Transformation of Alkylated Pseudoephedrine Amides to Highly Enantiomerically Enriched Carboxylic Acids and Ketones

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Abstract

The noncatalyzed aldol addition of *O*-methylsilacyclobutane-*O,O*-ketene acetals to aldehydes and the transformation of alkylated pseudoephedrine amides to highly enantiomerically enriched carboxylic acids and ketones are described. In Chapter 1, constraining of the silicon atom of an *O*-silyl ketene-*O,O*-acetal within a four-membered ring is shown to greatly accelerate the rate of its noncatalyzed aldol addition to aldehydes and ketones. This reaction is highly syn selective and is proposed to proceed through a boat transition state involving pentacoordinate silicon. In Chapter 2, the preparation of carboxylic acids and ketones from alkylated pseudoephedrine amides is described. Acidic, basic, and slightly acidic metal-mediated hydrolysis conditions have been developed. In addition, the treatment of alkylated pseudoephedrine amides with alkyllithium reagents is shown to be a practical method for the preparation of highly enantiomerically enriched ketones.

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List of Abbreviations

Bn	benzyl
BOM	benzyloxymethyl
bp	boiling point
Bu	butyl
calcd	calculated
℃	degrees Celsius
CI	chemical ionization
cm^{-1}	reciprocal centimeters
δ	chemical shift (parts per million)
de	diastereomeric excess
dec	decomposed
DMAP	4-dimethylaminopyridine
E	entgegen
ee	enantiomeric excess
EI	electron impact
equiv	equivalent(s)
EtOAc	ethyl acetate
FAB	fast atom bombardment
FTIR	Fourier transform infrared
g	gram(s)
GC	gas chromatography
h	hour(s)
HRMS	high resolution mass spectroscopy
Hz	Hertz
i	iso

isol	isolated
J	coupling constant
L	liter(s)
LDA	lithium diisopropylamide
M	molar (concentration)
$(M)^+$	molecular ion
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mmol	millimole(s)
MsOH	methanesulfonic acid
μL	microliter(s)
m/z	mass to charge ratio
n	normal
N	normal (concentration)
NMR	nuclear magnetic resonance
OTf	trifluoromethanesulfonate
Ph	phenyl
pH	power of hydrogen (concentration)
ppm	parts per million
Pr	propyl
R	rectus
S	sinister
t	tertiary
TFA	trifluoroacetic acid

THF	tetrahydrofuran
TLC	thin-layer chromatography
v/v	volume to volume ratio
wt %	weight percent
Xψ+	(+)-pseudoephedrine
Z	zusammen

Chapter 1

Rate Acceleration by Small Rings: The Noncatalyzed Aldol Addition of *O*-Methylsilacyclobutane Ketene-*O*,*O*-Acetals

Introduction

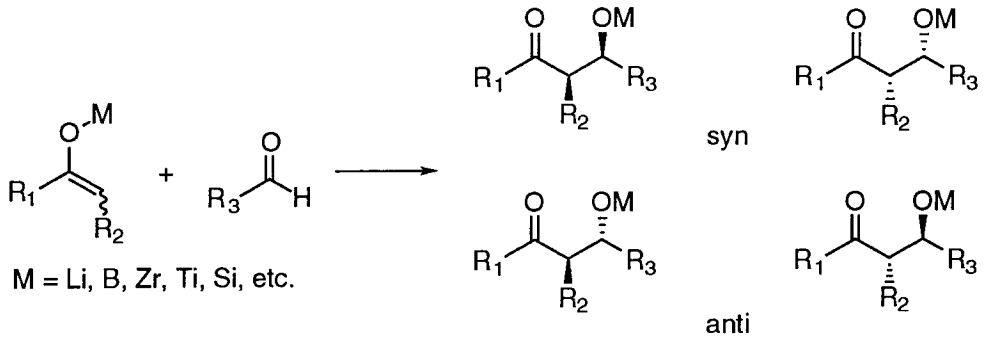
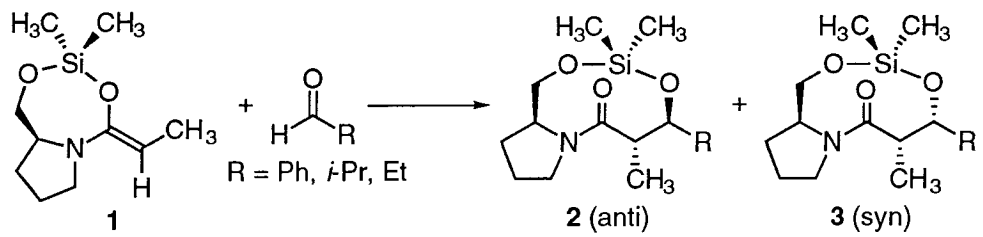


Figure 1. The aldol addition

The "directed" aldol addition of enolates/enol ethers with carbonyl electrophiles is an important reaction for the formation of carbon-carbon bonds.[1] This transformation generates two new stereocenters (if both components are prochiral) and four stereoisomeric products are possible (Figure 1). Any effort to obtain only one of these isomers must address both enantioselectivity and diastereoselectivity issues.

Among the enol components that have been utilized in aldol chemistry are the silyl enol derivatives of carbonyl compounds. While the trialkylsilyl enol derivatives of aldehydes, ketones, and esters do not add to carbonyl electrophiles under mild thermal conditions, they do react (even at –78 °C) in the presence of 1 equiv of $TiCl_4$.[2] In 1990, Myers and Widdowson[3] reported that the triethylsilyl enol derivative (*O*-triethylsilyl ketene-*N*,*O*-acetal) of *N*,*N*-dimethyl propionamide undergoes noncatalyzed addition to aldehydes at or below ambient temperature. They also found that the *O*-dimethylsilyl ketene-*N*,*O*-acetal of (*S*)-prolinol propionamide (**1**) reacts with aldehydes



Scheme I

(at 23 °C in CH_2Cl_2) to give a ≥38:1 ratio of anti (**2**) to syn (**3**) products (Scheme I). They proposed a pseudorotational mechanism involving a transition state with pentacoordinate silicon (Figure 2).[4] As seen in Figure 2, the proposed reactive transition state (**C**) could be accessed by a single pseudorotation from either isomer **A** with one axial and one equatorial methyl group or isomer **B** with two equatorial methyl groups. To distinguish between a mechanism proceeding through isomer **A** and one proceeding through isomer **B**, Myers and Kephart[5] prepared the silacyclobutane derivative (**4**) of **1**. They hypothesized that the silacyclobutane ring would accelerate the formation of **A** but would make **B** prohibitively strained. In support of the mechanism proceeding through isomer **A**, they found that the reaction of **4** not only proceeds, it does so with a rate acceleration of ≈2 × 10^6. Such a dramatic rate enhancement prompted us to ask if

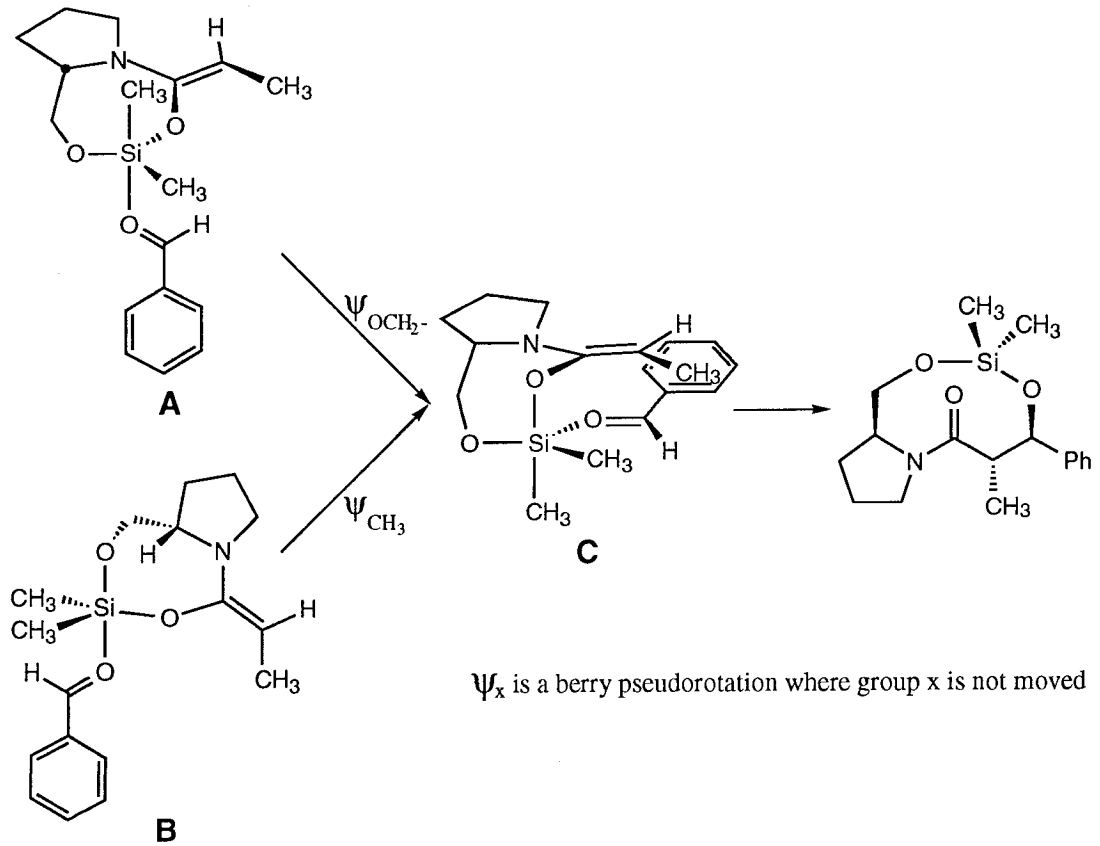
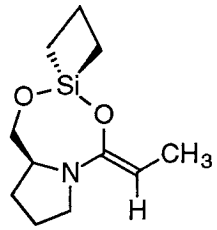


Figure 3. Proposed pseudorotational mechanism for the noncatalyzed aldol addition of **1** to benzaldehyde.



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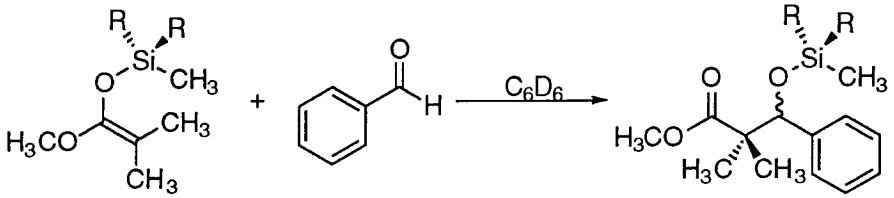
this silacyclobutane strategy might also promote the uncatalyzed aldol additions of other silyl enol derivatives. The *O*-methylsilacylobutane ketene-*O,O*-acetals of several esters thus were studied.

Aldol Reactions of *O*-Methylsilacylclobutane Ketene Acetals

O-Methylsilacyclobutane ketene-*O,O*-acetals were prepared by kinetic trapping of the lithium enolates (LDA) of the corresponding esters with 1-chloro-1-methyl silacyclobutane. 1-chloro-1-methylsilacyclobutane was obtained by intramolecular Grignard reaction of 3-chloropropylmethyldichlorosilane.[6,7] Initial attempts focused on the preparation of the *O*-silyl ketene-*O,O*-acetal of ethyl acetate, but only the *C*-silylated ester was obtained. As increasing the steric bulk at the ester α-carbon has been shown to increase the proportion of*O*-silylation,[8] attempts were next made to prepare the *O*-silyl ketene-*O,O*-acetal of methyl propionate. Although the desired *O*-silylated product was observed, it was formed in a 3:2 ratio with the *C*-silylated ester. Further increasing the bulk at the α-carbon by employing methyl isobutyrate as the substrate made it possible to obtain only *O*-methylsilacyclobutane ketene-*O,O*-acetal **5** as the product.



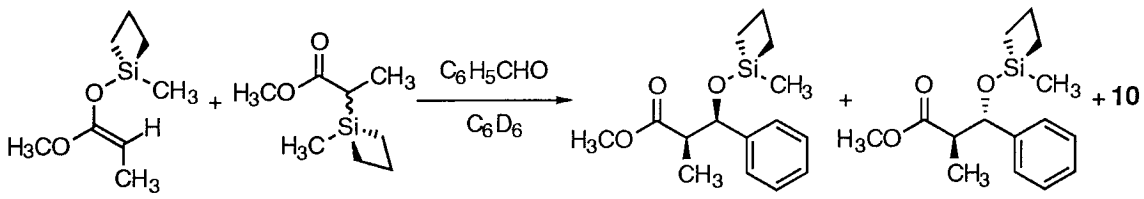
5: R = $(CH_2)_3$
6: R = CH_3

7: R = $(CH_2)_3$
8: R = CH_3

Scheme II

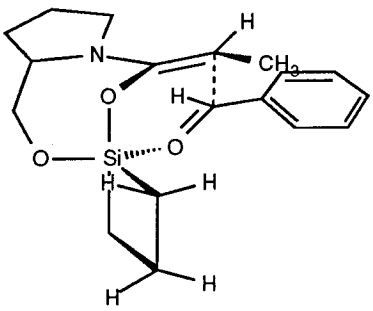
The aldol chemistry of *O*-methylsilacyclobutane ketene-*O,O*-acetal **5** was then examined. Although Creger[9] has reported that the trimethylsilyl analog of **5**, *O*-trimethylsilyl ketene-*O,O*-acetal **6**, does undergo noncatalyzed aldol addition to benzaldehyde, this reaction was conducted at high concentration and temperature (neat, 150 °C, 18 h, 81% yield). As a control, *O*-trimethylsilyl ketene-*O,O*-acetal **6** was heated with benzaldehyde (0.2 M each in benzene-d_6), forming less than 25% of aldol product **8** after 24 h at 150 °C. By contrast, *O*-methylsilacyclobutane ketene-*O,O*-acetal **5** reacted cleanly with benzaldehyde in 4 h at 27 °C (0.2M each in benzene-d_6) to give aldol product **7** quantitatively (Scheme II). Under the same conditions, **6** showed no reaction even after 24 h. *O*-Methylsilacyclobutane ketene-*O,O*-acetal **5** also added to less reactive substrates such as isobutyraldehyde (0.2M, benzene-d_6, 1 day, 60 °C, 80% conversion) and acetone (excess, benzene-d_6, 3 days, 65 °C, 85% conversion), albeit much more slowly.

