Silicon-Directed Carbon–Carbon Bond Forming Reactions

Thesis by

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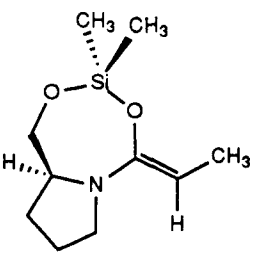
Abstract

It is shown that *O*-silyl ketene *N,O*-acetals react with aldehydes, without catalysis, to form aldol-type products with high diastereoselectivity. For example, the prolinol-derived *O*-silyl ketene *N,O*-acetal **7** reacts with benzaldehyde to form the anti aldol product **9** with >98% diastereoselectivity. Mechanistic studies are presented which support a scheme involving formation of trigonal bipyramid (tbp) **G**, pseudorotation to form tbp $\mathbf{T_{boat}}$, and rate-determining C–C bond formation to produce **9**.



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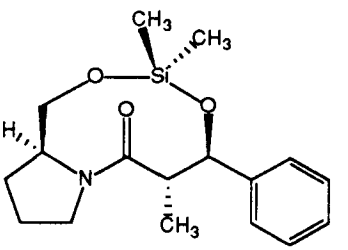

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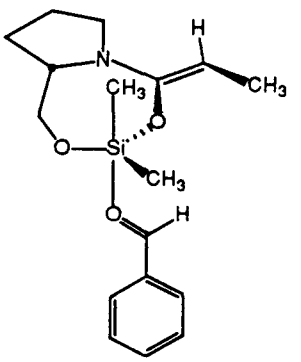

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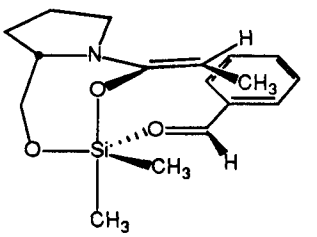
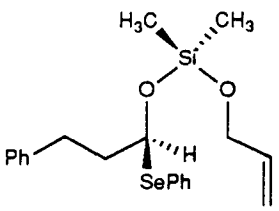


$\mathbf{T_{boat}}$

It is shown that aldehydes react with pyridine, benzeneselenol, dichlorodimethylsilane, and an allylic alcohol to form *O*-allyloxy dimethylsilyl hemiselenoacetals in high yield. These derivatives undergo efficient free radical-mediated cyclization upon treatment with Bu_3SnH, as exemplified by the transformation of **7**→**8**. Together these steps provide an efficient method for carbon–carbon bond formation between the carbonyl carbon of an aldehyde and the terminus of an allylic alcohol.



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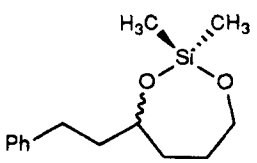

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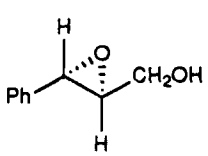
2,3-Epoxy alcohols are transformed to C2-inverted cyclic carbonates upon treatment with cesium carbonate under an atmosphere of carbon dioxide (e.g., **5**→**6**). The reaction is completely stereospecific, within experimental error, and forms only 5-membered ring cyclic carbonates.



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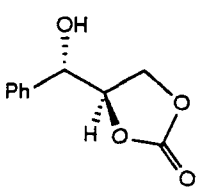

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List of Abbreviations[1]

Å	angstrom
Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
ASTM	American Society for Testing Materials
atm	atmospheres
$[\alpha]$	optical rotation
Bu	butyl
c	concentration (g/100 mL)
cal	calories
CI	Chemical Ionization
cm	centimeters
CSA	camphorsulfonic acid
℃	degrees Celsius
DMAP	(4-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
E	entgegen (together)
ee	enantiomeric excess
EI	Electron Impact Ionization
equiv	equivalents
Et	ethyl
ether	diethyl ether
eu	entropy units
ϵ	dielectric constant

FAB	Fast Atom Bombardment Ionization
FT	fourier transform
g	grams
GC	gas chromatography
h	hours
H	enthalpy
HMPA	hexamethylphosphoramide
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectroscopy
hυ	light
Hz	hertz
i	iso
IR	infrared
irr	irradiation
J	coupling constant
k	rate constant
K_{eq}	equilibrium constant
KHMDS	potassium hexamethyldisilazane
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazane
m	meters
m	meta
M	Molar (moles/L)
M^+	molecular ion
m-CPBA	*meta*-chloroperoxybenzioc acid
Me	methyl

mg	milligrams
MHz	megahertz
min	minutes
mL	milliliters
mm	millimeters
mM	millimolar
mmol	millimoles
mol	moles
mp	melting point
MS	mass spectrometry
MTAP	α-methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher acid)
MTAPCl	α-methoxy-α-(trifluoromethyl)phenylacetyl chloride
μL	microliters
μm	micrometers
n	normal (unbranched)
nm	nanometers
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
p	para
pet. ether	petroleum ether (bp: 30-60 °C)
Ph	phenyl
ppm	parts per million
Pr	propyl
pyr	pyridine

(*R*)	rectus (clockwise priority)
R_f	retention factor
(*S*)	sinister (counterclockwise priority)
t	tertiary
TBDMS	tertbutyldimethylsilyl
tert	tertiary
tbp	trigonal bipyramid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
tol	toluene
Torr	millimeters of mercury
UV	ultraviolet
W	watts
w/w	weight percent
ψ	pseudorotation
Z	zusammen (together)
>	greater than
<	less than
~	approximately
(±)	racemic

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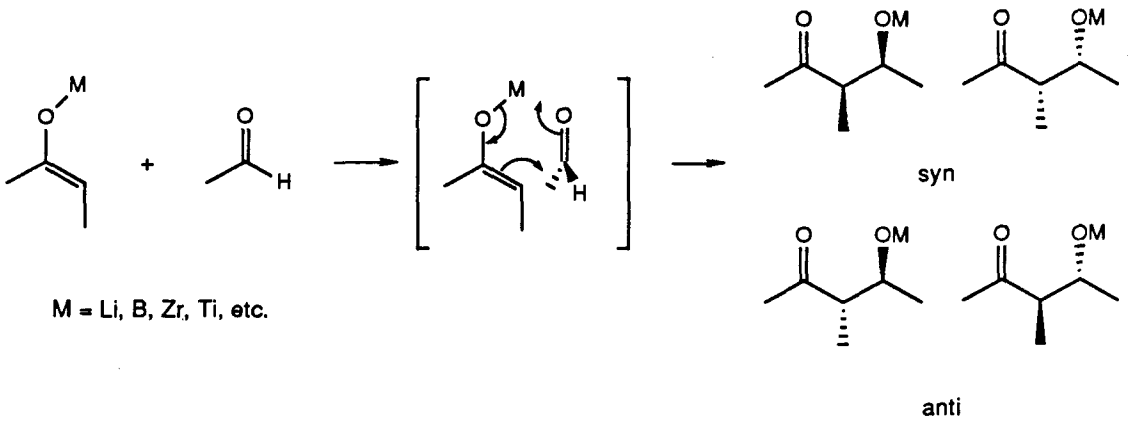
[1]Abbreviations used in the compilation of spectral data are defined in the beginning of each experimental section.

CHAPTER I

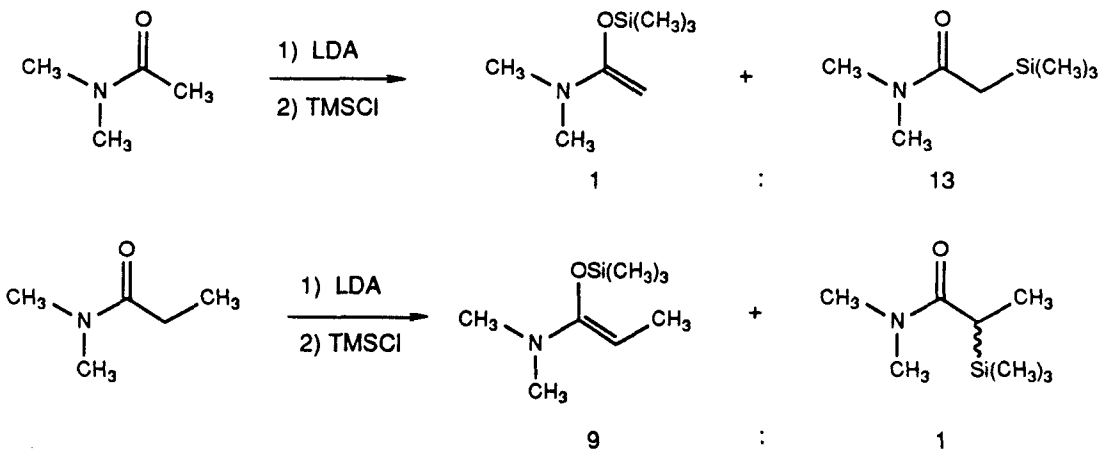
Aldol Reactions of *O*-Silyl Ketene *N,O*-Acetals

The aldol reaction is one of the oldest carbon–carbon bond forming reactions in organic chemistry.[1] In the last 10 years it has developed into one of the most powerful ways of generating acyclic stereocenters.[2] Because two sp^3 centers are generated in the aldol condensation, a maximum of four stereoisomers can be formed. Two different issues of stereocontrol need to be addressed: control of relative sense of π facial attack (anti vs. syn) and control of absolute sense of π facial attack ($anti_1$ vs. $anti_2$ and syn_1 vs. syn_2).



The reactivity of *O*-silyl enol derivatives of amides (*O*-silyl ketene *N,O*-acetals) toward aldehydes was explored with the goal of developing new aldol methodology and improving stereocontrol in the process. We chose to investigate these compounds since amide enolates are generally more nucleophilic than their ketone or ester counterparts. Also, these enolates can be formed with high *Z* stereoselectivity.[3] One of our goals was to develop a silicon-directed aldol reaction of *O*-silyl ketene *N,O*-acetals. Extrapolation of recent mechanistic proposals for group transfer polymerization reactions, involving a hexavalent transition state with the carbonyl oxygen bound directly to the silicon, suggested that such a strategy might be feasible.[4,5]

A survey of the literature revealed that only a few *O*-silyl ketene *N,O*-acetals had been synthesized, primarily by condensation of a lithium amide enolate with chlorotrimethylsilane.[6] In this procedure, *O*-silyl ketene *N,O*-acetal formation is often accompanied by significant amounts of *C*-silylated product. Rathke demonstrated that the amount of *C*-silylated product is strongly affected by sterics, increasing when the carbon α to the carbonyl is less hindered.[6b] For example, the lithium enolate of *N,N*-dimethylacetamide reacts with chlorotrimethylsilane to produce both *C*- and *O*-silylated products (13:1, respectively), while the lithium enolate of *N,N*-dimethylpropionamide affords a 1:9 ratio of *C*- and *O*-silylated products.[6b]



We found that hydrosilylation of acrylamides is a convenient way to produce *O*-silyl ketene *N,O*-acetals on a large scale, with little competitive *C*-silylation.[7] A number of catalysts were screened for this reaction. Wilkinson's catalyst ($Rh(PPh_3)_3Cl$) worked best for less reactive silanes such as triethylsilane and triethoxysilane while $Pd(CH_3CN)_2Cl_2$ worked better for the more reactive chlorodimethylsilane. These hydrosilylations produced the *O*-silyl ketene *N,O*-acetal fairly cleanly; a small amount (5-10%) of siloxane ($R_3SiOSiR_3$) was also formed as a by-product.

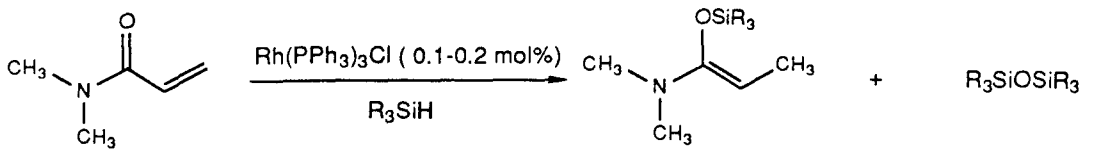
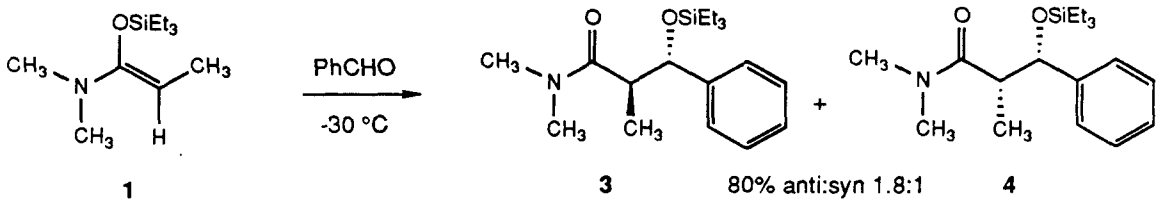


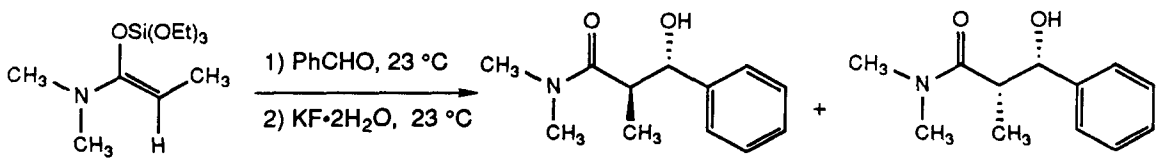
Table I

N,O-acetal	R	Time (h)	Temp (°C)	Solvent	%Yield[a]	%Purity[b]
1	Et	10	50	-	65	90
2	OEt	3	65	C_6H_6	79	93

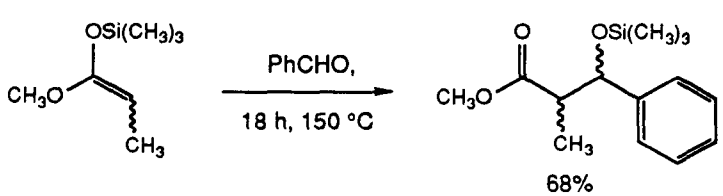
[a]Represents total distilled yield including impurity. [b]Major impurity is siloxane; represents %purity by weight, as determined by ^1H NMR.

O-Silyl ketene *N,O*-acetals **1** and **2** reacted without catalysis with benzaldehyde at -30 °C to 0 °C.[8]

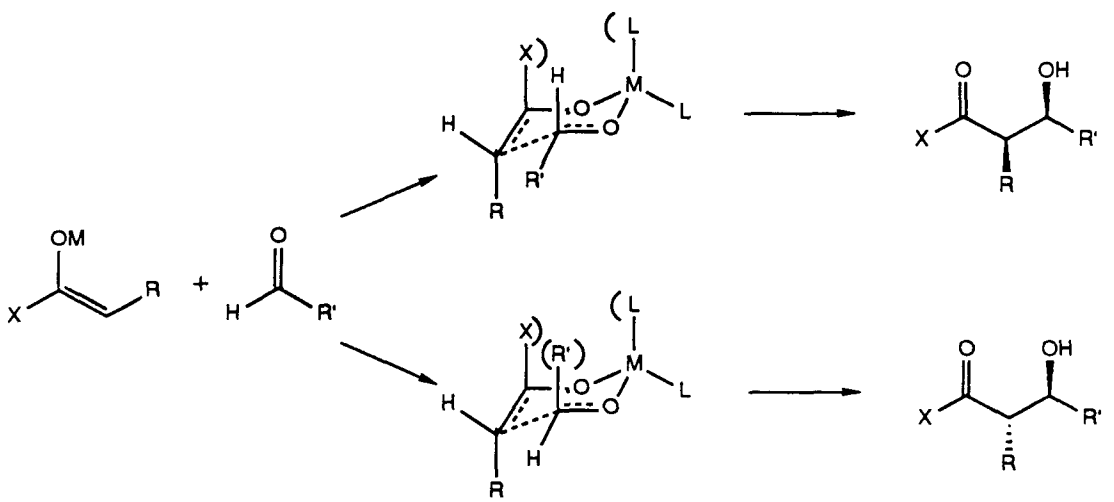




This type of reactivity is not completely unprecedented; Creger reported that an *O*-silyl enol derivative of an ester (*O*-silyl ketene acetals) reacted with benzaldehyde at 150 °C to afford the aldol adduct in 68% yield (relative stereochemistry not reported).[9]

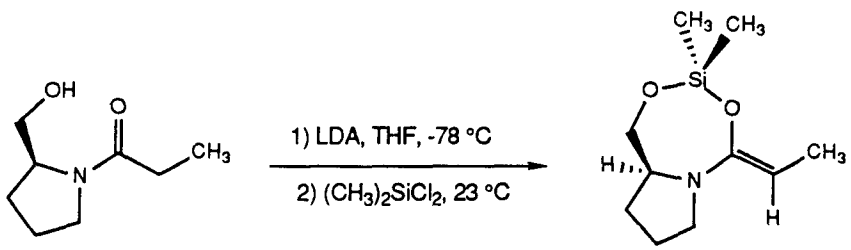


Aldol reactions of *O*-silyl ketene *N,O*-acetals are dramatically accelerated as compared to reactions of the corresponding *O*-silyl ketene acetals. *O*-Silyl ketene *N,O*-acetal **1** was observed to react with benzaldehyde at -78 °C, although reactions conducted at higher temperatures (-30 °C) afforded higher yields of aldol products. The reaction of **1** with benzaldehyde was slightly anti selective (1.8:1). When the ligands on silicon were changed from ethyl to ethoxy the reaction rate decreased while the anti selectivity increased (6.2:1). Anti selectivity is unusual for *Z* enolates.[2] The syn selectivity observed with most *Z* enolates is often explained by invoking a chair transition state.[10] The chair transition state leading to the syn product contains fewer unfavorable 1,3-diaxial interactions than the chair transition state leading to the anti product. Consistent with this analysis, *E* enolates are generally anti selective, though *E* enolates are often less diastereoselective than *Z* enolates.[2] Thus the development of anti selective aldol reactions remains a challenging problem.



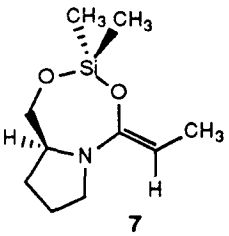
To address the stereochemical issue of differentiation between the two possible anti aldol products, chiral *O*-silyl ketene *N,O*-acetals were examined. We chose to prepare cyclic *O*-silyl ketene *N,O*-acetals from prolinol (e.g., **7**) for several reasons: (1)

the chiral auxiliary prolinol is readily available in both enantiomeric forms, (2) the derived secondary amide should selectively enolize in the *Z* form,[3] and (3) the formation of a bicyclic system should impart more rigidity to the *O*-silyl ketene *N,O*-acetal and hopefully increase diastereoselectivity.



7 78%

Initial attempts to synthesize the desired *O*-silyl ketene *N,O*-acetal **7** from the corresponding acrylamide, in analogy to the experiments described previously, were abandoned due to the instability of the acrylamide. A second route involving condensation of the dianion (prepared from prolinol propionamide and 2 equiv of LDA at -78 °C) with dichlorodimethylsilane was investigated. In the optimized procedure, dichlorodimethlysilane was added to a solution of dianion at room temperature. Concentration and distillation afforded *O*-silyl ketene *N,O*-acetal **7** as a water-sensitive liquid in 78% yield. Irradiation of protons NCH_2 led to an nOe enhancement of the vinylic proton of **7** supporting the assignment of *Z* stereochemistry for the double bond. The enolization was highly selective; none of the *E* isomer could be detected by ^{13}C or ^{1}H NMR.



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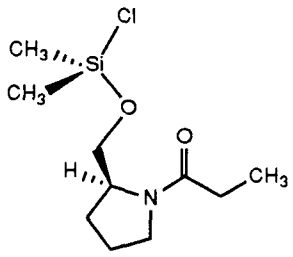

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Table II. Synthesis of *O*-Silyl ketene *N,O*-acetal **7**

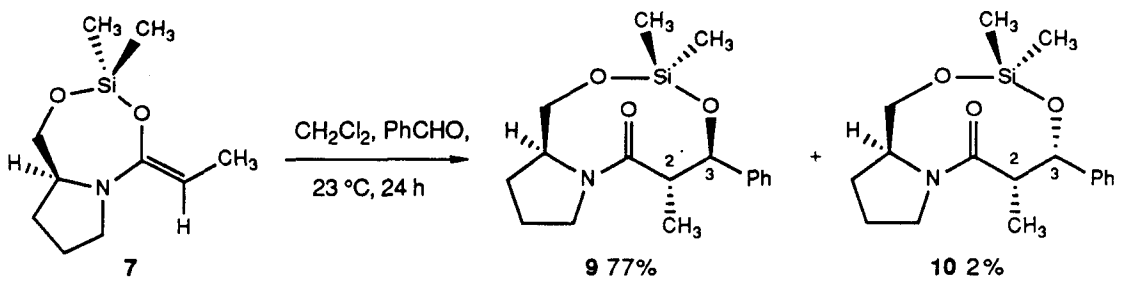
Me_2SiCl_2 Addition Temperature (°C)	Base	Ratio of **7**:**8**	%Yield[c]
-78	LDA	1:0	49
0	LDA	1:0	58
23	LDA	1:0	78
0[a]	LDA	8.4:1.0	66
-78[b]	LDA	8.4:1.0	-
23	LHMDS	1:1[e]	-
23	KHMDS	1:1[e]	-

[a]Inverse addition (lithium enolate to Me_2SiCl_2). [b]Ratio determined from integration of crude NMR. [c]Distilled yield.

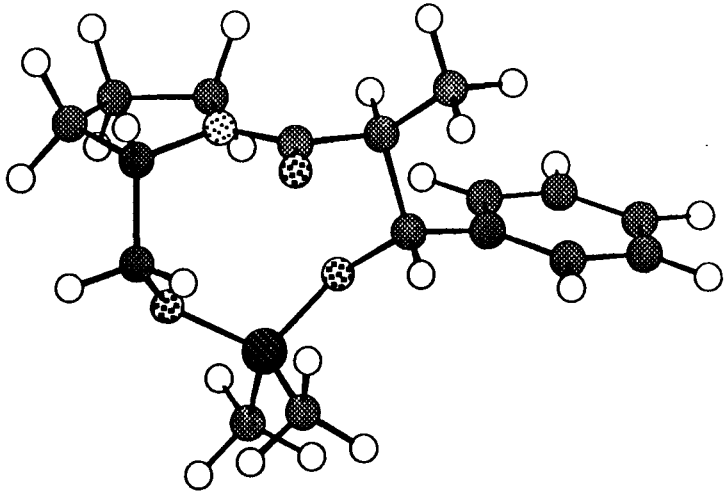
The yield of **7** was strongly dependent upon the temperature at which the dichlorodimethylsilane was added. The major by-products in this reaction appeared to be polymeric; formed when the dichlorodimethylsilane reacted with two different molecules of lithium enolate. The amount of polymer decreased as the temperature of dichlorodimethylsilane addition increased – correspondingly higher yields of *O*-silyl ketene *N,O*-acetal **7** were obtained (Table II). Inverse addition (lithium enolate to dichlorodimethylsilane) also decreased the amount of polymer, but a new impurity was formed. Removal of this impurity, tentatively assigned as **8**, was especially problematic

since it co-distilled with the desired product. A two-step synthesis in which one of the silicon-oxygen bonds was preformed (by addition of dichlorodimethylsilane (10 equiv) and triethylamine to the prolinol propionamide prior to enolization) also produced **7**, but the reaction was not as clean. The alternative bases lithium hexamethyldisilazane and potassium hexamethyldisilazane failed to enolize the amide completely as determined by ^{1}H NMR of crude reaction mixtures.

Reaction of *O*-silyl ketene *N,O*-acetal **7** with benzaldehyde at room temperature produced adducts **9** and **10** in a 39:1 ratio.[8]



Anti aldol product **9** crystallized directly from the reaction mixture in 77% yield. The anti stereochemical assignment of **9** was suggested by the observation of a 9.7 Hz coupling constant between protons H2 and H3. X-ray crystallography confirmed the assignment and further established the product as the (2*S*,3*R*)-*anti* stereoisomer (Figure 1).[11] This product results from attack of the aldehyde on the more hindered concave face of the enolate, supporting the idea that the aldehyde is directed to that face by prior coordination, perhaps in a cyclic transition state. The reaction takes place readily in noncoordinating solvents (CH_2Cl_2, hexanes, benzene) but is slow in coordinating solvents (THF, DMF), an observation supporting coordination of the aldehyde to the silicon.



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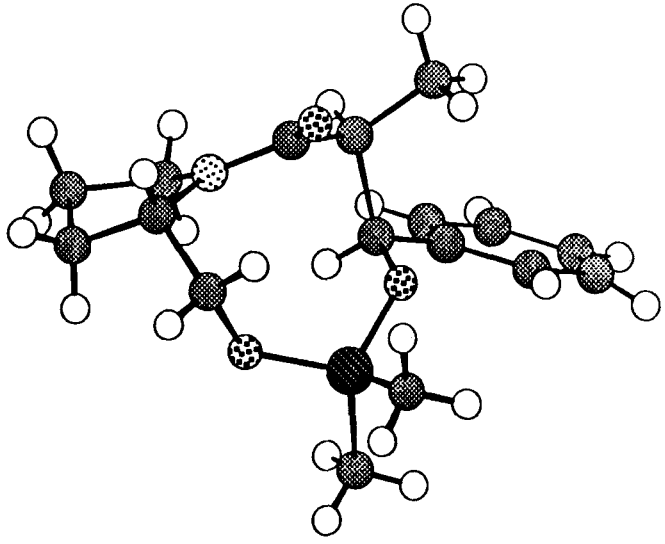

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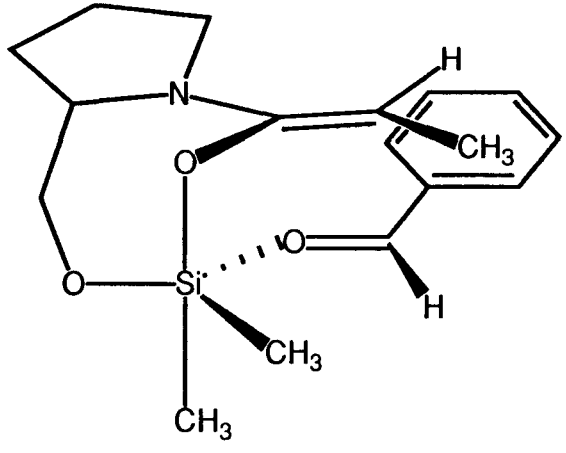
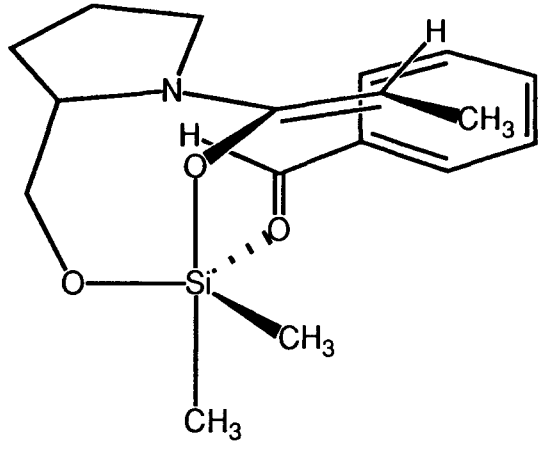


T_{boat}



T_{chair}

Figure 1

Interestingly, the reaction is quite rapid in acetonitrile, which is often considered a coordinating solvent. However; acetonitrile coordination usually contains a large π back-bonding component and silicon is a poor π acceptor. The rate of the reaction in hexanes ($\epsilon = 2$) is similar to that in acetonitrile ($\epsilon = 37$) a fact which disfavors mechanisms that involve highly polar transition states (e.g., an open transition state).

The formation of monomeric 9-membered ring siloxanes is also suggestive of a pericyclic transition state. These products (**9** and **10**) appear to be unstable with respect to polymerization and can not be formed directly from the diols and difunctional silicon compounds ($(CH_3)_2SiCl_2$, $(CH_3)_2Si(N(CH_3)_2)$), even under high dilution conditions.

A small amount (2%) of syn aldol adduct **10** was also isolated from the reaction mixture. The syn stereochemical assignment is suggested by the small coupling constant (3.9 Hz) between protons H2 and H3. X-ray crystallography[11] establishes the product as the (2*S*, 3*S*)-*syn* stereoisomer, resulting from attack on the same π face of the enolate, but the opposite π face of the aldehyde. No products resulting from attack on the convex face of the enolate were observed.

Crystal structures **9** and **10** provide insight into the mechanism of the reaction. In each structure, the amide carbonyl lies over one face of the silicon-centered tetrahedron; with the carbonyl oxygen in van der Waals contact with the silicon. The portion of the molecule derived from the enolate reflects the original *Z* orientation. It is easy to visualize the hypothetical transition states $\mathbf{T_{boat}}$ and $\mathbf{T_{chair}}$ within structures **9** and **10** by reversing the bond formation of the aldol reaction. More accurately, the transition states are viewed to lie somewhere *between* $\mathbf{T_{boat}}$ and **9**, and $\mathbf{T_{chair}}$ and **10**; however, for simplicity they will be referred to as $\mathbf{T_{boat}}$ and $\mathbf{T_{chair}}$. The important features of these hypothetical transition states are: (1) the silicon is trigonal bipyramidal, (2) the enol oxygen is apically bonded to the silicon through a p-type orbital, and (3) the aldehyde is

equatorially bonded to the silicon through the carbonyl lone pair which is trans to the phenyl ring. This transition state is supported by crystal structures of silyl enol ethers in which Si-O-C=C dihedral angles range from 60 to 120 degrees.[12] The Si-O-C angle for the enol oxygen in the hypothetical transition states $\mathbf{T_{boat}}$ and $\mathbf{T_{chair}}$, is smaller than the typical Si-O-C angle in these crystal structures (110°-150°) because the enol oxygen in these transition states is bonded to the silicon through a p-type orbital instead of a sp^3 hybridized orbital.[12,13] An appealing feature of this hypothesis is that bonding of the enol oxygen to the silicon through a p-type orbital allows for continuous overlap during C–C bond formation and Si–O bond cleavage.

The unusual anti selectivity of this reaction is believed to result from a boat-like transition state (as represented in $\mathbf{T_{boat}}$) and stands in contrast to chair-like transition states invoked for other metalloenolate reactions. The minor stereoisomer is believed to be produced by a chair transition state. Two possible reasons for this preference are suggested. First, the boat transition state provides better overlap between the π systems of the aldehyde and the *O*-silyl ketene *N,O*-acetal. Second, the boat transition state lacks the unfavorable steric interaction between the interior hydrogen on the CH_2O and the aldehyde proton which is present in the chair transition state. The latter is probably not solely responsible for the anti selectivity observed since the achiral *O*-silyl ketene *N,O*-acetals **1** and **2** are also anti selective.

Aldol reactions of *O*-silyl ketene *N,O*-acetal **7** with aliphatic aldehydes are found to proceed with even greater diastereoselectivity than with benzaldehyde (Table III). The stereochemistry of the aliphatic aldol adducts is assumed to be analogous to the stereochemistry observed with the benzaldehyde adduct, an assertion supported by the similarity in coupling constants between protons H2 and H3 exhibited by these products (J_{23} = 9.7, 9.7, and 9.3 Hz for R = Ph, *i*-Pr, and Et, respectively).

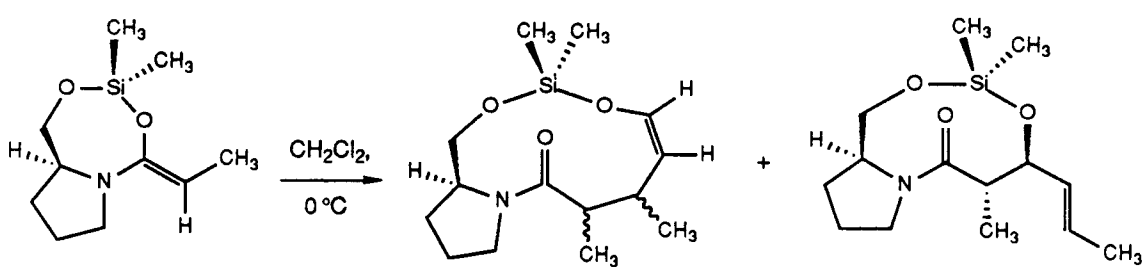
Table III. Diastereoselective Addition Reactions of **7** with Aldehydes

RCHO	Diastereoselectivity[a]			(2*S*)-*anti*	
	%(2*S*)-*anti*	%(2*S*)-*syn*	%(2*R*)-*anti,syn*[b]	yield (%)[c]	mp (°C)
Ph-	97.2	2.5	0.3	77	50-51
i-Pr-	98.5	0.7	0.8	68	77-79
Et-	97.7	1.3	1.0	58	33-35

[a]Based on capillary GC and highfield NMR analysis of crude reaction mixtures. Numbers for (2*S*)-diastereomers are minimum values. [b]Maximum combined yield of (2*R*)-diastereomers as estimated by capillary GC. [c]Isolated yield of pure (2*S*)-*anti* diastereomer.

The Si–O bonds of the 9-membered ring siloxanes are relatively stable to hydrolytic cleavage, and the siloxanes can be isolated by crystallization or by silica gel chromatography.[14] Further investigation reveals that the yields of aldol products can be improved by employing higher reaction temperatures, with little decrease in diastereoselectivity. Reaction of benzaldehyde with *O*-silyl ketene *N,O*-acetal **7** at 60 °C gave pure **9** in 88% isolated yield.

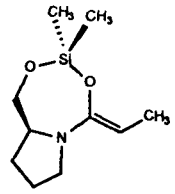
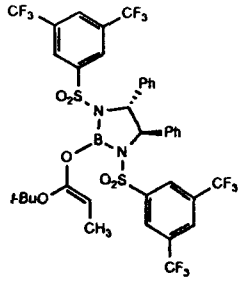
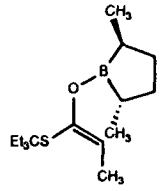
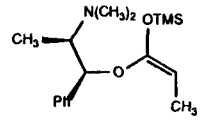
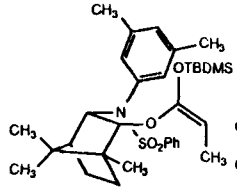
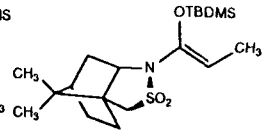
Interestingly, crotonaldehyde reacted with **7** in a predominantly Michael fashion to produce a 7:1 ratio of two diastereomeric 11-membered ring *O*-silyl enol ethers (stereochemistry not known).



7 73% (7:1) 5%

It is worthwhile to compare the diastereoselectivity of aldol reactions of **7** with the existing methods for anti aldol bond construction (Table IV).[15]

Table IV[15a-e]

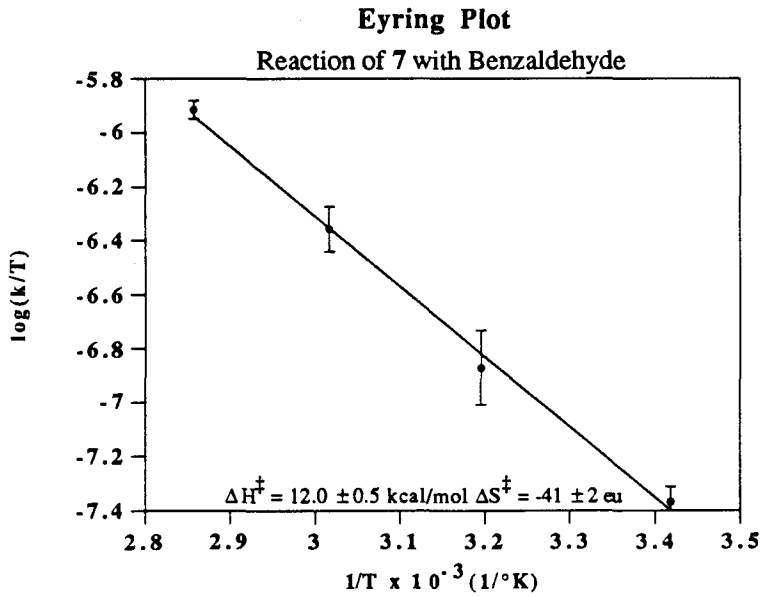
Ketene *N,O*-acetal						
	7	**11**	**12**	**13**	**14**	**15**
Lewis acid	-	-	-	$TiCl_4$	$TiCl_4$	$TiCl_4$
Aldehyde	Diastereoselectivity (%)					
	7	**11**	**12**	**13**	**14**	**15**
C_6H_5CHO	97.2	95.1	94.9	93.7	-	99.5
$(CH_3)_2CHCHO$	99.6	-	94.4	-	92	98.9
C_2H_5CHO	97.4	-	93.5	76.4	-	99.2

These methods often require lengthy syntheses (**11** and **12**), expensive starting materials (**14** and **15**) or Lewis acid co-reagents (**13**, **14** and **15**). Interestingly, *O*-silyl ketene *N,O*-acetal **15** is the only other substrate which has a *Z* configuration. It has been proposed that the aldol reaction of **15** proceeds by an open transition state, rather than the boat transition state believed to operate in our system.[15e]

As previously mentioned, the solvent effects and product structures in the reaction of *O*-silyl ketene *N,O*-acetal **7** with benzaldehyde suggested an associative mechanism in which the aldehyde binds to silicon prior to aldol condensation (equation 1).[16]

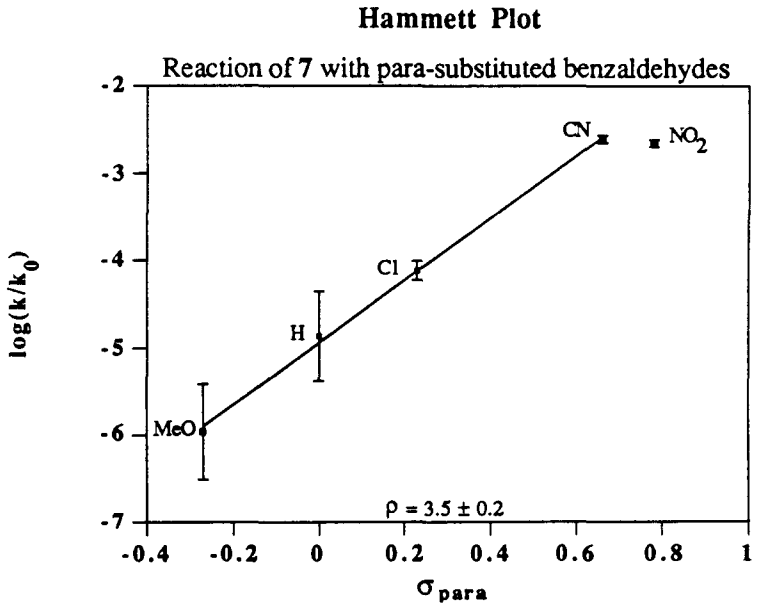
$$\mathbf{7} + \mathrm{PhCHO} \underset{?}{\rightleftharpoons} \{\mathbf{7} \cdot \mathrm{PhCHO}\} \longrightarrow \mathbf{9} \qquad (1)$$

Because of the unique features of this reaction, we decided to study it in more detail. Kinetic analysis of the reaction of **7** with benzaldehyde over a 60-degree range showed that it was second-order overall, and first-order in each reagent.[17,18] The following activation parameters were obtained from the Eyring plot: $\Delta H^{\ddagger} = 12.0 \pm 0.5$ kcal/mol and $\Delta S^{\ddagger} = -41 \pm 2$ eu. Both the reaction order and the large negative entropy of activation are consistent with the associative mechanism proposed in equation 1.



Reaction of **7** with a 1:1 mixture of C_6H_5CHO:C_6H_5CDO (10.5 equiv) afforded the anti aldol adduct **9** disproportionately enriched in deuterium (50% yield). The calculated secondary isotope effect (k_H/k_D = 0.76) is close to the theoretical maximum (~0.71),[19] suggesting the existence of a later transition state, involving carbon–carbon bond formation instead of aldehyde coordination. The direction of the deuterium isotope effect (k_H/k_D < 1) supports the proposed mechanism wherein the hybridization of the carbon bonded to H/D undergoes an increase in p-character.[20]

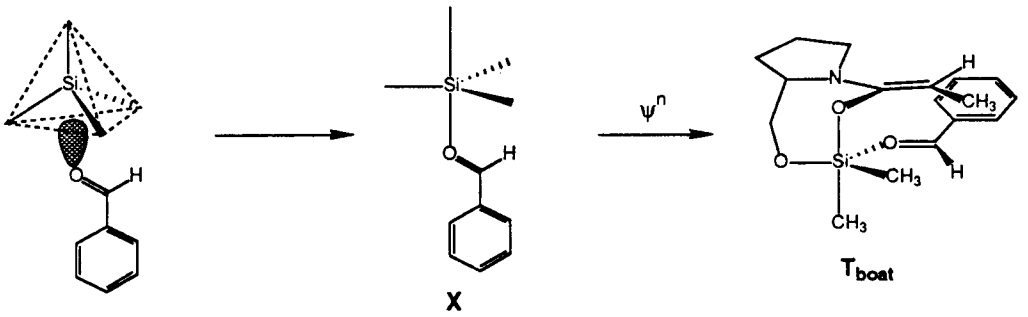
Kinetic analysis of the reaction with a series of para-substituted benzaldehydes showed that electron-withdrawing groups greatly accelerate the reaction (Hammett ρ = 3.5 ± 0.2).[21]



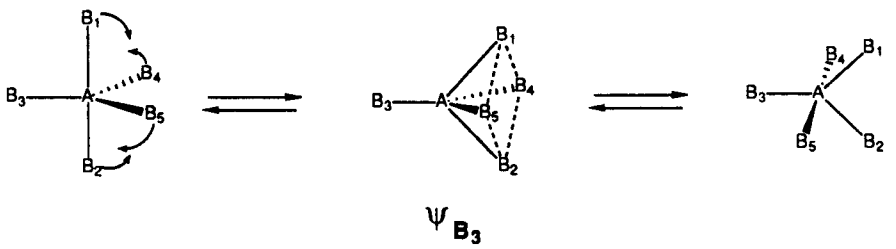
This result also supports a later transition state, involving carbon–carbon bond formation. By contrast, rate-determining aldehyde coordination would be anticipated to exhibit a negative ρ value.[22] At high σ values the Hammett plot becomes nonlinear, indicating a change in mechanism. This is interpreted as a shift towards an earlier transition state involving aldehyde complexation. The positive ρ value is likely attributable to a

destabilization of the ground state by electron-withdrawing groups, rather than a stabilization of the transition state.[23]

The hypothetical transition state $\mathbf{T_{boat}}$ contains equatorially-bound aldehyde. Direct formation of $\mathbf{T_{boat}}$ requires attack on the edge of the silicon-centered tetrahedron.[24]



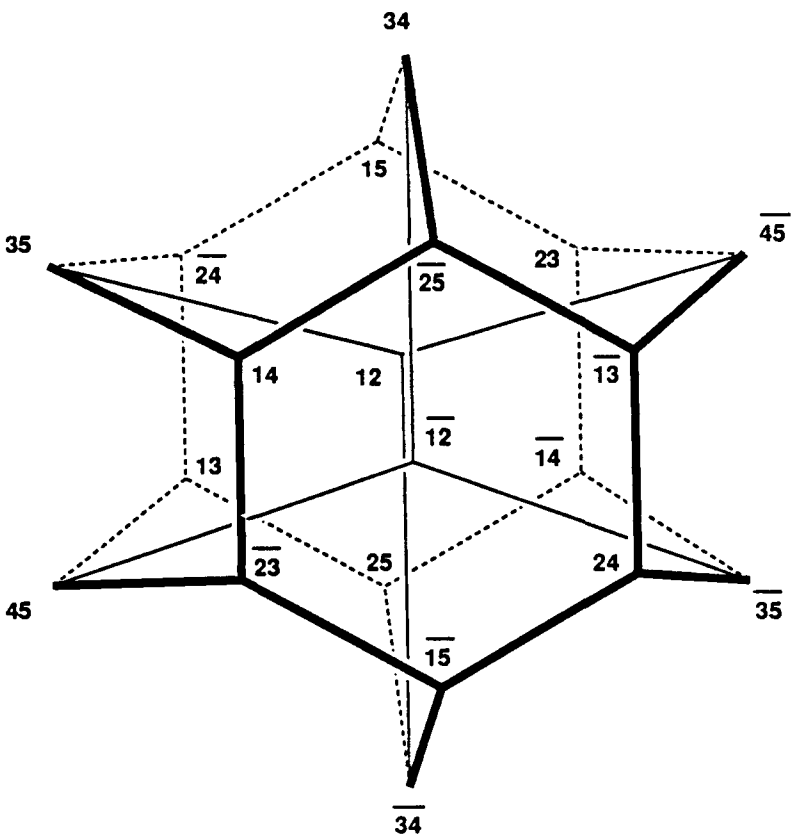
Alternatively, formation of $\mathbf{T_{boat}}$ may arise by facial attack of benzaldehyde, forming trigonal bipyramid **X**. One or more pseudorotations (ψ^n) then may transform this intermediate with apically-bound benzaldehyde into $\mathbf{T_{boat}}$.[25] This theory is more consistent with the consensus of mechanistic and theoretical studies concerning pentavalent silicon since it allows for apical attack of the aldehyde.[24,25]



First proposed in 1960, Berry pseudorotation is the most commonly invoked mechanism for interconversion of two isomeric trigonal bipyramids.[27,28] The process is

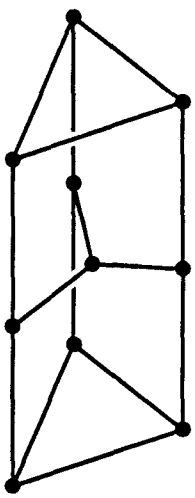
believed to go through an intermediate square-pyramid which is accessed by simultaneous opening of the B_4AB_5 angle and closing of the B_1AB_2 angle.

For a trigonal bipyramid with five different ligands there are twenty unique isomers. Each trigonal bipyramid can be converted into three other isomers by pseudo-rotation around one of its three equatorial ligands. These isomers and the pseudorotations interconverting them can be represented by the Desargues-Levi graph shown below.[29]



Deargues-Levi graph projected on a plane. Vertices represent isomeric tbps and the lines represent pseudorotations interconverting those structures. Each isomer is designated by the indices of its apical ligands. Thus 14, has ligands 1 and 4 apical and $\overline{1}\ \overline{4}$ is its mirror image.[26b]

Analysis of all possible tbp isomers of {**7**•PhCHO} is simplified by the presence of two identical ligands. This reduces the number of possible stereoisomers from 20 to 10. The graphical representation of these isomers can be represented by the trigonal prism shown below. The dots on the graph represent the tbp isomers and the lines represent pseudorotations interconverting those isomers.[25b]



The center point of the prism represents the structure where the two identical ligands are axial. The other points in the central plane represent structures where the two identical ligands are equatorial.

The graph can be further simplified for the 7-membered ring *O*-silyl ketene *N,O*-acetal **7**. The isomer which requires the 7-membered ring to span the axial positions can be eliminated from further consideration (this structure is extremely strained) thus reducing the number of plausible structures to nine (Figure 2). Study of this figure shows that isomer **T** lies one pseudorotation from isomers **G** and **A**, each with apically-bound benzaldehyde. The other two tbps with apically-bound benzaldehyde (**E** and **C**) require at least two pseudorotations to form **T**.

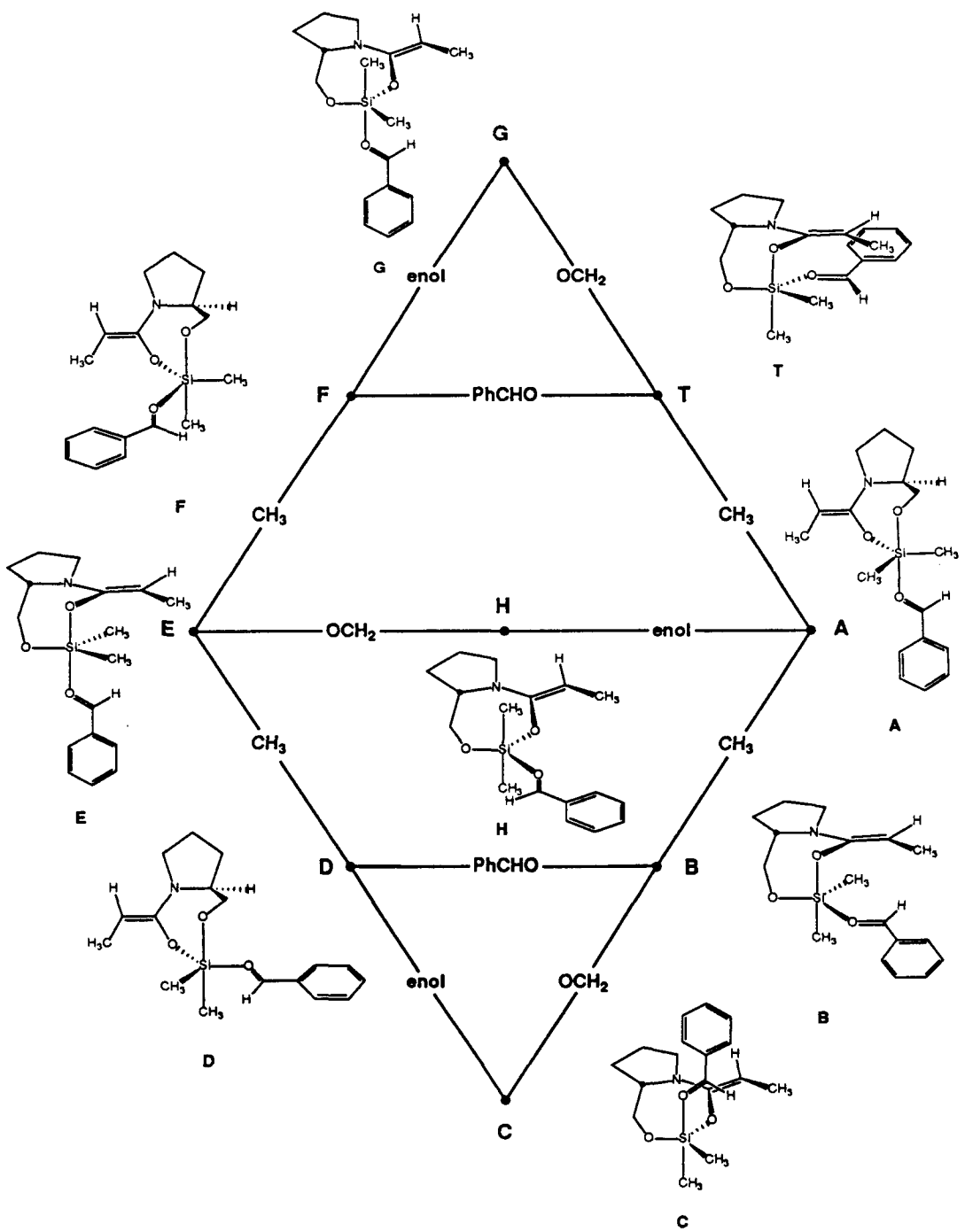
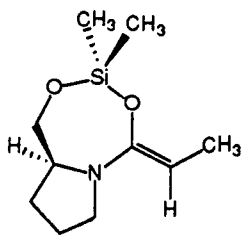
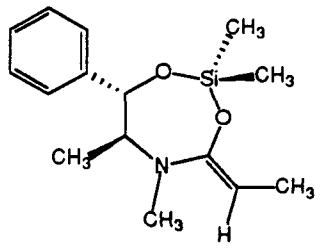


Figure 2. A graph of all tbp *O*-silyl *N,O*-acetal **7**•benzaldehyde complexes and pseudorotational paths interconverting these isomers (the isomer where the 7-membered ligand spans axial positions is omitted).

Attempts to observe any reaction intermediates, by ^{13}C or ^{1}H NMR were unsuccessful. Solutions of benzaldehyde (1.6 M) and **7** (1.3 M) in $C_6D_5CD_3$ showed no evidence of complex formation between -80 °C and 23 °C. Thus, if an equilibrium between PhCHO and {PhCHO•**7**} exists, it lies far to the left ($K_{eq} \leq 0.03$). A number of other complexing agents were also examined with *O*-silyl ketene *N,O*-acetals **7** and **16** (Table V, *vide infra*).



7



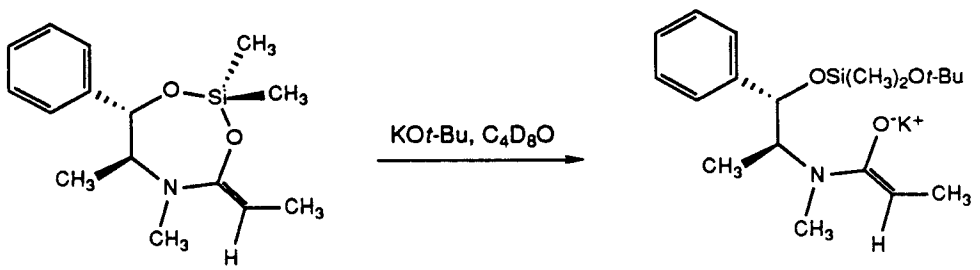
16

Table V

Reagents (conc., M)		Deuterated		Estimated detection limit for	Upper limit for
N,O-acetal	Lewis base	solvent	Comments	complex formation (%)	K_{eq}
7 (1.3)	PhCHO (1.6)	toluene	no complexation	3[a]	0.03
7 (1.3)	HMPA (1.5)	toluene	"	5[a]	0.07
7 (0.13)	DMF (d_7) (12)	DMF	"	20[b]	0.02
7 (0.07)	THF (d_8) (11)	THF	"	20[b]	0.02
7 (0.66)	TASF (0.71)	THF	decomposition[c]	-	-
7 (0.66)	KO*t*-Bu (1.3)	THF	potassium enolate	-	-
16 (1.1)	HMPA (1.6)	toluene	no complexation	5[a]	0.12
16 (1.1)	DMF (4.1)	toluene	"	3[a]	0.03
16 (0.86)	TASF (0.76)	THF	decomposition[c]	-	-
16 (0.46)	KO*t*-Bu (0.76)	THF	potassium enolate	-	-

[a]Determined from ^{13}C chemical shifts of Lewis base. [b]Determined from ^{1}H chemical shifts of *O*-silyl ketene *N,O*-acetal. [c]No enolic peaks other than starting material observed.

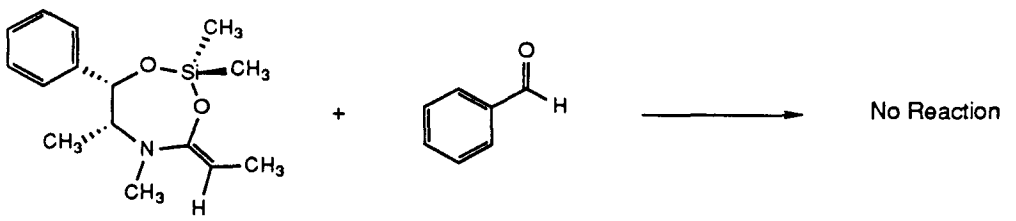
Only potassium *tert*-butoxide reacted cleanly with either *O*-silyl ketene *N,O*-acetal. The reaction product formed from **16** and KO*t*-Bu displayed a peak at δ 7 in the ^{29}Si NMR spectrum, suggesting formation of the potassium enolate rather than a pentavalent silicon complex.[30]



16

It is interesting to note that pathways which involve odd numbers of pseudorotations invert the configuration of the central atom. In the case of **7** and **16** reversible complexation of benzaldehyde interceded by an odd number of pseudorotational steps will serve to exchange the diastereotopic methyl groups. We never observed coalescence of the methyl groups under any conditions and thus conclude that a hypothetical reaction path such as **G→T→F→G** is slow on the NMR time scale.

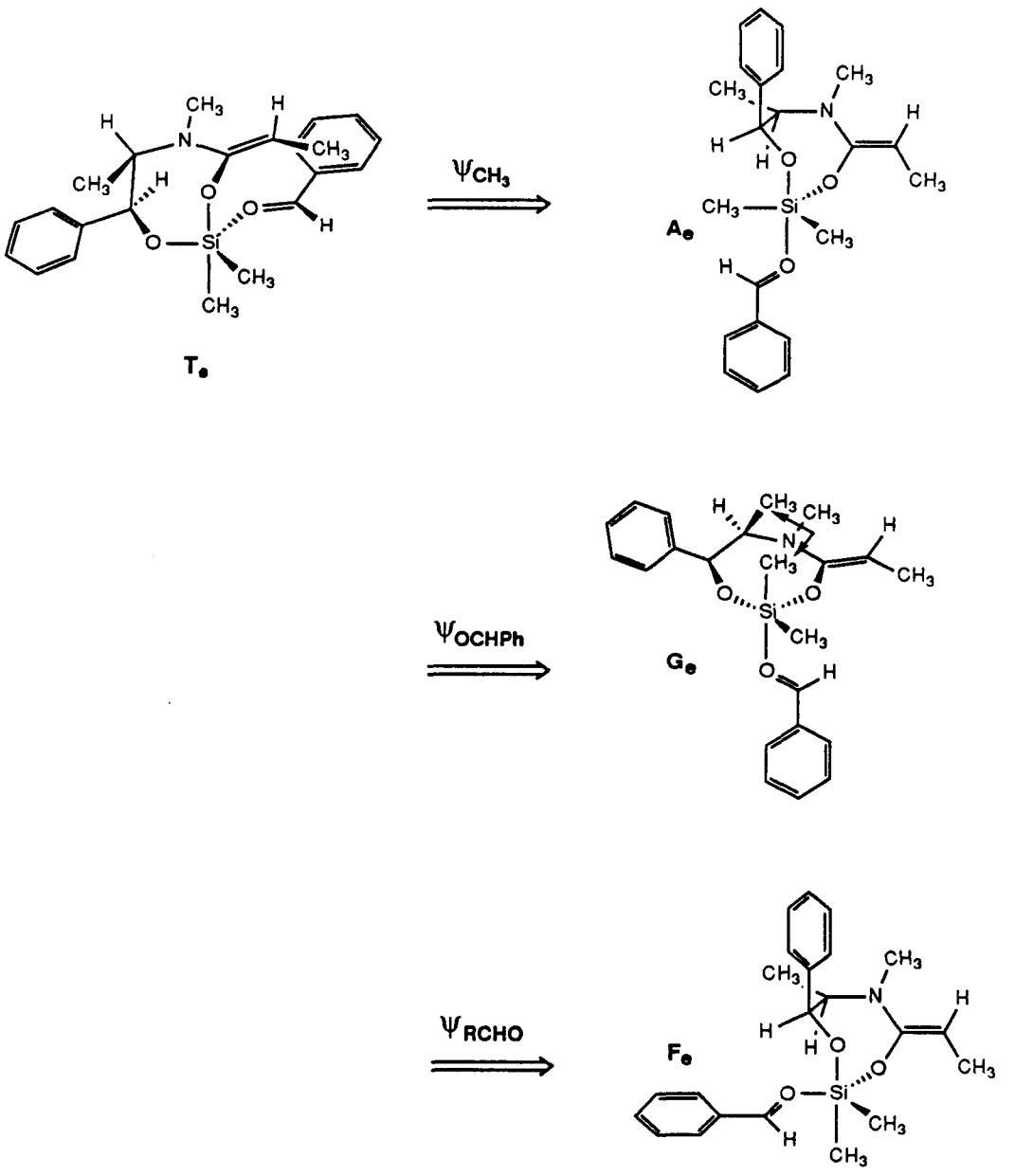
Although direct experimental evidence for a tbp precursor does not exist, some indirect information is available from a parallel study, in which Dr. Paivi Kukkola synthesized the *O*-silyl ketene *N,O*-acetal **17** derived from (1*R*,2*S*)-ephedrine.[31] Dr. Kukkola found that **17** did not react with benzaldehyde, even under forcing conditions (110 °C, slow addition of **17**).



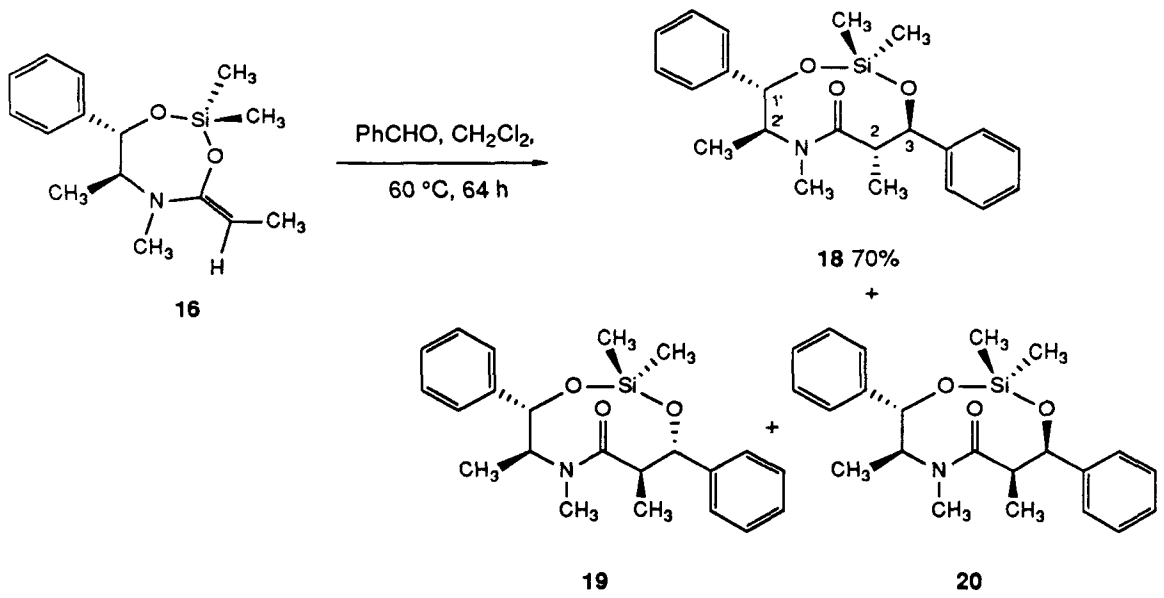
17

The analogous transition state ($\mathbf{T_e}$)[31] for substrate **17** appears quite reasonable and offers no explanation for the lack of reactivity of **17** (see page 23). However, consideration of the tbp precursors of **17** suggest a rationale for the observed reactivity difference between **7** and **17**. Derivation of the pseudorotational pathway is easier when the process is analyzed in reverse. Of the three tbps accessible from $\mathbf{T_e}$ by a single pseudorotation only $\mathbf{G_e}$[31] explains the experimental results observed. Examination of $\mathbf{G_e}$ reveals a severe steric interaction between the methyl group on the 7-membered ring and the apical aldehyde. Since $\mathbf{G_e}$ contains apically-bound benzaldehyde it can be immediately decomposed to **7** and benzaldehyde without further pseudorotation.

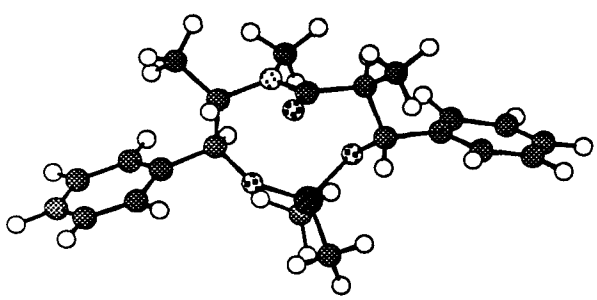
In contrast, the structures $\mathbf{A_e}$[31] and $\mathbf{F_e}$[31] do not appear to be sterically encumbered. A pathway involving $\mathbf{F_e}$ is unlikely because this pathway requires pseudorotation around benzaldehyde which is the most apicophilic ligand. At present, it is unclear which features disfavor $\mathbf{A_e}$. It may be the case that attack of benzaldehyde on **17** to form $\mathbf{A_e}$ is disfavored for steric reasons.



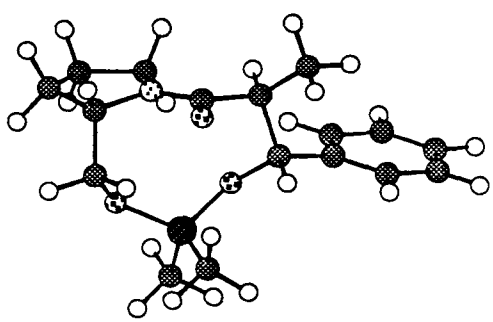
Inspection of the tbp $\mathbf{G_e}$ suggests that a viable intermediate might be produced by epimerization of the axial methyl group on the enolate ligand. To test this theory the (1*S*,2*S*)-pseudoephedrine-derived *O*-silyl ketene *N*,*O*-acetal **16** was synthesized.[32]



O-Silyl ketene *N,O*-acetal **16** reacted with benzaldehyde at 60 °C to form the (2*S*,3*R*)-*anti* aldol product **18** in 70% yield. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed three isomers (**18**, **19**, and **20**) were present in a 9.2:1.0:1.7 ratio, respectively. X-ray analysis establishes the major product **18** as the (2*S*,3*R*)-*anti* isomer.[33] The similarities between this structure and the prolinol-derived crystal structure **9**, support but do not prove a common reaction mechanism.

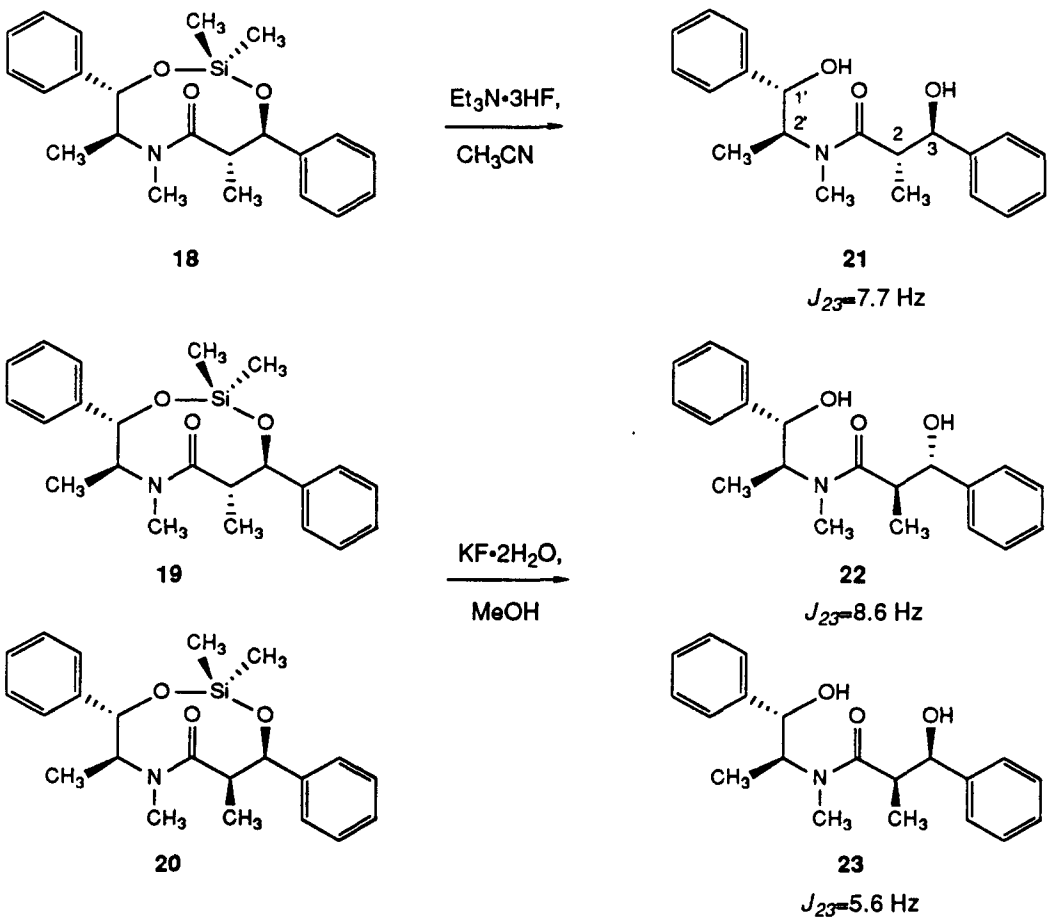


Crystal Structure of **18**



Crystal Structure of **9**

The relative stereochemistry of the C2 and C3 centers in siloxanes **19** and **20** was tentatively assigned by converting the siloxanes to their respective diols **22** and **23** and examining the coupling constant between protons H2 and H3 (J_{23} = 8.3 and 5.6 Hz for diols **22** and **23**, respectively).



18

21
J_{23}=7.7 Hz

19

22
J_{23}=8.6 Hz

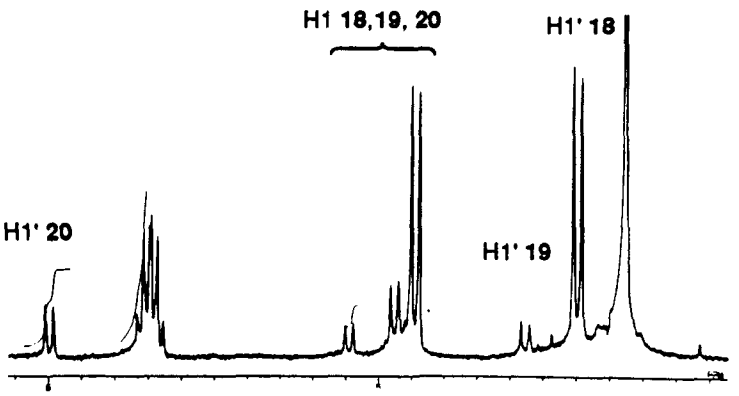
20

23
J_{23}=5.6 Hz

These coupling constants suggested a syn stereochemical assignment for **20** and an anti stereochemical assignment for **19** (the protons H1' and H3 were assigned by spectroscopic analysis of the products isolated from reaction of **16** with C_6H_5CDO).[2] For the purposes of comparison, the major product **18** was also desilylated; the resulting diol

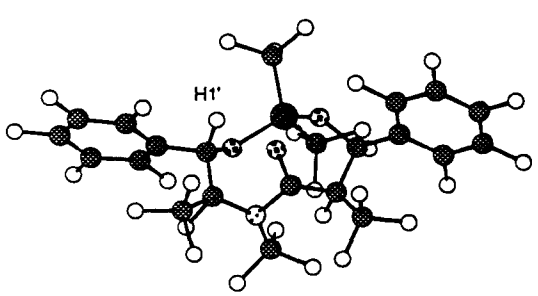
had a proton coupling constant (J_{23}) of 7.7 Hz, consistent with the anti stereochemical assignment determined from the X-ray crystal structure.

The absolute stereochemistry of C2 and C3 of the syn stereoisomer **20** was tentatively assigned by examining the ^{1}H NMR spectrum of this compound. Proton H1' was much more deshielded in isomer **20** (δ 5.99) than in either isomer **18** (δ 4.39) or **19** (δ 4.54).

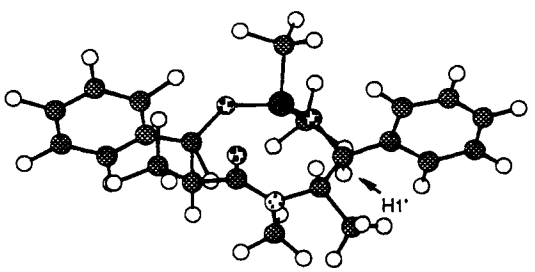


Midfield region of ^{1}H NMR for crude reaction mixture from reaction of 16 with benzaldehyde

Models of the (1'*S*,2'*S*,2*R*,3*R*)-*syn* stereoisomer predict that the H1' proton will be about 2Å away from the carbonyl oxygen which could lead to significant deshielding. There is no obvious reason why proton H1' should be shifted so far downfield in the (1'*S*,2'*S*,2*S*,3*S*)-*syn* stereoisomer.

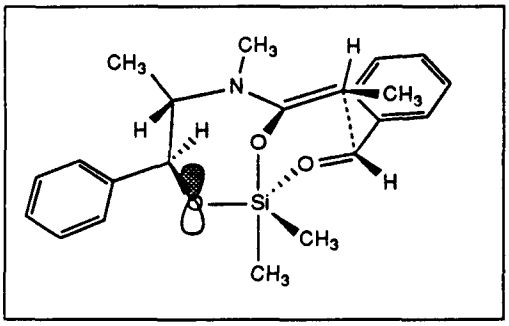


(1'*S*,2'*S*,2*R*,3*R*)-*syn* stereoisomer **20**

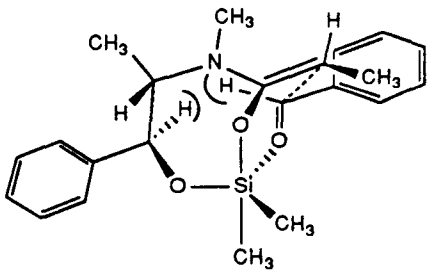


(1'*S*,2'*S*,2*S*,3*S*)-*syn* stereoisomer

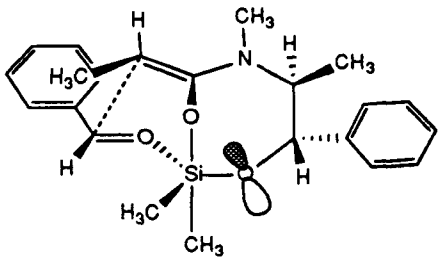
An examination of the four hypothetical transition states gives a possible explanation for the selectivity observed.



