DISSERTATION

PROGRESS TOWARD AN ASYMMETRIC TOTAL SYNTHESIS OF THE STEMONA ALKALOID TUBEROSTEMONINOL

Submitted by
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In partial fulfillment of the requirements
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WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY XIANGNA JIA ENTITLED PROGRESS TOWARD AN ASYMMETRIC TOTAL SYNTHESIS OF THE STEMONA ALKALOID TUBEROSTEMONINOL AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

Committee on Graduate Work

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Department Head

ABSTRACT OF DISSERTATION

PROGRESS TOWARD AN ASYMMETRIC TOTAL SYNTHESIS OF THE STEMONA ALKALOID TUBEROSTEMONINOL

Presented herein is a twenty-five linear step synthetic progress toward an asymmetric total synthesis of the *Stemona* alkaloid tuberostemoninol. A diastereoselective intramolecular Pauson-Khand reaction of a glycinate derivative served to construct the BC ring system and set one of the two quaternary carbon centers present in the target molecule in high yield. The γ-lactone E ring and azepine D ring were constructed subsequently. Several approaches were explored for the introduction of the γ-lactone E ring carbon skeleton containing the α-methylene group. Further elaboration of the BCDE tetracycle toward tuberostemoninol was performed to afford the corresponding ketone compound, which makes completion of the total synthesis possible in ten steps.

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List of Abbreviations

Ac	acetyl
AIBN	azobisisobutyronitrile
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
Bz	benzoyl
CAN	cerium ammonium nitrate
Cbz	benzyloxycarbonyl
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DEPC	diethyl phosphoryl cyanide
DIAD	diisopropyl azodicarboxylate
DIEA	diisopropylethylamine
DIBAL	diisobutylaluminium hydride
DIC	*N,N*-diisopropylcarbodiimide
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DME	dimethoxyethane

DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
DMTSF	dimethylthiomethyltetrafluoroborate
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
FDPP	pentafluorophenyl diphenylphosphinate
IBX	2-iodoxybenzoic acid
Im	imidazol-1-yl
NaHMDS	sodium bis(trimethylsilyl)amide
LAH	lithium aluminum hydride
LDA	lithium diisoproplyamide
LHMDS	lithium bis(trimethylsilyl)amide
*m*CPBA	*m*-chloroperoxybenzoic acid
MOM	methoxymethyl
Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
NMM	4-methylmorpholine
NMO	4-methylmorpholine *N*-oxide
NMP	4-methoxypyridine-*N*-oxide
Ns	4-nitrobenzenesulfonyl
PCC	pyridinium chlorochromate
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium
Ph	phenyl
phth	phthalimidyl

Piv	pivoyl
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
Pyr	pyridine
Red Al	sodium bis(2-methoxyethoxy)aluminum hydride
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBDP	*tert*-butyldiphenylsilyl
TEMPO	2,2,6,6-tetramethyl-piperidin-1-oxyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TMANO	trimethyl *N*-oxide
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
TIPS	triisopropylsilyl
TPAP	*tetra-n*-propylammonium perruthenate
Troc	2,2,2-trichloroethoxycarbonyl
Ts	*p*-toluenesulfonyl

Chapter 1: Introduction

1.1 Stemona Alkaloids

1.1.1 Natural Sources and Phytochemical Studies

Stemona alkaloids represent a unique class of natural products, to date detected only from the monocotyledonous family *stemonaceae* distributing from continental Asia and Japan through southeast Asia to tropical Australia and, with one species of *Croomia*, even to the southeast United States.[1, 2]

Stemonaceae consists of three genera: *Stemona*, *Croomia,* and *Stichoneuron*, comprising about 32 species, 25 of which belong to genus *Stemona*, the main source of *Stemona* alkaloids. Many species prefer a seasonal climate and occur mainly as perennial climbers or subshrubs with tufted tuberous roots in rather dry vegetation (**Figure 1**)[2,3]. The species are usually differentiated by their morphological characteristics (e.g. appearances of the flowers). However, in spite of the good delimitation of *Stemona* from *Croomia* and *Stichoneuron* and already revisionary treatments for the Flora Malesiana and Flora of China, there are still many taxonomic problems at the species level that remain to be solved.[2,4]

Figure 1. Three Traditional Representatives of *Stemona* Species

The *Stemona* alkaloids represent a class of polycyclic alkaloids with intricate structures emerged from the structural elucidation of its first representative tuberostemonine in the 1960's. The first review of *Stemona* alkaloids by Götz and Strunz in 1975 included the structural elucidation of seven alkaloids of this family.[5] The number had grown to 42 in the second review by Pilli and Oliveira in 2000.[1a] In 2005, Greger reported a relatively detailed review on the structural relationships, distribution, and biological activities of 82 *Stemona* alkaloids.[4] To date, phytochemical investigations have led to isolation and structural elucidation of over 100 alkaloids from *Stemonaceae* species.[6] Except a few alkaloids from genera *Croomia* and *Stichoneuron*, most of them were isolated from the 25 species of genus *Stemona*.[7]

1.1.2 Structure Diversity and Classification

Most *Stemona* alkaloids are characterized by a pyrrolo[1,2-a]azepine nucleus linked with one or two carbon chains mostly forming terminal lactone rings. A minor group of alkaloids isolated recently from Thailand *Stemona* species share a pyrido[1,2-a]azepine nucleus (**Figure 2**).[8]

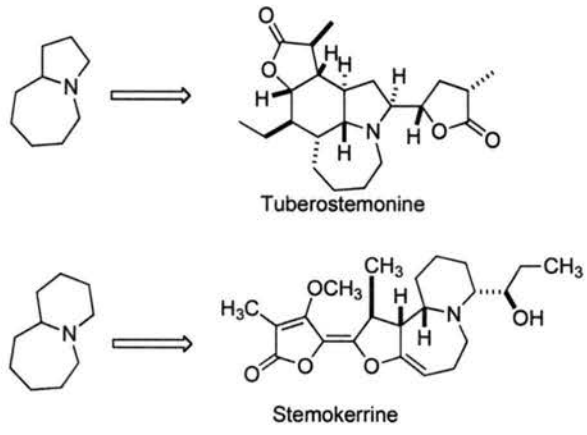


Figure 2. Examples of Pyrrolo[1,2-a]azepine and Pyrido[1,2-a]azepine Alkaloids

In 1994, Xu and coworkers suggested that the known *Stemona* alkaloids could be separated into eight structural groups according to the sites of connection between the basic ring and the side chain.[9] In 2000, Pillia and Oliveira also classified these alkaloids according to their structural features into five groups (stenine I, stemoamide II, tuberostemospironine III, stemonamine IV, tuberostemoamide V) containing the pyrrolo[1,2-a]azepine nucleus characteristic of the majority of the *Stemona* alkaloids (**Figure 3**) and a miscellaneous group lacking this basic nucleus.[1a]

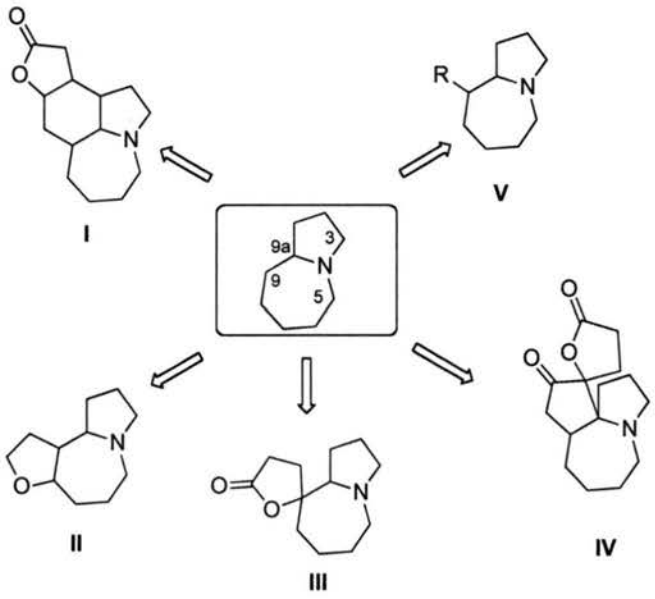


Figure 3. Five Groups of *Stemona* Alkaloids

Continuing phytochemical investigations have led to isolation of many new *Stemona* alkaloids and discovery of new structural features. In 2003, five novel pyrido[1,2-a]azepine derivatives, representing a minor skeleton of *Stemona* alkaloids, were isolated from *S. kerrii* Craib by Greger and coworkers.[8] Thereafter in 2006, Greger grouped the already known 82 *Stemona* alkaloids into three skeletal types (Stichonerine-

type, Protostemonine-type and Croomine-type) based on biosynthetic considerations and their various distribution (**Figure 4**).[4] Each type contains a large number of members with diverse structural features, as shown in figures 6 and 7. Croomine-type alkaloids so far have only 8 members possessing the same structure skeleton as croomine (**Figure 5**).

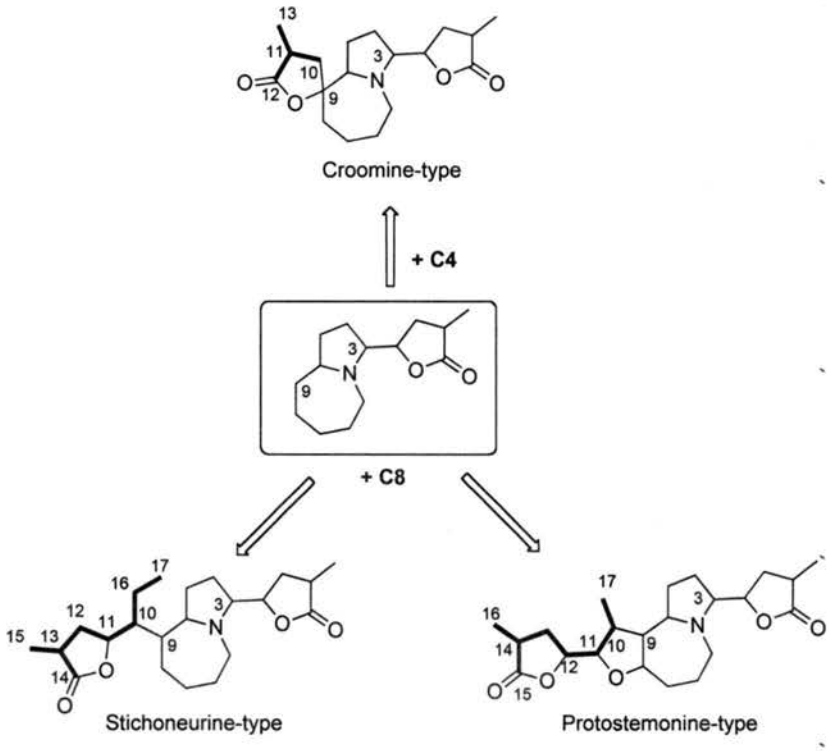


Figure 4. Classification Based on Different Carbon Chains Attached to C-9 of the Pyrroloazepine Core

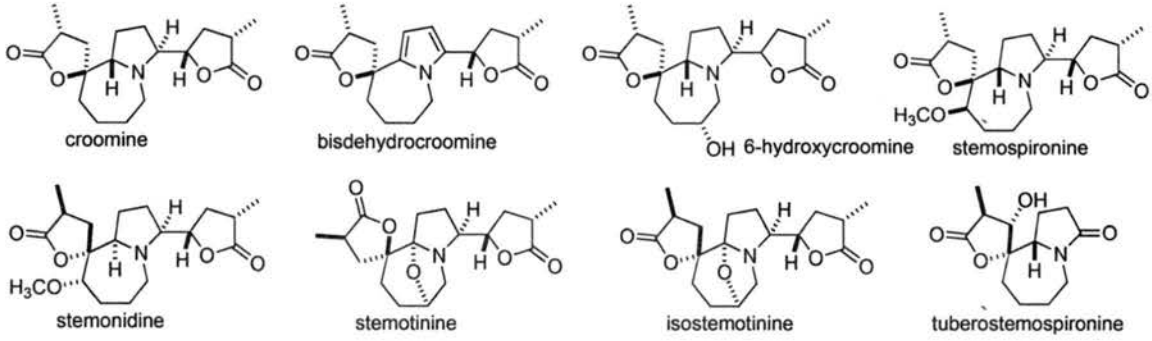


Figure 5. Croomine-Type Alkaloids

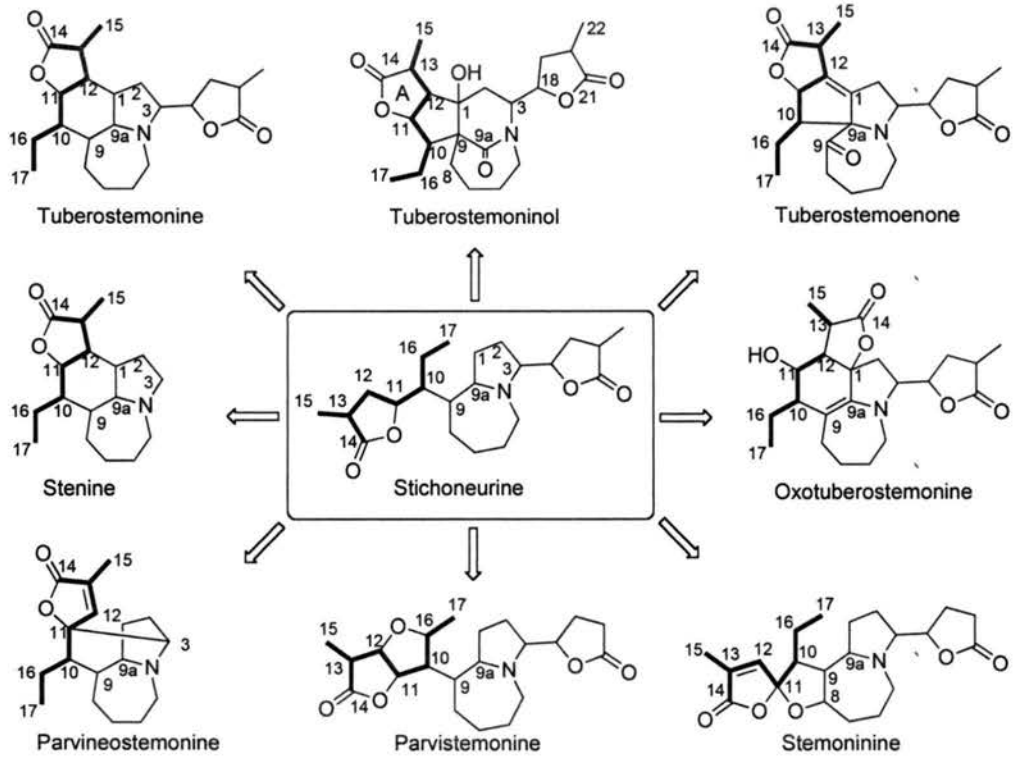


Figure 6. Structural Diversity of Stichoneurine-Type Alkaloids

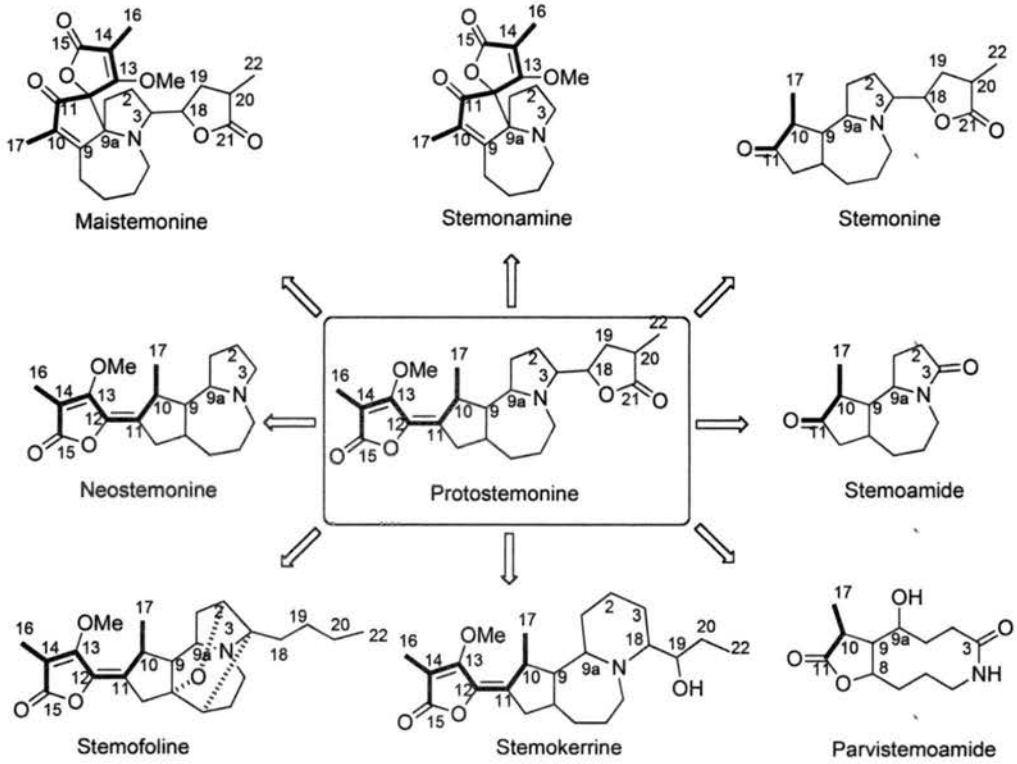


Figure 7. Structural Diversity of Protostemonine-Type Alkaloids

1.1.3 Biological Activities and Structure Activity Relationships

Herbal extracts of various species of genus *Stemona* have long been recognized in China and other southeast Asia countries (Japan, Thailand and Vietnam, for instrance) for a broad range of applications including cough relief, anthelmintics, and insecticides.[1,10,11] Especially, *S. tuberosa* Lour, *S. japonica (Bl.) Miq.*, and *S. sessilifolia (Miq.)*, known as "Radix Stemonae", have been officially listed in the Chinese Pharmacopoeia (2000 edition) as antitussive traditional Chinese medicinal herbs.[12] However, despite their historic medicinal applications, until recent years only some preliminary investigations had been reported mostly without an accurate evaluation of the activities[4,9,10,11,13] (except some insecticidal alkaloids). In the 2000's, detailed systematic bioassay studies of stemona species started to appear, aiming to allocate specific biological effects to certain species and active compounds, as well as to understand the SARs and the modes of action.[2,4,14,15]

1.1.3.1 Insecticidal Activities

As early as in 1975, Sakata et al. reported marked insecticidal activity of fresh leaves of *S. japonica* against fourth instar larvae of the silkworm *Bombyx mori* L, with stemofoline (**Figure 8**) exhibiting the most activity in feeding experiments with artificial diet, 10^4 times as toxic as stemospironine (**Figure 5**) with a croomine-type structure.[16] But surprisingly, stemofoline was completely inactive against fifth instar larvae of the cabbage army worm *Mamestra brassicae*.[17]

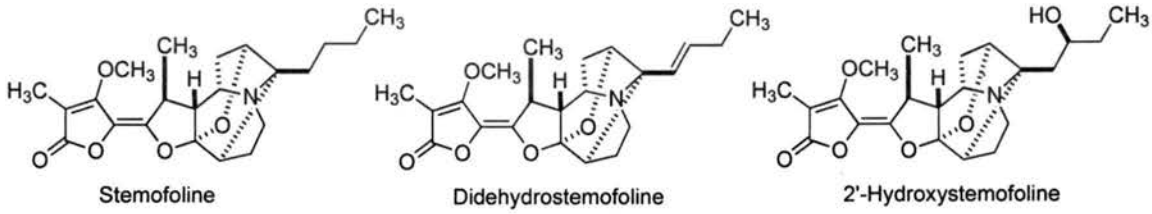


Figure 8. Stemofoline Derivatives Tested in Bioassay

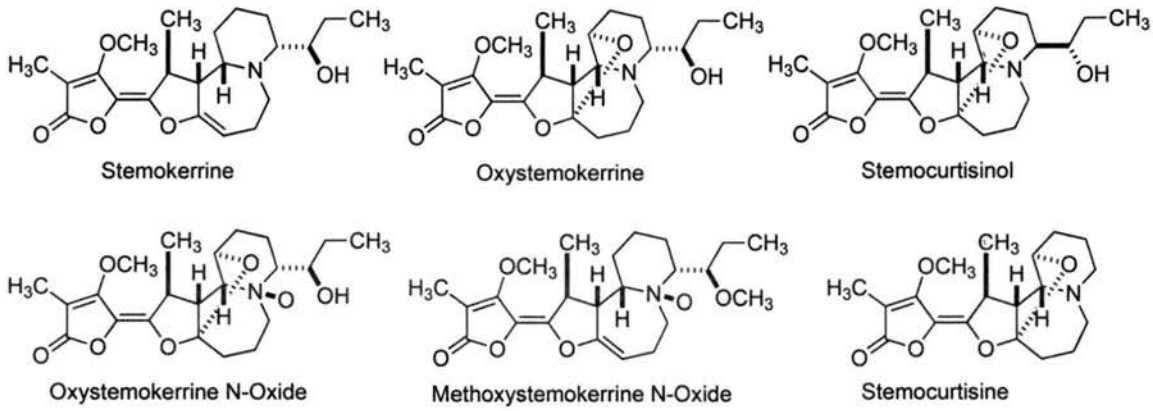


Figure 9. Stemokerrine Derivatives Tested in Bioassay

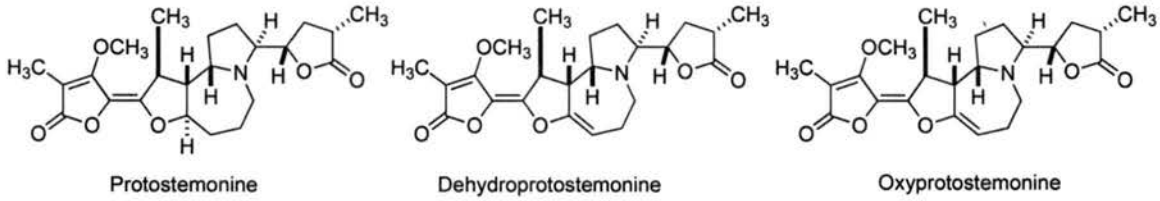


Figure 10. Protostemonine Derivatives Tested in Bioassay

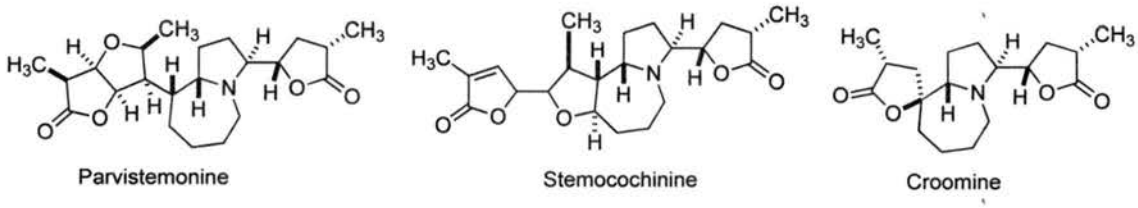


Figure 11. Derivatives Lack the Unsaturated Lactonic 4-Methoxy-3-methyl-2-furanone Unit

In 2006, Greger el al. reported that on the basis of chronic feeding bioassays with neonate larvae of the cotton leaf worm *Spodopera littoralis* Boisduval (Lepidoptera, Noctuidae) reared on artificial diet, derivatives of protostemonine-type (**Figure 7**) from methanolic leaf and root extracts of *S. collinsae*, *S. cochinchiensis*, some provenances of *S. curtisii,* and *S. kerrii* displayed pronounced insecticidal activities.[4] The stemofoline derivative (**Figure 8**) didehydrostemofoline, accumulated in *S. collinsae*, showed the highest activity with an LC_{50} value as low as 0.8 ppm, which is significantly more active than that of the well-known natural insecticide azadirachtin (LC_{50}= 8.2 ppm). A comparison of the LC_{50} values of didehydrostemofoline, stemofoline, and 2'-hydroxystemofoline demonstrated the structure–activity relationships: the unsaturated *n*-butenyl side chain displayed the strongest toxicity, while saturated *n*-butyl side chain diminished the activity, and the free hydroxyl group at C-2' of the side chain caused a significant decrease of activity. In the same bioassay studies, pyridoazepine derivatives (**Figure 9**) stemokerrine (LC_{50} = 58.4 ppm), oxystemokerrine (LC_{50} = 5.9 ppm), and oxystemokerrine *N*-oxide (LC_{50} = 12.5 ppm) displayed strong insecticidal activity. It appeared that the oxygen bridge in oxystemokerrine and oxystemokerrine *N*-oxide increased the activity compared to that of stemokerrine, and the lack of the propyl side chain in stemocurtisine caused a dramatic drop of the activity to an LC_{50} of 148.9 ppm. However, the formation of the open side chain and oxygen bridge of stemofolines and stemokerrines appeared not to be a prerequisite for high insect toxicity: protostemonine (**Figure 10**) and dehydroprotostemonine, with a lactone ring attached at C-3 without an oxygen bridge, also displayed strong activity. Surprisingly, a significant decrease was observed in oxyprotostemonine containing an oxygen bridge. However, this compound

was shown to posses a significant larvicidal activity on mosquito larvae of Anopheles minimus with an LC_{50} of 4 ppm, more effective than stemocurtisine (**Figure 9**) with 18 ppm, and stemocurtisinol (**Figure 9**) with 39 ppm. Comparing the insecticidal and growth inhibitory activities known so far from the alkaloids listed above, it became apparent that the unsaturated lactonic 4-methoxy-3-methyl-2-furanone unit plays a crucial role. In fact, very weak or even no activity was observed in tuberostemonine (**Figure 6**) and neotuberostemonine as well as in stemocochinine (**Figure 11**) and parvistemonine (**Figure 11**), where that ring was either modified or lacking. However, in a fifth instar larvae *of S. littoralis* leaf-disk choice bioassay, tuberostemonine demonstrated strong repellent activity (0.1 $\mu g/cm^2$), a comparable level to that of azadirachtin from the neem tree, *Azadirachta indica* A. Juss., Meliaceae, but much higher level than that of Pyrethrum extract, which showed no activity at 0.5 $\mu g /cm^2$.

Table 1. Insecticidal (LC_{50}) and Growth Inhibitory Activities (EC_{50}) of *Stemona* Alkaloids Compared with Commercial Azadirachtin Against Neonate Larvae of *Spodoptera littoralis*[4, 2, 17]

Alkaloids	LC_{50}	(95%FL) ppm	EC_{50}	(95%FL) ppm
Didehydrostemofoline	0.8	0.7-1.1	0.5	0.3-0.6
Stemofoline	2.0	1.6-2.6	1.5	1.3-1.6
2'-hydroxystemofoline	30.3	26.6-34.7	38.5	7.3-182.2
Oxystemokerrine	5.9	4.2-9.1	0.7	0.1-0.3
Oxystemokerrine *N*-oxide	12.5	7.2-22.5	0.4	0.1-0.9
Stemokerrine	58.4	48.0-73.0	14.1	12.0-16.3
Stemocurtisine	148.9	92.8-336.7	96.1	61.3-218.7
Methoxystemokerrine *N*-oxide	~150		16.3	10.0-27.3
Dehydroprotostemonine	6.1	4.3-9.1	0.8	0.4-1.3
Protostemonine	17.7	13.2-24.8	2.2	1.5-2.9
Oxyprotostemonine	159.0	99.2-838.8	46.9	29.9-75.2
Croomine	~120		~20	
Stemospironine				
Stemocochinine	170.4	150.4-199.5	60.9	37.9-95.8
Parvistemonine	~350		162.7	133.3-233.5
Tuberostemonine	>500		~500	
Neotuberostemonine	>500		>500	
Azadirachtin	8.2	6.6-11.6	0.04	0.02-0.07

Table 2. Larvicidal Activity of *Stemona* Alkaloids from *S. curtisii* on Mosquito Larvae (*Anopheles minimus HO*) Using the WHO Method[18]

Alkaloids	LC_{50} (ppm)
Stemocurtisine	18
Stemocurtisinol	39
Oxyprotostemonine	4

1.1.3.2 Antitussive Activities

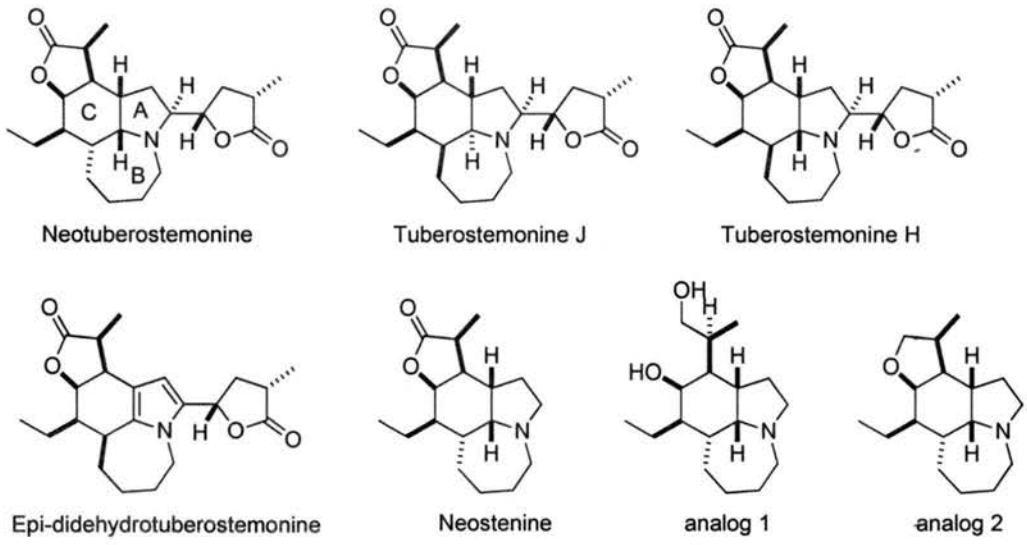


Figure 12. Five Alkaloids in An Antitussive Activity Directed Fractionation

To date, only a few derivatives of the stichoneurine-type have been tested in bioassays specifically for the well-known antitussive activities. In 2003, Lin et al. reported that bioactivity-directed fractionation of the crude extracts of *Stemona tuberosa* led to the isolation and characterization of four unknown stenine-type *Stemona* alkaloids: tuberostemonine J, tuberostemonine H, epi-bisdehydrotuberostemonine, and neostenine,

together with the known neotuberostemonine.[14a] On the citric acid-induced guinea pig cough model, tuberostemonine J and neostenine exhibited the strongest activity with 85% (ID_{85}) and 77% (ID_{77}) inhibition of cough episodes on a single molar dose of 133 μmol/kg (i.p.). The estimated ID_{50} of 66±7 μmol/kg, i.p. for tuberostemonine J was comparable to 53±14 μmol/kg, i.p. for codeine, one of the most commonly used potent antitussive agents. However, to produce a similar potency, the oral dosage was significantly higher than the i.p. dosage. Its ID_{85} value for the oral administration was

Table 3. Comparison of Antitussive Activity of 7 Compounds on Guinea Pig Cough Model[14a]

Alkaloids	No. Animals	Dose (μmol/kg)	No. Cough Episode	%1st Challenge
Intraperitoneal administration				
Vehicle	9		18.0±3.4	98.7±16.7
Neotuberostemonine	5	133	2.2±1.1	13.5±6.1
Tuberostemonine J	5	133	8.6±2.5	54.5±10.5
Tuberostemonine H	5	133	7.4±2.8	42.5±13.9
Neostenine	9	133	3.6±0.9	23.0±5.5
Analog **1**	5	133	7.4±2.0	48.9±8.5
Analog **2**	6	133	12.3±3.6	62.1±12.1
Oral adminisration				
Vehicle	9		14.9±1.5	99.0±11.2
Neotuberostemonine	5	400	2.4±1.2	16.1±6.6
Epi-didehydrotuberostemonine	6	400	14.8±1.4	101.4±19.0

found to be 400 μmol/kg (equal to 150 mg/kg). Tuberostemonine H, epi-disdehydrotubrostemonine, and analogs **1** and **2** with different substitutions at ring C displayed weaker activity in the studies (**Table 3**). These results indicated that the saturated tricyclic pyrrolo[3,2,1-jk]benzazepine moiety, consisting of a pyrrolidine ring (A), an azepine ring (B), and a cyclohexane ring (C), was the primary key nucleus of stenine-type *Stemona* alkaloids contributing to antitussive activity. All *cis* configurations at ring junctions represent the optimal configuration. The substituted groups in both rings A and C may markedly influence the potency of antitussive activity. Tuberostemonine J, with an α-methyl-γ-butyrolactone substitution at the C-3 position in ring A and an α-methyl-γ-butyrolactone fused with ring C at the C-11 and C-12 positions, produced the most potent antitussive activity. In a study of action of mode by Liao et al. in 1997, a water extract of "Bai Bu" was examined for the spasmolytic effect on the guinea-pig tracheal smooth muscle in vitro.[19] They showed that the effect was not due to an activation on β-adrenoceptors. Receptor binding assays indicated that the extract interacted with the muscarinic receptors and the dihydropyridine binding site of L-type Ca^{2+} channels, but not with the histamine H_1 receptors. In this study no determination of isolated active compounds has been carried out. In a continuing study of the oral effectiveness and pharmacokinetic properties of the main bioactive *Stemona* alkaloids in *Stemona tuberosa* lour, the same group in 2005 reported the investigation of intestinal absorption of two alkaloids, neotuberostemonine and neostenine, using the human colon adenocarcinoma monolayer cell line Caco-2 model.[15] The results demonstrated that both alkaloids exhibit good intestinal absorptions ($P_{app(AB)}$=12.03±1.14x10^{-6} cm/s and 9.27±0.79x10^{-6} cm/s, respectively), and thus are likely to be orally active components

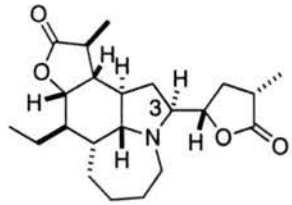
responsible for the clinical outcomes of herbal *S. tuberosa*. Furthermore, both alkaloids were identified to be P-glycoprotein substrates and have a transport preference from the basolateral to apical direction with efflux ratios 2 and 3. Cyclosporin A dose-dependently inhibited the secretory permeability of these alkaloids and abolished their active efflux transport.

In the most recent antitussive tests of species *S. tuberosa* collected from different areas of China and with different chemical profiles, But et al.[14b] found that all species demonstrated different degrees of activity, with the species containing croomine and stemoninine (**Figure 5**) displaying the strongest activity, suggesting that antitussive activity was not limited to only stenine-type *Stemona* alkaloids.

1.1.3.3 Other Activities

In preliminary anti-tumor tests, crude extracts of *S. tuberosa* and *S. collinsae* were compared for their effects on medullary thyroid carcinoma cells. Both extracts altered the phenotype of the cells from originally aggregating cells towards single-cell suspensions. Very interestingly and attractively, the extract of *S. tuberosa* considerably enhanced apoptosis, whereas *S. collinsae* only moderately increased the apoptotic effect. Since this type of cancer cell is known to be relatively insensitive to chemo- or radiation therapy, it was believed that this marked activity could offer a new approach towards successful chemotherapy.[20] In this study, it was not clear that to what extent *Stemona* alkaloids were involved in the effect of the root extracts and what the causative compounds were. Further studies will have to be done for resolution of these issues.

1.2 Tuberostemonine



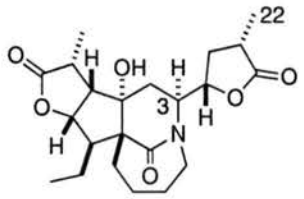
Tuberostemonine

1

The isolation of tuberostemonine (**1**), the major component of *S. tuberosa* Lour, was first reported by Suzuki in 1934, then by Schild from *S. sessilifolia* Franch in 1936. Its bond connectivities were determined by Götz's and Feniak's groups in the 1960's based on chemical investigations, and the final stereochemical assignment was completed by Uyeo and coworkers in 1967, based on the X-ray structure of tuberostemonine's methobromide salt.[21] No complete reliable spectroscopic data had been reported to date.[22] Even in 2002 when Wipf et al. reported the first total synthesis of tuberostemonine (**1**), they still failed to get successful ^{1}H and ^{13}C NMR data because of the unusual lability of this natural product.[23a]

According to Wipf et al., it was hypothesized that its high rate of decomposition property derived from the spatial disposition of the nitrogen lone pair. The chair like six-membered ring of tuberostemonine (**1**) forces an anti-orientation of the nitrogen lone pair and the methine hydrogen at C-3. The preference for the chair-like conformation of **1** was confirmed by the solid state structure of this compound.[23a] The strong influence of conformational properties on the rate of oxidation α to a tertiary nitrogen atom is nicely precedented in the chemistry of Rauwolfia alkaloids.[23b] The conversion of tuberostemonine (**1**) to didehydrotuberostemonine was succeeded through silver oxide reported by Lin et al.[22b], and repeated by Wipf and coworkers.[23a]

1.3 Tuberostemoninol



Tuberostemoninol

2

1.3.1 Isolation and Structure Determination

Tuberostemoninol (**2**) was a minor component isolated from species *S. tuberosa* Lour. In 1994, Lin et al. reported that 53 mg of **2** was obtained from 25 kg of the chloroform extract of the roots of *S. tuberosa* Lour (purchased from a local distribution source of medicinal material in May county, Guangdong Province, China) after repeated chromatography on silica gel.[26] Tuberostemoninol (**2**), mp 217-219 °C, had the molecular formula $C_{22}H_{31}NO_6$ ($[M]^+$ m/z 405.2170) with eight degrees of unsaturation. The strong IR absorptions at 3520, 1770, and 1679 cm^{-1} in combination with ^{13}C NMR carbonyl region signals at δ 185.00 (s), 180.63 (s) and 179.09 (s) suggested the presence of two saturated γ–lactones, a lactam and a hydroxyl group. The entire structure was suggested based on mass spectra, ^1H-^1H COSY, and HMBC. The relative configuration was proposed on the basis of ROESY and *J* values in combination with the Karplus equation. The relative configuration of the C-22 methyl γ-lactone ring annexed to C-3 was identified as having an α-orientation from biogenetic relationships in the *Stemona* alkaloids. The stereostructure was finally confirmed by X-ray diffraction. The absolute stereochemistry of this alkaloid has not been determined. Tuberostemoninol has a novel 1-azabicyclo[4.3.1]decan-10-one skeleton different from the most commonly observed octahydro-1*H*-pyrrolo[1,2-*a*]azepine skeleton in *Stemona* alkaloids, and this novel

skeleton is rarely observed in natural products. Only three of the *Stemona* alkaloids which have been isolated recently share a similar carbon skeleton with tuberostemoninol: neotuberostemoninol (**3**) with (α-H-11, α-H-12), isolated in the same species *S. tuberosa* Lour by Mak et al. in 2002;[27] maireistemoninol (**4**), isolated from *S. mairei* (levl.) Krause in 2007;[6j] and sessilifoliamide (**5**), isolated from *S. sessilifolia* by Takeya and co-workers in 2007.[6k]

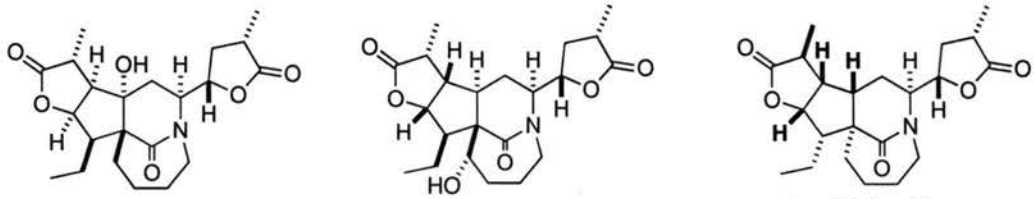


Figure 13. Other *Stemona* Alkaloids with 1-Azabicyclo[4.3.1]decan-10-one Skeleton

1.3.2 Tuberostemoninol's Biogenesis

It is thought that tuberostemoninol (**2**) is biogenetically related to tuberostemonine (**1**),[26,27,1a,23a,4] the major component in *S. tuberosa* Lour and by nature very labile to air exposure with a decay time of hours. It was found that treatment of tuberostemonine (**1**) with a mild oxidant $Hg(OAc)_2$ gave oxotuberostemonine (**6**),[22c] a natural product isolated from the same species *S. tuberosa* Lour. Thus, hypothetical oxidative cleavage of the C-1 and C-9a bond of oxotuberostemonine (**6**) to form dicarbonylic product tuberostemonone (**7**), an aldol reaction, i.e. nucleophilic attack of the α-carbonanion of the C-9a carbonyl group at the C-1 carbonyl group, would provide tuberostemoninol (**2**) (**Figure 14**).[23a]

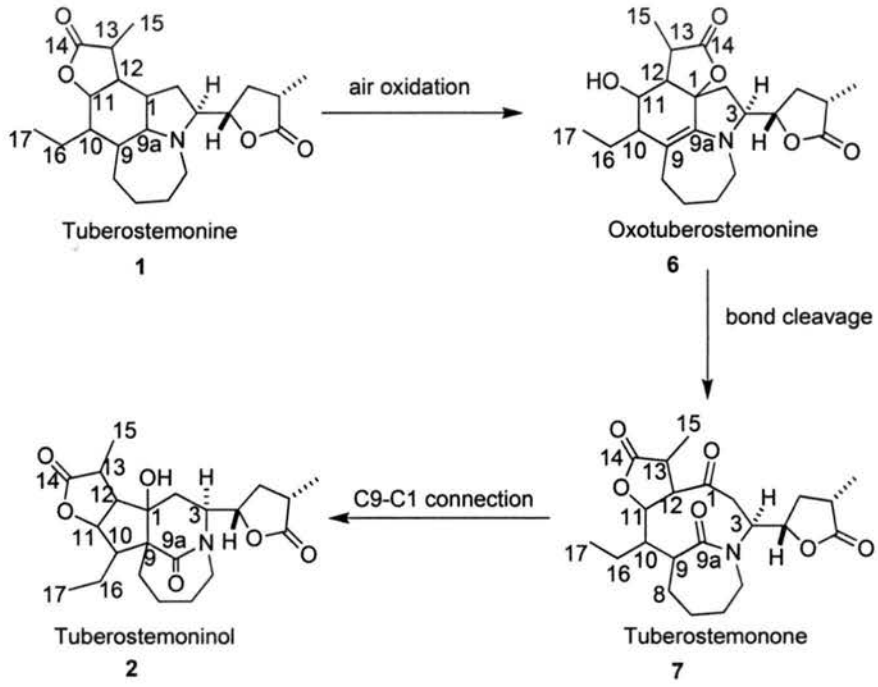


Figure 14. Proposed Biogenetic Relationship Between **2** And **1**

1.4 Previous Synthetic Achievements

In addition to the extensive interests in their broad biological activities and pharmaceutical applications, the structurally intricate and diverse *Stemona* alkaloids have served as inspiring targets for application as well as exploitation of various methodologies and strategies for synthetic organic chemists during the past twenty years. Since the pioneering total synthesis of croomine by Williams' group in 1989, many other total syntheses of *Stemona* alkaloids[28] have been accomplished, including two stichoneurine-type alkaloids (**1**, **8**), five protostemonine-type alkaloids (**12**, **13**, **14**, **15**, **16**), and three croomine-type alkaloids (**9**, **10**, **11**) (**Figure 15**). Structurally, tuberostemoninol (**2**) shares common moieties of either an appended or annexed butyro-lactones with alkaloids **1**, **8**, **9**, **10**, and **11**. However, no synthetic studies have been

reported for this structurally novel alkaloid itself. The next section is a chronological discussion of the synthetic approaches to alkaloids **1**, **8**, **9**, **10**, and **11**.

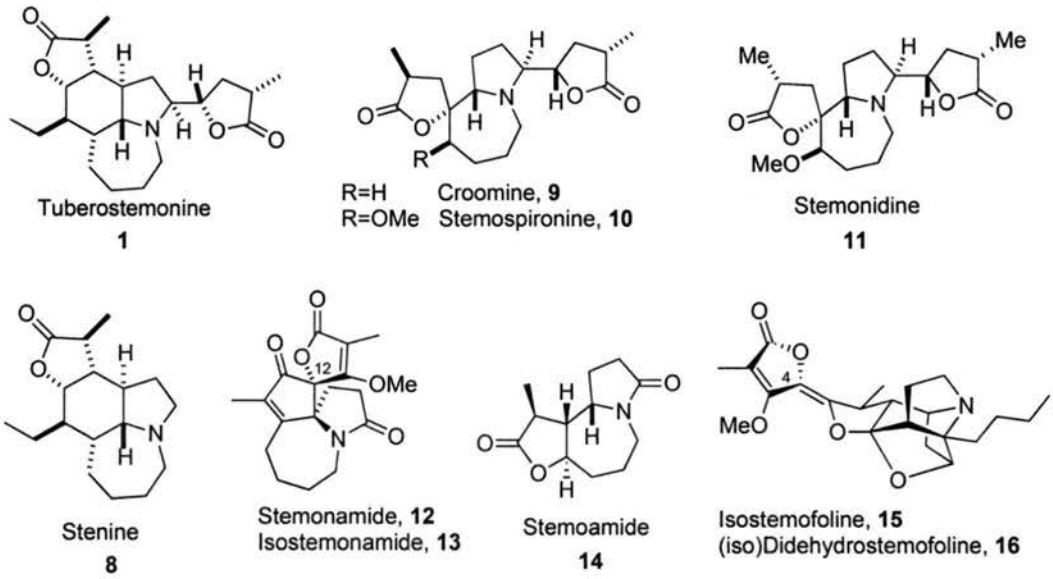


Figure 15. Totally Synthetic *Stemona* Alkaloids

1.4.1 Hart and Chen's Total Synthesis of dl-Stenine

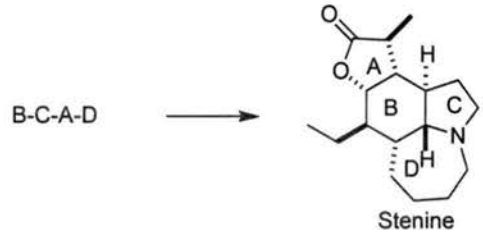


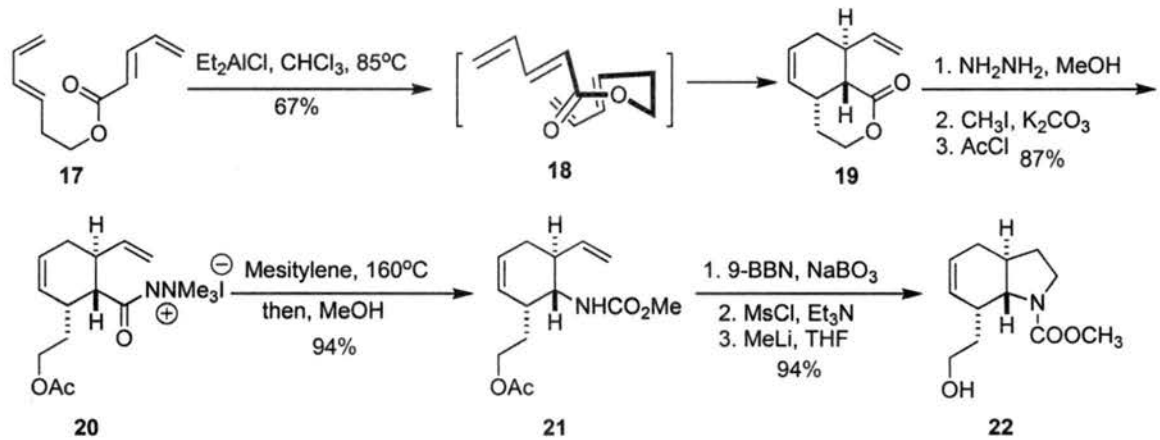
Figure 16. Ring Construction Sequence in Hart and Chen' Stenine Total Synthesis

Hart and Chen reported the first total synthesis of (-)-stenine in a racemic form in 1990.[28c] Their synthesis featured an intramolecular Diels-Alder cyclization to construct the cyclohexane B ring with required functionalities, which was further elaborated to

stenine via Curtius rearrangement, Eschenmoser-Claisen rearrangement, and stereoselective free radical allylation reactions (**Figure 16**). Hart and Chen's synthesis became the foundation for the total syntheses of this molecule and related derivatives from many other groups thereafter.

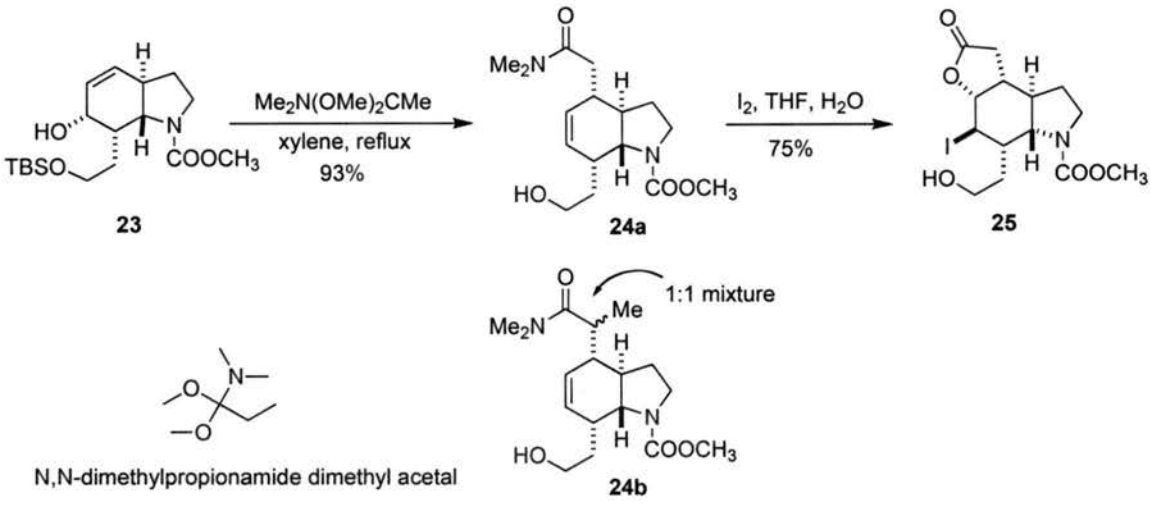
1.4.1.1 An Intramolecular Diels-Alder Cyclization-Aminimide Rearrangement Sequence for BC Ring Construction

Intramolecular Diels-Alder reaction of tetraene 17 (**Scheme 1**) gave only polymerization of the starting material in thermolysis, but under Lewis acid-promoted conditions in chloroform at 85 °C or toluene at reflux, *syn* cycloadduct **19** was obtained as a single isomer in 67% or 49% yield, respectively. In a three-step sequence, aminimide salt **20** was obtained in quantitative yield. Thermolysis of **20** in mesitylene at 160 °C followed by addition of anhydrous methanol to the intermediate isocyanate gave the Hoffman-type rearrangement product carbamate **21**, which was converted to perhydroindole **22** in three steps via hydroboration-oxidation of the double bond, followed by mesylation and intramolecular S_N2 displacement.



Scheme 1. Hart and Chen's BC Ring Construction

1.4.1.2 An Eschenmoser-Claisen Rearrangement-Iodolactonization Sequence for A Ring Formation

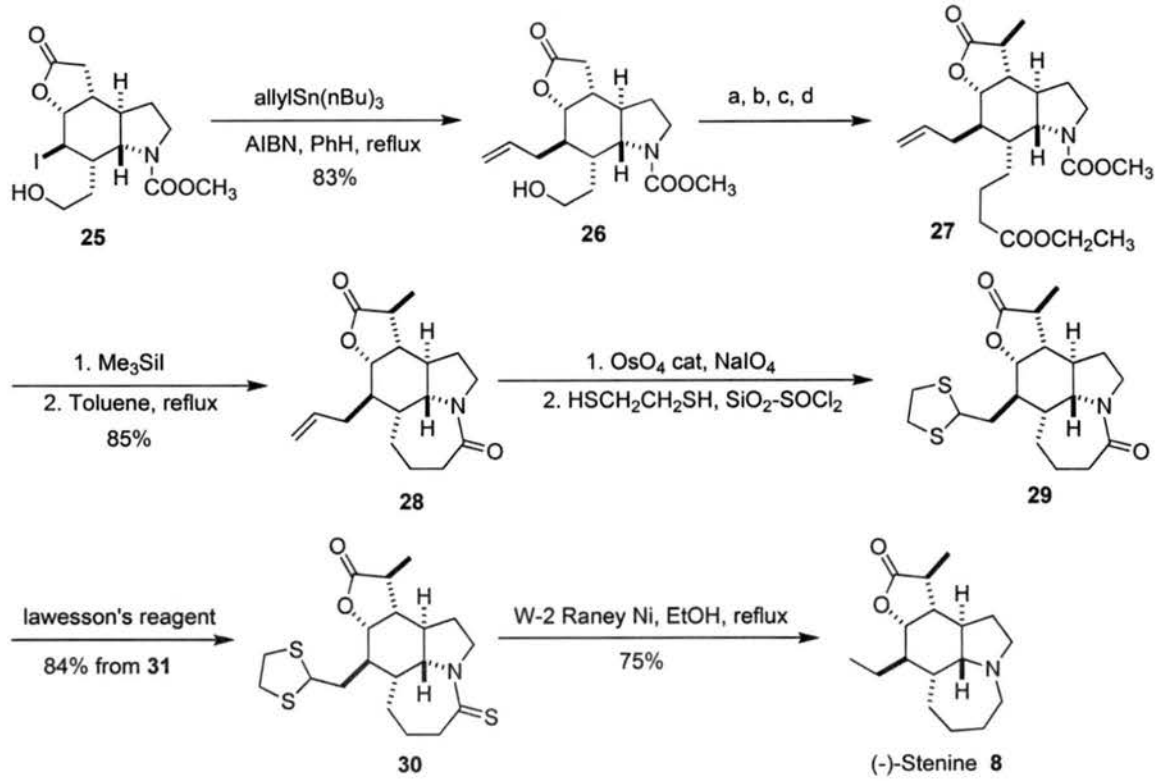


23 **24a** **25** **24b**

Scheme 2. Hart and Chen's A Ring Construction

Allylic alcohol **23** (**Scheme 2**) was treated with *N,N*-dimethylacetamide dimethyl acetal in xylenes to give the Eschenmoser-Claisen rearrangement product (**24a**) in high yield. The C-14 methyl group of stenine could also be introduced at this stage. Treatment of **23** with *N,N*-dimethylpropionamide dimethyl acetal, however, gave the tentatively assigned structure (**24b**) as a 1:1 mixture of diastereomers. This approach was not further investigated, since the problem was solved in another manner at a later stage. Thus, **24a** was converted to the *syn* annexed iodolactone (**25**) with iodine in aqueous tetrahydrofuran to set the stage for introduction of the ethyl group.

1.4.1.3 Ethyl Group Introduction and D Ring Formation



a) LDA, MeI; b) Swern oxidation; c) $Ph_3P{=}CHCO_2Et$; d) Red-Al

Scheme 3. Hart and Chen's Ethyl Group and D Ring Construction

Free-radical Keck allylation of iodide **25** (**Scheme 3**) gave compound **26**, two carbon homologation of which installed the required chain for azepine ring formation. Removal of the methyl carbamate with iodotrimethylsilane followed by reflux in toluene afforded the lactam (**28**). At this stage, the allyl group was contracted to ethanedithiol ethyl acetal and the lactam carbonyl converted to thiocarbonyl with Lawesson's reagent. Finally, reduction of the thiol compound (**30**) with Raney Ni reagent completed the total synthesis of racemic stenine in a total of 28 steps with 7.2% overall yield.

1.4.2 Wipf's Asymmetric Total Synthesis of (-)-Stenine and (-)-Tuberostemonine

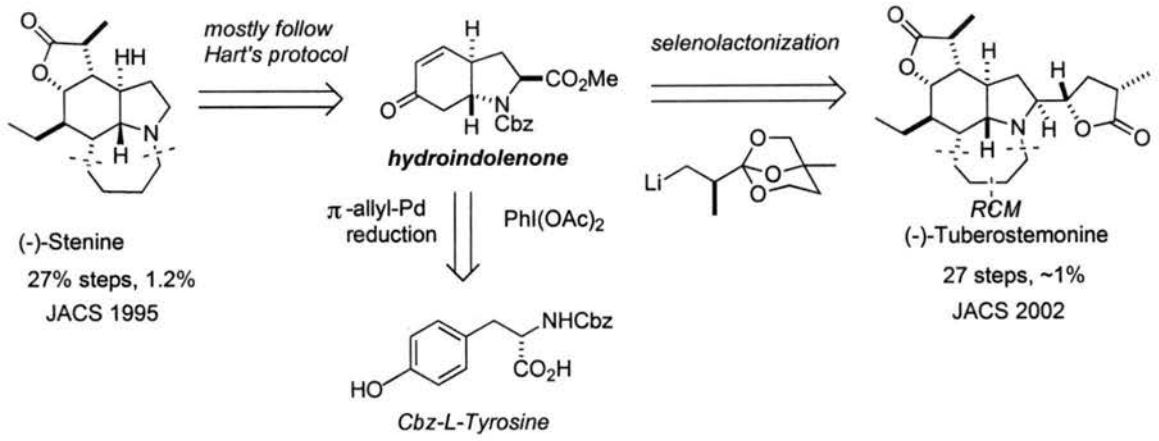


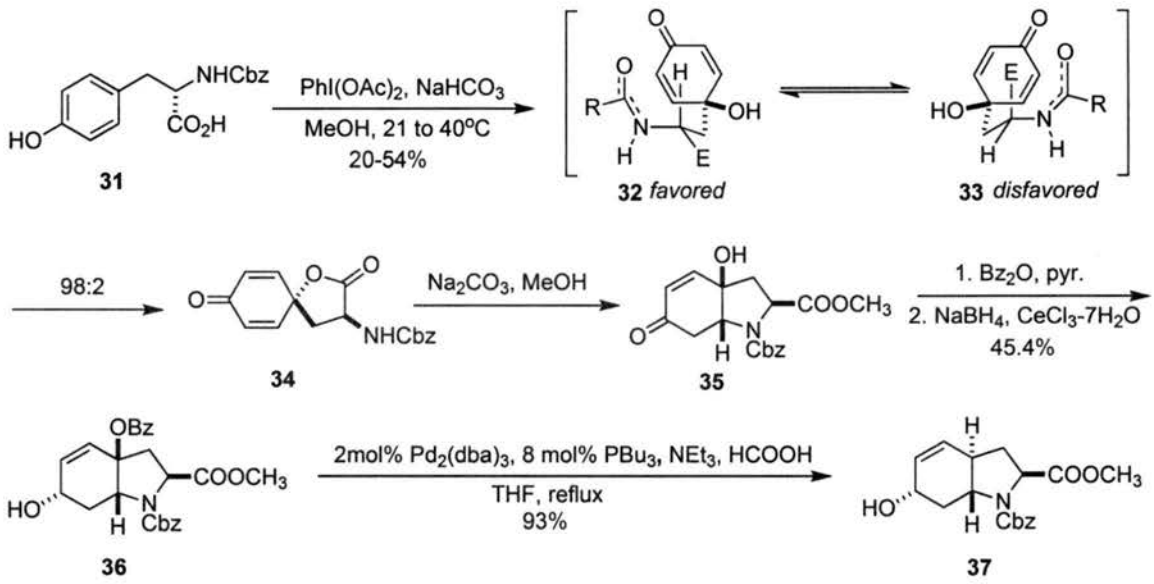
Figure 17. Wipf's Retrosynthetic Analysis of Stenine and Tuberostemonine

Retrosynthetically, Wipf and coworkers envisaged that both stenine and tuberostemonine could derive from the highly functionalized perhydroindolenone shown in Figure 17. Following their successful preparation of this core intermediate in 1992, they were able to achieve the first two asymmetric total syntheses of (-)-stenine and (-)-tuberostemonine in 1995 and 2002, respectively.[28a, 28d]

1.4.2.1 Oxidative Spirocyclization and π-Allylpalladium Reduction Sequence for BC Ring Formation

L-Cbz-tyrosine (**31**, **Scheme 4**) was converted to bicycle **35** in fair yield via spirolactone **34** when treated with oxidant iodobenzene diacetate in methanol under basic conditions. The scalability of this reaction was limited when methanol was used as the solvent. The highest yield (54%) was obtained on a 500 mg scale with an optimum concentration of 0.08 M. Their continuing investigation revealed that nitromethane was best suited for larger scale reactions (100 g) at higher concentrations (0.3 M) with a yield

of 35%. Bz_2O protection of the tertiary alcohol followed by a Luche reduction afforded the allylic alcohol (**36**). The π-allylpalladium reduction of **36** gave the *trans* fused bicycle **37**, the scaffold for installation of the rest rings and stereocenters in stenine and tuberostemonine. The mechanism of the ring junction conversion is shown below in Figure 18.



Scheme 4. Wipf's BC Ring Formation in Stenine and Tuberostemonine

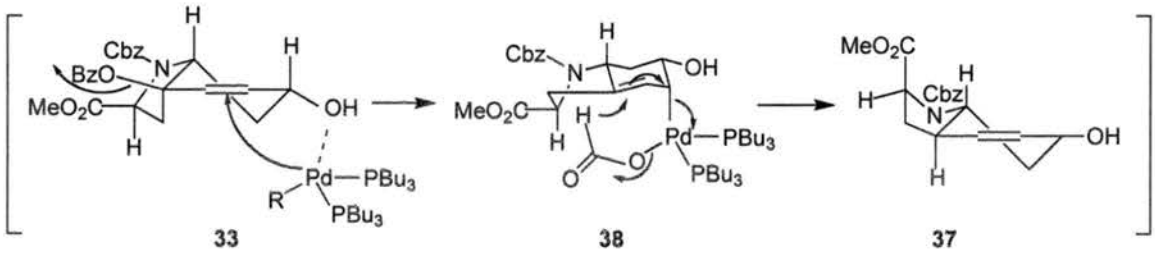
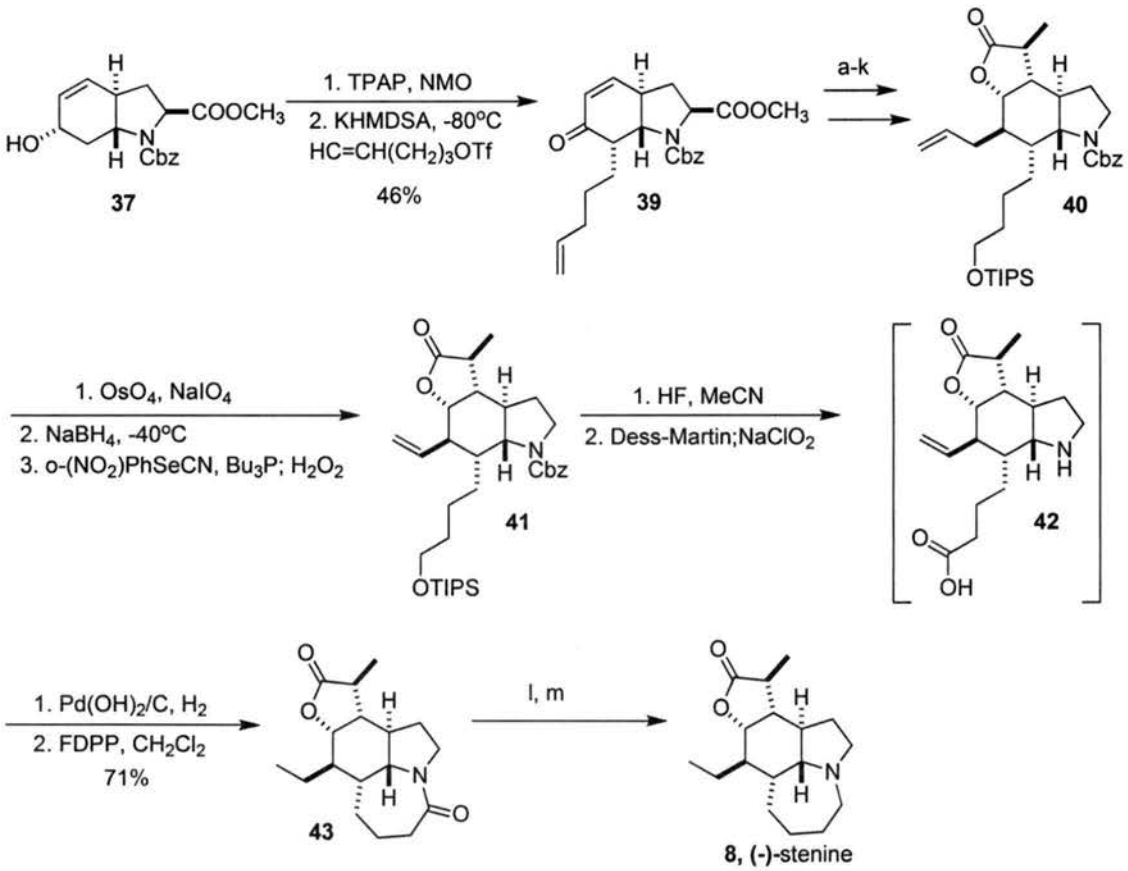


Figure 18. Stereochemistry Outcome from π-Allylpalladium Reduction

1.4.2.2 Azepine D Ring Formation and Completion of Stenine Synthesis

For the seven-membered D ring formation, Wipf used an α-alkylation of ketone **39** to introduce the needed carbon arm (**37** to **43, Scheme 5**). They concluded that the low



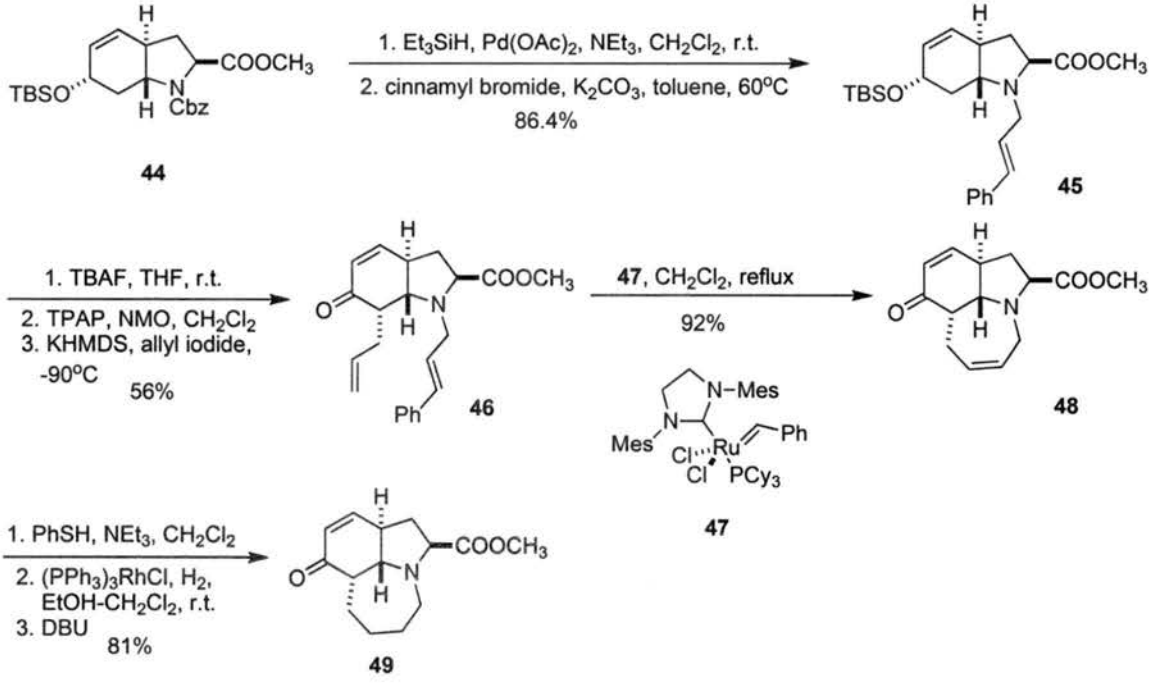
a. $NaBH_4$, $CeCl_3 \cdot 7H_2O$; b. $H_3CC(OMe)_2NMe_2$, 130°C; 77% c. AD-mix β, $NaIO_4$; d. $NaBH_4$; e. TIPSCl, DMAP; 76% f. LiOH, H_2O-THF; g. $PhOPOCl_2$, NEt_3, PhSH; h. Bu_3SnH, AIBN, 130°C; 70% i. I_2, pH 5.5; j. $AllylSnBu_3$, AIBN; 77% k. LDA•HMPA, MeI; l. Lawesson's reagent; m. Raney-Ni, EtOH; 73%

Scheme 5. D Ring Construction in Stenine and Completion of Synthesis

yield (51% based on recovered starting material) of this reaction was due to the low reactivity and unstability (possibly due to β-elimination of the carbamate) of the cross-conjugated dienolate generated in situ. Construction of lactone A ring and introduction of the allyl group in **40** following Hart's protocol was achieved in 11 steps from bicyclic

enone **39**. Allyl carbon chain contraction was realized by a Johnson-Lemieux oxidation, reduction, and Grieco-elimination sequence to provide vinyl compound **41**. Closure of the azepine, the last remaining ring, was initiated by desilylation and oxidation of the resulting alcohol to acid by sequential treatment with Dess-Martin periodinane and sodium chlorite (**41** to **42**). Without purification, the resulting acid **42** was directly subjected to hydrogenation and cyclization with coupling reagent FDPP to give lactam **43**. Decarbonylation of **43** finally completed the total synthesis in a total of 27 steps with 1.2 % yield.

1.4.2.3 Ring Closing Metathesis for Azepine D Ring Formation in Tuberostemonine

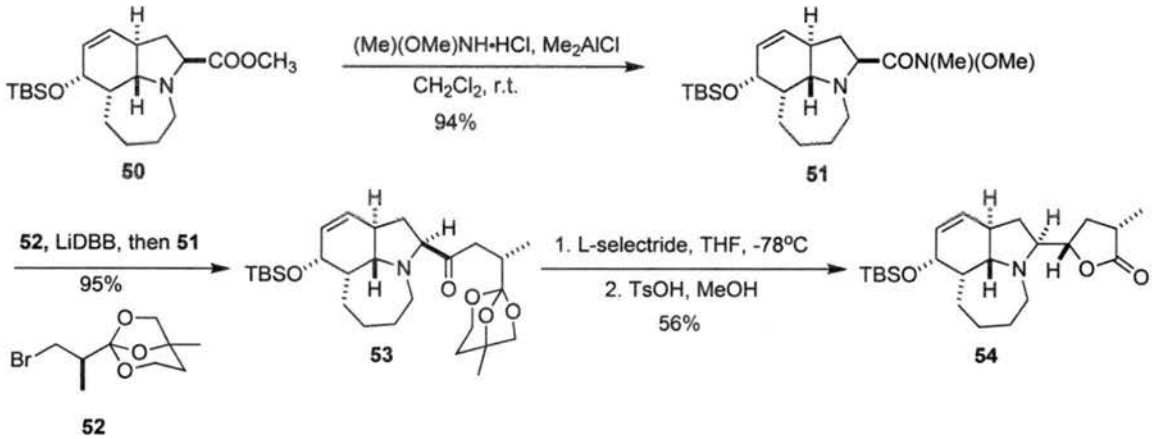


Scheme 6. RCM Reaction

In Wipf's synthesis of tuberostemonine, the azepine was constructed by a ring closing metathesis approach. Triethylsilane deprotection of the carbamate followed by cinnamyl bromide allylation gave intermediate **45** (**Scheme 6**), which was further elaborated to **46** through stereoselective (>95% dr) axial dienolate alkylation with KHMDS and allyl iodide. The ring closing metathesis was performed in the presence of 2-5 % of ruthenium catalyst **47** at reflux in dichloromethane. The resulting double bond in azepine **48** was then selectively reduced to give tricyclic compound **49** by transient protection of the enone double bond with thiophenol.

1.4.2.4 Right Side Butyro-Lactone E Ring Attachment in Tuberostemonine

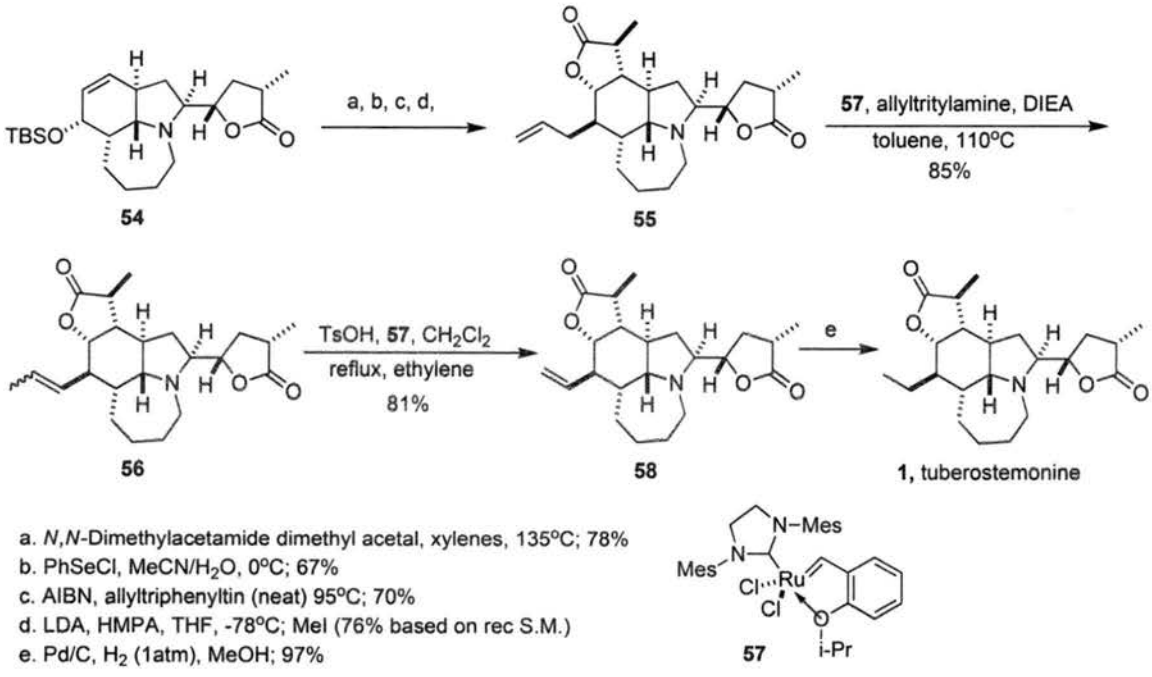
The ester functionality of **50** was converted to Weinreb amide **51** (**Scheme 7**), followed by the addition of the lithiated ortho ester resulting an excellent yield of ketone **53**. The carbonyl group was subsequently reduced with L-Selectride to give a 7:1 ratio of diastereomeric alcohols favoring the Felkin-Anh product. Acid-catalyzed deprotection of the ortho ester and silyl ether groups followed by spontaneous cyclization afforded nicely the desired lactone (**54**) as a single isomer.



Scheme 7. Butyrolactone E Ring Attachment

1.4.2.5 Completion of Total Synthesis of (-)-Tuberostemonine

The completion of the total synthesis included installation of the butyrolactone A ring and introduction of the ethyl group in a very similar manner to that of Hart and Chen's synthesis, as well as the access in Wipf's synthesis of stenine. Since the previously successful oxidative chain contraction of the allyl group to ethyl group failed, they developed a new method for this transformation. They first isomerized the allyl group to an internal alkene **56** (**Scheme 8**) with Grubbs II catalyst, then performed an ethylene cross-metathesis with Ru catalyst **57** to access the vinyl compound **58**, which was easily transformed to the final target (-)-tuberostemonine. Thus, **1** was first synthesized asymmetrically in 28 linear steps with ~1 % yield and a total of 37 steps with 0.7% overall yield if the 9 step synthesis of the homoenolate equivalent of the β-bromo ABO-ester (**52**) was included.



Scheme 8. Completion of Total Synthesis

1.4.3 Morimoto's Stereo-Controlled Total Synthesis of Stenine

Shortly after Wipf's asymmetric total synthesis of (-)-stenine, Morimoto and coworkers reported their stereocontrolled total synthesis of (-)-stenine.[28e] Strategically, their ring construction sequence was the same as that of Hart and Chen's (**Figure 16**). They also used an intramolecular Diels-Alder reaction to build up the cyclohexane B ring, however in an asymmetric manner (**Figure 19**).

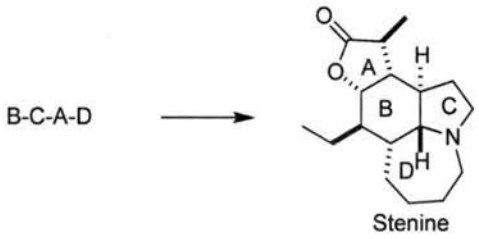


Figure 19. Morimoto's Ring Construction Sequence

1.4.3.1 Asymmetric Intramolecular Diels-Alder Cycloaddition for B Ring Formation

Intramolecular Diels-Alder reaction of triene **59** (**Scheme 9**), possessing an oxazolidinone chiral auxiliary, proceeded smoothly in the presence of dimethylaluminum chloride to provide the bicyclic compound (**60**) with good facial and complete *endo* selectivities (**60**/B ring antipode 10:1). The good diastereoselectivity may be interpreted by consideration of the transition state (**Figure 20**). According to the author, triene **59** adopted a more stable chelated configuration in the presence of aluminum Lewis acid and an s-*cis* conformation of the α,β-unsaturated carboximide moiety as shown below. When the diene approaches the dienophile from the less hindered backside, the *endo* transition state would be more favored than the *exo* transition state because of less steric interactions.

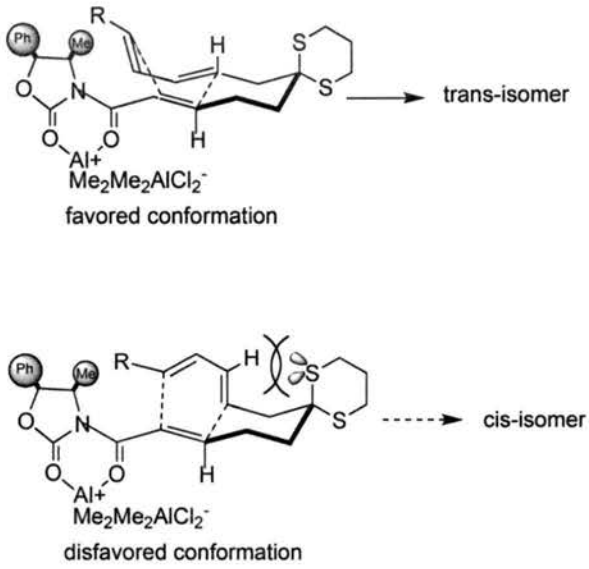
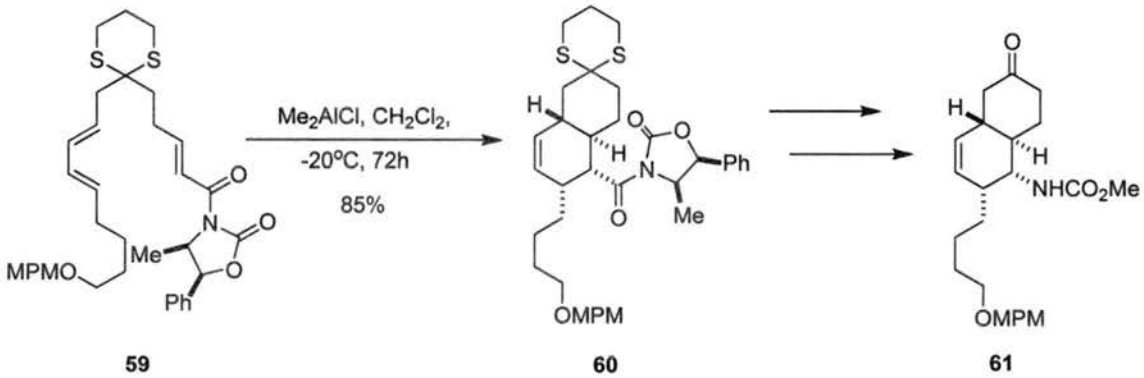


Figure 20. Plausible Transition State Explaining the *endo* Product[28e]

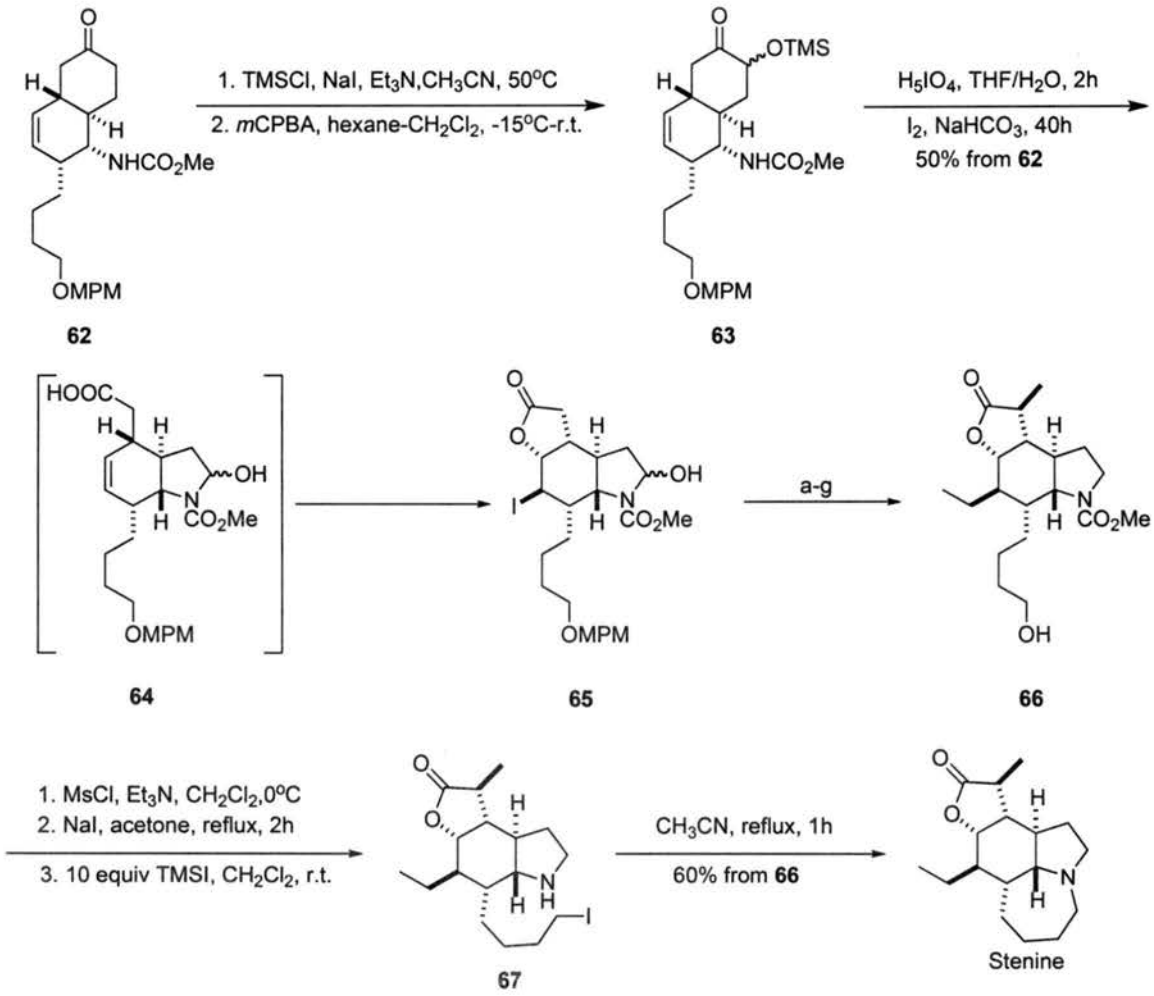
Cycloadduct **60** was converted to bicyclic ketone **61** in a relatively long sequence (5 steps) including desulfurization, removal of the auxiliary (3 steps), and a modified Curtius rearrangement to introduce the amine element.



59 **60** **61**

Scheme 9. Morimoto's B ring Construction and Amine Introduction

1.4.3.2 A and C Ring Formation



a. CSA, $CH(OMe)_3$, MeOH, CH_2Cl_2, r.t., 1h; 90% b. allyltributyltin, AIBN, toluene, 80°C, 4h; 80% c. LDA, HMPA, THF, -78°C then MeI; 73% d. Et_3SiH, $BF_3 \bullet OEt_2$, CH_3CN, 0°C; 82% e. cat OsO_4, $NaIO_4$, THF-H_2O, r.t., 1h; 75% f. 1,2-ethanedithiol, $BF_3 \bullet OEt_2$, CH_2Cl_2, -15°C; 81% g. Raney Ni (W-2), EtOH, reflux, 85%

Scheme 10. Morimoto's Completion of Total Synthesis

Lactone A ring introduction utilized an approach other than the Eschenmoser-Claisen-iodolactonization sequence. Since the required side chains for A ring and C ring formation were already introduced at the first stage of synthesis, oxidative cleavage of the

silyl ether ketone **63** (**Scheme 10**) released the carbon chains to give carboxylic acid and simultaneous cyclization of the C ring (**64**). In one pot, iodolactonization of **64** gave iodolactone **65**, which was transformed to **66** using similar methods as those of Hart and Chen.[28c] Alcohol **66** was then converted to iodide **67,** and subsequent iodoamination under reflux in acetonitrile finished the synthesis of stenine in a total of 30 steps with <0.1% yield.

