts of $ZnCl_2$ followed by lactonization of the intermediate hydroxy ketone under acidic conditions provided the lactones in > 99:1 ratio favoring the *syn* lactone **3**. The aromatic ketone seems to be an essential structural motif for highly selective reduction as typified by cyclohexyl keto acid **2**, which upon reduction using standard conditions afforded the products *syn* **4** and *anti* **4** in diminished selectivity. Since Frenette's seminal report, several other groups have reported the diastereoselective reduction of similar acyclic keto acids using nearly identical conditions.[11]

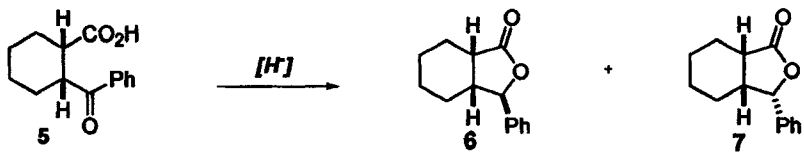
Scheme 2.



Like the diastereoselective reduction of acyclic 1,4-keto acids, reports detailing the use of keto acids bearing cyclic backbones have been rare. The reduction of phenyl keto acid **5** with lithium trialkylborohydrides followed by acidic work-up provided the corresponding *anti* lactone **6** in excellent yield and selectivity (Scheme 3).[12] The complementary *syn* lactone **7** was obtained by PtO_2-catalyzed hydrogenation of keto acid

5, albeit in modest selectivity. The *syn* lactone **7** has also been accessed by a multi-step route.[13] The reduction of **5** to selectively obtain lactones **6** and **7** under different reaction conditions represents, to our knowledge, the only example of a complementary reduction of 1,4-keto acids containing a cyclic backbone. Furthermore, this report details the complementary reduction of only **5** and no other structural variants.

Scheme 3.

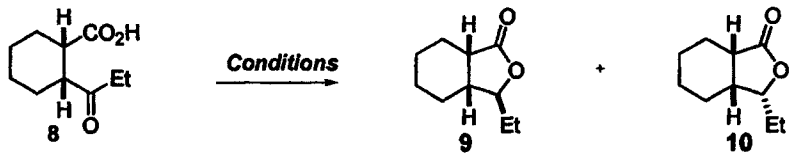


[H⁻]	Yield (%)	6 : 7
Et_3BHLi	82	94 : 6
PtO_2 / H_2	85	24 : 76

Our initial efforts to discover a set of conditions that provide access to each diastereomer focused on reducing agents known to participate in substrate-directed reduction manifolds (Table 1).[14] Alkyl aluminum hydrides have been shown to reduce acyclic 1,4-keto acids with high levels of stereocontrol (*vide supra*). Reduction of *cis*-cyclohexyl keto acid **8** with DIBAL-H at low temperature followed by cyclization, affords the desired lactone in modest yield and selectivity favoring *syn* lactone **10** (entry 1). Silanes have seen application as hydride sources under acidic conditions and have been shown be effective for the reduction of α-hydroxyketones.[15] Ttreatment of keto acid **8** with Et_3SiH under acidic conditions provids an isomeric mixture of the desired lactones in modest yield but improved selectivity favoring **10** in a 80:20 ratio (entry 2). Increasing the steric demand of the silane source in the form of $PhMe_2SiH$ leads to a dramatic increase in both reaction efficiency and selectivity supplying **10** in 93:7 ratio (entry 3).[16] With efficient entry to the *syn* diastereomer, we turned our attention to the

search for conditions that would favor the corresponding *anti* isomer. Lithium trialkylborohydrides have been shown to provide the *anti* lactones in similar systems (*vide supra*). Subjection of keto acid **8** to 2.4 equiv of Super-Hydride (Et_3BHLi) in THF provided the desired products after cyclization in 83 % yield and a 85:15 ratio favoring *anti* lactone **9** (entry 4). Increasing the steric demand of the reducing agent in the form of L-Selectride resulted in reduced selectivity (entry 5).

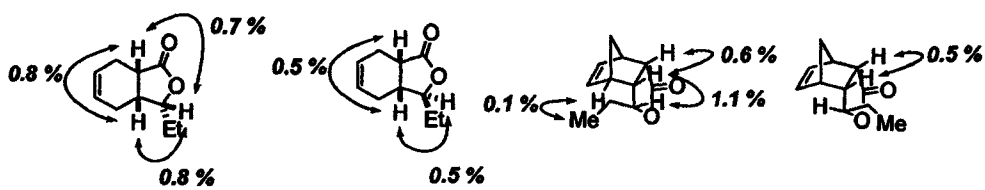
Table 1.



Entry	Conditions	Yield (%)[a]	9 : 10[b]
1	DIBAL-H THF, -78 °C	64	25 : 75
2	Et_3SiH TFA/CH_2Cl_2 (1:3), 0 °C	54	20 : 80
3	$PhMe_2SiH$ TFA/CH_2Cl_2 (1:3), 0 °C	90	7 : 93
4	Et_3BHLi THF, -78-23 °C	83	85 : 15
5	*s*-Bu_3BHLi THF, -78-23 °C	65	75 : 25

[a]Isolated yields. [b]Diastereomeric ratios determined by NMR analysis of the unpurified reaction mixture.

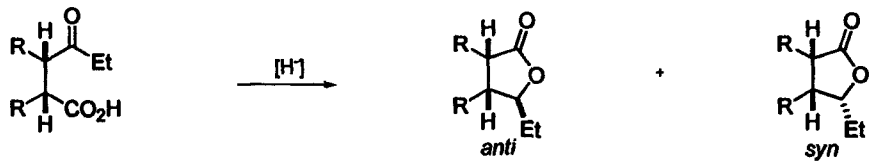
nOe Relationships

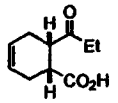
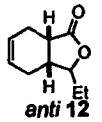
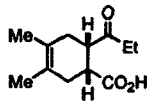
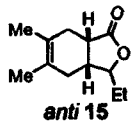
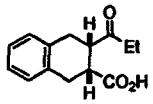
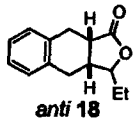
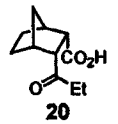
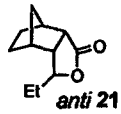
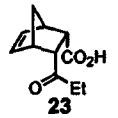
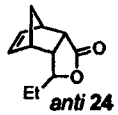
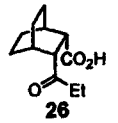
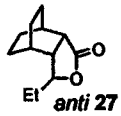
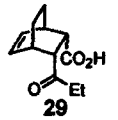
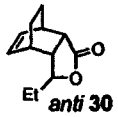
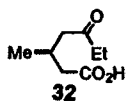
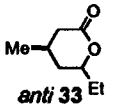


With the identification of two discrete reducing agents that provide complementary diastereomers of the product γ-butyrolactones in synthetically useful selectivities, we sought to examine the effects of backbone architecture (Table 2). Unsaturation present in the cyclohexyl ring has little effect on the selectivity or efficiency

of the reaction. Super-Hydride reduction of cyclohexenyl keto acid **11** provides the corresponding *anti* product as a 75:25 mixture, while silane reduction favors the *syn* product **13** (90:10) (entry 1). Tetrasubstituted olefin-containing keto acid **14** and benzofused oxoacid **17** undergo smooth reduction under both conditions supplying each respective isomeric lactone in slightly elevated selectivity (entries 2 and 3). Keto acids bearing bicyclic [2.2.1] and [2.2.2] backbones also efficiently participate in the reaction manifold. Upon reduction with the silane system, saturated and unsaturated bicyclic keto acids **20, 23, 26,** and **29** afford the expected *syn* lactones in uniformly high yield and selectivity. Submission of bicyclic keto acids to Super-Hydride reduction provides the corresponding lactones in lower selectivity. Saturated bicyclic keto acids **20** and **26** provide the *anti* lactones **21** and **27** preferentially, albeit in moderate selectivity (entries 4 and 6). Lithium trialkylborohydride reduction of unsaturated bicylic ketones **23** and **29** provides the corresponding lactones in nearly a 1:1 diastereomeric ratio (entries 5 and 7). We attribute this effect to the presence of the *endo* hydrogen atoms in the saturated substrates that provide a steric bias not present in the unsaturated analogues. Finally, submission of the acyclic δ-keto acid **32** to silane reduction fails to yield any reduced product, while Super-Hydride affords the product δ-lactone in good yield slightly favoring the formation of the *syn* diastereomer **34** (entry 8).

Table 2.

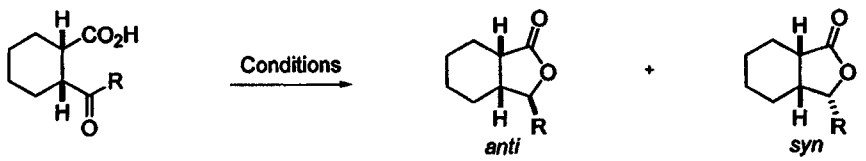


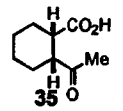
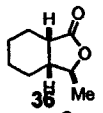
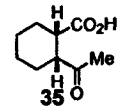
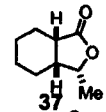
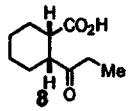
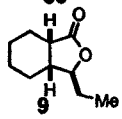
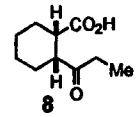
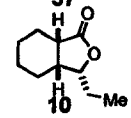
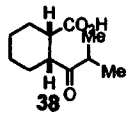
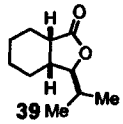
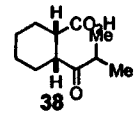
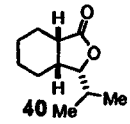
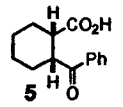
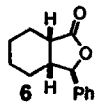
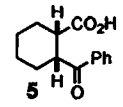
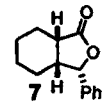
Entry	Substrate	Product	Conditions[a,b]	Yield (%)[c]	*anti* : *syn*[d]
1	 **11**	 *anti* **12** *syn* **13**	Et_3BHLi $PhMe_2SiH$	94 88	79 : 21 10 : 90
2	 **14**	 *anti* **15** *syn* **16**	Et_3BHLi $PhMe_2SiH$	87 75	81 : 19 7 : 93
3	 **17**	 *anti* **18** *syn* **19**	Et_3BHLi $PhMe_2SiH$	92 82	79 : 21 8 : 92
4	 **20**	 *anti* **21** *syn* **22**	Et_3BHLi $PhMe_2SiH$	88 87	75 : 25 5 : >95
5	 **23**	 *anti* **24** *syn* **25**	Et_3BHLi $PhMe_2SiH$	83 82	53 :47 5 : >95
6	 **26**	 *anti* **27** *syn* **28**	Et_3BHLi $PhMe_2SiH$	90 94	62 : 38 5 : >95
7	 **29**	 *anti* **30** *syn* **31**	Et_3BHLi $PhMe_2SiH$	87 91	47 : 53 5 : >95
8	 **32**	 *anti* **33** *syn* **34**	Et_3BHLi $PhMe_2SiH$	77 NR	55 : 45 –

[a]Reaction conducted in the presense of 2.4 equiv of Et_3BHLi in THF from -78 °C to ambient temperature for 4h. [b]Reaction conducted in the presence of 1.2 equiv of $PhMe_2SiH$ in 3:1 CH_2Cl_2/TFA from 0 °C to ambient temperature for 14h. [c]Isolated yield. [d]Diastereomeric ratios determined by NMR or GC.

Having examined the substrate scope with respect to the keto acid backbone, we focused our attention on the effect the ketone substituent may have on the course of the reaction (Table 3). Methyl keto acid **35** provides the corresponding *anti* lactone **36** when subjected to Super-Hydride in modest yield and selectivity. Silane reduction of **35** efficiently provides the complementary *syn* lactone **37** in >95:5 selectivity (entry 1). Branched ketones, namely *iso*-propyl oxo acid **38**, proficiently afford each respective lactone in excellent yield and high diastereoselectivity (entry 3). Aromatic ketones also participate in the reaction. Phenyl keto acid **5** undergoes a highly selective reduction under Super-Hydride conditions supplying the *anti* lactone **6** in superb yield.[10c] Unfortunately, when keto acid **5** is reduced with the $PhMe_2SiH$/TFA system, the product lactone is produced as a 1:1 mixture of diastereomers. We attribute the low selectivity to an epimerization event of the benzylic stereocenter under the acidic reaction conditions that presumably proceeds via an S_N1-type ionization pathway.[17] In an attempt to suppress the epimerization of phenyl ketone **5** under the reaction conditions, several different acids of a slightly lower pKa were examined (AcOH and Cl_2CHCO_2H); unfortunately, these modifications failed to provide product.

Table 3.



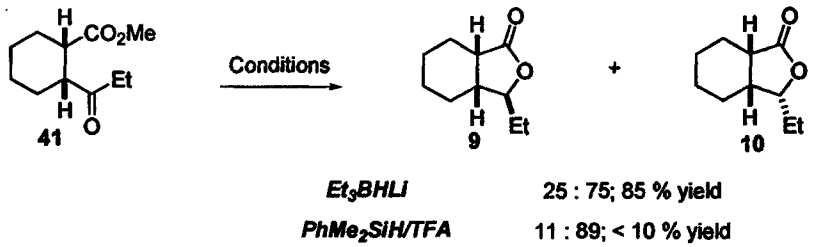
		Et_3BHLi				$PhMe_2SiH/TFA$	
Substrate	Product	Yield (%)[a]	*anti* : *syn*[b]	Substrate	Product	Yield (%)[a]	*anti* : *syn*[b]
		75	86 :14			82	5 : >95
		83	85 : 15			90	7 : 93
		85	95 : 5[c]			78	8 : 92[c]
		83	>95 : 5			91	50 : 50

[a]Isolated yields. [b]Diastereomeric ratios determined by NMR of crude lactone. [c]Diastereomeric ratio determined by GC.

To this point all of the reductions had been performed on keto acid derivatives. Although we reasoned that the carboxylic acid was acting as a directing or activating group in light of the low selectivity and reactivity of acyclic keto acids (*vide infra*), we could not rule out simple conformational effects being responsible for the observed results. In order to delineate between these two possibilities, keto ester **41** was subjected to each of the respective reaction conditions (eq. 1). Super-Hydride reduction of methyl ester **41** provided an 85% yield of a 75:25 mixture of isomeric lactones favoring *syn* lactone **10**. Clearly, the formation of the lithium carboxylate under the reaction conditions plays a crucial role in the stereochemical course of hydride delivery to keto acids. The acid functionality also plays a fundamental role in the silane reduction process. Subjection of keto ester **41** to standard reaction conditions provides a 89:11

mixture of lactones favoring *syn* **10**, but in dramatically reduced yield. These results suggest that the carboxylic acid is acting as an activating group, facilitating the efficient reduction of the ketone presumably via an intramolecular coordination event.

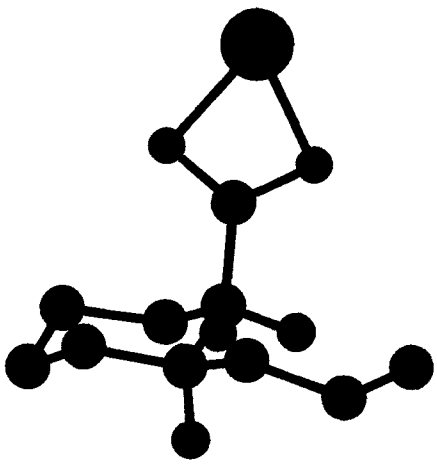
Scheme 4.



In light of the dramatic influence imparted by the carboxylic acid functionality on the selectivity of the reaction, we propose two tentative stereochemical models that fit our observations (Figure 1). Reaction of methyl ester **41** with Super-Hydride supplies the same diastereomer as the silane reduction, suggesting that the intermediate lithium carboxylate formed in the reduction of keto acids plays a crucial role in substrate preorganization. The lithium carboxylate was modeled with the aide of SPARTAN (PM3) molecular mechanics calculations. The lowest energy conformer was shown to be **C**, in which one face of the carbonyl is effectively shielded by the bulky carboxylate favoring hydride delivery from the sterically more accessible *pro-S* face. Reduction via **C** results in the formation of the experimentally observed *anti* lactone product. The stereochemical course of silane reduction is the same whether the ester or acid is used as the substrate. The protonated keto acid was modeled and conformation **D** shown to be the most stable, in which the ketone participates in a hydrogen bonding interaction with the pendant acid functionality. Conformation **D** not only explains the stereochemical course of the reaction, with reduction occurring from the more sterically accessible *pro-R*

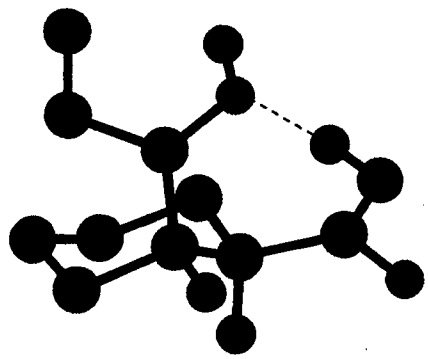
carbonyl π-face, but also suggests that the intramolecular hydrogen bond is responsible for the activation of keto acid substrate.

Figure 1.



C

Super-Hydride Reduction



D

Silane Reduction

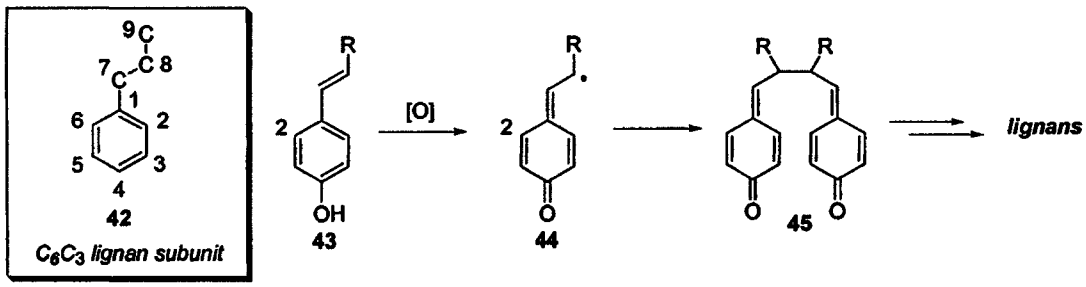
In conclusion, we have identified a set of complementary reducing conditions to afford either diastereomer of trisubstituted lactone starting from the γ-keto acids bearing cyclic backbones. We observe increased selectivity with increasing steric bulk on the ketone. We further note that the carboxylic acid functionality is a key element of this reaction controlling facial selectivity in Et_3BHLi reductions and affecting reactivity in silane reductions.

3.3 Synthesis of Lignan Natural Products

The lignan family of natural products encompasses a large number of diverse members.[18] Lignans share a carbon skeleton that is derived from the linking of C_6C_3 units exemplified by **42**, which arise biogenetically through the shikimate pathway (Figure 2).[19] The term lignan implies structures consisting of two **42** units linked at the C8-C8' position as in **45**, which presumably arises from the coupling of two radicals **44**

derived from the oxidation of two oxygenated cinnamyl precursors (**43**). Almost all examples of lignan natural products contain highly oxygenated aromatic rings which may be necessary to stabilize the proposed radical intermediates in the biosynthetic pathway. Lignans are plant-derived natural products generally present in woody tissue and are believed to be responsible for the use of these plant sources in traditional Japanese and Chinese folk medicine. This class of natural products have been shown to possess a diverse range of biological activity including antiviral, immunosuppressive, anticancer, and antifungal properties. In light of their diverse biological activity and interesting structural features, the lignans have been attractive targets for synthesis.[20]

Figure 2.

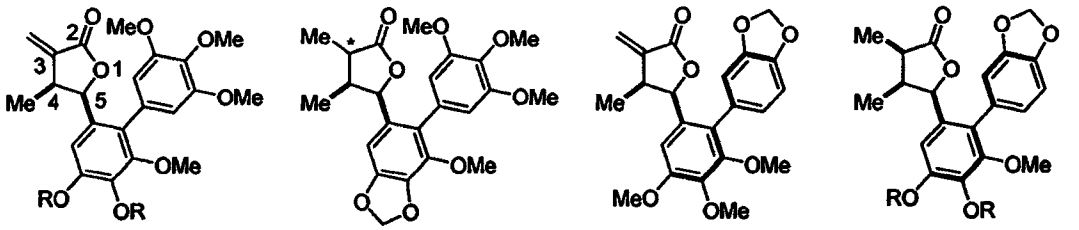


3.3.1 The Eupomatilones

Isolated in 1991 by Carroll and Taylor from Australian shrub *Eupomatia bennettii*, the eupomatilones are a structurally unique subset of the broader lignan family.[21] The eupomatilones are characterized by a tri-substituted γ-butyrolactone core that bears a biaryl moiety at the γ-postion of the lactone representing a novel class of lignan natural products (Figure 3). The biaryl portion of the eupomatilones represents an additional stereochemical element in cases where the second aromatic ring is not C_2-symmetric (eupomatilones 5-7). Rotation about the biaryl bond is slow and each respective diastereomeric atropisomer can be observed by ^1H and ^{13}C NMR. The non-

seperable biaryl atropisomers readily equilibrate at room temperature, existing as a 1:1 diastereomeric mixture. Although it has been shown that many members of lignan family exhibit biological activity, none has been reported for the eupomatilones.

Figure 3.



R, R = -CH_2- eupo-1 (46)
R, R = CH_3 eupo-2 (47)

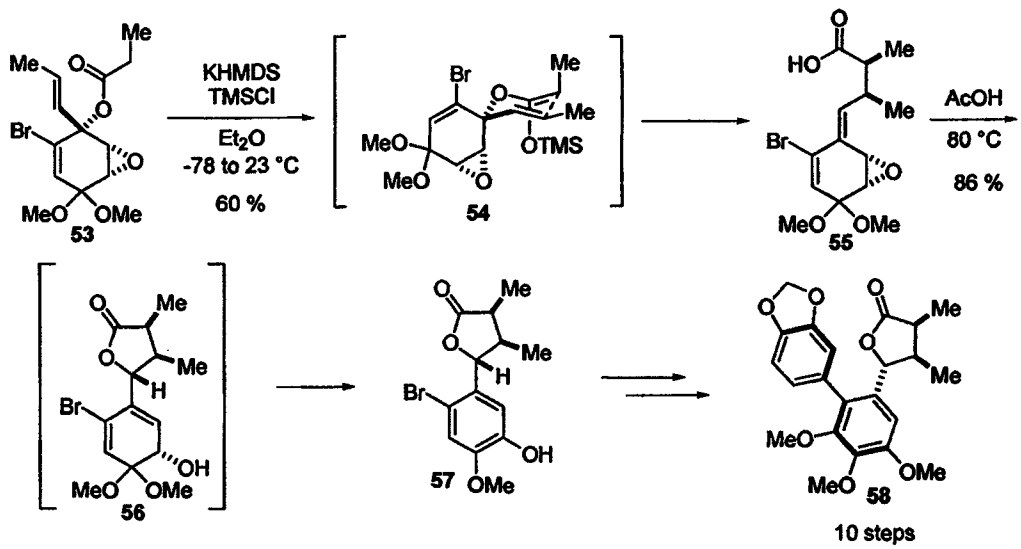
eupo-3 (α-48)
eupo-4 (β-49)

eupo-5 (50)

R, R = -CH_2- eupo-6 (51)
R, R = CH_3 eupo-7 (52)

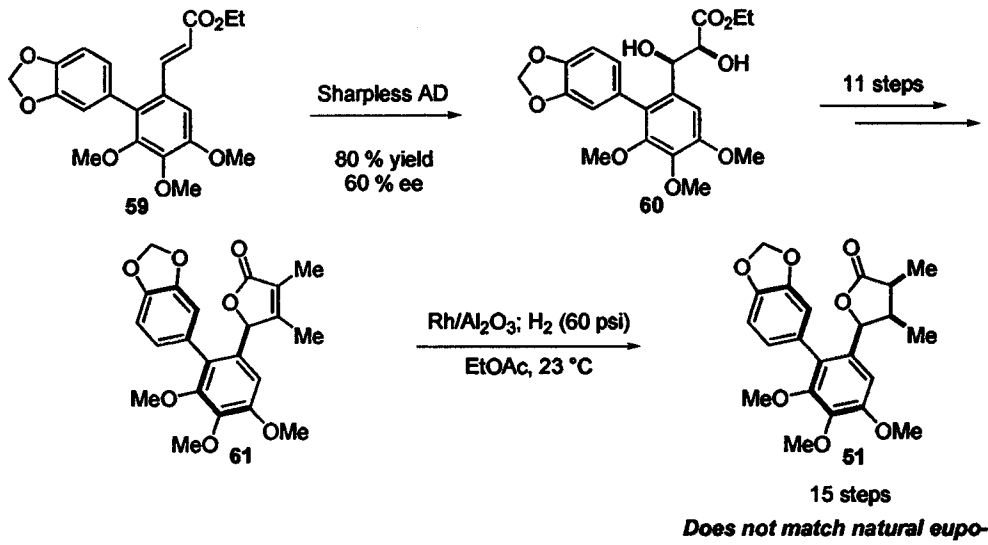
At the time we initiated our studies directed toward the total synthesis of the eupomatilones, no reports of approaches to this class of molecules had been reported; however, during the course of our studies several reports detailing the synthesis of members of this family of natural products have appeared. McIntosh and co-workers were the first to describe an approach to the eupomatilones culminating in the synthesis of 5-*epi*-eupomatilone-6 **58**.[22] Utilizing an Ireland-Claisen rearrangement to set the two *syn* methyl groups in the backbone of the lactone, epoxy ester **53** was treated with strong base in the presence TMSCl to afford the silyl enol ether **54** which upon rearrangement via a chair transition state provides carboxylic acid **55** as a single isomer. Having set the proper relative stereochemistry of the two backbone methyl groups with a 3,3-sigmatropic rearrangement, the lactone core was assembled via an intramolecular S_N2' cyclization of allylic epoxide **55** which upon aromatization provides γ-lactone **57**. The synthesis was completed with the installation of the biaryl in subsequent steps constituting a 10-step synthesis of 5-*epi*-eupomatilone-6 **58**. Extensive effort was expended trying to epimerize the 5-position, but unfortunately all attempts failed.

Scheme 5.



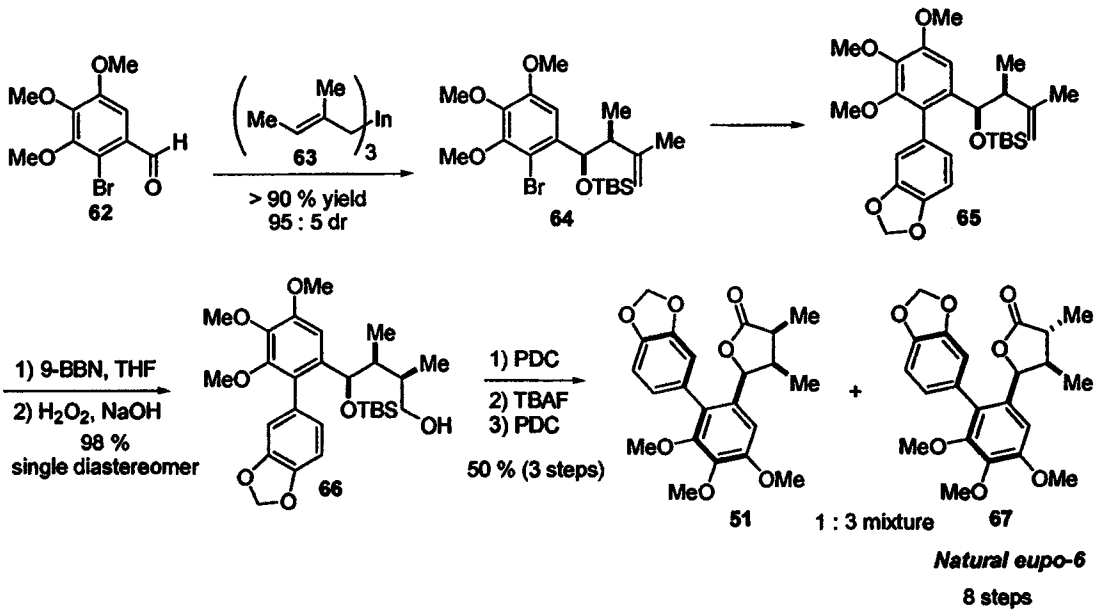
The first synthesis of the proposed structure of eupomatilone-6 (**51**) was reported by Gurjar and co-workers (Scheme 6).[23] Taking advantage of a Sharpless asymmetric dihydroxylation, unsaturated ester **59** was dihydroxylated providing diol **60** in 80 % yield and 60 % enantiomeric excess. Conversion of chiral diol **60** to the unsaturated lactone **61** was accomplished in 11 steps, setting the stage for hydrogenation. In the event, catalytic hydrogenation of **61** provided the all *syn* lactone **51** in 60 % yield comprising a 15 step synthesis of the proposed structure of eupomatilone-6 **51**. Interestingly, the compound **51** did not match the data presented for natural eupomatilone-6. The authors reasoned, based on the previous work by McInthosh, that the true structure of eupomatilone-6 is epimeric at C3 or C4.

Scheme 6.



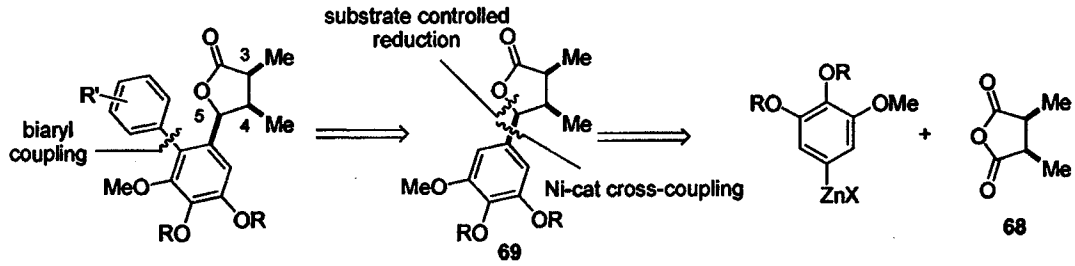
Recently, Coleman and co-workers reported the synthesis of eupomatilone-4 (**49**) and eupomatilone-6 (**67**) which culminated in the structural revision of the latter.[24] Coleman's approach to the C3-C4-C5 stereochemistry relied on a diastereocontrolled hydroboration/oxidation sequence. Crotylation of aldehyde **62** with the corresponding indium reagent **63** provided the product **64** in excellent yield and selectivity. With the relative configuration of C4-C5 set, the biaryl moiety was installed via a copper-mediated process providing **65**. Hydroboration/oxidation of **65** proceeded smoothly supplying primary alcohol **66** as a single diastereomer. Oxidation of **66** with PDC followed by silyl group cleavage provided the corresponding lactol that was again treated with PDC affording a 1:3 mixture of α-epimers **51** and **67**. Following separation, **67** was found to match natural eupomatilone-6 instead of the originally proposed all *syn* lactone **51** representing a concise 8-step synthesis of the target molecule.

Scheme 7.



We envisioned a relatively general approach to the eupomatilones utilizing our nickel-catalyzed anhydride cross-coupling reaction. We reasoned that the *syn* dimethyl relationship present in the lactone backbone could be set in a relative sense by the coupling of the appropriately substituted diarylzinc reagent and *meso*-dimethyl succinic anhydride **68** (Scheme 8). Diastereoselective substrate-controlled reduction of the resulting keto acid followed by cyclization would provide the desired all *syn* lactone **69**. Late stage biaryl installation via a halogenation/cross-coupling sequence would then provide ready access to the eupomatilone family of natural products. We felt our route would offer several advantages including rapid assembly of the stereochemically complex core and structural flexibility involving a cassette-like approach, in which each respective aromatic ring can be easily modified.

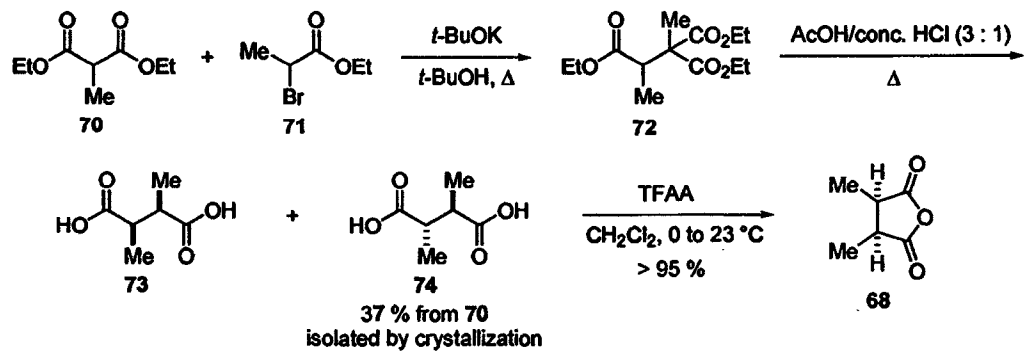
Scheme 8.



3.3.2 Synthesis of Eupomatilones 4, 6, and 7

Our initial studies were focused on the assembly of the requisite keto acid precursor assembled from the cross-coupling of *meso*-dimethylsuccinic anhydride **68** and the appropriate zinc reagent. Although *meso*-dimethylsuccinic acid **68** is commercially available, due to its cost we chose to synthesize it via a modified literature procedure (Scheme 9). Diethylmethyl malonate **70** was treated with bromopropionate **71** in the presence of potassium *tert*-butoxide to provide triester **72**. Hydrolysis and decarboxylation of triester **72** was accomplished by treatment with concentrated HCl and AcOH, providing a mixture of *meso*- and *d,l*-dimethylsuccinic anhydride.[25] *meso*-Dimethylsuccinic acid **74** is isolated by crystallization from the reaction mixture supplying **74** in 37 % overall yield from malonate **70** with no chromatography. Diacid **74** is then dehydrated by treatment with TFAA (trifluoroacetic anhydride) in CH_2Cl_2

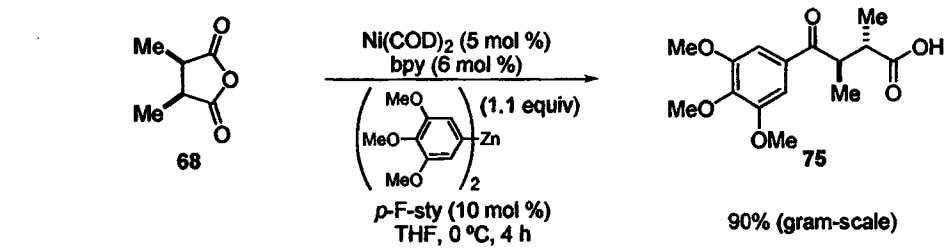
Scheme 9.



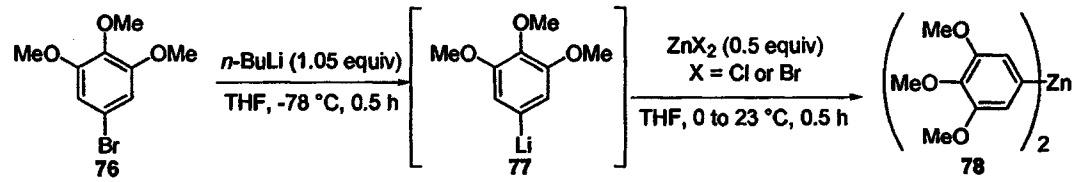
followed by distillation, affording *meso*-dimethylsuccinic anhydride **68** in excellent yield.

With an efficient synthesis of the anhydride starting material in hand we were able to examine the nickel-catalyzed cross-coupling of functionalized aromatic nucleophiles (Scheme 10). Our preliminary efforts were focused on the synthesis of the putative structure of eupomatilone-6 (**51**). At the time we started our efforts to apply the nickel cross-coupling reaction, organozinc reagents prepared from the reaction of organolithium compounds and zinc salts had not been used. Preparation of the requisite diarylzinc reagent was accomplished by treatment of commercially available aryl bromide **76** with *n*-BuLi, generating the aryl lithium species **77** *in situ*. Quenching of **77** with 0.5 equiv of halozinc salt (either $ZnCl_2$ or $ZnBr_2$) provides the desired diarylzinc reagent **78**. To our gratification, subjection of the *meso*-dimethylsuccinic anhydride **68** to the prescribed reaction conditions using 5 mol % catalyst loading in the presence of prepared diarylzinc reagent **78** provided the desired keto acid **75** in excellent yield. The reaction is scaleable and has been routinely run on multi-gram scale with a simple acid-base work-up affording analytically pure material.

Scheme 10.

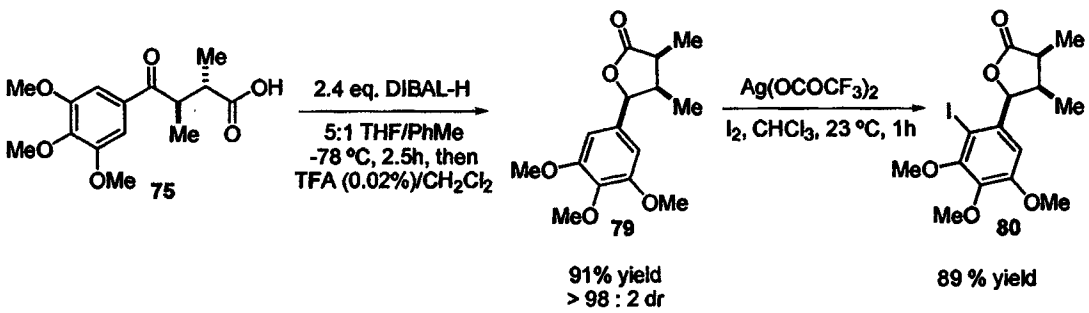


Preparation of zinc reagent



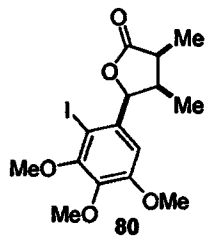
Having established a viable protocol for the preparation of keto acid **75**, we turned our attention to the diastereoselective substrate-controlled reduction. Although we have developed an efficient substrate-controlled diastereoselective reduction of 1,4-keto acids to provide either diastereomer of the product trisubstituted γ-lactones, acyclic derivatives were beyond the scope of the transformation (*vide supra*). We reasoned that perhaps Frenette's protocol would provide ready access to the desired lactone, although this method had not been applied to oxoacids bearing two contiguous stereocenters. In the event, keto acid **75** was treated with 2.4 equiv of DIABL-H at low temperature, followed by cyclization of the intermediate hydroxyl acid under acidic conditions providing the desired all *syn* γ-lactone **79** in excellent yield and selectivity (Scheme 11). Contrary to Frenette's observations, the addition of $ZnCl_2$ to the reaction made no difference in reaction selectivity. Electrophilic halogenation of the electron-rich aromatic lactone **79** was accomplished by treatment with I_2 in the presence of stoichiometric silver salt providing the desired aryl iodide **80** in 89 % yield.

Scheme 11.

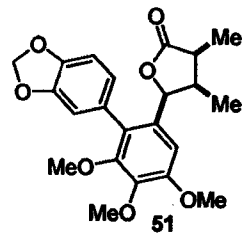


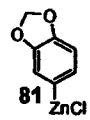
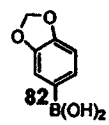
Transition metal catalyzed cross-coupling is the most powerful method for the formation of biaryls.[26] Having established a highly efficient route to the desired electrophilic cross-coupling partner **80**, we investigated the installation of the biaryl moiety (Scheme 12). We reasoned that use of **80** as an electrophilic cross-coupling partner may be a formidable challenge for several reasons: the presence of the lactone functionality may require the use of anhydrous reaction conditions to avoid potential hydrolysis, and the aromatic ring is extremely electron-rich and bears two *ortho*-substituents which may retard oxidative addition to a low-valent metal catalyst. Our initial investigations focused on the use of arylzinc halides as nucleophiles to avoid the use of aqueous reaction conditions. Unfortunately, Negishi cross-coupling conditions[27] failed to provide the desired product in appreciable amounts. The Suzuki cross-coupling is known to be a very effective method for the synthesis of sterically hindered biaryls[28] with the caveat that basic aqueous conditions are generally required. To our gratification, subjection of **80** to the Suzuki protocol using commercially available boronic acid **82** in the presence of catalytic amounts of $Pd(PPh_3)_4$ smoothly provided the desired cross-coupled product **51** in excellent yield. Our approach represents a four-step synthesis of **51** that proceeds in 59 % overall yield with the three stereocenters resident in the γ-lactone core being set in two operations.

Scheme 12.



Conditions →

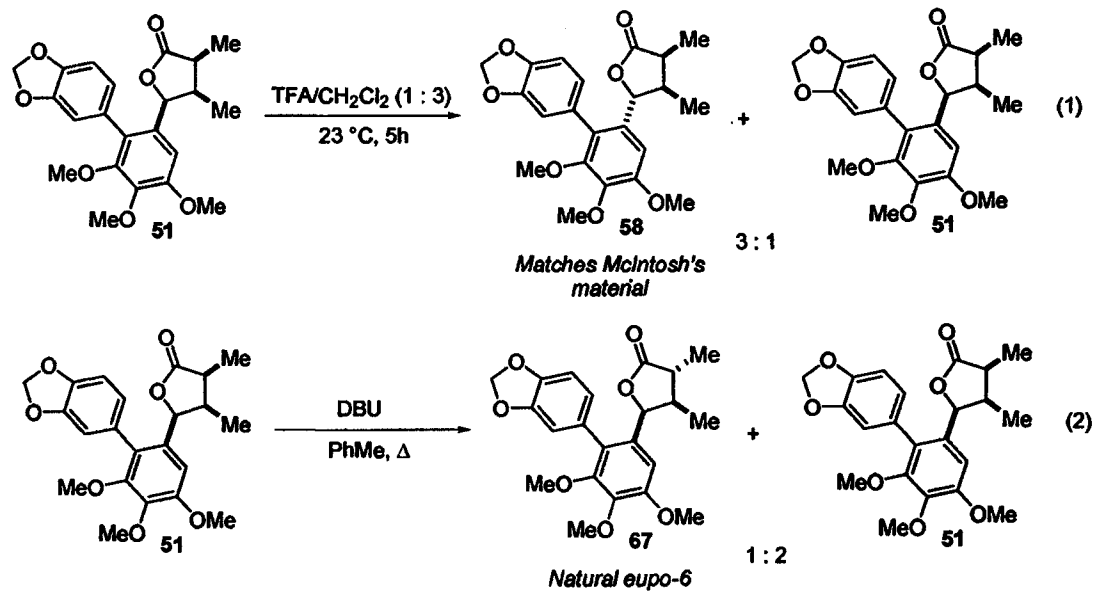


Conditions	Nucleophile	Yield (%)
$Pd(PPh_3)_4$ (10 mol %) THF, 23 °C, 18 h	 81 ZnCl	NR
$Pd(Pt\text{-}Bu_3)_2$ (10 mol %) THF/NMP, 23 to 100 °C, 18h		trace
$Pd(PPh_3)_4$ (7 mol %) $NaHCO_3$, DME/H_2O (10 : 1) Δ, 18h	 82 $B(OH)_2$	87

It was quickly realized that compound **51** did not match natural eupomatilone-6 and we initiated studies directed at the elucidation of the true structure of the natural material. In order to determine whether or not we had obtained the proper structure we carried out extensive NMR studies, all of which supported our initial structural assignment. Compound **51** was then subjected to conditions known to epimerize the 5-position of the lactone core (TFA/CH_2Cl_2) in order to compare the material obtained with McIntosh's ultimate product **58** which at the time was the only published report of the synthesis of eupomatilone-type products. The material obtained by treatment of **51** under acidic conditions matched the material that McIntosh had reported (Scheme 13, eq. 1). Interestingly, in the purified sample of **51** an impurity that was present in small amounts (< 5%) seemed to match natural eupomatilone-6. We reasoned that natural eupomatilone-6 could potentially be the α-epimer of **51** which could be obtained by minor epimerization of the α-position under the weakly basic conditions used in the Suzuki cross-coupling reaction. In order to test this theory, lactone **51** was subjected to

DBU in hot toluene providing a 2:1 mixture of 3-*epi*-eupomatilone-6 **51** and natural eupomatilone **67**, confirming the findings of Coleman (Scheme 13, eq. 2).

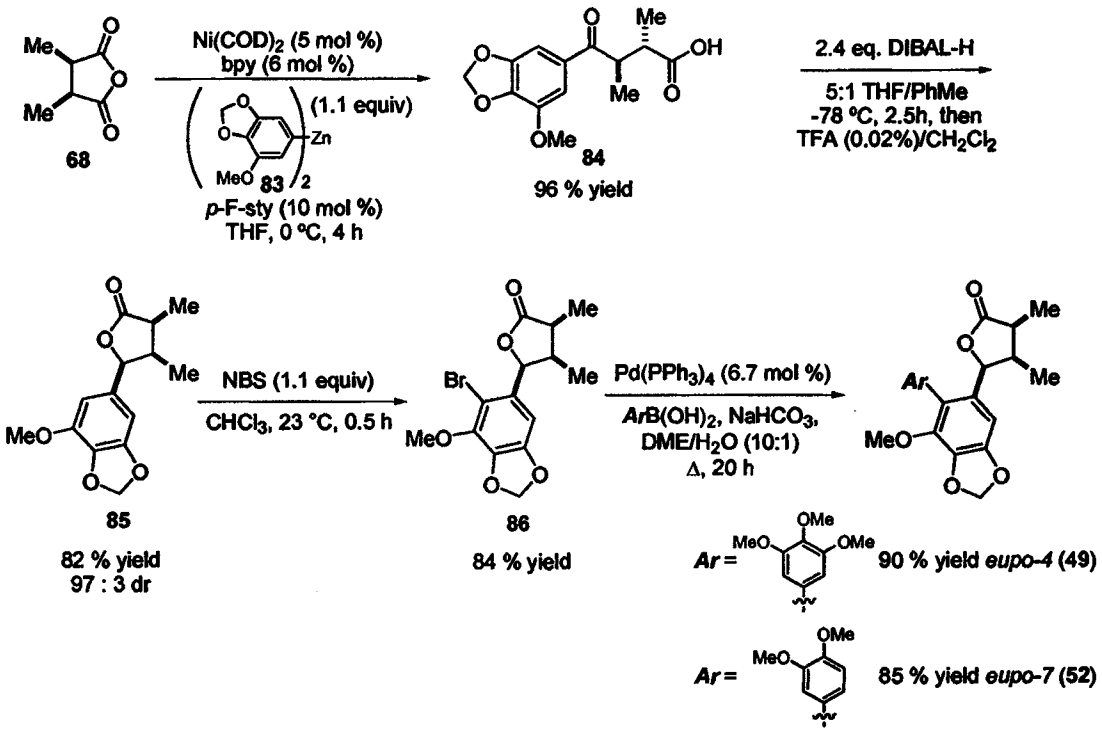
Scheme 13.



Concurrent with our work toward the synthesis of eupomatilone-6 we examined the preparation of other members of the family. We envisioned a route to eupomatilones 4 and 7 (**49** and **52**, Figure 3) that would take advantage of a common intermediate, the *syn* lactone core as the electrophilic cross-coupling partner. Upon coupling with each respective boronic acid, this route would provide access to each target. Utilizing the strategy implemented for the synthesis of 3-*epi*-eupomatilone-6, *meso*-dimethylsuccinic anhydride **68** was cross-coupled with the diarylzinc reagent **83** in 96 % yield (Scheme 14). The diastereoselective reduction of keto acid **84** with DIBAL-H proceeded uneventfully to supply the desired all *syn* lactone **85** in 82 % yield and a 97:3 diastereomeric ratio. Halogenation of the electron-rich aromatic **85** was accomplished by treatment with NBS in $CHCl_3$ at room temperature efficiently providing aryl bromide **86** as the exclusive regioisomer.[29] Cross-coupling of **86** under standard Suzuki protocol

with the trimethoxyaryl boronic acid affords eupomatilone-4 **49** in 85 % isolated yield. Likewise, coupling of **86** with dimethoxyaryl boronic acid gives eupomatilone-7 **52** in 90 % yield. Both natural products proved to match the reported data for the respective authentic samples.

Scheme 14.



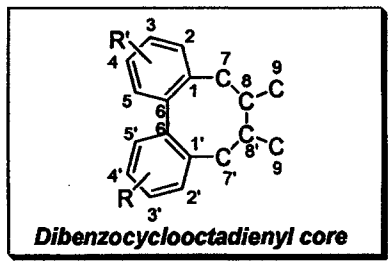
The nickel-catalyzed cross-coupling of meso cyclic anhydrides and diorganozinc regents has been successfully applied to the synthesis of several members of the eupomatilone family of lignan natural products. The devised synthesis is concise, consisting of four-synthetic steps in which three stereocenters are set with virtually complete control proceeding in over 50 % yield over all steps for each target molecule. The synthetic route is very flexible, taking advantage of a cassette approach which allows easy manipulation of the biaryl portion of the eupomatilones. We sought to expand the

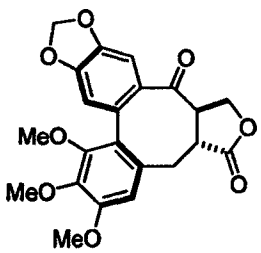
general strategy used in the eupomatilone scheme to other related natural products that contain some of the same stereochemical elements.

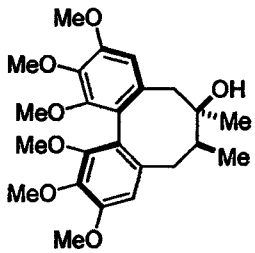
3.3.3 Dibenzocyclooctadiene Lignans

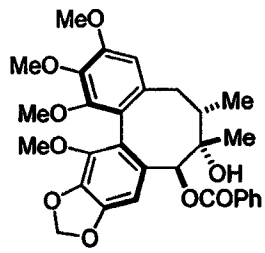
The dibenzocyclooctadiene (DBC) lignans are a sub-class of the broader lignan family of natural products typified by the presence of an eight-membered ring bearing substituents at the C8-C8'carbons containing a fused electron-rich biphenyl moiety (Figure 4). The biaryl component is highly oxygenated, and the eight-membered ring possesses a variety of functionality and stereochemical relationships. Members also contain an additional stereochemical element in the form of axial chirality present in the biaryl. There have been over 50 DBC lignans identified to date isolated from a variety of plant sources native to East Asia.[30] Due to their unique structure and biological activity, the DBC lignans have been attractive targets for total synthesis.[31]

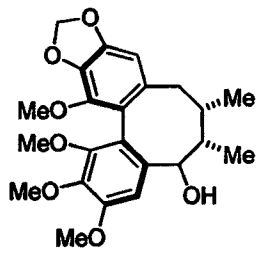
Figure 4.




stegnone (**87**)

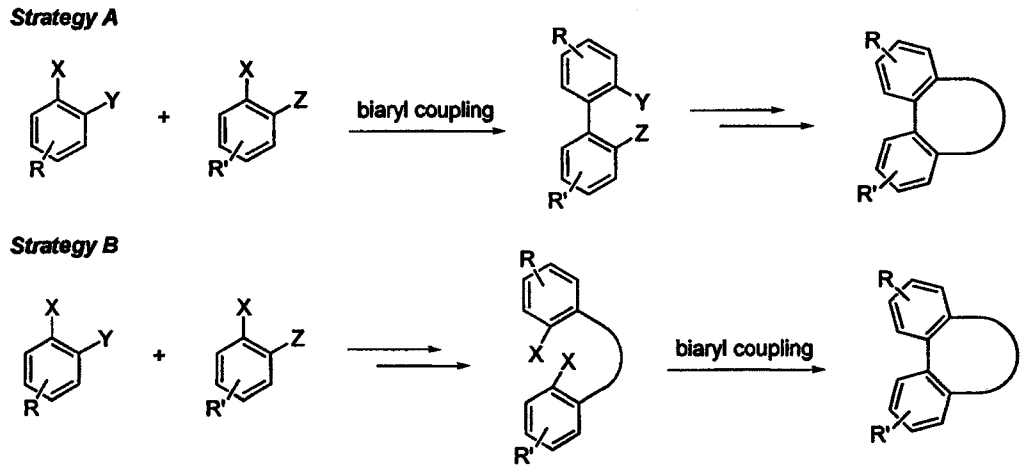

isoschizandrin (**88**)


gomisin G (**89**)


epigomisin O (α-OH; **90**)
gomisin O (β-OH; **91**)

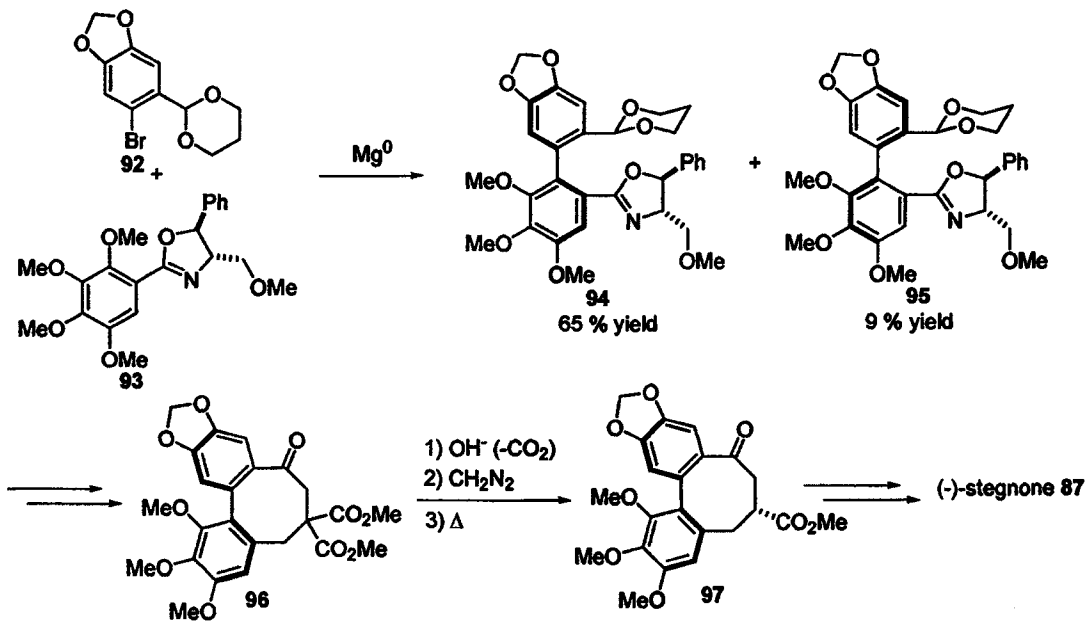
The approaches to the DBC lignans can be loosely grouped according to the strategy used for the assembly of the core (Figure 5). Strategy A consists of assembly of the biaryl followed by closure of the medium ring by making a C-C bond. The second tactic that has been exploited involves construction of the backbone to provide a compound that is then cyclized using a biaryl bond forming event to provide the elaborated core. Both of the aforementioned methods rely on the relay of stereochemical elements present in the cyclization precursor to set the relationship of the resultant cyclic product.

Figure 5.



Isolated by Kupchan in 1973,[32] the antileukemic DBC lignan stegnone **87** has attracted considerable synthetic interest.[33] Meyers and co-workers[34] reported an asymmetric total synthesis of stegnone **87** using strategy A, in which they took advantage of an axially chiral biaryl precursor to construct the eight-membered ring (Scheme 15). The chiral biphenyl was constructed via a nucleophilic aromatic substitution using Meyers' chiral oxazoline methodology[35] in which aryl bromide **92** was treated sequentially with magnesium metal and then oxazoline **93** providing a mixture of chiral biaryls **94** and **95** favoring the biphenyl possessing the desired stereochemistry. After several operations the eight-membered ring was assembled providing **96**, which was subjected to a hydrolysis/decarboxylation furnishing the intermediate acid. Esterification by treatment with diazomethane provides **97** which was then advanced to (-)-stegnone **87**. Unfortunately, the product was isolated in 80 % ee indicating that the biaryl had undergone some epimerization during the synthesis.

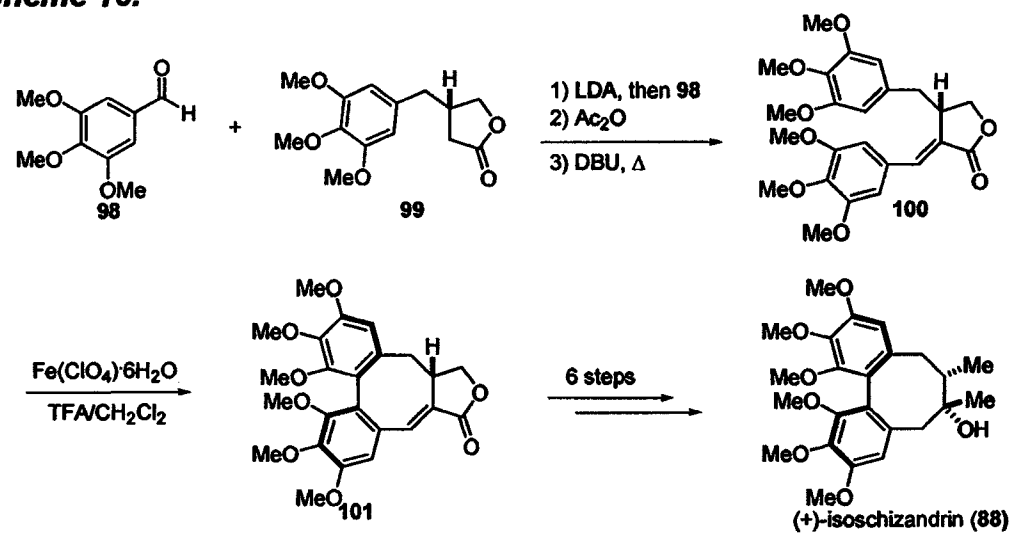
Scheme 15.



DBC natural products that do not possess the fused lactone moiety present in the backbone have received less attention from the synthetic community.[36] One potential reason for the lack of approaches to these molecules could be the difficulty in controlling the relative stereochemistry of the two or three contiguous stereocenters resident in the eight-membered ring. Tanaka and co-workers[37] reported the synthesis of (+)-isoschizandrin **88** along with other related natural products utilizing a route falling under strategy B (Scheme 16). The synthesis of the biaryl coupling precursor was accomplished by subjection of chiral lactone **99** to a stepwise aldol condensation with aldehyde **98** to provide biaryl coupling precursor **100**. Oxidative biaryl coupling[38] of **100** using $Fe(ClO_4)_3$ in acidic medium efficiently provides the desired compound **101** as a single diastereomer. Six additional steps, many of which show little or no selectivity, are required to transform lactone **101** into the target molecule **88**. Although this route is very powerful in setting the proper atropisomer, it suffers from a cumbersome endgame

requiring multiple synthetic manipulations to convert the cyclic lactone to the natural product.

Scheme 16.

