Synthetic and Mechanistic Studies on a Silicon-Mediated Aldol Reaction

Thesis by

Susan E. Kephart

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SCHEMES

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List of Abbreviations

Å	angstrom
Ac	acetyl
Ar	aryl
aq	aqueous
bp	boiling point
Bu	butyl
℃	degrees Celsius
C_6D_6	benzene-d_6
CI	chemical ionization
cm^{-1}	reciprocal centimeters
Cy	cyclopropyl
δ	chemical shift in parts per million
d	days
de	diastereomeric excess
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
∈	dielectric constant
E	entgegen
ee	enantiomeric excess
EI	electron impact
equiv	equivalent
Et	ethyl

Et_2O	diethyl ether
EtOH	ethyl alcohol
EtOAc	ethyl acetate
FAB	fast atom bombardment
FT	Fourier transform
g	gram
GC	gas chromatography
H	enthalpy
hr	hour
HMDS	hexamethyldisilazide
HRMS	high resolution mass spectroscopy
Hz	Hertz
i	iso
IR	infrared
J	coupling constant
k	rate constant
kcal	kilocalories
L	liter
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
M	molar (moles/L)
$[M^+]$	molecular ion
Me	methyl
MeOH	methyl alcohol
mg	milligram
MHz	megahertz

min	minute
mL	milliliter
mmol	millimole
mol	mole
mp	melting point
μL	microliter
N	normal (concentration)
nm	nanometer
NMR	nuclear magnetic resonance
p	para
pet. ether	Petroleum ether (bp: 30–60 °C)
pH	hydrogen ion concentration (log scale)
Ph	phenyl
PhCHO	benzaldehyde
PMA	phosphomolybdic acid
ppm	parts per million
Pr	propyl
Py	pyridine
R	rectus
R_f	retention factor
s	seconds
S	entropy
S	sinister
t	tertiary
TBAF	tetrabutylammonium fluoride
tbp	trigonal bipyramid

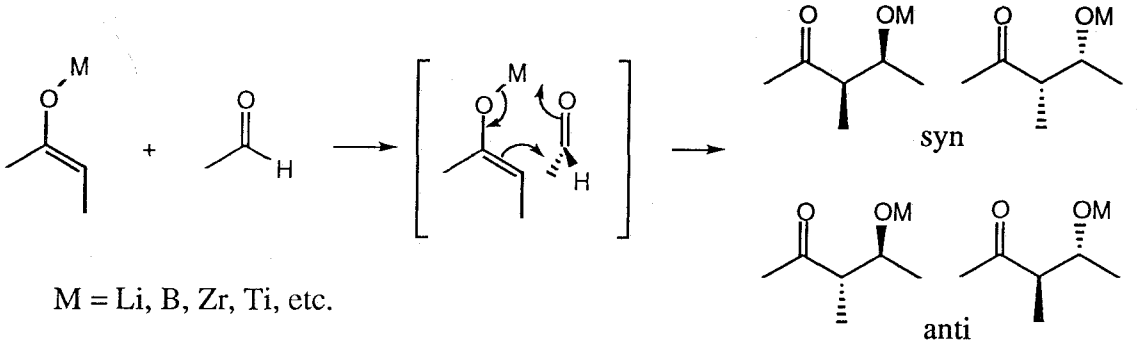
TBS	*tert*-butyldimethylsilyl
TDS	*tert*-butyldiphenyl
tert-	tertiary
Tf	trifluoromethylsulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Torr	millimeters of mercury
UV	ultraviolet
v/v	volume-to-volume ratio
w/v	weight-to-volume ratio
xs	excess
Z	zusammen
Ψ_x	pseudorotation about ligand x

List of Products

38	41	118	237
39	41	122	239
40	41	122	241
41	41	127	243
42	41	127	245
43	41	131	247
44	41	131	249
45	47	158	274
46	47	158	274
47	48	152	270
48	48	153	270
49	48	155	272
50	48	156	272
52	49	161	277
53	49	161	280
54	49	162	280
55	49	162	277
56	51	168	283
57	51	170	285
58	51	172	289
59	51	174	292
60	53	176	294
61	53	176	297

BACKGROUND

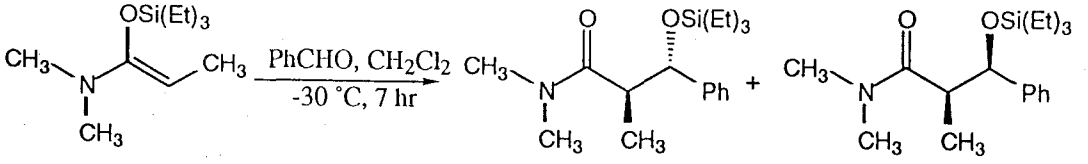
In the past twenty years, the aldol addition reaction has been widely used to form carbon-carbon bonds stereoselectively.[1] Two new chiral centers are formed in this reaction, leading to four possible stereoisomers:



M = Li, B, Zr, Ti, etc.

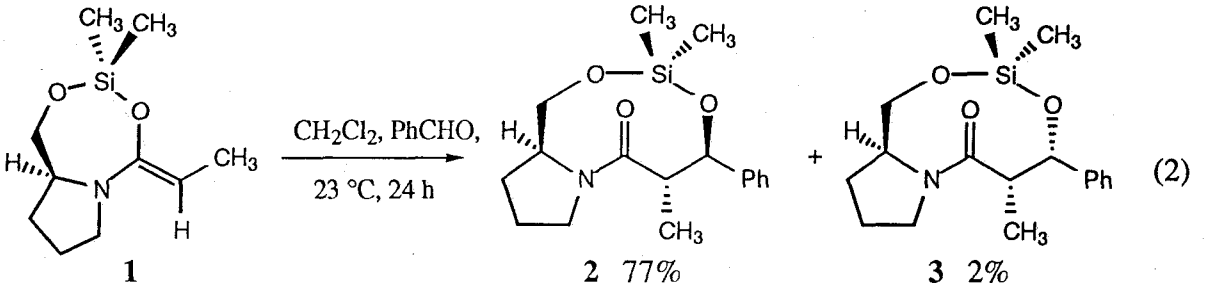
O-silyl enol derivatives of aldehydes, ketones, and esters have been known to form aldol addition products with aldehydes in the presence of a coreactant such as fluoride ion[2] or Lewis acid[3], or at high temperatures.[4] Earlier work in the Myers group has shown that certain *O*-silyl ketene *N,O*-acetals (the *O*-silyl enol derivatives of amides) react with aldehydes to form predominantly anti aldol products.[5] These reactions are uncatalyzed and occur at or below room temperature.

For example, the *O*-triethylsilyl ketene *N,O*-acetal derivative of a simple *N,N*-dimethyl amide reacts cleanly with benzaldehyde at –30 °C to give an 80% yield of a 1.8:1 mixture of anti and syn aldol adducts (reaction 1).[5]



80% 1.8:1 (1)

Stereoselectivity is improved dramatically by the use of a chiral auxiliary. *(S)*-Prolinol-derived *O*-silyl ketene *N,O*-acetal **1** reacts with benzaldehyde at room temperature to form anti aldol product **2** and syn aldol product **3** in a 39:1 ratio (reaction 2).[5]



1 **2** 77% **3** 2% (2)

X-ray crystal structures of **2** and **3** show a very short Si-O distance, suggesting the intermediacy of a pentacoordinate silicon species (Figure 1).

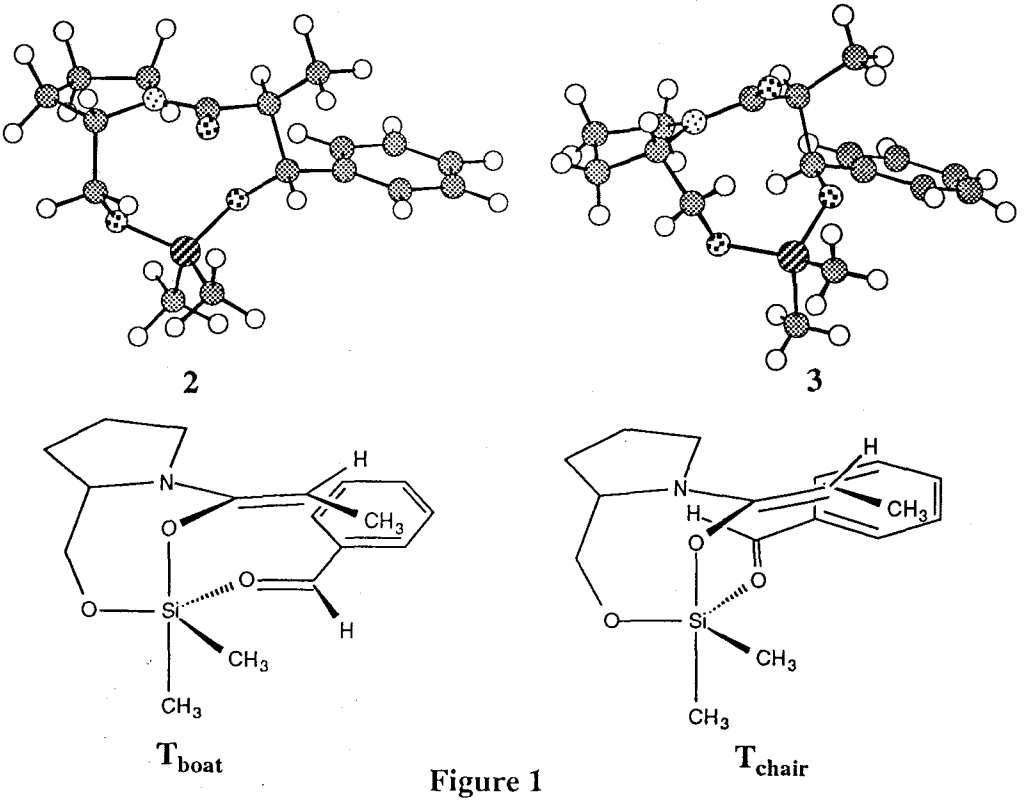


Figure 1

The major, anti product could arise from a trigonal bipyramidal, boat-like transition state (similar to $\mathbf{T}_{boat}$), and the minor, syn product from a chair-like one (similar to $\mathbf{T}_{chair}$). While both proposed structures show bond formation to the same face of the enolate, orbital overlap is proposed to be greater in $\mathbf{T}_{boat}$.

In both $\mathbf{T}_{boat}$ and $\mathbf{T}_{chair}$, the aldehyde is coordinated to the silicon atom in an equatorial position. This coordination mode could be the result of either aldehyde attack on an edge of the ground-state silicon tetrahedron, on attack on a face of the silicon tetrahedron followed by pseudorotation of this axial ligand in to an equatorial position (Figure 2). The original mechanism proposed for this silicon-mediated aldol reaction focused on facial attack followed by pseudorotation because edge attack was thought to be sterically unfavorable.

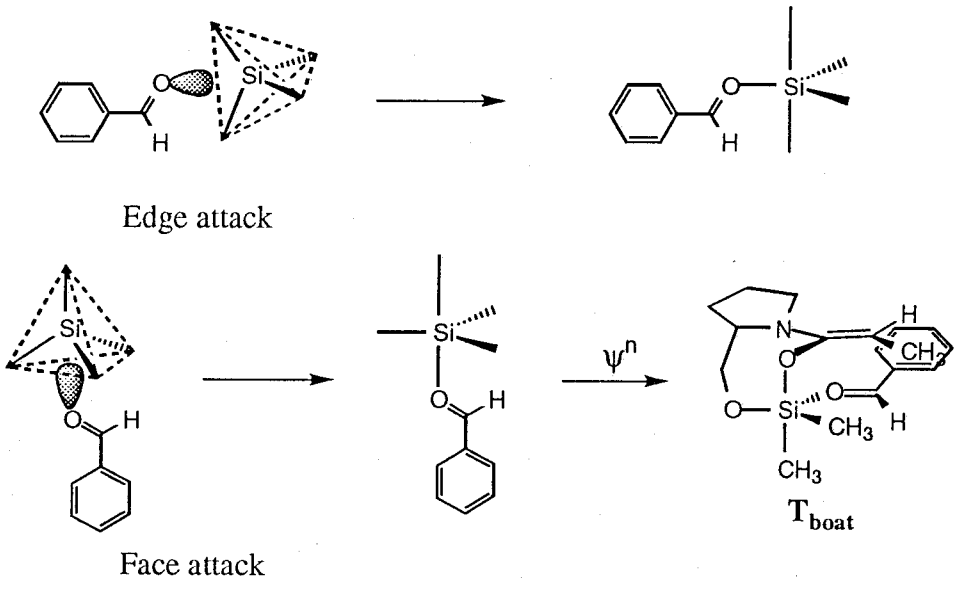


Figure 2

The original mechanism (Figure 3) begins with reversible aldehyde coordination through facial attack, followed by a rapid pseudorotation to place the aldehyde in a

equatorial position. Rate-determining carbon-carbon bond formation then occurs from either T_{boat} or T_{chair} to give the observed aldol products.[6]

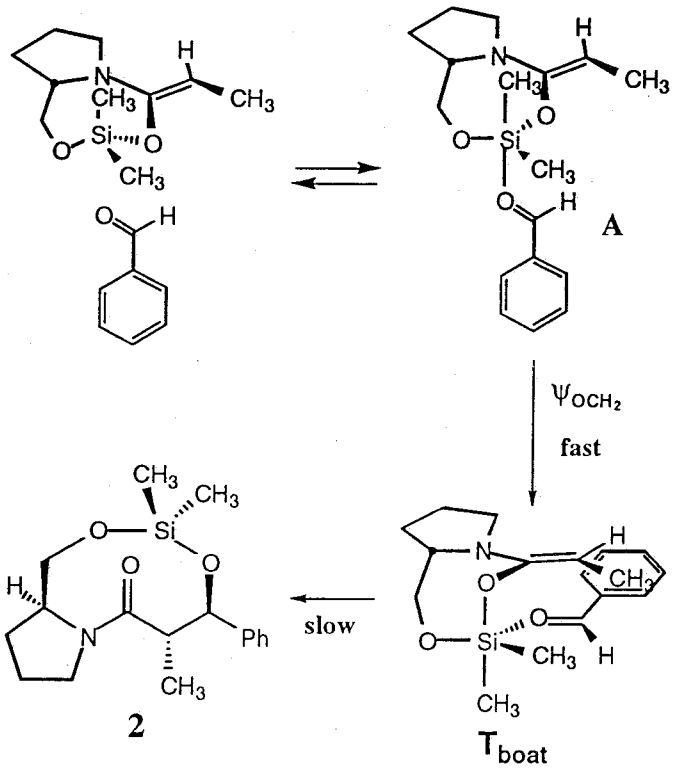


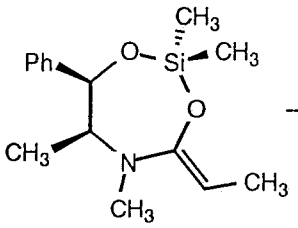
Figure 3: Original Mechanism Proposed for Silicon-Mediated Aldol Reaction

Several pieces of evidence were gathered to support this mechanism. The reaction proceeded well in solvents which were poor σ donors (dichloromethane, benzene, hexane, acetonitrile) but was not observed in coordinating solvents (THF, DMF).[6,7] This implied that aldehyde coordination to silicon did occur. The rate of the reaction was approximately the same in both hexane and acetonitrile.[6] Since these solvents differ greatly in polarity, this supported a transition state which was not highly polar. Kinetic analysis in benzene over a 60 °C range showed the reaction to be rigorously second order, first order in each reactant, with activation parameters $\Delta H^{\ddagger} = 12.0 \pm 0.5$ kcal/mol and $\Delta S^{\ddagger} = -41 \pm 2$ eu.[6]

The reaction order and large negative entropy of activation suggest an associative mechanism.

Competition reactions between benzaldehyde-*d* and benzaldehyde-*h* with **1** yielded a secondary deuterium isotope effect, $k_H/k_D = 0.76 \pm 0.05$, indicating a later transition state involving carbon-carbon bond formation.[6] Kinetic analysis of the reaction of **1** with a series of para-substituted benzaldehydes showed that electron-withdrawing groups accelerate the reaction. A Hammet ρ value of 3.5 ± 0.2 was determined, ruling out rate-determining aldehyde complexation (for which a $\rho < 0$ would be expected).[6] However, the Hammet plot became nonlinear for *p*-nitrobenzaldehyde, possibly suggesting a change in mechanism.

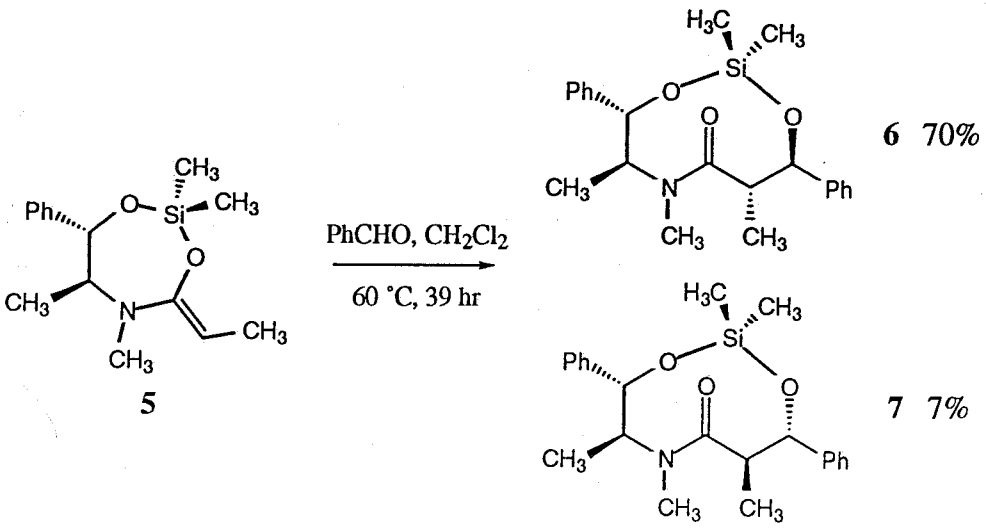
The most subtle argument for the pseudorotational mechanism was based on the differing reactivity of **4**, derived from (–) ephedrine, and its epimer **5**, derived from (+) pseudoephedrine. No reaction of **4** with benzaldehyde was observed under 110 °C.[8] (Reaction 3).



4

PhCHO, Up to 110 °C → **No Reaction Observed** (3)

The pseudoephedrine-derived epimer **5**, however, smoothly adds to benzaldehyde at 60 °C to give the (2*S*, 3*R*)-anti aldol adduct **6** in 70% yield.[6,9] (Reaction 4)



5 (4)

This (apparent) difference in reactivity was difficult to rationalize by considering the proposed transition structures $\mathbf{T_e}$ and $\mathbf{T_p}$ (Figure 4) alone. However, if these structures are the result of a single pseudorotation from the proposed initial trigonal bipyramidal structures $\mathbf{A_e}$ and $\mathbf{A_p}$, the difference can be explained.[6,10] Structure $\mathbf{A_e}$, which would be formed by facial attack of the aldehyde opposite one of the silylmethyl groups, would suffer severe steric interaction between that silylmethyl group and a methyl group on the ephedrine ligand. In contrast, structure $\mathbf{A_p}$ would not experience as great a steric interaction. Thus it was reasoned that the non-reactivity of ephedrine-derived **4** supported the intermediacy of the trigonal bipyramidal structure **A** on the reaction pathway.

This is a very involved argument, and one based on an absence of evidence. More direct evidence was needed to justify the inclusion of structure **A** in the proposed reaction mechanism. This evidence was provided by studying the rate of the silicon-mediated aldol reaction when the silicon atom was incorporated in small rings.

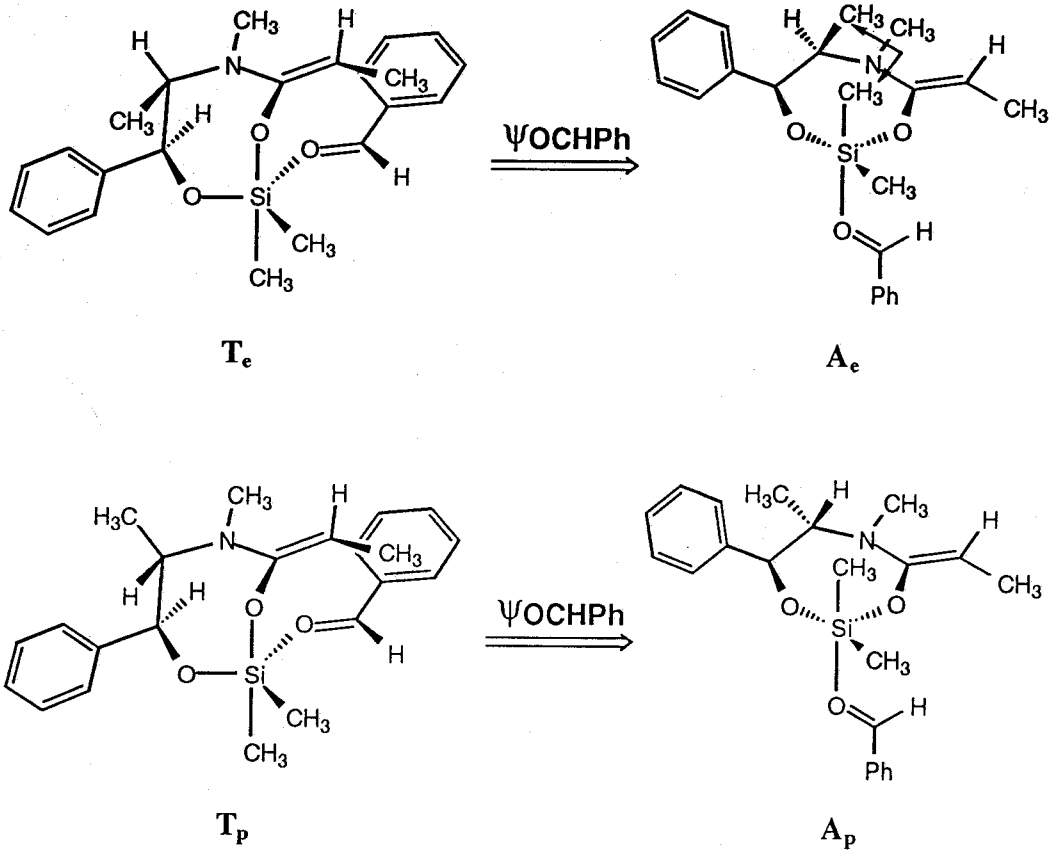


Figure 4: Comparison of ephedrine (top) and pseudoephedrine (bottom) derived silyl ketene *N,O*-acetals in the proposed pseudorotational mechanism

RATE ACCELERATION BY SMALL RINGS

Introduction

Only three of the possible trigonal bipyramidal isomers can form the proposed transition structure **T** by a single pseudorotation. Of those three, only two, structures **A** and **B**, arise directly from aldehyde attack on a face of the silicon tetrahedron.

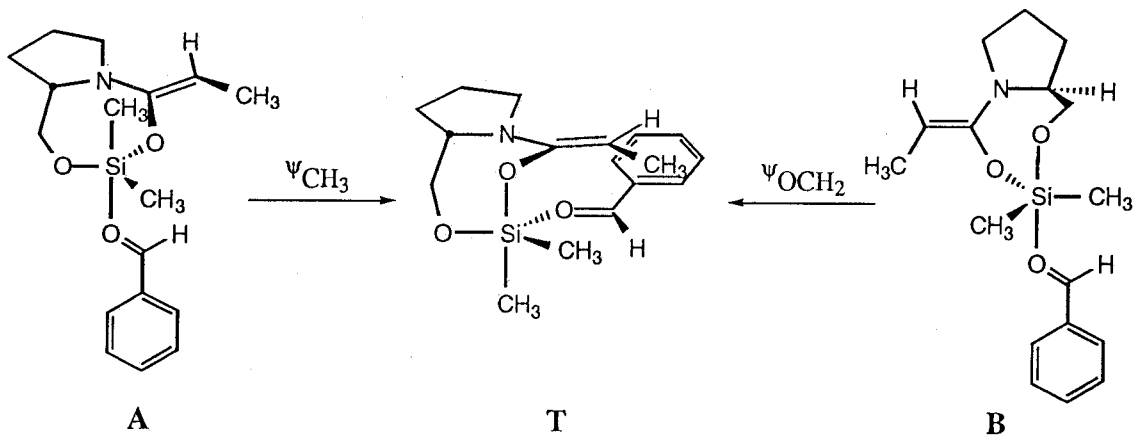


Figure 5

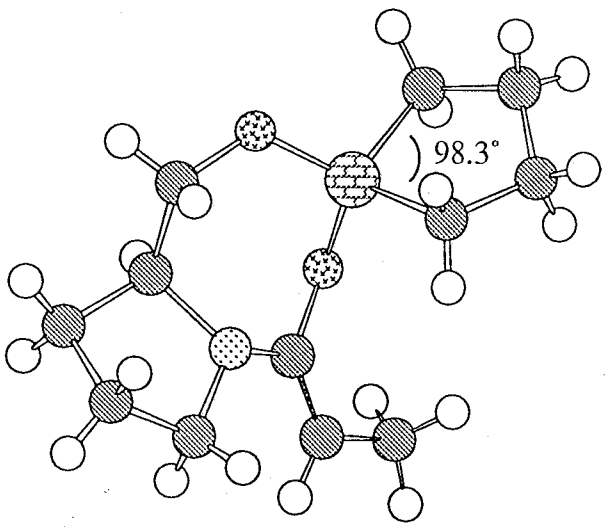
Structure **A** has already been discussed. The most important difference between structure **B** and structure **A** is that both silylmethyl groups occupy equatorial positions in **B**. In the original mechanism shown in figure 3, the angle between these methyl groups is 90° both before and after pseudorotation. A mechanism involving **B** would require that they be separated by 120° on initial attack. If the methyl groups on the silicon atom were replaced by a small (4- or 5-membered) ring, structure **B** would be more strained than the tetrahedral ground state, while trigonal bipyramid **A** would be stablilized relative to the ground state.

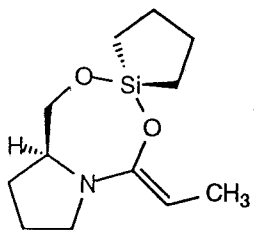
The incorporation of phosphorus in a four- or five-membered ring is known to accelerate tbp formation to relieve ring strain.[11] This causes rate enhancement in reactions

in which the leaving group can attain an apical position through pseudorotation. When this is not possible rate retardation and ring-opening reactions are seen instead. A similar effect is also seen in the basic hydrolysis of 1-methylsilacyclobutane, which is 10^4-10^5 times faster than for triethylsilane.[12] Nucleophilic substitutions of silacyclobutanes are well known, and unlike acyclic or non-strained cyclic silanes, these reactions usually proceed with retention of stereochemistry.[13] Although this has been attributed to equatorial leaving, retention of stereochemistry is also consistent with tbp formation followed by pseudorotation to allow apical leaving.

Silacyclic *O*-silyl ketene *N,O*-acetals

To test the effect of small rings on the silicon-directed aldol reaction, silacyclopentane and silacyclobutane ketene *N,O*-acetals **8** and **9** were prepared in analogy to **1**. Both reacted cleanly with benzaldehyde at accelerated rates to form mixtures of syn and anti aldol addition products (**10-13**).



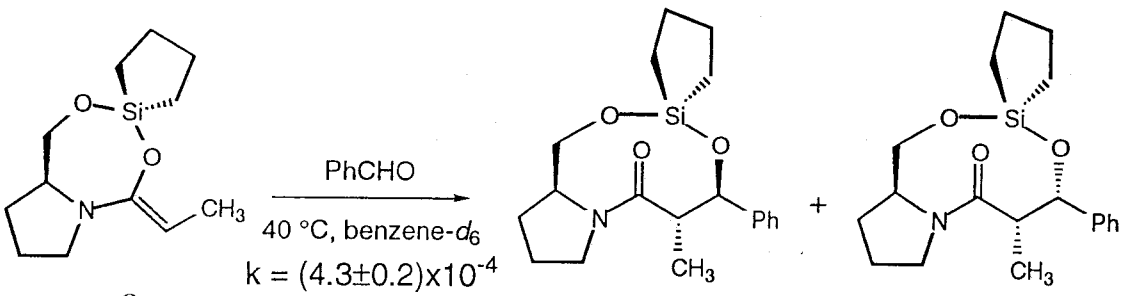


8

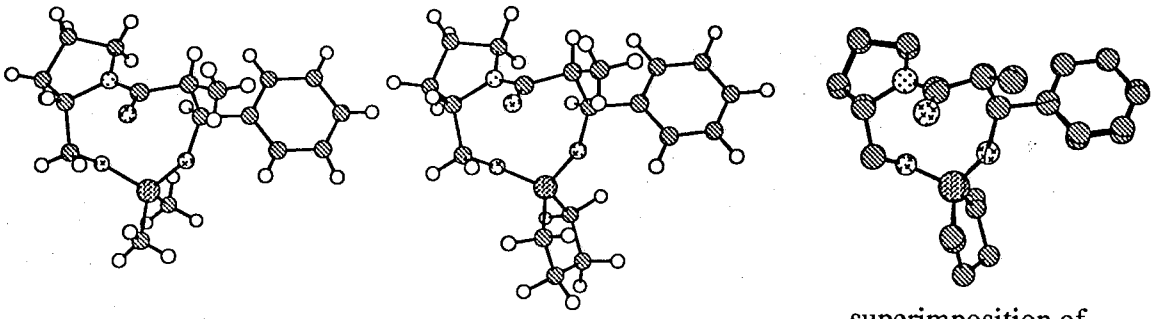
Figure 6: X-Ray structure of silacyclopentane ketene *N,O*-acetal **8**

Silacyclopentane ketene *N,O*-acetal **8**, formed by trapping the dianion of *(S)*-prolinol propionamide with 1,1-dichlorosilacyclopentane, was isolated as moisture-sensitive crystalline solid. X-ray crystal structure analysis performed by Dr. Joseph Ziller (University of California, Irvine) confirmed the *Z*-geometry of the double bond (Figure 6). Interestingly, the amide nitrogen is somewhat distorted from the expected planar hybridization.

Kinetic studies (^{1}H NMR) of the addition of this slightly strained ($<CH_2$-Si-CH_2 = 98.3°) ketene *N,O*-acetal to benzaldehyde at 40 °C show approximately a tenfold rate acceleration over that of the dimethyl analog[10] at the same temperature ($k_8 = 4.3 \pm 0.2 \times 10^{-4}$ $M^{-1}s^{-1}$; $k_1 = 4.2 \pm 0.9 \times 10^{-4}$ $M^{-1}s^{-1}$). Unlike the dimethyl compound, which was strongly anti selective, the ratio of aldol addition products **10** and **11** is 1:1 (reaction 5)[14].

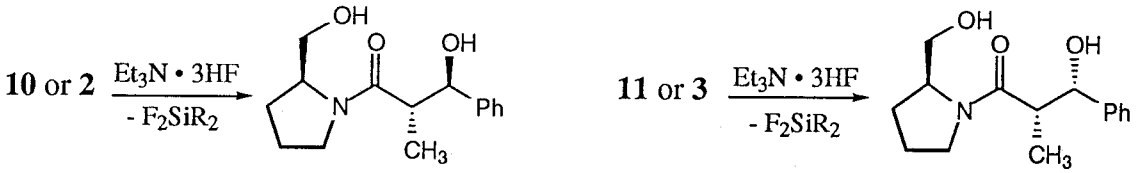


Although the NMR spectra of **10** and **11** were extremely similar to those of the corresponding dimethyl compounds, an independent determination of the absolute stereochemistry was desired. Fortunately, these aldol products were somewhat stable to silica gel and could be isolated by column chromatography. Anti adduct **10** was more sensitive to hydrolysis and decomposition, but syn adduct **11** proved stable enough to obtain an X-ray structure.[15] The *(S,S,S)* stereochemistry and nine-membered ring conformation are essentially identical to that of dimethyl adduct **3**[16]:



3 **11** superimposition of **3** and **11**

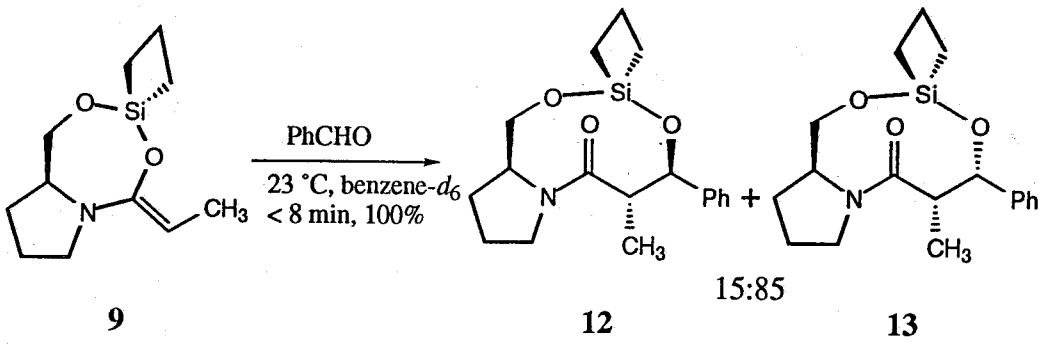
X-ray quality crystals of **10** could not be prepared, but desilylation of both **10** and its anti dimethyl analog **2** yield the identical anti diol **14.** Desilylation of both **11** and **3** yield identical syn diol **15.**



14 **15**

Despite the change in stereoselectivity, which will be considered later, the structural similarity of the products indicates that there is no other change in the reaction mechanism. Thus, the moderately strained five-membered ring accelerates the silicon-directed aldol reaction, presumably by stabilizing the initially formed trigonal bipyramidal structure **A** relative to the strained ground state.

A more dramatic effect is seen in the aldol reaction of the silacyclobutane homolog. Ketene *N,O*-acetal **9** results from trapping the *(S)*-prolinol propionamide dianion with 1,1-dichlorosilacyclobutane. When reacted with an equimolar amount of benzaldehyde (0.25 M in C_6D_6) at room temperature, the addition is complete almost immediately. In this case, the reaction is syn selective by almost 6 to 1 (reaction 6).[14]



(6)

9 **12** **13**

Kinetic analysis (^{1}H NMR) of this reaction was carried out at –80 °C. At this temperature the rate ($k_9 = 2.6 \pm 0.1 \times 10^{-4}$ $M^{-1}s^{-1}$)[14] is even faster than that of the dimethyl analog[10] at 60 °C ($k_1 = 1.5 \pm 0.2 \times 10^{-4}$ $M^{-1}s^{-1}$). The activation parameters determined for **1** over the range 20-80 °C ($\Delta H^{\ddagger} = 12.0 \pm 0.5$ kcal/mol and $\Delta S^{\ddagger} = -41 \pm 2$ eu)[6] can be used to extrapolate the rate of this reaction at –80 °C. The calculated value ($k_1 \sim 1.2 \times 10^{-10}$ $M^{-1}s^{-1}$) is six orders of magnitude smaller than that of the silacyclobutane compound, indicating remarkable effect of the small ring. By incorporating the silicon atom in a four-membered ring, a million fold rate acceleration was achieved.

Silacyclobutane ethers **12** and **13** were so sensitive to hydrolysis that they could not be isolated themselves, but desilylation of the crude reaction mixture gave syn diol **15** in 80% yield. No anti diol was recovered, however. This might be due to decomposition of anti adduct **12** before hydrolysis, perhaps through a retro-aldol mechanism. As will be discussed in the next section, retro-aldol reactions were observed in the desilylation of silacyclobutane enol ether-derived aldol products. Like the silacyclopentane adducts, the NMR spectra of the silacyclobutane adducts **12** and **13** are extremely similar to those of their dimethyl analogs, for which the absolute stereochemistry is known. Assuming that silacyclobutane ketene *N,O*-acetal **9** follows the same reaction path as **1** in its addition to benzaldehyde, it is possible to rationalize the change in stereoselectivity with respect to the original pseudorotational mechanism.

The trend seen in the reactions of these three prolinol-derived *O*-silyl ketene *N,O*-acetals is that increased ring strain leads to increased syn selectivity. Dimethyl silyl **1** is overwhelmingly anti selective (syn:anti = 2:98), its silacyclopentane analog **8** is non-selective (syn:anti = 50:50), and silacyclobutane derivative **9** is moderately syn selective (syn:anti = 85:15). If all three are assumed to follow the proposed reaction path, the hypothetical transition state structures can be examined for causes. Figure 7 shows structures T_{boat} and T_{chair} and their analogs for the silacyclobutane case, T_{boat}' and T_{chair}'.

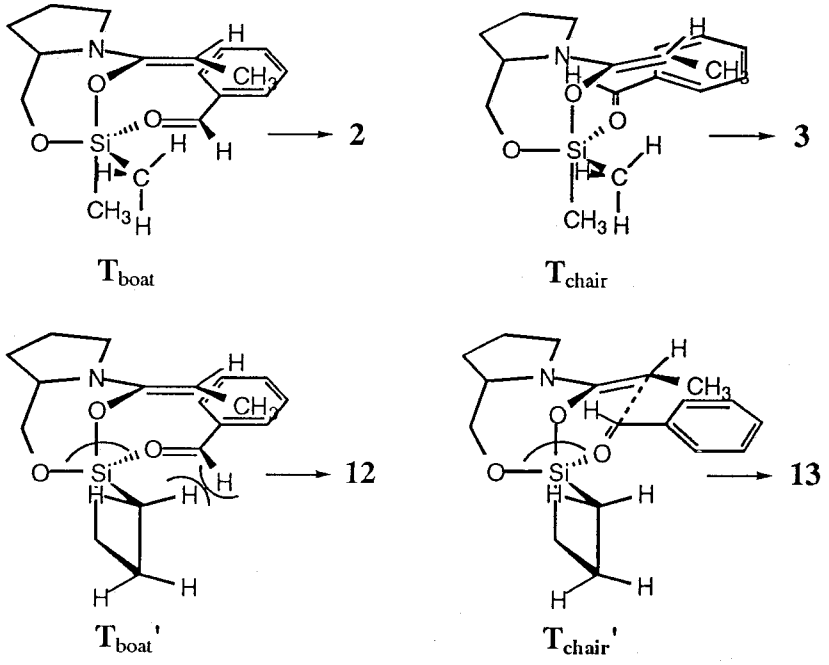


Figure 7: Comparison of proposed transition structures for the reactions of **1** and **9** with benzaldehyde

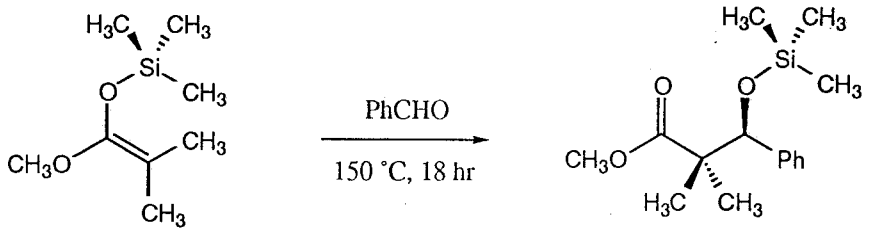
In the dimethyl case, steric repulsion between the methyl groups may force the C-Si-C angle to be greater than 90°, causing the equatorial O-Si-O angle to be distorted to less than 120°. This shift would increase π-overlap in the boat conformation, but decrease

π-overlap in the chair conformation. Thus anti products predominate. In the silacyclobutane case, the C-Si-C angle would be much closer to 90°, so the equatorial O-Si-O angle may be wider than before. This improves π-overlap in the chair conformation, making carbon-carbon bond formation more favorable for structure T_{chair}' than for structure T_{chair}. In addition, the ring hydrogens would now be constrained to lie close to the equatorial plane, where steric repulsion with the aldehyde proton may become significant.[17] Along with this steric repulsion, the greater O-Si-O bond angle would reduce overlap in the boat conformation. Both of these factors disfavor anti product formation, so the reaction becomes syn selective. The silacyclopentane case lies between these two extremes. The ring hydrogens would not be as close to the equatorial plane, but the C-Si-C bond angle may remain somewhat distorted. The 1:1 ratio of syn and anti products indicates that, for this substrate, the proposed chair-like and boat-like transition states may be approximately equal in energy.

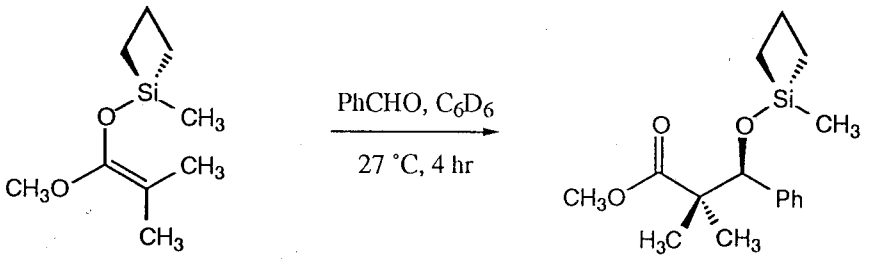
Incorporation of the silicon atom in a small ring was found to accelerate the silicon-directed aldol reaction of *O*-silyl ketene *N,O*-acetals derived from *(S)*-prolinol propionamide. This supports the proposed reaction pathway in which the silicon-bound alkyl groups remain disposed apically-equatorially rather than the pathway in which they are, even temporarily, disposed diequatorially. The rate acceleration is accompanied by a dramatic change in stereoselectivity, which can be rationalized by considering distortion of the tbp-like transition state by the small ring and by steric interactions between ring and aldehydic hydrogens. The million-fold rate acceleration seen with the silacyclobutane functional group suggested that the rates of other carbon-carbon bond forming reactions involving pentavalent silicon could also be enhanced. The next step was to apply this aldol methodology to the reactions of other carbonyl-derived organosilicon species, specifically silyl enol ethers of ketones and esters.

Silacyclobutane silyl enol ethers

Amide enolates are generally more nucleophilic than ester or ketone enolates, so it was uncertain if the silacyclobutane methodology could be used to make this uncatalyzed silicon-directed aldol reaction feasible for less reactive carbonyl compounds. The reaction of *O*-trimethylsilyl ketene acetals derived from esters with aromatic aldehydes at very high temperatures had been reported[4], and work by others both inside and outside the Myers group has shown that *O*-silacyclobutane ketene acetals do react faster and at lower temperatures than their non-cyclic analogs.[14,18] For example, the reaction of *O*-trimethylsilyl ketene acetal **16** with benzaldehyde is reported to require heating at 150 °C (neat, 18 hr) for completion and affords the addition product **17** in 81% yield.[4] (Reaction 7) In contrast, the methylsilacyclobutane derivative **18** reacted completely and cleanly with benzaldehyde within 4 hours at 27 °C (0.2 M each, benzene) to give adduct **19** quantitatively.[14] (Reaction 8)



16 **17** 81% (7)



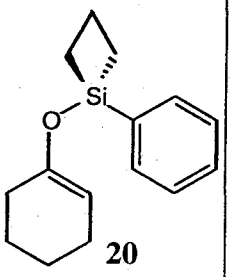
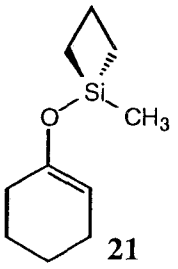
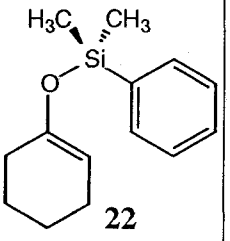
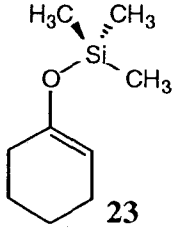
18 **19** 100% (8)

No precedent was available for the thermal, non-catalyzed aldol reaction of ketone silyl enol ethers with aldehydes, so it was uncertain if even a 10^6 rate acceleration due to a silacyclobutane group would make the reaction energetically accessible.

Cyclohexanone was chosen as the first enol ether precursor for study because the enolate geometry is constrained to be *E*, and because many references are available on catalyzed reactions of its trimethylsiloxy derivative. Enolization with lithium diisopropylamide followed by trapping with the appropriate trialkyl silyl chloride gave silacyclobutane enol ethers **20** and **21** as well as dimethylphenyl silyl **22**, which was used as a control. The TMS enol ether **23** is commercially available. 1-Phenyl silacyclobutane enol ether **20** was observed to react with benzaldehyde at room temperature, although very slowly ($t_{1/2}$ ~4 days, 0.8 M each, C_6D_6) to give predominantly syn products (12:1 syn:anti). This promising result led to a series of sealed-tube reactions carried out at higher temperatures. The results are summarized in table 1.

As anticipated, the dimethylalkyl enol ethers did not react, even at elevated temperatures. Dimethylphenylsilyl enol ether **22** showed slow hydrolysis to cyclohexanone, while trimethylsilyl enol ether **23** remained unchanged even after eight days at 150 °C. The phenylsilacyclobutane enol ether **20** was more reactive and more selective than the methyl-substituted analog **21**, indicating a possible electronic effect. The increased susceptibility to hydrolysis of **22** over **23** may also be a manifestation of this effect.

Table 1. Sealed tube reactions of cyclohexanone enol ethers with aldehydes[a]

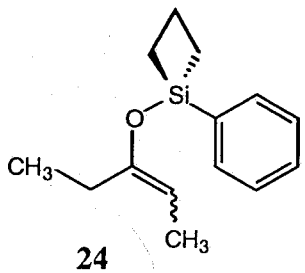
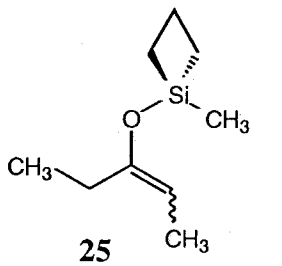
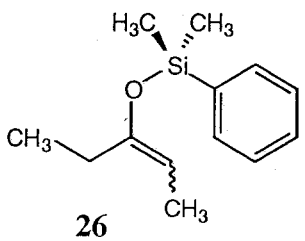
Enol Ether	Benzaldehyde	Isobutyraldehyde
 **20**	100 °C, 33.5 hr 88% yield (0% unreacted) 5.0:1 syn:anti syn: 5.78[c] (d, J = 3.2 Hz) anti: 5.37 (d, J = 8.1 Hz)	100 °C, 337 hr 58% yield (9% unreacted) 1.6:1 syn:anti[b] syn: 4.05 (dd, J = 3.0, 8.4 Hz) anti: 4.73 (dd, J = 4.5, 6.0 Hz)
 **21**	100 °C, 84 hr 100% yield (0% unreacted) 2.1:1 syn:anti syn: 5.70 (d, J = 3.1 Hz) anti: 5.32 (d, J = 7.8 Hz) Si–CH_3: syn 0.32, anti 0.29	100 °C, 303 hr 32% yield (49% unreacted) 1.4:1 syn:anti[b] syn: 4.00 (dd, J = 2.7, 8.1 Hz) anti: 4.13 (dd, J = 4.2, 6.6 Hz) Si–CH_3: syn 0.47, anti 0.39
 **22**	150 °C, 201.5 hr NO ALDOL PRODUCTS (71% unreacted)[d]	150 °C, 201.5 hr NO ALDOL PRODUCTS (81% unreacted)[d]
 **23**	150 °C, 201.5 hr NO ALDOL PRODUCTS (100% unreacted)	150 °C, 201.5 hr NO ALDOL PRODUCTS (100% unreacted)

[a]0.5 M solutions in C_6D_6, 0.1 M *cis*-dichloroethylene used as internal standard. [b]Stereochemical assignments for isobutyraldehyde adducts based on coupling constants. [c]Chemical shift for the formerly aldehydic proton in parts per million, relative to *cis*-dichloroethylene δ=5.605 ppm. [d]Hydrolysis to cyclohexanone observed.

The silacyclobutane enol ethers reacted much faster with benzaldehyde than with isobutyraldehyde, and with greater stereoselectivity. The syn and anti assignments of the benzaldehyde adducts have been confirmed by desilylation and comparison of the melting points, NMR chemical shifts, and FTIR spectra to the literature values for the resulting β-keto alcohol. Desilylation of the isobutyraldehyde adducts, however, led to decomposition by retro-aldol reactions. Thus, the syn and anti assignments are based on the coupling constants, in analogy to those reported for the aldol adducts of trimethylsiloxy cyclopentene and isobutyraldehyde: *erythro* (syn) 3.80, d, J = 8 Hz; *threo*(anti) 3.56, dd, J = 4, 7 Hz (CCl_4).[19] These assignments also correlate the shifts of the silyl methyl singlets for the aldol adducts of **21**. The anti singlet appears at higher field than the syn in the benzaldehyde case, and this relationship is also seen in the isobutyraldehyde case as assigned based on coupling constants.

Silyl enol ethers of 3-pentanone were studied next to determine the effect of double bond geometry on the aldol reaction. Kinetic deprotonation of 3-pentanone by lithium diisopropylamide and trapping the enolate mixture with 1-phenyl or 1-methyl-1-chlorosilacyclobutane gave enol ethers **24** and **25** with isomer ratios ~2:1 *E* to *Z*. The same procedure was used to generate dimethylphenyl silyl enol ether **26**, but distillation of the crude enol ether caused isomerization to a mixture which was 4:1 *Z* to *E*. A *Z*-rich mixture of enol ether **24** was adventitiously obtained when a second batch isomerized on distillation. Presumably, these isomerizations were caused by basic impurities present during distillation. Table 2 summarizes the results of a series of sealed-tube reactions of these enol ethers.

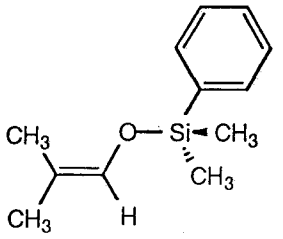
Table 2. Sealed-tube reactions of 3-pentanone enol ethers with aldehydes[a]

Enol Ether	Benzaldehyde	Isobutyraldehyde
 **24**	15:85*E/Z* 100 °C, 92.5 hr 86% yield (0% unreacted) 2.8:1 syn:anti 66:34*E/Z* 100 °C, 103.4 hr 95% yield (5% unreacted) 7.6:1 syn:anti syn: 5.23[c] (d, J = 6.9 Hz) anti: 5.04 (d, J = 9.6 Hz)	100 °C, 243 hr 64% yield (28% unreacted) 4.2:1 anti:syn[b] 100 °C, 103.5 hr 64% yield (30% unreacted) 2.6:1 anti:syn syn: 3.96 (dd, J = 2.4, 9.0 Hz) anti: 4.00 (dd, J = 5.0, 6.4 Hz)
 **25**	69:31*E/Z* 100 °C, 196 hr 86% yield (14% unreacted) 5.3:1 syn:anti syn: 5.12 (d, J = 7.0 Hz) anti: 4.91 (d, J = 9.6 Hz) Si–CH_3: syn 0.17, anti 0.11	100 °C, 197 hr 32% yield (35% unreacted) 1.5:1 anti:syn syn: 3.85[d] (dd, J = 2.4, 9.3 Hz) anti: 3.89 (dd, J = 5.1, 6.3 Hz) Si–CH_3: syn 0.25, anti 0.21
 **26**	20:80*E/Z* 150 °C, 201.5 hr NO ALDOL PRODUCTS (73% unreacted)[e]	150 °C, 201.5 hr NO ALDOL PRODUCTS clean reaction to 3-pentanone and new product

[a]0.5 M solutions in C_6D_6, 0.1 M *cis*-dichloroethylene used as internal standard. [b]Stereochemical assignments for isobutyraldehyde adducts based on coupling constants. [c]Chemical shift for the formerly aldehydic proton in parts per million relative to *cis*-dichloroethylene δ=5.605 ppm. [d]Chemical shift of formerly aldehydic proton in parts per million, relative to benzene-d_6 δ=7.150 ppm. [e]Hydrolysis to 3-pentanone is observed.

As before, the stereochemical assignments for the isobutyraldehyde adducts are based on the coupling constants, in this case in analogy to those reported for the corresponding alcohol: *erythro* (syn) 3.48, dd, J = 3, 8 Hz; *threo*(anti) 3.41, t, J = 7 Hz.[20] The non-cyclic control **26** did not react with benzaldehyde after eight days at

150 °C, but it did react with isobutyraldehyde to produce the starting 3-pentanone and a new, silicon-bearing product. This reaction was complete after 83 hours, and showed no change on extended heating. This new product could be the enol ether of isobutyraldehyde:



New product?

The reaction of silacyclobutane enol ethers **24** and **25** with isobutyraldehyde was considerably slower and much less syn selective than with benzaldehyde. In fact, these reactions were anti selective, even more so than the cyclohexanone enol ethers. Their reactions with benzaldehyde, however, were still moderately syn selective. The phenyl-substituted silacyclobutane was once again more reactive than the methyl-substituted equivalent.

The enolate geometry has a noticeable effect on the rate and stereoselectivity of these reactions. In every case, the *E* isomer was consumed faster than the *Z* isomer. For example, in the reaction of the *Z*-rich mixture of **24** with benzaldehyde, all the *E* isomer was consumed after only 9.5 hours, only one-tenth the total reaction time. In the reaction with the *E*-rich mixture, the *E*-isomer was consumed in the first 39 hours. The greater reactivity of the *E* isomer is consistent with the shorter reaction times seen for the cyclohexanone-derived silyl enol ethers. Assuming no isomer interconversion, the stereoselectivity of each isomer is also different, which can be rationalized by the proposed pseudorotational mechanism.

It was proposed in the discussion of the amide-derived ketene *N,O*-acetals that a *Z* isomer would react from a boat-like transition state to give anti products and from a chair-like transition state to syn products. For the *E* isomer, this situation is reversed, and the boat-like transition state would give the syn adduct. In the reactions of **24** with benzaldehyde, the greater overlap of the boat transition state seems to determine the syn selectivity of the *E* isomer, while the weak syn selectivity of *Z* isomer is attributable to the destabilization of the boat conformation by steric interference from the ring hydrogens as discussed earlier. The anti selectivity of both isomers in the reactions with isobutyraldehyde may be due to the steric bulk of the isopropyl group.

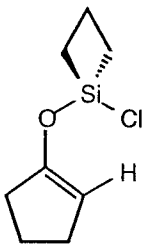
One question which remains unresolved is whether the *Z* enol ethers are reacting directly, or whether they first equilibrate to *E* isomers under reaction conditions. Since *E* to *Z* isomerization was a problem on distillation of the enol ethers, it is possible that isomerization in the reverse direction could also occur. During the course of the sealed-tube reactions, the *E/Z* ratio was observed to decrease uniformly. Fast isomer equilibration followed by a slower reaction of the *E* isomer with aldehyde would be expected to show a constant *E/Z* ratio. However, slow isomer equilibration followed by fast consumption of *E* enol ether would show consumption of the two isomers at different rates as seen. To determine whether slow isomer equilibration occurs, a sealed sample of the *E*-rich mixture of **24** was studied by high temperature ^{1}H NMR under reaction conditions. The spectrum showed no change in the isomer ratio, chemical shifts, or peak shapes up to 90 °C (monitoring above 90 °C was hampered by the solution refluxing in the tube above the level of the probe). Furthermore, the isomer ratio after heating to 100 °C for 2 hours was identical to the room temperature ratio. Attempts to observe spin saturation transfer[21] at 75 °C were inconclusive.

In summary, the rate accelerating effect of the silacyclobutane group was studied in the reactions of ketone-derived silyl enol ethers, and shown to induce the silicon-directed

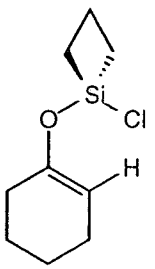
aldol reaction in ordinarily unreactive carbonyl species. Even so, the reaction rates are very slow, even at 100 °C, and diastereoselectivity is modest. The reaction is cleaner and faster with benzaldehyde; addition to isobutyraldehyde is plagued by side reactions and impractically slow rates. Furthermore, the stereochemistry of the isobutyraldehyde adducts needs to be resolved. Enol ether geometry has a significant effect on the rate and stereoselectivity, as shown in the reactions of 3-pentanone-derived enol ethers. The *E* isomer is more reactive and more syn-selective, which suggests preference of the boat-like transition state, although the chair-like transition state is favored in some cases.

Silacyclobutanes with electron-withdrawing substituents

The increased reactivity of phenyl-substituted silacyclobutane enol ether **20** over its methyl-substituted analog **21** suggested that electron-withdrawing groups on silicon might accelerate the reaction by making the silicon center more susceptible to nucleophilic attack. To test this, chlorine-substituted silacyclobutane enol ethers **27** and **28** were synthesized.



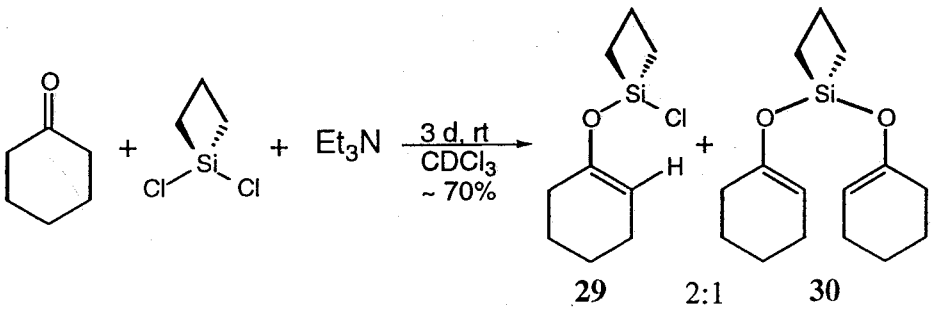
27



28

Enol ethers **20** and **21** had been obtained by enolization of cyclohexanone with lithium diisopropylamide and trapping of the lithium enolate with the appropriate 1-alkyl-1-chlorosilacyclobutane. For **27** and **28**, however, a procedure using milder, trialkylamine bases was developed. Early NMR experiments showed that cyclohexanone and

dichlorosilacyclobutane reacted in the presence of an equivalent of triethylamine to give two enol ether products, **29** and **30** (reaction 9). No reaction was seen in the absence of triethylamine.



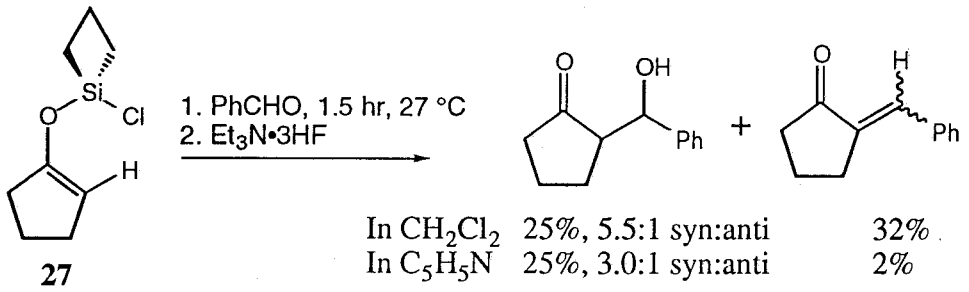
29 2:1 **30** (9)

Several experiments to optimize this reaction were performed. The order of addition was shown to have little effect on the rate or product distribution. As well as triethylamine, diisopropylethylamine, *N*-methylpiperidine, and pyridine each acted as effective bases. Pyridine was chosen for further study because the byproduct, pyridinium chloride, was insoluble and thus the enol ether products were easier to observe by NMR. The effect of amine stoichiometry was also studied. In the presence of one to five equivalents of pyridine, a product ratio of about 6:1 of **29** and **30** was obtained. However, in pyridine as solvent, only the monoadduct, **29** was observed.

Enol ethers **27** and **28** were isolable in moderate yield (see experimental) Although chlorine substitution could not be confirmed by NMR, when added to one equivalent of silver triflate both immediately form an insoluble white precipitate. The mass spectra of these compounds are also consistent with the proposed silyl chloride structures.

Both **27** and **28** react with benzaldehyde at room temperature (reactions 10 and 11). Since the silylated aldol adducts were unstable to column chromatography, desilylation with fluorine and isolation of the β-keto alcohols was used to determine the stereoselectivities of these reactions. Cyclohexanone enol ether **28** was somewhat anti

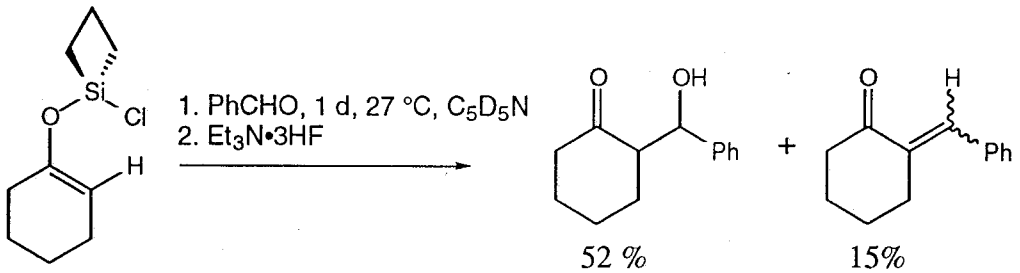
selective (1:2.1 syn:anti) while cyclopentanone enol ether **27** was syn selective (5.5:1 syn:anti). Both reactions also produced significant amounts of the α,β-unsaturated ketone, possibly from an HCl catalyzed elimination. When **27** was reacted in pyridine rather than methylene chloride, formation of the enone was suppressed (2% rather than 32%). Pyridine could serve as an HCl trap by forming insoluble pyridinium chloride. As expected, chlorine substitution on silicon led to rate acceleration. The room-temperature half life in the reaction of **20** with benzaldehyde is about four days; for **28** it is less than one day.



27

In CH_2Cl_2 25%, 5.5:1 syn:anti 32%
In C_5H_5N 25%, 3.0:1 syn:anti 2%

(10)



28

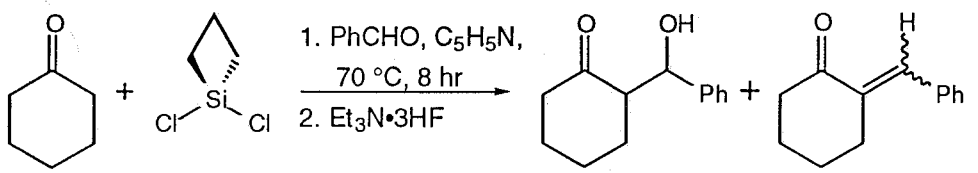
52 %
syn:anti = 1:2.1

15%

(11)

Since the aldol addition was rapid compared to enol ether formation, a one-pot enolization-aldol procedure was developed. For example, dichlorosilacyclobutane, cyclohexanone, and benzaldehyde were stirred in pyridine for eight hours at 70 °C. On desilylation, the β-keto alcohols were obtained in 52% yield and the enone in 29% yield (reaction 12). This procedure, however, led to little stereoselectivity. Product ratios were

generally 1:1.5 syn:anti. No reaction was seen in the absence of dichlorosilacyclobutane or with either isobutyraldehyde or pivalaldehyde. In the latter two cases, only enol ether formation was observed. Similar results were obtained using dimethyldichlorosilane. Heating for 29 hours at 50 °C led to 50% yield of the aldols (1:1.9 syn:anti) and 11% of the enone.



(12)

52%
29%
syn:anti = 1:1.6

Silacyclobutane enol ethers with substituents even more electron-withdrawing than chlorine were also desired. Silacyclobutane compounds bearing *tert*-butoxy and diisopropyl amine groups had been isolated before, but attempted syntheses of silacyclobutane triflates from triflic acid or triflic anhydride had led to ring opening rather than substitution on silicon.[22] Thus, an alternate substitution procedure using silver triflate was developed.

To test whether silver triflate would displace a silacyclobutane-bound chlorine atom, dichlorosilacyclobutane itself was reacted with two equivalents of dry silver triflate. After only five minutes at room temperature, the product, a dense colorless liquid which could be distilled and handled under argon but fumed violently on exposure to air, was formed in 82% yield. The ^{13}C NMR of this liquid shows a characteristic trifluoromethyl quartet and only two other signals. The mass of the liquid recovered is too great to be due to a mono-triflate product, so this liquid is assumed to be silacyclobutane ditriflate.

Unfortunately, satisfactory mass spectral data on this very reactive product could not be obtained.

A mixture of cyclohexanone-derived enol ether **28** in pyridine-d_5 and silver triflate was allowed to equilibrate for two hours and then treated with benzaldehyde (2 days, 27 °C). After desilylation, the β-keto alcohols were isolated in 37% yield with a 1:1 syn:anti ratio and the enone isolated in 1% yield. Compared to the same reaction without triflate substitution (only 1 day at 27 °C, 52% aldol adducts, 15% enone), this does not seem to be an improvement.

The chloride and triflate-substituted silacyclobutane enol ethers, while more reactive that their alkyl-substituted analogs, gave poor stereoselectivity in their reactions with benzaldehyde and no reaction with other aldehydes. These reactions were plagued by elimination of the aldol adducts to α,β-unsaturated ketones, although the amount of elimination could be reduced by using pyridine as solvent.

KINETIC ISOTOPE EFFECT - NITROBENZALDEHYDE

Previous experiments had determined a kinetic isotope ratio of $k_H/k_D = 0.76$ for the reaction of **1** with benzaldehyde.[6] This, along with other evidence, suggested that the transition state for this reaction involved carbon-carbon bond formation. The theoretical minimum kinetic isotope effect is 0.71, in the case of rate-determining rehybridization of a carbon atom from sp^2 to sp^3. A late transition state was also supported by the determination of a Hammet ρ value of 3.5 for the reaction of *para*-substituted benzaldehydes with **1**.[6] If aldehyde coordination were the rate-determining step, electron-withdrawing substituents would be expected to slow the reaction, leading to a negative ρ value. For *para*-nitrobenzaldehyde, however, the Hammet plot became non-linear, possibly indicating a change of mechanism to rate-limiting aldehyde complexation.

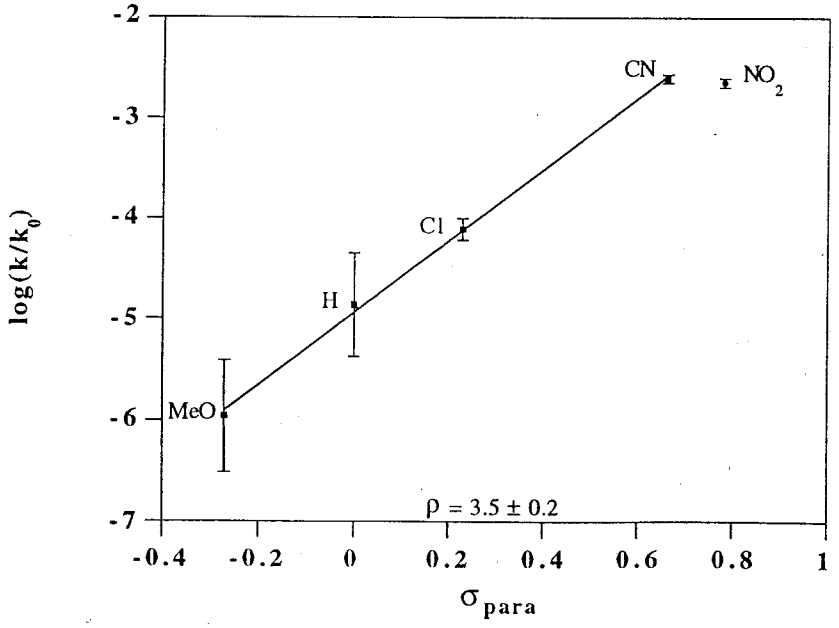
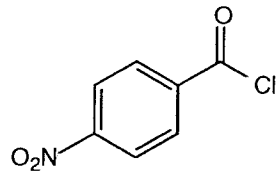
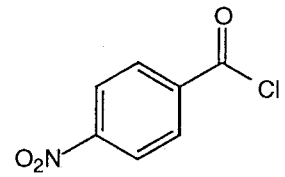
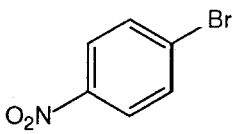


Figure 8: Hammet Plot for the reactions of **1** with *para*-substituted benzaldehydes (From ref. 10)

To learn more about the mechanism of this reaction, the secondary kinetic isotope effect for the addition of *para*-nitrobenzaldehyde to **1** needed to be determined. In order to run a competition reaction between deuterated and non-deuterated *p*-nitrobenzaldehyde it was first necessary to obtain the labelled aldehyde. Since *p*-nitrobenzaldehyde-*d* was not commercially available, and since the published preparative procedure[23] seemed unnecessarily lengthy, a few alternate routes were first explored (Table 3)

Table 3. Attempted syntheses of *p*-nitrobenzaldehyde-*d*

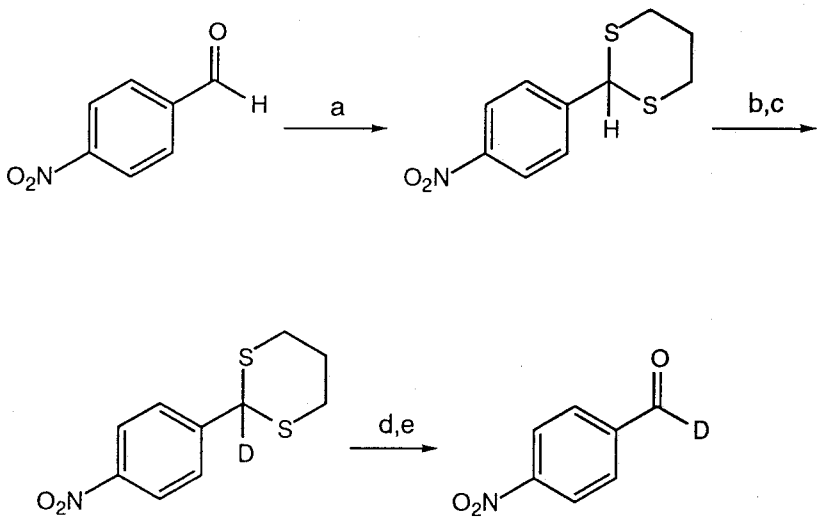
	Scheme	outcome	ref.
1)		*p*-nitrobenzoic acid only	24
2)		*p*-nitrobenzoic acid only	25
3)		complex mixture with reduction of nitro group	26

None of these procedures, however, produced satisfactory results, so the labelled aldehyde was ultimately synthesized by the literature procedure[23], as shown in Scheme I.

Recrystallized *p*nitrobenzaldehyde is first protected as the dithiane using propane dithiol and HCl gas. The crystalline dithiane was deprotonated with catalytic sodium

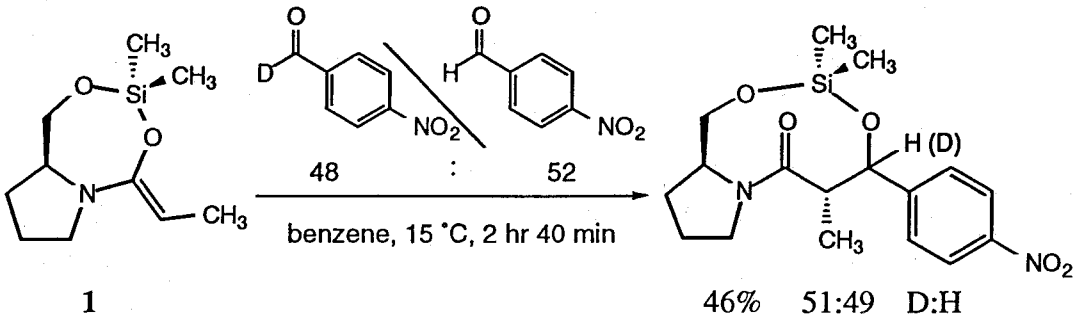
hydroxide in D_2O and deuterated with DCl in D_2O. Finally, the protecting group was removed with bromine followed by lead diacetate. This procedure gave the desired *p*-nitrobenzaldehyde-*d* in good yield and with very high deuterium incorporation (>96% D by both NMR and HRMS).

Scheme I



Reagents and conditions: (a) 1.0 equiv $HS(CH_2)_3SH$, HCl (g), $CHCl_3$, 0 °C, 5 min then rt, 30 min, 96% crude, 83% recrystallized from EtOH; (b) 0.11 equiv NaOH in D_2O, dioxane, rt, 1 hr; (c) 0.21 equiv 20 wt.% DCl in D_2O, rt, 15 min, 83% recrystallized from EtOH, >97% D; (d) 4.3 equiv Br_2, H_2O/HOAc/dioxane, rt, 5 min; (e) excess $Pb(OAc)_2 \cdot 3H_2O$, H_2O, rt, 20 min, 71%, >96% D

Once the deuterated aldehyde had been obtained, the deuterium isotope effect was determined by a competition reaction. Silyl ketene *N,O*-acetal **1** was allowed to react with an excess of a 1:1 mixture of labeled and unlabeled aldehyde (equation 13).



(13)

1

46% 51:49 D:H

Mass spectroscopic analysis of the initial aldehyde mixture and the isolated aldol adducts both showed 50% deuterium incorporation, within experimental error. Thus the rate constant ratio, k_H/k_D, is very close to 1 for this reaction, indicative of a transition state in which no rehybridization is occurring on the deuterium-bearing carbon. This secondary isotope effect is consistent with rate-determining aldehyde coordination for *p*-nitrobenzaldehyde, as was suggested by the Hammet plot.

The large, positive Hammet ρ value (3.5) originally calculated for the reaction of **1** with *para*-substituted benzaldehydes showed that electron-withdrawing groups accelerated the silicon-mediated aldol reaction and suggested a mechanism in which carbon-carbon bond formation was the rate-limiting step. However, the anomalous result with *p*-nitrobenzaldehyde suggested that for some aldehydes, coordination can be so slow as to become the rate-determining step. The secondary deuterium isotope effect calculated for *p*-nitrobenzaldehyde is consistent with a transition state in which carbon-carbon bond formation is not occurring, and confirms that aldehyde coordination may be rate-limiting.

CLEAVAGE OF β-HYDROXY AMIDES

Since the discovery of the highly diastereoselective silicon-mediated aldol reactions of amide derivatives of (*S*)-prolinol and (+)-pseudoephedrine **1** and **5** (Figure 9), an important concern has been the removal of these chiral auxiliaries after the reaction.

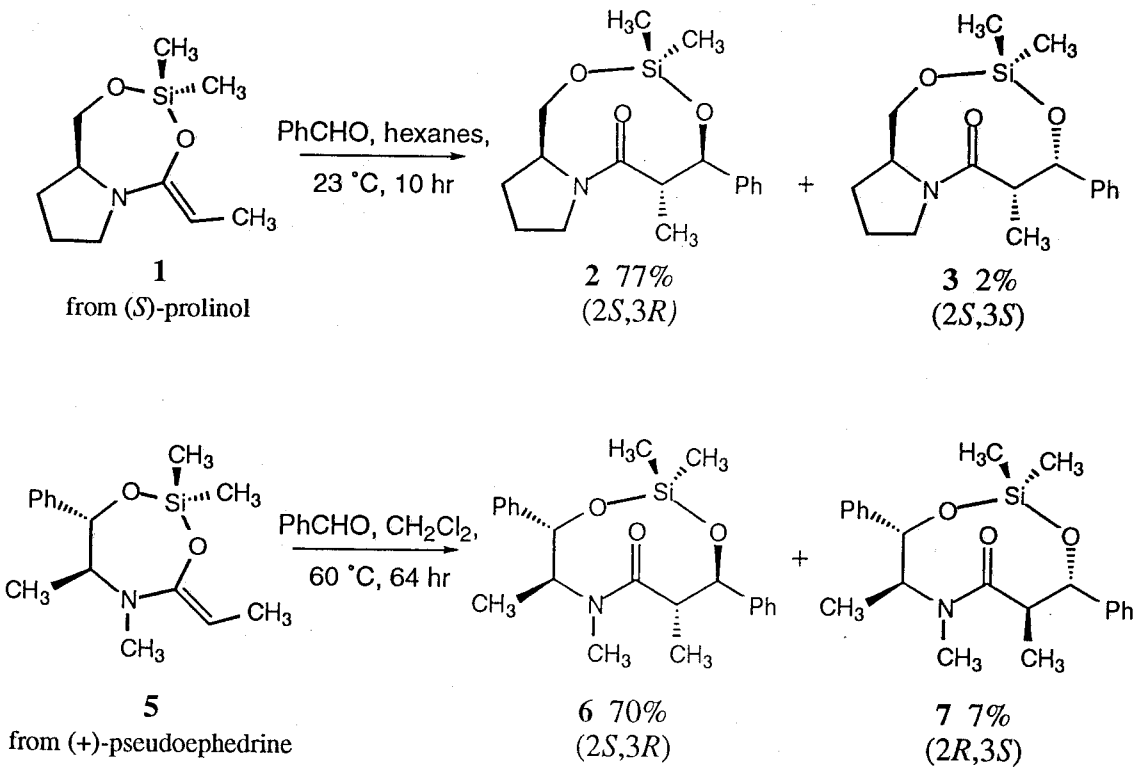
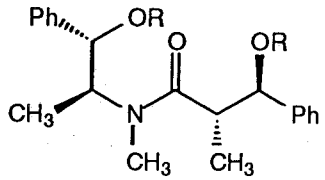
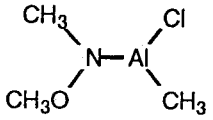


Figure 9. Highly diastereoselective aldol reactions using β-hydroxy amide auxiliaries.[5,6]

Previous attempts to remove the prolinol auxiliary focused on cleaving the amine by reductive methods, but gave very poor results.[27] Very little had been done on the pseudoephedrine system, so a wide variety of techniques were explored to remove this auxiliary from both the silylated and desilylated aldol adducts, as shown in table 4.

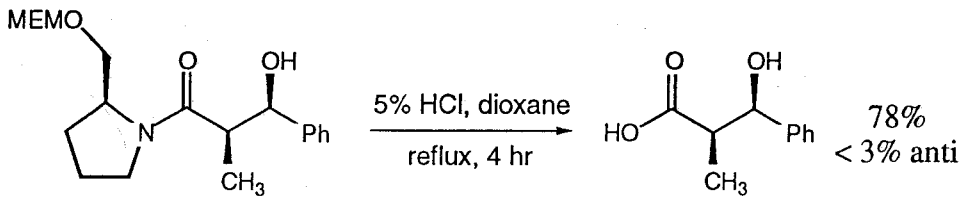
Table 4. Selected cleavage attempts - Pseudoephedrine auxiliary

	reagent	outcome	ref.
 R = $(CH_3)_2Si$ or R = H		no reaction	28
	Na_2O_2 or KO_2	desilylation or no reaction	29
	NaOMe/ MeOH	desilylation or no reaction	30
	$Et_3O^+BF_4^-$	two new products, neither is ethyl ester	31
	10% HCl, H_2O, 85 °C, 26 hr,	desilylation, acid with epimerization (1:1 anti:syn)	32
	5% HCl, dioxane, reflux, 3-17 hr	desilylation, acid with epimerization (1:1 anti:syn)	32

Attempts to transamidate using Weinreb's aluminum amide complex,[28] to oxidize using sodium peroxide or potassium superoxide,[29] and to transesterify using sodium methoxide in methanol[30] or triethoxytetrafluoroborate[31] gave either no reaction, desilylation only, or undesired products. Acidic hydrolysis conditions gave some of the desired carboxylic acid, but with complete epimerization.

The conditions shown in the last entry of table 4, 5% HCl in refluxing dioxane, were those used by Evans and McGee to remove a prolinol-derived chiral auxiliary after

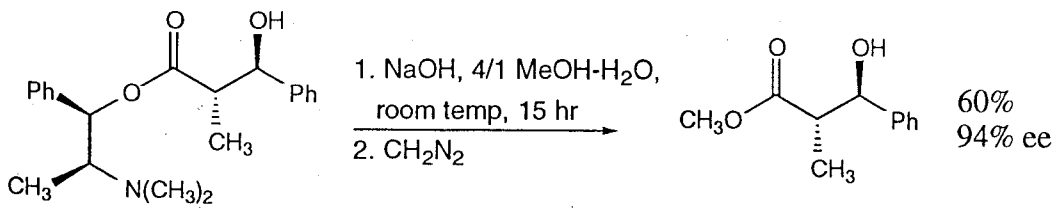
zirconium-mediated, syn-selective aldol reactions. Under these conditions, hydrolysis of a comparable benzaldehyde adduct gave the syn acid with less than three percent epimerization (equation 14).[32]



(14)

Although these conditions yielded much more epimerization for the pseudoephedrine system, this paper did provide a useful clue for further experiments. Evans suggests that the first step in the acidic hydrolysis mechanism is an N→O acyl transfer, followed by slow, acid-catalyzed cleavage of the resulting β-amino ester. Treatment of the reaction solution with aqueous sodium bicarbonate after acyl transfer gave much faster, base-catalyzed ester cleavage.[32]

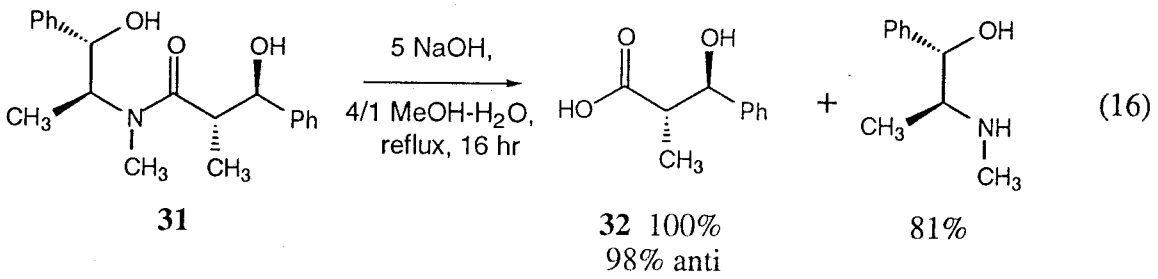
If the same mechanism is operating in the acid-catalyzed hydrolysis of the pseudoephedrine aldol adducts, then a pseudoephedrine ester could be an intermediate. Base-catalyzed hydrolysis of similar esters is known to occur. N-methyl ephedrine esters give anti-selective aldol adducts under $TiCl_4$ catalysis, and these aldol adducts can then be cleaved using sodium hydroxide with 4:1 methanol-water as solvent (equation 15).[33]



(15)

These conditions were also successful for removal of the pseudoephedrine chiral auxiliary. Diol **31** is derived by desilylation of (2*S*, 3*R*) anti aldol adduct **6** with triethylamine trihydrofluoride in acetonitrile. When refluxed with 5 equivalents of sodium hydroxide (0.33 M) in a solution of four parts methanol to one part water, **31** gives a quantitative yield of (2*S*, 3*R*)-3-hydroxy-2-methyl-3-phenylpropionic acid **32** and 81% recovery of the auxiliary (equation 16).

Similar results can be obtained using the silylated aldol adducts themselves, but the yields are slightly lower, perhaps because desilylation is slow under basic conditions. The resulting silyl side product is slightly acidic and thus difficult to separate from the β-hydroxy acid itself. This side product appears to be a polymer: the ^{1}H NMR shows multiple peaks around 0 ppm, and the ^{13}C NMR has broadened, low intensity peaks in the 0 ppm region. Because of the difficulty removing this impurity, it is preferable to first remove the dimethyl silyl group with triethylamine trihydrofluoride and then subject the purified diols to the hydrolysis conditions.



31 **32** 100% (98% anti) 81% (16)

Although the N-methyl ephedrine esters could be removed at room temperature, the pseudoephedrine amides required heating to reflux for several hours. The difference in reactivity is probably due to the different relative concentrations of amide and ester forms. Under basic conditions the N-acylated form is more stable,[34] but the O→N acyl transfer is blocked for N-methyl ephedrine. This acyl transfer would be facile for a hypothetical

pseudoephedrine ester, however. Under alkaline conditions, the amide form of the pseudoephedrine auxiliary would predominate, but a trace of the ester form would exist. Thus, alkaline cleavage of β-hydroxy amides probably involves a slow, reversible N→O acyl transfer, followed by a much faster ester hydrolysis step, as shown in figure 10. The proposed pseudoephedrine ester intermediate has not been observed, however. When the hydrolysis reaction is stopped before completion, the only other species observed is unreacted diol.

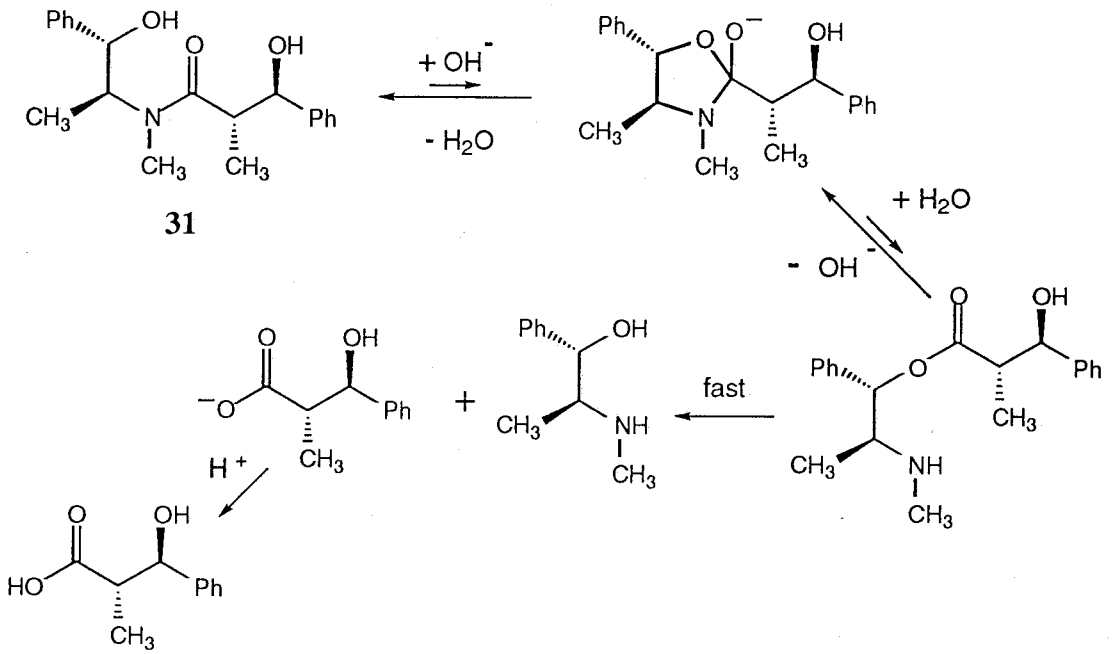
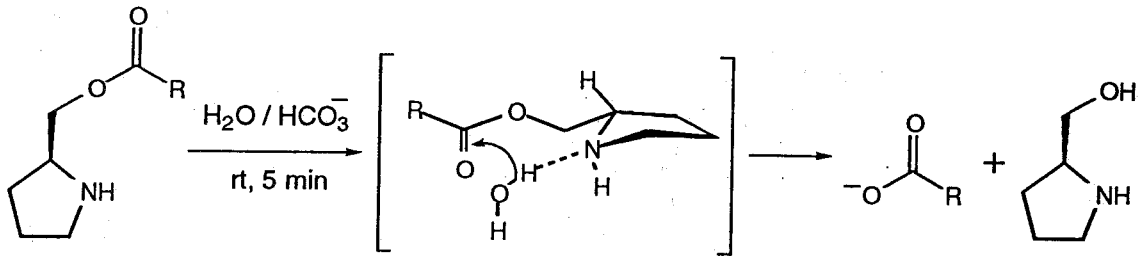


Figure 10. Proposed mechanism for alkaline hydrolysis of β-hydroxy amides.

Precedent for very rapid basic cleavage of β-amino esters can also be found from the Evans group. When treated with aqueous sodium bicarbonate at room temperature, prolinol-derived β-amino esters **33** are cleaved completely in only five minutes; the rapidity of this reaction is attributed to a catalytic, hydrogen-bonding role for the amine nitrogen (figure 11).[35]



33

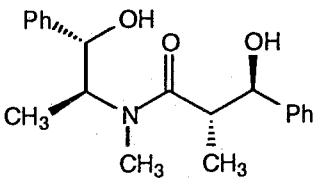
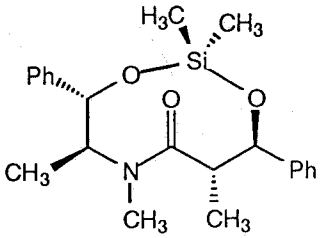
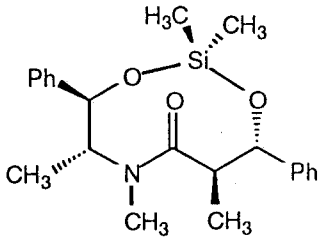
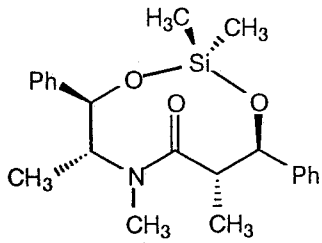
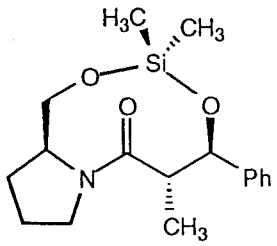
Figure 11. Rapid basic hydrolysis of β-amino esters (from ref. 35)

The enantiomeric purity of the resulting β-hydroxy acids was determined by esterification with diazomethane and chiral GC analysis of the resulting β-hydroxy methyl esters. The (2*S*, 3*R*) geometry of **6**, the major product of the silicon-mediated aldol reaction between benzaldehyde and (+)-pseudoephedrine derived silyl ketene *N,O*-acetal **5**, was confirmed by X-ray crystallography.[36] After desilylation, hydrolysis of the resulting diol **31**, and esterification with diazomethane, Methyl (2*S*, 3*R*)-3-hydroxy-2-methyl-3-phenylpropionate was obtained in > 93% ee (see table 5).

The enantiomeric silyl ketene *N,O*-acetal **34**, derived from (–)-pseudoephedrine, was also reacted with benzaldehyde to give both anti diastereomers **35** and **36** (see p. 39), which were also hydrolyzed in the same manner. The major (2*R*, 3*S*) adduct **35**, which is spectroscopically identical to **6**, gave the opposite enantiomer of the methyl ester, as indicated by a distinct, different peak in the chiral GC trace. On the other hand, the minor product **36**, on hydrolysis and esterification gave the same enantiomer of the methyl ester as **6**, the (2*S*, 3*R*) enantiomer, in ≈90% ee. Even though **36** appears to be two compounds in the NMR spectra, hydrolysis shows it to be a single diastereomer, perhaps existing in rotameric forms.

The prolinol auxiliary can also be removed under slightly more basic conditions, but auxiliary recovery is poor. All these results are summarized in table 5.

Table 5. Pseudoephedrine and Prolinol Auxiliary Cleavage.

Substrate (Concentration)	NaOH	Reflux Time	Yield Acid	Ratio Anti:Syn[a]	Yield Auxiliary	Yield Ester[b]	Ester ee[c]
 **31** (0.066 M)	5 eq 0.33 M	16 hr	100%	98:2	81%	85%	93.6%
 **6** (0.066 M)	5 eq 0.33 M	16 hr	77%[d]	96:4	71%	N/A	N/A
 **35** (0.066 M)	5 eq 0.33 M	17 hr	100%[d]	>98:2	84%	80%	84.3%
 **36** (0.066 M)	5 eq 0.33 M	19 hr	88%[d]	93:7	65%	62%	89.5%
 **2** (0.09 M)	5 eq 0.45 M	24 hr	78%[d]	>98:2	not recovered	N/A	N/A

[a]Based on integration of ^{1}H NMR spectrum. When available, GC ratios agree. [b]Yield of methyl ester after treatment with diazomethane. [c]Determined by capillary GC on Chirasil-Val column at 110 °C. Average of three runs. [d]Uncorrected for the presence of polymeric silyl impurities.

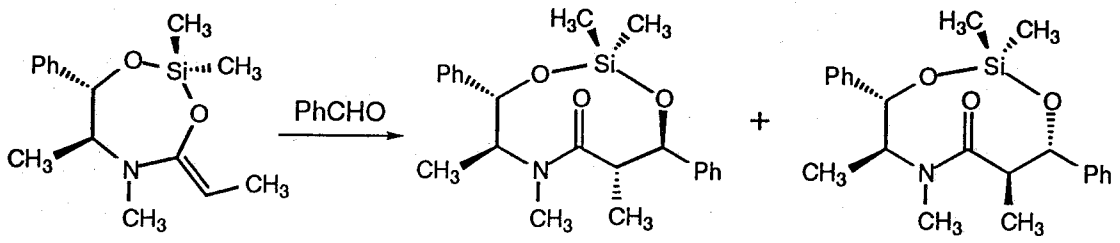
MORE SILICON-MEDIATED ALDOL REACTIONS

Pseudoephedrine Auxiliary

With an efficient auxiliary-cleavage technique now in hand, it made sense to explore the scope of aldol reactions available using the pseudoephedrine auxiliary. As was seen in the case of cyclohexanone-derived silacyclobutane enol ethers **20** and **21**, substrates which react smoothly with benzaldehyde are often unreactive to non-aromatic aldehydes. Earlier work studied the reaction of (+)-pseudoephedrine propionamide-derived silyl ketene *N,O*-acetal **5** with benzaldehyde only (reaction 4). As reported, the yield for this reaction was 70% for the major product and 7% for the minor product.[6] In this case, the products crystallized out of solution after stirring at 60 °C for more than two days. The concentration of each reactant had to be very high; the small amount of methylene chloride present at the beginning of the reaction certainly had evaporated by the end.