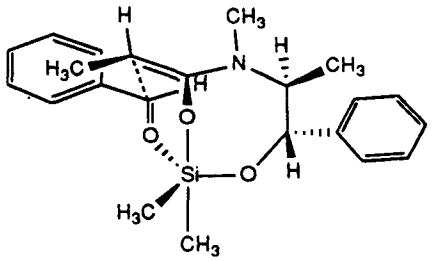
attack on
Si face of enolate
Anti-**18**



attack on
Si face of enolate
Syn not observed



attack on
Re face of enolate
Anti-**19**

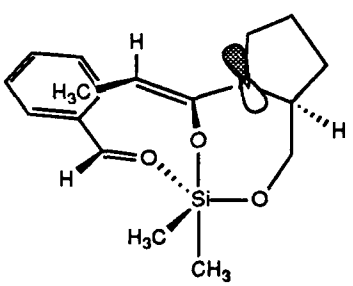


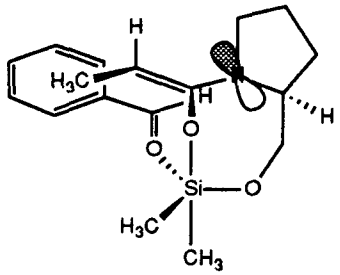
attack on
Re face of enolate
Syn-**20**

Attack appears to occur predominantly from the *Si* face of the enolate, via a boat-like transition state.[34] This transition state is probably favored for considerations of overlap. The syn product resulting from attack on the *Si* face of the enolate is not observed because in the corresponding chair-like transition state there appears to be a unfavorable steric interaction between the aldehydic proton and the H1' proton on the enolate. The π overlap also seems poor in this transition state. Attack from the *Re* face of the enolate also occurs to a limited extent and may be disfavored by poorer overlap. It is interesting to note that attack at the *Re* face favors syn aldol formation.

The hypothetical transition states resulting from attack at the *Re* face of the enolate have the p-orbitals of the equatorial OCHPhR ligands parallel to the equatorial plane while in the other transition states this orbital is perpendicular. Calculations on pentavalent phosphorous indicate that the former orientation is favored thermodynamically for π donors,[35] although the larger radius of silicon should diminish the importance of this effect.[36] In any case, these effects are apparently outweighed by the better π overlap obtained by attack on the *Si* face of the enolate from a boat transition state.

Models suggest that it is difficult for the nitrogen lone pair to conjugate fully with the enol double bond when attack occurs at the *Re* face of the prolinol-derived *O*-silyl ketene *N,O*-acetal **7**. This may be responsible for the almost perfect facial selectivity of **7**.



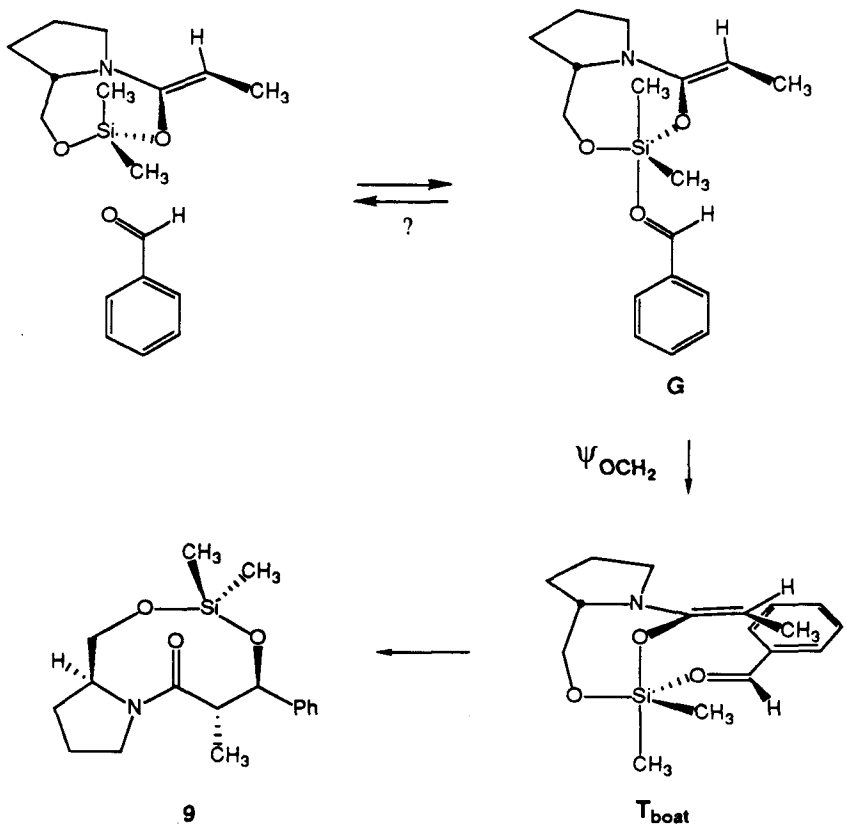


attack on
Re face of enolate
not observed

Although crystal structures of *O*-silyl ketene *N,O*-acetals[12] and lithium amide enolates[37] show that the nitrogens are at least partially pyramidalized and hence not fully conjugated with the enol double bond, it is reasonable to assume that conjugation might be a necessary condition for these (late) aldol transition states, since planar amides are produced.[11]

In summary, we have discovered that *O*-silyl ketene *N,O*-acetals undergo aldol condensation without catalysis. The chiral *O*-silyl ketene *N,O*-acetal **7** reacts with

aldehydes at room temperature to produce a single anti diastereomer, with > 98% diastereoselectivity. The unusual selectivity observed for this *Z* enolate is rationalized by invoking the boat transition state $\mathbf{T_{boat}}$. Since $\mathbf{T_{boat}}$ contains apically-bound aldehyde, it is probably not formed directly by attack of the aldehyde on the *O*-silyl ketene *N,O*-acetal **7**. Instead the silicon-centered tetrahedron suffers facial attack forming **G**. This trigonal bipyramid then undergoes pseudorotation about the OCH_2 ligand to form the transition state $\mathbf{T_{boat}}$.



Although other mechanisms are not ruled out, this is the simplest mechanism which explains the differences in reactivity observed with the ephedrine- and pseudoephedrine-derived *O*-silyl ketene *N,O*-acetals. Kinetic analysis of the reaction is consistent with the

associative mechanism shown and suggests that carbon–carbon bond formation is involved in the rate-determining step.

Experimental Section

Melting points were recorded with a Büchi SMP-20 melting point apparatus and are uncorrected. Infrared spectra were recorded with a Beckman 4240 Infrared spectrometer or a Perkin Elmer 1600 FTIR spectrometer. Data are represented as follows: frequency of absorption (cm^{-1}), and intensity of absorption (s=strong, m=medium, w=weak, br=broad). The ^{1}H NMR spectra were recorded on a JEOL JNM-GX400 (400 MHz) NMR spectrometer; peaks are reported in ppm (δ scale), using the residual solvent peak as reference ($CHCl_3$:7.26, C_6D_5H:7.15). Data are represented as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, qn=quintet, m=multiplet, br=broad), integration, coupling constants in Hertz, and assignment. The ^{13}C NMR were obtained on a JEOL FX-90Q (22.5 MHz) or a JEOL JNM-GX400 (100 MHz) NMR spectrometer and are reported in ppm (δ scale) using the solvent as reference. The ^{29}Si NMR were obtained on a JEOL FX-90Q (17.87 MHz) or a JEOL JNM-GX400 (79.43 MHz) NMR spectrometer and are reported in ppm (δ scale) using tetramethylsilane (0 ppm) as reference. Combustion analyses were performed by Mr. Fenton Harvey (California Institute of Technology). Crystal structures were obtained by Dr. Bill Schaefer, Dr. Richard Marsh, and Mr. Lawrence Henling (California Institute of Technology). Mass spectra and high resolution mass spectra were obtained from the UC Riverside Mass Spectrometry Facility.

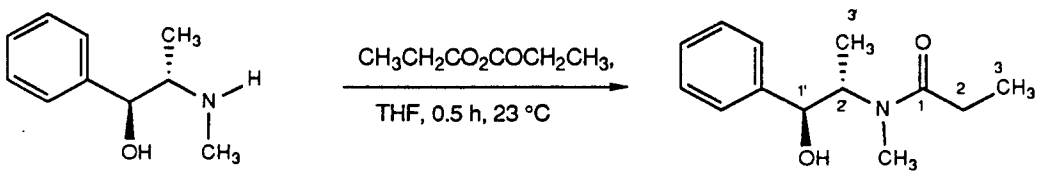
Analytical gas-liquid chromatography (GC) was carried out on a Hewlett Packard 5890 gas chromatograph equipped with a splitless mode capillary injection system and a flame ionization detector, using a 25 m x 0.2 mm x 0.5 μm HP-5 flexible, fused silica capillary column coated with 5% Phenyl Methyl Silicone or a 25 m x 0.25 mm Alltech Chirasil-Val III chiral fused silica capillary column. Data are reported as follows: column type, oven temperature, and retention time.

Liquid chromatography was performed using a forced flow (flash-chromatograpy)[38] with the indicated solvent using JT Baker Silica Gel (40 μm) or Merck Silica Gel 60 (230-400 mesh ASTM). Analytical thin-layer chromatography was performed using Merck pre-coated silica gel 60 F-254 plates (0.25 mm, glass-backed, fluorescent at 254 nm).

Tetrahydrofuran and diethyl ether were distilled from sodium-benzophenone ketyl. *N,N*-Dimethylformamide, acetonitrile, methylene chloride, hexanes, pyridine, triethylamine, diisopropylamine, and HMPA were distilled at reduced pressure from calcium hydride. Benzene and toluene were distilled from sodium. Toluene (d_9), C_6D_6, and 1,1-diphenylethylene were dried over activated 3-Å molecular sieves. *N,N*-Dimethylformamide (d_7), and CD_2Cl_2, were vacuum transferred from CaH_2 and stored in the glovebox. Tetrahydrofuran (d_8) was vacuum transferred from sodium-benzophenone ketyl and was stored in a nitrogen-filled glovebox. All nonaqueous reactions were performed in flame-dried glassware under argon, unless otherwise noted. Deoxygenation of solutions was accomplished by evacuating and flushing the solutions with argon five times, unless otherwise specified. Organic solutions were concentrated on a Büchi rotatory evaporator at 10-20 Torr, unless otherwise specified. Solvents used in the workup and purification of compounds were HPLC-reagent grade and were used without further purification.

Benzaldehyde and dimethyl acrylamide were distilled from CaH_2 under reduced pressure. Propionaldehyde, isobutryaldehyde, and crotonaldehyde were distilled from $CaCl_2$ immediately prior to use. Triethylsilane, triethoxysilane and oxalyl chloride were distilled prior to use. Dichlorodimethylsilane was distilled from magnesium. Potassium *tert*-butoxide was sublimed under vacuum (0.1 Torr) and stored in a nitrogen-filled

glovebox. The molarity of *n*-BuLi was determined by titration against diphenylacetic acid.[39] All other reagents were used as received.



92%

Synthesis of (1'*S*,2'*S*)-Pseudoephedrine Propionamide

Propionic anhydride (21.3 mL, 166 mmol, 1.1 equiv) was added over 10 min to a solution of (1*S*,2*S*)-(+)-pseudoephedrine (25.0 g, 152 mmol, 1.0 equiv) in THF (250 mL). The solution was stirred for 30 min, then was partitioned between ethyl acetate (250 mL) and saturated aqueous sodium bicarbonate solution (200 mL). The organic layer was separated and the aqueous layer was washed with two 200-mL portions of ethyl acetate. The organic phases were combined, dried over sodium sulfate, filtered and concentrated *in vacuo*. Recrystallization of the solid product (70% ether-CH_2Cl_2), afforded two batches of (1'*S*,2'*S*)-pseudoephedrine propionamide (30.57 g, 92%, mp: 114.5-115.0 °C) as a white, crystalline solid.

(1'*S*,2'*S*)-Pseudoephedrine Propionamide (rotameric mixture)

^{1}H NMR (400 MHz, C_6D_6): 7.00-7.38 (m, 5H, arom), 4.88 (s, 1H, OH), 4.52 (t, 1H, *J*=6.0, H1'), 4.19 (s, 1H, OH), 4.12 (t, 1H, *J*=8.0, H1'), 3.68 (m, 1H, H2'), 3.07 (m, 1H, H2'), 2.78 (s, 3H, NCH_3), 2.44 (m, 2H, H2), 2.08 (s, 3H, NCH_3), 1.73 (m, 2H, H2), 1.21 (t, 3H, *J*=7.5, H3), 1.01 (t, 3H, *J*=7.5, H3), 0.95 (d, 3H, *J*=8.0, H3'), 0.55 (d, 3H, *J*=8.0, H3').

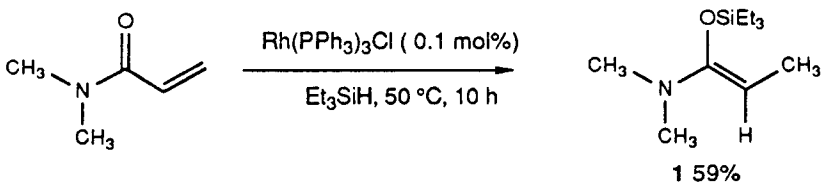
FTIR (neat film), cm^{-1}: 3378 (m), 2966 (m), 1614 (s), 1449 (m), 1402 (m), 1402 (w), 1296 (w), 1120 (w), 1049 (m), 1020 (w), 767 (w), 703 (m).

MS (CI:NH_3): 222 (MH^+), 204 (MH^+-H_2O).

HRMS (CI:NH_3): Calculated for $C_{13}H_{20}NO_2Si$ (MH^+): 222.1494
Found: 222.1488

TLC (ether):

Pseudoephedrine propionamide	0.51 (UV)
Pseudoephedrine	0.05 (UV)



1 59%

O-Silyl Ketene *N,O*-Acetal **1**

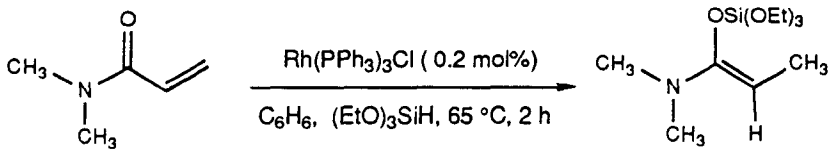
Triethylsilane (10.0 mL, 62.6 mmol, 1.0 equiv) was added rapidly to a solution of $Rh(PPh_3)_3Cl$ (0.058 g, 0.062 mmol, 0.0010 equiv) in *N,N*-dimethylacrylamide (6.45 mL, 62.5 mmol, 1.0 equiv). The reaction mixture was warmed to 50 °C and was held at that temperature 10.5 h (the solution darkened within 30 min). The mixture was distilled at reduced pressure (70-77 °C, 2 Torr) to afford **1** (7.89 g, 65%, 90% pure by weight).

O-Silyl Ketene *N,O*-Acetal **1**

^{1}H NMR (400 MHz, C_6D_6): 3.72 (q, 1H, *J*=10.0, olefinic), 2.31 (s, 6H, NCH_3), 1.75 (d, 3H, *J*=10.0, CH_3), 1.03 (t, 9H, *J*=12.0, $SiCH_2\mathbf{CH_3}$), 0.71 (q, 6H, *J*=12.0, $SiCH_2CH_3$).

FTIR (neat film), cm^{-1}: 2954 (s), 1665 (s), 1458 (m), 1413 (m), 1381 (m), 1332 (s),1239 (m), 1165 (s), 1083 (m), 1044 (s), 1007 (m), 860 (m), 730 (m).

MS (CI:NH_3): 216 (MH^+), 186 (MH^+-CH_3CH_3).



2 73% (24:1 *Z*:*E*)

O-Silyl Ketene *N*,*O*-Acetal **2**

Triethoxysilane (30.0 mL, 16 mmol, 1.0 equiv) was added to a solution of $Rh(PPh_3)_3Cl$ (0.250 g, 0.27 mmol, 0.0020 equiv) and *N*,*N*-dimethylacrylamide (17.6 mL, 171 mmol, 1.0 equiv) in benzene (20 mL). The reaction mixture was heated at 65 °C for 2 h. The reaction mixture was cloudy after 1 h and completely black after 2 h. Analysis of an aliquot of the reaction mixture by ^1H NMR indicated that the reaction was complete. Benzene was removed under vacuum (0.10 Torr), and the residue was fractionally distilled (45-50 °C, 0.07 Torr) producing **2** (24:1 *Z*:*E*-mixture, 34.0 g, 79%, 7% impurity by weight) as a light yellow, moisture-sensitive liquid.

O-Silyl Ketene *N*,*O*-Acetal **2**

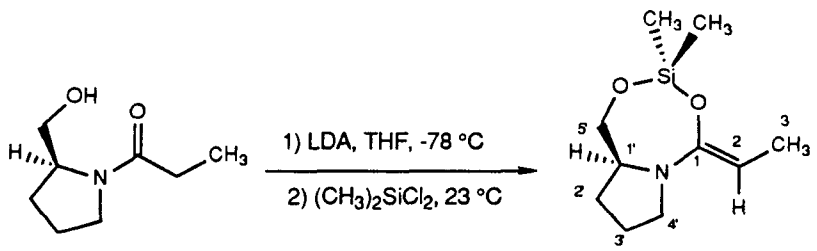
^1H NMR (400 MHz, C_6D_6): 3.92 (q, 6H, *J*=7.2, $SiOCH_2CH_3$), 5.19 (q, 1H, *J*=7.5, olefinic), 2.42 (s, 6H, NCH_3), 2.49 (d, 3H, *J*=7.2, CH_3), 1.18 (t, 9H, *J*=7.5, $SiOCH_2CH_3$).

FTIR (neat film), cm^{-1}: 2976 (m), 1671 (m), 1479 (w), 1457 (w), 1396 (w), 1336 (m), 1168 (m), 1086 (s), 969 (m), 884 (m), 792 (m), 739 (m).

MS (EI): 262 (MH^+), 206 (MH^+-CH_3CHCO).

HRMS (EI): Calculated for $C_{11}H_{24}NO_4Si$ (MH^+): 262.1474

Found: 262.1478



7 78%

(1'*S*)-*O*-Silyl Ketene *N,O*-Acetal **7**

n-Butyllithium (135 mL, 63.7 mmol, 2.57 M in hexanes, 2.2 equiv) was added over 10 min to a deoxygenated solution of diisopropylamine (19.8 mL, 141 mmol, 2.3 equiv) in THF (200 mL) at -78 °C. The flask was placed in an icebath for 10 min, then was recooled to -78 °C. A solution of (1'*S*)-prolinol propionamide[39] (9.208 g, 58.6 mmol, 1.0 equiv) in THF (20 mL) was then added by cannula to the LDA solution. The transfer was quantitated by rinsing the flask with two 10-mL portions of THF. The reaction mixture was stirred at -78 °C for 1 h, at 0 °C for 1 h, and then was diluted with THF (500 mL) at 0 °C. The reaction mixture was warmed to 23 °C and $(CH_3)_2SiCl_2$ (4 mL, 33.0 mmol, 1.13 equiv) was added rapidly over 5 min. After the reaction mixture was stirred for 30 min, all the volatile components were removed under vacuum (0.1 Torr). The residue was taken up in toluene (15 mL), and a fine precipitate formed. The precipitate was allowed to settle and the supernatent was decanted by cannula from the solid. The transfer was quantitated with two 10-mL portions of toluene. The combined toluene washes were concentrated under vacuum (0.1 Torr). The product was carefully distilled (Kügelrohr, 100 °C, 0.04 Torr) affording pure (1'*S*)-**7** (9.70 g, 78%) as a nonviscous, clear liquid.

(1'*S*)-*O*-Silyl Ketene *N,O*-Acetal **7**

^{1}H NMR (400 MHz, C_6D_6): 3.71 (q, 1H, *J*=6.5, H2), 3.52 (dd, 1H, *J*=1.5, 9.4, H5'), 3.41 (m, 1H, H1'), 3.35 (dd, 1H, *J*=9.4, 10.5, H5'), 2.86 (m, 1H, H4'), 2.81 (m, 1H, H4'), 1.91 (d, 3H, *J*=6.5, H3), 1.31 (m, 3H, H2', H3'), 0.87 (m, 1H, H3'), 0.31 (s, 3H, $SiCH_3$), 0.29 (s, 3H, $SiCH_3$)

^{13}C NMR (100 MHz, C_6D_6): 150.9, 74.9, 70.9, 62.0 , 50.4, 28.0, 24.6, 10.7, -1.8, -3.3.

^{29}Si NMR (18 MHz, C_4D_8O): -8

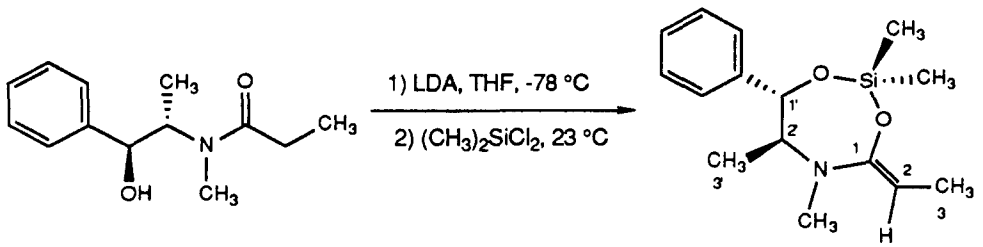
FTIR (neat film), cm^{-1}: 2916 (m), 1667 (s), 1339 (s), 1296 (s), 1260 (s), 1184 (s), 1118 (s), 1060 (s), 861 (s), 798 (s).

MS (FAB): 436 (MH^++3$(CH_3)_2SiO$), 362 (MH^++2$(CH_3)_2SiO$), 288 (MH^++$(CH_3)_2SiO$), 214 (MH^+).

HRMS (FAB): Calculated for $C_{10}H_{20}NO_2Si$ (MH^+): 214.1263
Found: 214.1260

ELEMENTAL ANALYSIS: Calculated for $C_{10}H_{19}NO_2Si$: C, 56.30; H, 8.98; N, 6.57.

Found: C, 56.36; H, 8.61; N, 6.20.



16 80%

(1'*S*,2'*S*)-*O*-Silyl Ketene *N*,*O*-Acetal **16**

n-Butyllithium (20.0 mL, 2.50 M in hexanes, 50 mmol, 2.2 equiv) was added over 5 min to a deoxygenated solution of diisopropylamine (7.0 mL, 51 mmol, 2.2 equiv) in THF (300 mL) at -78 °C. After 5 min at -78 °C, the solution was placed in an icebath for 10 min. The reaction mixture was recooled to -78 °C and a solution of (1'*S*,2'*S*)-pseudoephedrine propionamide (5.01 g, 22.7 mmol , 1.0 equiv) in THF (50 mL) was added by cannula over 30 min. Two 5-mL portions of THF were used to quantitate the transfer. The solution was stirred at -78 °C for 3.5 h more and then was gradually warmed to room temperature over 30 min. After 30 min at 23 °C, dichlorodimethylsilane (3.01 mL, 24.8 mmol, 1.09 equiv) was added over 5 min and the reaction mixture was stirred for an additional 2.5 h at 23 °C. The reaction mixture was concentrated to ~10 mL under vacuum (0.1 Torr). The residue was taken up in hexanes (10 mL) and a fine white solid precipitated. The supernatent was decanted off using a cannula and the transfer was quantitated with two 5-mL portions of hexanes. The combined hexanes extracts were concentrated under vacuum (0.1 Torr). The residue was purified by distillation (Kügelrohr, 100 °C, 0.005 Torr) into a flask cooled with liquid N_2 affording (1'*S*,2'*S*)-**16** (5.01 g, 80.0%) as a moisture-sensitive oil.

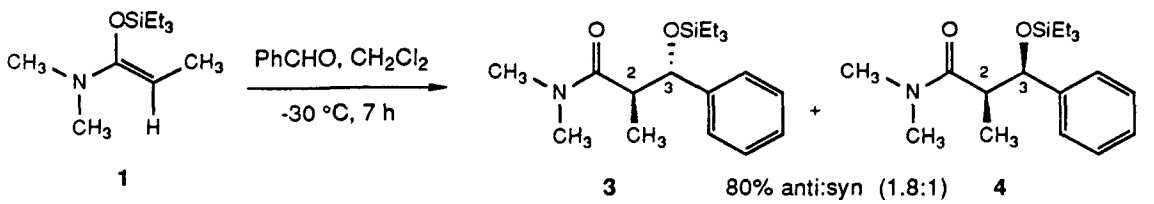
(1'*S*,2'*S*)-*O*-Silyl Ketene *N*,*O*-Acetal **16**

^{1}H NMR (400 MHz, C_6D_6): 7.04-7.28 (m, 5H, arom), 4.53 (d, 1H, *J*=8.8, H1'), 3.82 (q, 1H, *J*=6.1, H2), 3.10 (dq, 1H, *J*=8.8, 6.6, H2'), 2.32 (s, 3H, NCH_3), 1.88 (d, 3H, *J*=5.7, H3), 0.63 (d, 3H, *J*=6.6, H3'), 0.40 (s, 3H, $SiCH_3$), 0.26 (s, 3H, $SiCH_3$).

^{29}Si NMR (18 MHz, C_4D_8O): -3

FTIR (neat film), cm^{-1}: 2964 (m), 1675 (s), 1451 (m), 1376 (m), 1317 (m), 1253 (m), 1221 (m), 1136 (m), 1077 (m), 1034 (m), 906 (m), 863 (m), 794 (m), 703 (m).

ELEMENTAL ANALYSIS: Calculated for $C_{15}H_{23}NO_2Si$: C, 64.9; H, 8.36; N, 5.04.
Found: C, 64.9; H, 8.28; N, 5.37.



1 3 4

Reaction of *O*-Silyl Ketene *N,O*-Acetal **1** with Benzaldehyde

O-Silyl ketene *N,O*-acetal **1** (0.46 mL, 0.396 g, 1.84 mmol, 1.69 mmol corrected for impurity, 1.01 equiv) was added dropwise to a solution of benzaldehyde (0.171 mL, 1.68 mmol, 1.00 equiv) in CH_2Cl_2 (1 mL) at -78 °C. The reaction was stirred 1 h at -78 °C and then warmed to -30 °C. After 7 h at -30 °C the reaction appeared complete, so the reaction mixture was warmed to room temperature and concentrated *in vacuo*. Purification of the residue by flash chromatography (20% ethyl acetate-hexanes) afforded a mixture of **3** and **4** (0.4336 g combined, 80%, 1.75:1 anti:syn ratio), as colorless oil. A portion of the reaction mixture was further purified by thin-layer preparative chromatography (50% ethyl acetate-hexanes) to separately afford pure (±)-**3** and (±)-**4**.

Racemic Anti Aldol Adduct **3**

^{1}H NMR (400 MHz, C_6D_6): 6.95-7.50 (m, 5H, arom), 5.02 (d, 1H, *J*=10.0, H3), 2.92 (dq, 1H, *J*=7.5, 10.0, H2), 2.42 (s, 3H, NCH_3), 1.92 (s, 3H, NCH_3), 1.50 (d, 3H, *J*=7.5, CH_3), 0.91 (t, 6H, *J*=12.2, $SiCH_2CH_3$), 0.57 (q, 9H, *J*=12.2, $SiCH_2CH_3$).

FTIR (neat film), cm^{-1}: 2944 (m), 2872 (m), 1643 (s), 1490 (s), 1455 (m), 1408 (m), 1237 (w), 1079 (m), 1061 (m), 1002 (w), 820 (m), 738 (m), 697 (m).

MS (CI:NH_3): 322(MH^+), 292 (MH^+-C_2H_6), 190 (MH^+-$(CH_3CH_2)_3SiOH$).

HRMS (CI:NH_3): Calculated for $C_{18}H_{32}NO_2Si$ (MH^+): 322.2202
Found: 322.2200

Racemic Syn Aldol Adduct **4**

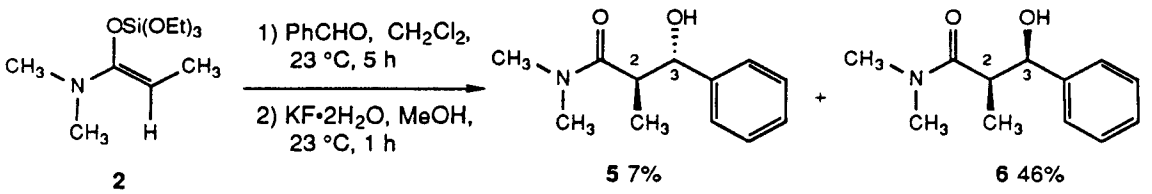
^1H NMR (400 MHz, C_6D_6): 7.30-7.00 (m, 5H, arom), 4.97 (d, 1H, *J*=9.4, H3), 2.94 (dq, 1H, *J*=9.4, 6.7, H2), 2.80 (s, 3H, NCH_3), 2.58 (s, 3H, NCH_3), 0.91 (t, 6H, *J*=7.9, $SiCH_2CH_3$), 0.83 (d, 3H, *J*=6.7, CH_3), 0.57 (m, 9H, $SiCH_2CH_3$).

FTIR (neat film), cm^{-1}: 3389 (m), 2931 (m), 1619 (s), 1490 (m), 1449 (m), 1414 (m), 1396 (m), 1337 (w), 1302 (w), 1249 (m), 1149 (m), 1032 (m), 761 (m), 697 (m).

MS (CI:NH_3): 322(MH^+), 292 (MH^+-C_2H_6), 190 (MH^+-$CH_3CH_2)_3SiOH$).

HRMS (CI:NH_3): Calculated for $C_{18}H_{32}NO_2Si$ (MH^+): 322.2202
Found: 322.2206

TLC (50% EtOAc-hexanes):	Anti aldol adduct **3**	0.62 (UV)
	Syn aldol adduct **4**	0.66 (UV)
	Benzaldehyde	0.75 (UV)



2 **5** 7% **6** 46%

Reaction of *O*-Silyl Ketene *N,O*-Acetal **2** with Benzaldehyde

Benzaldehyde (0.82 mL, 8.0 mmol, 1.3 equiv) was added dropwise to a solution of *O*-silyl ketene *N,O*-acetal **2** (2.02 mL, 1.83 g, 7.01 mmol, 6.58 mmol corrected for impurity, 1.0 equiv) in CH_2Cl_2 (3 mL) at 0 °C. After 1 h the reaction mixture was warmed to 23 °C and stirred for 5 h at that temperature. The reaction mixture was concentrated *in vacuo* and the residue was treated with a solution of $KF•2H_2O$ (3.13 g, 53.9 mmol) in methanol (25 mL) for 1 h at 23 °C. The reaction mixture was neutralized with solid ammonium chloride (5 g) and concentrated *in vacuo*. The residue was dissolved in ethyl acetate and the solid was removed by filtration through a pad of silica gel (2 cm x 2 cm). The filtrate was concentrated *in vacuo*, and purified by flash chromatography (50% ethyl acetate-hexanes) affording separately (±)-**5** (0.620 g, 46%, mp: 87.5-88.5 °C) and (±)-**6** (0.100 g, 7%, mp: 110-111 °C) as white, crystalline solids.

Racemic Anti Aldol Product **5**

^{1}H NMR (400 MHz, C_6D_6): 7.00-7.36 (m, 5H, arom), 5.15 (d, 1H, *J*=7.0, OH), 4.80 (dd, 1H, *J*=5.3, 7.0, H3), 3.98 (dq, 1H, *J*=7.0, 7.0, H2), 2.41 (s, 3H, NCH_3), 1.96 (s, 3H, NCH_3), 1.10 (d, 3H, *J*=7.0, CH_3).

FTIR (neat film), cm^{-1}: 3378 (m), 2928 (m), 1621 (s), 1493 (m), 1452 (m), 1411 (m), 1396 (m), 1258 (w), 1150 (m), 1109 (w), 1043 (m), 1017 (w), 895 (w), 757 (w), 701 (m).

MS ($CI:NH_3$): 208 (MH^+), 190 (MH^+-H_2O).

HRMS ($CI:NH_3$): Calculated for $C_{12}H_{18}NO_2$ (MH^+): 208.1338
Found: 208.1340

Racemic Syn Aldol Product **6**

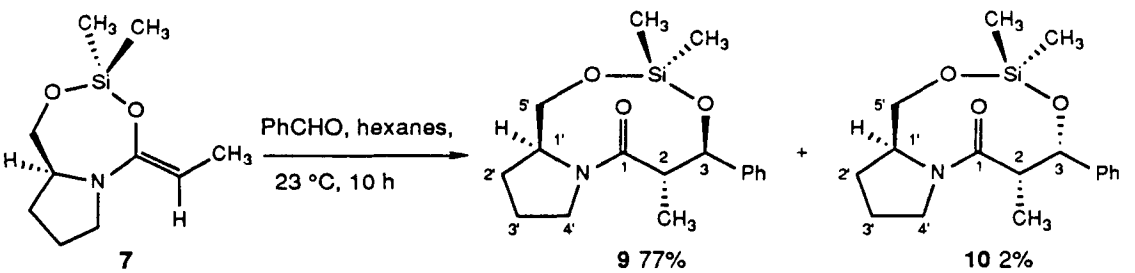
^1H NMR (400 MHz, C_6D_6): 7.5-7.08 (m, 5H, arom), 5.66 (d, 1H, J=1.2, H3), 5.19 (s, 1H, OH), 2.51 (s, 3H, NCH_3), 2.49 (dq, 1H, J=1.2, 7.0, H2), 2.00 (s, 3H, NCH_3), 0.94 (d, 3H, J=7.0, CH_3).

FTIR (neat film), cm^{-1}: 3388 (m), 2928 (m), 1621 (s), 1493 (m), 1447 (m), 1411 (m), 1396 (m), 1334 (w), 1304 (w), 1252 (w), 1196 (m), 1150 (w), 1104 (w), 1027 (m), 767 (m), 700 (s).

MS ($CI:NH_3$): 208 (MH^+), 190 (MH^+-H_2O).

HRMS ($CI:NH_3$): Calculated for $C_{12}H_{18}NO_2$ (MH^+): 208.1338
Found: 208.1327

TLC (50% EtOAc-hexanes):	Anti aldol product **5**	0.19 (UV)
	Syn aldol product **6**	0.32 (UV)
	Benzaldehyde	0.75 (UV)



(1'*S*,2*S*,3*R*)-*Anti* Aldol Product **9**

A solution of (1'*S*)-*O*-silyl ketene *N*,*O*-acetal **7** (0.5028 g, 2.36 mmol, 1.0 equiv) in hexanes (0.1 mL) was treated with benzaldehyde (0.25 mL, 2.4 mmol, 1.0 equiv) for 10 h at 23 °C, at which point the product had precipitated from solution. Cold hexanes (2 mL, -20 °C) was added to quantitatively precipitate the product. The crystals were collected by vacuum filtration and washed twice with two 1-mL portions of cold hexanes (-20 °C). Pure (1'*S*,2*S*,3*R*)-**9** (0.5827 g, 1.82 mmol, 77%, mp: 139-142 °C) was collected as a white, crystalline solid.

Synthesis of Aldol Adduct **9** under Conditions used in Kinetics Experiments

A solution of (1'*S*)-*O*-silyl ketene *N*,*O*-acetal **7** (0.300 mL, 320 mg, 1.50 mmol, 1.0 equiv), and benzaldehyde (0.170 mL, 1.67 mmol, 1.11 equiv) in benzene (4 mL) was subjected to three pump-freeze-thaw degas cycles. The reaction mixture was heated at 60 °C for 6 days, and then was concentrated *in vacuo*. Purification of the residue by flash chromatography (50% ether-petroleum ether) afforded pure (1'*S*,2*S*,3*R*)-**9** (0.4205 g, 88%, mp: 141-142 °C) as a white, crystalline solid. The (1'*S*,2*S*,3*S*)-diastereomer (**10**, 0.005 g, 1%, mp: 117-120 °C) was isolated in a separate fraction.

(1'*S*,2*S*,3*R*)-*Anti* Aldol Product **9**

^{1}H NMR (400 MHz, C_6D_6): 7.05-7.40 (m, 5H, arom), 4.99 (dd, 1H, *J*=3.2, 10.8, H5'), 4.80 (d, 1H, *J*=9.7, H3), 3.98 (dt, 1H, *J*=2.9, 6.7, H1'), 3.57 (dt, 1H, *J*=2.9, 9.4, H4'), 3.31 (d, 1H, *J*=11.1, H5'), 3.00 (dt, 1H, *J*=2.9, 8.8, H4'), 2.83 (dq, 1H, *J*=9.7, 6.6, H2), 1.79 (m, 1H), 1.57 (m, 2H), 1.30 (m, 1H), 1.10 (d, 3H, *J*=6.6, CH_3), 0.33 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$).

^{13}C NMR (23 MHz, CD_2Cl_2): 174, 143, 128, 128, 127, 81, 62, 59, 49, 47, 29, 25, 13, -1, -6.

FTIR (neat film), cm^{-1}: 2964 (w), 2872 (w), 1631 (s), 1431 (m), 1251 (m), 1200 (w), 1108 (m), 1067 (m), 1051 (m), 990 (w), 908 (w), 872 (m), 846 (m), 795 (m), 697 (m).

MS (EI): 319 (M^+), 213 (M^+-C_7H_6O).

HRMS (EI): Calculated for $C_{17}H_{25}NO_3Si$ (M^+): 319.1604
Found: 319.1598

(1'*S*,2*S*,3*S*)-*Syn* Aldol Adduct **10**

^{1}H NMR (400 MHz, C_6D_6): 7.05-7.35 (m, 5H, arom), 5.47 (d, 1H, *J*=3.8, H3), 4.88 (dd, 1H, *J*=2.7, 10.9, H5'), 4.02 (dt, 1H, *J*=3.0, 8.7, H1'), 3.23 (dt, 1H, *J*=7.5, 3.2, H4'), 3.22 (d, 1H, *J*=10.7, H5'), 3.05 (t, 1H, *J*=7.5, H4'), 2.79 (dq, 1H, *J*=4.0, 6.7, H2), 1.73 (m, 1H), 1.50 (m, 2H), 1.27 (m, 1H), 1.08 (d, 3H, *J*=6.6, CH_3), 0.29 (s, 3H, $SiCH_3$), -0.05 (s, 3H, $SiCH_3$).

FTIR (neat film), cm^{-1}: 2995 (m), 2873 (m), 1632 (s), 1432 (s), 1254 (s), 1197 (s), 1092 (s), 1021 (s), 985 (m), 882 (m), 795 (m), 692 (m).

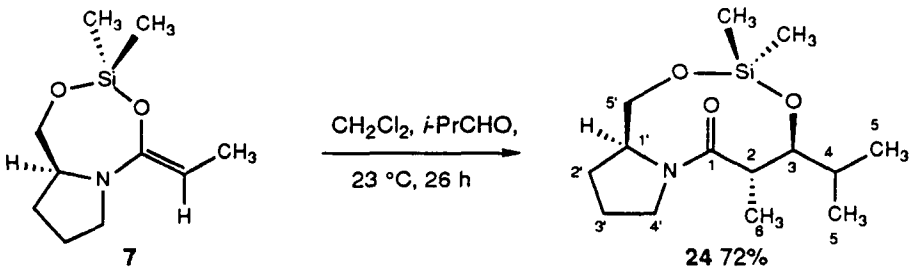
MS (FAB): 320 (MH^+), 213 (M^+-C_7H_6O).

HRMS (FAB): Calculated for $C_{17}H_{26}NO_3Si$ (MH^+): 320.1682
Found: 320.1682

TLC (40% EtOAc-hexanes):

Anti aldol product **9**	0.26 (UV)
Syn aldol product **10**	0.19 (UV)
Benzaldehyde	0.55 (UV)

GC (Ph-Me Silicone, 200 °C):	Anti aldol product **9**	36.65 min
	Syn aldol product **10**	46.81 min



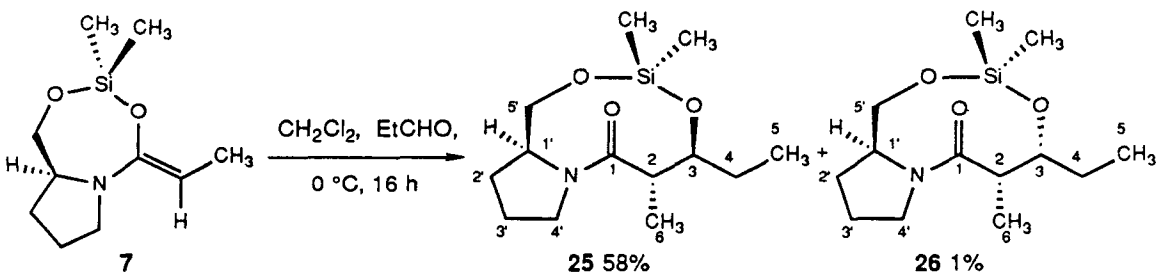
(1'*S*,2*S*,3*S*)-*Anti* Aldol Product **24**

A solution of (1'*S*)-*O*-silyl ketene *N*,*O*-acetal **7** (0.510 g, 2.39 mmol, 1 equiv) in CH_2Cl_2 (0.2 mL) was treated with isobutryaldehyde (0.228 mL, 0.181 g, 2.5 mmol, 1.05 equiv) for 26 h at 23 °C, at which point the product had precipitated from solution. The reaction mixture was purified by flash chromatography (20% ethyl acetate-hexanes) affording (1'*S*,2*S*,3*S*)-**24** (0.4893 g, 72%, mp: 99-100 °C) as a white, crystalline solid.

(1'*S*,2*S*,3*S*)-*Anti* Aldol Product **24**

^{1}H NMR (400 MHz, C_6D_6): 4.94 (dd, 1H, *J*=2.9, 10.9, H5'), 3.95 (dt, 1H, *J*=2.9, 7.3, H1'), 3.70 (dd, 1H, *J*=2.1, 9.7, H3), 3.41 (dt, 1H, *J*=6.5, 9.6, H4'), 3.29 (d, 1H, *J*=11.1, H5'), 2.97 (dt, 1H, *J*=9.7, 3.2, H4'), 2.72 (dq, 1H, *J*=9.7, 6.4, H2), 1.87 (m, 1H), 1.68 (m, 1H), 1.54 (m, 2H), 1.21 (m, 1H, H4), 1.06 (d, 3H, *J*=6.4, H6), 0.96 (d, 3H, *J*=4.4, H5), 0.93 (d, 3H, *J*=4.4, H5), 0.26 (s, 3H, $SiCH_3$), 0.18 (s, 3H, $SiCH_3$).

^{13}C NMR (100 MHz, C_6D_6):	173.8, 82.0, 61.9, 58.9, 48.8, 42.1, 29.3, 28.6, 24.8, 20.8, 13.9, 12.7, -1.2, -6.1.	
FTIR (neat film), cm^{-1}:	2942 (w), 2877 (w), 1620 (s), 1433 (m), 1246 (m), 1125 (w), 1105 (w), 1044 (m), 984 (w), 867 (w), 847 (w), 827 (w), 787 (m).	
MS (CI:NH_3):	286 (MH^+), 213 (M^+-C_4H_8O).	
HRMS (CI:NH_3):	Calculated for $C_{14}H_{28}NO_3Si$ (MH^+): 286.1838 Found: 286.1843	
TLC (40% EtOAc-hexanes):	Anti aldol product **24**	0.284
GC (Ph-Me Silicone, 170 °C):	Anti aldol product **24**	27.98 min



7 **25** 58% **26** 1%

(1'*S*,2*S*,3*S*)-*Anti* Aldol Product **25**

A solution of (1'*S*)-*O*-silyl ketene *N*,*O*-acetal **7** (0.379 g, 2.36 mmol, 1.0 equiv) in CH_2Cl_2 (0.1 mL) was treated with propionaldehyde (0.132 mL, 0.106 g, 1.02 equiv) for 16 h at 0 °C, at which point the product had precipitated from solution. The reaction mixture was purified by flash chromatography (25% ethyl acetate-hexanes) affording (1'*S*,2*S*,3*S*)-**25** (0.2729 g, 58%, mp: 46-47 °C) as a white, crystalline solid. A separate fraction afforded (1'*S*,2*S*,3*R*)-**26** (0.0028 g, 1%) as a colorless oil.

(1'*S*,2*S*,3*S*)-*Anti* Aldol Product **25**

^{1}H NMR (400 MHz, C_6D_6): 4.95 (dd, 1H, *J*=3.6, 9.3, H5'), 3.94 (dt, 1H, *J*=3.6, 7.6, H1'), 3.66 (dt, 1H, *J*=2.2, 9.3, H3), 3.43 (dt, 1H, *J*=5.7, 9.8, H4'), 3.30 (d, 1H, *J*=9.3, H5'), 2.97 (dt, 1H, *J*=3.1, 9.7, H4'), 2.53 (dq, 1H, *J*=7.1, 9.3, H2), 1.77 (m, 1H), 1.53 (m, 3H), 1.23 (m, 1H), 1.07 (d, 3H, *J*=7.0, H6), 0.88 (t, 3H, *J*=7.2, H5), 0.27 (s, 3H, $SiCH_3$), 0.21 (s, 3H, $SiCH_3$).

^{13}C NMR (100 MHz, C_6D_6): 173.7, 79.7, 62.2, 58.9, 48.9, 45.2, 28.6, 28.1, 24.6, 13.3, 10.4 , -1.0, -6.0.

FTIR (neat film), cm^{-1}: 2954 (m), 2872 (m), 1631 (s), 1431 (m), 1256 (m), 1123 (m), 1067 (m), 1016 (w), 846 (m), 795 (m).

MS (EI): 271 (M^+), 256 (M^+-CH_3), 213 (M^+-CH_3CH_2CHO).

HRMS (EI): Calculated for $C_{13}H_{25}NO_3Si$ (M^+): 271.1617
Found: 271.1617

(1'*S*,2*S*,3*R*)-*Syn* Aldol Adduct **26**

^1H NMR (400 MHz, C_6D_6): 4.89 (dd, 1H, *J*=2.7, 10.9, H5'), 4.02 (dt, 1H, *J*=3.0, 8.7, H3), 3.92 (dt, 1H, *J*=2.7, 9.8, H1'), 3.17 (d, 1H, *J*=10.7, H5'), 3.05 (m, 1H, H4'), 3.05 (t, 1H, *J*=7.5, H4'), 2.45 (dq, 1H, *J*=3.0, 6.7, H2), 1.68 (m, 1H), 1.15-1.55 (m, 5H), 1.08 (d, 3H, *J*=6.6, H6), 0.76 (t, 3H, *J*=7.2, H5), 0.22 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$).

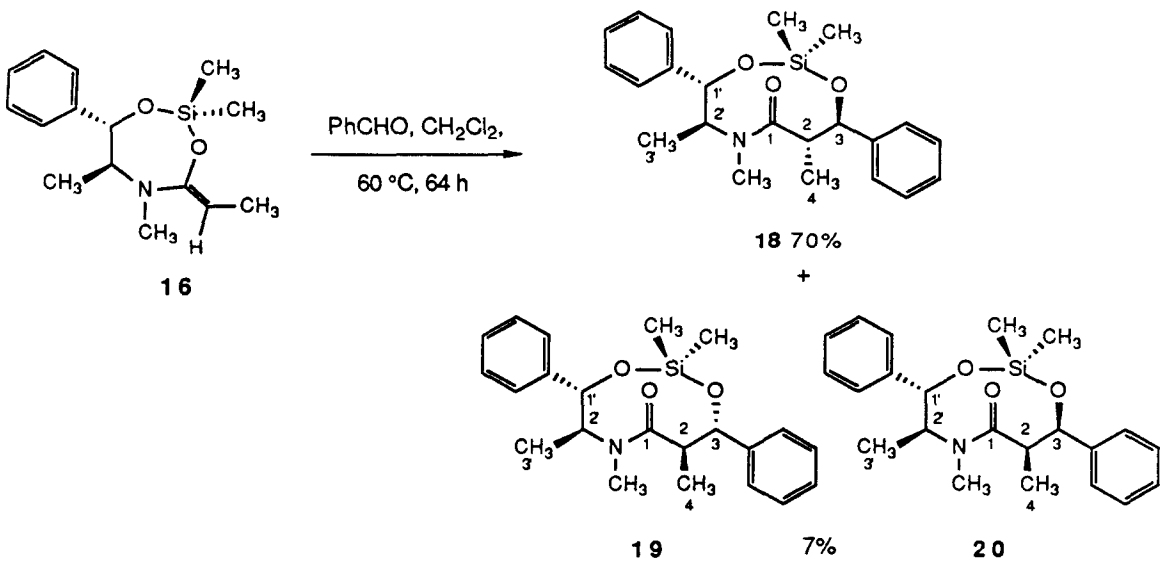
FTIR (neat film), cm^{-1}: 2954 (m), 2872 (m), 1631 (s), 1431 (m), 1256 (m), 1123 (m), 1067 (m), 1016 (w), 846 (m), 795 (m).

MS (EI): 271 (M^+), 256 (M^+-CH_3), 213 (M^+-CH_3CH_2CHO).

HRMS (EI): Calculated for $C_{13}H_{25}NO_3Si$ (M^+): 271.1617

Found: 271.1612

TLC (ether):	Anti aldol product **25**	0.27
	Syn aldol product **26**	0.19
GC (Ph-Me Silicone, 170 °C):	Anti aldol product **25**	26.70 min
	Syn aldol product **26**	36.03 min



(1'*S*,2'*S*,2*S*,3*R*)-*Anti* Aldol Product **18**

Benzaldehyde (0.095 mL, 0.93 mmol, 1.1 equiv) and CH_2Cl_2 (0.2 mL) were added sequentially to (1'*S*,2'*S*)-*O*-silyl ketene *N*,*O*-acetal **16** (0.2310 g, 0.83 mmol, 1.0 equiv) at 23 °C. The solution was subjected to three pump-freeze-thaw degas cycles and heated at 60 °C for 64 h, at which point the product had crystallized from solution. Analysis of the crude reaction mixture by ^{1}H NMR revealed three diastereomeric products **18**, **19**, and **20** (77.1, 8.4, and 14.4% respectively). Purification of the reaction mixture by flash chromatography afforded (1'*S*,2'*S*,2*S*,3*R*)-**18** (0.222 g, 70%) as a white solid (mp: 156-158 °C) and a mixture of (1'*S*,2'*S*,2*R*,3*S*)-**19** and (1'*S*,2'*S*,2*R*,3*R*)-**20** (2:3 ratio, 21.2 mg, 7%) as a colorless oil.

(1'*S*,2'*S*,2*S*,3*R*)-*Anti* Aldol Product **18**

^{1}H NMR (500 MHz, C_6D_6): 7.02-7.36 (m, 10H, arom), 5.7 (dq, 1H, *J*=10.0, 7.4, H2'), 4.89 (d, 1H, *J*=9.7, H3), 4.40 (d, 1H,

J=10.1, H1'), 3.22 (dq, 1H, *J*=9.7, 8.6, H2), 2.88 (s, 3H, NCH_3), 1.08 (d, 3H, *J*=7.4, H3'), 0.62 (d, 3H, *J*=8.7, H4), 0.09 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$).

FTIR (neat film), cm^{-1}: 2966 (m), 1643 (s), 1484 (m), 1449 (m), 1402 (m), 1367 (w), 1284 (m), 1255 (s), 1202 (w), 1132 (m), 1079 (s), 1049 (s), 1020 (m), 932 (m), 879 (s), 867 (s), 797 (m), 697 (s), 550 (m).

MS (CI:CH_4): 384 (MH^+), 306 (MH^+-C_6H_6), 278 (MH^+-C_6H_5CHO).

HRMS (CI:CH_4): Calculated for $C_{22}H_{30}NO_3Si$ (MH^+): 384.1995
Found: 384.1981

(1'*S*,2'*S*,2*S*,3*R*)-*Anti* Aldol Product **18** Deuterated at C3

^1H NMR (400 MHz, C_6D_6): 7.02-7.36 (m, 10H, arom), 5.7 (dq, 1H, *J*=10.1, 7.4, H2'), 4.40 (d, 1H, *J*=10.1, H1'), 3.22 (q, 1H, *J*=8.6, H2), 2.88 (s, 3H), 1.08 (d, 3H, *J*=7.4, H3'), 0.62 (d, 3H, *J*=8.7, H4), 0.09 (s, 3H, $SiCH_3$), 0.01 (s, 3H, $SiCH_3$).

FTIR (neat film), cm^{-1}: 2966 (m), 1643 (s), 1484 (m), 1449 (m), 1402 (m), 1367 (w), 1284 (m), 1255 (s), 1202 (w), 1132 (m), 1079 (s), 1049 (s), 1020 (m), 932 (m), 879 (s), 867 (s), 797 (m), 697 (s), 550 (m).

MS (CI:NH_3): 385 (MH^+), 278 (MH^+-C_6H_5CDO).

HRMS (CI:NH_3): Calculated for $C_{22}H_{29}DNO_3Si$ (MH^+): 385.2058
Found: 385.2067

(1'*S*,2'*S*,2*R*,3*S*)-Diastereomer **19**

^1H NMR (400 MHz, C_6D_6): 7.02-7.36 (m, 10H, arom), 5.09 (d, 1H, *J*=9.8, H1'), 4.95 (dq, 1H, *J*=9.8, 6.5, H2'), 4.56 (d, 1H, *J*=9.7, H3), 3.41 (dq, 1H, *J*=9.8, 6.2, H2), 2.91 (s, 3H, NCH_3), 1.02 (d, 3H, *J*=6.6, H3'), 0.60 (d, 3H, *J*=6.2, H4), 0.29 (s, 3H, $SiCH_3$), -0.26 (s, 3H, $SiCH_3$).

(1'*S*,2'*S*,2*R*,3*R*)-Diastereomer **20**

^1H NMR (400 MHz, C_6D_6): 7.02-7.36 (m, 10H, arom), 6.00 (d, 1H, *J*=9.5, H1'), 4.96 (d, 1H, *J*=9.5, H3), 2.94 (m, 2H, H2, H2'), 2.86 (s, 3H, NCH_3), 1.38 (d, 3H, *J*=6.8,

H3'), 0.96 (d, 3H, *J*=6.5, H4), 0.34 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$).

(1'*S*,2'*S*,2*R*,3*S*)-**19** and (1'*S*,2'*S*,2*R*,3*R*)-**20**

FTIR (neat film), cm^{-1}: 2964 (w), 1636 (s), 1487 (w), 1451 (w), 1405 (w), 1369 (m), 1292 (w), 1251 (m), 1205 (w), 1077 (s), 851 (s), 795 (m), 692 (s).

MS (CI:NH_3): 384 (MH^+), 277 (M^+-C_7H_6O).

HRMS (CI:NH_3): Calculated for $C_{22}H_{30}NO_3Si$ (MH^+): 384.1995
Found: 384.2015

TLC (50% ether-pet. ether):

Diastereomer **18**	0.61 (UV)
Diastereomer **19**	0.35 (UV)
Diastereomer **20**	0.35 (UV)
Benzaldehyde	0.85 (UV)

(1'*S*,2'*S*,2*R*,3*S*)-Diastereomer **19** Deuterated at C3

^1H NMR (400 MHz, C_6D_6): 7.02-7.36 (m, 10H, arom), 5.09 (d, 1H, *J*=9.8, H1'), 4.95 (dq, 1H, *J*=9.8, 6.5, H2'), 3.41 (q, 1H, *J*=6.2, H2), 2.91 (s, 3H, NCH_3), 1.38 (d, 3H,

J=6.6, H3'), 0.60 (d, 3H, *J*=6.2, H4), 0.29 (s, 3H, $SiCH_3$), -0.26 (s, 3H, $SiCH_3$).

(1'*S*,2'*S*,2*R*,3*R*)-Diastereomer **20** Deuterated at C3

^{1}H NMR (400 MHz, C_6D_6): 7.02-7.36 (m, 10H, arom), 6.00 (d, 1H, *J*=9.5, H1'), 2.94 (m, 2H, H2', H2), 2.86 (s, 3H, NCH_3), 1.38 (d, 3H, *J*=6.8, H3'), 0.96 (d, 3H, *J*=6.5, H4), 0.34 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$).

(1'*S*,2'*S*,2*R*,3*S*)-**19** and (1'*S*,2'*S*,2*R*,3*R*)-**20** Deuterated at C3

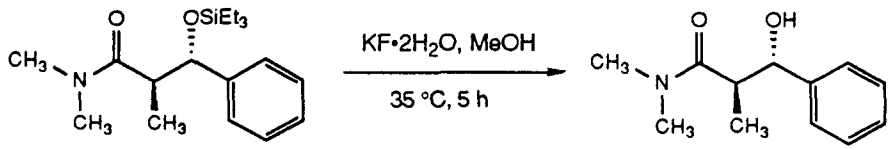
FTIR (neat film), cm^{-1}: 2964 (w), 1636 (s), 1487 (w), 1451 (w), 1405 (w), 1369 (m), 1292 (w), 1251 (m), 1205 (w), 1077 (s), 851 (s), 795 (m), 692 (s).

MS (CI:CH_4): 385 (MH^+), 278 (M^+-C_7H_6O).

HRMS (CI:CH_4): Calculated for $C_{22}H_{29}DNO_3Si$ (MH^+): 385.2058
Found: 385.2055

TLC (50% ether-pet. ether):

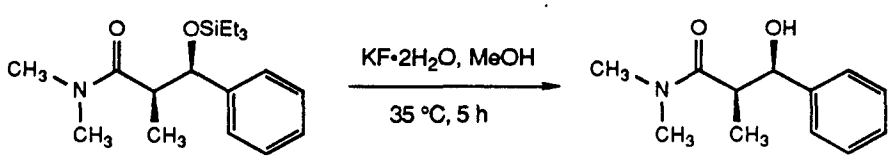
Diastereomer **18**	0.61 (UV)
Diastereomer **19**	0.35 (UV)
Diastereomer **20**	0.35 (UV)
Benzaldehyde	0.85 (UV)



3 5 76%

Desilylation of Racemic Anti Aldol Adduct 3

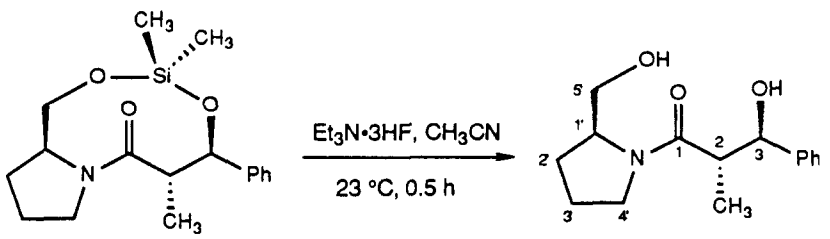
Racemic anti aldol adduct **3** (5.3 mg, 0.016 mmol, 1.0 equiv) was treated with $KF \cdot 2H_2O$ (15 mg, 0.16 mmol, 9.6 equiv) in MeOH (0.5 mL) at 35 °C for 5 h. The reaction was cooled and concentrated *in vacuo*. The residue was partitioned between ethyl acetate (30 mL) and saturated brine. The aqueous layer was separated and extracted once more with ethyl acetate (30 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated. Purification of the residue by flash chromatography (40% ethyl acetate-hexanes) afforded **5** (2.6 mg, 76%).



4 6 76%

Desilylation of Racemic Syn Aldol Adduct 4

Racemic syn aldol adduct **4** (7.2 mg, 0.022 mmol, 1.0 equiv) was treated with $KF \cdot 2H_2O$ (20 mg, 0.21 mmol, 9.5 equiv) in MeOH (0.5 mL) at 35 °C for 5 h. The reaction was cooled and concentrated *in vacuo*. The residue was partitioned between ethyl acetate (30 mL) and saturated brine. The aqueous layer was separated and extracted once more with ethyl acetate (30 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. Purification of the residue by flash chromatography (40% ethyl acetate-hexanes) afforded **6** (3.5 mg, 76%).



9 **27**

Desilylation of (1'*S*,2*S*,3*R*)-*Anti* Aldol Adduct **9**

A solution of (1'*S*,2*S*,3*R*)-*anti* aldol adduct **9** (21.5 mg, 0.067 mmol, 1 equiv) in CH_3CN (1 mL) was treated with Et_3N•HF (54 mg, 0.39 mmol, 5.9 equiv) for 30 min at 23 °C. Concentration and purification of the residue by flash chromatography (ethyl acetate) afforded (1'*S*,2*S*,3*R*)-**27** (17.3 mg, 98%) as a colorless oil.

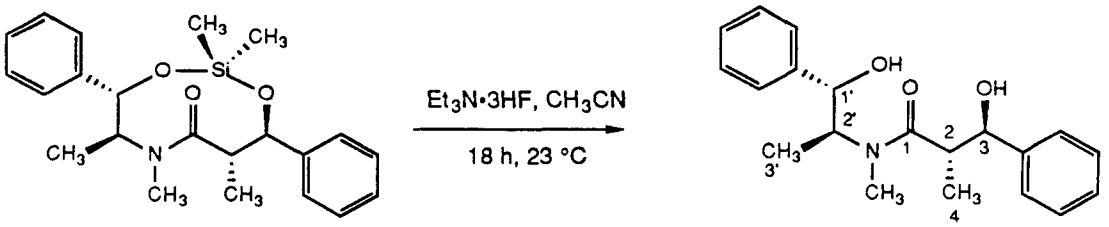
(1'*S*,2*S*,3*R*)-Diol **27** (rotameric mixture)

^{1}H NMR (400 MHz, DMSO): 7.2-7.4 (m, 5H, arom), 5.25 (br, 1H, OH), 4.51 (d, 1H, *J*=8.5, H3), 4.44 (d, 1H, *J*=8.8, H3), 4.13 (m, 1H, H1'), 3.94 (m, 1H, H1'), 3.58 (m, 2H, H5'), 3.25 (m, 3H, H4'), 2.92 (dq, 1H, *J*=8.5, 6.7, H2), 2.77 (dq, 1H, *J*=8.5, 6.7, H2), 1.80 (m, 4H, H2', H3'), 0.73 (d, 3H, *J*=6.7, H4), 0.68 (d, 3H, *J*=6.7, CH_3).

FTIR (neat film), cm^{-1}: 3389 (s), 2966 (s), 1614 (s), 1449 (s), 1373 (w), 1332 (w), 1237 (w), 1185 (w), 1126 (w), 1044 (m), 997 (m).

MS (CI:NH_3): 264 (MH^+), 246 (MH^+-H_2O).

HRMS (CI:NH_3):	Calculated for $C_{15}H_{22}NO_3$ (MH^+): 264.1600	
	Found: 264.1593	
TLC (EtOAc):	Aldol product **9**	0.56 (UV)
	Diol **27**	0.18 (UV)



18 **21** 90%

Desilylation of (1'*S*,2'*S*,2*S*,3*R*)-*Anti* Aldol Product **18**

A solution of (1'*S*,2'*S*,2*S*,3*R*)-*anti* aldol adduct **18** (30.0 mg, 0.078 mmol, 1 equiv) in CH_3CN (1 mL) was treated with Et_3N•3HF (105 mg, 0.76 mmol, 9.8 equiv) for 18 h at 23 °C. Concentration and purification of the residue by flash chromatography (ether) afforded **21** (23.1 mg, 90%) as a colorless oil.

(1'*S*,2'*S*,2*S*,3*R*)-Diol **21** (rotameric mixture)

^{1}H NMR (400 MHz, $CDCl_3$): 7.08-7.35 (m, 10H, arom), 4.71 (d, 1H, *J*=7.5, H3), 4.50 (br, 1H, OH), 4.46 (d, 1H, *J*=8.3, H1'), 4.41 (d, 1H, *J*=8.6, H1'), 3.70 (dq, 1H, *J*=8.6, 6.9, H2'), 3.08 (dq, 1H, *J*=7.2, 6.5, H2), 2.98 (dq, 1H, *J*=7.5, 6.5, H2), 3.75 (s, 3H, NCH_3), 3.75 (m, 1H, H2'), 3.73 (s, 3H, NCH_3), 1.25 (d, 3H, *J*=6.9, H3'), 0.98 (d, 3H, *J*=6.5, H4), 0.95 (d, 3H, *J*=6.9, H3'), 0.43 (d, 3H, *J*=6.5, H4).

FTIR (neat film), cm^{-1}: 3389 (m), 2978 (w), 1614 (s), 1484 (m), 1408 (w), 1373 (w), 1202 (w), 1108 (w), 1079 (w), 1044 (m), 1020 (m), 914 (w), 750 (m), 703 (s).

MS (CI:NH_3): 328 (MH^+), 310 (MH^+-H_2O).

HRMS (CI:NH_3): Calculated for $C_{20}H_{26}NO_3$ (MH^+): 328.1913
Found: 328.1935

TLC (50% EtOAc-hexanes):

Aldol product **18**	0.52
Diol **21**	0.09

(1'*S*,2'*S*,2*S*,3*R*)-Diol **21** Deuterated at C3 (rotameric mixture)

^{1}H NMR (400 MHz, $CDCl_3$): 7.08-7.35 (m, 10H, arom), 4.50 (br, 1H, OH), 4.46 (d, *J*=8.3, H1'), 4.41 (d, 1H, *J*=8.6, H1'), 3.70 (dq, 1H, *J*=8.6, 6.9, H2'), 3.08 (q, 1H, *J*=6.5, H2), 2.98 (q, 1H, *J*=6.5, H2), 3.75 (s, 3H, NCH_3), 3.75 (m, 1H, H2'), 3.73 (s, 3H, NCH_3), 1.25 (d, 3H, *J*=6.9, H3'), 0.98 (d, 3H, *J*=6.5, H4), 0.95 (d, 3H, *J*=6.9, H3'), 0.43 (d, 3H, *J*=6.5, H4).

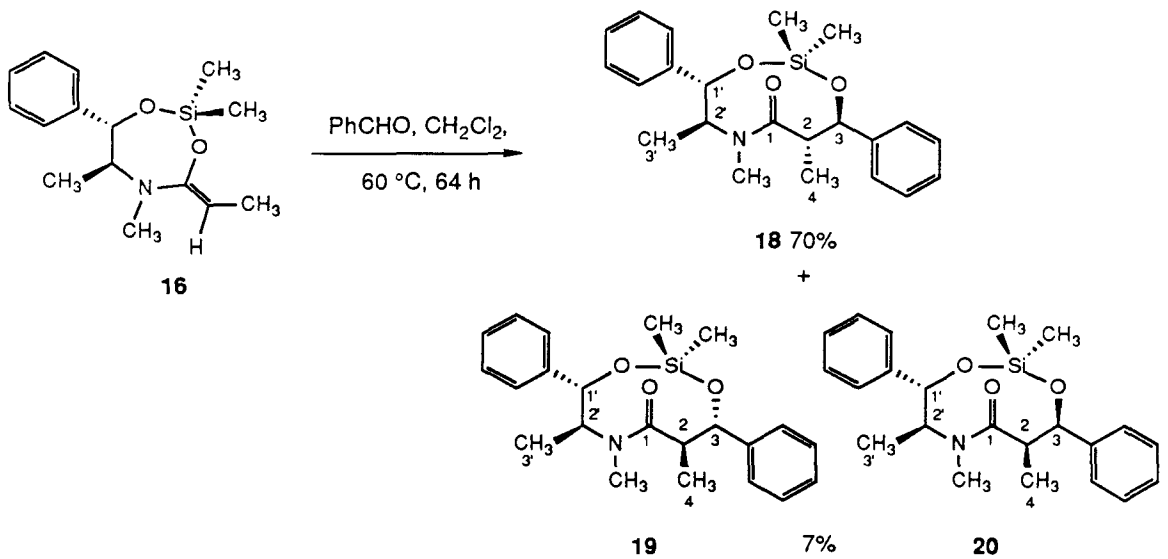
FTIR (neat film), cm^{-1}: 3389 (m), 2978 (w), 1614 (s), 1484 (m), 1408 (w), 1373 (w), 1202 (w), 1108 (w), 1079 (w), 1044 (m), 1020 (m), 914 (w), 750 (m), 703 (s).

MS (CI:NH_3): 329 (MH^+), 311 (MH^+-H_2O).

HRMS (CI:NH_3): Calculated for $C_{20}DH_{25}NO_3$ (MH^+): 329.1975

Found: 328.1969

TLC (50% EtOAc-hexanes):	Aldol product **18**	0.52
	Diol **21**	0.09



Desilylation of (1'*S*,2'*S*,2*R*,3*S*)-**19** and (1'*S*,2'*S*,2*R*,3*R*)-**20**

A mixture of **19** and **20** (20.2 mg, 0.052 mmol, 1.0 equiv) was treated with KF•2H_2O (30 mg, 0.32 mmol, 5.5 equiv) in MeOH (1 mL) at 23 °C for 3 h. The reaction mixture was diluted with ethyl acetate and flushed through a silica gel plug (ethyl acetate, 2 cm x 2 cm). After the reaction mixture was concentrated *in vacuo*, the residue was purified by flash chromatography (80% ether-petroleum ether) affording a mixture of (1'*S*,2'*S*,2*R*,3*S*)-**22** and (1'*S*,2'*S*,2*R*,3*R*)-**23** (2:3 ratio, 14.2 mg, 84%) as a colorless oil.

(1'*S*,2'*S*,2*R*,3*S*)-Diol **22**

^{1}H NMR (400 MHz, $CDCl_3$): 7.10-7.40 (m, 10H, arom), 4.82 (d, 1H, *J*=8.3, H3), 4.50 (d, 1H, *J*=9.3, H1'), 4.19 (dq, 1H, *J*=9.3, 6.8, H2'), 3.33 (dq, 1H, *J*=8.1, 6.8, H2), 2.92 (s, 3H, NCH_3), 1.96 (d, 3H, *J*=6.8, H4), 1.02 (d, 3H, *J*=6.8, H3').

(1'*S*,2'*S*,2*R*,3*R*)-Diol **23**

^{1}H NMR (400 MHz, $CDCl_3$): 7.00-7.40 (m, 10H, arom), 5.02 (d, *J*=5.6, H3), 4.59 (d, 1H, *J*=9.3, H1'), 4.50 (br, 1H, H2'), 3.00 (dq, 1H, *J*=7.1, 5.6, H2), 2.75 (s, 3H, NCH_3), 1.16 (d, 3H, *J*=7.1, H4), 0.92 (d, 3H, *J*=6.8, H3').

(1'*S*,2'*S*,2*R*,3*S*)-Diol **22** and (1'*S*,2'*S*,2*R*,3*R*)-Diol **23**

FTIR (neat film), cm^{-1}: 3378 (m), 2978 (w), 1614 (s), 1484 (m), 1408 (w), 1373 (w), 1202 (w), 1108 (w), 1079 (w), 1044 (m), 1020 (m), 914 (w), 750 (m), 703 (s).

MS (CI:NH_3): 328 (MH^+), 310 (MH^+-H_2O).

HRMS (CI:NH_3): Calculated for $C_{20}H_{26}NO_3$ (MH^+): 328.1913
Found: 328.1918

TLC (50% EtOAc-hexanes):

Aldol Adduct **19**	0.35
Aldol Adduct **20**	0.35
Diol **22**	0.09
Diol **23**	0.09

(1'*S*,2'*S*,2*R*,3*S*)-Diol **22** Deuterated at C3

^{1}H NMR (400 MHz, $CDCl_3$): 7.10-7.40 (m, 10H, arom), 4.50 (d, 1H, *J*=9.3, H1'), 4.19 (dq, 1H, *J*=9.3, 6.8, H2'), 3.33 (q, 1H, *J*=6.8, H2), 2.92 (s, 3H, NCH_3), 1.96 (d, 3H, *J*=6.8, H4), 1.02 (d, 3H, *J*=6.8, H3').

(1'*S*,2'*S*,2*R*,3*R*)-Diol **23** Deuterated at C3

^{1}H NMR (400 MHz, $CDCl_3$): 7.10-7.40 (m, 10H, arom), 4.59 (d, 1H, *J*=9.3, H1'), 4.50 (br, 1H, H2'), 3.00 (q, 1H, *J*=7.1, H2), 2.75 (s, 3H, NCH_3), 1.16 (d, 3H, *J*=7.1, H4), 0.92 (d, 3H, *J*=6.8, H3').

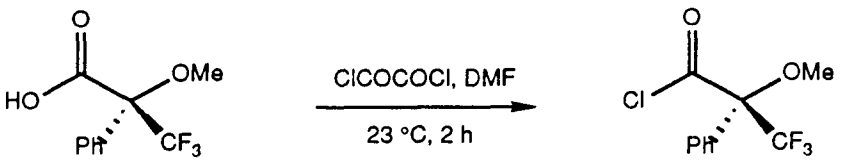
(1'*S*,2'*S*,2*R*,3*S*)-Diol **22** and (1'*S*,2'*S*,2*R*,3*R*)-Diol **23** Deuterated at C3

FTIR (neat film), cm^{-1}: 3378 (m), 2978 (w), 1614 (s), 1484 (m), 1408 (w), 1373 (w), 1202 (w), 1108 (w), 1079 (w), 1044 (m), 1020 (m), 914 (w), 750 (m), 703 (s).