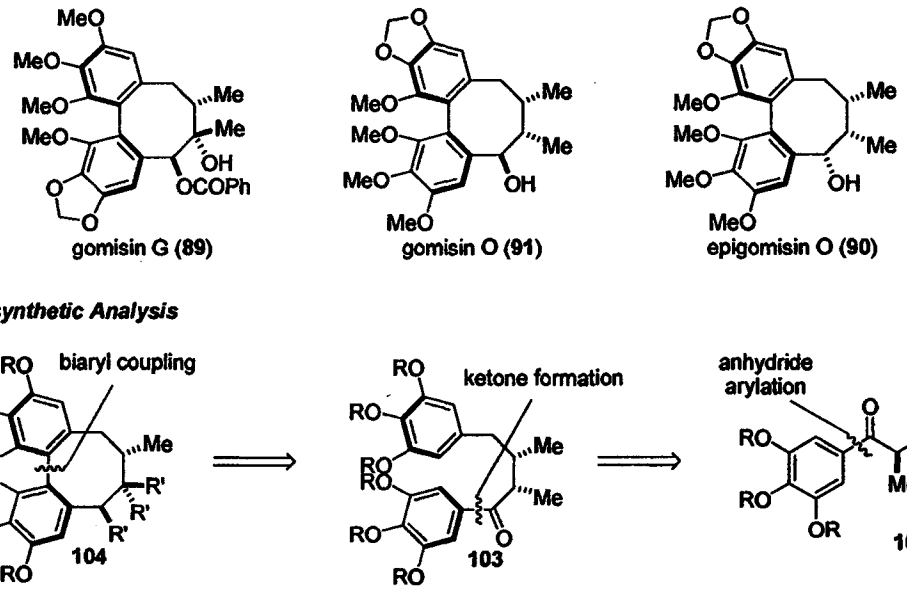


3.3.4 Synthetic Plan

Our approach to the DBC lignans centered on the use of our anhydride cross-coupling methodology which we felt would offer an expedient, flexible, and general approach to this class of molecules. Three targets were initially chosen, gomisins G (**89**) and O (**91**) as well as epigomisin O (**90**). We envisioned an approach that would apply strategy B in which a stereodefined acylic precursor would be used to assemble the eight-membered ring with simultaneous formation and control of the fused biaryl. We reasoned that the adjacent stereogenic methyl groups present in the backbone of many DBC natural products could potentially arise from *meso*-dimethylsuccinic anhydride. Exploiting an approach similar to the one employed for the synthesis of the related eupomatilone family, the nickel-mediated anhydride arylation would provide keto acids of type **102** (Scheme 17). With access to oxoacids **102** already established, reduction of the ketone functionality followed by manipulation of the carboxylic acid would supply

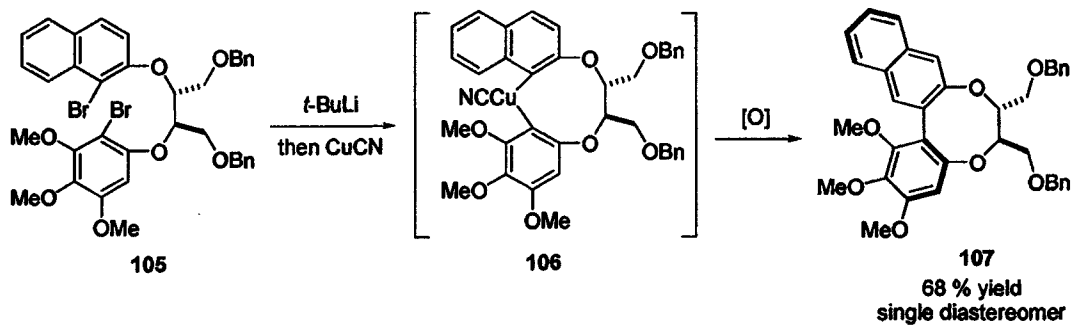
ketone **103**. Biaryl coupling of **103** should provide the DBC core which upon limited synthetic manipulations would afford the desired target molecules.

Scheme 17.



All of the approaches to DBC lignans relying on control of biaryl stereochemistry via relay from the backbone (strategy B) have almost exclusively used cyclic precursors, with few exceptions.[39,40] Command of atropisomerisim by the cyclization of *acyclic* precursors containing stereochemistry in the skeleton is known. Lipshutz and co-workers[41] have reported a biaryl coupling whose stereochemical outcome is completely controlled by the stereochemistry present in the bridging group (Scheme 18).[42] Treatment of diaryl bromide **105** with 4 equiv of *t*-BuLi provides the intermediate diaryl lithium that is treated with CuCN to provide the intermediate higher order cuprate **106**. Oxidation of **106** with molecular oxygen supplies the desired coupled product **107** as a single diastereomer. In light of this example, we reasoned that the stereoselective synthesis of the desired biaryl via cyclization of a stereochemically defined acylic precursor should be a viable entry to the DBC core.

Scheme 18.

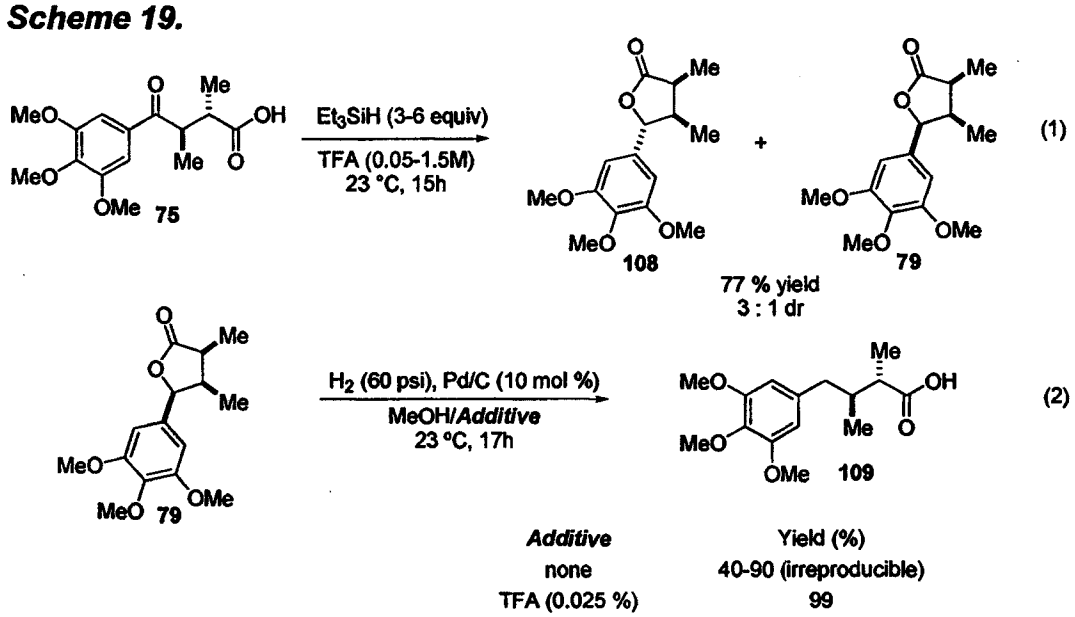


3.3.5 Toward the Synthesis of Gomisin G

Our initial objective toward the total synthesis of gomisin G (**89**) was the synthesis of the ketone biaryl coupling precursor of type **103** (Scheme 17) bearing the requisite substitution patterns on the aromatic rings and carbon skeleton. Toward this goal, the reduction of the aromatic ketone **75** (prepared as previously described) possessing a potentially labile α-stereocenter was investigated (Scheme 19). Unfortunately, subjection of ketone **75** to conditions known to fully reduce aromatic ketones (TFA/Et_3SiH)[43] only provided the corresponding lactones **108** and **79** as a 3:1 mixture of diastereomers at the benzylic position (Scheme 19, eq. 1). We reasoned that the benzylic C-O bond in lactone **79**, which was used in the synthesis of the eupomatilones, should undergo reduction when subjected to catalytic hydrogenolysis thereby providing a mild reduction method that would preserve the stereocenter adjacent to the carbonyl functionality. In the event, lactone **79** was treated with H_2 (60 psi) in the presence of palladium on carbon in MeOH smoothly providing the desired carboxylic acid **109** in excellent yield (Scheme 19, eq. 2). To our surprise, it was soon realized that the hydrogenation reaction failed to provide reproducible yields of the desired product. We reasoned that performing the reaction in a slightly acidic medium may render the reaction reproducible by effectively weakening the benzylic C-O bond via protonation of

the lactone carbonyl. It was soon found that the addition TFA rendered the process reliable.

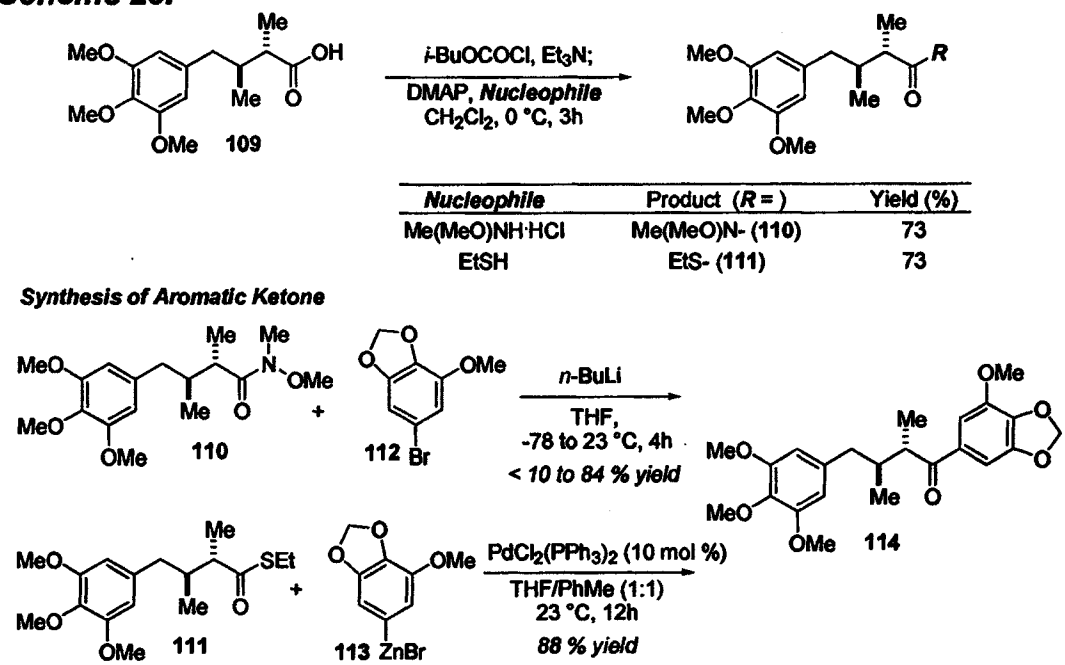
Scheme 19.



With a reliable route to the desired acid derivative in hand we focused on the conversion of **109** to the corresponding aromatic ketone derivative **114** (Scheme 20). Alkylation of so-called Wienreb amides has been shown to be a reliable method for the synthesis of a variety of ketones.[44] Accordingly, carboxylic acid **109** was smoothly converted to the *N,O*-dimethylamide **110** using standard conditions. Amide **110** was then treated with the aryl lithium reagent, derived from the reaction of aryl bromide **112** with *n*-BuLi, to provide the desired aromatic ketone **114**. Although the amide alkylation protocol provided product in some cases, the reaction was erratic with yields ranging from less than 10 % to 84 %. Optimization efforts were met with little success. Transition metal-mediated cross-coupling of activated acyl compounds has been shown to be a mild and efficient method for the preparation of ketones (see Chapter 2). In light of our experience in this field, we examined the cross-coupling of thioesters and arylzinc

reagents as a route to **114**.[45] Treatment of acid **109** with *i*-BuOCOCl in the presence of Et_3N followed by addition of DMAP and EtSH provided the desired thioester **111** in good yield. Subjection of thioester **111** to Fukuyama's cross-coupling conditions in the presence of arylzinc halide **113** afforded aromatic ketone **114** in 88 % yield. In our hands, this cross-coupling reaction has been very reliable, consistently supplying the desired product in good yields even on relatively large scale. Furthermore, there are no special precautions that need to be taken in the preparation of the nucleophilic coupling partner (prepared from the aryl bromide by an identical route to that used in our anhydride arylation protocol).

Scheme 20.

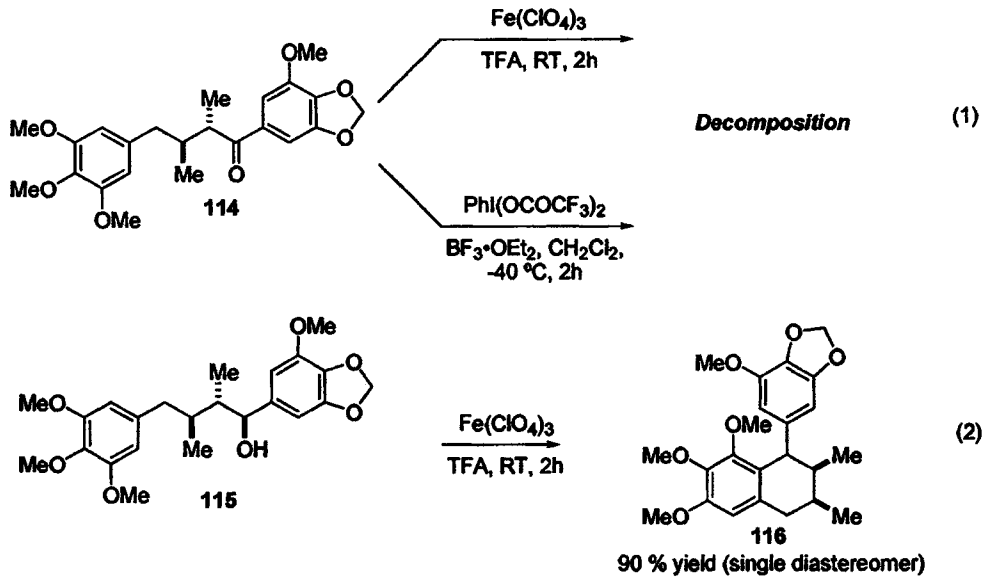


Nucleophile	Product (*R* =)	Yield (%)
Me(MeO)NH·HCl	Me(MeO)N- (110)	73
EtSH	EtS- (111)	73

Having established an efficient and reproducible route to ketone **114**, our attention turned to the realization of a stereoselective biaryl coupling method. Our preliminary efforts focused on the intramolecular oxidative biaryl coupling of ketone **114**. Subjection of aromatic ketone **114** to standard oxidative biaryl coupling conditions using $Fe(ClO_4)_3$

as well as hypervalent iodine reagents[46] resulted in complete consumption of starting material but failed to provide any discernible products after repeated attempts (Scheme 21, eq. 1). We also investigated the oxidative coupling of alcohol **115**, which possess more electronically similar aromatic rings,[47] under the prescribed conditions. Unfortunately, due to the acidic reaction conditions, product **116**, resulting from intramolecular Friedel-Crafts alkylation, was isolated in 90 % yield (Scheme 21, eq. 2). Magnus and co-workers[48] have reported that the presence of heteroatom substitution at the benzylic position of the biaryl coupling precursor results in no formation of the desired product under oxidative conditions.

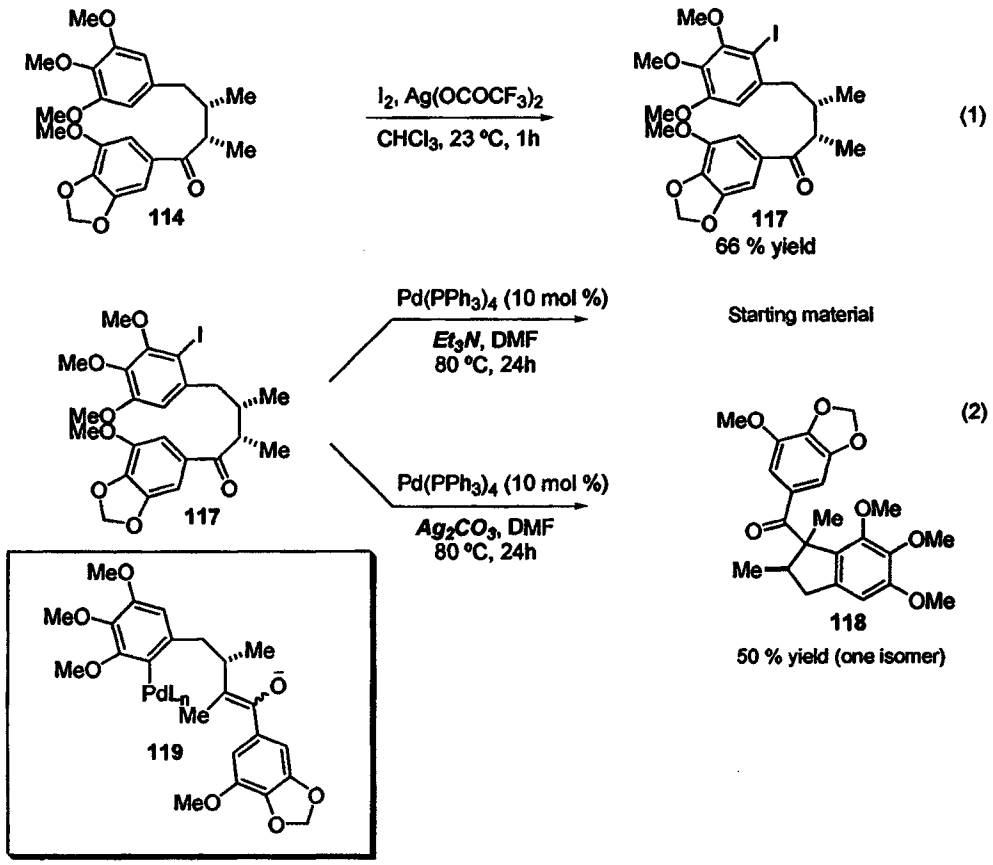
Scheme 21.



Transition metal-catalyzed processes represent extremely powerful tools in the context of biaryl synthesis.[49] Recently, the direct arylation of electron-rich aromatics has been shown to be an effective method for the synthesis of biaryls with concomitant ring formation.[50] We envisioned that the direct arylation of electron-rich aromatics of aryl halides in the presence of a palladium catalyst may provide a facile route to the desired

ring-closed product. Iodination of the more electron-rich aromatic ring of ketone **114** under standard conditions provided the desired biaryl coupling precursor **117** in modest yield (Scheme 22, eq. 1). Treatment of **117** with catalytic amounts of $Pd(PPh_3)_4$ in the presence of an amine base (Et_3N) returned starting material along with trace amounts of the dehalogenated compound **114** (Scheme 22, eq. 2). We speculated that oxidative addition of palladium to the C-I bond was occurring (since some reduced product was observed) but the pendent aromatic ring may not be nucleophilic enough to react with the oxidative addition adduct. In an effort to increase the reactivity of the insertion intermediate, the base was changed to Ag_2CO_3, which is known to facilitate the formation of more reactive cationic palladium intermediates.[51] In the event, aryl iodide **117** was subjected to the prescribed reaction conditions in the presence of the silver base, which provided a 1:1 inseparable mixture of starting material and the unusual product **118**, arising from an intramolecular α-arylation reaction. We believe that the reaction proceeds through intermediate **119**, in which the palladium catalyst inserts into the C-I bond and the enolate (formed from deprotonation with carbonate) collapses, liberating catalyst and producing the observed product. Unfortunately, none of the corresponding biaryl product was observed even if the ketone is reduced and the resultant alcohol protected.

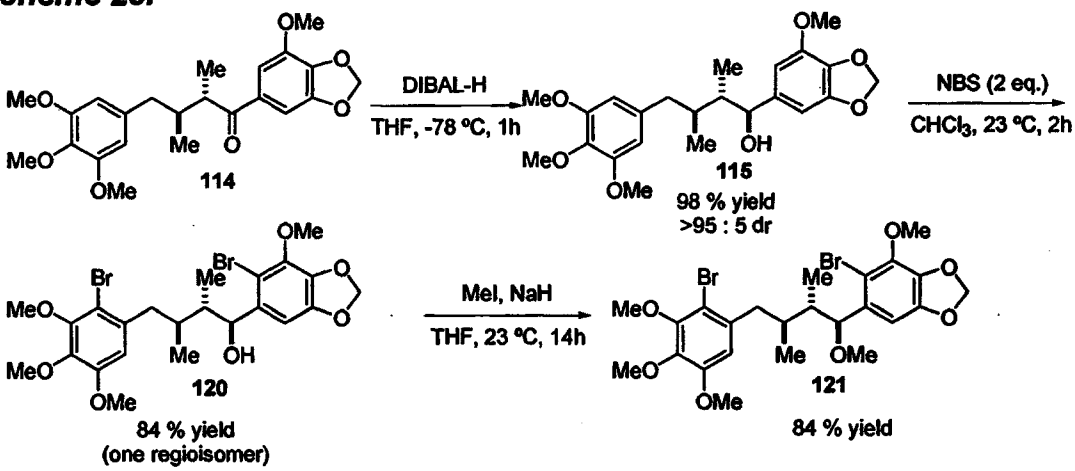
Scheme 22.



In light of both the palladium-catalyzed and oxidative biaryl synthesis failing to provide the desired product we turned our attention to an Ullmann strategy based on the precedent of Lipshutz and co-workers (*vide supra*). Synthesis of the required coupling precursor was carried out starting with ketone **114** (Scheme 23). Reduction of **114** proceeded smoothly in presence of DIBAL-H to provide benzylic alcohol **115** in a > 95:5 ratio favoring the all *syn* product (determined by x-ray crystallography, *vide infra*). Dibromination of **115** was accomplished by stepwise treatment with 2 equiv of NBS in $CHCl_3$ at room temperature supplying **120** in 84 % yield as one regioisomer (although the regioisomeric outcome is precedented,[52] this result was unexpected). With **120** in hand,

the benzylic alcohol was methylated under standard conditions, affording the desired biaryl coupling precursor **121** in excellent yield.

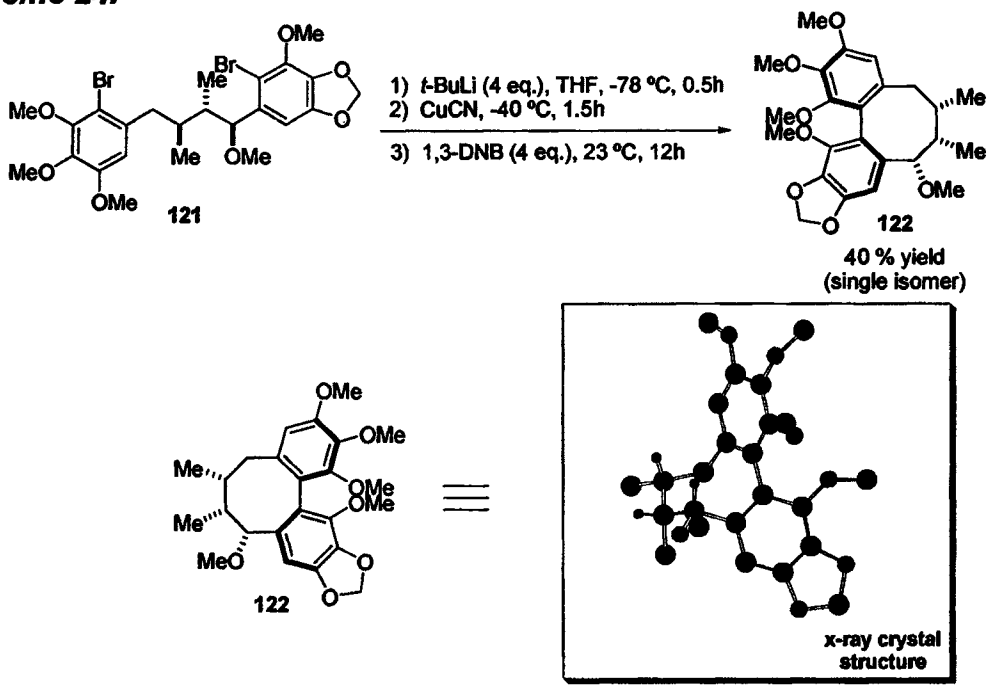
Scheme 23.



With a viable route to diaryl bromide **121** we examined its competence in the biaryl coupling reaction (Scheme 24). Using the Schreiber modification[53] of the Lipshutz protocol, diaryl bromide **121** was treated with four equiv of *t*-BuLi at low temperature followed by the addition of one equiv of CuCN to provide the intermediate higher order cuprate which was then oxidized by the addition of an electron deficient nitro-aromatic. To our gratification, the desired biaryl **122** was isolated in 40 % yield as a single diastereomer. The relative stereochemical configuration was determined by x-ray crystallography and proved to possess the same relative stereochemistry as present in gomisin G.

In order to garner insight into the stereochemical course of the reaction we attempted to determine whether the biaryl product obtained was the thermodynamic or kinetic product. Molecular mechanics calculations performed using SPARTAN (PM3) suggested that the product obtained in the reaction corresponds to the more thermodynamically stable atropisomer (Scheme 25). Furthermore, heating compound

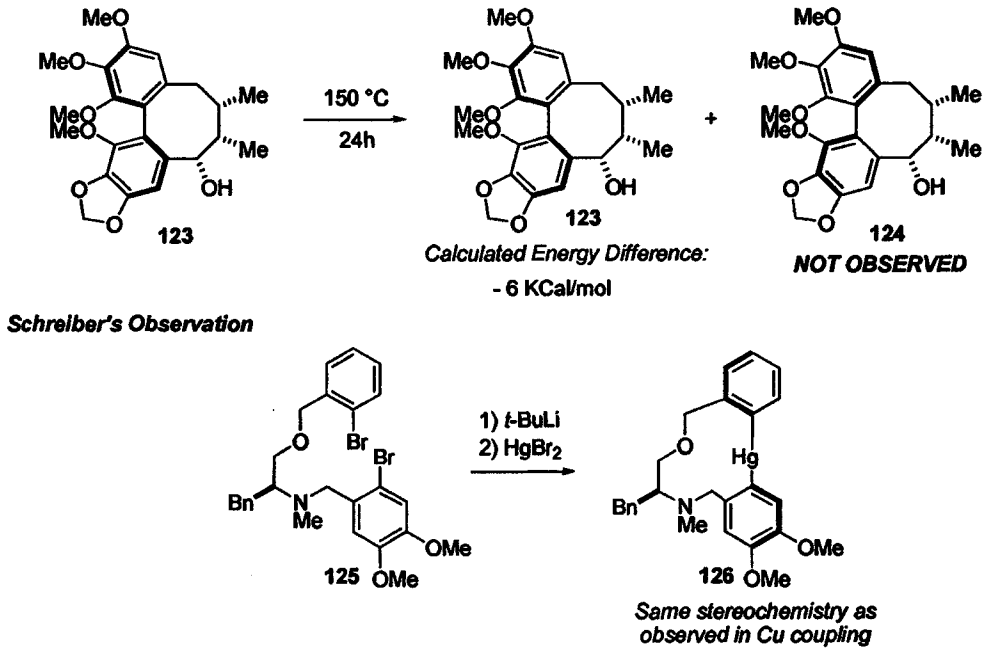
Scheme 24.



123 to 150 °C under argon for 24 hours returned **123** unchanged, providing further evidence that the stereoisomer obtained in the reaction is the thermodynamically favored product. The rotational barrier for BINOL, a relatively close approximation to the biaryl product **123** in that both compounds are tetra-ortho-substituted biphenyls, has been reported to be fairly low; it isomerizes in a matter of hours at temperatures as low as 50 °C suggesting that the rotational barrier associated with **123** should be accessible at 150 °C with the caveat that BINOL does not contain a fused ring.[54] Schreiber and co-workers have examined the Ullmann coupling in the context of very similar systems.[55] In an attempt to probe the origins of the observed stereochemistry in the coupling reaction, they examined the isolable mercury (II) compound **126**, which can be considered a close mimic of the intermediate higher order cuprate, in the solution and solid phase (Scheme 25). In the solid state, compound **126** adopts the same relative stereochemistry that is observed in the product obtained from Cu-mediated coupling. Interestingly, NMR

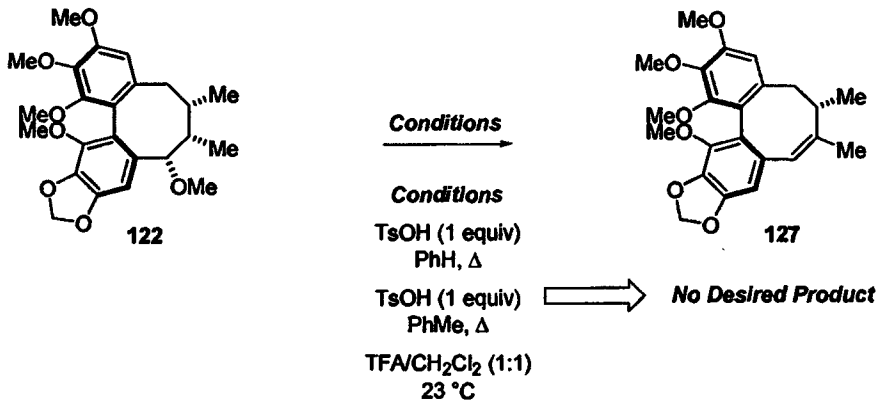
experiments revealed that mercury compound **126** is not atropisomeric in solution, indicating that the intermediate nine-membered ring is conformationally flexible and the "biaryl" is not stereodefined. In light of these observations, Schrieber and co-workers conclude that the stereochemical outcome of the reaction is determined in the oxidation of the higher order cuprate and is a consequence of steric interactions of the two aromatic rings, induced by the backbone, in the transition state.[56]

Scheme 25.



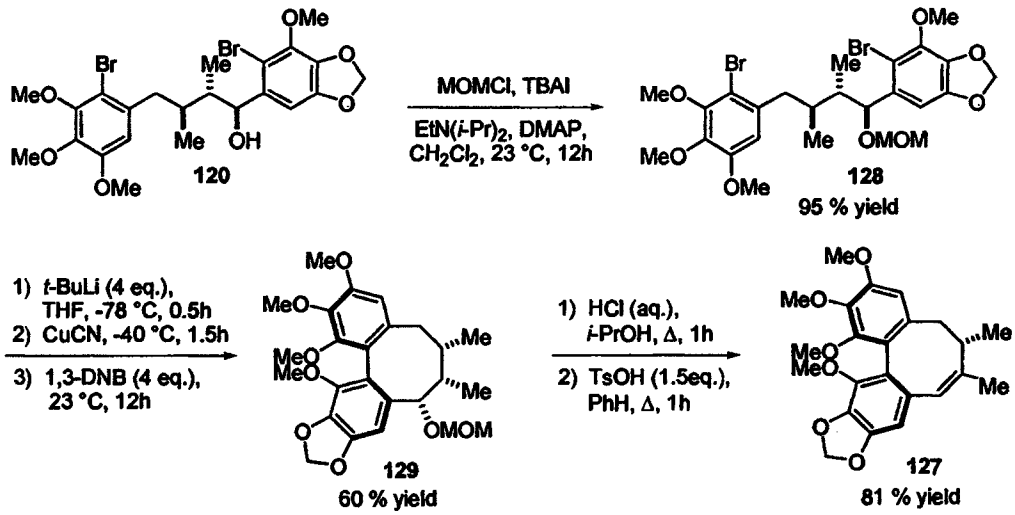
With the core of gomisin G assembled our efforts focused on elaboration of the backbone. Installation of the diol moiety present in gomisin G (**89**, Scheme 17) was envisioned to proceed through oxidation of the corresponding olefin. In light of the electron-rich nature of the aromatic rings in **122** we reasoned that treatment of compound **122**, containing a benzylic methoxy group, under acidic conditions should provide access to the corresponding olefin. Unfortunately, treatment of compound **122** under a variety of acidic conditions failed to provide any of the desired olefin **127** (Scheme 26).

Scheme 26.



With the elimination of the benzylic methoxy ether proving to be problematic, we set out to change the protecting group resident on the benzylic alcohol with the hope that elimination of the parent alcohol would proceed smoothly. To this end, the acyclic dibromoaromatic alcohol **120** was protected with the acid-labile MOM protecting group

Scheme 27.



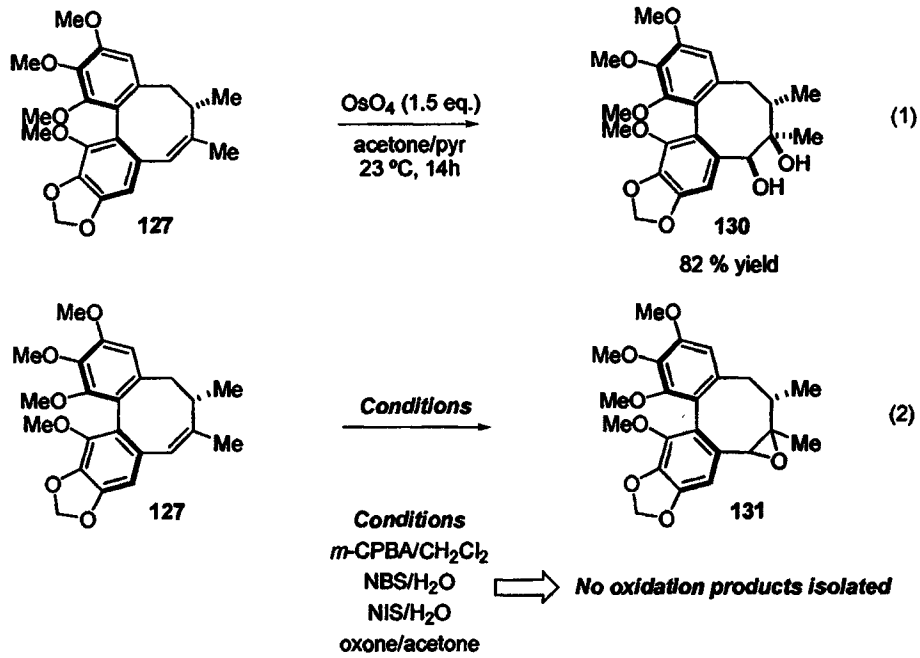
under optimized conditions providing cyclization precursor **128** in good yield (Scheme 27). Biaryl precursor **128** was subjected to the standard cyclization protocol affording the desired biaryl **129** in 60 % isolated yield as a single diastereomer, illustrating that the nature of the protecting group present on the benzylic alcohol does not have a deleterious

effect on reaction selectivity. Submission of MOM ether **129** to conc. HCl in *i*-PrOH smoothly supplied the intermediate benzylic alcohol, which upon reaction with TsOH in refluxing benzene provided the desired olefin **127** in 81 % yield over two steps.

To access the *trans* diol relationship present in the gomisin G, backbone oxidation of olefin **127** was investigated using two methods: facially selective dihydroxylation to set the tertiary alcohol, followed by inversion of the benzylic center and diastereoselective epoxidation, followed by epoxide ring opening. Dihydroxylation reactions utilizing stoichiometric or catalytic amounts of OsO_4 as the oxidant are known to be highly diastereoselective in systems bearing allylic stereocenters, with oxygen delivery occurring at the more sterically accessible olefin face.[57] We hoped that the dihydroxylation of olefin **127** would occur with an orientation *syn* to the allylic methyl group present in the eight-membered ring. It was reasoned that the conformation of the biaryl moiety may override the "allylic control element" providing the desired diastereomer.[58] In the event, compound **127** was treated with stoichiometric amounts of OsO_4 in pyridine to efficiently supply the diol **130** as a single diastereomer in good yield (Scheme 28, eq. 1). Unfortunately, the diastereomer obtained proved to be the undesired isomer. With the failure of the dihydroxylation tactic, epoxidation of **127** was investigated. Martinelli and co-workers had identified a complementary pair of epoxidation conditions that provides each diastereomeric epoxide of cyclic styrene derivatives.[59] In light of this report, several attempts were made to convert olefin **127** into the desired epoxide. To our disappointment, a variety of epoxidation conditions did not provide any oxidation products, usually returning starting material (Scheme 28, eq. 2). Although we were confident that the olefin oxidation problem encountered in the

synthesis of gomisin G could be overcome, our focus turned to the broader goal of the project, the development of a general and modular approach to the DBC lignan family.

Scheme 28.

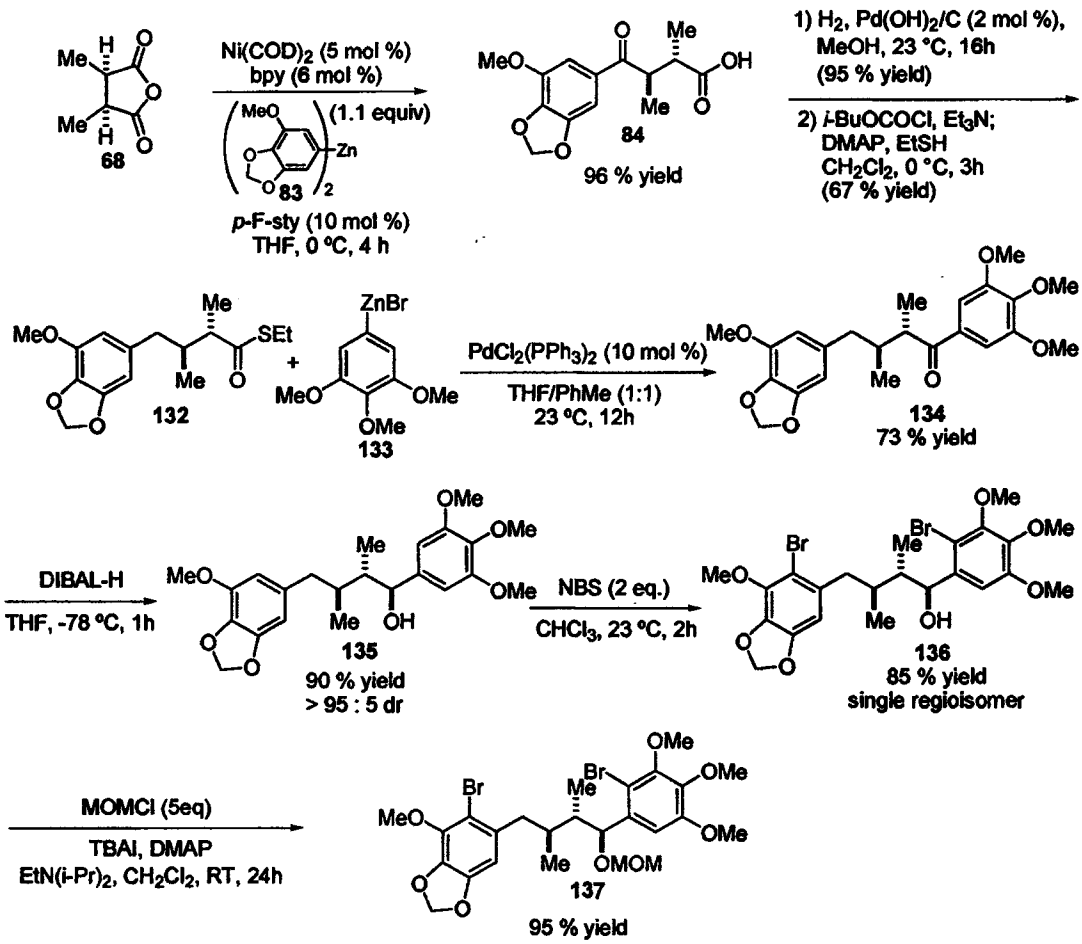


3.3.6 The Synthesis of Gomisin O and Epigomisin O

At the outset of our studies directed toward a general synthetic approach to the DBC lignans we envisioned that a modular route would provide access to a variety of members of the family due to their close structural similarities. Examination of gomisin O (**90**, Scheme 17) and epigomisin O (**91**, Scheme 17) revealed that the biaryl moiety present in the core is a permutation of the gomisin G (**89**, Scheme 17) core. In accord with our route to DBC ring system, we reasoned that gomisin O and epigomisin could be accessed by simple introduction of each respective aromatic portion at different points in the synthesis. Utilizing the concepts learned during our synthetic studies toward gomisin G, the syntheses of gomisin O and epigomisin O were undertaken.

Our preliminary objective was the synthesis of the requisite biaryl precursor possessing the proper aromatic substitution pattern (Scheme 29). Toward this goal, *meso*-dimethylsuccinic anhydride **68** was cross-coupled with diarylzinc reagent **83** in the presence of 5 mol % Ni-catalyst, supplying the desired keto acid **84** in excellent yield. The direct reduction of keto acids of type **84** in the context of the gomisin G synthesis had been problematic, prompting us to use a two-step reduction protocol (*vide supra*). After some efforts directed at the realization of a direct reduction of keto acid **84**, we found that submission of **84** to catalytic hydrogenation conditions using Pearlman's catalyst ($Pd(OH)_2$) on carbon under 1 atm of H_2 in MeOH effected the efficient reduction to the desired intermediate acid in high yields. Conversion of the intermediate acid to the corresponding thioester **132** via the mixed carbonic anhydride proceeded uneventfully. Fukuyama cross-coupling of thioester **132** and arylzinc halide **133** in the presence of catalytic amounts of a low-valent palladium catalyst affords the desired ketone **134** in a respectable 73 % isolated yield. Diastereoselective reduction of ketone **134** with DIBAL-H efficiently delivers the desired alcohol **135** in 90 % yield and > 95:5 diastereomeric ratio favoring the all *syn* configuration. Regioselective dibromination of alcohol **135** was accomplished by the action of NBS at room temperature providing diarylbromide **136** in high yield. Finally, protection of **136** with MOMCl under optimized conditions affords the requisite biaryl precursor **137** in excellent yield.

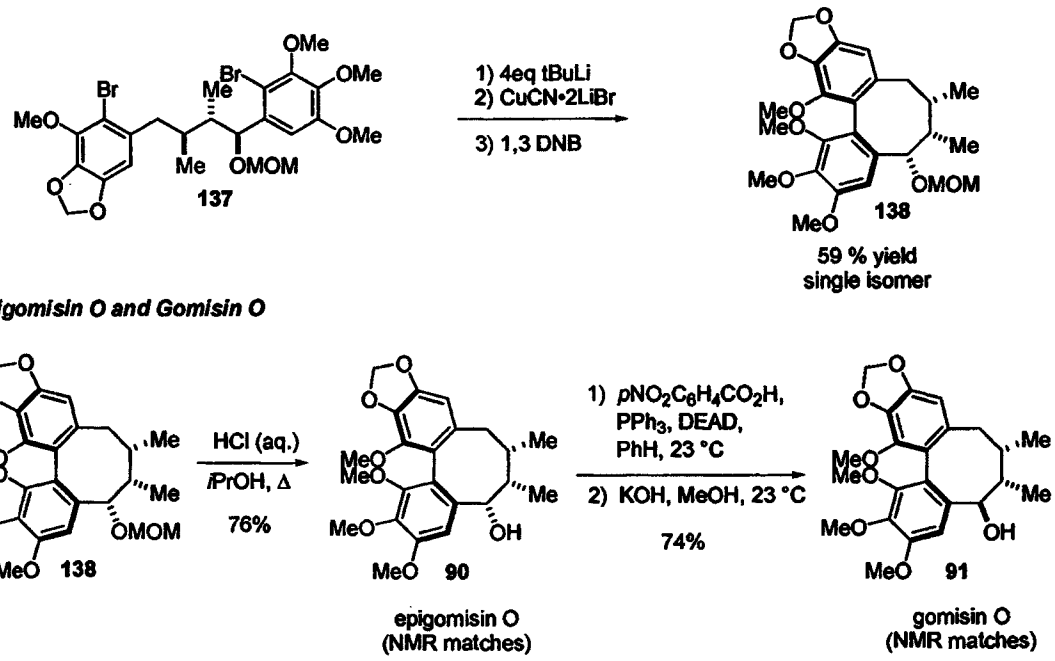
Scheme 29.



With efficient access to the required biaryl precursor, the syntheses of epigomisin O and gomisin O were completed by a route analogous to our previous strategy (Scheme 30). Diarylbromide **137** was treated with four equiv of *t*-BuLi to provide the intermediate diaryllithium which was treated with LiBr complex of CuCN, forming the higher order cuprate *in situ* followed by subsequent treatment with 1,3-DNB, supplying the desired biaryl **138** in 59 % yield as the sole diastereomer. Deprotection of **138** under standard conditions provided epigomisin O **90** in 76 % yield, constituting a nine-step total synthesis proceeding in 11 % overall yield. Subjection of epigomisin O **90** to Mitsunobu

inversion efficiently affords gomisin O **91** in 74 % yield over two steps which comprises a 11 step synthesis occurring in 9 % overall yield.

Scheme 30.



3.4 Conclusion

The nickel-catalyzed anhydride cross-coupling reaction developed in our laboratories has been applied in two discrete settings, both of which take advantage of the synthetically important keto acids obtained from the process. The complementary diastereoselective reduction of 1,4-cyclic oxoacids has been explored resulting in an expedient synthesis of stereodefined trisubstituted γ-lactones, important motifs in the context of natural products. Furthermore, several members of two families of the lignan natural products have been synthesized using our anhydride arylation methodology to set the key stereochemical relationships present in the target molecules. Eupomatilones -4, -6, and -7 have been prepared via a four-step synthetic protocol that proceeds in greater than 50 % overall yield in all cases with nearly complete stereocontrol. Additionally, two

members of the DBC lignan family, gomisin O and epigomisin O, have succumbed to total synthesis for the first time. Taking advantage of a modular approach to this family of natural products, we have devised what we believe is a general route to many of the DBC lignans using our anhydride alkylation protocol.

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Chapter 1 Experimental

Decarbonylative Cross Coupling of Cyclic Anhydrides

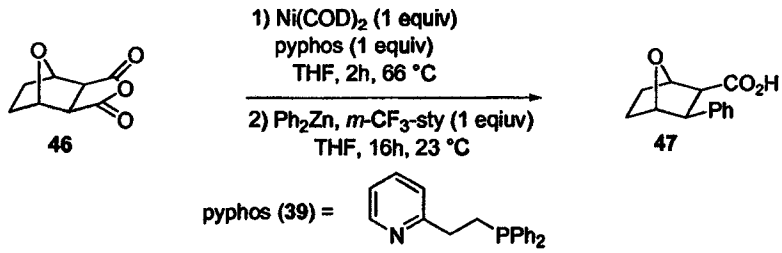
General Methods. All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Tetrahydrofuran, diethylether, and dichloromethane were degassed with argon and passed through two columns of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light, $KMnO_4$, aqueous ceric ammonium molybdate, anisaldehyde, or bromocresol green dips followed by heating.

Melting points were measured with a MelTemp II melting point apparatus outfitted with a Fluke 51 thermocouple and are uncorrected. Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^1H NMR and spectra were recorded on a Varian 300, 400, or 500 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ, ppm) from an internal standard [tetramethylsilane (TMS; taken as 0.00 ppm) or deuterated chloroform ($CDCl_3$; taken as 7.26 ppm)], multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR were recorded on a Varian 75, 100, or 125 MHz spectrometer at ambient temperature. Chemical shifts are reported in ppm from ($CDCl_3$) taken as 77.0 ppm. Mass spectra were obtained on Fisons VG Autospec. Analytical high performance liquid chromatography (HPLC) was performed on a Dynamax model SD-200 HPLC equipped with a Dynamax model UV-1 variable

wavelength UV detector using Chiracel chiral columns as indicated. Gas chromatography was performed on a Varian Cp 3800 gas chromatograph equipped with a flame ionization detector using a Chrompack CP-Sil8CB (15 M X 0.25 mm) capillary column.

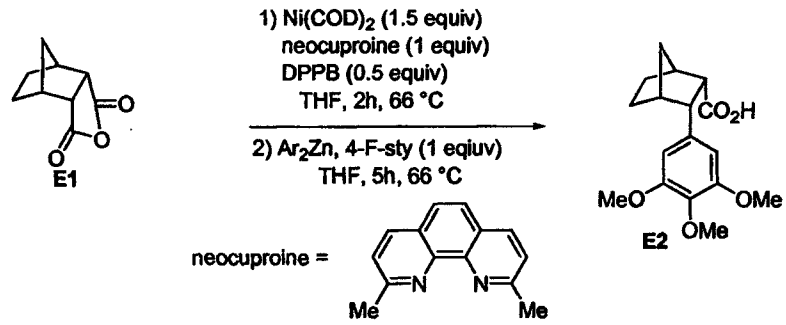
Representative Procedure for Ligand Screen

A flame-dried round bottom flask was charged with 32 mg (0.12 mmol) of $Ni(COD)_2$ and 33 mg (0.12 mmol) of pyphos **39** in an inert atmosphere glove box. Upon removal the reaction was place under argon 3 mL of THF were added via syringe and the resulting brown-green solution was stirred for 15 min. 18 mg (0.12 mmol) of pthalic anhydride **29** in 0.5 mL of THF were added via syringe and the reaction stirred at ambient temperature for 2 h. 30 mL (0.20 mmol) of m-CF_3-sty **38** were added via syringe followed by the addition of 0.3 mL (0.3 mmol) of Et_2Zn (1.0 M in hexanes) and the resulting reaction mixture was stirred for 5 h at ambient temperature before the addition of 0.2 mL of CH_3CO_2D. The reaction mixture was diluted with Et_2O (10 mL) and washed with 1 M aq. HCl (1 X 10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (1 X 10 mL). The organic layers were combined, extracted with 1 M aq. NaOH (2 X 5 mL). The basic layers were combined and brought to pH ~ 1 with conc. HCl. The acidified aqueous layer was extracted with Et_2O (2 X 10 mL), washed with brine, dried over $MgSO_4$, filtered and concentrated to yield crude acid that was purified by flash column chromatography (1:1 EtOAc/Hex) to provide 11 mg (60 %) yield of a 97:1:2 mixture of desired **32**:**34**:**31**.



Preparation of 47. A flame-dried round bottom flask equipped with a reflux condenser was charged with 32 mg (0.12 mmol) of $Ni(COD)_2$ and 33 mg (0.12 mmol) of pyphos **39** in an inert atmosphere glove box. Upon removal the reaction was placed under argon and 3 mL of THF were added via syringe and the resulting brown-green solution was stirred for 15 min. 19 mg (0.11 mmol) of pthalic anhydride **46** in 0.5 mL of THF were added via syringe and the reaction was brought to reflux for 2 h. The reaction was cooled to ambient temperature and 30 mL (0.20 mmol) of *m*-CF_3-sty **38** were added via syringe followed by the addition of 0.3 mL (0.3 mmol) of Et_2Zn (1.0 M in hexanes) and the resulting reaction mixture was stirred for 14 h at ambient temperature before the addition of 0.2 mL of CH_3CO_2D. The reaction mixture was diluted with Et_2O (10 mL) and washed with 1 M aq. HCl (1 X 10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (1 X 10 mL). The organic layers were combined, extracted with 1 M aq. NaOH (2 X 5 mL). The basic layers were combined and brought to pH ~ 1 with conc. HCl. The acidified aqueous layer was extracted with Et_2O (2 X 10 mL), washed with brine, dried over $MgSO_4$, filtered and concentrated to yield crude acid that was purified by flash column chromatography (1:3 EtOAc/Hex) to provide 5 mg (21 %) yield of **47**.

Optimized Procedure



***endo*-3-(3,4,5-trimethoxyphenyl)-bicyclo[2.2.1]heptane-2-carboxylic acid (E2).**

Preparation of bis-(3,4,5-trimethoxyphenyl) zinc: A flame-dried 10ml heart shaped flask equipped with a magnetic stir bar under argon was charged with 148 mg (0.60 mmol) of 3,4,5-trimethoxybromobenzene in 2 ml of THF. The resulting solution was cooled to –78°C and 0.4 ml (0.64 mmol) of *n*-butyllithium (1.6 M in hexanes) were added via syringe. After 0.5 h, 0.63 ml (0.32 mmol) of $ZnCl_2$ (0.5 M in THF) were added and the reaction was allowed to warm to room temperature over 0.5h prior to use. According to the general procedure, 62 mg (0.23 mmol) of $Ni(COD)_2$, 32 mg of neocuproine (0.15 mmol) , and 31 mg of dppb (0.08 mmol) in 2 ml of THF was stirred for 15 minutes at room temperature. 25 mg (0.15 mmol) of anhydride **E1** in 0.5 ml of THF were added via cannula and the reaction stirred for 3 hours at 66 °C. 18 µl (0.15 mmol) of 4-fluorostyrene and bis-(3,4,5-trimethoxyphenyl) zinc (see above) were added via cannula and the reaction was stirred for 5 hours at 66 °C. After standard work-up, column chromatography (99:1 CH_2Cl_2/MeOH) yielded 28 mg (52%) the desired acid as a white solid: mp 190-194°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33-1.72 (m, 5H), 2.05-2.12 (m, 1H), 2.44 (s, 1H), 2.59 (s, 1H), 3.18 (dd, 1H, J = 2.2, 12.3 Hz), 3.50 (dd, 1H, J = 3.0, 12.0 Hz), 3.79 (s, 6H), 3.81 (s, 3H), 6.33 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 23.6,

40.5, 40.6, 43.3, 48.2, 48.3, 55.9, 60.8, 105.5, 135.7, 152.4, 179.2; IR (NaCl, $CHCl_3$) 2956, 2875, 1687, 1591, 1512, 1427, 1252, 1124 cm^{-1}

Chapter 2 Experimental

Nickel Catalyzed Anhydride Alkylation

General Methods. All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Tetrahydrofuran, diethylether, and dichloromethane were degassed with argon and passed through two columns of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light, $KMnO_4$, aqueous ceric ammonium molybdate, or bromocresol green dips followed by heating.

Anhydrides **10**, **25**, **27**, **39**, **43**, **47**, **53**, and **63** were purchased from Aldrich Chemical Co. and used without purification. Anhydrides **51**, **75**, and **77** were purchased from Rieke Metals Inc. and used without further purification. Anhydrides **38**, **44**, and **60** were prepared from the corresponding commercially available diacids (Aldrich) using the cyclization protocol below. Saturated anhydrides **39**, **41**, and **45** were prepared by hydrogenation (H_2, Pd/C, EtOAc) of the corresponding unsaturated anhydrides. Anhydrides **29**,[1] **31**,[2] **33**,[3] **49**,[4] **57**,[5] **71**,[6] and **73**[7] were prepared by literature methods. $Ni(COD)_2$ was purchased from Strem Chemical, Inc. and used without further purification.

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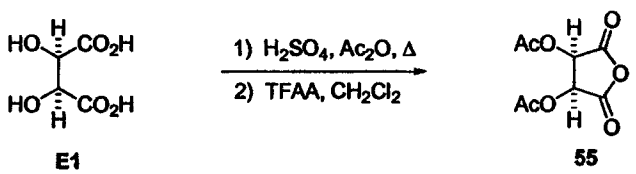
Melting points were measured with a MelTemp II melting point apparatus outfitted with a Fluke 51 thermocouple and are uncorrected. Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^{1}H NMR and spectra were recorded on a Varian 300, 400, or 500 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ, ppm) from an internal standard [tetramethylsilane (TMS) or chloroform ($CHCl_3$) taken as 7.26 ppm], multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR were recorded on a Varian 75, 100, or 125 MHz spectrometer at ambient temperature. Chemical shifts are reported in ppm from ($CDCl_3$) taken as 77.0 ppm. Mass spectra were obtained on Fisons VG Autospec. Gas chromatography was performed on a Varian Cp 3800 gas chromatograph equipped with a flame ionization detector using a Chromopack CP-Sil 8 CB (15 M X .25 mm) capillary column.

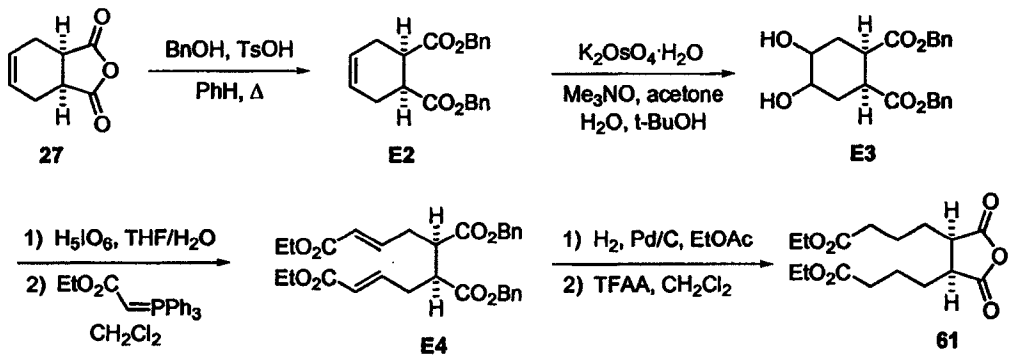
Synthesis of Starting Materials



E1 55

***meso*-3,4-diacetoxysuccinic anhydride (55).** A flame-dried round bottom flask equipped with a reflux condenser under argon was charged with 170 mg (1.13 mmol) of *meso*-tartaric acid (**E1**) in 2 mL of Ac_2O and 2 drops of conc. H_2SO_4, then brought to reflux for 10 minutes. Upon cooling to room temperature the reaction was diluted with CH_2Cl_2 (20 mL) and extracted with sat. aq. Na_2CO_3 (2 X 5 mL). The basic layers were combined and acidified with conc. HCl. The resulting aqueous layer was extracted with

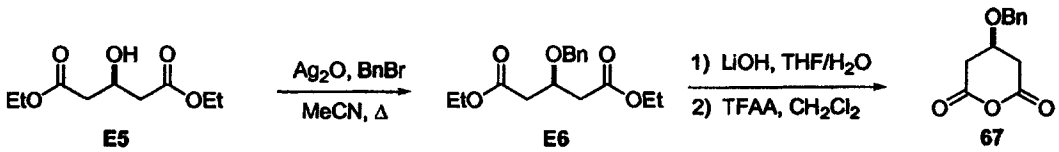
EtOAc (3 X 10 mL), the organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated to provide crude acylated diacid. The crude diacid was suspended in 4 mL of CH_2Cl_2 and cooled to 0 °C. 1.0 mL (7.2 mmol) of trifluoroacetic anhydride was then added dropwise via syringe. The reaction was stirred for 1 h at 0 °C then concentrated to provide 183 mg (75 %) of the desired anhydride **55** as a colorless oil that crystallized on standing: mp = 67-71 °C (CH_2Cl_2); R_f = 0.12 (95:5 CH_2Cl_2/MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 5.52 (s, 2H), 2.20 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) d 169.2, 164.9, 65.9, 19.6; IR (NaCl, dep from $CDCl_3$) 2947, 1802, 1755, 1377, 1215, 1038 cm^{-1}.



***meso*-3,4-di-(1-ethoxycarbonyl-propyl)-succinic anhydride (61).** A flame-dried round bottom flask under argon was charged with 2.00 g (13.1 mmol) of anhydride **27** and 249 mg (1.31 mmol) of *p*-toluenesulfonic acid monohydrate in 40 mL of dry benzene. 2.8 mL (27 mmol) of benzyl alcohol were added via syringe then the reaction was fitted with a Dean-Stark apparatus and brought to reflux for 13 h. Upon cooling the reaction was diluted with Et_2O (50 mL) and washed sequentially with sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated to provide 4.28 g (93 %) of *meso*-diester **E2**

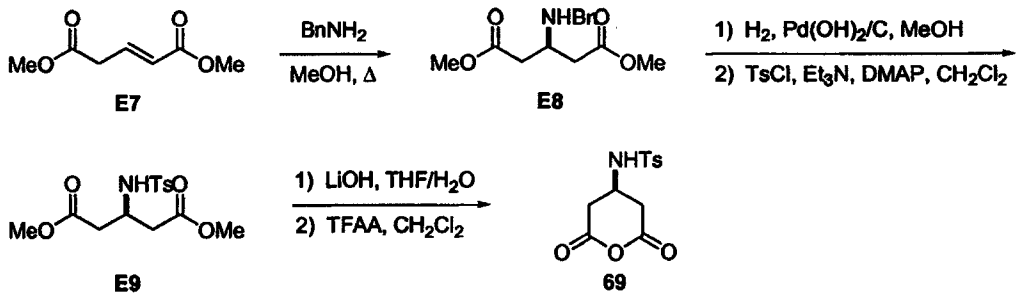
as a colorless oil. A round bottom flask was charged with 1.02 g (2.90 mmol) of diester **E2** in 7 mL of 6:1 acetone/water. 660 mg (5.94 mmol) of trimethylamine oxide were then added in one portion followed by 11 mg (0.035 mmol) potassium osmate dihydrate. 1 mL of *t*-BuOH was then added and the reaction stirred for 14 h at ambient temperature. The reaction was quenched with 5 mL of sat. aq. $NaHSO_3$ and allowed to stir for 1 h before the addition of 50 mL of water. The resulting aqueous reaction mixture was extracted with CH_2Cl_2 (3 X 50 mL). The organic extracts were combined, washed with brine, dried over Na_2SO_4, decanted and concentrated to yield the crude diol that was purified by column chromatography (97:3 CH_2Cl_2/MeOH) gave 877 mg (79 %) of diol **E3** as a viscous oil. A round bottom flask was charged with 590 mg (1.53 mmol) of diol in 10 mL of 4:1 THF/water. 420 mg (1.85 mmol) of periodic acid were added in one portion and the reaction stirred for 1 h at ambient temperature. The reaction was diluted with water (20 mL) and extracted with Et_2O (3 X 15 mL). Organic extracts were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated to provide crude dialdehyde as an oil that was directly used in the next step. A flame-dried round bottom flask was charged with crude dialdehyde in 15 mL of CH_2Cl_2. 1.61 g (4.62 mmol) of (carbethoxyethylidene)triphenylphosphorane were added in one portion and the reaction stirred for 14 h at ambient temperature. Upon completion the reaction was diluted with EtOAc (50 mL) and washed with sat. aq. NH_4Cl, sat. aq. $NaHCO_3$, brine, dried over MgSO4, filter, and concentrated providing crude diester. Purification by column chromatography (4:1 Hex/EtOAc) providing 337 mg (42 % from diol) of the desired diester **E4** as a colorless oil. A round bottom flask was charged with 337 mg (0.654 mmol) of diester **E4** in 10 mL of EtOAc. Argon was passed through the solution

for 5 min. before the addition of 30 mg (0.028 mmol Pd) of 10 % (wt) Pd/C. The reaction vessel was placed under an atmosphere of H_2 and stirred for 12 h at ambient temperature. The reaction mixture was passed through a celite pad that was thoroughly washed with EtOAc and the filtrate concentrated giving crude diacid. Diacid was suspended in 10 mL of CH_2Cl_2 and cooled to 0 °C before the addition of 0.20 mL (1.4 mmol) of trifluoroacetic anhydride via syringe. The reaction was stirred for 1 h at 0 °C at which time it had turned homogeneous. The reaction was concentrated supplying 200 mg (94 % from **E4**) anhydride **61** as an oil that crystallized upon standing: mp = 105-106 °C (CH_2Cl_2); R_f = 0.20 (1:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (q, 4H, J = 7.0 Hz), 2.72-2.70 (m, 2H), 2.35-2.31 (m, 4H), 1.76-1.50 (m, 8H), 1.24 (t, 6H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 173.5, 60.6, 40.1, 33.8, 29.0, 22.8, 14.2; IR (NaCl, dep from $CDCl_3$) 2989, 2958, 1732, 1697, 1416, 1292, 1196 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{25}O_7$, 329.1600. Found 329.1608.