On further study, this proved to be an extremely capricious reaction. Table 6 summarizes several attempts to reproduce the results shown in reaction 4. Both hands of the chiral auxiliary were used so that the hydrolysis products could be compared and so that the ee after hydrolysis could be assessed. Attempts to reproduce the published conditions (entry 1) exactly (entries 2, 3, and 7) led to a wide variation in the times at which crystallization of the reaction solution occurred (36, 18, and 64 hours), and also in the final yield.

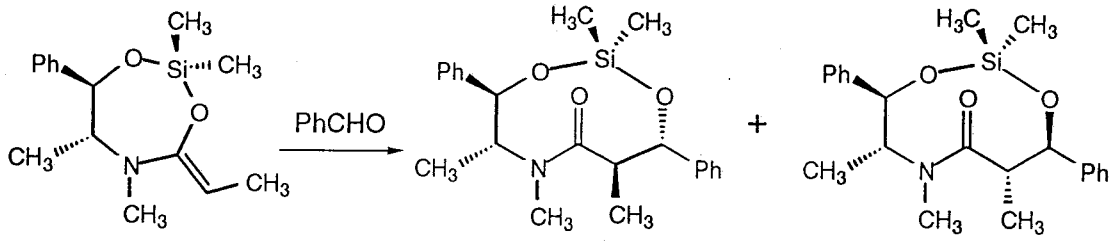
Table 6. Reactions of pseudoephedrine-derived silyl ketene acetals with benzaldehyde.



5 from (+) pseudoephedrine

6 major product (2*S*, 3*R*)

7 minor product (2*R*, 3*S*)



34 from (-) pseudoephedrine

35 major product (2*R*, 3*S*)

36 minor product (2*S*, 3*R*)

entry		silyl ketene acetal eq.	conc.	PhCHO eq.	conditions solvent	temp.	time	products major	minor
1	5	1.0	1.6 M	1.1	CH_2Cl_2	60 °C	64 hr[a]	70%[b]	7%[b]
2	5	1.0	1.9 M	1.1	CH_2Cl_2	60 °C	36 hr[a]	54%	
3	5	1.0	2.7 M	1.1	none	60 °C	18 hr[a]	38%	
4	5	1.0	2.5 M	1.5	none	60 °C	47 hr	25%	
5	5	1.0	1.3 M	5.0	none	80 °C	4 hr	36%	
6	5	1.0	1.4 M	4.2	none	80 °C	8 hr	46%	
7	34	1.0	1.1 M	1.1	CH_2Cl_2	60 °C	64 hr[a]	34%	
8	34	1.0	2.6 M	1.1	none	120 °C	1 hr	39%	
9	34	1.0	1.0 M	1.0	CH_2Cl_2	130 °C[c]	5 hr	48%	
10	34	1.0	1.1 M	1.0	CH_2Cl_2	105 °C[c]	16 hr	57%	
11	34	1.0	1.1 M	1.0	toluene	115 °C	13.5 hr	40%	
12	34	1.0	1.3 M	5.0	none	80 °C	4 hr	53%	7%
13	34	1.0	1.3 M	5.0	none	85 °C	3 hr	48%	
14	34	1.0	1.3 M	5.0	none	85 °C	12 hr	52%	12%
15	34	1.0	1.3 M	5.0	none	90 °C	4.5 hr	55%	
16	34	1.5	2.9 M	1.0	none	80 °C	12 hr[d]	26%	
17	34	2.0	2.2 M	1.0	toluene	100 °C	6 hr	44%	34%

[a]Reaction mixture had solidified by this time. [b]Widdowson, K.L., Ph.D. Thesis, California Institute of Technology, 1992, pp. 24 & 70. [c]Reaction run in a sealed tube. [d]An extremely viscous solution which had stopped stirring by this time.

At very high concentrations of reagents (no solvent, ~1:1 ratio of ketene acetal to benzaldehyde) this reaction becomes very viscous as it progresses, hindering efficient stirring. In the presence of nucleation sites the product will crystallize from solution. When this happens, the solution becomes essentially solid, and stirring stops completely. It can be assumed that reaction stops on crystallization of the solution. Since the time at which crystallization occurs seems to be almost random, the extent of reaction also varies widely.

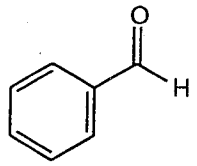
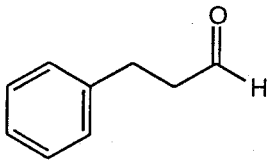
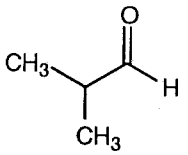
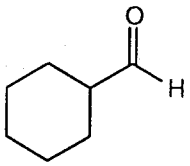
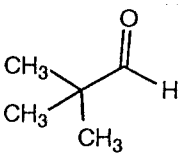
Two reactions (entries 9 and 10) were run in pressure tubes with methylene chloride as the solvent. This avoided the high viscosity and tendency to crystallize of the neat reactions, but also allowed higher reaction temperatures. The best yield, 57% of the major product, was obtained in a pressure tube reaction. (In most cases, the minor product was not isolated.) Toluene was used as a solvent for some higher temperature reactions (entries 11 and 17). Several reactions were run without any solvent at all, in hopes that the higher concentration of reagents would accelerate the reaction.

The most reproducible results, however, were obtained using an excess of benzaldehyde as solvent (entries 12–15). With a fivefold excess of benzaldehyde, 55% yield of the major product could be isolated after heating only 4.5 hours at 90 °C (entry 15). Although this is lower than the reported yield (70%) for this reaction, it is achieved in a much shorter reaction time. In brief, even though the published results may be difficult to reproduce, these conditions give a slight loss in yield offset by considerable savings in time.

The (–)-pseudoephedrine-derived silyl ketene acetal **34** was reacted with other aldehydes, with somewhat surprising results (table 7). As was seen in the prolinol system, aliphatic aldehydes also required higher temperatures and more time to react than benzaldehyde. Most of the reactions were run with excess aldehyde and no other solvent, with the exception of the hydrocinnamaldehyde experiment. Because this aldehyde was

both too high boiling to remove under vacuum and difficult to separate from the aldol adducts by column chromatography, an excess of enolate **34** was used, with toluene as solvent. Ketene acetal **34** is easily removed from the aldol adducts by chromatography. For the volatile aldehydes, isobutyraldehyde and pivalaldehyde, the reactions were run in sealed pressure tubes to prevent evaporation.

Table 7. Reactions of **34** with aldehydes.

aldehyde	eq. **34**	eq. RCHO	conditions	products[a] (2*R*, 3*S*)	(2*S*, 3*R*)
	1.0	5.0	no solvent[b] 80 °C, 4 hr	**35** 53%	**36** 7%
	2.0	1.0	toluene 100 °C, 6 hr	**37** 45%	**38** 45%
	1.0	3.5	no solvent sealed tube 120 °C,18.5 hr	**39** 22%	**40** 48%
	1.0	5.0	no solvent 80 °C, 16.5 hr	**41** 9%	**42** 63%
	1.0	5.0	no solvent sealed tube 100 °C, 42 hr	**43** 5%	**44** 48%

[a]Based on isolated yields of silylated aldol adducts after column chromatography on silica gel. [b]Entry 12 from table 6.

In all of these experiments, both anti diastereomers were obtained (the stereochemical assignments will be discussed shortly). Unlike the prolinol system, in which both major and minor products resulted from attack of aldehyde on the same face of the enolate double bond, it appears that the pseudoephedrine ketene acetal **34** is easily attacked from both faces of the double bond. In fact, the greater the steric bulk of the aldehydes, the more likely they were to add to the "less favored" face of the ketene acetal. As a result, there is a complete inversion in the sense of diastereoselectivity from benzaldehyde to pivalaldehyde. In the former case, the de is 76% for the (2*R*, 3*S*) isomer; in the latter it is 81% favoring the (2*S*, 3*R*) isomer. None of the syn isomers were observed.

As discussed earlier, the stereochemistry of the aldol adducts was assigned by hydrolysis of the pseudoephedrine chiral auxiliary, esterification with diazomethane, and chiral GC analysis of the methyl esters. The major product of the benzaldehyde reaction, **35**, was identical by ^{1}H NMR and FTIR spectra to the (1'*S*, 2'*S*, 2*S*, 3*R*) isomer **6** derived from (+)-pseudoephedrine,[36] implying that **35** is the enantiomeric (1'*R*, 2'*R*, 2*R*, 3*S*) isomer, as shown. It appears as a single spot on TLC analysis, and elutes as a single band off a silica gel column. After hydrolysis and esterification, only the (2*R*, 3*S*) methyl ester is obtained, the enantiomer of that derived from **6**.

On the other hand, minor product **36** elutes as two bands off a silica gel column and appears as two spots on TLC analysis, but 2-D TLC shows those spots convert into each other. The ^{1}H NMR spectrum of **36** also appears to contain two isomers in an approximately equal ratio. However, upon hydrolysis and esterification with diazomethane, **36** yields only the anti ester (with very minor syn impurities). This ester is identical by chiral GC to the ester derived from cleavage of (1'*S*, 2'*S*, 2*S*, 3*R*) aldol adduct **6** or diol **31**, the major aldol adduct from the reaction of the (+)-pseudoephedrine silyl ketene acetal **5** (see table 5). Thus **36** can confidently be assigned the (1'*R*, 2'*R*, 2*S*, 3*R*)

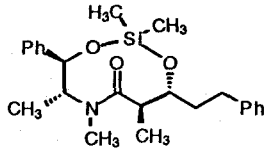
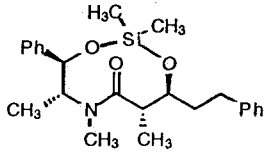
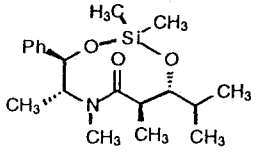
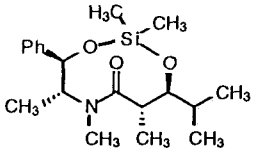
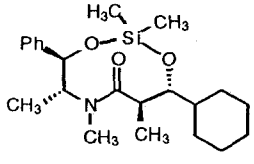
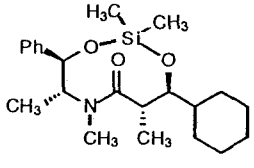
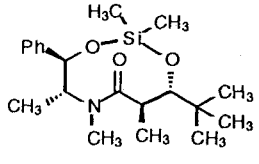
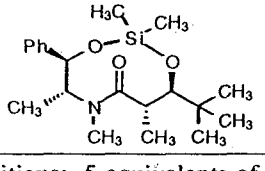
geometry as the other possible anti aldol adduct. This compound apparently exists in equilibrium between two conformers in solution. It should be noted that this minor product was originally identified as a mixture of anti and syn isomers.[10]

The stereochemical assignments for the hydrocinnamaldehyde, isobutyraldehyde, cyclohexanecarboxaldehyde, and pivalaldehyde adducts were made based on the assumption that the nature of the pendant alkyl group does not affect the conformation around the nine-membered siloxy ring, and thus similarities between NMR spectra of these adducts and the benzaldehyde adducts could be used to assign stereochemistry. Those products which appeared as a single spot on silica gel and as a single product in the ^{1}H NMR spectrum were assigned the (2*R*, 3*S*) geometry (**37**, **39**, **41**, and **43**). Those which appeared as two interconverting spots on silica gel and which exhibited a mixture of conformers in the ^{1}H NMR spectrum were assigned the (2*S*, 3*R*) geometry (**38**, **40**, and **42**).

An interesting exception to this rule was the major pivalaldehyde adduct **44**. This highly crystalline product (mp: 143–145 °C) elutes as a single spot on TLC analysis. In benzene-d_6 the ^{1}H NMR spectrum of **44** appears to contain only a single isomer, but in chloroform-*d* the ^{1}H NMR spectrum of **44** appears to contain *two* isomers in approximately a 2:1 ratio. The similarity of the chloroform spectrum to that of the minor benzaldehyde adduct implies that it is the (2*S*, 3*R*) anti aldol adduct, which adopts two conformers in chloroform solution, but which exists as a single conformer in the less polar benzene solution.

These aldol adducts were subjected to the hydrolysis conditions discussed in the previous section. The results are shown in table 8. In general, a greater degree of epimerization was observed, and yields were much poorer, perhaps due to the volatility of the resulting acids and esters.

Table 8. Cleavage of (–)-pseudoephedrine aldol adducts.[a]

	Substrate	Reflux Time	Yield Acid	Ratio Anti:Syn[b]	Yield Auxiliary	Yield Ester[c]	Ester ee[d]
37		20.5 hr	100%[e]	82:18	83%	90%	
38		20.5 hr	97%[e]	93:7	78%	73%	
39		9.5 hr	78%[e]	96:4	98%	24%	70.7%
40		9.5 hr	98%[e]	94:6	87%	23%	100%
41		11 hr	53%[e]	90:10	not isolated	29%	83.4%
42		11 hr	73%[e]	88:12	not isolated	50%	100%
43		5 days	76%[f]	92:8	77%		
44		3 days	74%[f]	91:9	100%		

[a]Conditions: 5 equivalents of 0.33 M NaOH in 4:1 MeOH-H_2O. Refluxed in oil bath for indicated time. [b]Based on integration of ^1H NMR spectrum. When available, GC ratios agree. [c]Yield of methyl ester after treatment with diazomethane. Based on silylated aldol adduct. [d]Determined by capillary GC on Chirasil-Val column. Average of three runs. [e]Uncorrected for the presence of polymeric silyl impurities.. [f]Based on diol derived from desilylation with triethylamine trihydrofluoride.

Pivalaldehyde adducts **43** and **44** were especially difficult to cleave. To avoid contamination with the polymeric silyl impurity mentioned earlier, they were first treated with triethylamine trihydrofluoride to remove the silyl group, then purified by a short silica plug before hydrolysis. Under the same conditions which gave complete hydrolysis of benzaldehyde-derived diol **31** in 16 hours, the pivalaldehyde-derived diols required several days to react. The (2*R*, 3*S*) isomer **43** still showed traces of the unreacted diol after refluxing for five days. In contrast, hydrolysis of the silylated isobutyraldehyde adducts **39** and **40** were complete by TLC in less than 10 hours.

The pivalaldehyde adducts also showed the greatest difference in reactivity between the two diastereomers, which must be a steric effect. It is clear from the ^{1}H NMR spectra that the pivalaldehyde-derived acids assume a very different solution conformation than their benzaldehyde analogs. In general, the stereochemistry of aldol adducts is assigned by invoking intramolecular hydrogen bonding between the β-hydroxyl proton and the carbonyl oxygen. This results in a vicinal coupling constant between the α and β protons of 2–6 Hz for the syn isomer and 7–10 Hz for the anti isomer (figure 12).[1]

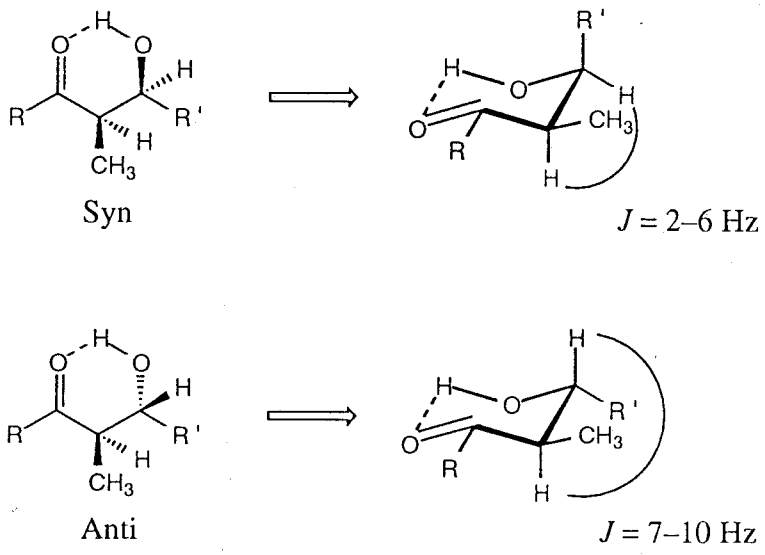


Figure 12. Hydrogen-bonding paradigm for assigning aldol adduct stereochemistry.

This hydrogen-bonding rule accurately describes the 3-hydroxy-2-methyl-3-phenylpropionic acids derived from cleavage of the benzaldehyde adducts; the syn acid has $J_{2,3}$ = 4.5 Hz, and the anti has $J_{2,3}$ = 8.9 Hz. On the other hand, the 3-hydroxy-2,4,4-trimethyl pentanoic acids derived from cleavage of the pivalaldehyde adducts have an anti coupling constant of 2.1 Hz, which is *smaller* than the syn coupling of 3.2 Hz. These experimental values are in good agreement with the literature (See ref. 1). Therefore, these acids must experience steric strain which prevents regular, intramolecular hydrogen bonding. Thus it is not unreasonable to suggest that the diols derived from desilylation of **43** and **44** also experience some steric strain which both prevents intramolecular hydrogen bonding and hinders hydrolysis by sodium hydroxide.

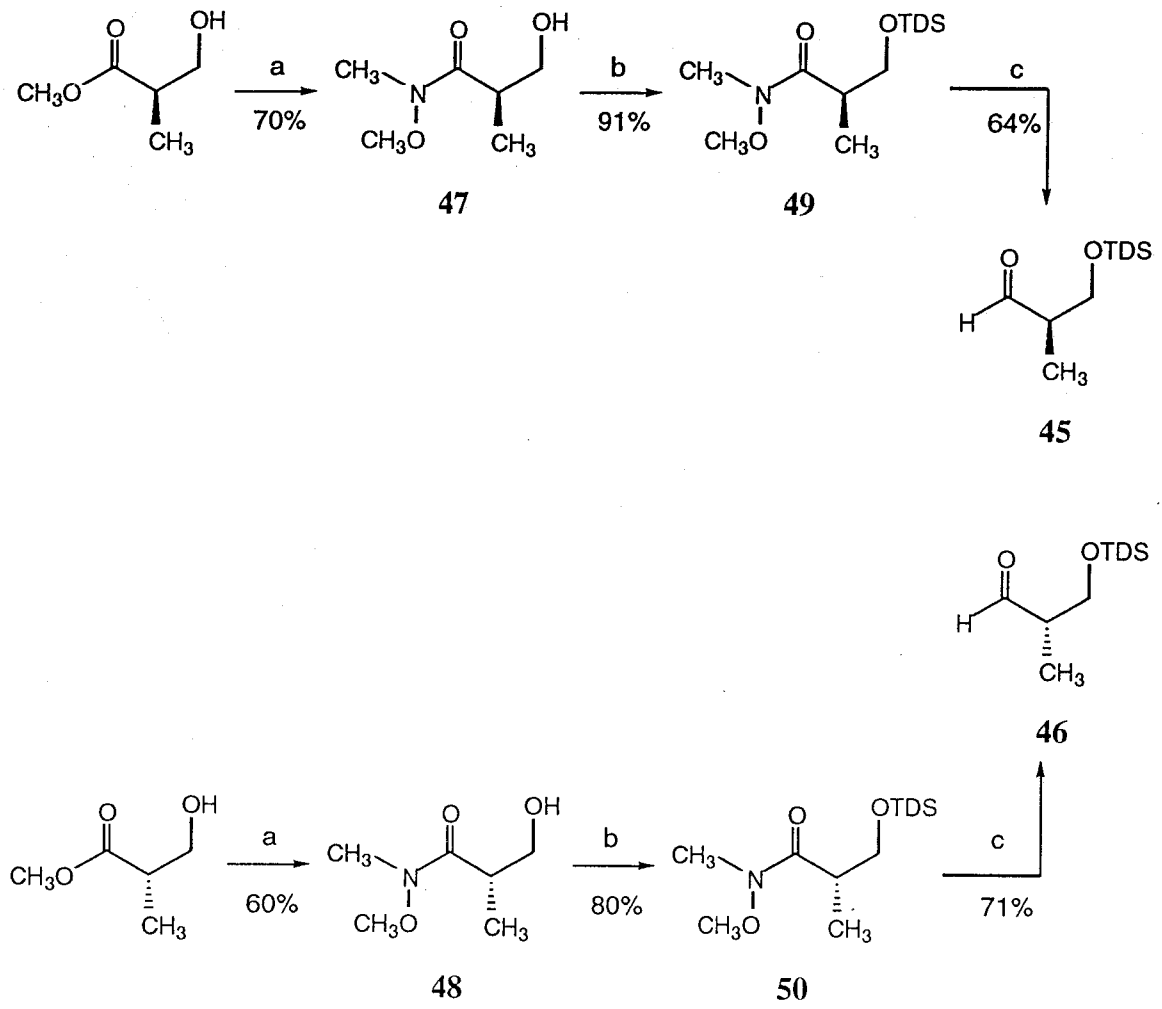
The enantiomeric purity of the methyl esters was determined by chiral GC. For the (2*R*, 3*S*) isobutyraldehyde adduct **39** an ee of 70.7% was found, but the (2*S*, 3*R*) isomer **40** gave enantiomerically pure ester to the limits of GC detection. Similar results were obtained for the cyclohexanecarboxaldehyde adducts. Adduct **41** gave (2*R*, 3*S*) methyl ester with ee of 83.4%; **42** gave enantiomerically pure (2*S*, 3*R*) methyl ester. It is questionable whether these values are significant, however, because the yields of the esters were very low (<50%). The methyl esters resulting from cleavage of hydrocinnamaldehyde adducts **37** and **38** could not be separated under reasonable GC conditions.

Chiral aldehydes

The next question approached in the study of silicon-mediated aldol reactions was whether a chiral aldehyde would produce matching and mismatching effects on reaction with a silyl ketene *N,O*-acetal bearing a chiral auxiliary. The prolinol system was chosen for study since the reactions of **1** were much faster than its pseudoephedrine analogs **5** and **34**. The aldehydes chosen for this purpose were (2*R*)- and (2*S*)-3-*tert*-butyldiphenyl-siloxy-2-methyl propionaldehydes **45** and **46**.

As shown in Scheme II, these aldehydes are easily synthesized in three steps from commercially available starting materials. Methyl (*R*)-(–)- or (*S*)-(+)-3-hydroxy-2-methyl propionate was refluxed in a benzene solution of the Weinreb N-methyl-N-methoxy aluminum complex (3.0 equiv) to give the corresponding N-methyl-N-methoxy amides in 70% and 60% yield, respectively. The β-hydroxy group was then protected with *tert*-butyldiphenylsilyl chloride (1.25 equiv) in the presence of imidazole (2.5 equiv) in DMF (91% and 80% yields after column chromatography). The protected amides were reduced with lithium aluminum hydride in ether at –78 °C to give the desired aldehydes in 64% and 71% yields after silica gel chromatography. Reduction at higher temperatures gave cleavage of the TDS protecting group. Overall yields were 41% for the *R* isomer **45** and 34% for the *S* isomer **46**.

Scheme II

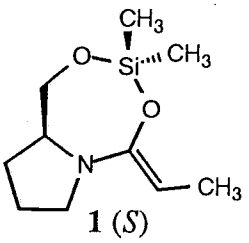
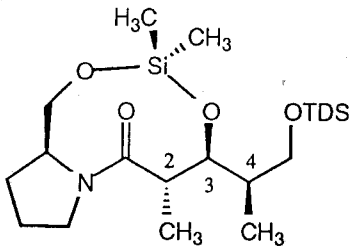
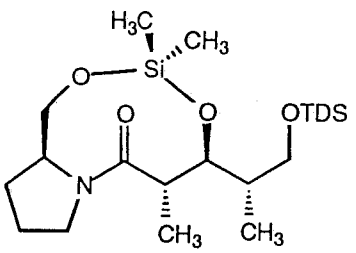
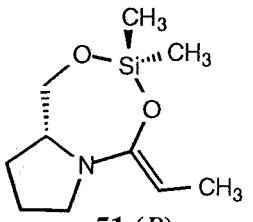
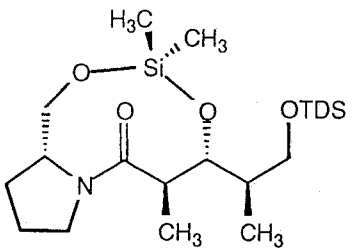
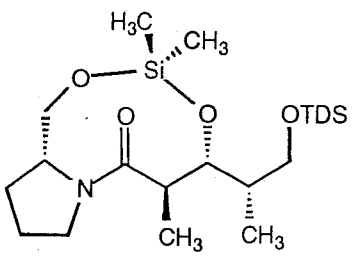


Reagents and conditions (TDS = $SiPh_2t$-Bu): (a) 3.0 equiv $CH_3(CH_3O)N$-Al(Cl)CH_3, C_6H_6, reflux, 2 hr; (b) 1.25 equiv TDSCl, 2.5 equiv imidazole, DMF, 31 °C, 3 hr; (c) 1.0 equiv $LiAlH_4$, Et_2O, –78 °C, 1.5 hr.

Both (*S*)- and (*R*)-prolinol propionamide *O*-silyl ketene *N,O*-acetals **1** and **51** were prepared according to the standard procedure.[10] Each of these silyl ketene acetals was reacted with both enantiomers of the chiral aldehyde at room temperature (30 °C) for 24

hours. In each case, only one aldol adduct was observed. Isolated yields from 24% to 42% were obtained, but with no definitive correlation between yield and reactant geometry. The results are shown in table 9.

Table 9. Aldol reactions of prolinol-derived silyl ketene acetals and chiral aldehydes.[a]

Silyl Ketene Acetal	Aldehyde: **45** (*R*)	Aldehyde: **46** (*S*)
 **1** (*S*)	 **52** 28% (2*S*, 3*R*, 4*R*)	 **53** 32% (2*S*, 3*R*, 4*S*)
 **51** (*R*)	 **54** 24% (2*R*, 3*S*, 4*R*)	 **55** 42% (2*R*, 3*S*, 4*S*)

[a]Conditions: 1.0 equiv each of ketene acetal and aldehyde, 0.5 M in CH_2Cl_2, 30 °C, 24 hours. Purification by flash column chromatography.

The 2, 3-anti configuration of each aldol adduct is suggested by a coupling constant of 10 Hz between those two protons in each isomer. For comparison $J_{2,3}$ = 9.7 Hz in anti aldol adduct **2**, and $J_{2,3}$ = 3.8 Hz for syn adduct **3**. The absolute stereochemical assignments for carbons 2 and 3 are only tentative – they have been drawn in analogy to **2**.

As expected, enantiomeric reagents gave enantiomeric products (**52/55** and **53/54**). However, the yields of these enantiomeric reactions were not identical. The (*S*) enolate + (*R*) aldehyde combination gave **52** in only 28% yield, but the (*R*) enolate + (*S*) aldehyde combination gave 42% yield of enantiomeric **55**. This is probably due to the purity of (*R*) aldehyde **45**, since the yield of **54** is also lower than that of **53**.

The reactions of (*S*) aldehyde **46** were repeated at 0 °C in hopes of enhancing diastereoselectivity. After 44 hours at 0 °C, the (*S*) + (*S*) combination of **1** and **46** afforded 42% of (2*S*, 3*R*, 4*S*) adduct **53**. The (*R*) + (*S*) combination of **51** and **46** gave 48% of adduct **55** after 55 hours at 0 °C. Thus it appears that aldehyde geometry has little effect on the rate and outcome of the reaction. The rate of reaction is roughly comparable to that of isobutyraldehyde with **1** (58% after 26 hours at room temperature).[10] Examination of models suggests that, for the proposed boat transition state, both enantiomers of the aldehyde can minimize steric interactions by adopting a configuration in which only the α-hydrogen atom is brought close to the reacting face of the silyl ketene acetal, as shown in figure 13.

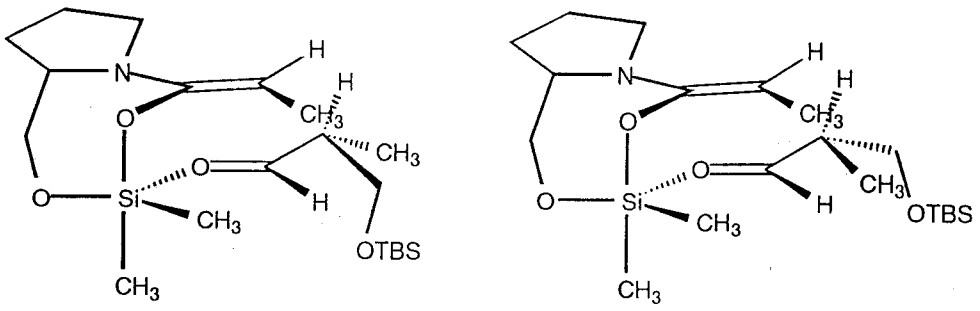
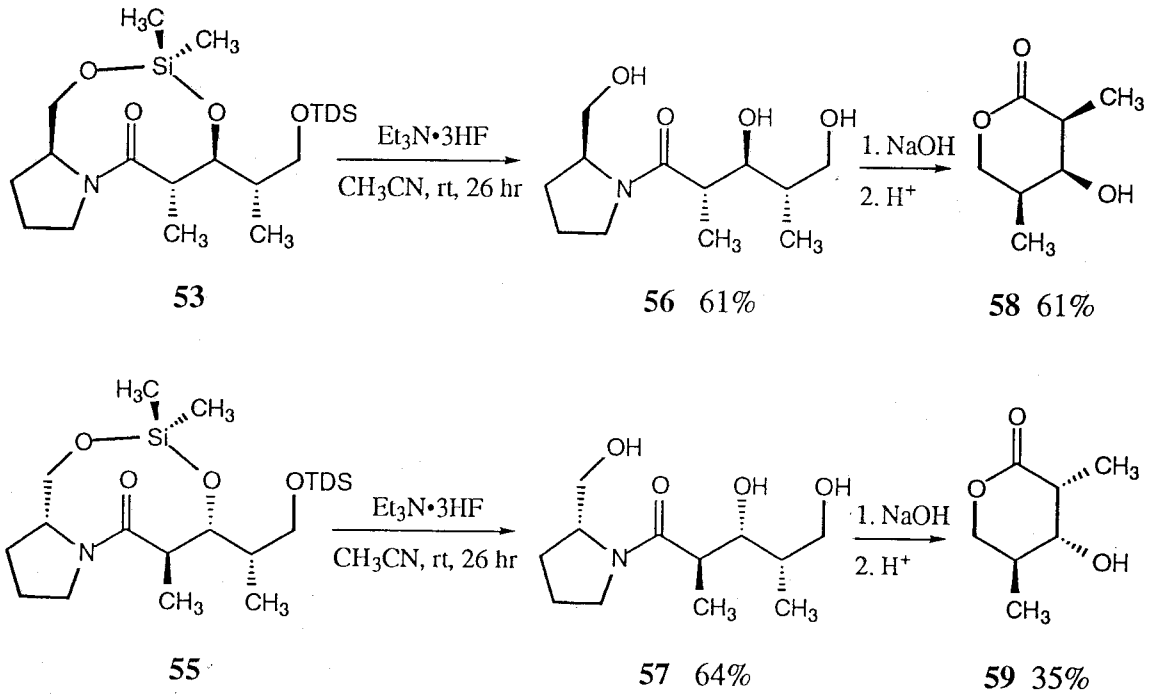


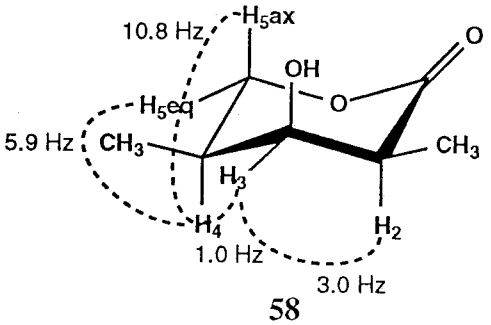
Figure 13. Possible transition state geometry for the reactions of chiral aldehydes **45** and **46** with silyl ketene acetal **1**.

Aldol adducts **53** and **55** were completely desilylated using triethylamine trihydrofluoride to triols **56** and **57** in 61% and 64% yield, respectively. When subjected to the alkaline hydrolysis conditions discussed earlier **56** and **57** afforded (*S*)- and (*R*)-prolinol in 78% and 58% yield, respectively. The acidic conditions of the work up, however, caused the resulting δ-hydroxy acids to cyclize, and only δ-lactones were recovered. On hydrolysis, triol **56** produced an 83:12:5 mixture of three lactones in 80% yield. Purification by chromatography gave 61% of major product **58**. Hydrolysis of triol **57** also afforded a 67:25:7 ratio of lactones in 71% yield, but none of these products were identical to **58**. Recrystallization from ether gave major lactone product **59** in 35% yield. These results are summarized in scheme III.

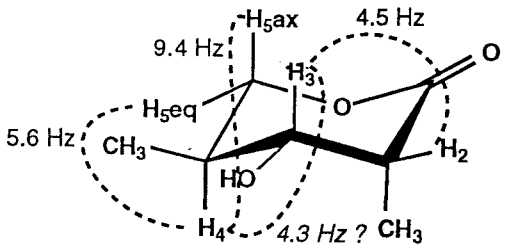
Scheme III



The stereochemistry of lactone **58** is supported by the coupling constants observed in the ^1H NMR spectrum. As shown in figure 14, the axial-axial relationship between the proton on carbon 4 and the axial proton on carbon 5 is indicated by a large coupling constant of 10.8 Hertz. The smaller couplings between protons 2 and 3 and between protons 3 and 4 (3.0 and 1.0 Hz) suggest axial-equatorial relationships. A very small "w" coupling (0.9 Hz) between the equatorial proton on carbon 5 and the proton on carbon 3 is also present. A similar pattern of coupling constants is also present in lactone **59**, but the relatively small coupling between protons 3 and 4 (4.3 Hz) is not consistent with the geometry at carbon 4 as assigned. If the hydroxyl group were axial instead of equatorial, as shown, the coupling constants would be consistent, but this would imply (2, 3)-*syn* geometry for aldol adduct **55** and triol **57**. Thus the exact stereochemistry of lactone **59** is still in question.



58



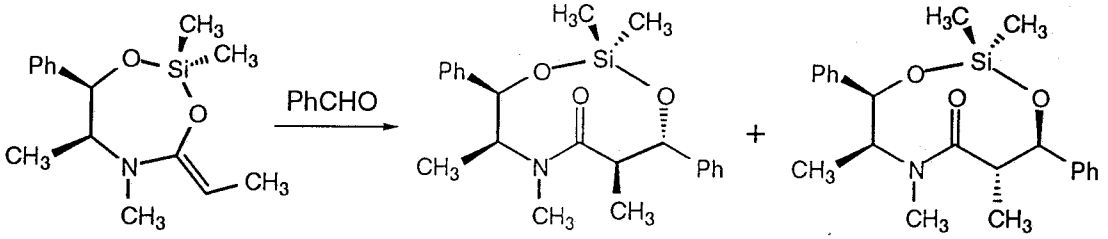
59

Figure 14. ^1H NMR coupling constants of lactones **58** and **59**.

Ephedrine auxiliary

In contrast to earlier observations, the dimethyl silyl ketene *N,O*-acetal derived from (–)-ephedrine propionamide **4** was found to react smoothly with benzaldehyde at room temperature to give moderate yields of both anti aldol adducts **60** and **61**. This ketene acetal is more reactive than the pseudoephedrine analogs **5** and **34**, which require elevated temperatures to react. (See table 6) The combined yield of products is roughly comparable to the pseudoephedrine reaction (about 70%), but the diastereoselectivity is poorer. A product ratio of 47:24 was obtained in comparison to 70:7 as reported in reference 5. Table 10 summarizes the results of several experiments using the ephedrine auxiliary.

Table 10. Reactions of (–)-ephedrine-derived **4** with benzaldehyde.



4
from (–)-ephedrine

60
major product
(2*R*,3*S*)

61
minor product
(2*S*,3*R*)

	silyl ketene acetal			PhCHO	conditions			products	
entry		eq.	conc.	eq.	solvent	temp.	time	major	minor
1	**4**	1.0[a]	1.5 M	1.0	C_6D_6	31 °C	5 days	45%	13%
2	**4**	1.0[a]	2.7 M	1.0	none	31 °C	19 hr[b]	45%	14%
3	**4**	1.0[c]	2.7 M	1.0	none	31 °C	46 hr[b]	37%	17%
4	**4**	1.0[c]	1.3 M	5.0	PhCHO	31 °C	20 hr	43%	19%
5	**4**	1.0[d]	2.7 M	1.0[e]	none	31 °C	22 hr[b]	36%	15%
6	**4**	1.0	2.7 M	1.0	none	31 °C	45 hr[b]	47%	24%

[a]First batch of ketene acetal **4**. [b]Reaction had crystallized by this time; stirring stopped. [c]Second batch of ketene acetal **4**. Distilled 1 day before use to ~85% purity. [d]Second batch of ketene acetal **4**. Redistilled one hour before use to ~95% purity. [e] Benzaldehyde distilled immediately before use.

The minor product, **61**, was assigned (2, 3)-anti stereochemistry based on a vicinal coupling constant of 9.7 Hz in the ^{1}H NMR spectrum. On desilylation and alkaline hydrolysis of the ephedrine auxiliary, the anti acid is obtained almost exclusively. After treatment with diazomethane, the methyl ester is obtained in a 97:3 anti:syn ratio. An ee of 83.0% for the anti ester was determined by chiral GC analysis. Furthermore, the anti ester co-elutes with the ester derived from cleavage of the major (+)-pseudoephedrine adduct **6**, a compound with (2*S*, 3*R*)-stereochemistry confirmed by X-ray crystal structure analysis.[36] Thus **61** is assigned (2*S*, 3*R*)-stereochemistry.

The major product **60** (mp: 151–153 °C) exhibits a ^{1}H NMR spectrum with curiously broadened peaks, except in the aromatic region, which is well defined. Because of this, it is difficult to make stereochemical assignments at this stage. On desilylation and auxiliary removal, however, the anti acid is again obtained almost exclusively, with only 3% epimerization to the syn acid After treatment with diazomethane, the anti methyl ester is formed in 100% ee, according to chiral GC analysis. This ester co-elutes with that obtained from cleavage of the major (–)-pseudoephedrine adduct **35.** Since **35** is the enantiomer of **6**, it is known to have (2*R*, 3*S*) stereochemistry. Thus the major (–)-ephedrine adduct **60** is also assigned the (2*R*, 3*S*) stereochemistry. Satisfactory FTIR, ^{13}C NMR, and HRMS data has been obtained for both aldol adducts, both silylated and desilylated.

Since earlier experiments suggested that the ephedrine propionamide ketene acetal **4** did not react with benzaldehyde, it is possible that these positive results were due to some catalytic impurity rather than the intrinsic reactivity of the reagents. In an attempt to rule this out, the first batch of **4** was set aside after the first two reactions (entries 1 and 2, table 10), and a fresh batch prepared. This second batch was distilled to about 85% purity from the crude and used in aldol reactions the following day. (This is approximately as pure as the silyl ketene acetals used in the pseudoephedrine and prolinol experiments. The enolates

are very moisture sensitive and difficult to get absolutely pure by distillation.) Freshly distilled benzaldehyde was also used in these reactions (entries 3 and 4, table 10). The results from these two runs were not significantly different those of the first two. Two more experiments were run, using reagents redistilled immediately (less than 1 hour) before use, again yielding similar results (entries 5 and 6, table 10).

Four of these experiments were run using a 1:1 ratio of reagents and no other solvent. In these four cases, (entries 2, 3, 5,and 6, table 10) the yields of major and minor aldol adducts **60** and **61** were almost identical, but reaction times varied from 19 to 46 hours. At the indicated reaction time, stirring had stopped because so much of the crystalline product had formed that the reaction mixture was essentially solid. In each of these cases, the reaction mixture became extremely viscous after only a few hours, and stirring was severely impaired. As was seen in the pseudoephedrine case (table 6), the time at which crystallization occurs is highly variable, possibly depending on the availability of nucleation sites in the reaction environment. Furthermore, the longer reaction times indicate when crystallization was first observed, not necessarily when crystallization occurred. It is reasonable to assume that little reaction occurs after crystallization, so the actual reaction times could be many hours shorter. In general, the aldol reactions of (−)-ephedrine-derived **4** are no less reproducible than those of its pseudoephedrine analogs **5** and **34**.

The question remains why Dr. Paivi Kukkola, who did the original experiments with ephedrine compound **4**, failed to observe any aldol reaction. Although she ran the reaction several times, under varied conditions, it appears she followed the reaction by TLC only. According to her notebook, she eluted with either diethyl ether, 4:1 ethyl acetate-pet. ether, or 3:1 ethyl acetate-pet. ether. All of these solvent systems are so polar that the aldol adducts **60** and **61** co-elute or nearly co-elute with benzaldehyde. Furthermore, she stained her TLC plates with ninhydrin, perhaps an unfortunate choice. While ninhydrin

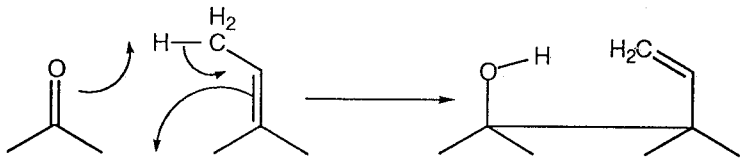
stains ephedrine propionamide strongly and the silyl ketene acetal **4** moderately, it stains the products only very faintly, if at all. Thus it is quite possible she actually observed the aldol adducts under UV, but since they did not stain, she may have attributed the spot to unreacted benzaldehyde. The product spots stain well in PMA, and in a less polar solvent (40% ether in pet. ether), the two aldol adducts **60** and **61** are slightly separated from each other and well separated from benzaldehyde.

In conclusion: the silicon-mediated aldol reaction of ephedrine-derived silyl ketene *N,O*-acetal **4** with benzaldehyde is real and reproducible. The reaction occurs at lower temperatures than the pseudoephedrine analogs, but stereoselectivity is not as good. The reaction was not observed in Dr. Kukkola's experiments, probably due to a poor choice of TLC conditions.

MECHANISTIC REASSESSMENT

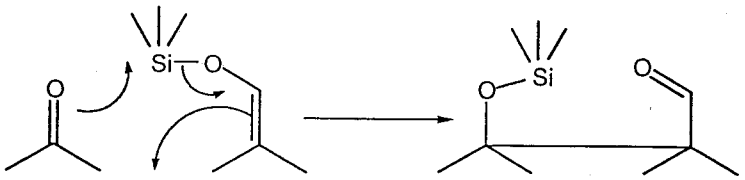
It is interesting to note that in the ephedrine case, as well as the pseudoephedrine case, only anti aldol adducts are observed, indicating that aldehyde attack occurs on both faces of the enolate double bond. This is inconsistent with the pseudorotational mechanism originally proposed for the prolinol system, in which attack occurs on only one face of the double bond. To account for these results, and alternative, ene-type reaction mechanism has been proposed.[37]

In one type ene reaction[38] an allylic hydrogen atom is transferred to a carbonyl oxygen in a concerted, pericyclic mechanism involving a six-membered transition state. (figure 15) Entropies of activation for intermolecular ene reactions are typically on the order of –30 eu.[39] In the proposed ene-type mechanism for the silicon-mediated aldol reaction, an enolic silicon atom is transferred to a carbonyl oxygen, also in a concerted, pericyclic fashion. No pseudorotational steps are involved.



Ene Reaction

$\Delta S^{\ddagger} = -30$ eu



Ene-Type Mechanism for Silicon-directed Aldol Reaction

$\Delta S^{\ddagger} = -41$ eu

Figure 15. Comparison of the ene and ene-type reaction mechanisms

In order to derive reasonable transition states for this ene-type mechanism, it is first necessary to consider the ground state conformation of the starting silyl ketene acetals. Unlike the silacyclopentane ketene acetal **8**, the pseudoephedrine and ephedrine silyl ketene acetals **5**, **34**, and **4** were liquids rather than solids. Since a crystal structure could not be obtained, a ground state conformation was calculated using molecular modeling. Figure 16 shows the lowest-energy conformer for the (–)-pseudoephedrine enolate **34**.[40]

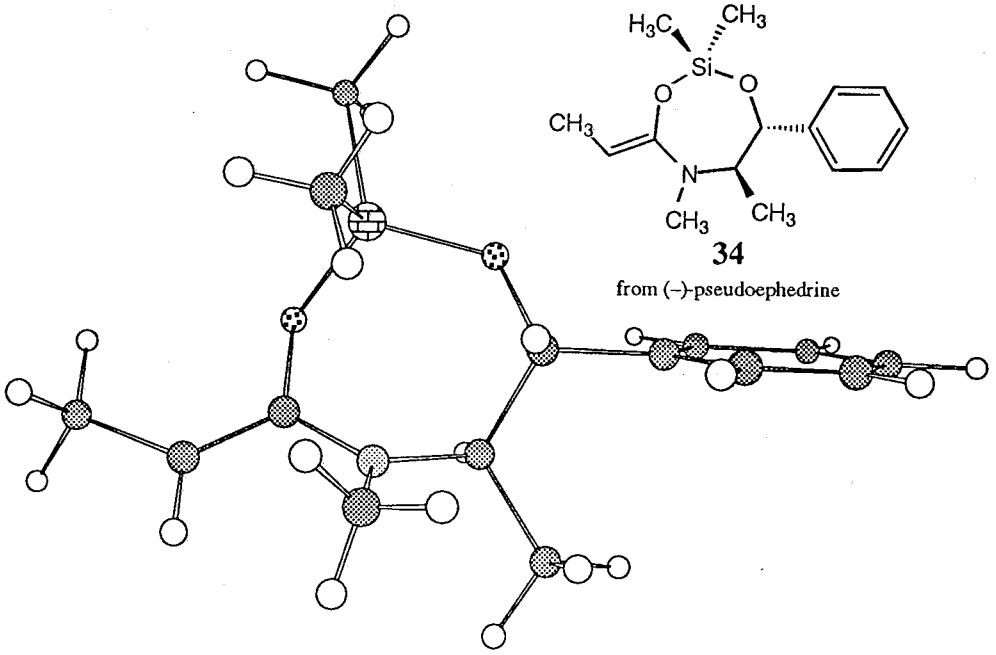


Figure 16. Calculated minimum energy conformation for **34**

As was seen in the crystal structure of **8** (figure 6), the molecule is somewhat concave. One face of the enolate double bond is somewhat blocked by one of the silyl alkyl groups, and one face of the silicon tetrahedron (defined by the two oxygen atoms and the forward silyl methyl group) is almost directly over the nitrogen methyl group. The back face of the silicon tetrahedron (defined by the two oxygen atoms and the other silyl methyl group), however, is on the "outside" and completely unhindered.

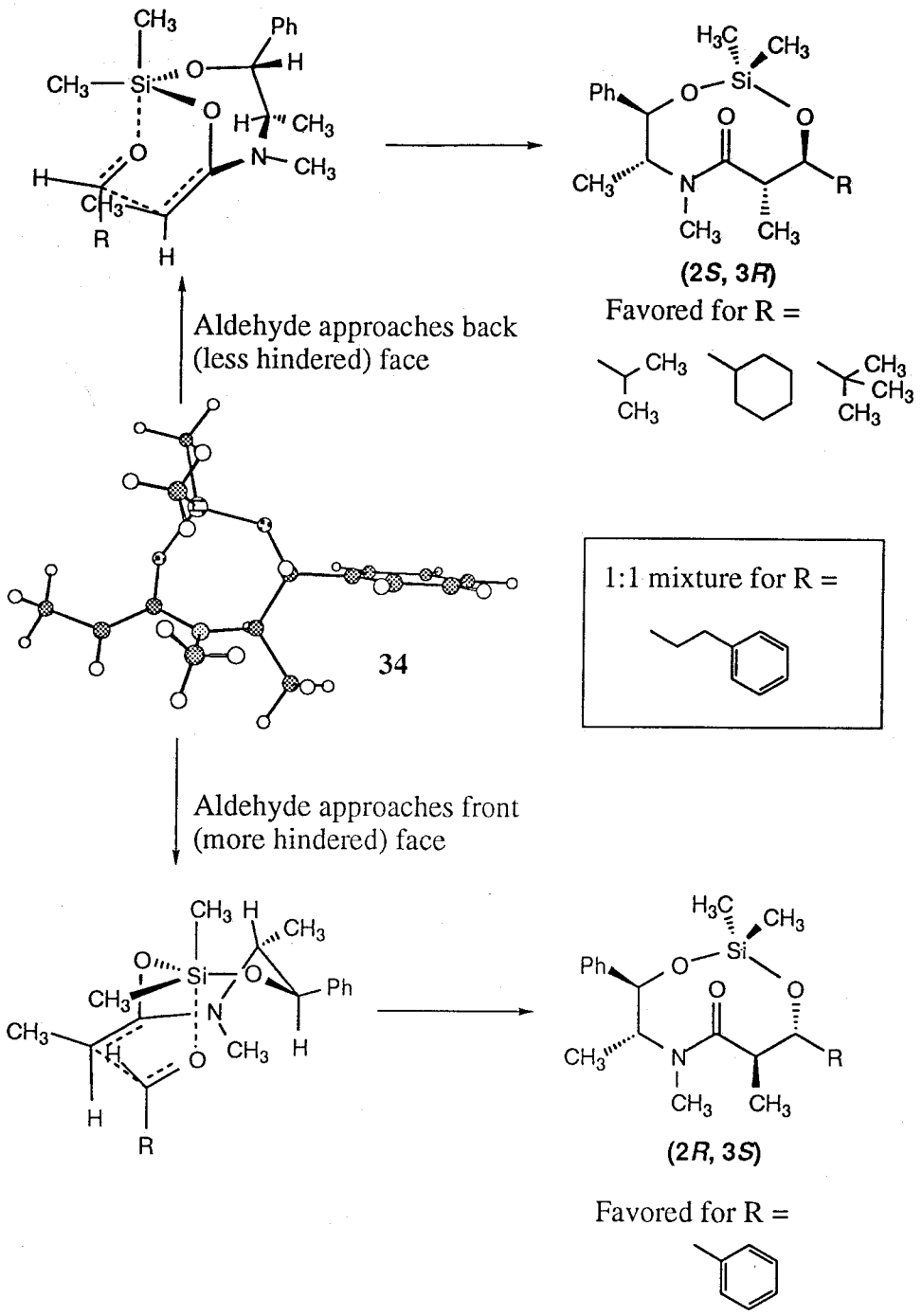


Figure 17. Possible transition states for ene-type mechanism

If the aldehyde were to attack the less hindered, back face of the silicon tetrahedron, a boat-like transition state would lead directly to the (2*S*, 3*R*) anti aldol adduct, as shown in figure 17. This seems to be the preferred addition mode for sterically bulky aldehydes such as pivalaldehyde, cyclohexane carboxaldehyde, and isobutyraldehyde. If, for whatever reason, the aldehyde were to approach the more hindered, front face of the silicon tetrahedron, the boat-like transition structure seen at the bottom of figure 17 would lead directly to the (2*R*, 3*S*) anti aldol adduct, which is preferred for only benzaldehyde. A 1:1 mixture of the two anti aldol adducts was obtained in the reaction of hydrocinnamaldehyde, indicating that both transition structures are equal in energy for this substrate.

Although these transition structures can be used to rationalize the experimental results, they do require the amide oxygen to leave from an equatorial position.[41] On the other hand, a concerted mechanism would explain why the hypothetical pentacoordinate silicon intermediate proposed by the pseudorotational mechanism was never observed.[10]

The concerted, ene-type mechanism also nicely explains the tremendous rate acceleration observed when the silicon atom is constrained in a small ring. In the original, pseudorotational mechanism, rate determining carbon-carbon bond formation occurs after, and in a separate step from, aldehyde coordination. Aldehyde coordination opposite one of the silyl methylene groups relieves ring strain by decreasing the bond angle between those silyl methylene groups. However, in the original mechanism this relief of ring strain happens before the proposed rate-limiting step (figure 18). Thus, only a modest rate acceleration would be expected with the small rings due to destabilization of the tetrahedral ground state relative to the dimethylsilyl analog. The transition state itself would not be expected to be significantly stabilized by the small ring (although the intermediate formed on initial aldehyde coordination would be).

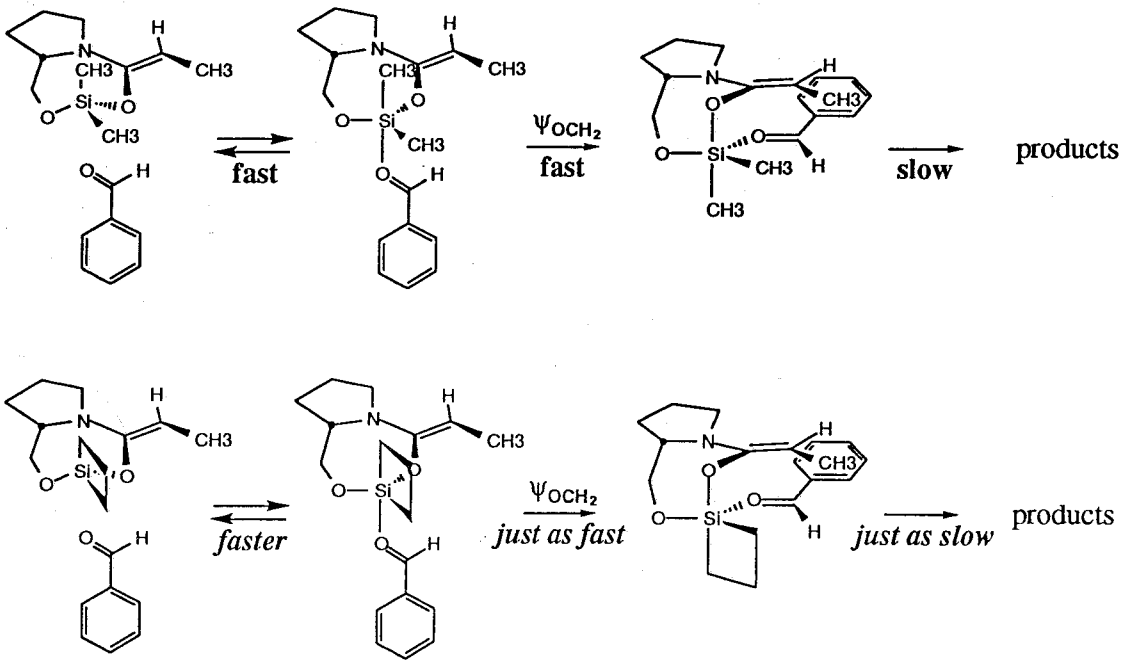


Figure 18. Rate comparison for pseudorotational mechanism. Since relief of ring strain is not involved in transition state, only modest rate acceleration expected.

In contrast, a concerted mechanism would be consistent with significant rate acceleration in the presence of a small ring. The dramatic increase in reaction rate from the dimethylsilyl enolate **1** to the silacyclobutane enolate **9** strongly suggests that C–Si–C bond angle rehybridization is occurring in the transition state. Since a separate, rate-limiting aldehyde coordination step had been ruled out by the large positive Hammet ρ value (3.5) determined earlier,[10] a single step mechanism in which aldehyde coordination and C–C bond formation occur simultaneously could be operating (figure 19).

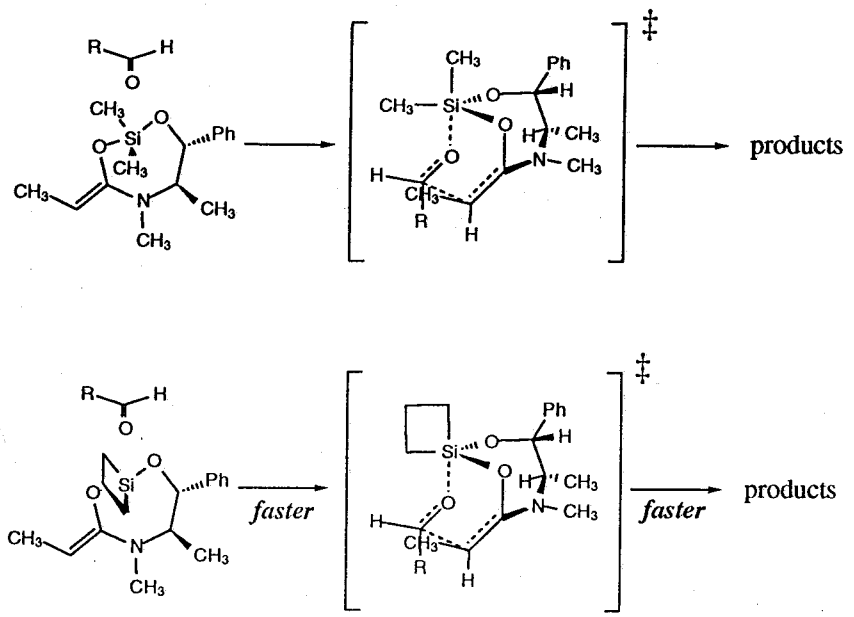


Figure 19. Rate comparison for concerted mechanism. Since relief of ring strain is involved in the transition state, significant rate acceleration is expected.

The pseudorotational mechanism satisfactorily rationalized the high anti selectivity for the silicon-mediated aldol reactions of *N,N*-dimethyl amides and the very strong facial selectivity of prolinol-derived silyl ketene *N,O*-acetal **1**. However, the facial selectivity of the silicon-mediated aldol reactions of pseudoephedrine-derived silyl ketene *N,O*-acetals **5** and **34** was found to be dependent on the steric bulk of the aldehyde. This, along with the observation that ephedrine-derived silyl ketene *N,O*-acetal **4** *does* react with benzaldehyde under conditions similar to the other enolates, suggests that another, non-pseudorotational mechanism, may be operating. The million fold increase in reactivity seen with the silacyclobutane compounds is also consistent with a mechanism in which relief of ring strain occurs in the rate-determining step. Thus, a concerted, pericyclic reaction mechanism is a plausible alternative to the original pseudorotational mechanism.

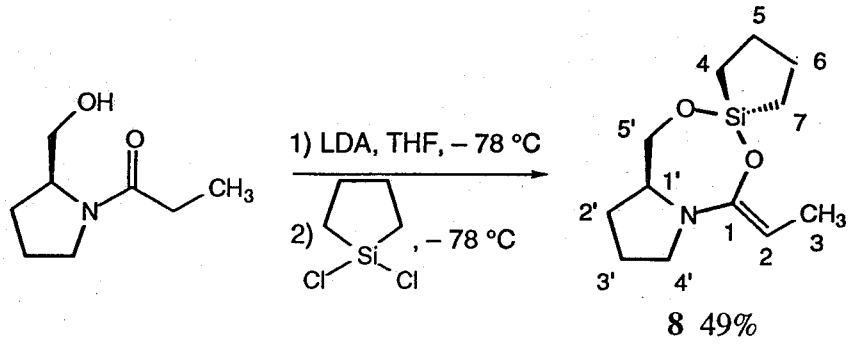
EXPERIMENTAL SECTION

General Procedures. All reactions were performed in flame-dried round bottom or modified Schlenk (Kjeldahl shape) flasks fitted with rubber septa under a positive pressure of dry argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Where necessary (so noted), solutions were deoxygenated by alternate evacuation for 10–15 seconds and flushing with argon (more than three iterations). Organic solutions were concentrated by rotary evaporation below 30 °C at ca. 25 Torr (water aspirator). Flash column chromatography was performed as described by Still et al.[42] employing 230–400 mesh silica gel. Analytical and preparative thin layer chromatography were performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin-layer chromatography plates were visualized by exposure to ultraviolet light (noted as 'UV') and/or by immersion in a staining solution (*p*-anisaldehyde or PMA as indicated) followed by heating on a hot-plate.

Materials. Commercial reagents and solvents were used as received with the following exceptions. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Methanol was distilled from magnesium turnings. Dichloromethane, *N*,*N*-diisopropylamine, triethylamine, toluene, benzene, and acetonitrile were distilled from calcium hydride. All aldehydes were distilled from calcium hydride at reduced pressure and stored under argon and over 4Å molecular sieves less than a week before use. All silyl chloride compounds, with the exception of TDSCl, were distilled from calcium hydride (at reduced pressure if necessary), and stored under argon. Cyclohexanone and 3-pentanone were distilled from calcium hydride immediately before use. The molarity of *n*-butyllithium

solutions was determined by titration using diphenylacetic acid as an indicator (average of three determinations).[43]

Instrumentation. Infrared (IR) spectra were obtained with a Perkin-Elmer 1600 FT-IR spectrophotometer referenced to a polystyrene standard. Data are presented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad), and assignment (when appropriate). Proton and carbon nuclear magnetic resonance (^1H NMR and ^{13}C NMR) spectra were recorded with a Bruker AM-500 (^1H, 500 MHz; ^{13}C, 125 MHz), JEOL JX-400 (^1H, 400 MHz; ^{13}C, 100 MHz), or General Electric QE-300 (^1H, 300 MHz; ^{13}C, 75 MHz) NMR spectrometer. Chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$, δ 7.26; C_6D_5H, δ 7.15). Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz), and assignment (H#). Elemental analyses were performed in the analytical laboratories of the Arnold and Mabel Beckman Laboratories of Chemical Synthesis. High resolution mass spectra were obtained from the University of California, Riverside Mass Spectrometry Facility and from the Midwest Center for Mass Spectrometry at the University of Nebraska, Lincoln. X-ray crystallographic analyses were obtained from the Arthur Amos Noyes Laboratory of Chemical Physics X-ray Facilities, Division of Chemistry and Chemical Engineering, California Institute of Technology, and from the University of California, Irvine Department of Chemistry X-ray Laboratory. Melting points were recorded with a Büchi SMP-20 melting point apparatus and are uncorrected.



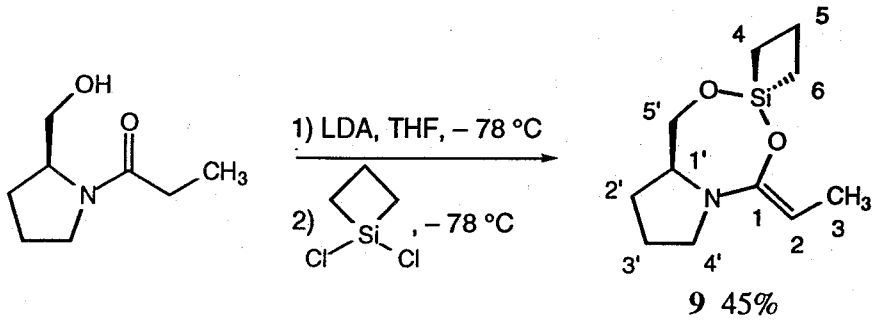
8 49%

Silacyclopentane (1'*S*)-*O*-Silyl Ketene *N,O*-acetal **8**

n-Butyllithium (23.2 mL, 2.50 M solution in hexanes, 57.9 mmol, 2.2 equiv) was added dropwise over 10 min to a deoxygenated solution of diisopropylamine (8.48 mL, 60.5 mmol, 2.3 equiv) in tetrahydrofuran (300 mL) at –78 °C. The solution was warmed to 0 °C and held at that temperature for 10 min. After the solution was recooled to –78 °C, a solution of (1'S)-prolinol propionamide (4.1355 g, 26.3 mmol, 1 equiv) in tetrahydrofuran (12 mL) was added by cannula. The transfer was quantitated by rinsing the amide flask with three 3-mL portions of tetrahydrofuran. After stirring the solution at –78 °C for 1.5 hours, dichlorosilacyclopentane (4.896 g, 31.6 mmol, 1.2 equiv) was added dropwise over 5 minutes. The solution was stirred at –78 °C for 2 more hours, then allowed to warm to 27 °C. The solvent was removed under vacuum (0.4 Torr), and the residue taken up in toluene (12 mL), from which a white solid precipitated. The supernatant was decanted by cannula and the precipitate washed with two aliquots of toluene (6 mL each). The combined toluene layers were concentrated (0.4 Torr) to an oily yellow solid which was purified by sublimation (0.4 Torr, dry-ice condenser, 100–120 °C oilbath), yielding **8** (3.0818 g, 12.9 mmol, 49%) as colorless, moisture sensitive, needle-like crystals. The *Z*-configuration was confirmed by X-ray crystal structure analysis (performed by Dr. Joseph Ziller, University of California, Irvine).

^{1}H NMR (300 MHz, C_6D_6), δ: 0.6–0.9 (m, 5H, H-3'a, H-4, H-7), 1.2–1.4 (m, 3H, H-2', H-3'b), 1.5–1.7 (m, 4H, H-5, H-6), 1.90 (q, 1H, J = 6.4 Hz, H-2), 2.67–2.80 (m, 1H, H-4'a), 2.81–2.87 (m, 1H, H-4'b), 3.25–3.40 (m, 2H, H-1', H-5'a), 3.54 (dd, J = 1.7, 9.3 Hz, H-5'b), 3.78 (q, 1H, J = 6.4 Hz, H-2)

^{13}C NMR (75 MHz, C_6D_6), δ: 9.1 (C-5), 10.2 (C-6), 11.0 (C-3), 25.0 (C-4), 25.3 (C-7), 25.9 (C-3'), 28.3 (C-2'), 50.8 (C-4'), 62.7 (C-1'), 71.1 (C-5'), 77.4 (C-2), 151.7 (C-1)

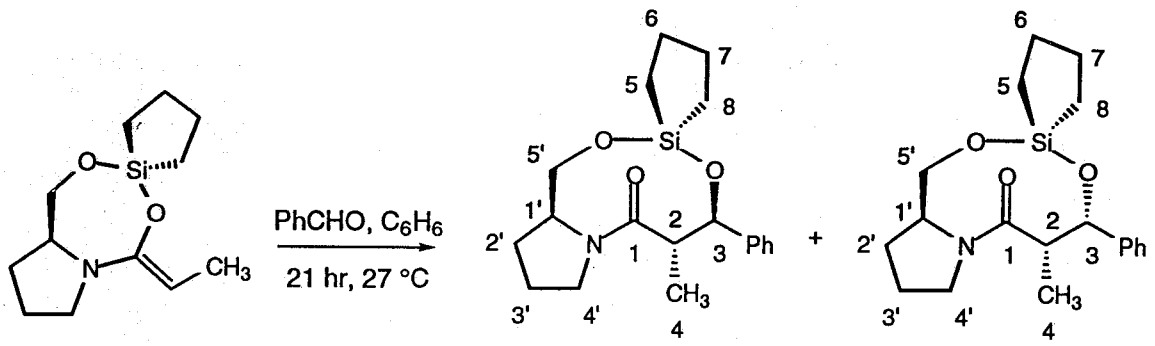


9 45%

Silacyclobutane (1'*S*)-*O*-Silyl Ketene *N,O*-acetal **9**

n-Butyllithium (23.0 mL, 2.50 M solution in hexanes, 57.5 mmol, 2.3 equiv) was added dropwise over 10 min to a deoxygenated solution of diisopropylamine (7.71 mL, 55 mmol, 2.2 equiv) in tetrahydrofuran (300 mL) at –78 °C. The solution was warmed to 0 °C and held at that temperature for 15 min. After the solution was recooled to –78 °C, a solution of (1'S)-prolinol propionamide (3.930 g, 25 mmol, 1 equiv) in tetrahydrofuran (10 mL) was added by cannula over 25 min. The transfer was quantitated by rinsing the amide flask with three 3-mL portions of tetrahydrofuran. After stirring the solution at –78 °C for 2 hours, a solution of dichlorosilacyclobutane (4.6138 g, 32.7 mmol, 1.3 equiv) in tetrahydrofuran (10 mL) was added by cannula over 20 minutes. The solution was stirred at –78 °C for 50 minutes, then allowed to warm to 27 °C. The solvent was removed under vacuum (0.4 Torr), and the residue taken up in toluene (15 mL), from which a white solid precipitated. The supernatant was decanted by cannula and the precipitate washed with two aliquots of toluene (5 mL each). The combined toluene layers were concentrated (0.4 Torr) and distilled (short path, 0.15 Torr, 77–95 °C) yielding **9** (2.544 g, 11.3 mmol, 45%) as a colorless, extremely moisture-sensitive liquid of 93% purity. (The major contaminant is an N-silylated diisopropylamine adduct which could not be separated by distillation)

^{1}H NMR (400 MHz, C_6D_6), δ:	0.81 (m, 1H, H-3'a), 1.05–1.35 (m, 3H, H-2', H-3'b), 1.45–1.85 (m, 6H, H-4, H-5, H-6), 1.92 (d, 3H, J = 6.4 Hz, H-3), 2.69 (m, 1H, H-4'a), 2.82 (m, 1H, H-4'b), 3.36 (m, 2H, H-1', H-5'a), 3.53 (d, 1H, J = 7.3 Hz, H-5'b), 3.80 (q, 1H, J = 6.4 Hz, H-2)
^{13}C NMR (100 MHz, C_6D_6), δ:	10.5 (C-3), 12.4 (C-5), 21.8 (C-4), 21.9 (C-6), 24.3 (C-3'), 27.6 (C-2'), 50.2 (C-4'), 62.2 (C-1'), 70.3 (C-5'), 77.4 (C-2), 150.7 (C-1)
FTIR (neat), cm^{-1}:	2929 (s), 2772 (m), 1669 (s), 1334 (s), 1128 (s), 1045 (m), 889 (m), 719 (m)



8 **10** 20% **11** 30%

Silacyclopentane Aldol Adducts: (1'*S*, 2*S*, 3*R*)-Anti **10** and (1'*S*, 2*S*, 3*S*)-Syn **11**

A solution of benzaldehyde (0.767 mL, 7.54 mmol, 1.05 equiv) in benzene (10 mL) was added over 6 minutes to a solution of silacyclopentane (1'S)-*O*-silyl ketene *N,O*-acetal **8** (1.72 g, 7.19 mmol, 1 equiv) in benzene (40 mL) at 27 °C. After stirring at 27 °C for 21 hours, the solution was concentrated under vacuum (0.4 Torr) and purified by flash column chromatography (30% ethyl acetate in hexanes eluent). Anti adduct **10** (0.4865 g, 1.41 mmol, 20%) was isolated as colorless, feathery crystals which decomposed on exposure to air. Syn adduct **11** (0.7492 g, 2.17 mmol, 30%) was isolated as a colorless, crystalline solid, mp 157–161 °C. The (1'*S*, 2*S*, 3*S*) geometry of **11** was confirmed by X-ray crystal structure analysis.[15]

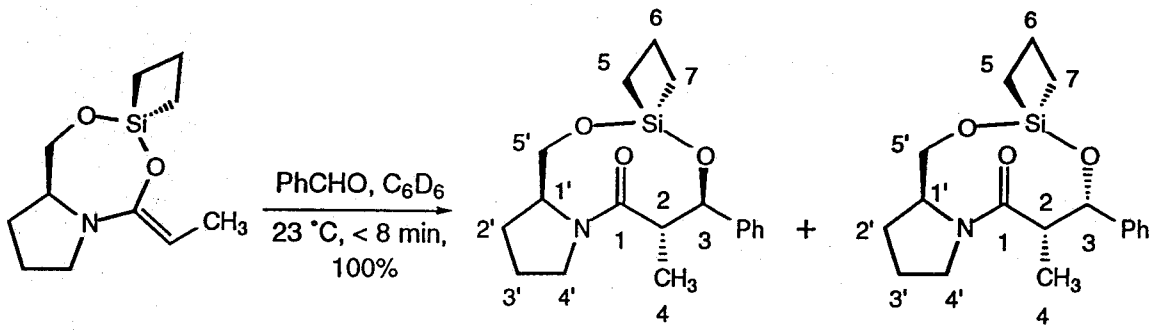
Silacyclopentane (1'*S*, 2*S*, 3*R*)-Anti Aldol Adduct **10**

^{1}H NMR (300 MHz, C_6D_6), δ: 0.47–0.61, 0.65–0.85, 0.96 (3m, 1H, 2H, 1H respectively, H-5, H-8), 1.01 (d, 3H, J = 6.6 Hz, H-4), 1.19–1.60, 1.82 (2m, 7H, 1H, respectively,

	H-2', H-3', H-6, H-7), 2.86 (dq, 1H, J = 6.7, 9.7 Hz, H-2), 2.98 (br t, 1H, J = 7.4, H-4'a), 3.41 (d, 1H, J = 10.8 Hz, H-5'a), 3.52 (dt, 1H, J = 6.5, 9.4 Hz, H-4'b), 3.96 (t of d, 1H, J = 3.0, 7.5 Hz, H-1'), 4.88 (d, 1H, J = 9.7 Hz, H-3), 5.09 (dd, 1H, J = 3.2, 10.9 Hz, H-5'b), 7.03–7.19, 7.25–7.32 (2m, 3H, 2H respectively, aromatic H)
^{13}C NMR (75 MHz, C_6D_6), δ:	6.4, 11.8, 13.6, 25.1, 25.2, 25.7, 28.9, 47.9, 49.5, 59.6, 63.4, 82.9, 127.6, 128.4, 128.9, 129.0, 143.6, 173.9
FTIR (neat), cm^{-1}:	2934 (m), 1636 (s, C=O), 1431 (s), 1250 (w), 1204 (w), 1110 (s), 1075 (s), 1028 (m), 990 (m), 911 (w), 840 (m), 807 (m), 741 (w), 700 (s)
MS (CI/NH_3), m/z:	346 (MH^+)
HRMS (CI/NH_3), m/z:	Calcd for $C_{19}H_{28}O_3NSi$ (MH^+): 346.1838 Found: 346.1837
TLC (50% Et_2O in Pet. Ether), R_f:	Anti Adduct **10**: 0.25 (PMA) Syn Adduct **11**: 0.18 (PMA)

Silacyclopentane (1'*S*, 2*S*, 3*S*)-Syn Aldol Adduct **11**

^{1}H NMR (300 MHz, C_6D_6), δ:	0.36–0.57, 0.71, 0.86 (3m, 2H, 1H, 1H, respectively, H-5, H-8), 1.07 (d, 3H, J = 6.8 Hz, H-4), 1.2–1.8 (3m, 8H total, H-2', H-3', H-6, H-7), 2.81 (dq, 1H, J = 3.6, 6.8 Hz, H-2), 3.05 (br t, 1H, J = 7.6 Hz, H-4'a), 3.17 (dt, 1H, J = 5.7, 10.3 Hz, H-4'b), 3.31 (d, 1H, J = 10.6 Hz, H-5'a), 4.02 (t of d, 1H, J = 2.7, 8.2 Hz, H-1'), 4.90 (br d, 1H, J = 9.2 Hz, H-5'b), 5.48 (d, 1H, J = 3.5 Hz, H-3), 7.07–7.30 (m, 5H, aromatic H)
^{13}C NMR (75 MHz, C_6D_6), δ:	8.9, 9.0, 9.3, 25.17, 25.21, 25.5, 27.6, 46.4, 48.2, 58.3, 61.5, 73.0, 125.6, 127.1, 128.4, 142.2, 171.6
FTIR (neat), cm^{-1}:	2936 (s), 2872 (m), 1634 (s, C=O), 1450 (s), 1422 (s), 1379 (m), 1250 (m), 1097 (s), 1076 (s), 1025 (s), 989 (m), 913 (m), 877 (m), 853 (m), 754 (m), 701 (s)
MS (CI/NH_3), m/z:	346 (MH^+), 239 ($MH^+ - C_7H_6O$)
HRMS (CI/NH_3), m/z:	Calcd for $C_{19}H_{28}O_3NSi$ (MH^+): 346.1838 Found: 346.1821



9 **12** **13**

Silacyclobutane Aldol Adducts: (1'*S*, 2*S*, 3*R*)-Anti **12** and (1'*S*, 2*S*, 3*S*)-Syn **13**

An initial 300 MHz ^{1}H NMR spectrum was recorded for a solution of silacyclobutane silyl ketene acetal 9 (31.6 mg, 0.14 mmol, 1 equiv) in deuterated benzene (0.50 mL). Benzaldehyde (15.7 μL, 0.15 mmol, 1.1 equiv) was injected, the sample was immediately replaced in the NMR probe, and a second spectrum taken. Less than 8 minutes after aldehyde injection, only aldol products (**12**:**13** = 1:6) and excess benzaldehyde are visible in the NMR spectrum.

Note: **12** and **13** are extremely moisture-sensitive and were not isolated.

Silacyclobutane (1'*S*, 2*S*, 3*R*)-Anti Aldol Adduct **12**

^{1}H NMR (300 MHz, C_6D_6), δ: 0.97 (d, 3H, *J* = 6.6 Hz, H-4), 1.20–1.75 (m, 10 H, H-2', H-3', H-5, H-6, H-7), 2.82 (dq, 1H, *J* = 6.6, 9.6 Hz, H-2), ~3.00 (br t, 1H, *J* = 7.8, H-4'a, partially obscured by syn resonance at 3.02) 3.34 (d, 1H, *J* = 10.8 Hz, H-5'a), 3.48 (dt, 1H,

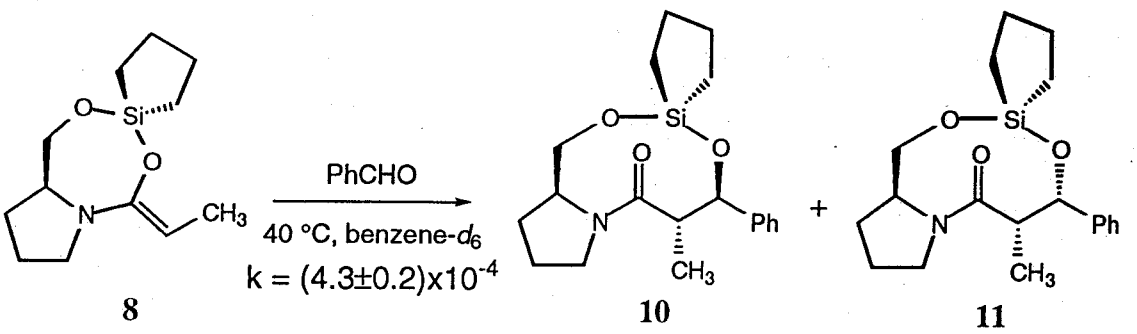
J = 6.3, 9.4 Hz, H-4'b), 4.95 (d, 1H, J = 8.1 Hz, H-3), 5.18 (dd, 1H, J = 3.0, 10.8 Hz, H-5'b) resonance for H-1' probably obscured by syn peak at 3.94.

^{13}C NMR (75 MHz, C_6D_6), δ: 12.6, 13.0, 18.2, 21.7, 24.7, 28.5, 47.4, 49.0, 59.1, 61.4, 81.0, 127.2, 128.6, 129.0, 142.8, 173.3

Silacyclobutane (1'*S*, 2*S*, 3*s*)-Syn Aldol Adduct **13**

^{1}H NMR (300 MHz, C_6D_6), δ: 1.04 (d, 3H, J = 6.6 Hz, H-4), 1.20–1.75 (m, 10 H, H-2', H-3', H-5, H-6, H-7), 2.79 (dq, 1H, J = 3.6, 6.9 Hz, H-2), 3.02 (br t, 1H, J = 7.8 Hz, H-4'a), 3.09 (dq, 1H, J = 5.7, 10.5 Hz, H-4'b), 3.27 (d, 1H, J = 10.5 Hz, H-5'a), 3.94 (dt, 1H, J = 3.3, 8.1 Hz, H-1'), 4.98 (dd, 1H, J = 3.3, 10.5 Hz, H-5'b), 5.55 (d, 1H, J = 3.6, H-3)

^{13}C NMR (75 MHz, C_6D_6), δ: 8.9, 12.3, 21.1, 21.5, 25.4, 27.9, 46.2, 48.2, 58.3, 60.5, 72.4, 125.6, 127.1, 128.5, 142.1, 171.8

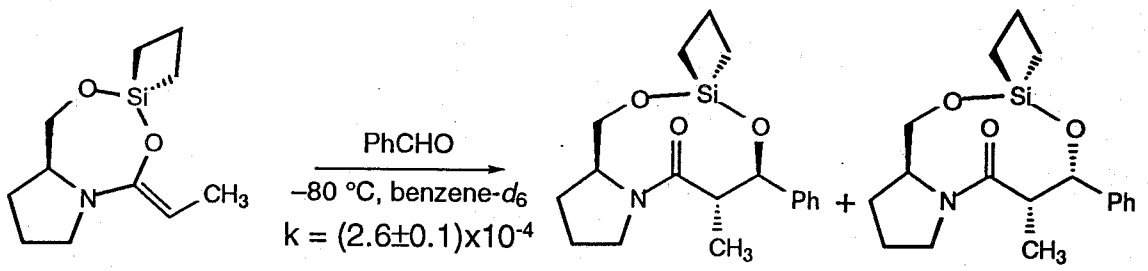


8 **10** **11**

Kinetic Analysis of Silacyclopentane ketene acetal **8** at 40 °C

Silacyclopentane ketene acetal **8** (31.8 mg, 0.13 mmol, 1 equiv) was weighed into an NMR tube capped with a septum, dissolved in benzene–d_6 (0.420 mL), and *cis*-stilbene (10.0 μL, 0.056 mmol, 0.44 equiv) added as an internal reference. The exact concentration of **8** was determined from an initial 400 MHz ^{1}H NMR spectrum taken at 27 °C. Benzaldehyde (12.9 μL, 0.127 mmol, 1.0 equiv) was added, and further spectra taken in an NMR probe warmed to 40 °C. The appearance of two product protons in the region 4.6–5.7 ppm was followed for 10 hours (80% conversion). The rate constant was derived from a plot of $([E]_o-[P])^{-1}$ vs. t.

$$k = (4.29\pm0.18)\times10^{-4}\ M^{-1}s^{-1}$$

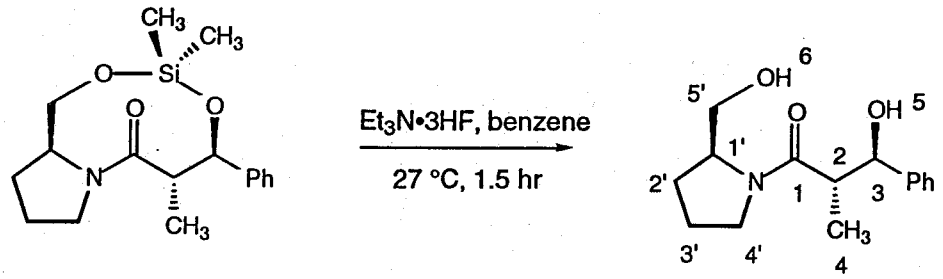


9 **12** **13**

Kinetic Analysis of Silacyclobutane ketene acetal **9** at –80 °C

Silacyclobutane ketene acetal **9** (30.4 mg, 0.135 mmol, 1.0 equivalents) was weighed into an NMR tube capped with a septum, dissolved in toluene-d_8 (0.420 mL), and *cis*-stilbene (10.0 μL, 0.056 mmol, 0.42 equiv) added as an internal reference. The exact concentration of **9** was determined from an initial 400 MHz ^{1}H NMR spectrum taken at 27 °C. The sample was frozen in liquid nitrogen, benzaldehyde (13.7 μL, 0.135 mmol, 1.0 equiv) added, and further spectra taken in an NMR probe cooled to –80 °C. The appearance of two product protons in the region 4.9–5.6 ppm was followed for 8 hours (65% conversion). The rate constant was derived from a plot of $([E]_o–[P])^{-1}$ vs. t.

$$k = (2.58\pm0.09)\times10^{-4}\ M^{-1}s^{-1}$$



2 **14** 89%

Authentic (1'*S*, 2*S*, 3*R*)-Anti Diol **14**

Triethylamine trihydrofluoride (0.248 mL, 1.52 mmol, 3.0 equiv) was added to a solution of dimethylsilyl (1'*S*, 2*S*, 3*R*)-anti aldol adduct **2**[10] (161.9 mg, 0.51 mmol, 1 equiv) in benzene (10 mL) at 27 °C. After stirring 1.5 hr, the solution was concentrated and the residue was purified by flash column chromatography (100% ethyl acetate) to yield anti diol **14** (118.5 mg, 0.45 mmol, 89%) as a colorless gel.

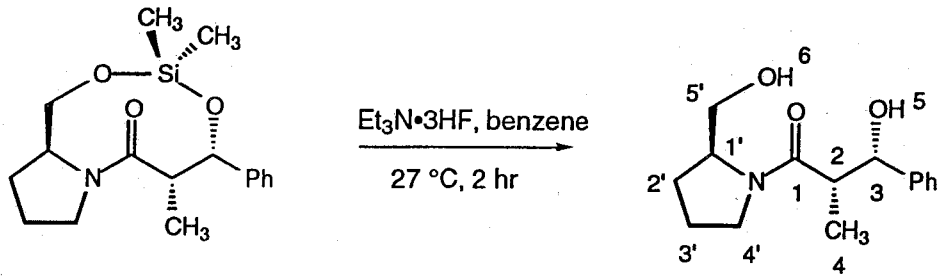
^{1}H NMR (400 MHz, $CDCl_3$), δ: Major rotamer: 1.15 (d, 3H, J = 7.0 Hz, H-4), 1.61, 1.72–1.85, 1.96 (3m; 1H, 2H, 1H, respectively; H-2', H-3'), 2.91 (quintet, 1H, J = 6.6 Hz, H-2), 3.26, 3.34, 3.63 (m; m; br d, J = 11.1 Hz; 1H, 2H, 1H, respectively; H-4', H-5'), 4.09 (m, 1H, H-1'), 4.32 (br s, 1H, H-6), 4.54 (br s, 1H, H-5), 4.77 (d, 1H, J = 5.9 Hz, H-3), 7.26–7.35 (m, 5H, aromatic H)

FTIR (neat), cm^{-1}: 3374 (s, br, –OH), 2969 (m), 2872 (m), 1612 (s, C=O), 1441 (s), 1076 (w), 1048 (m), 766 (m), 702 (s)

TLC (20% acetone in ethyl acetate), R_f: Anti Diol **14**: 0.22 (PMA)

(50% ethyl acetate in toluene), R_f: 0.05 (PMA)

(100% ethyl acetate), R_f: 0.15 (PMA)



3 **15** 79%

Authentic (1'*S*, 2*S*, 3*S*)-Syn Diol **15**

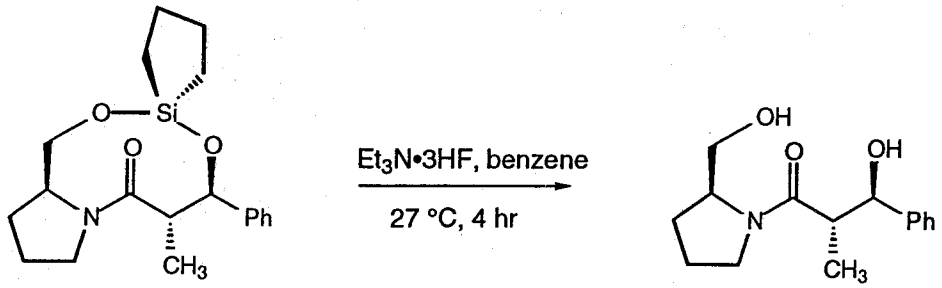
Triethylamine trihydrofluoride (43.5 μL, 0.27 mmol, 3.0 equiv) was added to a solution of dimethylsilyl (1'*S*, 2*S*, 3*S*)-syn aldol adduct **3**[10] (28.4 mg, 0.09 mmol, 1 equiv) in benzene (10 mL) at 27 °C. After stirring 2 hours, the solution was concentrated and the residue was purified by flash column chromatography (100% ethyl acetate) to yield syn diol **15** (18.4 mg, 0.07 mmol, 79%) as a colorless, crystalline solid.

^{1}H NMR (500 MHz, $CDCl_3$), δ: Major rotamer: 1.13 (d, 3H, J = 7.0 Hz, H-4), 1.72 (br s, 1H, H-6), 1.57, 1.80, 1.86, 2.02 (4m, 1H each, H-2', H-3'), 2.75 (dq, 1H, J = 4.2, 7.0 Hz, H-2), 3.32 (dt, 1H, J = 7.2, 10.2 Hz, H-5'a), 3.47, 3.62 (2m, 1H each, H-4'), 4.15 (dq, 1H, J = 2.6, 6.2 Hz, H-1'), 4.24 (br s, 1H, H-5), 4.60 (br d, 1H, J = 6.1 Hz, H-5'b), 5.05 (d, 1H,J = 4.1 Hz, H-3), 7.27, 7.34 (2m, 5H total, aromatic H)

^{13}C NMR (100 MHz, $CDCl_3$), δ: 10.9, 24.0, 27.9, 45.1, 47.8, 60.7, 65.9, 74.3, 126.0, 127.2, 127.9, 141.9, 176.7

FTIR (neat), cm^{-1}: 3372 (m, br, –OH), 2969 (m), 2876 (m), 1608 (s, C=O), 1454 (s), 1438 (m), 1079 (w), 1041 (m), 767 (m), 702 (s)

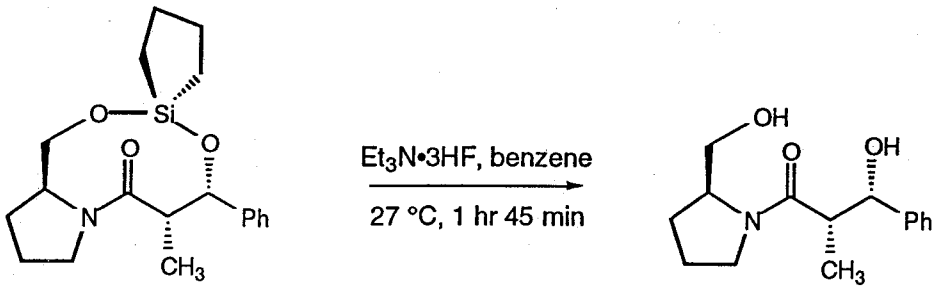
TLC (50% ethyl acetate in hexanes),	R_f:	Syn Diol **15**:	0.05 (PMA)
(10% MeOH in dichloromethane),	R_f:		0.43 (PMA)
(10% acetone in ethyl acetate),	R_f:		0.25 (PMA)
(20% acetone in ethyl acetate),	R_f:		0.31 (PMA)
(25% ethyl acetate in toluene),	R_f:		0.03 (PMA)
(50% ethyl acetate in toluene),	R_f:		0.05 (PMA)
(100% ethyl acetate),	R_f:		0.05 (PMA)



10 **14** 76%

Desilylation of Silacyclopentane (1'*S*, 2*S*, 3*R*)-Anti Aldol Adduct 10

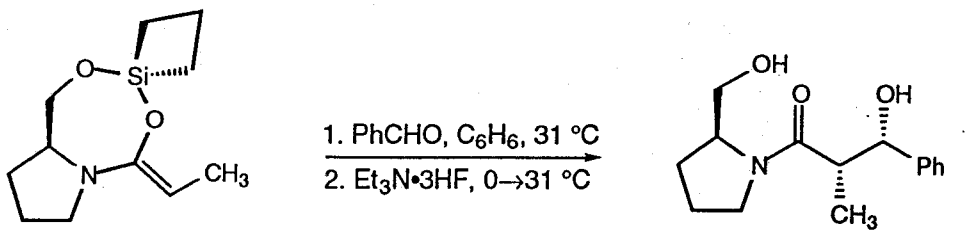
Triethylamine trihydrofluoride (0.236 mL, 1.45 mmol, 3.0 equiv) was added to a solution of silacyclopentane (1'*S*, 2*S*, 3*R*)-anti aldol adduct **10** (166.9 mg, 0.48 mmol, 1 equiv) in benzene (10 mL) at 27 °C. After stirring 4 hours, the solution was concentrated and the residue was purified by flash column chromatography (100% ethyl acetate) to yield anti diol **14** (96.7 mg, 0.37 mmol, 76%) as a colorless gel. ^{1}H NMR and FTIR spectra of ths compound were identical to those of the authentic anti diol obtained from the dimethylsilyl analog. The diol product also co-eluted with authentic **14** under several TLC conditions.



