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TOTAL SYNTHESIS OF PROSTAGLANDINS VIA SEQUENTIAL CYANOCUPRATE ADDITIONS

by

Roberto Fernández de la Pradilla Sainz de Aja

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Chemistry)
in The University of Michigan
1985

Doctoral Committee:

Professor Joseph P. Marino, Chairman
Professor Arthur J. Ashe III
Professor M. David Curtis
Professor John R. Wiseman
Assistant Professor Ronald W. Woodard

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A Jesús y Flora,

sin vosotros no hubiera podido.

A Vicki,

por tu paciencia y cariño a lo largo
de unos tiempos muy difíciles.

ACKNOWLEDGMENTS

I wish to express my gratitude to several people whose help has made this effort possible and more meaningful.

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To my parents, family and friends in Spain, for their love and encouragement; they showed that for some special people time and distance are merely words.

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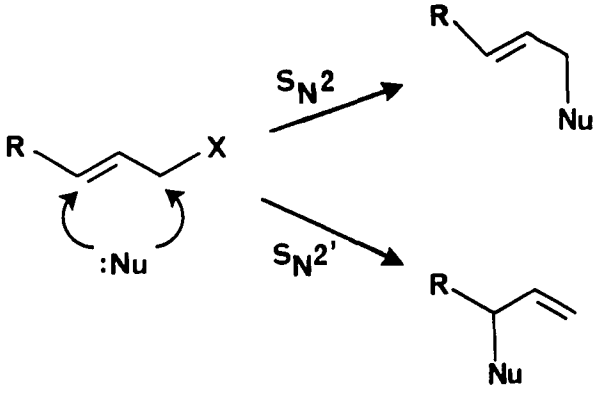
INTRODUCTION

For the past two decades organocopper chemistry has assumed an increasingly prominent role in organic synthesis.[1] A pivotal point for organocopper reagents came in their utilization in numerous syntheses of prostaglandins. The research described in this thesis represents a new chapter in the unique regioselectivity of organocopper reagents that allows for new synthetic approaches to the prostaglandins.

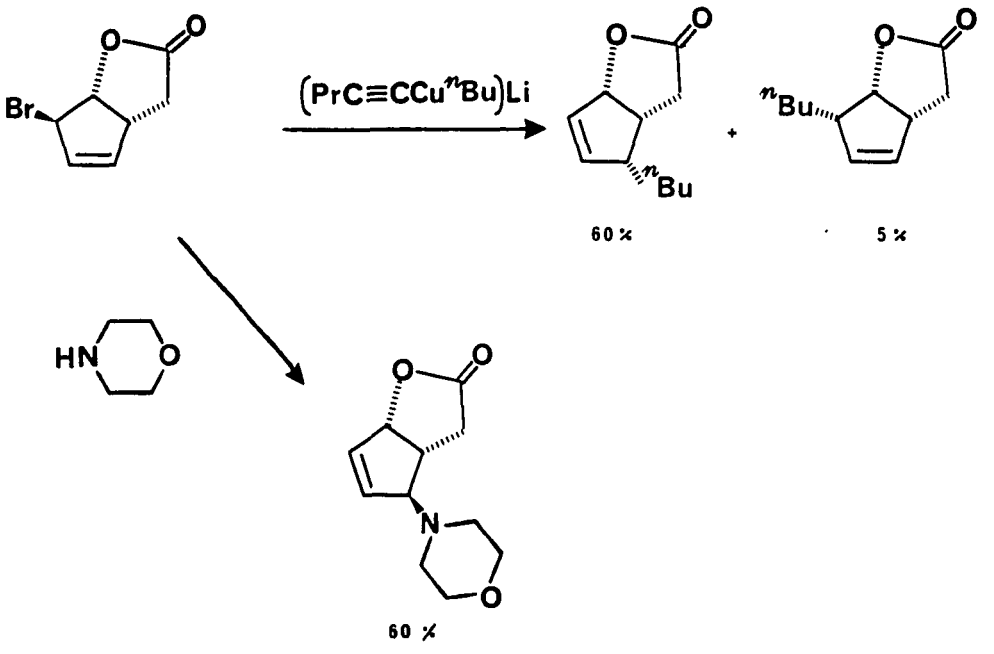
Since the central functional group in our synthetic approach to prostaglandins is an allylic epoxide, it would be appropriate to survey the recent literature on the reactions of nucleophiles with allylic electrophiles.

Allylic substrates are ambident electrophiles and their reaction with nucleophiles may take place by either S_N2 or S_N2' pathways. S_N2 displacements normally proceed

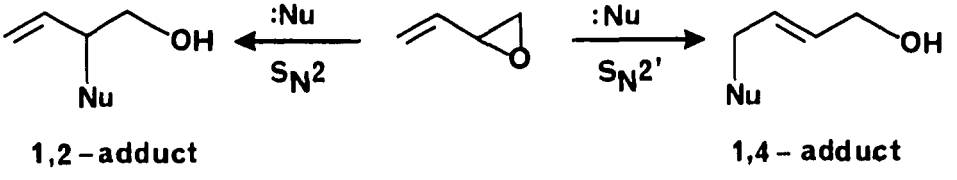


with inversion. S_N2' reactions may occur in an anti or syn fashion, depending upon the steric requirements of the substrate, the nature of the nucleophile, etc.

Roberts et al.:[2]



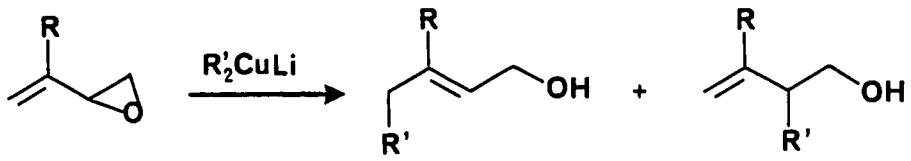
Allylic epoxides are especially interesting substrates since their reaction with nucleophiles yields highly functionalized products which may possess two chiral centers.



It has been known for quite some time that dialkylcuprates and acyclic allylic epoxides react in a highly

regioselective manner to yield the corresponding 1,4-adducts.[3] Cyclic allylic epoxides, however, lack such desirable regioselectivity. Indeed, mixtures of 1,2- and 1,4-adducts arise from the reaction of dialkylcuprates with cyclic allylic epoxides,[4] and this greatly diminishes the synthetic usefulness of the reaction.

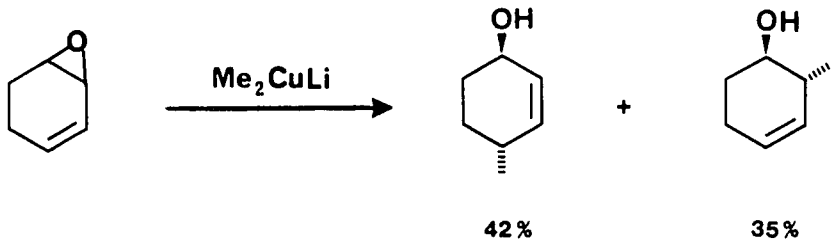
Anderson:[5]



A B

	A	B
R=H, R'=n-Bu	93	4
R=H, R'=Ph	85	15
R=Me, R'=Me	92	8

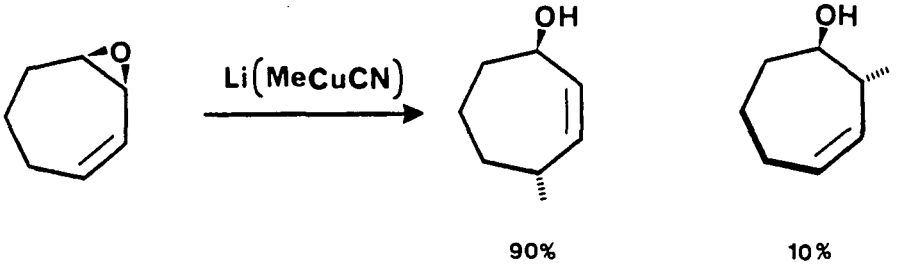
Rickborn et al.:[6]

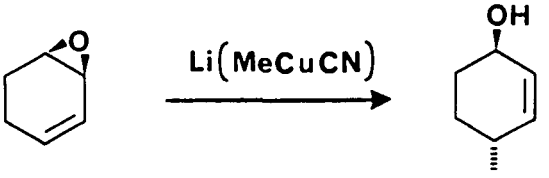


42% 35%

In 1979, Marino and Floyd discovered the high degree of regio- and stereoselectivity of the reaction of cuprates possessing an electron withdrawing ligand, such as cyano or acrylate, with cyclic 1,3-diene monoepoxides.[7] The exact role of these ancillary ligands is not clearly understood.

Marino and Floyd:[7]





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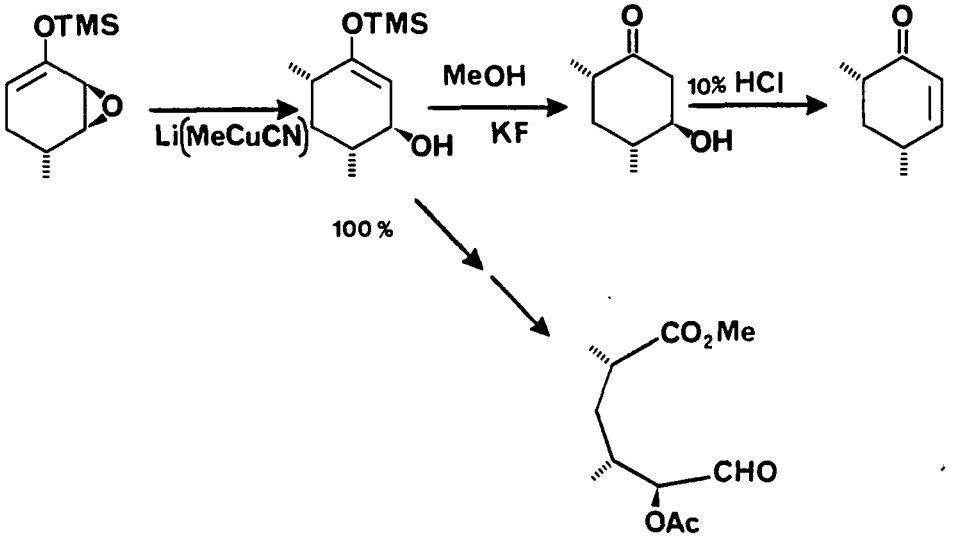
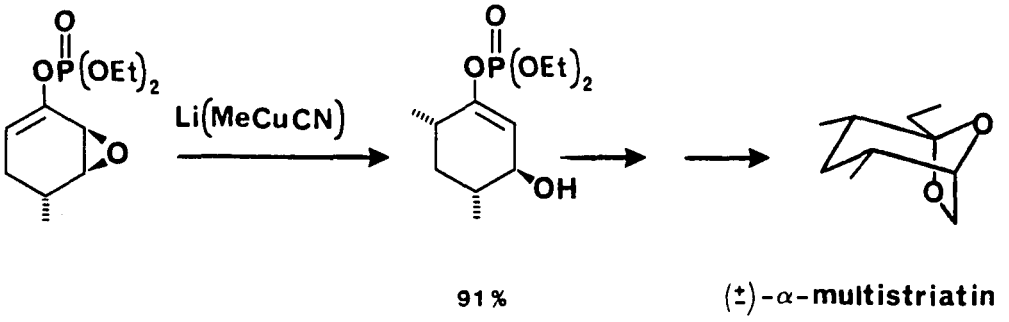
Subsequent work by Marino and Hatanaka[8] demonstrated that this methodology could be extended to silyl enol ethers of 4-methyl-2,3-epoxycyclohexanone.

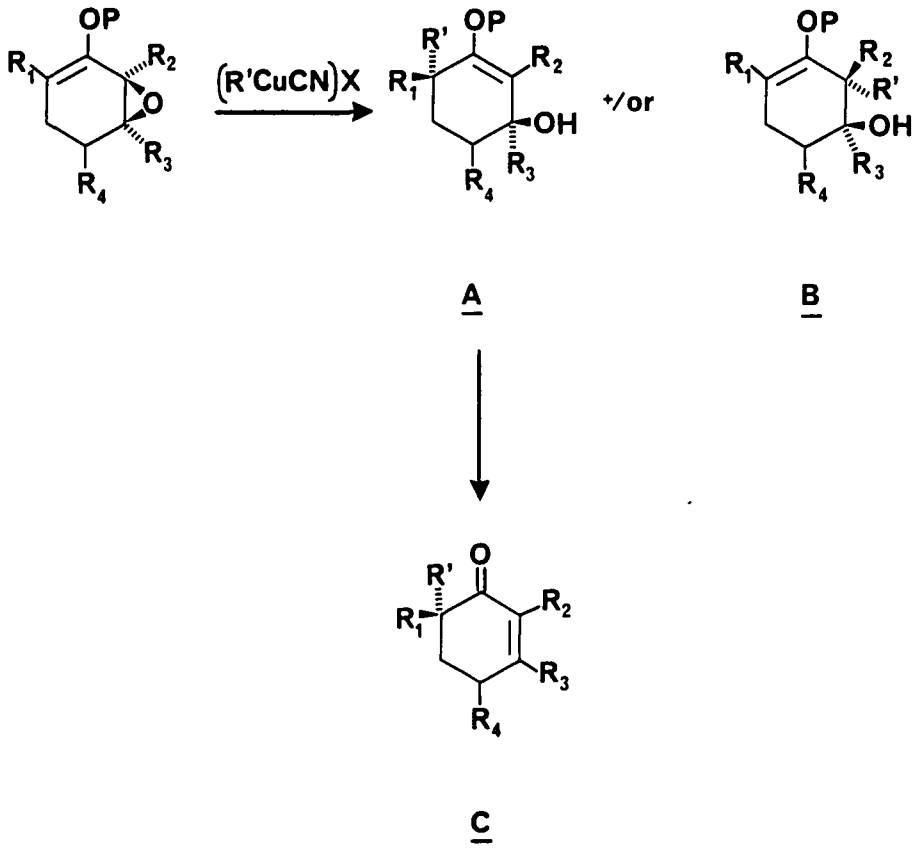


In 1981, Marino and Abe[9] successfully employed the reaction between cyanocuprates and epoxy enol phosphates to synthesize (±)-α-multistriatin.



Before the work described in this manuscript was begun, Marino and Jaen[10] had completed a general study of the reaction between cyanocuprates and enol ethers of α,β-epoxycyclohexanones. The effect of substitution within the reactive allylic epoxide moiety, as well as in the

cyanocuprate, was thoroughly researched. The influence of the hybridization of the carbon bound to copper was also investigated. Some of their results are summarized below.



P = $Si^{t}BuMe_2$, $SiMe_3$, $P(O)(OEt)_2$

R' = Me, n-Bu, tert-Bu, vinyl, phenyl, (Z-2-ethoxy-vinyl)

X = Li, MgBr

Alkylcyanocuprates were found to react in a completely regio- and stereospecific manner, producing exclusively 1,4-*trans* adducts, A, in good yields (74-100%). Hydrolysis to the corresponding cyclohexanones, C, was performed under very mild conditions and in excellent yields. Thus, highly substituted alkyl groups were introduced α to a ketone in a stereospecific manner; *gem*-disubstituted centers α to the ketone could be created with strict stereochemical control if both alkyl chains were sequentially introduced. A limitation to the use of this methodology was the failure to introduce a *tert*-butyl group into an already substituted position (R_1=R_3=Me; R_2=R_4=H; R'=*tert*-Bu; X=Li) which resulted in almost exclusive formation of the corresponding 1,2-adduct, B.

The reactivity of phenylcyanocuprates seemed to follow the same pattern as that of alkylcyanocuprates. It was also determined that, in most cases, the outcome of the reaction was not dependent upon the nature of the counterion, X. Thus, Grignard reagents were successfully used as precursors to cyanocuprates. Subsequent work by Marino and Jaen[10b] showed that in some cases the use of a cyanocuprate derived from an organomagnesium reagent may present serious problems.

Vinylcyanocuprates produced the *trans*-1,4-adducts, A, when reacted with the enol ethers of β-substituted α,β-epoxycyclohexanones (R_3=Me; R_1=R_2=R_4=H). When the

β-position was unsubstituted, mixtures of 1,2- and 1,4-adducts were usually obtained.

1. Mechanistic Aspects.

There are several mechanisms in the literature for the reactions between organocuprates and allylic systems,[11] although the differences among them are often a matter of degree rather than one of concept.[2,12] It is generally accepted[1c] that an oxidative addition of the Cu(I) reagent occurs initially to generate either a radical pair or a Cu(III) intermediate.[13]

Marino and Jaen[10] proposed two mechanisms for the reaction of cyanocuprates with cyclohexenyl epoxides. The first one is shown in Figure 1. The electron-withdrawing cyano ligand increases the Lewis acid character of the copper atom, thus facilitating the polarization of the allylic system by coordination of copper(I) to the epoxide oxygen. Subsequent oxidative addition of another cuprate complex in a trans-1,4 manner, followed by reductive elimination of CuCN, would produce the corresponding trans-1,4-adduct 3.

Figure 1. A Mechanistic Rationale for the Reaction of Cyanocuprates with Cyclohexenyl Epoxides.

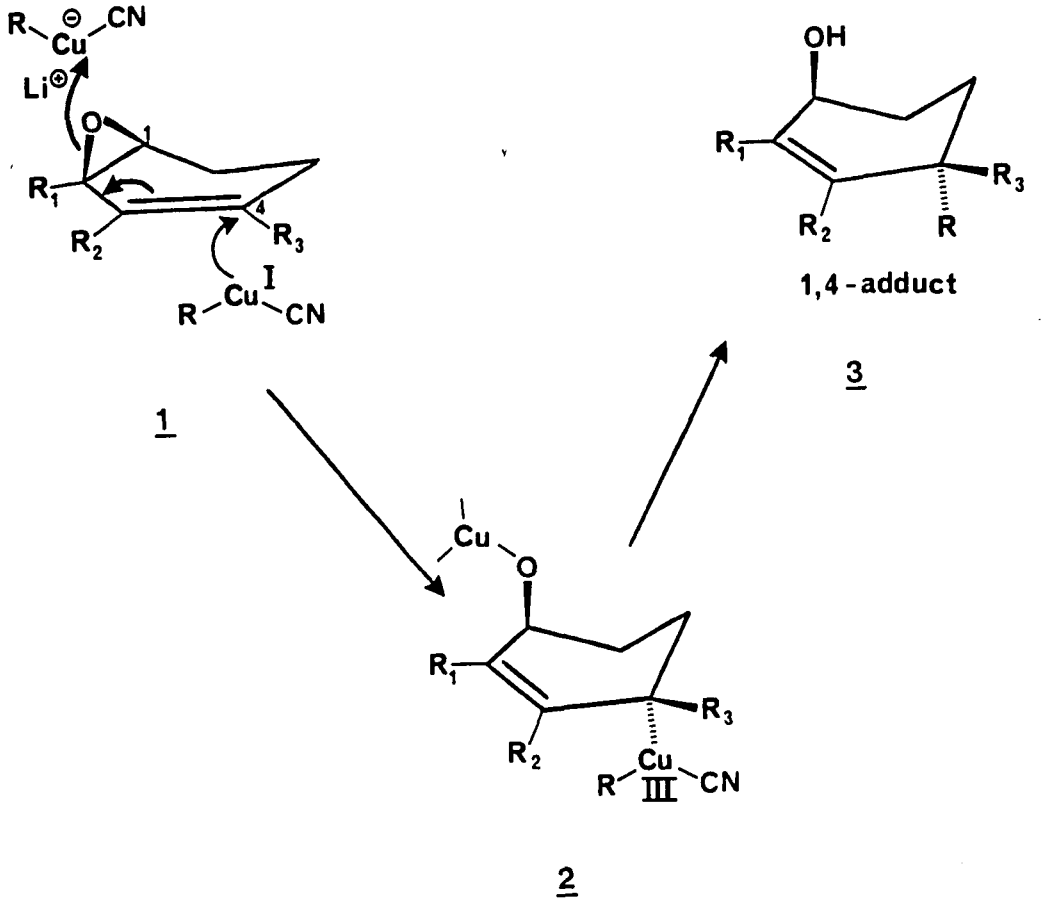
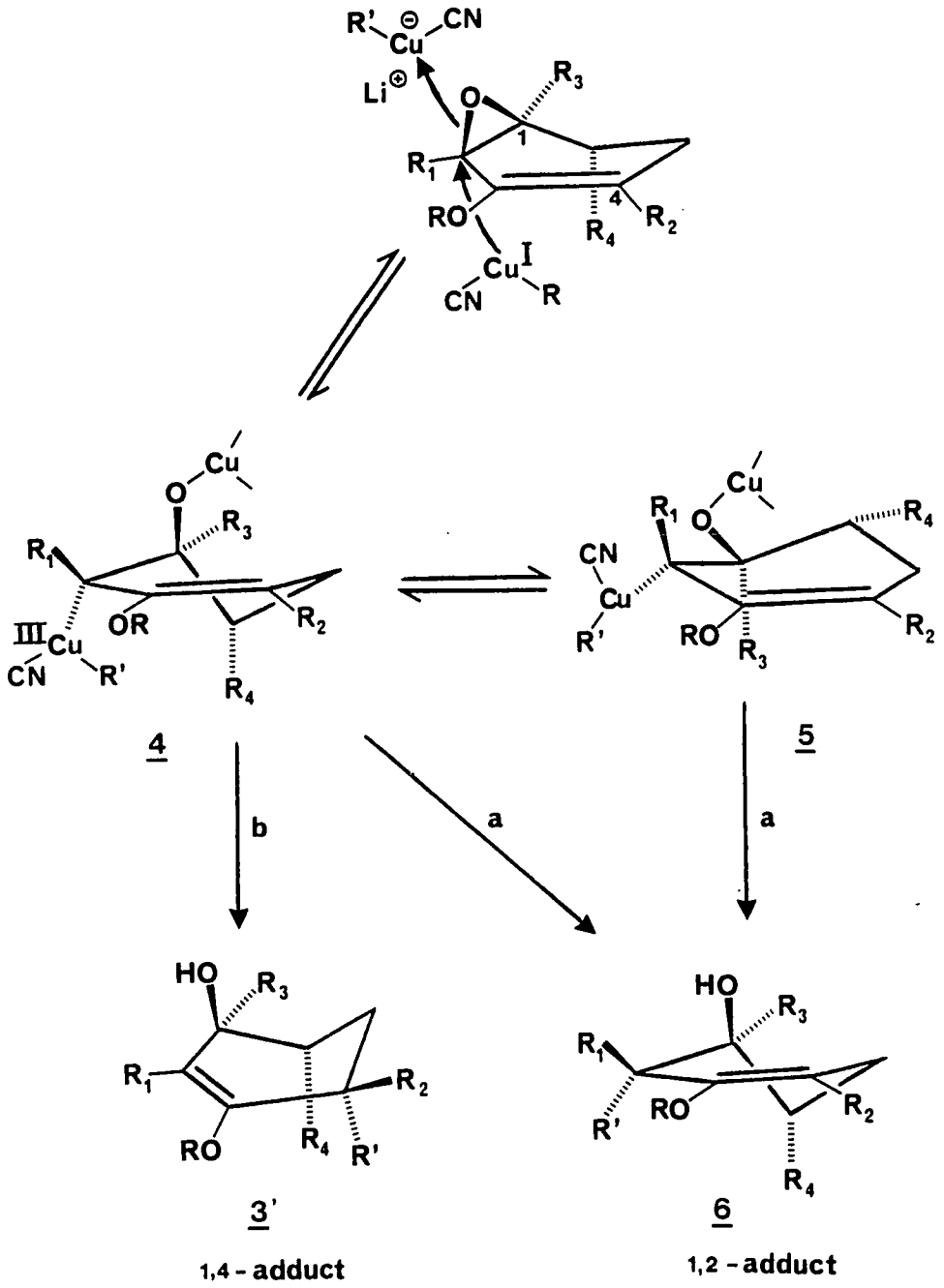


Figure 2 shows an alternative mechanism. In this model, a kinetic 1,2-opening of the vinyl epoxide, aided by complexation of the epoxide to another cuprate complex to generate the Cu(III) intermediate 4, is envisaged. Reductive elimination of CuCN would lead to a trans-1,2-product, 6, while allylic transposition of the double bond with concomitant transfer of the R' group could explain the trans-1,4-product 3'. Alternatively, when 4 is sufficiently

stable, its conformer 5 may play an important role by promoting a 1,2-reductive elimination to 6.

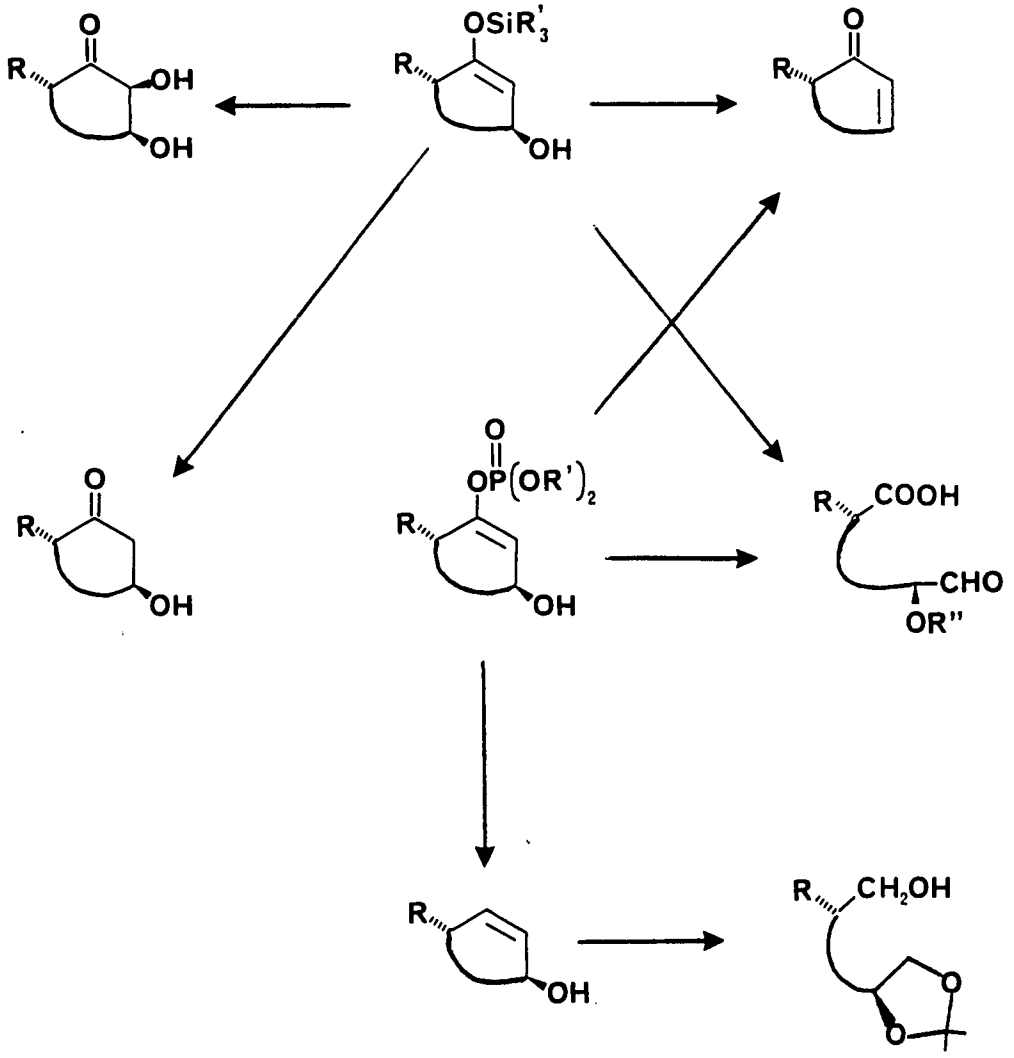
Figure 2. Alternative Mechanism for the Reaction of Cyanocuprates with Cyclohexenyl Epoxides.



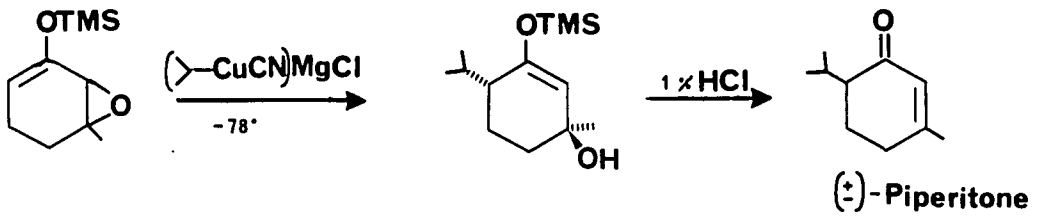
2. Synthetic Aspects.

Another important aspect of this methodology is the synthetic versatility of the intermediate 1,4-adducts. Shown in Scheme 1 are some of the possible applications of these hydroxy silyl enol ethers and hydroxy enol phosphates.

Scheme 1

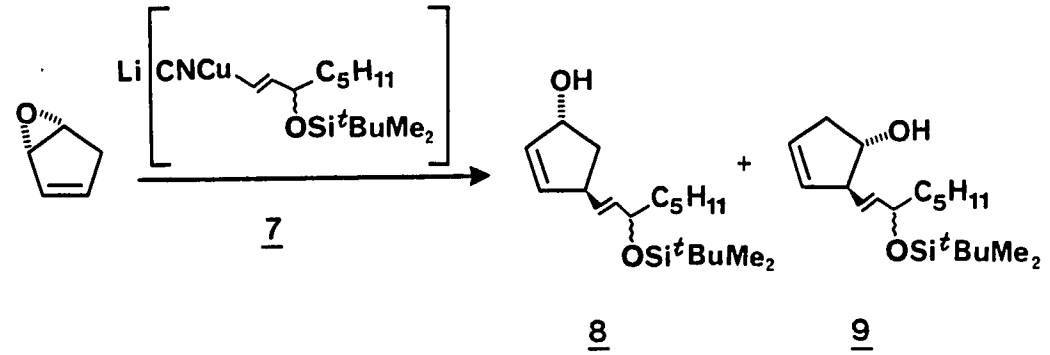


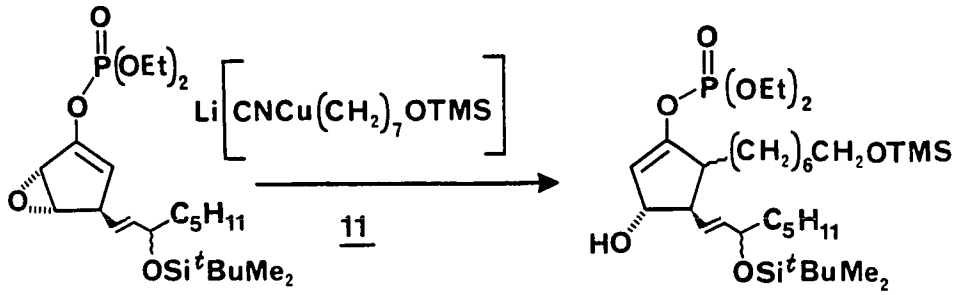
Some of these transformations have already been employed for the synthesis of natural products.[9,10b] An elegant example is the facile synthesis of the terpene piperitone in 85% yield from the readily available 2,3-epoxy-3-methyl-1-(trimethylsiloxy)-6-cyclohexene.[10b]

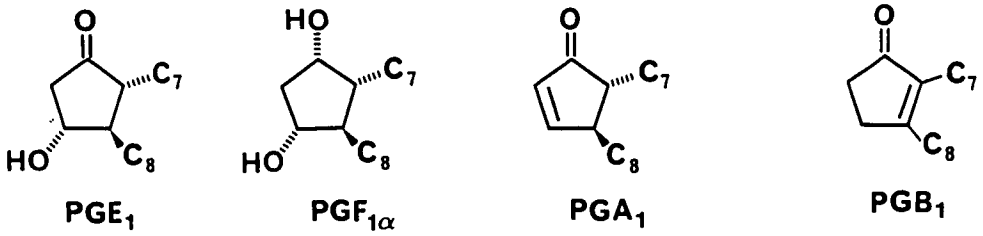


At the initiation of this research, the reactivity of six-membered ring allylic epoxides had been well studied.[7-10] The same could not be said, however, of the behavior of cyclopentenyl allylic epoxides. In 1981, Marino and Kelly[14] reported an application of this methodology to the synthesis of prostaglandins which involved two cyanocuprate conjugate additions onto five-membered ring allylic epoxides; the complete synthetic strategy will be discussed in detail later on in this manuscript.

The reaction of cyclopentadiene monoepoxide with cyanocuprate 7 gave a 4:1 mixture of trans-1,4- and trans-1,2-adducts (8 and 9) in 80% yield. This was the only example involving cyclopentadiene monoepoxide which had been carefully examined in our laboratory. Thus, a more thorough







study of the reaction of cyclopentadiene monoepoxide with different cyanocuprates was deemed to be a logical extension of the methodology developed for the six-membered ring allylic epoxides.

The reaction of cyanocuprate 11 with epoxy enol phosphate 10 gave 1,4-adduct 12 in 60% yield. While adduct 12 was completely characterized, its stereochemistry could not be conclusively assigned due to the fact that epoxy enol phosphate 10 was present as a pair of diastereomers at C 15 (prostaglandin numbering); therefore, the 360 MHz ^{1}H-NMR spectrum of hydroxy enol phosphate 12 was too complicated to allow for determination of the stereochemical relationship between the side chains.

Additionally, no mild hydrolysis of hydroxy enol phosphate 12, which would proceed without loss of the 11-hydroxyl group (prostaglandin numbering), could be developed. Several sets of conditions were examined, but all of them promoted dehydration to the corresponding cyclopentenone. Further studies were necessary in order to preserve that hydroxyl group and thus allow for a direct synthesis of PGE_1 and $PGF_{1\alpha}$.

In order to address a number of unanswered questions from our previous work, the following objectives were set at the start of this research. A systematic study of the reactions of cyanocuprates with cyclopentenyl epoxides was undertaken to further extend the synthetic methodology not only to prostaglandins but to other cyclopentanoid natural products. Results of this study with regard to regiochemistry and stereochemistry of the 1,4-addition reaction should also shed some light on the mechanism of this

process. Finally, a total synthesis of PGE and PGF was set as a realistic goal.

The research in this thesis is presented in three chapters. Chapter I deals with the reaction between cyclopentenyl epoxides and cyanocuprates. Chapter II describes the synthesis of several prostanoids. Chapter III details some synthetic work in an approach to the neolignan porosin as well as the synthesis of two oak lactones *via* lactonization of vinyl sulfoxides.

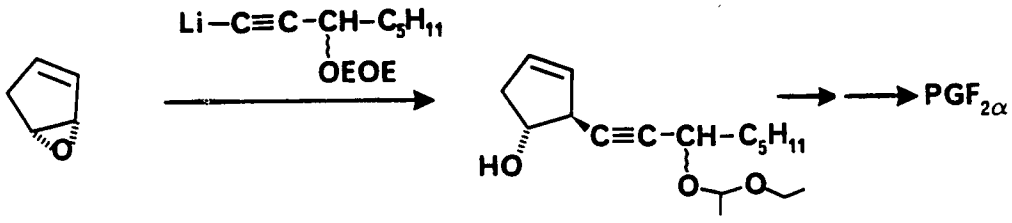
CHAPTER I

REGIO- AND STEREOSELECTIVITY OF THE REACTION BETWEEN CYANOCUPRATES AND CYCLOPENTENYL EPOXIDES

1. Study of the Reaction Between Cyanocuprates and Cyclopentadiene Monoepoxide.

Cyclopentadiene monoepoxide is one of the most readily available functionalized cyclopentane derivatives, easily prepared in multigram quantities by selective monoepoxidation of cyclopentadiene with peracetic acid.[15] It has been employed as a starting material for many synthetic efforts in the prostaglandin field, an example of which is shown below.

Stork:[16]



It should be emphasized, however, that all previous approaches to prostaglandins involved 1,2-openings. The development of the cyanocuprate methodology has made viable the utilization of the regioselective 1,4-opening of cyclopentadiene monoepoxide for the synthesis of prostaglandins.

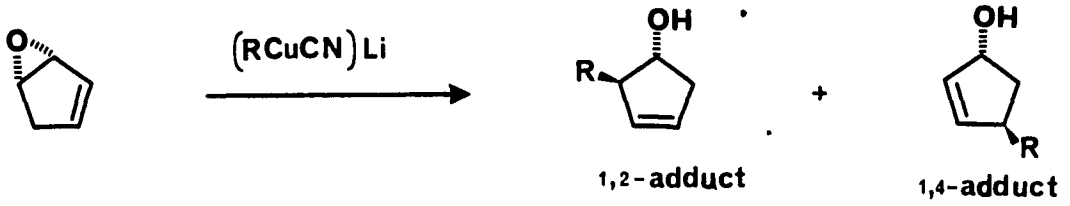
The addition of simple alkylcyanocuprates to cyclopentadiene monoepoxide was found to be completely regio- and stereospecific, producing exclusively 1,4-trans adducts (13-15) in excellent yields, as shown in Table I.[17] The purity of the crude products is usually very high, as determined from the 360 MHz ^{1}H-NMR spectra of the crude adducts. It should be pointed out that, generally, one equivalent of cuprate is sufficient to bring the reaction to completion.

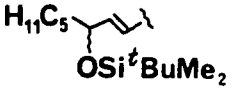
Vinylcyanocuprate yielded a 1:1 mixture of 1,4- and 1,2-adducts, which could not be separated by column chromatography. This "anomalous" behavior is consistent with previous results on cyclohexenyl systems reported by Marino and Jaen.[10] Entry 5 indicates that the regiochemical outcome of the reaction is highly dependent on the precise nature of the organic residue attached to copper. Furthermore, the effect of the cyano ligand on the regiochemistry of the reaction is very significant; when the same reaction is carried out with the corresponding homocuprate, 8 and 9 are obtained in roughly equal amounts. The effect of "dummy" ligands other than cyano was also explored (alkynes, phosphites, etc.); however, the regioselectivity observed for the cyanocuprate could not be equalled. From a preparative point of view, the 4:1 ratio of adducts 8 and 9 could be systematically reproduced.

The addition of phenylcyanocuprate showed a slightly better regioselectivity than that of vinylcyanocuprate;

Table I

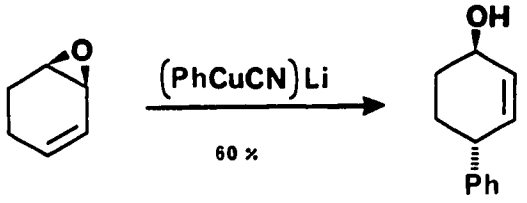
Reactions of Cyanocuprates with Cyclopentadiene Monoepoxide



Entry No.	R	1,2-Adduct	1,4-Adduct	Yield[a]	Ratio of 1,4/1,2
1	Me	--	13	78%	--
2	^{n}Bu	--	14	95%	--
3	^{t}Bu	--	15	88%	--
4	vinyl	16	17	75%	1:1
5		9	8	80%	4:1
6	Ph	18	19	50%	2:1
7	EtO_2CCH_2	--	20	17%	--
8	Bu_3SnCH_2	--	21	5%	--

[a]Yields of pure products.

however, a mixture of regioisomers 18 and 19 was produced. They were easily separated by column chromatography and fully characterized. These results differed markedly from those obtained for cyclohexadiene monoepoxide.[8]



A method to introduce, in a conjugate manner, a β-functionalized two-carbon piece was examined as well. Previous efforts in our laboratory to utilize the cuprate derived from the lithium enolate of tert-butyl acetate for this purpose had not been successful. It was considered that a less hindered ester enolate could achieve satisfactory results. Indeed, the cuprate derived from the lithium enolate of ethyl acetate and copper(I) cyanide reacted in a conjugate fashion with cyclopentadiene monoepoxide. The yield, however, was disappointingly low. Mention should be made of the fact that when copper(I) iodide was employed the results were comparable to those obtained with copper(I) cyanide, although the yield was somewhat lower. To our knowledge, this is the first example of a conjugate addition by a cuprate of this kind. These species have been previously utilized for S_N2 displacements of allylic halides.[18]

In an effort to utilize other functionalized cyanocuprates, tri-n-butylstannylmethyl iodide was subsequently prepared (see Chapter II), and the reaction of its corresponding cuprate with cyclopentadiene monoepoxide was examined. (Tri-n-butylstannyl)methyllithium was prepared according to Kauffmann[19] by halogen-lithium exchange with n-butyllithium in ether, and the formation of the anion was ensured by quenching the mixture with benzaldehyde and

$$(n\text{-Bu})_3SnCH_2I \xrightarrow[2)\ PhCHO]{1)\ n\text{-BuLi}} (n\text{-Bu})_3SnCH_2\text{-}\underset{\displaystyle OH}{\underset{|}{C}}HPh$$

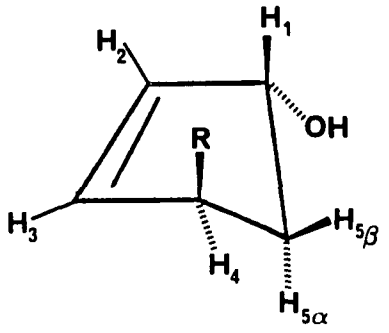
isolating the resulting carbinol. The corresponding cyanocuprate was formed by standard procedures (see Experimental) and its reaction with cyclopentadiene monoepoxide was effected. Unfortunately, the yield of 1,4-adduct 21 was extremely low. A large amount of non-polar material was isolated, presumably $(n\text{-Bu})_3\text{-}SnCH_2CH_2Sn(n\text{-Bu})3$, resulting from oxidative coupling of the cuprate.

The structural assignments for these adducts were derived from their spectral data, especially their ^{1}H-NMR spectra. A preliminary study of the 360 MHz ^{1}H-NMR and ^{13}C-NMR spectra of adducts 8, 9, 13-21 allowed for a conclusive regiochemical assignment, mostly based upon the chemical shift of the carbinol proton; typical values are 4.76-4.98 ppm for 1,4-adducts and 3.60-4.20 ppm for 1,2-adducts.

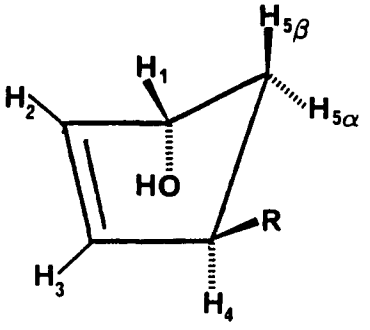
A much more thorough examination of their ^{1}H-NMR spectra was needed in order to assign the stereochemistry of the 1,4-adducts. Figure 3 presents some of the information obtained from the 360 MHz ^{1}H-NMR spectra of adducts 13, 14 and 15 as representative examples. These systems may adopt two envelope conformations (A, B) and a planar one. The planar conformation may be discarded on the basis of its severe eclipsing interactions. Of the envelope conformations, A appears to be the most favored since the bulkier substituent R takes a pseudoaxial disposition and thus the allylic strain (H_3-R) is diminished. That allylic strain should favor an increase of the dihedral angle between the C_1-C_2-C_3-C_4 plane and the C_1-C_5-C_4 plane, with an increase of the size of R. This increase of the torsional angle should bring about changes in the chemical shifts of the cyclopentyl protons; one of the factors contributing to these changes would be the different spatial relationship between each proton and the anisotropic carbon-carbon double bond.

It is generally accepted that cis-1,4-disubstituted cyclopentenes present large differences in the chemical shifts of $H_{5\alpha}$ and $H_{5\beta}$, often in the range of 1 ppm. This large difference is rationalized in terms of a very different magnetic environment for those protons. The upfield proton is normally assigned as the one which is syn to both substituents. This is based on the well-established

Figure 3. Conformations and NMR Data for Adducts 13, 14 and 15.



A

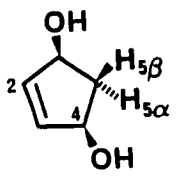


B

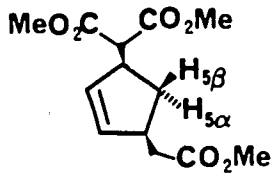
13	R-Me	14	R=n-Bu	15	R=tert-Bu
Chemical Shifts(δ)	J's(Hz)	Chemical Shifts(δ)	J's(Hz)	Chemical Shifts(δ)	J's(Hz)
H_1 =4.860	J_{12} =2.1	H_1 =4.820	J_{12} =2.2	H_1 =4.805	J_{12} =2.3
H_2 =5.771	J_{13} =0.5	H_2 =5.779	J_{13} =0.7	H_2 =5.840	J_{13} =0.9
H_3 =5.881	J_{14} =2.1	H_3 =5.920	J_{14} =2.1	H_3 =5.943	J_{14} =2.2
H_4 =2.937	$J_{15\alpha}$=2.6	H_4 =2.820	J_{15} =2.7	H_4 =2.719	J_{15} =2.9
$H_{5\alpha}$=1.944	$J_{15\beta}$=7.1	$H_{5\alpha}$=1.884	$J_{15\alpha}$=7.1	$H_{5\alpha}$=1.682	$J_{15\alpha}$=7.2
$H_{5\beta}$=1.693	J_{23} =5.5	$H_{5\beta}$=1.737	$J_{23\beta}$=5.6	$H_{5\beta}$=1.947	$J_{23\beta}$=5.7
	J_{24} =2.2		J_{24} =2.2		J_{24} =2.3
	J_{34} =2.1		J_{34} =2.0		J_{34} =2.1
	$J_{45\alpha}$=7.5		$J_{45\alpha}$=7.5		$J_{45\alpha}$=8.0
	$J_{45\beta}$=5.2		$J_{45\beta}$=5.2		$J_{45\beta}$=5.4

fact that protons syn to a substituent undergo an upfield shift.[20,21] Alternatively, this difference does not usually exceed 0.3 ppm for trans isomers.

Inspection of the literature coupling constant data for these systems reveals a potentially useful trend in which the anti vicinal coupling constants are generaly smaller than the syn within the same molecule. Some examples from the literature[22] are listed below. Extreme



22



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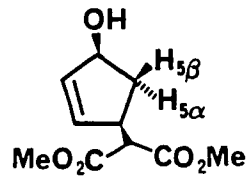
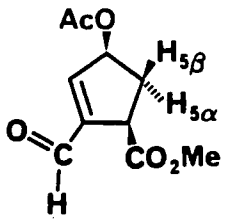
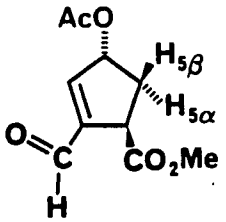


24



25



26

	22	23	24	25	26
$\delta H_{5\alpha}$=	2.66	2.42	2.56	2.86	2.62
$\delta H_{5\beta}$=	1.51	1.24	1.58	2.08	2.27
$J_{15\alpha}$=	7.3	7.8	7.5	8.0	5.0
$J_{45\alpha}$=	7.3	8.1	8.7	8.0	8.0
$J_{15\beta}$=	3.6	7.8	3.3	6.0	8.0
$J_{45\beta}$=	3.6	7.8	5.0	6.0	4.0

care must be exercised, however, in promoting configurational assignments in five-membered rings based purely upon the magnitudes of coupling constant data. In the absence of geometrically restraining factors, the conformational flexibility of cyclopentyl-ring systems makes application of the Karplus equation for prediction of vicinal coupling constants not as generally dependable as in conformationally fixed ring systems.

The trans stereochemistry of adducts 13-15 was thus assigned by the criteria discussed above. The difference of chemical shift between $H_{5\alpha}$ and $H_{5\beta}$ was found to be smaller than 0.3 ppm (Figure 3). Both protons present one large coupling constant (7.1-8.0 Hz) and one small coupling constant (2.6-5.4 Hz). This is consistent with a large cis coupling and a smaller trans coupling, its value further reduced in the case of $J_{15\alpha}$ by the electronegative oxygen atom. The certainty of these assignments is reinforced by the following facts:

(1) Upfield shift for H_1 with increasing steric bulk of R. This is consistent with a more pseudoaxial character of H_1.

(2) Fairly large homoallylic coupling of approximately 2 Hz between H_1 and H_4. Careful examination of molecular models shows that the stereochemical relationship between H_1 and H_4 is very similar to that encountered in cyclohexene derivatives for a 1,4-pseudoaxial-pseudoaxial

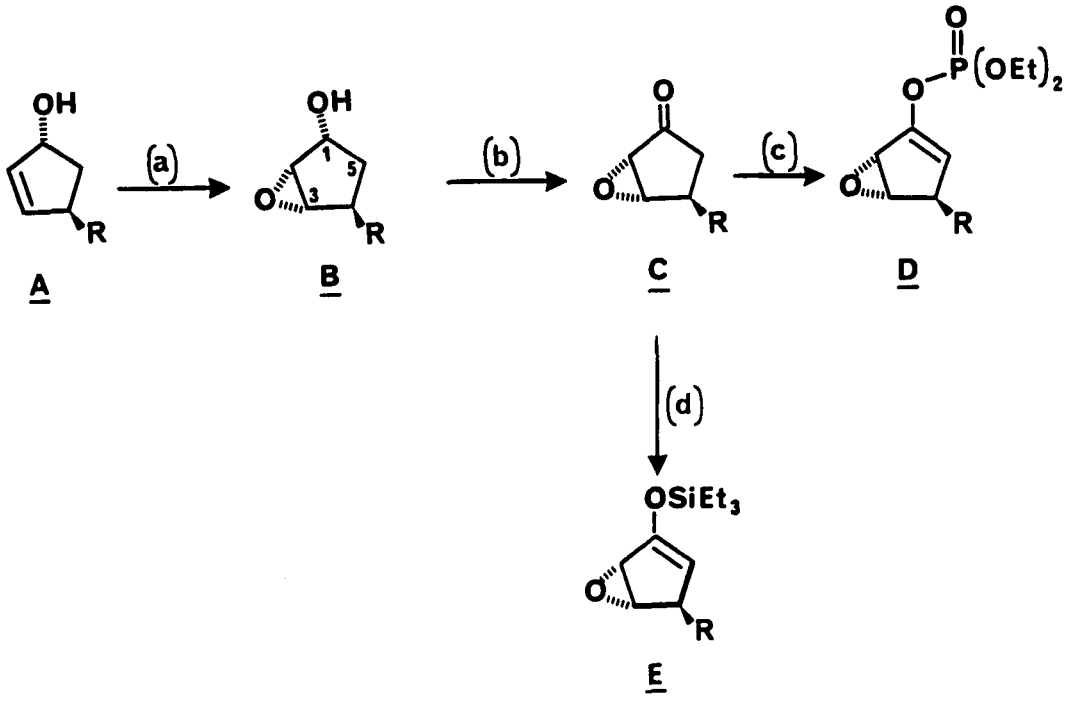
disposition, which, in turn, is known to be the most favorable situation for homoallylic couplings.

(3) Upfield shift for $H_{5\alpha}$ and downfield shift for $H_{5\beta}$ with increasing steric bulk of R. This is consistent with an increase of the relative population of conformation A and/or an increase of the torsional angle which renders $H_{5\beta}$ closer to being coplanar with C_1 and C_2, therefore, placing it in the deshielding cone of the double bond, and, consequently placing $H_{5\alpha}$ in the shielding region of the anisotropic double bond.

The stereochemistry of the other 1,4-adducts was assigned by correlation of their spectral data with that of adducts 13-15 whose stereochemistry had been proven beyond any doubt. It should be pointed out that while adducts 20 and 21 were completely characterized, their stereochemistry could not be firmly established and is tentatively assigned as trans on the basis of the presumed mechanism of formation.

Returning to the synthetic aspects of this methodology, Scheme 1 illustrates the transformations that led to epoxy enol phosphates, D, and epoxy enol ethers E, which will be the subject of the second part of this study. The yields of these transformations are summarized in Table II.

Scheme 1

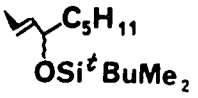


Reagents: a) tert-BuOOH, $VO(acac)_2$, PhH; b) CrO_3·pyridine, CH_2Cl_2; c) LDA, THF, -78°C, then $ClP(O)(OEt)_2$; d) LDA, THF, -78°C, then Et_3SiCl.

Hydroxyl directed cis epoxidation[23] with tert-butyl hydroperoxide and $VO(acac)_2$ gave epoxy alcohols B (27-30) in excellent yields (see Table II). It should be mentioned that this reaction proceeded with superb chemoselectivity; allylic alcohol 8 underwent selective epoxidation in the presence of its homoallylic isomer 9. This allowed for an easy separation of epoxy alcohol 29 from carbinol 9 by a simple column chromatography; this facilitated the preparation of large quantities of 29 which were required for the synthesis of prostaglandins (see Chapter II).

Table II

Synthesis of Epoxy Enol Phosphates and Epoxy Silyl Enol Ethers

A[a,b]		B	C	D	E
R = Me	13	27 (95)	31 (75)	35 (94)	--
R = ^{n}Bu	14	28 (100)	32 (80)	36 (90)	37 (100)
R = 	8	29 (98)	33 (82)	10 (85)	38 (100)
R = Ph	19	30 (90)	34 (79)	--	--

[a]See Scheme 1 for general structure of A, B, C, etc.

[b]Yields of pure products in parentheses.

The stereochemistry of epoxy alcohols 27-30 was assigned by spectral data as well as by the known stereochemical course of the epoxidation of allylic alcohols. Furthermore, one of them (29) was eventually transformed into natural products of known stereochemistry (see Chapter II). For instance, the stereochemistry of 27 is verified by the following spectral characteristics: J_{12} is 1.4 Hz, which is very small (due to the electronegative oxygen), but still larger than J_{34}, which is 0 Hz. This difference strongly

suggests a trans stereochemistry for H_3 and H_4 and a cis stereochemistry for H_1 and H_2.[22]

Collins oxidation[24] produced epoxy ketones C (31-34) in consistently good yields, as shown in Table II. Unfortunately, the work-up of a large-scale Collins oxidation is extremely cumbersome. Therefore, many other oxidants such as Jones reagent (in several sets of conditions), PDC, $DMSO/Ac_2O$, N-chlorosuccinimide/Me_2S/Et_3N, etc., were examined. However, none of them afforded comparable results to those obtained with Collins reagent.

Enolate formation with LDA (THF, -78°C, 1 h) followed by trapping with diethyl chlorophosphate proceeded in excellent yield to give epoxy enol phosphates D (10, 35, 36). Alternatively, trapping of the enolate with triethylsilyl chloride afforded epoxy silyl enol ethers E (37, 38) in quantitative yields.

2. Study of the Reaction Between Cyanocuprates and 4-Substituted Epoxy Cyclopentenyl Phosphates.

The chemical manipulation just described had set the stage for the study of a second conjugate addition. The stereochemistry of enol phosphates 10, 35 and 36 and silyl enol ethers 37 and 38 represents a challenge to the regio- and stereoselectivity of the cyanocuprate reaction. Indeed, if the reaction is to proceed in a trans 1,4-fashion, the incoming group would have to be placed 1,2-cis to another

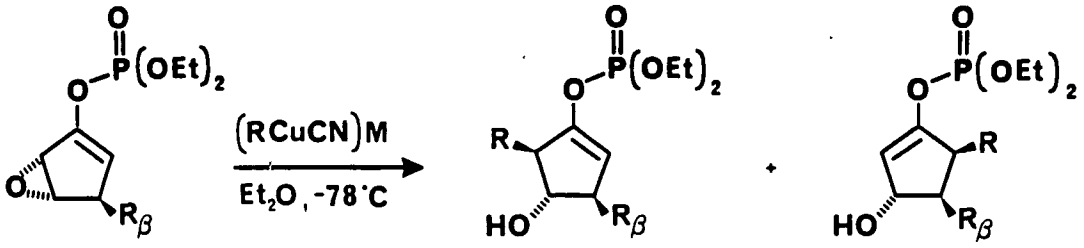
group in a cyclopentyl system. This was seen as a potentially limiting situation for the stereospecificity of the reaction and represented a substitution pattern previously untested in our laboratories.

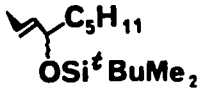
The reaction of epoxy enol phosphates 10, 35 and 36 with a variety of cyanocuprates was examined and the results obtained are shown in Table III.[17] It was found that the addition of simple alkylcyanocuprates proceeded in good to excellent yields (58%-95%) and was, in most cases, completely regio- and stereospecific. Entry 3, however, showed a surprising lack of regiochemical control and also the formation of an anomalous "reduction" product 43, formally produced by conjugate hydride transfer. This phenomenon is unprecedented in our laboratories; similar products have not been detected in other analogous reactions involving tert-butylcyanocuprate. A very tentative rationalization of this result is presented in Scheme 2. The transfer of the tert-butyl group may be an unfavorable process in this case due to the presence of the methyl group in a 1,2-cis disposition. This may allow for alternative reaction pathways to take place, such as formation of the 1,2-adduct or hydride transfer, both of which are observed. The hydride transfer pathway may be favored by the fact that the cuprate has 9β hydrogens. Thus, the chance of a hydride transfer is statistically large.

Table III

Reactions of Cyanocuprates with Epoxy Enol Phosphates

10, 35 and 36



R_β = Me (35), ^{n}Bu (36),  (10)

Entry	Sub-strate	R	M	1,2-Adduct	1,4-Adduct	Ratio of 1,4/1,2	Yield[a]
1	35	Me	Li	--	39	--	90
2	35	^{n}Bu	Li	--	40	--	95
3[b]	35	^{t}Bu	Li	41	42	2:3	60
4	35	vinyl	MgBr	44	--	--	98
5	35	allyl	Li,MgBr	45	--	--	99
6	35	Ph	Li	46	47	1:2	80
7	35	Ph	MgBr	46	47	1:6	75
8	36	^{n}Bu	Li	--	48	--	85
9	10	^{n}Bu	Li	--	49	--	58
10	10	^{t}Bu	Li	--	50	--	61
11	10	TMSO$(CH_2)_7^-$	Li	--	12	--	60

Table III (continued)

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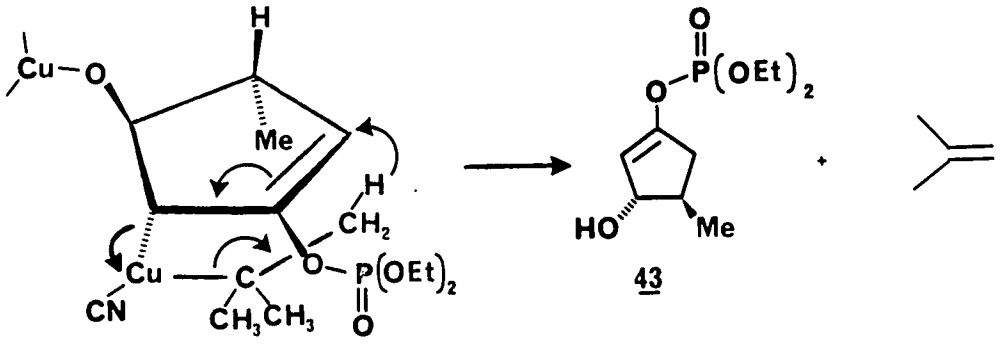
[a]Percent yields of pure products.

[b]In this case, a 10% yield of diethyl trans-3-hydroxy-4-methyl-2-cyclopentenyl phosphate, 43, was also obtained.

Scheme 2



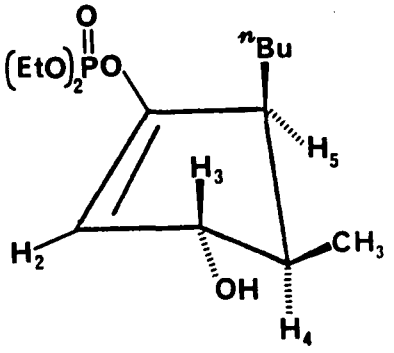
Vinyl and allylcyanocuprate gave exclusively 1,2-opening. The influence of the counterion (Li vs. MgBr) was studied for allylcyanocuprate, and no significant difference was found. Phenylcyanocuprate, however, did show a marked dependency on the nature of the counterion. The amount of 1,4-adduct was significantly increased when MgBr was replaced by Li. This kind of dependency, albeit not common, is not totally unprecedented in our group.[10b]

From a preparative point of view, the 1,2-adducts were found to be stable for an indefinite period of time if stored in a refrigerator. This was not the case for the 1,4-adducts. Complete decomposition to the corresponding 4,5-disubstituted-2-cyclopentenones was observed upon standing at room temperature for 2-3 days. Storage in a freezer preserved them for 7-10 days without noticeable decomposition. All adducts were sufficiently stable to be purified by column chromatography.

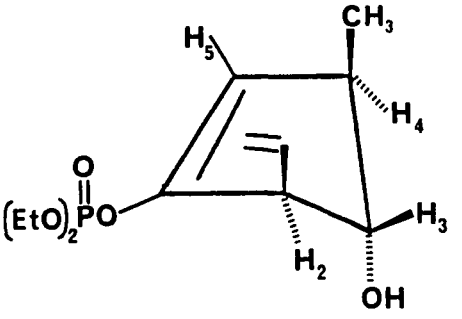
Figure 4 presents some of the information obtained from the 360 MHz ^{1}H-NMR spectra of adducts 40 and 44, as representative examples of a 1,4-trans adduct and a 1,2-trans adduct, respectively, as well as their presumably preferred conformations.

The preferred conformation for adduct 40 should minimize the allylic strain between the bulky phosphate residue and the n-butyl group. In order to accomplish this, the latter should adopt a pseudoaxial disposition. The same reasoning leads to the envelope conformation shown in Figure 4 for adduct 44. The regiochemical assignment may be done in a very straightforward manner by examination of the chemical shift of the carbinol proton, which presents an upfield shift for 1,2-adducts with respect to the 1,4-allylic alcohols.

Figure 4. Conformations and NMR Data for Adducts 40 and 44.



40



44

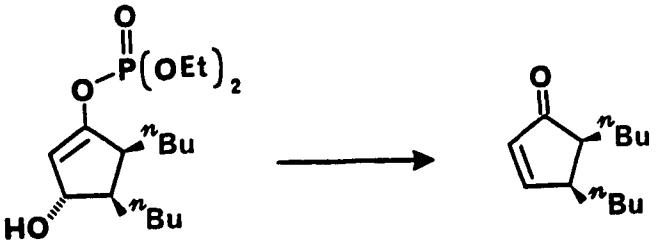
Chemical Shifts (δ)	J's (Hz)	Chemical Shifts (δ)	J's (Hz)
H_2=5.364	J_{23}=2.0	H_2=3.213	J_{23}=5.3
H_3=4.311	J_{34}=5.1	H_3=3.602	J_{34}=5.3
H_4=2.151	J_{35}=1.0	H_4=2.540	J_{45}=1.9
H_5=2.754	J_{45}=7.3	H_5=5.177	

The stereochemistry of 1,2-adduct 44 may be assigned as trans from the process of S_N2 displacement (nucleophilic opening of an epoxide). The spectral evidence corroborates this assumption; H_3 is unusually shielded for a cyclopentyl carbinol proton, which is consistent with the upfield shift caused by two cis 1,4-substituents. Furthermore, H_3 shows relatively small and equal couplings with H_2 and H_4, consistent with two trans couplings. No homoallylic coupling was detected between H_2 and H_4, which also supports the proposed

stereochemistry. 1,4-Adduct 40 does show a homoallylic coupling (H_3-H_5), typical of a 1,4-trans disposition of substituents at C_3 and C_5 (see discussion of assignments for 1,4-adducts derived from cyclopentadiene monoepoxide on previous pages). Moreover, H_4 shows two fairly different couplings of 7.3 Hz and 5.1 Hz, consistent with a cis and a trans coupling, respectively.

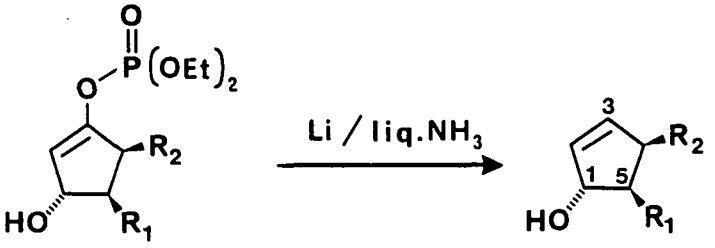
The stereochemistry of the other adducts was established by correlation of their spectral characteristics with those of 40 and 44. Adducts 12, 49 and 50 were the only cases in which, due to the complexity of their 360 MHz ^{1}H-NMR spectrum (mixture of diastereoisomers), their stereochemistry could not be conclusively ascertained.

In some cases, spontaneous hydrolysis of some 1,4-adducts led to 4,5-disubstituted cyclopentenones which were unequivocally characterized. Such is the case of dibutyl enol phosphate 48, which decomposed upon standing to an enone whose structure was confirmed as cis-4,5-di-n-butyl-2-cyclopentenone in the following part of this study. This chemical evidence reinforced the accuracy of the spectroscopic assignments.



48 70

Once the stereochemistry of these 1,4-adducts had been secured, the reductive cleavage of the phosphate group with lithium in liquid ammonia was examined.[9] Some initial attempts afforded the corresponding 4,5-cis-disubstituted-2-cyclopentenols in low yields.



40	R_1=Me, R_2=n-Bu	51 (30%)
48	R_1=R_2=n-Bu	52 (35%)

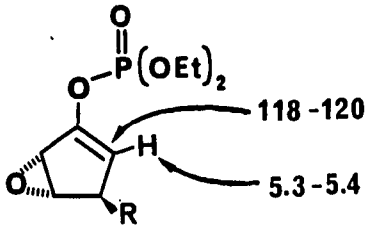
These results are in sharp contrast with those obtained in our group for cyclohexenyl phosphates,[9] for which good yields were consistently recorded. The stereochemistry of 51 and 52 was derived from their 360 MHz ^{1}H-NMR spectra which showed a homoallylic coupling between H_1 and H_4 (1.8 and 1.5 Hz, respectively) which is typical

for these 1,4-trans adducts. Furthermore, both presented significantly larger J_{45} than J_{15}, strongly suggesting a cis and a trans coupling, respectively.

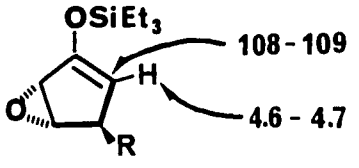
3. Study of the Reaction Between Alkylcyanocuprates and 4-Substituted Epoxy Cyclopentenyl Silyl Enol Ethers.

This part of the study arose in connection with our prostaglandin synthesis, which will be discussed in detail in Chapter II of this manuscript. The regio- and stereochemical results of the reaction between alkylcyanocuprates and epoxy cyclopentenyl silyl enol ethers will be examined here.

Silyl enol ethers 37 and 38 present the same substitution pattern as enol phosphates 10, 35 and 36. Therefore, they are subject to the same steric constraints (see previous section). However, the electronics of these two types of allylic epoxides are quite different, as can be seen by comparison of ^{13}C and ^{1}H-NMR chemical shifts. This difference in electronics may alter the selectivity of the reaction.

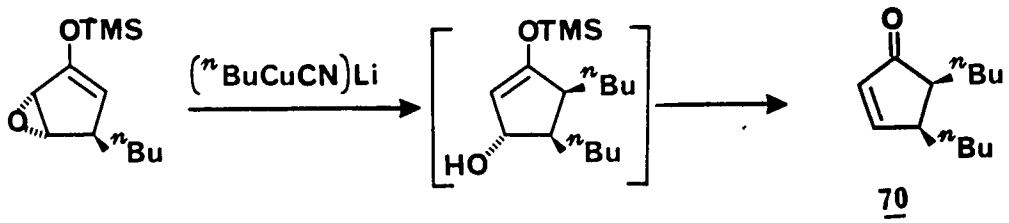


10, 35, 36



37, 38

At the initial stage of this study, trimethylsilyl epoxy enol ethers were examined. They were easily synthesized but, unfortunately, they were found to be too labile; complete hydrolysis to the corresponding epoxy ketones occurred after two or three days, even when they were stored under nitrogen in a freezer. Some preliminary attempts to carry out the 1,4-addition on freshly prepared trimethylsilyl epoxy enol ether were successful. However, the desired 1,4-adduct could not be isolated, but, instead, good yields of the corresponding enone 70 were obtained.



70

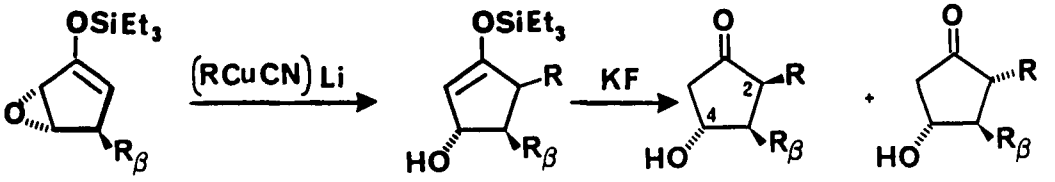
The preparation of a more stable epoxy silyl enol ether was then examined. It was found that triethylsilyl epoxy enol ethers 37 and 38 could be easily prepared from the corresponding epoxy cyclopentanones 32 and 33, and were stable for months if stored in a freezer. It was expected that a less labile protecting group would also make the isolation of the intermediate 1,4-adducts possible. This would allow for the development of hydrolytic conditions leading to the desired β-hydroxycyclopentanones. The

ability to effect this hydrolysis without concomitant dehydration was paramount for our strategy towards PGE_1.

The isolation of these triethylsilyl hydroxy enol ethers was not easily effected. Preliminary attempts to isolate dibutyl adduct 53 produced exclusively cyclopentenone 70 after standard workup. A systematic study of the reaction was then undertaken. A variety of factors, ranging from reagents to temperature and reaction time, were checked, and the reaction conditions were very carefully controlled. This study demonstrated that decomposition to the enone was taking place upon concentration *in vacuo* of a dry ethereal solution of the 1,4-adduct with a lukewarm water bath! This seemingly innocent factor proved to be crucial for the success of our overall strategy towards PGE_1. Indeed, when no external heat was applied while concentrating *in vacuo*, excellent yields of 1,4-adducts could be obtained. These triethylsilyl hydroxy enol ethers were found to be remarkably more unstable than their six-membered ring analogues. In most instances, they were not characterized, but they were immediately hydrolyzed to the corresponding β-hydroxycyclopentanones, which could be purified and characterized. This hydrolysis was best effected by treatment of the crude 1,4-adducts with potassium fluoride dissolved in pH 7 phosphate buffer/ethanol. The results obtained in the course of this research are summarized in Table IV.

Table IV

Reaction of Alkylcyanocuprates with Triethylsilyl Epoxy Enol Ethers 37 and 38



A B C

$R_\beta = {}^n\text{Bu}$ (37), C_5H_{11}, $OSi^t\text{BuMe}_2$ (38)

Entry No.	R_β	R	A	B[a]	C[a]	Yield[b]
1	^{n}Bu	^{n}Bu	53	59	--	85
2	^{n}Bu	^{n}heptyl	54	61(2)	62(1)	60
3	^{n}Bu	$TMSO(CH_2)_7^-$	55	63(1)[c]	64(7)[c]	78
4	C_5H_{11}, $OSi^t\text{BuMe}_2$	^{t}Bu	56	65	--	65
5	C_5H_{11}, $OSi^t\text{BuMe}_2$	^{n}heptyl	57	66(1)	67(4)	70
6	C_5H_{11}, $OSi^t\text{BuMe}_2$	$TMSO(CH_2)_7^-$	58	68(1)[c]	69(8)[c]	80

Table IV (continued)

---

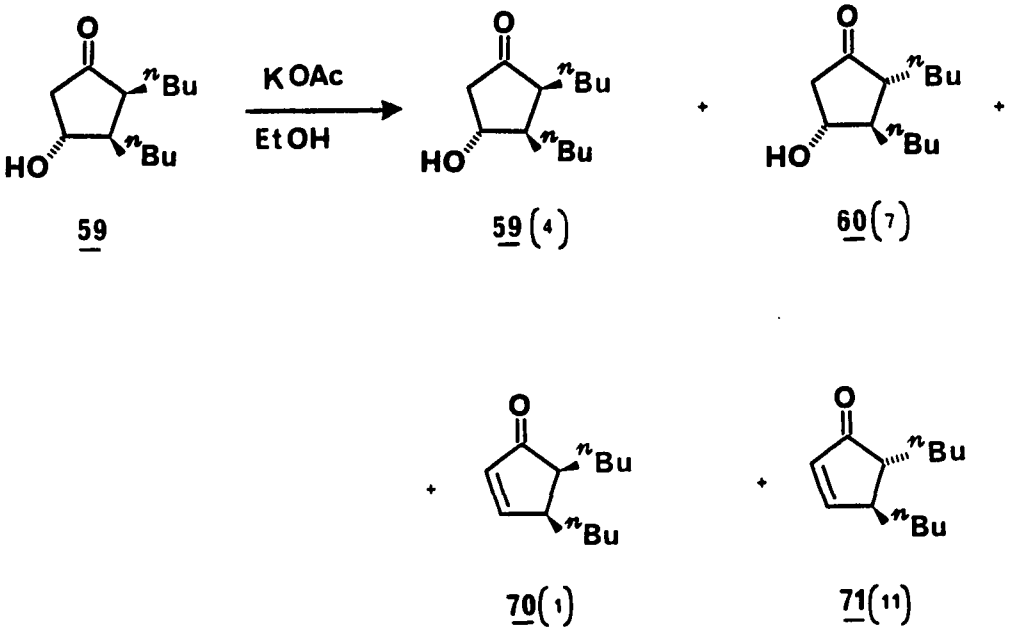
[a]Relative ratio of products indicated in parentheses when appropriate.