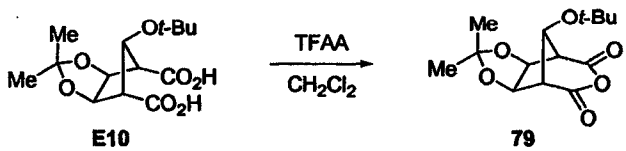
***meso*-4-(benzyloxy)-glutaric anhydride (67).** A flame dried round bottom flask equipped with a reflux condenser under an argon atmosphere was charged with 1.77 g (7.64 mmol) of Ag_2O suspended in 15 mL of freshly distilled MeCN. 1.00 g (4.91 mmol) of diethyl-3-hydroxy glutarate (**E5**) was added via syringe followed by the addition of 2.02 g (11.8 mmol) of benzyl bromide. The reaction was covered with foil and brought to reflux for 14 h. Upon cooling, the reaction was filtered through a celite pad that was

washed with EtOAc. The filtrate was concentrated and purified by column chromatography (9:1 Hex/EtOAc) yielding 351 mg (24 %) of the desired diester **E6** as a colorless oil. A round bottom flask was charged with 351 mg (1.19 mmol) of diester **E6** in 8 mL of 3:1 THF/water. 114 mg (4.76 mmol) of LiOH was added in one portion and the reaction stirred at ambient temperature for 15 h. 20 mL of water were added and the aqueous layer separated and washed with EtOAc (1 X 30 mL). The aqueous layer was acidified with conc. HCl and extracted with EtOAc (3 X 15 mL). Organic extracts were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated to yield 248 mg (87 %) of diacid as a white solid. 248 mg (1.04 mmol) of diacid was suspended in 7 mL of CH_2Cl_2 and cooled to 0 °C before the addition of 0.30 mL (2.2 mmol) of trifluoroacetic anhydride via syringe. The reaction was stirred for 1 h at 0 °C and warmed to ambient temperature and stirred an additional 1 h before being concentrated. The crude anhydride was dissolved in $CHCl_3$ (30 mL) and washed with 5 % aq. $NaHCO_3$ (1 X 20 mL). The organic layer was dried over $MgSO_4$ and concentrated yielding 203 mg (87 %) of anhydride **67** as a white solid: mp = 79-80 °C ($CHCl_3$); R_f = 0.27 (1:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.28 (m, 5H), 4.58 (s, 2H), 4.08 (dddd, 1H, J = 3.4, 3.4, 3.4, 3.4 Hz), 3.11 (dd, 2H, J = 16.6, 3.6 Hz), 2.74 (dd, 2H, J = 16.6, 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 136.4, 128.7, 128.3, 127.7, 70.9, 66.8, 35.8; IR (NaCl, dep from $CDCl_3$) 2943, 2908, 1813, 1778, 1759, 1346, 1250, 1072, 1034 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{13}O_4$, 221.0814. Found 221.0809.



***meso*-4-(*p*-toluenesulfonamide)-glutaric anhydride (69).** A flame-dried round bottom flask equipped with a reflux condenser under argon was charged with 0.70 mL (5.0 mmol) of dimethyl glutaconate **E7** in 6 mL of distilled MeOH. 0.60 mL (5.5 mmol) of benzyl amine was added via syringe and the reaction brought to reflux for 20 h. The reaction was concentrated and purified by column chromatography (4:1 Hex/EtOAc) providing 1.02 g (77 %) of conjugate addition product **E8** as a light brown oil. A round bottom flask was charged with 1.02 g (3.84 mmol) of benzylamine diester **E8** in 15 mL of MeOH. After passing argon through the solution for 15 min., 107 mg (0.0770 mmol $Pd(OH)_2$, 50 % wt. H_2O) of 20 % $Pd(OH)_2/C$ was added in one portion and the reaction was placed under an atmosphere of H_2 and stirred at ambient temperature for 12 h. The reaction was filtered through a celite pad that was thoroughly washed with EtOAc. The filtrate was concentrated to yield 657 mg (98 %) of amine as a colorless oil. The amine was immediately taken on to the next step. A flame-dried round bottom flask was placed under argon and charged with 657 mg (3.75 mmol) of amine in 8 mL of CH_2Cl_2. 1.50 mL (10.8 mmol) of triethylamine via syringe was followed by addition of 48 mg (0.39 mmol) of 4-dimethylamino pyridine. The reaction was cooled to 0 °C and 789 mg (4.14 mmol) of *p*-toluenesulfonyl chloride was added in one portion. After 15 min. the reaction was warmed to ambient temperature and stirred an additional 1.5 h. The reaction was diluted with CH_2Cl_2 (50 mL), washed with sat. aq. NH_4Cl, sat. aq. $NaHCO_3$, dried over

$MgSO_4$, filtered and concentrated to provide 1.14 g (93 %) of the desired product **E9** as a white solid. A round bottom flask was charged with 1.14 g (3.46 mmol) of diester **E9** in 20 mL of 3:1 THF/water. 359 mg (15.0 mmol) of LiOH was added in one portion and the reaction stirred at ambient temperature for 15 h. 50 mL of water were added and the aqueous layer separated and washed with EtOAc (1 X 30 mL). The aqueous layer was acidified with conc. HCl and extracted with EtOAc (3 X 25 mL). Organic extracts were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated to yield 945 mg (91 %) of diacid as a white solid. 945 mg (3.14 mmol) of diacid was suspended in 20 mL of CH_2Cl_2 and cooled to 0 °C before the addition of 0.90 mL (6.5 mmol) of trifluoroacetic anhydride via syringe. The reaction was stirred for 1 h at 0 °C and warmed to ambient temperature and stirred an additional 2 h before being concentrated, yielding 870 mg (98 %) of anhydride **69** as a white solid: mp = 161-164 °C (CH_2Cl_2); R_f = 0.26 (1:1 Hex/EtOAc); ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.20 (d, 1H, J = 4.7 Hz), 7.71 (d, 2H, J = 7.9 Hz), 7.43 (d, 2H, J = 7.9 Hz), 3.71 (m, 1H), 2.84 (dd, 2H, J = 16.8, 4.3 Hz), 2.74 (dd, 2H, J = 17.1, 6.0 Hz), 2.40 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 165.8, 143.2, 137.2, 129.9, 126.6, 43.6, 35.7, 21.0; IR (NaCl, dep from $CDCl_3$) 3252, 2920, 1817, 1767, 1335, 1161, 1080, 1041 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{14}NO_5S$, 284.0593. Found 284.0600.

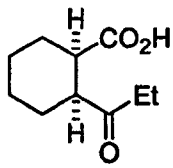


***meso*-glutaric anhydride 79.** A round bottom flask was charged with 161 mg (0.533 mmol) of diacid **E10**[8] suspended in 5 mL of CH_2Cl_2 and cooled to 0 °C before the addition of 0.31 mL (2.2 mmol) of trifluoroacetic anhydride via syringe. The reaction was stirred for 35 min. at 0 °C before being concentrated. The crude anhydride was dissolved in $CHCl_3$ (25 mL) and washed with 5 % aq. $NaHCO_3$ (1 X 20 mL). The organic layer was dried over $MgSO_4$ and concentrated yielding 130 mg (86 %) of anhydride **79** as a white solid: mp = 153-156 °C ($CHCl_3$); R_f = 0.55 (1:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 4.69 (s, 2H), 4.58 (t, 1H, J = 4.6 Hz), 3.34 (d, 2H, J = 4.3 Hz), 1.50 (s, 3H), 1.31 (s, 3H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 112.5, 77.5, 76.0, 70.2, 53.5, 27.9, 25.6, 23.7; IR (NaCl, dep from $CDCl_3$) 2985, 2970, 1821, 1778, 1365, 1192, 1107, 995 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{21}O_6$, 285.1338. Found 285.1329.

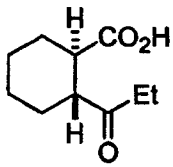
General procedure for the alkylative monofunctionalization of cyclic anhydrides: A flame-dried round bottom flask was charged with $Ni(COD)_2$ (0.05 to 0.1 eq) and 2,2'-dipyridyl (bpy) or (2-diphenylphosphino)ethylpyridine (PYPHOS) (0.06 to 0.12 eq) in an inert atmosphere (N_2) glove box. Upon removal from the glove box, 1 to 2 ml THF was added via syringe and the solution was stirred at ambient temperature for 15 minutes. The solution was then cooled to 0 °C in an ice bath and 4-(trifluoromethyl)styrene or 4-fluorostyrene (0.1 to 0.2 eq) followed by diethylzinc (1.0M solution in hexane or neat, 1.2-2.4 eq) were added via syringe. Anhydride (1 eq) in THF was added via cannula and the reaction was stirred for the time and temperature indicated. The reaction mixture was

[8] Ben Cheikh, A.; Craine, L. E.; Recher, S. G.; Zemlicka, J. *J. Org. Chem.* **1988**, *53*, 929-936.

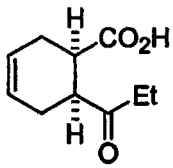
then diluted with 10 ml of ether and quenched with 10 ml 1M HCl (aq.). The layers were separated and the aqueous layer extracted with ether (2 X 10 mL). Organics were combined and extracted with 1M Na_2CO_3 (aq.) (2 X 5 mL), the basic layers were combined and brought to pH = 1-2 with concentrated HCl. The acidified aqueous layer was extracted with Et_2O (3 X 10 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. For reactions in which the product acids were not analytically pure or existed as a mixture of rotamers, the corresponding methyl ester was generated by treatment with CH_2N_2 in Et_2O or $TMSCHN_2$ (2.0M in Et_2O) in 1:1 MeOH/PhH at 0 °C.



(1*R, 2*S**)-2-propionyl-cyclohexanecarboxylic acid (20).** According to the general procedure, 97.0 mg (0.353 mmol) of $Ni(COD)_2$ and 62.1 mg (0.398 mmol) of bpy in 4 mL of THF was treated with 50 μL (0.34 mmol) of 4-(trifluoromethyl)styrene and 5.0 mL (1.0M solution in hexane, 5.0 mmol) of Et_2Zn at 0 °C. 560 mg (3.63 mmol) of anhydride **10** in 16 mL THF was added via cannula and the reaction was stirred for 3 h at 0 °C. Upon work-up 625 mg (93 %) of desired acid **20** was isolated as a white solid: mp = 71-73 °C (Et_2O); ^1H NMR (300 MHz, $CDCl_3$) δ 2.75-2.83 (m, 2H), 2.52 (dq, 1H, J = 18.0, 7.3 Hz), 2.44 (dq, 1H, J = 18.0, 7.3 Hz), 1.95-2.10 (m, 2H), 1.75-1.85 (m, 2H), 1.60 (m, 1H), 1.40 (m, 1H), 1.03 (dd, 3H, J = 7.5, 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) d 212.1, 180.3, 49.1, 42.5, 33.3, 26.2, 26.0, 24.0, 23.6, 7.8; IR (NaCl, $CDCl_3$) 3081, 2939, 2860, 1738, 1701, 1452, 1261 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{17}O_3$, 185.1178. Found 185.1178.

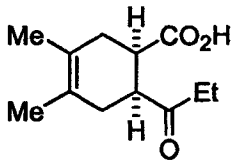


(1*R, 2*R**)-2-propionyl-cyclohexanecarboxylic acid (26).** According to the general procedure, 5.7 mg (0.021 mmol) of $Ni(COD)_2$ and 4.5 mg (0.029 mmol) of bpy in 1 mL of THF was treated with 5 μL (0.042 mmol) of 4-fluorostyrene and 45 μL (0.44 mmol) of Et_2Zn at 0 °C. 56 mg (0.36 mmol) of anhydride **25** in 1 mL THF was added via cannula and the reaction was stirred for 4 h at 0 °C. Upon work-up 58 mg (87 %) of desired acid **26** was isolated as a white solid: mp = 109-111 °C (CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 2.62-2.71 (m, 2H), 2.55 (dq, 1H, *J* = 17.6, 7.3 Hz), 2.46 (dq, 1H, *J* = 17.6, 7.1 Hz), 2.13 (m, 1H), 1.95 (m, 1H), 1.77-1.80 (m, 2H), 1.08-1.35(m, 4H), 1.01 (dd, 3H, *J* = 7.3, 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.6, 181.5, 50.9, 44.0, 34.4, 28.9, 28.7, 25.5, 25.3, 7.7; IR (NaCl, $CDCl_3$) 3034, 2860, 1699, 1450, 1265, 1209, 1136 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{17}O_3$, 185.1178. Found 185.1175.

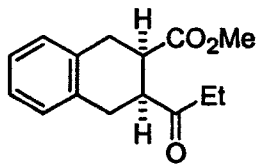


(1*R, 6*S**)-6-propionyl-cyclohex-3-enecarboxylic acid (28).** According to the general procedure, 39.0 mg (0.142 mmol) of $Ni(COD)_2$ and 26.5 mg (0.170 mmol) of bpy in 1 mL of THF was treated with 40 μL (0.27 mmol) of 4-(trifluoromethyl)styrene and 2.0 mL (1.0M solution in hexane, 2.0 mmol) of Et_2Zn at 0 °C. 212 mg (1.39 mmol) of anhydride **27** in 5 mL THF was added via cannula and the reaction was warmed to room temperature and stirred for 3 h. Upon work-up 240 mg (95 %) of desired acid **28** was isolated as a colorless oil: R_f = 0.48 (1:1 EtOAc/hex); ^1H NMR (300 MHz, $CDCl_3$) δ 5.63-5.71 (m, 2H), 3.03 (ddd, 1H, *J* = 6.4, 6.0, 3.3 Hz), 2.92 (ddd, 1H, *J* = 6.6, 6.2, 3.3 Hz), 2.29-2.64 (m, 7H), 1.03 (dd, 3H, *J* = 7.1, 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.2, 179.9, 125.7, 124.4, 46.2, 39.3, 33.0, 25.9, 25.5, 7.7; IR

(NaCl, neat) 3030, 1705, 1437, 1250 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{15}O_3$, 183.1021. Found 183.1021.

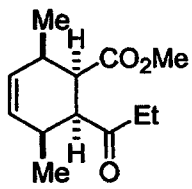


(1*R, 6*S**)-3,4-Dimethyl-6-propionyl-cyclohex-3-enecarboxylic acid (30).** According to the general procedure, 5.7 mg (0.021 mmol) of $Ni(COD)_2$ and 4.3 mg (0.028 mmol) of bpy in 1 mL of THF was treated with 5 μL (0.042 mmol) of 4-fluorostyrene and 50 μL (0.49 mmol) of Et_2Zn at 0 °C. 64 mg (0.36 mmol) of anhydride **29** in 1 mL THF was added via cannula and the reaction was stirred for 2 h at 0 °C. Upon work-up 67 mg (90 %) of desired acid **30** was isolated as a colorless oil: R_f = 0.45 (1:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 2.99 (ddd, 1H, *J* = 6.4, 6.4 3.5 Hz), 2.86 (ddd, 1H, *J* = 6.6, 6.6, 3.6 Hz), 2.48 (q, 2H, *J* = 7.0 Hz), 2.46-1.80 (m, 3H), 1.62 (s, 3H); 1.60 (s, 3H), 1.02 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6, 180.1, 124.7, 123.3, 47.0, 40.0, 33.0, 31.9, 31.6, 19.0, 18.8, 7.6; IR (NaCl, neat) 3272, 2982, 2922, 2859, 1701, 1248, 1112 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{19}O_3$, 211.1334. Found 211.1341.



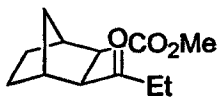
(2*R, 3*S**)-3-propionyl-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid methyl ester (32).** According to the general procedure, 5.1 mg (0.019 mmol) of $Ni(COD)_2$ and 3.4 mg (0.022 mmol) of bpy in 1 mL of THF was treated with 5 μL (0.042 mmol) of 4-fluorostyrene and 45 μL (0.44 mmol) of Et_2Zn at 0 °C. 73 mg (0.36 mmol) of anhydride **31** in 1 mL THF was added via cannula and the reaction was stirred for 4 h at 0 °C. Upon work-up the crude acid was taken up in 2 mL of MeOH/PhH (1:1) and $TMSCHN_2$ (2.0M in Et_2O)

was added dropwise until the persistence of yellow color, several drops of AcOH were then added. The reaction was concentrated and purified by column chromotograhpy (9 : 1 Hex/EtOAc) providing 80 mg (90 %) of methyl ester **32** as a colorless oil: $R_f = 0.18$ (4:1 EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (s, 4H), 3.66 (s, 3H), 3.32 (dd, 1H, J = 16.6, 6.6 Hz), 3.26-3.07 (m, 5H), 2.62 (dq, 1H, J = 17.9, 7.2 Hz), 2.52 (dq, 1H, J = 17.9, 7.2 Hz), 1.05 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.9, 173.7, 134.2, 133.6, 129.1, 128.9, 126.2, 126.0, 51.9, 47.1, 40.3, 33.4, 29.7, 29.4, 7.6; IR (NaCl, neat) 3061, 3019, 2976, 2938, 1739, 1709, 1436, 1363, 1198, 1107, 1022 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{19}O_3$, 247.1334. Found 247.1346.

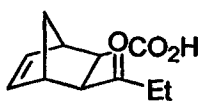


***(1R*, 2S*, 5R*, 6S*)*-2,5-Dimethyl-6-propionyl-cyclohex-3-enecarboxylic acid methyl ester (34).** According to the general procedure, 5.8 mg (0.021 mmol) of $Ni(COD)_2$ and 3.9 mg (0.025 mmol) of bpy in 1 mL of THF was treated with 5 μL (0.042 mmol) of 4-fluorostyrene and 50 μL (0.49 mmol) of Et_2Zn at 0 °C. 67 mg (0.37 mmol) of anhydride **33** in 1 mL THF was added via cannula and the reaction was stirred for 3 h at 0 °C. Upon work-up the crude acid was taken up in 2 mL of MeOH/PhH (1:1) and $TMSCHN_2$ (2.0M in Et_2O) was added dropwise until the persistence of yellow color, several drops of AcOH were then added. The reaction was concentrated and purified by column chromotograhpy (9 : 1 Hex/EtOAc) providing 51 mg (61 %) of methyl ester **34** as a colorless oil.: $R_f = 0.36$ (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61-5.57 (m, 1H), 5.51-5.47 (m, 1H), 3.66 (s, 3H), 3.14 (dd, 1H, *J* = 7.0, 4.3 Hz), 2.92 (dd, 1H, *J* = 6.8, 4.3 Hz), 2.72-2.67 (m 1H), 2.57-2.51 (m, 3H), 1.05 (d, 3H, *J* = 4.0 Hz), 1.03 (d, 3H, *J* = 7.0 Hz), 1.02 (t, 3H, J = 7.0

Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9, 173.7, 130.5, 129.4, 51.1, 51.0, 44.0, 36.4, 31.3, 30.7, 17.2, 17.0, 7.4; IR (NaCl, neat) 3016, 2972, 2880, 1730, 1715, 1456, 1436, 1373, 1159 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{21}O_3$, 225.1491. Found 225.1489.

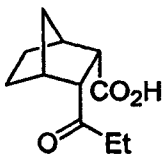


(2*S, 3*R**)-3-propionyl-bicyclo[2.2.1]heptane-2-carboxylic methyl ester (38).** According to the general procedure, 10.6 mg (0.0385 mmol) of $Ni(COD)_2$ and 6.9 mg (0.044 mmol) of bpy in 1 mL of THF was treated with 10 μL (0.068 mmol) of 4-(trifluoromethyl)styrene and 0.5 mL (1.0M solution in hexane, 0.5 mmol) of Et_2Zn at 0 °C. 60 mg (0.36 mmol) of anhydride **37** in 1 mL THF was added via cannula and the reaction was stirred 0 °C for 5 h. Upon work-up the crude acid was taken up in 2 mL of MeOH/PhH (1:1) and $TMSCHN_2$ (2.0M in Et_2O) was added dropwise until the persistence of yellow color, several drops of AcOH were then added. Upon concentration, 60 mg (79 %) of pure methyl ester **38** were obtained: R_f = 0.38 (4:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 3.57 (s, 3H), 2.89 (d, 1H, J = 9.6 Hz), 2.61-2.58 (m, 2H), 2.52-2.40 (m, 2H), 2.38 (s, 1H), 1.92 (d, 1H, J = 10.2 Hz), 1.64-1.53 (m, 2H), 1.27-1.17 (m, 3H), 1.01 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.9, 173.7, 57.1, 51.4, 50.8, 40.3, 39.0, 36.5, 35.3, 29.4, 28.6, 7.8; IR (NaCl, $CDCl_3$) 2953, 2875, 1742, 1714, 1456, 1435, 1346, 1238, 1198, 1174 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{19}O_3$, 211.1334. Found 211.1343.

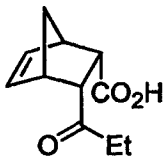


(2*R, 3*S**)-3-propionyl-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (40).** According to the general procedure, 9.8 mg (0.036 mmol) of $Ni(COD)_2$ and 6.8 mg (0.044 mmol) of bpy in 1 mL of THF was treated with 10 μL

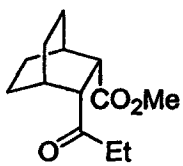
(0.068 mmol) of 4-(trifluoromethyl)styrene and 0.5 mL (1.0M solution in hexane, 0.5 mmol) of Et_2Zn at 0 °C. 63 mg (0.39 mmol) of anhydride **39** in 1 mL THF was added via cannula and the reaction was stirred 0 °C for 4 h. Upon work-up 68 mg (91 %) of desired acid **40** was isolated as an oil. Due to rotomers in NMR, the acid was converted to the corresponding methyl ester for characterization: $R_f = 0.28$ (4:1 Hex/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 6.18-6.22 (m, 2H), 3.61 (s, 3H), 3.13 (m, 1H), 2.91 (m, 1H), 2.80 (dd, 1H, J = 9.5, 1.6 Hz), 2.47-2.54 (m, 3H), 2.02 (m, 1H), 1.43 (m, 1H), 1.04 (dd, 3H, J = 7.0 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.1, 173.9, 138.0, 53.0, 51.7, 47.5, 45.9, 45.1, 45.0, 37.2, 7.9; IR (NaCl, $CDCl_3$) 2977, 1739, 1713, 1240 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{17}O_3$, 209.1178. Found 209.1179.



(2*S, 3*R**)-3-propionyl-bicyclo[2.2.1]heptane-2-carboxylic acid (42).** According to the general procedure, 10.3 mg (0.0374 mmol) of $Ni(COD)_2$ and 6.3 mg (0.040 mmol) of bpy in 1 mL of THF was treated with 10 μL (0.068 mmol) of 4-(trifluoromethyl)styrene and 0.5 mL (1.0M solution in hexane, 0.5 mmol) of Et_2Zn at 0 °C. 60 mg (0.36 mmol) of anhydride **41** in 1 mL THF was added via cannula and the reaction was stirred 0 °C for 3 h. Upon work-up 62 mg (88 %) of desired acid **42** was isolated as a white solid: mp = 96-97 °C (Et_2O); ^1H NMR (300 MHz, d_6-DMSO) δ 11.92 (s, 1H), 3.05 (dd, 1H, J = 11.2, 3.1 Hz), 2.94 (dd, 1H, J = 11.7, 3.7 Hz), 2.40-2.44 (m, 2H), 2.31 (dq, 1H, J = 17.2, 7.5 Hz), 2.25 (dq, 1H, J = 17.0, 7.3 Hz), 1.23-1.62 (m, 6H), 0.89 (dd, 3H, J = 7.2, 7.2 Hz); ^{13}C NMR (75 MHz, d_6-DMSO) δ 209.6, 178.5, 53.6, 46.9, 40.8, 40.0, 39.9, 35.8, 24.6, 23.3, 7.7; IR (NaCl, $CDCl_3$) 3095, 1734, 1709, 1205 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{17}O_3$, 197.1178. Found 197.1179.

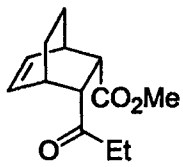


(2*S, 3*R**)-3-propionyl-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (44).** According to the general procedure, 10.0 mg (0.0364 mmol) of $Ni(COD)_2$ and 6.6 mg (0.042 mmol) of bpy in 1 mL of THF was treated with 10 μL (0.068 mmol) of 4-(trifluoromethyl)styrene and 0.5 mL (1.0M solution in hexane, 0.5 mmol) of Et_2Zn at 0 °C. 60 mg (0.37 mmol) of anhydride **43** in 1 mL THF was added via cannula and the reaction was stirred 0 °C for 4 h. Upon work-up 68 mg (96 %) of desired acid **44** was isolated as an oil. Due to rotomers in NMR, the acid was converted to the corresponding methyl ester for characterization: $R_f = 0.20$ (4:1 Hex/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 6.31 (dd, 1H, J = 5.5, 3.3 Hz), 6.07 (dd, 1H, J = 5.8, 3.3 Hz), 3.58 (s, 3H), 3.46 (dd, 1H, J = 9.3, 3.4 Hz), 3.19 (dd, 1H, J = 9.3, 3.7 Hz), 3.12-3.17 (m, 2H), 2.47 (dq, 1H, J = 17.6, 7.4 Hz), 2.38 (dq, 1H, J = 17.7, 7.1 Hz), 1.33 (m, 1H), 1.00 (dd, 3H, J = 7.1, 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.9, 173.3, 135.5, 133.5, 55.1, 51.5, 48.6, 48.2, 46.8, 46.2, 36.2, 7.9; IR (NaCl, neat) 2978, 1738, 1715, 1435, 1338 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{17}O_3$, 209.1178. Found 209.1174.

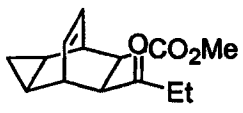


(2*R, 3*S**)-3-Propionyl-bicyclo[2.2.2]oct-5-ene-2-carboxylic acid methyl ester (46).** According to the general procedure, 5.1 mg (0.019 mmol) of $Ni(COD)_2$ and 3.8 mg (0.024 mmol) of bpy in 1 mL of THF was treated with 5 μL (0.042 mmol) of 4-fluorostyrene and 45 μL (0.44 mmol) of Et_2Zn at 0 °C. 65 mg (0.36 mmol) of anhydride **45** in 1 mL THF was added via cannula and the reaction was stirred 0 °C for 4 h. Upon work-up 69 mg (91 %) of desired acid **46** was

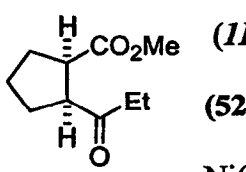
isolated as an oil. Due to rotomers in NMR, the acid was converted to the corresponding methyl ester for characterization: $R_f = 0.27$ (4:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 3.60 (s, 3H), 3.15 (dd, 1H, $J = 10.7, 2.1$ Hz), 2.68 (d, 1H, $J = 7.7$ Hz), 2.50-2.31 (m, 2H), 2.09-2.07 (m, 1H), 1.98 (s, 1H), 1.93-1.88 (m, 1H), 1.72-1.56 (m, 4H), 1.49-1.29 (m, 2H), 1.04 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3, 174.5, 51.7, 51.2, 43.4, 34.7, 27.3, 26.2, 25.8, 21.3, 21.1, 7.9; IR (NaCl, $CDCl_3$) 2944, 2869, 1735, 1717, 1458, 1434, 1356, 1192 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{21}O_3$, 225.1491. Found 225.1482.



(2*R, 3*S**)-3-Propionyl-bicyclo[2.2.2]oct-5-ene-2-carboxylic acid methyl ester (48).** According to the general procedure, 5.0 mg (0.018 mmol) of $Ni(COD)_2$ and 3.4 mg (0.022 mmol) of bpy in 1 mL of THF was treated with 5 μL (0.042 mmol) of 4-fluorostyrene and 45 μL (0.44 mmol) of Et_2Zn at 0 °C. 65 mg (0.36 mmol) of anhydride **47** in 1 mL THF was added via cannula and the reaction was stirred 0 °C for 4 h. Upon work-up 64 mg (84 %) of desired acid **48** was isolated as an oil. Due to rotomers in NMR, the acid was converted to the corresponding methyl ester for characterization: $R_f = 0.27$ (4:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 6.37 (t, 1H, $J = 7.2$ Hz), 6.16 (t, 1H, $J = 7.2$ Hz), 3.55 (s, 3H), 3.18 (dd, 1H, $J =$ 10.8, 1.6 Hz), 2.94-2.91 (m, 2H), 2.81-2.79 (m, 1H), 2.49-2.33 (m, 2H), 1.60-1.49 (m, 2H), 1.37-1.25 (m, 2H), 1.00 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.0, 173.8, 133.2, 131.4, 54.2, 51.4, 47.8, 35.7, 32.6, 32.1, 25.0, 24.5, 7.9; IR (NaCl, $CDCl_3$) 30.52, 2945, 2870, 1740, 1718, 1460, 1434, 1197, 1166 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{19}O_3$, 223.1334. Found 223.1331.

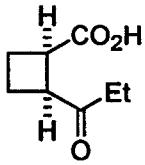


Tricyclic methyl ester 50. According to the general procedure, 11.4 mg (0.0414 mmol) of $Ni(COD)_2$ and 6.8 mg (0.044 mmol) of bpy in 1 mL of THF was treated with 10 μL (0.084 mmol) of 4-fluorostyrene and 50 μL of Et_2Zn (0.49 mmol) at 0 °C. 75 mg (0.36 mmol) of anhydride **49** in 1.0 mL THF was added via cannula and the reaction was stirred for 18 h at 0 °C. Upon work-up crude acid was taken up in 2 mL of MeOH/PhH (1:1) and $TMSCHN_2$ (2.0M in Et_2O) was added dropwise until the persistence of yellow color, several drops of AcOH were then added. The reaction was concentrated and purified by column chromotograhpy (9 : 1 Hex/EtOAc) providing 66 mg (68 %) of methyl ester **50** as a colorless solid: mp = 74-76 °C; R_f = 0..19 (4 : 1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 5.93 (t, 1H, J = 7.2 Hz), 5.74 (t, 1H, J = 7.2 Hz), 3.56 (s, 3H), 3.26 (dd, 1H, J = 10.2, 1.9 Hz), 3.18-3.16 (m, 1H), 3.05-3.03 (m, 1H), 3.02 (dd, 1H, J = 10.2, 2.0 Hz), 2.52-2.36 (m, 2H), 1.01 (t, 3H, J = 7.2 Hz), 0.98-0.92 (m, 2H), 0.20-0.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.4, 174.1, 128.5, 127.0, 55.2, 51.7, 48.9, 36.4, 34.6, 34.1, 10.2, 9.7, 8.1, 3.1; IR (NaCl, dep. $CHCl_3$) 3059, 3014, 2978, 2951, 1734, 1711, 1430, 1372, 1196, 1047, 949 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{19}O_3$, 235.1334. Found 235.1335.

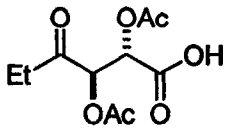


***(1R*,2S*)*-2-Propionyl-cyclopentanecarboxylic acid methyl ester (52).** According to the general procedure, 5.6 mg (0.020 mmol) of $Ni(COD)_2$ and 4.0 mg (0.026 mmol) of bpy in 1 mL of THF was treated with 5 μL (0.042 mmol) of 4-fluorostyrene and 50 μL of Et_2Zn (0.49 mmol) at 0 °C. 50 mg (0.36 mmol) of anhydride **51** in 1 mL THF was added via cannula and the reaction

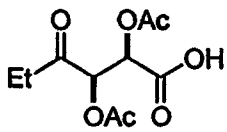
was stirred for 3 h at 0 °C. Upon work-up the crude acid was taken up in 2 mL of MeOH/PhH (1:1) and $TMSCHN_2$ (2.0M in Et_2O) was added dropwise until the persistence of yellow color, several drops of AcOH were then added. The reaction was concentrated and purified by column chromotograhpy (9:1 Hex/EtOAc) providing 47 mg (71 %) of methyl ester **52** as a colorless oil: R_f = 0.27 (4:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 3.60 (s, 3H), 3.15 (q, 1H, J = 7.9 Hz), 2.97 (q, 1H, J = 7.9 Hz), 2.47 (q, 1H, J = 7.1 Hz), 2.08-1.76 (m, 5H), 1.67-1.56 (m, 1H), 1.01 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.0, 174.7, 53.4, 51.5, 46.8, 35.3, 28.4, 28.3, 23.9, 7.6; IR (NaCl, neat) 2966, 2952, 2876, 1734, 1710, 1456, 1436, 1363, 1201 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{17}O_3$, 185.1178. Found 185.1179.



(1*R, 2*S**)-2-propinoyl-cyclobutanecarboxylic acid (54).** According to the general procedure, 11.4 mg (0.0414 mmol) of $Ni(COD)_2$ and 12.9 mg (0.0443 mmol) of PYPHOS in 1 mL of THF was treated with 10 μL (0.068 mmol) of 4-(trifluoromethyl)styrene and 0.5 mL (1.0M solution in hexanes, 0.5 mmol) Et_2Zn at 0°C. 46 mg (0.37 mmol) of anhydride **53** in 1 mL THF was added via cannula and the reaction was stirred 0 °C for 4 h. Upon work-up 35 mg (61 %) of desired acid **54** was isolated as an oil: R_f = 0.28 (1:1 Hex/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 3.32-3.57 (m, 2H), 2.07-2.49 (m, 6H), 1.03 (dd, 3H, J = 7.3 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.5, 179.7, 47.0, 40.7, 34.3, 21.9, 21.8, 7.9; IR (NaCl, neat) 3073, 2741, 1699, 1414 cm^{-1}; HRMS (FAB+) calcd for $C_8H_{13}O_3$, 157.0865. Found 157.0864.

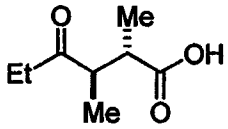


***(2S*, 3R*)*-2,3-diacetoxy-4-oxo-hexanoic acid (56).** According to the general procedure, 5.2 mg (0.019 mmol) of $Ni(COD)_2$ and 3.5 mg (0.022 mmol) of bpy in 1 mL of THF was treated with 5 μL (0.042 mmol) of 4-fluorostyrene and 50 μL (0.49 mmol) of Et_2Zn at 0 °C. 77 mg (0.35 mmol) of anhydride **55** in 1 mL THF was added via cannula and the reaction was stirred 0 °C for 16 h. Upon work-up 65 mg (74 %) of desired acid **56** was isolated as an oil: R_f = 0.23 (95:5 CH_2Cl_2/MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 5.71 (d, 1H, J = 2.6 Hz), 5.63 (d, 1H, J = 2.6 Hz), 2.62 (dq, 1H, J = 19.1, 7.2 Hz), 2.43 (dq, 1H, J = 19.0, 7.2 Hz), 2.21 (s, 3H), 2.15 (s, 3H), 1.06 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 170.9, 169.8, 169.6, 76.7, 70.8, 32.5, 20.7, 20.5, 6.9; IR (NaCl, neat) 3214, 2982, 2945, 1749, 1375, 1221, 1106, 1049 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{15}O_7$, 247.0818. Found 247.0827.

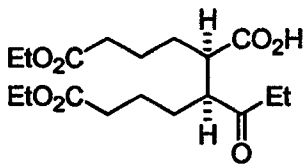


***(2R*, 3R*)*-2,3-diacetoxy-4-oxo-hexanoic acid (58).** According to the general procedure, 10.9 mg (0.0396 mmol) of $Ni(COD)_2$ and 6.4 mg (0.041 mmol) of bpy in 1 mL of THF was treated with 10 μL (0.068 mmol) of 4-(trifluoromethyl)styrene and 0.5 mL (1.0M solution in hexane, 0.5 mmol) of Et_2Zn at 0 °C. 79 mg (0.36 mmol) of anhydride **57** in 1 mL THF was added via cannula and the reaction was stirred 0 °C for 5 h. Upon work-up 80 mg (88 %) of desired acid **58** was isolated as an oil: R_f = 0.61 (4:1 CH_2Cl_2/MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 5.70 (d, 1H, *J* = 2.5 Hz), 5.64 (d, 1H, *J* = 2.6 Hz), 2.58 (dq, 1H, *J* = 18.6, 7.3 Hz) , 2.43 (dq, 1H, *J* = 18.6, 7.3 Hz), 2.20 (s, 3H), 2.13 (s, 3H), 1.06 (dd, 3H, *J* = 7.1, 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.6, 170.9, 170.0, 169.6, 76.3, 70.2, 32.3, 20.5, 20.3, 7.7; IR (NaCl,

neat) 3196, 2983, 1755, 1713, 1375 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{15}O_7$, 247.0818. Found 247.0816.

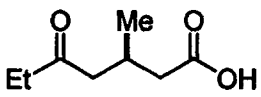


***(2S*, 3R*)*-2,3-dimethyl-4-oxo-hexanoic acid (60).** According to the general procedure, 10.3 mg (0.0374 mmol) of $Ni(COD)_2$ and 6.0 mg (0.0384 mmol) of bpy in 1 mL of THF was treated with 10 μL (0.068 mmol) of 4-(trifluoromethyl)styrene and 0.5 mL (1.0M solution in hexane, 0.5 mmol) of Et_2Zn at 0 °C. 46 mg (0.36 mmol) of anhydride **59** in 1 mL THF was added via cannula and the reaction was stirred 0 °C for 5 h. Upon work-up 53 mg (93 %) of desired acid **60** was isolated as an oil: $R_f = 0.38$ (1:1 Hex/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 2.74-2.85 (m, 2H), 2.57 (dq, 1H, $J = 18.0, 7.2$ Hz) , 2.43 (dq, 1H, $J = 18.0, 7.2$ Hz), 1.12-1.17 (m, 6H), 1.05 (dd, 3H, $J = 7.3$ 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.2, 180.9, 48.2, 41.8, 35.3, 15.2, 15.0, 7.7; IR (NaCl, neat) 3093, 2941, 1713, 1381 cm^{-1}; HRMS (FAB+) calcd for $C_8H_{15}O_3$, 159.1021. Found 159.1026.

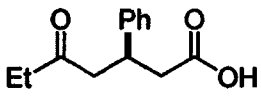


***(5R*, 6S*)*-5-carboxy-6-propionyl-decanedioic acid diethyl ester (62).** According to the general procedure, 5.4 mg (0.020 mmol) of $Ni(COD)_2$ and 4.3 mg (0.028 mmol) of bpy in 1 mL of THF was treated with 5 μL (0.042 mmol) of 4-fluorostyrene and 50 μL (0.49 mmol) of Et_2Zn at 0 °C. 116 mg (0.353 mmol) of anhydride **61** in 1.0 mL THF was added via cannula and the reaction was stirred 0 °C for 4 h. Upon work-up 95 mg (75 %) of desired acid **62** was isolated as an oil: $R_f = 0.38$ (1:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 4.08 (q, 2H, $J = 6.9$ Hz), 4.07 (q, 2H, $J = 7.0$ Hz), 2.81-2.77 (m, 1H), 2.67-2.62 (m,

1H), 2.47 (q, 2H, J = 7.2 Hz), 2.32-2.22 (m, 4H), 1.68-1.43 (m, 7H), 1.36-1.29 (m, 1H), 1.21 (t, 6H, J = 7.0 Hz), 1.02 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.0, 178.9, 173.3, 173.2, 60.4, 53.0, 47.2, 37.3, 34.0, 33.7, 29.8, 29.7, 22.8, 22.3, 14.1, 7.3; IR (NaCl, neat) 3208, 2980, 2941, 1735, 1701, 1459, 1375, 1185, 1030 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{31}O_7$, 359.2070. Found 359.2070.

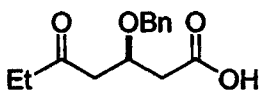


3-methyl-5-oxo-heptanoic acid (64). According to the general procedure, 11.1 mg (0.0404 mmol) of $Ni(COD)_2$ and 14.0 mg (0.0481 mmol) of PYPHOS in 1 mL of THF was treated with 10 μL (0.0675 mmol) of 4-(trifluoromethyl)styrene and 0.5 mL (1.0M solution in hexane, 5.0 mmol) of Et_2Zn at 0 °C. 49 mg (0.38 mmol) of anhydride **63** in 1 mL THF was added via cannula and the reaction was stirred for 10 h at ambient temperature. Upon work-up 49 mg (81 %) of desired acid **64** was isolated as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.70 (br s, 1H), 2.54-2.20 (m, 7H), 1.02 (t, 3H, J = 7.3 Hz), 0.98 (d, 3H, J = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.4, 178.6, 48.4, 40.6, 36.4, 26.2, 20.0, 7.8.

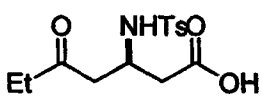


3-phenyl-5-oxo-heptanoic acid (66). According to the general procedure, 9.5 mg (0.035 mmol) of $Ni(COD)_2$ and 13.1 mg (0.0450 mmol) of PYPHOS in 1 mL of THF was treated with 10 μL (0.068 mmol) of 4-fluorostyrene and 50 μL of Et_2Zn (0.49 mmol) at 0 °C. 69 mg (0.36 mmol) of anhydride **65** in 1 mL THF was added via cannula and the reaction was stirred for 4 h at 0 °C. Upon work-up 62 mg (78 %) of desired acid **66** was isolated as a white solid: mp = 82-84 °C (EtOAc); R_f = 0.21 (1:1 EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.35-7.31 (m, 2H),

7.26-7.24 (m, 3H), 3.72 (dddd, 1H, J = 7.2, 7.2, 7.2, 7.2 Hz), 2.84-2.82 (m, 2H), 2.77 (dd, 1H, J = 16.0, 7.0 Hz), 2.68 (dd, 1H, J = 16.0, 7.7 Hz), 2.39 (dq, 1H, J = 17.7, 7.3 Hz), 2.31 (dq, 1H, J = 17.9, 7.3 Hz), 0.99 (t, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 177.4, 142.9, 128.7, 127.2, 126.9, 48.1, 40.2, 37.0, 36.5, 7.5; IR (NaCl, dep from $CHCl_3$) 3032, 2982, 2943, 1713, 1416, 1269, 1115, 960 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{17}O_3$, 221.1178. Found 221.1178.

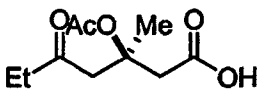


3-benzyloxy-5-oxo-heptanoic acid (68). According to the general procedure, 5.0 mg (0.018 mmol) of $Ni(COD)_2$ and 6.1 mg (0.021 mmol) of PYPHOS in 1 mL of THF was treated with 5 μL (0.042 mmol) of 4-fluorostyrene and 45 μL of Et_2Zn (0.44 mmol) at 0 °C. 80 mg (0.36 mmol) of anhydride **67** in 1 mL THF was added via cannula and the reaction was stirred for 4 h at 0 °C. Upon work-up 47 mg (52 %) of desired acid **68** was isolated as a colorless oil: R_f = 0.21 (1:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.24 (m, 5H), 4.58 (d, 1H, J = 11.1 Hz), 4.51 (d, 1H, J = 11.1 Hz), 4.35 (dddd, 1H, J = 6.0, 6.0, 6.0, 6.0 Hz), 2.82 (dd, 1H, J = 16.4, 6.8 Hz), 2.67-2.62 (m, 3H), 2.41 (q, 2H, J = 7.2 Hz), 1.02 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 176.7, 138.0, 128.6, 128.1, 128.0, 72.5, 72.2, 47.0, 39.4, 37.2, 7.7; IR (NaCl, neat) 3163, 3032, 2978, 2939, 1713, 1454, 1408, 1377, 1211, 1092, 1065 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{19}O_4$, 251.1283. Found 251.1284.



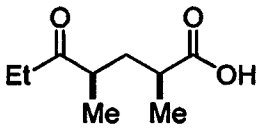
5-oxo-3-(toluene-4-sulfonylamino)-heptanoic acid (70). According to the general procedure, 5.0 mg (0.018 mmol) of $Ni(COD)_2$ and 6.1 mg (0.021 mmol) of PYPHOS in 1 mL of THF was treated with 5 μL

(0.042 mmol) of 4-fluorostyrene and 50 μL of Et_2Zn (0.49 mmol) at 0 °C. 87 mg (0.36 mmol) of anhydride **69** in 1 mL THF was added via cannula and the reaction was stirred for 6 h at 0 °C then warmed to ambient temperature and stirred an additional 18 h. Work-up afforded the crude acid that was purified by column chromatography (95:5 CH_2Cl_2/MeOH) providing 55 mg (57%) of the desired acid **70** was isolated as a white solid: mp = 138-140 °C ($CHCl_3$/MeOH); R_f = 0.13 (1:1 EtOAc/Hex); ^1H NMR (400 MHz, CD_3OD) δ 7.72 (d, 2H, J = 8.3 Hz), 7.36 (d, 2H, *J* = 8.1 Hz), 3.98 (m, 1H), 2.67 (dd, 1H, *J* = 16.8, 6.2 Hz), 2.59 (dd, 1H, *J* = 16.8, 6.4 Hz), 2.42 (s, 3H), 2.41-2.40 (m, 2H), 2.33 (q, 2H, *J* = 7.3 Hz), 0.91 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 210.9, 174.3, 144.9, 139.9, 130.9, 128.3, 47.7, 40.4, 37.1, 21.6, 7.9; IR (NaCl, dep. $CHCl_3$) 3163, 3032, 2978, 2939, 1713, 1454, 1408, 1377, 1211, 1092, 1065 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{20}NO_5S$, 314.1062. Found 314.1069.

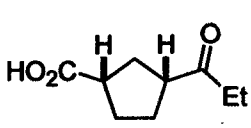


3-acetoxy-3-methyl-5-oxo-heptanoic acid (72). According to the general procedure, 5.0 mg (0.018 mmol) of $Ni(COD)_2$ and 6.1 mg (0.021 mmol) of PYPHOS in 1 mL of THF was treated with 5 μL (0.042 mmol) of 4-fluorostyrene and 50 μL of Et_2Zn (0.49 mmol) at 0 °C. 34 mg (0.18 mmol) of anhydride **71** in 1 mL THF was added via cannula and the reaction was stirred for 4 h at 0 °C. Work-up afforded the 29 mg (75 %) of the desired acid **72** as a colorless oil: R_f = 0.26 (1:1 EtOAc/Hex); ^1H NMR (400 MHz, $CDCl_3$) δ 3.25 (d, 1H, *J* = 16.8 Hz), 3.18 (d, 1H, *J* = 17.2 Hz), 3.11 (s, 2H), 2.44 (q, 2H, *J* = 7.3 Hz), 2.00 (s, 3H), 1.64 (s, 3H), 1.04 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.6, 174.9, 170.5, 79.5, 48.6, 41.9, 37.4,

24.9, 22.2, 7.5; IR (NaCl, neat) 3243, 2979, 2941, 1734, 1718, 1372, 1251 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{17}O_5$, 217.1076. Found 217.1069.

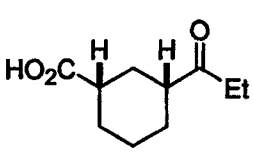


(*2S*,4R)-2,4-Dimethyl-5-oxo-heptanoic acid (74).** According to the general procedure, 9.8 mg (0.036 mmol) of $Ni(COD)_2$ and 13.5 mg (0.0463 mmol) of PYPHOS in 1 mL of THF was treated with 10 μL (0.084 mmol) of 4-fluorostyrene and 50 μL of Et_2Zn (0.49 mmol) at 0 °C. 52 mg (0.37 mmol) of anhydride **73** in 0.4 mL THF was added via syringe and the reaction was stirred for 14 h at 0 °C. Upon work-up 53 mg (85 %) of desired acid **74** was isolated as a colorless oil: R_f = 0.21 (1:1 EtOAc/Hex); ^1H NMR (300 MHz, $CDCl_3$) δ 10.49 (br s, 1H), 2.68-2.58 (m, 1H), 2.55-2.38 (m, 2H), 2.07 (ddd, 1H, *J* = 13.9, 8.9, 6.2 Hz), 1.27 (ddd, 1H, *J* = 14.2, 7.9, 6.0 Hz), 1.19 (d, 3H, *J* = 7.1 Hz), 1.09 (d, 3H, *J* = 6.9 Hz), 1.03 (dd, 3H, *J* = 7.1, 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.3, 182.3, 43.8, 37.3, 36.2, 34.1, 17.7, 16.9, 7.8; IR (NaCl, neat) 3093, 2976, 2939, 1737, 1713, 1464, 1379 cm^{-1}; HRMS (FAB+) calcd for $C_9H_{17}O_3$, 172.1099. Found 172.1097.

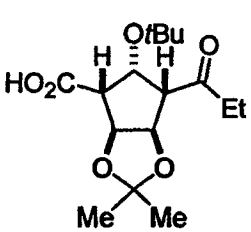


(*1S*,3R)-3-Propionyl-cyclopentanecarboxylic acid (76).** According to the general procedure, 24.5 mg (0.0891 mmol) of $Ni(COD)_2$ and 28.1 mg (0.0965 mmol) of PYPHOS in 4 mL of THF was treated with 20 μL (0.17 mmol) of 4-fluorostyrene and 250 μL of Et_2Zn (2.44 mmol) at 0 °C. 264 mg (1.88 mmol) of anhydride **75** in 2 mL THF was added via cannula and the reaction was stirred for 14 h at 0 °C. Upon work-up 288 mg (90 %) of the desired acid **76** was isolated as a colorless oil: R_f = 0.42 (1:1 EtOAc/Hex); ^1H NMR (400 MHz, $CDCl_3$) δ 2.94 (dddd,

1H, J = 7.9, 7.9, 7.9, 7.9 Hz), 2.85 (dddd, 1H, J = 7.9 7.9 7.9 7.9 Hz), 2.48 (q, 2H, J = 7.2 Hz), 2.21-2.14 (m, 1H), 2.11-2.03 (m, 1H), 1.99-1.84 (m, 4H), 1.05 (t, 2H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.6, 181.1, 51.0, 43.8, 34.7, 32.1, 29.1, 28.4, 7.8; IR (NaCl, neat) 3095, 2973, 2943, 2879, 1734, 1709, 1452, 1414, 1377, 1240 cm^{-1}; HRMS (FAB+) calcd for $C_9H_{15}O_3$, 171.1021. Found 171.1027.

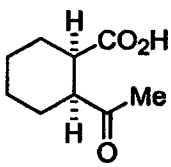


(*1S*,3R)-3-Propionyl-cyclohexanecarboxylic acid (78).** According to the general procedure, 5.4 mg (0.020 mmol) of $Ni(COD)_2$ and 7.0 mg (0.024 mmol) of PYPHOS in 1 mL of THF was treated with 5.0 μL (0.042 mmol) of 4-fluorostyrene and 45 μL of Et_2Zn (0.44 mmol) at 0 °C. 55 mg (0.36 mmol) of anhydride **77** in 1 mL THF was added via syringe and the reaction was stirred for 4 h at 0 °C. Upon work-up 58 mg (88 %) of the desired acid **78** was isolated as a colorless oil: R_f = 0.24 (1:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 2.45 (q, 2H, *J* = 7.3 Hz), 2.41-2.29 (m, 2H), 2.13-2.09 (m, 1H), 1.90-1.84 (m, 2H), 1.46 (q, 1H, *J* = 12.5 Hz), 1.35-1.22 (m, 3H), 1.00 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.4, 181.4, 49.4, 42.4, 33.8, 30.2, 28.1, 27.8, 24.8, 7.7; IR (NaCl, neat) 3180, 2937, 2861, 1735, 1707, 1448, 1413, 1378, 1264, 1218 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{17}O_3$, 185.1178. Found 185.1181.



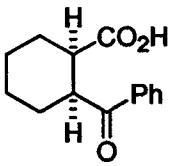
(*1S*,3R)-5-tert-Butoxy-2,2-dimethyl-6-propionyl-tetrahydro-cyclopenta[1,3]dioxole-4-carboxylic acid (80).** According to the general procedure, 4.7 mg (0.017 mmol) of $Ni(COD)_2$ and 6.1 mg

(0.021 mmol) of PYPHOS in 1 mL of THF was treated with 5 μL (0.042 mmol) of 4-fluorostyrene and 45 μL of Et_2Zn (0.440 mmol) at 0 °C. 50 mg (0.176 mmol) of anhydride **79** in 1 mL THF was added via syringe and the reaction was stirred for 19 h at 0 °C. A modified work-up was used. The reaction was diluted with Et_2O (10 mL) washed with 1M aq. citric acid. The aqueous layer was separated and extracted with Et_2O (2 X 10 mL). Organics were combined and extracted with 1M aq. Na_2CO_3 (2 X 5 mL). Basic layer were combined and acidified with solid citric acid (~1.3 g). The acidified aqueous layer was extracted with Et_2O (3 X 10 mL). Organics were combined, washed with H_2O (3 X 10 mL), brine, dried over $MgSO_4$, filtered and concentrated to provide 58 mg (88 %) of the desired acid **80** was isolated as a colorless oil: $R_f = 0.44$ (1:1 Hex/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 5.23 (dd, 1H, $J = 6.2, 1.2$ Hz), 4.72 (dd, 1H, $J = 7.7, 7.7$ Hz), 4.63 (d, 1H, $J = 6.2$ Hz), 3.30 (d, 1H, $J = 7.4$ Hz), 2.92 (dd, 1H, $J = 8.2, 1.0$ Hz), 2.60 (dq, 1H, $J = 18.3, 7.2$ Hz), 2.49 (dq, 1H, $J = 18.5, 7.2$ Hz), 1.44 (s, 3H), 1.32 (s, 9H), 1.27 (s, 3H), 1.02 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.0, 170.5, 110.0, 80.6, 78.4, 73.1, 59.7, 52.2, 38.7, 27.6, 26.5, 23.8, 7.2; IR (NaCl, neat) 3417, 2979, 2939, 1770, 1714, 1548, 1252, 1214, 1007 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{27}O_6$, 315.1808. Found 315.1801.

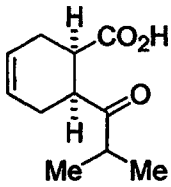


***(1R*, 2S*)*-2-acetyl-cyclohexanecarboxylic acid (E11).** According to the general procedure, 11.2 mg (0.0407 mmol) of $Ni(COD)_2$ and 15.6 mg (0.0535 mmol) of PYPHOS in 1 mL of THF was treated with 10 μL (0.068 mmol) of 4-(trifluoromethyl)styrene and 0.5 mL (1.0M solution in hexane, 0.5 mmol) of Me_2Zn at 0 °C. 56.0 mg (0.36 mmol) of anhydride **10** in 1 mL THF was added

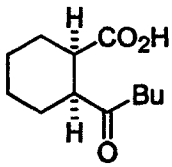
via cannula and the reaction was stirred for 15 min. at 0 °C. Upon work-up 53 mg (86%) of desired acid **E11** was isolated as a white solid: mp = 71-73 °C (Et_2O); ^1H NMR (300 MHz, $CDCl_3$) δ 2.72-2.82 (m, 2H), 2.15 (s, 3H), 1.94-2.10 (m, 2H), 1.71-1.85 (m, 2H), 1.53 (m, 1H), 1.33-1.45 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.7, 180.1, 50.0, 42.3, 27.9, 26.1, 25.9, 23.8, 23.7; IR (NaCl, $CDCl_3$) 3084, 2937, 1770, 1705, 1223 cm^{-1}; HRMS (FAB+) calcd for $C_9H_{15}O_3$, 171.1021. Found 171.1018.



***(1R*, 2S*)*-2-benzoyl-cyclohexanecarboxylic acid (E12).** According to the general procedure, 9.5 mg (0.035 mmol) of $Ni(COD)_2$ and 12.2 mg (0.0419 mmol) of PYPHOS in 1 mL of THF was treated with 10 μL (0.068 mmol) of 4-(trifluoromethyl)styrene and 86 mg (0.39 mmol) of Ph_2Zn in 1 mL THF at 0 °C. 56 mg (0.36 mmol) of anhydride **10** in 1 mL THF was added via cannula and the reaction was stirred for 2 h at 0 °C then warmed to room temperature and stirred an additional 11 h. Upon work-up 74 mg (88%) of desired acid **E12** was isolated as a white solid. The acid was characterized as the corresponding methyl ester: R_f = 0.23 (4:1 Hex/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.85-7.88 (m, 2H), 7.53 (m, 1H), 7.41-7.47 (m, 2H), 3.89 (m, 1H), 3.61 (s, 3H), 2.73 (ddd, 1H, J = 9.0, 4.3, 4.3), 2.20 (m, 1H), 2.07 (m, 1H), 1.95 (m, 1H), 1.71-1.86 (m, 2H), 1.31-1.50 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 174.3, 136.6, 132.4, 128.4, 128.0, 51.6, 44.4, 42.9, 27.5, 25.6, 24.3, 22.8; IR (NaCl, $CDCl_3$), 2945, 1734, 1682, 1448 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{19}O_3$, 247.1334. Found 247.1339.

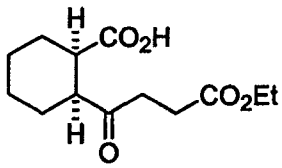


(1*R, 6*S**)-6-Isobutyryl-cyclohex-3-enecarboxylic acid (E13).** According to the general procedure, 5.4 mg (0.020 mmol) of $Ni(COD)_2$ and 4.4 mg (0.028 mmol) of bpy in 1 mL of THF was treated with 5 μL (0.042 mmol) of 4-fluorostyrene and 0.4 mL (1.0 M in hexanes, 0.400 mmol) of ι-Pr_2Zn at 0 °C. 50 mg (0.33 mmol) of anhydride **27** in 1 mL THF was added via cannula and the reaction was stirred for 1 h at 0 °C. Upon work-up 51 mg (77 %) of desired acid **E13** was isolated as a colorless oil: R_f = 0.29 (1:1 EtOAc/hex); ^1H NMR (400 MHz, $CDCl_3$) δ 5.71-5.64 (m, 2H), 3.15 (ddd, 1H, *J* = 6.4, 6.4, 3.6 Hz), 2.95 (ddd, 1H, *J* = 6.8, 6.8, 3.6 Hz), 2.97-2.82 (m, 1H), 2.67-2.61 (m, 1H), 2.47-2.32 (m, 3H), 1.10 (d, 3H, *J* = 6.8 Hz), 1.04 (d, 3H, *J* = 6.8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.9, 179.8, 125.9, 124.2, 44.5, 39.3, 37.4, 25.7, 25.5, 19.0, 18.3; IR (NaCl, neat) 3277, 3028, 2973, 2930, 1704, 1436, 1251, 1212 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{17}O_3$, 197.1178. Found 197.1177.