11 **15**

Desilylation of Silacyclopentane (1'*S*, 2*S*, 3*S*)-Syn Aldol Adduct **11**

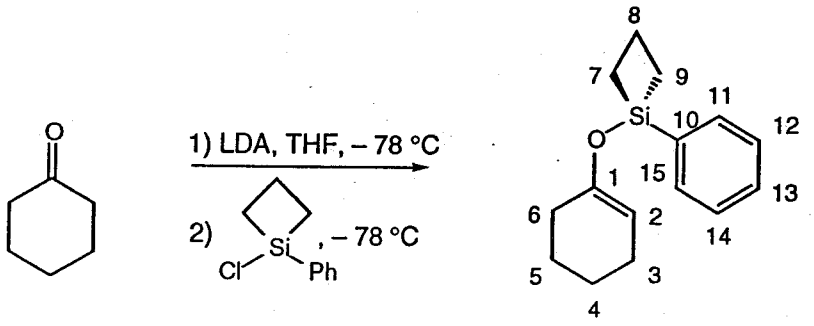
Triethylamine trihydrofluoride (0.105 mL, 0.65 mmol, 3.0 equiv) was added to a solution of silacyclopentane (1'*S*, 2*S*, 3*S*)-syn aldol adduct **11** (74.5 mg, 0.22 mmol, 1 equiv) in benzene (10 mL) at 27 °C. After stirring 1 hour 45 minutes, the solution was concentrated and the residue was purified by flash column chromatography (100% ethyl acetate) to yield syn diol **15** (86.1 mg, >100%, contaminated with silica gel?) as a colorless solid. ^{1}H NMR and FTIR spectra of ths compound were identical to those of the authentic syn diol obtained from the dimethylsilyl analog. The diol product also co-eluted with authentic **15** under several TLC conditions.



9 **15** 80%

Desilylation of Silacyclobutane Aldol Adducts

Silacyclobutane silyl ketene acetal 9 (0.7519g, 3.34 mmol, 1.06 equiv) was added to a solution of benzaldehyde (0.322 mL, 3.17 mmol, 1 equiv) in benzene (30 mL) at 31 °C (warm room). The solution was stirred at 31 °C for 10 minutes, then cooled to 0 °C, and treated with triethylamine trihydrofluoride (1.63 mL, 10.0 mmol, 3.15 equiv). After stirring 1 hr 15 min at 0 °C, the reaction mixture was warmed to 31 °C and held at that temperature for 45 min. The solution was concentrated, and the residue was purified by flash column chromatography (20% acetone in ethyl acetate), affording diol **15** (0.6678 g, 2.54 mmol, 80%) as a colorless crystalline solid. The syn stereochemistry was confirmed by comparison of the NMR, IR, and TLC data with that from an authentic sample derived from the dimethyl analog.

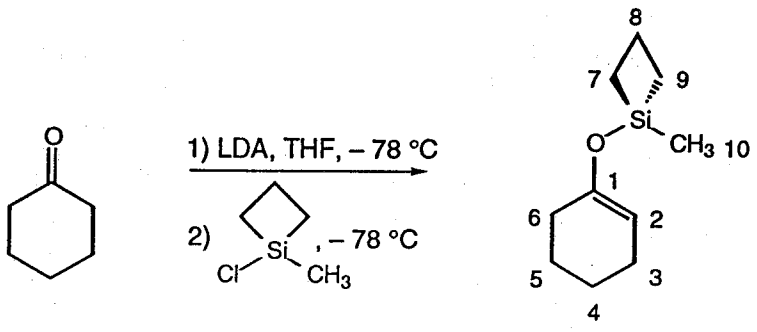


20 92%

Silylphenyl-Silacyclobutane Enol Ether **20**

n-Butyllithium (4.38 mL, 2.51 M solution in hexanes, 11 mmol, 1.1 equiv) was added dropwise over 4 min to a deoxygenated solution of diisopropylamine (1.68 mL, 12 mmol, 1.2 equiv) in tetrahydrofuran (50 mL) at –78 °C. After stirring 10 min at –78 °C, the solution was warmed to 0 °C and held at that temperature for 10 min. The reaction mixture was recooled to –78 °C and cyclohexanone (1.04 mL, 0.9815 g, 10 mmol, 1 equiv) was added by syringe over 5 min. Stirring was continued at –78 °C for 1 hour, then 1-phenyl-1-chloro-1-silacyclobutane (2.27 g, 2.00 mL, 12.4 mmol, 1.24 equiv) was added over 3 min. The solution was warmed to 27 °C and concentrated under vacuum (1 Torr). The residue was taken up in pentane (10 mL), from which a white solid precipitated. The supernatant was decanted by cannula and the precipitate washed with two aliquots of pentane (5 mL each). The combined pentane layers were filtered under argon through a fine frit to remove suspended precipitate, concentrated (1 Torr), and distilled (short path, 11 mTorr, 78–80 °C) providing enol ether **20** (2.2433 g, 9.2 mmol, 92%) as a colorless liquid.

^{1}H NMR (300 MHz, C_6D_6), δ:	1.35 (m, 2H, H-4), 1.45–1.77 (m, 7H, H-5, H-7, H-9, H-8a), 1.90 (m, 2H, H-3), 2.11 (m, 3H, H-6, H-8b), 5.11 (t of t, 1H, J = 3.9, 1.5 Hz, H-2), 7.22 (m, 3H, H-12, H-13, H-14), 7.73 (m, 2H, H-11, H-15)
^{13}C NMR (75 MHz, C_6D_6), δ:	14.6 (C-8), 18.9 (C-7, C-9), 22.5 (C-4), 23.4 (C-5), 24.1 (C-3), 30.2 (C-6), 104.9 (C-2), 128.3 (C-12, C-14), 130.4 (C-13), 133.9 (C-11, C-15), 136.1 (C-10), 150.5 (C-1)
FTIR (neat), cm^{-1}:	2929 (s), 1669 (m), 1428 (m), 1365 (m), 1265 (m), 1181 (s), 1168 (s), 1123 (s), 987 (m), 910 (s), 853 (m), 739 (s), 699 (s)
MS (CI/NH_3), m/z:	245 (MH^+)
HRMS (CI/NH_3), m/z:	Calcd for $C_{15}H_{21}OSi$ (MH^+): 245.1362 Found: 245.1354

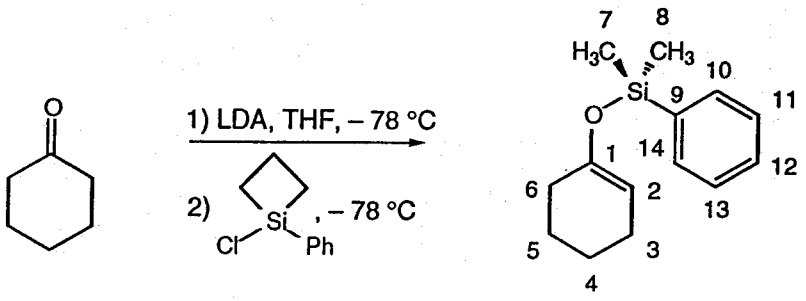


21 73%

Silylmethyl-Silacyclobutane Enol Ether **21**

n-Butyllithium (4.38 mL, 2.51 M solution in hexanes, 11 mmol, 1.1 equiv) was added dropwise over 5 min to a deoxygenated solution of diisopropylamine (1.68 mL, 12 mmol, 1.2 equiv) in tetrahydrofuran (50 mL) at –78 °C. After stirring 10 min at –78 °C, the solution was warmed to 0 °C and held at that temperature for 10 min. The reaction mixture was recooled to –78 °C, and cyclohexanone (1.04 mL, 0.9815 g, 10 mmol, 1 equiv) was added by syringe over 4 min. Stirring was continued at –78 °C for 1 hour, then 1-methyl-1-chloro-1-silacyclobutane (1.52 g, 1.6 mL, 12.6 mmol, 1.26 equiv) was added over 5 min. The solution was warmed to 27 °C and concentrated under vacuum (35 Torr). The residue was taken up in pentane (10 mL), from which a white solid precipitated. The supernatant was decanted by cannula and the precipitate washed with two aliquots of pentane (5 mL each). The combined pentane layers were filtered under argon through a fine frit to remove suspended precipitate, concentrated (35 Torr), and distilled (short path, 38 Torr, 74–79 °C) yielding enol ether **21** (1.3253 g, 7.3 mmol, 73%) as a colorless liquid.

^{1}H NMR (300 MHz, C_6D_6), δ:	0.28 (s, 3H, H-10), 1.19 (m, 2H, H-7a, H-9a), 1.39 (m, 2H, H-7b, H-9b), 1.51 (m, 6H, H-4, H-5, H-8), 1.96 (m, 2H, H-3), 2.06 (m, 2H, H-6), 5.06 (t of t, 1H, J = 3.9, 1.4 Hz, H-2)
^{13}C NMR (75 MHz, C_6D_6), δ:	–1.3 (C-10), 14.1 (C-8), 19.4 (C-7, C-9), 22.7 (C-4), 23.4 (C-5), 24.1 (C-3), 30.2 (C-6), 104.4 (C-2), 150.5 (C-1)
FTIR (neat), cm^{-1}:	2932 (s), 2841 (m), 1671 (m), 1366 (m), 1266 (w), 1252 (m), 1182 (s), 1121 (m), 987 (m), 916 (s), 865 (m), 780 (m)
MS (CI/NH_3), m/z:	183 (MH^+)
HRMS (CI/NH_3), m/z:	Calcd for $C_{10}H_{19}OSi$ (MH^+): 183.1205 Found: 183.1197



22 69%

Phenyldimethyl Silyl Enol Ether **22**

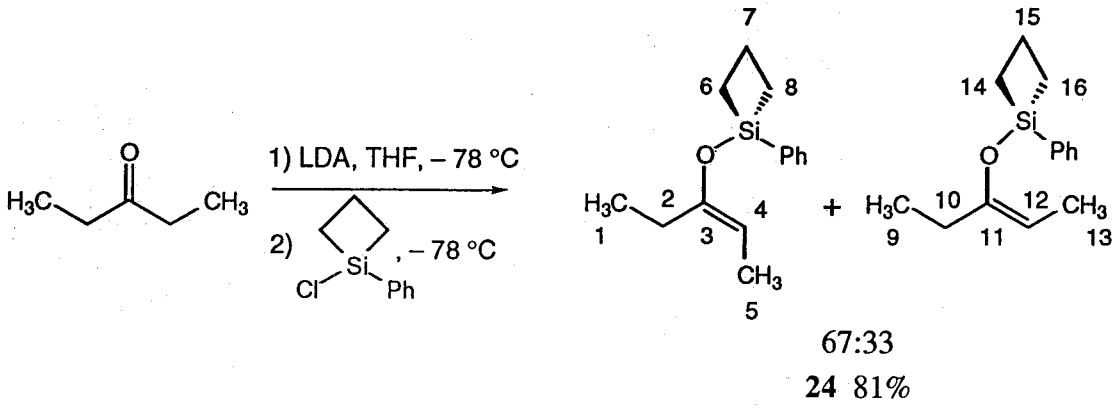
Cyclohexanone (0.644 mL, 6.2 mmol, 1 equiv) was added dropwise over 6 min to a deoxygenated solution of lithium diisopropyl amide (0.7322 g, 6.8 mmol, 1.1 equiv) in tetrahydrofuran (40 mL) at –78 °C. The solution was warmed to 0 °C and held at that temperature for 10 min. The reaction mixture was recooled to –78 °C, and phenyldimethylchlorosilane (1.233 mL, 7.5 mmol, 1.2 equiv) was added by syringe over 4 min. The solution was allowed to gradually warm to 27 °C overnight. Solvent was removed under reduced pressure (100 Torr), and the residue was taken up in pentane (10 mL), from which a white solid precipitated. The supernatant was decanted by cannula and the precipitate washed with two aliquots of pentane (3 mL each). The combined pentane layers were concentrated (100 Torr) and distilled (Kugelrhor, 30–35 Torr, 120–150 °C) furnishing enol ether **22** (0.9916 g, 4.27 mmol, 69%) as a colorless liquid.

^{1}H NMR (300 MHz, C_6D_6), δ: 0.41 (s, 6H, H-7, H-8), 1.35 (m, 2H, H-4), 1.46 (m, 2H, H-5), 1.89 (m, 2H, H-3), 2.06 (m, 2H, H-6), 4.97 (t of t, 1H, J = 3.9, 1.4 Hz, H-2), 7.21

(m, 3H, H-11, H-12, H-13), 7.63 (m, 2H, H-10, H-14)

^{13}C NMR (75 MHz, C_6D_6), δ: –0.8 (C-7, C-8), 22.6 (C-4), 23.4 (C-5), 24.1 (C-3), 30.3 (C-6), 104.2 C-2), 128.1 (C-11, C-13), 129.6 (C-12), 129.6 (C-12), 133.7 (C-10, C-14), 138.5 (C-9), 150.8 (C-1)

FTIR (neat), cm^{-1}: 2931 (m), 1717 (w), 1591 (w), 1428 (m), 1366 (w), 1339 (w), 1253 (s), 1186 (s), 1119 (s), 1049 (m), 986 (w), 893 (s), 832 (s), 787 (s), 7279 (m), 699 (s), 650 (w)



Silylphenyl-Silacyclobutane Enol Ethers **24**

n-Butyllithium (4.38 mL, 2.51 M solution in hexanes, 11 mmol, 1.1 equiv) was added dropwise over 5 min to a deoxygenated solution of diisopropylamine (1.68 mL, 12 mmol, 1.2 equiv) in tetrahydrofuran (100 mL) at –78 °C. The solution was warmed to 0 °C and held at that temperature for 10 min. The reaction mixture was recooled to –78 °C, and 3-pentanone (1.01 mL, 0.861 g, 10 mmol, 1 equiv) was added by syringe over 3 min. Stirring was continued at –78 °C for 1 hour, then 1-phenyl-1-chloro-1-silacyclobutane (2.0 mL, 2.25 g, 12 mmol, 1.2 equiv) was added over 3 min. The mixture was stirred at –78 °C for 1.5 hours more, then warmed to 27 °C. Solvent was removed under vacuum (1 Torr), and the residue was taken up in pentane (10 mL), from which a white solid precipitated. The supernatant was decanted by cannula and the precipitate washed with two aliquots of pentane (5 mL each). The combined pentane layers were filtered under argon through a fine frit to remove suspended precipitate, concentrated (1 Torr), and distilled (short path, 16–17 mTorr, 110–117 °C) affording enol ether mixture **24** (1.8902 g, 8.13 mmol, 81%) as a colorless liquid along with N-silylated diisopropylamine as an impurity (8%). The isomer ratio was determined by ^{1}H NMR

analysis to be 67% *E*, 33% *Z*. (*Note*: This enol ether is prone to isomerize on standing or distillation to a mixture which is ~20% *E*, ~80% *Z*.)

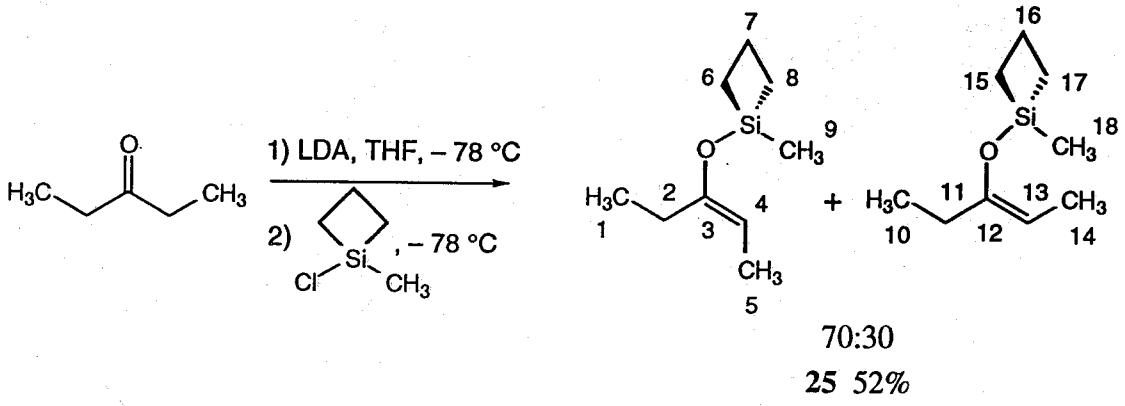
^{1}H NMR (300 MHz, C_6D_6), δ: *E* isomer: 1.08 (t, 3H, *J* = 7.5 Hz, H-1), 1.42 (d, 3H, *J* = 6.9 Hz, H-5), 1.49–1.70 (m, 5H, H-6, H-8, H-7a), 2.0–2.2 (m, 3H, H-2, H-7b), 4.84 (q, 1H, *J* = 7.0 Hz, H-4), 7.22 (m, 3H, aromatic H), 7.73 (m, 2H, aromatic H)

Z isomer: 0.99 (t, 3H, *J* = 7.4 Hz, H-9), 1.49–1.70 (m, 5H, H-14, H-16, H-15a), 1.64 (d of t, 3H, *J* = 6.7, 1.4 Hz, H-13), 2.0–2.2 (m, 3H, H-10, H-15b), 4.57 (q of t, 1H, *J* = 6.7, 1.1 Hz, H-12), 7.22 (m, 3H, aromatic H), 7.73 (m, 2H, aromatic H)

^{13}C NMR (75 MHz, C_6D_6), δ: *E* isomer: 11.8 (C-1), 11.8 (C-5), 14.5 (C-7), 19.0 (C-6, C-8), 24.4 (C-2), 101.46 (C-4), 128.29, 130.4, 133.8, 136.1, 152.6 (C-3)

Z isomer: 11.1 (C-9), 11.9 (C-13), 14.2 (C-15), 19.6 (C-14, C-16), 30.0 (C-10), 101.49 (C-12), 128.32, 130.5 , 133.9, 135.9, 153.2 (C-11)

FTIR (neat), cm^{-1}: 2970 (s), 2932 (m), 1670 (m), 1429 (m), 1266 (w), 1197 (s), 1115 (s), 1083 (m), 1064 (m), 907 (m), 867 (m), 854 (m), 699 (m)



Silylmethyl-Silacyclobutane Enol Ethers **25**

n-Butyllithium (6.57 mL, 2.51 M solution in hexanes, 16.5 mmol, 1.1 equiv) was added dropwise to a deoxygenated solution of diisopropylamine (2.52 mL, 18 mmol, 1.2 equiv) in tetrahydrofuran (100 mL) at –78 °C. The solution was warmed to 0 °C and held at that temperature for 10 min. The reaction mixture was recooled to –78 °C, and 3-pentanone (1.51 mL, 15 mmol, 1.0 equiv) was added by syringe over 5 min. Stirring was continued at –78 °C for 1.5 hours, then 1-methyl-1-chloro-1-silacyclobutane (2.6 g, 21.3 mmol, 1.4 equiv) was added over 10 minutes. The solution was allowed to warm to 27 °C, concentrated under vacuum (90 Torr), and the residue taken up in hexanes (25 mL), from which a white solid precipitated. The supernatant was decanted by cannula and the precipitate washed with two aliquots of hexanes (6 mL each). The combined hexane layers were filtered under argon through a fine frit to remove suspended precipitate, concentrated (40 Torr), and distilled (short path, 35 Torr, 53–55 °C) yielding enol ether mixture **25** (1.3201 g, 7.75 mmol, 52%) as a colorless liquid. The isomer ratio was determine by ^{1}H NMR analysis to be 70% *E*, 30% *Z*.

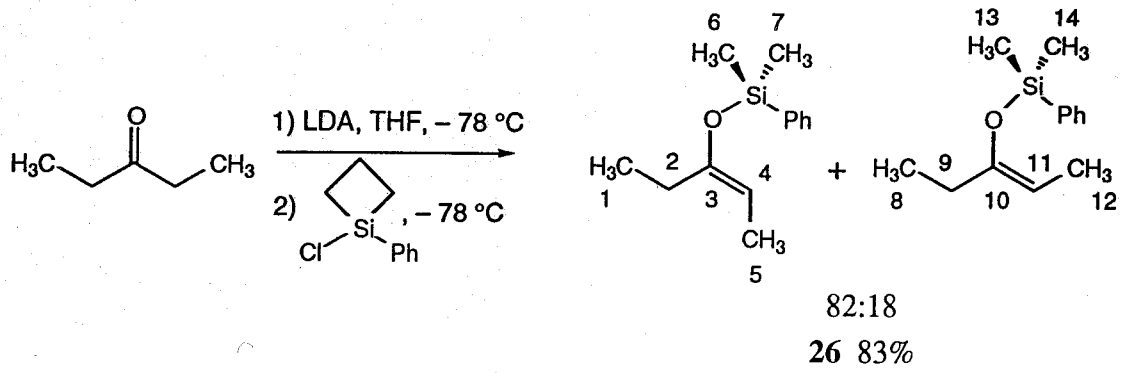
^{1}H NMR (300 MHz, C_6D_6), δ: *E* isomer: 0.28 (s, 3H, H-9), 1.05 (t, 3H, J = 7.5 Hz, H-1), 1.1–1.3 (m, 2H, H-6a, H-7a), 1.46 (d, 3H, J = 6.9 Hz, H-5), 1.3–.55 (m, 3H, H-6b, H-8b, H-7a), 1.95–2.15 (m, 3H, H-2, H-7b), 4.78 (q, 1H, J = 6.9 Hz, H-4)

Z isomer: 0.26 (s, 3H, H-18), 1.00 (t, 3H, J = 7.5 Hz, H-10), 1.1–1.3 (m, 2H, H-15a, H-17a), 1.3–1.55 (m, 3H, H-15b, H-17b, H-16a), 1.60 (d of t, 3H, J = 6.6, 1.4 Hz, H-14), 1.95–2.15 (m, 3H, H-11, H-16b), 4.55 (q of t, 1H, J = 6.6, 1.1 Hz, H-13)

^{13}C NMR (75 MHz, C_6D_6), δ: *E* isomer: –1.4 (C-9), 11.75 (C-1), 11.80 (C-5), 14.0 (C-7), 19.6 (C-6, C-8), 24.3 (C-2), 101.2 (C-4), 153.3 (C-3)

Z isomer: –1.6 (C-18), 11.0 (C-10), 11.9 (C-14), 13.8 (C-16), 20.2 (C-15, C-17), 30.0 (C-11), 100.9 (C-13), 152.7 (C-12)

FTIR (neat), cm^{-1}: 2968 (s), 2935 (s), 2877 (m), 1670 (m), 1253 (m), 1200 (s), 1123 (s), 1107 (m), 1083 (m), 1064 (m), 914 (s), 873 (m), 789 (s), 663 (m)



Phenyldimethyl Silyl Enol Ethers **26**

n-Butyllithium (6.57 mL, 2.51 M solution in hexanes, 16.5 mmol, 1.1 equiv) was added dropwise to a deoxygenated solution of diisopropylamine (2.52 mL, 18 mmol, 1.2 equiv) in tetrahydrofuran (100 mL) at –78 °C. The solution was warmed to 0 °C and held at that temperature for 10 min. The reaction mixture was recooled to –78 °C, and 3-pentanone (1.51 mL, 15 mmol, 1.0 equiv) was added by syringe over 5 min. Stirring was continued at –78 °C for 25 minutes, then dimethylphenylchlorosilane (3.23 mL, 3.33 g, 19.5 mmol, 1.3 equiv) was added over 3 minutes. The solution was allowed to warm to 27 °C and concentrated under vacuum (100 Torr). The residue was taken up in pentane (20 mL), from which a white solid precipitated. The supernatant was decanted by cannula and the precipitate washed with two aliquots of pentane (6 mL each). The combined pentane layers were filtered under argon through a fine frit to remove suspended precipitate, concentrated (50 Torr), and the residue distilled (short path, 35 Torr, 47–81 °C) to give enol ether mixture **26** (2.7593 g, 12.5 mmol, 83%) as a colorless liquid. The isomer ratio was determined by ^{1}H NMR analysis to be 82% *E*, 18% *Z*. A second distillation (short path, 35 Torr, 75–86 °C) afforded **26** with an isomer ratio of 20% *E*, 80% *Z*.

^{1}H NMR (300 MHz, C_6D_6), δ: *E* isomer: 0.40 (s, 6H, H-6, H-7), 1.07 (t, 3H, *J* = 7.5 Hz, H-1), 1.40 (d, 3H, *J* = 6.9 Hz, H-5), 2.08 (q, 2H, *J* = 7.5 Hz, H-2), 4.68 (q, 1H, *J* = 6.9 Hz, H-4), 7.20 (m, 3H, aromatic H), 7.63 (m, 2H, aromatic H)

Z isomer: 0.38 (s, 6H, H-13, H-14), 0.94 (t, 3H, *J* = 7.4 Hz, H-8), 1.61 (d of t, 3H, *J* = 6.6, 1.4 Hz, H-12), 1.95 (q of t, 2H, *J* = 7.4, 1.2 Hz, H-9), 4.52 (q of t, 1H, *J* = 6.6, 1.0 Hz, H-11), 7.20 (m, 3H, aromatic H), 7.63 (m, 2H, aromatic H)

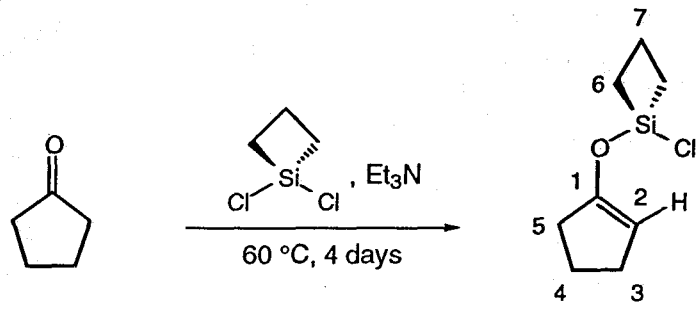
^{13}C NMR (75 MHz, C_6D_6), δ: *E* isomer: –0.9 (C-6, C-7), 11.8 (C-1), 11.9 (C-5), 24.5 (C-2), 100.5 (C-4), 128.1, 129.8, 133.7, 138.7, 153.6 (C-3)

Z isomer: –0.6 (C-13, C-14), 11.1 (C-8), 29.8 (C-9), 101.1 (C-11), 128.2, 129.9, 133.6, 138.5, C-10 not visible, C-12 may be obscured by peak at 11.9

FTIR (neat), cm^{-1}: 2966 (m), 1677 (m), 1428 (m), 1253 (s), 1194 (s), 1118 (s), 1084 (s), 1064 (s), 878 (s), 832 (s), 811 (s), 786 (s), 739 (m), 699 (s)

General Procedure for Sealed-Tube Aldol Reactions: Silyl Enol Ethers **20** to **26** Tables 1 and 2

Silyl enol ether (**20** to **26**, 0.25 mmol, 1 equiv), aldehyde (benzaldehyde or isobutyraldehyde, 0.25 mmol, 1 equiv), and *cis*-dichloroethylene (3.8 μL, 4.9 mg, 0.05 mmol, 0.2 equiv) were injected into a septum-capped, sealable NMR tube under argon. Enough benzene-d_6 (400–420 μL) was added to bring the total volume to 0.500 mL. Under positive argon pressure, the septum was replaced with a vacuum adapter, and the solution degassed by three freeze-pump-thaw cycles in liquid nitrogen and under high vacuum (<50 mTorr). The tube was then sealed permanently under vacuum, so excess pressure would not develop on heating. An initial ^{1}H NMR spectrum was recorded, then the sealed tube was completely submerged in an oil bath (100 °C for silacyclobutane enol ethers **20**, **21**, **24**, and **25**; 150 °C for dimethyl silyl enol ethers **22**, **23**, and **26**) and held at that temperature for the times indicated in tables 1 and 2. Relevant product ^{1}H NMR signals are listed in the tables.



27 25%

Chlorosilyl Silacylcobutane Enol Ether **27**

Dichlorosilacyclobutane (3.25 mL, 3.61 g, 25.6 mmol, 1.3 equiv) was added dropwise over 2 minutes to triethylamine (20 mL, 143 mmol, 7.2 equiv) under argon, causing white fumes to develop. After stirring at 27 °C for fifteen minutes until fuming stopped, cyclopentanone (1.77 mL, 1.68 g, 20 mmol, 1 equiv) was added rapidly. The reaction mixture was warmed to 60 °C, and stirred for four days at this temperature. Over this time copious white precipitate formed. After four days, the solution was concentrated under vacuum (1 Torr), and the white solid residue washed with four aliquots (10 mL each) of dry ether. Each aliquot was transferred by cannula to a fine porosity filter frit. The combined ether fractions were filtered under argon, concentrated under vacuum (1 Torr) , and distilled under reduced pressure (short path, 1.8 Torr, 62–63 °C) to yield enol ether **27** (0.9732 g, 5.1 mmol, 25%) as a yellow liquid.

^{1}H NMR (300 MHz, C_6D_6), δ: 1.47–1.71 (m, 8H, H-4, H-6, H-7), 2.11–2.18 (m, 2H, H-3), 2.25–2.32 (m, 2H, H-5), 4.88 (quintet, J = 2.1, 1H, H-2)

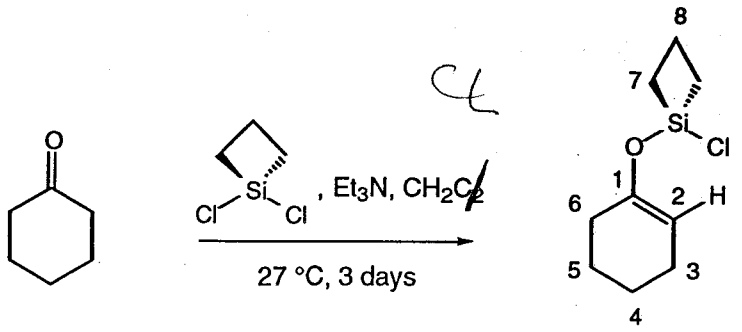
^{13}C NMR (75 MHz, C_6D_6), δ: 12.66 (C-7), 21.44 (C-4), 24.95 (C-6), 28.82 (C-3), 33.19 (C-5), 105.23 (C-2), 152.73 (C-1)

HRMS (EI), m/z: Calcd for $C_8H_{13}O^{35}ClSi$: 188.0425

Found: 188.0420

Calcd for $C_8H_{13}O^{35}ClSi$: 190.0394

Found: 190.0395

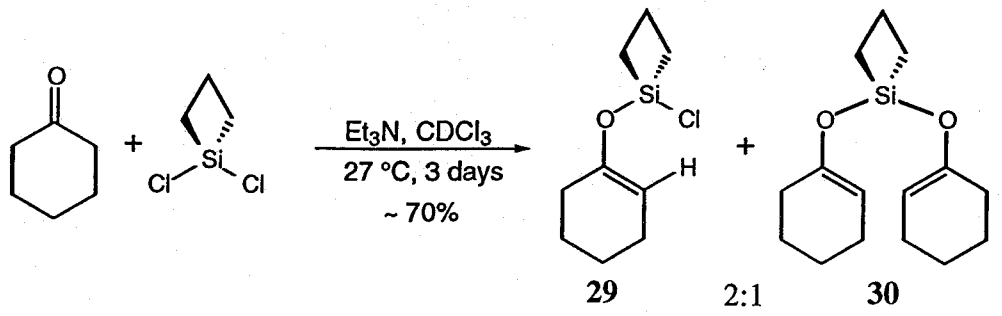


28 26%

Chlorosilyl Silacylcobutane Enol Ether **28**

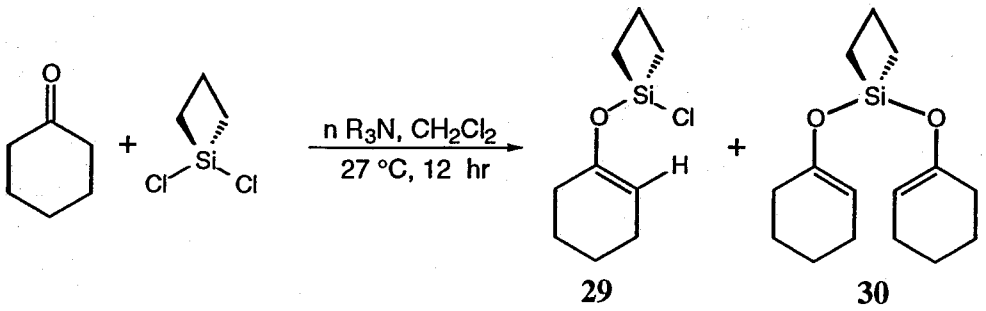
Triethylamine (3.48 mL, 2.53 g, 25 mmol, 1.01 equiv) was added to a solution of dichlorosilacyclobutane (3.0 mL, 3.4922 g, 24.7 mmol, 1.0 equiv) in dry dichloromethane (20 mL) under argon at 27 °C. The solution fumed on amine contact. After stirring five minutes, cyclohexanone (2.59 mL, 2.45 g, 25 mmol, 1.01 equiv) was rapidly added. The reaction mixture was stirred at 27 °C under argon for three days, during which time a white precipitate formed. After 3 days, the solution was concentrated under vacuum (1 Torr) and the yellow residue dissolved in dry ether (2 mL). The liquid portion was removed by cannula to a fine porosity filter frit, and filtered under argon pressure. The residual white solid was washed with three aliquots of ether (5 mL each)which were also passed through the same filter frit. The combined etherial fractions were concentrated under vacuum (1 Torr) and then distilled at reduced pressure (Kugelrhor, 0.3 Torr, 75–80 °C) to yield enol ether **28** (1.299 g, 6.4 mmol, 26%) as a pale brown liquid.

^{1}H NMR (300 MHz, C_6D_6), δ:	1.50–1.57 (m, 2H, H-8), 1.65–1.97 (m, 8H, H-4, H-5, H-7), 2.00–2.15 (m, 4H, H-3 and H-6), 5.07 (t of t, J = 1.4, 3.9 Hz, H-2)
^{13}C NMR (75 MHz, C_6D_6), δ:	12.36 (C-8), 21.95 (C-7), 22.85, 23.58 (C-4 and C-5), 25.04 (C-3), 29.23 (C-6), 106.13 (C-2), 148.63 (C-1)
FTIR (neat), cm^{-1}:	2934 (s), 2860 (m), 2842 (m), 1673 (s), 1442 (m), 1336 (m), 1265 (m), 1165 (s), 1138 (m), 1123 (m), 1047 (m), 991 (s), 920 (s), 853 (s), 722 (s), 689 (s)
HRMS (EI), m/z:	Calcd for $C_9H_{13}O^{35}ClSi$: 202.0581 Found: 202.0575 Calcd for $C_9H_{13}O^{35}ClSi$: 204.0551 Found: 204.0551



Enolization with Triethylamine: NMR Experiment

Cyclohexanone (65.3 μL, 61.8 mg, 0.63 mmol, 1 equiv) was added to a solution of dichlorosilacyclobutane (75 μL 88.9 mg, 0.63 mmol, 1 equiv) in deuteriochloroform (0.5 mL) in a septum-capped NMR tube under argon. Monitoring for one hour by ^{1}H NMR showed no reaction. Triethylamine (87.8 μL, 63.7 mg, 0.63 mmol, 1.0 equiv) was then added, bringing the final concentration of each reactant to 0.9 M. The tube was allowed to stand at 27 °C and the reaction periodically monitored by ^{1}H NMR. After 3 days, a crystalline precipitate had formed and two sets of vinylic proton signals had appeared (tt at 4.82 and 4.78 J = 1.2, 3.8 Hz for both) which were attributed to enol ethers **29** and **30** respectively. Integration of these signals indicated at 2:1 ratio of products with about 70% conversion of cyclohexanone. ^{13}C NMR at this time also indicated formation of two enol products with peaks at 148.4, 148.1, 105.7 and 104.5.

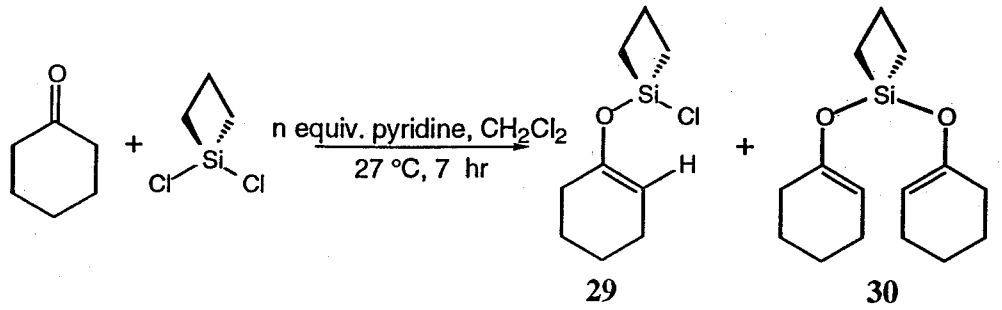


29 **30**

R_3N =		
	diisopropylethylamine	5:1
	N-methylpiperidine	10:1
	pyridine	4:1

General Procedure: Trialkyl Amine Bases

To a solution of dichlorosilacyclobutane (200 μL, 244 mg, 1.73 mmol, 1 equiv) in dichloromethane (1.38 mL) under argon was added 1 equiv of either diisopropylethylamine (301 μL, 233 mg, 1.73 mmol), N-methylpiperidine (210 μL, 171 mg, 1.73 mmol) or pyridine (140 μL, 137 mg, 1.74 mmol), causing brief fuming. Cyclohexanone (179 μL, 169 mg, 1.73 mmol, 1.0 equiv) was then added. After stirring 12 hours at 27 °C, an aliquot was removed and the product ratios determined by ^{1}H NMR, as indicated above. Only the pyridine solution formed a precipitate during this time. The other two solutions turned yellow but remained clear.

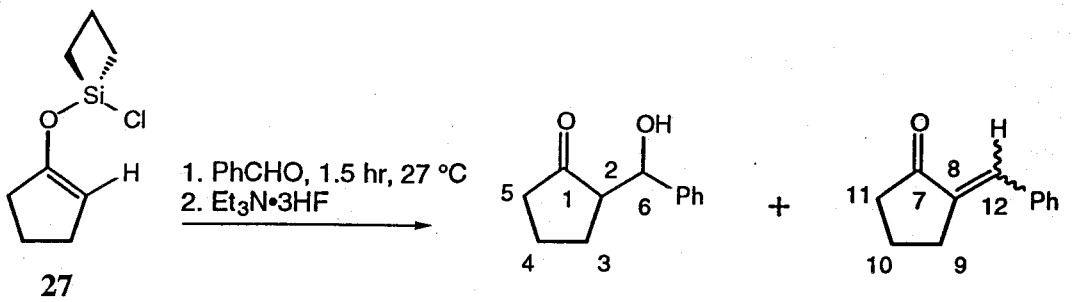


29 **30**

n = 1	4:1
n = 0	no reaction
n = 5	6:1
n = 10	100:0 (no other solvent)

General Procedure: Stoichiometry of Pyridine

To a solution of dichlorosilacyclobutane (200 μL, 244 mg, 1.73 mmol, 1.1 equiv) in dichloromethane (either 1.27, 0.653, or 0 mL) under argon was added either 0, 5, or 10 equivalents of pyridine (0, 0.653, or 1.27 mL), causing fuming on amine-silyl chloride contact. Cyclohexanone (163 μL, 154 mg, 1.57 mmol, 1 equiv) was added and the reactions stirred at 27 °C for 7 hours. An aliquot was then removed and the product ratios were determined by ^{1}H NMR, as shown above. No reaction was observed in the absence of amine, and only the monoadduct **30** was observed in the reaction with neat pyridine.



27

In CH_2Cl_2	25%, 5.5:1 syn:anti	32%
In C_5H_5N	25%, 3.0:1 syn:anti	2%

Aldol Reactions of Silyl Enol Ether **27**

Benzaldehyde (52.6 μL, 54.9 mg, 0.52 mmol, 1.0 equiv) was added to a solution of enol ether **27** (90μL, 98.2 mg, 0.52 mmol, 1 equiv) in either dichloromethane or pyridine (0.5 mL). The solutions were stirred at 27 °C for 1.5 hours, then triethylamine trihydrofluoride (169 mL, 166.9 mg, 1.04 mmol, 2.0 equiv) was added by syringe. The reaction mixtures were partitioned between saturated ammonium chloride solution and ethyl acetate. The organic layers were dried over sodium sulfate, filtered, and concentrated. The products were separated by column chromatography (20% ether in petroleum ether). The enone was isolated as a yellow crystalline solid (CH_2Cl_2: 28.8 mg, 0.17 mmol, 32%. C_5H_5N: 1.5 mg, 0.009 mmol, 1.7%). The aldol adducts were obtained together as a yellow oil and the isomer ratio determined by ^1H NMR of the oil. (CH_2Cl_2: 24.3 mg, 0.13 mmol, 25%, 5.5:1 syn: anti. C_5H N: 24.3 mg, 0.13 mmol, 25% 3:1 syn:anti).

Enone

^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.03 (quintet, J = 7.5 Hz, 2H, H-10), 2.41 (t, J = 7.9 Hz, 2H, H-11), 2.98 (t of d, J = 2.7, 7.2 Hz, 2H, H-9), 7.32–7.45 (m, 4H, aromatic H), 7.51–7.62 (m, 2H, H-12, aromatic H)

^{13}C NMR (75 MHz, $CDCl_3$), δ: 20.15 (C-10), 29.31 (C-9), 37.76 (C-11), 128.64, 129.26, 130.45, 132.23 (aromatics), 135.48 (C-12), 136.01 (C-8), 208.06 (C-7)

FTIR (neat), cm^{-1}: 2969 (s), 2954 (s), 1712 (s, C=O), 1622 (s, C=C), 1572 (m), 1489 (m), 1448 (s), 1402 (m), 1321 (m), 1306 (m), 1290 (m), 1276 (m), 1235 (s), 1175 (s), 1128 (m), 1078 (m), 1028 (m), 783 (s), 750 (s), 696 (s)

Syn Aldol Adduct

^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.6–2.5 (m, 7H, H-2, H-3, H-4, H-5), 2.55 (br s, 1H, OH), 5.30 (d, J = 2.8 Hz, 1H, H-6), 7.22–7.40 (m, 5H, aromatics)

^{13}C NMR (75 MHz, $CDCl_3$), δ: 20.45 (C-4), 22.74 (C-3), 39.18 (C-5), 56.10 (C-2), 71.50 (C-6), 125.53, 127.30, 128.33, 142.68 (aromatics), 220.49 (C-1)

FTIR (neat), cm^{-1}: (5:1 syn:anti mixture): 3452 (br, –OH), 2965 (m), 2880 (m), 1736 (s, C=O), 1494 (m), 1451 (m), 1403 (m), 1333 (m), 1273 (m), 1199 (m), 1155 (s), 1104 (m), 1025 (s), 969 (m), 840 (m), 729 (s), 701 (s)

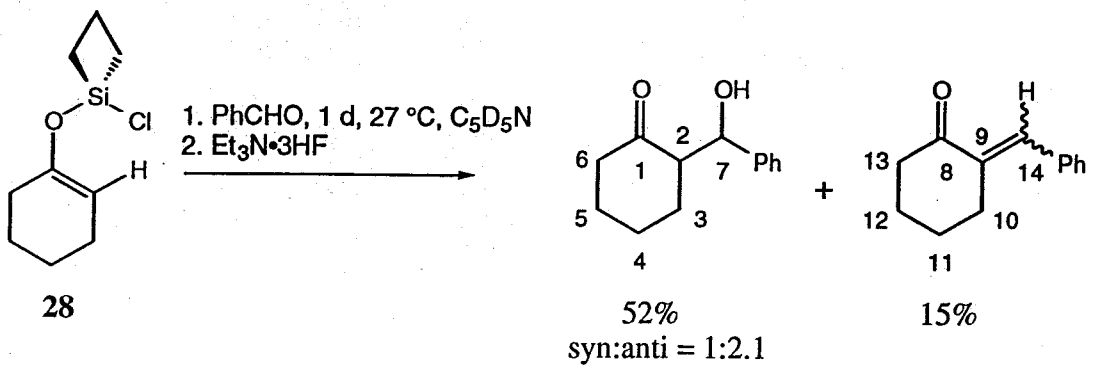
Anti Aldol Adduct

^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.6–2.5 (m, 7H, H-2, H-3, H-4, H-5), 4.57 (br s, 1H, OH), 4.70 (d, J = 9.2 Hz, 1H, H-6), 7.22–7.40 (m, 5H, aromatics)

^{13}C NMR (75 MHz, $CDCl_3$), δ: 20.39 (C-4), 26.98 (C-3), 38.72 (C-5), 55.31 (C-2), 75.21 (C-6), 126.54, 127.97, 128.41, 141.38 (aromatics), 201.00? (C-1)

TLC (40% Et_2O in pet. ether), R_f:

Enone	0.54 (strong UV, anisaldehyde)
Syn adduct	0.23 (anisaldehyde)
Anti adduct	0.19 (anisaldehyde)



28

52%
syn:anti = 1:2.1

15%

Aldol Reactions of Silyl Enol Ether **28**

Benzaldehyde (48.8 μL, 50.9 mg, 0.48 mmol, 1 equiv) was added to a solution of chlorosilyl enol ether **28** (90 μL, 96.9 mg, 0.48 mmol, 1 equiv) in pyridine-d_5 (410 μL) under argon. The sample was allowed to stand at 27 °C for one day, with periodic monitoring by ^{1}H NMR. A crystalline, colorless precipitate formed in this time. After one day, triethylamine trihydrofluoride (78.2 μL, 77.4 mg, 0.48 mmol, 1 equiv) was added, and the reaction mixture partitioned between saturated ammonium chloride solution and 15% ethyl acetate in hexanes. The organic layer was dried over sodium sulfate, filtered, concentrated, and the three products separated by column chromatography (15% ethyl acetate in hexanes). The enone (13.5 mg, 0.07 mmol, 15%) was isolated as a yellow oil. The syn aldol adduct (19.7 mg, 0.10 mmol, 20%) was isolated as a white crystalline solid (mp 99–101 °C), and the anti aldol adduct (31.6 mg, 0.15 mmol, 32%) as a white solid (mp 66–67 °C).

Enone

^{1}H NMR (300 MHz, C_6D_6), δ:	1.18 (m, 2H, H-11), 1.33 (m, 2H, H-12), 2.26 (t, J = 6.7 Hz, 2H, H-13), 2.39 (t of d, J = 2.2, 6.4 Hz, 2H, H-10), 7.02–7.17 (m, 5H, aromatics), 7.80 (t, J = 2.2 Hz, 1H, H-14)
^{1}H NMR (300 MHz, $CDCl_3$), δ:	1.62 (m, 2H, H-11), 1.77 (m, 2H, H-12), 2.40 (t, J = 6.7 Hz, 2H, H-13), 2.70 (t of d, J = 2.3, 6.4 Hz, 2H, H-10), 7.14–7.28 (m, 5H, aromatics), 7.37 (t, J = 2.3 Hz, 1H, H-14)
^{13}C NMR (75 MHz, $CDCl_3$), δ:	23.21 (C-11), 23.71 (C-12), 28.77 (C-10), 40.16 (C-13), 128.16, 128.36, 130.13, 136.49 (aromatics), 135.38 (C-14), 135.42 (C-9), 201.50 (C-8)
FTIR (neat), cm^{-1}:	2940 (s), 2865 (m), 1682 (s, C=O), 1593 (s, C=C), 1573 (m), 1491 (m), 1446 (s), 1317 (m), 1257 (s), 1203 (m), 1143 (s), 1068 (m), 822 (m), 762 (m), 719 (m), 697 (s)

Syn Aldol Adduct

^{1}H NMR (300 MHz, C_6D_6), δ: 0.84 (m, 1H, H-4a), 1.14 (q of t, *J* = 3.8, 13.1, 1H, H-4b), 1.24, 1.42, 1.54 (3m, 1H, 1H, 2H, respectively, H-3 and H-5), 1.73 (t of d, *J* = 6.0, 13.4 Hz, 1H, H-6a), 2.12 (m, 2H, H-6b and H-2), 3.11 (d, *J* = 3.2 Hz, 1H, exchanges with D_2O, OH. *In* $CDCl_3$: 3.02, d, *J* = 3.3 Hz), 5.39 (t, *J* = 2.4 Hz, 1H, H-7. *In* $CDCl_3$: 5.40, t, *J* = 2.6 Hz), 7.16 (m, 3H, aromatics), 7.32 (m, 2H, aromatics)

^{13}C NMR (75 MHz, $CDCl_3$), δ: 24.74 (C-4), 25.87 (C-5), 27.83 (C-3), 42.55 (C-6), 57.07 (C-2), 70.44 (C-7), 125.64, 126.84, 128.02, 141.42 (aromatics), 214.67 (C-1)

FTIR (neat), cm^{-1}: 3547 (br,–OH), 2933 (m), 1696 (s, C=O), 1447 (s), 1313 (m), 1132 (s), 1060 (s), 985 (m), 699 (s)

Anti Aldol Adduct

^{1}H NMR (300 MHz, C_6D_6), δ: 0.81 (m, 2H, H-4), 1.10 (m, 2H, H-5), 1.25, 1.35 (2m, 1H each, H-3), 1.65 (t of d, *J* = 5.0, 13.5, 1H, H-6a), 2.13 (m, 1H, H-6b), 2.24 (m, 1H, H-2), 4.14 (d, *J* = 2.8, 1H, exchanges with D_2O, OH. *In* $CDCl_3$: 3.97, d, *J* = 2.7), 4.76 (dd,

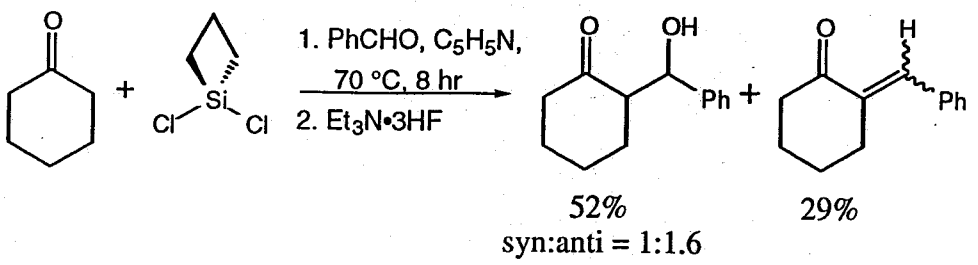
J = 2.8, 8.6 Hz, 1H, H-7. *In $CDCl_3$:* 4.78, dd, J = 2.4, 8.7), 7.16 (m, 3H, aromatics), 7.32 (m, 2H, aromatics)

^{13}C NMR (75 MHz, $CDCl_3$), δ: 24.38 (C-4), 27.57 (C-5), 30.54 (C-3), 42.35 (C-6), 57.16 (C-2), 74.35 (C-7), 126.79, 127.58, 128.08, 140.79 (aromatics), 215.20 (C-1)

FTIR (neat), cm^{-1}: 3510 (br, –OH), 2936 (m), 1696 (s, C=O), 1451 (s), 1129 (m), 1042 (m), 746 (m), 702 (s)

TLC 30% EtOAc in hexanes), R_f:

Enone	0.60	(Strong UV, anisaldehyde)
Syn adduct	0.46	(anisaldehyde)
Anti adduct	0.36	(anisaldehyde)

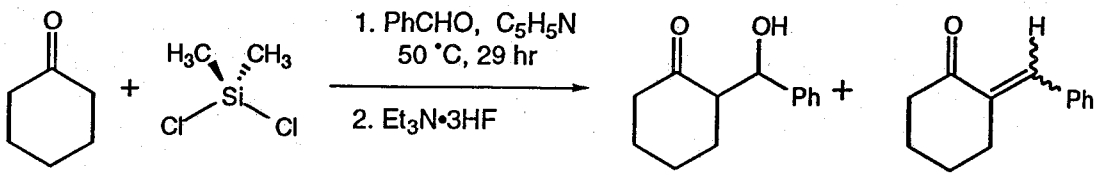


52%
syn:anti = 1:1.6

29%

One-Pot Enolization-Aldol Addition with Dichlorosilacyclobutane

Cyclohexanone (207 μL, 196 mg, 2.0 mmol, 1 equiv) and benzaldehyde (203μL, 212 mg, 2.0 mmol, 1.0 equiv) were added to a solution of dichlorosilacyclobutane (270μL, 320 mg, 2.26 mmol, 1.13 equiv) in pyridine (970 μL) under argon. The reaction mixture was stirred at 70 °C until no more cyclohexanone could be detected by TLC (8 hours). After cooling to 0 °C, the solution was treated with triethylamine trihydrofluoride (750μL, 241 mg, 4.6 mmol, 2.3 equiv). The reaction mixture was partitioned between saturated ammonium chloride solution (10 mL) and ethyl acetate (5 mL). The aqueous layer was separated and extracted further with two 5-mL portions of ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated; the products were isolated by flash column chromatography (20% ethyl acetate in hexanes). The enone was isolated as yellow crystalline solid (107.1 mg, 1.04 mmol, 29%), the syn aldol adduct as colorless needles (81.3 mg, 0.40 mmol, 20%), and the anti aldol adduct as a colorless solid (131.8 mg, 0.65 mmol, 32%)

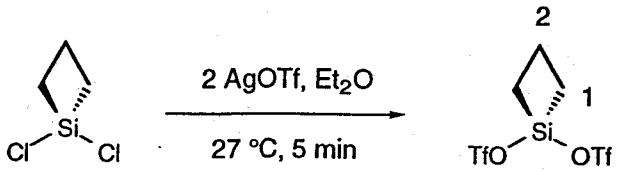


50%
syn:anti = 1:1.9

11%

One-Pot Enolization-Aldol Addition with Dimethyldichlorosilane

Cyclohexanone (207 μL, 196 mg, 2.0 mmol, 1 equiv) and benzaldehyde (203 μL, 212 mg, 2.0 mmol, 1.0 equiv) were added to a solution of dimethyldichlorosilane (279 μL, 297 mg, 2.3 mmol, 1.15 equiv) in pyridine (970 μL) under argon. The reaction mixture was stirred at 50 °C until no more cyclohexanone could be detected by TLC (29 hours). After cooling to 0 °C, the solution was treated with triethylamine trihydrofluoride (750μL, 241 mg, 4.6 mmol, 2.3 equiv). The reaction mixture was partitioned between saturated ammonium chloride solution (10 mL) and ethyl acetate (5 mL). The aqueous layer was separated and extracted further with two 5-mL portions of ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated; the products were isolated by flash column chromatography (20% ethyl acetate in hexanes). The enone was isolated as yellow oil (41.8 mg, 0.22 mmol, 11%), the syn aldol adduct as colorless needles (71.3 mg, 0.35 mmol, 18%), and the anti aldol adduct as a colorless solid (133.1 mg, 0.65 mmol, 32%)

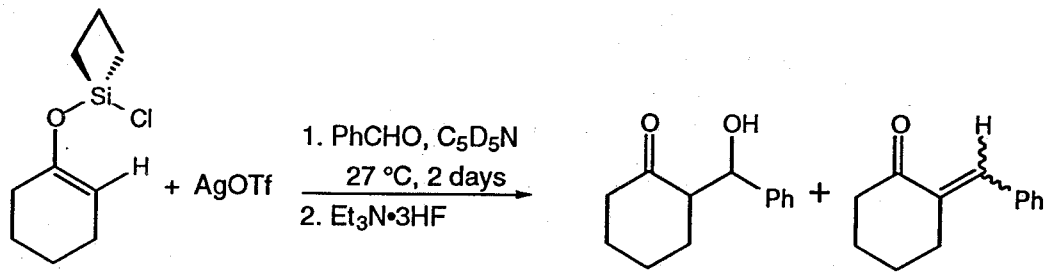


Silacyclobutane ditriflate

Silacyclobutane dichloride (0.491 mL, 564.4 mg, 4.0 mmol, 1 equiv) was added to a suspension of silver triflate (2.17 g, 8.45 mmol, 2.2 equiv) in dry ether (15 mL). Thick white precipitate formed immediately. The solution was stirred under argon at 27 °C for approximately five minutes, then transferred by cannula to a fine porosity filter frit and filtered under argon. The residual solid was rinsed twice with 5-mL aliquots of ether, and the combined ether fractions were concentrated under reduced pressure (150 Torr), then distilled (Kugelrhor, 35 Torr, 90–100 °C) to yield silacyclobutane ditriflate (1.2109 g, 3.29 mmol, 82%) as a colorless liquid, density 1.63 g/mL. Proton and carbon NMR of this liquid are consistent with substitution on silicon.

^{1}H NMR (300 MHz, C_6D_6), δ: 1.38 (m, 2H, H-2), 1.55 (m, 4H, H-1)

^{13}C NMR (75 MHz, C_6D_6), δ: 11.30 (C-2), 24.19 (C-1), 118.76 (q, J = 318 Hz, CF_3)



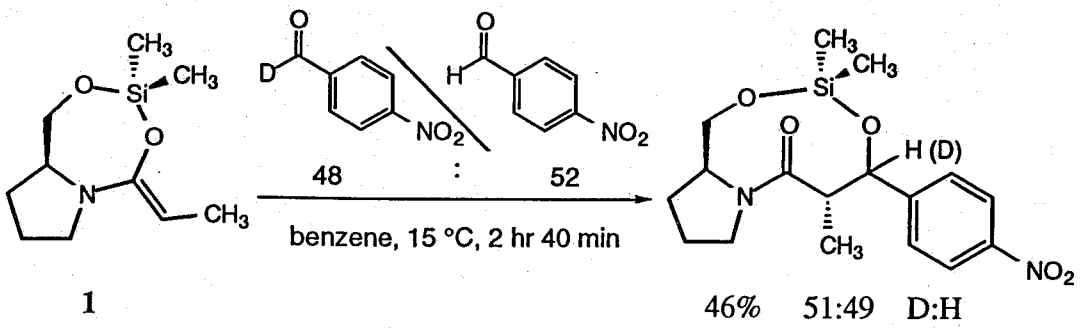
28

37%
syn:anti = 1.06:1

1%

Aldol Reaction of Silyl Enol Ether **28** with silver triflate

Silyl enol ether **28** (90 μL, 96.9 mg, 0.48 mmol, 1 equiv) was added to a solution of silver triflate (123.6 mg, 0.48 mmol, 1.0 equiv) in pyridine-d_5 (400 μL), protected from light, and stirred at 27 °C for 2 hours 15 minutes, giving a clear solution. Benzaldehyde (49 μL, 51 mg, 0.48 mmol, 1.0 equiv) was added, causing a white precipitate to fall out of solution. The supernatant was transferred by cannula to a dry NMR tube under argon and the reaction monitored periodically by ^{1}H NMR. After standing in the dark at 27 °C for 2 days, the solution was treated with triethylamine trihydrofluoride (78 μL, 77 mg, 0.48 mmol, 1.0 equiv). The reaction mixture was partitioned between saturated ammonium chloride solution (10 mL) and ethyl acetate (5 mL). The aqueous layer was separated and extracted further with two 5-mL portions of ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated; the products were isolated by flash column chromatography (20% ethyl acetate in hexanes). The enone (0.9 mg, 0.005 mmol, 1%) was isolated as a yellow oil; the syn aldol adduct (19 mg, 0.093 mmol, 19%) as a colorless solid; and the anti (17.9 mg, 0.88 mmol, 18%) as a colorless solid.



1

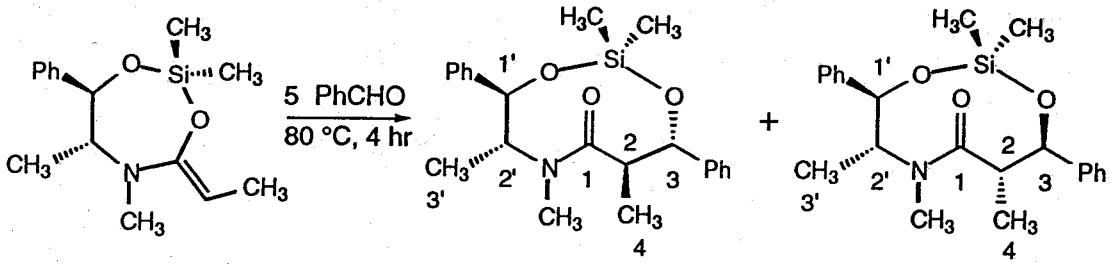
46% 51:49 D:H

Deuterium isotope experiment

Dimethyl silyl ketene acetal **1** (40 μL, 40.7 mg, 0.19 mmol, 1.0 equiv) was added to a deoxygenated solution of 4-nitrobenzaldehyde (48:52 mixture of $NO_2C_6H_4CDO$: $NO_2C_6H_4CHO$, exact ratio determined by mass spectrometry. 438.6 mg, 2.89 mmol, 14 equiv) in benzene (4 mL) cooled to 15 °C in an ice/water bath. The reaction was stirred at 15 °C for 2 hours, 40 minutes. Aldol adducts were then isolated by flash column chromatography (50% ether in petroleum ether) as a white solid (16.8 mg, 0.087 mmol, 46%). Exact deuterium incorporation was determined by mass spectrometry.

Mass Spectral Results

	Aldehyde		Aldol adducts	
Run	% D	% H	% D	% H
H reference	0	100	0	100
D reference	100	0	97	3
Run 1	48	52	51	49
Run 2	48	52	51	49
Run 3	48	52	51	49



34 **35** 53% (2*R*, 3*S*) **36** 7% (2*S*, 3*R*)

(–)-Pseudoephedrine–Benzaldehyde Aldol Adducts **35** and **36**

Benzaldehyde (523 μL, 546 mg, 5.14 mmol, 5 equiv) and the *O*-silyl *N,O*-ketene acetal derived from (–)-pseudoephedrine propionamide **34** (285.3 mg, 1.03 mmol, 1 equiv) were combined in a 10-mL Schlenk tube under argon. The solution was stirred in an 80 °C oil bath for 4 hours, then excess benzaldehyde was removed under vacuum (1 Torr). Purification by flash column chromatography (30% ethyl acetate in hexanes) afforded major product **35** (209.0 mg, 53%) as a colorless solid (mp: 156-161 °C) and minor product **36** (28.3 mg, 7%) as a colorless oil.

The major product, **35**, has ^{1}H NMR and FTIR spectra identical to the (1'*S*, 2'*S*, 2*S*, 3*R*) isomer derived from (+)-pseudoephedrine, (See Marsh, R.E.; Schafer, W.P.; Widdowson, K.L.; Myers, A.G. *Acta. Crystallogr.*, **1992**, *C48*, 1948.) implying that **35** is the enantiomeric (1'*R*, 2'*R*, 2*R*, 3*S*) isomer, as shown.

Upon TLC analysis, **36** appears as two spots, but 2-D TLC shows those spots inter convert into each other. The ^{1}H NMR spectrum of **36** also appears to contain two isomers in an approximately equal ratio. Upon hydrolysis, however, **36** yields only the anti acid (with very minor syn impurities), implying that it is the other anti aldol adduct, the (1'*R*, 2'*R*, 2*S*, 3*R*) isomer, perhaps existing in equilibrium between two conformers.

(1'*R*, 2'*R*, 2*R*, 3*S*) Anti Aldol Adduct **35**

^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.06 (s, 3H, Si–CH_3), 0.09 (s, 3H, Si–CH_3), 0.87 (d, J = 6.5 Hz, 3H, H-4), 0.88 (d, J = 7.1 Hz, 3H, H-3'), 3.19 (s, 3H, N–CH_3), 3.29 (dq, J = 6.6, 9.7 Hz, 1H, H-2), 4.52 (d, J = 9.6 Hz, 1H, H-1'), 4.70 (d, J = 9.7 Hz, 1H, H-3), 5.28 (dq, J = 7.1, 9.6 Hz, 1H, H-2'), 7.27–7.41 (m, 10H, aromatics)

^{13}C NMR (75 MHz, $CDCl_3$), δ: –3.99 (Si–CH_3), -3.85 (Si–CH_3), 13.27 (C-4), 14.15 (C-3'), 29.33 (N–CH_3), 44.30 (C-2), 55.09 (C-2'), 77.42 (C-1'), 80.73 (C-3), 126.74, 126.92, 127.62, 127.69. 128.19, 128.22, 141.63, 142.56 (aromatics), 177.34 (C-1)

FTIR (neat), cm^{-1}: 3029 (w), 2979 (m), 2936 (w), 2878 (w), 1639 (s, C=O), 1491 (w), 1455 (m), 1406 (m), 1372 (w), 1290 (w), 1258 (s), 1230 (w), 1206 (w), 1139 (w), 1080 (s), 1051 (s), 1027 (m), 934 (m), 883 (s), 866 (s), 855 (s), 800 (m), 743 (m), 700 (s)

(1'*R*, 2'*R*, 2*S*, 3*R*) Anti Aldol Adduct **36**

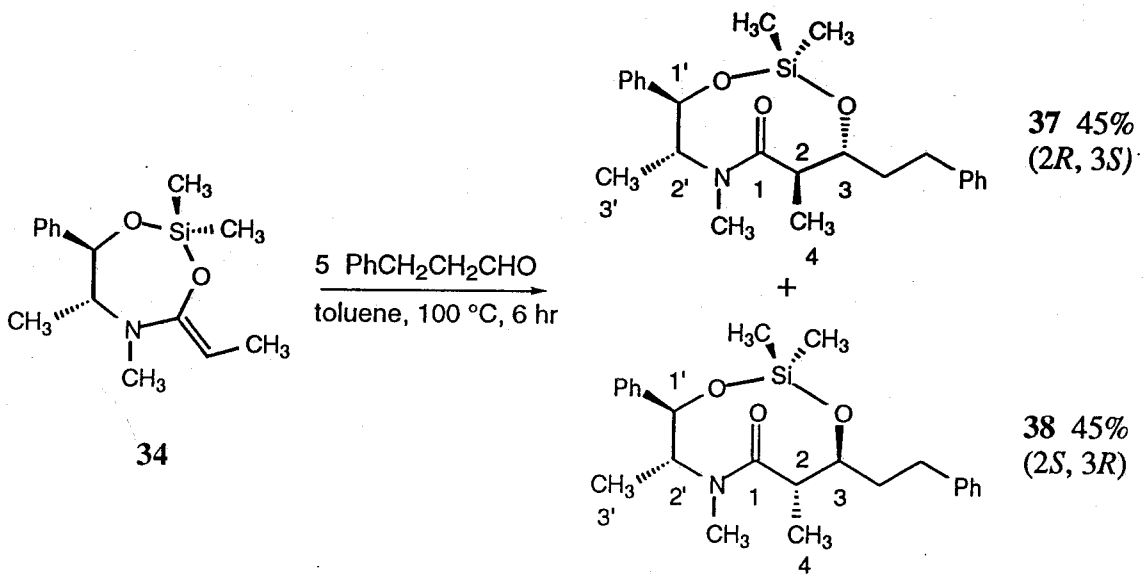
^{1}H NMR (300 MHz, $CDCl_3$), δ: Appears as ~1:1 mixture of isomers

–0.31 (s, 3H, Si–$\mathbf{CH_3}$), 0.02 (s, 3H, Si–$\mathbf{CH_3}$), 0.15 (s, 3H, Si–$\mathbf{CH_3}$), 0.22 (s, 3H, Si–$\mathbf{CH_3}$), 0.85 (d, J = 6.6 Hz, 3H, H-4), 0.89 (d, J = 6.6 Hz, 3H, H-4), 0.97 (d, J = 6.8 Hz, 3H, H-3'), 1.24 (d, J = 7.0 Hz, 3H, H-3'), 3.01 (s, 3H, N–$\mathbf{CH_3}$), 3.07 (dq, J = 6.6, 9.6 Hz, 1H, H-2), 3.08 (dq, J = 7.0, 9.5 Hz, 1H, H-2'), 3.31 (s, 3H, N–CH_3), 3.51 (dq, J = 6.7, 9.7 Hz, 1H, H-2), 4.74 (d, J = 9.5 Hz, 1H, H-3), 4.75 (d, J = 9.9 Hz, 1H, H-3), 4.86 (d, J = 9.9 Hz, 1H, H-1'), 5.05 (d, J = 6.7, 9.9 Hz, 1H, H-2'), 5.70 (d, J = 9.5, 1H, H-1'), 7.25–7.88 (m, 20H, aromatics)

FTIR (neat), cm^{-1}: 2970 (m), 1637 (s, C=O), 1491 (w), 1452 (w), 1375 (m), 1256 (m), 1079 (s), 852 (s), 800 (s), 700 (s)

TLC (30% EtOAc in hexanes), R_f: **35**: 0.33 (UV and PMA)

36: 0.15 and 0.48 (UV and PMA)



(–)-Pseudoephedrine–Hydrocinnamaldehyde Aldol Adducts **37** and **38**

Hydrocinnamaldehyde (122.8 μL, 125.1 mg, 0.933 mmol, 1 equiv) was added to a solution of the *O*-silyl *N,O*-ketene acetal derived from (–)-pseudoephedrine propionamide **34** (517.4 mg, 1.86 mmol, 2 equiv) in dry toluene (250 μL) in a 10 mL Schlenk tube. The solution was stirred in a 100 °C oil bath for 6 hours. Purification of the reaction mixture by flash column chromatography (30% ethyl acetate in hexanes) afforded separately **37** (174.4 mg, 45%) as a colorless oil and **38** (171.2 mg, 45%) also as a colorless oil.

Product **37** was assigned the (1'*R*, 2'*R*, 2*R*, 3*S*) geometry based on the similarity of its ^{1}H NMR spectrum to the corresponding benzaldehyde adduct. Upon TLC analysis, **38** appears as two spots, but 2-D TLC shows those spots convert into each other. The ^{1}H NMR spectrum of **38** also appears to contain two isomers in an approximately 1.3:1 ratio. Upon hydrolysis, however, **38** yields only the anti acid (with very minor syn

impurities), implying that it is the other anti aldol adduct, the (1'*R*, 2'*R*, 2*S*, 3*R*) isomer, perhaps existing in equilibrium between two conformers.

(1'*R*, 2'*R*, 2*R*, 3*S*) Anti Aldol Adduct **37**

^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.11 (s, 3H, Si–CH_3), 0.14 (s, 3H, Si–CH_3), 0.85 (d, J = 7.1 Hz, 3H, H-3'), 1.12 (d, J = 6.5 Hz, 3H, H-4), 1.74 (m, 1H, Ph–CH_2–CH_2–), 2.00 (m, 1H, Ph–CH_2–C**H**$_2$–), 2.55 (ddd, J = 4.9, 11.9,13.4 Hz, 1H, Ph–CH_2–), 2.80 (ddd, J = 5.0, 12.1, 13.4 Hz, 1H, Ph–C**H**$_2$–), 3.07 (s, 3H, N–CH_3), 3.08 (dq, J = 6.4, 9.7 Hz, 1H, H-2), 3.88 (t of d, J = 2.3, 9.2 Hz, 1H, H-3), 4.48 (d, J = 9.6 Hz, 1H, H-1'), 5.22 (dq, J = 7.1, 9.6 Hz, 1H, H-2'), 7.18–7.50 (m, 10 H, aromatics)

FTIR (neat), cm^{-1}: 3026 (w), 2960 (w), 2875 (w), 1643 (s, C=O), 1492 (w), 1454 (m), 1406 (m), 1375 (w), 1290 (w), 1257 (m), 1216 (w), 1138 (w), 1090 (s), 1029 (w), 977 (w), 932 (w), 873 (m), 853 (m), 847 (m), 799 (m), 747 (w), 700 (s)

HRMS (FAB), m/z: Calcd for $C_{24}H_{34}O_3NSi$ (MH^+): 412.2308
Found: 412.2305

(1'*R*, 2'*R*, 2*S*, 3*R*) Anti Aldol Adduct **38**

^{1}H NMR (300 MHz, $CDCl_3$), δ: Appears as ~1.3:1 mixture of isomers

–0.10 (s, 3H, Si–CH_3), 0.04 (s, 3H, Si–CH_3), 0.11 (s, 3H, Si–CH_3), 0.13 (s, 3H, Si–CH_3), 0.90 (d, J = 6.7 Hz, 3H, H-3'), 1.07 (d, J = 6.6 Hz, 3H, H-4), 1.11 (d, J = 6.6 Hz, 3H, H-4), 1.25 (d, 7.0 Hz, 3H, H-3'), 1.75 (m, 3H, H-2 and two of Ph–CH_2–CH_2–), 2.02 (m, 2H, Ph–CH_2–CH_2–), 2.60 (m, 2H, Ph–CH_2–), 2.89 (m, 2H, Ph–CH_2–), 2.95 (s, 3H, N–CH_3), 3.02 (dq, J = 7.0, 9.6 Hz, 1H, H-2'), 3.20 (s, 3H, N–CH_3), 3.22 (dq, J = 6.7, 9.8 Hz, 1H, H-2), 3.82 (t of d, J = 2.2, 9.6 Hz, 1H, H-3), 3.92 (t of d, J = 2.3, 9.6 Hz, 1H, H-3), 4.69 (d, J = 10.0 Hz, 1H, H-1'), 4.88 (dq, J = 6.7, 10.0, 1H, H-2'), 5.62 (d, J = 9.6 Hz, 1H, H-1'), 7.17–7.51 (m, 20 H, aromatics)

^{13}C NMR (75 MHz, $CDCl_3$), δ: Appears as ~1.3:1 mixture of isomers

–6.08 (Si–CH_3), –3.27 (Si–CH_3), –0.92 (Si–CH_3), 0.98 (Si–CH_3), 13.32 (C-3'), 14.79 (C-4), 14.95 (C-4), 15.83 (C-3'), 26.93 (N–CH_3), 31.83 (N–CH_3), 32.14, 36.47, 36.72, 41.54 (Ph–CH_2–CH_2–), 42.39 (C-2), 43.88 (C-2), 56.36 (C-2'), 68.90 (C-2'), 74.78 (C-3), 77.22 (C-3), 78.32 (C-1'), 79.18 (C-1'), 125.81, 125.89,

126.98, 127.48, 127.82, 128.13, 128.34, 128.37, 128.43, 128.67, 140.75, 141.87, 142.03, 142.86 (aromatics), 175.79 (C-1), 176.50 (C-1)

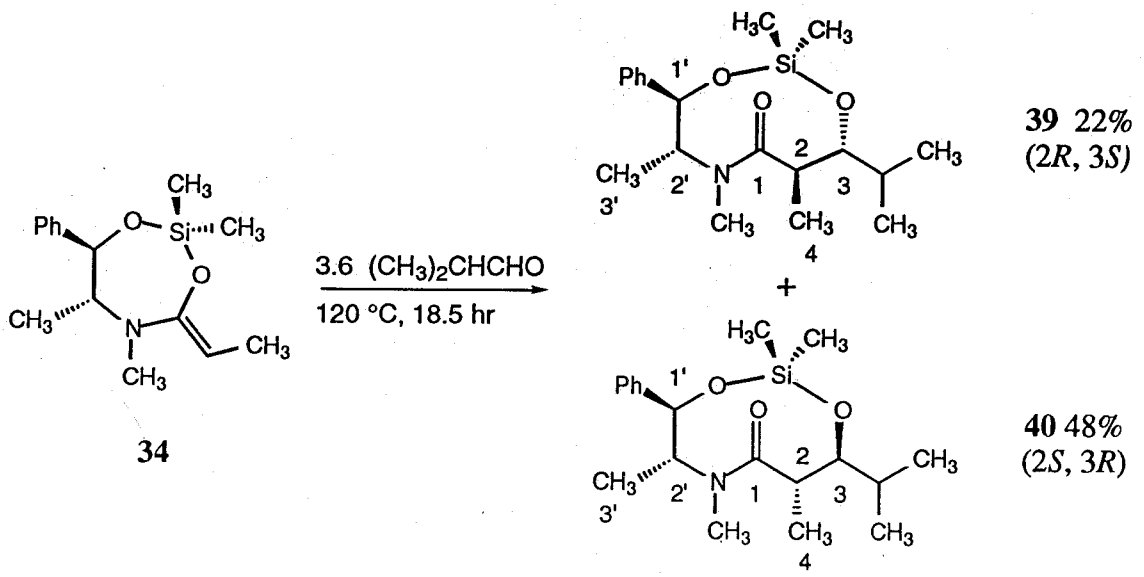
FTIR (neat), cm^{-1}: 2936 (w), 1637 (s, C=O), 1453 (w), 1356 (w), 1256 (m), 1078 (m), 873 (w), 845 (m), 799 (m), 699 (s)

HRMS (FAB), m/z: Calcd for $C_{24}H_{34}O_3NSi$ (MH^+): 412.2308

Found: 412.2303

TLC (20% EtOAc in hexanes), R_f: **37**: 0.35 (UV and PMA)

38: 0.56 and 0.22 (UV and PMA)



(–)-Pseudoephedrine–Isobutyraldehyde Aldol Adducts **39** and **40**

Isobutyraldehyde (600 μL, 476.4 mg, 6.61 mmol, 3.6 equiv) and the *O*-silyl *N,O*-ketene acetal derived from (–)-pseudoephedrine propionamide **34** (509.7 mg, 1.84 mmol, 1 equiv) were combined in a sealable pressure tube under argon. The solution was subjected to three freeze-pump-thaw degas cycles, evacuated, sealed, and heated in a 120 °C oil bath for 18.5 hours. Excess aldehyde was removed *in vacuo*. Purification by flash column chromatography (25% ethyl acetate in hexanes) afforded minor product **39** (142.4 mg, 22%) as a colorless, crystalline solid (mp: 121–127 °C) and major product **40** (310.3 mg, 48%) as a colorless oil which crystallized on standing to a colorless solid (mp: 96–98 °C).

The minor product, **39**, was assigned the (1'*R*, 2'*R*, 2*R*, 3*S*) geometry based on the similarity of its ^{1}H NMR spectrum to the corresponding benzaldehyde adduct. The major product, **40**, appears as two spots on TLC analysis, but 2-D TLC shows those spots convert into each other. The ^{1}H NMR spectrum of **40** also appears to contain two isomers

in an approximately 1:1 mixture of isomers. Upon hydrolysis, however, **40** yields only the anti acid (with minor syn impurities), implying that it is the other anti aldol adduct, the (1'*R*, 2'*R*, 2*S*, 3*R*) isomer, perhaps existing in equilibrium between two conformers.

(1'*R*, 2'*R*, 2*R*, 3*S*) Anti Aldol Adduct **39**

^{1}H NMR (300 MHz, C_6D_6), δ: 0.02 (s, 3H, Si–C**H**$_3$), 0.06 (s, 3H, Si–C**H**$_3$), 0.60 (d, J = 7.2 Hz, 3H, H-3'), 0.80 (d, J = 6.8 Hz, 3H, one of –CH(C**H**$_3$)$_2$), 0.83 (d, J = 6.7 Hz, 3H, one of –CH(C**H**$_3$)$_2$), 1.13 (d, J = 6.5 Hz, 3H, H-4), 1.70 (quintet of d, J = 1.7, 6.7 Hz, 1H, –C**H**(CH$_3$)$_2$), 2.64 (s, 3H, N–C**H**$_3$), 3.02 (dq, J = 6.5, 9.9 Hz, 1H, H-2), 3.80 (dd, J = 1.8, 9.9 Hz, 1H, H-3), 4.34 (d, J = 9.6 Hz, 1H, H-1'), 5.58 (dq, J = 7.2, 9.6 Hz, 1H, H-2'), 7.04–7.16 (m, 3H, aromatics), 7.29–7.32 (m, 2H, aromatics)

^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.05 (s, 3H, Si–C**H**$_3$), 0.07 (s, 3H, Si–C**H**$_3$), 0.82 (d, J = 7.2 Hz, 3H, H-3'), 0.88 (d, J = 6.7 Hz, 3H, one of –CH(C**H**$_3$)$_2$), 0.89 (d, J = 6.8 Hz, 3H, one of –CH(C**H**$_3$)$_2$), 1.06 (d, J = 6.5 Hz, 3H, H-4), 1.89 (quintet of d, J = 1.7, 6.7 Hz, 1H, –C**H**(CH$_3$)$_2$), 3.01 (s, 3H, N–C**H**$_3$), 3.14 (dq, J = 6.5, 9.9 Hz, 1H, H-2), 3.69 (dd, J = 1.7, 9.9 Hz, 1H, H-3), 4.44 (d, J = 9.6 Hz, 1H, H-1'),

5.18 (dq, J = 7.2, 9.6 Hz, 1H, H-2'), 7.22–7.36 (m, 5H, aromatics)

^{13}C NMR (75 MHz, $CDCl_3$), δ: –4.23 (Si–CH_3), –3.56 (Si–CH_3), 13.00 (C-3'), 13.40 (one of –$CH(CH_3)_2$), 14.10 (one of –$CH(CH_3)_2$), 20.68 (C-4), 29.21 (N–CH_3), 39.45 (C-2), 53.32 (–$CH(CH_3)_2$), 54.80 (C-2'), 76.96 (C-1'), 81.22 (C-3), 126.86, 127.56, 128.11, 141.66 (aromatics), 177.41 (C-1)

FTIR (neat), cm^{-1}: 2964 (m), 2937 (w), 2875 (w), 1643 (s, C=O), 1490 (w), 1455 (m), 1406 (m), 1376 (w), 1366 (w), 1291 (m), 1258 (s), 1146 (m), 1114 (m), 1096 (s), 1071 (s), 1047 (s), 975 (w), 932 (w), 879 (s), 853 (s), 799 (s), 701 (s)

HRMS (FAB), m/z: Calcd for $C_{19}H_{32}O_3NSi$ (MH^+): 350.2151
Found: 350.2152

(1'*R*, 2'*R*, 2*S*, 3*R*) Anti Aldol Adduct **40**

^{1}H NMR (300 MHz, $CDCl_3$), δ: Appears as ~1:1 mixture of isomers
–0.24 (Si–CH_3), 0.03 (Si–CH_3), 0.04 (Si–CH_3), 0.12 (Si–CH_3), 0.86 (d, J = 6.7 Hz, 3H,

CH–CH_3), 0.89 (d, J = 6.8 Hz, 3H, CH–CH_3), 0.90 (d, J = 6.7 Hz, 3H, CH–CH_3), 0.94 (d, J = 6.8 Hz, 3H, CH–CH_3), 0.98 (d, J = 7.0 Hz, 3H, CH–CH_3), 1.01 (d, J = 6.8 Hz, 3H, CH–CH_3), 1.07 (d, J = 6.6 Hz, 3H, CH–CH_3), 1.23 (d, J = 7.0 Hz, 3H, CH–CH_3), 1.85 (quintet of d, J = 1.8, 6.7 Hz, 1H, –$CH(CH_3)_2$), 1.93 (quintet of d, J = 1.9, 6.7 Hz, 1H, –$CH(CH_3)_2$), 2.93 (s, 3H, N–CH_3), 2.99 (dq, J = 6.5, 9.7 Hz, 1H, H-2), 3.00 (dq, J = 7.0, 9.5 Hz, 1H, H-2'), 3.17 (s, 3H, N–CH_3), 3.18 (m, 1H, H-2), 3.66 (dd, J = 1.8, 9.8 Hz, 1H, H-3), 3.75 (dd, J = 1.9, 10.0 Hz, 1H, H-3), 4.67 (d, J = 10.2 Hz, 1H, H-1'), 4.96 (dq, J = 6.7, 10.2 Hz, 1H, H-2'), 5.59 (d, J = 9.6 Hz, 1H, H-1'), 7.21–7.50 (m, 5H, aromatics)

^{13}C NMR (75 MHz, $CDCl_3$), δ: Appears as ~1:1 mixture of isomers

–6.34 (Si–CH_3), –3.51 (Si–CH_3), –1.37 (Si–CH_3), 0.40 (Si–CH_3), 12.71 (–CH–CH_3), 13.39 (–CH–CH_3), 13.60 (–CH–CH_3), 14.05 (–CH–CH_3), 15.07 (–CH–CH_3), 15.62 (–CH–CH_3), 20.41 (–CH–CH_3), 20.44 (–CH–CH_3), 28.95 (N–CH_3), 29.03 (N–CH_3), 39.79 (C-2), 40.47 (C-2), 55.71 (–CH–$(CH_3)_2$), 68.98 (C-2'), 74.57 (C-1'), 79.41 (C-1'), 81.01

(C-3), 82.13 (C-3), 126.88, 127.34, 127.92, 128.02, 128.28, 128.63, 140.71, 142.84 (aromatics), 175.88 (C-1), 176.96 (C-1)

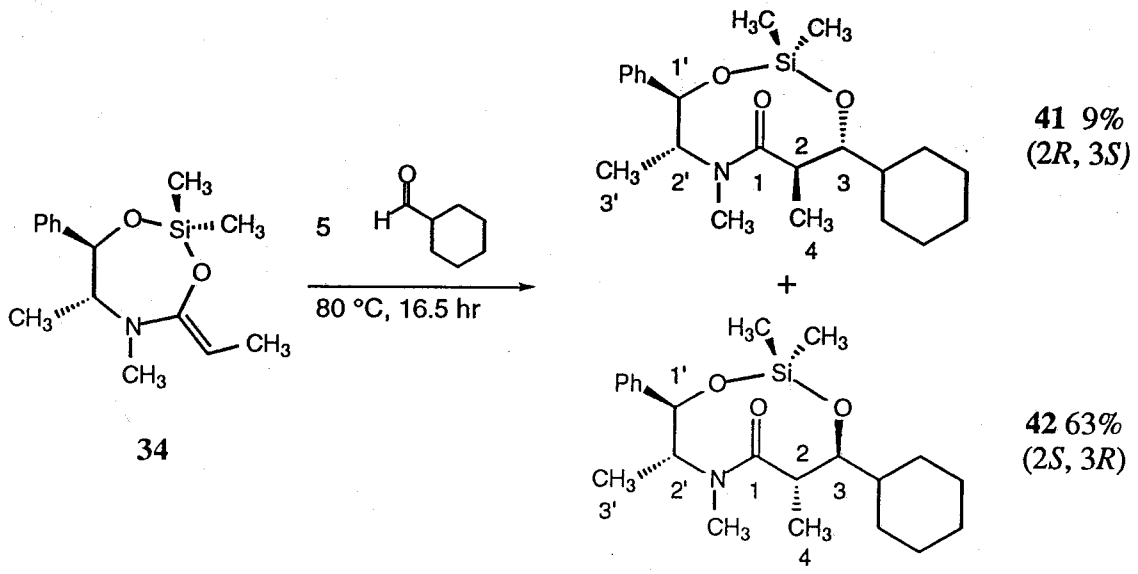
FTIR (neat), cm^{-1}: 2964 (s), 2875 (m), 1644 (s, C=O), 1486 (m), 1455 (m), 1410 (m), 1376 (s), 1295 (m), 1257 (s), 1228 (m), 1203 (m), 1182 (m), 1136 (s), 1051 (s), 979 (w), 933 (w), 857 (s), 799 (s), 701 (s)

HRMS (FAB), m/z: Calcd for $C_{19}H_{32}O_3NSi$ (MH^+): 350.2151

Found: 350.2154

TLC (25% EtOAc in hexanes), R_f: **39**: 0.22 (UV and PMA)

40: 0.38 and 0.16 (UV and PMA)



(–)-Pseudoephedrine–Cyclohexanecarboxaldehyde Aldol Adducts **41** and **42**

Cyclohexanecarboxaldehyde (1.116 mL, 1.033 g, 9.21 mmol, 5 equiv) and the *O*-silyl *N,O*-ketene acetal derived from (–)-pseudoephedrine propionamide **34** (511.2 mg, 1.84 mmol, 1 equiv) were combined in a 10 mL Schlenk tube under argon. The solution was heated in a 80 °C oil bath for 16.5 hours. Excess aldehyde was removed *in vacuo*. Purification by flash column chromatography (10→30% ethyl acetate in hexanes) afforded minor product **41** (62.8 mg, 9%) as a colorless, crystalline solid (mp: 121–126 °C) and major product **42** (451.9 mg, 63%) as a slightly yellow oil.

The minor product, **41**, was assigned the (1'*R*, 2'*R*, 2*R*, 3*S*) geometry based on the similarity of its ^{1}H NMR spectrum to the corresponding benzaldehyde adduct. The major product, **42**, appears as two spots on TLC analysis, and the ^{1}H NMR spectrum of **42** also appears to contain two isomers in an approximately 1:1 ratio. The ^{1}H NMR spectrum of **42** is also very similar to that of the minor benzaldehyde adduct, which also appears as two isomers. Furthermore, **42** yields only the anti acid (with minor syn

impurities) upon hydrolysis, implying that it is the other anti aldol adduct, the (1'*R*, 2'*R*, 2*S*, 3*R*) isomer, perhaps existing in equilibrium between two conformers.

(1'*R*, 2'*R*, 2*R*, 3*S*) Anti Aldol Adduct **41**

^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.05 (s, 3H, Si–CH_3), 0.07 (s, 3H, Si–CH_3), 0.81 (d, J = 7.1 Hz, 3H, H-3'), 1.05 (d, J = 6.5 Hz, 3H, H-4), 1.08–1.80 (m, 11H, cyclohexyl H), 3.00 (s, 3H, N–CH_3), 3.22 (dq, J = 6.5, 9.9 Hz, 1H, H-2), 3.66 (dd, J = 1.4, 9.9 Hz, 1H, H-3), 4.43 (d, J = 9.6 Hz, 1H, H-1'), 5.18 (dq, J = 7.1, 10.0 Hz, 1H, H-2'), 7.26–7.39 (m, 5H, aromatics)

^{13}C NMR (75 MHz, $CDCl_3$), δ: –4.09 (Si–CH_3), –3.40 (Si–CH_3), 13.12 (C-4), 14.16 (C-3'), 23.93 (cyclohexyl –CH_2–), 26.23 (cyclohexyl –CH_2–), 26.49 (cyclohexyl –CH_2–), 26.59 (cyclohexyl –CH_2–), 29.17 (cyclohexyl –CH_2–), 31.30 (N–CH_3), 38.55 (cyclohexyl –CH–), 39.58 (C-2), 54.84 (C-2'), 77.00 (C-3), 81.30 (C-1'), 126.93, 127.61, 128.16, 141.75 (aromatics), 178.14 (C-1)

FTIR (neat), cm^{-1}: 2928 (s), 2853 (m), 1642 (s, C=O), 1490 (w), 1451 (m), 1406 (m), 1375 (w), 1290 (w), 1256 (s), 1218 (w), 1145 (m), 1082 (s), 1069 (s), 1021 (m),

973 (w), 934 (w), 898 (w), 871 (m), 840 (m), 797 (m), 700 (m)

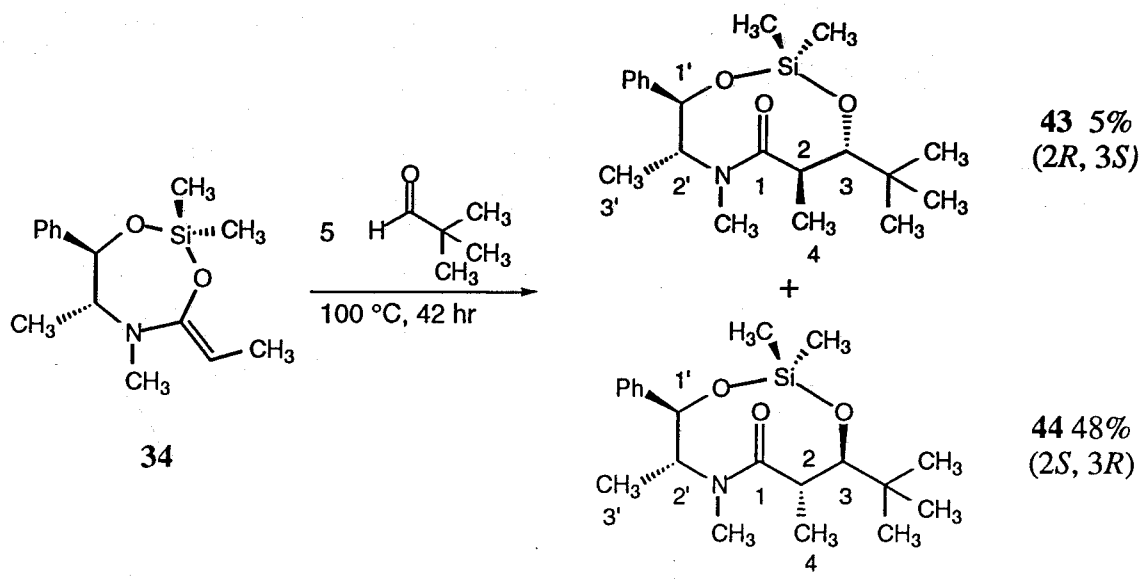
HRMS (FAB), m/z: Calcd for $C_{22}H_{36}NO_3Si$ (MH^+): 390.2464
Found: 390.2469

(1'*R*, 2'*R*, 2*S*, 3*R*) Anti Aldol Adduct **42**

^1H NMR (300 MHz, $CDCl_3$), δ: Appears as ~1:1 mixture of isomers
–0.20 (s, 3H, Si–CH_3), 0.03 (s, 3H, Si–CH_3), 0.04 (s, 3H, Si–CH_3), 0.11 (s, 3H, Si–CH_3), 0.88 (d, J = 6.7 Hz, 3H, H-3'), 1.00 (d, J = 6.5 Hz, 3H, H-3'), 1.06 (d, J = 6.5 Hz, 3H, H-4), 1.22 (d, J = 7.0 Hz, 3H, H-4), 1.12-1.87 (m, 22H, cyclohexyl H), 2.92 (s, 3H, N–CH_3), 2.99 (dq, J = 7.0, 9.5 Hz, 1H, H-2), 3.07 (dq, J = 6.5, 9.7 Hz, 1H, H-2), 3.16 (s, 3H, N–CH_3), 3.25 (dq, J = 6.6, 9.8 Hz, 1H, H-2'), 3.63 (dd, J = 0.8, 9.4 Hz, 1H, H-3), 3.72 (dd, J = 1.3, 9.9 Hz, 1H, H-3), 4.66 (d, J = 10.2 Hz, 1H, H-1'), 4.95 (dq, J = 6.7, 10.2 Hz, 1H, H-2'), 5.59 (d, J = 9.6 Hz, 1H, H-1'), 7.21–7.49 (m, 10H, aromatics)

^{13}C NMR (75 MHz, $CDCl_3$), δ: Appears as ~1:1 mixture of isomers

	-6.24 (Si-CH_3), -3.46 (Si-CH_3), -1.26 (Si-CH_3), 0.50 (Si-CH_3), 12.77 (-CH-CH_3), 14.16 (-CH-CH_3), 15.07 (-CH-CH_3), 15.62 (-CH-CH_3), 24.03 (cyclohexyl -CH_2-), 24.12 (cyclohexyl -CH_2-), 26.14 (cyclohexyl -CH_2-), 26.20 (cyclohexyl -CH_2-), 26.54 (cyclohexyl -CH_2-), 26.65 (cyclohexyl -CH_2-), 30.82 (N-CH_3), 30.96 (N-CH_3), 39.07 (cyclohexyl -CH-), 39.36 (cyclohexyl -CH-), 39.50 (C-2), 41.52 (C-2), 55.67 (C-2'), 68.98 (C-2'), 74.56 (C-3), 79.38 (C-3), 80.90 (C-1'), 82.11 (C-1'), 126.88, 127.33, 127.94, 128.00, 128.24, 128.63, 140.69, 142.86 (aromatics), 176.09 (C-1), 177.11 (C-1)
FTIR (neat), cm^{-1}:	2929 (s), 2853 (s), 1642 (s, C=O), 1485 (m), 1452 (s), 1411 (m), 1376 (s), 1296 (m), 1255 (s), 1204 (w), 1109 (s), 1071 (s), 1028 (s), 975 (w), 935 (m), 898 (m), 866 (s), 847 (s), 798 (s), 735 (w), 701 (s), 558 (m)
HRMS (FAB), m/z:	Calcd for $C_{22}H_{36}NO_3Si$ (MH^+): 390.2464 Found: 390.2465
TLC (20% EtOAc in hexanes), R_f:	**41**: 0.18 (UV and PMA) **42**: 0.39 and 0.11 (UV and PMA)



(–)-Pseudoephedrine–Pivalaldehyde Aldol Adducts **43** and **44**

Pivalaldehyde (797 μL, 632.3 mg, 7.34 mmol, 5 equiv) and the *O*-silyl *N,O*-ketene acetal derived from (–)-pseudoephedrine propionamide **34** (407.3 mg, 1.47 mmol, 1 equiv) were combined in a sealable pressure tube under argon. The solution was subjected to three freeze-pump-thaw degas cycles, evacuated, sealed, and heated in a 100 °C oil bath for 42 hours. Some crystallization occurred on cooling The supernatant was carefully removed and the crystals rinsed with cold hexanes. This afforded aldol adduct **44** (162.2 mg, 30%) as colorless, needle-like crystals (mp: 143–145 °C).