1.4.4 Padwa's Total Synthesis of dl-Stenine

Padwa and coworkers envisioned a different approach from the previous synthesis about ring construction sequence, which all built the hydroindole BC ring first, then the A or D ring. Padwa's synthesis[28f] incorporated the D ring at a very early stage, then used it as a template for setting the remaining rings and stereochemistry (**Figure 21**).

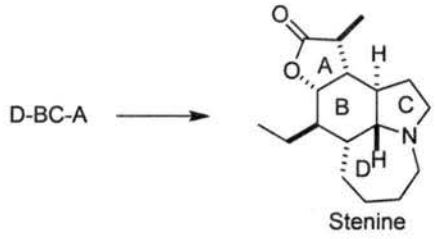
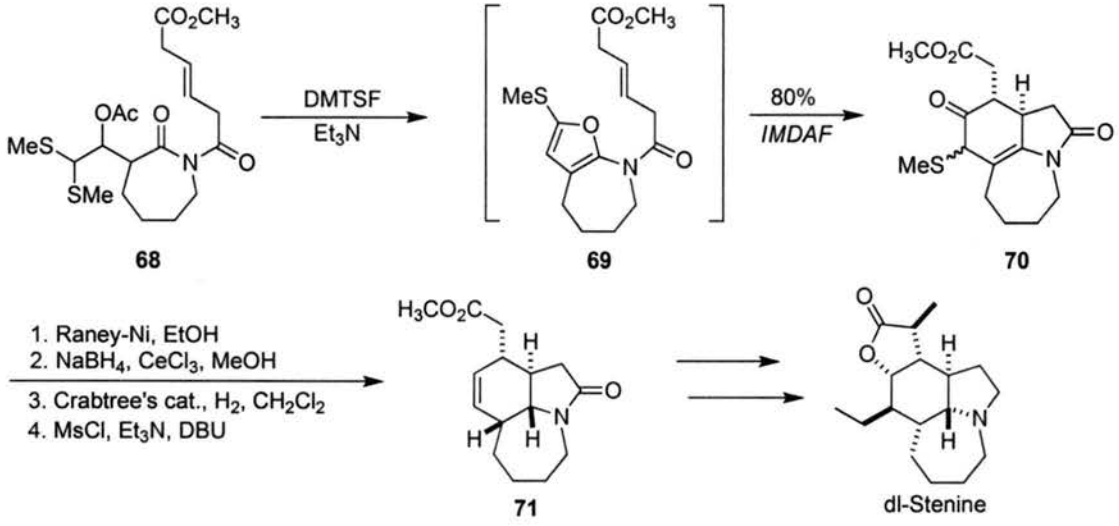


Figure 21. Ring Construction Sequence in Padwa's Synthesis of dl-Stenine

1.4.4.1 Intramolecular Diels-Alder Reaction with Amidofuran (IMDAF)

Since the D ring was chosen as the template, the major tasks were the construction of BC rings. With compound **68** (**Scheme 11**) in hand, using their well-developed intramolecular Diels-Alder reaction with amidofuran (**69**), they were able to obtain tricycle **70** in good yield. In this reaction, dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) induced a thionium-promoted formation of amidofuran (**69**)

from **68**. Intermediate **69** was not isolable and underwent rapid cyclization at room temperature to afford azepinoindole **70** in 80% yield as a 1:1 mixture of diastereomers. They believed that conformational effects imposed by the placement of a carbonyl group within the tether, combined with a rotational bias about the C2-N bond, enhanced the rate of the IMDAF reaction of **69**. Compound **70** was transformed to cyclohexene **71** in a four-step sequence including removal of the methylthio group, reduction of the carbonyl to hydroxyl group, facial selective hydrogenation of the double bond with Crabtree's catalyst, and elimination of the hydroxyl group to give the double bond in **71**. Compound **71** was converted to stenine according to Hart and Chen's sequence for A ring formation and ethyl group introduction.

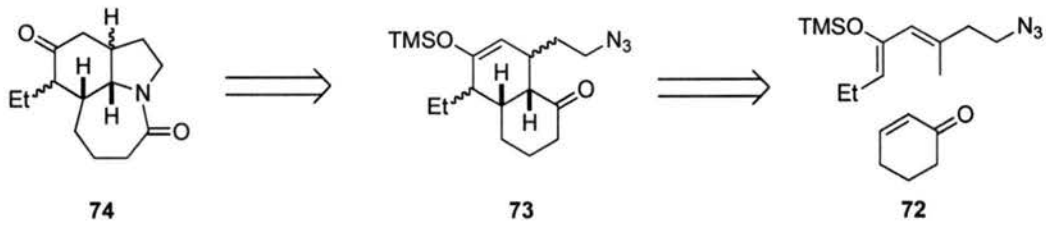


Scheme 11. An IMDA Approach for BC Ring Formation

1.4.5 Aubé's Expeditious Total Synthesis of dl-Stenine

Aubé and coworkers investigated domino reactions that combined an intermolecular Diels-Alder reaction with a Schmidt reaction for a retrosynthetic analysis

of stenine as shown in Figure 22.[28g] With **74** in hand, only a butyrolactone attachment was needed.

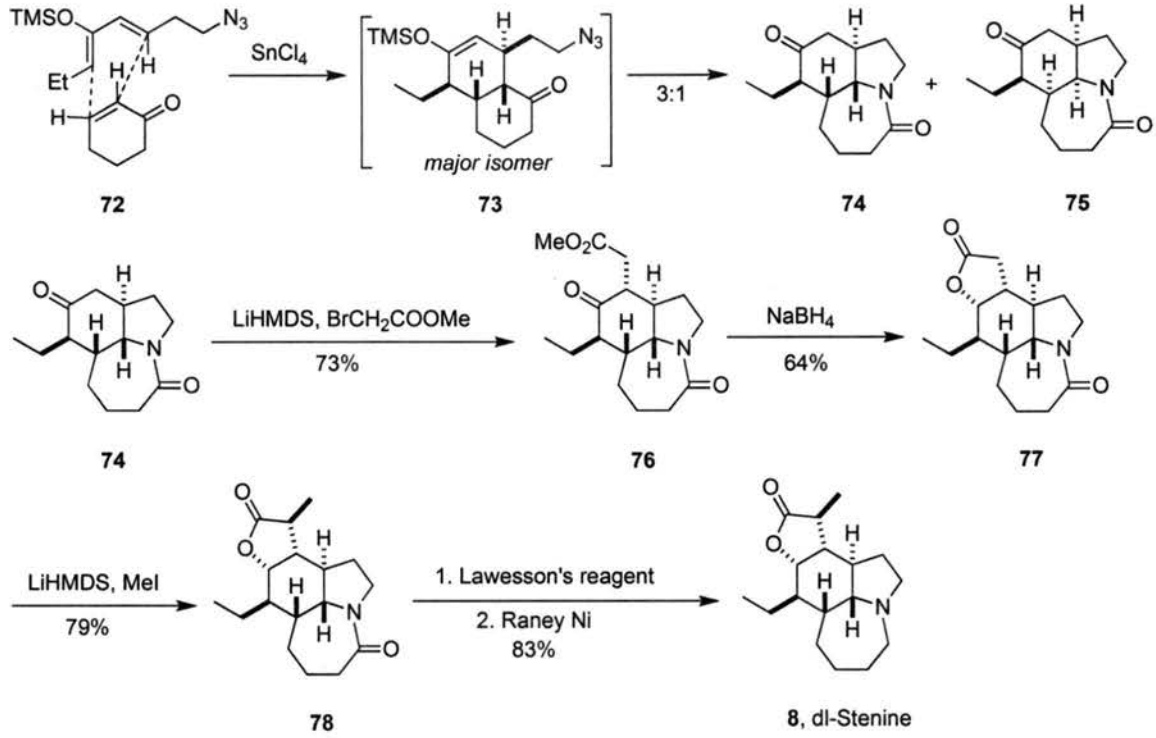


74 73 72

Figure 22. Aubé's Domino Reaction Strategy

1.4.5.1 A Diels-Alder-Schmidt Domino Reaction Approach for BCD Ring Construction

Treatment of the diene with cyclohexenone and $SnCl_4$ afforded a 3:1 mixture of the *exo* and *endo* adducts **74** and **75** in 82% yield (**Scheme 12**). The major isomer, *exo* product **74,** was then transformed to stenine in five more steps, including an axially directed alkylation and reduction of the ketone, followed by methylation to complete the A ring attachment (**78**). Finally decarbonylation via thiolactam furnished the nine-step total synthesis of racemic stenine in 14% overall yield.



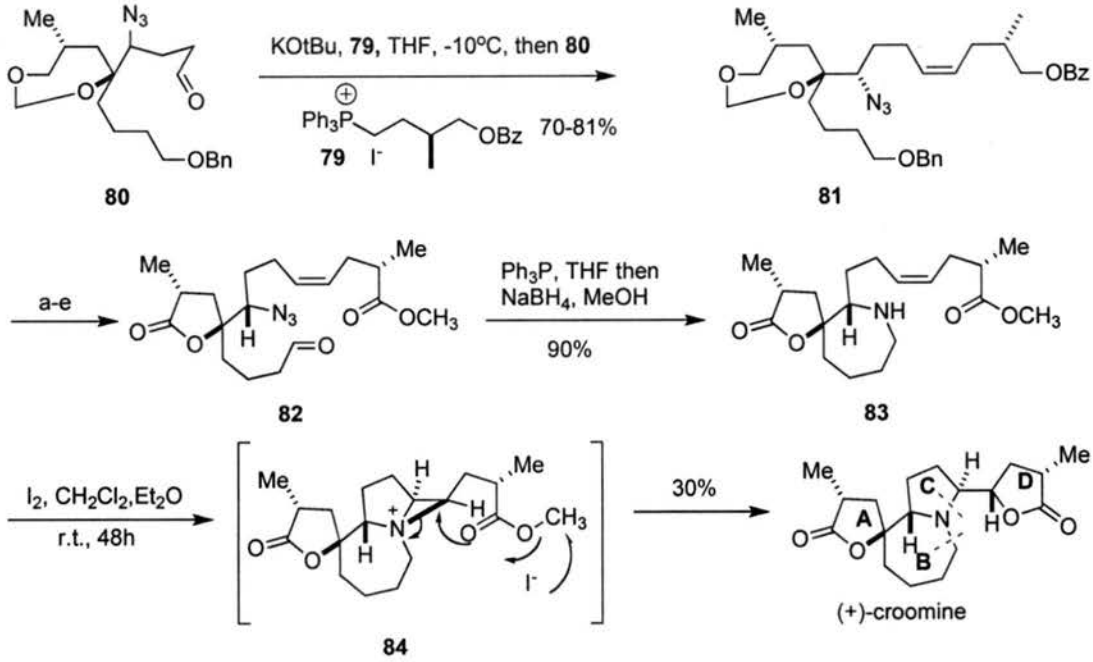
Scheme 12. Aubé's Total Synthesis of dl-Stenine

1.4.6 Williams' Asymmetric Total Synthesis of (+)-Croomine and (-)-Stemospironine

As mentioned already, Williams's pioneering total synthesis of (+)-Croomine in 1989[28h] opened a window for the area of synthesis of *Stemona* alkaloids. Twenty years later this area has been and is still attracting many synthetic efforts from organic scientists. Williams's synthesis of both molecules featured a rather straightforward construction of a fully functionalized acyclic carbon chain in a stereocontrolled manner followed by sequential ring closure reactions.[28h,28j]

1.4.6.1 An Azo-Wittig-Iodine Double Cyclization Sequence for CD Ring Construction

Wittig olefination of aldehyde **80** with chiral ylide **79** gave Z-alkene **81**, setting the stage for formation of all four rings (**Scheme 13**). Firstly, the A ring lactone was formed in a three-step sequence. Deprotection of the benzyl group and subsequent oxidation provided aldehyde **82**. An intramolecular aza-Wittig reaction was performed in the presence of triphenyl phosphine in anhydrous THF. The resulting imine was reduced to amine upon addition of sodium borohydride in methanol to afford the azepine B ring in compound **83** in 90% yield. Iodine-induced double cyclization involved the formation of C ring and aziridinium salt **84** followed by ester-participated aziridine ring opening to finish the first total synthesis of (+)-croomine,[28h] also the first total synthesis of a *Stemona* alkaloid. This synthesis took 24 steps with 0.01% overall yield. In a similar manner, they finished the total synthesis of (-)-stemospironine in 26 steps in 2001 (**Figure 23**).[28j]



a. aq. HBF_4, CH_3OH; 72% b. LiOH, THF; CH_3OH-H_2O (3:1); 86% c. Jones reagent, THF; ethereal diazomethane; 78% d. BCl_3, CH_2Cl_2, -78°C-0°C; then MeOH at -78°C; 77% e. Swern oxidation; 92%

Scheme 13. Azepine B Ring and Lactone D Ring Construction

Figure 23. Synthesis of Stemospironine

1.4.7 Martin's Total Synthesis of (+)-Croomine

Strategically different from Williams's synthesis, Martin and coworkers' synthesis featured a sequential attachment of the rings onto the template via a double use of chiral pyroglutamic acid-directed diastereofacially selective vinylogous Mannich reactions for

AC ring and CD ring connection and a bromoamination for azapine B ring formation (**Figure 24**).[28i]

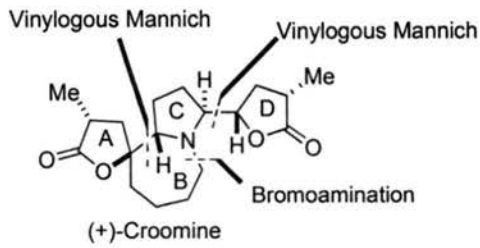
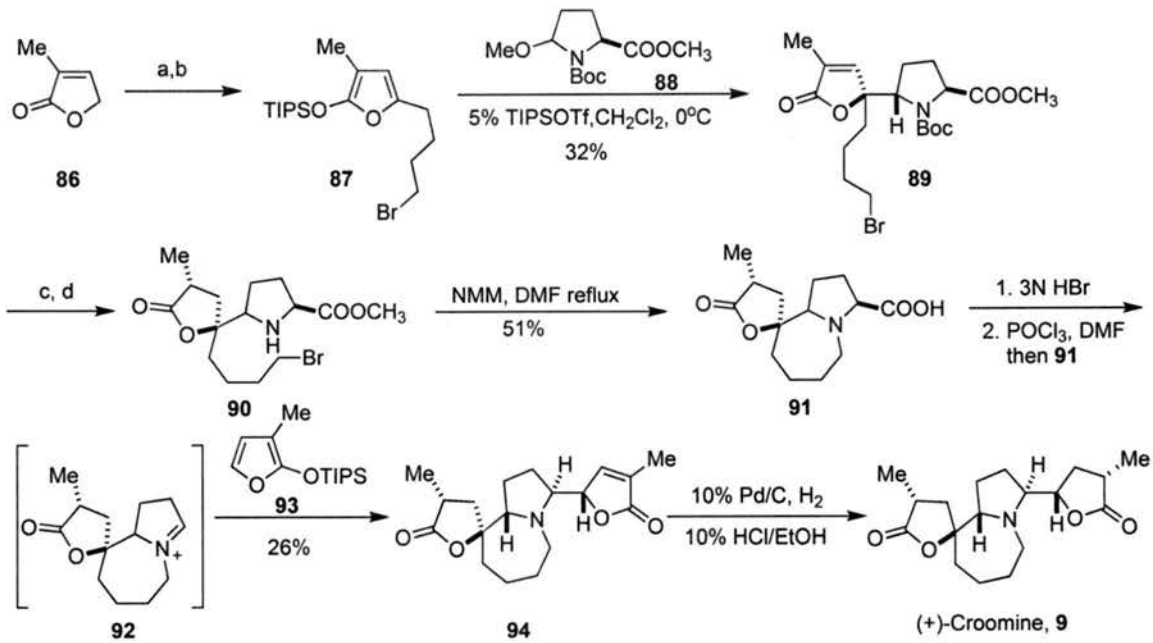


Figure 24. Retrosynthetic Disconnection of Croomine

1.4.7.1 Vinylogous Mannich Approach for CD Ring Attachment

The first vinylogous Mannich reaction was between furan **87** and the *in situ*-generated imine from **88** (prepared from L-pyroglutamic acid, **Scheme 4**). A mixture was obtained with *threo* adduct **89** crystallized in 32% yield. Highly facial selective hydrogenation and deprotection of the Boc group gave amine **90**, which when treated with *N*-methylmorpholine (NMM) in DMF under reflux formed the azepine B ring (**91**) in 51% yield. Subsequent hydrolysis of the methyl ester in 3N aqueous HBr followed by decarboxylation with $POCl_3$ in DMF generated the iminium ion compound (**87**) *in situ*, and subsequent treatment with furan (**88**) furnished the second vinylogous Mannich reaction product as a 2:1 mixture of the desired *threo*-product (**89**) and its *erythro* isomer in 47% combined yield. The double bond in D ring was stereoselectively hydrogenated to deliver (+)-croomine in 85% yield. This concise asymmetric total synthesis required only 9 linear steps and a total of 11 steps from commercially available starting material. However, the key Mannich reactions proceeded with low yield and *threo-erythro* selectivity was not significant.



a. TIPSOTf, Et_3N, CH_2Cl_2, 0°C-r.t.; 77% b. *s*-BuLi, TMEDA, THF, 0°C then $Br(CH_2)_4Br$; 83% c. TFA (10 equiv), CH_2Cl_2, r.t.; d. 3% Rh-C, H_2, EtOAc-EtOH(2:1); 96%

Scheme 14. Azepine B Ring and Lactone D Ring Construction

1.4.8 Figueredo's Total Synthesis of (-)-Stemonidine

Most recently, Figueredo and coworkers reported their asymmetric total synthesis of (-)-stemonidine[28r] and confirmed the second assignment of the structure by Xu shown below.

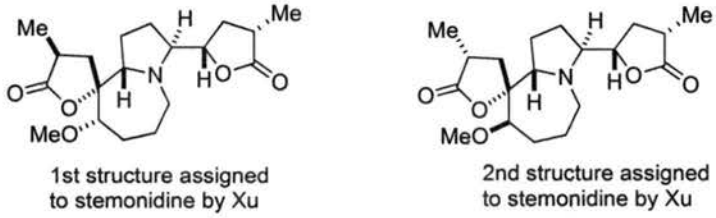
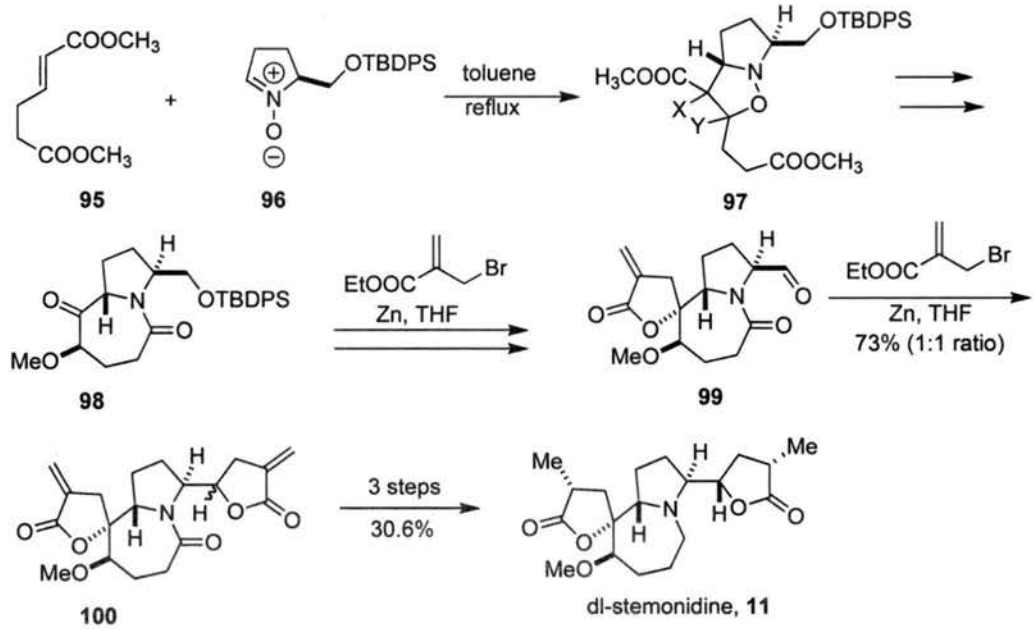


Figure 25. Revised Structure of Stemonidine

Their synthesis started with a 1,3-dipolar cycloaddition of a chiral nitrone (**96**, **Scheme 15**), derived from *S*-prolinol, with unsaturated diester **95** to form the C ring (**97**) and set the stage for B ring formation, which was realized in nine steps to deliver lactam **98**. Most interesting transformations were their quick installation of the two butyrolactones by a double use of the Zinc enolate of ethyl bromomethylacrylate in carbonyl or aldehyde additions. **99** was obtained in complete facial selectivity in 86% yield, but there was no selectivity in the attachment of the D ring; **100** was obtained as a 1:1 mixture of diastereomers in 73% yield. After separation, the desired isomer was transformed to (-)-stemonidine by selective hydrogenation and decarbonylation of the lactam.



Scheme 15. A 1, 3-Dipolar Cycloaddition and Spirolactonization Approach to Stemonidine

1.5 Conclusions and Objectives

The above-mentioned syntheses demonstrate a diverse application of methodologies and strategies in *Stemona* alkaloid synthesis, especially for five to seven membered ring constructions. Diels-Alder reactions have been applied for stereoselective construction of cyclohexanes in racemic or asymmetric form. The seven-membered ring construction was furnished through *N*-haloamination, *N*-acetylation followed by decarbonylation, ring closing metathesis, or ring expansion reactions. The butyrolactones were introduced by ring closure through iodolactonization, selenolactonization, or from aldol reaction of ortho ester, ethylbromoacrylate, or by direct ring attachement from Mannich reaction with furan derivative. However, it is obvious that the listed syntheses, except Martin's concise synthesis of (+)-croomine and Aubé's expeditious synthesis of dl-stenine, needed around 30 linear steps to accomplish an stereocontrolled or asymmetric synthesis, and required tremendous amounts of work. The syntheses either suffered from tedious transformations, such as in the ethyl group and both butyrolactone introductions in stenine and tuberostemonine, or low efficiency of the stereocontrol. In addition to the discussed total syntheses, there are many other synthetic methods in the literature, which are not included here in this thesis.[29]

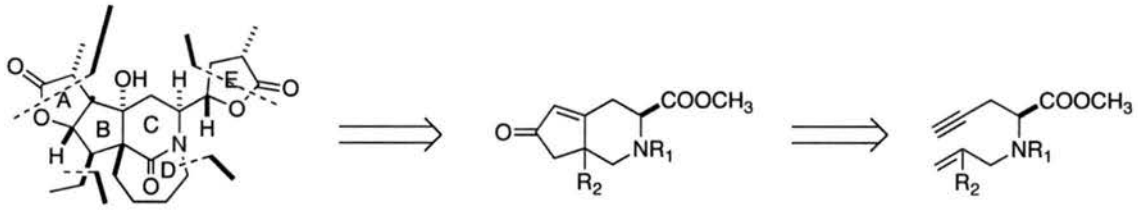
All the synthetic efforts of *Stemona* alkaloids were focused on the major alkaloids containing a pyrrolo[1,2-a]azepine nucleus. Synthetic studies toward tuberostemoninol and alkaloids with similar carbon skeleton, have not been seen in the literature. We started the project with objectives to achieve the first asymmetric total synthesis of tuberostemoninol and provide a sufficient amount to determine the absolute stereochemistry of the target while improving the existed synthetic methods utilized; test

its biological activities (for example, antitussive and anticancer activities) as well as modes of action, and make analogs for the study of structure-activity relationships.

Chapter 2: Synthetic Research Toward Tuberostemoninol

2.1 Structural Analysis and Retrosynthetic Strategy of Tuberostemoninol

Tuberostemoninol (**2**, **Figure 26**) has five rings and a total of nine stereocenters, including a highly substituted cyclopentane ring possessing a quaternary carbon center and a tertiary alcohol. The CD ring system of the target is rarely seen in natural products. All these structure features provide us an initial synthetic challenge. Retrosynthetically, disconnection of the lactones (A, E) and azepine D ring delivers bicyclic enone **101** (BC ring) containing proper functionality, which is envisaged to be the scaffold for the building of the target molecule. The tertiary alcohol was proposed to derive from an epoxidation-Wharton oxygen transposition sequence[30] of the enone double bond. Finally, bicycle **101** is perceived as a product of an intramolecular Pauson-Khand reaction[31] from a chiral amino acid derivative, 1,7-enyne **102**.



Tuberostemoninol (**2**) **101** **102**

Figure 26. A Tentative Retrosynthetic Analysis of Tuberostemoninol

2.2 Introduction of Pauson-Khand Reaction

Cyclopentanes are present in many *Stemona* alkaloids (**Figure 6, 7**) as well as in other natural products, such as palau'amine, citrinadine A, methyl rocaglate, etc. Many methods and strategies have been applied to its synthesis.[32]

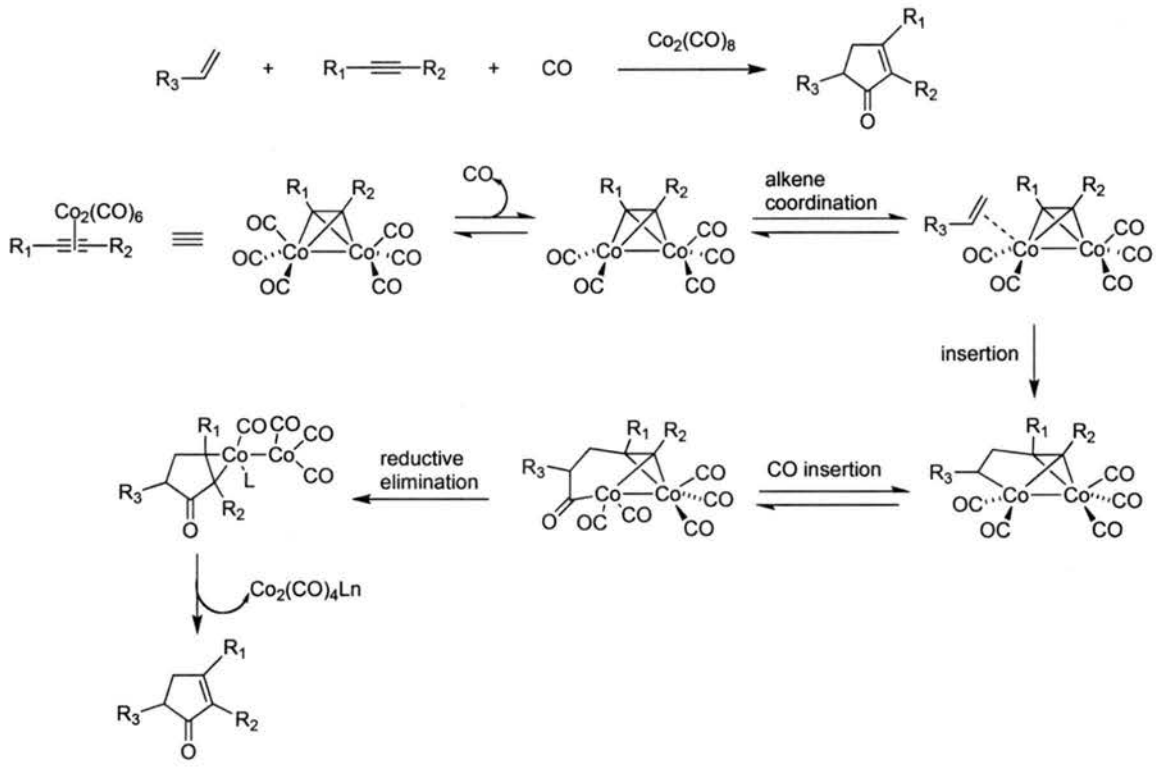
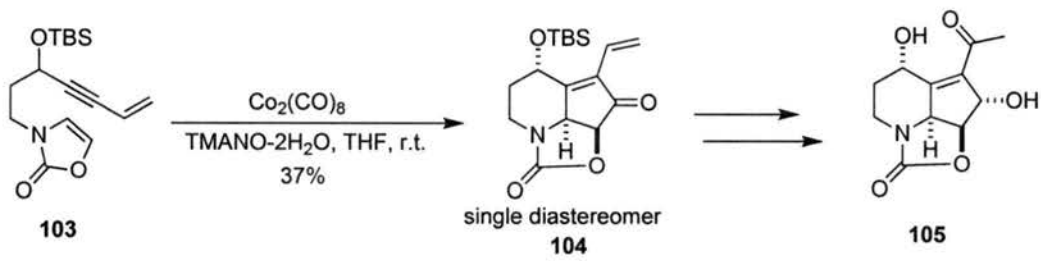


Figure 27. Proposed Mechanism of Pauson-Khand Reaction

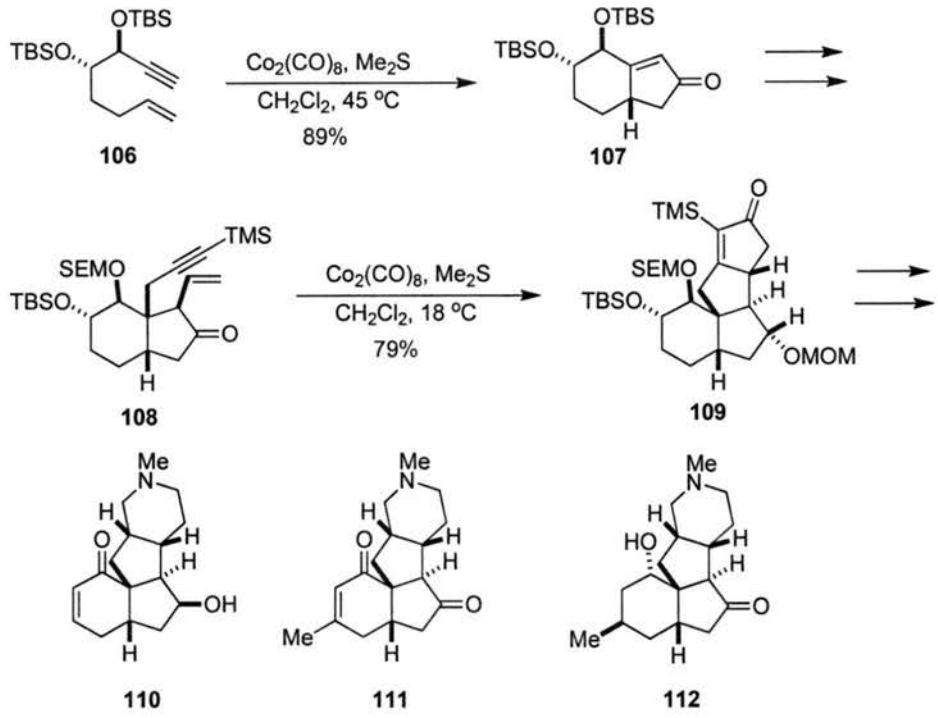
The Pauson-Khand reaction is widely utilized for making cyclopentenones by cyclization of an alkyne, olefin, and carbon monoxide in the presence of $Co_2(CO)_8$ in a formal [2+2+1] cycloaddition.[33] While this reaction is not fully understood, a mechanism had been proposed based on regio- and stereochemical observations from many examples (**Figure 27**).[34] The only intermediate that had been isolated was the initial, stable alkyne-$Co_2(CO)_6$ complex.[35] It was assumed that the next step involved dissociation of a CO ligand and coordination of the alkene. The alkene then irreversibly inserted into one of

the cobalt-carbon bonds. This step was thought to be rate as well as product determining. Migratory insertion of a CO ligand bound to cobalt formed the carbonyl moiety, and reductive elimination of the $Co(CO)_3$ fragment followed. Loss of the $Co_2(CO)_5L$ fragment allowed liberation of the cyclopentenone product.[34] The early events of the proposed mechanism were supported by both Gimbert and Nakamurai's recent mechanistic studies.[35a,35d] At the same time, their research revealed that the decarbonylation step was the most energy demanding step (26.4 kcal/mol for acetylene as the alkyne) and the activation energy for cobalt cycle formation was around 10.0-14.4 kcal/mol, the subsequent steps proceeded rapidly to the product. [35a]

Pauson-Khand reactions, as one of the primary methods for the synthesis of cyclopentanes, have been extensively used in a variety of approaches to natural product synthesis.[33] Some interesting applications were reported recently by Mukai's group. As part of their study on the total synthesis of natural products based on the Pauson-Khand reaction, Mukai and coworkers synthesized the azabicyclo[4.3.0] framework (**Scheme 15, 104**) common in streptazolin and its related derivatives, and completed the first total synthesis of dl-8α-hydroxystreptazolone (**105**).[36a]



Scheme 15. IMPK in dl-8α-Hydroxystreptazolone Synthesis



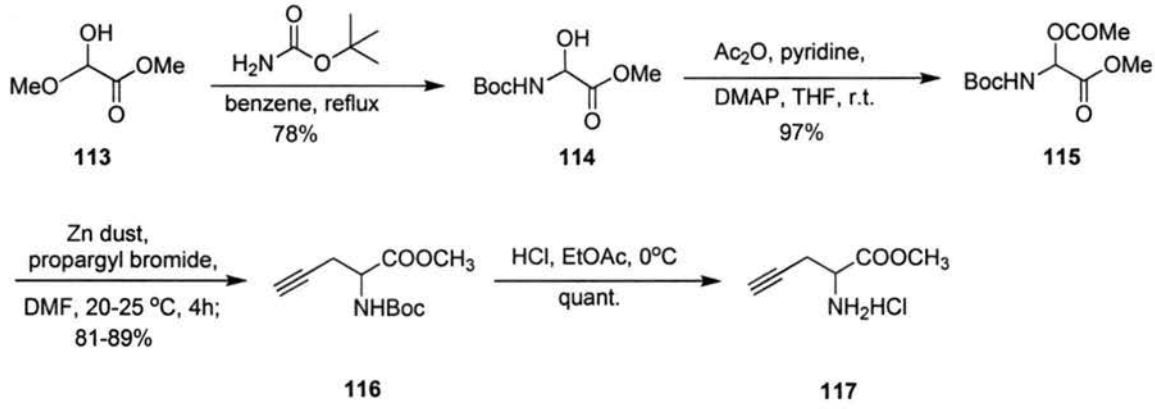
Scheme 16. Double IMPK Applications in (-)-Magellanine, (+)-Magellaninone and (+)-Paniculatine Synthesis

Another elegant application was the double use of IMPK reactions in the total synthesis of (-)-Magellanine (**110**), (+)-Magellaninone (**111**) and (+)-Paniculatine (**112**) (**Scheme 16**) by the same group.[36b] These molecules have a common structural feature of a [6-5-5-6] tetracyclic framework, which was built by the first IMPK reaction to give [6-5] bicycle. Another IMPK reaction was applied to construct the second cyclopentane ring to get [6-5-5]-5, and the final cyclopentane ring, also resulting from the IMPK, was then converted to the piperidine ring present in the target molecules to complete the [6-5-5-6] ring system.

2.3 Racemic Synthetic Studies

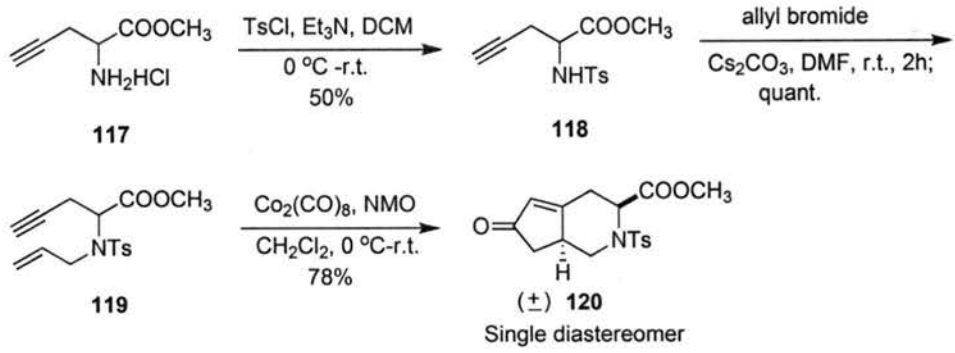
2.3.1 Intramolecular Pauson-Kand Reaction toward Tuberostemoninol

We found that the enantiopure propargyl glycine was impractically expensive (US$ 422/250mg, Fluka), racemic propargyl glycine methyl ester (**117**) was made from a modification of a known synthetic method.[37] Hemiacetal **113** was treated with *tert*-butyl carbamate in benzene under reflux, providing hemiaminal **114** in 78% yield. Acylation of **114** followed by a Reformatsky type reaction of the resulting aminal (**115**) gave Boc-protected propargyl glycine methyl ester (**116**), which was further deprotected to liberate propargyl glycine methyl ester (**117**) as the hydrochloric acid salt in excellent overall yield (**Scheme 17**).

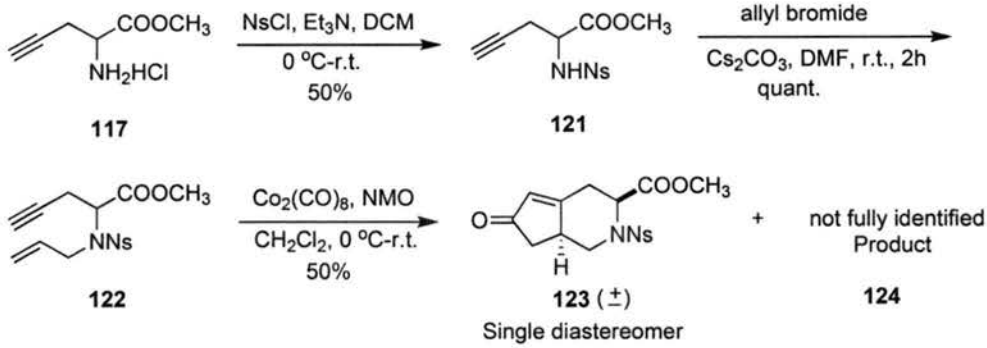


Scheme 17. Racemic Synthesis of Propargyl Glycine Methyl Ester

Bicycle **120** was prepared according to Bolt et al.'s three-step sequence[31a] through tosylation of the amine in **117,** monoallylation to give the IMPK precursor, 1,7-enyne **119**, and subsequent IMPK reaction under *N*-methyl morpholine *N*-oxide promoted condition (**Scheme 18**).



Scheme 18. IMPK Reaction with Tosyl Protecting Group

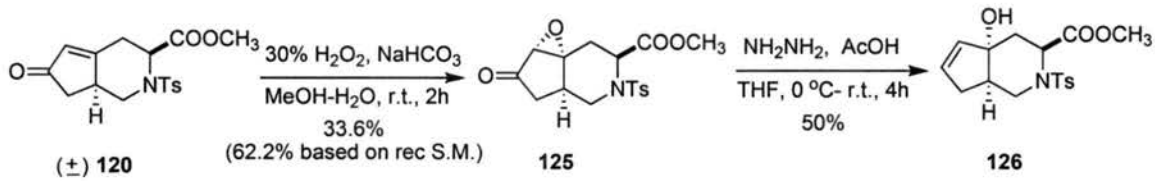


Scheme 19. IMPK Reaction with Nosyl Protecting Group

Bicycle **123** with a nosyl protecting group was made in a similar manner in good yield, along with an incompletely identified IMPK product **124**. Conditions were not further optimized. The nosyl group could be easily deprotected by treatment with thiophenol and potassium carbonate in acetonitrile (47% yield was obtained without optimization of the condition); however, very harsh conditions (Na/Naphthalene, Red-Al, acidic hydrolysis in 48% HBr)[38] are usually needed to remove the tosyl group, in which a lot of other functionalities could not survive.

2.3.2 Introduction of the Tertiary Alcohol

Wharton oxygen transposition reactions are not often seen in natural product synthesis because of the harsh conditions involved and the low yield caused by many possible side reactions.[30] To test the feasibility of this reaction for introduction of the tertiary alcohol in the target molecule, model studies were performed on substrate **120**. Epoxidation of the enone double bond with hydrogen peroxide under basic conditions in methanol and water gave 33.6% yield of epoxyketone **125**, which was further treated with hydrazine and acetic acid in THF to provide the desired allylic alcohol **126** in a satisfactory yield, along with a side product (possibly the corresponding carbohydrazide).



(±) **120** **125** **126**

Scheme 20. Epoxidation and Warton Oxygen Transposition Reaction

2.4 First Generation Retrosynthetic Analysis of Tuberostemoninol

The model studies provided us confidence that a bicycle with proper functionalities and chiralities derived from an IMPK reaction could serve as a scaffold for further elaboration for the total synthesis of tuberostemoninol. Thus, a detailed retrosynthetic analysis of an asymmetric total synthesis was generated. We believed that the Williams's lactone would serve perfectly as a chiral template for construction of the IMPK precursor

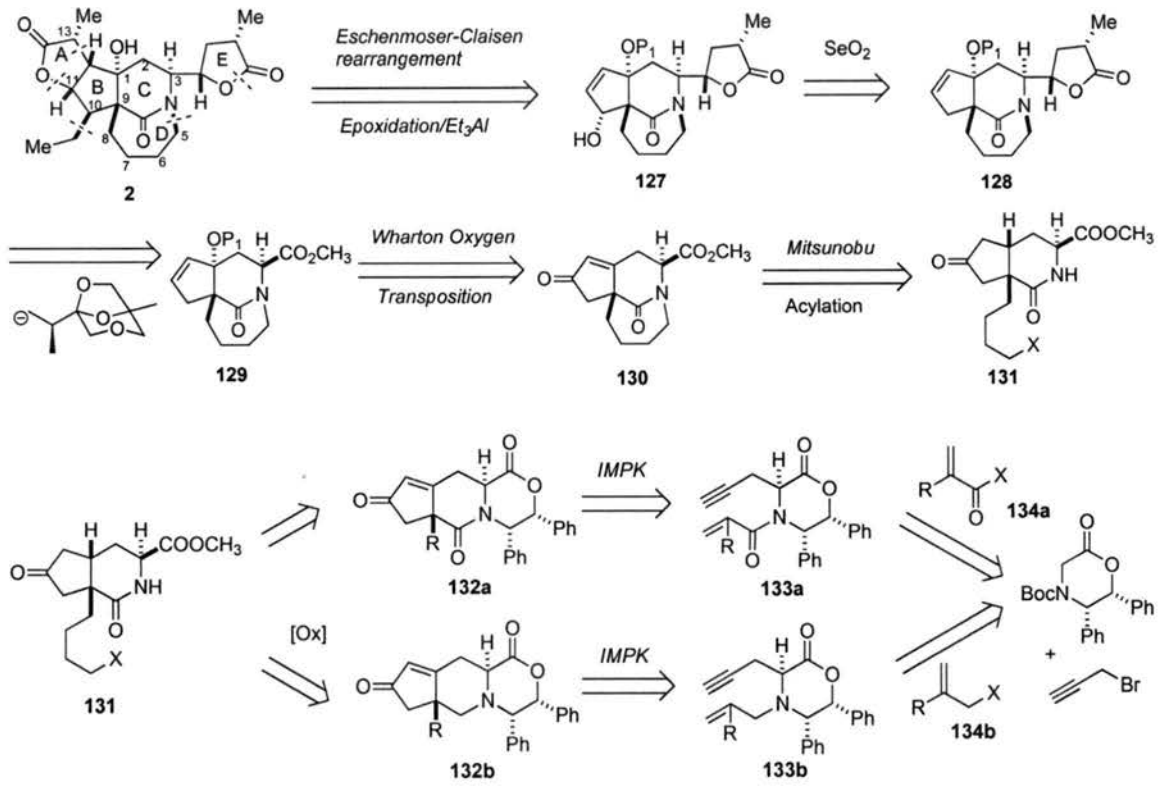
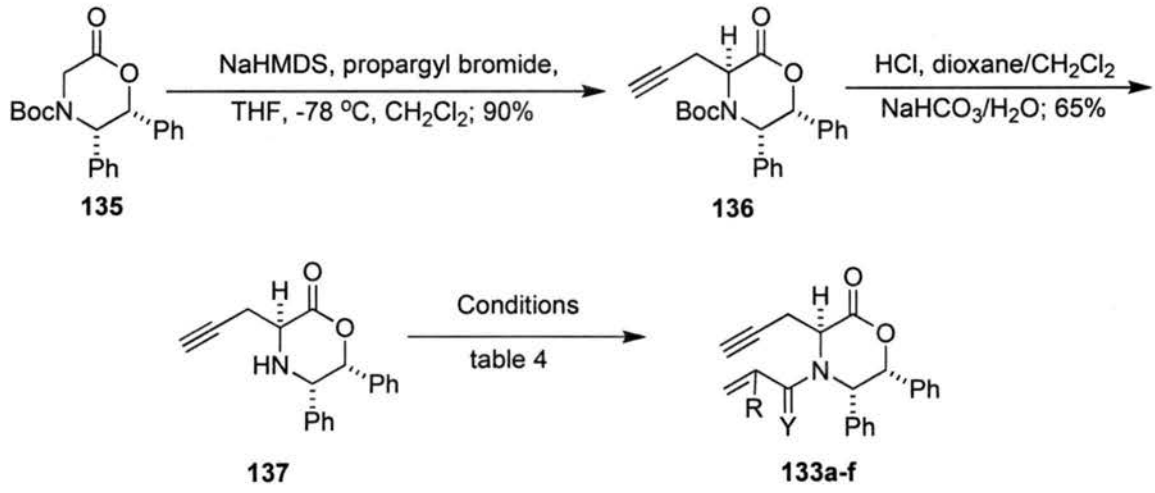


Figure 28. First Generation Retrosynthetic Analysis of Tuberostemoninol

(either **133a** or **133b**), and thus the cycloadduct (either **132a** or **132b**). After removal of the template, bicycle **131** would be liberated. A Mitsunobu reaction could be used to form the seven-membered lactam (**130**). Then, a Wharton oxygen transposition would introduce the tertiary alcohol (**129**). The right side butyrolactone ring could be installed according to Wipf's protocol (**128**),[28a,b] and the left side butyrolactone and ethyl group could be installed based on the Eschenmoser-Claisen rearrangement concept according to Hart and Wipf's protocol (**127, 2**).[28c,a,b] The lactam carbonyl could be introduced at an early stage from **133a** of the synthesis if possible, or at a later stage by amine oxidation of intermediates derived from **133b**.

2.4.1 IMPK Precursor Synthesis

As planned in the retrosynthetic analysis (**Figure 28**), IMPK precursors **133a-f** (**Figure 29**) were prepared by monoalkylation of the α-position of the N-Boc glycinate **135**[39] with propargyl bromide, followed by *t*-butyl carbamate deprotection with hydrochloric acid in dioxane, providing after basic workup, the secondary amine (**137**), which was then further transformed to **133a-f** (**Scheme 21**).



Scheme 21. Preparation of IMPK Precursors **133a-f**

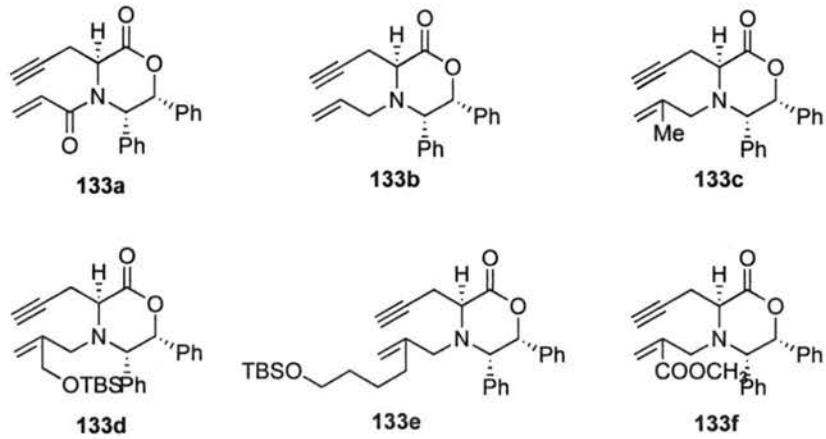
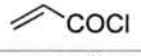
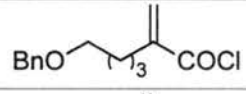
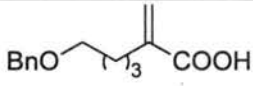
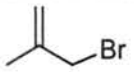
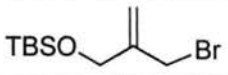
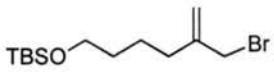
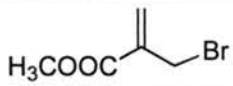
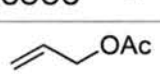
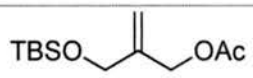
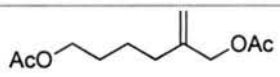
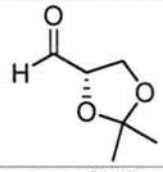
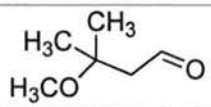


Figure 29. IMPK Precursors **133a-f**

Compound **133a** (entry 1, **Table 4**) was obtained from a simple acylation of the amine with acrylol chloride in dichloromethane in the presence of triethylamine. Compound **133b** (entry 8) was prepared in high yield from a Tsuji-Trost allylation reaction with allylic acetate using $Pd_2(dba)_3$ as catalyst and triphenylphosphine as the ligand.[40] Enynes **133c-e** (entries 4, 5 and 6) were obtained only in very low yield and needed tremendous work of purification. Efforts to improve the yield by addition of the phase transfer catalyst TBAI, running a longer time, or at elevated temperature failed: no obvious increase in yield was observed, and the recovered amine (**137**) was slowly epimerized at temperature above 60 °C. The attempted Tsuji-Trost allylation reaction as shown in entries 9 and 10 was not successful. To our delight, **133f** (entry 7) was easily made by N-alkylation with methyl 2-(bromomethyl)acrylate in excellent yield. Efforts to make the enynes with both the carbonyl and the R side chain were not successful by acylation or reductive amination of **137** with the corresponding chloride, carboxylic acid, or aldehyde, as shown in entries 2, 3 and 11, respectively.

Table 4. IMPK Precursor Synthetic Studies

Entry	Substrates	Conditions	Results
1		1. Et_3N, CH_2Cl_2, 0-r.t.	*desired product, ~61% yield*
2[41]		2. DCC, DMAP, CH_2Cl_2, r.t. 3. DCC, DMAP, DMF, 60 °C	unidentified product only
3[41]		4. DCC, DMAP, toluene, 110 °C 5. DEPC, Et_3N, DMF, r.t.-60 °C 6. EDCI, DMF, 60 °C 7. FDPP, DMF, 60 °C	no rxn, except S.M. was epimerized under elevated temperatures

4		1. Cs_2CO_3, TBAI, DMF, r.t.-60 °C 2. KH, 18-crown-6, DMF, 0 °C-r.t. 3. K_2CO_3, MeCN, r.t., 12 h 4. K_2CO_3, TBAI, DMF, r.t., 89 h 5. $NaHCO_3$, DMF, 36 h, excess bomide used 6. K_2CO_3, DMF, r.t., 12 h	*16%* *product <10%,* recovered S.M., and S.M. was partially epimerized at elevated temperature
5[42]			
6[43a]			
7		Condition 6	*desired product, 98%*
8		7. $Pd_2(dba)_3$, dppb, THF, 3 d 8. $Pd_2(dba)_3$, PPh_3, K_2CO_3, THF, 3 d 9. $Pd_2(dba)_3$, $P(OEt)_3$, K_2CO_3 , MeCN, 3 d	*desired product, decent yield (70-90%)*
9[42]			no reaction
10[43b]			no reaction
11[44]		$NaHB(OAc)_3$, CH_2Cl_2, r.t.	no P observed
12		$NaCNBH_3$, MeCN	no P observed
13		$NaCNBH_3$, MeCN	*desired P, decent yield*

2.4.2 IMPK Reaction Studies

Substrates **133a-f** were subjected to IMPK conditions for cycloadducts formation (**Table 5**). Treatment of these substrates with dicobalt octacarbonyl in dichloromethane at room temperature allowed alkyne-dicobalt hexacarbonyl complex formation. Then, oxidant *N*-methyl morpholine *N*-oxide was added to promote the cyclopentenone formation (**132a-f**), or instead of adding NMO, the complex was subjected to thermal conditions in acetonitrile (**132a**). Thus, cycloadducts **132a-e** (**Figure 30**) were obtained

as expected. However, precursor **133f** failed to give cycloadduct **132f** in several conditions that had been investigated.[35e]

Table 5. IMPK Reaction Conditions and Results

IMPK Precursors	Conditions	Results	Yields
133a	B	**132a**	16%
133b	A	**132b**	65%
133c	A	**132c**	<50%
133d	A	**132d**	<50%
133e	A	**132e**	<50%
133f	A, B, C, D, E	**132f**, not observed	0

IMPK conditions:[35e] A. $Co_2(CO)_8$, NMO, CH_2Cl_2, 0 °C-r.t.; B. $Co_2(CO)_8$, CH_2Cl_2,then MeCN, reflux;
C. $Co_2(CO)_8$, toluene, DMSO, 75 °C; D. $Co_2(CO)_8$, toluene, PhSMe, 75 °C;
E. $Co_2(CO)_8$, MeCN, Me_2S , 35 °C

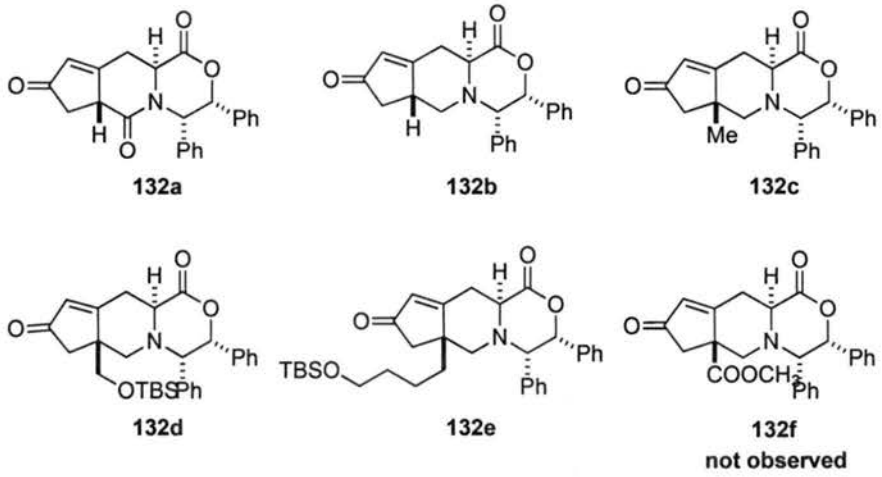
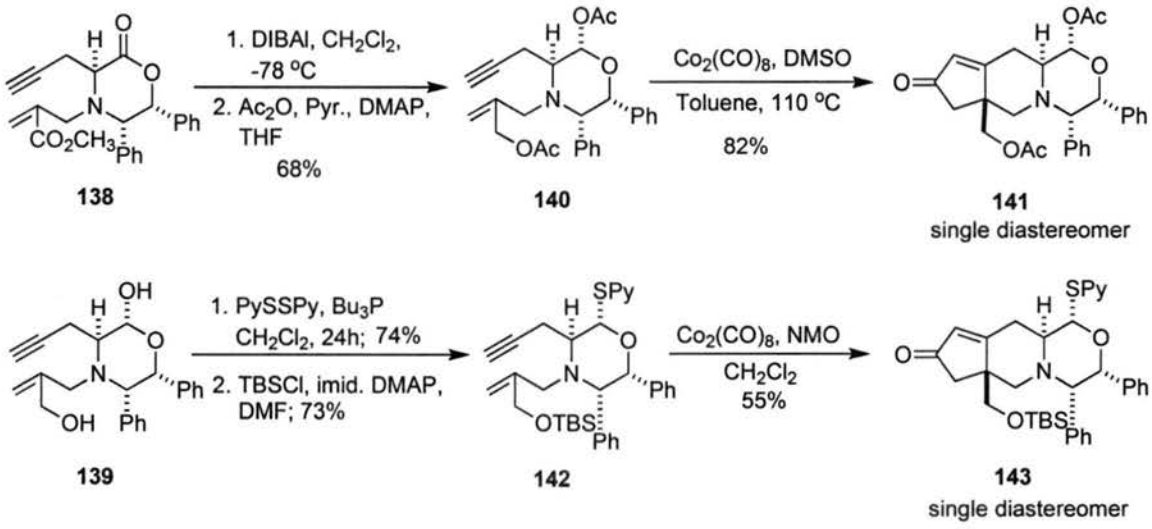


Figure 30. IMPK Cycloadducts

Modification of the electronic properties of substrate **138** (**Scheme 22**) was believed to be a solution for successful IMPK reaction. DIBAl reduction of **138** gave diol **139**, which was followed by acylation to provide diacetate enyne **140**. Compound **140**

was then treated with dicobalt octacarbonyl under NMO-promoted condition gave desired cycloadduct **141** as a single diastereomer in 45-50% average yield. Alternatively, the lactol could be selectively protected with pyridine disulfide in the presence of tributyl phosphine,[45] followed by *tert*-butyldimethyl silyl protection of the allylic alcohol to give **142**. This enyne also underwent IMPK reaction to give cycloadduct **143** as a single diastereomer in 55-73% yield. The relative stereochemistry of the IMPK product was confirmed by X-ray crystallography of **141** (**Figure 31**). The yield of cycloadduct **141** was improved to above 80% using DMSO or *n*BuSMe as the promoter under reflux in toluene (110 °C) or dichloroethane (82 °C) for 2-5 hours.



Scheme 22. Successful Modification of IMPK Reactions

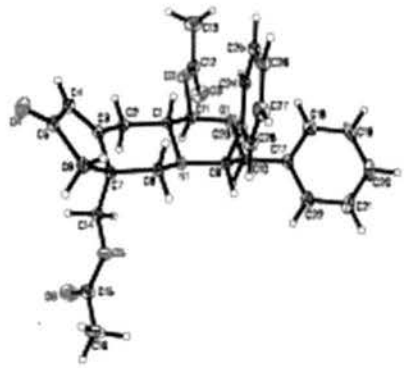


Figure 31. ORTEP Diagram of Enone Tricycle **141**

Removal of the template on tricycles **141** or **143** at this stage with 20% $Pd(OH)_2/C$ under high hydrogen pressure and heating gave unsatisfactory mixtures due to the reduction of the carbonyl to alcohols and partial loss of the acetate group on the anomeric carbon, which made this a less convenient and attractive route for further elaboration. In addition, attempted epoxidation of the enone double bond on substrate **132b** with hydrogen peroxide or *m*CPBA intending an early stage introduction of the C-1 tertiary alcohol was not successful.

2.5 Second Generation Retrosynthetic Analysis of Tuberostemoninol

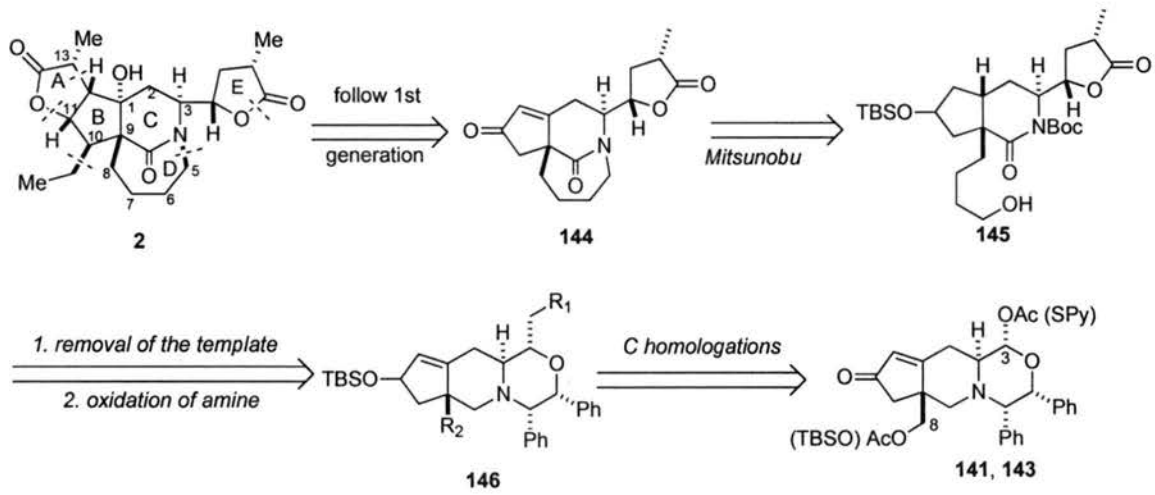


Figure 32. Second Generation Retrosynthetic Analysis

The second generation synthetic strategy of tuberostemoninol (**Figure 32**) involved an early stage introduction of the right side butyrolactone including a two-carbon homologation (**141**, **143** to **146**) and removal of the template to liberate the tricycle (**146** to **145**). After amine oxidation to the lactam, a Mitsunobu reaction could be applied to form the seven-membered lactam (**145** to **144**). The resulting tetracycle would be further elaborated to the final target following the first generation synthetic strategy.

2.5.1 C-3 Homologation Studies

2.5.1.1 Homologation through Acetal Allylation

One of the glycinate methodologies developed in Williams's group was the C-C formation from acetals via an oxocarbenium ion (**Figure 33**).[46] I started to use this concept in our synthesis on a series of substrates as shown below in Scheme 23.

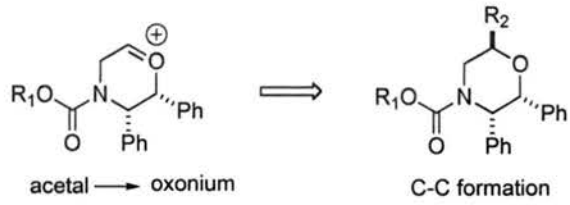
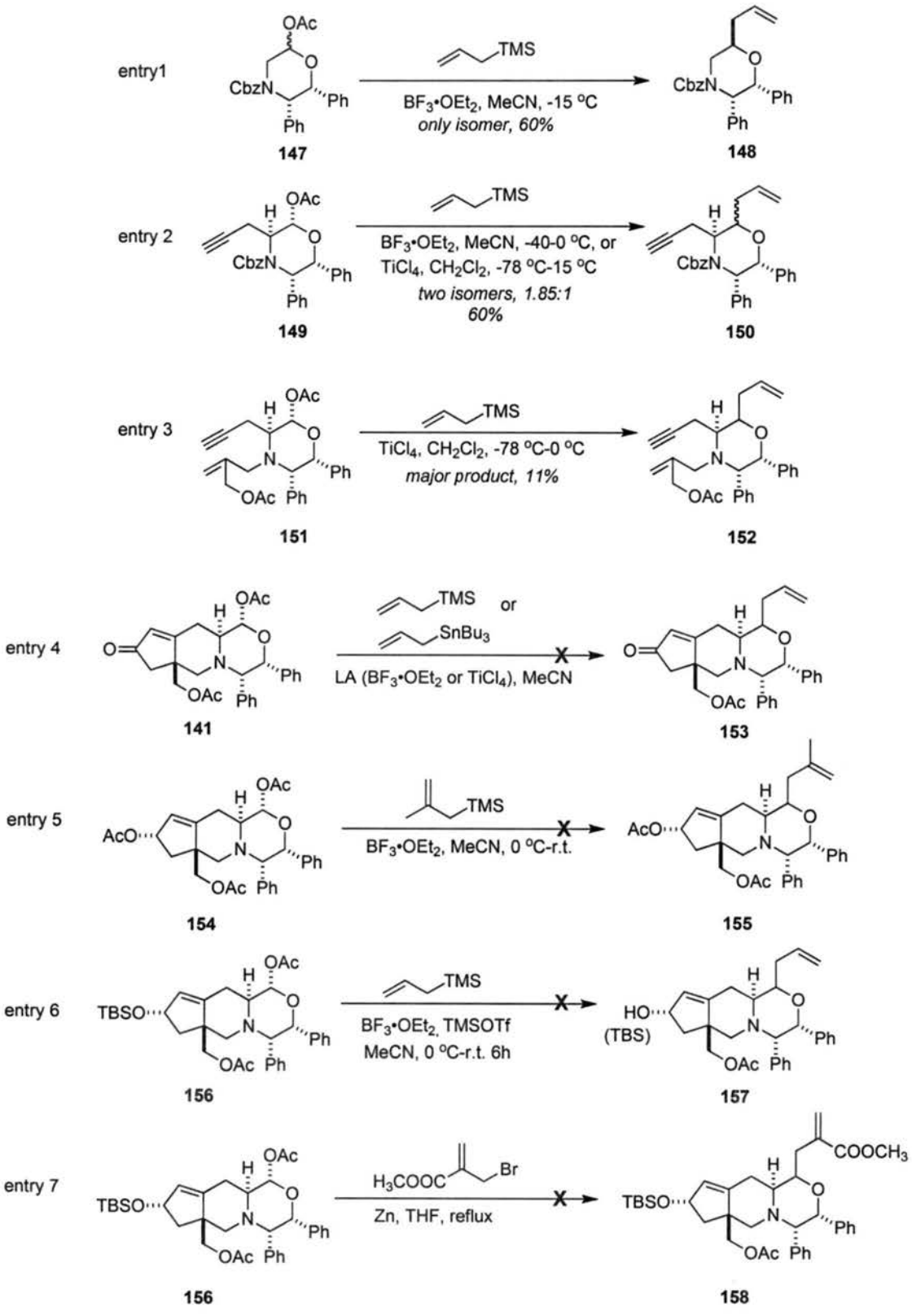
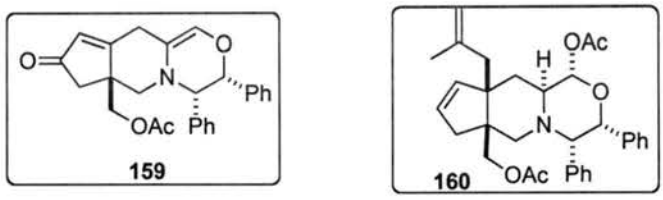


Figure 33. C-C Formation via Oxocarbenium Ion

Among all the substrates that had been investigated under the shown conditions, products **148**, **150** and **152** were obtained in various yields. Compound **148** was obtained as a single diastereomer as reported by coworkers in the Williams's group. **150** was obtained as a mixture of diastereomers with a ratio of 1.85 to 1, while **152** was obtained as the major product in 11% yield without further determination of the newly generated stereochemistry. In entry 4, when **141** was subjected to Lewis acid catalyzed allylation conditions with allysilane or allytributyltin, desired C-C formation product **153** was not observed. Instead, an elimination product (**159**) was obtained (**Figure 34**). The steric hindrance of the oxocarbenium ion generated from **141** rendered α-H elimination, a more competitive reaction than the nucleophilic attack of the oxocarbenium ion itself. In entry 5, the structure of product **160** was proposed based on its proton NMR and HRMS analysis. In entry 7, a Reformatsky type reaction failed to provide the desired C-C formation product (**158**) with unsaturated allylic bromide in the presence of zinc dust with or without Lewis acid catalysis. Other Lewis acid catalyzed nucleophilic addition efforts on substrates **141**, **143** and **154** with silyl ether (trimethyl(prop-1-en-2yloxy)silane) were not successful either.


entry1
OAc
CbzN
Ph
Ph
147
TMS
BF3•OEt2, MeCN, -15 °C
only isomer, 60%
148
entry 2
149
BF3•OEt2, MeCN, -40-0 °C, or
TiCl4, CH2Cl2, -78 °C-15 °C
two isomers, 1.85:1
60%
150
entry 3
151
TiCl4, CH2Cl2, -78 °C-0 °C
major product, 11%
152
entry 4
141
or
SnBu3
LA (BF3•OEt2 or TiCl4), MeCN
153
entry 5
AcO
154
BF3•OEt2, MeCN, 0 °C-r.t.
155
entry 6
TBSO
156
BF3•OEt2, TMSOTf
MeCN, 0 °C-r.t. 6h
HO
(TBS)
157
entry 7
H3COOC
Br
Zn, THF, reflux
COOCH3
158



Scheme 23. Attempted Allylation Reactions from Acetal Compounds

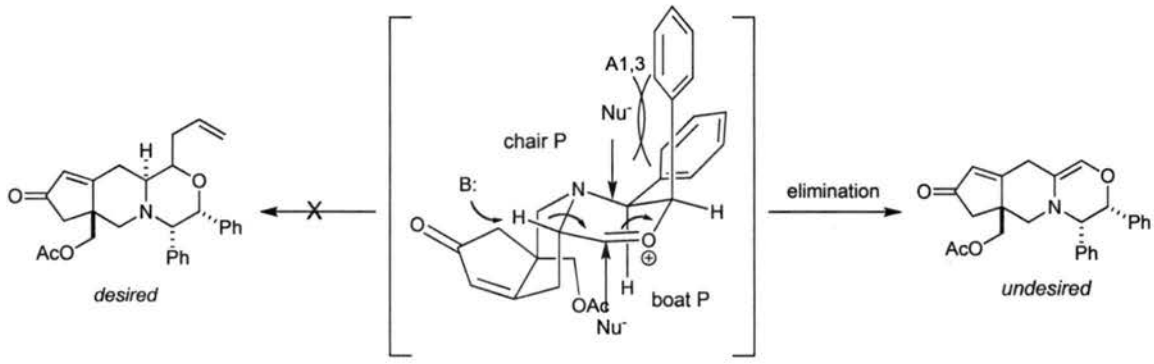


Figure 34. Proposed Pathways for Elimination Product Formation and Possible Reason for Failure of the C-C Formation

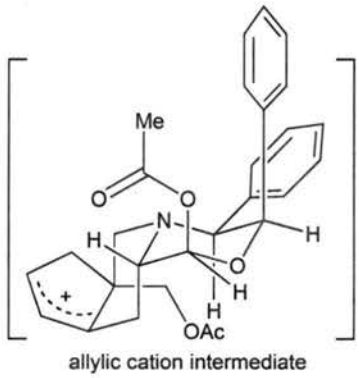


Figure 35. Proposed Allylic Cation Intermediate for Possible **160** Formation

2.5.1.2 C-3 Homologation Studies through Wittig Olefination

2.5.1.2.1 Wittig Olefination Studies with Unstablized Ylides

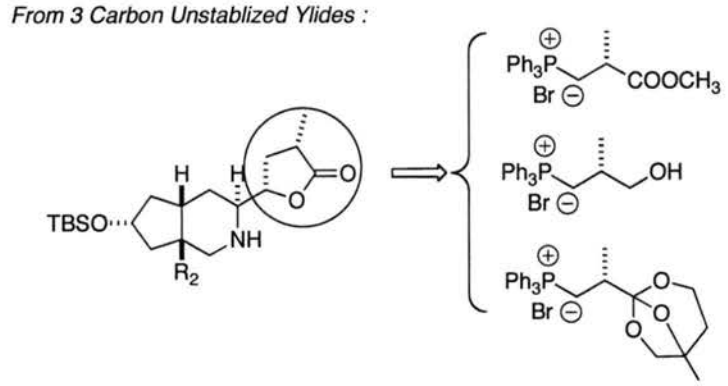
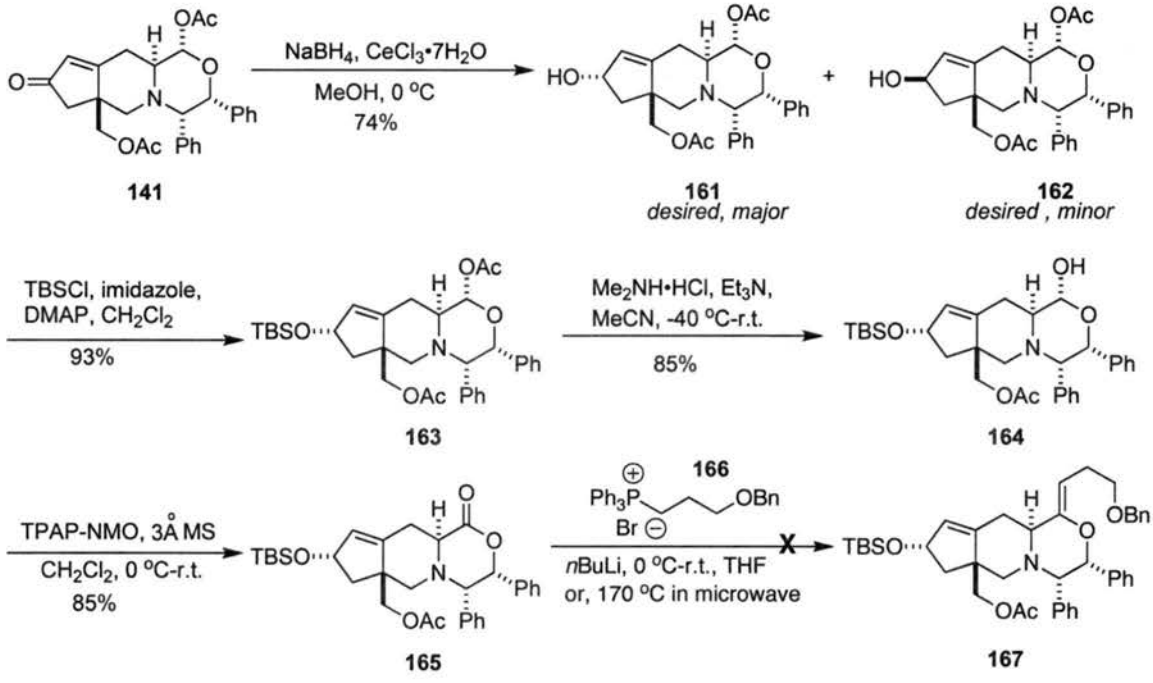


Figure 36. Retrosynthetic Analysis for Lactone E Ring Installation

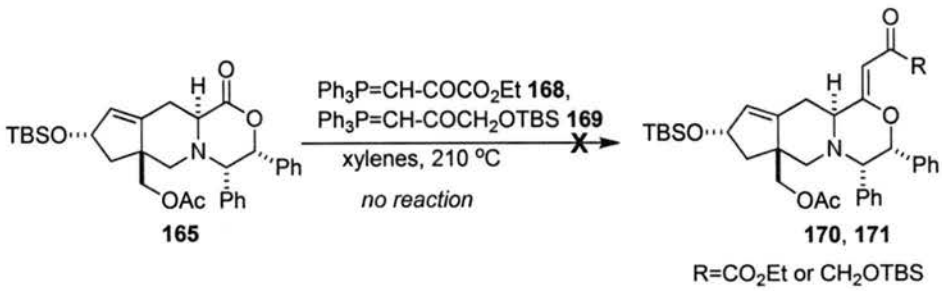
Wittig olefination reaction of carbonyl or lactone with the above shown ylides might be an option to introduce three carbons for the right side butyrolactone E ring formation (**Figure 36**).



Scheme 24. Attempted Wittig Olefination with Unstablized Ylide

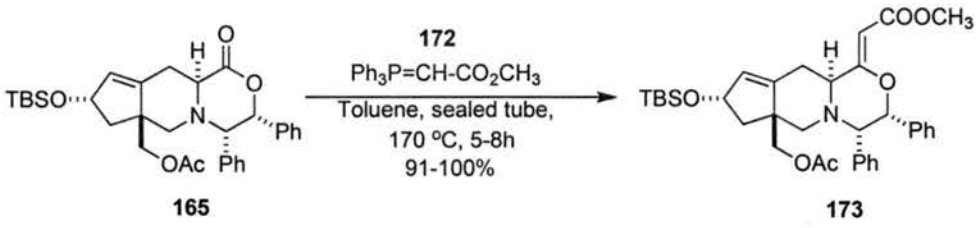
Luche reduction of enone **141** gave the desired allylic alcohol (**161**), along with its isomer **162** as a minor product (<5%) (**Scheme 24**).[47] Slow addition of the reducing agent under cooling could minimize the formation of **162**. The stereochemistry at the carbon center bearing the allylic alcohol was of no consequence since it would be destroyed at a later stage during the introduction of the C-1 tertiary alcohol. Although, the reduction was reproducible on very small scales (0.5 mmol), I met with great difficulty extending it to a larger scale, which usually resulted in low yield (30-50 %) of **161** with a mixture of undesired polar products with the loss of one or two acetate groups and recovered starting material. The main problem is the limited solubility of crystalline **141** in methanol or ethanol at lower than room temperature. When precipitation happened, dichloromethane was added to the mixture as a co-solvent. The problem was finally overcome by reduction of **141** with 9-BBN in THF giving a mixture of **161** (13%) and **162** (62%) as a 1 to 5 ratio. TBS protection of allylic alcohol **161** gave **163** in good yield. Selective deprotection of the acetal to lactol with dimethylamine in acetonitrile[48] followed by TPAP-NMO or Swern oxidation gave lactone **165** in good yield.[28d] Treatment of this lactone with ylide **166**[49], however, failed to give the desired olefination product **167** at low or high temperature (**Scheme 24**).

2.5.1.2.2 Wittig Olefination Studies with Stablized Ylides



Scheme 25. Attempted Wittig Olefination with Three-Carbon Stablized Ylides

Lactone **165** (**Scheme 25**), treated with ylide **168**[50] and **169**[51] in xylenes at high temperature respectively, did not give the desired products **170** and **171**, only starting material was recovered.



Scheme 26. Successful Wittig Olefination

To our delight, we found that lactone **165** underwent Wittig olefination reaction with commercially available ylide **172** to give desired product **173** in fair yield under thermal conditions in xylenes (**Scheme 26, Table 6**).[52] A problem of this reaction was the incompletion of the reaction and the difficult separation of the product from the unreacted starting material. After careful investigation of solvents, reaction time, temperature in sealed tube and microwave,[53] it was found that quantitative yield could be obtained when

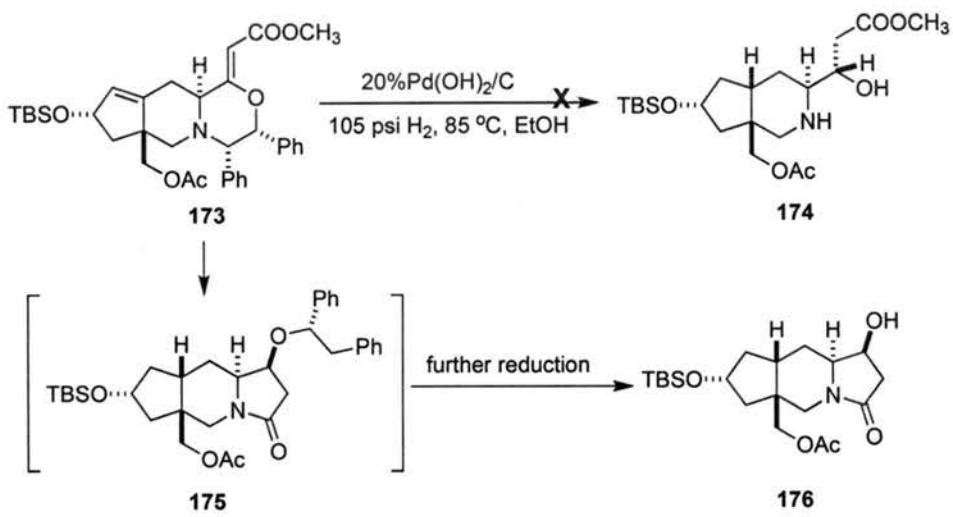
the reaction mixture (0.1 M-0.2 M) was heated to 170 °C for 5-8 hours in a sealed tube (entry 6). This reaction was repeatable on scales up to 1 g starting material.

Table 6. Optimization of Wittig Olefination Conditions

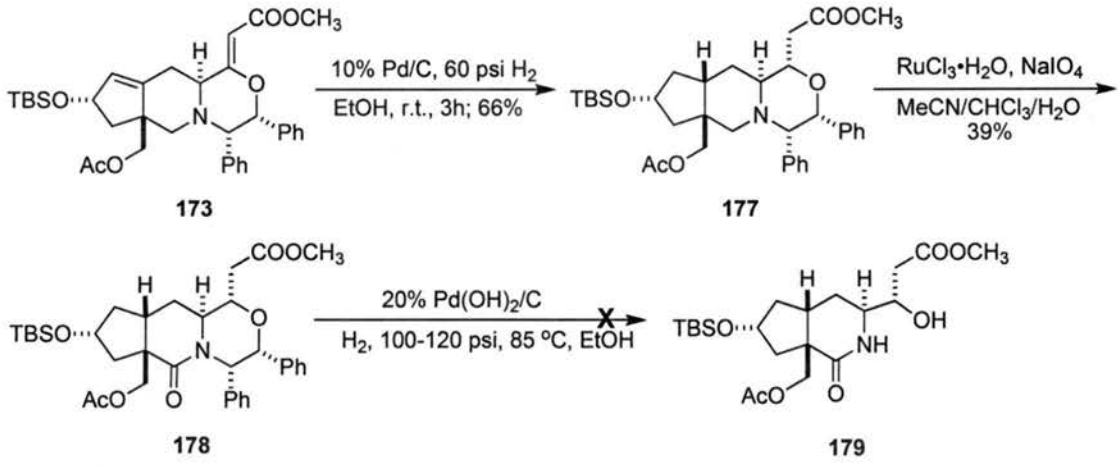
Entry	Conditions	Results
1	xylenes, reflux (150-180 °C), 18 h	30-50% P + rec S.M.
2	xylenes, 210 °C, sealed tube, 2-4 h (C=0.05M)	10-30% P + rec S.M.
3	xylenes, 210 °C, sealed tube, 2.5 h (C=0.1M)	30% P
4	toluene, 170 °C, microwave, 1-4 h (C=0.05M)	P + rec S.M.
5	toluene, 170 °C, microwave, 5 h (C=0.05M)	50% P
6	toluene, 170 °C, sealed tube, 5-8 h (C=0.1-0.2M)	69%-quantitative P

2.5.2 Initial Studies of the Removal of the Template

The removal of the template was then studied on substrate **173**,[54] which was treated with 20% $Pd(OH)_2/C$ in ethanol at 85 °C under 105 psi H_2 for 3 hours. Partially cleaved intermediate **175** was first observed. After further hydrogenolysis, **176** was obtained as the final product. The desired product (**174**) was not observed at all (**Scheme 27**). This result suggested that during the hydrogenolysis, cleavage was easier at the C-N bond than at the C-O bond. Once the C-N bond was cleaved, the resulting amine would cyclize very quickly with the ester group to form the undesired five-membered lactam in **175**.



Scheme 27. Unexpected Lactam Formation



Scheme 28. Studies of Cleavage of the Template

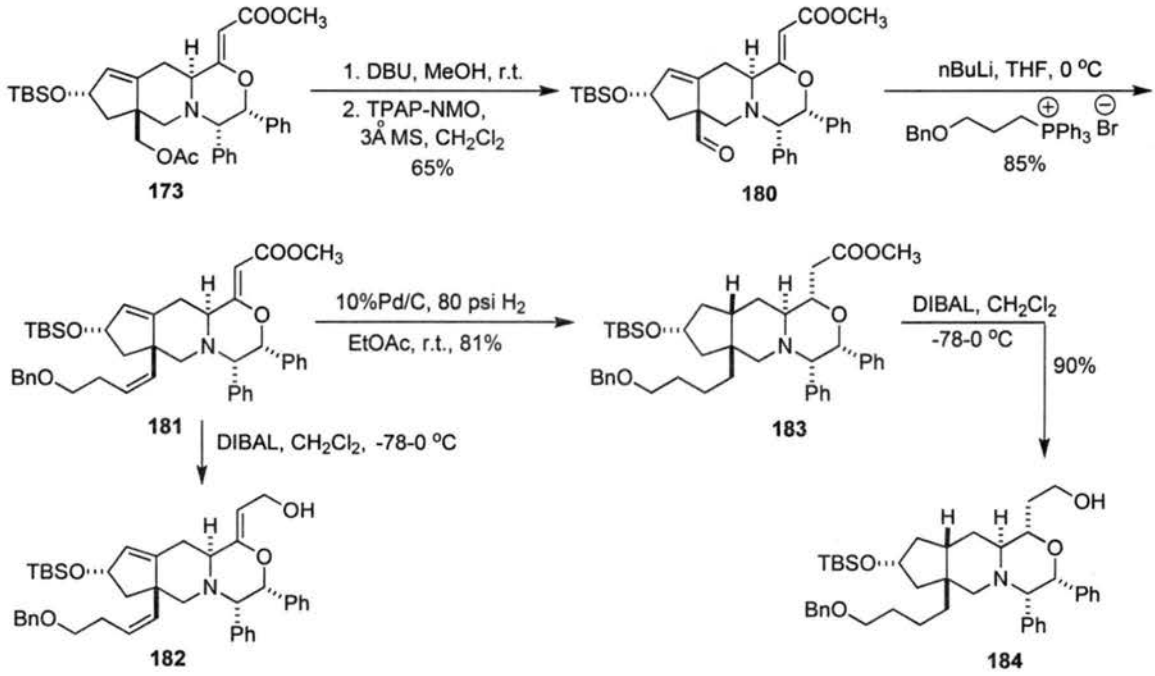
The introduction of the carbonyl group before the removal of the template would possibly reduce the chance of the undesired lactam cyclization. So, hydrogenation of the double bonds in **173** gave saturated compound **177** (**Scheme 28**). Ruthenium chloride-sodium metaperiodate oxidation of the tertiary amine gave lactam **178** in 39% yield without further optimization. However, cleavage of the template from lactam **178** was

very difficult under the hydrogenolysis condition shown above. It was thought that a Birch reduction of **178** might be a possibility to cleave the template.