[b]Percent yield of purified B+C when two isomers were obtained.

[c]Fluoride treatment deprotected the primary alcohol but did not affect the allylic alcohol.

Higher yields were obtained when the conjugate additions were carried out with 3-4 equivalents of cyanocuprate reagent. All the cases examined proceeded with excellent regiochemical control, as evidenced by the fact that only 2,3-disubstituted hydroxycyclopentanones B and C were detected. Chronologically, 59 was the first β-hydroxycyclopentanone isolated. A quick inspection of its 360 MHz ^{1}H-NMR spectrum allowed for elucidation of its regiochemistry. A more detailed study strongly suggested a cis arrangement of both alkyl chains. However, it was considered that some chemical verification was necessary. This was achieved by epimerization of 59 with ethanolic potassium acetate. These conditions have been successfully employed to effect the epimerization of 8-iso-PGE_1 to PGE_1.[25] The results obtained are presented in Scheme 3 (the relative ratio of products is indicated in parentheses). It should be pointed out that this reaction was not optimized. No

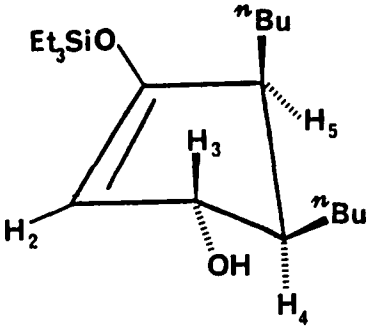
Scheme 3



attempts were made to reduce the amount of enones formed since the only objective of this experiment was to unequivocally prove the structure of hydroxycyclopentanone 59.

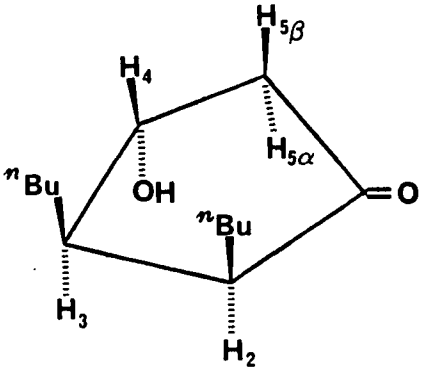
Column chromatography allowed for the separation of cyclopentenones 70 and 71 from hydroxy ketones 59 and 60. These epimeric hydroxycyclopentanones could not be separated in this manner, nor was it necessary; the spectral characteristics of trans isomer 60 were easily obtained from the spectrum of the mixture. Figure 5 summarizes some ^{1}H-NMR data for hydroxy enol ether 53 and isomeric hydroxy ketones 59 and 60.

Figure 5. ^{1}H-NMR Data for Adducts 53, 59 and 60.



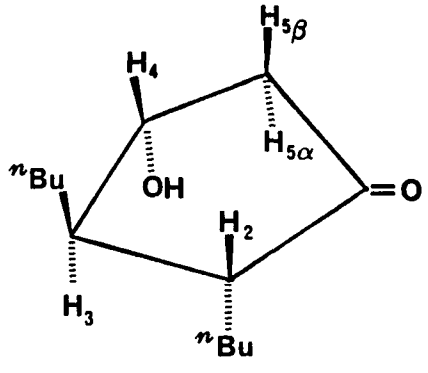
53

	Chemical Shift (δ)	J's (Hz)
	H_2=4.625	J_{23}=2.5
	H_3=4.345	J_{34}=5.4
	H_4=1.846	J_{35}=2.0
	H_5=2.555	J_{45}=7.3



59

	$H_{5\alpha}$=2.201	$J_{5\alpha 4}$=0.0
	$H_{5\beta}$=2.428	$J_{5\alpha 2}$=1.7
	H_4 =4.362	$J_{5\beta 4}$=5.9
	H_3 =2.189	J_{43} =2.3
	H_2 =2.611	J_{32} =7.0



60

	$H_{5\alpha}$=2.200	$J_{5\alpha 4}$=6.8
	$H_{5\beta}$=2.650	$J_{5\beta 4}$=6.8
	H_4 =4.125	$J_{5\beta 2}$=1.0
	H_2 =1.866	J_{43} =6.8
	H_3 =1.866	J_{32} = --

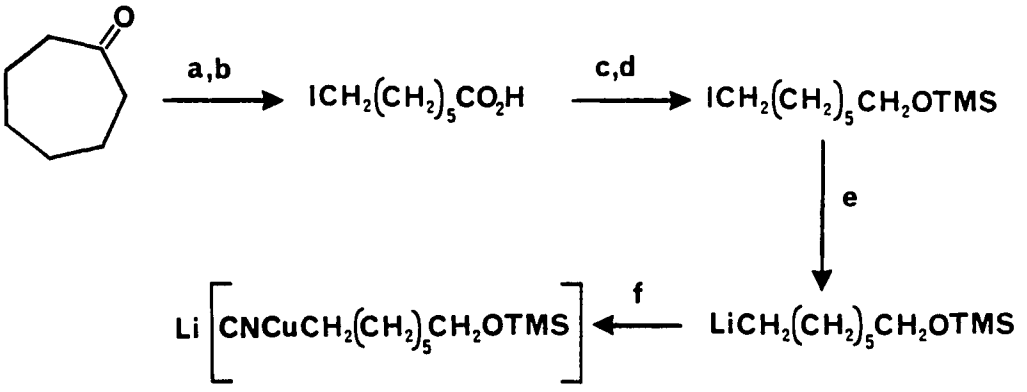
The proposed 1,4-trans stereochemistry of hydroxy enol ether 53 is strongly supported by several facts: there is a fairly large homoallylic coupling between H_3 and H_5; there is a large cis coupling between H_4 and H_5 and a smaller trans coupling between H_3 and H_4; finally, hydroxycyclopentanone 59 was the only product detected upon fluoride induced hydrolysis of 53.

The most striking spectroscopic difference between 59 and 60 is the tremendous upfield shift for H_2 in the trans isomer, 60, accompanied by a smaller upfield shift for H_3. This trend is consistent with the fact that both protons are shielded by cis alkyl groups in the trans isomer. Also, remarkable is the long distance coupling between $H_{5\alpha}$ and H_2 for 59 and $H_{5\beta}$ and H_2 for 60. This implies a cis-relationship between the protons which are coupled and, therefore, supports the assigned stereochemistry.

The spectral characteristics of the other adducts in Table IV followed the same trends as those discussed above and the assignments were always very conclusive. Whenever mixtures of epimers were obtained, their relative ratios were easily measured by integration of their 360 MHz ^{1}H-NMR spectra, especially of the carbinol protons (typical chemical shifts for H_4 are 4.3 ppm for "cis" isomers, B, and 4.1 ppm for "trans" isomers C).

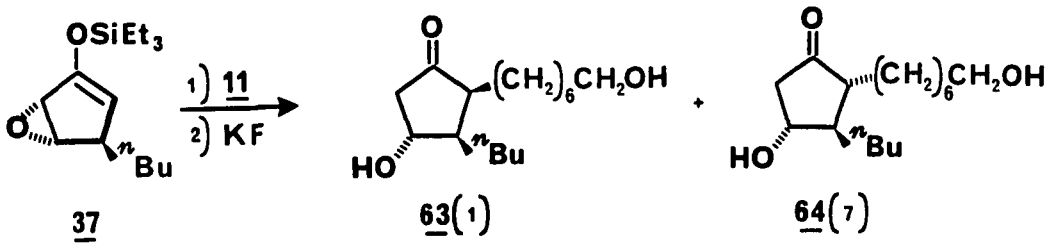
The reaction of epoxy enol ether 37 with the mixed cyanocuprate 11 (the preparation of which is presented in Scheme 4) was then examined. It was found that considerable amounts of 37 remained unreacted after stirring at -78°C for several hours (see Experimental). Gradual increase of temperature brought the reaction to completion. Standard workup, followed by immediate hydrolysis to the corresponding β-hydroxyketone gave, much to our surprise, a 1:7 mixture of cis and trans ketols, 63 and 64, which could not be separated by column chromatography.

Scheme 4



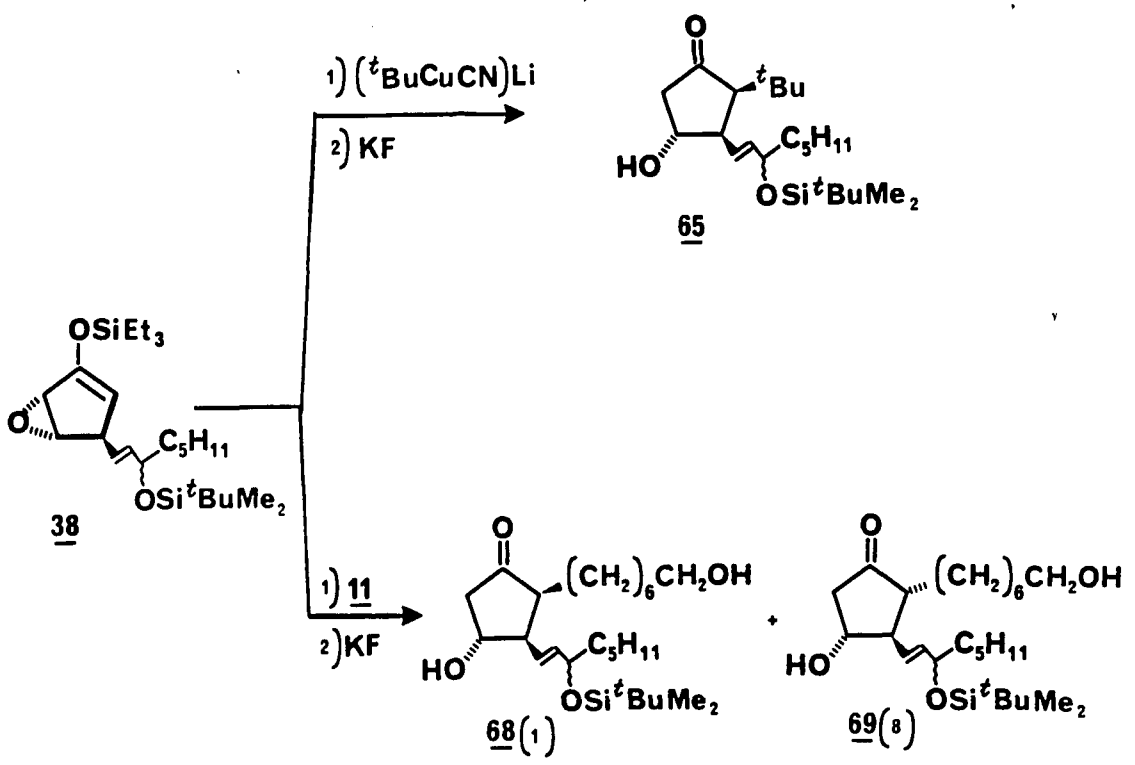
11

Reagents: a) MCPBA, CH_2Cl_2, 80%; b) TMSCl, NaI, CH_3CN; c) $BH_3 \cdot THF$; d) hexamethyldisilazene, TMSCl, diethyl ether (66% overall from ω lactone); e) tert-butyllithium, diethyl ether, -78°C; f) CuCN, diethyl ether, -40°C.



These anomalous results indicated the necessity of examining this sequence more in depth. Thus, treatment of epoxy enol ether 38 with tert-butylcyanocuprate, followed by fluoride induced hydrolysis, gave exclusively cis-2,3-disubstituted ketol 65, while a mixture of cis and trans cyclopentanones 68 and 69 (predominantly trans) was obtained when 38 were treated with cyanocuprate 11, derived from 1-lithio-7-trimethylsilyloxyheptane.

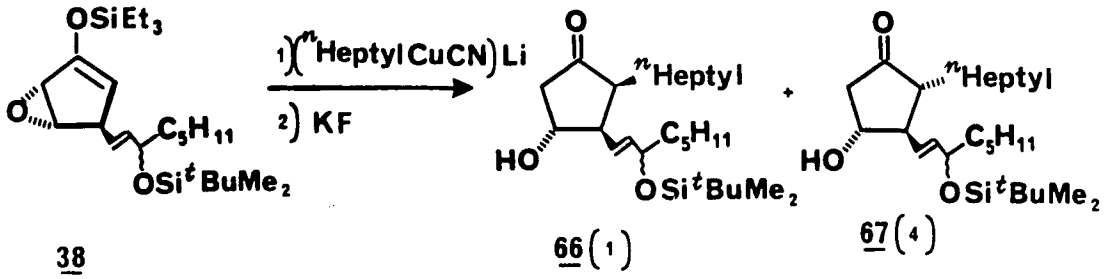
The only apparent difference between these two reactions was considered to be the origin of the alkyllithium employed as precursor to the cyanocuprate. Commercially available tert-butyllithium is salt-free. On the other hand, 1-lithio-7-trimethylsilyloxyheptane was generated by metal-halogen exchange in ether at -78°C. When the corresponding cyanocuprate 11 was formed, one equivalent of lithium iodide was present, due to its relatively high solubility in ether, even at -78°C. The presence of this salt in the reaction medium appeared to be the only difference



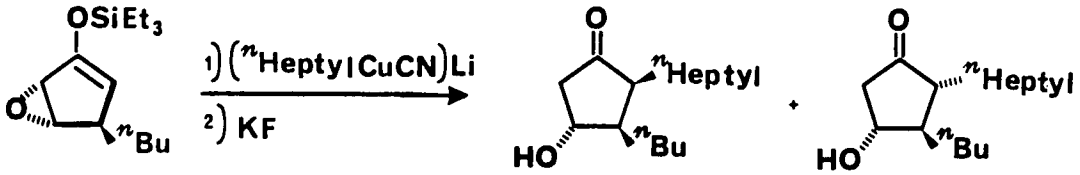
between these reactions which could account for the anomalous results observed.

In order to test this hypothesis, n-heptyllithium was prepared by metal-halogen exchange from n-heptyl iodide and tert-butyllithium, and the corresponding cyanocuprate was formed. Treatment of epoxy enol ether 38 with n-heptylcyanocuprate, in the presence of lithium iodide and subsequent fluoride induced hydrolysis, produced a mixture of hydroxycyclopentanones 66 and 67, predominantly trans. Pure cis isomer 66 was submitted to the hydrolytic conditions employed (KF, pH 7 buffer, ethanol) for several days, and it was found that the ^{1}H-NMR spectrum of the crude

product showed no signs of either epimerization or dehydration to the corresponding cyclopentenone. Finally, treatment of epoxy enol ether 37 with n-heptylcyanocuprate, generated as above, and quenching of the reaction before completion (see Experimental), followed by fluoride induced hydrolysis, gave a predominantly cis mixture of β-hydroxyketones 61 and 62.



38 66(1) 67(4)



37 61(2) 62(1)

This capricious influence of the presence of salts in reactions of mixed cyanocuprates with α,β-unsaturated epoxides is unprecedented in our laboratories. The fact that when the addition of n-heptylcyanocuprate onto epoxy

enol ether 37 was quenched before completion a predominantly cis mixture of ketols was obtained (Table IV, Entry 2) strongly suggests that the cyanocuprate addition, even in the presence of lithium iodide, proceeds via an overall 1,4-trans opening of the allylic epoxide, followed by epimerization, presumably by the excess cuprate reagent. Lithium iodide may be responsible for reducing the solubility of the cyanocuprate, making higher temperatures and longer reaction times necessary to bring the reaction to completion, thus facilitating epimerization by the excess cuprate. When salt-free conditions were employed (Entries 1 and 4), the reaction proceeded in good yields and was completely regio- and stereospecific, even in situations very sterically demanding. The preparation of β-hydroxycyclopentanone 65 with its 1,2-cis arrangement of a tert-butyl group and the bulky prostaglandin β chain constitutes, in our opinion, a remarkable achievement.

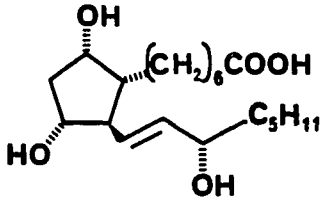
CHAPTER II

TOTAL SYNTHESIS OF PROSTAGLANDINS VIA SEQUENTIAL CYANOCUPRATE ADDITIONS

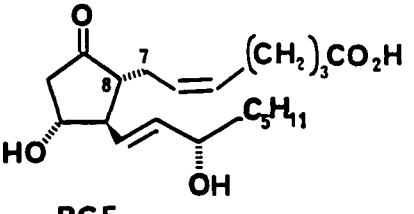
1. Introduction.

The prostaglandins[27-33] are a group of hydroxylated fatty acids characterized by a highly potent and diverse spectrum of biological activities. They have been detected in virtually all tissues investigated and they appear to be biosynthesized on demand, which suggests their role could be that of a tissue hormone. Once formed, prostaglandins are rapidly inactivated by enzymatic reactions; this property, and their wide spectrum of action, have limited their medicinal usefulness and encouraged synthetic chemists to explore synthetic routes to find more selective and stable derivatives. Currently, some prostaglandins are used as abortifacients and in treating certain congenital heart abnormalities while many more are being investigated for other actions.[26]

There are two major problems encountered in the synthesis of prostaglandins: stereochemical control, and sensitivity of the functional groups present in the molecule. Natural prostaglandins present a maximum number of five asymmetric centers, one of them located in a conformationally mobile side-chain, and at a considerable distance from the ring. This represents a challenge to the synthetic chemist in the control of stereochemistry. Prostaglandins contain at least one double bond which renders them susceptible to air oxidation. The E-type prostaglandins, key to the production of all other types (Scheme 5), contain an extremely labile β-hydroxycyclopentanone functionality, sensitive to both acids and bases.

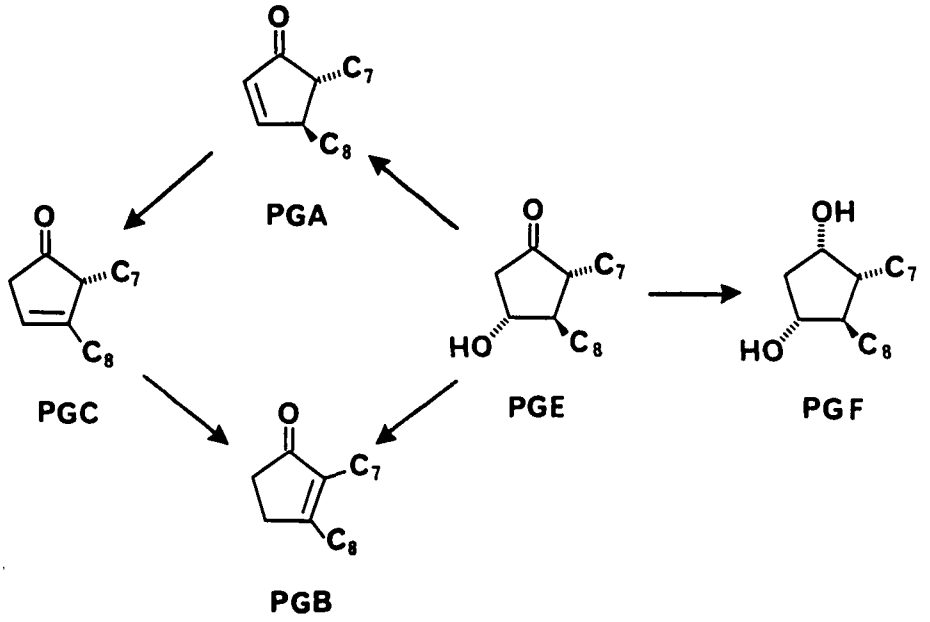


$PGF_{1\alpha}$



PGE_2

Scheme 5



Many of the synthetic strategies employed for prostaglandins have been thoroughly discussed in excellent reviews.[34] However, the search for shorter, more convergent syntheses of optically active prostaglandins still continues. Three synthetic schemes that will put our own research into perspective will be presented here.

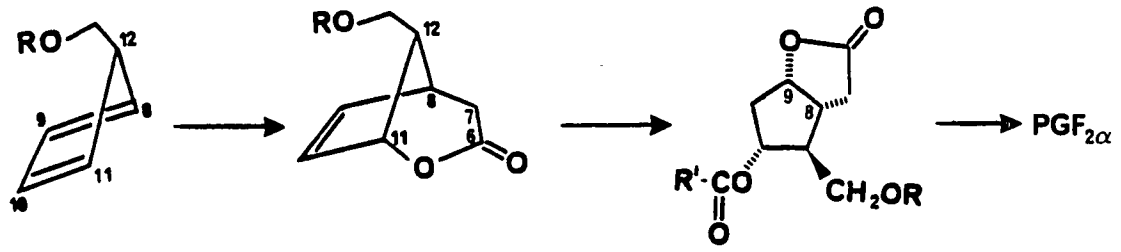
One of the classic syntheses of prostaglandins is one of E. J. Corey's which utilizes a bicyclo[2.2.1]heptane intermediate.[35] A brief outline of this approach is shown in Scheme 6. The synthesis is quite lengthy but each step proceeds in good yields. The main features of Corey's synthesis are:

(1) excellent stereochemical control;

(2) optical resolution at an early stage and

(3) large-scale reactions.

Scheme 6

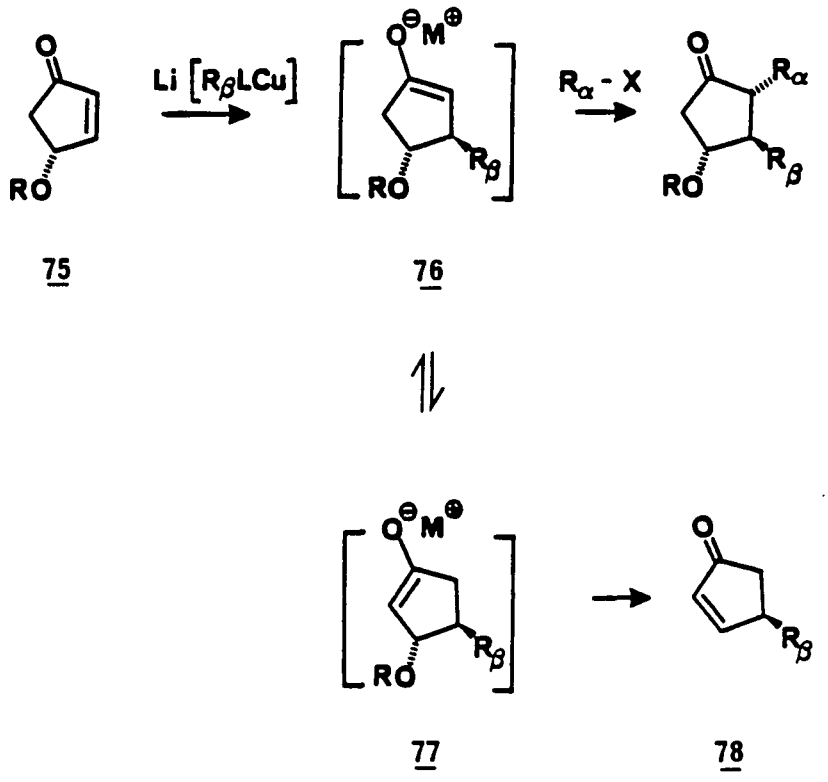


72 73 74

Lactone 74, commonly referred to as the "Corey lactone," can be efficiently converted into $PGF_{2\alpha}$ via modified Wittig reactions. The synthesis of intermediates with that general structure is now considered a formal total synthesis of prostaglandins.

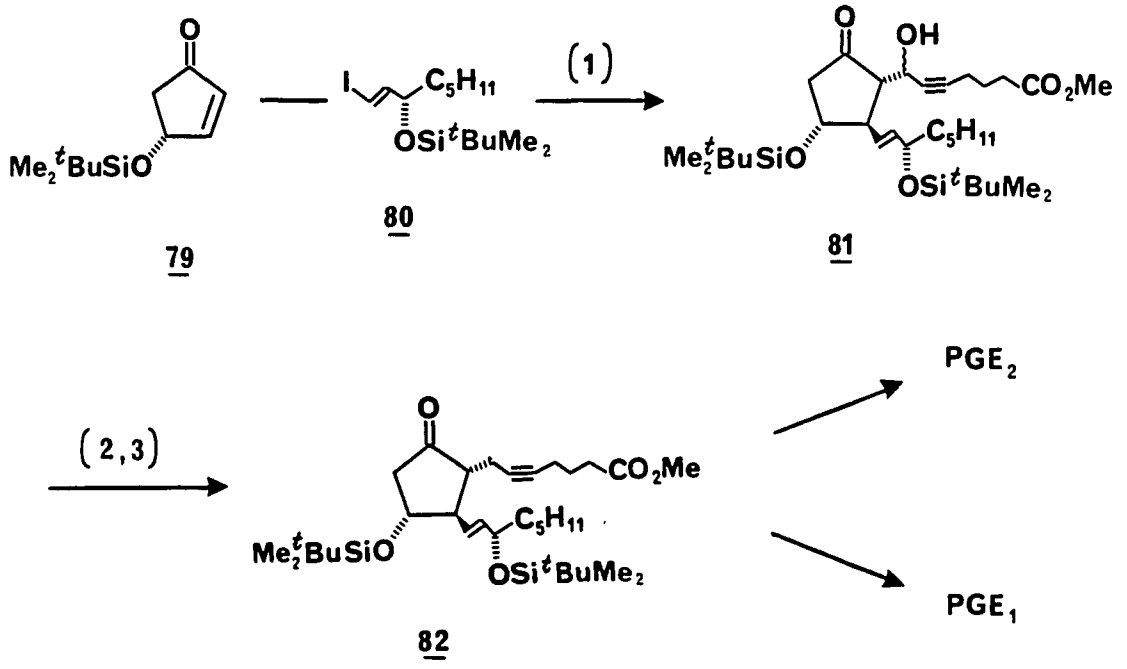
Another general approach to prostaglandins involves the conjugate addition of the β-chain to a protected 4-hydroxycyclopent-2-enone, followed by trapping of the corresponding enolate with a fully functionalized α-chain or an appropriate synthon. The Michael addition is known to proceed trans to the 11-hydroxyl group, and the alkylation should give the thermodynamically more stable all-trans orientation around the ring. In practice, the slow rate of enolate trapping leads to equilibration of enolates and subsequent elimination to give cyclopentenone 78.[36] The nature of the enolate and the choice of a suitable electrophile are crucial for the success of this approach.[37]

Scheme 7



One of the most recent adaptations of the conjugate addition approach is Noyori's general synthesis of primary prostaglandins[38] (Figure 6). Optically active enone 79 was reacted with one equivalent of the organocuprate derived from optically active vinyl iodide 80.[39] Trapping of the resulting enolate with one equivalent of 6-methoxycarbonyl-2-hexynal at -78°C resulted in formation of aldol 81. Deoxygenation was achieved by treatment of the corresponding

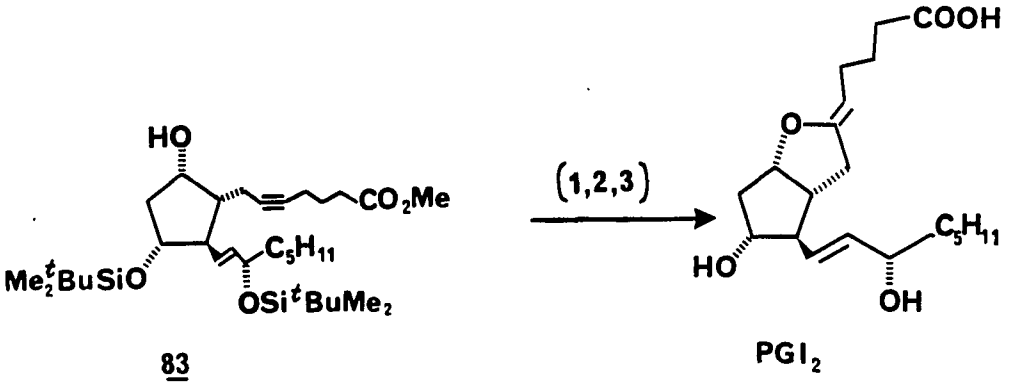
Figure 6. Noyori's Approach to Prostaglandins.



Reagents: (1) 1.0 eq. vinyl iodide, 2.0 eq. tert-BuLi, 1.0 eq. CuI, 2.6 eq. n-Bu_3P/Et_2O, -78°C, 1 h; then 1.0 eq. HOC-C≡C-$(CH_2)_3CO_2Me$, -78°C, 30 min. (2) PhC(S)Cl, DMAP, CH_2Cl_2, 18°C, 3 h. (3) n-Bu_3SnH, di-tert-butyl peroxide, 50°C, 35 min.

thiobenzoate with tributyltin hydride to give a 5,6-dehydroprostaglandin E_2 derivative, 82, which can be transformed to a variety of chiral primary prostaglandins in a stereoselective manner.[40] Shortly after this work was reported, the methodology was expanded and a very short synthesis of prostacyclin (PGI_2), via intramolecular

Figure 7. Noyori's Synthesis of PGI_2.



Reagents: (1) mercury(II) trifluoroacetate and triethyl amine (1.1 eq. each), THF, -78°C, 1h; then 5 eq. $NaBH_4$ in 1N methanolic NaOMe, -78°C, 1 h. (2) $(n\text{-Bu})_3N^+F^-$ (8 eq.), THF. (3) alkaline hydrolysis.

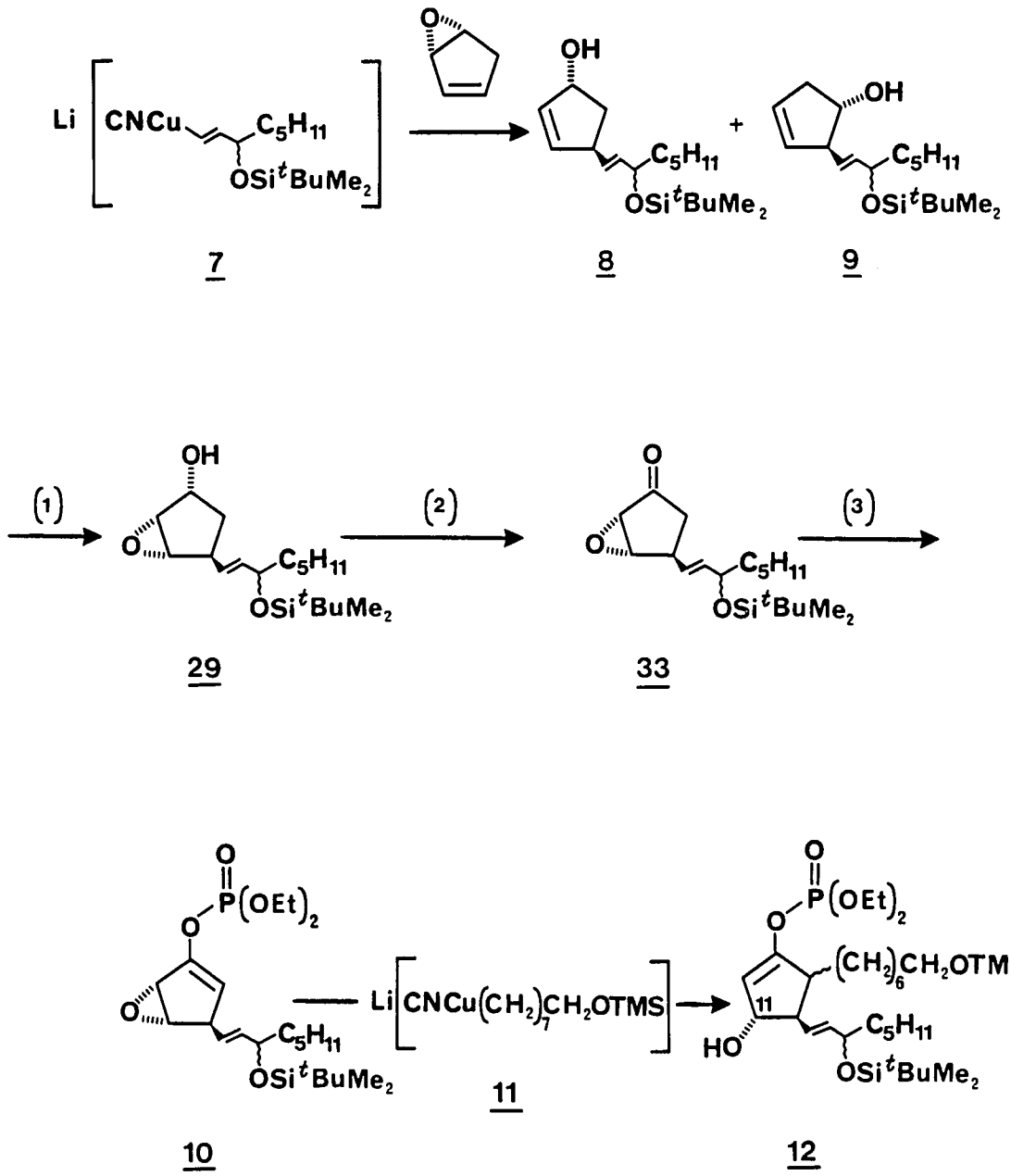
oxymercuration of acetylenic alcohol 83, was achieved.[41,42] The success of this synthesis relies heavily on the stereospecificity of the reductive demercuration of vinylic mercury compounds with sodium borohydride, which proceeds with retention of configuration.

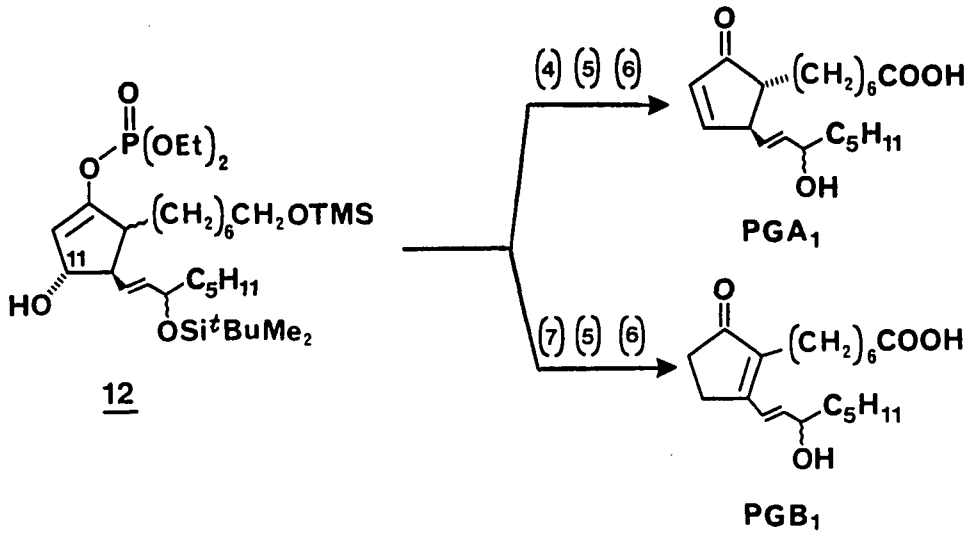
A number of successful syntheses have employed a 1,2-opening of a cyclopentane oxide or cyclopentadiene monoepoxide itself to introduce the prostaglandin β-chain.[43] The major drawback of this strategy has been the lack of regioselectivity of the epoxide opening. The regioselective

1,4-opening of cyclopentadiene monoepoxide had not been previously explored. The application of the methodology discussed earlier in this manuscript to the synthesis of prostaglandins was first reported by Marino and Kelly[14] in 1981 and is outlined in Figure 8. The reaction of cyanocuprate 7 with freshly distilled cyclopentadiene monoepoxide at -78°C gave a 4:1 mixture of the trans-1,4 and trans-1,2 adducts (8 and 9) in 80% yield. These regioisomers were easily separated by column chromatography or preparative HPLC. Cis epoxidation of the 1,4-adduct and subsequent oxidation with Collins reagent afforded the key epoxy-ketone 33.

The introduction of the top chain was performed by using a second conjugate addition of cyanocuprate 11 onto epoxy enol phosphate 10, which gave exclusively the 1,4-regioisomer 12. The conversion of enol phosphate 12 into PGA_1 and PGB_1 was effected by two different sets of basic conditions. A number of additional attempts were made in order to effect a milder hydrolysis of enol phosphate 12 with retention of the 11-hydroxyl group (prostaglandin numbering), but these were unsuccessful.

Figure 8. Marino/Kelly Synthesis of PGA_1 and PGB_1.



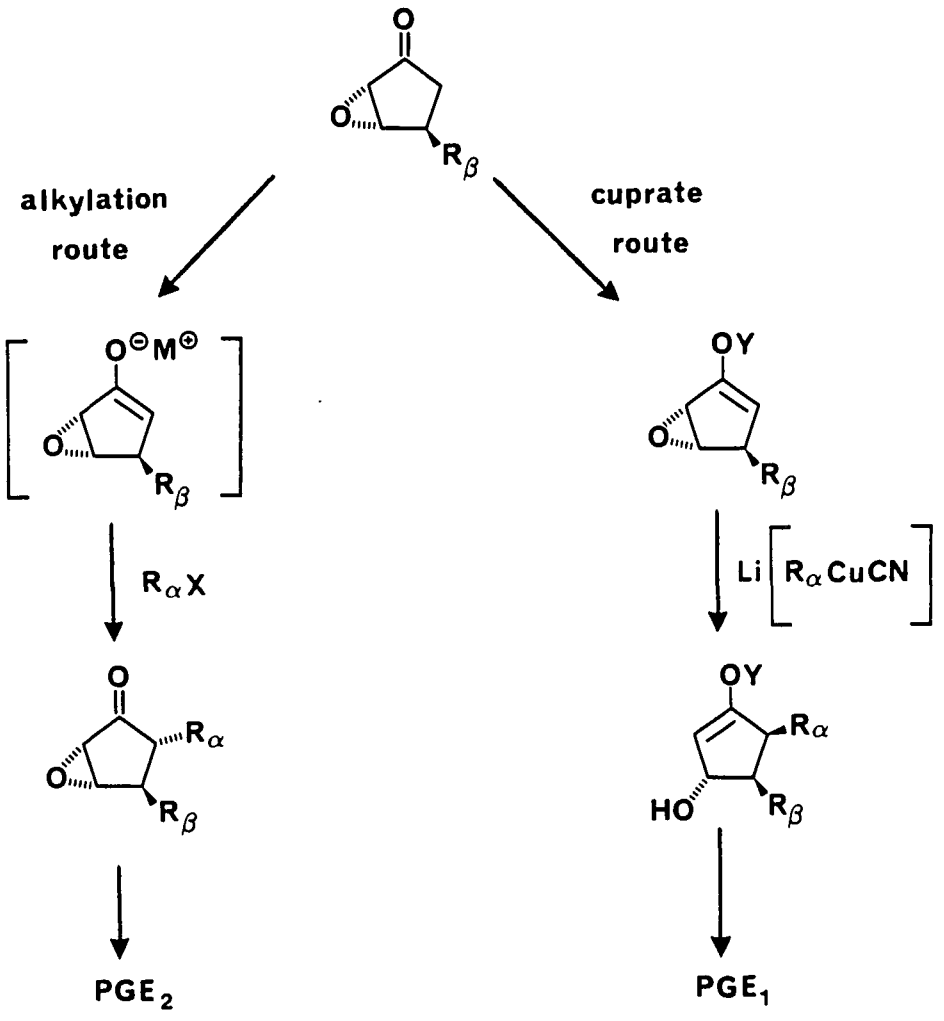


Reagents: (1) tert-BuOOH, $VO(acac)_2$,PhH. (2) CrO_3·pyridine/CH_2Cl_2. (3) LDA/THF, -78°C, then $(EtO)_2P(O)Cl$. (4) NaH,BzBr/THF. (5) Jones reagent. (6) aq. HF/CH_3CN. (7) NaOMe/MeOH.

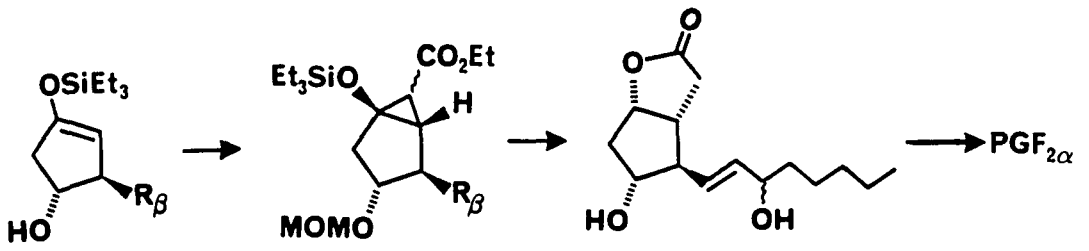
At the inception of this thesis, epoxy ketone 33 was envisioned as a general precursor to prostanoids in two different routes (Scheme 8). In an alkylation reaction, a reactive halide could be used to introduce the α-chain. The cuprate route, alternatively, would be best suited for the introduction of saturated α-chains.

A great deal of effort was devoted in our laboratories to develop the alkylation route.[44] The results were not satisfactory, and therefore a different approach was sought.

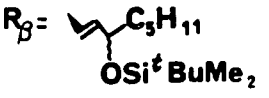
Scheme 8



Eventually, a synthesis of prostaglandins via siloxycyclopropanes was developed within our group[44,45] by Laborde. A brief outline of that approach is shown below.



84 85 86



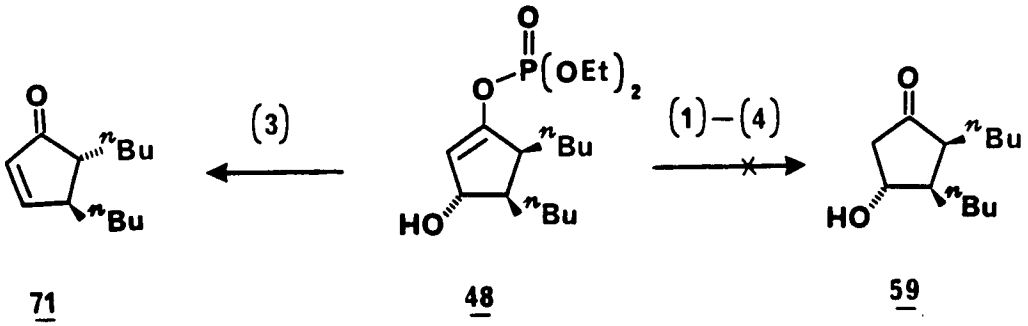
The second major route outlined in Scheme 8, namely, the sequential cuprate route, was one of the major objectives of this thesis. The following sections of this chapter will present the results of this endeavor.

2. Model Studies.

It was initially considered that additional studies on the mild hydrolysis of hydroxy enol phosphates such as 12 were necessary. It was anticipated that a model system would be extremely helpful in order to accomplish that goal. The reasons for this were twofold: a simpler spectral profile would allow for an easier interpretation of experimental results, and secondly, the greater ease of preparation of a dibutyl model would facilitate studies on

the hydrolysis of the enol phosphate functionality, while maintaining most of its key structural features. Hydroxy enol phosphate 48 was then synthesized as described in the previous chapter and was subjected to various conditions in order to effect a mild hydrolysis to the corresponding β-hydroxycyclopentanone 59. A summary of these hydrolysis attempts is given in Scheme 9.

Scheme 9



Reagents: (1) (n-Bu)$_4$NF/THF, i-PrOH, RT, 1 day. (2) KF/MeOH, RT, 96 h. (3) tert-BuLi (1 eq.), then MeLi (1 eq.)/THF. (4) $LiAlH_4$/THF.

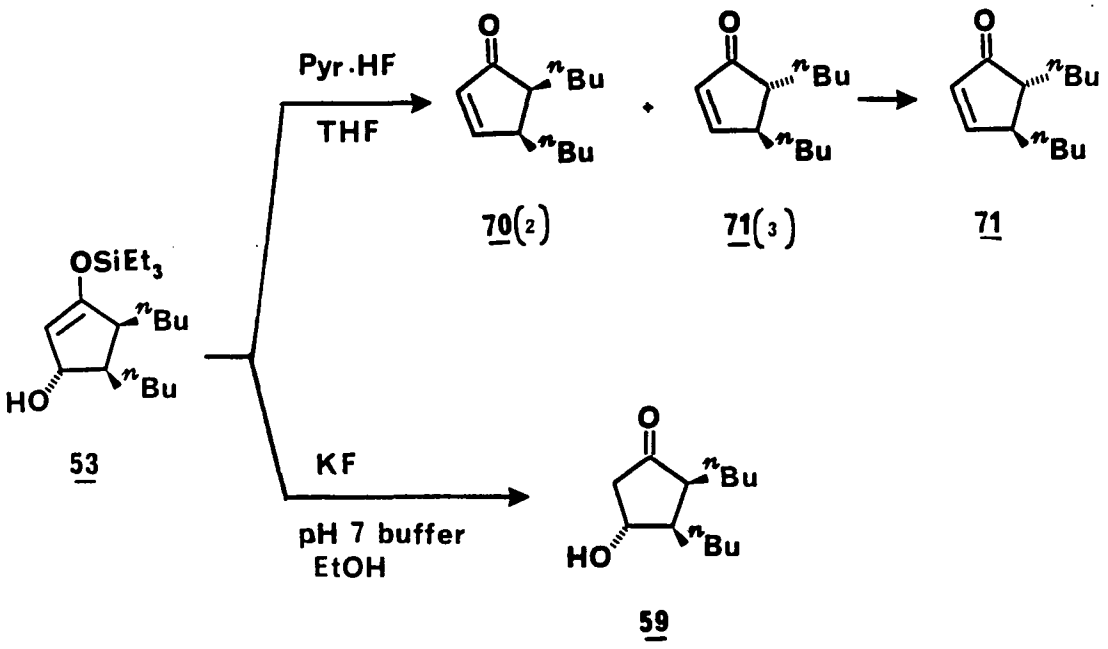
Fluoride catalyzed transesterification of phosphate esters[46] was envisioned to be an attractive possibility since it is reported to occur under very mild, neutral conditions. Unfortunately, when this reaction was attempted on enol phosphate 48, it was found that short reaction times led to recovery of starting material. If the reaction was

allowed to continue for longer periods of time or the temperature was increased, complete decomposition was observed. The reaction of enol phosphate 48 with lithium aluminum hydride failed to effect the desired transformation as well. Finally, deprotonation of hydroxy enol phosphate 48 with tert-butyllithium, followed by addition of methyllithium, gave, after standard workup, a 50% yield of trans-4,5-di-n-butyl-2-cyclopentenone, 71.

It became apparent that a different protecting group had to be employed. A trialkyl silyl group appeared to be a good alternative since silyl enol ethers are cleaved under very mild conditions. After some initial studies (see Chapter I), enol ether 53 could be isolated and conditions to hydrolyze it were examined (Scheme 10).

Treatment of hydroxy enol ether 53 with a slight excess of pyridine polyhydrogen fluoride in THF at low temperature proceeded with concomitant dehydration and epimerization of the side chains. The mixture of cyclopentenones (predominantly trans) was transformed into exclusively the trans isomer 71 upon standing for a few days in the NMR tube. This transformation was presumably catalyzed by a trace of acid present in the deuterochloroform. Treatment of hydroxy enol ether 53 with methanolic potassium fluoride produced the desired β-hydroxy ketone 59 but it was accompanied by substantial amounts of cyclopentenones 70 and 71. The reaction of 53 with potassium fluoride in

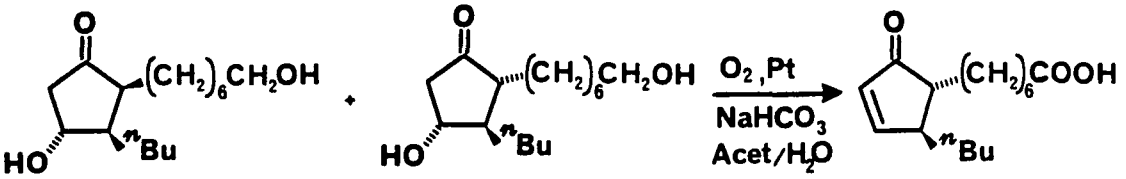
Scheme 10



pH 7 phosphate buffer with ethanol as cosolvent gave excellent yields of the labile β-hydroxyketone 59 without any contamination by enones 70 and 71, as determined from the 360 MHz ^{1}H-NMR spectra of crude reaction mixtures.

The introduction of the prostaglandin α-chain was then examined and epimeric β-hydroxyketones 63 and 64 were prepared as described in Chapter I. These isomers could not be separated by chromatography. Therefore, the mixture was employed as a model system for the next step, namely, the selective oxidation of the primary alcohol in the presence of the sensitive β-hydroxyketone functionality. Selective catalytic oxidation was envisioned to be the best choice

since it is reported to be extremely sensitive to steric hindrance,[47] and furthermore, it had been employed for the synthesis of prostanoids of the F type.[43d] These oxidations are generally performed in the presence of variable amounts of sodium bicarbonate. However, basic conditions were not appropriate for this particular reaction. Selective oxidation of the primary alcohol occurred with concomitant base catalyzed dehydration to give a good yield of enone 87. A few additional attempts, such as replacing sodium bicarbonate with potassium acetate, or utilizing a



63(1) 64(7) 87

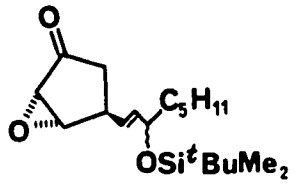
mixture of pH 7 phosphate buffer and acetone as solvent, were not successful. At this point, the supply of hydroxyketone 64 was exhausted. It was decided, therefore, to proceed with these studies on the system possessing the prostaglandin β-chain.

These model studies had solved one of the major problems in our approach to prostaglandins, namely, the preparation of β-hydroxyketones from hydroxy enol ethers such

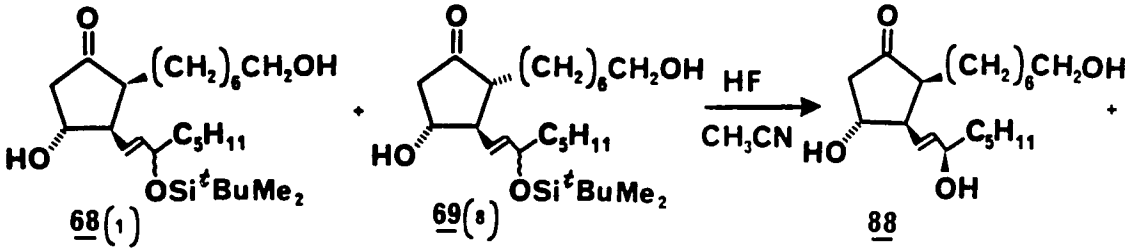
as 53. This would allow for the completion of the synthesis of a PGE type prostanoid which was one of our major objectives.

3. Synthesis of Prostaglandins.

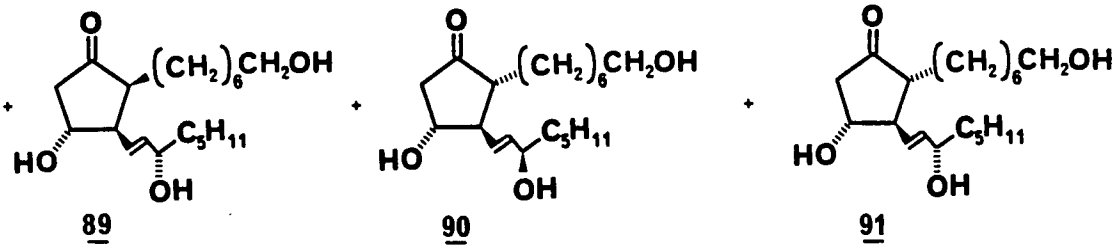
Hydroxyketone 69 was easily prepared from epoxy cyclopentanone 33 by formation of the triethylsilyl enol ether, cuprate addition of the α chain and fluoride induced hydrolysis, as described in Chapter I; however, it was contaminated by small amounts of its cis epimer 68. Both were present as a mixture of diastereomers at C15 (prostaglandin numbering) and separation of these four isomers by column chromatography was not possible at this stage. Removal of the tert-butyldimethylsilyl group with aqueous hydrofluoric acid in acetonitrile[48] gave a good yield of the bronchodilator, 2-decarboxy-2-hydroxymethyl-PGE_1, 91, accompanied by the corresponding isomers (88-90). All of these isomers could be easily separated by column chromatography and were fully characterized. The spectral characteristics of our synthetic (±)-2-decarboxy-2-hydroxymethyl-PGE_1, 91 (Figure 9), were identical to those of an authentic sample.[49] Catalytic oxidation of triol 91, without any added base, proceeded in good yield. However, all conditions examined proceeded with concomitant oxidation



33



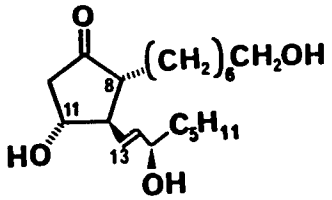
68(1) + 69(8) → 88



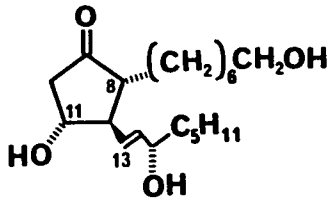
89 + 90 + 91

of the 15-hydroxyl group to give exclusively 15-dehydroprostaglandin E_1, 92. Conditions to selectively oxidize the primary alcohol in the presence of the unprotected allylic alcohol, thus leading to PGE_1, could not be found.

Figure 9. ^{1}H-NMR Data for Compounds 90 and 91.

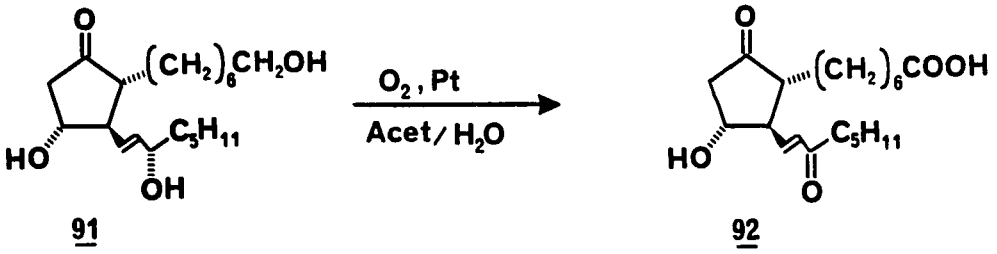


90



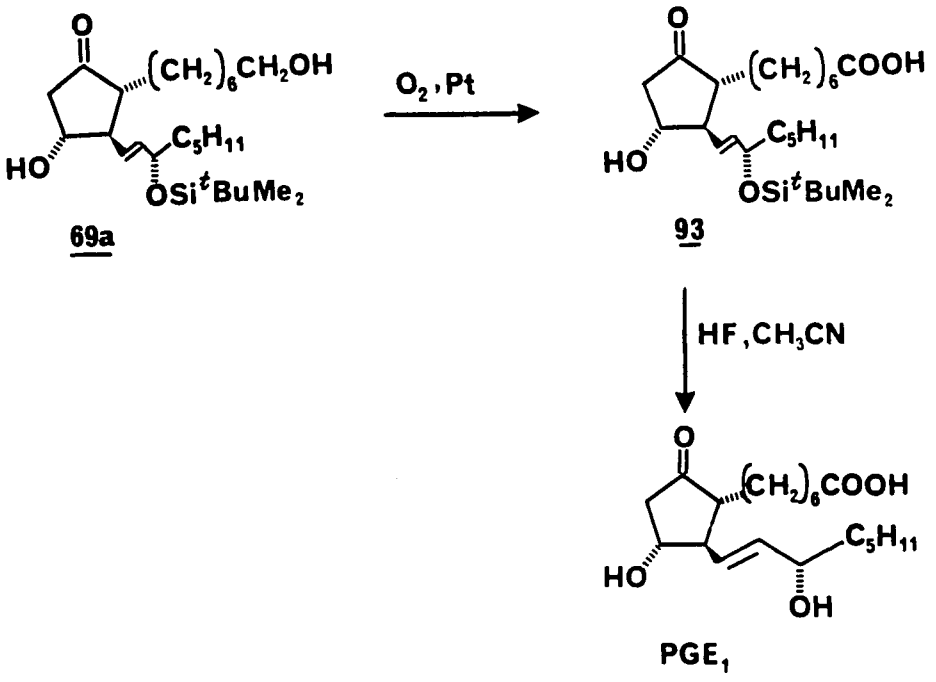
91

^{1}H-NMR				
2.006	(dist dt, J=12.0, 6.0 Hz)	H_8	1.965	(dist dt, J=12.0, 6.0 Hz)
2.212	(dd, J=18.4, 9.6 Hz)	$H_{10\alpha}$	2.193	(dd, J=18.4, 9.9 Hz)
2.363	(dt, J=12.0, 8.5 Hz)	H_{12}	2.321	(dt, J=12.0, 8.7 Hz)
2.723	(ddd, J=18.4, 7.4, 0.8 Hz)	$H_{10\beta}$	2.700	(ddd, J=18.4, 7.4, 0.8 Hz)
4.055	(dist q, J=8.2 Hz)	H_{11}	3.965-4.032 (m)	
4.113-4.164 (m)		H_{15}	4.038-4.089 (m)	
5.583	(dd, J=15.4, 8.2 Hz)	H_{13}	5.503	(dd, J=15.2, 8.7 Hz)
5.727	(dd, J=15.4, 5.9 Hz)	H_{14}	5.627	(dd, J=15.2, 7.4 Hz).

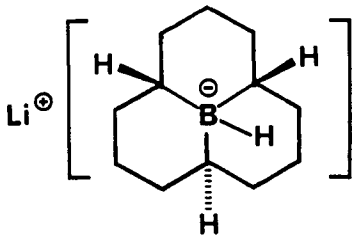


91 92

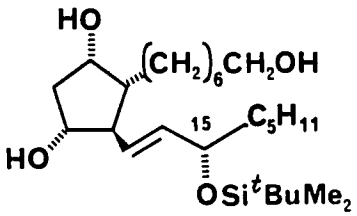
It was then realized that in order to complete the synthesis of PGE_1, it would be necessary to separate isomers at the stage of hydroxyketones 68 and 69. This was achieved by HPLC, although only small amounts of diastereomerically pure trans isomer 69a could be obtained, since the separation was very difficult. The synthesis of isomerically pure PGE_1 was completed by selective oxidation to the corresponding carboxylic acid 93 with oxygen and platinum, followed by removal of the tert-butyldimethylsilyl group with aqueous hydrofluoric acid in acetonitrile.[48] To our knowledge, this is the first case in which a PGE system, with its labile β-hydroxyketone functionality, has been selectively oxidized at the primary hydroxyl.



Having completed the total synthesis of PGE_1, work towards $PGF_{1\alpha}$ was started. The first step was envisioned to be the reduction of the ketone functionality present in 69a. Initial studies with the cyclic trialkyl borohydride reagent 94[50] (lithium cis,cis,trans-perhydro-9β-borophenalyl hydride PBPH) proceeded cleanly, as determined by TLC analysis of the crude reaction mixture. Oxidative work-up and column chromatography afforded impure triol 95, presumably contaminated with the cyclic triol derived from the borohydride reagent. It was not possible to purify triol 95 by conventional methods. Therefore, other reducing agents were examined. The first reagent employed was KS-Selectride[51] (potassium trisiamylborohydride), which, due



94

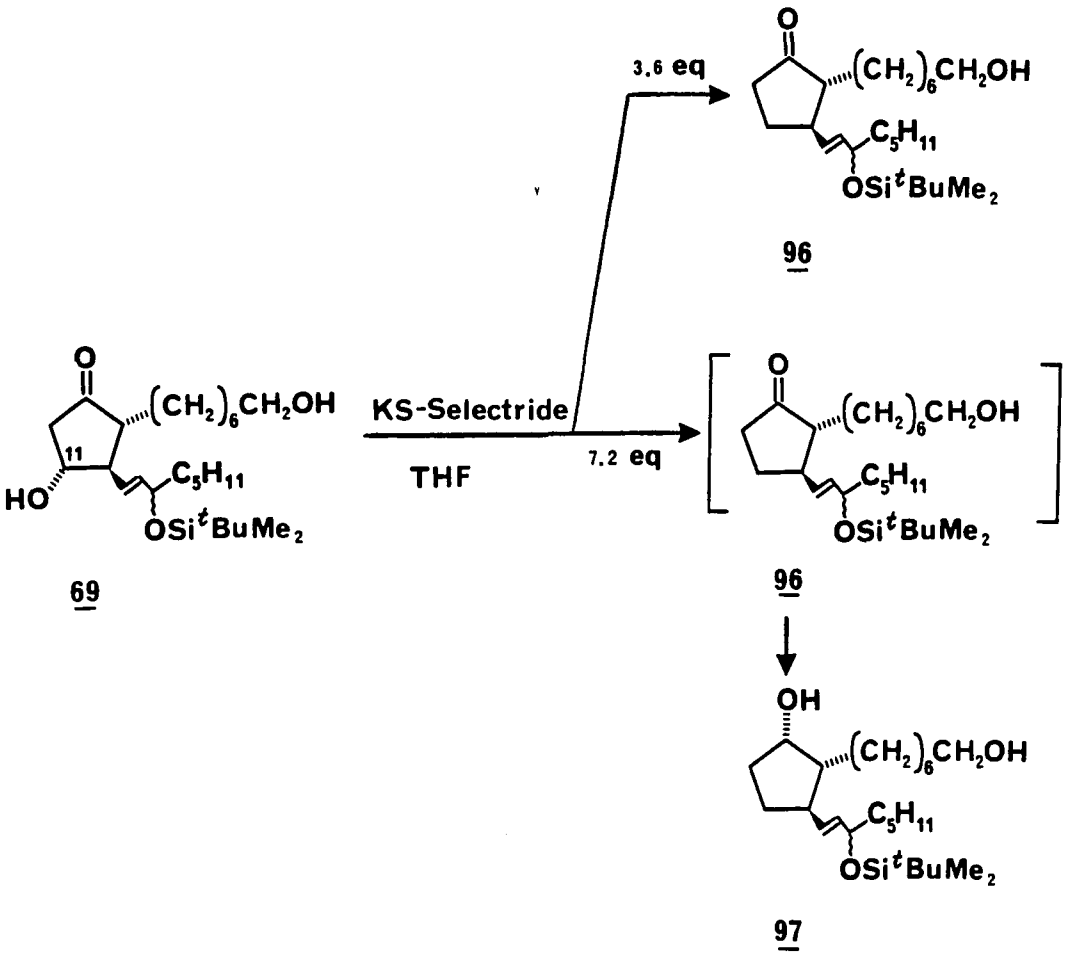


95

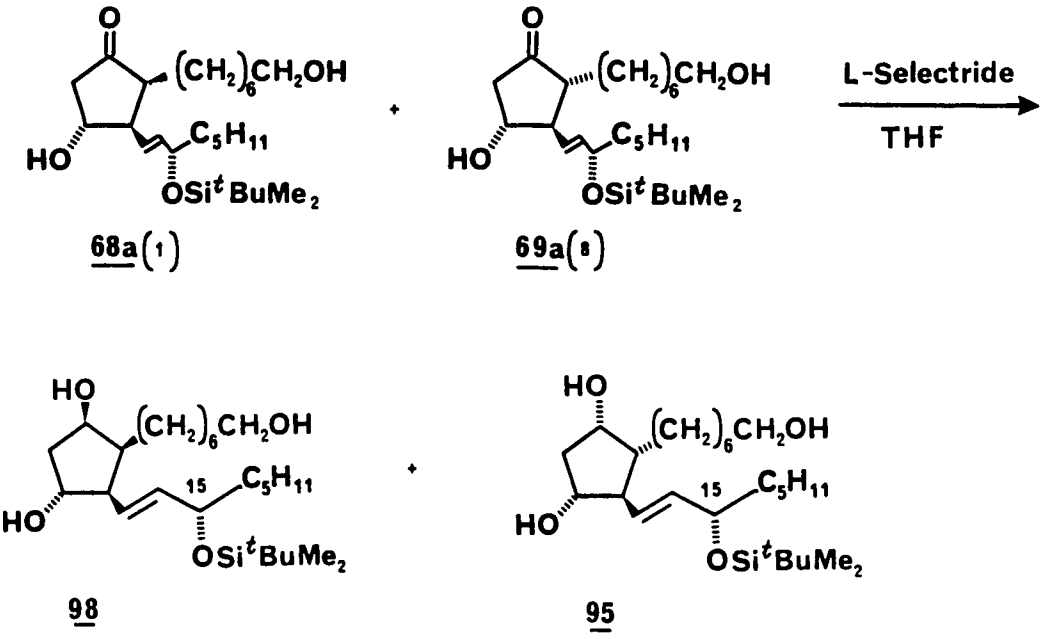
to its basicity, promoted elimination of the 11-hydroxyl group to the corresponding cyclopentenone. Conjugate reduction of that enone yielded cyclopentanone 96. When a larger excess of the reducing agent was employed, 96 was initially formed, as determined by TLC analysis of the reaction mixture. This was subsequently reduced to cyclopentanol 97 upon stirring at room temperature overnight (Scheme 11).

The second reducing agent employed was L-Selectride[52] (lithium tri-sec-butylborohydride), which proved to be the most convenient in terms of stereoselectivity and simplicity of workup. From a practical point of view, the separation of diastereomerically pure 69a was very cumbersome. Therefore, the reaction was attempted on a mixture of 68a and 69a, homogeneous at C15 (this was achieved in a straightforward manner by purification via HPLC or by careful column chromatography and HPLC analysis of the

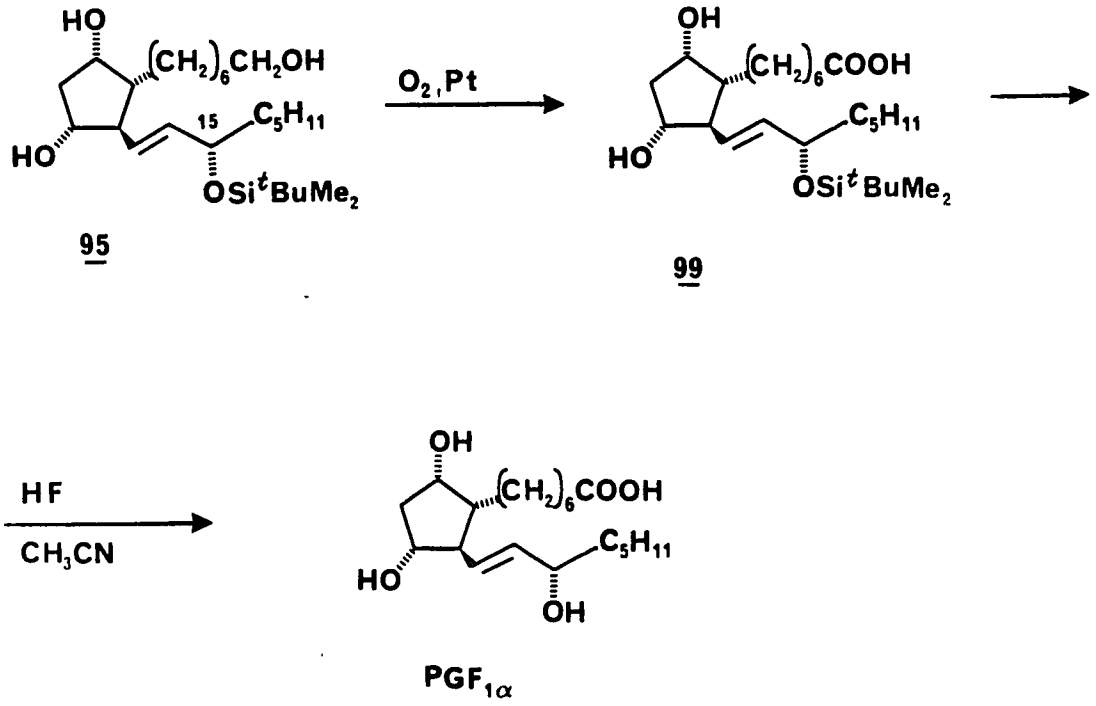
Scheme 11



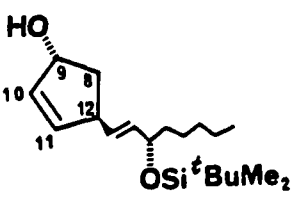
fractions). It was found that isomeric triols 95 and 98 could be easily separated by a simple column chromatography and, therefore, the desired triol 95 was subsequently prepared in this manner.



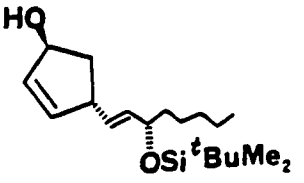
Finally, the synthesis of $PGF_{1\alpha}$ was completed by selective oxidation of the primary alcohol to the corresponding carboxylic acid 99 and removal of the tert-butyldimethylsilyl group with aqueous hydrofluoric acid in acetonitrile.[48]



The successful completion of a short synthesis of PGE_1 from the readily available cyclopentadiene monoepoxide amply demonstrates the synthetic utility of the strategy involving the sequential addition of cyanocuprates onto cyclopentenyl epoxides. This sequence has been carried forward in a racemic manner. It should be mentioned that its chiral version, although not effected, does not seem too problematic. Indeed, the use of an optically active β-chain precursor[39] should give adducts 8a and 8b as the major products of the cuprate conjugate addition. Separation of these diastereomers[53] should give optically active 8a,



8a

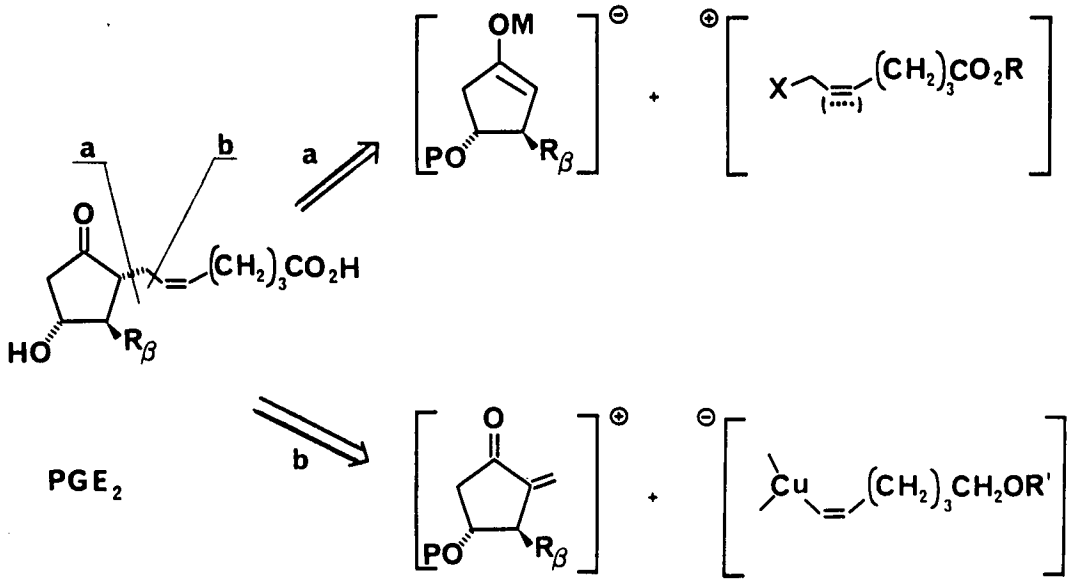


8b

which would ultimately lead to optically active prostanoids without any further resolution.

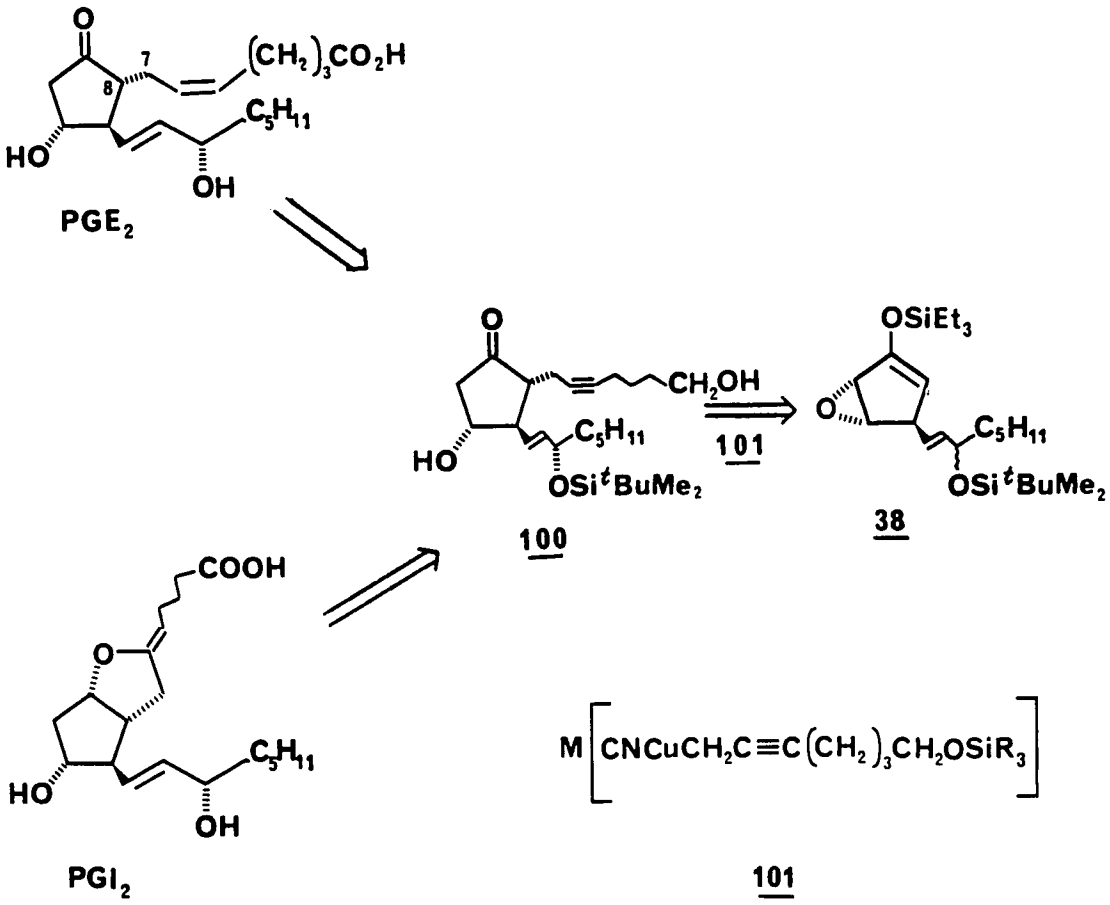
4. Synthetic Studies Towards PGE_2.

