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DISSERTATION

I. STUDIES TOWARD THE TOTAL SYNTHESIS OF TRIPTOQUINONE A AND TRIPTININ A
II. CONJUGATE ADDITION OF SULFONYL CARBANIONS TO CHIRAL α,β-UNSATURATED OXAZOLINES

Submitted by Laura F. Basil
Department of Chemistry

In partial fulfillment of the requirements
for the Degree of Doctor of Philosophy
Colorado State University
Fort Collins, Colorado
Spring 2001

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COLORADO STATE UNIVERSITY

February 8, 2001

WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY LAURA F. BASIL ENTITLED "I. STUDIES TOWARD THE TOTAL SYNTHESIS OF TRIPTOQUINONE A AND TRIPTININ A II. CONJUGATE ADDITION OF SULFONYL CARBANIONS TO CHIRAL α,β-UNSATURATED OXAZOLINES" BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

Committee on Graduate Work

C. M. Elliott

Advisor

C. M. Elliott

Department Head

ABSTRACT OF DISSERTATION

I. STUDIES TOWARD THE TOTAL SYNTHESIS OF TRIPTOQUINONE A AND TRIPTININ A

II. CONJUGATE ADDITION OF SULFONYL CARBANIONS TO CHIRAL α,β-UNSATURATED OXAZOLINES

1. The synthesis of the natural products triptoquinone A and triptinin A was approached by a strategy that involved a tandem addition to a chiral 3,4-dihydronaphthyl oxazoline. The tandem addition of a vinyl lithium and a homoallylic iodo-electrophile was successful and highly stereoselective. The synthesis of the requisite oxazoline and the electrophile was developed. The tandem-addition product then underwent a ring-closing metathesis to close the C-ring thereby putting in place the triptinin/triptoquinone ring system and carbon backbone. Transformation of the oxazoline moiety into a quaternary methyl group was studied, as was the removal of an allylic alcohol protecting group.

II. Several examples of conjugate addition of sulfonyl carbanions to acyclic, chiral α,β-unsaturated oxazolines were shown to occur with very high stereoselectivity and good yield. In the examples where cyclization followed addition, three contiguous stereocenters were set in one reaction step. It was noted that the pK_a's of both the sulfonyl nucleophile and the oxazolinyl acceptor should be matched appropriately in order for the reaction to be efficient.

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All my life, my parents, Ron and Jane Frain, have been extremely emotionally and spiritually supportive. They gave my brother, sister and me a happy, carefree childhood and have made it possible for me to achieve my educational goals.

Lastly, but no means leastly, I would like to publicly thank the most important men in my life, my husband Tom and our son Daniel. Tom has been my soulmate and support system, without which this degree would have not been obtained. Daniel is a little boy with a great smile that makes everything worthwhile.

DEDICATION

To my loving husband, my B

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Chapter One

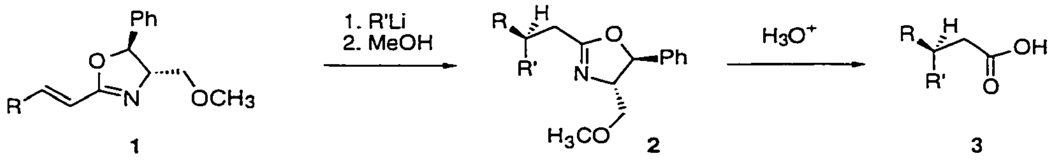
Studies Toward the Total Synthesis of Triptoquinone A and Triptinin A

I. Introduction

A. Conjugate Additions to Chiral α,β-Unsaturated Oxazolines

Chiral 2-oxazolines have found great use in asymmetric synthesis for three decades.[1] The oxazoline functionality has served not only as a carboxylic acid masking group, but also as a chiral promoter in many carbon-carbon bond-forming reactions. In 1975, Meyers and Whitten[2] first reported conjugate additions to chiral α,β-unsaturated oxazolines (Scheme 1). The chemical yields were modest to good, but more importantly the optical purity of the products was higher than any C-C bond that had been constructed to date. Because either enantiomer of the starting oxazoline could be easily obtained, this represented a synthesis of 3-substituted alkanoic acids, **3**, that allowed for both recovery of the chiral reagent and either enantiomer of the product.

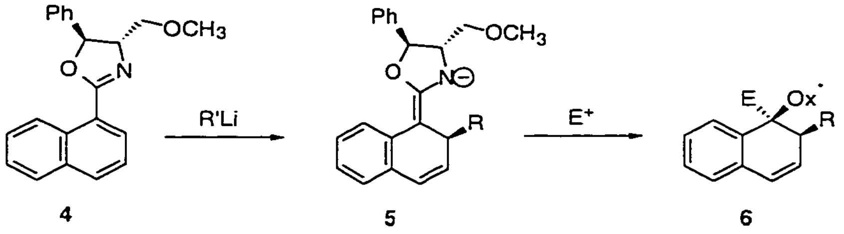
Scheme 1



R	R'	Overall yield, %	Optical purity, %
Me	*n*-Bu	38	91
Ph	*n*-Bu	64	>95
Ph	Et	66	97

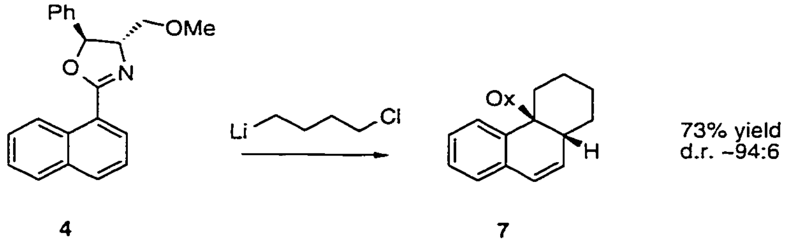
Taking advantage of the azaenolate **5** formed from initial addition, Barner and Meyers[3] reported tandem alkylations on chiral naphthyl oxazolines (Scheme 2). For example, when *n*-butyl lithium was added to oxazoline **4** followed by methyl chloroformate, the tandem addition product **6** was obtained in 88% yield with a high diastereomeric ratio (94:6). For the major diastereomer, the nucleophile (R) was *trans* to the electrophile. This pattern has been seen consistently with numerous examples of tandem addition reactions with intermolecular electrophiles.[1-4] It should be noted that, with one reaction sequence, two adjacent stereocenters are set very selectively. Importantly, one center is a quaternary carbon, which has been historically more difficult to make selectively than a tertiary carbon center.

Scheme 2



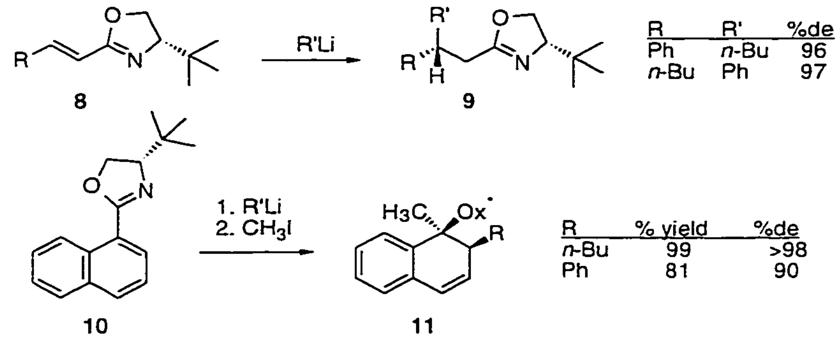
R	E^+	diastereomeric ratio	% yield
n-Bu	$MeCO_2Cl$	94:6	88
Ph	MeI	83:17	88

Meyers and Licini[5] reported an intramolecular variant of a tandem addition to a chiral naphthyl oxazoline. With the electrophile part of the nucleophile, a stereoselective annulation resulted to give compound 7. Interestingly, the electrophilic addition occurred on the same face as nucleophilic addition, giving the *cis* ring junction. This was counter to the many intermolecular examples. Presumably, the ring size restricted the *trans*-ring formation.



More recently, it has been shown that oxazolines derived from amino-alcohols devoid of a potential chelating group, such as a methoxy, are capable of inducing great stereoselectivity (Scheme 3).[6] In fact, conjugate additions of *t*-leucinol derived oxazolines have resulted in very high diastereomeric ratios both with acyclic α,β-unsaturated oxazolines and the more conformationally rigid naphthyl oxazolines.

Scheme 3

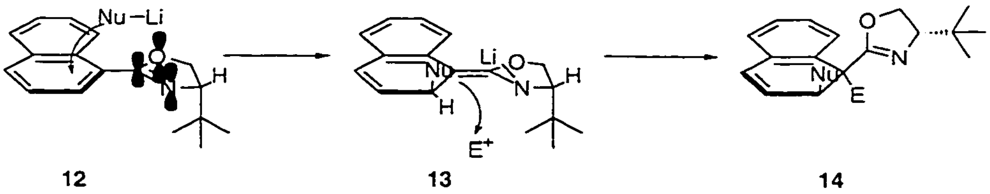


R	R'	%de
Ph	*n*-Bu	96
n-Bu	Ph	97

R	% yield	%de
n-Bu	99	>98
Ph	81	90

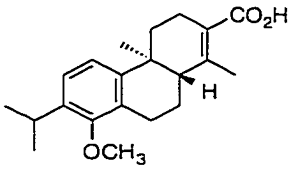
The rationale for the selectivity was based on coordination and steric arguments (Scheme 4).[6a] The π-cloud of the oxazoline functions as a Lewis base, attracting the alkyl lithium to the face distal from the bulky *t*-butyl group. Electrophilic addition then occurs on the opposite face from nucleophilic addition. Other than alkyl lithiums, a variety of nucleophiles have been shown to undergo the conjugate addition including Grignard reagents, lithium dialkylamides,[7] and trialkylsilyl lithiums.[8]

Scheme 4

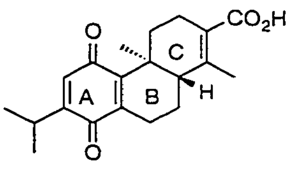


B. Triptoquinone A and Triptinin A Background

Triptoquinone A, **16**, and triptinin A, **15**, are members of a family of structurally related diterpenoid natural products isolated from the plant *Tripterygium wilfordii* var *regelii*.[9,10] This plant has been used in traditional Chinese medicine to treat rheumatoid arthritis and spondylitis. With rheumatoid arthritis, a strong relationship has been reported between increased interleukin-1 (IL-1) production and degree of inflammation. Triptoquinone A has been shown to inhibit IL-1 α and IL-1 β release from lipopolysaccharide-stimulated human peripheral mononuclear cells.[9] It has also been shown to inhibit the expression of inducible nitric oxide synthase (iNOS) gene with IC_{50}=25.5 μM in rat glial cell line CCL-107-C6.[11] Induction of iNOS by various stimuli contribute to septic shock, auto-immune and inflammatory diseases. Triptinin A has been indicated as a competitive leukotriene-D_4 (LTD_4) antagonist using smooth tracheal muscles of guinea pig.[10] Overproduction of LTD_4 leads to asthmatic attacks. It is clear that **15** and **16** are important compounds rich with biological activity and with great potential.



(+)-Triptinin A, **15**

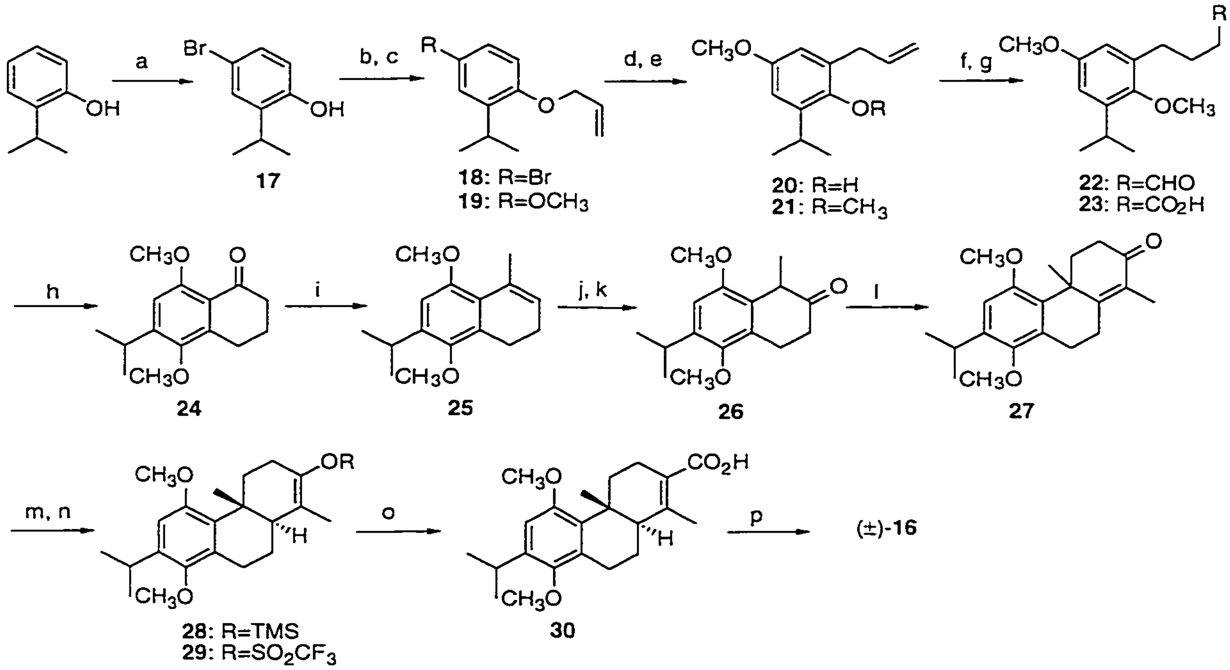


(+)-Triptoquinone A, **16**

Because of its biological relevance and interesting structural features, Shishido et al.[12] embarked on the first total synthesis of (±)-triptoquinone A and (+)-triptoquinone A. The racemic synthesis is shown in Scheme 5.

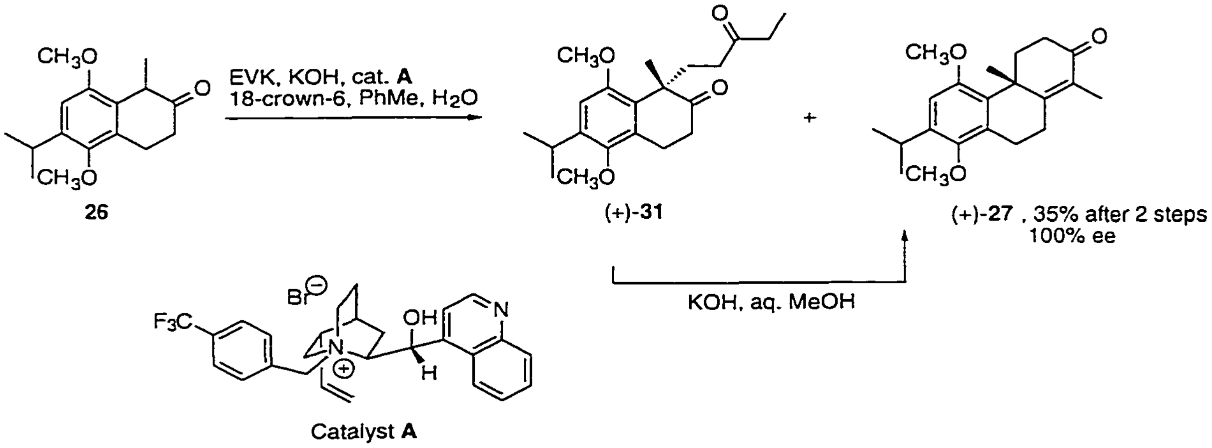
Their approach involved first synthesizing the appropriately functionalized α-tetralone **24** which would become the A and B rings. After some manipulations, the C-ring was built from the B-ring using the Robinson annulation[13] to give tricyclic enone **27**. At this juncture, chirality was introduced in the asymmetric synthesis (Scheme 6). Using chiral catalyst **A** developed by Vandewalle[14], the Robinson annulation was carried out stereospecifically to give (+)-**27** with 35% yield after resubjecting the Michael product (+)-**31** to an aldol condensation. The rest of the synthesis was achieved by a parallel sequence to the racemic series with similar results. Shishido et al.[12] were able to complete the total synthesis of (+)-triptoquinone A in 18 linear steps with an overall yield of 1.8%.

Scheme 5



(a) dioxane•Br_2, 95% (b) allyl bromide, K_2CO_3, DMF, 78% (c) NaOMe, CuI, MeOH, DMF, 92% (d) 200°C, 91% (e) Me_2SO_4, K_2CO_3, acetone, 99% (f) 9-BBN, CO, LiAlH(*t*-BuO)$_3$; $^-$OOH, 39% (g) H_2NSO_3H, $NaClO_2$, aq. dioxane, 97% (h) PPA, 78% (i) 1. MeMgI, PhH, Et_2O 2. *p*-TsOH, PhH, 88% (j) BH_3•DMS; $^-$OOH, 87% (k) $(COCl)_2$, DMSO, Et_3N, 90% (l) EVK, KOH, aq. MeOH, 60% (m) Li, liq. NH_3, *t*-BuOH; TMSCl, Et_3N, THF, 94% (n) MeLi, THF, $PhNTf_2$, 94% (o) cat. $Pd(OAc)_2$, cat. DPPF, *n*-Bu_3N, CO, DMF, 53% (p) $(NH_4)_2Ce(NO_2)_6$, aq. CH_3CN, 83%

Scheme 6

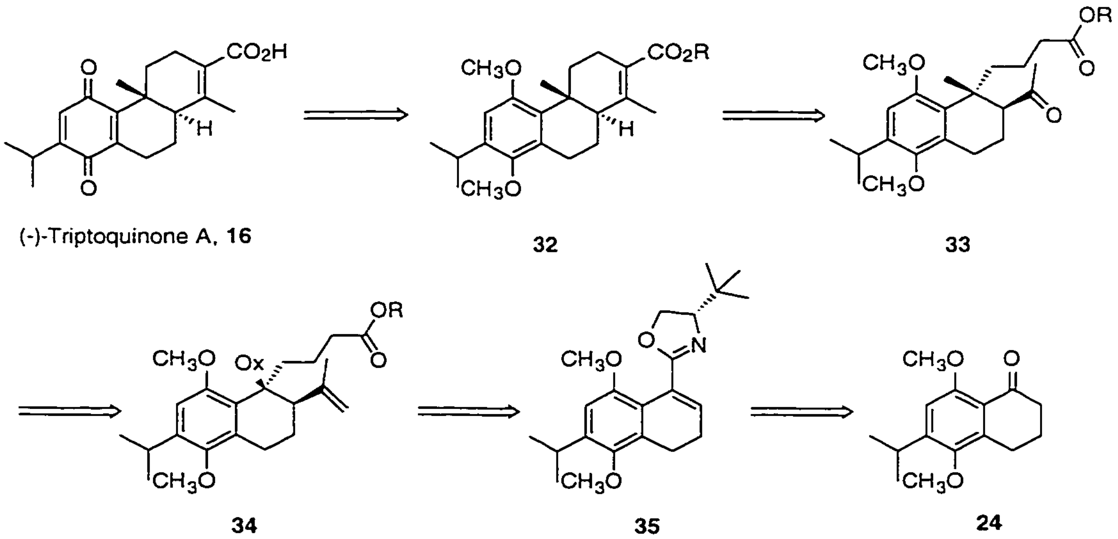


C. Initial Attempts to Synthesize Triptoquinone A via Tandem Additions to Chiral 3,4-Dihydronaphthyl Oxazolines

By all appearances, triptoquinone A, **16**, is an ideal synthetic target for showcasing the tandem addition chemistry on chiral 3,4-dihydronaphthyl oxazolines. It is a relatively simple natural product with two adjacent stereocenters which one could easily imagine originating from a naphthylene system. These stereocenters would be set quickly and efficiently by a tandem addition such as those described previously. It was the goal of this project to make triptoquinone A by a synthesis that was more convergent, higher yielding, and with fewer steps than the previous synthesis by Shishido, et al.[12] A convergent synthetic strategy, as opposed to a linear one, not only gives the opportunity for making analogs but also has potential to be more generally applied to other synthetic targets. While the final goal was to synthesize triptoquinone A (or later, triptinin A), the main purpose was to extend the scope of tandem addition to chiral oxazolines and hopefully develop new chemistry along the way. With this in mind, Meyers and Frutos first began the synthetic project.

The original retrosynthetic plan (unpublished results) is shown in Scheme 7. The last transformation planned was the oxidation of the dimethoxy-aromatic compound **32** to the quinone to give **16**, as reported by Shishido et al.[12] The C-ring was expected to be introduced from an intramolecular aldol condensation of the dicarbonyl **33**. The quaternary methyl group would ultimately arise from transformation of the oxazoline moiety of **34** which would represent the tandem addition product derived from the dihydronaphthyl oxazoline **35**. The crucial chiral oxazoline would be built from the α-tetralone **24**. It should be noted that due to the more accessible (*S*)-*t*-leucinol (versus (*R*)-*t*-leucinol) necessary for constructing the oxazoline, the actual synthetic target would lead to the enantiomer of the natural product.

Scheme 7



(-)-Triptoquinone A, **16**

32

33

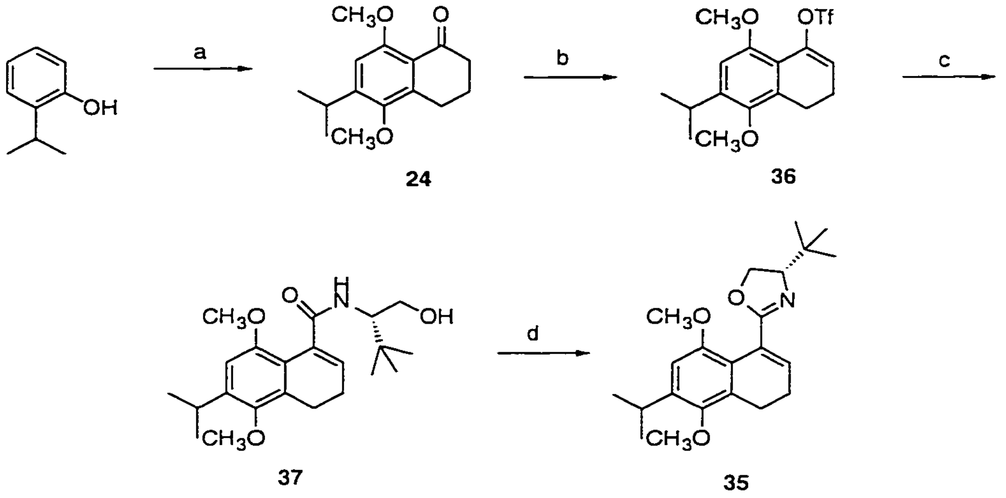
34

35

24

The first aim of the project was to prepare the starting chiral oxazoline **35** (Scheme 8). Following the procedure of Shishido et al.,[12] tetralone **24** was synthesized and transformed into the vinyl triflate **36** which was then subjected to a palladium-catalyzed carbonylation[15] in the presence of (*S*)-*t*-leucinol to give amide-alcohol **37** in low yield. Standard dehydrating conditions then produced the desired oxazoline **35**.

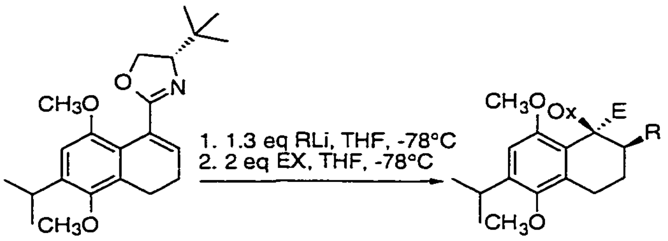
Scheme 8



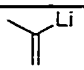
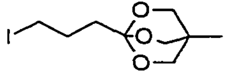
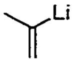
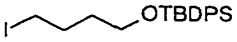
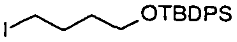
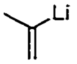
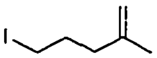
(a) ref. 12, 8 steps, 18% (b) $(CF_3SO_2)_2O$, 2,6-di-*t*-butyl-4-methylpyridine (c) cat. $Pd(OAc)_2$, cat. DPPP, Et_3N, (*S*)-*t*-leucinol, DMSO, 33% (2 steps) (d) 1. $SOCl_2$ 2. aq. K_2CO_3, 73%

With the first few tandem additions attempted, it was readily apparent that there was something different about additions to oxazoline **35** compared to the less-substituted naphthyloxazolines reported earlier in the literature.[3,4] Where previous examples of alkyl lithium additions gave essentially one diastereomer, the selectivity here was much lower. The tandem additions resulted in two diastereomers, usually inseparable by chromatography with the major diastereomer isolated as the expected *trans* addition product. The minor diastereomer was shown to be the *cis* addition product in which the initial addition step occurred anti from the *t*-butyl group of the oxazoline and then electrophile added to the same face as the nucleophile. Some representative tandem additions are depicted in Table 1. The products have appropriate functionalities that could readily be transformed into the requisite C-ring using an intramolecular aldol condensation.

Table 1: Tandem Additions with Oxazoline 35

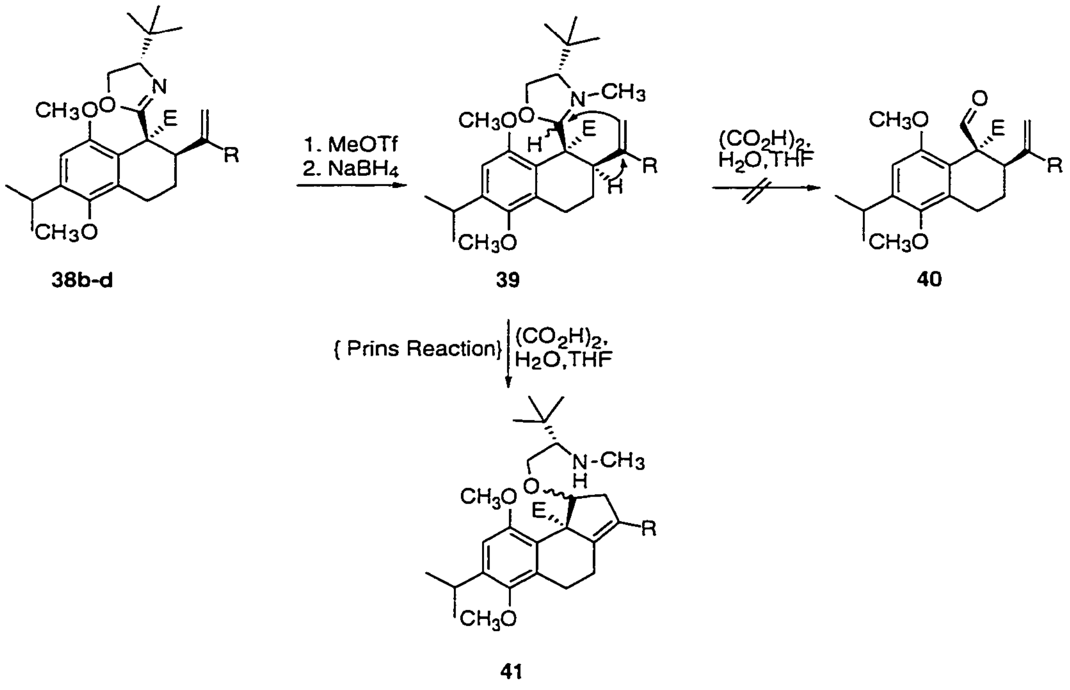


35 **38a-d**

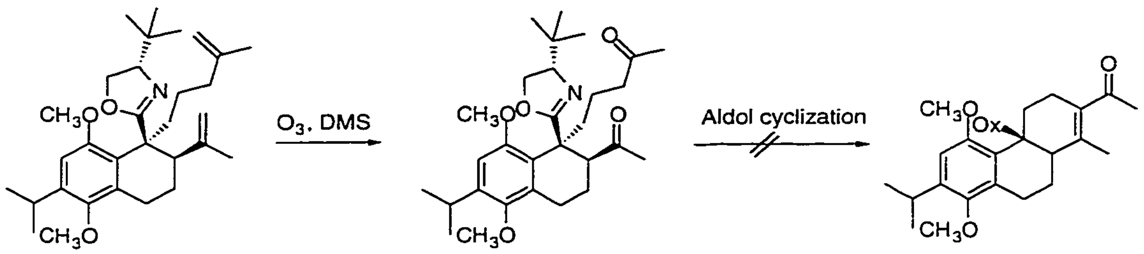
	RLi	EX	Product	d.r.	yield, %
1			**38a**	14:1	83
2			**38b**	6.5:1	72
3	$(CH_2{=}CH)_4Sn$ + *n*-BuLi		38c	6.5:1	87
4			**38d**	4:1	84

With the tandem addition product **38a**, the stereoselectivity was quite satisfactory and appeared lower for the other examples. However, the tandem addition products **38a-d**, failed to respond to many known acidic and basic hydrolyzing protocols to remove the oxazoline moiety. With compounds **38b-d**, conversion of the oxazoline to the formyl group was attempted using the well established procedure shown in Scheme 9.[4b] Formation of oxazolidine 39 occurred by quaternization of the oxazoline nitrogen followed by reduction with $NaBH_4$. Hydrolysis of the oxazolidine was then attempted with oxalic acid, but no aldehyde group could be detected. Rather, compound **41**, identified as product from a Prins addition[16] of the olefin to the oxazolidine, was isolated. Transforming the oxazoline at this stage in the sequence seemed unlikely.

Scheme 9



Based on these results, it was felt that the closure of the C-ring should precede removal of the oxazoline moiety. To this end, tandem addition product **38d** was converted to the diketone **42** by ozonolysis, in preparation to effect intramolecular aldol condensation. Both basic and acidic conditions which were known to be successful with other aldol cyclizations produced no product **43**.

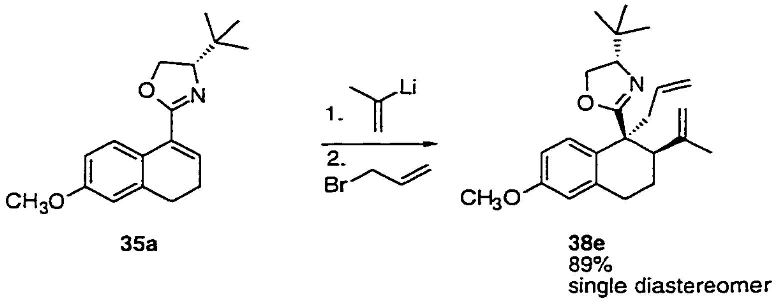


38d 4:1 mixture of diastereomers

42 45-60% of major diastereomer

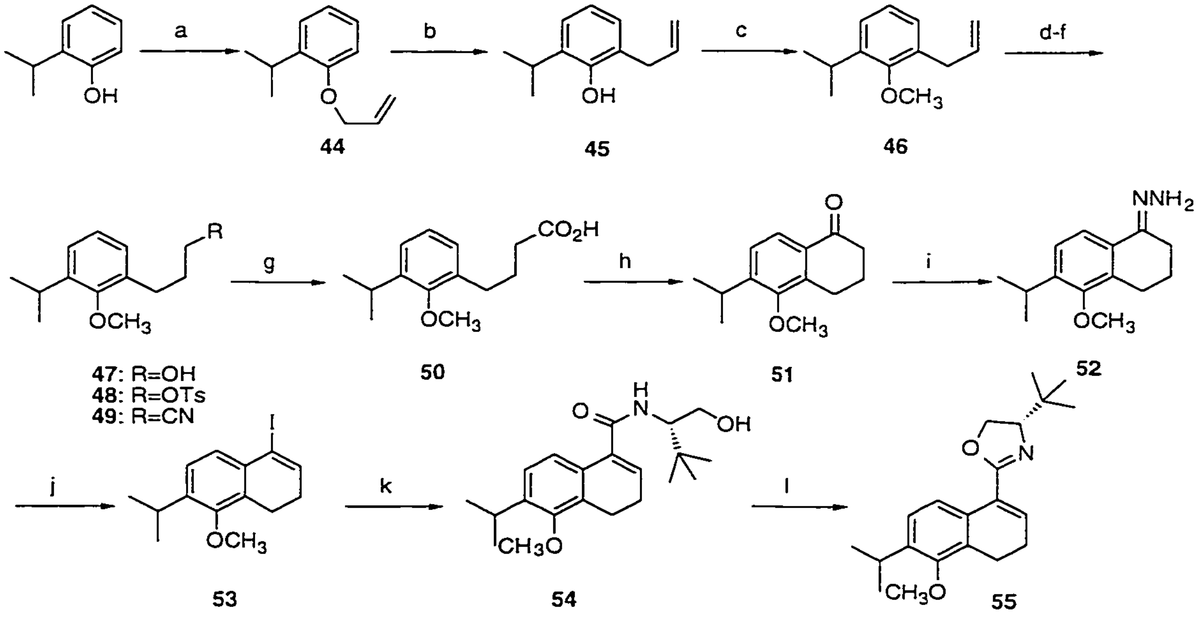
43

At this stage it seemed apparent that the steric crowding due to the oxazoline and the adjacent aryl methoxyl group in the tandem addition products might be contributing both to the lack of selectivity and to problems of removing the oxazoline. Furthermore, the proximity of the groups to each other might also be responsible for the lack of aldol ring closure mentioned above. To explore this issue, a model oxazoline, 3,4-dihydronaphthyl oxazoline **35a** (made from a commercially available α−tetralone), was subjected to the tandem addition described in Table 1 (entry 4) giving only one diastereomer, as opposed to a 4:1 d.r. Thus the removal of the methoxyl group at C-8 made a huge difference in the tandem additions. With this result, efforts were begun to make the des-8-methoxy analog of oxazoline **35**. Mono-hydroxybenzene rings can be oxidized to quinones with Fremy's salt,[17] so it was thought that this change would not greatly impact the synthetic strategy to triptoquinone A, **16**. Furthermore, though at the time it was not known, triptinin A, **15**, has the exact substitution pattern.



The synthesis of the des-8-methoxy oxazoline **55** is summarized in Scheme 10. It was carried out by Meyers and Frutos with some modifications by Meyers and Kopach (unpublished results). The sequence employed is similar to the synthesis of the dimethoxy oxazoline **35** with one important improvement. Vinyl iodide **53** was used in the palladium-carbonylation step resulting in a higher overall yield than with the corresponding vinyl triflate.

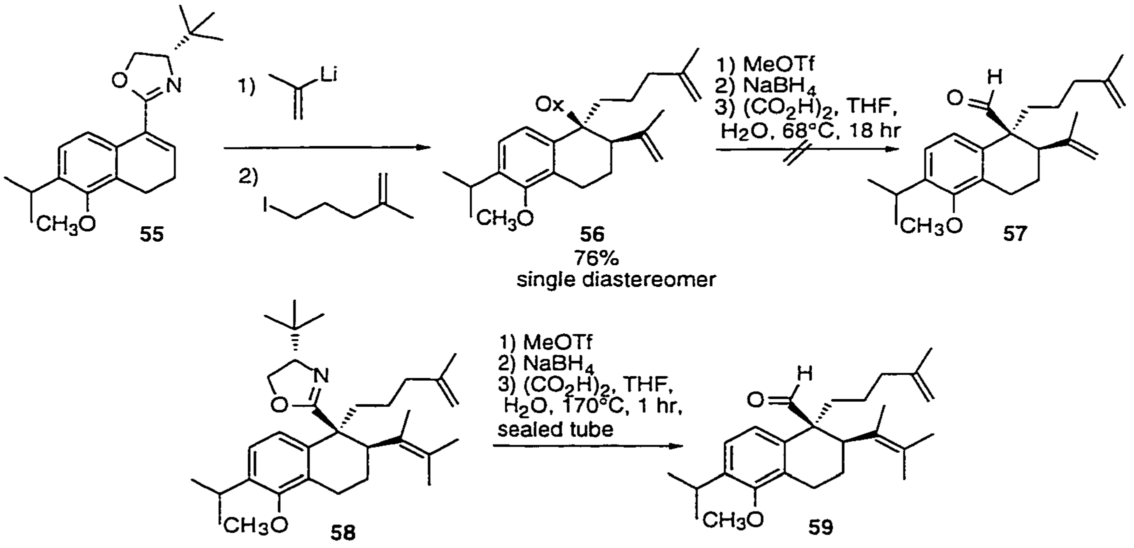
Scheme 10



(a) allyl bromide, K_2CO_3, DMF, 90% (b) 210°C, 95% (c) Me_2SO_4, acetone, 80% (d) $BH_3 \bullet THF$, H_2O_2, 95% (e) TsCl, DMAP, pyridine (f) NaCN, DMF, 54% (2 steps) (g) H_2O_2, KOH, 95% (h) PPA, 90°C, 88% (i) $NH_2NH_2 \bullet H_2O$ (j) I_2, *N,N,N,N*-tetramethylguanidine, 64% (2 steps) (k) cat. $Pd(OAc)_2$, cat. DPPP, Et_3N, (*S*)-*t*-leucinol, CO, 83% (l) $SOCl_2$; aq. K_2CO_3, CH_3CN, Δ, 80%

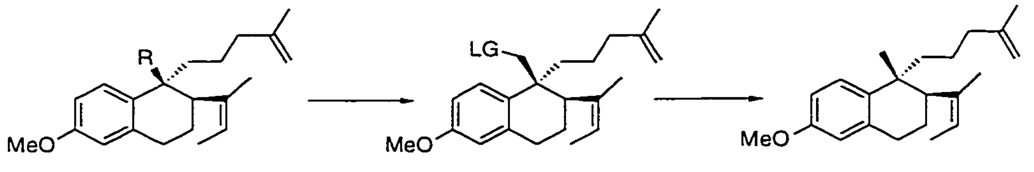
Once in hand, tandem additions to oxazoline **55** proceeded well, with good yields and extremely high selectivity (Scheme 11). However, the removal of the oxazoline in **56** was still somewhat problematic. For example, asymmetric tandem addition product **56** was made as a single diastereomer in 76% yield, but the conversion of the oxazoline did not furnish the aldehyde **57**, but gave, instead, a Prins-addition product analogous to compound **41**. Meyers and Kopach (unpublished results) found that use of a more substituted vinyl nucleophile in the addition affording **58**, followed by careful hydrolysis conditions (oxalic acid, H_2O, THF, 170°C, sealed tube, 1 hour), produced the aldehyde **59**, reached in very good yield with no Prins product detected.

Scheme 11



The aquisition of chiral aldehyde **59** appeared to overcome a major hurdle and now attention was focused by Meyers, Kopach, and Nakano (unpublished results) on transforming **59** to have an angular methyl group. Several different deoxygenation conditions on **59** were screened and due to the sterically encumbered nature of the neopentyl aldehyde and its corresponding alcohol, forming the desired methyl group proved to be very difficult. Attempts were made to transform either the aldehyde or the hydroxyl moiety into a group which could then be reductively removed (Table 2). Success was finally achieved by following chemistry first developed by Ireland et al.[18a] and later modified by Liu et al.[18b,c] Phosphorodiamidate **61** (LG= $-OP(=O)(NMe_2)_2$) was formed and then reductively cleaved by lithium naphthalenide to yield the desired methyl compound **62**.

Table 2: Summary of Deoxygenation Attempts

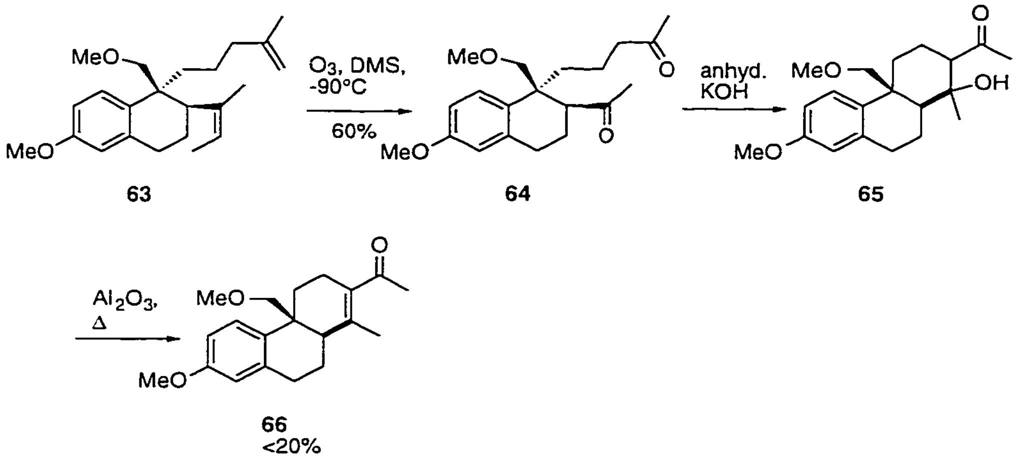


60 **61** **62**

R	LG	Conditions	Results
OH	OTs, OMs	$LiBHEt_2$, $NaBH_4$/DMSO, $LiAlH_4$	either starting material or complex mixtures
	I, Br		unable to convert hydroxyl to halide
	-C(=S)SMe, -C(=S)Imid.	*n*-Bu_3SnH, AIBN	either starting material or complex mixtures
	$-P(=O)(NMe_2)_2$	Lithium Naphthalenide	54% desired, deoxygenated product **62**
CHO	$-SCH_2CH_2S-$ $=NHNH_2$		unable to form thioketal or hydrazone

While studies leading to deoxygenation were being investigated, closure of the C-ring was pursued in an effort to reduce the formyl or its alcohol under mild conditions. With the ring formed, it was thought that the hydroxymethyl would be more exposed and therefore easier to cleave reductively. Conditions were found that gave material that appeared to be the aldol product **65** by NMR analysis (Scheme 12). Unfortunately, a variety of different dehydrating conditions were attempted and never produced more than a trace amount of a compound that seemed consistent with the dehydration product **66**.

Scheme 12



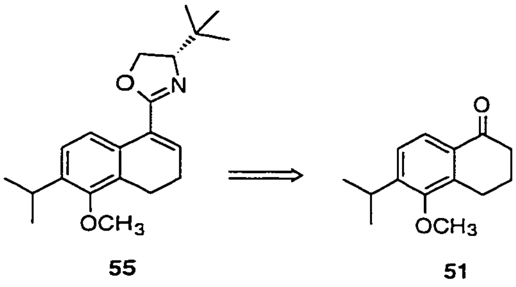
The progress made to this point generated further understanding of the asymmetric tandem additions to chiral α,β-unsaturated oxazolines. In particular, it was shown that 3,4-dihydronaphthyl oxazolines with a methoxy substitutuent at C-8 give poor selectivity, presumably due to steric constraints. Further progress was made when experimental parameters were found to convert hindered oxazolines to methyl groups. However, it remained to be seen if these conditions were sufficiently general to tolerate a variety of functionalities. Up to this point, no efficient method had yet been found to form the C-ring of **16** from the tandem addition product.

II. Results and Discussion

A. Synthesis of the Chiral Dihydronaphthyl Oxazoline

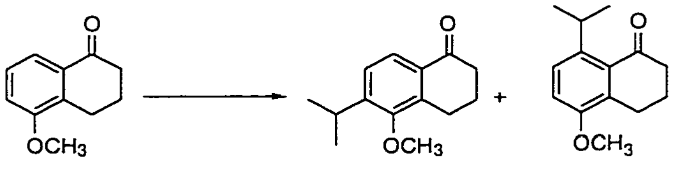
Because the previous synthesis of the required dihydronaphthyl oxazoline, **55**, was fairly long and time-consuming, steps were taken to shorten the synthesis. The overall strategy remained the same; 6-isopropyl-5-methoxytetralone, **51**, was to be produced and then the oxazoline would be built (Figure 1). Several approaches were tried including some taking advantage of commercially available tetralones.

Figure 1



Friedel-Crafts alkylation was attempted on 5-methoxytetralone, **69**, with isopropylium species (Table 3). It was thought that a significant amount of the requisite *ortho* alkylation might occur. This would give very rapid access to the desired tetralone **51**. With electrophilic aromatic substitution, undesired *para* substitution often predominates due to steric constraints adjacent to the directing group.[19] In this system, the position *para* to the methoxy group is also *ortho* to the carbonyl. Because both positions are sterically encumbered it was supposed that the more electron-rich position *ortho* to the methoxy group may become substituted. However, only unwanted isopropyl addition in the 8-position was observed.

Table 3: Friedel-Crafts Alkylation of Tetralone 69

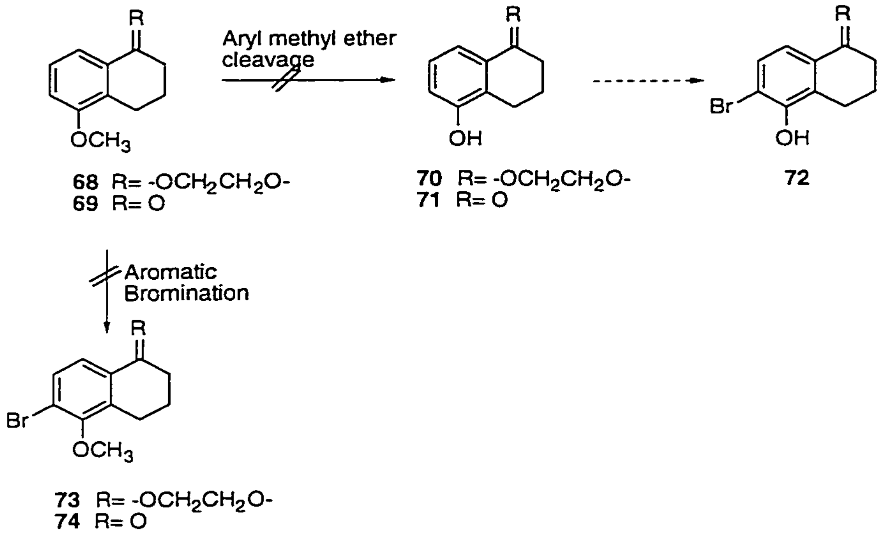


69 **51** **67**

	Conditions	Results
1	2-bromopropanol, CH_3NO_2, $AlCl_3$ (catalytic and 1 equiv.)	Starting Material (**69**)
2	2-isopropanol, conc. H_2SO_4 RT	~50% **67** and starting material
3	2-isopropanol, conc. H_2SO_4 -10°C, 36 hours	~50% **67** and starting material

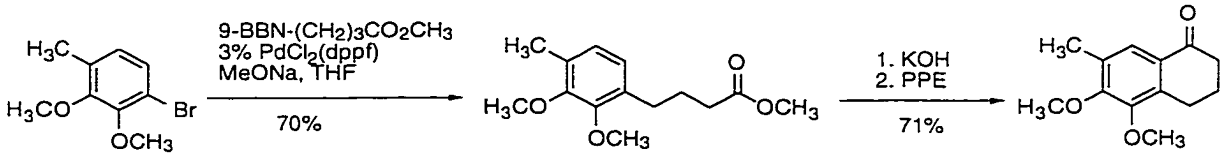
Another approach using 5-methoxytetralone, **69**, was attempted involving aromatic bromination at the 6-position (Scheme 13). Phenols can be *ortho* brominated preferentially over *para* substitution.[20] Unfortunately, attempts to cleave the methyl ether of both **69** and the ketal **68** yielded only complex mixtures and did not give either **70** or **71**. Standard aromatic brominating conditions on both **69** and **68** led only to 2-bromo-5-methoxytetralone and no aromatic bromination.

Scheme 13



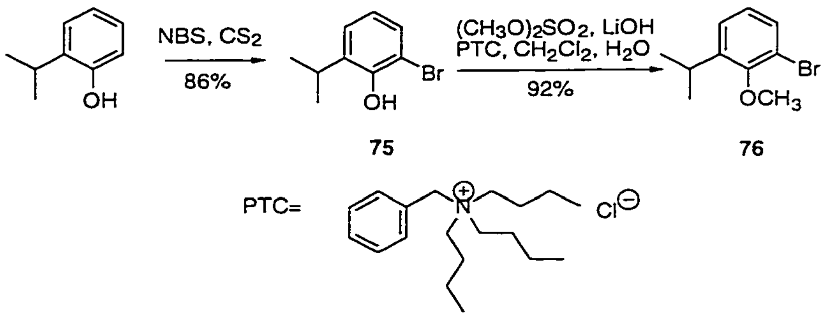
Plumet et al.[21] described a short synthesis of tetralones which involved using a Suzuki coupling with aryl bromides. They reported several examples of *ortho*-substituted electron-rich aryl bromides, such as the one shown (Scheme 14), that worked well. Formation of 2-bromo-6-isopropylanisole was developed in order to use this chemistry to form tetralone **51**.

Scheme 14



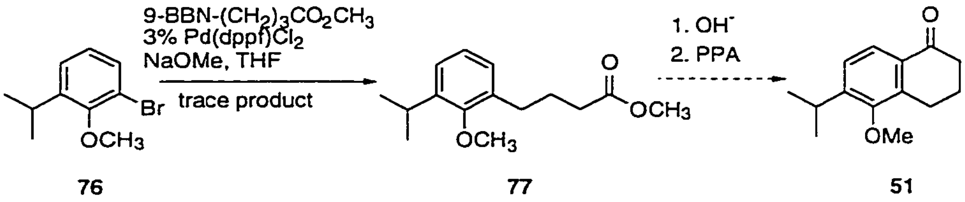
The commercial compound 2-isopropylphenol was brominated with *N*-bromosuccinimide in carbon disulfide (Scheme 15). As long as the reaction was performed in dilute solution (~0.15M), the *ortho*-brominated product **75** was obtained in 86% yield. If the reaction was carried out in a more concentrated solution, then *para* substitution began to be significant. The next step, to form the methyl ether, utilized methyl iodide with K_2CO_3 in acetone, but the yield was never better than 60%. Phase transfer conditions developed by McKillop and coworkers[22] are known to methylate hindered phenols in high yields. This proved to be the case here with a yield greater than 90% to give aryl bromide **76**.

Scheme 15



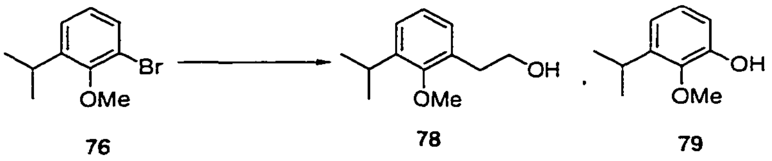
With the necessary aryl bromide in hand, the Suzuki coupling was tried (Scheme 16). The conditions of Plumet et al.[21] were used, but not more than a trace amount of the γ-butanoic ester **77** was ever observed by GC/MS. The main products obtained were reduced starting material (where the bromide had been replaced by a hydrogen) and 9-BBN-derived material. If this reaction had been successful, saponification followed by Friedel-Crafts acylation would have yielded the desired tetralone **51** in a total of five steps from 2-isopropylphenol.

Scheme 16



Because aryl bromide **76** was easy to aquire, it was thought that it would still serve as useful starting material to obtain the desired tetralone. Metal-halogen exchange with *n*-butyllithium gave the aryl lithium of **76** (Table 4). This lithium reagent was sensitive to oxygen and, if one did not degas the reagents and solvent, a significant amount of a phenolic by-product **79** resulted. Addition of $BF_3 \bullet Et_2O$ followed by ethylene oxide gave the phenethyl alcohol **78** in 80% yield. In order to get consistent, useful yields, several different reaction conditions were employed and are summarized in Table 4. A major aliphatic contaminant occurred if the reaction was not quenched below 0°C and separation of this from the desired material was not possible. However, the mixture could be carried on to the next transformation where desired product was easily separated from impurity. Both the phenol **79** and the aliphatic impurity were avoided under the optimum conditions (entry 7).

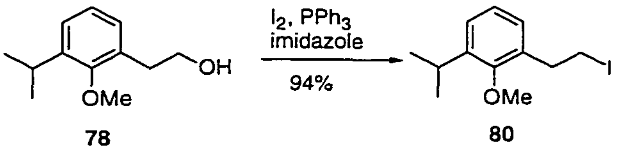
Table 4: Formation of Phenethyl Alcohol 78



	Conditions	Results
1	(a) *t*-BuLi, THF, -78°C (b) $BF_3 \bullet Et_2O$, 10 min., -78°C (c) ethylene oxide, -78°C (10 min.), warm to RT	57% **78** ~20% **79**
2	as entry 1, except with Et_2O	complex mixture
3	as entry 1, except degassed all solvents	~80% yield **78**[a] & inseparable impurity
4	(a) *n*-BuLi, degassed THF (b) $BF_3 \bullet Et_2O$ (c) DMPU (d) ethylene oxide	no **78** only H^+quenched anion after workup
5	(a) *n*-BuLi, degassed THF (b) ethylene oxide	30% **78**
6	(a) *n*-BuLi, degassed THF (b) $BF_3 \bullet Et_2O$ (10 min.), -78°C (c) ethylene oxide -78°C-0°C	~75% yield **78**[a] & inseparable impurity
7	(a) *n*-BuLi, degassed THF (b) $BF_3 \bullet Et_2O$ (20 min.), -78°C (c) ethylene oxide -78°C (2 hrs.)	80% **78** no significant **79**

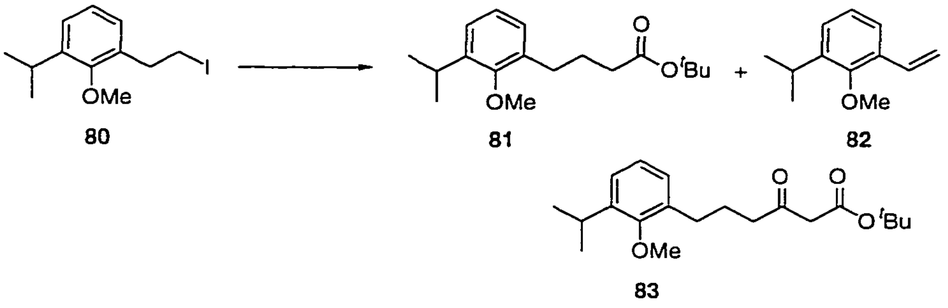
[a] Yield estimated by converting alcohol to iodide and removing impurity

After formation of the phenethyl alcohol **78**, conversion of the hydroxyl group to an iodide, **80**, was performed in 94% yield using PPh_3, I_2, and imidazole in CH_2Cl_2. Because the next step was to be an alkylation, the alkyl iodide, as opposed to an alkyl bromide or tosylate, was made to minimize the potential of elimination to form a styryl compound. The β-hydrogen of **80**, it was assumed, would be less acidic than the bromo analog due to decreased electronegativity of the iodide.