2.5.3 C-8 and C-20 Homologations

2.5.3.1 C-8 Homologation

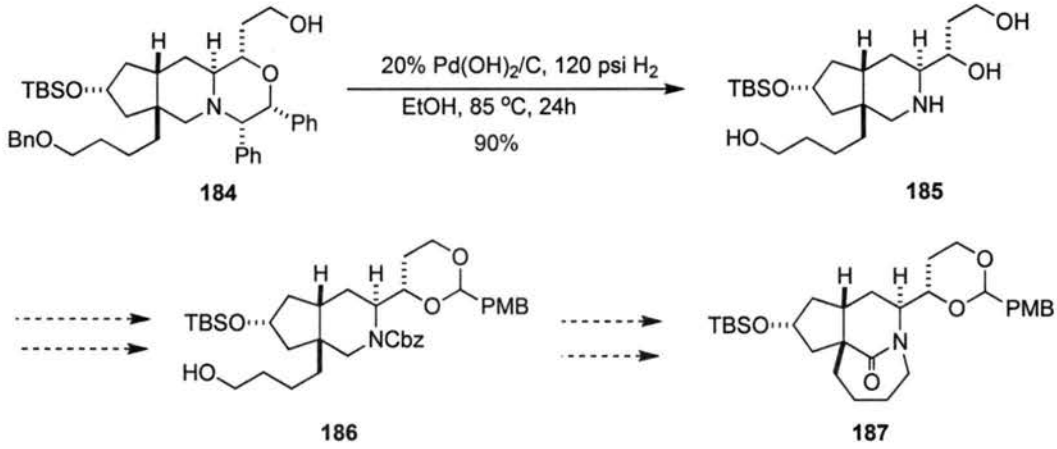
Following the retrosynthetic strategy (generation II), an early stage of C-8 homologation was studied. As shown below in Scheme 42, **173** was converted to aldehyde **180** in two steps in 65% yield. Wittig olefination of the aldehyde with ylide **166** gave triene **181** in 85% yield, which could be reduced to **182** by DIBAl. The reaction often gave a mixture of products including **182**. Alternatively, hydrogenation of the triene to saturated compound **183,** followed by treatment with DIBAl gave the desired alcohol **184** in good overall yield.



Scheme 29. C-8 Homologation and Alcohol Formation

2.5.3.2 Removal of the Template and Attempted Further Elaboration

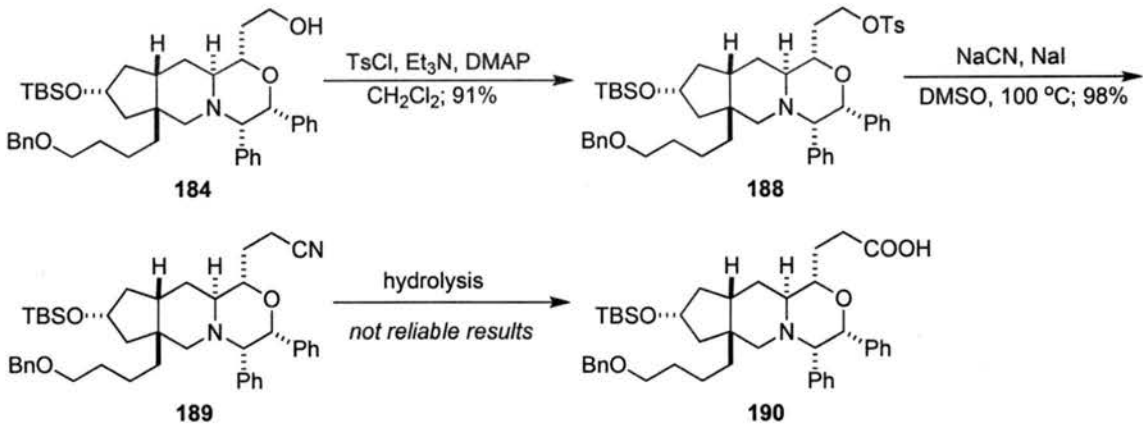
The following removal of the template from **184** successfully gave the desired very polar triol (**185**) in high yield. Next step was planned to protect the amine and the hydroxyl groups to **186**, which would be converted to **187** in a few more steps. But the very polar nature of **185** made the further manipulation of this intermediate very difficult. **185** was lost and no desired product was obtained when treated with CbzCl and $NaHCO_3$ (saturated aqueous) in dichloromethane (**Scheme 30**).



Scheme 30. Template Removal and Attempted Further Elaboration

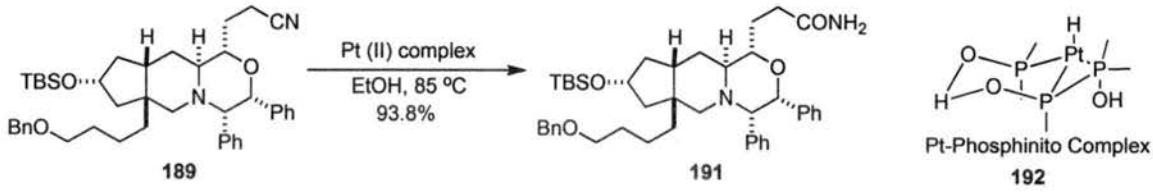
2.5.3.3 One Carbon Homologation of C-20

Alternatively, to avoid tedious protecting group manipulations, one carbon homologation of C-20 would provide the right side butyrolactone carbon skeleton, and hopefully cyclization would happen spontaneously during removal of the template.



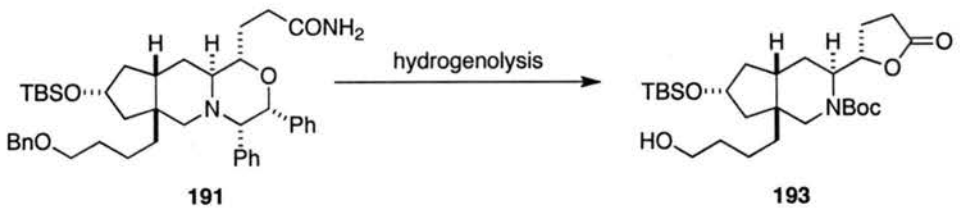
Scheme 31. One Carbon Homologation via a Three-Step Sequence.

As shown above, carboxylic acid **190** could be made in a three step sequence from alcohol **184** by tosylation of the alcohol followed by cyanide displacement to give **189**, which could be converted to **190** through strong base hydrolysis (**Scheme 31**). In practice, treatment of **189** with sodium hydroxide in ethanol under reflux for a couple of days gave **190** and several undetermined products. On the other hand, Pt-Phosphinito[55] complex catalyzed hydration of the cyanide in ethanol gave primary amide **191** in very good yield (**Scheme 32**).



Scheme 32. Cyanide Hydration

2.5.4 Removal of the Template and Lactone E Ring Formation

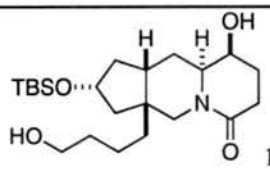
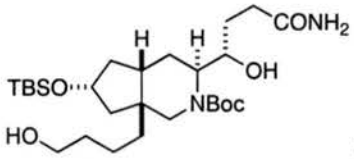
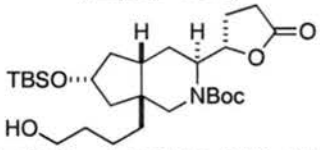


191 193

Figure 37. Removal of the Template

To remove the template (**Figure 37**), **191** was treated with 20% $Pd(OH)_2/C$ in ethanol under 120 psi H_2 at 85 °C for 36 h. The template was successfully cleaved, however again, to give an undesired lactam **194** (**Table 7**, entry 1), which was derived from an intramolecular cyclization of the secondary amine and the primary amide after the cleavage of the template in a similar manner as that of **176** (**Scheme 27**). Hydrogenolysis under acidic condition as in entry 2 did not give a clean result. Since we learned from the formation of **176** that the C-N cleavage was faster than that of C-O, we thought immediate protection of the resulting amine would be helpful to avoid the lactam formation; and this turned out to be true. When Boc_2O was added to the hydrogenolysis condition as shown in entry 3 with a reaction scale of 5-33 mg of substrate **191**, desired product **195** was obtained in high yield and as the major observed product. In entry 4, a mixture of **193**, **194** and **195** were obtained with a reaction scale of 120 mg under 130 psi H_2 pressure instead of 120 psi and in more concentrated solution. However, trying to improve the ratio of the lactone **193** by running longer time and in a little more concentrated condition only gave decomposition of the products (entry 5).

Table 7. Hydrogenolysis Studies

Entry	Conditions	Results
1	20% $Pd(OH)_2/C$, 120 psi H_2, EtOH, 85 °C, 36 h	 **194**
2	$PdCl_2$, 1N HCl, 120 psi H_2, EtOH, 85 °C, 16 h	decomposed?
3	*20% $Pd(OH)_2/C$, **Boc_2O, 120 psi H_2**, EtOH, 85 °C, 36 h, 0.012M*	 **195** (major, 91.5%)
4	*20% $Pd(OH)_2/C$, **Boc_2O, 120-130 psi H_2**, EtOH, 85 °C, 36-44 h, 0.05M*	 **193** (20-35%) and **195** (46-56%), **194** (~10%)
5	*20% $Pd(OH)_2/C$, **Boc_2O, 130 psi H_2**, EtOH, 85 °C, 48 h, 0.058M*	decomposed

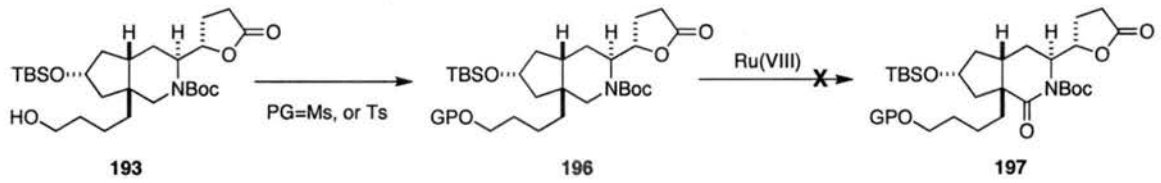
Since a considerable amount of primary amide **191** was obtained, it was necessary to find a way to convert it to lactone **193**. However, though several conditions (**Table 8**) were investigated,[56] none of them provided clean reaction with lactone cyclization as the major product.

Table 8. Studies of Lactone Formation from Primary Amide

Entry	Conditions	Results
1	$CuCl_2$, MeCN-H_2O, 50 °C-reflux 5 h	no product obtained
2	1N HCl, dioxane-H_2O, pH=2, r.t., 2 d	multiple products
3	1N NaOH (20 equiv), EtOH-H_2O, 50 °C, 6-9 h; 1N HCl, pH=3, 1-12 h	multiple products
4	1N NaOH (2 equiv), EtOH-H_2O, 50 °C, 20 h; 1N HCl, pH=3, 1 h	multiple products
5	MeCN, Boc_2O, DMAP, Et_3N, r.t., 24 h	no desired P
6	EtOH, Boc_2O, 85 °C, 9 d	trace **193** observed

2.5.5 Studies of the Lactam D Ring Construction

2.5.5.1 Attempted Introduction of the Carbonyl Group



Scheme 33. Attempted Amine Oxidation

The hydroxyl group was protected to the corresponding mesylate **196a** (MsCl, Et_3N, CH_2Cl_2, 0 °C), or tosylate **196b** (TsCl, DMAP, Et_3N, CH_2Cl_2, r.t.) before subjection to oxidation conditions intending to introduce the carbonyl functionality in **197a**, **197b** (**Scheme 33**).

Table 9. Tertiary Amine Oxidation

Entry	OPG	Conditions	Results
1	OTs	$RuCl_3$, $NaIO_4$, MeCN-$CHCl_3$-H_2O (2:2:3), 12 h	no reaction
2	OTs	$RuCl_3 \cdot H_2O$, $NaIO_4$, MeCN-$CHCl_3$-H_2O (2:2:3), 30 h	no reaction
3	OTs	$RuCl_3 \cdot H_2O$, $NaIO_4$, MeCN-$CHCl_3$-H_2O (2:2:3), 85 °C, 10 h	no reaction
4	OMs	$RuO_2 \cdot H_2O$, $NaIO_4$, EtOAc-H_2O, r.t., 2-3 h	<5% conversion, mostly rec S.M.
5	Entry 4 Rec S.M.	$RuO_2 \cdot H_2O$, $NaIO_4$, MeCN-$CHCl_3$-H_2O, 60 °C, 3 d	unidentified P, no rec S.M
6	OMs	$RuO_2 \cdot H_2O$, $NaIO_4$, MeCN-$CHCl_3$-H_2O, rt, 3 d	rec S.M.
7	OMs	$RuO_2 \cdot H_2O$, $NaIO_4$, MeCN-$CHCl_3$-H_2O, 60 °C, 3 d	rec S.M. + unidentified P.
8	Entry 7 Rec S.M.	RuO_4, CCl_4, r.t., 12 h, then $NaIO_4$, H_2O	unidentified p no rec S.M.
9	2OTBDPS	$RuO_2 \cdot H_2O$, $NaIO_4$, EtOAc-H_2O, r.t., 36 h	rec S.M. + ???

Unexpectedly however, the tertiary amine on substrates **196a**, **196b** was much more difficult to oxidize than that of **177** (**Scheme 28**). Entries 1 to 7 (**Table 9**) were performed in heterogeneous conditions, while entry 8 was carried out under homogeneous condition, hoping for an increase of the oxidation ability.[57] Except entry 4, a trace product peak observed on HRMS, which was not a reliable result, all other efforts failed to detect the desired lactam.

It was reported that the ease of oxidation of the tertiary amine relied on how easily the nitrogen lone pair could be approached and the spatial disposition of the CH_2 to be oxidized.[57] So we thought that the electron-withdrawing Boc group and the relative steric

hindrance of the CH_2 position were the possible reasons causing the failure of the reaction. In addition, we thought that the ease oxidation of substrate **177** might be assisted with neighboring group participation of the acetate. With these in mind, the introduction of the carbonyl group will be postponed to a later stage of the synthesis, hoping that the tertiary alcohol could serve as the directing group for the oxidation of the amine to the desired lactam (**Figure 38**).

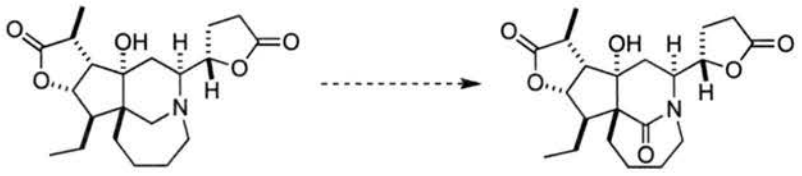
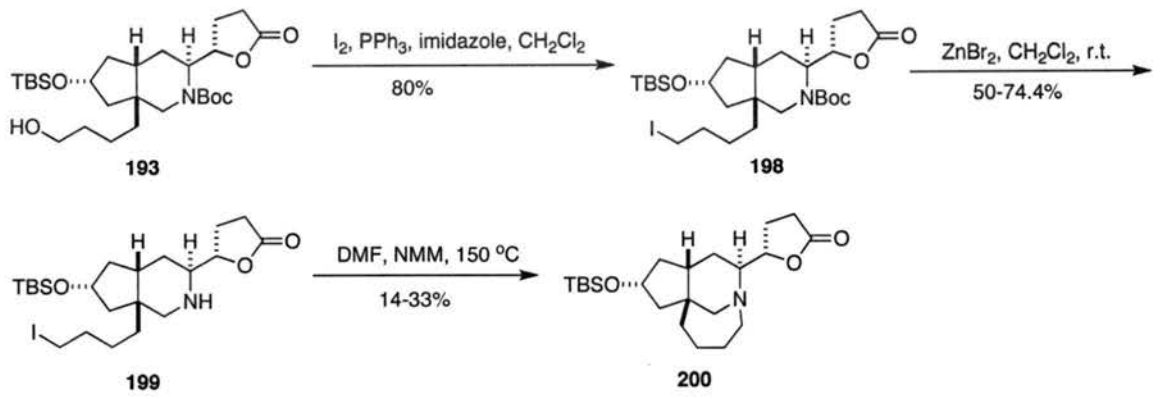


Figure 38. Proposed Late Stage Introduction of the Carbonyl Functionality

2.5.5.2 Azepine Formation via S_N2 Displacement Approaches

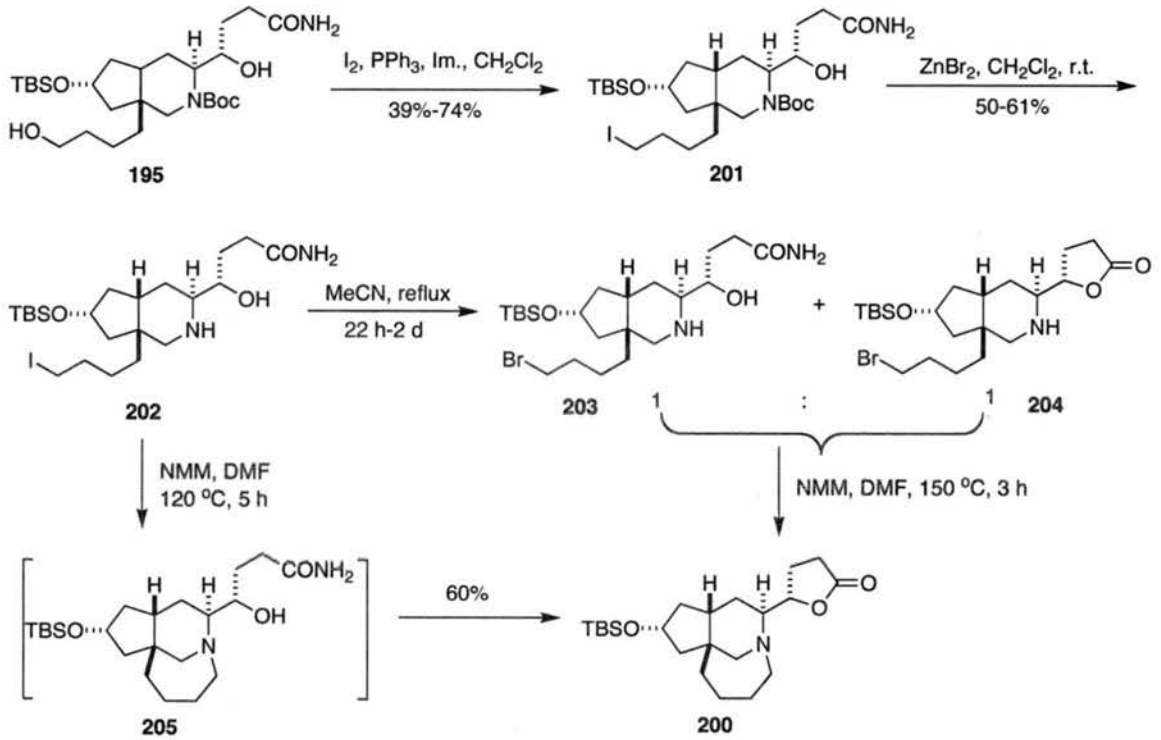
Attempt toward the azepine formation via Mitsunobu reaction was not successful by treatment of **199** with triphenylphosphine and diethylcarbodiimide in THF at 0 °C to room temperature. We next turned to the haloamination approach. Amine **199** was prepared from **193** in a three-step sequence by mesylation (MsCl, Et_3N, CH_2Cl_2, 0 °C, 74%) and iodide displacement (NaI, acetone, reflux, 47%) followed by deprotection of the Boc group (TFA, CH_2Cl_2, 0 °C, ~50%), or through an improved procedure in two steps (I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C-r.t., 80-82%; then $ZnBr_2$, CH_2Cl_2, 50-74.4%, **Scheme 34**). Amine **199** was then heated to 150 °C in DMF in the presence of *N*-methyl morpholine (NMM) for 3 h, providing the desired tetracycle (**200**) in 14-33% yield.



Scheme 34. Azepine Formation via S_N2 Displacement Involved with Haloamination

Another potential approach is intramolecular reductive amination to construct the azepine ring, which is especially important if compound **195** could be utilized in the synthesis. However, selective oxidation of the primary alcohol of **195** with $PhI(OAc)_2$ and TEMPO in dichloromethane at room temperature for long hours did not give the desired aldehyde. Then, the haloamination protocol as shown in Scheme 34 was adopted on substrate **195** (**Scheme 35**). Iodide **201** was obtained with careful control of the addition of the iodine and triphenylphosphine mixture in 39-74% yield along with an unidentified product. Deprotection of the Boc group with TMSCl, NaI in acetonitrile at room temperature gave baseline decomposition, oxidative cleavage with catalytic amount of cerium ammonium nitrate (CAN) in acetonitrile at 82 °C for 1-4 h did not give the desired product either. Treatment of **201** with excess anhydrous zinc bromide in dichloromethane gave the desired compound **202** in 50-61% yield along with undetermined side products. Several times of purification of amine **202** usually were needed to completely remove zinc bromide. Amine **202** containing zinc bromide was dissolved in acetonitrile and heated to reflux for long hours, cyclization did not happen as expected, but provided a mixture of the corresponding bromide products **203** and **204** as a

rough 1:1 mixture. This mixture was then treated with NMM in DMF under reflux for 3 h, tetracycle **200** was observed. Subjection of pure amine **202** in acetonitrile under reflux for 3-4 days, the azepine product was not observed. Amine **202** was then treated with NMM in DMF under reflux for 2 h, both azepine products **205** and **200** were observed. When a mixture of amine **202** and NMM was heated to 120 °C in DMF for 5 h, tetracycle **200** was obtained in 60% yield as the major product, presumably through intermediate **205**. A side product (possibly the elimination product) was also obtained as minor product in this process. Thus, both **193** and **195** were transformed to tetracycle **200** in a similar three-step sequence, at the same time solving the previous difficulty in conversion of the primary amide alcohol on **193** to the corresponding γ-lactone.



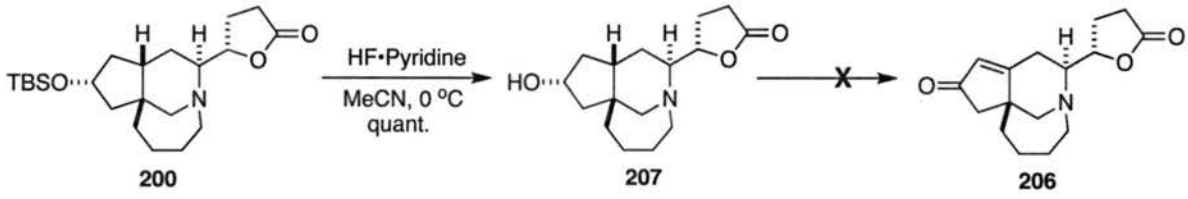
Scheme 35. Azepine and Lactone Formation from **195**

2.5.5.3 Efforts toward the Cyclopentenone Formation

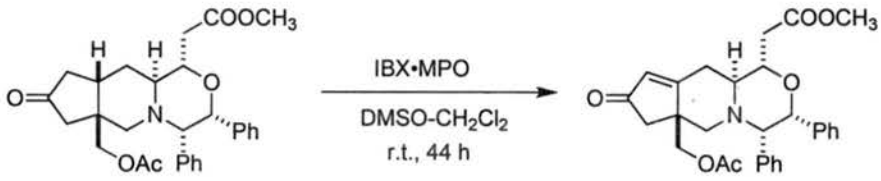
200 **206**

Cyclopentenone **206** is an important intermediate for the introduction of the C-1 tertiary alcohol. Deprotection of the silyl ether group was performed on substrate **200** with HCOOH-H_2O-THF (3:1:6) at room temperature, the silyl ether group was gone, however, the γ-lactone was hydrolyzed at the same time, only trace amount of desired alcohol **201** was observed. A problem using TBAF in THF at room temperature to deprotect the silyl ether group was the purification of the resulting crude product, especially for small-scale reactions. Fortunately, using excess amount of HF•Pyridine in acetonitrile at 0 °C provided quantitative yield of the alcohol **207** after chromatography (**Scheme 36**). The resulting alcohol **201** was then attempted to oxidize to the corresponding enone **206** in one step using IBX or IBX•*N*-oxide complex but failed (**Table 10**, entries 1, 2, 3 and 4). In a model study according to Nicolaou's protocol[58] for mild oxidation of ketone to conjugated ketone, enone **209** was obtained when treatment of **208,** which was obtained in three steps by hydrogenation of the diene of **173**, HF•Pyridine deprotection of the silyl ether followed by oxidation of the resulting alcohol with TPAP-NMO, and then with IBX•MPO in DMSO-CH_2Cl_2 at room temperature for 24-44 h (**Scheme 37**). Thus, alcohol **207** was converted to the ketone **210** in good yield by Swern oxidation (entry 6 and **Scheme 38**). Somehow the TPAP-

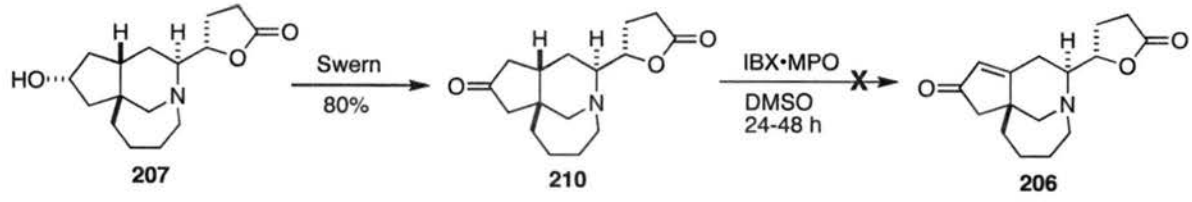
NMO oxidation only gave recovered starting material (entry 5). When treatment of the ketone **210** with IBX•MPO complex in DMSO for 24-48 h, very disappointingly, the desired enone product **206** was not observed (entry 7). Preliminary studies were performed on less than 1 mg scale starting material. We thought that more investigation of the IBX (or its complex) oxidation of ketone might be needed. Otherwise, we would have to turn to the conventional methods involved with oxidation of the TMS enol ether of the ketone with $Pd(OAc)_2$, or oxidation of selenium compound to form conjugated double bond.[59]



Scheme 36. Attempted Cyclopentenone Formation from Alcohol



Scheme 37. Model Study of IBX•MPO Oxidation of Ketone



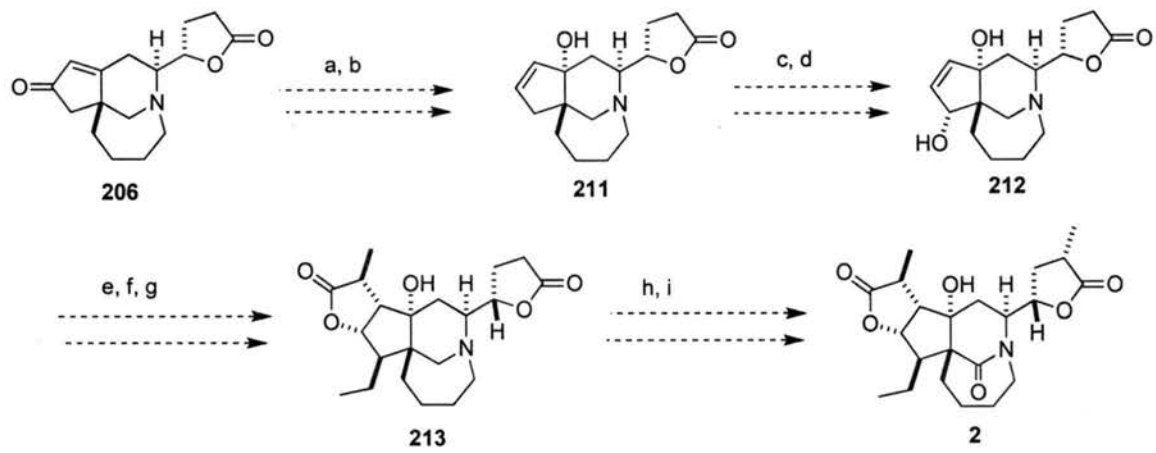
Scheme 38. Attempted Cyclopentenone Formation from Ketone

Table 10. Studies toward the Enone Formation

Substrates	Oxidants	Solvents	Temp.	Time	Results
1, **207**	IBX	DMSO-Toluene (1:2)	50 °C	5 h	ketone **210**?
2, **207**	IBX	DMSO	80-90 °C	24 h	no P
3, **207**	IBX•NMO	DMSO	85 °C	15 h	no P
4, **207**	IBX•MPO	DMSO	85 °C	7 h	no P
5, **207**	TPAP-NMO	CH_2Cl_2	0 °C-r.t.	1 h	S.M.
6, **207**	Swern	CH_2Cl_2	0 °C	30 min	ketone **210**
7, **210**	IBX•MPO	DMSO	r.t.	24-48 h	no P

2.5.6 Planned Completion of the Total Synthesis

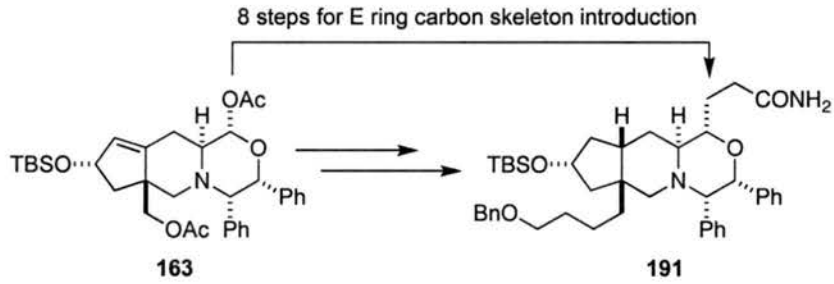
Planned completion of total synthesis of tuberostemoninol include the tertiary alcohol introduction in **211** via an epoxidation-hydrazine reduction sequence (Wharton oxygen transposition); allylic oxidation with selenium dioxide followed by Luche reduction to install the secondary alcohol in **212**; Eschenmoser-Claisen rearrangement to introduce the carbon skeleton in γ-lactone A ring followed by epoxidation-epoxide ring opening with triethyl aluminum to introduce the ethyl group in **213** as well as spontaneously cyclization of the A ring; regioselective oxidation of the azepine with *in situ*-generated Ruthenium (VIII) to the lactam and the final introduction of the α-methyl group on the E ring via electrophilic addition of methyl iodide to the enol ether to complete the total synthesis of tuberostemoninol **2** (**Scheme 39**).



a. H_2O_2, $NaHCO_3$; b. NH_2NH_2, HOAc; c. SeO_2; d. Luche; e. 1,1-dimethoxy-*N*,*N*-dimethylpropan-1-amine f. *m*CPBA; g. Et_3Al; h. $RuCl_3/NaIO_4$; i. LDA, MeI.

Scheme 39. Future work

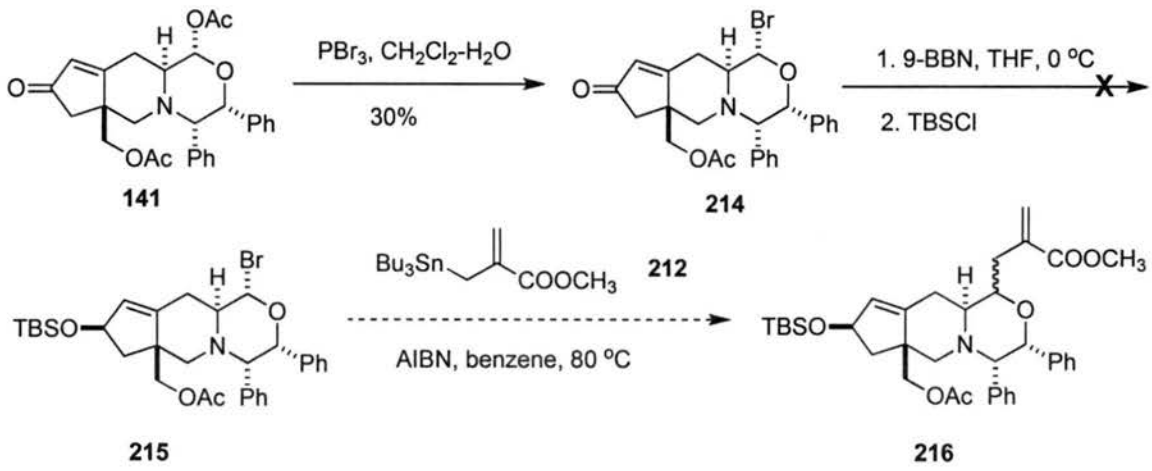
2.5.7 Other Efforts toward the Installation of the E Ring Carbon Skeleton



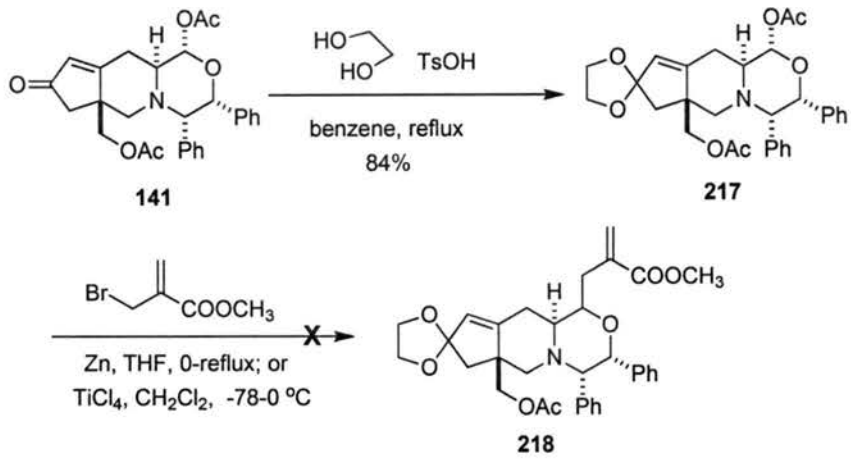
Scheme 40. Previous Synthetic Route for E Ring Installation

Previous successful synthetic route for the installation of E ring carbon skeleton without the methyl group in **193** needed 8 steps from compound **163** (**Scheme 40**). To shorten the synthesis, introduction of the carbon skeleton in E ring in one single step were further studied after the attempted C-C formation via Lewis acid promoted allylation of the acetal failed (entry 7, **Scheme 23**). Other potential approaches worth exploration for

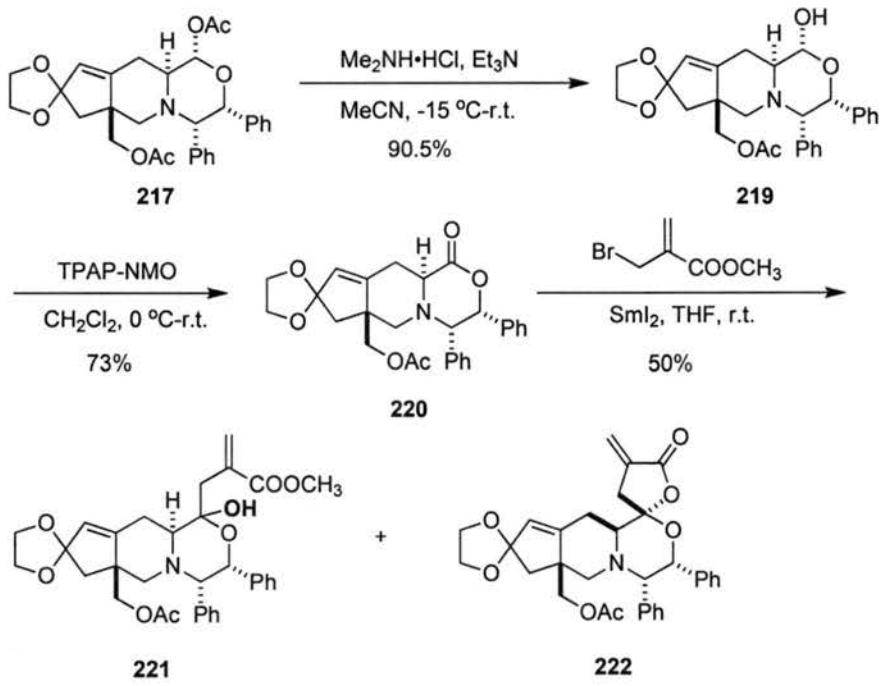
C-C formation via anomeric carbon include radical C-C formation,[60] Lewis acid-promoted Reformatsky-type reaction,[61] and SmI_2 promoted Reformatsky-type reaction.[62] Attempted bromide compound **215** was not able to make from the planned reactions (**Scheme 41**). $TiCl_4$ catalyzed Reformatsky reaction of the acetate compound **217** with methyl 2-(bromomethyl)acrylate in the presence of zinc also failed (**Scheme 42**). Delightfully, SmI_2 promoted reaction of lactone **220** with methyl 2-(bromomethyl)acrylate in THF was successful with half conversion of the starting material. Lactone **221** was obtained as the only product instead of **222** (**Scheme 43**). We think that with **221**, being made in 10 steps from commercially available glycinate **135**, the synthesis of tuberostemoninol could be shortened within 30 steps via an advanced intermediate **224** (**Scheme 44**). Most importantly, the reactions for making **221** were large-scale suitable to provide sufficient amount of material for later stage synthesis, solving the problems we have in the previous route.



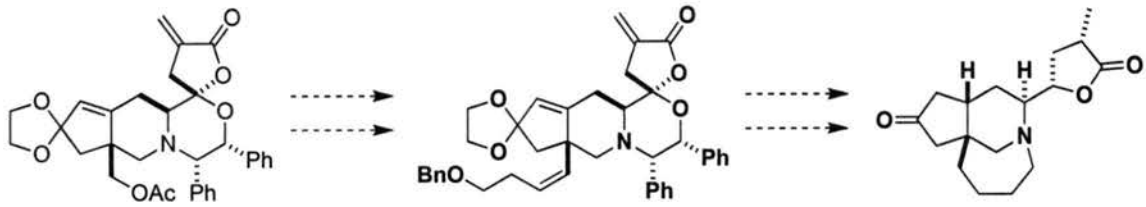
Scheme 41. Attempted Radical C-C Formation



Scheme 42. Attempted Lewis Acid Catalyzed Reformatsky-Type Reaction



Scheme 43. SmI_2 Promoted Reformatsky C-C Formation



Scheme 44. Plausible Tetracycle **224** Formation from **221**

2.6 Conclusions

A highly stereocontrolled synthesis of tetracycle **210** have been achieved as an initial effort toward *Stemona* alkaloids containing a novel [5-6-7] nucleus. Preliminary studies for further elaboration of this intermediate toward tuberostemoninol were performed. Other approaches for appended γ-lactone E ring installation have been explored aiming an efficient concise synthesis. We believe that tetracycle **210** could serve as the scaffold to approach to four natural products of the *Stemona* family: tuberostemoninol (**2**), neotuberostemoninol (**3**), maireistemoninol (**4**), and sessilifoliamide (**5**).

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c) es.wikipedia.org/wiki/Stemona d) www.fzrm.com/.../Stemona_Root_extract.htm
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Chapter 3: Experimental Section

3.1 General Considerations

Unless otherwise noted, materials were obtained from commercial sources and used without purification. Dichloromethane, diethyl ether, tetrahydrofuran, acetonitrile, toluene, dimethylformamide, dimethyl sulfoxide, triethyl amine, and methanol were degassed with argon and passed through a solvent system (J. S. Meyers of glass Contour) containing either alumina or molecular sieves. The molecular sieves were activated by heating at 150 °C in oil-bath under vacuum (1 mm Hg) for 12 h. Analytical and preparation TLC used Merck silica gel 60 F-254 plates, and silica gel 60 (200-300 mesh, Merck) was used for flash chromatography.

All reactions requiring anhydrous conditions were performed under an inert atmosphere (Ar) dried by passage of a column packed with $CaSO_4$ in flame-dried glassware. Flash chromatography was performed on Merck silica gel Kiesegel 60 (230-400 mesh) from EM science with indicated solvents under a positive air pressure.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Varian 300 MHz or 400 MHz spectrometers. The chemical shifts (δ) are reported in parts per million (ppm) relative to $CHCl_3$, CH_3COCH_3, or MeOH internals using the following format: chemical shift [multiplicity (s=singlet, br=broad singlet, d=doublet, t=triplet, q=quartet, m=multiplet, app=apparent, comp=complicated), coupling constants (*J* in Hz), integral]. ^{13}C NMR spectra were recorded at 100 MHz or 75 MHz, and chemical shifts were reported relative to $CHCl_3$, MeOH, or CH_3COCH_3 peaks.

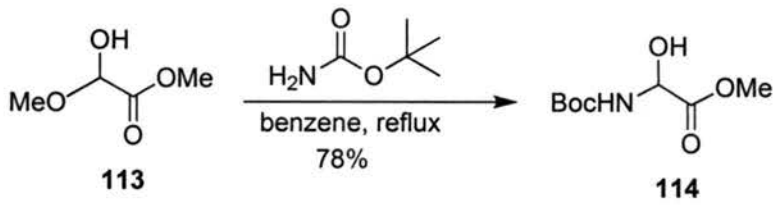
Mass Spectra were obtained at the Colorado State Univeristy CIF on a Fisons VG Autospec or Finnigan LCQ-DUO with HP1100 Series HPLC. Infrared spectra were recorded on a Perkin-Elmer FT-IR 1600 series as thin films deposited from methylene chloride or methanol solutions on NaCl plates followed by solvent evaporation. IR absorptions were reported in cm^{-1}. Not all peaks were included in the thesis. Optical rotations were obtained on a Rudolph Research Autopol III automatic polarimeter.

Both glycinates (2*R*, 3*S*)-*tert*-butyl 6-oxo-2,3-diphenylmorpholine-4-carboxylate and its enantiomer were used in experimentals.

3.2 Experimental Procedures

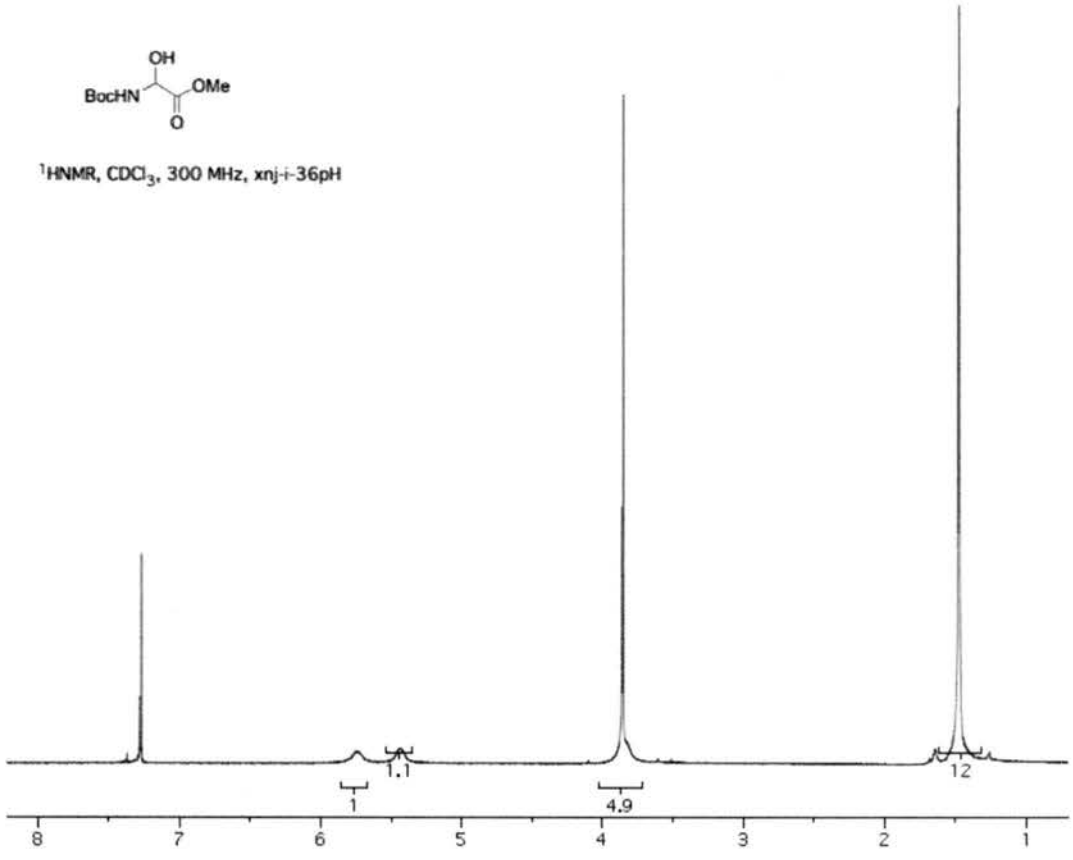
3.2.1 Racemic Synthetic Studies

methyl 2-(*tert*-butoxycarbonylamino)-2-hydroxyacetate (114)

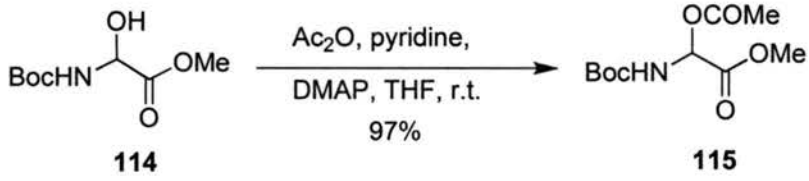


tert-Butylcarbamate (2.51 g, 21.45 mmol) was dissolved in benzene (50 mL) at stirring followed by the addition of hemiacetal **113** (5.66 g, 47.2 mmol) dropwise via syringe at room temperature. The resulting mixture was heated to reflux for 19-24 hours. Solvent was removed under rotavap. The residue was triturated with ether-hexane (1:1) and filtered to give 6.25 g (71%) of hemiaminal **114** as white amorphose solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.74 (br, 1H), 5.43 (br, 1H), 3.86 and 3.85 (s, 3H), 1.482 and 1.47 (s, 9H).



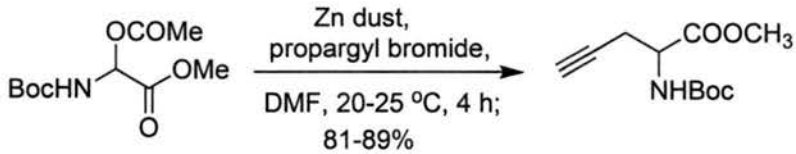
methyl 2-acetoxy-2-(*tert*-butoxycarbonylamino)acetate (115)



To an ice-cooled solution of hemiaminal **114** (6.2 g, 30.26 mmol) in THF (31 mL) was added pyridine (4.89 mL, 60.5 mmol) followed by acetic anhydride (3.14 mL, 33.3 mmol) dropwise followed by DMAP (369 mg, 10 mmol%). Remove cold bath and stir for 3 h. Solvent was removed under reduced pressure. The residue was partitioned

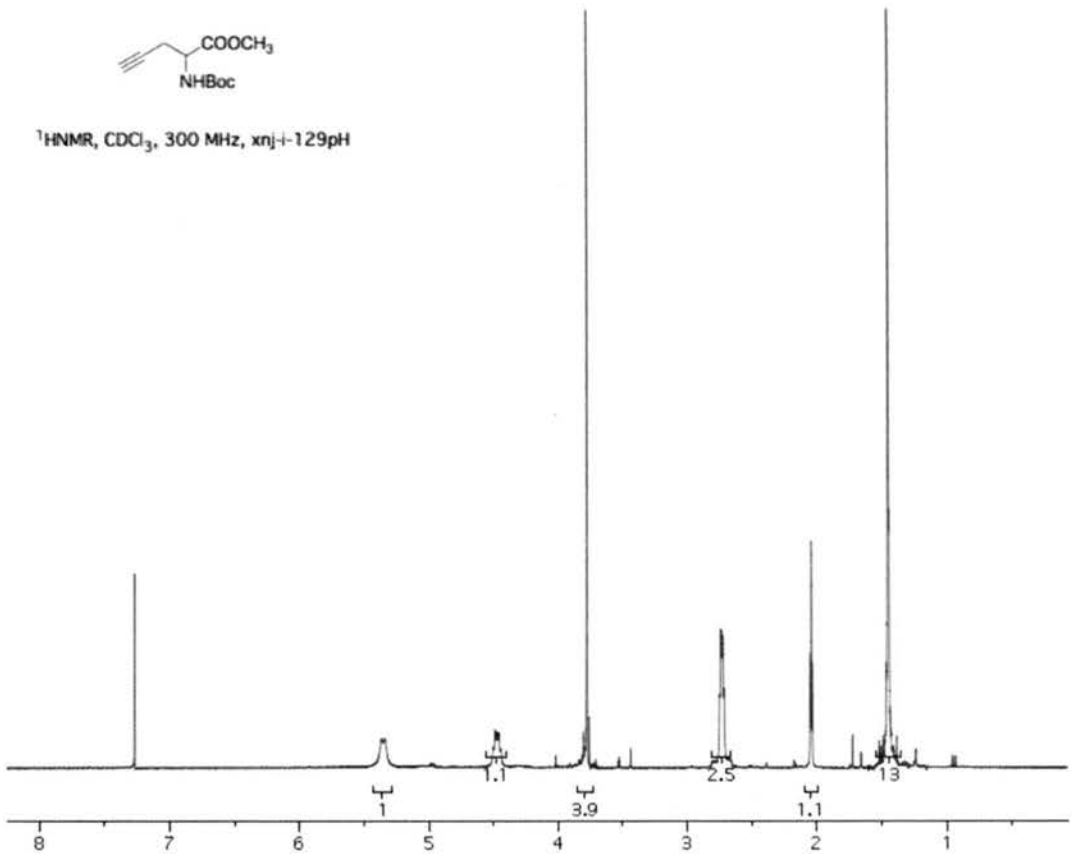
between ethyl acetate and saturated aqueous $NaHCO_3$, separated. The aqueous layer was extracted with ethyl acetate three times and the combined organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated to give 6.84 g (91.4%) of product **115** as light yellow oil. The crude product was put onto vacuum for overnight and was used without further purification.

dl-methyl 2-(*tert*-butoxycarbonylamino)pent-4-ynoate (116)

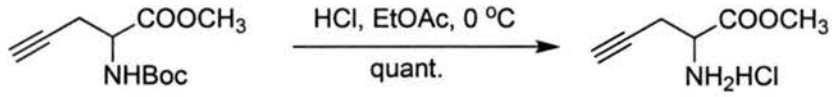


115 **116**

To an ice-cooled suspension of **115** (2.0 g, 8.1 mmol) and zinc dust (1.315 g, 20.25 mmol) in DMF (15 mL) was added slowly propargyl bromide (2.26 mL, 20.25 mmol) via syringe in such a manner that the reaction mixture temperature was maintained between 20-25 °C. Cold bath was removed after finishing addition. The resulting mixture was then stirred for an additional 4 h. The reaction was diluted with ethyl acetate, washed successively with 0.5 N HCl, saturated $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated. Flash chromatography (1:2 EtOAc/Hexanes) gave 1.584 g (86%) of propargyl glycine derivative **116** as colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.37 (d, J=7.5Hz, 1H), 4.50-4.44 (ddd, J=4.5Hz, 4.5Hz, 9Hz, 1H), 3.78 (s, 3H), 2.75-2.72 (ddd, J=2.7Hz, 2.7Hz, 4.8Hz, 2H), 2.05-2.03 (t, J=2.7Hz, 1H), 1.45 (s, 9H).



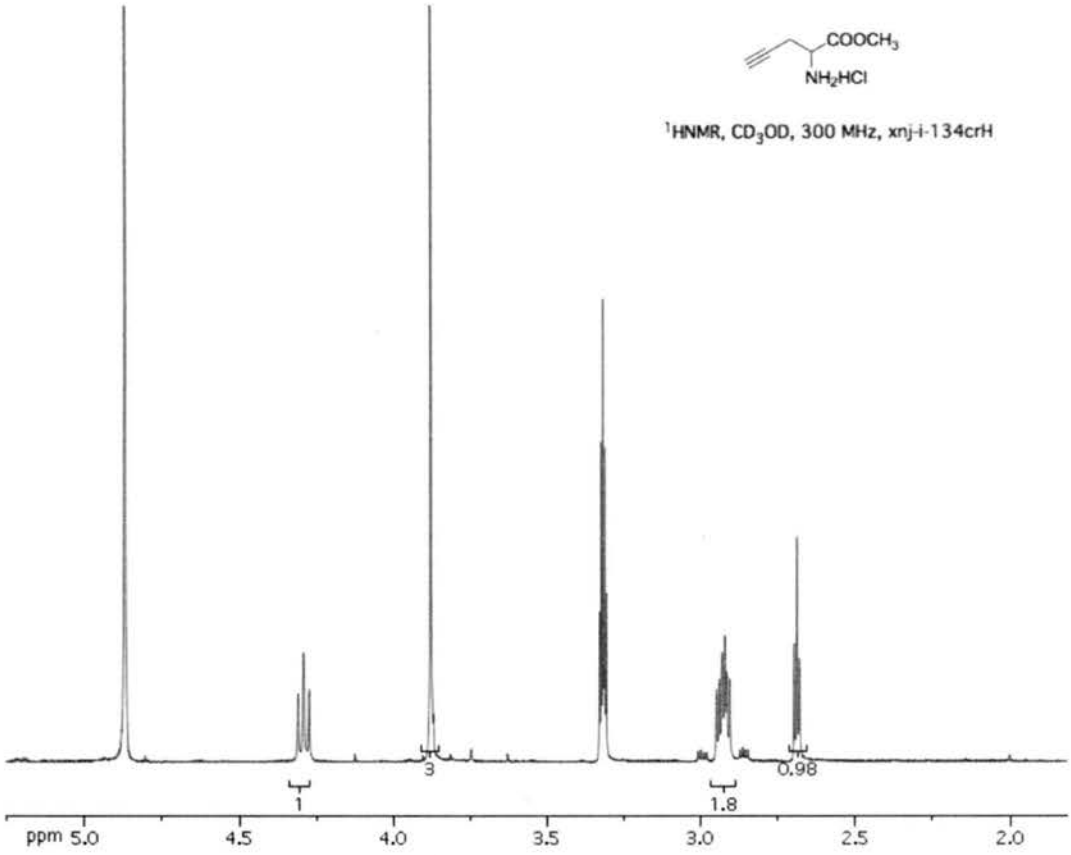
dl-methyl 2-aminopent-4-ynoate hydrochloride (117)



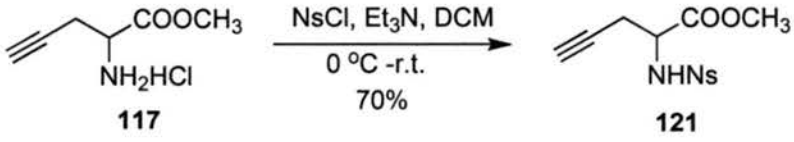
116 **117**

To a solution of compound **116** (1.003 g, 4.413 mmol) in ethyl acetate (20 mL) and ethanol (1.287 mL, 22.07 mmol) was added dropwise under ice-cold bath acetyl chloride (1.575 mL, 22.07 mmol). After the cold bath was removed, the reaction was stirred for an additional 5 h. Excess solvent was removed under rotavap to give crude product **117** in quantitative yield as white solid. ^{1}H NMR (CD_3OD, 300 MHz): 4.31-4.27 (t, J=10.8Hz,

1H), 3.88 (s, 3H), 2.95-2.91 (ddd, J=2.7Hz, 5.4Hz, 8.1Hz, 2H), 2.70-2.68 (t, J=2.5Hz, 1H).

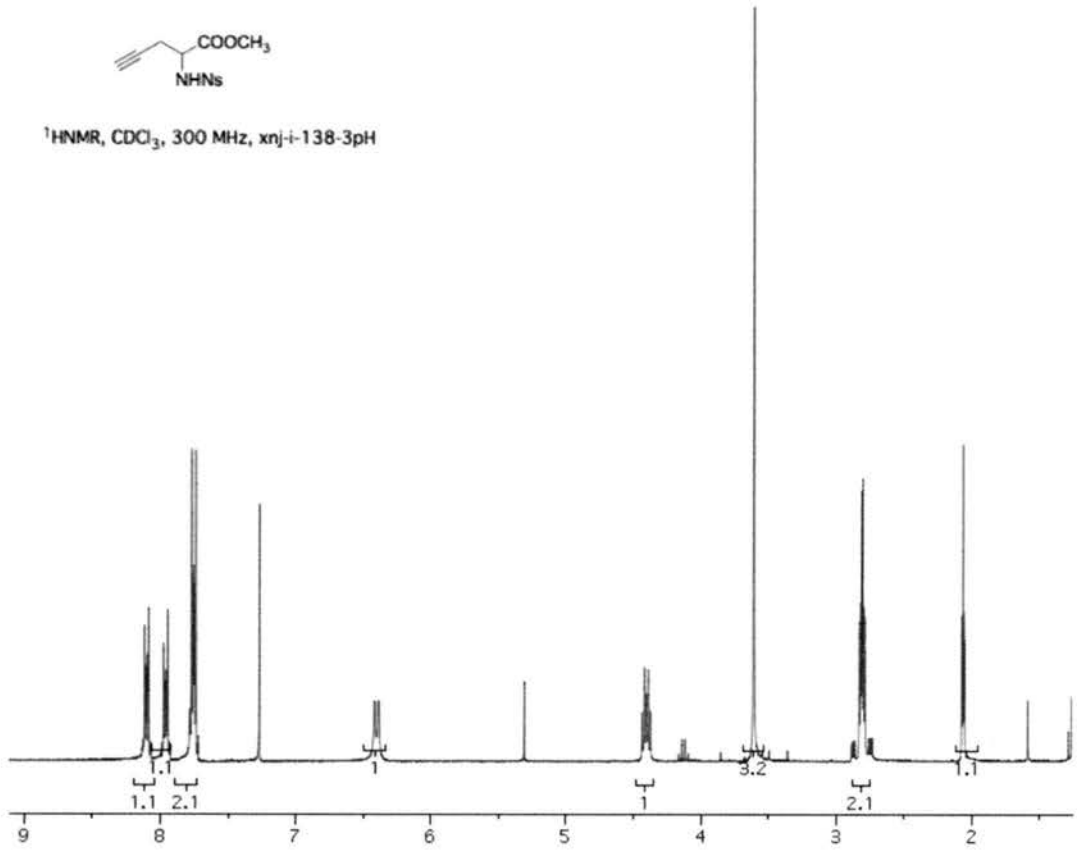


dl-methyl 2-(4-methylphenylsulfonamido)pent-4-ynoate (121)

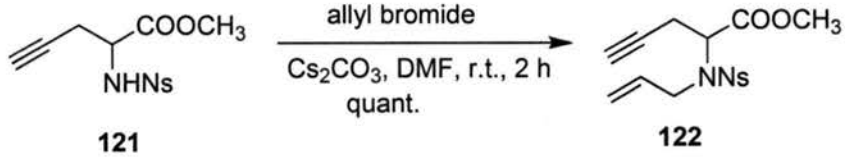


o-*N*-nitrophenylsulfonyl chloride was added to an ice-cold solution of **117** (0.722 g, 4.413 mmol) and Et_3N (1.85 mL, 13.24 mmol) in dichloromethane (35 mL). The

mixture was warmed up to room temperature and stirred 19 h or until the disappearance of the starting material on TLC. The reaction mixture was poured into 50 mL water, and separated. The organic layer was washed with water twice and combined aqueous layers were extracted with dichloromethane two times. Combined organic layers were dried over $MgSO_4$, filtered and concentrated. Flash chromatography (3:1 Hexanes/EtOAc) gave 0.99 g (70%) of desired product **121** as light yellow solid. ^1H NMR ($CDCl_3$, 300 MHz): 8.13-8.07 (m, 1H), 7.99-7.93 (m, 1H), 7.79-7.72 (m, 2H), 6.42 (d, J=9Hz, 1H), 4.43-4.37 (ddd, J=5.1Hz, 5.1Hz, 9Hz, 1H), 3.61 (s, 3H), 2.83-2.79 (ddd, J=2.7Hz, 4.8Hz, 7.2Hz, 2H), 2.08-2.06 (t, J=2.7Hz, 1H).

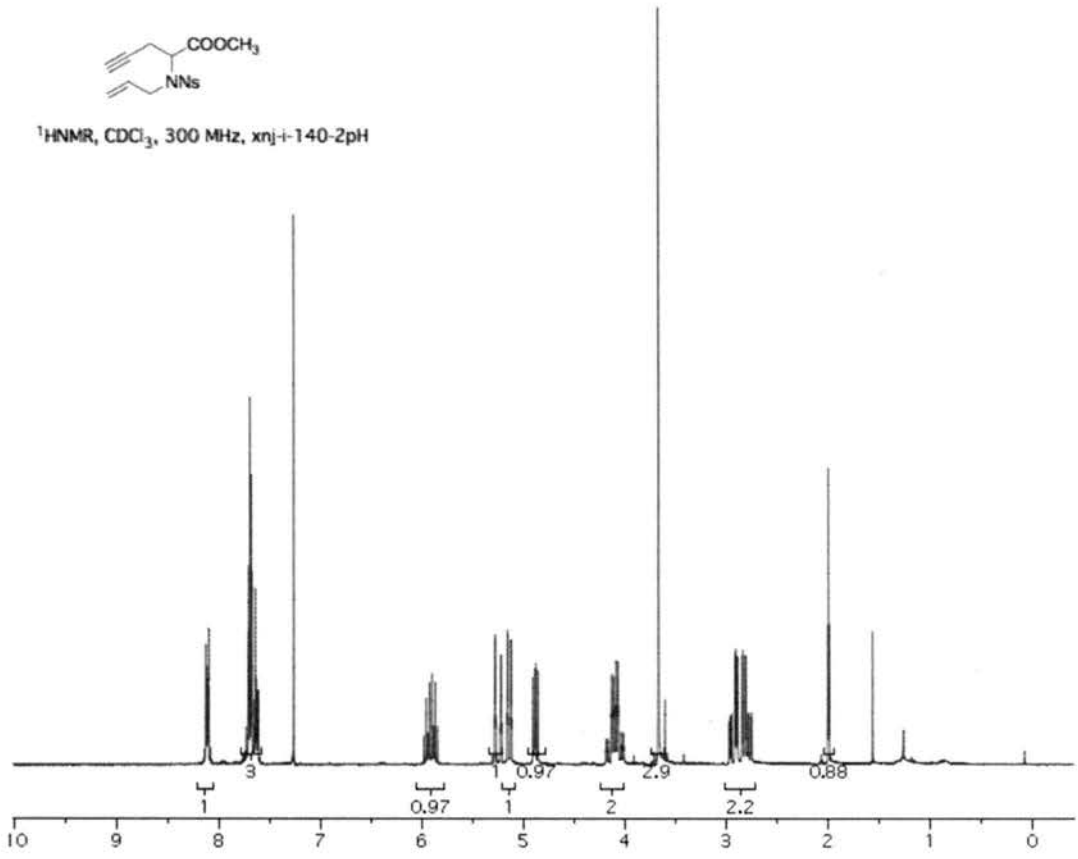


dl-methyl 2-(*N*-allyl-4-methylphenylsulfonamido)pent-4-ynoate (122)

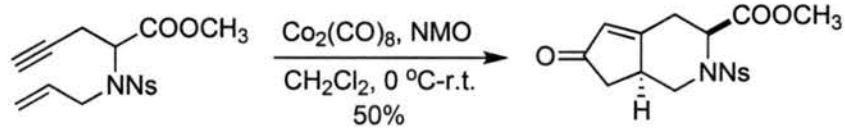


121 **122**

Cesium carbonate (240.9 mg, 0.7395 mmol) was added to a solution of the sulfonamide **121** (154 mg, 0.493 mmol) in DMF (5 mL). The reaction mixture was stirred for 30 min at room temperature before allyl bromide (85.3 μL, 0.986 mmol) was added. Reaction was stirred for 180 min and diluted with dichloromethane, washed with ammonium chloride, water and brine, dried over Na_2SO_4, filtered and concentrated. Flash chromatography (1:2 EtOAc/Hexanes) gave 1,7-enyne product **122** 142 mg (82%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.15-8.09 (m, 1H), 7.74-7.67 (m, 2H), 7.67-7.61 (m, 1H), 5.99-5.85 (dddd, J=6.3Hz, 6.3Hz, 10.2Hz, 22.8Hz, 1H), 5.29-5.22 (dddd, J=17.4Hz, 1.5Hz, 1.5Hz, 2.7Hz, 1H), 5.17-5.12 (dddd, J=10.2Hz, 1.2Hz, 1.2Hz, 2.4Hz, 1H), 4.91-4.86 (dd, J=5.7Hz, 8.7Hz, 1H), 4.20-4.4.11 (dt, J=1.2Hz, 6.3Hz, 1H), 4.10-4.01 (dt, J=1.5Hz, 6.3Hz, 1H), 3.67 (s, 3H), 2.98-2.89 (dd, J=2.4Hz, 5.4Hz, 1H), 2.85-2.75 (dd, J=2.7, 8.7Hz, 1H), 2.01-1.99 (t, J=2.7Hz, 1H).



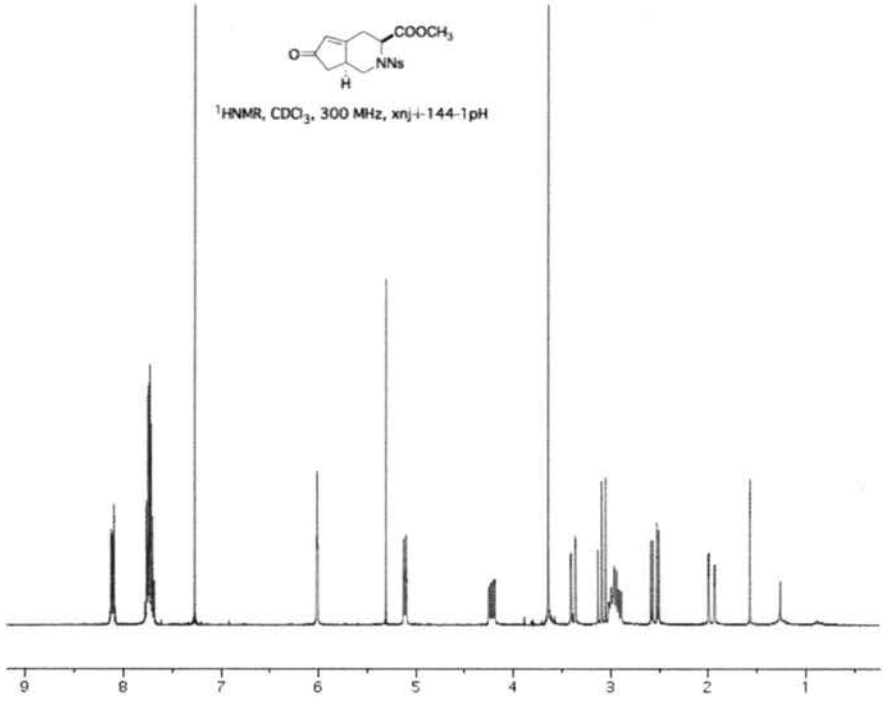
dl-(3*S*,7a*S*)-methyl 6-oxo-2-tosyl-2,3,4,6,7,7a-hexahydro-1*H*-cyclopenta[*c*]pyridine-3-carboxylate (123)

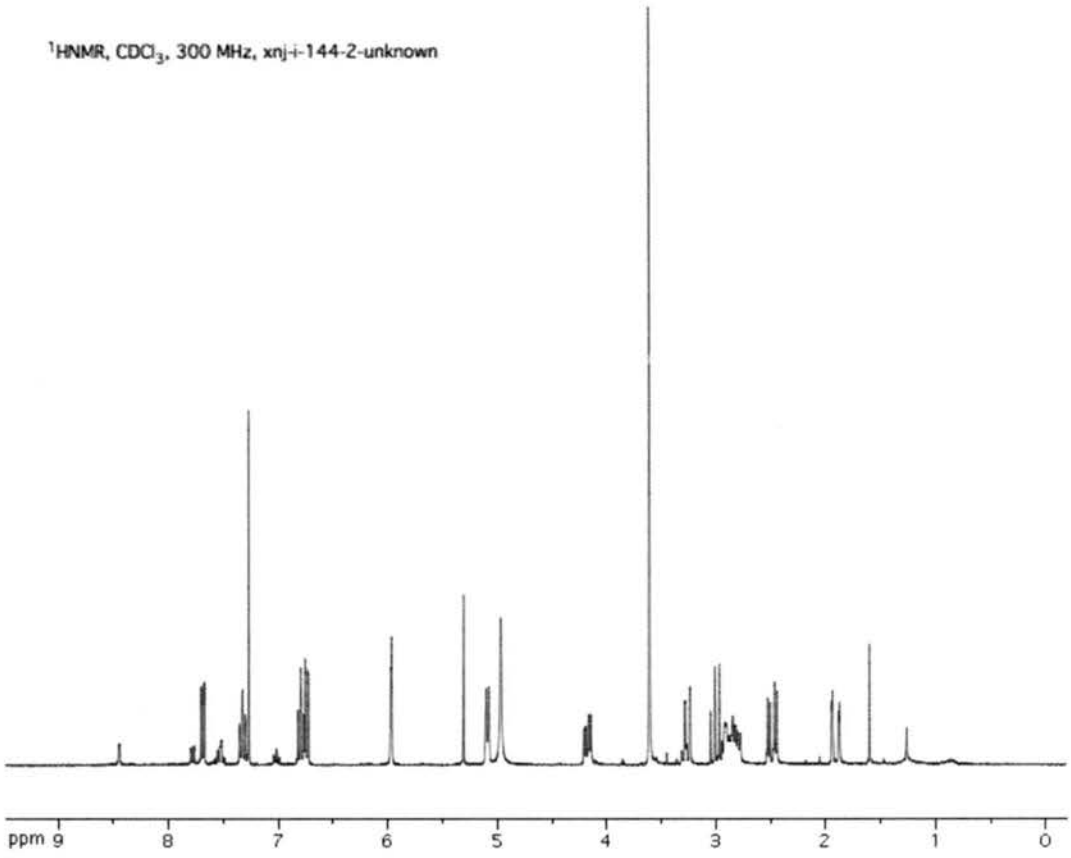


122 **dl-123**

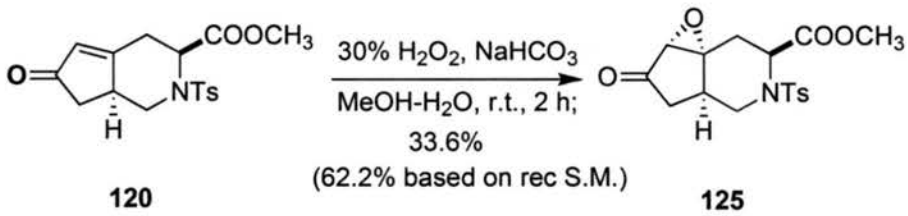
To a solution of the 1,7-enyne **122** (41.5 mg, 0.1178 mmol), was added $Co_2(CO)_8$ at room temperature, stirred for 1 h. The suspension was then cooled to 0 °C, first portion of NMO was added. Remove cold bath, the resulting purple suspension was stirred for an additional 1 h. Recooled with ice bath, second portion of NMO was added. Again,

remove cold-bath, stir for an additional 1.8 h or until the disappearance of complex spot on TLC. Reaction mixture was filtered through a pad of silica gel, washed with EtOAc, concentrated. The residue was purified by flash chromatography (2:1 EtOAc/Hexanes) to provide 22.2 mg (50%) of desired product **123** and 12 mg (27%) of unidentified product **124**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.14-8.08 (m, 1H), 7.78-7.69 (m, 3H), 6.02-6.01 (t, J=3.0Hz, 1H), 5.13-5.10 (dt, J=6.5Hz, 1.5Hz, 1H), 4.25-4.19 (ddd, J=1.2Hz, 6.0Hz, 6.9Hz, 1H), 3.64 (s, 3H), 3.41-3.36 (dd, J=1.5Hz, 14.1Hz, 1H), 3.13-3.05 (d, J=14.1Hz, 1H), 3.02-2.89 (m, 2H), 2.59-2.50 (dd, J=6.6Hz, 18.9Hz, 1H), 2.00-1.93 (dd, J=2.4Hz, 18.9Hz, 1H). **124** : δ 7.71-7.67 (dd, J=1.5Hz, 8.1Hz, 1H), 7.36-7.30 (ddd, J=1.5Hz, 1.5Hz, 5.4Hz, 1H), 6.82-6.73 (comp m, 2H), 5.97 (s, 1H), 5.10 (d, J=7.2Hz, 1H), 4.97 (s, 2H), 4.21-4.14 (dd, J=5.7Hz, 12.6Hz, 1H), 3.61 (s, 3H), 3.29-3.24 (dd, J=0.9Hz, 14.1Hz, 1H), 3.05-2.92 (m, 1H), 2.97-2.78 (comp m, 3H), 2.53-2.44 (dd, J=6.6Hz, 18.9Hz, 1H), 1.95-1.88 (dd, J=2.4Hz, 18.9Hz, 1H).





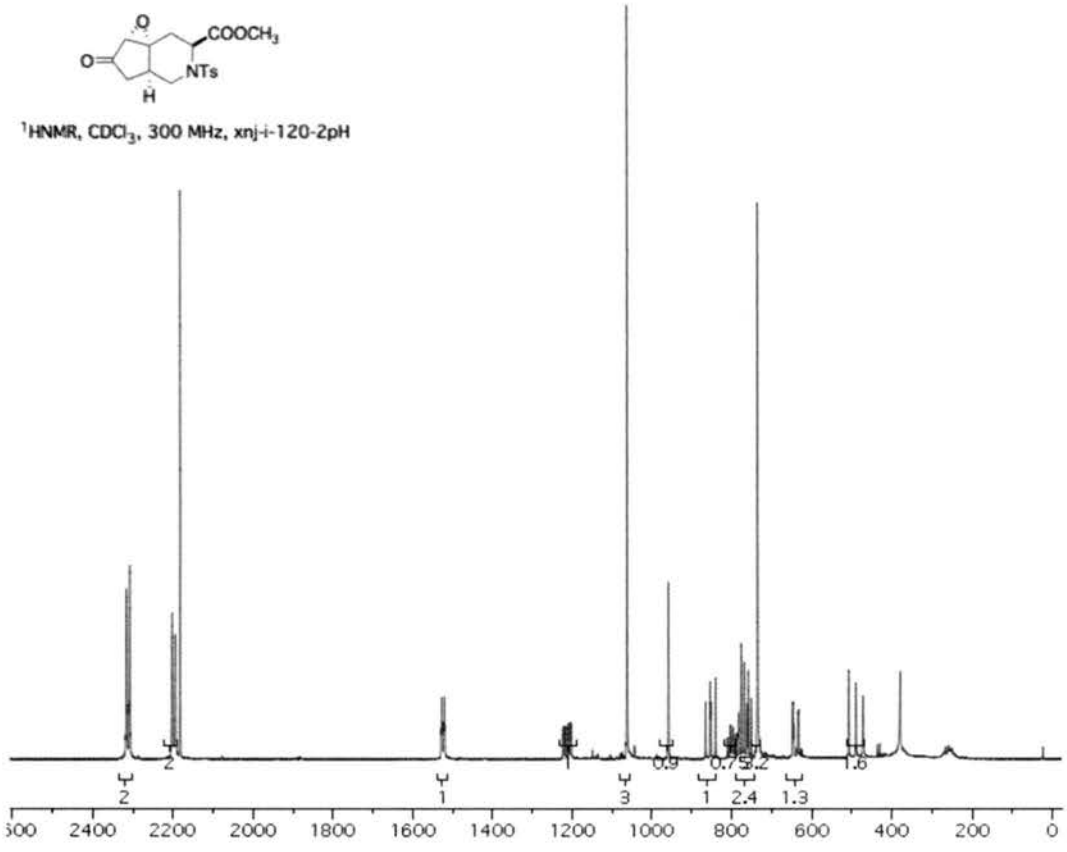
dl-Epoxide (125)

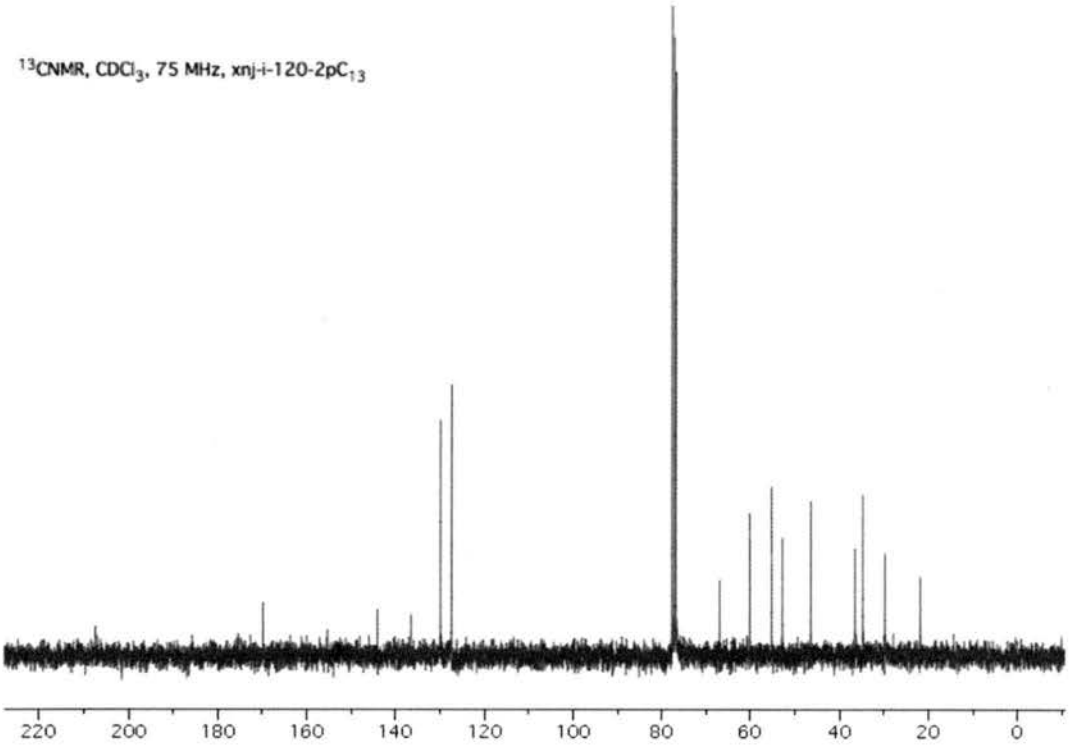


120 **125**

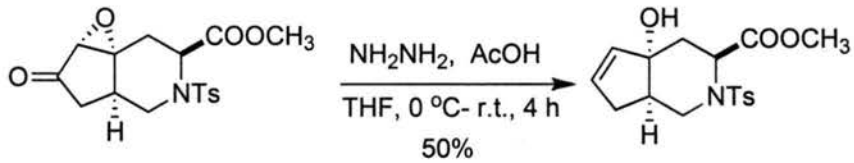
To an ice-cold solution of enone **120** (62 mg, 0.1775 mmol) in MeOH-H_2O (1:1) was added sodium bicarbonate (29.82 mg, 0.355 mmol) followed by 30% hydrogen peroxide (177.6 μL). The reaction was warmed up to room temperature and stirred for 2

h. The mixture was then poured into 60 mL saturated ammonium chloride and 60 mL ethyl acetate. The aqueous layer was extracted with 30 mL ethyl acetate, combined organic layers were dried over $MgSO_4$, filtered and concentrated. Flash chromatography (1:2 to 2:3 EtOAc/Hexanes) gave 21.8 mg (33.6%) of desired product **125** as a single diastereomer as colorless oil, and 28.5 mg (46%) of recovered starting material. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.72-7.69 (d, J=8.1Hz, 2H), 7.34-7.31 (d, J=8.7Hz, 2H), 5.09-5.07 (dt, J=6.6Hz, 1.5Hz, 1H), 4.07-4.01 (ddd, J=13.2Hz, 5.7Hz, 2.4Hz, 1H), 3.54 (s, 3H), 3.20 (s, 1H), 2.88-2.80 (dd, J=11.7Hz, 13.2Hz, 1H), 2.70-2.64-2.50 (comp m, 3H), 2.45 (s, 3H), 2.16-2.11 (dd, J=13.8Hz, 1.5Hz, 1H), 1.69-1.63 (d, J=17.7Hz, 1H). ^{13}CNMR ($CDCl_3$, 75 MHz): δ 207.39, 169.79, 144.07, 136.46, 129.86, 127.35, 66.93, 60.14, 55.25, 52.83, 46.45, 36.52, 34.81, 29.85, 21.90. FAB-HRMS: calcd for C17H20NO6S $[MH]^+$ 366. 0933, found 366.10105.


O
COOCH3
O
NTs
H
1HNMR, CDCl3, 300 MHz, xnj-i-120-2pH
2
2
1
3
0.9
1
0.7
2.4
1.3
1.6
500 2400 2200 2000 1800 1600 1400 1200 1000 800 600 400 200 0

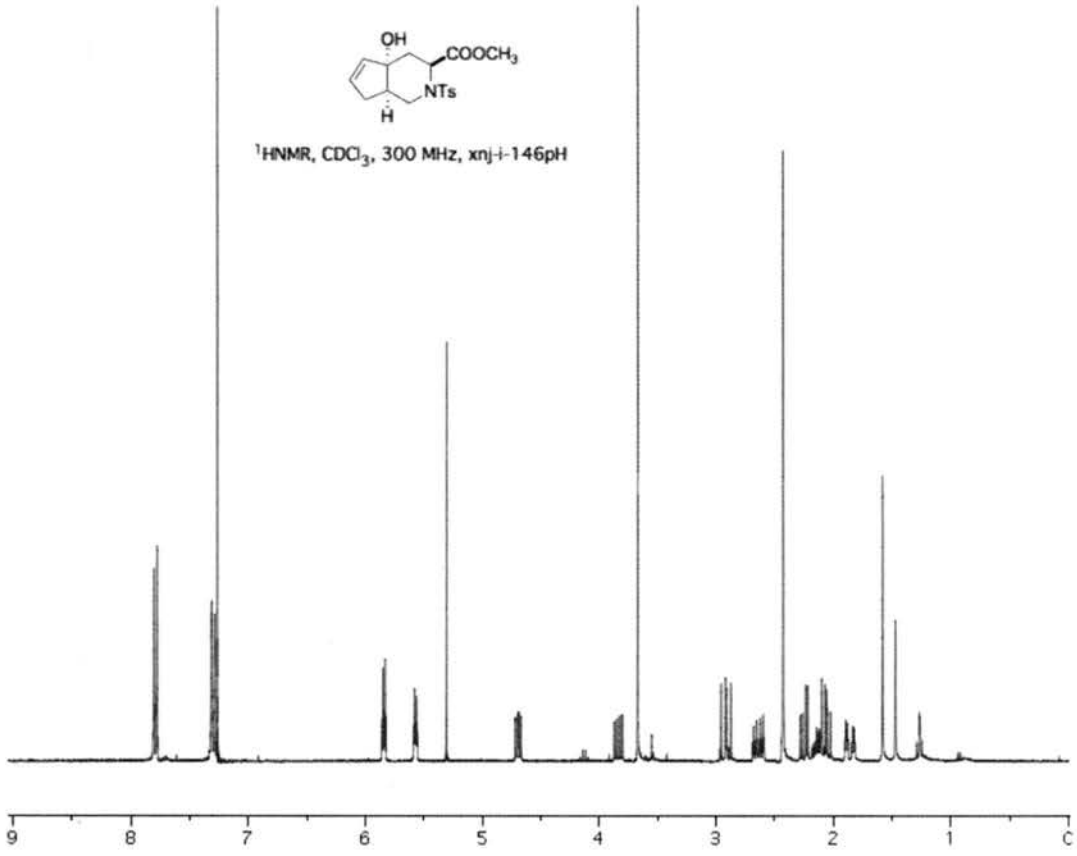

13CNMR, CDCl3, 75 MHz, xnj-i-120-2pC13
220 200 180 160 140 120 100 80 60 40 20 0

dl-(3*S*,4a*S*,7a*R*)-methyl 4a-hydroxy-2-tosyl-2,3,4,4a,7,7a-hexahydro-1*H*-cyclopenta[*c*]pyridine-3-carboxylate (126)



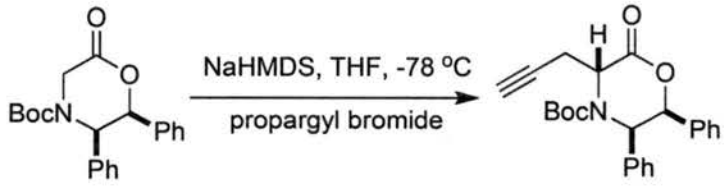
125 **126**

To a solution of **125** (20.9 mg, 0.0572 mmol) in THF (0.1 mL) was added hydrazine anhydrous (10.2 μL, 0.326 mmol) dropwise via syringe at room temperature, followed by a drop of glacial acetic acid. The resulting mixture was stirred at room temperature for 4 h. The reaction was diluted with chloroform and washed with 5% H_2SO_4. The acid washings were extracted with chloroform three times. The combined organic extracts were dried over $MgSO_4$, filtered through a small pad of silica gel. The solvent was removed via *vacuum*. Flash chromatography (1:2 EtOAc/Hexanes and then 5% MeOH in CH_2Cl_2) gave 10 mg (50%) of compound **126** as colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.81-7.78 (d, J=8.7Hz, 2H), 7.32-7.29 (d, J=8.1Hz, 2H), 5.86-5.834 (ddd, J=2.1Hz, 2.1Hz, 4.5Hz, 1H), 5.58-5.57 (ddd, J=2.1Hz, 2.1Hz, 5.4Hz, 1H), 4.72-4.67 (ddd, J=0.6Hz, 5.7Hz, 6.6Hz, 1H), 3.88-3.81 (dd, J=6.9Hz, 14.4Hz, 1H), 3.67 (s, 3H), 2.96-2.87 (dd, J=11.4Hz, 14.1Hz, 1H), 2.68-2.60 (ddt, J=7.8Hz, 17.4Hz, 2.1Hz, 1H), 2.43 (s, 3H), 2.28-2.22 (dd, J=5.7Hz, 13.8Hz, 1H), 2.18-2.03 (comp m, 2H), 1.90-1.83 (dddd, J=2.4Hz, 2.4Hz, 4.5Hz, 17.4Hz, 1H). FAB-HRMS: calcd for C17H22NO5S $[MH]^+$ 352.114, found 352.1222.