To determine the diastereoselectivity of this noncatalyzed aldol reaction, it was necessary to utilize the *O*-methylsilacyclobutane ketene-*O,O*-acetal of methyl propionate (**9**) even though **9** could not be separated from its 3:2 mixture with *C*-silylated ester **10** (distillation was ineffective and the moisture sensitivity of **9** made purification by flash chromatography impossible). Fortunately, **10** proved not to be a problem since it was inert under the noncatalyzed reaction conditions. Thus, the reaction of *E*-**9** (geometry based on the known predominant geometry of the Li enolate from LDA[1]) with



Scheme III

benzaldehyde in benzene-d_6 gave quantitative conversion to the syn adduct **11** with good stereocontrol [19:1 syn(**11**): anti (**12**)] after 45 min at 27 °C (Scheme III). The Mukaiyama aldol, by contrast, was reported to give only modest selectivity (3:1 syn:anti, from ethyl propionate) even at –78 °C.[10]



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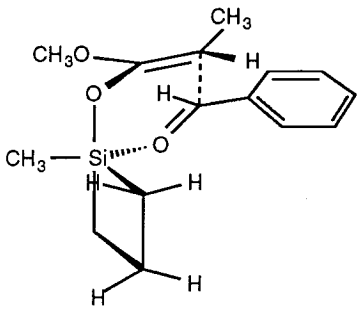
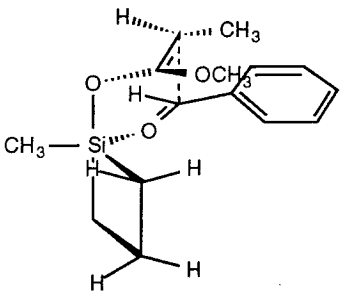
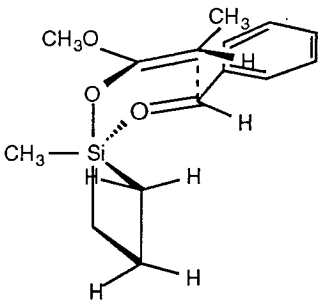


E



F



G

The high syn selectivity of the noncatalyzed aldol addition of *E*-**9** with benzaldehyde was unexpected. Syn selectivity (≈6:1 syn to anti) had also been observed in the noncatalyzed aldol addition of *O*-silacyclobutane ketene-*N,O*-acetal *Z*-**4** to benzaldehyde,[5] and had been rationalized by chair transition state **D**. The analogous chair transition state for *E*-**9** (**E**), however, predicted anti products. On the other hand, the boat transition state obtained by rotation of the enolate in **E** around the C–OSi bond (**F**) would explain the observed syn selectivity. Perhaps, the 1,3-diaxial interaction between the silicon methyl group and the enolate methoxy group in anti-chair **E** induced a preference for syn-boat **F** which lacked such unfavorable 1,3-diaxial interactions. The two eclipsing interactions in syn-boat **F** would tend to disfavor it, but the bonds connecting the eclipsed

bonds, the Si–$O_{enolate}$ bond and the forming C–C bond, would be lengthened in the transition state as one was breaking while the other was forming. Thus, the disadvantage of the eclipsing interactions would be reduced.

Rotation around the Si–$O_{benzaldehyde}$ bond in **E** would also afford a syn-boat transition state (**G**), but previous work argued against transition state **G**. As shown in Figure 3, the anti selectivity of the noncatalyzed aldol addition of *O*-dimethylsilyl ketene-*N,O*-acetal **1** to benzaldehyde and the syn selectivity of the analogous reaction with *O*-silacyclobutane ketene-*N,O*-acetal **4** had been rationalized to arise from anti-boat **H** and syn-chair **D** respectively. It was proposed that the constraint of the silicon atom in a four-membered ring increased the steric repulsion between the protons of the equatorial carbon with the aldehyde proton (**H** vs **J**), inducing a preference for syn-chair **D** over anti-boat **J**.[11] These same steric interactions would also be present in syn-boat **G** and would be expected to disfavor it versus anti chair **E**.

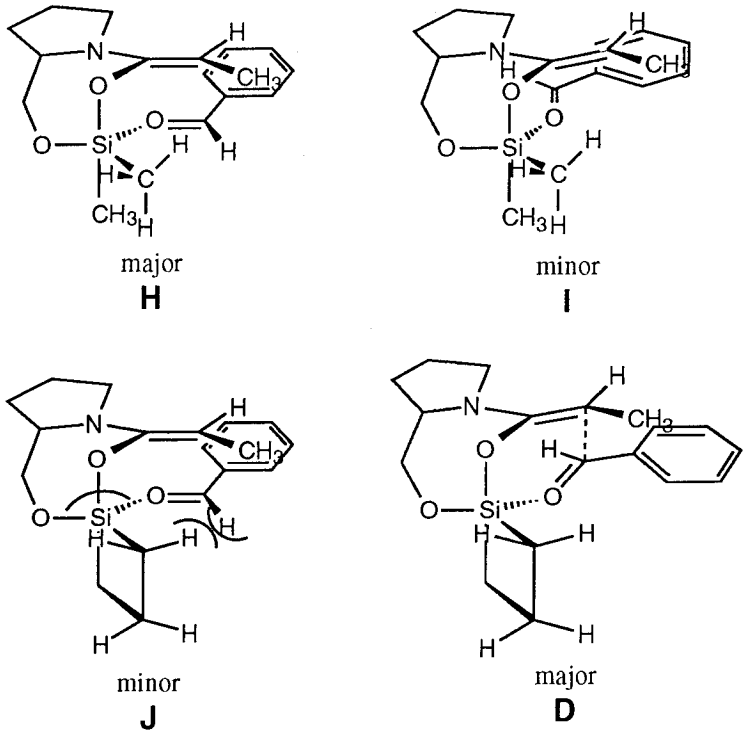
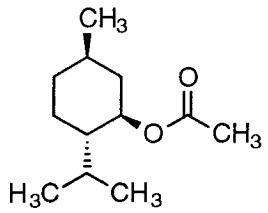


Figure 6. Proposed transition states to rationalize the change in diastereoselectivity between **1** and **4** in the noncatalyzed aldol addition to benzaldehyde.

A serendipitous observation made in the course of this aldol study was that catalytic amounts of an alkoxide base (potassium *tert*-butoxide) could greatly accelerate the aldol reaction. For example, the addition of *O*-methylsilacyclobutane ketene-*O,O*-acetal **5** to benzaldehyde (0.2 M each, benzene-d_6) was complete in 5 min at 27 °C when 0.05 equiv of potassium *tert*-butoxide was present. Under the same conditions, even the extremely sluggish reaction of trimethylsilyl analog **6** proceeded quantitatively in 45 min. Unfortunately, this alkoxide-catalyzed reaction displayed poor syn selectivity. The reaction of *O*-methylsilacylclobutane ketene-*O,O*-acetal **9** with benzaldehyde (0.12 M each, benzene-d_6) in the presence of catalytic *t*-BuOK gave only a 1.7:1 ratio of syn : anti aldol products. Interestingly, the *C*-silylated ester (**10**) was slowly consumed in this reaction, probably by isomerization to the *O*-silyl ketene acetal.



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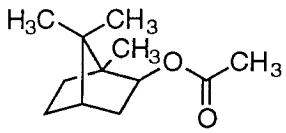

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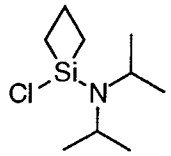
In hopes of making this non-catalyzed aldol reaction asymmetric, the *O*-methylsilacyclobutane ketene acetals of (–)-menthyl acetate (**13**) and (–)-bornyl acetate (**14**) were prepared in situ by the addition of 1-chloro-1-methylsilacylclobutane to their respective potassium enolates (to avoid excessive *C*-silylation) and then were reacted with benzaldehyde. In both cases, however, both the yield and the diastereoselectivity of these aldol reactions were poor (29% yield and 1:1.7 with **13** and 15% yield and 1.3:1 with **14**). By comparison, the direct reaction of the potassium enolates of **13** and **14** with benzaldehyde gave much higher yields but comparable diastereoselectivities (77% yield and 2.4:1 with **13** and 76% yield and 1.2:1 with **14**). Curiously, there was a reversal in diastereoselectivity between the silicon-mediated aldol and the potassium enolate aldol of

13. This poor diastereoselectivity was attributed to rotational freedom around the ester linkage and further work with these chiral esters was not pursued.

We also attempted to develop a solution to the *C*-silylation problem observed in the preparation of *O*-methylsilacyclobutane ketene-*O,O*-acetal **9**. Since increasing the steric bulk at the α-carbon of the ester substrate had been found to increase the proportion of *O*-silylation, it was hypothesized that greater steric bulk at the silicon atom might produce a similar effect. The reaction of diisopropylamine with dichlorosilacyclobutane had been found to afford a monoamino compound, and this 1-chloro-1-(diisopropylamino)-silacyclobutane (**15**) seemed an ideal silylating agent for testing our premise. As hoped, when the lithium enolate of methyl propionate was trapped with (**15**), only *O*-silylated product was obtained. However, both the *E* and *Z* isomers of the *O*-diisopropylaminosilacyclobutane ketene-*O,O*-acetal (**16**, 2:1 *E* : *Z*) were formed. In the noncatalyzed aldol reaction of **16** with benzaldehyde, *E*-**16** reacted slowly (≈75% conversion after 24 h at 27 °C, 0.5 M each in benzene-d_6) to afford predominantly syn aldol products (15:1 syn : anti) while *Z*-**16** proved to be inert under the reaction conditions. This strategy thus offered no advantage over the methylsilacyclobutane system (**9** and **10**) as unreactive *C*-silylated ester **10** was now replaced by unreactive *Z*-**16**.



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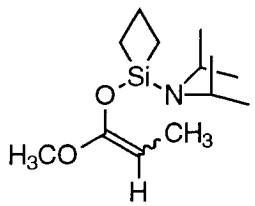

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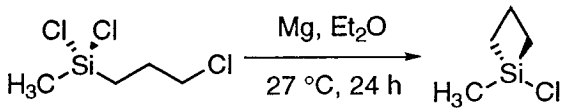
Experimental Section

General Procedures. All non-aqueous reactions were performed in flame-dried, round-bottomed flasks, equipped with a magnetic stirring bar and fitted with a rubber septum under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation at ~25 Torr. Flash column chromatography was performed as described by Still et al.[12] employing 230–400 mesh silica gel. Analytical thin-layer chromatography was performed using glass plates precoated with 0.25-mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm).

Materials. Commercial reagents and solvents were used as received with the following exceptions. Tetrahydrofuran and ether were distilled under nitrogen from sodium benzophenone ketyl. Diisopropylamine, triethylamine, chlorotrimethylsilane, 3-chloropropylmethyldichlorosilane, methyl propionate, and methyl isobutyrate were distilled under nitrogen from calcium hydride. The molarity of *n*-butyllithium was determined by titration against diphenylacetic acid as an indicator (average of three determinations).[13] Solvents used for flash column chromatography were reagent-grade.

Instrumentation. Infrared data are presented as follows: frequency of absorption (cm^{-1}), intensity of absorption (br = broad, s = strong, m = medium). ^1H NMR spectra were recorded at 400 or 300 MHz, and ^{13}C NMR spectra were recorded at 100 or 75 MHz; chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane. ^1H NMR chemical shifts are referenced to the signal for residual hydrogen in the NMR solvent ($CHCl_3$: δ 7.26, C_6HD_5: δ 7.15). Data are presented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sx = sextet, m = multiplet), integration, and coupling constant in

Hertz. ^{13}C NMR chemical shifts are referenced to the carbon signal for the solvent ($CDCl_3$: δ 77.0, C_6D_6: δ 128.0). Mass spectrometry was performed at the University of California at Irvine.

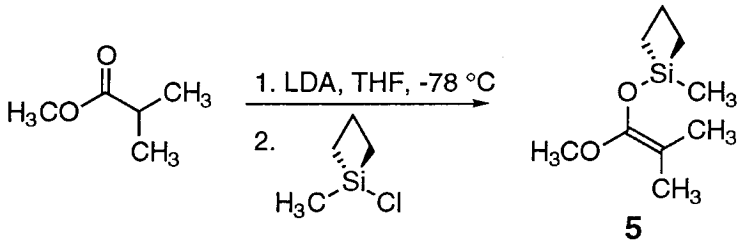


1-Chloro-1-methylsilacyclobutane

A 1-L 3-necked flask equipped with a mechanical stirrer, a 125-mL pressure-equalizing addition funnel, and a condensor was charged with magnesium turnings (24.3 gm, 1.0 mol, 4 equiv). The reaction flask was flushed with dry argon and the magnesium turnings were stirred for 10-15 h at 27 °C, causing them to change from a shiny metallic color to a dull gray-black. Ether (150 mL) containing a catalytic amount of iodine was added, followed by 3-chloropropylmethyldichlorosilane (40.0 mL, 0.25 mol, 1 equiv). The resulting mixture was stirred for 24 h at 27 °C, giving a thick, white, mud-like slurry. To facilitate the stirring, ether (100 mL) was added dropwise over this period. The mixture was diluted with anhydrous pentane (600 mL), then was filtered through celite under an argon atmosphere to give a clear, slightly maroon filtrate. This filtrate was concentrated by distillation at atmospheric pressure to remove the pentane and ether. The resulting concentrate then was further distilled to give 1-chloro-1-methylsilacyclobutane (16.2 g, 53%, bp 98-100 °C) as a clear colorless liquid.

^{1}H NMR (400 MHz, C_6D_6) δ: 2.00 (m, 1H, one of $SiCH_2CH_2$), 1.63 (m, 1H, one of $SiCH_2CH_2$), 1.34 (m, 2H, one of $SiCH_2$), 1.11 (m, 2H, one of $SiCH_2$), 0.28 (s, 3H, $SiCH_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.7, 15.8, 3.5.

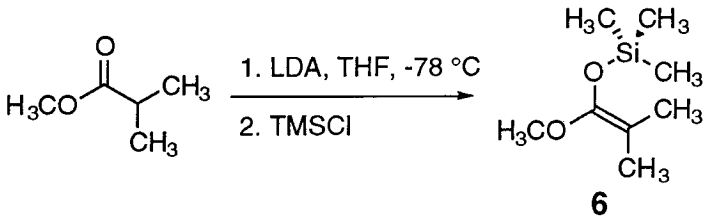


5

O-Methylsilacyclobutane ketene-*O,O*-acetal **5**

A 50-mL round-bottomed flask equipped with a magnetic stirring bar was charged with tetrahydrofuran (20 mL) and diisopropylamine (4.2 mL, 30 mmol, 1.2 equiv). This solution was cooled to –78 °C and a solution of *n*-butyllithium in hexanes (2.43 M, 10.3 mL, 25 mmol, 1 equiv) was added via syringe. The resulting solution was stirred for 15 min at –78 °C and methyl isobutyrate (3.4 mL, 30 mmol, 1.2 equiv) was then added dropwise via syringe. The reaction mixture was stirred for an additional 15 min at –78 °C, and 1-chloro-1-methylsilacyclobutane (3.75 mL, 30 mmol, 1.2 equiv) was then added via syringe. The reaction mixture was stirred at –78 °C for an additional 4 h, then was concentrated at 0 °C and 10 millitorr to give a pasty concentrate. Pentane (25 mL) was added to this concentrate to precipitate lithium chloride and the resulting mixture was allowed to settle. The clear supernatent was collected via cannula, then was concentrated as before until no further bubbling was observed for 20 min. This cloudy concentrate was purified by Kugelrohr bulb-bulb distillation (23 °C and 10 millitorr) to give *O*-methylsilacyclobutane ketene-*O,O*-acetal **5** (3.9 g, 85%) as a cloudy liquid.

^{1}H NMR (400 MHz, C_6D_6) δ:	3.33 (s, 3H, OCH_3), 2.00 (m, 1H, one of $SiCH_2CH_2$), 1.73 (s, 3H, one of $C(CH_3)_2$), 1.65 (s, 3H, one of $C(CH_3)_2$), 1.50 (m, 3H, one of $SiCH_2CH_2$, one of $SiCH_2CH_2$), 1.15 (m, 2H, one of $SiCH_2CH_2$), 0.28 (s, 3H, $SiCH_3$).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	148.8, 90.7, 56.4, 19.1, 16.8, 16.1, 13.5, 1.6.
FTIR (neat, cm^{-1}):	2925 (m), 1704 (s), 1258 (m), 1167 (s), 1027 (m), 941(m), 906 (m), 871 (m), 776 (m), 720 (w), 665 (w).