MS (CI:NH_3): 329 (MH^+), 311 (MH^+-H_2O).

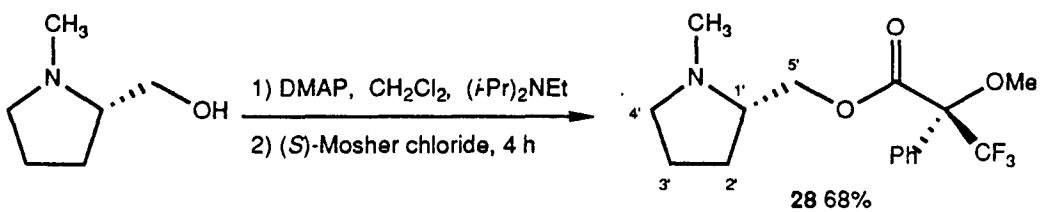
HRMS (CI:NH_3): Calculated for $C_{20}H_{25}DNO_3$ (MH^+): 329.1975
Found: 328.1969

TLC (50% EtOAc-hexanes):	Aldol Adduct **19**	0.35
	Aldol Adduct **20**	0.35
	Diol **22**	0.09
	Diol **23**	0.09



(*S*)-Mosher Chloride

(*R*)-(+)-MTAP (0.35 g, 1.71 mmol , 2.23 equiv, azeotropically dried with one portion of benzene) was treated with oxalyl chloride (151 μL, 1.72 mmol, 2.56 equiv) and a catalytic amount of DMF (40 μL) for 2 h at 23 °C. Considerable gas evolution was observed. The reaction mixture was concentrated under vacuum (0.1 Torr) and used in the following reactions without further purification.



(1'*S*,2*R*)-Mosher Ester **28**

A solution of (*S*)-MTAPCl (1.49 mmol, 2.23 equiv) in CH_2Cl_2 (2 mL) was added by cannula to a mixture containing (1*S*)-*N*-methyl prolinol[40] (77 mg, 0.67 mmol, 1.0 equiv), DMAP (120 mg, 0.98 mmol, 1.46 equiv), diisopropylethylamine (0.6 mL), 3-Å molecular sieves (100 mg) and CH_2Cl_2 (2 mL). After 4 h at 23 °C the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution (20 mL) and ethyl acetate (30 mL). The organic layer was separated, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (ethyl acetate) affording (1'*S*,2*R*)-**27** (150 mg, 68%) as colorless oil.

(1'*S*,2*R*)-Mosher Ester **28**

^{1}H NMR (400 MHz, C_6D_6): 7.20 (d, 2H, *J*=8.6, arom), 7.00-7.15 (m, 3H, arom), 4.22 (dd, 1H, *J*=5.4, 11.0, H5'), 3.96 (dd, 1H, *J*=4.8, 11.0, H5'), 3.41 (s, 3H, OCH_3), 2.75 (dd, 1H, *J*=4.8, 5.4, H1'), 2.12 (s, 3H, OCH_3), 2.12 (m, 1H, H4'), 1.87 (m, 1H, H4'), 1.45 (m, 2H), 1.32 (m, 2H).

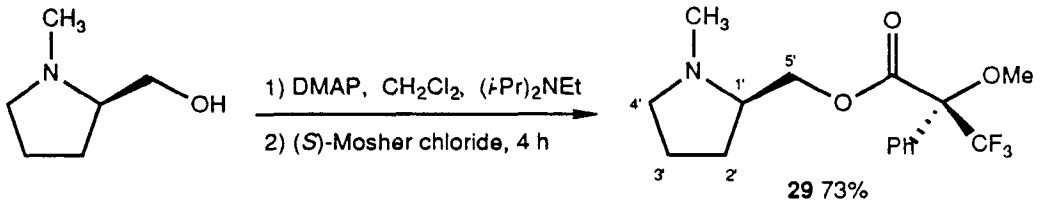
FTIR (neat film), cm^{-1}: 2952 (w), 1750 (s), 1451 (w), 1272 (m), 1246 (m), 1168 (s), 1122 (m), 1081 (w), 1024 (m), 719 (m).

MS (EI): 332 (MH^+), 189 ($C_6H_5CH_3OCF_3^+$).

HRMS (EI): Calculated for $C_{16}H_{21}F_3NO_3$ (M^+): 332.1474
Found: 332.1453

TLC (acetone):

Amine	0.34
Mosher ester **28**	0.72



29 73%

(1'*R*,2*R*)-Mosher Ester **29**

A solution of (*S*)-MTAPCl (1.71 mmol, 2.55 equiv) in CH_2Cl_2 (2 mL) was added by cannula to a suspension containing (1*R*)-*N*-methyl prolinol[40] (77 mg, 0.67 mmol, 1.0 equiv), DMAP (120 mg, 0.98 mmol, 1.46 equiv), diisopropylethylamine (0.6 mL), 3-Å molecular sieves (100 mg) and CH_2Cl_2 (2 mL). After 4 h at 23 °C the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution (20 mL) and ethyl acetate (30 mL). The organic layer was separated, dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography (ethyl acetate) afforded (1'*R*,2*R*)-**29** (162 mg, 73%) as a colorless oil.

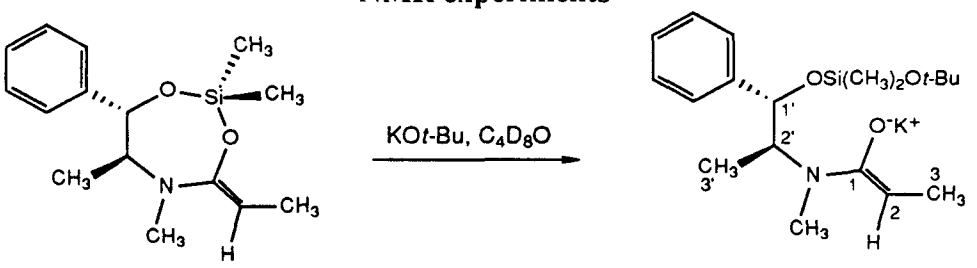
(1'*R*,2*R*)-Mosher Ester **29**

^{1}H NMR (400 MHz, C_6D_6): 7.20 (d, 2H, *J*=8.6, arom), 7.00-7.15 (m, 3H, arom), 4.28 (dd, 1H, *J*=5.4, 11.0, H5'), 3.91 (dd, 1H, *J*=4.8, 11.0, H5'), 3.47 (s, 3H, OCH_3), 2.78 (dd, 1H, *J*=4.8, 5.4, H1'), 2.10 (s, 3H, OCH_3), 2.10 (m, 1H, H4'), 1.87 (m, 1H, H5'), 1.45 (m, 2H, H3'), 1.28 (m, 2H, H4').

FTIR (neat film), cm^{-1}: 2952 (w), 1750 (s), 1451 (w), 1272 (m), 1246 (m), 1168 (s), 1122 (m), 1081 (w), 1024 (m), 719 (m).

MS (EI):	332 (MH^+), 189 ($C_6H_5CH_3OCF_3^+$).	
HRMS (EI):	Calculated for $C_{16}H_{21}F_3NO_3$ (M^+): 332.1474	
	Found: 332.1473	
TLC (acetone):	Amine	0.36
	Mosher ester **29**	0.75
GC (Chirasil Val III, 110 °C):	Mosher ester **28**	51.84 min
	Mosher ester **29**	53.02 min

NMR experiments



16 30

(1'*S*, 2'*S*)-Potassium Enolate **30**

Potassium *tert*-butoxide (30.0 mg, 0.27 mmol, 1.46 equiv) and C_4D_8O (0.4 mL) were combined in an NMR tube in a nitrogen-filled glovebox. The NMR tube was sealed with a septum and removed from the box. (1'*S*, 2'*S*)-*O*-Silyl ketene *N,O*-acetal **16** (0.040 mL, 45 mg, 0.185 mmol, 1.0 equiv) was added dropwise to the reaction mixture. The NMR tube was shaken after each drop of enolate was added. A clear yellow solution resulted.

(1'*S*, 2'*S*)-Potassium enolate **30**

^{1}H NMR (400 MHz, C_4D_8O): 7.37-7.12 (m, 10H, arom), 4.68 (d, 1H, *J*=10.5, H1'), 4.05 (m, 1H, H2'), 2.97 (q, 1H, *J*=6.3, H2), 2.32 (s, 3H, NCH_3), 1.08 (d, 3H, *J*=6.3, H3), 1.20 (s, 9H, O*t*-Bu), 0.51 (d, 3H, *J*=8.7, H3'), 0.15 (s, 3H, $SiCH_3$), -0.27 (s, 3H, $SiCH_3$).

^{29}Si NMR (79 MHz, C_4D_8O): -8

Kinetics

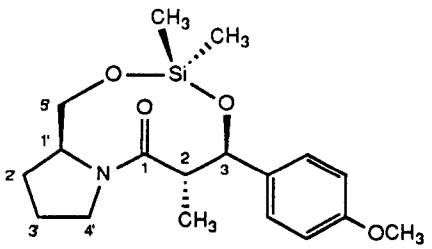
General Procedure for Liquid Aldehydes

(1'*S*)-*O*-Silyl ketene *N,O*-acetal **7** (30 μL, ~33 mg, 0.0154 mmol, 1 equiv) was weighed into a dry NMR tube (equipped with screw threads) sealed with two septa. 1,1-diphenylethylene (12.6-10 μL, 12.9-10.2 mg, 0.071-0.056 mmol, ~0.5 equiv) and C_6D_6 (400 μL) were added. The solution was subjected to three pump-freeze-thaw degas cycles, then aldehyde (0.0154 mmol, 1 equiv) was added by syringe. The septa were replaced with a Teflon seal. The solution was subjected to three more pump-freeze-thaw degas cycles. The solution was kept at -78 °C until monitoring was started. The sample was protected from light when not in the NMR probe since the standard is slightly light-sensitive.

General procedure for solid aldehydes

Solid para-substituted benzaldehyde (1 equiv, 0.0154 mmol) was weighed into a dry NMR tube (equipped with screw threads) fitted with two septa. 1,1-diphenylethylene (12.6-10.0 μL, 12.9-10.2 mg, 0.071-0.056 mmol, ~0.5 equiv), C_6D_6 (400 μL) and (1'*S*)-*O*-silyl ketene *N,O*-acetal **7** (30 μL, ~33 mg, 0.0154 mmol, 1 equiv) were syringed into the NMR tube. The septa were replaced with a Teflon seal. The solution was subjected to one pump-freeze-thaw degas cycle. The solution was kept at -78 °C until monitoring commenced.

All samples (except the one used for the 20 °C benzaldehyde run) were kept in the NMR probe for the entire measurement period. The 20 °C benzaldehyde sample was protected from light and immersed in a constant temperature bath between monitorings.



31

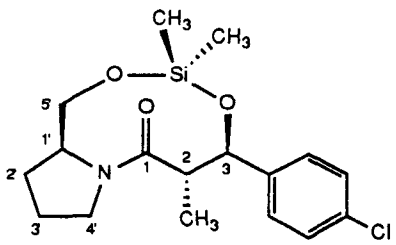
p-Methoxybenzaldehyde Adduct **31**

^{1}H NMR (400 MHz, C_6D_6): 7.25 (d, 1H, *J*=8.8, arom), 6.81 (d, 2H, *J*=8.8, arom), 5.02 (dd, 1H, *J*=3.2, 11.2, H5'), 4.82 (d, 1H, *J*=9.7, H3), 4.00 (dt, 1H, *J*=3.0, 7.7, H1'), 3.60 (dt, 1H, *J*=6.5, 9.7, H4'), 3.33 (d, 1H, *J*=10.8, H5'), 3.29 (s, 3H, OCH_3), 3.03 (dt, 1H, *J*=2.9, 7.9, H3'), 2.88 (dq, 1H, *J*=6.7, 9.7, H2), 1.82 (m, 1H), 1.59 (m, 2H), 1.27 (m, 1H), 1.06 (d, 3H, *J*=6.7, CH_3), 0.34 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$).

FTIR (neat film), cm^{-1}: 2961 (m), 2879 (m), 1629 (s), 1510 (m), 1458 (m), 1427 (m), 1298 (w), 1247 (s), 1169 (w), 1112 (m), 1066 (m), 1030 (m), 983 (m), 911 (m), 875 (m), 849 (m), 797 (m).

MS (CI:CH_4): 350 (MH^+).

HRMS (CI:CH_4):	Calculated for $C_{18}H_{28}NO_4Si$ (MH^+): 350.1788	
	Found: 350.1780	
MP:	113-115 °C	
TLC (30% ether-pet. ether):	**31**	0.16
	p-Methoxybenzaldehyde	0.40
	1,1-Diphenylethylene	0.80



32

p-Chlorobenzaldehyde Adduct **32**

^{1}H NMR (400 MHz, C_6D_6): 7.12 (d, 1H, *J*=8.8, arom), 6.98 (d, 2H, *J*=8.8, arom), 4.96 (dd, 1H, *J*=3.2, 11.2, H5'), 4.66 (d, 1H, *J*=9.7, H3), 3.96 (dt, 1H, *J*=3.0, 7.7, H1'), 3.48 (dt, 1H, *J*=6.5, 9.7, H4'), 3.32 (d, 1H, *J*=10.8, H5'), 2.94 (dt, 1H, *J*=2.9, 7.9, H4'), 2.65 (dq, 1H, *J*=6.7, 9.7, H2), 1.76 (m, 1H), 1.55 (m, 2H), 1.23 (m, 1H), 0.92 (d, 3H, *J*=6.7, CH_3), 0.30 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$).

FTIR (neat film), cm^{-1}: 2961 (w), 1624 (s), 1484 (w), 1453 (w), 1427 (s), 1252 (m), 1107 (m), 1066 (s), 1050 (m), 1009 (w), 906 (w), 875 (w), 854 (m), 797 (w).

MS (CI:CH_4): 354 (MH^+).

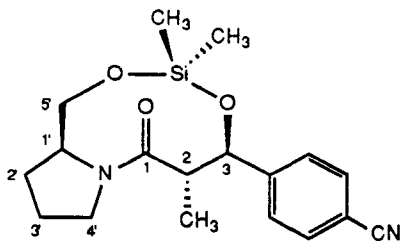
HRMS (CI:CH_4): Calculated for $C_{17}H_{25}ClNO_3Si$ (MH^+): 354.1292

Found: 354.1288

MP: 168-170 °C

TLC (ether):

32	0.62
p-Chlorobenzaldehyde	0.85
1,1-Diphenylethylene	0.96



33

p-Cyanobenzaldehyde Adduct

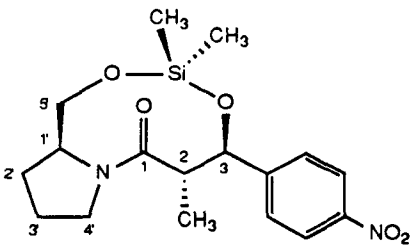
^{1}H NMR (400 MHz, C_6D_6): 7.03 (d, 1H, *J*=6.8, arom), 6.93 (d, 2H, *J*=7.1, arom), 4.92 (dd, 1H, *J*=3.2, 10.8, H5'), 4.59 (d, 1H, *J*=9.8, H3), 3.93 (dt, 1H, *J*=3.0, 7.7, H1'), 3.40 (dt, 1H, *J*=2.9, 9.4, H4'), 3.29 (d, 1H, *J*=11, H5'), 2.93 (dt, 1H, *J*=2.9, 7.6, H4'), 2.55 (dq, 1H, *J*=6.8, 9.6, H2), 1.75 (m, 1H), 1.58 (m, 2H), 1.24 (m, 1H), 0.81 (d, 3H, *J*=6.6, CH_3), 0.25 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$).

FTIR (neat film), cm^{-1}: 2959 (w), 2885 (w), 2231 (m), 1630 (s), 1429 (m), 1255 (m), 1113 (m), 1081 (m), 1049 (w), 991 (w), 912 (w), 870 (m), 854 (m), 796 (m).

MS (CI:CH_4): 345 (MH^+).

HRMS (CI:CH_4): Calculated for $C_{18}H_{25}N_2O_3Si$ (MH^+): 345.1634
Found: 345.1643

MP:	168-170 °C	
TLC (ether):	**33**	0.54
	p-Cyanobenzaldehyde	0.85
	1,1-Diphenylethylene	0.96



34

<u>*p*-Nitrobenzaldehyde Adduct</u>

^{1}H NMR (400 MHz, C_6D_6): 7.84 (d, 1H, *J*=8.8, arom), 6.93 (d, 2H, *J*=8.8, arom), 4.92 (dd, 1H, *J*=3.2, 11.2, H5'), 4.64 (d, 1H, *J*=9.7, H3), 3.95 (dt, 1H, *J*=3.0, 7.7, H1'), 3.42 (dt, 1H, *J*=6.5, 9.7, H4'), 3.30 (d, 1H, *J*=10.8, H5'), 2.95 (dt, 1H, *J*=2.9, 7.9, H4'), 2.56 (dq, 1H, *J*=6.7, 9.7, H2), 1.75 (m, 1H), 1.58 (m, 2H), 1.26 (m, 1H), 0.81 (d, 3H, *J*=6.7, CH_3), 0.13 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$).

FTIR (neat film), cm^{-1}: 2959 (w), 2874 (w), 1635 (s), 1609 (m), 1519 (s), 1456 (w), 1435 (m), 1345 (s), 1255 (m), 1113 (w), 1081 (m), 1049 (w), 986 (w), 912 (w), 849 (m), 838 (m), 796 (m).

MS (CI CH_4): 365 (MH^+).

HRMS (EI): Calculated for $C_{17}H_{25}N_2O_5Si$ (MH^+): 365.1532

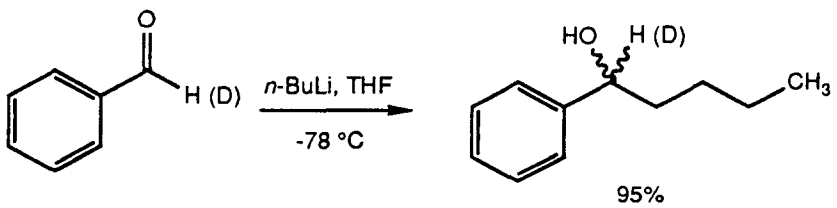
Found: 365.1537

MP: 160-162 °C

TLC (ether):

34	0.42
p-Nitrobenzaldehyde	0.79
1,1-Diphenylethylene	0.92

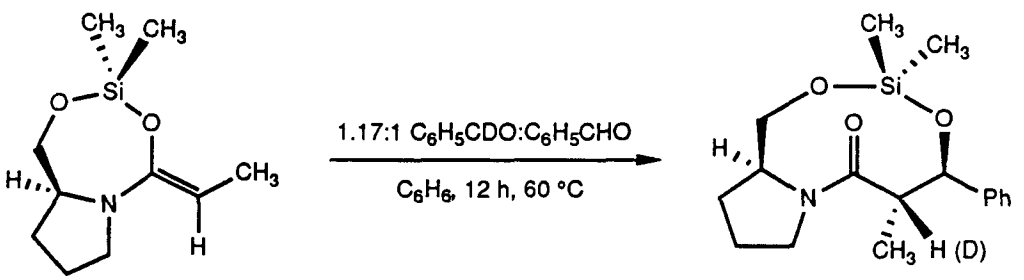
Deuterium Isotope Experiments



95%

Determination of Deuterium Enrichment of Benzaldehyde

n-Butyllithium (0.59 mL, 2.5 M in hexanes, 1.475 mmol, 1.5 equiv) was added dropwise over 5 min to a deoxygenated solution of benzaldehyde (~1:1 mixture of C_6H_5CHO:C_6H_5CDO, 100 μL, 0.98 mmol, 1 equiv) in THF (2 mL) at -78 °C. The reaction was kept at -78 °C for 2 h, then warmed to 0 °C for 15 min to ensure complete reaction. The reaction mixture was then partitioned between 3:1 ethyl acetate-hexanes (10 mL) and H_2O (2 mL). The organic layer was separated, dried with sodium sulfate, filtered and concentrated *in vacuo*, affording 1-phenyl 1-pentanol (152.6 mg, 95%). The percentage of deuterium present in the 1-phenyl 1-pentanol was determined by mass spectrometry.



7

9 50% (0.88:1 d_1:d_0)

Determination of the Deuterium Incorporation of **9**

(1'*S*)-*O*-Silyl ketene *N,O*-acetal **7** (112.3 mg, 0.526 mmol, 1.0 equiv) was added to a deoygenated solution of benzaldehyde (~1:1 mixture of C_6H_5CHO:C_6H_5CDO, 0.75 mL, 0.78 g, 7.3 mmol, 14 equiv) in benzene (1.5 mL). The foil-covered reaction flask

was heated at 60 °C for 12 h, then the reaction mixture was cooled and concentrated *in vacuo*. Flash chromatography (50% ether-petroleum ether) afforded **9** (85 mg, 50%) as a white solid.

Run 1

%Deuterium incorporation:	1-Phenyl 1-pentanol	54%
	Aldol adduct **9**	47%

Run 2

%Deuterium incorporation:	1-Phenyl 1-pentanol	54%
	Aldol adduct **9**	47%

References

[1]Kane, R. *Ann. Physik Chem.* **1838**, *44*, 475.

[2]Reviews on stereoselective aldol reactions: (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (b) Heathcock, C. H. In *Asymmetric Synthesis;* Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 2.

[3]The preference for *Z* configuration found with amide enolates is perhaps due to developing $A_{1,3}$ strain present in the transition state leading to the *E* enolate: (a) Fataftah, Z. A.; Kopka, I. E.; Rathke, M. W. *J. Am. Chem. Soc.* **1980**, *102,* 3959. (b) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *46*, 1066. (c) Evans, D. A.; McGee, L. R. *Tetrahedron Lett.* **1980**, *21*, 3975. (d) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233. (e) Takacs, J. M. Ph.D. Thesis, California Institute of Technology, 1981.

[4]Sogah, D. Y.; Hertler, W. R.; Webster, O. W.; Cohen, G. M. *Macromolecules* **1987**, *20*, 1473.

[5]This mechanism is controversial. An open transition state is proposed for fluoride-catalyzed aldol reactions: Noyori, R.; Nishida, I.; Sakata, J.; Nishizawa, M. *J. Am. Chem. Soc.* **1980**, *102*, 1223.

[6](a) Hudrlik, P. F.; Peterson, D.; Chou, D. *Synth. Commun.* **1975**, *5*, 359. (b) Woodbury, R. P.; Rathke, M. W. *J. Org. Chem.* **1978**, *43*, 881, and references therein.

[7]Ojima, I.; Kogure, T. *Organometallics* **1982**, *1*,1390.

[8]Myers, A. G.; Widdowson, K. L. *J. Am. Chem. Soc.* **1990**, *112*, 9672.

[9]Creger, P. L. *Tetrahedron Lett.* **1972**, 79.

[10]Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

[11]Schaefer, W. P.; Widdowson, K. L.; Myers, A. G. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1991**, *C47*, 9672.

[12]Crystal structures of *O*-silyl enol ethers: (a) Seebach, D.; Maetzke, T.; Petter, W.; Klotzer, B; Plattner, D. A. *J. Am. Chem. Soc.* **1991**, *113*, 1781. (b) Appel, R.; Hünerbein, J.; Knoch, F. *Angew Chem., Int. Ed. Engl.* **1983**, *22*, 61. (c) Cheng, P.-T.; Nyburg, S. C. *Acta Crystallogr. Sect. B* **1976**, *32*, 930. (d) Fenske, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 635. (e) Merzweiler, K.; Crossland, I.; Bock, K.; Norrostam, R. *Acta Chem. Scand. Ser. B* **1985**, *39*, 7. (f) Seebach, D.; Ertas, M.; Löcher, R.; Schweizer, W. B. *Helv. Chim. Acta.* **1985**, *68*, 264. (g) House, H. O.; Nomura, G. S.; VanDerveer, D.; Wissinger, J. E. *J. Org. Chem.* **1986,** *51*, 2408. (h) Mena, M.; Pellinghelli, M. A.; Royo, P.; Serrano, R.; Tiripiccihio, A. *J. Chem. Soc., Chem. Commun.* **1988**, 1116. (i) Groth, P. *Acta Chem. Scand. Ser. A.* **1977**, *31*, 641. (j) Brook, A. G.; Chatterton, W. J.; Sawyer, J. F.; Hughes, D. W.; Vorspohl, K. *Organometallics* **1987**, *6*, 1247. (k) Brisse, F.; Thoraval, D.; Chan, T. H. *Can. J. Chem.* **1986**, *64*, 739. (l) Maas, G.; Schneider, K.; Ando, W. *J. Chem. Soc., Chem. Commun.* **1988**, 72.

[13]For a theoretical study on the size of the Si-O-C bond angle see: Shambayati, S.; Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 697.

[14]This parallels an observation made in Chapter II, the larger ring siloxanes (7-9 membered rings) are stable to silica gel, while the smaller ring siloxanes are not.

[15]Chiral anti selective aldol reactions: (a) Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976. (b) Masamune, S.; Sato, T.; Kim, B. M.; Wollman, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279. (c) Gennari, C.; Bernardi, A.; Colombo, L.; Scolastico, C. *J. Am. Chem. Soc.* **1985**, *107*, 5812. (d) Helmchen, G.; Leikauf, U.; Taufer-Knöpfel, I. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 874. (e) Oppolzer, W.; Starkemann, C.; Rodriguez, I.; Bernardinelli, G. *Tetrahedron Lett.* **1991**, *32*, 61. (f) Meyers, A. I.; Yamamoto, Y. *Tetrahedron* **1984**, *40*, 2309. (g) Palazzi, C.; Colombo, L.; Gennari, C. *Tetrahedron Lett.* **1986**, *27*, 1735. (h) Oppolzer, W.; Marco-Contelles, J. *Helv. Chem. Acta.* **1986**, *69*, 1699. (i) Danda, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem.* **55**, *32*, 173. (j) Corey, E. J.; Kim, S. S. *Tetrahedron Lett.* **1990**, *31*, 3715.

[16]The complex {**7**•PhCHO} may not be an energy minimum but rather a point on the reaction-coordinate surface.

[17]These results are summarized in two papers: (a) Myers, A. G.; Widdowson, K. L.; Kukkola, P. K. *J. Am. Chem. Soc.*, in press. (b) Myers, A. G.; Kephart, S. E.; Widdowson, K. L. *J. Am. Chem. Soc.*, manuscript in preparation.

[18]All slopes and associated uncertainties were calculated using weighted-least-squares formulas found in: Bevington, P. *Data Reduction and Error Analysis for the Physical Sciences* McGraw & Hill, New York, 1969; p. 92-118. Concentrations were calculated using the vinylic resonance of 1,1-diphenyl ethylene as the standard. Relative errors of integration of proton NMR spectra were assigned as 1-2% of value on the basis of peak shape and evidence of decomposition. The pulse delay for the sample was set at 20 seconds. Relative and absolute uncertainties were propagated following standard formulas outlined in: Skoog, D. A.; West, D. M. *Fundamentals of Analytical Chemistry* Holt, Rinehart, and Winston, 1976, pp. 42-88. The NMR probe temperature was calibrated using ethylene glycol according to formulas outlined in: Gordon, A. G.; Ford, R. A. *The Chemist's Companion.* Wiley & Sons, New York, 1972; p. 303. Volumes were assumed to be additive, except with solid aldehydes where the NMR tube was precalibrated. This assumption was tested for benzaldehyde and appeared to be valid.

[19]Carpenter, B. K. *Determination of Organic Reaction Mechanisms* John Wiley & Sons, New York, 1984; p. 96.

[20]Review: Halevi, E. A. *Progress in Physical Organic Chemistry* **1963**, *1*, 109.

[21]*p*-Methoxy benzaldehyde and benzaldehyde samples were monitored at 19.4 °C and 76.9 °C, respectively, and extrapolated back to 21.3 °C. All other *p*-substituted benzaldehydes were monitored at 21.3 °C.

[22]It is interesting to compare these results with those of ref. 24 d and f, where a Hammett ρ of -1.52 was obtained in a kinetic study of the racemization of a tetracoordinated silane by a series of *p*-substituted benzaldehydes.

[23]Prof. John E. Bercaw, personal communication.

[24]Pseudorotation reviews: (a) Westheimer, F. H. *Acc. Chem. Res.* **1968**, *1*, 70. (b) Mislow, K. *Acc. Chem. Res.* **1970**, *3*, 321.

[25]Mechanistic work on pseudorotation around silicon: (a) Klanberg, F.; Muetterties, E. L. *Inorg. Chem.* **1968**, *7*, 155. (b) Gibson, J. A.; Ibbott, D. G.; Janzen, A. F. *Can. J. Chem.* **1973**, *51*, 3203. (c) Farnham, W. B.; Harlow, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 4608. (d) Stevenson, W. H., III; Martin, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 309. (e) Stevenson, W. H., III; Wilson, S.; Martin, J. C.; Farnham, W. B. *J. Am. Chem. Soc.* **1985**, *107*, 6340. f) Stevenson, W. H., III; Martin, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 6352.

[26]Theoretical work on pseudorotation around silicon: Deiters, J. A.; Holmes, R. R. *J. Am. Chem. Soc.* **1987**, *109*, 1686.

[27]Berry, R. S. *J. Am. Chem. Soc.* **1968**, *90*, 6722. see also 24 b and references therein.

[28]An alternative turnstile mechanism for interconverting tbps has been proposed. However, structural and theoretical studies favor the Berry pseudorotational mechanism: (a) Muettereties, E. L. *J. Am. Chem. Soc.* **1969**, *91*, 4115. (b) Marsden, C. J.; *J. Chem. Soc., Chem. Commun.* **1984**, 40. (c) Holmes, R. R.; Brown, R. K. *J. Am. Chem. Soc.* **1977**, *99*, 3326. (d) Holmes, R. R.; Day, R. O.; Harland, J. J.; Sau, A. C.; Holmes, J. M. *Organometallics* **1984**, *3*, 343. (e) Holmes, R. R.; Day, R. O.; Chandrasekhar, V.; Harland, J. J.; Holmes, J. M. *Inorg. Chem.* **1985**, *24*, 2016.

[29]Lauterbur, P. C.; Ramirez, F. *J. Chem. Phys.* **1960**, 933.

[30]Review on ^{29}Si NMR: Williams, E. A., Cargioli, J. D. *Ann. Rep. NMR Spectroscopy* **1970**, *9*, 221.

[31]The enantiomer is depicted for visual comparison of homochiral structures.

[32]*O*-Silyl *N,O*-acetal **16** was synthesized in an analogous manner to **7** in a 80% distilled yield.

[33]Schaefer, W. P.; Widdowson, K. L.; Myers, A. G. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1991**, *C47*, 000.

[34]Hanson, K. R. *J. Am. Chem. Soc.* **1966**, *88*, 2731.

[35]Hoffmann, R.; Howell, J. M.; Muetterties, E. L. *J. Am. Chem. Soc.* **1972**, *94*, 3047.

[36]Huheey, J. E. *Inorganic Chemistry* Harper & Row: New York, 1983; p. 258. see also 24 e.

[37](a) Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chem. Acta.* **1985**, *68*, 1373. (b) Bauer, W.; Laube, T.; Seebach, D. *Chem. Ber.* **1985**, *118*, 764.

[38]Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

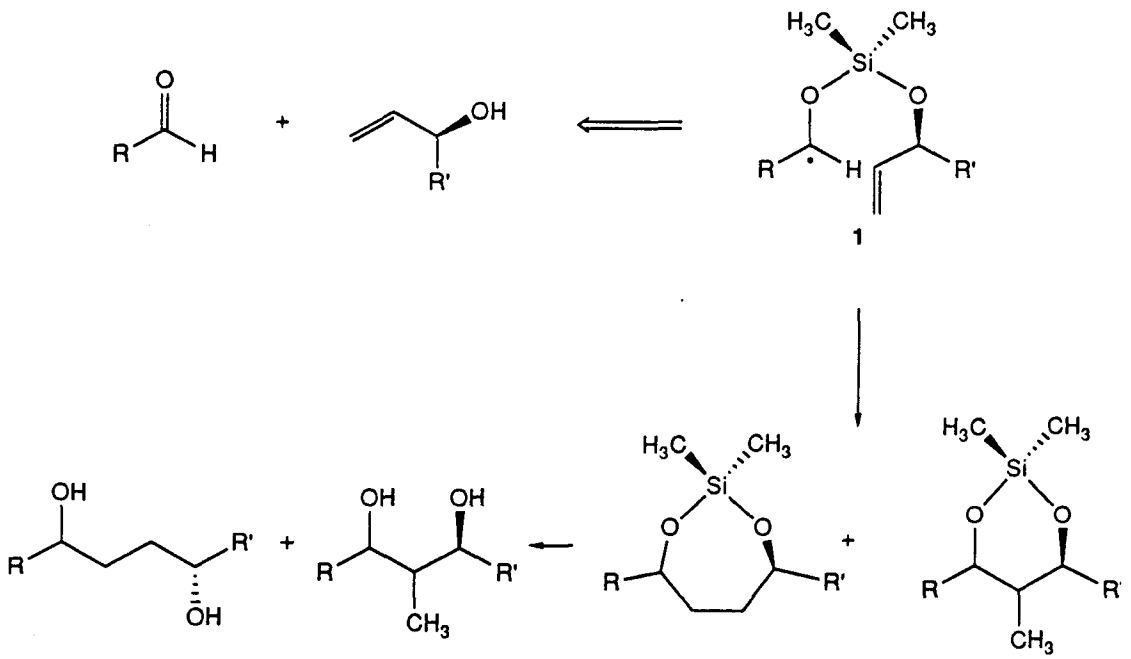
[39]Kofron, W. G.; Baclawski, L. H. *J. Org. Chem.* **1976**, *41*, 1879.

[40]Chavdarian, C. G.; Sanders, E. B. *Org. Prep. Proc. Int.* **1981**, *13*, 389.

CHAPTER II

Radical Cyclizations of *O*-Alloxy Dimethylsilyl Hemiselenoacetals

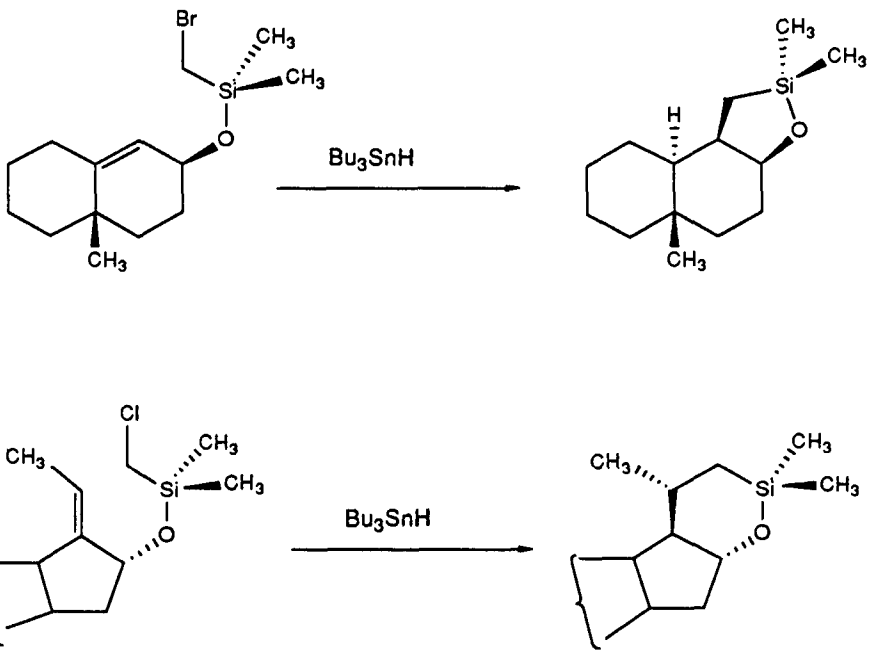
We wanted to study the cyclization of siloxane-linked radicals such as **1**, as a potential stereoselective carbon-carbon bond forming reaction. Radical **1** is an especially attractive intermediate; the transition from inter- to intramolecular radical-olefin addition generally improves both yield and selectivity. We envisioned that **1** might be generated from an allylic alcohol and an aldehyde. Control of absolute stereochemistry of the cyclization products can then be achieved using optically active allylic alcohols.



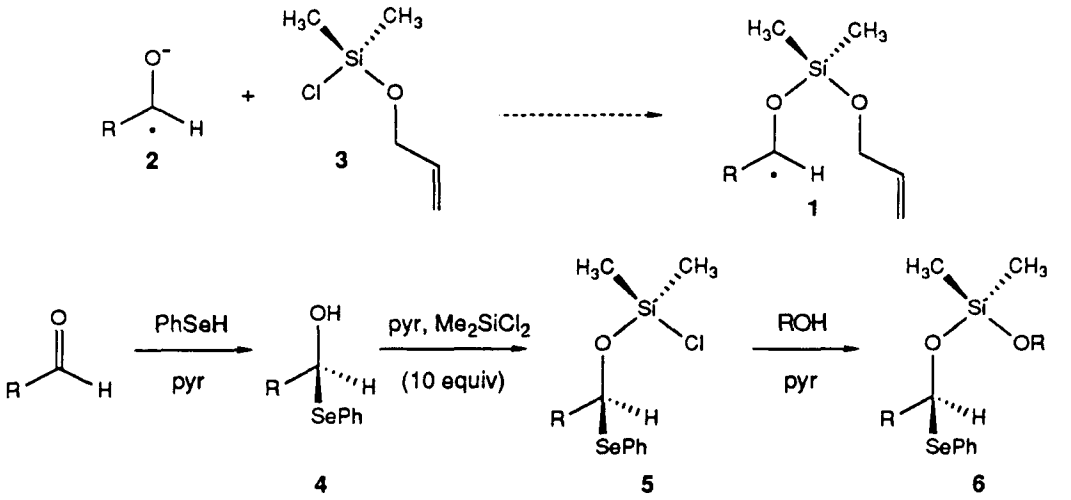
Both 6-exo and 7-endo cyclization of **1** can be envisioned. Previous studies with all-carbon chains demonstrate that 6-exo cyclization is kinetically favored.[1] This selectivity generally applies when the ring contains only first row elements; however, when silicon is included in the ring system the regiochemistry of radical attack is less predictable.[2]

At the outset of our studies no data was available concerning the cyclizations of siloxanes such as **1**, though results with related systems suggested that the regioselectivity

of radical attack is highly dependent upon the substitution of the allyl alcohol (*vide infra*).[2] The increased tendency for endo attack in these cases, relative to all-carbon systems has been rationalized by trajectory analysis; longer bonds created by incorporating silicon in the ring make endo attack more favorable.[2h]



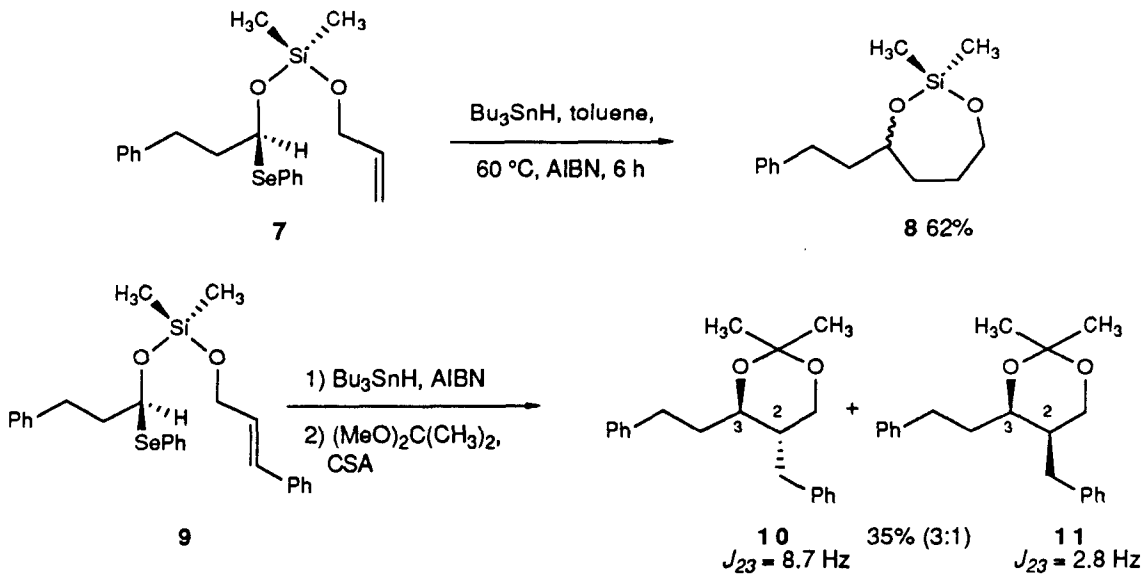
Initial efforts to access the intermediate **1** by generation of the radical anion **2** in the presence of silyl chloride **3**, led to the exclusive formation of dimeric pinacol products. To circumvent this problem, we decided to form the silicon-oxygen bond prior to radical generation. The hemiselenoacetal **6** seemed a nearly ideal precursor in this regard since the selenium-carbon bond is readily cleaved with trialkyltin radicals.[3] This cleavage should be especially facile in the present case given the stability of the product radical.



Trimethylsilyl hemiselenoacetals have been synthesized previously by reaction of an aldehyde with benzeneselenol, pyridine and chlorotrimethylsilane.[4] Modification of this procedure by substitution of chlorotrimethylslane with dichlorodimethylsilane (~10 equiv) afforded the monochlorosilyl intermediate **5**, in high yields. Rather than attempt purification of this hydrolytically unstable intermediate, **5** was directly transformed to siloxane **6** by reaction with an allylic alcohol.[5] Siloxanes **6** were stable to aqueous extraction but hydrolyzed readily on silica gel, and so they were used without purification. Small amounts of diphenydiselenide (~5%) and starting aldehyde (<5%) were the only detectable impurities. This methodology appears to be fairly general and gave high yields of product with a number of allylic alcohols. The corrected yields for the products from reaction with allyl alcohol, (*E*)-cinnamyl alcohol, and methallyl alcohol were 93, 92, and 87%, respectively.

Mixing aldehyde and benzeneselenol prior to the addition of silyl chloride (as opposed to combining the reagents all at once) appeared to accelerate the reaction. This mode of addition may prevent the formation of the less reactive silyl selenide.[6] The order of addition of **4** and allylic alcohols to the dichlorodimethylsilane is also important.

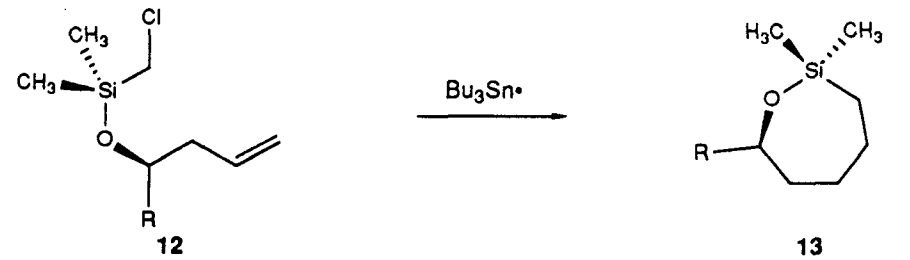
Addition of the allylic alcohol prior to the presumed benzeneselenol-aldehyde adduct (**4**), results in about 15% of the symmetrically substituted siloxane ($(CH_3)_2Si(OR)_2$).



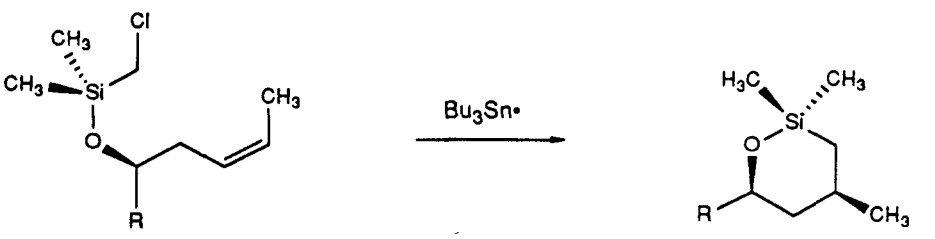
Hemiselenoacetals **7** and **9** reacted smoothly with tributyltin hydride to form both cyclization products and products resulting from simple reductive cleavage of selenium. The seven-membered ring **8** was the sole cyclization product obtained from reaction of hemiselenoacetal **7**. In addition, small amounts (~5%) of hydrocinnamyl alcohol were formed, presumably resulting from competitive trapping of the radical intermediate with tributyltin hydride. The reaction of (*E*)-cinnamyl alcohol derivative **9** with tributyltin hydride produced a 3:1 mixture of anti and syn diastereomers. As these six-membered ring siloxanes were sensitive to silica gel, they were converted directly to the corresponding acetonides for characterization (35%, two steps). The relative stereochemistry of each acetonide was determined by examining coupling constants between protons H2 and H3. The anti diastereomer, in which protons H2 and H3 are diaxial, exhibited the larger coupling constant.

The different regioselectivities observed with **7** and **9** can be rationalized by both electronic and steric factors. The radical derived from **7** attacks at the less hindered terminus of the double bond to form a more stable secondary radical. Longer silicon-oxygen bonds also favor formation of the 7-membered ring. The regioselectivity is different for **9**, where both ends of the double bond are substituted, and the more stable benzylic radical is produced by 6-exo cyclization. It is not to be inferred that these radical cyclizations are reversible; since the thermodynamic stabilities of the product radicals may well be reflected in the relative stabilities of the respective transition states.

Similar results have recently been observed by Koreeda[7] during his investigation of the radical cyclizations of silyl ethers **12** and **14**. With substrate **12** where the olefinic terminus is unsubstituted exclusive 7-endo attack is observed. However, exclusive 6-endo attack is observed with the *Z* olefin **14**.



12 **13**



14 **15**

The ratio of cyclic products to simple reduction products was dependent on temperature , concentration, and solvent (Table I).

Table I. Influence of reaction variables on radical cyclization of **7** and **9**

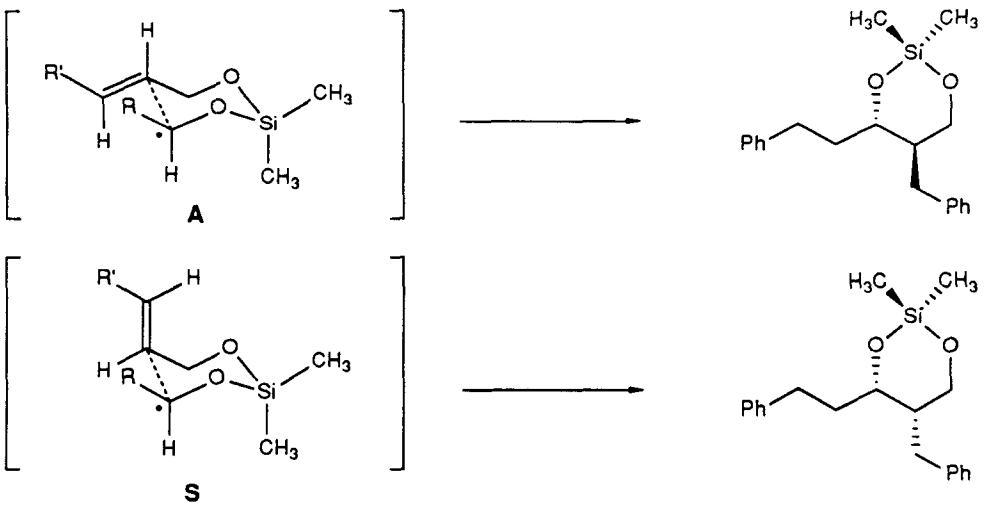
Substrate	Temperature (°C)	Cyclized/Reduced[a]	[Bu_3SnH] (mM)	Solvent	Yield (%)	Ratio[b] anti:syn
7	30	1:5	5.9	toluene	-	-
7	60	9:1	5.9	toluene	71[c]	-
7	110	6:1	5.9	toluene	59[c]	-
7	60	9:1	3.0	toluene	55[c]	-
7	60	2:3	5.9	THF	-	-
9	30	1:10	5.9	toluene	-	-
9	60	3:1	5.9	toluene	41[d]	3:1
9	110	3:1	5.9	toluene	35[d]	1.8:1

[a]Determined by integration of ^1H NMR of crude reaction mixtures. [b]Determined by integration of the corresponding acetonides. [c]Isolated yield of 7-membered siloxane **8**. [d]Isolated yield of 1,3-diols.

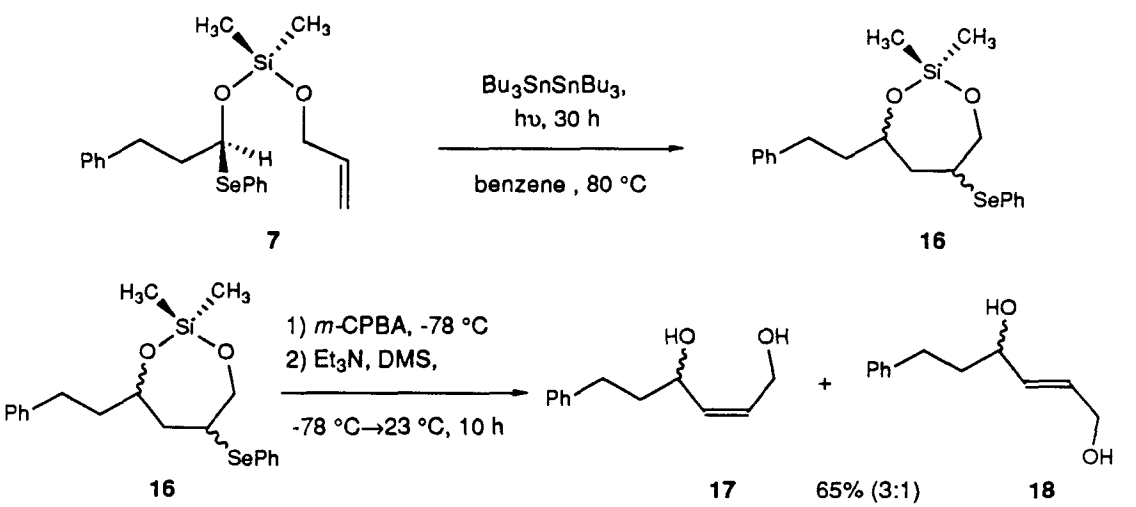
There appears to be a thermal barrier to cyclization, since reduction predominates below 60 °C. The proportion of noncyclized products decreased upon lowering the concentration of tributyltin hydride. This is not surprising, since the formation of reduced product is expected to be a bimolecular process (first order in both tributyltin hydride and substrate), while the cyclization is unimolecular (first order in substrate alone). This effect levels off at tributyltin hydride concentrations below 5.9 mM, perhaps because at that point the solvent competes effectively as a hydrogen atom donor. Solvent was also an important factor; increased amounts of reduction product resulted when tetrahydrofuran was used instead of toluene.

The diastereoselectivity for the cyclization of **7** increases at lower reaction temperatures, favoring the anti isomer. This selectivity may be explained by invoking chair-like transition states such as **A** and **S**. In transition state **A**, both bulky substituents can adopt an equatorial orientation. In transition state **S** the olefinic substituent is axial.

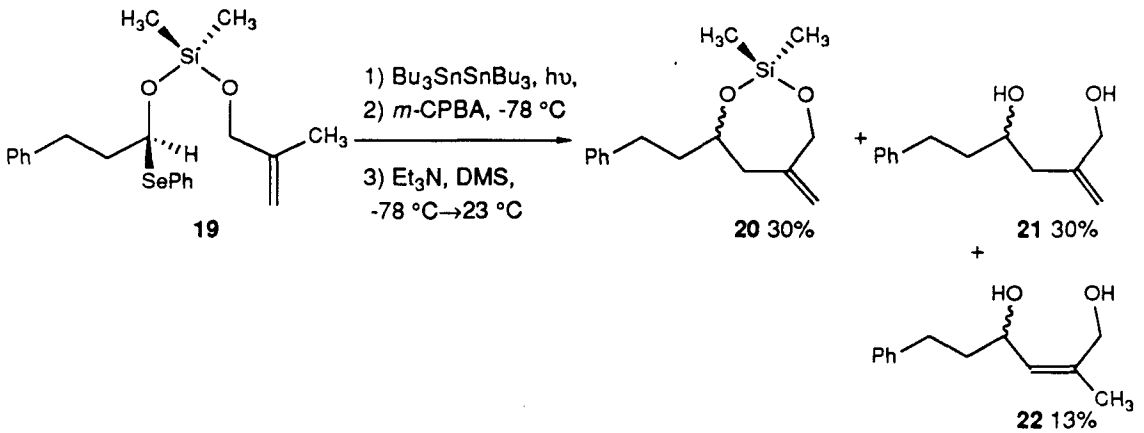
The poor discrimination between anti and syn diastereomers is perhaps not surprising given the weak 1,3-diaxial interactions in **S**.



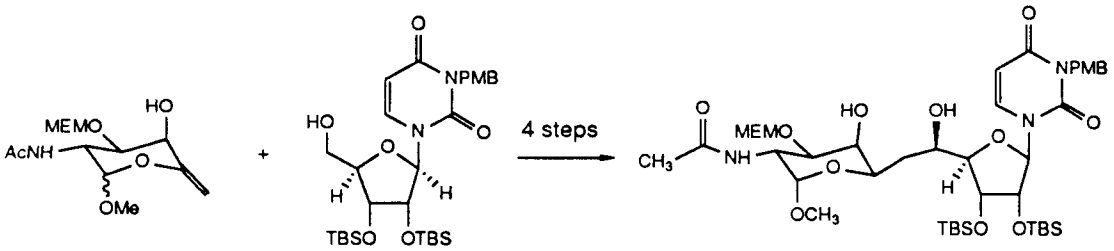
We have also studied group transfer radical cyclization with substrate **7**. Primarily through the efforts of Curran,[8] this reaction has become a valuable way to incorporate functionality in radical cyclizations. Curran's research has focused on the transfer of iodides. The group transfer of selenium, on the other hand, has received very little attention.[9]



Irradiation of siloxane **7** with a tungsten lamp in the presence of a catalytic (10 mol%) amount of hexabutylditin gave almost quantitative yields of diastereomeric group transfer products **16**. Since these products partially hydrolyzed on silica, they were not purified at this stage. Treatment of the product selenides with *m*-CPBA and triethylamine led to the olefins **17** and **18** in moderate yield.[10] The presence of the *E* olefin **18** among the products is almost certainly due to cleavage of the siloxane functional group prior to elimination to form the double bond. Only *m*-CBPA and *t*-BuOOH were screened as oxidants in the reaction and it is possible that other reagents (e.g., dimethyldioxirane, ozone) would lead to less siloxane cleavage.



Substrate **19** was examined to explore the possibility of generating trisubstituted double bonds using this methodology. This siloxane reacted smoothly upon irradiation to give high yields of group transfer products. Unfortunately these selenides eliminated to give the exocyclic olefin when treated with mCPBA in the presence of triethylamine. Only a small amount of the desired trisubstituted olefin **22** was isolated.



23 **24** **25** 57%

In summary, we have developed new methodology for reductively coupling an allylic alcohol and an aldehyde. Terminally unsubstituted allylic alcohols give 1,4-diols in good to moderate yields. The mild reaction conditions are especially favorable for use with complex substrates, as exemplified by the transformation of **23** and **24** to the diol **25**, a precursor in the synthesis of tunicaminyluracil.[5]

Experimental Section

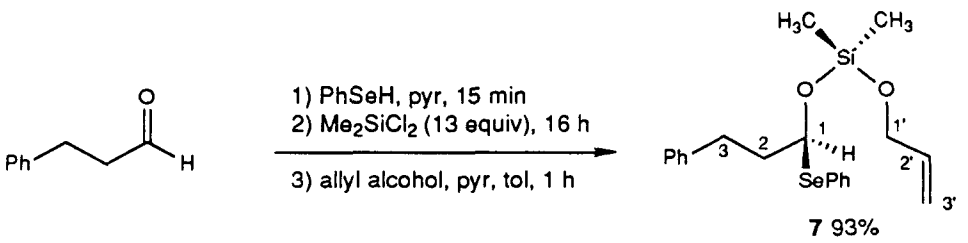
Melting points were recorded with a Büchi SMP-20 melting point apparatus and are uncorrected. Infrared spectra were recorded on either a Beckman 4240 Infrared spectrometer or a Perkin Elmer 1600 FTIR spectrometer. Data are represented as follows: frequency of absorption (cm^{-1}), and intensity of absorption (s=strong, m=medium, w=weak, br=broad). The ^1H NMR spectra were obtained on a JEOL JNM-GX400 spectrometer (400 MHz), and peaks are reported in ppm (δ scale), using the residual solvent peak as reference ($CHCl_3$:7.26, C_6D_5H:7.15). Data are represented as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, qn=quintet, m=multiplet, br=broad), integration, coupling constants in Hertz, and assignment. Mass spectra and high resolution mass spectra were obtained from the UC Riverside Mass Spectrometry Facility. Photolyses were performed with a GE 1000 W tungsten industrial lamp.

Liquid chromatography was performed using a forced flow (flash-chromatograpy)[11] with the indicated solvent using JT Baker Silica Gel (40 μm) or Merck Silica Gel 60 (230-400 mesh ASTM). Analytical thin-layer chromatography was performed using Merck pre-coated silica gel 60 F-254 plates (0.25 mm, glass-backed, fluorescent at 254 nm).

Tetrahydrofuran, and diethyl ether were distilled from sodium-benzophenone ketyl. *N,N*-Dimethylformamide, acetonitrile, methylene chloride, hexanes, pyridine, triethylamine, diisopropylamine, and chlorotrimethylsilane were distilled from calcium hydride. Benzene and toluene were distilled from sodium. All nonaqueous reactions were performed in flame-dried glassware under argon, unless otherwise noted. Deoxygenation of solutions was accomplished by evacuating and flushing the solutions with argon five times. Organic solutions were concentrated on a Büchi rotatory

evaporator at 10-20 Torr, unless otherwise specified. Solvents used in the workup and purification of compounds were HPLC-reagent grade and were used without further purification.

Dichlorodimethylsilane (Petrarch) was distilled from magnesium. Hydrocinnamaldehyde was distilled under reduced pressure. 2-Propen-1-ol (allyl alcohol) and 2-methyl-2-propen-1-ol (methallyl alcohol) were distilled from CaH_2 and stored over 3-Å molecular sieves. All other reagents were obtained from commercial sources unless otherwise noted and used as received.



Racemic *O*-(Allyloxy) Dimethylsilyl Hemiselenoacetal 7

Benzeneselenol[12] (0.132 mL, 1.24 mmol, 1.04 equiv) was added dropwise to a solution of hydrocinnamaldehyde (0.161 g, 1.20 mmol, 1.0 equiv) in pyridine (10 mL). After 15 min, the light yellow solution was added by cannula to a deoxygenated solution of Me_2SiCl_2 (2.0 mL, 17 mmol, 14 equiv) in pyridine (10 mL). The solution was covered with foil, and allowed to stir at 23 °C for 16 h, then the volatile components were removed under vacuum (0.1 Torr). The residue was taken up in a mixture of pyridine (2 mL), and toluene (10 mL) and a white solid precipitated out of solution. The suspension was treated with allyl alcohol (0.085 mL, 0.073 g, 1.04 equiv) for 1 h at 23 °C, then the solution was concentrated *in vacuo*. The residue was partitioned between 1:1 ethyl acetate-hexanes (50 mL) and cold saturated aqueous sodium bicarbonate solution (50 mL). The organic layer was separated, dried over sodium sulfate, and concentrated affording a yellow oil (±)-**7** (482.8 mg, 99%, 94% pure by weight).

Racemic *O*-(Allyloxy) Dimethylsilyl Hemiselenoacetal 7

^{1}H NMR (400 MHz, C_6D_6): 7.67 (m, 2H, arom), 7.07-7.23 (m, 8H, arom), 5.80 (m, 1H, H2'), 5.49 (dd, *J*= 6.3, 6.6, H1), 5.28 (m, 1H, H3'), 5.00 (m, 1H, H3'), 4.11 (m, 2H, H1'), 2.72 (m, 2H, H3), 2.25 (m, 2H, H2), 0.10 (s, 6H, $SiCH_3$).

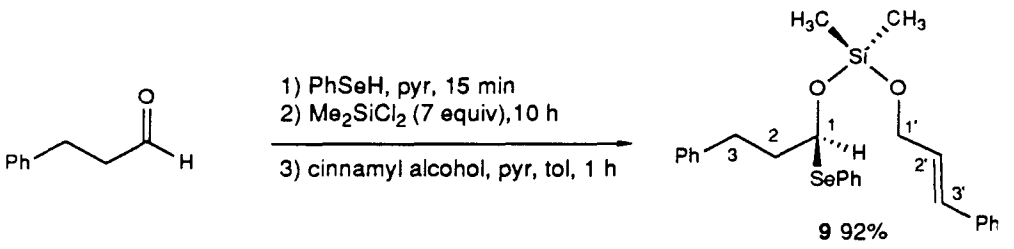
FTIR (neat film), cm^{-1}: 3060 (w), 2943 (w), 1643 (w), 1578 (m), 1490 (m), 1472 (m), 1449 (m), 1437 (m), 1255 (s), 1096 (s), 1038 (s), 914 (m), 861 (s), 797 (s), 732 (s), 691 (s).

MS (FAB): 405 (MH^+), 249 (MH^+-SePh), 193 (MH^+-SePh $-OC_3H_4$).

HRMS (FAB): Calculated for $C_{20}H_{25}O_2SeSi$ (MH^+): 405.0789
Found: 405.0775

TLC (40% CH_2Cl_2-hexanes):

Hemiselenoacetal **7**	0.36 (UV) (unstable)
Hydrocinnamaldehyde	0.19 (UV)
Diphenyl diselenide	0.66 (UV)



9 92%

Racemic *O*-(Cinnamyloxy) Dimethylsilyl Hemiselenoacetal **9**

Benzeneselenol[12] (0.264 mL, 2.48 mmol, 1.0 equiv) was added dropwise to a deoxygenated solution of hydrocinnamaldehyde (0.322 g, 2.4 mmol, 1.0 equiv) in pyridine (15 mL). After 15 min, the light yellow solution was added by cannula to a deoxygenated solution of Me_2SiCl_2 (2 mL, 17 mmol, 6.9 equiv) in pyridine (5 mL). The transfer was quantitated with one 5-mL portion of pyridine. The solution was covered with foil, and allowed to stir at 23 °C for 10 h, then the volatile components were removed under vacuum (0.1 Torr). The residue was taken up in a mixture of pyridine (1 mL), and toluene (5 mL) and a white solid precipitated out of solution. The suspension was treated with (*E*)-cinnamyl alcohol (0.360 g, 2.68 mmol, 1.1 equiv) for 1 h at 23 °C, then the solution was concentrated *in vacuo*. The residue was taken up in hexanes (100 mL), filtered, and concentrated affording (±)-**9** (1.106 g, 96%, 96% pure by weight) as a yellow oil .

Racemic *O*-(Cinnamyloxy) Dimethylsilyl Hemiselenoacetal **9**

^{1}H NMR (400 MHz, C_6D_6): 7.69 (m, 2H, arom), 6.95-7.30 (m, 13H, arom), 6.62 (d, 1H, *J*=16.4, H3'), 6.19 (dt, *J*=16.4, 6.2, H2'), 5.54 (t, 1H, *J*=7.5, H1), 4.30 (m, 2H, H1'), 2.77 (m, 2H, H3), 2.27 (m, 2H, H2), 0.17 (s, 6H, $SiCH_3$).

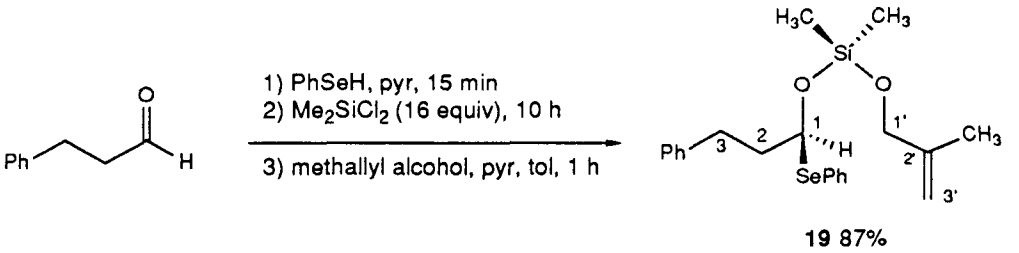
FTIR (neat film), cm^{-1}: 2943 (w), 1492 (m), 1472 (m), 1449 (m), 1431 (m), 1255 (s), 1076 (s), 1032 (s), 934 (m), 841 (s), 775 (s), 727 (s), 692 (s).

MS (FAB): 483 (MH^+), 325 (M^+-SePh).

HRMS (FAB): Calculated for $C_{26}H_{31}O_2SeSi$ (MH^+): 483.1259
Found: 483.1255

TLC (40% CH_2Cl_2-hexanes):

Hemiselenoacetal **9**	0.30 (UV) (unstable)
Hydrocinnamaldehyde	0.18 (UV)
Diphenyl diselenide	0.66 (UV)
Cinnamyl alcohol	0.04 (UV)



19 87%

Racemic *O*-(Methallyloxy) Dimethylsilyl Hemiselenoacetal **19**

Benzeneselenol[12] (0.410 mL, 3.86 mmol, 1.03 equiv) was added dropwise to a deoxygenated solution of hydrocinnamaldehyde (0.501 g, 3.73 mmol, 1.0 equiv) in pyridine (15 mL). After 15 min, the light yellow solution was added by cannula to a deoxygenated solution of Me_2SiCl_2 (7.0 mL, 58 mmol, 16 equiv) in pyridine (5 mL). The transfer was quantitated with one 5-mL portion of pyridine. The solution was covered with foil, and allowed to stir at 23 °C for 10 h, then the volatile components were removed under vacuum (0.1 Torr). The residue was taken up in a mixture of pyridine (1 mL), and toluene (5 mL) and a white solid precipitated out of solution. The suspension was treated with 2-methyl-2-propen-1-ol (methallyl alcohol, 0.325 mL, 0.380 g, 5.25 mmol, 1.3 equiv) for 1 h at 23 °C, then the solution was concentrated *in vacuo*. The residue was taken up in hexanes (100 mL), filtered, and concentrated affording (±)-**19** (1.4235 g, 91%, 95% pure by weight) as a yellow oil.

Racemic *O*-(Methallyloxy) Dimethylsilyl Hemiselenoacetal **19**

^{1}H NMR (400 MHz, C_6D_6): 7.68 (m, 2H, arom), 7.15-6.89 (m, 8H, arom), 5.49 (t, 1H, *J*=6.6, H1), 5.14 (s, 1H, H3'), 4.83 (s, 1H, H3'), 4.04 (m, 2H, H1'), 2.76 (m, 2H, H3), 2.27 (m, 2H, H2), 1.57 (s, 3H, CH_3), 0.12 (s, 6H, $SiCH_3$).

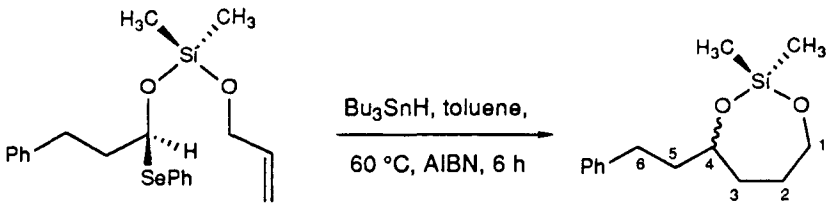
FTIR (neat film), cm^{-1}: 2943 (m),1578 (m), 1496 (m), 1431 (m), 1091 (s), 1044 (s), 867 (s), 797 (s), 732 (s).

MS (FAB): 419 (MH^+), 263 (MH^+-SePh).

HRMS (FAB): Calculated for $C_{21}H_{27}O_2SeSi$ (MH^+): 419.0946
Found: 419.0934

TLC (40% CH_2Cl_2-hexanes):

Hemiselenoacetal **19**	0.41 (UV) (unstable)
Diphenyl diselenide	0.66 (UV)
Hydrocinnamaldehyde	0.19 (UV)



7 **8** 62%

Racemic Siloxane **8**

A deoxygenated solution of AIBN (4 mg, 0.02 mmol, 0.06 equiv), and Bu_3SnH (0.240 mL, 259.7 mg, 0.892 mmol, 2.2 equiv) in toluene (5 mL) was added rapidly dropwise to a deoxygenated solution of racemic hemiselenoacetal **7** (0.150 mL, 174 mg, 0.403 mmol, corrected for impurity, 1 equiv) in toluene (150 mL) at 60 °C. After 6 h at 60 °C, the reaction mixture was cooled to 23 °C and concentrated under vacuum (0.1 Torr). A ^1H NMR of the crude reaction mixture showed a 9:1 ratio of cyclized:reduced product. The residue was purified by flash chromatography (40% CH_2Cl_2-hexanes) affording (±)-**8** (63.0 mg, 62%) as a colorless oil.

Racemic Siloxane **9**

^1H NMR (400 MHz, C_6D_6): 7.11 (m, 5H, arom), 3.80 (m, 1H, H4), 3.65 (m, 2H, H1), 2.84 (m, 1H, H6), 2.57 (m, 1H, H6), 1.80 (m, 1H, H5), 1.57 (m, 1H, H5), 1.35 (m, 4H, H2, H3), 0.20 (s, 3H, $SiCH_3$), 0.17 (s, 3H, $SiCH_3$).

FTIR (neat film), cm^{-1}: 2921 (s), 1604 (w), 1495 (w), 1454 (w), 1368 (w), 1256 (s), 1090 (s), 1047 (s), 966 (m), 842 (m),

796 (s), 699 (s).

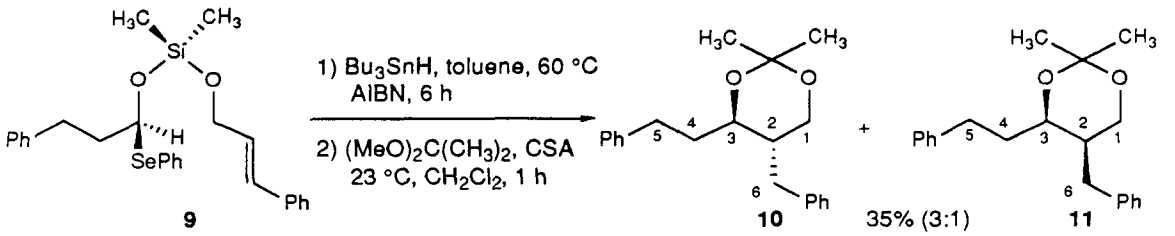
MS (EI): 250 (M^+), 235 (M^+-CH_3), 158 (M^+-C_6H_6).

HRMS (EI): Calculated for $C_{14}H_{22}O_2Si$ (M^+): 250.1389

Found: 250.1396

TLC (CH_2Cl_2):

Siloxane **8**	0.41 (UV)
Hemiselenoacetal **7**	0.75 (UV) (unstable)
$Bu_3SnSePh$	0.80 (UV)
Hydrocinnamaldehyde	0.52 (UV)



9 **10** **11**

Racemic Acetonides **10** and **11**

A deoxygenated solution of AIBN (2 mg, 0.01 mmol, 0.1 equiv) and Bu_3SnH (0.080 mL, 87 mg, 0.30 mmol, 2.4 equiv) in toluene (2 mL) was added dropwise over 5 min to a deoxygenated solution of racemic hemiselenoacetal **9** (62 mg, 0.12 mmol, corrected for impurity, 1 equiv) in toluene (60 mL). After 6 h at 60 °C the reaction mixture was cooled and concentrated *in vacuo*. The residue was filtered through a pad of silica gel (1.5 cm x 2 cm, 40% CH_2Cl_2-hexanes) to remove the higher R_f tin species. The pad of silica was washed with ethyl acetate (110 mL) to ensure complete elution of the diols. After concentration *in vacuo*, the residue was further purified by flash chromatography (50% EtOAc-hexanes) to afford a mixture of anti and syn diols (14.1 mg, 42%). The diastereomers could be separated by thin-layer preparative chromatography (R_f in 50% ethyl acetate-hexanes syn = 0.23, anti = 0.22).

The diols were converted to corresponding acetonides as follows. The mixture of diols (14.1 mg, 0.0519 mmol, 1 equiv) in CH_2Cl_2 (5 mL), was treated with CSA (5 mg, 0.021 mmol, 0.4 equiv) and 2,2-dimethoxypropane (1 mL, 847 mg, 8.13 mmol, 162 equiv) for 1 h at 23 °C. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography (CH_2Cl_2) affording the two diastereomeric acetonides (±)-**10** and (±)-**11** as a 3:1 mixture (14.7 mg, 92%, 35% for two steps). The diastereomers could be separated by thin-layer preparative chromatography (R_f in CH_2Cl_2, syn = 0.42, anti = 0.41).