Excess aldehyde was removed from the supernatant *in vacuo*. Purification by flash column chromatography (20% ethyl acetate in hexanes) afforded minor product **43** (24.9 mg, 4.7%) as a colorless solid (mp: 158–162 °C) and more of the major product **44** (95.1 mg, 18%) as a colorless solid (mp: 140–143 °C).

The minor product, **43**, was assigned the (1'*R*, 2'*R*, 2*R*, 3*S*) geometry based on the similarity of its ^{1}H NMR spectrum to the corresponding major benzaldehyde adduct.

The major product, **44**, appears as a single spot on TLC analysis. In benzene-d_6 the ^{1}H NMR spectrum of **44** appears to contain only a single isomer, but in chloroform-*d* the ^{1}H NMR spectrum of **44** appears to contain *two* isomers in an approximately 2:1 ratio. The similarity of this spectrum to that of the minor benzaldehyde adduct implies that **44** is the (1'*R*, 2'*R*, 2*S*, 3*R*) anti aldol adduct, which equilibrates between two conformers in chloroform solution, but which does not in the less polar benzene solution.

(1'*R*, 2'*R*, 2*R*, 3*S*) Anti Aldol Adduct **43**

^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.05 (s, 3H, Si–C**H**$_3$), 0.08 (s, 3H, Si–C**H**$_3$), 0.80 (d, J = 7.2 Hz, 3H, H-3'), 0.98 (s, 9H, –C(C**H**$_3$)$_3$), 1.20 (d, J = 6.4 Hz, 3H, H-4), 3.00 (s, 3H, N–C**H**$_3$), 3.22 (dq, J = 6.4, 9.4 Hz, 1H, H-2), 3.56 (d, J = 9.4 Hz, 1H, H-3), 4.46 (d, J = 9.5 Hz, 1H, H-1'), 5.19 (dq, J = 7.2, 9.5 Hz, 1H, H-2'), 7.24–7.38 (m, 5H, aromatics)

^{13}C NMR (75 MHz, $CDCl_3$), δ: –3.70 (both Si–**C**H$_3$), 14.40 (C-3'), 15.82 (C-4), 27.20 (–C(**C**H$_3$)$_3$), 29.32 (N–**C**H$_3$), 36.55 (–**C**(CH$_3$)$_3$), 39.45 (C-2), 54.79 (C-2'), 77.12 (C-1'), 84.65 (C-3), 126.94, 127.63, 128.20, 141.80 (aromatics), 178.13 (C-1)

FTIR (neat), cm^{-1}: 2961 (m), 2872 (w), 1637 (s, C=O), 1490 (w), 1456 (w), 1403 (m), 1380 (w), 1361 (w), 1340 (w),

1291 (m), 1252 (m), 1219 (w), 1139 (m), 1107 (s), 1088 (s), 1066 (s), 1028 (m), 946 (w), 932 (w), 876 (m), 846 (m), 796 (m), 702 (m)

HRMS (FAB), m/z: Calcd for $C_{20}H_{34}O_3NSi$ (MH^+): 364.2308
Found: 364.2307

(1'*R*, 2'*R*, 2*S*, 3*R*) Anti Aldol Adduct **44**

^{1}H NMR (300 MHz, C_6D_6), δ: Appears as only one product.
0.14 (s, 3H, Si–CH_3), 0.30 (s, 3H, Si–CH_3), 0.91 (s, 9H, –$C(CH_3)_3$), 1.18 (d, J = 6.5 Hz, 3H, H-4), 1.34 (d, J = 6.8 Hz, 3H, H-3'), 2.79 (s, 3H, N–CH_3), 2.86 (dq, J = 7.0, 9.5 Hz, 1H, H-2'), 2.92 (dq, J = 6.5, 9.2 Hz, 1H, H-2), 3.65 (d, J = 9.2 Hz, 1H, H-3), 5.99 (d, J = 9.5 Hz, 1H, H-1'), 7.05–7.39 (m, 5H, aromatics)

^{1}H NMR (300 MHz, $CDCl_3$), δ: Appears as ~2:1 mixture of isomers.
major: 0.04 (s, 3H, Si–CH_3), 0.16 (s, 3H, Si–CH_3), 0.97 (s, 9H, –$C(CH_3)_3$), 1.16 (d, J = 6.5 Hz, 3H, H-4), 1.21 (d, J = 6.9 Hz, 3H, H-3'), 2.99 (dq, J = 6.9, 9.6 Hz, 1H, H-2'), 3.08 (dq, J = 6.5, 9.2 Hz, 1H, H-2), 3.16 (s, 3H,

N–CH_3), 3.53 (d, J = 9.2 Hz, 1H, H-3), 5.68 (d, J = 9.6 Hz, 1H, H-1'), 7.22–7.50 (m, 5H, aromatics)

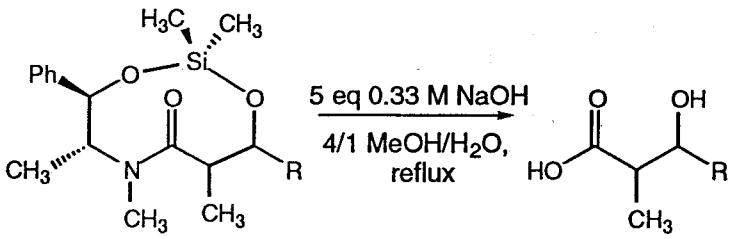
minor: –0.22 (s, 3H, Si–CH_3), 0.07 (s, 3H, Si–CH_3), 0.91 (d, J = 6.7 Hz, 3H, H-3'), 1.05 (s, 9H, –$C(CH_3)_3$), 1.21 (d, J = 6.9 Hz, 3H, H-4), 2.93 (s, 3H, N–CH_3), 3.31 (dq, J = 6.8, 9.6 Hz, 1H, H-2), 3.68 (d, J = 9.6 Hz, 1H, H-3), 4.66 (d, J = 10.1 Hz, 1H, H-1'), 4.98 (dq, J = 6.7, 10.2 Hz, 1H, H-2'), 7.22–7.50 (m, 5H, aromatics

^{13}C NMR (75 MHz, $CDCl_3$), δ: Appears as ~2:1 mixture of isomers.

major: –6.08 (Si–CH_3), –0.99 (Si–CH_3), 14.76 (CH–CH_3), 15.48 (CH–CH_3), 27.12 (–$C(CH_3)_3$), 36.23 (N–CH_3), 41.39 (C-2), 41.46 (–$C(CH_3)_3$), 68.89 (C-2'), 75.10 (C-1'), 85.40 (C-3), 127.01, 127.91, 128.06, 143.15 (aromatics), 177.10 (C-1)

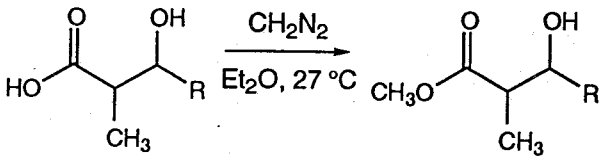
minor: –3.46 (Si–CH_3), 0.74 (Si–CH_3), 15.71 (CH–CH_3), 16.50 (CH–CH_3), 26.80 (–$C(CH_3)_3$), 36.31 (N–CH_3), 40.46 (C-2), 55.86 (C-2'), 79.53 (C-1'), 84.34 (C-3), 127.38, 128.30, 128.66 (aromatics), 176.81 (C-1)

FTIR (neat), cm^{-1}:	2944 (m), 2877 (w), 1632 (s, C=O), 1484 (m), 1454 (m), 1410 (w), 1375 (m), 1360 (m), 1291 (w), 1256 (s), 1103 (s), 1083 (s), 1062 (s), 953 (w), 930 (w), 911 (w), 854 (s), 796 (s), 718 (m), 705 (m)
HRMS (FAB), m/z:	Calcd for $C_{20}H_{34}O_3NSi$ (MH^+): 364.2308 Found: 364.2322
TLC (30% EtOAc in hexanes), R_f:	**43**: 0.47 (UV and PMA) **44**: 0.57 (UV and PMA)



General Procedure for Hydrolysis of Pseudoephedrine Auxiliary:

The silylated anti aldol adducts were dissolved in 5 equiv of a 0.33 M solution of NaOH in 4:1 methanol-water, then heated to reflux until TLC showed only the acid as a long, low R_f streak. When complete, the cooled reaction mixture was concentrated *in vacuo* to remove methanol. The remaining basic solution was extracted with three 10-mL portions of dichloromethane. The organic extracts were dried over sodium sulfate, filtered, and concentrated to yield the pseudoephedrine auxiliary. The remaining aqueous layer was acidified with 1 N aqueous hydrochloric acid to pH < 2, saturated with solid sodium chloride, and extracted with several (> 5) portions of dichloromethane (15–20 mL). These organic extracts were dried over sodium sulfate, filtered, and concentrated to yield the crude carboxylic acids and a polymeric silyl contaminant.



General Procedure for Esterification of Acids

A solution of diazomethane in ether was prepared by slow addition of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald®) to a stirred solution of 40% potassium hydroxide in water in the presence of catalytic 2-(2-ethoxyethoxy)ethanol while heating to reflux. The resulting yellow solution was distilled in glass apparatus with non-ground glass joints and collected and stored over potassium hydroxide. This ether solution of diazomethane was added dropwise by fire-polished pipette to a solution of the crude acid in dry ether (15 mL) at 27 °C until the acid solution remained a persistent yellow color. The reaction mixture was allowed to stir open to the atmosphere at 27 °C until the yellow color dissipated (5–10 minutes). Concentration of this solution and purification by flash column chromatography yielded the pure methyl esters.

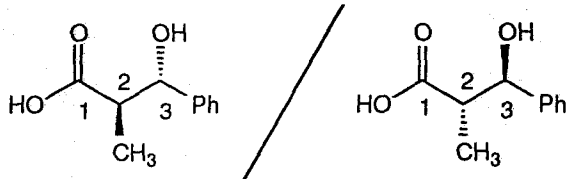
Hydrolysis of Benzaldehyde Adduct **35**

Hydrolysis of (2*R*, 3*S*) benzaldehyde aldol adduct **35** (205.1 mg, 0.53 mmol) according to the general procedure for 17 hours afforded (–)-pseudoephedrine (73.2 mg, 0.44 mmol, 83.6%) as a crystalline solid and a crude mixture of (2*R*, 3*S*)-3-hydroxy-2-methyl-3-phenylpropionic acid with the polymeric silyl contaminant (99.6 mg, 0.55 mmol based on acid, >100%, uncorrected for impurity) as a crystalline solid film. The ^{1}H NMR spectrum of this crude acid shows <2% of the syn acid, relative to the anti isomer. Esterification of this acid mixture with diazomethane and purification by flash column chromatography (50% ethyl acetate in hexanes) gave methyl (2*R*, 3*S*)-3-hydroxy-2-methyl-3-phenylpropionate (85.1 mg, 0.44 mmol, 83% from **35**) as a colorless oil. The ^{1}H NMR spectrum of this purified methyl ester also shows <2% of the syn ester. Chiral GC analysis showed the anti ester to have an ee of 84.3%

Hydrolysis of Benzaldehyde Adduct **36**

Hydrolysis of (2*S*, 3*R*) benzaldehyde aldol adduct **36** (59.5 mg, 0.155 mmol) according to the general procedure for 19 hours afforded (–)-pseudoephedrine (16.7 mg, 0.101 mmol, 65.2%) and a crude mixture of (2*S*, 3*R*)-3-hydroxy-2-methyl-3-phenylpropionic acid with the polymeric silyl contaminant (24.7 mg, 0.137 mmol based on acid, 88%, uncorrected for impurity). The ^{1}H NMR spectrum of this crude acid shows 7% of the syn acid, relative to the anti isomer. Esterification of this acid mixture with diazomethane and purification by flash column chromatography (20% ethyl acetate in hexanes, silica gel) gave methyl (2*S*, 3*R*)-3-hydroxy-2-methyl-3-phenylpropionate (18.6 mg, 0.095 mmol, 62% from **36**) as a colorless oil. The ^{1}H NMR spectrum of this

purified methyl ester also shows 7% of the syn ester. Chiral GC analysis showed the anti ester to have an ee of 89.5%. This ester was identical to that derived from the major (+)-pseudoephedrine aldol adduct **6**.



(2*R*, 3*S*) (2*S*, 3*R*)

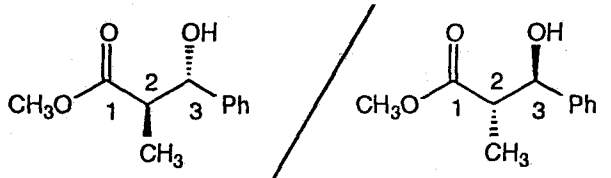
(2*R*, 3*S*)- and (2*S*, 3*R*)-3-Hydroxy-2-Methyl-3-Phenylpropionic Acids

^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.02 (d, J = 7.2 Hz, 3H, $-CH_3$), 2.84 (dq, J = 7.2, 8.9 Hz, 1H, H-2), 4.76 (d, J = 8.9 Hz, 1H, H-3), 6.44 (br s, D_2O exchangeable, 2H, –OH), 7.28–7.40 (m, 5H, aromatics)

^{13}C NMR (75 MHz, $CDCl_3$), δ: 14.38 ($-CH_3$), 67.21 (C-2), 76.41 (C-3), 126.78, 128.22, 128.56, 141.15 (aromatics), 180.77 (C-1)

FTIR (neat), cm^{-1}: 3378 (br, -OH), 1712 (s, C=O), 1494 (w), 1456 (m), 1408 (m), 1258 (m), 1203 (m), 1125 (w), 1089 (w), 1014 (m), 913 (w), 764 (m), 701 (s)

TLC (30% EtOAc in hexanes), R_f: **Acid**: streaks, depends on concentration (PMA)
Methyl Ester: 0.23 (PMA)



(2*R*, 3*S*) (2*S*, 3*R*)

Methyl (2*R*, 3*S*)- and (2*S*, 3*R*)-3-Hydroxy-2-Methyl-3-Phenylpropionate

^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.97 (d, J = 7.5 Hz, 3H, –CH–**CH$_3$**), 2.79 (dq, J = 7.2, 8.7 Hz, 1H, H-2), 3.13 (br d, J = 3.6 Hz, D_2O exchangeable, 1H, –**OH**), 3.70 (s, 3H, –O**CH$_3$**), 4.72 (dd, J = 2.7, 8.7 Hz, 1H, H-3), 7.20–7.40 (m, 5H, aromatics)

^{13}C NMR (75 MHz, $CDCl_3$), δ: 14.26 (–CH–**CH$_3$**), 47.06 (C-2), 51.77 (–O**CH$_3$**) 76.23 (C-3), 126.57, 127.89, 128.32, 141.49 (aromatics), 176.14 (C-1)

FTIR (neat), cm^{-1}: 3457 (br, –OH), 2979 (m), 2951 (m), 1736 (s, C=O), 1494 (w), 1456 (s) 1436 (m), 1375 (m), 1342 (m), 1309 (m), 1249 (m), 1199 (s, C–O), 1170 (s, C–O), 1124 (m), 1089 (m), 1073 (m), 1053 (m), 1034 (m), 1023 (m), 908 (m), 768 (s) 704 (s) 611 (m)

GC (Chirasil-Val, 110 °C), min: (2*R*, 3*S*) 10.9

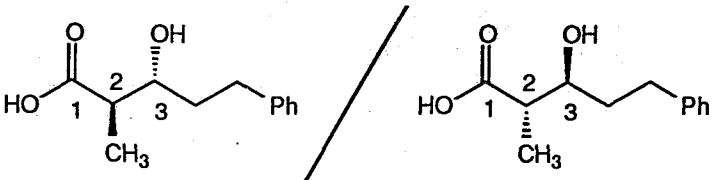
(2*S*, 3*R*) 11.3

Hydrolysis of Hydrocinnamaldehyde Adduct 37

Hydrolysis of (2*R*, 3*S*) hydrocinnamaldehyde aldol adduct **37** (77.1 mg, 0.187 mmol) according to the general procedure for 20.5 hours afforded (–)-pseudoephedrine (25.6 mg, 0.155 mmol, 82.9%) and a crude mixture of (2*R*, 3*S*)-3-hydroxy-2-methyl-5-phenylpentanoic acid with the polymeric silyl contaminant (42.9 mg, 0.206 mmol based on acid, >100%, uncorrected for impurity). The ^{1}H NMR spectrum of the crude acid shows an anti:syn ratio of 82:18. Esterification with diazomethane and purification by filtration through a short silica gel plug (100 % ethyl acetate) gave methyl (2*R*, 3*S*)-3-hydroxy-2-methyl-5-phenylpentanoate (37.6 mg, 0.169 mmol, 90.4% from **37**) as a slightly yellow oil. This methyl ester could not be cleanly separated from its enantiomer on the chiral GC column (Chirasil–Val), so the ee was not determined.

Hydrolysis of Hydrocinnamaldehyde Adduct 38

Hydrolysis of (2*S*, 3*R*) hydrocinnamaldehyde aldol adduct **38** (59.2 mg, 0.128 mmol) according to the general procedure for 20.5 hours afforded (–)-pseudoephedrine (16.5 mg, 0.100 mmol, 78.0%) and a crude mixture of (2*S*, 3*R*)-3-hydroxy-2-methyl-5-phenylpentanoic acid with the polymeric silyl contaminant (25.8 mg, 0.124 mmol based on acid, 96.8%, uncorrected for impurity). The ^{1}H NMR spectrum of the crude acid shows an anti:syn ratio of 93:7. Esterification with diazomethane and purification by filtration through a short silica gel plug (100% ethyl acetate) gave methyl (2*S*, 3*R*)-3-hydroxy-2-methyl-5-phenylpentanoate (20.9 mg, 0.094 mmol, 73.4% from **38**) as a slightly yellow oil. This methyl ester could not be cleanly separated from its enantiomer on the chiral GC column (Chirasil–Val), so the ee was not determined.



(2*R*, 3*S*) (2*S*, 3*R*)

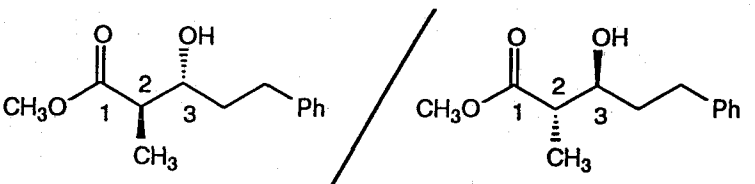
(2*R*, 3*S*)- and (2*S*, 3*R*)-3-Hydroxy-2-Methyl-5-Phenylpentanoic Acids

^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.24 (d, J = 7.2 Hz, 3H, $-CH_3$), 1.84 (m, 2H, $PhCH_2CH_2-$), 2.58 (quintet, J = 7.0, Hz, 1H, H-2), 2.71 (ddd, J = 6.9, 9.4, 13.7 Hz, 1H, one of $PhCH_2-$), 2.87 (ddd, J = 5.5, 9.5, 13.5 Hz, 1H, one of $PhCH_2-$), 3.72 (ddd, J = 3.5, 6.5, 9.5 Hz, 1H, H-3), 5.94 (br s, 2H, –OH), 7.16–7.37 (m, 5H, aromatics)

FTIR (neat), cm^{-1}: 3500 (br, –OH), 3025 (m), 2942 (m), 1707 (s, C=O), 1496 (w), 1458 (m), 1406 (w), 1260 (m), 1203 (m), 1030 (m), 937 (w), 804 (m), 749 (m), 700 (s)

TLC (20% EtOAc in hexanes), R_f: **Acid**: streaks, depends on concentration (PMA)

Methyl Ester: 0.28 (PMA)



(2*R*, 3*S*) (2*S*, 3*R*)

Methyl (2*R*, 3*S*)- and (2*S*, 3*R*)-3-Hydroxy-2-Methyl-5-Phenylpentanoate

^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.21 (d, J = 7.2 Hz, 3H, –CH–C**H**$_3$), 1.76 (m, 2H, PhCH$_2$C**H**$_2$–), 2.55 (dq, J = 6.4, 7.1, Hz, 1H, H-2), 2.69 (d, J = 6.9 Hz, 1H, –O**H**), 2.70 (ddd, J = 6.9, 9.6, 13.7 Hz, 1H, one of PhC**H**$_2$), 2.87 (ddd, J = 5.5, 9.6, 13.9 Hz, 1H,one of PhC**H**$_2$), 3.67 (ddd, J = 3.5, 6.5, 8.7 Hz, 1H, H-3), 3.70 (s, 3H, –OC**H**$_3$), 7.16–7.33 (m, 5H, aromatics)

^{13}C NMR (75 MHz, $CDCl_3$), δ: 14.34 (–CH–C**H**$_3$), 31.88 (PhC**H**$_2$–), 36.62 (PhCH$_2$C**H**$_2$–), 45.19 (C-2), 51.76 (–OC**H**$_3$) 72.61 (C-3), 125.84, 128.38, 128.43, 141.87 (aromatics), 176.42 (C-1)

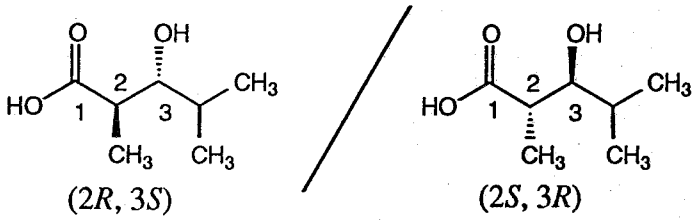
FTIR (neat), cm^{-1}: 3448 (br, –OH), 2950 (m), 1734 (s, C=O), 1603 (w), 1496 (w), 1456 (m), 1436 (m), 1357 (w), 1262 (m), 1199 (m, C–O), 1167 (m, C–O), 1044 (m), 935 (w), 748 (w), 700 (s)

Hydrolysis of Isobutyraldehyde Adduct **39**

Hydrolysis of (2*R*, 3*S*) isobutyraldehyde aldol adduct **39** (94.7 mg, 0.271 mmol) according to the general procedure for 9.5 hours afforded (–)-pseudoephedrine (44.0 mg, 0.266 mmol, 98.3%) and a crude mixture of (2*R*, 3*S*)-3-hydroxy-2,4-dimethylpentanoic acid with the polymeric silyl contaminant (31.2 mg, 0.213 mmol based on acid, 78.6%, uncorrected for impurity) as a yellow oil. The ^{1}H NMR spectrum of the crude acid shows an anti:syn ratio of 96:4. Esterification with diazomethane and purification by flash column chromatography (20% ethyl acetate in hexanes) gave methyl (2*R*, 3*S*)-3-hydroxy-2,4-dimethylpentanoate (10.3 mg, 0.064 mmol, 23.7% from **39**) as a colorless oil. Chiral GC analysis showed the anti ester to have an ee of 70.3%

Hydrolysis of Isobutyraldehyde Adduct **40**

Hydrolysis of (2*S*, 3*R*) isobutyraldehyde adduct **40** (117.4 mg, 0.336 mmol) according to the general procedure for 9.5 hours afforded (–)-pseudoephedrine (48.3 mg, 0.292 mmol, 86.9%) and a crude mixture of (2*S*, 3*R*)-3-hydroxy-2,4-dimethylpentanoic acid with the polymeric silyl contaminant (48.3 mg, 0.330 mmol based on acid, 98.3%, uncorrected for impurity) as a yellow oil. The ^{1}H NMR spectrum of the crude acid shows an anti:syn ratio of 94:6. Esterification with diazomethane and purification by flash column chromatography (20% ethyl acetate in hexanes, silica gel) gave methyl (2*S*, 3*R*)-3-hydroxy-2,4-dimethylpentanoate (12.3 mg, 0.076 mmol, 22.8% from **40**) as a colorless oil. Chiral GC analysis showed the anti ester to enantiomerically pure (100% ee).



(2*R*, 3*S*) (2*S*, 3*R*)

(2*R*, 3*S*)- and (2*S*, 3*R*)-3-Hydroxy-2,4-Dimethylpentanoic Acids

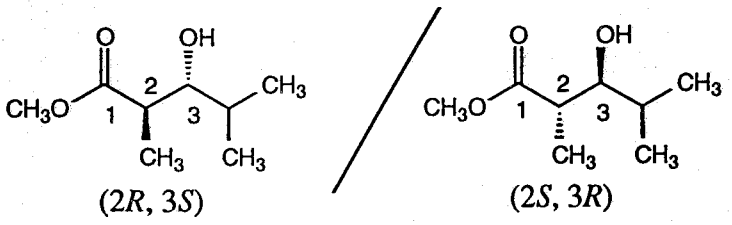
^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.92 (d, J = 6.7 Hz, 3H, –**CH$_3$**), 0.98 (d, J = 6.8 Hz, 3H, –**CH$_3$**), 1.23 (d, J = 7.2 Hz, 3H, –**CH$_3$**), 1.79 (m, 1H, –**CH**Me$_2$), 2.67 (quintet, J = 7.0 Hz, 1H, H-2), 3.43 ("t", J = 5.9 Hz, 1H, H-3), 6.23 (br s, 2H, –**OH**)

^{13}C NMR (75 MHz, $CDCl_3$), δ: 14.60 (–**C**H$_3$), 16.14 (–**C**H$_3$), 19.74 (–**C**H$_3$), 30.72 (–**C**HMe$_2$), 42.65 (C-3), 78.06 (C-2), 181.16 (C-1)

FTIR (neat), cm^{-1}: 3410 (br, –OH), 2964 (s), 1711 (s, C=O), 1465 (m), 1388 (m), 1261 (s), 1204 (m), 1133 (m), 1097 (m), 1035 (m), 998 (m), 966 (m), 898(w), 804 (m), 658 (w)

TLC (30% EtOAc in hexanes), R_f: **Acid**: streaks, depends on concentration (PMA)

Methyl Ester: 0.33 (PMA)



Methyl (2*R*, 3*S*)- and (2*S*, 3*R*)-3-Hydroxy-2,4-Dimethylpentanoate

^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.92 (d, J = 6.7 Hz, 3H, –CH_3), 0.96 (d, J = 6.8 Hz, 3H, –CH_3), 1.20 (d, J = 7.2 Hz, 3H, –CH_3), 1.71 (quintet of d, J = 5.4, 6.8 Hz, 1H, –$CHMe_2$), 1.65 (br s, 1H, –OH), 2.66 (dq, J = 6.6, 7.2 Hz, 1H, H-2), 3.38 (t, J = 5.8 Hz, 1H, H-3), 3.71 (s, 3H, –OCH_3)

^{13}C NMR (75 MHz, $CDCl_3$), δ: 14.79 (–CH_3), 16.34 (–CH_3), 19.75 (–CH_3), 30.99 (–$CHMe_2$), 42.50 (C-3), 51.76 (–OCH_3), 78.21 (C-2), 176.88 (C-1)

FTIR (neat), cm^{-1}: 3504 (br, –OH), 2961 (s), 2878 (m), 1724 (s, C=O), 1459 (m), 1437 (m), 1376 (m), 1260 (s), 1199 (s, C–O), 1171 (s, C–O), 1134 (m), 1100 (m), 1040 (m), 1003 (m), 965 (w), 892 (w), 851 (w), 803 (m)

GC (Chirasil-Val, 55 °C), min: (2*R*, 3*S*) 7.36

(2*S*, 3*R*) 7.74

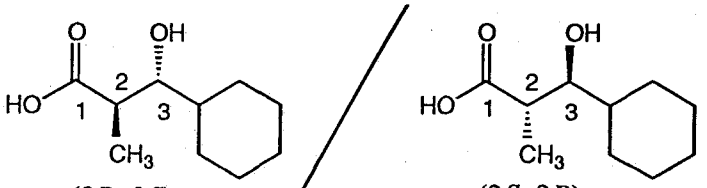
Hydrolysis of Cyclohexanecarboxaldehyde Adduct **41**

Hydrolysis of (2*R*, 3*S*) cyclohexanecarboxaldehyde aldol adduct **41** (74.7 mg, 0.192 mmol) according to the general procedure for 11 hours afforded (–)-pseudoephedrine (amount undetermined) and a crude mixture of (2*R*, 3*S*)-3-hydroxy-2-methyl-3-cyclohexanepropionic acid with the polymeric silyl impurity (19.0 mg, 0.102 mmol based on acid, 53%, uncorrected for impurity) as a yellow oil. The ^{1}H NMR spectrum of this crude acid shows an anti:syn ratio of 90:10. Esterification of the crude acid mixture and purification by flash column chromatography (20% ethyl acetate in hexanes) gave methyl (2*R*, 3*S*)-3-hydroxy-2-methyl-3-cyclohexanepropionate (11.0 mg, 0.055 mmol, 28.6% based on **41**) as a colorless oil. The ^{1}H NMR spectrum of the methyl ester shows an anti:syn ratio of 86:14, perhaps as an artifact of the very poor yield of acid. Chiral GC analysis showed the anti ester to have an ee of 83.4%.

Hydrolysis of Cyclohexanecarboxaldehyde Adduct **42**

Hydrolysis of (2*S*, 3*R*) cyclohexanecarboxaldehyde aldol adduct **42** (200.7 mg, 0.515 mmol) according to the general procedure for 11 hours afforded (–)-pseudoephedrine (amount undetermined) and a crude mixture of (2*S*, 3*R*)-3-hydroxy-2-methyl-3-cyclohexanepropionic acid with the polymeric silyl impurity (70.5 mg, 0.379 mmol based on acid, 73.5%, uncorrected for impurity) as a yellow oil. The ^{1}H NMR spectrum of this crude acid shows an anti:syn ratio of 88:12. Esterification of the crude acid mixture and purification by flash column chromatography (20% ethyl acetate in hexanes) gave methyl (2*S*, 3*R*)-3-hydroxy-2-methyl-3-cyclohexanepropionate (51.6 mg, 0.258 mmol, 50.0% based on **42**) as a colorless oil. The ^{1}H NMR spectrum of the methyl

ester also shows an anti:syn ratio of 88:12. Chiral GC analysis showed the anti ester to be enantiomerically pure (100% ee)



(2*R*, 3*S*) (2*S*, 3*R*)

(2*R*, 3*S*)- and (2*S*, 3*R*)-3-Hydroxy-2-Methyl-3-Cyclohexylpropionic Acids

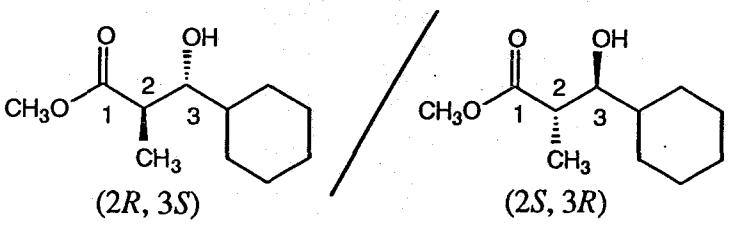
^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.00–1.32 (m, 4H), 1.24 (d, J = 7.2 Hz, 3H, $-CH_3$), 1.40–1.49 (m, 1H), 1.61–1.68 (m, 3H), 1.74–1.82 (m, 3H), 2.71 (quintet, J = 6.9 Hz, 1H, H-2), 3.42 (t, J = 5.9 Hz, 1H, H-3), 6.30 (br s, 2H, –OH)

^{13}C NMR (75 MHz, $CDCl_3$), δ: 14.73 ($-CH_3$), 25.97, 26.26, 26.29 (cyclohexyl $-CH_2-$), 40.74 (cyclohexyl –CH), 41.89 (C-3), 77.66 (C-2), 181.25 (C-1)

FTIR (neat), cm^{-1}: 3394 (br, –OH), 2927 (s), 2853 (s), 1708 (s, C=O), 1450 (m), 1406 (w), 1259 (m), 1204 (m), 1101 (m), 1028 (m), 982 (w), 892 (w), 803 (s)

TLC (100% toluene), R_f: **Acid**: streaks, depends on concentration (PMA)

Methyl Ester: 0.34 (PMA)



(2*R*, 3*S*) (2*S*, 3*R*)

Methyl (2*R*, 3*S*)- and (2*S*, 3*R*)-3-Hydroxy-2-Methyl-3-Cyclohexylpropionate

^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.03–1.18 (m, 5H), 1.20 (d, J = 7.2 Hz, 3H, $-CH_3$), 1.24–1.38 (m, 1H), 1.58–1.66 (m, 2H), 1.73–1.82 (m, 3H), 2.43 (br s, 1H, –OH), 2.69 (dq, J = 6.2, 7.1 Hz, 1H, H-2), 3.36 (t, J = 5.8 Hz, 1H, H-3), 3.70 (s, 3H, $-OCH_3$)

^{13}C NMR (75 MHz, $CDCl_3$), δ: 14.81 ($-CH_3$), 26.01, 26.28, 26.31, 26.89, 29.91 (cyclohexyl $-CH_2-$), 40.97 (cyclohexyl –CH), 41.82 (C-3), 51.69 ($-OCH_3$), 77.71 (C-2), 176.90 (C-1)

FTIR (neat), cm^{-1}: 3490 (br, –OH), 2928 (s), 2853 (s), 1732 (s, C=O), 1451 (s), 1375 (m), 1259 (s), 1199 (s, C–O), 1172 (s, C–O), 1103 (s), 1036 (s), 992 (m), 891 (w), 872 (w), 850 (w), 803 (m)

GC (Chirasil-Val, 55 °C), min: (2*R*, 3*S*) 13.1

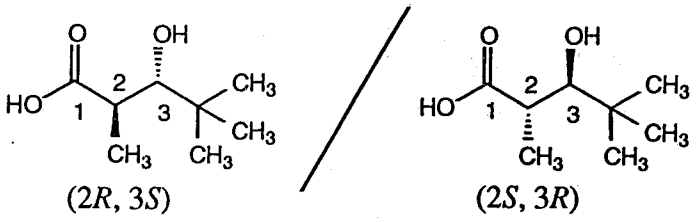
(2*S*, 3*R*) 13.6

Hydrolysis of Pivalaldehyde Adduct **43**

The minor (2*R*, 3*S*) pivalaldehyde aldol adduct **43** (22.8 mg, 0.063 mmol, 1 equiv) was treated with triethylamine trihydrofluoride (101 mg, 102 μL, 0.63 mmol, 10 equiv) in acetonitrile (1.0 mL) for 12 hours at 27 °C. Purification by filtration through a short silica plug (100% ethyl acetate) yielded crude diol (16.9 mg, 0.055 mmol, 87.6%) as a white solid. This diol was then subjected to the standard hydrolysis conditions for 5 days. After the standard aqueous extraction procedure, (2*R*, 3*S*)-3-hydroxy-2,4,4-trimethylpropionic acid (6.7 mg, 0.042 mmol, 76.4% from diol) was isolated as a crystalline film. The ^{1}H NMR spectrum of this acid shows an anti:syn ratio of 92:8. (–)-Pseudoephedrine (7.0 mg, 0.042 mmol, 77.0% from diol) was also recovered.

Hydrolysis of Pivalaldehyde Adduct **44**

The major (2*S*, 3*R*) pivalaldehyde aldol adduct **44** (89.9 mg, 0.247 mmol, 1.0 equiv) was treated with triethylamine trihydrofluoride (169 mg, 171 μL, 1.04 mmol, 4.2 equiv) in acetonitrile (10 mL) for 10 hours at 27 °C. Purification by filtration through a short silica plug yielded crude diol (32.2 mg, 0.105 mmol, 42.4%) as a white solid. This diol was subjected to the standard hydrolysis conditions for 3 days. After the standard aqueous extraction procedure, (2*S*, 3*R*)-3-hydroxy-2,4,4-trimethylpropionic acid (12.4 mg, 0.077 mmol, 73.7% from diol) was isolated as a crystalline film. The ^{1}H NMR spectrum of this acid shows an anti:syn ratio of 91:9. (–)-Pseudoephedrine (17.3 mg, 0.105 mmol. 100% from diol) was also recovered.



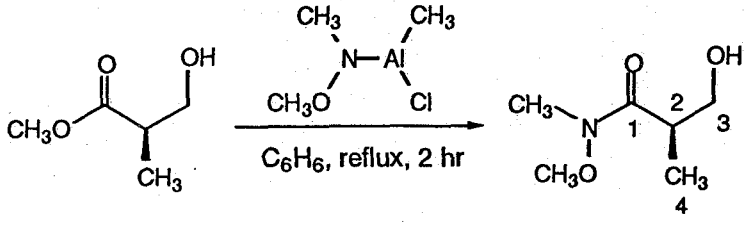
(2*R*, 3*S*) (2*S*, 3*R*)

(2*R*, 3*S*)- and (2*S*, 3*R*)-3-Hydroxy-2,4,4-Methylpropionic Acids

^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.94 (s, 9H, $-C(CH_3)_3$), 1.40 (d, J = 7.2 Hz, 3H, $-CHCH_3$), 2.78 (dq, J = 2.0, 7.3 Hz, 1H, H-2), 3.25 (d, J = 2.1 Hz, 1H, H-3)

^{13}C NMR (75 MHz, $CDCl_3$), δ: 18.16 ($-CHCH_3$), 26.07 ($-C(CH_3)_3$), 36.02 ($-CMe_3$), 82.46 (C-3), 181.60 (C-1)

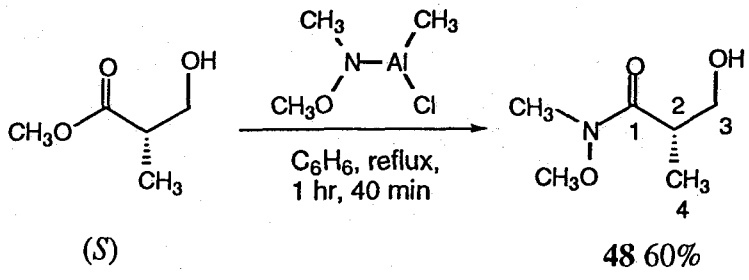
FTIR (neat), cm^{-1}: 3287 (very br, –OH), 2961 (s), 2682 (m), 2607 (m), 1694 (s, C=O), 1465 (s), 1349 (m), 1289 (s), 1220 (s), 1198 (s), 1119 (m),1055 (m), 976 (s), 811 (w), 730 (w)



(*R*) **47** 70%

N-methoxy-*N*-methyl (2*R*)-3-Hydroxy-2-Methylpropionamide **47**

Triethylaluminum (2.0 M in toluene, 30 mL, 60 mmol, 3.0 equiv) was added dropwise via cannula to a solution of *N,O*-dimethyl hydroxylamine hydrochloride (5.85 g, 60 mmol, 3.0 equiv) in dry benzene (60 mL) at 0 °C. After stirring at 0 °C for 10 minutes, the solution was warmed to 27 °C and stirred 1 hour, 45 minutes further. To this aluminum amide complex was added a solution of methyl (*R*)-(–)-3-hydroxy-2-methyl propionate (2.3626 g, 2.22 mL, 20 mmol, 1 equiv) in dry benzene (40 mL) via dropping funnel over 40 minutes. When the addition was complete, the solution was heated to reflux for 2 hours. After cooling to 0 °C, 1 N HCl (30 mL) was added to quench excess aluminum amide complex. The layers were separated and the aqueous layer extracted further with three 30-mL portions of dichloromethane . The combined organic layers were dried over sodium sulfate, filtered, concentrated, and purified by flash column chromatography (100% ethyl acetate→30% methanol in ethyl acetate) affording (*R*) propionamide **47** (2.0572 g, 13.98 mmol, 69.9%) as a pale yellow oil.



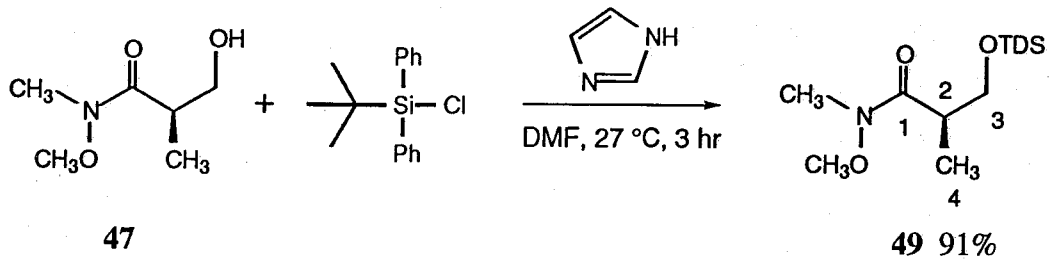
(*S*) **48** 60%

N-methoxy-*N*-methyl (2*S*)-3-Hydroxy-2-Methylpropionamide **48**

Triethylaluminum (2.0 M in toluene, 54.1 mL, 108.3 mmol, 3.0 equiv) was added dropwise via cannula to a solution of *N,O*-dimethyl hydroxylamine hydrochloride (10.56 g, 108.3 mmol, 3.0 equiv) in dry benzene (100 mL) at 0 °C. After stirring at 0 °C for 15 minutes, the solution was warmed to 27 °C and stirred 1 hour further. To this aluminum amide complex was added a solution of methyl (*S*)-(+)-3-hydroxy-2-methyl propionate (4.264 g, 4.00 mL, 36.1 mmol, 1 equiv) in dry benzene (25 mL) via dropping funnel over 30 minutes. When the addition was complete, the solution was heated to reflux for 1 hour, 40 minutes. After cooling to 0 °C, 1 N HCl (80 mL) was added to quench excess aluminium complex. The layers were separated and the aqueous layer extracted further with three 30-mL portions of dichloromethane. The combined organic layers were dried over sodium sulfate, filtered, concentrated, and purified by flash column chromatography (100% ethyl acetate) affording (*S*) propionamide **48** (3.1789 g, 21.6 mmol, 59.8%) as a colorless oil

Propionamides **47** and **48**

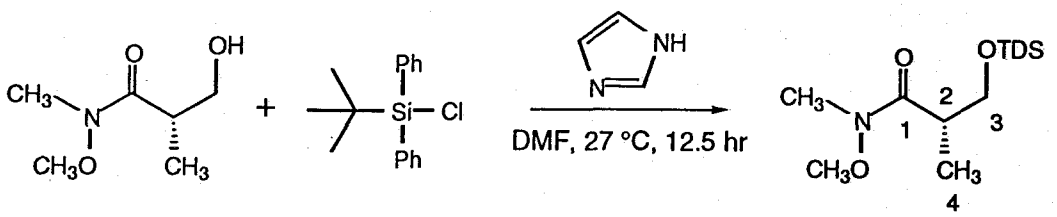
^{1}H NMR (300 MHz, C_6D_6), δ:	1.06 (d, J = 7.1 Hz, 3H, H-4), 2.81 (s, 3H, N–CH_3), 2.89 (m, 2H, one H-3 and –OH), 3.03 (s, 3H, N–OCH_3), 3.60 (m, 1H, one H-3), 3.80 (m, 1H, H-2)
^{13}C NMR (75 MHz, C_6D_6), δ:	13.94 (C-4), 31.87 (N–CH_3), 38.32 (N–OCH_3), 61.12 (C-2), 64.92 (C-3), 176.68 (C-1)
FTIR (neat), cm^{-1}:	3417 (br, –OH), 2976 (m), 2940 (m), 2880 (w), 1634 (s, C=O), 1464 (m), 1392 (m), 1325 (w), 1118 (m), 1070 (m), 1035 (m), 991 (m)



47 **49** 91%

N-methoxy-*N*-methyl (2*R*)-3-(*tert*-Butyldiphenyl)Siloxy-2-Methylpropionamide **49**

tert-Butyldiphenyl silyl chloride (2.36 g, 2.24 mL, 9.53 mmol, 1.25 equiv) was added to a solution of (*R*) hydroxy amide **47** (1.1222 g, 1.00 mL, 7.63 mmol, 1 equiv) and imidazole (1.298 g, 19.1 mmol, 2.5 equiv) in DMF (7.6 mL). After stirring 3 hours at 27 °C, the solution was diluted with ether (20 mL), then washed sequentially with saturated aqueous solutions of citric acid (20 mL), sodium bicarbonate (20 mL), and sodium chloride (20 mL). The organic layer was dried over sodium sulfate, filtered, concentrated, and purified by flash column chromatography (hexanes→40% ethyl acetate in hexanes), affording (*R*) siloxy amide **49** (2.6785 g, 6.95 mmol, 91.0%) as a colorless oil which crystallizes on standing.



48 **50** 80%

<u>*N*-methoxy-*N*-methyl (2*S*)-3-(*tert*-Butyldiphenyl)Siloxy-2-Methylpropionamide **50**</u>

tert-Butyldiphenyl silyl chloride (5.92 g, 5.60 mL, 23.9 mmol, 1.25 equiv) was added to a solution of (*S*) hydroxy amide **48** (2.8130 g, 2.50 mL, 19.11 mmol, 1 equiv) and imidazole (3.253 g, 47.8 mmol, 2.5 equiv) in DMF (19.1 mL). After stirring 12.5 hours at 27 °C, the solution was diluted with ether (25 mL), then washed sequentially with saturated aqueous solutions of citric acid (15 mL), sodium bicarbonate (15 mL), and sodium chloride (15 mL). The organic layer was dried over sodium sulfate, filtered, concentrated affording (*S*) siloxy amide **50** (5.91 g, 15.33 mmol, 80.2%) as a colorless oil which crystallizes on standing.

<u>Siloxy Amides **49** and **50**</u>

^{1}H NMR (300 MHz, C_6D_6), δ: 1.01 (d, J = 7.0 Hz, 3H, H-4), 1.14 (s, 9H, $-C(CH_3)_3$), 2.93 (s, 3H, N–CH_3), 3.18 (s, 3H, N-OCH_3), 3.23 (m, 1H, H-2), 3.65 (dd, J = 5.8, 9.4 Hz,1H, H-3), 4.15 (dd, J = 8.8, 9.2 Hz, 1H,

H-3), 7.18–7.28 (m, 6H, aromatics), 7.75–7.85 (m, 4H, aromatics)

^{13}C NMR (75 MHz, C_6D_6), δ: 13.89 (C-4), 19.46 (–CMe_3), 27.02 (–$C(CH_3)_3$), 32.06 (N–CH_3), 38.33 (N–OCH_3), 61.04 (C-2), 66.74 (C-3), 127.79, 128.05, 129.94, 133.82, 134.22, 135.94, 136.12 (aromatics), 175.76 (C-1)

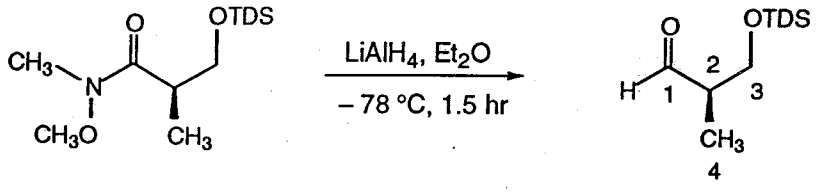
FTIR (neat), cm^{-1}: 3071 (m), 3049 (m), 2960 (s), 2933 (s), 2857 (s), 1661 (s, C=O), 1472 (s), 1427 (s), 1388 (s), 1361 (w), 1318 (w), 1260 (w), 1168 (m), 1152 (m), 1112 (s), 998 (s), 824 (s), 739 (s), 703 (s), 689 (s), 614 (s)

HRMS (FAB), m/z: Calcd for $C_{22}H_{31}O_3NSi$ (MH^+): 386.2151

Found, **49**: 386.2150

Found, **50**: 386.2150

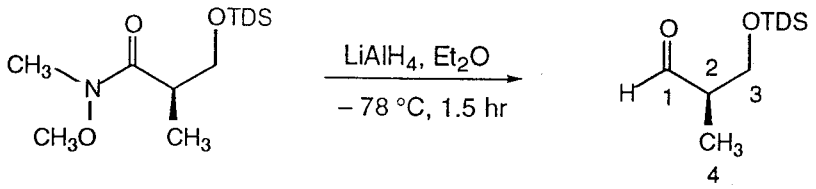
TLC (30% EtOAc in hexanes), R_f: Amides **49** and **50**: 0.35 (UV and PMA)



49 **45** 64%

(2*R*)-3-(*tert*-Butyldiphenyl)siloxy-2-Methylpropionaldehyde **45**

Lithium aluminum hydride (1.0 M in ether, 2.1 mL, 2.1 mmol, 1.0 equiv) was added to a solution of (*R*) siloxy amide **49** (804.6 mg, 2.09 mmol, 1 equiv) in dry ether (20 mL) at –78 °C. After stirring at –78 °C for 1.5 hours, excess lithium aluminium hydride was quenched with a saturated solution of citric acid in THF (30 mL) at –78 °C. After warming to 27 °C, the solution was diluted with ether (20 mL), and washed sequentially with saturated aqueous solutions of citric acid (10 mL), sodium bicarbonate (10 mL), and sodium chloride (10 mL). The organic layer was dried, filtered, concentrated, and purified by flash column chromatography (10%→30% ethyl acetate in hexanes), affording (*R*) aldehyde **45** (436.0 mg, 1.34 mmol, 64.9%) as a colorless oil.



50 **46** 71%

(2*S*)-3-(*tert*-Butyldiphenyl)siloxy-2-Methylpropionaldehyde **46**

Lithium aluminum hydride (1.0 M in ether, 5.14 mL, 5.14 mmol, 1.0 equiv) was added to a solution of (*S*) siloxy amide **50** (1.98 g, 5.14 mmol, 1 equiv) in dry ether (50

mL) at –78 °C. After stirring at –78 °C for 1.5 hours, excess lithium aluminium hydride was quenched with a saturated solution of citric acid in THF (50 mL) at –78 °C. After warming to 27 °C, the solution was diluted with ether (50 mL), and washed sequentially with saturated aqueous solutions of citric acid (25 mL), sodium bicarbonate (25 mL), and sodium chloride (25 mL). The organic layer was dried, filtered, concentrated, and purified by flash column chromatography (10%→50% ethyl acetate in hexanes, silica gel), affording (*S*) aldehyde **46** (1.1908 g, 3.65 mmol, 70.9%) as a colorless oil.

Siloxy Aldehydes **45** and **46**

^{1}H NMR (300 MHz, C_6D_6), δ: 0.80 (d, J = 7.1 Hz, 3H, H-4), 1.09 (s, 9H, $-C(CH_3)_3$), 2.05 (m, 1H, H-2), 3.57 (dd, J = 6.0, 10.3 Hz, 1H, H-3), 3.63 (dd, J = 4.8, 10.3 Hz, 1H, H-3), 7.16–7.23 (m, 6H, aromatics), 7.66–7.71 (m, 4H, aromatics), 9.48 (d, J = 1.5 Hz, 1H, aldehyde H)

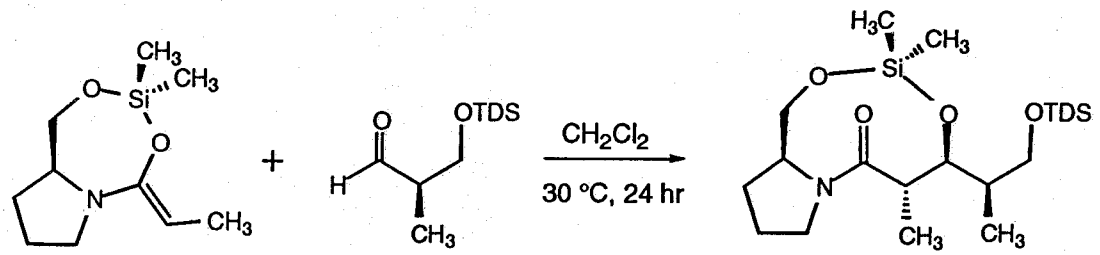
^{13}C NMR (75 MHz, C_6D_6), δ: 10.20 (C-4), 19.40 ($-CMe_3$), 26.94 ($-C(\mathbf{CH_3})_3$), 48.82 (C-2), 64.18 (C-3), 128.10, 128.20, 129.72, 130.10, 133.60, 135.94, 136.06, (aromatics), 202.43 (C-1)

FTIR (neat), cm^{-1}: 3071 (w), 3050 (w), 2959 (s), 2931 (s), 2858 (s), 1738 (s, C=O), 1589 (w), 1472 (m), 1462 (m), 1428 (s), 1391 (w), 1362 (w), 1330 (w), 1307 (w), 1260 (w), 1188 (w), 1112 (s), 1035 (m), 1008 (w),

998 (w), 961 (w), 937 (w), 823 (s), 805 (s), 740 (s), 702 (s), 614 (s)

TLC (30% EtOAc in hexanes), R_f: Amides **49** and **50**: 0.35 (UV and PMA)

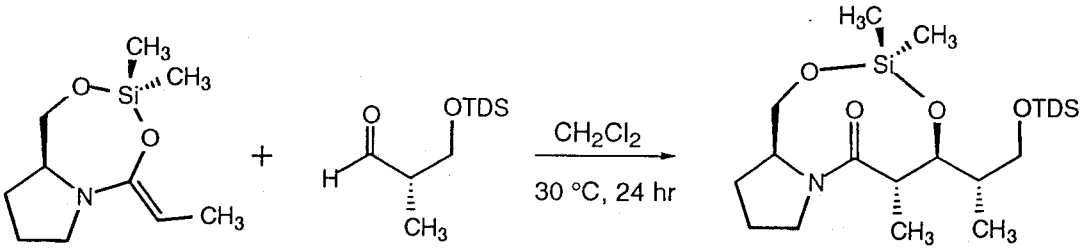
Aldehydes **45** and **46**: 0.56 (UV and PMA)



1 (*S*) **45** (*R*) **52** 28% (2*S*, 3*R*, 4*R*)

(1'*S*, 2*S*, 3*R*, 4*R*) Aldol Adduct **52**

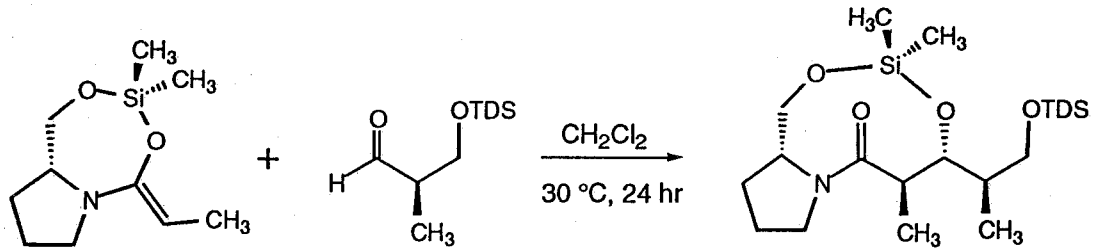
The silyl ketene acetal derived from (*S*)-prolinol propionamide **1** (102.6 mg, 100 μL, 0.48 mmol, 1 equiv), was syringed into a tared, empty 10-mL Schlenk tube under argon, then weighed. A solution of (*R*) aldehyde **45** (157.2 mg, 0.48 mmol, 1.0 equiv) in dry dichloromethane (1.0 mL) was then added by syringe. After stirring at 30 °C for 24 hours, the reaction solution was concentrated and purified by flash column chromatography (40%→90% ether in pet. ether), affording aldol adduct **52** (73.0 mg, 0.135 mmol, 28.2%) as a viscous, colorless oil.



1 (*S*) **46** (*S*) **53** 32% (2*S*, 3*R*, 4*S*)

(1'*S*, 2*S*, 3*R*, 4*S*) Aldol Adduct **53**

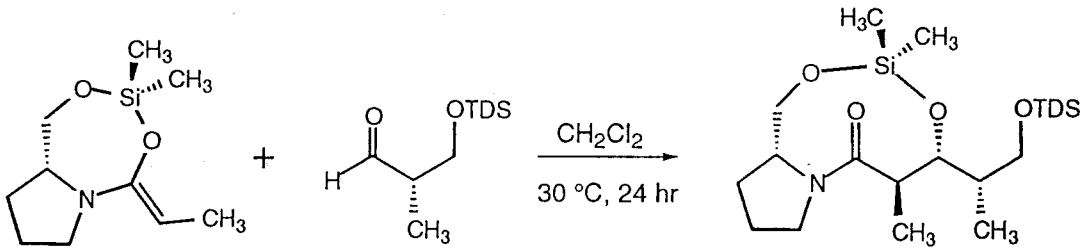
By the preceding procedure, (*S*) silyl ketene acetal **1** (212.8 mg, 213 μL, 1.0 mmol, 1 equiv) and (*S*) aldehyde **46** (326.0 mg, 1.0 mmol, 1.0 equiv) in dry dichloromethane (2.0 mL) produced aldol adduct **53** (171.1 mg, 0.317 mmol, 31.7%) as a viscous, colorless oil.



51 (*R*) **45** (*R*) **54** 24% (2*R*, 3*S*, 4*R*)

(1'*R*, 2*R*, 3*S*, 4*R*) Aldol Adduct **54**

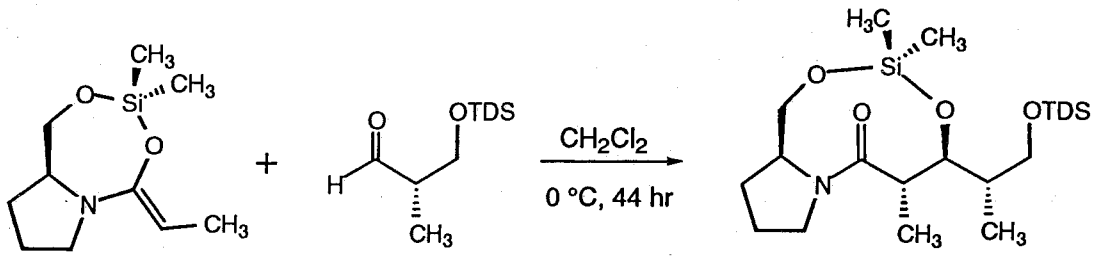
By the same procedure, (*R*) silyl ketene acetal **51** (106.1 mg, 100 μL, 0.50 mmol, 1 equiv) and (*R*) aldehyde **45** (162.5 mg, 0.50 mmol, 1.0 equiv) in dry dichloromethane (1.0 mL) produced aldol adduct **54** (64.8 mg, 0.12 mmol, 24%) as a viscous, colorless oil.



51 (*R*) **46** (*S*) **55** 42% (2*R*, 3*S*, 4*S*)

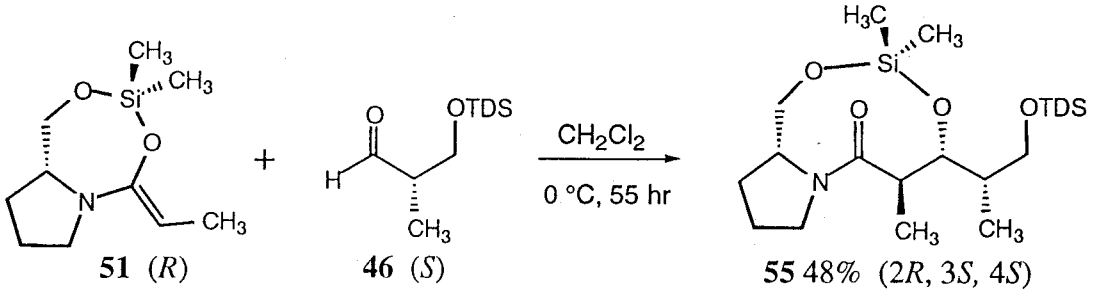
(1'*R*, 2*R*, 3*S*, 4*S*) Aldol Adduct **55**

By the same procedure, (*R*) silyl ketene acetal **51** (222.9 mg, 213 μL, 1.05 mmol, 1 equiv) and (*S*) aldehyde **46** (341.5 mg, 1.05 mmol, 1.0 equiv) in dry dichloromethane (2.1 mL) produced aldol adduct **55** (235.7 mg, 0.437 mmol, 42%) as a viscous, colorless oil with a strong peanut odor.



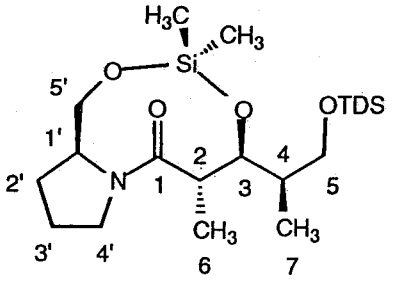
(1'*S*, 2*S*, 3*R*, 4*S*) Aldol Adduct **53** (Low Temperature Conditions)

A solution of the silyl ketene acetal derived from (*S*)-prolinol propionamide **1** (948 mg, 905 μL, 4.45 mmol, 1.08 equiv) and (*S*) aldehyde **46** (1.3365 g, 4.09 mmol, 1 equiv) in dry dichloromethane (4.0 mL) was stirred under argon for 44 hours at 0 °C. After concentration and purification by flash column chromatography (40%→100% ether in pet. ether), aldol adduct **53** (171.1 mg, 0.317 mmol, 31.7%) was recovered as a viscous, colorless oil.

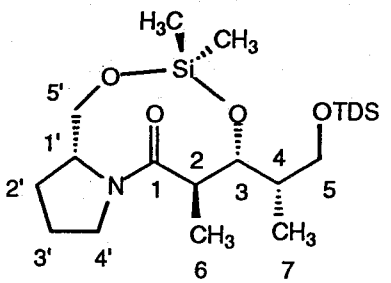


(1'*R*, 2*R*, 3*S*, 4*S*) Aldol Adduct **55** (Low Temperature Conditions)

A solution of the silyl ketene acetal derived from (*R*)-prolinol propionamide **51** (929.1 mg, 890 μL, 4.36 mmol, 1.10 equiv) and (*S*) aldehyde **46** (1.2933 g, 3.96 mmol, 1.0 equiv) in dry dichloromethane (4.0 mL) was stirred under argon for 55 hours at 0 °C. After concentration and purification by flash column chromatography (50%→100% ether in pet. ether), aldol adduct **55** (1.034 g, 1.92 mmol, 48.5%) was recovered as a viscous, colorless oil with a strong peanut odor.



52 (2*S*, 3*R*, 4*R*)



55 (2*R*, 3*S*, 4*S*)

(1'*S*, 2*S*, 3*R*, 4*R*) Aldol Adduct **52** and (1'*R*, 2*R*, 3*S*, 4*S*) Aldol Adduct **55**

^{1}H NMR (300 MHz, C_6D_6), δ: 0.10 (s, 3H, Si–C**H**$_3$), 0.35 (s, 3H, Si–C**H**$_3$), 0.80 (d, *J* = 6.9 Hz, 3H, H-7), 1.10 (d, *J* = 6.5 Hz, 3H, H-6), 1.20 (m, 1H, H-2'), 1.21 (s, 9H, –C(C**H**$_3$)$_3$), 1.36 (m, 2H, H-2', H-3'), 1.72 (m, 1H, H-3'), 1.98 (m, 1H, H-4), 2.76 (dq, *J* = 6.5, 10.0 Hz, 1H, H-2), 2.94 (t of d, *J* = 3.0, 8.5 Hz, 1H, H-4'), 3.28 (d, *J* = 10.9 Hz, 1H, H-5'), 3.37 (dt, *J* = 6.4, 9.3 Hz, 1H, H-4'), 3.59 (dd, *J* = 6.3, 9.9 Hz, 1H, H-5), 3.72 (dd, *J* = 8.2, 9.9 Hz, 1H, H-5), 3.93 (t of d, *J* = 2.9, 7.4 Hz, 1H, H-1'), 4.23 (dd, *J* = 1.4, 10.0 Hz, 1H, H-3), 4.94 (dd, *J* = 3.1, 10.9 Hz, 1H, H-5'), 7.20–7.27 (m, 6H, aromatics), 7.77–7.82 (m, 4H, aromatics)

^{13}C NMR (75 MHz, C_6D_6), δ: –5.86 (Si–**C**H$_3$), –1.04 (Si–**C**H$_3$), 9.05 (C-7), 12.88 (C-6), 19.43 (–**C**Me$_3$), 24.75 (C-2'), 27.18 (–C(**C**H$_3$)$_3$), 28.62 (C-3'), 37.77 (C-4), 41.51

(C-2), 48.89 (C-4'), 58.95 (C-1'), 61.98 (C-5'), 67.05 (C-5), 77.04 (C-3), 128.07, 130.00, 130.05, 134.22, 135.93, 136.03 (aromatics), 173.69 (C-1)

FTIR (neat), cm^{-1}: 3071 (w), 3049 (w), 2963 (m), 2933 (m), 2879 (m), 2858 (m), 1638 (s, C=O), 1472 (m), 1428 (s), 1256 (m), 1130 (m), 1110 (s), 1084 (s), 1049 (s), 990 (w), 912 (w), 872 (w), 855 (m), 838 (m), 825 (m), 799 (m), 739 (w), 703 (s), 690 (w), 614 (m)

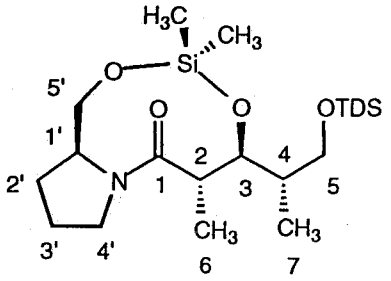
HRMS (FAB), m/z: Calcd $C_{30}H_{46}O_4NSi_2$ (MH^+): 540.2982

Found, **52**: 540.2966

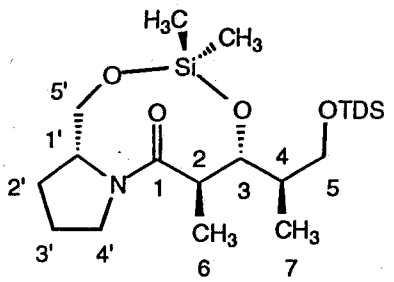
Found, **55**: 540.2977

TLC (30% EtOAc in hexanes), R_f: Aldehydes **45** and **46**: 0.56 (UV and PMA)

Aldol Adducts **52** and **55**: 0.22 (UV and PMA)



53 (2*S*, 3*R*, 4*S*)



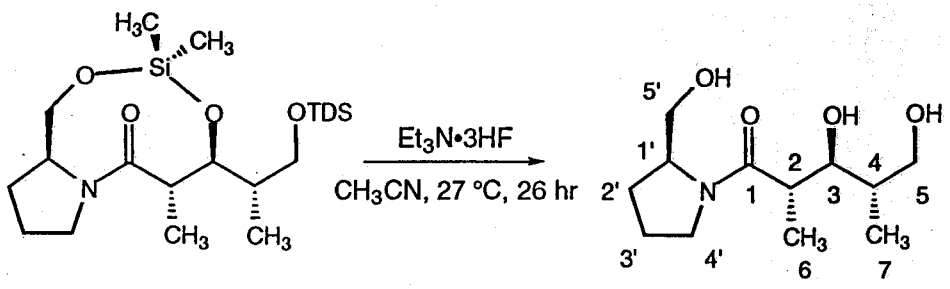
54 (2*R*, 3*S*, 4*R*)

(1'*S*, 2*S*, 3*R*, 4*S*) Aldol Adduct **53** and (1'*R*, 2*R*, 3*S*, 4*R*) Aldol Adduct **54**

^{1}H NMR (300 MHz, C_6D_6), δ: 0.10 (s, 3H, Si–C**H**$_3$), 0.22 (s, 3H, Si–C**H**$_3$), 0.86 (d, *J* = 6.9 Hz, 3H, H-7), 1.16 (s, 9H, –C(C**H**$_3$)$_3$), ~1.16 (d, 3H, H-6, partially obscured), ~1.18 (m, 1H, H-2', partially obscured), 1.50 (m, 2H, H-2', H-3'), 1.73 (m, 1H, H-3'), 2.07 (sextet of d, *J* = 1.3, 6.7 Hz, 1H, H-4), 2.98 (t of d, *J* = 2.9, 8.6 Hz, 1H, H-4'), 3.17 (dq, *J* = 6.5, 10.1 Hz, 1H, H-2), 3.27 (d, *J* = 10.9 Hz, 1H, H-5'), 3.39 (dt, *J* = 6.5, 9.4 Hz, 1H, H-4'), 3.61 (dd, *J* = 6.4, 10.1 Hz, 1H, H-5), 3.79 (dd, *J* = 1.3, 10.1 Hz, 1H, H-3), 3.92 (dt, *J* = 2.9, 7.4 Hz, 1H, H-1'), 4.90 (dd, *J* = 3.2, 10.9 Hz,1H, H-5'), 7.22 (m, 6H, aromatics), 7.79 (m, 4H, aromatics)

^{13}C NMR (75 MHz, C_6D_6), δ: –6.16 (Si–**C**H$_3$), –1.10 (Si–**C**H$_3$), 13.22 (C-7), 16.33 (C-7), 19.35 (–**C**Me$_3$), 24.70 (C-2'), 27.07

	(–C(CH_3)$_3$), 28.57 (C-3'), 37.36 (C-4), 42.55 (C-2), 49.00 (C-4'), 58.85 (C-1'), 61.92 (C-5'), 64.67 (C-5), 81.67 (C-3), 128.04, 130.01, 133.91, 134.20, 135.97 (aromatics), 174.21 (C-1)
FTIR (neat), cm^{-1}:	3071 (w), 3049 (w), 2961 (s), 2932 (s), 2879 (s), 2858 (s), 1634 (s, C=O), 1471 (s), 1462 (s), 1428 (s), 1390 (w), 1372 (w), 1337 (w), 1311 (w), 1286 (w), 1257 (s), 1202 (w), 1188 (w), 1162 (w), 1112 (s), 1076 (s), 1050 (s), 990 (m), 912 (m), 872 (m), 855 (s), 839 (s), 800 (s), 740 (m), 703 (s), 614 (m)
HRMS (FAB), m/z:	Calcd for $C_{30}H_{46}O_4NSi_2$ (MH^+): 540.2982 Found, **53**: 540.2966 Found, **54**: 540.2968
TLC (30% EtOAc in hexanes), R_f:	Aldehydes **45** and **46**: 0.56 (UV and PMA) Aldols Adducts **53** and **54**: 0.23 (UV and PMA)



53 **56** 61%

(1'*S*, 2*S*, 3*R*, 4*S*) Triol **56**

Triethylamine trihydrofluoride (553.9 mg, 560 μL, 3.436 mmol, 2.0 equiv) was added to a solution of silylated aldol adduct **53** (927.3 mg, 1.718 mmol, 1 equiv) in dry acetonitrile (25 mL). After 26 hours at 27 °C, the solution was concentrated and partitioned between hexanes (15 mL) and distilled water (10 mL). The hexane layer was further washed with distilled water (2 x 10 mL). The combined aqueous layers were saturated with solid sodium chloride and extracted with dichloromethane (3 x 10 mL). The combined dichloromethane layers were dried over sodium sulfate, filtered, and concentrated. The residue was purified by filtration through a short silica plug (ethyl acetate) to give triol **56** (257.1 mg, 1.048 mmol, 61%) as a colorless oil.

^{1}H NMR (300 MHz, C_6D_6), δ: 0.81 (d, J = 7.0 Hz, 3H, H-7), 1.09 (d, J = 7.0 Hz, 3H, H-6), 1.30 (m, 4H, H-2', H-3'), 1.79 (ddq, J = 5.0, 5.4, 7.0 Hz, 1H, H-4), 2.44 (dq, J = 4.4, 7.0 Hz, 1H, H-2), 2.74 (m, 1H, –OH), 2.86 (m, 1H, H-4'), 3.30 (m, 1H, H-4'), 3.43 (dd, J = 6.3, 11.1 Hz, 1H, H-5'), 3.48 (m, 1H,

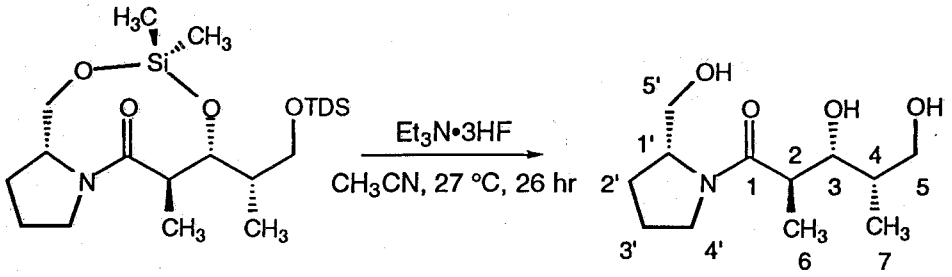
H-3), 3.67 (dd, J = 3.5, 11.1 Hz, 1H, H-5'), 3.75 (d, J = 5.3 Hz, 2H, H-5), 3.97 (m, 1H, H-1'), 4.42 (br s, 1H, –OH), 5.23 (br d, J = 7.9 Hz, 1H, –OH)

^{13}C NMR (75 MHz, $CDCl_3$), δ: 14.50 (C-6), 14.70 (C-7), 24.17 (C-2'), 27.97 (C-3'), 38.56 (C-4), 39.36 (C-2), 48.02 (C-4'), 60.59 (C-1'), 65.70 (C-5), 66.69 (C-5'), 79.59 (C-3), 177.17 (C-1)

FTIR (neat), cm^{-1}: 3370 (s, br, –OH), 2966 (m), 2927 (m), 2877 (m), 1604 (s, C=O), 1458 (s), 1040 (m), 989 (m)

HRMS (FAB), m/z: Calcd for $C_{12}H_{24}O_4N(MH^+)$: 246.1705
Found: 246.1702

TLC (10% MeOH in EtOAc), R_f: Aldol Adduct **53**: 0.65 (UV and PMA)
Triol **56**: 0.18 (PMA, not UV active)



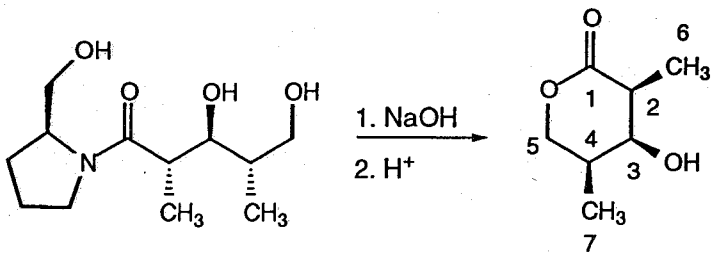
55 **57** 64%

(1'*R*, 2*R*, 3*S*, 4*S*) Triol **57**

Triethylamine trihydrofluoride (594.5 mg, 601 μL, 3.688 mmol, 2.0 equiv) was added to a solution of silylated aldol adduct **55** (995.3 mg, 1.844 mmol, 1 equiv) in dry acetonitrile (25 mL). After 26 hours at 27 °C, the solution was concentrated and partitioned between hexanes (15 mL) and distilled water (10 mL). The hexane layer was further washed with distilled water (2 x 10 mL). The combined aqueous layers were saturated with solid sodium chloride and extracted with dichloromethane (3 x 10 mL). The combined dichloromethane layers were dried over sodium sulfate, filtered, and concentrated. The residue was purified by filtration through a short silica plug (ethyl acetate) yielding triol **57** (289.2 mg, 1.179 mmol, 63.9%) as a colorless oil.

^{1}H NMR (300 MHz, C_6D_6), δ: 0.89 (d, J = 7.0 Hz, 3H, H-7), 1.07 (d, J = 6.9 Hz, 3H, H-6), 1.76–1.87 (m, 3H, H-4, H-2', H-3'), 1.94–2.03 (m, 2H, H-2', H-3'), 2.78 (dq, J = 7.1, 8.0 Hz, 1H, H-2), 3.49 (dd, J = 5.8, 11.2 Hz, 1H, H-5'), 3.50 (m, 1H, H-4'), 3.61 (d, J = 5.8 Hz, 2H, H-5), 3.65 (m, 1H, H-4'), 3.80

	(dd, J = 3.6, 11.2 Hz, 1H, H-5'), 3.94 (dd, J = 3.0, 8.2 Hz, 1H, H-3), 4.18 (m, 1H, H-1'), 4.40 (br s, 1H, –OH)
^{13}C NMR (75 MHz, $CDCl_3$), δ:	9.71 (C-7), 13.72 (C-6), 24.17 (C-2'), 27.92 (C-3'), 36.86 (C-4), 41.08 (C-2), 48.06 (C-4'), 59.88 (C-1'), 64.79 (C-5'), 65.88 (C-5), 74.88 (C-3), 176.84 (C-1)
FTIR (neat), cm^{-1}:	3380 (br, s, –OH), 2968 (m), 2880 (m), 1600 (s, C=O), 1455 (s), 1376 (w), 1335 (w), 1247 (w), 1192 (w), 1158 (w), 1114 (w), 1043 (s), 983 (m), 901 (w)
HRMS (FAB), m/z:	Calcd for $C_{12}H_{24}O_4N(MH^+)$: 246.1705 Found: 246.1706
TLC (10% MeOH in EtOAc), R_f:	Aldol Adduct **55**: 0.65 (UV and PMA) Triol **57**: 0.18 (PMA, not UV active)



56 **58** 61%

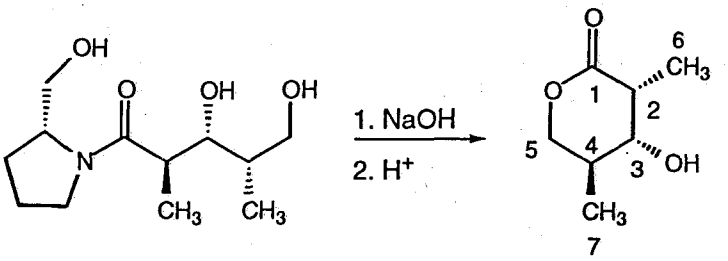
Lactone **58**

(1'*S*, 2*S*, 3*R*, 4*S*) Triol **56** (253.5 mg, 1.033 mmol, 1 equiv) was dissolved in a 0.33 M solution of sodium hydroxide in 4:1 methanol-water (15.6 mL, 5.17 mmol, 5.0 equiv) and refluxed for 18 hours. The solution was concentrated to dryness *in vacuo*, acidified with 1 N aqueous HCl (10 mL), then extracted with dichloromethane (3 x 15 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated to yield a crude lactone mixture (119.2 mg, 0.827 mmol, 80.0%) as a yellow, non-viscous liquid. The ^{1}H NMR spectrum of this crude product shows a 83:12:5 ratio of three products. Purification of the crude mixture by flash column chromatography (100% ether) afforded major lactone **58** (90.4 mg, 0.627 mmol, 60.7%) as a colorless oil.

The acidic aqueous layer was saturated with solid sodium chloride, basified with solid sodium hydroxide to pH > 10, and extracted with dichloromethane (3 x 15 mL). The organic extracts were dried over sodium sulfate, filtered, and concentrated to yield (*S*)-prolinol (81.3 mg, 0.804 mmol, 77.8%) as a colorless oil.

^{1}H NMR (300 MHz, C_6D_6), δ: 0.71 (d, J = 6.8 Hz, 3H, H-7), 1.31 (d, J = 7.2 Hz, 3H, H-6), 1.59 (dddq, J = 1.0, 5.7, 12.0, 6.8

	Hz, 1H, H-4), 2.08 (dq, J = 3.0, 7.1 Hz, 1H, H-2), 3.39 (br s, 1H, H-3), 3.74 (br s, 1H –OH), 3.79 (ddd, J = 0.9, 5.9, 10.8 Hz, 1H, H-5_{eq}), 4.15 (dd, J = 10.8, 11.8 Hz, 1H, H-5_{ax})
^{13}C NMR (75 MHz, C_6D_6), δ:	12.77(C-7), 13.21 (C-6), 33.91 (C-4), 42.90 (C-2), 70.68 (C-5), 70.98 (C-3), 174.36 (C-1)
FTIR (neat), cm^{-1}:	3448 (br, –OH), 2974 (m), 2907 (m), 1718 (s, C=O), 1417 (w), 1414 (w), 1377 (w), 1349 (w), 1249 (w), 1193 (m), 1167 (s, C–O as. st.), 1125 (m), 1037 (s, C–O sy. st.), 975 (m)
HRMS (EI), m/z:	Calcd for $C_7H_{12}O_3$ ($M^{\circ+}$): 144.0786 Found: 144.0783
TLC (100% Et_2O), R_f:	Lactone **58**: 0.25 (PMA, not UV active)



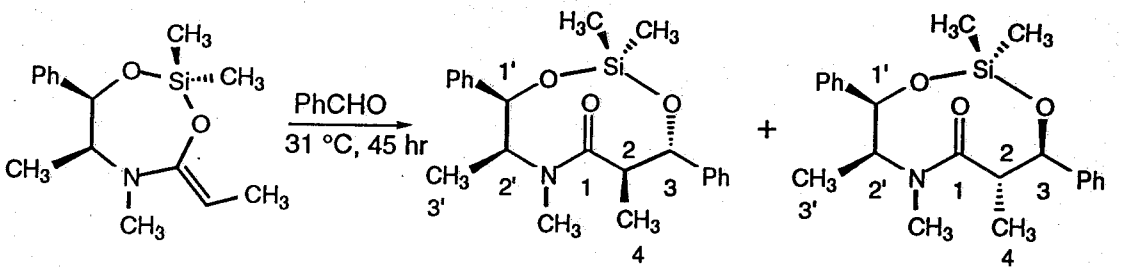
57 **59** 35%

Lactone **59**

By the proceeding procedure, triol **57** (283.7 mg, 1.156 mmol, 1 equiv) was refluxed with sodium hydroxide (0.33 M in 4:1 MeOH-H_2O, 17.4 mL, 5.8 mmol, 5.0 equiv) for 18 hours. After the aqueous workup, a crude lactone mixture (118.2 mg, 0.82 mmol, 70.9%) is recovered as a crystalline film. The ^1H NMR spectrum of this crude product shows a 67:25:7 ratio of three products, none of which are identical to lactone **58**. Recrystallization from ether afforded major lactone **59** (59.0 mg, 0.409 mmol, 35.4%) as colorless needles (mp: 91–92 °C). (*R*)–Prolinol (68.1 mg, 0.673 mmol, 58.2%) was also recovered as a colorless oil.

^1H NMR (300 MHz, C_6D_6), δ: 0.41 (d, J = 7.2 Hz, 3H, H-7), 1.10 (d, J = 7.0 Hz, 3H, H-6), 1.48 (br s, 1H, –OH), 1.56 (dddq, J = 4.2, 5.5, 9.7, 7.1 Hz, 1H, H-4), 1.95 (dq, J = 4.5, 7.0 Hz, 1H, H-2), 3.01 (t, J = 4.3 Hz, 1H, H-3), 3.10 (dd, J = 9.4, 11.4 Hz, 1H, H-5_{ax}), 3.77 (dd, J = 5.6 Hz, 1H, H-5_{eq})

^{13}C NMR (75 MHz, C_6D_6), δ:	11.56 (C-7), 14.58 (C-6), 36.63 (C-4), 38.76 (C-2), 69.72 (C-5), 74.13 (C-3)
FTIR (neat), cm^{-1}:	3492 (s, sharp, –OH), 2985 (m), 2962 (m), 2929(m), 2895 (m), 1744 (s, C=O), 1725 (s, C=O), 1452 (m), 1400 (m), 1267 (m), 1178 (s), 1164 (s, C–O as. st.), 1118 (m), 1074 (m), 1030 (m, C–O sy. st.), 989 (s), 737 (m), 620 (m)
TLC (100% Et_2O), R_f:	Lactone **59**: 0.20 (PMA, not UV active)



4 **60** 47% (2*R*, 3*S*) **61** 24% (2*S*, 3*R*)

(–)-Ephedrine–Benzaldehyde Aldol Adducts **60** and **61**

Benzaldehyde (1.209 g, 1.158 mL, 11.39 mmol, 1.0 equiv) and the *O*-silyl ketene *N,O*-acetal derived from (–)-ephedrine propionamide **4** (3.1595 g, 3.00 mL, 11.39 mmol, 1 equiv) were combined in a 25 mL Schlenk tube under argon. The solution was stirred at 31 ° for 45 hours, by which time the products had crystallized from solution. Purification by flash column chromatography (30% ether in pet. ether) afforded separately major product **60** (2.03 g, 5.30 mmol, 46.5%) as a colorless, crystalline solid (mp: 151–153 °C) and minor product **61** (1.07 g, 2.79 mmol, 24.5%) as a colorless oil which crystallized on standing to a colorless solid (mp: 70–76 °C).

(1'*R*, 2'*S*, 2*R*, 3*S*) Anti Aldol Adduct **60**

^{1}H NMR (300 MHz, C_6D_6), δ: –0.03 (s, 3H, Si–CH_3), 0.31 (s, 3H, Si–CH_3), 0.86 (br s, 3H, H-3'), 0.99 (d, J = 6.7 Hz, 3H, H-4), 2.66 (slightly br s, 3H, N–CH_3), 3.19 (br s, 1H, H-2), 4.91 (br s, 2H, H-1', H-2'), 5.14 (br d, J = 8.2 Hz, 1H, H-3), 7.04–7.33 (m, well resolved, 10 H, aromatics)

^{1}H NMR (300 MHz, $CDCl_3$), δ:	0.10 (slightly br s, 3H, Si–CH_3), 0.25 (sharp s, 3H, Si–CH_3), 0.74 (d, J = 6.5 Hz, 3H, H-4), 1.26 (d, J = 5.8 Hz, 3H, H-3'), 2.52 (slightly br s, 3H, N–CH_3), 3.16 (slightly br dq, J = 7.1, 8.2 Hz, 1H, H-2), 4.90 (d, J = 8.7 Hz, 1H, H-3), 5.07 (m, 2H, H-1', H-2'), 7.24–7.43 (m, well resolved, 10 H)
^{13}C NMR (75 MHz, $CDCl_3$), δ:	–4.35 (Si–CH_3), –3.19 (Si–CH_3), 15.85 (C-4), 17.10 (C-3'), 30.71 (N–CH_3), 45.24 (C-2), 55.20 (C-2'), 75.24 (C-1'), 78.70 (C-3), 126.78, 127.27, 127.56, 127.60, 128.13, 139.89, 142.51 (aromatics), 177.07 (C-1)
FTIR (neat), cm^{-1}:	3063 (w), 3025 (w), 2973 (m), 2935 (w), 2890 (w), 1634 (s, C=O), 1494 (m), 1475 (m), 1454 (s), 1410 (m), 1372 (m), 1352 (m), 1296 (m), 1260 (s), 1223 (m), 1130 (s), 1071 (s), 1029 (m), 944 (m), 893 (s), 868 (s), 803 (s), 765 (m), 722 (m), 700 (s), 655 (m)
HRMS (FAB), m/z:	Calcd for $C_{22}H_{30}O_3NSi$ (MH^+): 384.1995 Found: 384.1996

(1'*R*, 2'*S*, 2*S*, 3*R*) Aldol Adduct **61**

^{1}H NMR (300 MHz, C_6D_6), δ: 0.00 (s, 3H, Si–CH_3), 0.11 (s, 3H, Si–CH_3), 0.75 (d, J = 7.5 Hz, 3H, H-3'), 1.03 (d, J = 6.5 Hz, 3H, H-4), 2.95 (s, 3H, N–CH_3), 3.23 (dq, J = 6.6, 9.8 Hz, 1H, H-2), 4.80 (d, J = 9.7 Hz, 1H, H-3), 4.96 (dq, J = 4.2, 7.5 Hz, 1H, H-2'), 6.16 (d, J = 4.1 Hz, 1H, H-1'), 7.07–7.45 (m, 10H, aromatics)

^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.06 (s, 3H, SiCH_3), 0.15 (s, 3H, SiCH_3), 0.888 (d, J = 7.9, 3H, H-3'), 0.891 (d, J = 6.5, 3H, H-4), 3.29 (s, 3H, NCH_3), 3.37 (dq, J = 6.6, 9.6, 1H, H-2), 4.69 (d, J = 9.7, 1H, H-3), 4.78 (dq, J = 4.2, 7.4, 1H, H-2'), 5.86 (d, J = 4.1, 1H, H-1'), 7.21–7.44 (m, 10H, aromatics)

^{13}C NMR (75 MHz, $CDCl_3$), δ: –6.55 (Si–CH_3), –1.29 (Si–CH_3), 11.48 (C-3'), 13.21 (C-4), 33.49 (N–CH_3), 45.00 (C-2), 56.03 (C-2'), 71.24 (C-1'), 81.74 (C-3), 125.19, 126.56, 126.61, 127.69, 128.03, 128.20, 141.60, 142.70 (aromatics), 176.41 (C-1)

FTIR (neat), cm^{-1}: 3062 (w), 3030 (w), 2982 (m), 2937 (w), 1631 (s, C=O), 1493 (m), 1454 (m), 1404 (m), 1292 (w), 1258 (s), 1230 (w), 1206 (w), 1150 (m),

	1124 (m), 1082 (s), 1038 (s), 1028 (s), 1016 (m), 928 (w), 886 (s), 866 (s), 852 (s), 802 (s), 771 (w), 735 (m), 700 (s)
HRMS (FAB), m/z:	Calcd for $C_{22}H_{30}O_3NSi$ (MH^+): 384.1995 Found: 384.1992
TLC (60% Et_2O in pet ether), R_f:	**60**: 0.54 (UV and PMA) **61**: 0.58 (UV and PMA)

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7. Later experiments showed that the reaction did occur in THF. Hou Chen, unpublished results.

8. Later experiments showed that **4** does react with benzaldehyde. For a further discussion of the reactivity of **4**, see p. 53

9. The minor product, (2*R*,3*S*)-anti aldol adduct **7** was originally misidentified as a mixture of this and the (2*R*,3*R*)-syn adduct. (ref. 10) Later work showed it to be **7** exclusively. See p. 36.