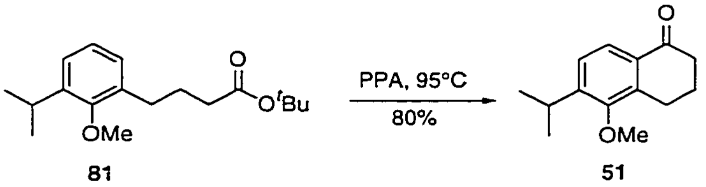
The remaining carbons for the desired precursor to the tetralone **51** were added by addition of the enolate of *t*-butyl acetate to **80**. The *t*-butyl ester was used in order to suppress self-condensation of the anion and also additional condensation with the product. Conditions had to be modified in order to minimize undesired side reactions and the key variations are summarized in Table 5. Despite using the alkyl iodide, elimination remained somewhat problematic to give the styrene **82**. Furthermore, although the *t*-butyl ester was employed, condensation of product **81** and remaining ester enolate did occur to some extent to give the β-keto ester **83**. Both of these side reactions could be minimized by adding the *t*-butyl acetate enolate to a slight excess of iodide **80** (entry 3).

Table 5: Formation of Ester 81



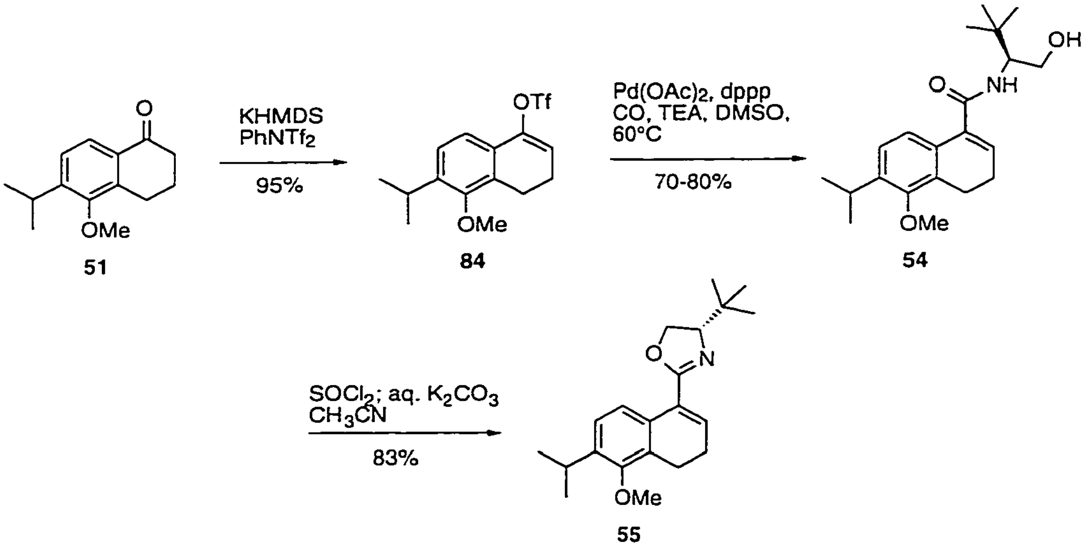
	Conditions	Results
1	(a) 1.5 eq CH_3CO_2*t*Bu, 1.3 eq LDA, THF, -78°C (b) 2 eq HMPA, -78°C (c) add electrophile **80** to anion, -78°C-RT	~65 % **81** rest of material was ~1:1 mix of **82** and **83**
2	(a) 1 eq CH_3CO_2*t*Bu, 1.1 eq LICA, THF, -78°C (b) 1.5 eq HMPA, -78°C (c) add electrophile **80** to anion, -78°C-RT	~50 % **81** rest of material was ~1:1 mix of **82** and **83**
3	(a) CH_3CO_2*t*Bu, LDA, THF, -78°C (b) 2 eq HMPA, -78°C (c) slow addition of anion to electrophile **80**, -78°C (2 hr)	85% **81** <10% of **82** and **83**

Once the ester **81** was successfully and efficiently formed (Table 5, entry 3), it was then treated with Friedel-Crafts acylation conditions (PPA, 95°C) to yield the desired tetralone **51**. Because the *t*-butyl ester was used, it was not necessary to perform a separate saponification prior to cyclization since the polyphosphoric acid was acidic enough for deesterification in situ. As long as the heat source was maintained near 95°C with good stirring, the yield of tetralone **51** was around 80%.



With the tetralone in hand, the chiral oxazoline could now be constructed. Previous workers had performed this transformation using a four step sequence via the vinyl iodide (Scheme 10). Not only did the vinyl iodide require two steps to synthesize, but also the overall yield of this process was quite low. It was found that the vinyl triflate **84** could be easily made in one step (Scheme 17) by using potassium hexamethyldisilazide as the base which upon addition of the triflimide gave O-triflation with no sign of the undesired C-triflation. The subsequent palladium-catalyzed amidation occurred in good yield to furnish amide-alcohol **54**. The previous protocol for the amidation had been to carry out the reaction in dilute solution (~.15 M of **84** in DMSO). While this procedure gave very good yields of **84** from the vinyl iodide (~90%), it did not work as well for the vinyl triflate (30-50%). However, by carrying out the transformation with much less DMSO, indeed almost neat, the yield from the vinyl triflate improved greatly (70-80%). After formation of the amide-alcohol **54**, standard cyclization procedures produced the desired oxazoline **55** in good yield. The desired dihydronaphthyl oxazoline **55** was now achieved in nine steps starting from 2-isopropylphenol, representing a reduction from twelve steps.

Scheme 17

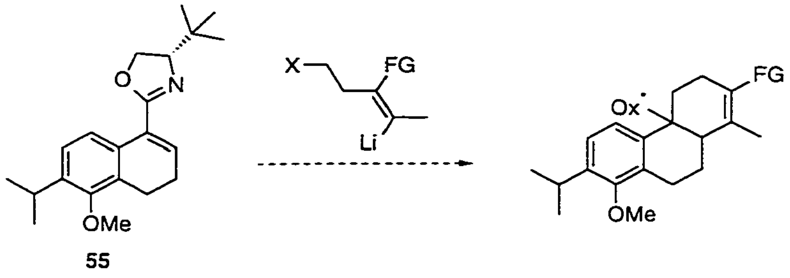


B. Formation of the C-Ring

Several approaches were investigated to put in the C-ring of the triptinin/triptoquinone ring system. These involved intramolecular tandem additions and tandem additions followed by ring-closing metathesis. The details of these studies are presented below.

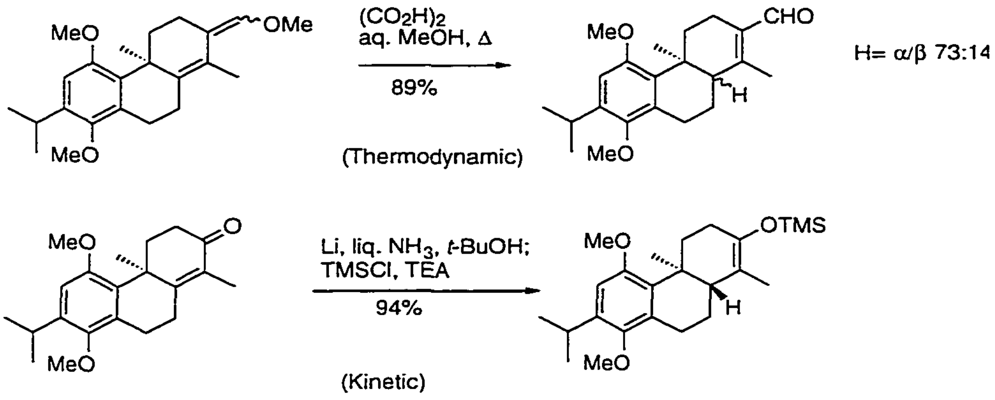
i. Intramolecular Tandem Addition

Figure 2



From the work of Licini and Meyers,[5] it was thought that an intramolecular tandem addition might suffice to put the C-ring together in a single reaction (Figure 2). If the tandem addition were to follow precedent, the *cis*-ring junction between the B and C rings may result. However, in the previous work only simple saturated alkyl chains were reported, and with a more structurally complex nucleophile the desired *trans*-ring junction might also be formed. If the undesired *cis*-ring junction should prevail, work by Shishido et al.[12] showed that the ring system stereochemistry could be manipulated (Scheme 18). They found that kinetic conditions led exclusively to the desired *trans*-ring junction, whereas thermodynamic conditions gave a mixture with the *cis*-ring system favored.

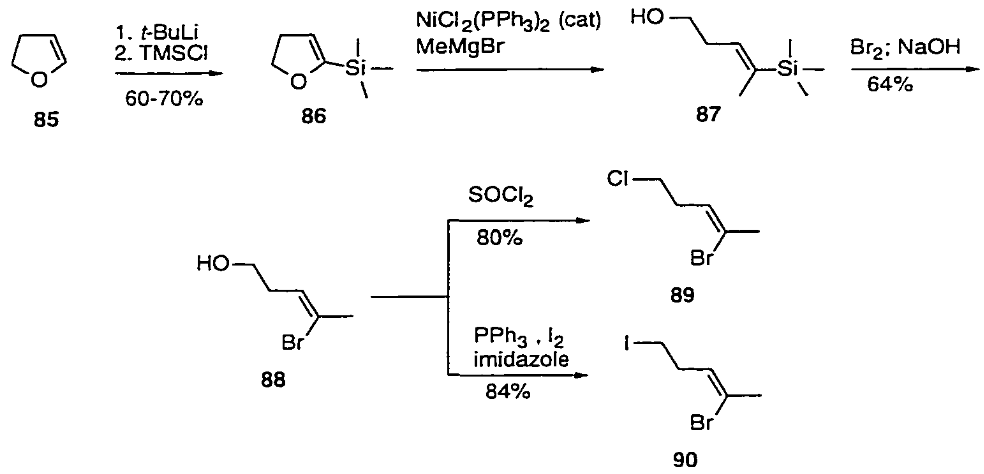
Scheme 18



Before embarking on a long synthesis of a complex lithio-nucleophile that might or might not readily lead to the triptinin ring system, a more simple model system was investigated. The first nucleophile chosen was the corresponding vinyl lithium reagent from **89** (Scheme 19). An alkyl chloride was first tried as the electrophilic portion because alkyl chlorides had been shown previously to work in intramolecular tandem additions, and the anion might be less likely to dimerize than an alkyl bromide or iodide.

The synthesis of the model nucleophile follows the work of Kocienski et al.[23] with their synthesis of the vinyl bromide **88** (Scheme 19). Dihydrofuran **85** was deprotonated and treated with trimethylsilylchloride to give **86**. Nickel-catalyzed Grignard addition of methylmagnesium bromide gave the ring-opened alcohol **87** with only one olefin isomer detected. The yield on this reaction was variable, giving between 30% and 60%. However enough material was generated to serve the intended purpose of the model study. Bromine addition followed by bromotrimethylsilane elimination resulted in the vinyl bromide **88**, again with only one olefin isomer detected. Conversion of the alcohol to a halide easily occurred following standard procedures to give both chloride **89** and iodide **90**.

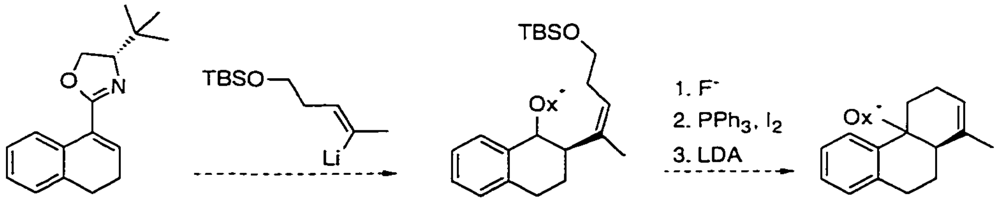
Scheme 19



It quickly became apparent after trying several tandem additions to the unsaturated oxazoline, **55**, with both **89** and **90** that the intramolecular approach would probably not be feasible, at least with a homoallylic electrophile. Upon treating the vinyl bromide **90** with *t*-butyl lithium to form the lithio salt, the species was added to the dihydronaphthyl oxazoline **55**. Only starting oxazoline and a <10% yield (by GC) of initial addition (no cyclization) was detected. Apparently, with both the chloro and iodo compounds, elimination to form diene occurs before the addition/cyclization could take place.

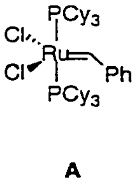
While the idea of making the addition/cyclization stepwise was entertained, it was decided that this would not be very efficient. For example, the TBS ether of alcohol **88**, which was easily formed, could be added to the oxazoline (Scheme 20). After exchanging the silyl group for a leaving group, deprotonation α to the oxazoline moiety and cyclization may occur. Of course, elimination to form a diene may again be a problem. Given this and the fact that the wrong *cis* ring-junction stereochemistry was very likely to form, this approach was not investigated further. Another factor in this decision was the reality of the number of chemical transformations that would be required to put in the C-ring, including the synthesis of more functionalized lithio nucleophile necessary for the natural product.

Scheme 20

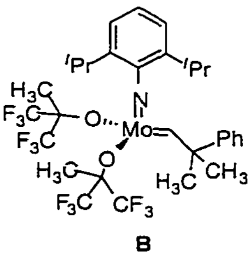


ii. Ring-Closing Metathesis

In recent years, ring-closing metathesis (RCM) of olefins has been used extensively as a remarkably efficient method for forming rings and several reviews have appeared on olefin metathesis.[24] Complex, macrocyclic natural products with a wide variety of functionalities have been synthesized using RCM as a key transformation.[25] With this in mind, studies were undertaken to use RCM to put in place the C-ring of the triptinin ring system.



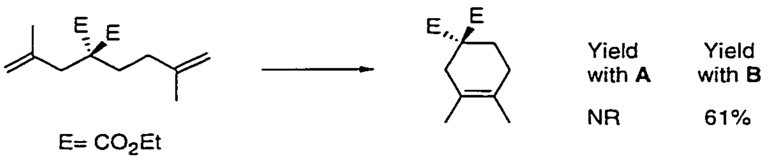
A



B

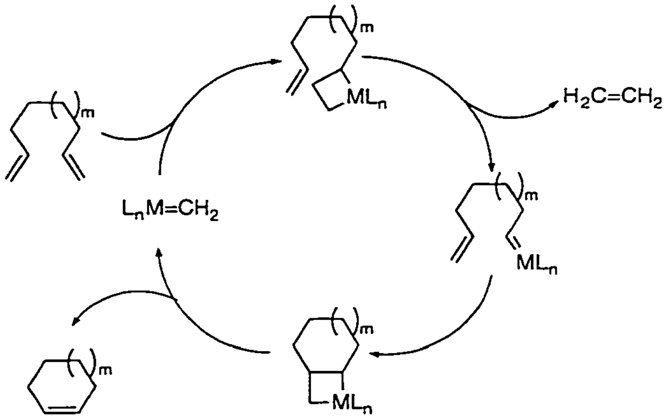
With ring-closing metathesis, the two catalysts used are mainly the Grubbs catalyst (**A**)[26] and the Schrock catalyst (**B**)[27] with both catalysts having advantages and disadvantages. The Grubbs catalyst is the less reactive of the two, which gives it greater air and water stability. However, it is unable to form tetrasubstituted and other sterically congested olefins.[28] The Schrock catalyst, on the other hand, must be used under air-free, moisture-free conditions and is sensitive to functionalities with reactive protons (i.e. ROH, RCO_2H, etc.).[24a] The primary advantage of the Schrock catalyst is that reacts quickly and is capable of forming sterically encumbered products including tetrasubstituted olefins (Figure 3).[28]

Figure 3



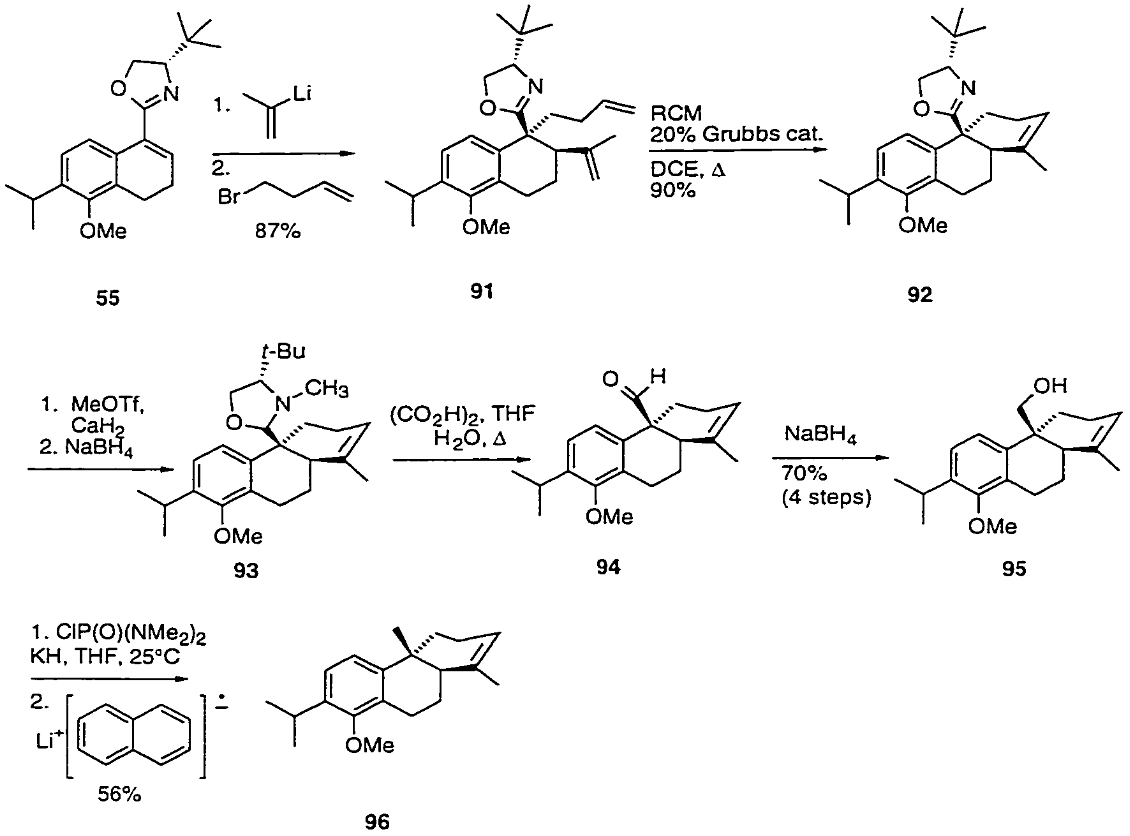
The accepted, schematic mechanism for ring-closing metathesis is shown in Scheme 21. The methylidene is the propagating species of the catalytic cycle. Grubbs has mechanistically studied the ring closure of diethyl diallylmalonate by $H_2C{=}Ru(PCy_3)_2Cl_2$.[29] From this study, it was shown that the major mechanistic pathway for this catalyst was loss of phosphine before metallacyclobutane formation. With the Schrock catalyst, no ligand needs to leave before the catalysis can occur.

Scheme 21



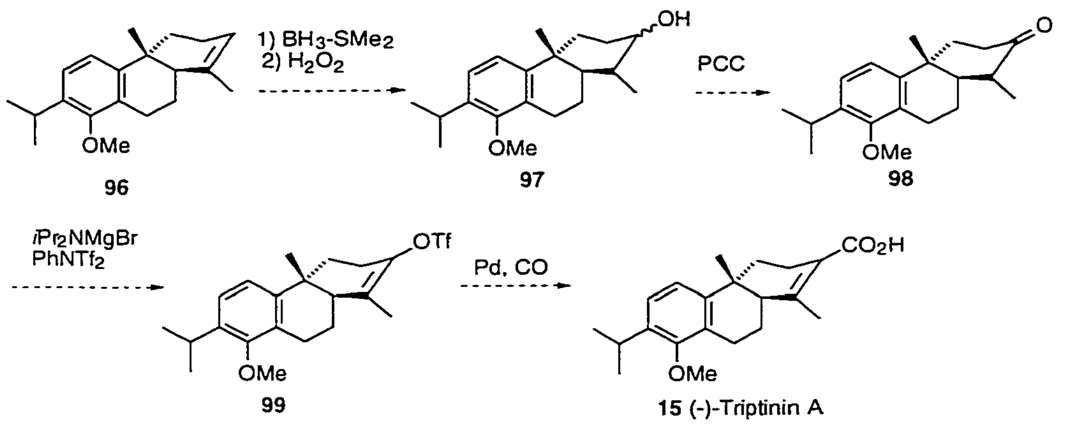
In the initial RCM approach for the C-ring formation, Meyers and Nakano (unpublished results) performed the addition to oxazoline **55** with 2-lithiopropene and 4-bromobutene as the electrophile to give tandem addition product **91** as a single diastereomer (Scheme 22). The addition took place in high yield and no significant elimination with the homoallylic electrophile was observed. Treatment of **91** with 20% Grubbs catalyst and heat resulted in a good yield of the cyclized material **92**. Manipulation of the oxazoline moiety to a methyl group occurred in a six step process. Quaternization of the oxazoline nitrogen took place in the presence of CaH_2 as triflic acid trap. Without CaH_2, there was notable olefin isomerization. Reduction with $NaBH_4$ gave the oxazolidine **93**, which was then hydrolyzed to give aldehyde **94**. Aldehyde **94** was readily reduced to alcohol **95** with $NaBH_4$. The latter was converted into a phosphorodiamidite and following the procedure of Liu, et al.[18b] (which worked well with the model compound **61**) was then treated with lithium naphthalenide to give the methyl compound **96**. Concomitant reduction of the aromatic ring (i.e. Birch reduction) during the lithium-naphthalenide reduction was not observed.

Scheme 22



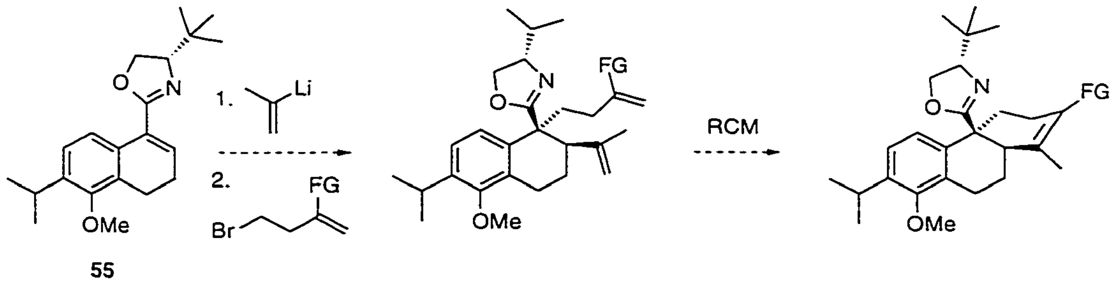
With the C-ring constructed in an efficient manner to provide **96**, the route to furnish triptinin A involved putting in place the carboxylic acid moiety. One potential way of producing the carboxylic acid from **96** is outlined in Scheme 23. Unfortunately, initial results by Meyers and Nakano (unpublished results) were not promising with respect to forming the correct enolate isomer of **98** in particular. Because of this and the number of reactions still required to obtain the desired natural products (e.g. **15** and **16**), a more efficient RCM approach was sought.

Scheme 23



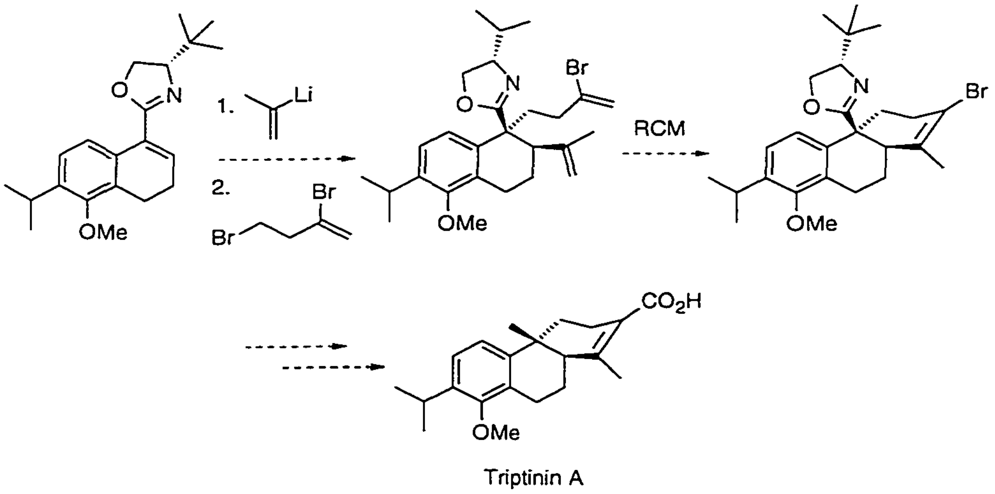
Inasmuch as the ring-closing metathesis approach to the C-ring had been the most promising method to this point, it was thought that utilizing an RCM precursor containing predisposed functionality would be a streamlined and effective pathway to the ultimate goal (Scheme 24). Because the carboxylic acid or its ester would not be compatible with the organolithium of the tandem addition or with removal of the oxazoline moiety, a functional group needed to be chosen that could withstand these reaction conditions and also be readily converted to the carboxylic acid.

Scheme 24



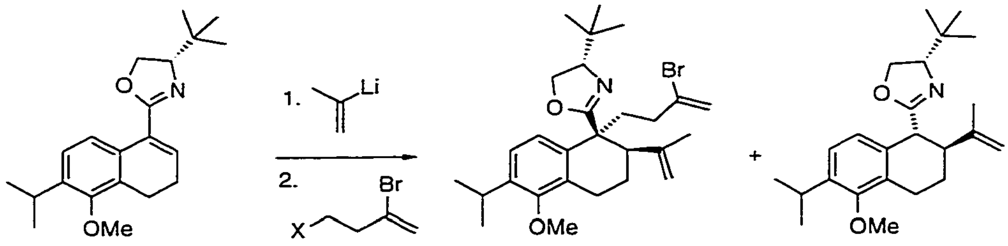
With the aforementioned requirements in mind, a tandem addition using a bromoalkyl-vinyl bromide electrophile was pursued (Scheme 25). While no literature precedent could be found for vinyl bromides to undergo RCM, it was thought that this might indeed work. If successful, following the tandem addition and ring-closing metathesis, the oxazoline could then be transformed into a methyl group. Conversion of the cyclohexenyl bromide to the carboxylic acid should then be a straightforward, single transformation by either palladium-catalyzed carbonylation or by formation of the Grignard or lithium and trapping with CO_2.

Scheme 25



Unfortunately, the tandem addition to form the necessary RCM precursor **102** did not proceed (Scheme 26). Both the bromo- and iodoelectrophiles, **100** and **101**, were easily made from the commercially available carbinol (PPh_3, I_2 or Br_2, imidazole, CH_2Cl_2). It was necessary to add imidazole as an acid scavenger or else side reactions occurred. The tandem addition reaction yielded only initial addition product **103**.

Scheme 26



55

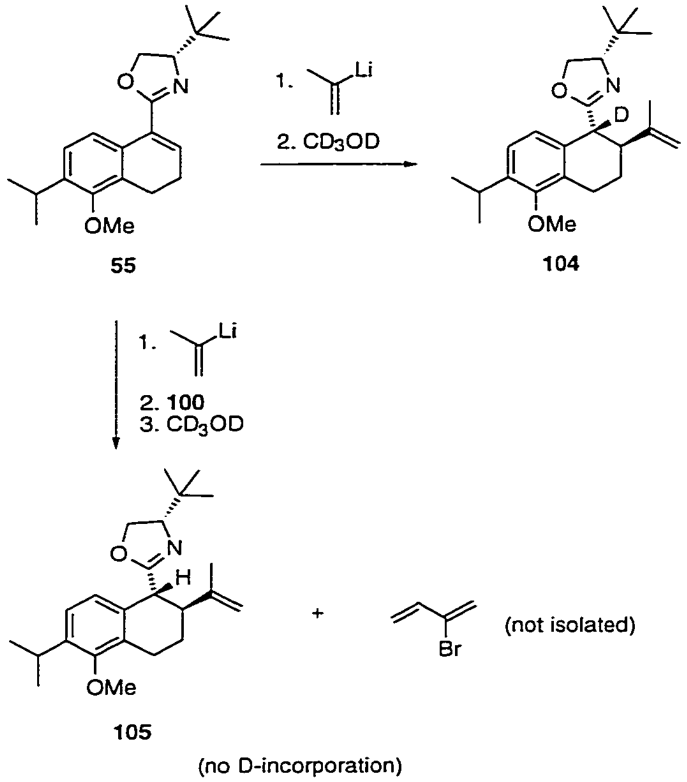
100 X= Br
101 X= I

102
0%

103
~80%

To determine the reasons for the failure of **100** and **101** to alkylate the azaenolate, a deuterium quench study was performed. Addition of CD_3OD showed that the azaenolate was being protonated by the electrophile (Scheme 27). Addition of 2-lithiopropene followed by CD_3OD gave complete deuterium incorporation (**104**). However, if CD_3OD was added after electrophile **100**, no deuterium incorporation was observed indicating that the azaenolate had already been protonated. The likely proton source was at the allyl position, deprotonation of which led to elimination of bromide ion and diene formation. Therefore, this electrophile proved problematic even though a homoallylic electrophile worked well to form the initial, less substituted RCM precursor **91**. In that case, significant elimination was not detected. The reason for the difference in reactivity is probably due to the presence of the vinyl bromide species (**100** or **101**), whose allylic protons are more acidic due to the electron-withdrawing nature of the olefinic bromine and are therefore more likely to be deprotonated.

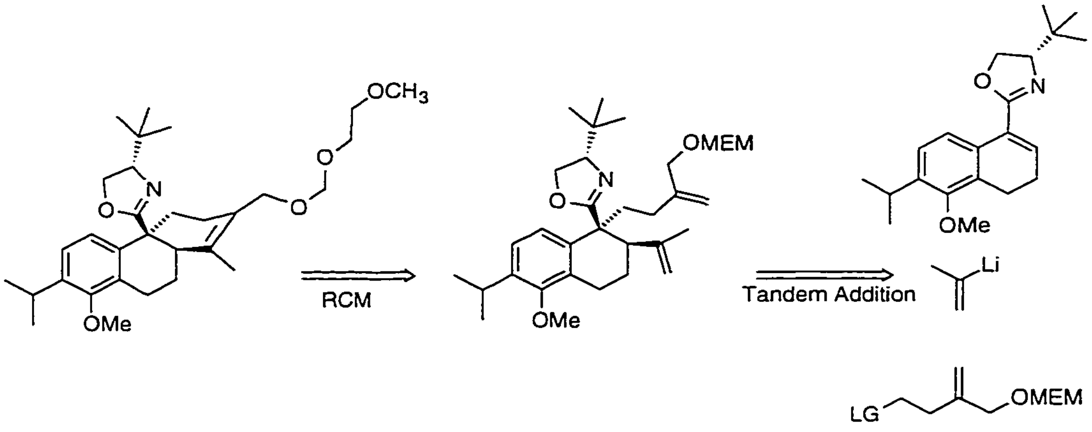
Scheme 27



Due to the inability to perform the tandem addition with the vinyl bromide electrophiles (e.g. **100**), another more compatible functional group was sought. In order to withstand the conditions for both tandem addition and subsequent removal of the oxazoline, the functional group needed to be base-stable, relatively acid-stable, unreactive to nucleophilic attack, and readily converted to a carboxylic group. Therefore, it was thought that a protected allylic alcohol might serve the purpose at hand. The protecting group would need to have the already mentioned characteristics, plus the ability to be removed without destroying the rest of the molecule, in particular reducing or scrambling the double bond. For these reasons, a 2-

methoxyethoxymethyl group (MEM) was chosen to allow the sequence depicted (Scheme 28).

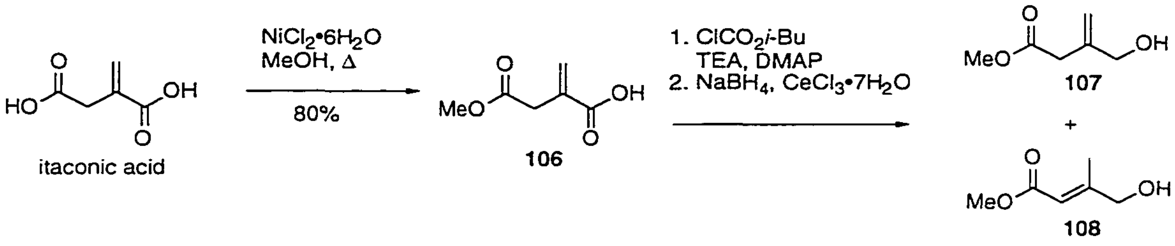
Scheme 28



The 2-methoxyethoxymethyl group was first described as a hydroxyl protecting group by Corey and coworkers.[30] Differentiating it from other hydroxyl protecting groups, the MEM group is stable to a wide variety of conditions including strong bases, many organometallic reagents, reducing agents, most oxidizing agents, and mild acids. MEM ethers can be cleaved with a Lewis acid, such as $ZnBr_2$. Though this often works well with aliphatic ethers, cleavage of allylic MEM-ethers is known to be more difficult. Monti et al.[31] described using excess pyridinium *p*-toluenesulfonate (PPTS) in refluxing *t*-butyl alcohol as an efficient method for removal of the MEM group from allylic alcohols. While no examples with allylic alcohols were found in the literature, boron halides[32] have also been used to selectively cleave various types of MEM ethers in the presence of other acid-sensitive groups. For example, Williams et al.[32a] used 2-chloro-1,3,2-dithioborolane to remove MEM ethers in the presence ot TBDMS and THP ethers. It was thought that either PPTS or a boron halide would serve to remove the MEM group in the present study.

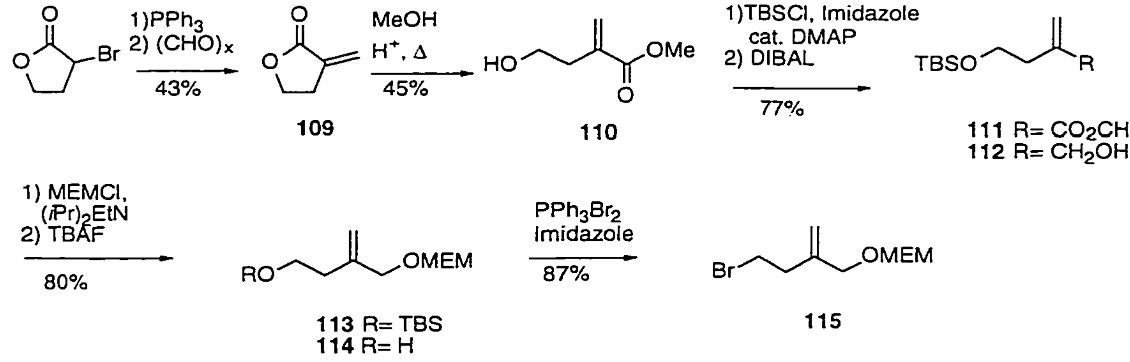
With hopes of finding a quick and efficient synthetic route to **15** and **16**, the construction of the required MEM-protected electrophile was then undertaken. One of the first methods examined was starting with the abundantly available diacid, itaconic acid (Scheme 29). Differentiation of the carboxyl groups took place using the procedure of Ram and Charles.[33] With $NiCl_2 \bullet 6H_2O$ in MeOH, the aliphatic carboxyl was esterified, leaving free the α,β-unsaturated carboxyl group. Mixed anhydride formation followed by a Luche reduction[34] gave the allylic alcohol **107**. On a small scale (~100 mg), no significant olefin isomerization was detected. However, on scale-up (~1 g) significant isomerization to **108** could not be avoided despite numerous attempts.

Scheme 29



Another approach to the electrophile was explored via α-methylene butyrolactone, **109**, (Scheme 30) using the method of Grieco and Pogonowski.[35] Starting with α-bromobutyrolactone, the phosphorus ylide was made, and a Wittig reaction was carried out with paraformaldehyde. The yield was low (~40%) which matched the yield reported by Grieco and Pogonowski. Careful methanolysis gave the ring-opened alcohol-ester **110**. If one terminated the reaction at about 50% conversion, then the starting material could be easily separated from the product and recycled. However, allowing the reaction to proceed until starting material was consumed resulted in a low yield of product and a large amount of an unidentified, insoluble white solid. Protection of alcohol **110** as a *tert*-butyldimethylsilyl ether was followed by reduction with DIBAL to give allylic alcohol **112** (77% over 2 steps).

Scheme 30

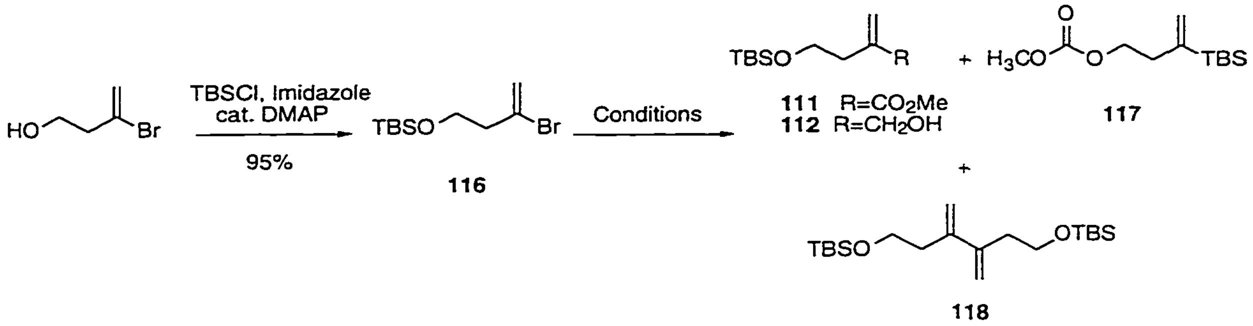


The alcohol **112** was transformed into a MEM ether in the presence of MEMCl and excess diisopropylethylamine. Deprotection of the TBS-ether with tetrabutylammonium fluoride gave the homoallylic alcohol **114**, which was converted into the homoallylic bromide **115**, by use of PPh_3Br_2-imidazole in 87% yield.

While the preceding synthesis yielded the required electrophile **115**, a shorter sequence to this material was desired. A synthesis starting with 3-bromo-3-buten-1-ol was investigated (Table 6). The alcohol was protected as a TBS ether, then halogen-metal exchange followed. The generation of the organolithium was somewhat erratic. Metal-halogen exchange in THF as the solvent resulted in dimerization (entry 1), while Et_2O employed as the solvent gave the required organolithium. Forming the analogous Grignard reagent directly from magnesium metal again yielded dimerization (entry 5), whereas Grignard formation via transmetallation of the organolithium did result in the formation of **111** but gave a poorer yield than with just the organolithium (entry 6). An additive, HMPA, was added in order to make the resulting carbanion more nucleophilic (entry 7). However, this only promoted a rearranged product **117**, in which the lithium carbanion attacked the TBS group giving a lithium alkoxide, which then gave the carbonate **117**, following methylchloroformate addition.

Both methyl chloroformate and formaldehyde were added to the carbanion **116**. Successful addition of formaldehyde would have given allylic alcohol **112** in two steps as opposed to 5 steps as noted in the previous synthesis (Scheme 30); however, formaldehyde was apparently not a reactive enough electrophile. The best results were observed with conditions shown in Table 6, entry 4. While an excellent yield of this reaction was not achieved, the synthesis of the desired electrophile **115** was now more efficient overall than starting from α-bromobutyrolactone.

Table 6: Attempts to Shorten Synthesis of Ester 111 and Alcohol 112

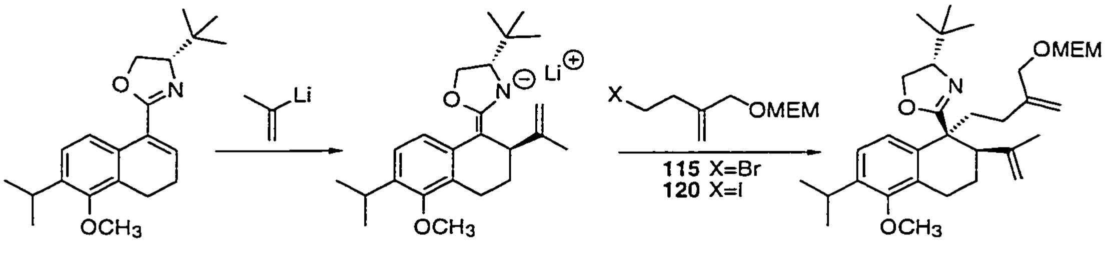


	Conditions	Results
1	2.2 eq *t*-BuLi, THF; dry HCHO, $^{-}$78°C	Dimer **118**
2	2.2 eq *t*-BuLi, Et$_2$O; dry HCHO, $^{-}$100°C to $^{-}$78°C to RT	H$^+$ quenched anion (after workup) no dimer or addition
3	3 eq LDBB, THF, HCHO $^{-}$78°C	Dimer **118**
4	2.2 eq *t*-BuLi, Et$_2$O; ClCO$_2$CH$_3$, $^{-}$78°C	50% **111**
5	Mg^0, Br(CH$_2$)$_2$Br, Et$_2$O	Dimer **118**
6	2.2 eq *t*-BuLi, Et$_2$O; MgBr$_2$; ClCO$_2$CH$_3$, $^{-}$78°C to RT	40% **111**
7	2.2 eq *t*-BuLi, Et$_2$O; HMPA; ClCO$_2$CH$_3$, $^{-}$78°C	40% **111** 40% **117**

Having obtained the desired electrophile **115**, tandem addition reactions again using oxazoline **55** were attempted. Previously reported electrophiles that have given good results in the second step were fairly simple alkyl chains without much functionality (vide supra). In this case, the electrophile was both homoallylic and highly oxygenated. The propensity of homoallylic electrophiles to undergo diene formation has already been observed and discussed earlier. Also, the oxygenated nature of **115** could potentially lead to a complex structure in solution that may render the molecule less reactive. Given these facts, it was not surprising that the reaction conditions had to be adjusted in order to obtain sufficient and reproducible results.

The first tandem additions were tried with the bromo-electrophile **115** (Table 7). The protocol developed by Meyers and Frutos (unpublished results) was followed for generating 1.6 molar equivalents of 2-lithiopropene. The oxazoline **55** was then added, after which the electrophile was added. Using these conditions, the chemical yield of product ranged between 30% and 40% while the bulk of the material appeared to be an uncharacterized mixture of compounds. Part or all of the MEM group in **115** did not remain intact. These impurities had similar TLC properties as both the starting oxazoline **55** and the initial addition product, protonated **119**, making it difficult to monitor the reaction progress.

Table 7: Tandem Addition Reactions with Oxazoline 55



55 **119** **121**

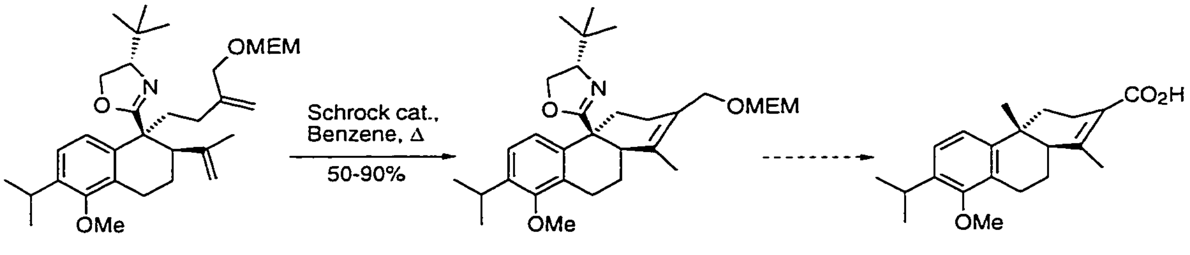
	Conditions	Results
1	(a) 4 eq *t*-BuLi, 2.4 eq 2-bromopropene, -78°C (b) **55** (c) **115**, -78°C to RT	30%-40% **121** plus uncharacterized mixture
2	(a) 4 eq *t*-BuLi, 2.4 eq 2-bromopropene, -78°C (b) **55** (c) **120**, -78°C to 0°C	20-60% **121**
3	(a) 4 eq *t*-BuLi, 2.4 eq 2-bromopropene, -78°C--50°C (b) **55** (c) **120**, -50°C to 0°C	15% **121** -some O_2-quenched **119** plus side-products from entry 1
4	(a) 2.2 eq *t*-BuLi, 1.2 eq 2-bromopropene, -78°C (b) **55** (c) 2 eq HMPA (20 min) (d) **120**, -78°C to 0°C (1 hr)	30% **121** plus side-products from entry 1

5	(a) 2.2 eq *t*-BuLi, 1.2 eq 2-bromopropene, $^{-}78$°C (b) **55** (c) 2 eq HMPA (20 min.) (d) **120**, $^{-}78$°C (5 min.)	85%-90% **121**

Changing from a bromo-electrophile to the iodo derivative, **120** (Table 7, entry 2) gave irreproducible results. Because significant addition was not detected at $^{-}78$°C, the temperature for the reaction was raised (entry 3) but with poor results. Finally, good yields for this reaction were found by adding 1 equivalent of 2-lithiopropene to the oxazoline **55**, followed by 2 equivalents of HMPA for 20 minutes and then the iodo-electrophile **120** for 5 minutes (entry 5). Apparently, $^{-}78$°C without HMPA was too cold for the nucleophilic addition step, but still an adequate temperature for undesired reactions to occur. However, $^{-}78$°C with HMPA present provided for good addition with minimal side products as long as the reaction mixture was not allowed to stir too long. The HMPA was probably responsible for more ion-pairing of the organolithium reagent making it more nucleophilic, and thus more reactive at lower temperature. *Therefore, we were able to perform a tandem addition using a functionalized, homoallylic electrophile that resulted in consistently high chemical yields and, importantly, only one detectable diastereomer.*

Having successfully synthesized tandem addition product **121** in good, reproducible yields, ring-closing metathesis (RCM) was then re-investigated to form the C-ring of the triptoquinone ring system to provide the cyclohexene **122**. Because the formation of a tetrasubstituted olefin was being attempted in the RCM process, it was not surprising that the Grubbs catalyst, known to behave poorly for highly substituted olefins,[28] failed to produce the desired product **122** (Figure 4). The Schrock catalyst[27] (purchased from Strem Chemical Co., Inc.) indeed furnished **122**. *This represented the first time that the carbon backbone of the triptoquinone ring system had been put in place* *from a compound derived from a tandem addition to a chiral 3,4-dihydronaphthyl oxazoline.* All that remained to achieve triptinin A was to convert the oxazoline to a methyl group via a previously described route and, after removal of the MEM ether, oxidize the allylic alcohol to a carboxylic acid present in the final product, triptinin A.

Figure 4



121 **122** **15** (-)-Triptinin A

For the reaction described above (Figure 4), the variations in the yield seemed to depend upon the quality of the catalyst, i. e. as evidenced by its color. Also, it was crucial to scrupulously degas all solvents via freeze/pump/thaw cycles and use the Schlenk-line technique. Furthermore, the tandem addition product **121** and the cyclized product **123** were inseparable by chromatography. Because of this and the need to avoid air in the reaction vessel, monitoring the course of the RCM without stopping it was not practical. The reaction time and temperature (30 min. at RT and 1 hr at 65°C) was decided upon by examining many literature examples of RCM reactions with the Schrock catalyst.[28,36] Any remaining starting material could not be removed until subsequent transformations resulted in products that could be separated and purified.

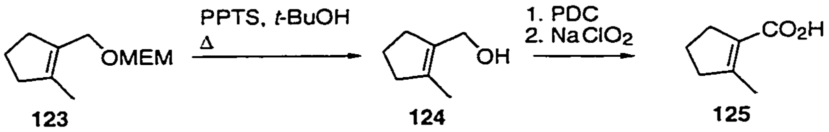
C. The Final Transformations

As previously stated, the remaining transformations to synthesize either triptinin A or triptoquinone A appeared straightforward and relatively simple, given that most of the chemistry was already known for analogous systems. For triptinin A, **15**, conversion of the oxazoline moiety to a methyl group followed by deprotection and oxidation of the allylic alcohol was all that was left to be done. Oxidation of the aromatic ring to a *p*-quinone moiety would also give triptoquinone A, **16**.

i. Model System Study

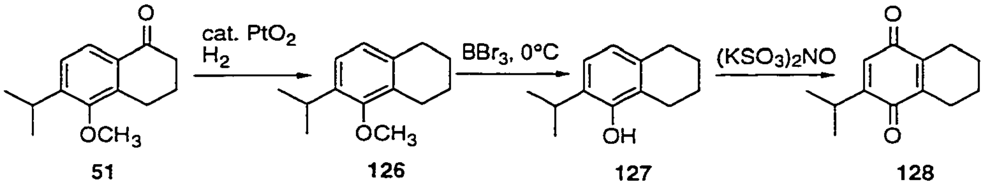
While developing a synthetic scheme for the final manipulations to triptoquinone A, a small model study was undertaken, in the hope that methods could be found to combine some of the required transformations. Compounds were chosen to mimic both the steric and electronic environment of the actual system. The cyclopentenyl MEM-ether **123** was readily deprotected following the procedure of Monti et al.[31] (Scheme 31). With the goal of combining the deprotection and oxidation steps, treatment of **125** with ceric ammonium nitrate (CAN) and sodium bromate was attempted. This method has been shown to cleave benzylic ethers;[37] however, in the present case it led to an intractable mixture. Therefore, more acceptable procedures for stepwise deprotecting and then oxidizing an allylic alcohol to a carboxylic acid gave acid **125** in good yield.[12]

Scheme 31



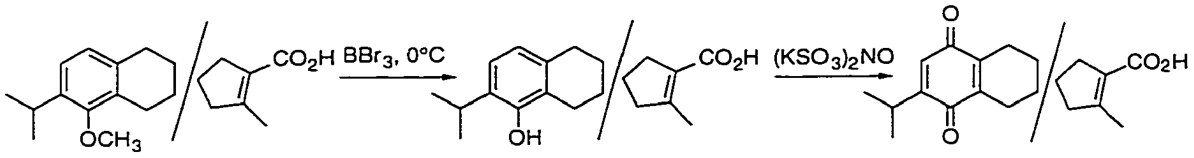
To explore the quinone oxidation, tetralone **51** was reduced to tetralin **126** with H_2 and catalytic platinum oxide (Scheme 32). The aryl methyl ether was cleaved (BBr_3, 0°C) to yield phenol **127**. Reaction temperatures below 0°C did not allow ether cleavage to occur, presumably due to the steric environment. Treatment of the phenol **127** with Fremy's salt, $(KSO_3)_2NO$,[17] gave the quinone **128** in good yield with no sign of benzylic oxidation. On the other hand, oxidation with CAN gave no quinone, but did result in some benzylic oxidation. The attempts to oxidize the aryl ether **126** directly to the quinone with both Fremy's salt and CAN were not successful.

Scheme 32



In an attempt to mimic the functional group situation of the actual system, aryl ether cleavage and oxidation to the quinone were carried out in the presence of acid **125** (Scheme 33). Both transformations worked well and the acid remained untouched. From this model study, it was concluded that the deprotection of the MEM group and oxidation sequence would have to be carried out in a stepwise fashion. Notwithstanding, it seemed that the required manipulations should be obtainable.

Scheme 33

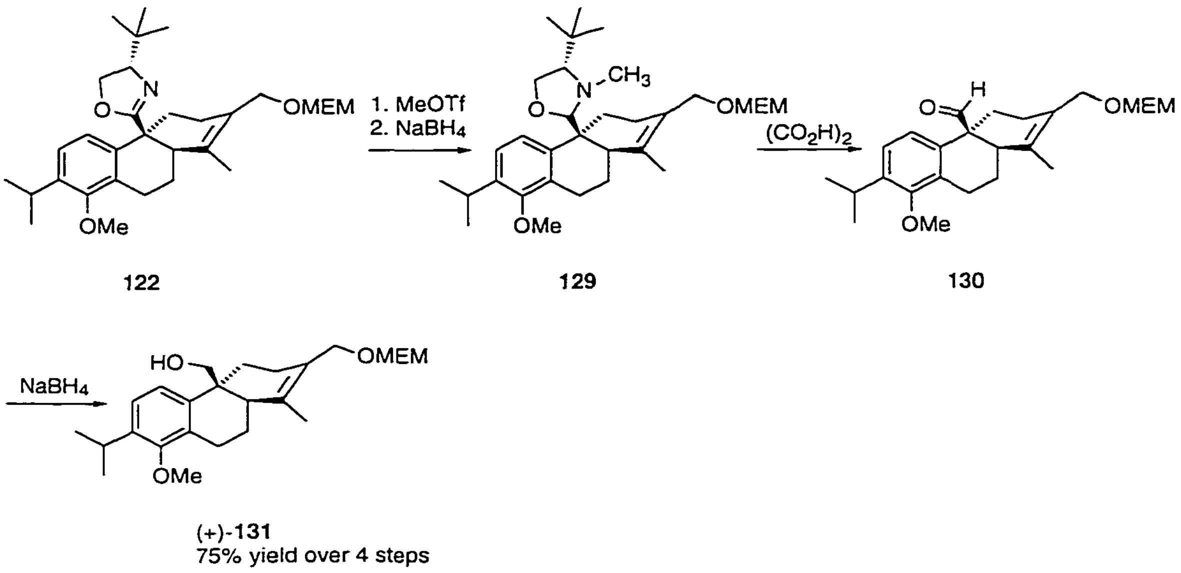


126 **125** **127** **125** **128** **125**

*ii. Conversion of Oxazoline **122** to Carbinol **131***

Returning now to the total synthesis of triptinin A, oxazoline **122** was first converted to oxazolidine **129** (Scheme 34) following the standard protocol, which at first resulted in very low yields of desired product. Oxazoline **122** was originally quaternized with 2-3 equivalents of methyl triflate in a concentrated solution of CH_2Cl_2 (~0.5M in **122**). When this material was reduced with $NaBH_4$, a complex mixture resulted with a major side product not having the MEM group intact. Apparently, the high concentration of methyl triflate allowed for oxonium ion formation and partial cleavage of the MEM group. When the procedure was changed to adding only 1.1 equivalent of methyl triflate to a 0.1M solution of **122** in CH_2Cl_2, the reaction mixture, after $NaBH_4$ reduction, became much cleaner. Further complicating matters, flash chromatography on regular silica gel led to low mass recovery, indicating the material's sensitivity to acidic conditions. Hence, the material, thereafter, was used crude after a basic aqueous workup. When the starting oxazoline **122** contained some non-cyclized material from the RCM reaction, the oxazolidine **129** could be separated from its non-cyclized counterpart on TLC, but, because of the sensitivity to silica gel, the mixture had to remain until the next step, otherwise significant loss of material occurred. No satisfactory purification of **129** was found using a neutral stationary phase.