The successful completion of the short, convergent synthesis of PGE_1 described in the previous section prompted us to examine the extension of this methodology to prostaglandins in which the α-chain is unsaturated. Previous approaches to these prostaglandins involved the utilization of the cyclopentyl moiety as nucleophile and a suitable α-chain derivative as electrophile.[34,38] In other cases,[37] the cyclopentyl moiety was elaborated to an α-methylen-cyclopentanone, and the α-chain was introduced by a conjugate addition of the corresponding syn vinylic cuprate. The application of the sequential cyanocuprate methodology to the synthesis of PGE_2 would involve the unprecedented introduction of the entire α-chain in a nucleophilic fashion.



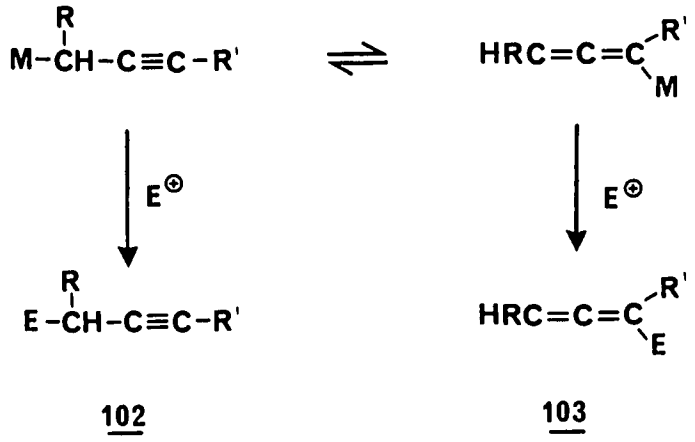
Two possibilities were initially considered: the first required the utilization of propargylic organometallics; the second involved allylic organometallics. Of these routes, the former appeared more versatile since it would not only allow for the synthesis of PGE_2 but would also constitute a promising entry to prostacyclin. Our retrosynthetic analysis for this route is presented in Scheme 12. It was envisioned that conjugate addition of propargyl cyanocuprate 101 onto silyl enol ether 38 could result in 5,6-dehydro PGE_2 derivative 100, which in turn could be transformed into PGE_2 by selective catalytic hydrogenation. Alternatively, selective reduction of the

Scheme 12



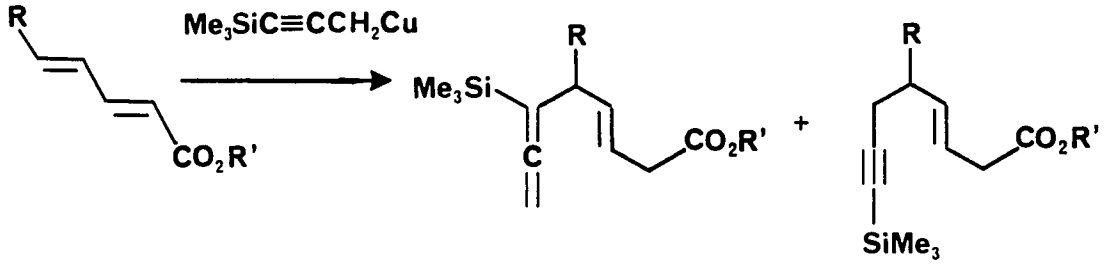
carbonyl group[52] and transition metal assisted cyclization[41] should, after manipulation of functional groups, give an entry to prostacyclin (PGI_2).

Preliminary examination of the propargyl organometallic literature[54] pointed out the capricious behavior of these species. In most cases, mixtures of propargylic products, 102, and allenic ones, 103, are obtained. Its relative ratio is highly dependent on the nature of R',[55] the nature of the metal,[56] the nature of R,[57] etc. The search for new reagents of this type still continues.[58]



102 103

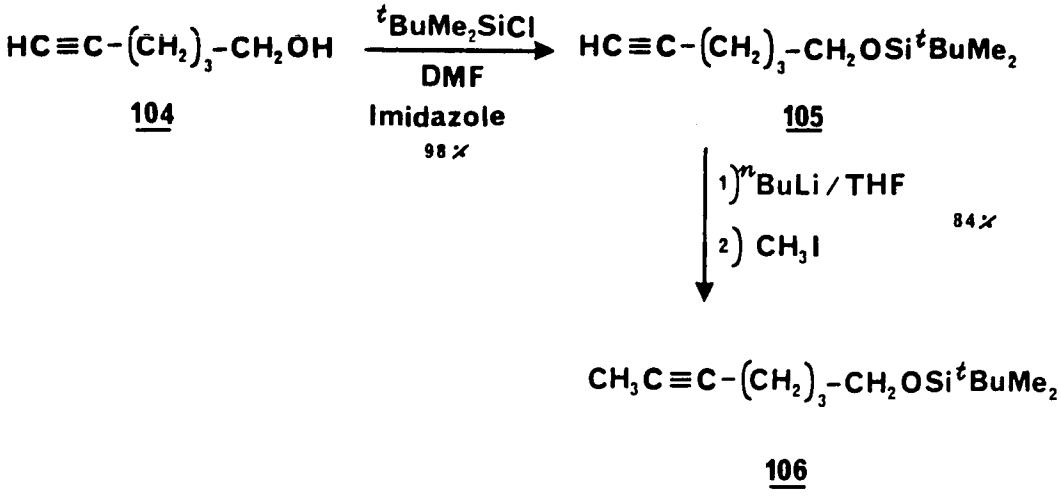
At the time this work was begun, there were few precedents of propargylic copper compounds effecting conjugate additions. One of them is presented below.[59] The allene: acetylene ratio was observed to be strikingly sensitive to the steric environment around the δ-carbon of the dienoate.



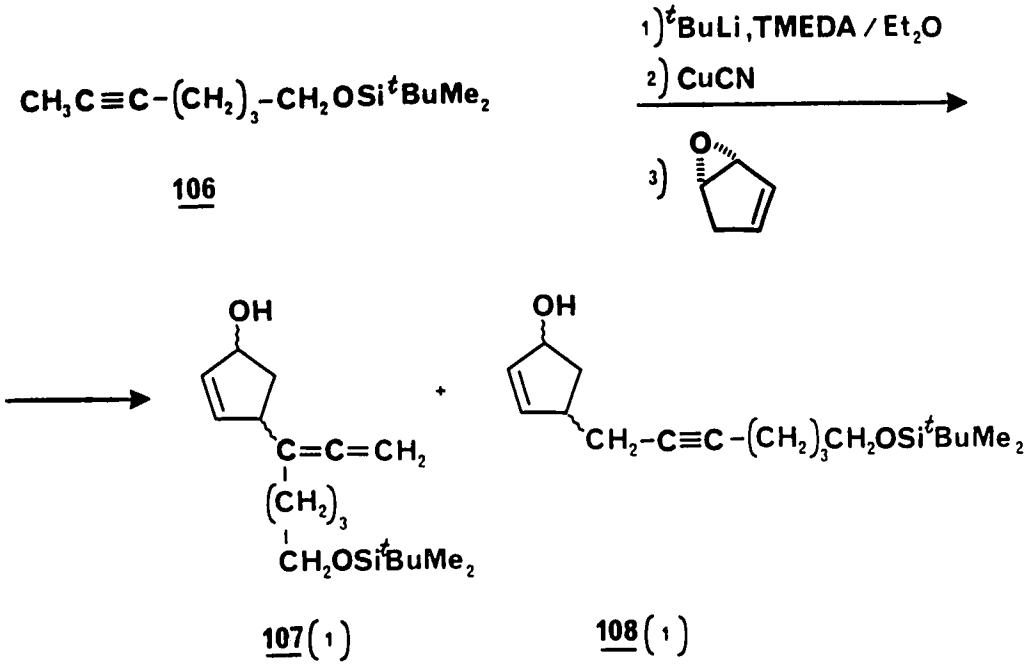
R=H (80%)	80	20
R=Me (70%)	18	82

Several approaches toward the generation of propargyl cyanocuprate 101 were examined. Propargyl lithium compounds are generally prepared by metalation of 2-alkynes with tert-butyllithium in ether in the presence of TMEDA (tetramethylethylenediamine).[54a,60] The preparation of the corresponding starting material by standard transformations is shown in Scheme 13.

Scheme 13



The efficiency of the metalation was then tested, and analogous results to those reported by Zweifel[58b] were obtained. The corresponding cyanocuprate 101 was then formed by standard techniques and its reaction with cyclopentadiene monoepoxide was examined. Careful chromatography of the complex reaction mixture afforded a low yield of a 1:1 mixture of 107 and 108, which were tentatively assigned as

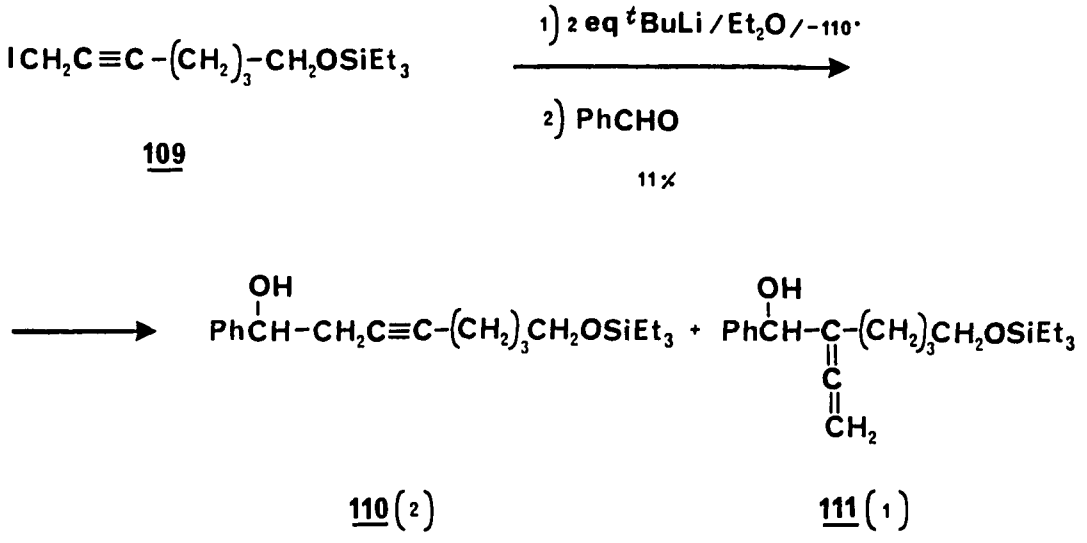


1,4-adducts. These isomers could not be separated nor could their stereochemistry be firmly established due to the high complexity of their 360 MHz ^{1}H-NMR spectrum.

It is well known that the outcome of reactions involving propargyl organometallics is extremely sensitive to the steric requirements of the substrate.[59b] Therefore, it was decided that the addition should be attempted on the prostanoid system 38, using the same conditions just developed, i.e., cuprate addition, immediately followed by fluoride induced hydrolysis. When this was performed, no desired β-hydroxyketone 100 could be detected. It was then thought that the presence of the strong complexing agent TMEDA in the reaction medium could be the cause of the failure of the reaction. A systematic examination of

different metalation conditions showed that the lithio derivative could be generated with tert-butyllithium in tetrahydrofuran. This was not completely satisfactory since it is well known that the reaction of cyanocuprates with epoxy enol ethers proceeds more regioselectively in ether than in tetrahydrofuran.[61] Nevertheless, the conjugate addition was attempted with identical results to those obtained in the presence of TMEDA.

It was then considered that a clean, effective method of generating cyanocuprate 101 in ether and without TMEDA was paramount for the success of our strategy. Propargylic iodide 109 was synthesized by standard procedures[62] and its metal-halogen exchange with tert-butyllithium in ether at different temperatures was studied. It was found that, even at low temperatures, the yields of anion were extremely low. The metal-halogen exchange was



109

110 (2)

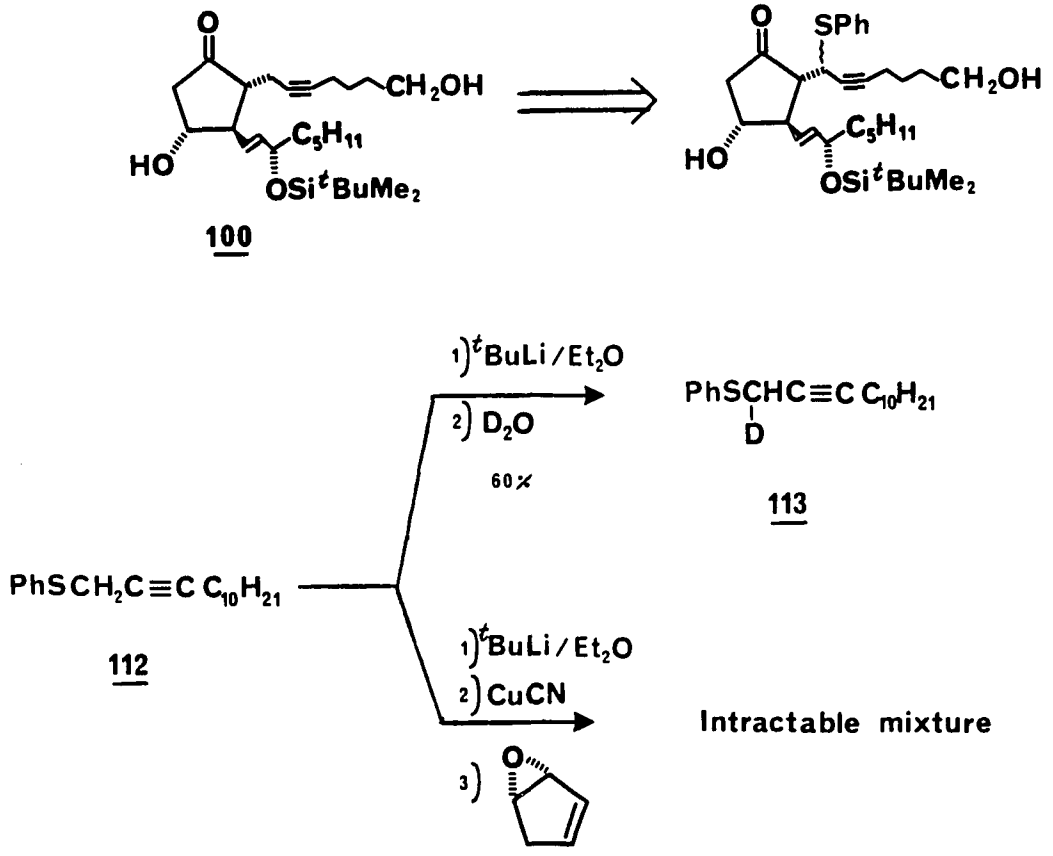
111 (1)

also tried with a propargylic bromide but without success. It is reasonable to believe that the cause of this failure is the high reactivity of the propargylic halide functionality towards nucleophilic displacement, even when hindered nucleophiles (such as tert-butyllithium) are employed. This hypothesis is supported by the fact that large amounts of non-polar materials were obtained in these trials.

Generation of cyanocuprate 101 (Scheme 12) from the corresponding Grignard reagent (M=MgBr) was also attempted, and its reaction with cyclopentadiene monoepoxide was effected. Unfortunately this led to an intractable mixture; therefore, this approach was not pursued.

Finally, activation of the propargylic position with a sulfide group was examined. It was expected that this would facilitate the metalation and furthermore alter the allene:alkyne ratio, in favor of the latter.[66] Additionally, it was considered that the presence of a sulfide group in the corresponding prostanoid would not be synthetically inefficient since no major problems were anticipated to achieve desulfurization. In order to test these hypotheses, phenylsulfide 112 was prepared by standard methods[64] and it was found that the formation of the anion was easily effected with tert-butyllithium in ether at -78°C (Scheme 14). The reaction of the corresponding cyanocuprate with cyclopentadiene monoepoxide was then

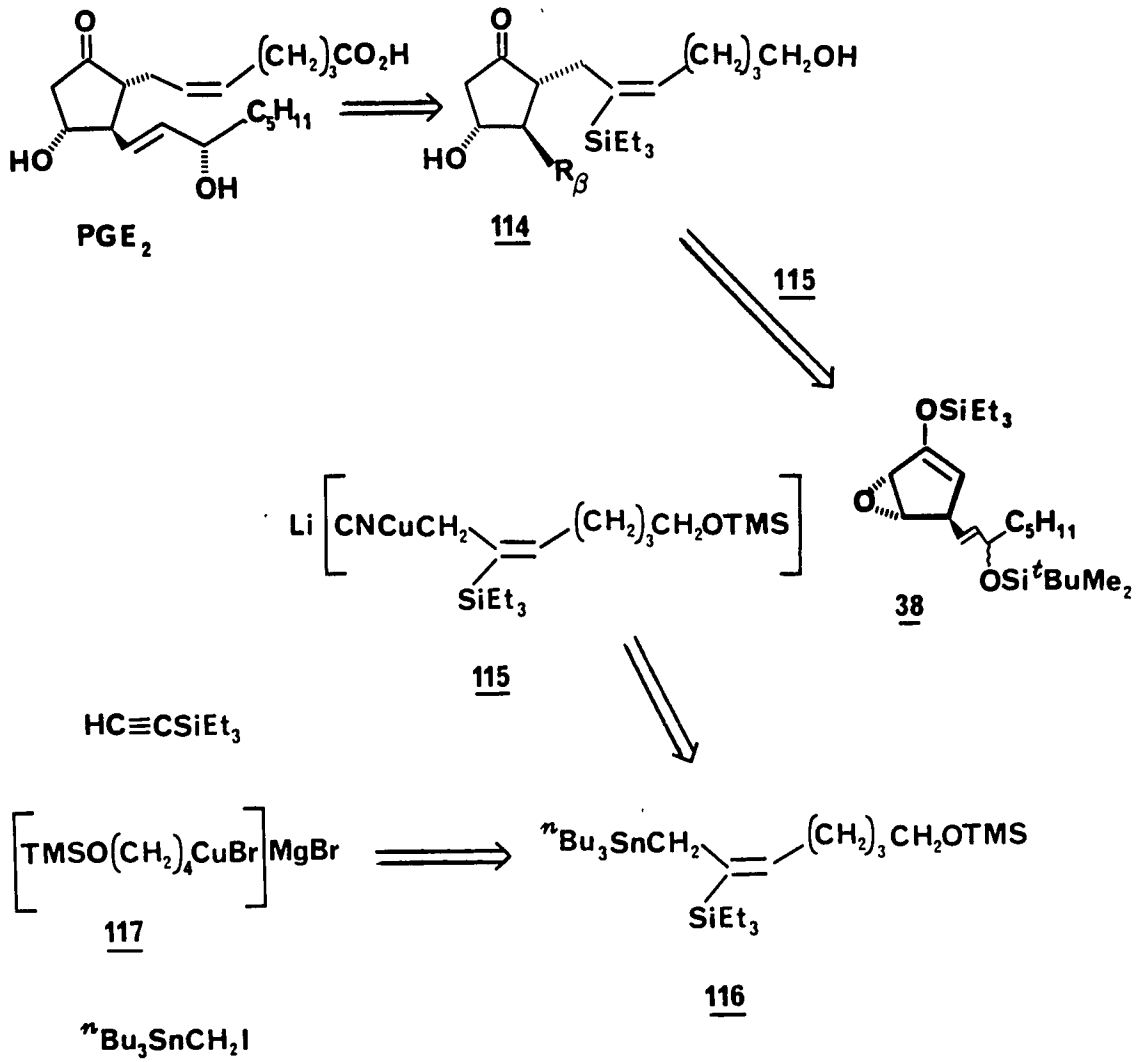
Scheme 14



attempted and an intractable mixture was obtained. Though some allenic 1,4- and 1,2-adducts appeared to have been formed, no major product could be characterized.

All of these unsuccessful efforts prompted a change in strategy. It was decided to focus our attention on an alternative approach which involved the utilization of allylic organometallics. The corresponding retrosynthetic analysis is shown in Scheme 15. It was envisioned that

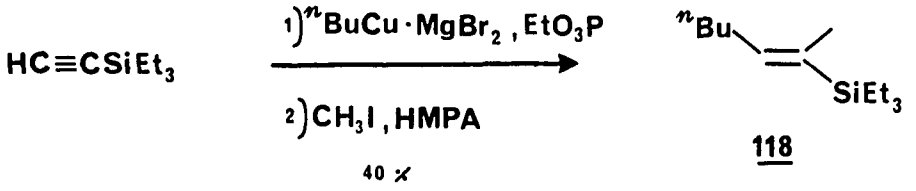
Scheme 15



Prostaglandin E_2 could be obtained by desilation and functional group manipulation from hydroxyketone 114. This, in turn, could arise from the conjugate addition of allylcyanocuprate 115 onto epoxy enol ether 38 and subsequent fluoride induced hydrolysis. There are two intrinsic problems associated with the utilization of substituted allylic organometallics: first, allylic organometallics are ambident nucleophiles[65] and thus may react by either or both

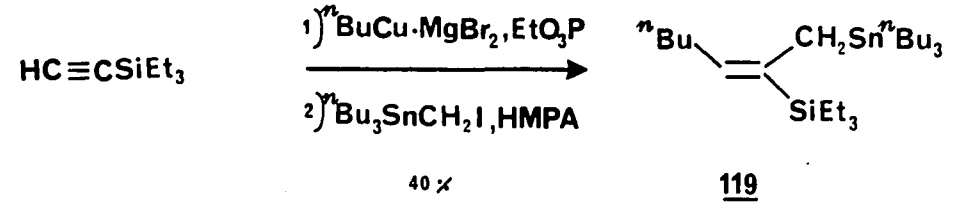
ends of the allylic system; secondly, if the desired regiochemistry is obtained, the stereochemistry of the double bond could be Z or E or a mixture of both. It was expected that the bulky triethylsilyl group in 115 would serve a double function: first, it would favor reaction by the least substituted end of the allylic system, and second, it would lock the double bond into the desired E stereochemistry, which would result in a Z alkene after desilation. The situation is even more complex in this case since epoxy enol ether 38 is an ambident electrophile. Crucial to the viability of this approach was the stereospecific carbometallation of triethylsilylacetylene[66] with cuprate 117, followed by alkylation of the resulting vinylic cuprate with tri-n-butylstannylmethyl iodide.

Triethylsilyl acetylene was prepared from triethylsilyl chloride and ethynyllithium in tetrahydrofuran. Tri-n-butylstannylmethyl iodide was prepared by literature procedures.[67] It was decided that for these initial studies a more accessible cuprate could be employed as a model system. Thus, the reaction of n-butylcopper with triethylsilyl acetylene was examined (following the procedure developed by Utimoto for the trimethylsilyl analog[68]). Several alternative routes were attempted, but this was found to be the most efficient procedure. Trapping of the intermediate vinylcopper species with



118

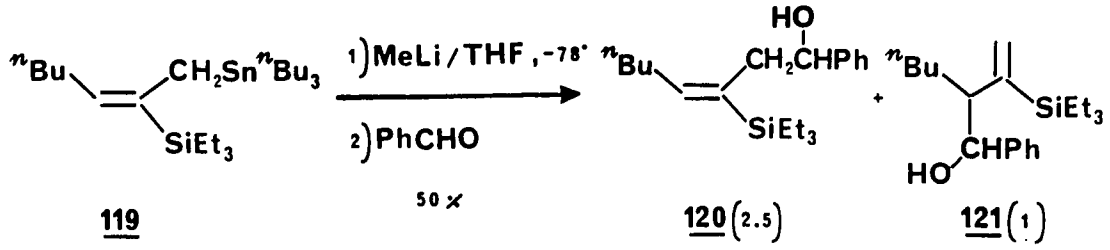
tri-n-butylstannylmethyl iodide was then attempted by the same procedure utilized before. Allyl tin compound 119 was



119

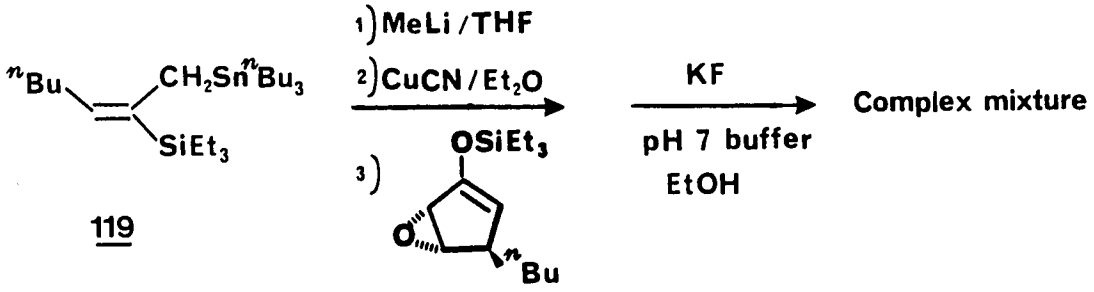
thus obtained in approximately 40% yield. It should be mentioned that this is, to our knowledge, a novel synthetic route for silyl allyl tin compounds of well-defined stereochemistry. However, its scope and generality have not yet been determined. Since 119 could not be separated from uncharacterized by-products, several alternative routes were examined. When a more effective method could not be found, the next step of the sequence was attempted on the relatively impure material. Anion formation was best achieved

by treatment with methyllithium in THF at -78°C, as determined by quenching the anion with benzaldehyde and subsequent isolation of adducts 120 and 121.



119 120 (2.5) 121 (1)

The next step in our synthetic strategy was then tried. Allyl tin compound 119 was treated with methyllithium as described before, and the corresponding cyanocuprate was formed by standard methods. The reaction of vinyl epoxide 37 with the cyanocuprate derived from 119 was carried out and the crude reaction mixture was immediately treated with potassium fluoride in pH 7



119

37

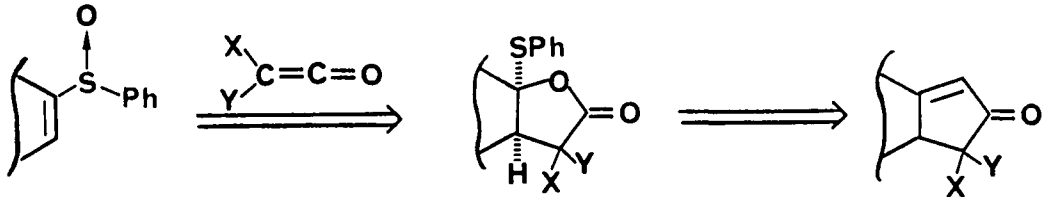
buffer/ethanol. Workup led to an intractable mixture that resisted even the most careful purification and characterization attempts. Further studies with this type of silyl allyl cuprate were discontinued; thus, a suitable solution for the use of stereochemically defined allyl cuprates remains to be found.

CHAPTER III

AN APPROACH TO POROSIN AND THE SYNTHESIS OF β-METHYL-γ-OCTALACTONES (OAK LACTONES) VIA LACTONIZATION OF VINYL SULFOXIDES

1. Introduction.

In 1981, Marino and Neisser[69] developed a new reaction that led to α-substituted-γ-arylthio-γ-lactones, 122. This reaction was a new type of cyclization directed by a sulfoxide functionality. The lactone products were deemed of



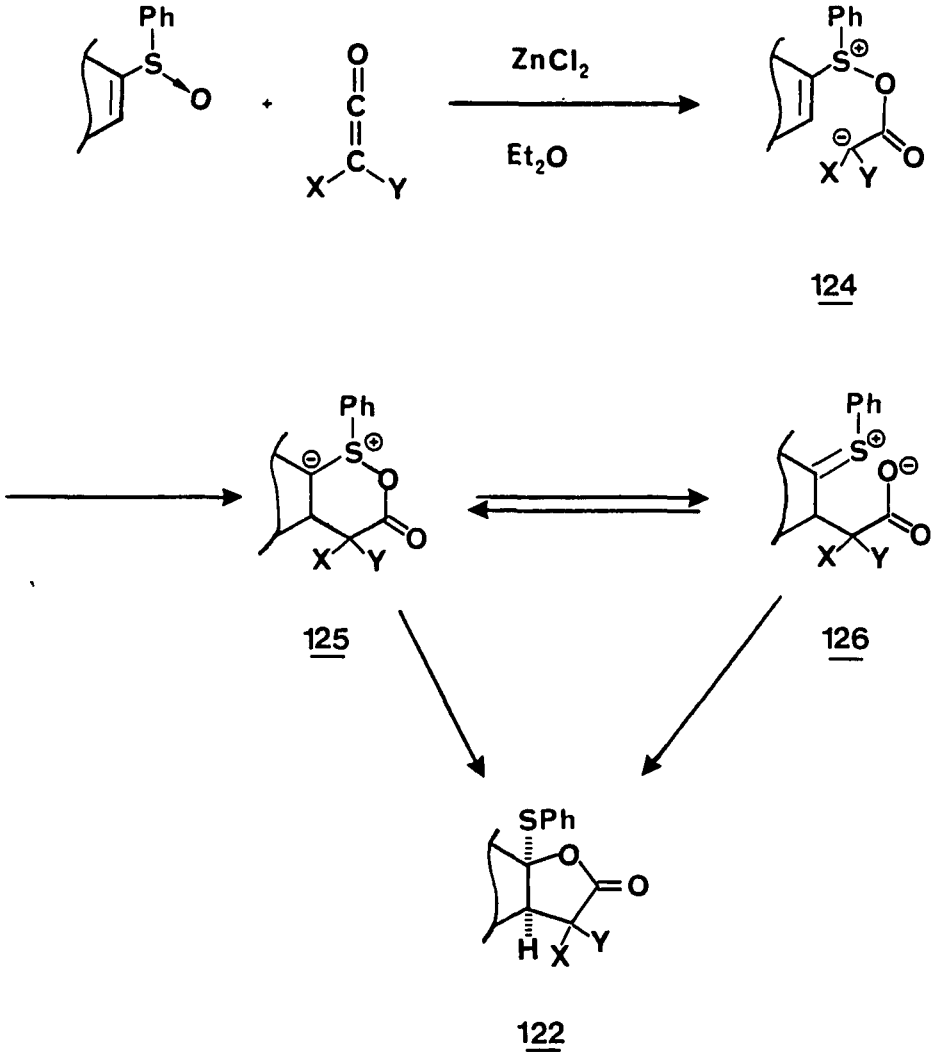
122 123

special interest for two reasons: First, γ-lactones are present in many natural products which possess antibiotic and antitumor properties. Second, the γ-carbon in these lactones is in the oxidation state of a ketone, which suggests the possibility of further annulation processes

leading to cyclopentenones such as 123,[70] also present in many biologically active products.

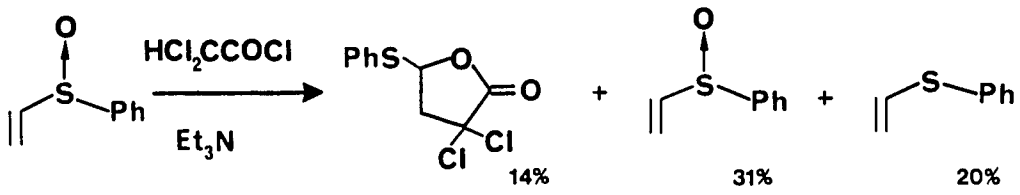
The proposed mechanism for this lactonization is shown in Figure 10. Nucleophilic attack of the sulfinyl

Figure 10. Mechanism of the Sulfoxide-Directed Lactonization of Vinyl Sulfoxides.



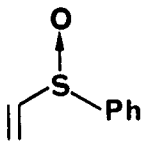
oxygen upon a ketene generates enolate 124, which then may add to the β-carbon of the vinyl sulfoxide producing ylide 125, which then rearranges, possibly via zwitterion 126, to give the lactone 122.

Initial work on this reaction employed the dehydrohalogenation of dichloroacetyl chloride with triethylamine as the method of ketene generation. This led to low yields of lactones, together with unreacted starting



127 128 127

material and vinyl sulfide. The method of ketene generation was then changed to reductive dehalogenation of trichloroacetyl chloride, which proved to be much cleaner and afforded higher yields. Some of the substrates examined by Marino and Neisser[71] are shown below. It was found that the reaction proceeded in a stereospecific manner; thus, cis vinyl sulfoxide 129 gave a cis-β,γ-substituted lactone, and the corresponding trans vinyl sulfoxide 130 yielded the trans-disubstituted lactone. Another interesting feature of this reaction is that each diastereomer of 133 led to a different cis-fused lactone, with remarkable



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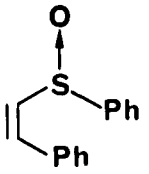

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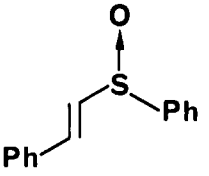

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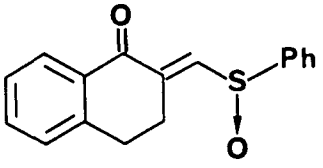

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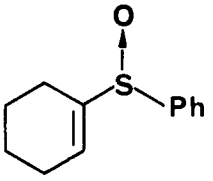

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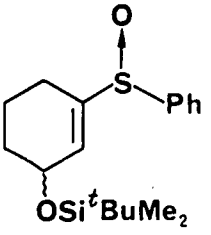
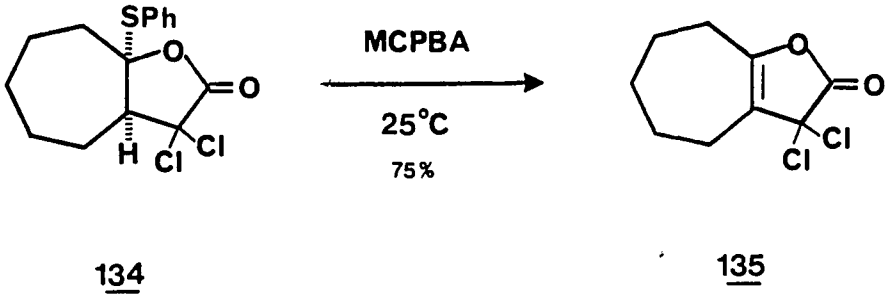


133

stereoselectivity. This suggested that the stereochemical outcome of the reaction was controlled by the absolute configuration of the sulfur atom, and, therefore, a high degree of asymmetric induction might be attainable if an optically active sulfoxide were employed.

Subsequent work by Marino and Perez[70] further expanded the scope of this methodology. The reactions of a variety of cyclic sulfoxides with different ketenes (dichloro, monochloro, bromomethyl, chloromethyl, monobromo) were explored. It was found that the yields were highest when dichloroketene was employed. Several chemoselective

transformations of these α,α-dichloro-γ-arylthiolactones were developed as well. Some examples are listed below.



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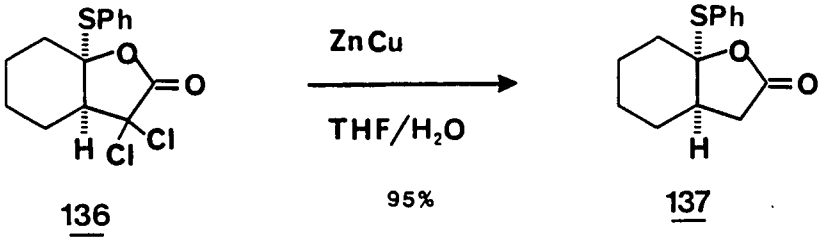
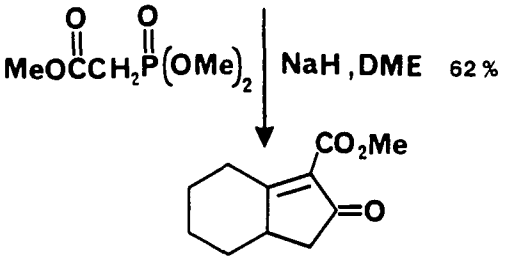


136 137

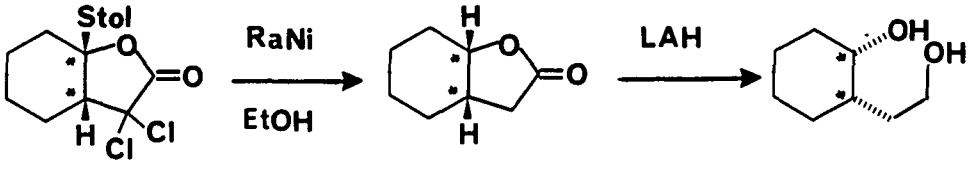


138

The possibility of achieving asymmetric induction with this lactonization was also addressed. (R)- and (S)-1-Tolylsulfinylcyclohexenes were prepared and their lactonization was studied. Optically active dichlorolactones

were obtained and they were degraded to the corresponding diols as shown in Scheme 16. The enantiomeric purity of

Scheme 16



136a 139a 140a

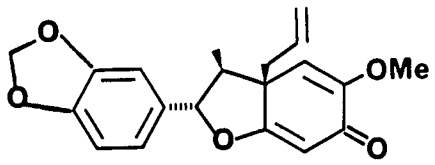
diol 140a was evaluated by esterification with the chiral acid developed by Mosher,[72] α-methoxy-α-phenyl-α-trifluoromethyl acetic acid (MPTAA), and careful analysis of the 360 MHz ^{1}H-NMR spectrum of the corresponding ester. Within the limits of detection, the sulfoxide-directed lactonization was found to be enantiospecific, allowing for the generation of two new chiral centers at the expense of the sulfur chirality. The starting materials were readily accessible and the absolute configuration of the lactones could be controlled by using either enantiomer of the sulfoxide.

At the inception of this part of the thesis, there were several problems to be addressed for the further development of this methodology. First, it was desirable to

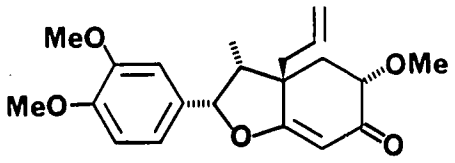
expand the range of acyclic sulfoxides, especially trisubstituted vinyl sulfoxides. Second, the development of a higher yielding desulfurization method was deemed important since the use of Raney nickel (Scheme 16) resulted in very low yields of desulfurized products. Furthermore, the stereochemical outcome of such a reaction in monocyclic cases had not been previously researched within our group. The third aim was to attempt the application of this lactonization to the total synthesis of natural products. The results obtained are discussed in the following sections.

2. Synthetic Strategy Towards the Neolignan Porosin.

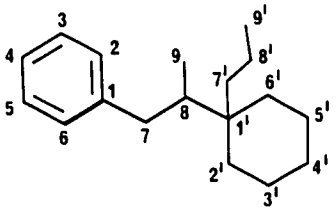
Lignans are natural products of plant origin that arise from the oxidative coupling of two p-hydroxyphenylpropene units.[73] The neolignans constitute a class of lignans characterized by the propenylphenyl and/or allylphenyl units contained in their structures. Among these, the 8.1' neolignan skeleton is of particular interest since members of this group have shown promising antitumor activity.[74] Listed below are some examples of this class of compounds.

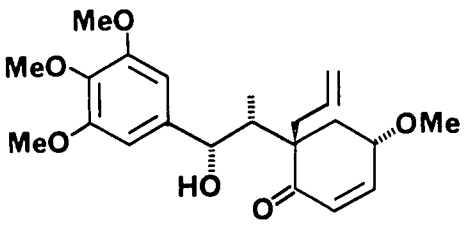


BURCHELLIN



POROSIN

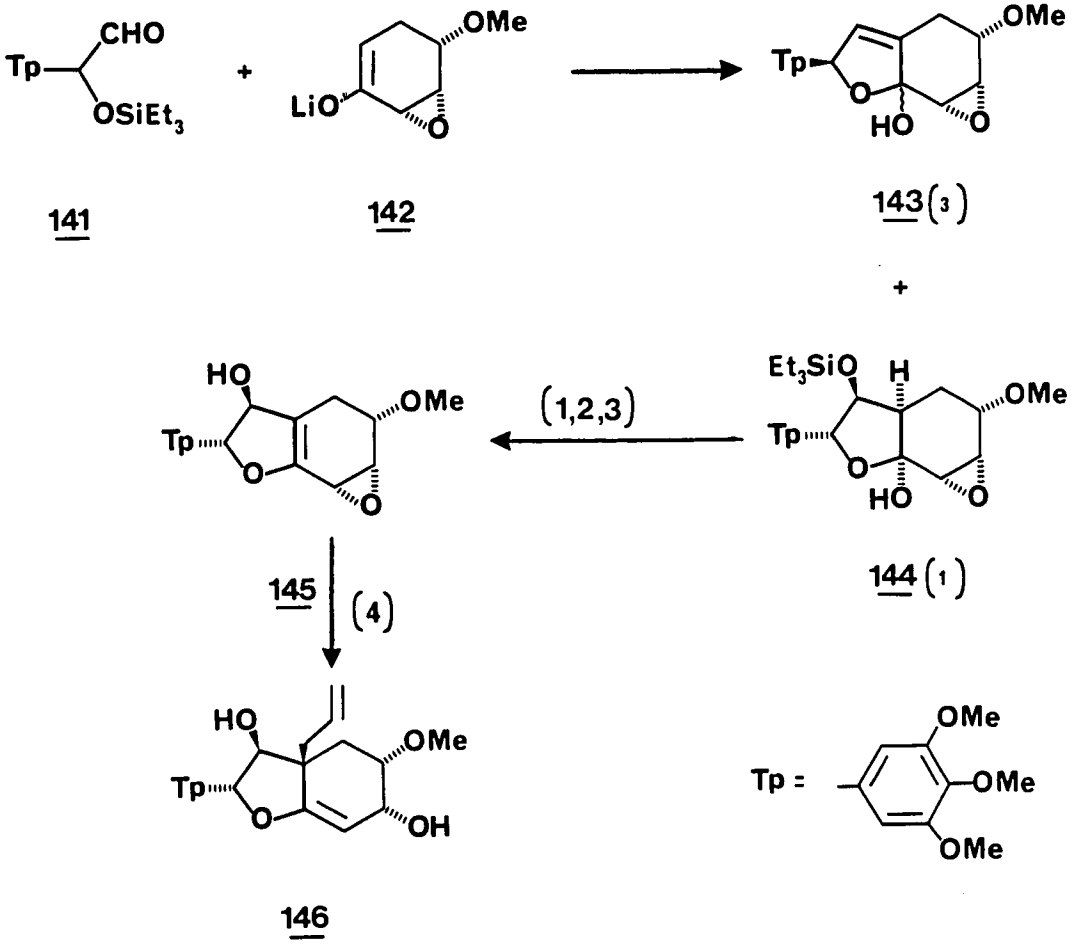




MEGAPHONE

The synthesis of this class of compounds has been explored recently in our group. Marino and Jaen[10b] studied three synthetic schemes towards megaphone,[75,76] the most promising of which is shown in Figure 11. Lithium enolate 142 was treated with triethylsilyloxy aldehyde 141 to give a quantitative yield of adducts 143 and 144 (ca. 3:1 ratio). Treatment of hemiketal 144 with CH_3SO_2Cl followed by elimination (DBN) and removal of the triethylsilyl group gave epoxy alcohol 145, which reacted very cleanly with several cyanocuprates to give the corresponding 1,4-trans-adducts if organolithium

Figure 11. "Bicyclic Epoxy Enol Ether" Approach to 8.1' Neolignans.



Reagents: (1) MsCl, Et_3N, CH_2Cl_2, 0°C. (2) DBN, CH_2Cl_2, 25°C. (3) n-Bu_4NF, THF, 25°C. (4) Allylcyanocuprate, Et_2O, -78°C.

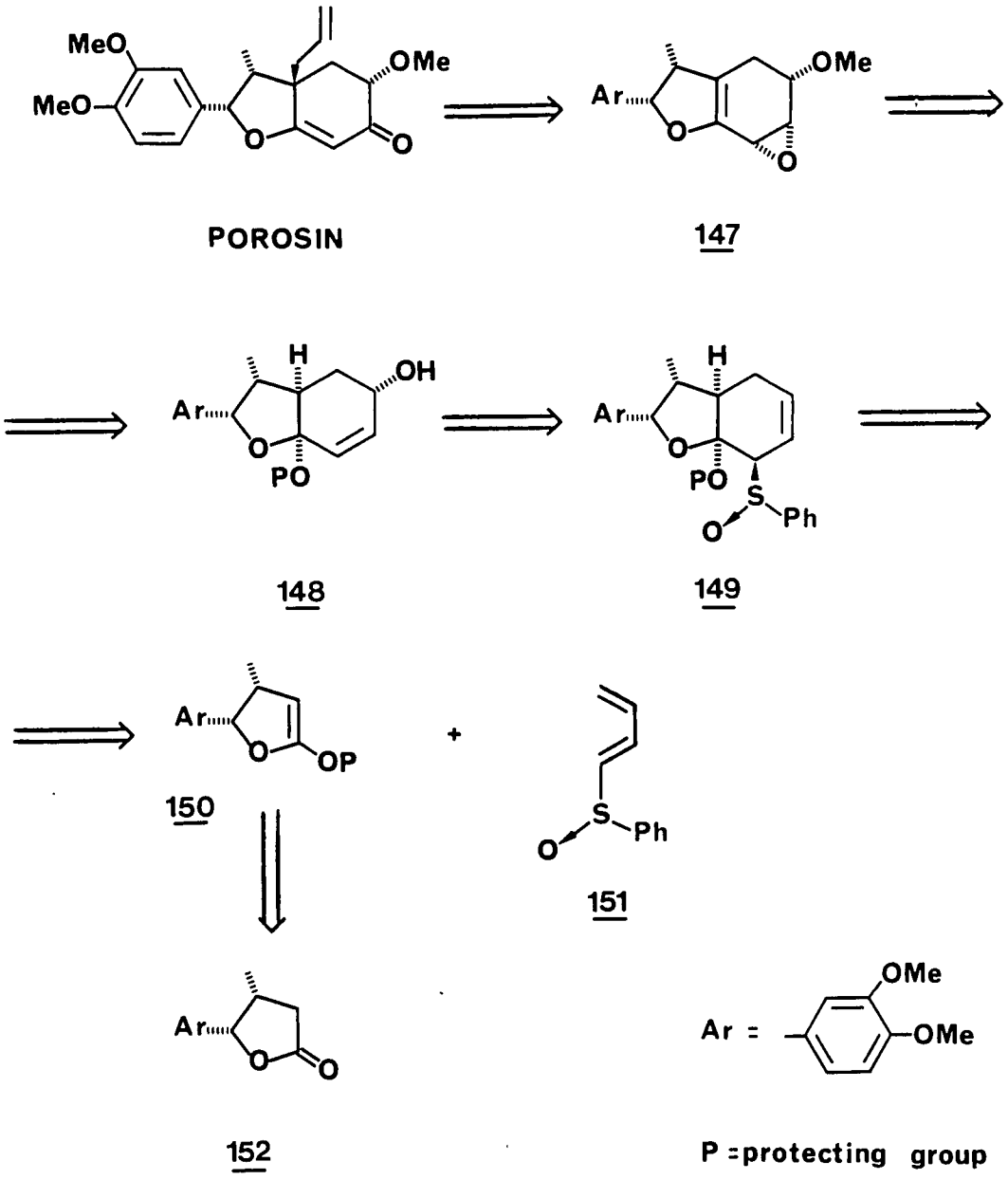
compounds were employed as precursors of the cuprate reagents. Adduct 146 contains all the structural and stereochemical features required for the synthesis of megaphone. The completion of this synthesis is currently being investigated in our group.

The fascinating synthetic possibilities of the sulfoxide directed lactonization together with our interest in the synthesis of 8.1' neolignans originated the following approach to porosin.[77] The retrosynthetic analysis is presented in Scheme 17. The key step in this approach was the inverse electronic demand cycloaddition between a suitably protected cyclic ketene acetal, 150, and dienyl sulfoxide 151 to give allylic sulfoxide 149. Sigmatropic rearrangement, followed by inversion of the carbinol carbon would lead to allylic alcohol 148. Alternatively, if the cycloaddition was not to proceed in an endo fashion, no inversion would be needed. Hydroxyl directed epoxidation, methylation and elimination (see Figure 11) would afford allylic epoxide 147. The synthesis could then be completed by conjugate addition of allylcyanocuprate and oxidation.

An interesting feature of this approach is the initial elaboration of the five-membered ring that then serves as a building block on which the six-membered ring is attached. Other syntheses of neolignans proceed by initially building

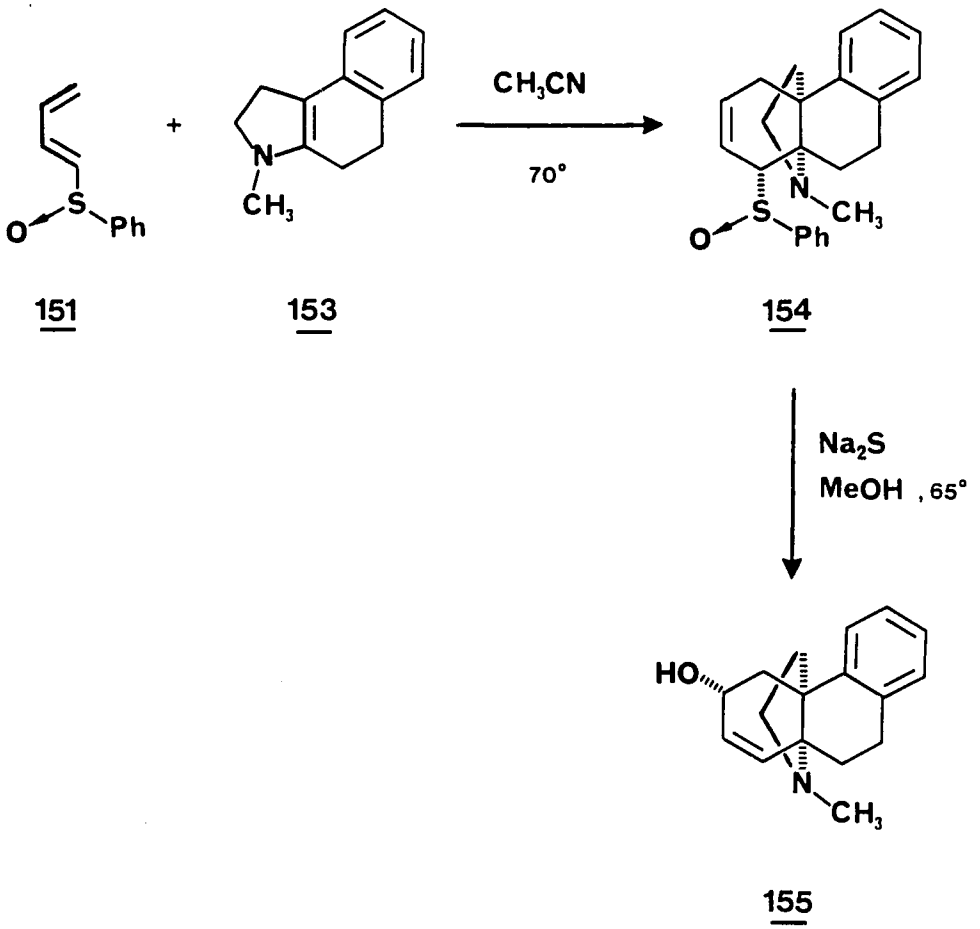
the six-membered ring and then attaching the five-membered ring.

Scheme 17



Similar cycloadditions to the one proposed are precedented in the literature. Evans[78] developed an elegant route to functionalized hasubanan derivatives (Scheme 18), which involved the cycloaddition of enamine 153 with

Scheme 18

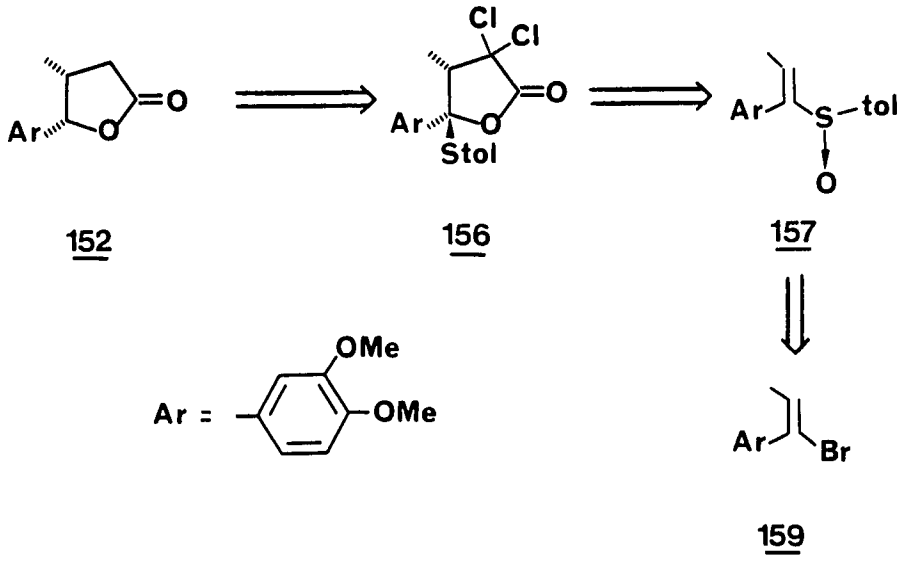


151 153 154 155

1-butadienyl phenyl sulfoxide. This resulted in a diastereomeric mixture of allylic sulfoxides 154. The sequence was then completed by a [2,3] sigmatropic rearrangement[79] to give isomerically pure amino alcohol 155. The cycloaddition was found to occur with an endo orientation.

The synthesis of lactone 152 was considered to be a good probe for the stereospecificity of the sulfoxide directed lactonization and for the stereochemical outcome of the desulfurization in monocyclic systems. The retrosynthetic analysis is shown in Scheme 19. Lactonization

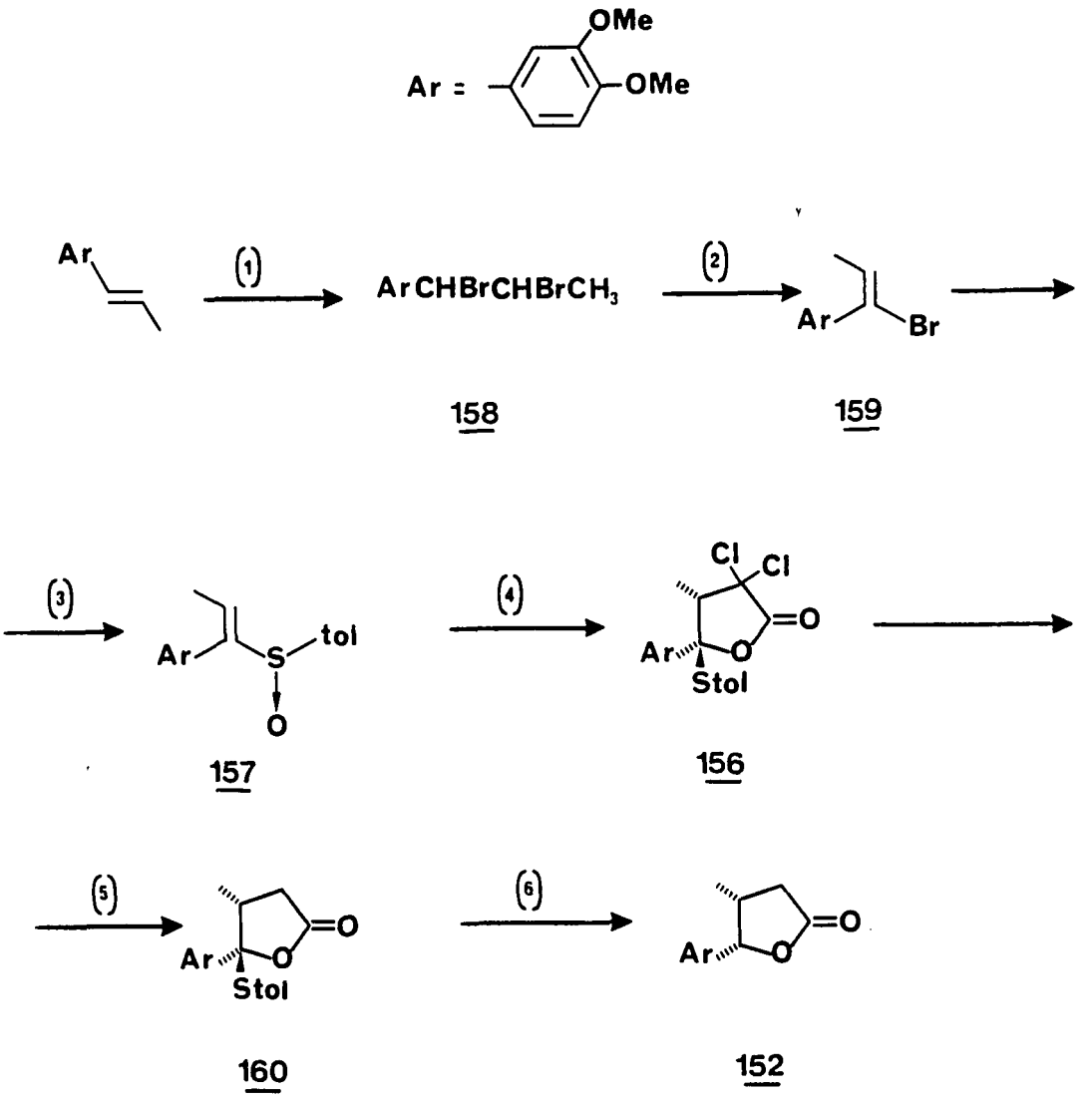
Scheme 19



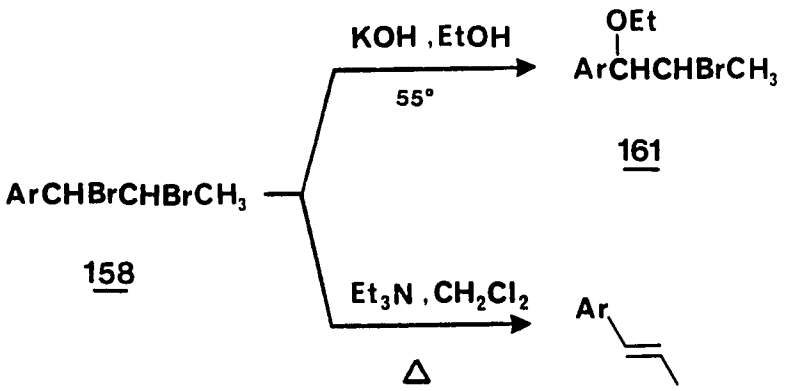
of the vinyl sulfoxide 157 with dichloroketene should give lactone 156, if the stereochemistry of the substituents in the sulfoxide is preserved. Dehalogenation and

desulfurization should provide lactone 152, if the latter proceeds in a stereospecific manner. Moreover, the possibility of achieving a chiral synthesis of 152 via optically active 157 made this approach very attractive. Lactone 152 was prepared as shown in Figure 12. Bromination of commercially available trans-isoeugenol methyl ether with bromine in carbon tetrachloride at 0°C gave a mixture of dibromides in ca 4-5:1, erythro:threo ratio. Alternatively, bromination in chloroform at -30°C produced mixtures of dibromides in ca. 10:1, erythro:threo ratio, from which the desired erythro isomer, 158, was obtained by fractional recrystallization with 5% i-PrOH/hexane. Dibromide 158 could be dehydrohalogenated in good yield with potassium hydroxide in isopropanol/dichloromethane to give vinyl bromide 159. Other conditions were initially attempted, such as ethanolic potassium hydroxide[80] and triethylamine in dichloromethane. The results are shown below.

Figure 12. Synthesis of Lactone 152.



Reagents: (1) Br_2, $CHCl_3$, -30°C; fractional recrystallization, hexane/i-PrOH. (2) KOH, i-PrOH, CH_2Cl_2, 0°C → RT. (3) sec-butyllithium, Et_2O, -78°C; then p-tolS(O)Cl, 53% from 158. (4) Cl_3CCOCl, Zn(Cu), Et_2O, reflux, 60%. (5) Al(Hg), THF/H_2O, 0°C → RT, 90%. (6) RaNi, EtOH, RT, 20%.

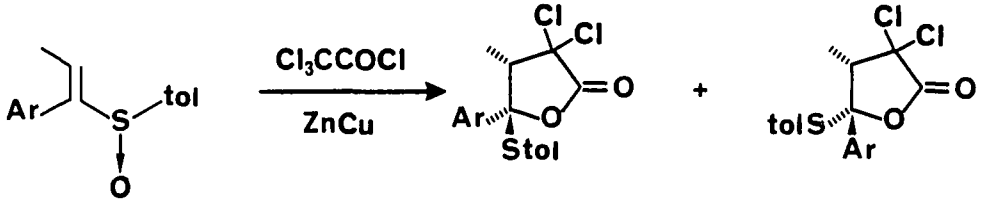


Vinyl bromide 159 was found to be rather thermally unstable and was used without purification shortly after it had been prepared. A sample of pure bromide 159 was kept at room temperature and monitored periodically by 360 MHz ^{1}H-NMR. This showed a significant amount of isomerization to its Z isomer after 2-3 days. Unfortunately, this process could not be utilized in a synthetic fashion since prolonged standing of the sample led to complete decomposition.

The preparation of vinyl sulfoxide 157 was then examined. At this stage of the synthesis, it was considered that racemic 157 was the appropriate target. Nevertheless, some preliminary attempts to synthesize optically active 157 were made. Thus, metal-halogen exchange of bromide 159 with n-butyllithium in THF, followed by quenching of the anion with menthol p-toluenesulfinate, resulted in

very low yields of the corresponding sulfoxide. A more reactive electrophile, p-toluene sulfinyl chloride, was then tried and, surprisingly, the yields were also very low. The cause for this could conceivably be an inherent lack of stability of the vinyl anion in THF. This hypothesis was verified when the lithium-halogen exchange was performed with sec-butyllithium in ether as solvent. Indeed, quenching of the anion with p-toluene sulfinyl chloride afforded substantially higher yields (53% overall from dibromide 158).

Sulfoxide directed lactonization of 157 with dichloroketene (generated by dehalogenation of trichloroacetyl chloride) was effected under standard conditions[70] to give a 60% yield of dichlorolactone 156. It should be mentioned that when this reaction was carried out on a large scale a trace amount of isomeric dichlorolactone 162 was



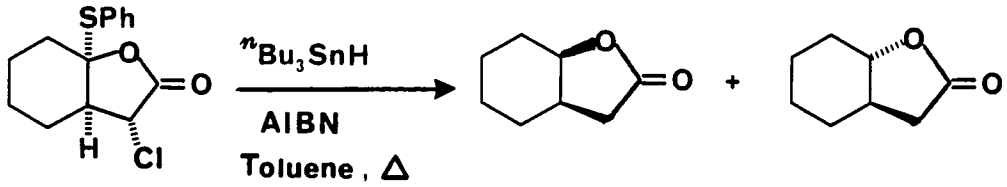
157 156 (30) 162 (1)

fortuitously isolated and fully characterized (see Experimental). The ratio of isomeric lactones 156 and 162 was found to be ca. 30:1. Such a ratio might well be attributed to some contamination of (E)-vinyl sulfoxide 157 with trace amounts of its (Z) isomer.

Treatment of dichlorolactone 156 with aluminum amalgam[81] produced dechlorinated lactone 160 in excellent yield. γ-Arylthio-lactones of this type are remarkably unstable in deuterochloroform solution which is in sharp contrast with their chlorinated analogues. They are indefinitely stable, however, when stored neat in a refrigerator.

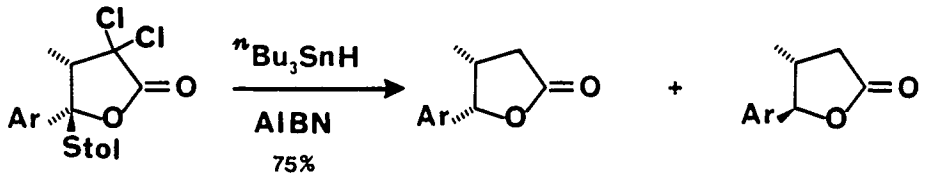
Desulfurization was then achieved with Raney nickel[82] in ethanol and was found to be highly stereoselective. Lactone 152 was obtained in 20% yield (not optimized), accompanied by 25% recovery of starting material. Detailed examination of the 360 MHz ^{1}H-NMR spectrum of 152 showed only trace amounts of its trans isomer 165. The synthesis of cis-3,4-disubstituted-γ-lactone 152 was thus completed, although the desulfurization step still needed improvement.

Tri-n-butyltin hydride has recently been explored in our group as a reagent to achieve simultaneous dehalogenation and desulfurization in analogous systems.[83] Some of the results obtained are shown below. Undoubtedly the



163 139 (10) 164 (1)

high ratio in favor of the cis isomer is related to the bicyclic character of this system. When dichlorolactone 156 was subjected to these conditions, a mixture of cis and trans lactones 152 and 165 was obtained. Surprisingly, the mixture was predominantly cis. These lactones



156 152 (2.5) 165 (1)

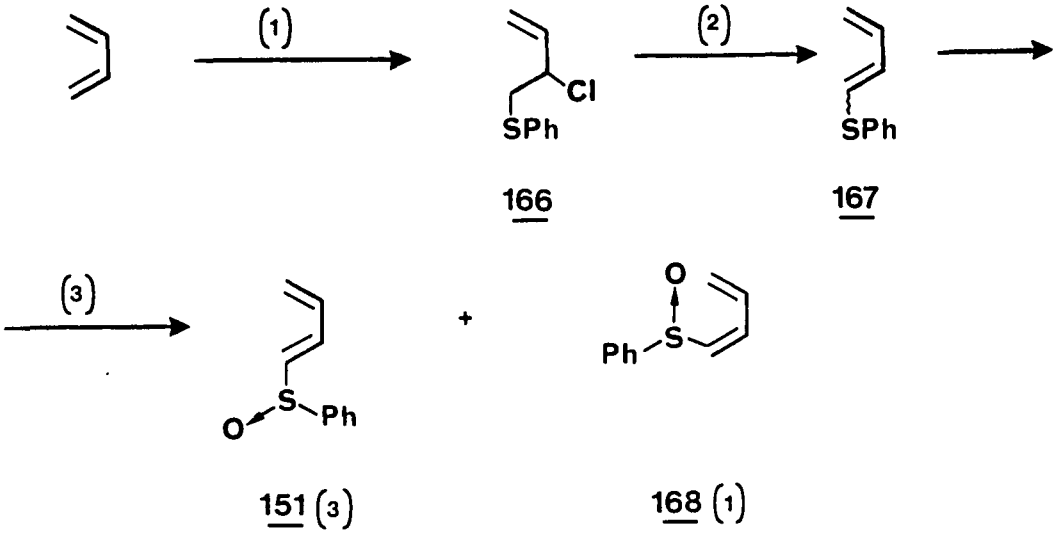
could be separated by careful flash chromatography or HPLC, and the trans isomer was fully characterized. The stereochemistry of these lactones was assigned on the basis of their 360 MHz ^{1}H-NMR spectra. Cis-lactone 152 presents an unusually shielded methyl group (0.699 ppm), while the trans-lactone 165 shows a more standard methyl

shift (1.156 ppm). The chemical shift of the benzylic proton varies substantially as well (5.537 ppm for the cis isomer vs. 4.862 ppm for the trans isomer). This is consistent with the well-known shielding effect of substituents cis to a given proton (see Chapter I). Finally, the coupling constant, J_{34}, is considerably smaller for the cis isomer (5.7 Hz) than for the trans isomer (8.6 Hz), which is typical for this class of lactones.[84]

Continuing with the retrosynthetic analysis depicted in Scheme 17, the next step would be the preparation of a suitably protected ketene acetal derived from lactone 152. No difficulties were anticipated for this transformation since analogous systems are well known in the literature. It was considered that the use of a model system would substantially simplify the experimental protocol; therefore, commercially available γ-butyrolactone would be employed for the initial studies on the cycloaddition reaction.

Sulfoxide 151 was then synthesized by a literature procedure,[78] as shown in Scheme 20. However, some modifications had to be introduced. First, dehydrohalogenation of chlorosulfide 166 was found to give a mixture of vinyl sulfides instead of exclusively trans isomer. Second, oxidation of vinyl sulfides 167 with sodium periodate in methanol had not occurred after stirring for two days at

Scheme 20



166 167

151 (3) 168 (1)

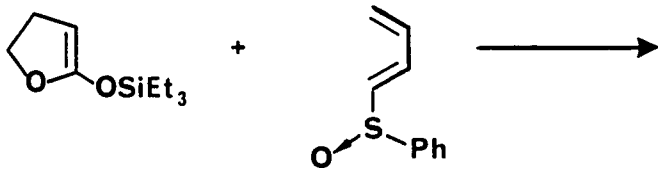
Reagents: (1) PhSCl, 90%. (2) Potassium tert-butoxide, THF, 0°C, 60%. (3) MCPBA, CH_2Cl_2, -78°C → RT, 80%.

room temperature. Peracid oxidation, alternatively, proceeded very efficiently, affording a mixture of cis and trans dienyl sulfoxides, which were easily separated by flash chromatography. Pure dienyl sulfoxides 151 and 168 could be stored in a refrigerator for months with only a small degree of decomposition.

Treatment of γ-butyrolactone with LDA, followed by trapping of the enolate with triethylsilyl chloride, gave

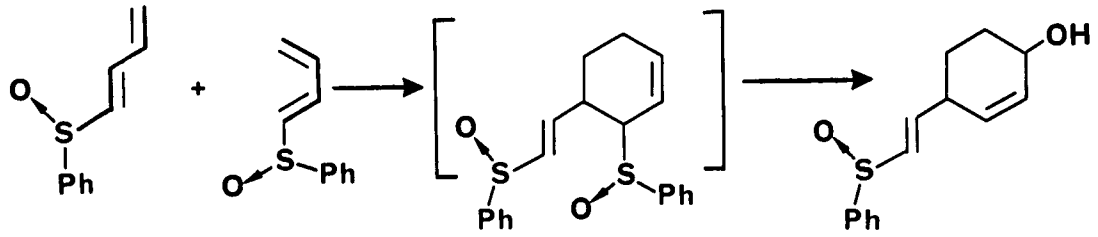
an excellent yield of silyl ketene acetal 169.[85] The choice of triethylsilyl as a protecting group was based on stability considerations.

Participation of a silyl enol ether as dienophile in a Diels-Alder reaction is rare. To our knowledge, there are only two examples of such reactivity, both involving the mono-trimethylsilyl derivative of biacetyl[86] and reactive dienes such as cyclopentadiene, 1,3-diphenylisobenzofuran, etc. It was thought, however, that the reaction of an extremely electron-rich alkene such as ketene acetal 169 with a fairly electron-deficient diene, 151, should have favorable electronics. With these considerations in mind, the cycloaddition was attempted. Initial



169 151

trials under Evans' conditions[78] (CH_3CN, 70°C) were not successful. If the reaction was allowed to proceed for several days, almost complete decomposition occurred, and the only product which could be isolated and characterized in very low yield was adduct 170. Adduct 170 was obtained as a single isomer although its stereochemistry



151 170 (7%)

could not be conclusively assigned. Formation of 170 was observed whenever the reaction was allowed to proceed for long periods of time. Many different sets of conditions were tried:

(a) refluxing p-cymene.

(b) CH_2Cl_2, $BF_3 \cdot OEt_2$, -78° → RT

(c) CH_3CN, RT, 2 days.

(d) DMSO, RT, 2 days.

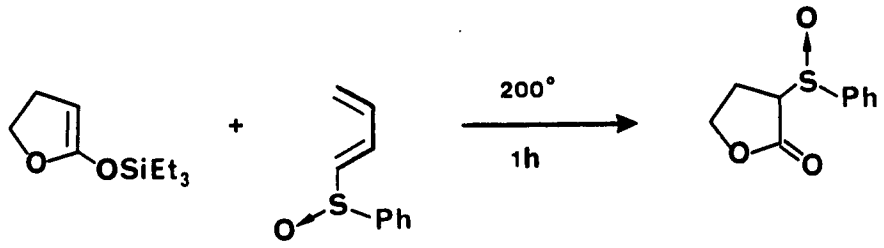
(e) CH_3CN, $ZnCl_2$, RT → 60°.