3.2.2 Asymmetric Synthetic Studies

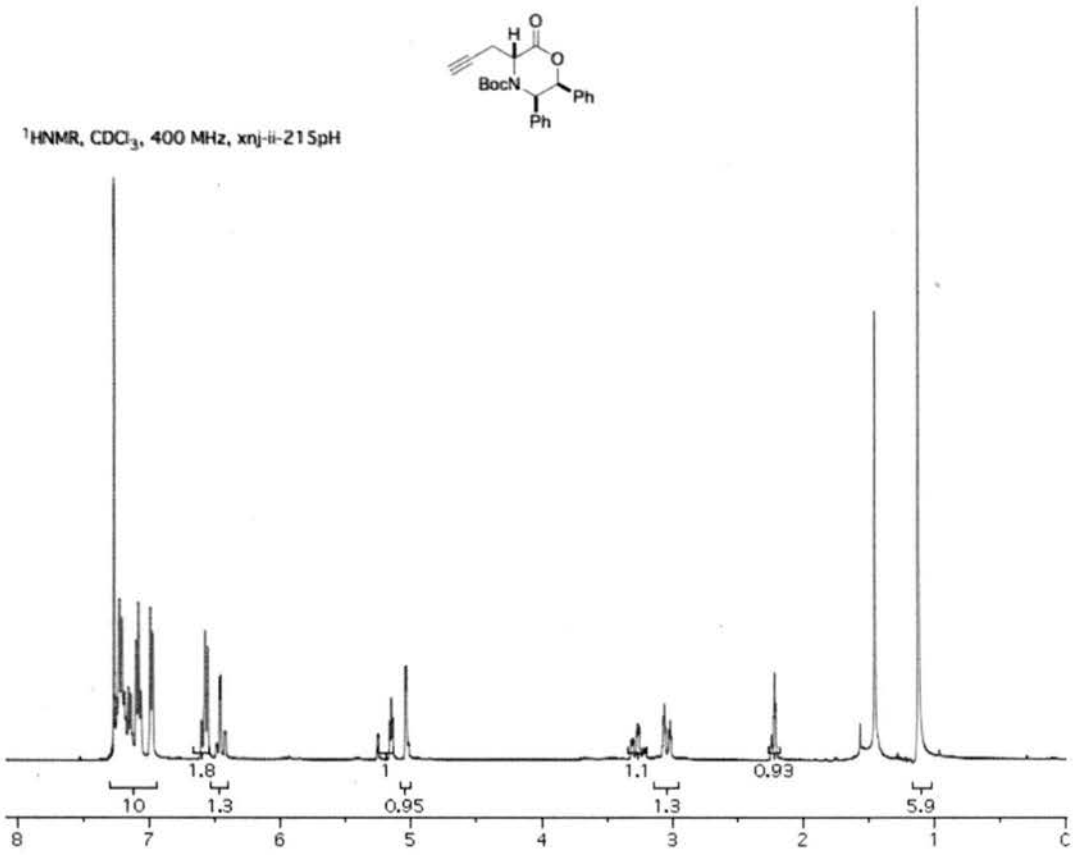
(3*S*,5*S*,6*R*)-*tert*-butyl 2-oxo-5,6-diphenyl-3-(prop-2-ynyl) morpholine-4-carboxylate (136)

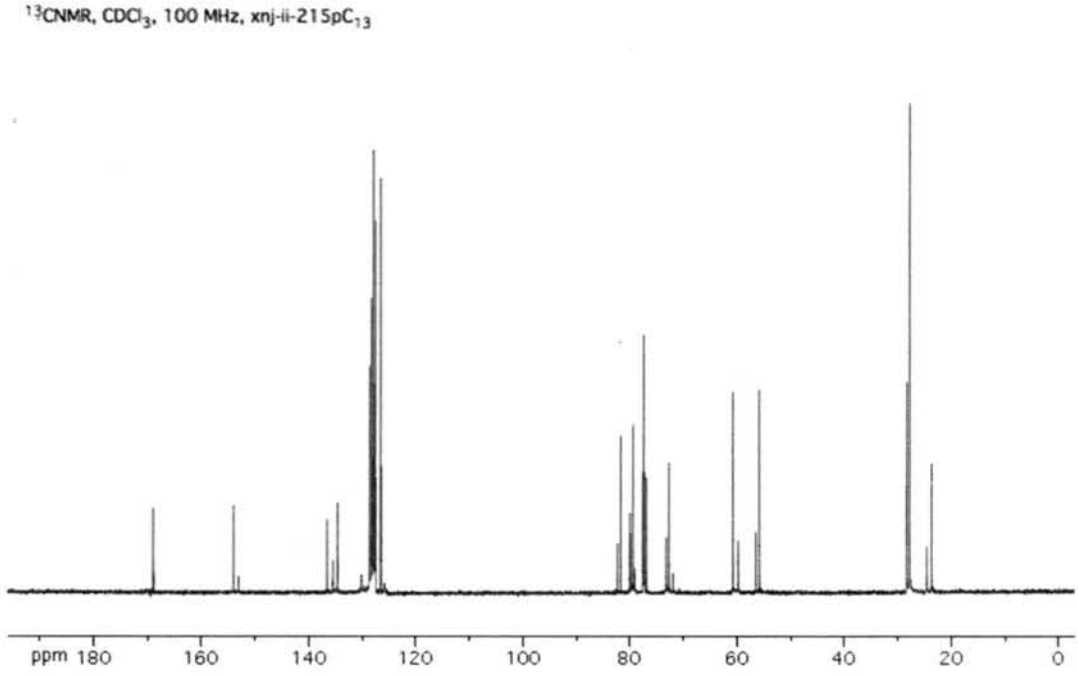


135 **136**

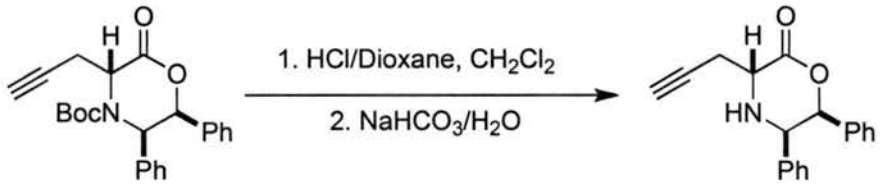
To -78 °C cooled solution of the oxazinone **135** (10.0 g, 28.30 mmol) in THF (180 mL) was added sodium bis(trimethylsilyl) amide (31.12 mL, 31.12 mmol, 1.0 M solution

in THF) dropwise via syringe during a period of 15 min. The resulting mixture was stirred for an additional 1 h at –78 °C. Propargyl bromide (4.1 mL, 36.78 mmol, 80% w/v in toluene) was added dropwise via syringe to the above mixture, stirred for 2.5 h under -78 °C. The reaction was then carefully quenched with ammonium chloride saturated aqueous solution and diluted with ethyl acetate. Remove cold and let it warm up to above 0 °C. The mixture was transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate for three times, the combined organic layer was washed with ammonium chloride saturated aqueous solution and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude residue was subjected to flash column chromatography (Hexanes/EtOAc, 8:1) to afford 9.2 g (83%) of compound **136** as white powder. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25–6.56 (m, 10H), 6.47 (d, J=2.8Hz, 1H), 5.16 (t, J=4.8Hz, 1H), 5.05 (d, J=3.2Hz, 1H), 3.32 (ddd, J=2.4Hz, 5.2Hz, 17.2Hz, 1H), 3.07 (td, J=3.2Hz, 17.2Hz, 1H), 2.22 (t, J=2.4Hz, 1H), 1.13 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.90, 153.95, 136.53, 134.57, 128.61, 128.19, 127.87, 127.75, 127.56, 126.54, 81.69, 79.97, 79.41, 72.69, 60.73, 55.80, 27.91, 23.80. IR (NaCl thin film): 3492.85, 3281.11, 3090.53, 3063.79, 3032.05, 2977.57, 2931.24, 2255.68, 1747.67, 1700.51, 1604.02, 1586.53, 1541.49, 1496.01, 1474.85, 1454.43, 1424.08, 1355.07, 1220.57, 1163.62, 1119.64, 1082.07, 1055.80, 1030.14, 994.70, 972.56, 953.53, 938.46, 911.79, 879.04, 768.50, 731.14, 700.94, 647.75, 607.86 cm^{-1}. FAB-HRMS: calcd for C24H26NO4 [MH^+] 392.1863, found 392.1825. $[\alpha]_D^{25}$ = -30.9 (*c*1, CH_2Cl_2).


H
O
O
BocN
Ph
Ph
1HNMR, CDCl3, 400 MHz, xnj-ii-215pH
1.8
1
1.1
0.93
10
1.3
0.95
1.3
5.9
8
7
6
5
4
3
2
1
0


13CNMR, CDCl3, 100 MHz, xnj-ii-215pC13
ppm 180
160
140
120
100
80
60
40
20
0

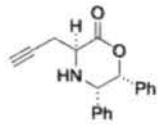
(3*S*,5*S*,6*R*)-5,6-diphenyl-3-(prop-2-ynyl)morpholin-2-one (137)

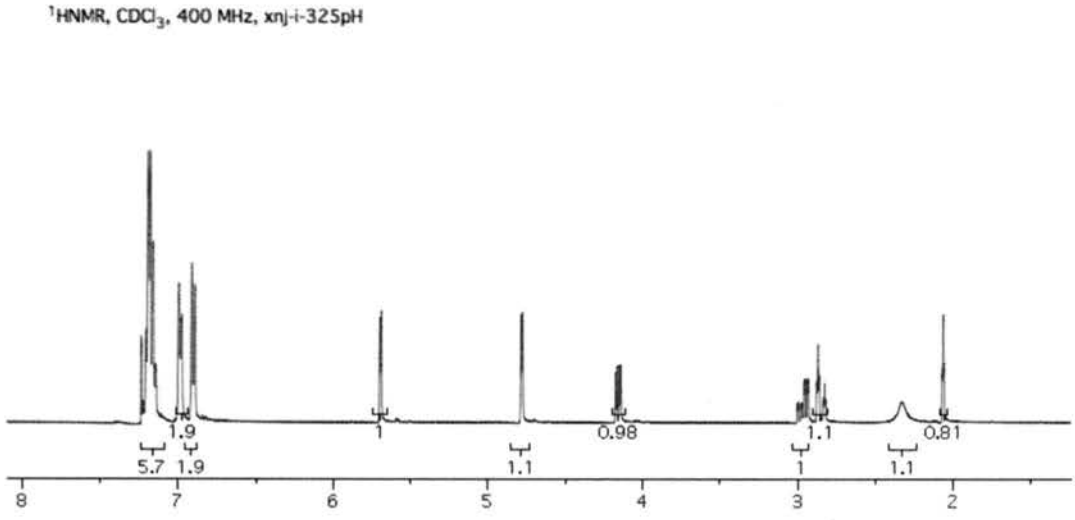


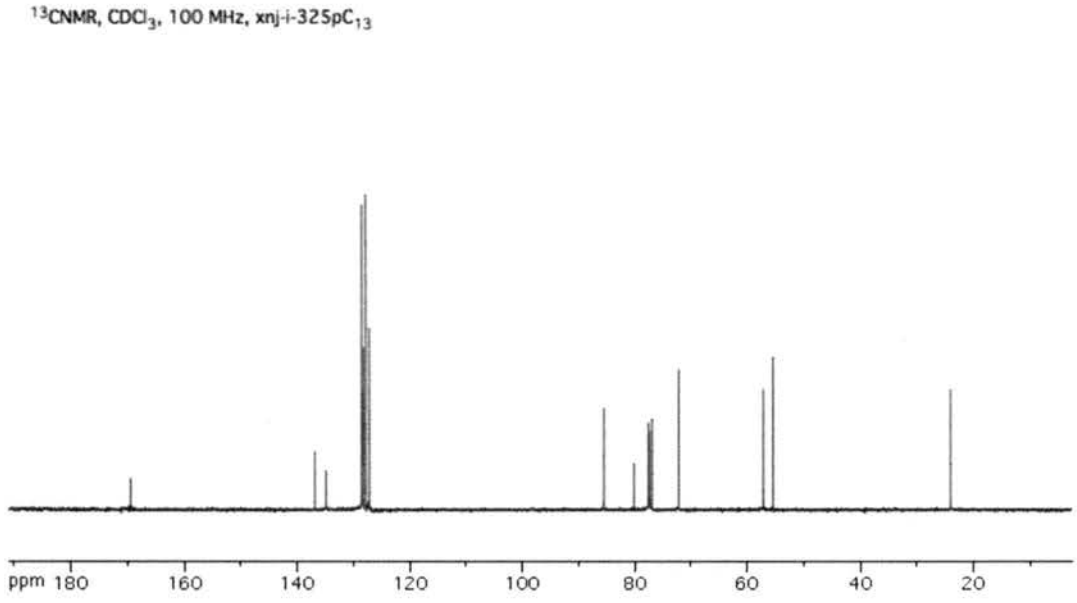
136 **137**

To an ice cooled solution of compound **136** (9.7 g, 24.78 mmol) in dichloromethane (62 mL) was added hydrochloric acid (75.4 mL, 4.0 M solution in dioxane) in a 10 min period. The cooling bath was removed, the reaction was stirred for 3 to 5 h or until the disappearance of starting material monitored by TLC. Excess solvent was removed under rotavaporation. Diethyl ether was added to precipitate the hydrochloride salt and the solvent was decanted. The white solid was rinsed with diethyl ether and air dried to provide 6.0 g white powder, which was redissolved in dichloromethane (70 mL). Saturated sodium bicarbonate (0.95 mL) was added followed by slowly addition of solid sodium bicarbonate (1.54 g) under cooling. The resulting suspension was stirred at room temperature for 3 h. Magnesium sulfate anhydrous was added and stirred for an additional 1 h. The solid was filtered out, and the filtrate was concentrated. Flash chromatography (Hexanes/EtOAc, 3:1 to 2:1 to 1:1) provided 4.71 g (65%) of compound **137** as light yellow powder. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27–7.17 (m, 6H), 7.03-7.01 (m, 2H), 6.95 (d, J=8.0Hz, 2H), 5.73 (d, J=3.6Hz, 1H), 4.82 (d, J=3.6Hz, 1H), 4.21 (d, J=3.6Hz, 1H), 3.04 (dddd, J=0.8Hz, 2.4Hz, 8.8Hz, 16.8Hz, 1H), 2.91 (dddd, J=1.2Hz, 2.8Hz, 3.6Hz, 16.8Hz, 1H), 2.37 (br s, 1H), 2.106

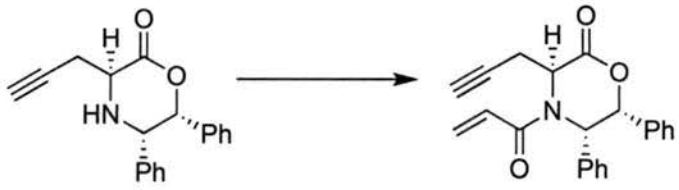
(ddd, J=1.2Hz, 2.8Hz, 3.6Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.49, 136.89, 134.93, 128.57, 128.32, 128.27, 127.86, 127.83, 127.21, 85.49, 80.12, 7 2.15, 57.09, 55.38, 24.03. IR (NaCl thin film): 3326.53, 3287.77, 3033.33, 2868.65, 1732.27, 1499.24, 1469.75, 1454.35, 1415.82, 1384.65, 1368.01, 1341.72, 1238.44, 1192.62, 1155.58, 1096.24, 1045.76, 1030.64, 1008.44, 963.83, 916.17, 868.70, 814.18, 779.93, 767.54, 750.60, 741.58, 699.29, 685.87, 643.13 cm^{-1}. FAB-HRMS: calcd for C19H18NO2 [MH^+] 292.1338, found 292.1338. $[\alpha]_D^{25}$ = -117.3 (*c*1, CH_2Cl_2).







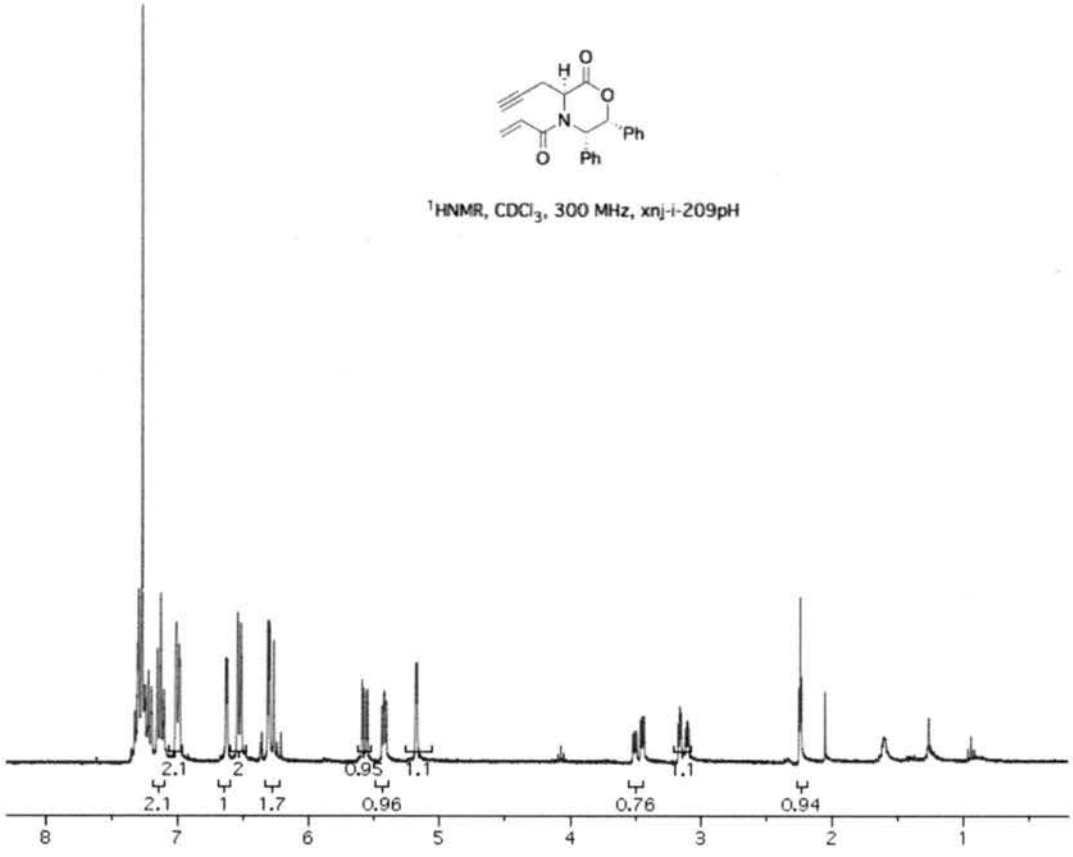
(3*S*,5*S*,6*R*)-4-acryloyl-5,6-diphenyl-3-(prop-2-ynyl)morpholin-2-one (133a)



137 **133a**

To an ice-cooled solution of the secondary amine **137** (117 mg) in dichloromethane (4 mL) was added triethyl amine (72 μL) followed by acryloyl chloride (42.5 μL). The reaction mixture was continued to stir at 0 °C for 2 h or until the disappearance of the starting material monitored by TLC. Solvent was removed and the residue was subjected to flash chromatography (3:1 Hexanes/EtOAc) to give product **133a** 85 mg (61%) as colorless crystals. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32-7.20 (m, 4H), 7.15-7.10 (m, 2H),

7.01-6.98 (m, 2H), 6.63-6.62 (d, J=3.0Hz, 1H), 6.54-6.52 (app d, J=7.2Hz, 2H), 6.31-6.27 (d, J=13.8Hz, 1H), 6.31-6.30 (d, J=1.8Hz, 1H), 5.59-5.55 (dd, J=3.0Hz, 9.3Hz, 1H), 5.44-5.41 (dd, J=3.9Hz, 5.7Hz, 1H), 5.18-5.17 (d, J=3.0Hz, 1H), 3.52-3.49 (ddd, J=17.25Hz, 3.0Hz, 6.0Hz, 1H), 3.17-3.09 (ddd, J=17.25Hz, 2.7Hz, 3.9Hz, 1H), 2.25-2.23 (t, J=2.7Hz, 1H). FAB-HRMS: calcd for C22H20NO3 $[MH]^+$ 346.1443, found 346.1445.



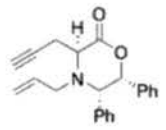
General procedure for N-alkylation with allylic bromides: to 0 °C cooled solution of the amine **137** in DMF was added potassium carbonate solid followed by dropwise addition of allylic bromide. The resulting mixture was stirred at room temperature for 24 h or until no more obvious conversion. The reaction was filtered, the filtrate was partitioned between ammonium chloride saturated aqueous and ethyl acetate and

separated. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated. Flash chromatography gave products **133b-f**, respectively.

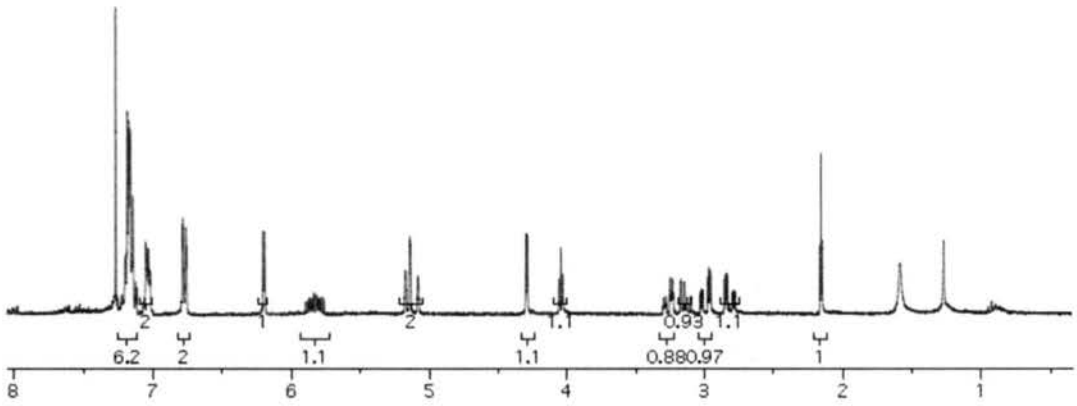
(3*S*,5*S*,6*R*)-4-allyl-5,6-diphenyl-3-(prop-2-ynyl)morpholin-2-one (141)

137 **133b**

A mixture of $Pd_2(dba)_3$ (8 mg), PPh_3 (27 mg), K_2CO_3 (28 mg) in anhydrous THF was strirred under argon, secondary amine **137** (30 mg, 0.103 mmol) was added followed by allyl acetate (13.3 μL, 0.1236 mmol), the resulting mixture was stirred at room temperature for 2-5 days during which more allyl acetate was added. The reaction was filtered through a pad of celite, concentrated. The residue was subjected to small column (3:1 Hexanes/EtOAc) to give the desired product **133b** in 70-90% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20-7.12 (m, 6H), 7.05-7.02 (m, 2H), 6.79-6.76 (m, 2H), 6.21-6.20 (d, J=3.0Hz, 1H), 5.90-5.76 (ddd, J=4.8Hz, 7.8Hz, 10.2Hz, 1H), 5.18-5.17 and 5.09-5.07 (app d, J=27.6Hz, 1H), 5.14 (br, 1H), 4.30-4.29 (d, J=3.0Hz, 1H), 4.06-4.03 (t, J=4.2Hz, 1H), 3.30-3.23 (dddd, J=14.4Hz, 1.8Hz, 1.8Hz, 5.1Hz, 1H), 3.17-3.10 (app dd, J=14.4Hz, 7.8Hz, 1H), 3.03-2.95 (ddd, J=16.8Hz, 2.7Hz, 3.6Hz, 1H), 2.85-2.77 (dd, J=16.8Hz, 2.4Hz, 4.5Hz, 1H), 2.16-2.15 (t, J=2.55Hz, 1H). FAB-HRMS: calcd for C22H22NO2 $[MH]^+$ 332.1651, found 332.2 (nominal MS).



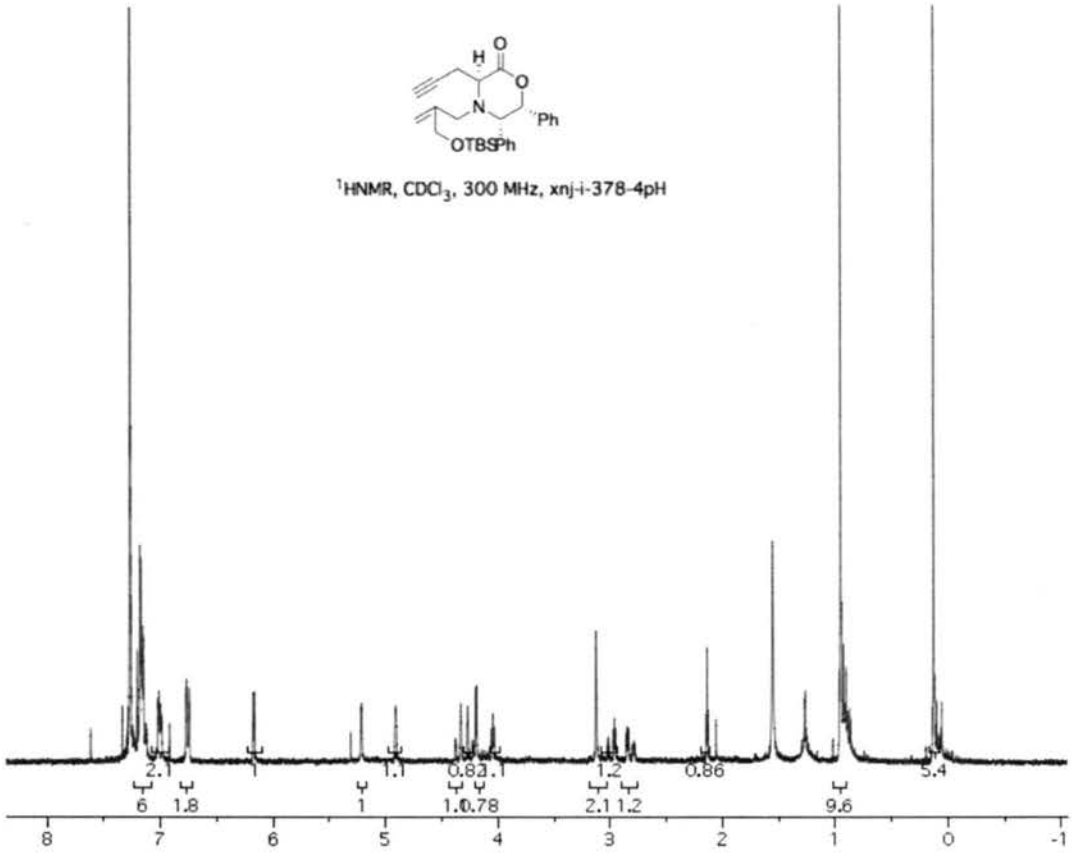
^{1}HNMR, $CDCl_3$, 300 MHz, xnj-i-248pH



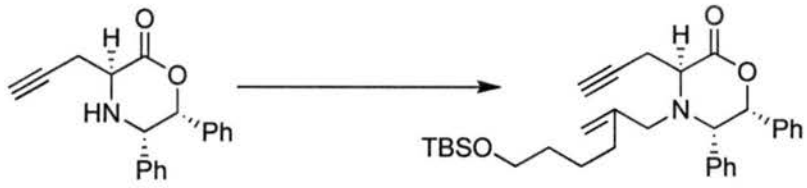
(3*S*,5*S*,6*R*)-4-(2-((*tert*-butyldimethylsilyloxy)methyl)allyl)-5,6-diphenyl-3-(prop-2-ynyl)morpholin-2-one (133d)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20-7.12 (m, 6H), 7.02-6.99 (m, 2H), 6.78-6.74 (m, 2H), 6.18-6.17 (d, J=3.0Hz, 1H), 5.21 (br, 1H), 4.91 (br, 1H), 4.20-4.19 (d, J=3.0Hz, 1H), 4.06-4.03 (dd, J=3.3Hz, 4.2Hz, 1H), 3.13 (s, 2H), 3.03-2.96 (ddd, J=16.8Hz, 2.7Hz,

3.3Hz, 1H), 2.86-2.78 (ddd, J=16.8Hz, 2.7Hz, 4.5Hz, 1H), 2.15-2.13 (t, J=2.7Hz, 1H). 0.96 (s, 9H), 0.13 (s, 6H).

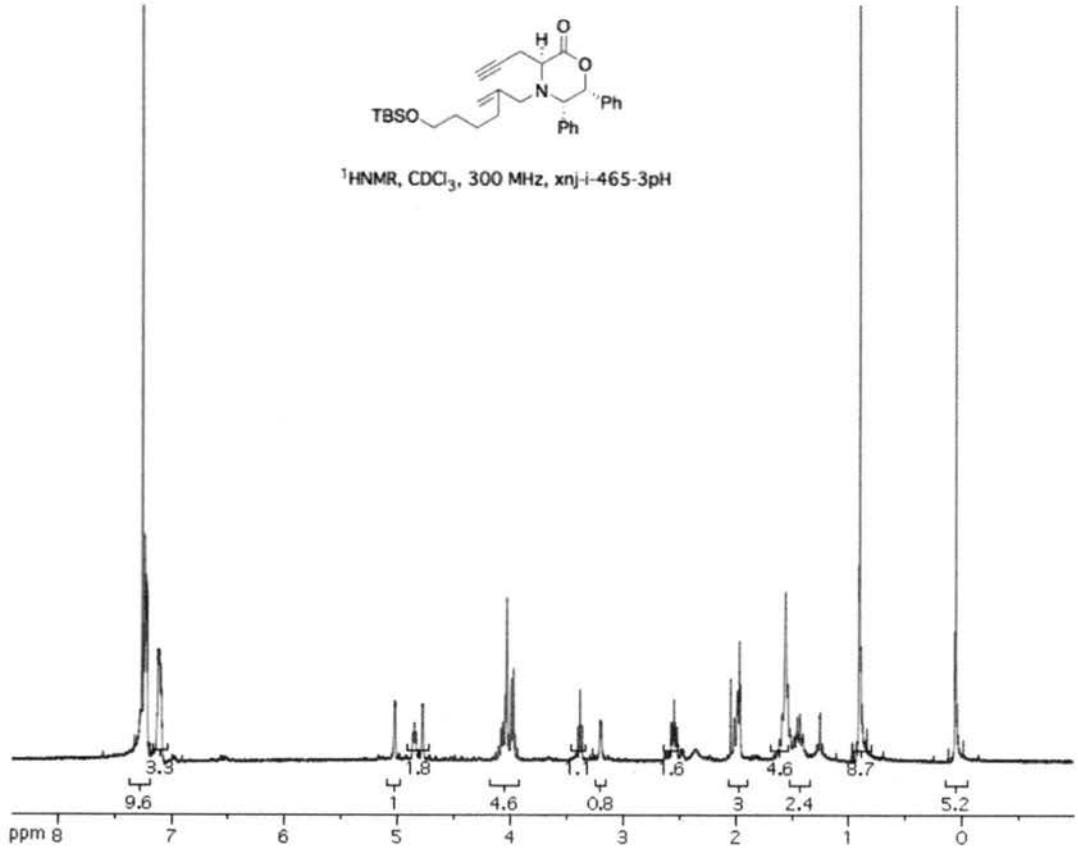


(3*S*,5*S*,6*R*)-4-(6-(*tert*-butyldimethylsilyloxy)-2-methylenehexyl)-5,6-diphenyl-3-(prop-2-ynyl)morpholin-2-one (133e)

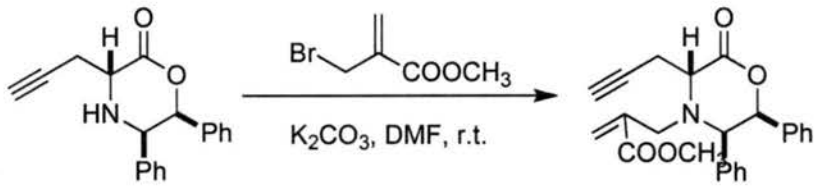


137 **133e**

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25-7.21 (m, 6H), 7.12-7.08 (m, 4H), 5.03 (d, J=1.8Hz, 1H), 4.86-4.83 (t, J=2.25Hz, 1H), 4.78-4.77 (d, J=1.5Hz, 1H), 4.05-3.97 (comp m, 4H), 3.40-3.36 (t, J=3.9Hz, 1H), 3.20-3.19 (d, J=4.2Hz, 1H), 2.57-2.52 (ddd, J=2.7Hz, 5.4Hz, 11.1Hz, 1H), 2.01-1.96 (m, 2H), 1.61-1.52 (m, 4H), 1.48-1.40 (m, 2H), 0.91 (s, 9H), 0.06 (s, 6H). FAB-HRMS: calcd for C32H44NO3Si $[MH]^+$ 518.3090, found 518.3103.



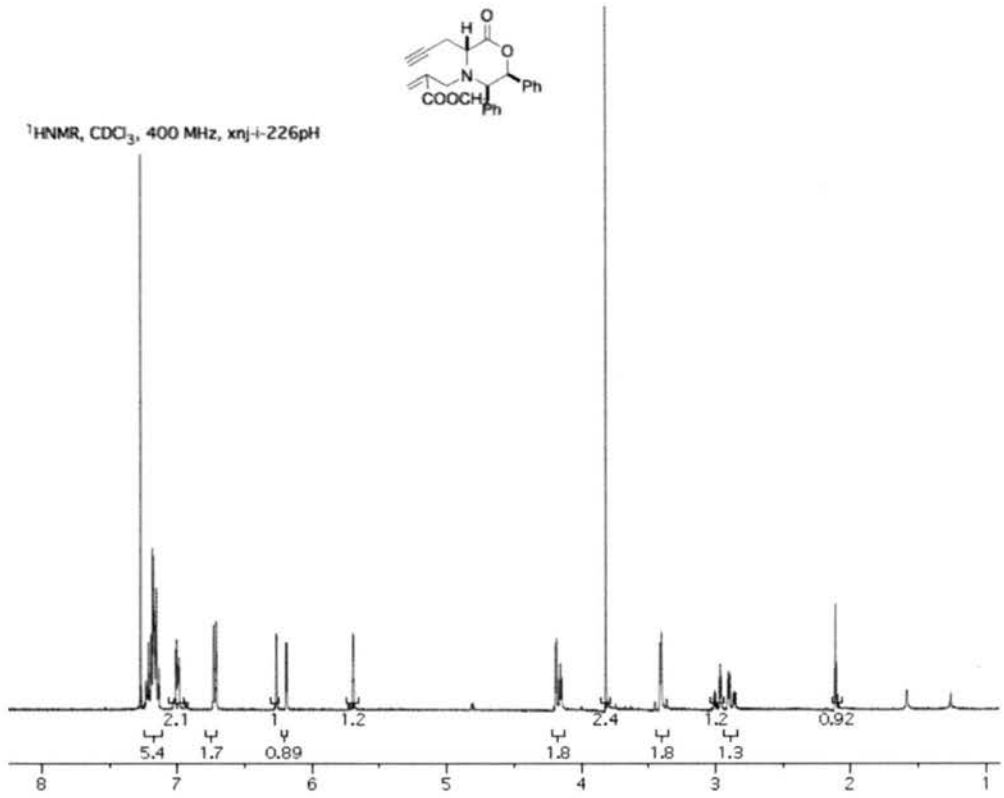
methyl 2-(((3*S*,5*S*,6*R*)-2-oxo-5,6-diphenyl-3-(prop-2-ynyl)morpholino)methyl) acrylate (138)

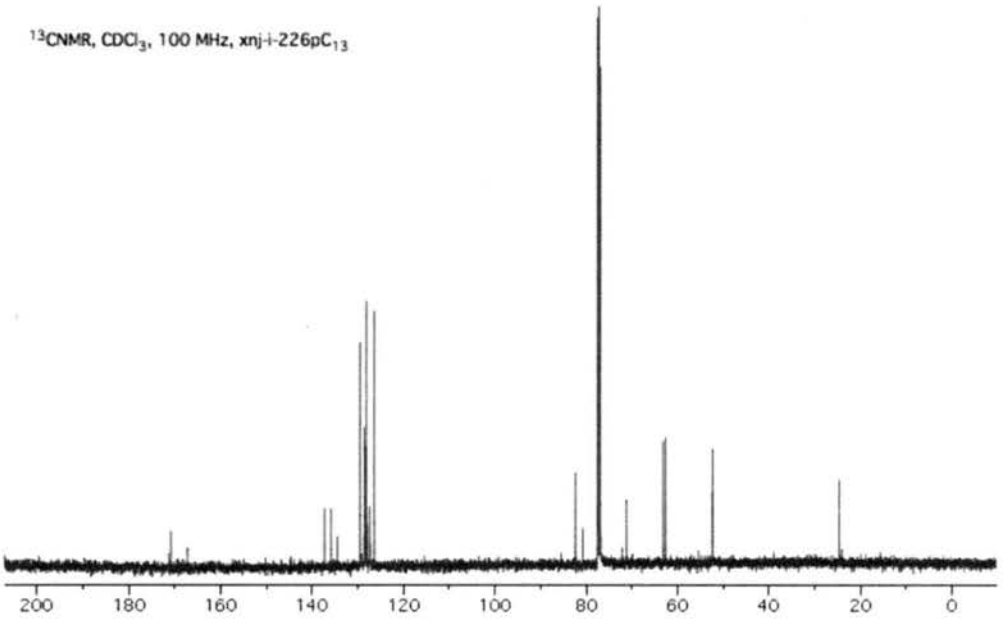


137 **138**

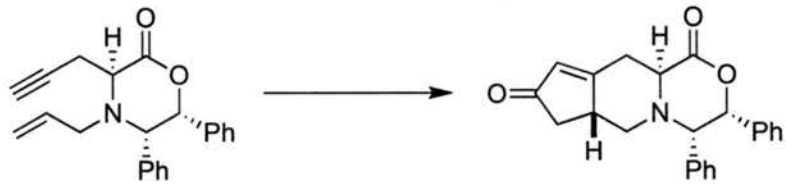
To 0 °C cooled solution of the amine **137** (6.735 g, 23.12 mmol) in DMF (23 mL) was added potassium carbonate solid (4.7 g, 34.68 mmol) followed by dropwise addition of methyl 2-(bromomethyl)acrylate (4.48 g, 24.27 mmol). The resulting mixture was stirred at room temperature for 24 h. Solid was filtered out, the filtrate was partitioned between ammonium chloride saturated aqueous solution and ethyl acetate, separated. The aqueous layer was extracted with ethyl acetate for three times. The combined organic layer was washed with water for three times, dried over anhydrous magnesium sulfate, filtered and concentrated. Flash chromatography (Hexanes/EtOAc, 8:1) gave 8.82 g (98%) of product **138** as light yellow sticky gum. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23–7.14 (m, 6H), 7.01-6.99 (m, 2H), 6.73-6.71 (m, 2H), 6.27 (d, J=1.4Hz, 1H), 6.20 (d, J=3.0Hz, 1H), 5.70 (d, J=1.4Hz, 1H), 4.19 (d, J=3.0Hz, 1H), 4.16 (t, J=4.0Hz, 1H), 3.82 (s, 3H), 3.41 (d, J=4.0Hz, 1H), 3.82 (s, 3H), 3.41 (d, J=4.4Hz, 2H), 3.02 (ddd, J=2.8Hz, 3.6Hz, 16.8Hz, 1H), 2.91 (ddd, J=2.4Hz, 4.4Hz, 16.8Hz, 1H), 2.12 (t, J=2.4Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.80, 167.22, 137.29, 135.87, 134.48, 129.51, 128.50, 128.22, 127.39, 126.38, 82.38, 80.77, 71.20, 63.16, 62.61, 52.37, 52.30, 24.71. IR (NaCl thin film): 3293.66, 3061.76, 3031.07, 2950.84, 2922.65, 2849.68, 1742.83, 1635.77, 1603.27, 1496.82, 1453.39, 1437.46, 1419.50, 1346.64, 1314.02, 1297.75, 1266.14, 1205.70, 1167.58, 1126.77, 1085.44, 1063.87, 1031.66, 1001.20, 968.04,

816.48, 772.82, 754.20, 736.51, 701.74, 624.60, 613.36 cm^{-1}. FAB-HRMS: calcd for C24H24NO4 [MH^+] 390.1706, found 390.1700. $[\alpha]_D^{25}$ = -41.3 (*c*1, CH_2Cl_2).



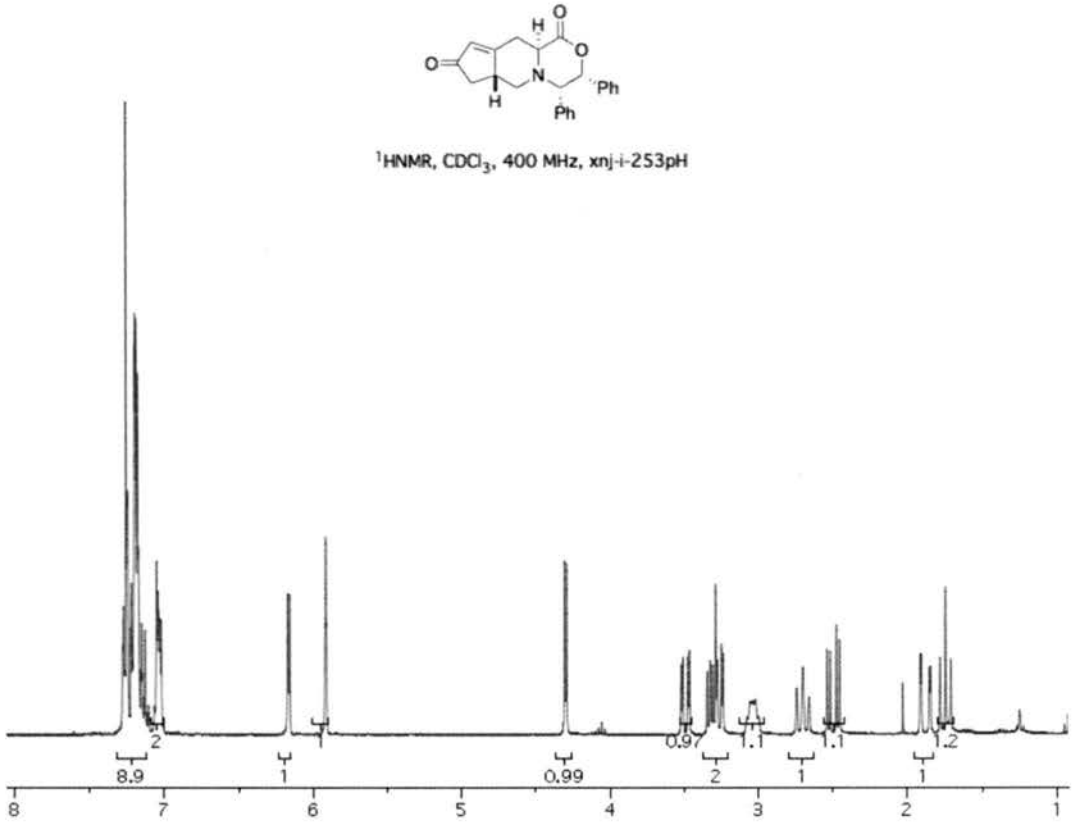


Cyclopentenone (132b)

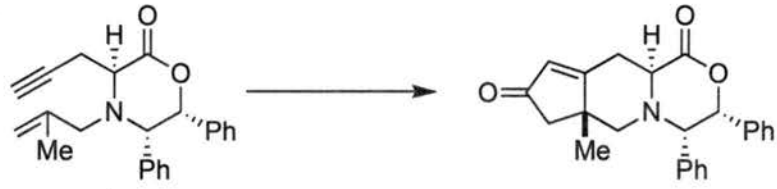


133b **132b**

Procedure A, 65% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24-7.16 (m, 7H), 7.12-7.09 (m, 2H), 7.03-7.00 (m, 2H), 6.14-6.14 (d, J=3.6Hz, 1H), 5.89 (s, 1H), 4.28-4.27 (d, J=3.6Hz, 1H), 3.49-3.44 (dd, J=3.2Hz, 13.6Hz, 1H), 3.31-3.27 (dd, J=6.0Hz, 10.8Hz, 1H), 3.01 (br., 1H), 2.71-2.64 (t, J=12.4Hz, 1H), 2.50-2.44 (dd, J=6.4Hz, 18.4Hz, 1H), 1.88-1.83 (dd, J=2.4Hz, 21.2Hz, 1H), 1.74-1.69 (t, J=22.0Hz, 1H). FAB-HRMS: calcd for C23H22NO3 [MH^+] 360.1600, found 360.1585.



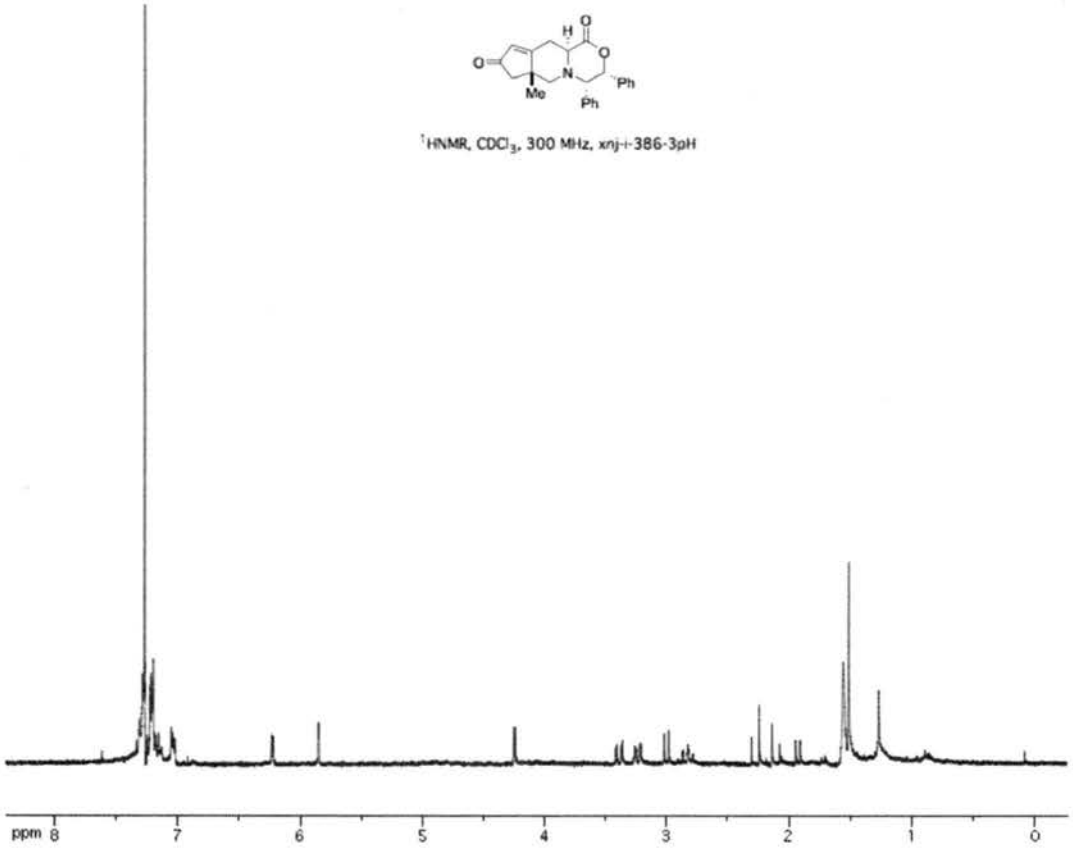
Cyclopentenone (132c)

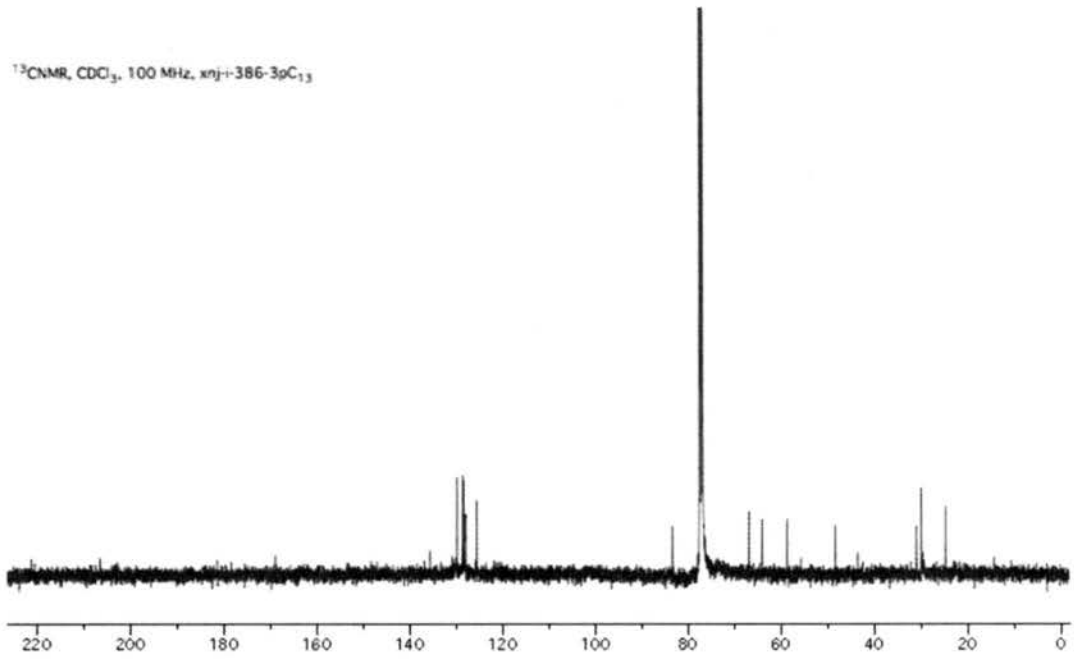


133c **132c**

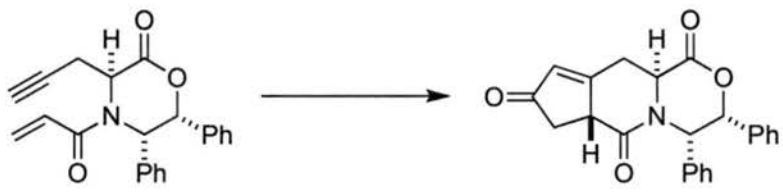
Procedure A. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32–7.02 (m, 10H), 6.24 (d, J=3.6Hz, 1H), 5.86 (d, J=1.5Hz, 1H), 4.25 (d, J=3.6Hz, 1H), 3.42-3.36 (dd, J=3.6Hz, 13.5Hz, 1H), 3.26-3.21 (dd, J=3.3Hz, 12.3Hz, 1H), 3.02 (d, J=10.8Hz, 1H), 2.87-2.78 (m, 1H), 2.303 (d,

J=18.5Hz, 1H), 2.14 (d, J=18.5Hz, 1H), 1.95 (d, J=10.8Hz, 1H), 1.51 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.66, 181.55, 169.03, 135.73, 129.88, 128.65, 128.57, 128.45, 128.04, 128.01, 125.65, 83.36, 66.84, 64.02, 58.63, 48.30, 43.50, 30.95, 24.67. HRMS-TOF: calcd for C24H24NO3 [MH^+] 374.1756, found 374.1748. $[\alpha]_D^{25}$= +135.3 (*c*1, CH_2Cl_2.



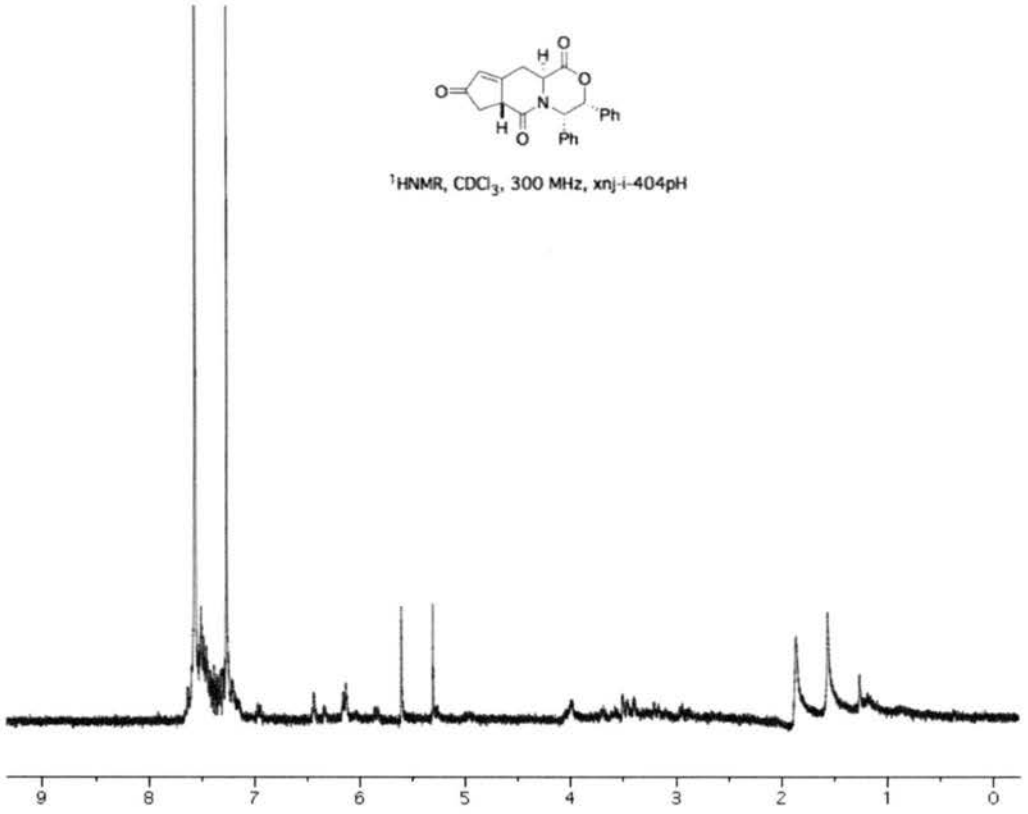


Cyclopentenone (132a)

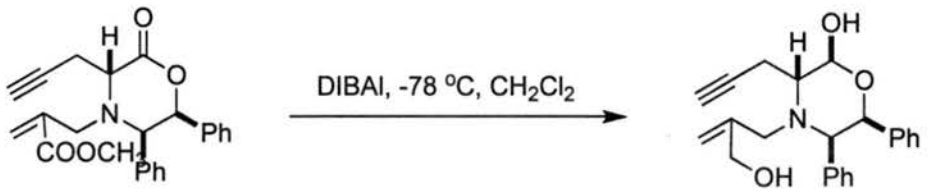


133a **132a**

Procedure B: To a solution of **133a** (84.2 mg) in dichloromethane was added $Co_2(CO)_8$ (91.8 mg), stir for 1 h. Solvent was removed, the residue was redissolved in acetonitrile (2 mL) and heated to reflux for 19 h. The reaction mixture was filtered through a pad of celite, concentrated and the residue was subjected to column (1:1 Hexanes/EtOAc) to give 15 mg (16%) of product **132a**. ^{1}H NMR was not good enough for accurate assignment. FAB-HRMS: calcd for C23H20NO4 [MH^+] 374.1392, found 374.1398.



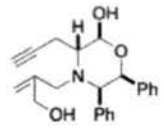
(2*R*,3*S*,5*S*,6*R*)-4-(2-(hydroxymethyl)allyl)-5,6-diphenyl-3-(prop-2-ynyl)morpholin-2-ol (139)



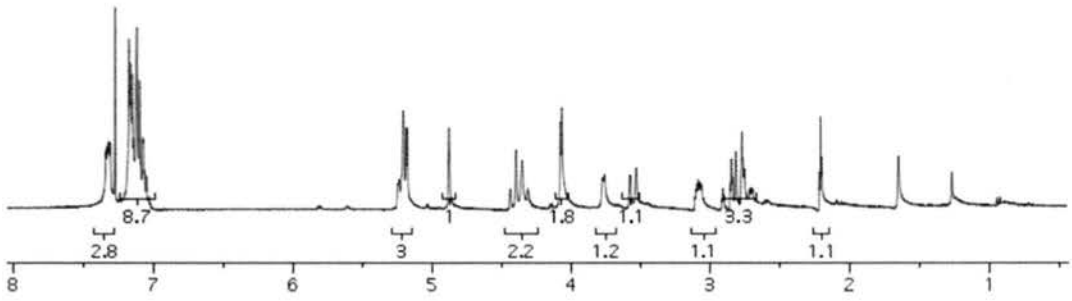
138 **139**

To -78 °C cooled solution of compound **138** (4.0 g, 10.27 mmol) was added DIBAl (41.1 mL, 1.0 M solution in dichloromethane) dropwise during a period of 20 min. The reaction was stirred for an additional 20 min and the cold-bath was removed. After stirring for another 20 min, the reaction was quenched slowly with sodium

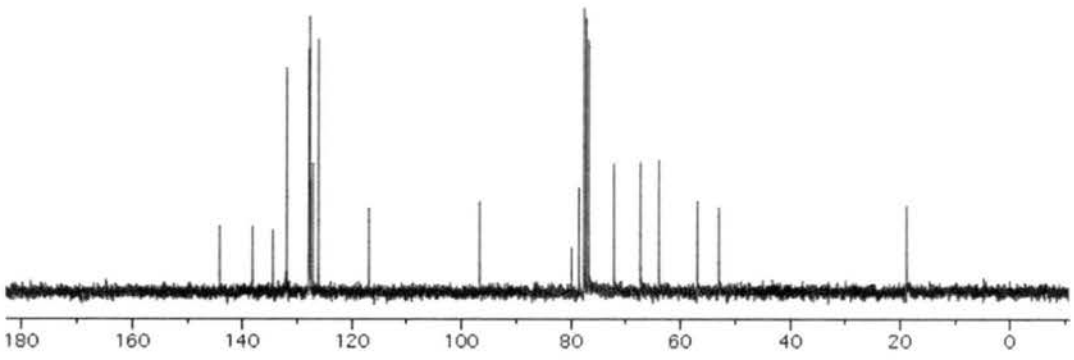
potassium tartrate saturated aqueous solution, diluted with ethyl acetate, and then stirred at room temperature for 2 h, the mixture was transferred to a separatory funnel and separated. The aqueous layer was extracted with ethyl acetate for three times. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. Flash chromatography (Hexanes/EtOAc, 3:1 to 1:1) gave 12.73 g (4 batches, 79.3% on average) of product **139** as white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34-7.31 (m, 2H), 7.17-7.04 (m, 8H), 5.25-5.21 (m, 2H), 5.19-5.18 (d, J=4.0Hz, 1H), 4.88 (s, 1H), 4.44-4.31 (app q, J=17.6Hz, 1H), 4.08-4.07 (d, J=4.0Hz, 1H), 3.77-3.76 (d, J=5.6Hz, 1H), 3.58-3.53 (d, J=17.6Hz, 1H), 3.11-3.06 (m, 1H), 2.91-2.84 (dt, J=24Hz, 3.2Hz, 1H), 2.81-2.69 (comp m, 2H), 2.21-2.19 (t, J=3.6Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.19, 138.18, 134.48, 131.95, 127.89, 127.74, 127.59, 127.19, 127.17, 116.92, 96.72, 79.91, 78.58, 72.16, 67.32, 63.91, 56.88, 52.96, 18.84. IR (NaCl thin film): 3293.83, 3061.39, 3028.66, 2853.11, 1719.94, 1653.98, 1603.57, 1493.20, 1451.93, 1373.87, 1312.52, 1267.86, 1202.94, 1121.19, 1098.31, 1073.48, 1058.82, 1029.65, 967.57, 918.93, 780.97, 755.18, 704.58, 602.49 cm^{-1}. HRMS-TOF: calcd for C23H26NO3 [MH^+] 364.1907, found 364.1892. $[\alpha]_D^{25}$ = + 60.0 (*c*1, CH_2Cl_2).



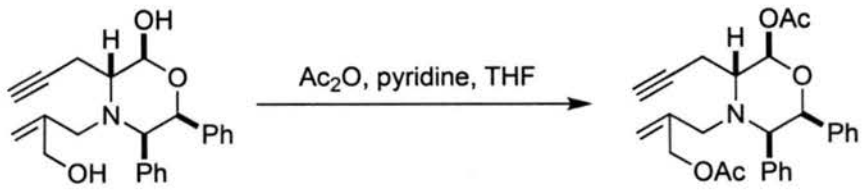
^{1}HNMR, $CDCl_3$, 400 MHz, xnj-iii-216/217pH



^{13}CNMR, $CDCl_3$, 100 MHz, xnj-iii-216/217pC_{13}



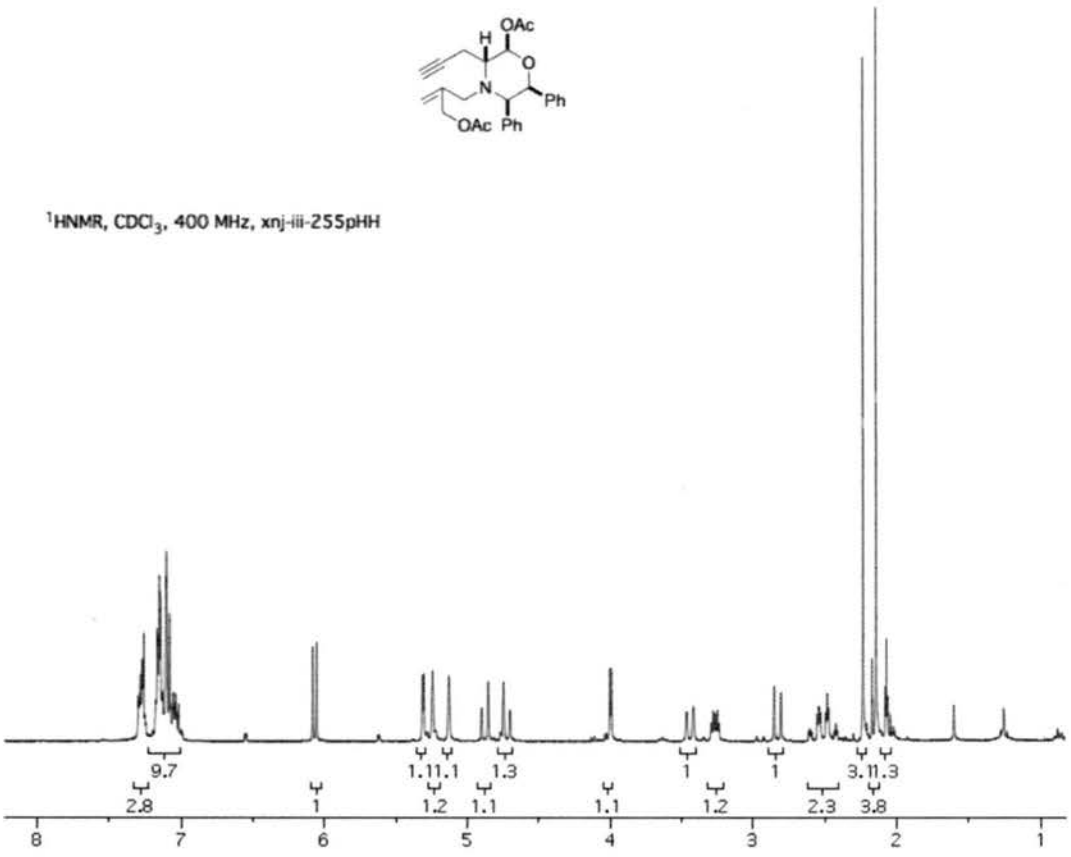
2-(((2*S*,3*S*,5*S*,6*R*)-2-acetoxy-5,6-diphenyl-3-(prop-2-ynyl)morpholino)methyl)allyl acetate (140)

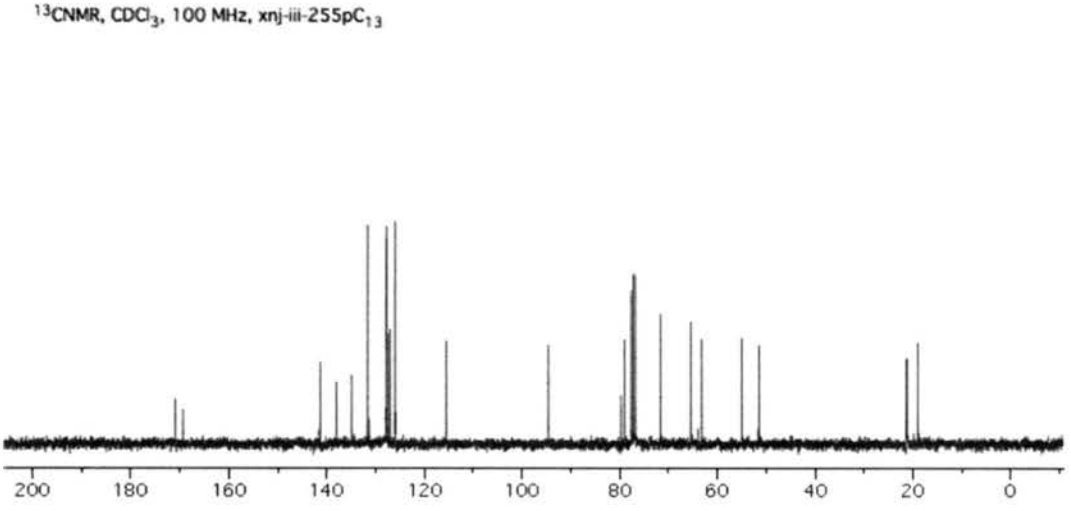


139 **140**

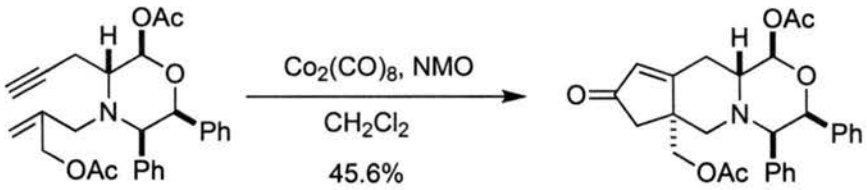
To an ice-cooled solution of diol **139** (12.73 g, 35.03 mmol) in tetrahydrofuran (146 mL) was added pyridine (14.64 mL, 175.15 mmol), acetic anhydride (13.64 mL, 140.10 mmol) followed by DMAP (860 mg, 20%). After removing the cold, the reaction was stirred for 5 to 9 h or until the disappearance of starting material as monitored by TLC. Excess solvent was removed under rotavap. The residue was subjected to flash chromatography (Hexanes/EtOAc, 5:1) and gave 13.38 g (85%) of product **140** as light yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28–7.26 (m, 2H), 7.16-6.97 (m, 8H), 6.07 (d, J=8.4Hz, 1H), 5.31 (d, J=3.2Hz, 1H), 5.23 (s, 1H), 5.11 (s, 1H), 4.90 (d, J=13.8Hz, 1H), 4.73 (d, J=13.8Hz, 1H), 4.00 (d, J=3.2Hz, 1H), 3.44 (d, J=14.0Hz, 1H), 3.27 (ddd, J=3.6Hz, 3.6Hz, 7.6Hz, 1H), 2.83 (d, J=14.0Hz, 1H), 2.58 (ddd, J=2.8Hz, 4.4Hz, 18.0Hz, 1H), 2.47 (dt, J=18.0Hz, 3.2Hz, 1H), 2.19 (s, 3H), 2.12 (s, 3H), 2.07 (t, J=2.6Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.74, 169.16, 141.27, 137.94, 134.78, 131.52, 127.68, 127.64, 127.35, 126.89, 115.36, 94.50, 79.66, 78.90, 77.22, 71.62, 65.29, 63.09, 54.88, 51.37, 21.29, 21.16, 18.96. IR (NaCl thin film): 3290.97, 3060.83, 3029.41, 2929.45, 2849.92, 1740.27, 1655.72, 1603.51, 1494.33, 1452.30, 1370.01, 1222.23, 1121.17, 1064.17, 969.97, 914.52, 894.70, 870.41, 846.90, 806.05, 780.03, 754.91, 736.69, 707.30,

645.37, 598.59 cm^{-1}. HRMS-TOF: calcd for C27H30NO5 [MH^+] 448.2118, found 448.2127. $[\alpha]_D^{25}$ = +57.3 (*c*1, CH_2Cl_2).





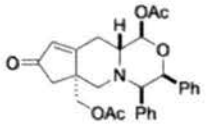
((3*R*,7a*S*)-2,3-dimethyl-6-oxo-2,3,4,6,7,7a-hexahydro-1*H*-cyclopenta[*c*]pyridin-7a-yl)methyl acetate (141)

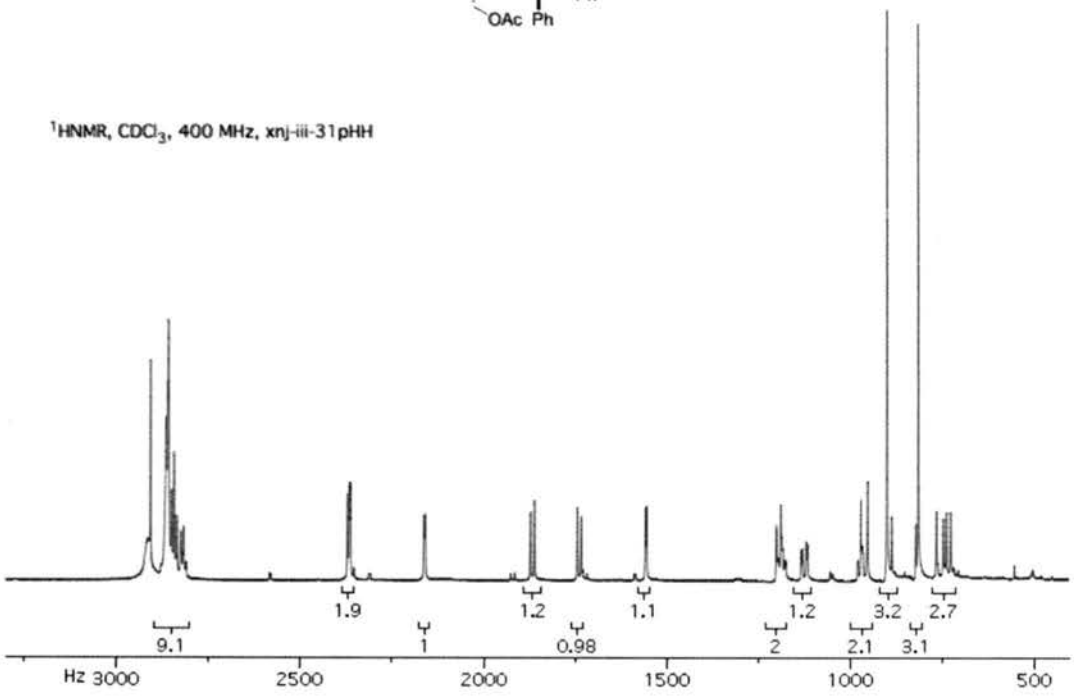


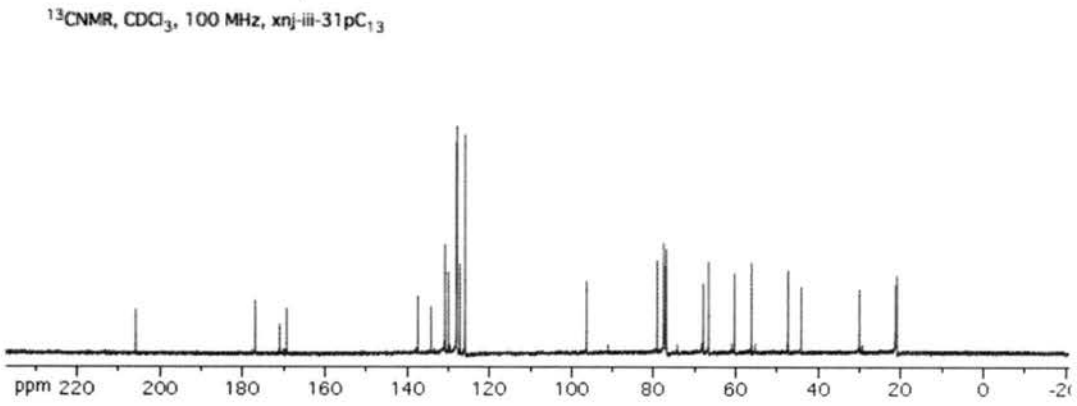
140 **141**

To a solution of acetate **140** (2.56 g, 5.720 mmol) in dichloromethane (57.2 mL) was added dicobalt octacarbonyl solid, the resulting dark purple suspension was stirred at room temperature for 2 h or until the disappearance of starting material monitored by TLC. The reaction solution was diluted to 114.4 mL and cooled to 0 °C, first batch of *N*-methyl morpholine *N*-oxide (3.02 g, 25.74 mmol) was added slowly to the reaction as solid, stirred for 30 min before removing the cold bath. After 2 h, reaction was cooled down to 0 °C, a second batch of *N*-methyl morpholine *N*-oxide was added and stirred for 30 min, and then an additional 21 h at room temperature. The purple reaction mixture was filtered through celite and concentrated. The residue was subjected to flash chromatography (Hexanes/EtOAc, 2:1 to 1:1) to provide 1.24 g (45.6%) of compound **141** as light yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29–7.03 (m, 10H), 5.93 (d, J=8.6Hz, 1H), 5.92 (d, J=1.6Hz, 1H), 5.41 (d, J=3.2Hz, 1H), 4.68 (d, J=11.0Hz, 1H), 4.36 (d, J=11.0Hz, 1H), 3.89 (d, J=3.2Hz, 1H), 3.00 (d, J=11.6Hz, 1H), 2.99 (ddd, J=3.6Hz, 8.6Hz, 11.6Hz, 1H), 2.83 (dd, J=3.6Hz, 14.0Hz, 1H), 2.45-2.41 (m, 1H), 2.43 (d, J=18.4Hz, 1H), 2.25 (s, 3H), 2.04 (s, 3H), 1.91 (d, J=18.4Hz, 1H), 1.85 (d, J=11.6Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 205.85, 176.89, 171.00, 169.28, 137.34, 134.15, 130.81, 129.95, 128.03, 128.00, 127.97, 129.91, 127.86, 127.20, 125.91, 96.31, 79.13, 67.92, 66.58, 60.30, 56.20, 47.35, 44.14, 30.04, 21.27, 20.96. IR (NaCl thin film):

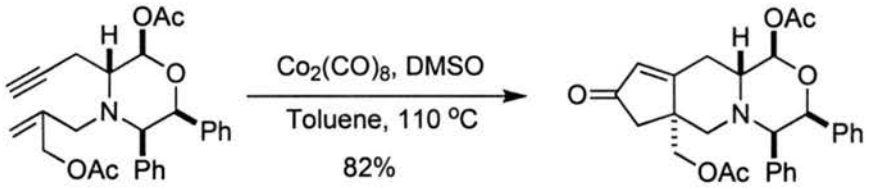
3060.40, 3029.41, 2905.52, 2832.32, 1742.45, 1714.11, 1630.75, 1494.21, 1452.42, 1432.26, 1372.64, 1288.69, 1227.54, 1123.89, 1064.29, 967.40, 905.29, 871.52, 840.84, 788.42, 757.73, 735.74, 708.43, 600.33 cm^{-1}. HRMS (TOF-ESI): calcd for C28H30NO6 $[MH]^+$ 476.20676, found 476.20495. $[\alpha]_D^{25}$ = +24.8 (*c*1, CH_2Cl_2).







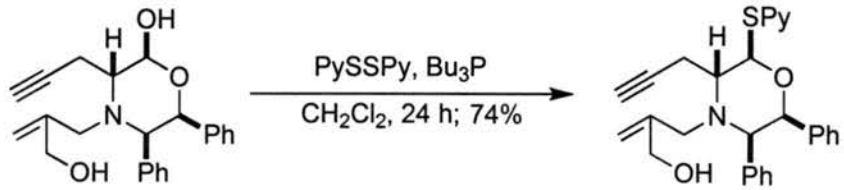
((3*R*,7a*S*)-2,3-dimethyl-6-oxo-2,3,4,6,7,7a-hexahydro-1*H*-cyclopenta[*c*]pyridin-7a-yl)methyl acetate (141)



140 **141**

To a solution of acetate **140** (3.682 g, 8.228 mmol) in toluene (164 mL) was added dicobaltoctacarbonyl (3.113g, 9.050 mmol) as solid, the resulting dark red solution was stirred at room temperature for 1 h. DMSO (6.06 mL, 82.28 mmol) was then introduced, the resulting mixture was heated to 110 °C for 2-3 h or until the disappearance of the complex spot as monitored by TLC. The reaction mixture was cooled down to room temperature, and the solvent was removed under reduced pressure. The residue was subjected to flash chromatography (3:1 to 2:1 to 1:1, Hexanes/EtOAc) to provide 3.21 g (82%) of enone **141** as light yellow solid.

Compound (142)

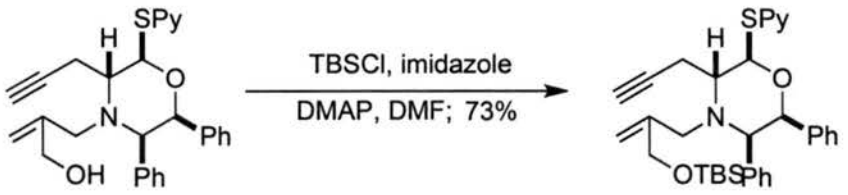


139 **142-1**

To 0 °C cooled solution of the diol **139** (55 mg, 0.1513 mmol) and PySSPy (35.7 mg, 0.1589 mmol) in dichloromethane (0.8 mL) was added Bu_3P (39 μL, 0.1513 mmol).

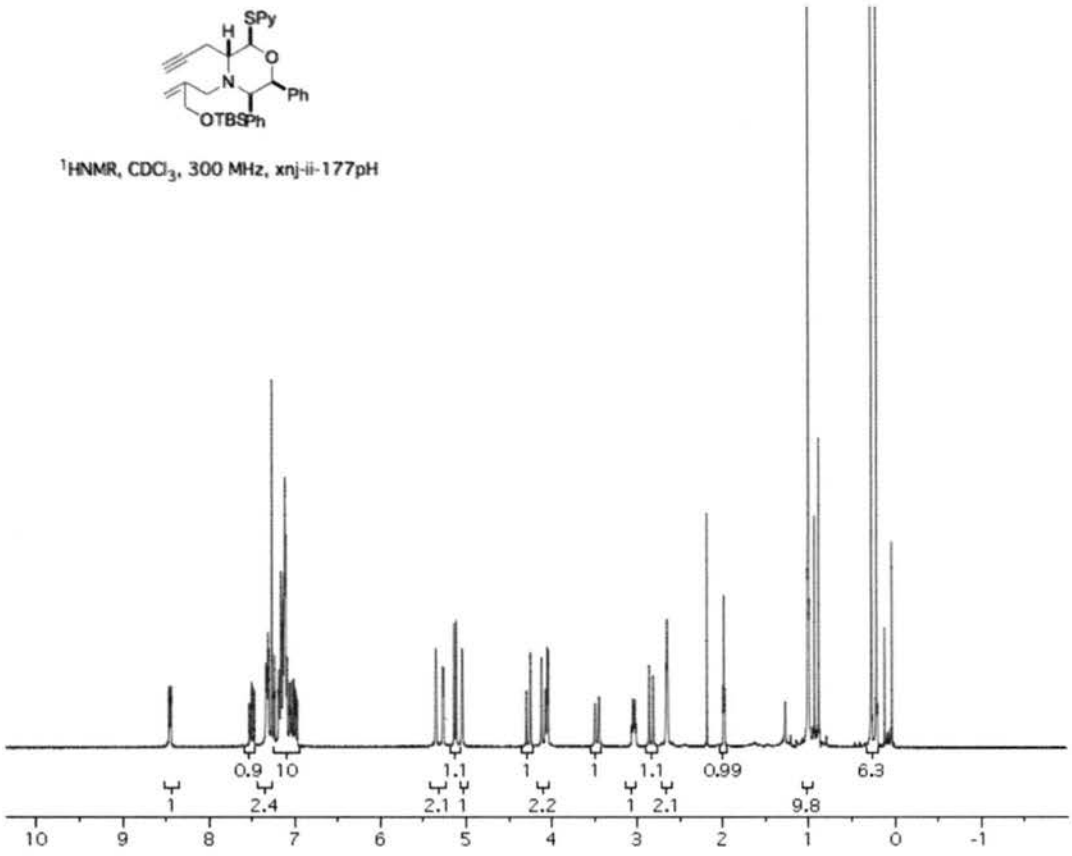
The reaction mixture was warmed up to room temperature and stirred for 12 h. Solvent was removed, the residue was subjected to column (5:1 to 3:1 Hexanes/EtOAc) and provided 53 mg (77%) of compound **142-1**.

Compound (142-2)



142-1 **142-2**

To a solution of compound **142-1** (53 mg, 0.1161 mmol) in DMF (0.2 mL) was added imidazole (39.6 mg, 0.5805 mmol), TBSCl (34.9 mg, 0.2322 mmol) and catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 36 h, and filtered. The filtrate was concentrated. Flash chromatography (5:1 Hexanes/EtOAc) gave product **142-2** 54 mg (81%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.47–8.440 (m, 1H), 7.53-7.47 (m, 1H), 7.34-6.97 (m, 12H), 5.36 (s, 1H), 5.28-5.27 (d, J=4.2Hz, 1H), 5.14-5.12 (d, J=10.0Hz, 1H), 5.05 (s, 1H), 4.30-4.25 (d, J=19.0Hz, 1H), 4.12-4.07 (d, J=19.0Hz, 1H), 4.05-4.04 (d, J=4.2Hz, 1H), 3.50-3.45 (d, J=18.8Hz, 1H), 3.07-3.02 (ddd, J=4.8Hz, 4.8Hz, 10.0Hz, 1H), 2.86-2.81 (d, J=18.8Hz, 1H), 2.67 (t, J=3.2Hz, 1H).