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40. Lowest energy conformation resulting from a Monte Carlo Conformational search using the MM2 force field and the program Macromodel v. 3.5x

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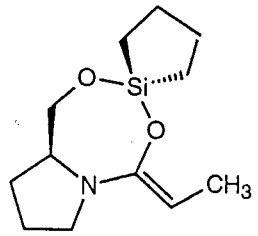
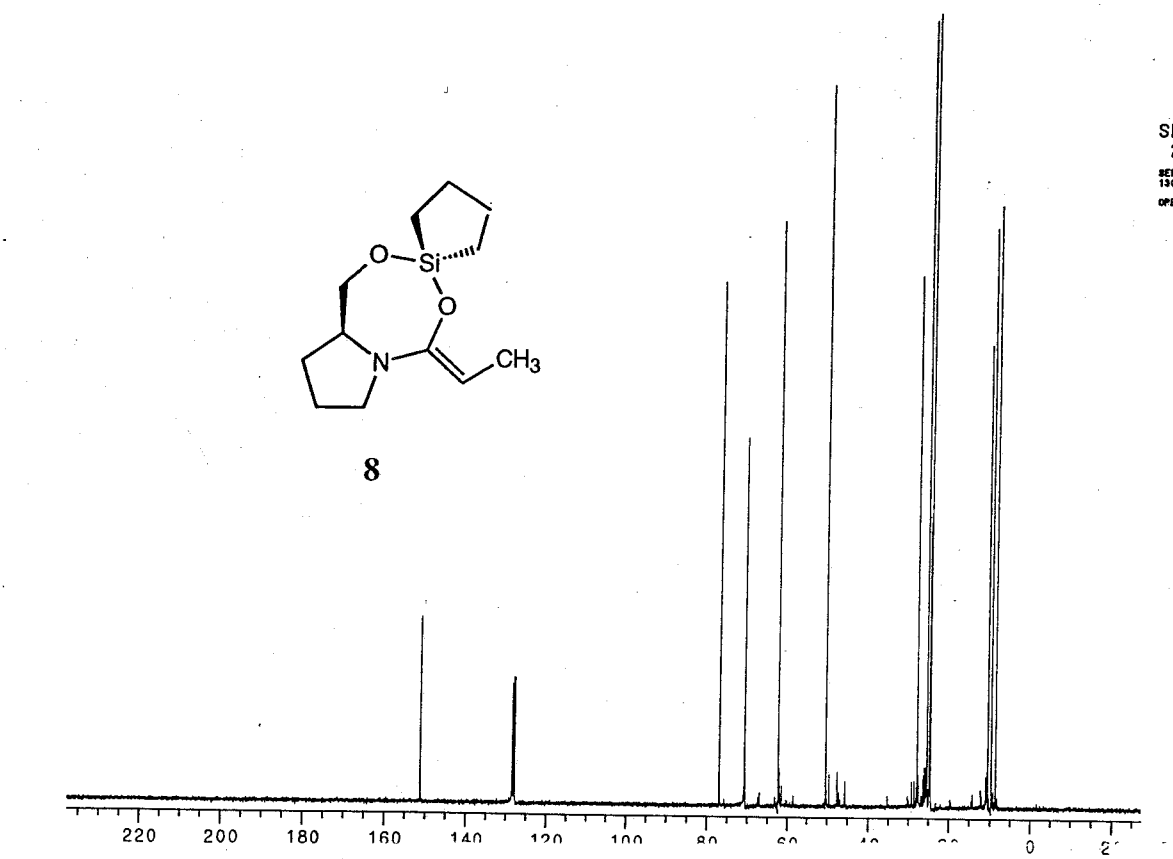
APPENDIX I

Catalog of Spectra


O
Si
O
N
CH3

8

GE NMR
QE PLUS
SEKI77.010
18NOV91
CGD6
OPERATOR: SEK
11
10
9
8
7
6
5
4
3
2
1
0
−1
PPM



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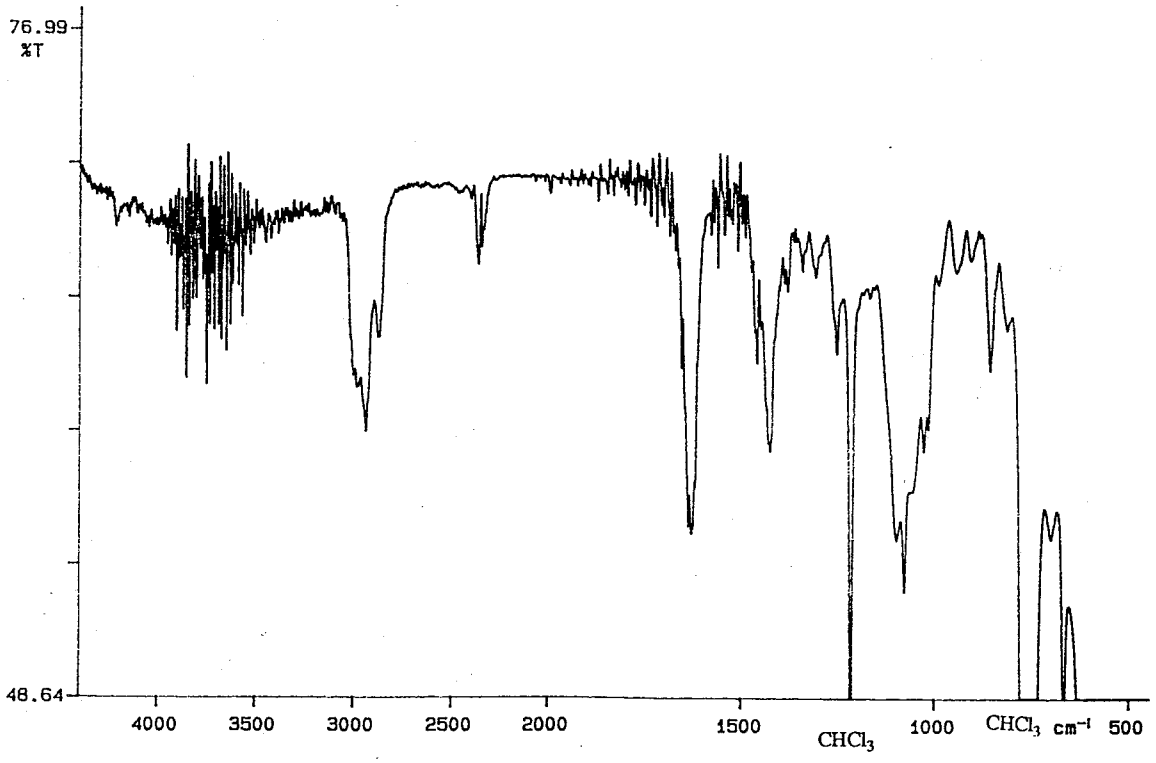
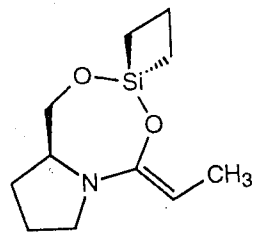
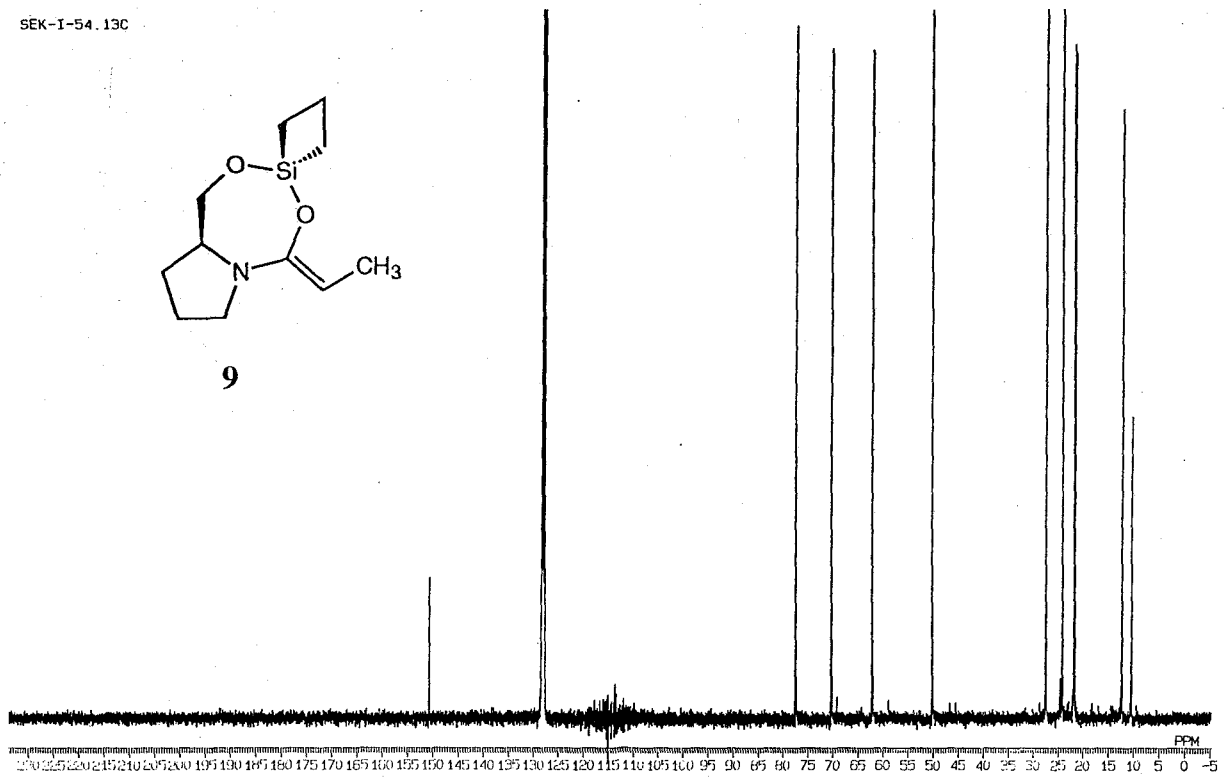


92/08/05 21:02
X: 4 scans, 4.0cm-1, flat

SEK-I-54B



9



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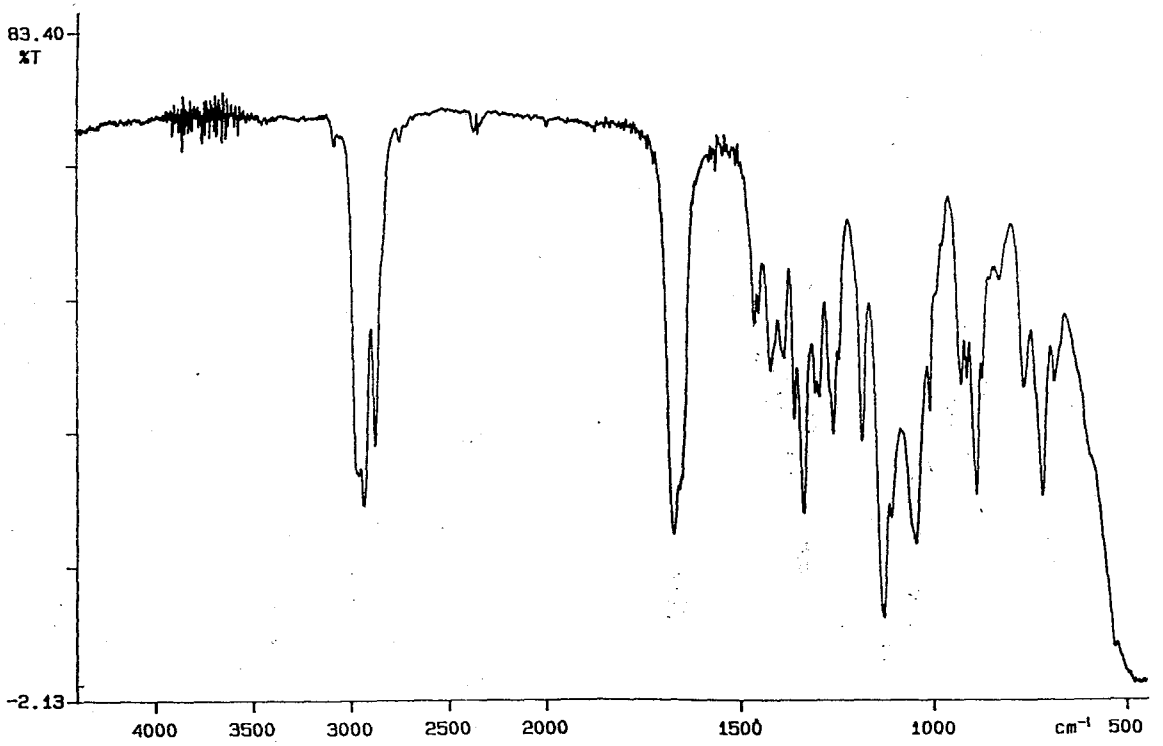
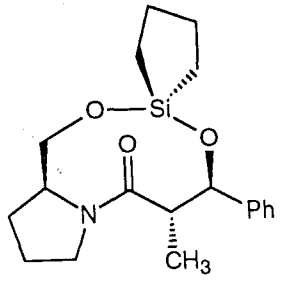
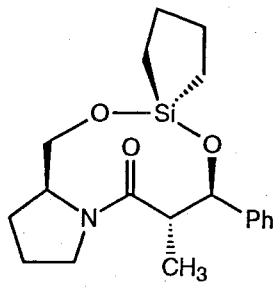


SEK-I-54
92/03/17 22:18
X: 1 scan, 4.0cm-1, flat


O
Si
O
O
N
Ph
CH3

10

GE NMR
QE PLUS
SEKI78.021
23NOV91
SEK-I-78 RF2
1H C6D6.
OPERATOR: SEK
10
9
8
7
6
5
4
3
2
1
0
−1
PPM



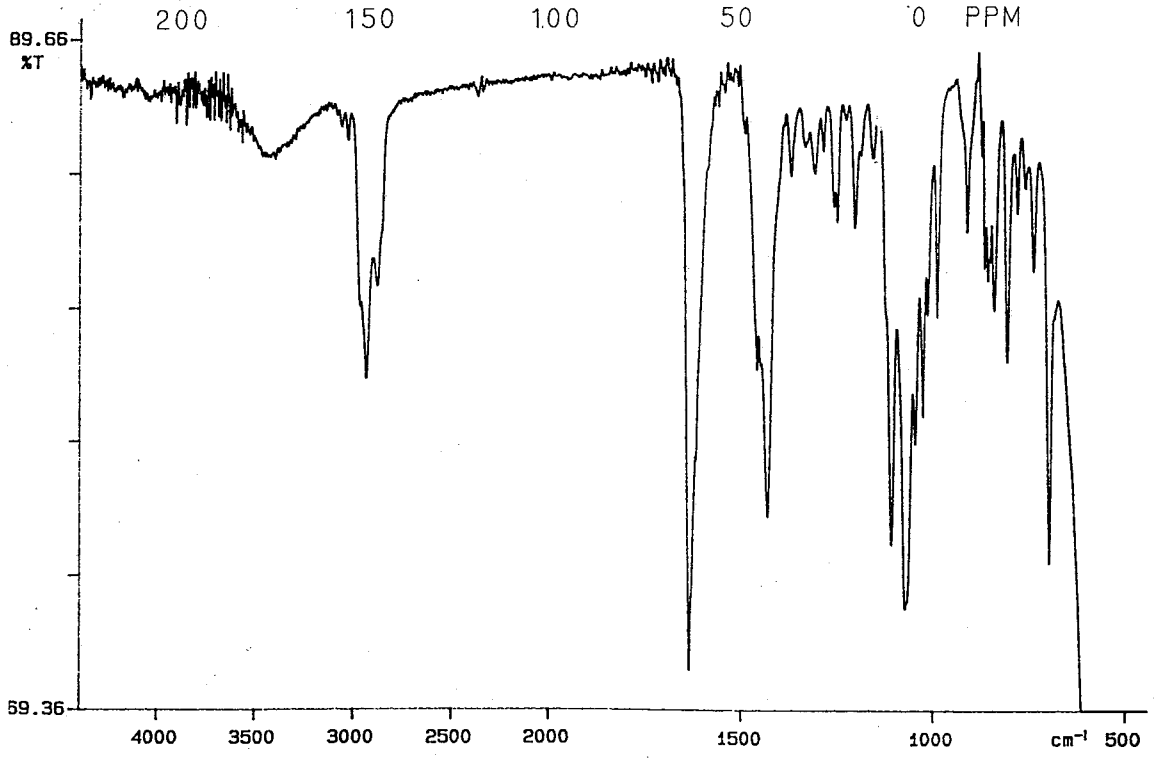
10

GE NMR
QE PLUS

SEKI78.200
23NOV91

SEK-I-78 RF2
13C C6D6
ANTI?

OPERATOR: SEK



92/06/09 13:42
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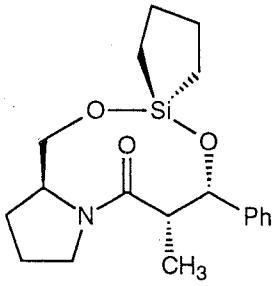
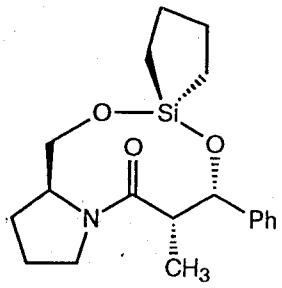
SEK-I-93 anti


O
Si
O
O
N
Ph
CH3

11

GE NMR
QE PLUS
SEKI93.030
25JAN92
SEK-I-93 RF3
SYNALDOL
1H C6D6
OPERATOR: SEK
11
10
9
8
7
6
5
4
3
2
1
0
−1
PPM



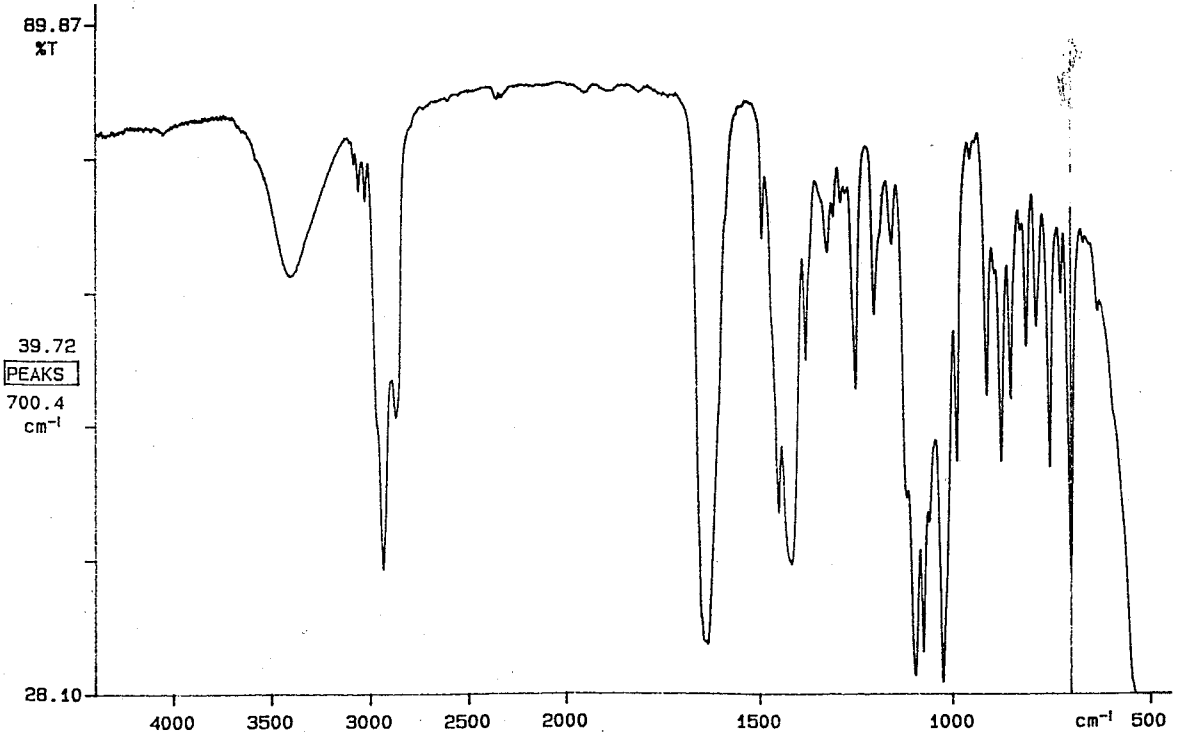
11

GE NMR
QE PLUS

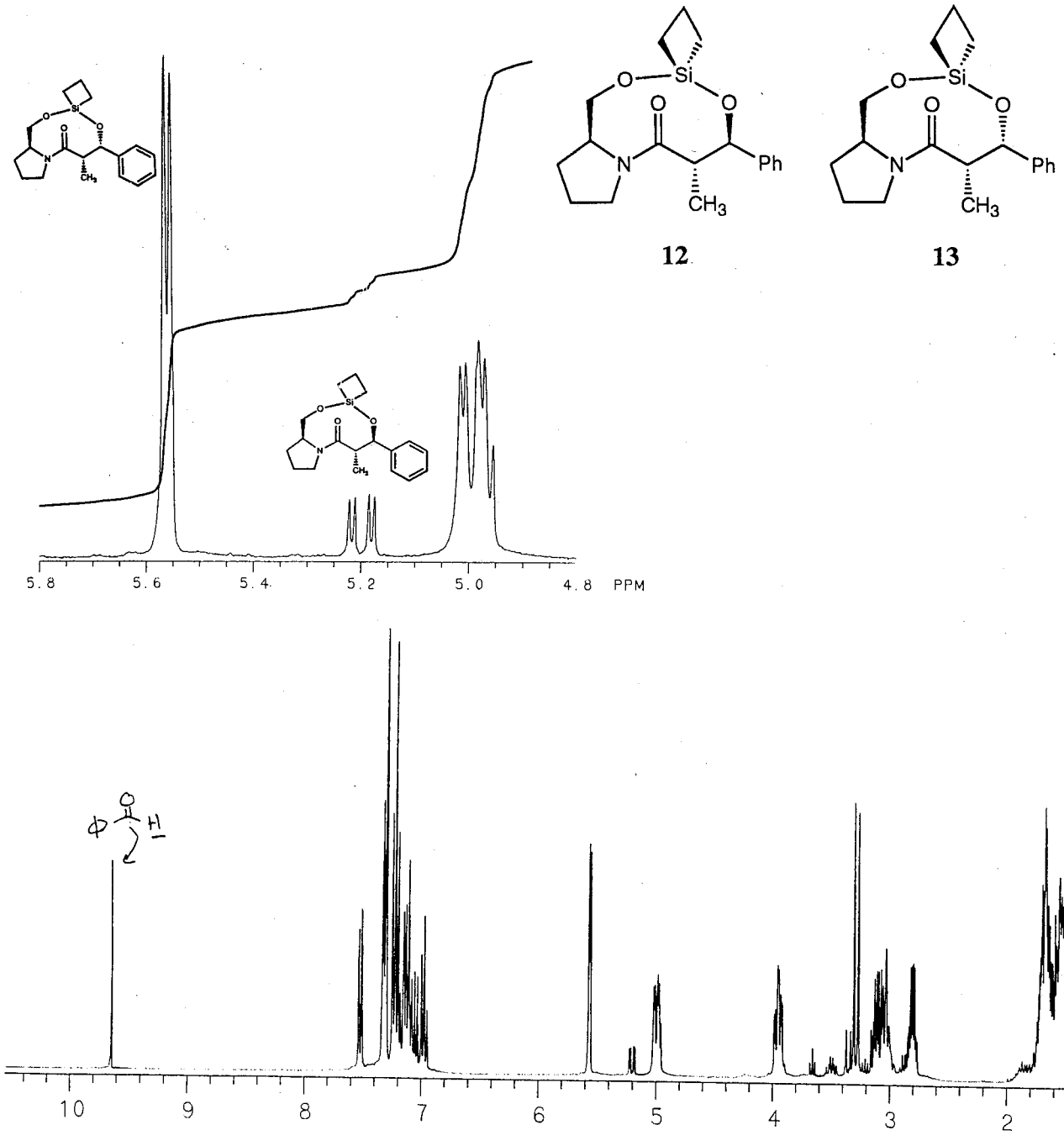
SEKI93.300
25JAN92

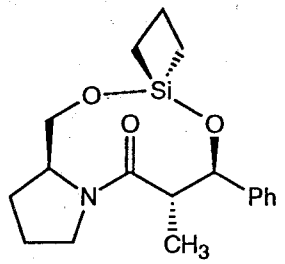
SEK-I-93 RF3
SYN ALDOL
13C C6D6

OPERATOR: SEK



92/06/09 13:33
X: 4 scans, 4.0cm-1, flat
SEK-I-70 syn


SEKI75.020
14NOV91
SEK-I-75 ENOLATE AND BENZALDEHYD
OPERATOR: SEK
12
13
Ph
CH3
5.8
5.6
5.4
5.2
5.0
4.8
PPM
10
9
8
7
6
5
4
3
2
1
0
−1
PPM



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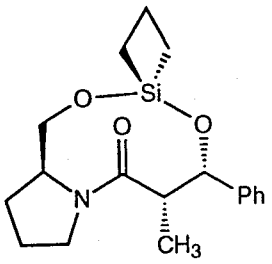

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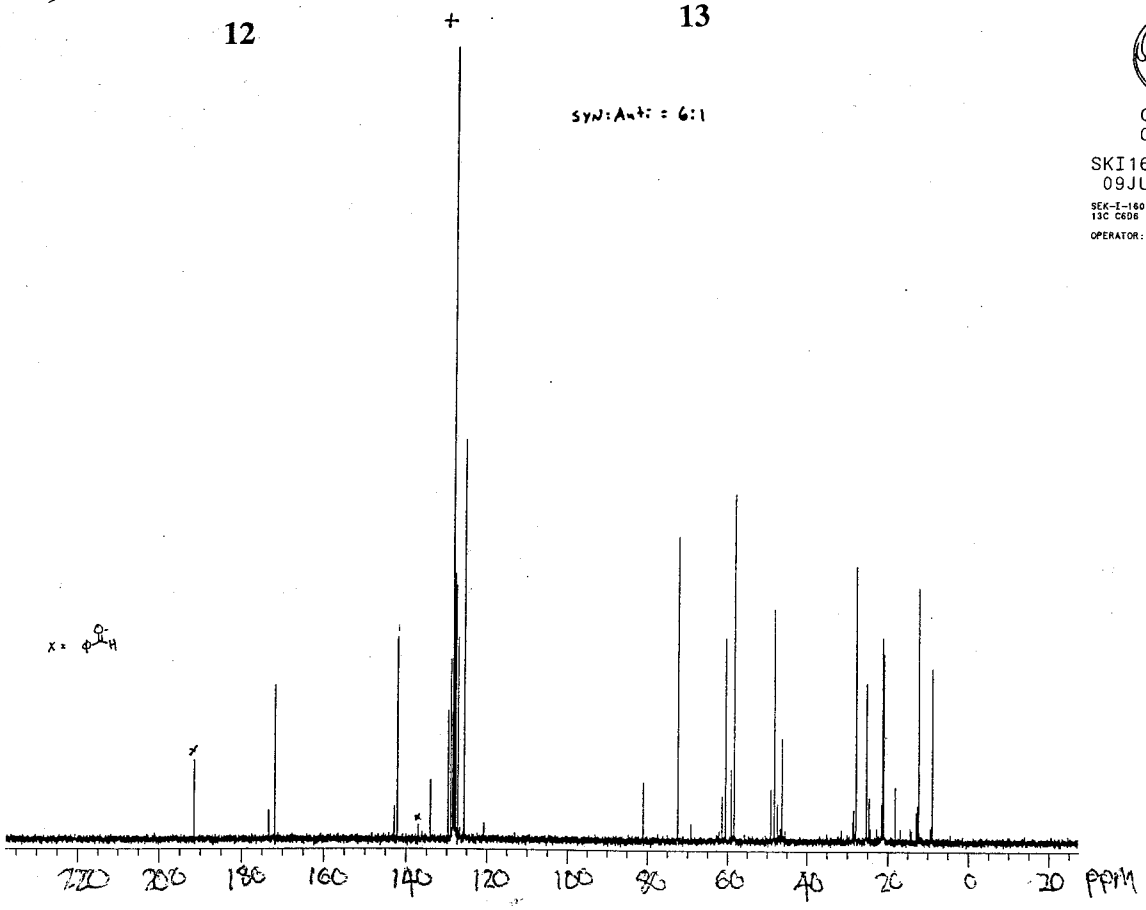


GE NMR
QE PLUS

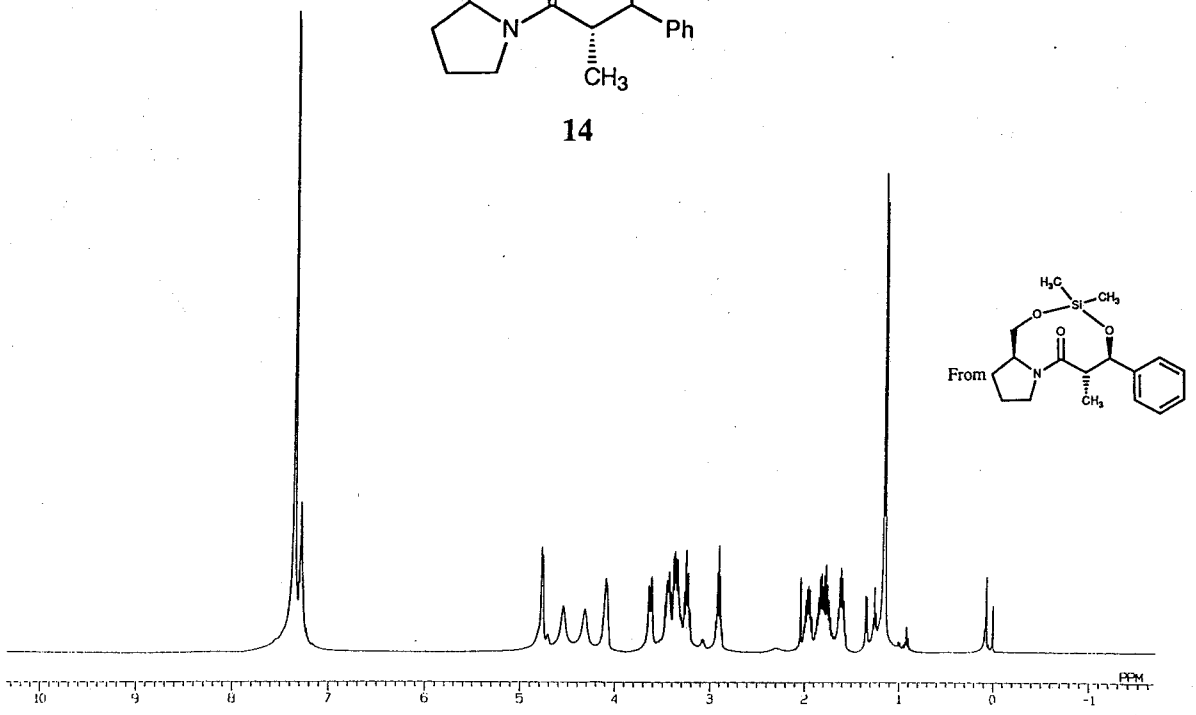
SKI160.100
09JUN92

SEK-I-160
13C C6D6

OPERATOR: SEK


OH
O
OH
N
Ph
CH3

14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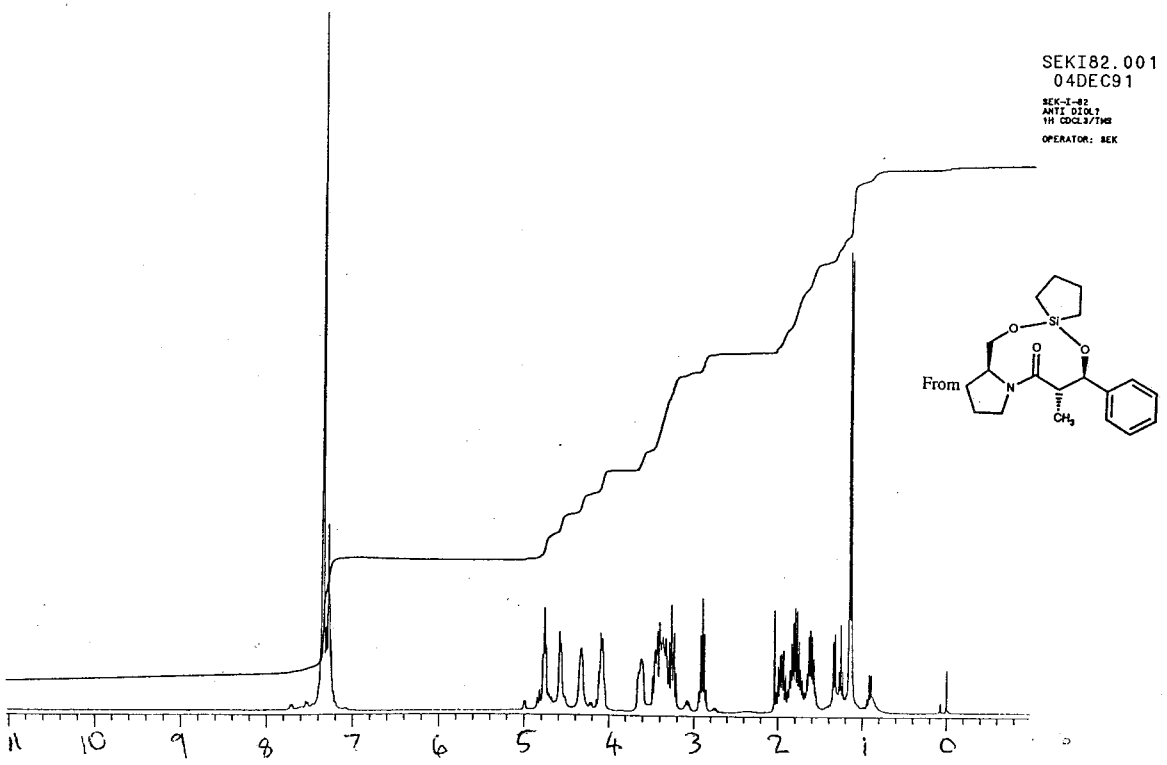
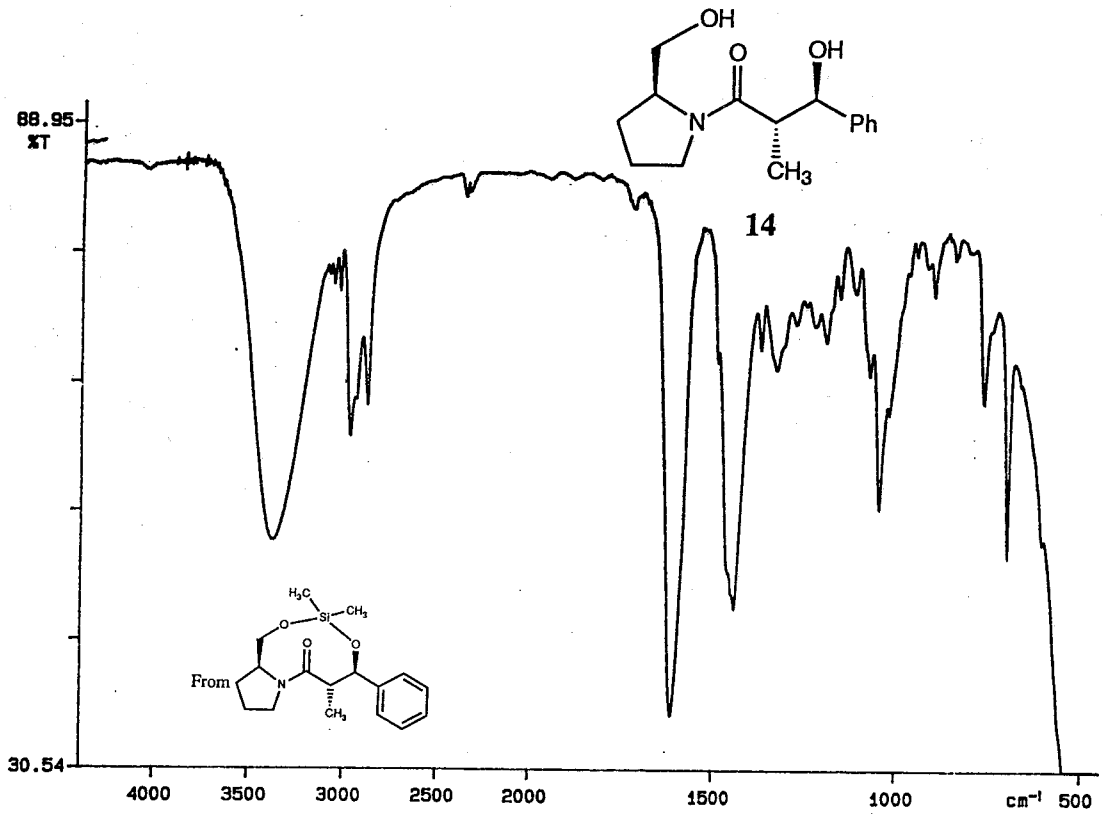
From
PPM


SEKI82.001
04DEC91
From



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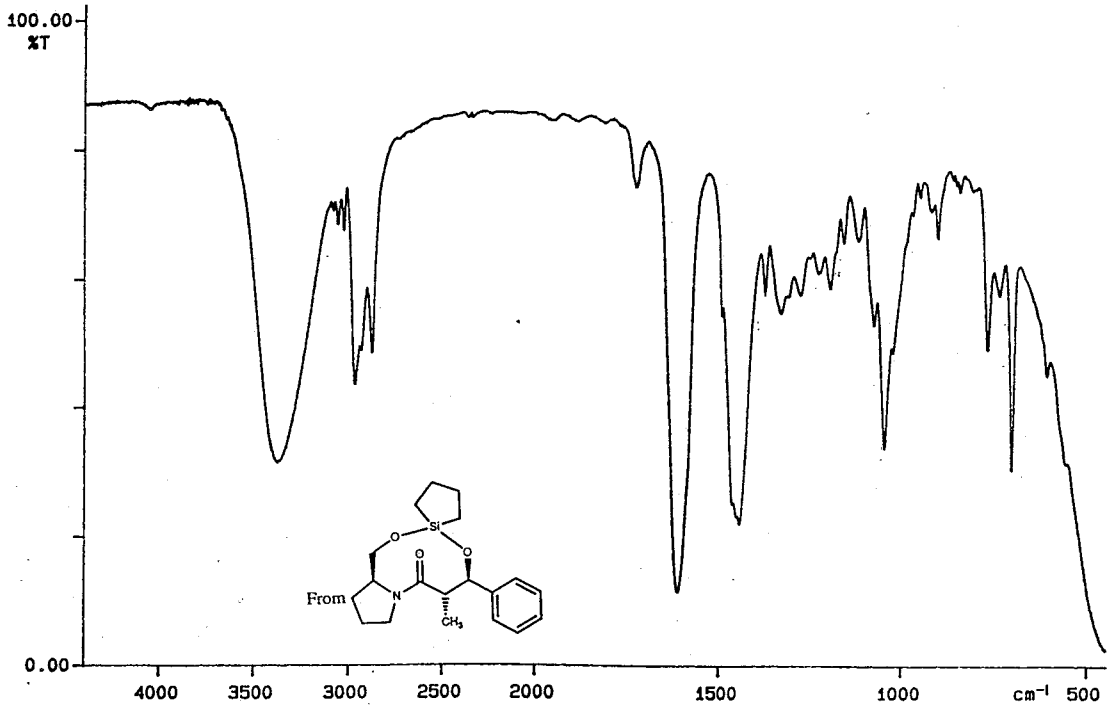
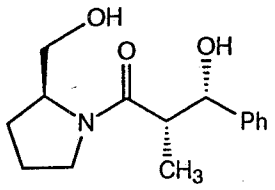


SEK-I-82
91/12/04 17:23
X: 4 scans, 4.0cm-1, flat



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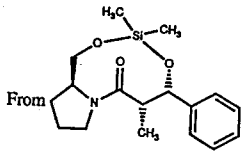
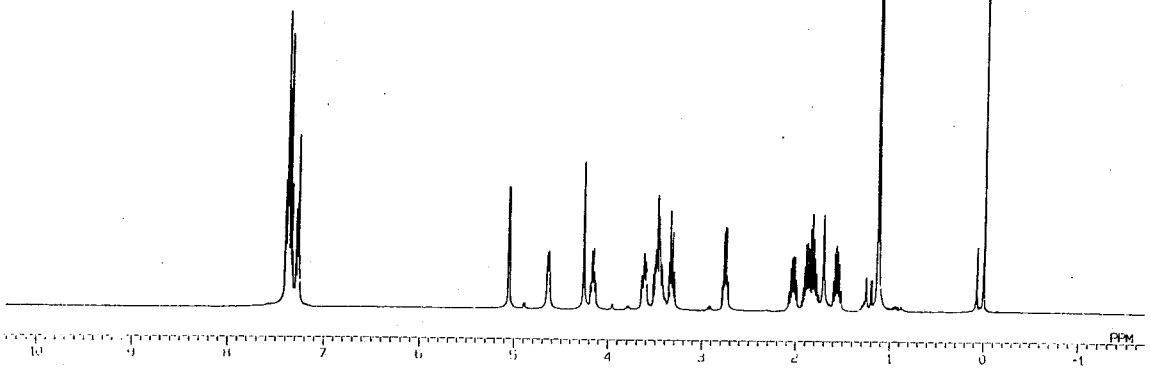
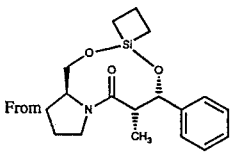
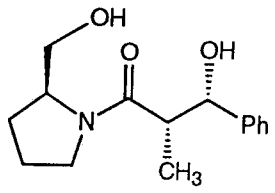
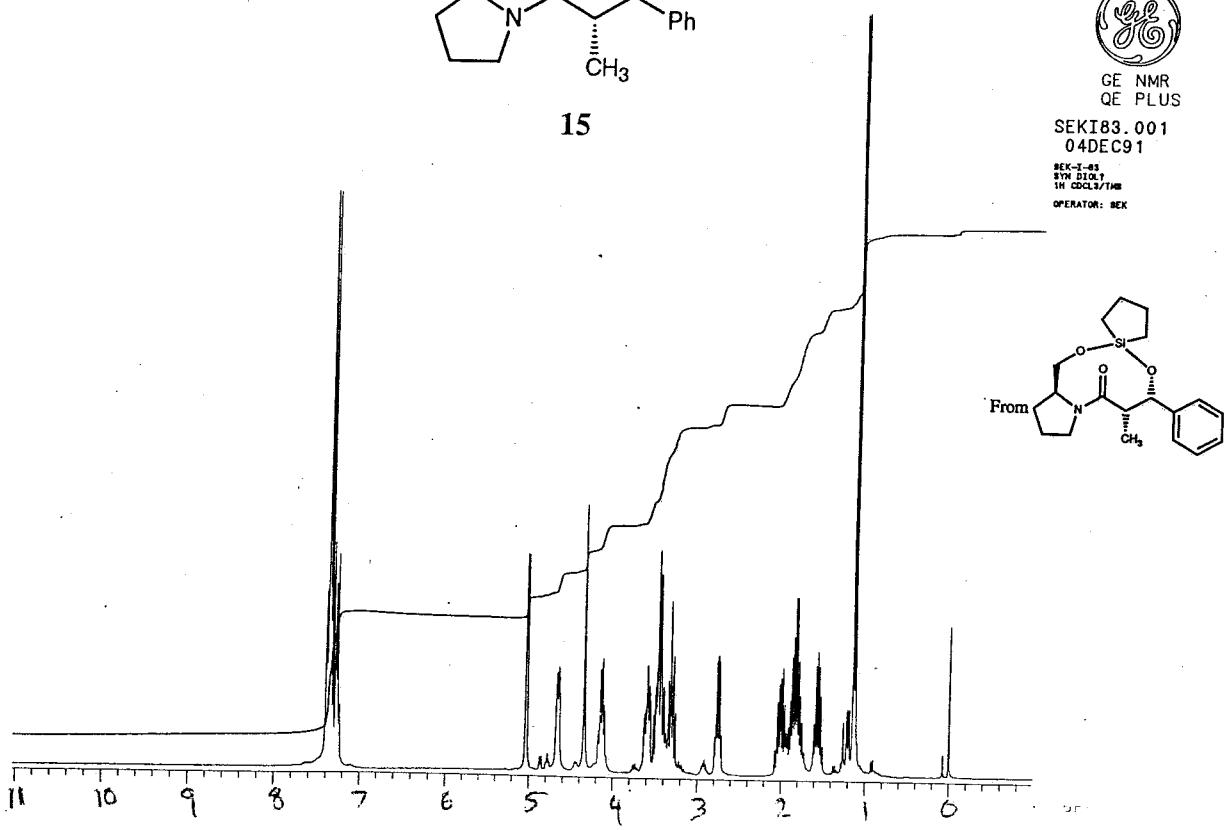


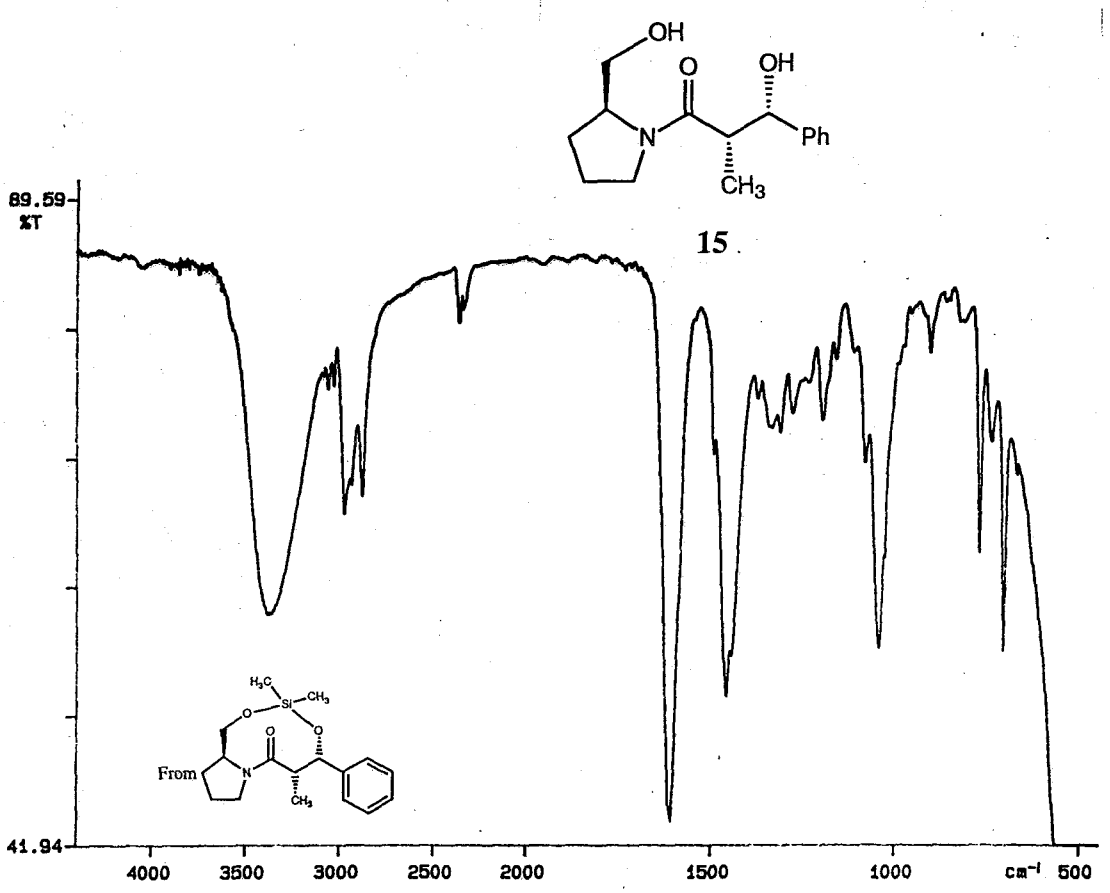





OH
O
OH
N
Ph
CH3

15


GE NMR
QE PLUS
SEKI83.001
04DEC91
SEK-I-83
SYN DIOL?
1H CDCL3/TMS
OPERATOR: SEK
From
Si
O
O
O
N
CH3
11
10
9
8
7
6
5
4
3
2
1
0



15

SEK-I-69
91/11/21 12:51
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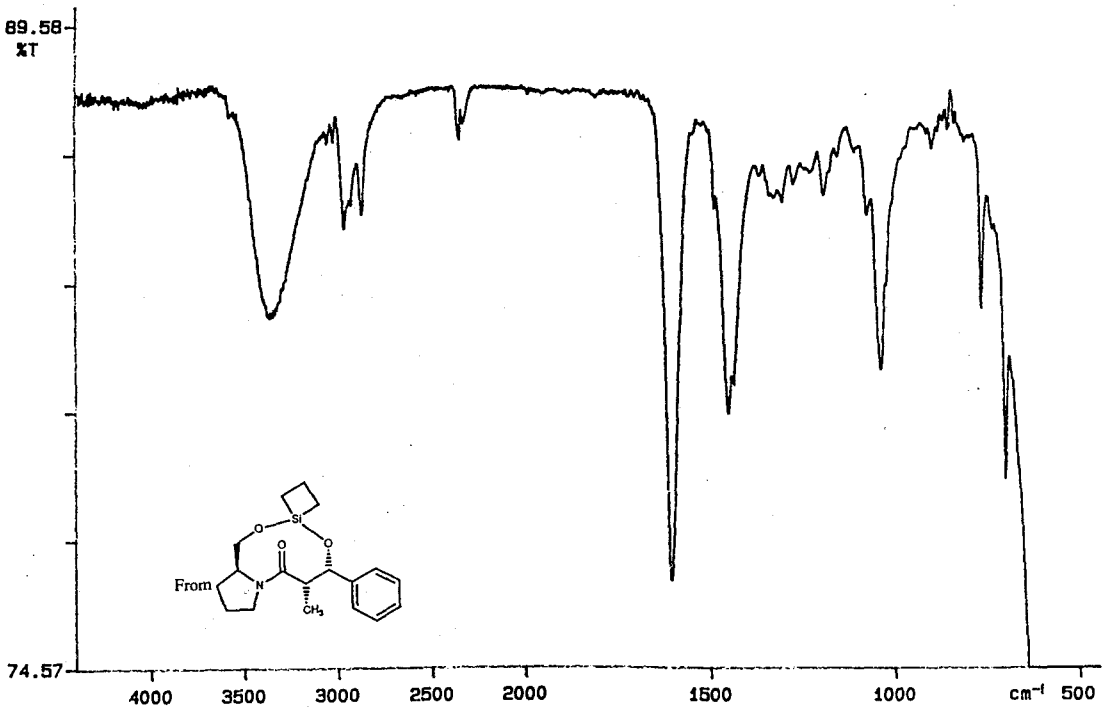

91/11/21 11:46
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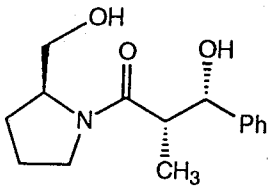
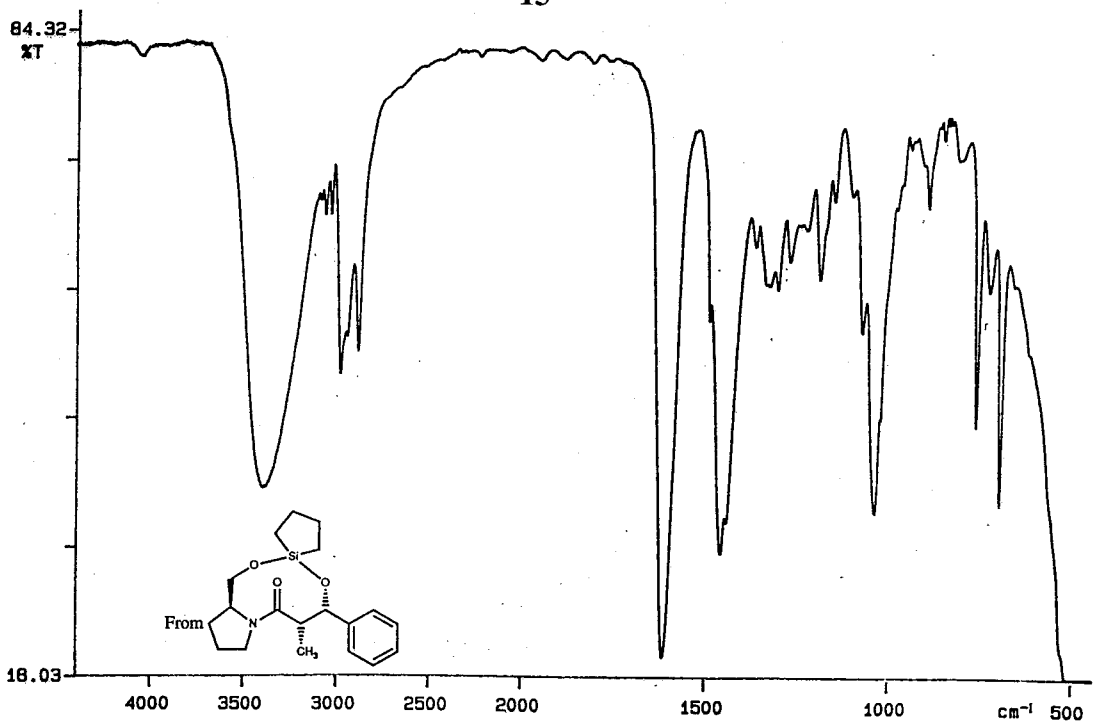

OH
O
OH
N
Ph
CH3

15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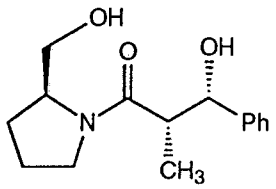
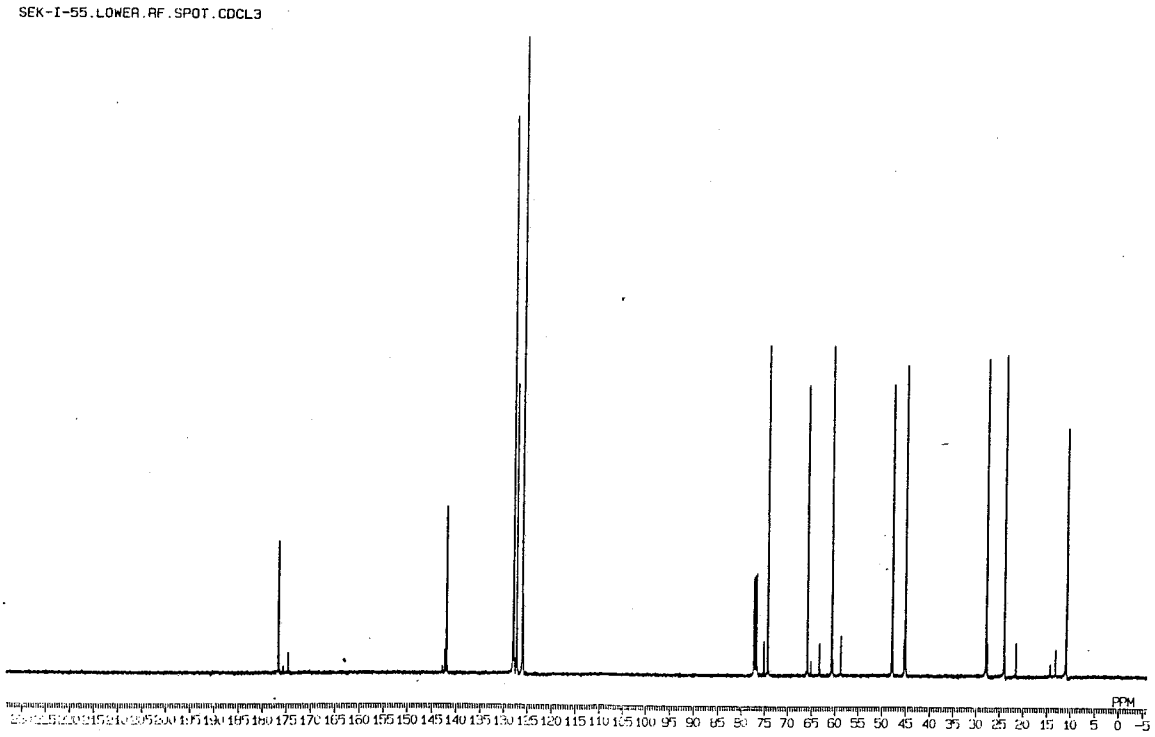
%T
18.03
From
4000
3500
3000
2500
2000
1500
1000
cm-1
500


OH
O
OH
N
Ph
CH3

15


SEK-I-55.LOWER.AF.SPOT.CDCL3
PPM
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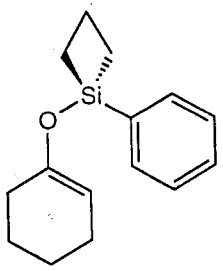


20

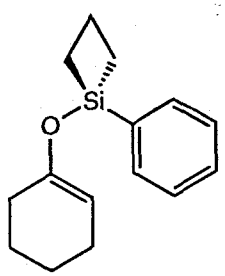
GE NMR
QE PLUS

SKI144.010
12MAY92

SEK-I-144
FRACTION1
78-80 DEG/11MTORR
1H C6D6

OPERATOR: SEK

11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 PPM



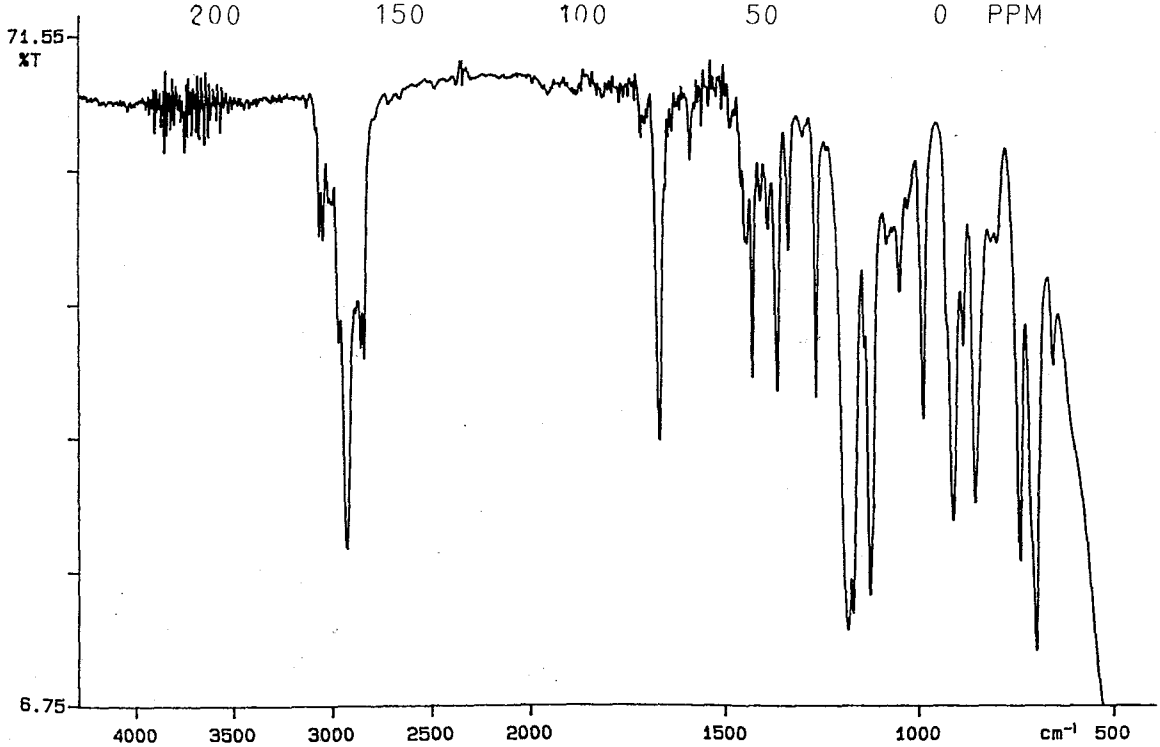
20

GE NMR
QE PLUS

SKI144.100
12MAY92

SEK-I-144
FRACTION 1
78-80 DEG 11 MTORR
13C C6D6

OPERATOR: SEK



SEK-I-144-1
92/05/13 11:18
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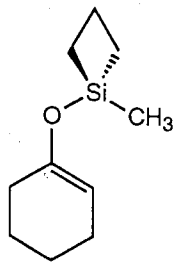
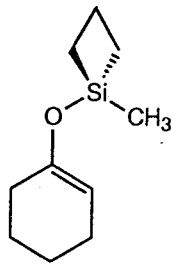
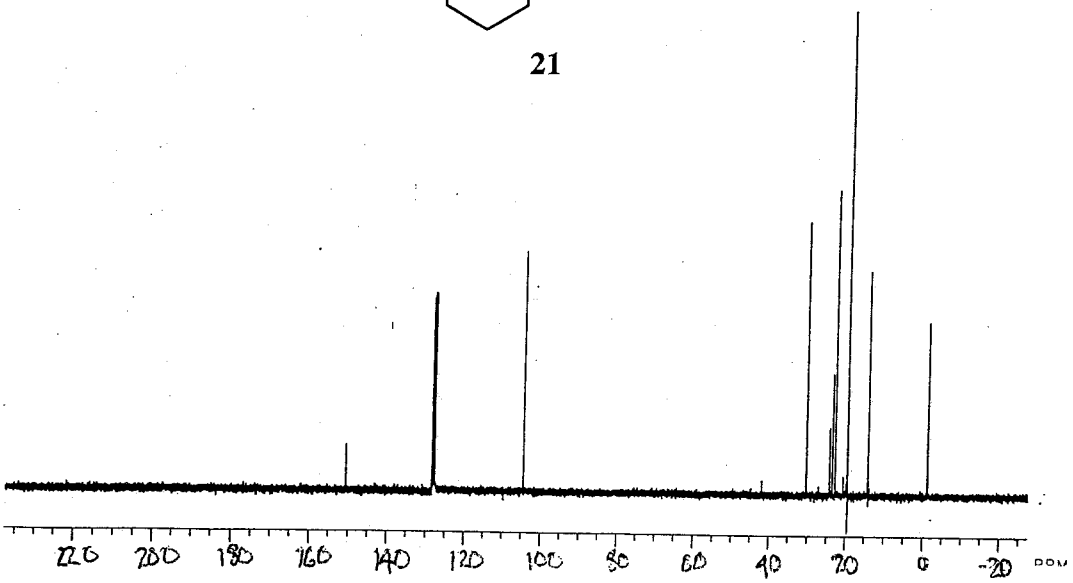

O
Si
CH3

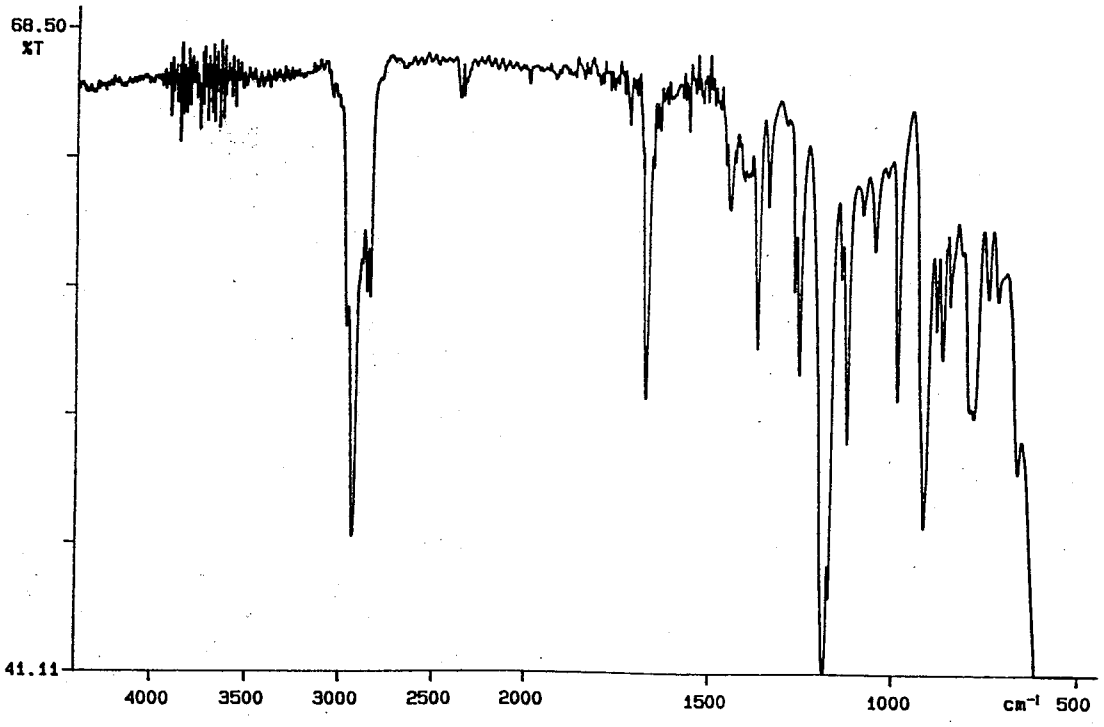
21

GE NMR
QE PLUS
SKI116.020
19MAR92
SEK-I-116 FRACTION2
63-64DEG 1.6MMHG
1H C6D6
OPERATOR: SEK
11
10
9
8
7
6
5
4
3
2
1
0
−1
−2
PPM

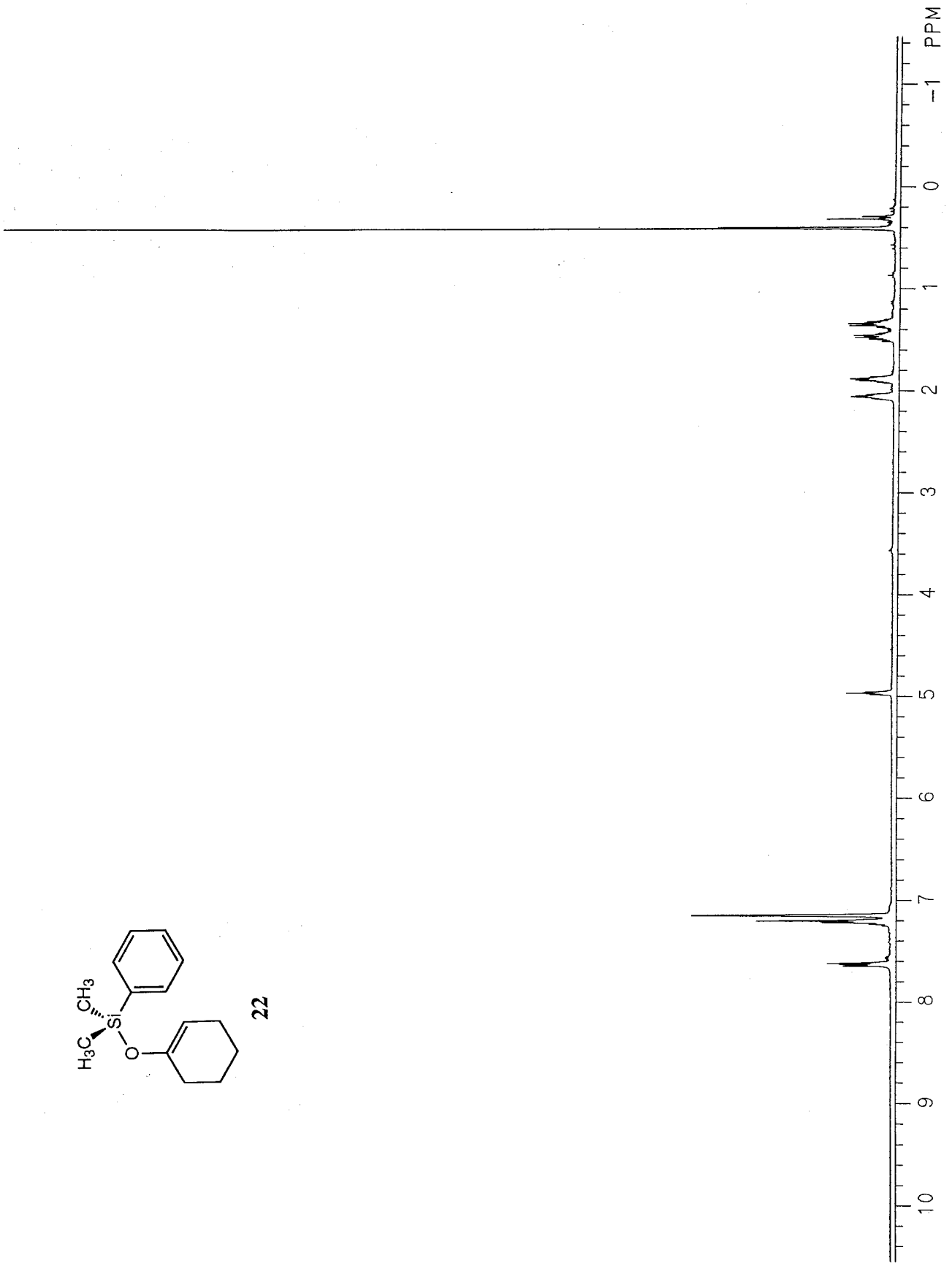


21

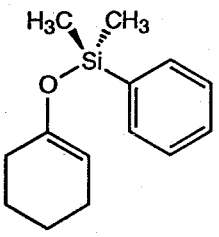




SEK-I-116 fraction 2
92/03/18 23:39
X: 4 scans, 4.0cm-1, flat



22



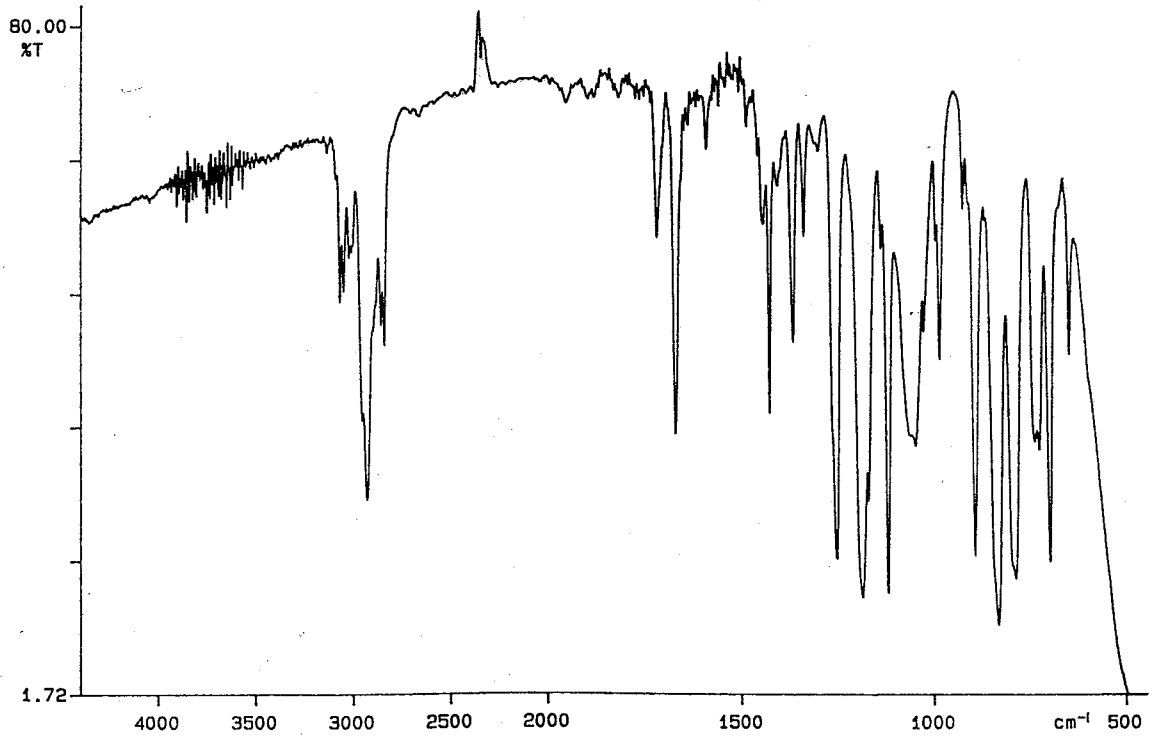
22

GE NMR
QE PLUS

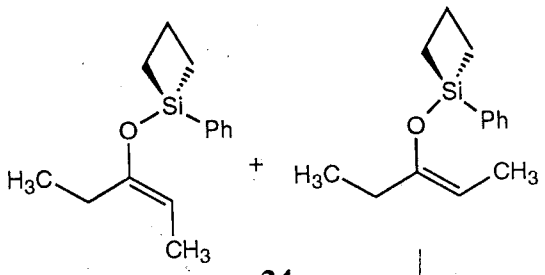
SEKI99.200
11FEB92

SEK-I-99 DISTILLED
60 UL 59.0 MG
13C CDCL3

OPERATOR: SEK



SEK-I-99
92/05/11 15:21
X: 4 scans, 4.0cm-1



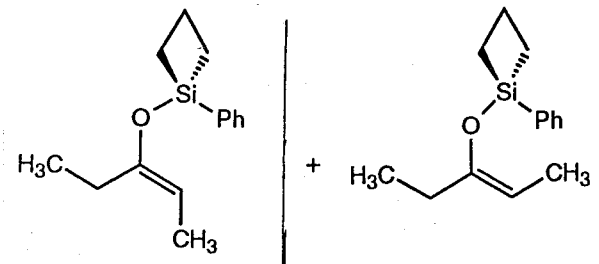
24

GE NMR
QE PLUS

SKI152.001
15MAY92

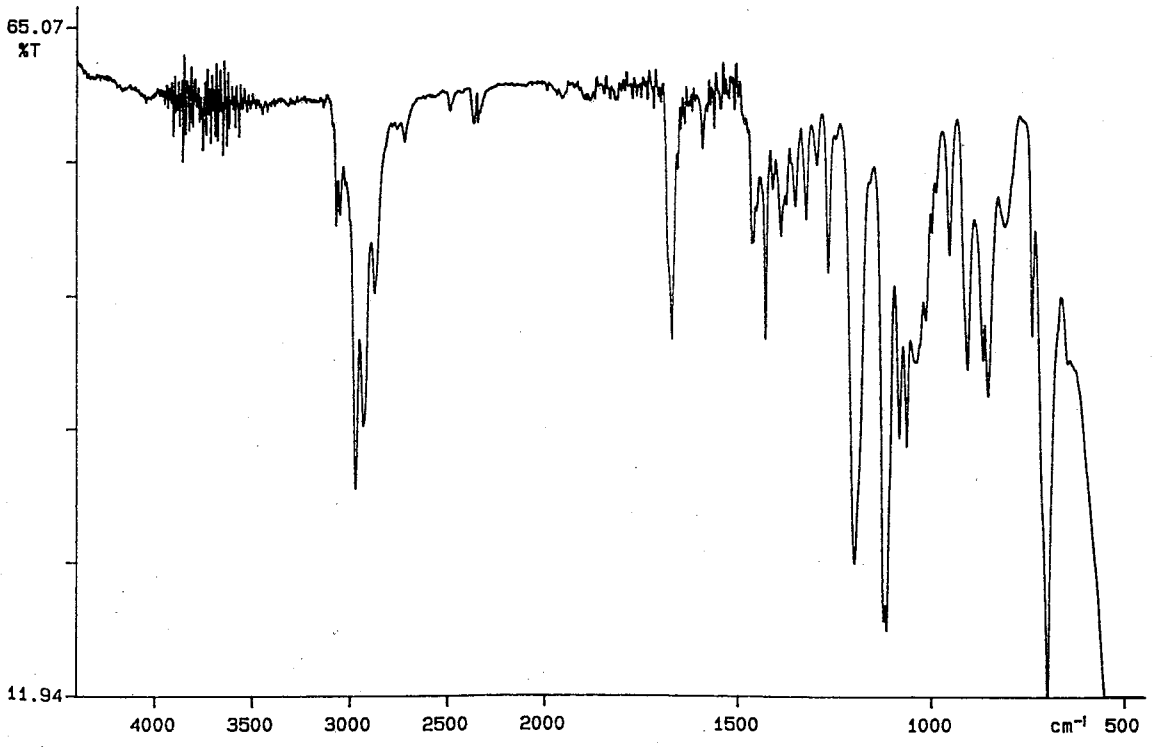
SEK-I-152
ORIGINAL SAMPLE
1H C6D6

OPERATOR: SEK

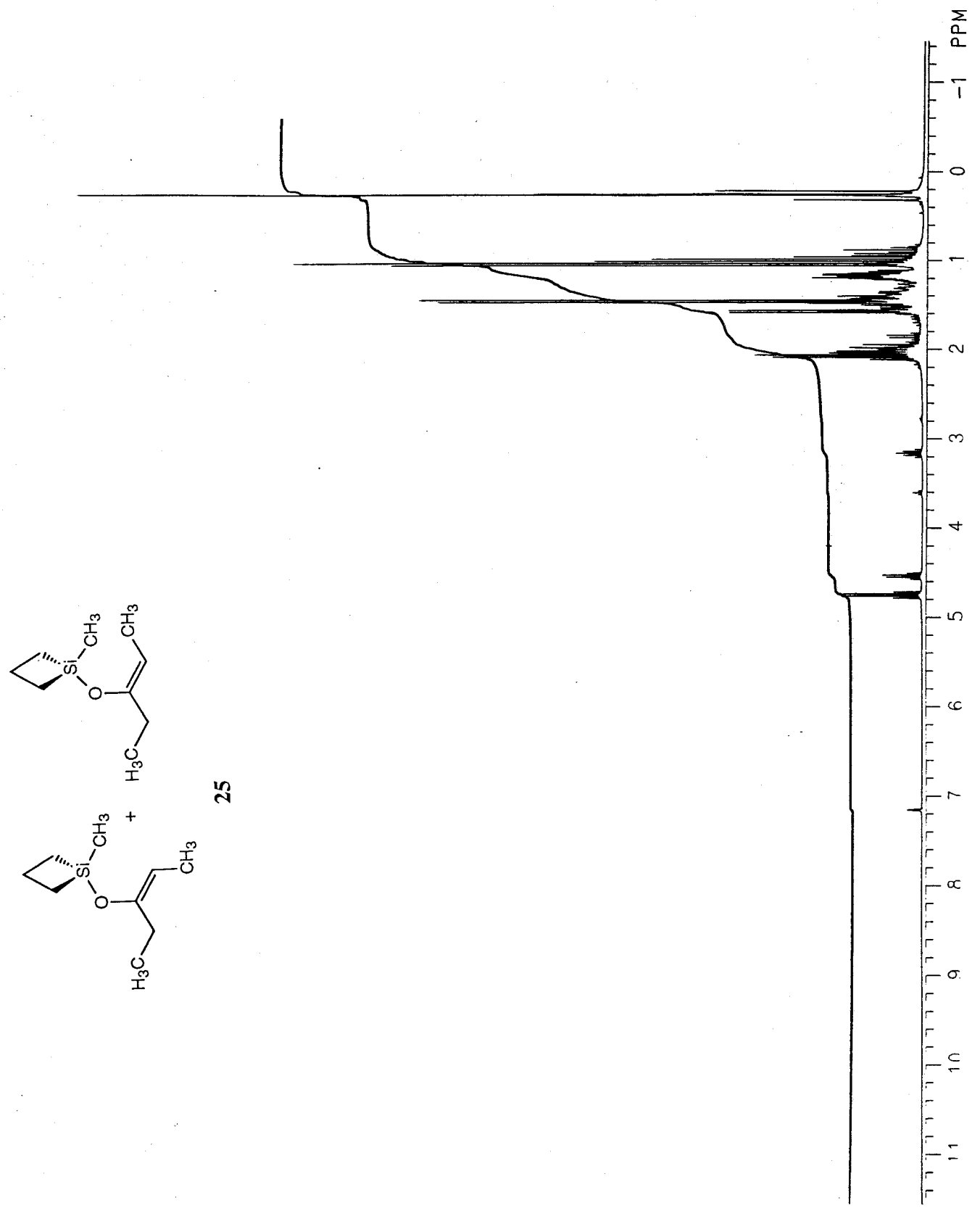


24

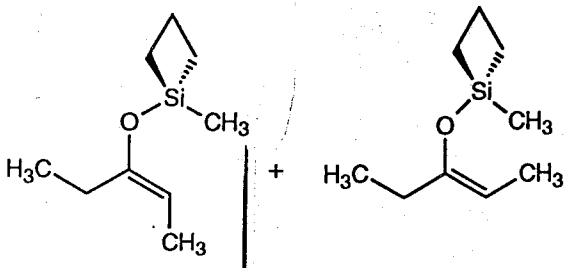
GE NMR
QE PLUS
SKI152.013
15MAY92
SEK-I-152
ORIGINAL SAMPLE
13C CDCl3
OPERATOR: SEK



SEK-I-150
92/05/23 16:54
X: 4 scans, 4.0cm-1, flat

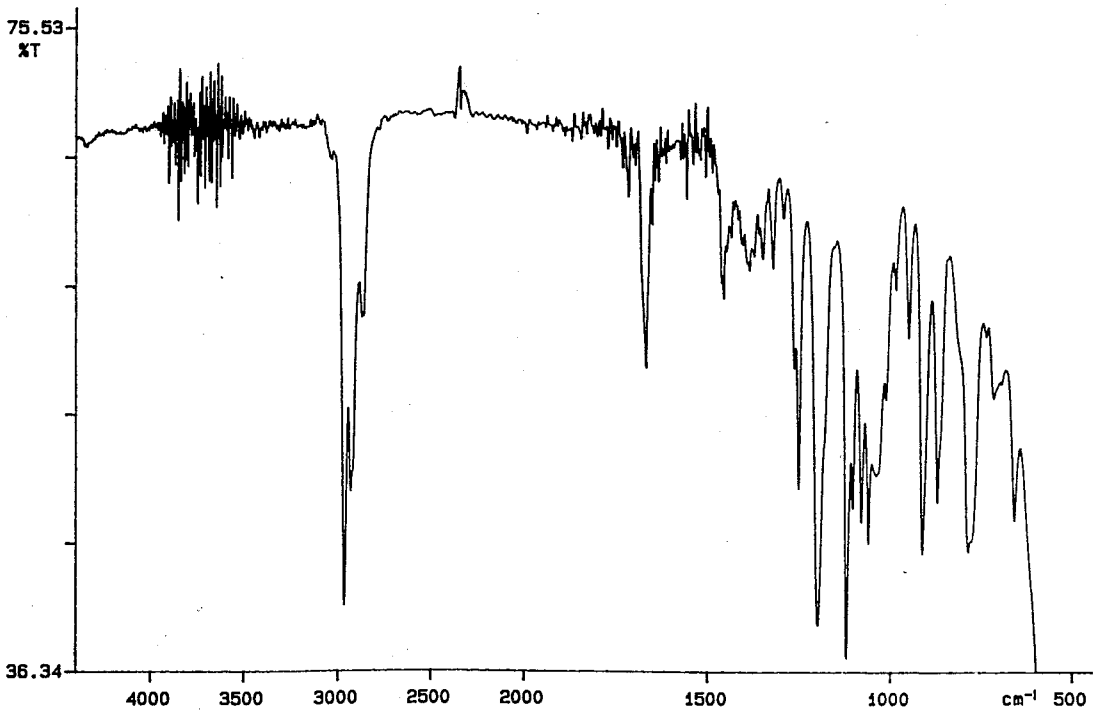


25

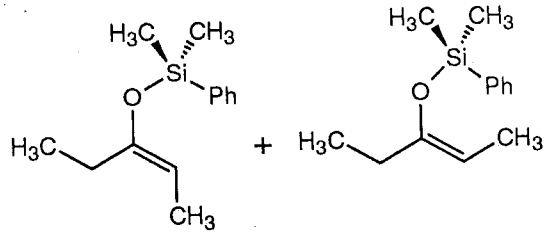


25

GE NMR
QE PLUS
SKI126.100
28MAY92
SEK-I-126
13C CDCl3
OPERATOR: SEK



92/05/28 14:46
X: 16 scans, 4.0cm-1, flat
SEK I 126



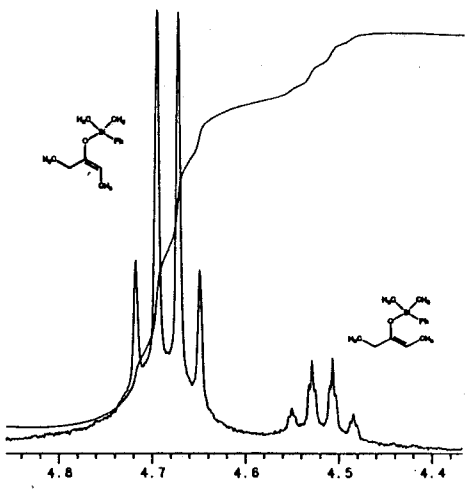
26

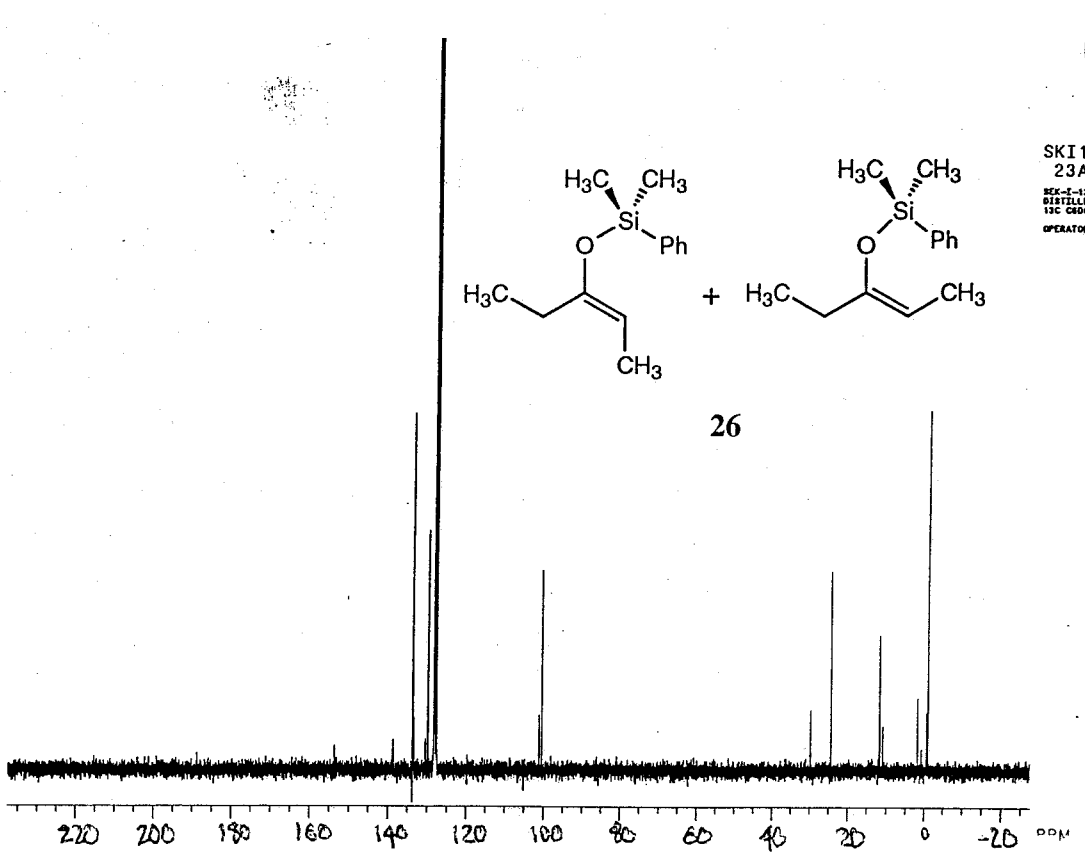
GE NMR
QE PLUS

SKI133.010
22APR92

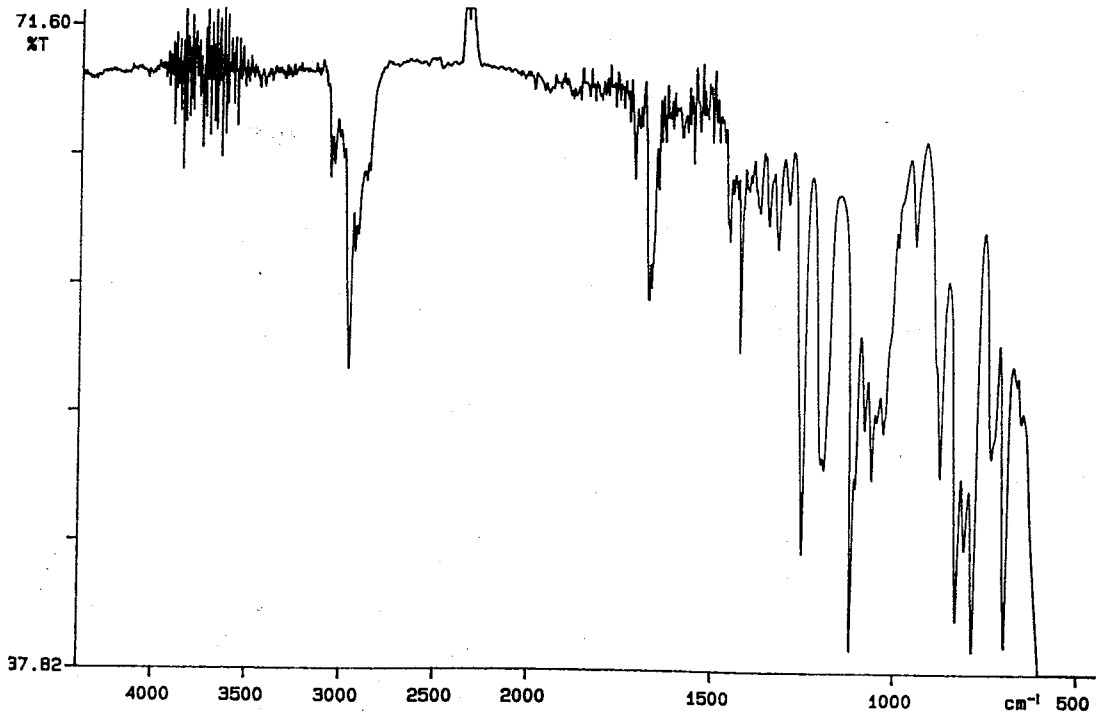
SEK-I-133
DISTILLED
1H C6D6

OPERATOR: SEK

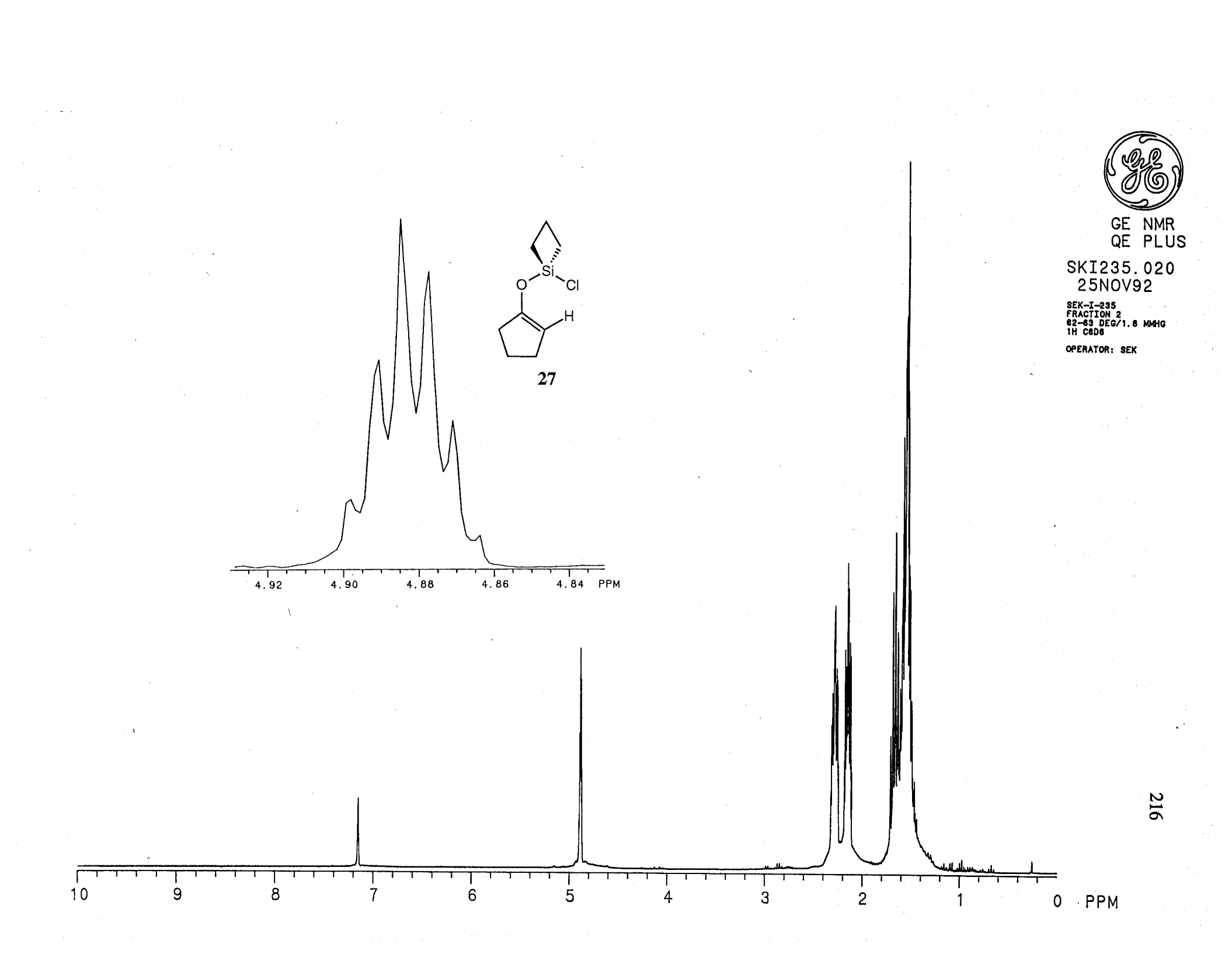


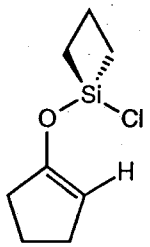


26

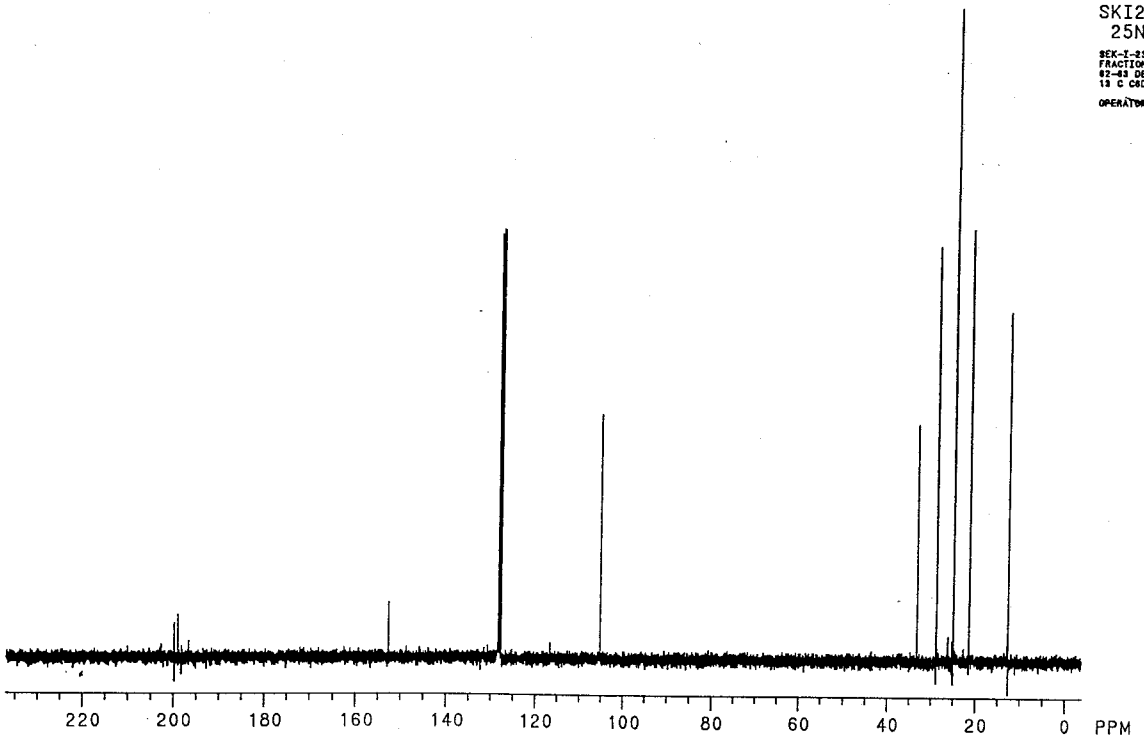


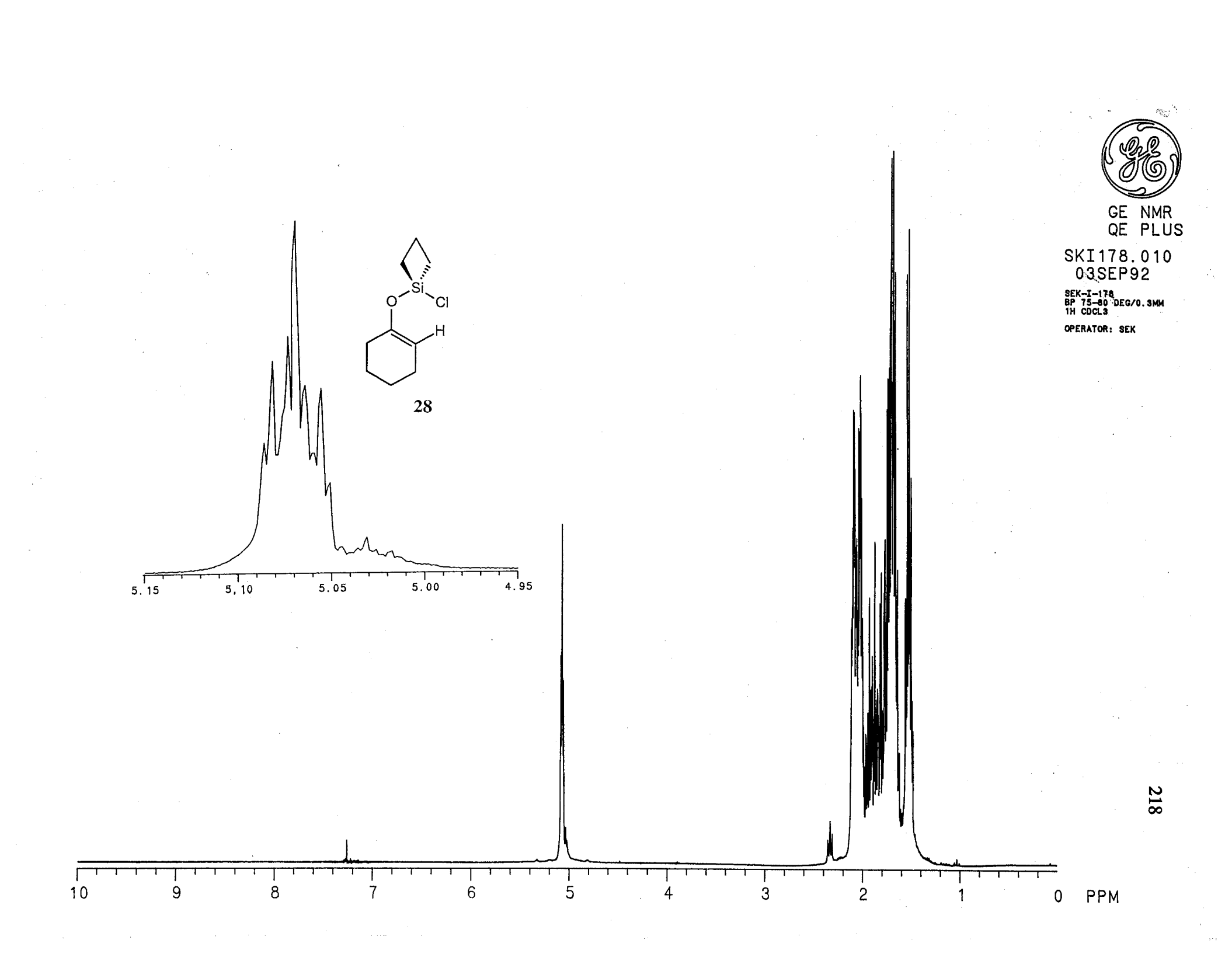
92/05/28 14:27
X: 16 scans, 4.0cm-1, flat
SEK I 133