(f) CH_2Cl_2, $Me_3SiOS(O)_2CF_3$, -78° → RT.

(g) Neat, 200°, 1 h.

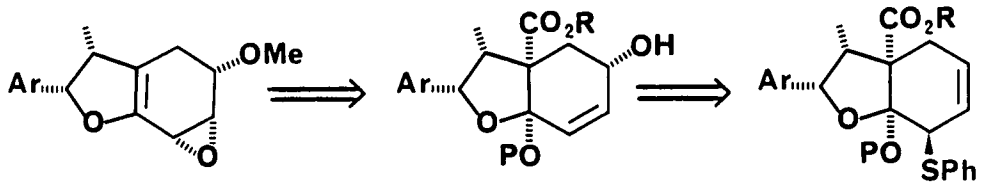
None of the desired adduct was detected in any of these trials; instead, intractable mixtures were obtained. In most cases, significant amounts of 1-butadienyl-phenyl-sulfoxide were recovered (30-60%). In many cases trace amounts of other products were isolated but could not be

identified. An exception is entry g, from which a 14% yield of adduct 171 was isolated and characterized by 360 MHz ^{1}H-NMR and mass spectrometry.



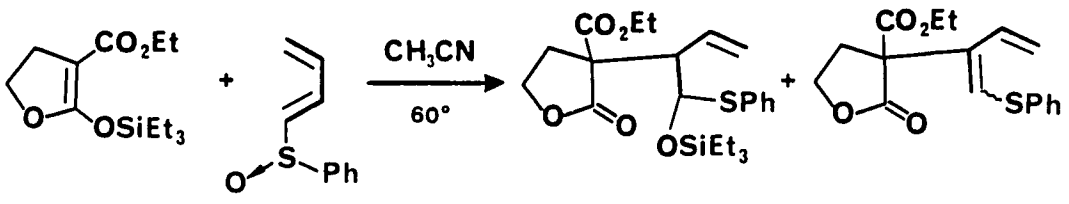
169 151 171

At this point, modification of the dienophile was pursued. It was thought that an electron-withdrawing group attached to the alkene might alter the electronics of the system and allow for the reaction with dienyl sulfide 167 to occur. The presence of an ester in an angular position, such as in 173, would not be synthetically inefficient since hydrolysis and decarboxylation could lead

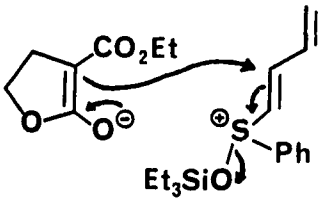


147 173 172

to the desired allylic epoxide 147. Oxidation of allylic sulfide 172 would provide the corresponding sulfoxide for the sigmatropic rearrangement leading to 173. Thus, silyl ketene acetal 174 was prepared by standard procedures[87] and its reaction with butadienyl phenyl sulfide 167 under several different conditions was examined. No desired adduct was detected. The reaction with dienyl sulfoxide 151 was also carried out and was found to give low yields

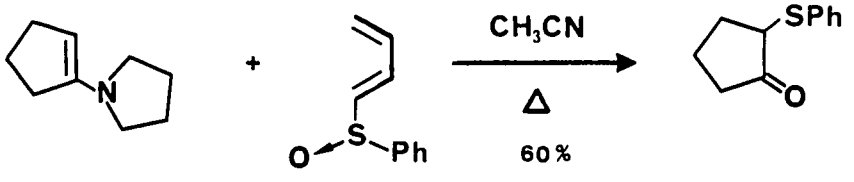


of adducts 175 and 176 as well as starting material and other unidentified products. The formation of 175 can be understood by considering the nucleophilicity of the sulfinyl oxygen, capable of effecting desilylation of 174 and thus generating a stable enolate which could then add in a 1,2-fashion to the silylated sulfoxide. Compound 175 was obtained as a mixture of diastereomers and compound 176 was formed as a single isomer whose stereochemistry could not be conclusively assigned.



At this point, a change in strategy was deemed necessary. The fact that the only known successful example of such a cycloaddition (Scheme 18) involved an enamine, 153, suggested that the presence of that functionality could be necessary for the reaction to occur. An additional model system was then examined and the results are shown in Scheme 21. It was considered that since the synthesis of the corresponding oxygenated analogue did not seem straightforward, an initial attempt should be effected with a readily available enamine. The reaction of the

Scheme 21

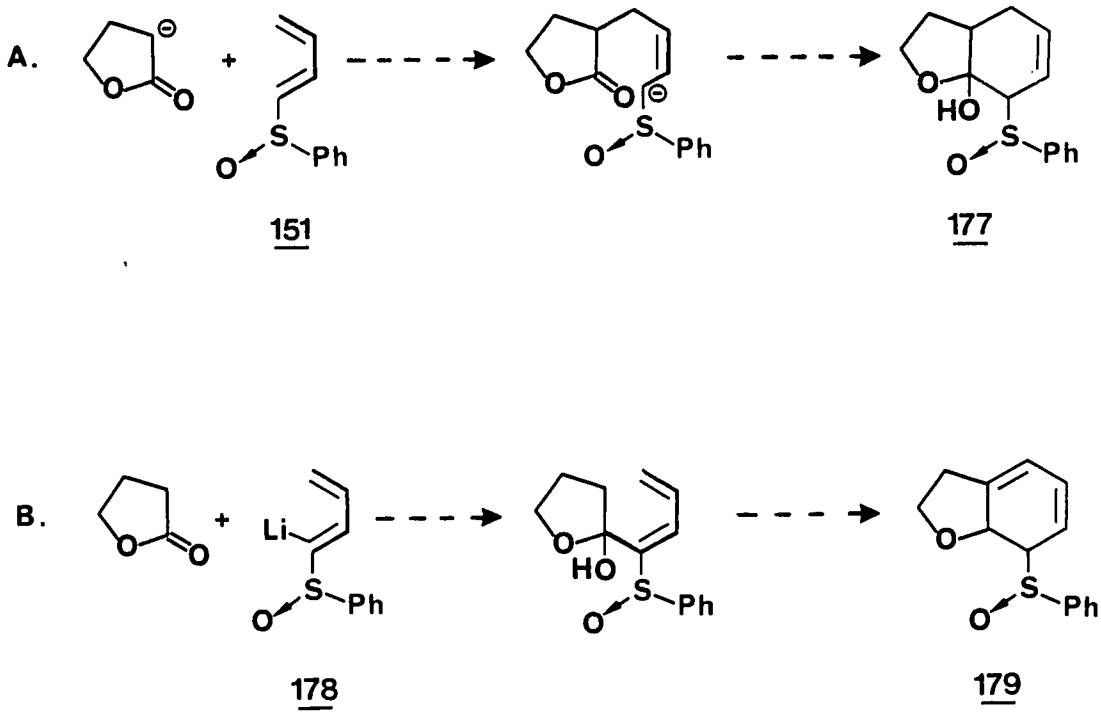


151

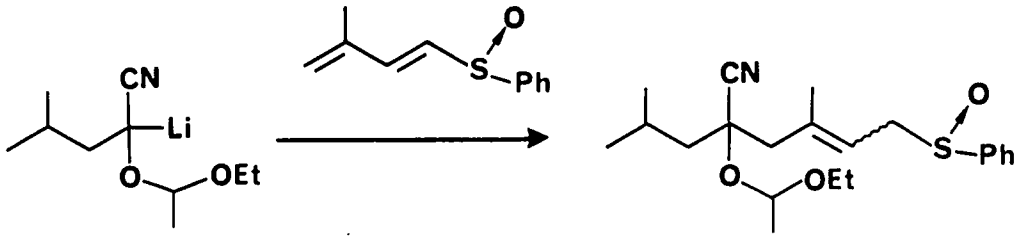
pyrrolidine enamine of cyclopentanone with sulfoxide 151 was thus examined and, surprisingly, it was found that the main product was 2-thiophenylcyclopentanone. The rest of the many reaction products were thoroughly analyzed. However, no cycloaddition adduct was detected. These puzzling results convinced us to abandon, at least temporarily, this approach.

Two additional routes remained to be explored. These are indicated in Scheme 22.

Scheme 22

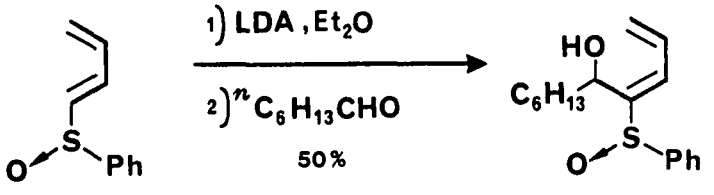


Michael additions of masked acyl carbanions to 3-methyl-1,3-butadienyl phenyl sulfoxide are precedented in the literature.[88] Unfortunately, treatment of



1-butadienyl phenyl sulfoxide with either the lithium enolate of γ-butyrolactone or the sodium enolate of 2-carboethoxy-γ-butyrolactone (route A) led only to decomposition.

The second route shown in Scheme 22 (route B) involved the utilization of γ-butyrolactone as an electrophile and a sulfoxide anion, 178. If this approach were successful, the basic carbon skeleton would be formed and subsequent functional group manipulation would possibly allow for the completion of the synthesis. The previously unknown anion 178 was prepared by deprotonation with LDA in ether and trapped with heptanal to give diastereomeric adducts 180a and 180b, which were easily separated by flash chromatography. The use of THF resulted in much lower yields of adducts, presumably due to decomposition of anion 178 in THF, even at low temperatures.



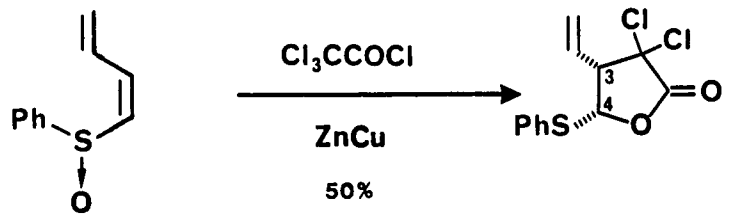
151 180a,b

The reaction of this anion with γ-butyrolactone was then attempted but without success. Compound 178 was found to be too basic and not sufficiently nucleophilic. No addition product was detected.

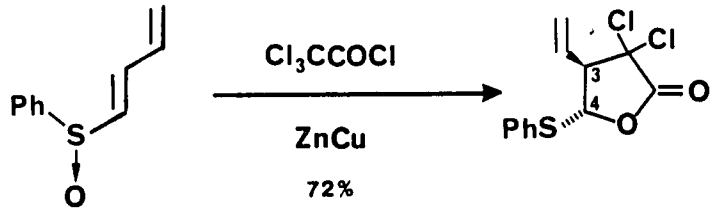
A great deal of time and effort had been devoted to the development of this approach to porosin, but unfortunately the results were extremely disappointing. It was decided, therefore, to interrupt our efforts in the total synthesis and continue the development of the methodology of the sulfoxide-directed lactonization for acyclic vinyl sulfoxides. The remainder of this manuscript will describe those results.

The availability of cis- and trans-1-butadienyl phenyl sulfoxides 168 and 151 prompted us to study their ketene cycloaddition reactions. Both isomers were found to react cleanly, in a stereospecific manner, as shown in Scheme 23.

Scheme 23



168 181



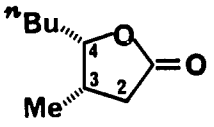
151 182

It was found, however, that dichlorolactones 181 and 182 decomposed extensively upon chromatography. They were purified by fast filtration through a small amount of deactivated silica gel. The stereochemistry of these isomeric lactones was established from the chemical shifts of H_3 and H_4 (both upfield in the trans isomer, with respect to the cis isomer) and by the values of the coupling constant between them: 6.2 Hz for 181 and 9.9 Hz for 182. These lactones are interesting intermediates since the presence of the vinyl group allows, in principle, for

subsequent elaboration, such as cleavage to the aldehyde, Diels-Alder cycloadditions, etc. The combination of this lactonization with the chemistry of anion 178, although not yet explored, should further expand the scope of this methodology.

3. Synthesis of Cis- and Trans-β-methyl-γ-octalactones (Oak Lactones).

Cis and trans 4-butyl-3-methyl-4-butanolides, 183 and 184, are natural products extracted by wine or other alcoholic beverages from oak barrels in which they are kept for maturing.[89] Hence they were named "quercus lactones" or "oak lactones." The structure elucidation of these compounds has been the subject of some controversy,[89c,90] and it is only recently that their structures have been conclusively established.[91]



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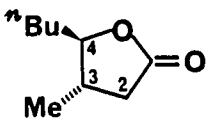

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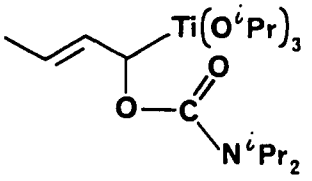
There are several non-selective syntheses of these lactones in the literature[92] as well as some selective

syntheses,[93] which proceed by stereoselective condensations of pentanal with the reagents shown below and subsequent functional group manipulation. A common feature of these syntheses is the formation of the C_3-C_4 bond in the key step.



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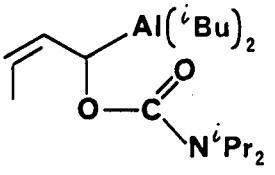

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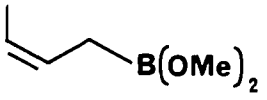

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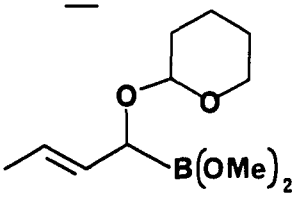


188

The synthesis of these oak lactones by means of the sulfoxide directed lactonization of vinyl sulfoxides seemed to be a relatively simple application of that methodology. From a retrosynthetic point of view, it would be different from previous approaches since the key step would form the C_2-C_3 bond. The synthesis of racemic lactones 183 and 184 was accomplished, as shown in Figure 13.

Figure 13. Synthesis of Oak Lactones 183 and 184.

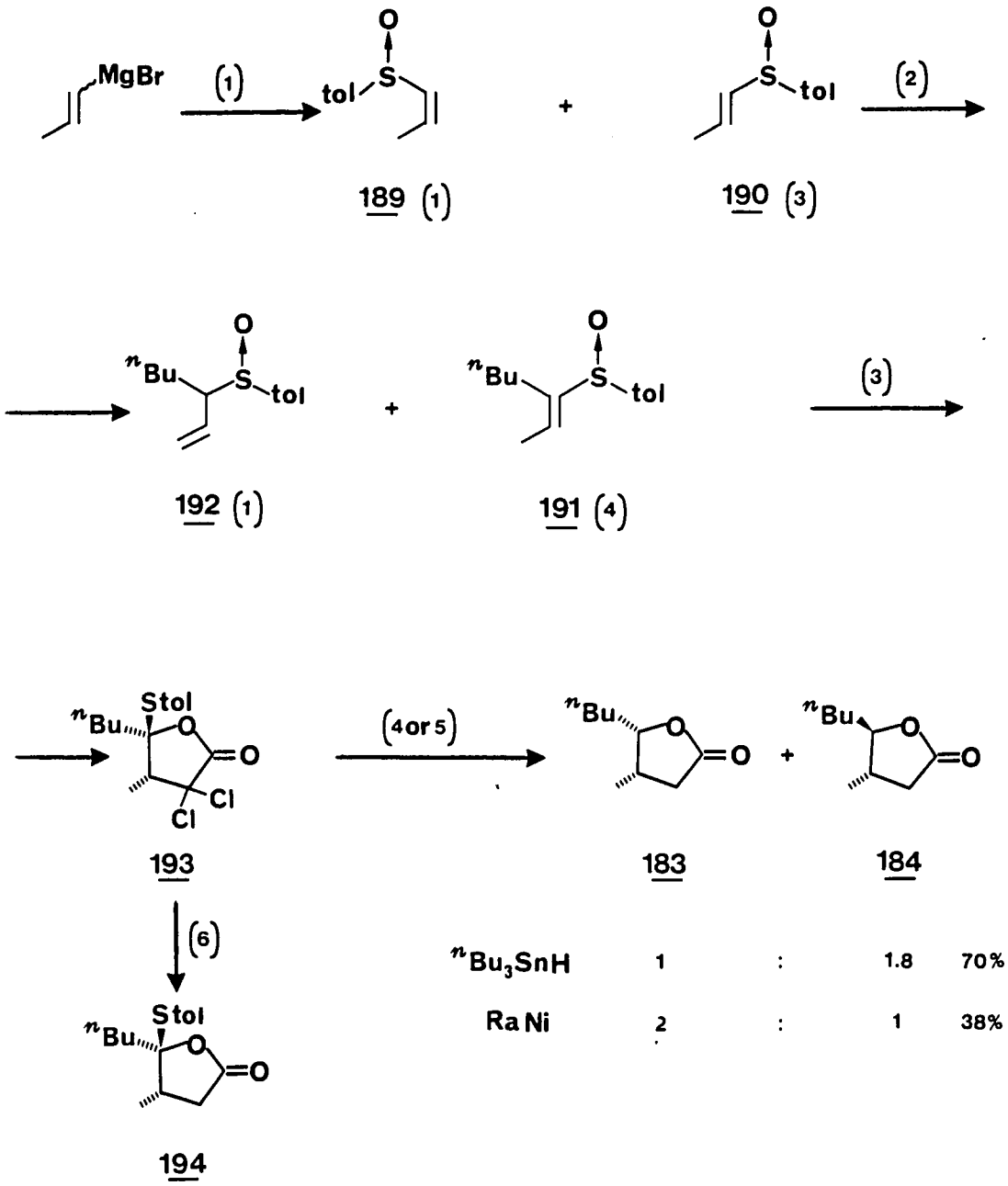


Figure 13 (continued)

Reagents: (1) tol-S(O)Cl, THF, 72%. (2) LDA, THF, -78°C, 20 min; then HMPA (1 eq.); then n-butyl iodide, 60%. (3) Cl_3CCOCl, Zn(Cu), ether, 75%. (4) n-Bu_3SnH, AIBN, toluene, 70% of a 1:1.8, cis/trans mixture. (5) Raney nickel, benzene, reflux, 38% of a 2:1 cis/trans mixture. (6) Al(Hg), THF/H_2O, 0° → RT, 90%.

1-Bromo-1-propene (as a 1:3 mixture of cis and trans isomers) was transformed into the corresponding Grignard reagent by standard methods and its reaction with p-toluene sulfinyl chloride was effected to give a 1:3 mixture of cis and trans sulfoxides 189 and 190.[94] These isomeric sulfoxides were easily separated by flash chromatography. Pure trans isomer 190 was then deprotonated α- to the sulfoxide functionality[95,96] with lithium diisopropylamide and alkylated with n-butyl iodide in the presence of HMPA to give a 4:1 mixture of vinyl sulfoxide 191 and allylic sulfoxide 192. This relatively large amount of allylic deprotonation appears to occur only in alkenyl sulfoxides substituted with a methyl group. Other substituents do not allow allylic deprotonation and exclusive formation of a vinylic lithium species is observed.[95]

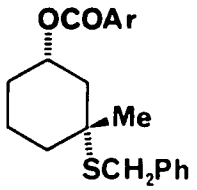
Separation of isomeric sulfoxides 191 and 192 was not necessary. The mixture was subjected to the lactonization conditions to give a 75% yield of dichlorolactone 193, which was easily purified by flash chromatography.

Dehalogenation and desulfurization could be effected by two different methods. Tri-n-butyltin hydride[97] was found to be a fairly efficient reagent, giving a 70% yield of a 1:1.8 mixture of cis and trans lactones 183 and 184, which were separated by flash chromatography and characterized by comparison of their 300 MHz ^{1}H-NMR spectra with literature values.[93c]

Alternatively, treatment of dichlorolactone 193 with Raney nickel[82] in refluxing benzene gave a predominantly cis mixture of lactones 183 and 184 in 38% yield. Selective dehalogenation of dichlorolactone 193 could be achieved in excellent yield by treatment with aluminum amalgam[81] in THF/water to give γ-arylthiolactone 194. A few attempts to improve the yield and stereoselectivity of the desulfurization of 194 were performed. Unfortunately, none of them was successful.

Raney nickel desulfurizations of organic sulfides are believed to proceed through free-radical mechanisms.[98] This is supported by the fact that desulfurizations of acyclic optically active sulfides, having sulfur at the asymmetric center, result in completely racemic products.[99]

It is believed, however, that the stereochemical course of sulfide desulfurization in cyclic systems is not thermodynamically controlled. This has been suggested by studies of van Tamelen and Grant[100] on the desulfurization of cis and trans-3-methyl-3-benzylmercapto-cyclohexyl β-naphthoate, 195 and 196.



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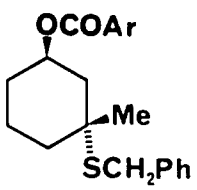

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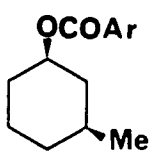

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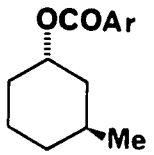
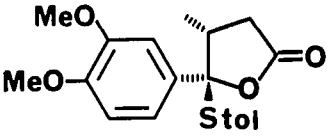


198

	cis (197)	trans (198)
cis (195)	37%	63%
trans (196)	56%	44%

The varying amounts of cis and trans products from the two precursors indicate that at least one of the product mixtures was not thermodynamically equilibrated. It was found that the reaction proceeded predominantly with retention for both isomers. That appears to be the case, as well, for γ-arylthio-γ-lactones 160 and 193. Desulfurization of 193 proceeded with moderate stereoselectivity (2:1) in good agreement with the results summarized above.



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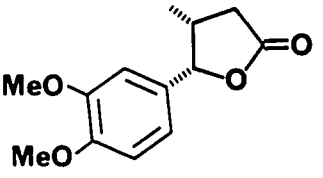
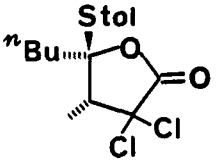


152



193

Alternatively, desulfurization of lactone 160 with Raney nickel proceeded with unusual selectivity to give cis-lactone 152, contaminated by trace amounts (ca. 30:1 ratio) of its trans epimer. This high selectivity may be produced by the presence of the 3,4-dimethoxyphenyl group in 160 which may have a distinct effect on the adsorption of the sulfide substrate on the catalyst surface and thereby on the steric course of the desulfurization.

In summary, the sulfoxide directed lactonization of several acyclic vinyl sulfoxides (151, 157, 168 and 191) has been studied. The reaction was found to proceed in a stereospecific manner and in good yields. Further studies are necessary, however, to improve the stereoselectivity of the desulfurization of the resulting γ-arylthiolactones. Raney nickel was found to proceed predominantly with retention, although in variable ratios and low yields.

Tri-n-butyltin hydride, alternatively, proceeds in good yields and is the reagent of choice for bicyclic systems.[83] In monocyclic cases, however, it shows a significant lack of stereoselectivity.

EXPERIMENTAL

1. General.

Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained at 60 MHz on a Varian T-60A, at 300 MHz on a Brüker AM-300 FT NMR spectrometer or at 360 MHz on a Brüker WM-360 FT NMR spectrometer, using tetramethylsilane or the 7.24 ppm resonance of residual chloroform as internal reference.

Carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra were measured at 22.5 MHz on a JEOL FX90Q, at 75.3 MHz on a Brüker AM-300 FT NMR spectrometer or at 90.4 MHz on a Brüker WM-360 FT NMR spectrometer in chloroform-d solution with a deuterium lock and proton-noise decoupling. The $CDCl_3$ resonance at 77.00 ppm was used as the internal reference.

In both ^{1}H-NMR and ^{13}C-NMR, chemical shifts are reported in δ units downfield from tetramethylsilane. The following abbreviations are used to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and dist = distorted.

Melting points (mp) were determined in Kimax-51 soft glass capillary tubes using a Thomas-Hoover Uni-Melt oil

immersion capillary melting point apparatus and are uncorrected.

Infrared (IR) spectra were recorded on either a Perkin-Elmer 727B or 457 grating infrared spectrophotometer calibrated with the 1601 cm^{-1} absorption of polystyrene. Band positions are reported in wavenumbers (cm^{-1}).

Low resolution mass spectra (MS) were obtained on a Finnigan 4021 GCMS/DS instrument at 70 eV. Masses are reported in units of mass over charge (m/z). The molecular and base peaks are indicated by (M) and (100%), respectively.

Elemental analyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, Michigan, or Galbraith Laboratories, Knoxville, Tennessee.

Air and/or moisture-sensitive reactions were conducted in flame-dried glassware, equipped with tight-fitting rubber serum septa, under an atmosphere of dry nitrogen. Reagents and solvents were handled using standard syringe techniques.

Reactions at 0°C, -20°C, -40°C, and -78°C were carried out in an ice/water, dry-ice/carbon tetrachloride, dry-ice/isopropanol bath, respectively.

The following solvents were dried and purified by distillation from the reagents indicated: diethyl ether

(ether), tetrahydrofuran (THF), and 1,2-dimethoxyethane (DME) from lithium aluminum hydride; dichloromethane, acetonitrile, and dimethylsulfoxide (DMSO) from calcium hydride; dimethylformamide (DMF), N,N-diisopropylamine and pyridine from barium oxide; benzene from sodium. All other solvents used were ACS reagent grade.

Commercial methyllithium (low halide in ether), n-butyllithium (in hexane) and tert-butyllithium (in hexane) were purchased from Alfa Chemicals and titrated[101] prior to use. Technical copper(I) cyanide was purchased from J. T. Baker and was employed without further purification.

Flash chromatography was performed on Baker 40 μm particle diameter silica gel. Other column chromatography was done on Merck 70-230 mesh, Grace 100-200 mesh, or Baker 40-140 mesh silica gel. Analytical thin-layer chromatography (tlc) was carried out on Analtech 250 μm or on Eastman chromagram 100 μm silica gel plates, with visualization by UV light (254 nm), or by staining with either iodine vapor, 2,4-dinitrophenylhydrazine or acidic vanillin solution.

2. Preparation of Relevant Compounds.

The following section describes the experimental procedures for the preparation of the relevant compounds included in this thesis.

Reaction of Cyclopentadiene Monoepoxide[15] with Cyanocuprates.

All cuprates were prepared in situ by reaction of organolithium or organomagnesium compounds with copper(I) cyanide in diethyl ether. The salt content of the starting organolithium or organomagnesium solution is very important, especially in the case of methyllithium. A common ion effect seems to cause the cyanocuprate to be quite insoluble, to the extent that the reaction with the epoxide may not take place at all or result in lower yields when the solutions are not salt free.

Ether solutions of (MeCuCN)Li appear as an intense yellow color, while (n-BuCuCN)Li and (tert-BuCuCN)Li solutions are dark brown-black in color. Other alkyl-, vinyl- and aryl-cyanocuprates range from light beige to black. No change in color is usually observed when the epoxide is added to the cuprate reagent, but the reactions invariably turn black upon warming to room temperature.

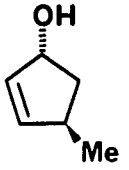
General Procedure for the Reaction of Cyclopentadiene Monoepoxide with Mixed Cyanocuprates.

In most cases a suspension of 1.5 equivalents of CuCN in ether was cooled to -40°C under nitrogen and 1.3 equivalents of the organolithium or organomagnesium solution was slowly added. The suspension would then be

stirred at -40°C for 1 h. In some runs, alkylcyanocuprates were allowed to warm up to 0°C for 1 h without any lowering of the yield of the reaction. After the solution was cooled to -78°C (acetone-dry ice bath), a solution of freshly distilled cyclopentadiene monoepoxide in ether was added dropwise, and the mixture was allowed to slowly warm up to room temperature.

In a typical run, a 1-L three-necked flask equipped with a mechanical stirrer and a pressure-equalizing addition funnel was charged with 34.0 g (0.38 mol) of technical-grade copper(I) cyanide and 500 mL of anhydrous ether. The above suspension was cooled to -40°C and 157 mL of n-BuLi (2.1 M, 0.33 mol) was added slowly from the dropping funnel. The resulting black solution of the cuprate was stirred at -40°C for 1 h and then cooled to -78°C. A solution of 20.5 g (0.25 mol) of freshly distilled cyclopentadiene monoepoxide in 50 mL of anhydrous ether was added dropwise, and the mixture was allowed to warm up to room temperature overnight.

The reaction mixture was quenched with 100 mL of a saturated ammonium chloride solution and filtered through a Celite pad. The organic layer was separated, washed with a saturated sodium chloride solution (2 x 50 mL), and dried over anhydrous magnesium sulfate. After filtration of the drying agent, the solvent was removed on a rotary evaporator to afford 58.2 g (95%) of 14 as a light yellow oil. The



13

crude product was of high purity as determined by tlc and ^{1}H-NMR. Only one product was detected by the mentioned techniques.

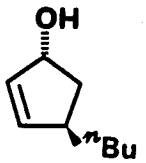
trans-4-Methylcyclopent-2-enol (13).

Cyclopentadiene monoepoxide (27.0 g, 0.33 mol) was reacted with (MeCuCN)Li according to the general procedure to give 25.2 g of 13 (78% yield) as a light yellow liquid. An analytical sample was obtained by distillation, bp 70-72°C (30 mm Hg).

^{1}H-NMR ($CDCl_3$, 360 MHz): 1.010 (3H, d, J = 7.10 Hz), 1.514-1.539 (1H, br), 1.693 (1H, ddd, J = 13.96, 7.08, 5.20 Hz), 1.944 (1H, ddd, J = 13.96, 7.47, 2.59 Hz), 2.937 (1H, m), 4.860 (1H, dqd, J = 7.10, 2.10, 0.53 Hz), 5.771 (1H, dt, J = 5.54, 2.20 Hz), 5.881 (1H, ddd, J = 5.54, 2.06, 0.53 Hz).

^{13}C-NMR ($CDCl_3$): 20.910, 38.409, 42.417, 77.197, 132.075, 141.501.

IR (neat): 840, 940, 980, 1020, 1090, 1190, 1360, 1460, 1615, 2870-3050, 3350.



14

MS: 90 (M), 81 (100%).

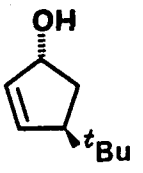
Anal. Calcd for $C_6H_{10}O$: C, 73.43; H, 10.27.
Found: C, 73.32; H, 10.43.

trans-4-n-Butylcyclopent-2-enol (14).

Cyclopentadiene monoepoxide (20.5 g, 0.25 mol) was reacted with (n-BuCuCN)Li according to the general procedure to give 58.2 g of 14 (95% yield) as a light yellow oil. An analytical sample could be obtained by distillation, bp 84°C (2.5 mm Hg) or flash chromatography (hexane: ethyl acetate, 5:1; R_f = 0.21).

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.865 (3H, t, J = 6.85 Hz), 1.206-1.374 (6H, m), 1.580-1.651 (1H, br), 1.737 (1H, ddd, J = 13.96, 7.08, 5.25 Hz), 1.884 (1H, ddd, J = 13.96, 7.49, 2.69 Hz), 2.801-2.839 (1H, m), 4.820 (1H, dqd, J = 7.10, 2.10, 0.70 Hz), 5.779 (1H, dt, J = 5.58, 2.19 Hz), 5.920 (1H, ddd, J = 5.58, 2.00, 0.70 Hz).

^{13}C-NMR ($CDCl_3$): 13.724, 22.555, 29.922, 35.394, 40.216, 43.845, 76.350, 132.755, 139.980.



15

IR (neat): 750, 1030, 1120, 1370, 1470, 1620, 2860-3050, 3350.

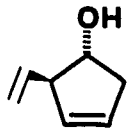
MS: 140 (M), 123 (52%).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50.
Found: C, 77.12; H, 11.57.

trans-4-tert-Butylcyclopent-2-enol (15).

Cyclopentadiene monoepoxide (820 mg, 10 mmol) was reacted with (tert-BuCuCN)Li according to the general procedure to give 1.23 g of 15 (88% yield) as a light yellow oil. An analytical sample could be obtained by distillation, bp 70-71°C (1.6 mm Hg) or flash chromatography (hexane:ethyl acetate, 5:1; R_f = 0.20).

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.820 (9H, s), 1.509-1.535 (1H, br), 1.682 (1H, ddd, J = 14.20, 8.00, 2.90 Hz), 1.947 (1H, ddd, J = 14.20, 7.25, 5.40 Hz), 2.719 (1H, ddq, J = 8.00, 5.40, 2.20 Hz), 4.805 (1H, dqd, J = 7.20, 2.20, 0.85 Hz), 5.840 (1H, dt, J = 5.70, 2.26 Hz), 5.943 (1H, ddd, J = 5.70, 2.10, 0.85 Hz).



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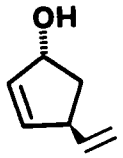


17

^{13}C-NMR ($CDCl_3$): 27.427, 29.120, 35.982, 55.539, 77.101, 133.819, 137.286.

IR (neat): 820, 875, 1165, 1390, 1430, 1500, 1510, 2820-3100, 3370.

MS: 140 (M), 123 (54.5%).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50.
Found: C, 77.20; H, 11.51.

trans-2-Vinylcyclopent-3-enol (16) and trans-4-Vinylcyclopent-2-enol (17).

Cyclopentadiene monoepoxide (12.30 g, 150 mmol) was reacted with (vinyl-CuCN)Li according to the general procedure to give 12.40 g of a pale yellow liquid (75% yield) of a 1:1 mixture of 16 and 17 after distillation (bp 70°C at 15 mm Hg) as determined by integration of its ^{1}H-NMR spectrum. The adducts could not be separated by chromatography or distillation.

Compound (16):[102]

^{1}H-NMR ($CDCl_3$, 60 MHz): 2.30-2.65 (2H, m), 3.12-3.43 (1H, m), 4.10-4.42 (1H, m), 4.83-5.21 (3H, m), 5.50-5.83 (2H, m).

IR (neat): 820, 850, 915, 990, 1040, 1320, 1420, 1640, 2850-3080, 3340.

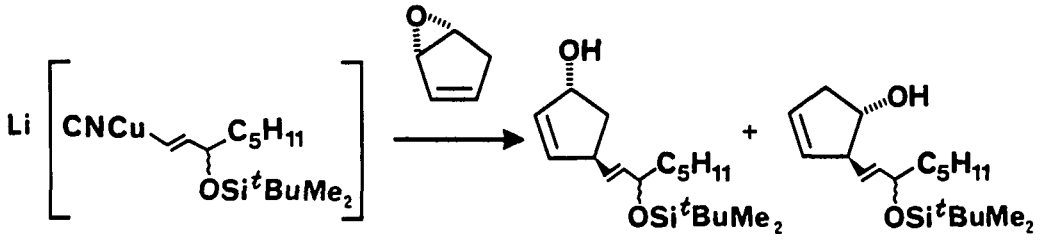
Anal. Calcd for $C_7H_{10}O$: C, 76.33; H, 9.08.
Found: C, 76.22; H, 9.15.

Compound (17) (in the mixture):

^{1}H-NMR ($CDCl_3$, 60 MHz): 1.80-2.21 (2H, m), 3.42-3.63 (1H, m), 4.75-5.30 (4H, m), 5.75-5.95 (2H, s).

IR (neat): 795, 915, 1000, 1035, 1645, 2850-3000, 3060, 3350.

Anal. (on mixture) Found: C, 76.05; H, 9.43.



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trans-2-[(1E)-3-tert-Butyldimethylsilyloxyoct-1-enyl]-cyclopent-3-enol (9) and trans-4-[(1E)-3-tert-Butyldimethylsilyloxyoct-1-enyl]-cyclopent-2-enol (8).

A 500 mL round bottomed flask equipped with a pressure equalizing addition funnel and a magnetic stirring bar was charged with 20.0 g (54.3 mmol) of (1E)-1-iodo-3-tert-butyldimethylsilyloxy-1-octene and 215 mL of anhydrous ether, and cooled to -78°C (nitrogen atmosphere). From the addition funnel was added dropwise 62 mL of tertBuLi (1.84 M, 114.0 mmol). After the addition was complete, the mixture was further stirred at -78°C for 3 h. The resulting solution of the corresponding vinyllithium was then transferred via a double-tipped needle to a mechanically stirred suspension of 10.2 g (114.0 mmol) of technical grade copper(I) cyanide in 215 mL of anhydrous ether at -40°C. After being stirred at this temperature for 1.5 h, the brown-orange solution of the organocuprate reagent was ready for use as evidenced by a negative Gilman's test.[103]

To the above solution was added dropwise 9.4 g (114.0 mmol) of freshly distilled cyclopentadiene monoepoxide. The mixture was stirred between -40°C and -30°C for 2 h and then allowed to warm up to room temperature over 5 h. The reaction was then quenched with 100 mL of a saturated ammonium chloride solution and filtered through a Celite pad. The organic layer was decanted, washed with a saturated sodium chloride solution (2 x 100 mL), and dried over anhydrous magnesium sulfate. The drying agent was filtered and the solvent was removed on a rotary evaporator to give 19.1 g of light yellow oil. Column chromatography (hexane:ethyl acetate, 5:1) provided 1.90 g of 3-tert-butyldimethylsilyloxy-1-octene and 14.07 g (80% yield based on vinyl iodide) of a 1:4 mixture of 1,2- and 1,4-adducts, 9 and 8, respectively. A second chromatography of an aliquot of this mixture provided analytically pure samples of each regioisomer.

Compound (9):

R_f = 0.35, hexane:ethyl acetate, 5:1.

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.00 (6H, 4 x s, two per epimer at C3'), 0.81-0.90 (3H, m), 0.86 and 0.87 (9H, 2 x s, one per epimer at C3'), 1.24-1.48 (8H, m), 2.26 (1H, m), 2.67 (1H, dtd, J = 17.0, 4.0, 2.0 Hz), 3.14-3.15 (1H, m), 4.01-4.03 (1H, m), 4.13 (1H, m), 5.41-5.46 (2H, m), 5.59-5.62

(1H, m), 5.71-5.74 (1H, m).

IR (neat): 770, 840, 965, 1080, 1255, 1360, 1470, 2860-3050, 3400.

Compound (8):

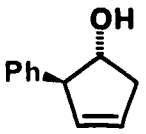
R_f = 0.30, hexane:ethyl acetate, 5:1.

^{1}H-NMR ($CDCl_3$, 360 MHz): -0.009 and 0.013 (6H, 2 x s), 0.81-0.88 (3H, m), 0.86 (9H, s), 1.24-1.48 (8H, m), 1.87 (1H, dddd, J = 13.9, 6.8, 5.1, 2.9 Hz), 1.95 (1H, ddt, J = 13.9, 7.6, 2.9 Hz), 3.48-3.50 (1H, m), 3.99 (1H, dt, J = 5.8, 5.5, 6.6 Hz), 4.85-4.89 (1H, m), 5.33 (1H, ddd, J = 15.4, 7.0, 1.0 Hz), 5.41 (1H, ddd, J = 15.4, 5.9, 1.3 Hz), 5.81-5.87 (2H, m).

^{13}C-NMR ($CDCl_3$): -4.0, -3.5, 14.7, 23.3, 25.7, 26.6, 28.0, 32.5, 39.0, 41.6, 47.4, 74.2, 77.5, 133.3, 134.0, 134.3, 138.9.

IR (neat): 770, 840, 970, 1080, 1260, 1360, 1405, 1470, 2860-3050, 3400.

Anal. Calcd for $C_{19}H_{36}O_2Si$: C, 70.31; H, 11.18.
Found: C, 70.21; H, 11.15.



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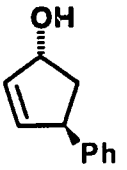


19

trans-2-Phenylcyclopent-3-enol (18) and trans-4-Phenylcyclopent-2-enol (19).

Cyclopentadiene monoepoxide (1 g, 12.2 mmol) was reacted with (PhCuCN)Li according to the general procedure to give 320 mg of 18 and 650 mg of 19 (50% combined yield) as light yellow oils after chromatography (hexane:diethyl ether, 1:1).

Compound (18):

R_f = 0.42, hexane:diethyl ether, 1:1.

^{1}H-NMR (CCl_4, 60 MHz): 2.20-2.60 (2H, m), 2.78-2.90 (1H, br s), 3.48-3.70 (1H, m), 3.90-4.25 (1H, m), 5.60-5.78 (2H, m), 7.02-7.20 (5H, s).

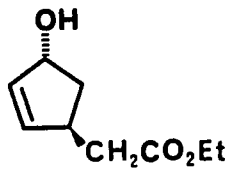
^{13}C-NMR ($CDCl_3$): 41.2, 60.5, 80.6, 126.4, 127.3, 128.4, 129.3, 132.2, 142.7.

IR (neat): 690, 745, 1045, 3350.

MS: 160 (M), 142 (100%), 115, 104, 91, 77.

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55.

Found: C, 82.35; H, 7.35.



20

Compound (19):

R_f = 0.20 hexane:diethyl ether, 1:1.

^{1}H-NMR (CCl_4, 60 MHz): 1.95-2.34 (2H, m), 3.86-3.97 (1H, br s), 3.96-4.28 (1H, m), 4.82-5.15 (1H, m), 5.94-6.02 (2H, s), 7.19-7.22 (5H, s).

^{13}C-NMR ($CDCl_3$): 44.0, 50.2, 77.0, 126.4, 127.2, 128.7, 134.3, 138.7, 145.1.

IR (neat): 690, 740, 1021, 1600, 3345.

MS: 160 (M), 142, 115 (100), 104, 91, 77.

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55.
Found: C, 82.35; H, 7.61.

4-Carboethoxymethylen-cyclopent-2-enol (20).

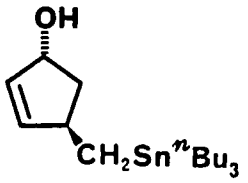
n-Butyllithium (8 mmol, 4.44 mL of 1.80 M solution) was added under a nitrogen atmosphere to a cold (0°C) solution of dry N,N-diisopropylamine (1.12 mL, 8 mmol) in 10 mL of anhydrous THF. After 30 min, the solution of LDA was cooled to -78°C and then transferred under nitrogen onto a well-stirred suspension of technical-grade copper(I) cyanide (1.61 g, 18 mmol) and dry ethyl acetate (700 mg,

8 mmol) in 30 mL of anhydrous THF at -100°C. The mixture was allowed to warm up to -30°C slowly and was then cooled down to -78°C. To the above solution was added dropwise 328 mg (4.0 mmol) of freshly distilled cyclopentadiene monoepoxide. The mixture was allowed to warm up to room temperature over 4 h. The reaction was then quenched with 30 mL of a saturated ammonium chloride solution and the organic layers were removed on a rotary evaporator. Then 50 mL of ether was added, and the mixture was filtered through a Celite pad. The organic layer was decanted and the aqueous extracted with ether (3 x 25 mL). The combined organic extracts were washed with brine and dried over magnesium sulfate. Filtration of the drying agent and evaporation of the solvent in vacuo gave a crude product which was chromatographed on flash silica using hexane-ether 1:1 as an eluent to give 115 mg of 20 as a light yellow liquid (17%).

R_f = 0.25, hexane:ether, 1:1.

^{1}H-NMR ($CDCl_3$, 360 MHz): 1.212 (3H, t, J = 7.1 Hz), 1.352 (1H, dt, J = 13.9, 4.8 Hz), 2.374 (1H, dd, J = 15.7, 7.4 Hz), 2.447 (1H, dd, J = 15.7, 6.5 Hz), 2.523 (1H, dt, J = 13.9, 8.0 Hz), 2.893-2.949 (1H, m), 4.087 (2H, q, J = 7.1 Hz), 4.761 (1H, dd, J = 8.0, 4.8 Hz), 5.776-5.823 (m, 2H).

^{13}C-NMR ($CDCl_3$): 14.212, 39.782, 40.432, 40.649, 60.368, 77.000, 134.315, 136.699, 172.616.



21

IR (neat): 770, 1035, 1075, 1370, 1730, 2880-3000, 3065, 3200-3600.

MS: 170 (M), 152, 125, 107, 95, 82, 79 (100%).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29.
Found: C, 63.56; H, 8.31.

4-tri-n-Butylstannylmethylen-cyclopent-2-enol (21).

n-Butyllithium (1 mmol, 0.38 mL of 2.63 M solution) was added under a nitrogen atmosphere to a cold (-50°C) solution of 431 mg (1 mmol) of tri-n-butylstannylmethyl iodide[67] in 5 mL of anhydrous ether. After 1 h, the solution was transferred under nitrogen onto a well-stirred suspension of copper(I) cyanide (134 mg, 1.5 mmol) in 5 mL of dry ether. From this point, the general procedure described before was followed to give 19 mg of 21 (5% yield) as a light yellow oil after chromatography (hexane:diethyl ether, 3:1; R_f = 0.36).

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.750-1.646 (31H, m), 1.994 (1H, dd, J = 14.2, 7.6 Hz), 3.031-3.112 (1H, m), 4.820-4.891 (1H, m), 5.736-5.754 (1H, m), 5.846-5.862 (1H, m).

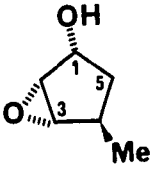
IR ($CDCl_3$): 1030-1050, 2860-3000, 3600.

Anal. Calcd for $C_{18}H_{36}OSn$: C, 55.85; H, 9.37.
Found: C, 55.62; H, 9.26.

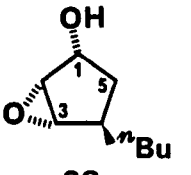
General Procedure for the Epoxidation of trans-4-Substituted Cyclopent-2-enoles.

In all cases the crude allylic alcohols could be employed without affecting the yield of the reaction. When the crude consisted of a mixture of 1,4- and 1,2-adducts, only the 1,4-adduct was epoxidized, thus allowing for an easier chromatographic separation.

In a typical run, a 1-L three-necked round-bottomed flask fitted with a magnetic stirring bar, dropping funnel and reflux condenser was charged with 217 mg (0.80 mmol) of vanadyl acetylacetonate and 50 mL of anhydrous benzene. A solution of 40.7 g of crude product from the previous cuprate reaction (8 and 9) in 250 mL of dry benzene was added dropwise followed by 16.3 g (0.16 mol) of 90% tert-butylhydroperoxide. The resulting light orange solution was stirred at 40°C for 24 h. The solvent was removed on a rotary evaporator and the residue taken up in ether and filtered through a Florisil pad. Concentration of the filtrate under reduced pressure afforded 46.3 g of a brown-orange oil which was chromatographed on silica gel (hexane:ethyl acetate, 5:1) to provide 6.0 g of 1,2-adduct 9 and 23.1 g (98%) of epoxyalcohol 29.



27



28

trans-4-Methyl-cis-2,3-epoxycyclopentanol (27).

The epoxidation of 13 (20.9 g, 0.21 mol) according to the general procedure gave 22.8 g of 27 (95% yield) as a brown-orange oil. An analytical sample was obtained by chromatography (hexane:ethyl acetate, 1:2; R_f = 0.57).

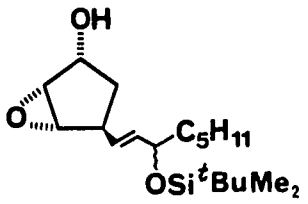
^{1}H-NMR ($CDCl_3$, 360 MHz): 0.885 (3H, d, J = 7.4 Hz), 1.379 (1H, dt, J = 13.0, 7.9 Hz), 1.617 (1H, dd, J = 13.0, 7.9 Hz), 2.356 (2H, quintet, J = 7.4 Hz and OH-broad), 3.236 (1H, d, J = 2.7 Hz), 3.456 (1H, td, J = 8.1, 1.4 Hz).

IR (neat): 810, 830, 850, 870, 930, 980, 1065, 1080, 1230, 1390, 1465, 2880-3010, 3420.

Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83.
Found: C, 63.21; H, 8.76.

trans-4-n-Butyl-cis-2,3-epoxycyclopentanol (28).

The epoxidation of 14 (120.3 g, 0.86 mol) according to the general procedure gave 134.3 g of 28 (100% yield) as a brown-orange oil. An analytical sample was obtained by chromatography (hexane:ethyl acetate, 3:1; R_f = 0.24).



29

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.813 (3H, dist t, J = 6.4 Hz), 1.051-1.228 (6H, m), 1.296 (1H, dt, J = 13.2, 8.0 Hz), 1.647 (1H, dd, J = 13.2, 8.0 Hz), 2.182 (1H, dist q, J = 7.5 Hz), 2.800-2.900 (1H, br), 3.234 (1H, d, J = 2.7 Hz), 3.408 (1H, dist dd, J = 2.7, 1.2 Hz), 4.225 (1H, td, J = 8.0, 2.0 Hz).

^{13}C-NMR ($CDCl_3$): 13.779, 22.555, 29.435, 31.223, 33.173, 38.320, 58.526, 59.772, 72.232.

IR (neat): 850, 870, 1070, 1450, 2880-3000, 3420.

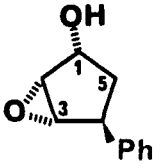
MS: 156 (M), 138, 109, 95, 83, 71, 57, 41 (100%).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32.
Found: C, 69.23; H, 10.21.

cis-2,3-Epoxy-trans-4-[(1E)-3-tert-butyldimethylsilyloxyoct-1-enyl]-cyclopentanol (29).

The epoxidation of 40.7 g of crude product containing 8 and 9 according to the general procedure gave 6.0 g of 9 and 23.1 g of 29 (98% yield), as light yellow oils, after chromatography (hexane:ethyl acetate, 5:1).

R_f = 0.29, hexane:ethyl acetate 4:1.



30

^{1}H-NMR ($CDCl_3$, 360 MHz): -0.015-0.016 (6H, 4xs, two of them collapsed), 0.82-0.91 (3H, m), 0.859-0.862 (9H, 2xs), 1.22-1.51 (9H, m), 1.81 (1H, ddd, J = 13.0, 10.3, 9.0 Hz), 1.87-1.92 (1H, m, OH), 2.94 (1H, t, J = 7.7 Hz), 3.32 (1H, dd, J = 5.3, 2.7 Hz), 3.49-3.51 (1H, m), 4.00 (1H, dist q, J = 5.8 Hz), 4.32 (1H, br t, J = 7.9 Hz), 5.36 (1H, dd, J = 15.6, 7.6 Hz), 5.48 (1H, dd, J = 15.6, 6.1 Hz).

^{13}C-NMR ($CDCl_3$): -4.64, -4.21, 13.94, 18.27, 22.61, 24.94, 25.91, 31.82, 34.20, 38.32, 40.81, 58.47, 58.91, 72.56, 73.26, 128.14, 135.61.

IR (neat): 780, 815, 840, 970, 1080, 1255, 1465, 2880-3000, 3430.

trans-4-Phenyl-cis-2,3-epoxycyclopentanol (30).

The epoxidation of 19 (328 mg, 2.05 mmol) according to the general procedure gave 325 mg of 30 (90% yield) as a brown-orange oil. An analytical sample was obtained by chromatography (hexane:ethyl acetate, 3:1).

^{1}H-NMR (CCl_4, 60 MHz): 1.42-2.16 (m, 2H), 3.35-3.66 (m, 4H), 4.34-4.70 (1H, t, J = 8.0 Hz), 6.92-7.34 (5H, m).

^{13}C-NMR ($CDCl_3$): 36.153, 44.441, 59.556, 60.097, 72,882, 126.839, 127.164, 128.789, 141.400.

IR (neat): 698, 760, 850, 972, 1165, 3400.

MS: 176 (M), 158, 115, 104 (100%). 91, 77.

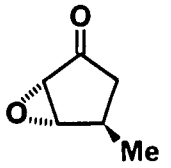
Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86.
Found: C, 74.68; H, 6.88.

General Procedure for the Synthesis of 4-Substituted-2,3-epoxycyclopentanones.

A large excess of chromium trioxide was always used (6-10 equivalents). Use of smaller amounts of oxidizing agent resulted in decreased yields. These yields were also highest when the reagent was preformed in situ. When the chromium trioxide-pyridine complex was isolated and subsequently used for the reaction, lower yields were obtained. Optimum yields were achieved when the oxidation was carried out under fairly dilute conditions (0.011 M in substrate).

In a typical run, a 3-L three-necked flask equipped with a mechanical stirrer and an addition funnel was charged with 28.0 g (354 mmol) of dry pyridine and 1.5 L of anhydrous dichloromethane. The flask was cooled to

0°C and 17.7 g (177 mmol) of vacuum-dried chromium trioxide was added in small portions. The resulting burgundy solution was stirred at 10-15°C for 15 min and then cooled to 0°C again. A solution of 6.0 g (17.6 mmol) of epoxyalcohol 29 in 100 mL of anhydrous dichloromethane was added slowly. After the addition was complete, the dark brown suspension was stirred at room temperature for an additional 2 h. The mixture was then filtered through a Celite pad , and the gummy residue was rinsed exhaustively with dichloromethane. The combined organic solution was concentrated on a rotary evaporator. The residue was taken up in 400 mL of ether and successively washed with cold 5% HCl, saturated sodium bicarbonate solution and brine and finally dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration under reduced pressure gave 5.60 g of a viscous brown-orange oil which was chromatographed on silica gel (hexane:ethyl acetate, 9:1) to afford 4.90 g (82%) of epoxyketone 33 as a light yellow oil.



31

trans-4-Methyl-2,3-epoxycyclopentanone (31).

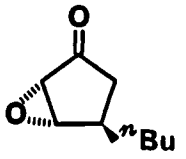
Epoxy alcohol 27 (4.7 g, 41 mmol) was oxidized according to the general procedure to give 3.5 g of 31 (75% yield) as a pale yellow liquid after chromatography on silica gel (hexane:ethyl acetate, 3:1).

^{1}H-NMR ($CDCl_3$, 360 MHz): 1.023 (3H, t, J = 7.2 Hz), 1.630 (1H, d, J = 17.7 Hz), 2.475 (1H, dd, J = 17.7, 7.8 Hz), 2.628 (1H, quintet, J = 7.2 Hz), 3.262 (1H, d, J = 2.4 Hz), 3.656 (1H, d, J = 2.4 Hz).

^{13}C-NMR ($CDCl_3$): 17.084, 29.652, 38.970, 54.030, 62.319, 209.725.

IR (neat): 800, 845, 990, 1180, 1215, 1385, 1415, 1465, 1755, 2880-3060.

Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19.
Found: C, 64.18; H, 7.24.



32

trans-4-n-Butyl-2,3-epoxycyclopentanone (32).

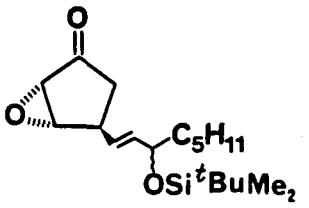
Epoxy alcohol 28 (7.8 g, 50 mmol) was oxidized according to the general procedure to give 6.2 g of 32 (80% yield) as a light yellow oil after chromatography on silica gel (hexane:ethyl acetate, 5:1; R_f = 0.60).

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.858-0.897 (3H, m), 1.275-1.464 (6H, m), 1.752 (1H, d, J = 17.9 Hz), 2.434 (1H, dd, J = 17.9, 8.0 Hz), 2.508-2.567 (1H, m), 3.277 (1H, d, J = 2.4 Hz), 3.719 (1H, d, J = 2.4 Hz).

^{13}C-NMR ($CDCl_3$): 13.83, 22.65, 28.85, 31.65, 35.23, 37.49, 54.35, 61.57, 209.89.

IR (neat): 735, 805, 905, 995, 1130, 1180, 1205, 1295, 1425, 1470, 1745, 2840-2980.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.09; H, 9.15.
Found: C, 69.10; H, 9.02.



33

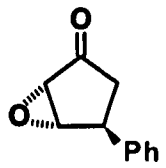
trans-2,3-Epoxy-4-[(1E)-3-tert-butyldimethylsilyl-oxyoct-1-enyl]-cyclopentanone (33).

Epoxy alcohol 29 (6.0 g, 17.6 mmol) was oxidized according to the general procedure to give 5.6 g of 33 (82% yield) as a light yellow oil after chromatography on silica gel (hexane:ethyl acetate, 9:1; R_f = 0.60).

^{1}H-NMR ($CDCl_3$, 360 MHz): -0.033-0.005 (6H, 4xs), 0.83-0.89 (3H, m), 0.846-0.851 (9H, 2xs), 1.17-1.43 (8H, m), 1.85 (1H, dd, J = 18.0, 6.7 Hz), 2.55 (1H, dd, J = 18.1, 8.1 Hz), 3.21 (1H, t, J = 8.1 Hz), 3.32 (1H, d, J = 1.9 Hz), 3.73 (1H, d, J = 2.0 Hz), 4.03 (1H, dist q, J = 6.1 Hz), 5.41 (1H, ddt, J = 15.6, 8.1, 1.4 Hz), 5.58 (1H, ddd, J = 15.6, 6.1, 0.9 Hz).

^{13}C-NMR ($CDCl_3$): -3.39, -2.91, 15.35, 19.58, 23.91, 26.19, 27.21, 33.07, 38.97, 39.51, 55.55, 62.21, 74.04, 128.03, 138.22, 210.27.

IR (neat): 780, 830, 970, 1060-1090, 1255, 1365, 1405, 1465, 1750, 2860-3060.



34

Anal. Calcd for $C_{19}H_{34}O_3Si$: C, 67.41; H, 10.12.
Found: C, 67.53; H, 10.12.

trans-4-Phenyl-2,3-epoxycyclopentanone (34).

Epoxy alcohol 30 (238 mg, 1.35 mmol) was oxidized according to the general procedure to give 186 mg of 34 (79% yield) as a pale yellow oil after chromatography on silica gel (hexane:diethyl ether, 1:1).

^{1}H-NMR (CCl_4, 60 MHz): 2.01 (1H, dd, J = 18.0, 2.0 Hz), 2.71 (1H, dd, J = 18.0, 8.0 Hz), 3.29-3.40 (1H, d, J = 2.0 Hz), 3.57-3.82 (2H, m), 6.94-7.42 (5H, m).

^{13}C-NMR ($CDCl_3$): 39.1, 40.6, 54.6, 61.8, 126.9, 127.4, 129.1, 209.2.

IR (neat): 700, 760, 787, 845, 1175, 1750.

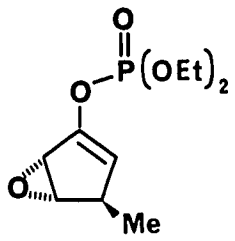
MS: 174 (M), 157, 131, 117 (100%), 77.

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79.
Found: C, 75.66; H, 5.85.

General Procedure for the Synthesis of Epoxycyclopentenyl Phosphates.

The crude products were in most cases sufficiently pure for further reaction with cyanocuprates. They could be purified by vacuum distillation or flash chromatography. When possible, distillation was the method of choice since significant decomposition takes place when the epoxy enol phosphates are chromatographed.

In a typical run: To a magnetically stirred solution of 3.64 mL (26 mmol) of dry N,N-diisopropylamine in 300 mL of anhydrous tetrahydrofuran in a 500-mL round bottomed flask at 0°C was added 15.2 mL of n-butyllithium (1.58 M, 24 mmol). After 30 min, the solution was cooled to -78°C and 2.24 g (20 mmol) of epoxy ketone 31 dissolved in 30 mL of anhydrous tetrahydrofuran was added dropwise. After 1 h at -78°C, the enolate was quenched with 3.47 mL (24 mmol) of freshly distilled diethyl chlorophosphate, and the reaction mixture was allowed to warm up to room temperature over 5 h. The solution was then quenched with 75 mL of a saturated ammonium chloride solution and tetrahydrofuran was removed under reduced pressure. The residue was extracted with ethyl acetate (3 x 50 mL) and the combined organic extracts were dried over anhydrous sodium sulfate. Filtration of the drying agent and concentration under reduced pressure gave a crude product which was distilled under reduced pressure to give 4.66 g (94%) of pure 35 as



35

a pale yellow liquid (bp = 100-110°C - bath temperature - at 0.025 mm Hg).

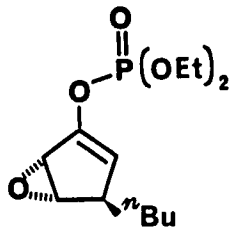
Diethyl trans-2,3-Epoxy-4-methyl-5-cyclopentenyl Phosphate (35).

The reaction of 31 (2.24 g, 20 mmol) with LDA and diethyl chlorophosphate according to the general procedure gave 4.66 g of 35 (94% yield) as a pale yellow liquid after distillation (bp 100-110°C - bath temperature - at 0.025 mm Hg).

^{1}H-NMR ($CDCl_3$, 360 MHz): 1.005 (3H, d, J = 7.3 Hz), 1.259-1.308 (6H, m), 2.715-2.735 (1H, m), 3.550 (1H, t, J = 2.8 Hz), 3.781 (1H, dd, J = 2.8, 2.2 Hz), 4.105-4.173 (4H, m), 5.327-5.338 (1H, m).

^{13}C-NMR ($CDCl_3$): 15.729, 16.054, 17.190, 37.610, 56.197, 56.522, 59.820, 64.431, 64.702, 118.226, 118.442, 151.055.

IR (neat): 825, 1000, 1180, 1280, 1340, 1375, 1450, 1630, 2850-3000.



36

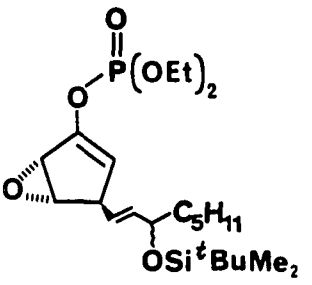
Anal. Calcd for $C_{10}H_{17}O_5P$: C, 48.39; H, 6.90.
Found: C, 48.36; H, 6.80.

Diethyl trans-2,3-Epoxy-4-n-butyl-5-cyclopentenyl Phosphate (36).

The reaction of 32 (3.08 g, 20 mmol) with LDA and diethyl chlorophosphate according to the general procedure gave 5.22 g of 36 (90% yield) as a yellow-orange oil. Compound 36 was not purified.

^{1}H-NMR ($CDCl_3$, 60 MHz): 0.70-1.10 (3H, m), 1.10-1.60 (12H, m), 2.50-2.90 (1H, m), 3.50-3.70 (1H, m), 3.70-3.90 (1H, m), 4.00-4.40 (4H, m), 5.20-5.40 (1H, m).

IR (neat): 820, 1000, 1170, 1280, 1370, 1445, 1630, 2800-3000.



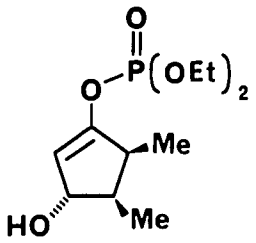
10

Diethyl trans-2,3-Epoxy-4-[1(E)-3-tert-butyldimethylsilyloxyoct-1-enyl]-5-cyclopentenyl Phosphate (10).

The reaction of 33 (340 mg, 1 mmol) with LDA and diethyl chlorophosphate according to the general procedure gave 430 mg of 10 (85% yield) as a yellow-orange oil. Compound 10 was not purified.

^{1}H-NMR (CCl_4, 60 MHz): 0.00 (6H, s), 0.80-0.90 (12H, m), 1.05-1.50 (14H, m), 3.15-3.30 (1H, m), 3.50-3.60 (1H, m), 3.60-3.70 (1H, m), 3.80-4.40 (5H, m), 5.10-5.25 (1H, m). 5.30-5.55 (2H, m).

IR (neat): 780, 840, 970, 1040, 1190, 1260, 1285, 1370, 1460, 1635, 2850-3050.



39

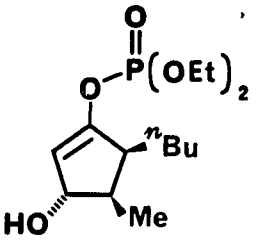
General Procedure for the Reaction of Epoxycyclopentenyl Phosphates with Mixed Cyanocuprates.

The generation of the cuprate was performed as described before. In most cases 3-4 equivalents were employed. In order to ensure good yields, the aqueous layer had to be extracted with ether or ethyl acetate. (The adducts were very polar and if the aforementioned extractions were not performed a significant amount of product was lost.) The adducts were sufficiently stable to be purified by chromatography.

In the case of the 1,4-adducts, complete decomposition was observed upon standing at room temperature for 2-3 days. Storage in a freezer allowed them to keep for 7-10 days without noticeable decomposition.

Diethyl 3α-Hydroxy-4β,5β-dimethyl-2-cyclopentenyl Phosphate (39).

The reaction of 35 (2.73 g, 11 mmol) with (MeCuCN)Li according to the general procedure gave 2.62 g of 39 (90% yield) as a pale yellow oil after chromatography on silica



40

gel (ethyl acetate; R_f = 0.20).

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.949 (3H, d, J = 7.2 Hz), 1.004 (3H, d, J = 7.2 Hz), 1.297-1.338 (6H, m), 2.106 (1H, quintet d, J = 7.2, 5.2 Hz), 2.380-2.460 (1H, br), 2.781 (1H, dist quintet, J = 7.2 Hz), 4.088-4.175 (4H, m), 4.308 (1H, ddd, J = 5.2, 3.0, 1.0 Hz), 5.293 (1H, dd, J = 3.0, 1.0 Hz).

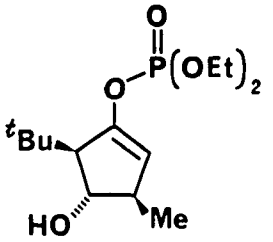
^{13}C-NMR ($CDCl_3$): 12.804, 13.292, 15.838, 16.163, 40.378, 40.649, 44.279, 64.377, 64.648, 80.358, 110.479, 110.641, 156.472.

IR (neat): 1010, 1260, 1445, 1650, 2850-3000, 3400.

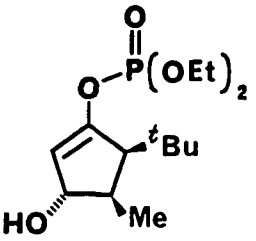
Anal. Calcd for $C_{11}H_{21}O_5P$: C, 49.99; H, 8.01.
Found: C, 48.25; H, 7.85.

Diethyl 5β-n-Butyl-3α-hydroxy-4β-methyl-2-cyclopentenyl Phosphate (40).

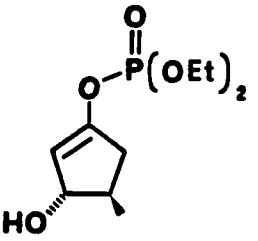
The reaction of 35 (4.72 g, 19 mmol) with (n-BuCuCN)Li according to the general procedure gave 5.53 g of 40 (95% yield) as a pale yellow oil after chromatography on silica gel (ethyl acetate; R_f = 0.33).



41



42



43

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.866 (3H, t, J = 6.9 Hz), 1.016 (3H, d, J = 7.3 Hz), 1.207-1.467 (12H, m), 1.811-1.894 (1H, br), 2.151 (1H, quintet d, J = 7.3, 5.1 Hz), 2.754 (1H, dist q, J = 7.3 Hz), 4.109-4.194 (4H, m), 4.311 (1H, ddd, J = 5.1, 2.0, 1.0 Hz), 5.364 (1H, br s, $W_{1/2}$ = 3.9 Hz).

^{13}C-NMR ($CDCl_3$): 13.237, 13.942, 15.892, 16.163, 22.934, 27.052, 29.760, 44.441, 45.525, 64.323, 64.594, 80.304, 110.858, 155.980.

IR (neat): 1030, 1275, 1650, 2880-3000, 3430.

Anal. Calcd for $C_{14}H_{27}O_5P$: C, 54.89; H, 8.88.
Found: C, 55.06; H, 8.84.

Diethyl 2β-tert-Butyl-3α-hydroxy-4β-methyl-5-cyclopentenyl Phosphate (41), Diethyl 5β-tert-Butyl-3α-hydroxy-4β-methyl-2-cyclopentenyl Phosphate (42) and Diethyl trans-3-Hydroxy-4-methyl-2-cyclopentenyl Phosphate (43).

The reaction of 35 (496 mg, 2 mmol) with (tert-BuCuCN)-Li according to the general procedure gave 180 mg of 41, 120 mg of 42 and 50 mg of 43 (60% combined yield of a 3:2:1 mixture) as pale yellow oils after chromatography on

silica gel (ethyl acetate).

Compound (41): R_f = 0.41, ethyl acetate

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.885 (9H, s), 0.987 (3H, d, J = 7.0 Hz), 1.215-1.257 (6H, m), 2.319-2.382 (2H, m), 3.100-3.300 (1H, br), 3.514-3.525 (1H, m), 4.005-4.068 (4H, m), 5.121 (1H, m).

^{13}C-NMR ($CDCl_3$): 15.729, 16.000, 19.196, 27.864, 31.873, 44.225, 62.752, 63.023, 63.998, 64.269, 79.708, 113.512, 113.675, 147.642, 148.075.

IR (neat): 755, 855, 910, 975, 1030, 1270, 1370, 1400, 1655, 2870-3000, 3430.

Anal. Calcd for $C_{14}H_{27}O_5P$: C, 54.89; H, 8.88.
Found: C, 54.78; H, 8.90.

Compound (42):

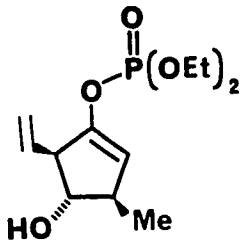
R_f = 0.35, ethyl acetate.

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.943 (9H, s), 1.15 (3H, d, J = 7.3 Hz), 1.258-1.300 (6H, m), 2.149-2.219 (1H, m), 2.520 (1H, d, J = 7.3 Hz), 4.048-4.114 (4H, m), 4.270 (1H, br d, J = 5.7 Hz), 5.448 (1H, br s).

^{13}C-NMR ($CDCl_3$): 14.863, 15.946, 16.112, 29.273, 34.090, 48.017, 56.197, 64.215, 64.486, 78.950, 114.000, 154.955, 155.389.

IR (neat): 855, 1040, 1275, 1370, 1400, 1650, 2880-3000, 3430.

Anal. Calcd for $C_{14}H_{27}O_5P$: C, 54.89; H, 8.88.
Found: C, 54.62; H, 8.75.



44

Compound (43):

R_f = 0.27, ethyl acetate.

^{1}H-NMR ($CDCl_3$, 360 MHz): 1.090 (3H, d, J = 7.1 Hz), 1.300-1.365 (6H, m), 1.976 (1H, ddd, J = 16.3, 6.1, 1.2 Hz), 2.061-2.140 (1H, m), 2.272-2.413 (1H, br), 2.760 (1H, ddd, J = 16.3, 8.2, 2.0 Hz), 4.087-4.176 (4H, m), 4.284-4.293 (1H, m), 5.293 (1H, br s).

^{13}C-NMR ($CDCl_3$): 15.838, 16.109, 19.196, 38.482, 38.699, 40.866, 64.323, 64.594, 81.604, 111.616, 111.833, 152.350, 152.730.

IR (neat): 755, 850, 960, 1030, 1170, 1270, 1660, 2880-3000, 3420.

Anal. Calcd for $C_{10}H_{19}O_5P$: C, 47.99; H, 7.65.
Found: C, 48.08; H, 7.78.

Diethyl 3α-Hydroxy-4β-methyl-2β-vinyl-5-cyclopentenyl Phosphate (44).

The reaction of 35 (496 mg, 2 mmol) with (vinyl CuCN)-MgBr according to the general procedure gave 540 mg of 44

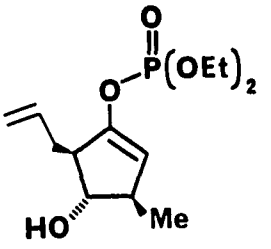
(98% yield) as a light brown oil. An analytical sample was obtained by chromatography on silica gel (diethyl ether; R_f = 0.24).

^{1}H-NMR ($CDCl_3$, 360 MHz): 1.087 (3H, d, J = 7.0 Hz), 1.276-1.357 (6H, m), 2.540 (1H, qdd, J = 7.0, 5.3, 1.9 Hz), 2.60-2.80 (1H, br), 3.194-3.232 (1H, m), 3.602 (1H, t, J = 5.3 Hz), 4.065-4.148 (4H, m), 5.120 (1H, ddd, J = 10.1, 1.6, 0.8 Hz), 5.182 (1H, ddd, J = 17.1, 2.1, 1.1 Hz), 5.177 (1H, q, J = 1.9 Hz), 5.711 (1H, ddd, J = 17.1, 10.1, 8.3 Hz).

^{13}C-NMR ($CDCl_3$): 15.784, 16.054, 18.980, 44.170, 57.226, 57.497, 64.323, 64.594, 83.229, 112.917, 113.133, 117.630, 136.699, 146.504, 146.938.

IR (neat): 850, 915, 980, 1030, 1270, 1655, 2880-3000, 3090, 3420.

Anal. Calcd for $C_{12}H_{21}O_5P$: C, 52.17; H, 7.66.
Found: C, 51.96; H, 7.61.



45

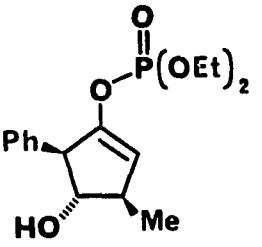
Diethyl 2β-Allyl-3α-hydroxy-4β-methyl-5-cyclopentenyl Phosphate (45).