Racemic Acetonide **10**

^{1}H NMR (400 MHz, C_6D_6): 7.01-7.29 (m, 10H, arom), 3.74 (dt, 1H, *J*=8.7, 2.4, H3), 3.55 (dd, 1H, *J*=3.6, 12.0, H1), 3.45 (dd, 1H, *J*=3.6, 12.0, H1), 3.11 (dd, 1H, *J*=12.0, 13.9, H6), 2.76 (m, 1H, H5), 2.68 (dd, 1H, *J*=3.8, 13.9, H6), 2.58 (m, 1H, H5), 1.96 (m, 1H, H4), 1.58 (s, 3H, CH_3), 1.51 (m, 1H, H4), 1.17 (s, 3H, CH_3), 1.07 (m, 1H, H2).

FTIR (neat film), cm^{-1}: 2925 (s), 1602 (w), 1495 (m), 1454 (s), 1380 (m), 1258 (s), 1199 (m), 1125 (m), 1058 (w), 986 (w), 858 (w), 750 (m), 699 (s).

MS (EI): 310 (M^+), 295 (MH^+-CH_4), 234 (M^+-C_3H_6O H_2O).

HRMS (EI): Calculated for $C_{21}H_{26}O_2$ (M^+): 310.1933
Found: 310.1938

Racemic Acetonide **11**

^{1}H NMR (400 MHz, C_6D_6): 6.95–7.30 (m, 10H, arom), 3.58 (dd, 1H, *J*=5.3, 11.5, H1), 3.55 (dt, 1H, *J*=2.8, 9.1, H3), 3.45 (dd,

1H, J=11.2, 11.5, H1), 2.86 (m, 1H, H5), 2.74 (dt, 1H, J=13.0, 7.6, H5), 2.38 (dd, 1H, J=4.4, 13.8, H6), 1.84 (m, 1H, H4), 1.81 (m, 1H, H2), 1.74 (dd, 1H, J=12.0, 13.9, H6), 1.72 (m, 1H, H4), 1.53 (s, 3H, CH_3), 1.28 (s, 3H, CH_3).

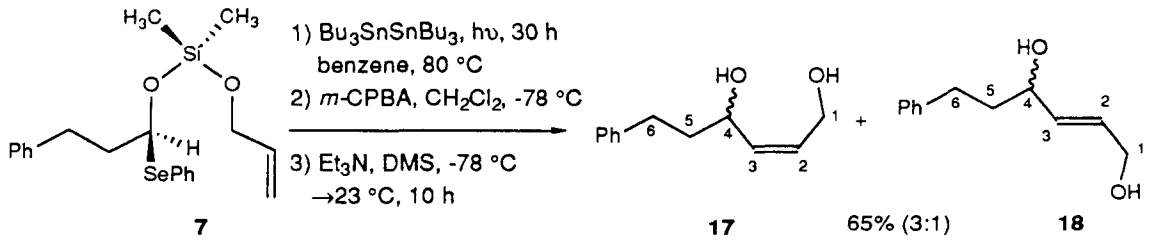
FTIR (neat film), cm^{-1}: 2940 (m), 1602 (w), 1495 (m), 1453 (m), 1379 (m), 1259 (w), 1196 (s), 1132 (m), 1052 (s), 979 (w), 859 (w), 744 (w), 699 (s).

MS (EI): 310 (M^+), 295 (MH^+-CH_4), 234 (M^+-C_3H_6O H_2O).

HRMS (EI): Calculated for $C_{21}H_{26}O_2$ (M^+): 310.1933
Found: 310.1938

TLC (20% EtOAc-hexanes):

Acetonide **10**	0.53 (UV)
Acetonide **11**	0.53 (UV)
Hemiselenoacetal **9**	0.58 (UV) (unstable)
Diols	0.06 (UV)



7 **17** **18**

Racemic Diols **17** and **18**

Racemic hemiselenoacetal **7** (0.100 mL, 116 mg, 0.269 mmol, corrected for impurity, azeotropically dried with one portion of toluene (5 mL)), $Bu_3SnSnBu_3$ (0.010 mL, 0.012 mmol, 0.07 equiv) and benzene (60 mL) were combined in a 100-mL side-arm flask equipped with a reflux condenser. The reaction mixture was irradiated with a tungsten light bulb placed 10 cm away from the flask, which heated the solution to reflux. After 30 h, monitoring by thin-layer chromatography (R_f in CH_2Cl_2, diphenyl diselenide = 0.91, **7** = 0.75, group transfer products = 0.58, 0.50, hydrocinnamaldehyde = 0.43) indicated the reaction was complete and the reaction mixture was concentrated under vacuum (0.1 Torr). A solution of the residue in CH_2Cl_2 (5 mL) was treated with *m*-CPBA (200 mg, 1.159 mmol, 4.3 equiv) at -78 °C for 1 h, then triethylamine (0.2 mL) was added. The reaction mixture was stirred at -78 °C an additional hour, then the excess oxidant was quenched with dimethylsulfide (1 mL). After another hour at -78 °C, the solution was slowly warmed to 23 °C and stirred for 10 h at that temperature. The reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution (30 mL) and ethyl acetate (40 mL). The organic layer was separated and the aqueous layer was washed with three 40-mL portions of ethyl acetate. The combined organic layers were dried over sodium sulfate, concentrated and purified by flash chromatography (ether) affording (±)-**17** and (±)-**18** (33.7 mg, 3:1 ratio, 65% combined yield) as a yellow

solid. The isomers could be further separated by thin-layer preparative chromatography (R_f in 20% toluene-ethyl acetate trans = 0.31, cis = 0.28).

Racemic Diol **17**

^{1}H NMR (400 MHz, C_6D_6): 7.10-7.34 (m, 5H, arom), 5.45 (d, 2H, J=5.4, H2, H3), 3.81 (br, 1H, H4), 3.75 (s, 2H, H1), 2.60 (m, 2H, H6), 1.66 (m, 2H, H5).

FTIR (neat film), cm^{-1}: 2921 (s), 1604 (w), 1495 (w), 1454 (w), 1368 (w), 1256 (s), 1090 (s), 1047 (s), 966 (m), 842 (m), 796 (s), 699 (s).

MS (CI:NH_3): 210 ($M+NH_4^+$), 193 (MH^+), 175 (MH^+-H_2O), 157 (MH^+-2H_2O).

HRMS (CI:NH_3): Calculated for $C_{12}H_{17}O_2$ (MH^+): 193.1229
Found: 193.1220

Racemic Diol **18**

^{1}H NMR (400 MHz, C_6D_6): 7.10-7.34 (m, 5H, arom), 5.47 (m, 1H, H2), 5.33 (m, 1H, H3), 4.11 (q, 1H, J=7.1, H4), 3.86 (m, 1H, H1), 3.74 (m, 1H, H1), 2.55 (m, 2H, H6),

1.75 (m, 1H, H5), 1.58 (m, 1H, H5), 1.35 (br, 1H, OH).

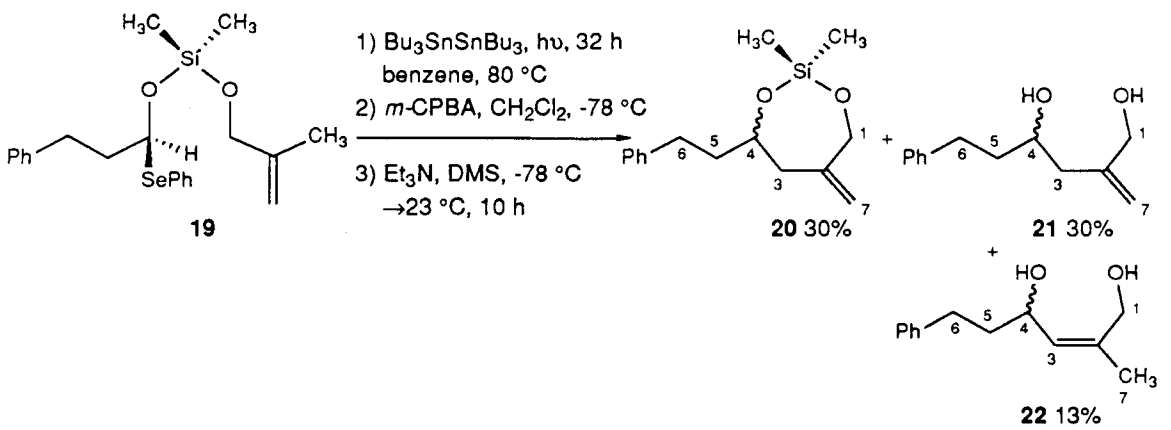
FTIR (neat film), cm^{-1}: 3260 (w), 2919 (m), 2849 (m), 1602 (w), 1498 (w), 1449 (m), 1255 (m), 1020 (s), 797 (s), 744 (w), 691 (m).

MS (CI:NH_3): 193 (MH^+), 175 (MH^+-H_2O), 157 (MH^+-$2H_2O$).

HRMS (CI:NH_3): Calculated for $C_{12}H_{17}O_2$ (MH^+): 193.1229
Found: 193.1224

TLC (ether):

Diol **17**	0.14 (UV)
Diol **18**	0.14 (UV)
Group transfer products	0.78 (UV) (unstable)
Hemiselenoacetal **7**	0.84 (UV) (unstable)



Group transfer reaction of Racemic Hemiselenoacetal **19**

A solution of racemic hemiselenoacetal **19** (0.100 mL, 106 mg, 0.241 mmol, corrected for impurity, azeotropically dried with one portion of toluene (5 mL)), and $Bu_3SnSnBu_3$ (0.010 mL, 0.020 mmol, 0.08 equiv) in benzene (50 mL) was irradiated with a 1000 W tungsten bulb, for 32 h at reflux until monitoring by thin-layer chromatography (R_f in CH_2Cl_2, diphenyl diselenide = 0.91, **19** = 0.75, group transfer products = 0.62, 0.58, hydrocinnamaldehyde = 0.43) indicated the reaction was complete. The reaction mixture was concentrated under vacuum (0.1 Torr). A solution of the residue in CH_2Cl_2 (5 mL) was sequentially treated with *m*-CPBA (125 mg, 0.869 mmol, 3.61 equiv) and Et_3N (0.1 mL) for 30 min at -78 °C. The excess oxidant was quenched with dimethylsulfide (0.5 mL) and the reaction mixture was stirred an additional hour at -78 °C. The reaction mixture was slowly warmed to 23 °C and stirred for 10 h at that temperature. The reaction mixture was partitioned between saturated aqueous sodium bicarbonate (30 mL) and ethyl acetate (40 mL). The organic layer was separated and the aqueous layer was washed with three 40-mL portions of ethyl acetate. The combined organic layers were dried over sodium sulfate, concentrated and purified by flash chromatography (50% CH_2Cl_2-hexanes) giving (±)-**20** (19.1 mg, 0.0725 mmol, 30%) and

a mixture of lower R_f diols and *m*-chlorobenzoic acid (23 mg). The lower R_f mixture was further purified by flash chromatography (50% ether-petroleum ether) affording (±)-**21** (15.0 mg, 0.073 mmol, 30%), and (±)-**22** (6.7 mg, 0.033 mmol, 13%) as clear, colorless oils.

Racemic Siloxane **20**

^{1}H NMR (400 MHz, C_6D_6): 7.05-7.35 (m, 5H, arom), 4.84 (s, 1H, H7), 4.68 (s, 1H, H7), 4.19 (m, 2H, H1), 3.77 (m, 1H, H4), 2.79 (m, 1H, H6), 2.57 (m, 1H, H6), 2.16 (m, 2H, H3), 1.80 (m, 1H, H5), 1.61 (m, 1H, H5), 0.37 (s, 3H, $SiCH_3$), 0.17 (s, 3H, $SiCH_3$).

FTIR (neat film), cm^{-1}: 2919 (w), 2849 (w), 1490 (w), 1449 (w), 1255 (m), 1091 (s), 1073 (s), 973 (m), 908 (m), 850 (s), 838 (s), 791 (s), 738 (w), 685 (m).

MS (CI:CH_4): 291 (MH^++H_2O), 263 (MH^+), 247 (MH^+-CH_4), 171 (M^+-$(CH_3)_2Si(OH)_2$).

HRMS (CI:CH_4): Calculated for $C_{15}H_{22}O_2Si$ (M^+): 262.1389
Found: 262.1377

Racemic Diol **21**

^{1}H NMR (400 MHz, C_6D_6): 7.00-7.30 (m, 5H, arom), 4.92 (s, 1H, H7), 4.72 (s, 1H, H7), 3.74 (s, 2H, H1), 3.49 (m, 1H, H4), 2.72 (m, 1H, H6), 2.55 (m, 1H, H6), 2.06 (dd, 1H, *J*=3.4, 13.9, H3), 1.95 (dd, 1H, *J*=8.3, 13.9, H3), 1.60 (m, 2H, H5).

FTIR (neat film), cm^{-1}: 3331 (s), 2919 (s), 2849 (m), 1649 (w), 1596 (w), 1496 (m), 1449 (m), 1049 (s), 1026 (s), 903 (m), 744 (m), 697 (s).

MS (CI:NH_3): 225 (MH^++H_2O), 207 (MH^+), 189 (MH^+-H_2O), 171 (MH^+-2H_2O).

HRMS (CI:NH_3): Calculated for $C_{13}H_{19}O_2$ (MH^+): 207.1385
Found: 207.1391

Racemic Diol **22**

^{1}H NMR (400 MHz, C_6D_6): 6.90-7.30 (m, 5H, arom), 5.17 (d, 1H, *J*=8.0, H3), 4.18 (dt, 1H, *J*=5.5, 7.5, H4), 3.84 (d, 1H, *J*=12.0, H1), 3.64 (d, 1H, *J*=12.0, H1), 2.59 (m, 2H, H6), 1.77 (m, 1H, H5), 1.61 (m, 1H, H5), 1.61 (s, 3H, H7).

FTIR (neat film), cm^{-1}: 3331 (s), 2919 (m), 2861 (m), 6102 (w), 1490 (m), 1449 (m), 1026 (m), 997 (s), 744 (m), 691 (s).

MS (CI:NH_3): 207 (MH^+), 190 (M^+-H_2O), 172 (M^+-$2H_2O$).

HRMS (CI:NH_3): Calculated for $C_{13}H_{19}O_2$ (MH^+): 207.1385
Found: 207.1384

TLC (ether):

Siloxane **20**	0.81 (UV)
Diol **21**	0.44 (UV)
Diol **22**	0.31 (UV)
Group transfer products	0.88 (UV) (unstable)

References

[1](a) Struble, D. L.; Beckwith A. L. J.; Gream, G. E. *Tetrahedron Lett.* **1968**, 3701. (b) Beckwith A. L. J.; Gream, G. E.; Struble, D. L. *Aust. J. Chem.* **1972**, 1081. (c) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, *107*, 734.

[2]Systems studying 5-exo vs. 6-endo radical cyclizations in silicon-substitiuted radicals: (a) Stork, G. A.; Mook, R., Jr. *J. Am. Chem. Soc.* **1983**, *105*, 3741. (b) Stork, G. A.; Sher, P. M. *J. Am. Chem. Soc.* **1983**, *105*, 6765. (c) Nishiyama, H.; Kitajima, T.; Matasumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298. (d) Wilt, J. W. *Tetrahedron* **1985**, *41*, 3979. (e) Stork, G. A; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500. (f) Wilt, J. W. *Tetrahedron* **1985**, *41*, 3979. (g) Koreęda, M.; George, I. A. *J. Am. Chem. Soc.* **1986**, *108*, 8098. (h) Wilt, J. W.; Lusztyk, J.; Perran, M.; Ingold, K. U. *J. Am. Chem. Soc.* **1988**, *107*, 281. (i) Kurek-Tyrlik, A.; Wicha, J. *Tetrahedron Lett.* **1988**, *29*, 4001. (j) Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900. (k) Stork, G. A.; Mah, R. *Tetrahedron Lett.* **1989**, *30*, 3609. (l) Tamoa, K.; Maeda, K.; Yamaguchi, T.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4984. (m) Journet, M.; Smadja, W.; Malacria, M. *Syn. Lett.* **1990**, 320. (n) Walkup, R. D.; Obeyesekere, N. U. *Chem. Lett.* **1990**, *31*, 1055. (o) Walkup, R. D.; Kane, R. R.; Obeyesekere, N. U. *Tetrahedron Lett.* **1990**, *31*, 1531. (p) Agnel, G.; Malacria, M. *Tetrahedron Lett.* **1990**, *31*, 3555. (q) Journet, M.; Magnol, E.; Agnel, G.; Malacria, M. *Tetrahedron Lett.* **1990**, *31*, 4445. (r) Curran, D. P.; Schwartz, C. E. *J. Am. Chem. Soc.* **1990**, *112*, 9272. (s) Hutchinson, J. H.; Daynard, T. S.; Gillard, J. W. *Tetrahedron Lett.* **1991**, *32*, 573.

[3]Generation of radicals from *O*-alkyl hemiseleno- or hemithio- acetals: (a) Yadav, V. K.; Fallis, A. G. *Tetrahedron Lett.* **1988**, *29*, 897. (b) Yadav, V. K.; Fallis, A. G. *Tetrahedron Lett.* **1989**, *30*, 3283. (c) De Mesmaeker, A.; Hoffmann, P.; Ernst, B.; Hug, P.; Winkler, T. *Tetrahedron Lett.* **1989**, *30*, 6307, 6311. (d) De Mesmaeker, A.; Waldner, A.; Hoffmann, P.; Mindt, T.; Hug, P.; Winkler, T. *Syn. Lett.* **1990**, 687.

[4]Methods for the synthesis of *O*-silyl hemithio- and hemiseleno- acetals: (a) Chan, T. H.; Ong, B. S. *Tetrahedron Lett.* **1976**, 319. (b) Dumont, W.; Krief, A. *Angew. Chem., Int. Engl.* **1977**, *16*, 540. (c) Glass, R. S. *Synth. Commun.* **1976**, *6*, 47. (d) Evans, D. A.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L. *J. Am. Chem. Soc.* **1977**, *99*, 5009. (e) Liotta, D.; Paty, P. B.; Johnston, J.; Zima, G. *Tetrahedron Lett.* **1978**, 5091. (f) Sassaman, M. B.; Surya Prakash, G. K.; Olah, G. A. *Synthesis* **1990**, 104.

[5]Myers, A. G.; Gin, D. Y.; Widdowson, K. L. *J. Am. Chem. Soc.* **1991**, *113*, 9661.

[6]This supports the mechanism suggested by Chan for *O*-trimethylsilyl hemiselenoacetal formation: see references 4 a and d.

[7]Systems studying 6-exo vs. 7-endo radical cyclizations in silicon-substitiuted radicals: (a) Koreeda, M.; Hamann, L. G. *J. Am. Chem. Soc.* **1990**, *112*, 8175. (b) Hutchinson, J. H.; Daynard, T. S.; Gillard, J. W. *Tetrahedron Lett.* **1991**, *32*, 573.

[8]Group transfer radical reactions involving iodides: (a) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1986**, *108*, 2489. (b) Curran, D. P.; Kim, D. *Tetrahedron Lett.* **1986**, *27*, 5821. (c) Curran, D. P.; Chen, M.-H. *J. Am. Chem. Soc.* **1987**, *109*, 6558.

(d) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140. (e) Barth, F.; Yang, C.-O. *Tetrahedron Lett.* **1990**, *31*, 1121. (f) Curran, D. P. *Synthesis* **1988**, 489. (g) Curran, D. P.; Chen, M.-H.; Spletzer, E.; Seong, C.; Chang, C.-T. *J. Am. Chem. Soc.* **1989**, *111*, 8872. (h) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1989**, *111*, 6265. (i) Curran, D. P.; Chang, C.-T. *Tetrahedron Lett.* **1987**, *28*, 1477.

[9]Byers, J. H.; Gleason, T. G.; Knight, K. S. *J. Chem. Soc., Chem. Commun.* **1991**, 355.

[10]Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *13*, 1697.

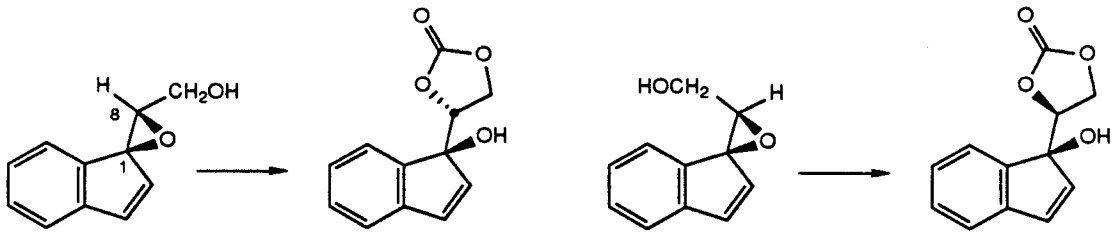
[11]Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

[12]Foster, D. G. In *Organic Syntheses, Collective Vol. 3* Horning, E. C., Ed.; John Wiley & Sons: New York, 1955; pp. 771-773.

CHAPTER III

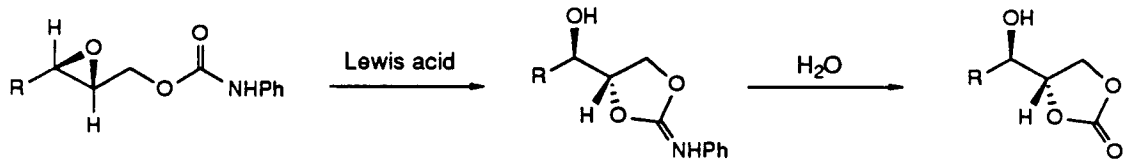
Synthesis of Hydroxy Carbonates from Epoxy Alcohols under Basic Conditions

It was necessary to synthesize the model compounds **2** and **4** to aid in the assignment of two stereogenic centers in the natural product neocarzinostatin.[1]

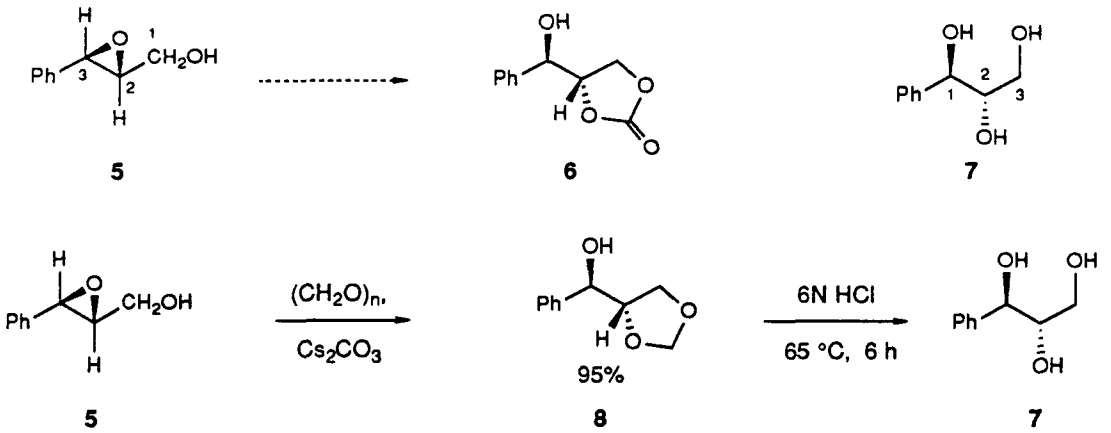


1 **2** **3** **4**

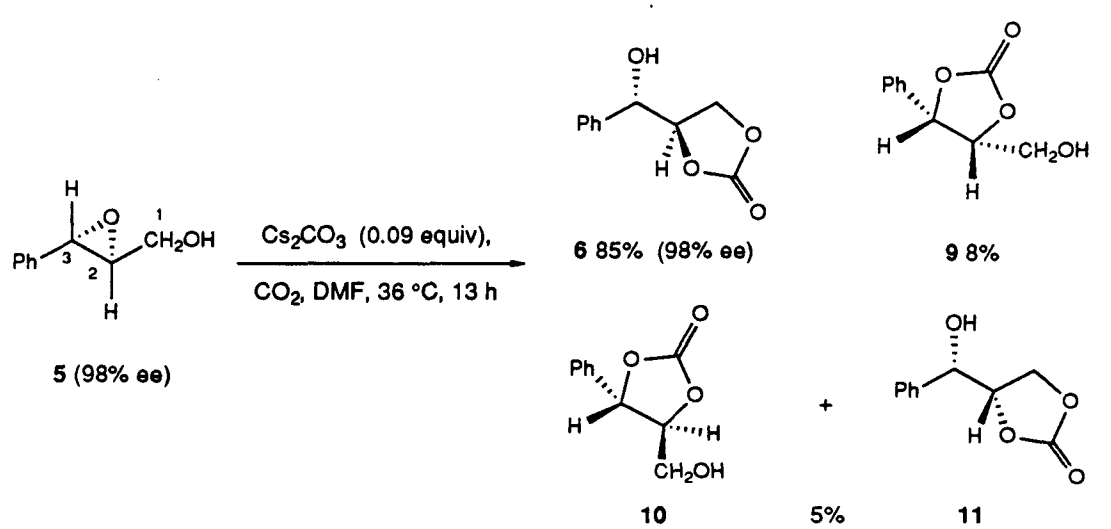
Retrosynthetic analysis suggested that these compounds could be synthesized expeditiously from the corresponding optically active epoxy alcohols **1** and **3**. The most general methodology for effecting the transformation of epoxy alcohols to hydroxy carbonates involves the Lewis acid-induced rearrangement of phenyl urethane derivatives.[2]



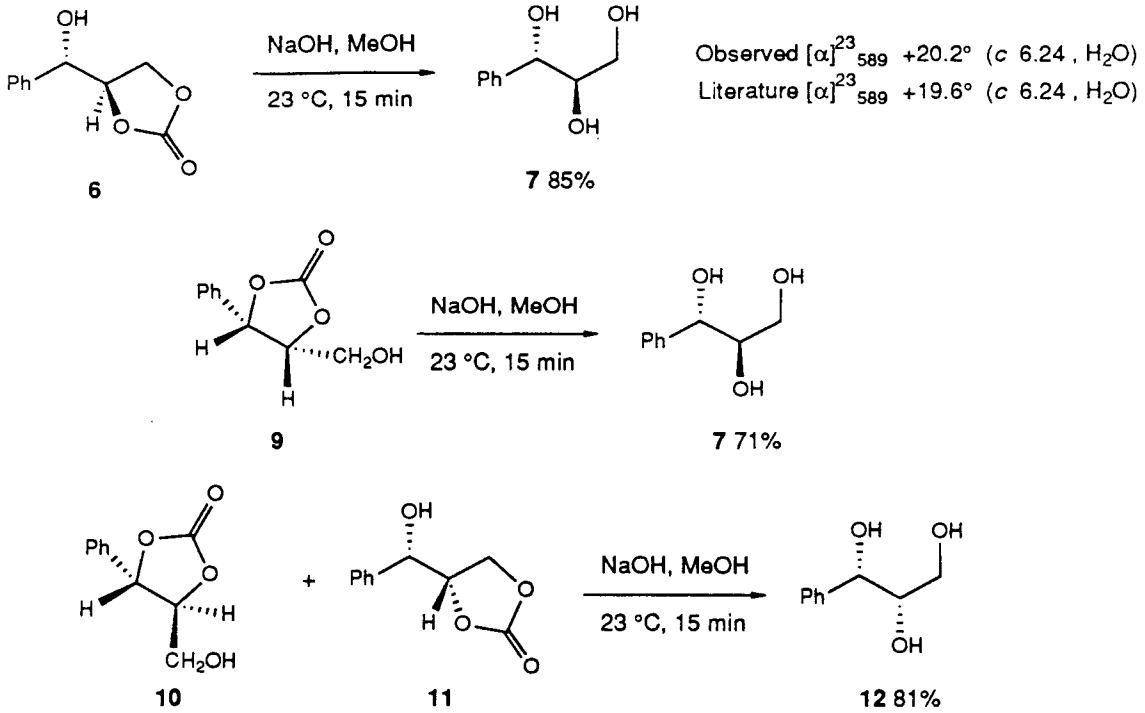
Application of this procedure to the model compounds **1** and **3** led to intractable product mixtures, presumably due to facile epoxide opening at C1. McCombie and Metz encountered similar problems in attempts to transform epoxy alcohol **5** to hydroxy carbonate **6**, enroute to triol **7**.[3] Though unsuccessful in this conversion, they found that treatment of **5** with cesium carbonate-paraformaldehyde mixtures provided the 1,3-dioxolane derivative **8** in good yield. This compound afforded the triol **7** upon acidic hydrolysis (6N HCl-MeOH). The extension of this approach by substitution of paraformaldehyde with carbon dioxide to produce hydroxy carbonates directly was investigated.



Scouting experiments established that treatment of **5** with carbon dioxide-cesium carbonate mixtures provided the desired C2-inverted hydroxy carbonate **6** as the major product along with three minor products **9**, **10** and **11**.[4]

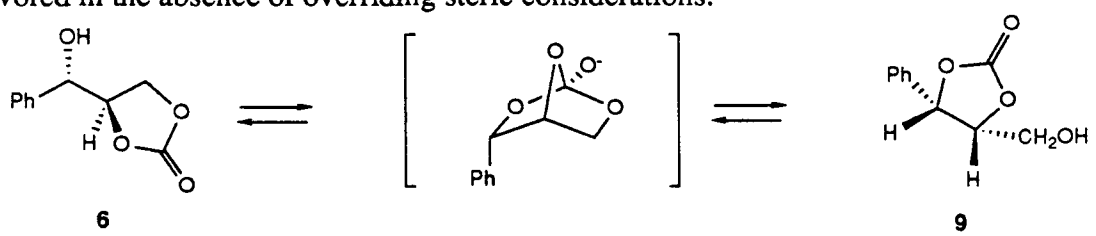


Examination of the Mosher esters[5] of the starting material **5** and the product **6** showed that the process was completely stereospecific, within experimental error. Hydrolysis of **6** afforded a triol which was found to be identical in all respects with authentic (1*S*,2*R*)-**7**,[6] confirming the absolute and relative stereochemistry of **6**.

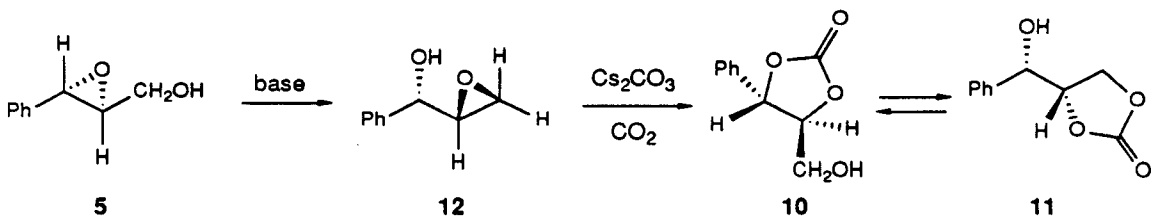


The cis stereochemistry of **9** is suggested by the observation of a 5.1 Hz coupling between protons H2 and H3 in the ^1H NMR spectrum. Saponification of **9** produced **7** confirming the assignment. Similarly, the trans stereochemistry of **10** is suggested by a 8.0 Hz coupling between protons H2 and H3. As expected, saponification of **10** and **11** produced the diastereomeric triol **8**, supporting the assignments of these products.

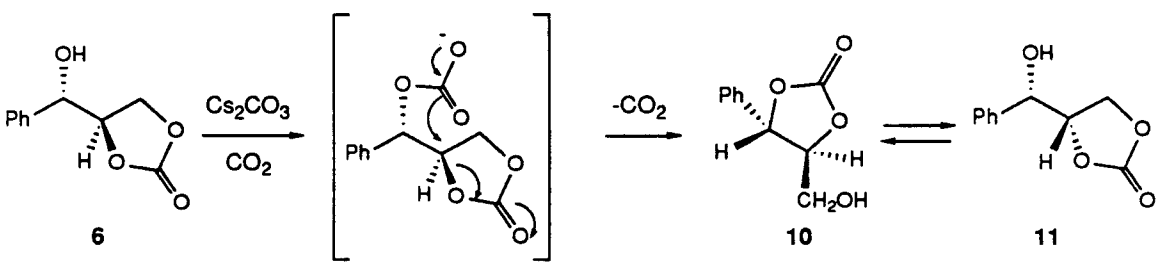
The major side product (**9**), is presumably derived from intramolecular carbonate equilibration. This process is rapid under the reaction conditions, thus a thermodynamic mixture of products results. The relative stability of carbonates is found to reflect that of the "parent" olefins. The more substituted carbonates (e.g., **9** and **10**) are generally favored in the absence of overriding steric considerations.



The minor side products **10** and **11** are thought to arise primarily from Payne rearrangement (**5**→**12**)[7] with subsequent reaction of **12** with carbon dioxide.



An alternative pathway involves attack of a carbonate anion on the cyclic carbonate.



Control experiments showed that direct conversion of **6** to **10** and **11** occurs, but is too slow to be the primary mode of formation of these products.

The transformation of **5** to **6**, **9**, **10**, and **11**, was studied in detail to determine optimum reaction conditions (Table I). Proper catalyst preparation was found to be critical for reducing the amount of C2 inverted products. The optimum conditions for catalyst preparation involve heating the solid *in vacuo*, with cooling under one atmosphere of carbon dioxide (as opposed to cooling *in vacuo*). This procedure provided a very active catalyst. The rationale behind this catalyst activation procedure was to scavenge any cesium oxide produced in the heating process, by reaction with CO_2 to reform cesium carbonate.

Table I. Influence of Reaction Variables on the Transformation of **5**→**6**, **9**, **10**, and **11**

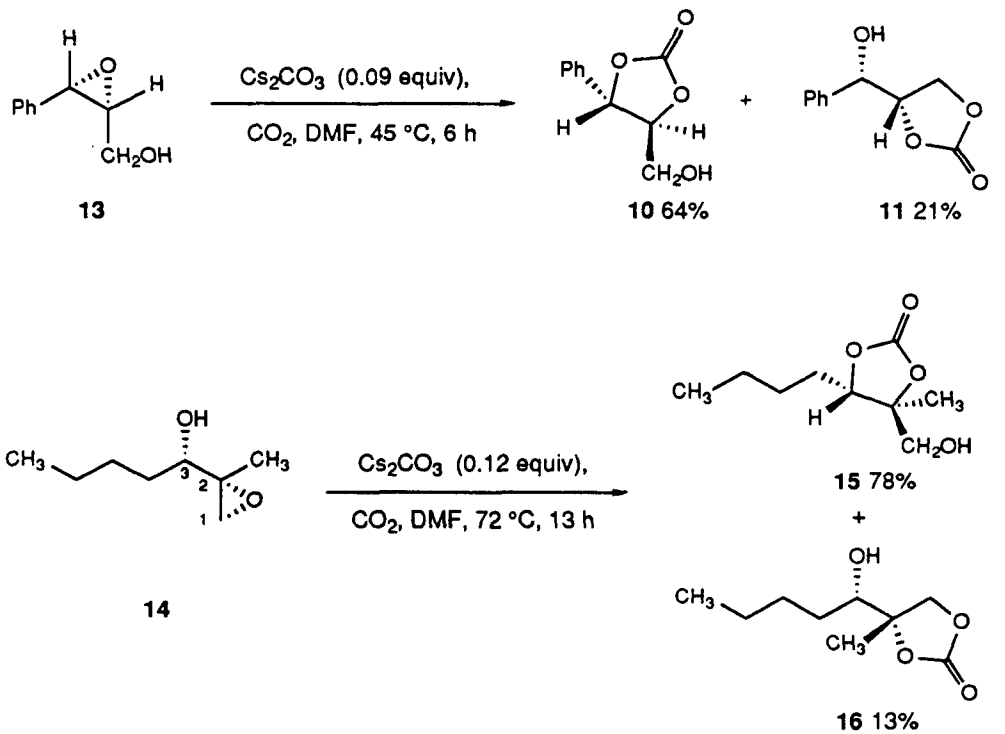
Catalyst	CO_2 pressure (atm)	Temp (°C)	Time (h)	Ratio of Products[a]				Catalyst Preparation	Yield of **6** (%)
				6	**9**	**10**	**11**		
Cs_2CO_3 (0.05 equiv) 3-Å molecular sieves	1	50	13	20	1.0	5.6	1.8	A[b]	73
Cs_2CO_3 (0.05 equiv) 3-Å molecular sieves	1	40	10	25	1.0	3.3	1.0	B[c]	85
Cs_2CO_3 (0.05 equiv) 3-Å molecular sieves	3.4	40	13	25	1.0	3.3	1.0	B	75
Cs_2CO_3 (0.05 equiv) 3-Å molecular sieves	54.4	40	13	20	4.0	1.0	1.2	B	71
Cs_2CO_3 (0.05 equiv)	1	40	24	20	1.0	1.8	1.8	B	74
K_2CO_3 (1 equiv) 3-Å molecular sieves Bu_4NCl (1 equiv)	1	40	12	25	1.0	15	5.0	B	-[d]
3-Å molecular sieves	1	80	24	-	-	-	-	B	-[e]
KH (1 equiv)	1	70	12	2	1	12	4	-	-
Et_3N (solvent)	1	80	24	-	-	-	-	-	-[e]

[a]Determined by integration of ^1H NMR of crude reaction mixtures. [b]Catalyst flame-dried and cooled under vacuum. [c]Catalyst flame-dried and cooled under an atmosphere of CO_2. [d]Incomplete reaction. [e]No reaction products detected.

The relative amounts of Payne rearrangement products can also be decreased by increasing the pressure of carbon dioxide, although this had only a small effect on the rate of the reaction. Quantitating the effect of increased pressure of carbon dioxide was difficult because variations in stirring efficiency were encountered with different reaction vessels employed, a parameter found to be critical in this heterogeneous reaction.

The exact role of molecular sieves in the reaction is uncertain, but their incorporation causes a twofold increase in reaction rate. Both 3-Å and 4-Å molecular sieves were equally effective in accelerating the reaction, however sieves alone do not catalyze the reaction. The highest selectivity occurred with DMF as the solvent, although the reaction also occurred in nonpolar (toluene) and protic (isopropanol) solvents.

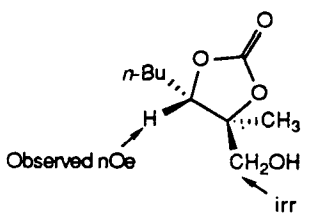
A number of other bases were also examined as possible catalysts. Potassium hydride was effective, but greatly increased the amount of side products derived from Payne rearrangement. Potassium carbonate and tetrabutylammonium chloride mixtures were less effective than cesium carbonate as catalysts, and triethylamine did not promote the reaction.



A variety of hydroxy epoxides of different substitution were studied. These substrates, unlike **6**, showed no propensity for competitive Payne rearrangement. As

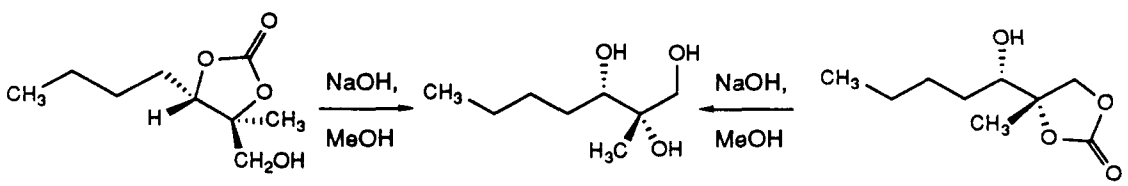
before, carbonate equilibration (presumably by intramolecular transesterification) occurred, producing a thermodynamic mixture of products. With substrate **13** the rearranged carbonate **10** predominated again reflecting the stability of the parent olefin.

Epoxy alcohol **14** was examined as a substrate to test for the possibility of 6-exo opening of the epoxide, the relative steric hindrance at C1 and C2 providing optimum opportunity for this mode of attack. However, only hydroxy carbonates **15** and **16** were observed, though not surprisingly higher reaction temperatures were required for the reaction to occur. The relative stereochemistry of hydroxy carbonate **15** was determined by nOe spectroscopy.



15

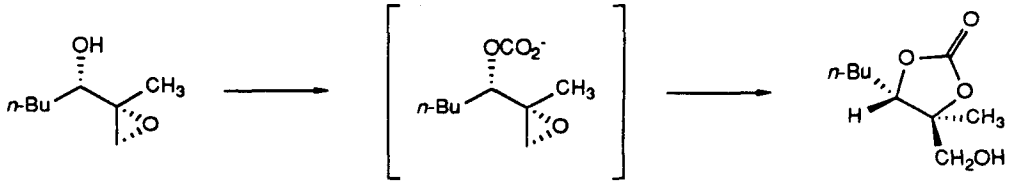
Irradiation of the hydroxy methylene protons led to a negative nOe of the methine proton, supporting a cis relationship between these two substituents. Saponification of **15** and **16** produced the same triol (**17**), supporting the stereochemical assignment of **16**.



15 **17** **16**

In an effort to determine the reaction mechanism, the transformation of **14** to **15** and **16** was monitored by NMR spectroscopy. The signals (^{13}C, ^{7}Li external lock) of

epoxy alcohol **14** were gradually replaced by those of hydroxy carbonates **15** and **16**. Thus, if carbonate **17** is an intermediate in the reaction, its concentration in solution must be quite low.



14 **17** **15**

Application of the methodology described above to epoxides **1** and **3** was found to produce the desired carbonates in high yield with complete stereospecificity, fulfilling the initial goals of the project.[1] This method is anticipated to be generally useful for the transformation of epoxy alcohols to hydroxy carbonates, especially with acid-sensitive substrates.

Experimental Section

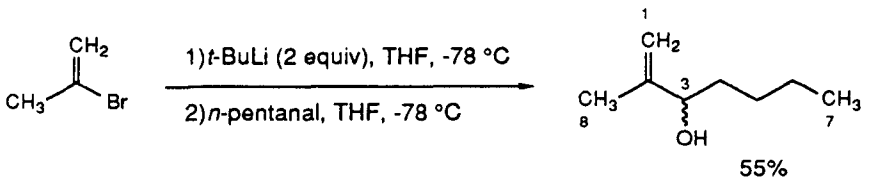
Melting points were recorded with a Büchi SMP-20 melting point apparatus and are uncorrected. Optical rotations were measured using a Jasco DIP-180 Digital Polarimeter at the sodium D line (589 nm) and are reported as follows: $[\alpha]^{25}_{589}$, concentration (*c* (g/100 mL)), and solvent. Infrared spectra were recorded with a Beckman 4240 Infrared spectrometer or a Perkin Elmer 1600 FTIR spectrometer. Data are represented as follows: frequency of absorption (cm^{-1}), and intensity of absorption (s=strong, m=medium, w=weak, br=broad). The ^1H NMR spectra were obtained on a JEOL JNM-GX400 NMR spectrometer (400 MHz), and peaks are reported in ppm (δ scale) using the residual solvent peak as reference ($CHCl_3$:7.26, C_6D_5H:7.15). Data are represented as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, qn=quintet, m=multiplet, br=broad), integration, coupling constants in Hertz, and assignment. Externally locked (^7Li), proton decoupled ^{13}C NMR spectra were obtained on a JEOL FX-90Q NMR spectrometer (22.5 MHz) and are reported in ppm (δ scale) using the residual solvent peak as reference (DMF:162.7, 35.2, 30.1). Mass spectra and high resolution mass spectra were obtained from the UC Riverside Mass Spectrometry Facility.

Liquid chromatography was performed using a forced flow (flash-chromatography)[8] with the indicated solvent using JT Baker Silica Gel (40 μm) or Merck Silica Gel 60 (230-400 mesh ASTM). Analytical thin-layer chromatography was performed using Merck pre-coated silica gel 60 F-254 plates (0.25 mm, glass-backed, fluorescent at 254 nm).

Tetrahydrofuran and diethyl ether were distilled from sodium-benzophenone ketyl. *N,N*-Dimethylformamide, acetonitrile, methylene chloride, hexanes, pyridine, triethylamine, diisopropylamine, and trimethylchlorosilane were distilled from calcium

hydride. Benzene and toluene were distilled from sodium. *t*-Butyllithium in hexanes was titrated with diphenylacetic acid according to Kofron and Baclawski.[9]

All nonaqueous reactions were performed in flame-dried glassware under argon, unless otherwise noted. Organic solutions were concentrated on a Büchi rotatory evaporator at 10-20 Torr, unless otherwise specified. Solvents used in the workup and purification of compounds were HPLC-reagent grade and were used without further purification.



Racemic 2-Methyl-1-hepten-3-ol

t-BuLi (63 mL, 1.82 M in hexanes, 115 mmol, 2.0 equiv) was added over 20 min to a solution of 2-bromopropene (4.9 mL, 6.93 g, 57.3 mmol, 1.0 equiv) in tetrahydrofuran (100 mL) at -78 °C. After 1 h, *n*-pentanal (6.1 mL, 4.939 g, 57.34 mmol, 1.0 equiv) was added dropwise over 5 min. After an additional 40 min, the reaction mixture was warmed to 0 °C and quenched with saturated aqueous ammonium chloride solution (50 mL). The solution was partitioned between 1:1 ethyl actetate-hexanes 100 mL) and brine (100 mL). The aqueous layer was extracted with 1:1 ethyl acetate-hexanes (2 x 100 mL) and the combined organic phases were dried over sodium sulfate. The solution was concentrated *in vacuo* and the residue was purified by flash chromatography (10% ether-petroleum ether→15% ether-petroleum ether) to afford pure racemic 2-methyl-1-hepten-3-ol (4.02 g, 55%) as a clear, colorless oil.

Racemic 2-Methyl-1-hepten-3-ol

^{1}H NMR (400 MHz, $CDCl_3$): 4.81 (s, 1H, H1), 4.21 (s, 1H, H1), 4.02 (t, 1H, *J*=6.5, H3), 1.87 (s, 1H, OH), 1.69 (s, 3H, H8), 1.51 (m, 2H), 1.36 (m, 2H), 1.22 (m, 2H), 0.88 (t, 3H, *J*=6.6, H7).

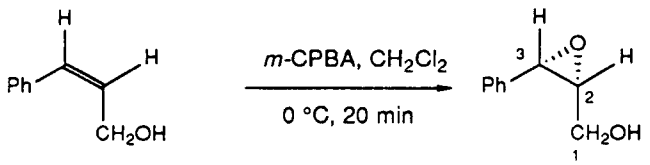
FTIR (neat film), cm^{-1}: 3378 (m), 2943 (s), 1449 (m), 1373 (m), 1002 (m), 891 (m).

MS (EI): 129 (MH^+).

HRMS (EI): Calculated for $C_8H_{16}O$ (M^+): 129.1268

Found: 129.1279

TLC (20% EtOAc-hexanes): 2-Methyl-1-hepten-3-ol 0.48



13 60%

Racemic Epoxy Alcohol **13**

A solution of (*Z*)-3-phenyl-2-propen-1-ol[10] (0.77 g, 5.74 mmol, 1 equiv) in CH_2Cl_2 (6 mL) was treated with *m*-CPBA (1.71 g, 10.3 mmol, 1.8 equiv) for 20 min at 0 °C. Excess oxidant was quenched with saturated aqueous $Na_2S_2O_3$ solution (10 mL). The reaction mixture was partitioned between CH_2Cl_2 (20 mL) and 5% aqueous NaOH solution (30 mL). The organic layer was separated, and the aqueous layer was extracted with one 10-mL portion of CH_2Cl_2. The organic phases were combined and washed with aqueous 5% NaOH solution (30 mL). The aqueous layer was washed with another 10-mL portion of CH_2Cl_2. The combined organic layers were washed with half-saturated brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (45% ethyl acetate-hexanes) to produce pure (±)-**13** (0.52 g, 60%) as a colorless oil.

Racemic epoxy alcohol **13**

^{1}H NMR (400 MHz, $CDCl_3$): 7.11-7.40 (m, 5H, arom), 4.19 (s, 1H, H3), 3.55 (m, 1H, H2), 3.42 (m, 2H, H1), 1.75 (s, 1H, OH).

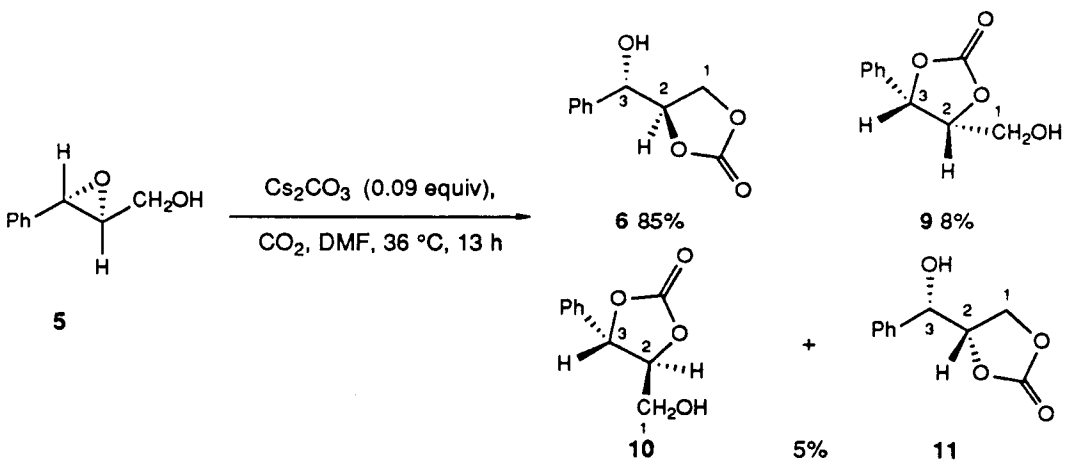
FTIR (neat film), cm^{-1}: 3401 (s), 2978 (m), 1602 (w), 1490 (m), 1449 (m), 1032 (s), 938 (w), 885 (m), 779 (w), 744 (s), 697 (s), 615 (m), 550 (m).

MS (EI): 150 (M^+), 132 (M^+-H_2O), 119 (MH^+-CH_3OH), 107 ($C_7H_7O^+$).

HRMS (EI): Calculated for $C_9H_9O_2$ ($(M-1)^+$): 149.0603
Found: 149.0600

TLC (50% EtOAc-hexanes):

(*Z*)-3-Phenyl-2-propen-1-ol	0.43
Epoxy alcohol **13**	0.32



(2*R*,3*S*)-Hydroxy Carbonate **6**

A 25-mL flask with a side-arm connection to vacuum/carbon dioxide was charged with anhydrous cesium carbonate (210.3 mg, 0.646 mmol, 0.09 equiv), powdered 3-Å molecular sieves (0.50 g), and a teflon-coated stir bar. The mixture was vigorously flame-dried under vacuum (0.1 Torr), and cooled under an atmosphere of CO_2. A solution of (2*S*,3*S*)-3-phenyloxiranemethanol[11] (**5**, 1.106 g, 7.37 mmol, 1.0 equiv, azeotropically dried with two portions of toluene (2 mL)) in DMF (0.5 mL) was transferred via cannula to the catalyst flask; the transfer was quantitated with additional DMF (4 x 0.5 mL). The resulting suspension was warmed to 36 °C, and reacted for 13 h under one atmosphere of carbon dioxide. The progress of the reaction can be conveniently monitored by thin-layer chromatography. The solution was neutralized with saturated aqueous ammonium chloride solution. The resulting suspension was partitioned between half saturated brine (100 mL)-saturated ammonium chloride (20 mL) and ethyl acetate (50 mL). The aqueous layer was extracted further with two 50-mL portions of ethyl acetate. The combined organic layers were dried with sodium sulfate and concentrated (since the hydroxy carbonates are quite polar, the aqueous layer should be checked by TLC to ensure that none of the products are left in the aqueous phase).

Purification of the residue by flash chromatography (20% ethyl acetate-toluene) afforded separately pure (2*R*,3*S*)-**6** (1.2172 g, 85%) and (2*R*,3*S*)-**9** (0.1121 g, 8%). A mixture of (2*S*,3*S*)-**10** and (2*S*,3*S*)-**11** (0.0733 g, 5% combined yield) were also isolated in a separate fraction.

(2*R*,3*S*)-Hydroxy Carbonate **6**

^{1}H NMR (400 MHz, $CDCl_3$): 7.15-7.40 (m, 5H, arom), 5.13 (t, 1H, *J*=3.8, H3), 4.82 (m, 1H, H2), 4.53 (dd, 1H, *J*=7.1, 8.6, H1), 4.21 (t, 1H, *J*=8.6, H1), 3.41 (s, 1H, OH).

FTIR (neat film), cm^{-1}: 3420 (m), 1775 (s), 1476 (w), 1453 (w), 1398 (m), 1180 (s), 1081 (s).

MS (EI): 194 (M^+), 91 ($C_7H_7^+$).

HRMS (EI): Calculated for $C_{10}H_{10}O_4$ (M^+): 194.0579
Found: 194.0591

(2*R*,3*S*)-Hydroxy Carbonate **9**

^{1}H NMR (400 MHz, $CDCl_3$): 7.23-7.54 (m, 5H, arom), 5.83 (d, 1H, *J*=5.1, H3), 4.98 (m, 1H, H2), 3.41 (m, 2H, H1), 1.48 (dd, 1H, *J*=8.0, 8.6, OH).

FTIR (neat film), cm^{-1}: 3448 (m), 2931 (w), 1796 (s), 1496 (w), 1449 (m), 1373 (m), 1173 (s), 1061 (s), 767 (m), 706 (m).

MS (EI): 194 (M^+), 120 (M^+-CO_2-CH_2O), 91 ($C_7H_7^+$).

HRMS (EI): Calculated for $C_{10}H_{10}O_4$ (M^+): 194.0579
Found: 194.0576

(2*S*,3*S*)-Hydroxy Carbonate **10**

^1H NMR (400 MHz, $CDCl_3$): 7.23-7.54 (m, 5H, arom), 5.62 (d, 1H, *J*=8.0, H3), 4.59 (m, 1H, H2), 4.09 (m, 1H, H1), 3.80 (m, 1H, H1), 2.38 (t, 1H, *J*=7.0, OH).

FTIR (neat film), cm^{-1}: 3413 (s), 2936 (w), 1781 (s), 1476 (m), 1380 (m), 1169 (s), 1085 (m), 1065 (s).

MS (EI): 194 (M^+), 132 (M^+-CO_2-H_2O), 120 (M^+-CO_2-CH_2O), 91 ($C_7H_7^+$).

HRMS (EI): Calculated for $C_{10}H_{10}O_4$ (M^+): 194.0579
Found: 194.0586

(2*S*,3*S*)-Hydroxy Carbonate **11**

^{1}H NMR (400 MHz, $CDCl_3$): 7.42 (m, 5H, arom), 4.84 (m, 2H, H2, H3), 4.33 (m, 2H, H1), 2.55 (d, *J*=4.0, 1H, OH).

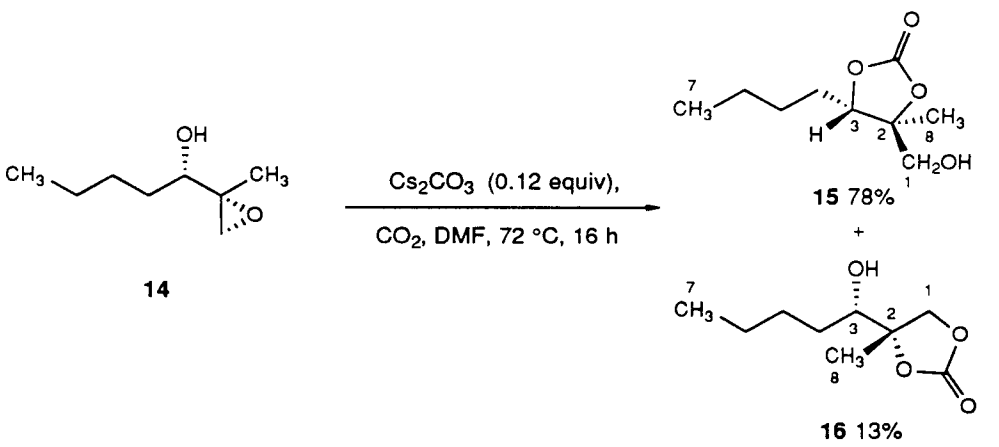
FTIR (neat film), cm^{-1}: 3413 (s), 2942 (w), 1771 (s), 1476 (w), 1453 (w), 1398 (m), 1169 (s), 1081 (s).

MS (EI): 194 (M^+), 107 ($C_7H_7O^+$), 91 ($C_7H_7^+$).

HRMS (EI): Calculated for $C_{10}H_{10}O_4$ (M^+): 194.0579
Found: 194.0569

TLC (ether):

Epoxy alcohol **5**	0.45
Hydroxy carbonate **6**	0.51
Hydroxy carbonate **9**	0.19
Hydroxy carbonate **10**	0.31
Hydroxy carbonate **11**	0.30



(2*S*,3*S*)-Hydroxy Carbonate **15**

A 25-mL flask with a side-arm connection to vacuum/carbon dioxide was charged with anhydrous cesium carbonate (65.2 mg, 0.20 mmol, 0.12 equiv), powdered 3-Å molecular sieves (2.32 g) and a teflon-coated stir bar. The mixture was vigorously flame-dried under vacuum (0.1 Torr), and cooled under an atmosphere of CO_2. A solution of (2*R*,3*S*)-epoxy alcohol **14**[11] (240.9 mg, 1.67 mmol, 1.0 equiv, azeotropically dried with toluene) in DMF (2.0 mL), was transferred via cannula to the catalyst flask; the transfer was quantitated with additional DMF (2 x 0.5 mL). The reaction mixture was warmed to 72 °C, and heated for 16 h under one atmosphere of carbon dioxide. The solution was allowed to cool and the basic mixture was neutralized by the addition of saturated aqueous ammonium chloride solution (1 mL). The reaction mixture was partitioned between half-saturated brine (200 mL) and ethyl acetate (100 mL). The organic layer was separated and the aqueous layer was washed with a 40-mL portion of ethyl acetate. The organic layers were combined, dried over sodium sulfate, and concentrated *in vacuo*. Purification of the residue by flash chromatography (25% ethyl acetate-hexanes) produced pure (2*S*,3*S*)-**15** (246.2 mg, 78%) as a colorless oil. The isomeric hydroxy carbonate (2*S*,3*S*)-**16** (37.9 mg, 13%) was also isolated in a separate fraction.

(2*S*,3*S*)-Hydroxy Carbonate **15**

^{1}H NMR (400 MHz, $CDCl_3$): 4.26 (dd, 1H, *J*=9.5, 9.8, H3), 3.22 (dd, 1H, *J*=5.5, 12.6, H1), 2.95 (dd, 1H, *J*=6.4, 12.6, H1), 2.41 (dd, 1H, *J*=5.5, 6.4, OH), 0.82-1.37 (m, 6H, $CH_2CH_2CH_2$), 0.78 (t, *J*=5.5, CH_3, H7), 0.72 (s, 3H, CH_3, H8).

FTIR (neat film), cm^{-1}: 3460 (m), 2943 (m), 1784 (s), 1461 (w), 1373 (w), 1296 (w), 1220 (w), 1067 (m), 773 (w).

MS (CI:CH_4): 189 (MH^+), 127 (MH^+-CO_2-H_2O), 109 (MH^+-CO_2-$2H_2O$).

HRMS (CI:CH_4): Calculated for $C_9H_{17}O_4$ (MH^+): 189.1127
Found: 189.1132

(2*S*,3*S*)-Hydroxy Carbonate **16**

^{1}H NMR (400 MHz, $CDCl_3$): 4.44 (d, 1H, *J*=8.1, H1), 4.11 (d, 1H, *J*=8.1, H1), 3.60 (m, 1H, H3), 1.97 (br, 1H, OH), 1.59 (m, 2H, CH_2), 1.59 (s, 3H, H8), 1.47 (m, 2H, CH_2), 1.36 (m, 2H, CH_2), 0.95 (t, 3H, *J*=6.6, H7).

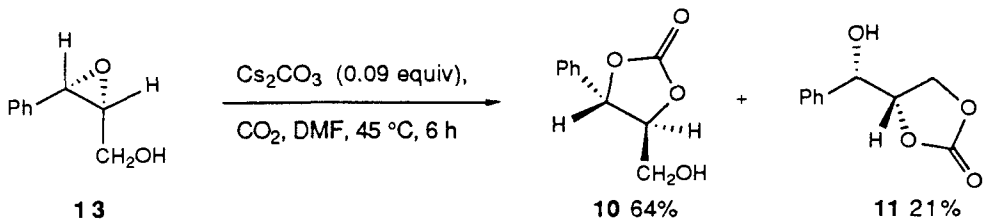
FTIR (neat film), cm^{-1}: 3441 (m), 2958 (m), 2874 (m), 1771 (s), 1462 (m), 1366 (m), 1300 (m), 1216 (m), 1079 (s), 1027 (s), 776 (m).

MS (CI:CH_4): 189 (MH^+), 127 (MH^+-CO_2-H_2O), 109 (MH^+-CO_2-$2H_2O$).

HRMS (CI:CH_4): Calculated for $C_9H_{17}O_4$ (MH^+): 189.1127
Found: 189.1131

TLC (50% EtOAc-hexanes):

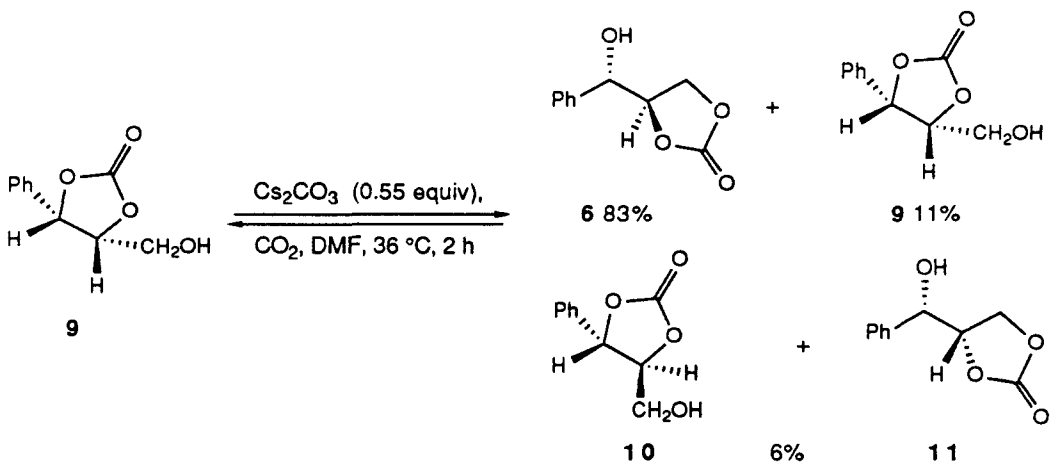
Epoxy alcohol **14**	0.40
Hydroxy carbonate **15**	0.26
Hydroxy carbonate **16**	0.32



13 **10** 64% **11** 21%

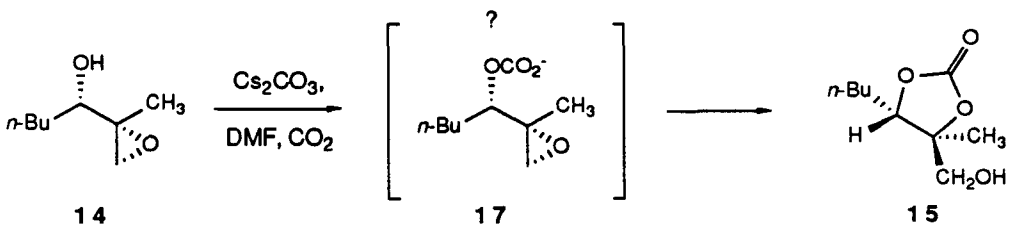
Reaction of CO_2, Cs_2CO_3 with Racemic Epoxy Alcohol **13**

A solution of (±)-**13** (156.0 mg, 1.04 mmol, 1.0 equiv, azeotropically dried with toluene) in DMF (1.0 mL) was added to a mixture of Cs_2CO_3 (41.5 mg, 0.127 mmol, 0.12 equiv) and 3-Å molecular sieves (210.9 mg), which had been vigorously flame-dried under vacuum (0.1 Torr). The catalyst mixture was cooled, flushed with carbon dioxide and warmed to 45 °C. After 6 h at 45 °C the reaction mixture was partitioned between 1:1 ethyl acetate-hexanes (40 mL) and saturated aqueous ammonium chloride solution (50 mL). The organic layer was separated and the aqueous layer was washed with a 40-mL portion of 1:1 ethyl acetate-hexanes. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (20% petroleum ether-ether) producing a 3:1 mixture of (±)-**10** and (±)-**11** (172.7 mg, 85%) as a colorless oil.



Equilibration of Hydroxy Carbonate **9**

Cs_2CO_3 (30.2 mg, 0.09 mmol, 1.8 equiv) and 3-Å molecular sieves were vigorously flame dried *in vacuo* then cooled under an atmosphere of CO_2. A solution of **9** (9.0 mg, 0.05 mmol, 1.0 equiv) in DMF (0.3 mL) was added to the catalyst flask by cannula. After heating 2 h at 35 °C, the product distribution was **6** (83%), **9** (11%), and **10** and **11** (6% combined).



Reaction of Epoxy Alcohol **14** as monitored by ^{13}C NMR

Cs_2CO_3 (47.2 mg, 0.145 mmol, 0.16 equiv) and 3-Å molecular sieves (100.2 mg) were vigorously flamed dried and allowed to cool under an atmosphere of carbon dioxide. The mixture was quickly transferred in air to an NMR tube containing a solution of epoxy alcohol **14** (132 mg, 0.92 mmol, 1 equiv) in DMF (0.2 mL). Carbon dioxide was bubbled through the solution, using a long, steel needle, every 30 min. Less than 2% of **14** had

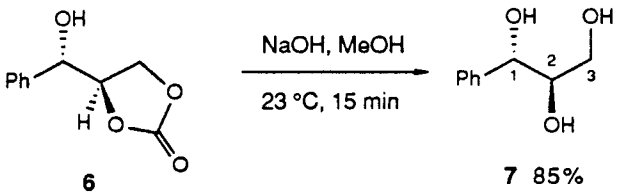
reacted after 12 h at 78 °C. After the solution was heated at 78 °C for 12 h, approximately 50% of the starting material had been cleanly converted to hydroxy carbonates **15** and **16**. There was no evidence of intermediate **17**.

Epoxy alcohol **14**

^{13}C NMR (22.5 MHz, DMF): 74.0, 58.5, 52.5, 32.7, 28.0, 22.7, 15.7, 13.8.

Hydroxy carbonate **15**

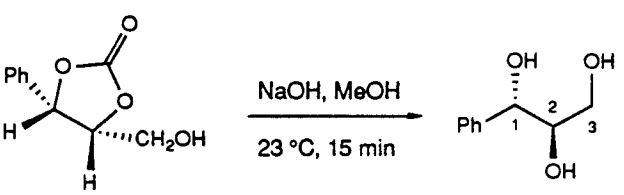
^{13}C NMR (22.5 MHz, DMF): 154, 85.7, 81.0, 66.0, 33.5, 28.5, 23.0, 16.3, 13.5.



6 **7** 85%

Hydrolysis of (2*R*,3*S*)-Hydroxy Carbonate **6**

A solution of (2*R*,3*S*)-hydroxy carbonate **6** (0.4697 g, 2.42 mmol) in MeOH (5 mL) was treated with 50% w/w aqueous NaOH (1 mL) for 15 min at 23 °C. The reaction mixture was partitioned between saturated ammonium chloride solution (50 mL), saturated brine (50 mL), and ethyl acetate (100 mL). The aqueous layer was further extracted with two 100-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate and concentrated. Purification of the residue by flash chromatography (ethyl acetate) afforded (1*S*,2*R*)-**7** (0.3456 g, 85%, 105-106.5 °C) as a white, crystalline solid.



9 **7** 71%

Hydrolysis of (2*R*,3*S*)-Hydroxy Carbonate **9**

A solution of (2*R*,3*S*)-hydroxy carbonate **9** (8.2 mg, 0.042 mmol) in MeOH (1 mL) was treated with 50% w/w aqueous NaOH (0.2 mL) for 15 min at 23 °C. The reaction mixture was partitioned between saturated ammonium chloride solution (20 mL), saturated brine (20 mL), and ethyl acetate (30 mL). The aqueous layer was further extracted with two 30-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo*. Purification of the residue by flash

chromatography (ethyl acetate) afforded (1*S*,2*R*)-**15** (5.0 mg, 71%, mp 104-106 °C) as a white, crystalline solid.

(1*S*,2*R*)-Triol **15**

^{1}H NMR (400 MHz, $CDCl_3$): 7.15-7.40 (m, 5H, arom), 4.89 (dd, 1H, *J*=3.6, 4.8, H1), 3.86 (m, 1H, H3), 3.77 (m, 1H, H2), 3.70 (m, 1H, H3), 2.60 (d, 1H, *J*=3.6, OH), 2.42 (d, 1H, *J*=5.5, OH), 2.03 (t, 1H, *J*=7.5, OH).

FTIR (Nujol mull), cm^{-1}: 3319 (s), 2908 (m), 1373 (m), 1243 (s), 1038 (s), 697 (s).

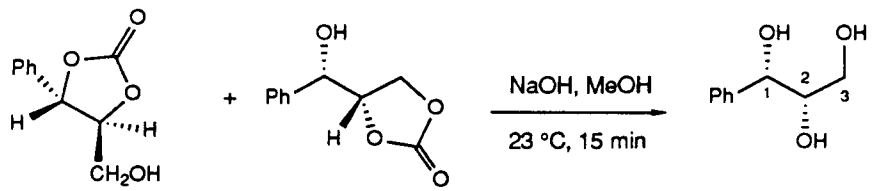
MS (CI:NH_3): 186 ($M+NH_4^+$), 168 (M^+), 133 (M^+-2H_2O)

HRMS (CI:NH_3): Calculated for $C_9H_{16}O_3N$ ($M+NH_4^+$): 186.1130
Found: 186.1138

TLC (EtOAc):

Hydroxy carbonate **6**	0.67
Hydroxy carbonate **7**	0.58
Triol **15**	0.25

Optical Rotation: Observed:$[\alpha]^{23}_{589}$ +20.2° (*c* 6.24, H_2O)
Literature:$[\alpha]^{23}_{589}$ +19.6° (*c* 6.24, H_2O)



Hydrolysis of (2*S*,3*S*)-Hydroxy Carbonates **10** and **11**

A solution of (2*S*,3*S*)-**10** and (2*S*,3*S*)-**11** (39.0 mg, 0.20 mmol) in MeOH (1 mL) was treated with 50% w/w aqueous NaOH (0.2 mL) for 15 min at 23 °C. The reaction mixture was partitioned between saturated ammonium chloride solution (20 mL), saturated brine (20 mL), and ethyl acetate (30 mL). The aqueous layer was further extracted with two 30-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate and concentrated. Purification of the residue by flash chromatography (ethyl acetate) afforded (1*S*,2*S*)-**12** (24.7 mg, 73%) as a colorless syrup.

(1*S*,2*S*)-Triol **12**

^{1}H NMR (400 MHz, $CDCl_3$): 7.15-7.40 (m, 5H, arom), 4.78 (dd, 1H, *J*=3.6, 4.8, H1), 3.80 (m, 1H, H2), 3.64 (m, 1H, H3), 3.56 (m, 1H, H3), 2.81 (d, 1H, *J*=3.6, OH), 2.62 (d, 1H, *J*=5.5, OH), 1.96 (t, 1H, *J*=7.5, OH).

FTIR (neat film), cm^{-1}: 3342 (s), 2919 (m), 1655 (w), 1449 (m), 1378 (m), 1249 (m), 1096 (s), 1026 (s), 873 (w), 756 (m), 697 (s).

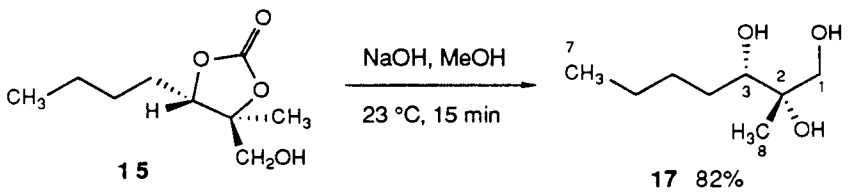
MS (CI:NH_3): 186 ($M+NH_4^+$), 168 (M^+), 133 (M^+-2H_2O).