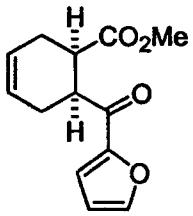
***(1R*, 2S*)*-2-pentanoyl-cyclohexanecarboxylic acid methyl ester (E14).** According to the general procedure, 11.4 mg (0.0414 mmol) of $Ni(COD)_2$ and 19.9 mg (0.0499 mmol) of 1,2-bis(diphenylphosphino)ethane (DPPE) in 1 mL of THF was treated with 10 μL (0.068 mmol) of 4-(trifluoromethyl)styrene and 1.0 mL (0.5M solution in THF, 0.5 mmol) of BuZnBr at 0 °C. 56 mg (0.36 mmol) of anhydride **10** in 0.32 mL THF was added via syringe and the reaction was stirred from 0 °C to room temperature for 14 h. Work-up (1M HCl (aq.) quench followed by extraction with Et_2O (3 X10 mL)) yielded 75 mg of crude acid which was esterified with CH_2N_2 in Et_2O at 0 °C. The crude methyl ester was purified via flash column chromotography (9:1 Hex/EtOAc) to yield 55 mg (67%) of desired ester **E14** as a colorless oil: R_f = 0.40 (4:1

Hex/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.62 (s, 3H), 2.78-2.71 (m, 2H), 2.44 (dd, 2H, J = 7.7, 6.9 Hz), 2.06-1.93 (m, 2H), 1.83-1.71 (m, 2H), 1.57-1.35 (m, 6H), 1.27 (tq, 2H, J = 9.5, 7.3 Hz), 0.87 (t, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.7, 174.3, 51.5, 49.5, 42.4, 39.9, 26.2, 26.0, 25.8, 23.9, 23.7, 22.4, 14.0; IR (NaCl, neat) 2935, 2860, 1734, 1709,1450, 1434, 1196 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{23}O_3$, 227.1647. Found 227.1643.

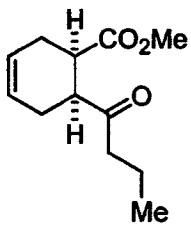


***(1R*, 2S*)*-2-(3-ethoxycarbonyl-propionyl)-cyclohexanecarboxylic acid methyl ester (E15).** According to the general procedure, 9.7 mg (0.035 mmol) of $Ni(COD)_2$ and 17.3 mg (0.0434 mmol) of 1,2-bis(diphenylphosphino)ethane (DPPE) in 1 mL of THF was treated with 10 μL (0.068 mmol) of 4-(trifluoromethyl)styrene and 1.0 mL (0.5M solution in THF, 0.5 mmol) of 3-ethoxy-3-oxopropylxinc bromide at 0 °C. 56 mg (0.36 mmol) of anhydride **10** in 0.21 mL THF was added via syringe and the reaction was stirred from 0 °C to room temperature for 14 h. Work-up (1M HCl (aq.) quench followed by extraction with Et_2O (3 X10 mL)) yielded 69.0 mg of crude acid which was esterified with CH_2N_2 in Et_2O at 0 °C. The crude methyl ester was purified via flash column chromotography (17:3 Hex/EtOAc) to yield 50 mg (53%) of desired ester **E15** as a colorless oil: R_f = 0.21 (4:1 Hex/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (q, 2H, J = 7.1 Hz), 3.62 (s, 3H), 2.89-2.72 (m, 4H), 2.55 (ddd, 2H, J = 6.5, 6.3, 2.7 Hz), 2.08-1.95 (m, 2H), 1.88-1.69 (m, 2H), 1.54-1.35 (m, 4H), 1.23 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.6, 174.2, 172.7, 60.5, 51.6, 49.4, 42.5, 34.9, 28.0, 26.4, 25.8, 23.8,

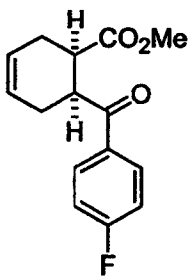
23.7, 14.2; IR (NaCl, neat) 2937, 2858, 1732, 1713,1450,1373, 1198 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{23}O_5$, 271.1545. Found 271.1544.



(1*R*, 6*S*) 6-(Furan-2-carbonyl)-cyclohex-3-enecarboxylic acid methyl ester (E16). Preparation of difurylzinc: A flame dried round bottom flask was charged with 0.160 mL (2.20 mmol) of freshly distilled furan in 1 mL of THF. The vessel was cooled to 0 °C and 0.63 mL (1.0 mmol) of *n*BuLi (1.6M in hexanes) was added via syringe. After stirring for 30 min., 136 mg (1.00 mmol) of $ZnCl_2$ in 1 mL of THF was added via cannula. The resulting solution was stirred an additional 30 min. before use providing a 0.38M solution of difurylzinc. According to the general procedure, 4.5 mg (0.016 mmol) of $Ni(COD)_2$ and 3.2 mg (0.021 mmol) of bpy in 1 mL of THF was treated with 5 μL (0.042 mmol) 4-fluorostyrene, nucleophile solution was added followed by addition of 50 mg (0.33 mmol) of anhydride **27** in 0.25 mL THF. The reaction was stirred for 4 h at 0 °C. Upon work-up the crude acid was converted corresponding methyl ester. Purification (9:1 Hex/EtOAc) yielded 47 mg (61 %) of product ester **E16** as a colorless oil. R_f = 0.17 (4:1 Hex/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, 1H, J = 1.8 Hz), 7.18 (d, 1H, J = 4.0 Hz), 6.52 (dd, 1H, J = 3.7, 1.8 Hz), 5.71-5.77 (m, 1H), 5.65-5.69 (m, 1H), 3.75 (ddd, 1H, J = 6.6, 6.6, 4.0 Hz), 3.62 (s, 3H), 3.06 (ddd, 1H, J = 6.6, 6.6, 3.7), 2.66-2.77 (m, 1H), 2.39-2.61 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.7, 173.7, 152.3, 145.6, 125.4, 123.9, 116.8, 112.1, 51.7, 42.0, 39.6, 26.2, 25.8; IR (NaCl, neat) 3134, 3028, 2951, 2918, 1736, 1676, 1568, 1468, 1435, 1202, 1016 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{15}O_4$, 235.0970. Found 235.0980.

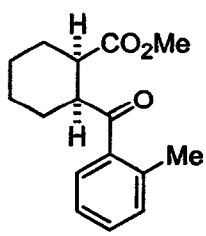


(1*R, 6*S**) 6-Butyryl-cyclohex-3-enecarboxylic acid methyl ester (E17).** Preparation of dipropylzinc: A flame dried round bottom flask was charged with 0.44 mL (2.0 M in Et_2O, 0.880 mmol) of *n*-propylmagnisium bromide in 1 mL of THF. Upon cooling to 0 °C, 62.0 mg of $ZnCl_2$ (0.440 mmol) in 1 mL of THF was added via cannula and reaction stirred for 0.5 h before warming to ambient temperature and stirring an additional 1.5 h before use. According to the general procedure, 5.0 mg (0.018 mmol) of $Ni(COD)_2$ and 3.4 mg (0.022 mmol) of bpy in 1 mL of THF was treated with 5 μL (0.042 mmol) 4-fluorostyrene, nucleophile solution was added via cannula followed by addition of 55 mg (0.36 mmol) of anhydride **27** in 1.0 mL THF. The reaction was stirred for 4 h at 0 °C. Upon work-up the crude acid was converted corresponding methyl ester by treatment with $TMSCHN_2$. Purification (9:1 Hex/EtOAc) yielded 47 mg (62 %) of product ester **E17** as a colorless oil: R_f = 0.26 (4:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 5.66 (s, 2H), 3.64 (s, 3H), 3.02 (ddd, 1H, J = 6.2, 6.2, 3.6 Hz), 2.89 (ddd, 1H, J = 6.6, 6.6, 3.6 Hz), 2.60-2.51 (m, 2H), 2.46 (t, 2H, J = 7.2 Hz), 2.42-2.31 (m, 2H), 1.63-1.54 (m, 2H), 0.89 (t, 3H, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.8, 174.0, 125.7, 124.5, 51.7, 46.5, 41.8, 39.3, 26.1, 25.2, 17.0, 13.7; IR (NaCl, neat) 3031, 2963, 2875, 1734, 1711, 1437, 1368, 1202, 1026 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{19}O_3$, 211.1334 Found 211.1338.



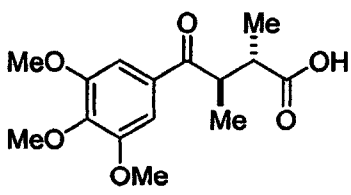
(1*R, 6*S**) 6-(4-Fluoro-benzoyl)-cyclohex-3-enecarboxylic acid methyl ester (E18).** Preparation of di(4-fluoropheny)zinc: A flame dried round bottom flask was charged with 0.44 mL (2.0 M in Et_2O, 0.880 mmol) of 4-fluorophenylmagnisium bromide in 1 mL of THF.

Upon cooling to 0 °C, 100 mg of $ZnBr_2$ (0.440 mmol) in 1 mL of THF was added via cannula and reaction stirred for 0.5 h before warming to ambient temperature and stirring an additional 1.5 h before use. According to the general procedure, 5.0 mg (0.018 mmol) of $Ni(COD)_2$ and 3.4 mg (0.022 mmol) of bpy in 1 mL of THF was treated with 5 μL (0.042 mmol) 4-fluorostyrene, nucleophile solution was added via cannula followed by addition of 55 mg (0.36 mmol) of anhydride **27** in 1.0 mL THF. The reaction was stirred for 4 h at 0 °C. Upon work-up the crude acid was converted corresponding methyl ester by treatment with $TMSCHN_2$. Purification (9:1 Hex/EtOAc) yielded 64 mg (68 %) of product ester **E18** as a colorless solid: mp = 68-71 °C; R_f= 0.19 (4:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.92-7.88 (m, 2H), 7.15-7.11 (m, 2H), 5.79-5.75 (m, 1H), 5.66-5.62 (m, 1H), 3.93 (ddd, 1H, J = 6.2, 6.2, 4.1 Hz), 3.63 (s, 3H), 3.00 (ddd, 1H, J = 6.6, 6.6, 4.1 Hz), 2.79-2.72 (m, 1H), 2.49-2.44 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 174.0, 165.4 (d, J_{C-F} = 254.7 Hz), 132.9 (d, J_{C-F} = 3.7 Hz), 130.8 (d, J_{C-F} = 9.2 Hz), 124.8 (d, J_{C-F} = 192.4 Hz), 115.8, 115.6, 51.8, 41.3, 39.8, 26.4, 25.9; IR (NaCl, dep. $CHCl_3$) 3028, 2951, 2920, 1732, 1686, 1596, 1435, 1223, 1157 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{16}FO_3$, 263.1083. Found 263.1084.



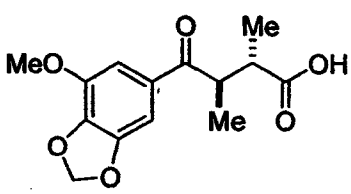
(1*R, 2*S**) 2-(2-Methyl-benzoyl)-cyclohexanecarboxylic acid methyl ester (E19).** Preparation of di(*o*-tolyl)zinc: A flame dried round bottom flask was charged with 0.12 mL of 2-bromotoluene (1.0 mmol) in 3 mL of THF. Upon cooling to -78 °C, 0.66 mL (1.6 M in hexanes, 1.05 mmol) were added dropwise via syringe. After 30 min, 114 mg of $ZnBr_2$ (0.510

mmol) in 1 mL of THF was added via cannula and reaction stirred for 0.5 h before warming to ambient temperature and stirring an additional 1.5 h before use. According to the general procedure, 5.8 mg (0.021 mmol) of $Ni(COD)_2$ and 4.3 mg (0.028 mmol) of bpy in 1 mL of THF was treated with 5 μL (0.042 mmol) 4-fluorostyrene, nucleophile solution was added via cannula followed by addition of 56 mg (0.36 mmol) of anhydride **10** in 1.0 mL THF. The reaction was stirred for 2 h at 0 °C. Upon work-up the crude acid was converted corresponding methyl ester by treatment with $TMSCHN_2$. Purification (3:1 CH_2Cl_2/Hex) yielded 60 mg (63 %) of product ester **E19** as a colorless oil: R_f= 0.17 (CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, 1H, J= 7.3 Hz), 7.32 (t, 1H, J= 8.3 Hz), 7.24-7.20 (m, 2H), 3.65 (s, 3H), 3.63-3.61 (m, 1H), 2.79-2.74 (m, 1H), 2.41 (s, 3H), 2.18-2.10 (m, 1H), 1.98-1.89 (m, 2H), 1.75-1.63 (m, 2H), 1.45-1.34 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.8, 174.5, 138.3, 137.3, 131.6, 130.3, 127.2, 125.4, 51.6, 47.5, 42.5, 26.5, 25.8, 24.2, 23.5, 20.2; IR (NaCl, neat) 2945, 2858, 1742, 1691, 1450, 1296, 1219, 1040, 968 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{21}O_3$, 261.1491. Found 261.1492.



(2*S, 3*R**)-2,3-Dimethyl-4-oxo-4-(3,4,5-trimethoxy-phenyl)-butyric acid (E20).** A flame-dried round bottom flask charged with 2.04 g (8.26 mmol) of aryl bromide in 25 mL of THF was cooled to -78 °C and 5.44 mL of *n*-BuLi (1.6 M in hexanes, 8.70 mmol) was added dropwise via syringe. The mixture was stirred for 0.5 h at -78 °C before the addition of 608 mg of $ZnCl_2$ (4.46 mmol) in 8 mL of THF via cannula and warming to

room temperature over 0.5 h. In a separate flask, a solution of 52 mg of $Ni(COD)_2$ (0.19 mmol), 35 mg of 2,2'-bipyridyl (0.22 mmol) in 5 mL of THF were stirred for 15 min. at room temperature before the addition of 50 μL (0.42 mmol) of 4-fluorostyrene via syringe. The solution of diarylzinc reagent was cooled to 0 °C before the addition of the deep purple catalyst solution via cannula. A solution of 490 mg of *meso* dimethylsuccinic anhydride **59** (3.82 mmol) in 5 mL of THF was then added via cannula. The resulting reaction mixture was allowed to stir at 0 °C for 4 h. The reaction mixture was partitioned between Et_2O (50 mL) and 1 M aq. HCl (50 mL) and transferred to a sepratory funnel where the layers were separated. The aqueous layer was extracted with Et_2O (2 X 10 mL), the organics were combined and extracted with 1M $NaCO_3$ (4 X 15 mL). The basic aqueous layers were combined and brought to pH ~ 1 with conc. HCl. The acidified aqueous layer was extracted with Et_2O (4 X 50 mL), organics were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide 1.02 g (3.44 mmol, 90%) of the desired product as a white solid: mp = 115-117 °C. R_f = 0.26 (1:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 2H); 3.93 (s, 9H); 3.67 (dq, 1H, J = 7.2, 7.2 Hz); 2.99 (dq, 1H, J = 7.2, 7.2 Hz); 1.27 (d, 3H, J = 7.0 Hz); 1.21 (d, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7, 180.6, 153.2, 143.0, 131.2, 106.0, 61.0, 56.3, 43.1, 42.1, 42.4, 16.8, 16.1; IR (NaCl, neat), 3302, 2978, 2941, 1703, 1672, 1581, 1414, 1128 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{21}O_6$, 297.1338. Found 297.1332.

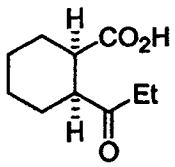


(2*S, 3*R**)-4-(7-Methoxy-benzo[1,3]dioxol-5-yl)-2,3-dimethyl-4-oxo-butyric acid (E21).** A flame-dried round

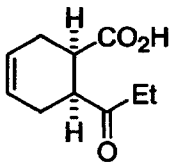
bottom flask charged with 1.91 g (8.27 mmol) of aryl bromide in 25 mL of THF was cooled to -78 °C and 5.45 mL of *n*-BuLi (1.6 M in hexanes, 8.72 mmol) was added dropwise via syringe. The mixture was stirred for 0.5 h at -78 °C before the addition of 606 mg of $ZnCl_2$ (4.45 mmol) in 8 mL of THF via cannula and warming to room temperature over 0.5 h. In a separate flask, a solution of 53 mg of $Ni(COD)_2$ (0.19 mmol), 37 mg of 2,2'-bipyridyl (0.24 mmol) in 5 mL of THF were stirred for 15 min. at room temperature before the addition of 50 μL (0.42 mmol) of 4-fluorostyrene via syringe. The solution of diarylzinc reagent was cooled to 0 °C before the addition of the deep purple catalyst solution via cannula. A solution of 484 mg of *meso* dimethylsuccinic anhydride **59** (3.78 mmol) in 5 mL of THF was then added via cannula. The resulting reaction mixture was allowed to stir at 0 °C for 15 h. The reaction mixture was partitioned between Et_2O (50 mL) and 1 M aq. HCl (50 mL) and transferred to a sepratory funnel where the layers were separated. The aqueous layer was extracted with Et_2O (2 X 10 mL), the organics were combined and extracted with 1M $NaCO_3$ (4 X 15 mL). The basic aqueous layers were combined and brought to pH ~ 1 with conc. HCl. The acidified aqueous layer was extracted with Et_2O (4 X 50 mL), organics were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide 1.02 g (3.64 mmol, 96%) of the desired product as a viscous oil that solidified upon standing: 93-95 °C. R_f = 0.30 (1:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 1H, J = 1.3 Hz); 7.17 (d, 1H, J = 1.3 Hz); 6.08 (s, 2H); 3.96 (s, 3H); 3.60 (dq, 1H, J = 7.0, 7.0 Hz); 2.96 (dq, 1H, J = 7.0, 7.0 Hz); 1.25 (d, 3H, J = 7.0 Hz); 1.20 (d, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.0, 180.6, 149.1, 143.7, 140.2, 131.0, 109.3, 103.0, 102.5, 56.7, 43.2, 42.4, 16.7, 16.1; IR (NaCl, neat), 3174, 2978, 2941, 1707,

1674, 1628, 1429, 1319, 1140, 1097 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{17}O_6$, 281.1025. Found 281.1022.

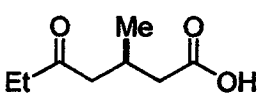
Nickel (II) Precatalyst



(1*R, 2*S**)-2-propionyl-cyclohexanecarboxylic acid (20).** A flame-dried round bottom flask equipped with a magnetic stir bar was charged with 39 mg (0.15 mmol) of anhydrous $Ni(acac)_2$ and 29 mg (0.18 mmol) of bpy. The reaction flask was then placed under vacuum for five minutes and then refilled with dry argon. After 3 vacuum/argon cycles the flask was placed under a static argon atmosphere. 10 mL of THF were added via syringe and the reaction mixture was cooled to 0 °C before adding 1.70 mL (16.6 mmol) of Et_2Zn dropwise via syringe followed by addition of 44 μL (0.30 mmol) of 4-(trifluoromethyl)styrene. After 15 min., an additional 30 mL of THF were added followed by the addition of 2.31 g (15.0 mmol) of anhydride **10** in 10 mL of THF via cannula to the deep green reaction mixture. The reaction was allowed to stir at 0 °C for 20 h (no SM by TLC). The reaction was then diluted with Et_2O (50 mL) and washed with 50 mL of 1M aq. HCl. The aqueous layer was separated and extracted with Et_2O (2 X 25 mL). Organic extracts were combined and extracted with 1M aq. Na_2CO_3 (5 X 10 mL). Basic aqueous layers were combined and acidified with conc. HCl. The resulting heterogeneous solution was extracted with Et_2O (3 X 50 mL). The organic extracts were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuuo* to yield 2.65 g (96 %) of the desired acid **20** as a white solid identical to material derived from the standard procedure.



(1*R, 2*S**)-2-propionyl-cyclohexanecarboxylic acid (28).** A flame-dried round bottom flask equipped with a magnetic stir bar was charged with 39 mg (0.15 mmol) of anhydrous $Ni(acac)_2$ and 29 mg (0.18 mmol) of bpy. The reaction flask was then placed under vacuum for five minutes and then refilled with dry argon. After 3 vacuum/argon cycles the flask was placed under a static argon atmosphere. 10 mL of THF were added via syringe and the reaction mixture was cooled to 0 °C before adding 1.70 mL (16.6 mmol) of Et_2Zn dropwise via syringe followed by addition of 44 μL (0.30 mmol) of 4-(trifluoromethyl)styrene. After 15 min., an additional 30 mL of THF were added followed by the addition of 2.28 g (15.0 mmol) of anhydride **27** in 10 mL of THF via cannula to the deep green reaction mixture. The reaction was allowed to stir at 0 °C for 20 h (no SM by TLC). The reaction was then diluted with Et_2O (50 mL) and washed with 50 mL of 1M aq. HCl. The aqueous layer was separated and extracted with Et_2O (2 X 25 mL). Organic extracts were combined and extracted with 1M aq. Na_2CO_3 (5 X 10 mL). Basic aqueous layers were combined and acidified with conc. HCl. The resulting heterogeneous solution was extracted with Et_2O (3 X 50 mL). The organic extracts were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuuo* to yield 2.61 g (95 %) of the desired acid **28** as a white solid identical to material derived from the standard procedure.



3-methyl-5-oxo-heptanoic acid (64). A flame-dried round bottom flask equipped with a magnetic stir bar was charged with 50 mg (0.20 mmol) of anhydrous $Ni(acac)_2$ and 65 mg (0.22 mmol) of bpy. The reaction flask was then placed under vacuum for five minutes and then refilled with dry argon. After 3

vacuum/argon cycles the flask was placed under a static argon atmosphere. 5 mL of THF were added via syringe and the reaction mixture was cooled to 0 °C before adding 0.48 mL (4.7 mmol) of Et_2Zn dropwise via syringe followed by addition of 50 μL (0.42 mmol) of 4-(trifluoromethyl)styrene. After 15 min., an additional 5 mL of THF were added followed by the addition of 505 mg (4.00 mmol) of anhydride **63** in 3 mL of THF via cannula to the deep green reaction mixture. The reaction was allowed to stir at 0 °C for 4 h (no SM by TLC). The reaction was then diluted with Et_2O (20 mL) and washed with 20 mL of 1M aq. HCl. The aqueous layer was separated and extracted with Et_2O (2 X 10 mL). Organic extracts were combined and extracted with 1M aq. Na_2CO_3 (2 X 10 mL). Basic aqueous layers were combined and acidified with conc. HCl. The resulting heterogeneous solution was extracted with Et_2O (3 X 20 mL). The organic extracts were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuuo* to yield 600 mg (96 %) of the desired acid **64** as a colorless oil identical to material derived from the standard procedure.

Palladium Catalyzed Anhydride Alkylation

General Methods. All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Tetrahydrofuran, diethylether, and dichloromethane were degassed with argon and passed through two columns of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM

Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light, $KMnO_4$, aqueous ceric ammonium molybdate, or bromocresol green dips followed by heating.

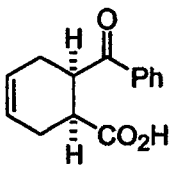
$Pd(OAc)_2$ was purchased from Aldrich Chemical Co. and used without further purification. Diphenylzinc was purchased from Strem Chemical, Inc.

Melting points were measured with a MelTemp II melting point apparatus outfitted with a Fluke 51 thermocouple and are uncorrected. Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^1H NMR and spectra were recorded on a Varian 300, 400, or 500 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ, ppm) from an internal standard [tetramethylsilane (TMS) or deuterated chloroform ($CDCl_3$)], multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR were recorded on a Varian 75, 100, or 125 MHz spectrometer at ambient temperature. Chemical shifts are reported in ppm from ($CDCl_3$) taken as 77.0 ppm. Mass spectra were obtained on Fisons VG Autospec. Analytical high performance liquid chromatography (HPLC) was performed on a Dynamax model SD-200 HPLC equipped with a Dynamax model UV-1 variable wavelength UV detector using Chiracel chiral columns as indicated. Gas chromatography was performed on a Varian Cp 3800 gas chromatograph equipped with a flame ionization detector using a Chiraldex B-DM or Chiraldex B-PH capillary column. Optical rotations were measured on an Autopol III automatic polarimeter in a 1 dm cell.

General procedure for the enantioselective desymmetrizaion of cyclic anhydrides:

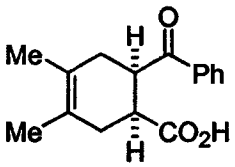
A flame-dried round bottom flask was charged with $Pd(OAc)_2$ (0.05 eq), (R)-(-)-1-[(S)-2-

diphenylphosphino)ferrocenyl]-ethyldicyclohexylphosphine [(*R,S*)-JOSIPHOS] (0.06 eq), and diphenylzinc (1.1 eq.) in an inert atmosphere (N_2) glove box. Upon removal from the glove box, 1.0 ml THF was added via syringe and the solution was stirred at ambient temperature for 15 minutes. Anhydride (1 eq) in THF (1 mL, typically 0.03-0.003M in substrate) was then added via cannula and the reaction was stirred for the time and temperature indicated. The reaction mixture was then diluted with 10 ml of ether and quenched with 10 mL 1M aq. HCl. The layers were separated and the aqueous layer extracted with ether (2 X 10 mL). Organic layers were combined and extracted with 1M aq. Na_2CO_3 (2 X 5 mL), the basic layers were combined and brought to pH = 1-2 with concentrated HCl. The acidified aqueous layer was extracted with Et_2O (3 X 10 mL). The combined organic extracts were then washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. For analytical analysis the corresponding methyl ester was generated by treatment with $TMSCHN_2$ (2.0M in Et_2O or Hexanes) in 2-4 mL of MeOH/PhH (1:1) at 23 °C for 5 min. followed by quenching with AcOH and purification.



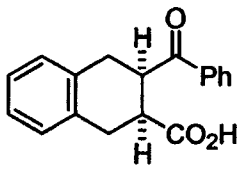
(1S, 6*R*) 6-benzoyl-cyclohex-3-enecarboxylic acid (166). According to the general procedure, 3.5 mg (0.016 mmol) of $Pd(OAc)_2$, 11.1 mg (0.019 mmol) of (*R,S*)-JOSIPHOS, and 85.0 mg of diphenylzinc (0.387 mmol) in 2 mL of THF was treated with 51.0 mg (0.335 mmol) of anhydride **27** in 0.25 mL THF. The reaction was stirred for 16 h at 23 °C. Standard work-up provided 60 mg crude acid that was purified by column chromotograhy (98:2 CH_2Cl_2/MeOH) providing 53.0 mg (69 %) of known acid **166** as an off white solid (mp = 106-108 °C, CH_2Cl_2/MeOH; Lit: mp =

130-131 °C, rac. Et_2O/Pet ether)[9]. The corresponding methyl ester was used for ee determination. HPLC analysis (Chiralcel OD-H, 97:3 hex/*i*-PrOH, 0.5 mL/min, 254 nm; tr (minor) = 31.9 min., tr (major) = 36.1 min.) gave the isomeric composition of the product: 91% ee. $[\alpha]_D^{23}$ (acid) = -31.9° (c = 0.48, $CHCl_3$).

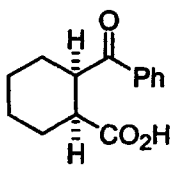


(1*S*, 6*R*) 6-benzoyl-3,4-dimethyl-cyclohex-3-enecarboxylic acid (167). According to the general procedure, 3.9 mg (0.017 mmol) of $Pd(OAc)_2$, 11.5 mg (0.019 mmol) of (*R,S*)-JOSIPHOS, and 81 mg of diphenylzinc (0.369 mmol) in 2 mL of THF was treated with 58.0 mg (0.322 mmol) of anhydride **29** in 0.25 mL THF. The reaction was stirred for 22 h at 23 °C. Standard work-up provided 87.0 mg (87 %) of the desired acid **167** as a white solid (mp = 168-170 °C, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.85-7.87 (m, 2H), 7.53-7.57 (m, 1H), 7.43-7.47 (m, 2H), 3.90 (ddd, 1H, *J* = 6.4, 6.4, 3.8 Hz), 3.00 (ddd, 1H, *J* = 7.2, 7.2, 3.8 Hz), 2.66-2.72 (m, 1H), 2.33-2.39 (m, 3H), 1.65 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 178.5, 136.3, 132.8, 128.6, 128.3, 124.6, 122.8, 42.6, 40.3, 32.8, 32.1, 18.9; IR (NaCl, dep from $CHCl_3$), 3429, 2920, 2858, 1700, 1676, 1445, 1327, 1225, 1180 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{19}O_3$, 259.1334. Found 259.1338; $[\alpha]_D^{23}$ = -55.6 ° (c = 0.16, $CHCl_3$). The product acid was converted the corresponding methyl ester for ee determination. HPLC analysis (Chiralcel OD-H, 97:3 hex/*i*-PrOH, 0.5 mL/min, 254 nm; tr (minor) = 22.8 min., tr (major) = 27.0 min.) gave the isomeric composition of the product: 90 % ee.

[9] (a) Fieser, L. F.; Novello, F. *J. Am Chem. Soc.* **1942**, *64*, 802-809; (b) Sugita, K.; Tamura, S. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2866-2867.

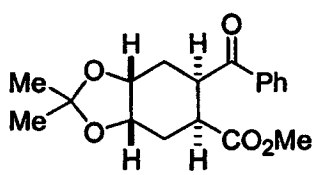


(2*S*, 3*R*) 3-benzoyl-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid (168). According to the general procedure, 4.1 mg (0.018 mmol) of $Pd(OAc)_2$, 11.7 mg (0.020 mmol) of (*R,S*)-JOSIPHOS, and 81.0 mg of diphenylzinc (0.369 mmol) in 2 mL of THF was treated with 65.0 mg (0.321 mmol) of anhydride **31** in 0.25 mL THF. The reaction was stirred for 22 h at 23 °C. Standard work-up provided 76.0 mg (84 %) of the desired acid **168** as a white crystalline solid (mp = 174-176 °C, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.88-7.90 (m, 2H), 7.45-7.59 (m, 3H), 7.00-7.17 (m, 4H), 4.12 (ddd, 1H, J = 7.0, 7.0, 3.6 Hz), 3.47 (dd, 1H, J = 16.2, 6.0 Hz), 3.16-3.27 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 177.3, 136.0, 134.2, 133.1, 129.0, 128.7, 128.4, 126.4, 126.0, 42.7, 40.3, 30.6, 29.9; IR (NaCl, dep from $CHCl_3$) 3408, 2924, 2849, 1691, 1676, 1551, 1155, 1115 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{17}O_3$, 281.1178. Found 281.1178; $[\alpha]_D^{23}$ = -61.0° (c = 0. 20, $CHCl_3$). The corresponding methyl ester was used for ee determination. HPLC analysis (Chiralcel OD-H, 95:5 hex/*i*-PrOH, 1.0 mL/min, 254 nm; tr (minor) = 25.4 min., tr (major) = 27.2 min.) gave the isomeric composition of the product: 95 % ee.



(1*S*, 2*R*) 2-benzoyl-cyclohexanecarboxylic acid (106). According to the general procedure, 3.7 mg (0.017 mmol) of $Pd(OAc)_2$, 11.5 mg (0.019 mmol) of (*R,S*)-JOSIPHOS, and 82.0 mg of diphenylzinc (0.373 mmol) in 10 mL of THF was treated with 52.0 mg (0.373 mmol) of anhydride **10** in 0.25 mL THF. The reaction was stirred for 16 h at 23 °C. Standard work-up provided 70.0 mg (89 %) of the known acid **106** as a white solid (mp = 114-115 °C, CH_2Cl_2, Lit = 130-132 °C, rac.

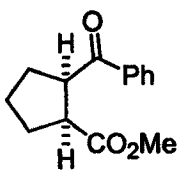
from PhH)[10]. .The corresponding methyl ester was used for ee detemination.[11] HPLC analysis (Chiralcel OD-H, 97:3 hex/*i*-PrOH, 0.5 mL/min, 254 nm; tr (minor) = 21.7 min., tr (major) = 23.5 min.) gave the isomeric composition of the product: 94 % ee. $[\alpha]_D^{23}$ (acid) = +4.9° (c = 0.35, $CHCl_3$).



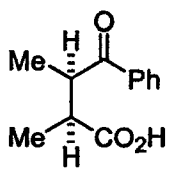
(2*S*, 3*R*, 5*R*, 6*S*) 6-benzoyl-2,2-dimethyl-hexahydro-benzo[1,3]dioxole-5-carboxylic acid methyl ester (171). According to the general procedure, 3.9 mg (0.017 mmol) of $Pd(OAc)_2$, 12.3 mg (0.021 mmol) of (*R,S*)-JOSIPHOS, and 83.0 mg of diphenylzinc (0.378 mmol) in 2 mL of THF was treated with 75.0 mg (0.332 mmol) of anhydride **170** in 0.25 mL THF. The reaction was stirred for 17 h at 23 °C. The reaction was allowed to cool to room temperature before diluting the reaction mixture with diethylether (10 ml) and quenched with 1M aq. citric acid (10 ml). The organic layer was separated and the aqueous layer extracted with ether (2 X 10 ml). The organics were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude brown oil was then taken up in MeOH/PhH (1:1) and treated with $TMSCHN_2$. Purification by column chromatography (4:1 Hex/EtOAc) yielded 88.0 mg (83 %) of the product ester **171** as a colorless oil. HPLC analysis (Chiralcel AD, 97:3 hex/*i*-PrOH, 1.0 mL/min, 254 nm; tr (major) = 20.8 min., tr (minor) = 23.8 min.) gave the isomeric composition of the product: 97% ee. Rf = 0.14 (4:1 Hex/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.88-7.92 (m, 2H), 7.53-7.59 (m, 1H), 7.43-7.48 (m, 2H),4.38 (ddd, 1H, *J* = 10.6, 10.6, 4.8 Hz),

[10] (a) Fieser, L. F.; Novello, F. *J. Am Chem. Soc.* **1942**, *64*, 802-809; (b) Van der Mey, M.; Hatzelmann, A.; Van Klink, G. P. M.; Van der Laan, I. J.; Strek, G. J.; Thibaut, U.; Ulrich, W. R.; Timmerman, H. *J. Med. Chem.* **2001**, *44*, 2523-2535; (c) Availible from Acros Organics, cat. num. 298600025.
[11] For ^1H and ^{13}C spectra, see: Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 174.

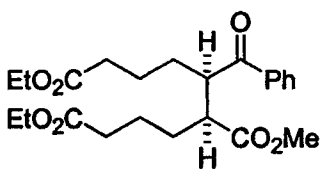
4.08 (ddd, 1H, J = 10.3, 10.3, 4.4 Hz), 3.54 (s, 3H), 3.09 (ddd, 1H, J = 10.3, 5.1, 5.1 Hz), 2.01-2.32 (m, 4H), 1.54 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.9, 173.8, 136.2, 132.9, 128.6, 128.1, 107.9, 72.2, 72.0, 51.6, 40.1, 38.4, 28.1, 28.0, 27.8, 25.5; IR (NaCl, neat) 2985, 2949, 1736, 1682, 1597, 1448, 1381, 1204, 1041 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{23}O_5$, 319.1545. Found 319.1554; $[\alpha]_D^{23}$ = +15.7° (c = 0.76, $CHCl_3$).



(1*S*, 2*R*) 2-benzoyl-cyclopentanecarboxylic acid methyl ester (176). According to the general procedure, 4.2 mg (0.019 mmol) of $Pd(OAc)_2$, 12.1 mg (0.020 mmol) of (*R,S*)-JOSIPHOS, and 81.0 mg of diphenylzinc (0.369 mmol) in 2 mL of THF was treated with 46.0 mg (0.328 mmol) of anhydride **51** in 0.25 mL THF. The reaction was stirred for 18 h at 40 °C. Standard work-up provided 64.0 mg (89 %) of the desired acid. The product acid was converted the corresponding methyl ester. Purification by column chromatography (9:1 Hex/EtOAc) yielded 57.0 mg (74 %) of product ester **176** as a colorless oil. HPLC analysis (Chiralcel OB-H, 95:5 hex/*i*-PrOH, 1.0 mL/min, 254 nm; tr (major) = 25.1 min., tr (minor) = 31.4 min.) gave the isomeric composition of the product: 89% ee. Rf = 0.20 (4:1 Hex/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94-7.91 (m, 2H), 7.57-7.52 (m, 1H), 7.48-7.42 (m, 2H), 4.11 (ddd, 1H, J = 8.1, 5.5, 5.5 Hz), 3.52 (s, 3H), 3.07 (ddd, 1H, J = 8.1, 8.1, 8.1 Hz), 2.26-1.62 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.6, 174.1, 136.4, 132.7, 128.4, 128.3, 51.4, 48.9, 47.6, 30.1, 28.3, 24.2; IR (NaCl, neat) 2591, 2874, 1738, 1682, 1597, 1448, 1209, 1001 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{17}O_3$, 233.1178. Found 233.1176; $[\alpha]_D^{23}$ = +6.3° (c = 0.63, $CHCl_3$).



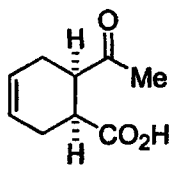
(2*S*, 3*R*) 2,3-dimethyl-4-oxo-4-pheny-butyric acid (181). According to the general procedure, 3.7 mg (0.017 mmol) of $Pd(OAc)_2$, 10.7 mg (0.018 mmol) of *(R,S)*-JOSIPHOS, and 81.0 mg of diphenylzinc (0.369 mmol) in 2 mL of THF was treated with 42.0 mg (0.324 mmol) of anhydride **59** in 0.25 mL THF. The reaction was stirred for 18 h at 80 °C. Standard work-up provided 48.0 mg (72 %) of the known acid **181** as a white solid (mp = 49-51 °C, CH_2Cl_2).[12] The corresponding methyl ester was used for ee determination. HPLC analysis (Chiralcel OB-H, 97:3 hex/*i*-PrOH, 0.5 mL/min, 254 nm; tr (minor) = 21.0 min., tr (major) = 22.2 min.) gave the isomeric composition of the product: 92% ee. $[\alpha]_D^{23} = -29.5°$ (c = 0.21, CH_3Cl).



(5*R*, 6*S*) 5-benzoyl-6-methoxycarbonyl-decanedioic acid diethyl ester (182). According to the general procedure, 3.7 mg (0.017 mmol) of $Pd(OAc)_2$, 10.7 mg (0.018 mmol) of (*R,S*)-JOSIPHOS, and 83.0 mg of diphenylzinc (0.378 mmol) in 2 mL of THF was treated with 105.0 mg (0.320 mmol) of anhydride **61** in 0.25 mL THF. The reaction was stirred for 17 h at 40 °C. The reaction was allowed to cool to room temperature before diluting the reaction mixture with diethylether (10 ml) and quenched with 1M aq. citric acid (10 ml). The organic layer was separated and the aqueous layer extracted with ether (2 X 10 ml). The organics were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude brown oil was then taken up in MeOH/PhH (1:1) and treated with $TMSCHN_2$. Purification by column chromatography (4:1 Hex/EtOAc)

[12] Schreiber, S. L.; Klimas, M. T.; Sammakia, T. *J. Am Chem. Soc.* **1987**, *109*, 5749-5759.

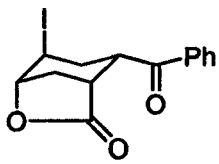
yielded 82.0 mg (61 %) of the product ester **182** as a colorless oil. HPLC analysis (Chiralcel AD, 97:3 hex/*i*-PrOH, 1.0 mL/min, 254 nm; tr (min.) = 33.5min., tr (maj.) = 51.6 min.) gave the isomeric composition of the product: 89% ee. Rf = 0.14 (4:1 Hex/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98-7.94 (m, 2H), 7.62-7.56 (m, 1H), 7.50-7.46 (m, 2H), 4.05 (q, 2H, J = 7.0 Hz), 4.04 (q, 2H, *J* = 7.0 Hz), 3.77 (ddd, 1H, *J* = 9.2, 9.2, 2.9 Hz), 3.70 (s, 3H), 2.87 (ddd, 1H, *J* = 9.9, 9.9, 3.3 Hz), 1.78-1.30 (m, 8H), 1.19 (t, 3H, *J* = 7.0 Hz), 1.18 (t, 3H, *J* = 7.0Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 174.7, 172.8, 172.7, 137.6, 133.4, 128.7, 128.2, 60.3, 51.7, 48.1, 47.5, 34.3, 33.9, 31.1, 30.5, 23.1, 22.4, 14.2; IR (NaCl, neat) 2953, 2872, 1738, 1682, 1695, 1579, 1448, 1159 cm^{-1}; HRMS (FAB+) calcd for $C_{23}H_{33}O_7$, 421.2226. Found 421.2228; $[\alpha]_D^{23}$ = -10.0° (c = 0. 51, $CHCl_3$).



(1*S*, 6*R*) 6-Acetyl-cyclohex-3-enecarboxylic acid (193).[13] According to the general procedure, 3.7 mg (0.016 mmol) of $Pd(OAc)_2$, 7.9 mg (0.013 mmol) of (*R,S*)-JOSIPHOS in 2 mL of THF was treated with 0.2 mL of dimethylzinc (0.4 mmol, 2.0M in PhMe) before adding 10 μL of 4-fluorostyrene (0.084 mmol) via syringe. After 15 min. an additional 8 mL of THF were added. To the resulting dark brown reaction solution was added 50.0 mg (0.329 mmol) of anhydride **10** in 0.25 mL THF. The reaction was stirred for 22 h at 23 °C. Standard work-up provided crude acid that was purified by column chromatography (98:2 CH_2Cl_2/MeOH) to provide 33 mg (60 %) of the desired acid **193** as a colorless oil. Rf = 0.14 (95:5 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (s, 2H), 3.05-3.07 (m, 1H), 2.87-

[13] The preparation of this material is much more reliable when using 0.8 eq. of ligand to metal.

2.90 (m, 1H), 2.32-2.62 (m, 4H), 2.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.9, 179.6, 125.7, 124.5, 47.0, 39.2, 27.7, 26.0, 25.4; IR (NaCl, neat) 3400, 3030, 2920, 1709, 1657, 1435, 1356, 1250, 1194, 933 cm^{-1}; HRMS (FAB+) calcd for $C_9H_{13}O_3$, 169.0865. Found 169.0865; $[\alpha]_D^{23} = +21.7^{\circ}$ (c = 1.43, $CHCl_3$). The corresponding benzyl ester was used for ee determination. HPLC analysis (Chiralcel OD-H, 97:3 hex/*i*-PrOH, 0.5 mL/min, 254 nm; tr (min.) = 24.9 min., tr (maj.) = 26.2 min.) gave the isomeric composition of the product: 91% ee.



(1*S*, 2*S*, 4*R*, 5*R*) 2-Benzoyl-4-iodo-6-oxa-bicyclo[3.2.1]octan-7-one (200). A flame-dried round bottom flask was charged with 53 mg (0.230 mmol, 91 % ee) of acid **166** in 2 mL of CH_2Cl_2 and 3 mL of 0.5M aq. $NaHCO_3$. A solution of 312 mg (1.23 mmol) of I_2 and 330 mg (1.99 mmol) of KI in 2 mL of water was added dropwise to the reaction mixture and the resulting deep red biphasic mixture was stirred in the dark for 17 h. The reaction was quenched with 15 mL of sat. aq. $NaHSO_3$. The organic layer was separated and the remaining aqueous layer extracted with CH_2Cl_2 (2 X 20 mL). Organics were combined, washed with sat. aq. $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide a crude white solid. Column chromatography (4:1 Hex/EtOAc) provided 69.0 mg (84 %) of the desired iodolactonized product **200** as a white crystalline solid: mp = 144 °C (dec). X-ray quality crystals were derived from slow evaporation of a methylene chloride solution. Rf = 0.50 (1:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.92-7.91 (m, 2H), 7.62-7.58 (m, 1H), 7.52-7.48 (m, 2H), 4.87 (dd, 1H, *J* = 4.7, 4.7 Hz), 4.63 (dd, 1H, *J* = 4.5, 4.5 Hz), 3.87 (ddd, 1H, *J* = 12.2, 4.4 0.0 Hz), 3.04-2.98 (m, 2H), 2.82 (ddd, 1H, *J* = 17.1, 12.4, 5.5

Hz), 2.53 (ddd, 1H, J = 11.5, 5.5, 5.5 Hz), 2.31 (ddd, 1H, J = 16.6, 4.1, 0.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 174.3, 134.9, 133.6, 128.9, 128.3, 79.3, 41.6, 40.8, 34.6, 32.0, 22.6; HRMS (FAB+) calcd for $C_{14}H_{14}IO_3$, 356.9988. Found 356.9996; $[\alpha]_D^{23}$ = +27.0° (c = 0.64, $CHCl_3$).

Chapter 3 Experimental

Diastereoselective Reduction of Keto Acids

General Methods. All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Tetrahydrofuran, diethylether, and dichloromethane were degassed with argon and passed through two columns of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light, $KMnO_4$, aqueous ceric ammonium molybdate, anisaldehyde, or bromocresol green dips followed by heating.

$PhMe_2SiH$ and Et_3BHLi (1.0M in THF) were purchased from Aldrich Chemical Co. and used without further purification. All starting keto-acids were prepared using a nickel-catalyzed cross-coupling reaction of the corresponding anhydride and zinc reagent previously reported from these laboratories.[1]

Melting points were measured with a MelTemp II melting point apparatus outfitted with a Fluke 51 thermocouple and are uncorrected. Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^1H NMR and spectra were recorded on a Varian 300, 400, or 500 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ, ppm) from an internal standard [tetramethylsilane (TMS; taken as 0.00 ppm) or deuterated chloroform ($CDCl_3$; taken as 7.26 ppm)], multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m =

[1] Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 173-174.

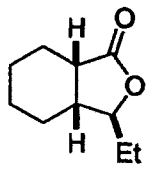
multiplet), integration, and coupling constant (Hz). ^{13}C NMR were recorded on a Varian 75, 100, or 125 MHz spectrometer at ambient temperature. Chemical shifts are reported in ppm from ($CDCl_3$) taken as 77.0 ppm. Mass spectra were obtained on Fisons VG Autospec. Analytical high performance liquid chromatography (HPLC) was performed on a Dynamax model SD-200 HPLC equipped with a Dynamax model UV-1 variable wavelength UV detector using Chiracel chiral columns as indicated. Gas chromatography was performed on a Varian Cp 3800 gas chromatograph equipped with a flame ionization detector using a Chrompack CP-Sil8CB (15 M X 0.25 mm) capillary column.

All diastereomeric ratios were determined using NMR spectroscopy of crude material. In cases where overlapping signals were present ratios were determined by gas chromatography. In cases where diastereomers were seperable by column chromotorgraphy each diastereomer was characterized individually. In cases where the diastereomers were inseperable each diastereomer was characterized as the mixture of reported ratio.

General procedure A (Super Hydride reduction): A flame-dried round bottom flask was charged with keto-acid (1 equiv) in 1 mL of THF. Upon cooling to -78 °C, Et_3BHLi (1.0 M in THF, 2.4 equiv) was added dropwise via syringe. After stirring for 0.5 h at -78 °C the reaction was allowed to warm to ambient temperature and stirred an additional 4 h. 1 mL of 1 M aq. HCl was then added via syringe and the biphasic mixture vigorously stirred for 0.5 h. The reaction mixture was then diluted with 10-15 mL of EtOAc and 10 mL of 1 M aq. HCl, the layers were separated and the aqueous layer extracted with

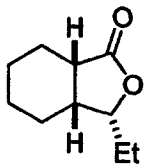
EtOAc (2 X 5 mL). The organic extracts were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude mixture of lactone and hydroxyacid were then taken up in 2 mL of 0.25 % (v/v) of TFA in CH_2Cl_2 and stirred at ambient temperature for 12 h. The reaction mixture was then diluted with 10-15 mL of CH_2Cl_2 and washed with 5 % (w/w) aq. $NaHCO_3$ (10 mL). The layers were separated and the organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude lactone was then purified by column chromatography if needed.

General procedure B (silane reduction): A flame-dried round bottom flask was charged with keto-acid (1 equiv) in 1 mL of CH_2Cl_2/TFA (3 : 1). Upon cooling to 0 °C, $PhMe_2SiH$ (1.2-1.5 equiv) was added via syringe and the reaction was allowed to warm to ambient temperature (melting ice bath) over 14 h. The reaction mixture was then diluted with 10-15 mL of CH_2Cl_2 and washed with 5 % (w/w) aq. $NaHCO_3$ (10 mL). The layers were separated and the organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude lactone was then purified by column chromotography.

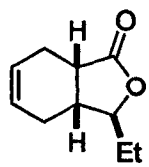


***anti*-lactone 9.** According to the general procedure A, 21 mg (0.11 mmol) of keto-acid **8** was treated with 0.27 mL (0.27 mmol) of Et_3BHLi (1.0M in THF). The reaction was stirred for 0.5 h at -78 °C, warmed to ambient temperature and stirred an additional 4 h. Standard work-up/cyclization provided 16 mg (83 %) of the desired lactone **9** as a colorless oil. Rf = 0.20 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 (1H, ddd, J = 8.5, 8.5, 3.2 Hz), 2.68 (1H, ddd, J = 6.6, 6.6, 6.6 Hz), 2.20-2.16 (1H, m), 1.99-1.93 (1H, m), 1.82-1.76 (1H, m), 1.69-1.50 (1H, m), 1.34-

1.24 (3H, m), 1.01 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 85.1, 39.9, 38.4, 27.3, 26.1, 23.2, 23.0, 22.9, 10.2; IR (NaCl, neat), 2935, 2856, 1772, 1450, 1369, 1161, 1124, 957 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{17}O_2$, 169.1229. Found 169.1231. NMR analysis of the crude lactone gave the diastereomeric composition: 15 : 85 (syn : anti).

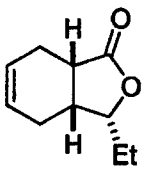


***syn*-lactone 10.** According to the general procedure B, 28 mg (0.15 mmol) of keto-acid **8** was treated with 35 μL (0.23 mmol) of $PhMe_2SiH$. The reaction was stirred for 14 h. The crude lactone was purified by column chromotograhy (9:1 Hex/EtOAc) providing 23 mg (90 %) of lactone **10** as a colorless oil. R_f = 0.20 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (1H, ddd, J = 7.0, 7.0, 7.0 Hz), 2.74-2.72 (1H, m), 2.34 (1H, dddd, J = 11.3, 5.8, 5.8, 5.8, 5.8 Hz), 2.20-2.16 (1H, m), 1.81-1.49 (6H, m), 1.18-1.06 (3H, m), 1.01 (3H, t, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 83.4, 42.1, 38.6, 23.5, 22.8, 22.6, 22.3, 22.2, 10.1; IR (NaCl, neat), 2935, 2858, 1774, 1448, 1392, 1182, 1130, 954 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{17}O_2$, 169.1229. Found 169.1223. NMR analysis of the crude lactone gave the diastereomeric composition: 93 : 7 (syn : anti).

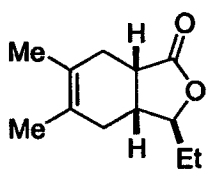


***anti*-lactone 12.** According to the general procedure A, 21 mg (0.12 mmol) of keto-acid **11** was treated with 0.28 mL (0.28 mmol) of Et_3BHLi (1.0M in THF). The reaction was stirred for 0.5 h at -78 °C, warmed to ambient temperature and stirred an additional 4 h. Standard work-up/cyclization provided 16 mg (94 %) of the desired lactone **12** as a colorless oil. Rf = 0.22 (4:1 Hex/EtOAc); ^{1}H NMR

(400 MHz, $CDCl_3$) δ 5.81-5.74 (2H, m), 4.06 (1H, ddd, J = 6.3, 6.3, 6.3 Hz), 2.83 (1H, dddd, J = 7.5, 7.5, 7.5, 7.5 Hz), 2.60-2.55 (1H, m), 2.40-2.25 (3H, m), 1.94-1.89 (1H, m), 1.73-1.65 (2H, m), 1.03 (3H, t, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 125.7, 125.2, 86.5, 36.8, 36.7, 26.7, 24.9, 22.2, 10.1; IR (NaCl, neat), 3032, 2968, 2937, 2845, 1772, 1464, 1437, 1363, 1176, 1140, 953 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{15}O_2$, 167.1072. Found 167.1070. NMR analysis of the crude lactone gave the diastereomeric composition: 26 : 74 (syn : anti).

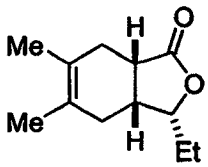


***syn*-lactone 13.** According to the general procedure B, 20 mg (0.11 mmol) of keto-acid **11** was treated with 25 μL (0.16 mmol) of $PhMe_2SiH$. The reaction was stirred for 14 h. The crude lactone was purified by column chromotograhy (9:1 Hex/EtOAc) providing 16 mg (88 %) of lactone **13** as a colorless oil. R_f = 0.22 (4:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 5.74-5.67 (2H, m), 4.29 (1H, ddd, J = 7.0, 7.0, 4.3 Hz), 2.86 (1H, t, J = 7.9 Hz), 2.60-2.55 (1H, m), 2.49-2.32 (2H, m), 2.02 (1H, ddd, J = 16.6, 6.0, 6.0 Hz), 1.89-1.79 (2H, m), 1.71-1.59 (1H, m), 1.04 (3H, t, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 125.2, 124.3, 83.9, 39.9, 34.9, 22.3, 21.9, 19.4, 10.1; IR (NaCl, neat), 3030, 2970, 2939, 2846, 1762, 1352, 1180, 1122, 982, 955 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_{15}O_2$, 167.1072. Found 167.1072. NMR analysis of the crude lactone gave the diastereomeric composition: 90 : 10 (syn : anti).

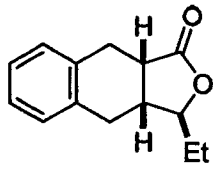


***anti*-lactone 15.** According to the general procedure A, 15 mg (0.071 mmol) of keto-acid **14** was treated with 0.17 mL (0.17 mmol) of Et_3BHLi (1.0M in THF). The reaction was stirred for 0.5 h at -78 °C,

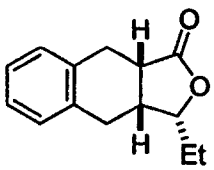
warmed to ambient temperature and stirred an additional 4 h. Standard work-up/cyclization provided 12 mg (87 %) of the desired lactone **15** as a colorless oil. Rf = 0.38 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (1H, ddd, J = 6.4, 6.4, 6.4 Hz), 2.82, (1H, ddd, J = 8.5, 8.5, 4.7 Hz), 2.48-2.14 (4H, m), 1.88-1.83 (1H, m), 1.69-1.64 (8H, m), 1.01 (3H, t, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6, 125.3, 124.6, 86.6, 38.2, 37.8, 32.4, 29.2, 27.2, 19.5, 19.0, 9.9; IR (NaCl, neat), 2968, 2920, 1770, 1443, 1365, 1192, 1142, 955 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{19}O_2$, 195.1385. Found 195.1383. NMR analysis of the crude lactone gave the diastereomeric composition: 19 : 81 (syn : anti).



***syn*-laconte 16.** According to the general procedure B, 33 mg (0.16 mmol) of keto-acid **14** was treated with 29 μL (0.18 mmol) of $PhMe_2SiH$. The reaction was stirred for 14 h. The crude lactone was purified by column chromotograhy (9:1 Pent/Et_2O) providing 23 mg (75 %) of lactone **16** as a colorless oil. Rf = 0.38 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (1H, ddd, J = 6.8, 6.8, 4.3 Hz), 2.84 (1H, t, J = 7.7 Hz), 2.49-2.42 (2H, m), 2.29-2.22 (1H, m), 1.86-1.79 (3H, m), 1.66-1.61 (7H, m), 1.03 (3H, t, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 123.8, 123.4, 83.9, 40.7, 35.8, 28.3, 26.3, 22.5, 19.6, 18.7, 10.2; IR (NaCl, neat), 2970, 2914, 2883, 1774, 1443, 1392, 1360, 1171, 1128, 979, 953 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{19}O_2$, 195.1385. Found 195.1376. NMR analysis of the crude lactone gave the diastereomeric composition: 93 : 7 (syn : anti).

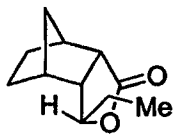


***anti*-lactone 18.** According to the general procedure A, 34 mg (0.15 mmol) of keto-acid **17** was treated with 0.35 mL (0.35 mmol) of Et_3BHLi (1.0M in THF). The reaction was stirred for 0.5 h at -78 °C, warmed to ambient temperature and stirred an additional 4 h. Standard work-up/cyclization provided 29 mg (92 %) of the desired lactone **18** as a colorless oil. Rf = 0.20 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.16 (4H, m), 3.92 (1H, ddd, J = 5.8, 5.8, 5.8 Hz), 3.17-2.83 (4H, m), 2.70-2.57 (2H, m), 1.75-1.68 (2H, m), 1.00 (3H, t , J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3, 136.2, 136.0, 128.0, 127.9, 127.0, 126.9, 86.2, 40.1, 39.1, 32.3, 29.3, 28.8, 9.4; IR (NaCl, neat), 2972, 2941, 1745, 1456, 1369, 1202, 1003, 964 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{17}O_2$, 217.1229. Found 217.1227. NMR analysis of the crude lactone gave the diastereomeric composition: 21 : 79 (syn : anti).

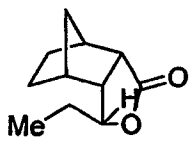


***syn*-lactone 19.** According to the general procedure B, 34 mg (0.15 mmol) of keto-acid **17** was treated with 27 μL (0.18 mmol) of $PhMe_2SiH$. The reaction was stirred for 14 h. The crude lactone was purified by column chromotograhy (9:1 Hex/EtOAc) providing 26 mg (82 %) of lactone **19** as a colorless oil. R_f = 0.20 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.13 (4H, m), 4.47 (1H, ddd, J = 8.7, 5.3, 5.3 Hz), 3.20-3.02 (3H, m), 2.70-2.59 (2H, m), 2.50 (1H, dd, J = 9.2, 3.8 Hz), 1.92-1.69 (2H, m), 1.10 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 136.4, 135.6, 128.0, 127.9, 126.8, 126.5, 83.5, 40.8, 38.5, 27.7, 27.1, 23.5, 10.6; IR (NaCl, neat), 2968, 2939, 2881, 1767, 1458, 1362, 1184, 1132, 987, 964 cm^{-1}; HRMS

(FAB+) calcd for $C_{14}H_{17}O_2$, 217.1229. Found 217.1226. NMR analysis of the crude lactone gave the diastereomeric composition: 92 : 8 (syn : anti).