The reaction of 35 (496 mg, 2 mmol) with either (allyl CuCN)Li or (allyl CuCN)MgBr according to the general procedure gave 570 mg of 45 (99% yield) as a light brown oil. An analytical sample was obtained by chromatography on silica gel (diethyl ether; R_f = 0.20).

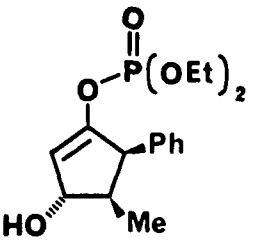
^{1}H-NMR (360 MHz, $CDCl_3$): 1.058 (3H, d, J = 7.0 Hz), 1.282-1.323 (6H, m), 2.095 (1H, dtd, J = 14.2, 7.1, 1.1 Hz), 2.415-2.518 (3H, m), 2.627-2.661 (1H, m), 3.541 (1H, t, J = 5.4 Hz), 4.067-4.155 (4H, m), 5.005-5.112 (3H, m), 5.787 (1H, ddt, J = 17.2, 10.2, 7.3 Hz).

^{13}C-NMR ($CDCl_3$): 15.784, 16.109, 19.196, 35.232, 44.279, 52.080, 52.351, 64.269, 64.486, 82.417, 112.212, 112.321, 116.709, 135.832, 147.696, 148.129.

IR (neat): 890, 1035, 1270, 1650, 2880-3000, 3090, 3420.



46



47

Anal. Calcd for $C_{13}H_{23}O_5P$: C, 53.79; H, 7.99.
Found: C, 53.66; H, 8.00.

Diethyl 3α-Hydroxy-4β-methyl-2β-phenyl-5-cyclopentenyl Phosphate (46) and Diethyl 3α-Hydroxy-4β-methyl-5β-phenyl-2-cyclopentenyl Phosphate (47).

The reaction of 35 (496 mg, 2 mmol) with (PhCuCN)Li according to the general procedure gave 350 mg of 46 and 172 mg of 47 (80% combined yield of a 2:1 mixture) as pale yellow oils after chromatography on silica gel (ethyl acetate).

Compound (46):

R_f = 0.41, ethyl acetate.

^{1}H-NMR ($CDCl_3$, 360 MHz): 1.162 (3H, d, J = 7.0 Hz), 1.185-1.225 (6H, m), 2.653-2.685 (1H, m), 2.830-3.050 (1H, br), 3.746 (1H, t, J = 5.6 Hz), 3.842 (1H, dd, J = 5.6, 1.5 Hz), 3.891-3.976 (4H, m), 5.372 (1H, d, J = 1.5 Hz), 7.204-7.330 (5H, m).

^{13}C-NMR ($CDCl_3$): 15.675, 15.946, 19.034, 44.116, 59.827, 64.160, 64.431, 86.967, 114.325, 126.839, 128.193, 128.410, 140.220, 146.450, 146.884.

IR (neat): 705, 760, 875, 970, 1020, 1265, 1455, 1655, 2870-3040, 3410.

Anal. Calcd for $C_{16}H_{23}O_5P$: C, 58.89; H, 7.10.
Found: C, 58.65; H, 7.00.

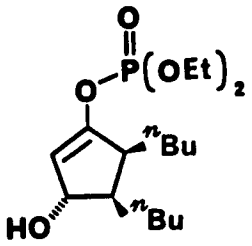
Compound (47):

R_f = 0.21, ethyl acetate.

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.720 (3H, d, J = 7.0 Hz), 1.190-1.280 (6H, m), 2.396-2.506 (2H, m), 3.916-4.023 (5H, m), 4.517 (1H, br d, J = 3.9 Hz), 5.674 (1H, br s, $W_{1/2}$ = 3 Hz), 7.078-7.307 (5H, m).

^{13}C-NMR ($CDCl_3$): 14.429, 15.729, 16.000, 46.392, 54.084, 128.248, 128.898, 137.620, 153.380.

IR (neat): 705, 735, 860, 965, 1035, 1270, 1655, 2880-3000, 3420.



48

Anal. Calcd for $C_{16}H_{23}O_5P$: C, 58.89; H, 7.10.
Found: C, 58.75; H, 7.05.

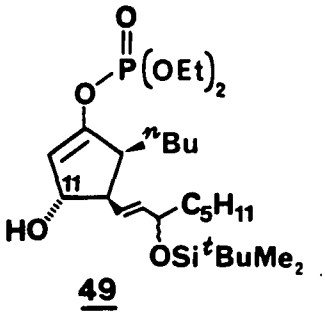
Diethyl 4β,5β-di-n-Butyl-3α-hydroxy-2-cyclopentenyl Phosphate (48).

The reaction of 36 (5.80 g, 20 mmol) with (n-BuCuCN)Li according to the general procedure gave 5.92 g of 48 (85% yield) as a light brown oil.

R_f = 0.43, ethyl acetate.

^{1}H-NMR ($CDCl_3$, 60 MHz): 0.80-1.10 (m, 6H), 1.10-1.70 (18H, m), 1.85-2.10 (1H, m), 2.70-3.00 (1H, m), 4.00-4.70 (5H, m), 5.50-5.60 (1H, br s, $W_{1/2}$ = 4 Hz).

IR (neat): 1020, 1170, 1270, 1470, 1650, 2850-3000, 3400.



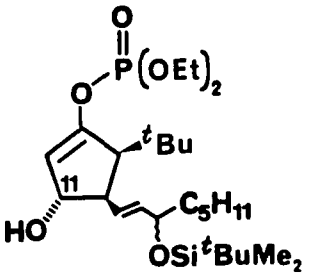
49

Diethyl 5β-n-Butyl-4β-[(1E)-3-tert-butyldimethylsilyloxyoct-1-enyl]-3α-hydroxy-2-cyclopentenyl Phosphate (49).

The reaction of 10 (470 mg, 1 mmol) with (n-BuCuCN)Li according to the general procedure gave 309 mg of 49 (58% yield) as a light yellow oil after chromatography on silica gel (diethyl ether; R_f = 0.53).

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.003-0.028 (6H, 4xs), 0.830-0.920 (15H, m), 1.19-1.44 (20H, m), 2.70-2.72 (1H, m), 2.84-2.86 (1H, m), 4.06-4.12 (1H, m), 4.13-4.21 (4H, m), 4.47-4.52 (1H, m), 5.40-5.41 (1H, br s), 5.49-5.60 (2H, m).

IR (neat): 780, 840, 880, 980, 1040, 1180, 1260, 1470, 1655, 2860-3050, 3400.



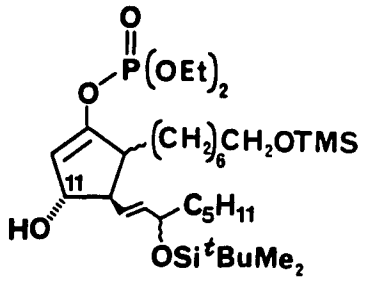
50

Diethyl 5β-tert-Butyl-4β-[(1E)-3-tert-butyldimethylsilyloxyoct-1-enyl]-3α-hydroxy-2-cyclopentenyl Phosphate (50).

The reaction of 10 (470 mg, 1 mmol) with (t-BuCuCN)Li according to the general procedure gave 324 mg of 50 (61% yield) as a pale yellow oil after chromatography on silica gel (diethyl ether; R_f = 0.49).

^{1}H-NMR (CCl_4, 60 MHz): 0.00 (6H, 2xs), 0.85 (12H, m), 0.95 (9H, s), 1.10-1.60 (14H, m), 2.55-2.80 (2H, m), 3.80-4.30 (6H, m), 5.35-5.60 (3H, m).

IR (neat): 840, 960, 1040, 1170, 1260, 1370, 1400, 1470, 1650, 2860-3050, 3420.



12

Diethyl 4β-[(1E)-3-tert-Butyldimethylsilyloxyoct-1-enyl]-5-[7-trimethylsilyloxyheptyl]-3α-hydroxy-2-cyclopentenyl Phosphate (12).

The reaction of 10 (470 mg, 1 mmol) with cyanocuprate 11 (for preparation see experimental for compound 58) according to the general procedure gave 398 mg of 12 (60% yield) as a light yellow oil after chromatography on silica gel (diethyl ether).

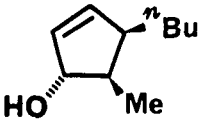
^{1}H-NMR ($CDCl_3$, 360 MHz): 0.00 (6H, 4xs), 0.09 (9H, s), 0.84-0.93 (12H, m), 1.17-1.60 (26H, m), 2.69-2.72 (1H, br m), 2.85 (1H, br m), 3.52-3.62 (2H, t, J = 6.6 Hz), 4.06-4.13 (1H, m), 4.14-4.22 (4H, m), 4.48-4.52 (1H, m), 5.40 (1H, br s), 5.47-5.59 (2H, m).

^{13}C-NMR ($CDCl_3$): -4.5, -4.3, 14.1, 16.0, 18.1, 22.4, 24.7, 25.8, 27.3, 28.2, 29.2, 29.5, 31.8, 32.7, 38.6, 46.4, 53.5, 62.1, 64.5, 73.1, 78.4, 111.4, 127.1, 136.5, 152.2.

IR (neat): 780, 840, 970, 1040, 1100, 1260, 1470, 1660, 2860-3050, 3420.

General Procedure for the Reductive Cleavage of Substituted Hydroxy Enol Phosphates.[9]

To a solution of 0.7 g (100 mmol) of lithium metal in 150 mL of liquid ammonia was added 10 mmol of the appropriate hydroxy enol phosphate. After the reaction mixture was stirred for 30 min, 2 mL of methanol was added, and the solution was neutralized with a saturated ammonium chloride solution. The liquid ammonia was then evaporated at room temperature, and the residue was extracted with ether. The organic layer was separated and dried over anhydrous magnesium sulfate. After filtration of the drying agent, the solvent was removed on a rotary evaporator. The products were then isolated by column chromatography.



51

4β-n-Butyl-5β-methyl-2-cyclopenten-1α-ol (51).

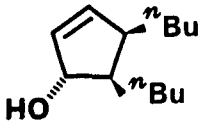
The reaction of 40 (3.06 g, 10 mmol) with lithium according to the general procedure gave 460 mg of 51 (30% yield) as a pale yellow liquid after chromatography on silica gel (hexane:ethyl acetate, 9:1; R_f = 0.20).

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.843 (3H, t, J = 7.0 Hz), 0.960 (3H, d, J = 7.3 Hz), 1.150-1.440 (6H, m), 2.023 (1H, quintet d, J = 7.3, 5.2 Hz), 2.120-2.210 (1H, br), 2.615-2.677 (1H, m), 4.320 (1H, dtd, J = 5.2, 1.8, 1.0 Hz), 5.718 (1H, dt, J = 5.8, 1.8 Hz), 5.897 (1H, ddd, J = 5.8, 2.4, 1.0 Hz).

^{13}C-NMR ($CDCl_3$): 13.183, 13.942, 22.880, 29.869, 30.519, 45.525, 46.454, 83.771, 132.744, 138.757.

IR (neat): 730, 1015, 1045, 1120, 1465, 2860-2960, 3060, 3340.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76.
Found: C, 77.70; H, 11.74.



52

4β,5β-di-n-Butyl-2-cyclopenten-1α-ol (52).

The reaction of 48 (3.50 g, 10 mmol) with lithium according to the general procedure gave 685 mg of 52 (35% yield) as a pale yellow oil after chromatography on silica gel (hexane:ethyl acetate, 9:1; R_f = 0.24).

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.851-0.952 (6H, m), 1.163-1.581 (12H, m), 1.815 (1H, qd, J = 7.4, 6.4 Hz), 2.648-2.656 (1H, m), 4.437 (1H, dq, J = 6.4, 1.5 Hz), 5.730 (1H, dt, J = 5.8, 1.5 Hz), 5.995 (1H, ddd, J = 5.8, 2.6, 1.4 Hz).

^{13}C-NMR ($CDCl_3$): 13.833, 22.826, 27.539, 30.194, 30.735, 45.416, 51.484, 81.442, 133.773, 137.674.

IR (neat): 1460, 1680, 2850-2950, 3300.

MS: 196 (M), 178, 139, 83 (100%).

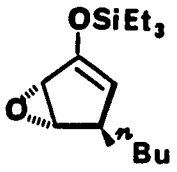
Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32.
Found: C, 79.49; H, 12.40.

General Procedure for the Synthesis of Epoxycyclopentenyl Silyl Enol Ethers.

The crude products were sufficiently pure for further reaction with cyanocuprates. Purification chould be achieved by flash chromatography on deactivated silica gel (washed with 5% sodium bicarbonate in methanol and oven dried). However, only mediocre results were obtained when purification was attempted on a medium or large scale; extensive decomposition was observed. The silyl enol ethers are stable for months when stored under nitrogen in a freezer.

In a typical run: To a magnetically stirred solution of 1.31 g (1.82 mL, 13 mmol) of dry N,N-diisopropylamine in 250 mL of anhydrous tetrahydrofuran in a 500-mL round bottomed flask at 0°C was added 7.6 mL of n-butyllithium (1.58 M, 12 mmol). After 30 min, the solution was cooled to -78°C and 1.54 g (10 mmol) of epoxy ketone 32 dissolved in 10 mL of tetrahydrofuran was added dropwise. After 1 h at -78°C, the enolate was quenched by the dropwise addition of 1.96 g (13 mmol) of freshly distilled triethylsilyl chloride, and the reaction mixture was allowed to warm up to room temperature over ca. 6 h.

The solvent was removed on a rotary evaporator and the residue was taken up in petroleum ether and filtered through a short column of Florisil. Concentration under



37

reduced pressure provided 2.70 g (100%) of silyl enol ether 37 as a light orange oil.

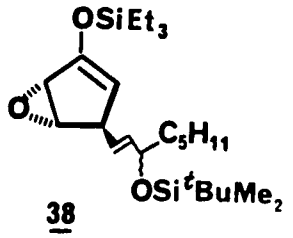
trans-3-n-Butyl-4,5-epoxy-1-triethylsilyloxycyclopentene (37).

The reaction of 32 (1.54 g, 10 mmol) with LDA and triethylsilyl chloride according to the general procedure gave 2.70 g of 37 (100%) as a light orange oil.

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.670-0.730 (6H, q, J = 7.9 Hz), 0.880-1.010 (12H, m), 1.280-1.316 (6H, m), 2.600-2.660 (1H, m), 3.531 (1H, t, J = 2.0 Hz), 3.563 (1H, t, J = 2.4 Hz), 4.725 (1H, dd, J = 4.8, 2.4 Hz).

^{13}C-NMR ($CDCl_3$): 4.570, 6.303, 13.225, 22.664, 28.460, 32.631, 42.816, 57.931, 59.122, 109.774, 155.822.

IR ($CDCl_3$): 1010, 1210, 1250, 1350, 1380, 1415, 1460, 1630, 2880-2960.



38

trans-2,3-Epoxy-4-[(1E)-3-tert-butyldimethylsilyloxy-oct-1-enyl]-1-triethylsilyloxy-5-cyclopentene (38).

The reaction of 33 (3.40 g, 10 mmol) with LDA and triethylsilyl chloride according to the general procedure gave 4.60 g of 38 (100%) as a light orange oil.

^{1}H-NMR ($CDCl_3$, 360 MHz): -0.016-0.022 (6H, 4xs), 0.67-0.73 (6H, q, J = 7.9 Hz), 0.84-0.89 (12H, m), 0.95-0.99 (9H, t, J = 7.9 Hz), 1.17-1.33 (6H, m), 1.34-1.47 (2H, m), 3.29 (1H, dist dd, J = 7.6, 2.7 Hz), 3.55-3.59 (2H, m), 4.02-4.05 (1H, m), 4.63-4.67 (1H, m), 5.37 (1H, ddd, J = 15.5, 7.6, 1.0 Hz), 5.49-5.57 (1H, m).

^{13}C-NMR ($CDCl_3$): -4.699, -4.162, 4.656, 6.444, 13.952, 18.243, 22.593, 24.917, 25.930, 31.830, 38.226, 45.476, 58.288, 58.884, 73.186, 108.046, 128.367, 136.412, 156.434.

IR (neat): 830, 970, 1080, 1200, 1255, 1345, 1380, 1465, 1630, 2860-3000.

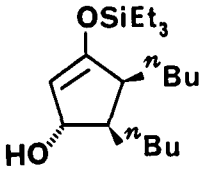
General Procedure for the Reaction of Epoxycyclopentenyl Silyl Enol Ethers with Mixed Cyanocuprates.

When commercially available alkyllithiums were employed, the generation of the cuprate was performed as described before. In other cases, alkyllithiums were generated by metal-halogen exchange from the corresponding alkyl iodide and tert-butyllithium as described below. When these alkyllithiums were employed, longer reaction times and higher temperatures were necessary to drive the reaction to completion. Generally the adducts could not be purified and were very thermally unstable (complete decomposition to the corresponding enone was observed upon standing at room temperature for 6-10 h). Yields were highest when the ethereal solutions of the adducts were thoroughly dried with magnesium sulfate and concentrated in vacuo without any external heat. The dry adducts could be stored in a freezer for 2-4 days without noticeable decomposition.

In a typical run: To a magnetically stirred solution of 3.92 g (12.45 mmol) of 1-iodo-7-trimethylsilyloxyheptane in 100 mL of anhydrous ether at -78°C was added 11.58 mL of tert-butyllithium (2.15 M, 24.92 mmol) and the mixture was stirred at that temperature for 4 h. The resulting

solution of 1-lithio-7-trimethylsilyloxyheptane was transferred *via* a double-tipped needle to a magnetically stirred suspension of 2.45 g (27.40 mmol) of copper(I) cyanide in 170 mL of anhydrous ether at -40°C. After being stirred at this temperature for 1.5 h, the organocuprate was ready for use as evidenced by a negative Gilman's test. The mixture was then cooled to -78°C and 1.41 g (3.11 mmol) of silyl enol ether *38* in 20 mL of anhydrous ether was added dropwise. Stirring was continued at -78°C for 5 h and then at 2 h between -40°C and -30°C. The reaction vessel was then sealed with Parafilm and kept at -10°C (freezer) overnight. The reaction was then quenched with 50 mL of a saturated ammonium chloride solution and filtered through a Celite pad. The organic layer was decanted, washed with a saturated sodium chloride solution (25 mL) and dried over magnesium sulfate. The drying agent was filtered off and the solvent was removed on a rotary evaporator whose water bath was kept at room temperature. In most runs the crude adduct *58* was immediately hydrolyzed (see below).

When cyanocuprates prepared from commercially available alkyllithiums were employed, the conjugate addition proceeded faster (typically 4 h at -78°C and then allowed to warm up to room temperature over *ca.* 4 h), as determined by monitoring the reaction by tlc.



53

4β,5β-di-n-Butyl-3α-hydroxy-1-triethylsilyloxycyclopentene (53).

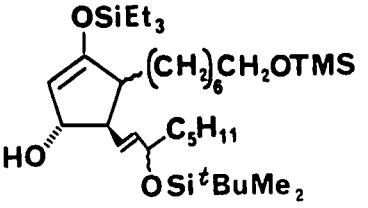
The reaction of 37 (1.34 g, 5 mmol) with (n-BuCuCN)Li according to the general procedure gave 1.65 g of 53 (100% yield) as a light yellow oil.

R_f = 0.28, hexane:ether, 9:1.

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.641-0.710 (6H, m), 0.836-0.972 (15H, m), 1.230-1.386 (12H, m), 1.846 (1H, qd, J = 7.3, 5.4 Hz), 2.555 (1H, dist q, J = 7.3 Hz), 4.345 (1H, m), 4.625 (1H, dist dd, J = 2.5, 2.0 Hz).

^{13}C-NMR ($CDCl_3$): 4.678, 6.520, 13.942, 23.043, 27.756, 28.027, 29.814, 30.790, 45.958, 50.888, 79.654, 104.032, 161.727.

IR (neat): 735, 750, 1010-1020, 1245, 1380, 1420, 1465, 1640, 3150-3600.



58

4β-[(1E)-3-tert-Butyldimethylsilyloxyoct-1-enyl]-3α-hydroxy-5-[7-trimethylsilyloxyheptyl]-1-triethylsilyloxy-2-cyclopentene (58).

The reaction of 38 (1.41 g, 3.11 mmol) with $(TMSOCH_2(CH_2)_5CH_2CuCN)Li$ according to the general procedure gave 3.80 g of crude product containing 58 and, presumably, $CH_3(CH_2)_5CH_2OTMS$ and $TMSOCH_2$-$(CH_2)_{12}$-CH_2OTMS. A sample of this crude (ca. 100 mg) was purified by fast filtration through ca. 2 g of silica gel (hexane:ether, 3:1), to give ca. 20 mg of not totally pure 38, for which the spectral data are reported.

R_f = 0.38, hexane:ether, 5:1.

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.006-0.019 (6H, 4xs), 0.082 (9H, s), 0.655-0.720 (6H, m), 0.832 (12H, m), 0.850-0.975 (9H, m), 1.233-1.612 (20H, m), 2.150-2.191 (1H, m), 2.601-2.732 (1H, m), 3.510-3.583 (2H, m), 3.998-4.061 (1H, m), 4.310-4.415 (1H, m), 4.623-4.702 (1H, m), 5.401-5.589 (2H, m).

^{13}C-NMR ($CDCl_3$): -4.639, -4.097, -0.413, 4.786, 6.574, 14.050, 18.275, 22.664, 25.047, 25.914, 27.052, 29.435, 30.032, 31.873, 32.848, 38.843, 50.292, 55.872, 62.752, 73.641, 79.817, 103.274, 131.823, 134.261, 160.481.

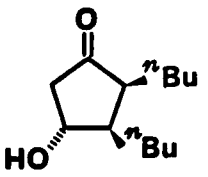
IR (neat): 750, 780, 840, 1095, 1250, 1465, 1645, 2880-3000, 3420.

General Procedure for the Hydrolysis of 3-Hydroxy-1-triethylsilyloxycyclopentenes.

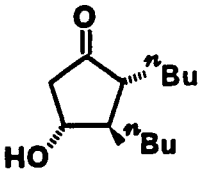
The β-hydroxy ketones obtained from this hydrolysis could be purified by column chromatography and the pure cis isomers were stored in a refrigerator for more than a year without appreciable decomposition or epimerization.

Whenever mixtures of epimers were obtained, their relative ratios were easily measured by integration of their 360 MHz ^{1}H-NMR spectra, especially of the cyclopentyl carbinol protons, H_4 (typical chemical shifts for H_4 are 4.3 ppm for 2,3-cis isomers and 4.1 ppm for 2,3-trans isomers).

In a typical run: To a magnetically stirred solution of 3.06 g (52.7 mmol) of potassium fluoride in 60 mL of pH=7 phosphate buffer was added 3.1 mmol of crude adduct 58 in 90 mL of ethanol and the mixture was stirred at room temperature for 3 h. Ethanol was then removed in vacuo, and the resulting aqueous layer was extracted with diethyl



59

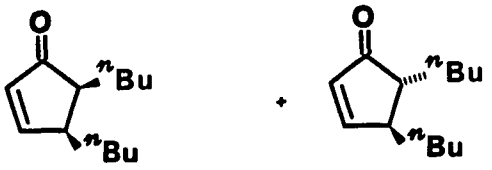


60

ether (3 x 100 mL). The combined organic extracts were washed with a saturated sodium chloride solution and dried over magnesium sulfate. After filtration of the drying agent, the solvent was removed on a rotary evaporator to give 2.76 g of a yellow oil which was purified by column chromatography (diethyl ether) to give 1.13 g (2.48 mmol) of a 1:8 mixture of 68 and 69 (80% yield) as a light yellow oil.

2β,3β-di-n-Butyl-4α-hydroxycyclopentanone (59) and 2α,3β-di-n-Butyl-4α-hydroxycyclopentanone (60).

Epoxy enol ether 37 (270 mg, 1 mmol) was reacted with four equivalents of (n-BuCuCN)Li according to the general procedure. Standard workup gave 1,4-adduct 53 which was hydrolyzed by treatment with KF (990 mg, 17 mmol) in 20 mL of pH 7 phosphate buffer, and 30 mL of ethanol, to give 180 mg (85% yield) of 59 (pale yellow oil) after chromatography (hexane:ether, 1:1; R_f = 0.21).



70 71

Compound (59):

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.830-0.890 (6H, m), 1.153-1.621 (12H, m), 1.900-1.967 (1H, br), 2.170-2.209 (1H, m), 2.201 (1H, dd, J = 19.4, 1.7 Hz), 2.428 (1H, dd, J = 19.4, 5.9 Hz), 2.611 (1H, dist q, J = 7.0 Hz), 4.362 (1H, dt, J = 5.9, 2.2 Hz).

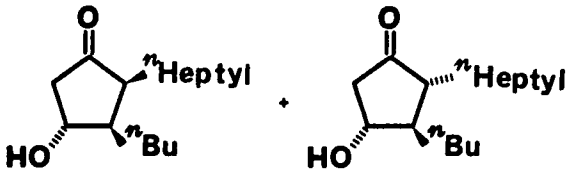
^{13}C-NMR ($CDCl_3$): 13.774, 22.712, 23.785, 26.586, 29.148, 29.804, 44.701, 47.264, 50.124, 70.564, 218.349.

IR (neat): 735, 915, 1465, 1745, 2860-2960, 3450.

MS: 212 (M), 194, 155, 99 (100%).

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39.
Found: C, 73.31; H, 11.21.

Treatment of pure 59 with 80 equivalents of potassium acetate in ethanol at room temperature for 100 h gave a 11:1:4:7 mixture of 71:70:59:60, as determined by 360 MHz ^{1}H-NMR of the crude mixture. Separation of β-hydroxy ketones 59 and 60 from enones 70 and 71 was easily effected by column chromatography (hexane:ether, 2:1). However, 59 and 60 could not be separated.



61(2) 62(1)

Compound (60):

^{1}H-NMR ($CDCl_3$, 360 MHz, from spectrum of mixture of 59 and 60): 0.830-0.920 (6H, m), 1.200-1.800 (12H, m), 1.855-1.878 (2H, m), 2.200 (1H, dd, J = 18.3, 6.8 Hz), 2.650 (1H, ddd, J = 18.3, 6.8, 1.0 Hz), 4.125 (1H, dist q, J = 6.8 Hz).

3β-n-Butyl-2β-n-heptyl-4α-hydroxycyclopentanone (61) and 3β-n-Butyl-2α-n-heptyl-4α-hydroxycyclopentanone (62).

Epoxy enol ether 37 (270 mg, 1 mmol) was treated with four equivalents of (n-heptyl CuCN)Li prepared from 0.66 mL of 1-iodoheptane, 3.8 mL of tert-butyllithium (2.1 M solution) and 716 mg (8 mmol) of copper(I) cyanide in 88 mL of ether. The reaction mixture was quenched after 5 h at -78°C and 30 min at -40°C. Thin layer chromatography analysis of the mixture still showed a significant amount of 37. Standard workup gave a crude 1,4-adduct 54 which was immediately hydrolyzed by treatment with KF (990 mg, 17 mmol) in 20 mL of pH 7 phosphate buffer, and 30 mL of ethanol, to give 150 mg (60% yield) of a 2:1 mixture of 61 and 62

(pale yellow oil) after chromatography (hexane:diethyl ether, 2:1). Compounds 61 and 62 could not be separated; however, their spectral characteristics were very easily obtained from the spectrum of the mixture.

Compound (61) (in the mixture):

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.818-0.905 (6H, m), 1.231-1.613 (18H, m), 2.199 (1H, dd, J = 19.3, 1.2 Hz), 2.153-2.226 (1H, m), 2.426 (1H, dd, J = 19.3, 5.9 Hz), 2.576-2.643 (1H, m), 4.346-4.362 (1H, m).

^{13}C-NMR ($CDCl_3$): upfield region very complex due to mixture of epimers, 44.701, 47.264, 50.243, 70.683, 218.349.

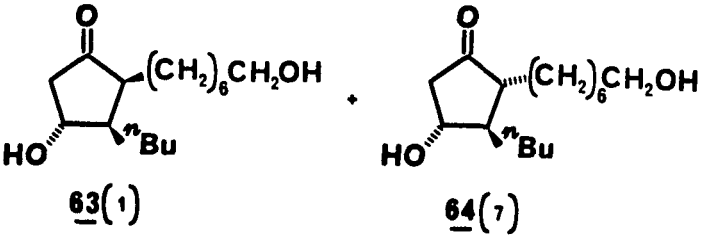
IR (neat): 1080, 1465, 1740, 2865-2965, 3450.

Anal. (on mixture) Calcd for $C_{16}H_{30}O_2$:
C, 75.53; H, 11.89.
Found: C, 75.53; H, 11.94.

Compound (62) (in the mixture):

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.818-0.905 (6H, m), 1.231-1.613 (18H, m), 1.838-1.868 (2H, m), 2.207 (1H, dd, J = 18.3, 6.8 Hz), 2.627 (1H, ddd, J = 18.3, 6.8, 1.0 Hz), 4.112 (1H, dist q, J = 6.8 Hz).

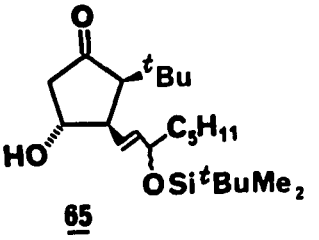
^{13}C-NMR ($CDCl_3$): upfield region very complex due to mixture of epimers, 32.306, 47.264, 49.171, 54.057, 73.067, 217.813.



63(1) + 64(7)

3β-n-Butyl-2β-[7-hydroxyheptyl]-4α-hydroxycyclopentanone (63) and 3β-n-Butyl-2α-[7-hydroxyheptyl]-4α-hydroxycyclopentanone (64).

Epoxy enol ether 37 (470 mg, 1.75 mmol) was treated with four equivalents of $(TMSOCH_2(CH_2)_5CH_2CuCN)Li$ prepared as described in the general procedure. Standard workup gave a crude 1,4-adduct 55 which was hydrolyzed by treatment with KF (1.7 g, 30 mmol) in 35 mL of pH 7 phosphate buffer and 52 mL of ethanol, to give 368 mg (78% yield) of a 1:7 mixture of 63 and 64 (pale yellow oil) after chromatography (hexane:diethyl ether, 1:4). Compounds 63 and 64 could not be separated and therefore spectral data for 63 could not be clearly ascertained due to its very small ratio in the mixture.



65

Compound (64):

R_f = 0.18, hexane:ether, 1:4.

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.873 (3H, t, J = 7.1 Hz), 1.190-1.568 (18H, m), 1.795-1.890 (2H, m), 2.162 (1H, dd, J = 18.3, 6.6 Hz), 2.599 (1H, ddd, J = 18.3, 6.6, 0.8 Hz), 3.565 (2H, t, J = 6.6 Hz), 4.072 (1H, dist q, J = 6.6 Hz).

^{13}C-NMR ($CDCl_3$): 13.893, 23.010, 25.573, 26.824, 29.089, 29.208, 29.327, 29.565, 32.306, 32.604, 47.145, 49.051, 53.938, 62.817, 72.888, 217.932.

IR (neat): 845, 965, 1080, 1380, 1735, 3400.

MS: 270 (M), 253, 156, 138, 99 (100%).

Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18.
Found: C, 70.96; H, 11.06.

2β-tert-Butyl-3β-[(1E)-3-tert-butyldimethylsilyloxy-oct-1-enyl]-4α-hydroxycyclopentanone (65).

Epoxy enol ether 38 (225 mg, 0.5 mmol) was treated with four equivalents of (tert-BuCuCN)Li according to the general procedure. Standard workup gave 1,4-adduct 56 which was immediately hydrolyzed by treatment with KF (490 mg, 8.4

mmol) in 10 mL of pH 7 phosphate buffer and 15 mL of ethanol, to give crude 65, which was chromatographed (hexane:diethyl ether, 2:1) to give 40 mg of 65a, 30.7 mg of 65b and 58 mg of a mixture of 65a and 65b (65% overall yield).

Compound (65a):

R_f = 0.20, hexane:diethyl ether, 2:1

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.009, -0.037 (6H, 2xs), 0.812-0.848 (12H, m), 0.985 (9H, s), 1.219-1.424 (8H, m), 2.228 (1H, br d, J = 19.2 Hz), 2.401 (1H, dd, J = 19.2, 5.4 Hz), 2.684 (1H, br d, J = 7.0 Hz), 3.015-3.064 (1H, m), 4.005 (1H, dist q, J = 6.4 Hz), 4.152 (1H, br d, J = 5.4 Hz), 5.201 (1H, dd, J = 15.2, 10.7 Hz), 5.568 (1H, dd, J = 15.2, 7.0 Hz).

^{13}C-NMR ($CDCl_3$): -4.579, -4.222, 13.893, 18.124, 22.593, 24.738, 25.871, 28.552, 31.651, 38.087, 45.476, 52.746, 58.824, 72.173, 73.305, 128.069, 136.769, 215.548.

IR (neat): 780, 840, 1250, 1465, 1745, 2880-3000, 3450.

MS: 339, 325, 295, 253, 75 (100%).

Anal. Calcd for $C_{23}H_{44}O_3Si$: C, 69.64; H, 11.18.
Found: C, 69.35; H, 11.19.

Compound (65b):

R_f = 0.14, hexane:diethyl ether, 2:1.

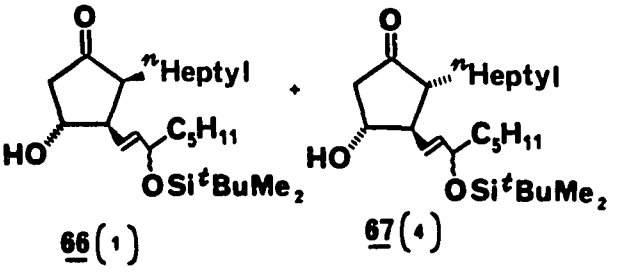
^{1}H-NMR ($CDCl_3$, 360 MHz): -0.048, -0.008 (6H, 2xs), 0.825-0.866 (12H, m), 1.005 (9H, s), 1.225-1.428 (8H, m), 2.220 (1H, br d, J = 19.1 Hz), 2.387 (1H, dd, J = 19.1, 5.4 Hz), 2.667 (1H, br d, J = 7.0 Hz), 3.019-3.067 (1H, m), 4.022-4.072 (1H, m), 4.097 (1H, br d, J = 5.3 Hz), 5.281 (1H, ddd, J = 15.2, 10.7, 1.0 Hz, 5.608 (1H, dd, J = 15.2, 5.1 Hz).

^{13}C-NMR ($CDCl_3$): -4.758, -4.520, 13.952, 18.124, 22.593, 24.858, 25.811, 28.612, 31.770, 38.266, 45.476, 52.806, 58.824, 72.352, 72.769, 127.115, 136.531, 215.310.

IR (neat): 780, 840, 1255, 1370, 1470, 1745, 2880-3000, 3450.

MS: 339, 325, 295, 253, 75, 57 (100%).

Anal. Calcd. for $C_{23}H_{44}O_3Si$: C, 69.64; H, 11.18.
Found: C, 69.42; H, 11.26.



3β-[(1E)-3-tert-Butyldimethylsilyloxyoct-1-enyl)-2β-n-heptyl-4α-hydroxycyclopentanone (66) and 3α-[(1E)-3-tert-butyldimethylsilyloxyoct-1-enyl]-2α-n-heptyl-4α-hydroxycyclopentanone (67).

Epoxy enol ether 38 (452 mg, 1 mmol) was treated with four equivalents of (n-heptyl CuCN)Li prepared from 0.66 mL of 1-iodoheptane, 3.8 mL of tert-butyllithium solution (2.1 M) and 716 mg (8 mmol) of copper(I) cyanide in 88 mL of ether, according to the general procedure. Standard workup gave a crude 1,4-adduct 57 which was immediately hydrolyzed by treatment with KF (990 mg, 17 mmol) in 20 mL of pH 7 phosphate buffer, and 30 mL of ethanol, to give a crude product which was chromatographed (hexane:diethyl ether, 2:1; R_f = 0.23); this allowed for the separation of 37 mg of 66a (diastereomerically pure), 115 mg of 67 (mixture of diastereomers at C15) and 150 mg of 66 and 67 (mixture of four diastereomers) (70% overall yield). All fractions were subsequently combined and the relative ratio of 66 and 67 was measured by integration of the carbinol

protons in the 360 MHz ^{1}H-NMR spectrum of the mixture and was found to be 1:4.

Compound (66a):

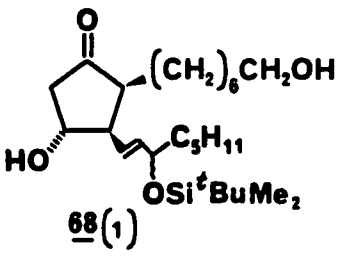
^{1}H-NMR ($CDCl_3$, 360 MHz): -0.020-0.006 (6H, 2xs), 0.830-0.867 (15H, m), 1.227-1.693 (21H, m), 2.282 (1H, dd, J = 19.2, 1.5 Hz), 2.474 (1H, dd, J = 19.2, 5.6 Hz), 2.589-2.650 (1H, m), 2.939 (1H, br t, J = 8.8 Hz), 4.011 (1H, q, J = 6.2 Hz), 4.310 (1H, dist d, J = 5.6 Hz), 5.125 (1H, ddd, J = 15.3, 10.0, 0.9 Hz), 5.599 (1H, dd, J = 15.3, 6.3 Hz).

^{13}C-NMR ($CDCl_3$): -4.639, -4.281, 14.072, 18.243, 22.653, 24.858, 25.215, 25.871, 27.480, 29.208, 29.625, 31.889, 38.385, 44.821, 50.124, 51.614, 72.352, 73.245, 125.328, 138.140, 217.515.

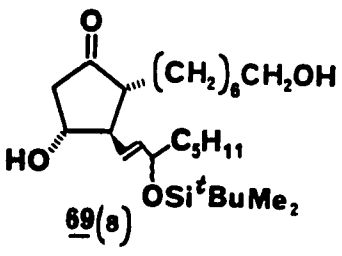
IR (neat): 780, 840, 970, 1075, 1255, 1465, 1740, 2870-2970, 3500.

Compound (67):

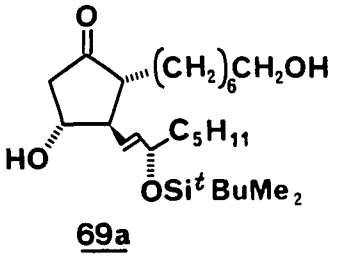
^{1}H-NMR ($CDCl_3$, 360 MHz): 0.007-0.037 (6H, 4xs), 0.818-0.869 (15H, m), 1.100-1.624 (20H, m), 2.092-2.128 (1H, m), 2.100-2.200 (1H, m), 2.195 (1H, dd, J = 18.4, 9.4 Hz), 2.336 (1H, dt, J = 11.6, 8.6 Hz), 2.698 (1H, dd, J = 18.4, 7.4 Hz), 4.005 (1H, dist q, J = 8.7 Hz), 4.096 (1H, dist q, J = 5.8 Hz), 5.457 (1H, dd, J = 15.3, 8.6 Hz), 5.655 (1H, dd, J = 15.3, 5.9 Hz).



68(1)



69(8)



69a

^{13}C-NMR ($CDCl_3$): -4.699, -4.281, 14.012, 18.243, 22.653, 24.977, 25.871, 26.824, 27.837, 29.089, 29.804, 31.830, 38.385, 46.191, 54.117, 54.295, 54.713, 72.292, 72.947, 128.665, 137.901, 214.893.

IR (neat): 780, 840, 970, 1075, 1255, 1465, 1740, 2870-2970, 3450.

MS: 381, 363, 349, 337, 241, 75 (100%).

Anal. Calcd for $C_{26}H_{50}O_3Si$: C, 71.17; H, 11.49.
Found: C, 71.05; H, 11.41.

3β-[(1E)-3-tert-Butyldimethylsilyloxyoct-1-enyl]-2β-[7-hydroxyheptyl]-4α-hydroxycyclopentanone (68) and 3β-[(1E)-3-tert-Butyldimethylsilyloxyoct-1-enyl]- 2α-[7-hydroxyheptyl]-4α-hydroxycyclopentanone (69).

Epoxy enol ether 38 (1.41 g, 3.11 mmol) was treated with four equivalents of $(TMSOCH_2(CH_2)_5CH_2CuCN)Li$, as described in the general procedure. The crude 1,4-adduct 58 was immediately hydrolyzed by treatment with KF (3.06 g, 52.7 mmol) in 60 mL of pH 7 phosphate buffer and 90 mL of ethanol to give 1.13 g (80% yield) of a 1:8 mixture of 68

and 69 (light yellow oil) after chromatography (diethyl ether). The ratio of isomers was determined as described in the general procedure. Pure 69a possessing the prostanoid relative stereochemistry (one diastereomer) was obtained *via* HPLC separation (hexane:ethyl acetate, 3:1; *ca.* 2 mg per run; μ PORASIL 8 mm x 10 cm analytical column; 4 mL/min; refraction index and ultraviolet-290 nm-detectors) of a mixture of 69a and one of the diastereomers in 68 obtained by careful column chromatography (hexane:ethyl acetate, 2:1) of a mixture of 68 and 69 and HPLC or NMR analysis of the fractions; the desired diastereomer was eluted first under these conditions although complete separation could not be achieved. In the HPLC separation, 69a was eluted last and was obtained by collecting the last "cuts" of the HPLC trace. A pure sample of 68 (either diastereomer) could not be obtained in this manner.

Compound (69a):

R_f = 0.28, diethyl ether.

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.025-0.050 (6H, 2xs), 0.708-0.884 (12H, m), 1.200-1.700 (20H, m), 1.974 (1H, dist dt, J = 11.1, 5.5 Hz), 2.212 (1H, dd, J = 18.3, 9.5 Hz), 2.340 (1H, dt, J = 11.9, 8.7 Hz), 2.720 (1H, ddd, J = 18.3, 7.4, 0.9 Hz), 3.607 (2H, t, J = 6.6 Hz), 4.016 (1H, dist q, J = 8.6 Hz), 4.104 (1H, dist q, J = 6.0

Hz), 5.478 (1H, ddd, J = 15.4, 8.6, 0.7 Hz), 5.672 (1H, dd, J = 15.4, 5.8 Hz).

^{13}N-NMR ($CDCl_3$): -4.639, -4.222, 14.012, 18.303, 22.653, 24.977, 25.930, 26.705, 27.718, 29.148, 29.744, 31.830, 32.783, 38.444, 46.132, 54.713, 62.996, 72.292, 72.947, 128.665, 138.021, 214.595.

IR (neat): 780, 835, 1075, 1255, 1470, 1745, 2880-3000, 3400.

MS: 397, 379, 253, 95, 75 (100%).

Anal. Calcd for $C_{26}H_{50}O_4Si$: C, 68.67; H, 11.08.
Found: C, 68.35; H, 10.94.

$I(CH_2)_6CH_2OTMS$

1-Iodo-7-trimethylsilyloxyheptane.

Crude 7-iodoheptanoic acid[104] (50.93 g, 199.02 mmol) was dissolved in 400 mL of dry tetrahydrofuran in a 1-L round-bottomed flask fitted with a pressure equalizing addition funnel. To the above solution was added with stirring 238 mL (238 mmol) of a 1M solution of $BH_3 \cdot THF$ complex in THF under an inert atmosphere. The solution was stirred at room temperature for 1 h. The excess borane was then destroyed by the addition of 100 mL of water, and the solution was concentrated in a rotary evaporator. The product was then isolated by extraction with ether. The

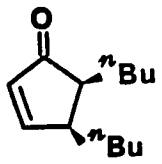
organic layer was washed with a saturated sodium chloride solution and dried over magnesium sulfate. Filtration of the drying agent and evaporation of the solvent in vacuo afforded 47.31 g (98%) of crude 1-iodo-7-hydroxyheptane.

^{1}H-NMR (CCl_4, 60 MHz): 1.20-2.40 (10H, m), 3.20 (2H, t, J = 7.0 Hz), 3.55 (2H, dist t, J = 6.0 Hz), 5.00-5.30 (1H, br).

The crude 1-iodo-7-hydroxyheptane (30.0 g, 124 mmol) was dissolved in anhydrous ether (186 mL) and 35 mL (148 mmol) of hexamethyldisilazide was added. The solution was placed under nitrogen and three drops of trimethylsilyl chloride were added. The mixture was then stirred at room temperature for 20 h after which time it was diluted with 300 mL of ether, washed with water and a saturated ammonium chloride solution and dried over anhydrous sodium sulfate. Filtration of the drying agent, concentration in vacuo and distillation gave 21.0 g of 1-iodo-7-trimethylsilyloxyheptane as a clear liquid (bp 60-64°C at 0.025 mm Hg) (66% yield overall).

^{1}H-NMR (CCl_4, 60 MHz): 0.00 (9H, s), 1.10-2.00 (10H, m), 3.05 (2H, t, J = 7.0 Hz), 3.45 (2H, dist t, J = 6.0 Hz).

IR (neat): 750, 840, 1100, 1250, 2860-3000.



70

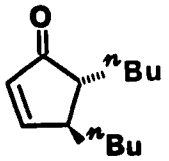
cis-4,5-di-n-Butyl-2-cyclopentenone (70).

The title compound could be obtained in several manners: spontaneous decomposition upon standing at room temperature of hydroxy enol phosphate 48; chromatography on silica gel of hydroxy silyl enol ether 53; stirring an ethereal solution of adduct 53 with an equal volume of 2% HCl for 5 min. When 70 was prepared by either of the last two ways, good yields (85-95%) were consistently realized after standard workup and chromatography (hexane: ethyl acetate, 3:1).

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.838-0.896 (6H, m), 1.274-1.480 (10H, m), 1.633-1.683 (2H, m), 2.268-2.320 (1H, m), 2.923-2.937 (1H, m), 6.128 (1H, dd, J = 5.8, 1.7 Hz), 7.692 (1H, dd, J = 5.8, 2.8 Hz).

^{13}C-NMR ($CDCl_3$): 13.996, 22.880, 28.081, 29.869, 30.573, 44.333, 49.804, 132.473, 166.657, 215.025.

IR (neat): 800, 1180, 1465, 1595, 1710, 2880-3000.



71

trans-4,5-di-n-Butyl-2-cyclopentenone (71).

To a solution of 348 mg (1 mmol) of hydroxy enol phosphate 48 in 20 mL of anhydrous THF (nitrogen atmosphere/-78°C) was added 0.56 mL of tert-butyllithium (1.96 M, 1.1 mmol). After 15 min, 0.69 mL of methyllithium (1.6 M, 1.1 mmol) was added, and the solution was allowed to warm up to room temperature and stirred overnight. The reaction was then quenched with 150 mL of a pH 7 buffer solution. The aqueous layer was extracted with ether and the organic extracts were dried over anhydrous sodium sulfate. Filtration of the drying agent, evaporation of the solvent in vacuo and column chromatography (hexane:ethyl acetate, 3:1) gave 100 mg of 71 (51%).

Alternatively, to a solution of 130 mg (0.4 mmol) of hydroxy silyl enol ether 53 in 10 mL of anhydrous tetrahydrofuran (nitrogen atmosphere/-78°C) was added 0.20 mL of pyridine polyhydrogen fluoride. After 1 h at -78°C, the

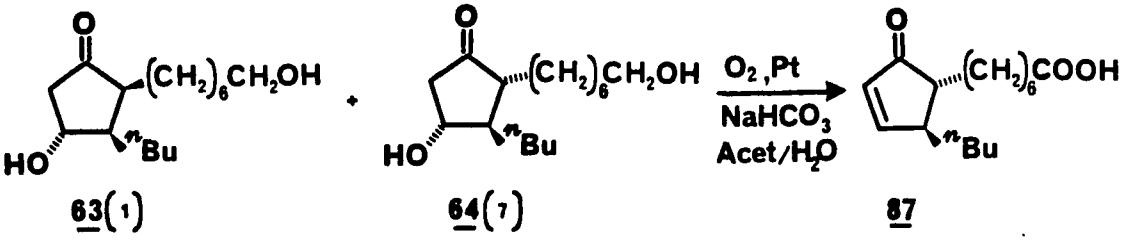
mixture was quenched with 25 mL of pH 7 buffer and extracted with ether. The combined organic extracts were dried over sodium sulfate. Fitlration of the drying agent, evaporation of the solvent *in vacuo* and filtration through Florisil (ether) gave 73.5 mg of a 3:2 mixture of *trans*-cyclopentenone 71 and its *cis* isomer 70 (95%), as determined by integration of the 360 MHz ^{1}H-NMR spectrum of the mixture. The mixture was transformed into exclusively the *trans* isomer 71 upon standing for *ca*. 10 days in the NMR tube. This transformation was presumably catalyzed by a trace of acid present in the deuterochloroform solution.

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.838-0.896 (6H, m), 1.274-1.480 (10H, m), 1.633-1.683 (2H, m), 1.898-1.933 (1H, m), 2.533-2.565 (1H, m), 6.074 (1H, dd, J = 5.6, 1.0 Hz), 7.577 (1H, dd, J = 5.6, 2.1 Hz).

^{13}C-NMR ($CDCl_3$): 13.887, 22,826, 29.219, 29.598, 31.006, 34.311, 47.963, 51.646, 132.798, 167.036, 212.325.

IR (neat): 800, 1180, 1465, 1595, 1710, 2880-3000.

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41.
Found: C, 80.29; H, 11.20.

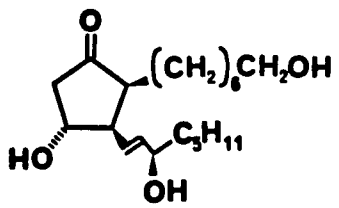


63(1) 64(7) 87

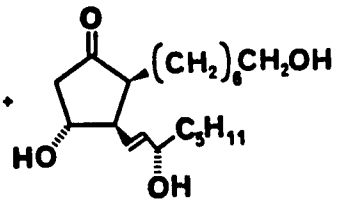
trans-4-n-Butyl-5-[6-carboxyhexyl]-2-cyclopentenone (87).

Platinum oxide (70 mg) was hydrogenated (Parr apparatus, 30 psi, 30 min) in 15 mL of a 1:1 mixture of acetone and water. The catalyst and solvents were then transferred to a 50 mL round bottomed flask and 65 mg (0.776 mmol) of sodium bicarbonate was added, followed by 70 mg (0.259 mmol) of a 1:7 mixture of ketols 63 and 64 in 6 mL of 1:1 acetone/water. The suspension was warmed to 55°C and oxygen was bubbled through for 6 h. The catalyst was then removed by filtration and the solution was concentrated in vacuo. The resulting aqueous layer was neutralized with saturated ammonium chloride solution and extracted with ethyl acetate. The combined organic extracts were dried on anhydrous magnesium sulfate. Filtration of the drying agent and concentration in vacuo gave a crude product which was purified by chromatography (ethyl acetate; R_f = 0.39) to give 46.8 mg of 87 (68%).

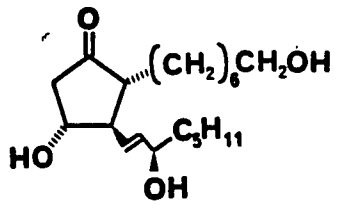
^{1}H-NMR ($CDCl_3$, 360 MHz): 0.871-0.953 (3H, m), 1.267-1.752 (16H, m), 1.903-1.939 (1H, m), 2.317 (2H,



88



89



90

t, J = 7.3 Hz), 2.529-2.690 (1H, m), 6.081 (1H, dd, J = 5.7, 2.2 Hz), 7.581 (1H, dd, J = 5.7, 2.5 Hz).

^{13}C-NMR ($CDCl_3$): 13.893, 22.772, 24.619, 26.764, 28.791, 29.327, 29.565, 31.115, 33.856, 34.213, 47.979, 51.554, 132.717, 167.220, 179.019, 212.450.

IR (neat): 1590, 1670-1750, 2860-2930, 2500-3600.

MS: 267 (M+1), 249, 95 (100%).

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84.
Found: C, 72.24; H, 9.78.

(±)-2-Decarboxy-2-hydroxymethyl-8-epi-15-epi-prostaglandin E_1 (88), (±)-2-Decarboxy-2-hydroxymethyl-8-epi-prostaglandin E_1 (89), (±)-2-Decarboxy-2-hydroxymethyl-15-epi-prostaglandin E_1 (90), and (±)-2-Decarboxy-2-hydroxymethyl-prostaglandin E_1 (91).

To a solution of 340 mg (0.747 mmol) of protected ketols 68 and 69 (as a 1:8 mixture of C8 epimers, each as a mixture of diastereomers at C15) in 10 mL of

acetonitrile was added 1.1 mL of aqueous hydrofluoric acid (47-52%). The mixture was stirred at room temperature for 1 h after which it was diluted with 50 mL of ethyl acetate. The combined organic extracts were washed with 5% sodium bicarbonate solution until the washings were neutral and then with a saturated sodium chloride solution. The solution was then dried over magnesium sulfate. Filtration of the drying agent and evaporation of the solvent in vacuo gave a crude product which was purified by chromatography on silica gel, by sequential elution with ether, then ether:ethyl acetate 1:1, then ethyl acetate, then ethyl acetate:acetone 1:1. Samples of all four isomers were thus isolated in 90% combined yield [15 mg of 88 (colorless oil), 9 mg of 89 (colorless oil), 30 mg of 90 (colorless oil), 37 mg of 91 (white solid) and 139 mg of a mixture of all isomers]. It should be mentioned that the stereochemistry at C15 of the "cis" epimers 88 and 89 is only tentatively assigned, based upon the order of elution (88, 90, 89, 91); generally 8-epi prostanoids are eluted before natural prostanoids.[25] The spectral (^{1}H-NMR, ^{13}C-NMR) and chromatographic characteristics of 91 were identical to those of an authentic sample.[49]

Compound (88):

R_f = 0.33, ethyl acetate.

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.865 (3H, t, J = 6.8 Hz), 1.150-1.698 (23H, m), 2.285 (1H, dd, J = 19.2,

1.5 Hz), 2.497 (1H, dd, J = 19.2, 5.7 Hz), 2.592-2.666 (1H, m), 2.927-2.976 (1H, m), 3.599 (2H, t, J = 6.5 Hz), 4.052 (1H, dist q, J = 6.1 Hz), 4.287-4.303 (1H, m), 5.259 (1H, ddd, J = 15.3, 9.8, 0.9 Hz), 5.666 (1H, dd, J = 15.3, 6.2 Hz).

^{13}C-NMR ($CDCl_3$): 14.012, 22.593, 25.096, 25.573, 26.586, 27.122, 28.969, 29.327, 29.684, 31.711, 32.664, 37.431, 44.940, 50.243, 51.554, 62.936, 72.292, 126.400, 137.365, 217.217.

IR ($CDCl_3$): 980-1080, 1740, 2865-3000, 3460, 3620.

MS: 323, 251, 196, 55, 43 (100%).

Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66.
Found: C, 70.36; H, 10.53.

Compound (89):

R_f = 0.23, ethyl acetate.

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.867 (3H, t, J = 6.8 Hz), 1.177-1.643 (23H, m), 2.299 (1H, dd, J = 19.2, 1.6 Hz), 2.512 (1H, dd, J = 19.2, 5.8 Hz), 2.598-2.661 (1H, m), 2.928-2.977 (1H, m), 3.615 (2H, t, J = 6.5 Hz), 4.043 (1H, dist q, J = 6.5 Hz), 4.329-4.345 (1H, m), 5.232 (1H, ddd, J = 15.2, 10.1, 0.8 Hz), 5.651 (1H, dd, J = 15.2, 6.7 Hz).

^{13}C-NMR ($CDCl_3$): 14.012, 22.593, 25.096, 25.632, 27.241, 29.148, 29.446, 31.711, 32.724, 37.431,

44.880, 50.184, 51.793, 62.996, 72.232, 72.709, 126.996, 137.365, 217.217.

IR ($CDCl_3$): 1740, 2870-2980, 3620.

MS: 322, 251, 99, 43 (100%).

Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66.
Found: C, 69.93; H, 10.19.

Compound (90):

R_f = 0.30, ethyl acetate.

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.874 (3H, t, J = 6.7 Hz), 1.186-1.628 (23H, m), 2.006 (1H, dist dt, J = 12.0, 6.0 Hz), 2.212 (1H, dd, J = 18.4, 9.6 Hz), 2.363 (1H, dt, J = 12.0, 8.5 Hz), 2.723 (1H, ddd, J = 18.4, 7.4, 0.8 Hz), 3.607 (2H, t, J = 6.5 Hz), 4.055 (dist q, J = 8.2 Hz), 4.113-4.164 (1H, m), 5.583 (1H, dd, J = 15.4, 8.2 Hz), 5.727 (1H, dd, J = 15.4, 5.9 Hz).

^{13}C-NMR ($CDCl_3$): 14.012, 22.593, 25.096, 25.513, 26.526, 27.778, 28.969, 29.446, 31.711, 32.664, 37.491, 46.191, 54.355, 54.593, 62.936, 72.232, 129.857, 137.127, 214.536.

IR ($CDCl_3$): 1075, 1745, 2870-2920, 3460, 3620.

MS: 323, 305, 251, 99, 55, 43 (100%).

Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66.
Found: C, 70.62; H, 10.73.

Compound (91):

R_f = 0.20, ethyl acetate.

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.863 (3H, t, J = 6.7 Hz), 1.233-1.595 (20H, m), 1.965 (1H, dist dt, J = 12.0, 6.0 Hz), 2.193 (1H, dd, J = 18.4, 9.9 Hz), 2.321 (1H, dt, J = 12.0, 8.7 Hz), 2.700 (1H, ddd, J = 18.4, 7.4, 0.8 Hz), 3.592 (2H, t, J = 6.5 Hz), 3.965-4.032 (1H, m), 4.038-4.089 (1H, m), 5.503 (1H, dd, J = 15.2, 8.7 Hz), 5.627 (1H, dd, J = 15.2, 7.4 Hz).

^{13}C-NMR ($CDCl_3$): 14.012, 22.593, 25.156, 25.632, 26.645, 27.718, 29.029, 29.565, 31.711, 32.724, 37.431, 46.012, 54.534, 54.713, 62.936, 71.994, 73.007, 131.525, 136.888, 214.595.

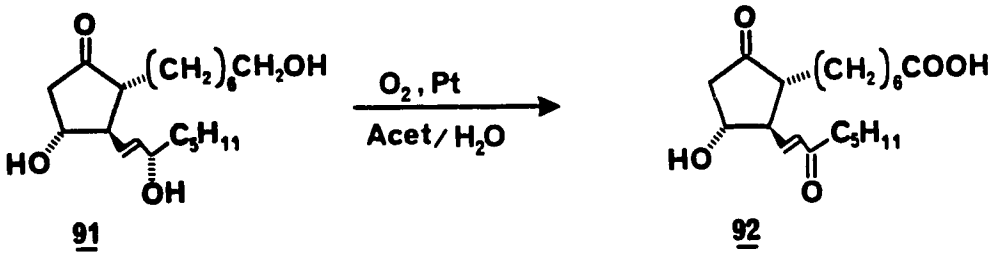
IR ($CDCl_3$): 975, 1075, 1745, 2870-2940, 3420, 3620.

MS: 323, 305, 269, 208, 95, 55, 43 (100%).

mp: 96-98°C.

Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66.

Found: C, 70.64; H, 10.60.



91 92

(±)-15-Dehydroprostaglandin E_1 (92).

Platinum oxide (30 mg) was hydrogenated (Parr apparatus, 30 psi, 30 min) in 7 mL of water. The catalyst was then added to a solution of 30 mg of 2-decarboxy-2-hydroxymethyl-PGE_1 in 10 mL of acetone kept at 50°C. Oxygen was bubbled through the suspension with rapid stirring for 4 h. The catalyst was then removed by filtration and the solution was concentrated in vacuo. The resulting aqueous layer was extracted with ethyl acetate. The organic extracts were dried over anhydrous magnesium sulfate. Filtration of the drying agent, evaporation of the solvent in vacuo and chromatography on silica gel (acetone:methanol, 4:1; R_f = 0.21) gave 18.6 mg of 92 (colorless oil, 60% yield).

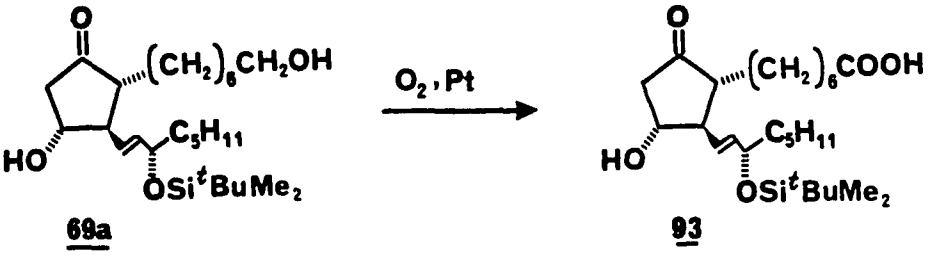
^{1}H-NMR ($CDCl_3$, 360 MHz): 0.878 (3H, t, J ≒ 6.8 Hz), 1.182-1.662 (16H, m), 2.133 (1H, dist dt, J = 11.9, 5.5 Hz), 2.240-2.327 (3H, m), 2.493-2.600 (3H, m), 2.777 (1H, ddd, J = 18.2, 6.9, 0.9 Hz), 4.204 (1H, dist q, J = 8.2 Hz), 6.296 (1H, d, J = 15.6 Hz), 6.737 (1H, dd, J = 15.6, 8.8 Hz).

^{13}C-NMR (acetone-d_6): 14.236, 23.175, 24.605, 25.618, 34.199, 40.575, 47.190, 54.639, 55.235, 72.039, 132.643, 147.005, 174.536, 199.922, 214.223.

IR ($CDCl_3$): 1630, 1685, 1710, 1750, 2500-3400, 3520, 3620.

MS: 352 (M), 281, 236, 218, 135, 43 (100%).

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15.
Found: C, 68.24; H, 9.20.



69a 93

3β-[(1E)-3-tert-Butyldimethylsilyloxyoct-1-enyl]-2α-[6-carboxylhexyl]-4α-hydroxycyclopentanone (93).

Platinum oxide (10 mg) was hydrogenated (Parr apparatus, 30 psi, 30 min) in 7 mL of water. The catalyst was then transferred to a solution of 8 mg of ketol 69a in 10 mL of acetone kept at 40°C and oxygen was bubbled through the suspension during 4 h. The catalyst was then removed by filtration and the solution was concentrated in vacuo. Extraction of the resulting aqueous layer with ethyl acetate, drying with magnesium sulfate, filtration of the drying agent and concentration in vacuo gave a crude product which was purified by chromatography on silica gel using ethyl acetate followed by 2% methanol:ethyl acetate to give 5.7 mg of 93 (70%).

R_f = 0.33, acetone:methanol, 9:1.

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.012-0.040 (6H, 2xs), 0.800-0.877 (12H, m), 1.207-1.554 (18H, m), 1.969-2.010 (1H, m), 2.197 (1H, dd, J = 18.5, 9.1 Hz), 2.312 (2H, dist t, J = 7.3 Hz), 2.342-2.396

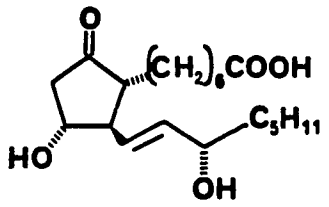
(1H, m), 2.712 (1H, ddd, J = 18.5, 7.2, 0.9 Hz), 4.010 (1H, dist q, J = 8.4 Hz), 4.104 (1H, dist q, J = 6.5 Hz), 5.475 (1H, ddd, J = 15.2, 8.3, 0.9 Hz), 5.674 (1H, dd, J = 15.2, 6.0 Hz).

^{13}C-NMR ($CDCl_3$): -4.639, -4.222, 14.012, 18.303, 22.653, 24.917, 25.930, 27.658, 28.850, 29.267, 31.830, 38.385, 46.250, 53.938, 54.593, 72.352, 73.007, 128.665, 137.901, 215.191.

IR (neat): 778, 835, 1075, 1260, 1715, 1740, 3100-3550.

MS: 411, 393, 301, 75 (100%).

Anal. Calcd for $C_{26}H_{48}O_5Si$: C, 66.62; H, 10.32.
Found: C, 66.45; H, 10.18.

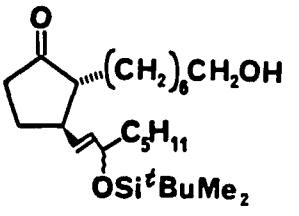


PGE$_1$

(±)-Prostaglandin E$_1$.

To a solution of 5.3 mg (0.0113 mmol) of protected ketol 93 in 2 mL of acetonitrile was added 0.1 mL of aqueous hydrofluoric acid (47-52%). The mixture was stirred at room temperature for 1 h after which it was diluted with ethyl acetate. The combined organic extracts were washed with 5% sodium bicarbonate solution until the washings were neutral and then with saturated sodium chloride solution. Drying over magnesium sulfate, filtration of the drying agent and evaporation of the solvent *in vacuo* gave a crude product which was chromatographed on silica gel (ethyl acetate, then 2%, 6% and 10% methanol/ethyl acetate mixtures) to give 3.2 mg of (±)-prostaglandin E$_1$ (80%).

^{1}H-NMR (acetone-d$_6$, 360 MHz): 0.905 (3H, t, J = 6.0 Hz), 1.261-1.682 (18H, m), 2.023-2.143 (2H, m), 2.293 (2H, t, J = 7.1 Hz), 2.309-2.383 (1H, m), 2.594 (1H, ddd, J = 18.4, 7.1, 0.7 Hz), 4.031-4.119 (2H, m), 5.614-5.669 (2H, m).



96

trans-3-[(1E)-3-tert-Butyldimethylsilyloxyoct-1-enyl]-2-[7-hydroxyheptyl]-cyclopentanone (96).

A 25 mL round-bottomed flask was charged with 0.95 mL (0.475 mmol) of a 0.5 M solution of KS-Selectride (potassium trisiamylborohydride) in THF, placed under nitrogen and cooled to -78°C. A solution of 60 mg (0.132 mmol) of ketol 69 in 10 mL of anhydrous tetrahydrofuran was then added dropwise via syringe, upon which the reaction mixture turned pink. The solution was stirred at -78°C for 2 h and then at room temperature for 1 h. The reaction was quenched by addition of 0.5 mL of water followed by 2 mL of ethanol and the borane was then oxidized with 5 mL of a 3 M solution of sodium hydroxide and 5 mL of 30% hydrogen peroxide. The aqueous layer was then saturated with sodium carbonate and the layers were separated. The aqueous layer was extracted with ether and the combined organic extracts were dried over anhydrous magnesium sulfate. Filtration of the drying agent and evaporation of the solvent in vacuo followed by column chromatography (diethyl ether) afforded 40.5 mg of 96 (70%), as a light yellow oil.

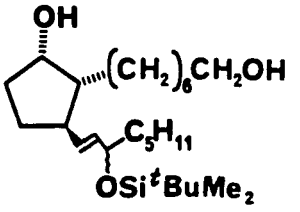
^{1}H-NMR ($CDCl_3$, 360 MHz): 0.007-0.030 (6H, 2xs), 0.813-0.918 (12H, m), 1.167-1.617 (22H, m), 1.770-1.823 (1H, m), 2.025-2.137 (2H, m), 2.295-2.432 (2H, m), 3.608 (2H, t, J = 6.6 Hz), 4.028-4.050 (1H, m), 5.474-5.526 (2H, m).

^{13}C-NMR ($CDCl_3$): -4.699, -4.162, 14.012, 18.303, 22.653, 24.977, 25.692, 25.930, 26.764, 27.718, 28.135, 29.208, 29.863, 31.830, 32.783, 37.729, 38.444, 45.297, 45.536, 54.832, 62.996, 73.245, 73.424, 131.764, 134.803, 219.839.

IR (neat): 775, 835, 1060, 1250, 1740, 2840-2980, 3420.

MS: 381, 363, 289, 281, 135, 75 (100%).

Anal. Calcd for $C_{26}H_{50}O_3Si$: C, 71.17; H, 11.49.
Found: C, 71.19; H, 11.55.



97

3β-[(1E)-3-tert-Butyldimethylsilyloxyoct-1-enyl]-2α-[7-hydroxyheptyl]-1α-hydroxycyclopentane (97).

A 0.5 M solution (2.22 mL) of KS-Selectride was added dropwise to a solution of 70 mg (0.154 mmol) of ketol 69 in 5 mL of anhydrous tetrahydrofuran kept at 0°C under an inert atmosphere. The reaction mixture was stirred at 0°C for 1 h and at room temperature for 16 h. TLC analysis of the mixture showed almost immediate formation of ketone 96 and slower conversion of this to alcohol 97. The reaction was quenched by addition of 1 mL of water and 2 mL of ethanol followed by 3 mL of 3 M sodium hydroxide and 3 mL of 30% hydrogen peroxide. The mixture was then stirred for 30 min after which time the aqueous layer was saturated with sodium carbonate and the layers were separated. The aqueous layer was extracted with ether and the combined organic extracts were dried over anhydrous magnesium sulfate. Filtration of the drying agent and evaporation of the solvent in vacuo followed by column chromatography (diethyl ether) yielded 57.7 mg of 97 (85%), as a pale yellow oil.

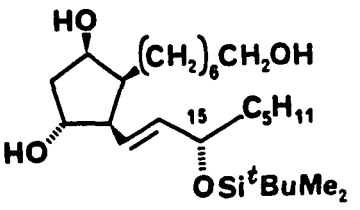
^{1}H-NMR ($CDCl_3$, 360 MHz): -0.009-0.018 (6H, 4xs, 2 per diastereomer), 0.855-0.861 (12H, m), 1.228-1.648 (28H, m), 1.861-2.023 (2H, m), 2.251-2.271 (1H, m), 3.604 (2H, t, J = 6.6 Hz), 3.964-4.015 (1H, m), 4.201 (1H, br s), 5.271-5.394 (2H, m).

^{13}C-NMR ($CDCl_3$): -4.639, -4.151, 13.986, 18.275, 22.609, 25.101, 25.697, 25.968, 27.106, 28.299, 29.327, 29.977, 31.819, 32.214, 33.877, 38.536, 45.579, 45.687, 51.701, 62.969, 73.695, 73.858, 74.074, 133.733, 133.936.

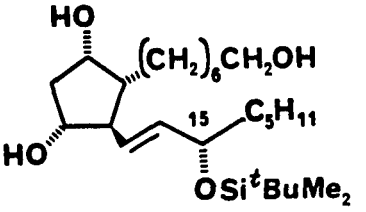
IR (neat): 780, 840, 1070, 1260, 1465, 2880-2950, 3400.

MS: 423, 365, 309, 291, 273, 219, 95, 75 (100%).

Anal. Calcd for $C_{26}H_{52}O_3Si$: C, 70.85; H, 11.89.
Found: C, 70.77; H, 11.85.



98



95

2β-[(1E)-3-tert-Butyldimethylsilyloxyoct-1-enyl]-3β-[7-hydroxyheptyl]-1α,4β-dihydroxycyclopentane (98) and 2β-[(1E)-3-tert-Butyldimethylsilyloxyoct-1-enyl]-3α-[7-hydroxyheptyl]-1α,4α-dihydroxycyclopentane (95).

A solution of 110.8 mg (0.244 mmol) of a 1:8 mixture of ketols 68a and 69a (homogeneous at C15) in 10 mL of anhydrous tetrahydrofuran was placed under nitrogen and cooled to 0°C. L-Selectride (1.75 mL of 1 M solution in tetrahydrofuran) was then added dropwise. The clear solution was allowed to reach room temperature over 6 h and then quenched by sequential addition of water (1 mL), ethanol (2 mL), 3 M sodium hydroxide (3 mL) and 30% hydrogen peroxide (3 mL). After stirring at room temperature for 30 min, the aqueous layer was saturated with sodium carbonate and the layers were separated. The aqueous layer was extracted with ether and the combined organic extracts were dried over anhydrous magnesium sulfate. Filtration of the drying agent and evaporation of the solvent in vacuo followed by column chromatography (diethyl ether, then ethyl

acetate) afforded 11.7 mg of 98 and 94.1 mg of 95 (95% combined yield; colorless oils).

Compound (98):

R_f = 0.35, ethyl acetate.

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.006-0.020 (6H, 2xs), 0.837-0.892 (12H, m), 1.207-1.536 (23H, m), 1.941 (1H, dt, J = 14.5, 5.5 Hz), 2.110 (1H, ddd, J = 14.5, 6.5, 2.0 Hz), 2.154-2.197 (1H, m), 2.461 (1H, td, J = 9.9, 2.4 Hz), 3.618 (2H, t, J = 6.6 Hz), 4.010 (1H, dist q, J = 6.3 Hz), 4.214-4.251 (1H, m), 4.285-4.320 (1H, m), 5.389 (1H, dd, J = 15.4, 6.6 Hz), 5.496 (1H, dd, J = 15.4, 9.6 Hz).

^{13}C-NMR ($CDCl_3$): -4.693, -4.210, 13.996, 18.275, 22.664, 24.993, 25.751, 25.914, 29.381, 29.923, 31.873, 32.794, 38.591, 44.170, 46.229, 54.518, 62.023, 73.425, 73.695, 74.237, 129.981, 135.724.