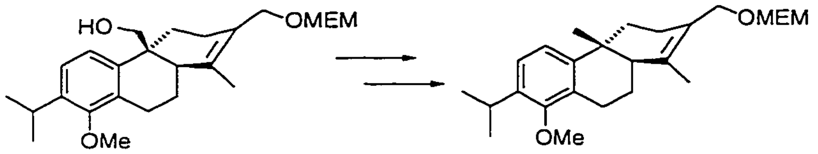
Scheme 34



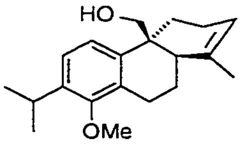
Previously, oxazolidine hydrolysis of a non-cyclized tandem addition product (compound **58**) necessitated heating to 170°C in a sealed tube. It was found that with the cyclized oxazolidine **129** hydrolysis occurred in THF/H_2O (4:1) at reflux and no elevated temperature (>80°C) was required. The oxazolidine in the cyclized case as in **129** is more accessible and therefore more readily hydrolyzed to the aldehyde **130**. Fortunately, in cases where some non-cyclized oxazolidine remained due to the incomplete RCM reaction, hydrolysis of the undesired material did not occur well and decomposition resulted, thereby allowing for easier separation of the non-cyclized contaminants. Here, once more, aldehyde **130**, like oxazolidine **129**, was sensitive to silica gel, but it could be purified using neutralized silica gel.

Finally, the important intermediate aldehyde **130** was reduced to alcohol **131** with $NaBH_4$ (Scheme 34). In order to achieve a clean reaction and good yield, it was important to keep the reaction temperature at 0°C during addition of $NaBH_4$. Also, only a slight excess of $NaBH_4$ was found to be optimum. Alcohol **131**, in enantiomerically pure form, was purified on neutralized silica gel, though it appeared not to be as sensitive to regular silica gel as its predecessors. The overall yield of the four transformations (**122**- **131**) was 75%.

iii. Deoxygenation and Oxidation



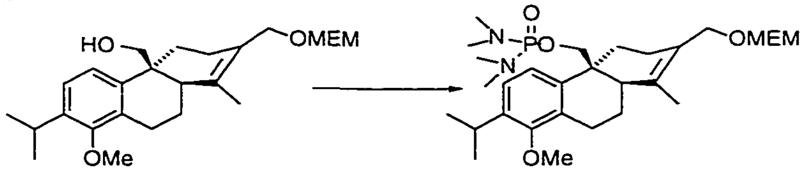
(+)-**131**   (-)-**132**



95

The next transformation in the conversion of the oxazoline moiety to a methyl group was to deoxygenate alcohol **131** to give the methyl derivative **132**. Because of the previous work done by Meyers, Kopach, and Nakano (unpublished results) on similar neopentyl alcohols, it was thought that forming the phosphorodiamidate followed by reducing with a single electron reductant would be the only likely successful method for deoxygenating alcohol **131**. Making the phosphorodiamidate was less straightforward with alcohol **131** than with the simpler analog **95** (Table 8). The same conditions that effected the formation of the phosphorodiamidate of **95** (NaH, $[N(CH_3)_2]_2P(=O)Cl$, DMF) did not perform as well with **131** (entry 1). The reasons for this dichotomy in behavior were not at all clear. Indeed, different phosphorylating reagents for each alcohol were required: $[N(CH_3)_2]_2P(=O)Cl$ for **95** and $[N(CH_3)_2]_2POCl_2$ for **131**.

Table 8: Phosphorodiamidate Formation



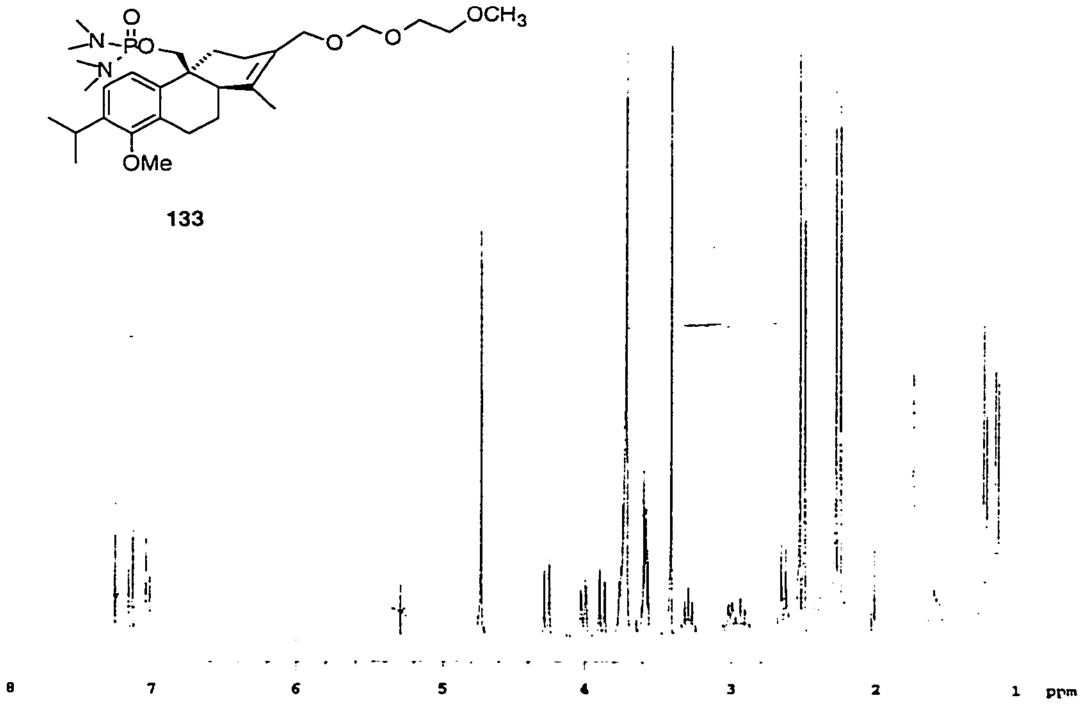
131 **133**

	Conditions	Results
1	(a) 2 eq. NaH or KH, DMF (b) 1-3 eq $[N(CH_3)_2]_2P(=O)Cl$, 0°C to RT	irreproducible yields, 10-30% **133**
2	1.1 eq. $[N(CH_3)_2]_2P(=O)Cl$, 1 eq. DMAP dry CH_3CN, 0°C	starting material
3	(a) 1.3 eq. MeLi, 2 eq. HMPA, THF, 0°C (b) 1.2 eq. $[N(CH_3)_2]POCl_2$ (c) $HN(CH_3)_2$	85% **133**

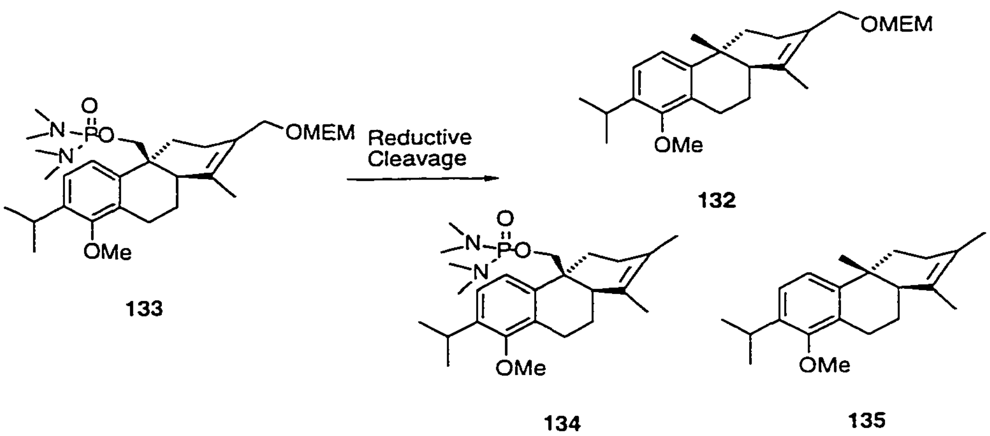
With very hindered alcohols, Liu et al.[18c] reported using N,N-dimethylphosphoramidic dichloride $\{[N(CH_3)_2]_2POCl_2\}$ followed by addition of dimethylamine to produce the N,N,N,N-tetramethylphosphorodimidate (TMPDA) moiety. By modifying the conditions reported by Liu[18c] slightly, a good yield was obtained of the phosphorodiamidate **133** (Table 8, entry 3). The lithium alkoxide was formed with methyl lithium, and then HMPA was added to increase the nucleophilicity of the anion. A chloro-N,N-dimethylphosphoramide was formed by addition of the very electrophilic $[N(CH_3)_2]POCl_2$. The desired compound **133** was then obtained upon addition of dimethylamine.

The structure of the phosphorodiamidate **133** was confirmed by ^{1}H NMR (Figure 5) and HRMS. The four singlets at 2.25, 2.28, 2.50 and 2.53 ppm represent the four -NCH$_3$ resonances of the phosphorodiamidate moiety, and the doublet at 4.0 ppm is part of an AB quartet (the other half is buried in the multiplet between 3.76 and 3.69 ppm) which corresponds to the -CH$_2$OP(=O)-. The MEM group is present as evidenced by the -OCH$_2$O- resonance at 4.73 ppm (s, 3H), and the -OCH$_3$ resonance at 3.4 ppm. The allylic -CH$_2$O- is represented by the AB system at 4.27 ppm (d, J= 11.1 hz, 1H) and 3.88 ppm (d, J= 11.1 hz, 1H).

Figure 5: 300 MHz ^{1}H NMR Spectrum of Phosphorodiamidate 133



Scheme 35

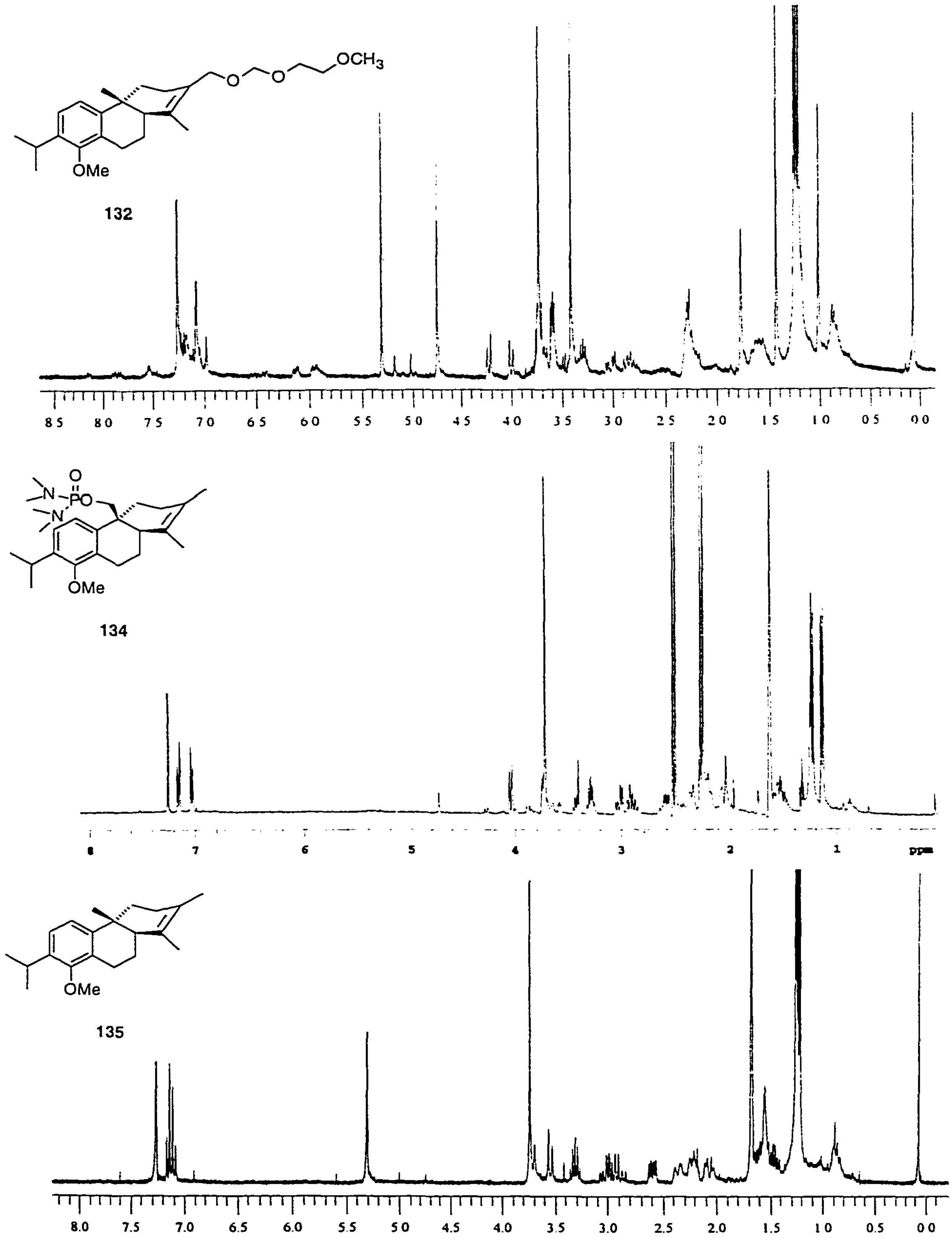


Following the procedure of Liu et al.,[18b] 3-5 equivalents of lithium naphthalenide (LN) at -10°C to 0°C was used as the single electron donor (Scheme 35). The reaction was fairly messy with a lot of the usual naphthalene by-products found with LN reactions.[38] After chromatography, analysis by NMR indicated that a small amount of product **132** was obtained. The yields of this reductive cleavage over time were inconsistent and were never greater than 20%. This material was never completely purified since a contaminant persisted even after several chromatographic attempts. Other products, **134** and **135**, which resulted from previously reported[39] allyl ether cleavage, could be separated from the desired product. For **134**, the phosphorodiamidate remained but the allyl ether was reductively cleaved, while in **135**, both substituents were reductively cleaved.

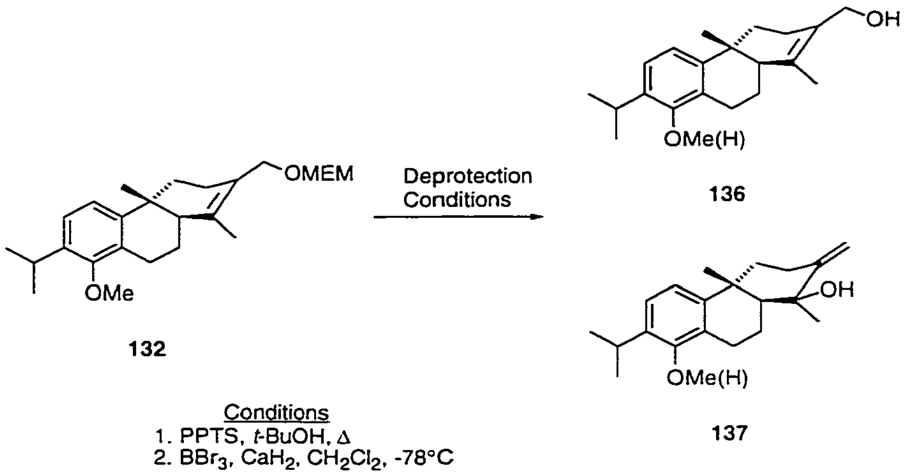
Another single electon donor, lithium 4,4'-di-*t*-butylbiphenyl (LDBB) was tried with similar results. Even though the reaction appeared to be somewhat cleaner than with LN, significant amounts of **134** and **135** were obtained. No literature examples could be found where allylic ether cleavage was performed with LDBB. With compound **133**, it was hoped that the reaction conditions could be attenuated such that no allyl ether cleavage took place. Attempts with lower reaction temperatures, fewer equivalents of reductant, different reductant (LDBB vs. LN), etc. unfortunately were not successful.

In Figure 6, the ^{1}H NMR spectra for compounds **132, 134**, and **135** are shown for comparison. As mentioned, compound **132** could not be purified; nevertheless, the presence of the MEM group (i. e. singlets representing the -OCH_2O- at 4.7 ppm and -OCH_3 at 3.4 ppm) and the lack of -NCH_3 resonances (from the phosphorodiamidate group) between 2.0 and 3.0 ppm indicate the structure shown. Furthermore, while the surrounding region is complex, the singlet resonance at 1.1 ppm most likely represents the newly formed quaternary -CH_3. With compound **134**, the spectrum shows clear -NCH_3 resonances (between 2.2 and 2.6 ppm) and no peaks corresponding to a MEM-ether indicating that the MEM-ether was cleaved while the phosphorodiamidate remained intact. With compound **135**, there are no MEM or phosphorodiamidate resonances, indicating that both moieties were reductively cleaved.

Figure 6: 300 MHz ^{1}H NMR Spectra for Compounds 132, 134, and 135



Scheme 36



132

136

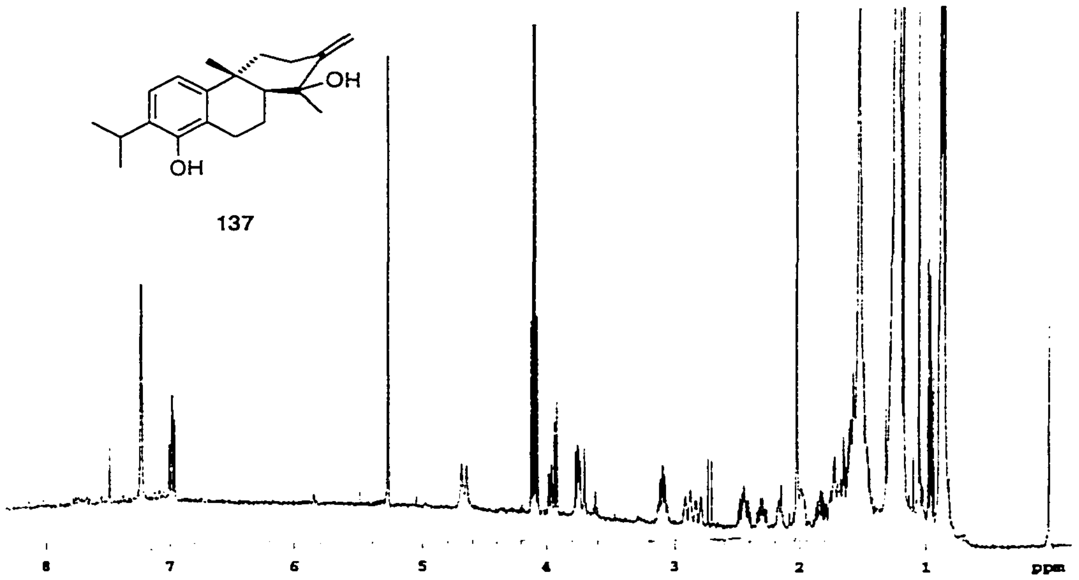
137

Conditions
1. PPTS, *t*-BuOH, Δ
2. BBr_3, CaH_2, CH_2Cl_2, -78°C

Having obtained a very small amount of the methyl derivative **132**, the removal of the MEM protecting group was attempted (Scheme 36). The procedure of Monti et al.[31] using PPTS (which worked well with the model system), was tried first. By TLC, a product of lower R_f appeared while most of the starting material still remained. It was later shown that this material was the desired product **136**. However, by the time that a significant amount of starting material was consumed, the desired product had disappeared on TLC to give material with a much higher R_f. However, BBr_3 cleavage at -78°C did result in clean conversion to **136**. Yet, despite efforts to keep both the reaction and the workup procedures nonacidic, the material, on standing, rearranged to the higher R_f material seen in the PPTS reaction. Exposure to silica gel facilitated the rearrangement.

Analysis by GC/MS indicated that the material **137** was a structural isomer of the desired product **136**. From both the mass spectra and NMR data, it was thought that the rearranged product was the tertiary alcohol **137**, the result of an apparent proton-catalyzed allylic (1,3)-rearrangement. In Figure 7, the ^1H NMR spectrum for **137** (phenol) shows vinyl peaks between 4.6 and 4.8 ppm, around where one would expect terminal olefin resonances. Because of the problems encountered in both the deoxygenation and deprotection steps, no more than a few milligrams of **136** (which could not be stored) was ever obtained. Further, the material was at best moderately pure. It was clear that this approach would never lead to a synthesis improved over that reported by Shishido and coworkers.[12]

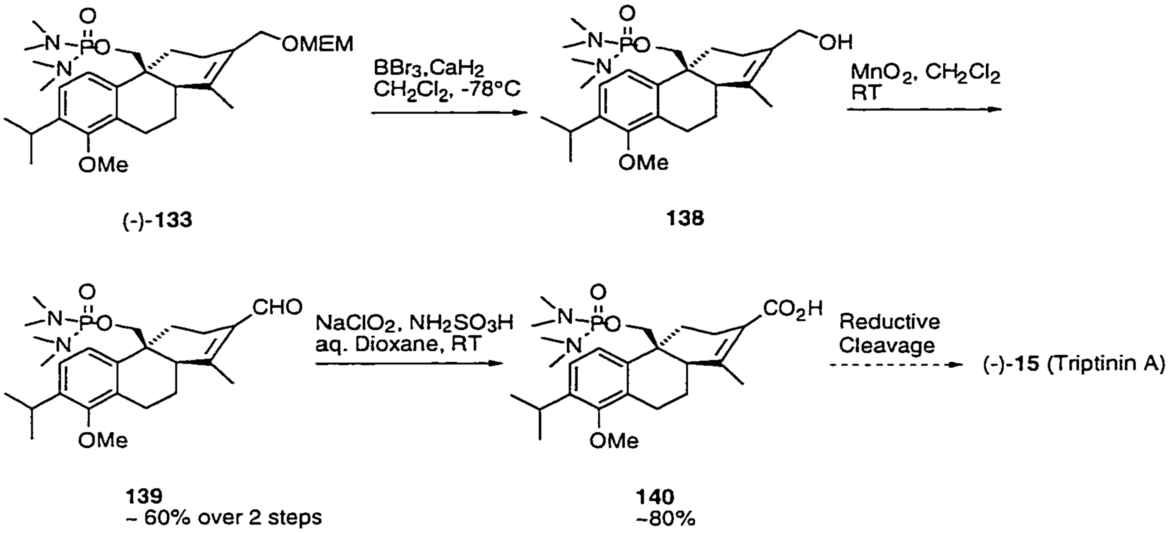
Figure 7: 300 MHz ^1H NMR Spectrum for Compound 137



Due to the problems encountered with the reductive cleavage step in the presence of an allyl ether (**133**→**132**), it was decided to leave the phosphorodiamidate group intact at this stage in the synthesis. It has been reported[18a] that the latter group is stable to CH_3Li (2.5 hr at 25°C), $LiAlH_4$-Et_2O (2.5 hr at 25°C), 1N KOH-EtOH (15 hr at reflux) and 0.2N aqueous HCl-acetone (2 hr at 25°C). Because of the relative inertness of the TMPDA as just described, it seemed that it could serve as a hydroxyl protecting group while

MEM removal and allylic oxidation were carried out. The reductive cleavage would then be postponed until the latter two steps were performed.

Scheme 37



The removal of the MEM group (Scheme 37) was done with BBr_3, as had been done with methyl derivative **132**. Because of the unstable nature of allylic alcohol **136**, the newly formed allylic alcohol **138** was never fully isolated and purified, but after washing the reaction mixture with 1N NaOH, it was treated directly with MnO_2 to furnish aldehyde **139**. The ^1H NMR spectrum of the crude aldehyde is shown in Figure 8 with the aldehydic proton clearly at 10.2 ppm. This two step procedure proceeded in ~60% yield. The resulting aldehyde **139** was oxidized with $NaClO_2$ and sulfamic acid, to afford the carboxylic acid **140** which proved to be very polar and therefore difficult to purify. The ^1H NMR spectrum of the acid **140** (Figure 8), while not clean, shows an absence of an aldehydic proton. More conclusive data came from the ^{13}C NMR, with a resonance at 171 ppm for the $-\underline{C}O_2H$ where one would expect a conjugated carboxylic acid (conjugated aldehydes are usually at 190-200 ppm). Furthermore, the HRMS data supported the correct empirical formula. At this point, all that remained to form (-)-triptinin A, **15**, was to reductively cleave the phosphorodiamidate of **140** to form the desired methyl group.

FIgure 8: 300 MHz ^{1}H NMR Spectra for Aldehyde 139 and Acid 140

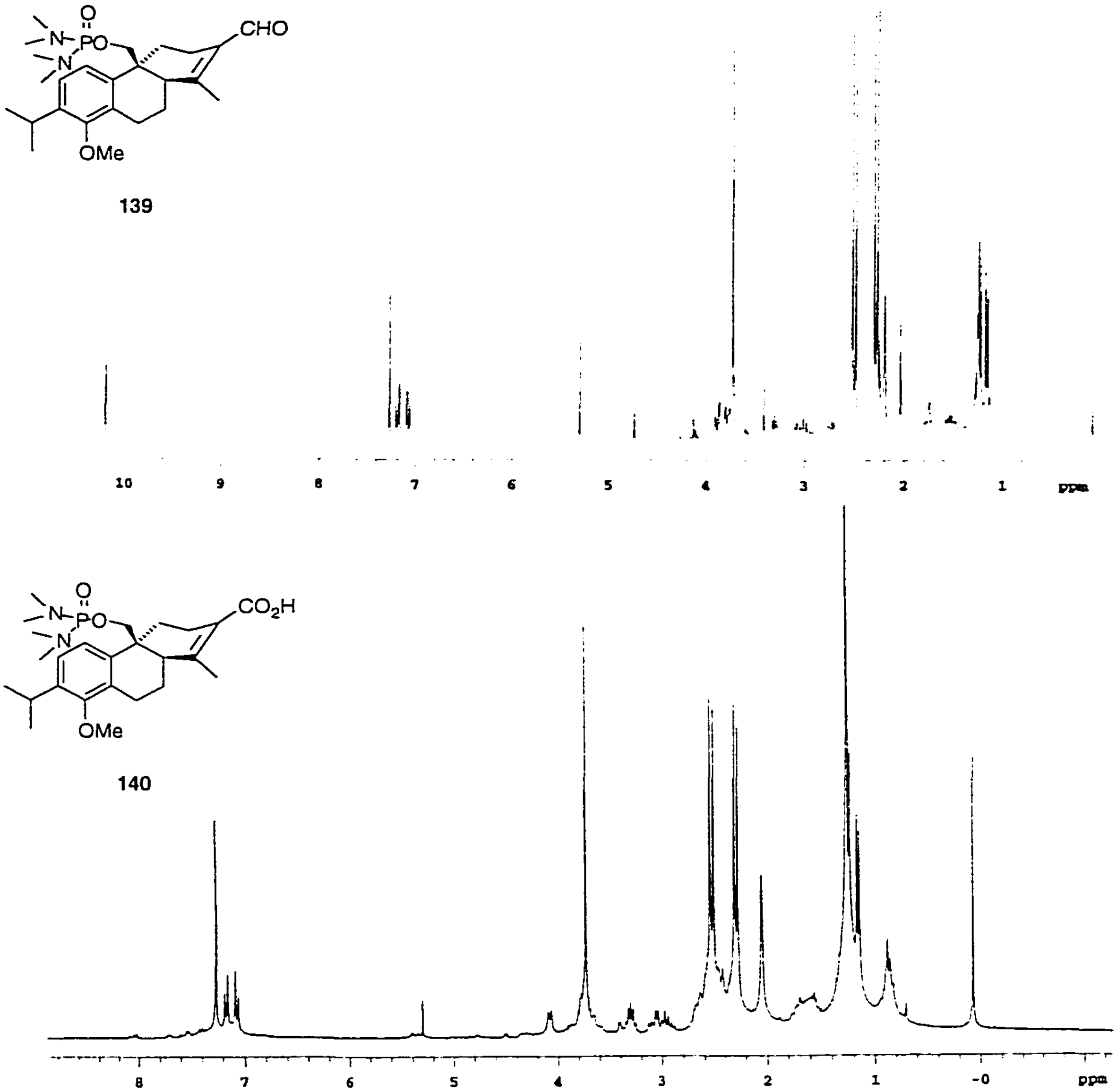
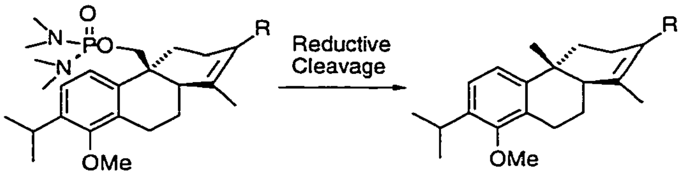


Figure 9



138 R= CH_2OH
139 R= CHO
140 R= CO_2H

Several attempts (Figure 9) were made with both LN and LDBB as reductant to cleave the phosphorodimidate of **138-140**, all of which resulted in complex reaction mixtures. Significant starting material always persisted unless excess reductant (10-20 equivalents) was added. After trying to isolate a single component by HPLC, a small amount of a mixture was obtained that possessed an NMR spectrum that was too complex to be conclusive. The mass spectral data were also inconclusive in that many peaks both of higher and lower mass were detected. The peak corresponding to the molecular weight of **15** was very small, and may have been from desired product or a fragment of another molecule. While it appeared that a trace of the natural product may have been obtained, this method seemed unlikely to ever produce the desired material in a reasonable yield.

The bulk of the material obtained in the reductive cleavage attempts on the carboxylic acid **140** was non-polar and multi-component in nature. It may have been the result of 1,4-reduction and/or reduction of the aromatic ring, similar to a Birch reduction. Reductive cleavage of aldehyde **139** also resulted in decomposition similar to that seen with **140**. Hoping to eliminate the possible problem of conjugate reduction, reductive cleavage of the TMPDA group was tried with the allylic alcohol **138**. This resulted in the very slow consumption of starting material and no sign of the desired product.

D. Summary

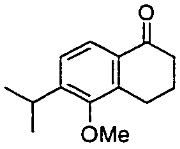
At this point, it was time to realistically examine the value of continuing this project. Due mainly to lack of material which resulted from low yielding transformations late in the synthetic scheme, further work on the project was stopped. Indeed, it is likely that approaching the natural products with both a quaternary oxazoline moiety and tetrasubstituted olefin/allylic MEM-ether functionalities, as in compound **122**, would not be viable regardless of the amount of material on hand. Even if one could devise a synthetic strategy that afforded the targets using this approach, it would be, at the very least, much longer and much lower yielding than the synthesis of Shishido et al.[12]

Although the research project was ended just short of the original ultimate goal, it was certainly a worthwhile endeavor producing important results. The scope of tandem addition chemistry on chiral naphthyl oxazolines was broadened. Methods were found to allow for addition of a complex, homoallylic electrophile avoiding the propensity for elimination. Also, the synthesis of the electrophile and the 3,4-dihydronaphthyl oxazoline was developed, and improved.

Ring-closing metatheses using both Grubbs and Schrock catalysts were successfully carried out in the presence of the oxazoline moiety, giving the first reported examples of such a case. This important reaction successfully put in place the correct ring system and the complete carbon backbone of triptoquinone/triptinin A. The remaining transformations subsequent to RCM were deceptively difficult. During the synthetic effort, conditions were worked out to convert sterically encumbered oxazolines (**58**, **92**, **122**) to the corresponding carbinols. Deoxygenation of neopentyl carbinols (**60, 95, 131**) was studied. Success was found using reductive cleavage of a phosphorodiamidate moiety in examples devoid of an allylic alcohol/ether or α,β-unsaturated aldehyde/acid, further defining the scope of the reaction.

III. Experimental

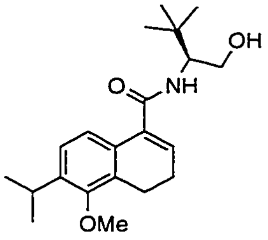
General: Nonaqueous reactions were performed under argon with flame-dried glassware. Diethyl ether, tetrahydrofuran, and benzene were dried by distillation over sodium-benzophenone. Dichloromethane, diisopropylamine, triethylamine, toluene, dimethylsulfoxide, and HMPA were distilled over CaH_2. Thin layer and flash chromatography were performed with E. Merck Kieselgel silica gel 60 (230-400 mesh A.S.T.M.) unlesss otherwise stated. Schrock catalyst was purchased from Strem Chemical Inc. and was washed with hexane under argon prior to use. N,N-Dimethylphosphoramidic dichloride was purchased from Lancaster Synthesis, Inc. and used without further purification. All other commercial compounds were purchased from Aldrich Chemical Co. and unless otherwise indicated, used without further purification. Melting points are uncorrected. Microanalyses were performed by Atlantic Microlab, Inc., Norcross, Georgia.



51

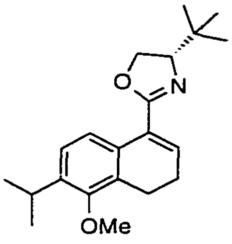
5-Methoxy-6-isopropyl-1-tetralone, 51. Using a mechanical stirrer and an oil bath that had been equilibrated to 95°C, ester **81** (2 g, 6.85 mmol) was heated in polyphosphoric acid (20 ml) for 2 h. The red reaction mixture was cooled, diluted with H_2O (100 ml) and extracted with EtOAc (3 x 50 ml). The EtOAc solution was washed with saturated aqueous $NaHCO_3$ (2 x 75 ml) and brine (100 ml). The solution was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (5% EtOAc/Hexane) of the crude, yellow residue gave 1.19 g of tetralone **51** as an off-white solid (80%); m.p.= 102-104°C; ^1H NMR

($CDCl_3$, 300 MHz) δ 1.24 (d, J= 6.6 Hz, 6H), 2.11 (dddd, J= 6.3, 6.3, 6.3, 6.3 Hz, 2H), 2.62 (dd, J= 7, 6 Hz, 2H), 2.98 (dd, J= 6,6 Hz, 2H), 3.37 (sept., J= 6.6 Hz, 1H), 3.75 (s, 3H), 7.23 (d, J= 8.2 Hz, 1H), 7.82 (d, J= 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 22.9, 23.5, 26.9, 38.8, 61.1, 123.2, 124.6, 131.9, 137.7, 147.7, 154.5, 198.1; IR (film) 1681, 1416 cm^{-1}; HRMS (FAB+) for $C_{14}H_{19}O_2$ $(M+H)^+$: Calcd 219.1385, Found 219.1382; Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.96; H, 8.33.



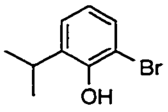
54

Amide-alcohol 54. The following were combined in order: vinyl triflate **84** (810 mg, 2.34 mmol), (*S*)-*t*-leucinol (548 mg, 4.68 mmol), triethylamine (0.82 ml, 5.88 mmol), 1,3-bis(diphenylphosphino)propane (48 mg, 0.12 mmol), and palladium (II) acetate (16 mg, 0.07 mmol). After diluting with dry DMSO (2 ml), the reaction was aerated with CO from a balloon for 15 min, and then heated at 65°C for 12 h under a CO atmosphere. After cooling to room temperature, the reaction was diluted with EtOAc (75 ml) and washed with brine (50 ml). The EtOAc solution was dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by flash chromatography (15% EtOAc/hexanes and 45% EtOAc/hexanes) to give 624 mg of **54** as a colorless foam (77%). $[\alpha]^{25}_D$= +13.7 (c=0.54, $CHCl_3$) ^1H NMR ($CDCl_3$, 300 MHz) δ 1.02 (s, 9H), 1.23 (d, J= 7.2 Hz, 6H), 2.31-2.42 (m, 2H), 2.85 (ddd, J= 7.5, 7.5, 3.3 Hz, 2H), 3.33 (sept., J= 6.9 Hz, 1H), 3.57-3.74 (m, 2H), 3.7 (s, 3H), 3.94-4.06 (m, 2H), 5.97 (br d, J= 9.3 Hz, 1H), 6.51 (app t, J= 4.6 Hz, 1H), 7.12 (d, J= 8.4 Hz, 1H), 7.22 (d, J= 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 20.6, 22.6, 23.7, 26.5, 27, 33.6, 59.7, 61.1, 63.3, 121.4, 124.4, 128.8, 130.2, 130.4, 136.5, 141.8, 154.3, 170.2; IR (film) 1644, 1610 cm^{-1}; HRMS (FAB+) for $C_{21}H_{32}NO_3$ $(M+H)^+$: Calcd 346.2382, Found 346.2388.



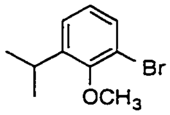
55

Dihydronaphthyl oxazoline 55. To a solution of amide-alcohol **54** (500 mg, 1.45 mmol) in CH_2Cl_2 (15 ml) at 0°C was slowly added thionyl chloride (0.23 ml, 3.19 mmol). After stirring for 2 h, the solvent was removed. The residue was dissolved in CH_3CN (8 ml) and saturated aqueous K_2CO_3 (5 ml). The solution was heated to reflux for 6 h. Upon cooling, the solvent was removed and the residue dissolved in EtOAc (100 ml) and washed with brine (2 x 50 ml). The EtOAc solution was dried over Na_2SO_4, filtered and concentrated. The crude material was purified by flash chromatography (5% EtOAc/hexanes and 10% EtOAc/hexanes) to yield **55** (394 mg, 83%) as a slow-forming, cream solid. The product could be stored under argon at -18°C for several weeks; however, at room temperature, decomposition began to occur within 24 h; mp= 78-80°C; $[\alpha]^{25}_{D}$= -149 (c=0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21 (d, J= 2.25 hz, 3H), 1.24 (d, J=2.25, 3H), 2.35 (m, 2H), 2.66 (ddd, J= 15.3, 11.7, 6.4 Hz, 1H), 2.94 (ddd, J= 15.2, 6.6, 6.6 Hz, 1H), 3.32 (ddd, J= 13.8, 6.8, 6.8 Hz, 1H), 3.67 (s, 3H), 4.04 (dd, J= 10.1, 7.7 Hz, 1H), 4.13 (dd, J= 8.1, 8.1 Hz, 1H), 4.24 (dd, J= 10.1, 8.4 Hz, 1H), 6.88 (dd, J= 5.4, 4.35 Hz, 1H), 7.14 (d, J= 8.1 Hz, 1H), 7.74 (d, J= 8,1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 20.5, 23, 23.7, 26, 26.5, 33.9, 61.1, 67.5, 77.6, 122.6, 124, 127.5, 128.9, 130.6, 135.1, 141, 153.9, 162.3; IR(film) 1650, 1482; HRMS (FAB+) for $C_{21}H_{30}NO_2$ $(M+H)^+$: Calcd 328.2276 Found 328.2281.



75

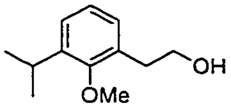
2-Bromo-6-isopropyl phenol, 75. To a solution of 2-isopropyl phenol (18.3 g, 0.134 mol) in CS_2 (500 ml) was added N-bromosuccinimide (24 g, 0.134 mol) as a solid over 1 h. The reaction was stirred at room temperature for 12 h and a off-white precipitate was formed. The solvent was removed, and the residue was dissolved in Et_2O (350 ml). The Et_2O solution was washed with 10% aqueous sodium thiosulfate (2 x 150 ml), and brine (100 ml). After drying over $MgSO_4$, the solution was filtered and concentrated. Flash chromatography (0.5% EtOAc/Hexane) of the crude material produced 24.9g of **75** as a clear liquid (86%). b.p= 125-130°C (25 mmHg); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24 (d, J= 6 Hz, 6H), 3.32 (sept., J= 6 Hz, 1H), 5.58 (s, 1H), 6.78 (t, J= 7.8 Hz, 1H), 7.14 (d, J=9.6 Hz, 1H), 7.30 (d, J= 9.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 22.4, 28.1, 110.6, 121.5, 125.8, 129, 136.3, 149.3; *m/z* 214/216 (M^+).



76

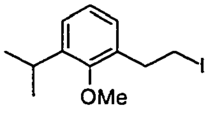
2-Bromo-6-isopropyl anisole, 76. Following the procedure of McKillop et al.,[22] a biphasic mixture of 2-bromo-6-isopropyl phenol **75** (15.83 g, 73.63 mmol), dimethyl sulfate (14 g, 111 mmol), $LiOH•H_2O$ (4.94 g, 118 mmol), and benzyl tributylammonium chloride (2.3 g, 7.3 mmol) in CH_2Cl_2/H_2O (1:1, 600 ml) was stirred at room temperature for 12 h. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 100 ml). The CH_2Cl_2 extracts were combined and stirred with 300 ml of a 10% NH_4OH solution for 5 h. The phases were separated and the organic phase was dried over Na_2SO_4

and concentrated. Flash chromatography (1% EtOAc/hexanes) yielded 15.5 g (92%) of a clear liquid, **76**; b.p.=120-125°C (20 mmHg); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23 (d, J= 6.9 Hz, 6H), 3.36 (sept., J= 6.9 Hz, 1H), 3.83 (s, 3H), 6.97 (t, J= 7.8 Hz, 1H), 7.2 (dd, J= 7.8, 1.5 Hz, 1H), 7.37 (dd, J= 7.8, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 23.7, 27.2, 61.3, 117.4, 125.6, 125.9, 130.8, 144, 154.2; *m/z* 228/230 (M^+); Anal. Calcd for $C_{10}H_{13}OBr$: C, 52.42; H, 5.72. Found: C, 52.13; H, 5.90.



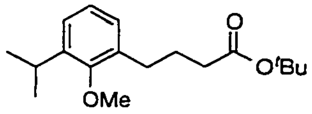
78

Phenethyl alcohol 78. A solution of 2-bromo-6-isopropyl anisole **76** (3 g, 13.1 mmol) in 10 ml dry THF (dried over NaH and decanted) at -78°C was degassed by evacuating the system under vacuum until solvent bubbled and then purging the system with Argon. This process was repeated 5 times. The solution was then slowly added via cannula to a solution of *n*-butyl lithium (2.4M in hexane, 5.7 ml, 13.7 mmol) at -78°C, which had also been degassed at described above. After stirring 15 min, $BF_3 \bullet Et_2O$ (2.04 g, 14.4 mmol) was added and the reaction was stirred 30 min, becoming brighter yellow over time. Ethylene oxide (~1 ml) was condensed into the reaction. After stirring for 2 h at -78°C, saturated aqueous NH_4Cl (30 ml) was added and the mixture was allowed to warm to room temperature. The mixture was extracted with EtOAc (3 x 50 ml). The extract was then dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (gradient from 10% to 25% EtOAc/Hexanes) yielded **78** (2.03 g, 80%) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24 (d, J= 6.9 Hz, 6H), 1.98 (t, J= 5.4 Hz, 1H), 2.93 (t, J= 6.6 Hz, 2H), 3.33 (sept, J= 6.9 Hz, 1J), 3.77 (s, 3H), 3.87 (q, J= 6 Hz, 2H), 7.02-7.10 (m, 2H), 7.17 (dd, J= 6.6, 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 24, 26.3, 33.9, 61.7, 63.5, 124.6, 125.3, 128.1, 131.7, 142.1, 155.8; IR (neat) 3358 (br), 1462 cm^{-1}; HRMS (FAB+) for $C_{12}H_{18}O_2$ (M)$^+$: Calcd 194.1307 Found 194.1289.



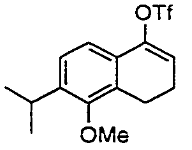
80

Phenethyl iodide 80. To 40 ml of CH_2Cl_2 was added triphenylphosphine (2.76 g, 10.5 mmol) and iodine (2.89 g, 11.38 mmol). After stirring 20 min, imidazole (835 mg, 12.3 mmol) was added, followed by phenethyl alcohol **78** in 10 ml CH_2Cl_2. The reaction was allowed to warm to room temperature slowly. After 12 h, the reaction was diluted with EtOAc (100 ml), washed with 10% aqueous sodium thiosulfate (2 x 75ml) and brine (50 ml). The EtOAc solution was dried over Na_2SO_4, filtered, and concentrated. The crude residue was flushed through a plug of silica with 10% EtOAc/Hexane to yield 2.49 g (94%) of **80** as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23 (d, J= 7.5 Hz, 6H), 3.21 (t, J= 7.5 Hz, 2H), 3.32 (sept, J= 6.6 Hz, 1H), 3.37 (t, J= 7.5 Hz, 2H), 3.76 (s, 3H), 7.01 (dd, J= 10.5, 2.1 Hz, 1H), 7.07 (t, J= 7.5 Hz, 1H), 7.2 (d, J= 10.5, 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 4.6, 24, 26.4, 35.5, 61.9, 124.5, 125.7, 127.3, 133.6, 142.2, 155.4; IR (neat) 1463 cm^{-1}.



81

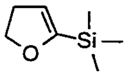
Ester 81. To a solution of dry diisopropylamine (0.31 g, 3.01 mmol) in 6 ml dry THF at -78°C was added *n*-butyl lithium (1.95M in hexane, 2.74 mmol, 1.4 ml). After stirring 15 min, *t*-butyl acetate (315 mg, 2.74 mmol) was added dropwise, and the reaction was stirred for 30 min at -78°C. In a separate flask, iodide **80** (1 g, 3.29 mmol) and dry HMPA (982 mg, 5.48 mmol) were mixed in 5 ml THF and cooled to -78°C. The anion was then added via cannula into the iodide **80**/HMPA solution, dropwise. After stirring 5 h at -78°C, the solution was quenched with saturated aqueous NH_4Cl (20 ml) and allowed to warm to room temperature. The mixture was extracted with EtOAc (3 x 25 ml). The organic phase was washed with brine (50 ml), dried over Na_2SO_4, filtered and concentrated. Flash chromatography (gradient: Hexanes to 2% EtOAc/Hexanes) yielded 685mg (85%) of **81** as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23 (d, J= 6.6 Hz, 6H), 1.45 (s, 9H), 1.9 (q, J= 7.5 Hz, 2H), 2.28 (t, J= 7 Hz, 2H), 2.66 (t, J= 7.8 Hz, 2H), 3.32 (sept., J= 6.6 Hz, 1H), 3.73 (s, 3H), 7.04-7.02 (m, 2H), 7.12 (dd, J= 6.3, 3.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 24.1, 26.2, 26.4, 28.2, 29.3, 35.4, 61.7, 80, 124.2, 124.4, 127.4, 134.4, 141.8, 155.4, 172.8; IR (neat) 1729, 1462 cm^{-1}; HRMS (FAB+) for $C_{18}H_{28}O_3$ $(M)^+$: Calcd 292.2038 Found 292.2040; Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.98; H, 9.72.



84

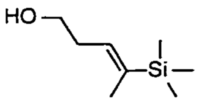
Vinyl triflate 84. To a solution of tetralone **51** (500 mg, 2.29 mmol) in 8 ml THF at -78°C was slowly added potassium bis(trimethylsilyl)amide (0.5M in toluene, 5.5 ml, 2.75 mmol). The reaction was stirred for 1 h, becoming homogenous. To this was added N-phenyltriflimide (1.07 g, 3 mmol) in 3 ml THF. After stirring 1 h at -78°C, the mixture was allowed to warm to room temperature. Saturated aqueous NH_4Cl (20 ml) was added, and the mixture was extracted with EtOAc (3 x 20 ml). The EtOAc solution was dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by flash chromatography (2.5% EtOAc/hexanes) to yield **84** as a light brown oil (800 mg, 99%). The material could be stored at -18°C under argon for several days. After that, significant decomposition was noted. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23 (d, J= 6.9 Hz, 6H), 2.48 (ddd, J= 8.4, 4.2, 4.2 Hz, 2H), 2.9 (dd, J= 8.1, 8.1 Hz, 2H), 3.32 (sept., J= 6.9 Hz, 1H), 3.71 (s, 3H), 5.96 (dd, J= 4.95, 4.95 Hz, 1H), 7.12 (d, J= 8.4 Hz, 1H), 7.16 (d, J= 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 20.4, 22.1, 23.7, 26.7, 61.2, 116.8, 117.5, 124.6, 127.6, 128.9, 130 (q, $J_{13C\text{-}19F}$= 75 Hz), 143.4, 146.2, 154.3; HRMS (FAB+) for $C_{15}H_{17}F_3O_4S$ $(M)^+$: Calcd 350.0800 Found 350.0801.

Compounds **86-89** were made following the procedures of Kocienski et al.[23] with slight modifications:



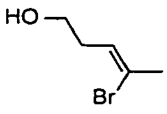
86

2-Trimethylsilyl-4,5-dihydrofuran, 86. A solution of 2,3-dihydrofuran (2 g, 28.6 mmol) in 5 ml dry THF was added dropwise to *t*-butyl lithium (1.7M in pentane, 18.5 ml, 31.5 mmol) at -78°C. A lemon yellow precipitate formed. After 10 min, the mixture was placed in a -40°C bath for 30 min, followed by a 0°C bath for 30 min. The mixture was then rechilled to -78°C, and a solution of trimethylsilyl chloride (3 ml, 23.9 mmol) in 8 ml THF was added slowly. Upon completion of addition, the solution was allowed to warm to room temperature and stir 1 h. The white slurry was then poured onto a mixture of 2 ml saturated aqueous NH_4OH and 18 ml saturated aqueous NH_4Cl. The mixture was extracted with Et_2O (3 x 30 ml). The extract was washed with brine (100 ml), dried over $MgSO_4$ and filtered. Careful concentration (via rotary evaporator with a 0°C bath) yielded **86** (2.3 g, 68%) as a volatile oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.15 (s, 9H), 2.58 (ddd, J= 9.9, 9.9, 2.7 Hz, 2H), 4.28 (t, J= 9.9 Hz, 2H), 5.19 (t, J= 2.7 Hz, 1H). Spectra were in agreement with previously reported data.[23]



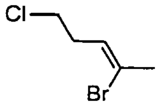
87

(E)-4-Trimethylsilylpent-3-en-1-ol, 87. To a solution of $NiCl_2(PPh_3)_2$ (460 mg, 0.7 mmol) in 10 ml dry benzene was added MeMgBr (3M in Et_2O, 7.5 ml, 22.5 mmol). The mixture was stirred for 20 min yielding a dark purple/brown color. 2-trimethylsilyl-4,5-dihydrofuran, **86** (1 g, 7.04 mmol) in 8 ml benzene was added and the reaction was heated to reflux for 3 h. After cooling to room temperature, the dark reaction mixture was poured onto a mixture of 2 ml saturated aqueous NH_4OH and 18 ml saturated aqueous NH_4Cl while stirring. After stirring 30 min, the mixture was extracted with EtOAc (3 x 50 ml). The EtOAc portion was washed with brine (100 ml), dried over $MgSO_4$, and concentrated to give ~500 mg of **87** as a yellow oil. The material was used without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.06 (s, 9H), 1.71 (s, 3H), 2.4 (q, J= 6.6 Hz, 2H), 3.68 (t, J= 6.6 Hz, 2H), 5.71 (t, J= 6.6 Hz, 1H). Spectra were in agreement with previously reported data.[23]



88

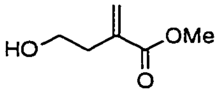
(Z)-4-Bromopent-3-en-1-ol, 88. A 2.4M solution of bromine in CH_2Cl_2 was added dropwise to 4-trimethylpent-3-en-1-ol, **87** in 4 ml CH_2Cl_2 at -78°C, until a yellow color persisted. Upon addition of 2 ml MeOH, the reaction was allowed to warm to room temperature. A saturated aqueous solution of sodium thiosulfate was added (~1 ml) and stirred until decolorization had occurred. Solvent was removed and the residue was dissolved in Et_2O (40 ml). The Et_2O solution was washed with H_2O (40 ml). After concentration, the residue was dissolved in a solution with 1.5 eq NaOMe and 10 ml MeOH. Stirring was maintained for 10 min and the mixture was diluted with 10 ml H_2O and extracted with Et_2O (40 ml). The Et_2O solution was dried over $MgSO_4$, filtered and concentrated to give 250 mg of **88** as a dark oil. The material was used without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.25 (s, 3H), 2.43 (q, J= 6.6 Hz, 2H), 3.71 (t, J= 6.6 Hz, 2H), 5.7 (t, J= 7.5 Hz, 1H). Spectra were in agreement with previously reported data.[23]



89

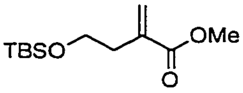
(Z)-2-Bromo-5-chloro-pent-2-ene, 89. To a solution of (Z)-4-bromopent-3-en-1-ol, **88** (200 mg, 1.21 mmol), in 2 ml CH_2Cl_2 at 0°C was added thionyl chloride (106 μl, 1.45 mmol). The solution was allowed to warm slowly to room temperature. After stirring 3 h, saturated aqueous $NaHCO_3$ (5 ml) was added. Upon addition of 10 ml CH_2Cl_2, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 ml). The CH_2Cl_2 solution was dried over Na_2SO_4, filtered and concentrated. Flash chromatography (2%

EtOAc/hexanes) yielded 177 mg (80%) of **89** as a slightly yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.31 (s, 3H), 2.53 (q, J= 6 Hz, 2H), 4.11-3.94 (m, 2H), 5.68 (t, J= 6.7 Hz, 1H). No further characterization was attempted.



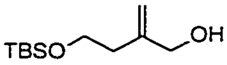
110

Methyl 4-hydroxy-2-methylene-butanoate, 110. To a solution of γ-methylene-butyrolactone[35] (2.16 g, 22 mmol) in 100 ml MeOH was added 0.5 ml concentrated H_2SO_4. The solution was heated at reflux for 6 h, cooled, and filtered. After addition of 100 ml H_2O, the MeOH was removed *in vacuo*. The residue was extracted with EtOAc (3 x 75 ml), washed with brine (100 ml), dried over Na_2SO_4 and concentrated. Flash chromatography (25% EtOAc/hexanes and 50% EtOAc/hexanes) removed product from remaining starting material to yield **110** as a clear liquid (1.2 g, 45%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, J= 7.2 Hz, 1H), 2.58 (t, J= 6 Hz, 2H), 3.77 (br s, 5H), 5.67 (d, J= 1.5 Hz, 1H), 6.24 (d, J= 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 35.5, 52, 61.6, 127.4, 137.3, 167.8; IR(neat) 3387 (br), 1719, 1629 cm^{-1}.



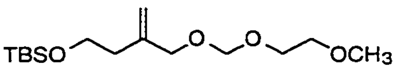
111

Methyl 4-(tert-butyldimethylsilyloxy)-2-methylenebutanoate, 111. *t*-Butyl lithium (2M in pentane, 4 ml, 8 mmol) was added slowly to a solution of 2-bromo-4-*t*-butyldimethylsilyloxy-1-butene (1 g, 3.77 mmol) in dry Et_2O (30 ml). After 15 min., methyl chloroformate (465 mg, 4.92 mmol) was added and the solution was stirred for 30 min. Saturated aqueous NH_4Cl (15 ml) was added and the mixture was allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 15ml). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo* at room temperature (30 mmHg). The crude residue was purified by flash chromatography (2.5% Et_2O/petroleum ether) to give **111** as a tan oil (460 mg, 50%). ^1H NMR ($CDCl_3$, 300 MHz) δ 2.53 (t, J= 6.6 Hz, 2H), 3.72 (t, J= 6.6 Hz, 2H), 3.74 (s, 3H), 5.62 (d, J= 1.5 Hz, 1H), 6.2 (d, J= 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.4, 18.3, 25.9, 35.5, 51.8, 61.8, 127, 137.2, 167.5; IR (neat) 1723, 1632 cm^{-1}.