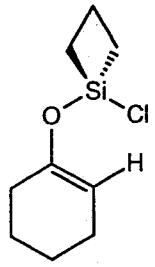

GE NMR
QE PLUS
SKI235.020
25NOV92
SEK-I-235
FRACTION 2
62-63 DEG/1.5 MMHG
1H C6D6
OPERATOR: SEK
Si
Cl
O
H
27
4.92
4.90
4.88
4.86
4.84
PPM
10
9
8
7
6
5
4
3
2
1
0
PPM


Si
Cl
O
H

27

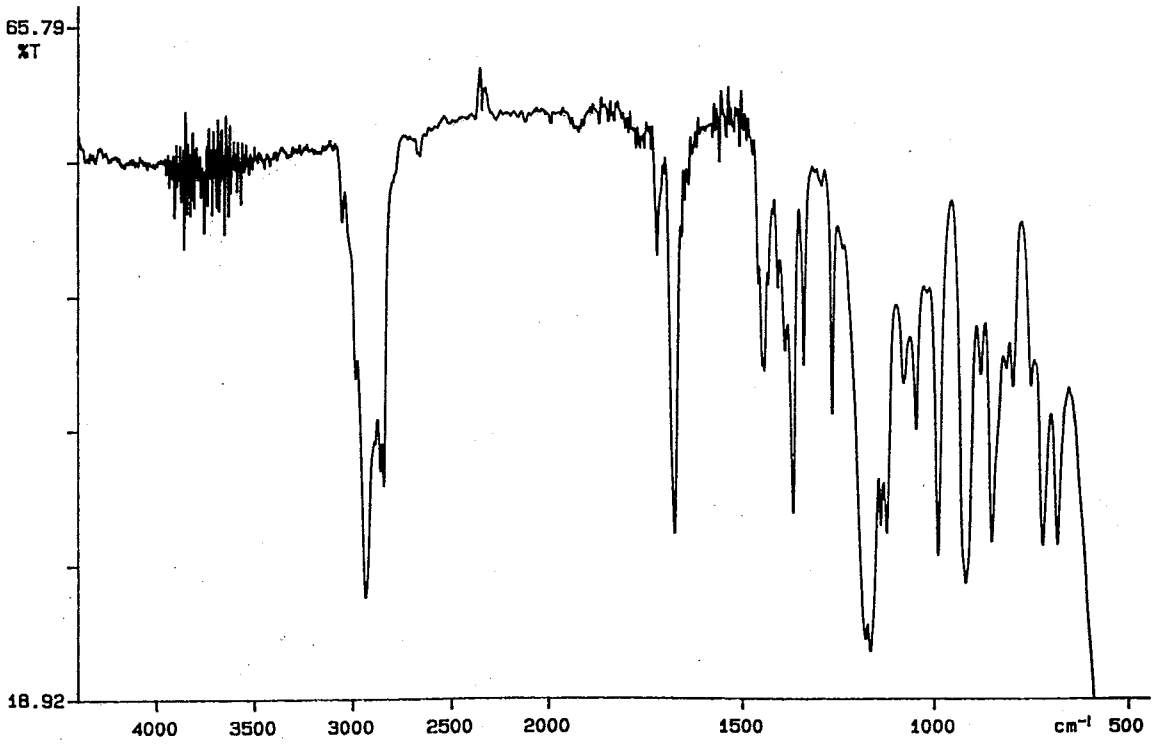

GE NMR
QE PLUS
SKI235.200
25NOV92
220
200
180
160
140
120
100
80
60
40
20
0
PPM


GE NMR
QE PLUS
SKI178.010
03SEP92
SEK-I-178
BP 75-80 DEG/0.3MM
1H CDCL3
OPERATOR: SEK
Si
O
Cl
H
28
5.15
5.10
5.05
5.00
4.95
10
9
8
7
6
5
4
3
2
1
0
PPM

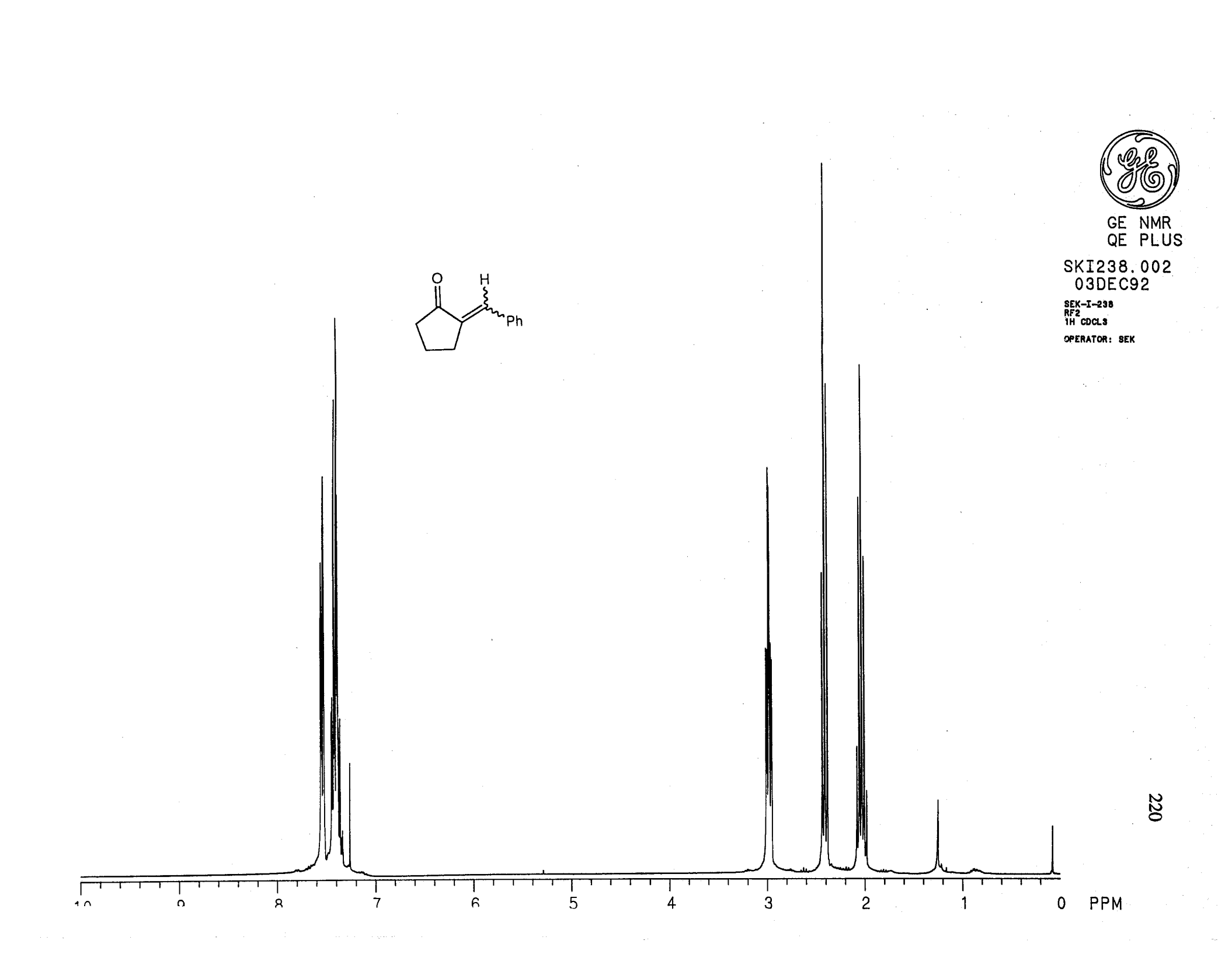


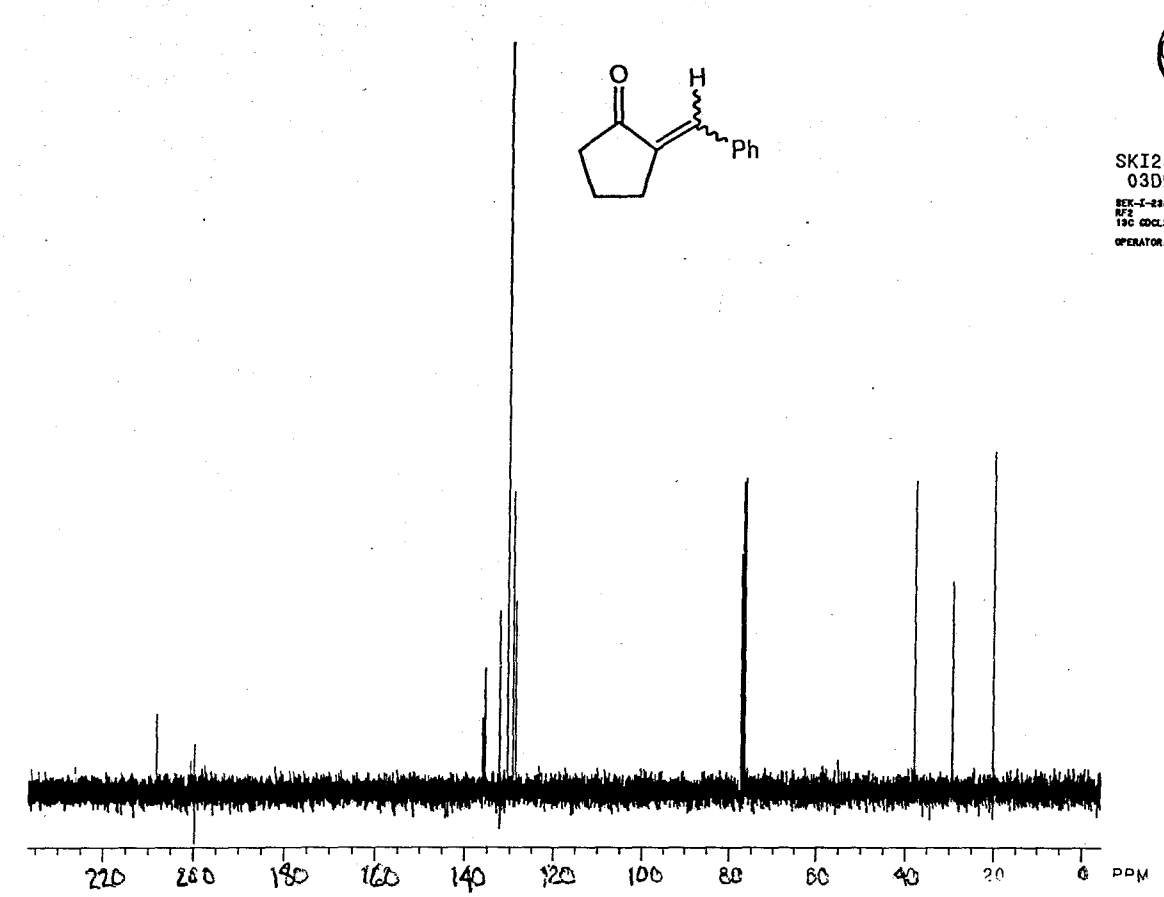
28

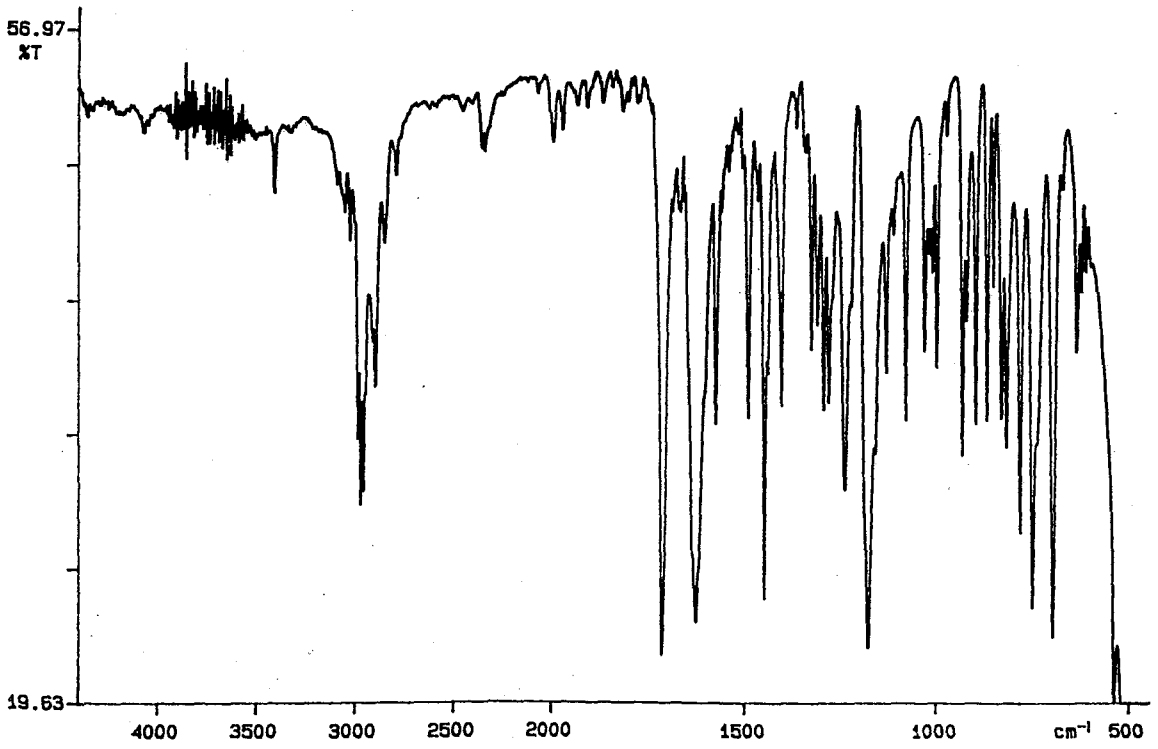
GE NMR
QE PLUS
SKI178.100
04SEP92
SEK-I-178
BP 75-80/0.3MM
13C CDCL3
OPERATOR: SEK



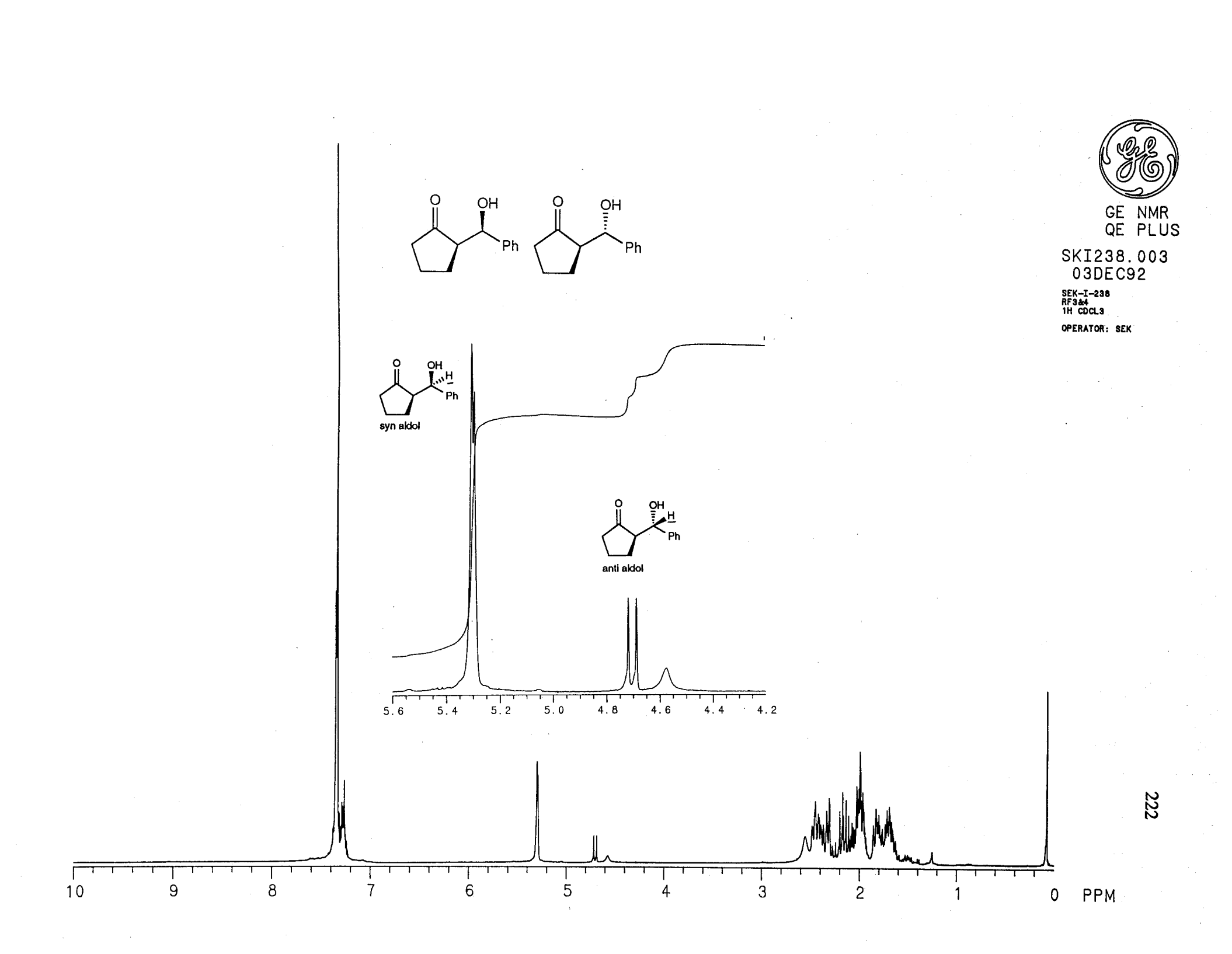
92/09/04 21:00
X: 4 scans, 4.0cm-1, flat
SEK-I-178

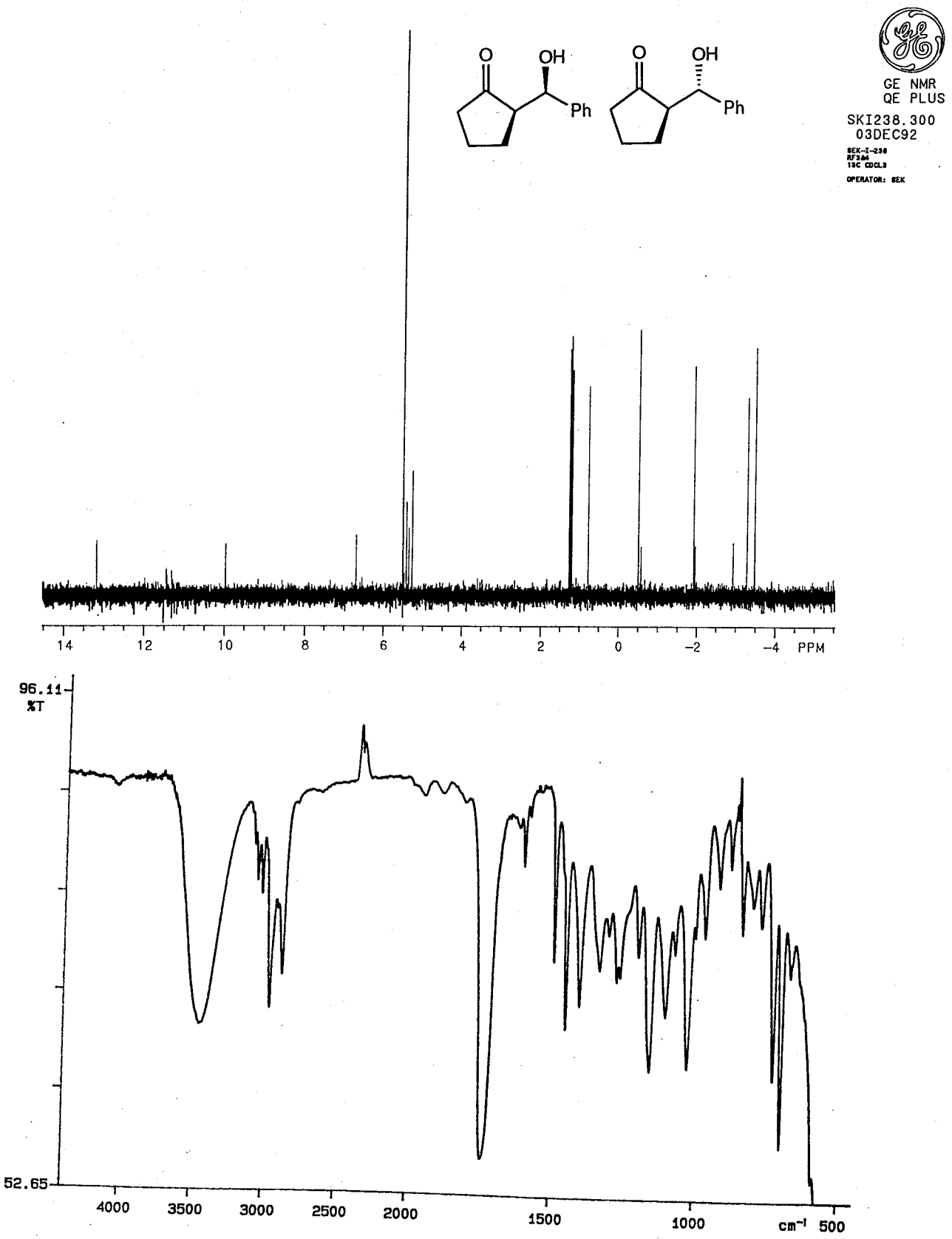

O
H
Ph
GE NMR
QE PLUS
SKI238.002
03DEC92
SEK-I-238
RF2
1H CDCL3
OPERATOR: SEK
10
9
8
7
6
5
4
3
2
1
0
PPM

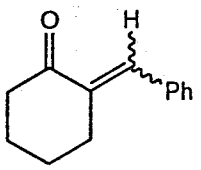




92/12/03 16:05
X: 4 scans, 4.0cm-1, flat
SEK-I-238 rf2 Neat Film

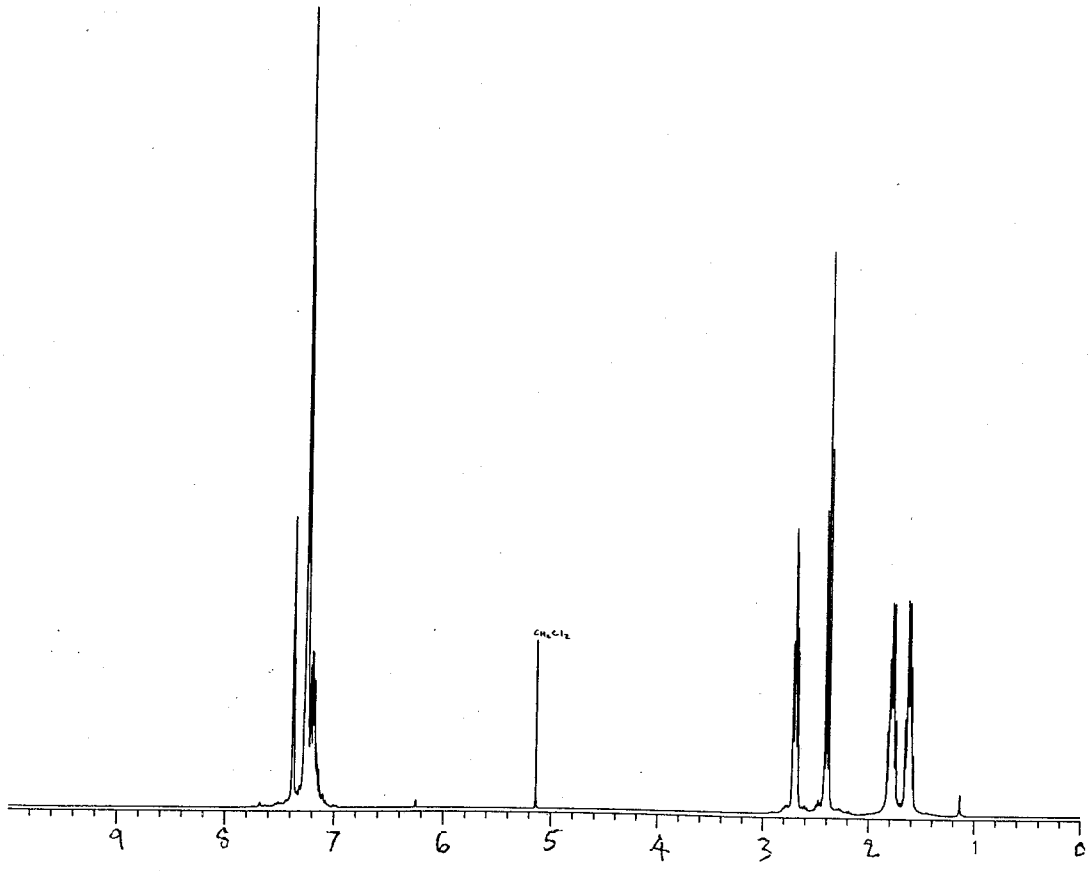

GE NMR
QE PLUS
SKI238.003
03DEC92
SEK-I-238
RF3&4
1H CDCL3
OPERATOR: SEK
syn aldol
anti aldol
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
10
9
8
7
6
5
4
3
2
1
0
PPM
222

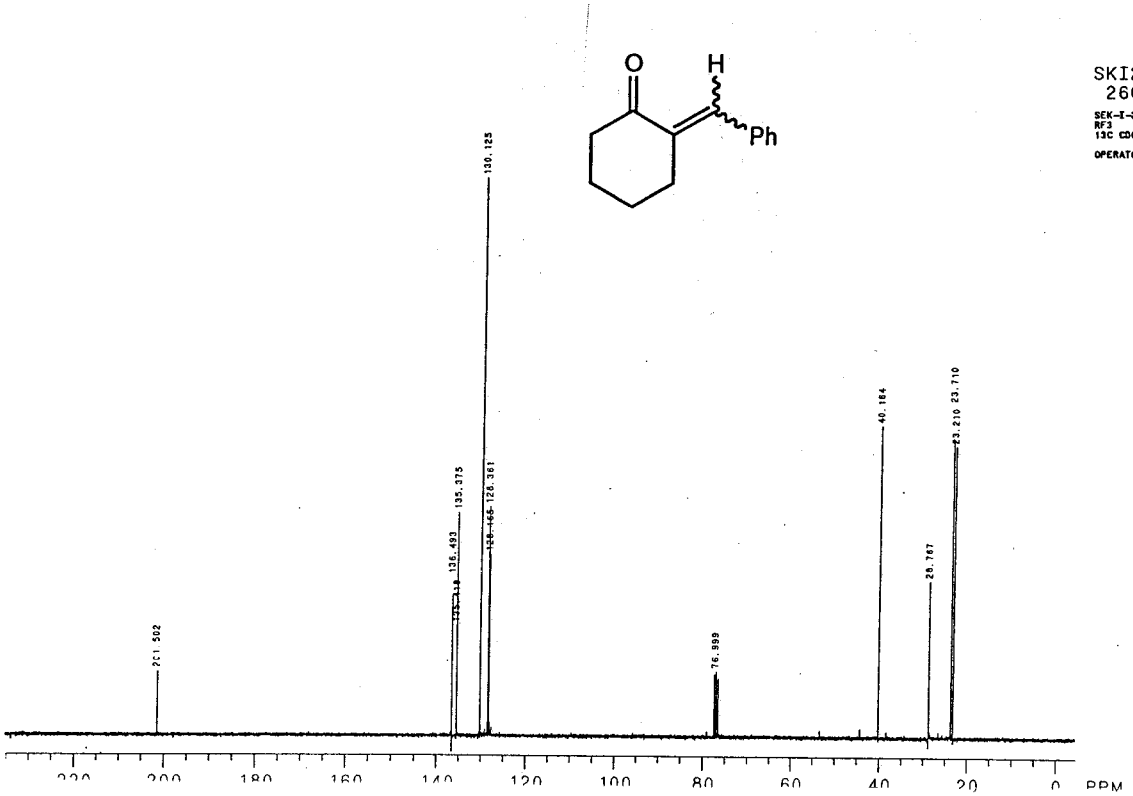

O
OH
Ph
O
OH
Ph
GE NMR
QE PLUS
SKI238.300
03DEC92
SEK-I-238
RF3&4
13C CDCL3
OPERATOR: SEK
14
12
10
8
6
4
2
0
−2
−4
PPM
96.11
%T
52.65
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500
92/12/03 17:18
X: 4 scans, 4.0cm-1
SEK-I-238 rf3&4 Neat Film

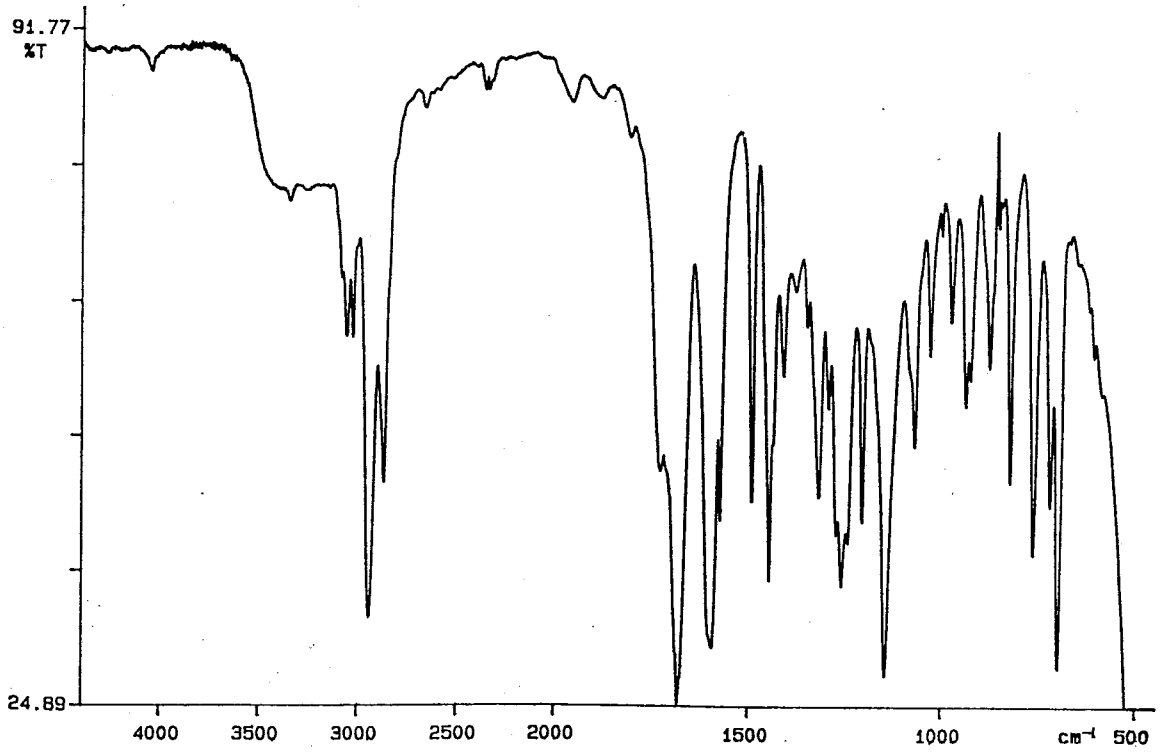


GE NMR
QE PLUS
SKI213.001
26OCT92
SEK-I-213
RF3
1H C6D6
OPERATOR: SEK

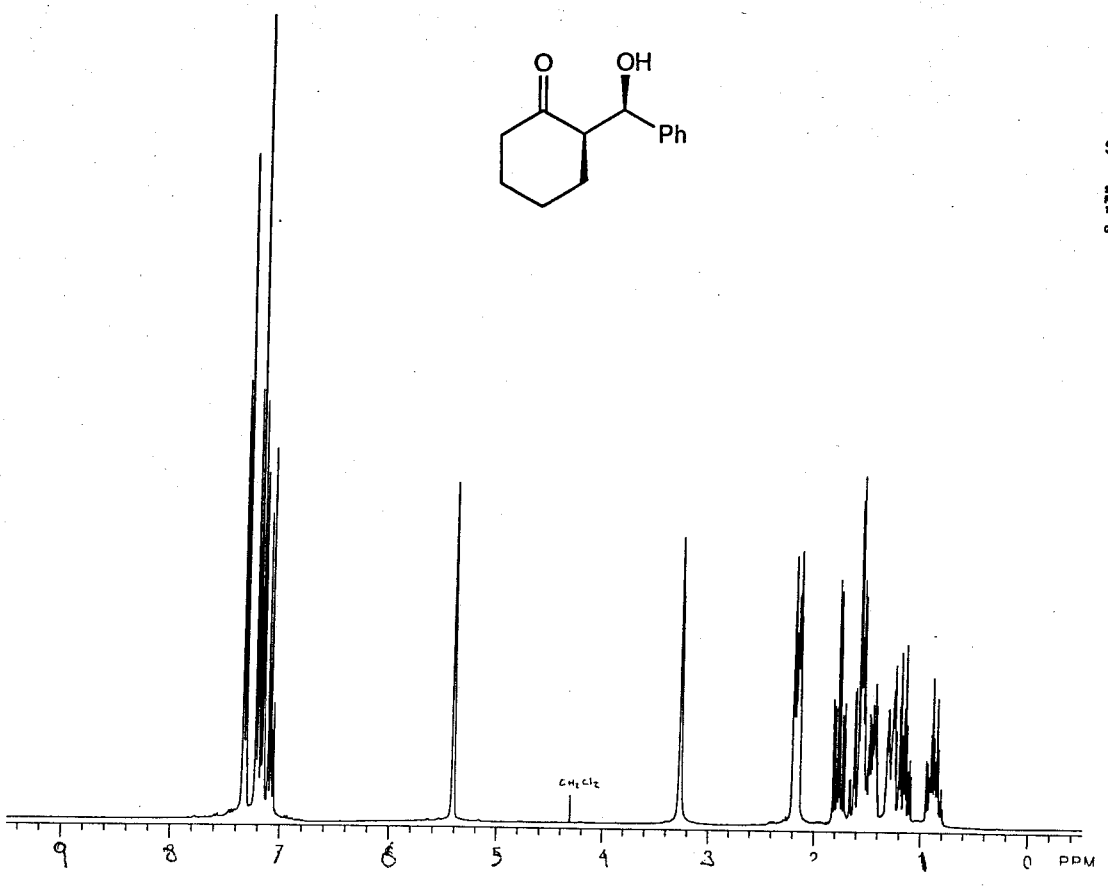
GE NMR
QE PLUS
SKI213.004
26OCT92
SEK-I-213
RF3
1H CDCL3
OPERATOR: SEK

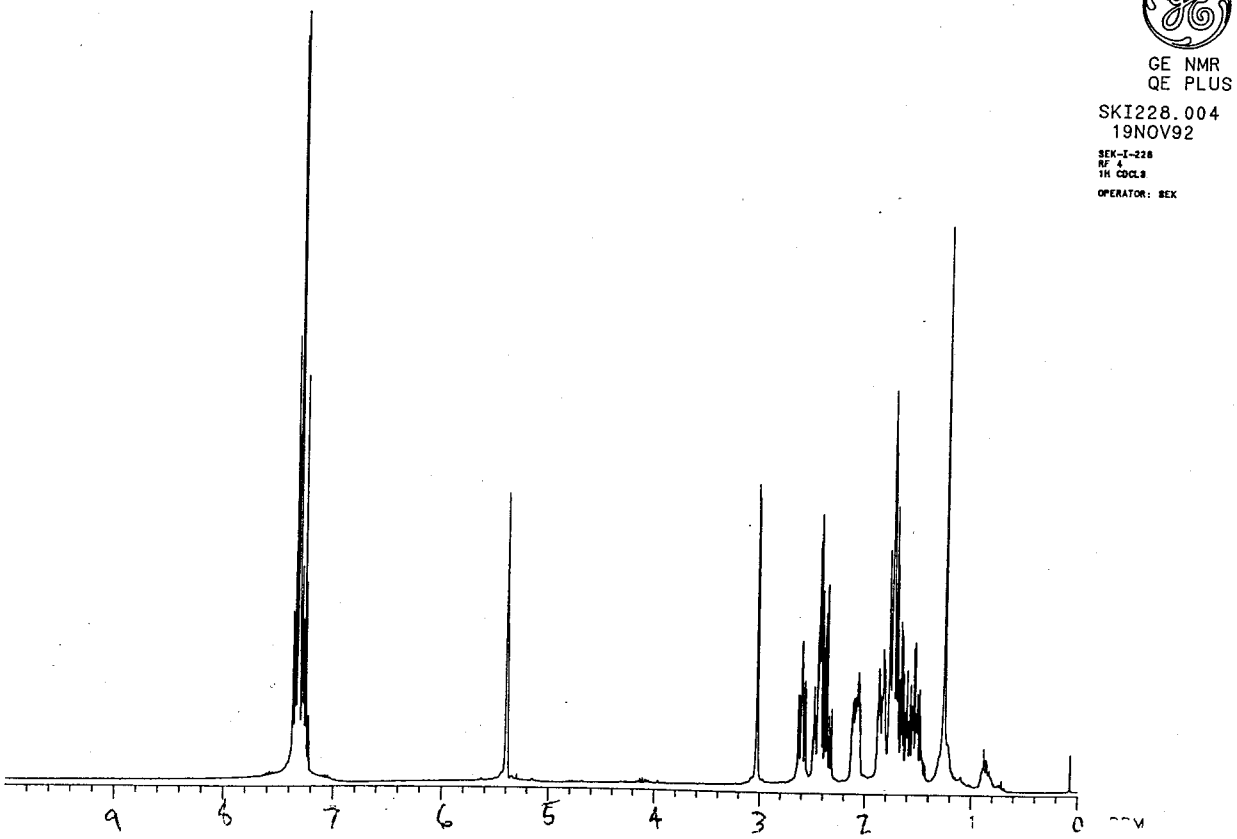


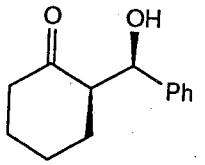




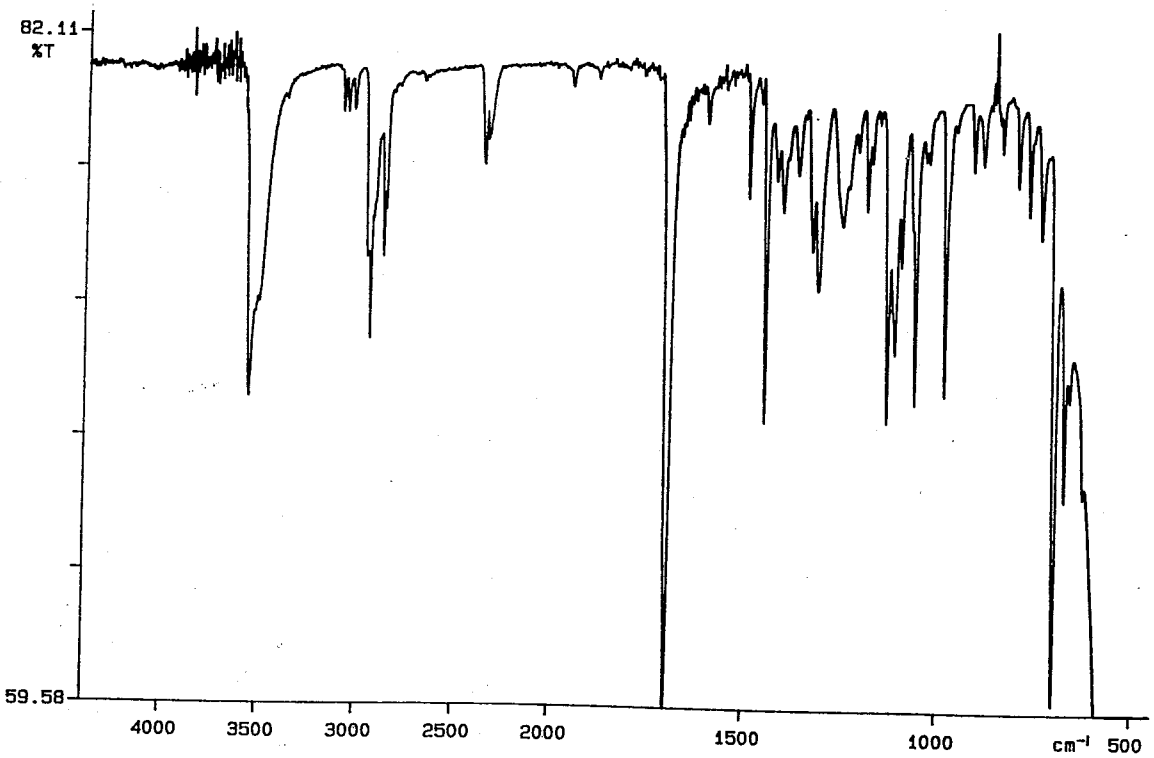
92/12/19 12:42
X: 4 scans, 4.0cm-1
SEK-I-213 rf3 enone


O
OH
Ph
GE NMR
QE PLUS
SKI215.003
28OCT92
SEK-I-215
RF 6
1H C6D6
OPERATOR: SEK
CH2Cl2
9 8 7 6 5 4 3 2 1 0 PPM

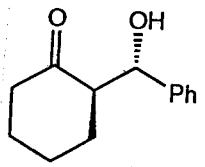

GE NMR
QE PLUS
SKI228.004
19NOV92
SEK-I-228
RF 1
1H CDCL3
OPERATOR: SEK
9 8 7 6 5 4 3 2 1 0



SKI215.400
20DEC92
SEK-I-215
RF4 SYN
13C CDCL3
OPERATOR: SEK

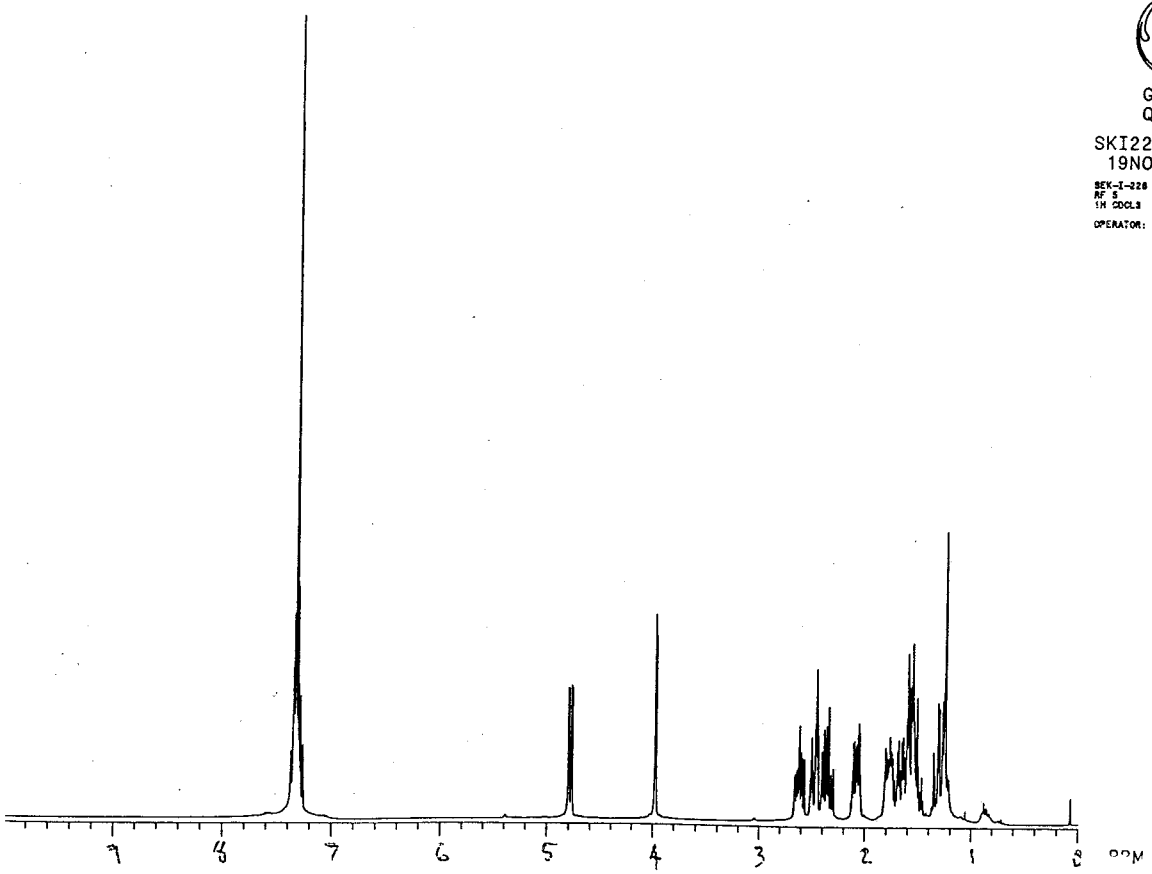


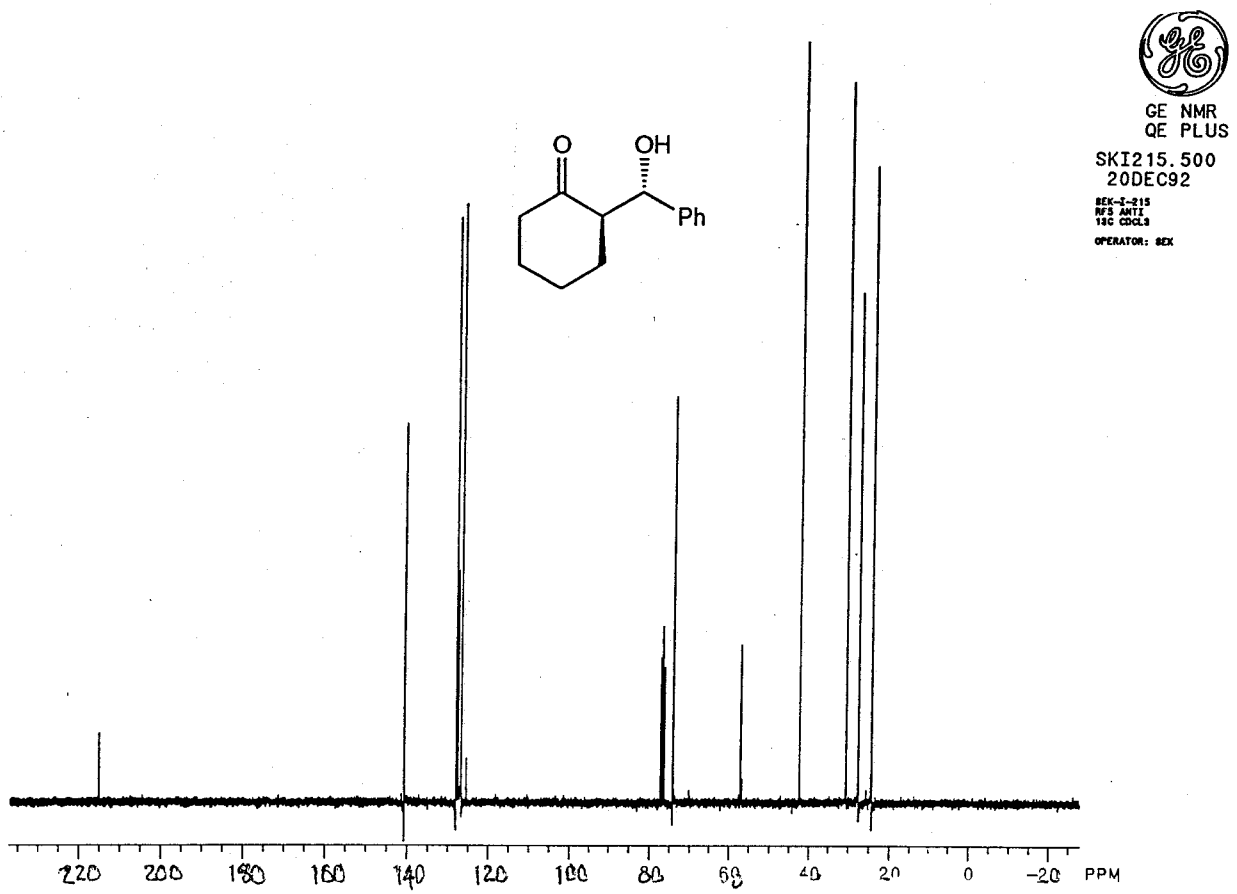
92/12/20 15:59
X: 4 scans, 4.0cm-1, flat
SEK-I-215 rf4 syn

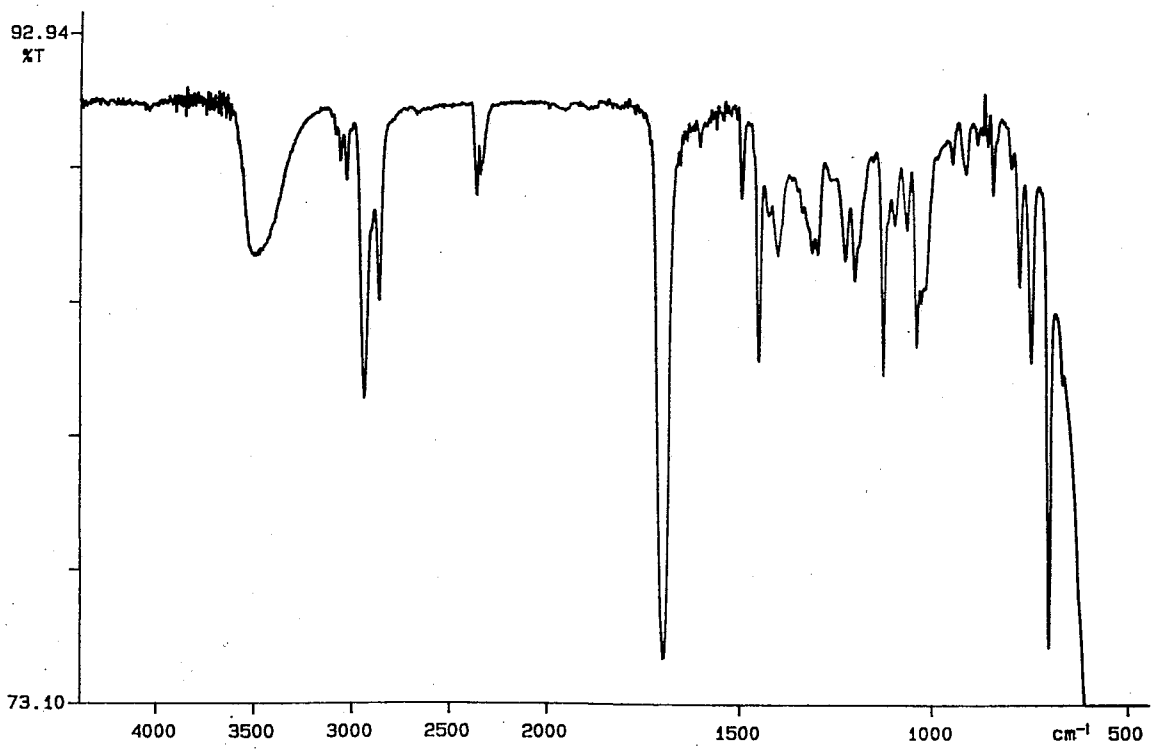


GE NMR
QE PLUS
SKI215.004
28OCT92
SEK-I-215
RF 5
1H CDCl3
OPERATOR: SEK

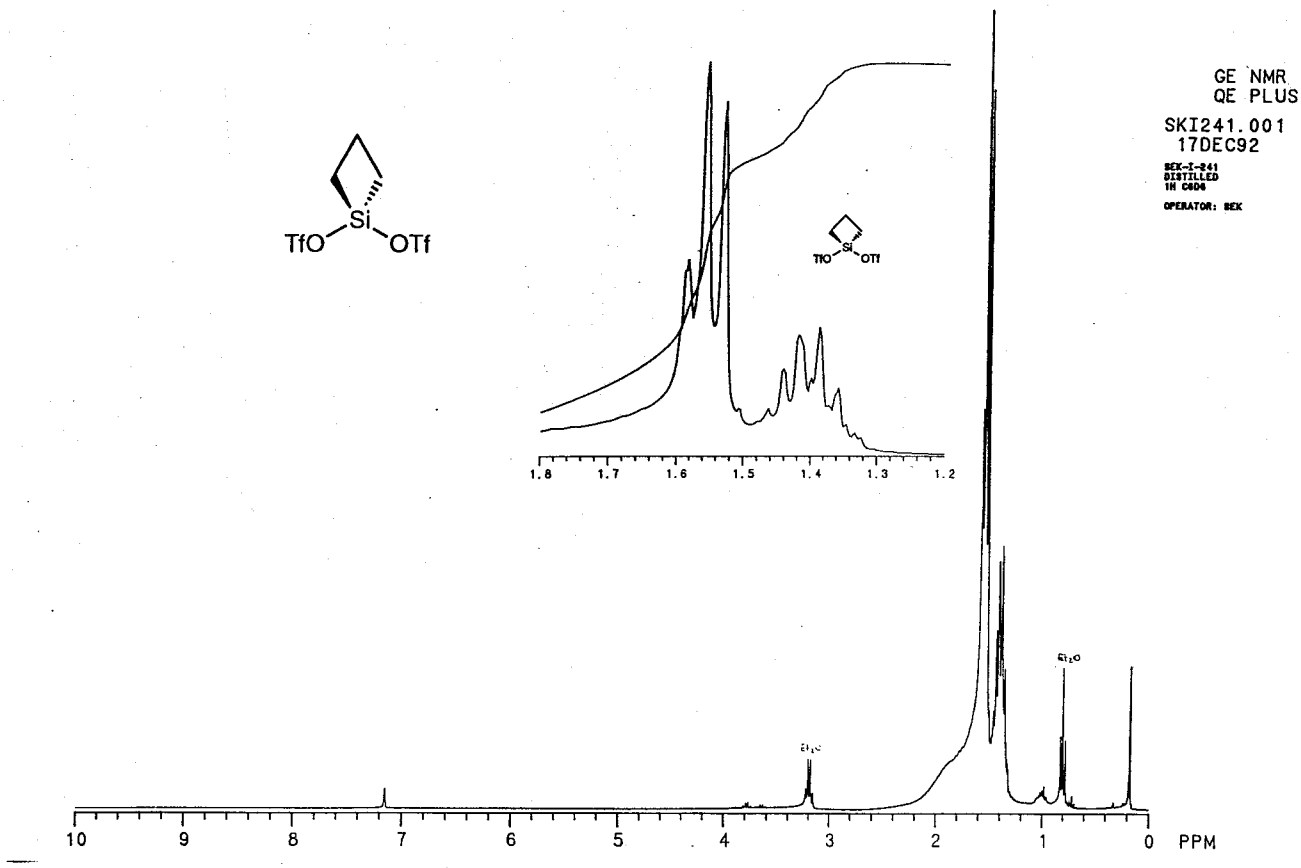
GE NMR
QE PLUS
SKI228.005
19NOV92
SEK-I-228
RF 5
1H CDCl3
OPERATOR: SEK

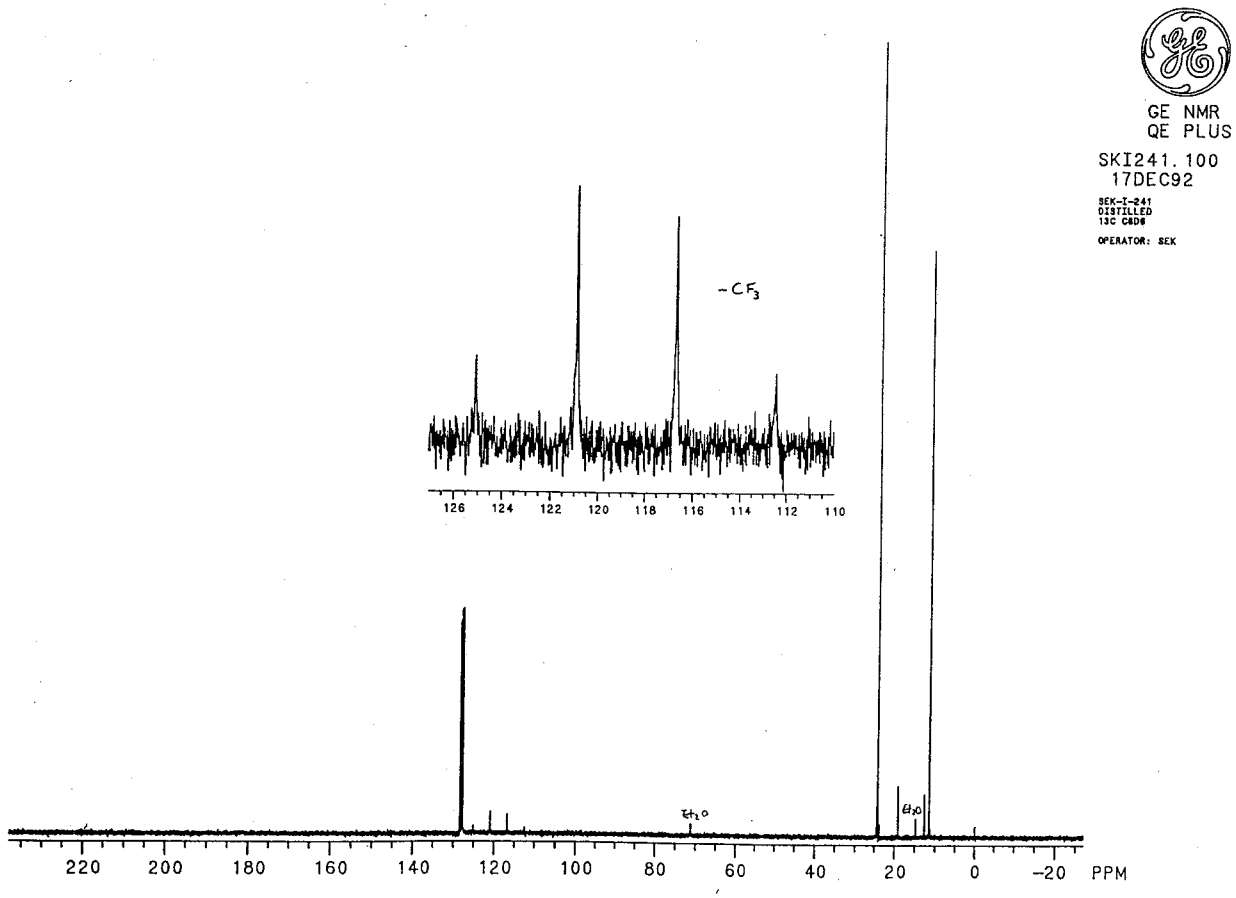


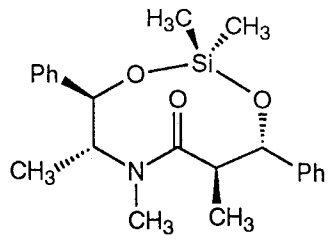




92/12/20 16:10
X: 4 scans, 4.0cm-1, flat
SEK-I-215 rf5 anti


TfO
Si
OTf
GE NMR
QE PLUS
SKI241.001
17DEC92
SEK-I-241
DISTILLED
1H C6D6
OPERATOR: SEK
1.8 1.7 1.6 1.5 1.4 1.3 1.2
Et2O
10 9 8 7 6 5 4 3 2 1 0 PPM

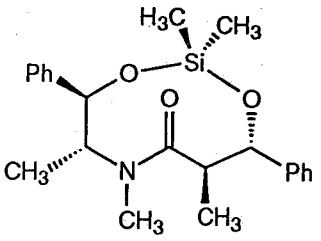

GE NMR
QE PLUS
SKI241.100
17DEC92
SEK-I-241
DISTILLED
13C C6D6
OPERATOR: SEK
-CF3
126 124 122 120 118 116 114 112 110
Et2O
220 200 180 160 140 120 100 80 60 40 20 0 -20 PPM



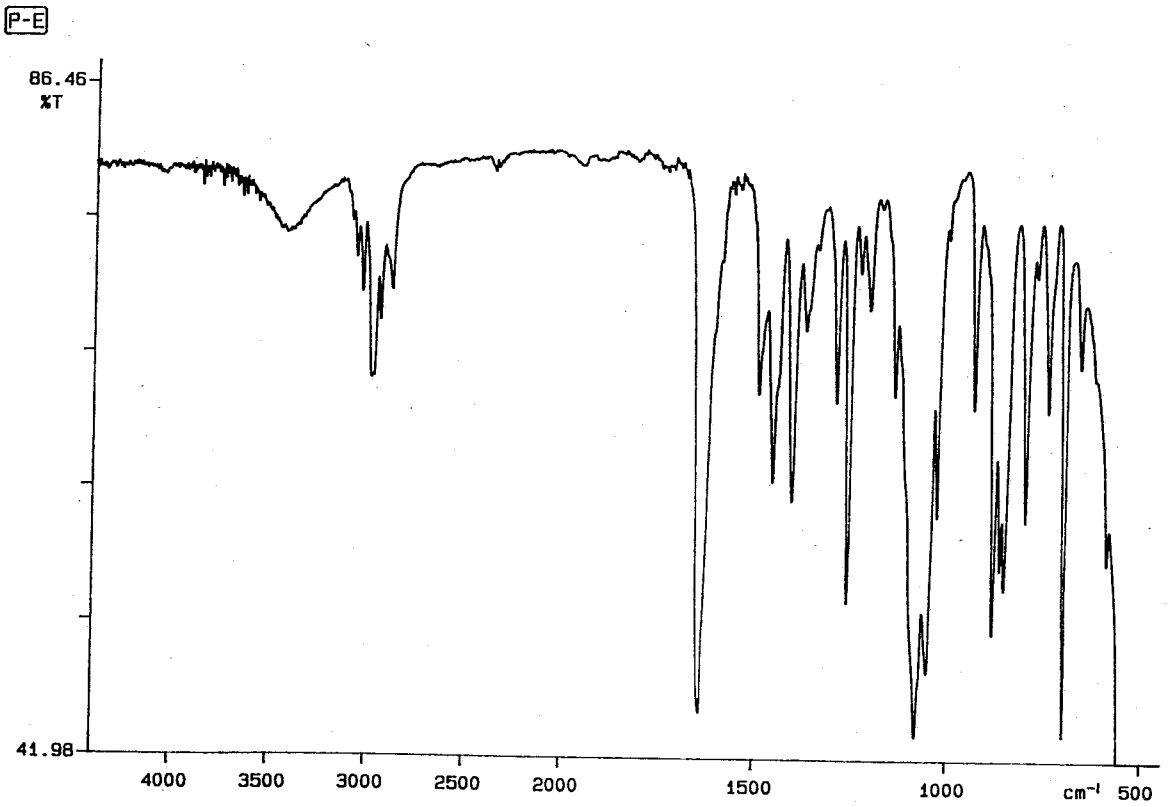
35
(2*R*, 3*S*)

GE NMR
QE PLUS
SK2047.002
09MAY93
SEK-II-47
SPOT 2
1H CDCL3
OPERATOR: SEK

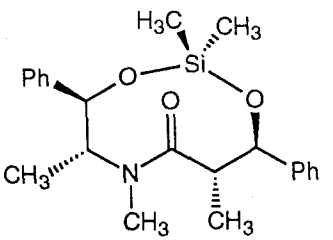
9 8 7 6 5 4 3 2 1 0 −1 PPM



35
(2R, 3S)



93/07/21 16:14
X: 1 scan, 4.0cm-1, flat
SEK-II-47 sp 2



36
(2*S*, 3*R*)

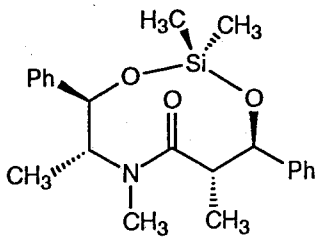
GE NMR
QE PLUS

SK2047.001
09MAY93

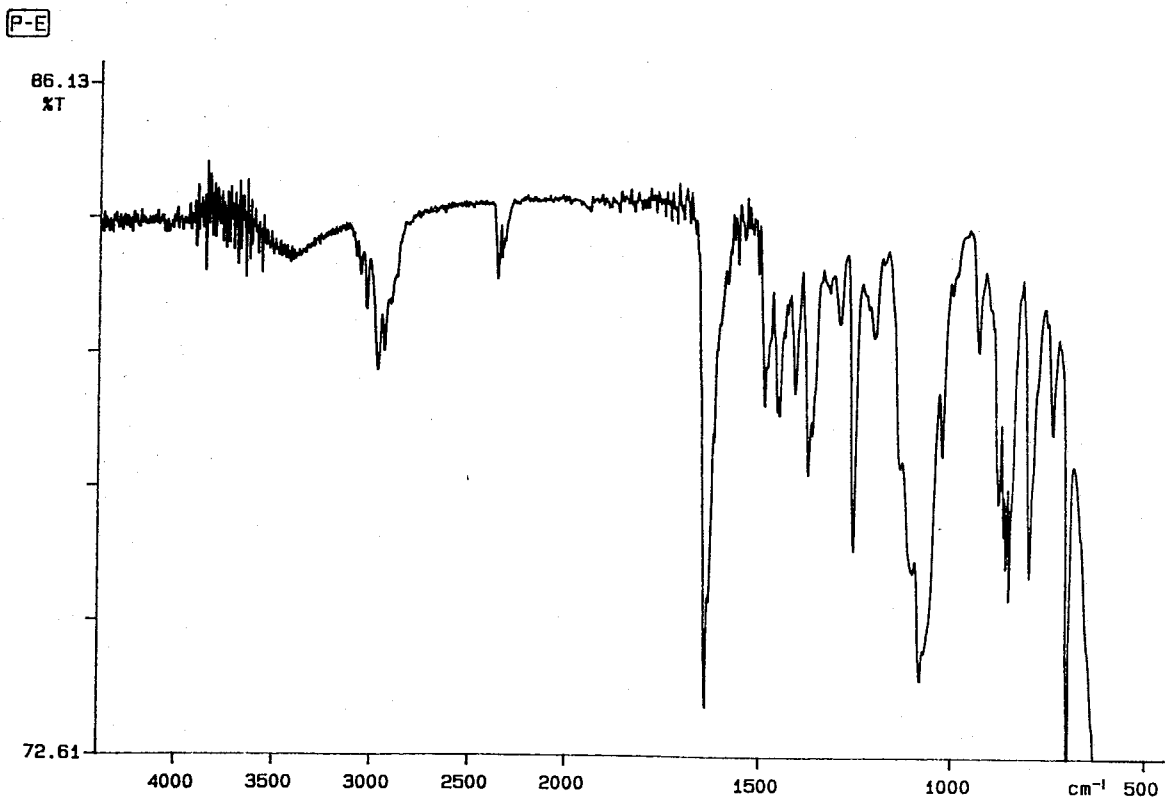
SEK-II-47
SPOT 1
1H CDCL3

OPERATOR: SEK

9 8 7 6 5 4 3 2 1 0 −1

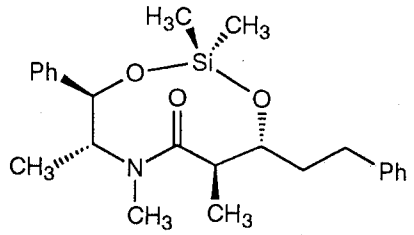


36
(2*S*, 3*R*)

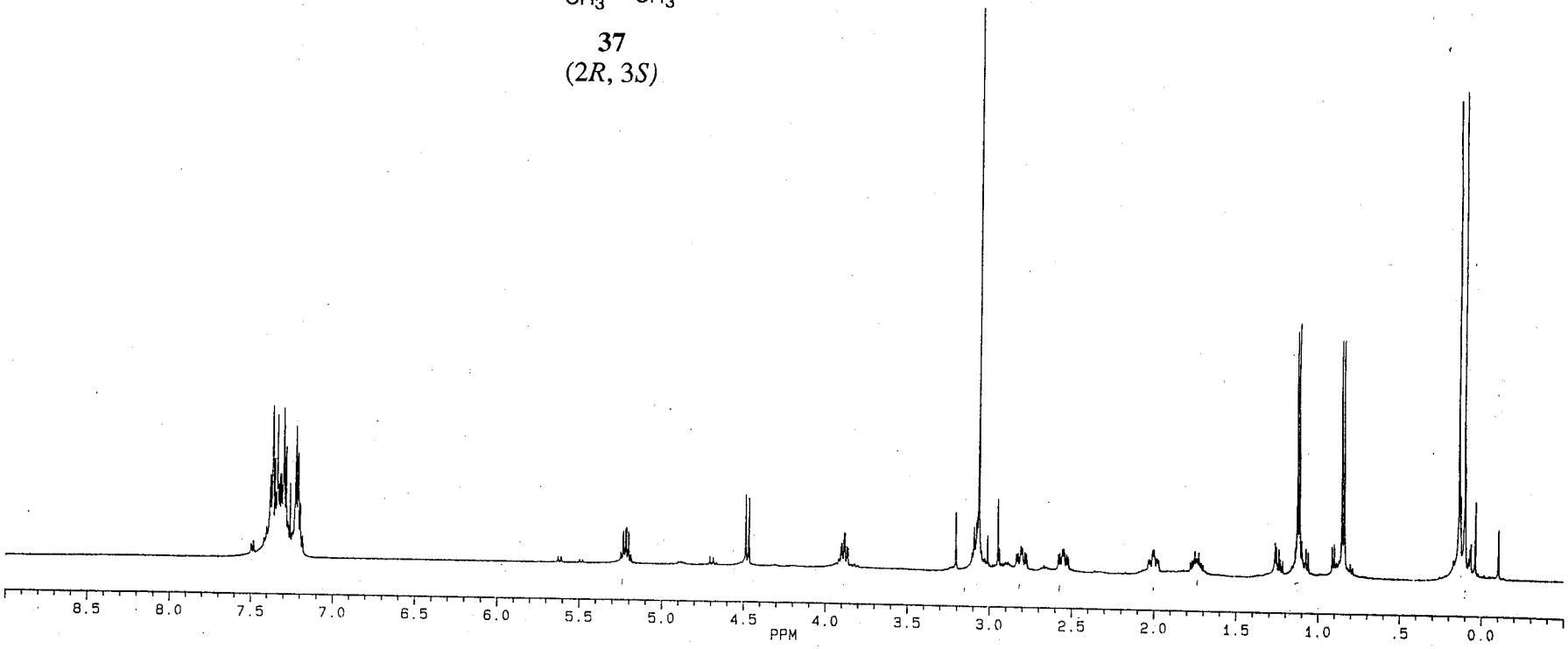


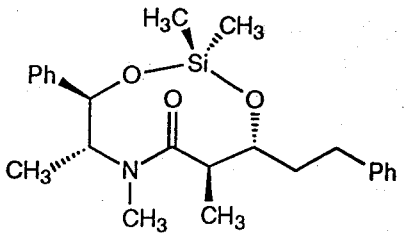
93/07/21 16:07
X: 1 scan, 4.0cm-1, flat
SEK-II-47 sp 1

SEK-II-37 SP 2 CDCL3

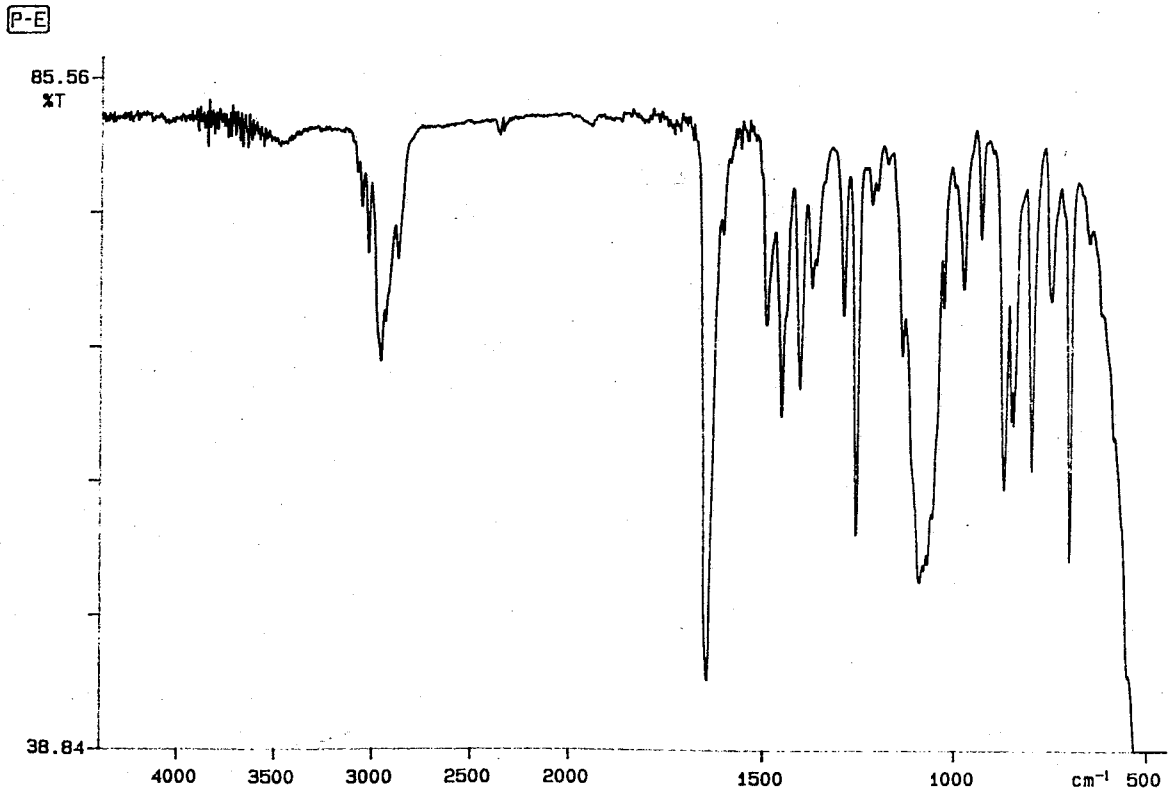


37
(2*R*, 3*S*)

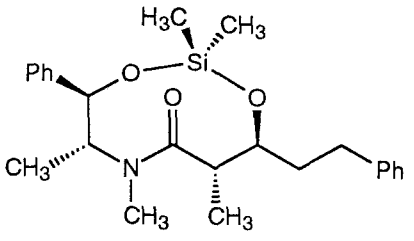




37
(2R, 3S)



93/04/28 11:34
X: 1 scan, 4.0cm-1, flat
SEK-II-37 sp2



38
(2*S*, 3*R*)

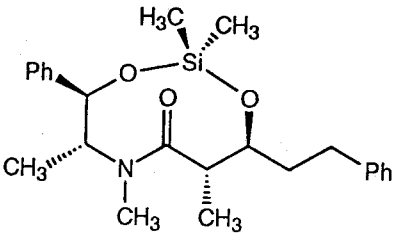
GE NMR
QE PLUS

SK2046.001
08MAY93

SEK-II-46
SPOT 1
1H CDCL3

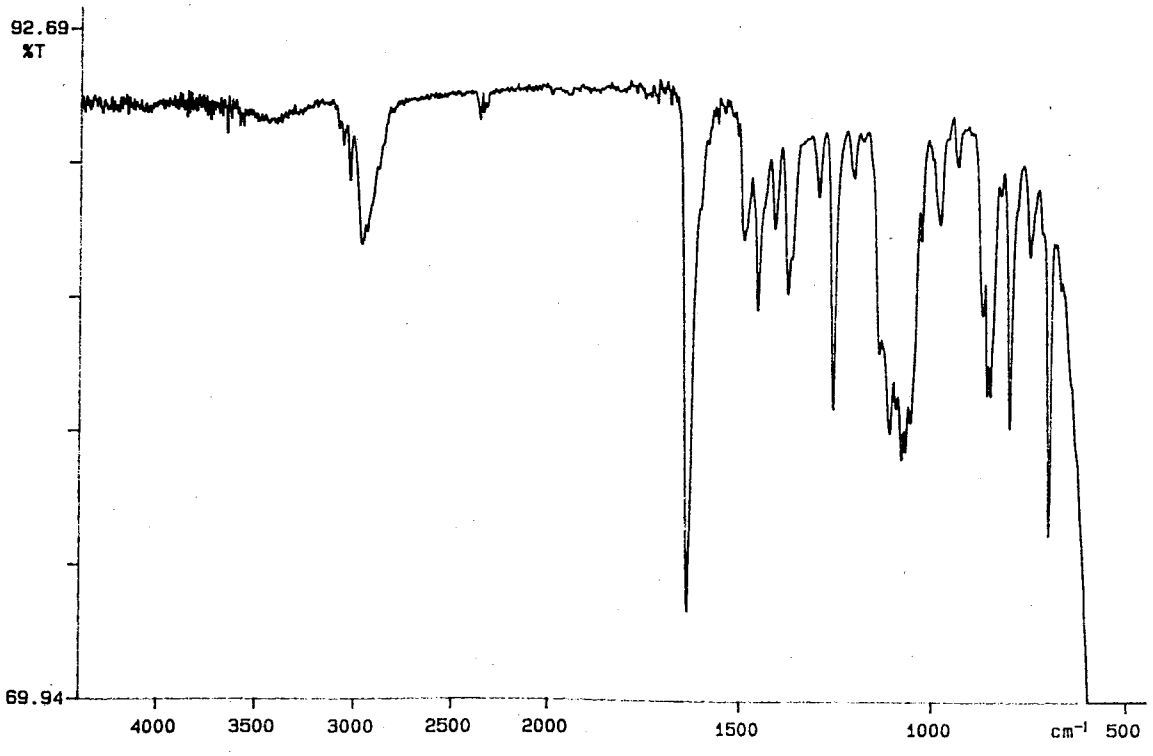
OPERATOR: SEK

9 8 7 6 5 4 3 2 1 0 −1 PF

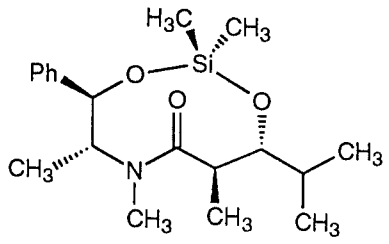


38
(2*S*, 3*R*)

SK2040.100
02MAY93
SEK-II-40
SPOT 1
13C CDCL3
OPERATOR: SEK



93/05/03 10:20
X: 1 scan, 4.0cm-1, flat
SEK-II-40 sp1



39
(2*R*, 3*S*)

GE NMR
QE PLUS

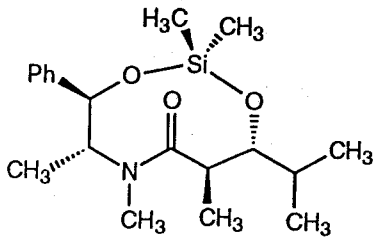
SK2061.002
21MAY93

SEK-II-61
SPOT 2
1H CDCL3

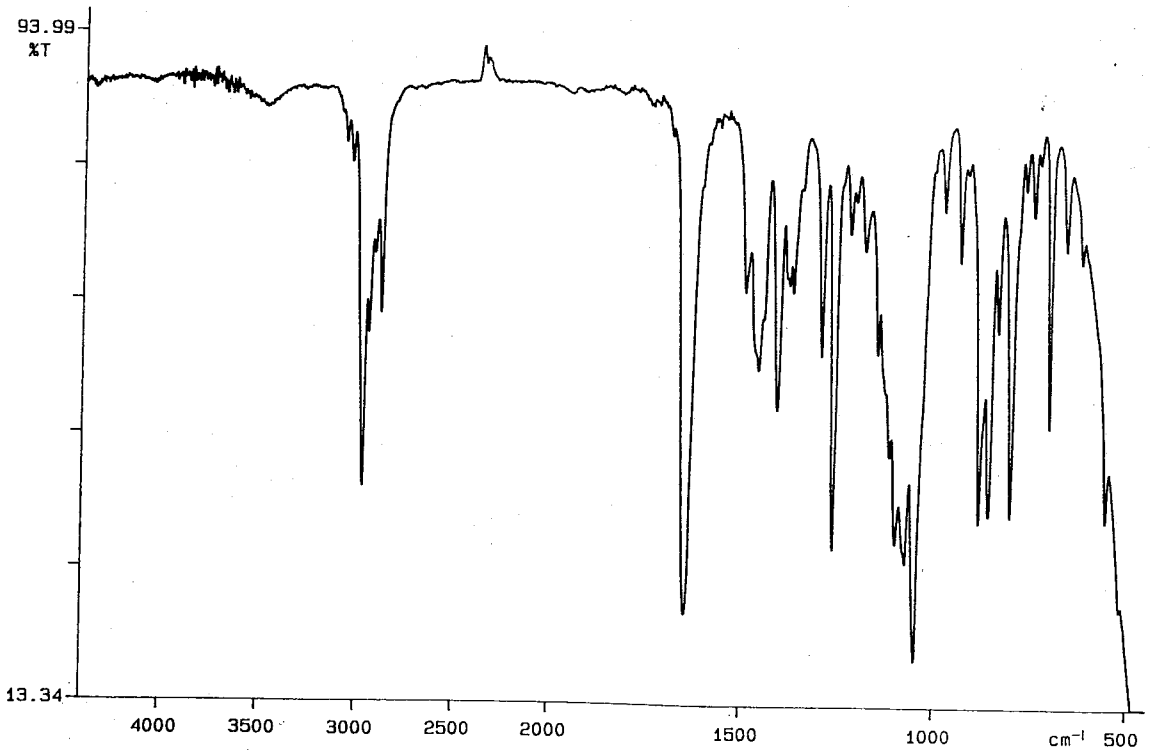
OPERATOR: SEK

9 8 7 6 5 4 3 2 1 0 −1 PPM

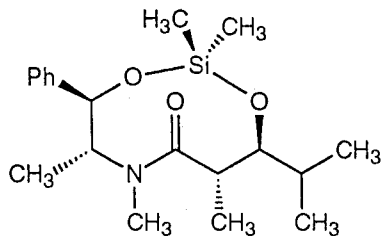
SK2061.200
27MAY93
SEK-II-61
SPOT 2
13C CDCL3
OPERATOR SEK



39
(2R, 3S)



93/05/22 16:10
X: 1 scan, 4.0cm-1, flat
SEK-II-61 sp2



40
(2*S*, 3*R*)

GE NMR
QE PLUS

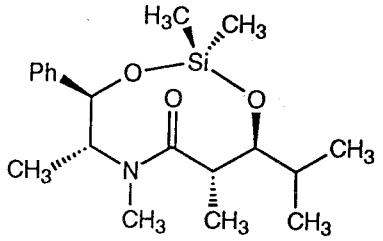
SK2061.001
21MAY93

SEK-II-61
SPOT 1
1H CDCL3

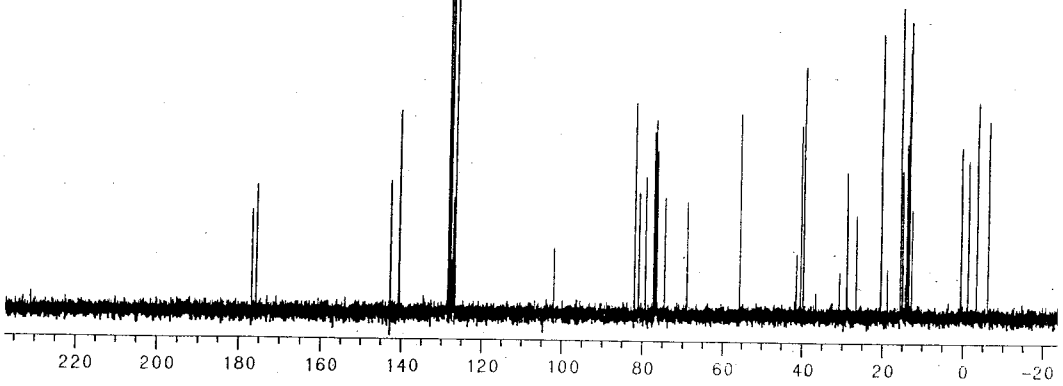
OPERATOR: SEK

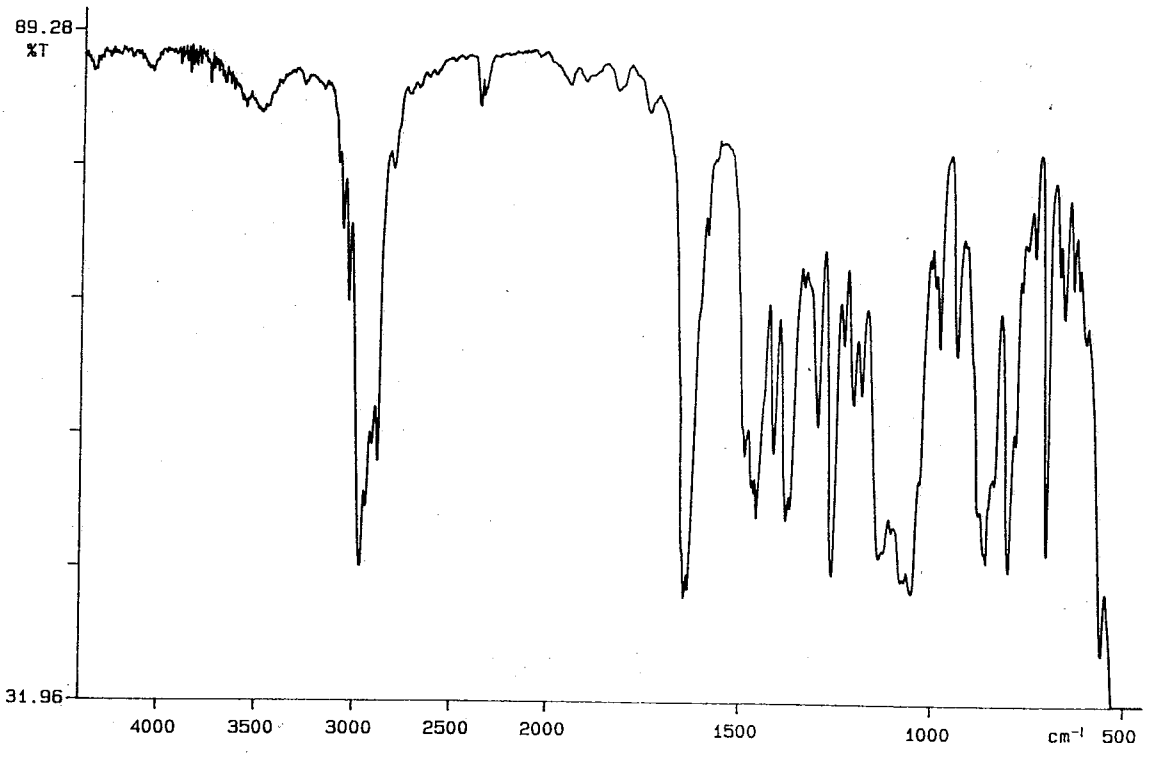
9 8 7 6 5 4 3 2 1 0 −1 PF

SK2061.100
27MAY93
SEK-II-61
SPOT 1
13C CDCL3
OPERATOR: SEK

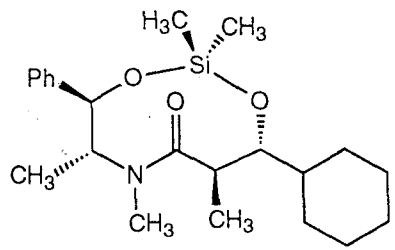


40
(2*S*, 3*R*)