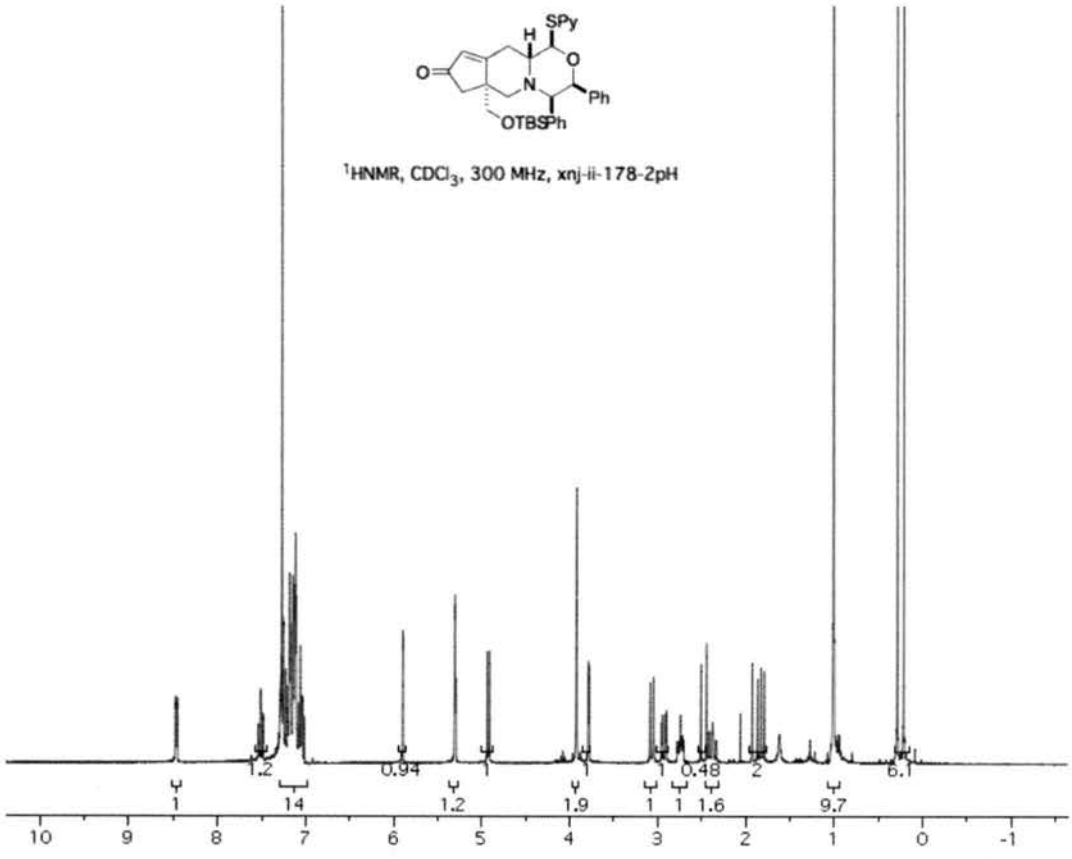


Cyclopentenone (143)

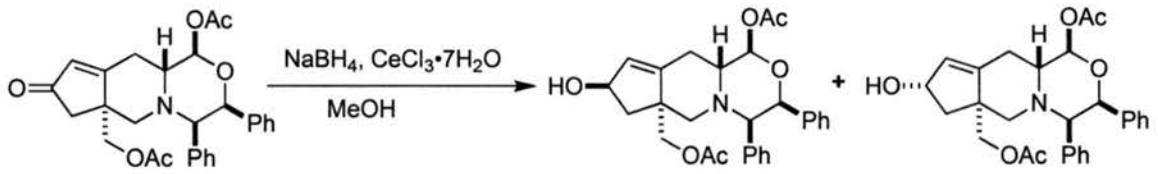
142 **143**

General procedure gave product **143** (73%-55%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.47-8.45 (m, 1H), 7.54-7.48 (m, 1H), 7.27-7.02 (m, 12H), 5.90-5.89 (d, J=2.0Hz, 1H), 5.31-

5.30 (d, J=4.2Hz, 1H), 4.937-4.912 (d, J=10.0Hz, 1H), 3.922 (s, 2H), 3.790-3.779 (d, J=4.2Hz, 1H), 3.08-3.05 (d, J=17.2Hz, 1H), 2.96-2.90 (dd, J=4.8Hz, 18.0Hz, 1H), 2.78-2.70 (ddd, J=4.4Hz, 9.6Hz, 18.4Hz, 1H), 2.51-2.44 (d, J=24.8Hz, 1H), 2.42-2.34 (app t, J= 14.8Hz, 1H). 1.93-1.86 (d, J=24.8Hz, 1H), 1.83-1.79 (d, J=17.2Hz, 1H), 1.01 (s, 9H), 0.29-0.21 (d, J=29.2Hz, 6H).

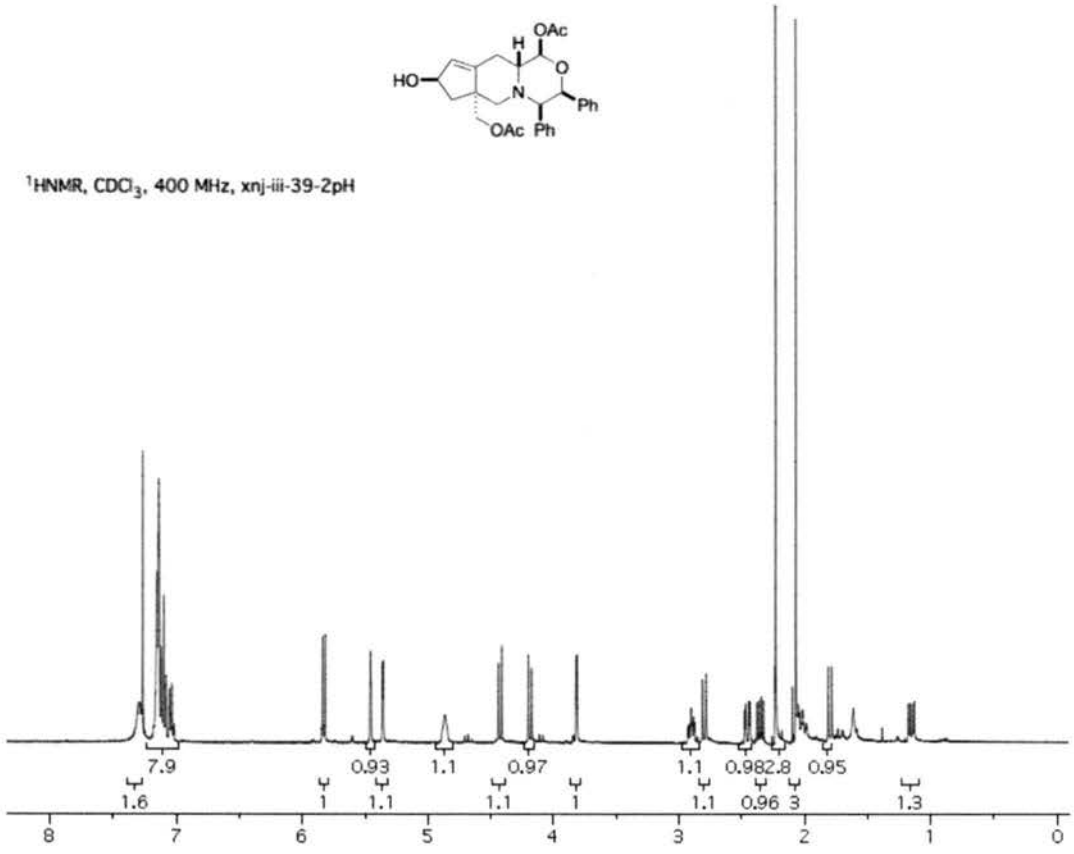


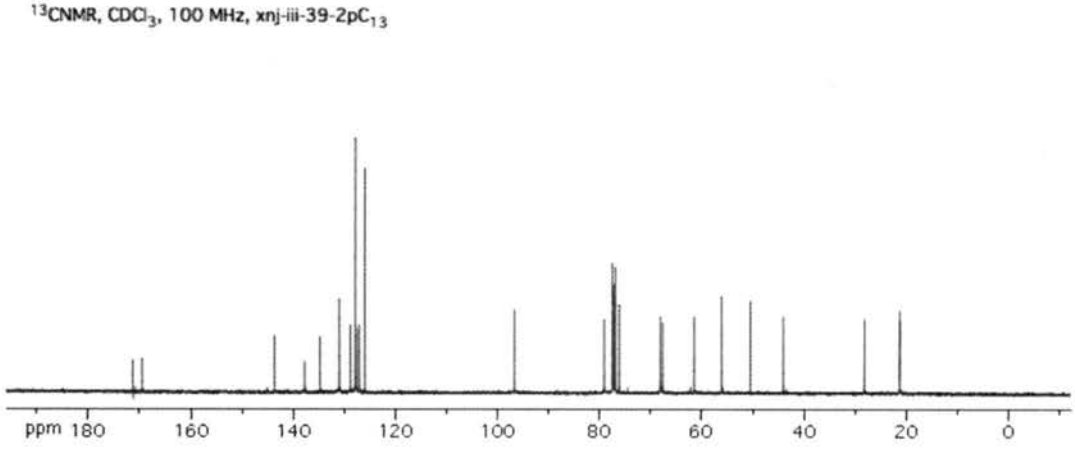
Allylic Alcohol (161)



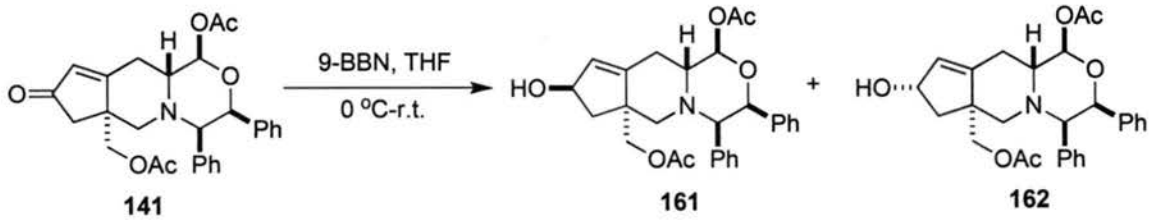
To 0 °C cooled clear solution of enone **141** (348.9 mg, 0.7337 mmol) and cerium chloride heptahydrate (287.1 mg, 0.7704 mmol) was added sodium borohydride (29.6 mg, 0.7704 mmol) very slowly as powder in a period of 10 min. The resulting mixture was stirred for 40 to 55 min or until the disappearance of starting material monitored by TLC. The reaction was quenched with acetone and partitioned between ammonium chloride saturated aqueous solution and ethyl acetate, separated. The aqueous layer was extracted with ethyl acetate three times. The combined organic layers were washed successively with 1N HCl, water and brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (Hexanes/EtOAc, 1:1) to provide 832.3 mg (3 batches, 73.2% on average) of product **161** as white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30 (br.s, 2H), 7.16-7.02 (m, 8H), 5.84 (d, J=8.2Hz, 1H), 5.46 (s, 1H), 5.37 (d, J=3.2Hz, 1H), 4.87 (br s, 1H), 4.44 (d, J=10.8Hz, 1H), 4.20 (d, J=10.8Hz, 1H), 3.82 (d, J=3.2Hz, 1H), 2.93 (ddd, J=3.4Hz, 8.2Hz, 11.2Hz, 1H), 2.81 (d, J=11.6Hz, 1H), 2.48 (dd, J=3.4Hz, 14.0Hz, 1H), 2.38 (dd, J=7.6Hz, 13.8Hz, 1H), 2.23 (s, 3H), 2.07 (s, 3H), 2.06 (dddd, J=2.4Hz, 2.8Hz, 11.2Hz, 14.0Hz, 1H), 1.82 (d, J=11.6Hz, 1H), 1.18 (dd, J=5.6Hz, 13.8Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.28, 169.46, 143.67, 137.77, 134.77, 130.98, 128.81, 127.82, 127.55, 127.05, 125.97 , 96.69, 79.12, 76.18, 68.08, 67.68, 61.46, 56.09, 50.48, 44.05, 28.18, 21.33, 21.25. IR (NaCl thin film): 3442.19, 3089.70, 3059.92, 3029.62, 2896.56, 2831.82, 1757.82,

1738.90, 1494.34, 1452.50, 1432.01, 1372.32, 1307.95, 1228.44, 1193.22, 1122.98, 1083.94, 1063.84, 908.61, 871.71, 836.85, 786.75, 756.11, 734.07, 707.17, 669.28, 647.53, 601.61 cm^{-1}. HRMS (TOF-ESI): calcd for C28H32NO6 $[MH]^+$ 478.2230, found 478.2218. $[\alpha]_D^{25} = +126.9$ (*c*1, CH_2Cl_2).

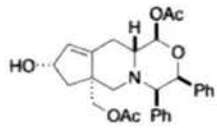




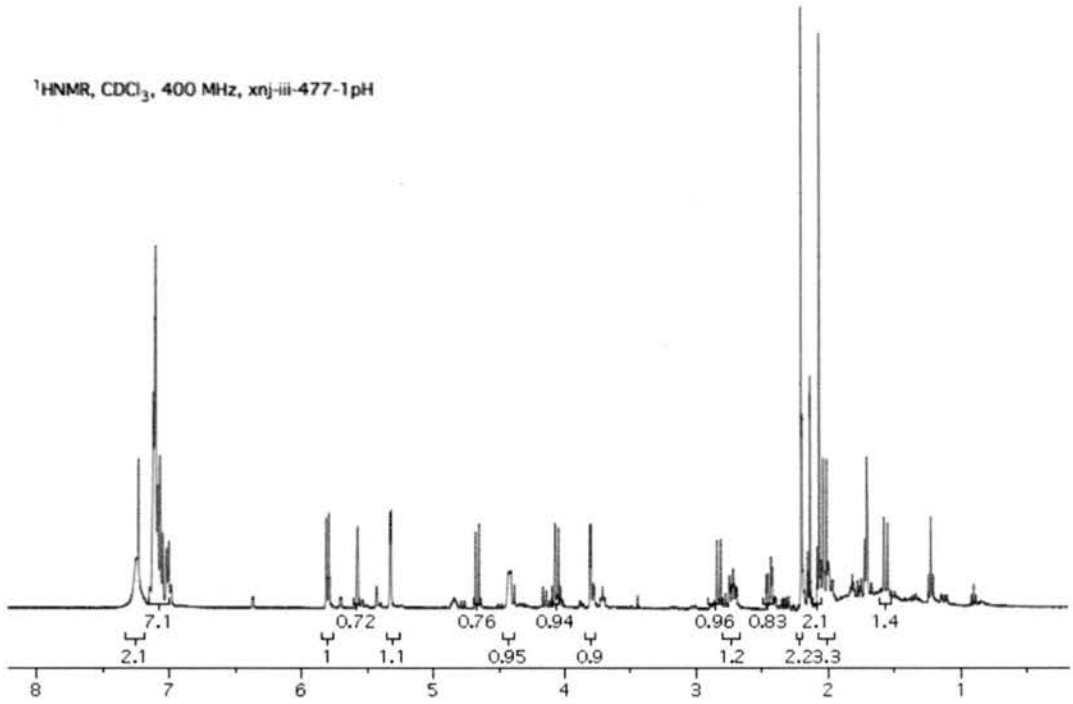
Allylic Alcohol (162)



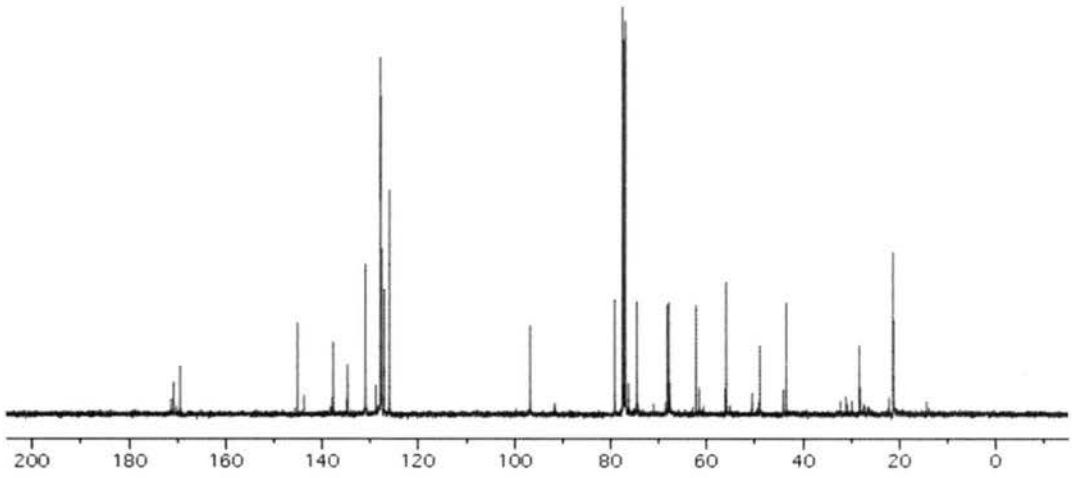
To an ice-cold bath cooled solution of **141** (63.2 mg, 0.1329 mmol) in THF (0.3 mL) was added 9-BBN dropwise (0.319 mL, 0.5 M solution in THF). The resulting mixture was stirred at 0 °C for 1 h and an additional 1 h at room temperature before methanol was added to quench the reaction. The excess solvent was removed under reduced pressure, the residue was subjected to column (1:1 Hexanes/EtOAc) to provide **161** 8 mg (12.7%) and **162** 39 mg (61.7%) as white solid. **162**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23 (br, 2H), 7.12-6.99 (m, 8H), 5.81 (d, J=8.0Hz, 1H), 5.57 (br s, 1H), 5.33 (d, J=4.0Hz, 1H), 4.68 (d, J=12.0Hz, 1H), 4.43 (br, 1H), 4.08 (d, J=12.0Hz, 1H), 3.81 (d, J=4.0Hz, 1H), 2.85 (d, J=12.0Hz, 1H), 2.78 (ddd, J=4.0Hz, 8.0Hzz, 16.0Hz, 1H), 2.47 (dd, J=4.0Hz, 16.0Hz, 1H), 2.21 (s, 3H), 2.07 (s, 3H), 2.04 (d, J=12.0Hz, 1H), 2.08-1.97 (comp m, 2H), 1.58 (d, J=12.0Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.83, 169.45, 145.09, 137.71, 134.71, 131.00, 127.89, 127.85, 127.59, 127.11, 126.00 , 96.73, 79.17, 74.52, 68.21, 67.86, 62.23, 55.97, 48.96, 43.49, 28.33, 21.28.



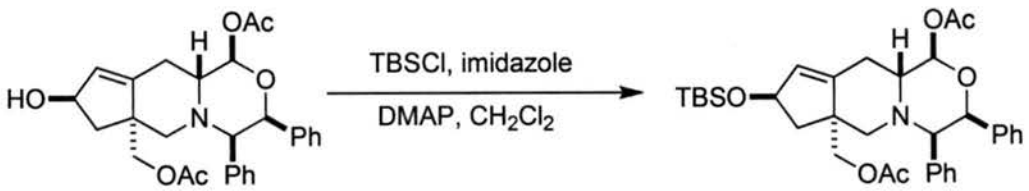
^{1}HNMR, $CDCl_3$, 400 MHz, xnj-iii-477-1pH



^{13}CNMR, $CDCl_3$, 100 MHz, xnj-iii-477-1pC_{13}



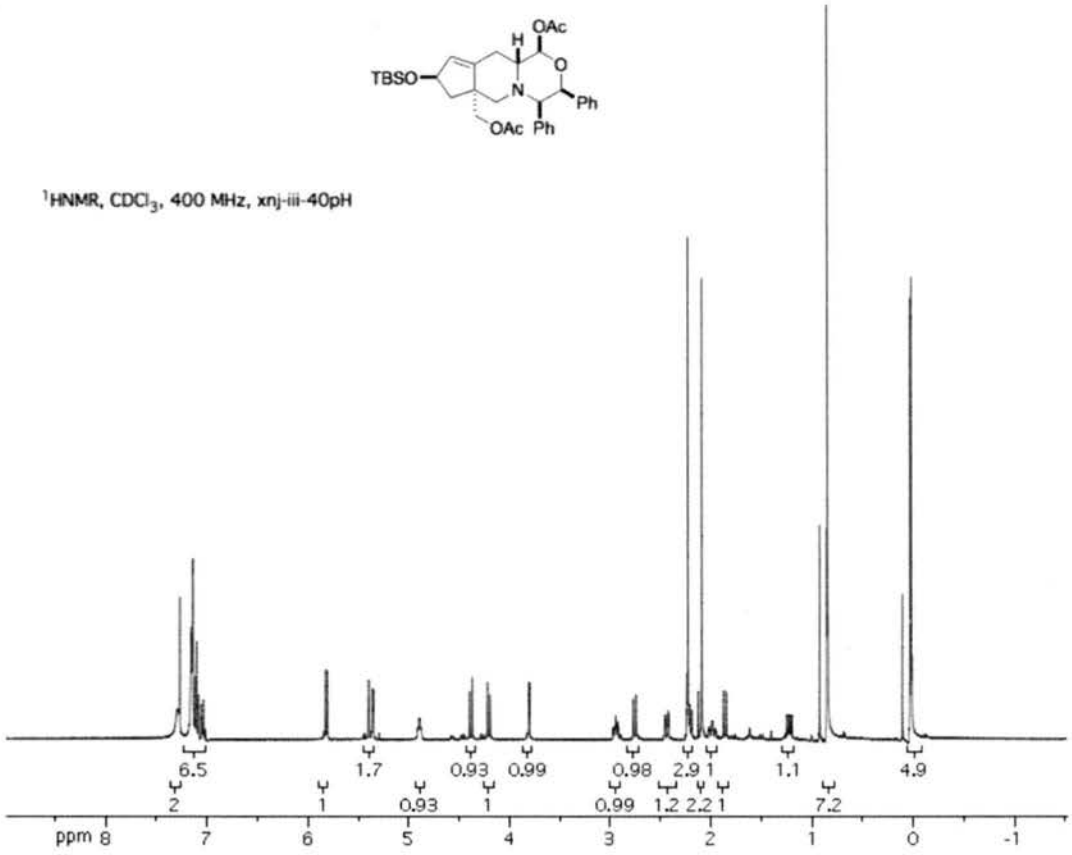
TBS Ether (163)

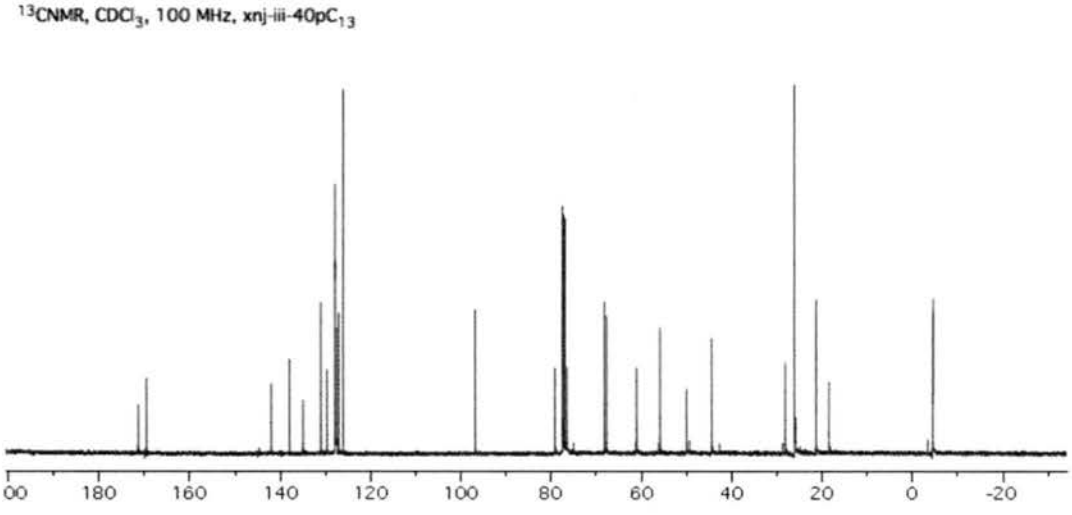


161 **163**

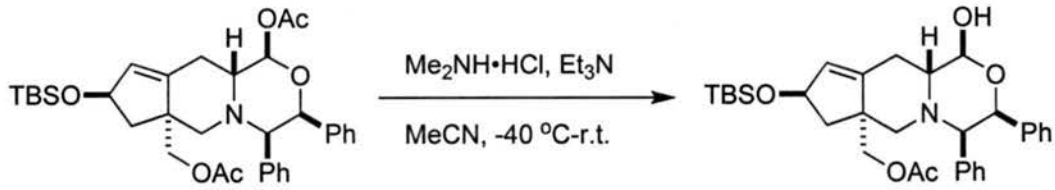
To 0 °C cooled solution of allylic alcohol **161** (832.3 mg, 1,743 mmol) in dichloromethane (3.5 mL) was added imidazole (596.4 mg, 8.715 mmol), *ter*-butyl dimethyl chlorosilane (523.8 mg, 3.486 mmol) and DMAP (43.7 mg, 20%). The reaction mixture was stirred at room temperature for 19 h. Solvent was removed and the residue was subjected to column (Hexanes/EtOAc, 10:1 to 5:1) gave 985 mg (93%) of product **163** as white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29 (br s, 2H), 7.18-7.02 (m, 8H), 5.83 (d, J=8.4Hz, 1H), 5.40 (s, 1H), 5.36 (d, J=3.2Hz, 1H), 4.90 (br.s, 1H), 4.40 (d, J=10.6Hz, 1H), 4.22 (J=10.6Hz, 1H), 3.81 (d, J=3.2Hz, 1H), 2.98 (ddd, J=3.6Hz, 8.4Hz, 11.0Hz, 1H), 2.77 (d, J=11.4Hz, 1H), 2.46 (dd, J=3.4Hz, 13.8Hz, 1H), 2.23 (s, 3H), 2.24 (dd, J=7.2Hz, 13.2Hz, 1H), 2.09 (s, 3H), 2.03 (dddd, J=2.8Hz, 5.6Hz, 11.0Hz, 13.8Hz, 1H), 1.88 (d, J=11.4Hz, 1H), 1.25 (dd, J=6.4Hz, 13.2Hz, 1H), 0.85 (s, 9H), 0.03 (d, J=5.2Hz, 6H). ^{13}C ($CDCl_3$, 100 MHz): δ 171.28, 169.52, 141.96, 137.91, 134.93, 131.02, 129.65, 127.85, 127.81, 127.54, 127.04, 126.04, 96.83, 79.17, 76.48, 68.16, 67.73, 61.02, 55.86, 50.00, 44.38, 28.18, 26.15, 21.36, 21.31, 18.51, -4.47, -4.51. IR (NaCl thin film): 3060.50, 3029.57, 2954.10, 2929.44, 2894.47, 2855.80, 1741.23 (d), 1667.83, 1603.33, 1494.99, 1471.39, 1452.80, 1432.31, 1371.94, 1225.02, 1123.29, 1064.31, 1005.37, 970.69, 956.10, 939.63, 907.75, 776.52, 755.64, 735.02, 705.58,

668.23, 601.68 cm^{-1}. TOF-HRMS: calcd for C34H46NO6Si $[MH]^+$ 592.3094, found 592.30844. $[\alpha]_D^{25} = +127.8$ (c1, CH_2Cl_2).





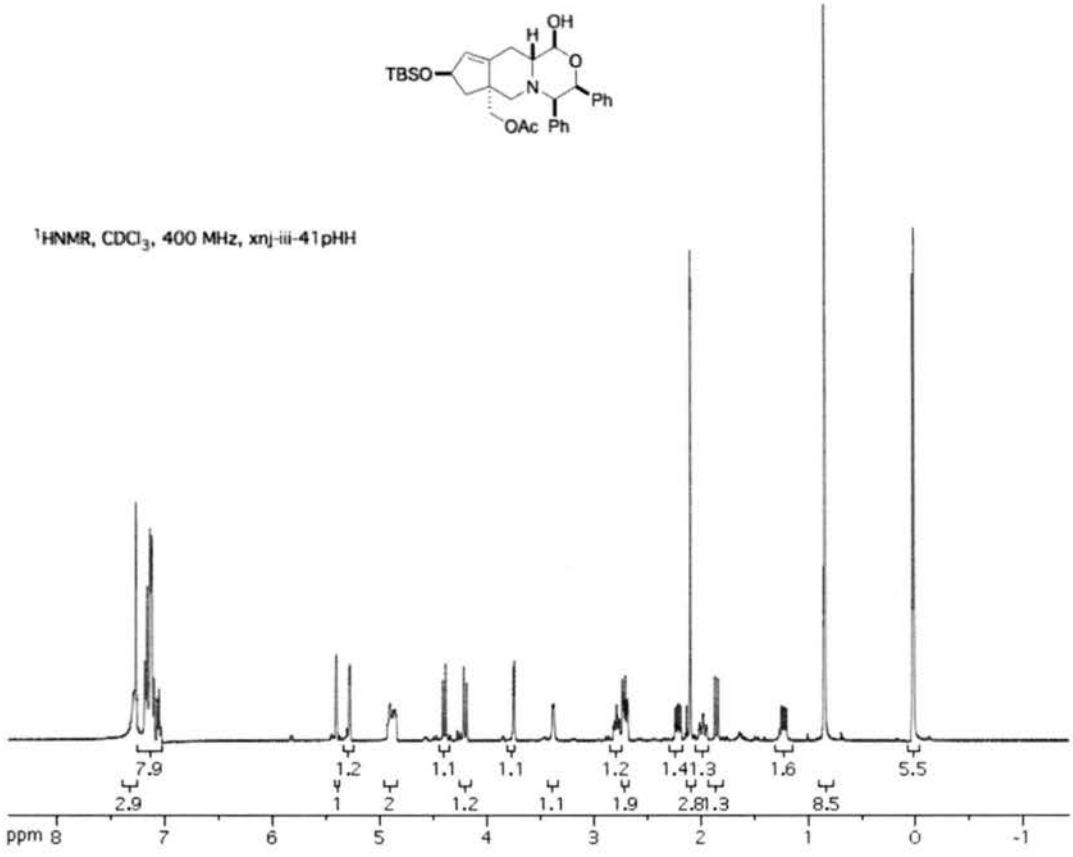
Lactol (164)

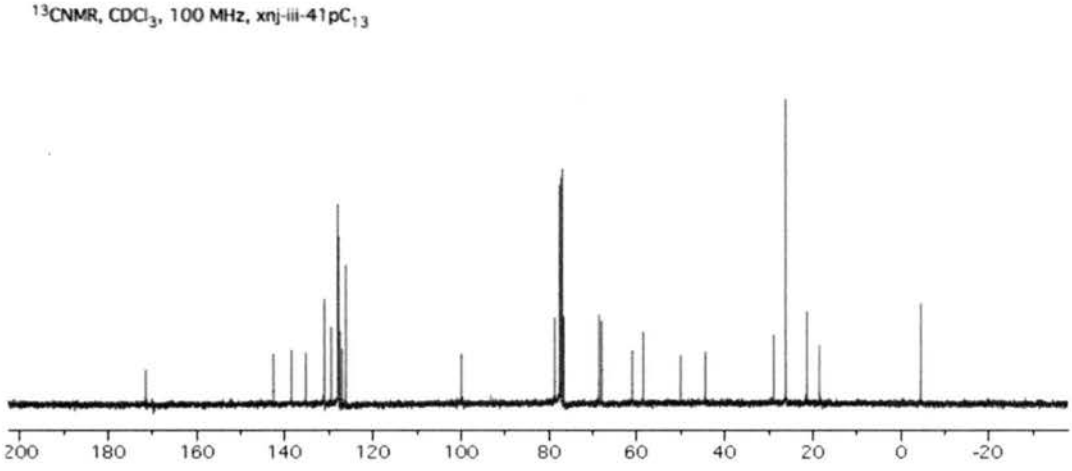


163 **164**

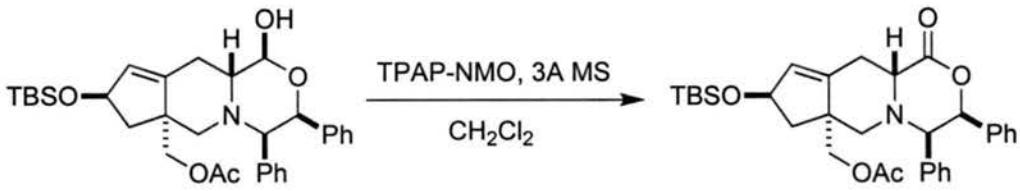
To -40 °C cooled suspension of dimethylamine hydrochloride (4.45 g, 54.07 mmol) in acetonitrile (27 mL) was added triethyl amine (8.6 mL, 59.5 mmol) and stir for 5 min. Compound **163** (1.6 g, 2.704 mmol) in acetonitrile (18.5 mL) was added slowly to the above cooled suspension. After removing the cold, the reaction was stirred at room temperature for 24 h. Excess solvent was removed under rotavap below 30 °C. The residue was purified by flash chromatography (Hexanes/EtOAc, 5:1 to 3:1) and gave 1.27 g (85%) of lactol **164** as white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29–7.28, 7.17–7.04 (m, 10H), 5.41 (s, 1H), 5.28 (d, J=3.2Hz, 1H), 4.91-4.84 (m, 2H), 4.41 (d, J=10.6Hz, 1H), 4.22 (d, J=10.6Hz, 1H), 3.75 (d, J=2.8Hz, 1H), 3.43 (d, J=5.6Hz, 1H), 2.82 (ddd, J=3.6Hz, 8.0Hz, 11.6Hz, 1H), 2.73 (d, J=11.6Hz, 1H), 2.73 (dd, J=3.6Hz, 14.4Hz, 1H), 2.24 (dd, J=7.2Hz, 13.2Hz, 1H), 2.02 (dddd, J=2.4Hz, 10.8Hz, 13.6Hz, 32Hz, 1H), 1.87 (d, J=11.6Hz, 1H), 1.25 (dd, J=6.4Hz, 13.2Hz, 1H), 0.85 (s, 9H), 0.035 (d, J=5.2Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.50, 142.58, 138.44, 135.23, 131.01, 129.44, 127.93, 127.76, 127.45, 127.08, 126.10, 99.86, 78.69, 76.60, 68.55, 67.96, 61.00, 58.47, 50.04, 44.39, 28.85, 26.24, 26.22, 26.20, 26.18, 26.15, 26.14, 21.37, 18.54, -4.45, -4.47. IR (NaCl thin film): 3418.44, 3060.06, 3028.56, 2954.49, 2929.11, 2889.76, 2855.81, 1740.14, 1494.31, 1471.29, 1452.48, 1374.80, 1250.63, 1127.32,

1097.41, 1073.66, 954.35, 898.06, 834.66, 776.17, 754.47, 735.99, 704.38, 667.28, 604.54 cm^{-1}. FAB-HRMS: calcd for C32H44NO5Si $[MH]^+$ 550.2989, found 550.29667. $[\alpha]_D^{25} = +128$ (*c*1, CH_2Cl_2).





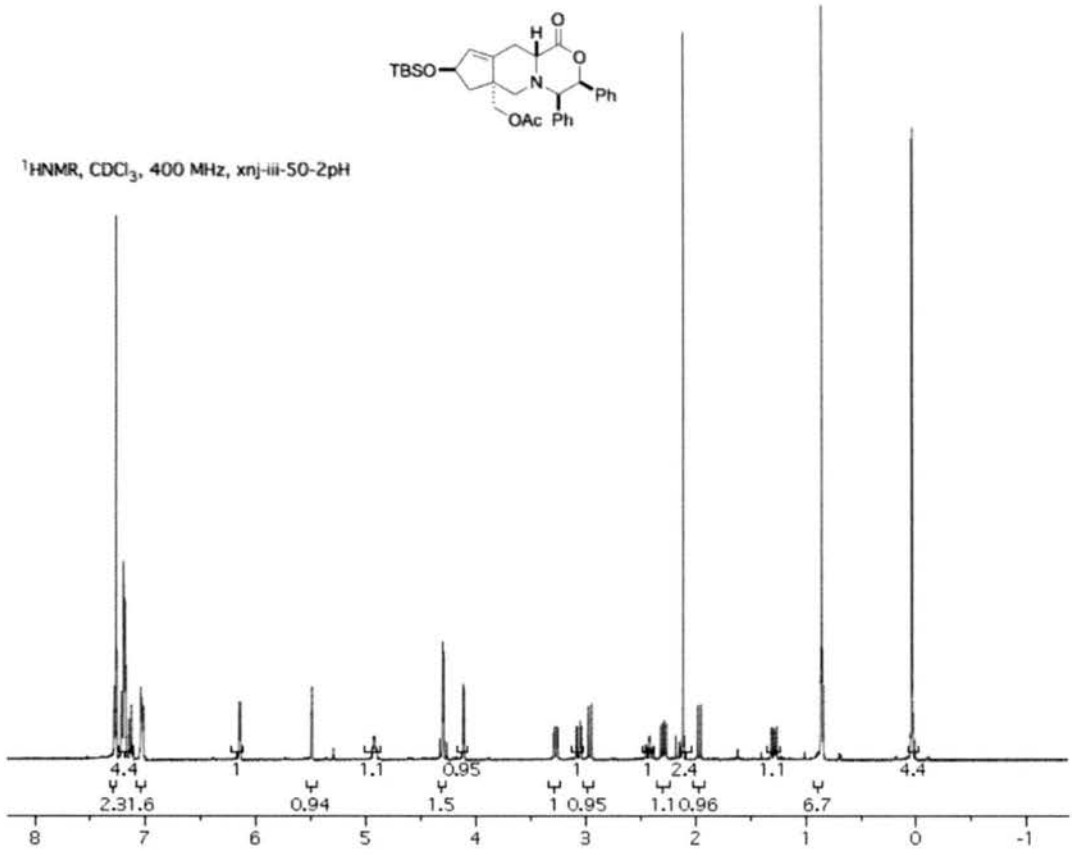
Lactone (165)

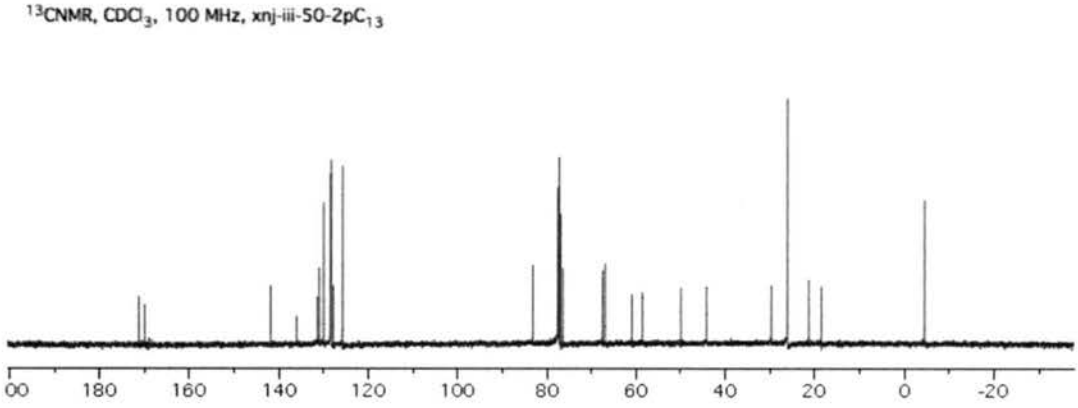


164 **165**

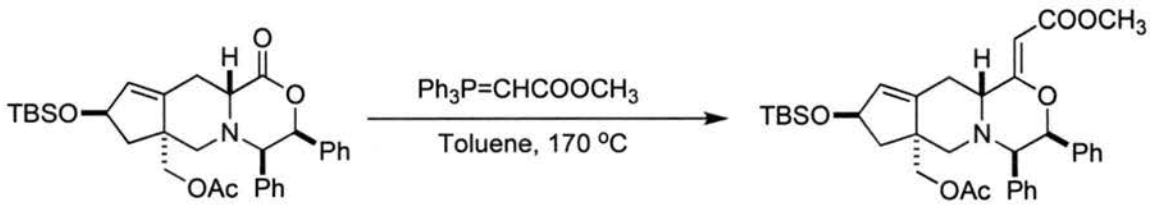
To 0 °C cooled suspension of lactol **164** (944 mg, 1.717 mmol) and 3Å molecular sieves (1.2 g) in dichloromethane (34.3 mL) was added *N*-methyl morpholine *N*-oxide (246.6 mg, 2.060 mmol) and tetrapropylammonium peruthanate (61.29 mg, 20 mmol%). After stirred at 0 °C for 2 h, the reaction mixture was filtered through celite and concentrated. Flash chromatography (Hexanes/EtOAc, 5:1) gave 800 mg (85%) of oxazinone **165** as colorless crystals. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29–7.02 (m, 10H), 6.15 (d, J=3.6Hz, 1H), 5.49 (s, 1H), 4.93 (m, 1H), 4.30 (d, J=3.2Hz, 2H), 4.12 (d, J=3.6Hz, 1H), 3.29 (dd, J=3.4Hz, 11.8Hz, 1H), 3.09 (dd, J=3.4Hz, 14.2Hz, 1H), 2.98 (d, J=11.2Hz, 1H), 2.46 (dddd, J=2.8Hz, 3.6Hz, 12.0Hz, 14.2Hz, 1H), 2.32 (dd, J=7.2Hz, 13.2Hz, 1H), 2.12 (s, 3H), 1.98 (d, J=11.2Hz, 1H), 1.31 (dd, J=6.4Hz, 13.2Hz, 1H), 0.86 (s, 9H), 0.04 (d, J=3.2Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.27, 169.98, 141.87, 136.07, 131.37, 131.02, 130.00, 128.51, 128.36, 127.87, 125.76, 83.11, 76.43, 67.52, 66.96, 60.93, 58.58, 49.97, 44.17, 29.69, 26.14, 21.33, 18.51, -4.48. IR (NaCl thin film): 3060.90, 3031.48, 2954.56, 2929.16, 2894.90, 2856.06, 1742.58, 1496.82, 1471.24, 1452.98, 1373.75, 1234.66, 1178.01, 1134.72, 1084.02, 1065.32, 1005.81, 973.69, 939.73, 908.36, 834.80, 777.46, 753.93, 733.69, 702.50,

669.28, 626.78, 611.96 cm^{-1}. FAB-HRMS: calcd for C32H42NO5Si $[MH]^+$ 548.2832, found 548.2832. $[\alpha]_D^{25} = +81.7$ (c1, CH_2Cl_2).





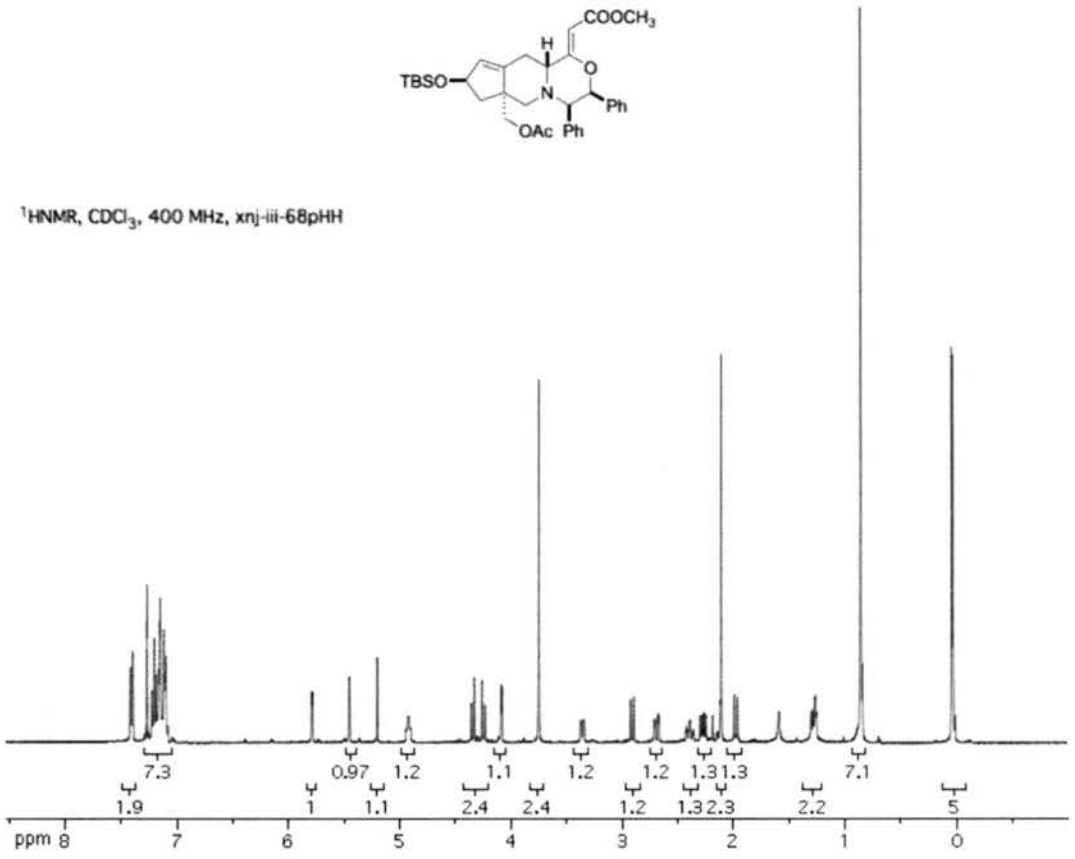
α, β-unsaturated Ester (173)

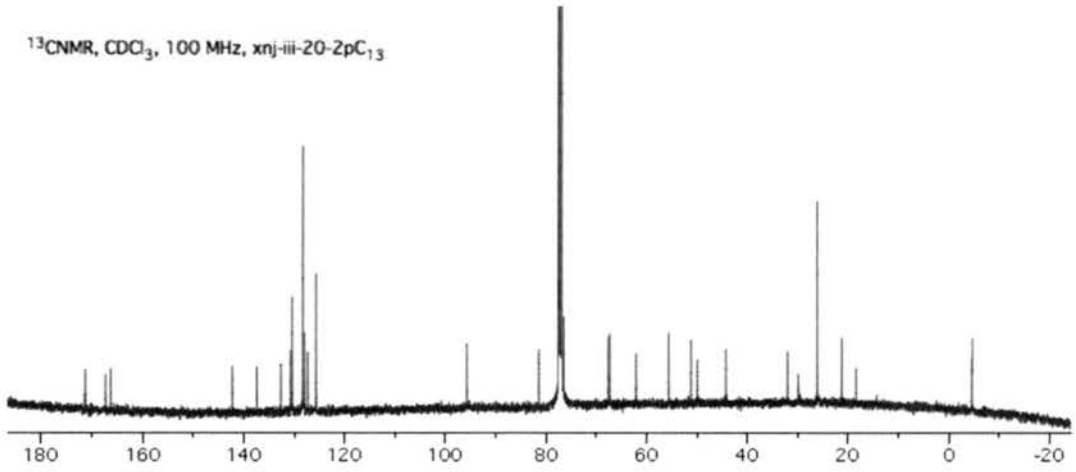


165 **173**

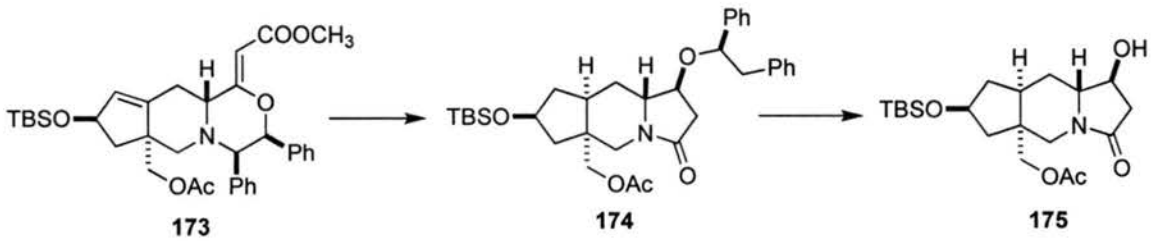
A mixture of methyl(triphenylphosphoranylidene) acetate (312 mg, 0.9128 mmol), lactone **165** (100 mg, 0.1826 mmol) in toluene (1.82 mL) was heated to 170 °C in sealed tube in a 20 min period, stirred at this temperature for 5 h. After removal of the heat and reaction was cooled down, ethyl acetate was added carefully. The mixture was filtered through a small pad of silica gel, washed with ethyl acetate sufficiently, and concentrated. The residue was subjected to column (Hexanes/EtOAc, 5:1) to provide 110 mg (quant.) of product **173** as light yellowish solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 (d, J=7.6Hz, 2H), 7.40-7.10 (m, 8H), 5.79 (d, J=3.4Hz, 1H), 5.45 (s, 1H), 5.20 (s, 1H), 4.92 (br s, 1H), 4.36 (d, J=10.6Hz, 1H), 4.26 (d, J=10.6Hz, 1H), 4.09 (d, J=3.4Hz, 1H), 3.75 (s, 3H), 3.37 (app d, J=9.2Hz, 1H), 2.92 (d, J=11.4Hz, 1H), 2.71 (dd, J=3.2Hz, 13.6Hz, 1H), 2.43 (ddd, J=2.4Hz, 11.2Hz, 13.6Hz, 1H), 2.30 (dd, J=7.2Hz, 13.2Hz, 1H), 2.11 (s, 3H), 1.99 (d, J=11.4Hz, 1H), 1.30 (dd, J=6.4Hz, 13.2Hz, 1H), 0.86 (s, 9H), 0.045 (d, J=4.4Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.25, 167.25, 166.21, 142.18, 137.36, 132.61, 130.65, 130.34, 128.26, 128.22, 127.97, 127.30, 125.64, 95.70, 81.41, 76.45, 67.62, 67.36, 62.11, 55.62, 51.17, 49.93, 44.26, 32.06, 26.15, 21.35, 18.52, -4.47, -4.49. IR (NaCl thin film): 3061.65, 3029.63, 2952.34, 2927.81, 2855.19, 1737.23, 1630.15, 1496.68, 1452.36, 1434.58, 1375.36, 1361.35, 1325.64, 1226.79, 1187.08, 1157.11, 1068.47, 1038.53, 1005.64, 972.58, 929.63, 898.55, 834.46, 777.08, 704.18, 668.58 cm^{-1}. FAB-HRMS:

calcd for C35H46NO6Si $[MH]^+$ 604.3094, found 604.3082. $[\alpha]_D^{25}$ = +115.2 (*c*1, CH_2Cl_2).





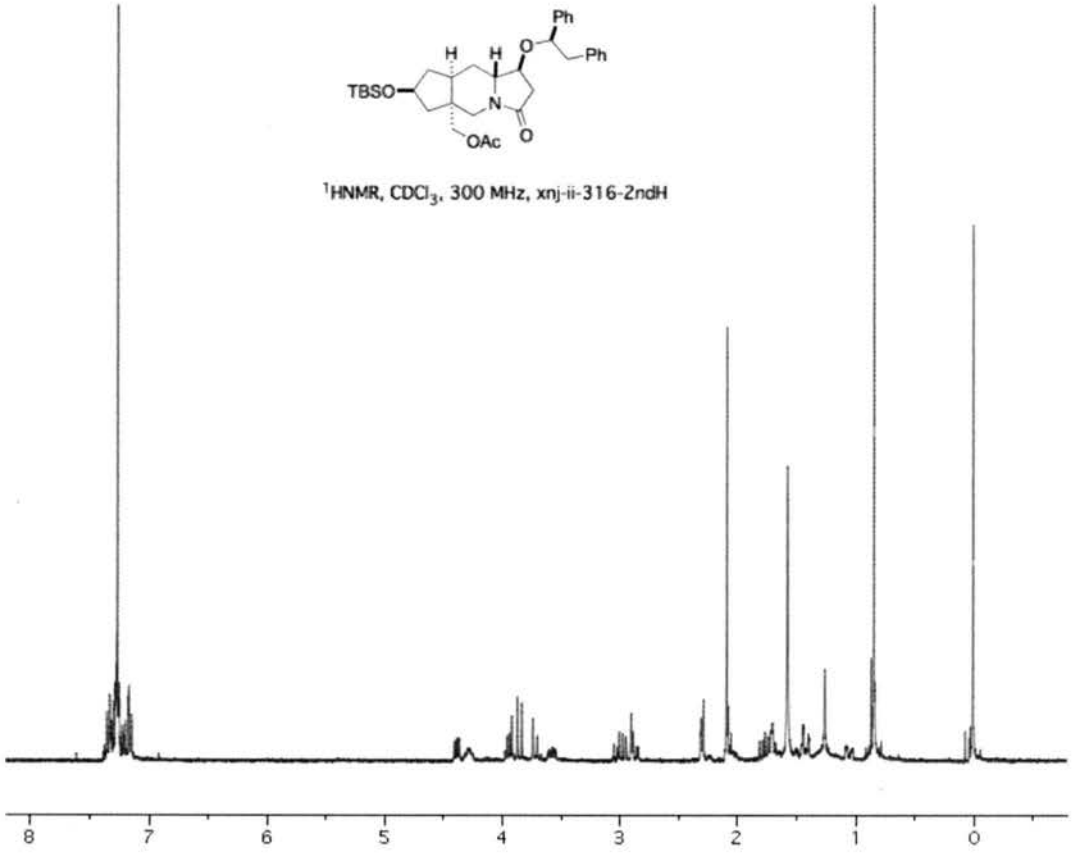
((1*R*,5a*S*,7*R*,8a*S*,9a*S*)-7-(*tert*-butyldimethylsilyloxy)-1-((*S*)-1,2-diphenylethoxy)-3-oxodecahydro-1*H*-cyclopenta[*f*]indolizin-5a-yl)methyl acetate (175) and ((1*R*,5a*S*,7*R*,8a*S*)-7-(*tert*-butyldimethylsilyloxy)-1-hydroxy-3-oxodecahydro-1*H*-cyclopenta[*f*]indolizin-5a-yl)methyl acetate (176)

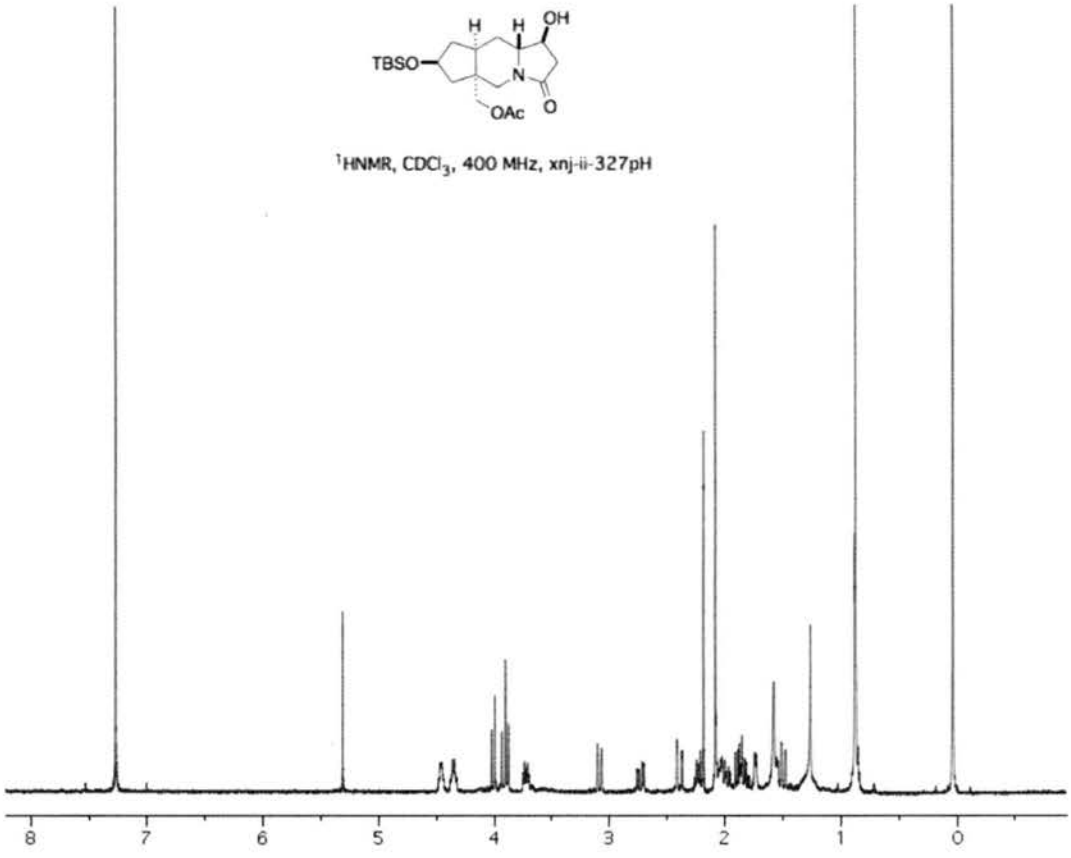


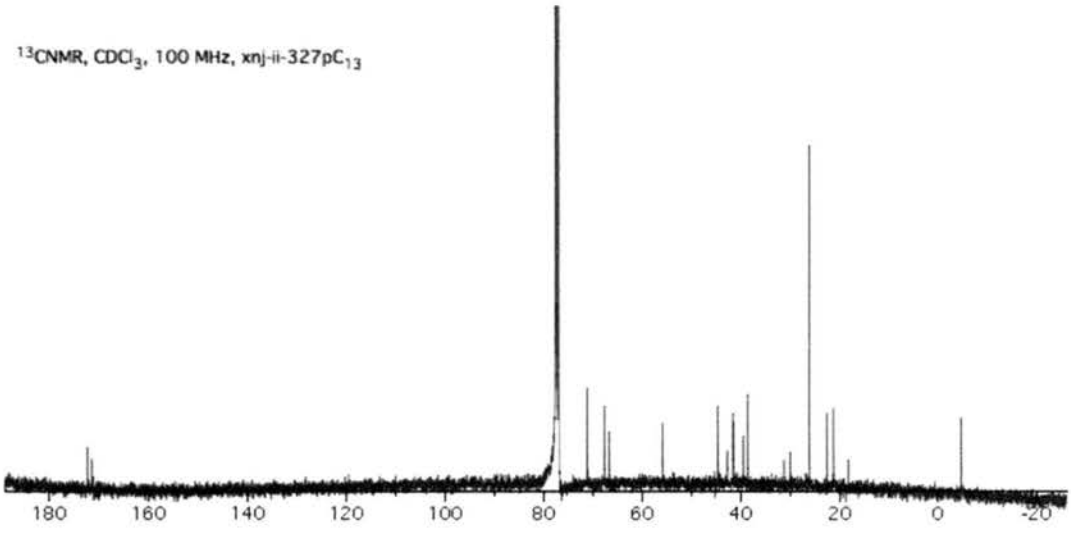
The mixture of **173** (9.4 mg, 0.01562 mmol) and 20% $Pd(OH)_2/C$ (11 mg) in ethanol (2 mL) was heated to 85 °C under 105 psi for 2.5 h. The reaction mixture was filtered through celite, washed sufficiently with ethanol, and concentrated. Preparation TLC (Hexanes/EtOAc, 5:1) gave compound **174** and **175**. The mixture of **173** (18.8 mg, 0.03116 mmol) and 20% $Pd(OH)_2/C$ (21.9 mg) in ethanol (2 mL) was heated to 85 °C under 105 psi for 4.5 h. Reaction suspension was filtered through celite, washed sufficiently with ethanol, and concentrated to give crude **175** only.

Compound **174:** ^{1}H NMR (300 MHz, CD_3Cl): δ 7.39-7.37 (m, 5H), 7.26-7.15 (m, 5H), 4.41 (dd, J=4.5, 8.7Hz, 1H), 4.35-4.25 (m, 1H), 3.98-3.93 (dd, J=6.3, 11.7Hz, 1H), 3.88 (d, J=11.4Hz, 1H), 3.74 (d, J=11.4Hz, 1H), 3.62-3.55 (m, 1H), 3.06-2.85 (comp m, 3H), 2.31 (d, J=5.1Hz, 2H), 2.10 (s, 3H), 1.82 (dd, J=8.4, 14.4Hz, 1H), 1.72-1.68 (m, 2H), 1.47-1.40 (m, 2H), 1.09-1.02 (m, 1H), 0.85 (s, 9H), 0.04 (s, 6H). FAB-HRMS: calcd for C34H48NO5Si $[MH]^+$ 578.3302, found 578.3315. Compound **175**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.47-4.42 (m, 1H), 4.39-4.31 (m, 1H), 4.04 (d, J=11.1Hz, 1H), 3.89 (d, J=11.4Hz, 1H), 3.93 (d, J=13.8Hz, 1H), 3.75-3.67 (m, 1H), 3.10 (d, J=14.1Hz, 1H), 2.77

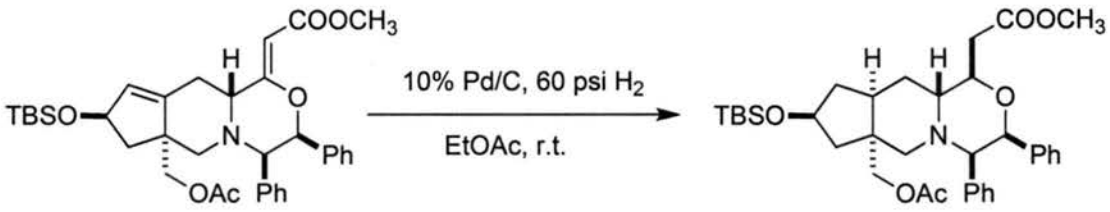
(ddd, J=1.5, 6.6, 17.4Hz, 1H), 2.43 (dd, J=2.1, 17.4Hz, 1H), 2.27-2.17 (m, 1H), 2.08 (s, 3H), 2.05-1.99 (m, 2H), 1.96-1.77 (m, 3H), 1.61-1.46 (m, 2H), 0.87 (s, 9H), 0.03 (s, 6H). IR (NaCl thin film): 3395.55, 2952.74, 2926.74, 2854.37, 1738.88, 1667.86, 1443.54, 1364.76, 1247.67, 1089.26, 1054.62, 835.89, 776.08 cm^{-1}. FAB-HRMS: calcd for C20H36NO5Si $[MH]^+$ 398.23572, found 398.23567.




H
H
OH
TBSO
N
O
OAc
^{1}HNMR, $CDCl_3$, 400 MHz, xnj-ii-327pH
8
7
6
5
4
3
2
1
0

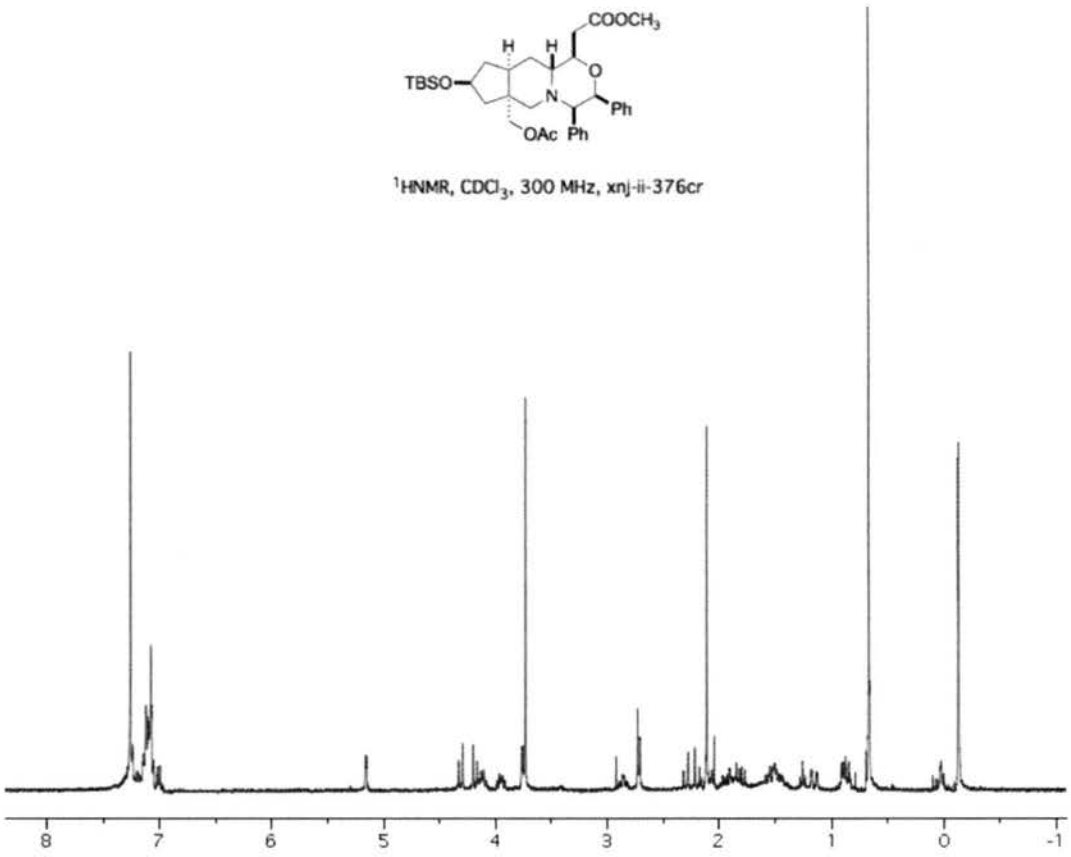

^{13}CNMR, $CDCl_3$, 100 MHz, xnj-ii-327pC_{13}
180
160
140
120
100
80
60
40
20
0
-20

Saturated Ester (177)

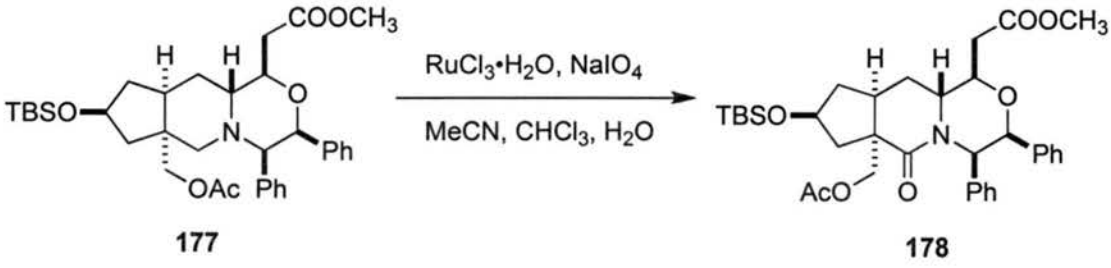


173 **177**

A mixture of compound **173** (50 mg, 0.08288 mmol) and 10% Pd/C (43.99 mg) in ethanol (5 mL) was stirred at room temperature under 60 psi H_2 atmosphere for 3 h. The reaction suspension was filtered through celite, washed sufficiently with ethyl acetate, and concentrated. Flash chromatography (Hexanes/EtOAc, 4:1) gave 33 mg (66%) of product **177.** ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23-7.20 (m, 1H), 7.18-7.06 (m, 8H), 7.04-6.98 (m, 1H), 5.17 (d, J=3.0Hz, 1H), 4.34 (d, J=10.8Hz, 1H), 4.21 (d, J=10.8Hz, 1H), 4.16-4.10 (m, 1H), 4.00-3.93 (m, 1H), 3.78 (d, J=3.3Hz, 1H), 3.74 (s, 3H), 2.93 (s, 3H), 2.92-2.82 (m, 1H), 2.74 (d, J=6.6Hz, 1H), 2.33 (d, J=12.6Hz, 1H), 2.23 (d, J=12.9Hz, 1H), 2.12 (s, 3H), 1.88-1.78 (m, 1H), 1.60-1.39 (m, 1H), 1.19-1.14 (m, 1H), 0.96-0.82 (m, 2H), 0.68 (s, 9H), -0.12 (d, J=1.5Hz, 6H). FAB-HRMS: calcd for C35H50NO6Si $[MH]^+$ 608.3407, found 608.33969.

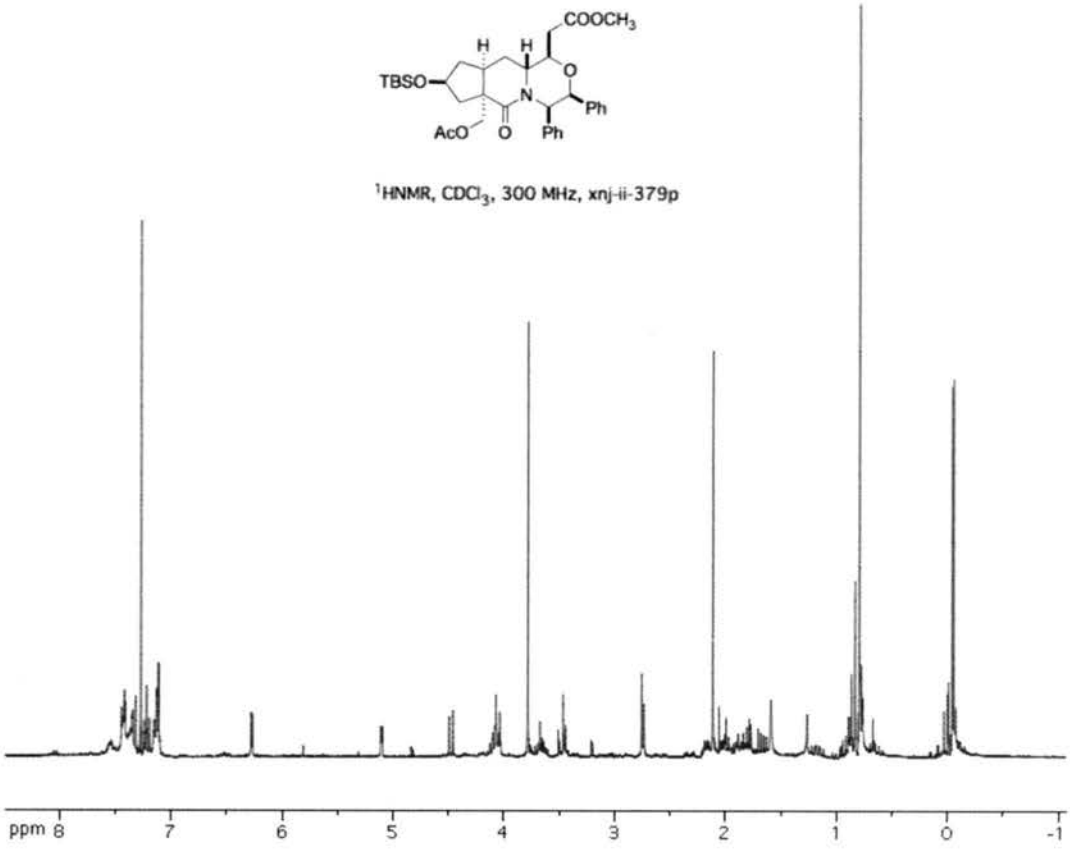


Lactam (178)

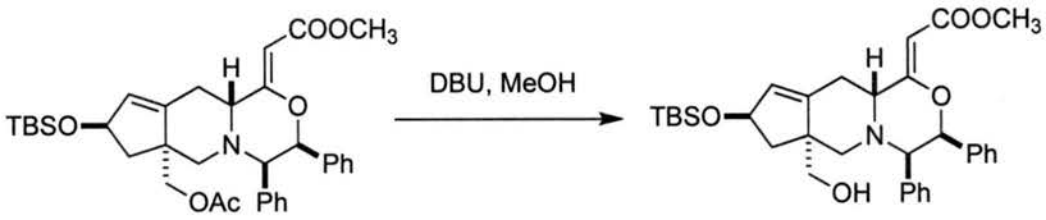


To a solution of compound **177** (33 mg, 0.05429 mmol) in MeCN-CH_3Cl-H_2O (0.2 /0.2/0.3 mL) was added $NaIO_4$ (48.1 mg, 0.226 mmol) and $RuCl_3 \bullet H_2O$ (1.1 mg, 10 mmol%). The resulting dark-color mixture was stirred at room temperature for 12 h, or

until the disappearance of the starting material monitored by TLC. Reaction solution was filtered through a pad of celite. Preparation TLC (Hexanes/EtOAc, 3:1) gave 10 mg (39%) of product **178**. ^{1}H NMR (300 MHz, CD_3Cl): δ 7.44-7.41 (m, 2H), 7.37-7.32 (m, 4H), 7.25-7.19 (m, 2H), 7.16-7.10 (m, 2H), 6.28 (d, J=3.6Hz, 1H), 5.11 (d, J=3.6Hz, 1H), 4.49 (d, J=10.2Hz, 1H), 4.13-4.03 (comp, 2H), 4.07 (d, J=10.5Hz, 1H), 3.78 (s, 3H), 3.72-3.60 (m, 1H), 2.75 (d, J=6.6Hz, 2H), 2.19-2.17 (m, 1H), 2.11 (s, 3H), 2.04-1.99 (m, 1H), 1.98-1.87 (m, 1H), 1.87-1.76 (m, 2H), 1.70 (dd, J=7.5, 14.1Hz, 1H), 1.22-1.11 (m, 1H), 0.80 (s, 9H), -0.04 (d, J=4.2Hz, 6H). FAB-HRMS: calcd for C35H48NO7Si $[MH]^+$ 622.3200, found 622.3202.

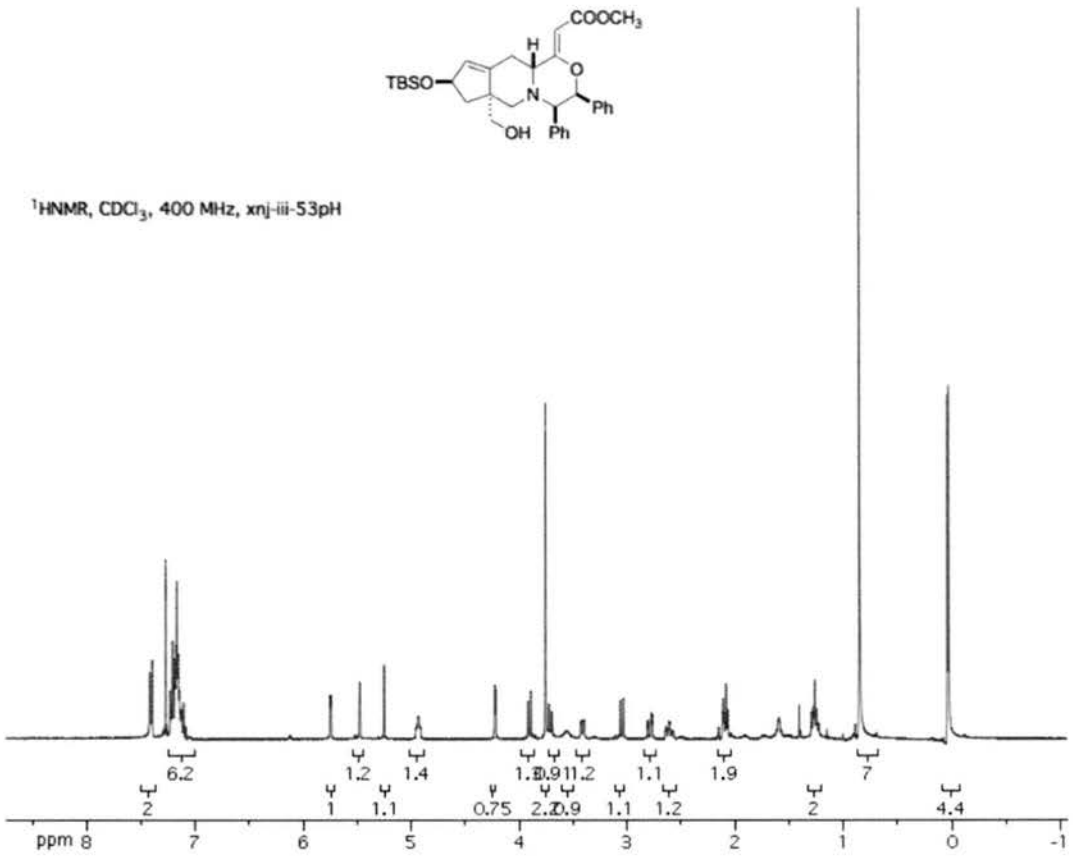


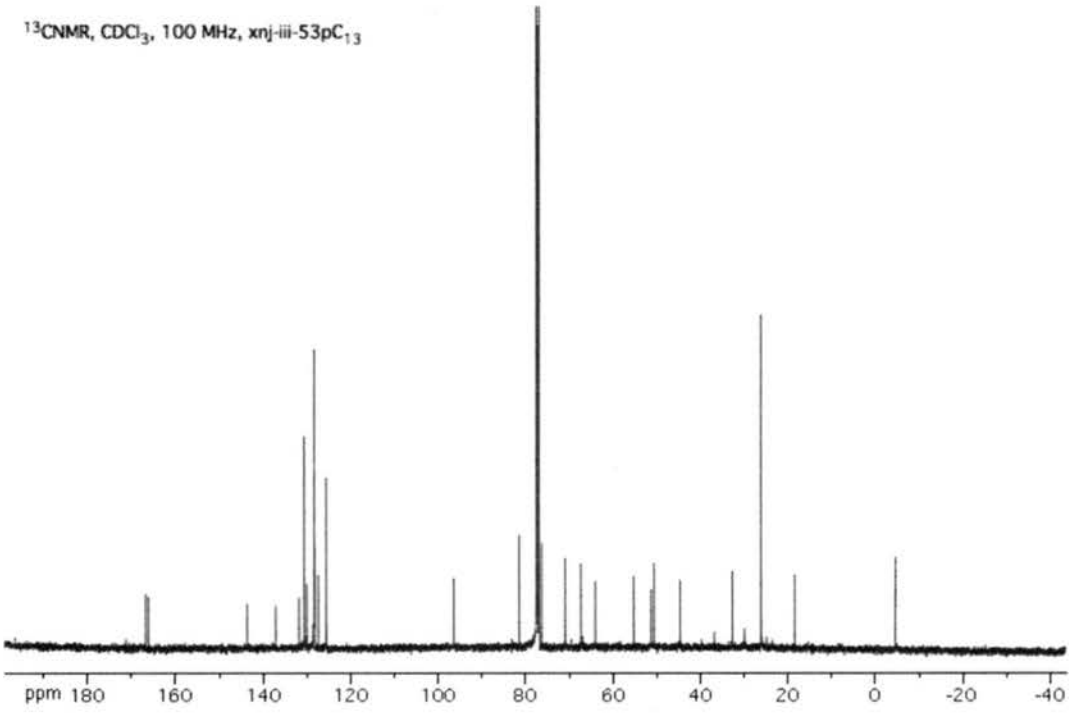
Alcohol (180-1)



173 **180-1**

To an ice-cooled solution of acetate **173** (231.2 mg, 0.3822 mmol) in methanol (3.83 mL) was added DBU (88.77 μL, 0.5748 mmol) dropwise. After removing the cold bath, the reaction was stirred at room temperature for 3.5 h or until the disapperance of starting material on TLC. Excess solvent was removed and the residue was subjected to flash chromatography (Hexanes/EtOAc, 4:1 to 3:1) and gave 206.6 mg (96%) of alcohol **180-1** as yellowish foam. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 (d, J=7.6Hz, 2H), 7.23-7.09 (m, 8H), 5.75 (d, J=3.4Hz, 1H), 5.48 (s, 1H), 5.25 (s, 1H), 4.94 (br s, 1H), 4.23 (d, J=3.4Hz, 1H), 3.92 (d, J=10.2Hz, 1H), 3.76 (s, 3H), 3.72 (d, J=10.2Hz, 1H), 3.43 (dd, J=3.0Hz, 10.6Hz, 1H), 3.06 (d, J=11.2Hz, 1H), 2.81 (dd, J=3.6Hz, 13.6Hz, 1H), 2.69 (app t, J=12.4Hz, 1H), 2.11 (d, J=10.8Hz, 1H), 2.10 (d, J=13.2Hz, 1H), 1.29 (dd, J=6.0Hz, 13.6Hz, 1H), 0.85 (s, 9H), 0.04 (d, J=4.8Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.72, 166.10, 143.65, 137.10, 131.78, 130.59, 130.05, 128.32, 128.21, 127.39, 125.55, 96.44, 81.44, 76.32, 70.59, 67.34, 64.04, 55.23, 51.24, 50.57, 44.65, 32.69, 26.15, 18.49, -4.45, -4.48. IR (NaCl thin film): 3446.19, 3029.87, 2951.97, 2927.97, 2927.63, 2855.29, 1719.04, 1628.37, 1496.42, 1452.31, 1435.35, 1360.10, 1256.75, 1221.80, 1186.68, 1156.67, 1067.59, 1005.10, 974.51, 929.97, 904.54, 834.31, 776.92, 751.40, 702.73, 667.50 cm^{-1}. HRMS (TOF-ESI): calcd for C33H44NO5Si $[MH]^+$ 562.2989, found 562.2983. $[\alpha]_D^{25}$= +105.7 (*c*1, CH_2Cl_2).


COOCH3
H
TBSO
O
N
Ph
OH
Ph
1HNMR, CDCl3, 400 MHz, xnj-iii-53pH
6.2
1.2
1.4
1.9
7
2
1
1.1
0.75
1.1
1.2
2
4.4
ppm 8
7
6
5
4
3
2
1
0
-1


13CNMR, CDCl3, 100 MHz, xnj-iii-53pC13
ppm 180
160
140
120
100
80
60
40
20
0
-20
-40

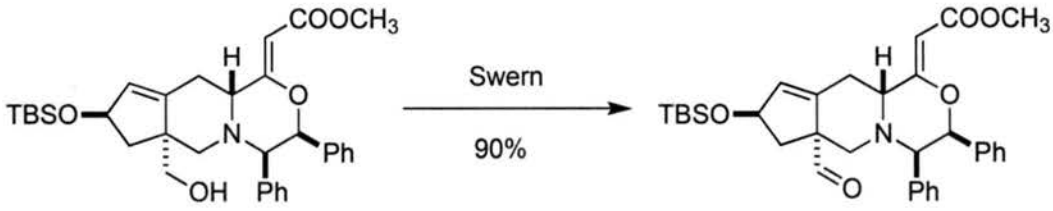
Aldehyde (180-2)

180-1 **180-2**

To an ice-cooled suspension of alcohol **180-1** (206.6 mg, 0.3678 mmol) and 3Å molecular sieves (257 mg) in dichloromethane (7.36 mL) was added *N*-methyl morpholine *N*-oxide (62.8 mg, 0.5516 mmol) followed by tetrapropylammonium peruthanate (26.2 mg, 20 mmol%). After removing ice bath, the reaction was stirred for an additional 30 min, filtered through a small pad of silica gel, washed with ethyl acetate and concentrated. The residue was purified by flash chromatography (Hexanes/EtOAc, 3:1) to give 431.2 mg (2 batches, 68% on average) of aldehyde **180-2** as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 7.40 (d, J=6.8Hz, 2H), 7.23-7.11 (m, 8H), 5.74 (d, J=3.6Hz, 1H), 5.65 (s, 1H), 5.21 (d, J=1.2Hz, 1H), 4.96 (br s, 1H), 4.22 (d, J=3.2Hz, 1H), 3.74 (s, 3H), 3.46 (app d, J=9.2Hz, 1H), 3.40 (d, J=11.6Hz, 1H), 2.81 (dd, J=3.6Hz, 14Hz, 1H), 2.39 (d, J=13.6Hz, 1H), 2.37 (d, J=13.6Hz, 1H), 2.15 (d, J=11.6Hz, 1H), 1.40 (dd, J=6.4Hz, 13.6Hz, 1H), 0.85 (s, 9H), 0.04 (d, J=5.2Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.44, 166.82, 166.09, 140.01, 137.16, 132.60, 132.41, 130.26, 128.39, 128.30, 128.12, 127.41, 125.65, 95.94, 81.32, 76.11, 67.41, 61.69, 60.23, 55.16, 51.21, 41.26, 33.23, 26.09, 18.42, -4.51, -4.49. IR (NaCl thin film): 3061.99, 3030.01, 2953.65, 2928.43, 2855.80, 1722.32, 1631.33, 1496.62, 1470.89, 1452.14, 1434.71, 1359.85,

1323.41, 1257.52, 1221.68, 1186.89, 1156.53, 1038.14, 1005.54, 1069.80, 909.07, 894.02, 834.93, 777.73, 751.10, 706.43, 669.92 cm^{-1}. HRMS (TOF-ESI): calcd for C33H42NO5Si $[MH]^+$ 560.2827, found 560.2822. $[\alpha]_D^{25} = +82.8$ (*c*1, CH_2Cl_2).