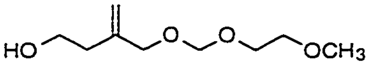
112

4-(tert-Butyldimethylsilyloxy)-2-methylene-1-butanol, 112. To a solution of methyl 4-(*t*-butyldimethylsilyloxy)-2-methylenebutanoate, **111** (520 mg, 2.13 mmol) in 15 ml THF at 0°C was slowly added diisobutyl aluminum hydride (2M in toluene, 3.2 ml, 6.4 mmol). The reaction was stirred for 3 h, afterwhich 25 ml of 1N NaOH was slowly added. The phases were separated and the aqueous phase was extracted with EtOAc (2 x 25 ml). The organic phase was dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (5% EtOAc/hexanes and 10% EtOAc/hexanes) gave 414 mg of **112** (90%) as a light yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.07 (s, 6H), 0.9 (s, 9H), 2.34 (t, J= 6 Hz, 2H), 2.77 (t, J= 6 Hz, 1H), 3.75 (t, J= 6 Hz, 2H), 4.07 (d, J= 5.7 Hz, 2H), 4.9 (br s, 1H), 5.04 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.5, 18.3, 25.9, 37.1, 63.4, 66.4, 112.5, 147.2; IR (neat) 3357 (br), 1649 cm^{-1}; Anal. Calcd for $C_{11}H_{24}O_2Si$: C, 61.06, H, 11.18. Found: C, 61.33, H, 11.28.



113

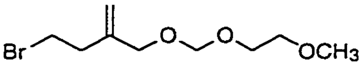
Allylic MEM-ether 113. To a solution of 4-(*t*-butyldimethylsilyloxy)-2-methylene-1-butanol, **112** (2 g, 9.26 mmol) and diisopropylethylamine (5.32 ml, 30.7 mmol) in 6 ml CH_2Cl_2 at room temperature was added 2-methoxyethoxymethyl chloride (MEM-Cl) (1.6 ml, 14 mmol). After stirring for 24 h, the reaction was diluted with EtOAc (40 ml), and then washed with 10% aqueous $CuSO_4$ (2 x 40 ml) and brine (40 ml). The solution was dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (10% EtOAc/hexanes) produced the product **113** as an oil (2.4 g, 85%). ^1H NMR ($CDCl_3$, 300 MHz) δ 0.04 (s, 6H), 0.88 (s, 9H), 2.28 (dd, J= 6, 6 Hz, 2H), 3.39 (s, 3H), 3.55-3.56 (m, 2H), 3.69-3.74 (m, 4H), 4.02 (br s, 2H), 4.73 (s, 2H), 4.93 (br s, 1H), 5.08 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.3, 18.3, 25.9, 36.7, 59, 62.1, 66.8, 70.4, 71.8, 94.7, 113, 142.8; IR (neat) 1652, 1464 cm^{-1}; HRMS (FAB+) for $C_{15}H_{33}O_4Si$ $(M+H)^+$: Calcd 305.2148 Found 305.2143 .



114

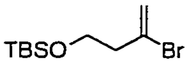
Alcohol 114. To a solution of the allylic MEM-ether **113** (2 g, 6.58 mmol) in THF (20 ml) at room temperature was added tetrabutylammonium fluoride (1M in THF, 8.6 ml) and the reaction was stirred for 3 h. The solvent was removed and the residue was dissolved with EtOAc (75 ml). The EtOAc solution was washed with brine (2 x 50 ml), dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (25% EtOAc/hexanes and 50% EtOAc/hexanes) yielded alcohol **114** (1.18 g, 94%) as a clear oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.36 (t, J= 6 Hz, 2H), 3.39 (s, 3H). 3.55-3.58 (m, 2H), 3.70-3.77 (m, 4H), 4.05 (s, 2H), 4.75 (s, 2H), 5.03 (br s, 1H), 5.16 (br s, 1H); ^{13}C NMR

($CDCl_3$, 75MHz) δ 37.1, 59, 61.1, 67, 70.4, 71.7, 94.7, 115, 142.5; IR (neat) 3444 (br), 1652 cm^{-1}; HRMS (FAB+) for $C_9H_{18}O_4$ $(M+H)^+$: Calcd 191.1283 Found 191.1282.



115

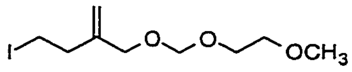
Bromide 115. To a solution of dibromotriphenylphosphorane (purchased from Aldrich Chemical Co.) (1.26 g, 2.99 mmol) and imidazole (234 mg, 3.44 mmol) in CH_2Cl_2 (5 ml) at 0°C was added alcohol **114** (435 mg, 2.29 mmol) in CH_2Cl_2 (3 ml). The mixture was stirred for 8 h while allowing it to gradually warm to room temperature. After removing the insolubles by filtration, the solvent was removed. The crude residue was flushed through a plug of basic alumina (30% EtOAc/hexanes) to yield **115** (504 mg, 87%) as a light yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.65 (t, J= 7.5 Hz, 2H), 3.4 (s, 3H), 3.5 (t, J= 7.5 Hz, 2H), 3.55-3.58 (m, 2H), 3.69-3.72 (m, 2H), 4.05 (s, 2H), 4.72 (s, 2H), 5.01 (br s, 1H), 5.16 (br s 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 30.6, 36.6, 58.9, 66.8, 69.6, 71.6, 94.5, 114.6, 142.4; IR (neat) 1653, 1455 cm^{-1}.



116

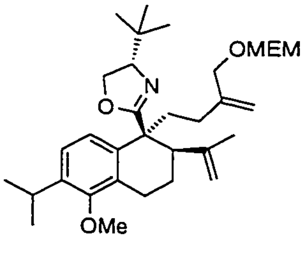
2-Bromo-4-(tert-butyl-dimethylsilyloxy)-1-butene, 116. To a solution of 3-bromo-3-buten-1-ol (860 mg, 5.7 mmol) in DMF (4 ml) was added *t*-butyldimethylsilyl chloride (1.12 g, 7.4 mmol), imidazole (582 mg, 8.55 mmol) and a catalytic amount of 4-dimethylaminopyridine. The reaction was allowed to stir at room temperature for 12 h, and then was diluted with Et_2O (50 ml). The solution was washed with brine (3 x 150 ml), dried over Na_2SO_4, and concentrated. The material was purified by flash chromatography (2% EtOAc/hexanes) to give the product **116** (1.25 g, 85%) as a clear liquid. ^1H

NMR ($CDCl_3$, 300 MHz) δ 0.07 (s, 6H), 0.89 (s, 9H), 2.62 (t, J= 6.3 Hz, 2H), 3.79 (t, J= 6.3 Hz, 2H), 5.45 (s, 1H), 5.63 (s, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ -5.3, 18.3, 25.9, 44.8, 60.8, 118.4, 130.8; Anal. Calcd for $C_{10}H_{21}BrOSi$: C, 45.28, H, 7.98. Found: C, 45.30, H, 8.04.



120

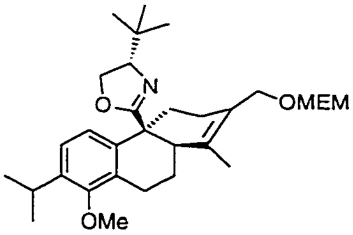
Iodide 120. To a solution of PPh_3 (497 mg, 1.89 mmol) in CH_2Cl_2 (8 ml) at 0°C was added iodine (522 mg, 2.06 mmol), and the mixture was stirred 30 min. Imidazole (150 mg, 2.2 mmol) was added followed by alcohol **114** (300 mg, 1.58 mmol) in CH_2Cl_2 (3 ml). The mixture was stirred for 10 h while allowing to warm to room temperature, and the insolubles were removed by filtration and washed with Et_2O (50 ml). After concentration of the mother liquor, the crude residue was flushed through a plug of basic alumina (30% EtOAc/hexanes) to give **120** as an oil (430 mg, 91% yield). ^1H NMR ($CDCl_3$, 300 MHz) δ 2.66 (t, J=7.8 hz, 1H), 3.28 (t, J= 7.5 hz, 2H), 3.4 (s, 3H), 3.55-3.58 (m, 2H), 3.70-3.73 (m, 2H), 4.04 (s, 2H), 4.72 (s, 2H), 4.99 (s, 1H), 5.16 (s, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 3.2, 37.7, 59.1, 67, 69.5, 71.8, 94.6, 114.3, 143.9; IR (neat) 1652, 1455 cm^{-1}; HRMS (FAB+) for $C_9H_{18}O_3I$ $(M+H)^+$: Calcd 301.0301 Found 301.0303.



121

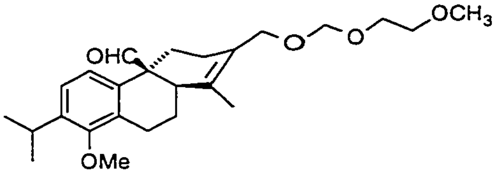
Oxazoline Adduct 121. *t*-Butyl lithium (1.7M in pentane, 0.94 ml, 1.59 mmol) was added dropwise to a solution of 2-bromopropene (92 μl, 1.03 mmol) in

6ml dry THF at -78°C. After stirring 15 min, a solution of oxazoline **55** in 2 ml dry THF was added and the reaction mixture was stirred 15 min at -78°C. Dry HMPA (277 µl, 1.59 mmol) was added and the solution was allowed to stir another 20 min at -78°C. Iodide **120** (358 mg, 1.19 mmol) was added and after 5 min the reaction was stopped by addition of saturated aqueous NH_4Cl (10 ml). After addition of EtOAc (6 ml), the phases were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by flash chromatography (5% EtOAc/hexanes and 15% EtOAc/hexanes) to yield **121** as a viscous, light yellow oil (370 mg, 86%). $[\alpha]^{25}{}_D$= -157 (c= 0.42, $CHCl_3$), ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (s, 9H), 1.24 (d, J= 6.6 Hz, 3H), 1.25 (d, J= 6.6 Hz, 3H); 1.45 (ddd, 14.7, 6.6, 6.6 Hz, 1H), 1.75 (s, 3H), 1.79-1.84 (m, 1H), 1.96 (ddd, J= 14.7, 6.6, 6.6 Hz, 1H), 2.35-2.68 (m, 5H), 3.14 (br d, J= 16.5 Hz, 1H), 3.31 (sept., J= 6.9 Hz, 1H), 3.43 (s, 3H), 3.56-3.59 (m, 2H), 3.69-3.8 (m, 3H), 3.76 (s, 3H), 3.92 (app t, J= 8.1 Hz, 1H), 3.99 (s, 3H), 4.05 (app t, J= 9,5 Hz, 1H), 4.7 (s, 2H), 4.84 (s, 1H), 4.91 (s, 1H), 4.95 (s, 1H), 5.01 (s, 1H), 6.95 (d, J= 8.4 Hz, 1H), 7.04 (d, J=8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 20.9, 23.7, 23.9, 24.4, 25.1, 26.1, 27.6, 34.1, 35.3, 46.4, 47.4, 59, 60.7, 66.8, 68.1, 70.1, 71.8, 74.9, 94.6, 111.4, 114.4, 123.2, 123.9, 131.2, 136.6, 138.7, 145.8, 146, 154.8, 170.7; IR (neat) 1652 cm^{-1}; HRMS (FAB+) for $C_{33}H_{52}NO_5$ $(M+H)^+$: Calcd 542.3845 Found 542.3839.



122

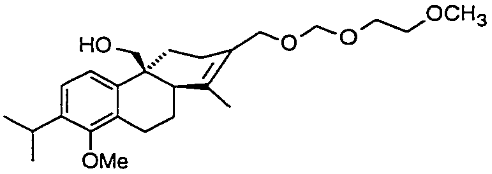
Oxazoline Adduct 122. The following procedure was performed using standard Schlenk-line techniques. A solution of oxazoline adduct **121** (250 mg, 0.46 mmol) in 5 ml benzene which had been degassed via freeze/pump/thaw cycles (liq. N_2, 4x) was added by cannula to ~50 mg $Mo(CHCMe_2Ph)(N(2,6\text{-}i\text{-}Pr)_2C_6H_3))(OCMe(CF_3)_2)_2$ [Schrock catalyst]. The reaction was stirred for 45 min at room temperature, then 1.5 h in a 60°C oil bath. After cooling, the crude reaction mixture was flushed through a plug of silica gel (1:1 EtOAc/hexanes). The material was concentrated and purified by flash chromatography (5% EtOAc/hexanes, 10% EtOAc/hexanes), to yield **122** as a yellow oil (210 mg, 90%). $[\alpha]^{25}_D$= -146 (c=0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.75 (s, 9H), 1.20 (d, J= 6.9 Hz, 3H), 1.22 (d, J=6.9 Hz, 3H), 1.72 (ddd, J= 12.8, 11.1, 7.6 Hz, 1H), 1.83 (s, 3H), 2.12-2.49 (m, 4H), 2.62-2.77 (m, 2H), 2.86 (br dd, J= 12.8, 5.6 Hz, 1H), 2.98-3.10 (m, 1H), 3.29 (sept., J= 6.3 Hz, 1H), 3.41 (s, 3H), 3.58 (dd, J= 5.6, 2.1 Hz, 2H), 3.63-3.74 (m, 5H), 3.72 (s, 3H), 3.84 (app t, J= 8.1 Hz, 1H), 3.93 (dd, J= 10.2, 9 Hz, 1H), 4.32 (d, J= 10.2 Hz, 1H), 4.72 (s, 2H), 7.06 (d, J= 8.3 Hz, 1H), 7.34 (d, J= 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 15.5, 21, 23.8, 24.1, 25.8, 26.2, 27.42, 33.5, 34.2, 43.3, 45.1, 59, 60.5, 66.7, 67.3, 67.7, 71.8, 75.8, 94.8, 123.1, 123.4, 125.3, 130.6, 135.1, 138.9, 139.2, 154.7, 167.3; HRMS (FAB+) for $C_{31}H_{47}NO_5$ $(M+H)^+$: Calcd 513.3454 Found 513.3444.



130

Aldehyde 130. Oxazoline **122** (69 mg, 0.13 mmol) was dissolved in 1 ml CH_2Cl_2 then chilled to 0°C, and CaH_2 (~5 mg) was added. To this was added methyl triflate (30 μl, 0.27 mmol), and the solution was stirred overnight, allowing to warm to room temperature. After filtration through a plug of cotton, the solution was concentrated and the residue was dissolved in 2.5 ml

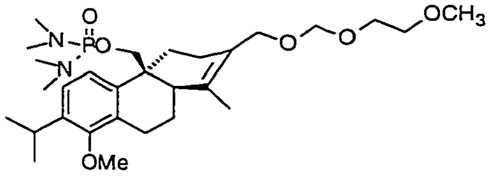
THF/H_2O (4:1). The mixture was chilled to 0°C and $NaBH_4$ (15 mg, 0.39 mmol) was added, portionwise. After stirring 30 min, 1 N NaOH (~2 ml) was added and the mixture was stirred an additional 3 h. The solution was extracted with EtOAc (3 x 10 ml), dried over $NaSO_4$, filtered, and concentrated. The crude oxazolidine **129** was dissolved in 2 ml THF/H_2O (4:1), and oxalic acid dihydrate (82 mg, 0.65 mmol) was added. The solution was heated at reflux for 6 h. After cooling, saturated aqueous $NaHCO_3$ (2 ml) was added, and the solution was extracted with EtOAc (3 x 10 ml). The organic phase was washed with brine (10 ml), dried over $NaSO_4$, filtered and concentrated to yield the crude aldehyde **130** which was generally used without further purification. The analytical sample was purified by flash chromatography (15% EtOAc/ hexanes). $[\alpha]^{25}_D$= -13.2 (c=1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.19 (d, J= 6.9 hz, 3H), 1.23 (d, J= 6.9 hz, 3H), 1.63-1.73 (m, 1H), 1.9 (s, 3H), 1.93-2.08 (m, 1H), 2.22-2.43 (m, 3H), 2.53 (br d, J= 12.9 hz, 1H), 2.69-2.87 (m, 2H), 3.12 (dd, J= 17.7, 6 hz, 1H), 3.3 (sept., J= 6.9 hz, 1H), 3.4 (s, 3H), 3.56-3.59 (m, 1H),3.7-3.74 (m, 2H), 3.73 (s, 3H), 3.88 (d, J= 11.1 hz, 1H), 4.22 (d, J= 11.1 hz, 1H), 4.7 (s, 2H), 7.13 (d, J= 8.4 hz, 1H)7.19 (d, J= 8.4 hz, 1H), 9.62 (s, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 15.6, 21, 23.7, 24.3, 26.2, 26.5, 30.7, 42.5, 52.7, 59, 60.7, 66.8, 67.3, 71.8, 94.7, 123.2, 124.5, 128.7, 131.7, 133.6, 133.9, 140.3, 155.1, 200.5; IR (film) 1716 cm^{-1}.



131

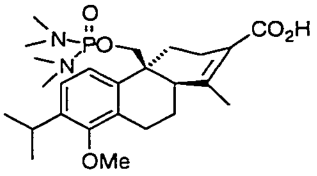
Carbinol 131. To a solution of crude aldehyde **130** (~0.13 mmol) in 2.5 ml THF/H_2O (1:1) at 0°C was slowly added $NaBH_4$ (12.5 mg, 0.33 mmol). The reaction was stirred for 30 min at 0°C and then diluted with 5ml 1N NaOH.

After stirring for 3 h, the mixture was extracted with EtOAc (3 x 8 ml) and washed with brine (10 ml). The EtOAc solution was dried over Na_2SO_4, filtered and concentrated. Flash chromatography (25% and 50% EtOAc/hexanes) yielded carbinol **131** as a light yellow oil (42 mg, 75% from oxazoline **122**). $[\alpha]^{25}_D$= +4.8 (c= 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.04 (dd, J= 8.7, 5.1 Hz, 1H), 1.22 (d, J= 3 Hz, 3H), 1.24 (d, J= 3 Hz, 3H), 1.44-1.7 (m, 2H), 1.78 (s, 3H), 2.18-2.44 (m, 4H), 2.65 (br d, J= 12 Hz, 1H), 2.94 (ddd, J= 18.3, 18.3, 9.5 Hz, 1H), 3.01 (ddd, J= 18.3, 18.3, 8 Hz, 1H), 3.31 (sept., J= 6.8 Hz, 1H), 3.41 (s, 3H), 3.52-3.61 (m, 3H), 3.67-3.76 (m, 3H), 3.74 (s, 3H), 4.00 (d, J= 10.8 Hz, 1H), 4.27 (d, J= 10.8 Hz, 1H), 4.74 (s, 2H), 7.10 (d, J= 8.2 Hz, 1H), 7.16 (d, J= 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 15.7, 20.3, 23.3, 23.9, 26.2, 28.4, 29.7, 40.5, 43.9, 59, 60.5, 64.6, 66.8, 67.7, 71.8, 94.8, 121.2, 123.5, 127.3, 129.7, 132.9, 139.4, 141.3, 155.6; IR (neat) 3478 cm^{-1} (br); HRMS (FAB+) for $C_{25}H_{39}O_5$ $(M+H)^+$: Calcd 419.2797 Found 419.2799.



133

Phosphorodiamidate 133. To a solution of carbinol **131** (23 mg, 0.055 mmol, dried via toluene azeotrope) in 1.2 ml THF at 0°C was added methyl lithium (0.5M in Et_2O, 145 μl, 0.072 mmol). After stirring 10 min, HMPA (15 μl, 0.11 mmol) was added and the solution was stirred an additional 20 min at 0°C. To this was added N,N-dimethylphosphoramidic dichloride (8 μl, 0.067 mmol). The solution was allowed to warm to room temperature and stirred for 30 min. After being rechilled to 0°C, dimethylamine (~1 ml) was added and the solution was stirred for 30 min. H_2O (5 ml) was added and the mixture was extracted with CH_2Cl_2 (3 x 5 ml) then washed with brine (5 ml). Flash chromatography on neutral alumina (EtOAc and 2% MeOH/EtOAc) yielded **133** (26 mg, 85%) as a light yellow oil. $[\alpha]^{25}_D$=-8.2 (c=1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.14 (d, J=7.2 Hz, 3H), 1.22 (d, J=7.2 Hz, 3H), 1.52-1.67 (m, 2H), 1.74 (s, 3H), 2.25 (s, 3H), 2.28 (s, 3H), 2.2-2.43 (m, 4H), 2.50 (s, 3H), 2.53 (s, 3H), 2.61-2.68 (m, 2H), 2.85-3.09 (m, 2H), 3.29 (sept., J= 6.8 Hz, 1H), 3.4 (s, 3H), 3.56-3.61 (m, 2H), 3.71 (s, 3H), 3.69-3.76 (m, 2H), 3.88 (d, J= 11.1 Hz, 1H), 4.0 (dd, J= 9.6, 3 Hz, 1H), 4.27 (d, J= 11.1 Hz, 1H), 4.73 (s, 2H), 7.04 (d, J= 8.4 Hz, 1H), 7.15 (d, J= 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.7, 20.3, 23, 23.6, 24.3, 25.8, 26.1, 28.5, 36.2, 36.4, 39.4, 43.9, 59, 60.5, 66.8, 67.5, 71.8, 94.8, 122.1, 122.8, 127.2, 129.1, 132.6, 139.2, 141.4, 155; IR (neat) 1044, 993 cm^{-1}; HRMS (FAB+) for $C_{29}H_{50}N_2O_6P$ $(M+H)^+$: Calcd 553.3407 Found 553.3393.



140

Phosphorodiamidate-acid 140. To a solution of phosphorodiamidate **133** (5 mg, 0.01 mmol) in 0.8 ml CH_2Cl_2 was added a catalytic amount of CaH_2 and the solution was chilled to -78°C. Boron tribromide (0.3 M in CH_2Cl_2, 40 μl) was slowly added, and the solution was stirred 10 min at -78°C. The mixture was diluted with 1 ml 1N NaOH, warmed to room temperature, and extracted with 5 ml CH_2Cl_2. The phases were separated, and the organic layer was dried over Na_2SO_4, filtered and concentrated. The crude alcohol **138** was dissolved in 1 ml CH_2Cl_2 and manganese dioxide (~20 mg) was added. After 2 h, the mixture was filtered through a plug of Celite and concentrated. The crude aldehyde **139** was dissolved in 0.8 ml in dioxane/H_2O (1:1), and sulfamic acid

(0.1M in dioxane/H_2O (1:1), 274 µl) and sodium chlorite (0.2 in dioxane/H_2O (1:1), 144 µl) were added sequentially. After stirring 3 h at room temperature, the solvent was removed, and the residue was dissolved in CH_2Cl_2 (5 ml) and washed with brine (5 ml). The organic phase was dried over Na_2SO_4, filtered, and concentrated. The residue was partially purified by flash chromatography (C-18 silica gel, CH_3CN) to give **140** (~2.5 mg) as a film. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.3, 20, 23.1, 23.6, 24.1, 26.1, 28.3, 29.7, 36.2, 36.3, 44.9, 60.6, 67.3, 125.7, 143.6, 122.1, 123.2, 129.1, 139.5, 141, 155.1, 171.3; HRMS (FAB+) for $C_{25}H_{40}N_2O_5P$ $(M+H)^+$: Calcd 479.2675 Found 479.2680.

IV. References

1. For reviews on the use of chiral oxazolines in synthesis see (a) Meyers, A. I. *J. Heterocycl. Chem.* **1998**, *35*, 991.

   (b) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297.

   (c) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837.

2. Meyers, A. I.; Whitten, C. E. *J. Am. Chem. Soc.* **1975**, *97*, 6266. A full account appeared: Meyers, A. I.; Smith, R. K.; Whitten, C. E. *J. Org. Chem.* **1979**, *44*, 2250.

3. Barner, B. A.; Meyers, A.I. *J. Am. Chem. Soc.* **1984**, *106*, 1865.

4. (a) Meyers, A. I.; Lutomski, K. A.; Laucher, D. *Tetrahedron* **1988**, *44*, 3107.

   (b) Meyers, A. I.; Roth, G. P.; Hoyer, D.; Barner, B. A.; Laucher, D. *J. Am. Chem. Soc.* **1988**, *110*, 4611.

5. Meyers, A. I.; Licini, G. *Tetrahedron Lett.* **1989**, *30*, 4049.

6 (a) Rawson, D. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2292.

   (b) Meyers, A. I.; Shipman, M. *J. Org. Chem.* **1991**, *56*, 7098.

7. Shimano, M.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7445.

8. (a) Hulme, A. N.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 952.

   (b) Degnan, A. P.; Meyers, A. I. *J. Org. Chem.* **2000**, *65*, 3503.

9. Takaishi, Y.; Shishido, K.; Wariishi, N.; Shibuya, M.; Goto, K.; Kido, M.; Takai, M.; Ono, Y. *Tetrahedron Lett.* **1992**, *33*, 7177.

10. Xu, J.; Ikekawa, T.; Ohkawa, M.; Yokota, I.; Hara, N.; Fujimoto, Y. *Phytochemistry* **1997**, *44*, 1511.

11. Niwa, M.; Nakamura, N.; Kitajima, K.; Ueda, M.; Tsutsumishita, Y.; Futaki, S.; Takaishi, Y. *Biochem. Biophys. Res. Commun.* **1997**, *239*, 367.

12. Shishido, K.; Goto, K.; Miyoshi, S.; Takaishi, Y.; Shibuya, M. *J. Org. Chem.* **1994,** *59,* 406.

13. Dufeu, E. C.; McQuillin, F. J.; Robinson, R. *J. Chem. Soc.* **1937,** *53.*

14. Nerinckx, W.; Vandewalle, M. *Tetrahedron: Asymmetry* **1990,** *1,* 265.

15. Meyers, A. I.; Robichaud, A. J.; McKennon, M. J. *Tetrahedron Lett.* **1992,** *33,* 1181.

16. Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952,** *51,* 505 and references cited therein.

17. Zimmer, H.; Lankin, D. C.; Horgan, S. *Chem. Rev.* **1971,** *71,* 229 and references cited therein.

18. (a) Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972,** *94,* 5098.

    (b) Liu, H.-J.; Shang, X. *Tetrahedron Lett.* **1998,** *39,* 367.

    (c) Liu, H.-J.; Lee, S. P.; Chan, W. H. *Can. J. Chem.* **1977,** *55,* 3797.

19. Nelson, Brown *J. Am. Chem. Soc.* **1951,** *73,* 5605.

20. Fujisaki, S.; Eguchi, H.; Omura, A.; Okamoto, A.; Nishida, A. *Bull. Chem. Soc. Jpn.* **1993,** *66,* 1576.

21. Esteban, G.; López-Sánchez, M. A.; Martínez, M. E.; Plumet, J. *Tetrahedron* **1998,** *54,* 197.

22. McKillop, A.; Fiaud, J.-C.; Hug, R. P. *Tetrahedron* **1974,** *30,* 1379.

23. Kocienski, P. J.; Pritchard, M.; Wadman, S. N.; Whitby, R. J.; Yeates, C. L. *J. Chem. Soc., Perkin Trans. I* **1992,** 3419.

24. For recent reviews see: (a) Schrock, R. R. *Tetrahedron* **1999,** *55,* 8141.

    (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998,** *54,* 4413.

    (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. I* **1998,** 371.

25. (a) Dvorak, C. D.; Schmitz, W. D.; Poon, D. J.; Pryde, D. C.; Lawson, J. P.; Amos, R. A.; Meyers, A. I. *Angew. Chem., Int. Ed. Engl.* **2000,** *39,* 1664.

(b) Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschangar, F.; Sarabia, F.; Ninkovic, S.; Yang, Z.; Trujillo, J. I. *J. Am. Chem. Soc.* **1997**, *119*, 7960.

26. Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

27. Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875.

28. Grubbs, R. H.; Kirkland, T. *J. Org. Chem.* **1997**, *62*, 7310.

29. Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3387.

30. Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.

31. Monti, H.; Léandri, G.; Klos-Ringuet, M.; Corriol, C. *Synth. Commun.* **1983**, 1021.

32. (a) Williams, D. R.; Sakdarat, S. *Tetrahedron Lett.* **1983**, *24*, 3965.

(b) Quindon, Y.; Morton, H.; Yoakim, C. *Tetrahedron Lett.* **1983**, *24*, 3969.

(c) Boeckman, R. K.; Potenza, J. C. *Tetrahedron Lett.* **1985**, *26*, 1411.

33. Ram, R. N.; Charles, I. *Tetrahedron* **1997**, *53*, 7335.

34. Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

35. Grieco, P. A.; Pogonowski, C. S. *J. Org. Chem.* **1974**, *39*, 1958.

36. Postema, M. H. D.; Calimente, D. *Tetrahedron Lett.* **1999**, *40*, 4755.

37. (a) Ho, T.-L. *Synthesis* **1978**, 936.

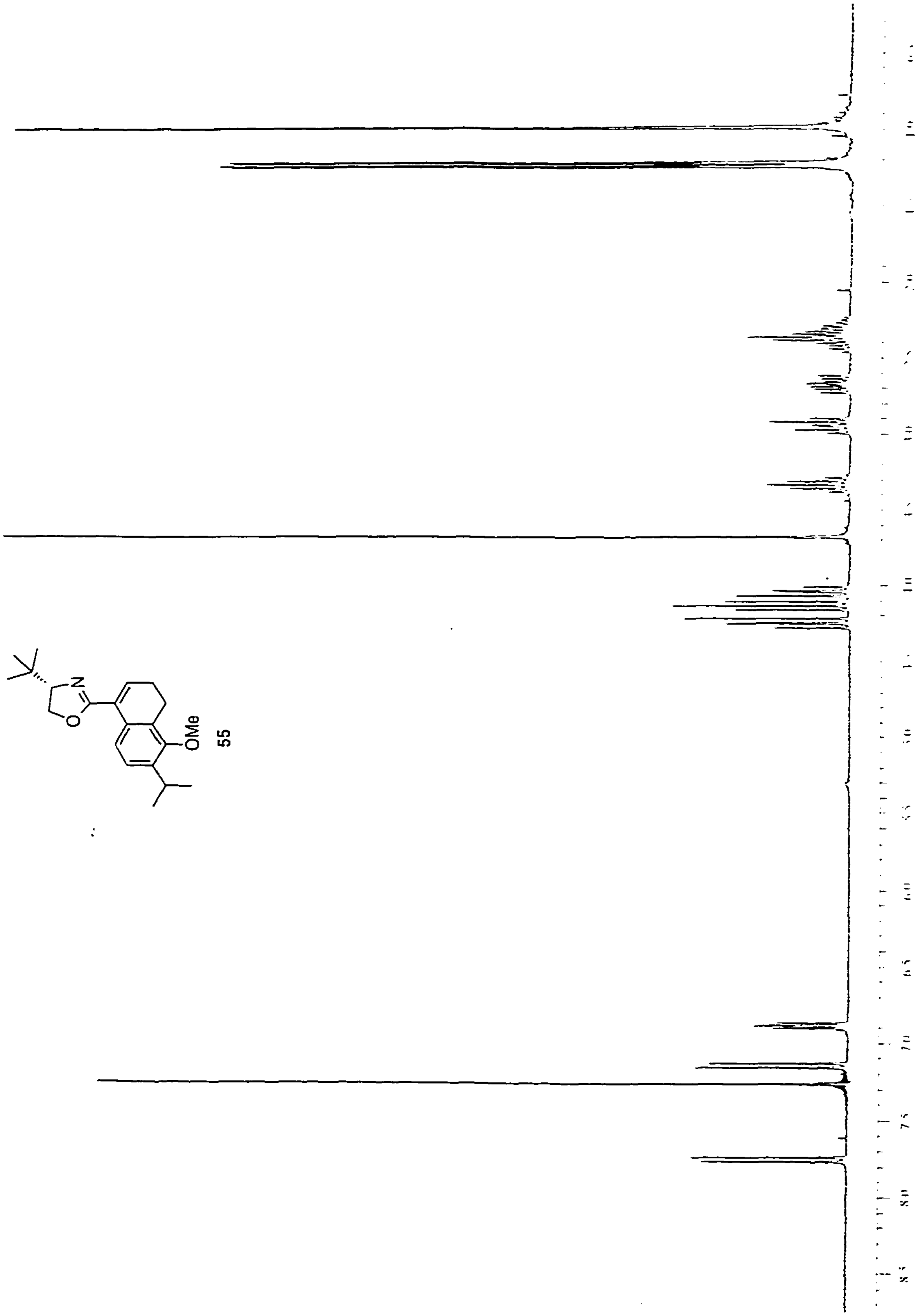
(b) Olah, G.; Balarum Gupta, B. G.; Fung, A. P. *Synthesis* **1980**, 897.

38. Freeman, P. K.; Hutchinson, L. L. *Tetrahedron Lett.* **1976**, 1849.

39. (a) Yus, M.; Alonso, E.; Ramón, D. J. *Tetrahedron* **1997**, *53*, 14355.

(b) Liu, H.-J.; Yip, J.; Shia, K.-S. *Tetrahedron Lett.* **1997**, *38*, 2253.

V. ^{1}H and ^{13}C NMR Spectra



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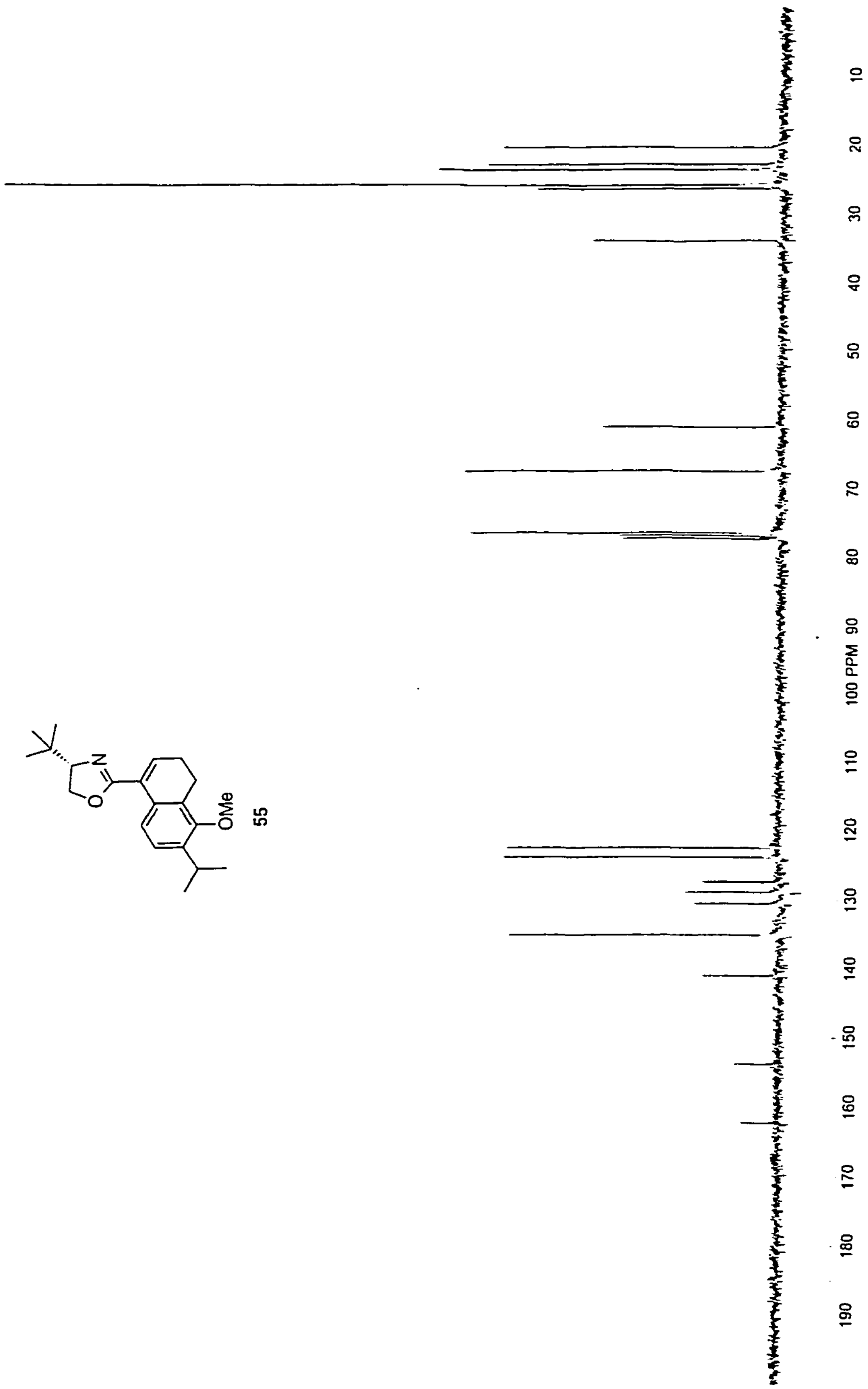
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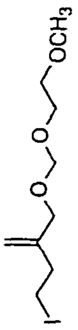

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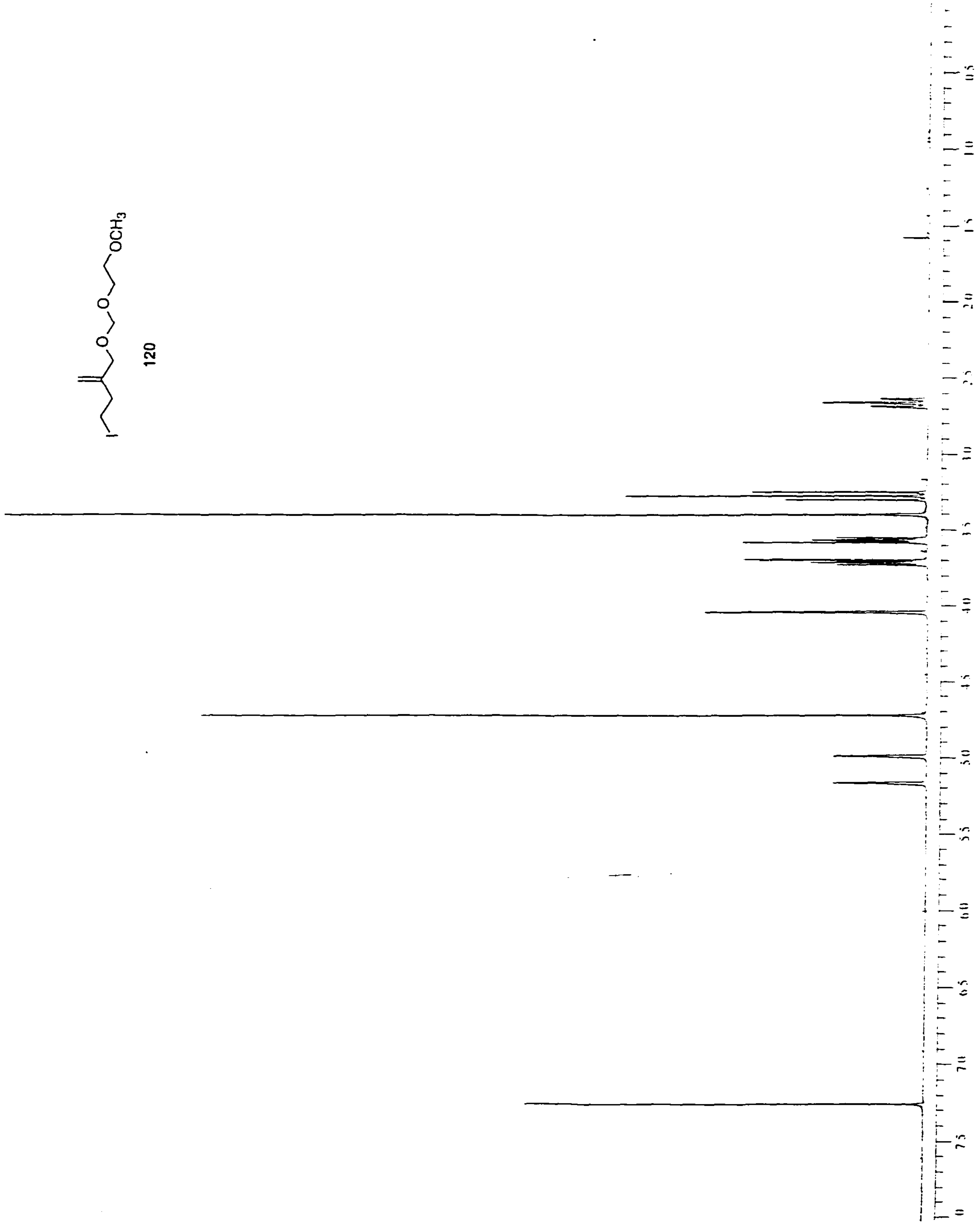

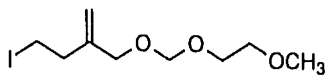

120

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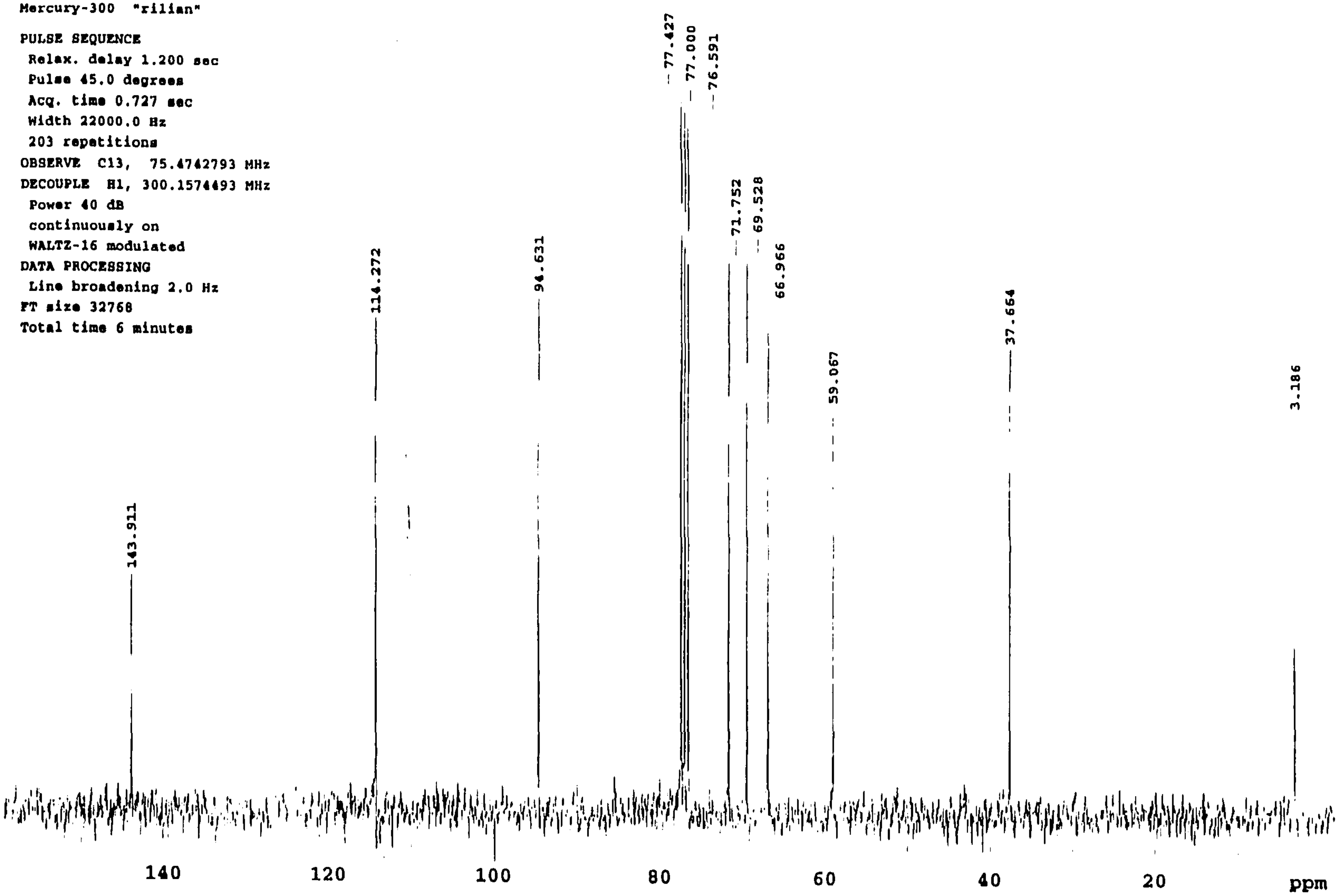

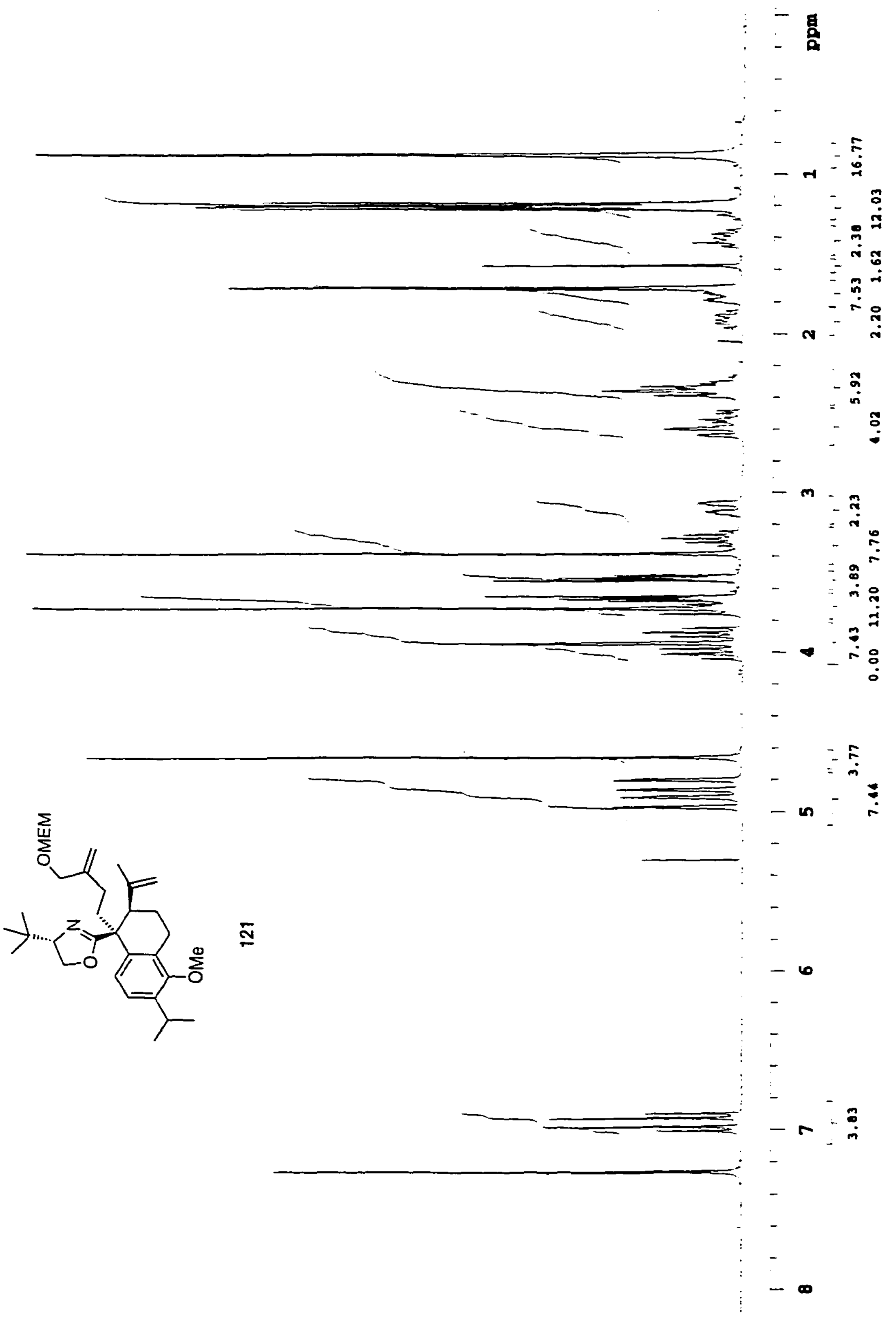
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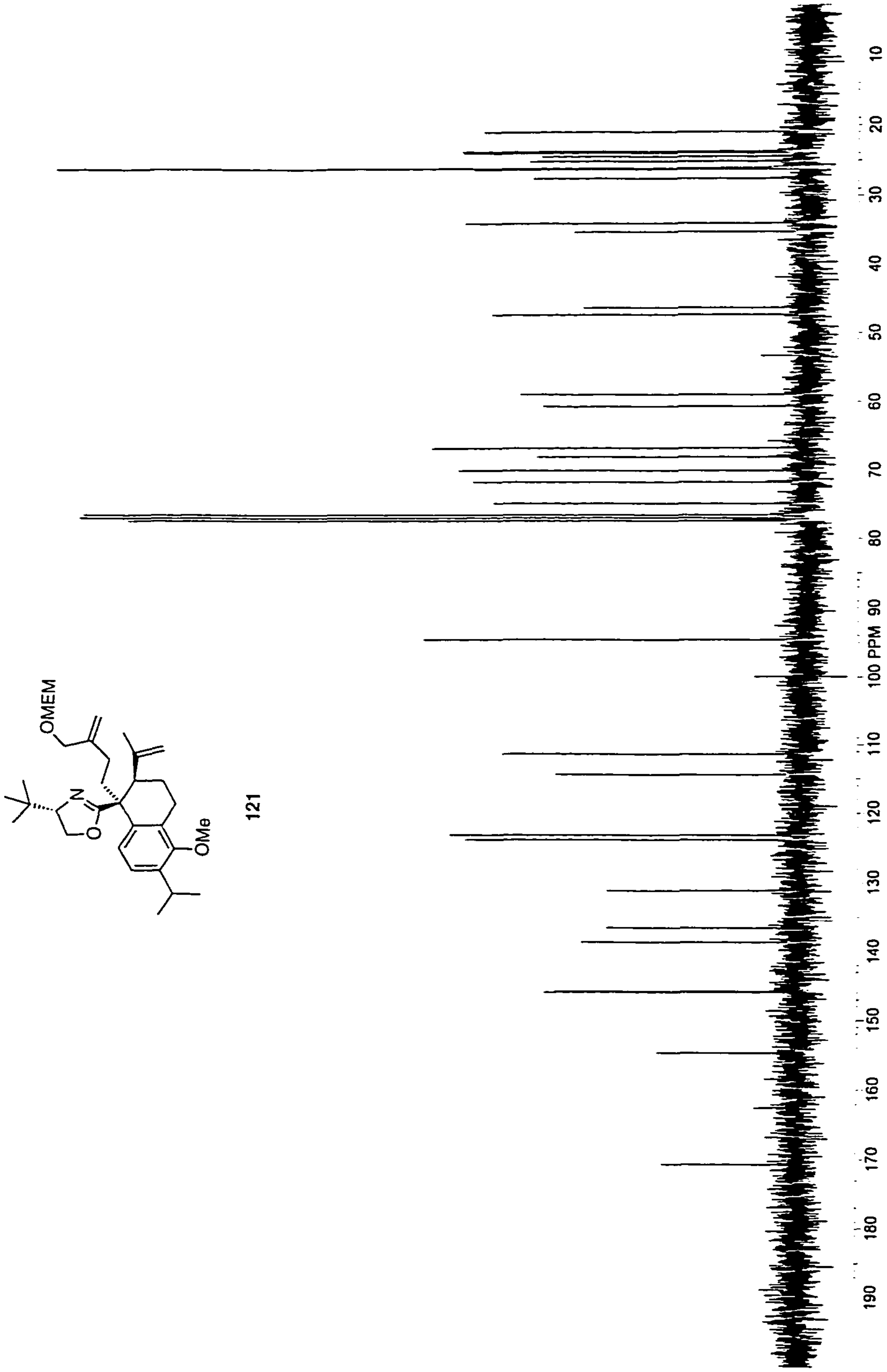
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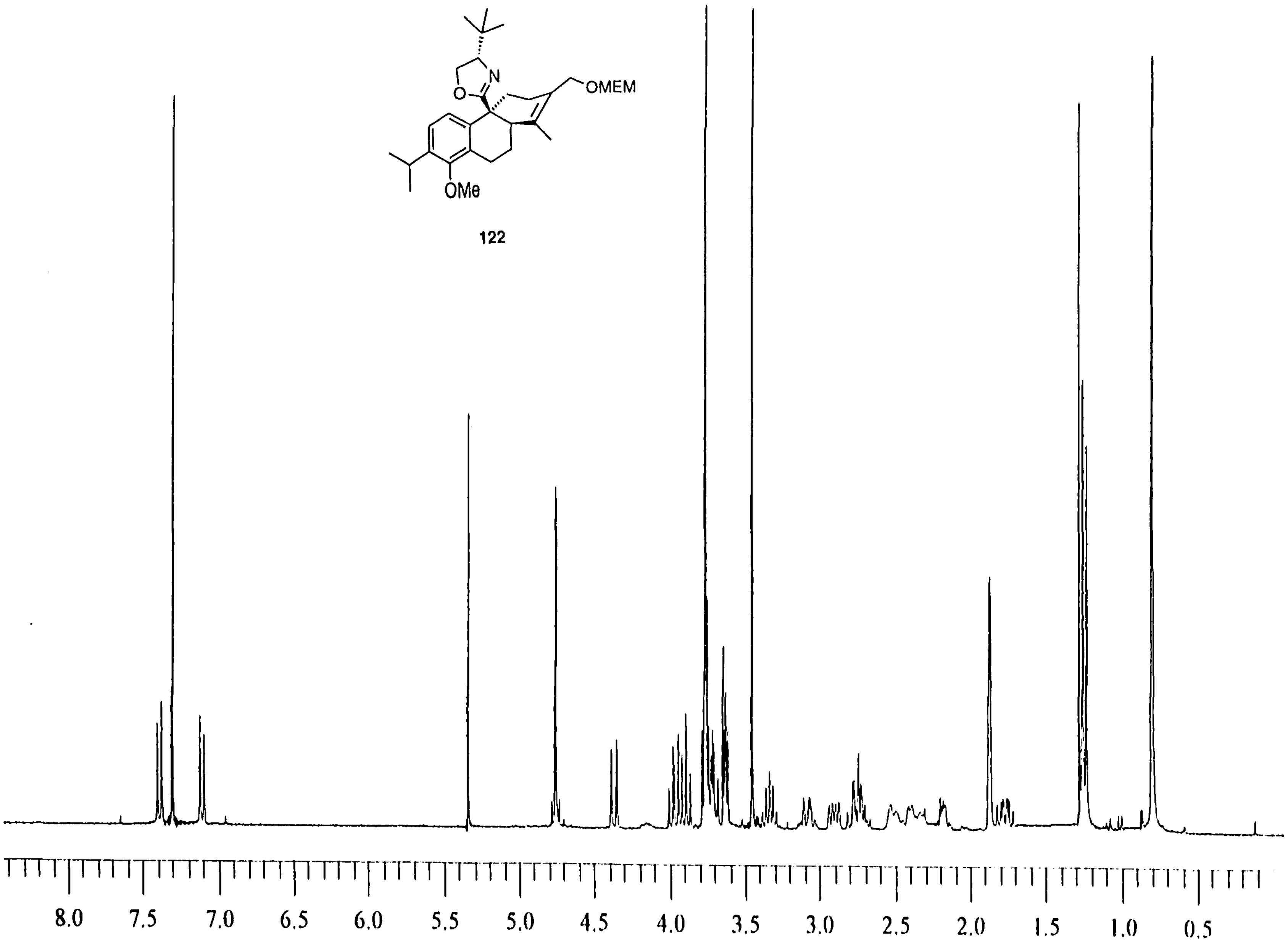