93/05/22 15:50
X: 1 scan, 4.0cm-1
SEK-II-61 sp1



41
(2*R*, 3*S*)

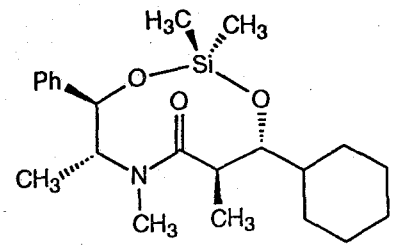
GE NMR
QE PLUS

SK2065.002
26MAY93

SEK-II-65
SPOT 2
1H CDCL3

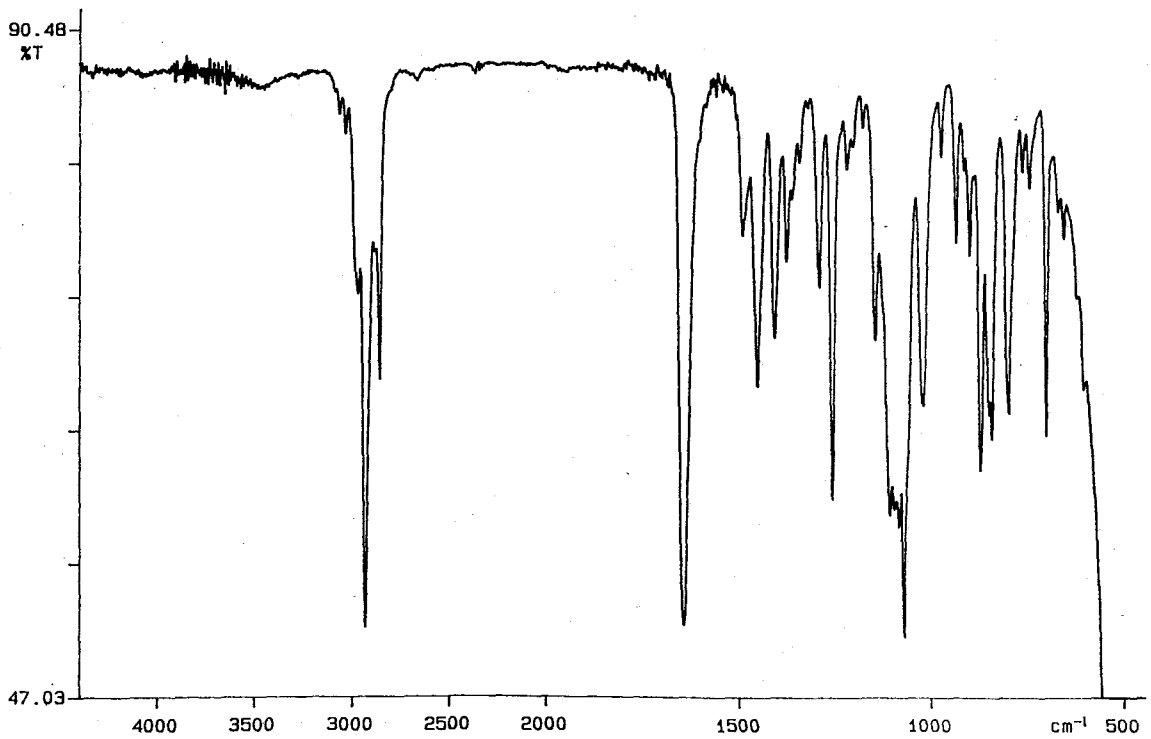
OPERATOR: SEK

9 8 7 6 5 4 3 2 1 0 −1 PPM

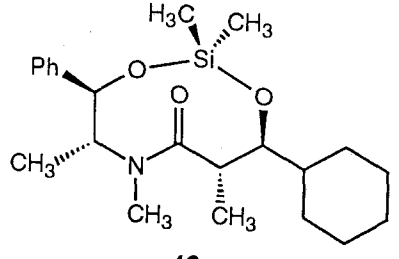


41
(2R, 3S)

2065.200
7MAY93
11-65
2
CDCL3
ATOR: SEK



93/05/27 11:36
X: 1 scan, 4.0cm-1, flat
SEK-II-65 sp2



42
(2*S*, 3*R*)

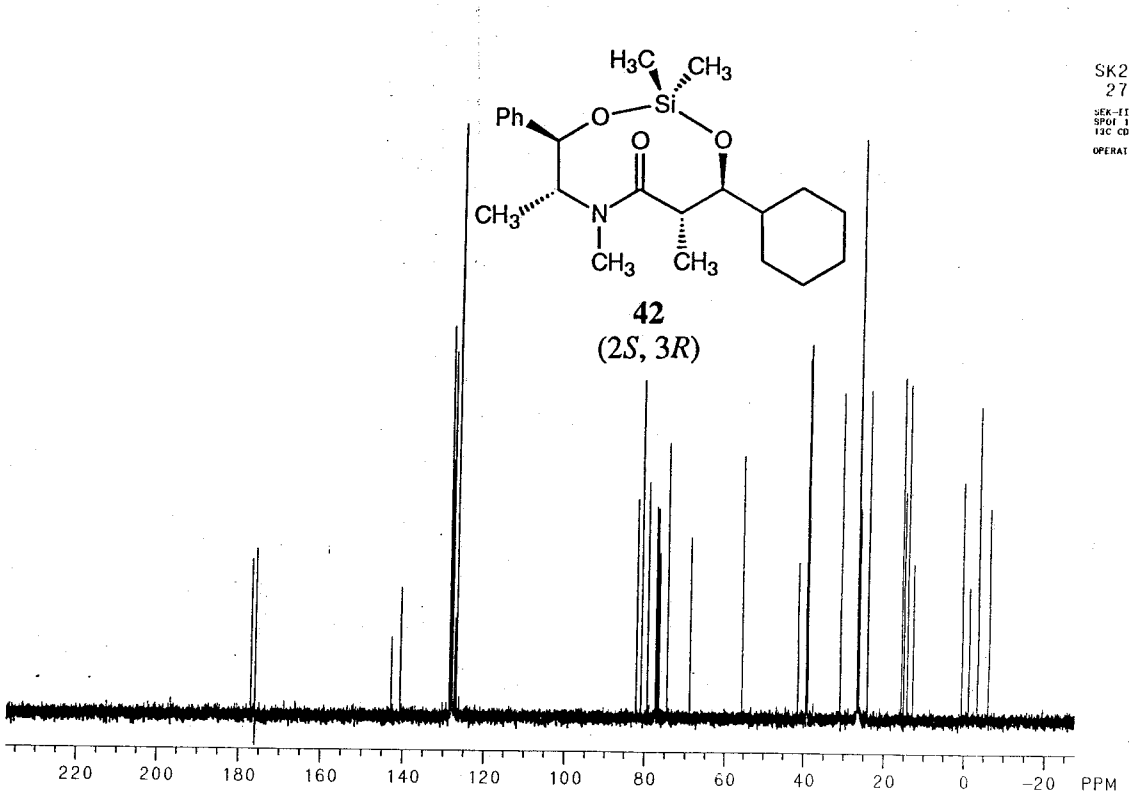
GE NMR
QE PLUS

SK2065.001
26MAY93

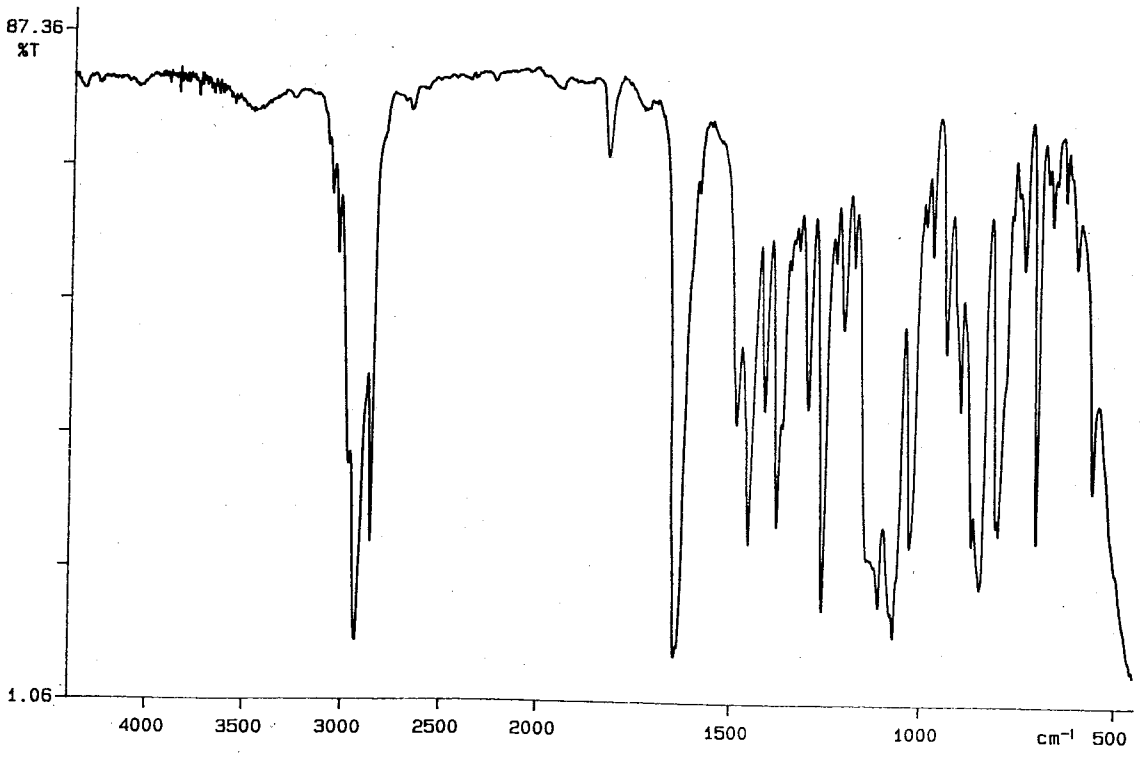
SEK-II-65
SPOT 1
1H CDCL3

OPERATOR: SEK

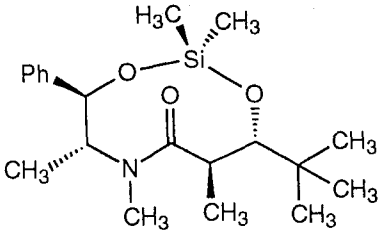
9 8 7 6 5 4 3 2 1 0 −1 PPM



42
(2*S*, 3*R*)



93/05/27 11:27
X: 1 scan, 4.0cm-1, flat
SEK-II-65 sp1



43
(2R, 3S)

GE NMR
QE PLUS

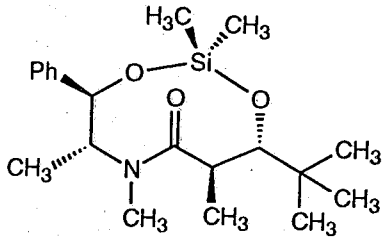
SK2074.020
24JUN93

SEK-II-74
SPOT 2
1H CDCL3

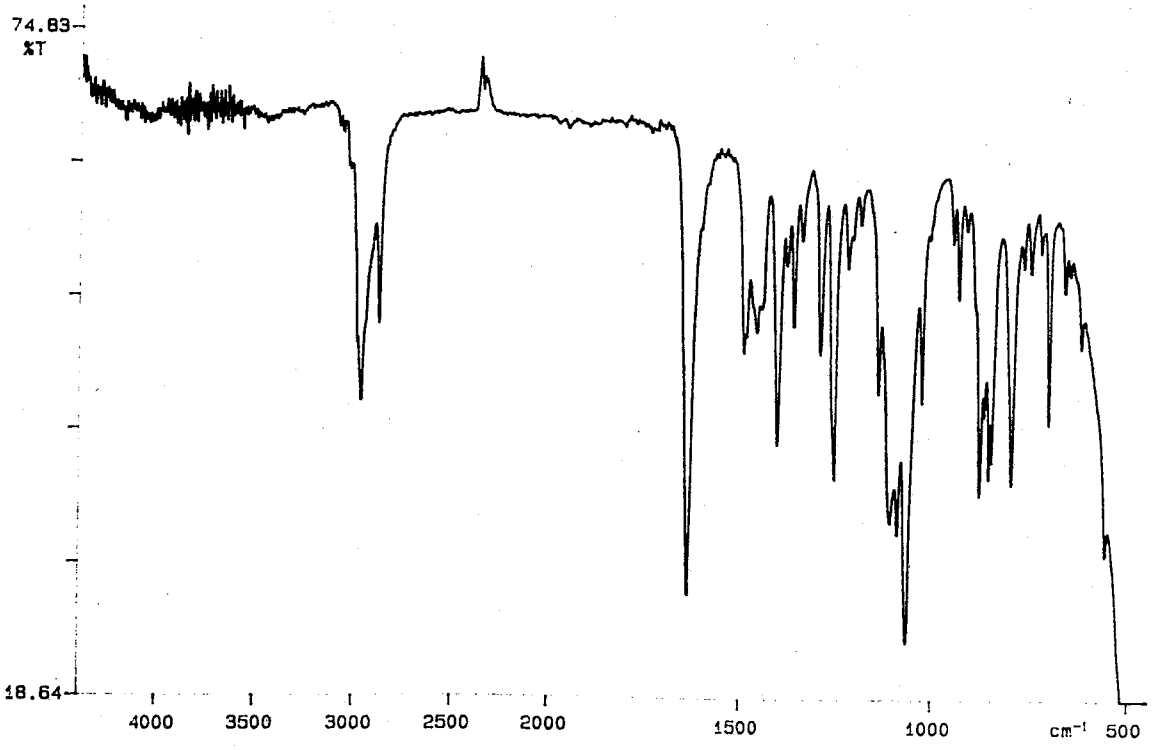
OPERATOR: SEK

8 7 6 5 4 3 2 1 0 −1 PPM

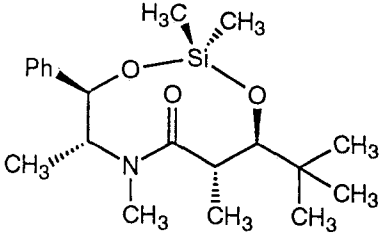
SEK-II-74
spot 2
CDCl3



43
(2R, 3S)



93/06/24 13:34
X: 1 scan, 4.0cm-1, flat
SEK-II-74 sp2



44
(2*S*, 3*R*)

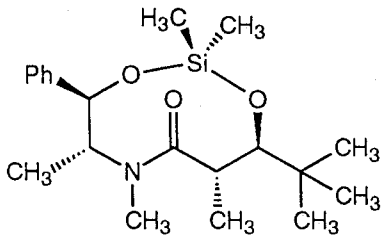
GE NMR
QE PLUS

SK2074.004
24JUN93

SEK-II-74
CRYSTALS FROM 002&003
1H C6D6 AGAIN

OPERATOR: SEK

9 8 7 6 5 4 3 2 1 0 −1 PPM



44
(2*S*, 3*R*)

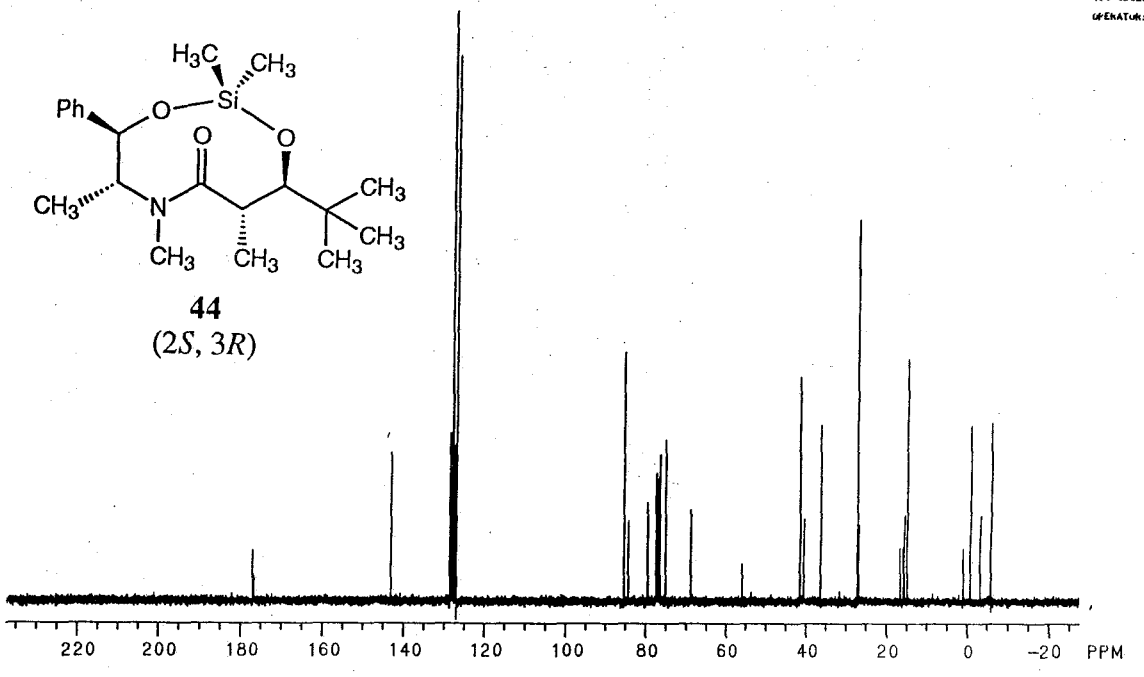
GE NMR
QE PLUS

SK2074.003
24JUN93

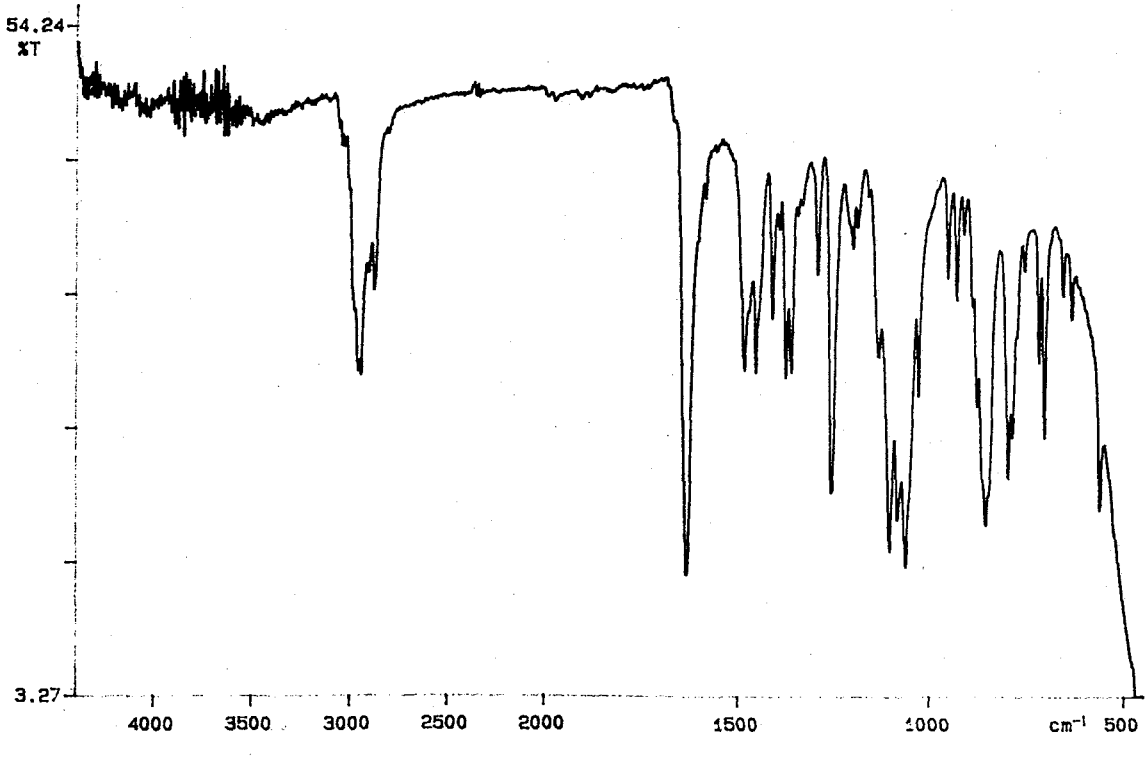
SEK-II-74
CRYSTALS
FRESH made
1H CDCL3

OPERATOR: SEK

9 8 7 6 5 4 3 2 1 0 −1 PPM



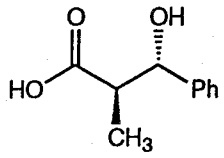
44
(2*S*, 3*R*)



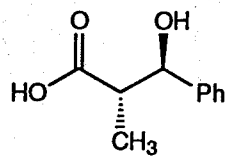
93/06/24 13:22
X: 1 scan, 4.0cm-1, flat
SEK-II-74 sp1

GE NMR
QE PLUS
SK2124.001
07OCT93
SEK-II-124
ACID
1H CDCL3
OPERATOR: SEK
(2R, 3S)
(2S, 3R)
9
8
7
6
5
4
3
2
1
0
−1
PPM

253

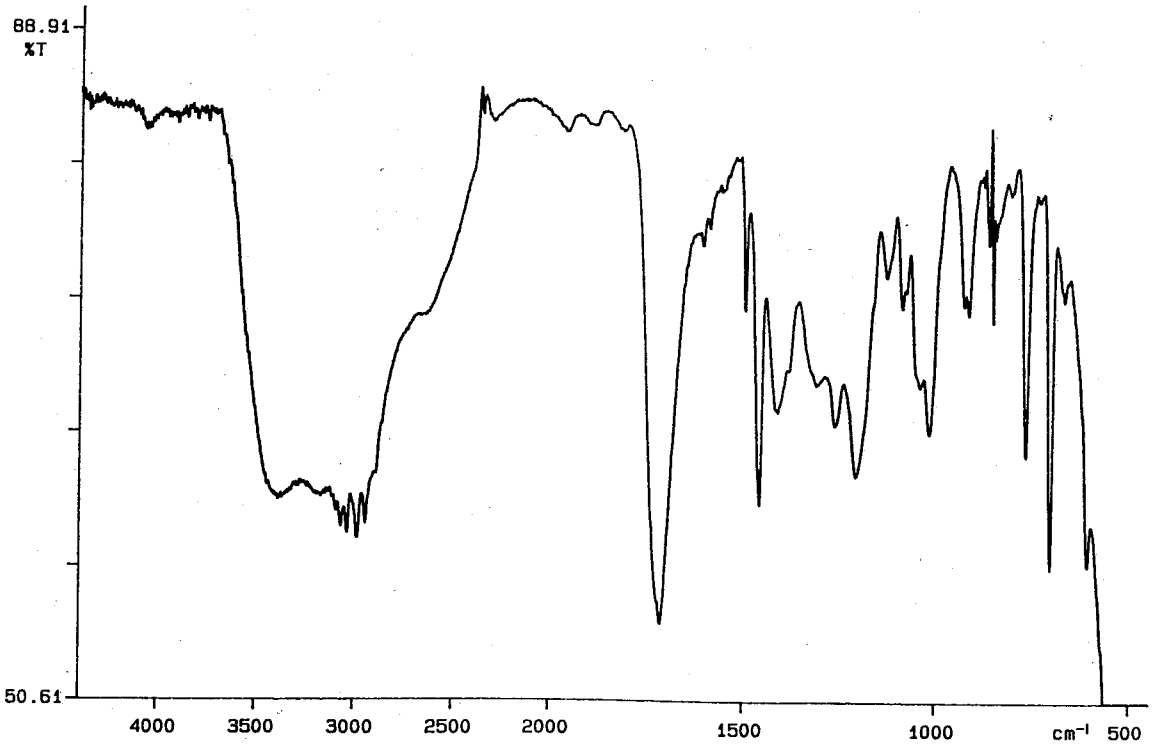


(2*R*, 3*S*)

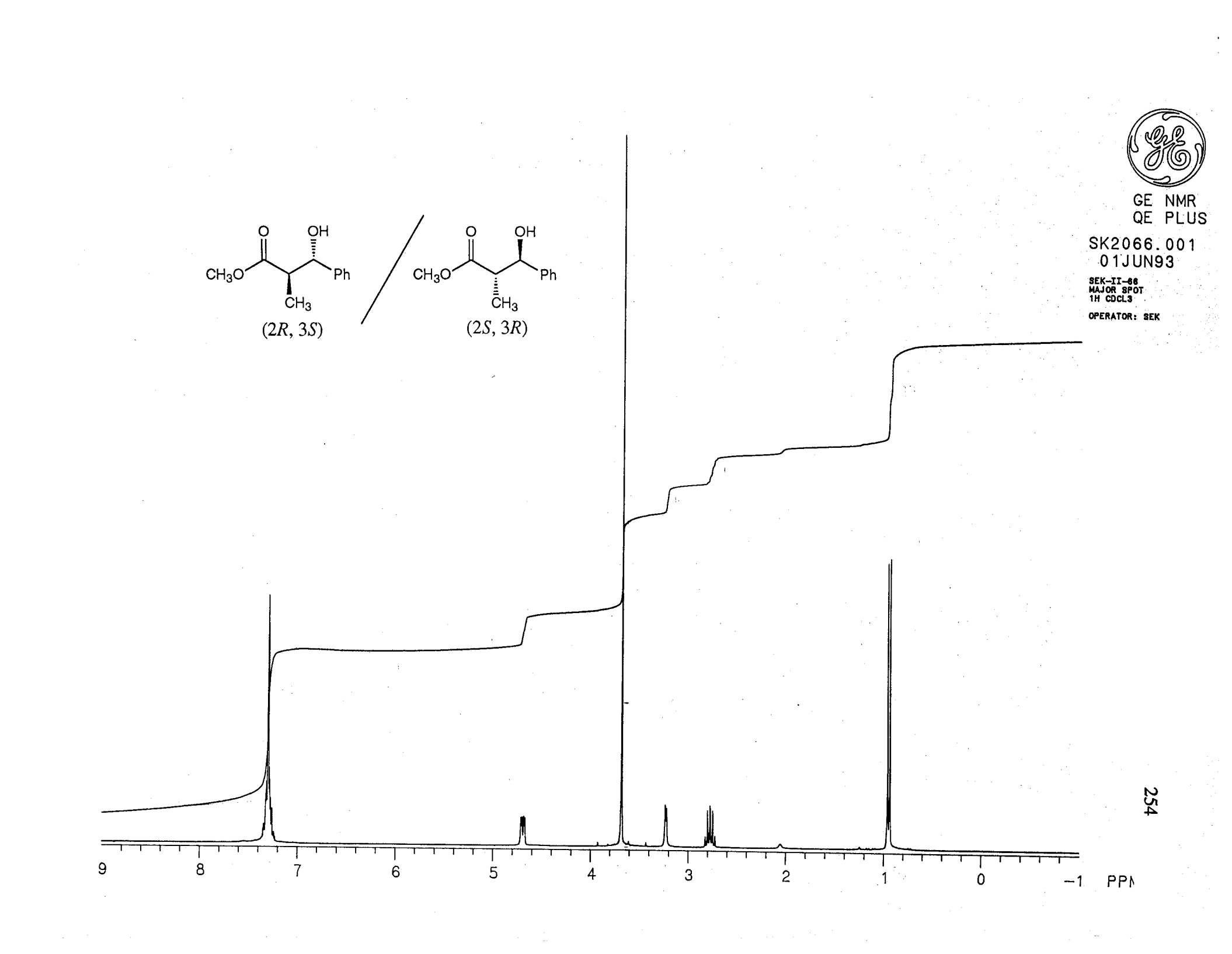


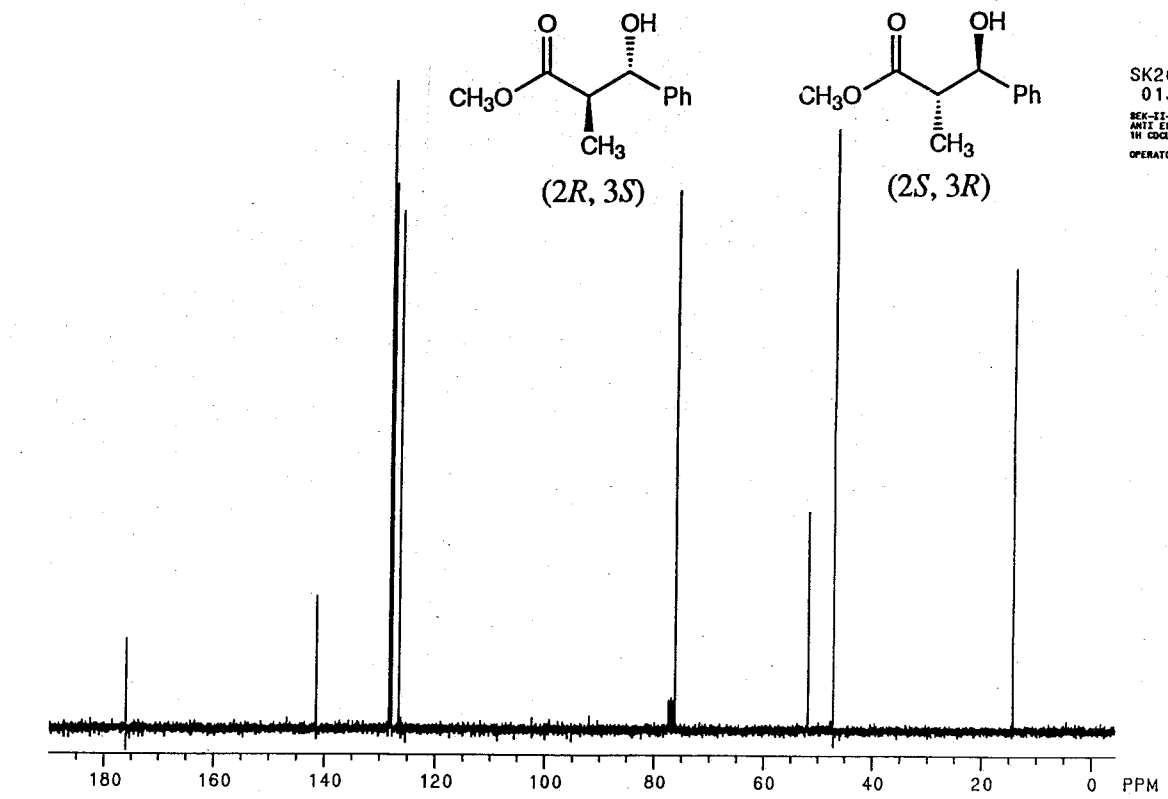
(2*S*, 3*R*)

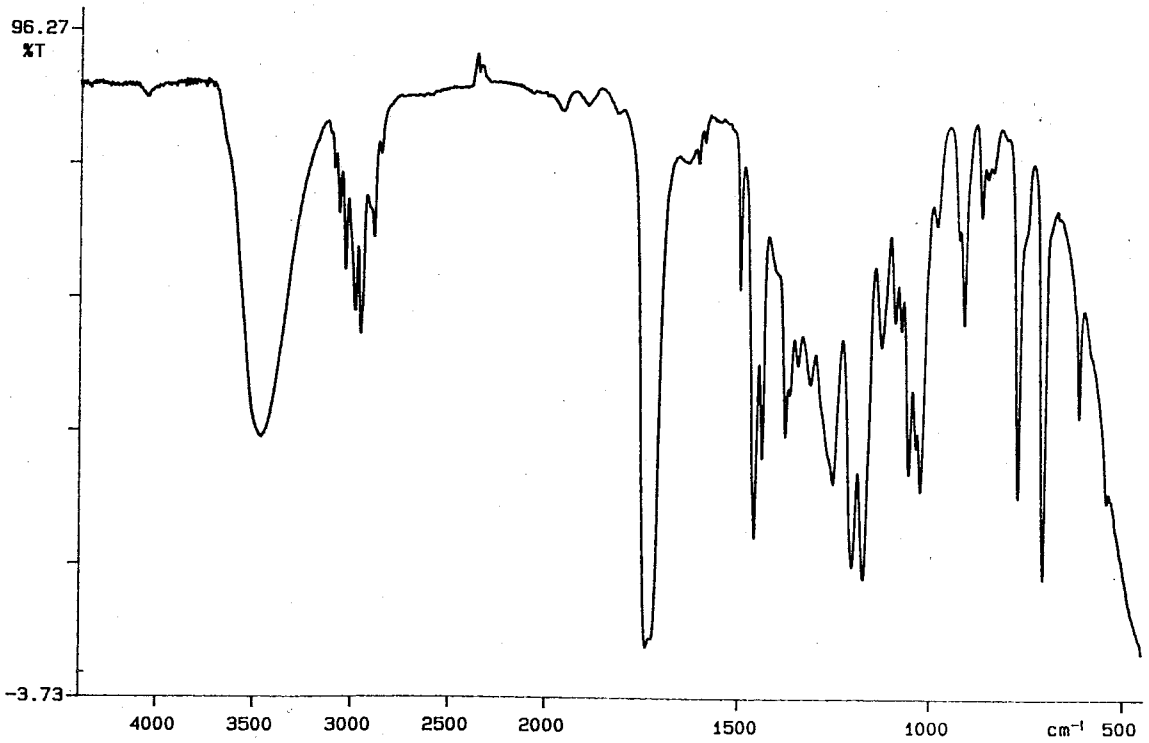
9.100
R93



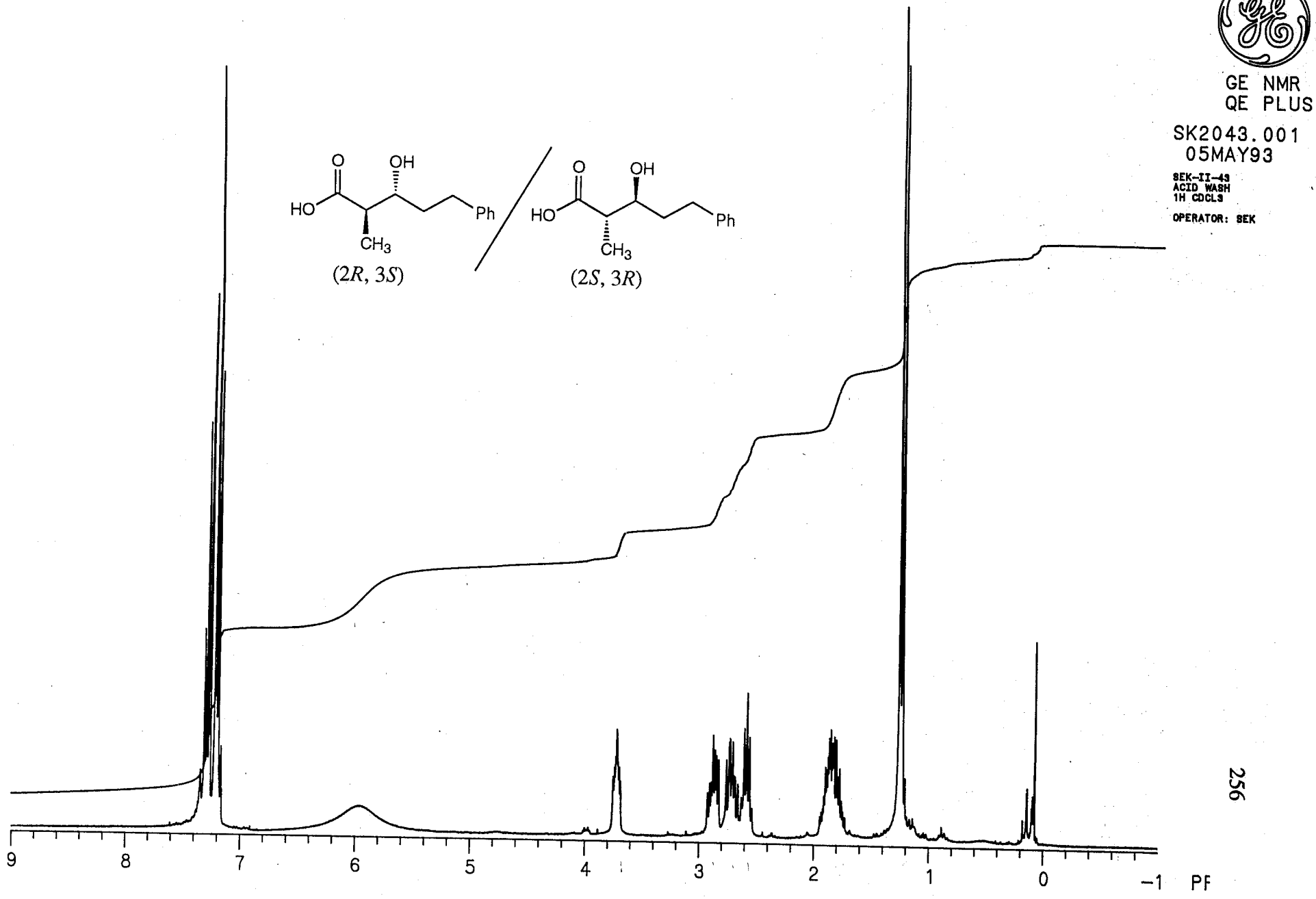
93/03/06 19:12
Z: 1 scan, 4.0cm-1, flat
SEK-I-289 acid

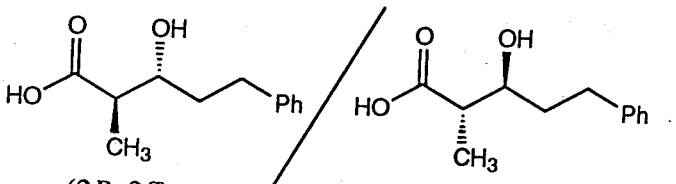

O
OH
CH3O
Ph
CH3
(2R, 3S)
O
OH
CH3O
Ph
CH3
(2S, 3R)
GE NMR
QE PLUS
SK2066.001
01JUN93
SEK-II-66
MAJOR SPOT
1H CDCL3
OPERATOR: SEK
9
8
7
6
5
4
3
2
1
0
−1
PPM



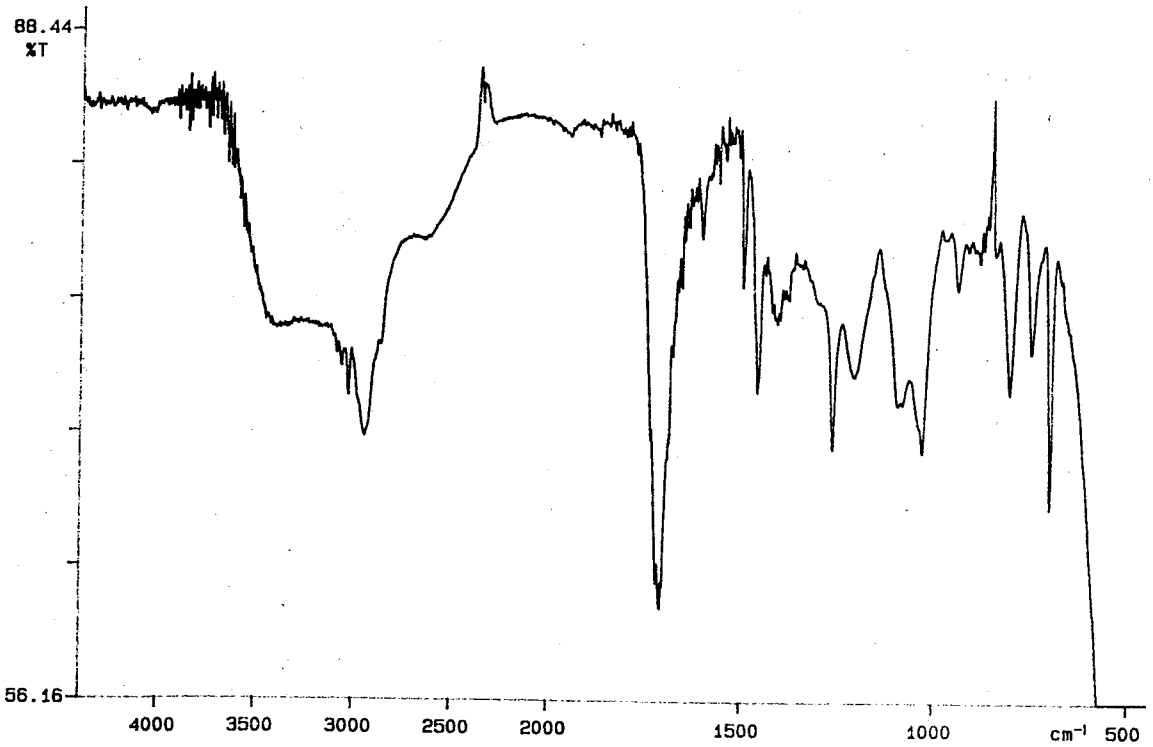


93/06/01 10:15
X: 1 scan, 4.0cm-1, flat
SEK-II-66 ester

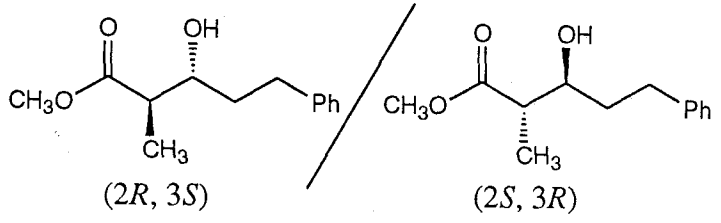

GE NMR
QE PLUS
SK2043.001
05MAY93
SEK-II-43
ACID WASH
1H CDCL3
OPERATOR: SEK
HO
O
OH
Ph
CH3
(2R, 3S)
(2S, 3R)
9
8
7
6
5
4
3
2
1
0
−1
PF



(2*R*, 3*S*) (2*S*, 3*R*)



93/05/04 21:07
X: 1 scan, 4.0cm-1, flat
SEK-II-44 acid



(2*R*, 3*S*)

(2*S*, 3*R*)

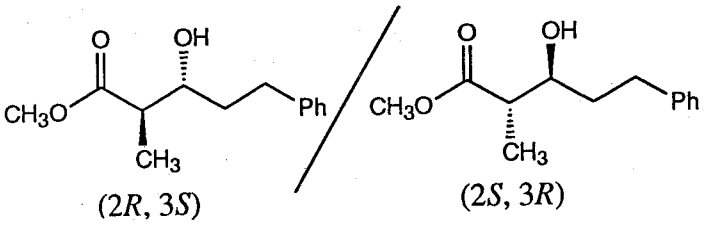
GE NMR
QE PLUS

SK2050.003
20OCT93

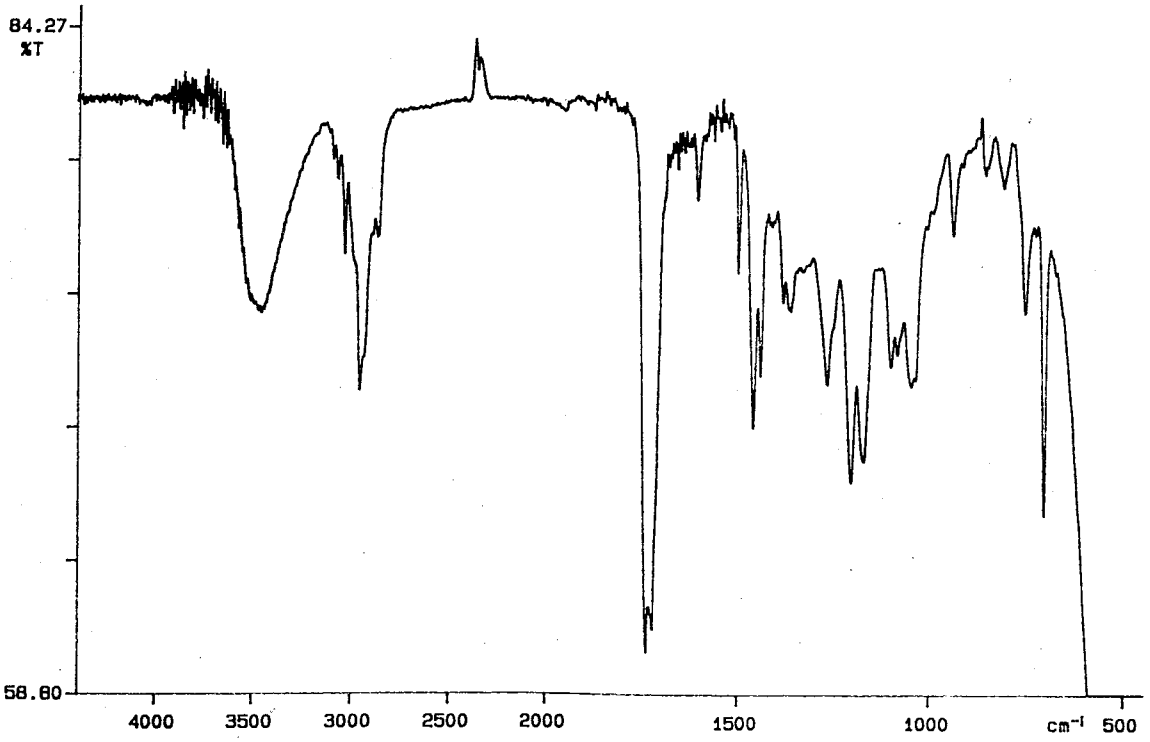
SEK-II-50
ME ESTER
1H CDCL3

OPERATOR: SEK

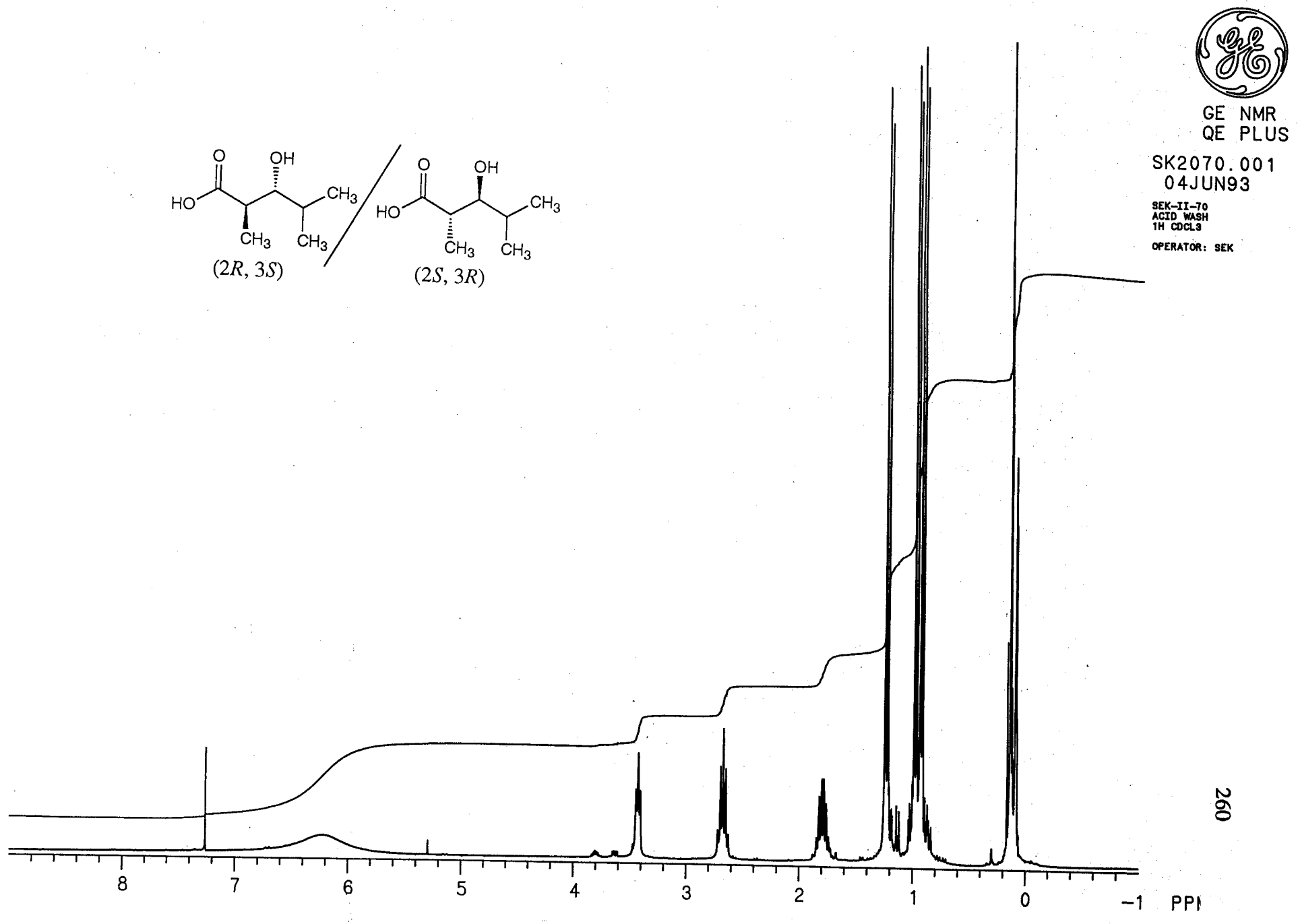
SK2050.300
23OCT93

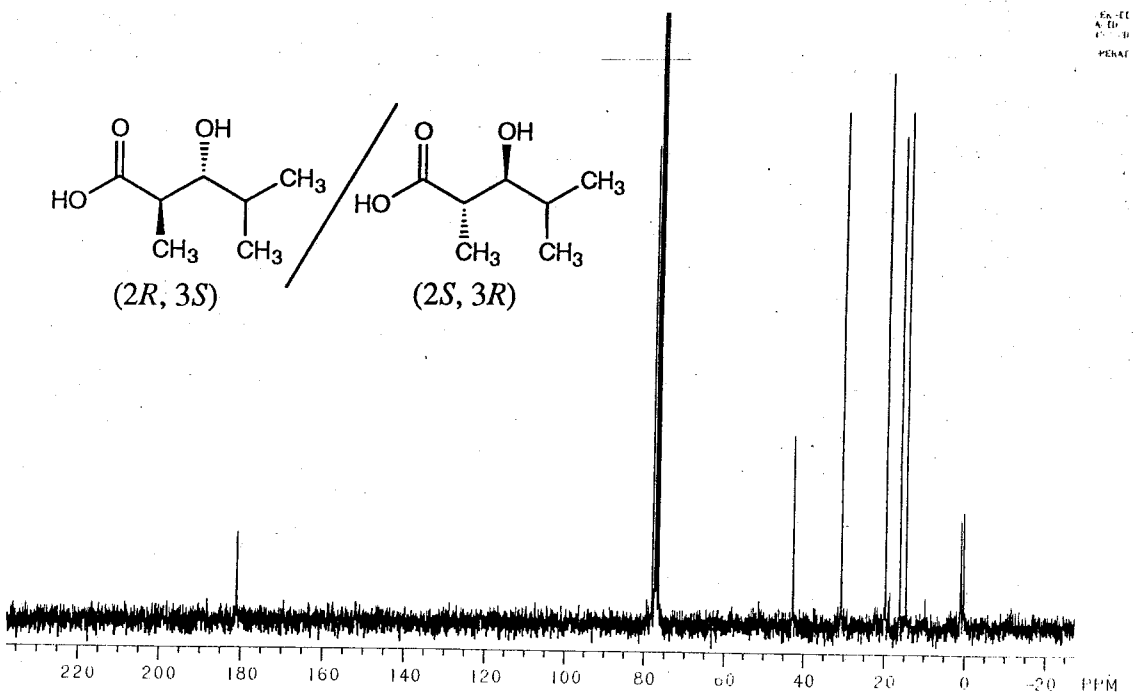


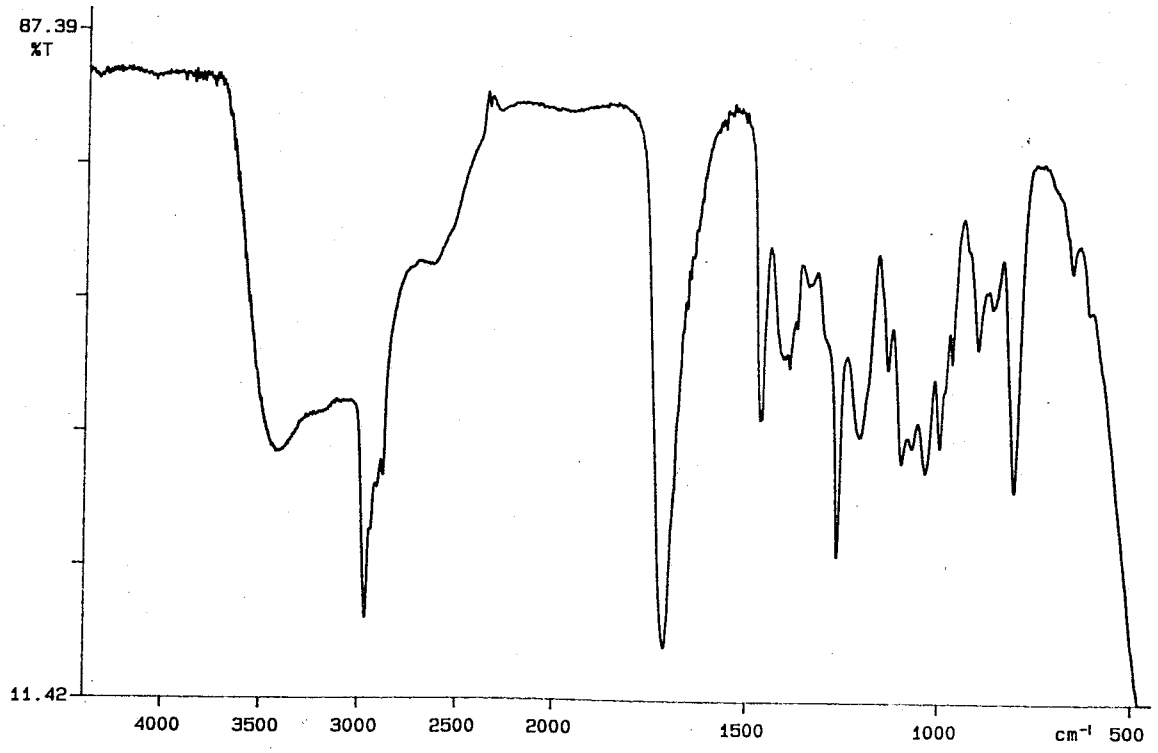
(2*R*, 3*S*) (2*S*, 3*R*)



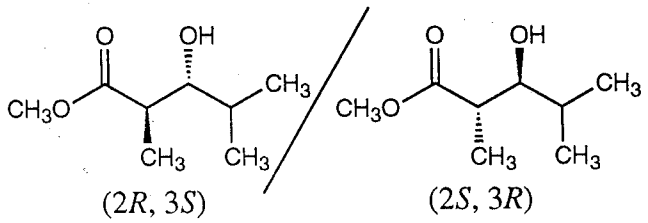
93/10/19 21:32
X: 1 scan, 4.0cm-1, flat
SEK-II-50 ester


GE NMR
QE PLUS
SK2070.001
04JUN93
SEK-II-70
ACID WASH
1H CDCL3
OPERATOR: SEK
(2R, 3S)
(2S, 3R)
8
7
6
5
4
3
2
1
0
−1
PPM
260





93/06/05 12:26
X: 1 scan, 4.0cm-1, flat
SEK-II-70 acid



(2*R*, 3*S*)

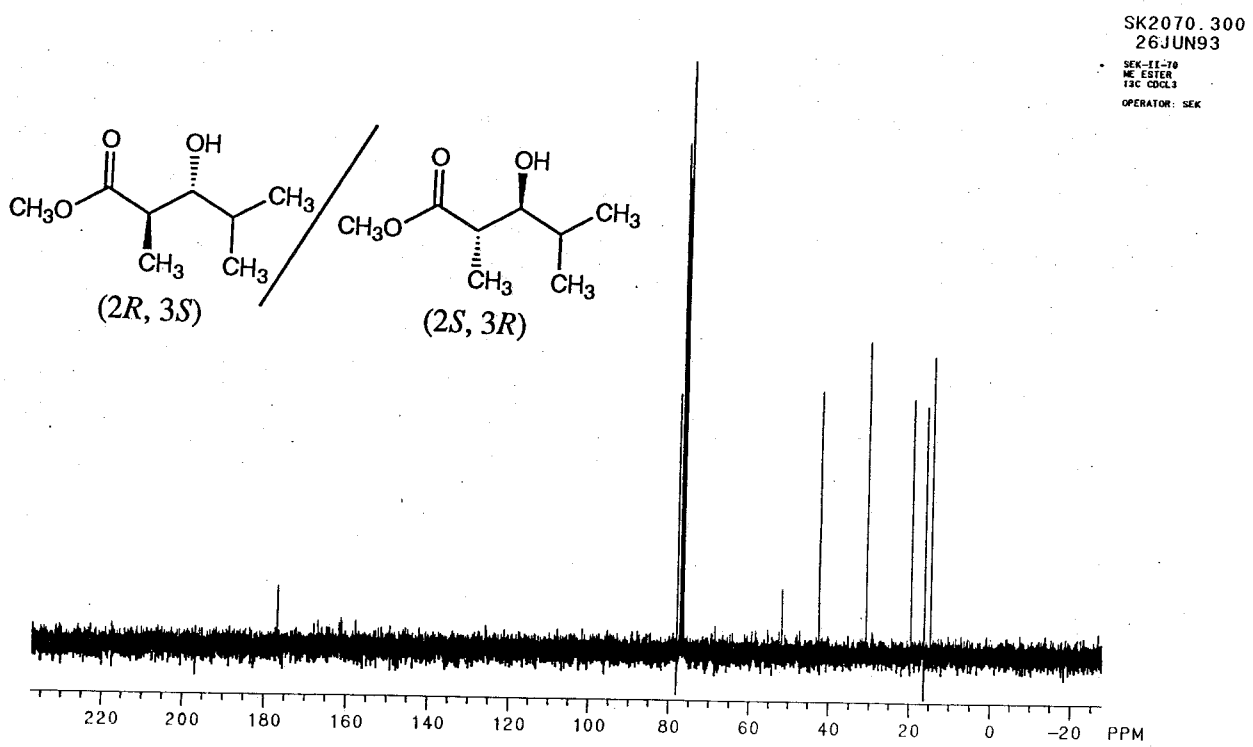
(2*S*, 3*R*)

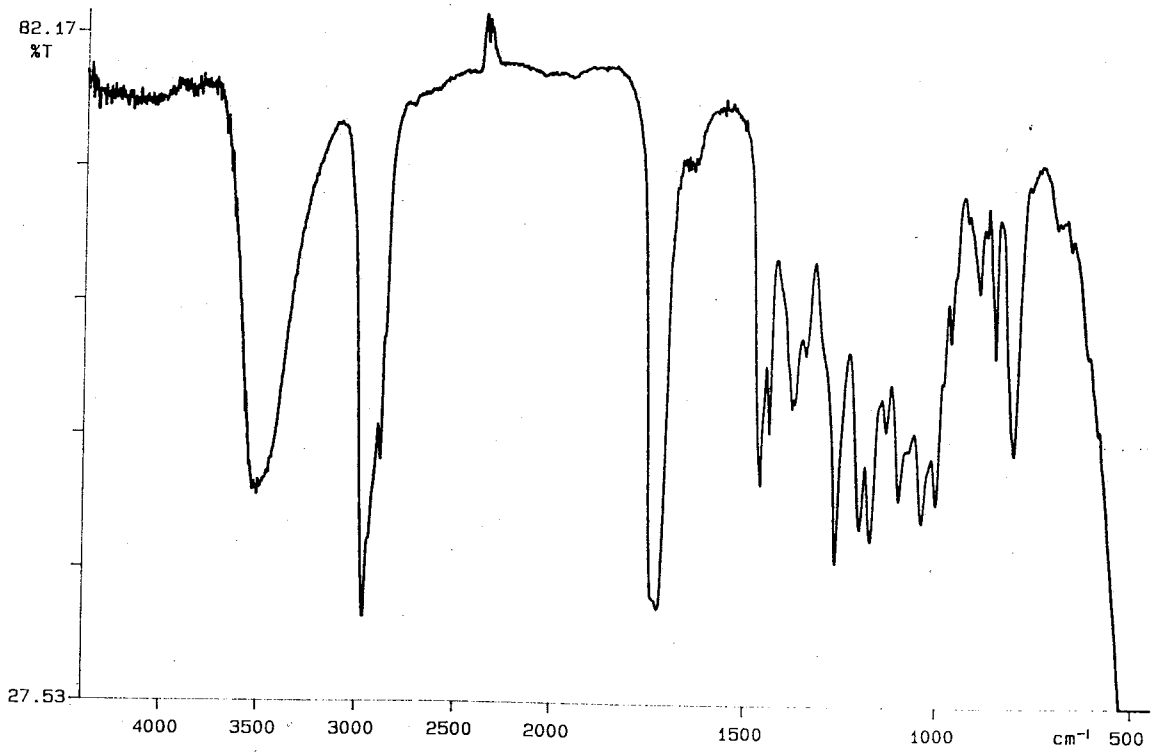
GE NMR
QE PLUS

SK2070.004
25JUN93

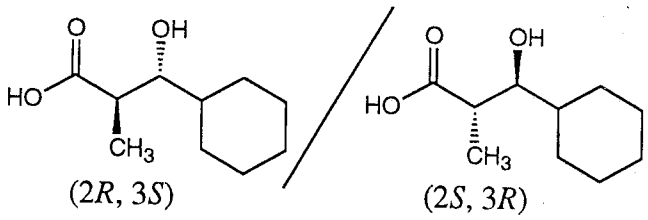
SEK-II-70
ME ESTER COLUMNED
1H CDCL3

OPERATOR: SEK





93/06/25 15:45
X: 1 scan, 4.0cm-1, flat
SEK-II-70 ester



(2*R*, 3*S*)

(2*S*, 3*R*)

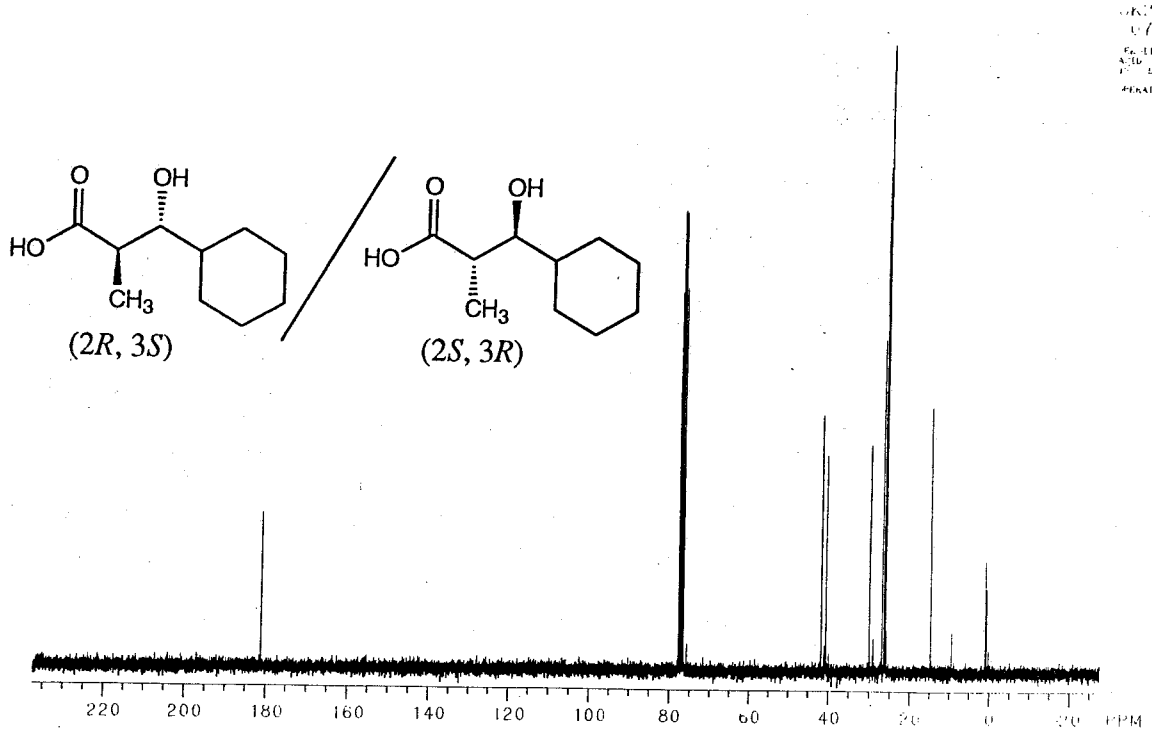
GE NMR
QE PLUS

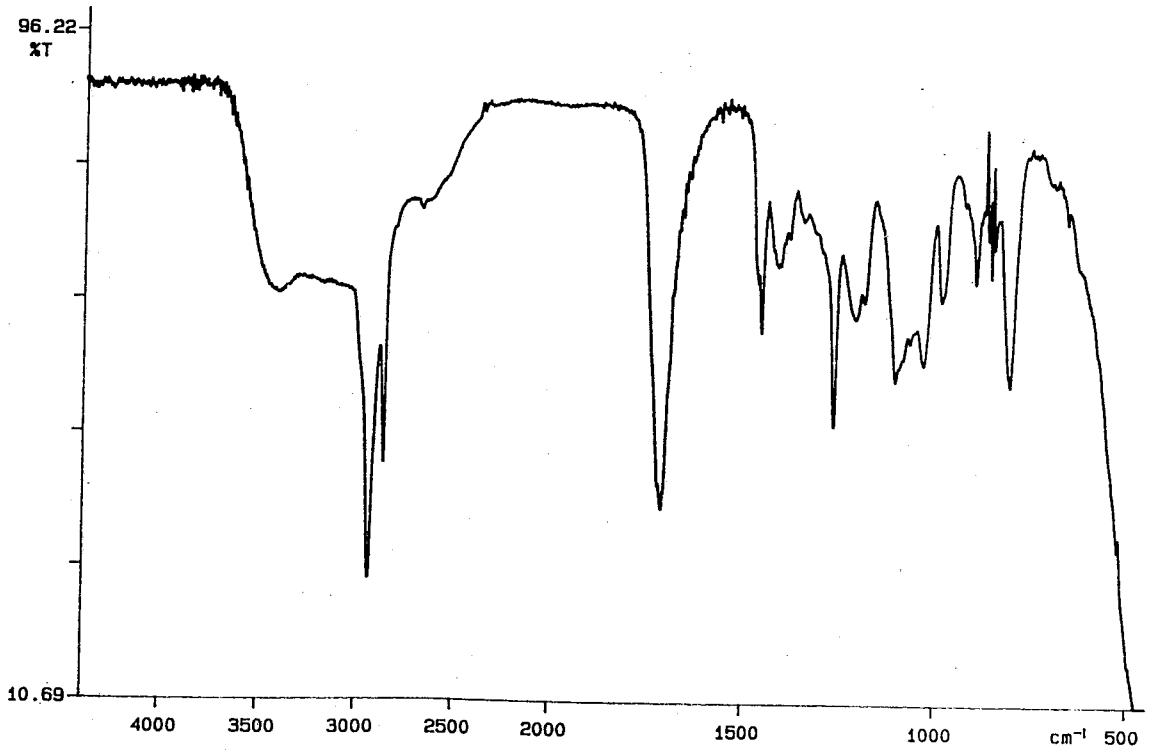
SK2072.001
07JUN93

SEK-II-72
ACID WASH
1H (DCL)

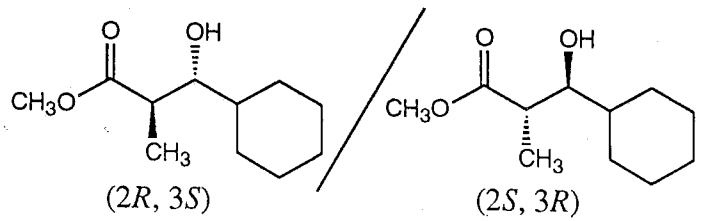
OPERATOR: SEK

9 8 7 6 5 4 3 2 1 0 −1 PPM





93/06/09 09:36
X: 1 scan, 4.0cm-1
SEK-II-72 acid



(2*R*, 3*S*)

(2*S*, 3*R*)

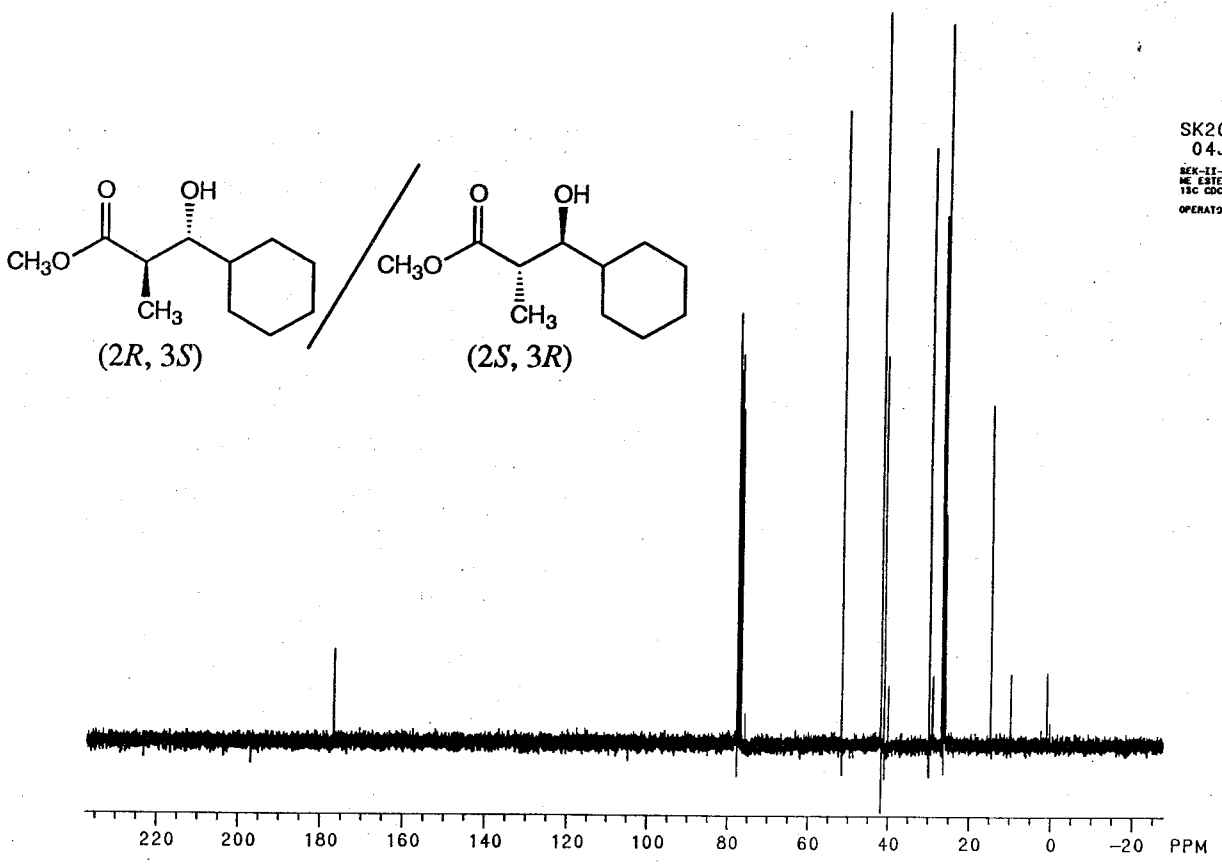
GE NMR
QE PLUS

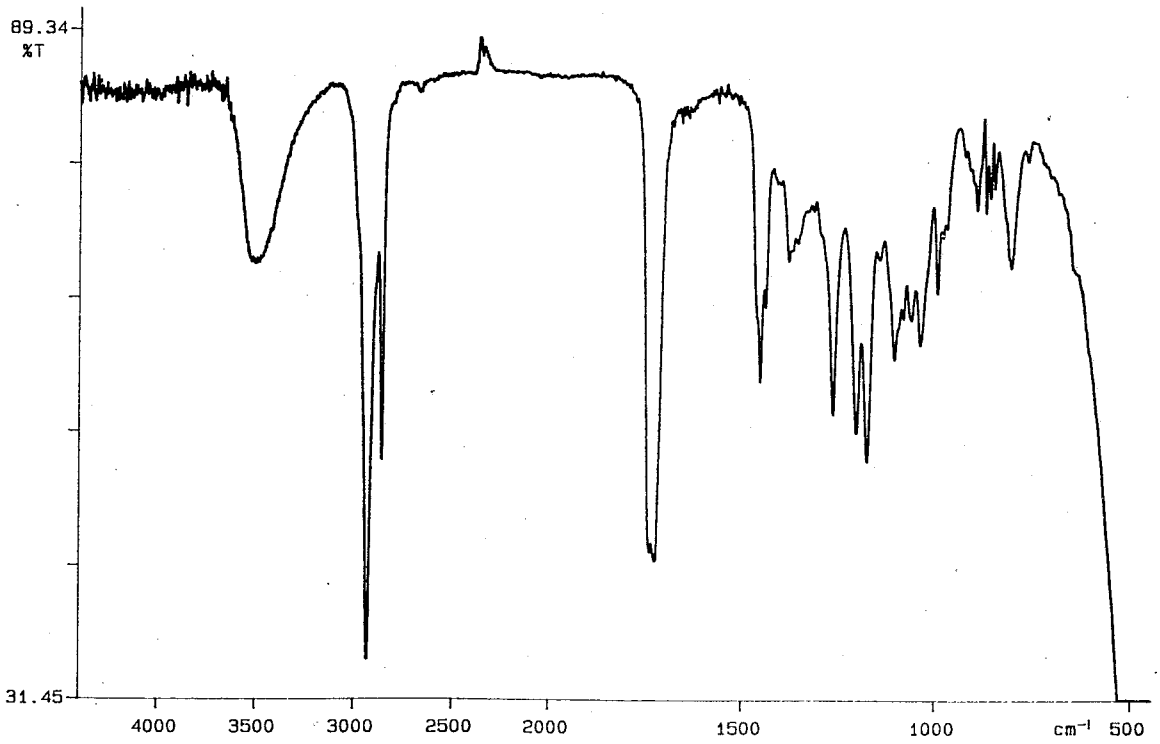
SK2073.003
25JUN93

SEK-II-73
ME ESTER
COLUMNED
1H CDCL3

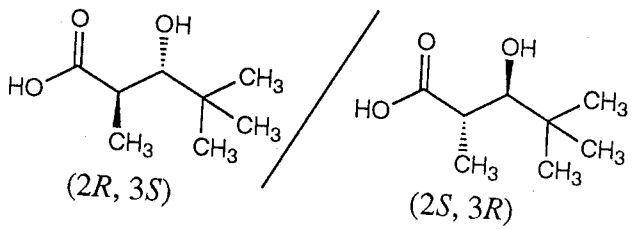
OPERATOR: SEK

9 8 7 6 5 4 3 2 1 0 −1 PPM





93/06/25 16:40
X: 1 scan, 4.0cm-1, flat
SEK-II-73 ester



(2*R*, 3*S*)

(2*S*, 3*R*)

GE NMR
QE PLUS

SK2148.002
25OCT93

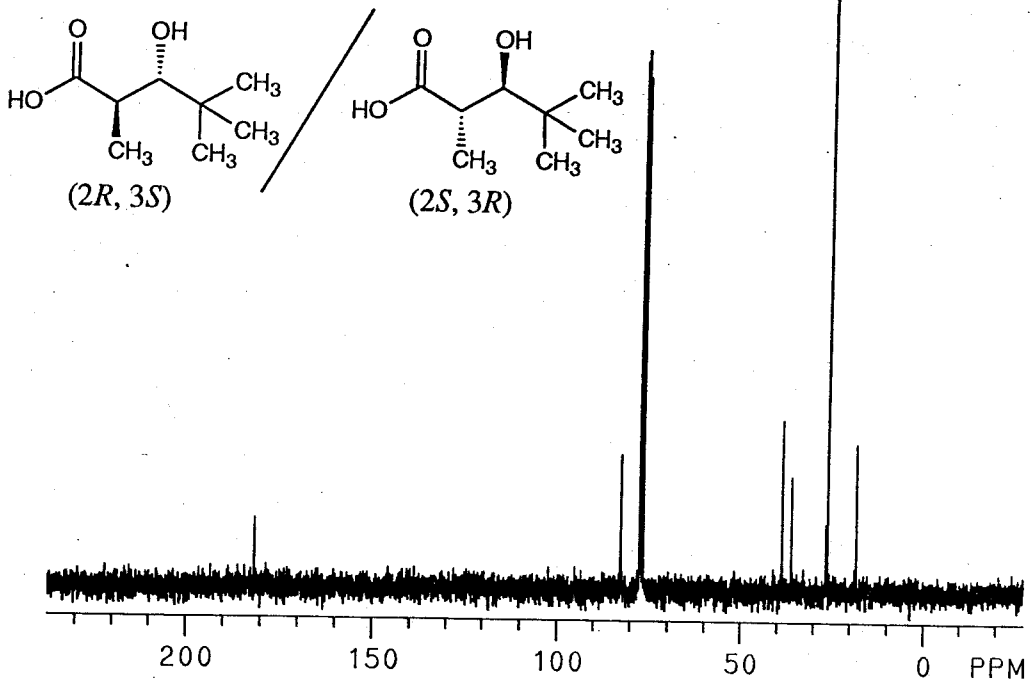
SEK-II-148
ACID WASH
1H CDCL3

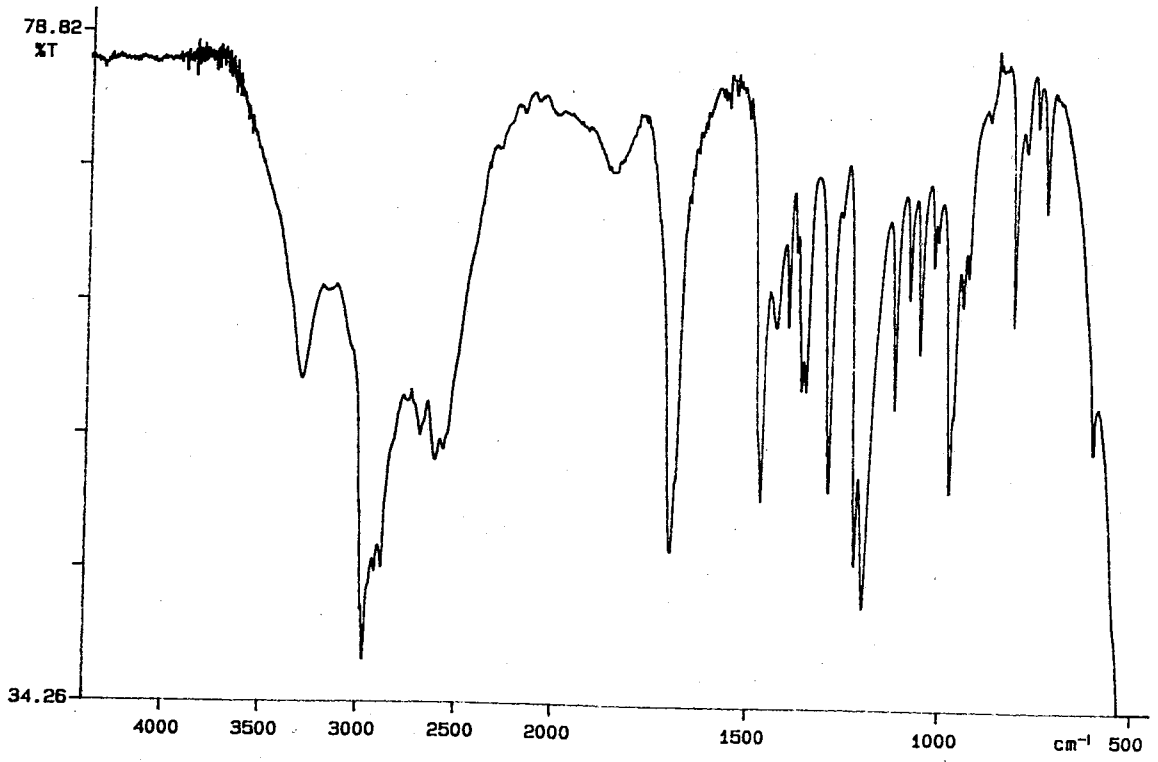
OPERATOR: SEK

SK2148.200
250CT93

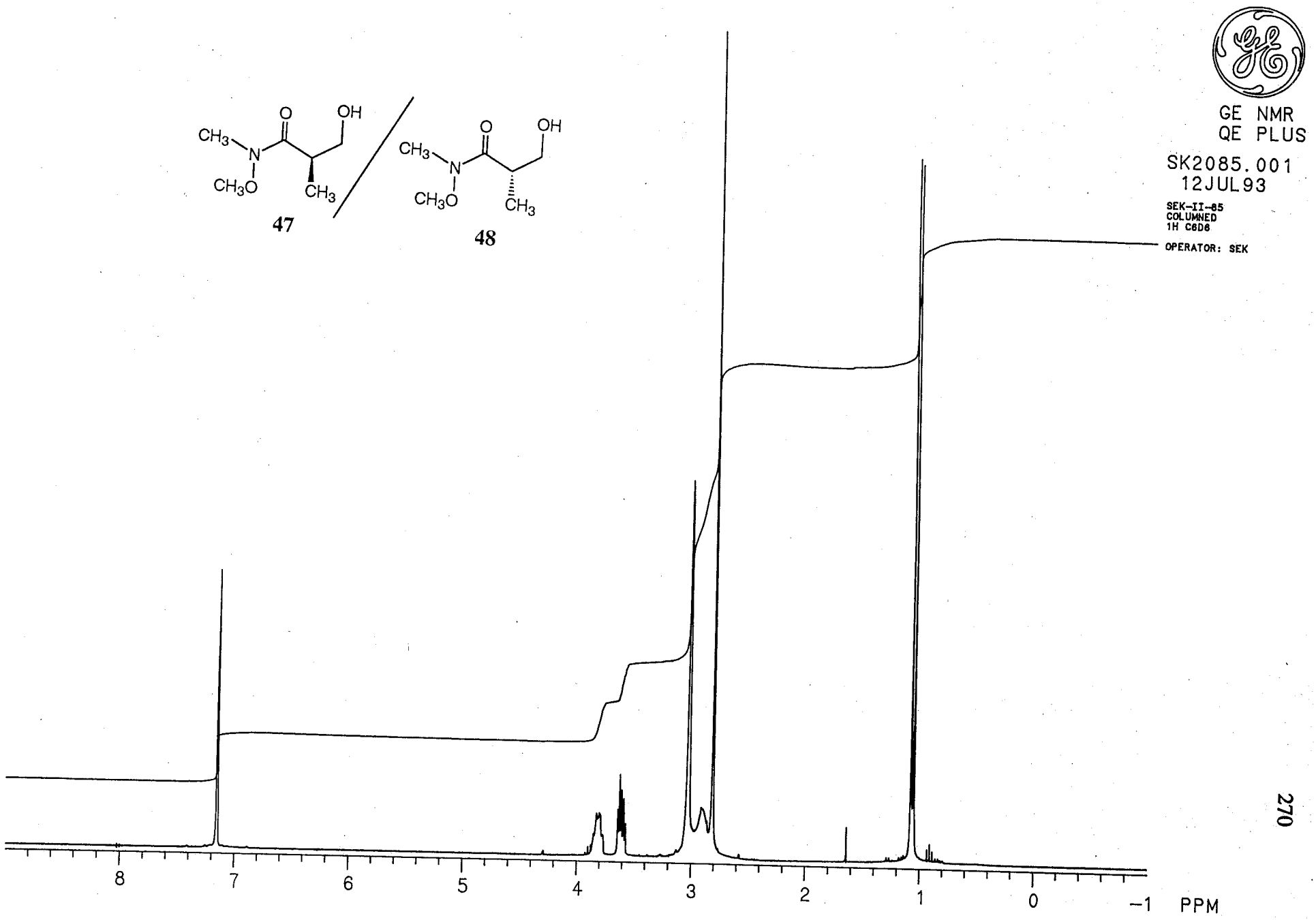
SEK-II-148
ACID
13 C CDCL3

OPERATOR: SEK

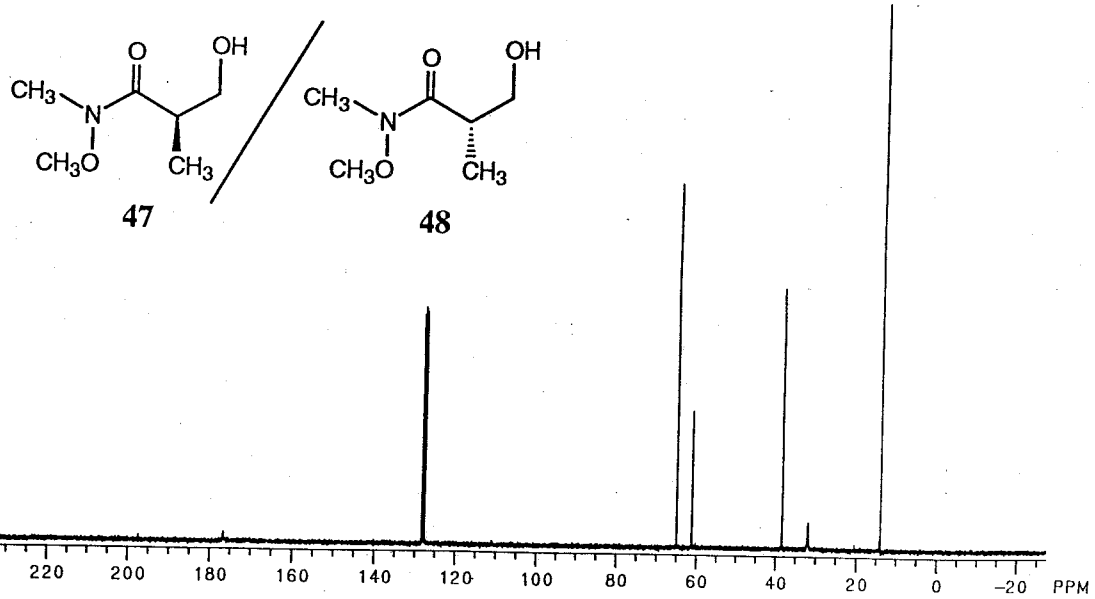


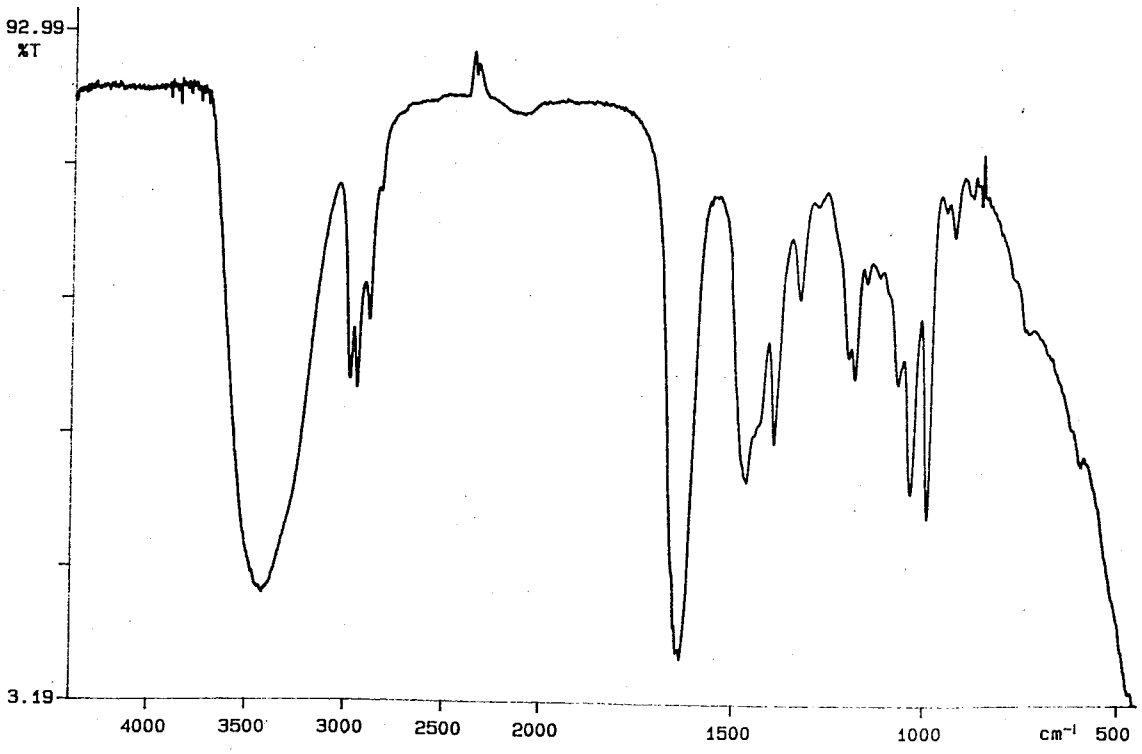


93/10/25 15:34
X: 1 scan, 4.0cm-1, flat
SEK-II-148 acid

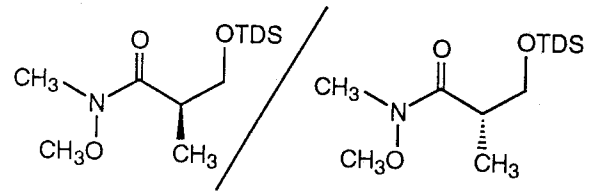

47
48
GE NMR
QE PLUS
SK2085.001
12JUL93
SEK-II-85
COLUMNED
1H C6D6
OPERATOR: SEK
8
7
6
5
4
3
2
1
0
−1
PPM

SK2086.100
12JUL93
SEK-II-66
COUMNED
13C CDCl3
OPERATOR: SEK





93/07/01 10:57
X: 1 scan, 4.0cm-1, flat
SEK-II-77 amide



49

50

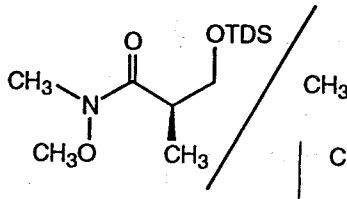
GE NMR
QE PLUS

SK2088.002
15JUL93

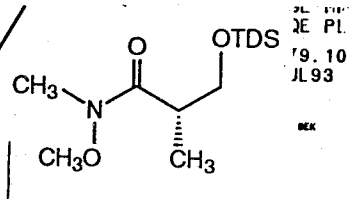
SEK-II-88
MAJOR
1H C6D6

OPERATOR: SEK

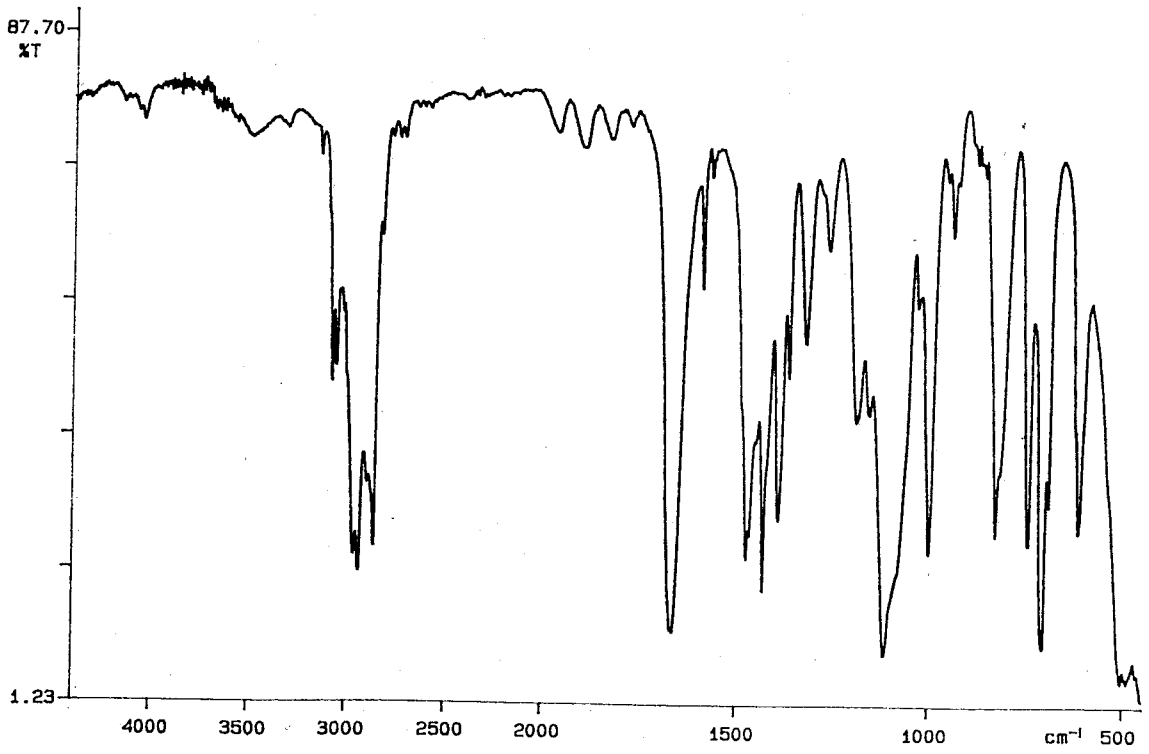
8 7 6 5 4 3 2 1 0 −1 PP



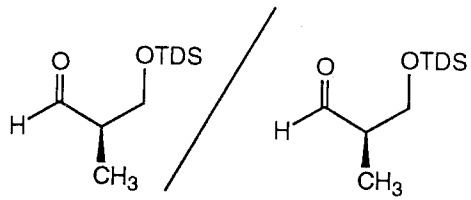
49



50



93/07/02 23:48
X: 1 scan, 4.0cm-1, flat
SEK-II-79



45

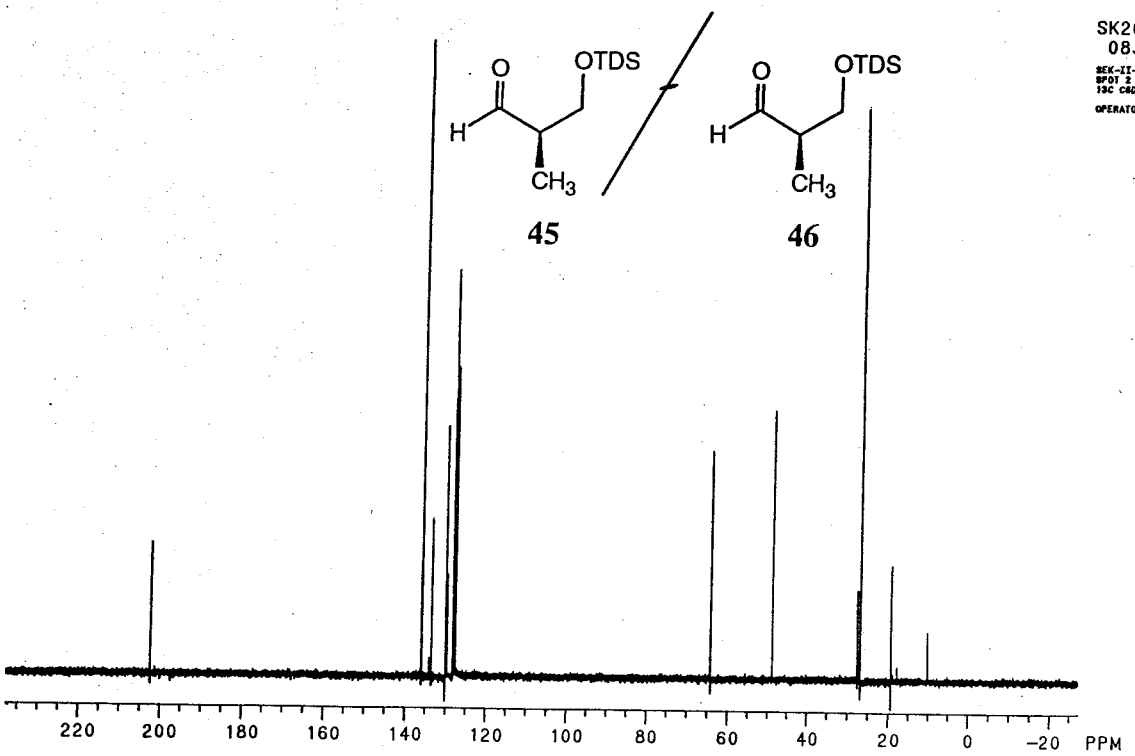
46

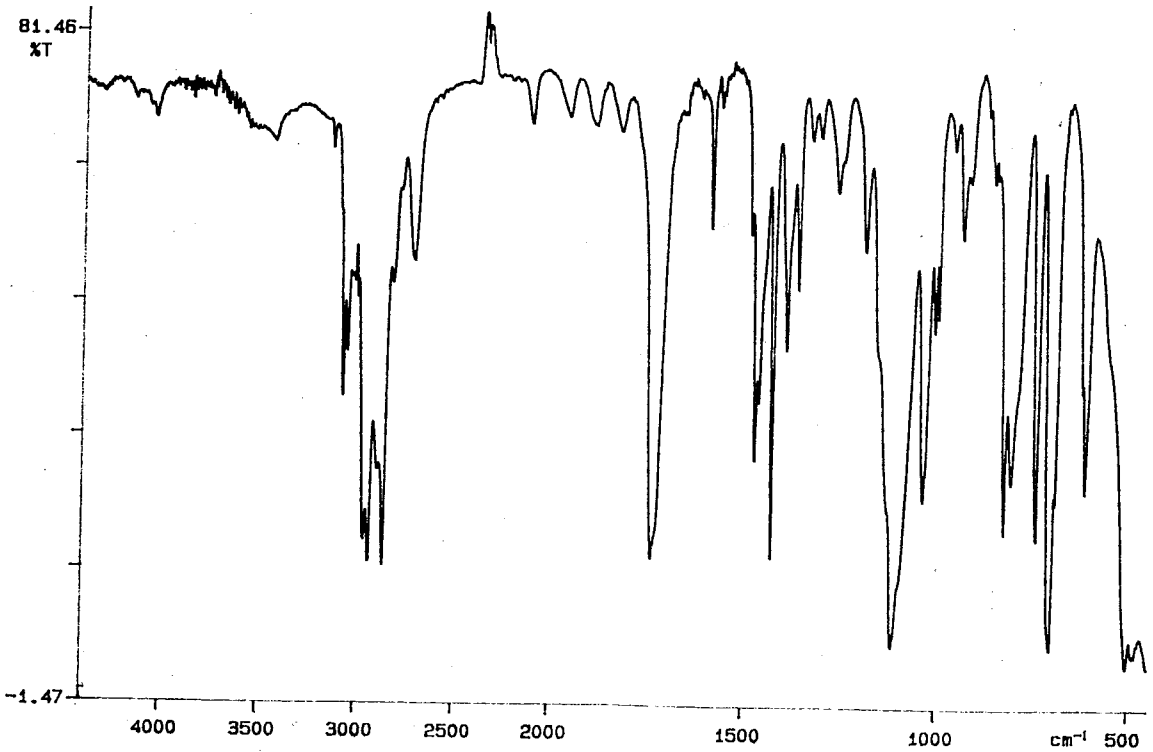
GE NMR
QE PLUS

SK2080.001
05JUL93

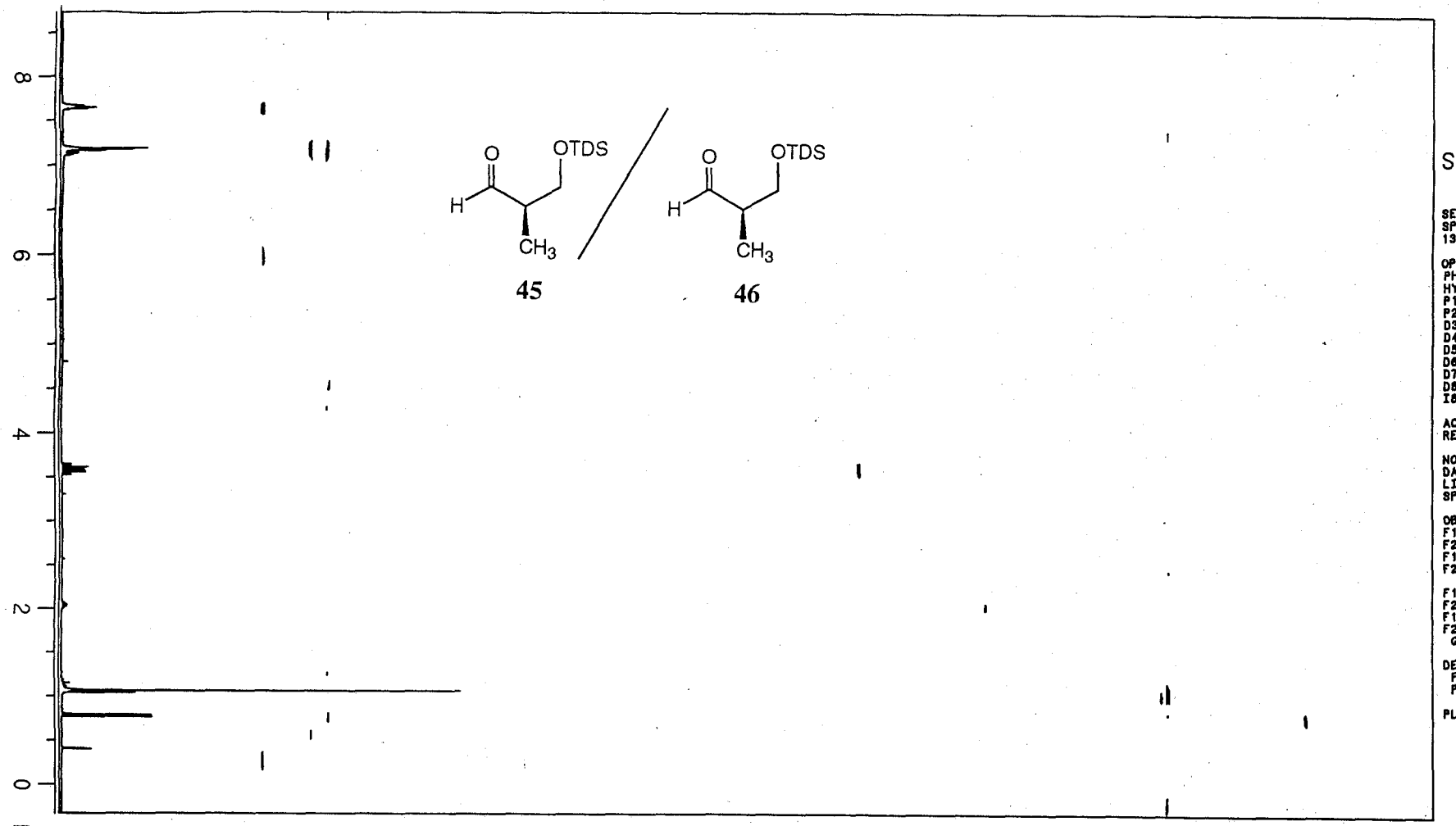
JEK-II-40
ALDEHYDE
COLUMNED
1H CoD6

OPERATOR: JEK





93/07/05 15:34
X: 1 scan, 4.0cm-1, flat
SEK-II-80 aldehyde



GE NMR
QE PLUS

SK2083.DAT
08JUL93

SEK-II-63
SPOT 2
13C C6D6

OPERATOR: SEK
PHASE SENSITIVE CSCM
HYPERCOMPLEX/TPPI
P1 = 20.80 USEC
P2 = 10.40 USEC
D3 = 1.85 MSEC
D4 = 2.20 MSEC
D5 = 800.00 MSEC
D6 = 41.00 USEC
D7 = 82.00 USEC
D8 = 1.00 USEC
I8 = 184.00 USEC