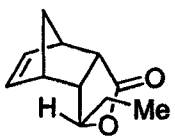


***anti*-lactone 21.** According to the general procedure A, 32 mg (0.16mmol) of keto-acid **20** was treated with 0.39 mL (0.39 mmol) of Et_3BHLi (1.0M in THF). The reaction was stirred for 0.5 h at -78 °C, warmed to ambient temperature and stirred an additional 4 h. Standard work-up/cyclization provided 26 mg (88 %) of the desired lactone **21** as a colorless oil. Rf = 0.25 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (1H, ddd, J = 6.4, 6.4, 2.4 Hz), 2.97 (1H, dd, J = 11.1, 5.8 Hz), 2.65- 2.63 (1H, m), 2.46-2.42 (1H, m), 2.36 (1H, s), 1.68-1.47 (8H, m), 0.95 (3H, t, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 81.6, 47.6, 47.3, 41.8, 40.5, 39.7, 30.1, 25.2, 22.2, 8.9; IR (NaCl, neat), 2962, 2883, 1765, 1460, 1352, 1217, 1174, 980 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{17}O_2$, 181.1229. Found 181.1226. NMR analysis of the crude lactone gave the diastereomeric composition: 25 : 75 (syn : anti).

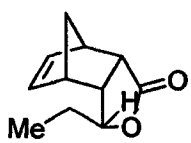


***syn*-lactone 22.** According to the general procedure B, 30 mg (0.15 mmol) of keto-acid **20** was treated with 28 μL (0.18 mmol) of $PhMe_2SiH$. The reaction was stirred for 14 h. The crude lactone was purified by column chromotograhy (9:1 Hex/EtOAc) providing 24 mg (87 %) of lactone **22** as a colorless oil. R_f = 0.18 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (1H, ddd, *J* = 6.8, 6.8, 6.8 Hz), 3.06 (1H, dd, *J* = 10.4, 6.2 Hz), 2.70-2.65 (1H, m), 2.41 (1H, s), 2.04-1.93 (1H, m), 1.81-1.42 (7H, m), 1.04 (3H, t, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 82.6, 47.8, 46.7, 42.1, 39.8, 38.3, 25.9, 23.7, 23.3, 11.1; IR (NaCl, neat), 2968, 2881,

1763, 1462, 1360, 1292, 1192, 976 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{17}O_2$, 181.1229. Found 181.1234. NMR analysis of the crude lactone gave the diastereomeric composition: >95 : 5 (syn : anti).

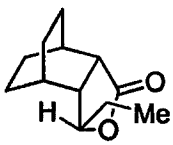


***anti*-lactone 24.** According to the general procedure A, 33 mg (0.17 mmol) of keto-acid **23** was treated with 0.41 mL (0.41 mmol) of Et_3BHLi (1.0M in THF). The reaction was stirred for 0.5 h at -78 °C, warmed to ambient temperature and stirred an additional 4 h. Standard work-up/cyclization provided 25 mg (83 %) of the desired lactone **24** as a colorless oil. Rf = 0.22 (4:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 6.30 (1H, dd, J = 5.8, 2.8 Hz), 6.24 (1H, dd, J = 5.5, 3.0 Hz), 3.86 (1H, ddd, J = 6.4, 6.4, 3.2 Hz), 3.30 (1H, s), 3.25 (1H, dd, J = 9.4, 4.7 Hz), 3.08 (1H, s), 2.72 (1H, ddd, J = 7.5, 3.6, 3.6 Hz), 1.71-1.59 (3H, m), 1.44-1.42 (1H, m), 0.96 (3H, t, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 136.7, 134.8, 84.0, 51.7, 48.5, 46.2, 45.6, 29.8, 9.1; IR (NaCl, neat), 3062, 2968, 2939, 2877, 1763, 1462, 1352, 1217, 1184, 978 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{15}O_2$, 179.1072. Found 179.1074. NMR analysis of the crude lactone gave the diastereomeric composition: 47 : 53 (syn : anti).

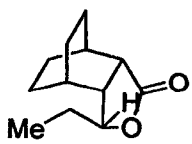


***syn*-lactone 25.** According to the general procedure B, 32 mg (0.17 mmol) of keto-acid **23** was treated with 38 μL (0.25 mmol) of $PhMe_2SiH$. The reaction was stirred for 14 h. The crude lactone was purified by column chromotograhy (9:1 Hex/EtOAc) providing 24 mg (82 %) of lactone **25** as a colorless oil. R_f = 0.17 (4:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 6.19 (2H, s), 4.36 (1H, ddd, J = 7.0, 7.0, 7.0 Hz), 3.39 (1H, dd, J = 8.7, 4.9 Hz), 3.26-3.24 (1H, m), 3.05-3.00 (2H, m),

1.76-1.54 (3H, m), 1.41 (1H, d, J = 7.5 Hz), 1.02 (3H, t, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 135.7, 135.0, 82.9, 52.7, 48.7, 45.1, 44.6, 44.5, 24.5, 11.0; IR (NaCl, neat), 3064, 2972, 2941, 2879, 1759, 1464, 1360, 1190, 972 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{15}O_2$, 179.1072. Found 179.1069. NMR analysis of the crude lactone gave the diastereomeric composition: >95 : 5 (syn : anti).

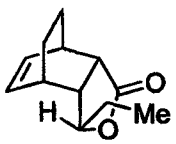


***anti*-lactone 27.** According to the general procedure A, 30 mg (0.14 mmol) of keto-acid **26** was treated with 0.34 mL (0.34 mmol) of Et_3BHLi (1.0M in THF). The reaction was stirred for 0.5 h at -78 °C, warmed to ambient temperature and stirred an additional 4 h. Standard work-up/cyclization provided 25 mg (90 %) of the desired lactone **27** as a colorless oil. Rf = 0.23 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (1H, ddd, J = 6.4, 6.4, 3.8 Hz), 2.70 (1H, dd, J = 11.5, 4.1 Hz), 2.21 (1H, d, J = 11.3 Hz), 2.05 (1H, d, J = 2.6 Hz), 1.73-1.42 (11H, m), 0.98 (3H, t, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6, 84.3, 42.7, 42.2, 29.8, 27.0, 25.6, 24.8, 21.5, 20.3, 9.1; IR (NaCl, neat), 2937, 2870, 1767, 1460, 1363, 1246, 1178, 980 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{19}O_2$, 195.1385. Found 195.1377. NMR analysis of the crude lactone gave the diastereomeric composition: 38 : 62 (syn : anti).

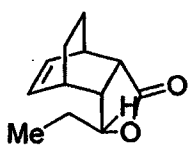


***syn*-lactone 28.** According to the general procedure B, 30 mg (0.14 mmol) of keto-acid **26** was treated with 26 μL (0.17 mmol) of $PhMe_2SiH$. The reaction was stirred for 14 h. The crude lactone was purified by column chromotograhy (9:1 Hex/EtOAc) providing 26 mg (94 %) of lactone **28** as a colorless oil. R_f = 0.23 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (1H, ddd, J = 8.3, 8.3,

6.6 Hz), 2.84 (1H, dd, J = 10.4, 5.1 Hz), 2.43 (1H, dd, J = 7.5, 7.5 Hz), 2.09 (1H, d, J = 4.3 Hz), 1.92-1.43 (10H, m), 1.38-1.30 (1H, m), 1.06 (3H, t, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3, 84.2, 43.9, 39.9, 25.3, 25.2, 24.8, 23.8, 23.5, 21.7, 21.3, 11.1; IR (NaCl, neat), 2941, 2874, 1759, 1460, 1363, 1290, 1186, 1115, 970 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{19}O_2$, 195.1385. Found 195.1384. NMR analysis of the crude lactone gave the diastereomeric composition: >95 : 5 (syn : anti).

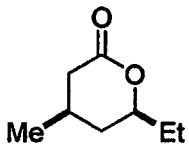


***anti*-lactone 30.** According to the general procedure A, 32 mg (0.15 mmol) of keto-acid **29** was treated with 0.37 mL (0.37 mmol) of Et_3BHLi (1.0M in THF). The reaction was stirred for 0.5 h at -78 °C, warmed to ambient temperature and stirred an additional 4 h. Standard work-up/cyclization provided 26 mg (87 %) of the desired lactone **30** as a colorless oil. Rf = 0.23 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (1H, t, J = 7.7 Hz), 6.25 (1H, t, J = 7.7 Hz), 3.93 (1H, ddd, J = 6.4, 6.4, 4.3 Hz), 3.06-3.05 (1H, m), 2.78 (1H, dd J = 10.2, 3.4 Hz), 2.68-2.66 (1H, m), 2.29 (1H, ddd, J = 10.0, 3.4, 3.4 Hz), 1.70-1.47 (4H, m), 1.36-1.27 (2H, m), 0.96 (3H, t, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 134.1, 133.0, 86.1, 45.9, 44.3, 33.4, 31.6, 29.4, 23.5, 23.4, 9.1; IR (NaCl, neat), 3047, 2939, 2870, 1759, 1362, 1242, 1190, 999 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{17}O_2$, 193.1228. Found 193.1224. NMR analysis of the crude lactone gave the diastereomeric composition: 53 : 47 (syn : anti).

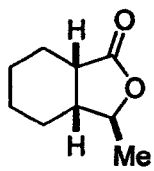


***syn*-lactone 31.** According to the general procedure B, 31 mg (0.15 mmol) of keto-acid **29** was treated with 34 μL (0.22 mmol) of $PhMe_2SiH$. The reaction was stirred for 14 h. The crude lactone was purified by column

chromotograhy (9:1 Hex/EtOAc) providing 26 mg (91 %) of lactone **31** as a colorless oil. R_f = 0.19 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (1H, t, *J* = 7.5 Hz), 6.19 (1H, t, *J* = 7.4 Hz), 4.34 (1H, ddd, *J* = 8.3, 8.3, 5.1 Hz), 3.10-3.08 (1H, m), 2.95 (1H, dd, *J* = 9.6, 3.8 Hz), 2.71-2.69 (1H, m), 2.59 (1H, ddd, *J* = 9.6, 9.6, 1.9 Hz), 1.74-1.63 (2H, m), 1.57-1.44 (2H, m), 1.38-1.21 (2H, m), 1.04 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 133.3, 132.8, 84.2, 47.0, 41.8, 31.6, 29.8, 25.2, 25.0, 22.4, 11.2; IR (NaCl, neat), 3045, 2949, 2872, 1736, 1464, 1360, 1217, 1192, 976 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{17}O_2$, 193.1229. Found 193.1225. NMR analysis of the crude lactone gave the diastereomeric composition: >95 : 5 (syn : anti).



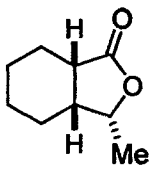
***syn*-lactone 34.** According to the general procedure A, 32 mg (0.20 mmol) of keto-acid **32** was treated with 0.49 mL (0.49 mmol) of Et_3BHLi (1.0M in THF). The reaction was stirred for 0.5 h at -78 °C, warmed to ambient temperature and stirred an additional 4 h. Standard work-up/cyclization provided 22 mg (77 %) of the known lactone **34**[2] as a colorless oil. NMR analysis of the crude lactone gave the diastereomeric composition: 55 : 45 (syn : anti).



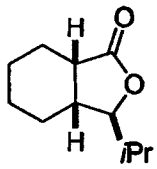
***anti*-lactone 36.** According to the general procedure A, 28 mg (0.16 mmol) of keto-acid **35** was treated with 0.39 mL (0.39 mmol) of Et_3BHLi (1.0M in THF). The reaction was stirred for 0.5 h at -78 °C, warmed to ambient temperature and stirred an additional 4 h. Standard work-up/cyclization provided 19 mg (75 %) of the desired lactone **36** as a colorless oil. Rf = 0.20 (4:1 Hex/EtOAc); ^{1}H NMR

[2] Tsunoi, S.; Ryu, I.; Okuda, T.; Tanaka, M.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc.* **1998**, *120*, 8692-8701.

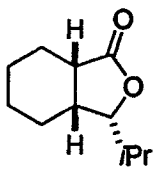
(400 MHz, $CDCl_3$) δ 4.30 (1H, dq, J = 6.4, 3.6 Hz), 2.71 (1H, ddd, J = 6.4, 6.4, 6.4 Hz), 2.16-2.10 (1H, m), 1.95-1.89 (1H, m), 1.82-1.64 (2H, m), 1.57-1.46 (2H, m), 1.33 (3H, d, J = 6.4 Hz), 1.32-1.26 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 79.4, 41.0, 38.4, 26.7, 23.2, 22.9, 22.8, 18.8; IR (NaCl, neat),2935, 2858, 1774, 1450, 1367, 1238, 1161, 1132, 1022, 953, 916 cm^{-1}; HRMS (FAB+) calcd for $C_9H_{15}O_2$, 155.1072. Found 155.1078. NMR analysis of the crude lactone gave the diastereomeric composition: 14 : 86 (syn : anti).



***syn*-lactone 37.** According to the general procedure B, 27 mg (0.16 mmol) of keto-acid **35** was treated with 30 μL (0.20 mmol) of $PhMe_2SiH$. The reaction was stirred for 14 h. The crude lactone was purified by column chromotograhy (4:1 Pent/Et_2O) providing 20 mg (82 %) of lactone **37** as a colorless oil. R_f = 0.15 (4:1 Pent/Et_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 4.44 (1H, dq, J = 11.3, 6.6 Hz), 2.74 (1H, ddd, J = 6.2, 6.2, 2.0 Hz), 2.32-2.25 (1H, m), 2.17 (1H, d, J = 13.2 Hz), 1.74-1.49 (4H, m), 1.31 (3H, d, J = 6.6 Hz), 1.17-1.05 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 77.7, 42.2, 39.6, 23.5, 22.8, 22.6, 22.5, 14.5; IR (NaCl, neat), 2935, 2858, 1767, 1448, 1390, 1333, 1182, 1128, 1037, 952 cm^{-1}; HRMS (FAB+) calcd for $C_9H_{15}O_2$, 155.1072. Found 155.1074. NMR analysis of the crude lactone gave the diastereomeric composition: 96 : 4 (syn : anti).

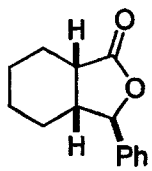


***anti*-lactone 39.** According to the general procedure A, 14 mg (0.071 mmol) of keto-acid **38** was treated with 0.17 mL (0.17 mmol) of Et_3BHLi (1.0M in THF). The reaction was stirred for 0.5 h at -78 °C, warmed to ambient temperature and stirred an additional 4 h. Standard work-up/cyclization provided 11 mg (85 %) of the desired lactone **39** as a colorless solid. Mp = 45-46 °C (Et_2O) Rf = 0.17 (4:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 3.72 (1H, dd, J = 8.3, 2.1 Hz), 2.70-2.66 (1H, m), 2.35-2.29 (1H, m), 2.06-2.02 (1H, m), 1.84-1.77 (2H, m), 1.65-1.54 (4H, m), 1.31-1.21 (3H, m), 0.99 (3H, d, J = 6.6 Hz), 0.96 (3H, d, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 89.4, 38.4, 36.8, 30.5, 28.6, 23.3, 23.1, 22.8, 18.9, 18.6; IR (NaCl, neat), 2943, 2854, 1757, 1472, 1437, 1363, 1165, 1128, 986 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{19}O_2$, 183.1385. Found 183.1392. GC analysis (CP-Sil8CB, 110 °C oven, 2.5 mL/min flow rate; tr (min.) = 7.79 min., tr (maj.) = 8.65 min.) gave the isomeric composition of the product: 5 : 95 (syn : anti).

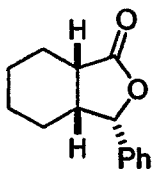


***syn*-lactone 40.** According to the general procedure B, 15 mg (0.076 mmol) of keto-acid **38** was treated with 18 μL (0.12 mmol) of $PhMe_2SiH$. The reaction was stirred for 14 h. The crude lactone was purified by column chromotograhy (9:1 Hex/EtOAc) providing 11 mg (78 %) of lactone **40** as a colorless solid. Mp = 54-56 °C (Et_2O); R_f = 0.17 (4:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 3.76 (1H, dd, J = 10.7, 3.8 Hz), 2.74-2.71 (1H, m), 2.40-2.34 (1H, m), 2.20-2.17 (1H, m), 1.89 (1H, dq, J = 17.3, 6.6 Hz), 1.73-1.71 (2H, m), 1.63-1.49 (3H, m), 1.20-1.11 (2H, m), 1.70 (3H, d, J = 6.4 Hz), 0.88 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 87.6, 42.6, 38.2, 27.3, 23.6, 22.9, 22.7, 22.1, 20.2, 17.6; IR (NaCl, dep from $CHCl_3$), 2956, 2873, 1756,

1471, 1446, 1173, 1130, 1022, 987 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_{19}O_2$, 183.1385. Found 183.1394. GC analysis (CP-Sil8CB, 110 °C oven, 2.5 mL/min flow rate; tr (min.) = 7.79 min., tr (maj.) = 8.65 min.) gave the isomeric composition of the product: 92 : 8 (syn : anti).



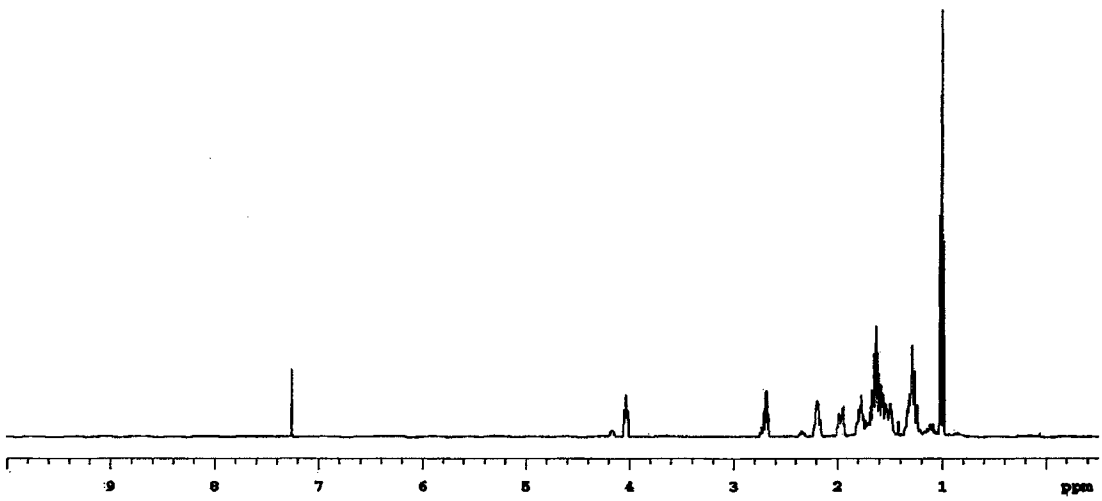
***anti*-lactone 6.** According to the general procedure A, 20 mg (0.086 mmol) of keto-acid **5** was treated with 0.21 mL (0.21 mmol) of Et_3BHLi (1.0M in THF). The reaction was stirred for 0.5 h at -78 °C, warmed to ambient temperature and stirred an additional 4 h. Standard work-up/cyclization provided 18 mg (96 %) of the known lactone **6**[3] as a colorless oil. NMR analysis of the crude lactone gave the diastereomeric composition: 5 : >95 (syn : anti).

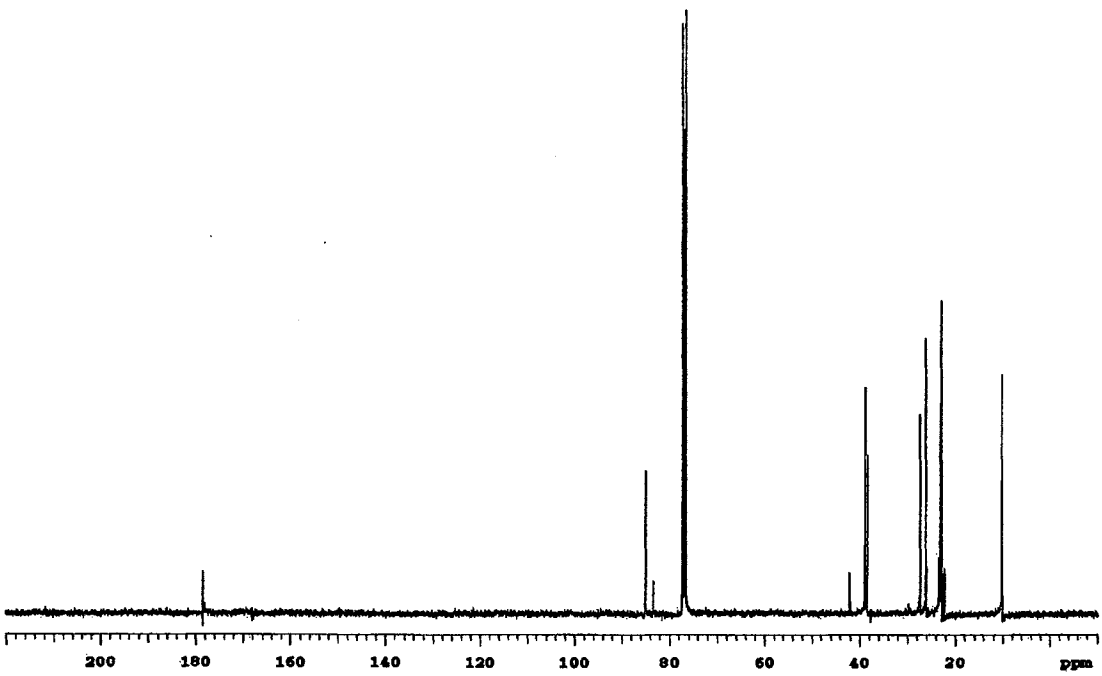


***syn*-lactone 7.** According to the general procedure B, 20 mg (0.086 mmol) of keto-acid **5** was treated with 20 μL (0.13 mmol) of $PhMe_2SiH$. The reaction was stirred for 14 h. The crude lactone was purified by column chromotograhy (9:1 Hex/EtOAc) providing 17 mg (91 %) of known lactone **7**[3] as a colorless oil. NMR analysis of the crude lactone gave the diastereomeric composition: 50 : 50 (syn : anti).

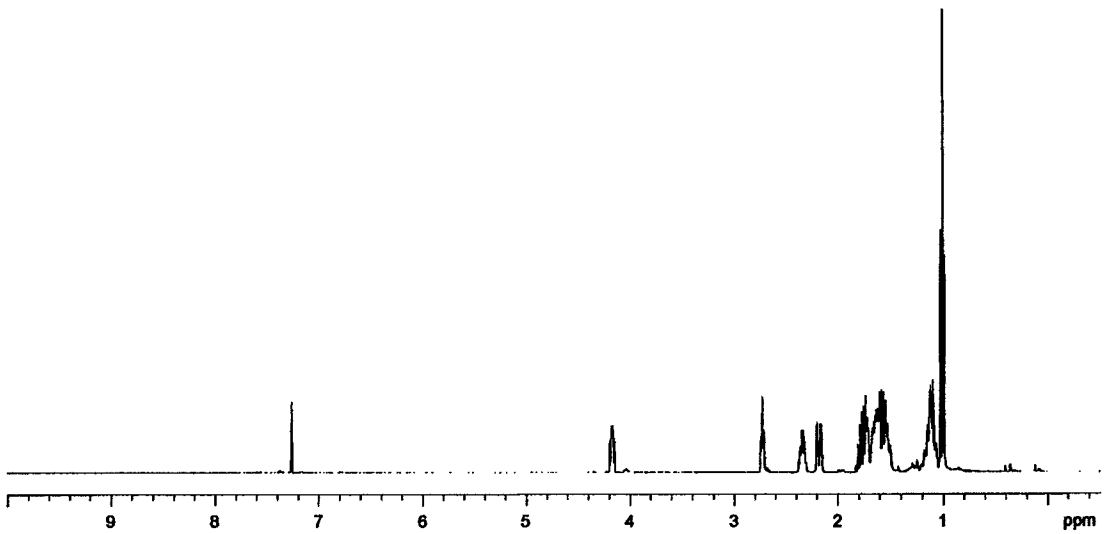
[3] Pourahmady, N.; Eisenbraun, E. J. *J. Org. Chem.* **1983**, *48*, 3067-3070.

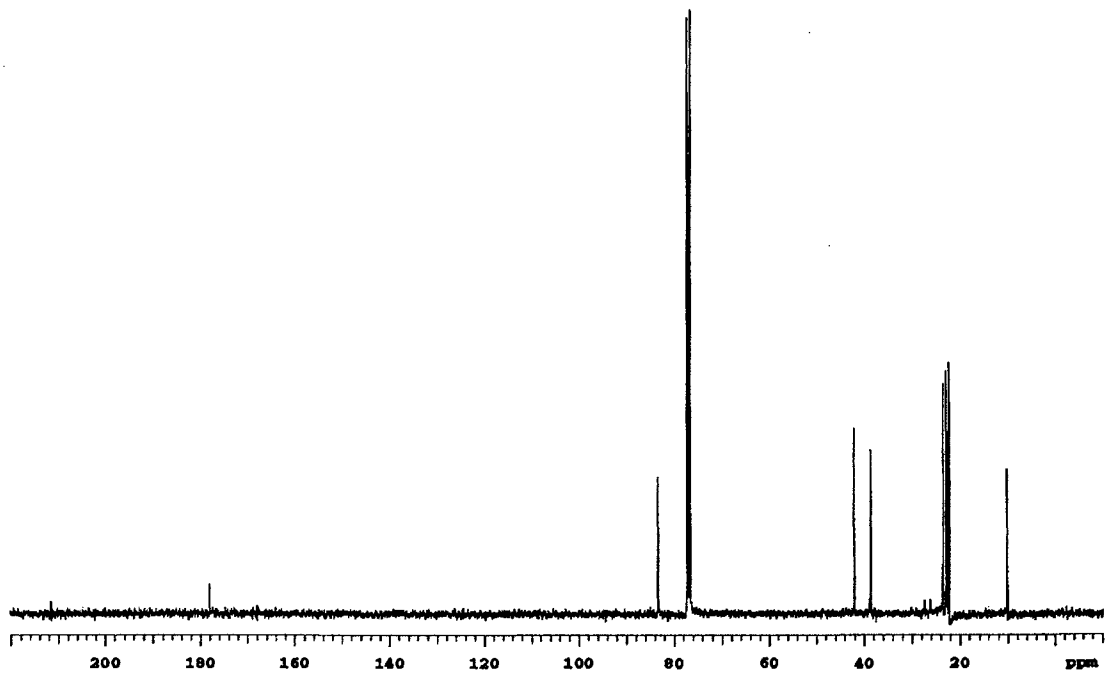
^{1}H and ^{13}C NMR spectra for **9**:



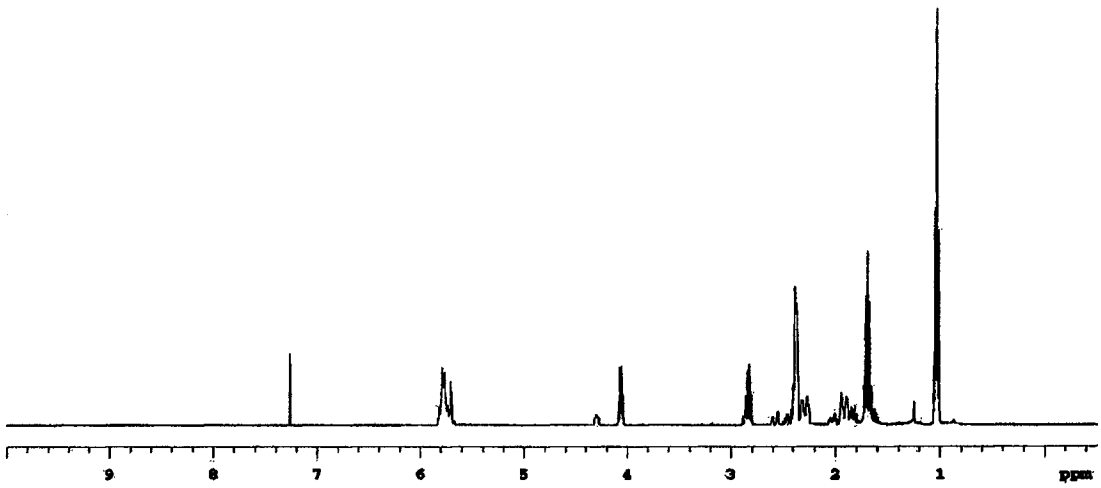


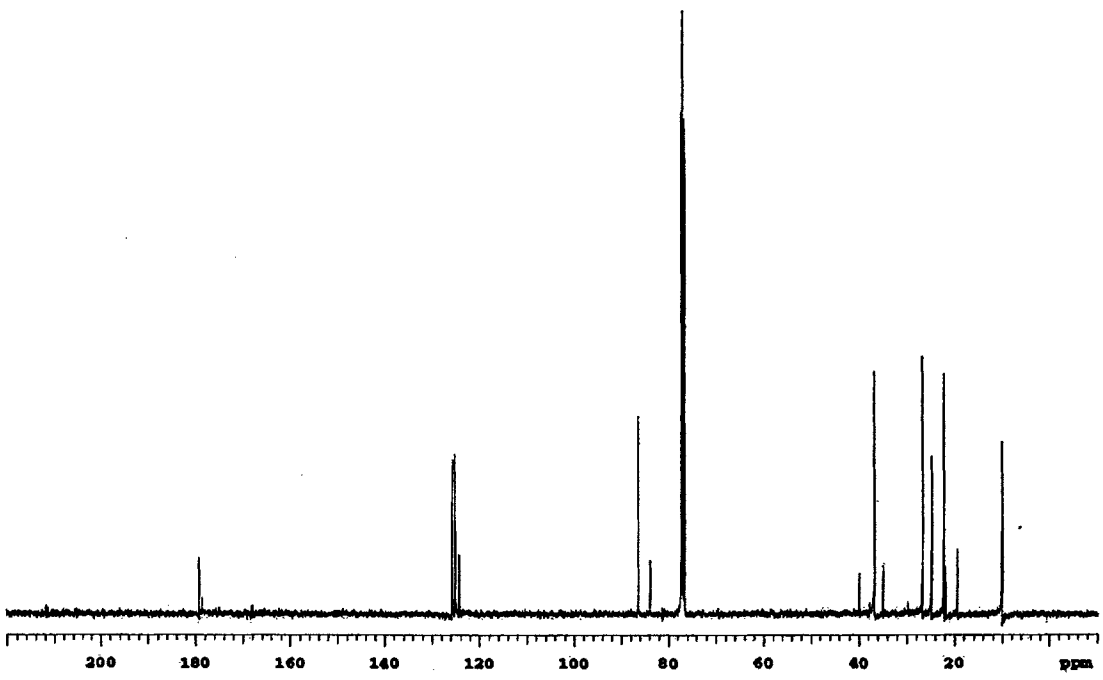
^{1}H and ^{13}C NMR spectra for **10**:



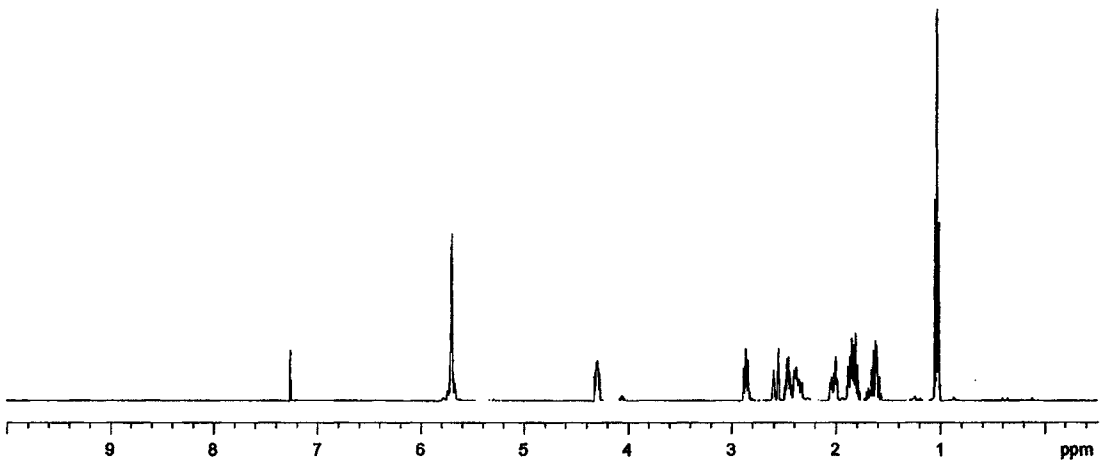


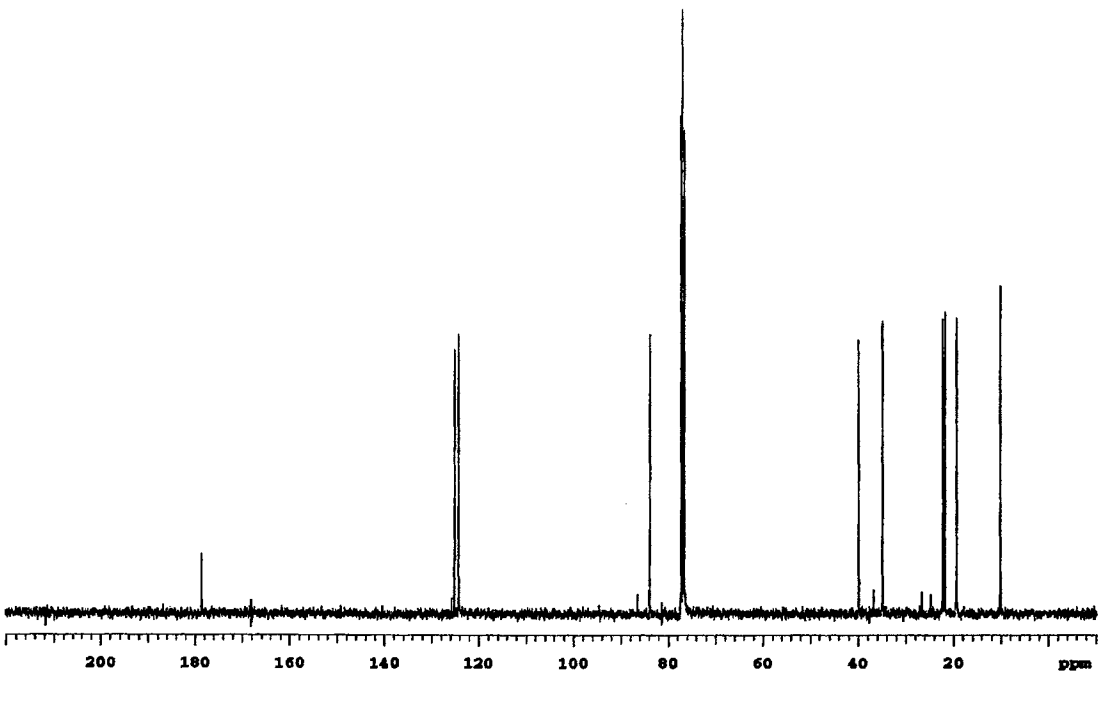
^{1}H and ^{13}C NMR spectra for **12**:



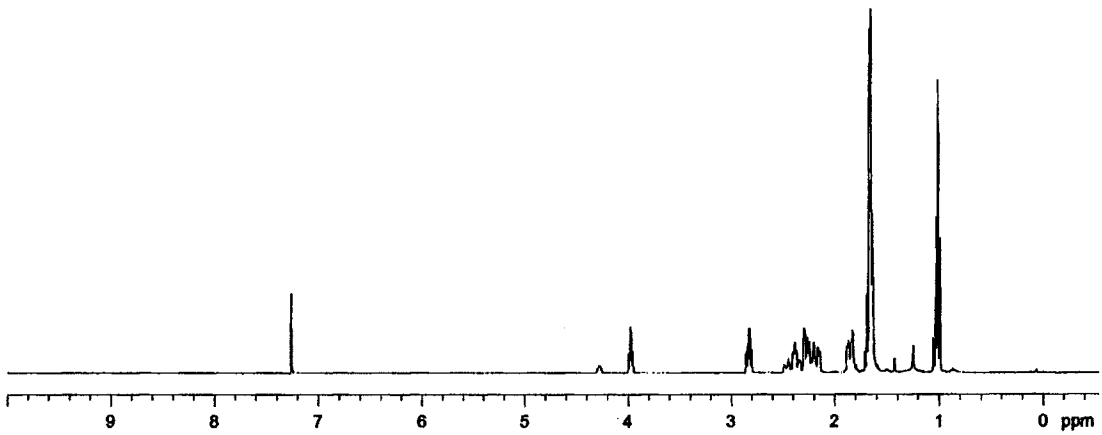


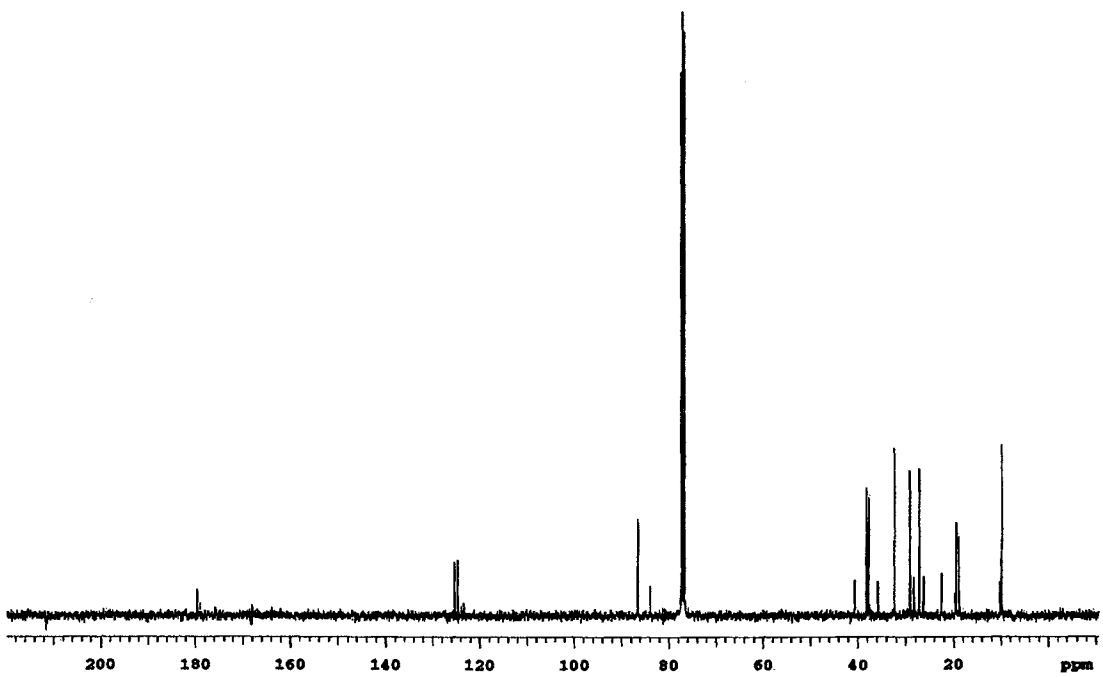
^{1}H and ^{13}C NMR spectra for **13**:



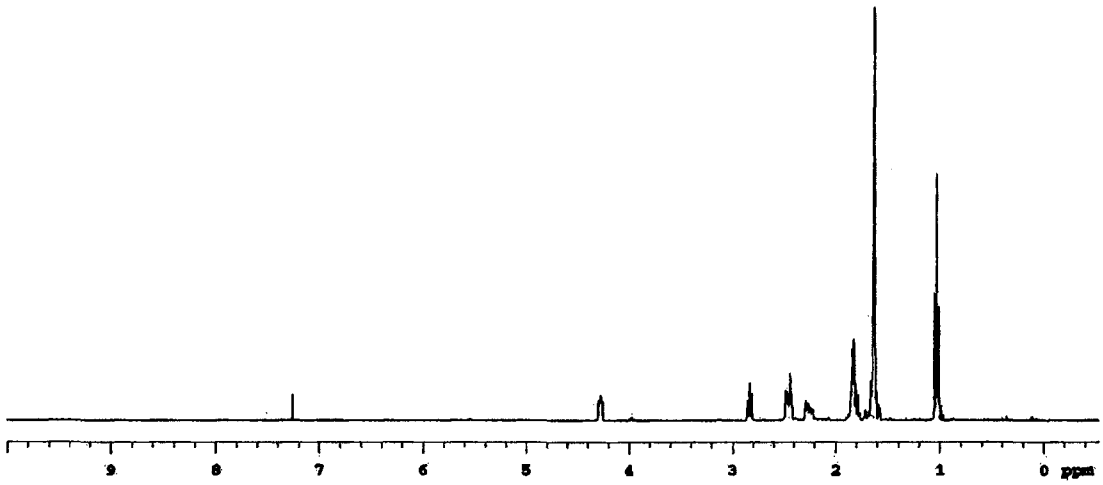


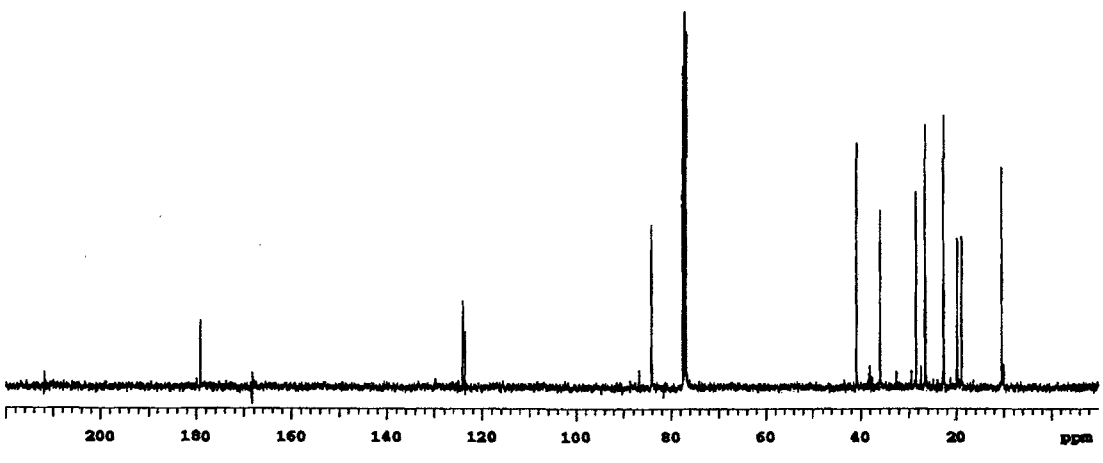
^{1}H and ^{13}C NMR spectra for **15**:



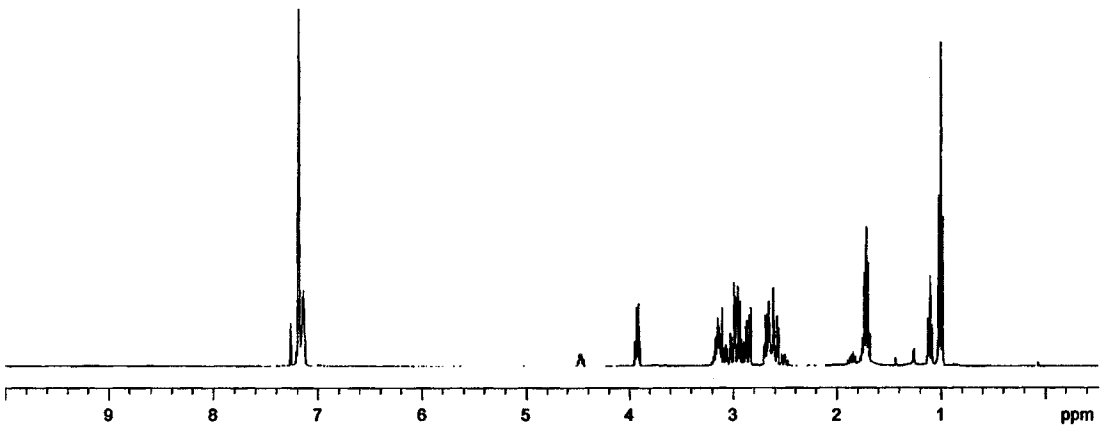


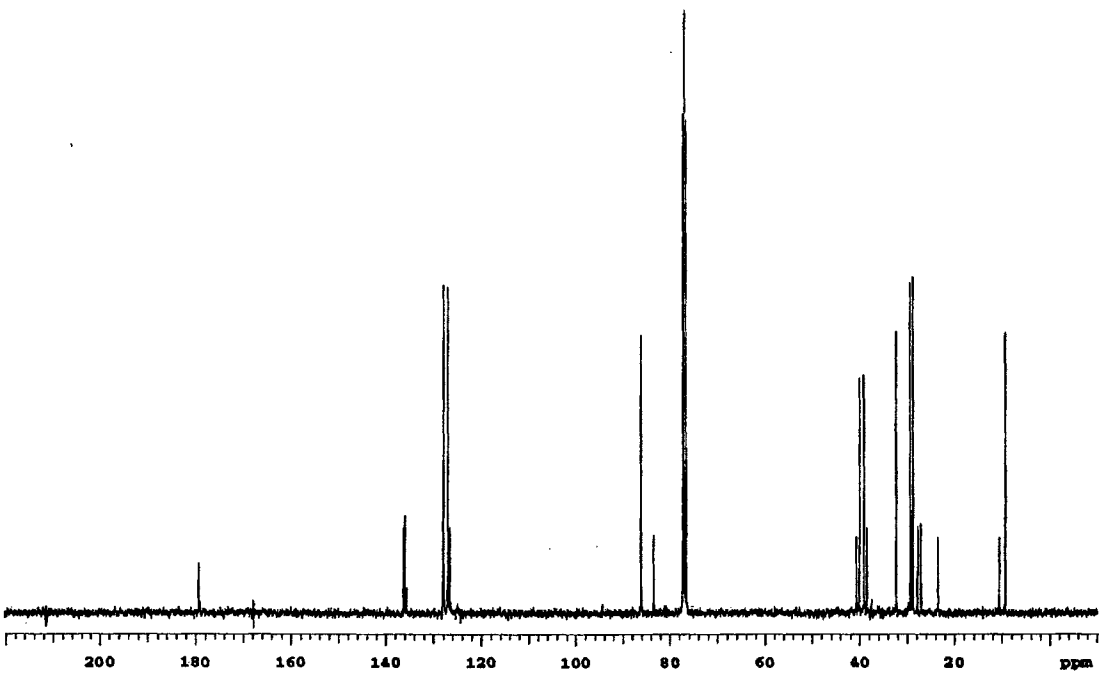
^{1}H and ^{13}C NMR spectra for **16**:



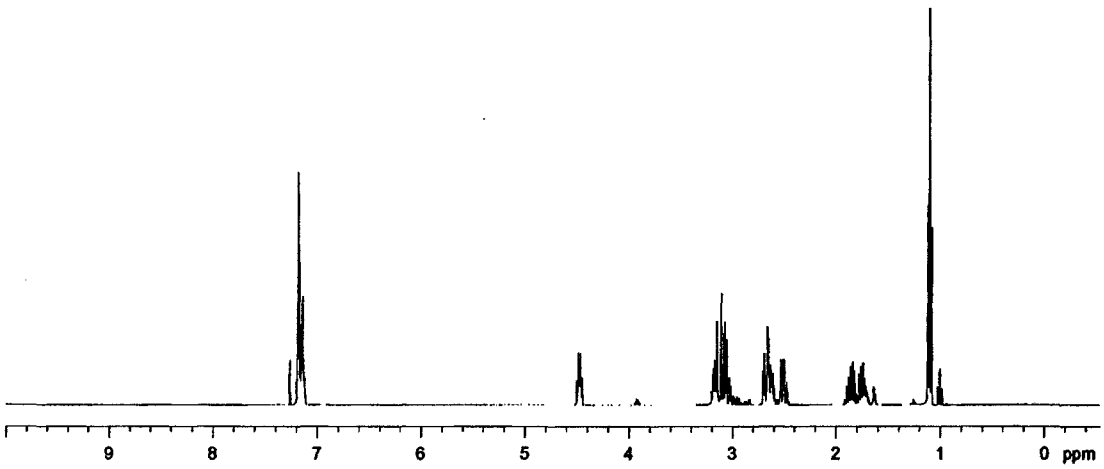


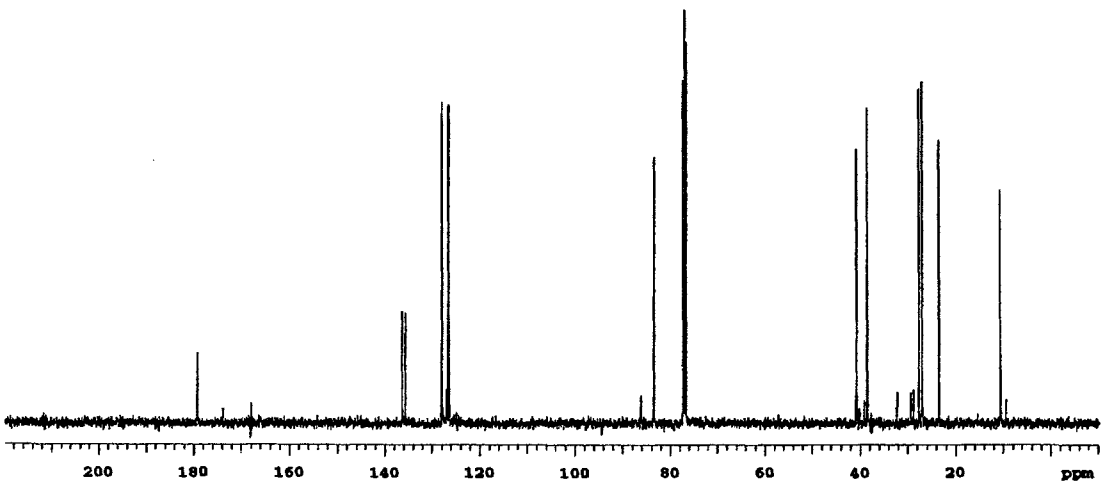
^{1}H and ^{13}C NMR spectra for **18**:



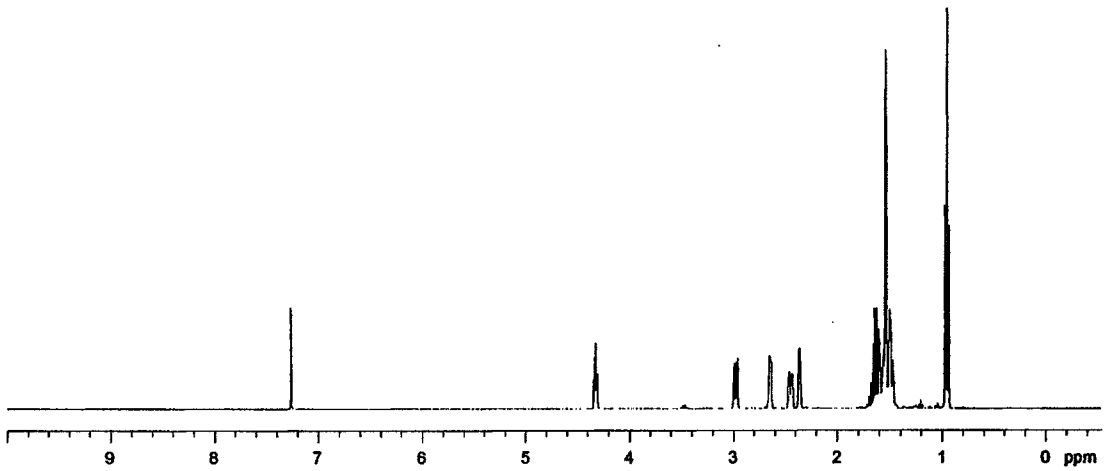


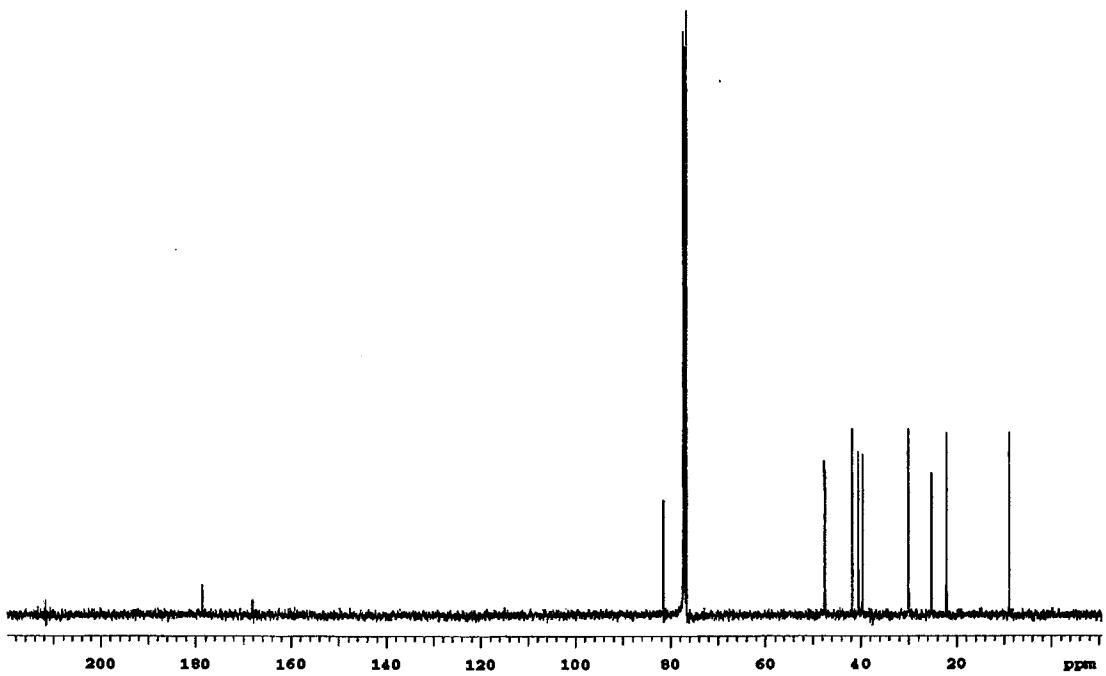
^{1}H and ^{13}C NMR spectra for **19**:



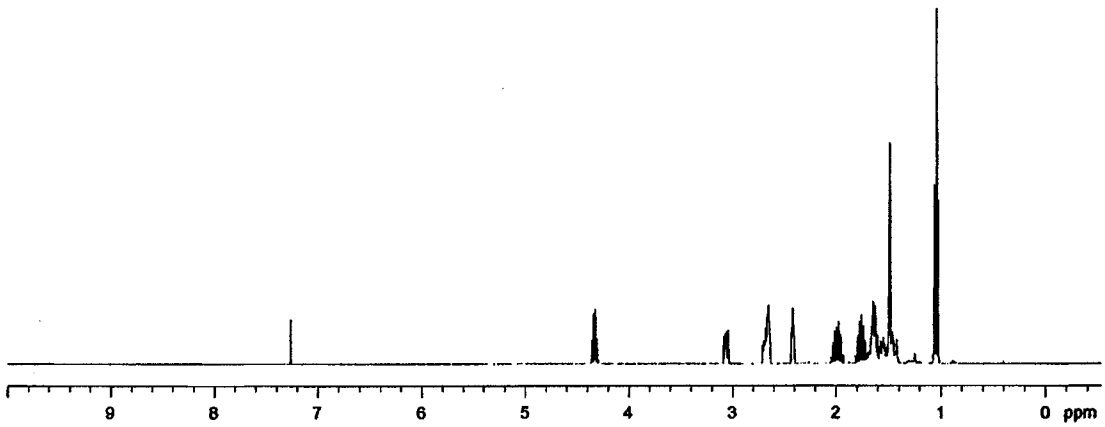


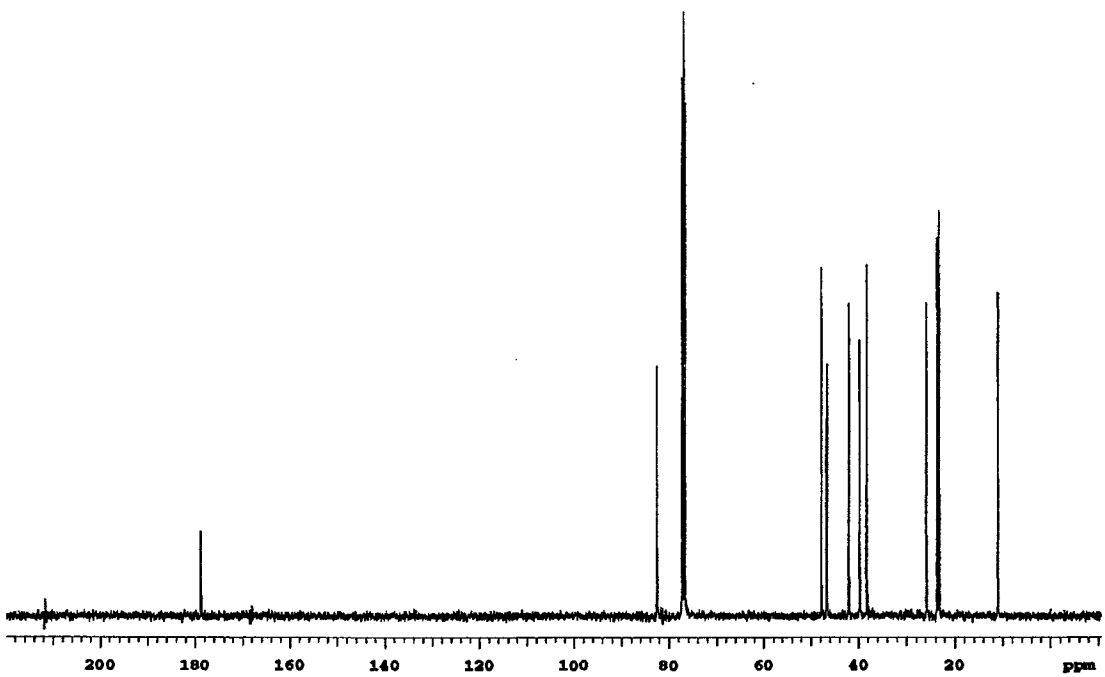
^{1}H and ^{13}C NMR spectra for **21**:



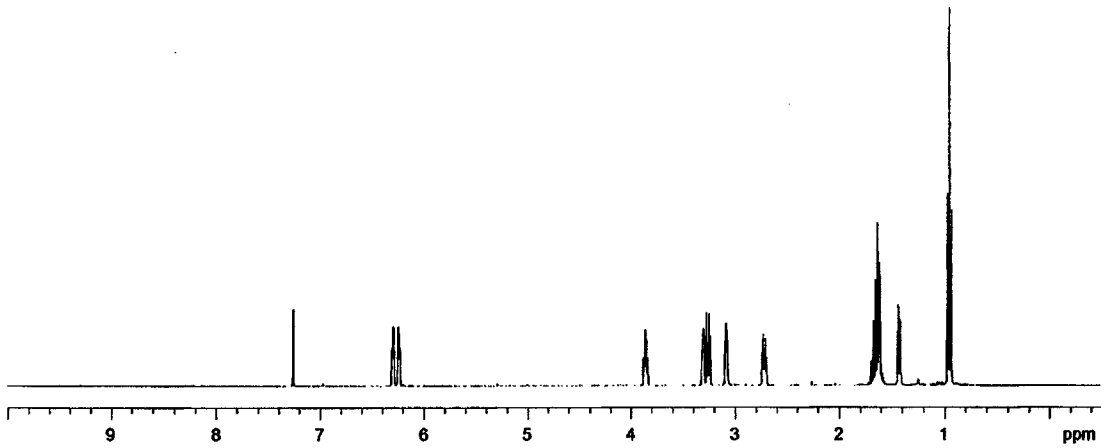


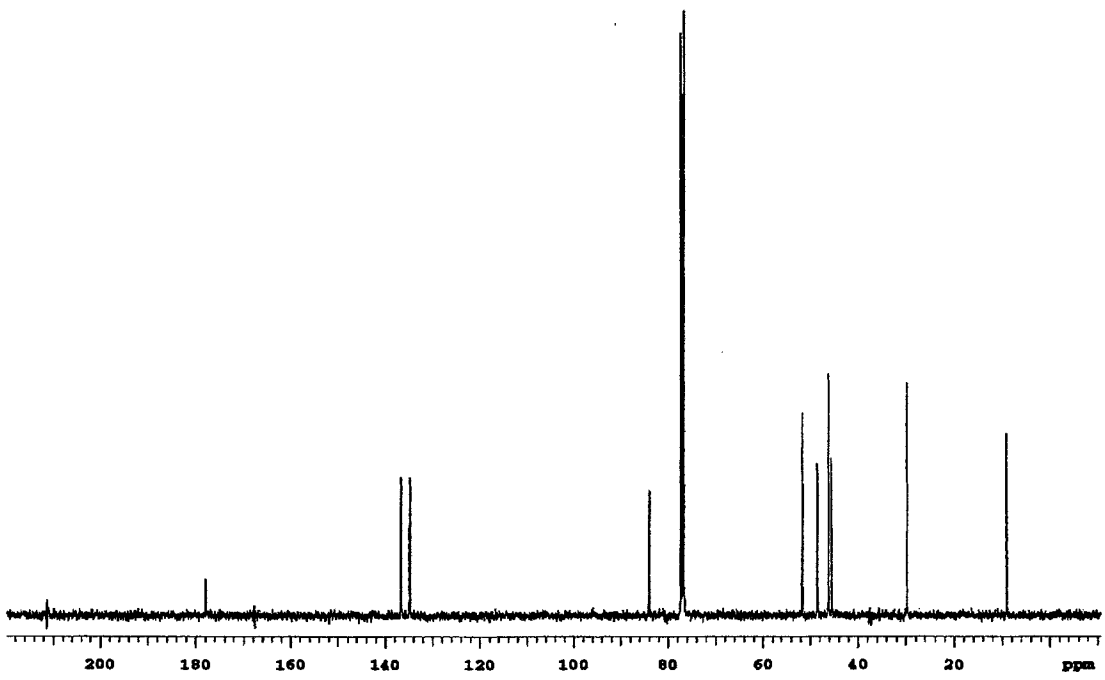
^{1}H and ^{13}C NMR spectra for **22**:



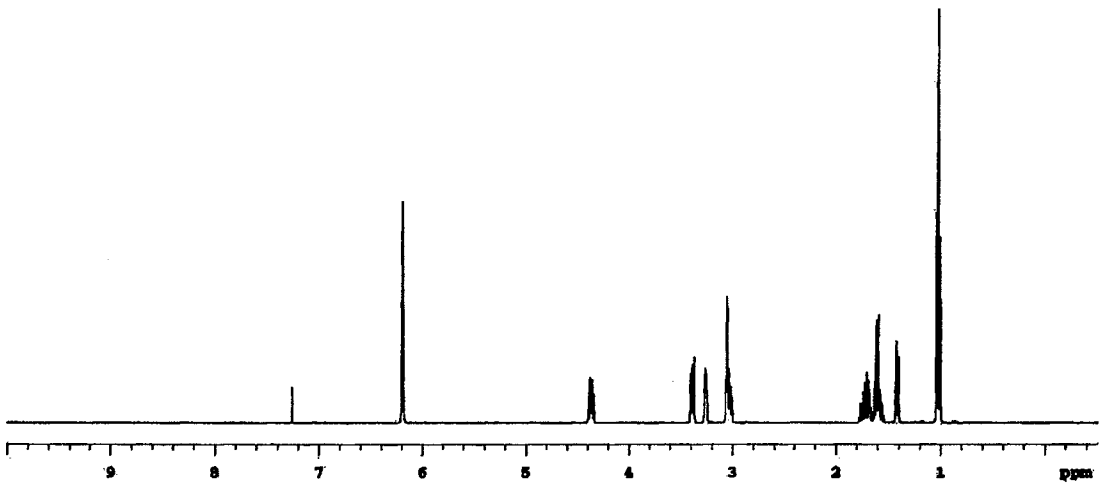


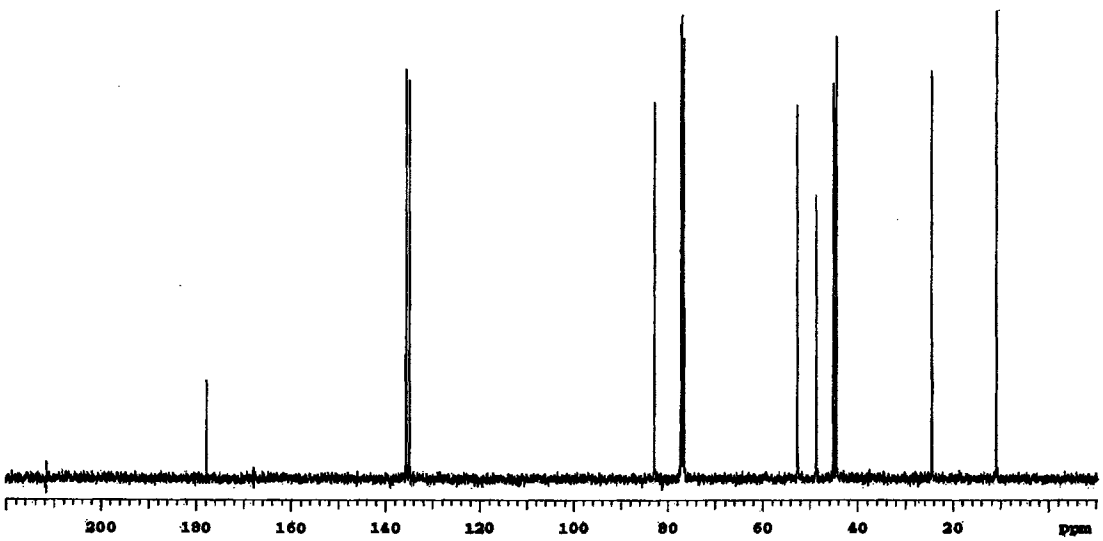
^{1}H and ^{13}C NMR spectra for **24**:



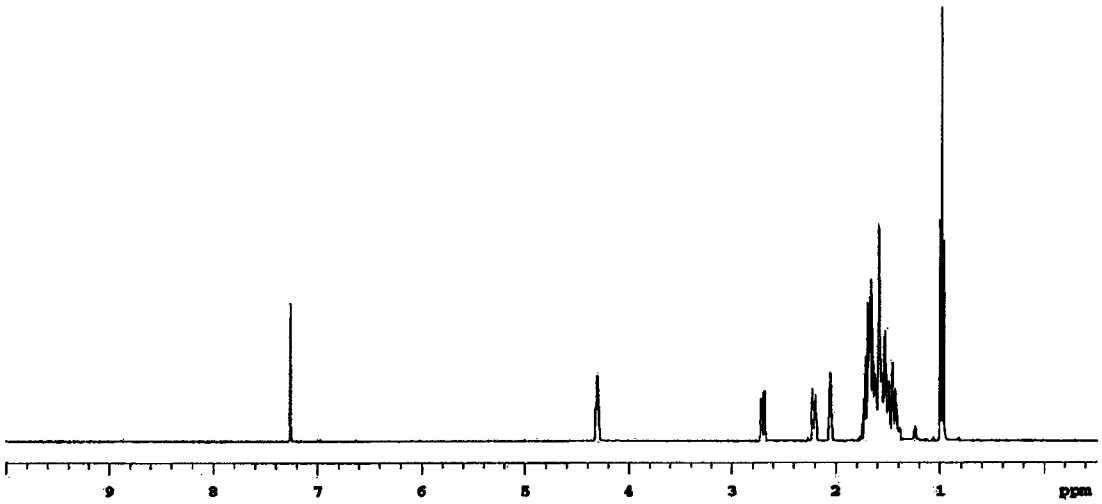


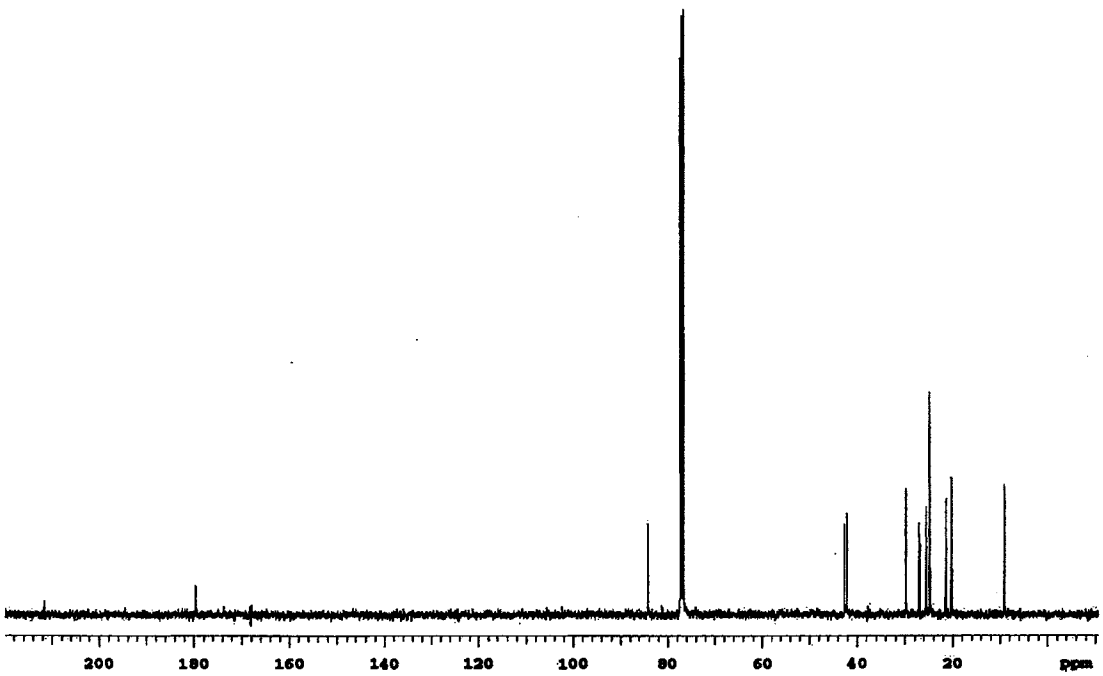
^{1}H and ^{13}C NMR spectra for **25**:



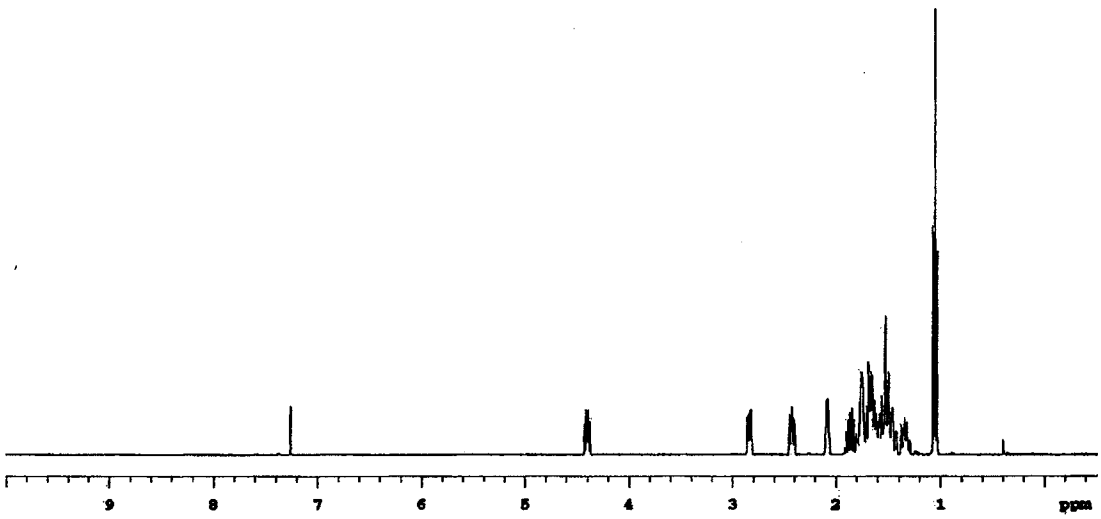


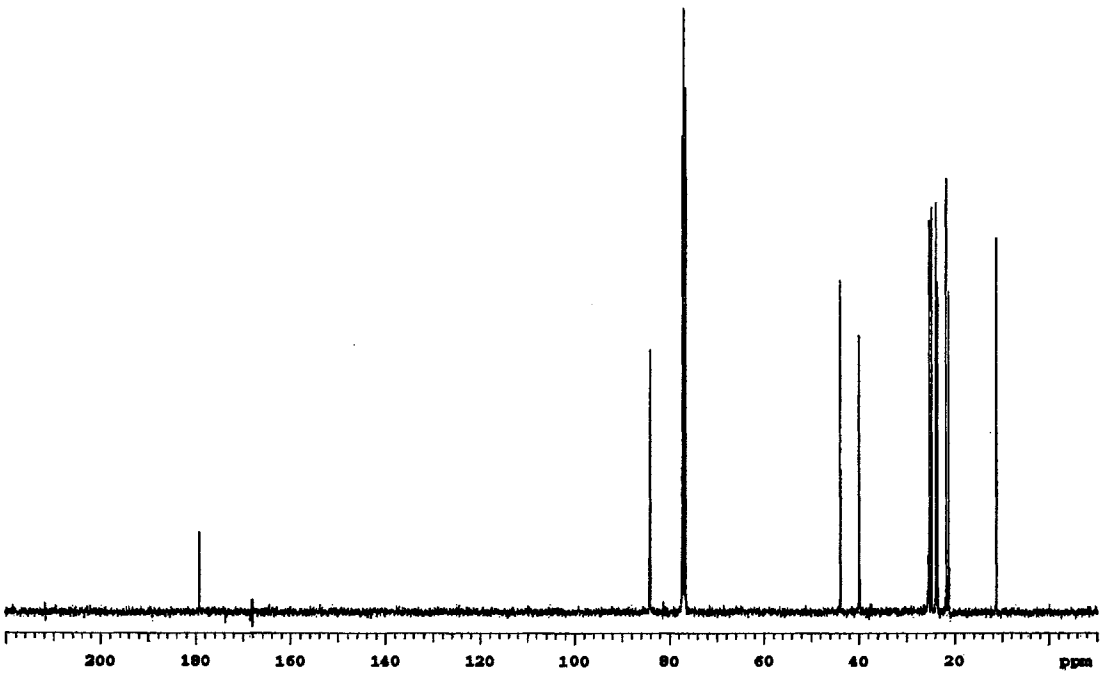
^{1}H and ^{13}C NMR spectra for **27**:



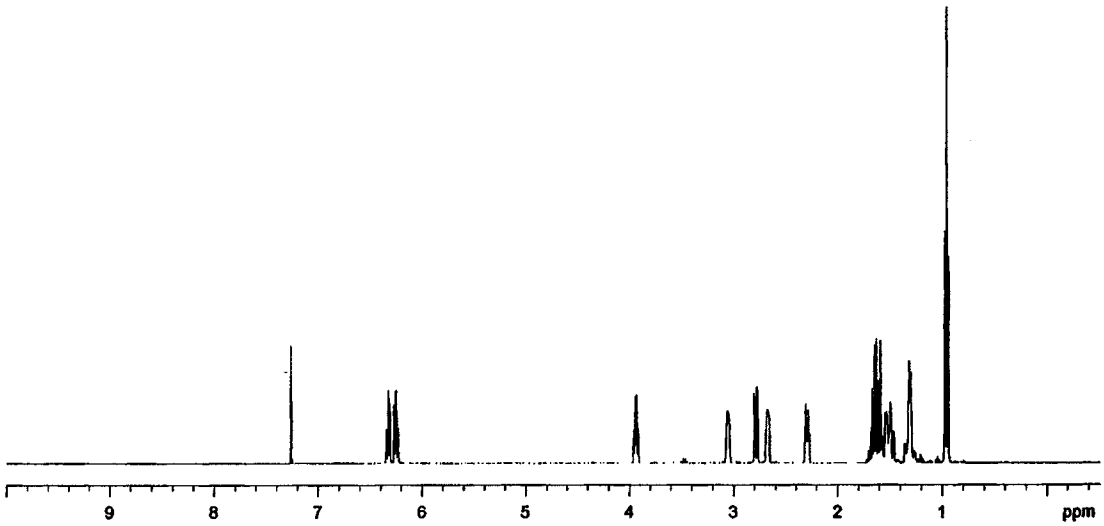


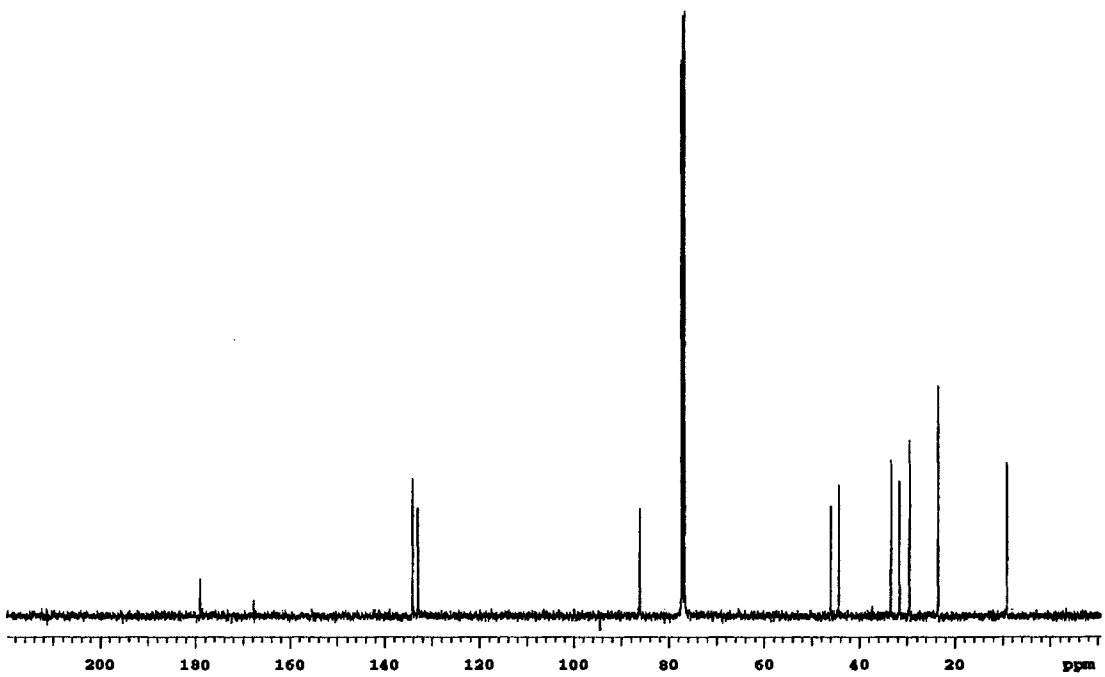
^{1}H and ^{13}C NMR spectra for **28**:



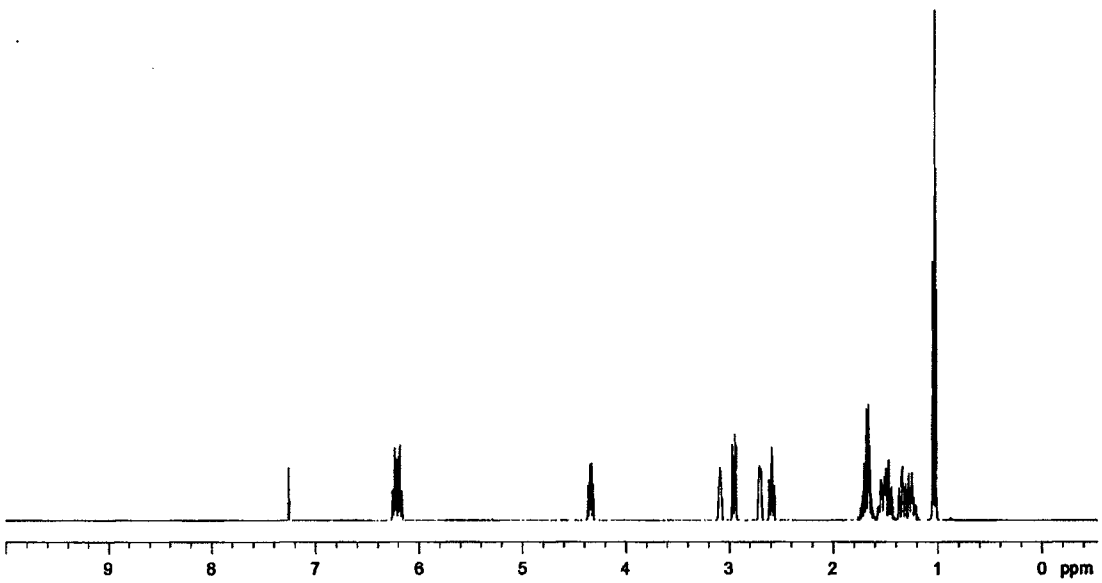


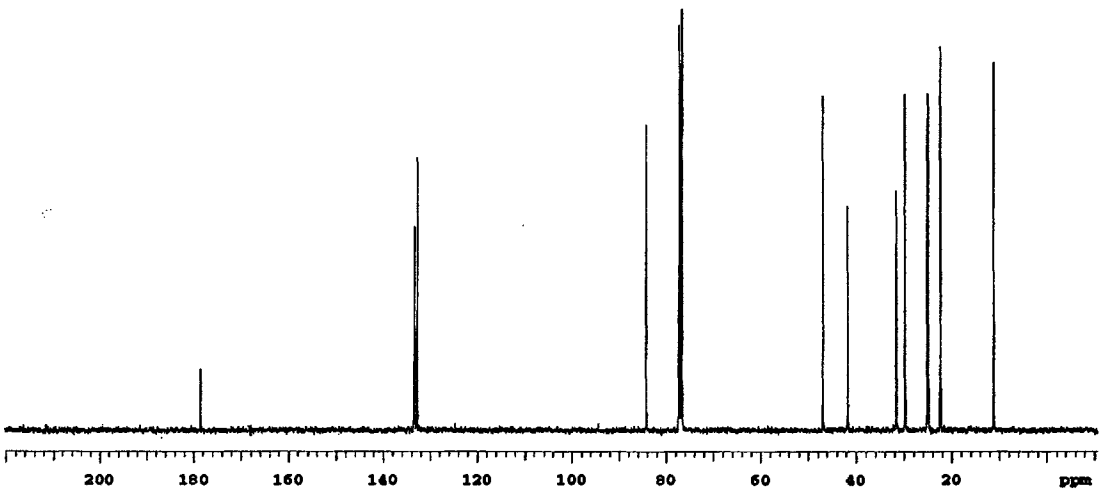
^{1}H and ^{13}C NMR spectra for **30**:



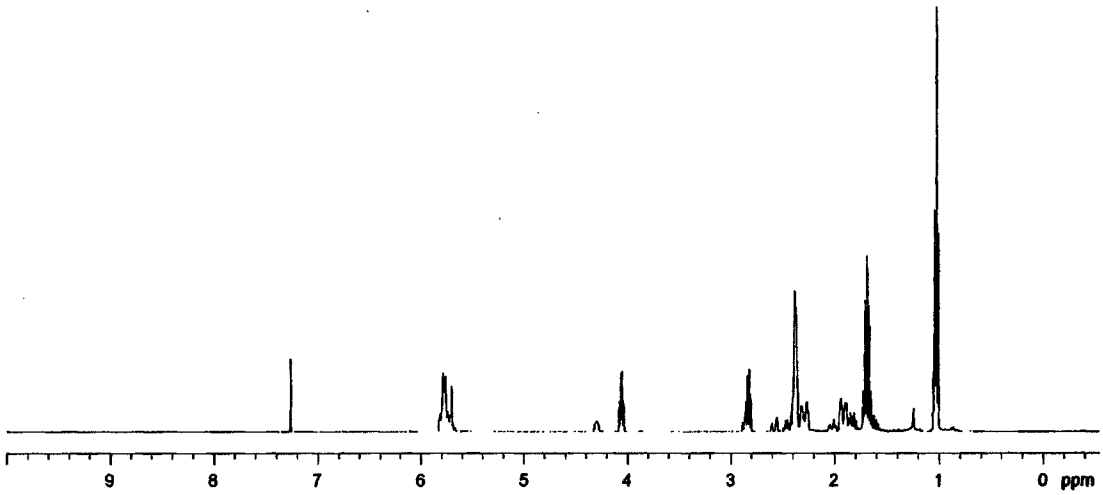


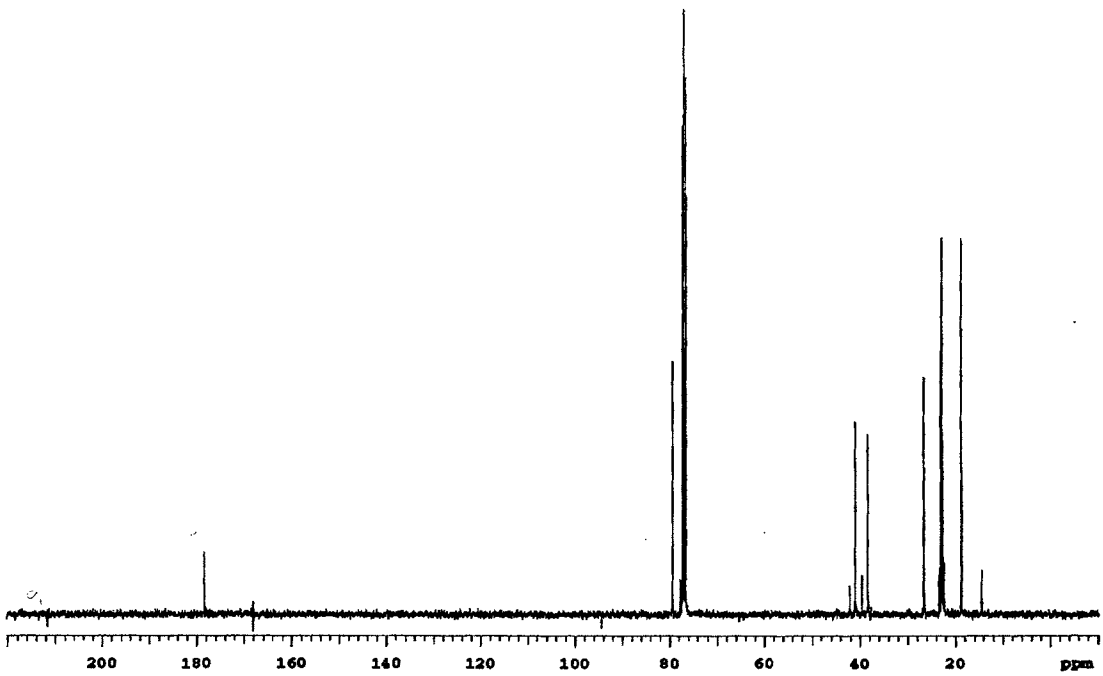
^{1}H and ^{13}C NMR spectra for **31**:



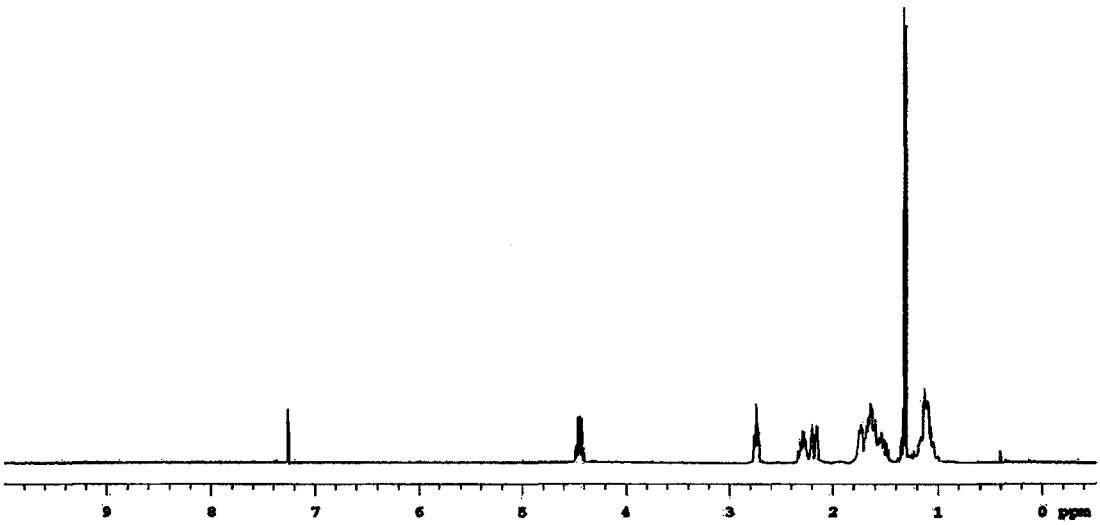


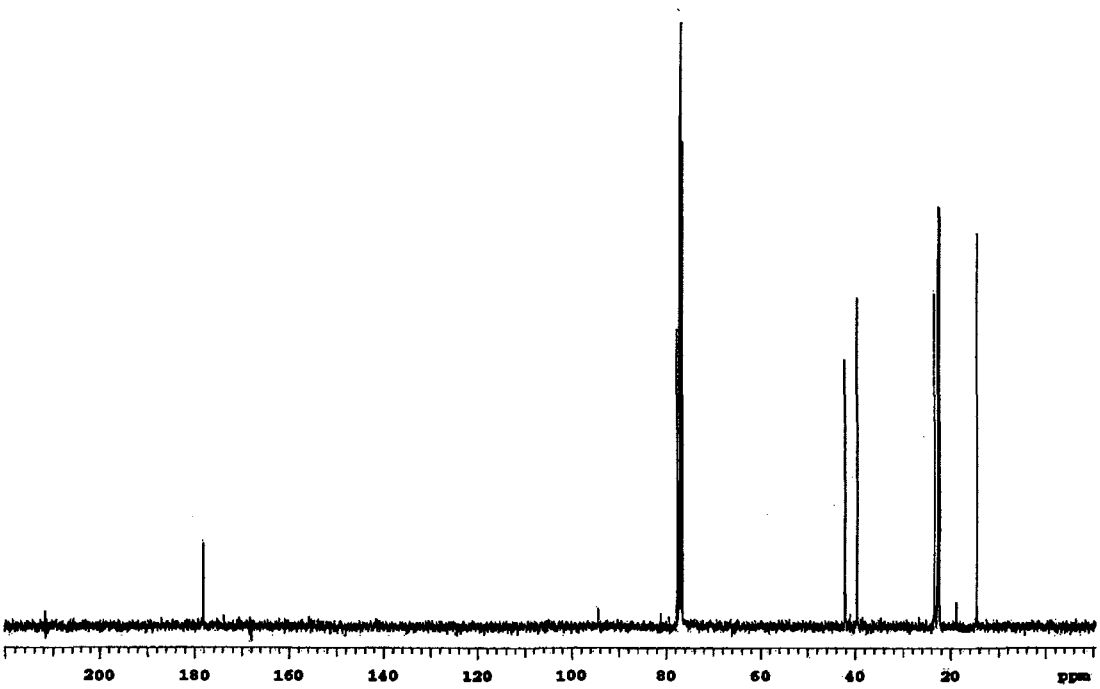
^{1}H and ^{13}C NMR spectra for **36**:



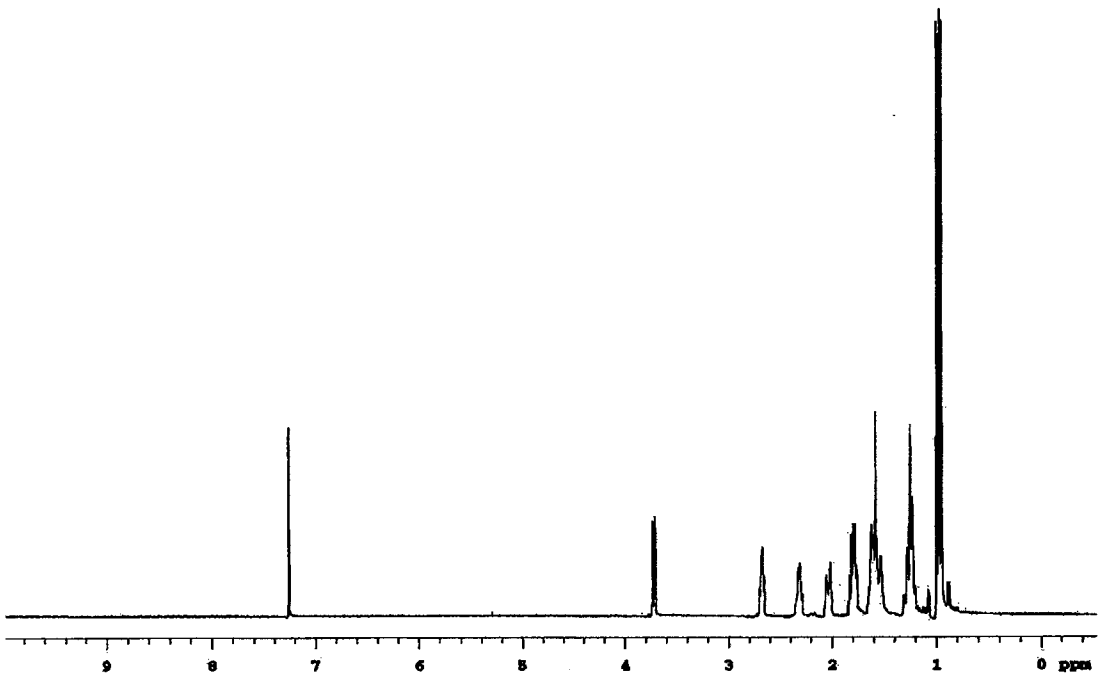


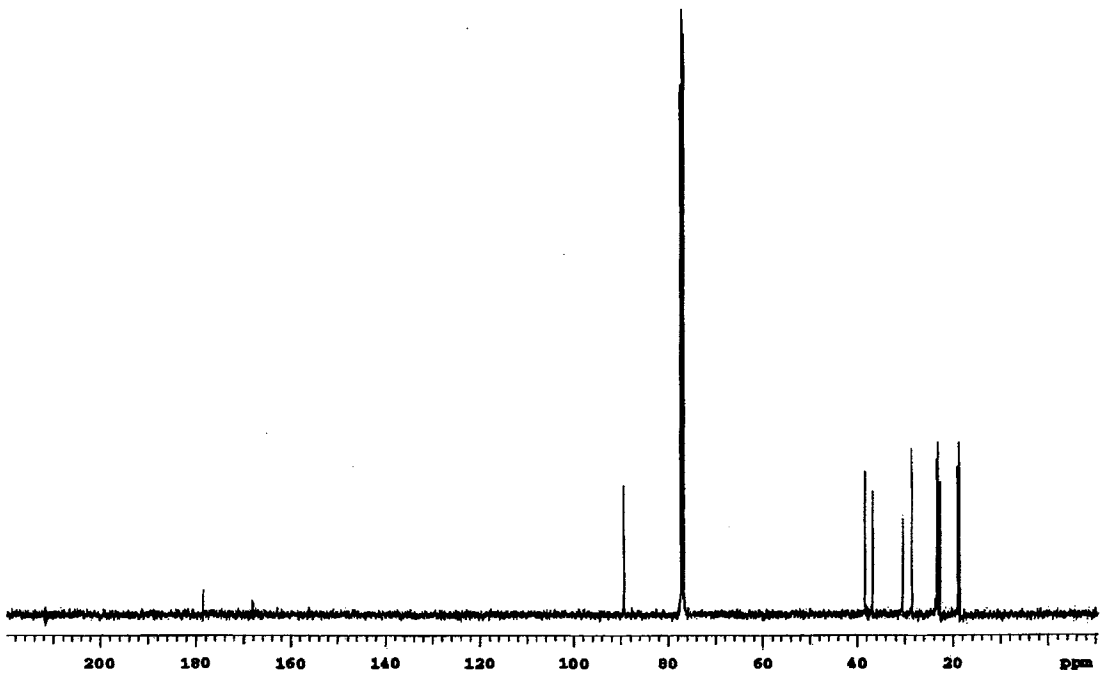
^{1}H and ^{13}C NMR spectra for **37**:



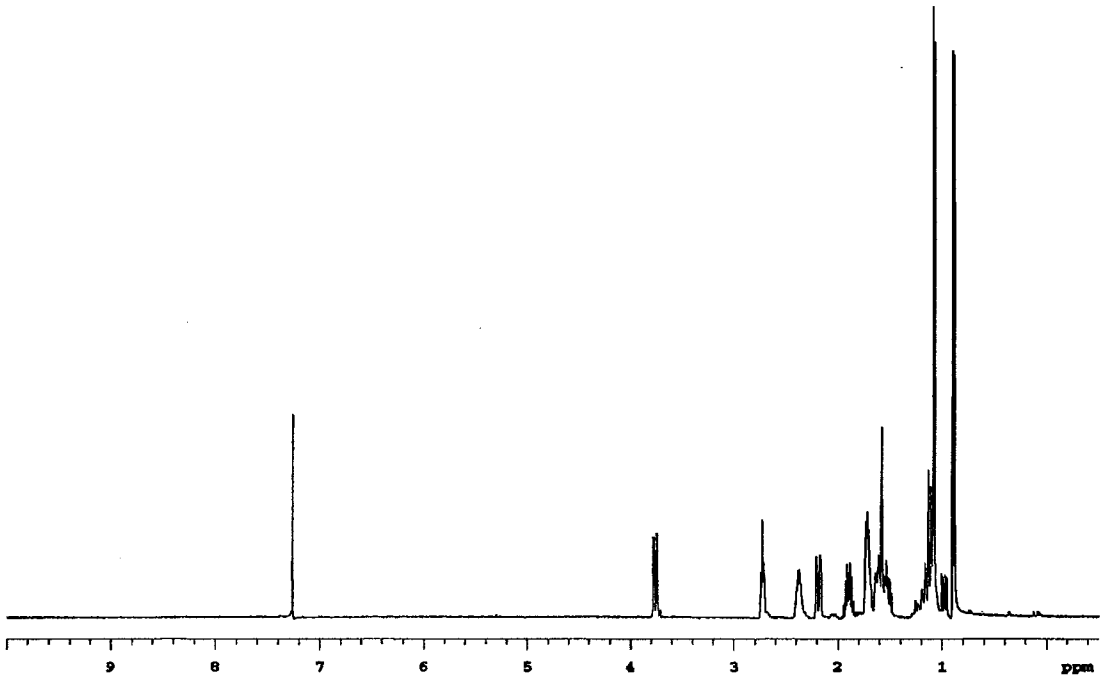


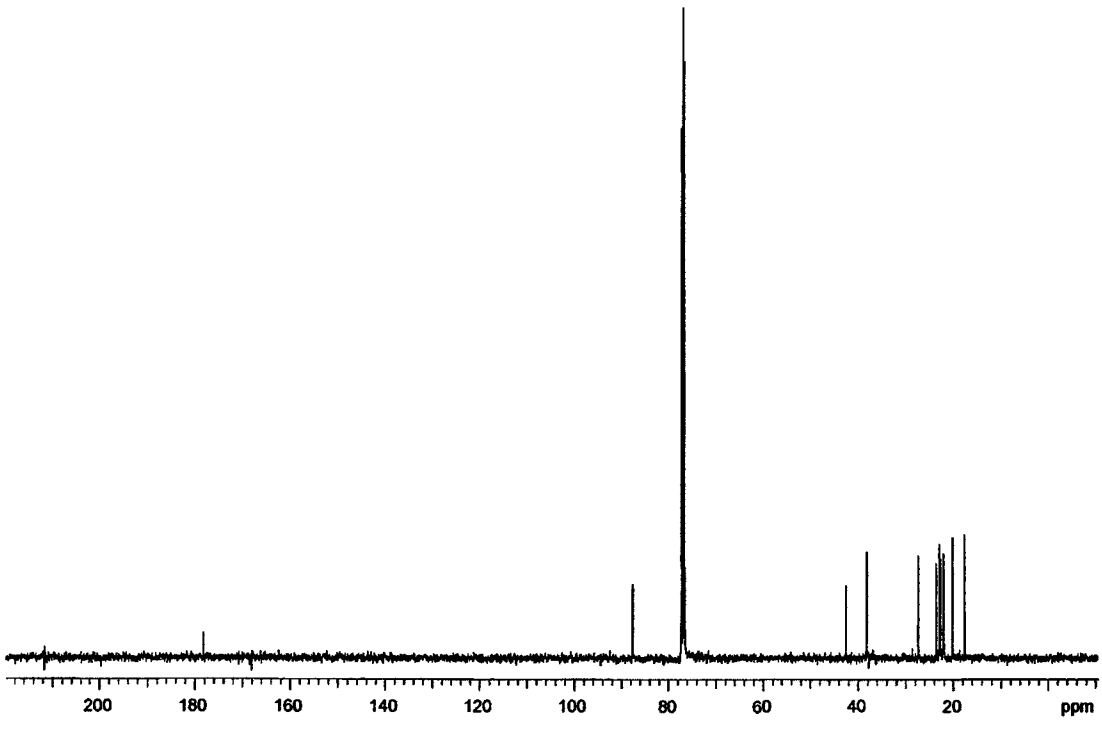
^{1}H and ^{13}C NMR spectra for **39**:





^{1}H and ^{13}C NMR spectra for **40**:



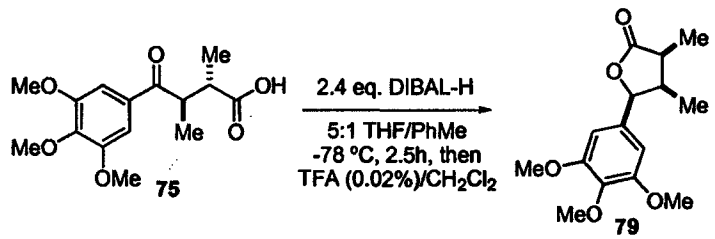


The Eupomatilones

General Methods. All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Tetrahydrofuran, diethylether, and dichloromethane were degassed with argon and passed through two columns of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light, $KMnO_4$, aqueous ceric ammonium molybdate, anisaldehyde, or bromocresol green dips followed by heating.

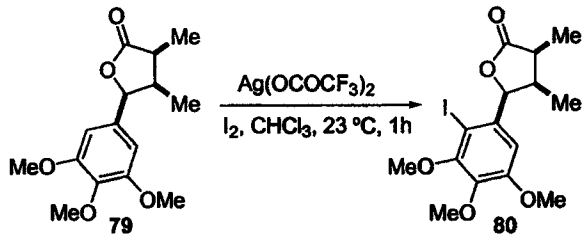
Melting points were measured with a MelTemp II melting point apparatus outfitted with a Fluke 51 thermocouple and are uncorrected. Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^1H NMR and spectra were recorded on a Varian 300, 400, or 500 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ, ppm) from an internal standard [tetramethylsilane (TMS; taken as 0.00 ppm) or deuterated chloroform ($CDCl_3$; taken as 7.26 ppm)], multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR were recorded on a Varian 75, 100, or 125 MHz spectrometer at ambient temperature. Chemical shifts are reported in ppm from ($CDCl_3$) taken as 77.0 ppm. Mass spectra were obtained on Fisons VG Autospec. Analytical high performance liquid chromatography (HPLC) was performed on a Dynamax model SD-200 HPLC equipped with a Dynamax model UV-1 variable wavelength UV detector using Chiracel chiral columns as indicated. Gas

chromatography was performed on a Varian Cp 3800 gas chromatograph equipped with a flame ionization detector using a Chrompack CP-Sil8CB (15 M X 0.25 mm) capillary column.

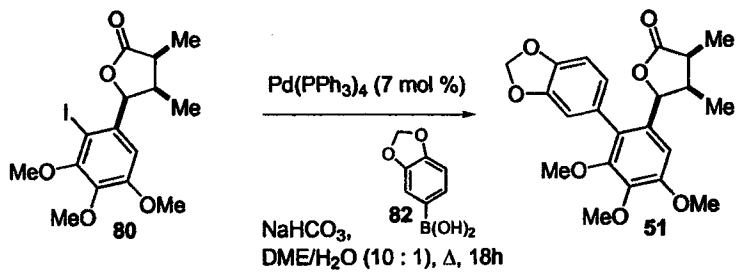


(3*S, 4*R**, 5*S**)-3,4-dimethyl-5-(trimethoxy-phenyl)-dihydro-furan-2-one (79).** A round bottom flask charged with 101 mg (0.341 mmol) of keto-acid **75** in 6 mL of THF/PhMe (5:1) was cooled to -78 °C and 0.15 mL of DIBAL (neat, 0.84 mmol) was added dropwise via syringe. The reaction was stirred for 2.5 h at -78 °C before the addition of 1 mL of 1 M aq. HCl and warming to room temperature. The reaction mixture was partitioned between EtOAc and 1 M aq. HCl (10 ml each) and transferred to a sepratory funnel where the layers were separated. The aqueous layer was extracted with EtOAc (2 X 10 mL), the organic were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide crude hydroxy acid. The crude hydroxy acid was then taken up in 5 mL of 0.02 % CH_2Cl_2/TFA (v/v) and stirred at room temperature for 3 h. The reaction was concentrated and purified by column chromatography (3:1 Hex/EtOAc) to provide 90 mg (0.32 mmol, 94%) of the desired *syn*-lactone **79** as a colorless oil that solidified on standing. dr = > 98:2. mp ($CHCl_3/Et_2O$) = 87-89 °C. Rf = 0.19 (1:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (s, 2H), 5.44 (d, 1H, J = 4.7 Hz), 3.84 (s, 6H), 3.82 (s, 3H), 2.98 (dq, 1H, J = 14.2, 7.1, 7.1 Hz), 2.81-2.73 (m, 1H), 1.21 (d, 3H, J = 7.2 Hz), 0.57 (d, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 153.3, 137.1, 131.7, 102.0, 82.1, 60.8, 56.2, 41.1, 40.1,

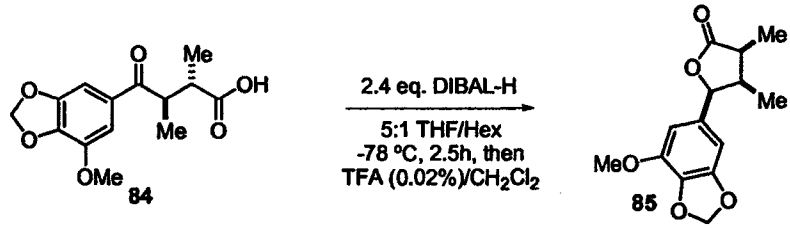
10.1, 9.5; IR (NaCl, dep from $CHCl_3$), 2974, 2941, 2841, 1778, 1593, 1338, 1172 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{20}O_5$, 280.1311. Found 280.1303.



(3*S, 4*R**, 5*S**)-5-(2-iodo-3,4,5-trimethoxy-phenyl)-3,4-dimethyl-dihydro-furan-2-one (80).** A round bottom flask under argon was charged with 133 mg (0.474 mmol) of lactone **79** in 3 mL of $CHCl_3$ and 111 mg (0.503 mmol) of $Ag(OCOCF_3)_2$ were added in one portion. 141 mg (0.555 mmol) of I_2 in 3 mL of $CHCl_3$ was added dropwise via syringe over 0.5 h. The reaction was stirred an additional 10 min. before being filtered through a pad of celite that was washed thoroughly with $CHCl_3$ (20 mL). The filtrate was washed with sat. aq. $NaHSO_3$, dried over $MgSO_4$, filtered, and concentrated to yield a crude oil that was purified by flash column chromatography (9:1 Hex/EtOAc) to provide 172 mg (89 %) of the 80 as a colorless oil that solidified upon standing. mp (Hex/EtOAc) = 91-93 °C. Rf = 0.52 (1:1 Hex/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 6.79 (s, 1H), 5.55 (d, 1H, J = 4.6 Hz), 3.88 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.30 (ddq, 1H, J = 14.6, 7.3, 7.3, 5.0 Hz), 3.04 (dq, 1H, J = 14.4, 7.2, 7.2 Hz), 1.21 (d, 3H, J = 7.3 Hz), 0.50 (d, 3H, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 153.8, 152.8, 141.5, 133.8, 107.0, 85.5, 61.0, 60.9, 56.3, 40.6, 37.2, 10.1, 9.8; IR (NaCl, CCl_4), 2974, 2939, 1786, 1566, 1481, 1389, 1169, 1107 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{19}O_5I$, 406.0277. Found 406.0284.



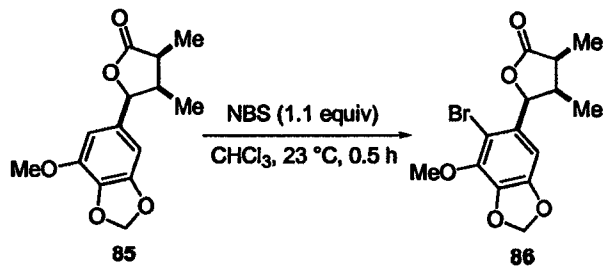
3-*epi*-eupomatilone-6 (51). A round bottom flask equipped with a reflux condenser was charged with 21 mg (0.052 mmol) of **80**, 13 mg (0.079 mmol) of **82**, and 16 mg (0.19 mmol) of $NaHCO_3$ in 1 mL of DME and 0.2 mL of H_2O. 4 mg (0.003 mmol) of $Pd(PPh_3)_4$ in 1 mL of DME was added and argon was passed through the solution for 10 min. before bring the reaction to reflux for 18 h. The reaction was quenched with 1M aq. HCl (10 mL) and the resulting aqueous layer was extracted with EtOAc (3 X 10 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated to provide a crude yellow oil that was purified by flash column chromatography (4:1 Hex/EtOAc) giving 18 mg (87 %) of 3-*epi*-eupomatilone-6 **(51)**[4] as yellow/brown foam.



(3*S, 4*R**, 5*S**)-5-(7-Methoxy-benzo[1,3]dioxol-5-yl)-3,4-dimethyl-dihydro-furan-2-one (85).** A round bottom flask charged with 140 mg (0.50 mmol) of keto-acid **84** in 5 mL of THF was cooled to -78 °C and 1.2 mL of DIBAL (1.0 M in hexanes, 1.2 mmol) was added dropwise via syringe. The reaction was stirred for 3 h at -78 °C before the

[4] Gurjar, M. K.; Cherian, J.; Ramana, C. V. *Org. Lett.* **2004**, *6*, 317-319.

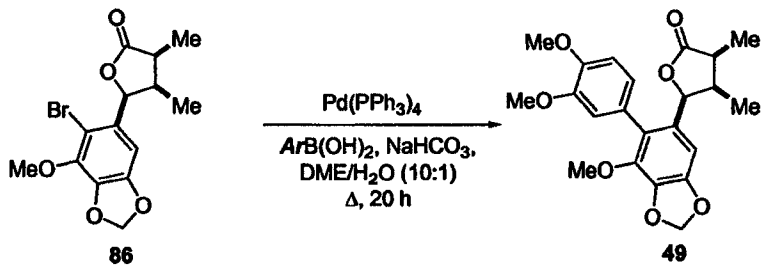
addition of 1 mL of 1 M aq. HCl and warming to room temperature. The reaction mixture was partitioned between EtOAc and 1 M aq. HCl (10 ml each) and transferred to a sepratory funnel where the layers were separated. The aqueous layer was extracted with EtOAc (2 X 10 mL), the organic were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide crude hydroxy acid. The crude hydroxy acid was then taken up in 5 mL of 0.02 % CH_2Cl_2/TFA (v/v) and stirred at room temperature for 3 h. The reaction was concentrated and purified by column chromatography (3:1 Hex/EtOAc) to provide 108 mg (0.41 mmol, 82%) of the desired *syn*-lactone **85** as a colorless oil. dr = 97:3. Rf = 0.12 (4:1 Hex/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 (s, 1H); 6.41 (s, 1H); 5.95 (s, 2H); 5.40 (d, 1H, J = 5.1 Hz); 3.87 (s, 3H); 2.96 (dq, 1H, J = 14.3, 7.0, 7.0 Hz); 2.72 (ddq, 1H, J = 14.3, 7.0, 7.0, 5.1 Hz); 1.19 (d, 3H, J = 7.3 Hz); 0.55 (d, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.5, 148.9; 143.5; 134.5; 130.6; 104.5; 101.5; 99.4; 82.0; 56.6; 41.0; 40.1; 10.1; 9.4; IR (NaCl, neat), 2976, 2941, 2881, 1774, 1635, 1514, 1452, 1433, 1173, 1095, 1051 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{16}O_5$, 264.0998. Found 264.0995.



85 86

(3*R, 4*S**, 5*R**)-5-(6-bromo-7-methoxy-benzo[1,3]dioxol-5-yl)-3,4-dimethyl-dihydro-furan-2-one (86).** A dry round bottom flask was charged with 174 mg (0.658

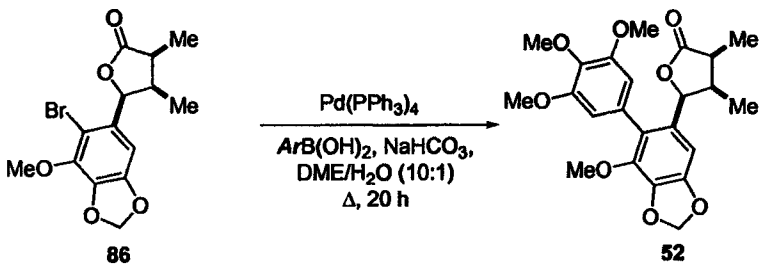
mmol) of **85** in 5 mL of $CHCl_3$. 128 mg (0.719 mmol) of NBS was added in one portion and the reaction stirred for 0.5 h at ambient temperature. Upon completion, 2 g of SiO_2 was added and the reaction concentrated. Column chromatography (9:1 Hex/EtOAc) yielded 184 mg (81 %) of the desired product as a colorless oil that solidified on standing. Rf = 0.25 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (s, 1H), 5.99 (s, 2H), 5.62 (d, 1H, J = 5.1 Hz), 4.05 (s, 3H), 3.22-3.13 (m, 1H), 3.00 (dq, 1H, J = 7.3, 7.3 Hz), 1.20 (d, 3H, J = 7.3 Hz), 0.52 (d, 3H, J = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 148.9, 140.2, 136.7, 130.0, 105.1, 102.2, 101.1, 82.0, 60.1, 40.5, 37.3, 10.0, 9.7; IR (NaCl, neat), 2956, 2945, 1770, 1606, 1479, 1408, 1282, 1171, 1059, 1012, 980 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{15}O_5Br$, 344.0082. Found 344.0080.



86 49

eupomatilone-4 (49). A round bottom flask equipped with a reflux condenser was charged with 20 mg (0.058 mmol) of **86**, 25 mg (0.12 mmol) of 3,4,5-trimethoxyphenylboronic acid, and 25 mg (0.30 mmol) of $NaHCO_3$ in 1 mL of DME and 0.2 mL of H_2O. 3.8 mg (0.0032 mmol) of $Pd(PPh_3)_4$ in 1 mL of DME was added and argon was passed through the solution for 10 min. before bring the reaction to reflux for 18 h. The reaction was quenched with 1M aq. HCl (10 mL) and the resulting aqueous layer was extracted with EtOAc (3 X 10 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated to provide a crude

yellow oil that was purified by flash column chromatography (9:1 Hex/EtOAc) giving 24 mg (96 %) of eupomatilone-4 (**49**)[5] as a colorless oil.

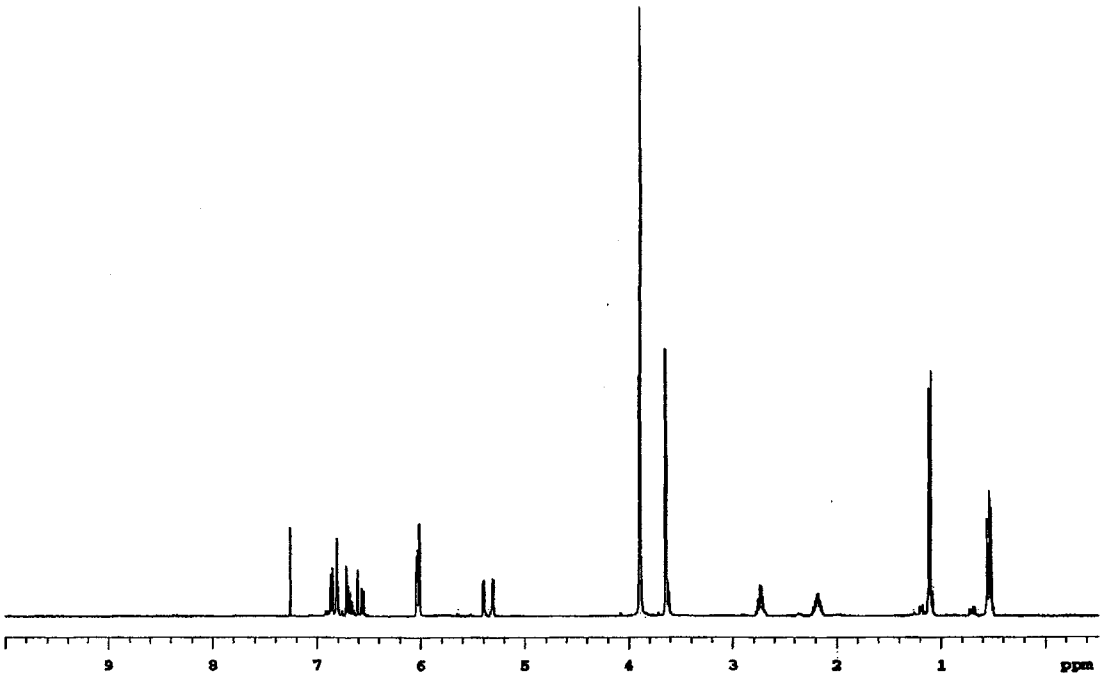


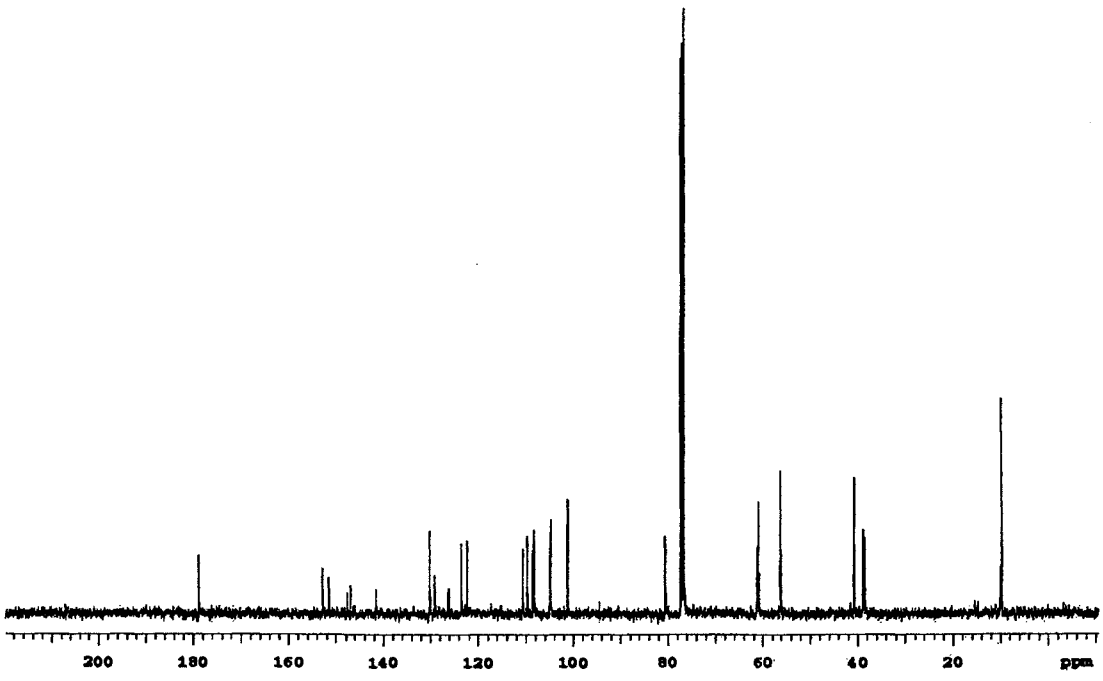
eupomatilone-7 (52). A round bottom flask equipped with a reflux condenser was charged with 26 mg (0.076 mmol) of **86**, 29 mg (0.16 mmol) of 3,4-dimethoxyphenylboronic acid, and 32 mg (0.38 mmol) of $NaHCO_3$ in 1 mL of DME and 0.2 mL of H_2O. 5 mg (0.004 mmol) of $Pd(PPh_3)_4$ in 1 mL of DME was added and argon was passed through the solution for 10 min. before bring the reaction to reflux for 18 h. The reaction was quenched with 1M aq. HCl (10 mL) and the resulting aqueous layer was extracted with EtOAc (3 X 10 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated to provide a crude yellow oil that was purified by flash column chromatography (9:1 Hex/EtOAc) giving 27 mg (90 %) of eupomatilone-7 (**52**)[6] as a colorless oil.