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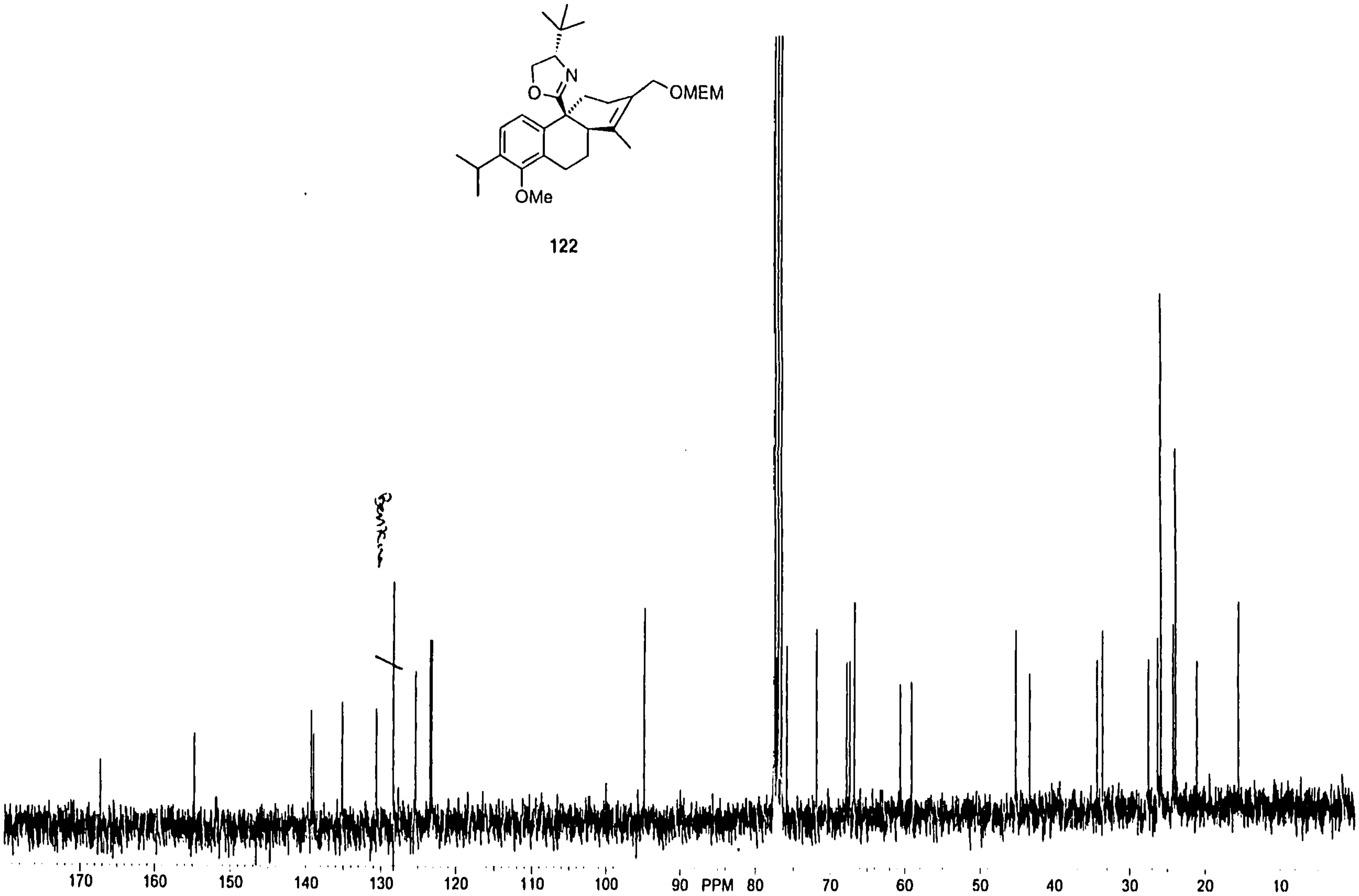OMEM
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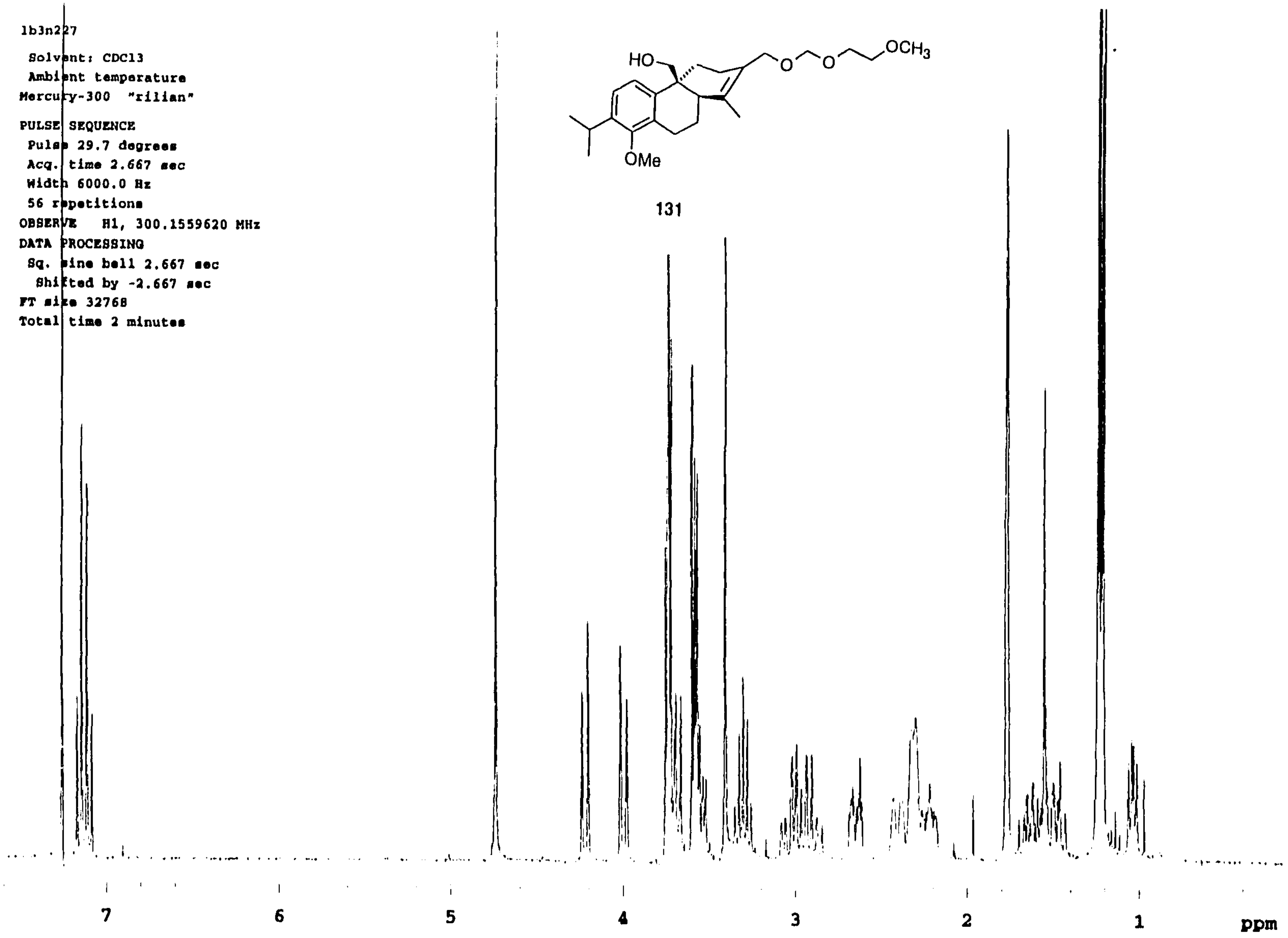
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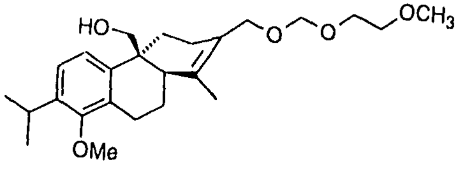
131



131

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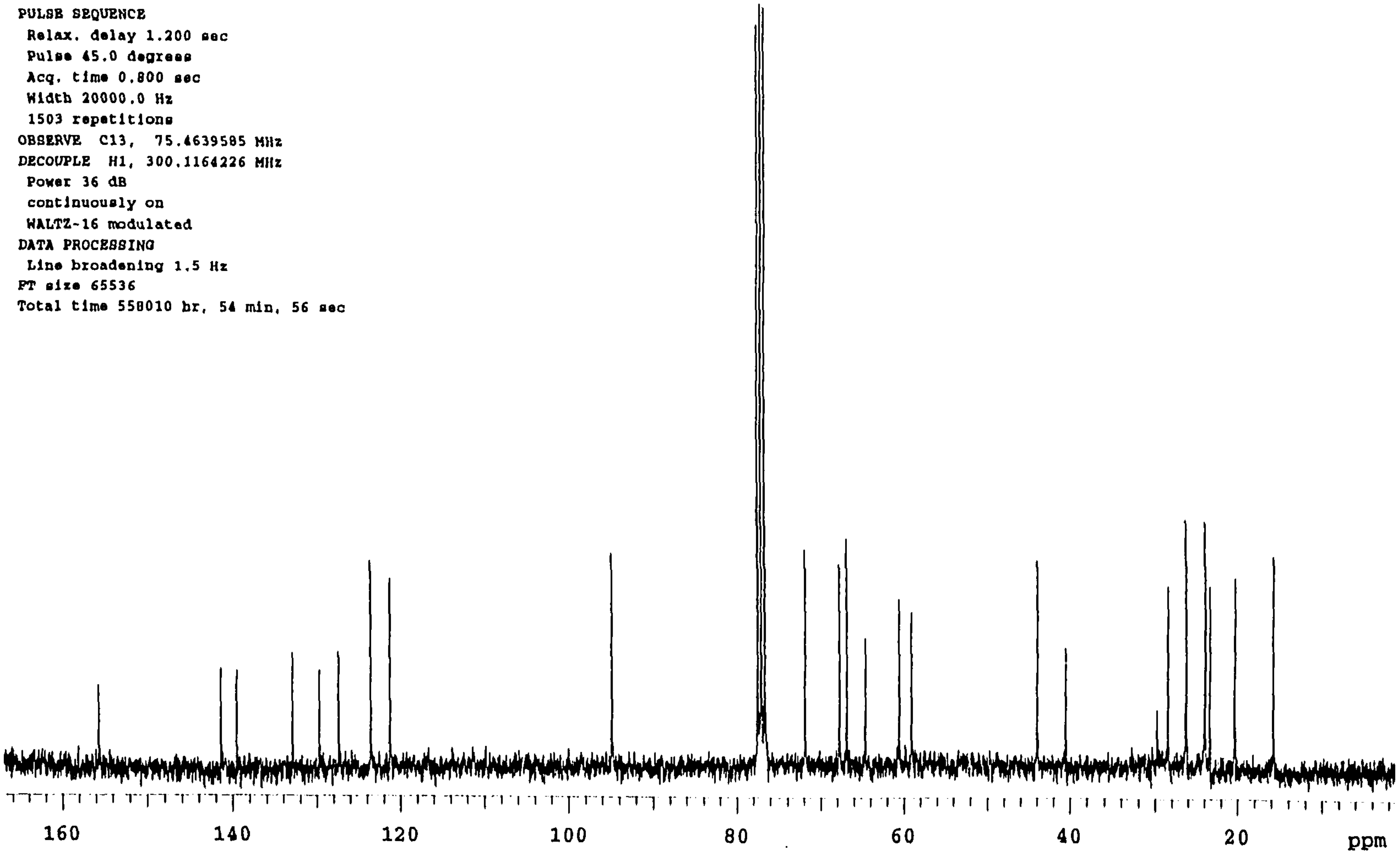

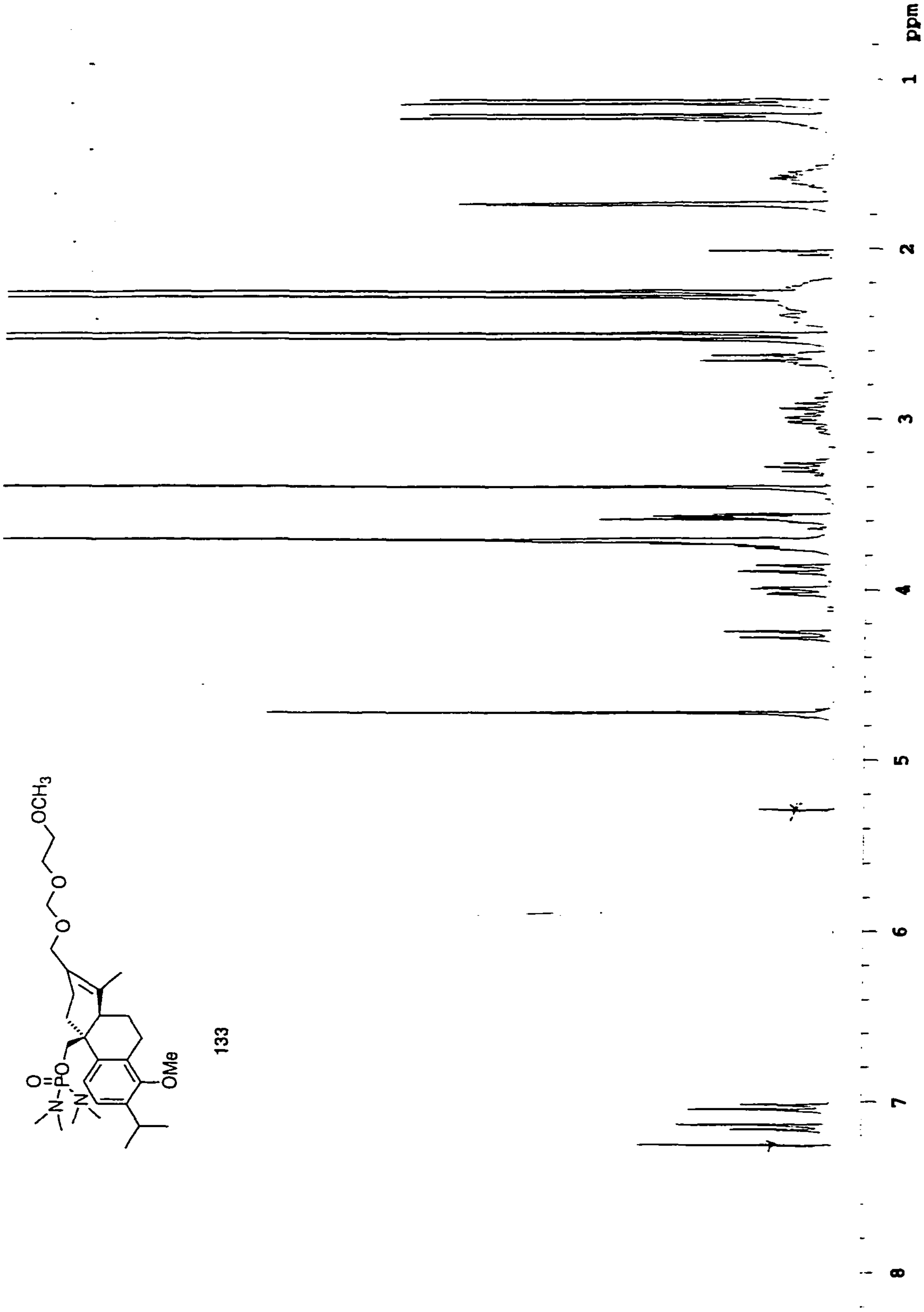
133

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1b3n222

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Mercury-300  "rilian"

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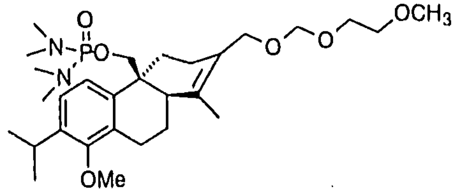

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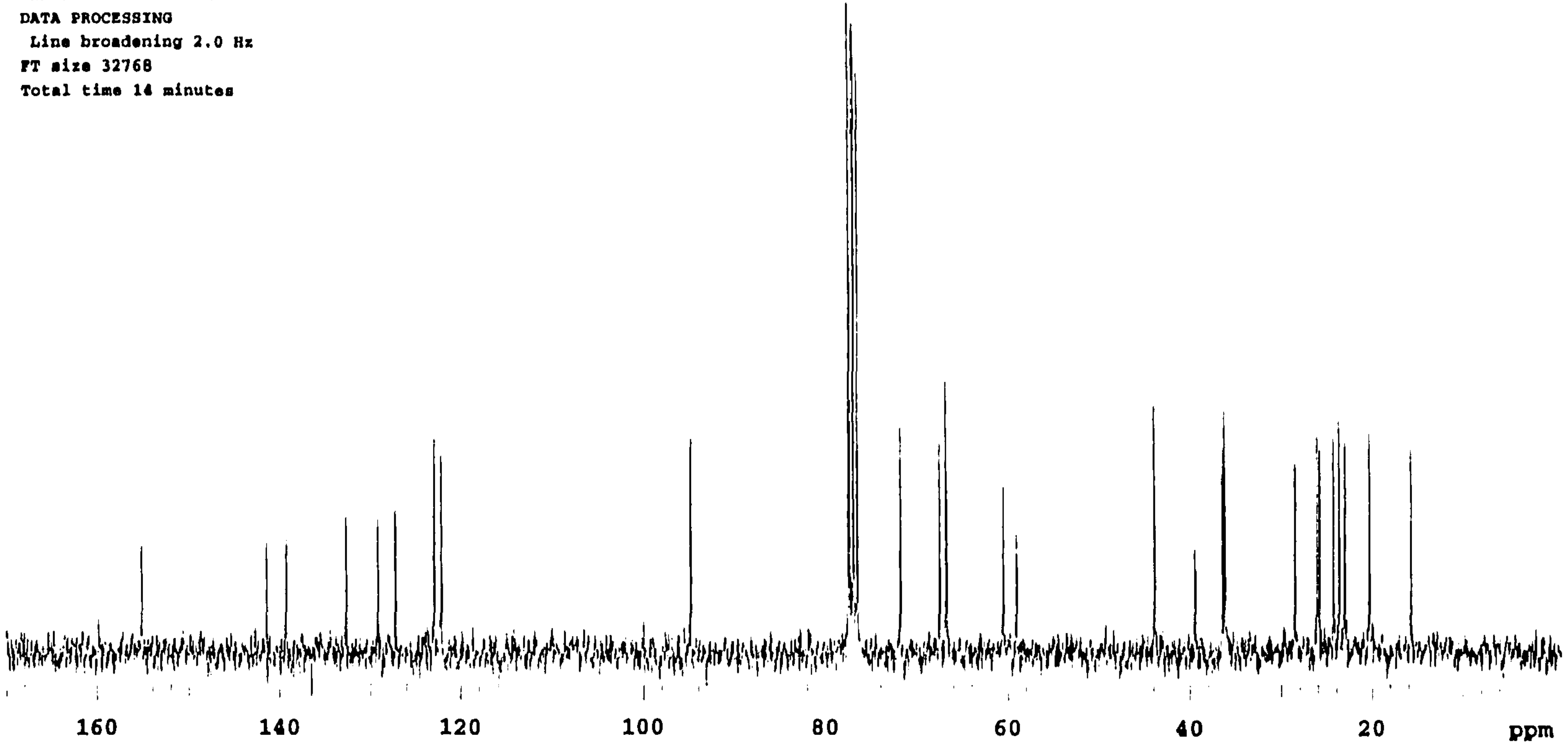
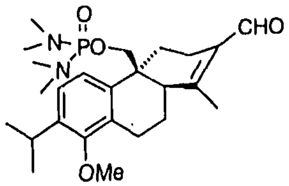
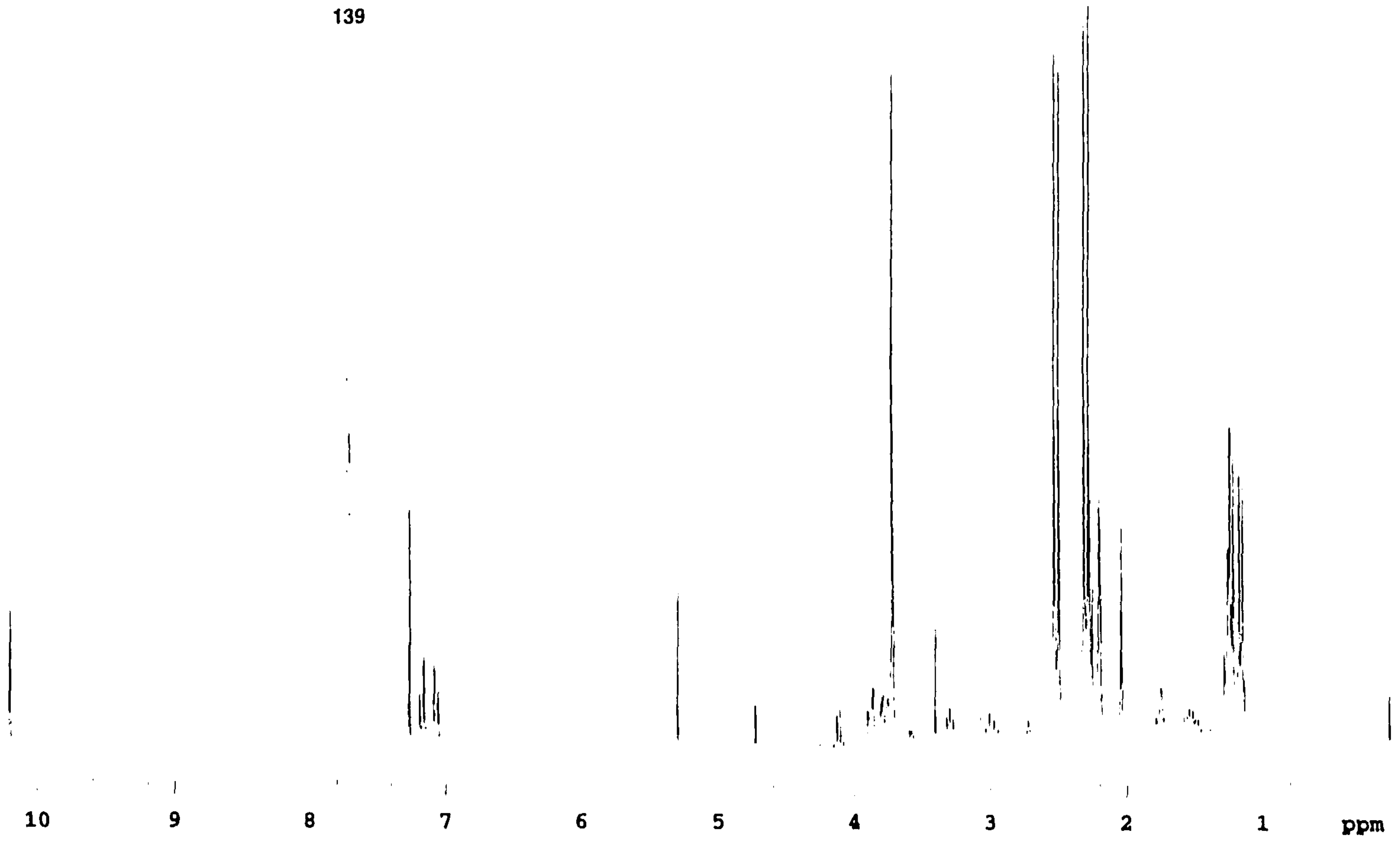
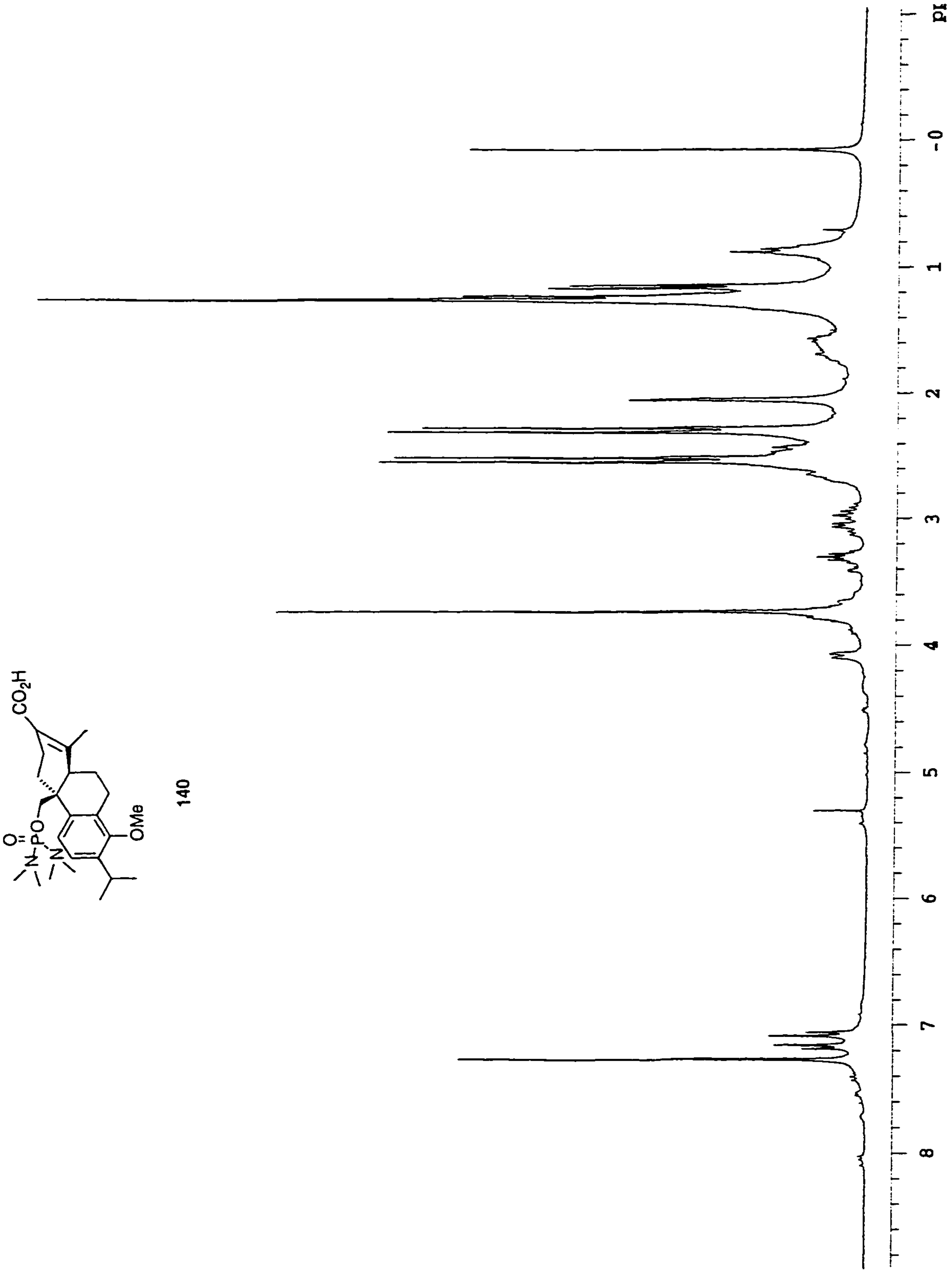




139





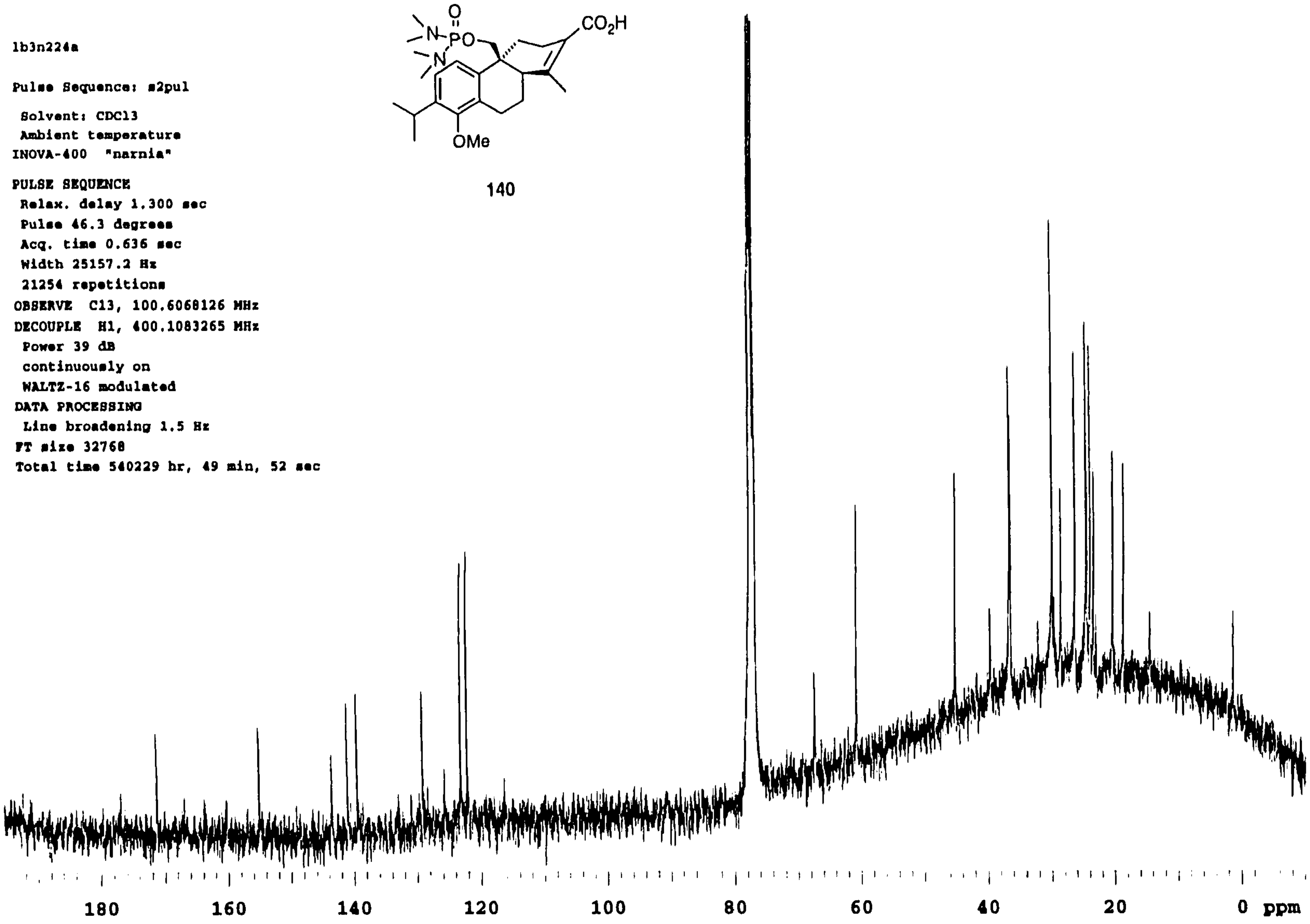
140

1b3n224a

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
INOVA-400 "narnia"

PULSE SEQUENCE
Relax. delay 1.300 sec
Pulse 46.3 degrees
Acq. time 0.636 sec
Width 25157.2 Hz
21254 repetitions
OBSERVE C13, 100.6068126 MHz
DECOUPLE H1, 400.1083265 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.5 Hz
FT size 32768
Total time 540229 hr, 49 min, 52 sec



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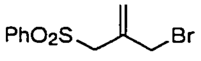
Chapter Two

Conjugate Addition of Sulfonyl Carbanions to Chiral α,β-Unsaturated Oxazolines

I. Introduction

The use of allyl sulfonyl carbanions is a topic of current interest in organic synthesis.[1-6] The allylic sulfone **1** has been used extensively by Hassner and coworkers as a 1,3-dipole synthon in [3+2] annulation reactions with electrophilic olefins.[1] Allyl sulfonyl carbanions undergo regioselective α-alkylation and not γ-alkylation (equation 1). Further, when the electrophile is an α,β-unsaturated carbonyl compound, 1,4-addition and not 1,2-addition is observed (equation 2).



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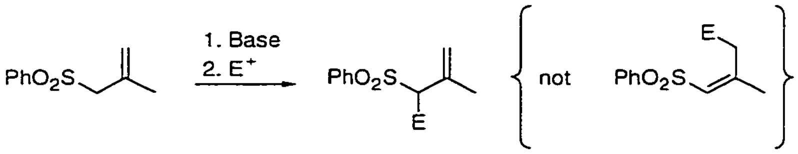
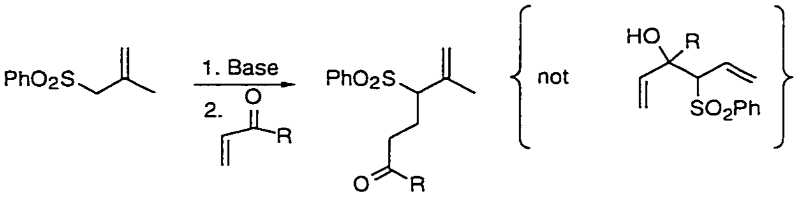


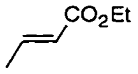
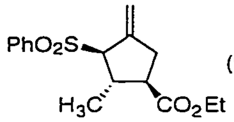
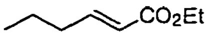
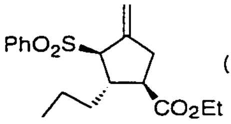
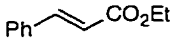
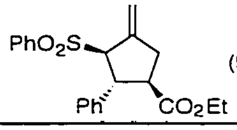
(1)



(2)

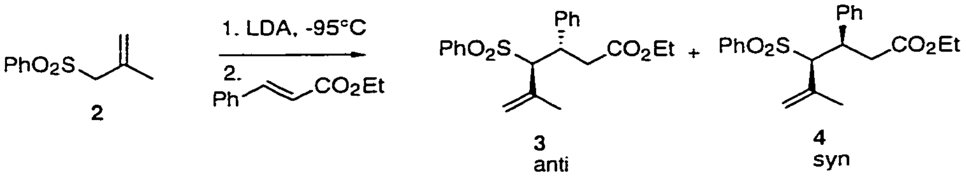
In the work described by Hassner and coworkers, the sulfonyl carbanion of **1** was added to a variety of cyclic and acyclic electrophilic (*E*)-olefins.[1a] A representative list of cyclopentanations is shown in Table 1. The cyclopentyl products were obtained in good yield with only one isomer detected (all trans). Impressively, three new relative stereocenters were set in one reaction, and only one of the four possible diastereomers was detected. The relative stereochemistry was determined by NMR studies (NOESY).

Table 1: Cyclopentanations with Allyl Sulfone 1[a]

Entry	Acceptor	Product (Yield %)
1		 (93)
2		 (93)
3		 (92)

[a] Deprotonation occurred with LDA in THF at -95°C. The acceptor was added to the sulfonyl anion.

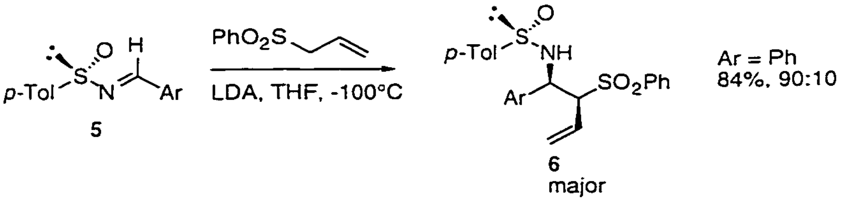
To probe the reaction further, Hassner et al.[1a] used an allylic sulfonyl carbanion that could not undergo cyclization. With allyl sulfone **2**, acyclic addition products **3** and **4** were obtained in an 85:15 *anti*/*syn* ratio. In the examples in Table 1 where addition was followed by cyclization, it was rationalized that reversibility in the Michael addition of the initial addition products allowed for the complete stereoselectivity that was observed.



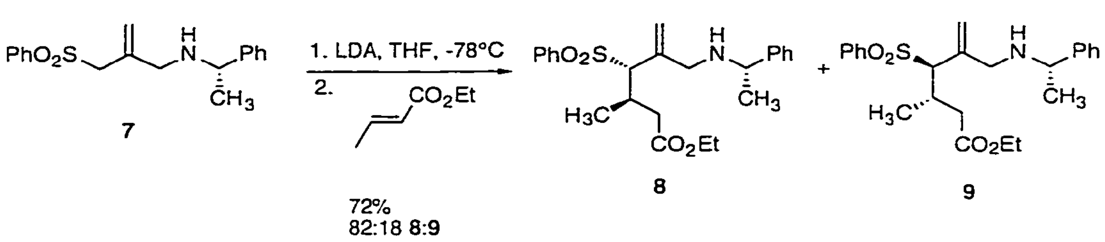
	Yield	anti/syn
w/ HMPA:	92	85:15
w/o HMPA:	92	40:60

With the acyclic adducts **3** and **4**, addition of HMPA caused a decrease in stereoselectivity. Also, a reversal was observed in which adduct was preferred (*anti* vs. *syn*). Because HMPA solvates the lithium cation thus making chelation less effective, this indicated the importance of chelation in the transition state.

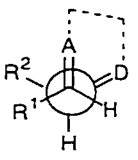
Asymmetric additions with allyl sulfonyl carbanions have also been studied by Hassner and coworkers.[3,5,6] The use of optically pure (+)-(*S*)-(*E*)-N-*p*-toluenesulfinyl imines as an electrophilic acceptor resulted in good yields with good stereoselectivity.[5] For example, with sulfinylimine **5**, the yield of allyl sulfone addition was 84% with a diastereomeric ratio of 90:10.



Hassner et al. have also studied asymmetric Michael additions with chiral allylic sulfones.[3] For example, with chiral sulfone **7** significant levels of stereoselectivity were obtained despite the remote nature of the chiral center. Once again, the addition resulted in an *anti* arrangement of the two new stereocenters.



Diastereoselective conjugate additions have been observed previously. For example, Seebach and Golinski[7] reported the reaction of open-chain nitro-olefins with open-chain enamines which gave γ-nitroketones with diastereomeric purities of 90-99%. They outlined a set of topological rules which were also applied to other similar reactions. The rules involve the approach of two prochiral centers in aprotic media under kinetic control.



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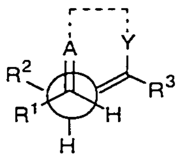

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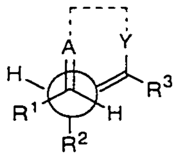

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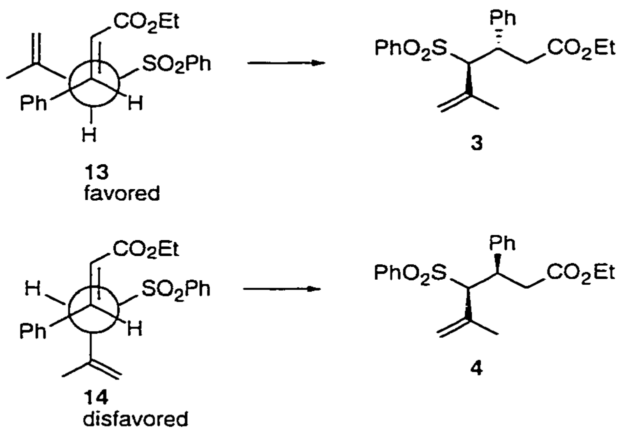
The model states that: a) all bonds are staggered around the bond about to be formed (**10-12**); b) there is a gauche arrangement of the donor group and the acceptor group between the acceptor C=A and C-H bonds; c) the smaller substituent of the donor is antiperiplanar to the C=A bond unless geometric constraints in the donor olefin preclude this arrangement (**12**).

One can extrapolate upon this model and apply it to the sulfonyl carbanion additions described above. With allyl sulfone **2** and ethyl cinnamate, this would result in **13** as the preferred approach (Scheme 1). Indeed, **13** leads to the anti arrangement seen in the major product **3**.

Scheme 1



While not invoking the aforementioned model of Seebach and Golinski,[7] Hassner et al.[1a] proposed possible transition states for the allyl sulfonyl additions. Their preferred transition state, which resulted in the anti addition product **3**, was the same as **13**. Further enhancing the observed selectivity, Hassner suggests that secondary orbital interactions involving a HOMO-LUMO complex between the enolate moiety and the allylic anion add to the approach **13** being favored.

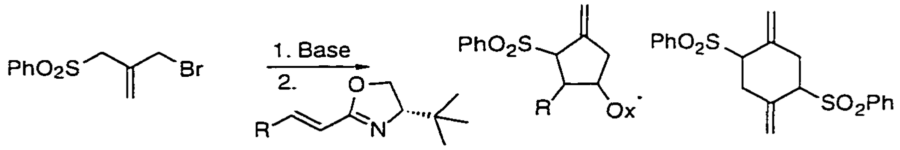
II. Results and Discussion

The high degree of relative stereoselectivity seen with the allyl sulfonyl carbanion-conjugate additions was intriguing. That, combined with the known directing ability of chiral oxazolines in conjugate additions,[8] led us to investigate sulfonyl carbanion additions to α,β-unsaturated oxazolines. It was believed that not only relative but also absolute stereochemistry would be controlled. Potentially, chiral building blocks with three contiguous stereocenters could be constructed in one reaction, while the versatility of the oxazoline moiety would further allow for rapid access to many different functionalities.

A. Conjugate Addition of Sulfonyl Carbanions to Chiral α,β-Unsaturated Oxazolines

The first sulfonyl carbanion additions attempted followed Hassner's experimental procedures.[1] The results were encouraging, but not very synthetically useful (Table 1). The best results were achieved when the anion of sulfone **1** was formed by adding it to a solution of LDA (1.2 eq) in THF at -95°C (entry 1) afterwhich oxazoline **15**[9] was added as a solution in THF. Because no reaction was noted after 30 minutes, HMPA (3 eq) was added, and the reaction mixture was then warmed to -78°C furnishing product **17**. Chromatography (silica gel) resulted in an approximate yield of 25% (the material could not be completely purified). Overall, mass recovery was good, and the bulk of the reaction material was found to be unreacted oxazoline **15** and the dimerized sulfone **19**. Analysis by GC/MS of the crude reaction mixture indicated that the product was a 6:1 ratio of diastereomers. Because three new stereocenters were formed, there was the possibility of eight diastereomers. However, only two were observed, with one diastereomer highly favored. Clearly this reaction was very selective, albeit low yielding to this point.

Table 1: Cyclopentanation Attempts with Allyl Sulfone 1

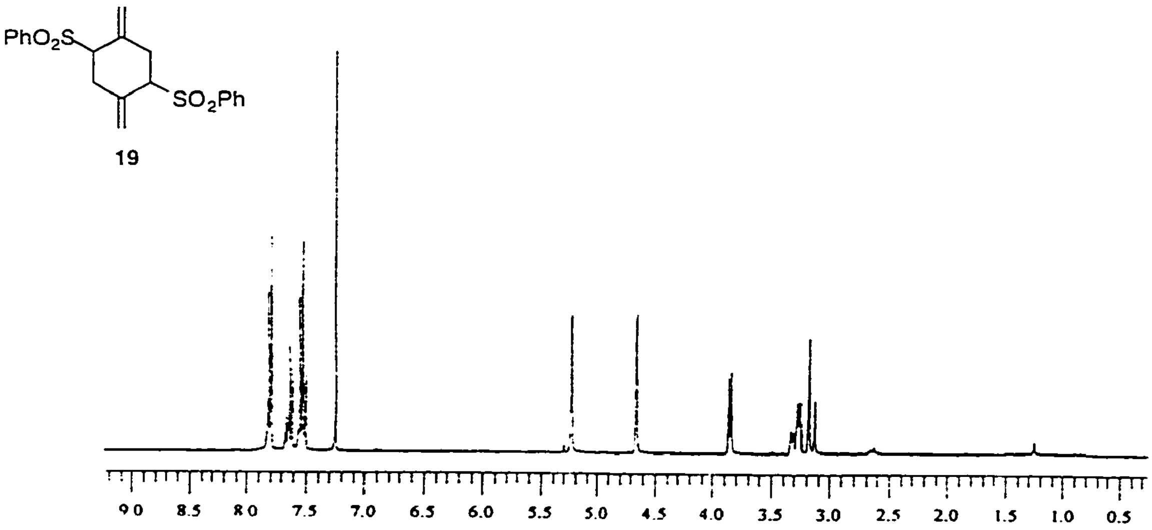


1 15, R= Ph 16, R= CH_3[9] 17, R= Ph 18, R= CH_3 19

Entry	R	Conditions	Results
1	Ph	(a) 1.4 eq **1**, 1.2 eq LDA in THF @ -95°C (b) **15** in THF (c) 3 eq HMPA, -95°C to -78°C (~0.08M in **15**)	~25% **17**, 6:1 d.r.; remainder was **15** and dimer **19**
2	Ph	as in entry 1, except 3 eq TMEDA added before addition of **15** (no HMPA)	-no **17**, only **15** & **19**
3	Ph	as in entry 1, except **15** and HMPA added together	as in entry 2
4	Ph	as in entry 1 except used Et_2O as solvent (with and without 2 eq LiCl)	as in entry 2
5	CH_3	as in entry 1	-no **18**, only **16** & **19**
6	Ph	as in entry 1 except added **15** to LDA then added sulfone **1**(with and without 3 eq HMPA)	-no **17**, only **15** & **19**
7	Ph CH_3	as in entry 1 except used LHMDS as base	-no **17** or **18**, only starting oxazoline and dimer **19**
8	Ph	as in entry 1 except used LTMP as base (with and without HMPA)	as in entry 2
9	Ph	as in entry 1 except ran with 5 eq **1** and 4.5 eq LDA, also ran with 5 eq **15**	<10% yield of **17**

The structure of dimer **19** was determined by both mass spectra and by ^1H NMR (Figure 1). The spectra showed resonances at 3.85 ppm (d, J= 6.3 Hz, 1H), 3.3 ppm (dd, J= 15.9, 6.6 Hz, 1H), and 3.16 (d, J= 15.9 Hz, 1H) which were assigned as the ring methine proton and the two ring methylene protons, respectively.

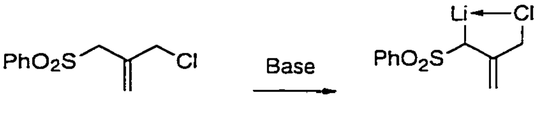
Figure 1: 300 MHz ^{1}H NMR Spectrum for Sulfone Dimer 19



It was expected that the initial results could be improved. To this end, several trials were performed, varying many different experimental parameters including different solvents, additives, bases, etc. (Table 1). Any manipulation to encourage addition of the sulfonyl anion into the oxazoline seemed to hasten the dimerization of the sulfonyl nucleophile to **19**.

By using the chloro sulfone **20**, it was thought that the tendency of the allylic sulfonyl carbanion to dimerize might be overcome. Dimerization should be somewhat slower thereby allowing for conjugate addition into the α,β-unsaturated oxazoline. However, no product was observed even when using the best conditions for obtaining cyclized product with the bromo sulfone **1** (Table 1, entry 1). Since chlorine is a harder Lewis base than bromine,[10] the more efficient complexation via electron donation of the chlorine atom into the hard lithium cation could result in a less reactive carbanion (Figure 2).

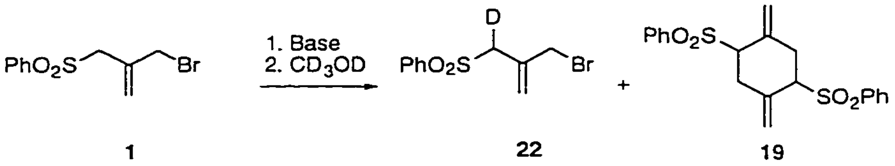
Figure 2



20 **21**

In order to better understand the dimerization of the sulfonyl carbanion of **1**, studies were conducted in which the anion was quenched with a deuterium donor (Table 2). After addition of CD_3OD and a standard aqueous workup, NMR spectra were taken of the crude product, and D-incorporation was determined by the diminishment of the allylic, sulfonyl resonance. Appearance of dimer was also noted in the NMR spectra. When D-incorporation was noted, this meant that there was a significant amount of non-dimerized, sulfonyl anion remaining. Little or no D-incorporation indicated that the anion was already quenched. The bulkier base, lithium tetramethylpiperidine, yielded an anion that was slower to dimerize than did LDA. Both addition of HMPA and warmer reaction temperatures accelerated the dimerization process, which was unfortunate as both HMPA and temperatures of -78°C or greater seemed to be necessary for addition to oxazoline **15** to occur (Table 1, entry 1). The results of these experiments underscored the fact that there is a small window of time for the anion to add to the oxazoline before dimerization to **19** occurs.

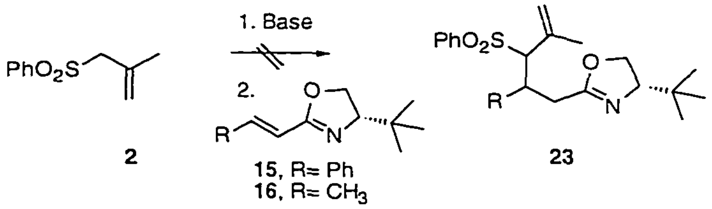
Table 2: Dimerization Studies of Allyl Sulfonyl Carbanion 1[a]



Entry	Base	Temp.	Time	Result
1	LDA	-95°C	5 min.	multiple products, mostly **22** and **19** (~1:1) plus another unidentified compound, <50% D incorporation in **22**
2	LDA	-95°C	20 min.	as entry 1
3	LDA	-95°C to -78°C	5 min. @ -78°C	complex mixture
4	LTMP	-95°C	25 min.	**22**, w/ >80% D incorporation
5	LTMP	-95°C to -78°C	5 min. @ -78°C	as entry 4
6	LTMP	-78°C	20 min.	as entry 4
7	LTMP w/ HMPA	-95°C	5 min.	complex mixture, mostly dimer **19**

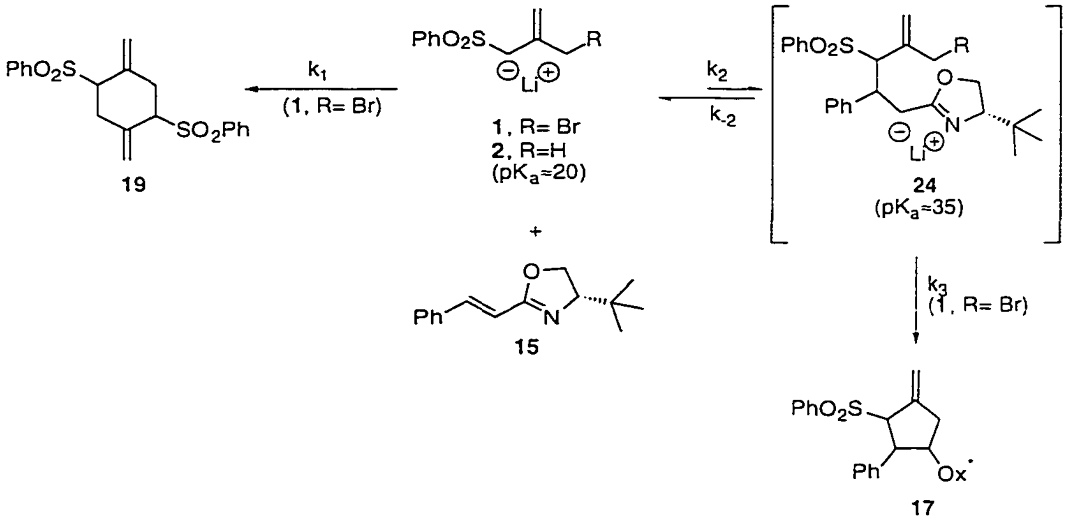
[a]Experiments run in THF and at 0.05M in **1**.

Because dimerization of the bromo sulfone nucleophile appeared to be an insurmountable problem, the allylic sulfone **2**, not containing bromine, was examined. This would lead to the absence of dimer **19**. Interestingly, no addition product **23** was detected with either oxazoline **15** or **16**. The best conditions found in the Hassner-cyclopentanation study (Table 1, entry 1) were utilized first. Also, attempts were made with different bases (LHMDS, LTMP, and LDA). In all cases, unreacted oxazoline and sulfone **2** were recovered.



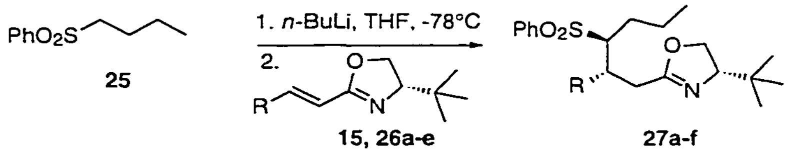
From the preceding results, it was soon concluded that the conjugate addition of an allyl sulfonyl carbanion into α,β-unsaturated oxazolines was not a favorable process. This may be explained by comparing the pK_a values of the different carbanions (Scheme 2). The pK_a of a C-H that is both allylic and α to a sulfone has been measured at 21.[11] However, the pK_a of an alkyl C-H that is α to an oxazoline is generally assumed to be in the mid-30's. Therefore, the sulfonyl carbanion is significantly more stable, and there is little driving force to form the carbanion α to the oxazoline upon addition. When intramolecular cyclization is an option (R= Br), the small amount of addition product **24** formed can proceed on to the final oxazoline adduct **17**. Meanwhile, most of the sulfone anion is shunted off to dimerization. When intramolecular cyclization is not an option (R= H), there is simply insufficient addition product **24** to be detected. Therefore, it appears from Scheme 2 that: $k_1 > k_2$, $k_{-2} > k_2$, and $k_{-2} > k_3$, which makes production of the cyclopentane **17** an unfavorable process.

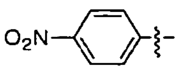
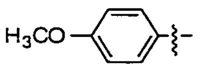
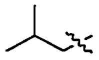
Scheme 2

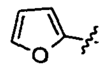
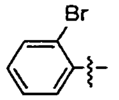


To increase the efficiency of addition, the less acidic alkyl sulfone **25** was utilized. Since the pK_a of an alkyl C-H that lies α to a sulfone is c.a. 30[9] and much closer to a C-H α to an oxazoline, it was thought that it may be feasible to push the equilibria toward addition. Indeed, addition of alkyl sulfone **25** proved to be much more favorable. When an excess of sulfone **25** was added to oxazoline **15** (Table 3, entry 1), a respectable yield of product **27a** was obtained. *Furthermore, only one diastereomer of the possible four was detected.* Interestingly, only if the reaction was quenched at -78°C was the adduct **27a** seen. If the reaction was allowed to warm before quenching only starting materials were observed, further supporting the reversibility of addition. Other chiral α,β-unsaturated oxazolines[9] were tested and the results are summarized in Table 3. The conjugate additions were all quenched with 2-isopropanol which gave a homogeneous solution at -78°C. Quenching with ammonium chloride yielded similar results for adduct **27a**, and treatment of the adduct with isopropyl lithium alkoxide did not change the diastereomeric composition or lead to reversal of addition.