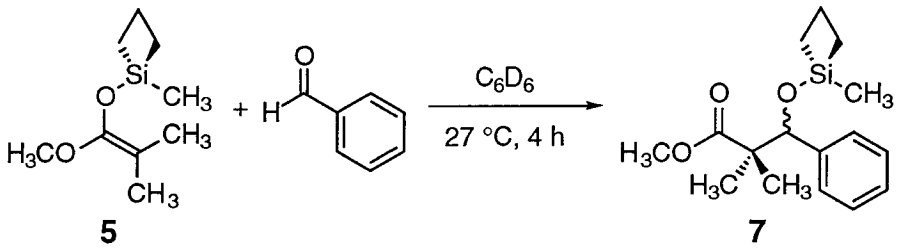


6

O-Trimethylsilyl ketene-*O*,*O*-acetal **6**

A 100-mL round-bottomed flask equipped with a magnetic stirring bar was charged with tetrahydrofuran (40 mL) and diisopropylamine (4.2 mL, 30 mmol, 1.2 equiv). This solution was cooled to –78 °C and a solution of *n*-butyllithium in hexanes (2.43 M, 10.3 mL, 25 mmol, 1 equiv) was added via syringe. The resulting solution was stirred for 20 min at –78 °C and methyl isobutyrate (3.4 mL, 30 mmol, 1.2 equiv) was then added dropwise via syringe. The reaction mixture was stirred for an additional 15 min at –78 °C, and chlorotrimethylsilane (3.81 mL, 30 mmol, 1.2 equiv) was then added via syringe. The reaction mixture was stirred at –78 °C for an additional 4.5 h, then was concentrated at 0 °C and 10 millitorr to give a pasty concentrate. Pentane (25 mL) was added to this concentrate to precipitate lithium chloride and the resulting mixture was allowed to settle. The clear supernatent was collected via cannula, then was concentrated as before until no further bubbling was observed for 20 min. This cloudy concentrate was purified by Kugelrohr bulb-bulb distillation (23 °C and 10 millitorr) to give *O*-trimethylsilyl ketene-*O*,*O*-acetal **6** (3.3 g, 76%) as a cloudy liquid.

^{1}H NMR (300 MHz, C_6D_6) δ:	3.32 (s, 3H, OCH_3), 1.72 (s, 3H, one of $C(CH_3)_2$), 1.65 (s, 3H, one of $C(CH_3)_2$), 0.17 (s, 9H, $SiCH_3$).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	149, 91, 57, 17, 16, 0.
FTIR (neat, cm^{-1}):	2958 (s), 2907 (s), 1702 (s), 1441 (m), 1252 (s), 1175 (s), 1027 (s), 945 (s), 870 (s), 843 (s), 756 (m), 690 (w), 665 (w).



5 **7**

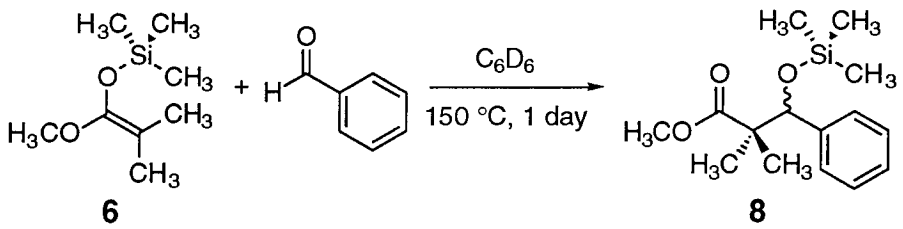
O-Methylsilacyclobutane aldol adduct **7**

An NMR tube filled with dry Ar and sealed with a rubber septum was charged with benzene-d_6 (0.60 mL), benzaldehyde (10 μL, 0.10 mmol, 1 equiv), and toluene (10 μL, internal reference). A reference ^{1}H NMR spectrum of this sample was taken and *O*-methylsilacyclobutane ketene-*O,O*-acetal **5** (20 μL, 0.10 mmol, 1 equiv) was added. The reaction was monitored by high resolution ^{1}H NMR, showing complete conversion of *O*-methylsilacyclobutane ketene-*O,O*-acetal **5** to aldol adduct **7** after 4 h at 27 °C.

^{1}H NMR (300 MHz, C_6D_6) δ: 7.2 (m, 5H, **H**-arom), 5.32 (s, 1H, PhC**H**), 3.38 (s, 3H, OC$\mathbf{H}_3$), 1.90 (m, 1H, one of SiCH$_2$C$\mathbf{H}_2$), 1.45 (m, 2H, one of SiC$\mathbf{H}_2$CH$_2$), 1.32 (s, 3H, one of C(C$\mathbf{H}_3$)$_2$), 1.05 (m, 3H, one of SiCH$_2$C$\mathbf{H}_2$, one of SiC$\mathbf{H}_2$CH$_2$), 1.04 (s, 3H, one of C(C$\mathbf{H}_3$)$_2$), 0.19 (s, 3H, SiC$\mathbf{H}_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 177.1, 140.3, 127.7, 127.6, 127.5, 79.5, 51.7, 48.9, 21.8, 19.0, 18.9, 18.2, 13.4, –1.5.

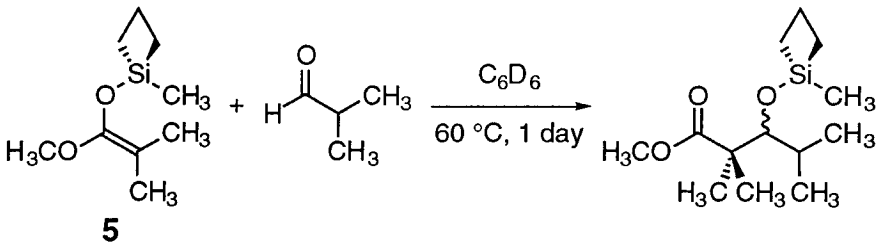
FTIR (neat, cm^{-1}): 2966 (m), 1743 (s), 1725 (s), 1249 (m), 1132 (s), 1090 (m), 1061 (s), 908 (m), 867 (m), 761 (m), 697 (s).



O-Trimethylsilyl aldol adduct **8**

A dry sealable NMR tube filled with dry Ar and sealed with a rubber septum was charged with benzene-d_6 (0.50 mL), benzaldehyde (11 μL, 0.10 mmol, 1 equiv), toluene (10 μL, internal reference), and *O*-trimethylsilyl ketene-*O,O*-acetal **6** (20 μL, 0.10 mmol, 1 equiv). The rubber septum was replaced with a vacuum adapter and the reaction mixture was degassed by three cycles of freezing the reaction mixture in liquid nitrogen, evacuating the NMR tube, and thawing the reaction mixture under static high vacuum. The sample then was frozen again and the NMR tube was sealed under high vacuum using a gas torch. The NMR tube was immersed in a 150 °C oil bath and the progress of the reaction monitored by high resolution ^{1}H NMR. After 24 h at 150 °C, ^{1}H NMR analysis showed <25% of the desired aldol product as well as the starting materials and unidentified decomposition products.

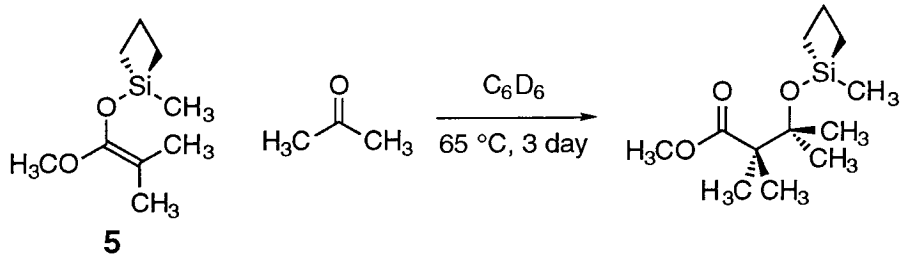
^{1}H NMR (300 MHz, C_6D_6) δ: 7.15 (m, 5H, **H**-arom), 5.12 (s, 1H, SiOC**H**), 3.39 (s, 3H, OC$\mathbf{H}_3$), 1.30 (s, 1H, one of C(C$\mathbf{H}_3$)$_2$), 1.02 (s, 3H, one of C(C$\mathbf{H}_3$)$_2$), 0.00 (s, 9H, Si(C$\mathbf{H}_3$)$_3$).



O-Methylsilacyclobutane aldol adduct of **5** with isobutyraldehyde

An NMR tube filled with dry Ar and sealed with a rubber septum was charged with benzene-d_6 (0.50 mL), isobutyraldehyde (10 μL, 0.10 mmol, 1 equiv), toluene (12 μL, internal reference), and *O*-methylsilacyclobutane ketene-*O,O*-acetal **5** (20 μL, 0.10 mmol, 1 equiv). The NMR tube was immersed in a 60 °C oil bath and the progress of the reaction was monitored by high resolution ^{1}H NMR. After 24 h at 60 °C, ^{1}H NMR analysis of the reaction mixture showed 80% conversion of *O*-methylsilacyclobutane ketene-*O,O*-acetal **5** to the aldol adduct.

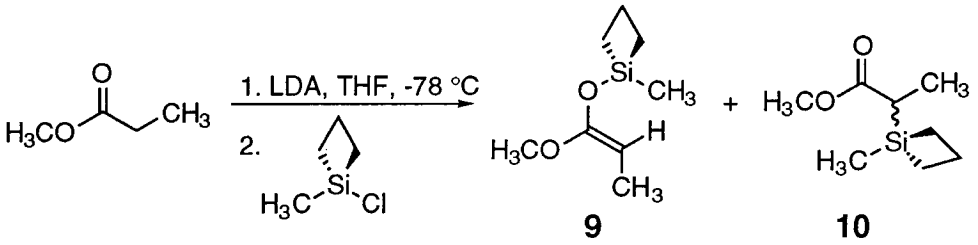
^{1}H NMR (300 MHz, C_6D_6) δ: 3.98 (d, 1H, J = 4.8 Hz, SiOC**H**), 3.33 (s, 3H, OCH_3), 1.95 (m, 1H, one of $SiCH_2CH_2$), 1.75 (m, 1H, one of $SiCH_2CH_2$), 1.40 (m, 2H, one of $SiCH_2CH_2$), 1.24 (s, 3H, one of $COC(CH_3)_2$), 1.20 (s, 3H, one of $COC(CH_3)_2$), 1.20 (m, 3H, $CH(CH_3)_2$, one of $SiCH_2CH_2$), 0.95 (d, 3H, J = 6.8 Hz, one of $CH(CH_3)_2$), 0.86 (d, 3H, J = 6.8 Hz, one of $CH(CH_3)_2$), 0.25 (s, 3H, $SiCH_3$).



O-Methylsilacyclobutane aldol adduct of **5** with acetone

An NMR tube filled with dry Ar and sealed with a rubber septum was charged with benzene-d_6 (0.20 mL), acetone (183 μL, 2.50 mmol, 5.0 equiv), *Z*-dichloroethylene (38 μL, internal reference), and *O*-methylsilacyclobutane ketene-*O,O*-acetal **5** (96 μL, 0.50 mmol, 1 equiv). The rubber septum was replaced with a vacuum adapter and the reaction mixture was degassed by three cycles of freezing the reaction mixture in liquid nitrogen, evacuating the NMR tube, and thawing the reaction mixture under static high vacuum. The sample then was frozen again and the NMR tube was sealed under high vacuum using a gas torch. The NMR tube was immersed in a 65 °C oil bath and the progress of the reaction was monitored by high resolution ^{1}H NMR. After 3 days at 65 °C, ^{1}H NMR analysis of the reaction mixture showed 85% conversion of *O*-methylsilacyclobutane ketene-*O,O*-acetal **5** to the aldol adduct.

^{1}H NMR (300 MHz, C_6D_6) δ:	3.34 (s, 3H, OCH_3), 2.05 (m, 1H, one of $SiCH_2CH_2$), 1.52 (m, 1H, one of $SiCH_2CH_2$), 1.34 (m, 2H, one of $SiCH_2CH_2$), 1.32 (s, 6H, $COC(CH_3)_2$ or $SiOC(CH_3)_2$), 1.25 (s, 6H, $COC(CH_3)_2$ or $SiOC(CH_3)_2$), 1.22 (m, 2H, one of $SiCH_2CH_2$), 0.23 (s, 3H, $SiCH_3$).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	176.9, 77.9, 51.4, 51.0, 26.7, 21.3, 21.1, 13.4, 0.5.
FTIR (neat, cm^{-1}):	2978 (s), 1725 (s), 1461(m), 1373 (m), 1273 (s), 1149 (s), 1120 (s), 1044 (s), 920 (s), 867 (s), 791 (s), 714 (w), 662 (w).
HRMS (CI: NH_3)	Calcd for $C_{12}H_{25}O_3Si$ $(MH)^+$: 245.1573. Found: 245.1585.



(*E*)-*O*-Methylsilacyclobutane ketene-*O*,*O*-acetal **9** and *C*-silylated methyl propionate **10**

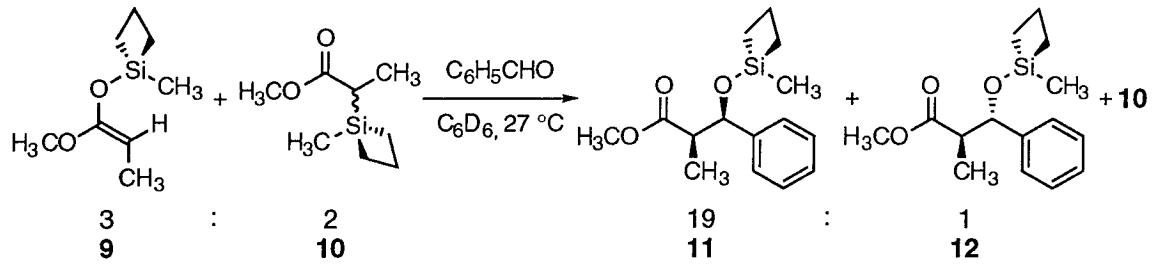
A 100-mL round-bottomed flask equipped with a magnetic stirring bar was charged with tetrahydrofuran (25 mL) and diisopropylamine (4.2 mL, 30 mmol, 1.2 equiv). This solution was cooled to –78 °C and a solution of *n*-butyllithium in hexanes (2.5 M, 10.0 mL, 25 mmol, 1 equiv) was added via syringe. The resulting solution was stirred for 15 min at –78 °C and methyl propionate (2.9 mL, 30 mmol, 1.2 equiv) was then added dropwise via syringe. The reaction mixture was stirred for an additional 15 min at –78 °C, and then 1-chloro-1-methylsilacyclobutane (3.75 mL, 30 mmol, 1.2 equiv) was added via syringe. The reaction mixture was stirred at –78 °C for an additional 3 h, then was concentrated at 0 °C and 10 millitorr to give a pasty concentrate. Pentane (25 mL) was added to this concentrate to precipitate lithium chloride and the resulting mixture was allowed to settle. The clear supernatent was collected via cannula, then was concentrated as before until no further bubbling was observed for 20 min. This cloudy concentrate was purified by Kugelrohr bulb-bulb distillation (23 °C and 10 millitorr) to give a mixture of *O*-methylsilacyclobutane ketene-*O*,*O*-acetal **9** and *C*-silylated ester **10** (3.1 g, 72% combined yield, 3 : 2 ratio of **9** : **10**) as a cloudy liquid.