HRMS (CI:NH_3): Calculated for $C_9H_{16}O_3N$ ($M+NH_4^+$): 186.1130

Found: 186.1130

TLC (EtOAc):

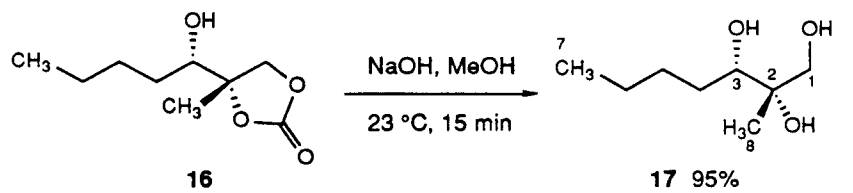
Hydroxy carbonate **10**	0.60
Hydroxy carbonate **11**	0.60
Triol **12**	0.21



15 17 82%

Hydrolysis of (2*S*,3*S*)-Hydroxy Carbonate **15**

A solution of (2*S*,3*S*)-hydroxy carbonate **15** (6.0 mg, 0.032 mmol) in MeOH (1 mL) was treated with 50% w/w aqueous NaOH (0.2 mL) for 15 min at 23 °C. The reaction mixture was partitioned between saturated ammonium chloride solution (20 mL), saturated brine (20 mL), and ethyl acetate (30 mL). The aqueous layer was further extracted with two 30-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate and concentrated. Purification of the residue by flash chromatography (ethyl acetate) afforded (2*S*,3*S*)-**17** (4.3 mg, 83%) as a white, crystalline solid.



16 17 95%

Hydrolysis of (2*S*,3*S*)-Hydroxy Carbonate **16**

A solution of (2*S*,3*S*)-hydroxy carbonate **16** (15.1 mg, 0.080 mmol) in MeOH (1 mL) was treated with 50% w/w aqueous NaOH (0.2 mL) for 15 min at 23 °C. The reaction mixture was partitioned between saturated ammonium chloride solution (20 mL), saturated brine (20 mL), and ethyl acetate (30 mL). The aqueous layer was further extracted with two 30-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate and concentrated. Purification of the residue by flash chromatography (ethyl acetate) afforded (2*S*,3*S*)-**17** (12.3 mg, 95%) as a colorless syrup.

(2*S*,3*S*)-Triol **17**

^{1}H NMR (400 MHz, $CDCl_3$): 3.35 (m, 1H, H3), 3.29 (dd, 1H, *J*=6.3, 7.3, H1), 3.22 (dd, 1H, *J*=6.3, 7.3, H1), 2.38 (s, 1H, OH), 1.89 (d, 1H, *J*=4.6, OH), 1.77 (t, 3H, *J*= 6.25, OH), 1.48 (m, 2H, CH_2), 1.25 (m, 4H, CH_2CH_2), 0.87 (t, 3H, *J*=6.6, H7), 0.86 (s, 3H, CH_3, H8).

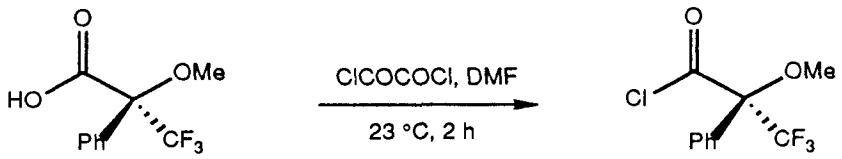
FTIR (neat film), cm^{-1}: 3378 (s), 2943 (s) 2861 (m), 1649 (w), 1461 (m), 1373 (m), 1320 (w), 1261 (w), 1044 (m).

MS (CI:CH_4): 180 (M^++H_2O), 163 (MH^+), 145 (MH^+-H_2O), 127 (MH^+-$2H_2O$).

HRMS (CI:CH_4): Calculated for $C_8H_{19}O_3$ (MH^+): 163.1334
Found: 163.1327

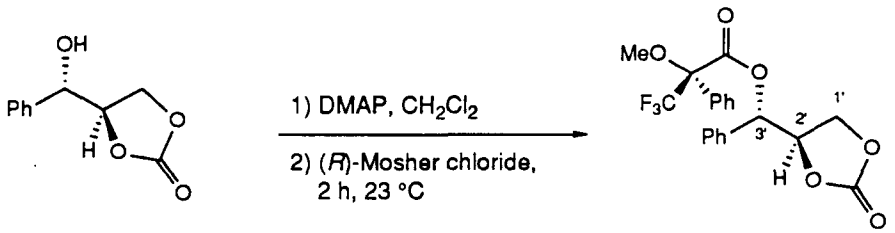
TLC (EtOAc):

Hydroxy carbonate **15**	0.87
Hydroxy carbonate **16**	0.87
Triol **17**	0.31



(*R*)-Mosher Chloride

(*S*)-(-)-Mosher acid (122.7 mg, 0.524 mmol, 1.0 equiv), oxalyl chloride (0.23 mL, 2.6 mmol, 5.0 equiv) and CH_2Cl_2 (3 mL) were combined in a 10-mL side-arm flask under argon. A 1-cm capillary containing DMF was added and the solution was stirred for 1 h. The reaction mixture was concentrated under vacuum (0.1 Torr) and used without further purification in the following reactions.



(2'*R*,3'*S*,2*S*)-Mosher Ester **19**

(*R*)-Mosher chloride (0.26 mmol, 4.7 equiv) in CH_2Cl_2 (5 mL) was added to a solution of DMAP (19.4 mg, 0.160 mmol, 2.76 equiv, azeotropically dried with two 1-mL portions of toluene), and (2*R*,3*S*)-**6** (11.2 mg, 0.058 mmol, 98% ee, 1 equiv) in CH_2Cl_2 (1 mL) at 0 °C. The reaction mixture was warmed to 23 °C and stirred for 2 h at that temperature. The reaction was quenched with saturated aqueous citric acid solution (5 mL) and the aqueous layer was extracted with two 20-ml portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. Purification of the residue by flash chromatography (7% ethyl acetate-toluene) gave (2'*R*,3'*S*,2*S*)-**19** (19.2 mg, 81%), as a clear oil.

(2'*R*,3'*S*,2*S*)-Mosher ester **19**

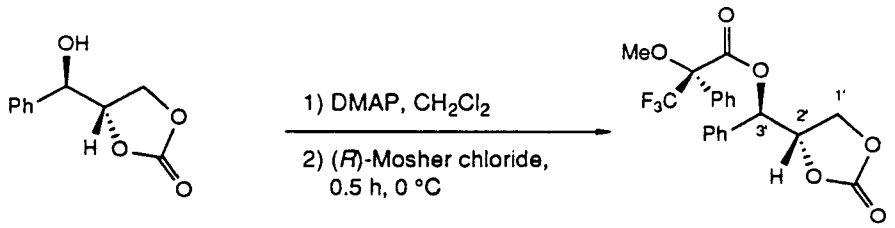
^{1}H NMR (400 MHz, C_6D_6): 7.53 (d, 2H, *J*=6.5, arom), 6.82-7.10 (m, 8H, arom), 5.94 (d, 1H, *J*=3.2, H3'), 3.84 (m, 1H, H2'), 3.63 (t, 1H, *J*=8.7, H1'), 3.25 (d, 3H, *J*=1.6, OCH_3), 3.10 (t, 1H, *J*=8.7, H1').

FTIR (neat film), cm^{-1}: 2952 (w), 1814 (s), 1758 (m), 1497 (w), 1453 (w), 1272 (m), 1243 (m), 1169 (s), 1122 (m), 1070 (m), 1016 (m), 766 (m), 722 (m), 700 (m).

MS (EI): 410 (M^+), 189 ($C_6H_5CF_3OCH_3^+$).

HRMS (EI): Calculated for $C_{20}H_{17}F_3O_6$ (M^+): 410.0977
Found: 410.0986

TLC (40% EtOAc-hexanes): Mosher ester **19** 0.57 (UV)
Hydroxy carbonate **6** 0.38 (UV)



20 **21** 87%

(2*S*,2'*S*,3'*R*)-Mosher Ester **21**

(*R*)-Mosher chloride (0.32 mmol, 6.4 equiv) in CH_2Cl_2 (5 mL) was added to a solution of DMAP (19.4 mg, 0.160 mmol, 3.14 equiv, azeotropically dried with two 1-mL portions of toluene), and (2*S*,3*R*)-**20** (9.8 mg, 0.051 mmol, 96% ee, 1.0 equiv) in CH_2Cl_2 (1 mL) at 0 °C. The reaction mixture was stirred for 30 min at that temperature. The reaction was quenched with saturated aqueous citric acid solution (5 mL) and the aqueous layer was extracted with two 20-ml portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. Purification of the residue by flash chromatography (7% toluene-ethyl acetate) gave (2*S*,2'*S*,3'*R*)-**21** (17.9 mg, 87%), as a clear oil.

(2*S*,2'*S*,3'*R*)-Mosher Ester **21**

^{1}H NMR (400 MHz, C_6D_6): 7.52 (d, 2H, *J*=6.5, arom), 6.87-7.34 (m, 6H, arom), 6.67 (d, 2H, *J*=7.6, arom), 5.89 (d, 1H, *J*=3.2, H3'), 3.81 (m, 1H, H2'), 3.69 (dd, 1H, *J*=5.5, 8.5, H1'), 3.44 (d, 3H, *J*=1.6, OCH_3), 3.02 (t, 1H, *J*=8.7, H1').

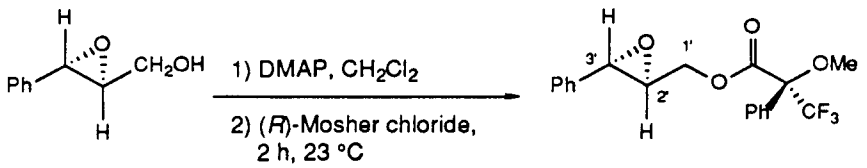
FTIR (neat film), cm^{-1}: 2952 (w), 1814 (s), 1758 (m), 1497 (w), 1453 (w), 1272 (m), 1243 (m), 1169 (s), 1122 (m), 1070 (m), 1016 (m), 766 (m), 722 (m), 700 (m).

MS (CI:NH_3): 428 (M^+), 189 ($C_6H_5CF_3OCH_3^+$).

HRMS (CI:NH_3): Calculated for $C_{20}H_{21}F_3NO_6$ ($M+NH_4^+$):428.1320
Found: 428.1310

TLC (40% EtOAc-hexanes):

Mosher ester **21**	0.57 (UV)
Hydroxy carbonate **20**	0.38 (UV)



5 **22** 74%

(2*S*,2'*S*,3'*S*)-Mosher Ester **22**

(*R*)-Mosher chloride (0.262 mmol, 4.94 equiv) in CH_2Cl_2 (5 mL) was added to a solution of DMAP (14.0 mg, 0.115 mmol, 2.16 equiv, azeotropically dried with two 1-mL portions of toluene), and (2*S*,3*S*)-**5** (8.0 mg, 0.053 mmol, 98% ee, 1 equiv) in CH_2Cl_2 (1 mL) at 0 °C. The reaction mixture was warmed to 23 °C and stirred for 2 h at that temperature. The reaction was quenched with saturated aqueous citric acid solution (5 mL) and the aqueous layer was extracted with two 20-ml portions of methylene chloride. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. Purification of the residue by flash chromatography (10% ethyl acetate-toluene) gave (2*S*,2'*S*,3'*S*)-**22** (14.2 mg, 74%), as a clear oil.

(2*S*,2'*S*,3'*S*)-Mosher Ester **22**

^{1}H NMR (400 MHz, C_6D_6): 7.71 (d, 2H, *J*=7.5, arom), 6.95-7.34 (m, 8H, arom), 4.19 (dd, 1H, *J*=12.0, 3.7, H1'), 3.92 (dd, 1H, *J*=8.3, 5.6, H1'), 3.51 (s, 3H, OCH_3), 3.41 (d, 1H, *J*=2.9, H3'), 2.79 (m, 1H, H2').

FTIR (neat film), cm^{-1}: 2952 (w), 1755 (s), 1490 (w), 1443 (w), 1267 (m), 1243 (m), 1167 (s), 1114 (m), 1079 (w), 1020 (m), 997 (m), 879 (w), 761 (w), 719 (m), 691 (m).

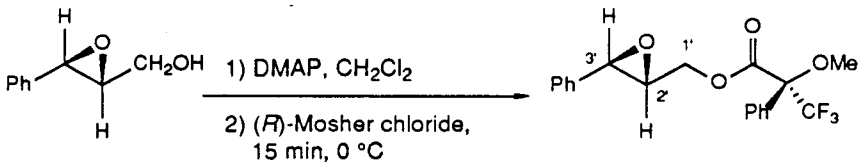
MS (CI:NH_3): 385 (MH^++H_2O), 367 (MH^+), 189 ($C_9H_8F_3O^+$).

HRMS (CI:NH_3): Calculated for $C_{19}H_{18}F_3O_4$ (MH^+): 367.1157

Found: 367.1151

TLC (30% EtOAc-hexanes):

Mosher ester **22**	0.55 (UV)
Epoxy alcohol **5**	0.18 (UV)



23 **24** 71%

(2*S*,2'*R*,3'*R*)-Mosher Ester **24**

(*R*)-Mosher chloride (0.082 mmol, 1.3 equiv) in CH_2Cl_2 (0.2 mL) was added to a solution of DMAP (15.7 mg, 0.129 mmol, 1.97 equiv, azeotropically dried with two 1-mL portions of toluene), and **23** (9.8 mg, 0.065 mmol, 96% ee) in CH_2Cl_2 (1 mL) at 0 °C. The reaction mixture was stirred at that temperature for 15 min. The reaction was quenched with saturated aqueous citric acid (5 mL) and the aqueous layer was extracted with two 20-ml portions of methylene chloride. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. Purification of the residue by flash chromatography (10% ethyl acetate-toluene) gave (2*S*,2'*R*,3'*R*)-**23** (16.8 mg, 71%), as a colorless oil.

(2*S*,2'*R*,3'*R*)-Mosher Ester **24**

^{1}H NMR (400 MHz, C_6D_6): 7.70 (d, 2H, *J*=7.5, arom), 6.95-7.34 (m, 8H, arom), 4.23 (dd, 1H, *J*=2.9, 12.2, H1'), 3.70 (dd, 1H, *J*=5.4, 12.2, H1'), 3.41 (s, 3H, OCH_3), 3.38 (d, 1H, *J*=2.9, H3'), 2.74 (m, 1H, H2').

FTIR (neat film), cm^{-1}: 2952 (w), 1755 (s), 1490 (w), 1443 (w), 1267 (m), 1243 (m), 1167 (s), 1114 (m), 1079 (w), 1020 (m), 997 (m), 879 (w), 761 (w), 719 (m), 691 (m).

MS (CI:NH_3): 385 (MH^++H_2O), 367 (MH^+), 189 ($C_9H_8F_3O^+$).

HRMS (CI:NH_3): Calculated for $C_{19}H_{18}F_3O_4$ (MH^+): 367.1157

Found: 367.1161

TLC (30% EtOAc-hexanes):

Mosher ester **23**	0.55 (UV)
Epoxy alcohol **22**	0.18 (UV)

References

[1](a)Myers, A. G.; Proteau, P. J.; Handel, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 7212. (b)Proteau, P. J. M. S. Thesis, California Institute of Technology, 1989.

[2](a)Roush, W. R.; Brown, R. J.; DiMare, M. *J. Org. Chem.* **1983**, *48*, 5083. (b)Roush, W. R.; Brown, R. J. *J. Org. Chem.* **1982**, *47*, 1371. (c)Corey, E. J.; Hopkins, P. B.; Munroe, J. E.; Marfat, A.; Hashimoto, S. *J. Am. Chem. Soc.* **1980**, *102*, 7987. (d)Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *1040*, 1109.

[3]McCombie, S. W.; Metz, W. A. *Tetrahedron Lett.* **1987**, *28*, 383.

[4]Myers, A. G.; Widdowson, K. L. *Tetrahedron Lett.* **1988**, *29*, 6389.

[5]Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

[6]Delton, M. H.; Yeun, G. U. *J. Org. Chem.* **1968**, *33*, 2478.

[7]Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819.

[8]Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

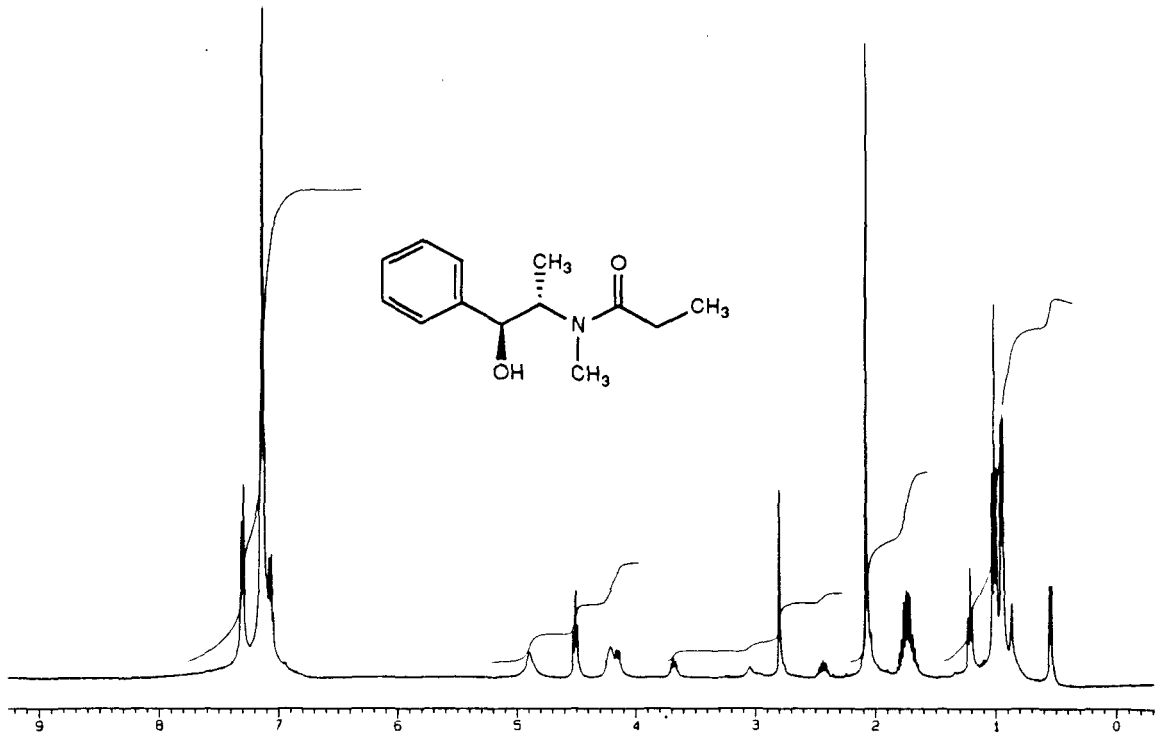
[9]Kofron, W. G.; Baclawski, L. H. *J. Org. Chem.* **1976**, *41*, 1879.

[10]Smith, P. A. S.; Choi, S.-S. P. *J. Org. Chem.* **1981**, *20*, 3974.

[11]Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masmune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5768.

Appendix I

Spectral Catalog for Chapter One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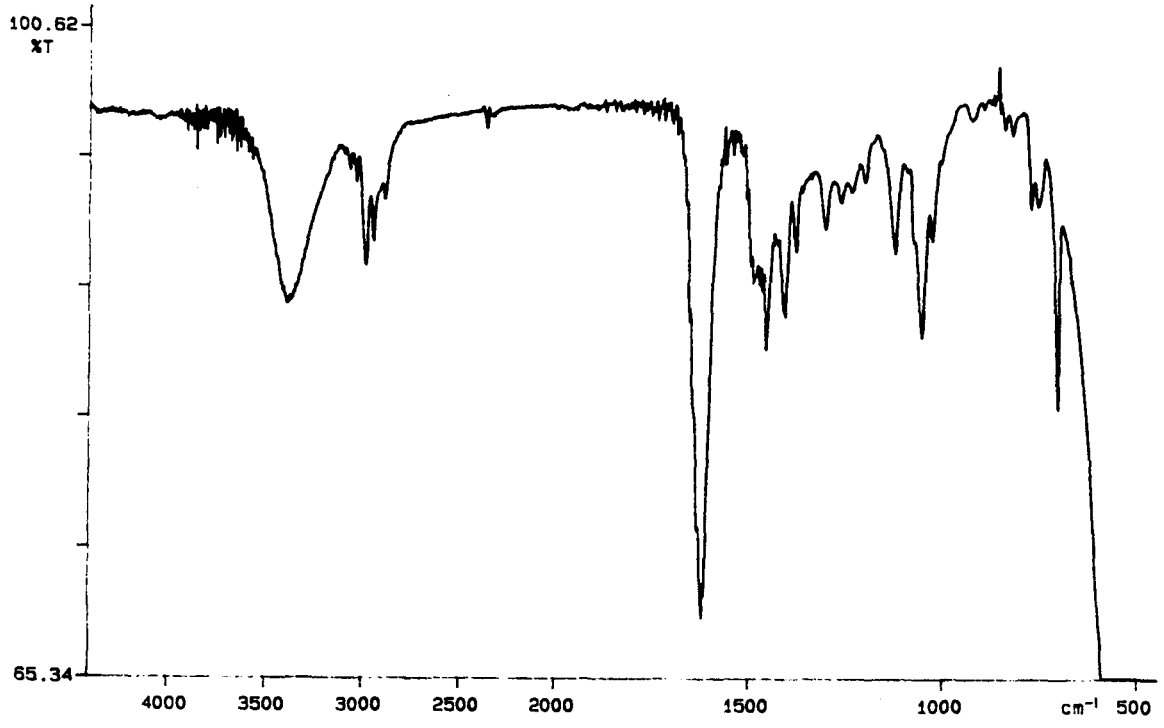
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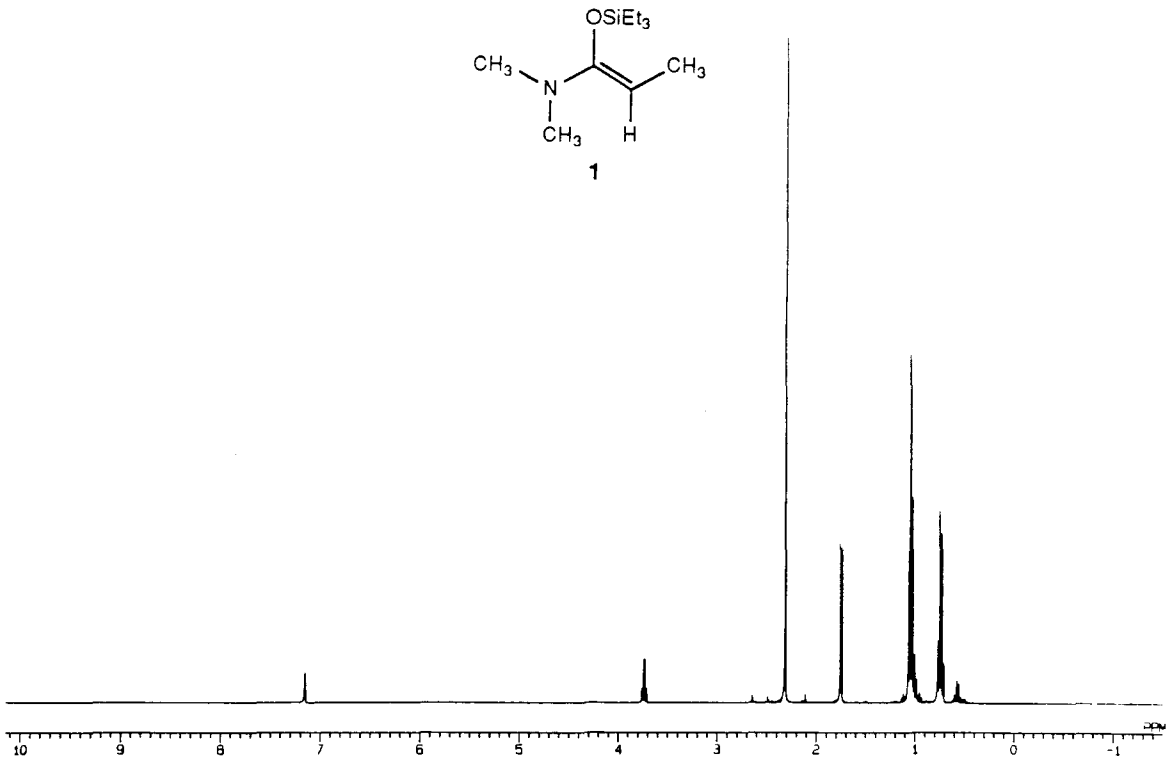
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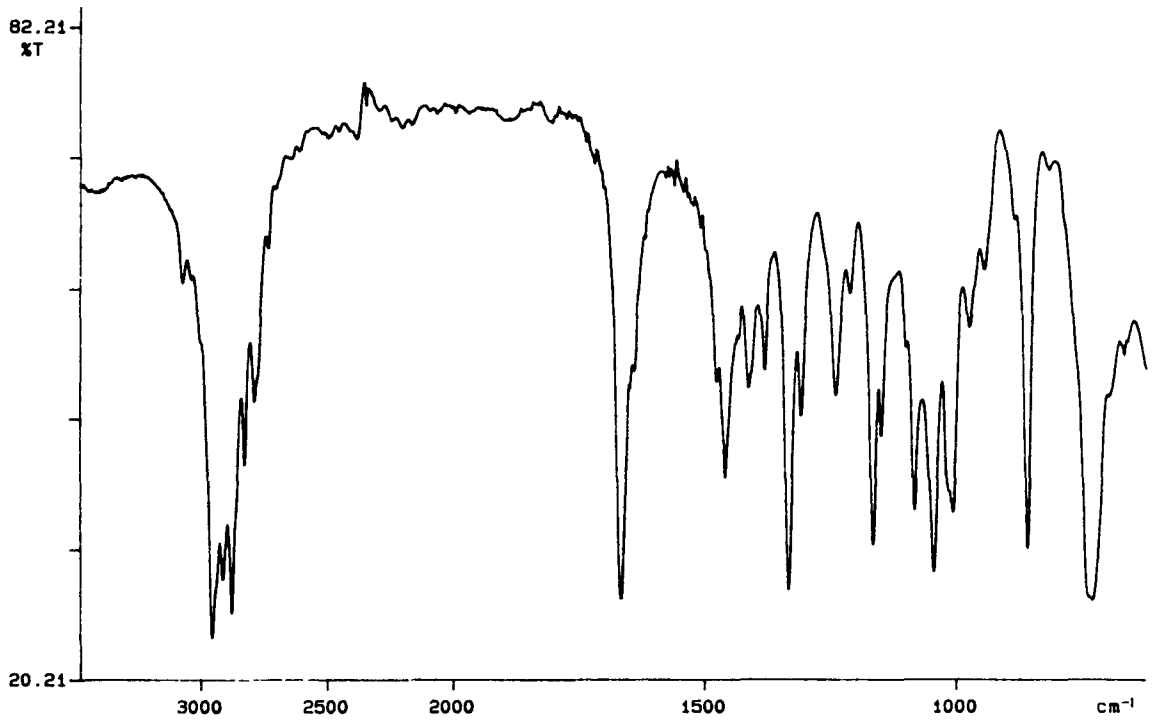
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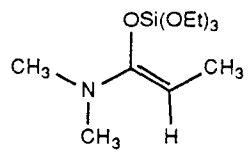
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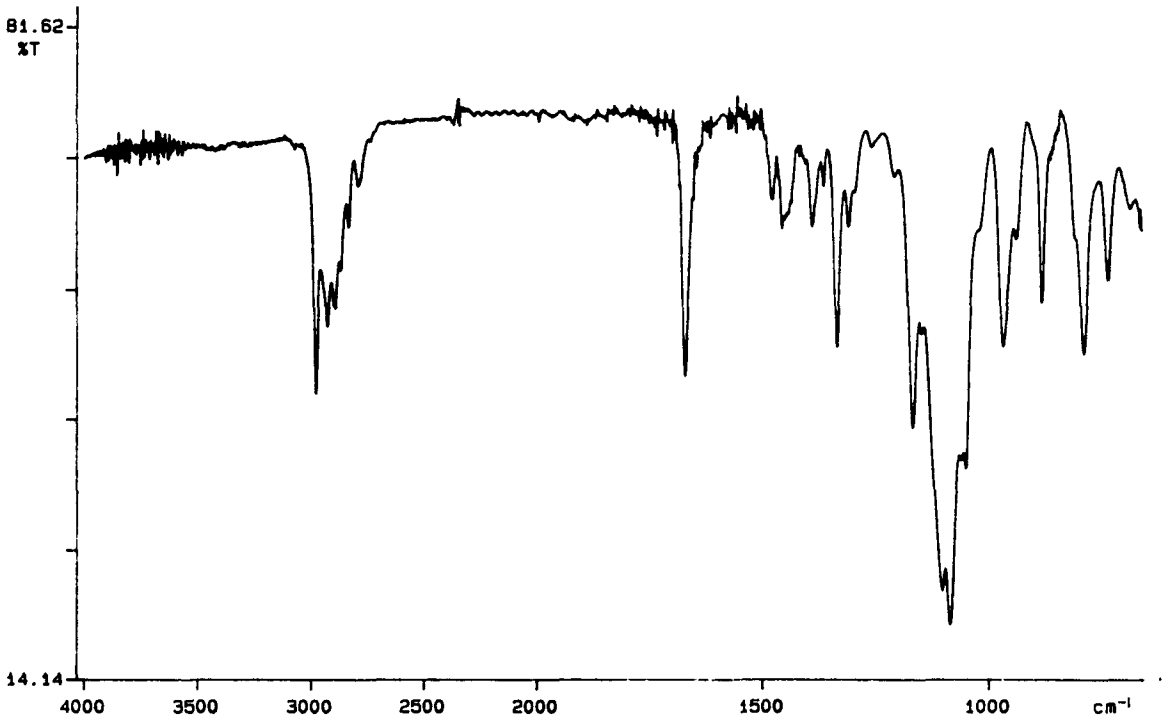
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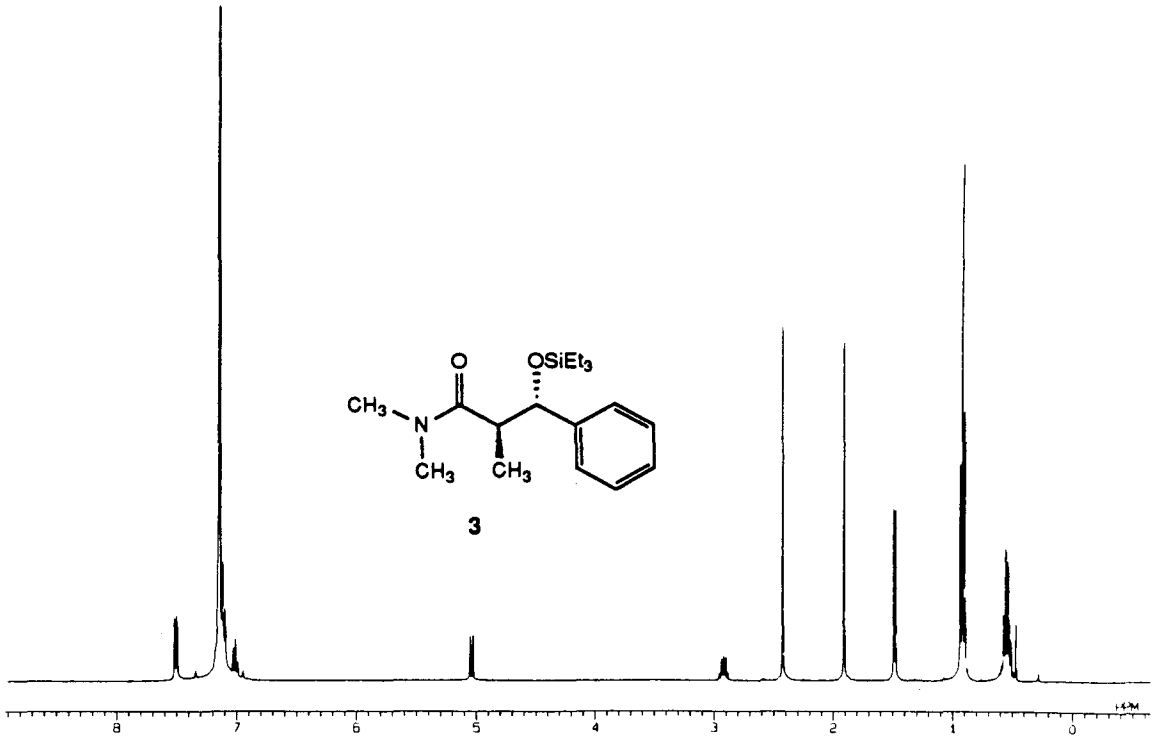
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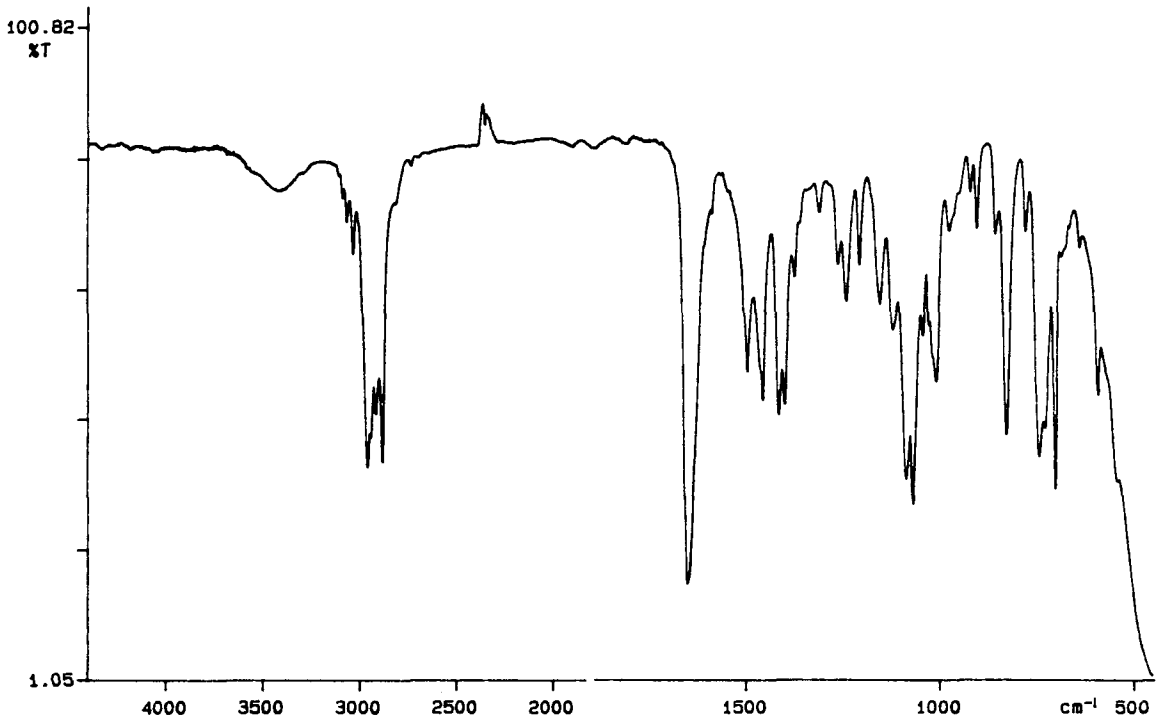
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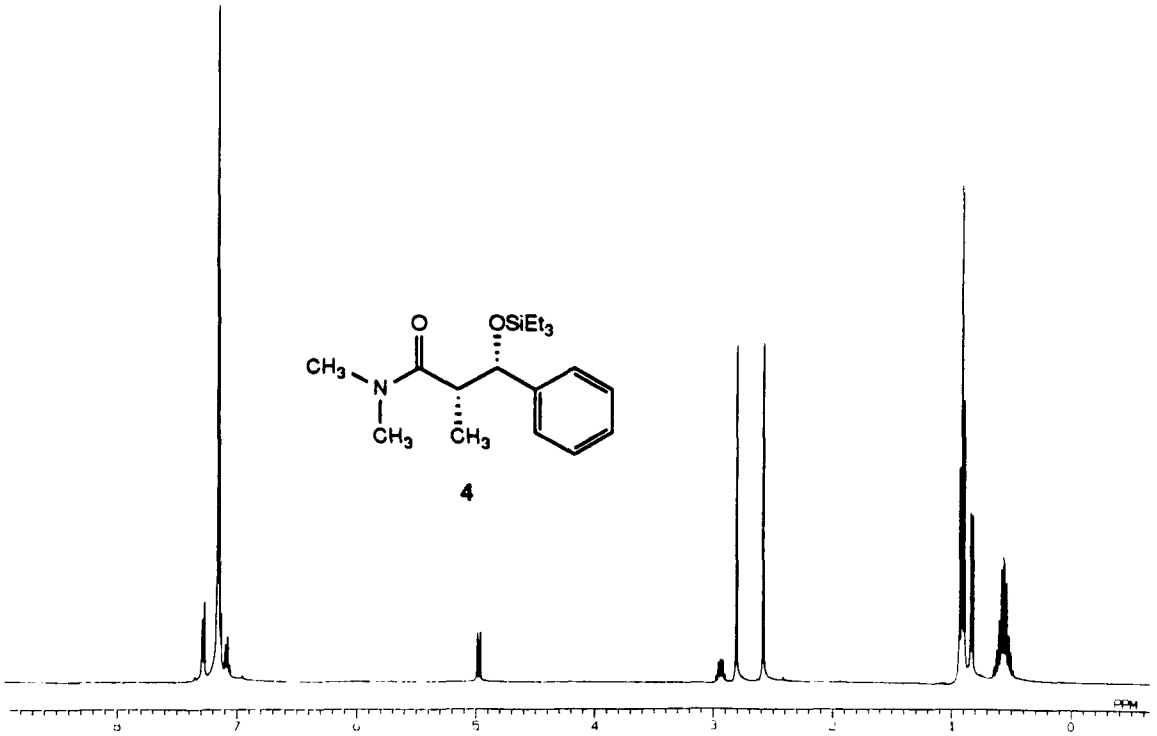
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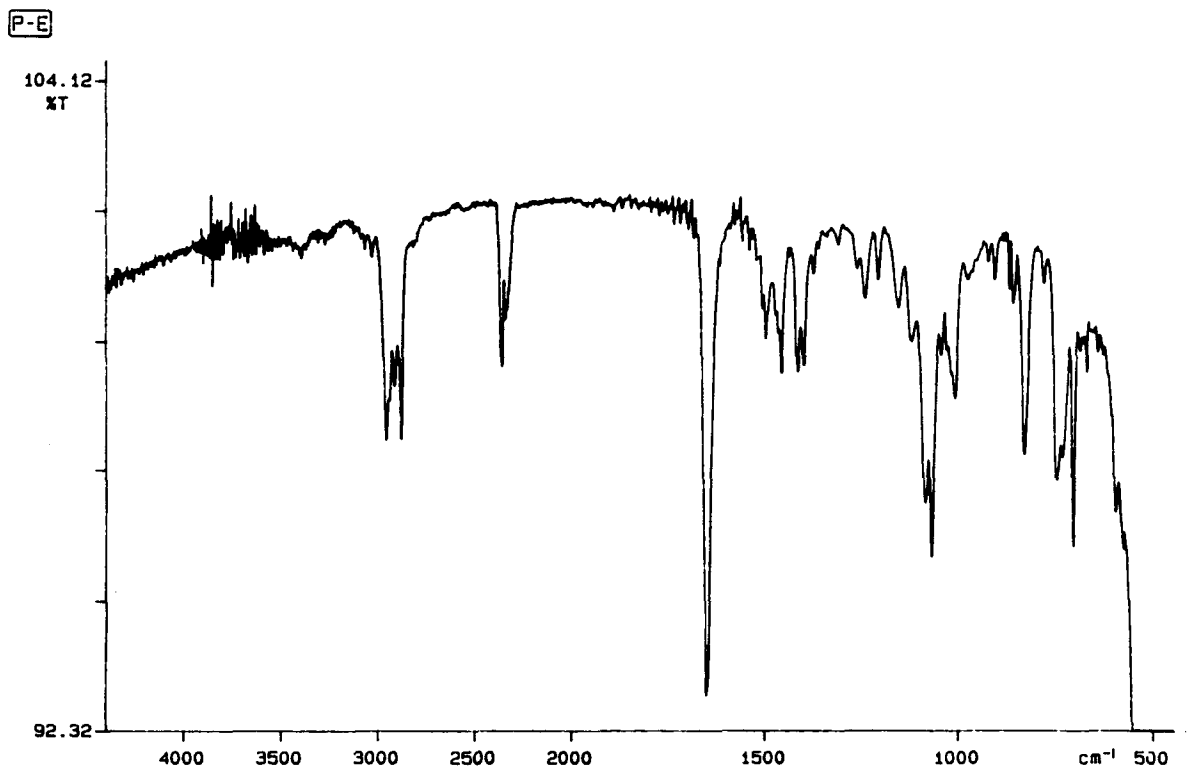
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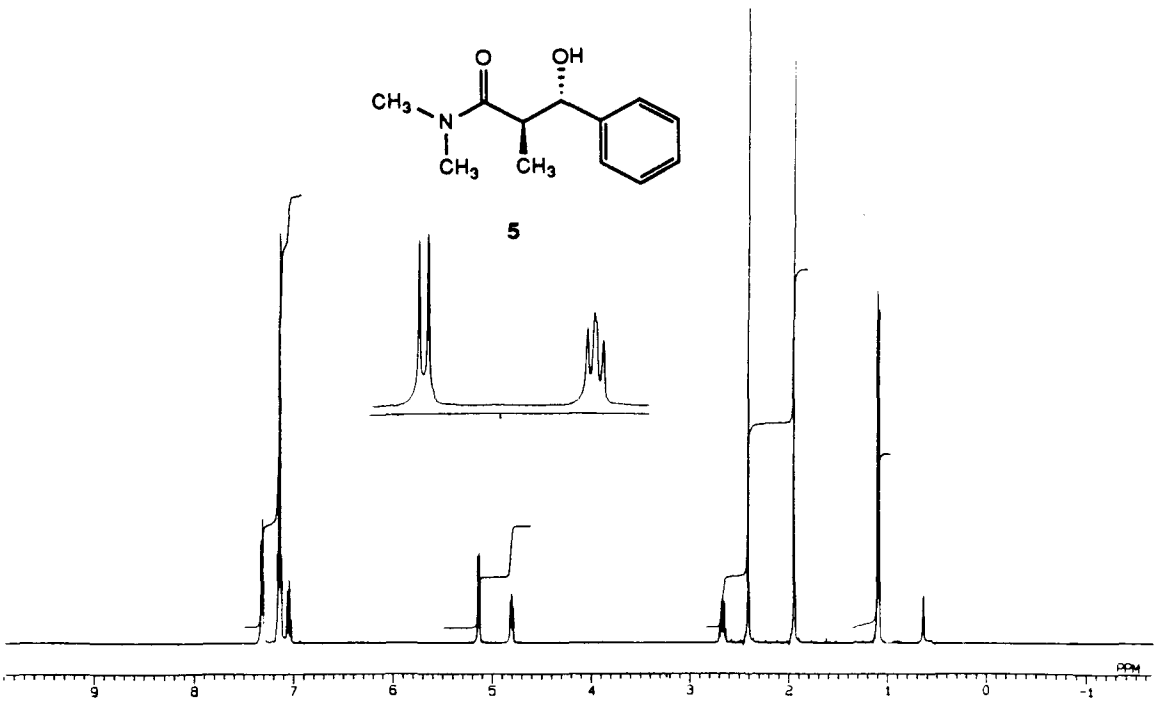
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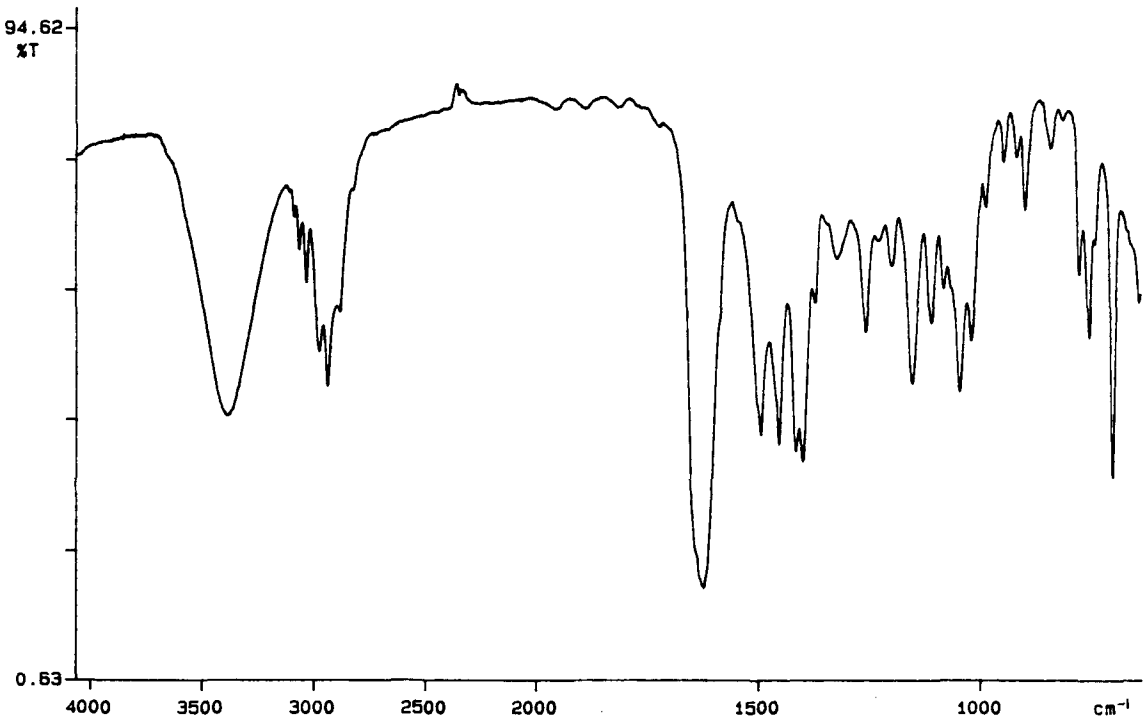
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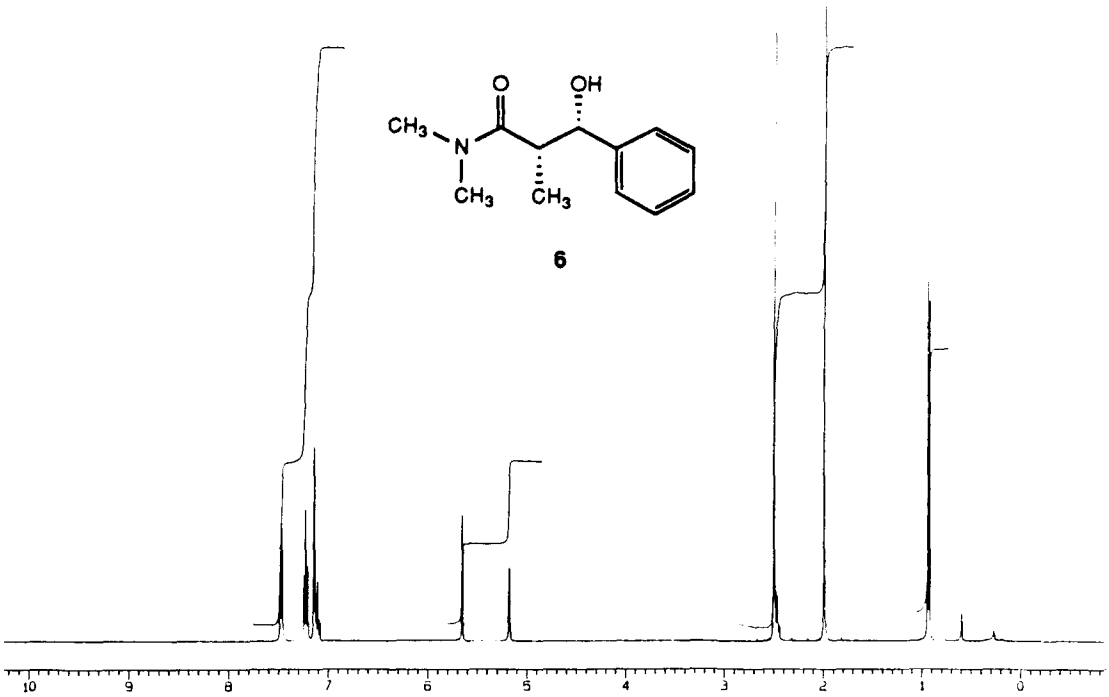
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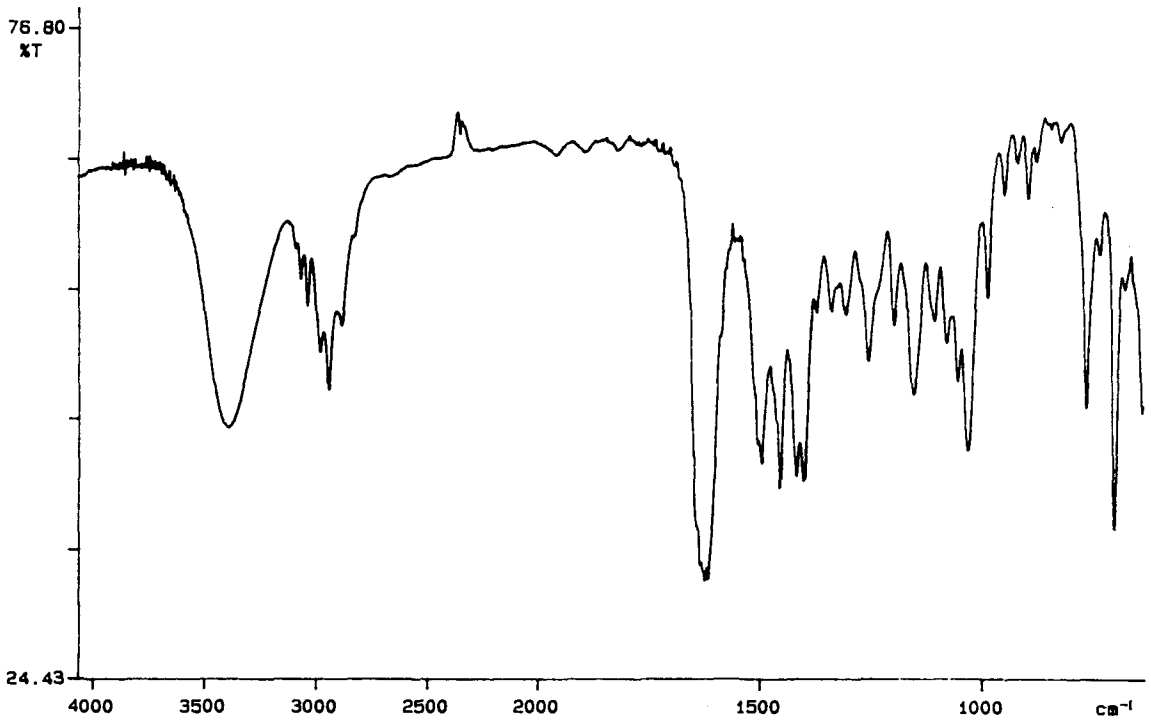
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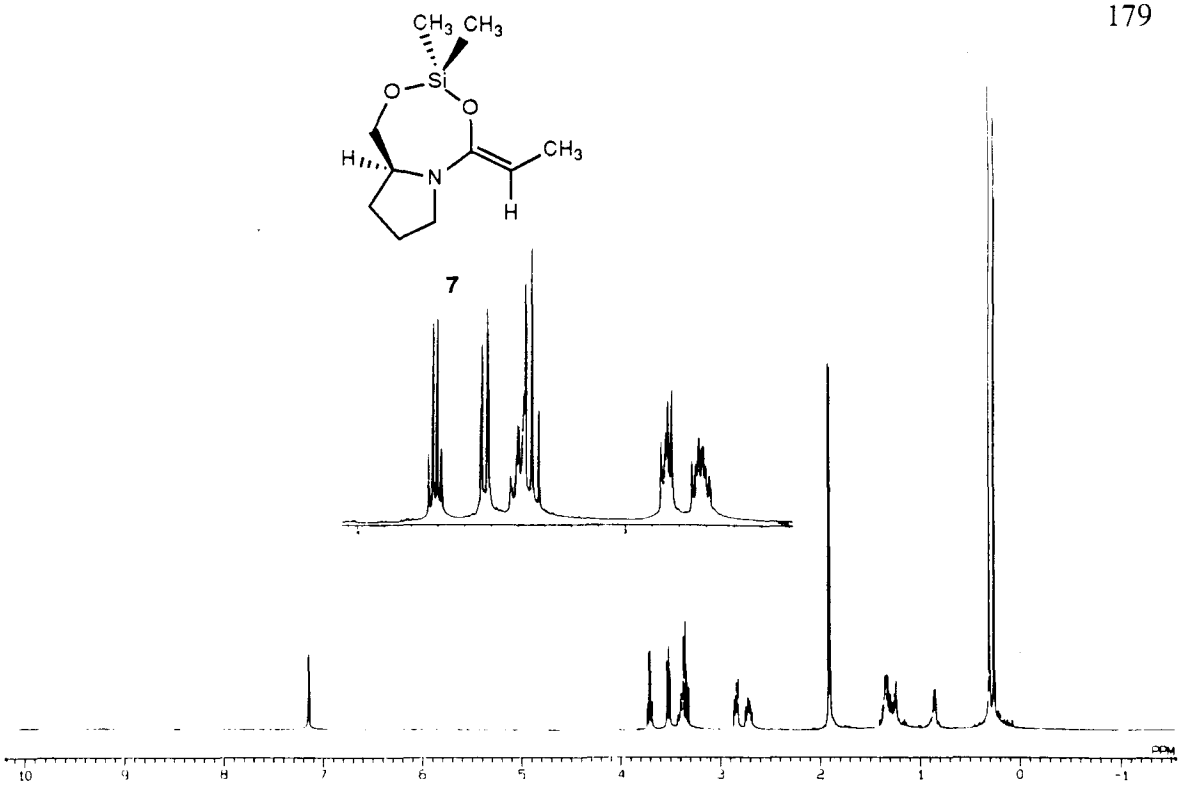
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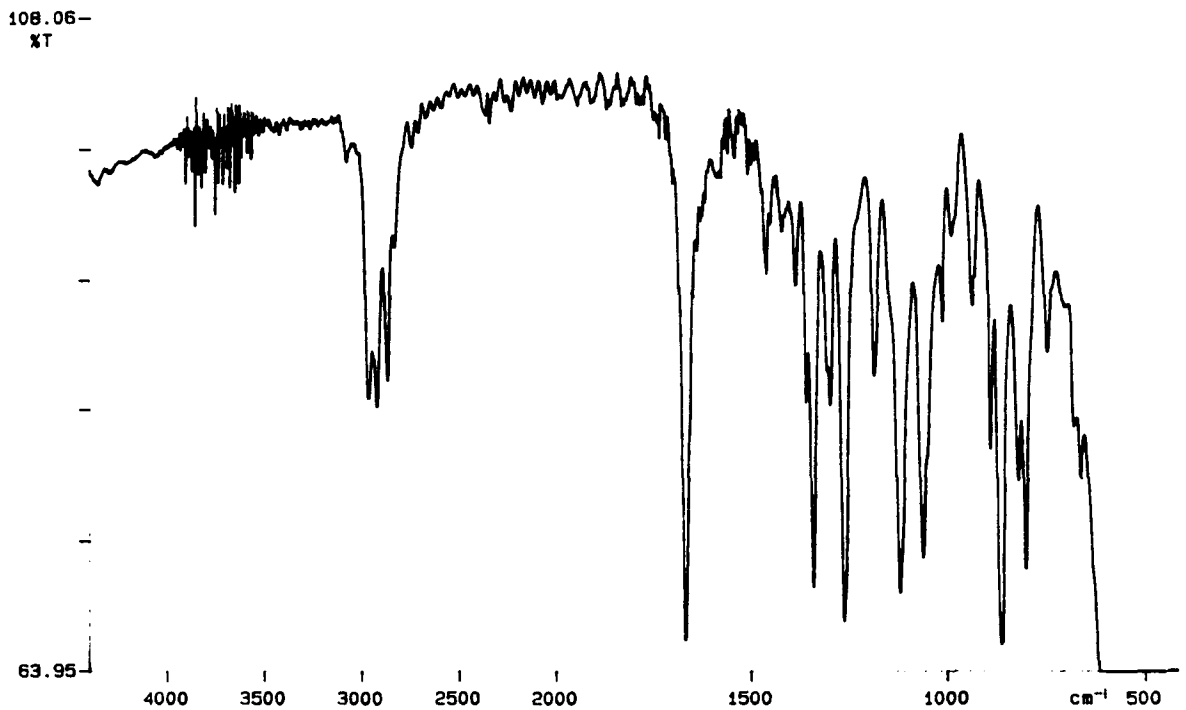
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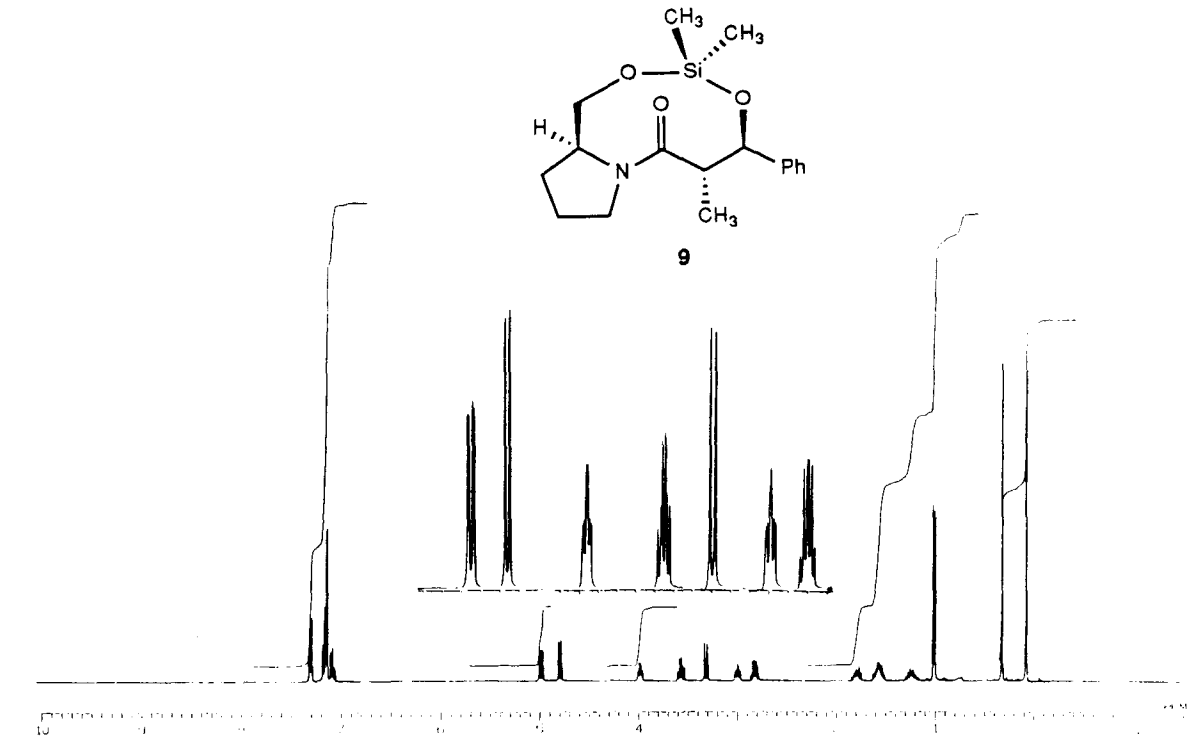
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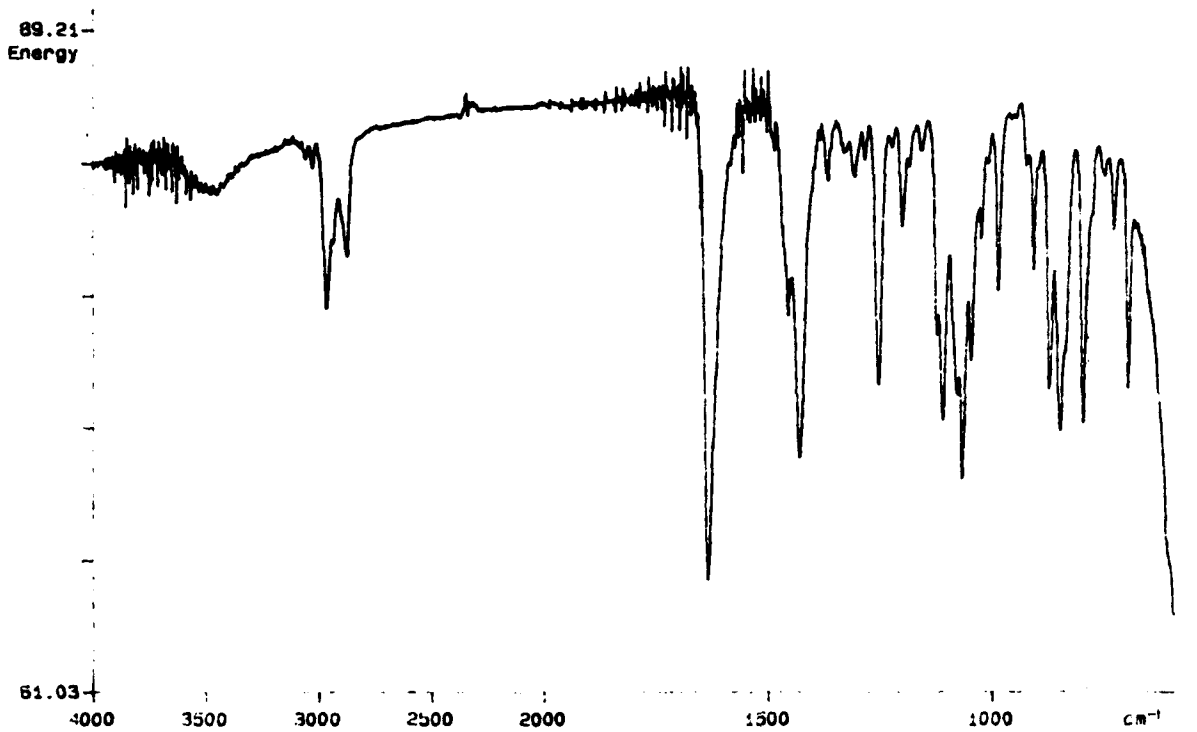
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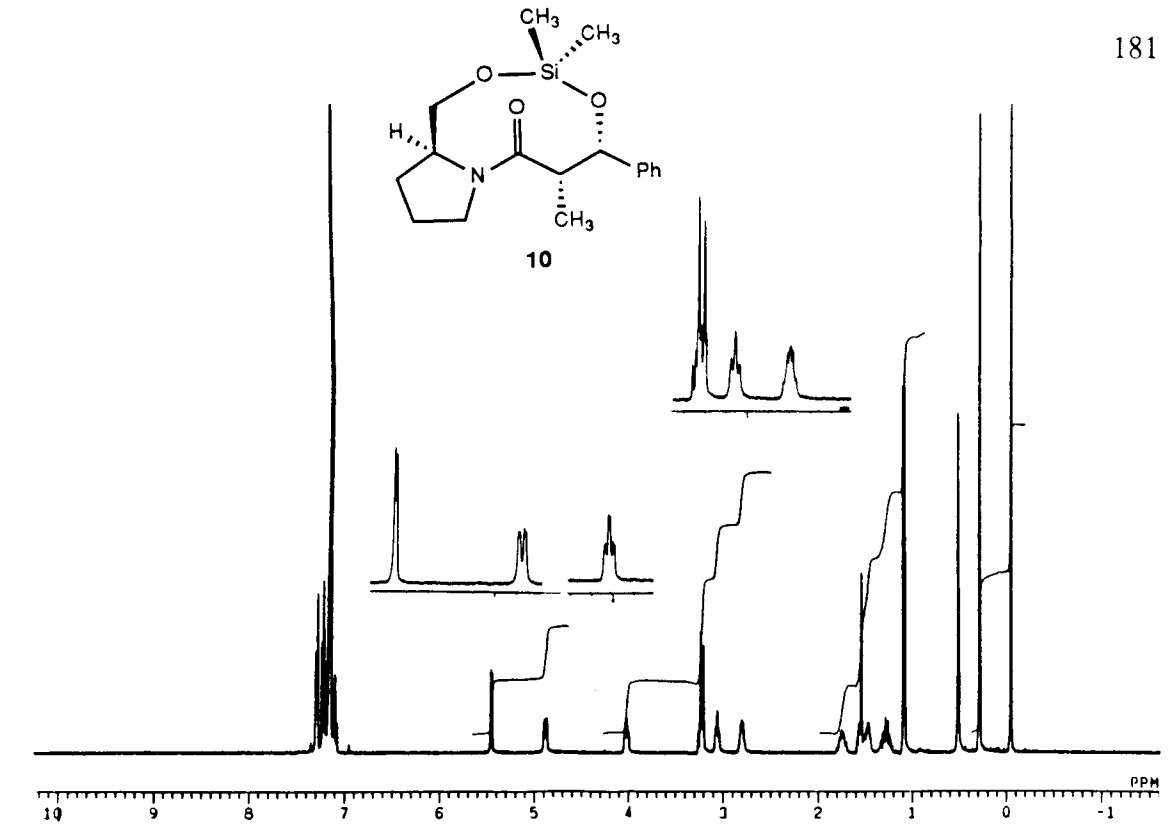
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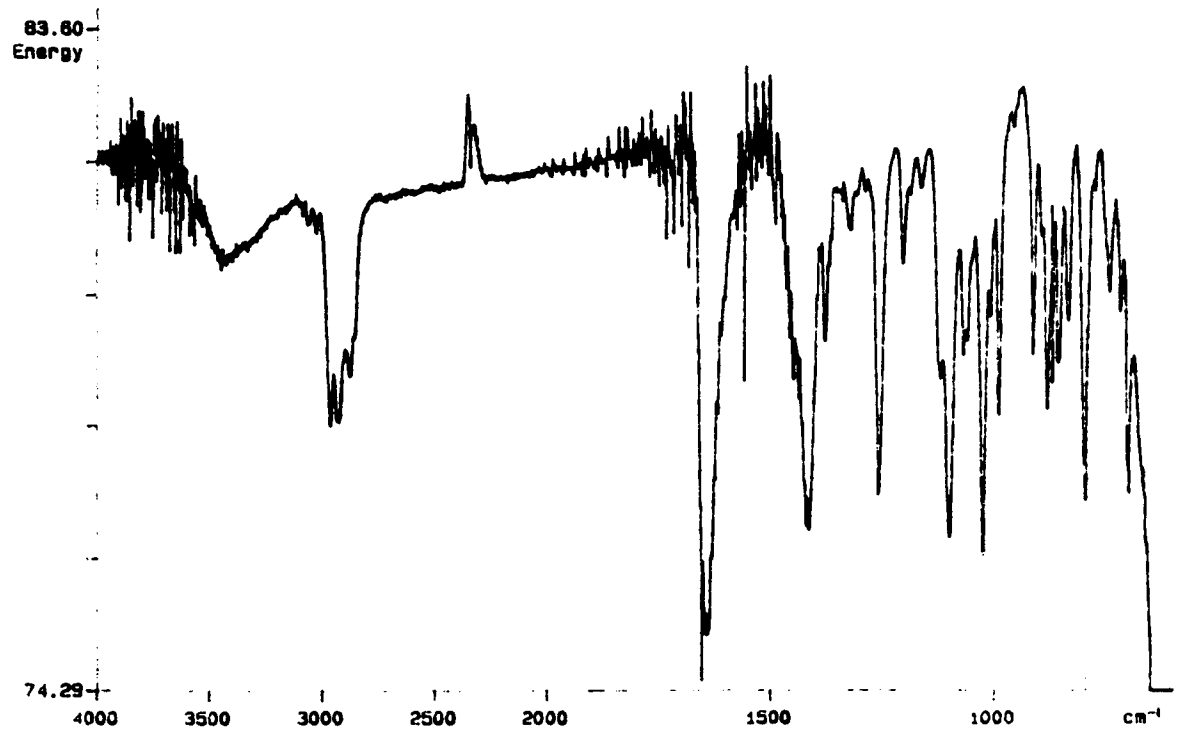
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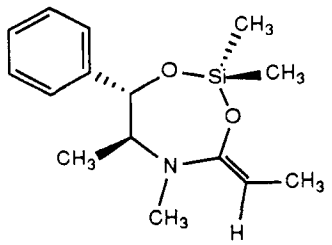
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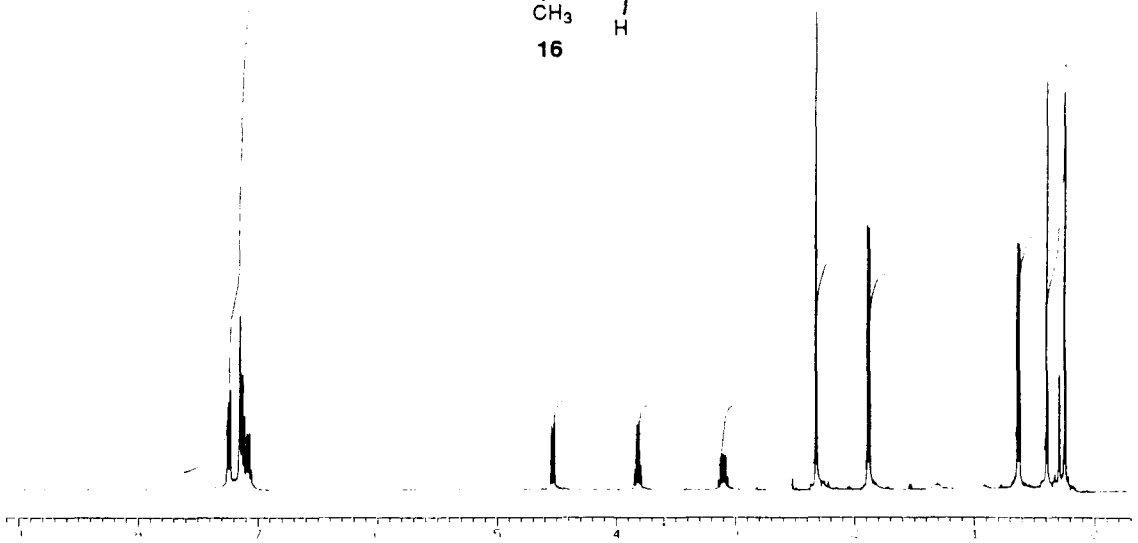

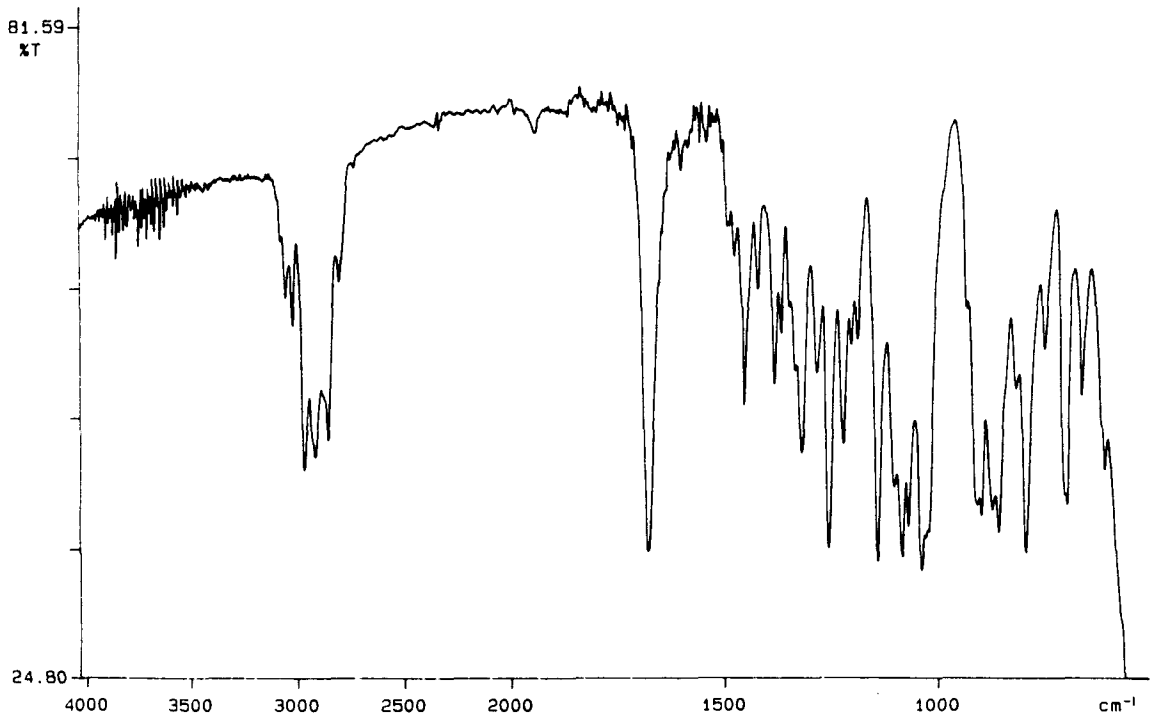
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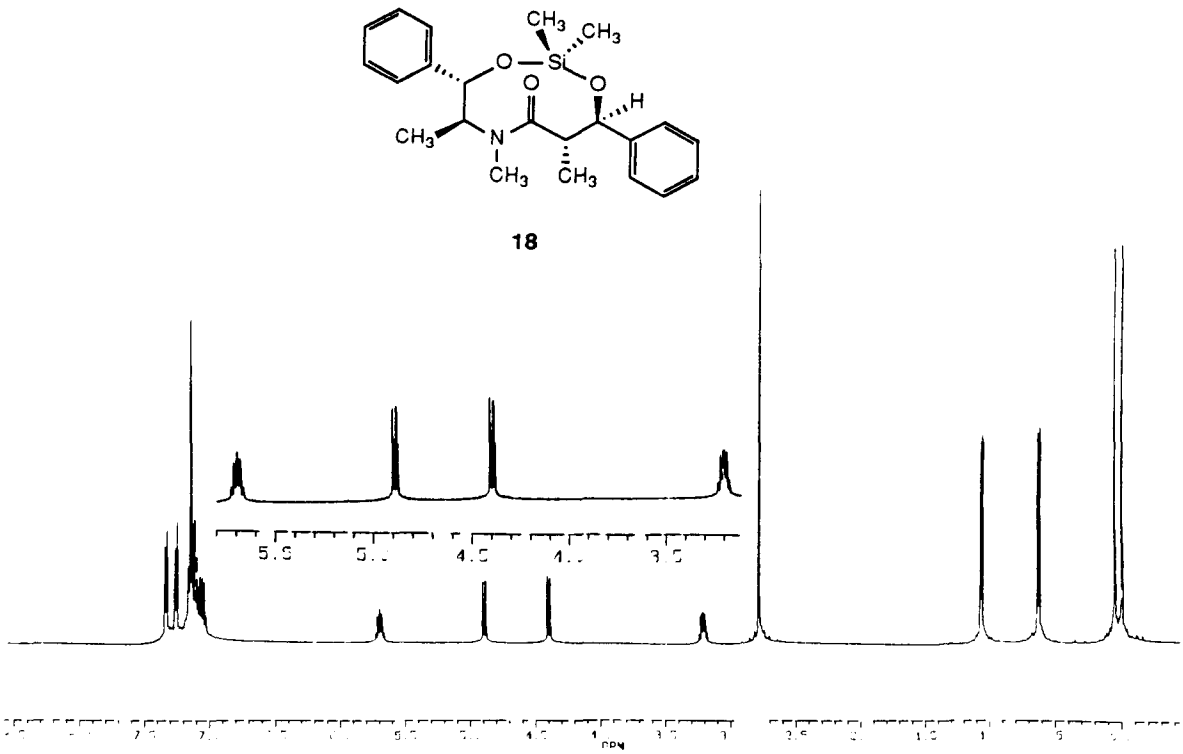