Anal. Calcd for $C_{26}H_{52}O_4Si$: C, 68.36; H, 11.47.

Found: C, 68.25; H, 11.36.

Compound (95):

R_f = 0.21, ethyl acetate.

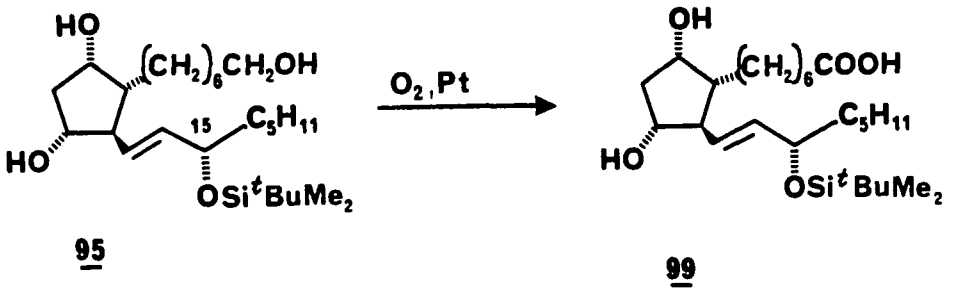
^{1}H-NMR ($CDCl_3$, 360 MHz): 0.003-0.027 (6H, 2xs), 0.840-0.894 (12H, m), 1.253-1.596 (22H, m), 1.794 (1H, ddd, J = 14.6, 2.0, 1.1 Hz), 2.060 (1H, ddd, J = 14.6, 7.0, 4.6 Hz), 2.242 (1H, dist td, J = 8.8, 4.1 Hz), 3.611 (2H, t, J = 6.5 Hz), 3.924-3.972 (1H, m), 4.027 (1H, dist q, J = 6.1 Hz), 4.199-4.203 (1H, m), 5.371 (1H, dd, J = 15.3, 8.5 Hz), 5.474 (1H, dd, J = 15.3, 6.1 Hz).

^{13}C-NMR ($CDCl_3$): -4.693, -4.206, 13.996, 18.275, 22.609, 25.047, 25.643, 25.914, 28.027, 29.219, 29.814, 31.819, 32.686, 38.428, 42.979, 50.834, 56.359, 62.914, 73.478, 73.749, 78.679, 78.841, 131.065, 135.019.

IR (neat): 775, 835, 970, 1065, 1255, 1465, 3100-3600.

MS: 399, 381, 363, 289, 75 (100%).

Anal. Calcd for $C_{26}H_{52}O_4Si$: C, 68.36; H, 11.47.
Found: C, 68.10; H, 11.17.



95 99

2β-[(1E)-tert-Butyldimethylsilyloxyoct-1-enyl]-3α-[6-carboxyhexyl]-1α,4α-dihydroxycyclopentane (99).

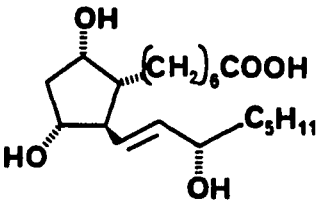
Triol 95 (6.6 mg) was oxidized following the same procedure described for the oxidation of diol 69a to give 5.1 mg of 99 (colorless oil) after chromatography (ethyl acetate, then 5%, 10% and 20% methanol/ethyl acetate mixtures (75% yield).

R_f = 0.18, ethyl acetate:methanol, 9:1.

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.007-0.028 (6H, 2xs), 0.851-0.924 (12H, m), 1.191-1.610 (21H, m), 1.809 (1H, ddd, J = 15.0, 2.0, 1.1 Hz), 2.047 (1H, ddd, J = 15.0, 7.5, 5.0 Hz), 2.241 (1H, m), 2.322 (2H, dist t, J = 7.4 Hz), 3.940-3.958 (1H, m), 4.033 (1H, dist q, J = 6.1 Hz), 4.196-4.210 (1H, m), 5.377 (1H, dd, J = 15.4, 8.7 Hz), 5.479 (1H, dd, J = 15.4, 6.1 Hz).

IR (neat): 775, 835, 970, 1075, 1255, 1710, 3150-3600.

MS: 395, 377, 351, 303, 187, 75 (100%).



$PGF_{1\alpha}$

Anal. Calcd for $C_{26}H_{50}O_5Si$: C, 66.34; H, 10.71.
Found: C, 66.49; H, 10.84.

(±)-Prostaglandin $F_{1\alpha}$.

Treatment of 99 (5.1 mg) with hydrofluoric acid in acetonitrile according to the procedure described for PGE_1 gave 3.5 mg of (±)-prostaglandin $F_{1\alpha}$ after chromatography (ethyl acetate, then 10% and 20% methanol/ethyl acetate mixtures) (90% yield). The spectral and chromatographic characteristics of our synthetic $PGF_{1\alpha}$ were identical to those of an authentic sample.[49]

^{1}H-NMR (acetone-d_6, 360 MHz): 0.873 (3H, t, J = 6.8 Hz), 1.228-1.646 (20H, m), 2.152-2.214 (2H, m), 2.254 (2H, t, J = 7.4 Hz), 3.794-3.846 (1H, ddd, J = 6.9, 6.0, 4.4 Hz), 3.975 (1H, dist q, J = 6.2 Hz), 4.095-4.127 (1H, m), 5.382-5.496 (2H, m).

$CH_3C{\equiv}C-(CH_2)_3-CH_2OSi^tBuMe_2$

106

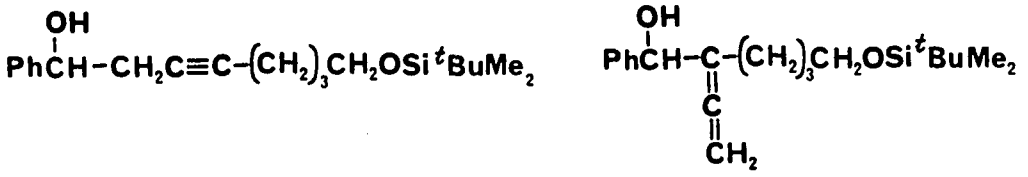
1-tert-Butyldimethylsilyloxy-5-heptyne (106).

Commercially available 5-hexyn-1-ol was transformed into 1-tert-butyldimethylsilyloxy-5-hexyne by standard procedures (tert-$BuMe_2SiCl$, DMF, imidazole, 50°C, 24 h), and the product was distilled under reduced pressure (bp 100-102°C at 15 mm Hg) to give pure 105 in 98% yield.

^{1}H-NMR (CCl_4, 60 MHz): 0.00 (s, 6H), 0.90 (s, 9H), 1.55-1.90 (5H, m), 2.00-2.20 (2H, m), 3.60 (2H, t, J = 6.0 Hz).

IR (neat): 770, 830, 1090, 1470, 2830-3000, 3330 (sharp).

To a solution of 2.12 g (10 mmol) of 105 in dry tetrahydrofuran (10 mL) kept at -78°C was added n-butyllithium (5.4 mL of 2.04 M solution in hexane), and the mixture was stirred at that temperature for 1 h. Methyl iodide (2.84 g, 20 mmol) was then added, and the reaction mixture was allowed to warm to room temperature over ca. 3 h. After stirring at that temperature for 1 h, the solution was diluted with ether, washed with water and a



saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Filtration of the drying agent, evaporation of the solvent in vacuo and distillation at reduced pressure afforded 1.908 g of 106 as a colorless liquid (bp 73-76°C at 8 mm Hg) (84%).

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.023 (6H, s), 0.875 (9H, s), 1.445-1.637 (4H, m), 1.746 (3H, t, J = 3.0 Hz), 2.074-2.163 (2H, m), 3.594 (2H, t, J = 6.0 Hz).

^{13}C-NMR ($CDCl_3$): -5.343, 3.324, 18.275, 18.492, 25.481, 25.914, 32.036, 62.698, 79.058.

IR (neat): 780, 840, 1110, 1260, 1365, 1390, 1465, 1475, 2860-3000.

Metalation of 1-tert-Butyldimethylsilyloxy-5-heptyne (106) in Tetrahydrofuran.

A flame-dried 25 mL round-bottomed flask was placed under nitrogen and was charged with 226 mg (1 mmol) of 106 dissolved in 5mL of anhydrous tetrahydrofuran. The solution was cooled down to 0°C and tert-butyllithium (0.53 mL of 2.10 M solution in pentane) was added dropwise.

After stirring at this temperature for 1 h, the anion was quenched with 0.12 mL (1.1 mmol) of benzaldehyde and the mixture was stirred at room temperature overnight. The reaction was then quenched with a saturated ammonium chloride solution, diluted with ether and the layers were separated. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Filtration of the drying agent and evaporation of the solvent *in vacuo* followed by flash chromatography (hexane:diethyl ether, 9:1) gave 27 mg of the allenic adduct, 61 mg of the propargylic carbinol and 78 mg of a mixture of both (50% combined yield, *ca*. 1:2 ratio of allenic: propargylic carbinols).

[7-*tert*-Butyldimethylsilyloxy-1,2-heptadien-3-yl]-phenyl methanol:

R_f = 0.21, hexane:ether, 9:1.

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.001 (6H, s), 0.858 (9H, s), 1.396-1.484 (4H, m), 1.773-1.829 (2H, m), 2.231-2.243 (1H, m), 3.524 (2H, t, J = 6.1 Hz), 4.968-4.995 (2H, m), 5.077 (1H, br s), 7.239-7.365 (5H, m).

^{13}C-NMR ($CDCl_3$): -5.289, 18.330, 23.855, 25.968, 27.702, 32.361, 62.914, 74.183, 79.762, 108.149, 126.677, 127.760, 128.302, 142.116, 204.253.

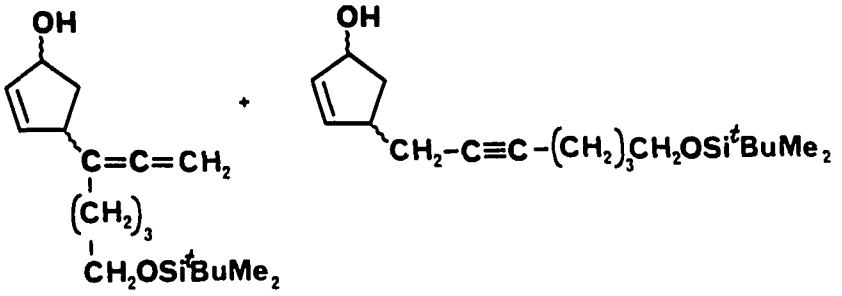
[7-tert-Butyldimethylsilyloxy-2-heptyn-1-yl] phenyl methanol:

R_f = 0.14, hexane:ether, 9:1.

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.043 (6H, s), 0.891 (9H, s), 1.504-.1594 (4H, m), 2.159-2.203 (2H, m), 2.517-2.523 (1H, br), 2.556-2.599 (2H, m), 3.599 (2H, t, J = 6.1 Hz), 4.783 (1H, dist t, J = 6.1 Hz), 7.261-7.378 (5H, m).

^{13}C-NMR ($CDCl_3$): -5.289, 18.546, 25.372, 25.968, 30.085, 31.927, 62.644, 72.612, 76.187, 83.338, 125.756, 127.706, 128.302, 142.929.

The data obtained from these adducts were very helpful in tentatively assigning the structures of the cyclopentadiene monoepoxide adducts 107 and 108. This was especially true for the ^{13}C data (i.e., allenic adduct: 204.253, 108.149 and 79.762 ppm); propargylic adduct: (83.338 and 76.187 ppm).



107(1) 108(1)

4-[7-tert-Butyldimethylsilyloxy-1,2-heptadien-3-yl]-cyclopent-2-enol (107) and 4-[7-tert-Butyldimethylsilyloxy-2-heptyn-1-yl]-cyclopent-2-enol (108).

A flame-dried 50 mL round bottomed flask was charged with 0.51 mL of a tert-butyllithium solution in pentane (2.15 M) and the solvent was evaporated under a stream of nitrogen at room temperature. The solid tert-butyllithium was cooled to -78°C and dissolved in 5 mL of anhydrous ether. After sequential addition of TMEDA (0.17 mL, 1.1 mmol) and 1-tert-butyldimethylsilyloxy-5-heptyne (226 mg, 1 mmol), the resulting yellow slurry was gradually warmed up to 0°C (yellow solution) and stirred for 1 h. The solution was then transferred under nitrogen onto a suspension of CuCN (197 mg, 2.2 mmol) in 5 mL of ether kept at -30°C. The reaction mixture was warmed up to 0°C and stirred for 15 min at that temperature. The dark red solution was cooled to -50°C, cyclopentadiene monoepoxide (181 mg, 2.2 mmol) was added and the reaction mixture was allowed to warm up to room temperature over ca. 4 h. Usual

workup (see general procedure for cuprate additions) gave a crude product which was chromatographed (hexane:diethyl ether, 5:1) to give an inseparable 1:1 mixture of 107 and 108 (92 mg, 30% yield, light yellow oil) as the only products that could be characterized. The structural assignment for 107 and 108 is tentative and based primarily on the ^{13}C-NMR data. The reaction was also attempted without TMEDA, by performing the metalation in THF, with identical results to those just described.

R_f = 0.15, hexane:ether, 5:1.

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.043 (6H, s), 0.891 (9H, s), 1.451-2.225 (11H, m), 3.550-3.636 (2H, m), 4.655-4.682 (1H, m), 4.857-4.896 (1H, m), 5.830-5.857 (1H, m), 5.916-5.948 (1H, m).

^{13}C-NMR ($CDCl_3$, the underlined values are tentatively assigned to the allenic adduct): -5.289, 18.330, 18.492, 23.910, 24.830, 25.481, 25.914, 30.248, 31.927, 32.469, 39.999, 43.900, 46.554, 62.698, 63.023, 77.000, 81.063, 106.091, 133.286, 133.719, 137.782, 138.649, 204.741.

IR (neat): 780, 840, 1100, 1255, 1465, 1960, 2860-3000, 3400.

$ICH_2C{\equiv}C-(CH_2)_3-CH_2OSiEt_3$

109

1-Iodo-7-triethylsilyloxy-2-heptyne (109).

Commercially available 5-hexyn-1-ol was transformed into 1-triethylsilyloxy-5-hexyne by standard procedures (Et_3SiCl, DMF, imidazole, 50°C, 24 h) and the product was distilled under reduced pressure (bp 113-115°C at 10 mm Hg) (95%).

^{1}H-NMR (CCl_4, 60 MHz): 0.25-1.20 (15H, m), 1.30-1.80 (5H, m), 1.95-2.25 (2H, m), 3.55 (2H, t, J = 6.0 Hz).

IR (neat): 760, 1025, 1120, 1250, 1470, 2850-2950, 3280 (sharp).

Under a nitrogen atmosphere, 10.68 g (50.3 mmol) of 1-triethylsiloxy-5-hexyne was dissolved in 50 mL of anhydrous THF and the solution was cooled to 0°C; n-butyllithium (1.1 eq, 27.1 mL of a 2.04 M solution) was then added and the solution was stirred at 0°C for 1 h. Paraformaldehyde (6.80 g) was then added and the reaction mixture was stirred at room temperature for 1 h and at reflux for ca. 10 h. The mixture was then cooled to room temperature and poured onto 40 mL of ice-water. The layers

were separated and the aqueous layer was extracted with ether (2 x 100 mL). The combined organic extracts were washed with a saturated ammonium chloride solution, brine and dried over magnesium sulfate. Filtration of the drying agent and evaporation of the solvent *in vacuo*, followed by distillation under reduced pressure (bp 90-93°C at 0.1 mm Hg) gave 9.1 g (75% yield) of 1-hydroxy-7-triethylsilyloxy-2-heptyne as a colorless liquid.

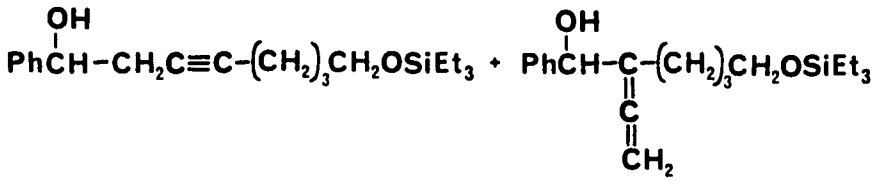
^{1}H-NMR (CCl_4, 60 MHz): 0.25-1.20 (15H, m), 1.35-1.80 (4H, m), 2.00-2.35 (2H, m), 3.60 (2H, t, J = 6.0 Hz), 4.00-4.20 (2H, m).

To a cold (0°C) solution of 4 g (16.5 mmol) of 1-hydroxy-7-triethylsilyloxy-2-heptyne in 30 mL of ether was added triethylamine (2.53 mL, 18.14 mmol) and mesyl chloride (1.54 mL, 19.8 mmol). The resulting white slurry was stirred at room temperature for 12 h and then filtered through Florisil. Evaporation *in vacuo* gave 5.0 g of crude mesylate (100%).

^{1}H-NMR (CCl_4, 60 MHz): 0.25-1.20 (15H, m), 1.35-1.80 (4H, m), 2.00-2.40 (2H, m), 3.00 (3H, s), 3.60 (2H, t, J = 6.0 Hz), 4.85 (2H, t, J = 3 Hz).

To a solution of the crude mesylate (5.02 g) in 48 mL of acetone was added sodium iodide (9.8 g, 65.9 mmol) and the reaction mixture was stirred at room temperature for 1 h, after which time the solvent was evaporated in vacuo. The residue was taken up into ether (100 mL) and water (20 mL) was added; the layers were separated and the organic extracts were washed with a 10% sodium thiosulfate solution and a saturated solution of sodium chloride. The solution was dried over magnesium sulfate; filtration of the drying agent and evaporation of the solvent gave a crude product which was purified by chromatography (hexane: ether, 99:1) to give 2.8 g of 109 as a pale yellow liquid (50% yield).

^{1}H-NMR ($CDCl_3$, 60 MHz): 0.25-1.20 (15H, m), 1.35-1.80 (4H, m), 2.00-2.40 (2H, m), 3.60-3.90 (4H, m).

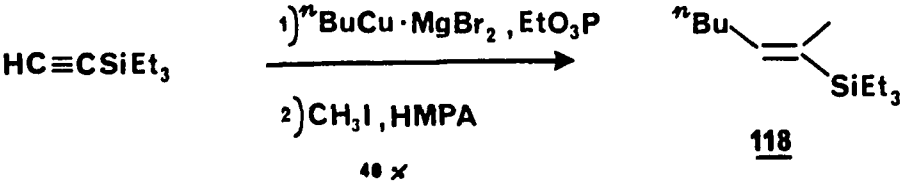


110(2) 111(1)

Metal-Halogen Exchange of 1-Iodo-7-triethylsilyloxy-2-heptyne (109).

1-Iodo-7-triethylsilyloxy-2-heptyne (350 mg, 1 mmol) was dissolved in 5 mL of anhydrous diethyl ether in a 25 mL round bottomed flask. Under a nitrogen atmosphere the solution was cooled to -110°C and tert-butyllithium (2.2 equivalents, 1.02 mL of a 2.15 M solution in pentane) was added dropwise. The mixture was stirred at -110°C for 2 h and then quenched with 0.15 mL of benzaldehyde and allowed to warm up to room temperature. After stirring at room temperature for 1 h, the mixture was quenched with a saturated ammonium chloride solution, the layers were separated and the organic layer was washed with a saturated sodium chloride solution and dried over magnesium sulfate. Filtration of the drying agent and evaporation of the solvent in vacuo gave a crude product which was chromatographed on silica gel (hexane:ether, 9:1) to give 37 mg (11%) of an inseparable 2:1 mixture of 110 and 111.

R_f = 0.17, hexane:ether, 9:1.

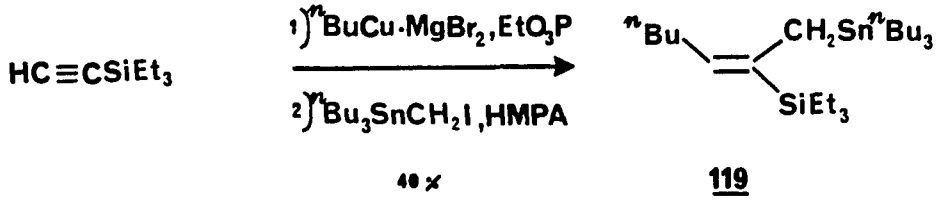


118

^{1}H-NMR ($CDCl_3$, 360 MHz; on mixture): 0.630 (6H, m), 0.880-1.010 (9H, m), 1.396-1.700 (4H, m), 2.159-2.203 (2H, m), 2.517-2.599 (3H, m), 3.580-3.631 (2H, m), 4.785 (1H, dist t, J = 6.1 Hz; 110), 4.968-4.995 (2H, m; 111), 5.077 (1H, br s; 111), 7.260-7.379 (5H, m).

2-Triethylsilyl-2(E)-heptene (118).

The reaction of triethylsilyl acetylene (140 mg, 1 mmol) with 1.5 equivalents of n-BuCu·$MgBr_2$ (prepared from 0.94 mL of 1.6 M solution of n-butyl MgBr and 230 mg of cuprous bromide) in the presence of EtO_3P (0.34 mL, 2 mmol), followed by alkylation with methyl iodide (0.13 mL, 2 mmol) in the presence of EtO_3P (0.68 mL, 4 mmol) and HMPA (1.5 mL), according to the procedure developed by Utimoto[68] for the carbometalation and alkylation of trimethylsilyl acetylene gave 80 mg (40% yield) of 118 (colorless liquid) after chromatography (hexane; R_f = 0.64).



40% **119**

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.550 (6H, q, J = 8.2 Hz), 0.892 (12H, t, J = 8.2 Hz), 1.243-1.363 (4H, m), 1.623 (3H, d, J = 2.0 Hz), 2.089 (2H, dist q, J = 6.6 Hz), 5.673 (1H, dist t, J = 6.1 Hz).

^{13}C-NMR ($CDCl_3$): 2.674, 7.387, 13.996, 14.917, 22.393, 28.027, 31.602, 132.527, 141.195.

IR (neat): 720, 1010, 1465, 1620, 2850-3010.

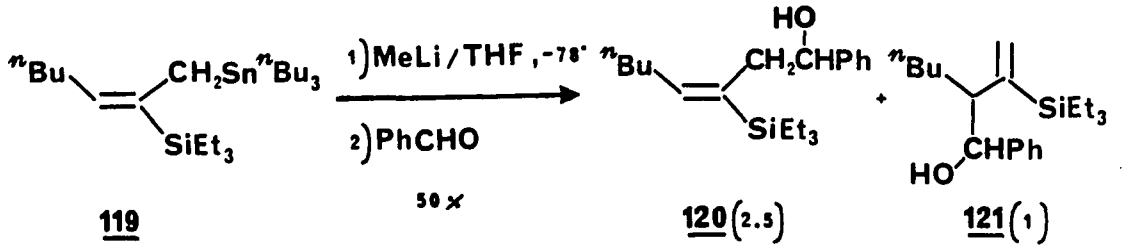
Anal. Calcd for $C_{13}H_{28}Si$: C, 73.50; H, 13.28.
Found: C, 73.21; H, 12.93.

1-(tri-n-Butylstannyl)-2-triethylsilyl-2(E)-heptene (119).

The reaction of triethylsilyl acetylene (1.54 g, 11 mmol) with 0.9 equivalents of n-BuCu·$MgBr_2$ (prepared from 6.25 mL of 1.6 M solution of n-butyl MgBr and 1.6 g of cuprous bromide) in the presence of EtO_3P (1.90 mL, 11 mmol), followed by alkylation with (tri-n-butylstannyl)-methyl iodide (4.32 g, 10 mmol) in the presence of EtO_3P (3.80 mL, 22 mmol) and HMPA (10 mL), according to the procedure developed by Utimoto[68] for the carbometalation and alkylation of trimethylsilyl acetylene, gave 3.50 g of

impure 119 (colorless liquid) after chromatography (hexane). Repeated attempts to obtain pure 119 by a second chromatography or distillation under reduced pressure were not successful; 119 was always contaminated by some tin by-product and this prevented the accurate measurement of the integrals in the upfield region of its ^{1}H-NMR spectrum. The reaction proceeded in ca. 40% yield (by integration of the 360 MHz ^{1}H-NMR spectrum of the mixture, under the assumption that the by-product was ^{n}pentyl $Sn^{n}Bu_3$).

^{1}H-NMR ($CDCl_3$, 360 MHz: 0.545 (6H, q, J = 6.7 Hz), 0.788-0.961 (m), 1.238-1.561 (m), 1.746 (2H, t, J = 32.3 Hz, coupling with tin), 1.936 (2H, dist q, J = 6.7 Hz), 5.386 (1H, dist t, J = 6.2 Hz).



119 120(2.5) 121(1)

Lithium Tin Exchange of Allyl Tin Compound 119. Preparation of [2-Triethylsilyl-2(E)-hepten-1-yl] Phenyl Methanol, (120), and [2-Triethylsilyl-1-hepten-3-yl] Phenyl Methanol (121).

Under an inert atmosphere of nitrogen, 0.19 mL of methyllithium solution was added to a cooled (-78°C) solution of 125 mg of 119 (0.25 mmol) in 3 mL of anhydrous tetrahydrofuran. The mixture was stirred at this temperature for 1 h and 0.04 mL of benzaldehyde (0.50 mmol) was then added. The mixture was allowed to warm up to room temperature and stirred at that temperature overnight. The reaction was then quenched with saturated ammonium chloride, diluted with ether, and the layers were separated. The organic layer was washed with a saturated sodium chloride solution and dried over magnesium sulfate. Filtration of the drying agent and concentration in vacuo followed by column chromatography (hexane:ether, 9:1) allowed for the separation of pure samples of 120 and 121 which were subsequently combined with the rest of the fractions to give

ca. 40 mg (50% yield) of a 2.5:1 mixture of 120 and 121, as determined by integration of the 360 MHz ^{1}H-NMR spectrum of the mixture. It should be mentioned that 121 was formed as a 3:1 mixture of diastereoisomers (by integration of the ^{1}H-NMR spectrum of pure 121) while only one isomer was detected for 120, whose stereochemistry was tentatively assigned as E.

Compound (120):

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.631 (6H, m), 0.856-0.943 (12H, m), 1.220-1.384 (2H, m), 2.076-2.189 (2H, m), 2.405 (1H, dd, J = 13.4, 4.2 Hz), 2.651 (1H, dd, J = 13.4, 9.8 Hz), 4.622 (1H, dd, J = 9.8, 4.2 Hz), 5.960 (1H, t, J = 6.9 Hz), 7.305-7.544 (5H, m).

Anal. Calcd for $C_{20}H_{34}SiO$: C, 75.41; H, 10.75.
Found: C, 74.88; H, 10.93.

Compound (121) (for major diastereomer):

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.554-.0671 (6H, m), 0.892-0.965 (12H, m), 1.221-1.403 (6H, m), 2.613-2.681 (1H, m), 4.624 (1H, d, J = 3.0 Hz), 5.638 (1H, d, J = 2.3 Hz), 5.857 (1H, br s), 7.302-7.538 (5H, m).

158

Experimental Procedures for an Approach to Porosin and The Synthesis of Oak Lactones via Lactonization of Vinyl Sulfoxides.

1,2-Dibromo-1-(3,4-dimethoxyphenyl)-propane (158). Under an inert atmosphere of nitrogen, 10.2 mL of bromine (0.2 mol) dissolved in 20 mL of chloroform was added dropwise to a cooled (-30°C) solution of 35.6 g (0.2 mol) of commercially available 1-(3,4-dimethoxyphenyl)-1-propene (ca. 95% E) in 60 mL of chloroform. After evaporation of the solvent in vacuo, the crystalline residue (67 g, 90% yield) was a 10:1, erythro:threo mixture (by integration of the ^{1}H-NMR spectrum of the mixture). Pure erythro isomer (mp 107-108°C[106]) could be obtained by recrystallization with 5% i-PrOH/hexane. In some instances, the crude dibromide was employed for the next reaction.

Erythro (118):

^{1}H-NMR ($CDCl_3$, 360 MHz): 2.014 (3H, d, J = 6.5 Hz), 3.861 (3H, s), 3.883 (3H, s), 4.576 (1H, dq, J = 10.3, 6.5 Hz), 5.011 (1H, d, J = 10.3 Hz), 6.797 (1H, d, J = 8.3 Hz), 6.872-6.946 (2H, m).

161

Threo (118):

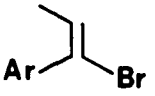
^{1}H-NMR ($CDCl_3$, 360 MHz): 1.691 (3H, d, J = 6.8 Hz), 5.174 (1H, d, J = 6.0 Hz) in the mixture.

1-Ethoxy-1-(3,4-dimethoxyphenyl)-2-bromopropane (161).

To a solution of potassium hydroxide (1.83 g, 32.5 mmol) in ethanol (30 mL) kept at 55°C was added 5 g of 1,2-dibromo-1-(3,4-dimethoxyphenyl)-propane, 158 (14.8 mmol). The solution was stirred at 55°C for 2 h after which time the starting material had been completely consumed. The solvent was then evaporated in vacuo and the residue was taken up into ether and filtered through a Celite pad. Concentration in vacuo and column chromatography gave 3.60 g (80% yield) of 161 as a yellow oil.

^{1}H-NMR ($CDCl_3$, 360 MHz): 1.148 (3H, t, J = 7.0 Hz), 1.610 (3H, d, J = 6.7 Hz), 3.314-3.437 (2H, m), 3.821 (3H, s), 3.837 (3H, s), 4.153 (1H, dist quintet, J = 6.3 Hz), 4.299 (1H, d, J = 5.4 Hz), 6.738-6.992 (3H, m).

IR (neat): 770, 810, 1025, 1260, 1415, 1450, 1510, 1580, 2820-3010.



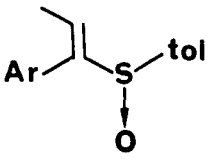
159

1-Bromo-1-(3,4-dimethoxyphenyl)-1(E)-propene (159).

A solution of 1.7 g (5 mmol) of dibromide 158 in 15 mL of dichloromethane was added to a cold (0°C) solution of 2.2 g of potassium hydroxide in 15 mL of isopropanol. The mixture was stirred at 0°C for 15 min and at room temperature for 30 min and was then concentrated *in vacuo*. The residue was taken up into ether and filtered through Florisil. The ether was removed *in vacuo* and the residue was chromatographed on silica gel (hexane:ether, 9:1) to give 0.9 g of pure 159 (70%) as a colorless oil. Crude 159 was sufficiently pure to be used for the next step without chromatography. Standing at room temperature for 2-3 days caused decomposition and partial isomerization to the Z-isomer.

^{1}H-NMR ($CDCl_3$, 360 MHz): 1.654 (3H, d, J = 7.3 Hz), 3.865 (3H, s), 3.869 (3H, s), 6.199 (1H, q, J = 7.3 Hz), 6.865-6.911 (3H, m).

^{13}C-NMR ($CDCl_3$, 75 MHz): 16.423, 55.944, 110.856, 112.771, 120.844, 121.855, 128.284, 131.195, 148.677, 149.190.



157

IR (neat): 760, 860, 1025, 1140, 1235, 1255, 1405, 1460, 1510, 1600, 2840-3020.

MS: 258 (M+2), 256 (M), 177 (100%), 146, 131, 91.

The Z isomer was characterized by its downfield methyl shift (1.906 ppm) and upfield vinylic shift (6.155).

1-(3,4-Dimethoxyphenyl)-1-(p-toluenesulfinyl)-1(E)-propene (157).

Sec-butyllithium (8.4 mmol, 5.8 mL of a 1.44 M solution in cyclohexane) was added under a nitrogen atmosphere to a precooled (-78°C) solution of 2.06 g (8 mmol) of crude vinyl bromide 159 in 80 mL of anhydrous ether. The reaction mixture was stirred at -78°C for 1 h, after which time 2.83 g (16 mmol) of p-toluenesulfinyl chloride was added via syringe. The reaction mixture was then allowed to warm up to room temperature over ca. 4 h. After quenching the mixture with 40 mL of saturated sodium bicarbonate, it was diluted with 50 mL of ether, and the resulting layers were separated. The organic layer was washed with a saturated sodium chloride solution, and dried over

magnesium sulfate. Filtration of the drying agent, evaporation of the solvent in vacuo and column chromatography (hexane:ethyl acetate, 1:1; R_f = 0.20) gave 1.33 g of pure 157 (53% overall from dibromide 158) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 360 MHz): 1.756 (3H, d, J = 7.0 Hz), 2.286 (3H, s), 3.630 (3H, s), 3.809 (3H, s), 6.237 (1H, d, J = 1.9 Hz), 6.471 (1H, dd, J = 8.2, 1.9 Hz), 6.621 (1H, q, J = 7.0 Hz), 6.722 (1H, d, J = 8.2 Hz), 7.089 (2H, d, J = 8.0 Hz), 7.182 (2H, d, J = 8.0 Hz).

^{13}C-NMR ($CDCl_3$): 14.429, 21.201, 55.655, 110.750, 112.592, 122.505, 123.426, 125.051, 129.223, 139.624, 141.033, 145.908, 148.400, 148.922.

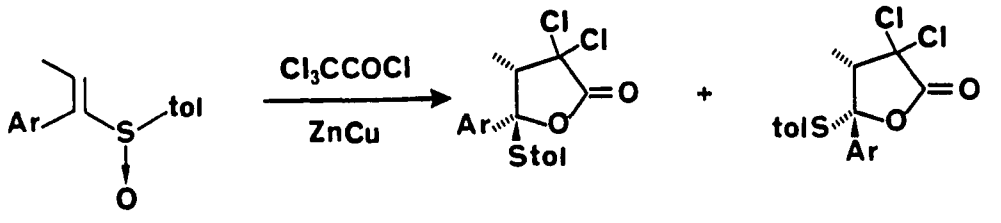
IR (neat): 765, 815, 1030, 1140, 1235, 1255, 1410, 1450, 1510, 1600, 2840-3020.

MS: 317 (M+1), 300, 177 (100%), 91.

Anal. Calcd for $C_{18}H_{20}O_3S$: C, 68.33; H, 6.37; S, 10.13.
Found: C, 68.24; H, 6.45; S, 10.09.

General Procedure for the Sulfoxide-Directed Lactonization of Vinyl Sulfoxides.[70]

A solution of five equivalents of an α-halo acid chloride in anhydrous ether (20 mL per mmol of sulfoxide) was added dropwise over a 15-min period to a rapidly stirred suspension containing twenty equivalents of zinc-copper



157 156 (30) 162 (1)

couple[107] in a refluxing ether solution of one equivalent of the vinyl sulfoxide (30 mL per mmol of sulfoxide). After addition of the acid chloride, reflux was continued for 15 min. The excess zinc was removed *via* filtration through Celite and the resulting yellow solution was poured into cold, saturated sodium bicarbonate (50 mL per mmol of sulfoxide). This mixture was stirred vigorously for 30 min and then the layers were separated. The aqueous portion was extracted once with 100 mL of ether, and the combined ether fractions were dried over magnesium sulfate. The ether was removed *in vacuo*, leaving the crude lactone as a brown oil. Purification was effected by chromatography on silica gel (hexane/ethyl acetate solvent systems).

2,2-Dichloro-4α-(3,4-dimethoxyphenyl)-3α-methyl-4β-*p*-tolylthio-γ-butyrolactone (156) and 2,2-Dichloro-4β-(3,4-dimethoxyphenyl)-3α-methyl-4α-*p*-tolylthio-γ-butyrolactone (162).

Vinyl sulfoxide 157 (1.33 g, 4.20 mmol) was treated with 2.34 mL (3.82 g, 21 mmol) of trichloroacetyl chloride and 5.48 g (84 mmol) of zinc-copper couple in 210 mL of ether as described in the general procedure. Column chromatography (hexane:ethyl acetate, 9:1) afforded 1.077 g of pure 156 (60%) as a yellow oil and ca. 70 mg of more polar products. A second column chromatography of the 70 mg (hexane:ethyl acetate, 9:1; 10 g of silica) provided 34 mg of isomeric lactone 162 (yellow oil), along with an uncharacterized, slightly more polar, material.

Compound (156):

R_f = 0.19, hexane:ethyl acetate, 9:1.

^{1}H-NMR ($CDCl_3$, 360 MHz): 1.322 (3H, d, J = 6.8 Hz), 2.306 (3H, s), 3.061 (1H, q, J = 6.8 Hz), 3.848 (6H, s), 6.783 (1H, d, J = 8.6 Hz), 6.878 (1H, d, J = 2.3 Hz), 6.959 (1H, dd, J = 8.6, 2.3 Hz), 7.111 (2H, d, J = 8.0 Hz), 7.385 (2H, d, J = 8.0 Hz).

^{13}C-NMR ($CDCl_3$): 10.198, 21.283, 54.593, 55.845, 80.813, 99.227, 110.251, 110.549, 120.084, 125.328, 126.579, 130.095, 136.173, 140.643, 148.091, 149.343, 166.803.

IR ($CHCl_3$): 845, 980, 1150, 1460, 1795, 2840-2980.

MS: 429, 427 (M+1), 347, 303, 165 (100%), 123, 77.

Anal. Calcd for $C_{20}H_{20}O_4SCl_2$: C, 56.21; H, 4.72, Cl, 16.59; S, 7.50.

Found: C, 55.88; H, 4.69; Cl, 16.04; S, 7.65.

Compound (162):

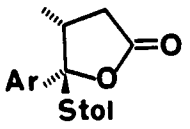
R_f = 0.16, hexane:ethyl acetate, 9:1.

^{1}H-NMR ($CDCl_3$, 360 MHz): 1.692 (3H, d, J = 6.9 Hz), 2.215 (3H, s), 3.277 (1H, q, J = 6.9 Hz), 3.737 (3H, s), 3.815 (3H, s), 6.720 (1H, d, J = 8.5 Hz), 6.764 (1H, d, J = 2.2 Hz), 6.911 (2H, d, J = 8.1 Hz), 6.957 (1H, dd, J = 8.5, 2.2 Hz), 7.097 (2H, d, J = 8.1 Hz).

^{13}C-NMR ($CDCl_3$, 90 MHz): 10.291, 21.092, 55.825, 59.357, 81.331, 99.161, 107.789, 110.578, 117.629, 124.732, 129.351, 132.355, 135.741, 139.224, 148.358, 148.780, 167.127.

IR ($CDCl_3$): 1020, 1215, 1260, 1410, 1445, 1505, 1595, 1795, 2850-3020.

MS: 428, 426 (M), 347, 303, 165 (100%), 123, 77.



160

4α-(3,4-Dimethoxyphenyl)-3α-methyl-4β-p-tolylthio-γ-butyrolactone (160).

To a solution of 216 mg (0.5 mmol) of dichlorolactone 156 in 25 mL of THF/H_2O, 9:1, was added ca. 243 mg (5 mmol) of aluminum amalgam generated from aluminum foil by the procedure of Corey.[81] The mixture was stirred at 0°C for 1 h and at room temperature overnight. The mixture was then filtered through a Celite pad and the filter cake was rinsed with ether. The combined organic extracts were then washed with a saturated ammonium chloride solution and dried over magnesium sulfate. Filtration of the drying agent, concentration in vacuo and column chromatography (hexane:ethyl acetate, 4:1; R_f = 0.23) gave 160 mg of lactone 160 (90%) as a colorless oil. It was observed that a $CDCl_3$ solution of 160 suffered complete decomposition of 160 upon standing at room temperature for ca. 24 h. Compound 160 could be stored indefinitely, however, if it was kept in a refrigerator without any solvent.

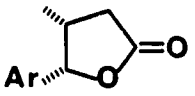
^{1}H-NMR ($CDCl_3$, 360 MHz): 0.791 (3H, d, J = 7.0 Hz), 2.240 (3H, s), 2.281 (1H, dd, J = 17.3, 2.9 Hz), 2.906 (1H, quintet d, J = 7.2, 2.9 Hz), 3.032 (1H, dd, J = 17.3, 7.8 Hz), 3.774 (3H, s), 3.832 (3H, s), 6.733 (1H, d, J = 8.4 Hz), 6.794 (1H, d, J = 2.1 Hz), 6.875 (1H, dd, J = 8.4, 2.1 Hz), 6.950 (2H, d, J = 8.0 Hz), 7.124 (2H, d, J = 8.0 Hz).

^{13}C-NMR ($CDCl_3$): 17.246, 21.093, 38.157, 40.812, 55.818, 100.836, 109.937, 110.262, 119.092, 126.189, 129.277, 130.035, 135.832, 139.137, 148.292, 175.324.

IR (neat): 735, 810, 920, 1025, 1260, 1510, 1595, 1785, 2860-3020,

MS: 359 (M+1), 283, 236, 165 (100%), 123, 79.

Anal. Calcd for $C_{20}H_{22}O_4S$: C, 67.02; H, 6.19; S, 8.94.
Found: C, 67.25; H, 6.10; S, 8.67.

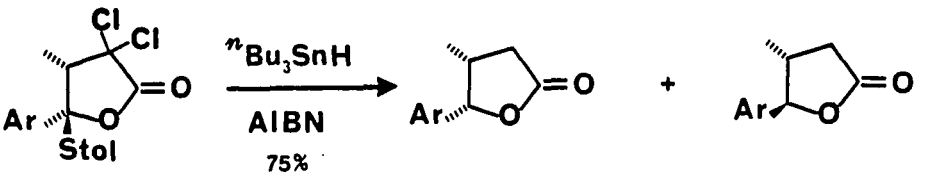


152

cis-4-(3,4-Dimethoxyphenyl)-3-methyl-γ-butyrolactone (152).

To a suspension of Raney nickel (prepared according to Burgstahler[82] from 657 mg of 50% alloy) in 5 mL of ethanol was added 100 mg (0.28 mmol) of arylthiolactone 160 in 10 mL of ethanol. The mixture was stirred at room temperature for 24 h and was then filtered through a Celite pad. The filter cake was washed with ethanol and the combined organic extracts were concentrated in vacuo. The residue was then taken up into ether, washed with a saturated sodium chloride solution and dried over magnesium sulfate. Filtration of the drying agent, evaporation of the solvent and column chromatography (hexane:ethyl acetate, 3:1, then 2:1) gave 22.1 mg of starting material, 160 (22%) and 13.2 mg of lactone 152 (20%), as a colorless oil, contaminated with trace amounts (ca: 30:1 ratio) of its epimer 165.

R_f = 0.13, hexane:ethyl acetate, 3:1.



156 152 (2.5) 165 (1)

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.699 (3H, d, J = 7.1 Hz), 2.298-2.373 (1H, m), 2.776-2.851 (2H, m), 3.863 (3H, s), 3.867 (3H, s), 5.537 (1H, d, J = 5.7 Hz), 6.725-6.769 (2H, m), 6.852 (1H, d, J = 8.2 Hz).

^{13}C-NMR ($CDCl_3$, 90 MHz): 15.190, 35.213, 37.244, 55.986, 56.064, 84.055, 108.696, 111.155, 117.808, 128.633, 148.784, 149.091, 176.769.

IR ($CDCl_3$): 1025, 1160, 1415, 1510, 1595, 1775, 2880-3010.

MS: 236 (M), 167 (100%), 151, 139, 95.

Reaction of 2,2-Dichloro-4α-(3,4-dimethoxyphenyl)-3α-methyl-4β-p-tolylthio-γ-butyrolactone (156) with tri-n-Butyltin Hydride.

To a solution of 213 mg (0.5 mmol) of dichlorolactone 156 in 10 mL of toluene was added 0.94 mL (3.5 mmol) of tri-n-butyltin hydride and 10 mg of AIBN. The solution

was refluxed for ca. 12 h under a nitrogen atmosphere. Concentration in vacuo and column chromatography (hexane: ethyl acetate, 2:1, then 1:1) afforded 88.6 mg of a 2.5:1 mixture of cis-lactone 152 and trans-lactone 165, as determined by integration of its 360 MHz ^{1}H-NMR spectrum (75% yield). A second chromatography (hexane:ethyl acetate, 2:1; 15 g silica) allowed for the separation of a sample of pure trans-lactone 165, as a colorless oil.

Compound (165):

R_f = 0.40, hexane:ethyl acetate, 1:1.

^{1}H-NMR ($CDCl_3$, 360 MHz): 1.156 (3H, d, J = 6.5 Hz), 2.326 (1H, dd, J = 16.8, 10.9 Hz), 2.422-2.515 (1H, m), 2.779 (1H, dd, J = 16.8, 7.5 Hz), 3.872 (3H, s), 3.879 (3H, s), 4.862 (1H, d, J = 8.6 Hz), 6.819-6.849 (3H, m).

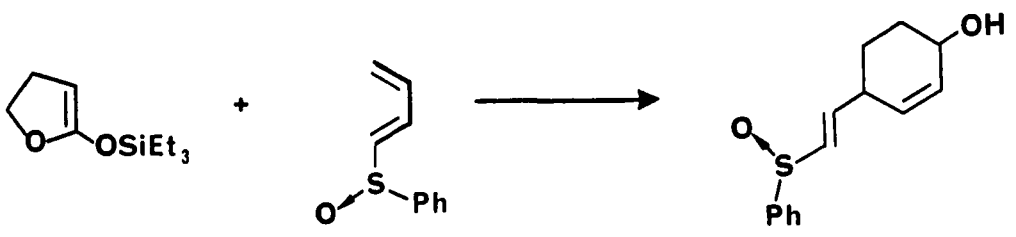
^{13}C-NMR ($CDCl_3$, 75 MHz): 16.476, 37.492, 39.789, 56.049, 56.096, 88.354, 109.039, 111.089, 118.869, 130.228, 149.455, 149.561, 176.047.

IR ($CDCl_3$): 1025, 1150, 1215, 1235, 1265, 1420, 1520, 1595, 1775, 2840-3020.

MS: 236 (M), 167 (100%), 151, 139, 95.

Anal. Calcd for $C_{13}H_{16}O_4$ (on the mixture): C, 66.09; H, 6.83.

Found: C, 65.93; H, 7.01.



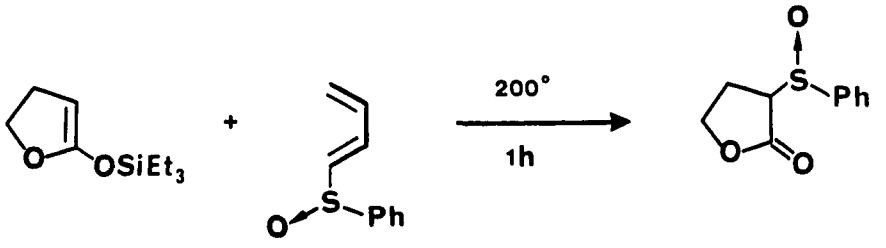
169 151 170 (7%)

Reaction of 2-Triethylsiloxy-4,5-dihydrofuran (169) with (E)-1-Butadienyl Phenyl Sulfoxide (151) in Acetonitrile.

To a solution of 178 mg (1 mmol) of diene 151[109] in 2 mL of dry acetonitrile was added 212 mg (1 mmol) of freshly distilled silyl ketene acetal 169[110] (bp 43°C at 0.025 mm Hg). The mixture was refluxed under nitrogen for 3 days after which time it was diluted with ether. The ether solution was washed with a saturated sodium chloride solution and dried with magnesium sulfate. Evaporation of the ether gave a crude product which was chromatographed on silica gel (hexane:ethyl acetate, 9:1, then 4:1, then 1:1, then ethyl acetate). Starting material 151 (43.4 mg) and 8.1 mg (7%) of adduct 170 were isolated as the only products which could be characterized.

Compound (170):

R_f = 0.15, hexane:ethyl acetate, 1:1).



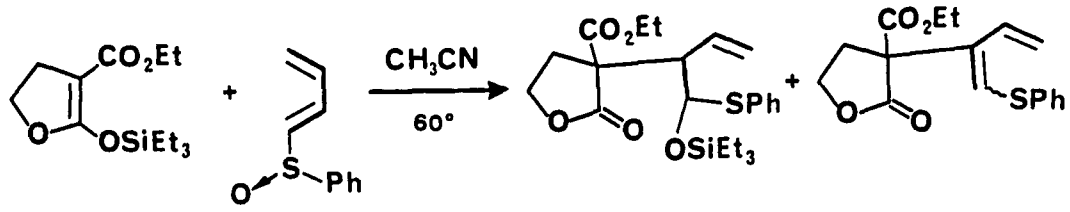
169 151 171

^{1}H-NMR ($CDCl_3$, 360 MHz): 1.606-1.841 (5H, m), 2.934-2.943 (1H, m), 4.161-4.171 (1H, m), 5.631-5.685 (1H, m), 5.839-5.882 (1H, m), 6.238 (1H, dt, J = 15.3, 1.6 Hz), 6.596 (1H, dd, J = 15.3, 6.7 Hz), 7.437-7.597 (5H, m).

IR ($CDCl_3$): 1030, 1445, 1620, 2850-3080, 3200-3550, 3620.

Reaction of 2-Triethylsilyloxy-4,5-dihydrofuran (169) with (E)-1-Butadienyl Phenyl Sulfoxide (151) at 200°C Neat.

A 25 mL round bottomed flask containing 425 mg of 169[110] (2 mmol) and 90 mg of diene 151[109] was kept in vacuo (1 mm Hg) for 1 h. The flask was then immediately flushed with nitrogen and heated at 200°C for 1 h. The mixture was chromatographed (hexane:ethyl acetate, 2:1) to give 12.0 mg of an uncharacterized product and 14.0 mg of 2-phenylsulfinyl-γ-butyrolactone 171 (14% yield).



174 151 175 (5%) 176 (4%)

Compound (171):

R_f = 0.33, hexane:ethyl acetate, 2:1.

^{1}H-NMR ($CDCl_3$, 360 MHz): 2.262 (1H, ddt, J = 13.5, 7.4, 6.1 Hz), 2.610-2.712 (1H, m), 3.850 (1H, dd, J = 8.6, 6.2 Hz), 4.173-4.280 (2H, m), 7.310-7.571 (5H, m).

IR ($CDCl_3$): 1020, 1150, 1370, 1440, 1585, 1765, 2900-3100.

MS: 210 (M), 125 (100%), 97, 73, 45.

Reaction of 3-Carboethoxy-2-triethylsilyloxy-4,5-dihydrofuran (174) with (E)-1-Butadienyl Phenyl Sulfoxide (151) in Acetonitrile.

A solution of 381 mg (1.4 mmol) of 174[87] and 180 mg (1 mmol) of diene 151[109] in 2 mL of dry acetonitrile was heated at 60°C for 16 h and then refluxed for 6 h. The solvent was then evaporated in vacuo and the residue was chromatographed on silica gel (hexane:ethyl acetate mixtures, 9:1, 7:1, 5:1, 4:1, 3:1, 2:1). This yielded 24.5 mg

(5% yield) of adduct 175 (pale yellow oil), which was formed as a 3:1 mixture of diastereomers (from integration of very complex 360 MHz ^{1}H-NMR spectrum), and 11.0 mg (4% yield) of adduct 176 (pale yellow oil), formed as a single isomer. Further elution produced 213 mg of a 3:1 mixture of 2-carboethoxy-γ-butyrolactone and diene 151.

Compound (175):

R_f = 0.48, hexane:ethyl acetate, 4:1.

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.495-0.723 (6H, m), 0.851-0.973 (9H, m), 1.123 (3H, m), 2.345-2.927 (2H, m), 3.472-3.568 (1H, m), 3.994-4.420 (5H, m), 5.221-5.417 (2H, m), 5.823-5.981 (1H, m), 7.243-7.541 (5H, m).

IR ($CDCl_3$): 1030-1160, 1240, 1735, 1770, 2880-3000.

MS: 341 (100), 319, 115, 109, 87.

Compound (176):

R_f = 0.29, hexane:ethyl acetate, 4:1.

^{1}H-NMR ($CDCl_3$, 360 MHz): 1.261 (3H, t, J = 7.1 Hz), 2.497 (1H, ddd, J = 13.1, 6.9, 4.1 Hz), 3.227 (1H, dt, J = 13.1, 8.2 Hz), 4.181-4.302 (3H, m), 4.380-4.439 (1H, m), 5.127 (1H, d, J = 17.8 Hz), 5.303 (1H, dd, J = 11.6, 1.2 Hz), 6.543 (1H, s), 6.624 (1H, dd, J = 17.8, 11.6 Hz), 7.236-7.368 (5H, m).

IR ($CDCl_3$): 1000-1120, 1730, 1770, 2880-3000.

MS: 318 (M), 245, 167 (100%), 109, 77.

Reaction of 1-Pyrrolydino-1-cyclopentene with (E)-1-Butadienyl Phenyl Sulfoxide (151) in Acetonitrile.

A solution of 180 mg (1 mmol) of 151[109] and 274 mg (2 mmol) of 1-pyrrolidino-1-cyclopentene in 1 mL of dry acetonitrile was heated at 60°C for 1 h under an atmosphere of nitrogen. The solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel (hexane: ethyl acetate mixtures, 9:1, 5:1, 2:1) to give 115 mg (60% yield) of 2-thiophenylcyclopentanone (pale yellow liquid) as the only product which could be characterized.

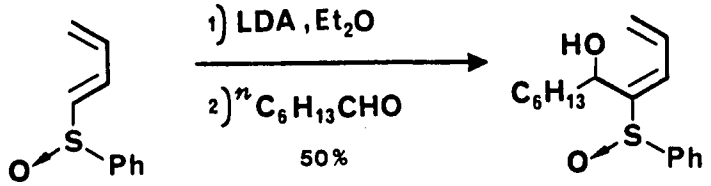
R_f = 0.23, hexane:ethyl acetate, 5:1.

^{1}H-NMR ($CDCl_3$, 360 MHz): 1.837-1.986 (2H, m), 2.004-2.095 (1H, m), 2.246-2.367 (3H, m), 3.558 (1H, t, J = 7.0 Hz), 7.222-7.298 (3H, m), 7.436-7.465 (2H, m).

IR (neat): 740, 1145, 1400, 1440, 1480, 1590, 1740, 2900-3080.

MS: 192 (M), 136 (100%), 109, 91.

The reaction was carried out several times with different stoichiometries of the reagents. In all cases, 2-thiophenylcyclopentanone was the predominant product and careful analysis of the other reaction products showed no signs of formation of the cycloaddition adduct.



151 180a,b

Lithiation of (E)-1-Butadienyl Phenyl Sulfoxide (151). Preparation of (E)-(1-Hydroxyheptyl)-1-phenylsulfinyl-1,3-butadiene (108a, 180b).

n-Butyllithium (1.1 mmol, 0.71 mL of 1.55 M solution) was added under a nitrogen atmosphere to a cold (0°C) solution of 0.16 mL (1.2 mmol) of dry N,N-diisopropylamine in 5 mL of anhydrous ether. After 30 min, the solution of LDA was cooled to -78°C and an ether solution (1 mL) of 180 mg (1 mmol) of dienyl sulfoxide 151[109] was added dropwise. After 30 min at -78°C, 0.27 mL of heptanal was added, and the reaction mixture was allowed to warm up to room temperature over 1 h. The solution was then quenched with a saturated ammonium chloride solution and diluted with ether. The organic layer was separated, washed with a saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration under reduced pressure gave a crude product which was chromatographed on silica gel (hexane:ethyl acetate, 2:1) to give 73 mg of 180a (least polar diastereomer) and 70 mg of

180b (more polar diastereomer) (50% combined yield), both as colorless oils.

Compound (180a):

R_f = 0.29, hexane:ethyl acetate, 2:1.

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.809 (3H, t, J = 7.0 Hz), 1.050-1.413 (9H, m), 1.616-1.680 (1H, m), 2.587-2.591 (1H, br), 4.516 (1H, dd, J = 8.2, 4.8 Hz), 5.470 (1H, dd, J = 9.9, 1.5 Hz), 5.575 (1H, dd, J = 16.5, 1.4 Hz), 6.742 (1H, ddd, J = 16.5, 11.3, 9.9 Hz), 6.892 (1H, d, J = 11.3 Hz), 7.417-7.473 (3H, m), 7.600-7.651 (2H, m).

IR (neat): 690, 750, 1035, 1440, 2850-3000, 3150-3600.

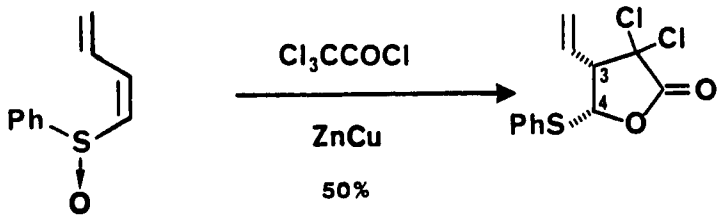
MS: 293, 292 (M), 275, 207, 126, 43 (100%).

Anal. Calcd for $C_{17}H_{24}O_2S$: C, 69.82; H, 8.27; S, 10.96. Found: C, 69.96; H, 8.45; S, 10.79.

Compound (180b):

R_f = 0.21, hexane:ethyl acetate, 2:1.

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.799 (3H, t, J = 7.1 Hz), 0.982-1.421 (10H, m), 3.113-3.201 (1H, br), 4.485 (1H, dd, J = 9.2, 4.2 Hz), 5.441-5.560 (2H, m), 6.799-6.885 (2H, m), 7.429-7.485 (3H, m), 7.586-7.624 (2H, m).



168 181

IR (neat): 690, 750, 1030, 1450, 2860-3000, 3100-3600.

MS: 293, 292 (M), 291, 275, 207, 126, 43 (100%).

Anal. Calcd for $C_{17}H_{24}O_2S$: C, 69.82; H, 8.27; S, 10.96. Found: C, 69.55; H, 8.44; S, 10.24.

cis-2,2-Dichloro-4-phenylthio-3-vinyl-γ-butyrolactone (181).

(Z)-1-Butadienyl phenyl sulfoxide 168[109] (534 mg, 3 mmol) was treated with 1.67 mL (2.73 g, 15 mmol) of trichloroacetyl chloride and 3.91 g (60 mmol) of zinc-copper couple in 150 mL of ether as described in the general procedure for the sulfoxide-directed lactonization of vinyl sulfoxides. Flash chromatography of the crude reaction mixture (hexane:ethyl acetate, 9:1) afforded 433 mg of 181 (50%) as a yellow oil. It was observed that both 181 and 182 were unstable to silica gel; this was determined by spotting a TLC plate with the lactones (practically pure by

^{1}H-NMR) and allowing it to stand for ca. 1 h before developing the plate. This qualitatively showed a large amount of decomposition products and a very small amount of lactone. Those same solutions of 181 and 182 when spotted on a plate which was immediately developed showed only traces of decomposition products.

Compound (181):

R_f = 0.25, hexane:ethyl acetate, 20:1.

^{1}H-NMR ($CDCl_3$, 360 MHz): 3.787 (1H, dd, J = 9.5, 6.2 Hz), 5.505 (1H, d, J = 16.6 Hz), 5.575 (1H, dd, J = 10.1, 1.0 Hz), 5.881 (1H, dt, J = 16.6, 10.1 Hz), 5.943 (1H, d, J = 6.2 Hz), 7.333-7.365 (3H, m), 7.509-7.536 (2H, m).

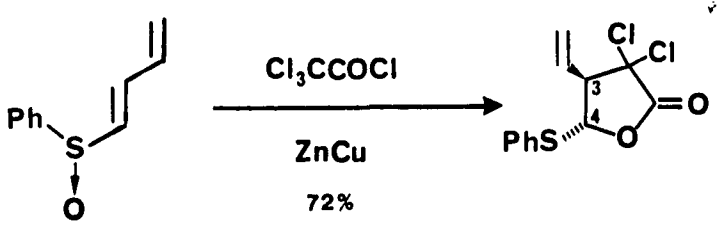
^{13}C-NMR ($CDCl_3$, 90 MHz): 60.602, 79.571, 90.536, 124.653, 127.505, 128.749, 129.402, 132.391, 132.553, 166.720.

IR (neat): 865, 965, 1175, 1290, 1445, 1485, 1595, 1800, 2950-3100.

MS: 290, 288 (M), 253, 209, 110 (100%), 87, 51.

Anal. Calcd for $C_{12}H_{10}O_2Cl_2S$: C, 49.84; H, 3.48; S, 11.09; Cl, 24.52.

Found: C, 50.05; H, 3.61; S, 10.89; Cl, 24.98.



151 182

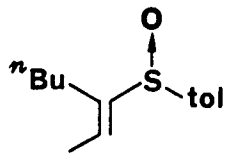
trans-2,2-Dichloro-4-phenylthio-3-vinyl-γ-butyrolactone (182).

(E)-1-Butadienyl phenyl sulfoxide, 151[109] (534 mg, 3 mmol) was treated with 1.67 mL (2.73 g, 15 mmol) of trichloroacetyl chloride and 3.91 g (60 mmol) of zinc-copper couple in 150 mL of ether, as described in the general procedure for the sulfoxide-directed lactonization of vinyl sulfoxides. The crude dichlorolactone was purified by filtration through deactivated silica gel (ca. 5 g, hexane:ethyl acetate, 9:1) to give 624 mg of "clean" trans-lactone 182 (82%). A sample for analysis was obtained by flash chromatography (hexane:ethyl acetate, 20:1).

Compound (182):

R_f = 0.30, hexane:ethyl acetate, 20:1.

^{1}H-NMR ($CDCl_3$, 360 MHz): 3.150 (1H, ddt, J = 9.9, 7.6, 0.8 Hz), 5.509 (1H, d, J = 9.9 Hz), 5.526 (1H, dt, J = 17.0, 0.9 Hz), 5.612 (1H, dt, J = 10.4, 0.7 Hz), 5.882 (1H, ddd, J = 17.0, 10.4, 7.6 Hz), 7.337-7.541 (5H, m).



191

^{13}C-NMR ($CDCl_3$, 90 MHz): 60.297, 80.551, 87.964, 125.240, 126.537, 129.488, 129.572, 129.641, 134.045, 166.006.

IR (neat): 650, 750, 810, 870, 970, 1190, 1210, 1440, 1470, 1800, 2850-3100.

MS: 290, 288 (M), 253, 209, 110 (100%), 87, 51.

Anal. Calcd for $C_{12}H_{10}O_2Cl_2S$: C, 49.84; H, 3.48; S, 11.09; Cl, 24.52. Found: C, 50.15; H, 3.77; S, 10.93; Cl, 24.21.

(E)-1-n-Butyl-1-(p-tolylsulfinyl)-1-propene (191).

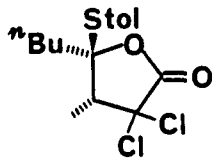
n-Butyllithium (7.98 mmol, 5.15 mL of 1.55 M solution) was added under a nitrogen atmosphere to a cold (0°C) solution of 1.21 mL (8.64 mmol) of dry N,N-diisopropylamine in 40 mL of anhydrous tetrahydrofuran. After 30 min, the solution of LDA was cooled to -78°C and a cold (-78°C) solution of 1.199 g (6.65 mmol) of (E)-1-propenyl p-tolylsulfoxide 190[111] in 15 mL of anhydrous tetrahydrofuran was added dropwise via a transfer needle under nitrogen. After 30 min at -78°C, 1.16 mL (6.65 mmol) of HMPA was added. The solution was stirred at -78°C for 10 min and then 1.63 mL of n-butyl iodide (11.30 mmol) was added. The reaction was

allowed to proceed for an additional 20 min at -78°C and was then quenched with a saturated ammonium chloride solution at that temperature. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic extracts were washed with a saturated sodium chloride solution and dried over magnesium sulfate. Filtration of the drying agent and evaporation of the solvent *in vacuo* gave a crude product which was chromatographed on silica gel (hexane:ethyl acetate, 3:1) to give 942 mg of a *ca.* 4:1 mixture of vinyl sulfoxide **191** and allylic sulfoxide **192** (60% yield) (pale yellow oil). This ratio was determined by integration of the 300 MHz ^{1}H-NMR spectrum of the mixture. This mixture was employed for the sulfoxide directed lactonization. A second careful chromatography (hexane:ethyl acetate, 2:1) provided an almost pure sample of vinyl sulfoxide **191**, as determined by 300 MHz ^{1}H-NMR.

Compound (**191**):

R_f = 0.20, hexane:ethyl acetate, 4:1.

^{1}H-NMR ($CDCl_3$, 300 MHz): 0.771 (3H, t, J = 6.7 Hz), 1.059-1.358 (4H, m), 1.836 (3H, d, J = 7.0 Hz), 1.929-2.087 (2H, m), 2.383 (3H, s), 6.482 (1H, q, J = 7.0 Hz), 7.253 (2H, d, J = 8.2 Hz), 7.471 (2H, d, J = 8.2 Hz).



193

^{13}C-NMR ($CDCl_3$, 75 MHz): 13.582, 13.838, 21.344, 22.606, 24.137, 31.050, 125.241, 129.609, 129.746, 140.134, 141.144, 145.698.

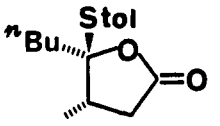
IR (neat): 810, 1045, 1080, 1450, 1490, 2885-3000.

MS: 237, 236 (M), 219, 140 (100%), 92, 55.

2,2-Dichloro-4α-n-butyl-3α-methyl-4β-p-tolylthio-γ-butyrolactone (193).

A 4:1 mixture of vinyl sulfoxide 191 and allylic sulfoxide 192 (2.22 g, 9.398 mmol) was treated with 5.24 mL (46.99 mmol) of trichloroacetyl chloride and 12.22 g (187.96 mmol) of zinc-copper couple in 470 mL of ether as described in the general procedure for the sulfoxide-directed lactonization of vinyl sulfoxides. The crude dichlorolactone was purified by flash chromatography (hexane:ether, 30:1) to give 1.96 g of pure 193 as an off-white solid (mp 88-90°C) (75% yield, based on 80% pure starting material).

^{1}H-NMR ($CDCl_3$, 360 MHz): 0.926 (3H, t, J = 7.3 Hz), 1.146-1.371 (2H, m), 1.332 (3H, d, J = 6.9 Hz), 1.639-1.792 (3H, m), 2.186-2.265 (1H, m), 2.332



194

(3H, s), 2.810 (1H, q, J = 6.9 Hz), 7.163 (2H, d, J = 8.0 Hz), 7.337 (2H, d, J = 8.0 Hz).

^{13}C-NMR ($CDCl_3$, 90 MHz): 8.285, 13.932, 21.385, 22.992, 26.172, 34.408, 52.645, 81.454, 99.243, 124.569, 130.424, 136.674, 140.800, 166.624.

IR ($CDCl_3$): 695, 740, 815, 835, 980, 1210, 1380, 1450, 1490, 1600, 1800, 2880-3050.

MS: 349, 347 (M+1), 223, 123 (100%), 91, 77, 57.

Anal. Calcd for $C_{16}H_{20}O_2SCl_2$: C, 55.33; H, 5.81; S, 9.21; Cl, 20.42.

Found: C, 55.01; H, 5.81; S, 8.97; Cl, 20.15.

4α-n-Butyl-3α-methyl-4β-p-tolylthio-γ-butyrolactone (194).

To a solution of 1.078 g (3.10 mmol) of dichlorolactone 193 in 200 mL of THF/H_2O, 9:1, was added ca. 1.23 g (45.5 mmol) of aluminum amalgam generated from aluminum foil by the procedure of Corey.[81] The mixture was stirred at 0°C for 1 h and at room temperature overnight, after

which time it was filtered through a Celite pad, and the filter cake was rinsed with ether. The combined organic extracts were washed with a saturated ammonium chloride solution and dried over magnesium sulfate. Filtration of the drying agent, concentration in vacuo and column chromatography (hexane:ethyl acetate, 9:1; R_f = 0.23) afforded 776 mg of thiolactone 194 (90%) as a colorless oil.

Compound (194).

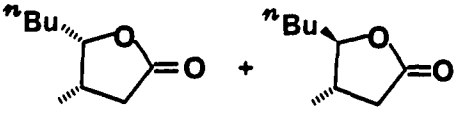
^{1}H-NMR ($CDCl_3$, 300 MHz): 0.890 (3H, t, J = 7.3 Hz), 1.083 (3H, d, J = 7.0 Hz), 1.209-1.329 (2H, m), 1.345-1.506 (1H, m), 1.511-1.779 (3H, m), 2.187 (1H, dd, J = 17.1, 6.4 Hz), 2.333 (3H, s), 2.437-2.555 (1H, m), 2.696 (1H, dd, J = 17.1, 8.1 Hz), 7.127 (2H, d, J = 8.1 Hz), 7.389 (2H, d, J = 8.1 Hz).

^{13}C-NMR ($CDCl_3$, 75 MHz): 13.898, 14.531, 21.242, 22.788, 26.467, 34.042, 37.613, 38.050, 100.088, 126.025, 129.810, 136.402, 139.610, 175.044.

IR (neat): 815, 925, 1130, 1210, 1380, 1460, 1490, 1595, 1785, 2980-3050.

MS: 278 (M), 155 (100%), 123, 109, 85, 57.

Anal. Calcd for $C_{16}H_{22}O_2S$: C, 69.03; H, 7.96; S, 11.52. Found: C, 69.11; H, 7.70; S, 11.74.



183 184

Reaction of 2,2-Dichloro-4α-n-butyl-3α-methyl-4β-p-tolylthio-γ-butyrolactone(193) with tri-n-butyltin Hydride.

To a solution of 213 mg (0.61 mmol) of dichloro-lactone 193 in 10 mL of toluene was added 1.15 mL (4.3 mmol) of tri-n-butyltin hydride and 10 mg of AIBN. The solution was placed under nitrogen and refluxed for ca. 12 h. Concentration in vacuo and column chromatography (hexane:ethyl acetate, 3:1) afforded 67 mg (70%) of a 1:1.8 mixture of cis-lactone, 183, and trans-lactone, 184, as a colorless liquid (determined by integration of its 300 MHz ^{1}H-NMR spectrum). A second chromatography (hexane:ethyl acetate, 5:1) allowed for the separation of pure samples of both isomeric lactones. Their 300 MHz ^{1}H-NMR spectra were in very good agreement with literature values.[93c]

Compound (183):

R_f = 0.27, hexane:ethyl acetate, 5:1.

^{1}H-NMR ($CDCl_3$, 300 MHz): 0.896 (3H, t, J = 7.1 Hz), 0.987 (3H, d, J = 7.0 Hz), 1.203-1.687 (6H, m),

2.173 (1H, dd, J = 16.8, 3.8 Hz), 2.513-2.593 (1H, m), 2.669 (1H, ddd, J = 16.8, 7.8 Hz), 4.407 (1H, ddd, J = 9.1, 5.7, 4.4 Hz).

Compound (184):

R_f = 0.33, hexane:ethyl acetate, 5:1.

^{1}H-NMR ($CDCl_3$, 300 MHz): 0.870 (3H, t, J = 7.1 Hz), 1.093 (3H, d, J = 6.4 Hz), 1.256-1.671 (6H, m), 2.092-2.205 (2H, m), 2.571-2.681 (1H, m), 3.964 (1H, td, J = 7.6, 4.0 Hz).

Reaction of 2,2-Dichloro-4α-n-butyl-3α-methyl-4β-p-tolylthio-γ-butyrolactone (193) with Raney Nickel in Benzene.

To a suspension of Raney nickel (prepared according to Burgstahler[82] from 3.5 g of 50% alloy) in 20 mL of benzene was added 236 mg (0.68 mmol) of dichlorolactone 193 in 5 mL of benzene. The mixture was placed under nitrogen and refluxed for ca. 12 h after which time it was filtered through a Celite pad. The filter cake was thoroughly washed with ether and methanol. The combined organic extracts were concentrated in vacuo, and the residue was purified by column chromatography (hexane:ethyl acetate, 3:1) to give 40.4 mg of a 2:1 mixture of cis-lactone 183 and trans-lactone 184, as determined by integration of its 300 MHz ^{1}H-NMR spectrum (38%).

APPENDICES

APPENDIX A

STRUCTURE AND NOMENCLATURE OF PROSTAGLANDINS AND THEIR METABOLIC INTERMEDIATES

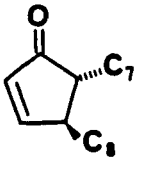
The prostaglandins are classified according to the general nomenclature shown below:[108]

$$PGX_{n\alpha}$$

where X denotes the functionality in the cyclopentane ring

n denotes the number of double bonds in the side chains

and α denotes the stereochemistry of the C_9 hydroxyl group.