(E)-*O*-Methylsilacyclobutane ketene-*O,O*- acetal **9**

^{1}H NMR (400 MHz, C_6D_6) δ: 3.90 (q, 1H, J = 6.7 Hz, C**H**CH_3), 3.36 (s, 3H, OCH_3), 1.95 (m, 1H, one of $SiCH_2CH_2$), 1.69 (d, 3H, J = 6.7 Hz, $CHCH_3$), 1.50 (m, 3H, one of $SiCH_2CH_2$, one of $SiCH_2CH_2$), 1.10 (m, 2H, one of $SiCH_2CH_2$), 0.24 (s, 3H, $SiCH_3$).

C-Silylated methyl propionate **10**

^{1}H NMR (400 MHz, C_6D_6) δ: 3.36 (s, 3H, OCH_3), 2.13 (q, 1H, J = 7.1 Hz, C**H**CH_3), 2.03 (qn, 2H, J = 8 Hz, $SiCH_2CH_2$), 1.18 (d, 3H, J = 7.1 Hz, $CHCH_3$), 1.10 (m, 2H, one of $SiCH_2CH_2$), 0.97 (m, 2H, one of $SiCH_2CH_2$), 0.16 (s, 3H, $SiCH_3$).



3 : 2 → 19 : 1

9 **10** **11** **12**

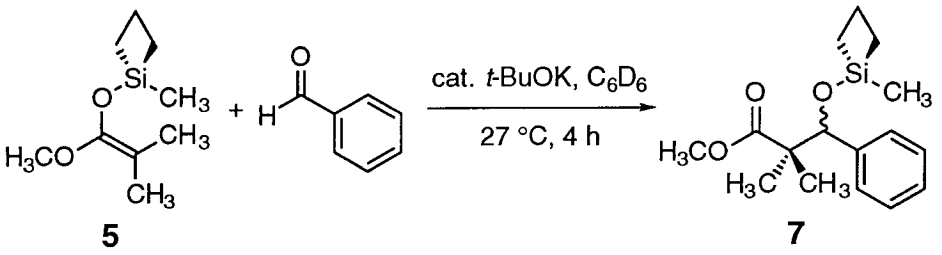
O-Methylsilacyclobutane aldol adducts **11** and **12**

An NMR tube filled with dry Ar and sealed with a rubber septum was charged with benzene-d_6 (0.60 mL), benzaldehyde (20 μL, 0.20 mmol, 3 equiv), and a 3 : 2 mixture of *O*-methylsilacyclobutane ketene-*O,O*-acetal **9** and *C*-silylated methyl propionate **10** (20 μL, 0.07 mmol of **9**, 1 equiv). The reaction was monitored by high resolution ^{1}H NMR, showing complete conversion of *O*-methylsilacyclobutane ketene-*O,O*-acetal **9** to a mixture of aldol products **11** and **12** (19 : 1, respectively) after 45 min at 27 °C. The *C*-silylated methyl propionate, **10**, was not consumed in this reaction.

Syn *O*-methylsilacyclobutane aldol adduct **11**

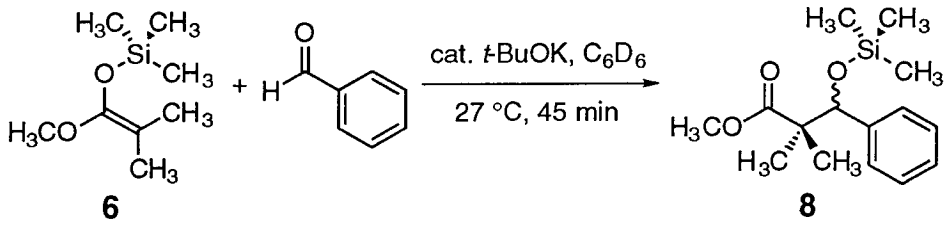
^{1}H NMR (300 MHz, C_6D_6) δ:	7.20 (m, 5H, **H**-arom), 5.39 (d, 1H, J = 5.4 Hz, SiOC**H**), 3.27 (s, 3H, O**CH$_3$**), 2.74 (dq, 1H, J_1 = 5.4 Hz, J_2 = 7.0 Hz, **CH**CH$_3$), 1.90 (m, 1H, one of SiCH$_2$C**H$_2$**), 1.40 (m, 2H, one of Si**CH$_2$**CH$_2$), 1.23 (d, 3H, J = 7.0 Hz, CHC**H$_3$**), 1.10 (m, 3H, one of Si**CH$_2$**CH$_2$, one of SiCH$_2$C**H$_2$**), 0.21 (s, 3H, Si**CH$_3$**).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	174.5, 142.4, 128.1, 127.4, 126.0, 75.9, 51.5, 48.4, 18.9, 18.4, 11.4, –1.5.
FTIR (neat, cm^{-1}):	3519 (br), 2955 (s), 1737 (s), 1455 (s), 1255 (s), 1196 (s), 1120 (s), 1061 (s), 914 (s), 873 (s), 773 (s), 703 (s), 662 (m), 544 (w), 503 (w).
HRMS (Et_2O / NBA):	Calcd for $C_{15}H_{23}O_3Si$ $(MH)^+$: 279.1416. Found: 279.1431.

In anti *O*-methylsilacyclobutane aldol adduct **12**, the SiOC**H** resonance is observed at 5.14 (d, 1H, J = 8.8 Hz).



O-Methylsilacyclobutane aldol adduct **7**

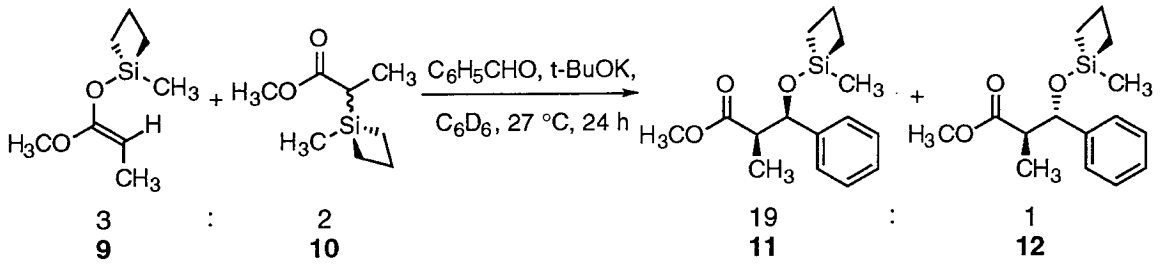
An NMR tube filled with dry Ar and sealed with a rubber septum was charged with a solution of potassium *tert*-butoxide in tetrahydrofuran (0.5 M, 10 μL, 0.05 equiv). The tetrahydrofuran was removed in vacuo and benzene-d_6 (0.50 mL) was added to the residue. *O*-methylsilacyclobutane ketene-*O,O*-acetal **5** (22 μL, 0.10 mmol, 1 equiv), toluene (11 μL, internal reference), and benzaldehyde (11 μL, 0.10 mmol, 1 equiv) were then added sequentially to the resulting solution. The reaction was monitored by high resolution ^{1}H NMR, showing complete conversion of *O*-methylsilacyclobutane ketene-*O,O*-acetal **5** to aldol adduct **7** within 5 min at 27 °C. This product showed spectral characteristics identical to that shown above for aldol adduct **7** obtained from the analogous noncatalyzed reaction.



6 **8**

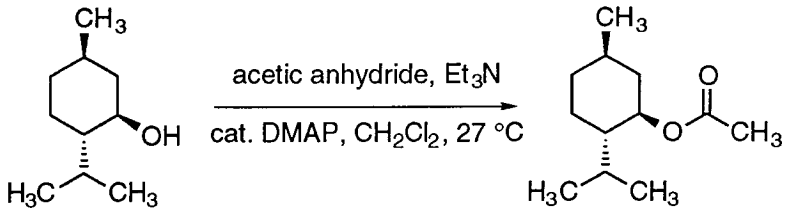
O-Trimethylsilyl aldol adduct **8**

An NMR tube filled with dry Ar and sealed with a rubber septum was charged with a solution of potassium *tert*-butoxide in tetrahydrofuran (0.5 M, 10 mL, 0.05 equiv). The tetrahydrofuran was removed in vacuo and benzene-d_6 (0.50 mL) was added to the residue. *O*-trimethylsilyl ketene-*O,O*-acetal **6** (20 μL, 0.10 mmol, 1 equiv), toluene (10 μL, internal reference), and benzaldehyde (11 μL, 0.10 mmol, 1 equiv) were then added sequentially to the resulting solution. The reaction was monitored by high resolution ^{1}H NMR, showing complete conversion of *O*-trimethylsilyl ketene-*O,O*-acetal **6** to aldol adduct **8** after 45 min at 27 °C. This product showed spectral characteristics identical to that shown above for aldol adduct **8** obtained from the analogous noncatalyzed reaction.



O-Methylsilacyclobutane aldol adducts **11** and **12**

An NMR tube filled with dry Ar and sealed with a rubber septum was charged with a solution of potassium *tert*-butoxide in tetrahydrofuran (0.5 M, 10 μL, 0.05 equiv). The tetrahydrofuran was removed in vacuo and benzene-d_6 (0.50 mL) was added to the residue. Toluene (11 μL, internal reference), benzaldehyde (11 μL, 0.10 mmol, 1 equiv), and a 3 : 2 mixture of*O*-methylsilacyclobutane ketene-*O,O*-acetal **9** and *C*-silylated methyl propionate **10** (20 μL, 0.07 mmol of **9**, 1 equiv) were added to the resulting solution. The mixture was analyzed by high resolution ^{1}H NMR, showing complete consumption of *O*-methylsilacyclobutane ketene-*O,O*-acetal **9** within 5 min at 27 °C followed by the slow disappearance of *C*-silylated methyl propionate **10**. After 24 h at 27 °C, ^{1}H NMR analysis of the reaction mixture showed no more of *C*-silylated methyl propionate **10** and a 1.7 : 1 mixture of aldol products **11** and **12**. These products showed spectral characteristics identical to that shown above for aldol adducts **11** and **12** obtained from the analogous noncatalyzed reaction.

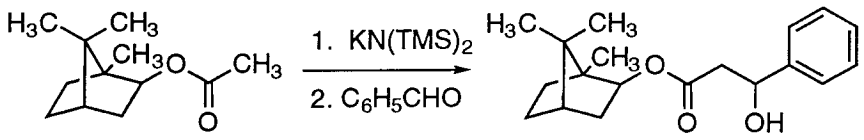


(–)-Menthyl acetate **13**

A 200-mL round-bottomed flask equipped with a magnetic stirring bar was charged with (–)-menthol (15.6 g, 100 mmol, 1 equiv), 4-dimethylaminopyridine (0.3 g, 2.5 mmol, 0.025 equiv), and triethylamine (15.3 mL, 110 mmol, 1.1 equiv). Acetic anhydride (14.2 mL, 150 mmol, 1.5 equiv) was added to this mixture, leading to the dissolution of the menthol and the evolution of heat. The reaction mixture was stirred for 30 min at 27 °C, then was quenched with water (50 mL). The resulting mixture was extracted with ether (5 × 75 mL) and the combined organic layers then were extracted with saturated aqueous sodium bicarbonate solution (3 × 75 mL) and 1 N aqueous hydrochloric acid solution (3 × 75 mL). The resulting organic layer was dried over sodium sulfate and was concentrated. This concentrate was vacuum distilled (0.75 mm Hg, 59 °C) to afford (–)-menthyl acetate (19.1 g, 96% yield) as a colorless oil.

^{1}H NMR (300 MHz, C_6D_6) δ: 4.86 (dt, 1H, J_1 = 4.4 Hz, J_2 = 10.8 Hz), 2.00 (m, 3H), 1.73 (s, 3H), 1.45 (m, 2H), 1.32 (m, 1H), 1.18 (m, 1H), 0.92 (m, 1H), 0.86 (d, 3H, J = 8.6 Hz), 0.83 (d, 3H, J = 8.6 Hz), 0.76 (d, 3H, J = 6.5 Hz), 0.65 (m, 1H).

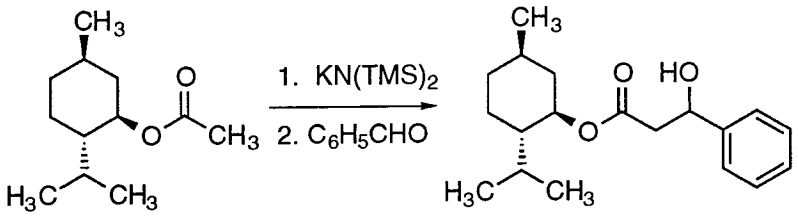
^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.6, 74.1, 47.0, 40.9, 34.2, 31.3, 26.3, 23.5, 22.0, 21.3, 20.7, 16.3.



Aldol adduct of (–)-borny acetate and benzaldehyde (both diastereomers)

A 250-mL round-bottomed flask equipped with a magnetic stirring bar was charged with tetrahydrofuran (30 mL) and a solution of potassium bis(trimethylsilyl)amide in toluene (0.5 M, 20.0 mL, 10 mmol, 1 equiv). The resulting solution was cooled to –78 °C and a solution of (–)-bornyl acetate (2.4 mL, 12 mmol, 1.2 equiv) in tetrahydrofuran was added dropwise via cannula. The mixture was stirred for 1.5 h at –78 °C whereupon benzaldehyde (1.0 mL, 10 mmol, 1 equiv) was added. The mixture was stirred at –78 °C for an additional 5 h, then was warmed to 0 °C. The reaction then was quenched by the addition of saturated aqueous ammonium chloride solution (50 mL). The resulting mixture was extracted with ether (2 × 50 mL) and combined ethereal phases then were extracted with water (2 × 50 mL). The resulting organic layer was dried over sodium sulfate and was concentrated. Purification of the residue by flash chromatography eluting with a gradient of ethyl acetate–hexanes (3 → 10%) afforded the desired aldol product (2.31 g, 76%) as a 1.2 : 1 ratio of diastereomers.