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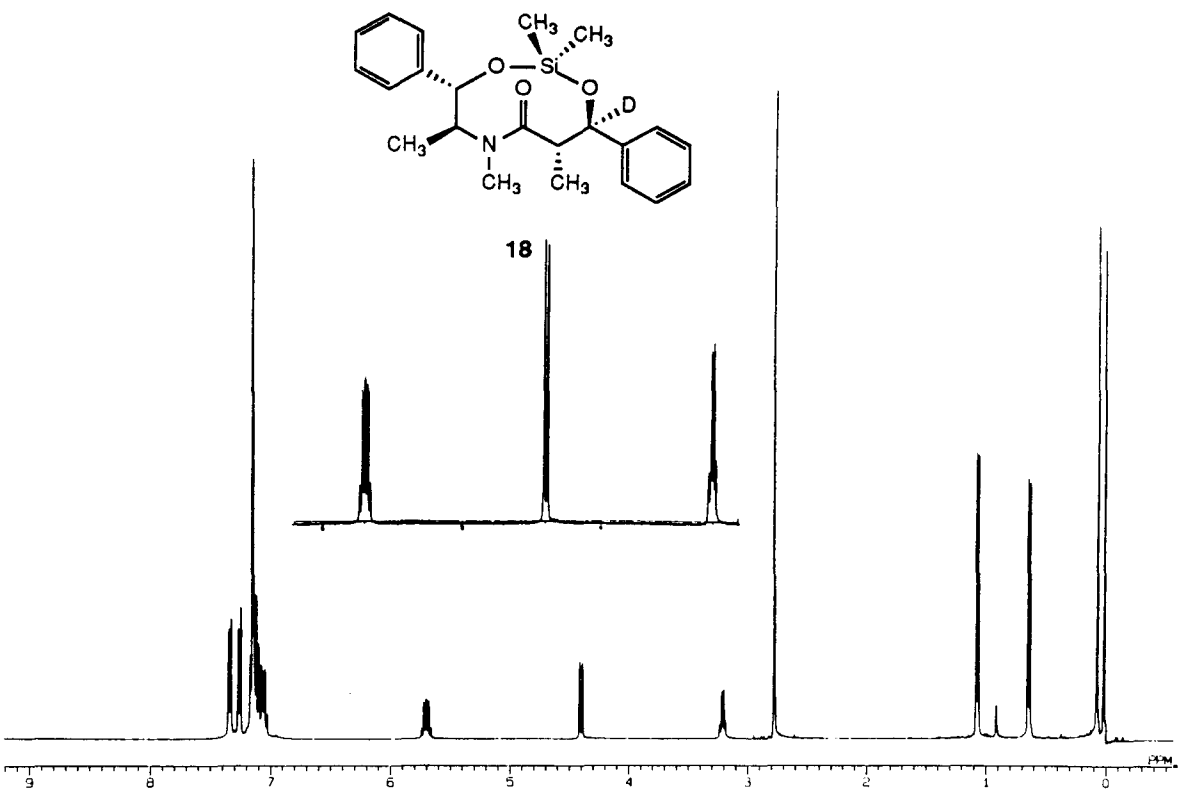

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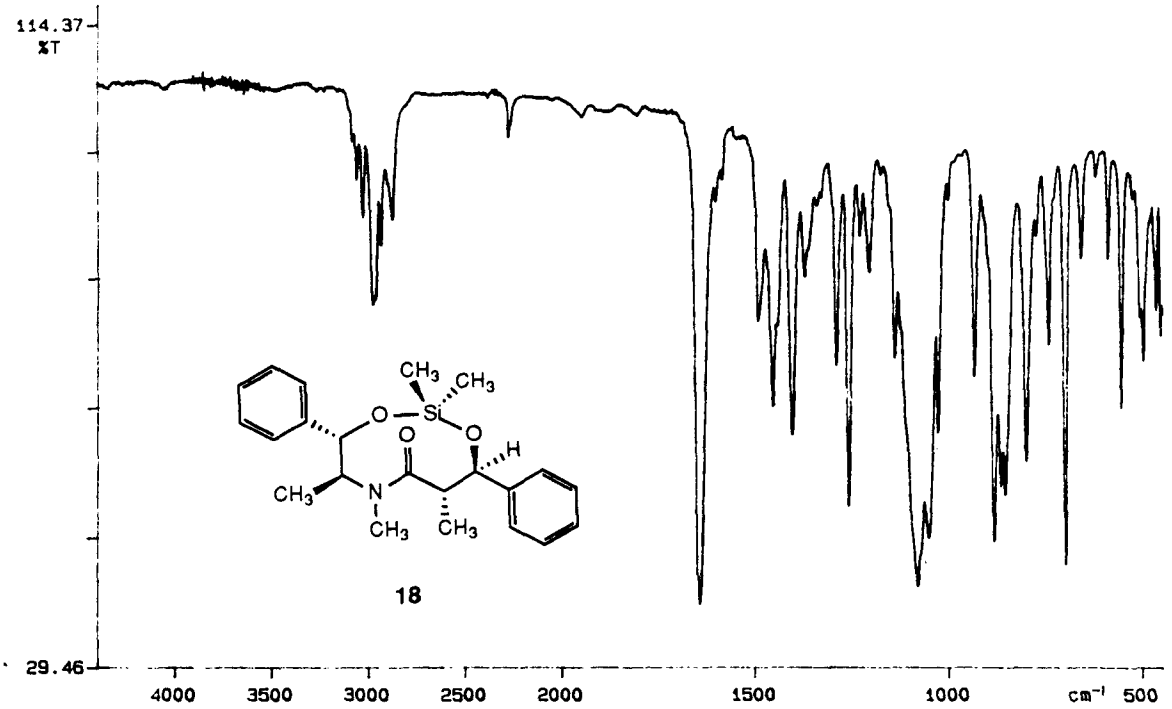
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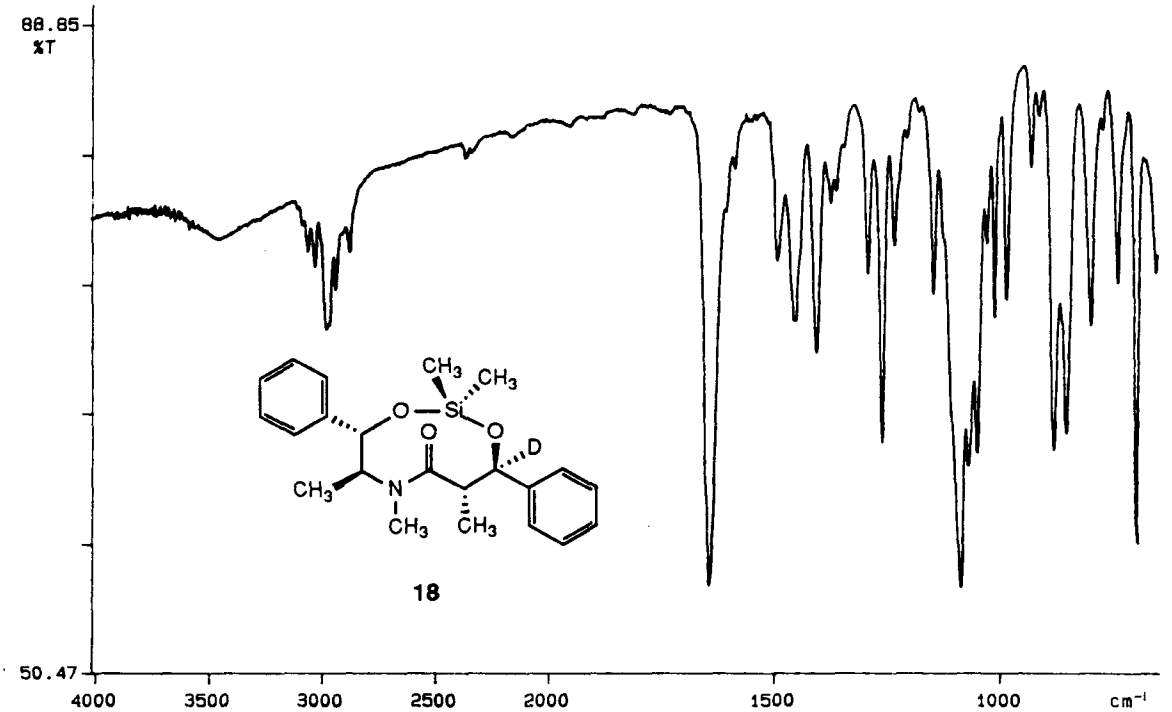
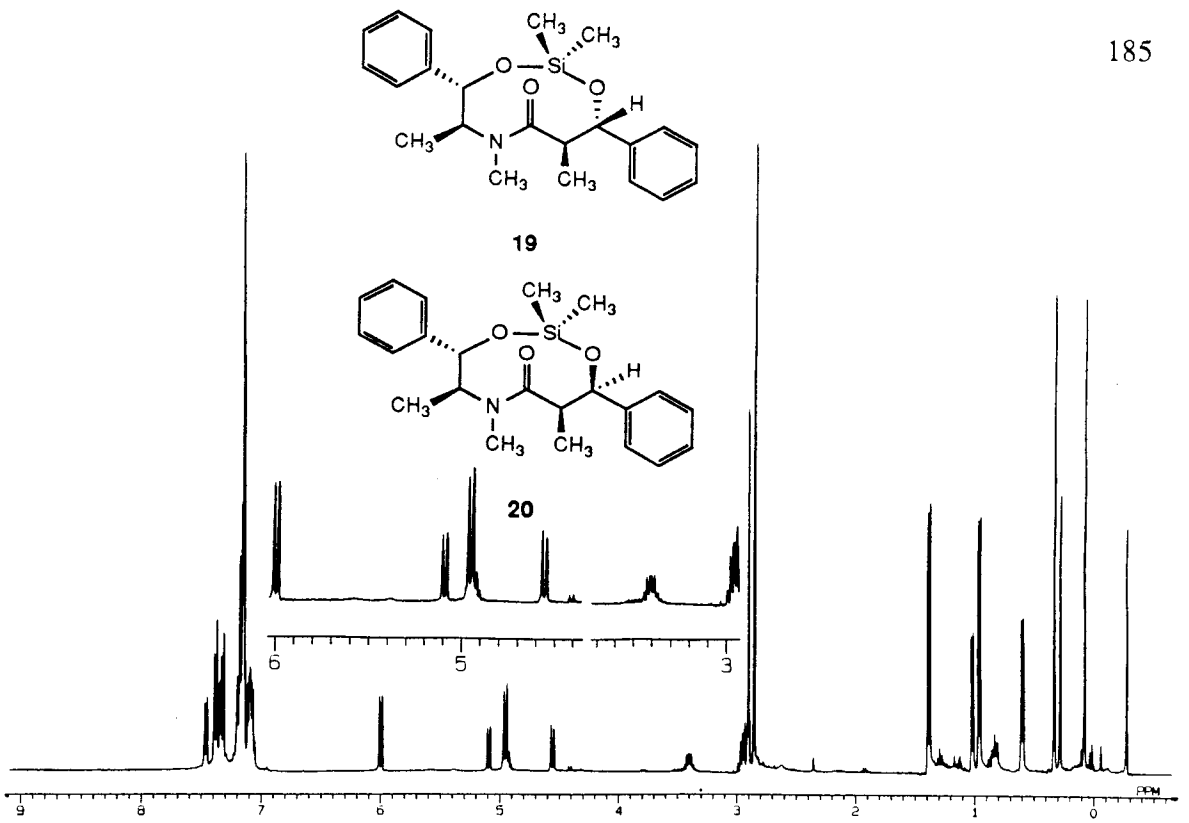
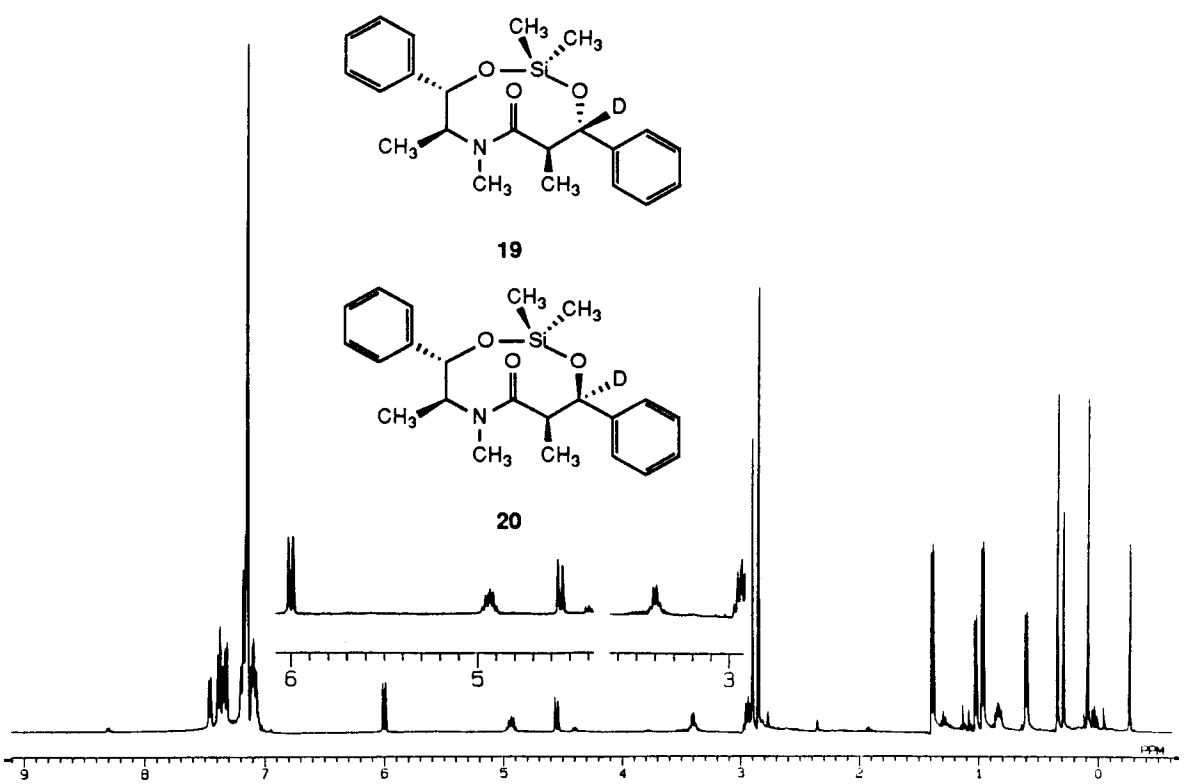
CH3

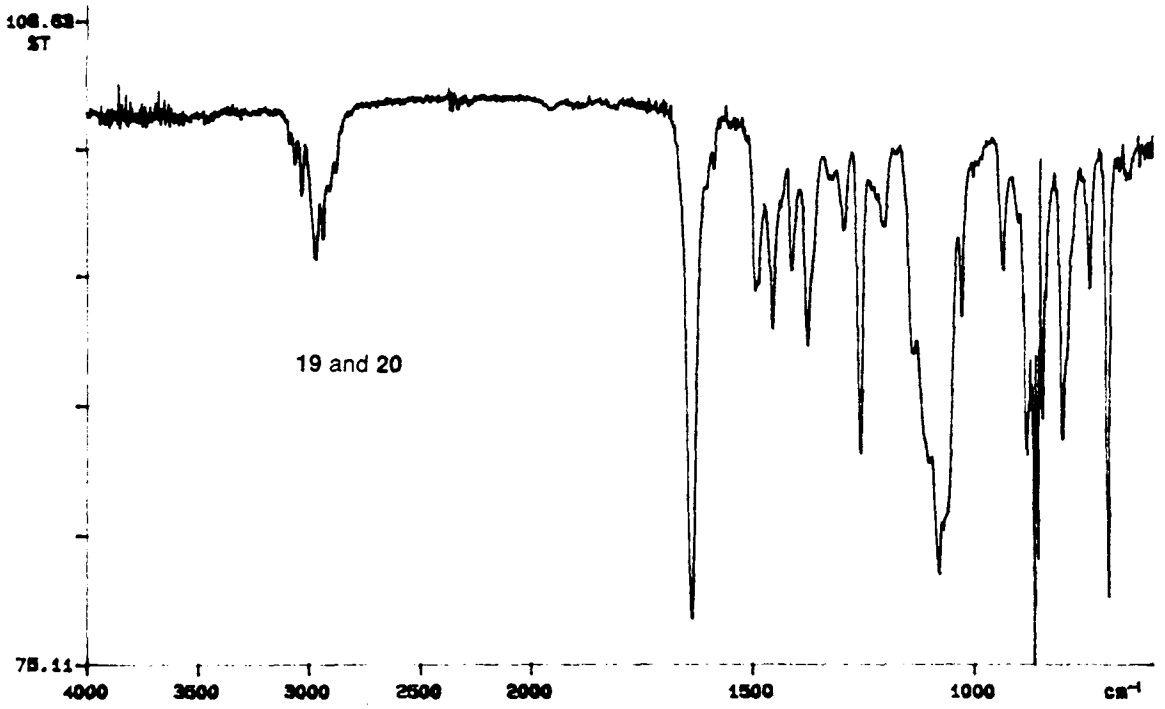
18

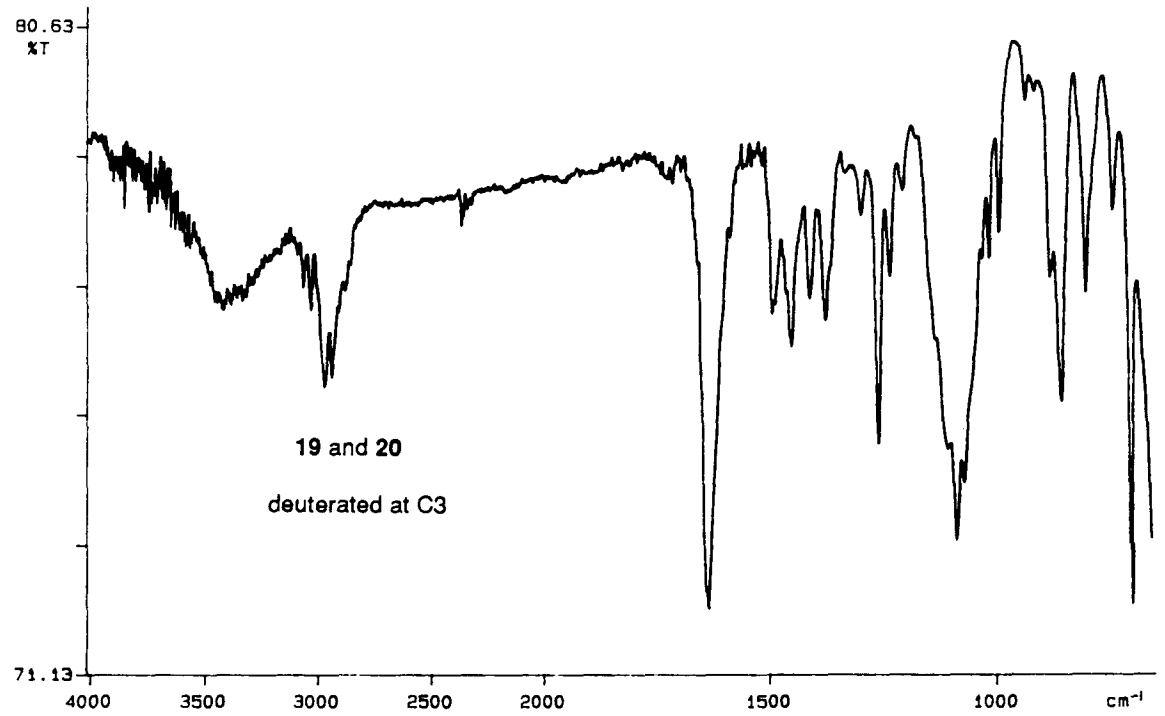

88.85
%T
50.47
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
CH3
CH3
Si
O
O
O
D
CH3
N
CH3
CH3

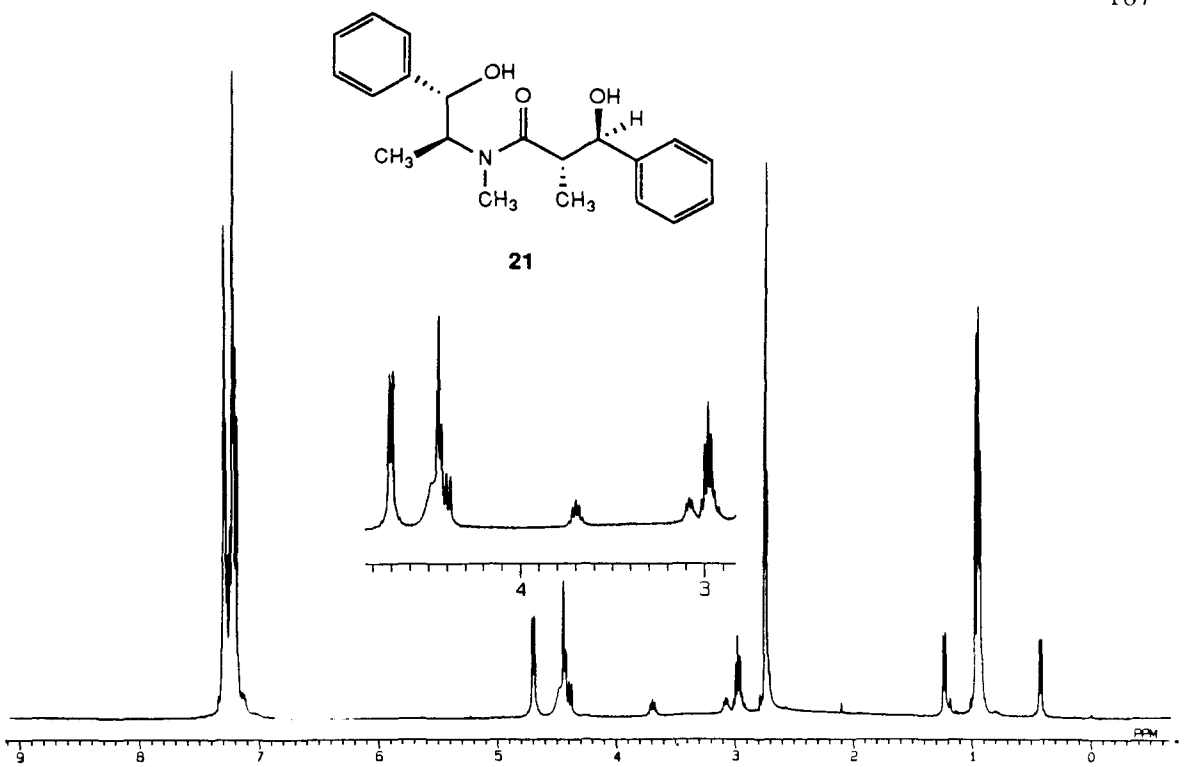
18

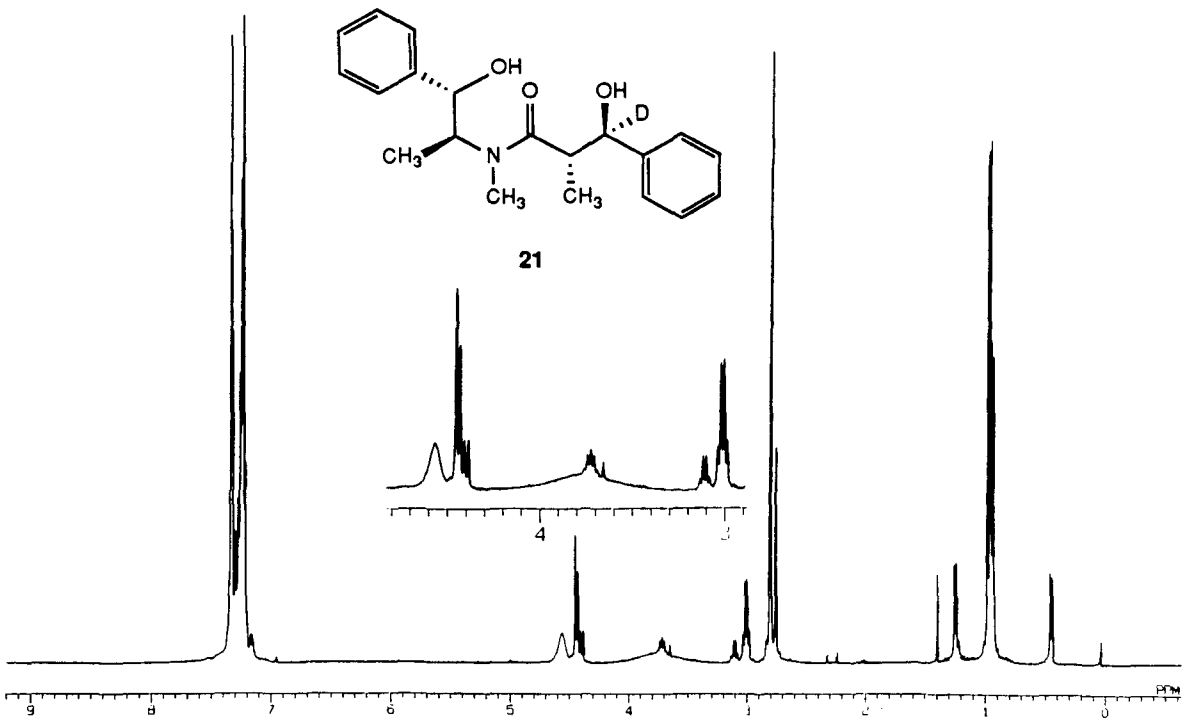

19
20
6
5
3
PPM

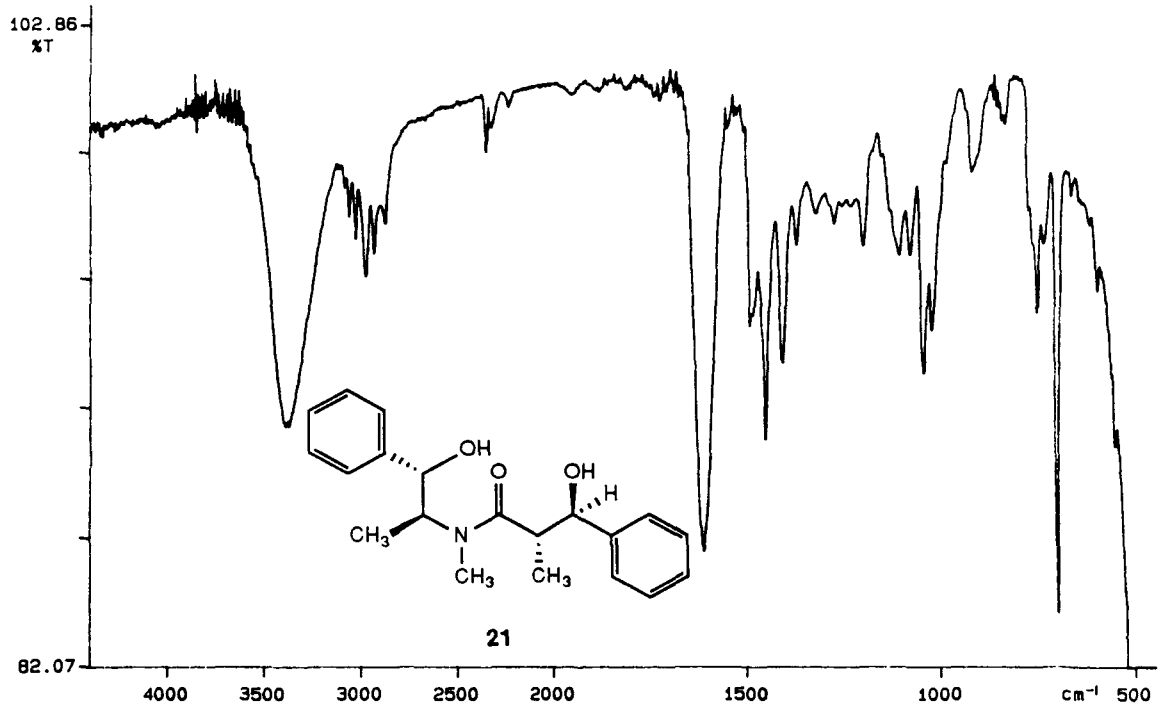

19
20
6
5
3
PPM

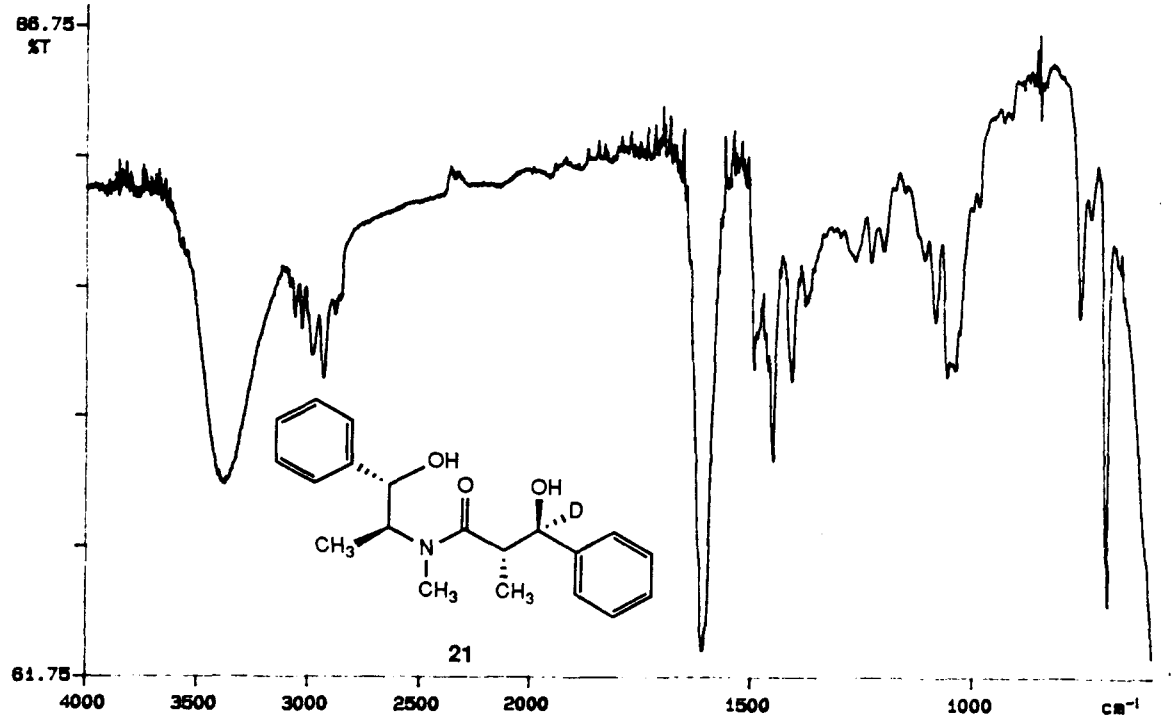

%T
19 and 20
75.11
4000
3500
3000
2500
2000
1500
1000
cm-1

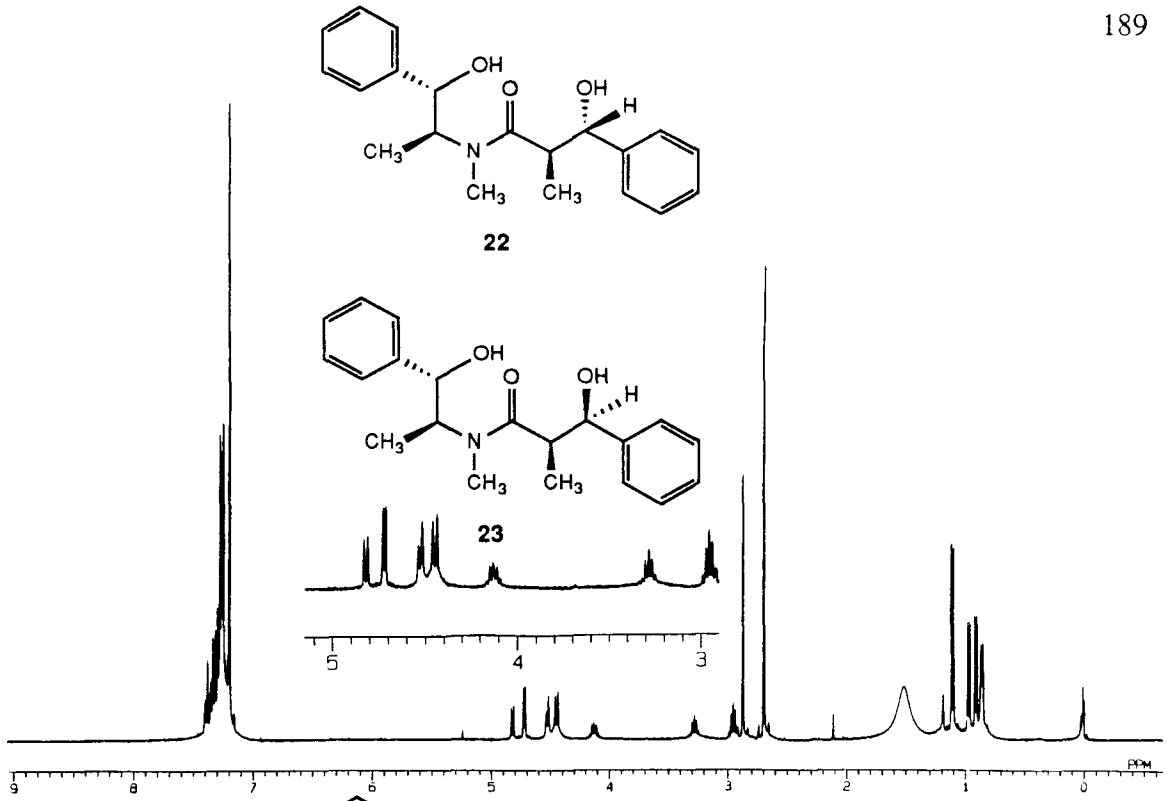

80.63
%T
19 and 20
deuterated at C3
71.13
4000
3500
3000
2500
2000
1500
1000
cm-1

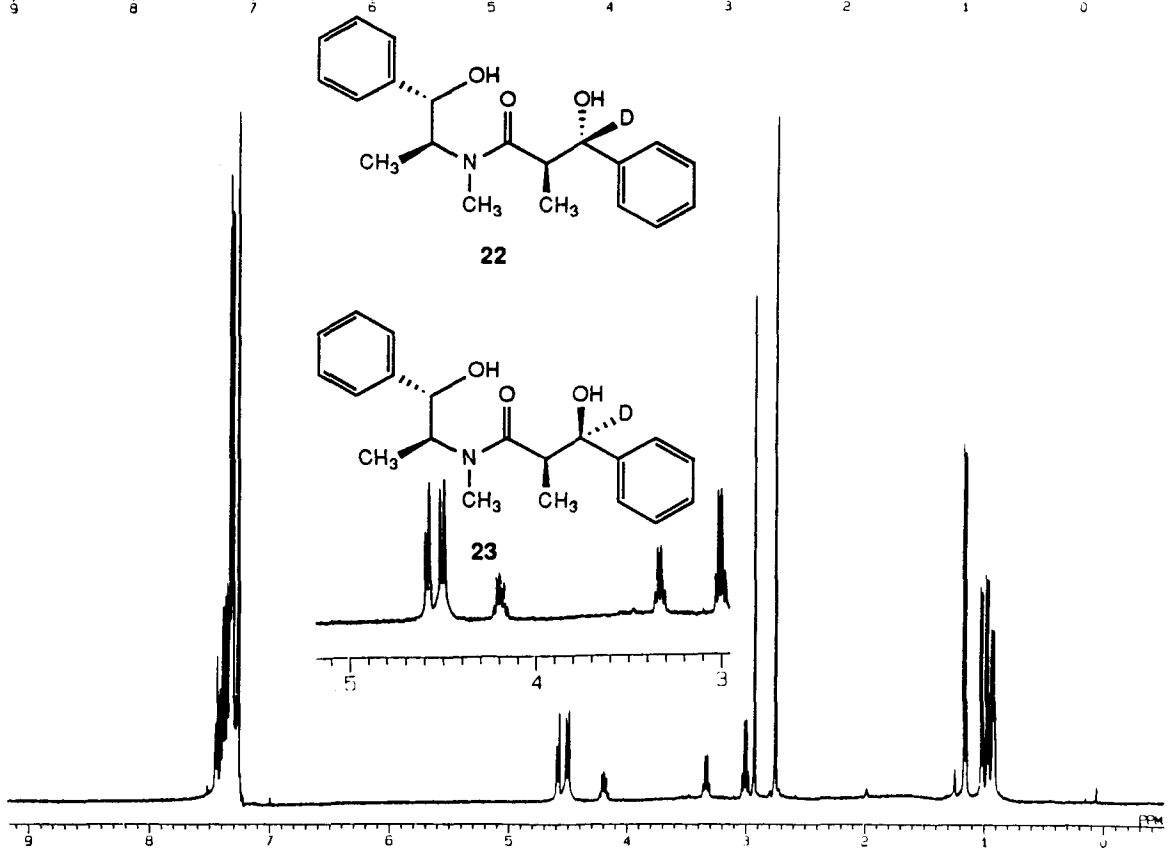

OH
O
OH
H
CH3
N
CH3
CH3
CH3
21
4
3
9
8
7
6
5
4
3
2
1
0
PPM

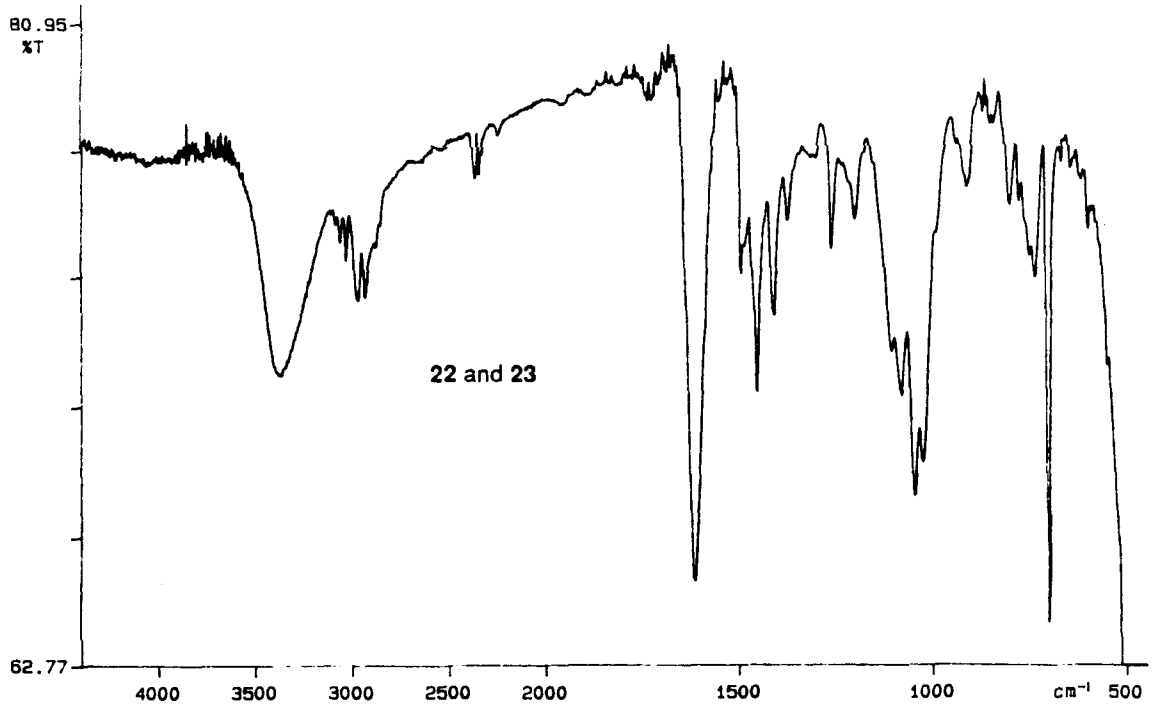

OH
O
OH
D
CH3
N
CH3
CH3
CH3
21
4
9
8
7
6
5
4
1
0
PPM

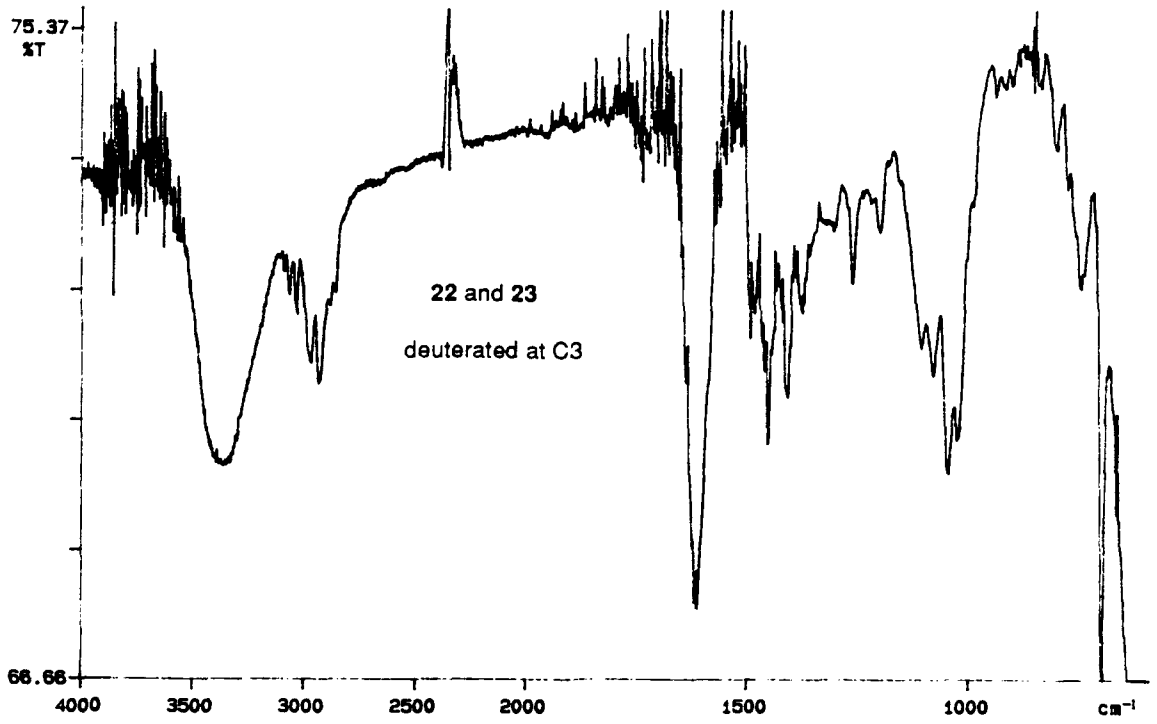

102.86
%T
82.07
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500
OH
O
OH
H
CH3
N
CH3
CH3
21

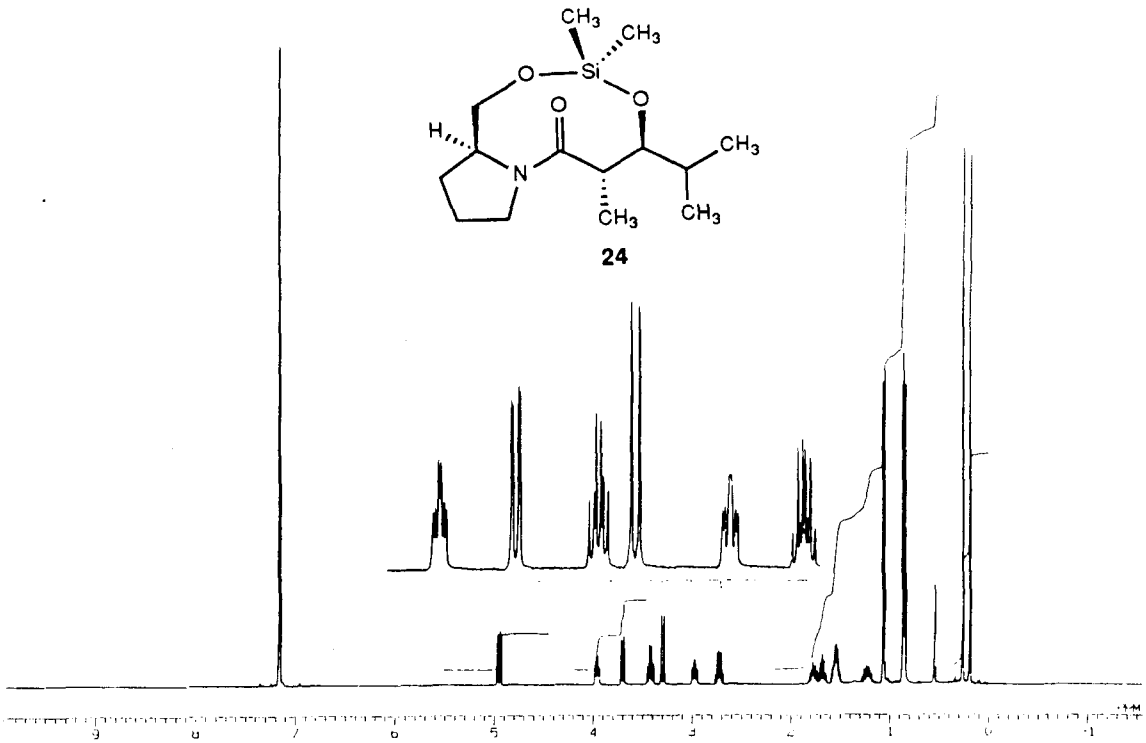

86.75
%T
61.75
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
OH
O
OH
D
CH3
N
CH3
CH3
21


OH
O
OH
H
CH3
N
CH3
CH3
CH3
22
OH
O
OH
H
CH3
N
CH3
CH3
CH3
23
5
4
3
9
8
7
6
5
4
3
2
1
0
PPM

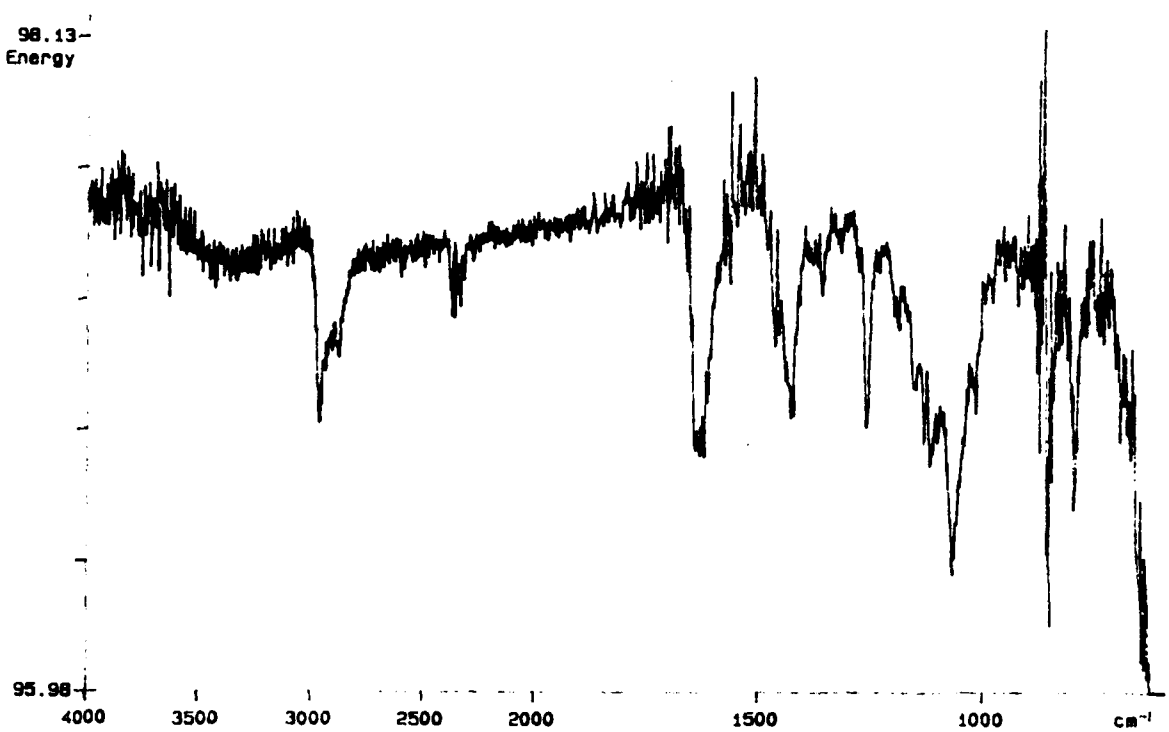

OH
O
OH
D
CH3
N
CH3
CH3
CH3
22
OH
O
OH
D
CH3
N
CH3
CH3
CH3
23
5
4
3
9
8
7
6
5
4
3
2
1
0
PPM

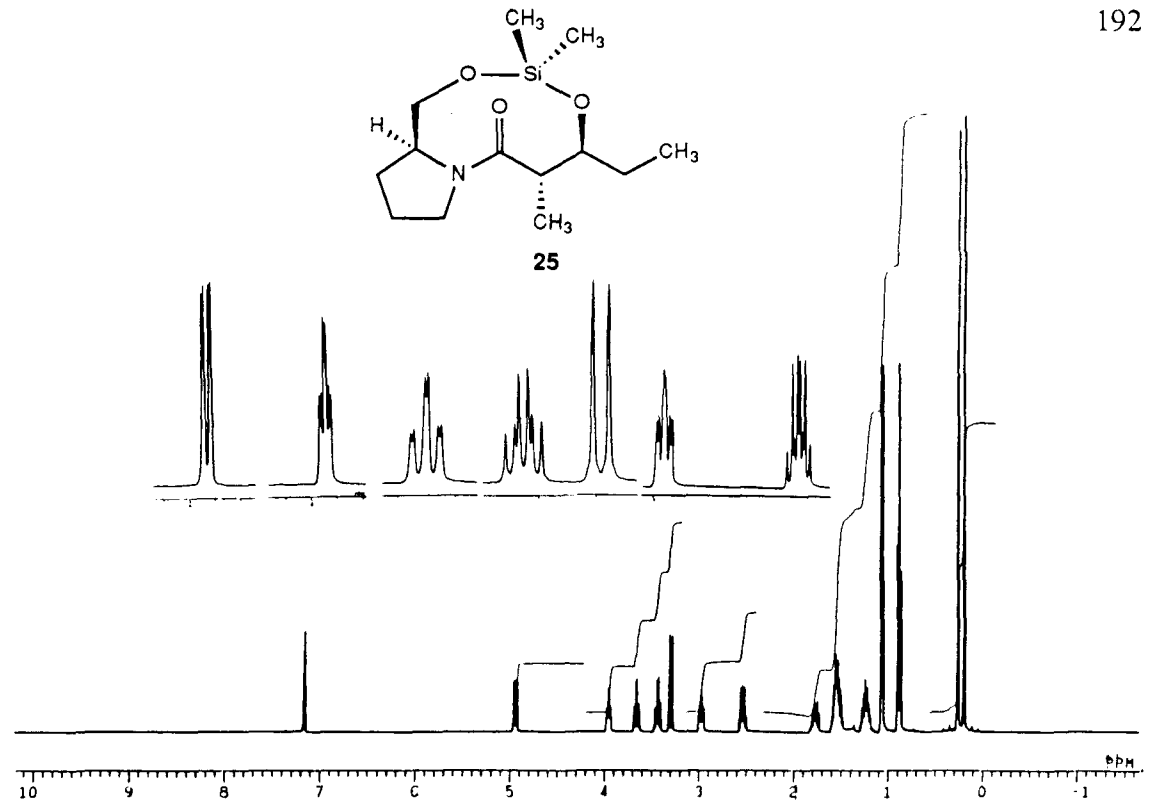

80.95
%T
62.77
22 and 23
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500


75.37
%T
66.66
22 and 23
deuterated at C3
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

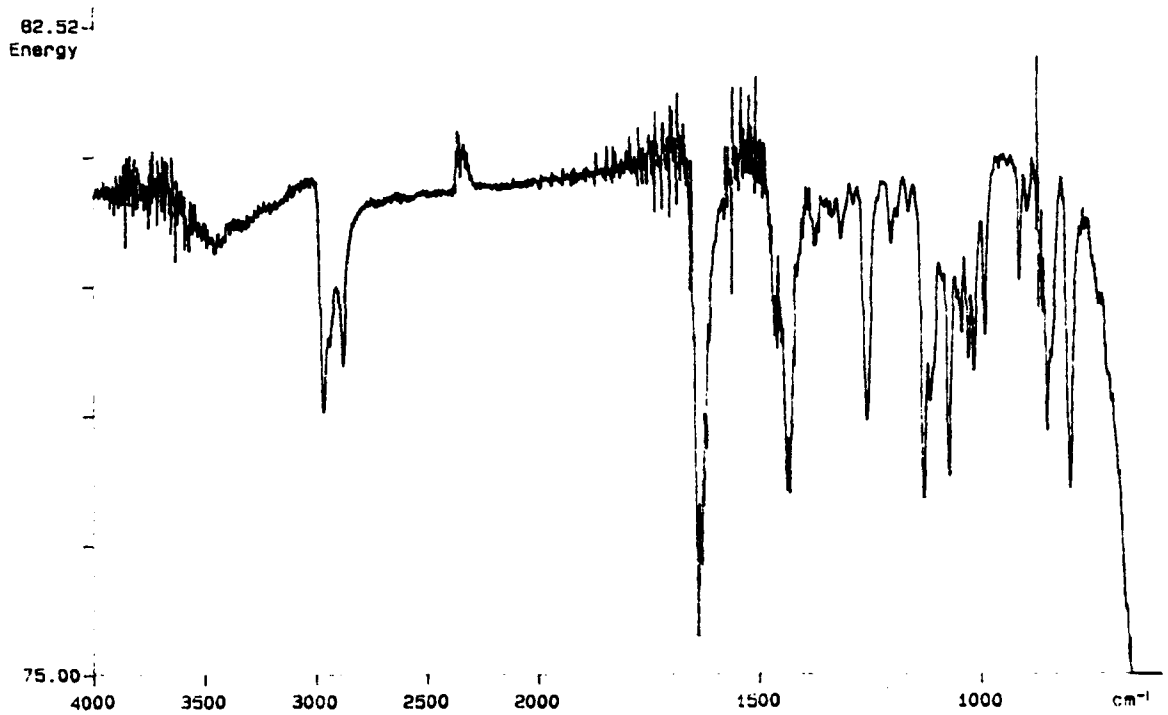

CH3
CH3
Si
O
O
O
H
N
CH3
CH3
CH3

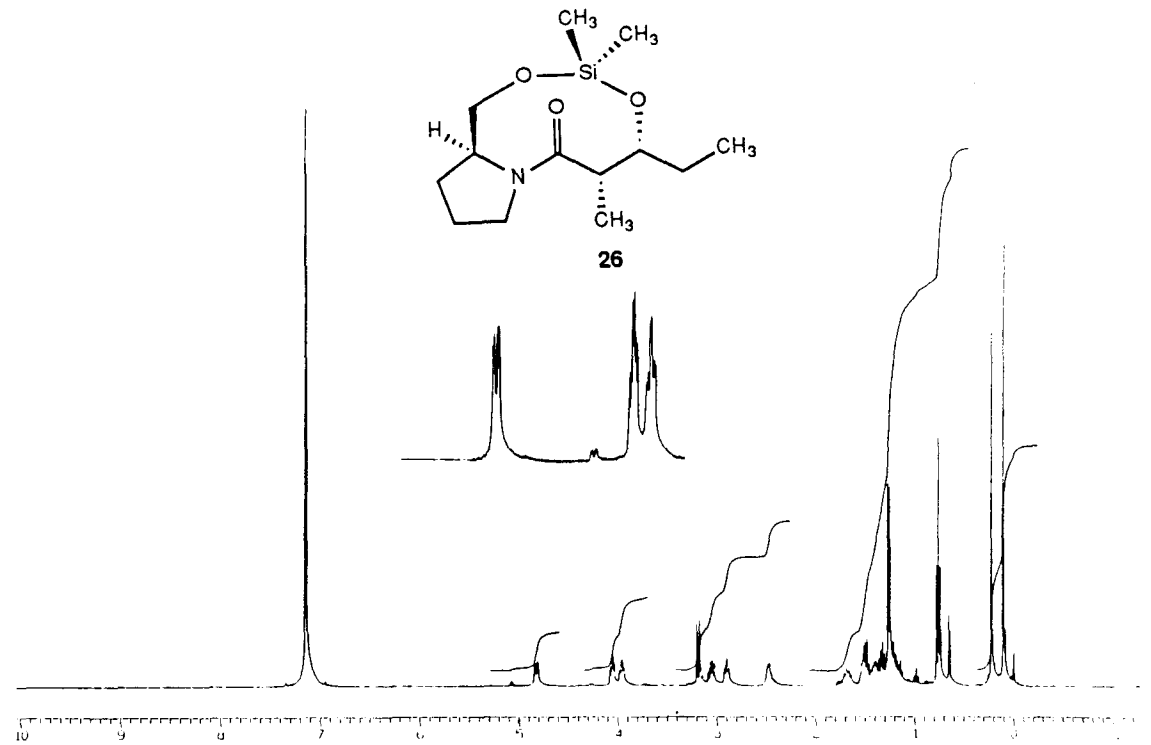
24


98.13
Energy
95.98
4000
3500
3000
2500
2000
1500
1000
cm-1

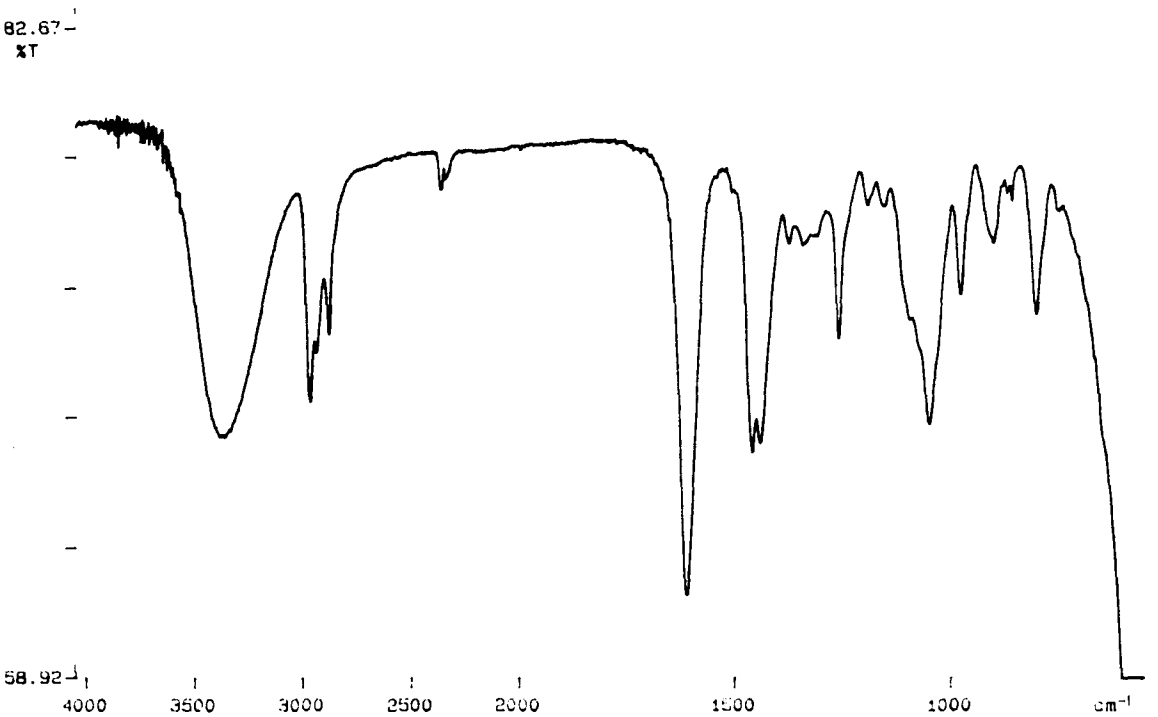

CH3
CH3
Si
O
O
O
H
N
CH3
CH3
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