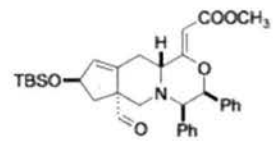
Aldehyde (180-2)



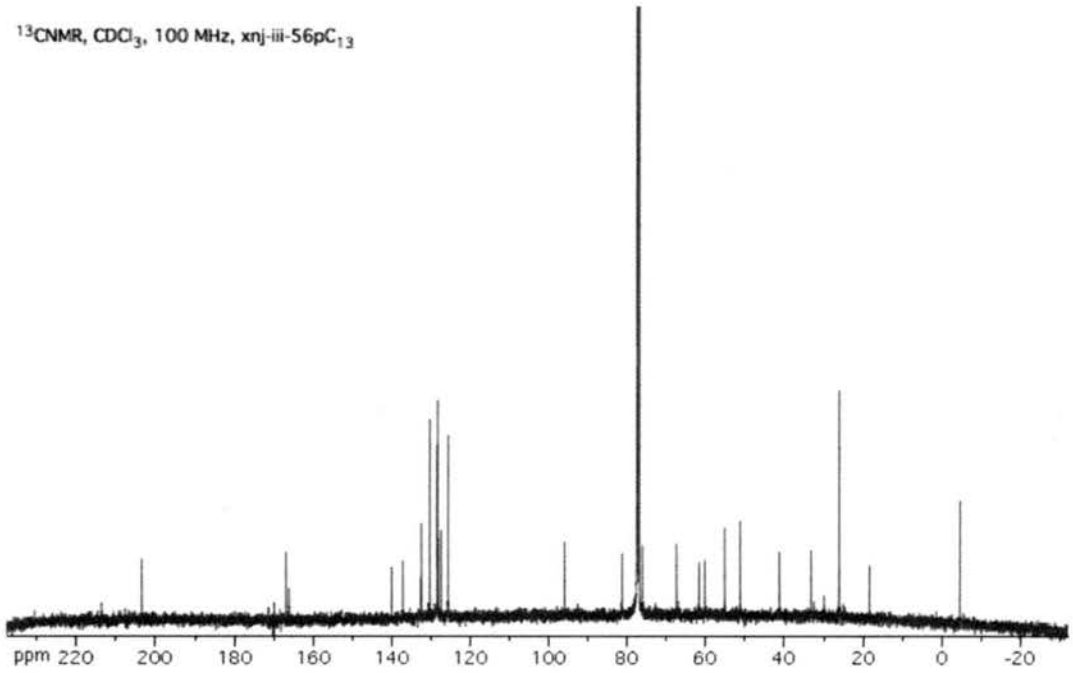
180-1 **180-2**

To -78 °C cooled solution of oxalyl chloride (167.0 μL, 1.909 mmol) in dichloromethane (3.2 mL) was added dimethylsulfoxide (270.0 μL, 3.818 mmol) dropwise. The resulting mixture was stirred for 5 min before alcohol **180-1** (715 mg, 1.273 mmol) in dichloromethane (3.2 mL) was added dropwise to the above mixture under cooling. The reaction was stirred for 40 min at the same temperature, then triethylamine (886.6 μL, 6.365 mmol) was added. The cold-bath was removed, and the reaction was continued to stir for an additional 30-40 min before water was added to quench the reaction. The resulting mixture was then extracted with ethylacetate, washed with brine, dried over anhydrous $MgSO_4$. Flash column chromatography (5:1 Hexanes/EtOAc) provided 971.7 mg (three batches, 90% on average) of the aldehyde **180-2** as light yellow oil.

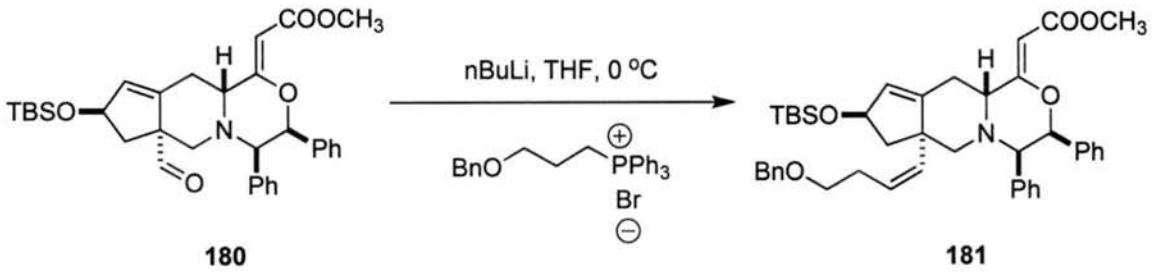
^{1}HNMR, $CDCl_3$, 400 MHz, xnj-iii-56pH



^{13}CNMR, $CDCl_3$, 100 MHz, xnj-iii-56pC_{13}



Triene (181)

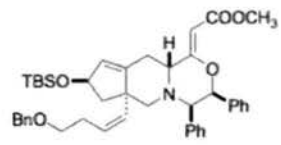


180 **181**

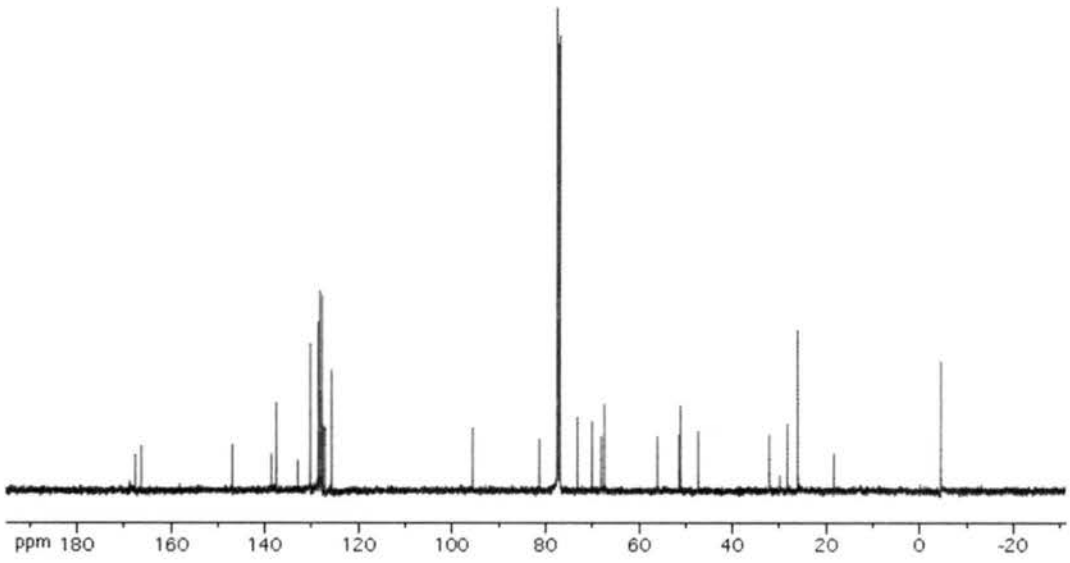
To an ice-cooled suspension of (3-(benzyloxy)propyl)triphenylphosphonium bromide (567.3 mg, 1.156 mmol) in tetrahydrofuran (2.3 mL) was added *n*-BuLi (720.3 μL, 1.6 M solution in hexanes) dropwise. The resulting red-orange solution was stirred at 0 °C for 1 h, aldehyde **180** (323.4 mg, 0.5777 mmol) in THF (9.3 mL) was added dropwise to the above red orange solution. The reaction was stirred for 30 min, quenched with saturated aqueous ammonium chloride. Tetrahydrofuran was removed via rotavap. The residue was partitioned between ethyl acetate and water, separated. The aqueous layer was extracted with ethyl acetate for three times. The combined organic layers were washed with brine and dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (Hexanes/EtOAc, 5:1) to provide 455.4 mg (2 batches, 85.5% on average) of triene **181** as yellowish foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.35 (m, 6H), 7.21-7.07 (m, 9H), 5.79 (d, J=3.4Hz, 1H), 5.72 (d, J=11.6Hz, 1H), 5.43 (dt, J=11.6Hz, 7.2Hz, 1H), 5.36 (s, 1H), 5.20 (d, J=1.2Hz, 1H), 4.96 (br.s, 1H), 4.54 (s, 2H), 4.15 (d, J=3.4Hz, 1H), 3.75 (s, 3H), 3.49 (t, J=6.4Hz, 2H), 3.37 (dd, J=2.0Hz, 10.4Hz, 1H), 3.02 (d, J=10.8Hz, 1H), 2.66 (dd, J=3.2Hz, 12.8Hz, 1H), 2.42-2.30 (comp m, 4H), 2.03 (d, J=10.8Hz, 1H), 1.53 (dd, J=4.8Hz, 13.6Hz, 1H),

0.814 (s, 9H), 0.005 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.56, 166.28, 146.91, 138.60, 137.54, 137.52, 132.95, 130.28, 128.62, 128.20, 127.82, 127.79, 127.69, 127.21, 127.17, 125.70, 95.59, 81.32, 73.18, 70.02, 68.08, 67.42, 56.04, 51.40, 51.13, 47.32, 32.15, 28.31, 26.15, 18.42, -4.38. IR (NaCl thin film): 3088.06, 3062.31, 3029.16, 2952.23, 2926.89, 2854.70, 1720.86, 1632.64, 1495.95, 1470.86, 1452.71, 1434.46, 1359.75, 1321.73, 1256.56, 1218.50, 1155.51, 1095.27, 1069.00, 929.08, 908.90, 834.16, 775.68, 736.68, 699.13 cm^{-1}. FAB-HRMS: calcd for C43H54NO5Si $[MH]^+$ 692.3771, found 692.3756. $[\alpha]_D^{25}$= +101.2 (*c*1, CH_2Cl_2).

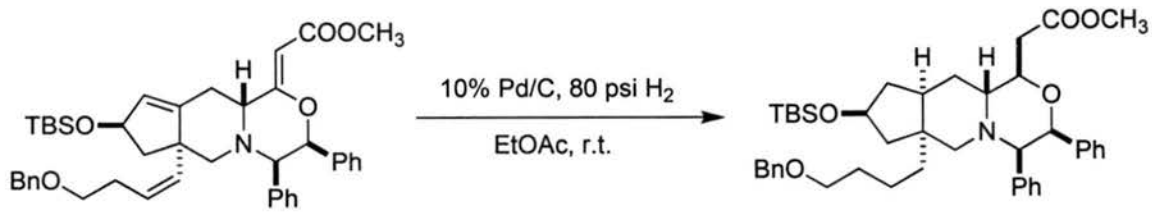
^{1}HNMR, $CDCl_3$, 400 MHz, xnj-iii-275pH



^{13}CNMR, $CDCl_3$, 100 MHz, xnj-iii-275pC_{13}p



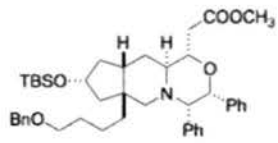
Saturated Ester (183)



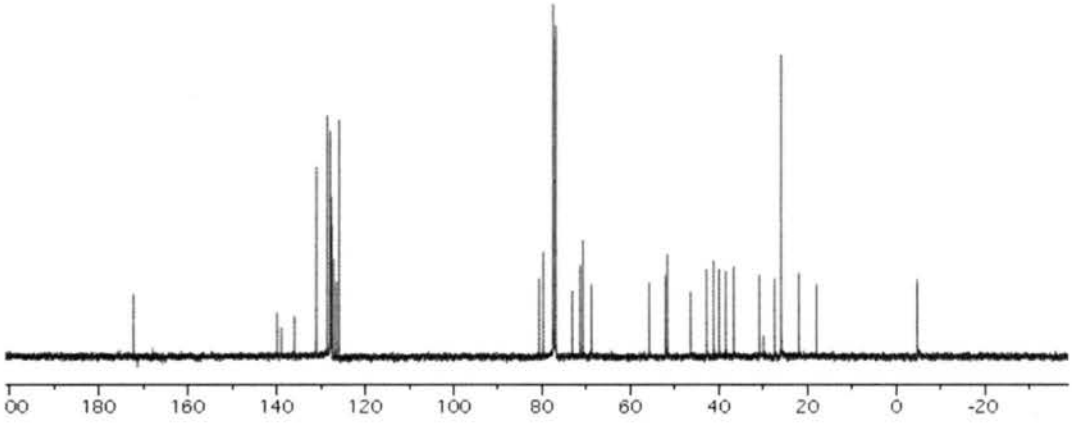
181 **183**

A mixture of triene **181** (455.4 mg, 0.6583 mmol), 10% Pd/C (701.2 mg, 0.9875 mmol) in ethyl acetate (13.2 mL) was stirred at room temperature under 80 psi H_2 for 13 h. The reaction mixture was filtered through celite, washed sufficiently with ethyl acetate and concentrated. Flash chromatography (Hexanes/EtOAc, 5:1) gave 373.8 mg (81.3%) of product **183** as colorless sticky oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40-6.99 (m, 15H), 5.20 (d, J=2.8Hz, 1H), 4.57 (s, 2H), 4.13–4.07 (m, 1H), 4.01–3.96 (m, 1H), 3.79 (d, J=3.2Hz, 1H), 3.75 (s, 3H), 3.56 (t, J=6.8Hz, 2H), 2.86–2.80 (m, 1H), 2.74 (s, 1H), 2.73 (d, J=3.2Hz, 1H), 2.22 (d, J=1.6Hz, 1H), 2.13 (d, J=1.6Hz, 1H), 2.01 (ddd, J=2.4, 5.6, 26.4Hz, 1H), 1.91 (ddd, 7.2, 6.4, 12.8Hz, 1H), 1.70-1.59 (m, 4H), 1.54-1.46 (m, 3H), 1.31-1.18 (m, 3H), 1.15 (dd, J=2.4, 14.0Hz, 1H), 0.68 (s, 9H), -0.12 (d, J=4.2Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.19, 139.87, 138.89, 135.93, 131.01, 128.60, 127.89, 127.75, 127.66, 127.52, 127.09, 126.45, 125.84, 80.70, 79.75, 77.54, 77.22, 76.91, 73.18, 71.38, 70.73, 68.81, 55.76, 52.06, 51.65, 46.39, 42.77, 41.20, 39.96, 38.47, 36.63, 30.86, 27.41, 26.00, 21.98, 17.98, -4.63, -4.67. IR (NaCl thin film): 3088.11, 3061.56, 3028.42, 2928.63, 2854.77, 1743.53, 1494.90, 1470.71, 1452.40, 1435.77, 1360.58, 1305.33, 1254.61, 1206.33, 1169.11, 1151.43, 1118.57, 1074.24, 1030.03, 1005.44, 937.75, 900.35, 835.74, 808.83, 775.04, 751.65, 734.65, 699.20, 603.07 cm^{-1} HRMS-TOF: calcd for C43H60NO5Si [MH^+] 698.4241, found 698.4241. $[\alpha]_D^{25}$ = +101.2 (*c*1, CH_2Cl_2).

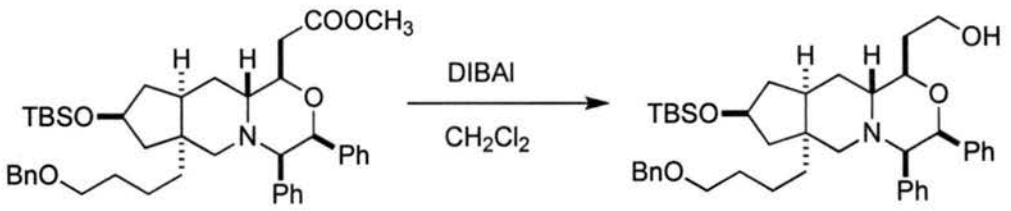
^{1}HNMR, $CDCl_3$, 400 MHz, xnj-iii-179pH



^{13}CNMR, $CDCl_3$, 100 MHz, xnj-iii-179pC_{13}



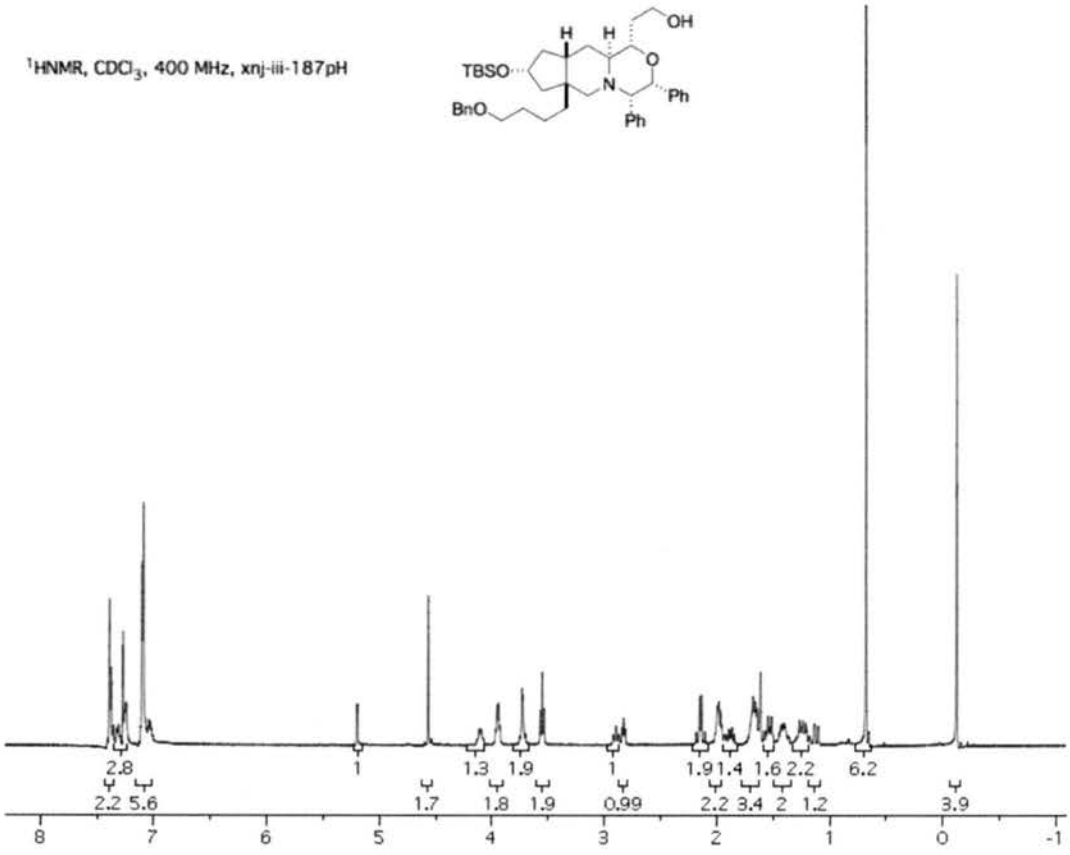
Alcohol (184)



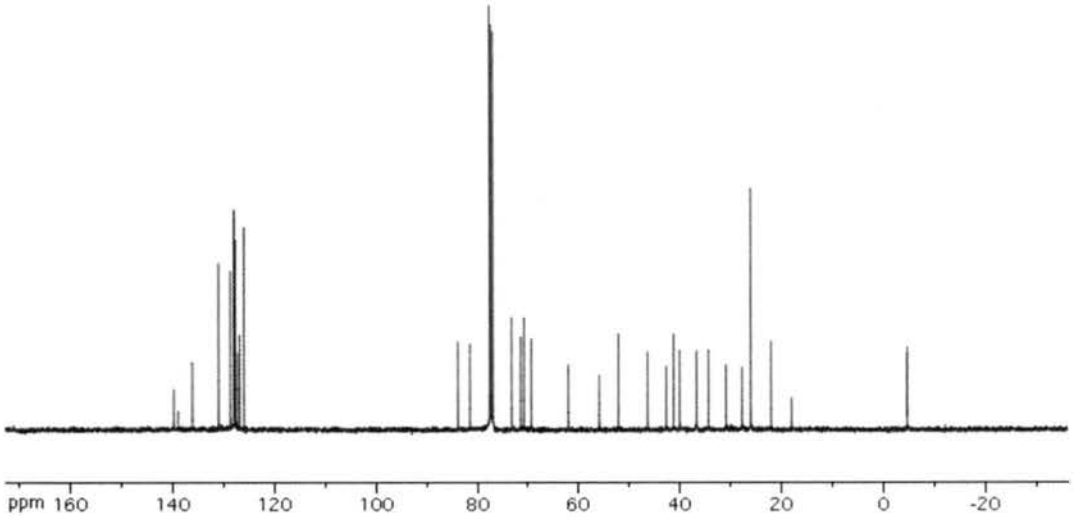
183 **184**

To -78 °C cooled solution of compound **183** (140.2 mg, 0.2008 mmol) in dichloromethane (4 mL) was added DIBAl (1 mL, 1.0 M solution in toluene) dropwise. The resulting mixture was stirred at -78 °C for 30 min. After cold bath was removed, the reaction was stirred for an additional 20 min, quenched carefully with sodium potassium tartrate saturated aqueous solution, diluted with ethyl acetate and stirred for 2 h. The two phases were separated. The aqueous layer was extracted with ethyl acetate for three times. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. Flash chromatography (Hexanes/EtOAc, 2:1) gave 121 mg (90%) of alcohol **184**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.07 (m, 15H), 5.20 (d, J=2Hz, 1H), 4.58 (s, 2H), 4.13-4.07 (m, 1H), 3.97 (app q, J=5.2Hz, 2H), 3.75-3.70 (m, 2H), 3.57 (t, J=6.4Hz, 2H), 2.92 (ddd, J=1.6Hz, 10.8Hz, 10.8Hz, 1H), 2.84 (t, J=5.2Hz, 1H), 2.18-2.10 (comp m, 2H), 2.05-1.93 (comp m, 3H), 1.91-1.85 (ddd, J=7.6Hz, 7.6Hz, 13.6Hz, 1H), 1.74-1.17 (comp m, 10H), 1.14 (dd, J=2.0Hz, 14Hz, 1H), 0.68 (d, J=1.6Hz, 9H), -0.12 (br s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.74, 138.89, 136.10, 130.92, 128.61, 127.90, 127.87, 127.77, 127.61, 127.19, 126.79, 125.94, 83.80, 81.43, 73.20, 71.43, 70.78, 69.34, 62.03, 55.94, 52.17, 46.38, 42.71, 41.26, 40.04, 36.71,

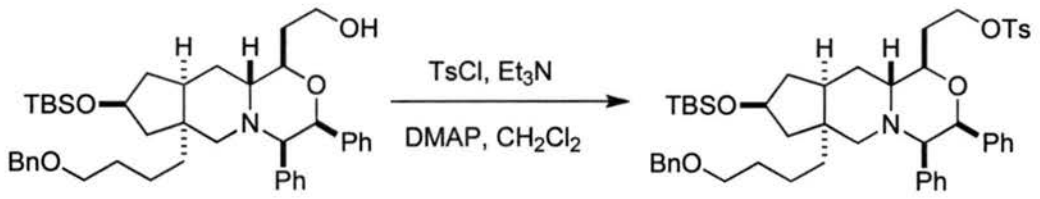
34.32, 30.89, 27.72, 26.00, -4.61, -4.67; IR (NaCl thin film): 3407.20, 3087.37, 3061.16, 3028.34, 2928.39, 2854.91, 1494.53, 1470.67, 1452.35, 1361.44, 1254.81, 1193.66, 1118.56, 1060.89, 898.15, 835.70, 774.71, 698.77 cm^{-1}. HRMS-TOF: calcd for C42H60NO4Si [MH^+] 670.4292, found 670.4288. $[\alpha]_D^{25}$ = +79.14 (*c*1, CH_2Cl_2).



^{13}CNMR, $CDCl_3$, 100 MHz, xnj-iii-187pC_{13}



Tosylate (188)

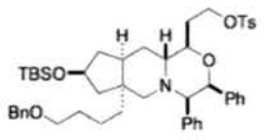


184 **188**

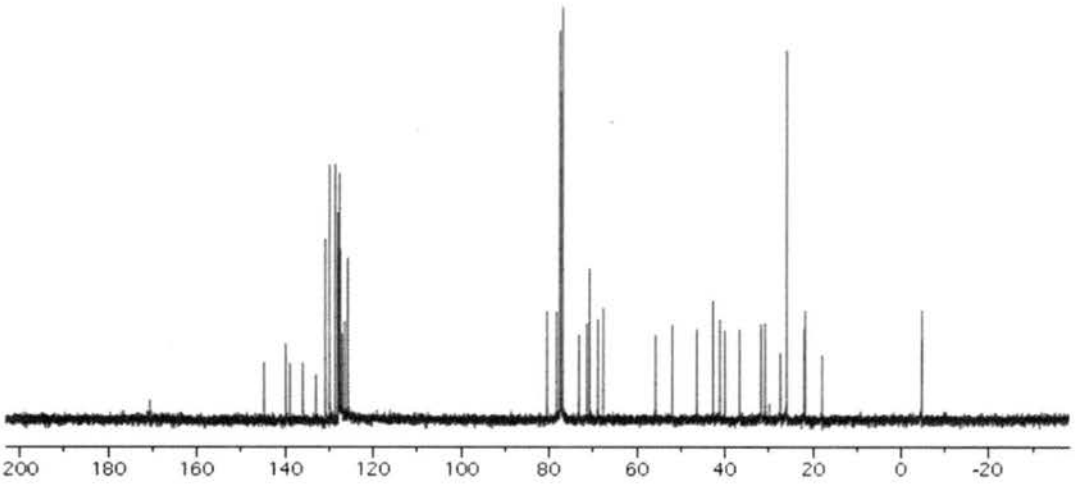
To a solution of alcohol **184** (35 mg, 0.05224 mmol) in dichloromethane (0.5 mL) was added triethyl amine (18.8 μL, 0.1306 mmol), TsCl (20.53 mg, 0.1045 mmol) and DMAP (cat.) under cooling. The reaction was stirred at room temperature for 12 h. The reaction was concentrated and subjected to column (Hexanes/EtOAc, 5:1) to provide 39 mg (90.7%) of tosylate **188** as white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76-7.74 (d,

J=8.4Hz, 2H), 7.42-7.00 (m, 17H), 4.96 (d, J=3.2Hz, 1H), 4.58 (s, 2H), 4.40-4.31 (comp m, 2H), 4.13-4.06 (m, 1H), 3.72 (d, J=3.2Hz, 1H), 3.61-3.54 (m, 2H), 3.53 (ddd, J=2Hz, 10.8Hz, 10.8Hz, 1H), 2.76 (ddd, J=2.8Hz, 10.8Hz, 10.8Hz, 1H), 2.28 (s, 3H), 2.22-2.12 (m, 1H), 2.18 (d, J=12.6Hz, 1H), 2.09 (d, J=12.6Hz, 1H), 1.99-1.90 (comp m, 2H), 1.89 (ddd, J=1.2Hz, 12.4Hz, 14.8Hz, 1H), 1.75-1.60 (comp m, 4H), 1.51-1.33 (comp m, 5H), 1.30-1.16 (comp m, 3H), 1.13 (dd, J=2.8Hz, 14Hz, 1H), 0.67 (s. 9H), -0.12 (d, J=4.8Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.76, 139.83, 138.86, 135.99, 133.00, 130.85, 129.89, 128.59, 127.95, 127.88, 127.74, 127.59, 127.46, 127.04, 126.46, 125.73, 80.48, 78.26, 77.21, 73.17, 71.34, 70.74, 68.87, 67.65, 55.74, 51.97, 46.36, 42.66, 41.13, 39.97, 36.62, 31.79, 30.87, 27.37, 25.97, 21.99, 21.76, -4.70. IR (NaCl thin film): 3087.97, 3061.26, 3028.91, 2927.52, 2854.60, 1598.84, 1494.71, 1470.53, 1452.23, 1362.18, 1254.80, 1188.68, 1177.19, 1120.45, 1069.38, 948.99, 836.12, 813.06, 775.42, 751.56, 737.00, 699.76, 664.54, 609.97 cm^{-1}. HRMS-TOF: calcd for C49H65NO6SSi [MH^+] 824.4302, found 670.4267. $[\alpha]_D^{25}$= +79.69 (*c*1, CH_2Cl_2).

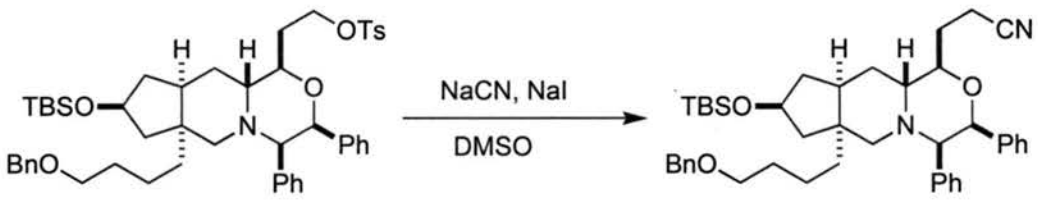
^{1}HNMR, $CDCl_3$, 400 MHz, xnj-iii-380pH



^{13}CNMR, $CDCl_3$, 100 MHz, xnj-iii-380pC_{13}



Nitrile (189)

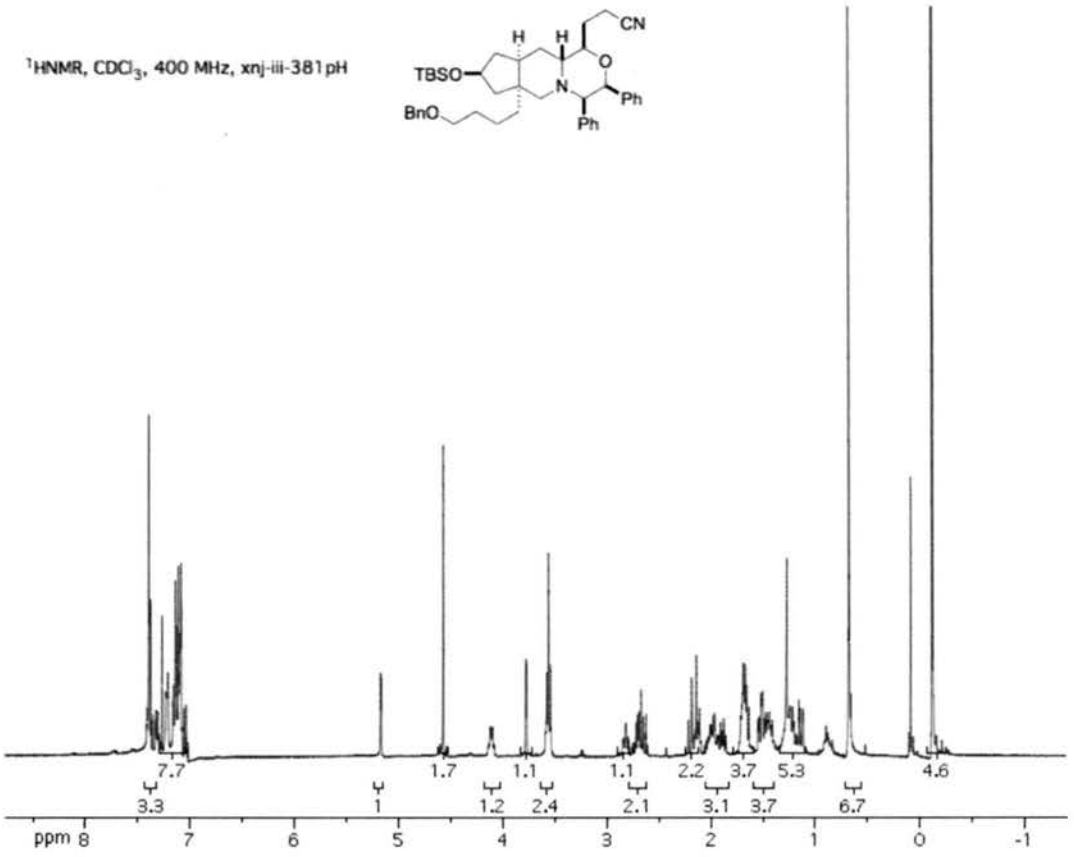


188 **189**

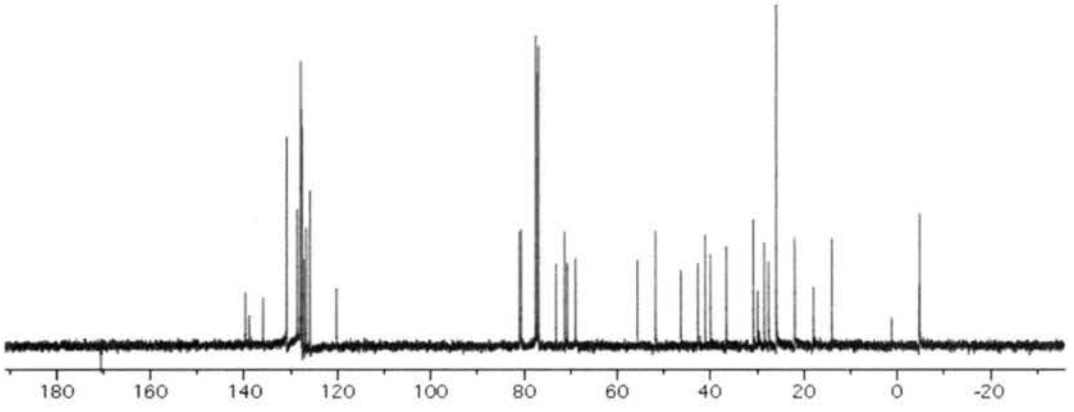
A mixture of compound **188** (99.8 mg, 0.1211 mmol), sodium cyanide (59.4 mg, 1.21 mmol), sodium iodide (3.4 mg, cat.) in DMSO (2.24 mL) was heated to 100 °C for 12 h. Reaction was cooled down and solvent was removed via rotavap. The residue was subjected to column (Hexanes/EtOAc, 5:1) to provide 80.8 mg (98%) of cyanide **189**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42-7.02 (m, 15H), 5.18 (d, J=3.2Hz, 1H), 4.57 (s, 2H), 4.14-4.08 (dddd, J=2.8Hz, 8.8Hz, 8.8Hz, 8.8Hz, 16Hz, 1H), 3.78 (d, J=3.2Hz, 1H), 3.59-3.54 (m, 1H), 3.59 (appt t, J=8Hz, 2H), 2.85 (ddd, J=3.6Hz, 10.8Hz, 10.8Hz, 1H), 2.76-2.61 (m, 2H), 2.22 (d, J=12.4Hz, 1H), 2.14 (d, J=12.4Hz, 1H), 2.17-2.10 (m, 1H), 2.02-1.93 (m, 2H), 1.93 (ddd, J=7.4Hz, 7.4Hz, 12.8Hz, 1H), 1.73-1.14 (comp m, 10H), 1.16 (dd, J=2.4Hz, 14Hz, 1H), 0.68 (s, 9H), -0.11 (d, J=4Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.68, 138.87, 135.93, 130.87, 128.58, 127.87, 127.74, 127.57, 127.17, 126.68, 125.87, 120.18, 80.96, 80.63, 73.15, 71.32, 70.71, 68.95, 55.68, 51.80, 46.37, 42.70, 41.13, 40.00, 36.60, 30.82, 29.90, 28.48, 27.54, 25.96, 21.97, -4.70. IR (NaCl thin film): 3087.85, 3060.57, 3028.58, 2846.75, 2246.85, 1603.82, 1584.77, 1539.91, 1494.50, 1451.98, 1360.79, 1254.92, 1190.03, 1121.06, 982.37, 940.09, 898.77, 835.24, 774.98,

611.04 cm^{-1}. HRMS-TOF: calcd for C43H59N2O3Si [MH^+] 679.4289, found 679.4314. $[\alpha]_D^{25} = +78.3$ ($c1$, CH_2Cl_2).

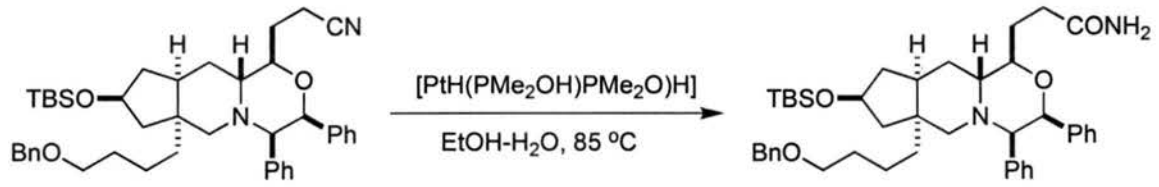
^{1}HNMR, $CDCl_3$, 400 MHz, xnj-iii-381pH



^{13}CNMR, $CDCl_3$, 100 MHz, xnj-iii-381pC13



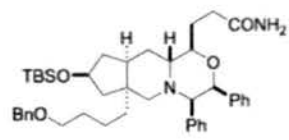
Primary Amide (191)



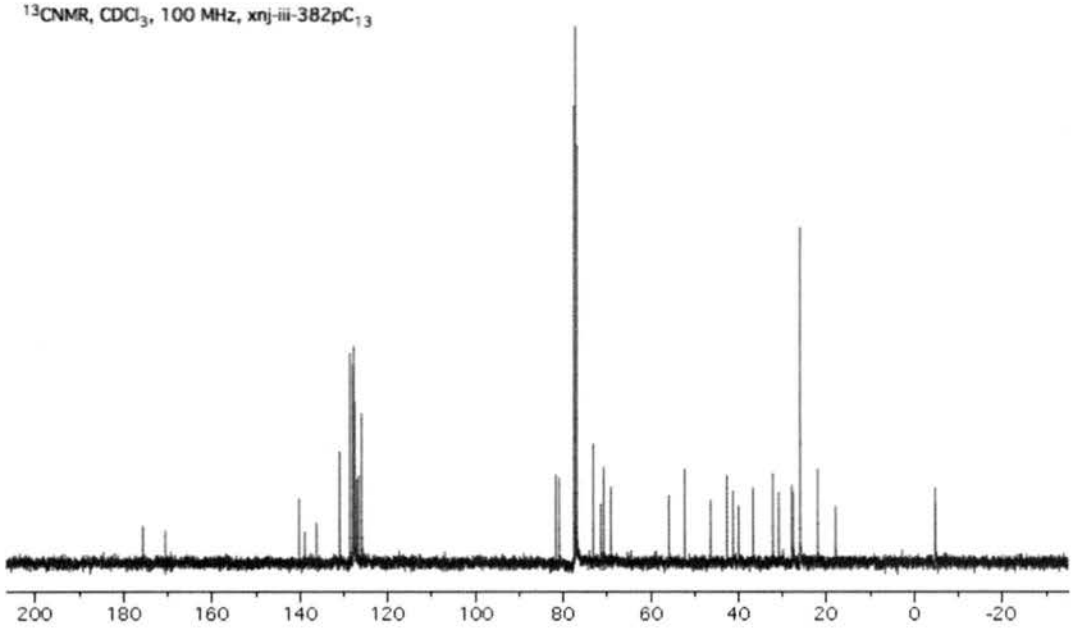
189 **191**

A mixture of the cyanide **189** (41.5 mg, 0.06112 mmol) and Pt-complex catalyst (6.66 mg, 25 mmol%) in ethanol and water (2.26 mL, 9/1) was heated to 85 °C in a sealed tube for 10 h, reaction was cooled down and solvent removed under rotavap. The residue was subjected to column (5% MeOH in DCM) to give 40 mg (93.9%) of primary amide **191**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.01 (m, 15H), 5.59 (s, 1H), 5.38 (s, 1H), 5.13 (d, J=3.2Hz, 1H), 4.56 (s, 2H), 4.13 (dddd, J=2.8Hz, 8.8Hz, 8.8Hz, 15.6Hz, 1H), 3.74 (d, J=3.2Hz, 1H), 3.56 (t, J=6.6Hz, 2H), 3.50 (ddd, J=2Hz, 10Hz, 10Hz, 1H), 2.85 (ddd, J=2.4Hz, 11.2Hz, 11.2Hz, 1H), 2.66-2.59 (m, 1H), 2.54-2.46 (m, 1H), 2.18 (d, J=12.6Hz, 1H), 2.12 (d, J=12.6Hz, 1H), 2.22-2.14 (m, 1H), 1.99-1.90 (comp m, 2H), 1.90 (ddd, J=5.2Hz, 10.4Hz, 12Hz, 1H), 1.71-1.16 (comp m, 10H), 1.13 (dd, J=2.8Hz, 14Hz, 1H), 0.67 (s, 9H), -0.12 (d, J=2.4Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.16, 138.88, 136.22, 130.93, 128.59, 127.88, 127.74, 127.52, 127.06, 126.63, 125.94, 81.72, 80.90, 71.44, 70.88, 69.16, 55.90, 52.31, 46.38, 42.68, 41.26, 40.00, 36.69, 32.21, 30.87, 27.62, 26.00, 21.99, -4.61, -4.70. IR (NaCl thin film): 3337.60, 3188.97, 3087.85, 3061.02, 3028.45, 2928.12, 2854.39, 1671.48 (strong), 1606.44 (weak), 1494.61, 1470.65, 1452.03, 1361.52, 1254.99, 1189.22, 1118.55, 1073.72, 1061.47, 899.09, 835.67, 774.66, 751.34, 734.62, 699.01, 609.62 cm^{-1}. HRMS-TOF: calcd for C43H61N2O4Si [MH^{+}] 697.4401, found 697.4338. $[\alpha]_D^{25}$ = +82 (*c*1, CH_2Cl_2).

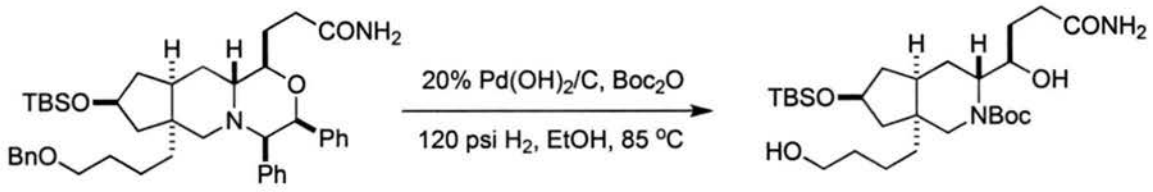
^{1}HNMR, $CDCl_3$, 400 MHz, xnj-iii-382pH



^{13}CNMR, $CDCl_3$, 100 MHz, xnj-iii-382pC_{13}

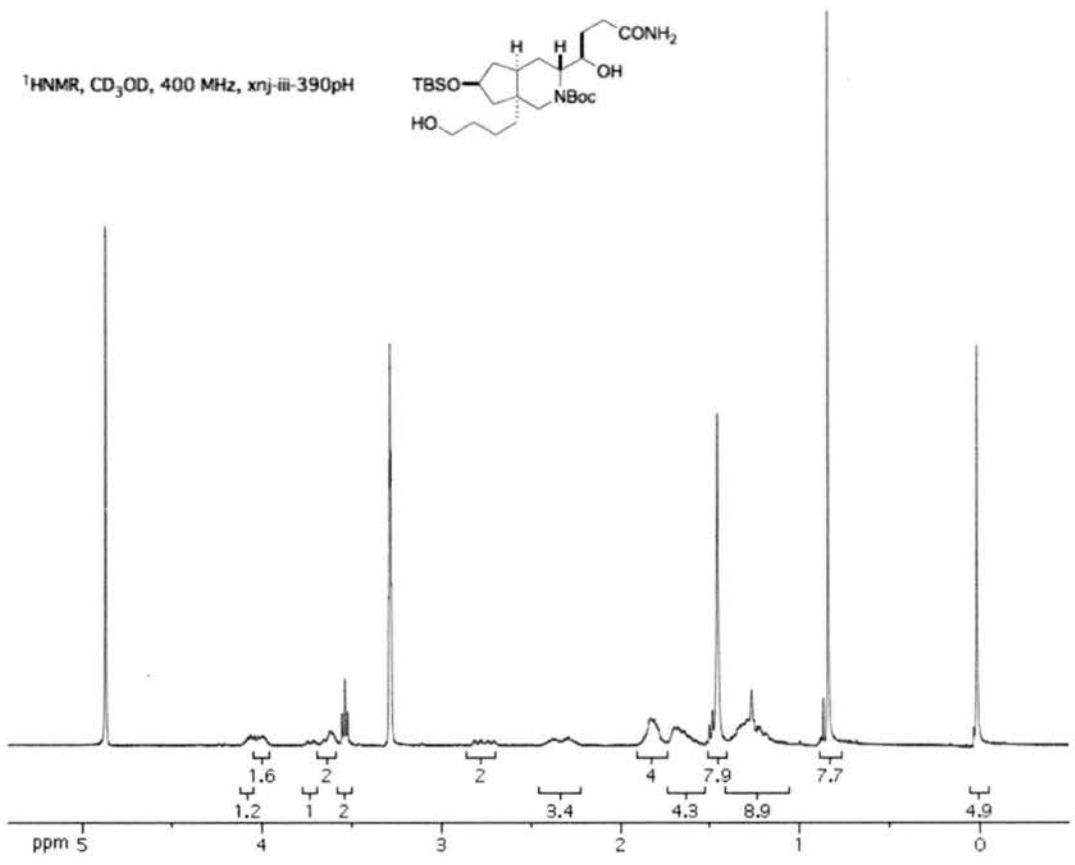


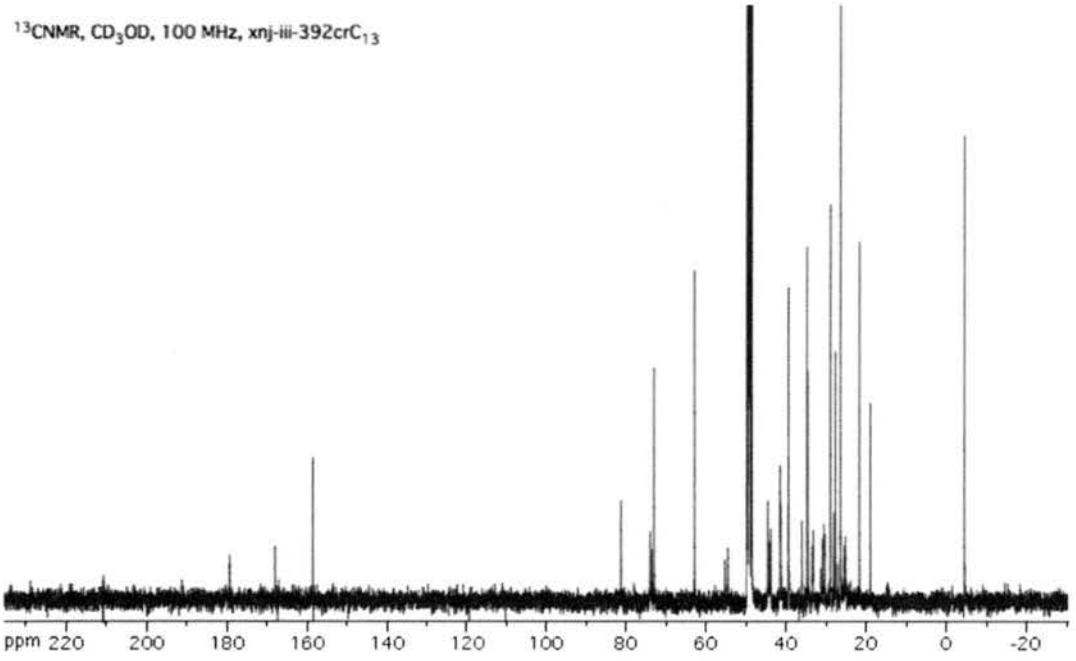
(3*S*,4a*S*,6*R*,7a*R*)-*tert*-butyl 3-((*S*)-4-amino-1-hydroxy-4-oxobutyl)-6-(*tert*-butyl dimethylsilyloxy)-7a-(4-hydroxybutyl)hexahydro-1*H*-cyclopenta[*c*]pyridine-2(3*H*)-carboxylate (195)



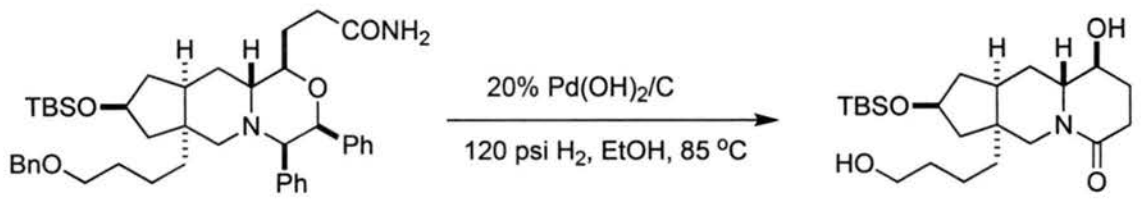
191 **195**

A mixture of primary amide **191** (10.8 mg, 0.01550 mmol), 20% $Pd(OH)_2/C$ (21.8 mg) and Boc_2O (33.8 mg, 0.1549 mmol) in ethanol (3 mL) was stirred at 85 °C under 120 psi H_2 for 39 h, filtered through celite, washed sufficiently with ethanol, concentrated and column (5% MeOH in DCM to DCM/MeOH/EtOH/NH_4OH, v/v 75:5:5:1) gave 7.5 mg (91.5%) of product **195** as colorless crystals. ^1H NMR (CD_3OD, 400 MHz): δ 4.11-4.00 (comp m, 3H), 3.75-3.71 (d, J=13.6Hz, 1H), 3.66-3.61 (comp m, 2H), 3.56-3.52 (t, J=6.4Hz, 2H), 2.82 (d, J=13.2Hz, 1H), 2.74 (d, J=13.6Hz, 1H), 2.40-2.23 (comp m, 3H), 1.83-1.81 (comp m, 4H), 1.70-1.54 (comp m, 4H), 1.46 (s, 9H), 1.38-1.18 (comp m, 7H), 0.85 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (CD_3OD, 100 MHz): δ 179.29, 158.48, 81.35, 74.05, 73.06, 62.88, 55.34, 54.55, 44.56, 43.83, 41.52, 41.39, 39.43, 34.57, 33.48, 33.20, 30.54, 30.41, 28.97, 26.48, 21.76, -4.38. IR (NaCl thin film): 3343.02, 2928.42, 2856.58, 1664.10, 1461.36, 1418.35, 1366.33, 1334.38, 1254.56, 1169.08, 1143.19, 1097.07, 907.99, 835.70, 773.87 cm^{-1}. HRMS-TOF: calcd for C27H52N2NaO6Si [MNa^+] 551.3487, found 551.3513. $[\alpha]_D^{25}$ = +34.8 (*c*1, CH_3OH).


^{1}HNMR, CD_3OD, 400 MHz, xnj-iii-390pH
CONH$_2$
H
H
OH
TBSO
NBoc
HO
1.6
2
2
4
7.9
7.7
1.2
1
2
3.4
4.3
8.9
4.9
ppm 5
4
3
2
1
0

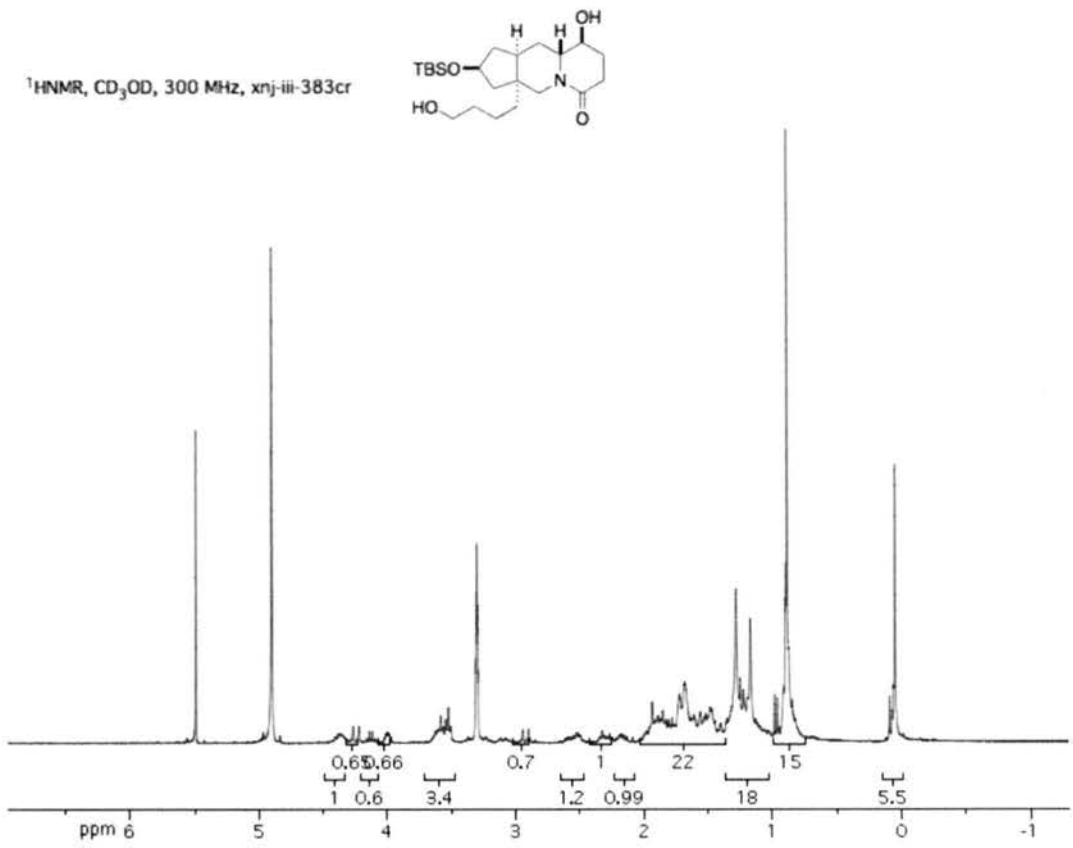

^{13}CNMR, CD_3OD, 100 MHz, xnj-iii-392crC$_{13}$
ppm 220
200
180
160
140
120
100
80
60
40
20
0
-20

(2*R*,3a*R*,9*R*,9a*S*,10a*S*)-2-(*tert*-butyldimethylsilyloxy)-9-hydroxy-3a-(4-hydroxybutyl) decahydrocyclopenta[*b*]quinolizin-6(1*H*)-one (194)

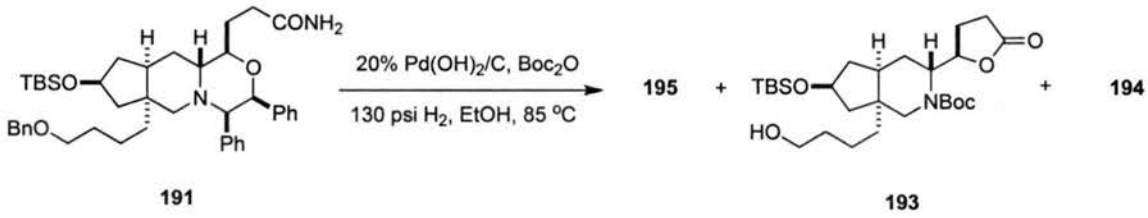


191 **194**

A mixture of primary amide **191** (15 mg, 0.02152 mmol), 20% $Pd(OH)_2/C$ (30.3 mg) in ethanol (3.5 mL) was stirred at 85 °C under 120 psi H_2 for 48 h, filtered through celite, washed sufficiently with ethanol and concentrated to give crude lactam **194**, which was purified by column (5% MeOH in DCM to DCM/MeOH/EtOH/NH_4OH, v/v 75:5:5:1). ^1H NMR (CD_3OD, 300 MHz): δ 4.41-4.33 (m, 1H), 4.27 (d, J=18.0Hz, 1H), 4.17-4.10 (m, 1H), 4.02-3.98 (m, 1H), 3.63-3.51 (comp m, 4H), 2.95 (d, J=18.0Hz, 1H), 2.61-2.47 (comp m, 2H), 2.35-2.25 (comp m, 1H), 2.222-2.136 (m, 1H), 2.009-1.172 (comp m, 13H). IR (NaCl thin film): 3391.42, 2926.92, 2854.66, 1617.85, 1462.08, 1372.36, 1255.87, 1055.68, 901.95, 835.75, 775.93 cm^{-1}. HRMS-TOF: calcd for C22H41NNaO4Si [MNa^+] 434.2697, found 434.2693.



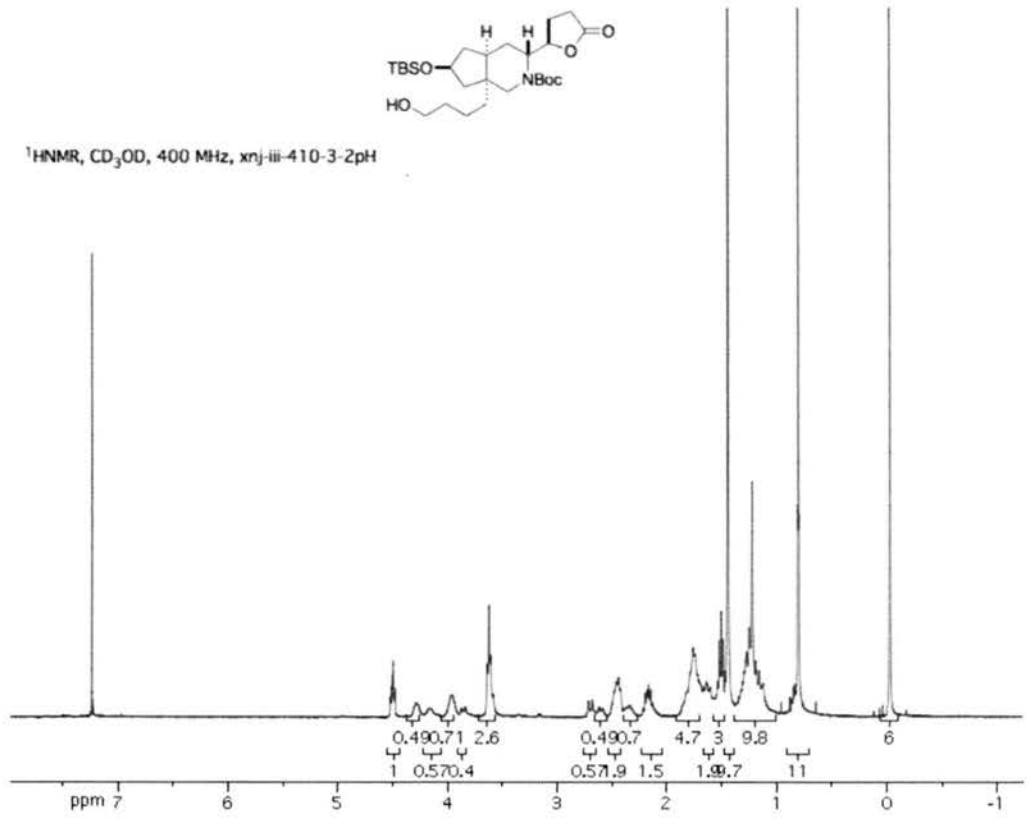
(3*R*,4a*R*,6*S*,7a*S*)-*tert*-butyl 6-(*tert*-butyldimethylsilyloxy)-7a-(4-hydroxybutyl)-3-((*R*)-5-oxotetrahydrofuran-2-yl)hexahydro-1*H*-cyclopenta[*c*]pyridine-2(3*H*) carboxylate (193)

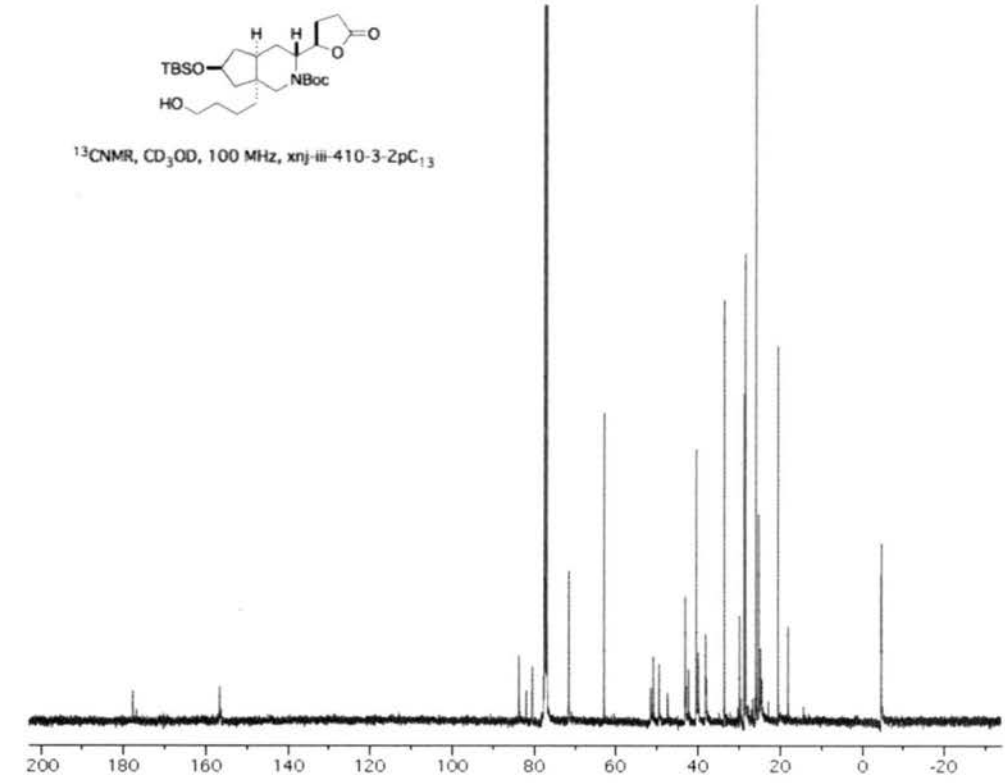


191 **193**

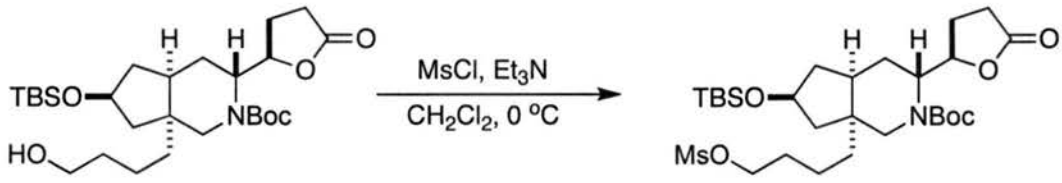
A mixture of **191** (119 mg, 0.1707 mmol), 20% $Pd(OH)_2/C$ (240.3 mg) and Boc_2O (372.5 mg, 1.707 mmol) in ethanol (3.4 mL) was heated to 85 °C under 130 psi H_2 pressure for 36 h. The reaction was cooled to room temperature, and the pressure was

released. The mixture was then filtered through celite, washed with ethanol sufficiently and concentrated. The residue was subjected to column chromatography (5% MeOH in DCM) to give 30 mg (34.3%) of the lactone compound **193**, then the column was eluted with (v/v 65:5:5:1, DCM/MeOH/EtOH/NH_4OH) to provide 41.6 mg (46%) of the primary amide compound **195** and 6 mg (8.5%) of **194**. ^1H NMR (400 MHz, $CDCl_3$): δ 4.52-4.48 (ddd, J=3.2Hz, 6.8Hz, 10.0Hz, 1H), 4.29 (br, 1H, with rotamer at 4.16), 3.97 (br s, 1H, with rotamer at 3.87 and 3.84), 3.64-3.61 (t, J=6.2Hz, 2H), 2.72 (d, J=14Hz, 1H, with rotamer at 2.62), 2.44 (br, 2H, with rotamer at 2.34), 2.22-2.13 (m, 1H), 1.85-1.47 (br m, 8H), 1.44 (s, 9H), 1.34-1.12 (m, 7H), 0.80 (s, 9H), -0.027 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.70, 156.62, 83.72, 80.43, 71.54, 62.93, 50.92, 49.52, 47.40, 43.12, 42.28, 40.49, 39.93, 38.18, 33.63, 29.89, 28.78, 28.50, 25.95, 25.25, 20.57, -4.49, -4.45. IR (NaCl thin film): 3456.20, 2930.44, 2857.37, 1779.07, 1688.55, 1472.17, 1461.98, 1412.08, 1391.87, 1366.75, 1329.16, 1252.55, 1172.56, 1140.45, 1098.43, 1031.21, 1006.66, 908.18, 869.42, 836.85, 775.11, 735.62, 667.45 cm^{-1}. HRMS: calcd for C27H50NO6Si $[MH]^+$ 512.3329, C27H49NNaO6Si $[MNa]^+$ 534.3227, found $[MNa]^+$ 534.3222 and $[MH]^+$ 512.3391. $[\alpha]_D^{25}$ = +25.8 (*c*1, CH_2Cl_2).


TBSO
HO
NBoc
H
H
O
O
^{1}HNMR, CD_3OD, 400 MHz, xnj-iii-410-3-2pH
0.49 0.71 2.6 0.49 0.7 4.7 3 9.8 6
1 0.57 0.4 0.57 1.9 1.5 1.9 9.7 11
ppm 7 6 5 4 3 2 1 0 -1

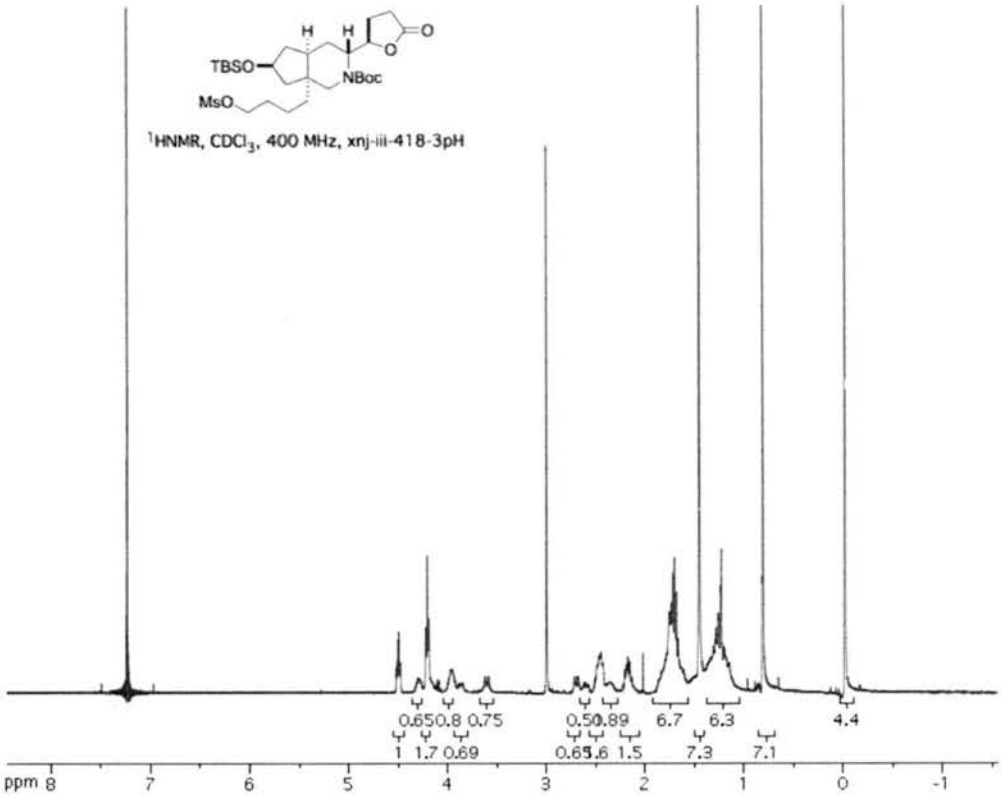

TBSO
HO
NBoc
H
H
O
O
^{13}CNMR, CD_3OD, 100 MHz, xnj-iii-410-3-2pC$_{13}$
200 180 160 140 120 100 80 60 40 20 0 -20

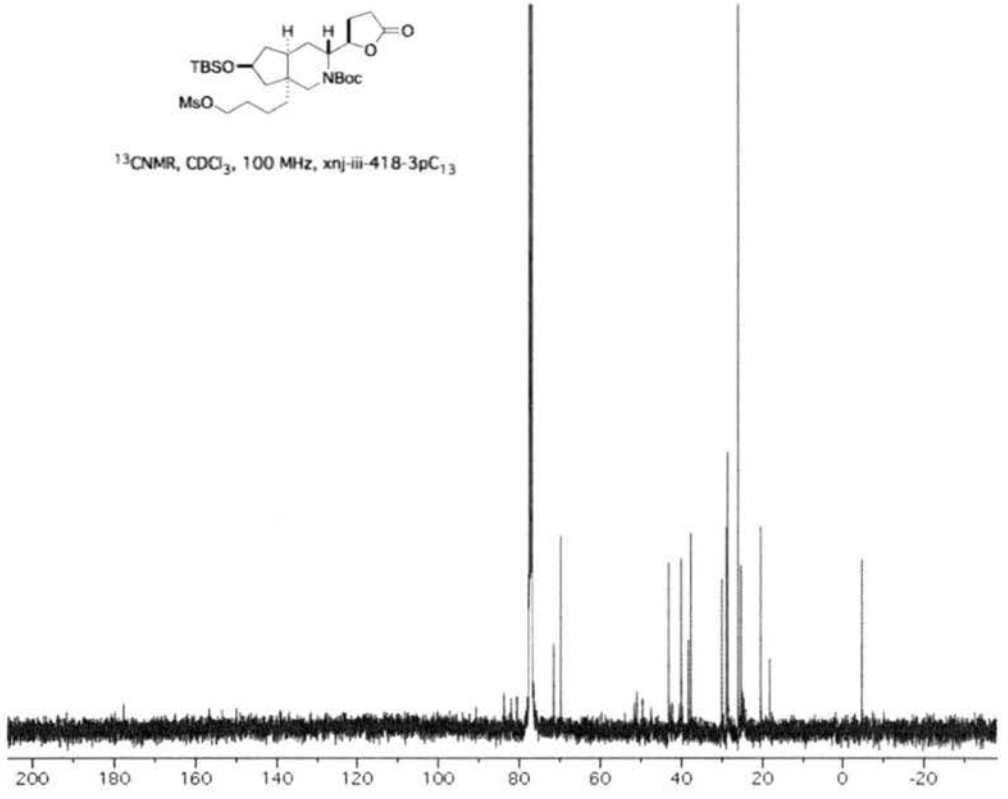
(3R,4aR,6S,7aS)-tert-butyl 6-(tert-butyldimethylsilyloxy)-7a-(4-(methylsulfonyloxy)butyl)-3-((R)-5-oxotetrahydrofuran-2-yl)hexahydro-1H-cyclopenta[c]pyridine-2(3H)-carboxylate (196a)



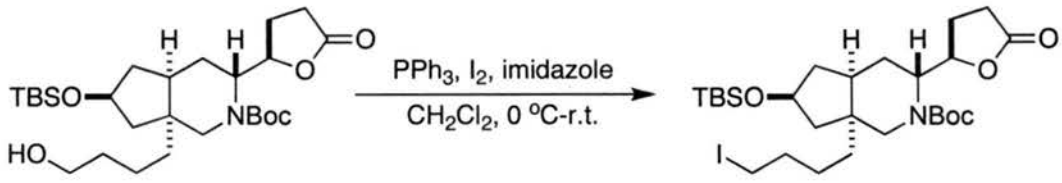
193 **196a**

To 0 °C cooled solution of **193** (5.52 mg, 0.01079 mmol) in dichloromethane (0.5 mL) was added triethylamine (4.72 μL, 0.03236 mmol) followed by MsCl (1.68 μL, 0.02158 mmol). After 1 h, another portion of triethyl amine and MsCl were added, the mixture was stirred for another 1 h under cooling. Solvent was evaporated and the residue was subjected to a small column (2:1 to 1:1 Hexanes/EtOAc) to provide 3 mg (47%) of the mesylate **196a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.52-4.48 (ddd, J=3.2Hz, 7.2Hz, 10.4Hz, 1H), 4.29 (br, 1H), 4.22-4.19 (t, J=6.4Hz, 2H), 3.96 (br, 1H, rotamer at 3.88 to 3.85), 2.62 (d, J=14.4Hz, 1H), 3.00 (s, 3H), 2.72 (d, J=14.4Hz, 1H, rotamer at 2.61 to 2.58), 2.48-2.42 (m, 2H, rotamer at 2.35), 2.22-2.14 (m, 2H), 1.85-1.61 (br m, 6H), 1.45 (s, 9H), 1.39-1.11 (br m, 7H), 0.81 (s, 9H), -0.019 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.66, 156.60, 83.79, 80.59, 71.49, 69.71, 51.56, 50.91, 49.55, 47.43, 43.08, 42.18, 40.02, 38.24, 37.63, 29.97, 28.79, 28.52, 25.96, 25.21, 20.37, -4.54. IR (NaCl thin film): 2932.10, 1777.06, 1686.26, 1471.99, 1411.18, 1355.23, 1252.61, 1174.43, 1099.74, 907.39, 836.67, 774.89 cm^{-1}. ESI-APCI-HRMS: calcd for C28H51NNaO8SSi $[MNa]^+$ 612.3002, found 612.30004. $[\alpha]_D^{25}$ = +15.9 (*c*1, CH_2Cl_2).


TBSO
MsO
NBoc
H
H
O
O
^{1}HNMR, $CDCl_3$, 400 MHz, xnj-iii-418-3pH
0.65 0.8 0.75 0.50 0.89 6.7 6.3 4.4
1 1.7 0.69 0.65 1.6 1.5 7.3 7.1
ppm 8 7 6 5 4 3 2 1 0 -1

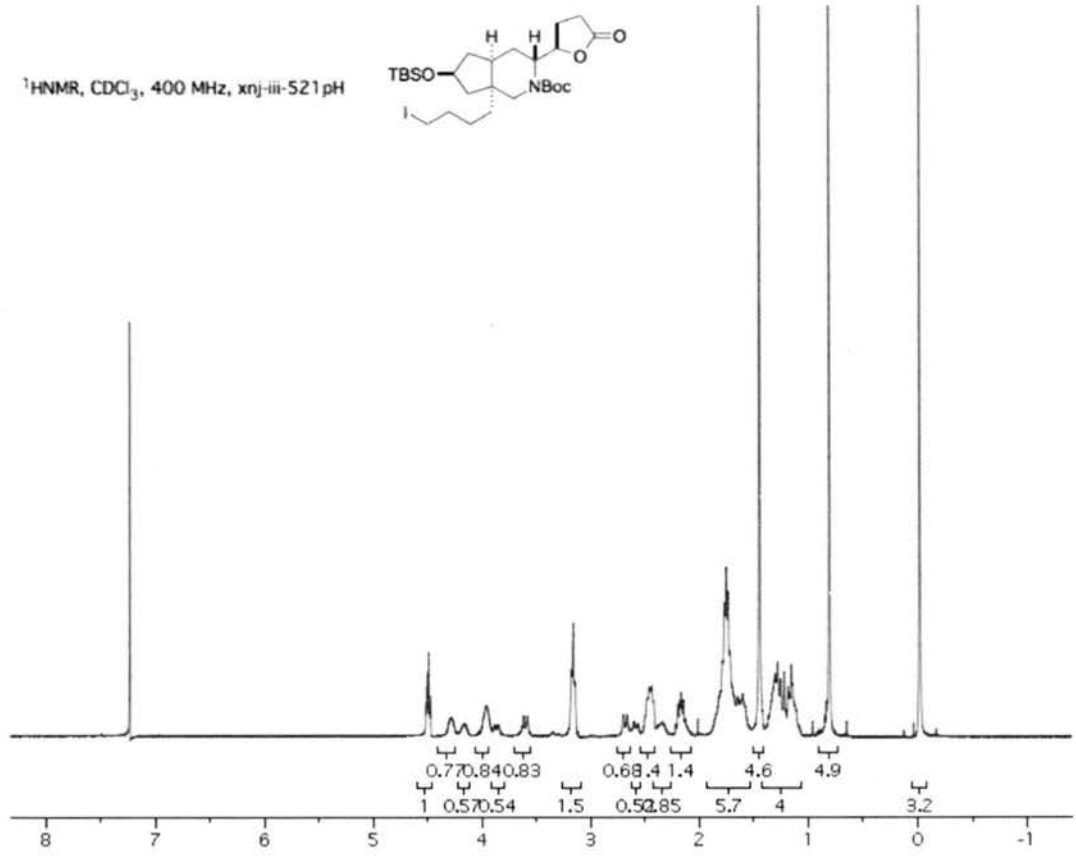

TBSO
MsO
NBoc
H
H
O
O
^{13}CNMR, $CDCl_3$, 100 MHz, xnj-iii-418-3pC_{13}
200 180 160 140 120 100 80 60 40 20 0 -20

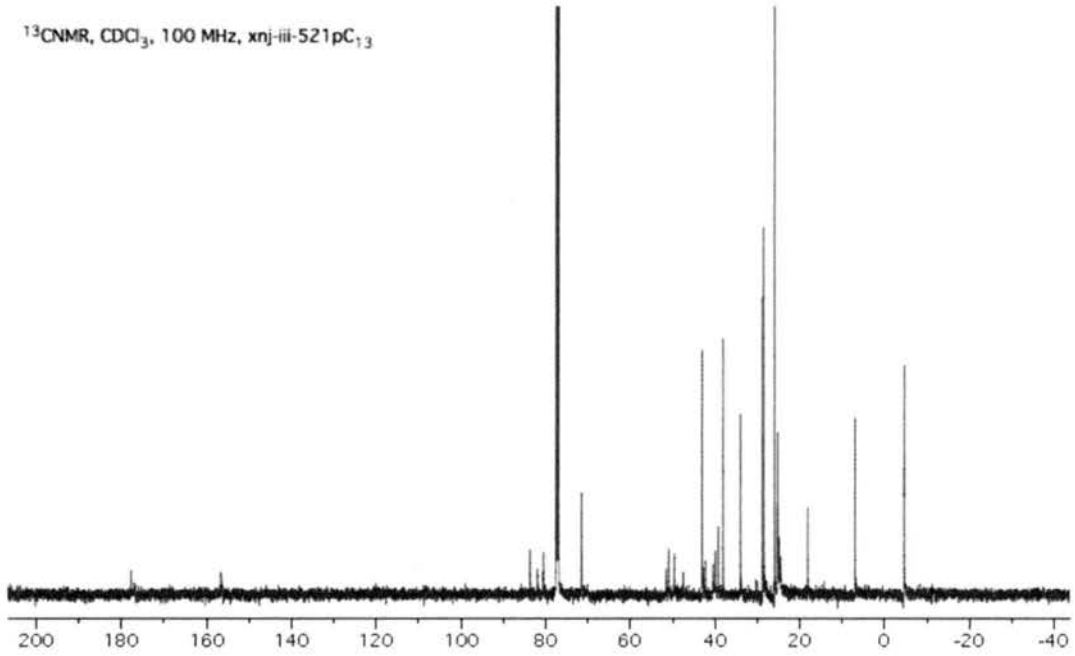
(3*R*,4a*R*,6*S*,7a*S*)-*tert*-butyl 6-(*tert*-butyldimethylsilyloxy)-7a-(4-iodobutyl)-3-((*R*)-5-oxotetrahydrofuran-2-yl)hexahydro-1*H*-cyclopenta[*c*]pyridine-2(3*H*)-carboxylate (198)



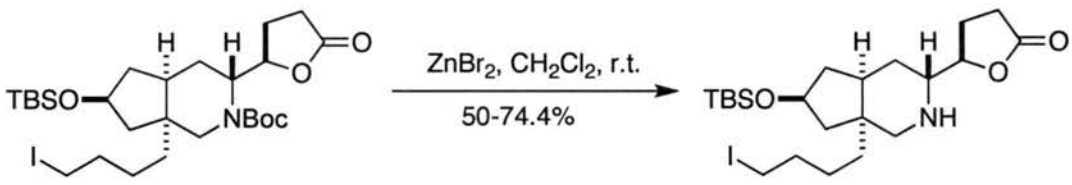
193 **198**

Iodine (41.31 mg, 0.1621 mmol) was added to a solution of triphenyl phosphine (42.55 mg, 0.1621 mmol) and imidazole (16.52 mg, 0.2431 mmol) in dichloromethane (1 mL), stirred at room temperature for about 10 min. The resulting red orange solution was cooled to 0 °C, alcohol **193** (41.47 mg, 0.0810 mmol) in dichloromethane (1 mL) was introduced to the above solution. Cold was removed and the mixture was stirred for 30 min. Excess solvent was removed under reduced pressure, the residue was purified by preparation TLC (5:1 Hexanes/EtOAc) to provide 40.3 mg (80.0%) of iodide **198** as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.52-4.47 (ddd, J=3.2Hz, 6.8Hz, 6.8Hz, 1H), 4.29 (br s, 1H), 3.96 (br s, 1H), 3.62 (d, J=13.6Hz, 1H), 3.18 -3.15 (app t, J=13.6Hz, 2H), 2.70 (d, J=13.6Hz, 1H), 2.48-2.42 (m, 2H), 2.22-2.13 (m, 2H), 1.85-1.60 (comp m, 7H), 1.45 (s, 9H), 1.367-1.11 (comp m, 6H), 0.81 (s, 9H), -0.02 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.65, 156.58, 83.65, 80.49, 71.51, 50.91, 49.60, 43.04, 42.20, 40.39, 39.89, 39.18, 38.07, 33.94, 28.76, 28.50, 25.96, 25.25, 25.13, 18.13, 7.01, -4.52. IR (NaCl thin film): 2931.98, 2856.83, 1779.99, 1688.66, 1471.69, 1462.01, 1410.24, 1391.49, 1366.23, 1328.27, 1251.66, 1169.14, 907.88, 836.67, 774.98 cm^{-1}. ESI-APCI-HRMS: calcd for C27H48INNaO5Si $[MNa]^+$ 644.2244, found 644.2229.


^{1}HNMR, $CDCl_3$, 400 MHz, xnj-iii-521pH
TBSO
NBoc
H
H
O
O
I
0.77
0.84
0.83
0.68
1.4
4.6
4.9
1
0.57
0.54
1.5
0.52
2.85
5.7
4
3.2
8
7
6
5
4
3
2
1
0
-1

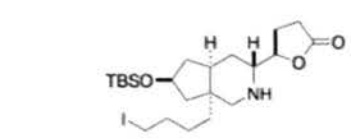

^{13}CNMR, $CDCl_3$, 100 MHz, xnj-iii-521pC_{13}
200
180
160
140
120
100
80
60
40
20
0
-20
-40

(R)-5-((3R,4aR,6S,7aS)-6-(tert-butyldimethylsilyloxy)-7a-(4-iodobutyl)octahydro-1H-cyclopenta[c]pyridin-3-yl)dihydrofuran-2(3H)-one (199)



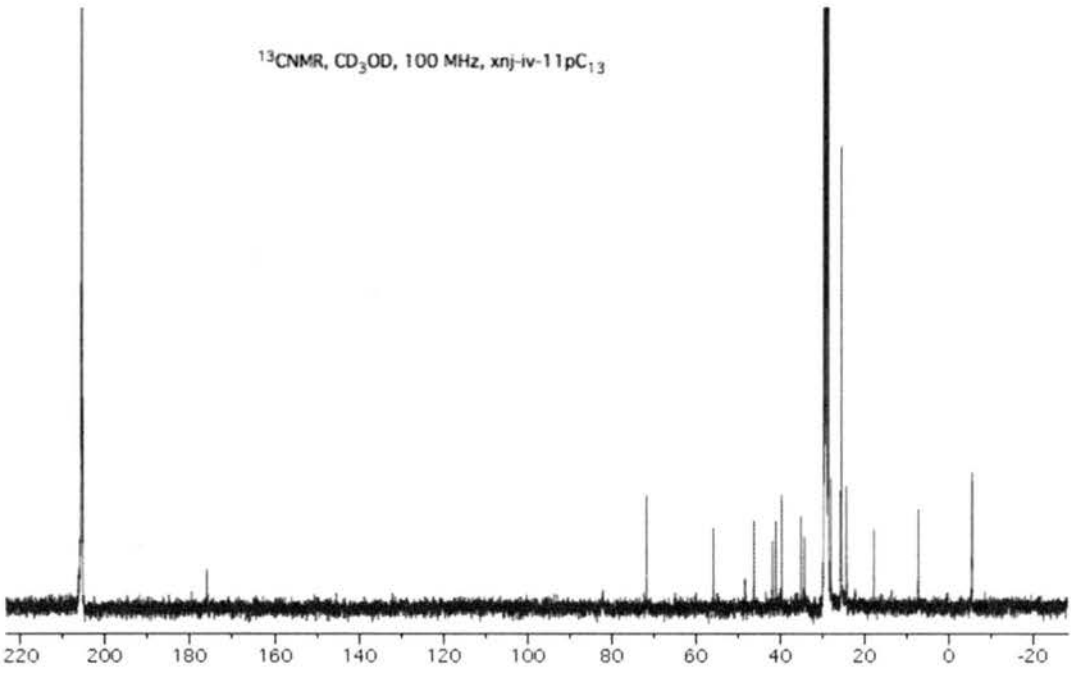
198 **199**

To a solution of iodide **198** (16.15 mg, 0.0260 mmol) in dichloromethane (1 mL) was added zinc bromide (59.15 mg, 0.2598 mmol), the resulting mixture was stirred at room temperature for 30 min to 3 h until the disappearance of the starting material monitored by TLC. Purification by preparation TLC (5% MeOH in DCM) provided 50-74.4% of amine **199** as colorless oil. ^{1}H NMR (CD_3COCD_3, 400 MHz): δ 4.61 (br s, 1H), 4.38 (br s, 1H), 3.29 (t, J=0.8Hz, 2H), 3.16 (br s, 1H), 3.11 (d, J=12Hz, 1H), 2.93 (d, J=12Hz, 1H), 2.60-1.36 (comp m, 18H), 0.86 (s, 9H), 0.03 (s, 6H). ^{13}C NMR (CD_3COCD_3, 100 MHz): δ -5.27, -5.32, 7.38, 17.84, 24.38, 25.56 ($3CH_3$-C-Si-), 25.76, 28.09, 34.28, 35.10, 39.67, 41.04, 41.86, 43.55, 46.19, 48.39, 55.82, 71.72, 176.01. IR (NaCl thin film): 2927.47, 2854.61, 1778.21, 1462.54, 1255.04, 1179.39, 1057.82, 835.52, 775.58 cm^{-1}. TOF-HRMS: calcd for C22H41INO3Si $[MH]^+$ 522.1900, found 522.1868.