[5] (a) Carroll, A. R.; Taylor, W. C. *Aust. J. Chem.* **1991**, *44*, 1705-1714. (b) Coleman, R. S.; Gurrala, S. R. *Org. Lett.* **2004**, *6*, 4025-4028.
[6] See reference 5a.

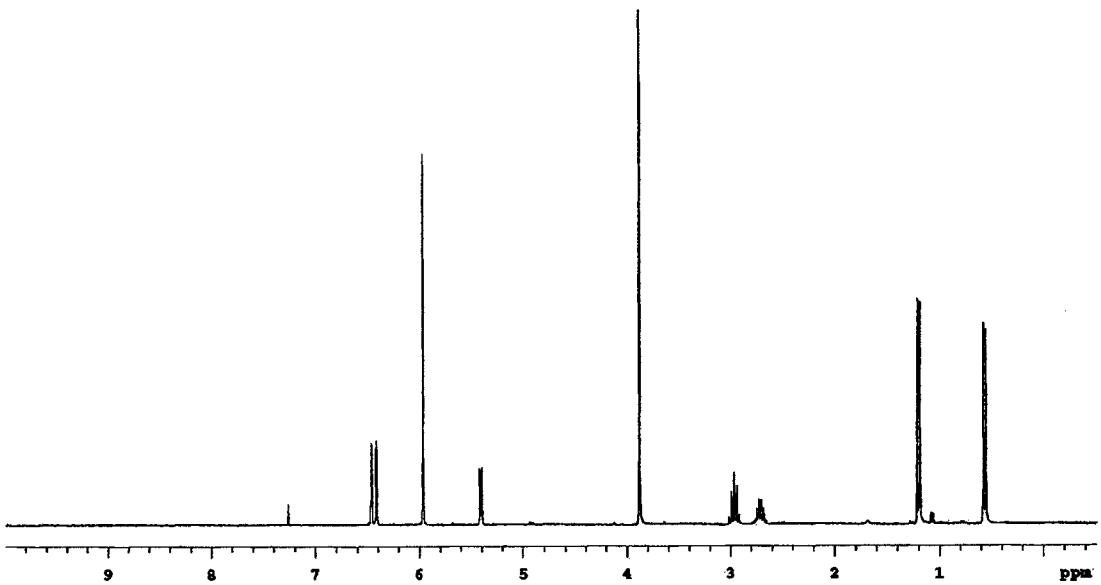
NMR spectra for selected compounds

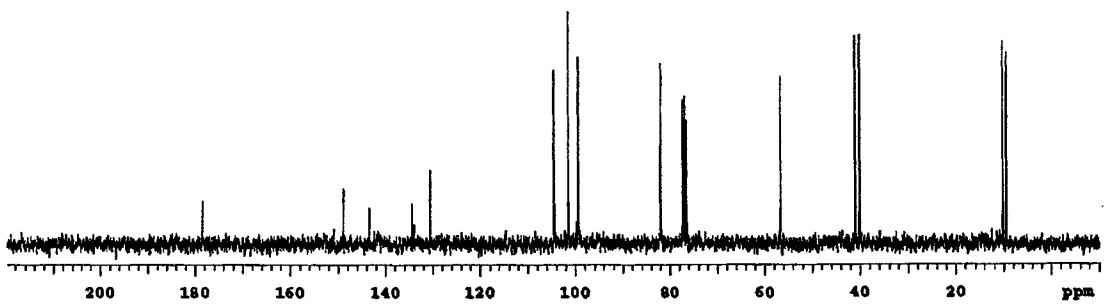
^{1}H and ^{13}C for **51**:



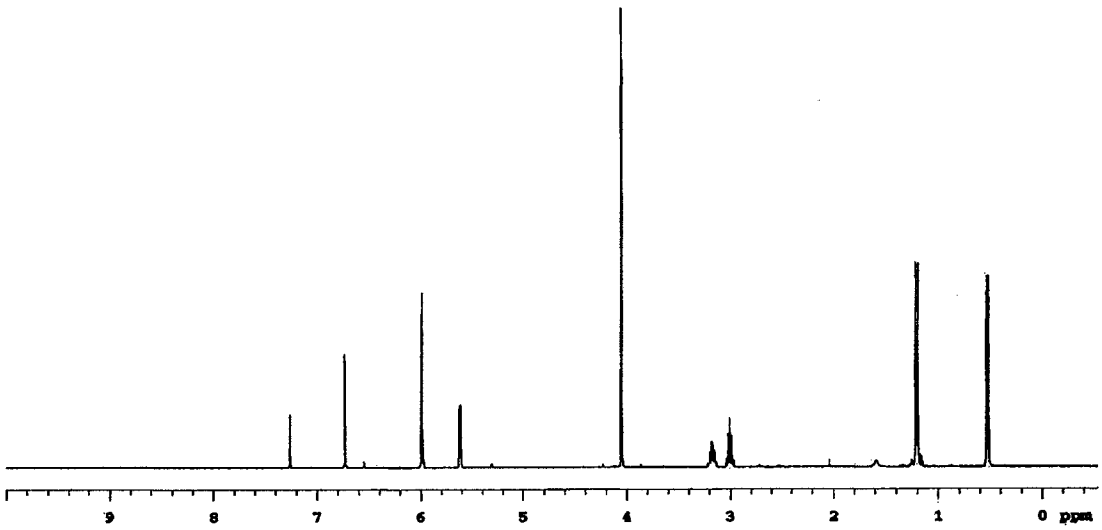


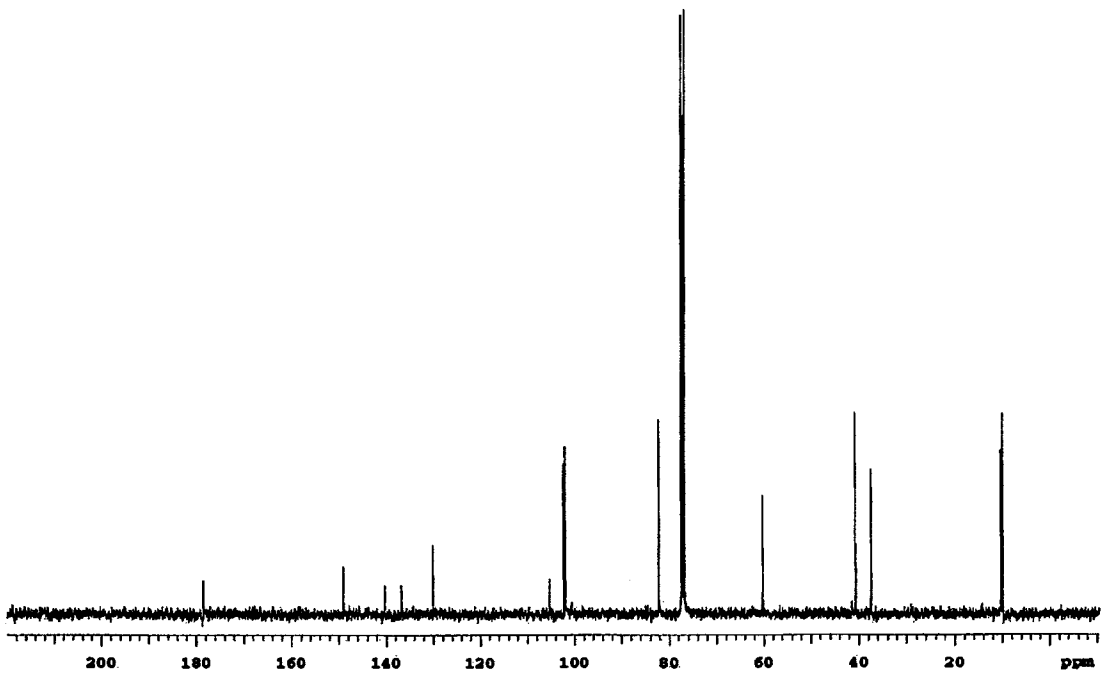
^{1}H and ^{13}C for **85**:



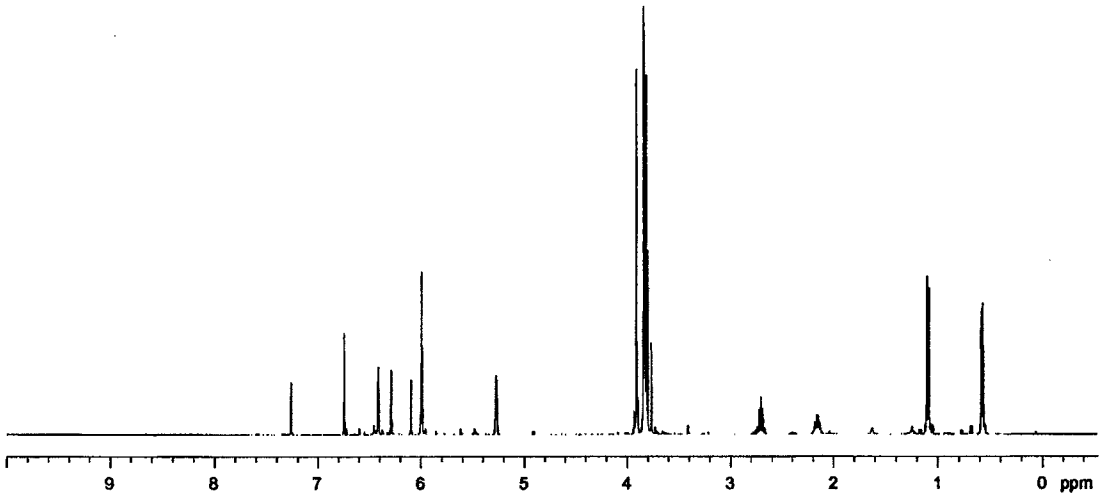


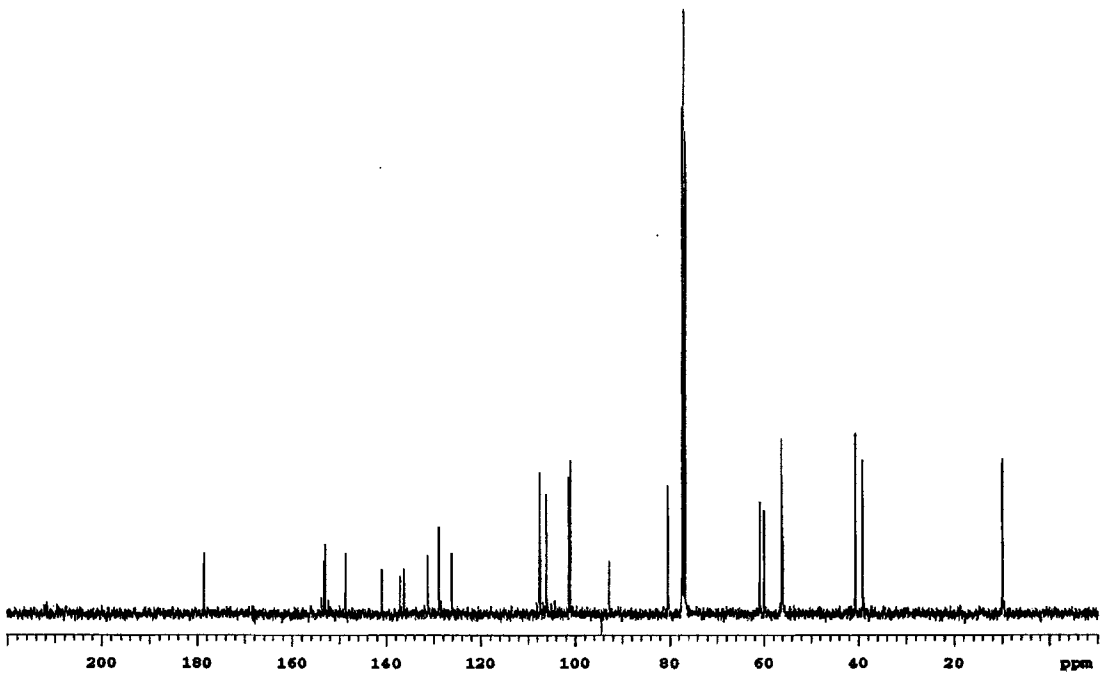
^{1}H and ^{13}C for **86**:



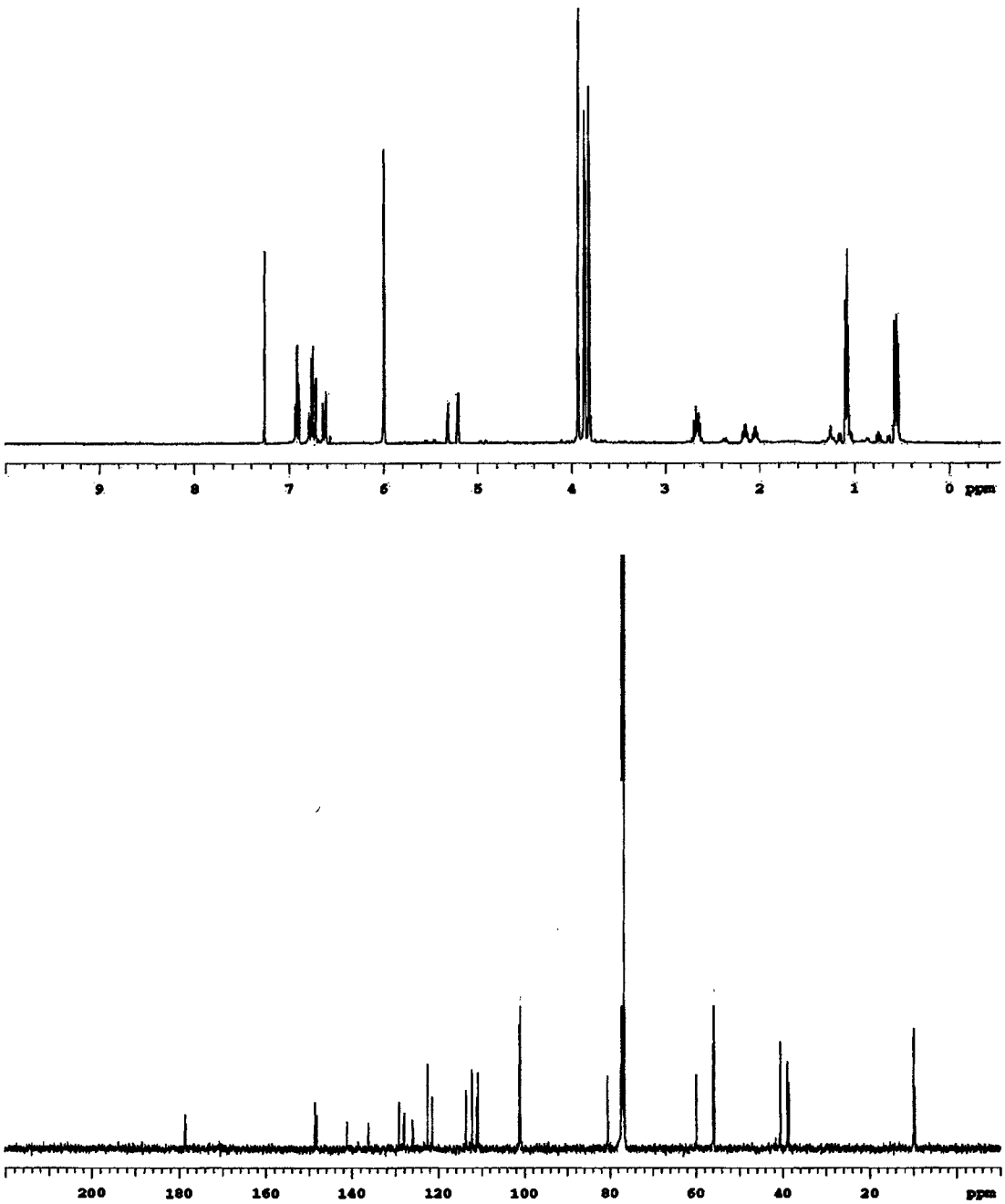


^{1}H and ^{13}C for **49**:

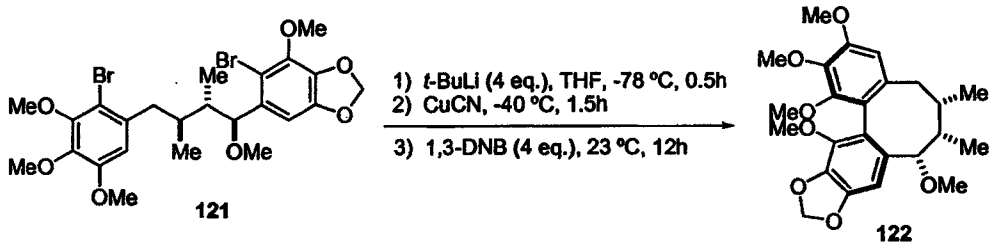




^{1}H and ^{13}C for **52**:

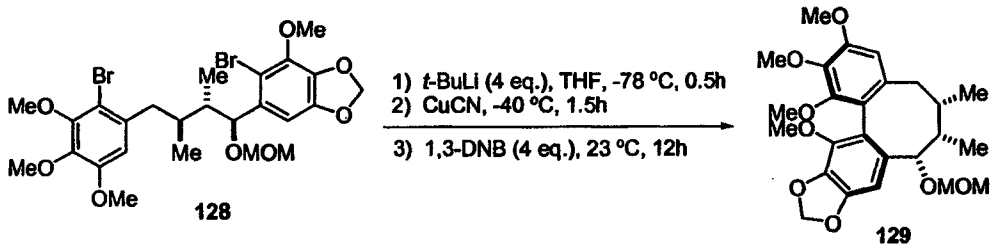


Gomisin G



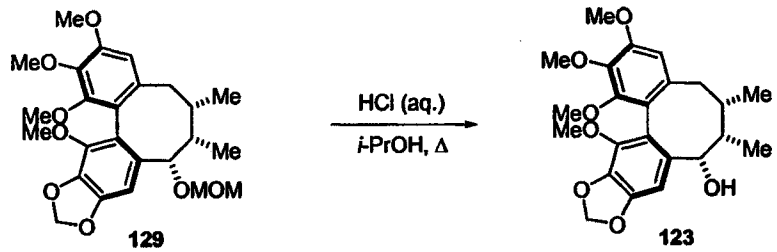
methoxybiaryl 122. A round bottom flask under argon was charged with 31 mg (0.053 mmol) of **121** in 2 mL of THF. The reaction was cooled to -78 °C and 145 μL (1.5 M in pentane, 0.218 mmol) of *t*-BuLi were added via syringe. The resulting yellow reaction mixture was stirred at -78 °C for 0.5 h before the addition of 9 mg (0.1 mmol) of CuCN suspended in THF. The reaction was warmed to -40 °C and stirred 1.5 h before the addition of 0.22 mL (1 M in THF, 0.22 mmol) of 1,3-dinitrobenzene via syringe. The resulting dark red/brown solution was allowed to warm to ambient temperature over 14 h. The reaction was quenched with 4 mL of 1 M HCl in MeOH and stirred 0.5 h before the addition of 10 mL of 3:1 (v/v) sat aq. NH_4Cl and conc. aq. NH_4OH. After 0.5 h, the resulting aqueous layer was extracted with Et_2O (3 X 15 mL), the organic layers were combined, washed with brine, dried over anhydrous K_2CO_3, filtered, and concentrated to provide a crude solid. The crude was first purified by flash column chromatography (CH_2Cl_2 followed by EtOAc strip) to remove excess 1,3-dinitrobenzene. The resulting crude biaryl was further purified by preparatory thin layer chromatography (4 X 17:3 Hex/EtOAc) providing 9 mg (40 %) of **122** as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$) δ 6.75 (s, 1H), 6.53 (s, 1H), 6.00 (d, 2H, $J = 2.6$ Hz), 3.96 (s, 1H), 3.90 (s, 6H),

3.85 (s, 3H), 3.54 (s, 3H), 3.07 (s, 3H), 2.20 (dd, 1H, J = 13.2, 9.5 Hz), 2.09-1.89 (m, 3H), 1.59 (s, 1H), 1.01 (d, 3H, J = 7.0 Hz), 0.67 (d, 3H, J = 7.0 Hz).



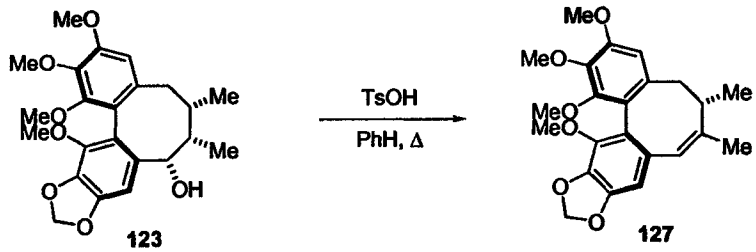
MOMbiaryl 129. A round bottom flask under argon was charged with 107 mg (0.173 mmol) of **128** in 3 mL of THF. The reaction was cooled to -78 °C and 0.43 mL (1.5 M in pentane, 0.73 mmol) of *t*-BuLi were added via syringe. The resulting yellow reaction mixture was stirred at -78 °C for 0.5 h before the addition of 0.42 mL (0.5 M in THF, 0.21 mmol) of 2LiBr·CuCN via syringe. The reaction was warmed to -40 °C and stirred 1.5 h before the addition of 112 mg (0.666 mmol) of 1,3-dinitrobenzene in 1 mL of THF via syringe. The resulting dark red/brown solution was allowed to warm to ambient temperature over 14 h. The reaction was quenched with 4 mL of 1 M HCl in MeOH and stirred 0.5 h before the addition of 10 mL of 3:1 (v/v) sat aq. NH_4Cl and conc. aq. NH_4OH. After 0.5 h, the resulting aqueous layer was extracted with Et_2O (3 X 15 mL), the organic layers were combined, washed with brine, dried over anhydrous K_2CO_3, filtered, and concentrated to provide a crude solid. The crude was first purified by flash column chromatography (CH_2Cl_2 followed by EtOAc strip) to remove excess 1,3-dinitrobenzene. The resulting crude biaryl was further purified by flash column chromatography (19:1 Hex/EtOAc) providing 48 mg (60 %) of **129** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 6.79 (s, 1H), 6.52 (s, 1H), 5.99 (d, 2H, J = 1.8 Hz), 4.45 (d,

1H, J = 6.6 Hz), 4.40 (d, 1H, J = 6.6 Hz), 4.39 (d, 1H, J = 1.1 Hz), 3.90 (s, 6H), 3.84 (s, 3H), 3.51 (s, 3H), 3.19 (s, 3H), 2.19 (dd, 1H, J = 13.2, 9.5 Hz), 2.07-1.89 (m, 3H), 1.02 (d, 3H, J = 7.0 Hz), 0.72 (d, 3H, J = 7.0 Hz).

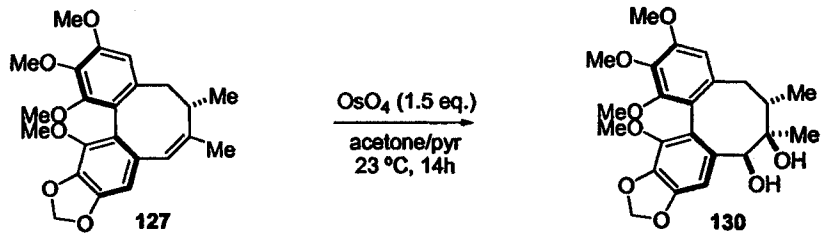


129 123

alcohol 123. A round bottom flask equipped with a reflux condenser was charged with 38 mg (0.083 mmol) of **129** in 4 mL of *i*-PrOH and 4 drops of conc. of HCl. The reaction was brought to reflux for 1 h. The reaction was cooled to ambient temperature and diluted with Et_2O (20 mL). The organic layer was washed with sat. aq. $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated to yield crude alcohol that was purified by flash column chromatography (3:1 Hex/EtOAc) to provide 32 mg (93 %) of **123** as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.51 (s, 1H), 5.99 (d, 1H, *J* = 1.5 Hz), 5.98 (d, 1H, *J* = 1.5 Hz), 4.52 (d, 1H, *J* = 1.1 Hz), 3.89 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H), 3.61 (s, 3H), 2.18 (dd, 1H, *J* = 13.6, 9.5 Hz), 2.04-1.90 (m, 3H), 1.02 (d, 3H, *J* = 7.0 Hz), 0.70 (d, 3H, *J* = 7.0 Hz).



olefin 127. A round bottom flask equipped with a reflux condenser was charged with 23 mg (0.055 mmol) of **123** in 3 mL of PhH and 13 mg (0.068 mmol) of TsOH. The reaction was brought to reflux for 1 h. The reaction was cooled to ambient temperature and diluted with Et_2O (20 mL). The organic layer was washed with sat. aq. $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated to yield crude alcohol that was purified by flash column chromatography (9:1 Hex/EtOAc) to provide 18 mg (82 %) of **127** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 6.50 (s, 1H), 6.40 (s, 1H), 5.97-5.95 (m, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.83 (s, 3H), 3.59 (s, 3H), 2.50-2.44 (m, 2H), 2.28-2.20 (m, 1H), 1.65 (d, 3H, J = 1.1 Hz), 1.08 (d, 3H, J = 6.6 Hz).

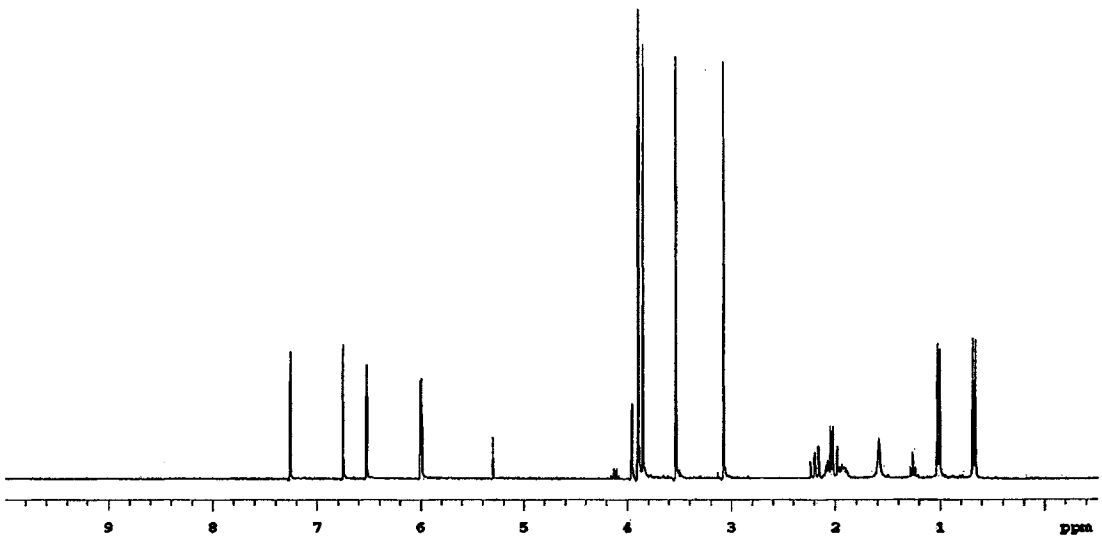


diol 130. A round bottom flask was charged with 9.0 mg (0.023 mmol) of **127** in 1 mL of 3:1 pyridine/acetone and 0.18 mL (4% wt. in H2O, 0.028 mmol) of OsO_4 were added via syringe and the reaction stirred at ambient temperature for 8 h. The reaction was quenched with 5 mL of sat. aq. $NaHSO_3$ and vigorously stirred overnight. The resulting aqueous layer was extracted with EtOAc (3 X 5 mL), organics were combined, washed

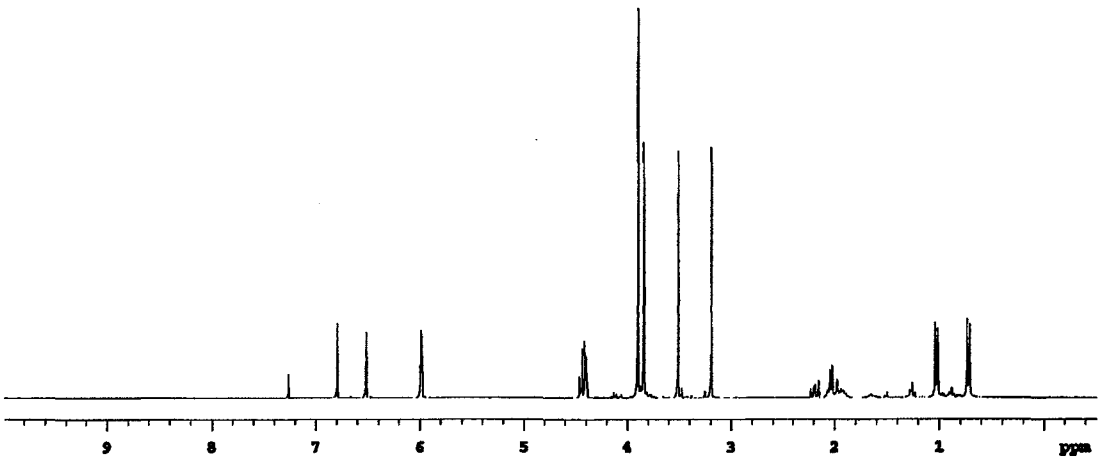
with brine, dried over Na_2SO_4, decanted, and concentrated to yield a crude oil that was purified by flash column chromatography (4:1 Hex/EtOAc) providing 8 mg of **130** as a colorless oil. dr = >95 : 5. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57 (s, 1H), 6.50 (s, 1H), 6.00 (s, 2H), 4.52 (br s, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.67 (s, 3H), 2.27-2.18 (m, 2H), 1.84-1.77 (m, 2H), 1.17 (d, 3H, J = 7.0 Hz), 1.00 (s, 3H).

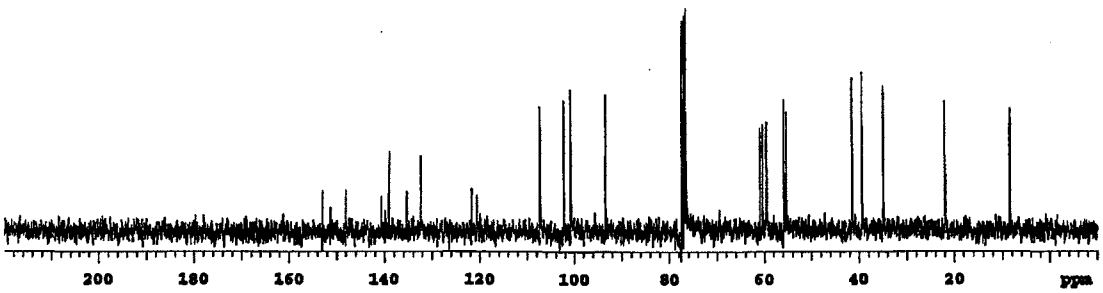
NMR spectra for selected compounds

^{1}H for 122:

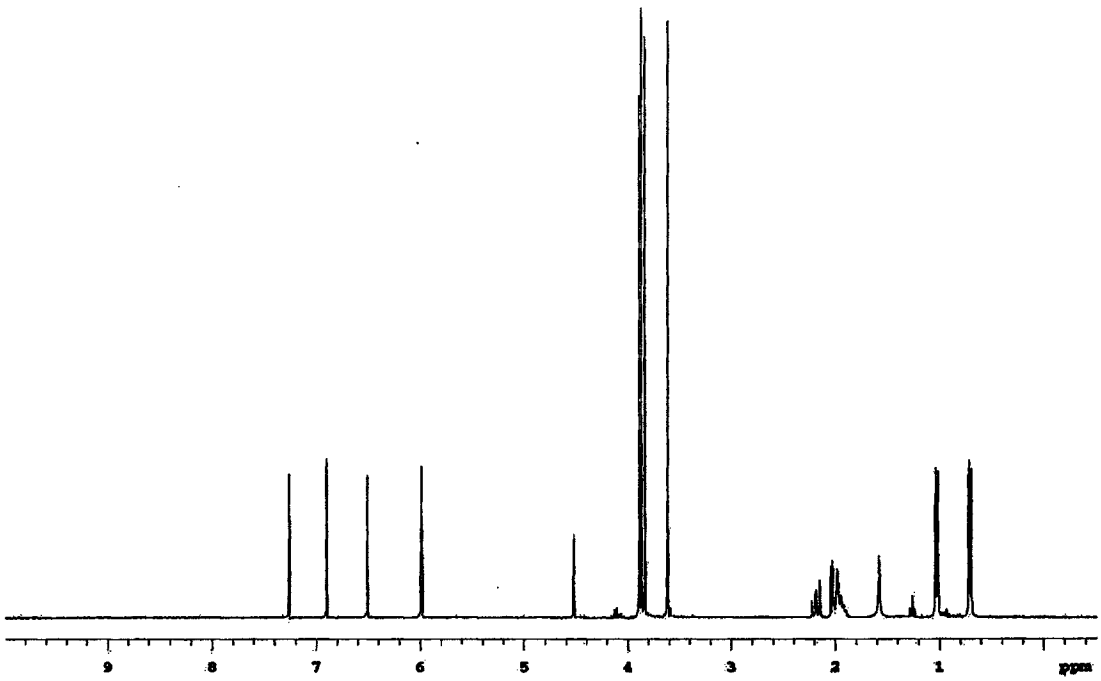


^{1}H and ^{13}C for **129**:

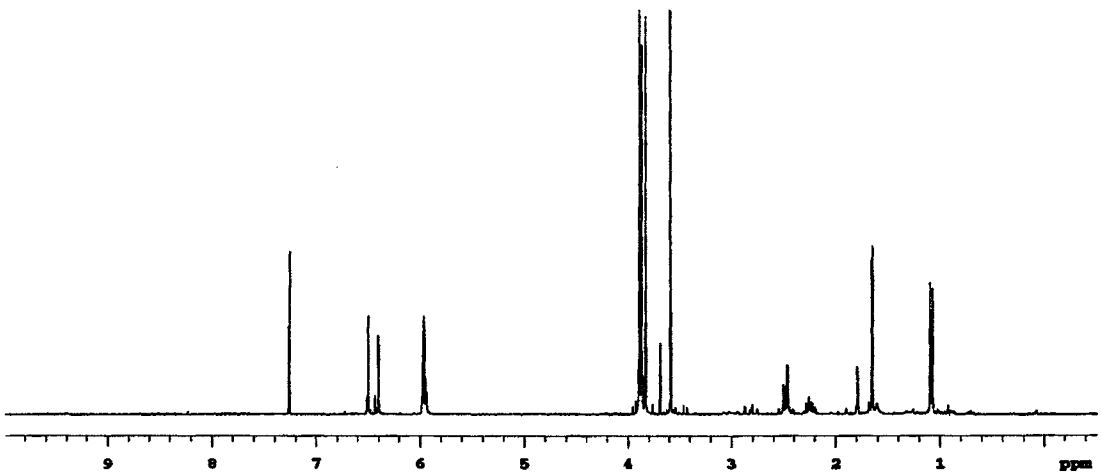




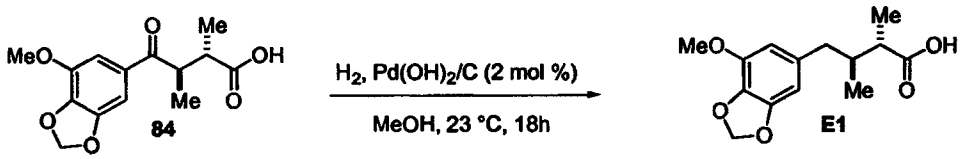
^{1}H for **123**:



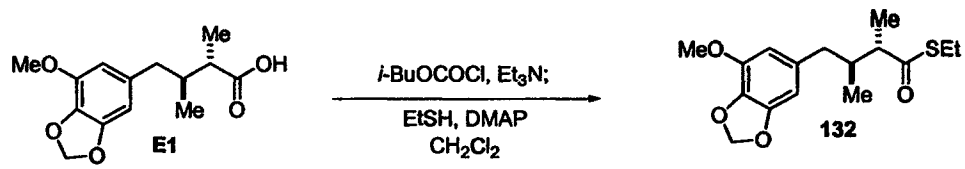
^{1}H for **127**:



Gomisin O and Epigomisin O



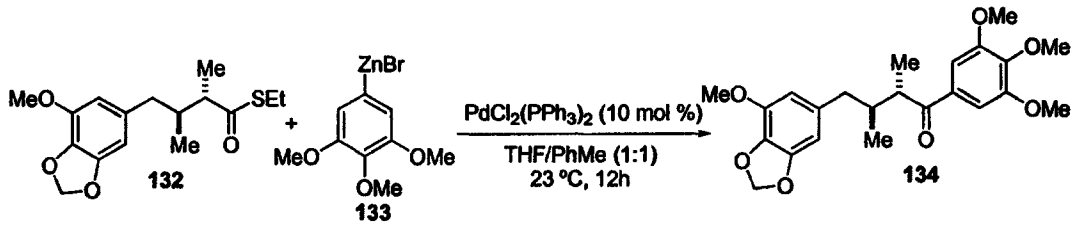
(2*S, 3*R**)-4-(7-methoxy-benzo[1,3]dioxol-5-yl)-2,3-dimethyl-butyric acid (E1).** A round bottom flask was charged with 303 mg (1.08 mmol) of **84** and 51 mg (0.036 mmol) $Pd(OH)_2$ (20 % wt. on carbon, 50 % wt. H_20) in 10 mL of MeOH. Argon was passed through the solution for 5 min. before placing the reaction under an atmosphere of H_2 and stirred at ambient temperature for 18 h. The reaction mixture was filtered through a celite pad and concentrated to provide 280 mg (97 %) of **E1** as a colorless oil. Rf = 0.25 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (s, 1H), 6.34, (s, 1H), 5.93 (s, 2H), 3.89 (s, 3H), 2.76 (dd, 1H, J = 13.4, 5.5 Hz), 2.49 (dq, 1H, J = 12.4, 7.0 Hz), 2.28 (dd, 1H, J = 13.4, 9.2 Hz), 2.07-1.97 (m, 1H), 1.19 (d, 3H, J = 7.0 Hz), 0.91 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.9, 148.7, 143.3, 135.2, 133.4, 108.3, 103.2, 101.2, 56.5, 43.5, 40.1, 38.4, 16.6, 13.9; IR (NaCl, neat), 3099, 2968, 2939, 1703, 1639, 1510, 1452, 1431, 1196, 1134, 1092, 1045 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{18}O_5$, 266.1154. Found 266.1160.



(2*S, 3*R**)-4-(7-methoxy-benzo[1,3]dioxol-5-yl)-2,3-dimethyl-thiobutyric acid *S*-ethyl ester (132).** A dry round bottom flask was charged with 85 mg (0.320 mmol) of **E1** in 4 mL of CH_2Cl_2. Upon cooling to 0 °C, 0.22 mL (1.6 mmol) of Et_3N was added via syringe followed by the dropwise addition of 45 μL (0.35 mmol) of *i*-BuOCOCl and the reaction was stirred for 0.5 h. 5 mg (0.04 mmol) of DMAP were added followed by the addition of 0.10 mL (1.4 mmol) of EtSH by syringe. After stirring the reaction at 0 °C for 4 h before the reaction was diluted with CH_2Cl_2 (20 mL) and the resulting organic layer was washed with 1M aq. HCl (10 mL), sat. aq. $NaHCO_3$ (10 mL), brine, dried over $MgSO_4$, filtered, and concentrated to yield crude **132**. The crude was purified by column chromatography (9:1 Hex/EtOAc) to provide 67 mg (67 %) of **132** as a colorless oil.

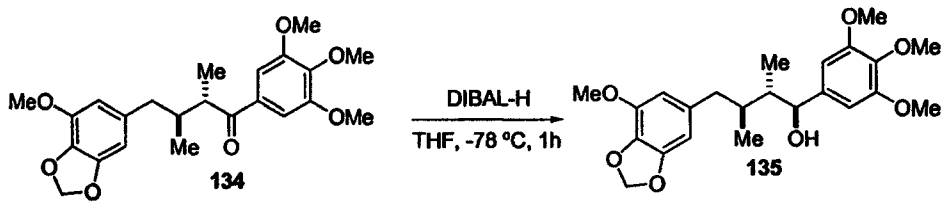
Alternative Procedure for 132. A dry round bottom flask was charged with 85 mg (0.320 mmol) of **E1** in 4 mL of CH_2Cl_2. Upon cooling to 0 °C, 0.10 mL (1.4 mmol) of EtSH were added via syringe followed by the addition of 5 mg (0.04 mmol) of DMAP. To the resulting solution, 55 uL (0.35 mmol) of DIC were added via syringe and the reaction was stirred for 6 h at 0 °C. The reaction was diluted with CH_2Cl_2 (20 mL) and the resulting organic layer was washed with 1M aq. HCl (10 mL), sat. aq. $NaHCO_3$ (10 mL), brine, dried over $MgSO_4$, filtered, and concentrated to yield crude **132**. The crude was purified by column chromatography (9:1 Hex/EtOAc) to provide 66 mg (67 %) of **132** as a colorless oil. Rf = 0.36 (4:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (s, 1H), 6.32 (s, 1H), 5.93 (s, 2H), 3.89 (s, 3H), 2.93-2.84 (m, 2H), 2.78 (dd, 1H, J = 13.2, 4.3 Hz), 2.58 (dq, 1H, J = 7.0, 7.0 Hz), 2.15 (dd, 1H, J = 13.2, 10.0 Hz), 2.09-2.00 (m,

1H), 1.26 (t, 3H, J = 7.5 Hz), 1.21 (d, 3H, J = 6.8 Hz), 0.86 (d, 3H, J = 6.6 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 148.7, 143.3, 135.2, 133.4, 108.3, 103.1, 101.2, 56.6, 53.2, 39.8, 38.8, 23.1, 16.9, 14.8, 14.5; IR (NaCl, neat), 2968, 2931, 1684, 1633, 1510, 1450, 1431, 1196, 1093, 1045 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{22}O_4S$, 310.1239. Found 310.1242.



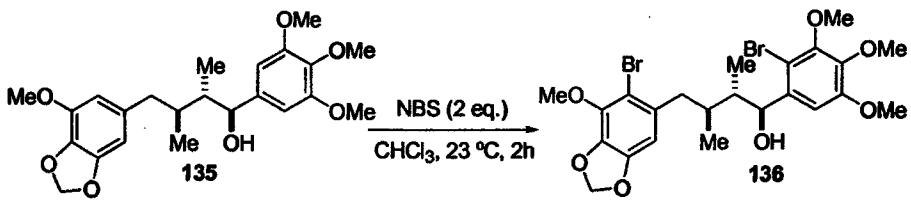
(2*S, 3*R**)-4-(7-methoxy-benzo[1,3]dioxol-5-yl)-2,3-dimethyl-1-(3,4,5-trimethoxy-phenyl)-butan-1-one (134).** A flame-dried round bottom flask charged with 295 mg (1.19 mmol) of 1-bromo-3,4,5-trimethoxybenzene in 3 mL of THF was cooled to -78 °C and 0.79 mL of *n*-BuLi (1.6 M in hexanes, 1.3 mmol) was added dropwise via syringe. The mixture was stirred for 0.5 h at -78 °C before the addition of 300 mg of $ZnBr_2$ (1.33 mmol) in 1 mL of THF via cannula. The reaction was warmed to room temperature and stirred and addition 0.5 h before use. A separate round bottom flask under argon was charged with 170 mg (0.548 mmol) of **132** and 30 mg (0.043 mmol) of $Pd(PPh_3)_2Cl_2$ in 4 mL of PhMe. The nucleophile solution was added via cannula and the resulting dark brown/black reaction mixture was stirred at ambient temperature for 16 h. The reaction was diluted with Et_2O (30 mL) and washed with 1M aq. HCl. The layers were separated and the aqueous layer was extracted with Et_2O (1 X 10 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated to yield a

crude oil that was purified by flash column chromatography (9 : 1 Hex/EtOAc) providing 207 mg (91 %) of the desired product as a yellow oil. Rf = 0.44 (1:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (s, 2H), 6.27 (s, 1H), 6.21 (s, 1H), 5.91 (s, 2H), 3.92 (s, 3H), 3.91 (s, 6H), 3.82 (s, 3H), 3.38 (dq, 1H, J = 6.6, 6.6 Hz), 2.78 (dd, 1H, J = 18.8, 9.6 Hz), 2.21-2.11 (m, 2H), 1.24 (d, 3H, J = 6.8 Hz), 0.89 (d, 3H, J = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.2, 153.1, 148.6, 143.3, 142.4, 135.9, 133.3, 132.5, 108.2, 105.7, 103.1, 101.2, 60.9, 56.5, 56.3, 44.9, 39.4, 38.2, 17.7, 14.2; IR (NaCl, neat), 2964, 2939, 1672, 1633, 1584, 1506, 1454, 1414, 1317, 1128 cm^{-1}; HRMS (FAB+) calcd for $C_{23}H_{29}O_7$, 417.1913. Found 417.1911.



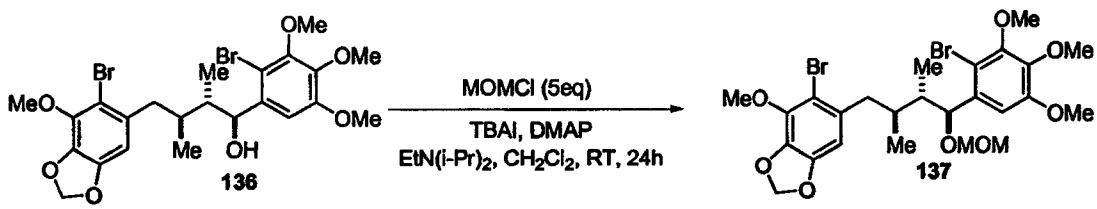
(1*S, 2*S**, 3*R**)-4-(7-methoxy-benzo[1,3]dioxol-5-yl)-2,3-dimethyl-1-(3,4,5-trimethoxy-phenyl)-butan-1-ol (135).** A flamed dried round bottom flask was charged with 200 mg (0.480 mmol) of **134** in 8 mL of THF. Upon cooling to -78 °C, 0.26 mL (1.5 mmol) of DIBAL-H were added dropwise via syringe. After 2 h at -78 °C before the reaction was quenched by the addition of 0.5 mL MeOH and allowed to warm to ambient temperature. The reaction was partitioned between Et_2O (20 mL) and sat. aq. Rochelle's salt (20 mL) and vigorously stirred for 1 h. The layers were separated and the aqueous layer was extracted with Et_2O (1 X 10 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated to yield a crude oil that was purified by flash column chromatography (4 : 1 Hex/EtOAc) supplying 163 mg (81 %) of

135 as a colorless oil. dr = > 95 : 5. Rf = 0.35 (1:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (s, 2H), 6.43 (s, 1H), 6.38 (s, 1H), 5.92 (s, 2H), 4.41 (d, 1H, J = 9.4 Hz), 3.89 (s, 3H), 3.86 (s, 6H), 3.84 (s, 3H), 2.86 (dd, 1H, J = 13.2, 3.8 Hz), 2.38-2.32 (m, 1H), 2.14 (dd, 1H, J = 13.0, 10.9 Hz), 1.89-1.80 (m, 2H), 0.89 (d, 3H, J = 6.8 Hz), 0.62 (d, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 148.6, 143.2, 140.3, 137.2, 136.8, 133.1, 108.2, 103.6, 103.1, 101.1, 77.4, 60.8, 56.5, 56.1, 44.9, 37.5, 35.1, 17.7, 11.4; IR (NaCl, neat), 3508, 2960, 2937, 1633, 1593, 1506, 1462, 1425, 1236, 1130 cm^{-1}; HRMS (FAB+) calcd for $C_{23}H_{30}O_7$, 418.1992. Found 418.1994.



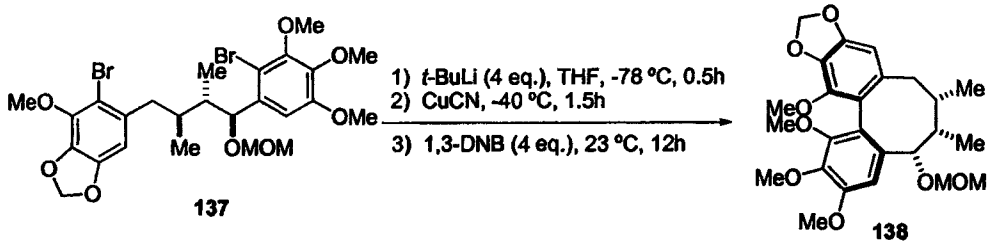
(1*S, 2*S**, 3*R**)-4-(6-bromo-7-methoxy-benzo[1,3]dioxol-5-yl)-1-(2-bromo-3,4,5-trimethoxy-phenyl)-2,3-dimethyl-butane-1-ol (136).** A round bottom flask was charged with 110 mg (0.263 mmol) of **135** in 5 mL of $CHCl_3$. In one portion, 50 mg (0.28 mmol) of NBS were added and the reaction stirred for 15 min. at ambient temperature. Another 50 mg (0.28 mmol) portion of NBS was added and the reaction stirred an additional 45 min. 800 mg of SiO_2 were added and the solvent removed *in vacuo*. Flash column chromatography (4:1 Hex/EtOAc) provided 130 mg of **136** as a colorless oil. Rf = 0.44 (1:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (s, 1H), 6.55 (s, 1H), 5.95 (s, 2H), 5.23 (d, 1H, J = 9.6 Hz), 4.03 (s, 3H), 3.89 (s, 9H), 3.08-3.03 (m, 1H), 2.49-2.42 (m, 2H), 1.90-1.85 (m, 1H), 0.95 (d, 3H, J = 6.4 Hz), 0.68 (d, 3H, J =

7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 150.1, 148.2, 142.2, 140.3, 139.0, 135.6, 135.2, 110.1, 109.2, 106.5, 105.6, 101.4, 74.5, 61.1, 61.0, 60.1, 56.1, 46.1, 38.0, 33.7, 17.6, 10.6; IR (NaCl, neat), 3508, 2964, 2937, 1477, 1396, 1105, 1051 cm^{-1}; HRMS (FAB+) calcd for $C_{23}H_{28}O_7Br_2$, 574.0202. Found 574.0190.



(2S*, 3R*, 4S*)-5-bromo-6-[4-(2-bromo-3,4,5-trimethoxy-phenyl)-4-methoxymethoxy-2,3-dimethyl-butyl]-4-methoxy-benzo[1,3]dioxole (137). A round bottom flask under argon was charged with 127 mg (0.220 mmol) of **136** in 4 mL of CH_2Cl_2. To the reaction mixture were added 0.25 mL (1.4 mmol) of $EtN(i\text{-}Pr)_2$, 8 mg (0.02 mmol) of TBAI, and 10 mg (0.082 mmol) of DMAP followed by the dropwise addition of 0.10 mL (1.3 mmol) of MOMCl via syringe. The reaction mixture was allowed to stir at ambient temperature for 14 h. Upon completion the reaction was diluted with CH_2Cl_2 (20 mL) and washed with 1M aq. HCl (2 X 15 mL), brine, dried over $MgSO_4$, filtered, and concentrated to yield a crude oil. Purification by flash column chromatography (9:1 Hex/EtOAc) supplied 120 mg (88 %) of **137** as a colorless oil. Rf = 0.50 (1:1 Hex/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 6.81 (s, 1H), 6.60 (s, 1H), 5.94 (s, 2H), 5.08 (d, 1H, J = 9.8 Hz), 4.53 (d, 1H, J = 6.4 Hz), 4.47 (d, 1H, J = 6.4 Hz), 4.03 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 3.36 (s, 3H), 2.97 (dd, 1H, J = 13.4, 4.3 Hz), 2.65 (dd, 1H, J = 13.4, 10.4 Hz), 2.39-2.36 (m, 1H), 1.98-1.89 (m, 1H), 0.92 (d, 3H, J = 7.0 Hz), 0.69 (d, 3H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 150.1, 148.2, 142.4,

140.2, 137.0, 135.6, 135.5, 109.6, 106.5, 105.1, 101.4, 95.6, 79.6, 61.1, 61.0, 60.0, 56.6, 56.2, 56.1, 44.9, 37.9, 34.6, 17.4, 11.2; IR (NaCl, neat), 2962, 2937, 1477, 1394, 1105, 1049, 1032 cm^{-1}; HRMS (FAB+) calcd for $C_{25}H_{32}O_8Br_2$, 618.0464. Found 618.0478.

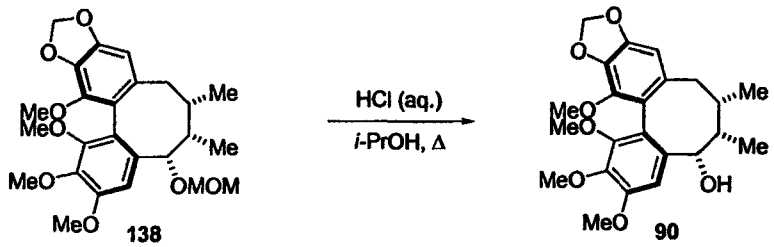


137 138

MOMbiaryl 138. A round bottom flask under argon was charged with 75 mg (0.12 mmol) of **137** in 3 mL of THF. The reaction was cooled to -78 °C and 0.30 mL (1.5 M in pentane, 0.51 mmol) of *t*-BuLi were added via syringe. The resulting yellow reaction mixture was stirred at -78 °C for 0.5 h before the addition of 0.30 mL (0.5 M in THF, 0.21 mmol) of 2LiBr·CuCN via syringe. The reaction was warmed to -40 °C and stirred 1.5 h before the addition of 0.49 mL (1M in THF, 0.49 mmol) of 1,3-dinitrobenzene via syringe. The resulting dark red/brown solution was allowed to warm to ambient temperature over 14 h. The reaction was quenched with 4 mL of 1 M HCl in MeOH and stirred 0.5 h before the addition of 10 mL of 3:1 (v/v) sat aq. NH_4Cl and conc. aq. NH_4OH. After 0.5 h, the resulting aqueous layer was extracted with Et_2O (3 X 15 mL), the organic layers were combined, washed with brine, dried over anhydrous K_2CO_3, filtered, and concentrated to provide a crude solid. The crude was first purified by flash column chromatography (CH_2Cl_2 followed by EtOAc strip) to remove excess 1,3-dinitrobenzene. The resulting crude biaryl was further purified by flash column chromatography (19:1 Hex/EtOAc) providing 32 mg (59 %) of **138** as a colorless oil. Rf

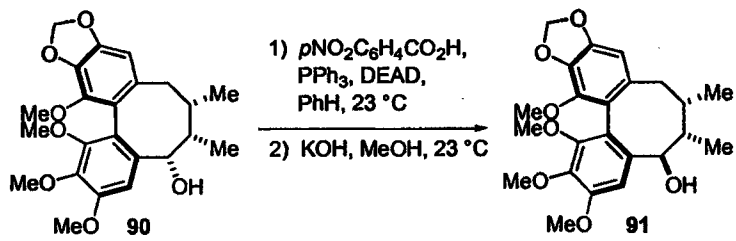
= 0.45 (1:1 Hex/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (s, 1H), 6.45 (s, 1H), 5.97 (s, 1H), 5.94 (s, 1H), 4.48 (d, 1H, J = 6.6 Hz), 4.43 (s, 1H), 4.42 (d, 1H, J = 6.6 Hz), 3.91 (s, 3H), 3.90 (s, 3H), 3.70 (s, 3H), 3.57 (s, 3H), 3.24 (s, 3H), 2.14-2.04 (m, 2H), 1.97-1.89 (m, 2H), 0.99 (d, 3H, J = 7.0 Hz), 0.70 (d, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 151.0, 149.0, 140.9, 140.6, 137.6, 135.2, 133.8, 122.3, 120.1, 106.6, 103.2, 100.9, 94.2, 60.9, 60.6, 59.7, 55.9, 55.5, 41.3, 39.2, 34.6, 22.0, 8.4; IR (NaCl, neat), 2935,

100.9, 94.2, 60.9, 60.6, 59.7, 55.9, 55.5, 41.3, 39.2, 34.6, 22.0, 8.4; IR (NaCl, neat), 2935,
2885, 1620, 1595, 1464, 1398, 1269, 1107, 1037 cm^{-1}; HRMS (FAB+) calcd for $C_{25}H_{32}O_8$, 460.2097. Found 460.2079.



Epigomisin O (90). A round bottom flask equipped with a reflux condenser was charged with 32 mg (0.070 mmol) of **138** in 4 mL of *i*-PrOH and 4 drops of conc. of HCl. The reaction was brought to reflux for 1 h. The reaction was cooled to ambient temperature and diluted with Et_2O (20 mL). The organic layer was washed with sat. aq. $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated to yield crude alcohol that was purified by flash column chromatography (3:1 Hex/EtOAc) to provide 22 mg (76 %) of epigomisin O (**90**)[7] as a white solid.

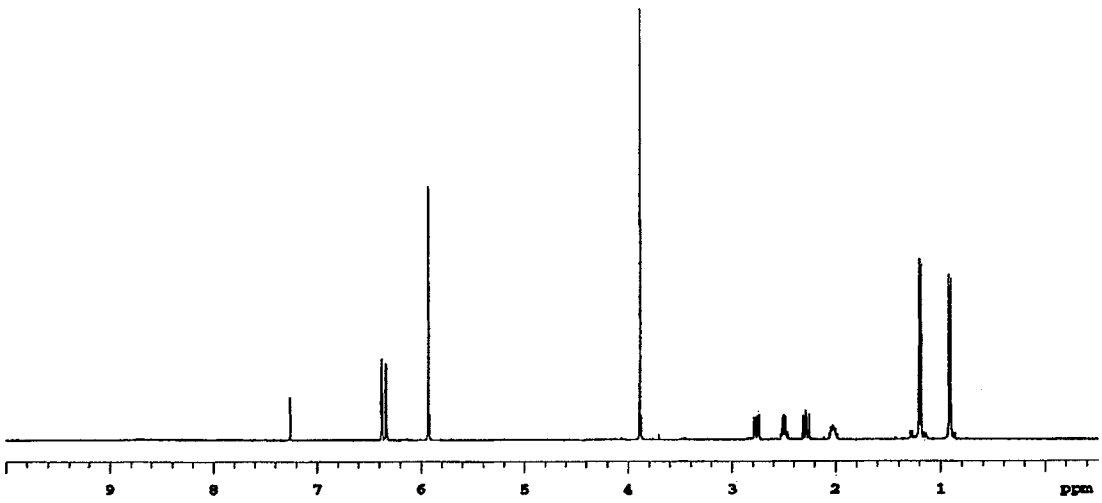
[7] Ikeya, Y.; Taguchi, H.; Yosioka, I.; Kobayashi, H. *Chem. Pharm. Bull.* **1979**, *27*, 2695-2709.