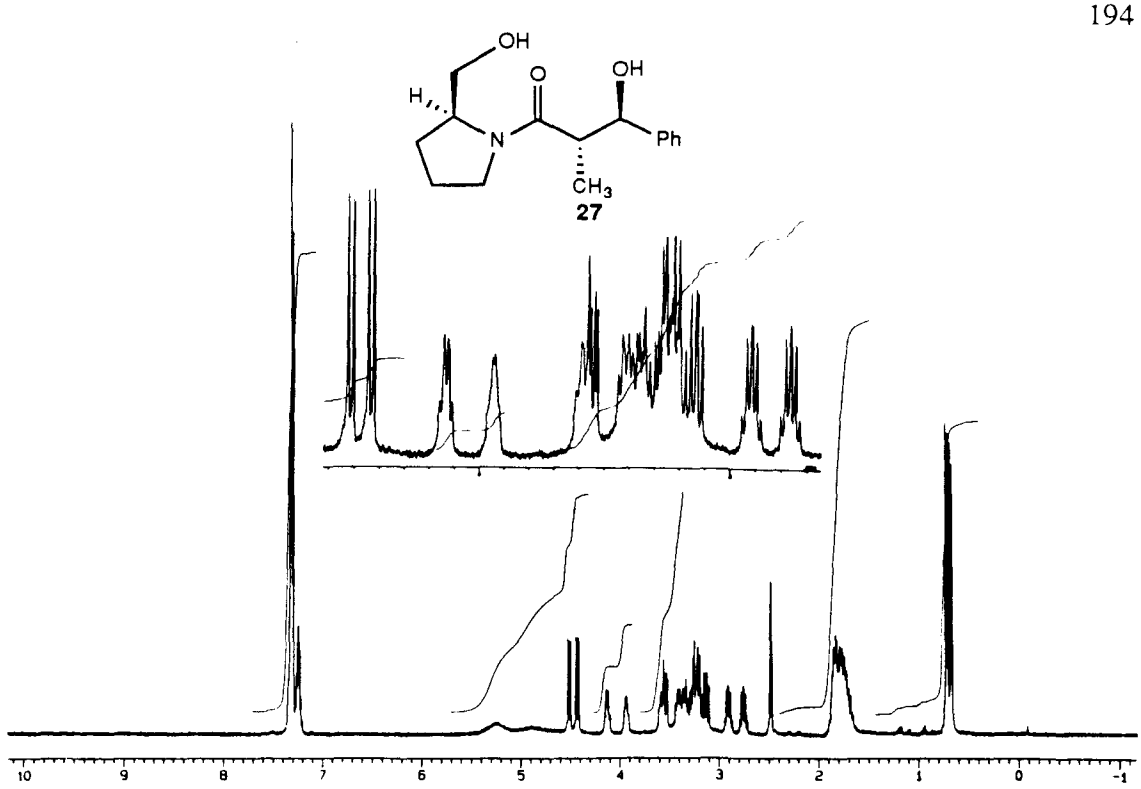
25

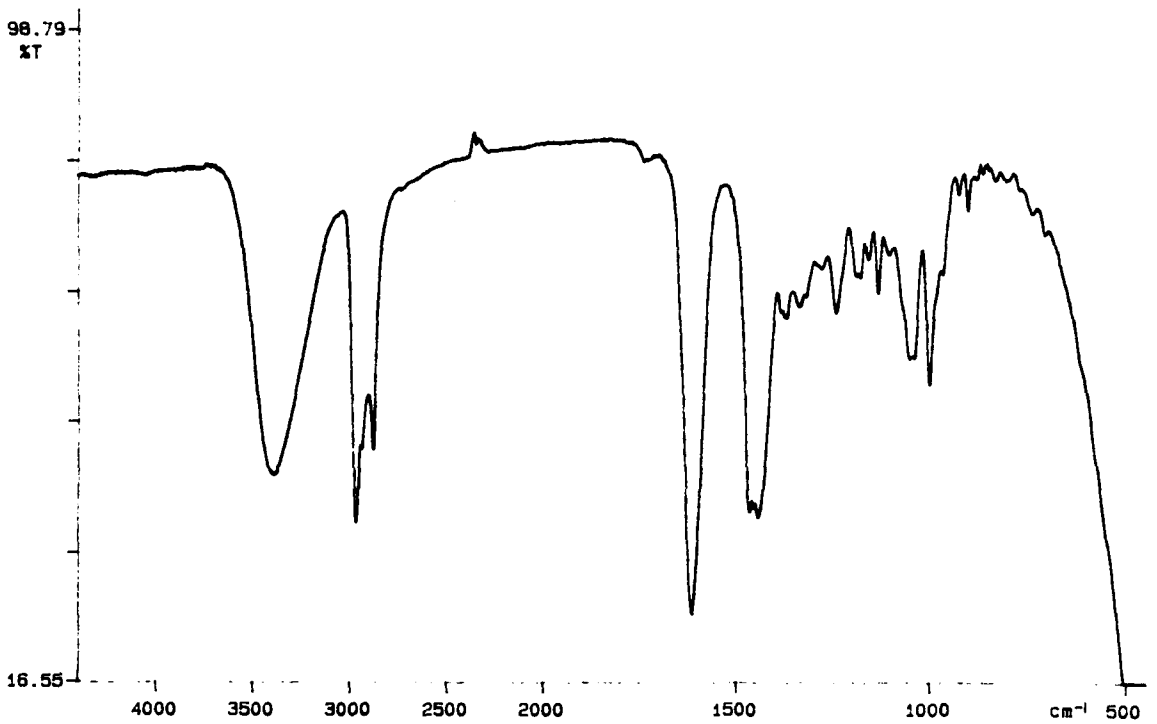

82.52
Energy
75.00
4000
3500
3000
2500
2000
1500
1000
cm-1

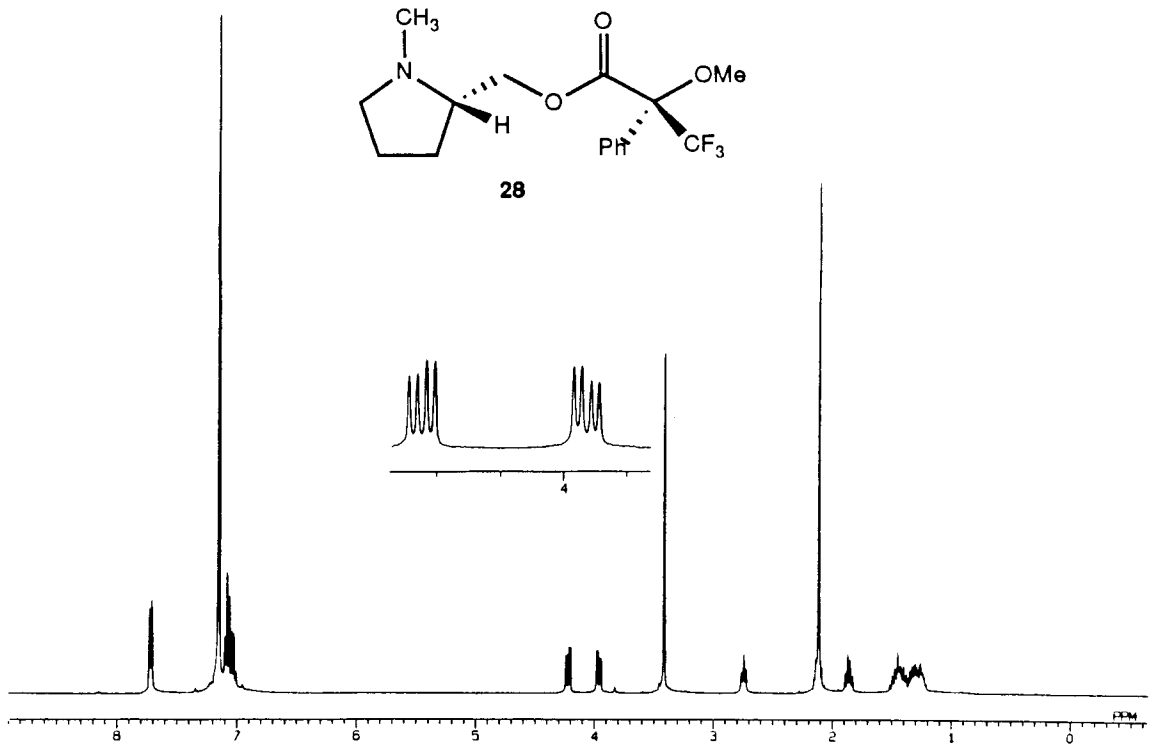

CH3
CH3
Si
O
O
O
H
N
O
CH3
CH3

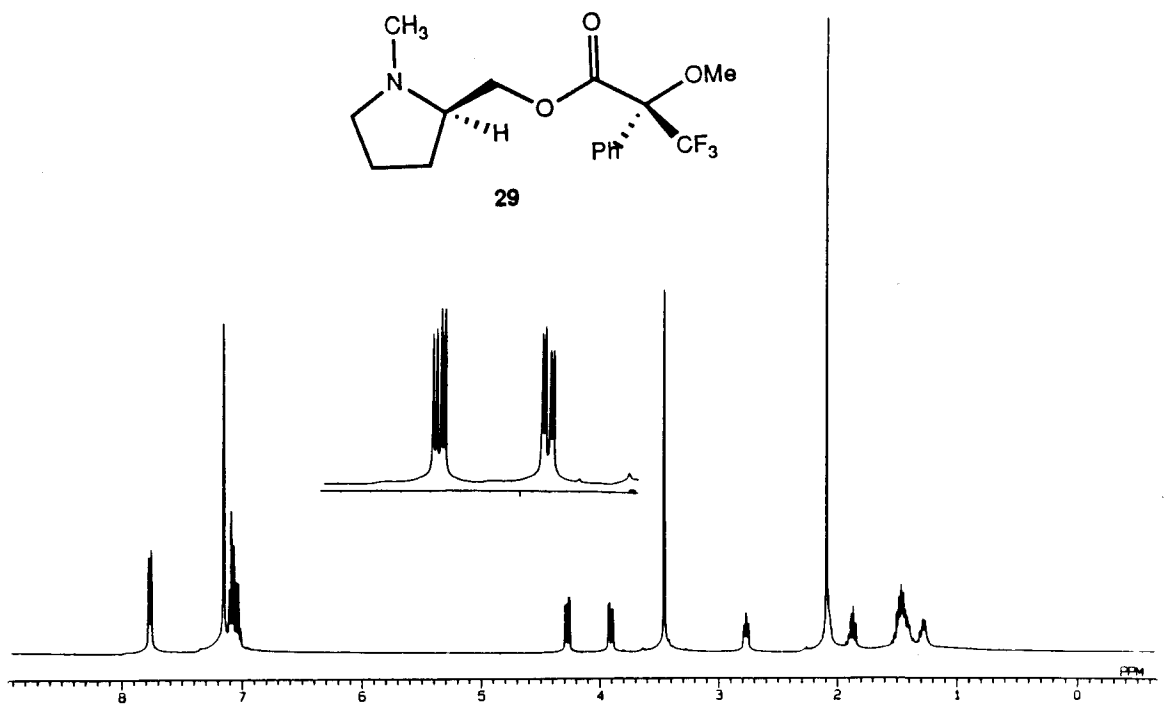
26

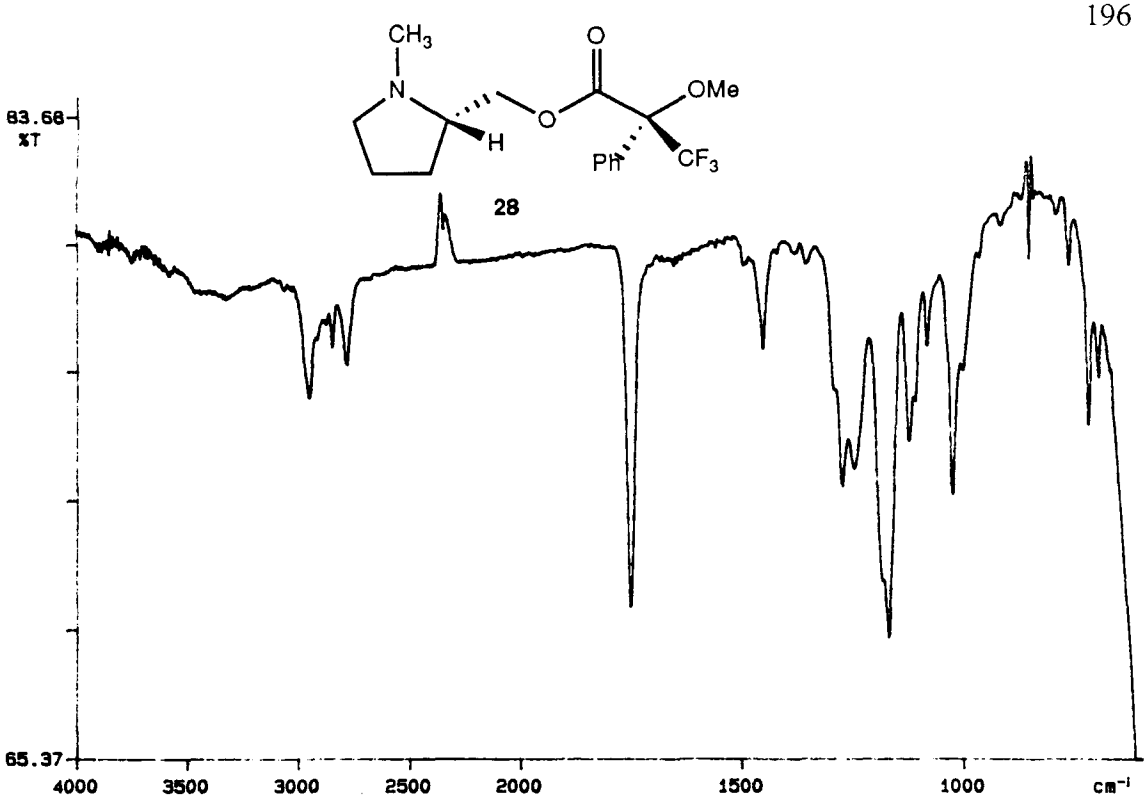

82.67
%T
58.92
4000
3500
3000
2500
2000
1500
1000
cm-1

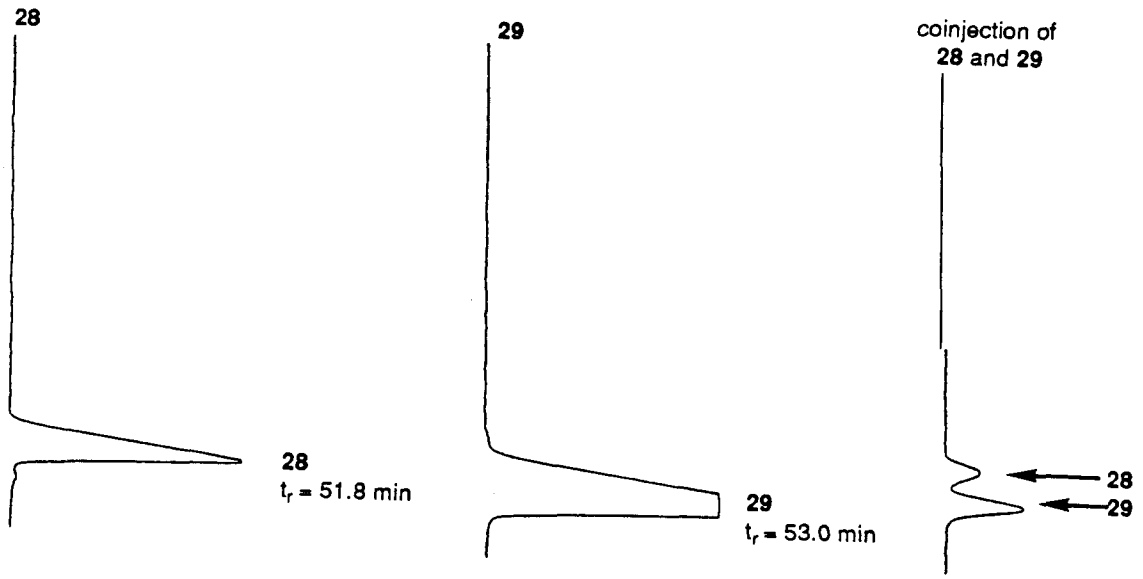

OH
O
OH
H
N
Ph
CH3
27
10
9
8
7
6
5
4
3
2
1
0
-1

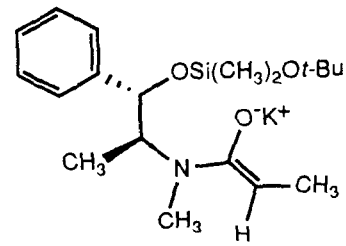

98.79
%T
16.55
4000
3500
3000
2500
2000
1500
1000
cm-1
500


CH3
N
O
OMe
H
O
Ph
CF3
28
4
8
7
6
5
4
3
2
1
0
PPM

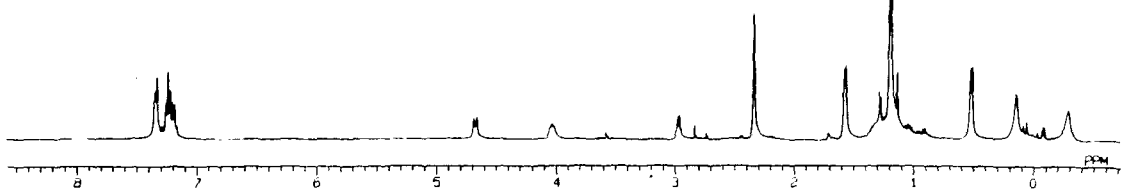

CH3
N
O
OMe
H
O
Ph
CF3
29
8
7
6
5
4
3
2
1
0
PPM

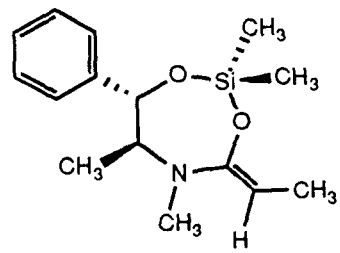

CH3
N
O
OMe
H
Ph
CF3
28
83.66
%T
65.37
4000
3500
3000
2500
2000
1500
1000
cm-1


28
28
tr = 51.8 min
29
29
tr = 53.0 min
coinjection of
28 and 29
28
29


OSi(CH3)2Ot-Bu
O-K+
CH3
N
CH3
CH3
CH3
H

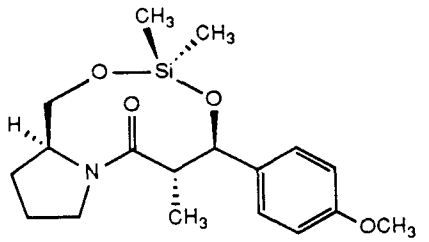
30


8
7
6
5
4
3
2
1
0
PPM

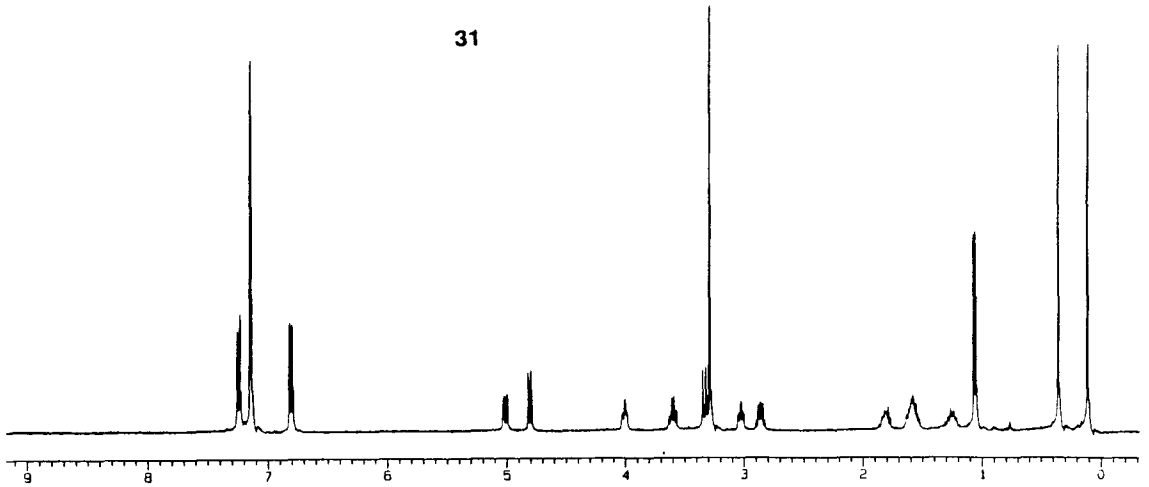

CH3
O
Si
CH3
O
CH3
N
CH3
CH3
H

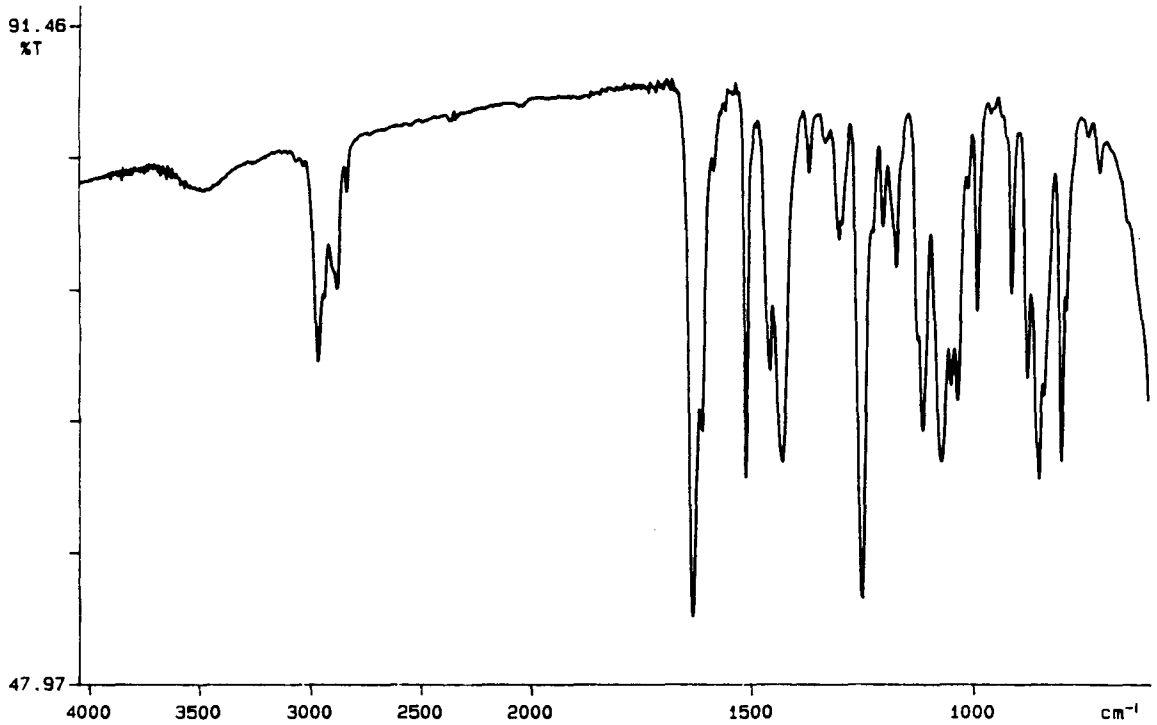
16

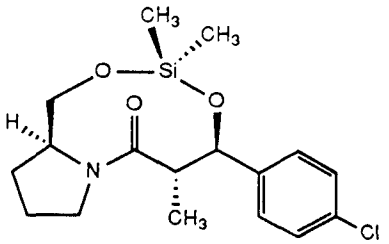
8
7
6
5
4
3
2
1
0


CH3
CH3
Si
O
O
O
H
N
CH3
OCH3

31

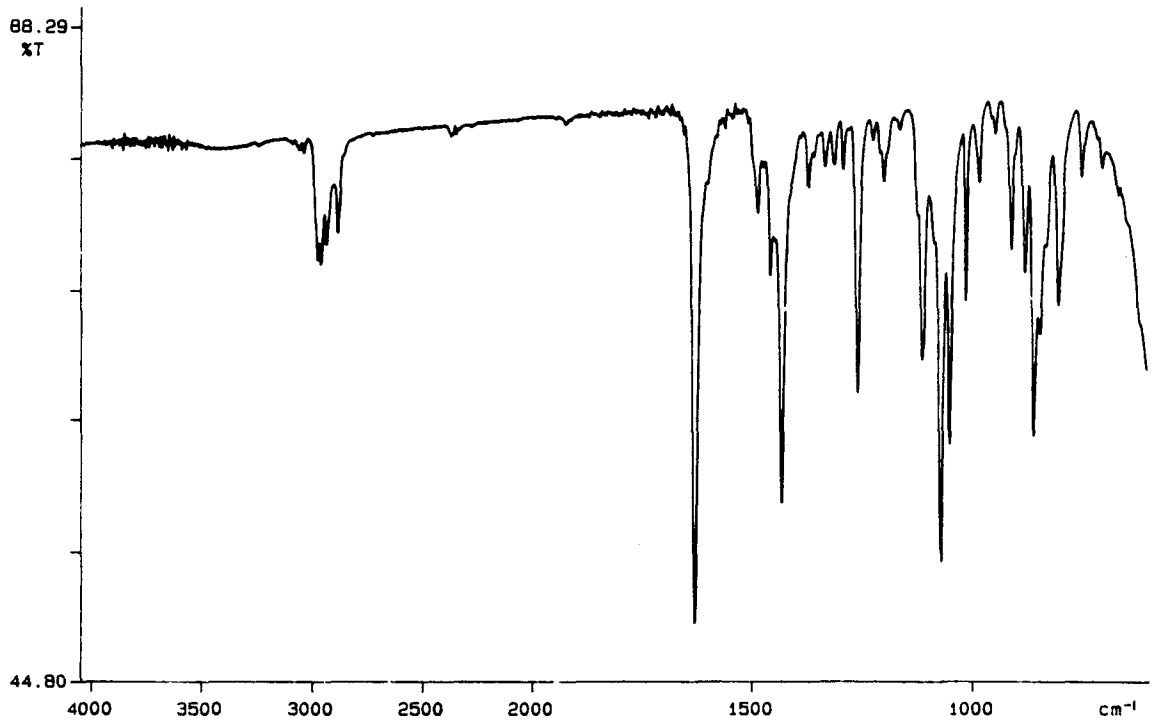

9
8
7
6
5
4
3
2
1
0

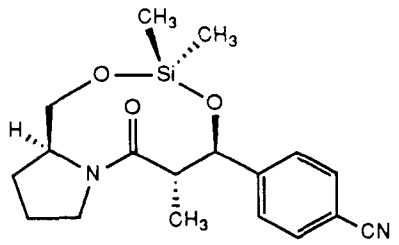

91.46
%T
47.97
4000
3500
3000
2500
2000
1500
1000
cm-1


CH3
CH3
Si
O
O
O
H
N
CH3
Cl

32

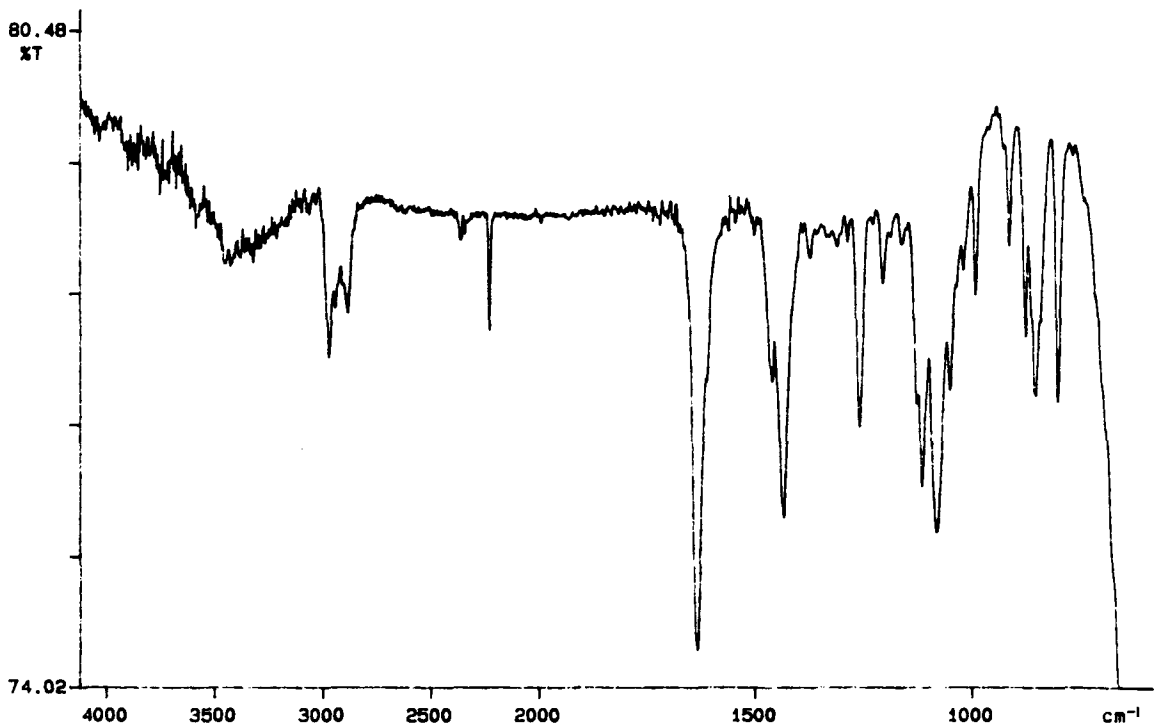
10
9
8
7
6
5
4
3
2
1
0
-1

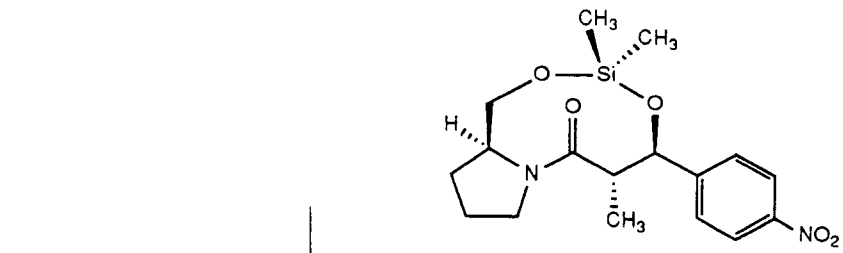

88.29
%T
44.80
4000
3500
3000
2500
2000
1500
1000
cm-1


CH3
CH3
Si
O
O
O
H
N
CH3
CN

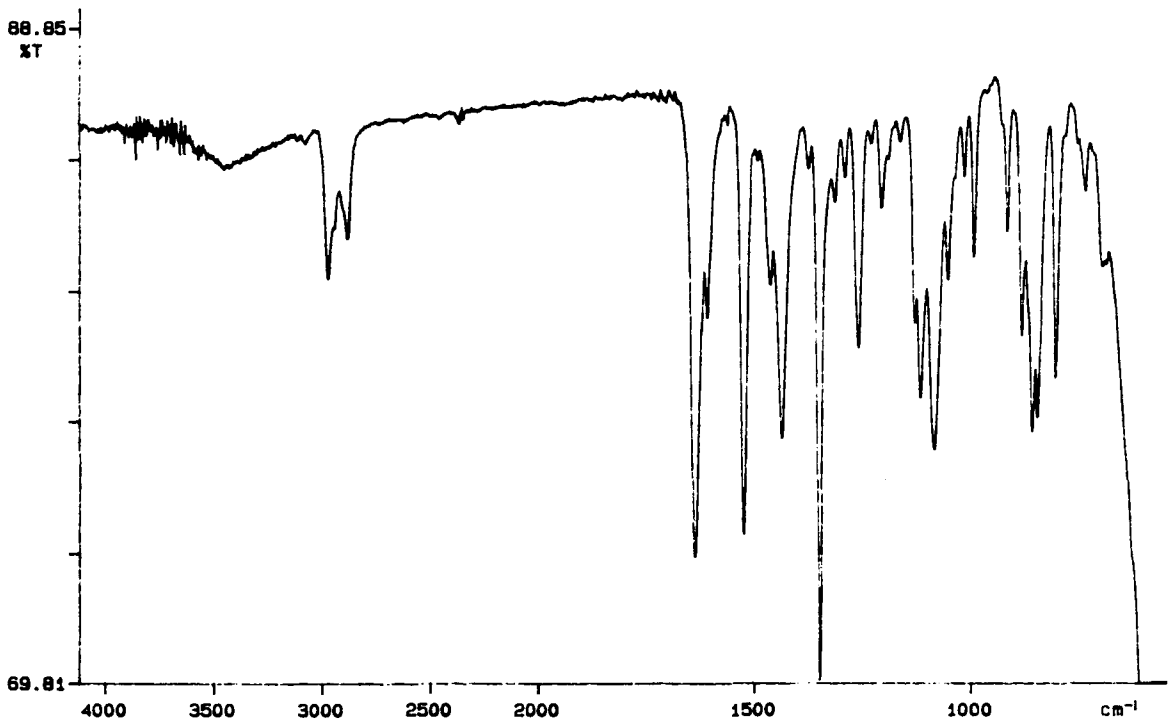
33

PPM


80.48
%T
74.02
4000
3500
3000
2500
2000
1500
1000
cm-1

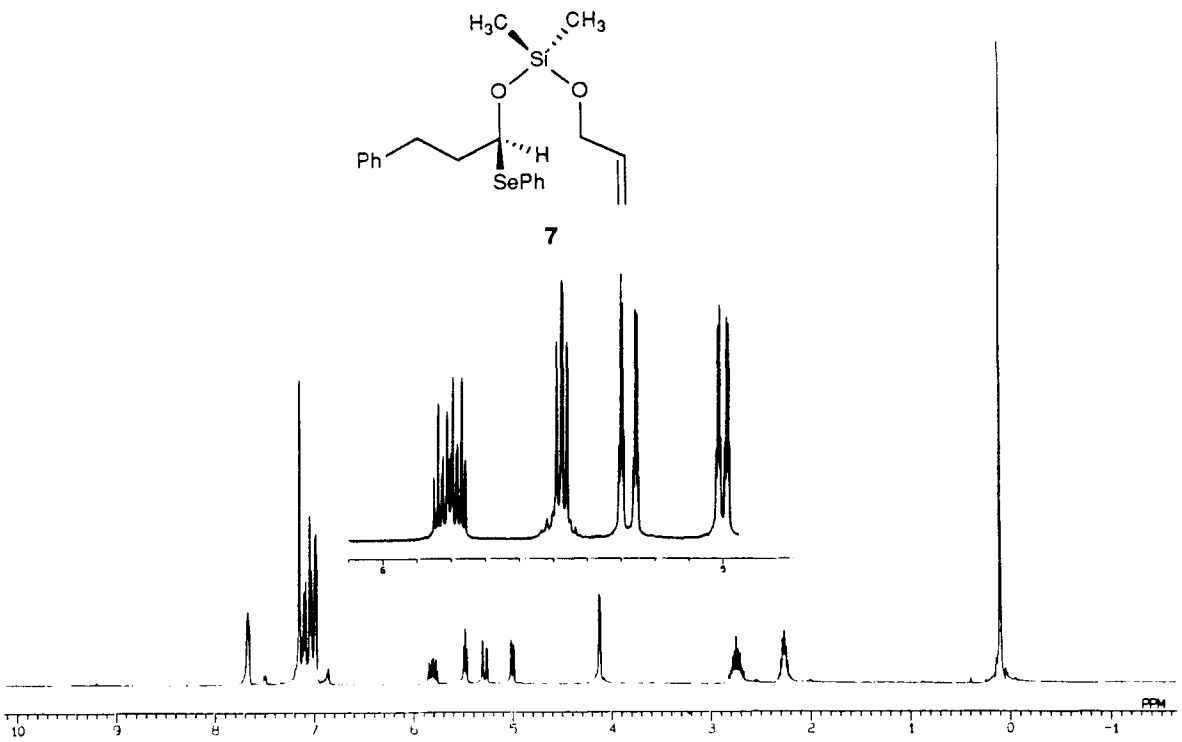

CH3
CH3
O
Si
O
O
H
N
CH3
NO2

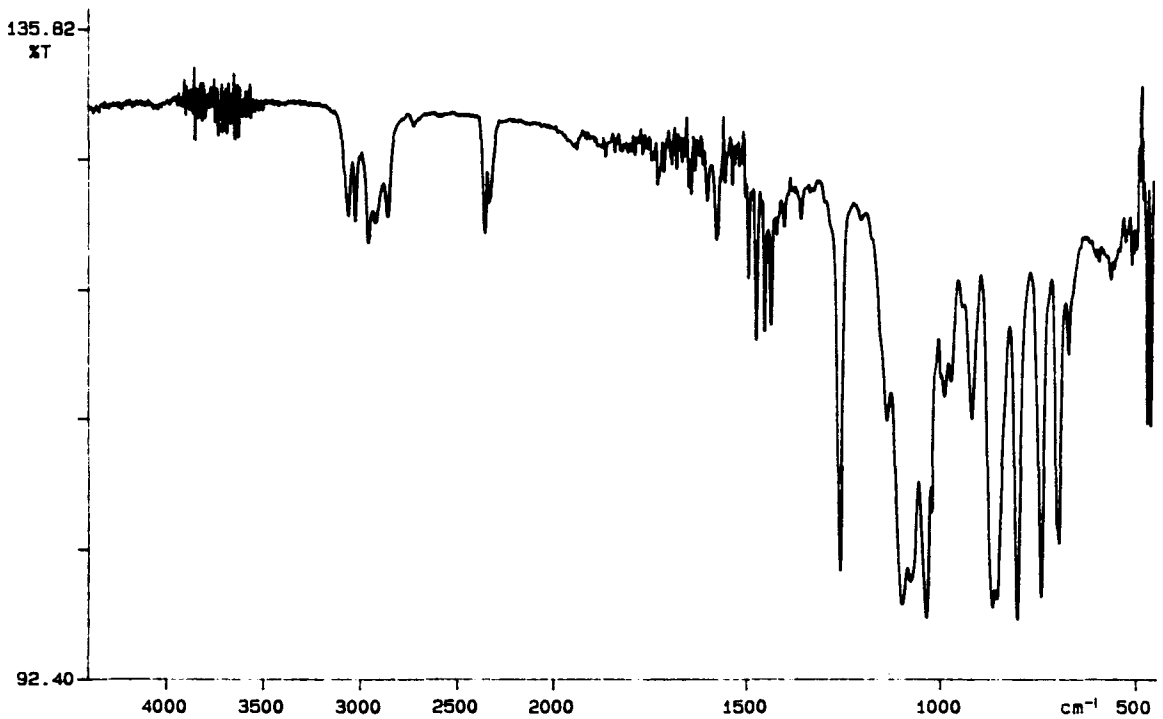
34

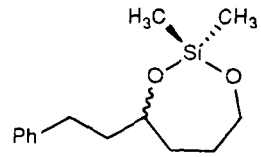

88.85
%T
69.81
4000
3500
3000
2500
2000
1500
1000
cm-1

Appendix II

Spectral Catalog for Chapter Two

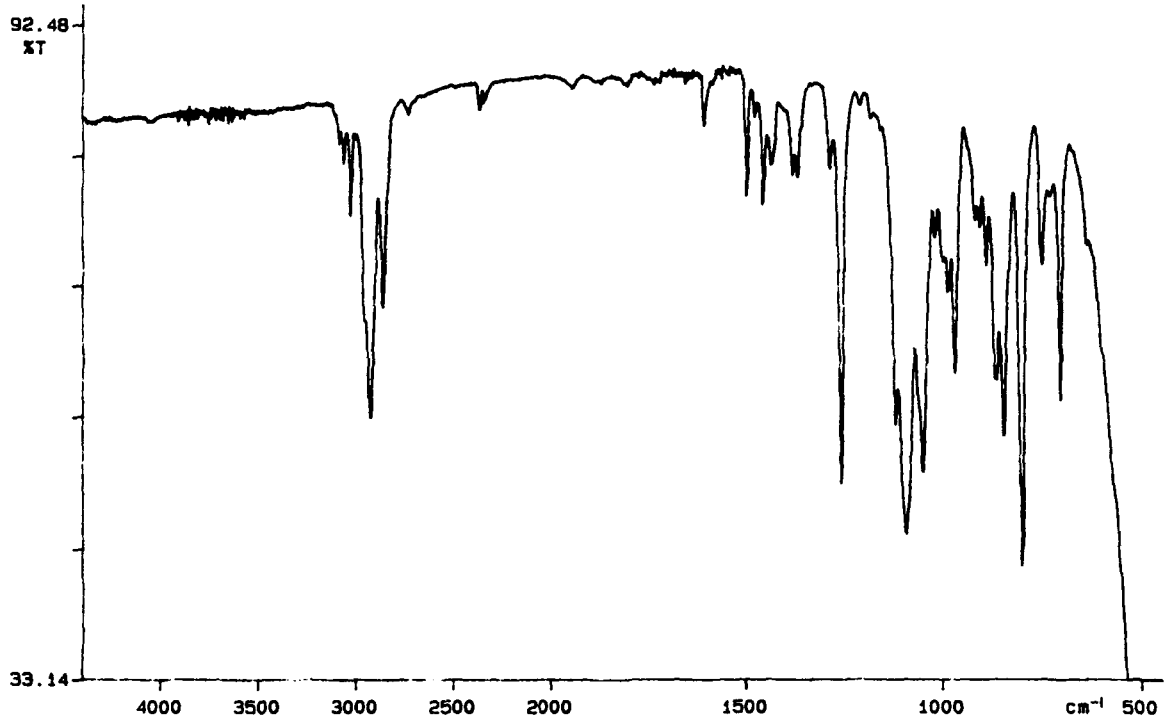

H3C
CH3
Si
O
O
Ph
H
SePh
7
PPM
10
9
8
7
6
5
4
3
2
1
0
-1

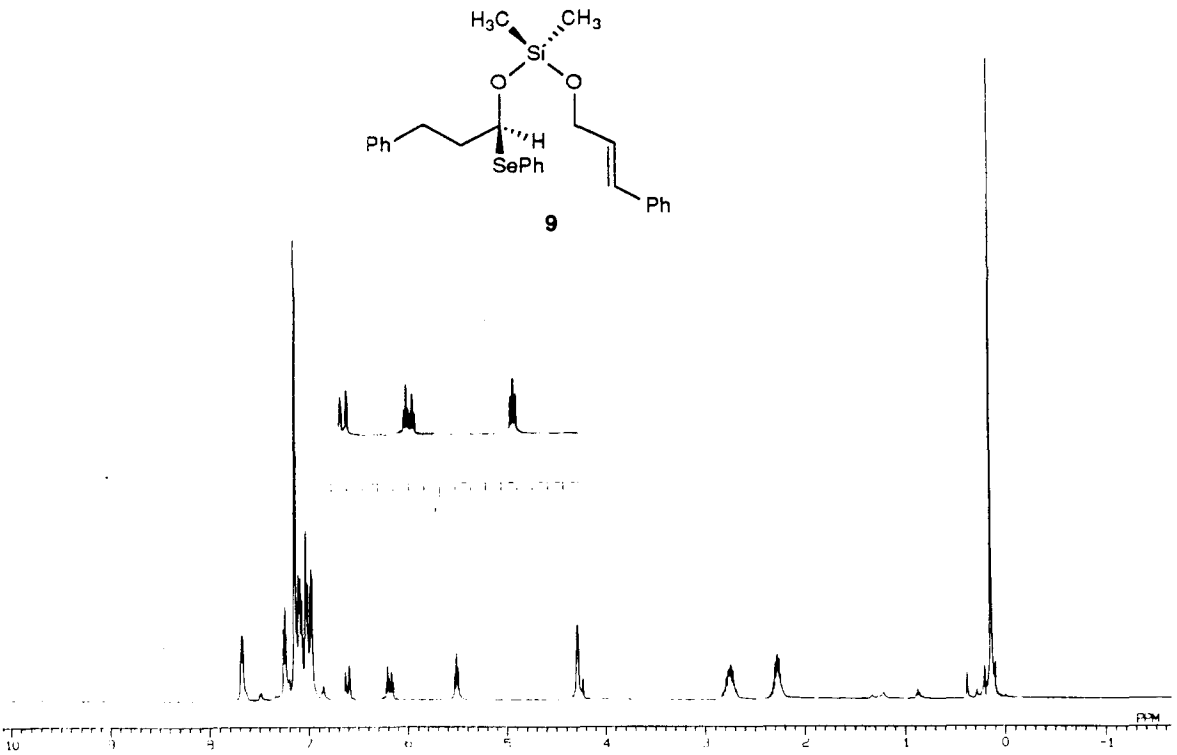

135.82
%T
92.40
4000
3500
3000
2500
2000
1500
1000
cm-1
500

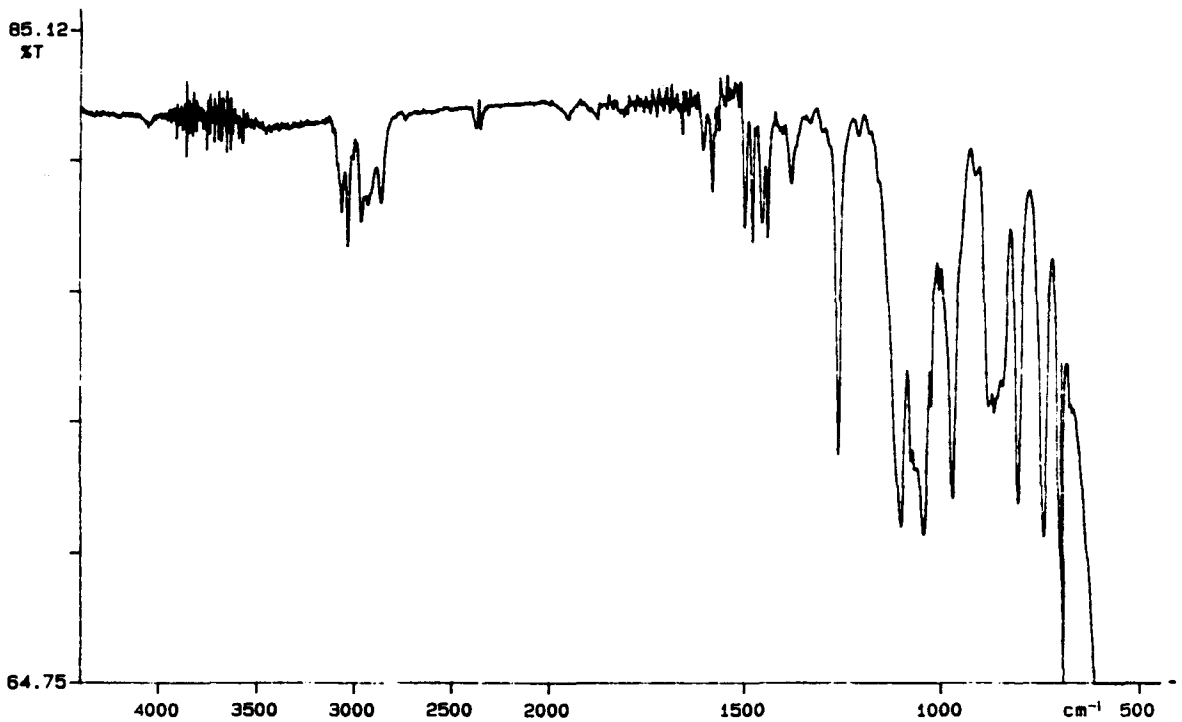

H3C
CH3
Si
O
O
Ph

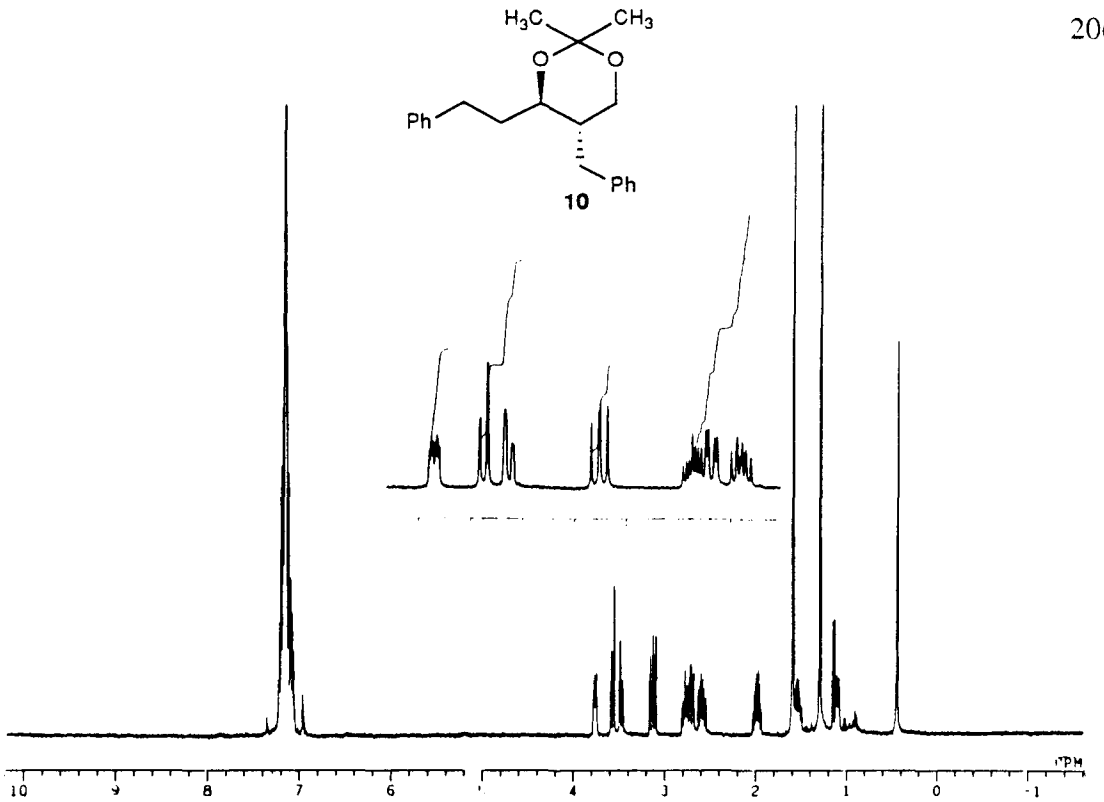
8

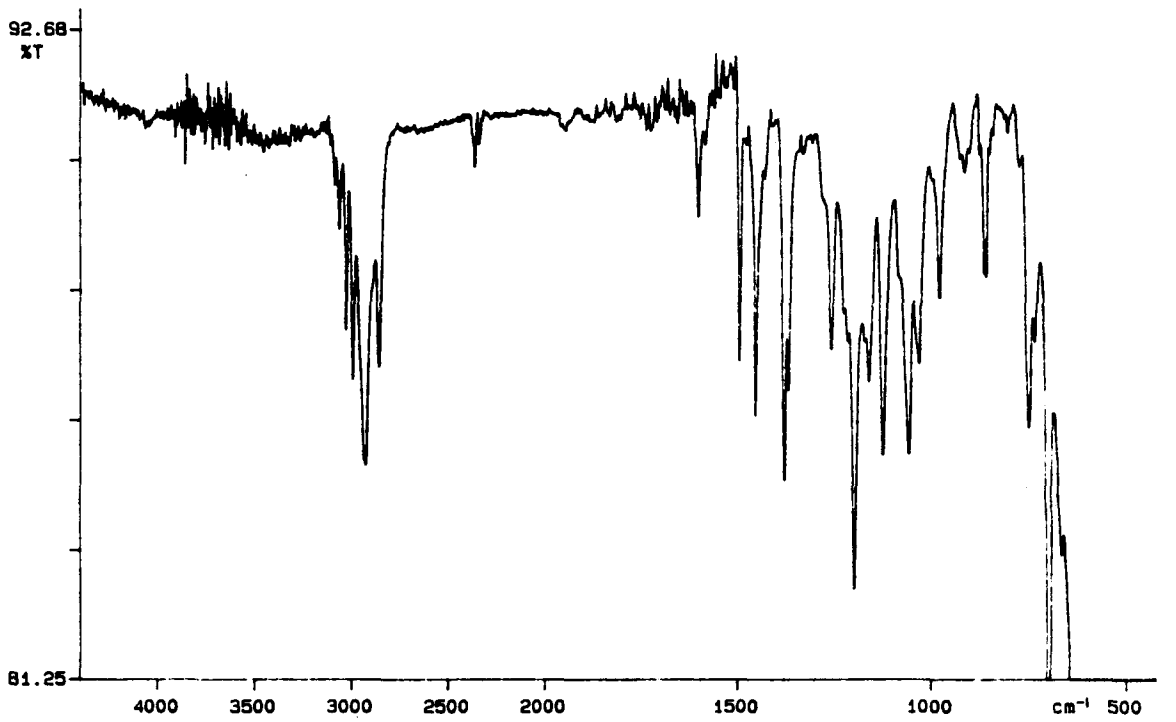
PPM
10
9
8
7
6
5
4
3
2
1
0
-1

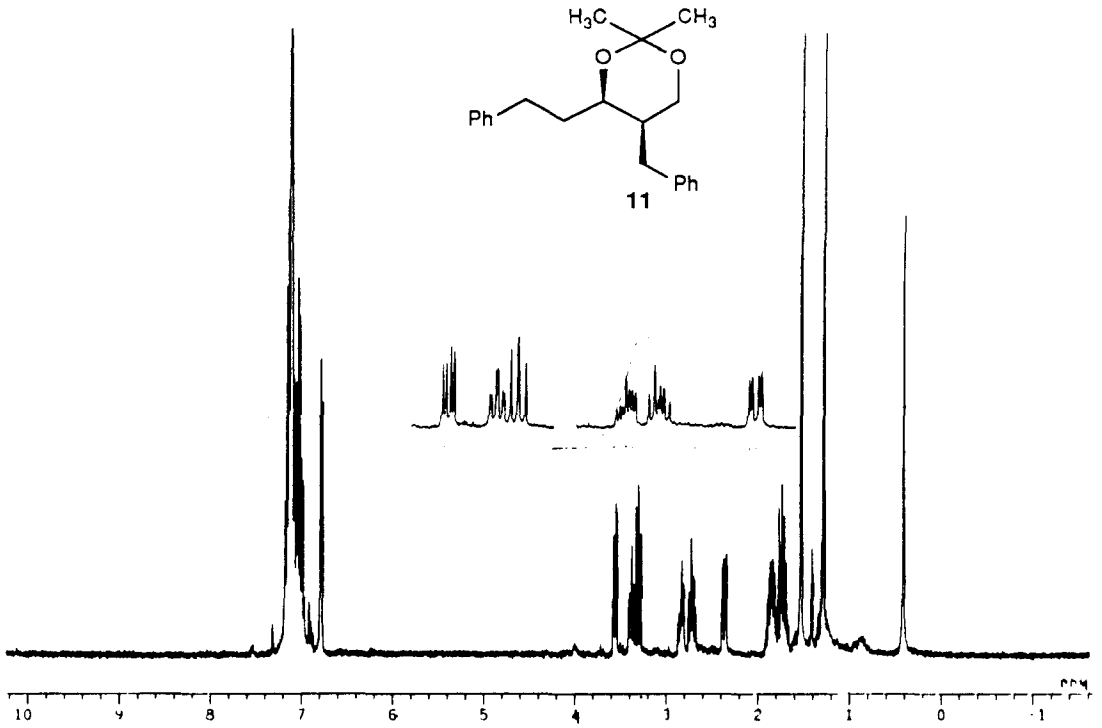

92.48
%T
33.14
4000
3500
3000
2500
2000
1500
1000
cm-1
500

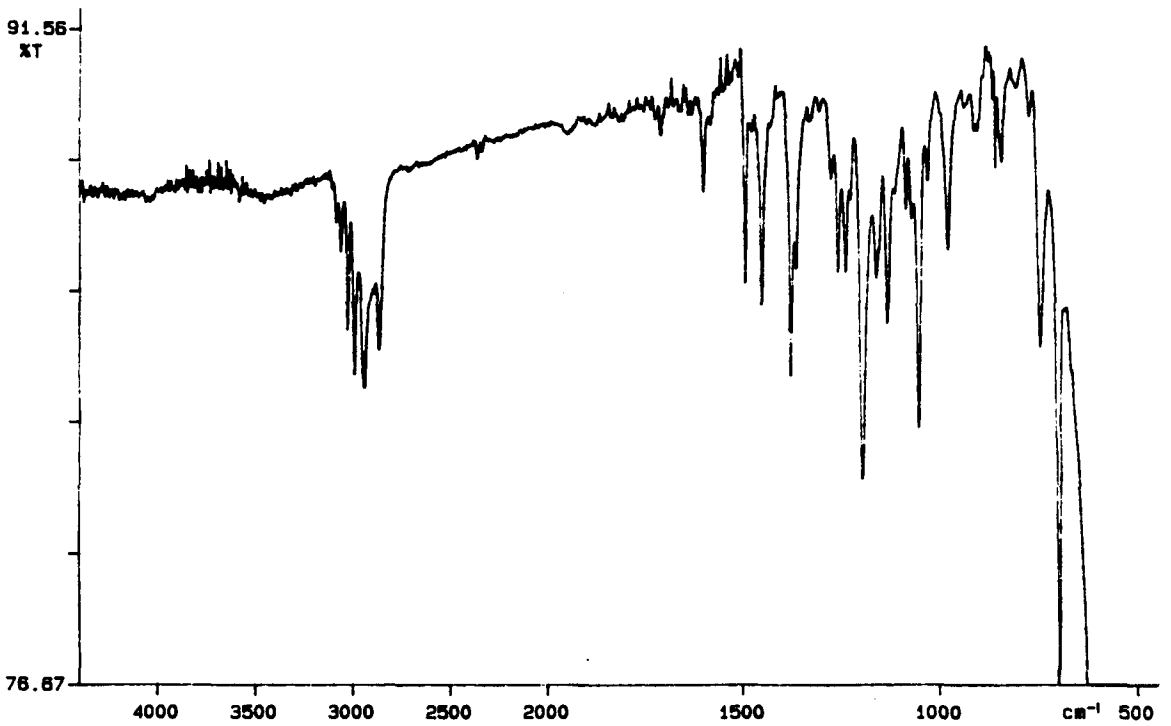

H3C
CH3
Si
O
O
Ph
H
SePh
Ph
9
PPM

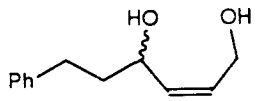

85.12
%T
64.75
4000
3500
3000
2500
2000
1500
1000
cm-1
500


H3C
CH3
O
O
Ph
Ph
10
PPM

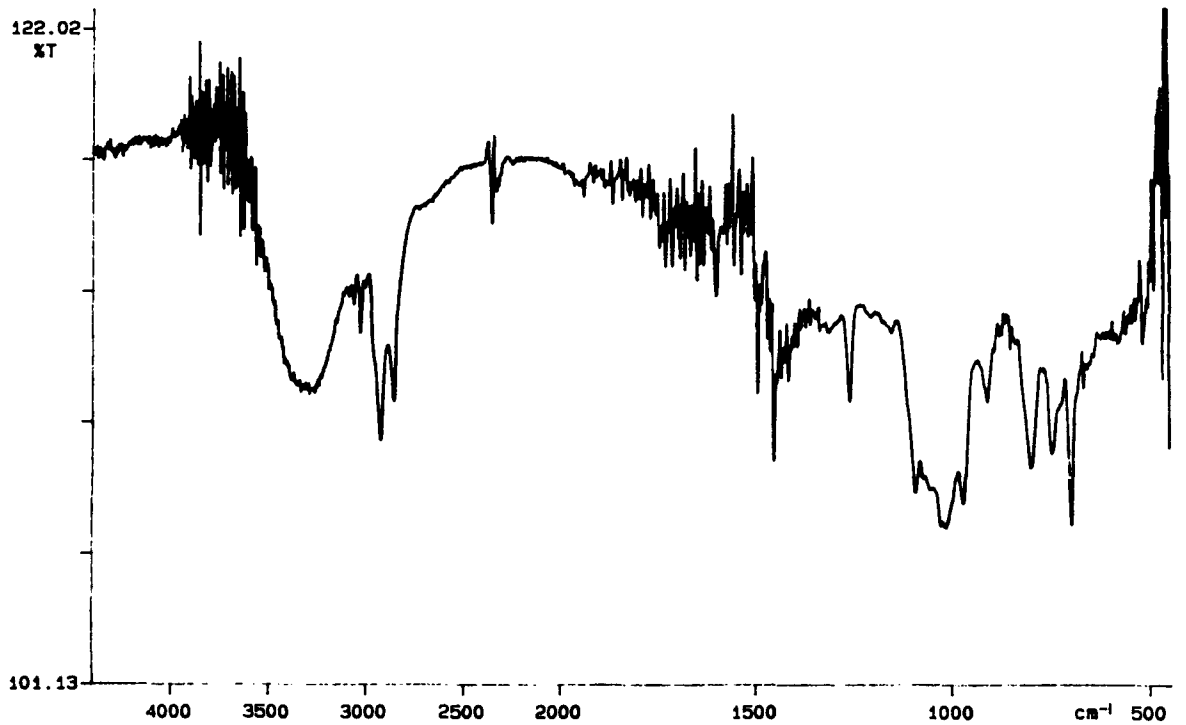

92.68
%T
81.25
4000
3500
3000
2500
2000
1500
1000
cm-1
500

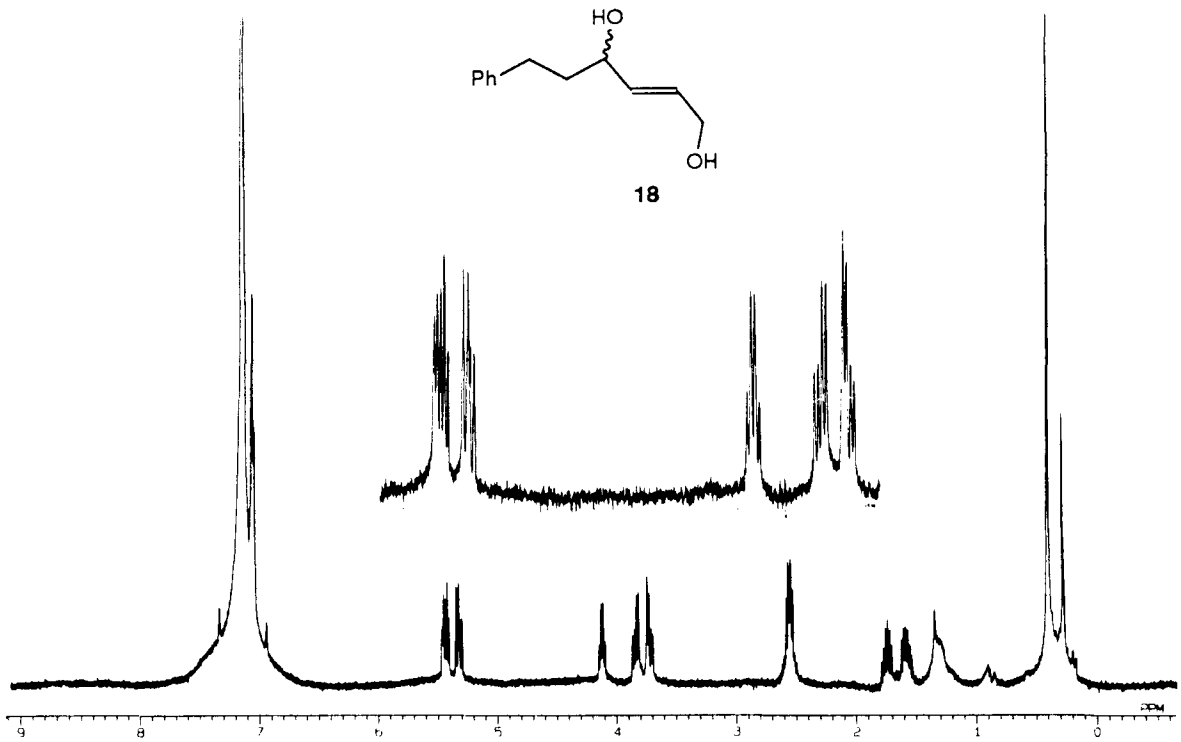

H3C
CH3
O
O
Ph
Ph
11
10
9
8
7
6
5
4
3
2
1
0
-1
PPM

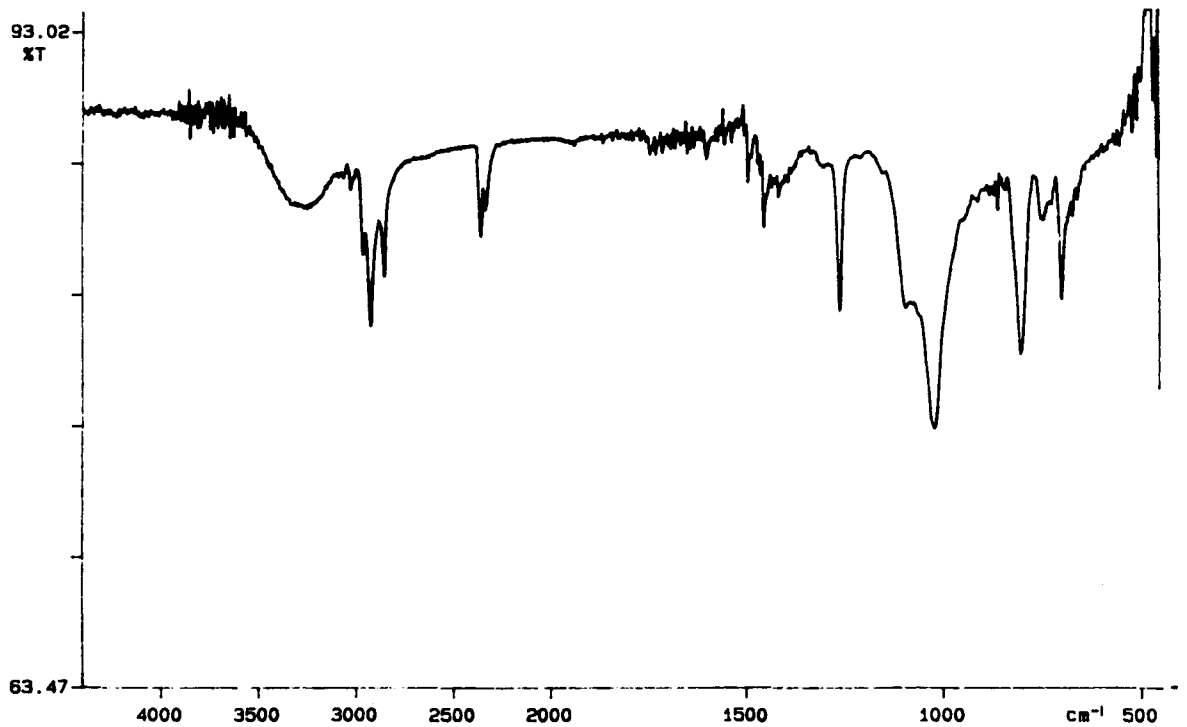

91.56
%T
76.67
4000
3500
3000
2500
2000
1500
1000
cm-1
500

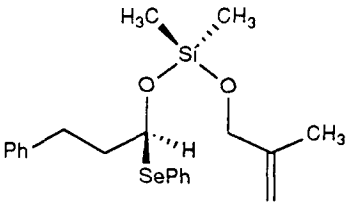

HO
OH
Ph

17


122.02
%T
101.13
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500

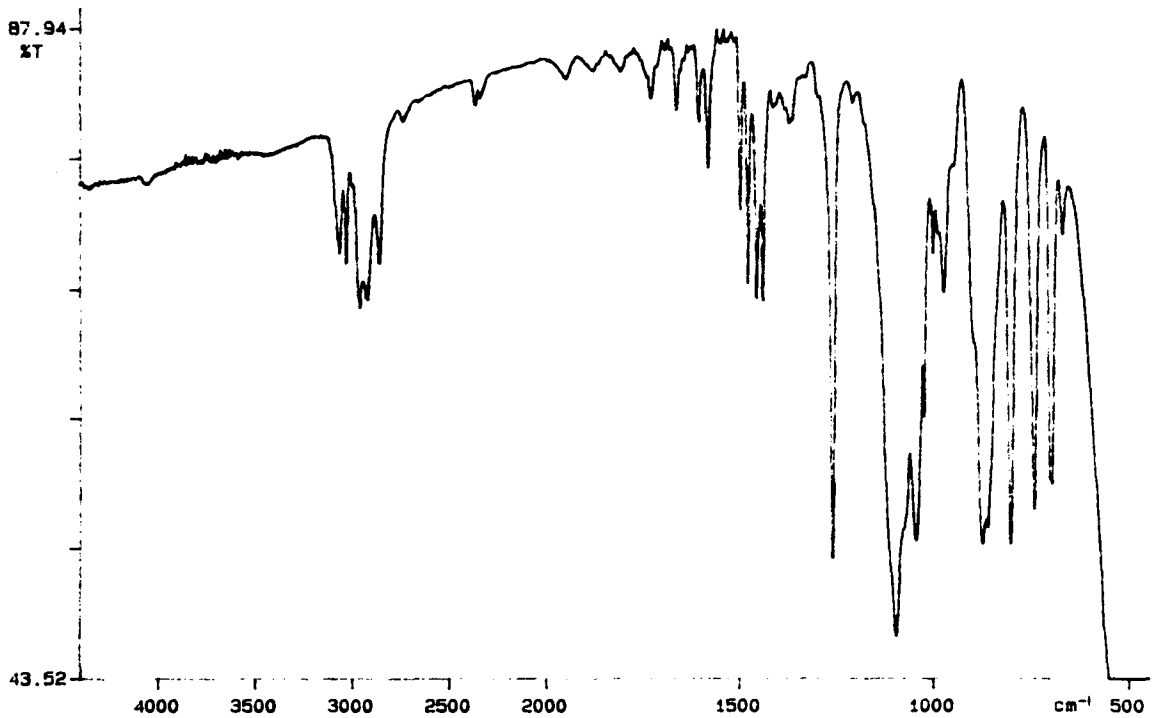

HO
Ph
OH
18
9
8
7
6
5
4
3
2
1
0
ppm

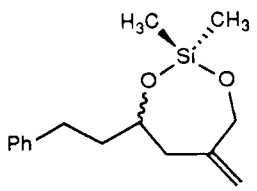

93.02
%T
63.47
4000
3500
3000
2500
2000
1500
1000
cm-1
500


H3C
CH3
Si
O
O
Ph
H
SePh
CH3

19

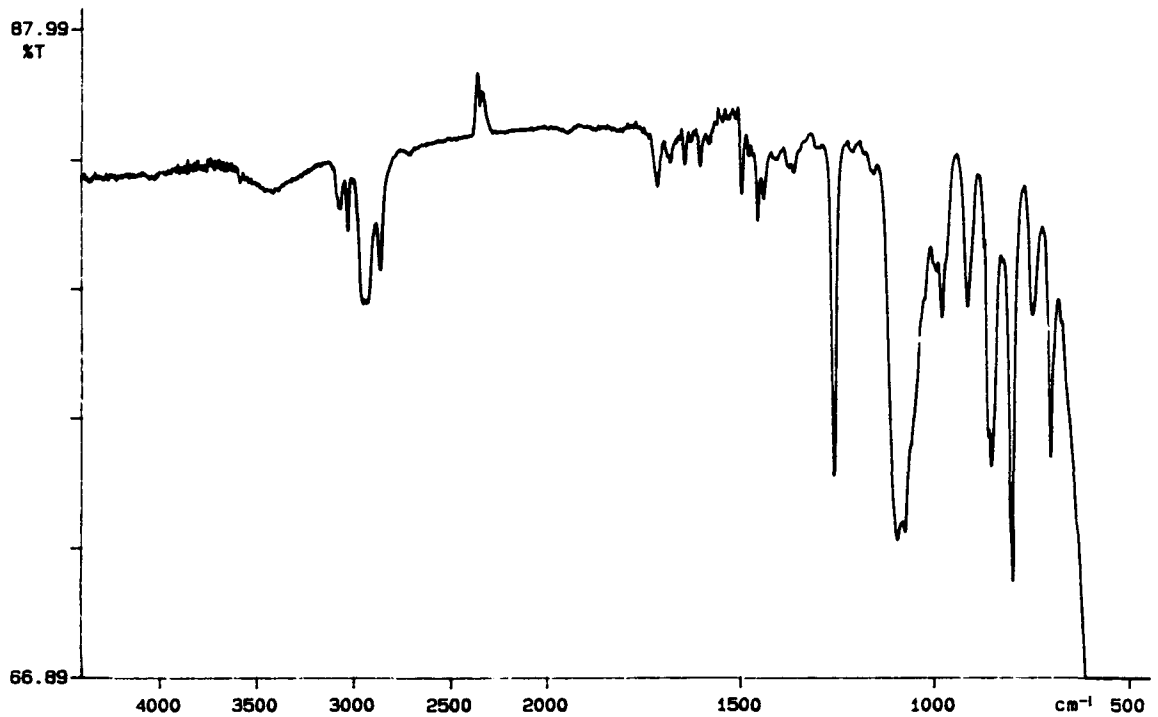
9
8
7
6
5
4
3
2
1
0
PPM

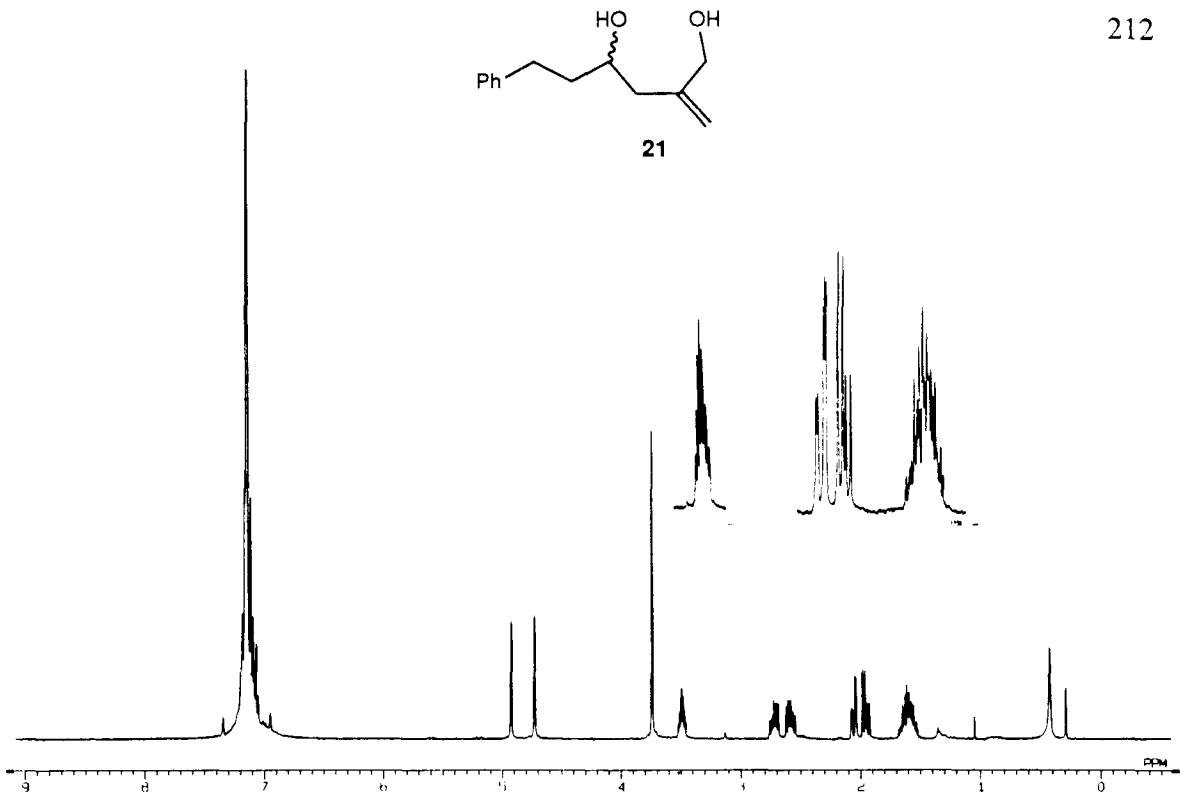

87.94
%T
43.52
4000
3500
3000
2500
2000
1500
1000
cm-1
500