Table 3: Alkyl Sulfone Addition into α,β-Unsaturated Oxazolines



Entry	R	Product	Conditions[a]	Yield(%)	d.r.[d]
1	Ph (**15**)	**27a**	A	72%[c]	>96:4
2	 **(26a)**	**27b**	B	78%[c]	~96:4
3	 **(26b)**	**27c**	A	20%[b]	>96:4
4	 **(26c)**	**27d**	A	<10%[b]	-

5	 **(26d)**	**27e**	A	70%[c]	>96:4
6	 **(26e)**	**27f**	A	<10%[b]	-

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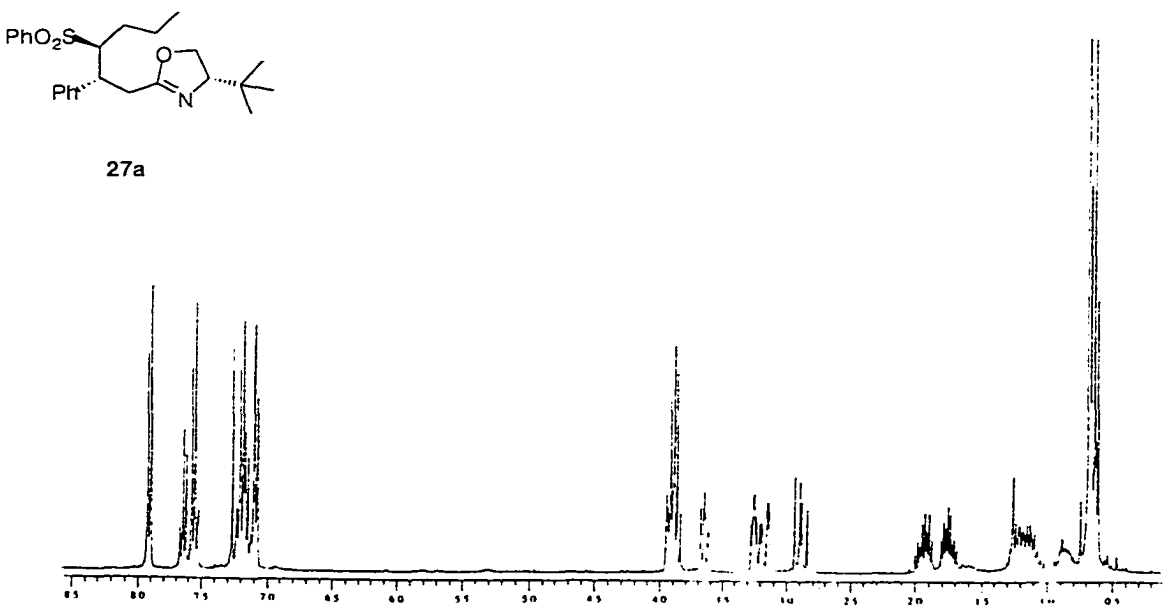
[a] A= To a solution of **25** (5 equiv.) with 4.5 equiv. *n*-BuLi in THF was added the oxazoline. The reaction was stirred at -78°C for 30 min., then quenched with 2-propanol. B= To a solution of **25** (1.2 equiv.) with 1 equiv. *n*-BuLi in THF was added the oxazoline. Upon addition the reaction was quenched immediately with 2-propanol. [b] GC yield [c] Isolated yield [d] Based on NMR and GC/MS data

The ^{1}H NMR spectrum of oxazoline adduct **27a** is shown in Figure 3. While the spectrum is complex with a fair amount of overlap, assignments were made based on 2D COSY studies. The phenyl protons on the sulfone are at 7.5-8.0 ppm. The resonance at 3.25 ppm (ddd, J= 4.5, 4.5, 3 Hz, 1H) is the methine α to the sulfone. Slightly upfield are the methylene protons adjacent to the oxazoline at 3.16 ppm (ddd, J= 15.9, 4.1, 1.5 Hz, 1H) and 2.88 ppm (dd, J= 16.2, 11.7 Hz, 1H).

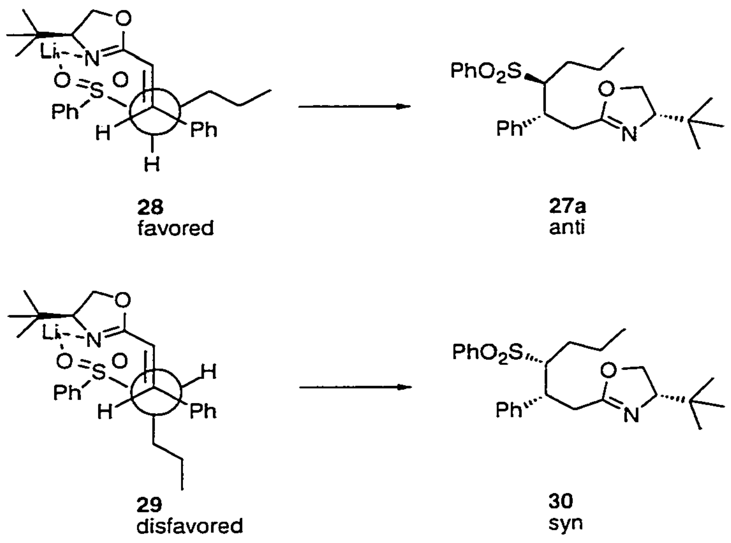
Figure 3: 300MHz ^{1}H NMR Spectrum of Oxazoline Adduct 27a



The examples shown in Table 3 further define the relative reactivities necessary for addition. Where R= *i*-Bu as with oxazoline **26c** (entry 4) the addition yield was poor. This indicated that, in the case of alkyl sulfonyl carbanions, α,β-unsaturated oxazolines where R= alkyl are not electrophilic enough to be good Michael acceptors. This lack of reactivity was also observed with the allylic sulfonyl carbanion **1** where no addition was seen with oxazoline **16** (R= CH_3). When R= aryl, a rational pattern emerged when the adducts **27** were formed. Electron-deficient aryl rings gave higher product yields, whereas electron-rich aryl rings resulted in lower yields. With the 2-bromo phenyl analog (entry 6), the lack of efficient addition may have been due to the steric congestion at the electrophilic center. In all cases where addition was successful, the diastereoselectivity was very high. Only in the case of the *p*-nitro compound **27b** was more than one diastereomer ever detected.

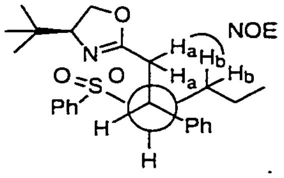
The *anti* configuration as drawn for the adduct **27** is thought to be correct based on precedent and experimental evidence. Sulfonyl carbanion additions to α,β-unsaturated oxazolines are likely to mimic the addition to electrophilic olefins as shown by Hassner et al.,[1] where the *anti* product predominated. As with Hassner's examples, the transition state model of Seebach and Golinski[7] can be applied to chiral oxazolines (Scheme 3). The model predicts that the *anti* configuration as opposed to the *syn* configuration is favored. Transition state **28** also shows a complex-induced proximity effect to aid in reaching **27a**.[12]

Scheme 3

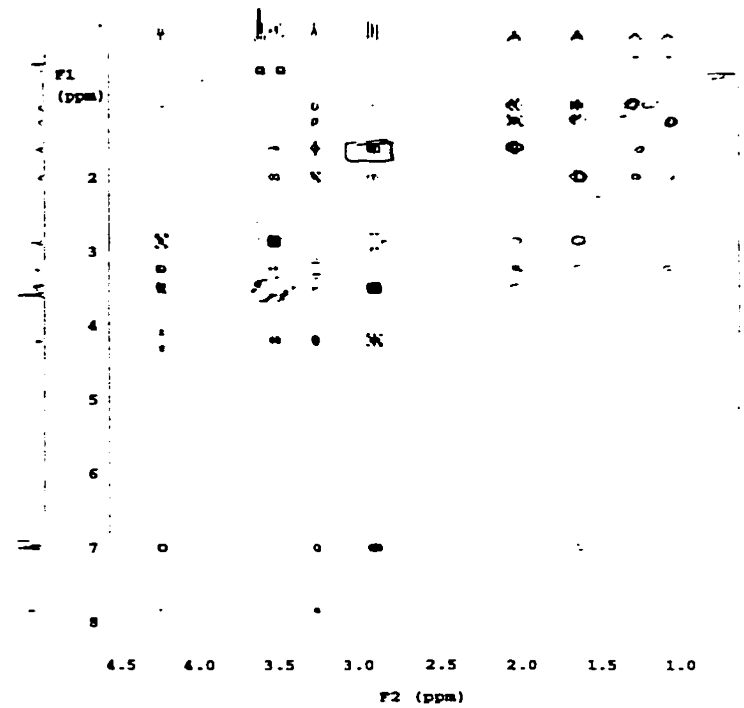


Hassner[1a] determined the configuration of both cyclic and acylic analogs in the sulfone additions to electrophilic olefins by NMR experiments (NOE). This was, therefore, applied to oxazoline adduct **27a**. In Scheme 3, the lowest energy conformation that results in the *anti* product, structure **28**, shows that the proximal methylene of the propyl group and the methylene to be formed α to the oxazoline are gauche to each other. With structure **29**, which leads to the *syn* product, the relationship is antiperiplanar. Indeed, the *anti* configuration of **27a** is confirmed by a strong NOE between one of the H_a's and one of the H_b's (Figure 3a).[23] The *anti* addition is further supported by an X-ray crystal determination of a cyclic analog of **27a** which will be discussed later. Because the oxazoline adducts **27a-f** were all oils or low-melting solids, it was not possible to obtain X-ray quality crystals.

Figure 3a: 500 MHz NOESY NMR Spectrum for 27a in Benzene-d_6[23]

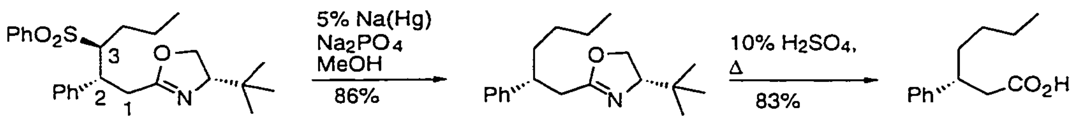


28a



The absolute configuration at C-2 of **27a** (Scheme 4) was determined by conversion to the known acid **32**.[14] This was accomplished by following the desulfonylation procedure of Trost and coworkers[13] with buffered 5% Na(Hg) afterwhich the oxazoline was hydrolyzed with 10% H_2SO_4 at reflux yielding **32**. Comparison of the sign of optical rotation of **32** with the literature value confirmed the configuration shown.

Scheme 4

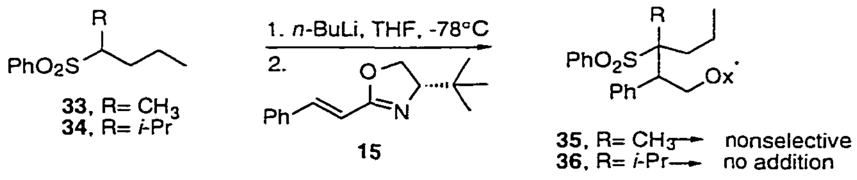


27a **31** **32**

$[\alpha]^{25}_{D}$= -21 (c=1, $CHCl_3$)
(lit.[14]= $[\alpha]^{25}_{583}$= -23.1 (neat))

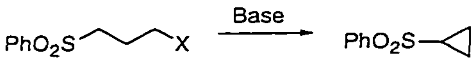
To assess whether a quaternary center could be formed upon addition, branched alkyl sulfones were investigated as nucleophiles (Scheme 5). It was not suprising that the methyl branched sulfone **33** was not selective, for the steric difference between a methyl group and an *n*-propyl group is not very large. The isopropyl-branched sulfone **34** was also prepared and proved to be too bulky to allow for effective addition.

Scheme 5



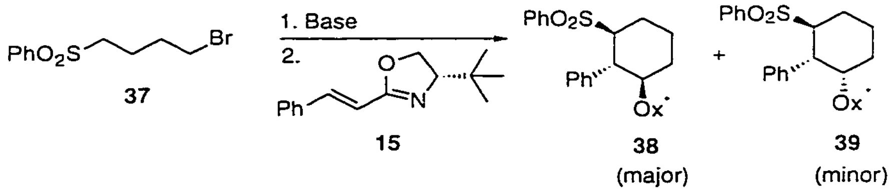
In order to fully utilize the conjugate addition (by making use of the oxazolinyl carbanion formed upon addition), alkyl sulfones with pendant leaving groups were examined. Cyclopentanation (which would closely follow the work of Hassner et al.)[1] was not possible with an alkyl sulfone because as soon as deprotonation occurred (Figure 4), cyclopropanation followed. With the allylic sulfone **1**, cyclopropanation did not take place due to added strain of the exocyclic methylene group.

Figure 4



Since cyclobutanation is a kinetically much less favorable process than cyclopropanation, the bromo butyl sulfone **37** was used successfully to generate cyclohexane derivatives, **38** and **39** (Table 4). Optimization of the addition/cyclization reaction is summarized in Table 4, with the best results shown in entry 7. The sulfone anion was formed in THF at -78°C with 5 equiv. of sulfone **37** and 4.5 equiv. of LTMP as the base, followed by addition of oxazoline **15**. After allowing the reaction to stir for 24 h at -78°C, the cyclic products **38** and **39** were obtained in 67% yield. The separation of **38** and **39** took place using chromatography (silica gel) and was found to be straightforward. As seen with the previously described cyclopentyl oxazoline adduct **17**, only two of the eight possible diastereomers were formed with the major diastereomer favored by 5:1. Also, in this case the chemical yield was much higher, rendering the reaction synthetically useful.

Table 4: Addition/Cyclization to Form Cyclohexanes



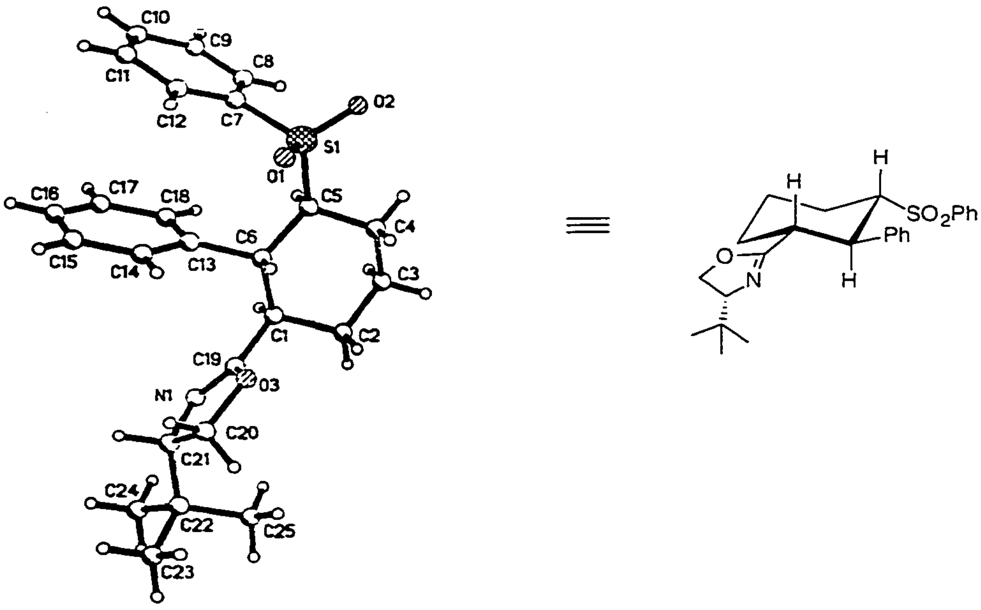
Entry	Conditions	Results
1	(a) 3 eq **37**, 2.5 eq *n*-BuLi, THF, -78°C (b) **15**, 6 h at -78°C	52% overall yield, 5:1 d.r.
2	as in entry 1, except allowed to stir for 72 h at -78°C	58% overall yield, 5:1 d.r.
3	as in entry 1, except formed sulfonyl carbanion with LTMP in Et_2O	no addition products
4	(a) 3 eq **37**, 2.5 eq LTMP, THF, -95°C (b)**15**, -95°C for 1 h then -78°C for 12 h	40% overall yield, 4:1 d.r.
5	added 2.5 eq LTMP to a mixture of **15** and 3 eq **37**	58% overall yield, 4:1 d.r.

6	(a) 3 eq **37**, 2.5 eq LTMP, THF, -95°C (b) added anion via cannula to **15** with 2 eq HMPA in THF at -78°C	only trace of cyclized products
7	as in entry 1, except 5 eq **37** and 4.5 eq LTMP	67% overall yield, 5:1 d.r.
8	added 3 eq **37** to a mixture of 2.5 eq LTMP and **15** in THF at -78°C	—poor mass recovery — mainly non-cyclized addition product (<25%)

When adducts **38** and **39** were separately resubjected to either sulfonyl carbanion **37** or to NaOMe, no change in diastereomeric composition was noted. This indicated that the observed diastereomeric ratio was not due to any equilibration during the reaction.

The structure of the major diastereomer **38** was determined by X-ray crystallography,[15] and showed all its substituents *trans* to each other and in the equatorial position (Figure 5). The structure shows that the initial addition gave the *anti* configuration between the sulfone and the phenyl groups in agreement with the results of Hassner et al.[1]

Figure 5: Single Crystal X-Ray Structure of Oxazoline Adduct 38[15]



Because only one diastereomer was observed with the acyclic oxazoline analogs, **27**, it was assumed that the initial addition step to form **38** and **39** was completely selective and the differing stereocenter α to the oxazoline arose from the cyclization step. Desulfonylation of **38** and **39** (Scheme 6) produced distinctly different diastereomers **40** and **41**, indicating that the sulfonyl carbon stereocenters were identical in **38** and **39**. Furthermore the ^1H NMR spectra of **40** and **41** (Figure 6) are quite different at the C-H's α to the oxazoline and to the phenyl ring, showing that H_a and H_b are *cis* to each other in **41** and *trans* to each other in **40**.

Scheme 6

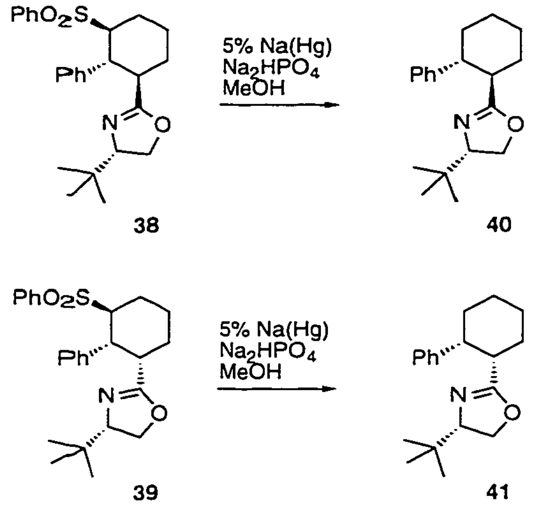
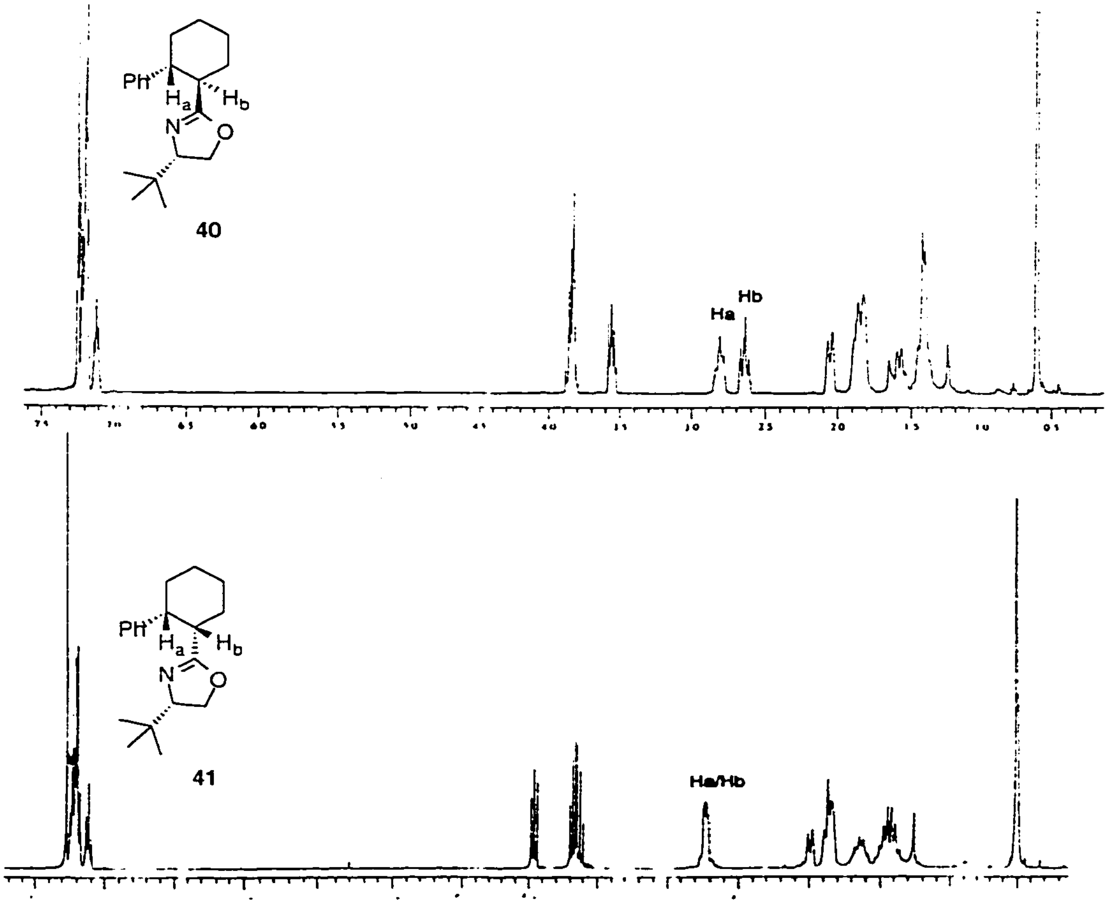
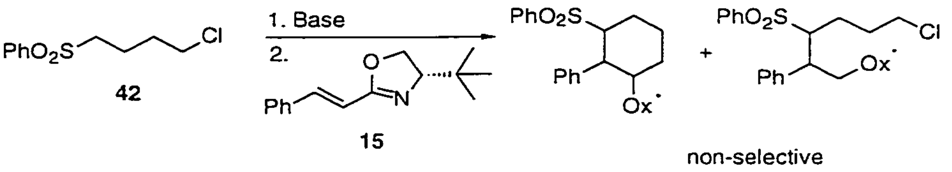


Figure 6: 300MHz ^{1}H NMR Spectra for Oxazoline Adducts 40 and 41



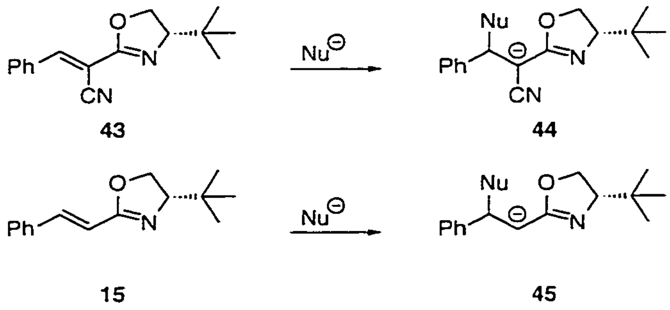
Because the stereocontrol was lost in the cyclization step, it was thought that using a chloro analog of sulfone **37** might slow down the cyclization enough to allow for better selectivity (Scheme 7). Unfortunately, the experiments with the chloro sulfone **42** were fraught with problems. Many experimental variations were tested, and regardless of conditions, several diastereomers of both the cyclized material and the initial adduct were observed. The non-cyclized initial adduct was not usually seen with the bromo sulfone **37**. As with the allyl chloro sulfone **20**, the solution structure of the sulfonyl carbanion of **42** appeared to be different from the bromo analog and not to allow good stereocontrol in the addition step.

Scheme 7



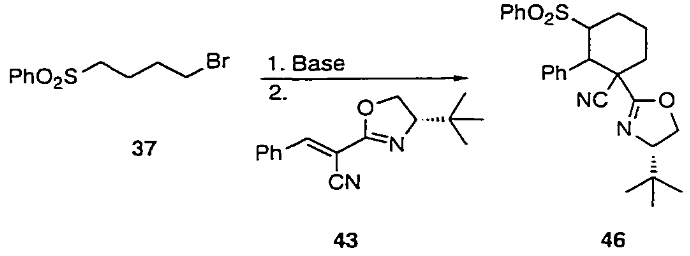
Further studies were initiated to enhance the reactivity of the Michael acceptor. To this end, cyano oxazoline **43** was examined (Scheme 8). The carbanion **44**, formed upon conjugate addition to oxazoline **43**, is additionally delocalized compared to carbanion **45**, therefore the addition should result in a more favored process.

Scheme 8



Whereas sulfonyl carbanion additions to **15** were slow and incomplete with alkyl sulfones and unsuccessful with allyl sulfones, addition to **43** was rapid and high yielding (Table 5). This was another example where comparing the relative pK_a's of the nucleophile and the addition product predicted the feasibility of the reaction. Because addition was so rapid, it was also nonselective. As seen in Table 5, typically six diastereomers were detected by GC/MS with one peak 66% of the total peak area. Since three stereocenters were set in the reaction and the fourth stereocenter was fixed, this meant that it was likely that two diastereomers were coeluting with two other diastereomers. Some experimental parameters were varied in an attempt to attenuate the reactivity; however, no significant change in diastereomeric composition was noted.

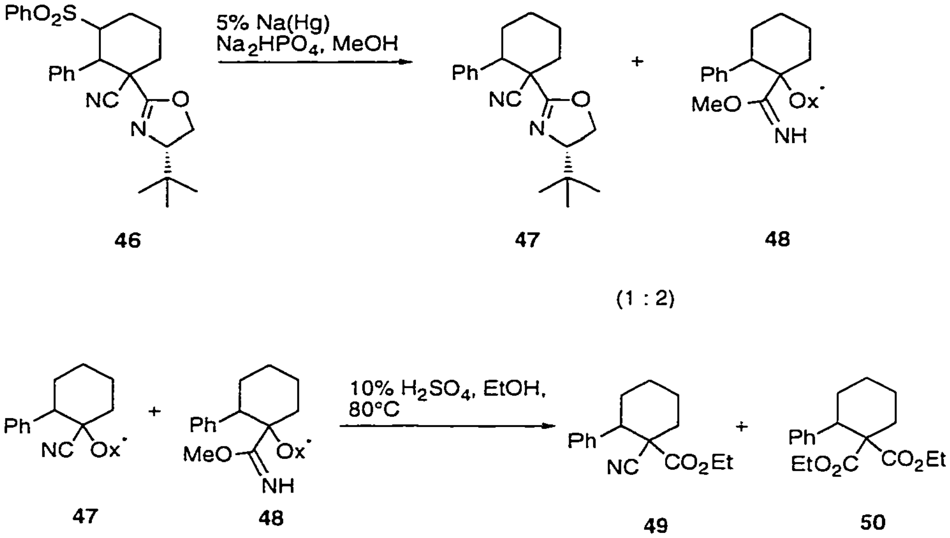
Table 5: Alkyl Sulfone Addition to Cyano Oxazoline 43



Entry	Reaction Conditions	Results
1	(a) 3 eq **37**, 2.5 eq LTMP, THF, -78°C (b) **43**, 30 min.	—starting materials consumed —>80% yield of **46** —nonselective, 6 diastereomers evident by GC/MS, inseparable by chromatography
2	as in entry 1, except -100°C	as in entry 1
3	as in entry 1, except Et_2O as solvent and -100°C	—starting materials consumed —nonselective, 4 diastereomers evident by GC/MS, inseparable by chromatography
4	(a) 2 eq **37**, 1.5 eq LDA, THF, -78°C (b) **43**	as in entry 1

In an effort to assess whether the diastereomeric composition might change, and also to determine future synthetic value, oxazoline **46** was desulfonylated to remove one stereocenter (Scheme 9). The reductive method of Trost[13] was again used and it proceeded to complete desulfonylation. However, significant formation of the undesired methyl imidate **48** could not be avoided occurring as a 2:1 ratio of imidate **48** to nitrile **47**. Furthermore, the mass recovery of this transformation was low (<50%), making subsequent reactions impractical. Even so, further hydrolysis of the mixture of **47** and **48** was undertaken, and after several days the reaction was still incomplete yielding a 50:50 mixture of **49** and **50**, as determined by GC/MS. Nitriles are stable to mild hydrolysis, and even fairly strong conditions (10% H_2SO_4/EtOH, 80°C) which are known to convert nitriles to esters[16] were not successful for hydrolyzing the quaternary cyano group in **47**. Imidates are readily converted into esters, and hence all of the imidate **48** was converted into its corresponding ester **50**. The compounds **49** and **50** were inseparable by chromatography and not utilized further.

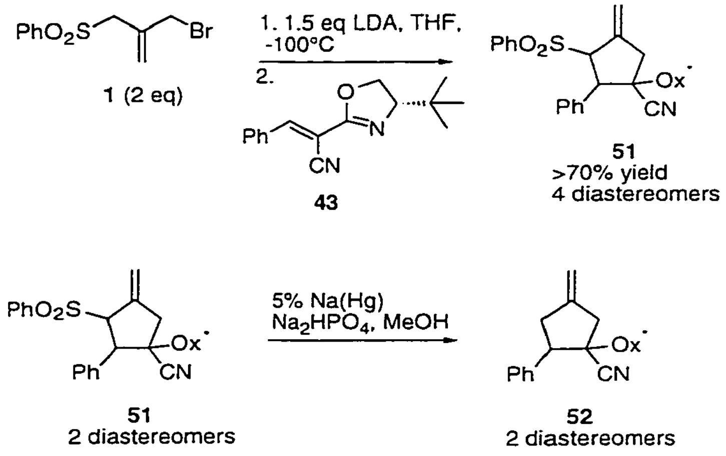
Scheme 9



Returning to the application of allylic sulfones as used by Hassner and coworkers,[1] addition to the more electrophilic cyano oxazoline **43** with allylic sulfone **1** was now a favorable process, with all starting materials consumed within 30 minutes (Scheme 10). Using 1.5 equivalents LDA and 2 equivalents

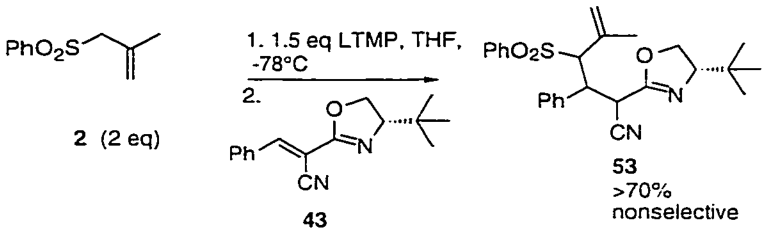
1 in THF at both -100°C and -78°C, oxazoline adducts **51** were formed in >70% yield, as a mixture.

Scheme 10



Once again, the sulfone addition-cyclization to **43** was nonselective, resulting in 4 diastereomers being detected by GC/MS and NMR. The bulk of the product **51** (74% by GC) consisted of two coeluting diastereomers in equal amounts which were separated from the remaining material by chromatography. This mixture of two diastereomers was desulfonylated and the resultant product was also a mixture of two diastereomers. This supports the notion that the differing stereocenters were not at the sulfonyl carbon. Interestingly, unlike with the cyclohexyl adduct **46**, imidate formation during desulfonylation was not significant. Presumably, this was due to the cyano group of the cyclopentane **51** being less accessible than with the cyclohexyl analogs, and therefore less likely to undergo addition of MeOH.

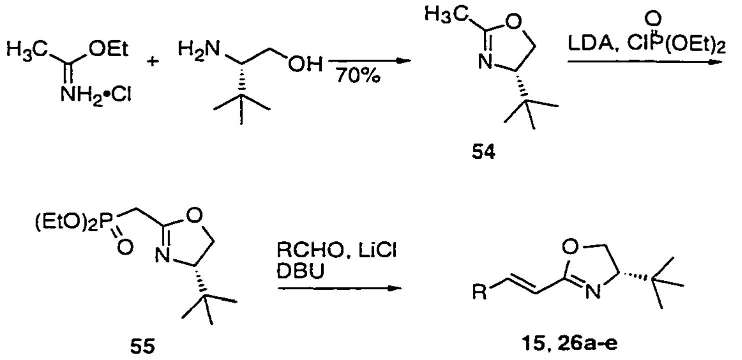
The simple allylic sulfone **2** was also added to oxazoline **43**, and as above, all starting materials were rapidly consumed. As expected, the reaction was also poorly selective.

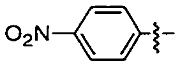
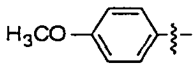
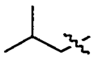
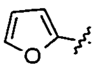
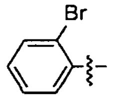


B. Synthesis of α,β-Unsaturated Oxazolinyl and Sulfonyl Starting Materials

The α,β-unsaturated oxazolines were synthesized by two approaches. Following the procedure of Meyers and Shipman,[17] the primary approach involved forming the oxazoline portion first (Table 6), and then carrying out a Masamune-Roush modified Horner-Emmons coupling[18] to form the olefinic portion. This procedure was easily applied to make a variety of oxazolines, and usually provided the desired products (**15**, **26a-e**) in an acceptable yield. With all cases, only one olefinic isomer (*E*) was isolated.

Table 6: Synthesis of α,β-Unsaturated Oxazolines

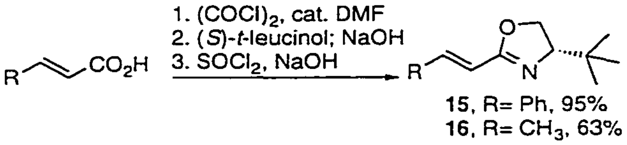


Entry	R	Product	Yield (2 steps from 54)[a]
1	Ph	**15**	70%
2		**26a**	52%
3		**26b**	51%
4		**26c**	62%
5		**26d**	44%
6		**26e**	45%

[a] Isolated yields

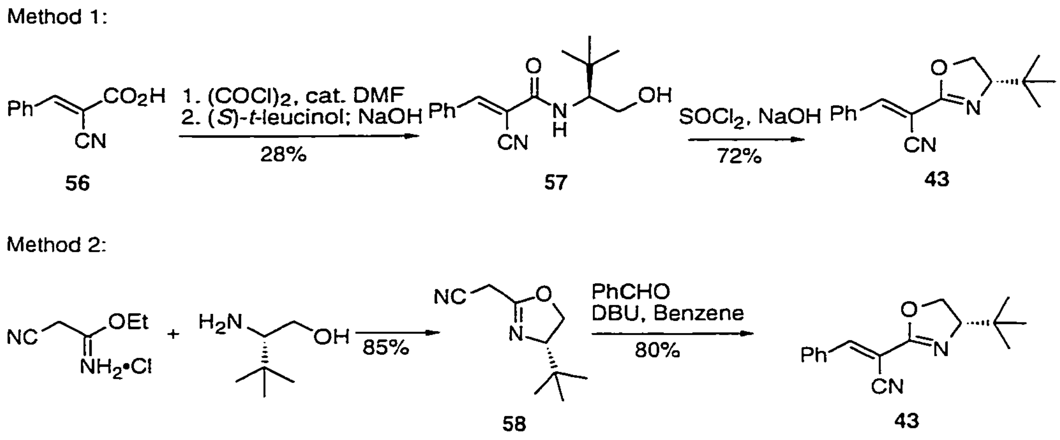
Alternatively, oxazolines **15**[17] and **16**[19] were more readily synthesized directly from the commercial carboxylic acids (Scheme 11). No evidence of any Z-olefin formation was found.

Scheme 11



The cyano oxazoline **43** was prepared by two pathways (Scheme 12). The first started with the known cyano acid **56**.[20] The acid was converted to the oxazoline following standard protocols. While the overall yield was too low to be practical (~20%), the synthesis of **43** was accomplished and the geometry about the double bond was known.

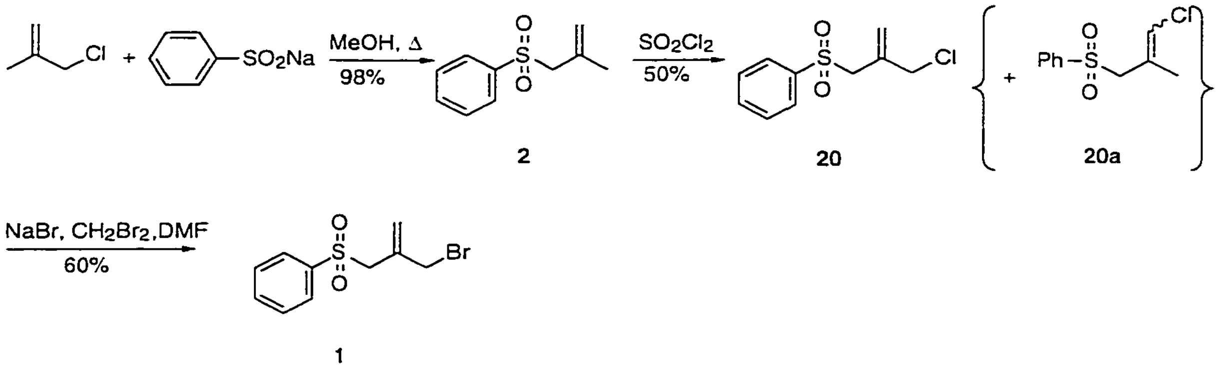
Scheme 12



Because the yield of Method 1 in Scheme 12 was so low, an alternative route was examined (Method 2). Starting with the mono-imidate of malononitrile, oxazoline **58** was formed, followed by a base-catalyzed condensation with benzaldehyde. This sequence furnished a single olefin isomer **43** in overall yield of 68%.

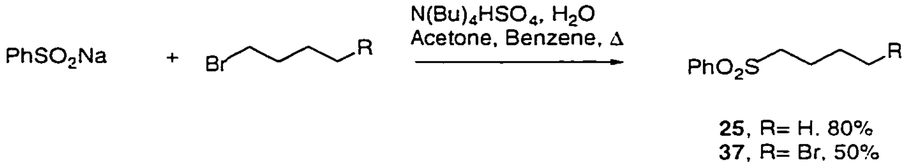
The allyl sulfones **1**, **2**, and **20** were prepared according to the following reported procedures (Scheme 13). The sodium salt of benzenesulfinic acid was treated with methallyl chloride to yield **2** in nearly quantitative yield.[4] Radical chlorination with sulfuryl chloride furnished the allyl chloride **20**.[21] After sequential recrystallizations from isopropyl ether, the yield obtained was around 50%. The major impurity appeared to be the isomeric vinyl chloride **20a**. Conversion to the allylic bromide **1** was accomplished using NaBr-DMF in about 60% yield after recrystallization.[1a]

Scheme 13



The synthesis of the alkyl sulfones **25** and **37** followed the procedure of Crandall and Pradat[22] (Scheme 14). This biphasic method suppressed unwanted O-alkylation which would give a sulfoxide.

Scheme 14



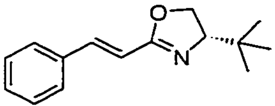
C. Summary

We have shown that the conjugate addition of sulfonyl carbanions to chiral α,β-unsaturated oxazolines may occur with very high selectivity with the first successful examples of stabilized carbanion additions. In many cases, the addition apparently resulted in complete stereocontrol. In the examples where cyclization followed addition, three contiguous stereocenters were selectively formed in one reaction step. When the pK_a of both partners are matched appropriately, the addition is not only stereochemically very efficient, but also is synthetically practical.

III. Experimental

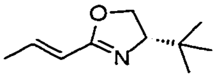
Thin layer chromatography (TLC) and flash chromatography were performed with E. Merck silica gel (230-400 mesh). All reagents were purchased from Aldrich Chemical, Co. All non-aqueous reactions were conducted under argon in oven or flame-dried apparatus. Melting points are uncorrected. Diethyl ether, tetrahydrofuran, and benzene were dried by distillation over sodium-benzophenone. Dichloromethane, diisopropylamine, triethylamine, toluene, dimethylsulfoxide, and HMPA were distilled over CaH_2.

General Procedure for forming an α,β–Unsaturated Oxazoline from Corresponding Acid: To a solution of 1 g carboxylic acid in 20 ml CH_2Cl_2 was added 1.5 eq oxalyl chloride followed by a catalytic amount of DMF. After stirring for 5 h, the solvent was removed, the residue dissolved in benzene and then concentrated. The crude acid chloride was dissolved in 25 ml CH_2Cl_2, and chilled to 0°C. A solution of 1.5 eq (*S*)-*t*-leucinol in 25 ml NaOH was added dropwise while maintaining vigorous stirring. The solution was allowed to warm to room temperature and stirred an additional 12 h. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 ml). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated. The crude amide-alcohol was dissolved in CH_2Cl_2, chilled to 0°C, and 3 eq thionyl chloride were added slowly. After 3 h, the solvent was removed, and the residue was dissolved in 10 ml CH_3CN and 2 ml saturated aqueous K_2CO_3. After heating at reflux for 6 h, the solution was cooled, and the solvent was removed. The residue was dissolved in EtOAc (75 ml), washed with brine and dried over Na_2SO_4. After filtration and concentration, the residue was purified by flash chromatography (5% EtOAC/hexanes and 10% EtOAc/hexanes).



15

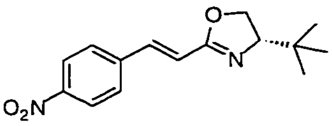
(4S)-4-tert-Butyl-2-((E)-2-phenylethenyl)-2-oxazoline, 15. (from *trans*-cinnamic acid, 95% yield) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.96 (s, 9H), 4.0 (dd, J= 10.2, 8.1 hz, 1H), 4.15 (dd. J= 8.4, 8.4 hz, 1H), 4.29 (dd, J= 10.2, 8.1 hz, 1H), 6.7 (d, J= 16 hz, 1H), 7.35 (m, 4H), 7.49 (d, J= 7.8 hz, 2H); IR (neat) 1656, 1610, 974 cm^{-1}. Spectra are in agreement with previously reported data.[17]



16

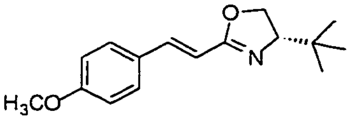
(4S)-4-tert-Butyl-2-((E)-1-propenyl)-2-oxazoline, 16. (from *trans*-crotonic acid, 63% yield) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (s, 9H), 1.84 (d, J= 6.9 hz, 3H), 3.87 (app t, J= 9 hz, 1H), 4.03 (dd, J= 8.4, 8.4 hz, 1H), 4.15 (dd, J= 10, 9.3 hz, 1H), 6.01 (d, J= 16 hz, 1H), 6.54 (dq, J= 16, 6.9 hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.3, 25.8, 33.7, 68.1, 75.9, 119.2, 138.6, 162.6. Spectra are in agreement with previously reported data.[19]

Synthesis of α,β-Unsaturated Oxazolines from Phosphonate 55: Compounds **26a**-**26e** were synthesized following the procedure of Meyers and Shipman.[17]



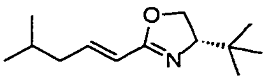
26a

(4S)-4-tert-Butyl-2-((E)-2-(4-nitrophenyl)ethenyl)-oxazoline, 26a. (from *para*-nitrobenzaldehyde, 52% yield as a yellow solid) mp= 97-99°C; $[\alpha]^{25}_D$= -81.6 (c=1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.93 (s, 9H), 4.01 (dd, J= 10.2, 8.1 hz, 1H), 4.15 (app t, J= 8.4 hz, 1H); 4.3 (dd, J= 9.9, 8.4 hz, 1H), 6.79 (d, J= 16.2 hz, 1H), 7.34 (d, J= 16.2 hz, 1H), 7.6 (d, J= 8.7 hz, 1H), 8.22 (d, J= 8.7 hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.8, 33.8, 68.5, 76.3, 119.6, 124.1, 127.8, 136.8, 141.5, 147.8, 162.2; IR (neat) 1652, 1610, 1530, 1346 cm^{-1}; HRMS (FAB+) for $C_{15}H_{19}N_2O_3$ $(M+H)^+$: Calcd 275.1397 Found 275.1394.



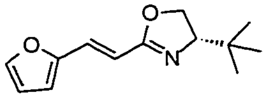
26b

(4S)-4-tert-Butyl-2-((E)-2-(4-methoxyphenyl)ethenyl)-oxazoline, 26b. (from *para*-anisaldehyde, 51% yield as a light yellow powder) $[\alpha]^{25}_D$= -74.8 (c=1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.93 (s, 9H), 3.82 (s, 3H), 3.97 (dd, J= 9.9, 7.8 hz, 1H), 4.12 (app t, J= 8.4 hz, 1H). 4.26 (dd, J= 10.2, 8.4 hz, 1H), 6.54 (d, J= 16.2 hz, 1H), 6.88 (d, J= 8.4 hz, 2H), 7.27 (d, J= 16.2 hz, 1H), 7.42 (d, J= 8.4 hz, 2H); *m/z* 259 $(M)^+$, 202 $(M\text{-}t\text{-}Bu)^{+\cdot}$



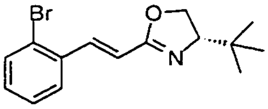
26c

(4S)-4-tert-Butyl-2-((E)-4-methylpentenyl)-oxazoline, 26c. (from isovaleraldehyde, 62% yield as an opaque oil) $[\alpha]^{25}_{D}$= -16.5 (c=0.56, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 0.89 (br s, 12H), 0.92 (s, 3H), 1.72 (sept., J= 6.6 hz, 1H), 2.06 (t, J= 7.5 hz, 2H), 3.89 (dd, J= 9.9, 8.1 hz, 1H), 4.04 (dd, J= 8.4, 8.4 hz, 1H), 4.19 (dd, J= 9.9, 8.6 hz, 1H), 5.99 (d, J= 15.9 hz, 1H), 6.51 (ddd, J= 15.2, 7.2, 7.2 hz, 1H); HRMS (FAB+) for $C_{13}H_{24}NO$ $(M+H)^+$: Calcd 210.1858 Found 210.1863.



26d

(4S)-4-tert-Butyl-2-((E)-2-(2-furanyl)ethenyl)-oxazoline, 26d. (from 2-furaldehyde, 44% yield as a yellow solid which darkens over time) mp= 74-76°C; $[\alpha]^{25}_{D}$= -83 (c=0.44, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 0.92 (s, 9H), 3.97 (dd, J=10.2, 7.8 hz, 1H), 4.1 (app t, J= 8.1 hz, 1H), 4.24 (dd, J= 9.9, 8.4 hz, 1H), 6.41-6.48 (m, 1H), 6.55 (d, J= 16.2 hz, 1H), 7.08 (d, J= 16.2 hz, 1H), 7.44 (s, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 25.9, 33.9, 68.2, 76.3, 111.8, 112.3, 113.2, 126.4, 143.8, 151.4, 162.8; IR (film) 1652, 1624, 981, 967 cm^{-1}; HRMS (FAB+) for $C_{13}H_{18}NO_2$ $(M+H)^+$: Calcd 220.1338 Found 220.1328.

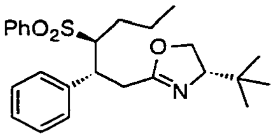


26e

(4S)-4-tert-Butyl-2-((E)-2-(2-bromophenyl)ethenyl)-oxazoline, 26e. (from 2-bromobenzaldehyde, 45% yield) $[\alpha]^{25}_{D}$= -86 (c=0.5, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 0.94 (s, 9H), 3.99 (dd, J= 9.9, 8.1 hz, 1H), 4.16 (app t, J= 8.4 hz, 1H), 6.64 (d, J= 16.2 hz, 1H), 7.18 (t, J= 6.3 hz, 1H), 7.31 (t, J= 6.3 hz, 1H), 7.59-7.61 (m, 1H), 7.67 (d, J= 16.2 hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26, 34, 68.8, 76.6, 118, 125, 127.5, 128, 131, 133.5, 135.5, 138.2, 163.1.

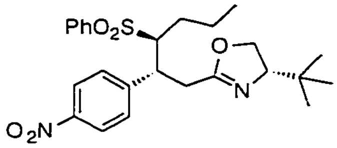
General Procedure for Addition of Sulfone 25 to α,β-Unsaturated Oxazolines: Method A: To a solution of **25** (2 mmol) in 5 ml THF at -78°C was added *n*-butyl lithium (2M in hexanes, 1.8 mmol). The bright yellow solution was stirred for 15 min at -78°C and the oxazoline (dried azeotropically with toluene) was added in 2 ml THF. A dark red color soon followed and, after stirring for 20 min, the reaction was quenched with 2-propanol. The solution was allowed to warm to room temperature, and then was diluted with H_2O (15 ml). The mixture was extracted with EtOAc (3 x 30 ml), dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (5% EtOAc/hexanes to 20% EtOAc/hexanes).

Method B: To a solution of **25** (0.48 mmol) in 5 ml THF at -78°C was added *n*-butyl lithium (2M in hexanes, 0.4 mmol). The bright yellow solution was stirred for 15 min at -78°C and the oxazoline (0.4 mmol, dried azeotropically with toluene) was added in 2 ml THF. A dark red color soon followed and, after stirring for 20 min, the reaction was quenched with 2-propanol. The solution was allowed to warm to room temperature, and then was diluted with H_2O (15 ml). The mixture was extracted with EtOAc (3 x 30 ml), dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (5% EtOAc/hexanes to 20% EtOAc/hexanes).



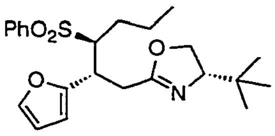
27a

(4S)-4-tert-Butyl-2-((2R,3S)-2-phenyl-3-phenylsulfonyl-hexyl)-oxazoline, 27a: (from oxazoline **15**,[17] Method A, 72% isolated yield as a viscous, colorless oil) $[\alpha]^{25}{}_D$= -13.8 (c=0.74, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.5-2.0 (m, 16H), 2.88 (dd, J= 15, 11 hz, 1H), 3.16 (dd, J= 15, 4.5 hz, 1H), 3.25 (ddd, J= 4.5, 4.5, 3 hz, 1H), 3.65 (ddd, J= 10.5, 9, 1.5 hz, 1H), 3.83-3.96 (m, 3H), 7.15-7.25 (m, 5H), 7.6 (dd, J= 7.8, 7.8 hz, 2H), 7.65 (d, J= 7.2 hz, 1H), 7.9 (d, J= 7.2 hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.6, 21.4, 25.6, 26.3, 27.1, 33.4, 40.2, 68.9, 75.5, 126.9, 127.9, 128.4, 128.6, 129.1, 133.5, 139, 140, 164.8; IR (neat) 1668 cm^{-1}; HRMS (FAB+) for $C_{25}H_{34}NO_3S$ $(M+H)^+$: Calcd 428.2259 Found 428.2266.



27b

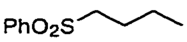
(4S)-4-tert-Butyl-2-((2R,3S)-2-(4-nitrophenyl)-3-phenylsulfonyl-hexyl)-oxazoline, 27b: (from oxazoline **26a**, Method B, 78% isolated yield as a colorless oil) $[\alpha]^{25}{}_D$= -15 (c=0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.6-0.7 (m, 12H), 1.15-1.28 (m, 2H), 1.85-2.10 (m, 2H), 3.19 (dd, J= 13.5, 11.4 hz, 1H), 3.38-3.49 (m, 3H), 3.7 (app t, J= 8.4 hz, 1H), 3.82 (app t, J= 8.7 hz, 1H), 4.03 (dd, J= 10.2, 8.7 hz, 1H), 7.47 (d, J= 9 hz, 2H), 7.59 (app t, J= 7.5 hz, 2H), 7.66-7.71 (m, 1H), 7.95 (d, J= 8 hz, 2H), 8.10 (d, J= 8 hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 21.6, 25.8, 26.9, 32.2, 33.3, 39.8, 65.2, 68.7, 75.8, 123.2, 128.3, 129.3, 130.3, 133.9, 138.9, 146.5, 147.8, 164.6; IR (neat) 1667, 1520 cm^{-1}; HRMS (FAB+) for $C_{25}H_{32}N_2O_5S$ $(M+H)^+$: Calcd 473.2112 Found 473.2095.



27e

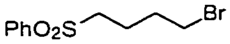
(4S)-4-tert-Butyl-2-((2R,3S)-2-(2-furyl)-3-phenylsulfonyl-hexyl)-oxazoline, 27e: (from oxazoline **26d**, Method A, 70% isolated yield as a light yellow oil) $[\alpha]^{25}{}_D$= -16.5 (c=0.55, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.67 (t, J= 7.2 hz, 3H), 0.78 (s, 9H), 1.11-1.25 (m, 2H), 1.62-1.99 (m, 2H), 2.76 (dd, J= 15.3, 11.1 hz, 1H), 3.16 (d, J= 14.1 hz, 1H), 3.47 (ddd, J= 10, 3.3, 3.3 hz, 1H), 3.74 (app t, J= 8.4 hz, 1H), 3.93-4.07 (m, 3H), 6.15 (d, J= 3.3 hz, 1H), 6.21 (br s, 1H), 7.21 (s, 1H), 7.53-7.67 (m, 3H), 7.93 (d, J= 6.9 hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.8, 21.1, 25.8, 26.6, 26.7, 33.7, 35.0, 65.9, 68.7, 75.7, 107.4, 110.5, 128.9, 129.3, 133.8, 138.8, 141.6, 153.4, 164.9; HRMS (FAB+) for $C_{23}H_{31}NO_4S$ $(M+H)^+$: Calcd 418.2052 Found 418.2056.

General Procedure for forming alkyl sulfones: The procedure follows that of Crandall and Pradat.[22] The appropriate alkyl bromide, 5 g (1.3 equiv) of benzenesulfinic acid sodium salt, and tetrabutylammonium hydrogen sulfate (0.1 equiv) were heated at 80°C in 20 ml H_2O, 10 ml benzene, and 10 ml acetone for 16 h. The biphasic mixture was allowed to cool to room temperature and the solvent was removed *in vacuo*. The residue was dissolved in Et_2O (150 ml) and saturated aqueous $NaHCO_3$ (150 ml). The layers were separated, and the aqueous phase was reextracted with Et_2O (100 ml). The Et_2O layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography (hexanes and 5% EtOAc/hexanes).