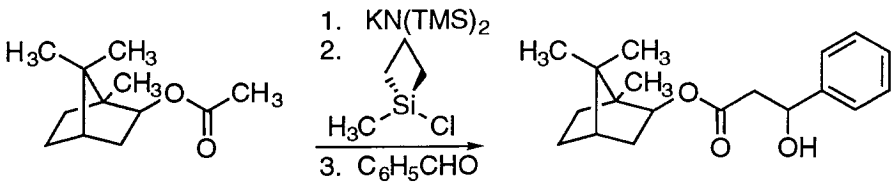
^{1}H NMR (300 MHz, C_6D_6) δ: 7.25 (m, 2H), 7.0-7.2 (m, 3H), 5.05 (m, 4H), 3.05 (d, 1H, J = 3.8 Hz), 3.00 (d, 1H, J = 3.8 Hz), 2.60 (dd, 2H, J_1 = 8.9 Hz, J_2 = 16.0 Hz), 2.47 (dd, 2H, J_1 = 3.9 Hz, J_2 = 16.0 Hz), 2.27 (m, 2H), 1.95 (m, 2H), 1.60 (m, 2H), 1.45 (m, 2H), 1.20 (m, 4H), 0.95 (m, 2H), 0.79 (s, 3H), 0.76 (s, 3H), 0.69 (s, 12H),



Aldol adduct of (–)-menthyl acetate and benzaldehyde (both diastereomers)

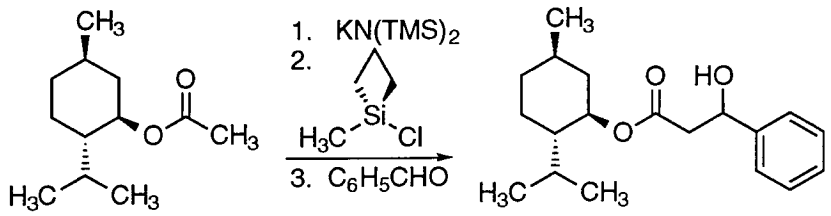
A 250-mL round-bottomed flask equipped with a magnetic stirring bar was charged with tetrahydrofuran (30 mL) and a solution of potassium bis(trimethylsilyl)amide in toluene (0.5 M, 20.0 mL, 10 mmol, 1 equiv). The resulting solution was cooled to –78 ℃ and a solution of (–)-menthyl acetate (2.6 mL, 12 mmol, 1.2 equiv) in tetrahydrofuran (10 mL) was added dropwise via cannula. The mixture was stirred for 2 h at –78 ℃ whereupon benzaldehyde (1.0 mL, 10 mmol, 1 equiv) was added. The reaction mixture was stirred at –78 °C for an additional 6 h, then was quenched by the addition of saturated aqueous ammonium chloride solution (10 mL). The resulting mixture was partitioned between water (40 mL) and ether (50 mL), and the aqueous layer was separated and further extracted with ether (50 mL). The combined organic layer was extracted with water (2 × 50 mL), was dried over sodium sulfate and was concentrated. Purification of the residue by flash chromatography eluting with a gradient of ethyl acetate–hexanes (3 → 20%) afforded the desired aldol product (2.35 g, 77%) as a 2.4:1 ratio of diastereomers.

^{1}H NMR (300 MHz, C_6D_6) δ: 7.25 (m, 2H, H-Ar), 7.10 (m, 3H), 5.05 (m, 2H), 4.85 (dt, 2H, J_1 = 4.4 Hz, J_2 = 10.9 Hz), 3.23 (d, 1H, J = 4.2 Hz), 3.01 (d, 1H, J = 3.9 Hz), 2.67 (dd, 1H, J_1 = 8.5 Hz, J_2 =16.0 Hz), 2.64 (dd, 1H, J_1 = 8.7 Hz, J_2 = 15.9 Hz), 2.53 (dd, 1H, J_1 = 4.2 HzJ_2 = 16.1 Hz), 2.54 (dd, 1H, J_1 = 4.3 Hz, J_2 = 16.02 Hz), 1.95 (m, 2H), 1.85 (m, 2H), 1.65 (m, 2H), 1.40 (m, 4H), 1.25 (m, 2H), 1.10 (m, 2H), 0.90 (m, 2H), 0.83 (d, 3H, J = 7.0 Hz), 0.82 (d, 3H, J = 7.0 Hz), 0.78 (d, 3H, J = 7.0 Hz), 0.76 (d, 3H, J = 7.0 Hz), 0.75 (d, 3H, J = 6.5 Hz), 0.75 (d, 3H, J = 6.9 Hz), 0.60 (m, 2H).



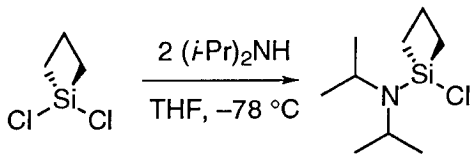
Aldol adduct of (–)-borny acetate and benzaldehyde (both diastereomers)

A 250-mL round-bottomed flask equipped with a magnetic stirring bar was charged with tetrahydrofuran (30 mL) and a solution of potassium bis(trimethylsilyl)amide (0.5 M, 20.0 mL, 10 mmol, 1 equiv). This solution was cooled to –78 °C and a solution of (–)-bornyl acetate (2.4 mL, 12 mmol, 1.2 equiv) in tetrahydrofuran (10 mL) was added dropwise via cannula. The mixture was stirred for 2 h at –78 °C whereupon 1-chloro-1-methylsilacyclobutane (1.9 mL, 15 mmol, 1.5 equiv) was added. The reaction mixture was stirred for 1 h at –78 °C, then was warmed slowly to 27 °C. Benzaldehyde (1.0 mL, 10 mmol, 1.0 equiv) was added and stirring was continued for another 15 h. The mixture then was concentrated under reduced pressure to give a cloudy gel. The gel was diluted with hexane (20 mL), causing the precipitation of a white flocculent material. The mixture was permitted to settle and the clear supernatent was collected via cannula and concentrated to give a cloudy pungent oil. Purification of this residue by flash chromatography eluting with a gradient of ethyl acetate–hexanes (3 → 10%) afforded the desilylated aldol product (0.44 g, 15%) as a mixture of diastereomers (1.3 : 1). The spectral characteristics of this mixture was identical to that shown above for the aldol addition of the potassium enolate of (–)-bornyl acetate to benzaldehyde.



Aldol adduct of (–)-menthyl acetate and benzaldehyde (both diastereomers)

A 250-mL round-bottomed flask equipped with a magnetic stirring bar was charged with tetrahydrofuran (40 mL) and a solution of potassium bis(trimethylsilyl)amide (0.5 M, 20.0 mL, 10 mmol, 1 equiv). This solution was cooled to –78 °C and (–)-menthyl acetate (2.6 mL, 12 mmol, 1.2 equiv) was added dropwise via syringe. The mixture was stirred for 1 h at –78 °C whereupon 1-chloro-1-methylsilacyclobutane (1.5 mL, 12 mmol, 1.2 equiv) was added. The reaction mixture was stirred for 1 h at –78 °C, then was warmed slowly to 27 °C. Benzaldehyde (1.0 mL, 10 mmol, 1.0 equiv) was added and stirring was continued for another 4 h. The mixture then was concentrated under reduced pressure to give a cloudy gel. This gel was diluted with hexane (100 mL), causing the precipitation of a white flocculent material. The mixture was permitted to settle and the clear supernatent was collected via cannula and was concentrated to give a cloudy pungent oil. This oil was dissolved in methanol (10 mL) and potassium fluoride was added to desilylate the product. The resulting mixture was stirred for 10 min and then was partitioned between ether (30 mL) and water (40 mL). The organic layer was separated and extracted with water (40 mL). The resulting organic layer was dried over sodium sulfate and was concentrated to give a clear colorless oil. Purification of this residue by flash chromatography eluting with a gradient of ethyl acetate–hexanes (3 → 10%) afforded the desilylated aldol product (0.89 g, 29%) as a mixture of diastereomers (1:1.7). The spectral characteristeristics of this mixture were identical to that shown above for the aldol addition of the potassium enolate of (–)-menthyl acetate to benzaldehyde.

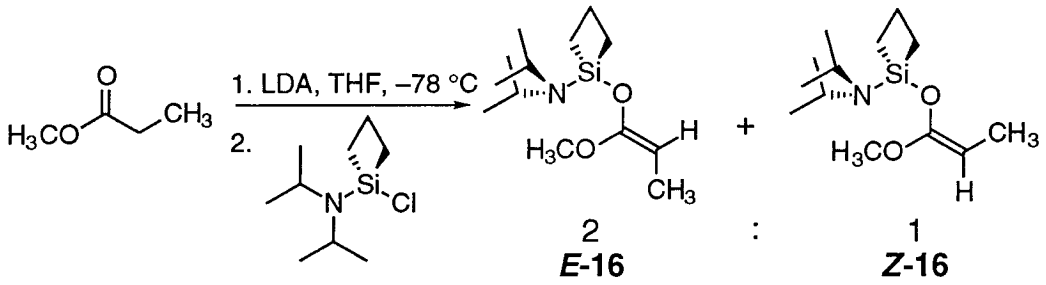


15

1-Chloro-1-(diisopropylamino)silacyclobutane **15**

A 100-mL round-bottomed flask equipped with a magnetic stirring bar was charged with tetrahydrofuran (40 mL) and 1,1-dichlorosilacyclobutane (6.1 mL, 50 mmol, 1.0 equiv). This solution was cooled to –78 °C and diisopropylamine (14.0 mL, 100 mmol, 2.0 equiv) was added dropwise via syringe. By the end of this addition, the reaction mixture had solidified due to precipitation of diisopropylamine hydrochloride. The mixture was diluted repeatedly with hexane (6 × 30 mL), the solid portion broken up with a cannula, and the resulting suspension transferred via cannula to a 250–mL round-bottomed flask. The resulting mixture was filtered under Ar through a bed of celite and the residue was washed with hexane (50 mL). The filtrate was then concentrated at 27 °C and 35 mm Hg until no further bubbling was observed for 15 min. This concentrate was distilled under reduced pressure (37 mm Hg) to give 1-chloro-1-(diisopropylamino)silacyclobutane **15** (8.47 g, 82%, bp 46–47 °C) as a cloudy liquid.

^{1}H NMR (300 MHz, C_6D_6) δ: 3.09 (sept, 2H, *J*=6.7 Hz, $CH(CH_3)_2$), 2.95 (m, 2H, $SiCH_2CH_2$), 1.50 (m, 4H, $SiCH_2CH_2$), 1.05 (d, 12H, *J*=6.7 Hz, $CH(CH_3)_2$).



O-(Diisopropylamino)silacyclobutane ketene-*O*,*O*-acetal **16**

A 100-mL round-bottomed flask equipped with a magnetic stirring bar was charged with tetrahydrofuran (25 mL) and diisopropylamine (1.7 mL, 12 mmol, 1.2 equiv). This solution was cooled to –78 °C and a solution of *n*-butyllithium in hexanes (2.5 M, 4.0 mL, 10 mmol, 1 equiv) was added via syringe. The resulting solution was stirred for 30 min at –78 °C and methyl propionate (0.96 mL, 12 mmol, 1.0 equiv) was then added dropwise via syringe. The reaction mixture was stirred an additional 1 h at –78 °C, and then 1-chloro-1-(diisopropylamino)silacyclobutane (2.5 g, 12 mmol, 1.2 equiv) was added via cannula. The resulting mixture was stirred at –78 °C for 1 h, then was warmed 0 °C for 2 h. The reaction mixture was diluted with hexane (25 mL) to precipitate lithium chloride and the resulting cloudy mixture was concentrated under reduced pressure (27 °C and 37 torr). The concentrate was diluted with hexanes (40 mL) and the resulting suspension was allowed to settle. The slightly cloudy supernatent was collected via cannula and was concentrated as before until no further bubbling was observed for 20 min. The resulting cloudy concentrate was purified by vacuum distillation (30 torr) to give the *O*-(diisopropylamino)silacyclobutane ketene-*O*,*O*-acetal **16** (1.18 g, 46%, bp 98 °C at 30 torr) as a mixture of *E* and *Z* isomers (2:1, respectively).

E-*O*-(Diisopropylamino)silacyclobutane ketene-*O,O*-acetal of methyl propionate *E*-**16**

^{1}H NMR (400 MHz, C_6D_6) δ: 3.98 (q, 1H, *J*=6.6 Hz, C=C**H**(CH_3)), 3.44 (s, 3H, OCH_3), 3.20 (sept., 2H, *J*=6.7 Hz, C**H**(CH_3)$_2$), 1.4 - 2.0 (m, 6H, Si**C**H_2CH_2, SiCH_2C**H**$_2$), 1.75 (d, 3H, *J*=6.6 Hz, C=CH(C**H**$_3$)), 1.10 (d,12H, *J*=6.7 Hz, CH(C**H**$_3$)$_2$).

Z-*O*-(Diisopropylamino)silacyclobutane ketene-*O,O*-acetal *Z*-**16**

^{1}H NMR (300 MHz, C_6D_6) δ: 3.55 (q, 1H, *J*=6.4 Hz, C=C**H**(CH_3)), 3.27 (sept, 2H, *J*=6.7 Hz, C**H**(CH_3)$_2$), 3.13 (s, 3H, O**C**H_3), 1.4-2.0 (m, 6H, Si**C**H_2CH_2, SiCH_2C**H**$_2$), 1.77 (d, 3H, *J*=6.4 Hz, C=CH(C**H**$_3$)), 1.14 (d, 12H, *J*=6.7 Hz, CH(C**H**$_3$)$_2$).

Chapter 2

Transformation of Alkylated Pseudoephedrine Amides to Highly Enantiomerically Enriched Carboxylic Acids and Ketones

Introduction

In 1993, Bryant H. Yang discovered that pseudoephedrine amide enolates could be alkylated in high yields and with high diastereoselectivities in the presence of lithium chloride (6 equiv).[14] The low cost and ready availability of the pseudoephedrine auxiliary as well as the reactivity of these amide enolates to unreactive electrophiles such as *n*-butyl iodide and β-branched primary alkyl iodides offered advantages over existing alkylation methodologies.[15] In addition, the crystallinity of many of the starting materials and products and the fact that carcinogenic reactivity-enhancing co-solvents such as HMPA were not required made this methodology amenable to large scale and process applications. The major diastereomeric product from these alkylation reactions arose from electrophilic attack on the putative *Z*-enolate (R syn to the enolate oxygen) from the same face (1,4 syn) as the carbon bound methyl group of the pseudoephedrine auxiliary when the enolate was drawn in a planar extended conformation (Figure 4).[14c] The observed selectivity of the pseudoephedrine amide enolate alkylation was rationalized by invoking the reactive conformation shown in Figure 5. In this conformation, the lithium alkoxide, and perhaps more importantly, the solvent molecules (tetrahydrofuran and possibly diisopropylamine) associated with the lithium cation, were proposed to block the β-face of the Z-enolate, forcing the alkylation to occur from the α-face.[14c]

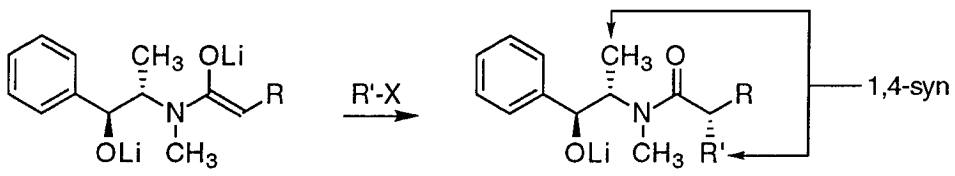


Figure 4. Mnemonic for pseudoephedrine amide enolate alkylation

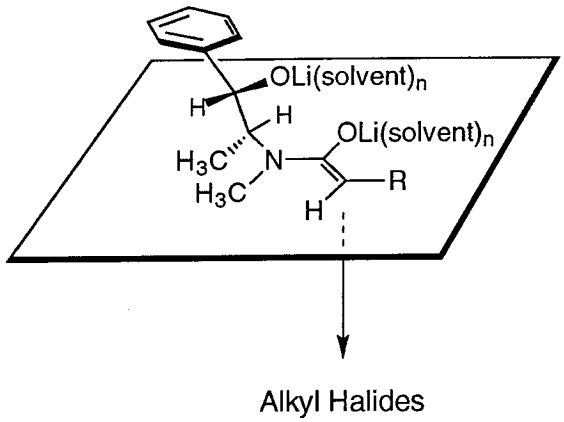


Figure 5. Proposed reactive conformation of pseudoephedrine amide enolates

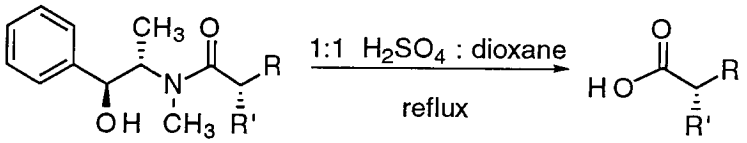
The highly efficient and diastereoselective alkylation of pseudoephedrine amide enolates, however, does not in and of itself constitute a valuable addition to synthetic methodology unless the alkylation products can be transformed into useful materials. For this reason, much of our effort has focused on the development of methods to cleave the pseudoephedrine auxiliary.[14c,16] While Bryant Yang examined the reduction of these alkylated pseudoephedrine amides to the corresponding alcohols and aldehydes, my work has focused on the hydrolysis of these amides to the corresponding carboxylic acids and their treatment with alkyllithium reagents to form ketones.[16,17]

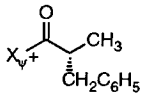
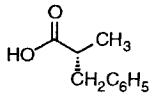
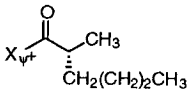
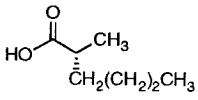
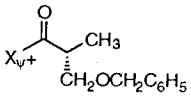
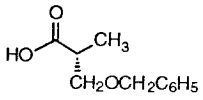
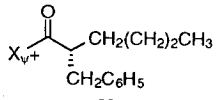
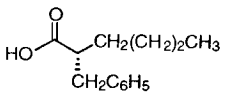
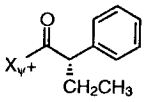
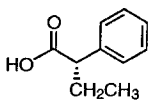
Hydrolysis of Alkylated Pseudoephedrine Amides

The most challenging of these transformations has been the simple hydrolysis reaction for which acidic, basic, and slightly acidic metal-mediated conditions have been developed. The choice of a hydrolysis method will be dictated by the substrate and then by the consideration of cost and convenience, as outlined below.