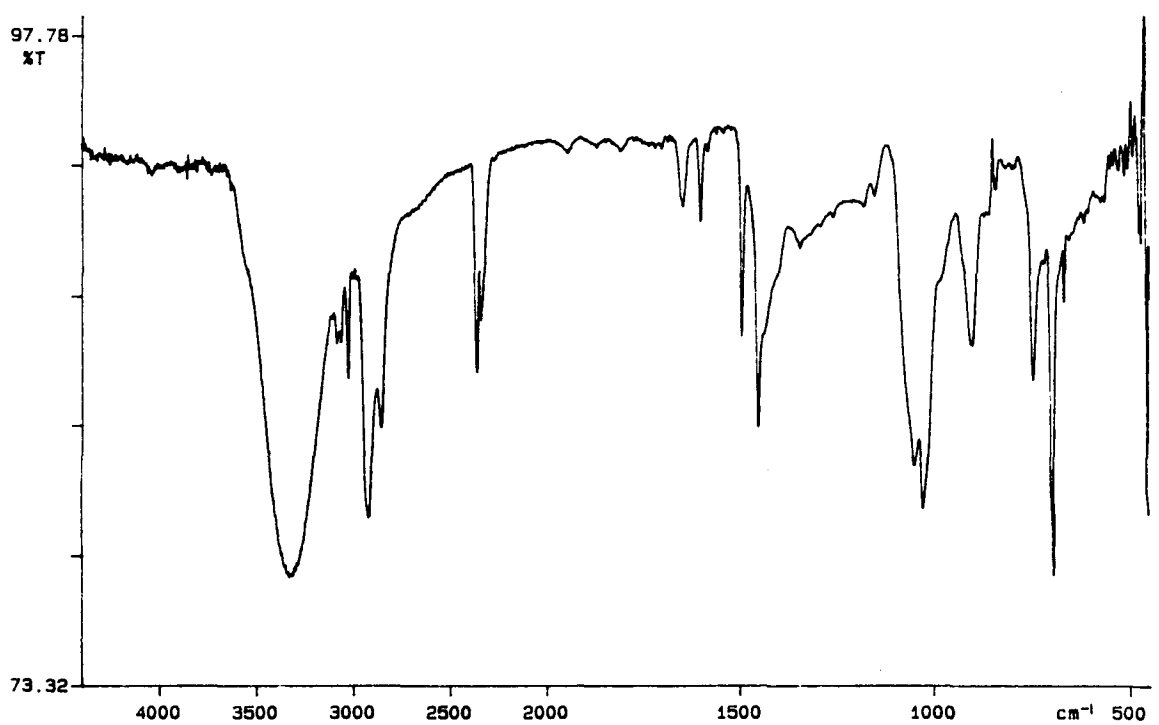

H3C
CH3
Si
O
O
Ph

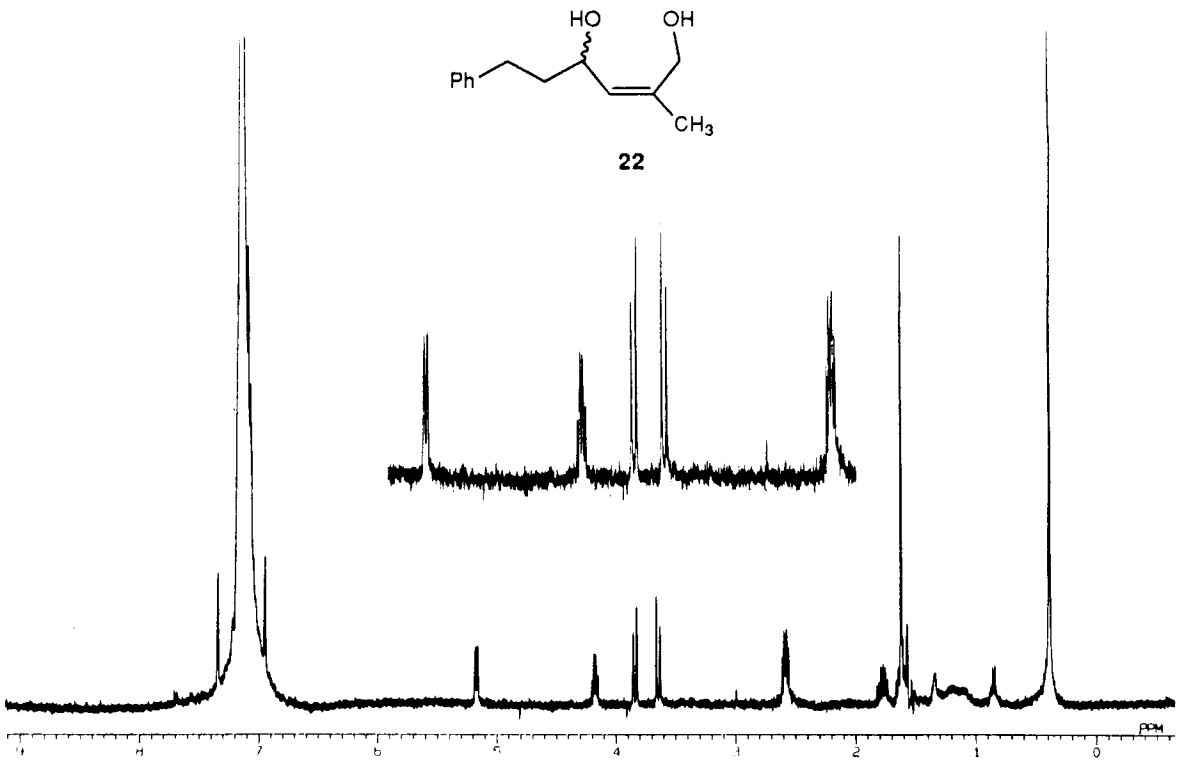
20

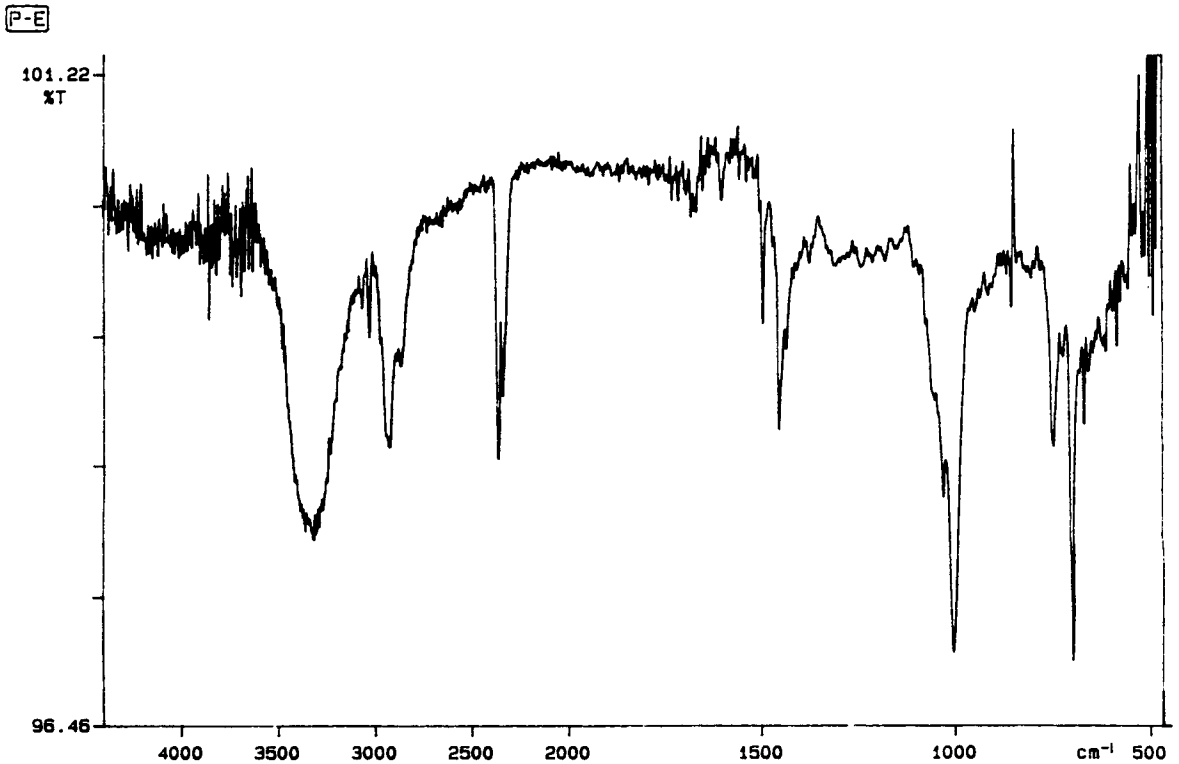
9
8
7
6
5
4
3
2
1
0
PPM


87.99
%T
66.89
4000
3500
3000
2500
2000
1500
1000
cm-1
500


HO
OH
Ph
21
PPM

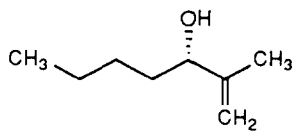

97.78
%T
73.32
4000
3500
3000
2500
2000
1500
1000
cm-1
500


HO
OH
Ph
CH3
22
PPM

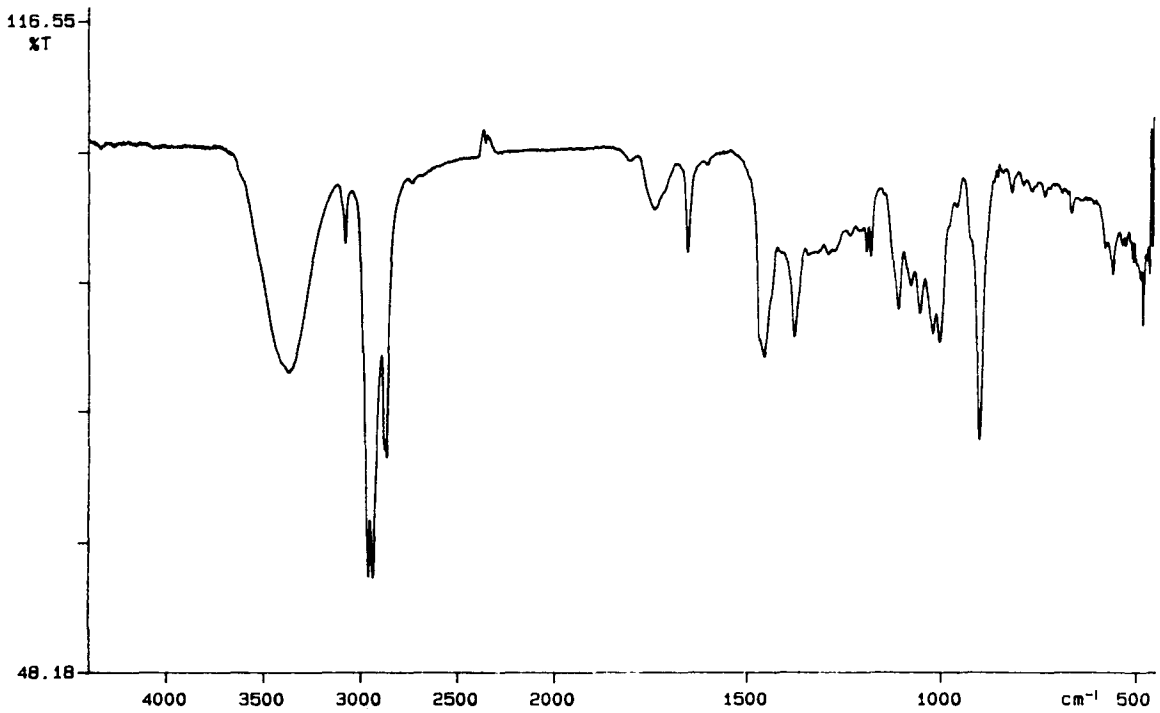

P-E
101.22
%T
96.46
4000
3500
3000
2500
2000
1500
1000
cm-1
500

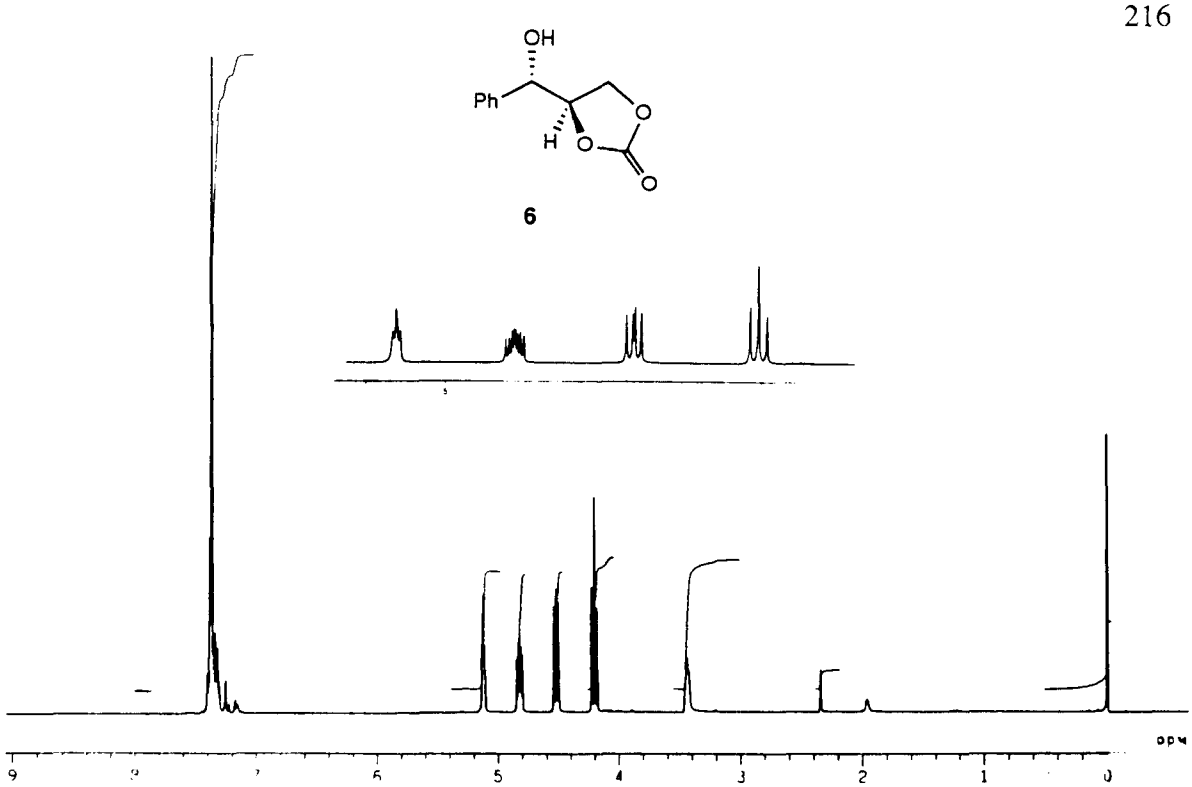
Appendix III

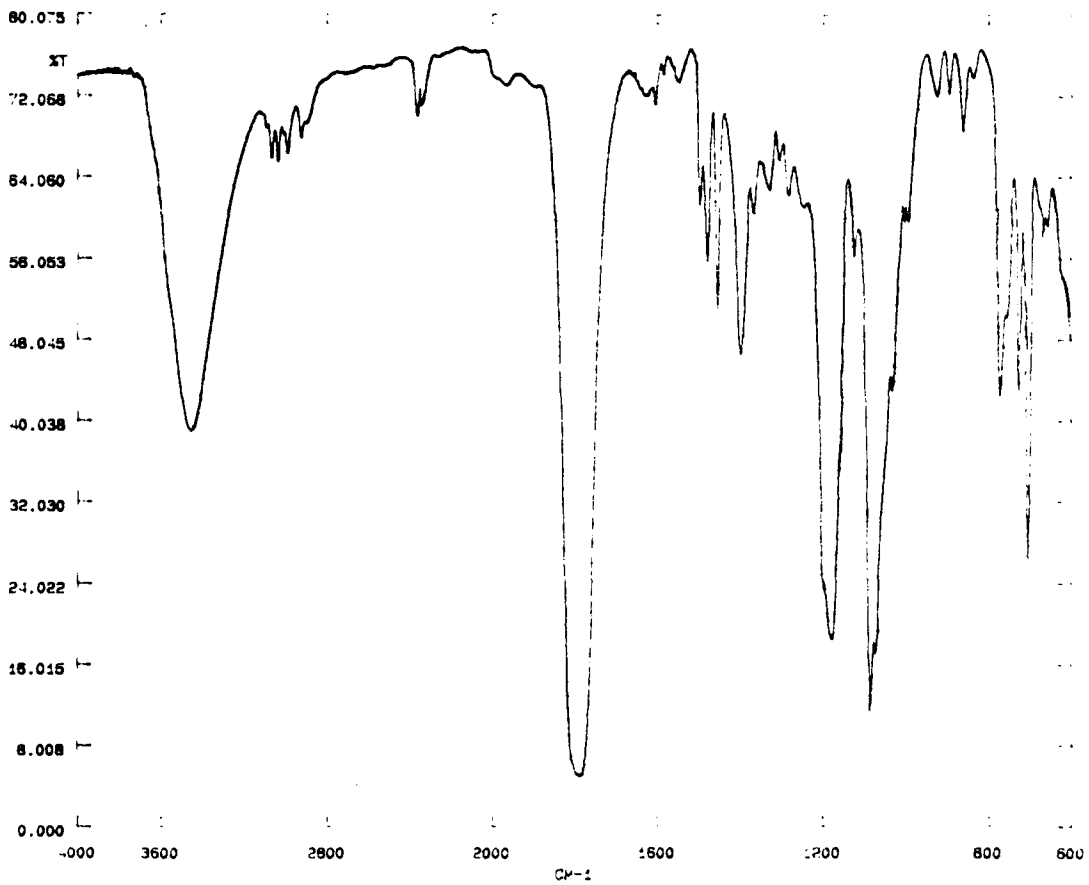
Spectral Catalog for Chapter Three

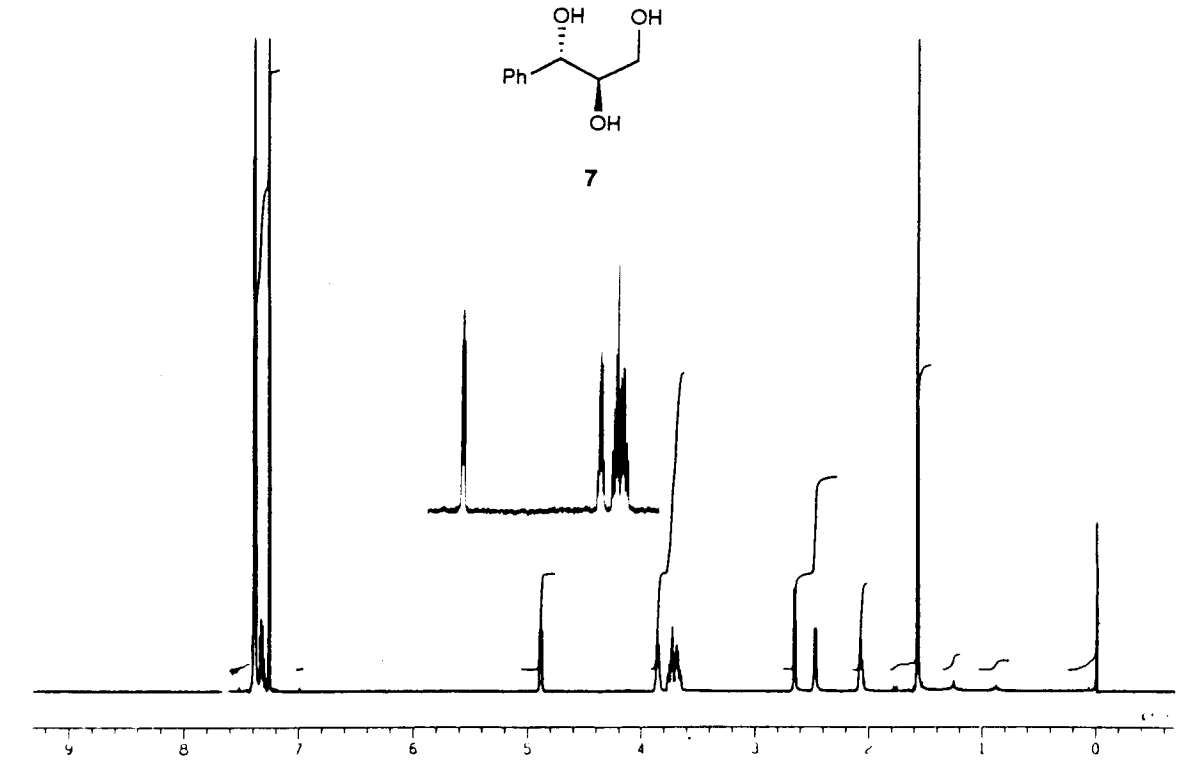

OH
CH3
CH3
CH2

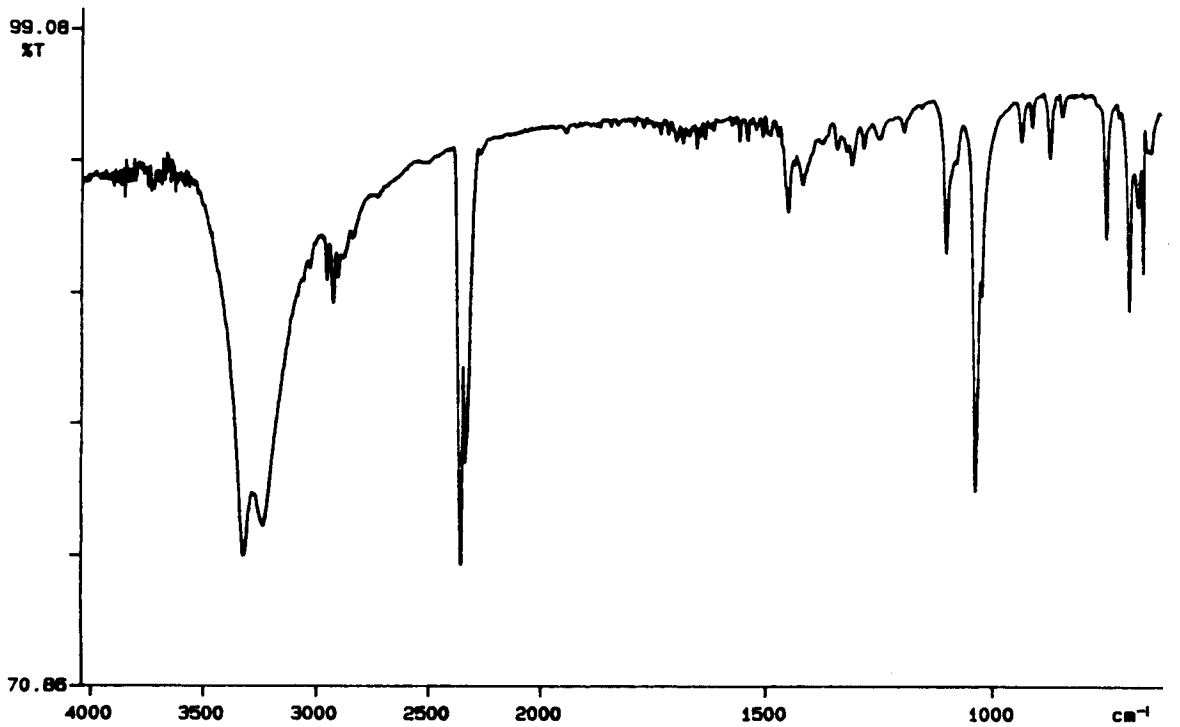
PPM
9
8
7
6
5
4
3
2
1
0

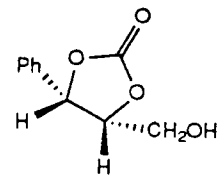

116.55
%T
48.18
4000
3500
3000
2500
2000
1500
1000
cm-1
500


OH
Ph
H
O
O
O
6
ppm
9
8
7
6
5
4
3
2
1
0


%T
80.075
72.068
64.060
56.053
48.045
40.038
32.030
24.022
16.015
8.008
0.000
4000
3600
2800
2000
1600
1200
800
600
CM-1

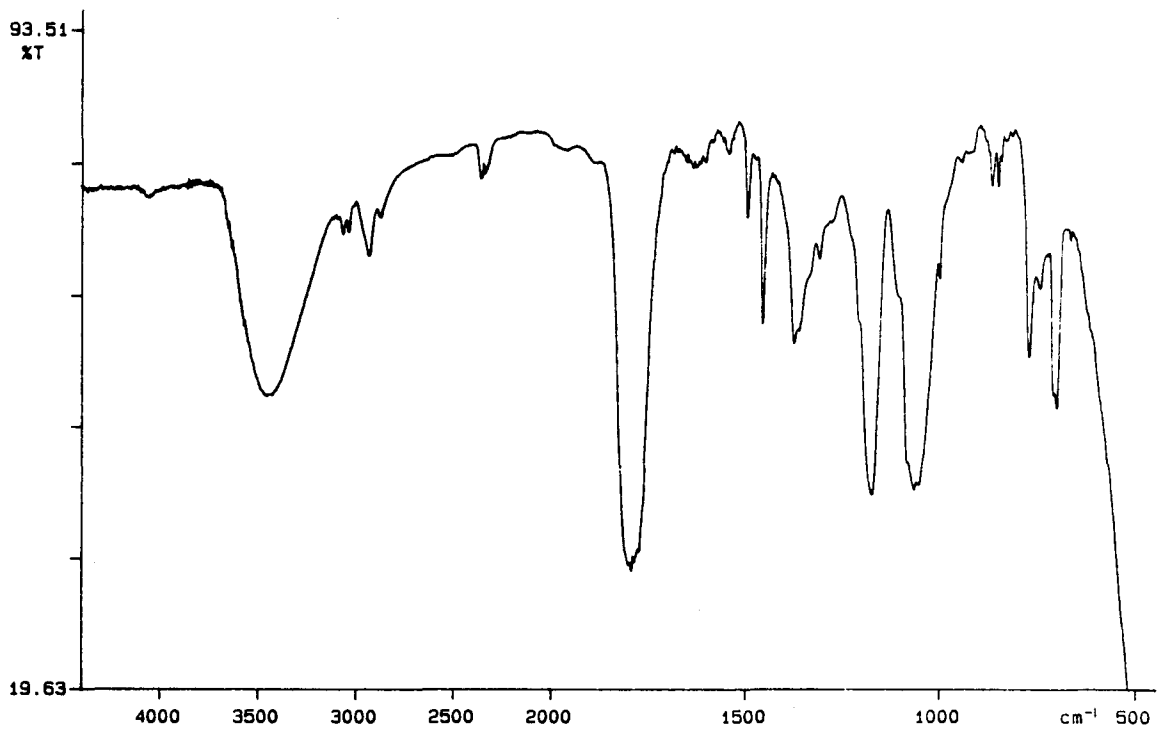

OH
OH
Ph
OH
7
9
8
7
6
5
4
3
2
1
0

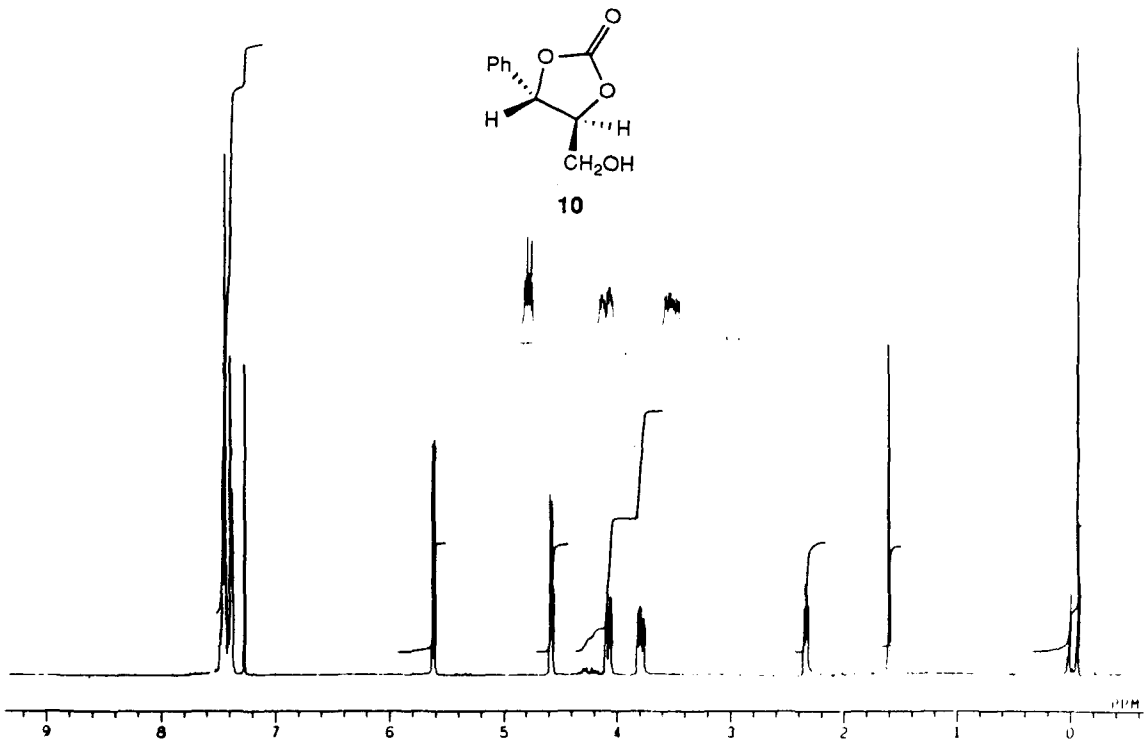

99.08
%T
70.86
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

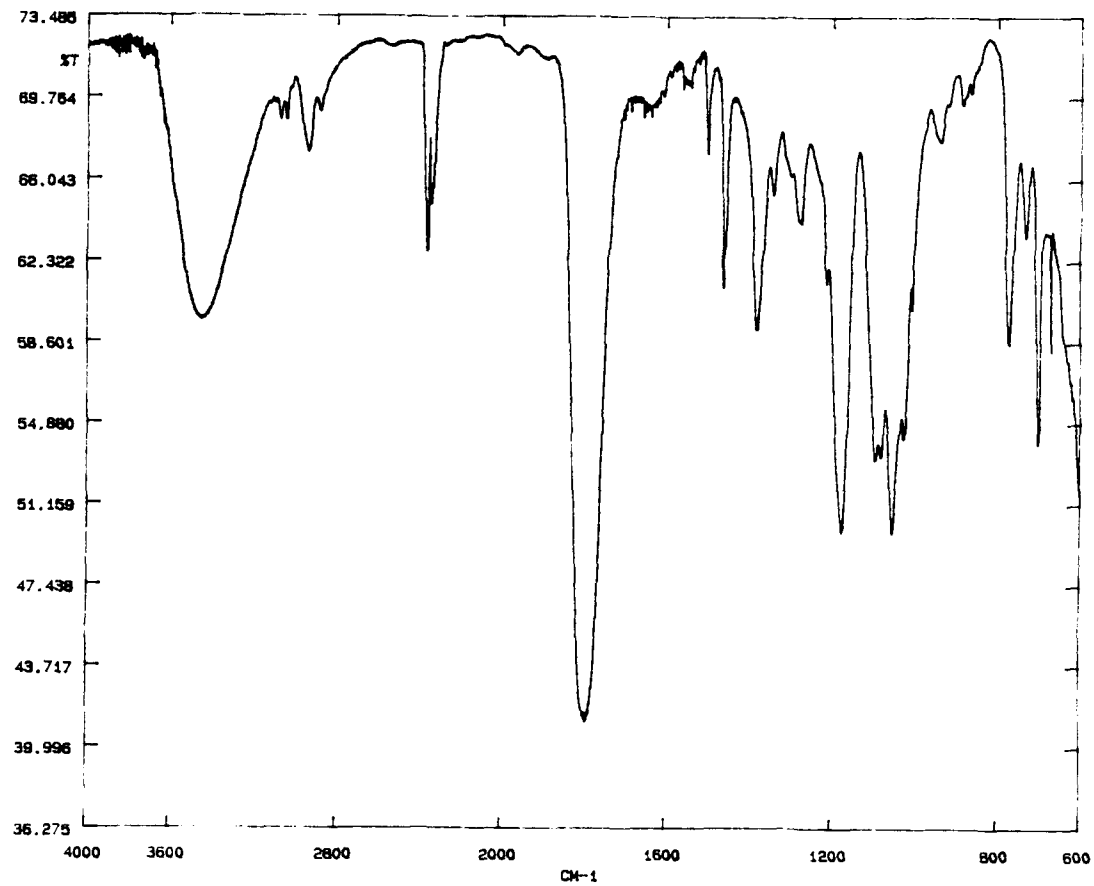

Ph
O
O
O
H
CH2OH
H

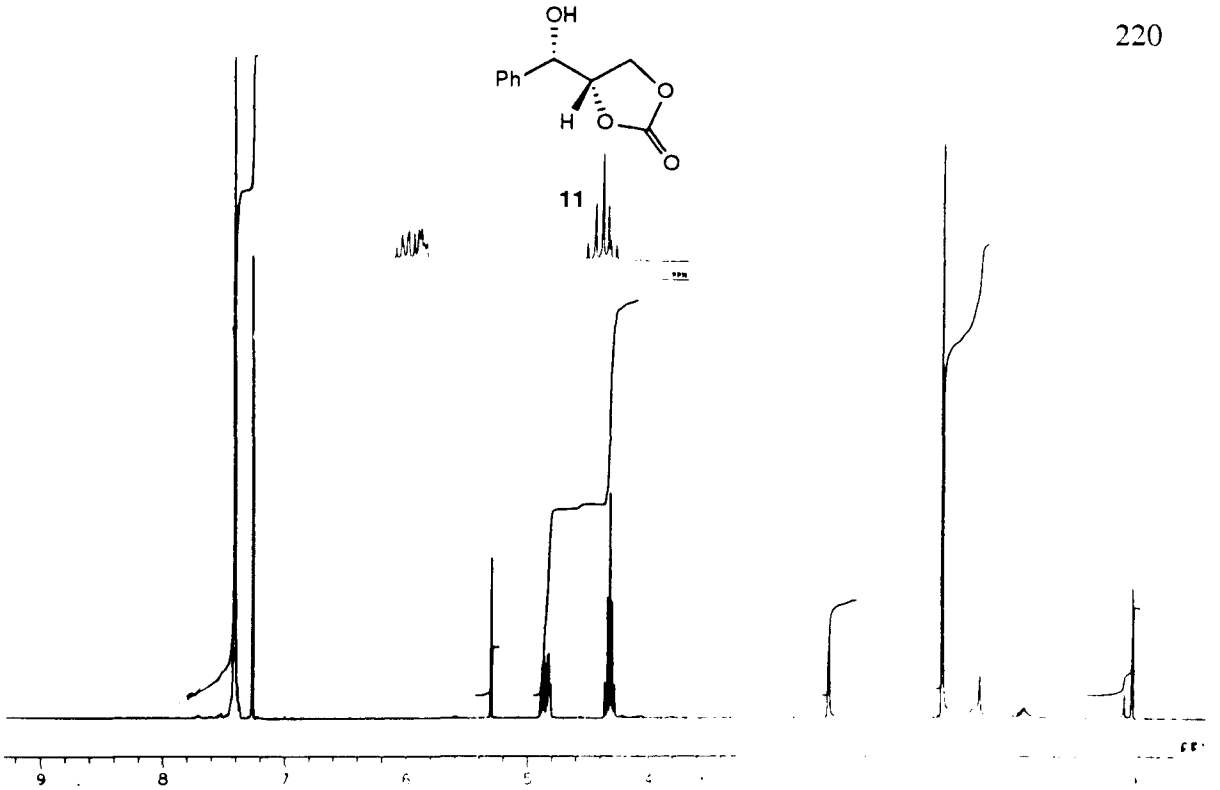
9

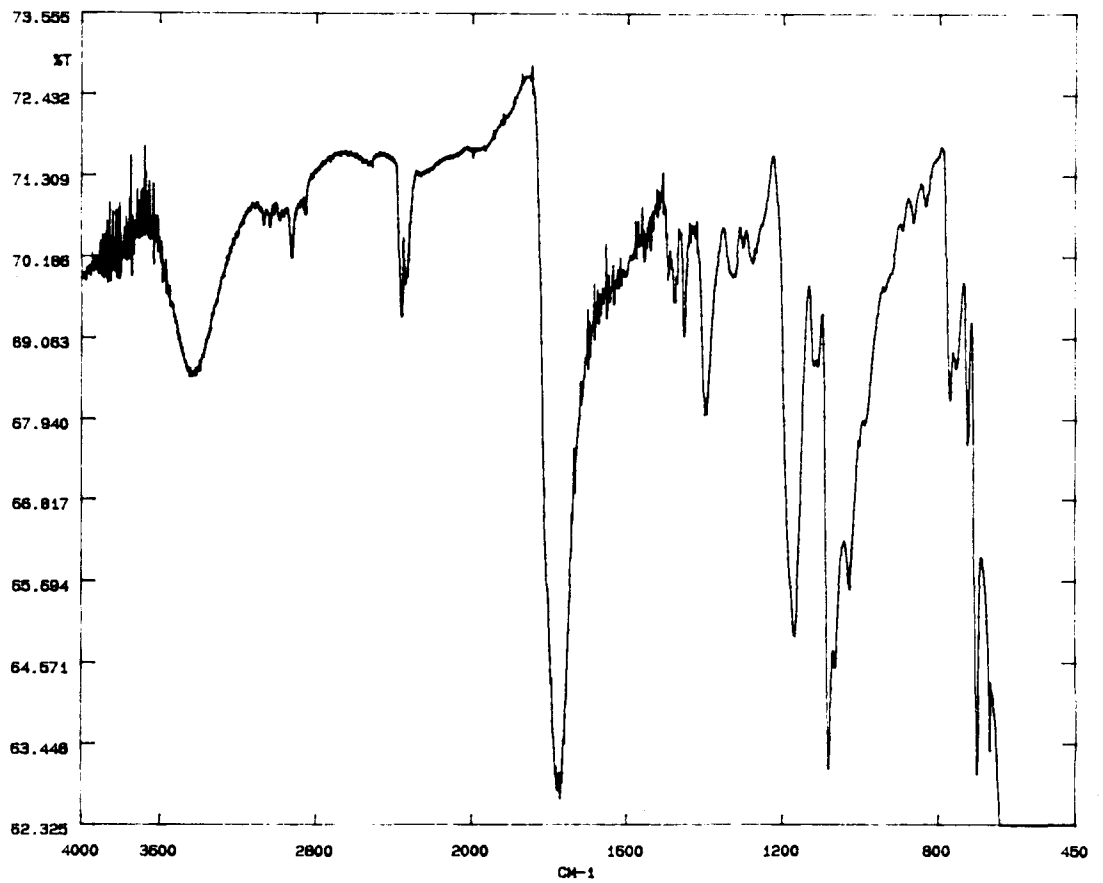
PPM

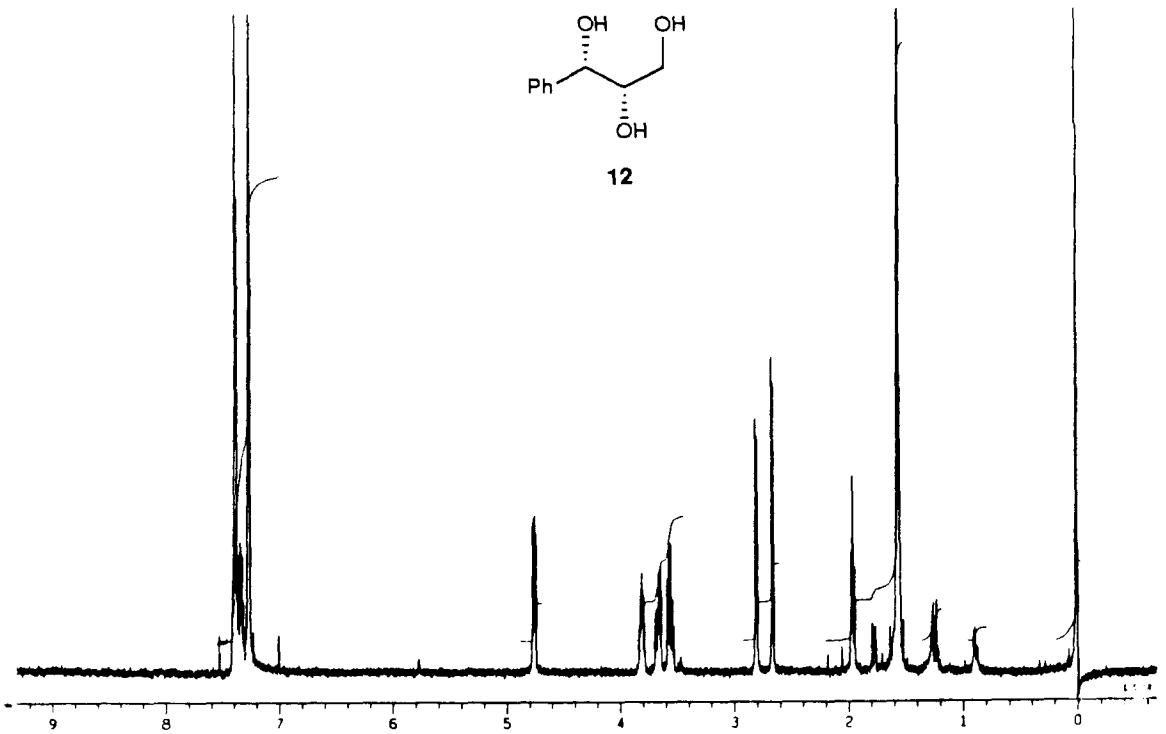

93.51
%T
19.63
4000
3500
3000
2500
2000
1500
1000
cm-1
500


Ph
O
O
O
H
H
CH2OH
10
9
8
7
6
5
4
3
2
1
0
PPM

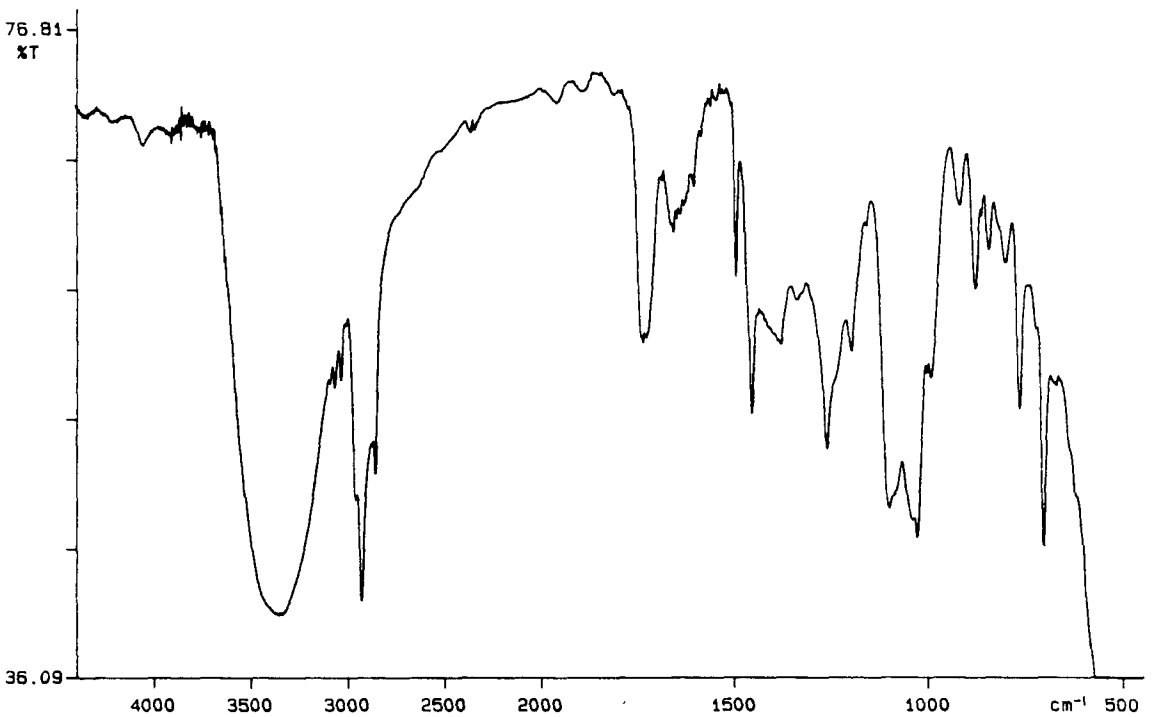

73.486
%T
69.764
66.043
62.322
58.601
54.880
51.159
47.438
43.717
39.996
36.275
4000
3600
2800
2000
1600
1200
800
600
CM-1

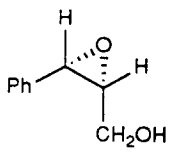

OH
Ph
H
O
O
O
11
9
8
7
6
5
4
3
2
1
0


73.555
%T
72.432
71.309
70.186
69.063
67.940
66.817
65.694
64.571
63.448
62.325
4000
3500
2800
2000
1600
1200
800
450
CM-1


OH
OH
Ph
OH
9
8
7
6
5
4
3
2
1
0

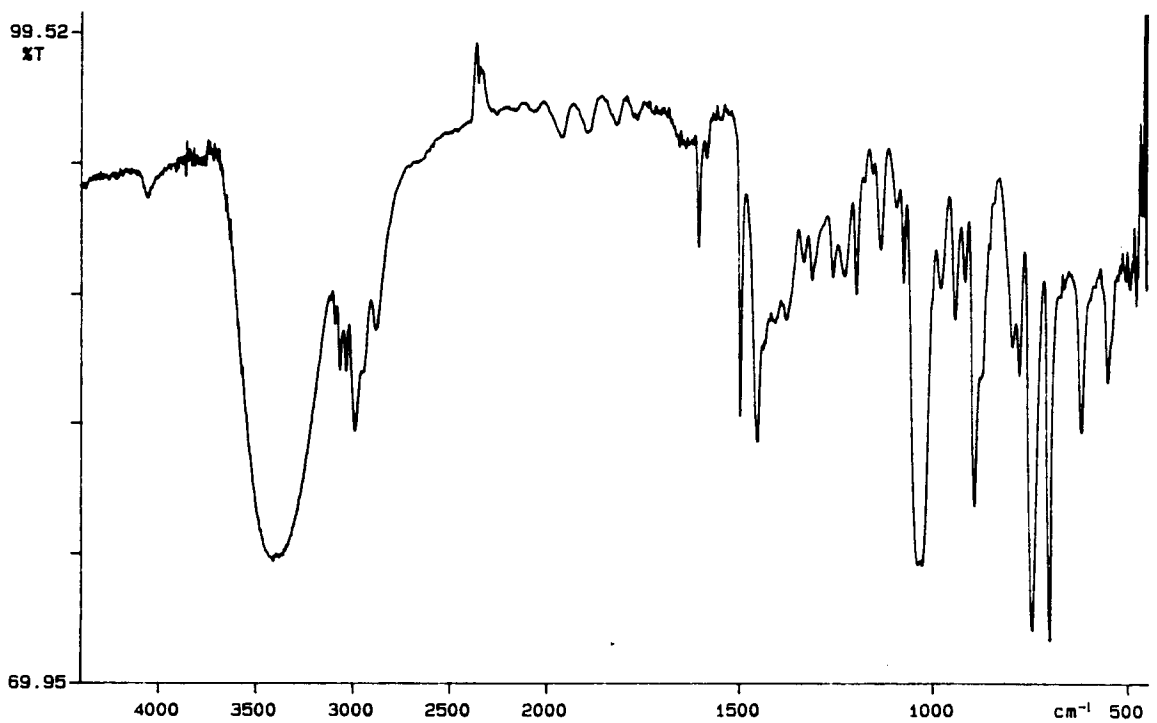
12

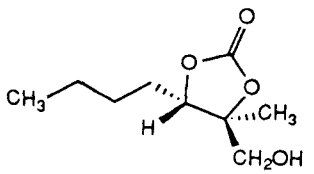

76.81
%T
36.09
4000
3500
3000
2500
2000
1500
1000
cm-1
500


H
O
Ph
H
CH2OH

13

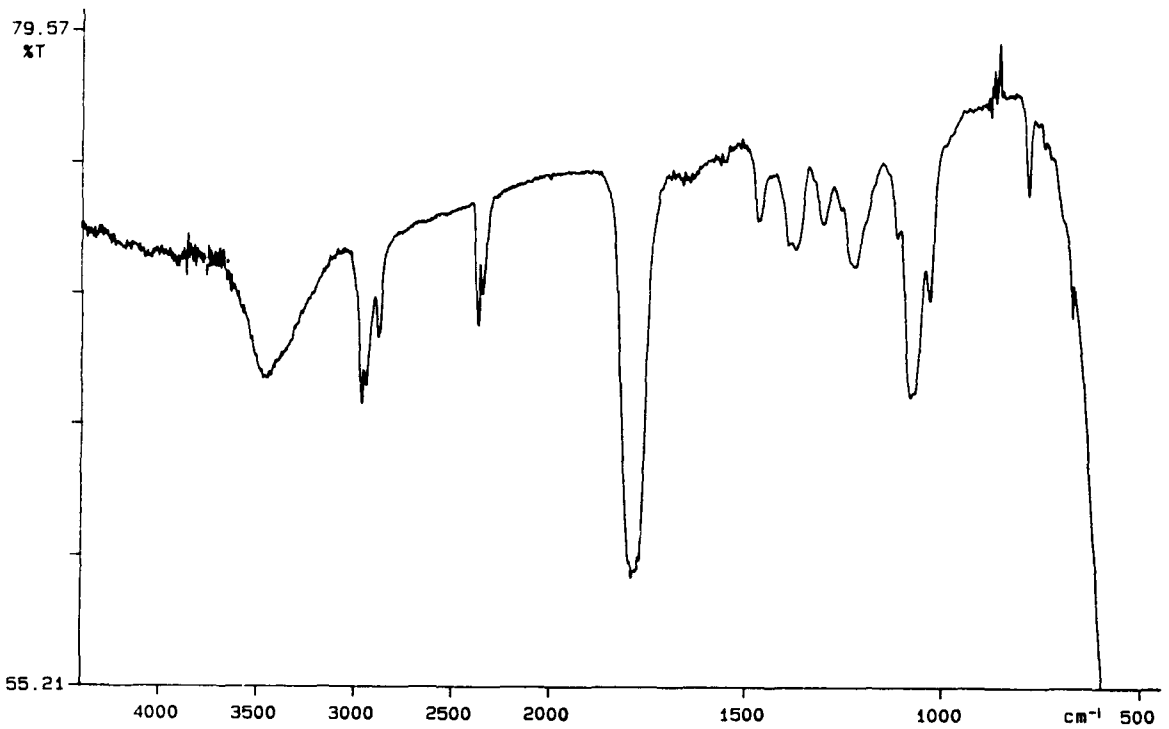
9
8
7
6
5
4
3
2
1
0

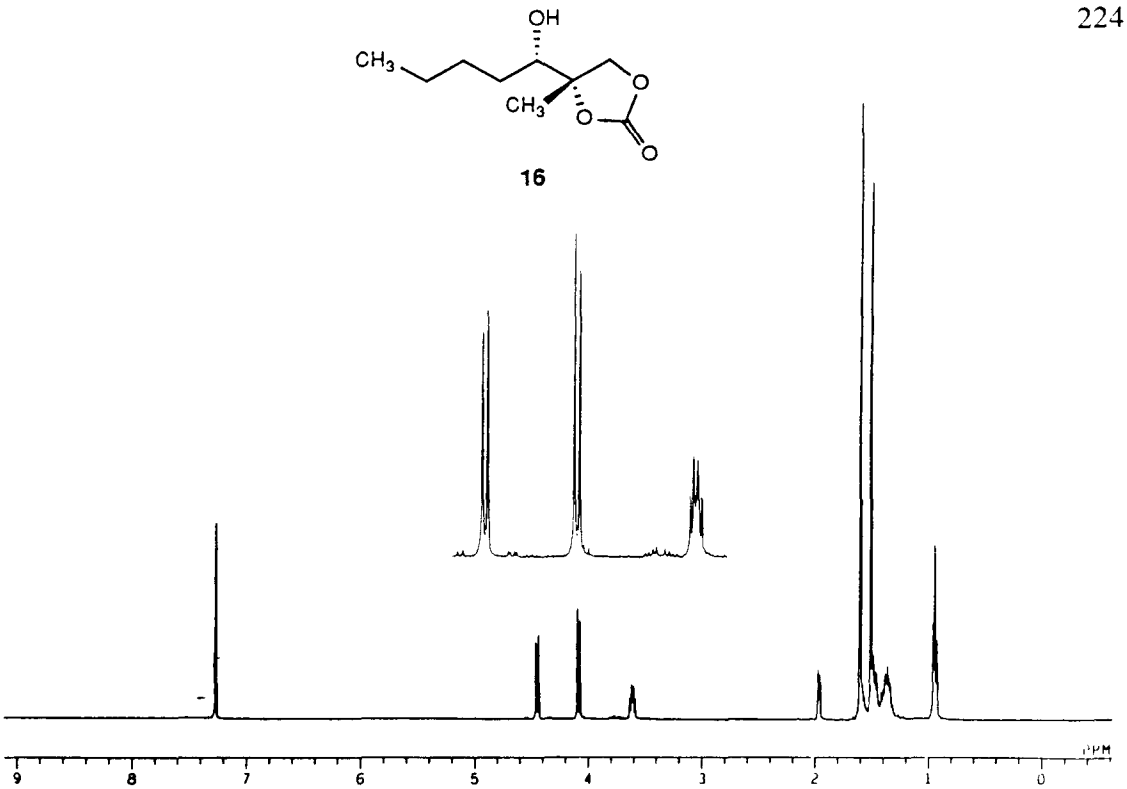

99.52
%T
69.95
4000
3500
3000
2500
2000
1500
1000
cm-1
500


O
O
O
CH3
H
CH3
CH2OH

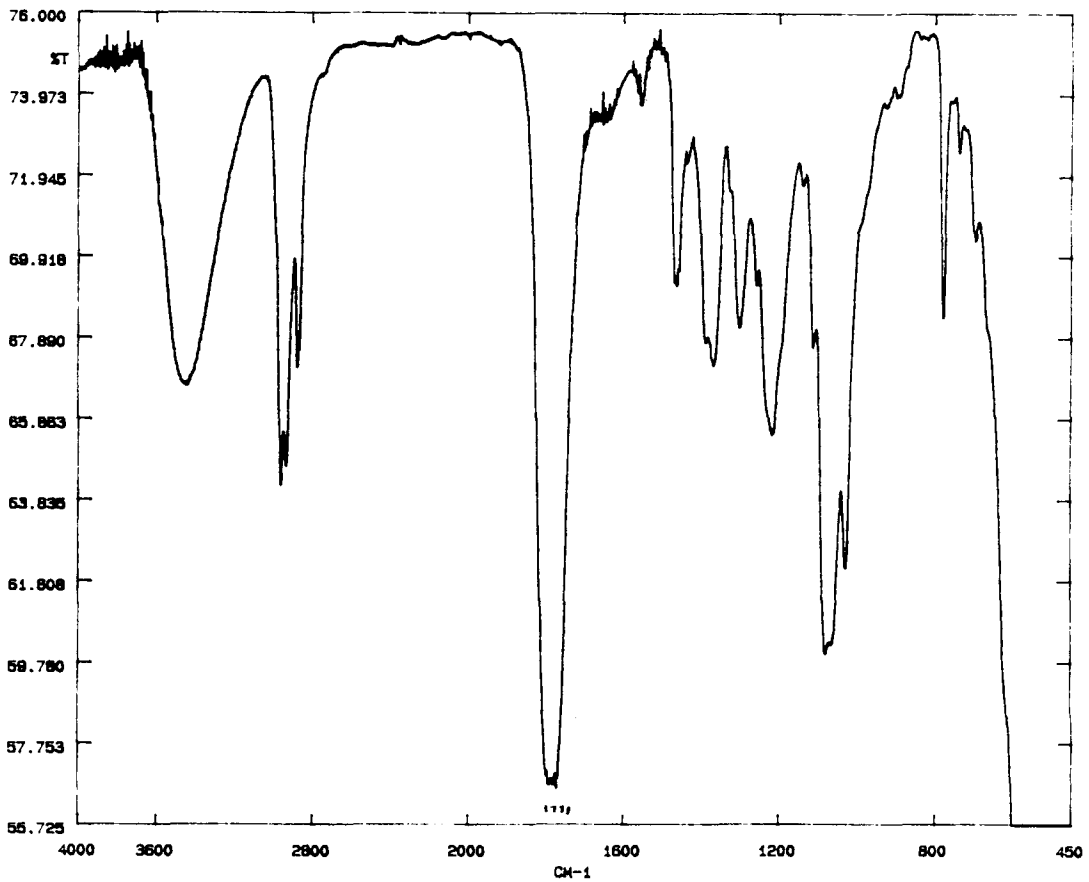
15

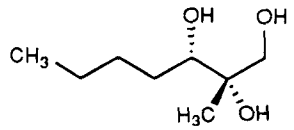
9
8
7
6
5
4
3
2
1
0
PPM


79.57
%T
55.21
4000
3500
3000
2500
2000
1500
1000
cm-1
500

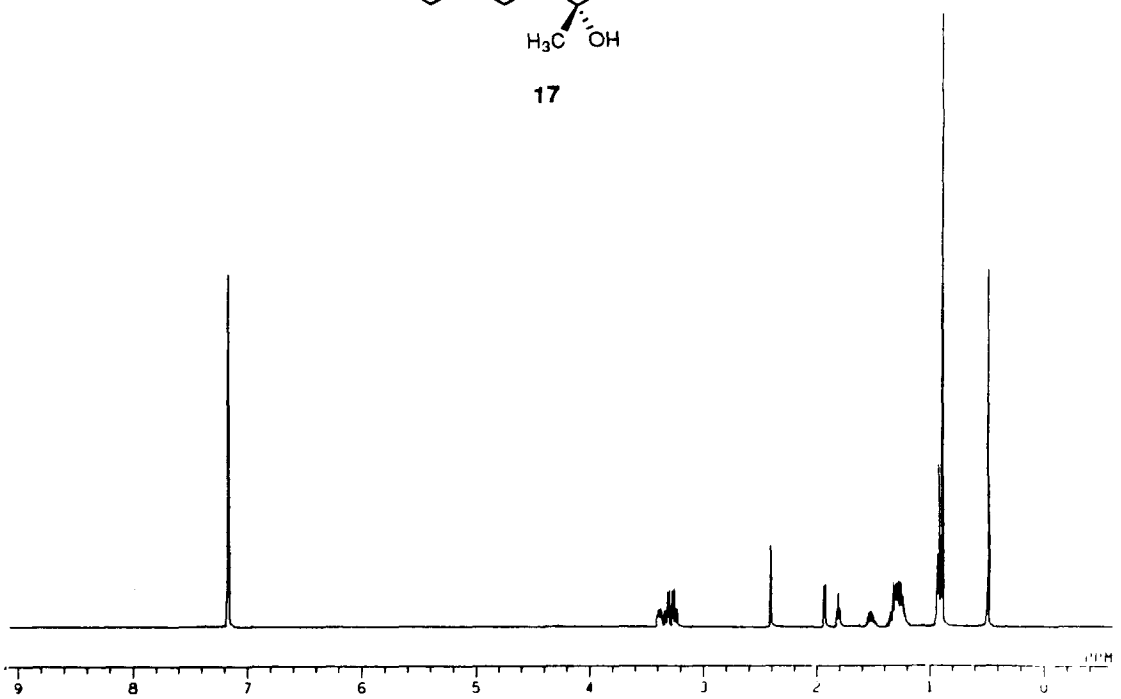

OH
CH3
CH3
O
O
O
9
8
7
6
5
4
3
2
1
0
PPM

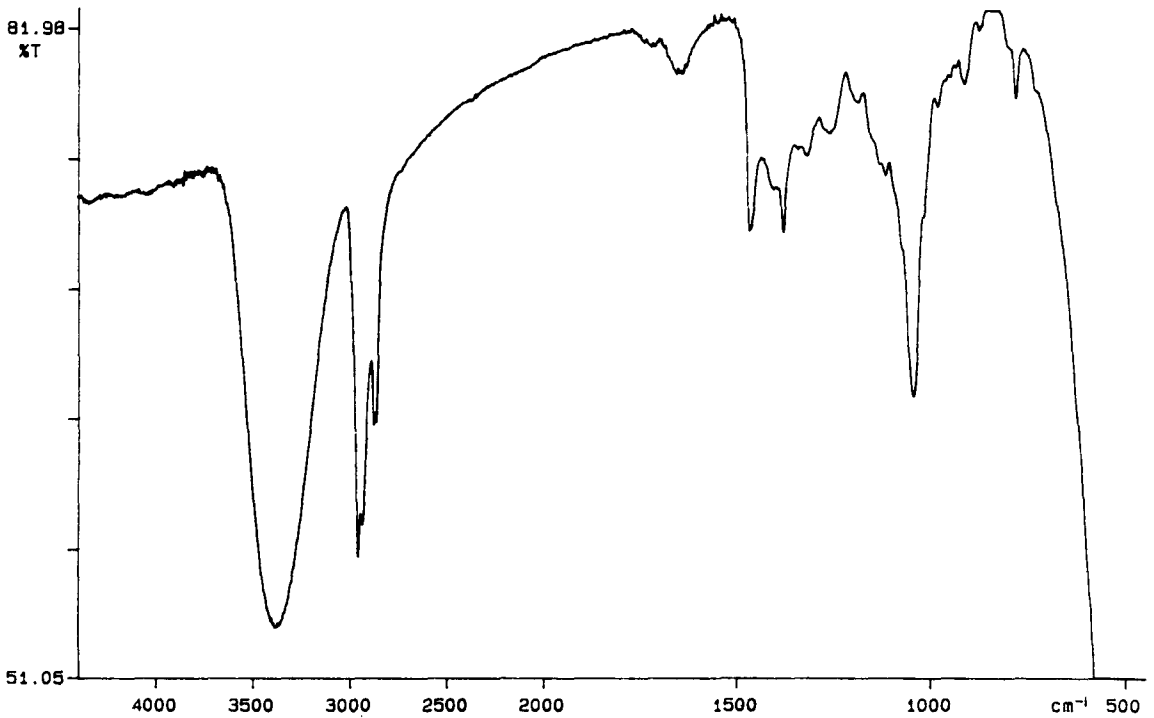
16

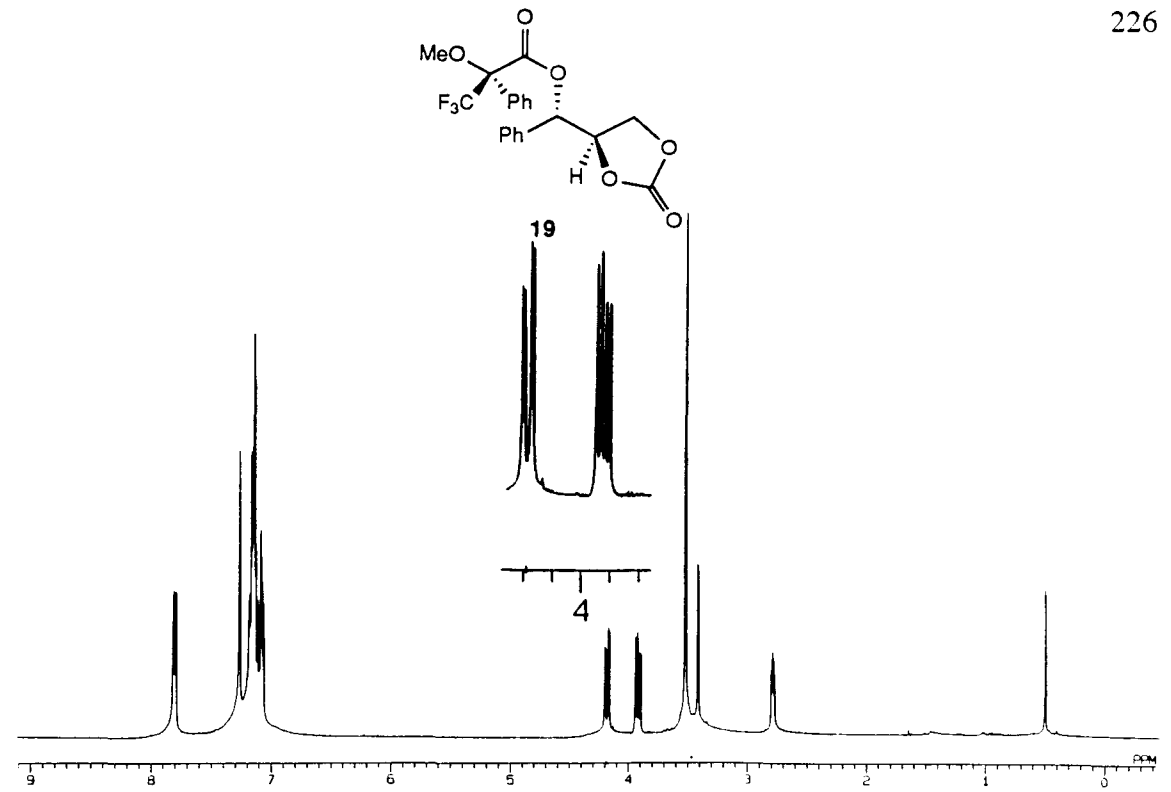

76.000
%T
73.973
71.945
69.918
67.890
65.863
63.836
61.808
59.780
57.753
55.725
4000
3600
2800
2000
1600
1200
800
450
CM-1

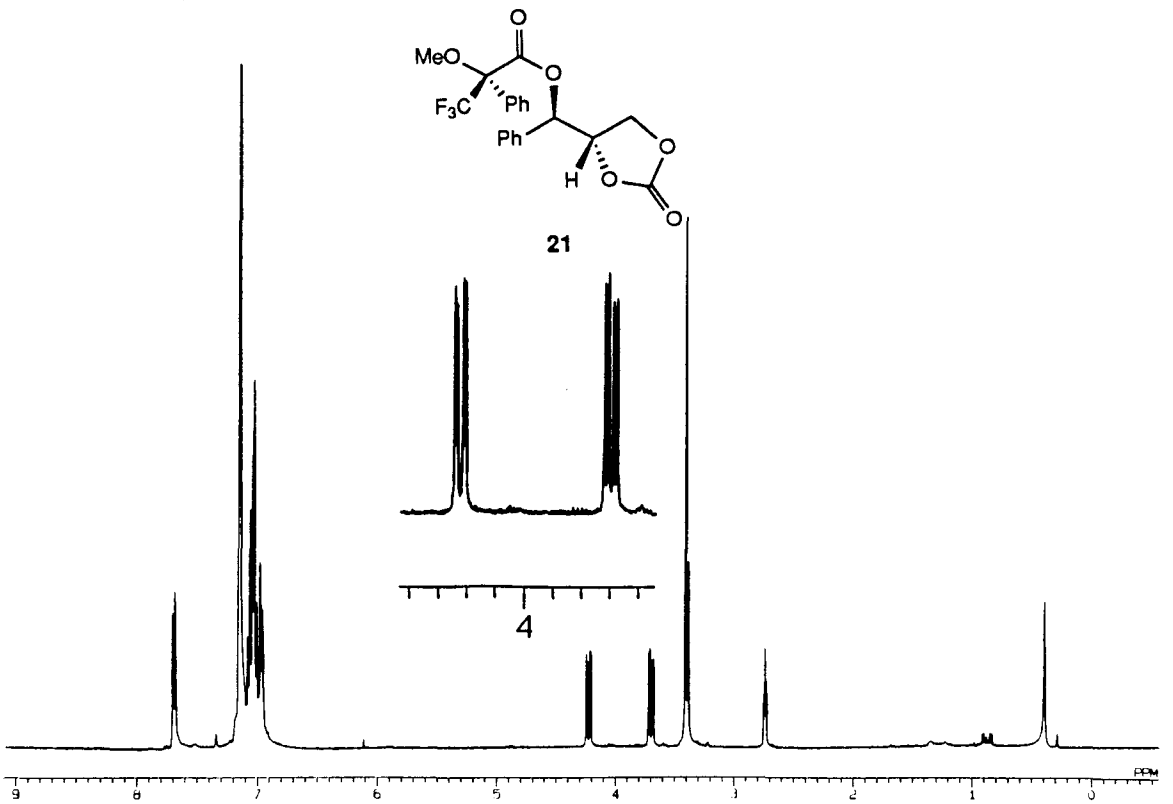

OH
OH
CH3
H3C
OH

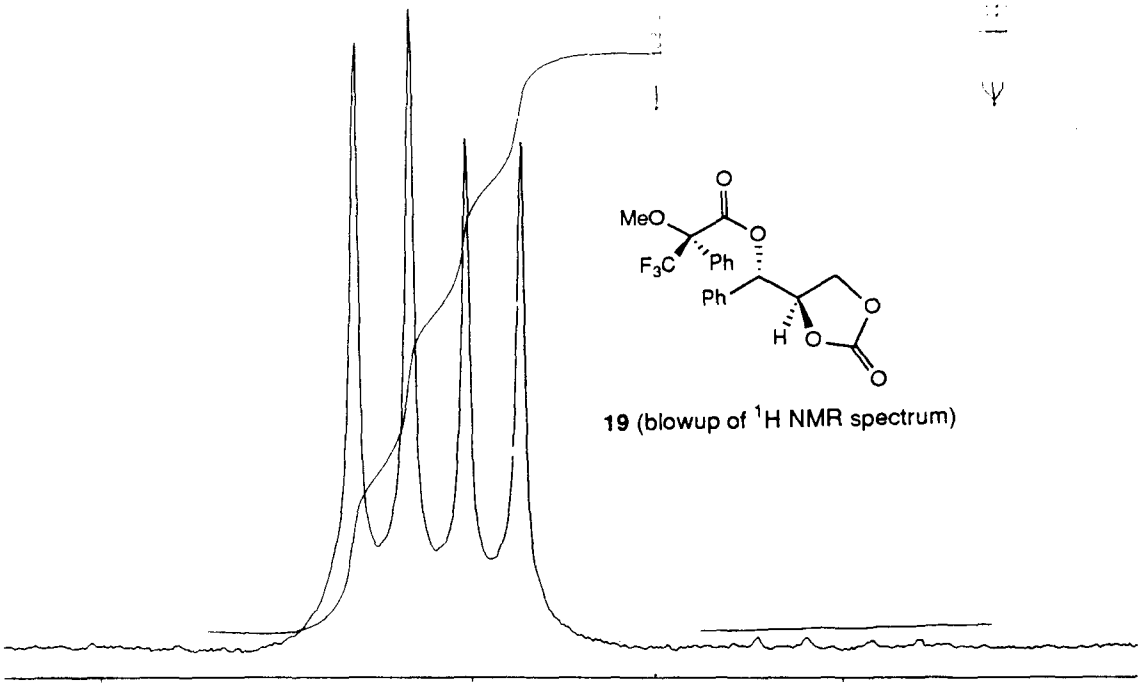
17


9
8
7
6
5
4
3
2
1
0

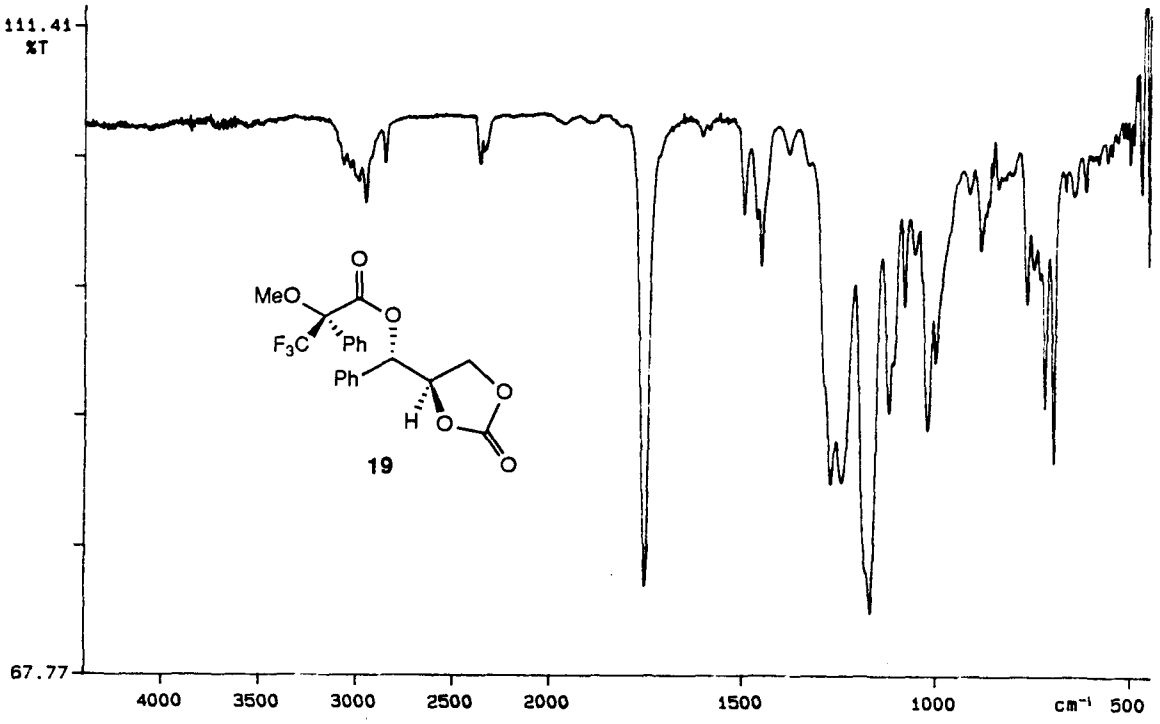

81.98
%T
51.05
4000
3500
3000
2500
2000
1500
1000
cm-1
500


MeO
F3C
Ph
Ph
O
H
19
4
PPM

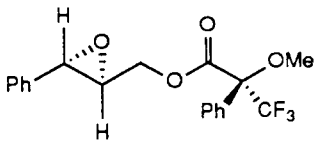

MeO
F3C
Ph
Ph
O
H
21
4
PPM



19 (blowup of ^{1}H NMR spectrum)

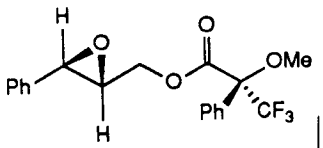


19


H
O
Ph
O
O
OMe
Ph
CF3
H

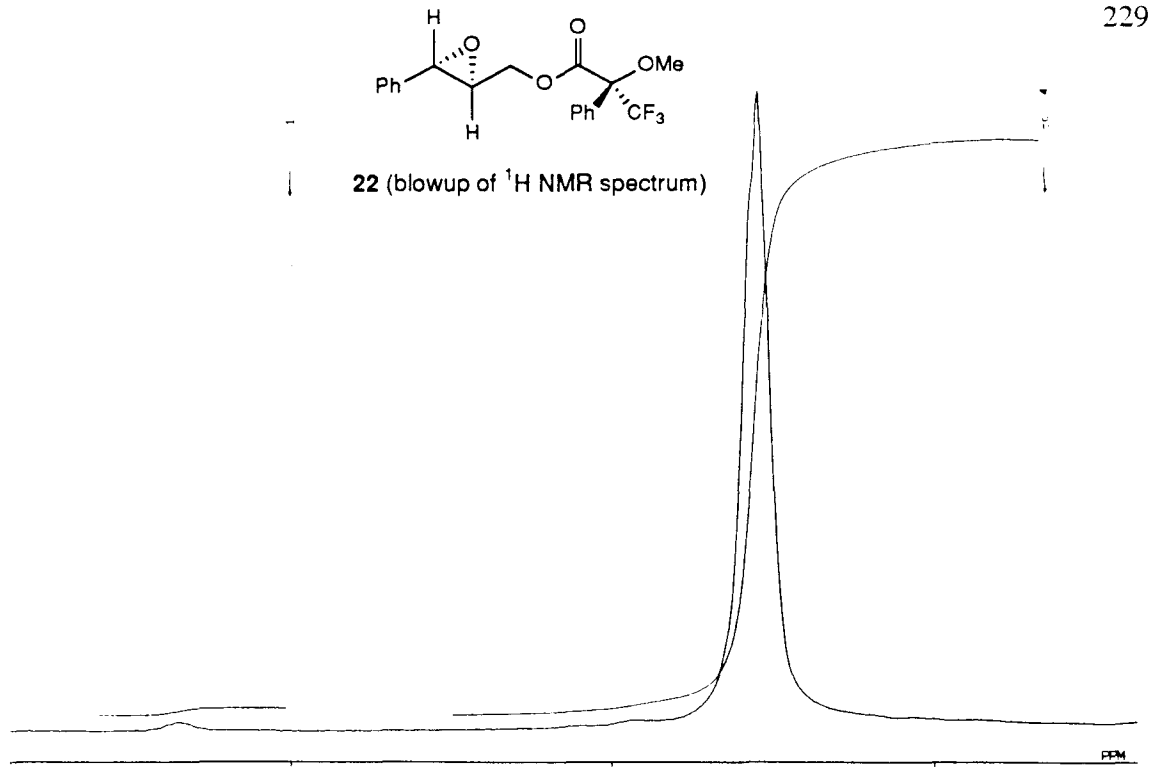
22

9
8
7
6
5
4
3
2
1
0
PPM

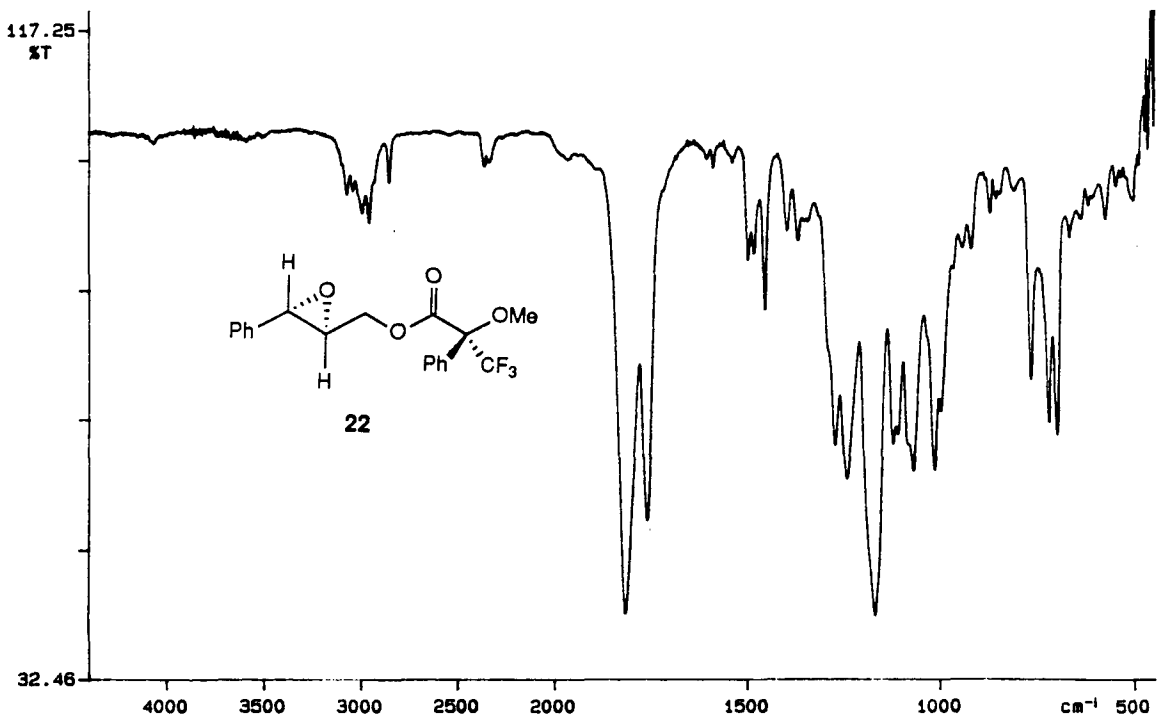

H
O
Ph
O
O
OMe
Ph
CF3
H

24

9
8
7
6
5
4
3
2
1
0
PPM



22 (blowup of ^{1}H NMR spectrum)



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Index of Products for Chapter One

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