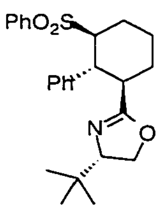
25

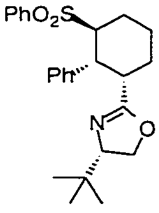
Phenylsulfonylbutane, 25. (from 1-bromobutane, a yellow-orange oil, 80% yield) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, J= 7.2 hz, 3H), 1.38 (dddd, J= 15, 7.5, 7.5, 7.5 hz, 2H), 1.68 (m, 2H), 3.08 (m, 2H), 7.55 (t, J= 7.4 hz, 2H), 7.64 (d, J= 6.6 hz, 1H), 7.9 (d, J= 7.2 hz, 2H). Spectrum is agreement with previously reported data.[22]



37

1-Bromo-4-phenylsulfonylbutane, 37. (from 1,4-dibromobutane (1.3 equiv); slow-forming, off-white solid, 50% yield): mp= 57-58°C, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.83-2.03 (m, 4H), 3.12 (t, J= 7.5 hz, 2H), 3.38 (dd, J= 6.6, 6.3 hz, 2H), 7.59 (dd, J= 7.4, 7.3 hz, 2H), 7.68 (dd, J= 7.5, 7.5 hz, 1H), 7.92 (d, J= 6 hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.6, 30.9, 32.3, 55.2, 127.9, 129.2, 133.7, 138.7; IR (neat) 1446, 1246, 1147 cm^{-1}; *m/z* 197 (M-Br)$^+$.



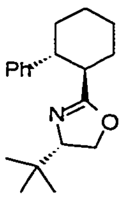


38 39

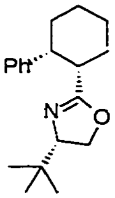
Cyclohexyl oxazolines 38 and 39: The sulfone **37** and the oxazoline **15** were dried azeotropically with toluene prior to use. To a solution of tetramethylpiperidine (0.86 mmol, 150 µl) in 2.5 ml THF at -78°C was added *n*-butyl lithium (2M in hexane, 0.4 ml, 0.77 mmol) and the solution was stirred for 20 min. Sulfone **37** (242 mg, 0.86 mmol) in 1.5 ml THF was added and the mixture was stirred for 10 min while the reaction turned yellow in color. The oxazoline **15** (40mg, 0.17 mmol) in 1 ml THF was added. The reaction was stirred at -78°C and after 16 h, 1 ml MeOH was added. The solvent was removed, and the residue was dissolved in EtOAc (30 ml) and H_2O (15 ml). The EtOAc layer was washed with a phosphate buffer (pH= 4) and brine (15 ml each). The EtOAc layer was then dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (10% EtOAc/hexanes and 25% EtOAc/hexanes) yielding 40 mg of oxazoline **38** (56%) and 18 mg of oxazoline **39** (11%).

cyclohexyl oxazoline 38. colorless needles (from EtOH); mp= 183-185°C; $[\alpha]^{25}_{D}$= -102 (c=0.55, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.66 (s, 9H), 1.44-1.82 (m, 3H), 1.94-2.16 (m, 2H), 2.46-2.54 (m, 1H), 2.61 (ddd, J= 11.4, 11.4, 3.3 hz, 1H), 3.3 (dd, J= 11.4, 11.4 hz, 1H), 3.38 (ddd, J= 7.5, 7.5, 7.5 hz, 1H), 3.47 (ddd, J= 11.4, 11.4, 3.3 hz, 1H), 3.76 (dd, J= 8.7, 8.7 hz, 1H), 3.81 (dd, J= 7.2, 7.2 hz, 1H), 6.94 (br s, 5H), 7.17 (dd, J= 9, 6 hz, 2H), 7.32 (d, J= 8.1 hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.8, 26.4, 26.5, 31.4, 32.4, 46.7, 47.8, 68, 69.1, 76.1, 128, 128.8, 128.9, 129.5, 130, 133.3, 139.5, 141, 168

cyclohexyl oxazoline 39. colorless solid; mp= 164-167°C; $[\alpha]^{25}_{D}$= +33 (c=0.32, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.38 (s, 9H), 1.42-1.84 (m, 3H), 1.95-2.0 (m, 1H), 2.07-2.14 (m, 1H), 2.5-2.55 (m, 1H), 2.69 (ddd, J= 11.7, 11.7, 3.3 hz, 1H), 3.3 (dd, J= 11.4, 11.4 hz, 1H), 3.47 (ddd, J= 12, 12, 3.6 hz, 1H), 3.54-3.64 (m, 2H), 3.92-4.02 (m, 1H), 6.93 (br s, 5H), 7.18 (dd, J= 7.8, 7.8 hz, 2H), 7.3-7.37 9m, 3H); Anal. Calcd for $C_{25}H_{31}NO_3S \bullet 1/2\ H_2O$: C, 69.09; H, 7.42. Found: C, 69.24; H, 7.30.



40

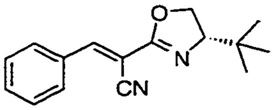


41

Cyclohexyl oxazolines 40 and 41. Compounds **40** and **41** were synthesized following the procedure of Trost et al.[13] To 2 ml dry MeOH was added the sulfonyl oxazoline **38** or **39** (20 mg), powdered Na_2HPO_4 (400 mg), and 5% Na(Hg) beads (~600 mg) at 0°C. The mixture was allowed to warm to room temperature and was stirred 12 h. The mercury was removed by filtration, and the solvent was removed *in vacuo*. The residued was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$. After drying over Na_2SO_4 and concentrating, the residue was purified by flash chromatography (5% EtOAc/hexanes).

cyclohexyl oxazoline 40. (from oxazoline **38**, 11 mg as a colorless oil, 85% yield) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.65 (s, 9H), 1.45-1.65 (m, 4H), 1.75-1.9 (m, 3H), 2.09-2.15 (m, 2H), 2.6-2.7 (m, 1H), 2.7-2.9 (m, 1H), 3.5-3.6 (m, 1H), 3.8-3.9 (m, 2H), 7.15-7.25 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.4, 26.8, 27.4, 32.7, 36.3, 44.4, 47.8, 69, 127.8, 128.5, 129.2, 146.4, 170; *m/z* 285 $(M)^+$, 228 (M-*t*-Bu)$^+$.

cyclohexyl oxazoline 41. (from oxazoline **39**, 8 mg as a colorless oil, 62% yield) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.58 (s, 9H), 1.22-1.98 (m, 9H), 2.68-2.72 (m, 2H), 3.57-3.67 (m, 2H), 3.92 (dd, J= 6.9, 6 hz, 1H), 7.08-7.23 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.5, 26.7, 31.9, 33.4, 35.8, 45.3, 48, 69.3, 76.4, 127.3, 128.6, 129.3, 145.7, 160.8.



43

(4S)-4-tert-Butyl-2-((E)-1-cyano-2-phenylethenyl)-oxazoline, 43. To 30 ml Et_2O was added malonitrile (21 mmol) adn ethanol (0.8 ml, 21 mmol). While maintaining vigorous stirring, the solution was aerated with dry HCl gas for 30 min. The mixture was allowed to stir for 6 h at room temperature, and then cooled to 0°C. The resultant precipitate (the desired imidate) was collected, washed with Et_2O, and used without further purification. The imidate was dissolved in dry CH_2Cl_2 (30 ml), (*S*)-*t*-leucinol was added, and the mixture was stirred for 12 h at room temperature. The solution was diluted with saturated aqueous $NaHCO_3$ (50 ml) and extracted with EtOAc (2 x 50 ml). The layers were separated and the organic phase was washed with saturated aqueous NH_4Cl (2 x 50 ml). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by flash chromatography (10% EtOAc/hexanes) to yield 1.3 g of oxazoline **58** as a dark yellow film (85% from the imidate). To a round-bottomed flask equipped with a Dean-Stark condenser was combined oxazoline **58** (1.4 g, 8.43 mmol), benzaldehyde (0.78 ml, 7.67 mmol), and 1-8-diazabicyclo[5.4.0]undec-7-ene (0.34 ml, 2.3 mmol) in benzene (40 ml). The solution was heated at reflux for 12 h, then cooled and washed with brine (30 ml). The organic layer was dried over Na_2SO_4, filteredm and concentrated. The residue was purified by flash chromatography (2% EtOAc/hexanes and 5% EtOAc/hexanes) to give oxazoline **43** (1.56 g, 80% yield) as off-white needles mp= 81-83°C; $[\alpha\}^{25}{}_D$= -89.7 (c=1.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94 (s, 9H), 4.06 (dd, J= 9.9, 7.8 hz, 1H), 4.23 (dd, J= 8.4, 8.3 hz, 1H), 4.35 (dd, J= 10.2, 8.6 hz, 1H), 7.41-7.51 (m, 3H), 7.88 (s, 1H), 7.9-7.93 (m, 2H); HRMS (FAB+) for $C_{16}H_{19}N_2O$ $(M+H)^+$: Calcd 255.14974 Found 255.14973.

IV. References

1. (a) Ghera, E.; Yechezkel, T.; Hassner, A. *J. Org. Chem.* **1996**, *61*, 4959.

(b) Yechezkel, T.; Ghera, E.; Ramesh, N.; Hassner, A. *Tetrahedron: Asymmetry* **1996**, *7*, 2423.

(c) Yechezkel, T.; Ghera, E.; Ostercamp, D.; Hassner, A. *J. Org. Chem.* **1995**, *60*, 5135.

(d) Yechezkel, T.; Ghera, E.; Hassner, A. *Tetrahedron Lett.* **1990**, *31*, 3653.

2. Alonso, D. A.; Falvello, L. R.; Mancheño, B.; Nájera, C.; Tomás, M. *J. Org. Chem.* **1996**, *61*, 5004.

3. Ghera, E.; Kleiman, V.; Hassner, A. *J. Org. Chem.* **1999**, *64*, 8.

4. Trost, B. M.; Schmuff, N. R. *J. Am. Chem. Soc.* **1985**, *107*, 396.

5. Kumareswaran, R.; Balasubramanian, T.; Hassner, A. *Tetrahedron Lett.* **2000**, *41*, 8157.

6. Nakache, P.; Ghera, E.; Hassner, A. *Tetrahedron Lett.* **2000**, *41*, 5583.

7. Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413.

8. For a summary of the use of chiral oxazolines in conjugate additions see: This document, Chapter I, I. Introduction and references cited therein.

9. The syntheses of the chiral α,β-unsaturated oxazolines and sulfonyl starting materials are fully described following this discussion (this document, Chapter II, II. Results and Discussion, part B)

10. Pearson, R. G. *Inorg. Chem.* **1988**, *27*, 734.

11. (a) Bordwell, F. G.; Van der Puy, M.; Vanier, N. R. *J. Org. Chem.* **1976**, *41*, 1883.

(b) Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006.

12. Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.

13. Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.

14. Levene, P. A.; Marker, R. F. *J. Biol. Chem.* **1932**, *97*, 563.

15. Susie Miller is gratefully acknowledged for solving the X-ray crystal structure of oxazoline **38**.

16. Anzalone, L.; Hirsch, J. A. *J. Org. Chem.* **1985**, *50*, 2128.

17. Meyers, A. I.; Shipman, M. *J. Org. Chem.* **1991**, *56*, 7098.

18. Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2182.

19. Meyers, A. I.; Stoianova, D. *J. Org. Chem.* **1997**, *62*, 5219.

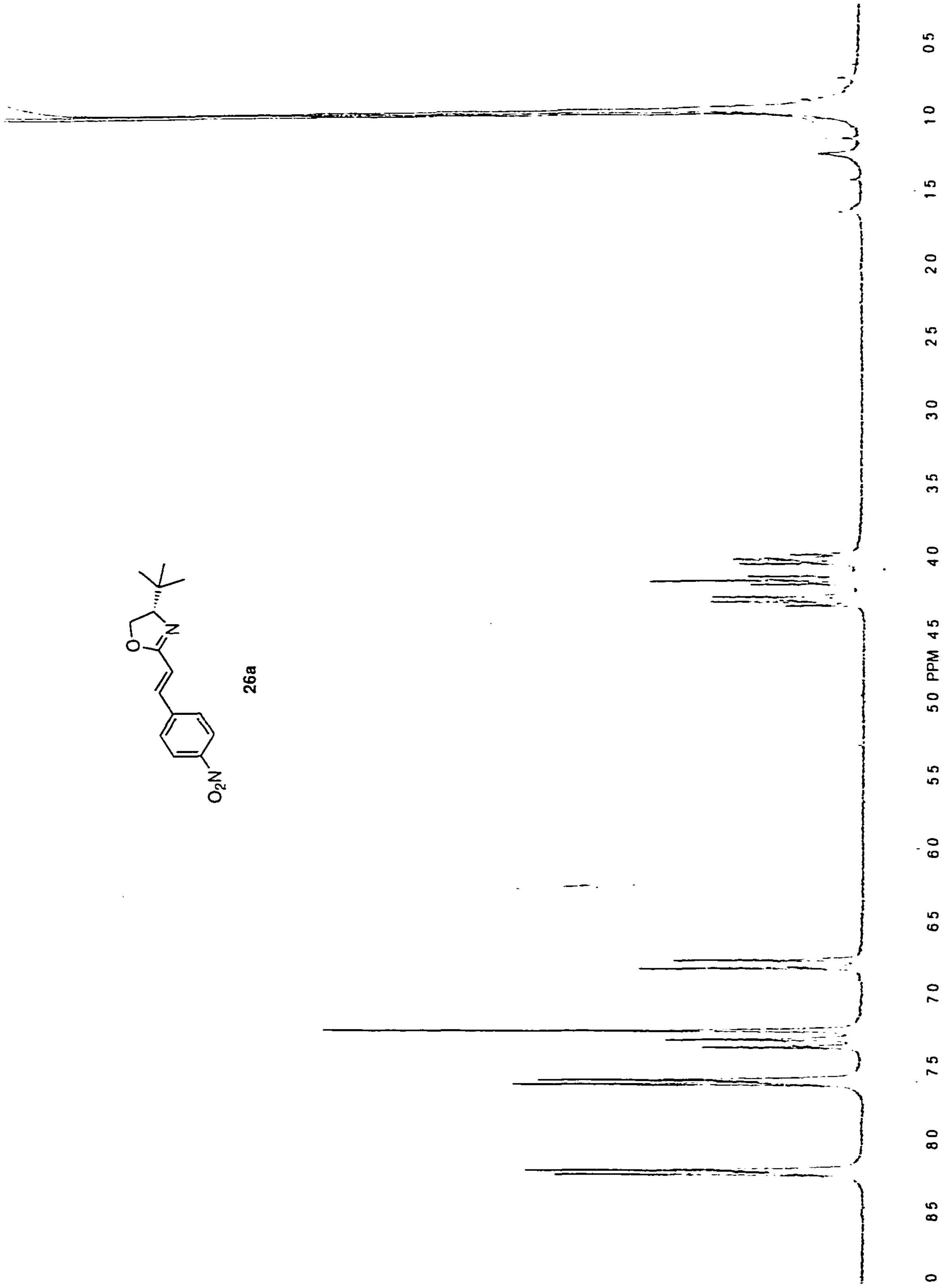
20. Freeman, F.; Kappos, J. C. *J. Org. Chem.* **1986**, *51*, 1655.

21. Breuilles, P.; Uguen, D. *Tetrahedron Lett.* **1987**, *28*, 6053.

22. Crandall, J.; Pradat, C. *J. Org. Chem.* **1985**, *50*, 1327.

23. Dr. Chris Rithner is gratefully acknowledged for aquiring the NOESY data.

V. ^{1}H and ^{13}C NMR Spectra and Single Crystal X-ray Data



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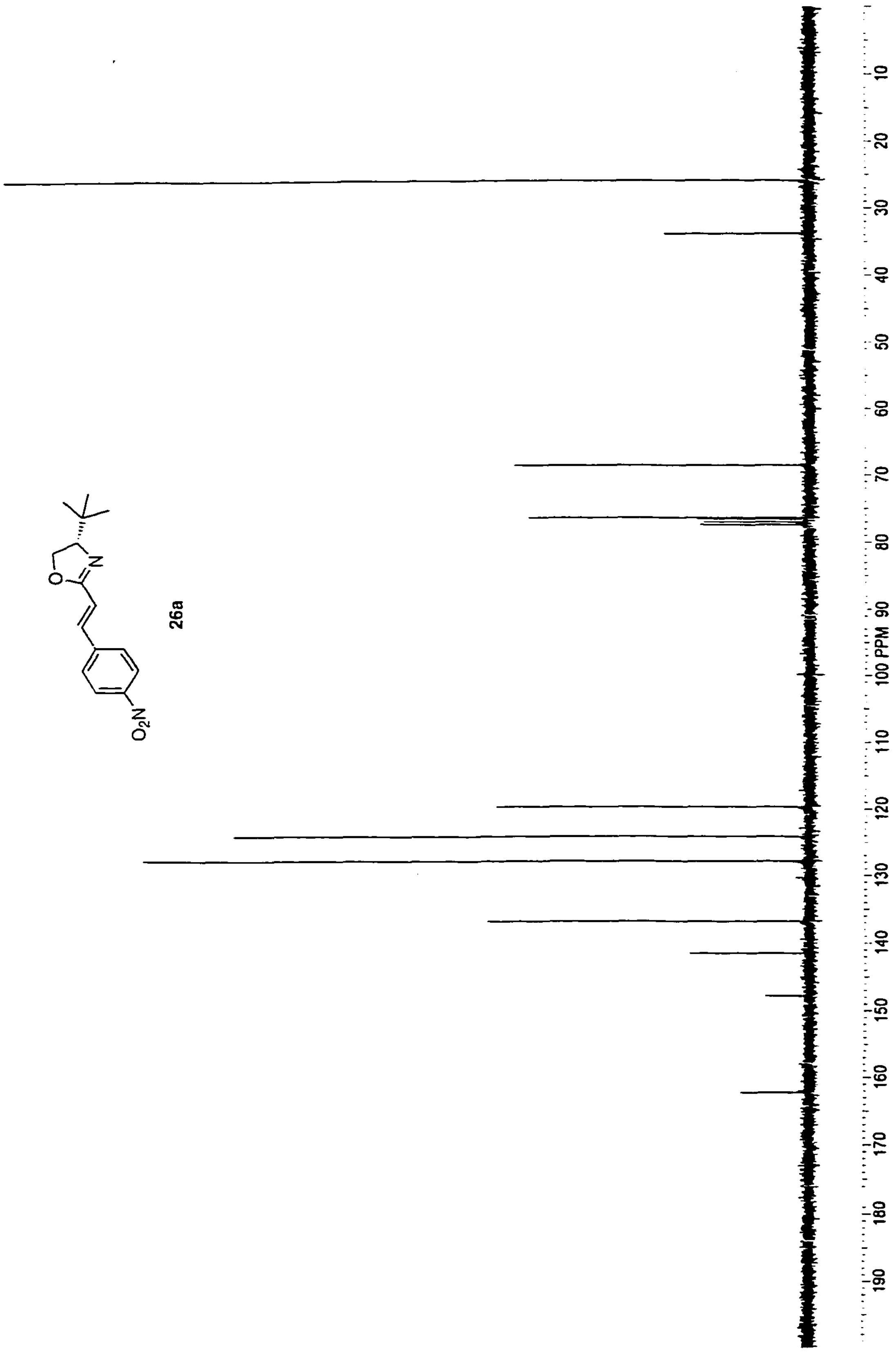
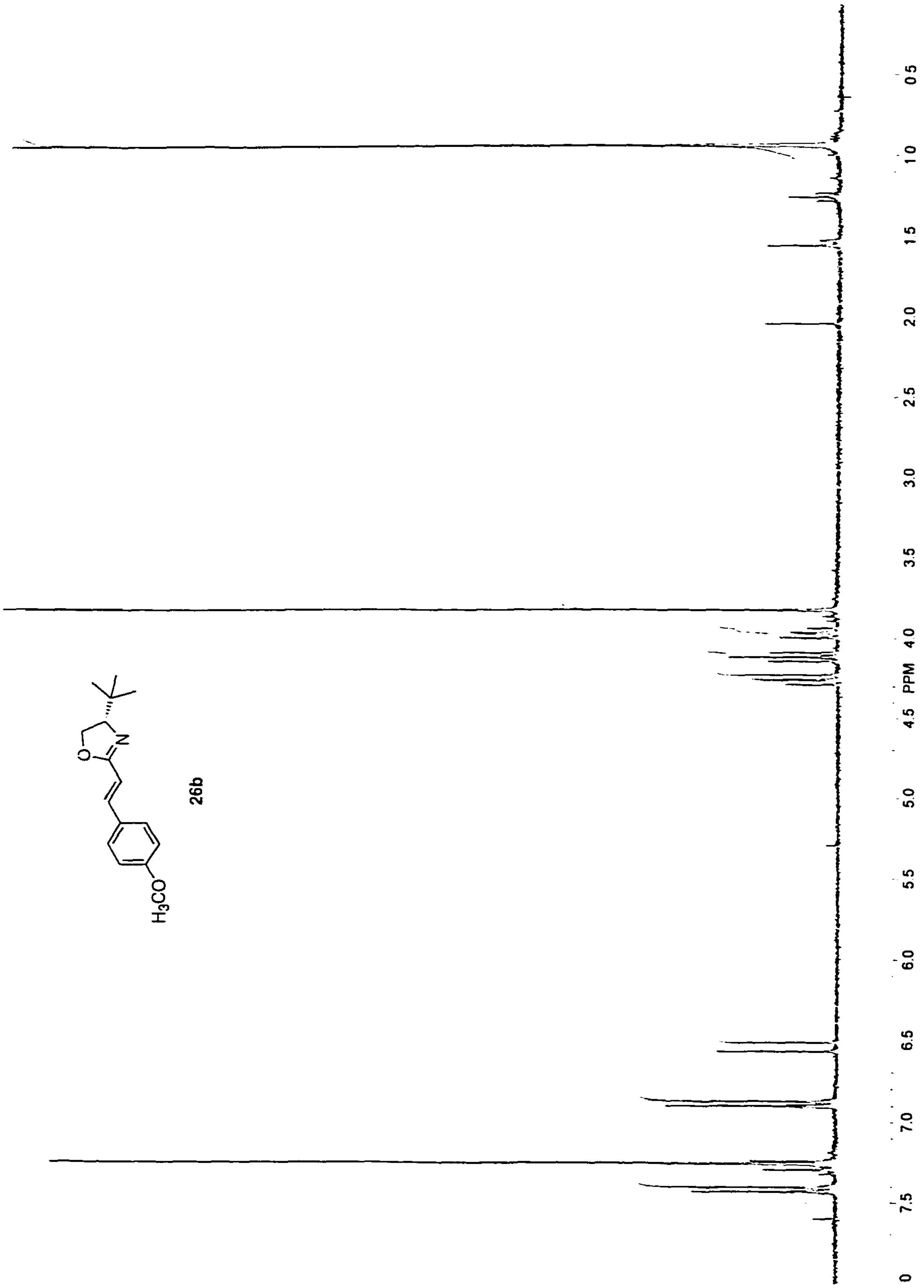


26a

O
N
O_2N
10
20
30
40
50
60
70
80
90
100 PPM
110
120
130
140
150
160
170
180
190



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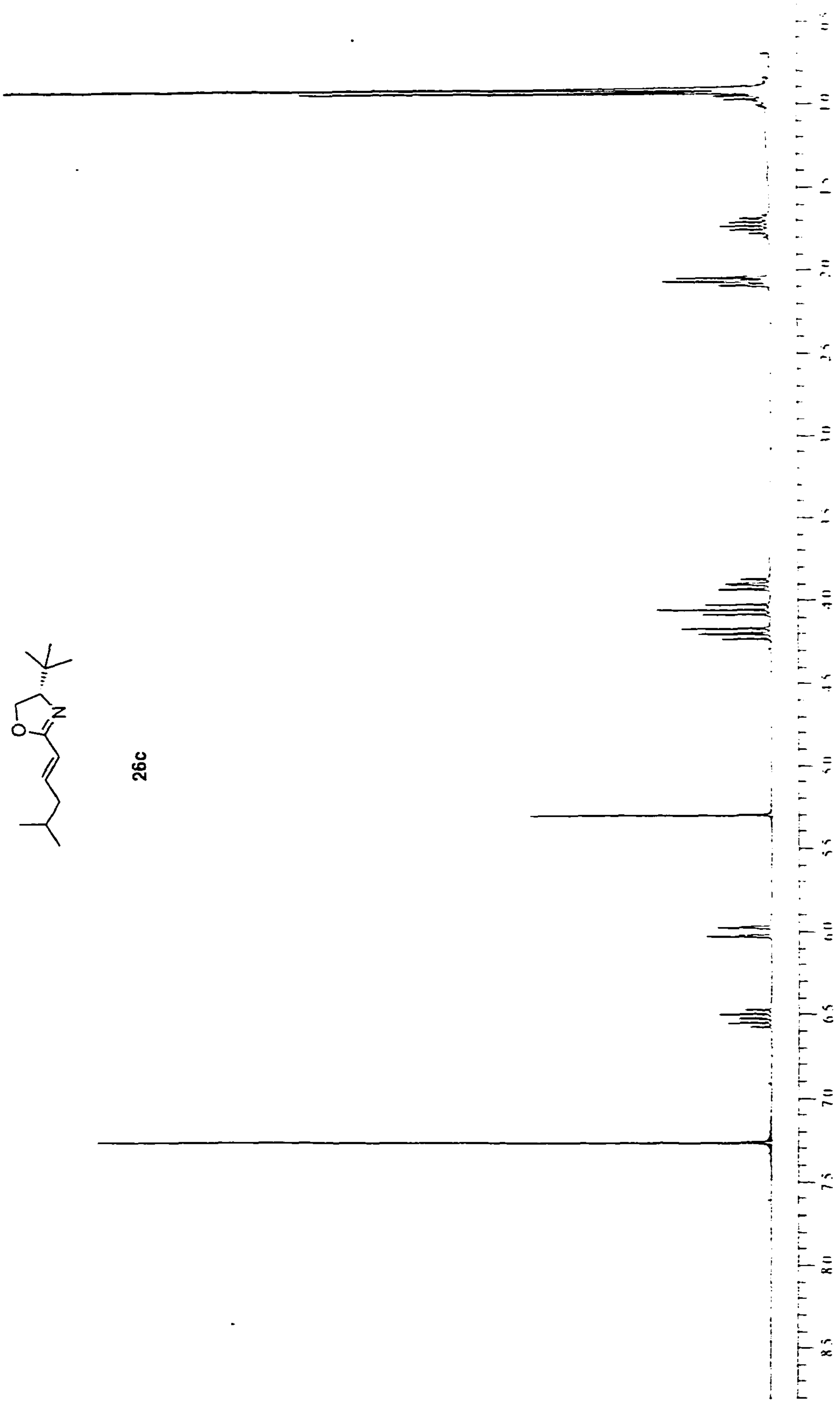

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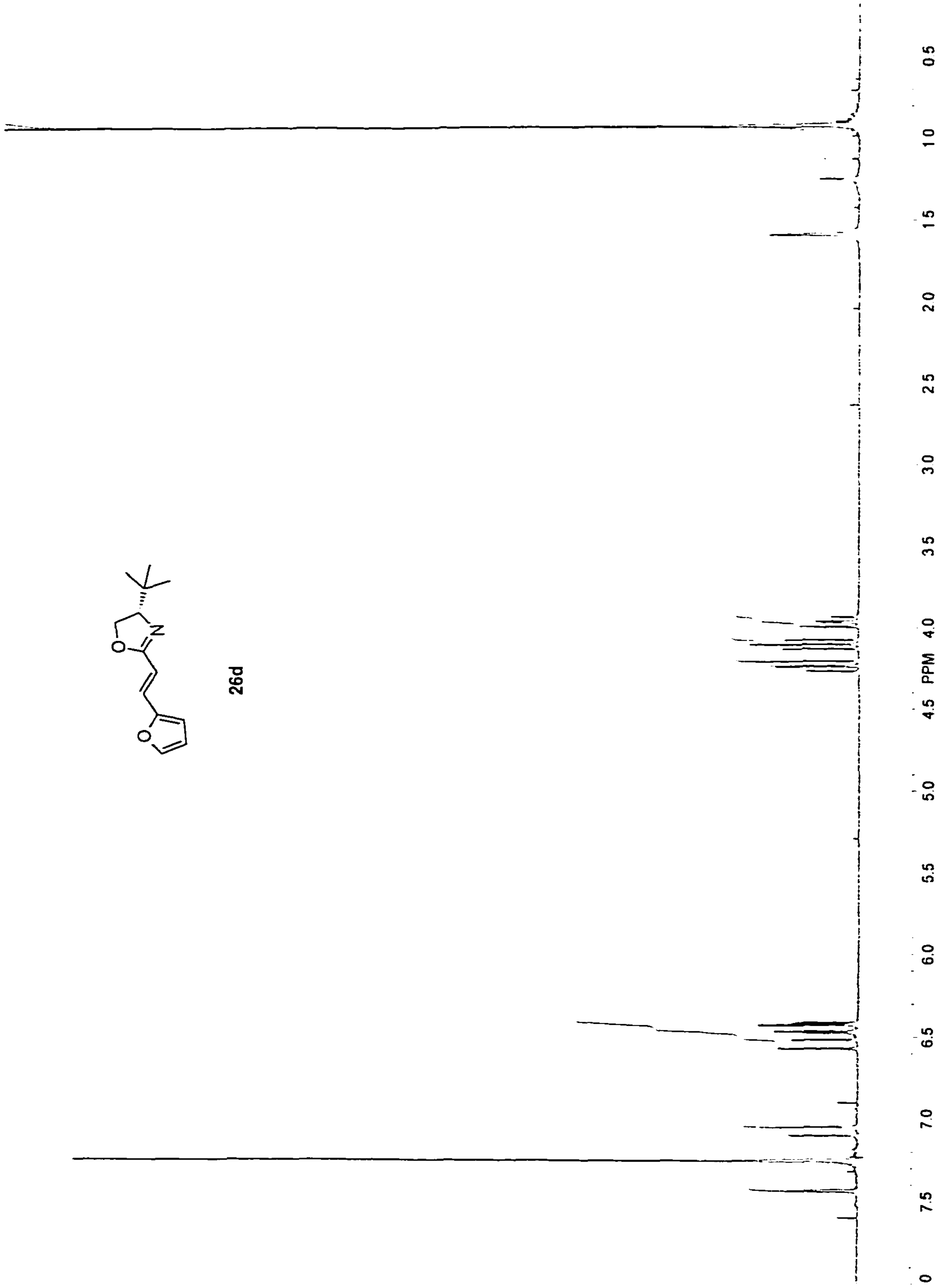

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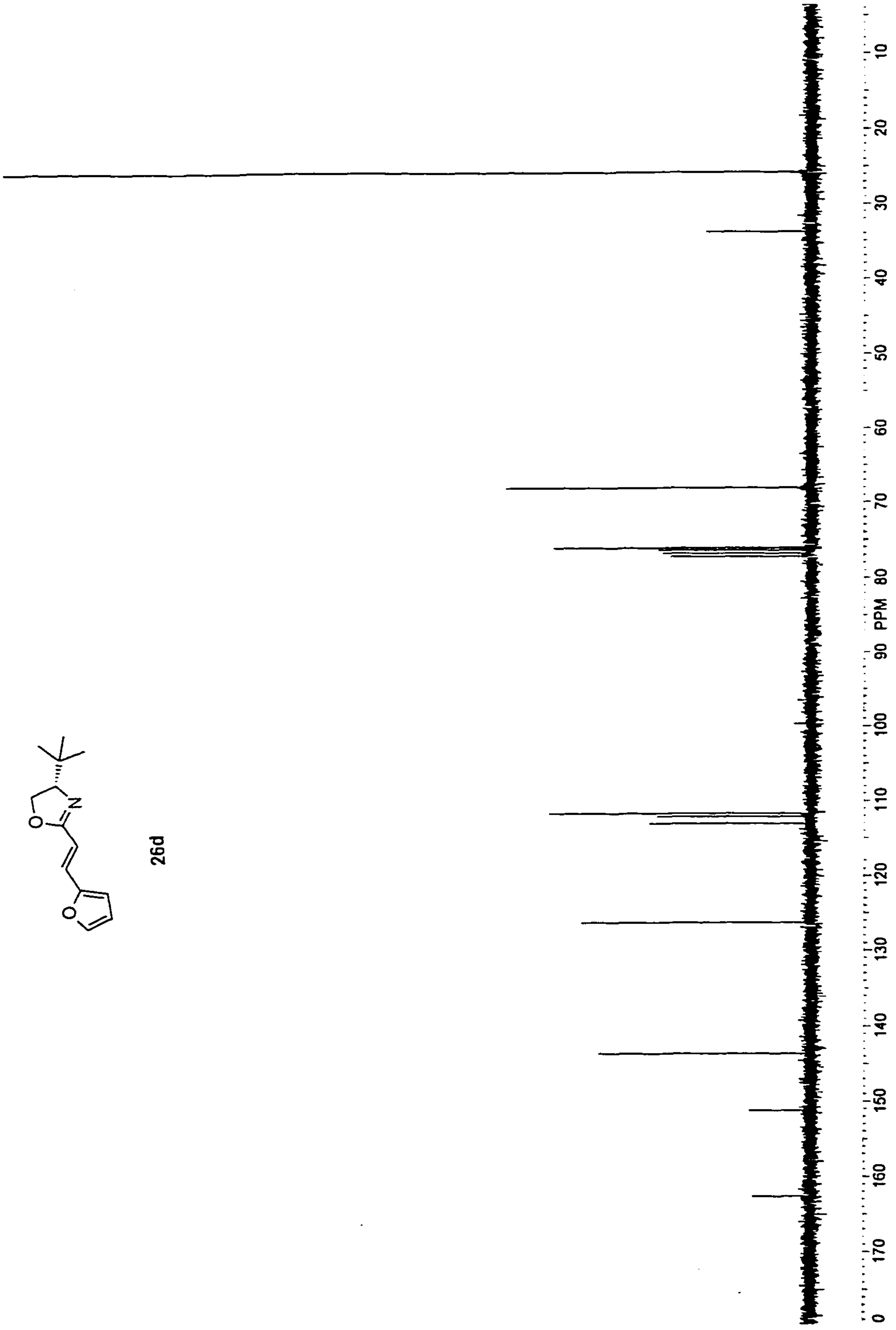

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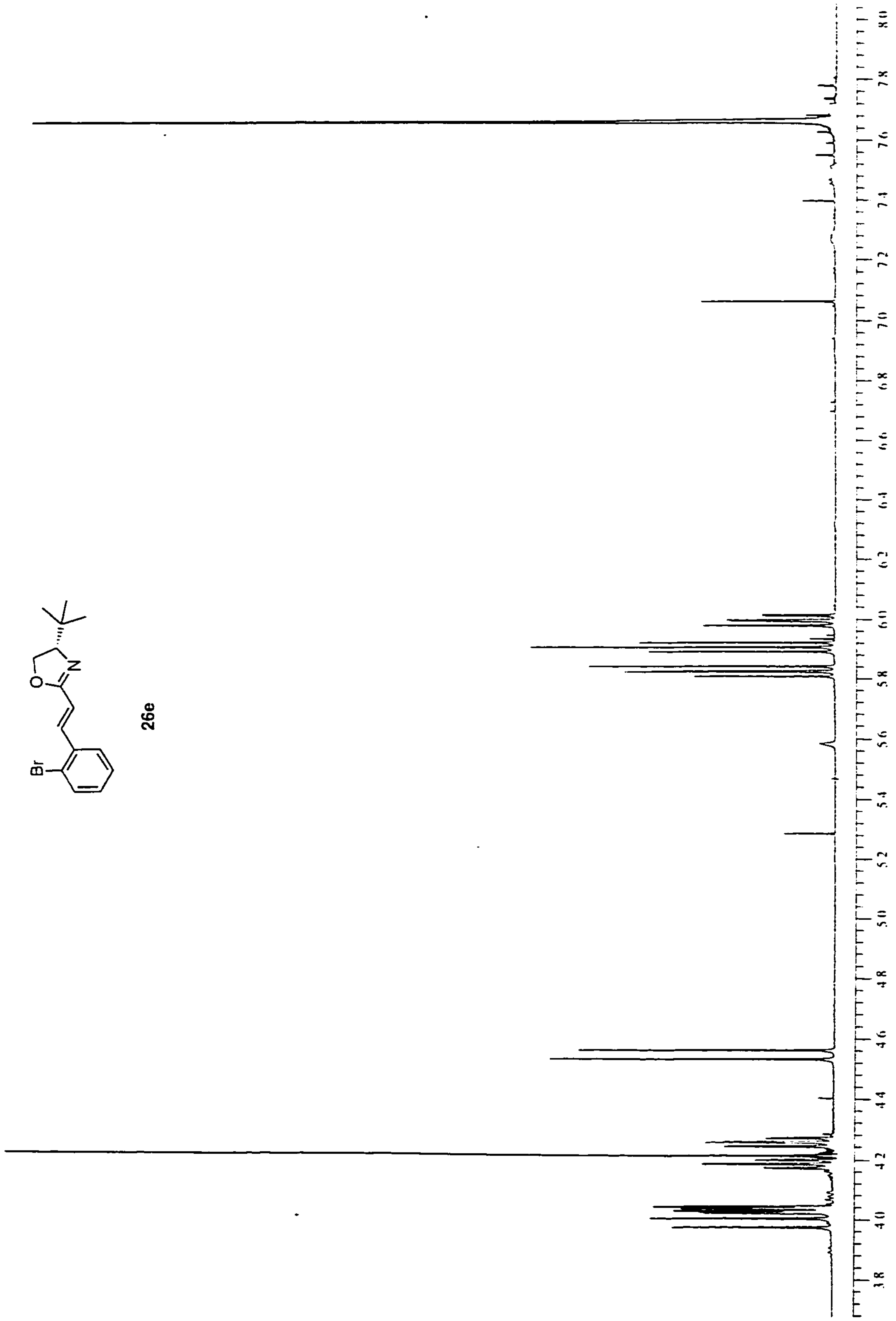

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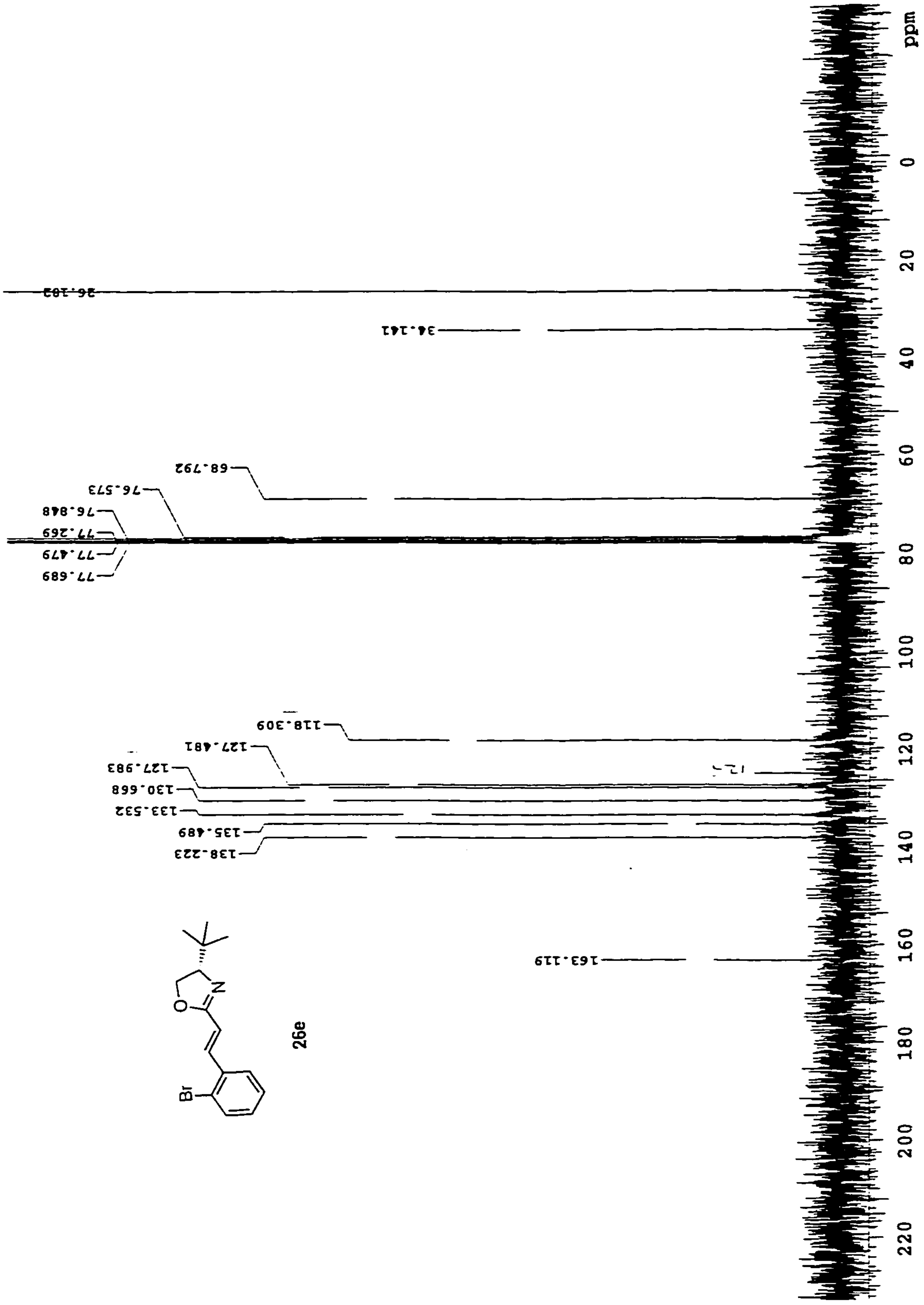
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68.792
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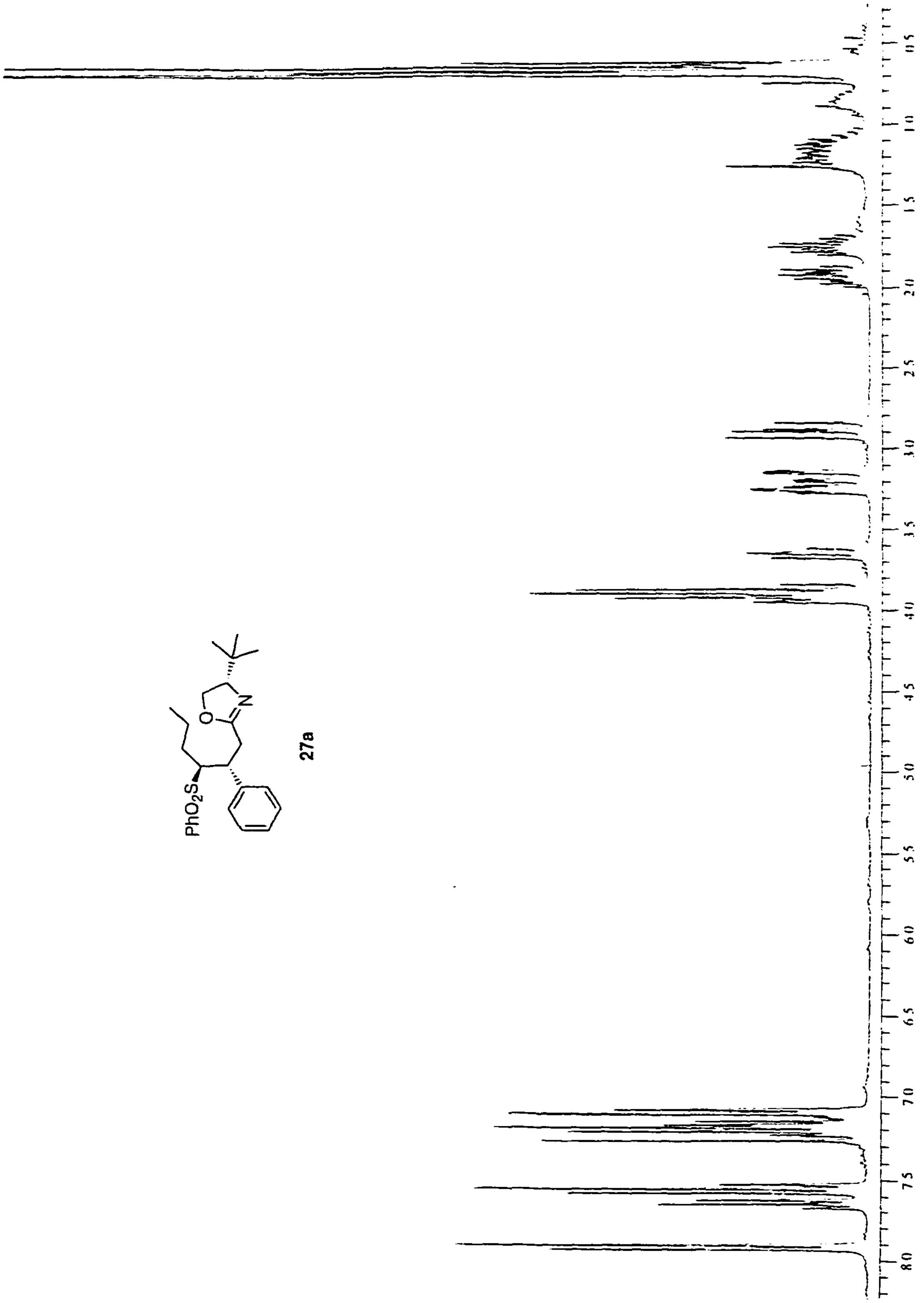
77.269
77.479
77.689
118.309
127.481
127.983
130.668
133.532
135.489
138.223
163.119
ppm
0
20
40
60
80
100
120
140
160
180
200
220
Br
O
N
26e



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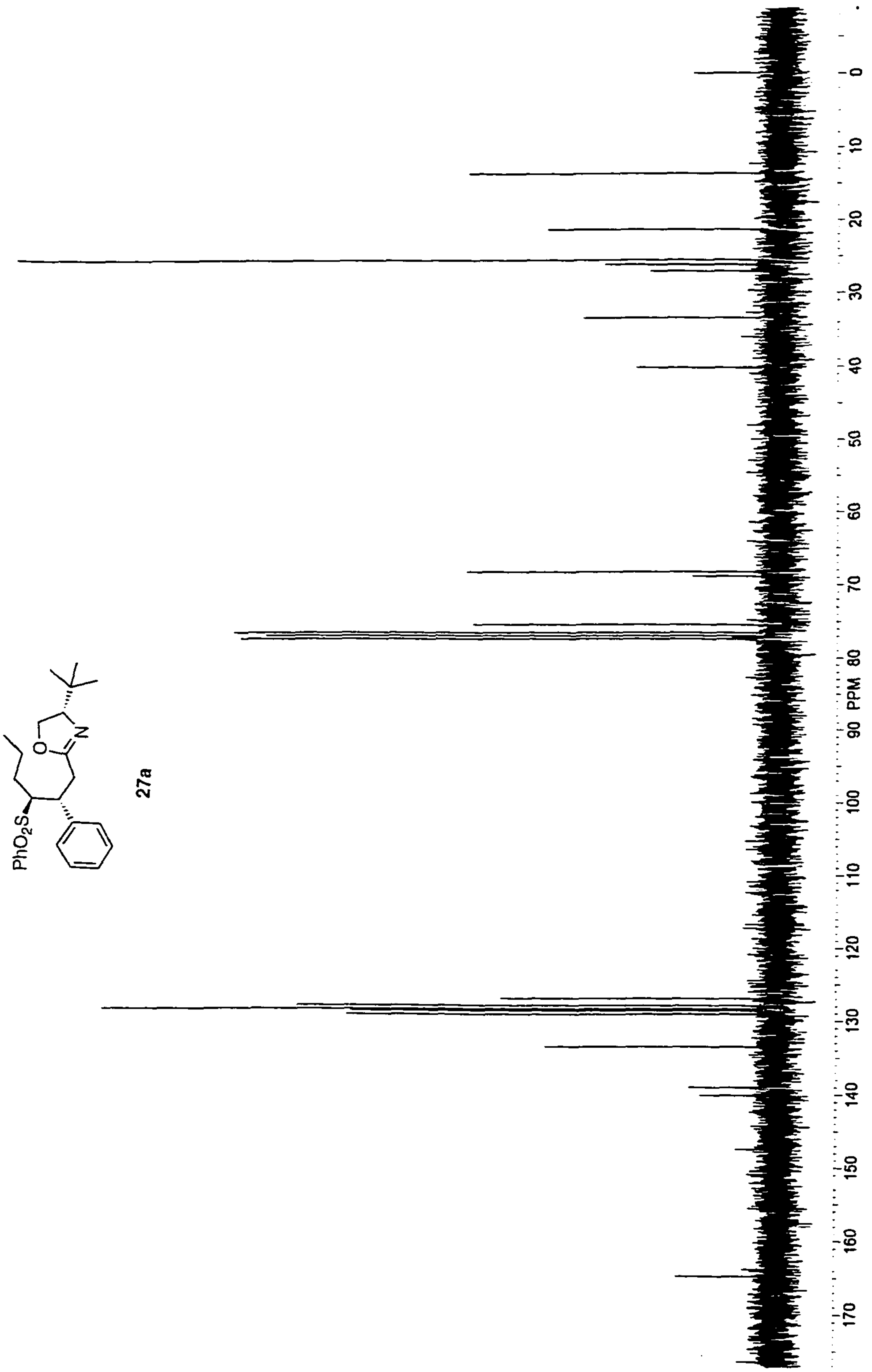
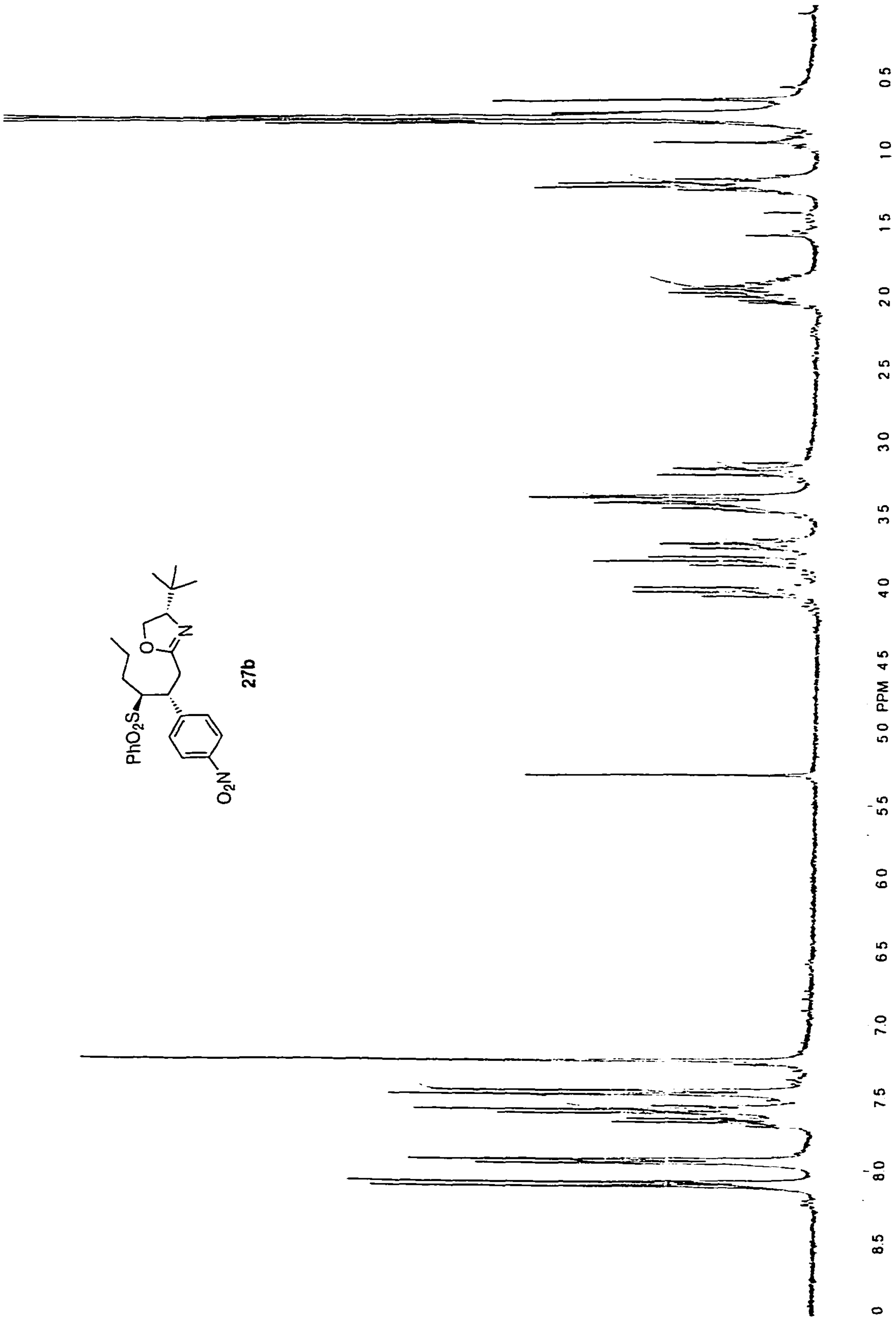