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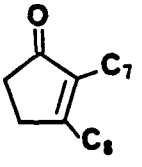
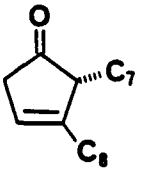
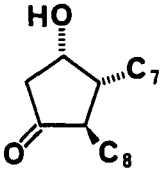


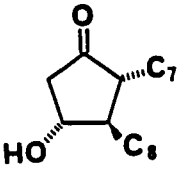
PGB



PGC



PGD



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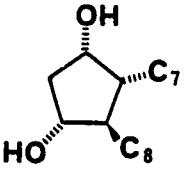
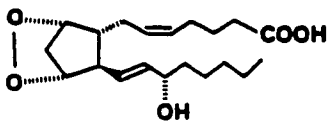
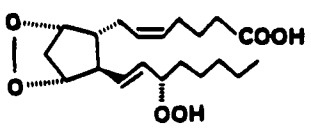


PGF

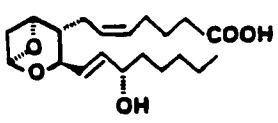
APPENDIX A (continued)



PGG_2



PGH_2



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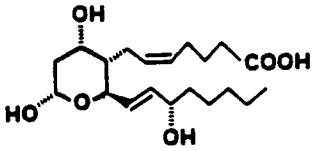
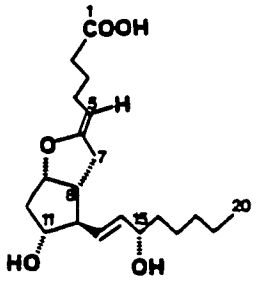


TXB_2



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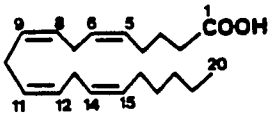
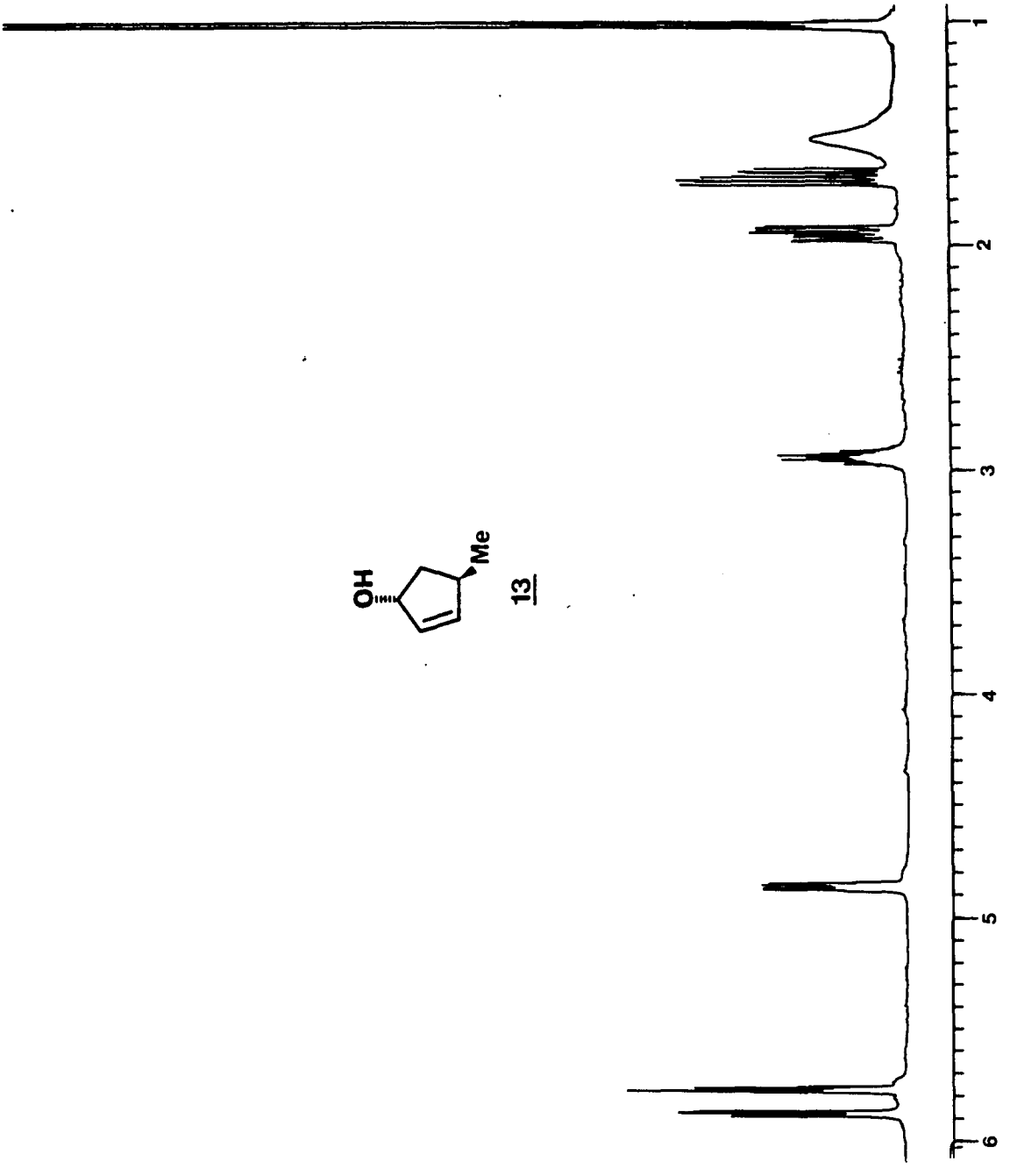
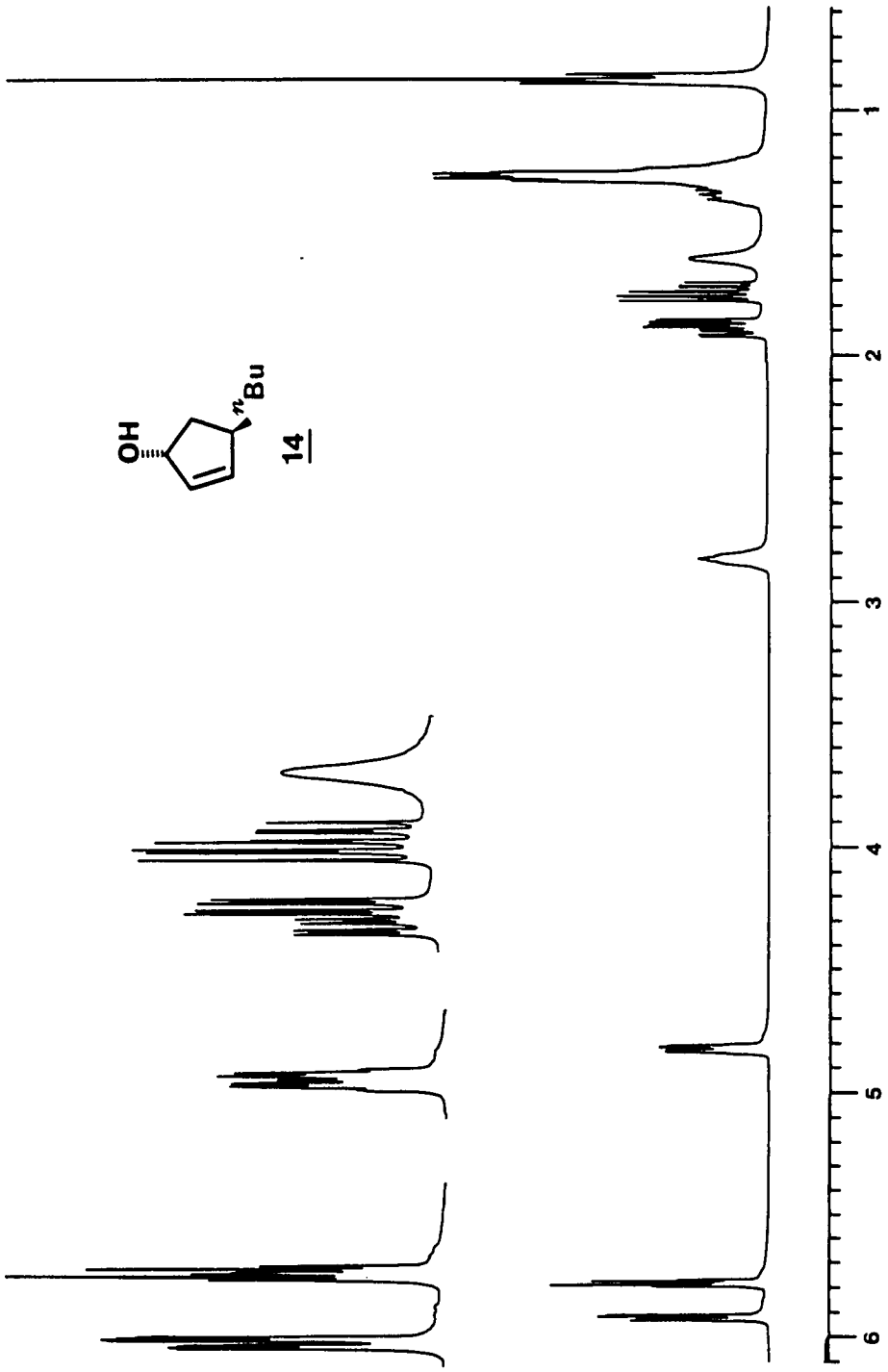


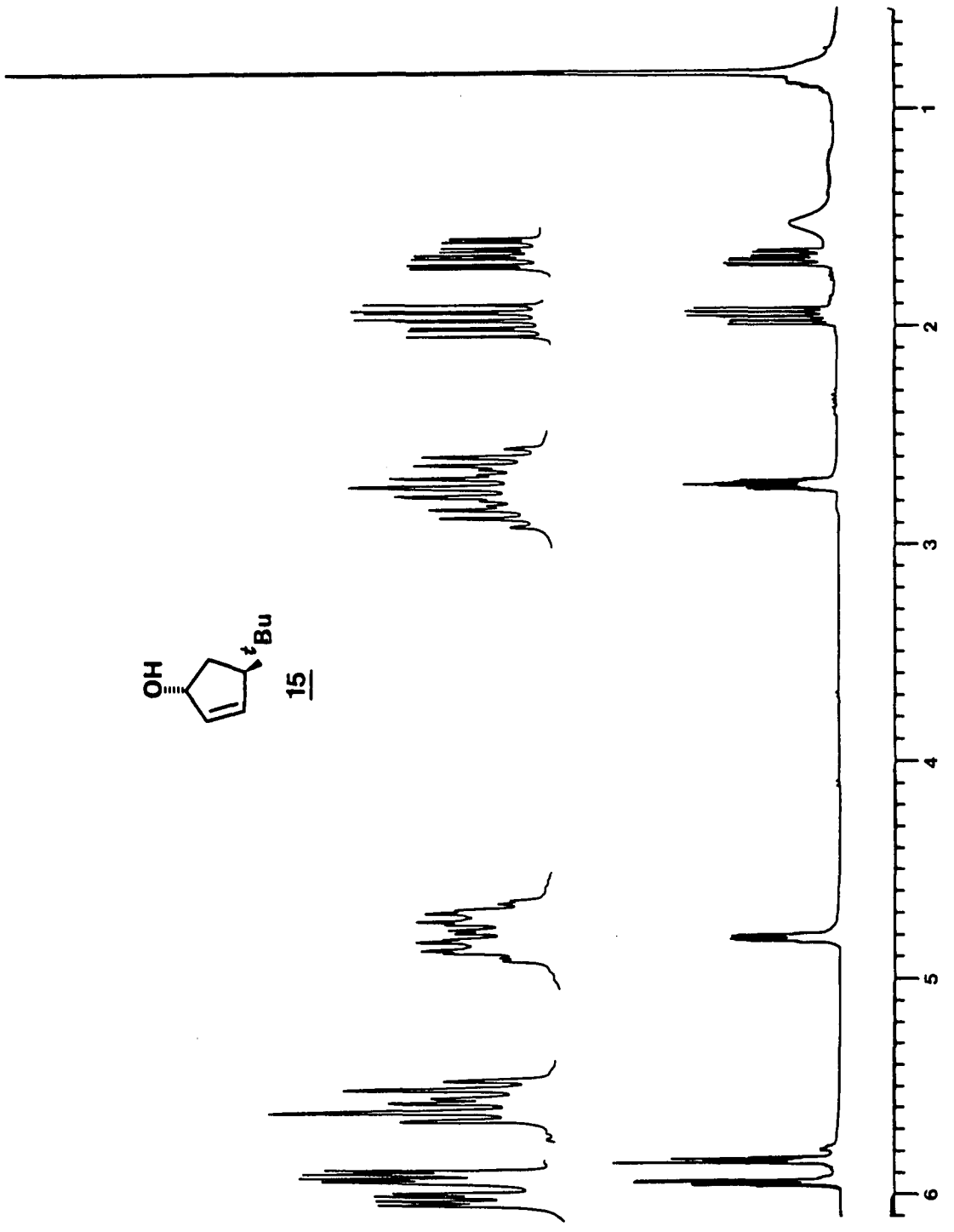
Arachidonic acid

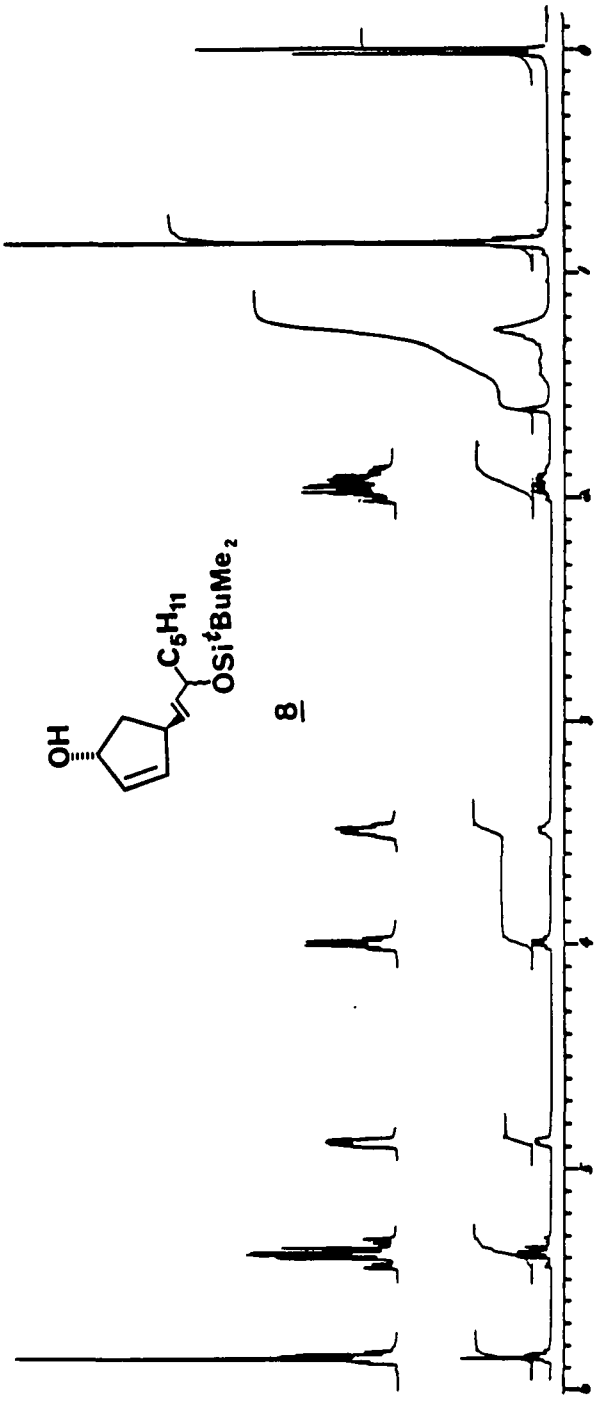
APPENDIX B

360 MHz ^{1}H-NMR SPECTRA OF SOME KEY COMPOUNDS


OH
Me
13
1
2
3
4
5
6


OH
nBu
14
1
2
3
4
5
6


OH
tBu
15
1
2
3
4
5
6



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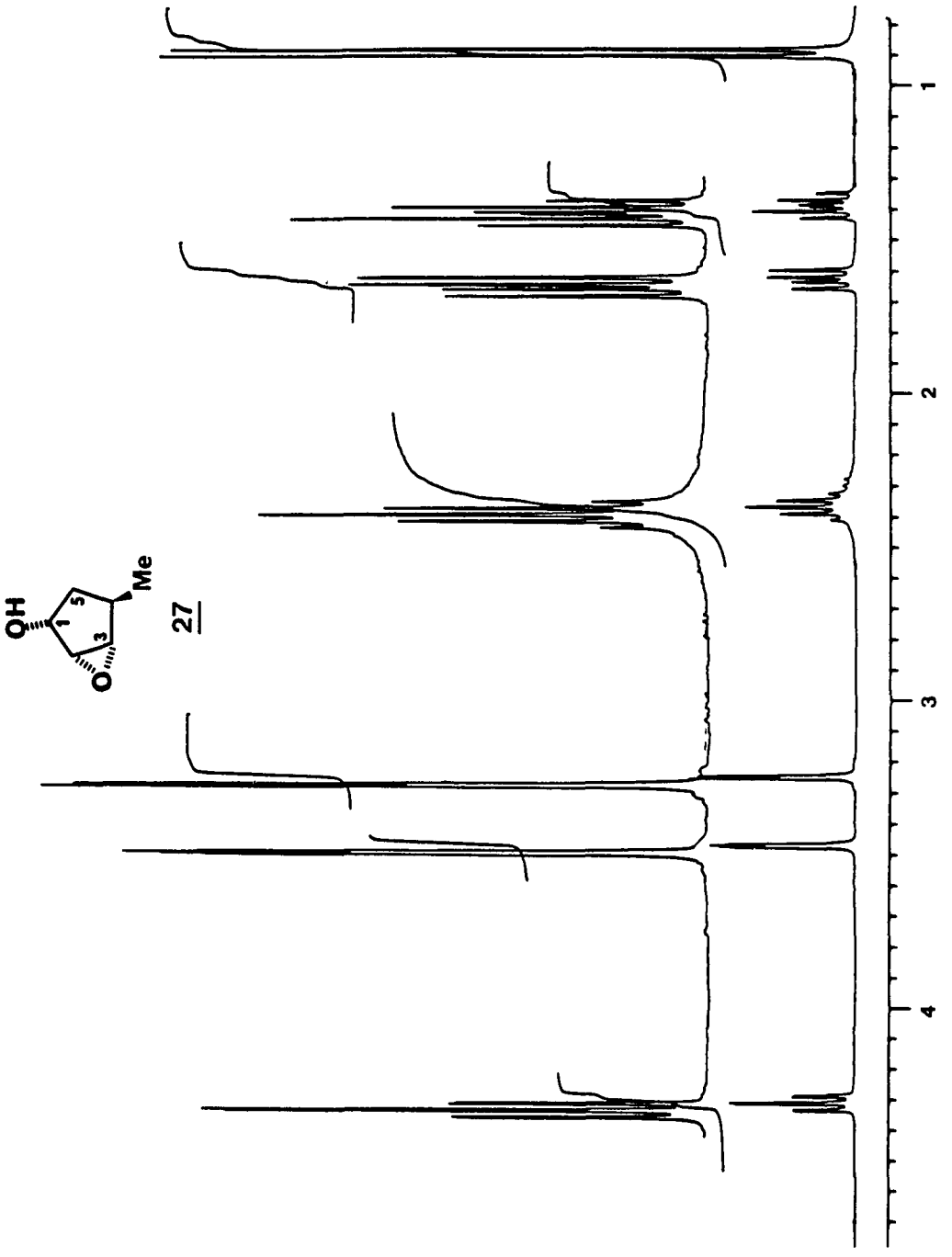

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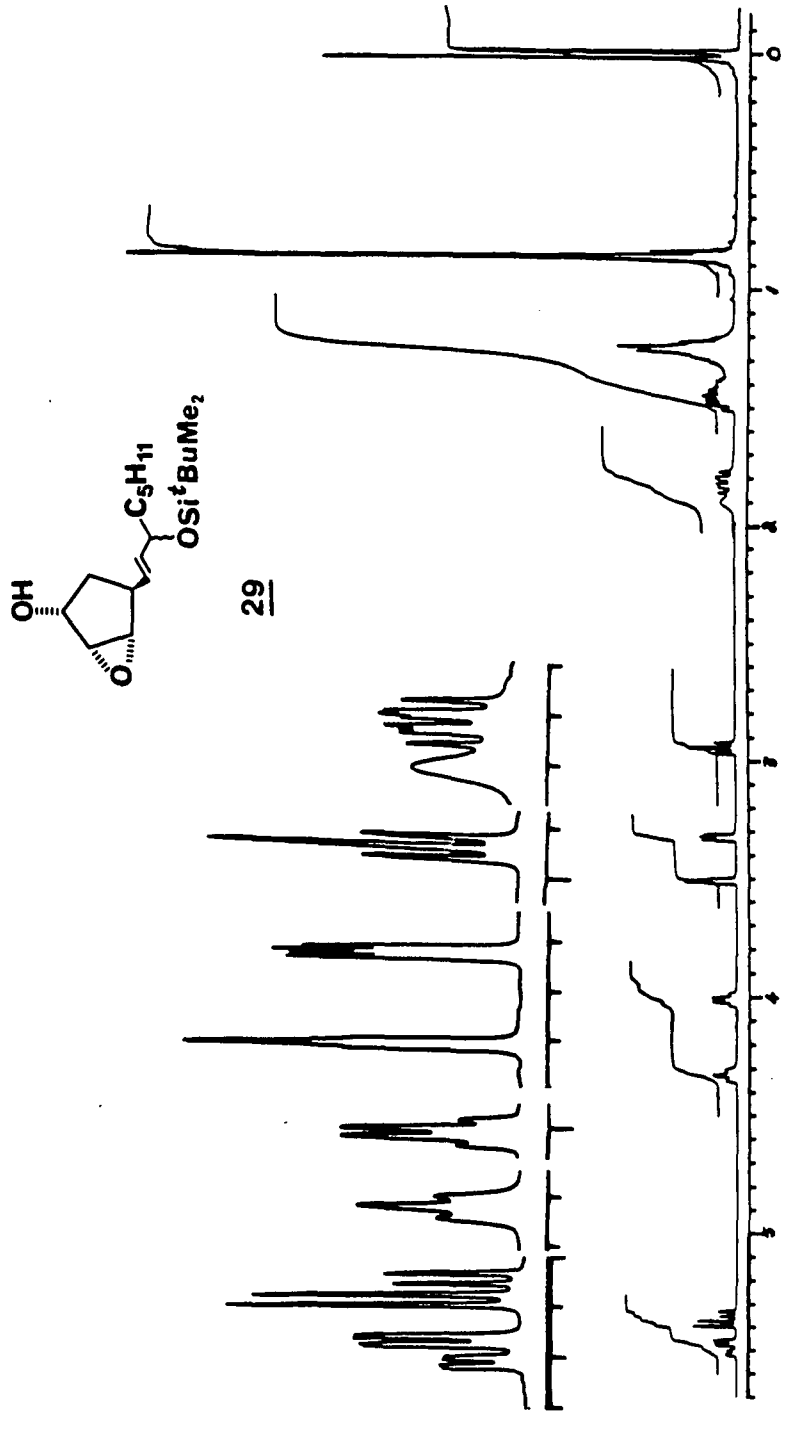
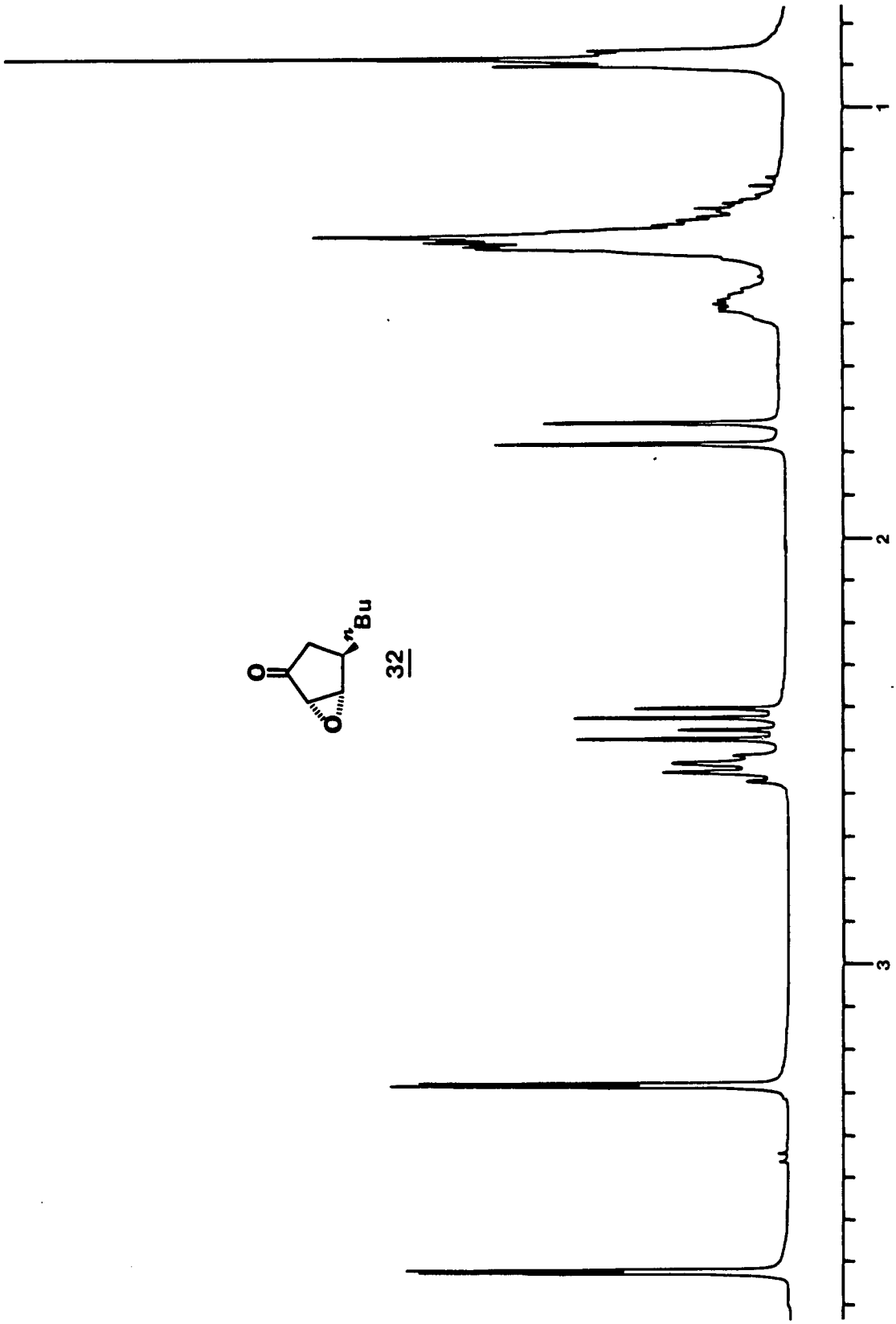

OH
O
C5H11
OSi tBuMe2
29
0
1
2
3
4
5



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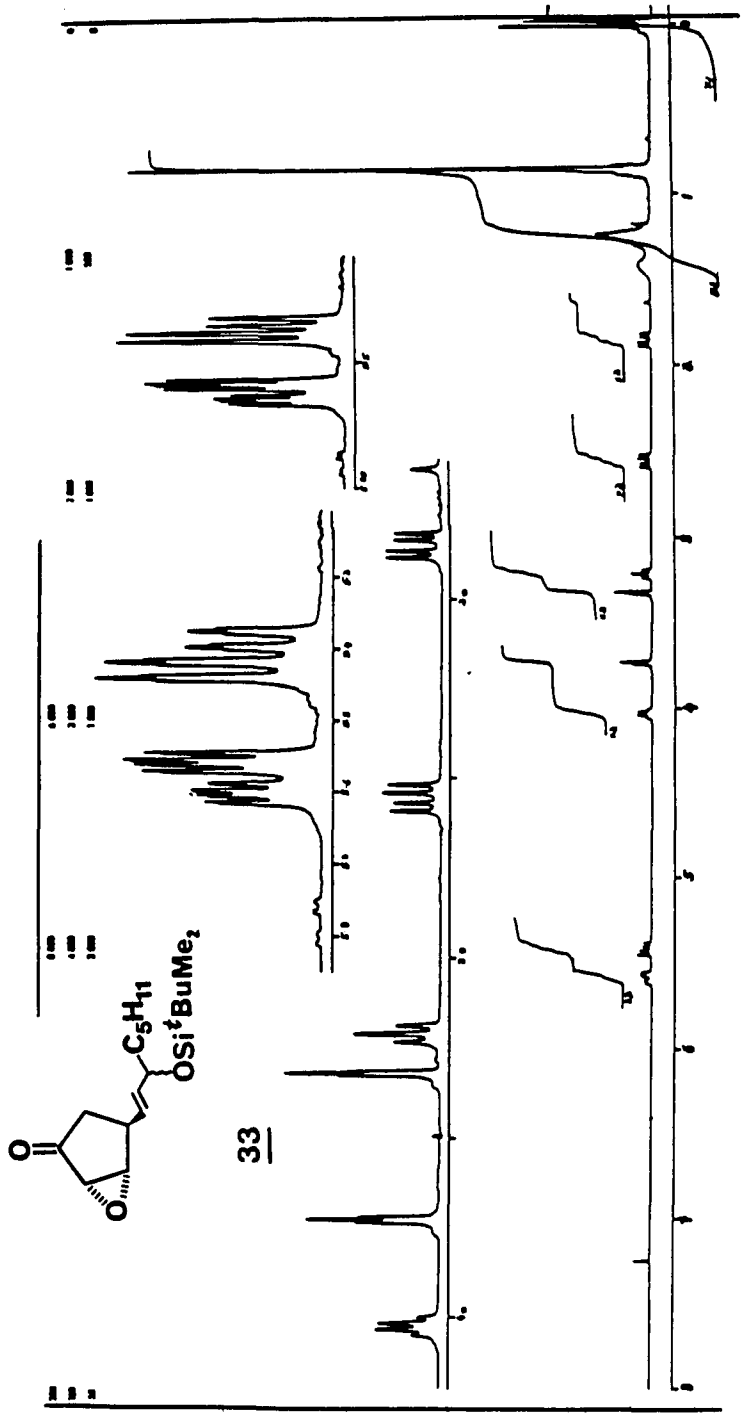

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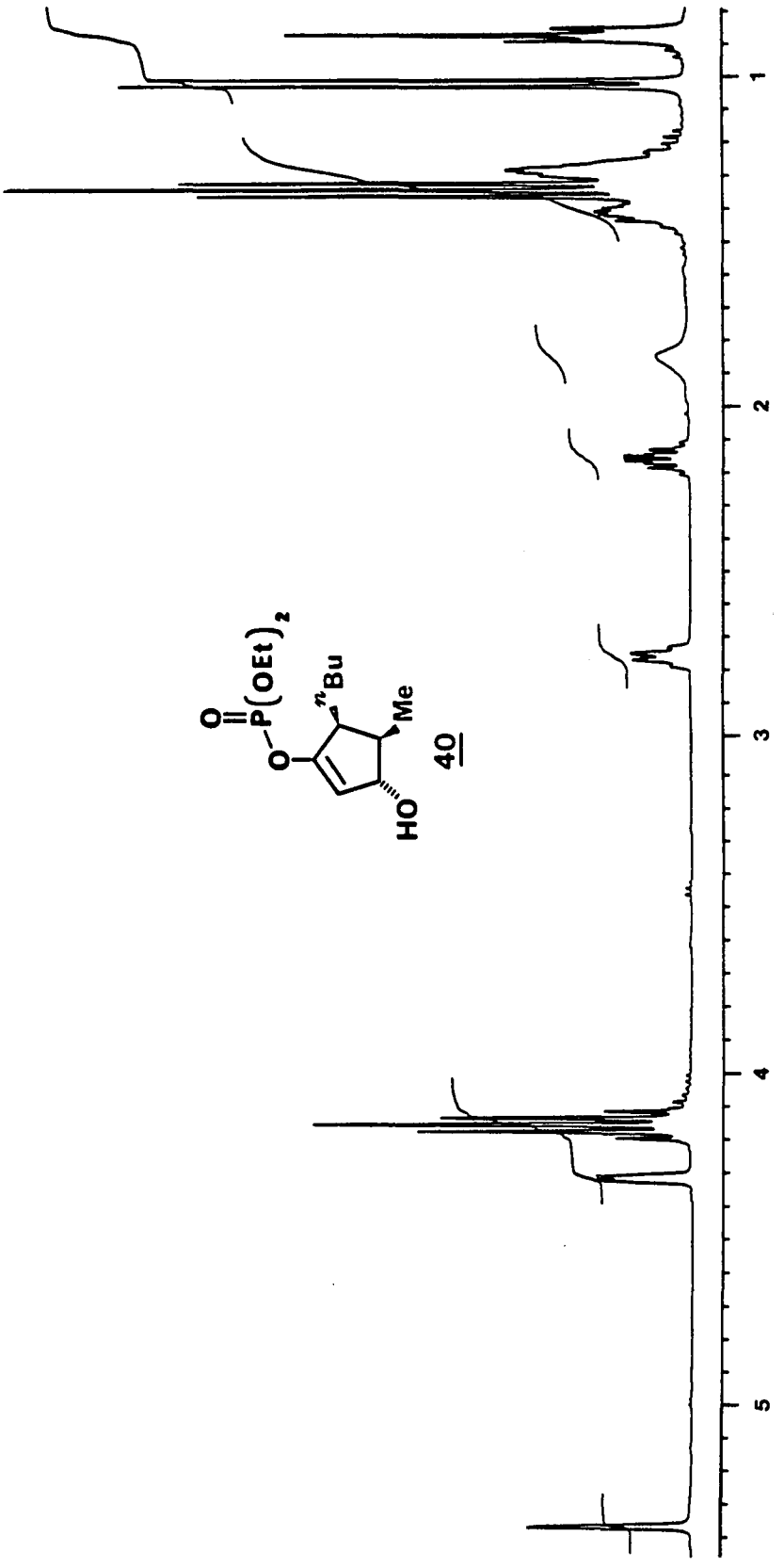
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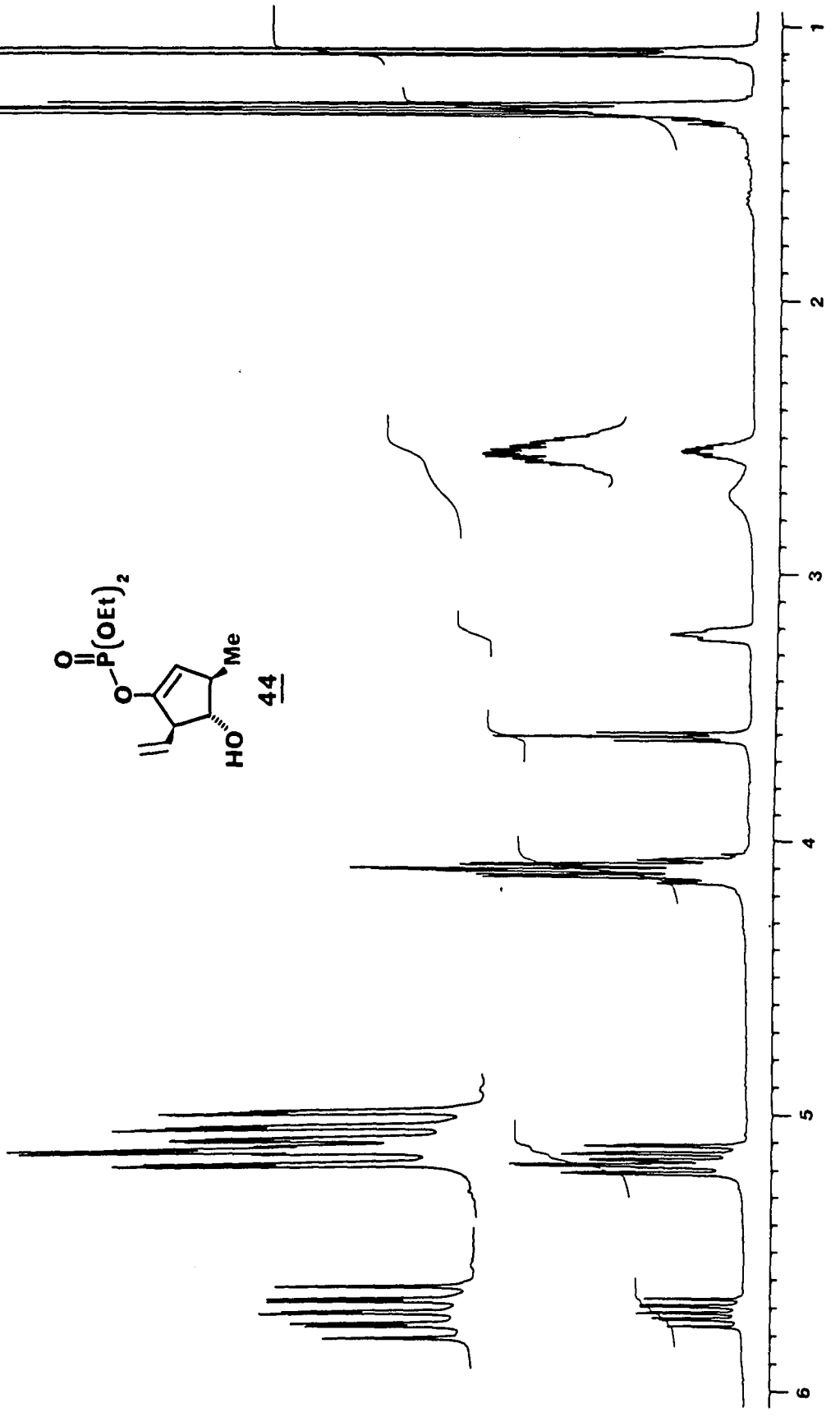
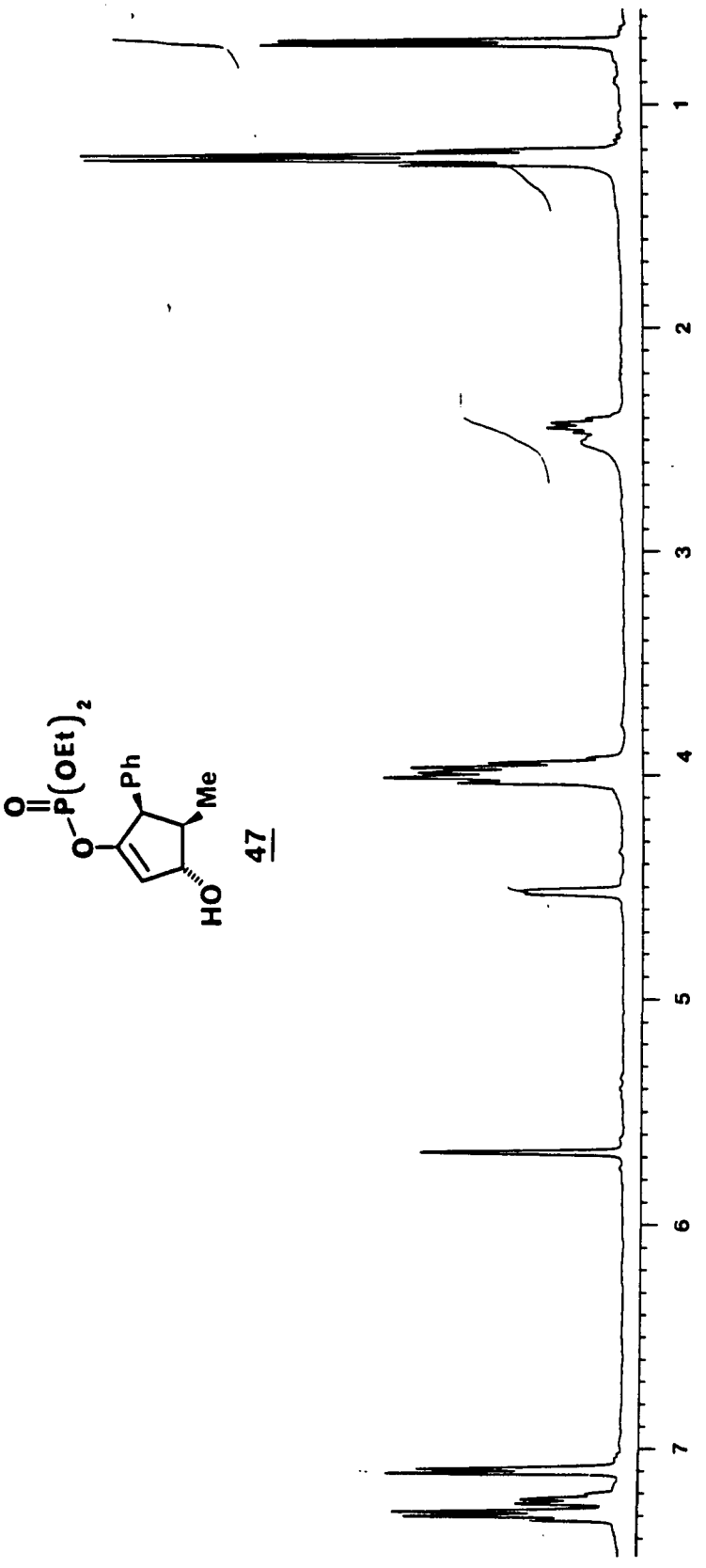
P(OEt)2
O
nBu
Me
HO
40
1
2
3
4
5


O
P(OEt)2
O
Me
HO
44
1
2
3
4
5
6



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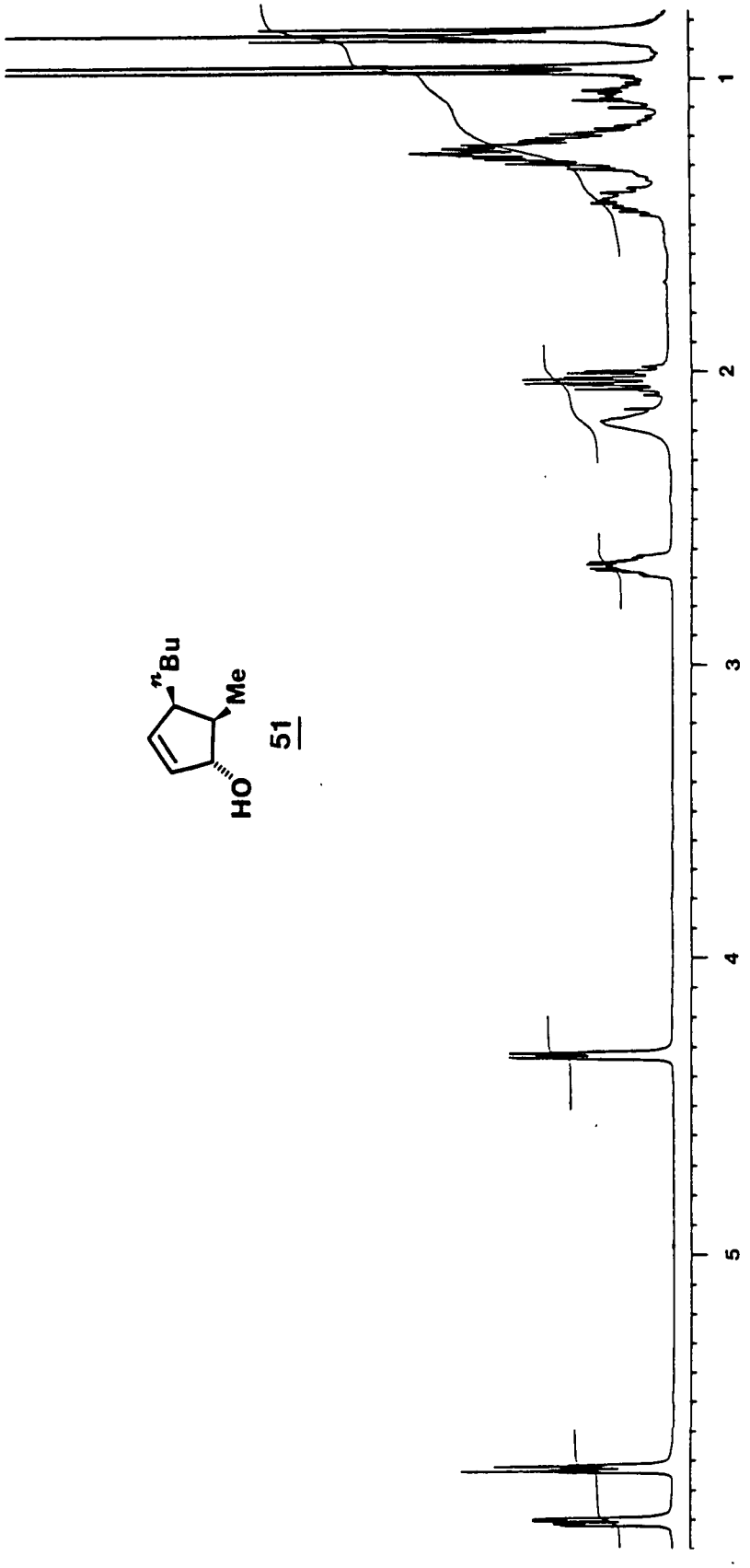
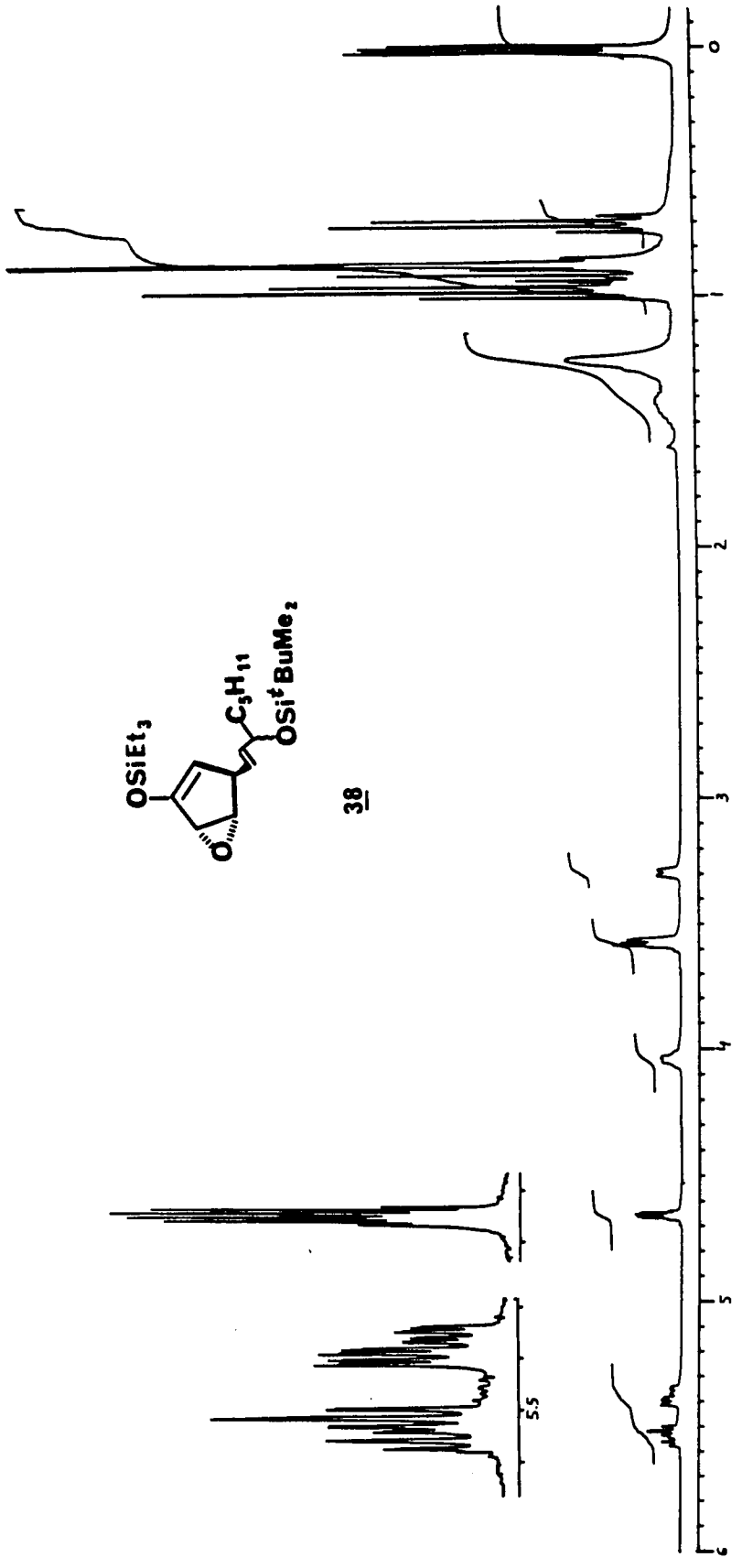

nBu
Me
HO
51
1
2
3
4
5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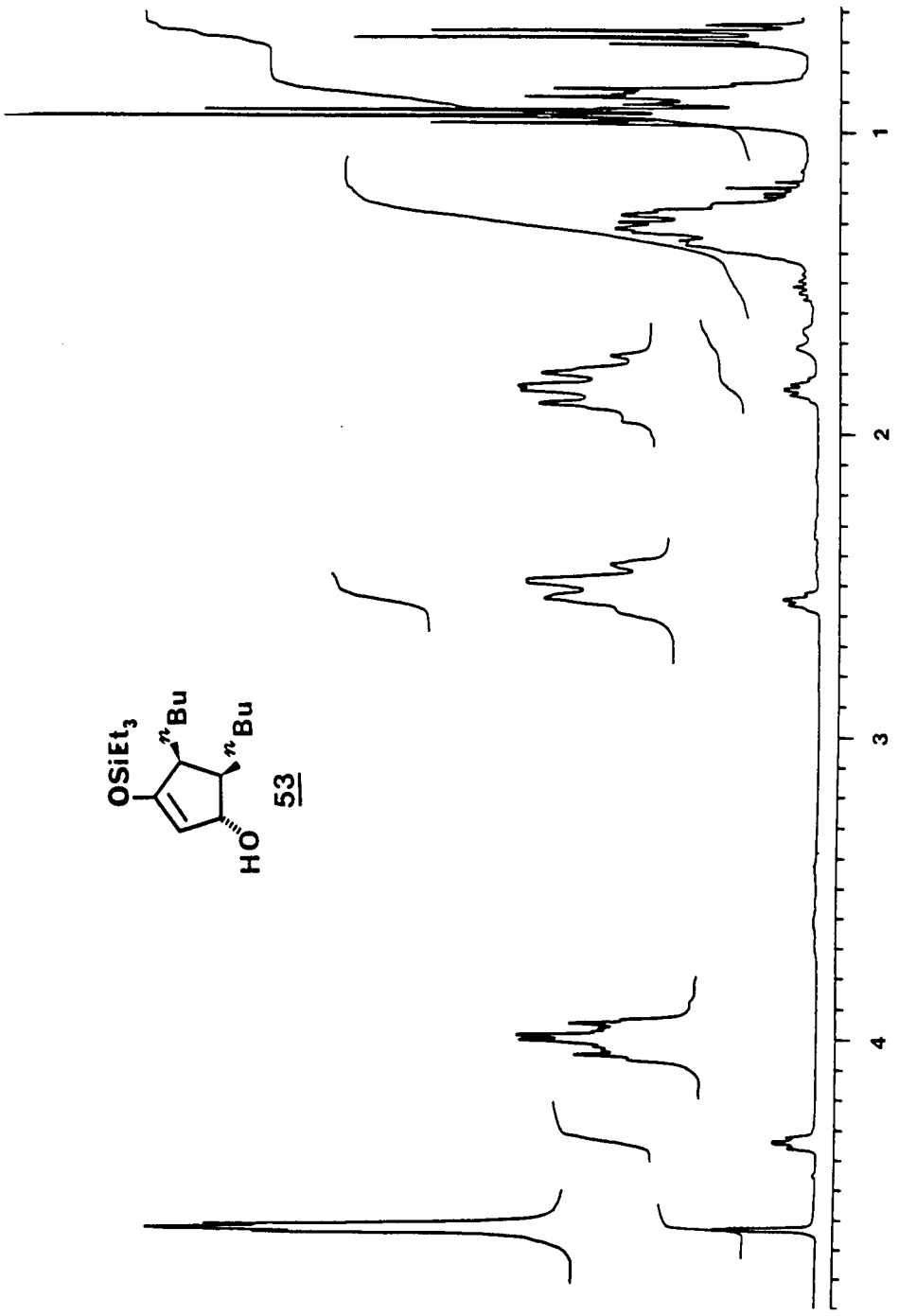
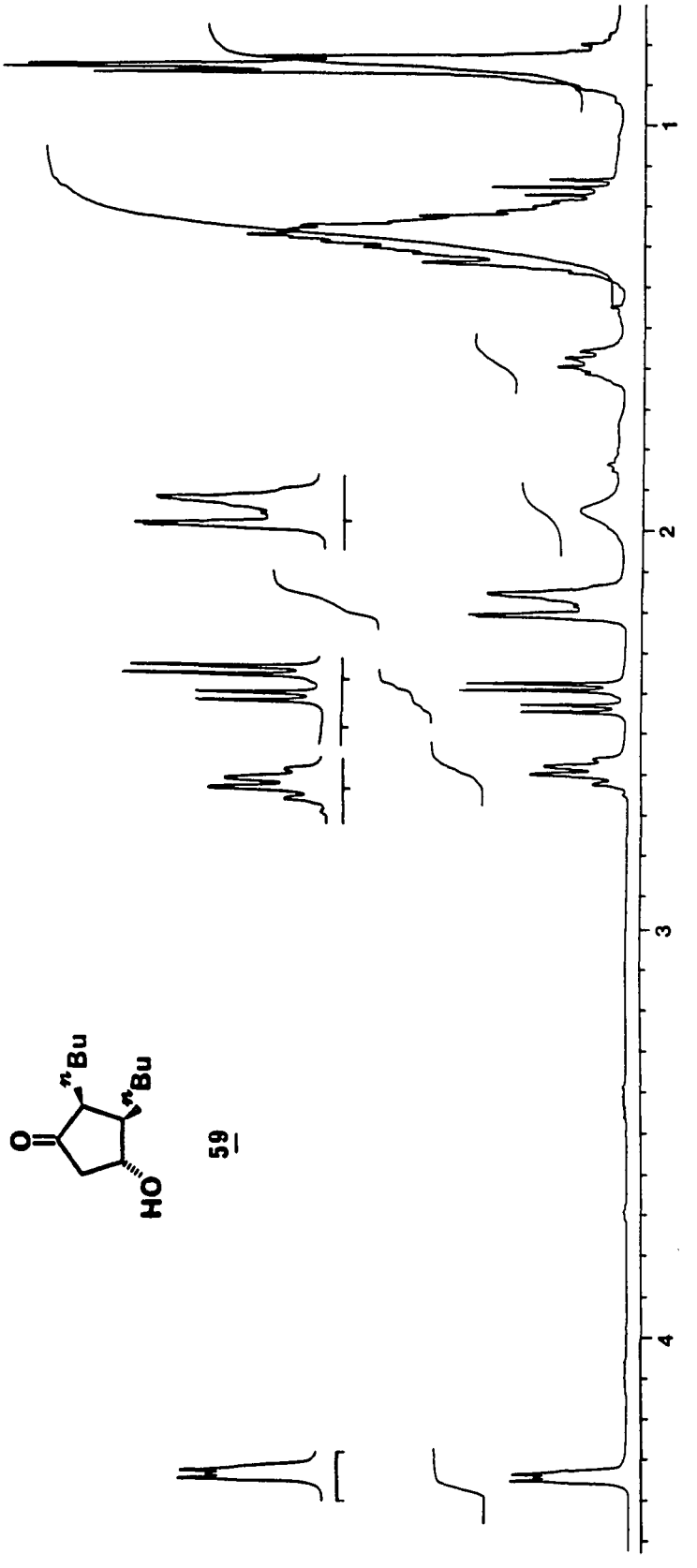
C5H11
OSi'BuMe2
O
38
5.5
0
1
2
3
4
5
6


OSiEt3
nBu
nBu
HO
53
1
2
3
4



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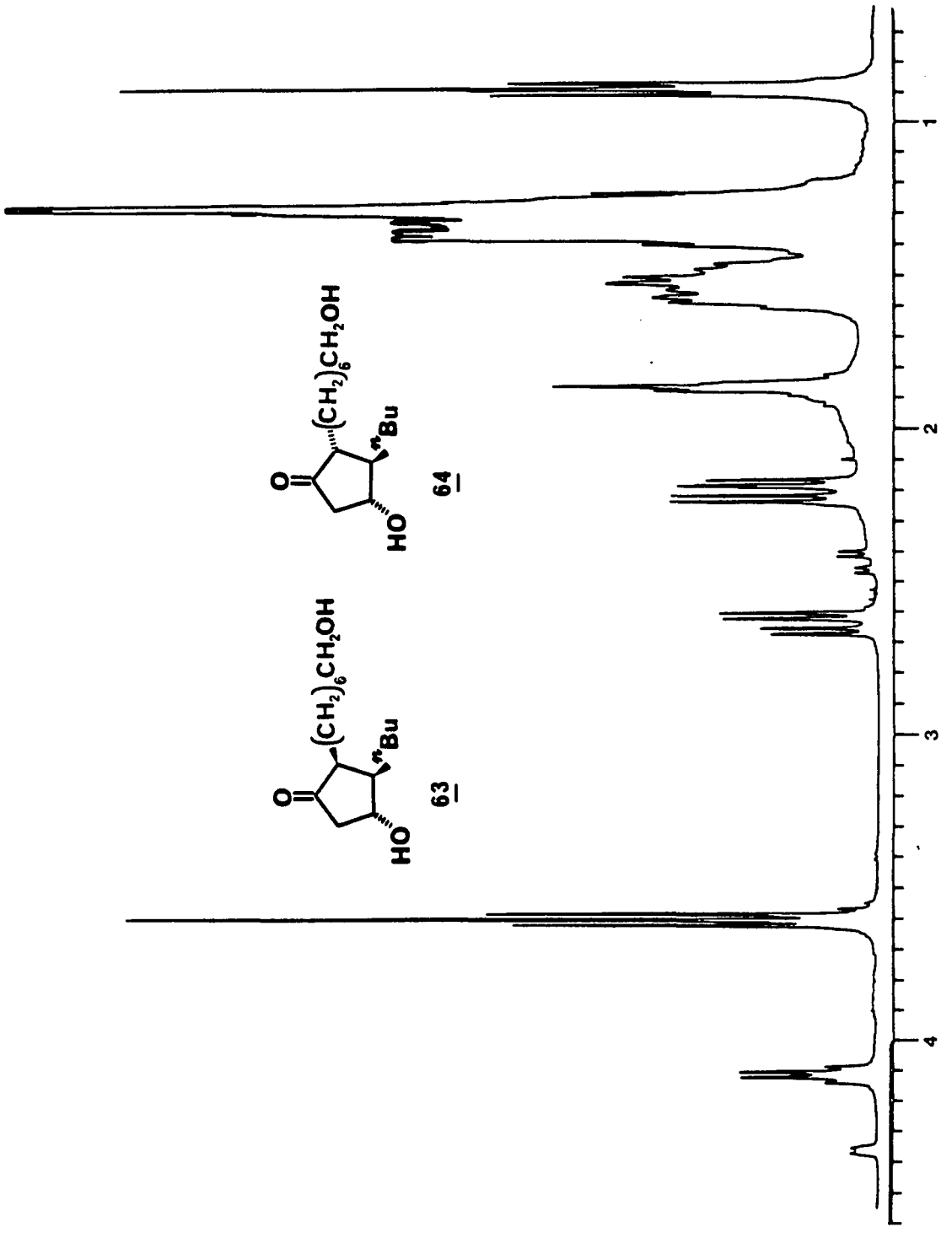
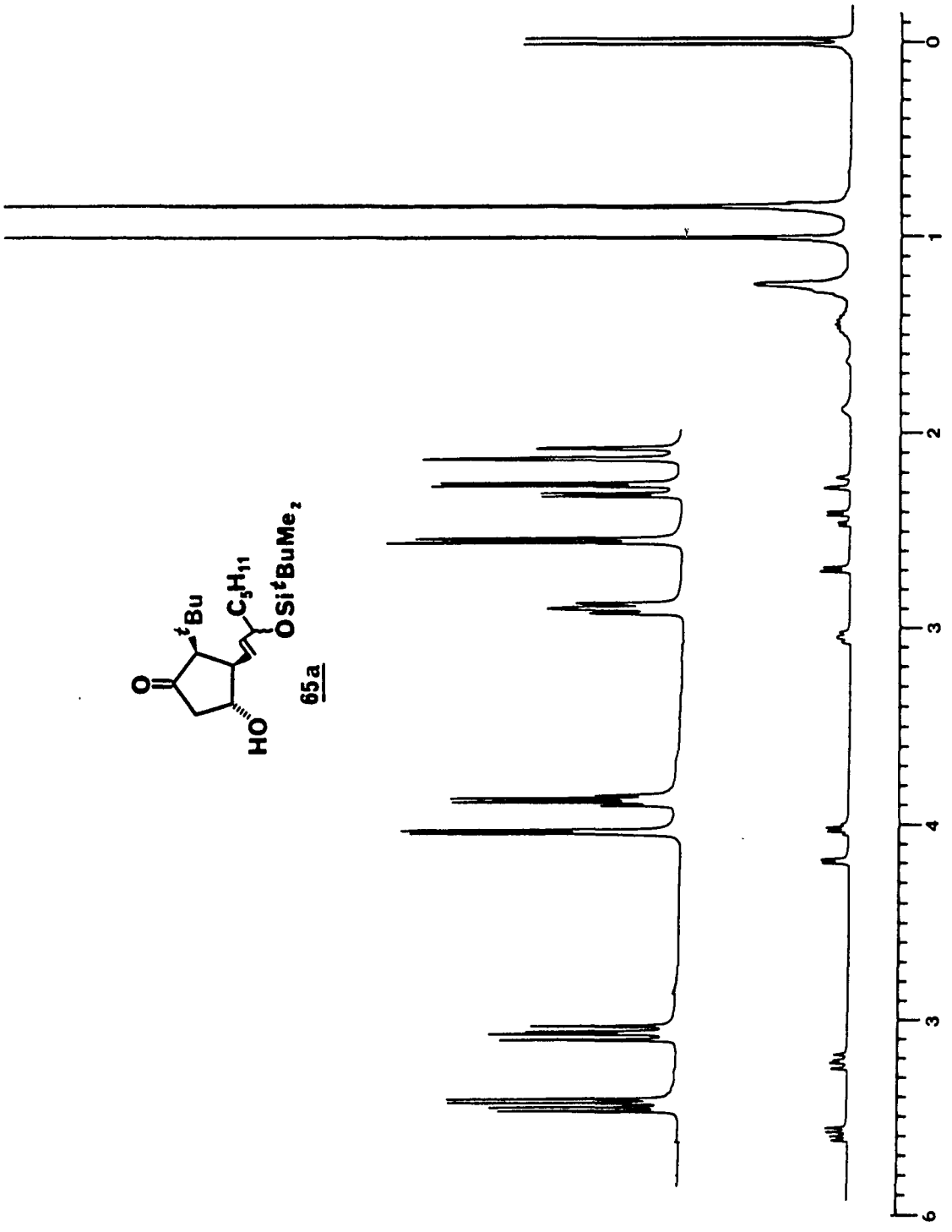