^{1}HNMR, CD_3COCD_3, 400 MHz, xnj-iv-11pH

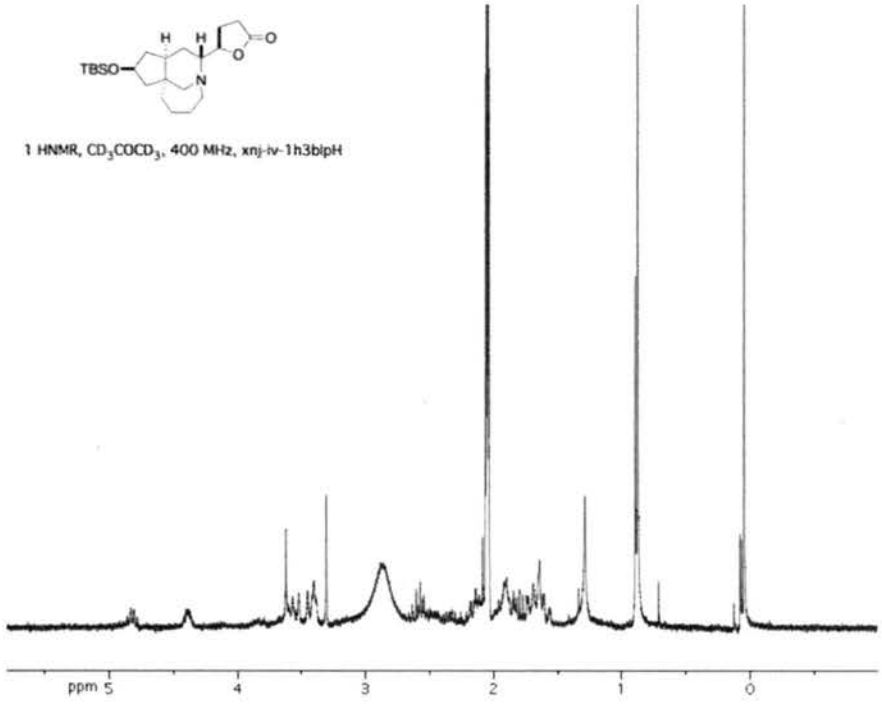
^{13}CNMR, CD_3OD, 100 MHz, xnj-iv-11pC_{13}



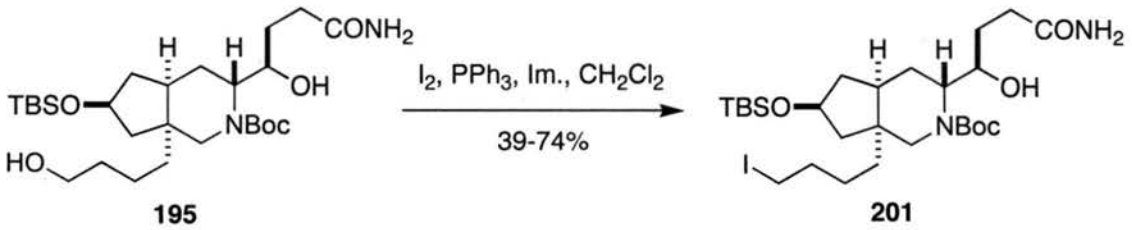
Tetracycle (200)

199 **200**

A mixture of amine **199** (1.0 equiv.) and NMM (6.0 equiv.) in DMF was heated to 150 °C for 3 h. Excess solvent was removed under reduced pressure and purification with (5% MeOH in dichloromethane) provided the tetracycle **200** in 14-33% yield. ^{1}H NMR (CD_3COCD_3, 400 MHz): δ 4.72-4.64 (m, 1H), 4.34 (br, 1H), 3.37-3.16 (comp m, 5H), 2.63-2.18 (comp m, 8H), 1.99-1.54 (comp m, 9H), 0.87 (s, 9H), 0.04 (s, 6H). IR (NaCl thin film): 2926.45, 2854.49, 1782.80, 1470.60, 1256.46, 1182.94, 1109.65, 1048.34, 904.68, 836.65, 776.78 cm^{-1}. HRMS: calcd for C22H40NO3Si $[MH]^+$ 394.2777, found 394.27699.

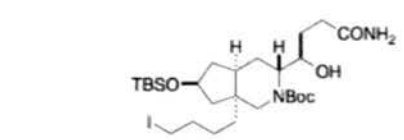


(3*R*,4a*R*,6*S*,7a*S*)-*tert*-butyl 3-((*R*)-4-amino-1-hydroxy-4-oxobutyl)-6-(*tert*-butyldimethylsilyloxy)-7a-(4-iodobutyl)hexahydro-1*H*-cyclopenta[*c*]pyridine-2(3*H*)-carboxylate (201)



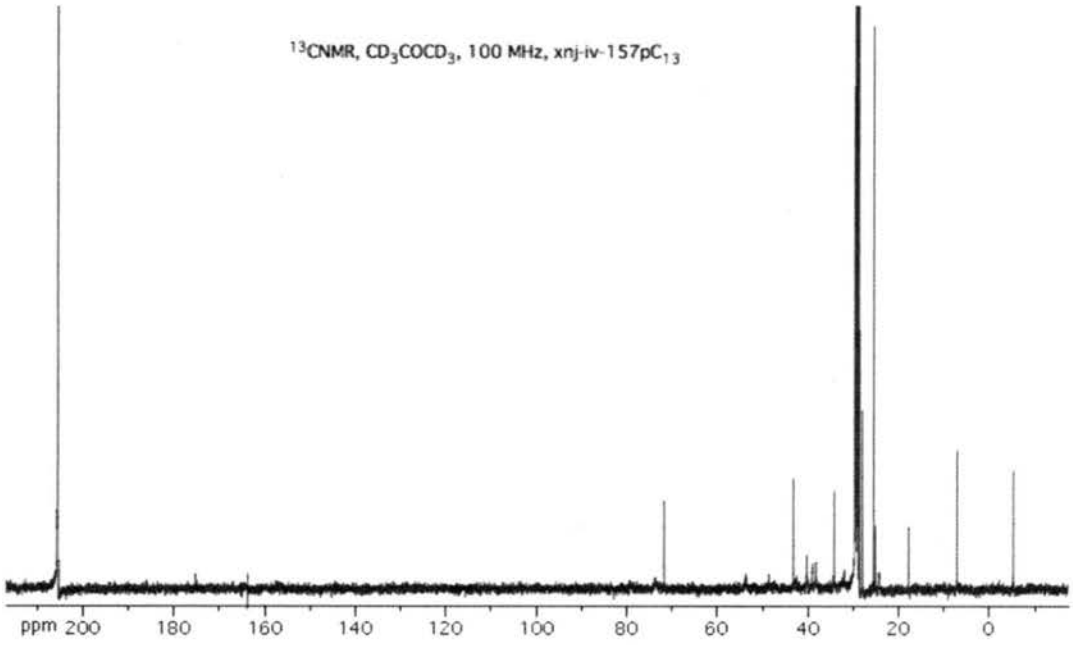
195 **201**

Iodine (37.49 mg, 0.1471 mmol) was added to a solution of triphenylphosphine (28.96 mg, 0.1103 mmol) and imidazole (15 mg, 0.2207 mmol) in dichloromethane (0.5 mL), stir at room temperature for 10 min. The resulting red orange solution was cooled to 0 °C, alcohol **195** (38.9 mg, 0.07356 mmol) in dichloromethane (1 mL) was introduced dropwise, stir for 5 min under cooling, then remove the cold-bath and stir for an additional 30 min to 2 h until the disappearance of starting material monitored by TLC. Purification by preparation TLC or column chromatography (5% MeOH in DCM) provided (39-74%) of iodide **201** as oil. ^{1}H NMR (CD_3COCD_3, 400 MHz): δ 6.79 (br s, 1H), 6.13 (br s, 1H), 4.06 (m, 1H), 4.00 (br, 1H), 3.60 (br, 1H), 3.31-3.27 (app, J=8.0Hz, 2H), 2.82 (br, 2H), 2.33 (br s, 2H), 1.83-1.60 (comp m, 9H), 1.45 (s, 9H), 1.43-1.18 (comp m, 7H), 0.85 (s, 9H), 0.03 (s, 6H). ^{13}C NMR (CD_3COCD_3, 100 MHz): δ 175.33, 163.77, 71.75, 53.68, 48.59, 43.20, 40.20, 38.94, 38.22, 38.18, 34.20, 29.73, 28.57, 27.97, 25.52, 25.10, 24.24, 17.82, 7.20, -5.16. ESI-HRMS: calcd for C27H52IN2O5Si $[MH]^+$ 639.2685, found 639.2675, or calcd for C27H52IN2O5Si $[MH]^+$ 639.2685, found 639.2675

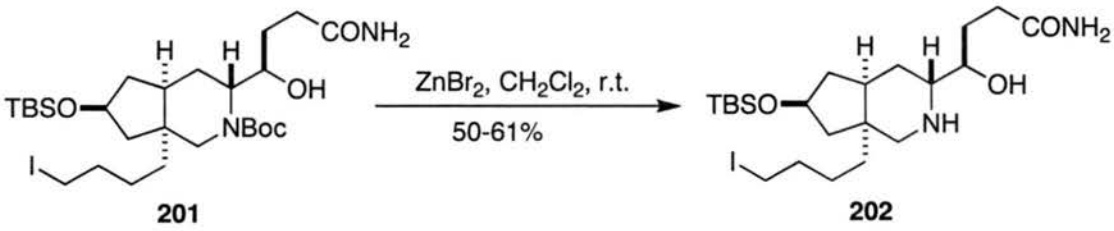


1 HNMR, CD_3COCD_3, 400 MHz, xnj-iv-157pH

^{13}CNMR, CD_3COCD_3, 100 MHz, xnj-iv-157pC_{13}

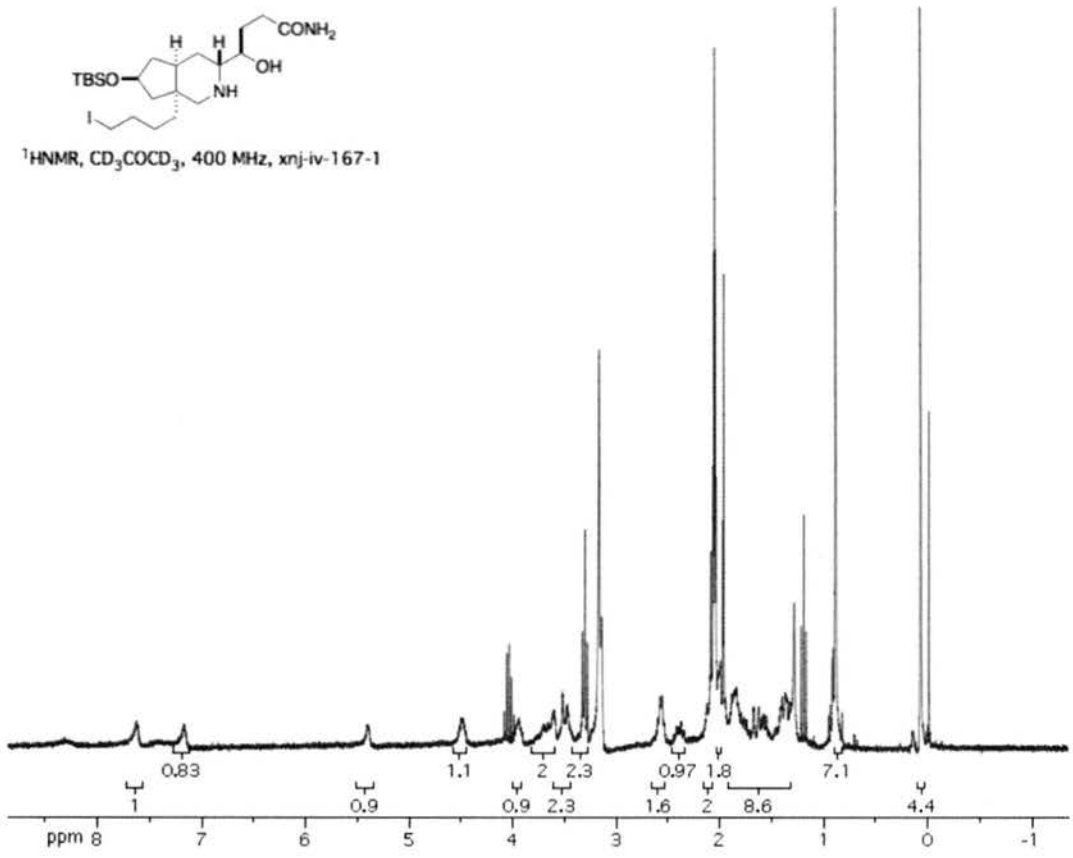


(*R*)-4-((3*R*,4a*R*,6*S*,7a*S*)-6-(*tert*-butyldimethylsilyloxy)-7a-(4-iodobutyl)octahydro-1*H*-cyclopenta[*c*]pyridin-3-yl)-4-hydroxybutanamide (202)

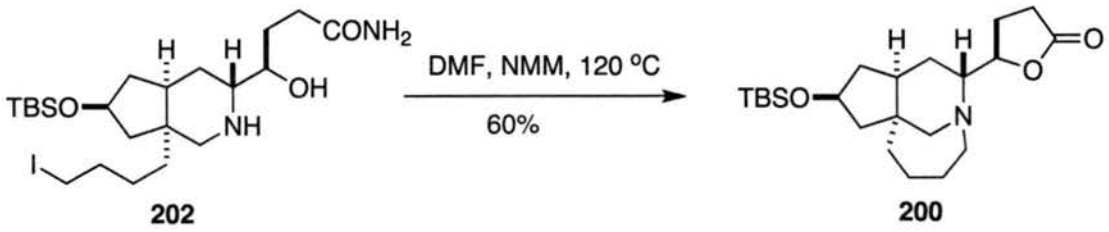


201 **202**

A mixture of **201** (18.3 mg, 0.02870 mmol) and zinc bromide (32.7 mg, 0.1435 mmol) in dichloromethane (1 mL) was stirred at room temperature for 3 h. Purification by preparation TLC (5% MeOH in DCM) for two times provided 9.4 mg (61%) of **202**, along with undetermined products. ^{1}H NMR (CD_3COCD_3, 400 MHz): δ 7.62 (br s, 1H), 7.17 (br s, 1H), 5.40 (br, 1H), 4.49 (br, 1H), 3.94 (br, 1H), 3.71-3.47 (comp m, 4H), 3.33 (t, J=8.0Hz, 2H), 2.60-2.54 (m, 2H), 2.45-2.34 (m, 1H), 2.13-1.28 (comp m, 14H), 0.89 (s, 9H), 0.07 (s, 6H). IR (NaCl thin film): 3564.46, 2928.19, 2854.95, 1650.47, 1469.91, 1414.62, 1256.36, 1221.63, 1180.62, 1058.88, 1005.44, 939.87, 903.74, 836.39, 777.10 cm^{-1}. HRMS: calcd for C22H44IN2O3Si $[MH]^+$ 539.2166, found 539.216. calcd for C22H43IN2O3SiNa $[MNa]^+$ 561.1985, found 561.1973.

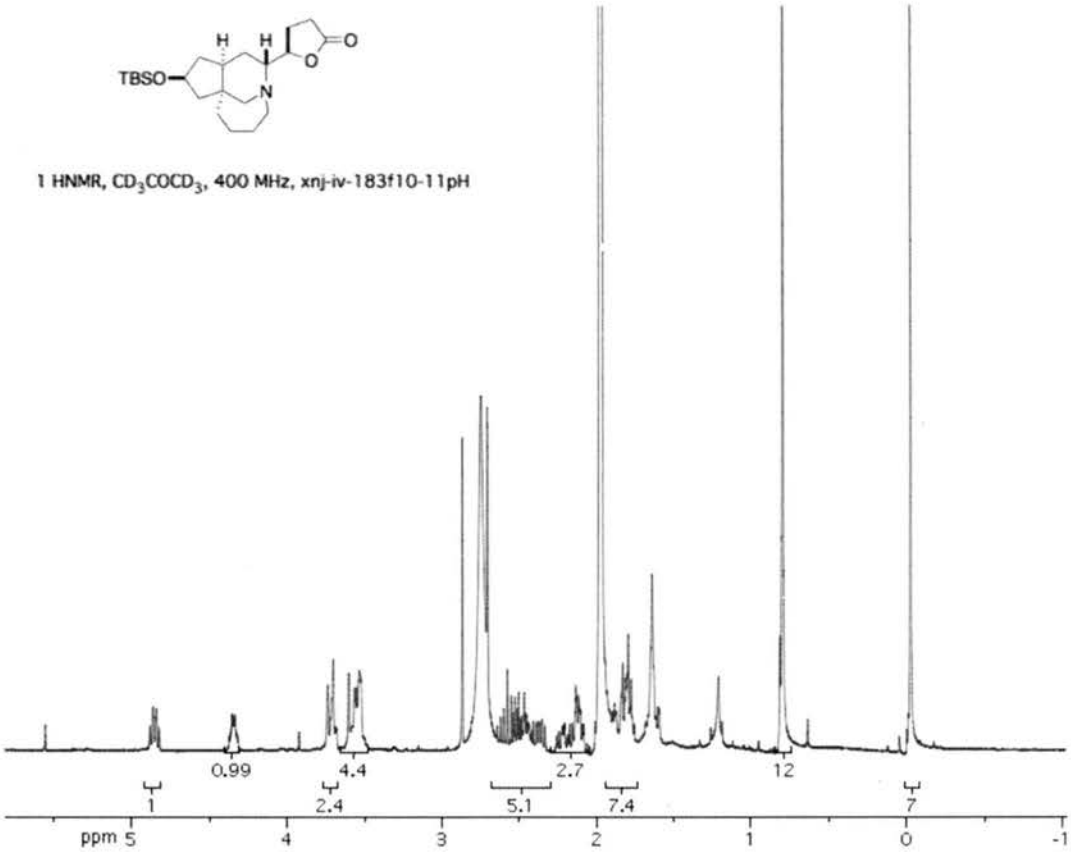

CONH2
H
H
OH
TBSO
NH
I
1HNMR, CD3COCD3, 400 MHz, xnj-iv-167-1
0.83
1.1
2
2.3
0.97
1.8
7.1
1
0.9
0.9
2.3
1.6
2
8.6
4.4
ppm 8
7
6
5
4
3
2
1
0
-1

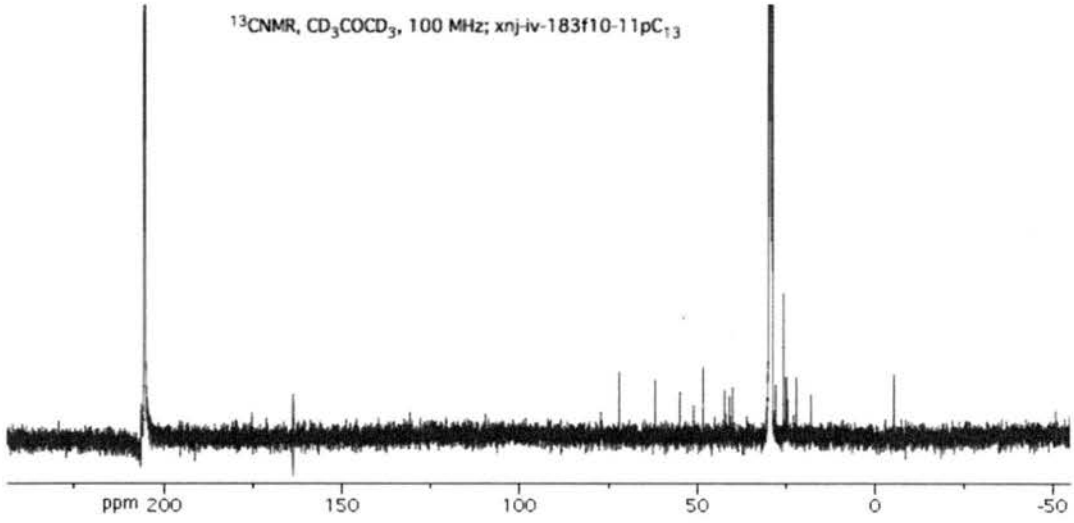
Tetracycle (200)



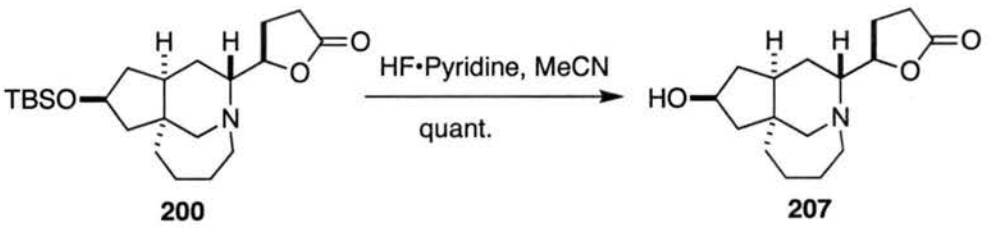
202 **200**

A mixture of **202** (8.4 mg, 0.0156 mmol) and NMM (17.14 μL, 0.156 mmol) in DMF (2 mL) was heated to 120 °C for 5 h. Cooled down to room temperature, excess solvent was removed under reduced pressure. Flash column chromatography (5% MeOH in DCM to 10% MeOH in DCM) provided 3.7 mg (60%) of tetracycle **200** as colorless oil. ^{1}H NMR (CD_3COCD_3, 400 MHz): δ 4.88-4.82 (app q, J=8.0Hz, 1H), 4.36-4.32 (m, 1H), 3.74-3.68 (comp m, 2H), 3.60-3.52 (comp m, 3H), 2.71-2.33 (comp m, 4H), 2.26-2.06 (comp m, 4H), 1.94-1.59 (comp m, 9H), 0.80 (s, 9H), -0.03 (s, 6H). ^{13}C NMR (CD_3COCD_3, 100 MHz): δ 175.20, 77.44, 71.87, 61.74, 54.84, 50.90, 48.25, 42.22, 40.82, 39.91, 36.01, 27.80, 25.61(2C), 25.03, 24.76, 24.48, 22.02, 17.89, -5.23, -5.34. IR (NaCl thin film): 2924.07, 2853.00, 1783.27, 1466.28, 1255.74, 1169.13, 1109.72, 1069.16, 929.04, 836.02, 775.89 cm^{-1}. ESI-APCI-HRMS: calcd for C22H40NO3Si $[MH]^+$ 394.2772, found 394.2773.


TBSO
H
H
O
O
N
1 HNMR, CD_3COCD_3, 400 MHz, xnj-iv-183f10-11pH
0.99
4.4
2.7
12
1
2.4
5.1
7.4
7
ppm 5
4
3
2
1
0
-1

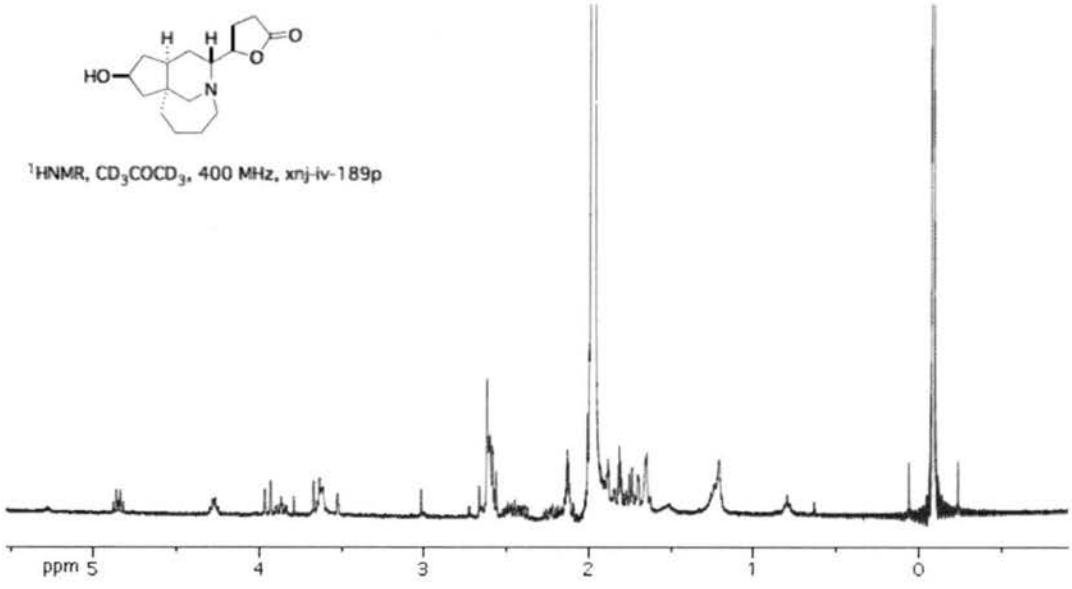

^{13}CNMR, CD_3COCD_3, 100 MHz; xnj-iv-183f10-11pC_{13}
ppm 200
150
100
50
0
-50

Tetracyclic Alcohol (207)

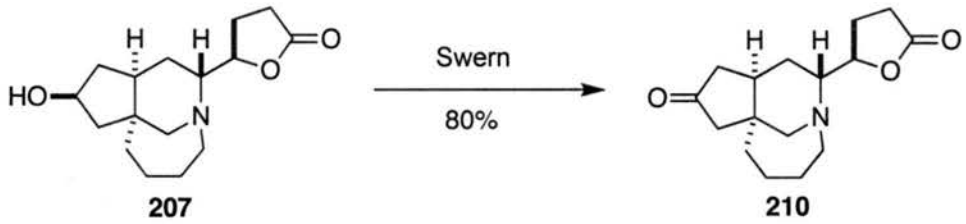


200 **207**

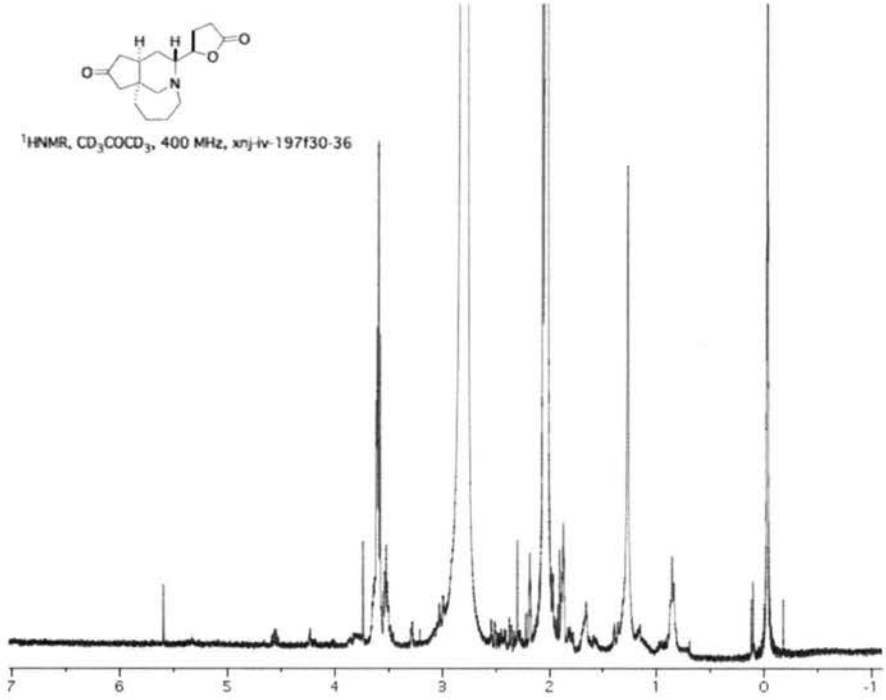
To an ice-bath cooled solution of compound **200** (1.5 mg, 0.00381 mmol) in MeCN (0.5 mL) was added HF•Pyridine (20 μL, 200 equiv), the resulting mixture was stirred under cooling for 1-4 h or until the disappearance of the starting material monitored by TLC. Excess solvent was removed under reduced pressure. The residue was purified by flash chromatography (10% MeOH in DCM) to provide quantitative yield of alcohol **207**. ^{1}H NMR (CD_3COCD_3, 400 MHz): δ 4.88-4.82 (app q, J=8.0Hz, 1H), 4.30-4.25 (m, 1H), 3.97 (d, J=16.0Hz, 1H), 3.90-3.83 (m, 1H), 3.67 (d, J=16.0Hz, 1H), 3.65-3.61 (comp m, 2H), 2.61-1.65 (comp m, 18H). ESI-APCI-HRMS: calcd for C16H26NO3 $[MH]^+$ 280.1907, found 280.1904, or calcd for C16H25NO3Na $[MNa]^+$ 302.1727, found 302.1723.



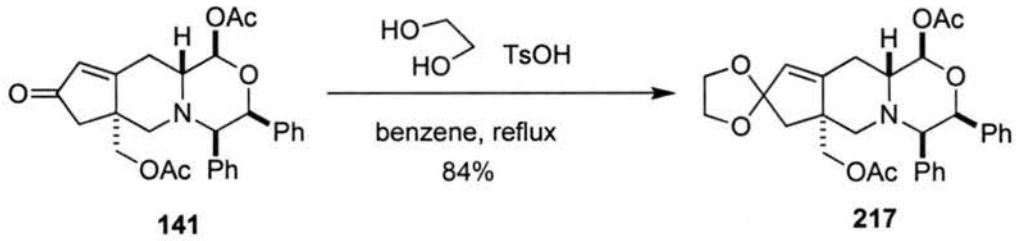
Tetracyclic Ketone (210)



To -78 °C cooled solution of oxalyl chloride (3 μL) in dichloromethane (0.2 mL) was added DMSO (6 μL), stir for 5 min. Alcohol **207** (0.82 mg) in dichloromethane (0.4 mL x 2) was introduced to the above mixture, and stirred for 30 min before triethylamine (12 μL) was added. The cold-bath was removed, and the reaction was stirred for an additional 30 min. Excess solvent was removed under reduced pressure. The residue was subjected to a small column (5% MeOH in DCM then 10% MeOH in DCM) to provide 0.66 mg (80%) of ketone **210.** ^{1}HNMR was not good enough for accurate assignment. ESI-APCI-HRMS: calcd for C16H24NO3 $[MH]^{+}$ 278.1751, found 278.1754.

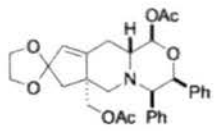


1,3-Dioxolane (217)

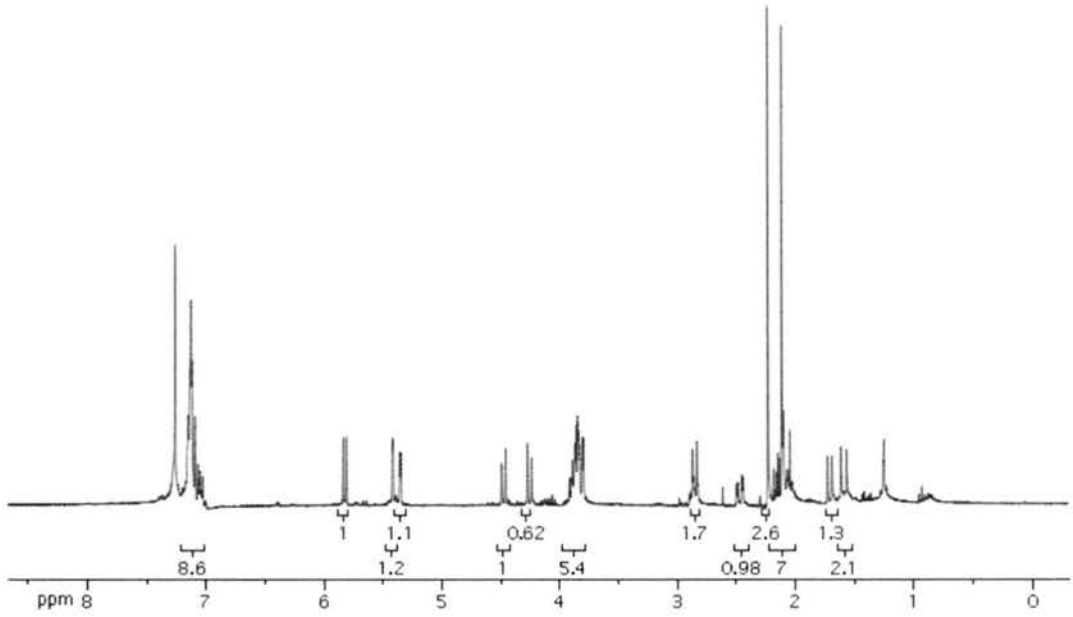


141 **217**

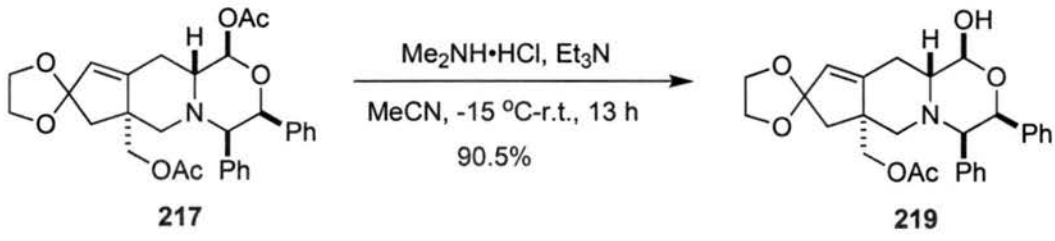
A mixture of **141** (50.6 mg, 0.1063 mmol), *p*-TsOH (catalyst, 2 mg), anhydrous ethylene glycol (11.9 μL, 2.0 equiv) in benzene was heated to reflux for 12-24 h using dean-stark to remove the water generated in the reaction. Excess solvent was removed under reduced pressure, the residue was subjected to flash chromatography (2:1 to 1:1 Hexanes/EtOAc) to provide dioxolane **217** 46.4 mg (84%) as white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26 (br, 2H), 7.15-7.03 (m, 8H), 5.84 (d, J=9.0Hz, 1H), 5.42 (d, J=3.0Hz, 1H), 5.36 (d, J=3.0Hz, 1H), 4.49 (d, J=9.0Hz, 1H), 4.27 (d, J=9.0Hz, 1H), 3.91-3.84 (m, 4H), 3.81 (d, J=3.0Hz, 1H), 2.90-2.82 (m, 1H), 2.87 (d, J=12.0Hz, 1H), 2.50 (dd, J=6.0Hz, 15.0Hz, 1H), 2.23 (s, 3H), 2.18 (dd, J=9.0Hz, 6Hz, 1H), 2.11 (s, 3H), 2.07-2.02 (m, 1H), 1.73 (d, J=12.0Hz, 1H), 1.61 (d, J=12.0Hz, 1H).



^{1}HNMR, $CDCl_3$, 300 MHz, xnj-iv-131-3pH



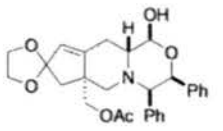
Lactol (219)



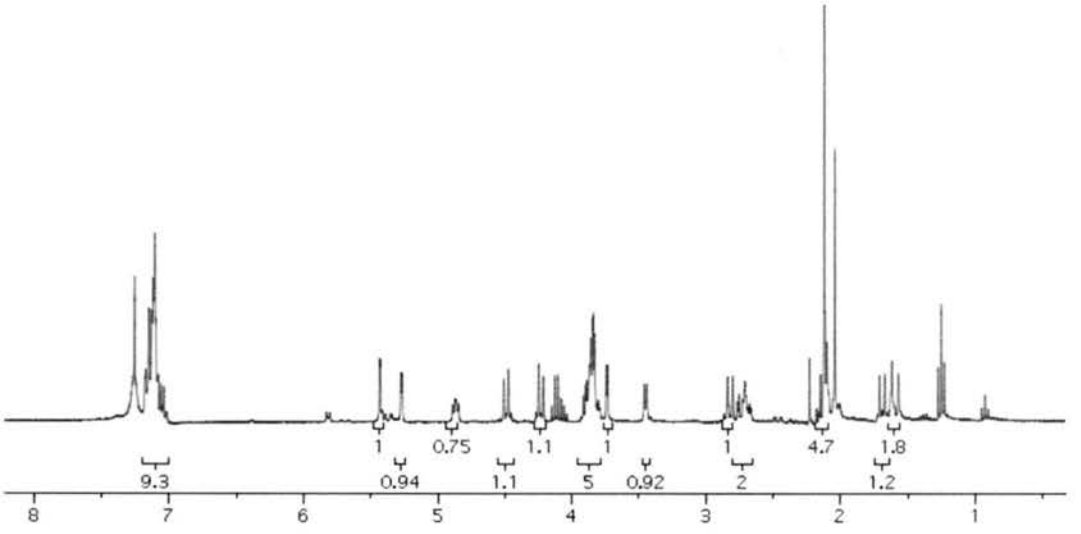
217 **219**

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26 (br, 2H), 7.18-7.04 (m, 8H), 5.44 (d, J=3.0Hz, 1H), 5.28 (d, J=3.0Hz, 1H), 4.89-4.85 (dd, J=6.0Hz, 9.0Hz, 1H), 4.51 (d, J=9.0Hz, 1H), 4.25 (d, J=9.0Hz, 1H), 3.92-3.83 (m, 4H), 3.75 (d, J=3.0Hz, 1H), 3.46 (d, J=6.0Hz, 1H), 2.84

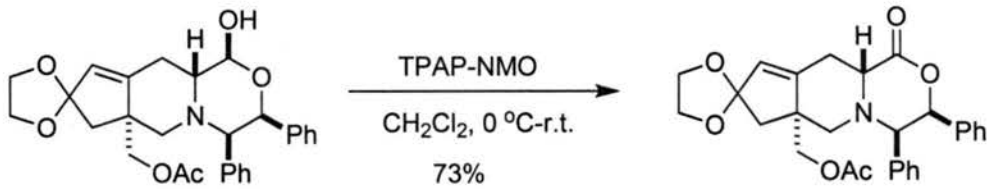
(d, J=12.0Hz, 1H), 2.77-2.66 (comp m, 2H), 2.12 (s, 3H), 2.15-2.10 (comp m, 2H), 1.71 (d, J=12.0Hz, 1H), 1.62 (d, J=15.0Hz, 1H).



^{1}HNMR, $CDCl_3$, 300 MHz, xnj-iv-147pH

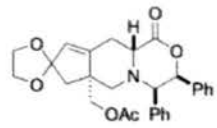


Lactone (220)

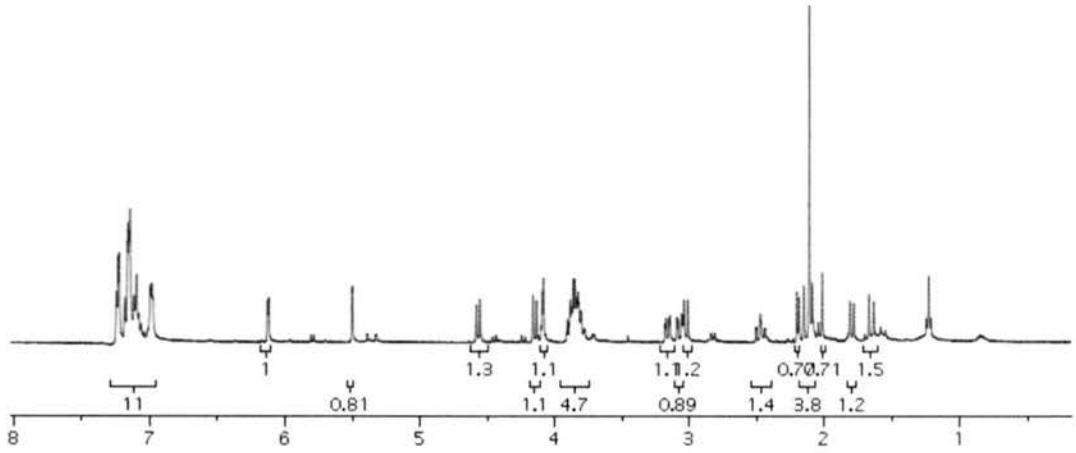


219 **220**

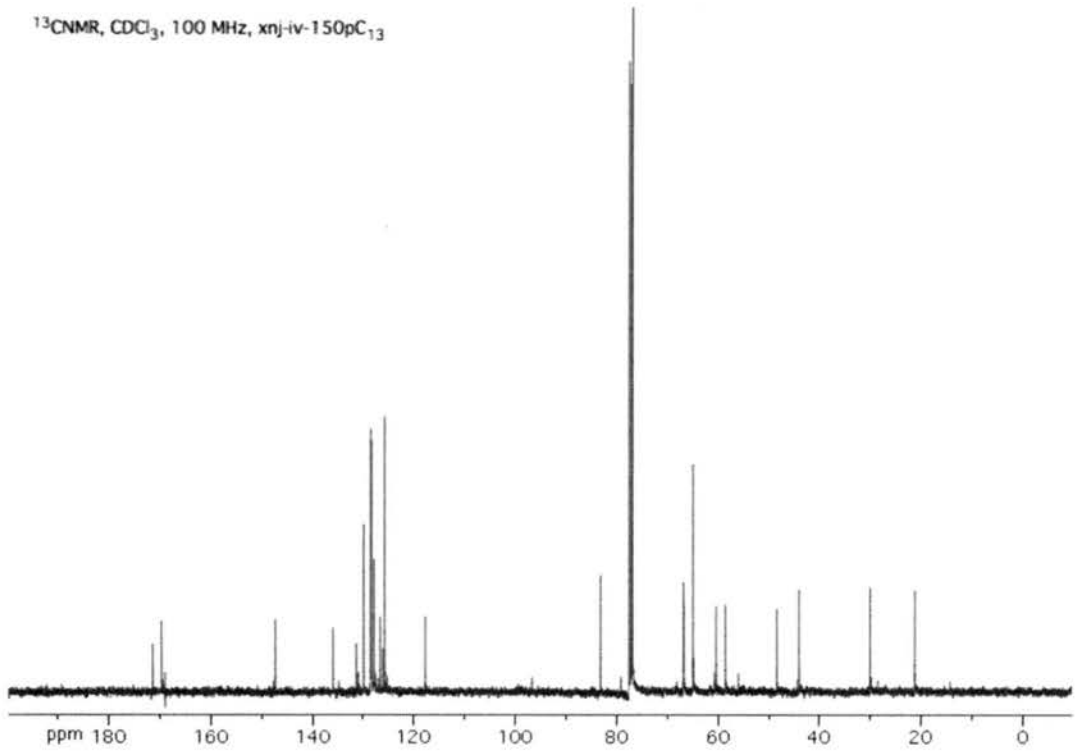
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24–6.98 (m, 10H), 6.12 (d, J=3.0Hz, 1H), 5.50 (s, 1H), 4.58 (d, J=8.0Hz, 1H), 4.16 (d, J=8.0Hz, 1H), 4.09 (d, J=4.0Hz, 1H), 3.91-3.77 (comp m, 4H), 3.18 (dd, J=4.0Hz, 12.0Hz, 1H), 3.09 (dd, J=4.0Hz, 12.0Hz, 1H), 3.04 (d, J=12.0Hz, 1H), 2.51-2.44 (m, 1H), 2.20 (d, J=4.0Hz, 1H), 2.11 (s, 3H), 1.81 (d, J=12.0Hz, 1H), 1.67 (d, J=16.0Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.36, 169.65, 147.27, 135.95, 131.34, 129.91, 128.53, 128.34, 127.88, 126.63, 125.77, 117.72, 83.19, 66.82, 66.74, 64.93, 60.36, 58.57, 48.38, 44.04, 30.07, 21.32.



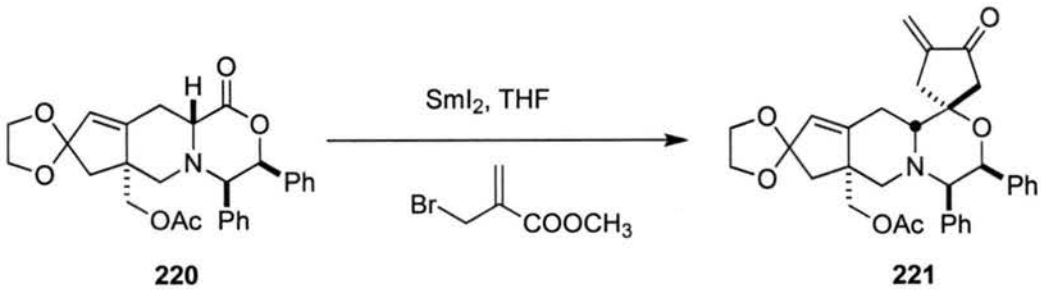
^{1}HNMR, $CDCl_3$, 400 MHz, xnj-iv-150pH



^{13}CNMR, $CDCl_3$, 100 MHz, xnj-iv-150pC_{13}



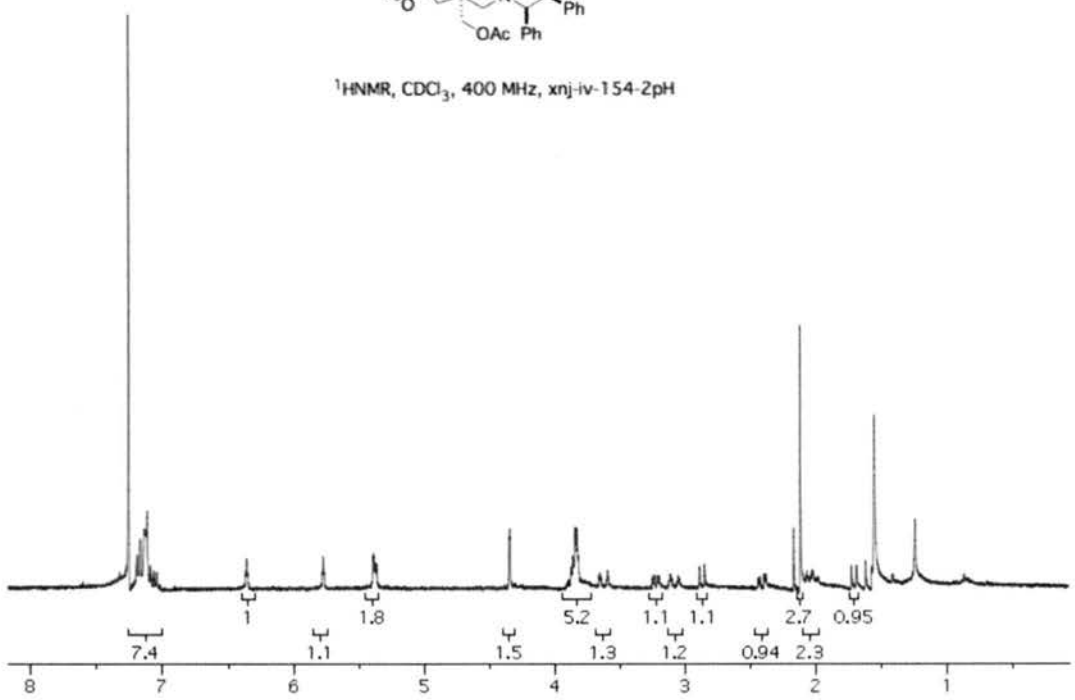
γ-Lactone (221)



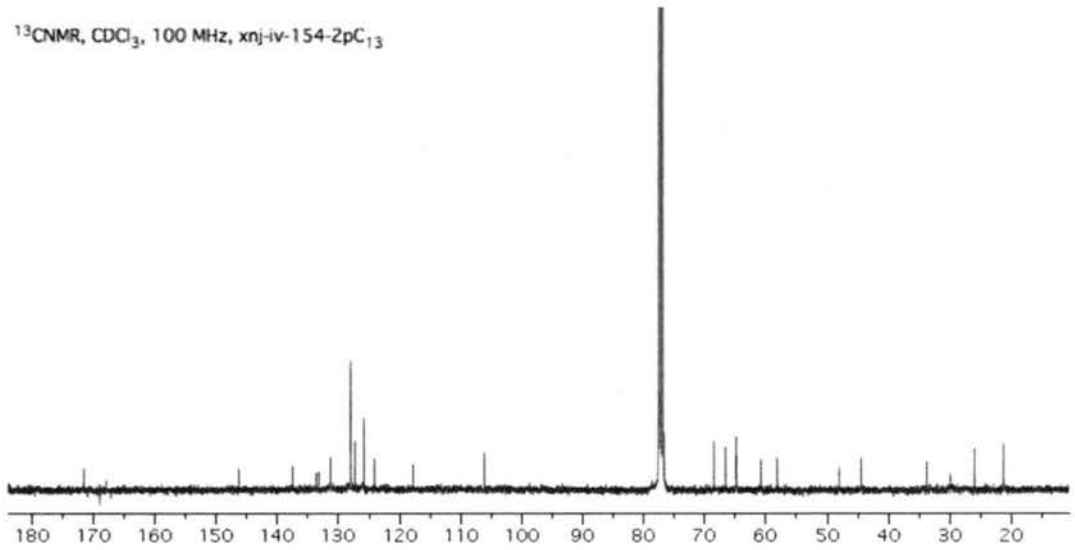
220 **221**

To 20 °C solution of **220** (10 mg, 0.0209 mmol) in anhydrous THF (0.1 mL) was added a solution of SmI_2 in THF (0.834 mL, 0.1 M in THF). The resulting dark blue solution was stirred for 5 min, methyl 2-(bromomethyl)acrylate (4.4 μL, 0.04188 mmoL) was added slowly under stirring. The reaction was completed in 2-5 min monitored by the color change of the solution to yellow. TLC showed half conversion of the starting material. The reaction mixture was poured to cooled $NaHCO_3$ saturated aqueous solution, and separated. The organic phase was extracted with ethyl acetate for three times. The combined organic phases were washed with $Na_2S_2O_3$, brine, dried over anhydrous $MgSO_4$. Preparation TLC (1:1 Hexanes/EtOAc) provided **221** as solid. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.31–7.04 (m, 10H), 6.36 (1H), 5.77(1H), 5.39-5.37 (2H), 4.35 (2H), 3.84 (m, 5H), 3.66-3.60 (1H), 3.35-3.20 (1H), 3.11-3.05 (1H), 2.89 (d, J=8.0Hz, 1H), 2.44-2.38 (dd, J=6.0Hz, 15.0Hz, 1H), 2.12 (s, 3H), 2.07-1.98 (m, 1H), 1.73 (d, J=12.0Hz, 1H), 1.62 (d, J=12.0Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.53, 167.89, 146.31, 137.50, 133.68, 133.23, 131.29, 128.02, 127.97, 127.28, 125.82, 124.11, 117.77, 106.12, 76.64, 68.48, 66.60, 64.80, 60.78, 58.13, 48.06, 44.48, 33.74, 29.89, 26.00, 21.28. HRMS: calcd for C32H34NO7 $[MH]^+$ 544.233, found 544.2318.

^{1}HNMR, $CDCl_3$, 400 MHz, xnj-iv-154-2pH



^{13}CNMR, $CDCl_3$, 100 MHz, xnj-iv-154-2pC_{13}



Appendix 1: 2D spectra of compound 164

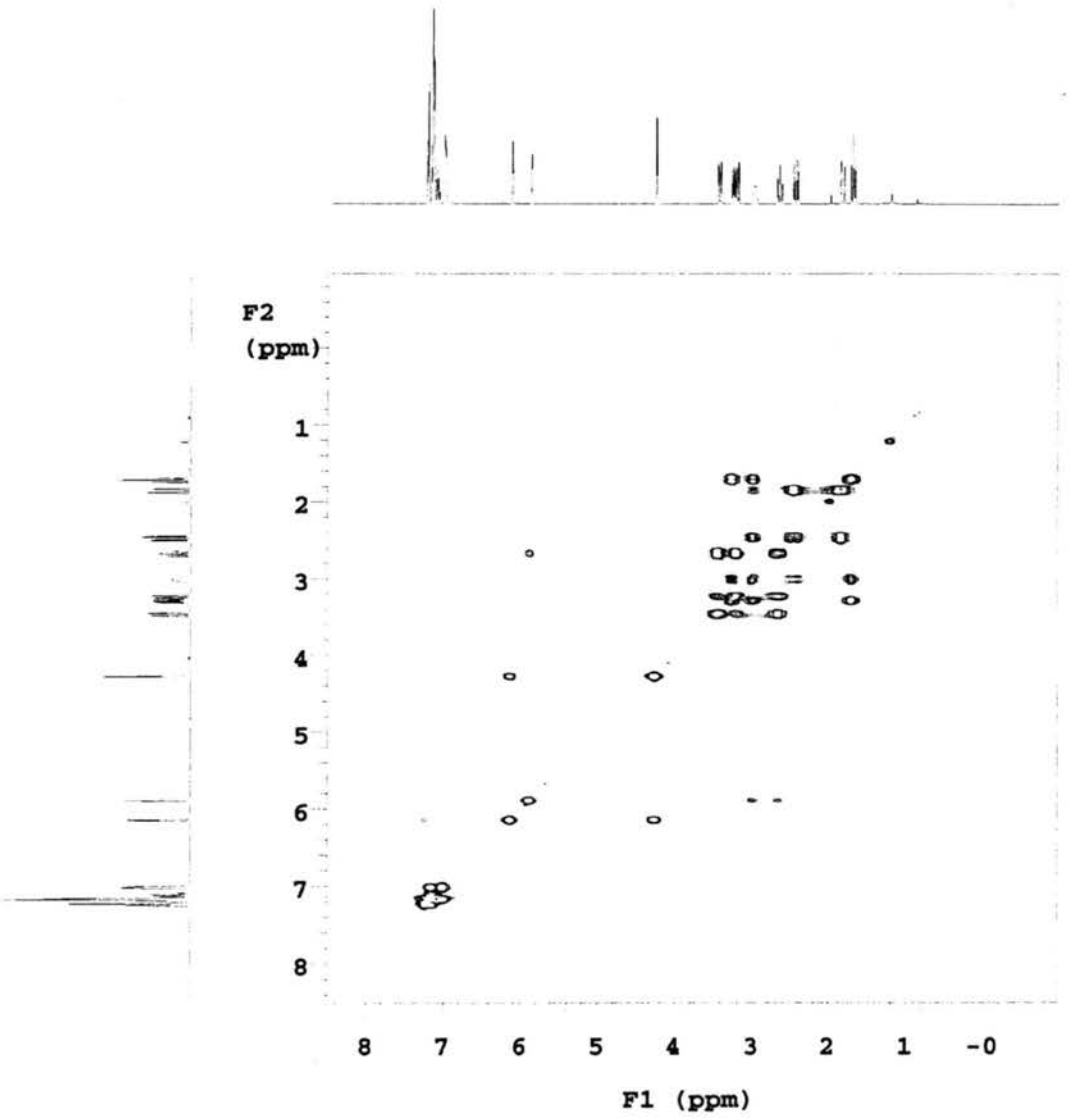
HSQc, Nosey, gCOSY

Archive directory: /i400/jdw/vnmrsys/data
Sample directory: xnj-i-253_21Jul2004

Pulse Sequence: gCOSY

Solvent: CDCl3
Ambient temperature
File: gCOSY
INOVA-500 "strmcld"

Relax. delay 1.000 sec
Acq. time 0.135 sec
Width 3782.9 Hz
2D Width 3782.9 Hz
2 repetitions
128 increments
OBSERVE H1, 400.1063260 MHz
DATA PROCESSING
Sq. sine bell 0.068 sec
F1 DATA PROCESSING
Sq. sine bell 0.034 sec
FT size 1024 x 1024
Total time 5 min, 16 sec



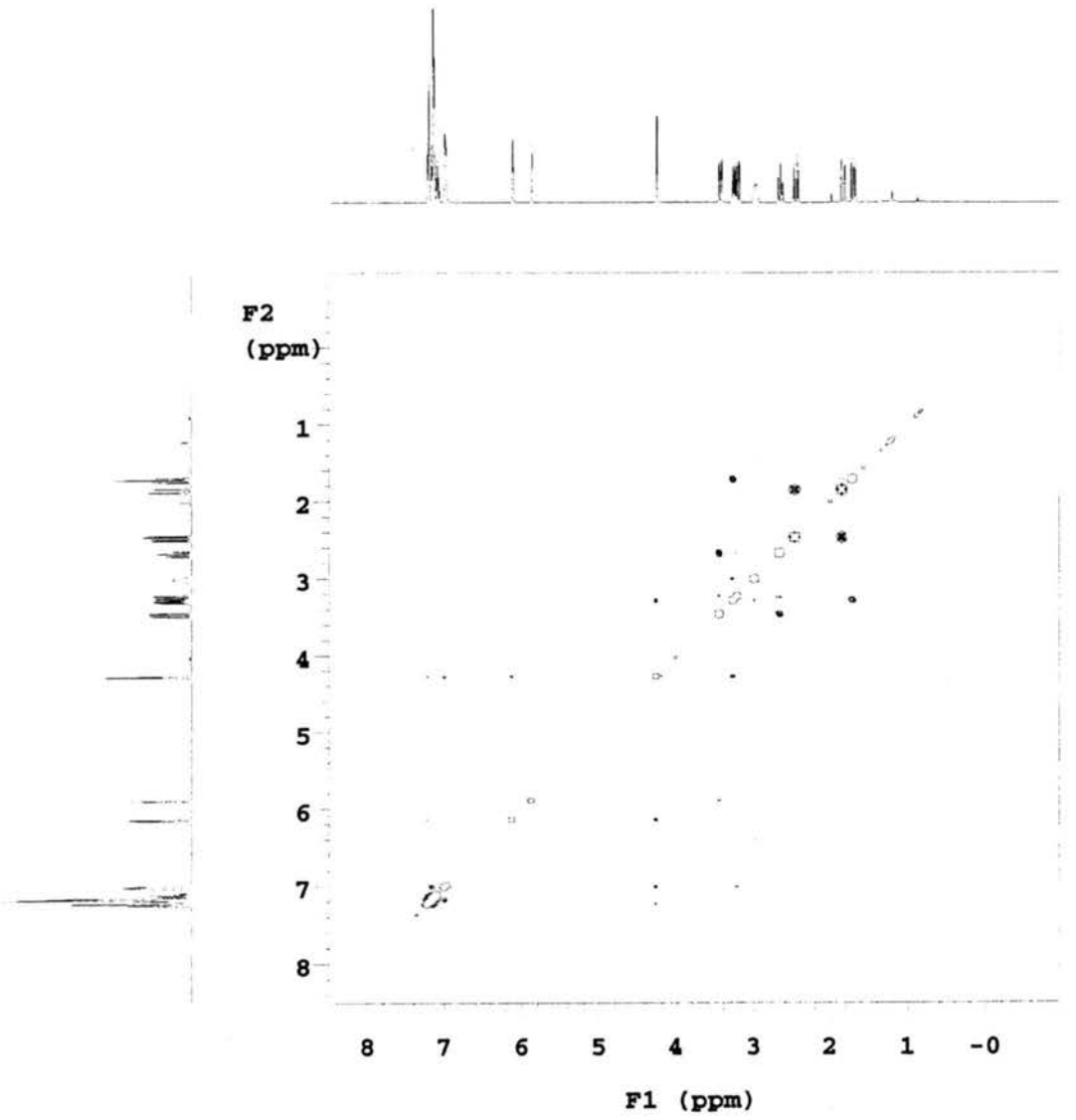
HSQc, Nosey, gCOSY

Archive directory: /i400/jdw/vnmrsys/data
Sample directory: xnj-i-253_21Jul2004

Pulse Sequence: NOESY

Solvent: CDCl3
Ambient temperature
File: NOESY
INOVA-500 "strmcld"

Relax. delay 1.500 sec
Mixing 0.300 sec
Acq. time 0.135 sec
Width 3782.9 Hz
2D Width 3782.9 Hz
16 repetitions
2 x 200 increments
OBSERVE H1, 400.1063260 MHz
DATA PROCESSING
Gauss apodization 0.063 sec
F1 DATA PROCESSING
Gauss apodization 0.049 sec
FT size 2048 x 2048
Total time 3 hr, 31 min, 44 sec



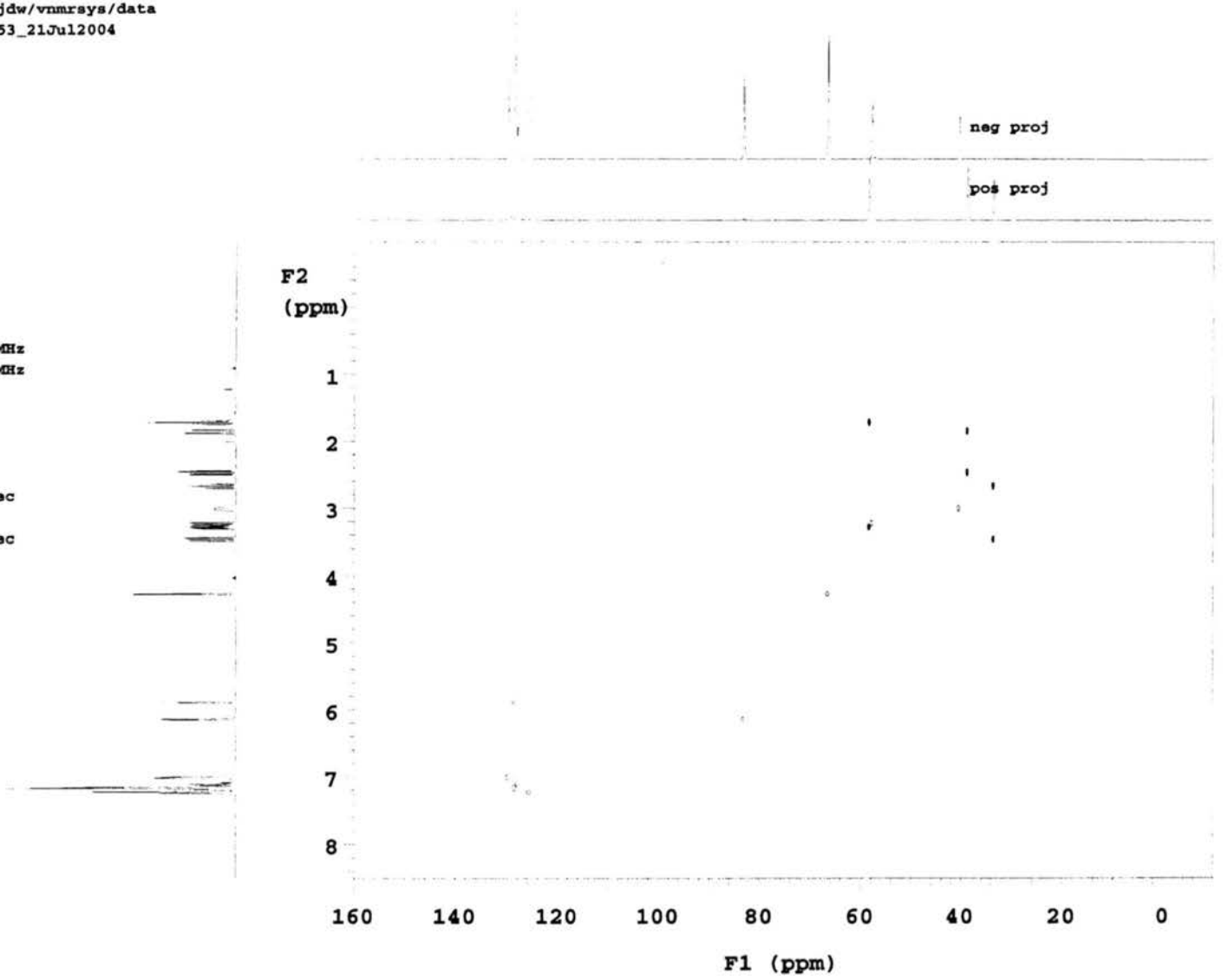
HSQc, Nosey, gCOSY

Archive directory: /i400/jdw/vnmrsys/data
Sample directory: xnj-i-253_21Jul2004

Pulse Sequence: HSQC

Solvent: CDCl3
Ambient temperature
File: HSQC
INOVA-500 "strmcld"

Relax. delay 1.000 sec
Acq. time 0.135 sec
Width 3782.9 Hz
2D Width 17105.0 Hz
4 repetitions
2 x 200 increments
OBSERVE H1, 400.1063260 MHz
DECOUPLE C13, 100.6143372 MHz
Power 38 dB
on during acquisition
off during delay
GARP-1 modulated
DATA PROCESSING
Gauss apodization 0.063 sec
F1 DATA PROCESSING
Gauss apodization 0.022 sec
FT size 1024 x 4096
Total time 32 min, 21 sec



Appendix 2: X-Ray Crystallography of Compound 176

Table 1. Crystal data and structure refinement for RW111_0m.

Identification code	rw111_0m	
Empirical formula	C29 H31 Cl2 N O6	
Formula weight	560.45	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.0637(10) Å	α= 90°.
	b = 15.372(2) Å	β= 90°.
	c = 21.891(3) Å	γ = 90°.
Volume	2713.5(6) $Å^3$	
Z	4	
Density (calculated)	1.372 Mg/m^3	
Absorption coefficient	0.284 mm^{-1}	
F(000)	1176	
Crystal size	0.46 x 0.27 x 0.13 mm^3	
Theta range for data collection	2.28 to 33.24°.	
Index ranges	-10<=h<=12, -23<=k<=20, -33<=l<=31	
Reflections collected	22254	
Independent reflections	9882 [R(int) = 0.0428]	
Completeness to theta = 33.24°	98.4 %	
Absorption correction	Multi-scans	
Max. and min. transmission	0.9641 and 0.8802	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9882 / 0 / 344	
Goodness-of-fit on F^2	1.052	
Final R indices [I>2sigma(I)]	R1 = 0.0624, wR2 = 0.1504	
R indices (all data)	R1 = 0.1007, wR2 = 0.1701	
Absolute structure parameter	-0.06(7)	
Largest diff. peak and hole	1.169 and -0.878 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for RW111_0m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	8515(2)	4500(1)	6796(1)	13(1)
O(1)	7766(2)	3138(1)	7619(1)	15(1)
O(2)	7295(2)	4094(1)	8370(1)	19(1)
O(3)	8956(3)	3241(1)	8940(1)	30(1)
O(4)	6788(3)	8160(1)	6640(1)	33(1)
O(5)	11164(2)	6027(1)	5849(1)	19(1)
O(6)	13804(2)	6387(2)	6079(1)	32(1)
C(1)	7921(3)	4697(1)	7413(1)	14(1)
C(2)	8753(3)	5526(2)	7653(1)	16(1)
C(3)	8419(3)	6242(2)	7213(1)	17(1)
C(4)	7619(3)	6988(2)	7300(1)	21(1)
C(5)	7406(3)	7445(2)	6716(1)	23(1)
C(6)	8062(3)	6852(2)	6214(1)	18(1)
C(7)	8867(3)	6083(2)	6548(1)	15(1)
C(8)	8103(3)	5203(1)	6361(1)	14(1)
C(9)	7825(3)	3659(1)	6571(1)	13(1)
C(10)	8388(3)	2962(1)	7024(1)	13(1)
C(11)	8299(3)	3946(2)	7842(1)	15(1)
C(12)	7696(3)	3646(2)	8888(1)	22(1)
C(13)	6335(4)	3718(2)	9346(1)	31(1)
C(14)	10765(3)	6102(2)	6492(1)	16(1)
C(15)	12756(3)	6214(2)	5707(1)	24(1)
C(16)	13007(4)	6176(2)	5028(1)	37(1)
C(17)	7880(3)	2045(1)	6854(1)	15(1)
C(18)	6826(3)	1553(2)	7223(1)	20(1)
C(19)	6473(3)	695(2)	7065(1)	26(1)
C(20)	7146(4)	320(2)	6543(1)	27(1)
C(21)	8179(4)	813(2)	6172(1)	25(1)
C(22)	8534(3)	1671(2)	6327(1)	21(1)
C(23)	5960(3)	3698(1)	6443(1)	14(1)
C(24)	4739(3)	3673(2)	6896(1)	16(1)

C(25)	3079(3)	3832(2)	6750(1)	20(1)
C(26)	2608(3)	3988(2)	6159(1)	21(1)
C(27)	3799(3)	3981(2)	5699(1)	24(1)
C(28)	5459(3)	3838(2)	5842(1)	18(1)
C(29)	10796(4)	8282(2)	10758(1)	30(1)
Cl(1)	12553(1)	8939(1)	10716(1)	51(1)
Cl(2)	9786(1)	8199(1)	10047(1)	41(1)

Table 3. Bond lengths [Å] and angles [°] for RW111_0m.

N(1)-C(1)	1.465(3)
N(1)-C(8)	1.477(3)
N(1)-C(9)	1.491(3)
O(1)-C(11)	1.402(3)
O(1)-C(10)	1.421(3)
O(2)-C(12)	1.366(3)
O(2)-C(11)	1.429(3)
O(3)-C(12)	1.197(3)
O(4)-C(5)	1.219(3)
O(5)-C(15)	1.351(3)
O(5)-C(14)	1.448(3)
O(6)-C(15)	1.205(3)
C(1)-C(11)	1.519(3)
C(1)-C(2)	1.534(3)
C(2)-C(3)	1.488(3)
C(3)-C(4)	1.330(3)
C(3)-C(7)	1.518(3)
C(4)-C(5)	1.468(4)
C(5)-C(6)	1.522(4)
C(6)-C(7)	1.534(3)
C(7)-C(14)	1.536(3)
C(7)-C(8)	1.542(3)
C(9)-C(10)	1.529(3)
C(9)-C(23)	1.531(3)
C(10)-C(17)	1.514(3)
C(12)-C(13)	1.491(4)
C(15)-C(16)	1.499(4)
C(17)-C(22)	1.393(3)
C(17)-C(18)	1.395(3)
C(18)-C(19)	1.393(4)
C(19)-C(20)	1.391(4)
C(20)-C(21)	1.387(4)
C(21)-C(22)	1.391(4)
C(23)-C(28)	1.394(3)

C(23)-C(24)	1.398(3)
C(24)-C(25)	1.398(3)
C(25)-C(26)	1.370(4)
C(26)-C(27)	1.391(4)
C(27)-C(28)	1.393(3)
C(29)-Cl(1)	1.743(3)
C(29)-Cl(2)	1.762(3)

C(1)-N(1)-C(8)	111.68(18)
C(1)-N(1)-C(9)	111.15(17)
C(8)-N(1)-C(9)	109.77(17)
C(11)-O(1)-C(10)	112.35(17)
C(12)-O(2)-C(11)	117.27(19)
C(15)-O(5)-C(14)	114.7(2)
N(1)-C(1)-C(11)	110.36(18)
N(1)-C(1)-C(2)	110.19(18)
C(11)-C(1)-C(2)	109.37(19)
C(3)-C(2)-C(1)	108.25(19)
C(4)-C(3)-C(2)	129.2(2)
C(4)-C(3)-C(7)	113.1(2)
C(2)-C(3)-C(7)	117.35(19)
C(3)-C(4)-C(5)	110.1(2)
O(4)-C(5)-C(4)	126.7(2)
O(4)-C(5)-C(6)	125.7(3)
C(4)-C(5)-C(6)	107.6(2)
C(5)-C(6)-C(7)	105.3(2)
C(3)-C(7)-C(6)	103.42(19)
C(3)-C(7)-C(14)	108.14(19)
C(6)-C(7)-C(14)	111.60(19)
C(3)-C(7)-C(8)	107.50(18)
C(6)-C(7)-C(8)	112.36(18)
C(14)-C(7)-C(8)	113.18(19)
N(1)-C(8)-C(7)	112.38(18)
N(1)-C(9)-C(10)	106.51(17)
N(1)-C(9)-C(23)	113.15(18)
C(10)-C(9)-C(23)	115.93(18)

O(1)-C(10)-C(17)	107.93(18)
O(1)-C(10)-C(9)	110.80(18)
C(17)-C(10)-C(9)	114.40(18)
O(1)-C(11)-O(2)	104.40(17)
O(1)-C(11)-C(1)	113.36(18)
O(2)-C(11)-C(1)	105.42(18)
O(3)-C(12)-O(2)	122.7(2)
O(3)-C(12)-C(13)	126.9(2)
O(2)-C(12)-C(13)	110.3(2)
O(5)-C(14)-C(7)	107.36(19)
O(6)-C(15)-O(5)	123.8(2)
O(6)-C(15)-C(16)	125.8(3)
O(5)-C(15)-C(16)	110.4(2)
C(22)-C(17)-C(18)	119.1(2)
C(22)-C(17)-C(10)	119.0(2)
C(18)-C(17)-C(10)	121.8(2)
C(19)-C(18)-C(17)	119.6(3)
C(20)-C(19)-C(18)	121.0(3)
C(21)-C(20)-C(19)	119.3(2)
C(20)-C(21)-C(22)	119.9(3)
C(21)-C(22)-C(17)	121.0(2)
C(28)-C(23)-C(24)	118.0(2)
C(28)-C(23)-C(9)	117.6(2)
C(24)-C(23)-C(9)	124.2(2)
C(25)-C(24)-C(23)	120.5(2)
C(26)-C(25)-C(24)	120.9(2)
C(25)-C(26)-C(27)	119.4(2)
C(26)-C(27)-C(28)	120.2(2)
C(27)-C(28)-C(23)	121.0(2)
Cl(1)-C(29)-Cl(2)	111.75(16)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for RW111_0m. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

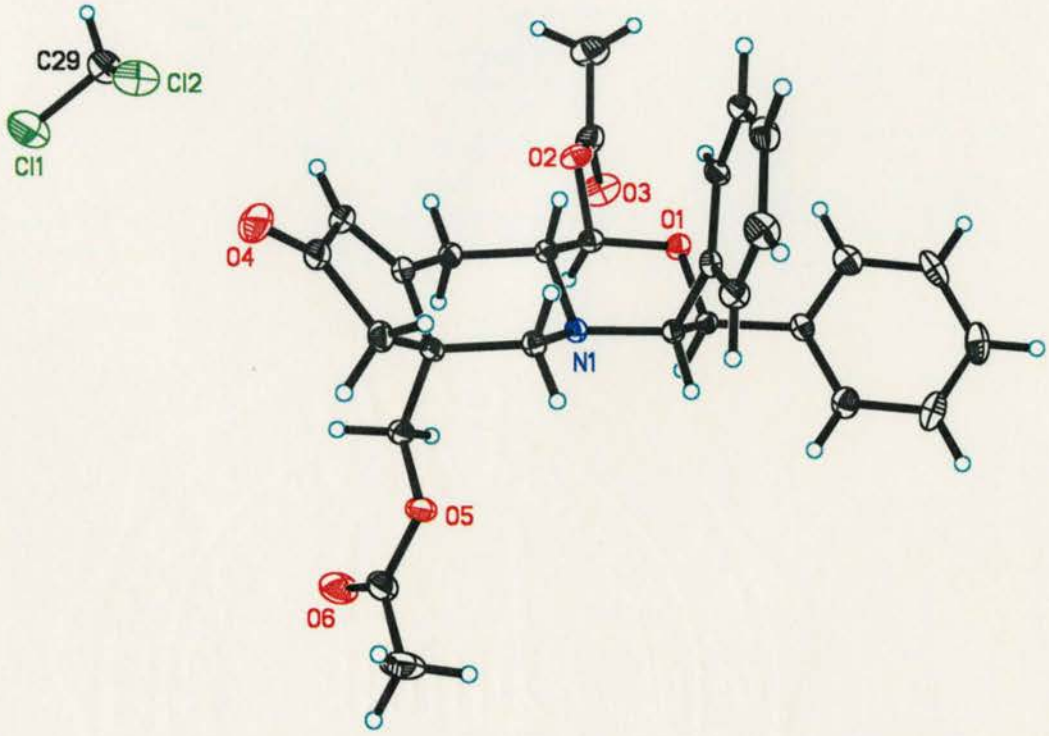
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	13(1)	11(1)	14(1)	1(1)	0(1)	-1(1)
O(1)	20(1)	17(1)	10(1)	-1(1)	-1(1)	-1(1)
O(2)	22(1)	21(1)	14(1)	1(1)	3(1)	6(1)
O(3)	32(1)	38(1)	20(1)	3(1)	-4(1)	12(1)
O(4)	41(1)	16(1)	43(1)	2(1)	9(1)	8(1)
O(5)	16(1)	24(1)	18(1)	-1(1)	4(1)	-2(1)
O(6)	18(1)	45(1)	35(1)	-6(1)	3(1)	-7(1)
C(1)	13(1)	14(1)	14(1)	-2(1)	1(1)	-1(1)
C(2)	19(1)	16(1)	14(1)	-3(1)	1(1)	-2(1)
C(3)	16(1)	15(1)	19(1)	-3(1)	1(1)	-3(1)
C(4)	21(1)	15(1)	26(1)	-4(1)	5(1)	1(1)
C(5)	20(1)	14(1)	34(1)	-2(1)	5(1)	0(1)
C(6)	17(1)	13(1)	24(1)	1(1)	-1(1)	-1(1)
C(7)	12(1)	14(1)	18(1)	1(1)	2(1)	-1(1)
C(8)	15(1)	14(1)	13(1)	1(1)	-1(1)	-1(1)
C(9)	12(1)	12(1)	14(1)	-1(1)	0(1)	0(1)
C(10)	14(1)	13(1)	12(1)	-1(1)	1(1)	0(1)
C(11)	14(1)	17(1)	14(1)	0(1)	0(1)	1(1)
C(12)	30(1)	23(1)	13(1)	-2(1)	-1(1)	0(1)
C(13)	39(2)	36(2)	19(1)	7(1)	9(1)	4(1)
C(14)	15(1)	18(1)	16(1)	-2(1)	1(1)	-2(1)
C(15)	19(1)	22(1)	30(1)	2(1)	5(1)	-1(1)
C(16)	33(1)	49(2)	28(2)	3(1)	15(1)	-3(1)
C(17)	14(1)	13(1)	17(1)	3(1)	-2(1)	-1(1)
C(18)	17(1)	22(1)	22(1)	3(1)	-4(1)	1(1)
C(19)	20(1)	23(1)	36(2)	9(1)	-6(1)	-10(1)
C(20)	32(1)	13(1)	36(2)	2(1)	-13(1)	-3(1)
C(21)	35(2)	17(1)	22(1)	-5(1)	-9(1)	3(1)
C(22)	26(1)	16(1)	20(1)	3(1)	-1(1)	-1(1)
C(23)	16(1)	11(1)	15(1)	0(1)	-2(1)	-1(1)
C(24)	14(1)	14(1)	19(1)	1(1)	2(1)	-2(1)

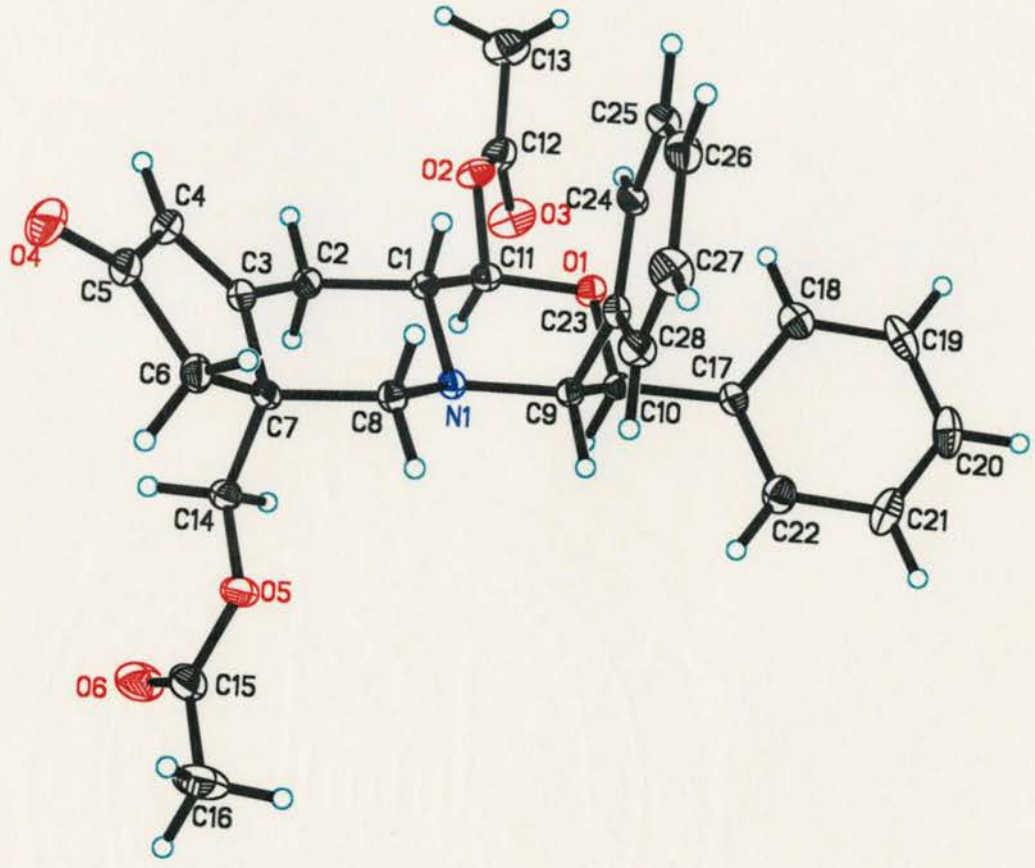
C(25)	16(1)	19(1)	24(1)	-1(1)	4(1)	-2(1)
C(26)	15(1)	20(1)	29(1)	0(1)	-6(1)	1(1)
C(27)	22(1)	29(1)	22(1)	2(1)	-7(1)	-1(1)
C(28)	19(1)	22(1)	14(1)	1(1)	-1(1)	-2(1)
C(29)	32(1)	36(2)	22(1)	4(1)	-3(1)	-4(1)
Cl(1)	51(1)	72(1)	30(1)	-16(1)	7(1)	-29(1)
Cl(2)	32(1)	64(1)	26(1)	1(1)	-5(1)	2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for RW111_0m.

	x	y	z	U(eq)
H(1A)	6694	4789	7399	16
H(2A)	8300	5678	8060	20
H(2B)	9963	5434	7694	20
H(4A)	7240	7196	7684	25
H(6A)	8889	7161	5960	22
H(6B)	7147	6649	5948	22
H(8A)	6882	5264	6337	17
H(8B)	8512	5042	5950	17
H(9A)	8384	3530	6174	15
H(10A)	9626	2979	7044	16
H(11A)	9503	3931	7951	18
H(13A)	6642	3399	9717	47
H(13B)	5314	3472	9176	47
H(13C)	6154	4332	9448	47
H(14A)	11208	6654	6658	20
H(14B)	11260	5613	6722	20
H(16A)	14166	6309	4932	55
H(16B)	12282	6602	4830	55
H(16C)	12736	5591	4880	55
H(18A)	6353	1801	7580	24
H(19A)	5761	360	7319	32
H(20A)	6900	-266	6440	33
H(21A)	8644	564	5813	30
H(22A)	9233	2006	6069	25
H(24A)	5039	3548	7307	19
H(25A)	2267	3831	7064	24
H(26A)	1478	4100	6064	25
H(27A)	3478	4073	5286	29
H(28A)	6263	3837	5525	22
H(29A)	10018	8528	11063	36

H(29B)	11122	7694	10898	36




C13
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C22
C21
O5
O6
C15
C16

Appendix 3: Publications

Tetrahedron: *Asymmetry* 19 (2008) 2901–2906

Contents lists available at ScienceDirect

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A diastereoselective intramolecular Pauson–Khand approach to the construction of the BC-ring system in tuberostemoninol

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ABSTRACT

Herein, we describe an asymmetric approach to the synthesis of a BC-ring synthon in tuberostemoninol via an intramolecular Pauson–Khand reaction stereocontrolled by a commercially available chiral glycinate.

1. Introduction

Stemona alkaloids represent a unique class of natural products detected to date only from the monocotyledonous family *Stemonaceae*.[1] Their intricate polycyclic structures and a broad range of biological activities have led to extensive phytochemical and biological studies[2] as well as synthetic studies[3] over the past two decades. Some representative examples of stemona alkaloids include stenine **1**, tuberostemonine **2**, croomine **3**, stemoamide **4**, and stemofoline **5** (Fig. 1), which are characterized as having a [1,2-a]azepine nucleus. Tuberostemoninol **6**, which lacks this [1,2-a]azepine nucleus, but possesses an azabicyclo[4.3.1]decan-10-one nucleus instead, was first isolated from the Chinese medicinal herb *Stemona tuberosa* Lour as a minor component in 1994 by Lin et al.[4] It is thought that tuberostemoninol is biogenetically related to tuberostemonine **2**,[3e] which is a major component isolated from *S. tuberosa* Lour. The other two *Stemona* alkaloids structurally close to tuberostemoninol are neotuberostemoninol **7**, isolated from *S. tuberosa* Lour in 2002,[5] and maireistemoninol **8**, isolated from species *S. mairei* in 2007.[6]

Published synthetic strategies and methodologies for *Stemona* alkaloids, such as stenine and tuberostemonine, included an early stage construction of the highly functionalized cyclohexane rings, the bicyclic hydroindole ring, or the tricyclic core via stereoselective Diels-Alder reactions in Hart's,[3a] Morimoto's[3b] and Padwa's[3c] syntheses of stenine, a tandem Diels–Alder/Azido–Schmit reaction in Aube's synthesis of stenine[3d], and a diastereoselective spirocyclization of a L-tyrosine derivative in Wipf's synthesis of tuberostemonine.[3e] Herein, we report a new approach to the construction of the functionalized cyclopenta[*c*]pyridine bicycle (BC ring) as part of our studies toward the total synthesis of tuberostemoninol **6**.