27a

PhO2S
O
N
0
10
20
30
40
50
60
70
80
90 PPM
100
110
120
130
140
150
160
170



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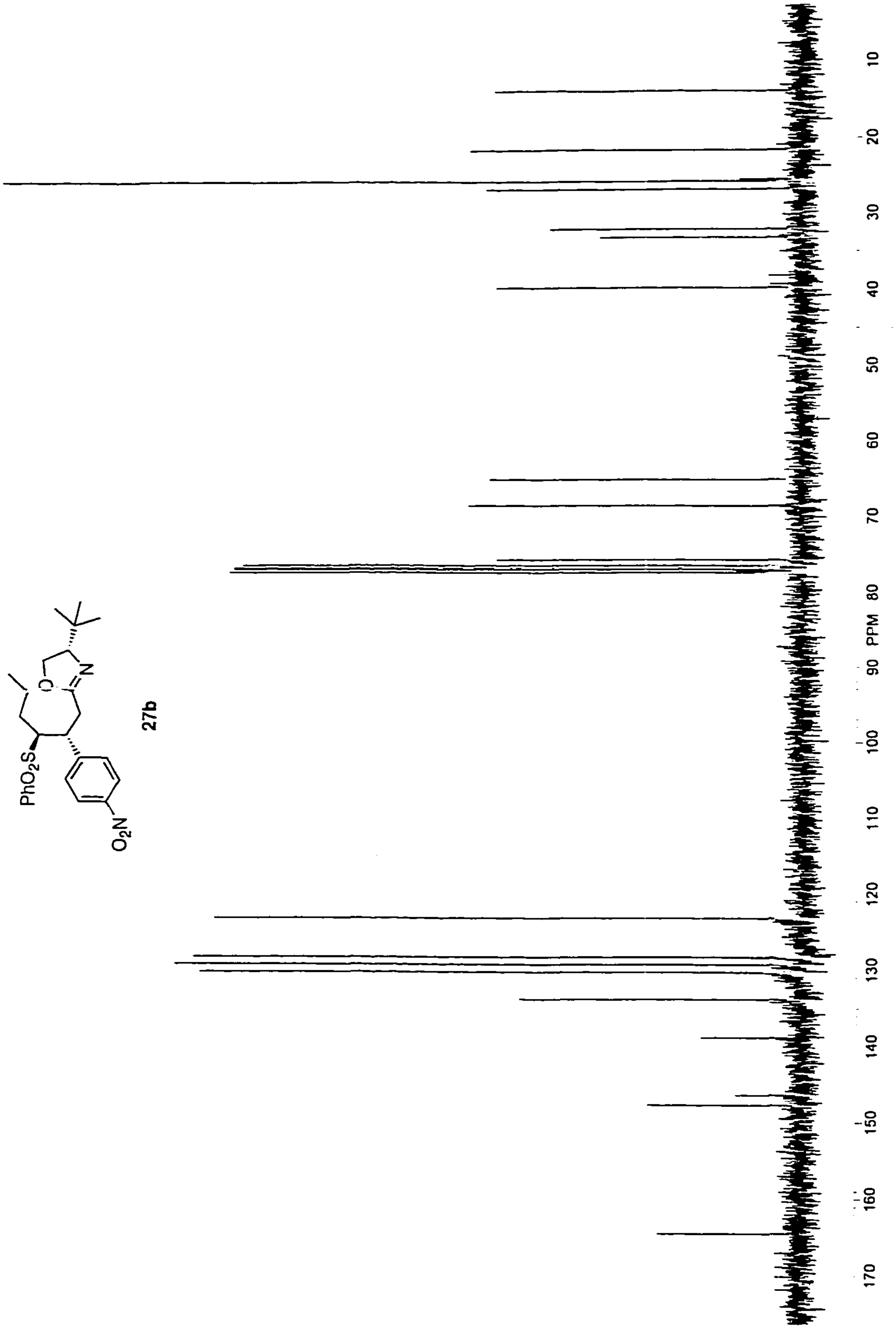
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O$_2$N
O
N
10
20
30
40
50
60
70
80
90 PPM
100
110
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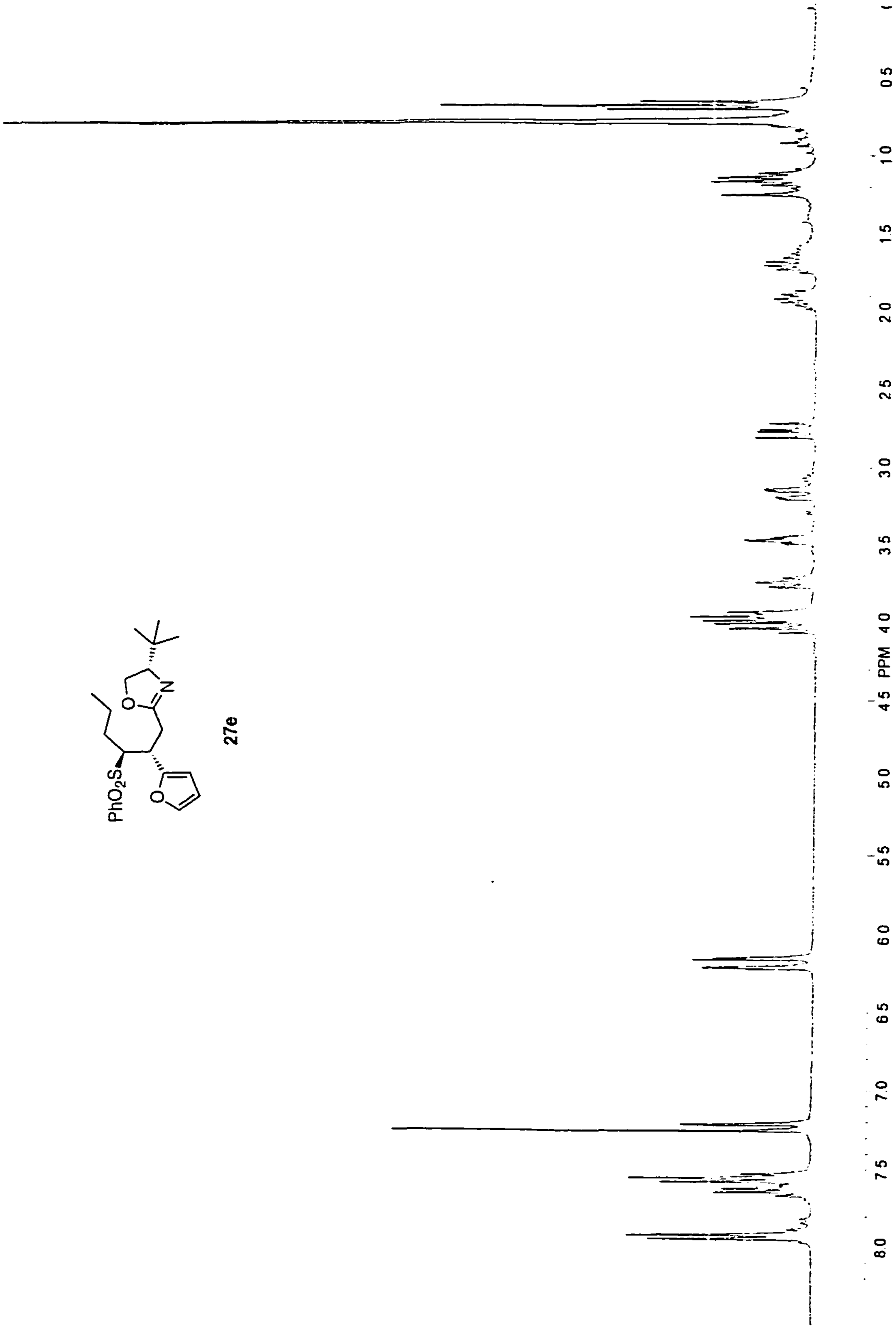
130
140
150
160
170

27b



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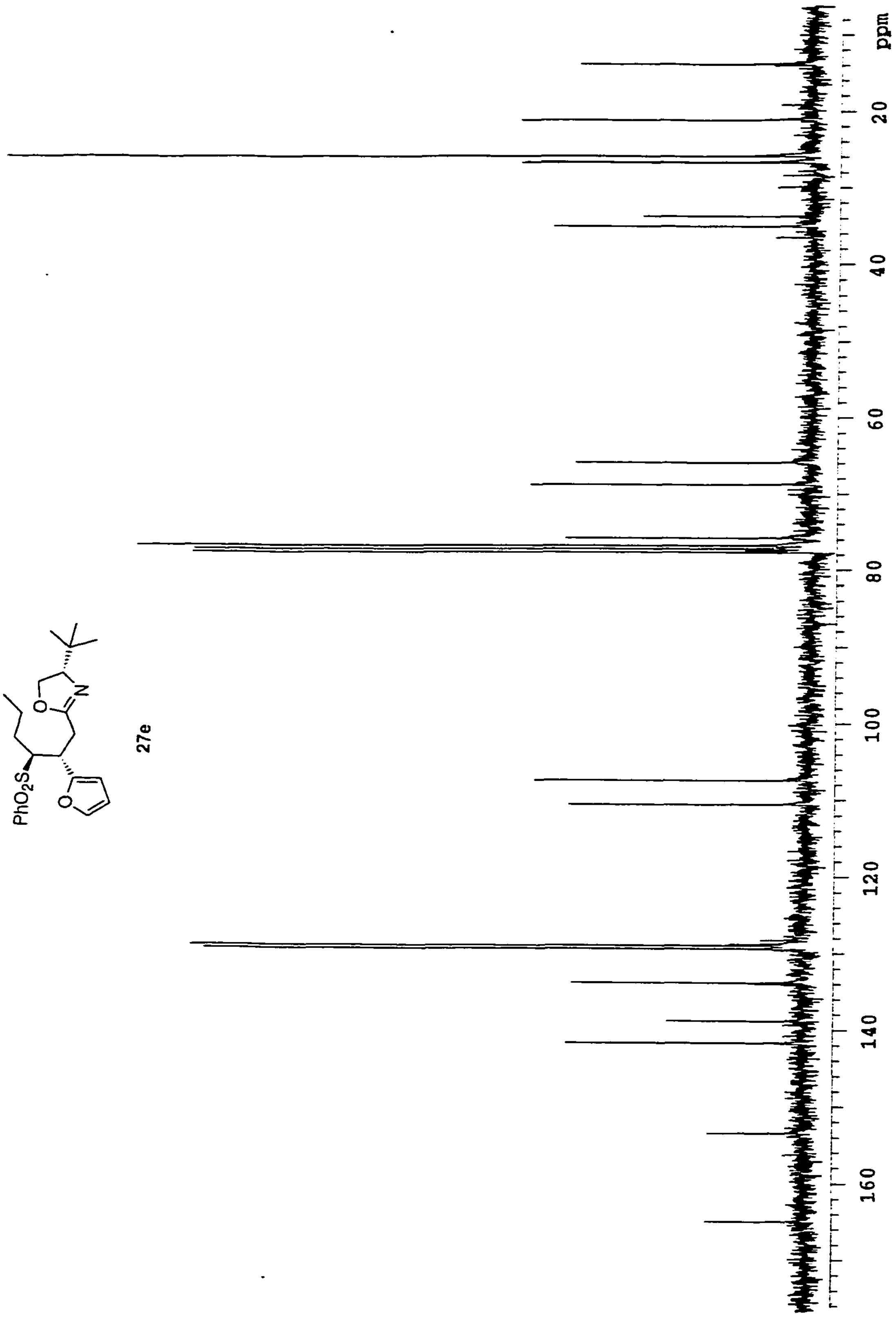

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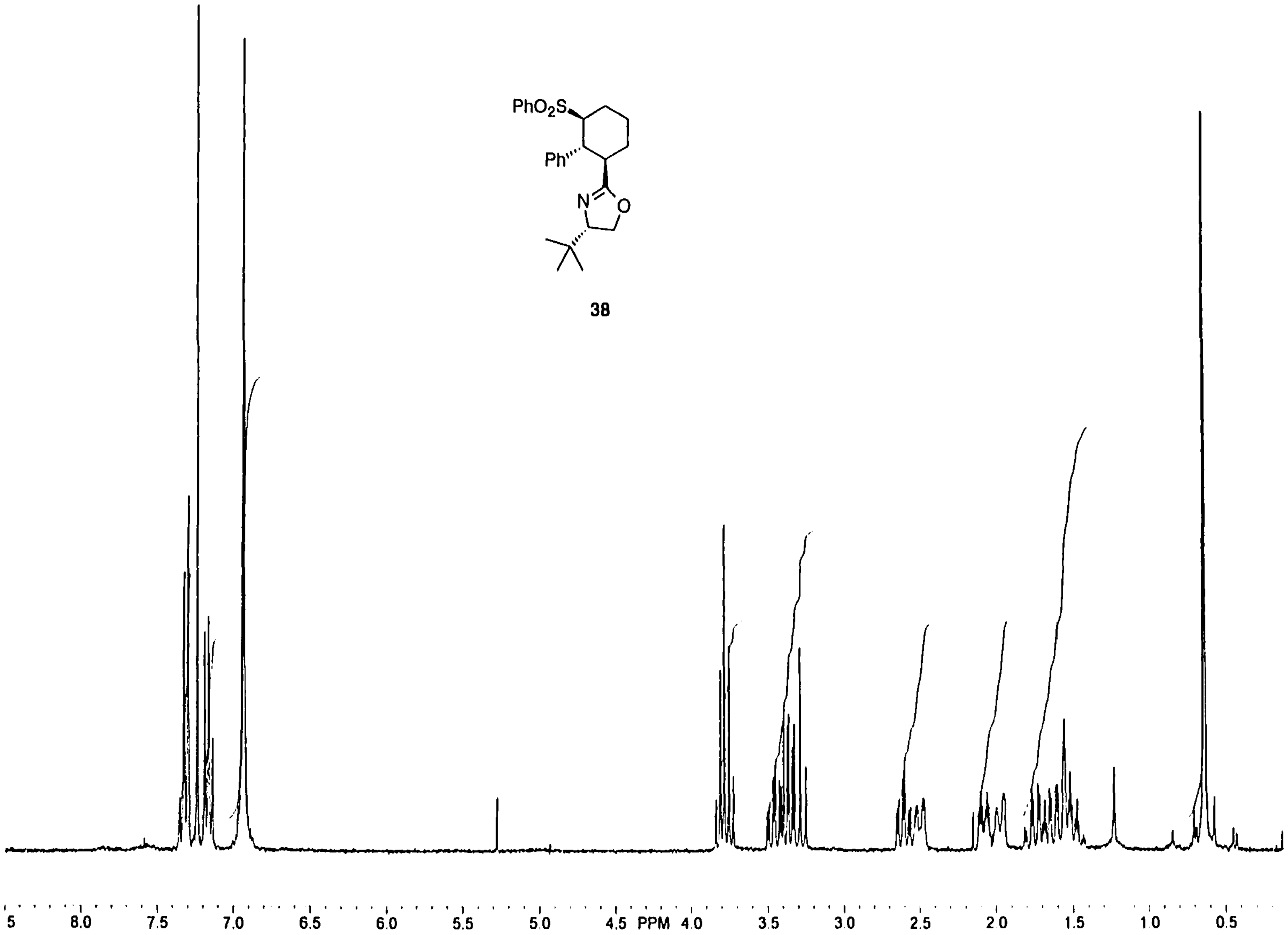


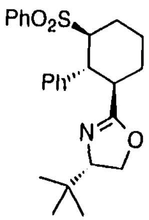
38

13C OBSERVE

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
File: 1bii191aC
INOVA-500 "chemenvy"

PULSE SEQUENCE
Relax. delay 1.300 sec
Pulse 45.0 degrees
Acq. time 0.639 sec
Width 25039.1 Hz
604 repetitions
OBSERVE C13, 100.6060486 MHz
DECOUPLE H1, 400.1057129 MHz
Power 45 dB
continuously on
WALTZ-16 modulated

DATA PROCESSING
Line broadening 2.0 Hz
FT size 32768
Total time 19 minutes



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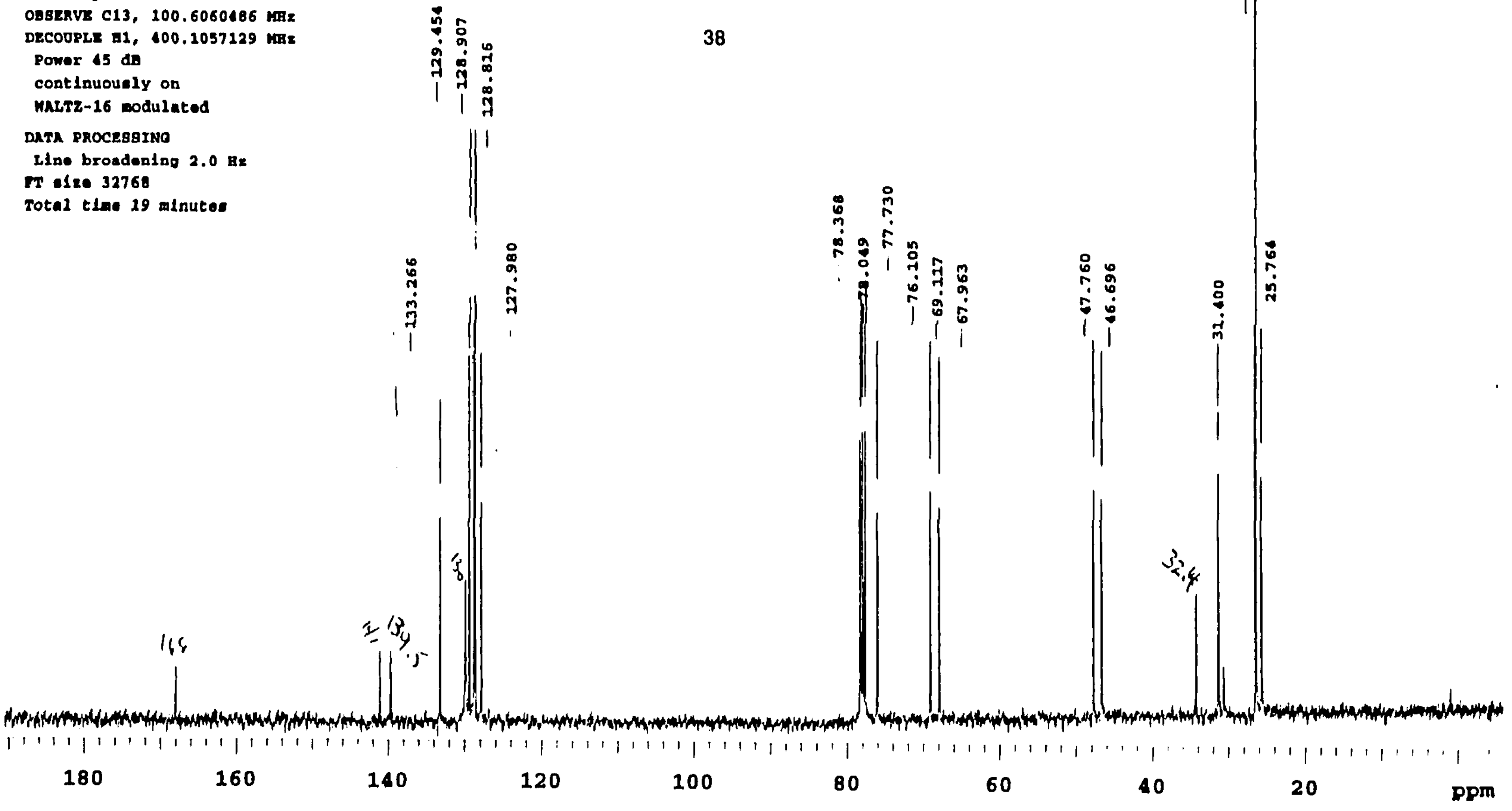

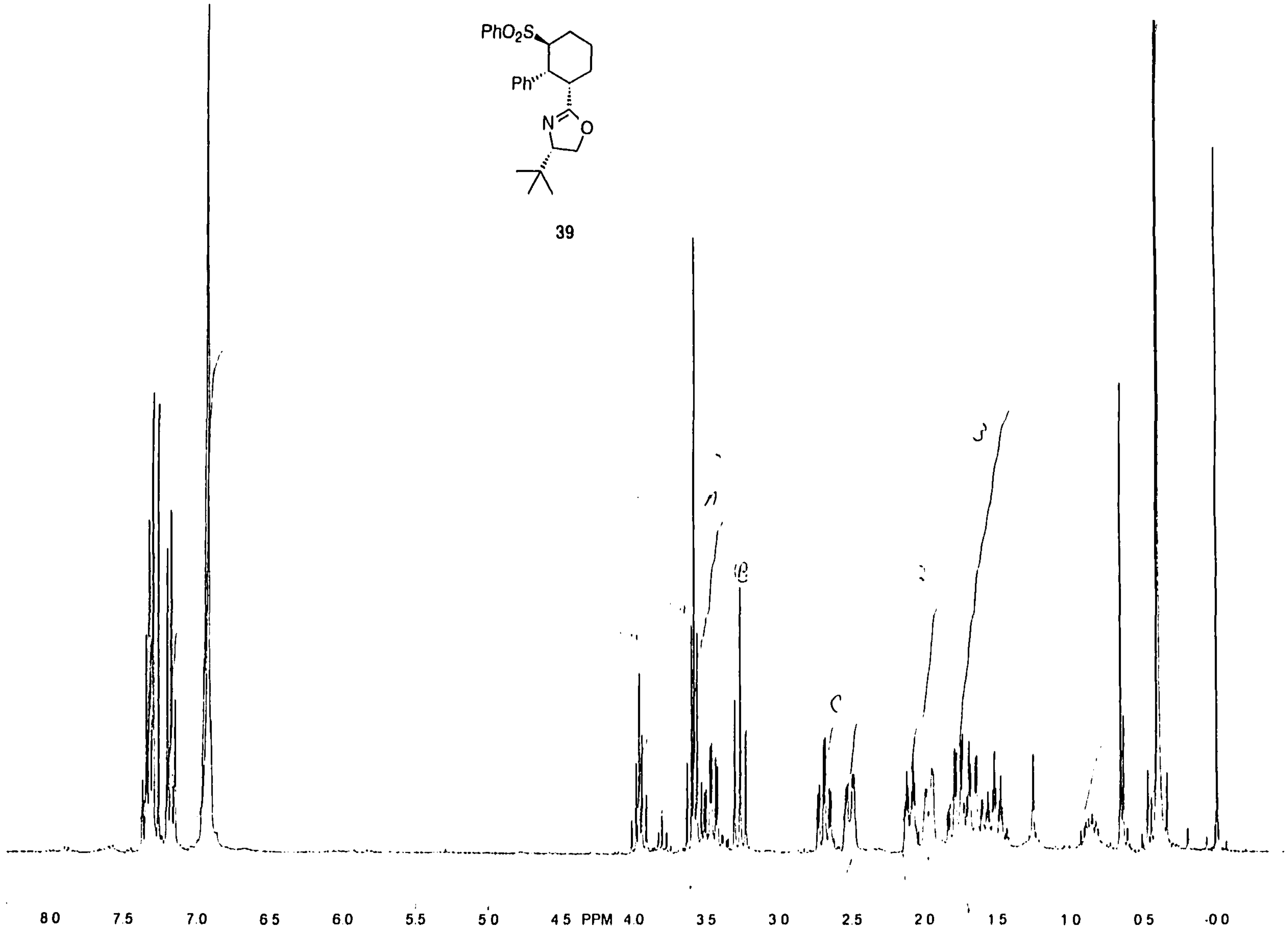

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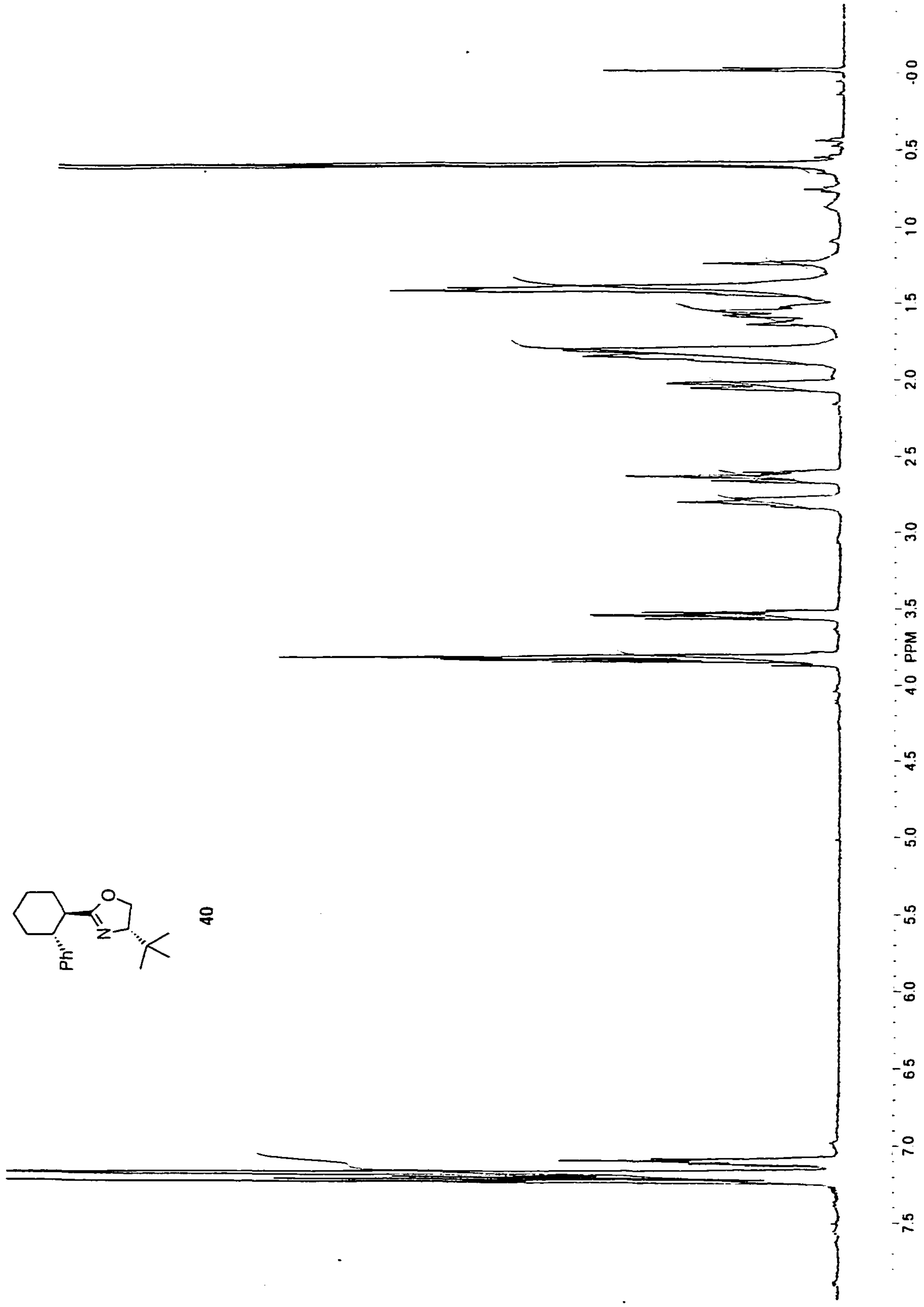

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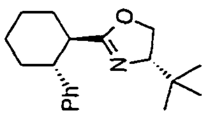

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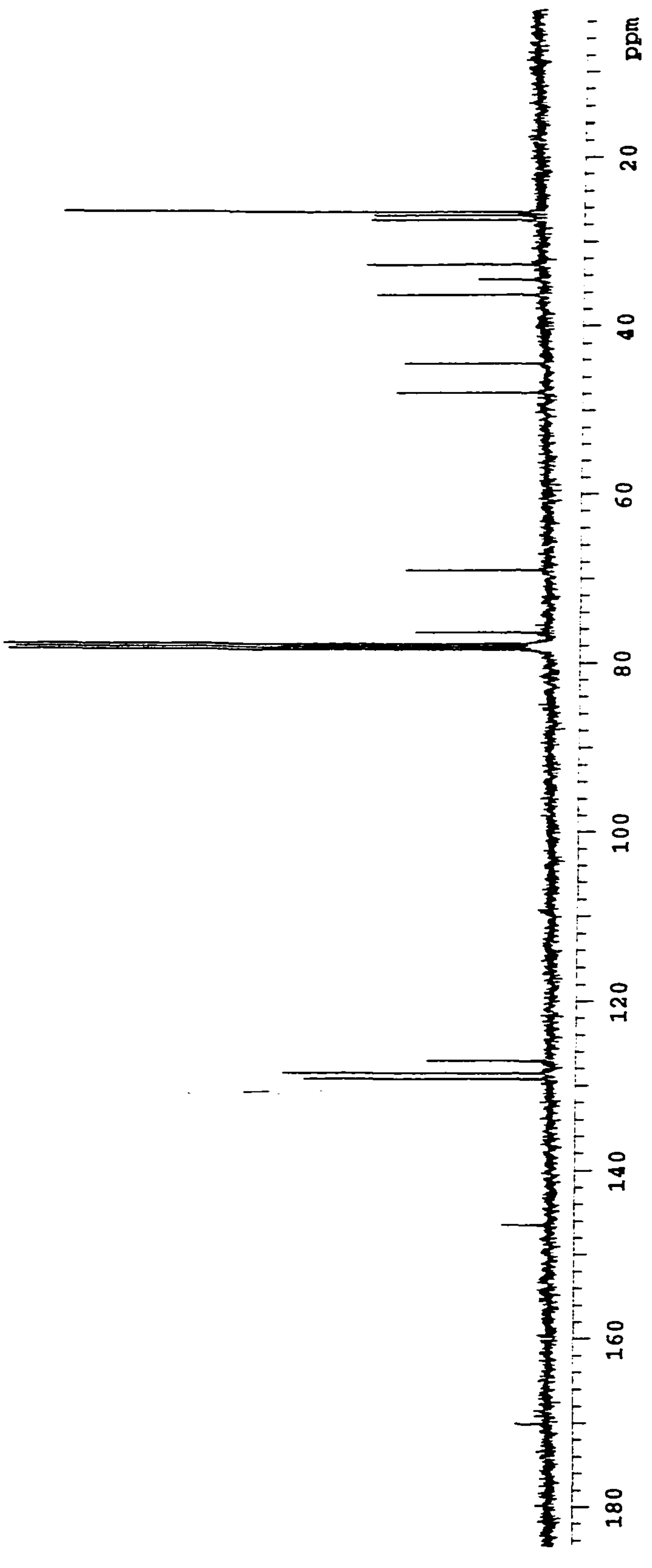

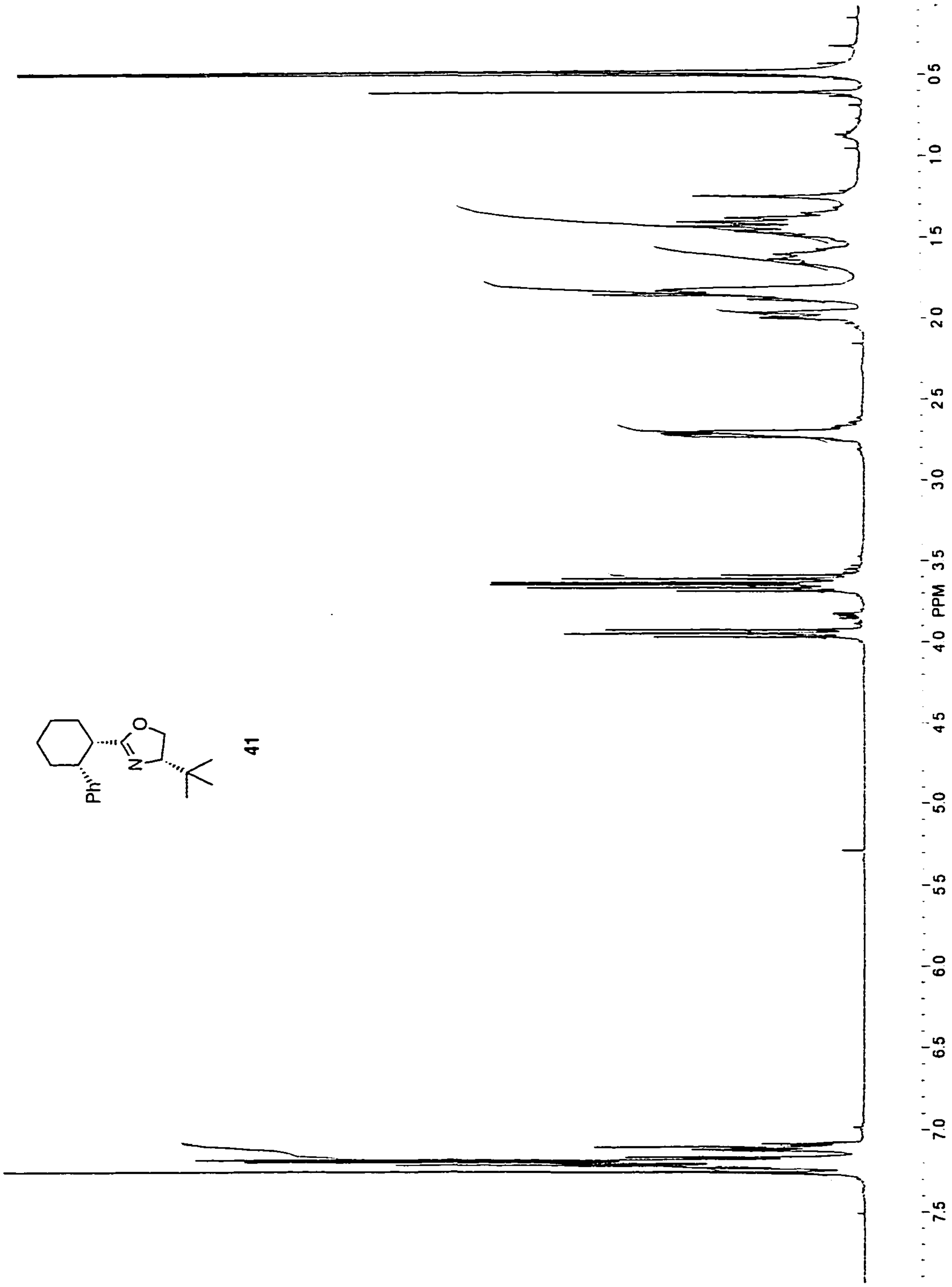
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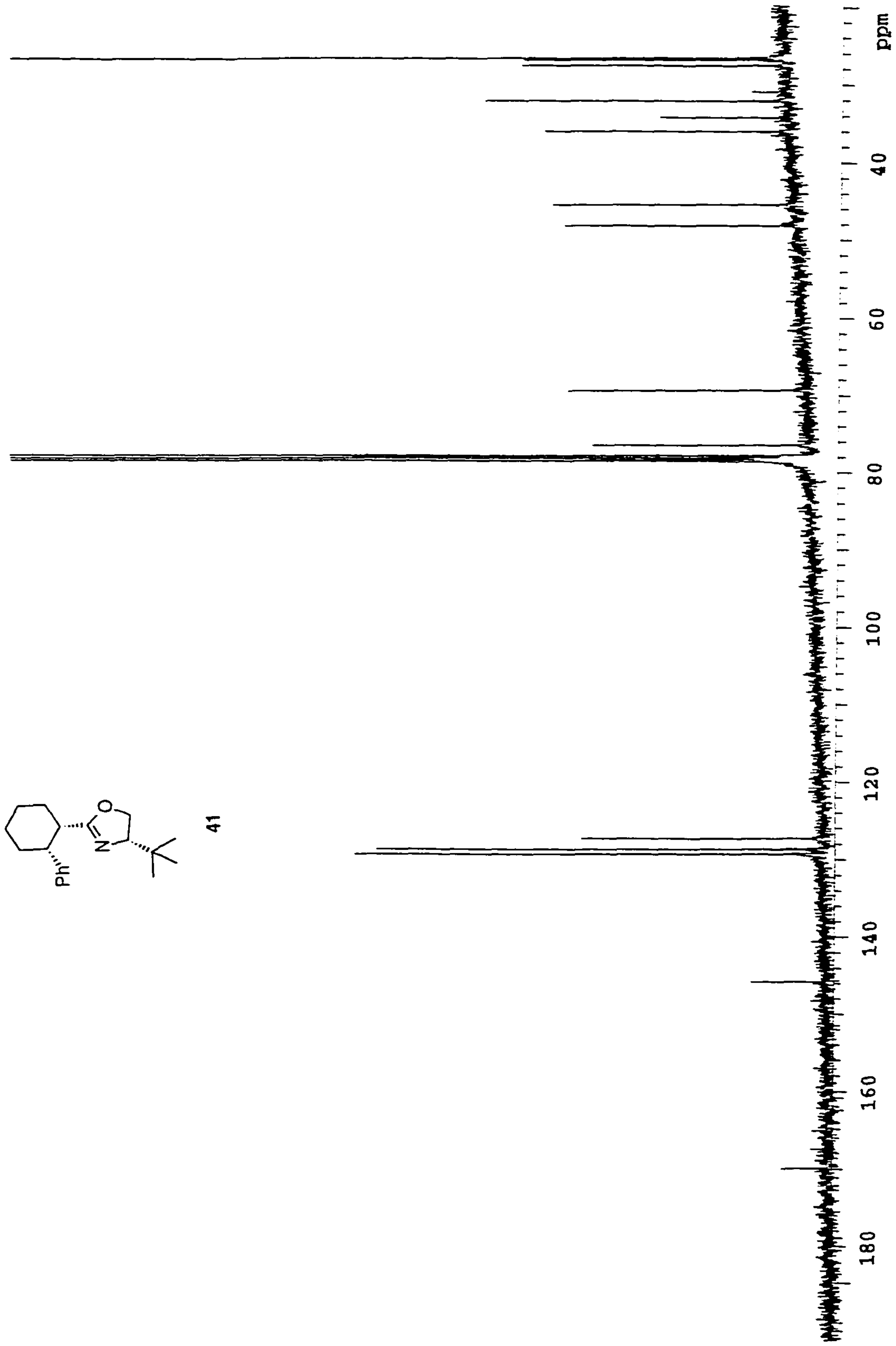
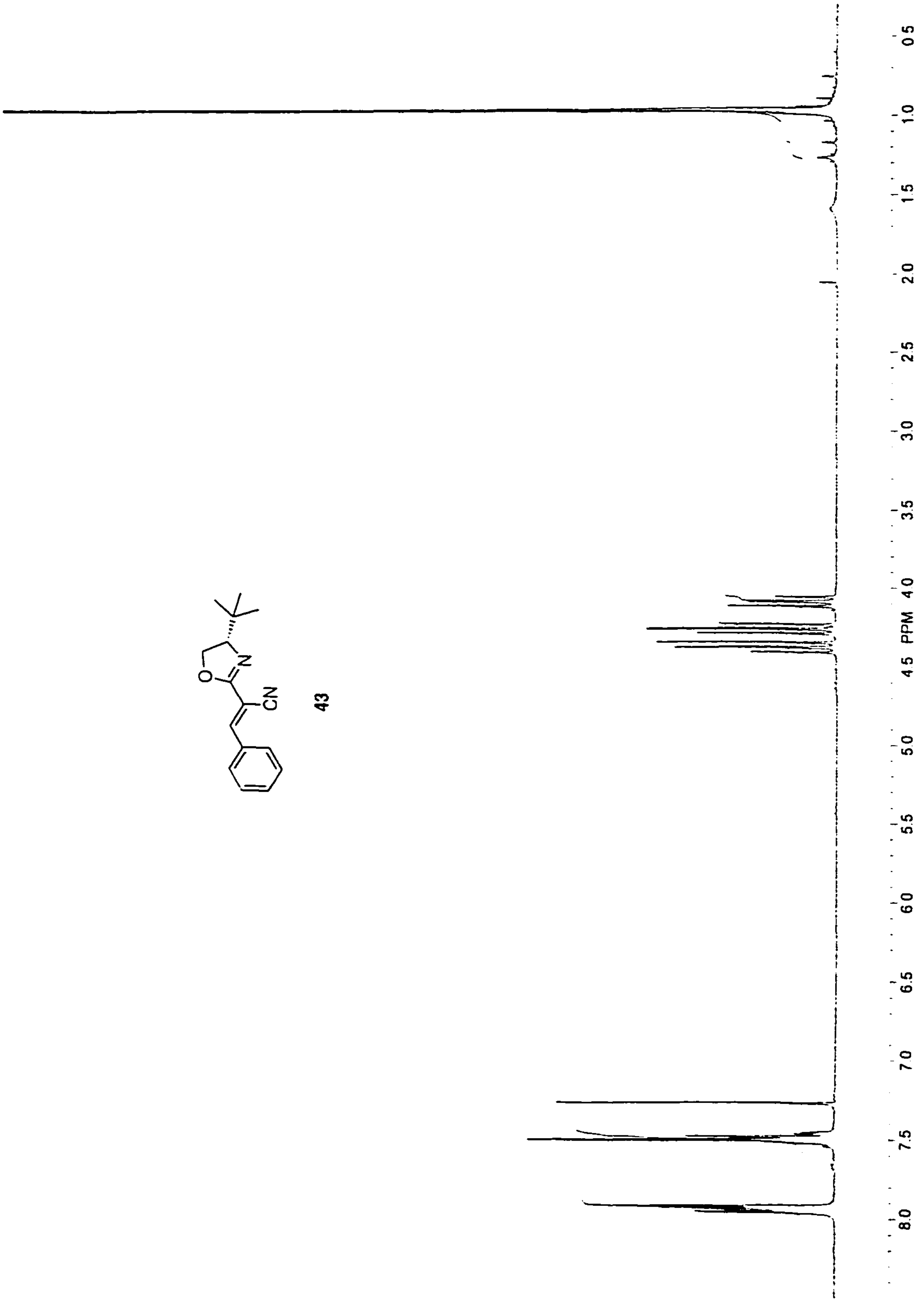

41
Ph
O
N
ppm
40
60
80
100
120
140
160
180



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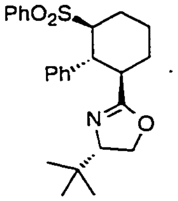
PhO2S
Ph
N
O

38

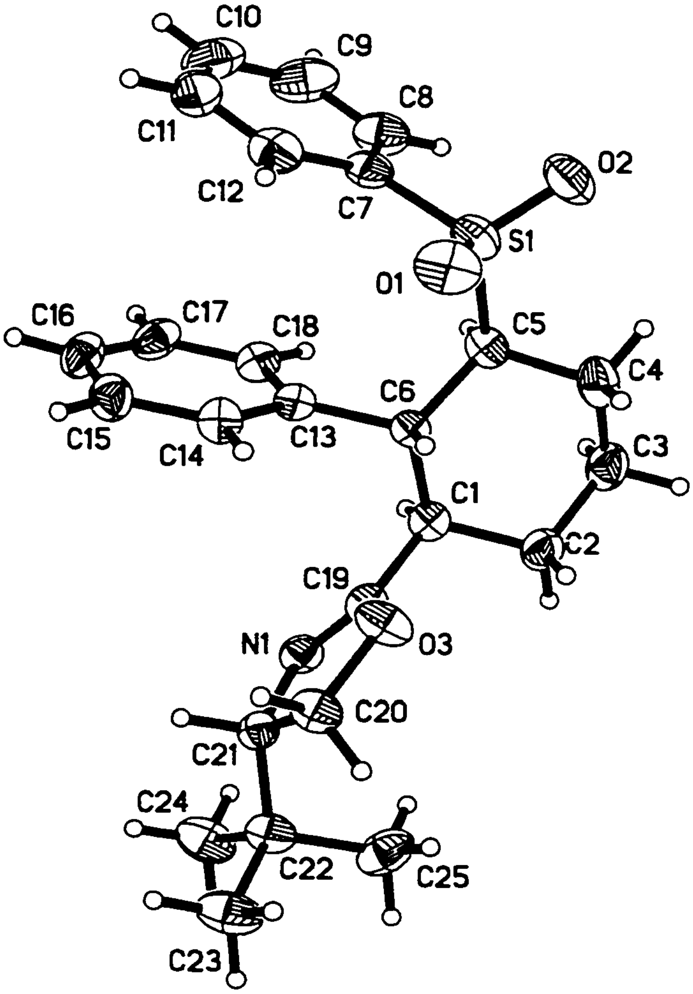
C10
C9
C8
C11
C12
C7
O2
S1
O1
C16
C17
C18
C5
C4
C6
C15
C14
C13
C3
C1
C2
C19
N1
O3
C20
C21
C24
C22
C25
C23

Table 1. Crystal data and structure refinement for 1.

Identification code	amccd15 (Meyers/Basil)
Empirical formula	$C_{25}H_{31}NO_3S$
Formula weight	425.57
Temperature	159(2) K
Wavelength	0.71073 Å
Crystal system	Trigonal
Space group	$P3_1$
Unit cell dimensions	*a* = 18.4097(2) Å alpha = 90° *b* = 18.4097(2) Å beta = 90° *c* = 5.78210(10) Å gamma = 120°
Volume, Z	1697.11(4) $Å^3$, 3
Density (calculated)	1.249 Mg/m^3
Absorption coefficient	0.169 mm^{-1}
F(000)	684
Crystal size	0.08 x 0.20 x 0.50 mm
θ range for data collection	1.28 to 28.27°
Limiting indices	$-23 \leq h \leq 23$, $-20 \leq k \leq 24$, $-7 \leq l \leq 7$
Reflections collected	11154
Independent reflections	4592 (R_{int} = 0.0480)
Absorption correction	SADABS
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4592 / 1 / 272
Goodness-of-fit on F^2	1.153
Final R indices [$I>2\sigma(I)$]	R1 = 0.0525, wR2 = 0.1111
R indices (all data)	R1 = 0.0854, wR2 = 0.1437
Absolute structure parameter	-0.01(10)
Extinction coefficient	0.014(3)
Largest diff. peak and hole	0.270 and -0.218 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 1. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
S(1)	3288(1)	3975(1)	2396(2)	35(1)
O(1)	2966(2)	3946(2)	92(4)	48(1)
O(2)	4162(2)	4552(2)	2842(5)	51(1)
O(3)	515(2)	4155(2)	1945(4)	38(1)
N(1)	-274(2)	3434(2)	5045(5)	29(1)
C(1)	1284(2)	4130(2)	5279(6)	28(1)
C(2)	1760(2)	5079(2)	5690(7)	38(1)
C(3)	2653(2)	5390(2)	6481(7)	41(1)
C(4)	3128(2)	5165(2)	4730(7)	41(1)
C(5)	2691(2)	4209(2)	4456(6)	30(1)
C(6)	1772(2)	3839(2)	3660(6)	26(1)
C(7)	3110(2)	2962(2)	3079(6)	32(1)
C(8)	3404(2)	2844(3)	5180(7)	43(1)
C(9)	3296(3)	2061(3)	5697(8)	53(1)
C(10)	2909(3)	1412(3)	4109(9)	58(1)
C(11)	2620(3)	1533(3)	2039(8)	52(1)
C(12)	2717(2)	2312(3)	1500(7)	41(1)
C(13)	1288(2)	2886(2)	3503(5)	26(1)
C(14)	823(2)	2488(2)	1535(6)	33(1)
C(15)	365(2)	1616(2)	1382(7)	38(1)
C(16)	376(2)	1131(2)	3194(7)	40(1)
C(17)	828(2)	1515(2)	5164(7)	37(1)
C(18)	1280(2)	2382(2)	5322(6)	31(1)
C(19)	444(2)	3868(2)	4158(6)	28(1)
C(20)	-338(2)	3872(2)	1193(6)	34(1)
C(21)	-886(2)	3372(2)	3260(6)	28(1)
C(22)	-1494(2)	3652(2)	4168(6)	34(1)
C(23)	-2054(2)	3625(3)	2175(7)	47(1)
C(24)	-2051(3)	3045(3)	6048(7)	47(1)
C(25)	-1003(3)	4544(3)	5147(7)	48(1)

Table 3. Bond lengths [Å] and angles [°] for 1.

S(1)-O(2)	1.441(3)	S(1)-O(1)	1.449(3)
S(1)-C(7)	1.769(4)	S(1)-C(5)	1.813(3)
O(3)-C(19)	1.366(4)	O(3)-C(20)	1.452(4)
N(1)-C(19)	1.263(4)	N(1)-C(21)	1.489(4)
C(1)-C(19)	1.515(4)	C(1)-C(2)	1.532(5)
C(1)-C(6)	1.566(5)	C(2)-C(3)	1.516(5)
C(3)-C(4)	1.523(5)	C(4)-C(5)	1.535(5)
C(5)-C(6)	1.545(4)	C(6)-C(13)	1.523(4)
C(7)-C(12)	1.386(5)	C(7)-C(8)	1.390(5)
C(8)-C(9)	1.386(6)	C(9)-C(10)	1.389(7)
C(10)-C(11)	1.372(7)	C(11)-C(12)	1.389(6)
C(13)-C(14)	1.392(5)	C(13)-C(18)	1.397(4)
C(14)-C(15)	1.394(5)	C(15)-C(16)	1.384(6)
C(16)-C(17)	1.379(5)	C(17)-C(18)	1.385(5)
C(20)-C(21)	1.538(5)	C(21)-C(22)	1.540(5)
C(22)-C(24)	1.528(5)	C(22)-C(23)	1.531(5)
C(22)-C(25)	1.533(5)		

O(2)-S(1)-O(1)	118.5(2)	O(2)-S(1)-C(7)	106.8(2)
O(1)-S(1)-C(7)	108.0(2)	O(2)-S(1)-C(5)	107.1(2)
O(1)-S(1)-C(5)	109.1(2)	C(7)-S(1)-C(5)	106.8(2)
C(19)-O(3)-C(20)	105.4(2)	C(19)-N(1)-C(21)	106.3(3)
C(19)-C(1)-C(2)	109.9(3)	C(19)-C(1)-C(6)	107.7(3)
C(2)-C(1)-C(6)	112.6(3)	C(3)-C(2)-C(1)	111.8(3)
C(4)-C(3)-C(2)	111.0(3)	C(3)-C(4)-C(5)	109.7(3)
C(4)-C(5)-C(6)	111.5(3)	C(4)-C(5)-S(1)	108.0(2)
C(6)-C(5)-S(1)	111.1(2)	C(13)-C(6)-C(5)	114.0(3)
C(13)-C(6)-C(1)	108.9(2)	C(5)-C(6)-C(1)	111.1(3)
C(12)-C(7)-C(8)	121.1(4)	C(12)-C(7)-S(1)	120.3(3)
C(8)-C(7)-S(1)	118.6(3)	C(9)-C(8)-C(7)	119.1(4)
C(8)-C(9)-C(10)	119.8(4)	C(11)-C(10)-C(9)	120.7(4)
C(10)-C(11)-C(12)	120.2(4)	C(7)-C(12)-C(11)	119.0(4)
C(14)-C(13)-C(18)	117.8(3)	C(14)-C(13)-C(6)	120.4(3)
C(18)-C(13)-C(6)	121.8(3)	C(13)-C(14)-C(15)	121.2(3)
C(16)-C(15)-C(14)	119.9(4)	C(17)-C(16)-C(15)	119.6(3)
C(16)-C(17)-C(18)	120.4(3)	C(17)-C(18)-C(13)	121.1(3)
N(1)-C(19)-O(3)	119.5(3)	N(1)-C(19)-C(1)	127.4(3)
O(3)-C(19)-C(1)	113.1(3)	O(3)-C(20)-C(21)	104.5(2)
N(1)-C(21)-C(22)	112.7(3)	N(1)-C(21)-C(20)	104.4(3)
C(22)-C(21)-C(20)	115.7(3)	C(24)-C(22)-C(23)	108.5(3)
C(24)-C(22)-C(25)	109.9(3)	C(23)-C(22)-C(25)	109.8(3)
C(24)-C(22)-C(21)	109.4(3)	C(23)-C(22)-C(21)	108.9(3)
C(25)-C(22)-C(21)	110.3(3)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [Å^2 x 10^3] for 1.
The anisotropic displacement factor exponent takes the form:
$-2\pi^2$ [$(ha^*)^2U_{11}$ + ... + $2hka^*b^*U_{12}$]

	U11	U22	U33	U23	U13	U12
S(1)	30(1)	43(1)	29(1)	4(1)	3(1)	15(1)
O(1)	55(2)	69(2)	25(1)	8(1)	4(1)	36(2)
O(2)	29(1)	54(2)	62(2)	0(1)	5(1)	13(1)
O(3)	31(1)	57(2)	25(1)	12(1)	0(1)	22(1)
N(1)	33(2)	30(2)	26(2)	1(1)	-2(1)	17(1)
C(1)	32(2)	30(2)	22(2)	1(1)	-2(1)	16(2)
C(2)	42(2)	33(2)	40(2)	-1(2)	-7(2)	21(2)
C(3)	45(2)	32(2)	43(2)	-9(2)	-14(2)	17(2)
C(4)	36(2)	34(2)	41(2)	-3(2)	-8(2)	8(2)
C(5)	28(2)	35(2)	23(2)	-1(1)	-2(1)	14(2)
C(6)	27(2)	29(2)	21(2)	3(1)	-3(1)	14(1)
C(7)	27(2)	41(2)	29(2)	-1(2)	3(1)	20(2)
C(8)	41(2)	59(3)	34(2)	-3(2)	-5(2)	30(2)
C(9)	66(3)	72(3)	42(3)	10(2)	6(2)	51(3)
C(10)	63(3)	59(3)	68(3)	12(2)	24(3)	43(3)
C(11)	40(2)	47(3)	66(3)	-15(2)	9(2)	20(2)
C(12)	36(2)	54(2)	32(2)	-8(2)	2(2)	22(2)
C(13)	25(2)	28(2)	23(2)	2(1)	2(1)	13(1)
C(14)	36(2)	33(2)	27(2)	1(2)	1(1)	15(2)
C(15)	36(2)	36(2)	37(2)	-10(2)	1(2)	13(2)
C(16)	44(2)	29(2)	46(2)	0(2)	14(2)	16(2)
C(17)	45(2)	31(2)	40(2)	10(2)	13(2)	23(2)
C(18)	34(2)	36(2)	26(2)	0(1)	2(1)	19(2)
C(19)	36(2)	28(2)	22(2)	0(1)	-1(1)	18(2)
C(20)	32(2)	45(2)	24(2)	-1(2)	-6(1)	20(2)
C(21)	31(2)	28(2)	25(2)	-4(1)	-4(1)	15(2)
C(22)	37(2)	47(2)	23(2)	-3(2)	-3(1)	26(2)
C(23)	45(2)	78(3)	30(2)	-6(2)	-4(2)	41(2)
C(24)	38(2)	70(3)	36(2)	3(2)	3(2)	28(2)
C(25)	71(3)	52(2)	39(2)	-9(2)	-6(2)	44(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

	x	y	z	U(eq)
H(1C)	1185(2)	3838(2)	6802(6)	34
H(2B)	1769(2)	5370(2)	4240(7)	45
H(2C)	1463(2)	5220(2)	6877(7)	45
H(3A)	2946(2)	6006(2)	6682(7)	49
H(3B)	2646(2)	5135(2)	7995(7)	49
H(4A)	3712(2)	5384(2)	5261(7)	49
H(4B)	3145(2)	5427(2)	3220(7)	49
H(5A)	2696(2)	3956(2)	5982(6)	36
H(6A)	1782(2)	4064(2)	2078(6)	31
H(8A)	3674(2)	3294(3)	6247(7)	51
H(9A)	3487(3)	1969(3)	7134(8)	64
H(10A)	2843(3)	878(3)	4458(9)	70
H(11A)	2354(3)	1083(3)	971(8)	63
H(12A)	2516(2)	2398(3)	71(7)	49
H(14A)	818(2)	2816(2)	275(6)	39
H(15A)	44(2)	1355(2)	34(7)	46
H(16A)	74(2)	536(2)	3082(7)	48
H(17A)	829(2)	1184(2)	6421(7)	45
H(18A)	1588(2)	2638(2)	6689(6)	38
H(20A)	-478(2)	3512(2)	-196(6)	40
H(20B)	-415(2)	4355(2)	833(6)	40
H(21A)	-1225(2)	2771(2)	2781(6)	33
H(23A)	-1706(2)	4011(3)	952(7)	70
H(23B)	-2450(2)	3793(3)	2742(7)	70
H(23C)	-2366(2)	3054(3)	1554(7)	70
H(24A)	-1701(3)	3056(3)	7340(7)	71
H(24B)	-2360(3)	2476(3)	5411(7)	71
H(24C)	-2449(3)	3214(3)	6596(7)	71
H(25A)	-647(3)	4929(3)	3933(7)	73
H(25B)	-652(3)	4556(3)	6436(7)	73
H(25C)	-1397(3)	4717(3)	5698(7)	73