Acidic Hydrolysis of Alkylated Pseudoephedrine Amides to Form Carboxylic Acids. For alkylation products that are not acid-sensitive, hydrolysis[18] to the corresponding carboxylic acid can be effected in excellent chemical yield and with little

Table 1. Acidic Hydrolysis of Pseudoephedrine Amides



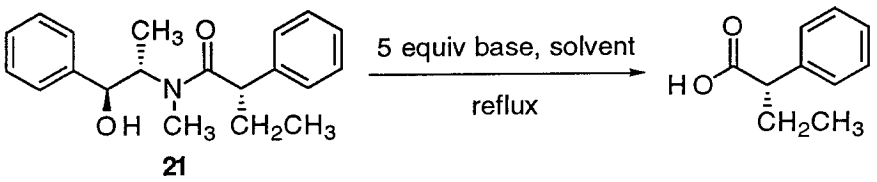
entry	substrate[a]	product	isol yield (%)	isol ee or de (%)
1	 **17**	 **27**	95	97
2	 **18**	 **28**	91	97
3	 **19**	 **29**	dec.	–
4	 **20**	 **30**	94	96
5	 **21**	 **31**	96	95

[a] The starting material was in all cases of ≥99%. For entry 1 9 N H_2SO_4 was used; for all others 18 N H_2SO_4 was employed.

epimerization simply by heating the amide at reflux in a 1:1 mixture of sulfuric acid (9–18 N) and dioxane (Table 1). Under these conditions, the substrate initially undergoes a rapid intramolecular $N \rightarrow O$ acyl transfer[18,19] reaction followed by rate-limiting hydrolysis of the resulting ammonium ester intermediate to the carboxylic acid. Despite the harsh reaction conditions (substrate **19** undergoes decomposition rather than hydrolysis), this method provides a convenient route to a large number of highly enantiomerically enriched

carboxylic acids. Even the epimerization-prone benzylic substrate of entry 5, Table 1 affords the corresponding acid in 95% ee. The pseudoephedrine auxiliary can be recovered from these hydrolyses in excellent yield by a simple extractive work-up. Lower concentrations of sulfuric acid have been employed in these hydrolyses without detectable degradation of the product yield or ee, but longer reaction times are required in these cases.

Table 2. Survey of Hydroxide Bases for the Hydrolysis of **21**



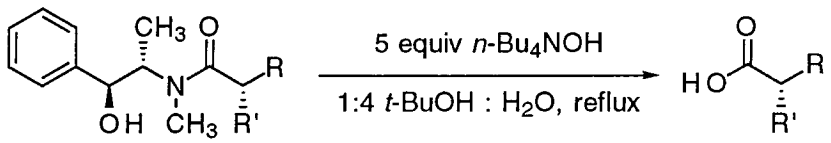
21

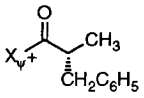
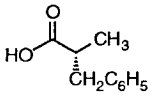
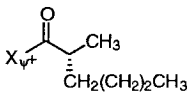
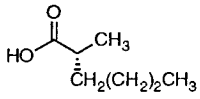
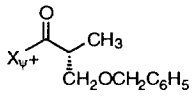
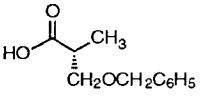
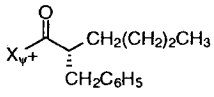
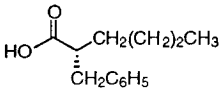
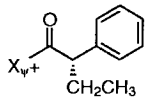
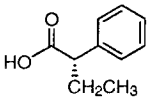
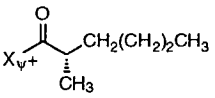
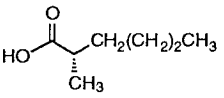
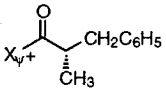
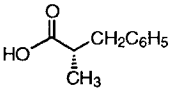
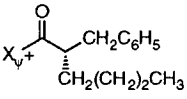
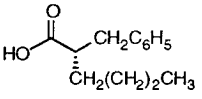
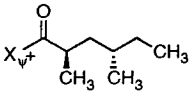
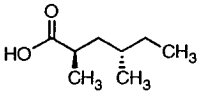
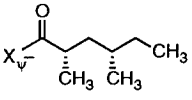
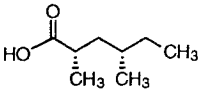
entry[a]	base	solvent	time (h)	isol yield (%)	isol ee (%)
1	NaOH	4:1 MeOH / H_2O	48	83	48
2	NaOH	4:1 *t*-BuOH / H_2O	24	N.R.	–
3	LiOH	4:1 MeOH / H_2O	48	82	48
4	KOH	4:1 MeOH / H_2O	48	80	46
5	CsOH	4:1 *t*-BuOH / H_2O	84	52	72
6	$Ba(OH)_2$	4:1 MeOH / H_2O	24	79	62
7	$Ba(OH)_2$	4:1 *i*-PrOH / H_2O	72	70	70
8	$Ba(OH)_2$	4:1 *t*-BuOH / H_2O	72	31	84
9	*n*-Bu_4NOH	2:1 *t*-BuOH / H_2O	24	71	60
10	*n*-Bu_4NOH	1:4 *t*-BuOH / H_2O	20	82	64
11	*n*-Bu_4NOH	1:9 *t*-BuOH/ H_2O	12	78	58
12	*n*-Bu_4NOH	*t*-BuOH	36	39	10
13	*n*-Bu_4NOH	H_2O	20	76	44

[a] The starting material was in all cases of ≥99% de.

Basic Hydrolysis of Alkylated Pseudoephedrine Amides to Form Carboxylic Acids. Basic conditions for the hydrolysis of pseudoephedrine amides[18] were also developed. The procedure was optimized for the highly epimerizable phenylacetamide substrate **21**. Hydrolyses were conducted using a wide range of hydroxide bases in a variety of solvent systems (Table 2). As shown by the results of Table 2, the hydrolysis of **21** with 5 equiv of tetra-*n*-butylammonium hydroxide in a mixture of *tert*-butyl alcohol and water (1:4, respectively) at reflux proved to be optimal with respect to reaction time, yield, and product ee (entry 10, Table 2). When Bryant Yang employed these conditions for the basic hydrolysis of other alkylated pseudoephedrine amides, the results were generally far superior to those observed with the highly epimerizable substrate **21** (Table 3). A convenient work-up procedure for these hydrolyses involved acidification with 3 N aqueous hydrochloric acid solution followed by extraction of the product into ether. Tetra-*n*-butylammonium salts were then readily removed by washing the ethereal product solution with water. Where the expense of tetra-*n*-butylammonium hydroxide is a consideration, or in cases where the product carboxylic acid is poorly soluble in ether (making removal of tetra-*n*-butylammonium salts difficult), a second alkaline hydrolysis procedure was developed employing sodium hydroxide (5–8 equiv) as the base in a 2:1:1 mixture of water, methanol, and *tert*-butyl alcohol at reflux. This alternative hydrolysis procedure produces products of slightly lower ee as compared to the method employing tetra-*n*-butylammonium hydroxide as base. For example, hydrolysis of substrate **17** with sodium hydroxide in a 2:1:1 mixture of water, methanol and *tert*-butyl alcohol affords the corresponding acid in 98% yield and 92% ee whereas hydrolysis of **17** with tetra-*n*-butylammonium hydroxide affords the desired acid in 93% yield and 94% ee (entry 1, Table 3).

Table 3. Basic Hydrolysis of Pseudoephedrine Amides



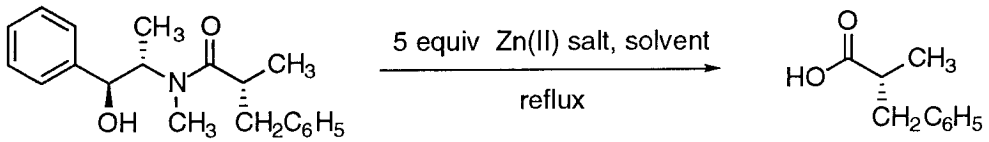
entry	substrate[a]	product	isol yield (%)	isol ee or de (%)
1	 **17**	 **27**	93	94
2	 **18**	 **28**	93	97
3	 **19**	 **29**	92	69
4	 **20**	 **30**	90	84
5	 **21**	 **31**	82	64
6	 **22**	 **32**	88	93
7	 **23**	 **33**	91	94
8	 **24**	 **34**	89	82
9	 **25**	 **35**	86	95
10	 **26**	 **36**	84	95

[a] Substrates **17**, **18**, **20**, and **21** were of ≥99% de. Substrates **19**, **24**, and **26** were of 98% de, substrates **23** and **25** were of 97% de, and substrate **22** was of 96% de.

These basic hydrolysis procedures offer viable alternatives for the hydrolysis of acid-sensitive substrates, but can lead to partial racemization in the hydrolysis of certain substrates (e.g., substrates **19**, **20**, **21**, and **24**, Table 3). In at least one case (entry 10, Table 3), basic hydrolysis proceeds with less racemization than the acidic hydrolysis method (95% ee versus 93% ee, respectively).

The mechanism of the base-induced hydrolysis reaction is believed to involve initial rate-limiting intramolecular *N* → *O* acyl transfer followed by rapid saponification of the resulting β-amino ester intermediate.[18b] As in the acidic hydrolysis protocol, the pseudoephedrine auxiliary may be recovered in high yield from basic hydrolyses, if desired, by a simple extractive isolation procedure.

Table 4. Survey of Zn(II) Salts in the Hydrolysis of **17**



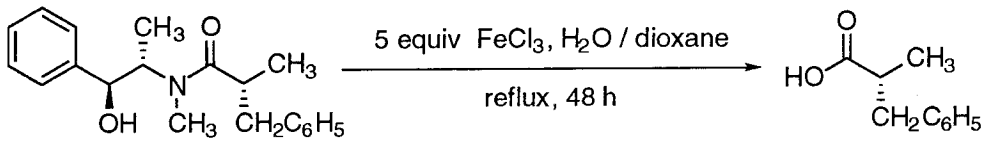
17

entry[a]	Zn(II) salt	solvent system	time (h)	isol yield (%)	isol ee (%)
1	$ZnCl_2$	1:1 H_2O / MeOH	24	33	94
2	$ZnCl_2$	1:1 H_2O / dioxane	48	90	83
3	$ZnCl_2$	1:1 H_2O / CH_3CN	48	48	92
4	$ZnCl_2$	1:1 H_2O / DMSO	48	86	78
5	$ZnCl_2$	dioxane + 2 equiv H_2O	24	96	50
6	$ZnBr_2$	1:1 H_2O / dioxane	48	79	79
7	$Zn(NO_3)_2$	1:1 H_2O / dioxane	48	60	92
8	$Zn(acac)_2$	1:1 H_2O / dioxane	48	90	73

[a] The starting material was in all cases of ≥99% de.

Efforts to Develop a Milder Hydrolysis Procedure. In an effort to develop milder conditions for the hydrolysis of pseudoephedrine amides, a wide variety of Lewis acidic metal salts was surveyed for the ability to promote the hydrolysis of the benzylated pseudoephedrine propionamide **17**. The first successful metal-promoted hydrolysis of **17** was achieved by heating **17** with 5 equiv of $ZnCl_2$ in a refluxing mixture of aqueous dioxane (1:1, pH 5) for 48 h. (*R*)-α-Methyl benzenepropionic acid was obtained in 90% yield and 83% ee. As seen from the data within Table 4, variation of the solvent system and the Zn(II) salt failed to afford conditions offering both an excellent yield and ee of the desired acid. Further experimentation revealed that the use of $FeCl_3$ in refluxing dioxane (1:1, pH 1) for the hydrolysis afforded (*R*)-α-methyl benzenepropionic in 97% ee, albeit in lower yield (63%, incomplete reaction). Continued study of this system showed that by increasing the proportion of water in the mixture (4:1 water : dioxane) the yield of the acid was increased to 94% without compromising its ee (Table 5).

Table 5. Solvent Effects in the $FeCl_3$-Promoted Hydrolysis of **17**



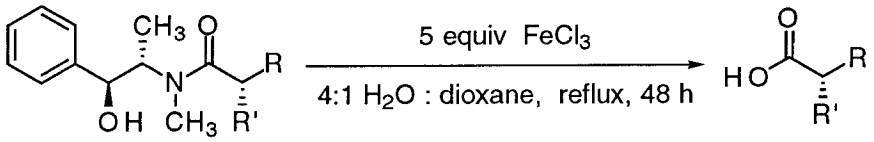
17

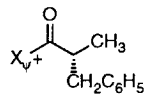
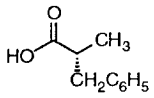
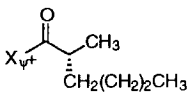
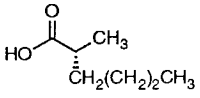
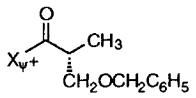
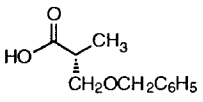
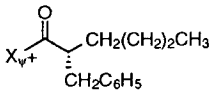
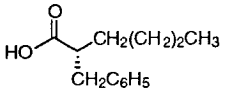
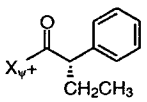
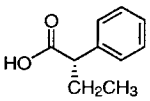
entry[a]	solvent system	isol yield (%)	isol ee (%)
1	1:2 H_2O / dioxane	50	97
2	1:1 H_2O / dioxane	61	97
3	2:1 H_2O / dioxane	76	98
4	4:1 H_2O / dioxane	94	98
5	H_2O	94	96

[a] The starting material was in all cases of ≥99% de.