ACQ. TIME = 81.92 MSEC
RECYCLE TIME = .86 SEC

NO. OF ACQS. = 2
DATA SIZE = 256
LINE BROADNG = 10.00 HZ
SPIN RATE = 18 RPS

OBSERVE:
F1 FREQ = 75.490821
F2 FREQ = 300.199760
F1 WIDTH = 12500
F2 WIDTH = 2717

F1 ORIG SIZE = 2048
F2 ORIG SIZE = 48
F1 FINAL SIZE = 1024
F2 FINAL SIZE = 128
GAIN = 60 +1

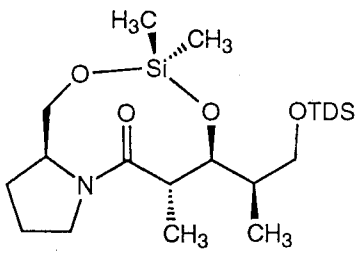
DECOUPLER: STANDARD-16 MODULAT
FREQUENCY = 4.201 PPM
POWER = 2900

PLOT SCALE:
135.86 HZ/CM
.4525 PPM/CM
FROM 8.72
TO -.25 PPM

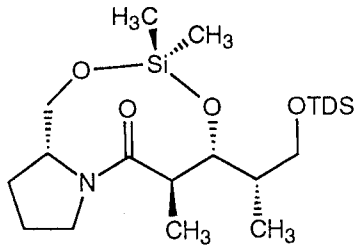
APT

^{13}C

160 140 120 100 80 60 40 20 0 PPM



52 (2*S*, 3*R*, 4*R*)



55 (2*R*, 3*S*, 4*S*)

GE NMR
QE PLUS

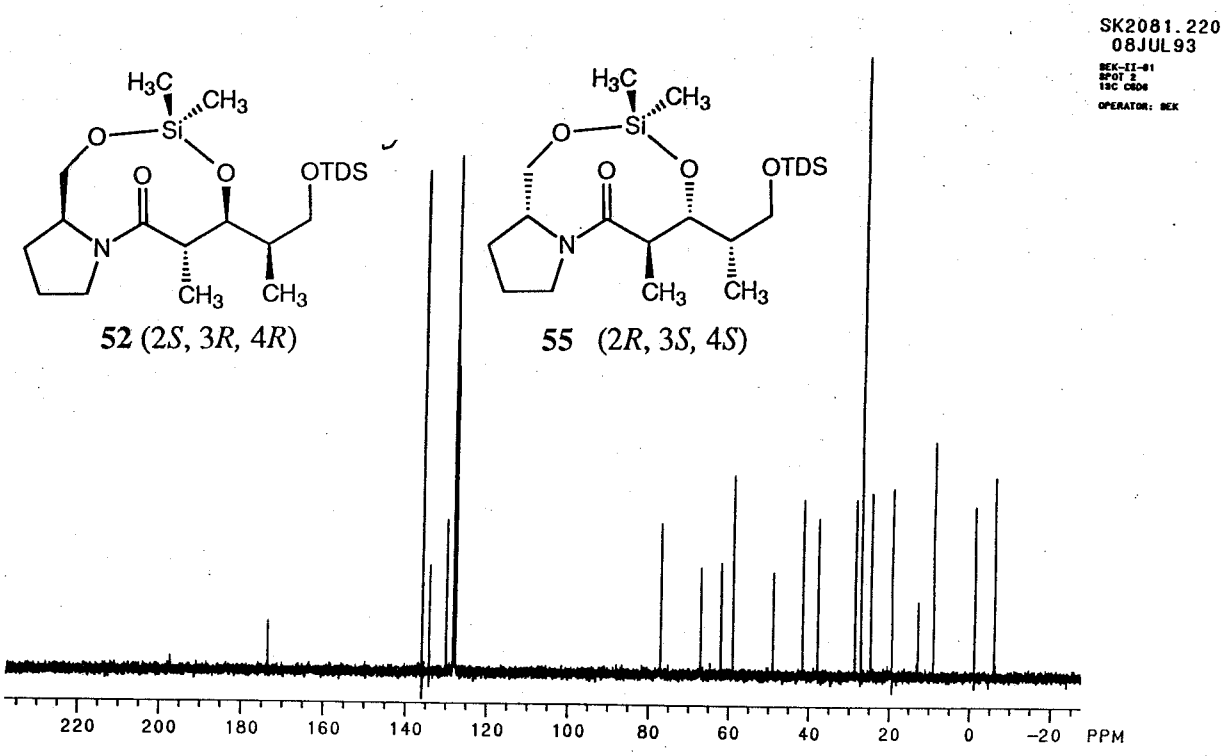
SK2097.003
26JUL93

SEK-II-87
SPOT 3
1H C6D6

OPERATOR: SEK

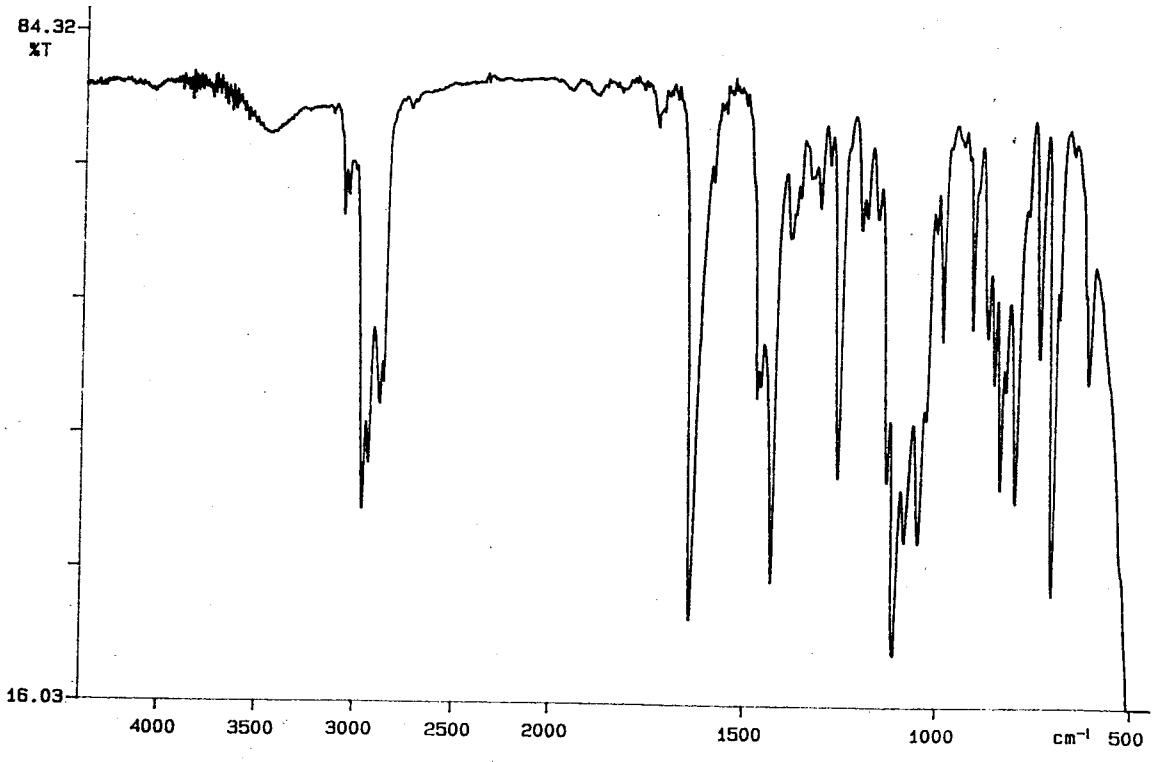
8 7 6 5 4 3 2 1 0 −1 PPM

277

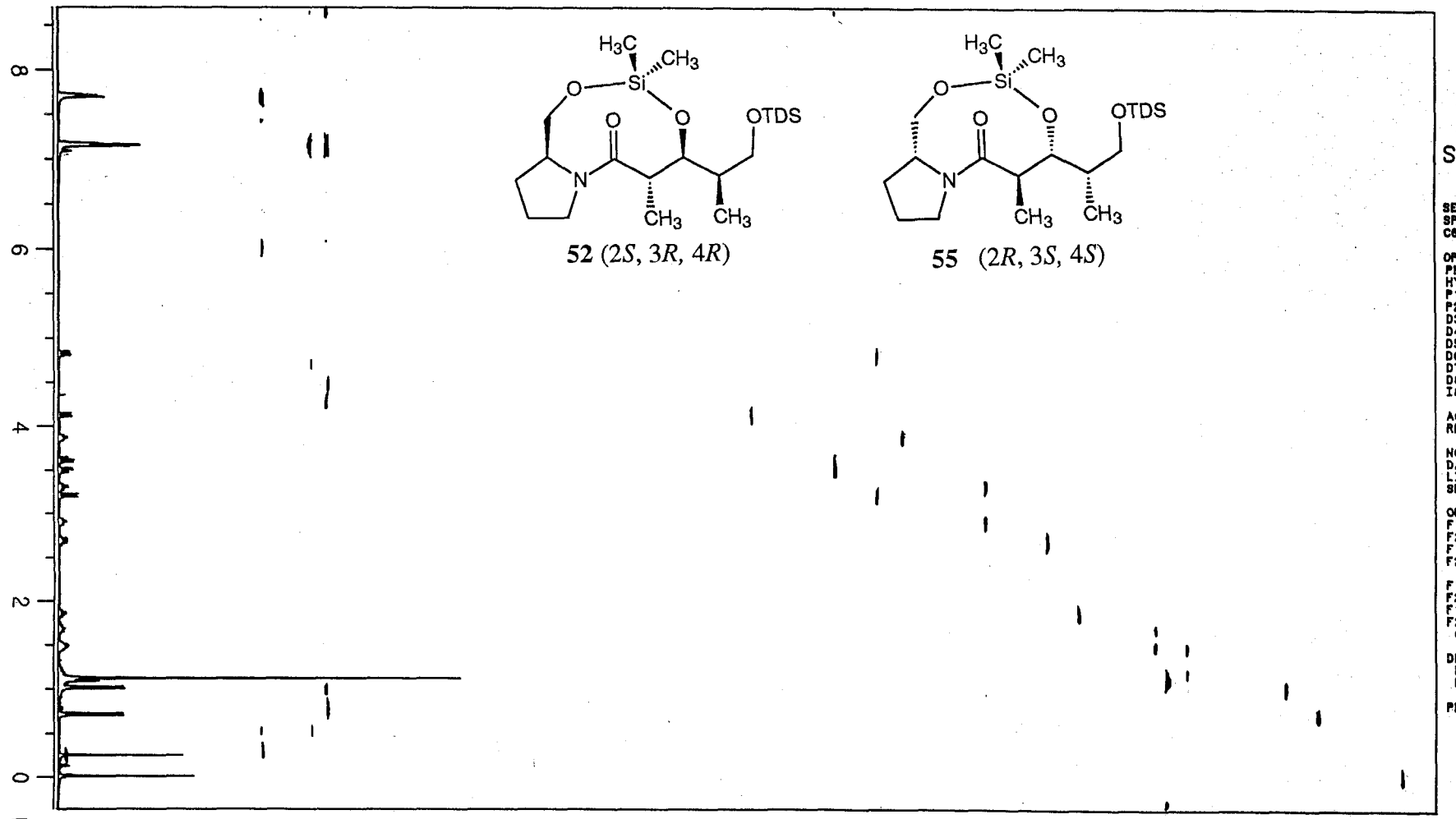


52 (2*S*, 3*R*, 4*R*)

55 (2*R*, 3*S*, 4*S*)



93/07/06 22:37
X: 1 scan, 4.0cm-1, flat
SEK-II-81 sp 2



52 (2*S*, 3*R*, 4*R*)

55 (2*R*, 3*S*, 4*S*)

GE NMR
QE PLUS

SK2081.DAT
08JUL93

SEK-II-81
SPOT 2
C6D6

OPERATOR: SEK
PHASE SENSITIVE CSCM
HYPERCOMPLEX/TPPI
P1 = 20.80 USEC
P2 = 10.40 USEC
D3 = 1.85 MSEC
D4 = 2.20 MSEC
D5 = 800.00 MSEC
D6 = 41.00 USEC
D7 = 82.00 USEC
D8 = 1.00 USEC
I8 = 184.00 USEC

ACQ. TIME = 81.92 MSEC
RECYCLE TIME = .86 SEC

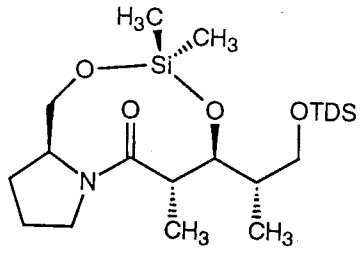
NO. OF ACQS. = 2
DATA SIZE = 256
LINE BROADNG = 10.00 HZ
SPIN RATE = 18 RPS

OBSERVE:
F1 FREQ = 75.490821
F2 FREQ = 300.199760
F1 WIDTH = 12500
F2 WIDTH = 2717

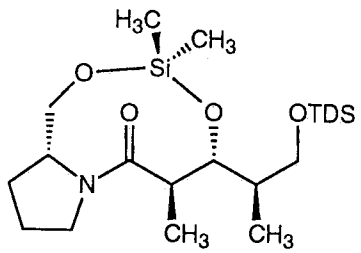
F1 ORIG SIZE = 2048
F2 ORIG SIZE = 48
F1 FINAL SIZE = 1024
F2 FINAL SIZE = 128
GAIN = 60 +1

DECOUPLER: STANDARD-16 MODULATIC
FREQUENCY = 4.201 PPM
POWER = 2900

PLOT SCALE:
135.86 HZ/CM
.4525 PPM/CM
FROM 8.69
TO -.28 PPM

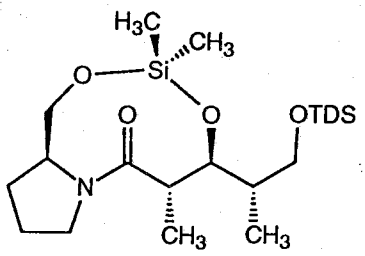


53 (2*S*, 3*R*, 4*S*)

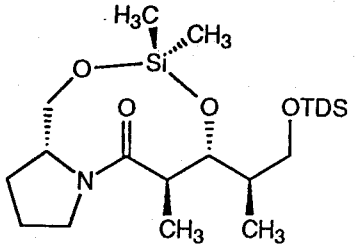


54 (2*R*, 3*S*, 4*R*)

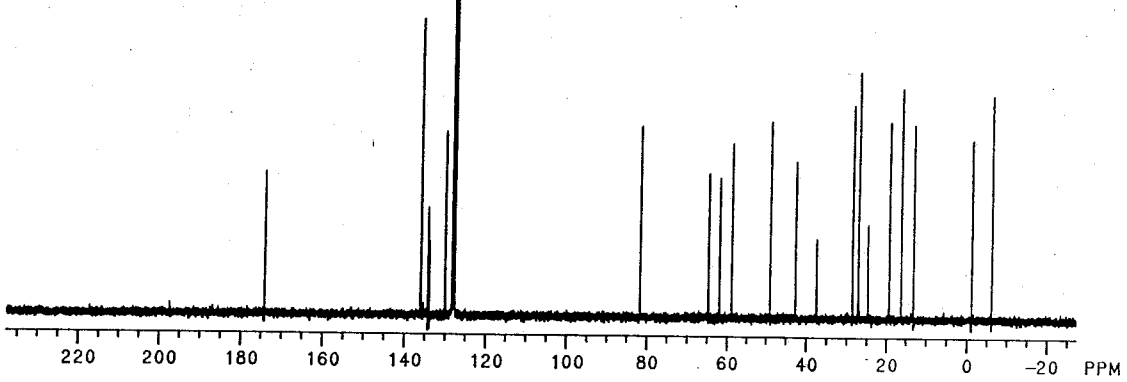
SK2096.300
24JUL93
SEK-II-96
SPOT 3
13C CDCl3
OPERATOR: SEK

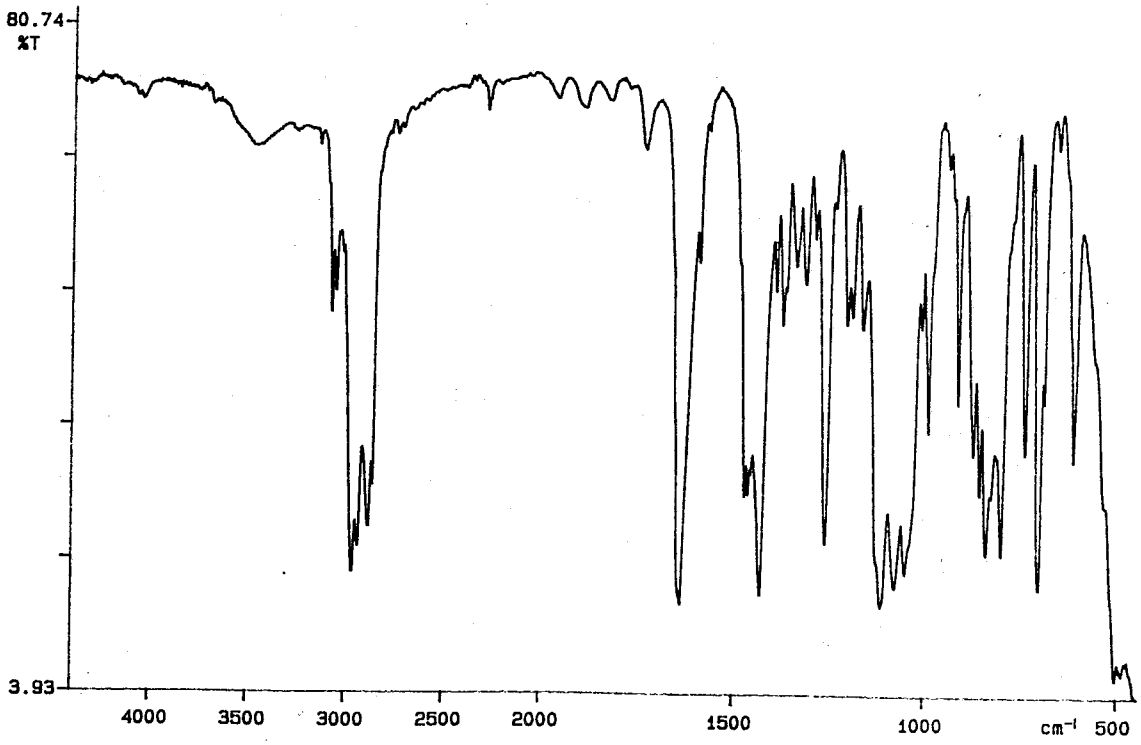


53 (2*S*, 3*R*, 4*S*)

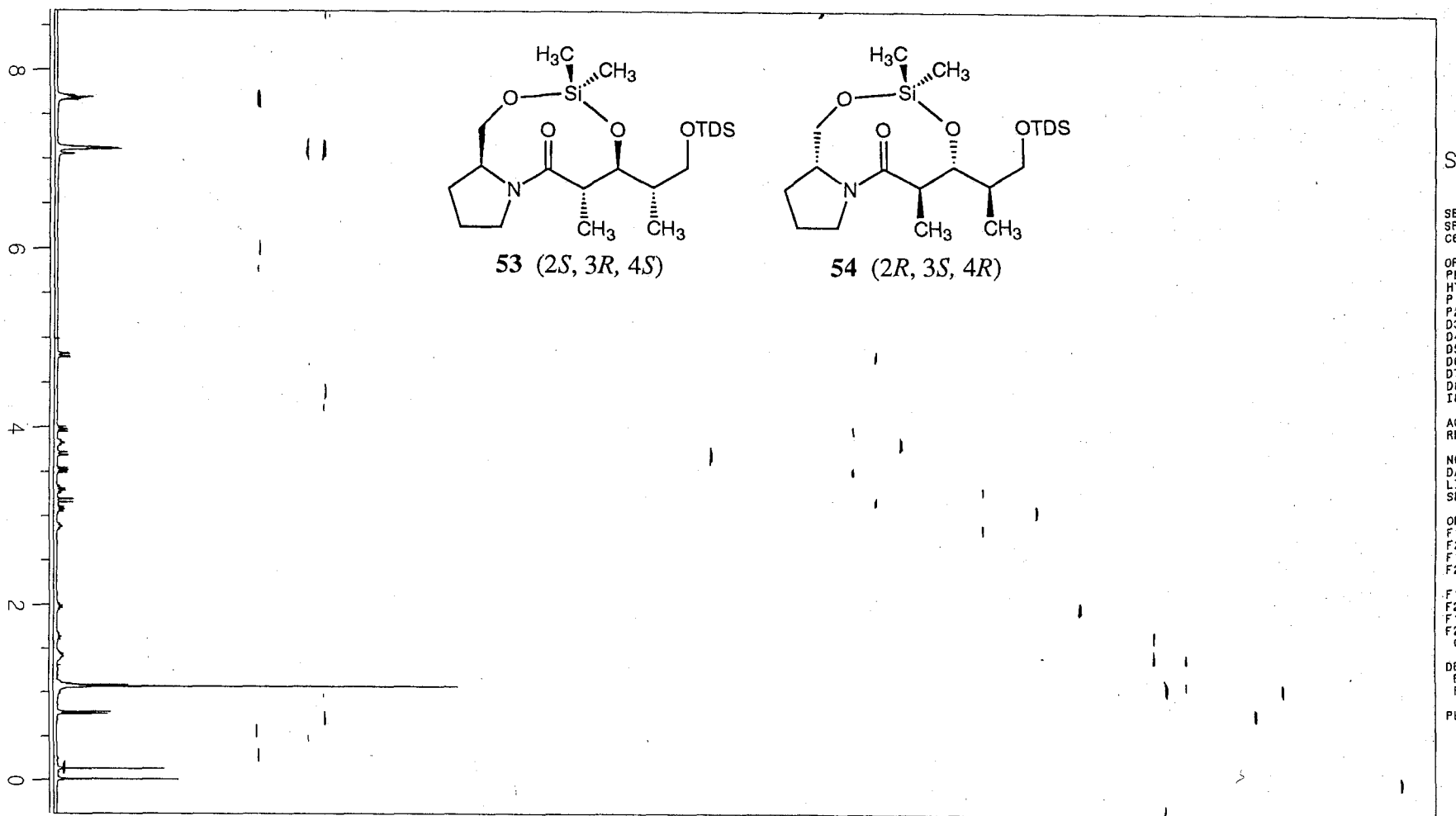


54 (2*R*, 3*S*, 4*R*)





93/07/26 09:13
X: 1 scan, 4.0cm-1, flat
SEK-II-96 spot 3



53 (2*S*, 3*R*, 4*S*)

54 (2*R*, 3*S*, 4*R*)

GE NMR
QE PLUS

SK2096.DAT
24JUL93

SEK-II-96
SPOT 3
C6D6

OPERATOR: SEK
PHASE SENSITIVE CSCM
HYPERCOMPLEX/TPPI
P1 = 20.80 USEC
P2 = 10.40 USEC
D3 = 1.85 MSEC
D4 = 2.20 MSEC
D5 = 800.00 MSEC
D6 = 41.00 USEC
D7 = 82.00 USEC
D8 = 1.00 USEC
I8 = 184.00 USEC

ACQ. TIME = 81.92 MSE
RECYCLE TIME = .86 SE

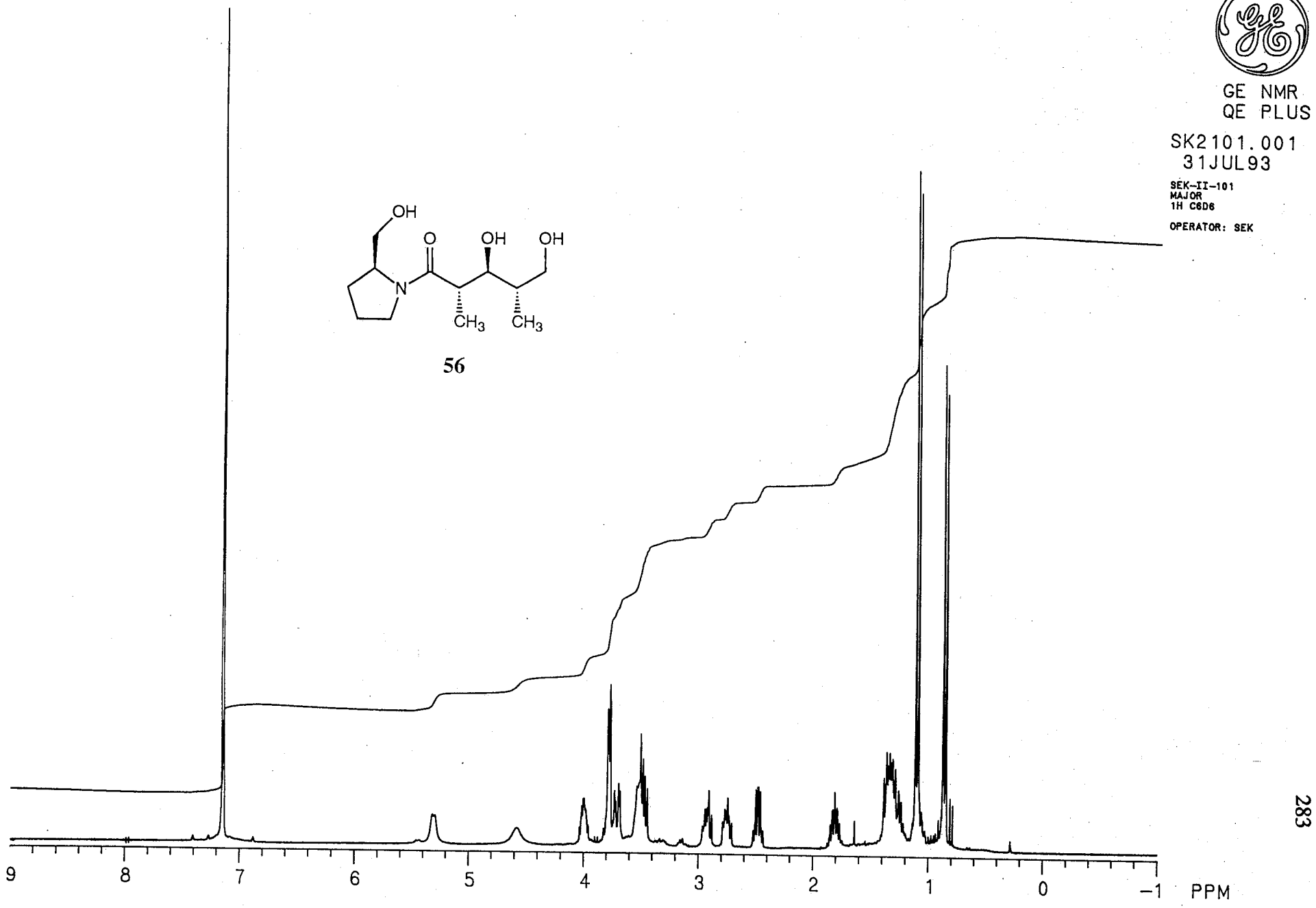
NO. OF ACQS. = 2
DATA SIZE = 256
LINE BROADNG = 10.00 HZ
SPIN RATE = 19 RPS

OBSERVE:
F1 FREQ = 75.490821
F2 FREQ = 300.199760
F1 WIDTH = 12500
F2 WIDTH = 2717

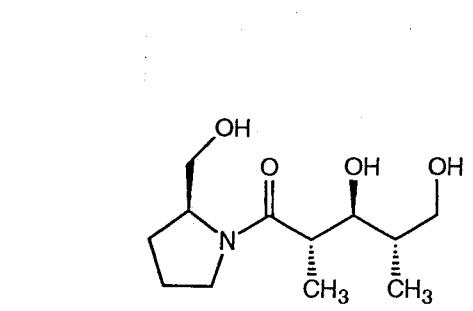
F1 ORIG SIZE = 2048
F2 ORIG SIZE = 48
F1 FINAL SIZE = 1024
F2 FINAL SIZE = 128
GAIN = 60 +1

DECOUPLER: STANDARD-16 MODULAT
FREQUENCY = 4.201 PPM
POWER = 2880

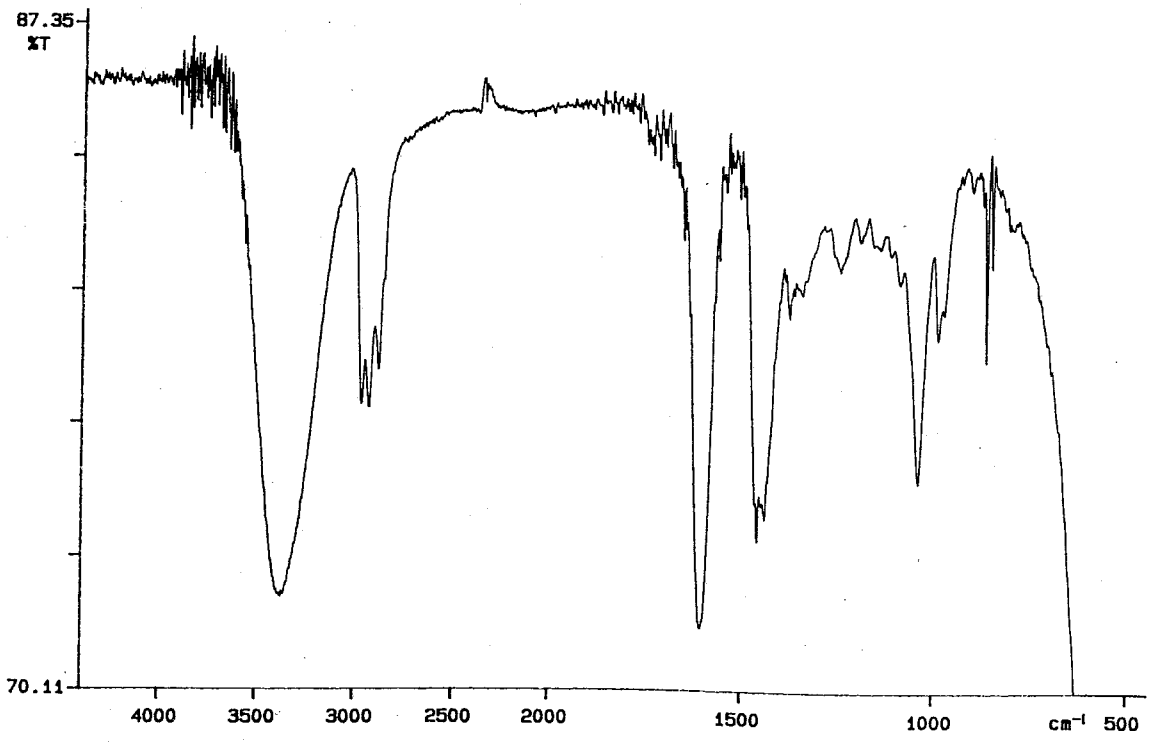
PLOT SCALE:
135.86 HZ/CM
.4525 PPM/CM
FROM 8.67
TO -.30 PPM


OH
O
OH
OH
N
CH3
CH3
GE NMR
QE PLUS
SK2101.001
31JUL93
SEK-II-101
MAJOR
1H C6D6
OPERATOR: SEK
9
8
7
6
5
4
3
2
1
0
−1
PPM

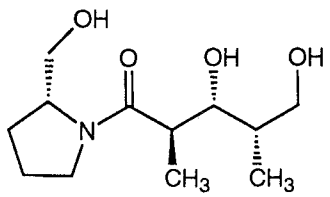
56



56



93/08/02 16:25
X: 1 scan, 4.0cm-1, flat
SEK-II-101 major



57

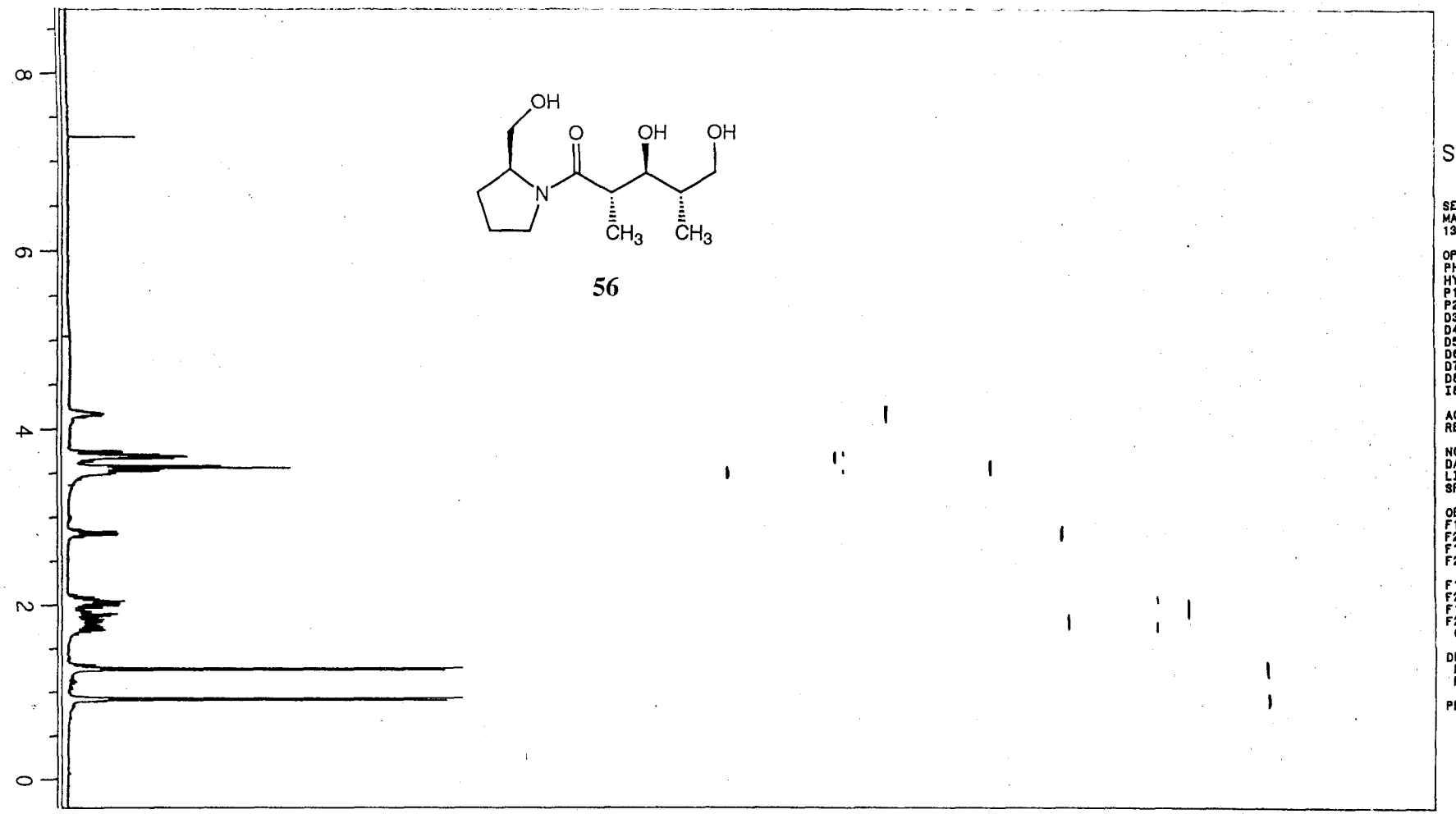
GE NMR
QE PLUS

SK2091.003
24JUL93

SEK-II-91
"BASELINE"
1H CDCL3

OPERATOR: SEK

9 8 7 6 5 4 3 2 1 0 −1 PPM



56

GE NMR
QE PLUS

SK2101.DAT
01AUG93

SEK-II-101
MAJOR
13C CDCL3

OPERATOR: SEK
PHASE SENSITIVE CSCM
HYPERCOMPLEX/TPPI
P1 = 20.80 USEC
P2 = 10.40 USEC
D3 = 1.85 MSEC
D4 = 2.20 MSEC
D5 = 800.00 MSEC
D6 = 41.00 USEC
D7 = 82.00 USEC
D8 = 1.00 USEC
I8 = 184.00 USEC

ACQ. TIME = 81.92 MSEC
RECYCLE TIME = .86 SEC

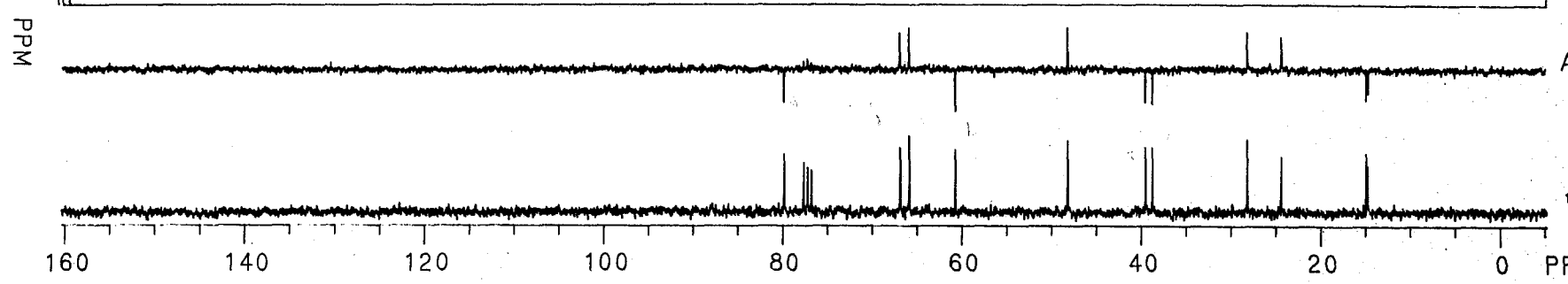
NO. OF ACQS. = 2
DATA SIZE = 256
LINE BROADNG = 10.00 HZ
SPIN RATE = 19 RPS

OBSERVE:
F1 FREQ = 75.490821
F2 FREQ = 300.199760
F1 WIDTH = 12500
F2 WIDTH = 2717

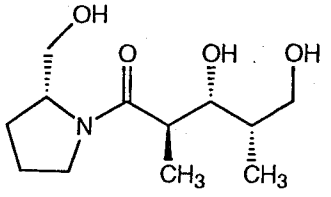
F1 ORIG SIZE = 2048
F2 ORIG SIZE = 48
F1 FINAL SIZE = 1024
F2 FINAL SIZE = 128
GAIN = 60 +1

DECOUPLER: STANDARD-16 MODULAT
FREQUENCY = 4.201 PPM
POWER = 2880

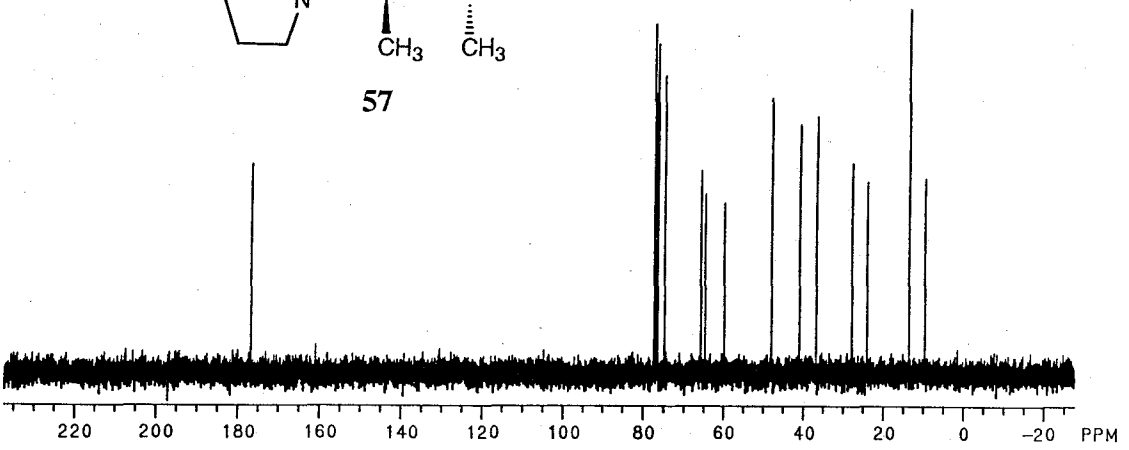
PLOT SCALE:
135.86 HZ/CM
.4525 PPM/CM
FROM 8.72
TO -.25 PPM

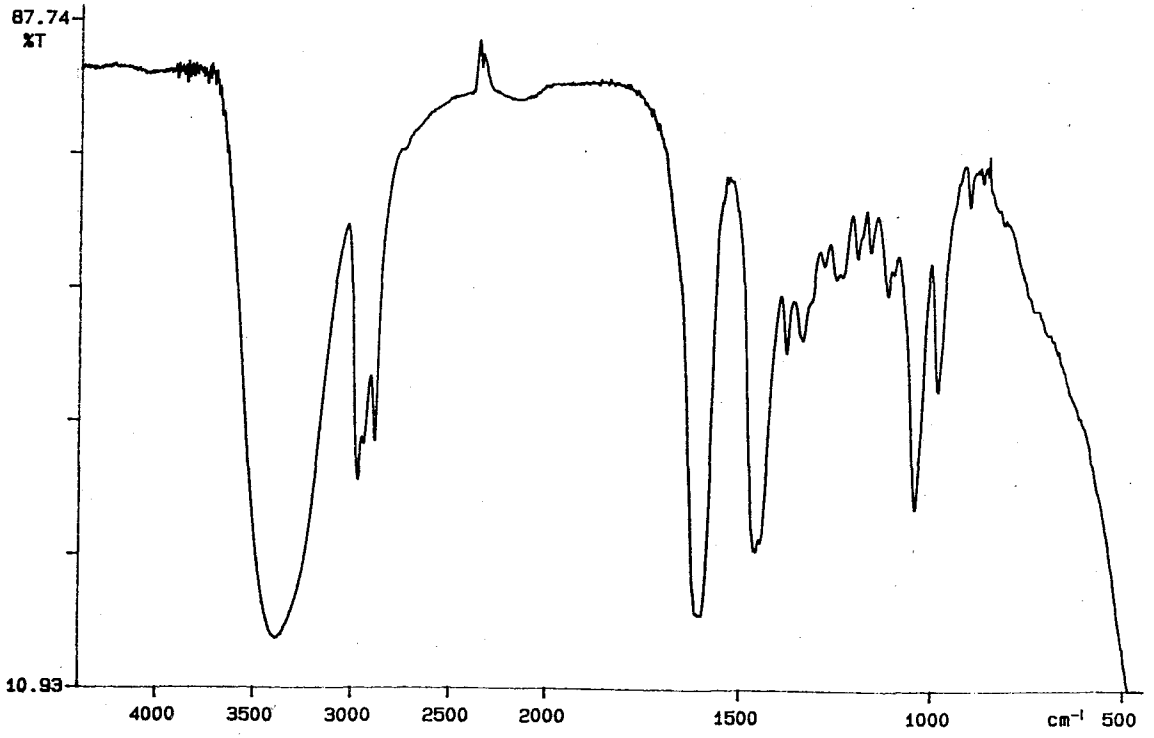


SK2091.300
24JUL93
SEK-II-91
BASELINE
13C CDCL3
OPERATOR: SEK

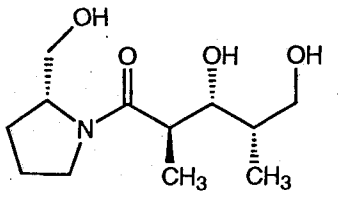


57





93/07/24 10:34
X: 1 scan, 4.0cm-1, flat
SEK-II-91 baseline



57

GE NMR
QE PLUS

SK2091.DAT
24JUL93

SEK-II-91
"BASELINE"
CDCL3

OPERATOR, SEK
QUICK COSY
HYPERCOMPLEX/TPPI
P2 = 9.50 USEC
D5 = 200.00 MSEC
D8 = 10.00 USEC
I8 = 368.00 USEC

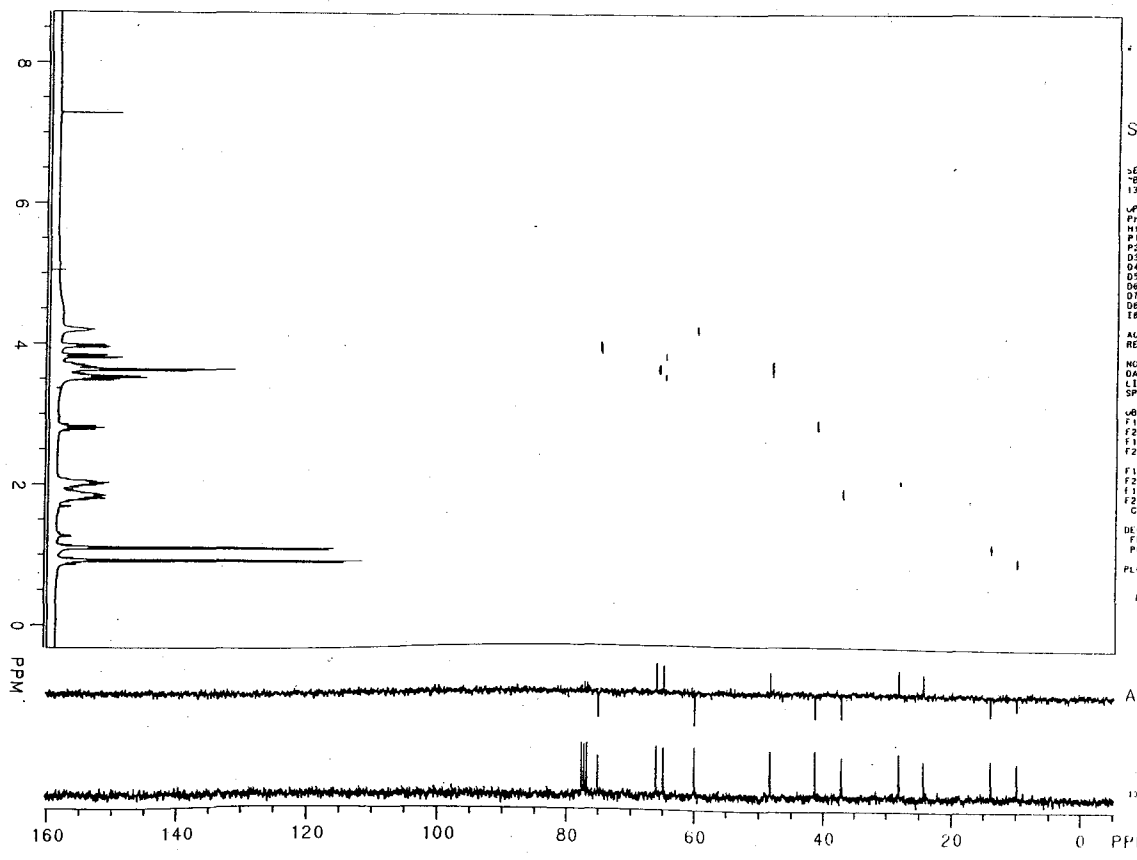
ACQ. TIME = 188.42 MSEC
RECYCLE TIME = 52 SEC

NO. OF ACQS. = 1
DATA SIZE = 1024
LINE BROADNG = .00 HZ
SPIN RATE = 19 RPS

OBSERVE
F1 FREQ = 300.199760
F2 FREQ = 300.199760
F1 WIDTH = 2717
F2 WIDTH = 2717

F1 ORIG SIZE = 1024
F2 ORIG SIZE = 256
F1 FINAL SIZE = 512
F2 FINAL SIZE = 512
GAIN = 47 +1

PLOT SCALE
108.69 HZ/CM
.3620 PPM/CM
FROM 8.72
TO -.30 PPM



GE NMR
QE PLUS

SK2091.DAT
24JUL93

SEK-II-91
"BASELINE"
13C CDCL3

OPERATOR, SEK
PHASE SENSITIVE ECOSY
HYPERCOMPLEX/TPPI
P1 = 20.96 USEC
P2 = 10.40 USEC
D3 = 1.65 MSEC
D4 = 2.20 MSEC
D5 = 800.00 MSEC
D6 = 41.00 USEC
D7 = 82.00 USEC
D8 = 1.00 USEC
I8 = 184.60 USEC

ACQ. TIME = 81.92 MS
RECYCLE TIME = 60 SE

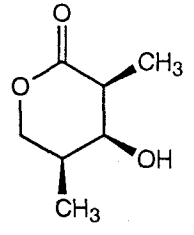
NO. OF ACQS = 2
DATA SIZE = 256
LINE BROADNG = 10.00 HZ
SPIN RATE = 19 RPS

OBSERVE
F1 FREQ = 75.490821
F2 FREQ = 300.199760
F1 WIDTH = 12500
F2 WIDTH = 2717

F1 ORIG SIZE = 2048
F2 ORIG SIZE = 48
F1 FINAL SIZE = 1024
F2 FINAL SIZE = 128
GAIN = 62 +1

DECOUPLER STANDARD-16 MODUL
FREQUENCY = 4.231 PPM
POWER = 2600

PLOT SCALE
135.86 HZ/CM
.4525 PPM/CM
FROM 8.72
TO -.25 PPM



58

GE NMR
QE PLUS

SK2112.003
12AUG93

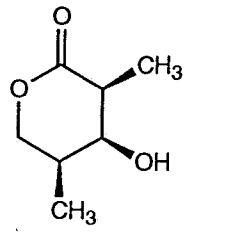
SEK-II-112
AW MAJOR SPOT
1H C6D6

OPERATOR: SEK

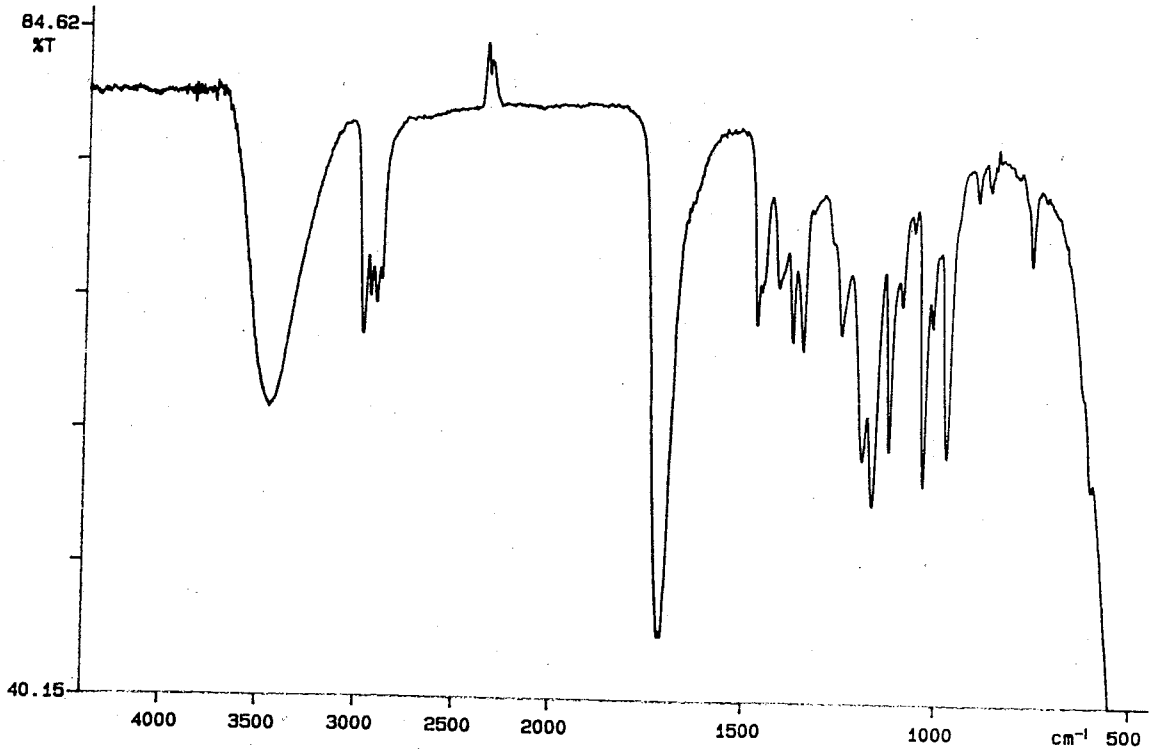
SK2112.300
12AUG93

SEK-II-112
AW MAJOR SPOT
13C C6D6

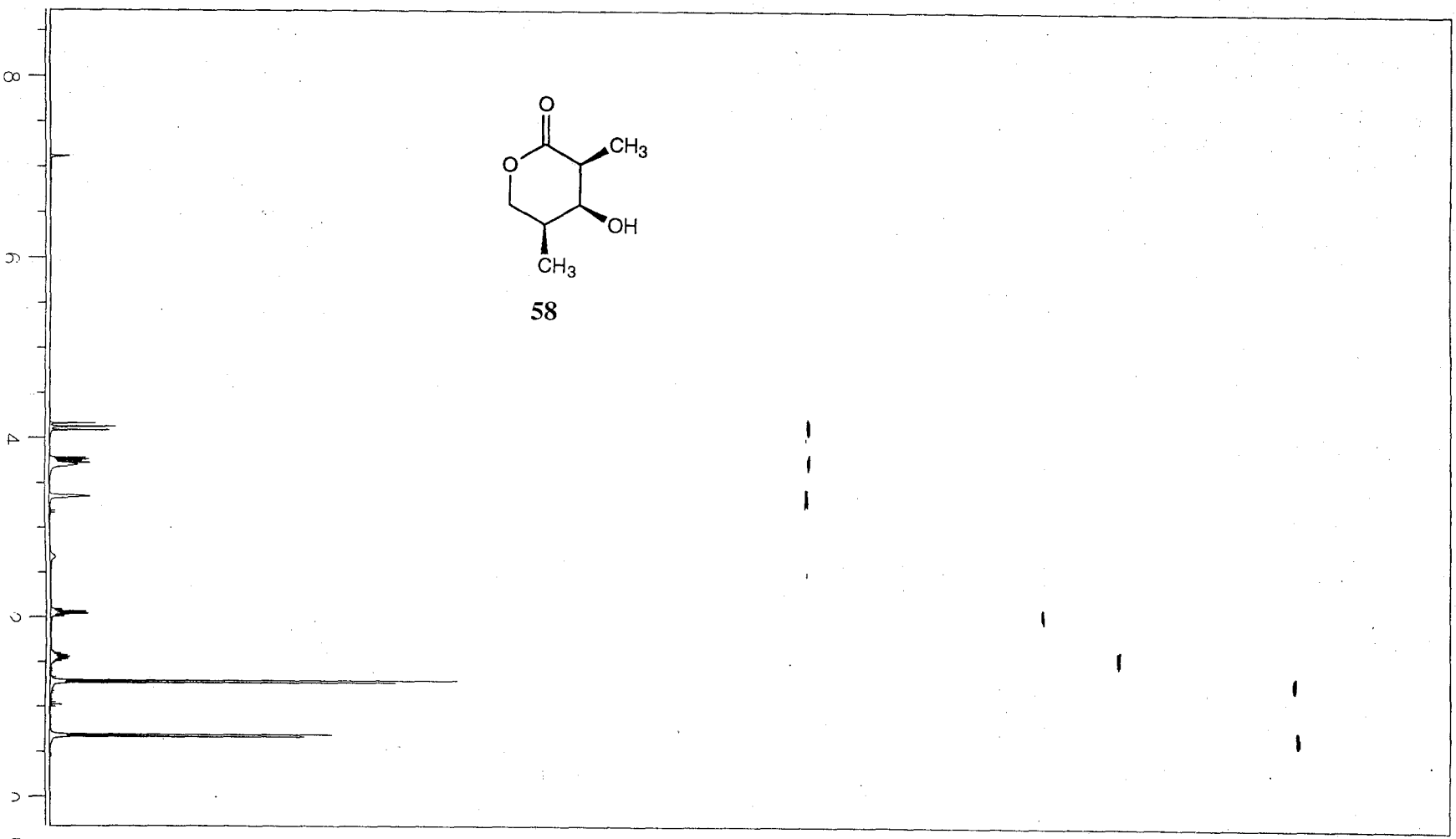
OPERATOR: SEK



58



93/08/11 19:38
X: 1 scan, 4.0cm-1, flat
SEK-II-112 acid



58

GE NMR
QE PLUS

SK2112.DAT
12AUG93

SEK-II-112
AW MAJOR SPOT
13C C6D6

OPERATOR: SEK
PHASE SENSITIVE CSCM
HYPERCOMPLEX/TPPI
P1 = 20.80 USEC
P2 = 10.40 USEC
D3 = 1.85 MSEC
D4 = 2.20 MSEC
D5 = 800.00 MSEC
D6 = 41.00 USEC
D7 = 82.00 USEC
D8 = 1.00 USEC
I8 = 184.00 USEC

ACQ. TIME = 81.92 MSEC
RECYCLE TIME = .86 SEC

NO. OF ACQS. = 2
DATA SIZE = 256
LINE BROADNG = 10.00 HZ
SPIN RATE = 19 RPS

OBSERVE:
F1 FREQ = 75.490821
F2 FREQ = 300.199760
F1 WIDTH = 12500
F2 WIDTH = 2717

F1 ORIG SIZE = 2048
F2 ORIG SIZE = 48
F1 FINAL SIZE = 1024
F2 FINAL SIZE = 128
GAIN = 60 *1

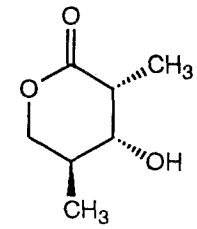
DECOUPLER: STANDARD-16 MODULATION
FREQUENCY = 4.201 PPM
POWER = 2880

PLOT SCALE:
135.86 HZ/CM
.4525 PPM/CM
FROM 8.72
TO -.25 PPM

APT

^{13}C

160 140 120 100 80 60 40 20 0 PPM



59

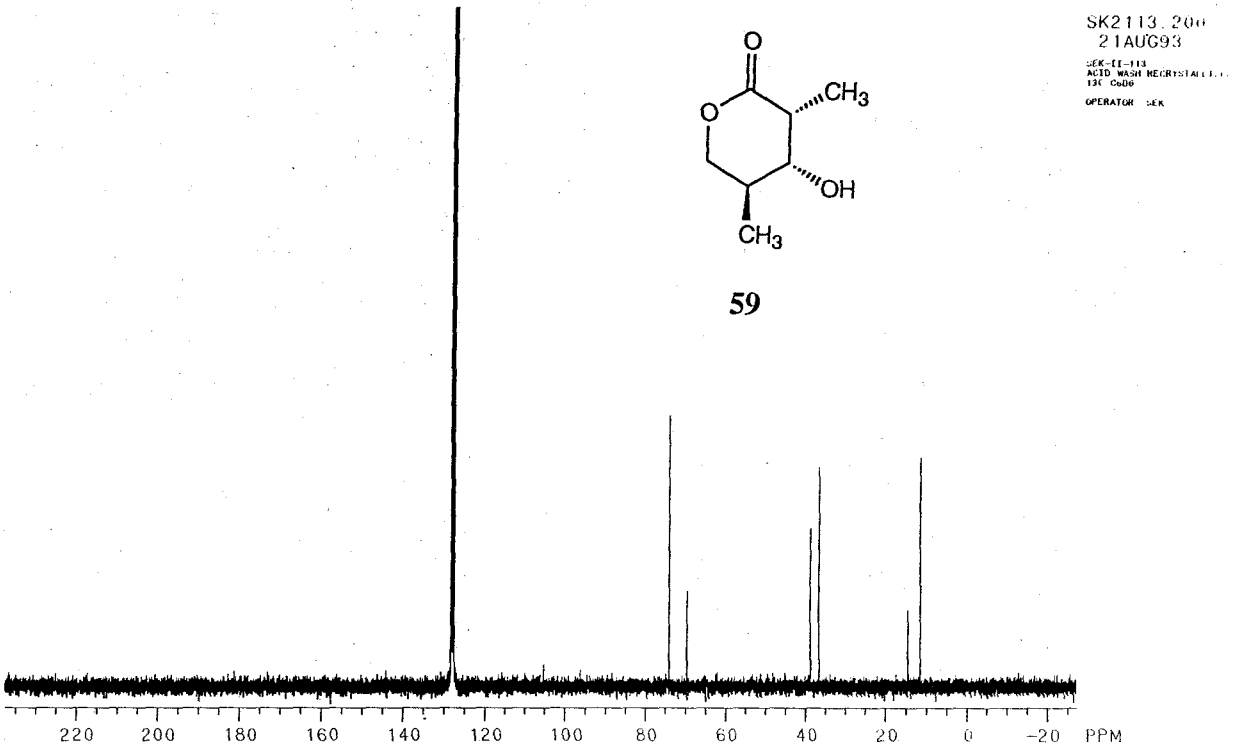
GE NMR
QE PLUS

SK2113.002
16AUG93

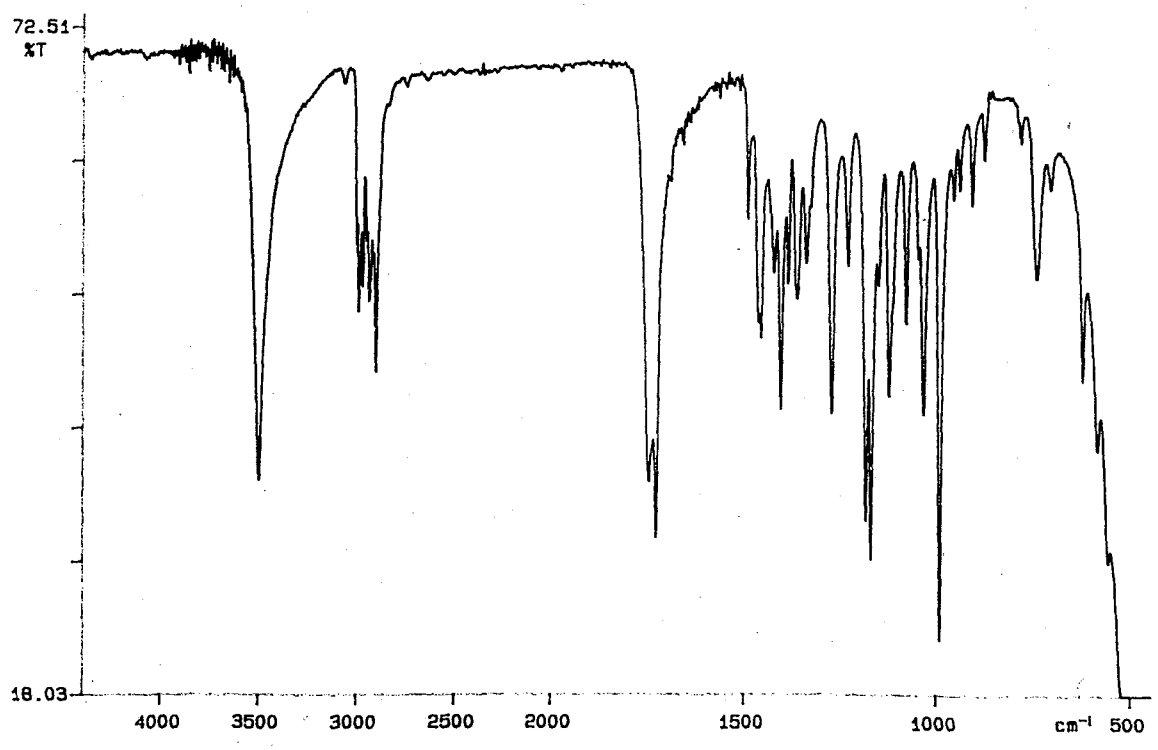
SEK-II-113
ACID WASH
RECRYSTALLIZED
1H C6D6

OPERATOR: SEK

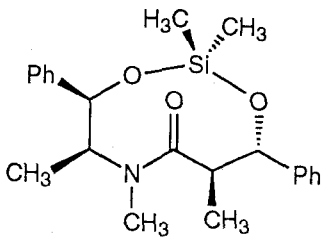
9 8 7 6 5 4 3 2 1 0 −1 PPM



59



93/08/16 14:04
Y: 1 scan, 4.0cm-1, flat
SEK-II-113 acid rextal



60
(2*R*, 3*S*)

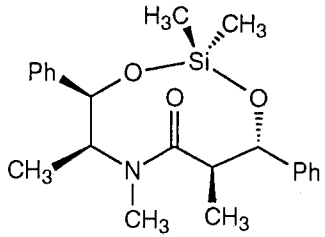
GE NMR
QE PLUS

SK2115.021
25AUG93

SEK-II-115
SPOT 2
RECRYSTALLIZED
1H C6D6

OPERATOR: SEK

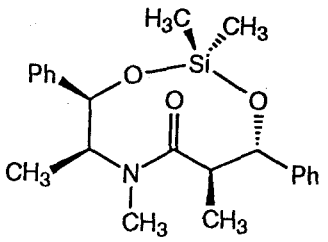
9 8 7 6 5 4 3 2 1 0 −1 PPM



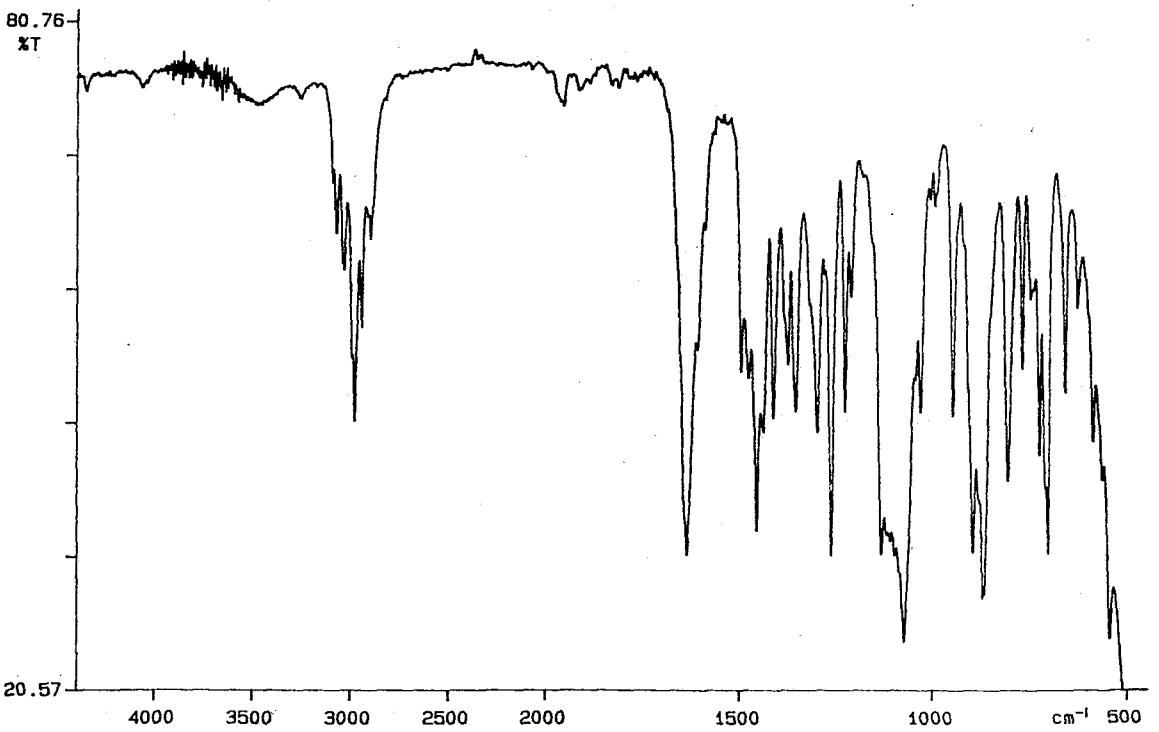
60
(2*R*, 3*S*)

GE NMR
QE PLUS

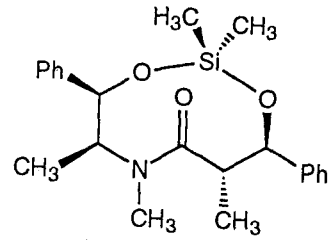
SER-II-118
sp. 2 CDCl3



60
(2*R*, 3*S*)



93/08/25 21:03
X: 1 scan, 4.0cm-1, flat
SEK-II-115 sp2 recrystal



61
(2*S*, 3*R*)

GE NMR
QE PLUS

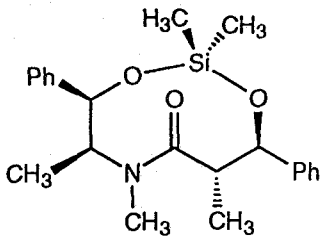
SK2118.001
25AUG93

SEK-II-118
SPOT 1
1H C6D6

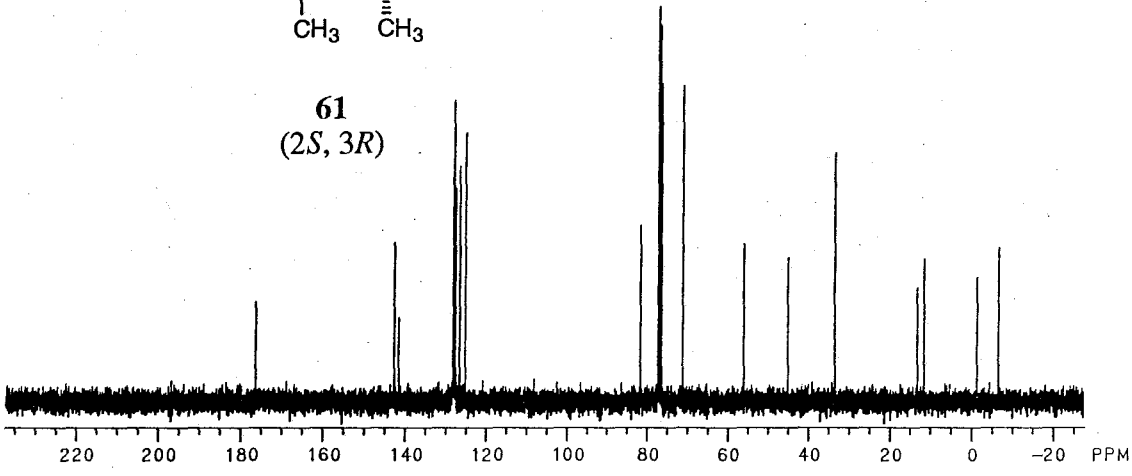
OPERATOR: SEK

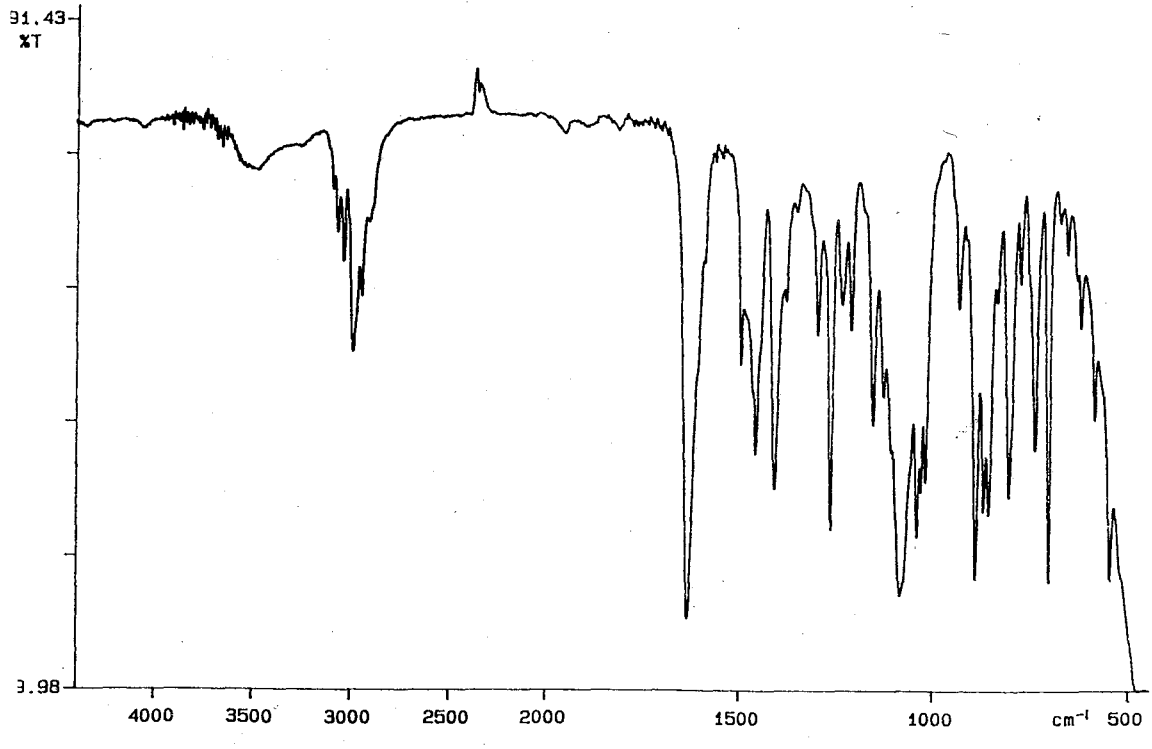
9 8 7 6 5 4 3 2 1 0 −1 PPM

SK2115.100
24AUG93
SEK-II-115
SPOT 1
13C CDCL3
OPERATOR: SEK



61
(2*S*, 3*R*)





93/08/24 08:51
C: 1 scan, 4.0cm-1, flat
SEK-II-115 sp1

APPENDIX II

Coordinates and Crystal Structure

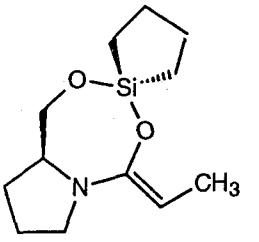
of

Silacyclopentane Silyl Ketene Acetal **8**

TITL AM1 in P2(1)2(1)2(1) Preliminary Data
CELL 1
ORTHOGONAL COORDINATES

SI1	5	0.00000	0.00000	0.00000
O1	4	0.17960	0.92507	-1.33334
O2	4	-1.06371	0.74182	1.04912
N1	3	0.11533	2.71270	1.10946
C1	1	0.47727	2.32259	-1.34749
C2	1	-0.31216	3.09952	-0.30127
C3	1	0.02696	4.61088	-0.37543
C4	1	1.12119	4.78950	0.68449
C5	1	0.62030	3.88536	1.80685
C6	1	-0.69002	1.81013	1.80684
C7	1	-1.07669	1.91875	3.07420
C8	1	-1.85319	0.85222	3.78436
C9	1	-0.69038	-1.66274	-0.43400
C10	1	0.47384	-2.60649	0.04429
C11	1	1.26162	-2.02650	1.11101
C12	1	1.54037	-0.56947	0.87709
H1A	2	0.29250	2.67817	-2.21981
H1B	2	1.41305	2.43973	-1.16792
H2A	2	-1.25234	2.94488	-0.41849
H3A	2	-0.73641	5.15313	-0.16382
H3B	2	0.34375	4.84199	-1.25172
H4A	2	1.19669	5.70073	0.97702
H4B	2	1.97066	4.49101	0.35154
H5A	2	-0.08095	4.31544	2.30175
H5B	2	1.32870	3.65024	2.41051
H7A	2	-0.86516	2.71644	3.56468
H8A	2	-2.05342	1.11458	4.68590
H8B	2	-2.67157	0.69997	3.30612
H8C	2	-1.33326	0.04525	3.79388
H9A	2	-0.86715	-1.73766	-1.37456
H9B	2	-1.49597	-1.83880	0.05756
H10A	2	1.04932	-2.77886	-0.70461
H10B	2	0.11204	-3.44498	0.34030
H11A	2	2.09251	-2.49781	1.20610
H11B	2	0.77696	-2.11253	1.93516
H12A	2	2.30966	-0.46002	0.31346
H12B	2	1.68025	-0.09015	1.69703

LINK	SI1	O1	1
LINK	SI1	O2	1
LINK	O1	C1	1
LINK	C1	H1A	1
LINK	C1	H1B	1
LINK	N1	C2	1
LINK	C1	C2	1
LINK	C2	H2A	1
LINK	C2	C3	1
LINK	C3	H3A	1
LINK	C3	H3B	1



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LINK C3   C4     1
LINK C4   H4A    1
LINK C4   H4B    1
LINK N1   C5     1
LINK C4   C5     1
LINK C5   H5A    1
LINK C5   H5B    1
LINK O2   C6     1
LINK N1   C6     1
LINK C6   C7     1
LINK C7   H7A    1
LINK C7   C8     1
LINK C8   H8A    1
LINK C8   H8B    1
LINK C8   H8C    1
LINK SI1  C9     1
LINK C9   H9A    1
LINK C9   H9B    1
LINK C9   C10    1
LINK C10  H10A   1
LINK C10  H10B   1
LINK C10  C11    1
LINK C11  H11A   1
LINK C11  H11B   1
LINK SI1  C12    1
LINK C11  C12    1
LINK C12  H12A   1
LINK C12  H12B   1

END
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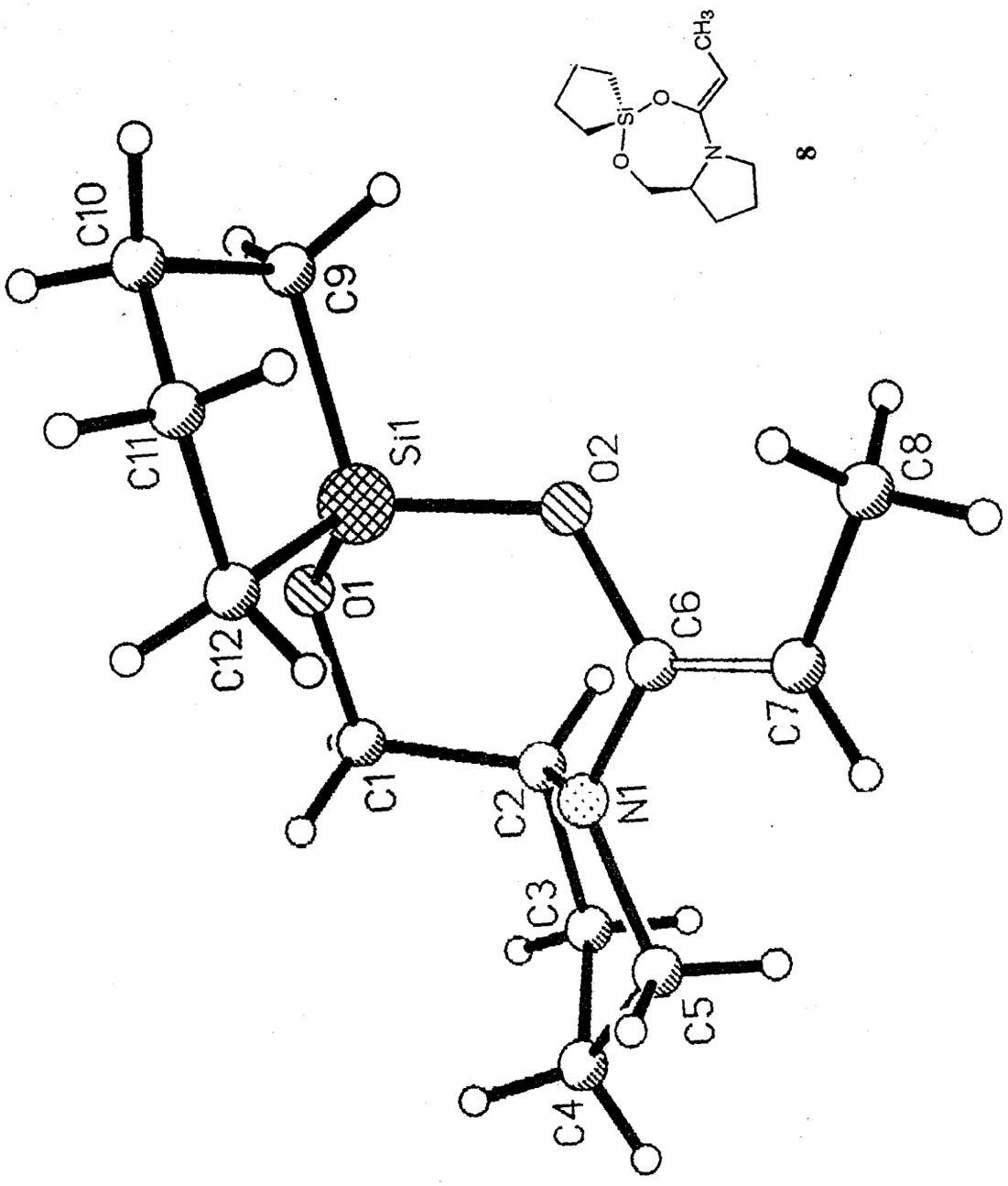

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