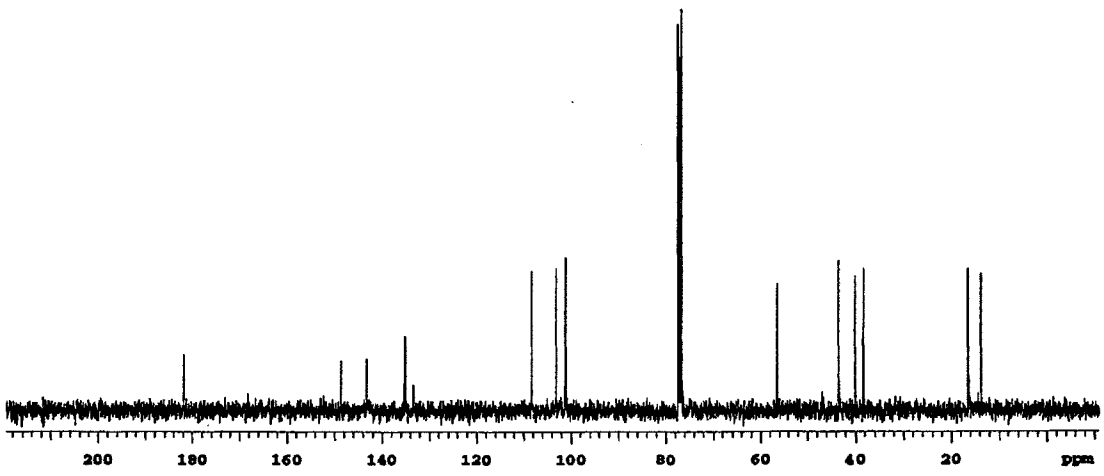


Gomisin O (91). A round bottom flask was charged with 14 mg (0.34 mmol) of **90** in 1 mL of PhH. To the reaction mixture was added 25 mg (0.15 mmol) of *p*-$NO_2C_6H_4CO_2H$, 47 mg (0.18 mmol) of PPh_3, followed by the addition of 40 mL (0.22 mmol) of DEAD dropwise via syringe. The reaction was stirred for 40 min. at ambient temperature before being concentrated and purified by flash column chromatography (9:1 Hex/EtOAc) providing 14 mg of the intermediate *para*-nitrobenzoate. A round bottom flask was charged with *para*-nitrobenzoate in 2 mL of MeOH. To the reaction mixture was added 94 mg (1.7 mmol) of KOH and the reaction stirred at ambient temperature for 12 h. The reaction was concentrated and the resulting crude taken up in Et_2O (15 mL). The organic layer was washed with H_2O (2 X10 mL), brine, dried over $MgSO_4$, filtered, and concentrated to yield 10 mg (71 %) of gomisin O (91)[7] as a colorless solid.

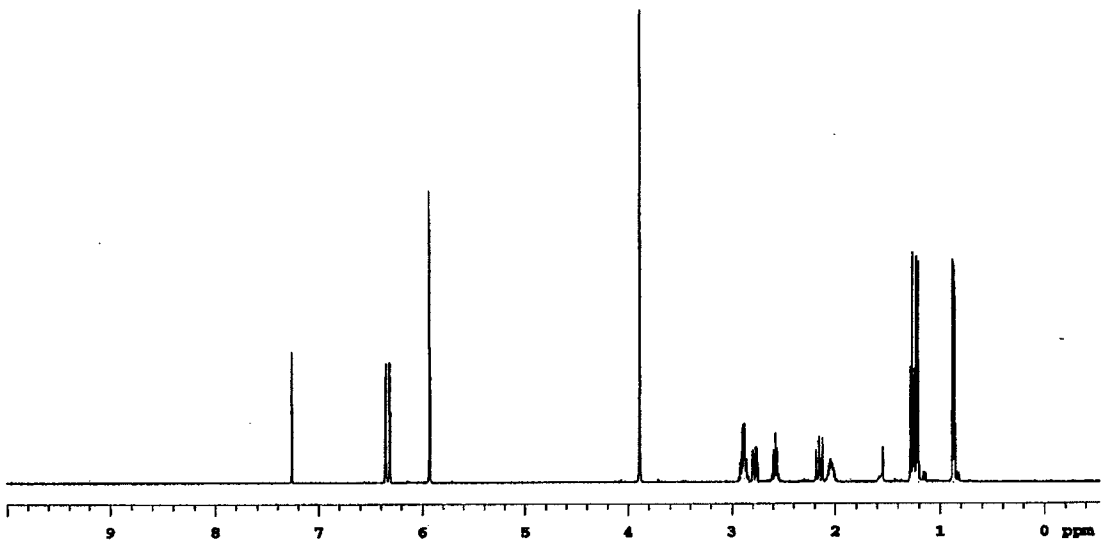
NMR spectra for selected compounds

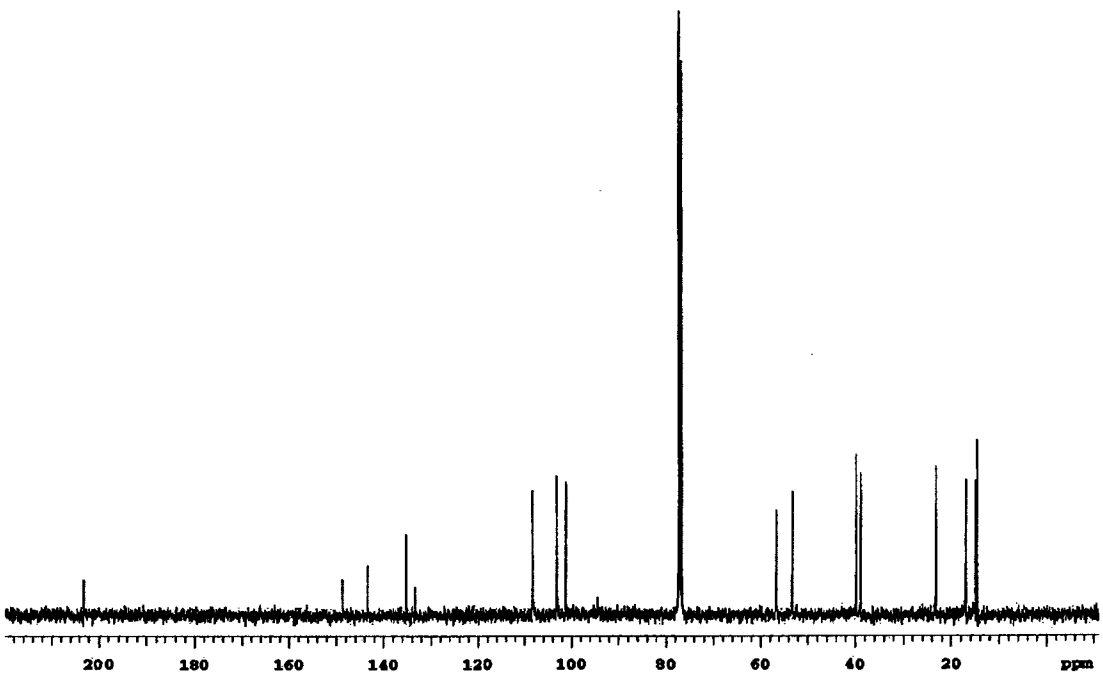
^{1}H and ^{13}C for **E1**:



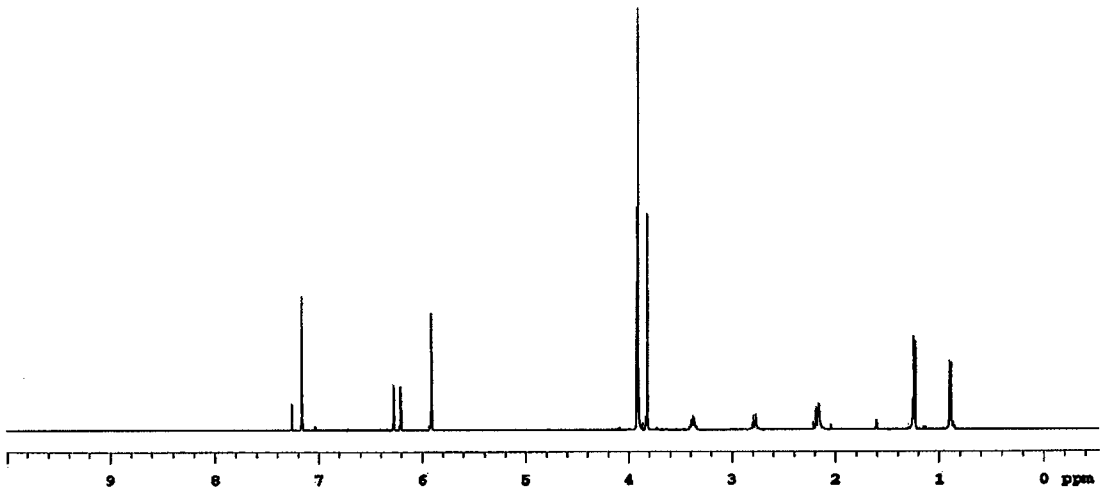


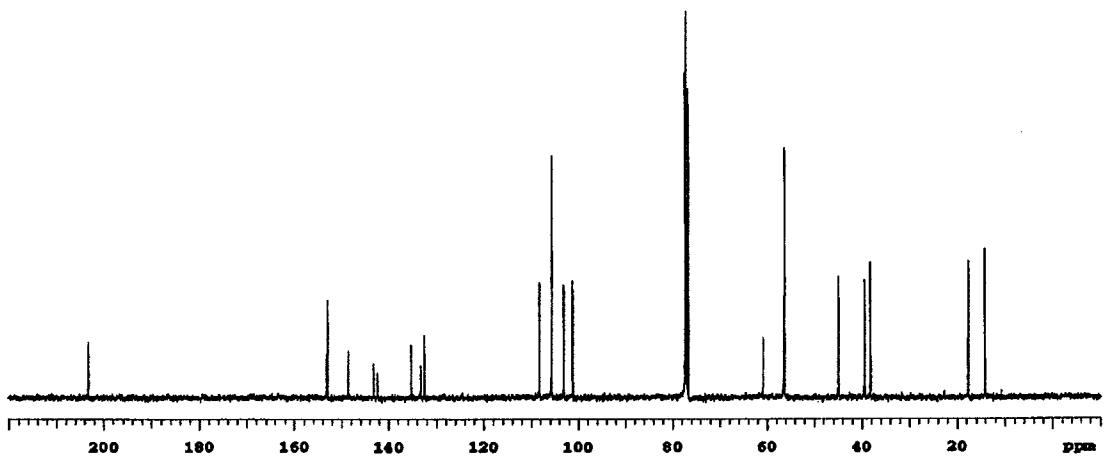
^{1}H and ^{13}C for **132**:



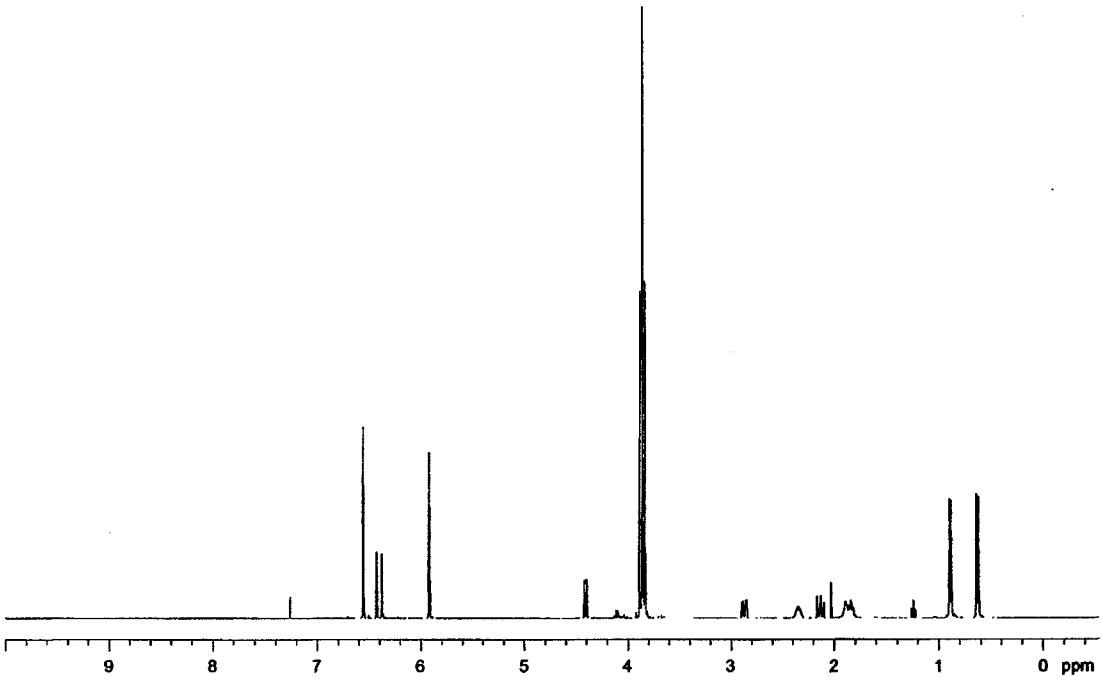


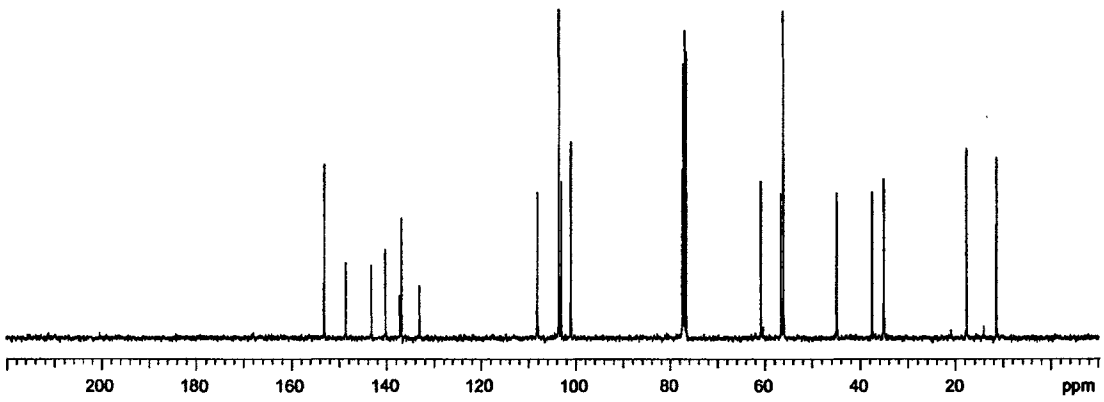
^{1}H and ^{13}C for **134**:



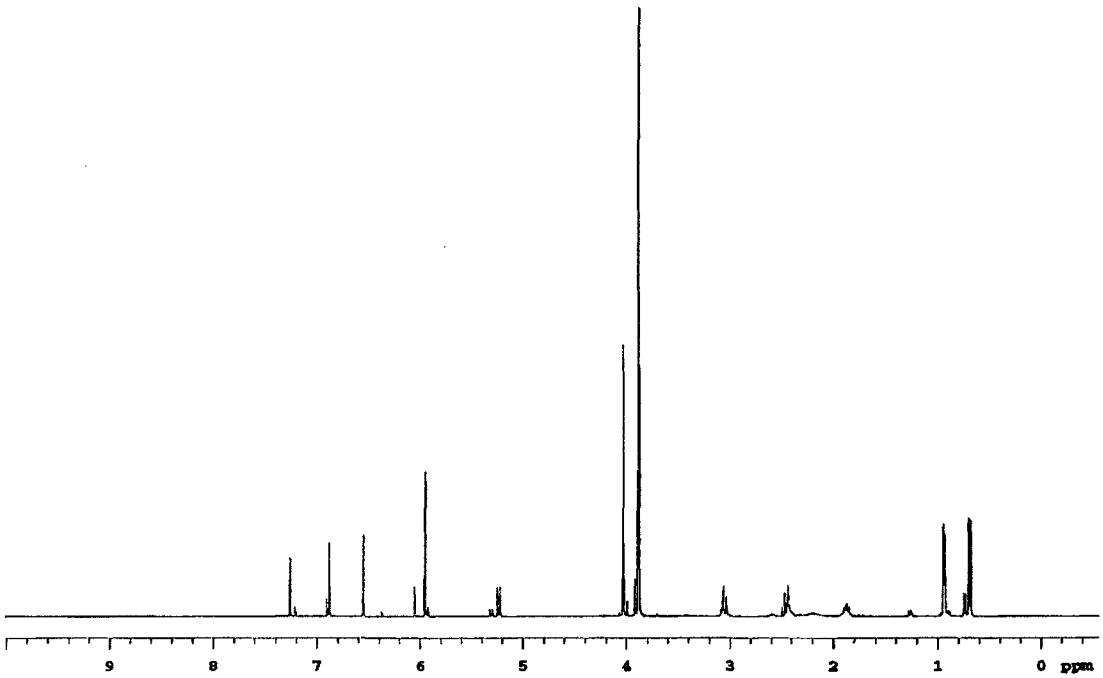


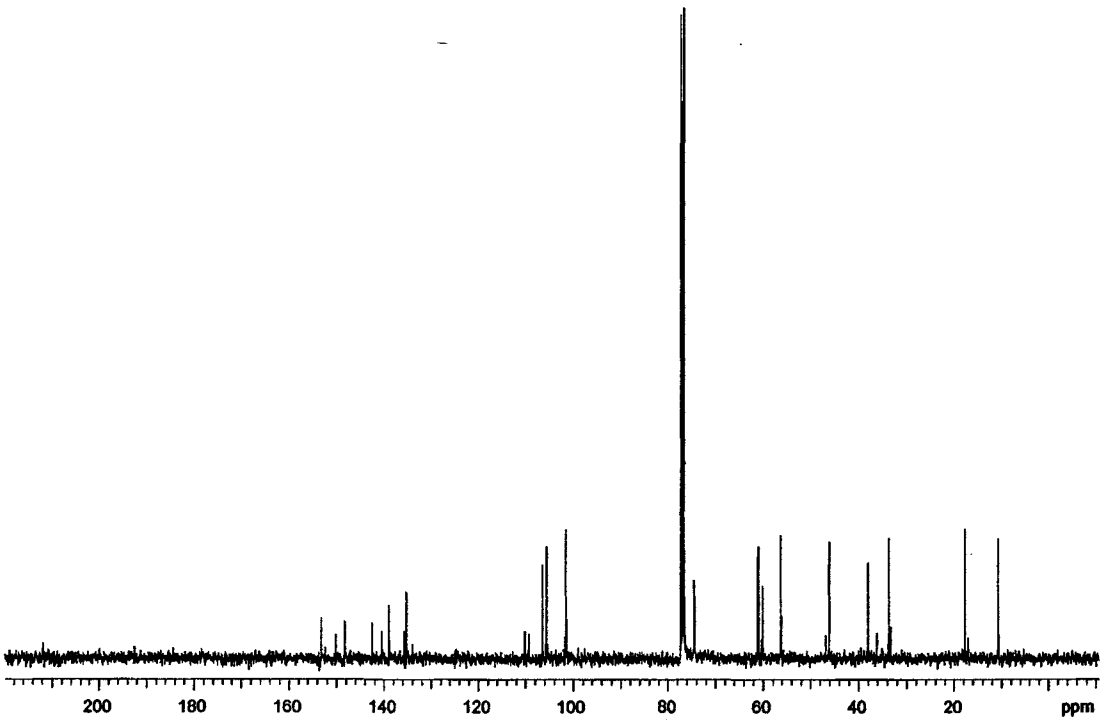
^{1}H and ^{13}C for **135**:



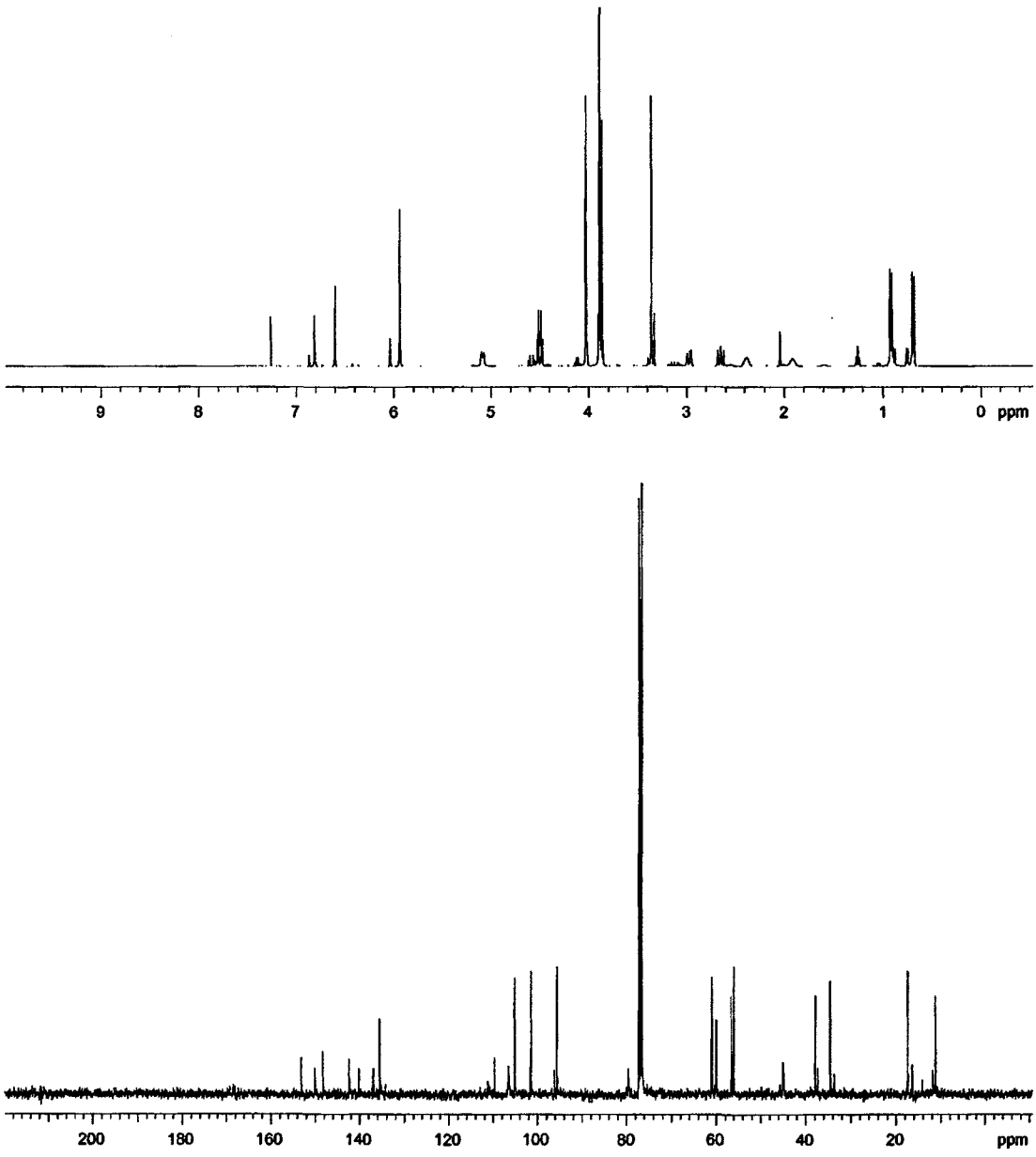


^{1}H and ^{13}C for **136**:

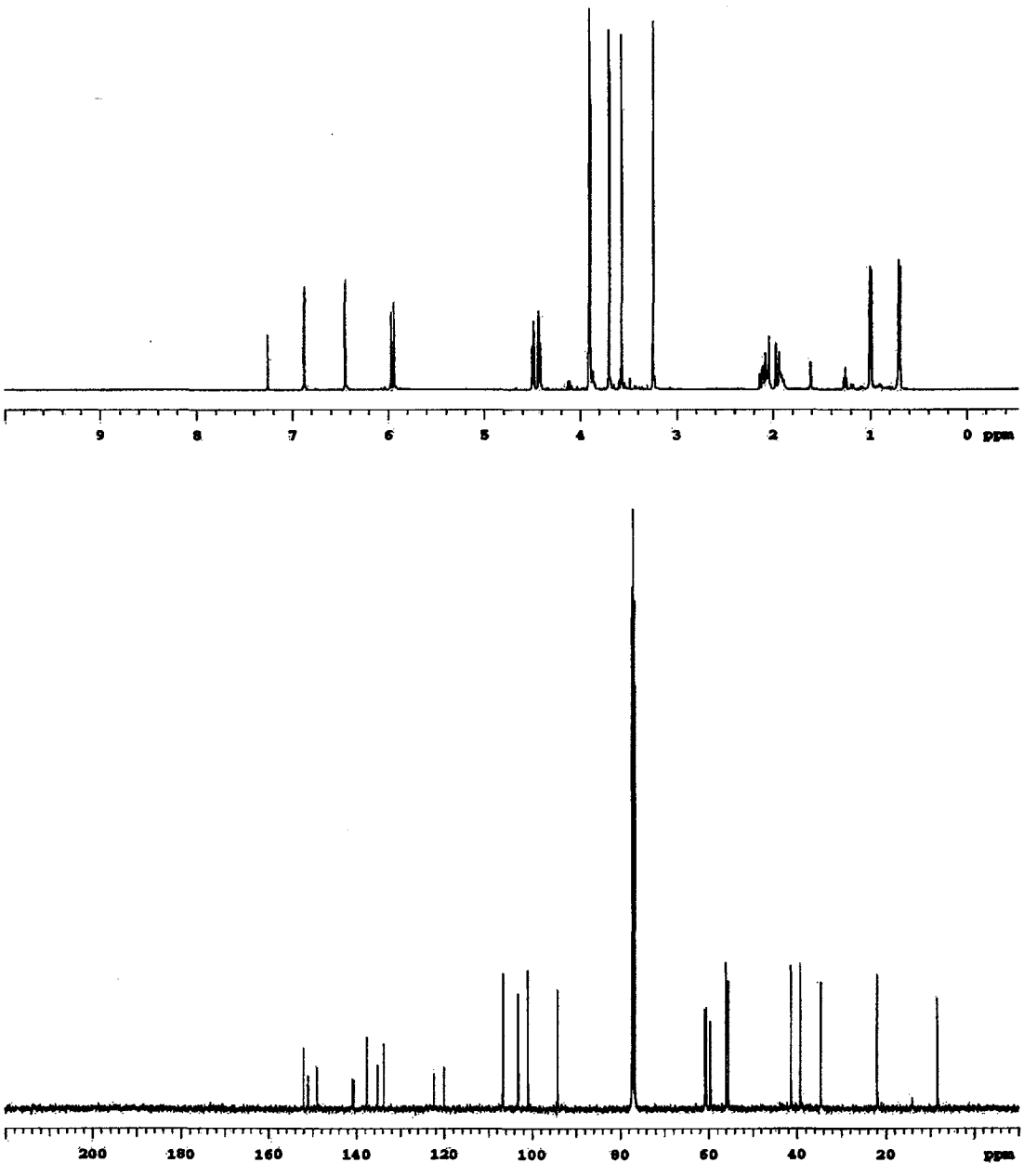




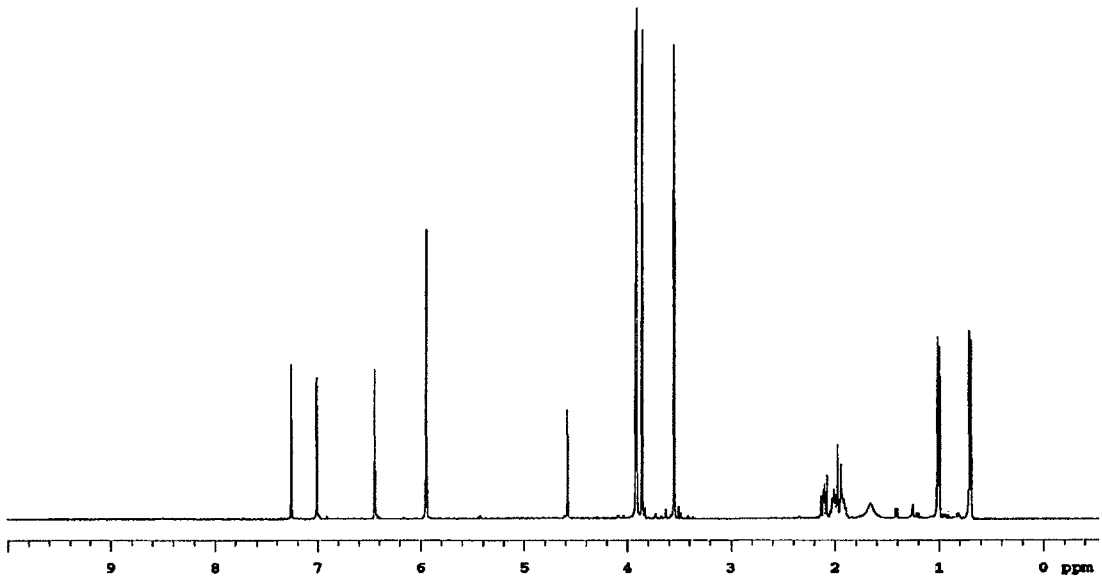
^{1}H and ^{13}C for **137**:

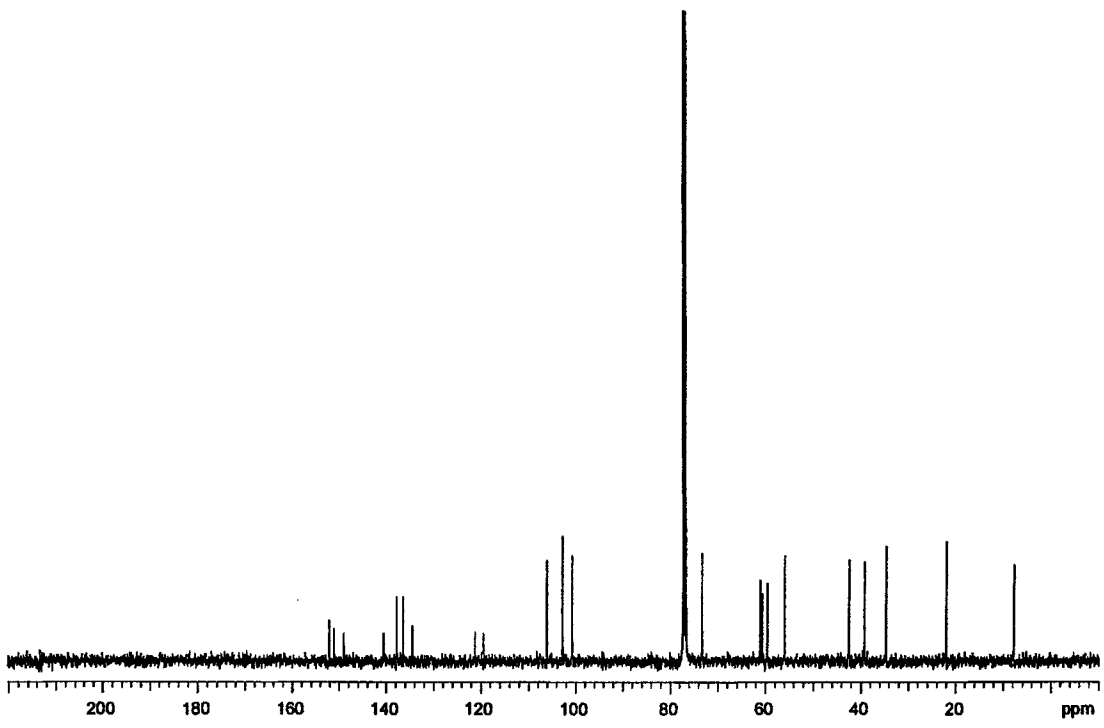


^{1}H and ^{13}C for **138**:

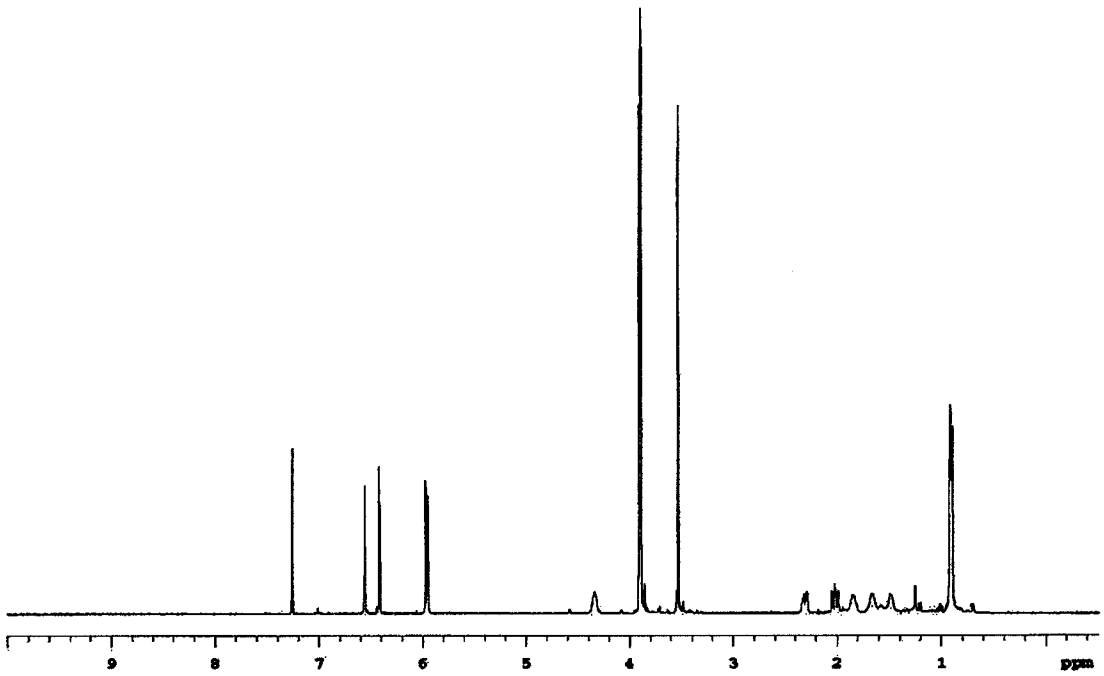


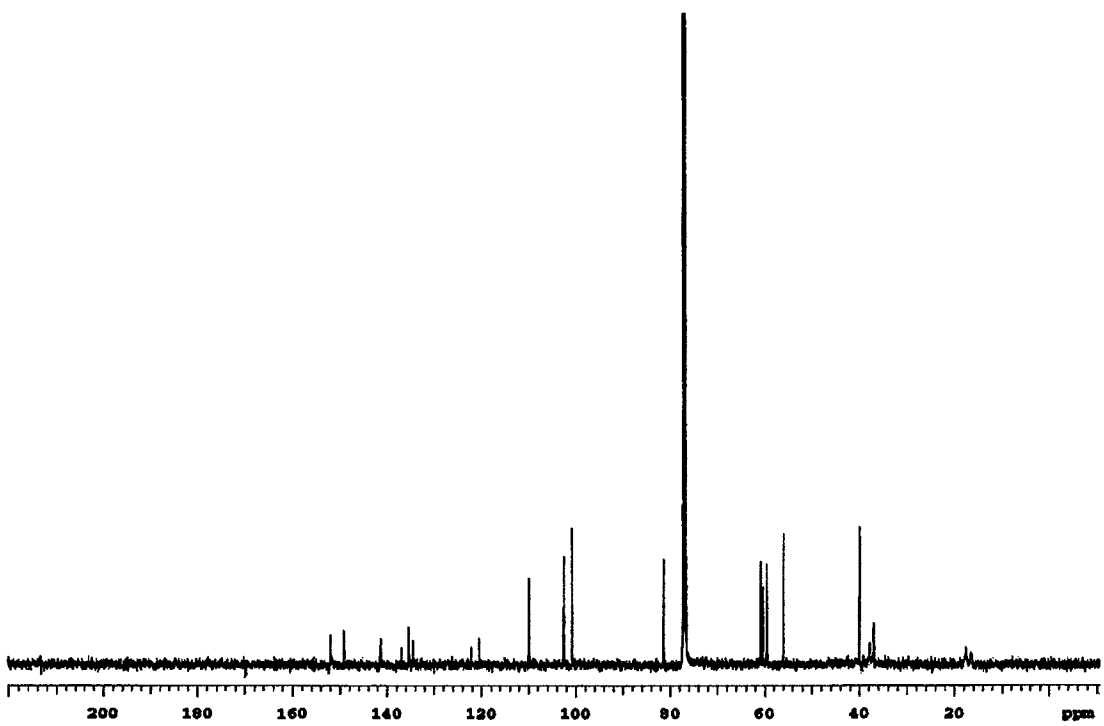
^{1}H and ^{13}C for **90**:





^{1}H and ^{13}C for **91**:





Appendices

Appendix 1

X-Ray Crystal Structure: Chapter 2, Compound 200

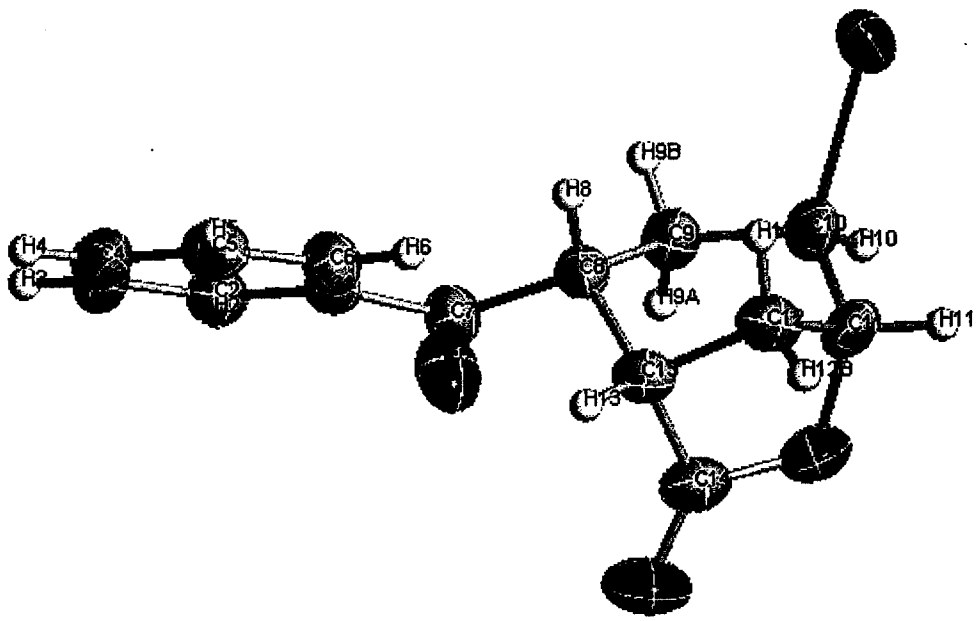


Table 1. Crystal data and structure refinement for rovis8m.

Identification code	rovis8m	
Empirical formula	C14 H13 I O3	
Formula weight	356.14	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 7.3666(8) Å	α= 90°.
	b = 5.9287(7) Å	β= 101.328(2)°.
	c = 15.0952(17) Å	γ = 90°.
Volume	646.43(13) Å^3	
Z	2	
Density (calculated)	1.830 Mg/m^3	
Absorption coefficient	2.474 mm^{-1}	
F(000)	348	
Crystal size	0.40 x 0.25 x 0.20 mm^3	
Theta range for data collection	2.75 to 28.28°.	
Index ranges	-9<=h<=9, -7<=k<=7, -19<=l<=18	
Reflections collected	6024	
Independent reflections	3094 [R(int) = 0.0191]	
Completeness to theta = 28.28°	98.5 %	
Absorption correction	SADABS	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3094 / 1 / 166	
Goodness-of-fit on F^2	1.078	
Final R indices [I>2sigma(I)]	R1 = 0.0338, wR2 = 0.0612	
R indices (all data)	R1 = 0.0387, wR2 = 0.0627	
Absolute structure parameter	0.03(2)	
Largest diff. peak and hole	0.995 and -0.498 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for rovis8m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	7381(5)	9898(7)	5589(3)	37(1)
C(2)	6988(5)	11439(8)	4882(3)	43(1)
C(3)	7202(5)	10813(13)	4025(2)	51(1)
C(4)	7822(6)	8689(9)	3877(3)	53(1)
C(5)	8182(6)	7156(8)	4567(3)	49(1)
C(6)	7929(6)	7741(7)	5426(3)	44(1)
C(7)	7236(5)	10749(10)	6509(3)	41(1)
C(8)	7081(5)	9029(6)	7254(3)	35(1)
C(9)	5917(5)	10075(7)	7884(2)	41(1)
C(10)	6070(6)	8894(7)	8792(3)	41(1)
C(11)	8013(6)	8084(7)	9154(3)	47(1)
C(12)	8739(6)	6579(6)	8497(3)	43(1)
C(13)	9022(5)	8335(6)	7798(3)	39(1)
C(14)	9878(6)	10216(7)	8418(3)	49(1)
I(1)	4194(1)	6041(1)	8730(1)	49(1)
O(1)	7269(5)	12740(6)	6668(2)	60(1)
O(2)	10963(5)	11652(5)	8304(3)	67(1)
O(3)	9227(4)	10084(5)	9200(2)	58(1)

Table 3. Bond lengths [Å] and angles [°] for rovis8m.

C(1)-C(6)	1.378(6)
C(1)-C(2)	1.391(5)
C(1)-C(7)	1.500(6)
C(2)-C(3)	1.385(6)
C(3)-C(4)	1.373(9)
C(4)-C(5)	1.369(6)
C(5)-C(6)	1.389(6)
C(7)-O(1)	1.204(7)
C(7)-C(8)	1.539(6)
C(8)-C(9)	1.531(5)
C(8)-C(13)	1.559(5)
C(9)-C(10)	1.524(5)
C(10)-C(11)	1.507(6)
C(10)-I(1)	2.175(4)
C(11)-O(3)	1.479(5)
C(11)-C(12)	1.508(6)
C(12)-C(13)	1.525(5)
C(13)-C(14)	1.512(6)
C(14)-O(2)	1.203(5)
C(14)-O(3)	1.361(6)
C(6)-C(1)-C(2)	119.8(4)
C(6)-C(1)-C(7)	123.7(4)
C(2)-C(1)-C(7)	116.5(4)
C(3)-C(2)-C(1)	119.7(5)
C(4)-C(3)-C(2)	120.1(5)
C(5)-C(4)-C(3)	120.4(4)
C(4)-C(5)-C(6)	120.2(4)
C(1)-C(6)-C(5)	119.8(4)
O(1)-C(7)-C(1)	120.8(4)
O(1)-C(7)-C(8)	120.3(4)
C(1)-C(7)-C(8)	118.8(4)
C(9)-C(8)-C(7)	108.5(3)
C(9)-C(8)-C(13)	110.3(3)

C(7)-C(8)-C(13)	111.6(3)
C(10)-C(9)-C(8)	114.9(3)
C(11)-C(10)-C(9)	111.7(3)
C(11)-C(10)-I(1)	108.6(3)
C(9)-C(10)-I(1)	112.6(3)
O(3)-C(11)-C(12)	102.5(3)
O(3)-C(11)-C(10)	106.5(3)
C(12)-C(11)-C(10)	112.6(3)
C(11)-C(12)-C(13)	99.5(3)
C(14)-C(13)-C(12)	100.0(3)
C(14)-C(13)-C(8)	111.1(3)
C(12)-C(13)-C(8)	108.0(3)
O(2)-C(14)-O(3)	121.5(4)
O(2)-C(14)-C(13)	129.9(5)
O(3)-C(14)-C(13)	108.6(4)
C(14)-O(3)-C(11)	108.5(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for rovis8m. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	31(2)	40(2)	40(2)	3(2)	6(2)	-3(2)
C(2)	41(2)	40(4)	47(2)	5(2)	6(2)	2(2)
C(3)	54(2)	59(3)	37(2)	6(3)	2(2)	0(3)
C(4)	50(3)	69(3)	40(2)	-6(2)	7(2)	-9(2)
C(5)	52(2)	46(2)	50(2)	-16(2)	14(2)	-7(2)
C(6)	48(2)	39(2)	45(2)	4(2)	11(2)	0(2)
C(7)	45(2)	37(3)	41(2)	6(2)	11(1)	4(2)
C(8)	38(2)	32(2)	35(2)	-2(2)	8(2)	-3(2)
C(9)	41(2)	41(2)	40(2)	0(2)	9(2)	6(2)
C(10)	46(2)	47(2)	33(2)	-6(2)	11(2)	1(2)
C(11)	49(2)	53(3)	33(2)	1(2)	-5(2)	-5(2)
C(12)	39(2)	37(3)	53(2)	6(2)	5(2)	2(1)
C(13)	35(2)	35(2)	48(2)	-1(2)	9(2)	2(2)
C(14)	38(2)	44(2)	59(3)	-1(2)	-1(2)	-2(2)
I(1)	44(1)	59(1)	46(1)	9(1)	15(1)	-3(1)
O(1)	94(3)	36(2)	54(2)	1(2)	25(2)	-6(2)
O(2)	54(2)	52(3)	91(2)	-5(2)	9(2)	-18(2)
O(3)	56(2)	61(2)	51(2)	-11(1)	-1(2)	-17(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3)
for rovis8m.

	x	y	z	U(eq)
H(2)	6583	12884	4985	52
H(3)	6924	11832	3549	61
H(4)	8000	8290	3304	64
H(5)	8596	5718	4461	58
H(6)	8130	6681	5889	52
H(8)	6447	7679	6973	42
H(9A)	6287	11637	7992	49
H(9B)	4629	10068	7578	49
H(10)	5750(60)	9990(70)	9220(30)	50
H(11)	8117	7364	9746	56
H(12A)	7842	5442	8240	52
H(12B)	9892	5855	8774	52
H(13)	9846	7798	7407	47

Appendix 2

X-Ray Crystal Structure: Chapter 3, Compound 122

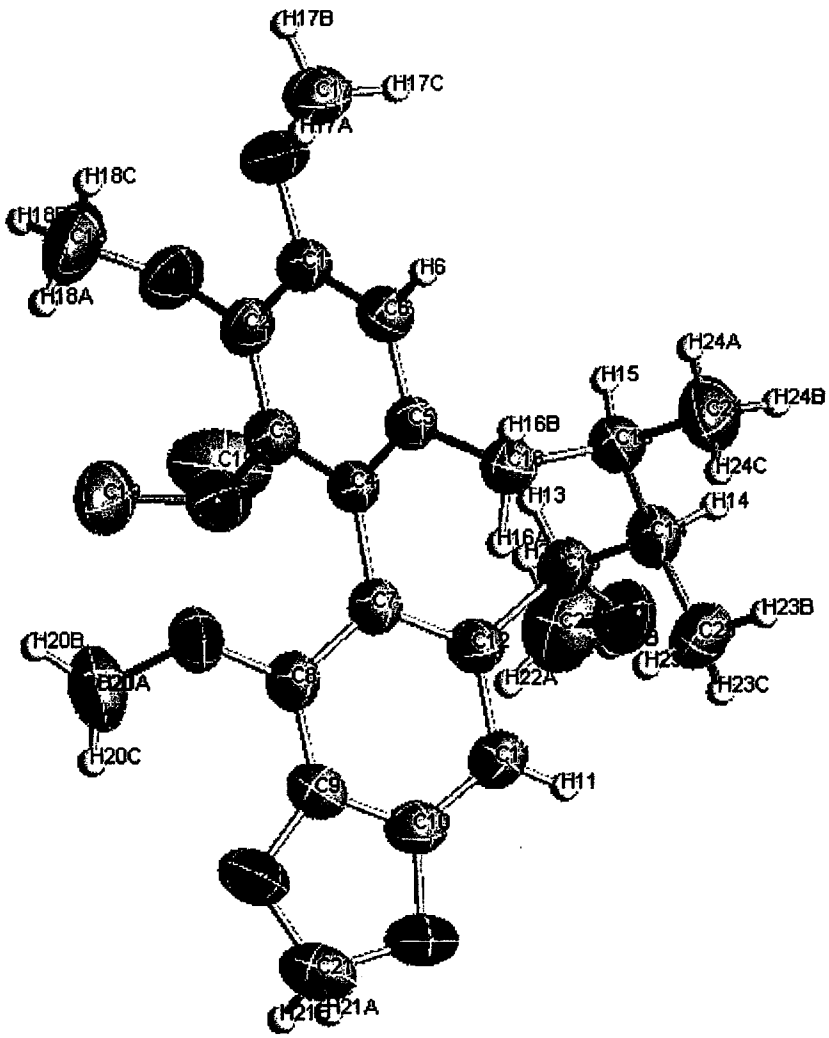


Table 1. Crystal data and structure refinement for rovis5m.

Identification code	rovis5m	
Empirical formula	C24 H30 O7	
Formula weight	430.48	
Temperature	298(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.6124(13) Å	α= 69.092(2)°.
	b = 11.5209(16) Å	β= 77.838(2)°.
	c = 11.6811(16) Å	γ = 66.075(2)°.
Volume	1101.3(3) Å^3	
Z	2	
Density (calculated)	1.298 Mg/m^3	
Absorption coefficient	0.095 mm^{-1}	
F(000)	460	
Crystal size	0.28 x 0.18 x 0.15 mm^3	
Theta range for data collection	1.87 to 23.36°.	
Index ranges	-10<=h<=10, -12<=k<=12, -12<=l<=12	
Reflections collected	7126	
Independent reflections	3164 [R(int) = 0.0316]	
Completeness to theta = 23.36°	99.0 %	
Absorption correction	SADABS	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3164 / 0 / 296	
Goodness-of-fit on F^2	0.764	
Final R indices [I>2sigma(I)]	R1 = 0.0566, wR2 = 0.1706	
R indices (all data)	R1 = 0.0808, wR2 = 0.2033	
Extinction coefficient	0.007(5)	
Largest diff. peak and hole	0.267 and -0.209 e.Å^{-3}	

Comment: C19 displays approx 0.55 to 0.45 disorder. Hydrogen atoms ommitted for clarity

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for rovis5m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	894(2)	6634(2)	7059(2)	73(1)
O(2)	7191(2)	5106(2)	8934(2)	73(1)
O(3)	6171(3)	3732(2)	8642(2)	79(1)
O(4)	1372(2)	13386(2)	5428(2)	66(1)
O(5)	1172(2)	12226(2)	7865(2)	69(1)
O(6)	2421(2)	9438(2)	8827(2)	69(1)
O(7)	5745(2)	8076(2)	8078(2)	63(1)
C(1)	1960(3)	12027(3)	5823(3)	52(1)
C(2)	1889(3)	11448(3)	7089(3)	52(1)
C(3)	2475(3)	10066(3)	7578(2)	50(1)
C(4)	3120(3)	9249(2)	6806(2)	47(1)
C(5)	3140(3)	9845(2)	5543(2)	48(1)
C(6)	2578(3)	11231(3)	5057(3)	52(1)
C(7)	3803(3)	7772(2)	7343(2)	48(1)
C(8)	5135(3)	7226(3)	7977(2)	51(1)
C(9)	5827(3)	5860(3)	8383(2)	55(1)
C(10)	5240(3)	5053(3)	8196(3)	56(1)
C(11)	3947(3)	5529(3)	7604(3)	60(1)
C(12)	3218(3)	6927(2)	7167(2)	51(1)
C(13)	1763(3)	7481(3)	6507(3)	57(1)
C(14)	1989(3)	7612(3)	5128(3)	62(1)
C(15)	2291(3)	8878(3)	4305(3)	59(1)
C(16)	3640(3)	9062(3)	4632(3)	55(1)
C(17)	1621(4)	14030(3)	4158(3)	68(1)
C(18)	1947(6)	13010(4)	7935(4)	107(1)
C(19)	2801(9)	9853(7)	9663(6)	90(2)
C(19A)	1012(10)	9744(9)	9484(8)	102(3)
C(20)	6163(5)	7813(4)	9279(3)	90(1)
C(21)	7380(4)	3759(3)	9137(3)	77(1)
C(22)	254(5)	6664(4)	8251(4)	101(1)
C(23)	3134(4)	6346(3)	4851(3)	79(1)
C(24)	2441(5)	8981(4)	2942(3)	89(1)

Table 3. Bond lengths [Å] and angles [°] for rovis5m.

		C(3)-C(4)	1.407(4)
O(1)-C(22)	1.405(4)	C(4)-C(5)	1.388(4)
O(1)-C(13)	1.432(3)	C(4)-C(7)	1.491(3)
O(2)-C(9)	1.386(3)	C(5)-C(6)	1.395(4)
O(2)-C(21)	1.423(4)	C(5)-C(16)	1.515(3)
O(3)-C(10)	1.383(3)	C(7)-C(12)	1.394(4)
O(3)-C(21)	1.417(4)	C(7)-C(8)	1.413(4)
O(4)-C(1)	1.363(3)	C(8)-C(9)	1.376(4)
O(4)-C(17)	1.421(4)	C(9)-C(10)	1.361(4)
O(5)-C(2)	1.384(3)	C(10)-C(11)	1.365(4)
O(5)-C(18)	1.415(4)	C(11)-C(12)	1.412(4)
O(6)-C(3)	1.379(3)	C(12)-C(13)	1.529(4)
O(6)-C(19A)	1.384(8)	C(13)-C(14)	1.539(4)
O(6)-C(19)	1.393(6)	C(14)-C(23)	1.526(4)
O(7)-C(8)	1.377(3)	C(14)-C(15)	1.537(4)
O(7)-C(20)	1.435(4)	C(15)-C(24)	1.533(4)
C(1)-C(6)	1.384(4)	C(15)-C(16)	1.538(4)
C(1)-C(2)	1.388(4)	C(19)-C(19A)	1.833(12)
C(2)-C(3)	1.392(4)		
C(22)-O(1)-C(13)	113.6(2)	C(1)-C(2)-C(3)	119.5(2)
C(9)-O(2)-C(21)	105.0(2)	O(6)-C(3)-C(2)	121.9(2)
C(10)-O(3)-C(21)	105.3(2)	O(6)-C(3)-C(4)	117.2(2)
C(1)-O(4)-C(17)	117.5(2)	C(2)-C(3)-C(4)	120.9(2)
C(2)-O(5)-C(18)	115.3(3)	C(5)-C(4)-C(3)	118.7(2)
C(3)-O(6)-C(19A)	117.6(4)	C(5)-C(4)-C(7)	120.9(2)
C(3)-O(6)-C(19)	122.9(3)	C(3)-C(4)-C(7)	120.3(2)
C(19A)-O(6)-C(19)	82.6(5)	C(4)-C(5)-C(6)	120.1(2)
C(8)-O(7)-C(20)	115.6(2)	C(4)-C(5)-C(16)	123.0(2)
O(4)-C(1)-C(6)	124.6(3)	C(6)-C(5)-C(16)	116.7(2)
O(4)-C(1)-C(2)	115.4(2)	C(1)-C(6)-C(5)	120.7(3)
C(6)-C(1)-C(2)	120.0(2)	C(12)-C(7)-C(8)	119.7(2)
O(5)-C(2)-C(1)	120.7(2)	C(12)-C(7)-C(4)	121.6(2)
O(5)-C(2)-C(3)	119.8(2)	C(8)-C(7)-C(4)	118.6(2)

O(7)-C(8)-C(9)	122.9(2)
O(7)-C(8)-C(7)	118.7(2)
C(9)-C(8)-C(7)	118.1(2)
C(10)-C(9)-C(8)	121.2(2)
C(10)-C(9)-O(2)	110.2(2)
C(8)-C(9)-O(2)	128.4(2)
C(9)-C(10)-C(11)	123.0(3)
C(9)-C(10)-O(3)	110.2(3)
C(11)-C(10)-O(3)	126.8(3)
C(10)-C(11)-C(12)	117.1(3)
C(7)-C(12)-C(11)	120.9(2)
C(7)-C(12)-C(13)	121.2(2)
C(11)-C(12)-C(13)	117.9(2)
O(1)-C(13)-C(12)	110.0(2)
O(1)-C(13)-C(14)	105.7(2)
C(12)-C(13)-C(14)	116.1(2)
C(23)-C(14)-C(15)	113.3(3)
C(23)-C(14)-C(13)	112.9(3)
C(15)-C(14)-C(13)	113.6(2)
C(24)-C(15)-C(14)	111.2(2)
C(24)-C(15)-C(16)	111.1(3)
C(14)-C(15)-C(16)	114.9(2)
C(5)-C(16)-C(15)	111.8(2)
O(6)-C(19)-C(19A)	48.5(3)
O(6)-C(19A)-C(19)	48.9(4)
O(3)-C(21)-O(2)	109.3(2)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for rovis5m. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	67(1)	79(2)	86(2)	-26(1)	-6(1)	-40(1)
O(2)	64(1)	63(1)	79(2)	-6(1)	-26(1)	-13(1)
O(3)	85(2)	46(1)	90(2)	-6(1)	-29(1)	-10(1)
O(4)	79(1)	43(1)	62(1)	-14(1)	-6(1)	-11(1)
O(5)	82(2)	58(1)	67(1)	-30(1)	-1(1)	-18(1)
O(6)	85(2)	63(1)	51(1)	-16(1)	-8(1)	-20(1)
O(7)	71(1)	68(1)	60(1)	-14(1)	-15(1)	-35(1)
C(1)	50(2)	46(2)	59(2)	-17(1)	-9(1)	-15(1)
C(2)	51(2)	54(2)	58(2)	-28(1)	-2(1)	-16(1)
C(3)	52(2)	51(2)	47(2)	-14(1)	-4(1)	-19(1)
C(4)	46(2)	46(2)	51(2)	-14(1)	-9(1)	-16(1)
C(5)	44(2)	47(2)	53(2)	-19(1)	-5(1)	-15(1)
C(6)	54(2)	52(2)	49(2)	-13(1)	-6(1)	-19(1)
C(7)	48(2)	50(2)	48(2)	-15(1)	-3(1)	-20(1)
C(8)	51(2)	55(2)	52(2)	-17(1)	-3(1)	-24(1)
C(9)	50(2)	56(2)	52(2)	-9(1)	-9(1)	-17(1)
C(10)	63(2)	47(2)	52(2)	-9(1)	-4(1)	-17(1)
C(11)	65(2)	52(2)	68(2)	-17(1)	-11(2)	-24(2)
C(12)	50(2)	48(2)	54(2)	-13(1)	-6(1)	-18(1)
C(13)	53(2)	54(2)	71(2)	-21(1)	-9(1)	-22(1)
C(14)	60(2)	64(2)	72(2)	-24(2)	-17(2)	-23(2)
C(15)	61(2)	56(2)	62(2)	-20(1)	-14(1)	-15(1)
C(16)	59(2)	54(2)	53(2)	-19(1)	-6(1)	-18(1)
C(17)	79(2)	54(2)	63(2)	-11(1)	-7(2)	-21(2)
C(18)	167(4)	93(3)	93(3)	-42(2)	-20(3)	-63(3)
C(19)	136(6)	86(4)	57(4)	-29(3)	-23(4)	-37(4)
C(19A)	76(5)	103(6)	80(6)	-12(5)	33(4)	-18(5)
C(20)	103(3)	120(3)	73(2)	-25(2)	-20(2)	-63(2)
C(21)	63(2)	67(2)	81(2)	-6(2)	-17(2)	-12(2)
C(22)	94(3)	123(3)	103(3)	-42(3)	22(2)	-65(3)
C(23)	102(3)	61(2)	83(2)	-30(2)	-15(2)	-28(2)

C(24)	117(3)	94(3)	68(2)	-21(2)	-28(2)	-44(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3)
for rovis5m.

	x	y	z	U(eq)
H(6)	2618	11624	4209	63
H(11)	3562	4958	7494	72
H(13)	1147	8363	6602	69
H(14)	1005	7715	4912	75
H(15)	1378	9633	4422	71
H(16A)	4400	8194	4981	66
H(16B)	4110	9525	3890	66
H(17A)	2693	13719	3915	102
H(17B)	1249	14976	4013	102
H(17C)	1087	13831	3687	102
H(18A)	2989	12458	8098	160
H(18B)	1459	13401	8584	160
H(18C)	1919	13703	7169	160
H(20A)	5322	7732	9873	135
H(20B)	6415	8534	9292	135
H(20C)	7031	6999	9477	135
H(21A)	8350	3315	8746	93
H(21B)	7377	3291	10012	93
H(22A)	1045	6203	8810	151
H(22B)	-482	6236	8500	151
H(22C)	-238	7572	8257	151
H(23A)	4145	6237	4965	118
H(23B)	3083	6413	4016	118
H(23C)	2894	5591	5397	118
H(24A)	2431	9852	2445	134
H(24B)	1603	8837	2766	134
H(24C)	3384	8320	2760	134