These conditions were then employed for the hydrolysis of a series of alkylated pseudoephedrine amides with generally excellent results (Table 6). The sterically hindered substrate **20** did provide an exception (entry 4, Table 6); its hydrolysis was prohibitively slow under the modified conditions. Other Fe(III) salts were also examined in the hydrolysis of substrate **17** (Table 7), but in general they offered no significant advantage over $FeCl_3$ with regard to reaction time, yield, or ee.

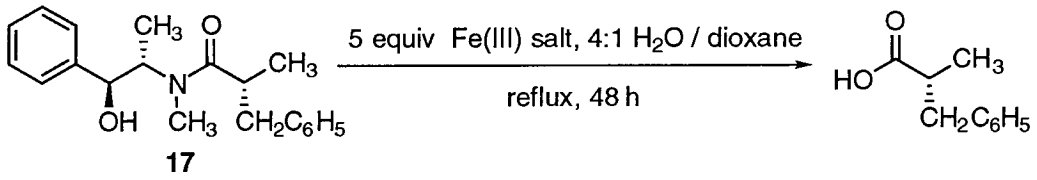
Table 6. Hydrolysis of Pseudoephedrine Amides with $FeCl_3$ in 4:1 Aqueous Dioxane



entry	substrate[a]	product	isol yield (%)	isol ee or de (%)
1	 **17**	 **27**	94	98
2	 **18**	 **28**	85	98
3	 **19**	 **29**	53	94
4	 **20**	 **30**	17[b]	99
5	 **21**	 **31**	91	92

[a] The starting material was in all cases of ≥99% de except for substrate **19** which was of 98% de. [b] The hydrolysis was not complete at t = 48 h.

Table 7. Survey of Fe(III) salts in the Hydrolysis of **17**



17

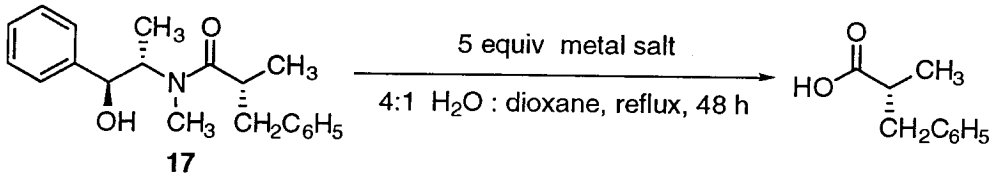
entry[a]	Fe(III) salt	isol yield (%)	isol ee (%)
1	$FeCl_3$	94	98
2	$Fe_2(SO)_4$	88	96
3	$Fe(NO_3)$	99	97
4	$Fe(OTf)_3$	94	97

[a] The starting material was in all cases of ≥99% de.

A broader survey of Lewis acidic metal salts (Table 8) failed to provide any candidate offering improved efficiency, rate, and enantioselectivity when compared to $FeCl_3$, although a surprisingly large number of metal salts examined did promote the hydrolysis of **17**. Two noteworthy alternatives revealed in this survey were the use of $ZrOCl_2$ (entry 9) or $Yb(OTf)_3$ (entry 15, 5 equiv each) in refluxing aqueous dioxane (4:1). The use of these metal salts for the hydrolysis of a series of pseudoephedrine amides is summarized in Table 9. Results were generally quite good, and particularly so in the case of the sensitive benzyl ether **19**.

The long reaction times required in these metal-mediated hydrolyses (typically 48 h) prompted us to continue our search for an alternative mild hydrolysis method. Under acidic conditions, the rate of hydrolysis of pseudoephedrine amides is limited by the slow hydrolysis of the $N \rightarrow O$ acyl transfer ester intermediate. It was reasoned, therefore, that a molecule possessing both acidic functionality to promote the $N \rightarrow O$ acyl transfer and basic

Table 8. Survey of Metal Salts in the Hydrolysis of **17**

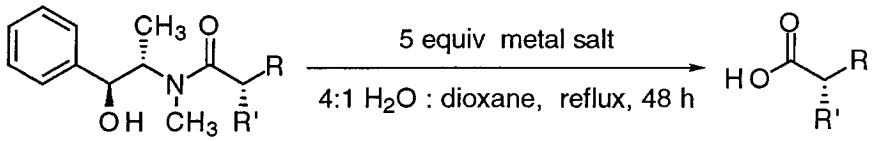


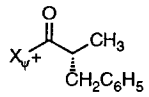
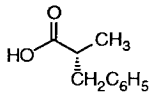
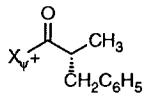
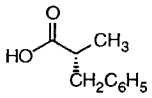
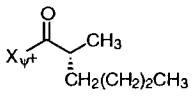
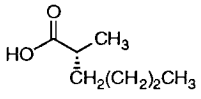
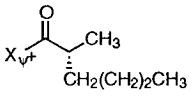
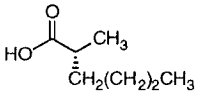
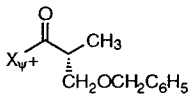
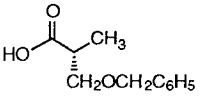
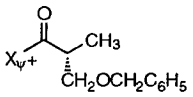
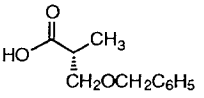
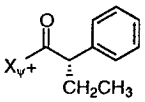
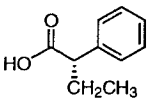
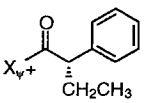
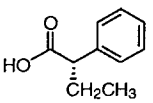
17

entry[a]	metal salt	isol yield (%)	isol ee (%)
1	$VOSO_4$	32	94
2	$Mn(ClO_4)_2$	7	–
3	$Co(ClO_4)_2$	11	–
4	$NiCl_2$	17	–
5	$CuCl_2$	no hydrolysis[b]	–
6	$Zn(OTf)_2$	79	83
7	$Al_2Zn(SO_4)_4$	44	88
8	YCl_3	57	57
9	$ZrOCl_2$	92	97
10	$Zr(SO_4)_2$	94	96
11	$Sn(OTf)_3$	90	97
12	$LaCl_3$	4[b]	95
13	$La(OTf)_3$	72	96
14	$YbCl_3$	58	61
15	$Yb(OTf)_3$	91	95
16	$PrCl_3$	60	56
17	$DyCl_3$	30	66

[a] The starting material was in all cases of ≥99% de. [b] Reaction was performed in 1:1 H_2O / dioxane.

Table 9. Hydrolysis of Pseudoephedrine Amides using $Yb(OTf)_3$ or $ZrOCl_2$ in 4:1 Aqueous Dioxane

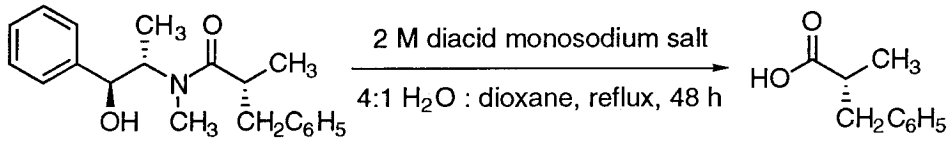


entry	substrate[a]	metal salt	product	isol yield (%)	isol ee or de (%)
1	 **17**	$ZrOCl_2$	 **27**	92	97
2	 **17**	$Yb(OTf)_3$	 **27**	91	95
3	 **18**	$ZrOCl_2$	 **28**	92	99
4	 **18**	$Yb(OTf)_3$	 **28**	73	98
5	 **19**	$ZrOCl_2$	 **29**	72	97
6	 **19**	$Yb(OTf)_3$	 **29**	92	94
7	 **21**	$ZrOCl_2$	 **31**	90	93
8	 **21**	$Yb(OTf)_3$	 **31**	69	82

[a] The starting material was in all cases of ≥99% de except **19** which was of 98% de.

functionality to promote hydrolysis of the resulting β-amino ester might prove an effective hydrolysis catalyst. Thus, the monosodium salts of a variety of organic diacids were tested in the hydrolysis of amide **17**. However, as seen in the data within Table 10, none of these compounds proved to be suitable in promoting hydrolysis. A similar study of phosphoric acid, pyrophosphoric acid, and their various sodium salts also failed to provide satisfactory results.

Table 10. Survey of Monosodium Salts of Organic Diacids in the Hydrolysis of **17**



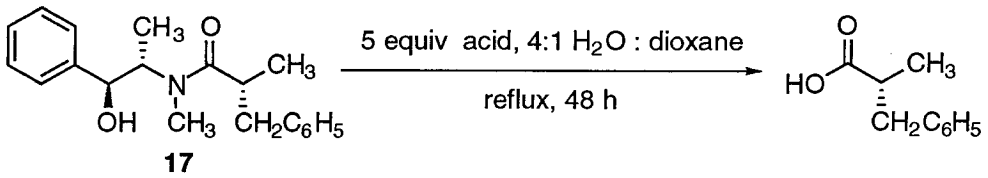
17

entry[a]	diacid	isol yield (%)	isol ee (%)
1	oxalic acid	14	73
2	malonic acid	17	14
3	succinic acid	24	10
4	maleic acid	–	-
5	fumaric acid	39	1
6	phthalic acid	20	21

[a] The starting material was in all cases of ≥99% de.

As the hydrolysis of **17** was observed even under the weakly acidic conditions of Table 10, acetic acid, chloroacetic acid, and trifluoroacetic acid were also evaluated for their effectiveness in promoting hydrolysis. As seen from the data within Table 11, both the yield and the ee of the product acid increased with increasing acidity of the carboxylic acid additive. In fact, the results obtained in the trifluoroacetic acid promoted hydrolysis of a range of substrates (Table 12) were comparable to those with $FeCl_3$.

Table 11. Survey of Carboxylic Acid as Promoters for the Hydrolysis of **17**

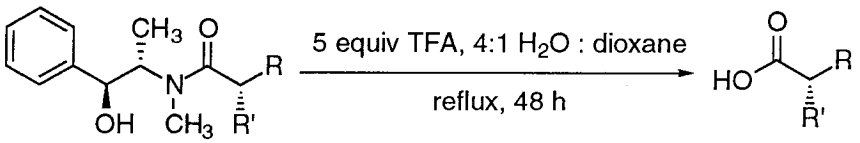


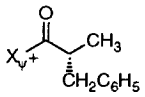
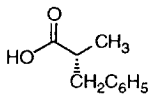
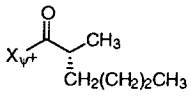
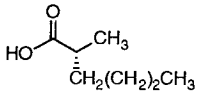
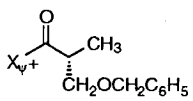
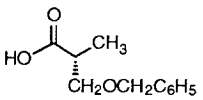
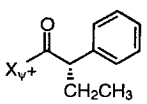
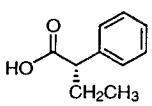
17

entry[a]	acid	isol yield (%)	isol ee (%)
1	None	–	–
2	CH_3CO_2H	30	21
3	$ClCH_2CO_2H$	55	82
4	CF_3CO_2H	89	95

[a] The starting material was in all cases of ≥99% de.

Table 12. Hydrolysis of Pseudoephedrine Amides with Trifluoroacetic Acid in 4:1 Aqueous Dioxane



entry[a]	substrate[a]	product	isol yield (%)	isol ee or de (%)
1	 **17**	 **27**	89	95
2	 **18**	 **28**	79	98
3	 **19**	 **29**	89	95
4	 **21**	 **31**	89	95

[a] The starting material was in all cases of ≥99% de except for substrate **19** which was of 98% de.

At this point, we chose to pursue a new strategy for effecting the hydrolysis of pseudoephedrine amides. Rather than promoting hydrolysis through activation of the amide carbonyl by coordination with a Lewis acid, we proposed to activate the nitrogen leaving group by formation of the oxazolidinone intermediate shown in Figure 6. When amide **17** was treated with 1,1'-carbonyldiimidazole or phosgene, however, instead

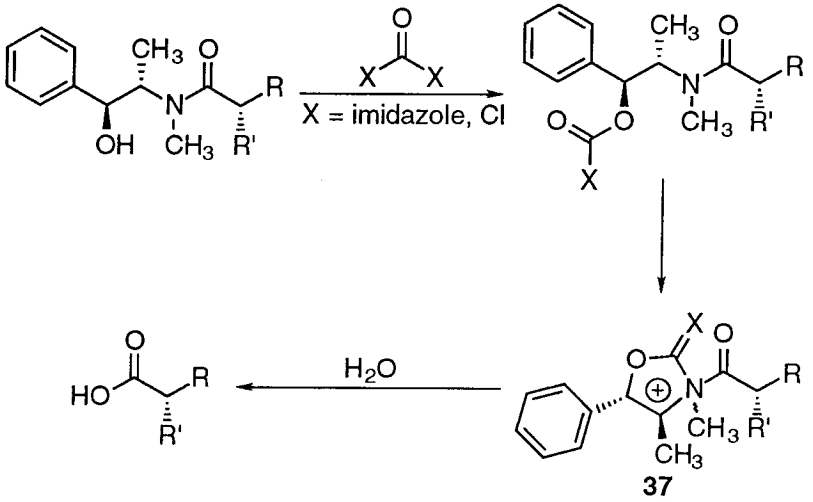


Figure 6. Proposed Strategy for Activation of Pseudoephedrine Amides

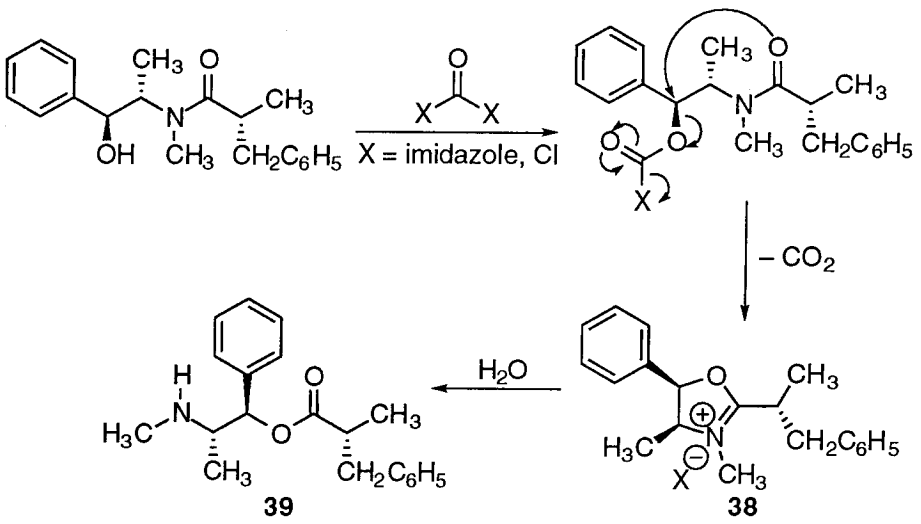


Figure 7. Mechanism for the Formation of the Ephedrine Ester **39**

of the expected activated oxazolidinone (**37**), the ephedrine ester (**39**) was formed, presumably through the mechanism[20] outlined in Figure 7. Although **39** could be hydrolyzed simply by heating it at reflux in 1:1 water–acetonitrile for 24 h, only moderate yields of the desired (*R*)-α-methyl benzenepropionic acid were obtained due to competing $O \rightarrow N$ acyl transfer to give the ephedrine amide. In addition, the acid isolated was of only moderate to good ee (depending on conditions of preparation), probably due to epimerization of the activated oxazoline intermediate (**38**) during formation of the ephedrine ester.