2. Results and discussion

Our synthetic strategy is outlined in Scheme 1, where tricycle **10** or amino acid derivative **9** could serve as a scaffold for the construction of the tricyclic core. This flexible strategy allows for the introduction of the stereogenic centers in the target natural product **6** as well as embracing neotuberostemoninol **7** and maireistemoninol **8** (Fig. 1). We envisioned an intramolecular Pauson–Khand reaction (IMPK)[7] of a chiral glycinate derivative, the 1,7-enyne **12**, to construct the tricycle **10** with the illustrated *trans*-stereochemical outcome between the R_2 and H groups, presumably via the more stable chair-like transition state of the coordinated complex **11** (Scheme 1). The chiral glycine template can be readily cleaved by hydrogenolysis.[8]

2.1. Preparation of IMPK precursors and studies of IMPK reactions

The preparation of the IMPK precursors **12** started with the commercially available optically pure glycinate **13**. Enolate monoalkylation of **13** in tetrahydrofuran (THF) with propargyl bromide (80% wt/v in toluene) in the presence of sodium bis(trimethylsilyl)amide (NaHMDS) (1.0 M solution in THF)[9] gave compound **14**. Deprotection of the *tert*-butyl carbonate group with hydrochloric acid (4.0 M solution in dioxane) in dichloromethane, followed by basic work-up, gave the free secondary amine **15** in 65% yield. Alkylation of amine **15** gave 1,7-enyne **12** (Scheme 2).

A screening of N-alkylation reactions with various allylic side chains was carried out (Table 1). It was found that the highly reactive methyl 2-(bromomethyl)acrylate (entry 5), acryloyl chloride (entry 6), and allylic acetate (entry 1)[10] gave the best results under the illustrated conditions. However, allylic bromides in entries 2, 3, and 4 gave very poor yields (10–16% as the best results), with mostly starting material recovered under concentrated conditions (1 M) in *N,N*-dimethylformamide (DMF) or acetonitrile in the presence of alkali metal (Na, K, Cs) carbonates. We also found that an

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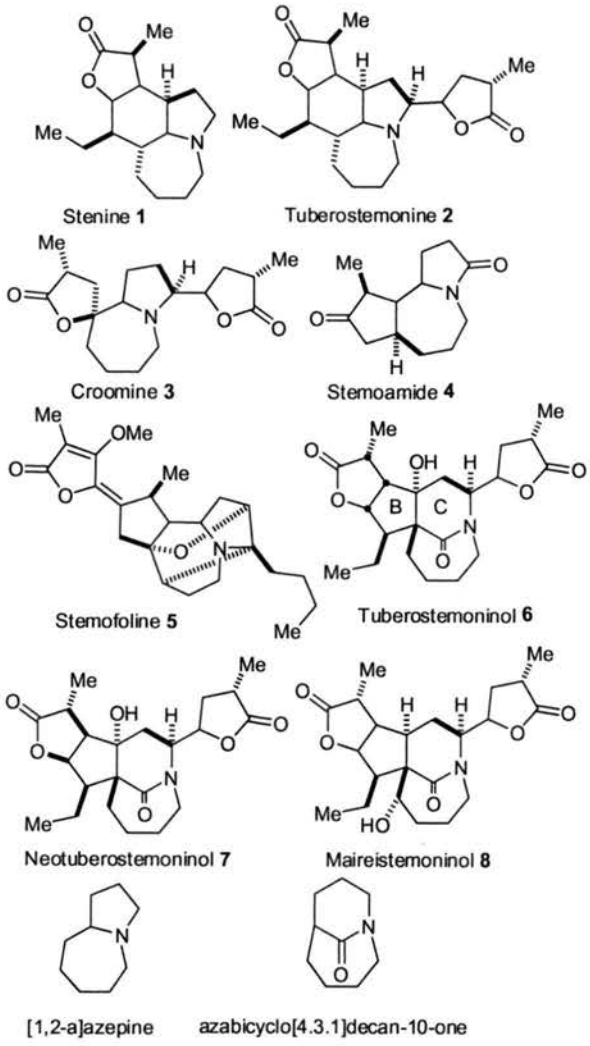
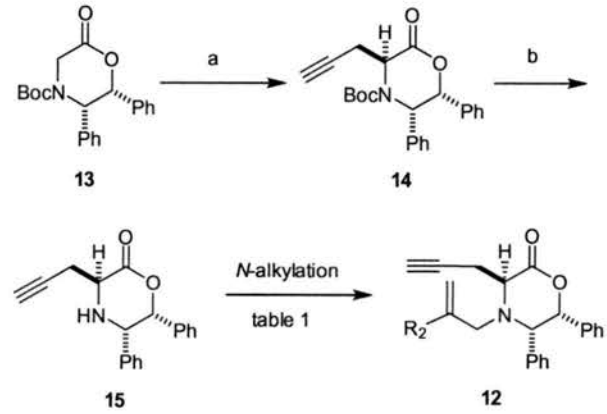


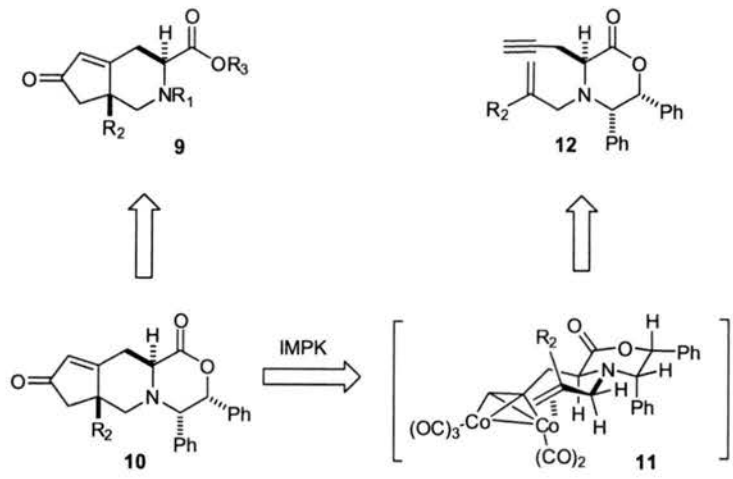
Figure 1. Examples of several *Stemona* alkaloids.

increase in the reaction temperature to 60–65 °C and addition of tetrabutylammonium iodide (TBAI) catalyst did not improve the yields for entries 2, 3, and 4, but instead we recovered mostly starting material with apparent epimerization at the α-position.

Treatment of precursors **12a–d** with dicobaltoctacarbonyl [$Co_2(CO)_8$] in dichloromethane followed by the addition of *N*-methyl morpholine N-oxide (NMO) to initiate the cyclization at 0 °C to room temperature (condition A, Table 2) provided the corresponding cyclopentenone products **10a–d** in 65% to fair yields. The newly generated stereochemistry as proposed was supported by nOe analysis of one of the IMPK cycloadducts **10a**.[13] Substrate **12f** provided the desired product **10f** under thermal condition B ($Co_2(CO)_8$, MeCN, reflux).[14] However, neither thermal (condition B) nor Lewis base (NMO (condition A), DMSO (condition C), nBuSMe (condition D), and Me_2S (condition E)) at a temperature range of 35–75 °C in acetonitrile or toluene were able to convert **12e** to the desired cycloadduct **10e**. With the exception of the cobalt-alkyne complex formed during the first stage of the reaction (as monitored by TLC), there was no evidence of other intermediates formed in the reaction.[15] Considering the successful (with a



Scheme 2. IMPK precursor preparation, reagents and conditions: (a) NaHMDS, propargyl bromide, THF, −78 °C, CH_2Cl_2; 90%; (b) HCl, dioxane/CH_2Cl_2, then $NaHCO_3/H_2O$; 65%.



Scheme 1. Planned IMPK and stereochemistry generation.

Table 1
Preparation of IMPK precursors **12**

Entry	Allylic side chains	Conditions	Products (yields)
1	CH_2=CH–CH_2OAc	$Pd_2(dba)_3$, PPh_3, K_2CO_3, THF, rt, 2d	**12a**, 70–90%
2	CH_2=C(CH_3)–CH_2Br	K_2CO_3, TBAI, DMF, rt, 2 d	**12b**, 16% and rec S.M.
3[a]	CH_2=C(CH_2OTBS)–CH_2Br	K_2CO_3, TBAI, DMF, rt, 3 d	**12c**, 5–10%, and rec S.M.
4[b]	CH_2=C($CH_2CH_2CH_2OTBS$)–CH_2Br	$NaHCO_3$, DMF, rt, 36 h	**12d**, 5–10%, and rec S.M.
5	CH_2=C($COOCH_3$)–CH_2Br	$KHCO_3$, DMF, rt, 12–24 h	**12e**, 98%
6	CH_2=CH–COCl	Et_3N, CH_2Cl_2, 0 °C–rt, 2 h	**12f**, 61%

[a] See Ref. 11 for preparation of the allylic bromide.
[b] See Ref. 12 for preparation of allylic bromide.

Table 2
IMPK reactions

Precursors **12**	Conditions	Products, yields
12a	A	**10a**, 65%
12b	A	**10b**, <50%
12c	A	**10c**, <50%
12d	A	**10d**, <50%
12e	A–E	**10e**, 0%
12f	B	**10f**, 16%

significant low yield though) reactions of the electron-deficient species **12f**, as well as the precursors with relatively hindered geminal alkenes **12b–d**, it could be that the more electron-deficient nature of **12e** adversely affected the conversion to **10e**.

2.2. Modification of IMPK reactions

Modification of the electronic properties of compound **12e** was easily achieved by diisobutylaluminum hydride (DIBAL-H) reduction of the ester group followed by acetylation of the resulting lactol alcohol **16**, providing diacetate compound **17**. When precursor **17** was subjected to IMPK conditions, a single diastereomer **18** was obtained in 45–50% yield under the *N*-methyl morpholine N-oxide-promoted conditions, while the yield was improved to above 80% under dimethyl sulfoxide (toluene, reflux, 3–5 h) or *n*-butyl methyl sulfide (1,2-dichloroethane, 82 °C, 2–3 h)-promoted thermal conditions (Scheme 3). In a similar manner, cyclopentenone **20** was also obtained from precursor **19** prepared by the respective protection of diol **16** with thiopyridyl (SPy)[16] and *tert*-butyl dimethyl silyl (TBS) groups. The proposed stereochemistry of the IMPK products **18** and **20** is shown in Scheme 3, and was confirmed by single crystal X-ray diffraction of diacetate cyclopentenone **18** (Fig. 2).[17]

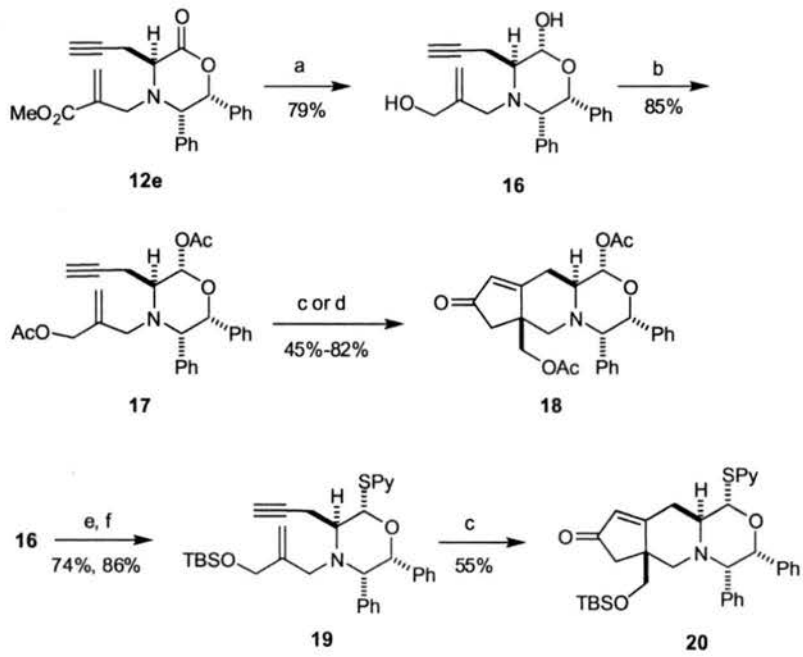
3. Conclusion

In conclusion, a diastereoselective intramolecular Pauson–Khand reaction was developed using a commercially available glycinate as the stereochemical-determining element for an efficient construction of the BC-ring system containing a quaternary carbon center present in tuberostemoninol. The IMPK methodology deployed herein should be quite useful in the preparation of cyclopenta[*c*]pyridine containing amino acid derivatives and natural products. In our laboratory, elaboration of these intermediates toward an asymmetric total synthesis of tuberostemoninol is currently under way, and will be reported in due course.

4. Experimental

4.1. General

All chemicals from commercial sources were used without further purification. Both glycinates **13** (2*R*,3*S*)-*tert*-butyl 6-oxo-2,3-diphenylmorpholine-4-carboxylate and its enantiomer were used in the reactions. All dry reactions were carried out using standard syringe-septum technique. Analytical and preparative TLC used Merck silica gel 60 F254 plates, while flash chromatography was performed on Merck silica gel 60 (230–400 mesh). Nuclear mag-



Scheme 3. Modified IMPK reactions, reagents and conditions: (a) DIBAL, CH_2Cl_2, −78 °C; (b) Ac_2O, pyr., THF, 85%; (c) $Co_2(CO)_8$, NMO, CH_2Cl_2, 45–50%; (d) $Co_2(CO)_8$, DMSO, toluene, 110 °C, 82%; (e) PySSPy, Bu_3P, CH_2Cl_2, 74%; (f) TBSCl, imidazole, DMAP, CH_2Cl_2, 86%.

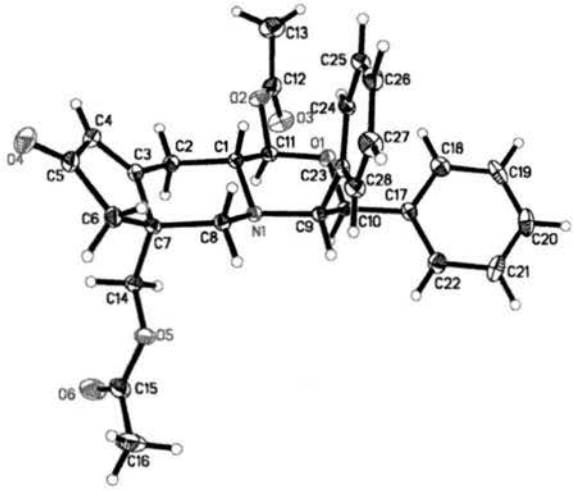


Figure 2. ORTEP diagram of compound **18**.[17]

netic resonance spectra ^{1}H NMR (300 MHz and 400 MHz) and ^{13}C NMR (75 MHz and 100 MHz) were recorded on Varian Inova spectrometers. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^{1}H) or the central line (77.23 ppm) of $CDCl_3$ (for ^{13}C). High-resolution mass spectra were recorded on a Fisons VG Autospec or Finnigan LCQ-DUO with HP1100 Series HPLC. Infrared spectra were recorded on a Perkin–Elmer FT-IR 1600 series. Optical rotations were measured on a Rudolph Research Autopol III automatic polarimeter.

4.1.1. (3*R*,5*R*,6*S*)-*tert*-Butyl 2-oxo-5,6-diphenyl-3-(prop-2-ynyl) morpholine-4-carboxylate 14

To a cooled solution (−78 °C) of oxazinone **13** (10.0 g, 28.30 mmol) in THF (180 ml) was added sodium bis(trimethylsilyl) amide (31.12 ml, 1.0 M solution in THF) dropwise via syringe over a period of 15 min. The resulting mixture was stirred for an additional 1 h at −78 °C. Propargyl bromide (4.1 ml, 36.78 mmol, 80% w/v in toluene) was added dropwise via syringe to the above mixture, and stirred for 2.5 h under −78 °C. The reaction mixture was then carefully quenched with ammonium chloride saturated aqueous solution and diluted with ethyl acetate. The solution was allowed to warm up to above 0 °C. The reaction mixture was transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate three times, and the combined organic layer was washed with ammonium chloride-saturated aqueous solution and brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude residue was subjected to flash column chromatography (hexanes/EtOAc, 8:1) to afford 9.2 g (83%) of compound **14** as white powder. $[\alpha]_D^{25} = -30.9$ (c 1, CH_2Cl_2). IR (NaCl thin film): 3492, 3281, 2255, 1747, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.2 5–6.5 6 (m, 10H), 6.47 (d, J = 2.8 Hz, 1H), 5.16 (t, J = 4.8 Hz, 1H), 5.05 (d, J = 3.2 Hz, 1H), 3.32 (ddd, J = 2.4 Hz, 5.2 Hz, 17.2 Hz, 1H), 3.07 (td, J = 3.2 Hz, 17.2 Hz, 1H), 2.22 (t, J = 2.4 Hz, 1H), 1.13 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.9 0, 153.9 5, 136.5 3, 134.5 7, 128.6 1, 128.1 9, 127.8 7, 127.7 5, 127.5 6, 126.5 4, 81.6 9, 79.9 7, 79.4 1, 72.6 9, 60.7 3, 55.8 0, 27.9 1, 23.8 0. FAB-HRMS: calcd for $C_{24}H_{25}NO_4$ [MH$^+$] 392.1863, found 392.1825.

4.1.2. (3*R*,5*R*,6*S*)-5,6-Diphenyl-3-(prop-2-ynyl) morpholine-2-one 15

To an ice-cooled solution of compound **14** (9.7 g, 24.78 mmol) in dichloromethane (62 ml) was added hydrochloric acid (75.4 ml, 4.0 M solution in dioxane) over a 10 min period. The cooling bath was removed, and the reaction mixture was stirred for 3–5 h or until the disappearance of starting material as monitored by TLC. The solvent was then removed under reduced pressure. Diethyl ether was added to precipitate the hydrochloride salt, after which the solvent was removed. The white solid was rinsed with diethyl ether and dried to provide 6.0 g of white milky powder, which was redissolved in dichloromethane (70 ml). Saturated sodium bicarbonate (0.95 ml) was added followed by the slow addition of solid sodium bicarbonate (1.54 g). The resulting suspension was stirred at room temperature for 3 h. Anhydrous magnesium sulfate was added and stirred for an additional 1 h, filtered, and concentrated. Flash chromatography (hexanes/EtOAc, 3:1 to 2:1 to 1:1) provided 4.71 g (65%) of compound **15** as light white solid. $[\alpha]_D^2 5 = -117.3$ (c 1, CH_2Cl_2). IR (NaCl thin film): 3326, 3287, 1732 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.2 7–7.1 7 (m, 6H), 7.03–7.01 (m, 2H), 6.95 (d, J = 8.0 Hz, 2H), 5.73 (d, J = 3.6 Hz, 1H), 4.82 (d, J = 3.6 Hz, 1H), 4.21 (d, J = 3.6 Hz, 1H), 3.04 (dddd, J = 0.8 Hz, 2.4 Hz, 8.8 Hz, 16.8 Hz, 1H), 2.91 (dddd, J = 1.2 Hz, 2.8 Hz, 3.6 Hz, 16.8 Hz, 1H), 2.37 (br s, 1H), 2.11 (ddd, J = 1.2 Hz, 2.8 Hz, 3.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.4 9, 136.8 9, 134.9 3, 128.5 7, 128.3 2, 128.2 7, 127.8 6, 127.8 3, 127.2 1, 85.4 9, 80.1 2, 72.1 5, 57.0 9, 55.3 8, 24.0 3. FAB-HRMS: calcd for $C_{19}H_{17}NO_2$ [MH$^+$] 292.1338, found 292.1337.

4.1.3. (3*S*,5*S*,6*R*)-4-Allyl-5,6-diphenyl-3-(prop-2-ynyl) morpholine-2-one 12a

A mixture of $Pd_2(dba)_3$ (8 mg), PPh_3 (27 mg), and K_2CO_3 (28 mg) in anhydrous THF (2 ml) was strirred under argon. The secondary amine **15** (30 mg, 0.103 mmol) was added followed by allyl acetate (13.3 μl, 0.1236 mmol), and the resulting mixture was stirred at room temperature for 1 day during which more allyl acetate was added. The reaction mixture was filtered through a pad of Celite, and concentrated. The residue was subjected to flash chromatography (3:1 hexanes/EtOAc) to give the desired product **12a** in decent yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20–7.12 (m, 6H), 7.05–7.02 (m, 2H), 6.79–6.76 (m, 2H), 6.21–6.20 (d, J = 3.0 Hz, 1H), 5.90–5.76 (ddd, J = 4.8 Hz, 7.8 Hz, 10.2 Hz, 1H), 5.18–517 and 5.09–5.07 (app d, J = 27.6 Hz, 1H), 5.14 (br., 1H), 4.30–4.29 (d, J = 3.0 Hz, 1H), 4.06–4.03 (t, J = 4.2 Hz, 1H), 3.30–3.23 (dddd, J = 14.4 Hz, 1.8 Hz, 1.8 Hz, 5.1 Hz, 1H), 3.17–3.10 (app dd, J = 14.4 Hz, 7.8 Hz, 1H), 3.03–2.95 (ddd, J = 16.8 Hz, 2.7 Hz, 3.6 Hz, 1H), 2.85–2.77 (dd, J = 16.8 Hz, 2.4 Hz, 4.5 Hz, 1H), 2.16–2.15 (t, J = 2.55 Hz, 1H). FAB-MS: calcd for $C_{22}H_{21}NO_2$ [MH]$^+$ 331.2, found 332.2 (low resolution MS).

4.1.4. General procedure for 12b, 12c, 12d, 12e preparation

To a 0 °C cooled solution of amine **15** in DMF (1 M) was added potassium carbonate (1.2 equiv) as a solid followed by dropwise addition of allylic bromide (1.5 or more equiv). The resulting mixture was stirred at room temperature for 12 h for two days. The reaction mixture was filtered, and the filtrate was partitioned between ammonium chloride saturated aqueous solution and ethyl acetate, and separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography gave products **12b**, **12c**, **12d**, and **12e**, respectively.

4.1.4.1. (3*S*,5*S*,6*R*)-4-(2-Methylallyl)-5,6-diphenyl-3-(prop-2-ynyl)morpholin-2-one 12b. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20–7.10 (m, 6H), 7.05–7.00 (m, 2H), 6.78–6.74 (m, 2H), 6.20 (d, J = 3.0 Hz, 1H), 4.90 (br s, 1H), 4.81 (br s, 1H), 4.16 (d, J = 3.0 Hz, 1H), 3.79–3.78 (d, J = 4.2 Hz, 1H), 3.08–3.05 (d, J = 17.2 Hz, 1H), 2.96–2.90 (dd, J = 4.8 Hz, 18.0 Hz, 1H), 2.78–2.70 (ddd, J = 4.4 Hz, 9.6 Hz, 18.4 Hz, 1H), 2.51–2.44 (d, J = 24.8 Hz, 1H), 2.42–2.34 (app t, J = 14.8 Hz, 1H). 1.93–1.86 (d, J = 24.8 Hz, 1H), 1.83–1.79 (d, J = 17.2 Hz, 1H), 1.01 (s, 9H), 0.29–0.21 (d, J = 29.2 Hz, 6H).

4.1.4.2. (3*S*,5*S*,6*R*)-4-(2-((*tert*-Butyldimethylsilyloxy)methyl)allyl)-5,6-diphenyl-3-(prop-2-ynyl)morpholin-2-one 12c. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20–7.12 (m, 6H), 7.02–6.99 (m, 2H), 6.78–6.74 (m, 2H), 6.18–6.17 (d, J = 3.0 Hz, 1H), 5.21 (br, 1H), 4.91 (br, 1H), 4.20–4.19 (d, J = 3.0 Hz, 1H), 4.03 (app t, J = 3.9 Hz, 1H), 3.04 (s, 2H), 3.02–2.95 (m, 1H), 2.84–2.75 (ddd, J = 2.7 Hz, 4.5 Hz, 16.8 Hz, 1H), 2.13 (t, J = 2.7 Hz, 1H). 1.85 (s, 3H).

4.1.4.3. (3*R*,5*R*,6*S*)-4-(6-(*tert*-Butyldimethylsilyloxy)-2-methylenehexyl)-5,6-diphenyl-3-(prop-2-ynyl)morpholin-2-one 12d. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.25–7.21 (m, 6H), 7.12–7.08 (m, 4H), 5.03 (d, J = 1.8 Hz, 1H), 4.86–4.83 (t, J = 2.3 Hz, 1H), 4.78–4.77 (d, J = 1.5 Hz, 1H), 4.05–3.97 (comp m, 4H), 3.40–3.36 (t, J = 3.9 Hz, 1H), 3.20–3.19 (d, J = 4.2 Hz, 1H), 2.57–2.52 (ddd, J = 2.7 Hz, 5.4 Hz, 11.1 Hz, 1H), 2.01–1.96 (m, 2H), 1.61–1.52 (m, 4H), 1.48–1.40 (m, 2H), 0.91 (s, 9H), 0.06 (s, 6H). FAB-HRMS: calcd for $C_{32}H_{43}NO_3$ [MH]$^+$ 518.3012, found 518.3103.

4.1.4.4. Methyl 2-(((3*R*,5*R*,6*S*)-2-oxo-5,6-diphenyl-3-(prop-2-ynyl)-morpholino)methyl)acrylate 12e. To a 0 °C cooled solution of amine **15** (6.735 g, 23.12 mmol) in DMF (23 ml) was added potassium carbonate (4.7 g, 34.68 mmol) followed by the dropwise addition of methyl 2-(bromomethyl)acrylate (4.48 g, 24.27 mmol). The resulting mixture was stirred at room temperature for 24 h. The reaction mixture was filtered, and the filtrate was portioned between ammonium chloride saturated aqueous solution and ethyl acetate, and separated. The aqueous layer was extracted with ethyl acetate for three times. The combined organic layer was washed with water for three times, then washed with brine, dried over magnesium sulfate anhydrous, filtered, and concentrated. Flash chromatography (hexanes/EtOAc, 8:1) gave 8.82 g (98%) of product **12e** as a light yellow sticky solid. $[\alpha]_D^{25} = -41.3$ (c1, CH_2Cl_2). IR (NaCl thin film): 3293, 3061, 3031, 2950, 2922, 2849, 1742, 1635, 1603 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23–7.14 (m, 6H), 7.01–6.99 (m, 2H), 6.73–6.71 (m, 2H), 6.27 (d, J = 1.4 Hz, 1H), 6.20 (d, J = 3.0 Hz, 1H), 5.70 (d, J = 1.4 Hz, 1H), 4.19 (d, J = 3.0 Hz, 1H), 4.16 (t, J = 4.0 Hz, 1H), 3.82 (s, 3H), 3.41 (d, J = 4.0 Hz, 1H), 3.82 (s, 3H), 3.41 (d, J = 4.4 Hz, 2H), 3.02 (ddd, J = 2.8 Hz, 3.6 Hz, 16.8 Hz, 1H), 2.91 (ddd, J = 2.4 Hz, 4.4 Hz, 16.8 Hz, 1H), 2.12 (t, J = 2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.8 0, 167.2 2, 137.2 9, 135.8 7, 134.4 8, 129.5 1, 128.5 0, 128.2 2, 127.3 9, 126.3 8, 82.3 8, 80.7 7, 71.2 0, 63.1 6, 62.6 1, 52.3 7, 52.3 0, 24.71. FAB-HRMS: calcd for $C_{24}H_{23}NO_4$ [MH$^+$] 390.1706, found 390.1700.

4.1.5. (3*S*,5*S*,6*R*)-4-Acryloyl-5,6-diphenyl-3-(prop-2-ynyl) morpholine-2-one 12f

To an ice-cooled solution of the secondary amine **15** (117 mg) in dichloromethane (4 ml) was added triethyl amine (72 µl) followed by acryloyl chloride (42.5 µl). The reaction mixture was stirred continously at 0 °C for 2 h or until the disappearance of the starting material spot on TLC. The solvent was removed, and the residue was subjected to flash chromatography (3:1 hexanes/EtOAc) to give 85 mg (61%) of product **12f** as colorless crystals. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32–7.20 (m, 4 H), 7.15–7.10 (m, 2H), 7.01–6.98 (m, 2H), 6.63–6.62 (d, J = 3.0 Hz, 1H), 6.54–6.52 (app d, J = 7.2 Hz, 2H), 6.31–6.27 (d, J = 13.8 Hz, 1H), 631–6.30 (d, J = 1.8 Hz, 1H), 5.59–5.55 (dd, J = 3.0 Hz, 9.3 Hz, 1H), 5.44–5.41 (dd, J = 3.9 Hz, 5.7 Hz, 1H), 5.18–5.17 (d, J = 3.0 Hz, 1H), 3.52–3.49 (ddd, J = 17.3 Hz, 3.0 Hz, 6.0 Hz, 1H), 3.17–3.09 (ddd, J = 17.3 Hz, 2.7 Hz, 3.9 Hz, 1H), 2.25–2.23 (t, J = 2.7 Hz, 1H). FAB-HRMS: calcd for $C_{22}H_{19}NO_3$ [MH]$^+$ 346.1365, found 346.1445.

4.1.6. (2*S*,3*R*,5*R*,6*S*)-4-(2-(hydroxymethyl)allyl)-5,6-diphenyl-3-(prop-2-ynyl)morpholin-2-ol 16

To a cooled solution (−78 °C) of compound **12e** (4.0 g, 10.27 mmol) was added DIBAL (41.1 ml, 1.0 M solution in dichloromethane) dropwise over a period of 20 min. The reaction mixture was stirred for an additional 20 min, and coldbath was removed. After stirring for another 20 min, the reaction mixture was quenched slowly with sodium potassium tartrate saturated aqueous solution, diluted with ethyl acetate, and then stirred at room temperature for 2 h. The mixture was transferred to a separatory funnel and was separated. The aqueous layer was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over sodium sulfate anhydrous, filtered, and concentrated. Flash chromatography (hexanes/EtOAc, 3:1 to 1:1) gave 2.95 g (79.3%) of product **16** as white foam. $[\alpha]_D^{25} = +60.0$ (c 1, CH_2Cl_2). IR (NaCl thin film): 3293, 2921, 2850 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.3 4–7.31 (m, 2H), 7.17–7.04 (m, 8H), 5.25–5.21 (m, 2H), 5.19–5.18 (d, J = 4.0 Hz, 1H), 4.88 (s, 1H), 4.44–4.31 (app q, J = 17.6 Hz, 1H), 4.08–4.07 (d, J = 4.0 Hz, 1H), 3.77–3.76 (d, J = 5.6 Hz, 1H), 3.58–3.53 (d, J = 17.6 Hz, 1H), 3.11–3.06 (m, 1H), 2.91–2.84 (dt, J = 24 Hz, 3.2 Hz, 1H), 2.81–2.69 (comp m, 2H), 2.21–2.19 (t, J = 3.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.19, 138.18, 134.48, 131.95, 127.89, 127.74, 127.59, 127.19, 127.17, 116.92, 96.72, 79.91, 78.58, 72.16, 67.32, 63.91, 56.88, 52.96, 18.84. HRMS-TOF: calcd for $C_{22}H_{25}NO_3$ [MH$^+$] 364.1834, found 364.1893.

4.1.7. 2-(((2*R*,3*R*,5*R*,6*S*)-2-Acetoxy-5,6-diphenyl-3-(prop-2-ynyl)morpholino)methyl)allyl acetate 17

To an ice-cooled solution of diol **16** (12.73 g, 35.03 mmol) in tetrahydrofuran (146 ml) were added pyridine (14.64 ml, 175.15 mmol) and acetic anhydride (13.64 ml, 140.10 mmol) followed by DMAP (860 mg, 20%). After removing the cold bath, the reaction mixture was stirred for 5–9 h or until the disappearance of starting material as monitored by TLC. Excess solvent was removed under rotavaporation. The residue was subjected to flash chromatography (hexanes/EtOAc, 5:1), and gave 13.38 g (85%) of product **17** as a light yellow solid. $[\alpha]_D^{25} = +57.3$ (c 1, CH_2Cl_2). IR (NaCl thin film): 3290, 2929, 2849, 1740 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.2 8–7.2 6 (m, 2H), 7.16–6.97 (m, 8H), 6.07 (d, J = 8.4 Hz, 1H), 5.31 (d, J = 3.2 Hz, 1H), 5.23 (s, 1H), 5.11 (s, 1H), 4.90 (d, J = 13.8 Hz, 1H), 4.73 (d, J = 13.8 Hz, 1H), 4.00 (d, J = 3.2Hz, 1H), 3.44 (d, J = 14.0 Hz, 1H), 3.27 (ddd, J = 3.6 Hz, 3.6 Hz, 7.6 Hz, 1H), 2.83 (d, J = 14.0 Hz, 1H), 2.58 (ddd, J = 2.8 Hz, 4.4 Hz, 18.0 Hz, 1H), 2.47 (dt, J = 18.0 Hz, 3.2 Hz, 1H), 2.19 (s, 3H), 2.12 (s, 3H), 2.07 (t, J = 2.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.7 4, 169.1 6, 141.2 7, 137.9 4, 134.7 8, 131.5 2, 127.6 8, 127.6 4, 127.3 5, 126.8 9, 115.3 6, 94.5 0, 79.6 6, 78.9 0, 77.2 2, 71.6 2, 65.2 9, 63.0 9, 54.8 8, 51.3 7, 21.2 9, 21.1 6, 18.9 6. HRMS-TOF: calcd for $C_{27}H_{29}NO_5$ [MH$^+$] 448.2125, found 448.2128.

4.1.8. IMPK precursor 19

To a 0 °C cooled solution of the diol **16** (55 mg, 0.1513 mmol) and 1,2-di(pyridin-2-yl)disulfane (35.7 mg, 0.1589 mmol) in dichloromethane (0.8 ml) was added Bu_3P (39 µl, 0.1513 mmol). The reaction mixture was warmed up to room temperature and stirred for 12 h. The solvent was removed, and the residue was subjected to column chromatography (5:1 to 3:1 hexanes/EtOAc), provided 53 mg (77%) of product. To a solution of the above product (53 mg, 0.1161 mmol) in DMF (0.2 ml) were added imidazole (39.6 mg, 0.5805 mmol), TBSCl (34.9 mg, 0.2322 mmol), and a catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 36 h to remove the solid and was then concentrated. Flash chromatography (5:1 hexanes/EtOAc) gave 54 mg (81%) of product **19**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.47–8.44 (m, 1H), 7.53–7.47 (m, 1H), 7.34–6.97 (m, 12H), 5.36 (s, 1H), 5.28–5.27 (d, J = 4.2 Hz, 1H), 5.14–5.12 (d, J = 10.0 Hz, 1H), 5.05 (s, 1H), 4.30–4.25 (d, J = 19.0 Hz, 1H), 4.12–4.07 (d, J = 19.0 Hz, m 1H), 4.05–4.04 (d, J = 4.2 Hz, 1H), 3.50–3.45 (d, J = 18.8 Hz, 1H), 3.07–3.02 (ddd, J = 4.8 Hz, 4.8 Hz, 10.0 Hz, 1H), 2.86–2.81 (d, J = 18.8 Hz, 1H), 2.67 (t, J = 3.2 Hz, 1H).

4.1.8.1. Cyclopentenone 18. *Procedure A*: To a solution of acetate **17** (2.56 g, 5.720 mmol) in dichloromethane (57.2 ml) was added dicobalt octacarbonyl (2.162 g, 6.292 mmol). The resulting dark purple suspension was stirred at room temperature for 2 h or until the disappearance of the starting material as monitored by TLC. The reaction solution was diluted to 114.4 ml and cooled to 0 °C. The first batch of *N*-methyl morpholine N-oxide (3.02 g, 25.74 mmol) was slowly added as a solid to the reaction, and stirred for 30 min before removing the cold bath. After 2 h, the reaction mixture was cooled down to 0 °C, and a second batch of *N*-methyl morpholine N-oxide was added and stirred for 30 min and then for an additional 21 h at room temperature. The purple reaction mixture was filtered through Celite and concentrated. The residue was subjected to flash chromatography (hexanes/EtOAc, 2:1 to 1:1) to provide compound **18** as light yellow solid 1.24 g (45.6%). $[\alpha]_D^{25} = +24.8$ (*c* 1, CH_2Cl_2). IR (NaCl thin film): 2905, 2832, 1742, 1714, 1630 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.2 9–7.0 3 (m, 10H), 5.93 (d, J = 8.6 Hz, 1H), 5.92 (d, J = 1.6 Hz, 1H), 5.41 (d, J = 3.2 Hz, 1H), 4.68 (d, J = 11.0 Hz, 1H), 4.36 (d, J = 11.0 Hz, 1H), 3.89 (d, J = 3.2 Hz, 1H), 3.00 (d, J = 11.6 Hz, 1H), 2.99 (ddd, J = 3.6 Hz, 8.6 Hz, 11.6 Hz, 1H), 2.83 (dd, J = 3.6 Hz, 14.0 Hz, 1H), 2.45–2.41 (m, 1H), 2.43 (d, J = 18.4 Hz, 1H), 2.25 (s, 3H), 2.04 (s, 3H), 1.91 (d, J = 18.4 Hz, 1H), 1.85 (d, J = 11.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 205.8 5, 176.8 9, 171.0 0, 169.2 8, 137.3 4, 134.1 5, 130.8 1, 129.9 5, 128.0 3, 128.0 0, 127.9 7, 127.9 1, 127.8 6, 127.2 0, 125.9 1, 96.3 1, 79.1 3, 67.9 2, 66.5 8, 60.3 0, 56.2 0, 47.3 5, 44.1 4, 30.0 4, 21.2 7, 20.9 6. HRMS (TOF-ESI): calcd for $C_{28}H_{29}NO_6$ $[MH]^+$ 476.1995, found 476.20495. Enantiomer: $[\alpha]_D^{25} = -24.9$ (*c* 1, CH_2Cl_2).

Procedure C: To a solution of acetate **17** (3.682 g, 8.228 mmol) in toluene (164 ml) was added dicobaltoctacarbonyl solid (3.113 g, 9.050 mmol), the resulting dark red solution was stirred at room temperature for 1 h. DMSO (6.06 ml, 82.28 mmol) was introduced, and the resulting mixture was then heated to 110 °C for 2–3 h or until the disappearance of the complex spot as monitored by TLC. The reaction mixture was cooled down to room temperature, and the solvent was removed by rotavaporation. The residue was subjected to flash chromatography (hexanes/EtOAc: 3:1 to 2:1 to 1:1) to give compound **18** as light yellow solid 3.21 g (82%).

4.1.8.2. Cyclopentenone 10a. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.24–7.16 (m, 7H), 7.12–7.09 (m, 2H), 7.03–7.00 (m, 2H), 6.14–6.14 (d, J = 3.6 Hz, 1H), 5.89 (s, 1H), 4.28–4.27 (d, J = 3.6 Hz, 1H), 3.49–3.44 (dd, J = 3.2 Hz, 13.6 Hz, 1H), 3.31–3.27 (dd, J = 6.0 Hz, 10.8 Hz, 1H), 3.01 (br, 1H), 2.71–2.64 (t, J = 12.4 Hz, 1H), 2.50–2.44 (dd, J = 6.4 Hz, 18.4 Hz, 1H), 1.88–1.83 (dd, J = 2.4 Hz, 21.2 Hz, 1H), 1.74–1.69 (t, J = 22.0 Hz, 1H). FAB-HRMS: calcd for $C_{23}H_{21}NO_3$ $[MH^+]$ 360.1521, found 374.1398.

4.1.8.3. Cyclopentenone 10b. $[\alpha]_D^{25} = +135.3$ (*c* 1, CH_2Cl_2). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.3 2–7.0 2 (m, 10H), 6.24 (d, J = 3.6 Hz, 1H), 5.86 (d, J = 1.5 Hz, 1H), 4.25 (d, J = 3.6 Hz, 1H), 3.42–3.36 (dd, J = 3.6 Hz, 13.5 Hz, 1H), 3.26–3.21 (dd, J = 3.3 Hz, 12.3 Hz, 1H), 3.02 (d, J = 10.8 Hz, 1H), 2. 87–2.78 (m, 1H), 2.30 (d, J = 18.5 Hz, 1H), 2.14 (d, J = 18.5 Hz, 1H), 1.95 (d, J = 10.8 Hz, 1H), 1.51 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 206.6 61, 181.5 5, 169.0 3, 135. 73, 129.8 8, 128.6 5, 128.5 7, 128.4 5, 128.0 4, 128.0 1, 125.6 5, 83.3 6, 66.8 4, 64.0 2, 58.6 3, 48.3 0, 43.5 0, 30.9 5, 24.6 7. HRMS-TOF: calcd for $C_{24}H_{23}NO_3$ [MH+] 374.1676, found 374.1748.

4.1.8.4. Cyclopentenone 20. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.47–8.45 (m, 1H), 7.54–7.48 (m, 1H), 7.27–7.02 (m, 12H), 5.90–5.89 (d, J = 2.0 Hz, 1H), 5.31–5.30 (d, J = 4.2 Hz, 1H), 4.94–4.91 (d, J = 10.0 Hz, 1H), 3.92 (s, 2H), 3.79–3.78 (d, J = 4.2 Hz, 1H), 3.08–3.05 (d, J = 17.2 Hz, 1H), 2.96–2.90 (dd, J = 4.8 Hz, 18.0 Hz, 1H), 2.78–2.70 (ddd, J = 4.4 Hz, 9.6 Hz, 18.4 Hz, 1H), 2.51–2.44 (d, J = 24.8 Hz, 1H), 2.42–2.34 (app t, J = 14.8 Hz, 1H). 1.93–1.86 (d, J = 24.8 Hz, 1H), 1.83–1.79 (d, J = 17.2 Hz, 1H), 1.01 (s, 9H), 0.29–0.21 (d, J = 29.2 Hz, 6H).

Acknowledgments

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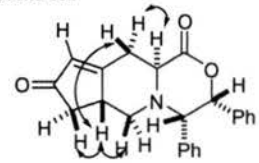
11. (2-(Bromomethyl)allyloxy)(*tert*-butyl)dimethylsilane was prepared from 2-methyleneпropane-1,3-diol in 2 steps by mono protection of the diol followed by *N*-bromosuccinimide bromination.
12. (4-(Bromomethyl)pent-4-enyloxy)(*tert*-butyl)dimethylsilane was prepared from ethyl 3-bromopropanoate through a modified procedure as reported: Jew, S.-U. et al *Tetrahedron: Asymmetry* **2002**, *13*, 155–159.
13. nOe analysis of compound **10a**



observed nOe correlations

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17. CCDC 690517 contains the supplementary crystallographic data for this paper. These data can be free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/deposit.

Appendix 4: Research Training Proposal

Total Synthesis of Berkeleydione

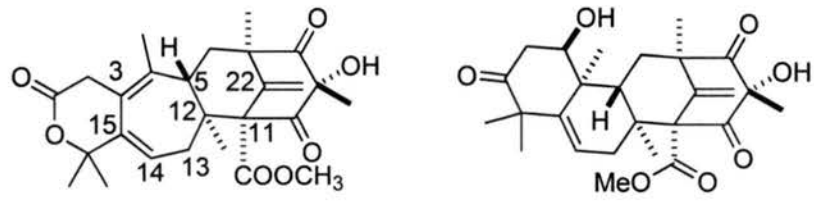
Specific Aims

This proposal aims to develop strategies of convergent total synthesis of berkeleydione via a combination of classical transformations-Diels-Alder reaction, 1,3-dipolar cycloaddition, and organometallic chemistry-Stille coupling, ring closing metathesis.

Background and Significance

Terpenes, originated from isoprenes, often found existing as hybrids, such as terpene alkaloids and terpene polyketides (meroterpenoids), represent one of the largest and most diverse classes of secondary metabolites, and have attracted an enormous amount of attention due to the synthetic challenges of their complex structures in terms of difficulty as well as a broad range of biological properties, ranging from anti-cancer and anti-malarial activities to tumor promotion and ion-channel binding.[1] Berkeleydione (**1**) and berkeleytrione (**2**) (**Fig. 1**) were isolated in 2004 by Stierle and coworkers from an acid mine organism *Penicillium* sp. from the Berkeley Pit Lake in Butte, Montana. They were found to inhibit both MMP-3 and Casp-1 in the micromolar range, and berkeleydione (**1**) also exhibited selective activity toward nonsmall cell lung cancer NCI-H460 with a $\log_{10}$ GI_{50} of –6.40.[2a]

Matrix metalloproteinase-3 (MMP-3) and caspase-1 (Casp-1) are two different signal transduction enzymes. As a new therapeutic approach to the treatment of cancers, MMP-3 inhibitors block the activity of proteolytic enzymes (matrix metalloproteinases) used by tumor cells to promote metastatic spread, they might also halt tumor progression and could be used as low toxicity complements to cytotoxic therapies.[2a] Casp-1 was the first of a novel type of cysteine proteases responsible for converting interleukin-1β to its mature form in monocytes, which is a key mediator of inflammation. Casp-1 is believed to be analogous to CED-3, a cell death protein in *Caenorhabitis elegans*. Casp-1 inhibitors have shown some promise in delaying the onset of Huntington's diease and amyotropic lateral sclerosis and in mitigating the effects of stroke.[2b,2c] However, as drug-resistance continues to pose a threat to strategies devoted to the treatment of cancer, the discovering of novel, more effective agents to perpetuate the viability of these strategies is very important.



Berkeleydione **1** Berkeleytrione **2**

Figure 1

Following berkeleydione and berkeleytrione's isolation, berkeleyacetals were isolated in 2007 from the same Pit Lake.[3] In 2008, three new structurally related polyketide-terpenoid hybrids were isolated, however, from *Penicillium minioluteum* 03HE3-1 obtained from sea mud of Heita Bay, Japan.[4] Studies on the biosynthesis of meroterpenes produced by *Aspergillus* and *Penicillium* have suggested that this group of metabolites are derived from farnesyl pyrophosphate and 3,5-dimethylorsellinic acid.[5] A detailed biosynthetic pathway of

the berkeleydione family was proposed by Kusumi and coworkers. The feature of a highly oxidized and highly substituted tetracycle possessing four quaternary carbons provides an initial synthetic challenge for berkeleydione. To date, there has not been published any total synthesis or synthetic approaches toward this polyketide-terpenoid.

Research Design and Methods

A. Synthesis Plan A

Plan A for the synthesis of berkeleydione (**1**) is outlined in Figures 2, 3 and 4. The general idea is to construct the molecule in convergent manner. Retrosynthetically, disconnection of B ring reveals two moieties, the vinylstanne **c** containing the A ring and the allylic acetate compound **d** containing the CD ring as shown in Figure 2. A Pd-catalyzed Stille coupling reaction will connect the two pieces together, which in the presence of Grubbs II catalyst, will undergo a ring closing metathesis to form the seven-membered B ring. The resulting advanced intermediate **a** will be further transformed to the target molecule **1** after double bound manipulation and isomerization. Finally, the bridgehead carbonyl is converted to the corresponding vinyl alkene. As shown in Figure 3, portion **c** could be prepared from a two-component coupling reaction of an aldehyde, a vinyl bromide in the presence of a bulkyl Grignard reagent. The highly substituted bicycle **d** (CD ring system) will be constructed from a regio- and stereo-selective intermolecular Diels-Alder reaction followed by α,α'-annulation and further functional group transformations as shown in Figure 4.

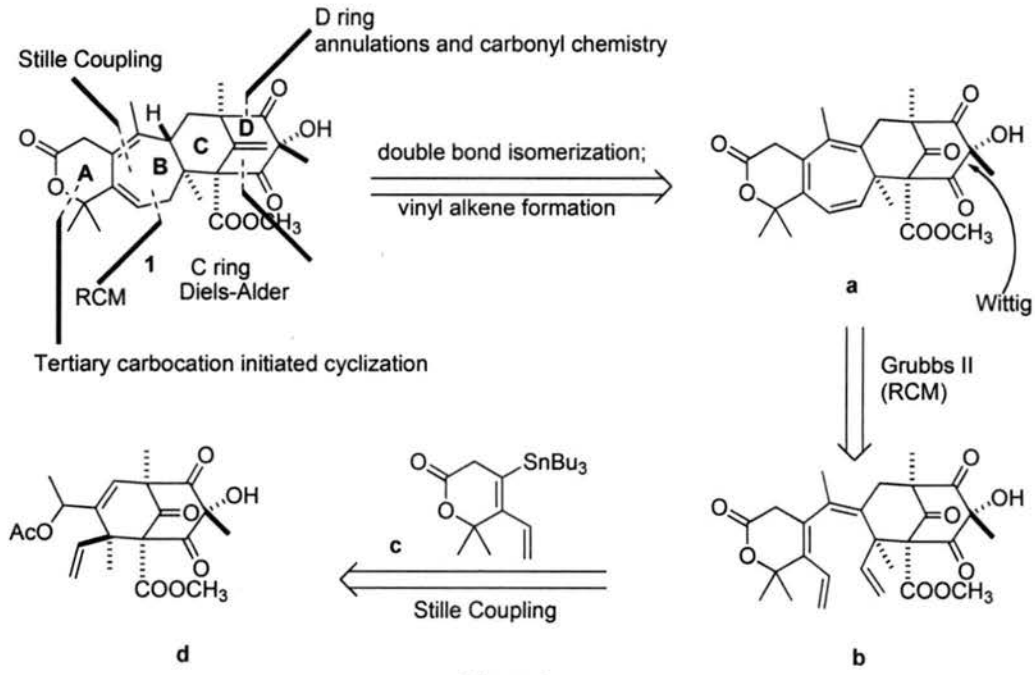


Figure 2

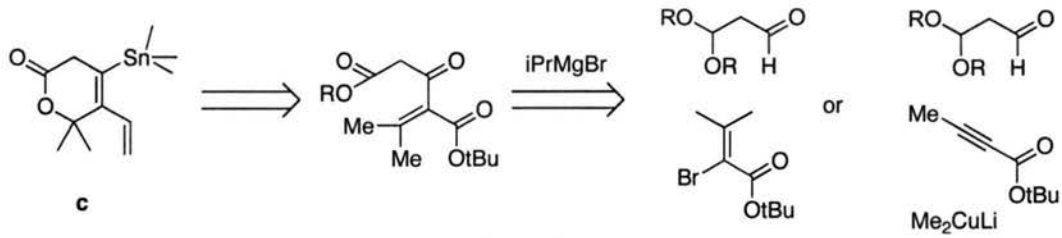


Figure 3

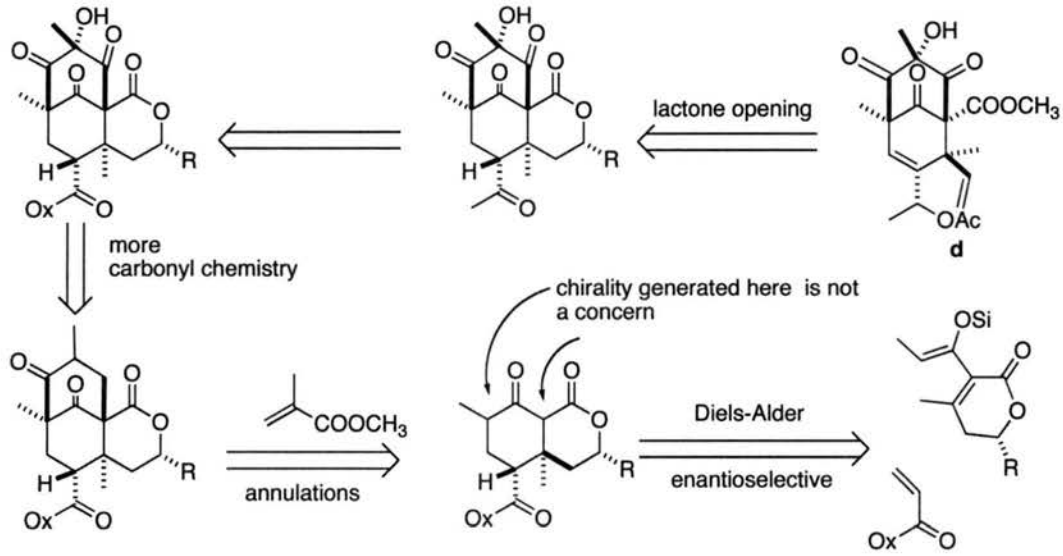
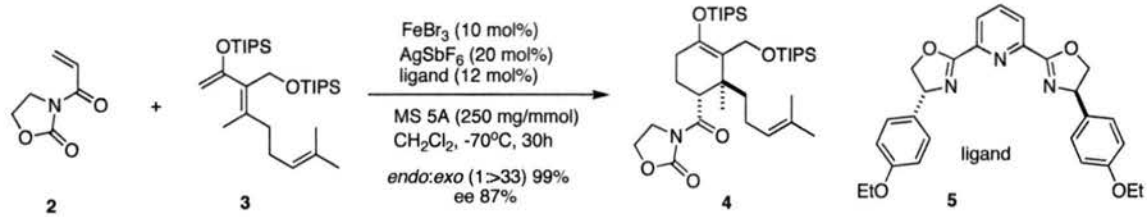


Figure 4

B. Predicting Selectivity of Enantioselective Diels-Alder Reactions with Polysubstituted Acyclic Dienes

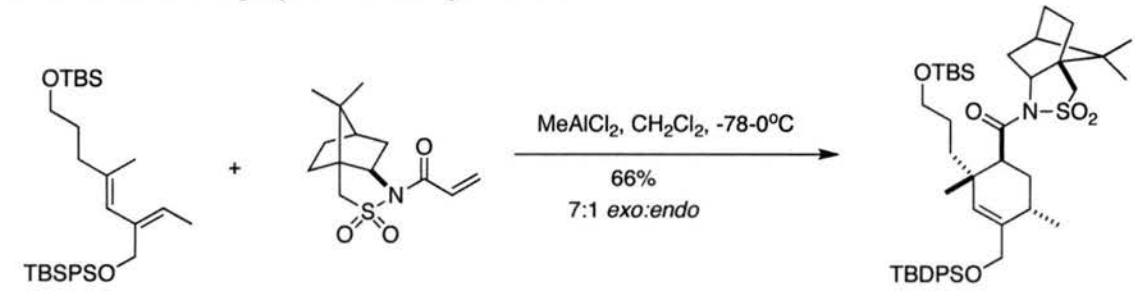
The presence of polysubstituted methylenecyclohexanes or cyclohexanones with three contiguous quaternary carbon centers in berkeleydione and related merotepenoids presents enormous synthetic challenges to organic chemists, especially in enatioselective synthesis. The methods available for their constructions are mainly racemic synthesis and rely on classical transformations such as enolate alkylation, Michael addition, [3,3]-sigmatropic rearrangement, aromatic ring manipulation.[6] Diels-Alder reaction is believed to be one of the most powerful reactions that could lead to strongly higher molecular complexity from simple starting materials in terms of molecular size, topology, stereochemistry, functionality, and appendages. However, the studies and applications of the enantioselective Diels-Alder reactions to the above mentioned targets are still rare except the successful employment in synthesis of bicyclic subunits of phloroglucinols reported by Shibasaki and coworkers recently.[7]



Scheme 1

Among the available strategies, the Diels-Alder method developed by Shibasaki and coworkers seems most efficient and appropriate for the construction of the densely substituted methylenecyclohexane ring in berkeleydione (**1**). Shibasaki's method utilizes a cationic Fe^{3+}-Ar-pybox complex as a catalyst in the first example of an enantioselective Diels-Alder reactions with acyclic 4,4-disubstitued 1,3-dienes (such as **3**) and 3-acryloyl-1,3-oxazolidin-2-ones (such as **2**). As expected, the *endo-exo* selectivities were significantly influenced by the substituents on the dienes, and the enantioselectivities were in seventies and eighties. Among their studies, reaction between **2** and **3** gave exceptional regio- and good entantio-selectivities (**Scheme 1**), which provides optimistic opportunities in the synthesis of polysubstituted cyclohexane C ring in berkeleydione in a similar manner, however with acyclic 1,2,3,4,4-pentasubstituted 1,3-dienes instead (**Fig. 4**). It is predicted that the reactions would need reconsiderations of all the reagents utilized in Shibasaki's method because of the more substitution pattern and the conjugation of the diene with an electron withdrawing lactone, which makes the diene less electron sufficient hence less reactive.

The chirality could also be derived from the reactants, especially from the dienophile with a chiral auxillary.[8] Roush and coworkers employed earlier a stronger Lewis acid $MeAlCl_2$ promoted enantioselective Diels-Alder reactions of 1,1,3,4-tetrasubstitued dienes stereocontrolled by a chiral dienophile N-acryloyl sultam in their synthetic studies of quartromicins (**Scheme 2**).[9] This simpler protocol is another potentially useful strategy for the construction of polysubstituted cyclohexanones.



Scheme 2

In Diels-Alder reactions of the planned 1,2,3,4,4-pentasubstituted dienes with dienophiles (**Fig. 4**), there are four possible preassemblies of the diene and dienophile for the *exo* approaching giving the desired relative stereochemistry of the substituents, the selectivity of which depends on the nature of the Lewis acids and ligands present in the reaction systems (**Fig. 5**, chelation is not shown for clarity). Similarly, there are also four possible corresponding preassemblies for the *endo* approaching (not shown), which usually are not favored because of steric hindrance. Screening of suitable Lewis acids, chiral ligands and catalysts as well as appropriate reaction conditions would possibly be a tedious and time-consuming task as well as a good opportunity for a better understanding of the chirality

control chemistry. The removal of the auxiliaries such as oxazolidinone or the sultam usually involves hydride reduction via thioester, both of which might also affect other functionalities, so careful design of the reactants is important.

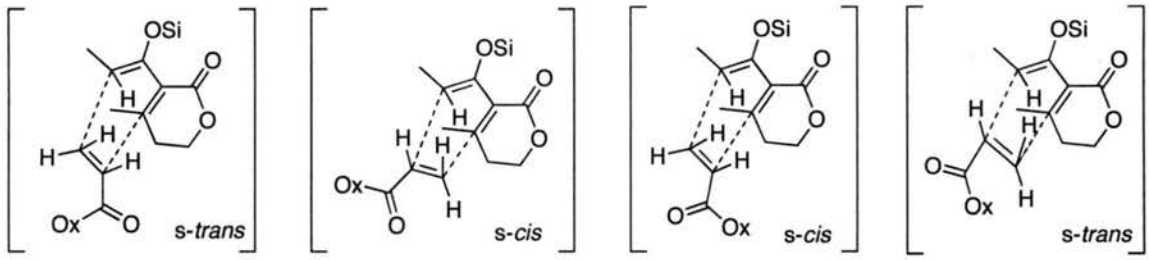
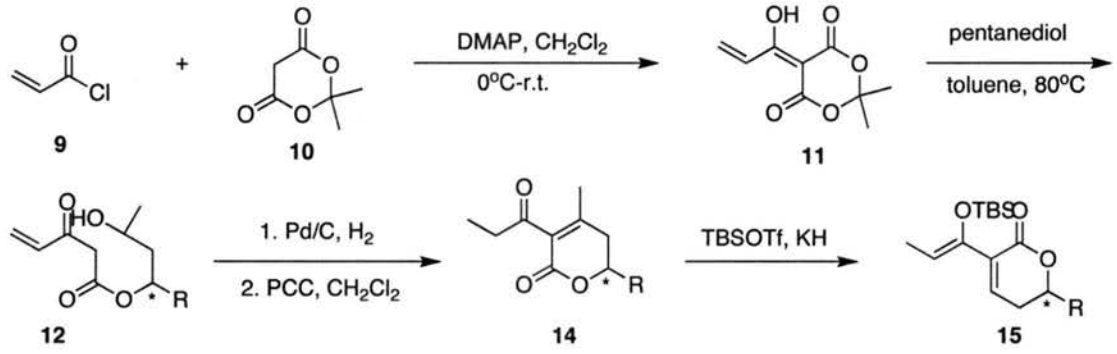


Figure 5

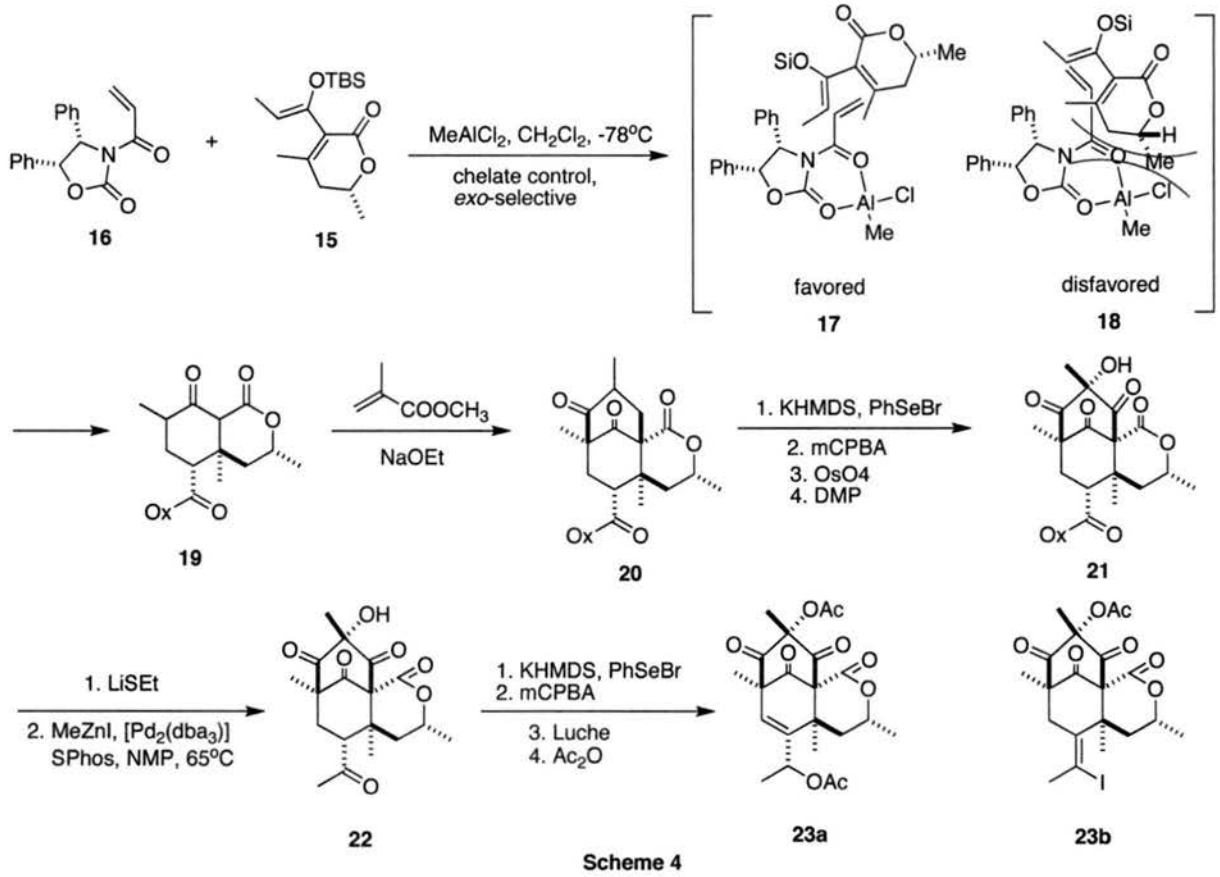
C. Execution of the Diels-Alder Reaction and Functionalized CD Ring Construction

The diene precursor (**15**) is an analog to the known dictyopyrones, which have been reported their syntheses by Oshima and coworkers.[10] The proposed construction of the diene (**15**) is a modification of their methods (**Scheme 3**). Coupling of acrylol chloride with the Meldrum's acid followed by transesterification with chiral pentanediol or 3-hydroxyl butanol will give intermediate **12**, which can be further converted to diene **15** by a hydrogenation, oxidative cyclization and enolization sequence. The R group in the diene could be hydrogen, or methyl group as a chiral center, which might be helpful in stereocontrol of the Diels-Alder reaction.



Scheme 3

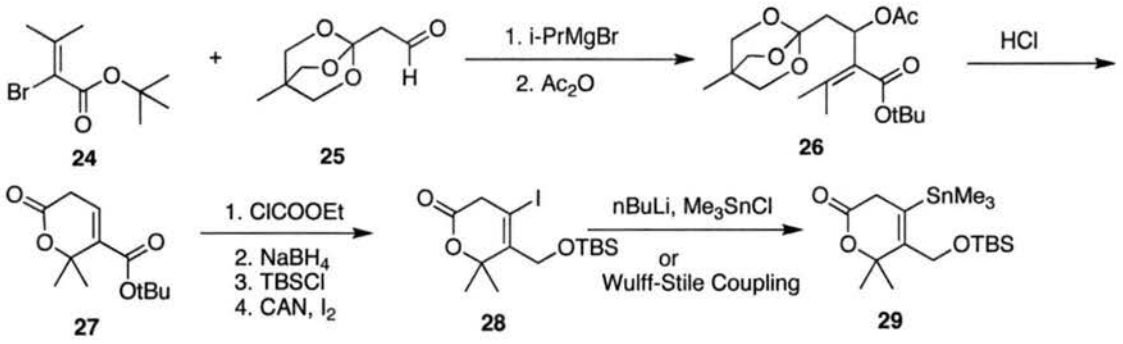
Following the successful synthesis of diene, Diels-Alder cycloaddition between **15** and **16** is planned to perform under Lewis acid (such as $MeAlCl_2$, $TiCl_4$, $SnCl_4$, etc.) promoted conditions as shown in Scheme 4. The predicted product **19** is derived from the *exo*-selective and chelation controlled preassembly **17** with an s-*cis* configuration which has less steric hindrance compared to the s-*trans* assembly **18**. The chiral methyl group on the diene also favors **17**.



Scheme 4

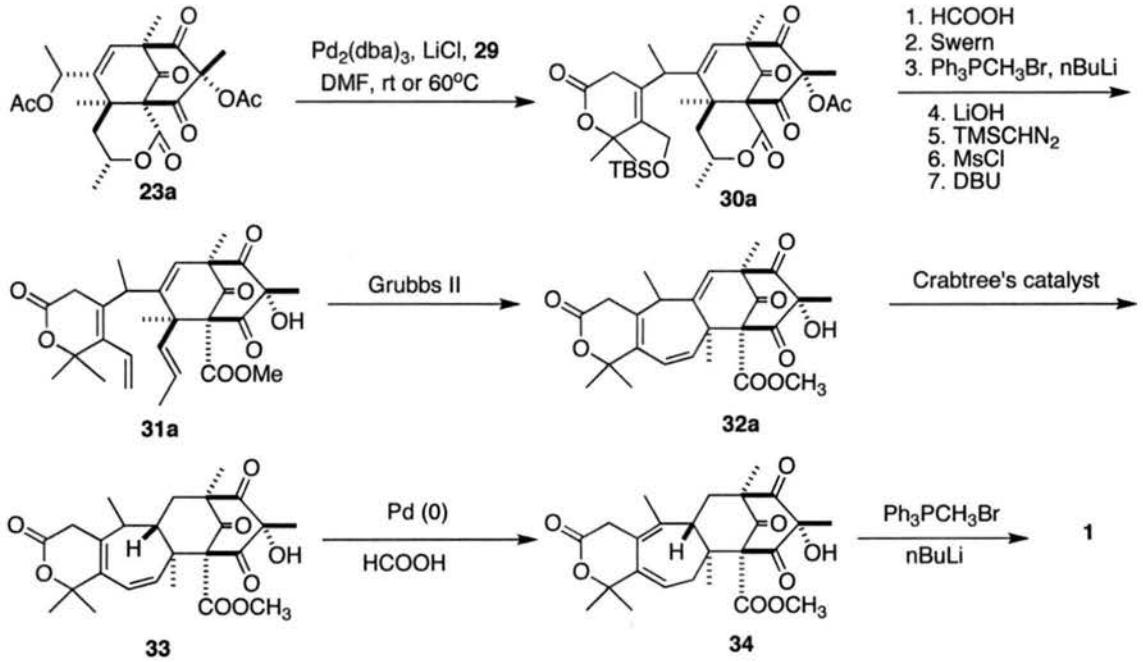
Next step of the planned synthesis is to installation of the D ring via α,α'-annulation with 2-methylacrylate (**19** to **20**).[11] A five-step sequence with a modification of that reported by Nicolaou and coworkers[12] will install the C9 tertiary alcohol and the C10 carbonyl on the D ring (**20** to **21**). Following the successful installation of the D ring, cleavage of the auxiliary comes next via a thioester, which is then converted to methyl ketone compound (**21** to **22**).[13] Enolization with KHMDS followed by trapping with phenylselenium bromide and oxidation with *m*-CPBA provide the allylic alcohol with a subsequent protection to give allylic acetate **23a** or alternatively, vinyl iodide **23b** could be obtained from **22**. Thus, the fully functionalized CD ring system is constructed enantioselectively in 17 steps from commercially available acrylol chloride and Meldrum's acid. The stereochemistry is controlled maily by the chiral auxiliary while the chiral diene is a minor assistance. For D ring cyclization, a number of approaches like radical cyclization,[14] nitrile oxide-allene cycloaddition,[15] ring closing metathesis,[16] lactone reduction induced rearrangement,[17] have been reported in synthetic studies of phloroglucins such as garsubellin A and hyperforin[6] possessing close bicyclic subunits to berkeleydione, thus providing alternative methods for D ring construction in berkeleydione.

D. Stille Coupling, Ring Closing Metathesis and Completion of Berkeleydione



Scheme 5

The vinylstanne compound **29** will be constructed in 8 steps (**Scheme 5**). Coupling of **24** and **25**[18] followed by activation of the resulting allylic alcohol as acetate gives **26**. Deprotection of the orboester followed by acid catalyzed lactone cyclization gives **27**. A four-step sequence, selective reduction of the t-Boc ester, protection of the resulting hydroxyl group followed by oxidative iodination provides **28**, which is then transformed to organotin compound **29**. Successful π-allyl Stille cross coupling reactions of vinylstanne with allyllic acetate, or trifluoroacetate, triflate, or carbonate in the presence of Pd-catalyst such as $Pd(Ph_3P)_4$, $PdCl_2(Ph_3P)_2$, $[Pd_2(dba)_3\text{-}CHCl_3]$ with LiCl, CuI or $AsPh_3$ or a combination as the additives in DMSO, DMF, THF or NMP as solvent have been seen in literature.[19] So Stille coupling of **23a** and **29** should be able to furnish the carbon-carbon bond formation with the shown *E* configuration as the major isomer (**Scheme 7**, compound **30a**). Or, alternatively, coupling **23b** and **29** gives the corresponding product **30b** (not shown in scheme). At this stage the resulting di-ene compound will be converted to the RCM precursor **31a** (or **30b to 31b**) in seven steps using conventional transformations. The following ring closing metathesis constructs the B ring to provide the triene compound **32a** (or **31b** to **32b**). Ring closing metathesis has become a very useful and successful tool for various sized carbocycle formation in natural product syntheses.[20] Even though no precedence of a double bond conjugated terminal olefin in the RCM tether has been seen, there is a good chance for the success of the designed ring closure. The left challenge is regio-selective enantio-selective hydrogenation of the C5-C6 double bond in C ring in the presence of di-ene in B ring followed by double bond isomerization. The conformation analysis of **32a** shows a very congested cage like top face so hydrogenation of C ring olefin from the top face might be problematic. However, **32b** conformation is flat and would be able to perform the desired asymmetric hydrogenation using Crabtree's catalyst to provide di-ene **33**,[21] which after Pd (0)-HCO_2H catalyzed olefin migration[22] and wittig olefination of the bridgehead carbonyl furnishes the non-racemic total synthesis of berkeleydione (**1**).



Scheme 7

E. Synthesis Plan B

A relatively concise racemic synthetic strategy of berkeleydione is planned based on a 1,3-dipoalr cycloaddition-fragmentation sequence for seven-membered B ring construction as outlined in Figure 7. After bridged ring fragmentation and H_2O elimination from intermediate **bb**, **aa** is obtained, and further elaborated to the final target.

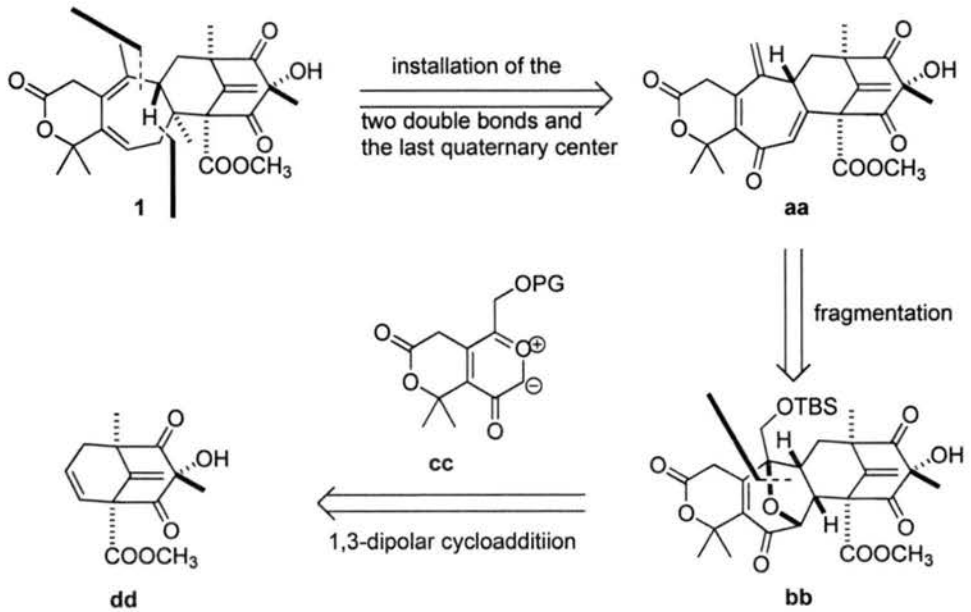


Figure 7

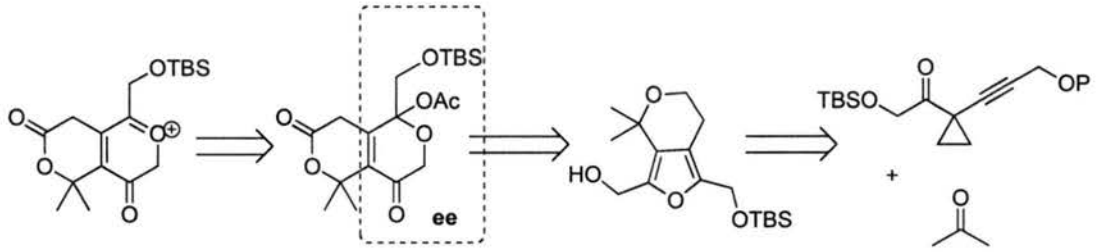
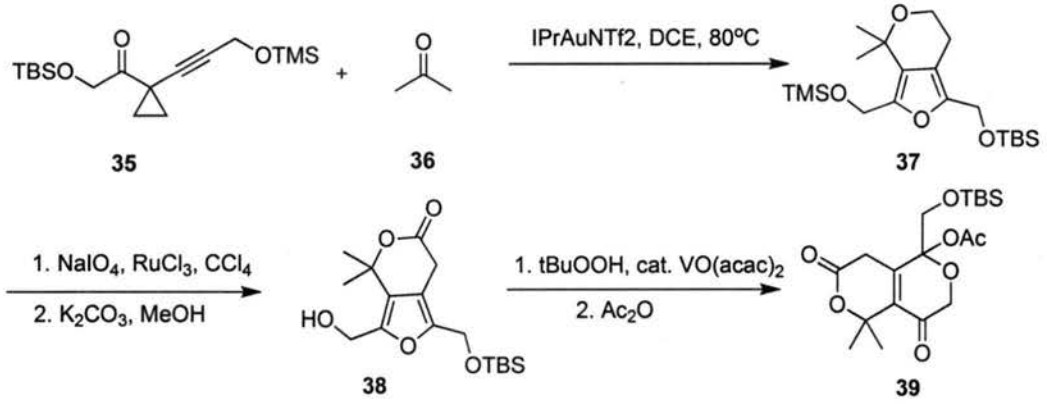


Figure 8

Cycloaddition of carbony ylid oxidopyrylium ion with alkene has been extensively studied since the nineteen fifties. 3-Pyrone acetal derivative **ee** (**Fig. 8**) in the rectangle is a widely used precursor of oxidopyrylium ion in seven-membered ring synthesis, first utilized by Wender and coworkers in their synthesis of phorbol ester.[23] It is usually prepared from substituted furan via oxidative ring expansion with *m*-CPBA followed by activation as the acetate.[24] In this case (**Scheme 8**), furan **37** is prepared efficiently from a [4+2] annulation reaction between cyclopropane alkyne **35** and acetone in the presence of gold-catalyst as shown in Scheme 8 according to most recent studies by Liming Zhang and coworkers.[25] Oxidation with in situ generated rhuthenium tetraoxide provides lactone **38**, then $VO(acac)_2$ catalyzed *m*-CPBA oxidation followed by acetate formation give pyrone acetal **39**.

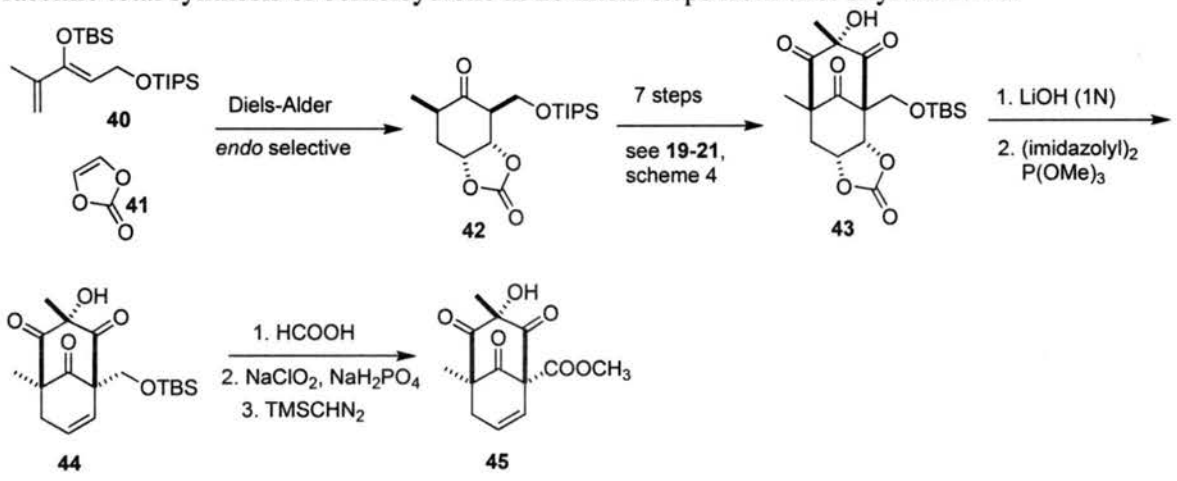


Scheme 8

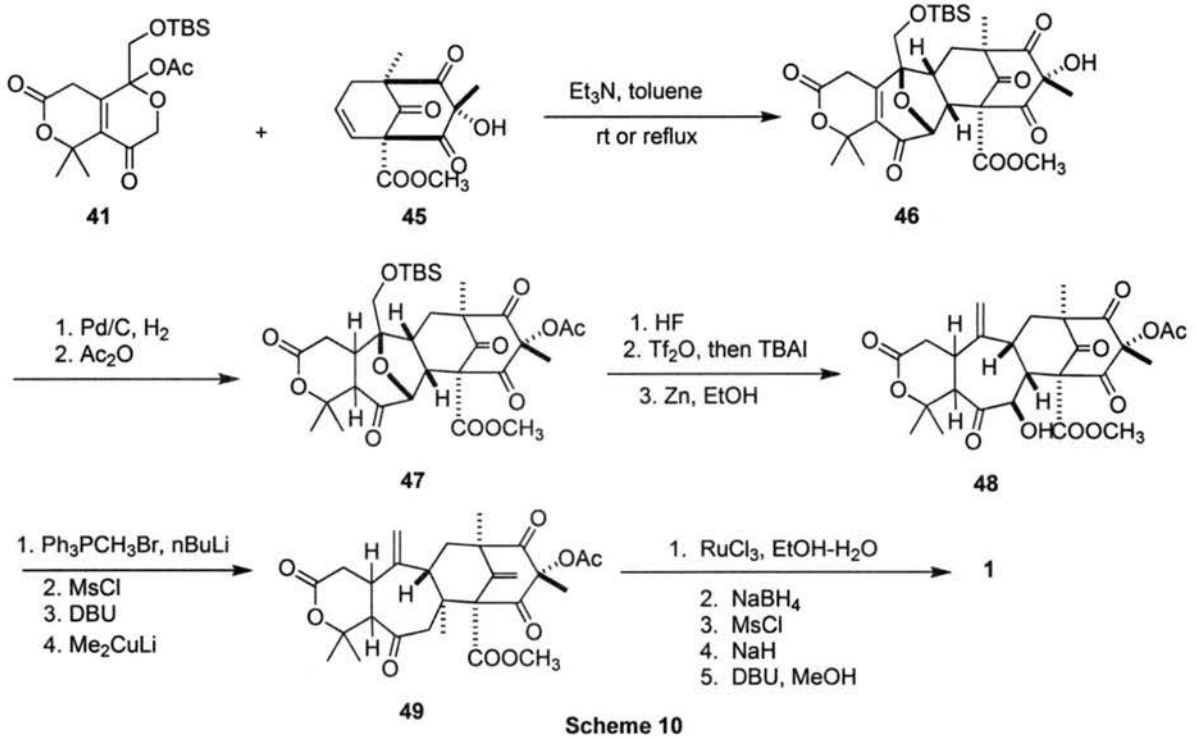
The bicyclic dipolarophile **45** is constructed using a similar protocol to that of **21** (**Scheme 4**) however in a racemic manner (**Scheme 9**). Diels-Alder cycloaddition of **40** with vinylene carbonate **41** gives the *endo*-selective product **42**, which is converted to tricycle **43** in 7 steps. Hydrolysis of the carbonate followed by subjection to Samuelsson conditions[26] provides alkene compound **44**. Then, deprotection of TBS group followed by oxidation and methylation of the resulting carboxylic acid furnishes dipolarophile **45** in 13 steps.

In synthesis plan A, two major concerns of the synthesis are the stereochemistry of the BC ring junction, and the generation of the two double bonds in B ring. In target **1**, the BC ring junction of the hydrogen and the methyl group at the quaternary carbon center is *trans*. However, It is predicted that the stereochemistry outcome of the 1,3-dipolar cycloadduct **46** is *cis* configuration (**Scheme 10**). So in the synthetic design, the methyl group is introduced at a later stage via a Michael addition (**48** to **49** step 4). Another potential strategy is an epoxidation/epoxide ring opening sequence, which might need more transformations. Thus, hydrogenation of the conjugated double bond followed by acetate

protection of the tertiary alcohol on D ring give **47**. Hydrofluric acid deprotection of the silyl ether group followed by iodide substitution and zinc promoted elimination provide the fragmentation product alcohol **48**.[23] Wittig olefination of the bridgehead carbonyl, elimination of the hydroxyl group via mesylate providing the conjugated compound, which is then treated with Me_2CuLi, $AlMe_3$ or $MeMgBr$[27] installs the methyl group with desired stereochemistry (**49**). Conformation analysis of the enone intermediate suggests that the Michael addition could occur from the bottom face of the molecule. The carbonyl group and the bridged oxygen on the B ring of **49** provide more opportunities for the two double bond generation. Indeed, the terminal olefin on B ring is isomerized to internal olefin using Ru-catalyst.[28] Reduction of the carbonyl on the B ring followed by elimination via mesylate is supposed to generate the second double bond at the desired position, accomplishing the racemic total synthesis of berkeleydione in 28 linear steps from enol silyl diene **40**.



Scheme 9



Scheme 10

F. Conclusion

In conclusion, two strategies are developed for the total synthesis of the highly oxygenated and unsaturated molecule berkeleydione. In the non-racemic synthesis, to the best of my knowledge, the first example of an asymmetric Diels-Alder reaction with an acyclic pentasubstituted diene is developed with a combination of stereocontrol by both chiral auxiliary dienophile and chiral diene. A novel ring closing metathesis is developed with conjugated olefins in the tether. In the racemic synthesis, the Diels-Alder reaction of 1,2,3-trisubstituted diene with vinylene carbonate adds a potential strategy for the synthesis of phloroglucinol subunits to the pool of the existed synthetic approaches. An intermolecular 1,3-dipolar cycloaddition is developed between an oxidopyrylium ion and a complicated dipolarophile enlarging the successful applications of the oxidopyrylium ion in seven-membered ring synthesis in natural products.

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