O
HO
^{n}Bu
(CH$_2$)$_6$CH$_2$OH
63
64
1
2
3
4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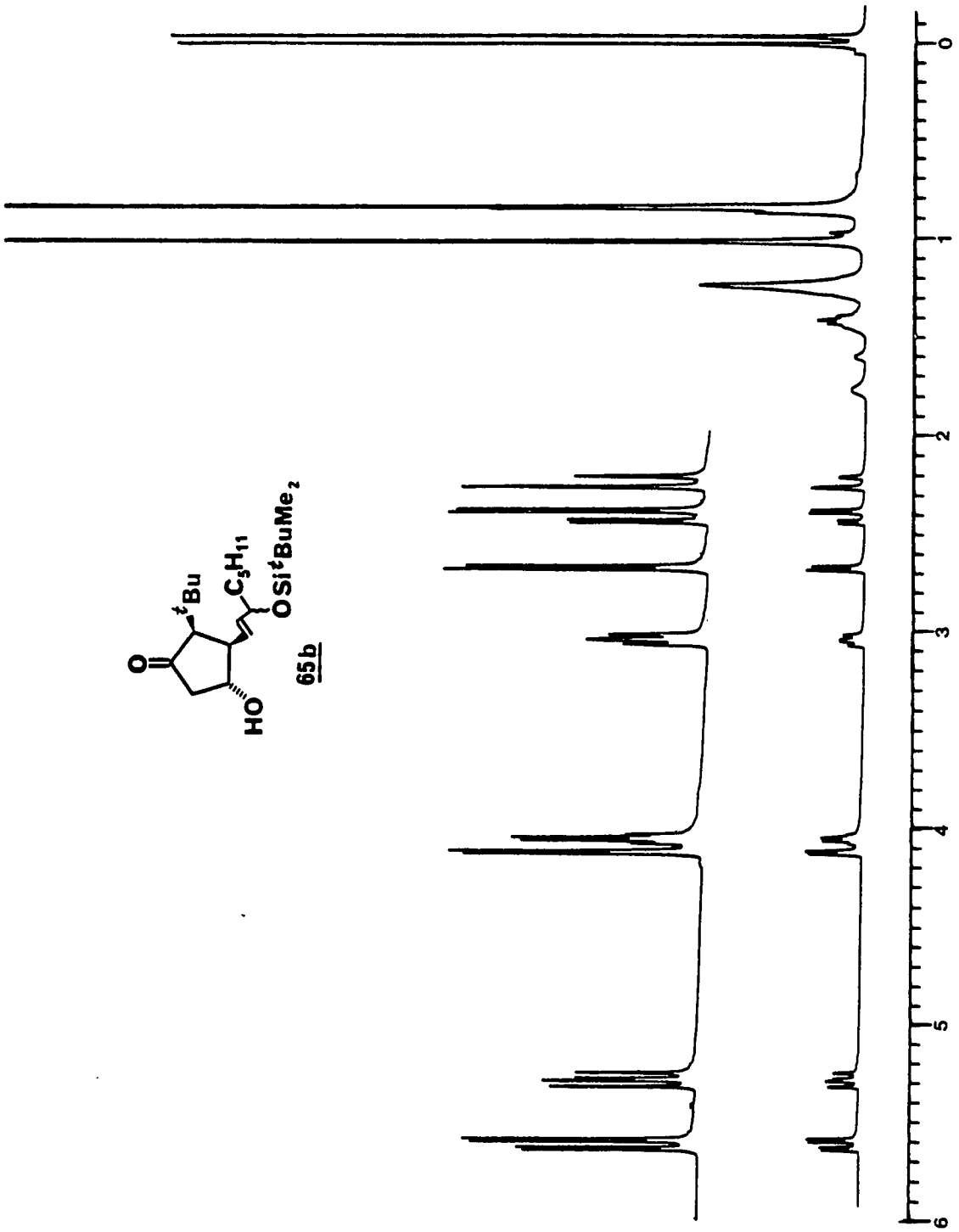
HO
tBu
C5H11
OSitBuMe2
65a
0
1
2
3
4
5
6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C5H11
OSitBuMe2
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3
4
5
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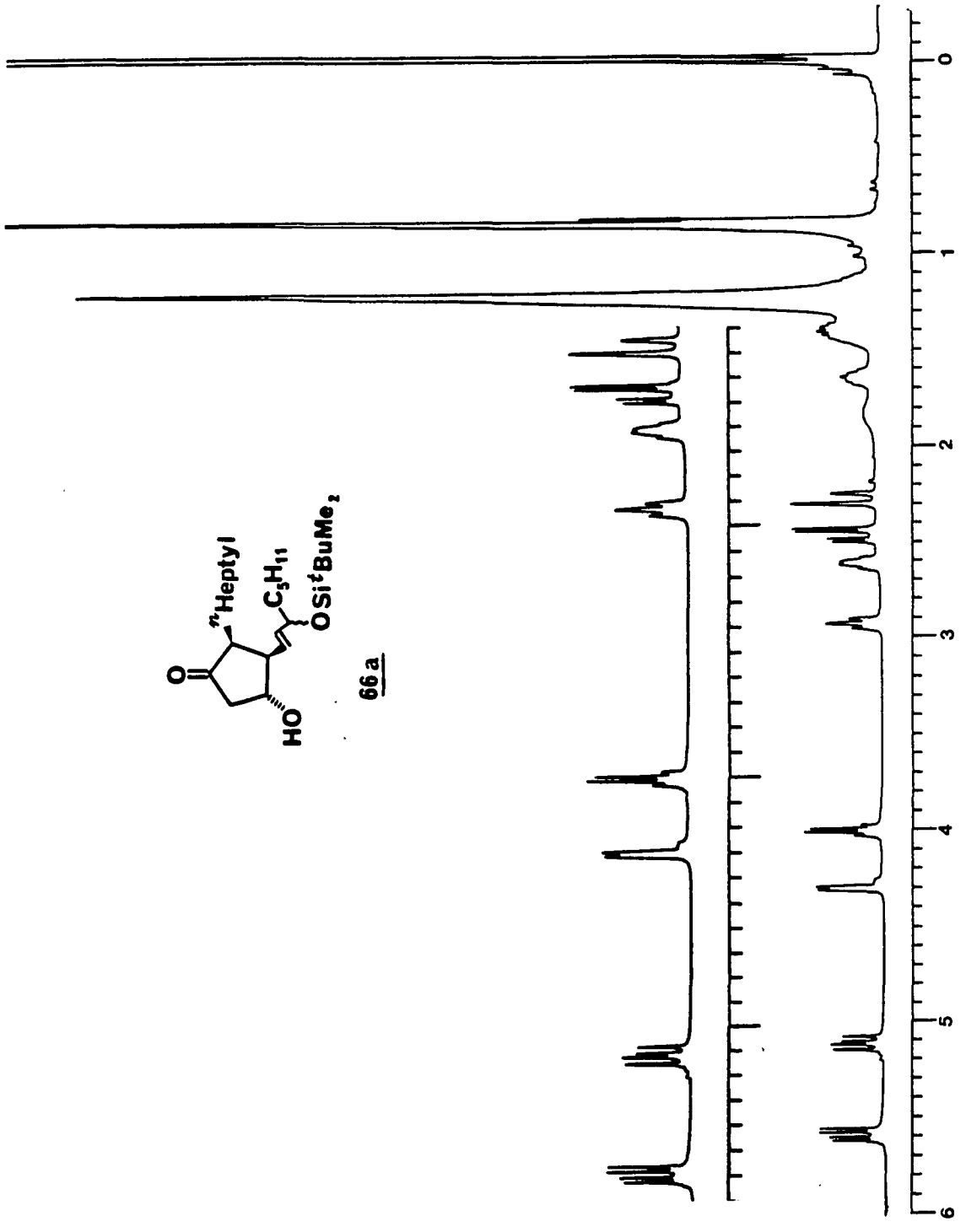
O
HO
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C_5H_{11}
OSi^{t}BuMe$_2$
66a
0
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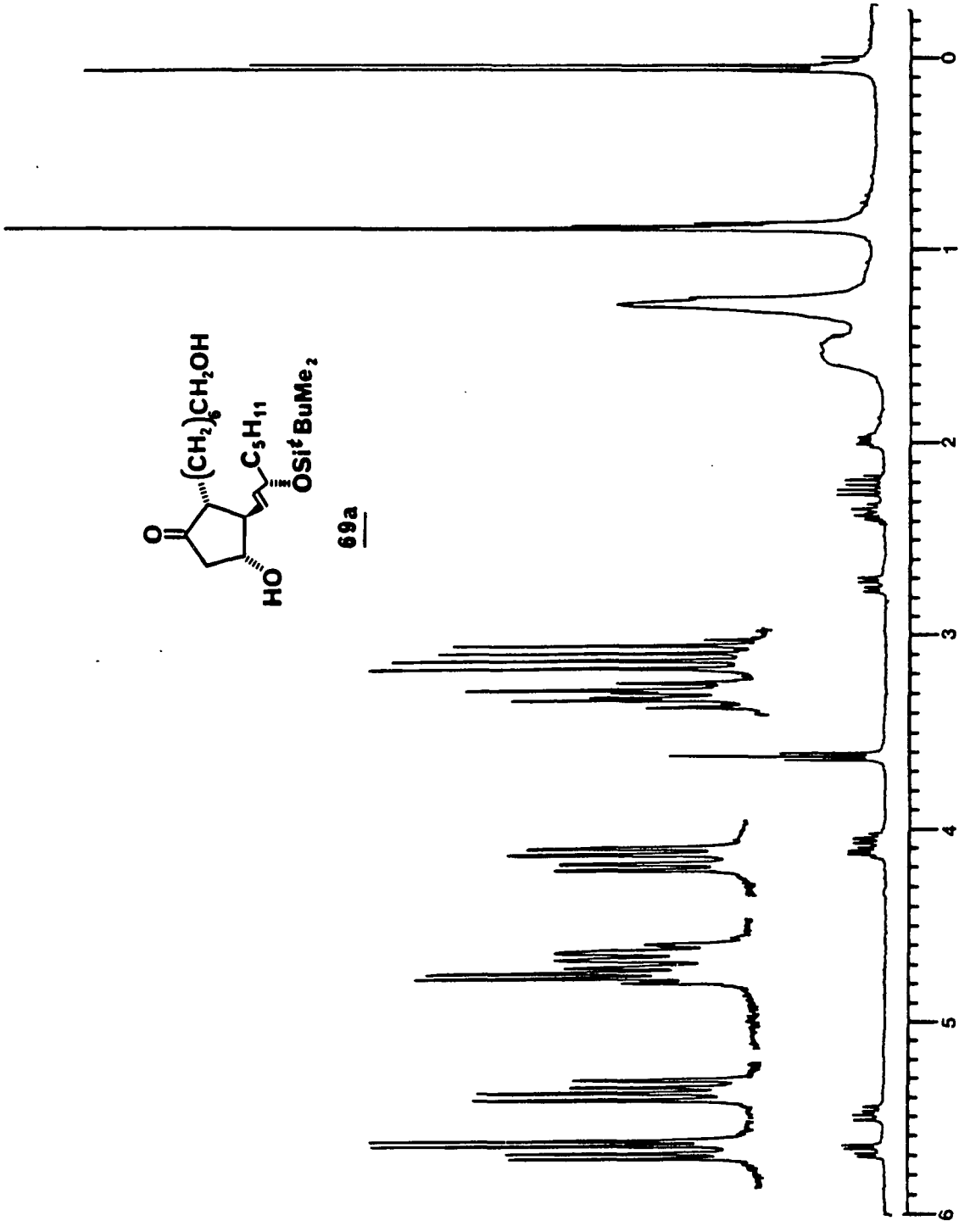
2
3
4
5
6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HO
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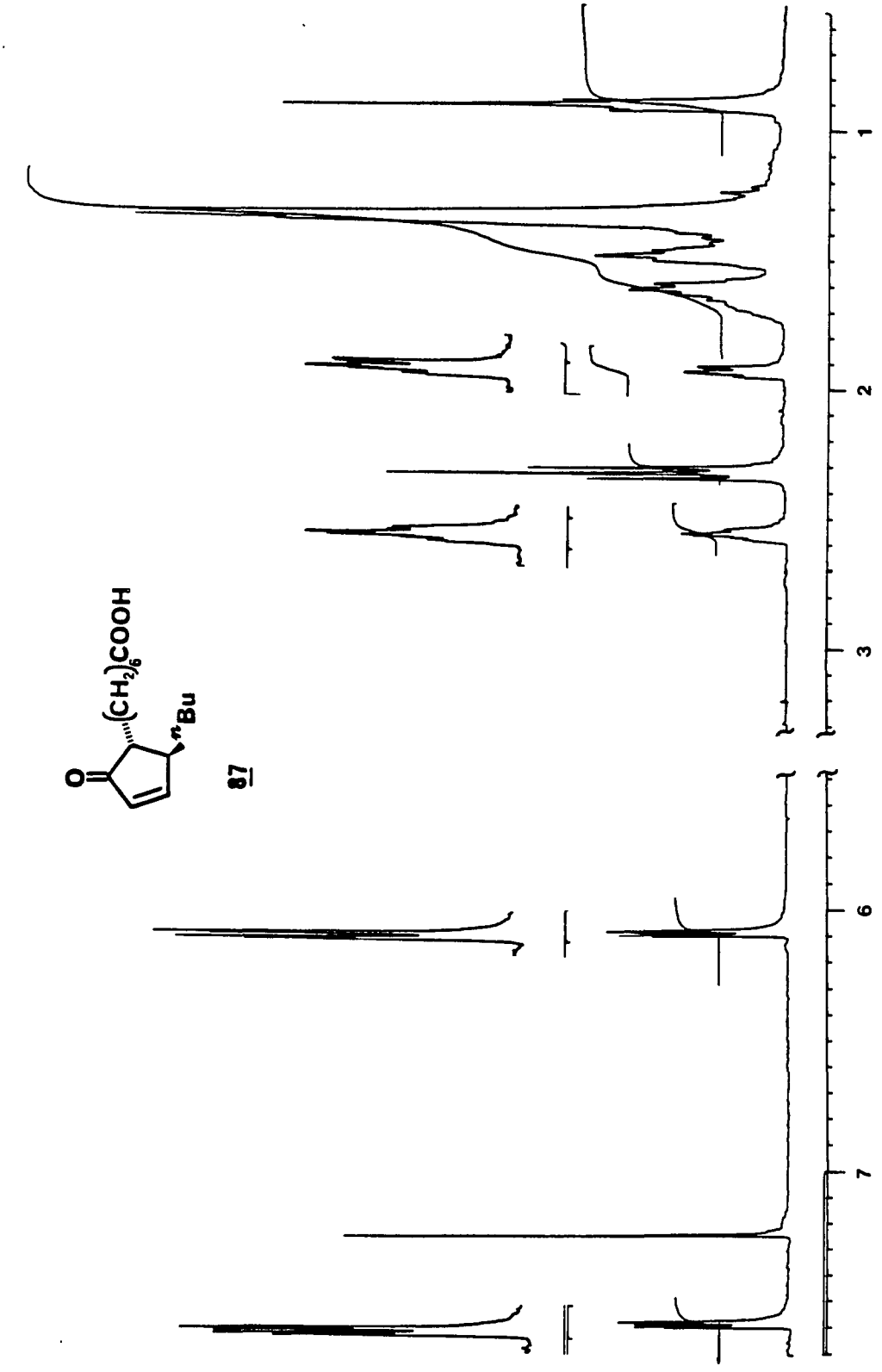
C5H11
OSitBuMe2
69a
0
1
2
3
4
5
6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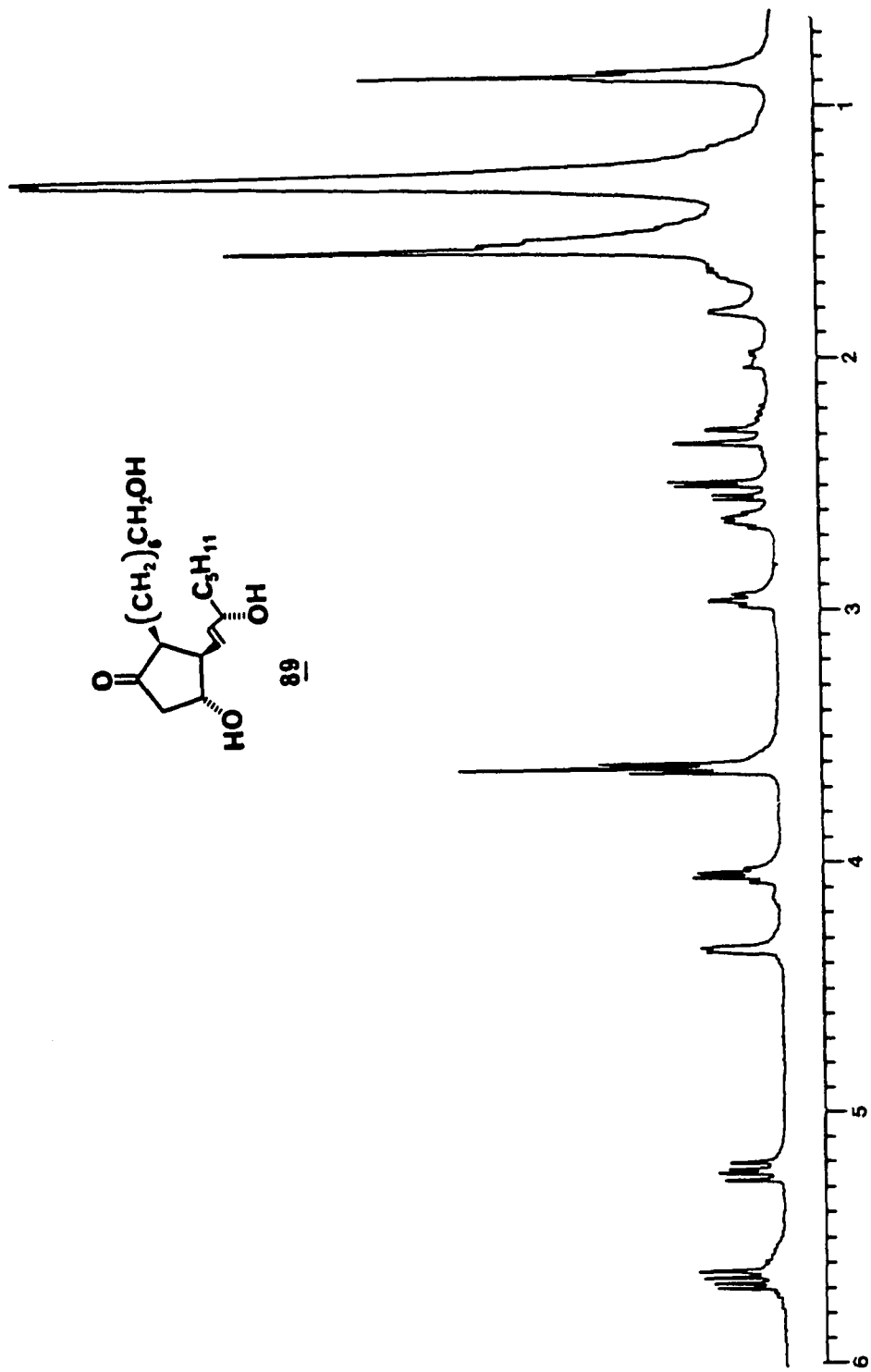
nBu
O
87
1
2
3
6
7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OH
HO
O
89
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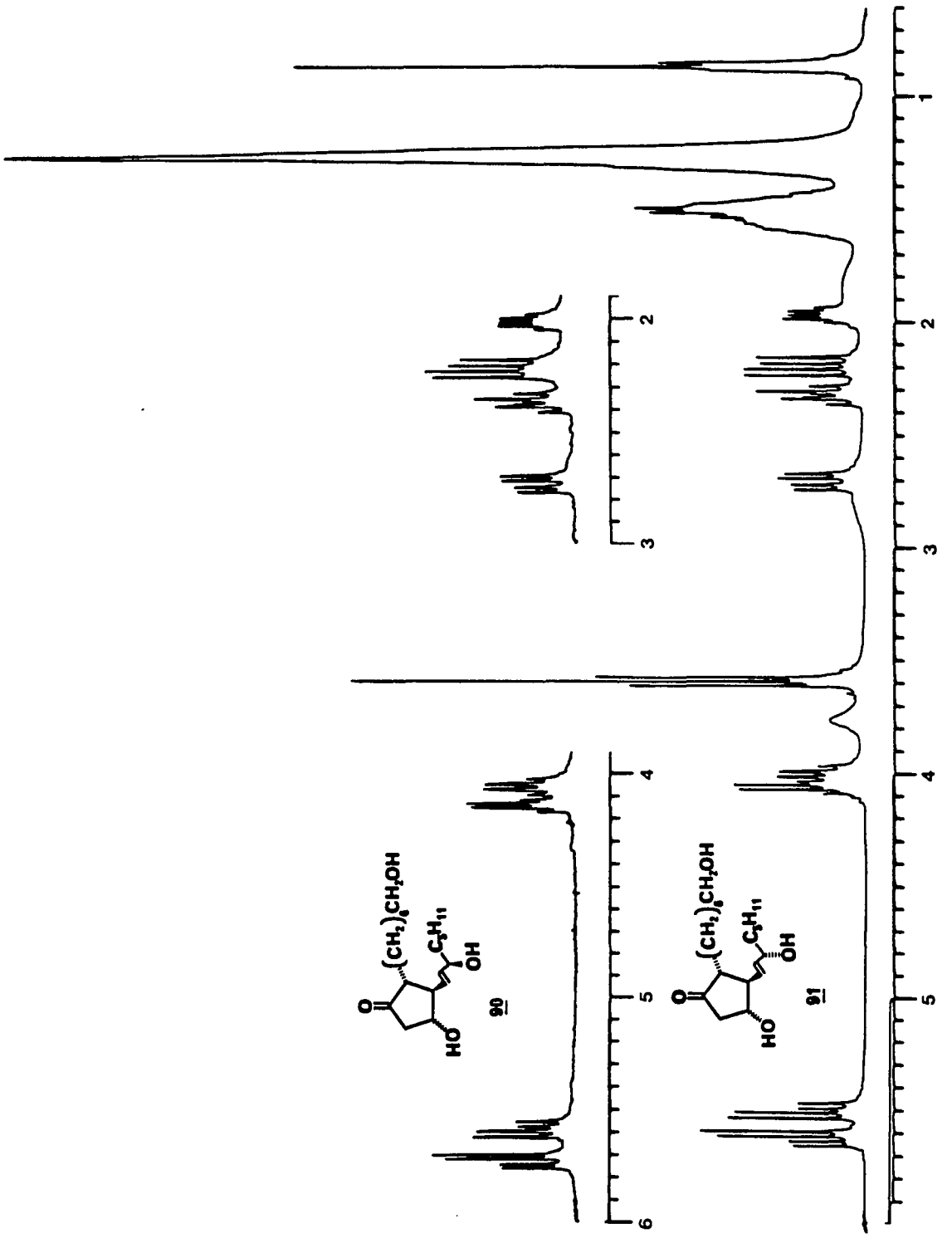
2
3
4
5
6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OH
HO
O
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C5H11
OH
HO
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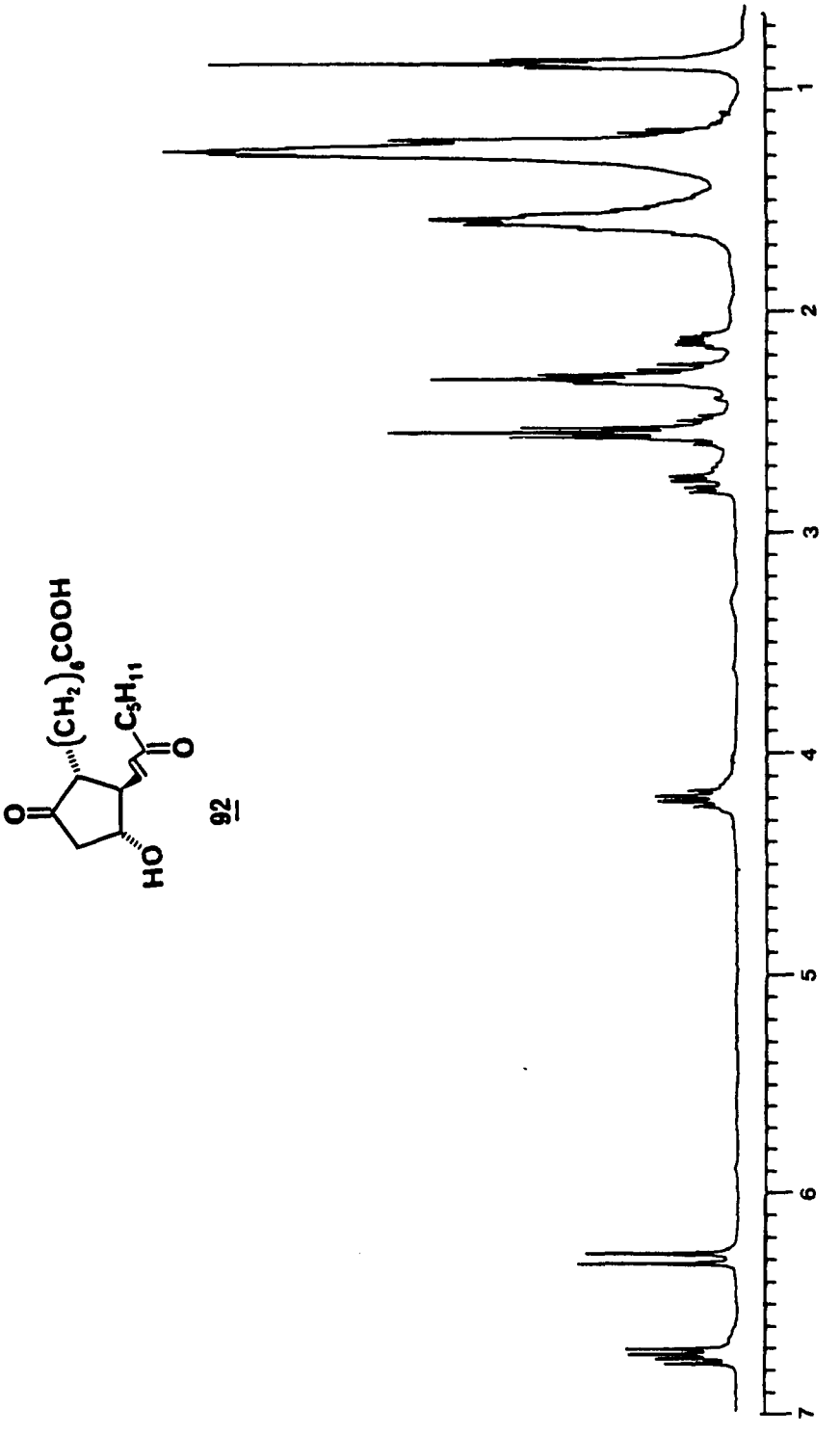
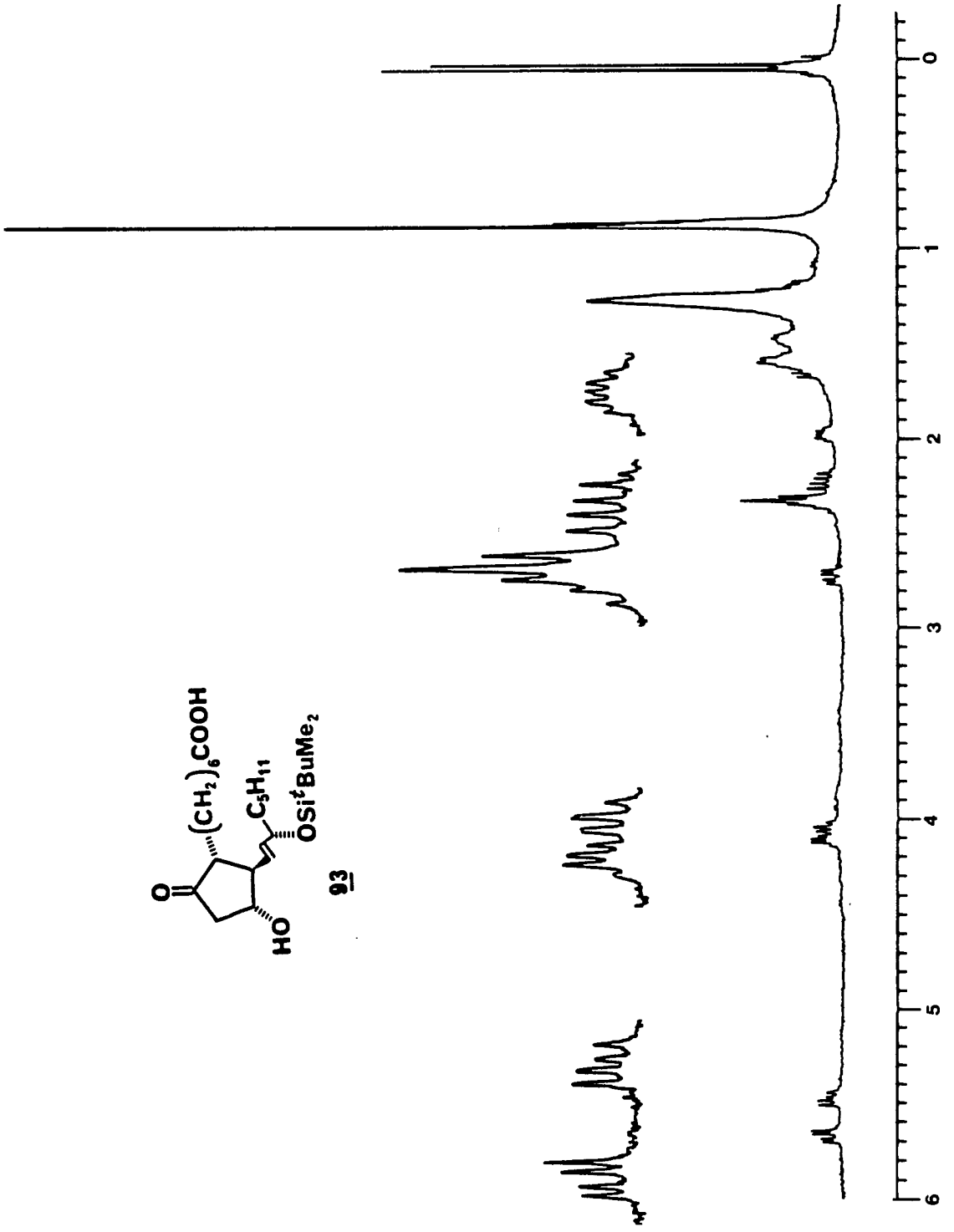
2
3
4
5
6


(CH2)6COOH
C5H11
O
O
HO
92
1
2
3
4
5
6
7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OSitBuMe2
HO
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4
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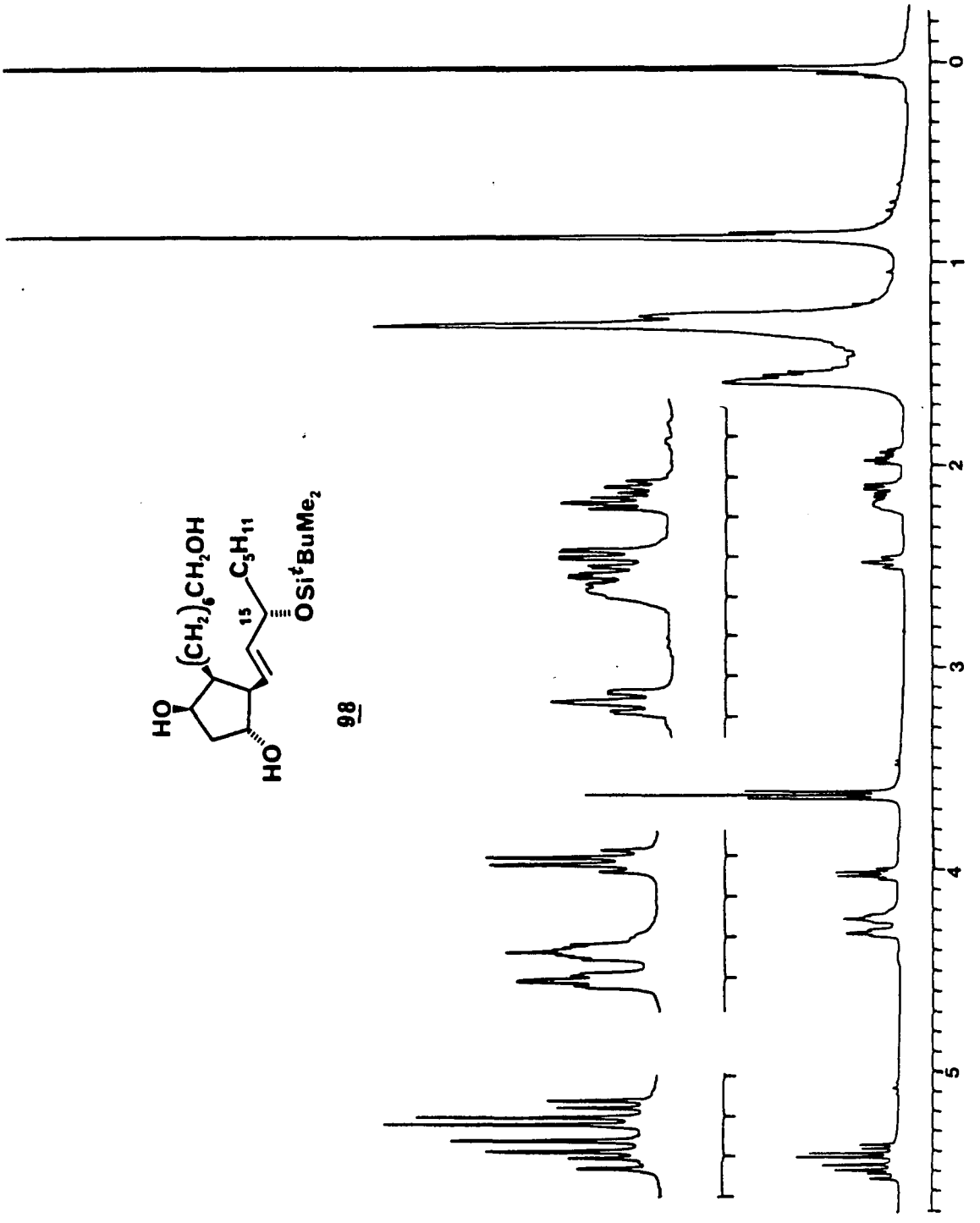
6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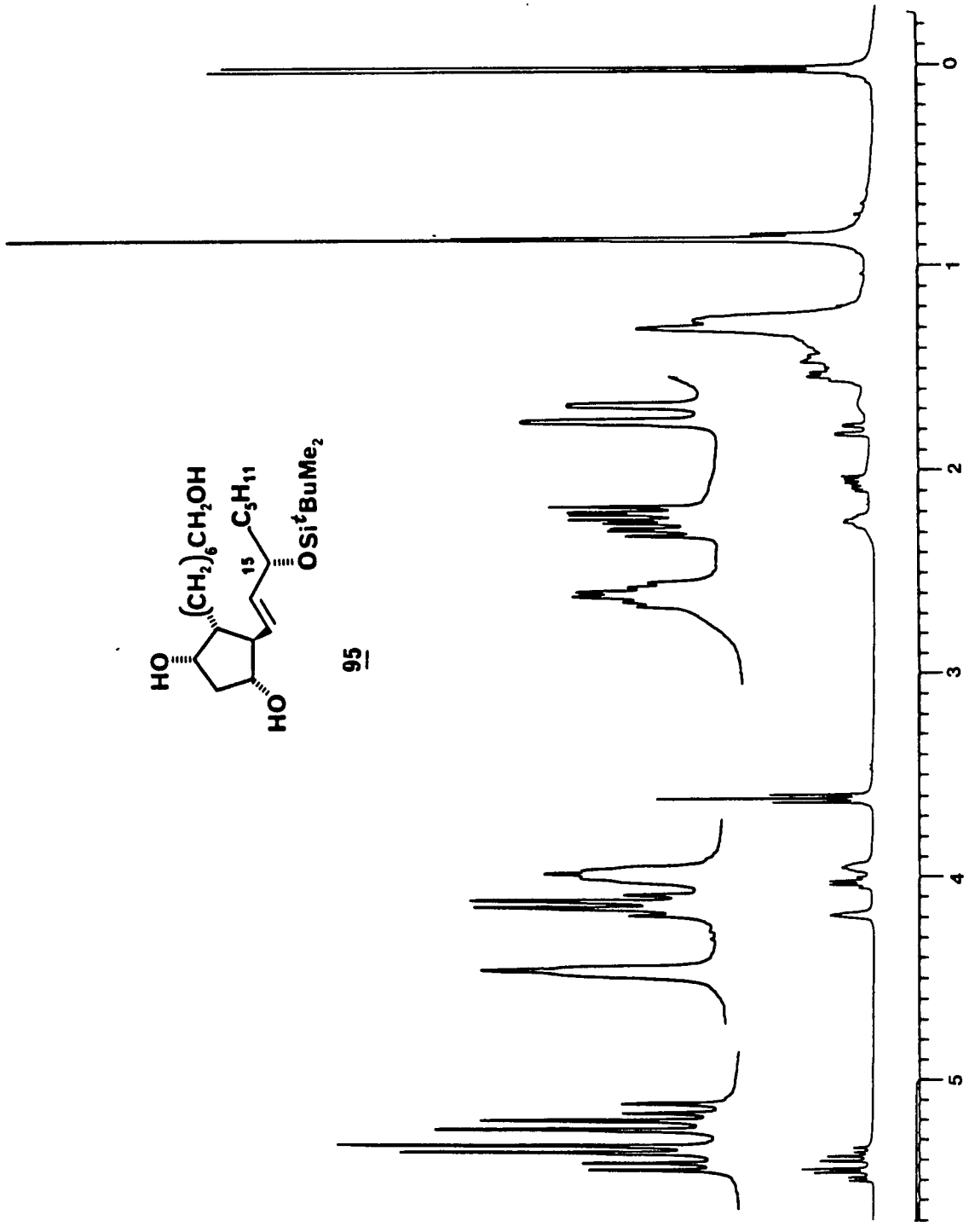
2
3
4
5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HO
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0
1
2
3
4
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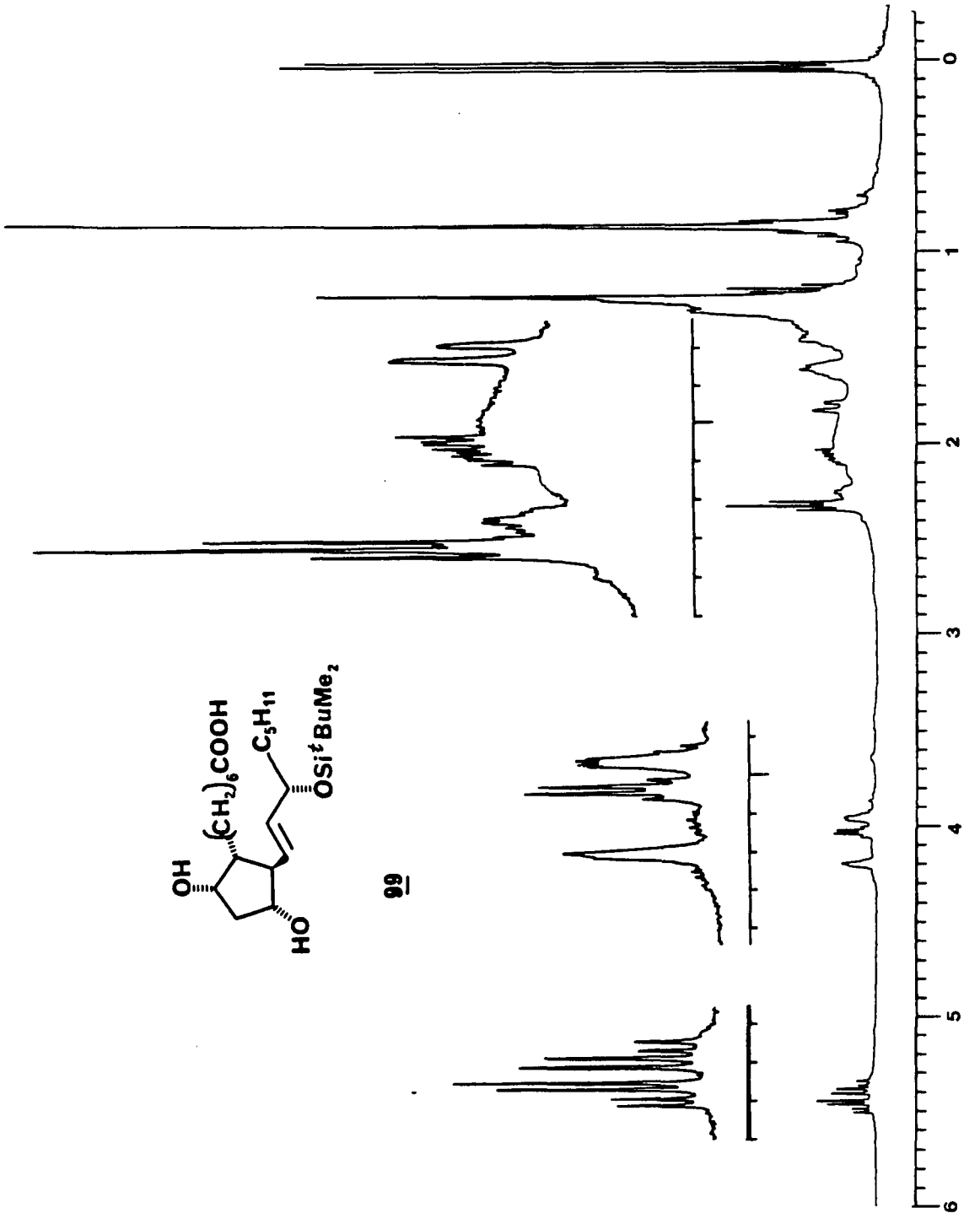
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HO
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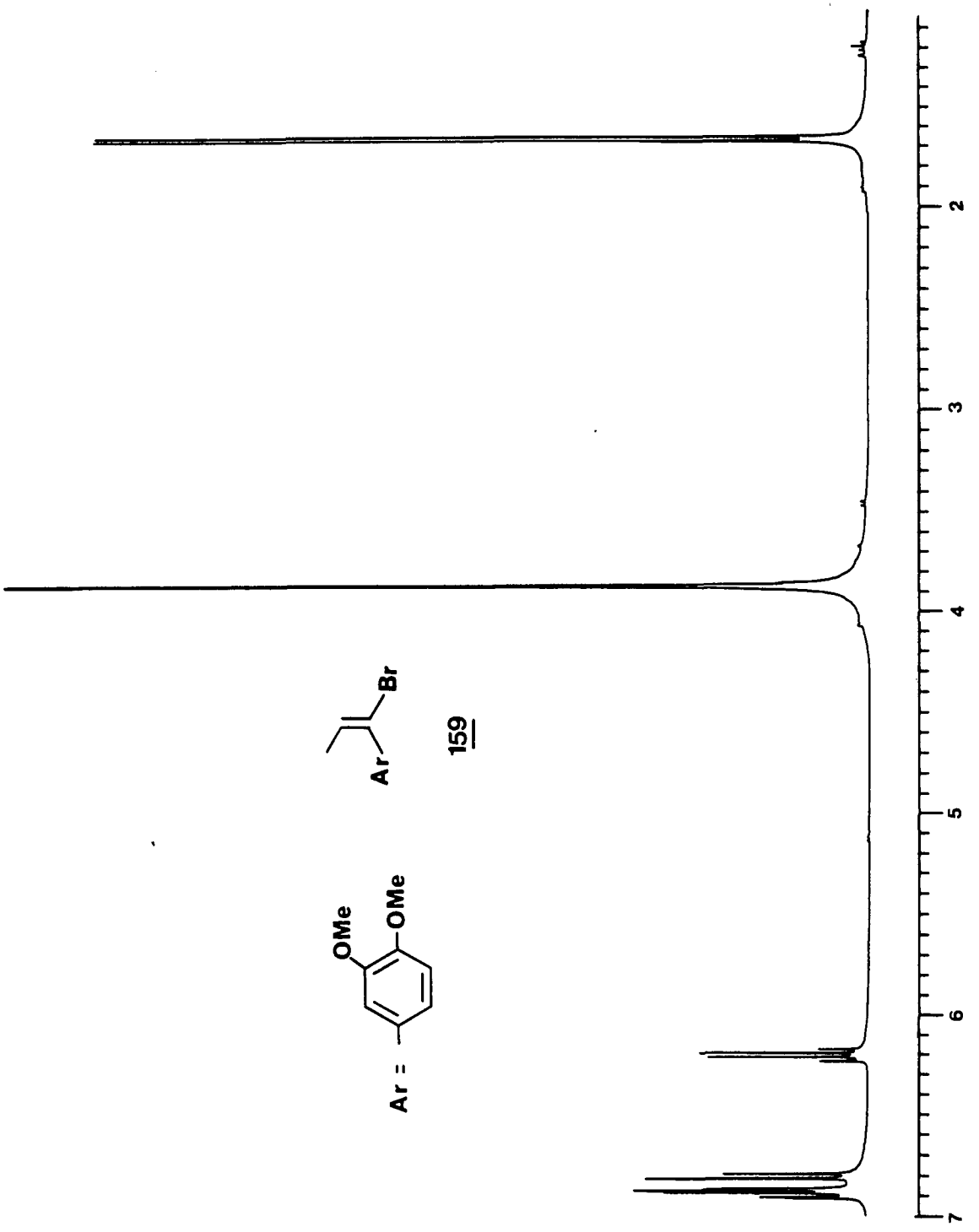
3
4
5
6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OMe
OMe
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4
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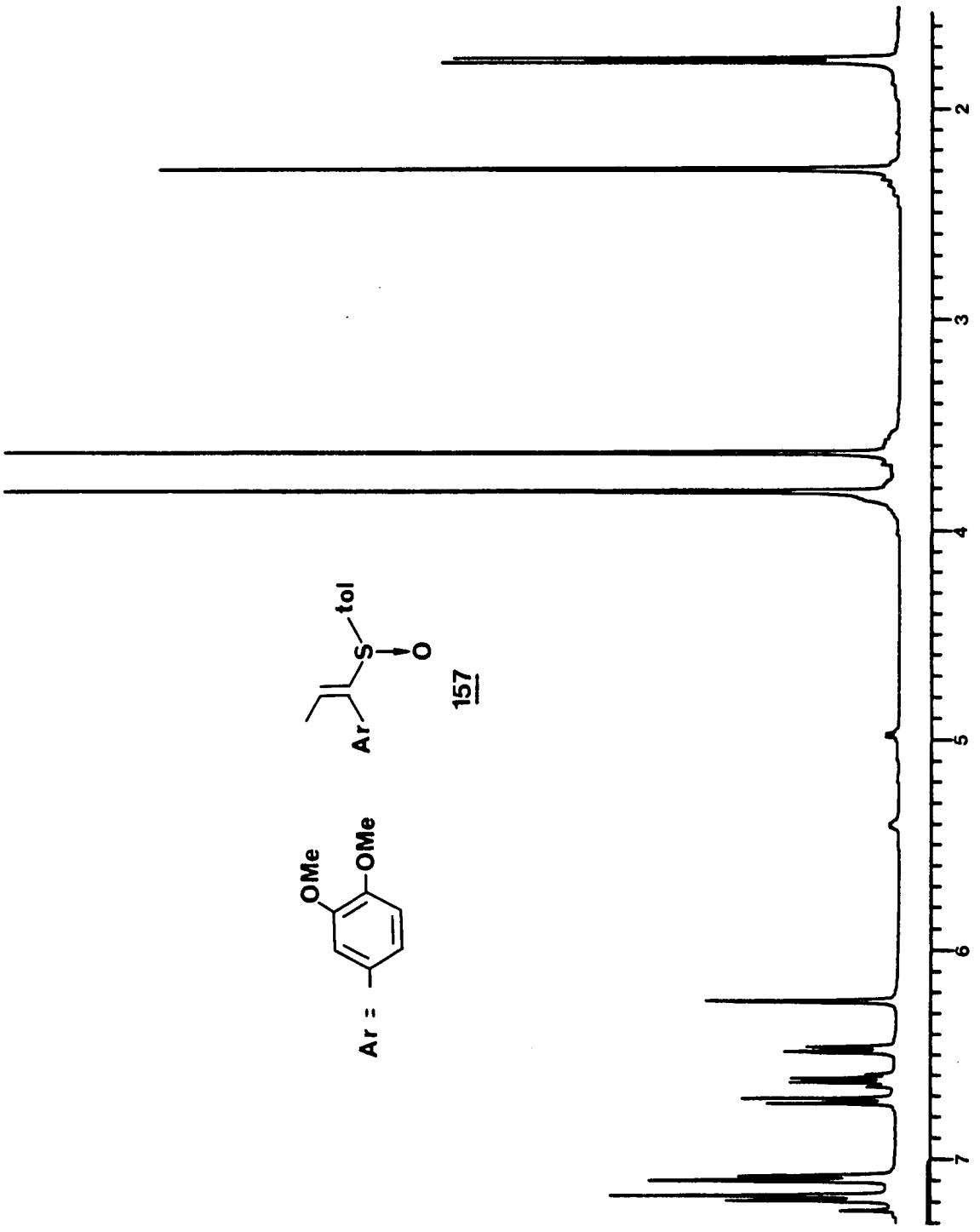
2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OMe
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4
5
6
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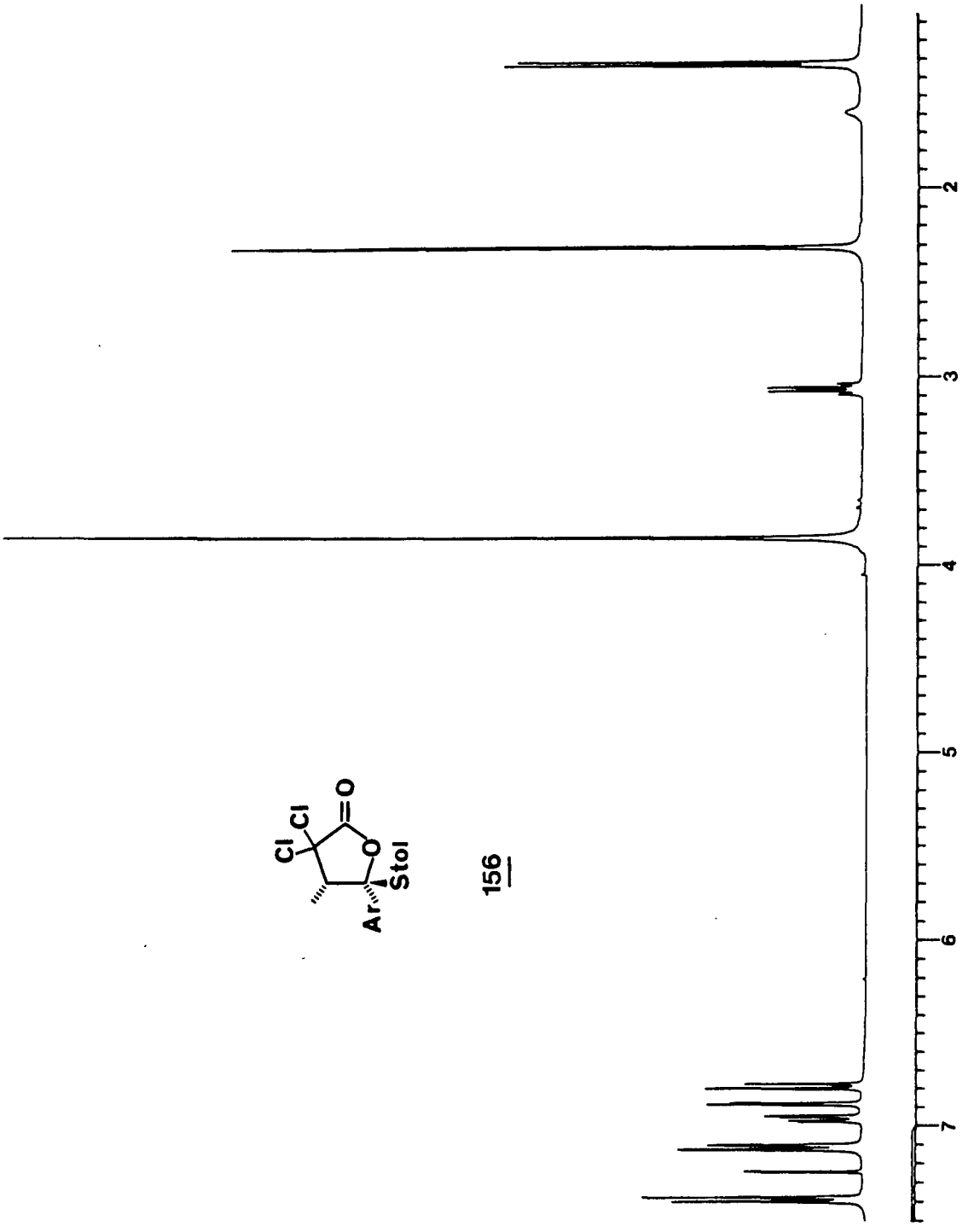
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4
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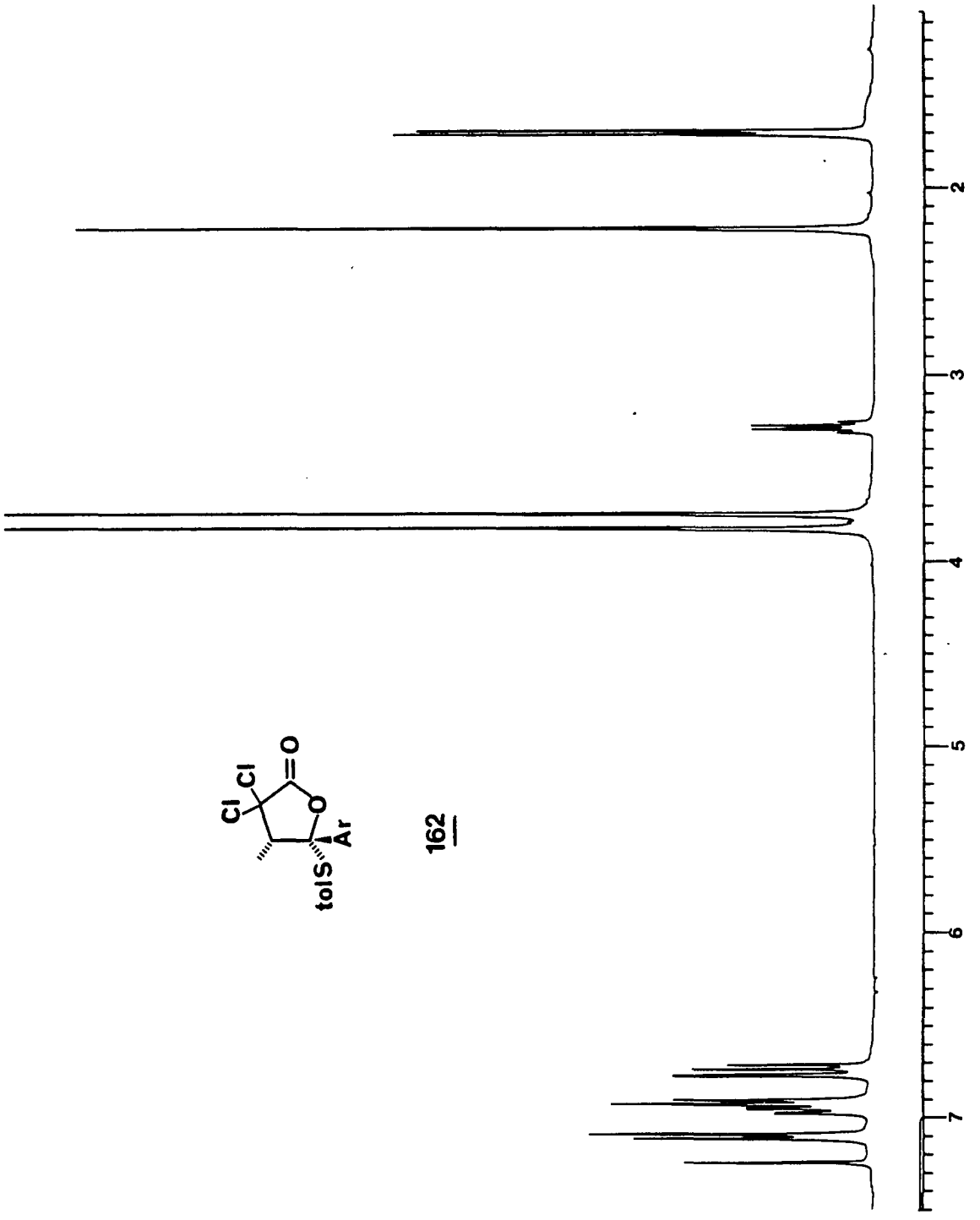
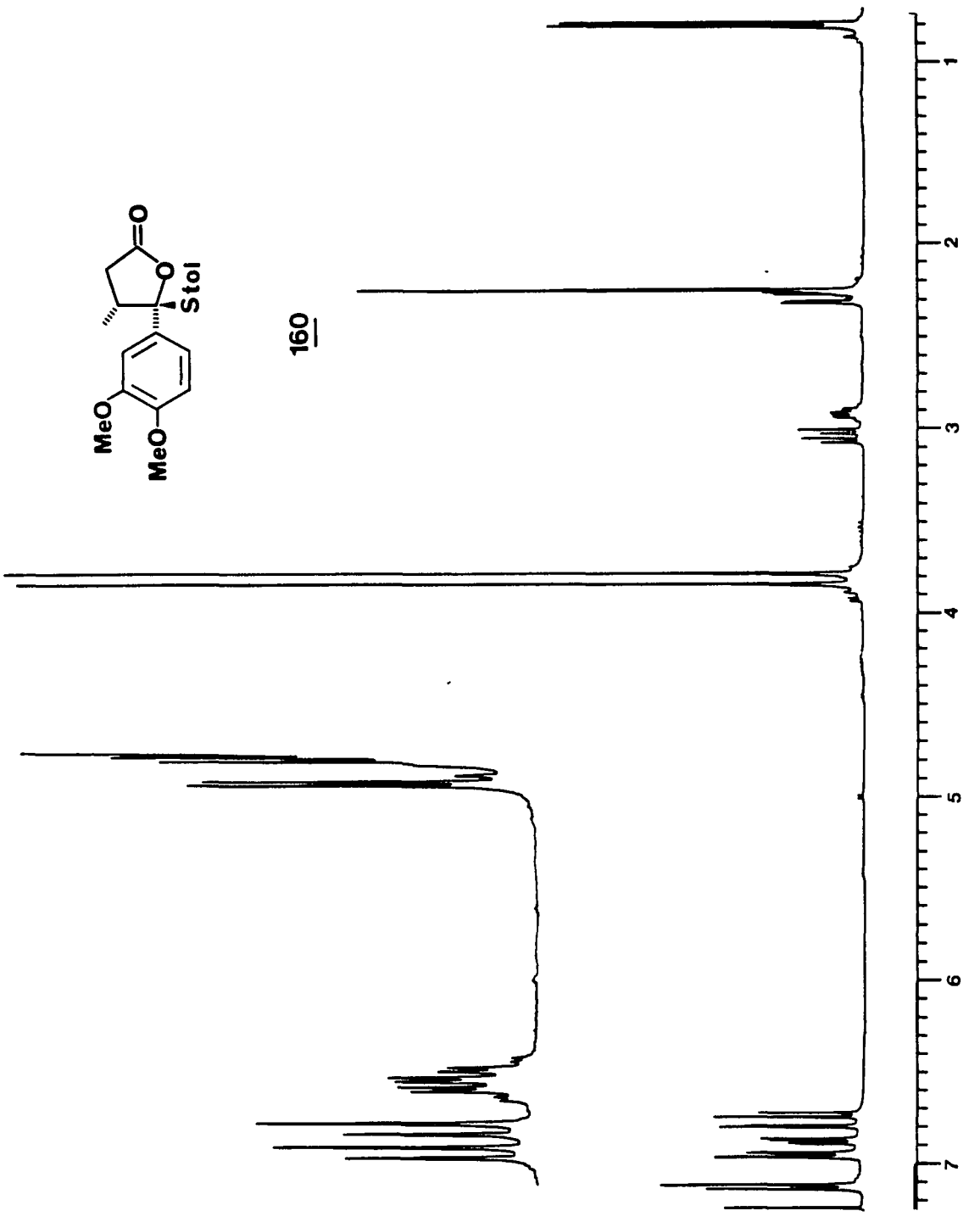
6
7



162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Stol
MeO
MeO
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5
6
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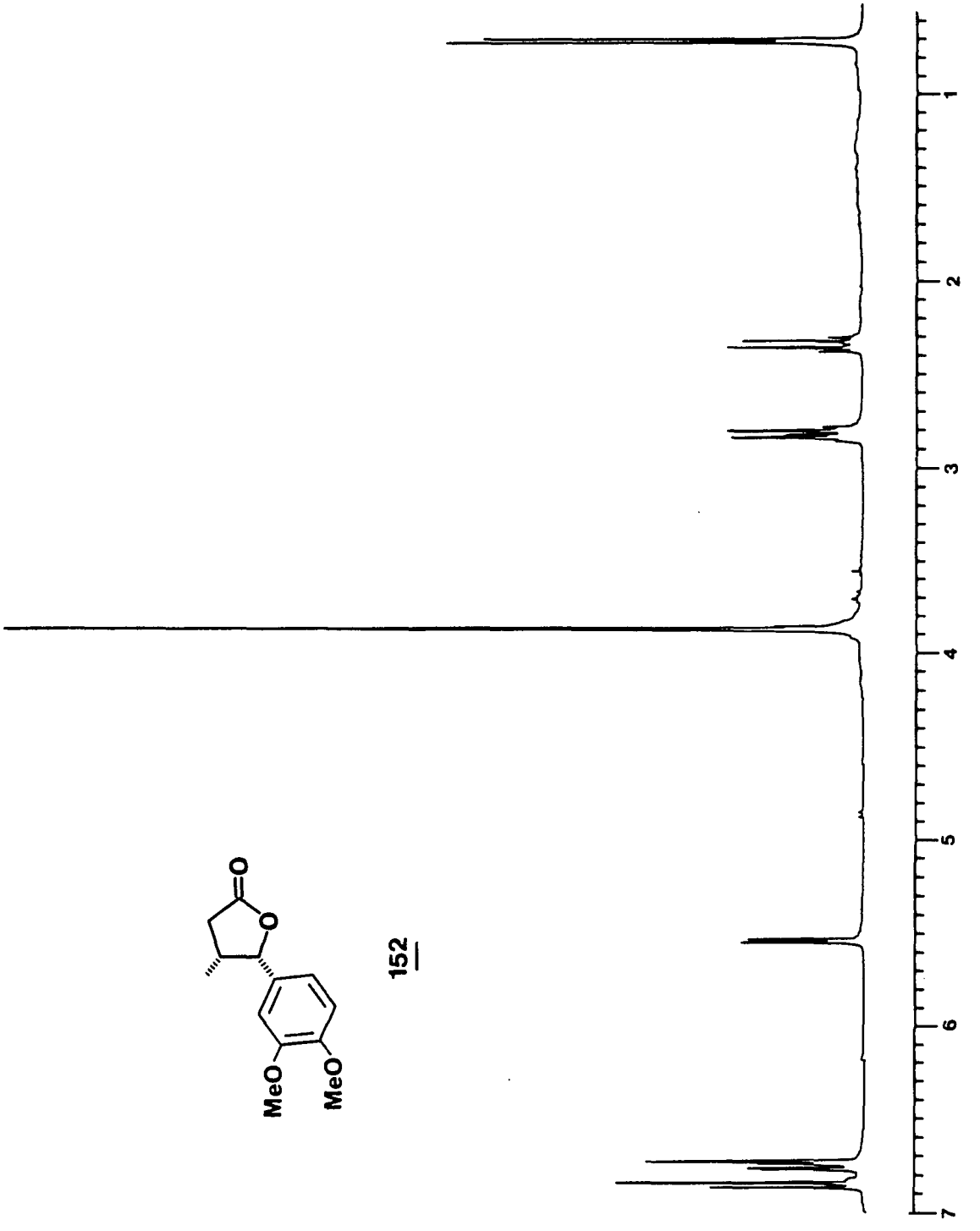

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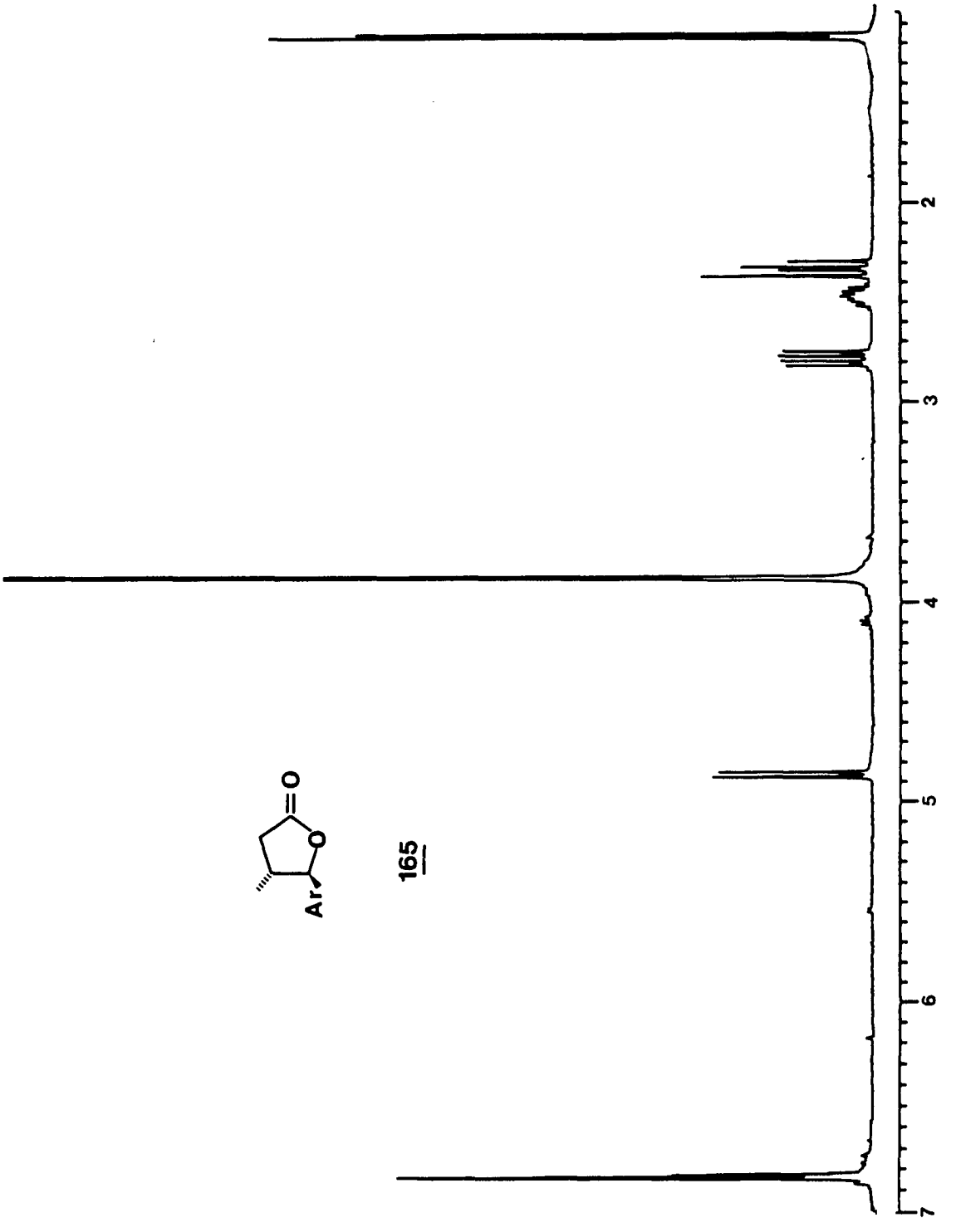

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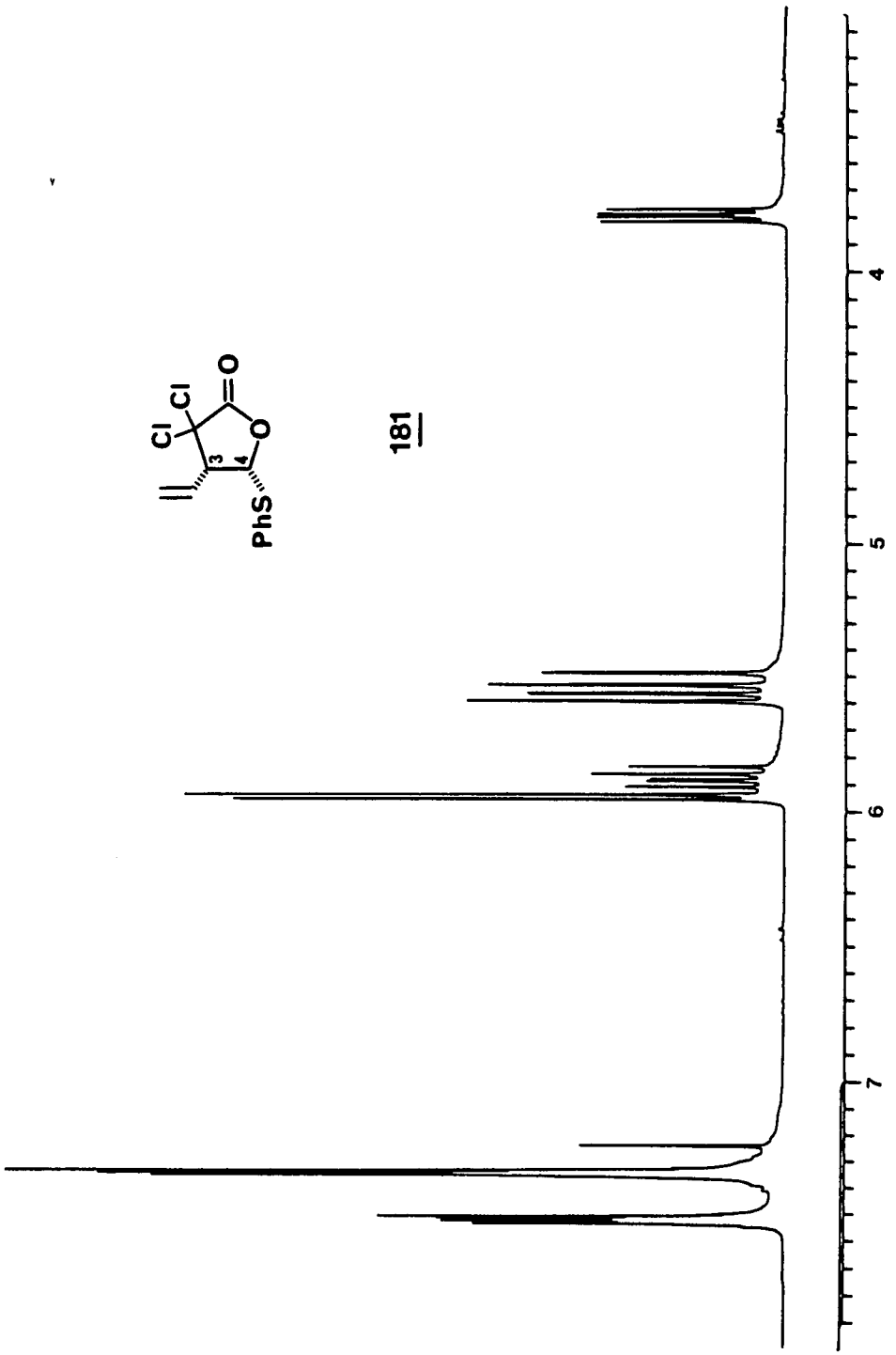
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3
4
PhS
181
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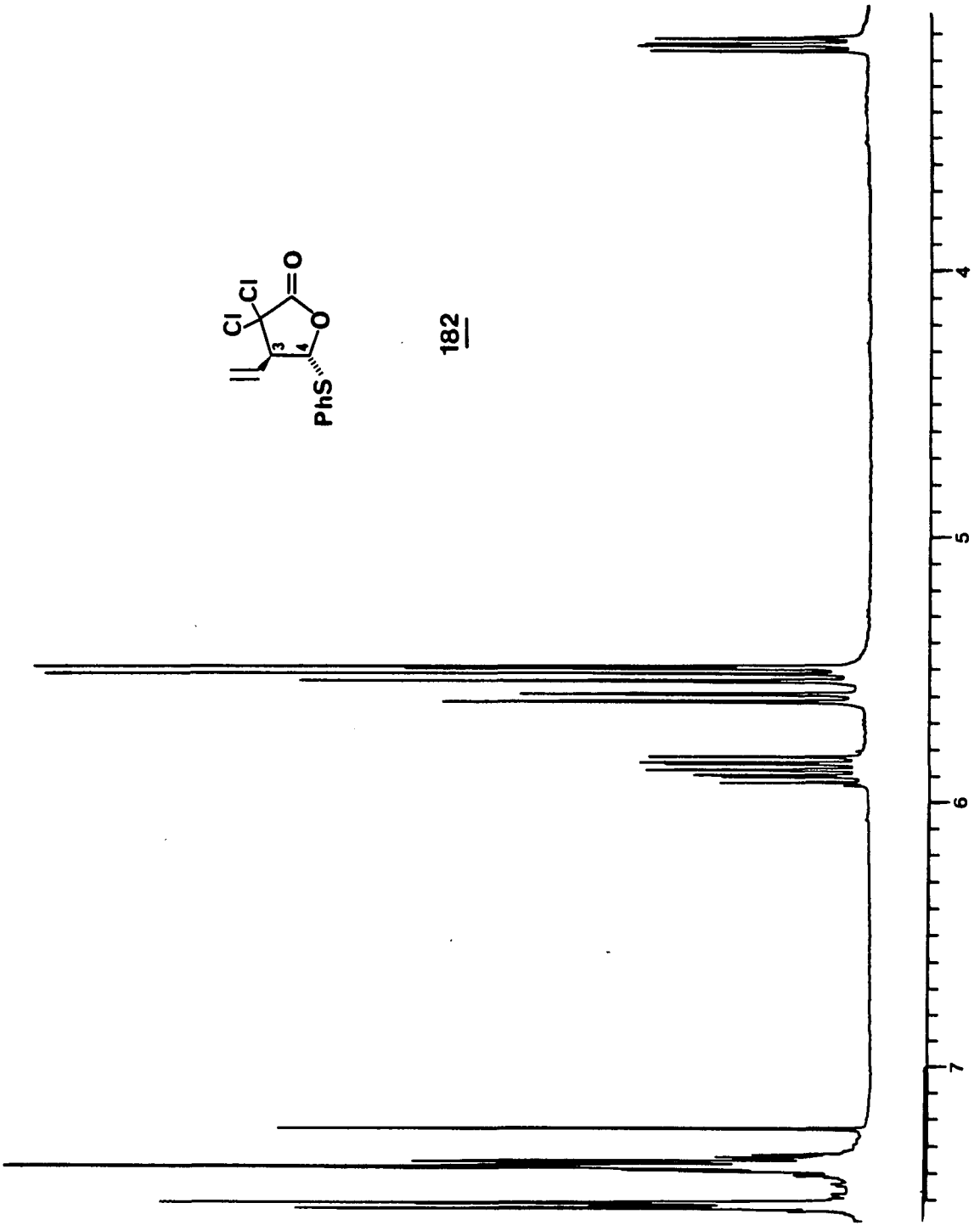
5
6
7



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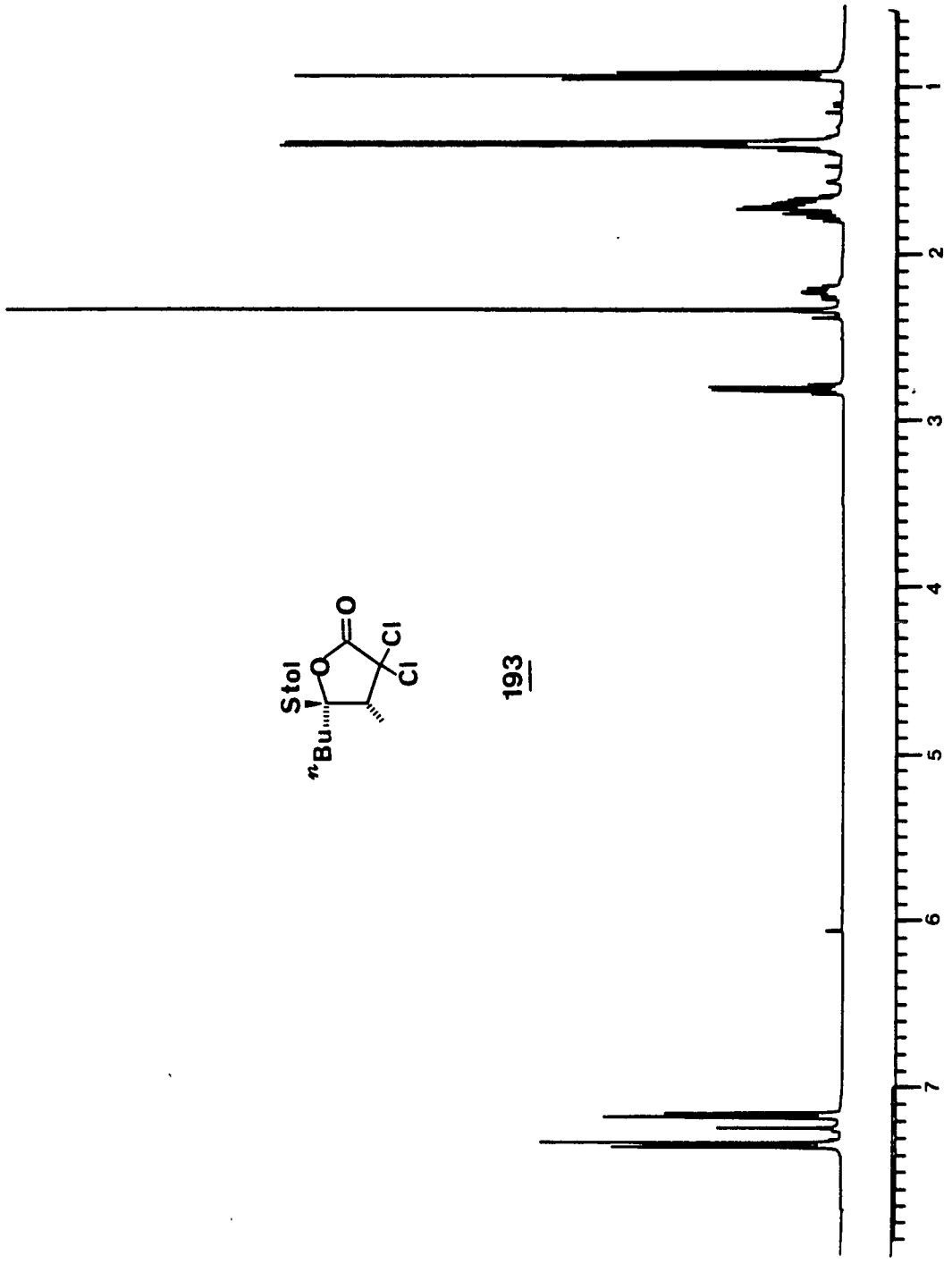
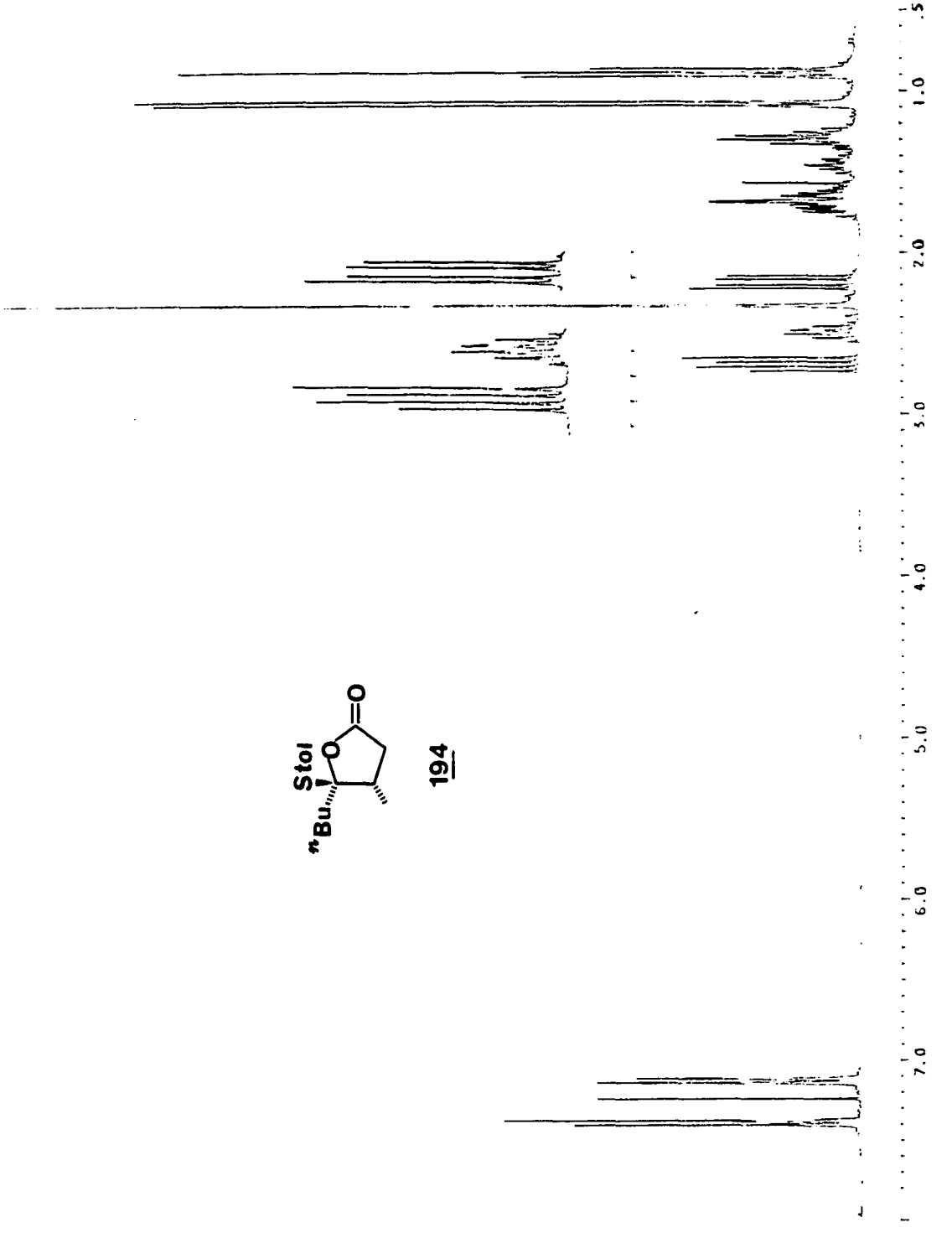


193


Stol
nBu
O
O
194
.5
1.0
2.0
3.0
4.0
5.0
6.0
7.0

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111. Prepared from commercially available 1-bromo-1-propene as follows: (1) Fractional distillation (75 cm column packed with glass beads) gave a ca. 1:3 mixture of cis and trans isomers; (2) Mg turnings, THF; then tolS(O)Cl, 72% yield; (3) Chromatographic separation of cis isomer 189 and trans isomer 190 (silica gel, hexane:ethyl acetate, 2:1).