Hydrolysis of Pseudoephedrine Amides Involving In Situ Borane-Amine Complex. Our next strategy sought to take advantage of the rapid $N \rightarrow O$ acyl transfer observed in the acid-promoted hydrolysis reaction while introducing nucleophilic hydroxide for the rapid hydrolysis of the resulting ester without inducing reversion to the amide by $O \rightarrow N$ acyl transfer. The key to accomplishing this involved the in situ formation of a stable amine-borane complex by the addition of lithium borohydride to the $N \rightarrow O$ acyl transfer intermediate. The moisture-sensitivity of lithium borohydride required that the $N \rightarrow O$ acyl transfer be conducted under anhydrous conditions. Initial studies employed trifluoroacetic acid (5 equiv) in tetrahydrofuran at reflux (1 h) to effect $N \rightarrow O$ acyl transfer, but these conditions were subsequently found to give almost complete epimerization of the α-stereocenter of the $N \rightarrow O$ acyl transfer ester intermediate. Fortunately, when $N \rightarrow O$ acyl transfer was conducted with methanesulfonic acid (1.5 equiv) in refluxing tetrahydrofuran (1 h), this epimerization could be avoided. The sequence of $N \rightarrow O$ acyl transfer, borane complexation, and saponification (Figure 8) was conducted in a one-pot procedure, as follows. A solution of the pseudoephedrine amide substrate in THF was heated at reflux with 1.5 equiv of methanesulfonic acid until complete $N \rightarrow O$ acyl transfer had occurred, as determined by thin-layer chromatographic analysis (typically 1–3 h). The mixture was then cooled to 23 °C and 1.5 equiv of lithium

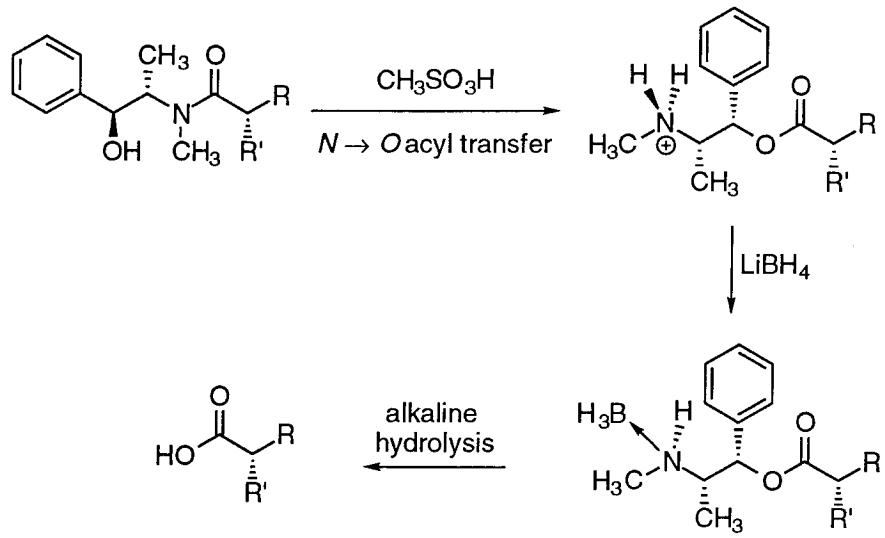
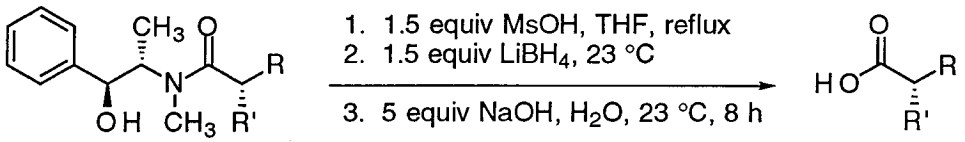
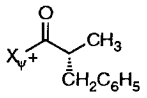
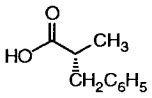
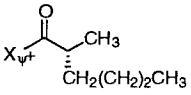
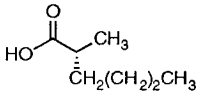
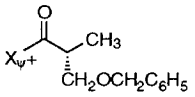
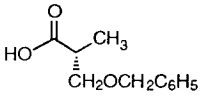
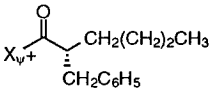
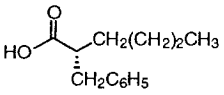
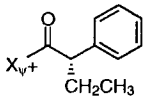
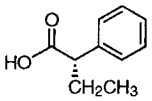


Figure 8. The hydrolysis of pseudoephedrine amides involving in situ borane–amine complexation

borohydride (2.0 M in THF) was added to form the amine-borane complex. The reaction mixture was diluted with an equal volume of water, and 5 equiv of sodium hydroxide or tetra-*n*-butylammonium hydroxide was added as base. The mixture was stirred at 23 °C until the hydrolysis was complete. Results for the hydrolysis of several pseudoephedrine amide substrates employing this procedure are summarized in Tables 13 (sodium hydroxide) and 14 (tetra-*n*-butylammonium hydroxide). Although sodium hydroxide-promoted hydrolyses were slower, typically requiring 8 h versus 1 h in the tetra-*n*-butylammonium hydroxide system, the work-up procedure was more convenient. On the other hand, for sterically congested substrates (e.g., substrate **20**), use of the more reactive tetra-*n*-butylammonium hydroxide base was necessary. The use of more than 1.5 equiv of lithium borohydride was found to reduce the yield of the desired acid, presumably by reduction of the *N* → *O* acyl transfer ester intermediate. For example, when 2.0 equiv of lithium borohydride was employed to trap the *N* → *O* acyl transfer ester intermediate of amide **17**, only a 76% yield of acid **27** was obtained after hydrolysis with sodium hydroxide (compared to 95% yield when 1.5 equiv of lithium borohydride was employed; entry 1 Table 13).

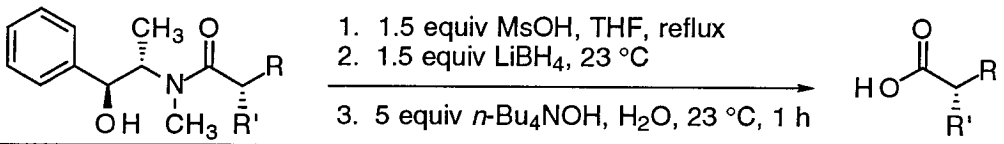
Table 13. Mild Hydrolysis of Pseudoephedrine Amides Involving In Situ Borane-Amine Complexation (Sodium Hydroxide)

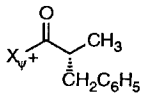
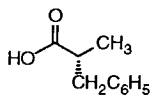
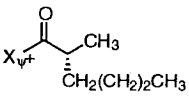
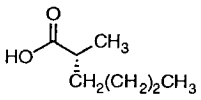
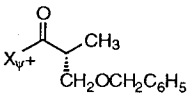
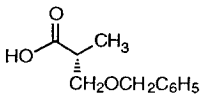
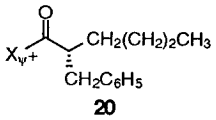
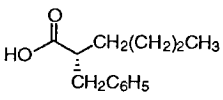
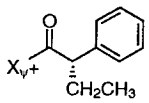
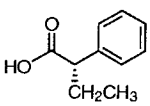


entry	substrate[a]	$N \rightarrow O$ acyl transfer time	product	isol yield (%)	isol ee or de (%)
1	 **17**	1 h	 **27**	94	98
2	 **18**	1 h	 **28**	84	99
3	 **19**	1 h	 **29**	96[b]	93
4	 **20**	1.5 h	 **30**	–[c]	–
5	 **21**	3 h	 **31**	89	83

[a] The starting material was in all cases of ≥99% de except for **19** which was of 98% de. [b] Hydrolysis required 16 h at 23 °C. [c] Hydrolysis was not complete even after 48 h at 23 °C.

Table 14. Mild Hydrolysis of Pseudoephedrine Amides Involving In Situ Borane-Amine Complexation (Tetra-*n*-butylammonium Hydroxide)



entry	substrate[a]	$N \rightarrow O$ acyl transfer time	product	isol yield (%)	isol ee or de (%)
1	 **17**	1 h	 **27**	91	98
2	 **18**	1 h	 **28**	75	98
3	 **19**	1 h	 **29**	87	93
4	 **20**	1.5 h	 **30**	84	97
5	 **21**	3 h	 **31**	88	84

[a] The starting material was in all cases of ≥99% de except for **19** which was of 98% de.

Addition of Alkyllithium Reagents to Pseudoephedrine Amides to Form Enantiomerically Enriched Ketones

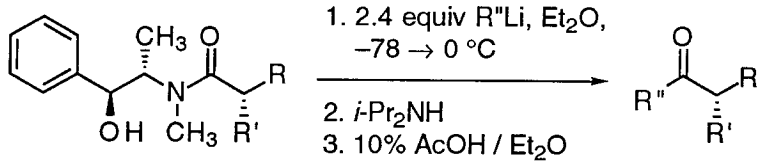
It has long been known that tertiary carboxamides can be transformed into ketones in one step by the addition of an organolithium reagent followed by an aqueous work-up.[21] The success of this reaction relies upon the formation of a stable tetrahedral intermediate which breaks down upon work-up to release the ketone. If breakdown of this intermediate occurs prior to work-up the liberated ketone can further react to give a tertiary alcohol by-product. The protocol developed to transform alkylated pseudoephedrine amides into ketones was optimized to avoid premature breakdown of the tetrahedral intermediate.

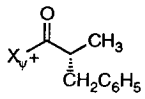
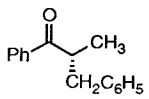
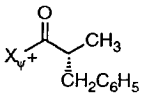
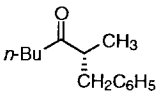
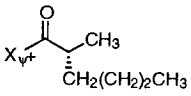
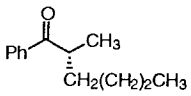
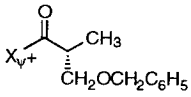
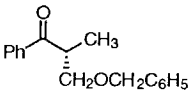
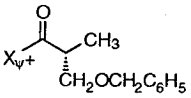
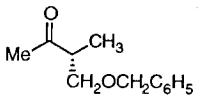
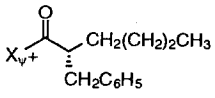
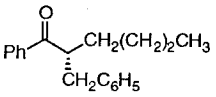
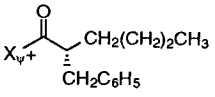
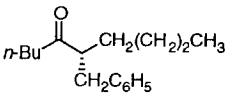
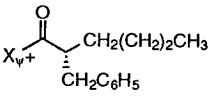
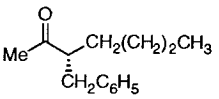
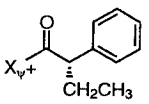
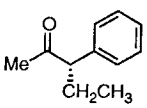
In a typical procedure, 2.4 equiv of an organolithium reagent was added to an ethereal solution (or suspension) of the amide at –78 °C followed by warming of the reaction mixture to 0 °C. Addition of the organolithium reagent to the carbonyl group did not occur until the mixture was warmed. By conducting the initial addition at –78 °C, however, complete deprotonation of the hydroxyl group of the pseudoephedrine auxiliary was ensured, thus preventing premature breakdown of the tetrahedral intermediate. Typically, the addition reaction was complete within a few minutes of warming to 0 °C. To quench the reaction, excess alkyllithium was first scavenged by the addition of diisopropylamine, then the tetrahedral intermediate was decomposed by the addition of a solution of acetic acid in ether (10% v/v).

As shown by the results of Table 15, the ketone products were generally obtained in excellent yields and with little to no epimerization of the α-stereocenter. In the case of substrate **19** (entries 4 and 5), competing β-elimination of benzyl alcohol attenuated the product yield somewhat, and in the case of substrate **21** (entry 9), the kinetic acidity of the benzylic proton both lowered the yield and ee of the product due to competing enolization.

The addition of alkyllithium reagents to dialkylated pseudoephedrine bis-amides to form ketoamides and diketones was also pursued, but these efforts were only partially

Table 15. Reaction of Pseudoephedrine Amides with Organolithium Reagents to Form Ketones

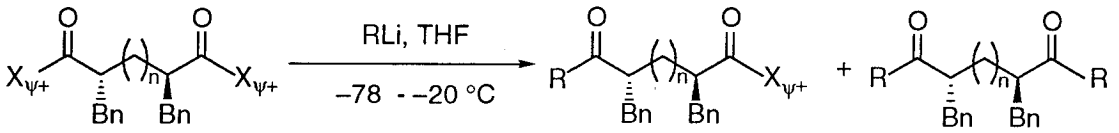


entry[b]	substrate	R"	product	isol yield (%)	isol ee or de (%)
1	 **17**	Ph	 **40**	94	≥95
2	 **17**	*n*-Bu	 **41**	89	≥95
3	 **18**	Ph	 **42**	93	≥95
4	 **19**	Ph	 **43**	64	≥95
5	 **19**	Me	 **44**	68	95
6	 **20**	Ph	 **45**	96	≥95
7	 **20**	*n*-Bu	 **46**	94	≥95
8	 **20**	Me	 **47**	98	≥95
9	 **21**	Me	 **48**	54	88

[a] The starting material was in all cases of ≥99% de except **19** which was of 98% de.

successful. However, as none of the other methodologies developed to date to cleave pseudoephedrine amides had proven effective on these bis-amide substrates, even this limited success was noteworthy. As seen from the data within Table 16 (additions to dibenzylated substrates) and Table 17 (additions to dimethylated substrates), the reactivity of these bis-amides toward alkyllithium reagents was highly dependent on the structure of the bis-amide. For example, for the dibenzylated diamide series (Table 16), ketoamides were readily obtained by the addition of 3.2–4.2 equiv of the alkyllithium reagent to the bis-amide substrate while diketones were difficult to prepare and required the addition of large excesses of the alkyllithium reagent. Even the addition of 10 equiv of phenyllithium to the pimelic (n = 3) bis-amide failed to afford a good yield of the diketone (Entry 3, Table 16). In addition, while 10 equiv of methyllithium was sufficient to obtain complete

Table 16. Reaction of Dibenzylated Pseudoephedrine Bis-Amides with Organolithium Reagents to Form Ketoamides and Diketones

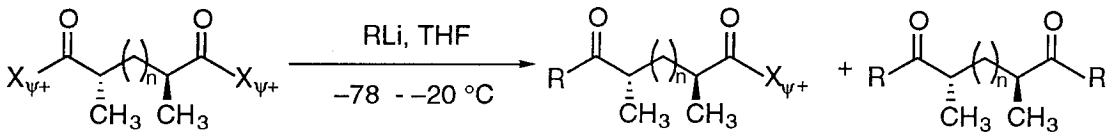


entry	n	R	equiv of RLi	ketoamide yield (%)	diketone yield (%)
1[a]	3	CH_3	10	–	87
2	3	CH_3	3.2	83	7
3	3	C_6H_5	10	45	18
4[a]	3	C_6H_5	3.5	77	2
5[b]	1	CH_3	10	25	57
6	1	CH_3	3.7	70	7
7[a]	1	C_6H_5	4.2	63	1

[a] The reaction mixture was warmed to 0 °C. [b] The reaction mixture was warmed to 23 °C.

conversion of pimelic bis-amide (n = 3) to the diketone (entry 1, Table 16), only a moderate yield of the corresponding diketone was obtained when 10 equiv of methyllithium was added to the glutaric bis-amide (n = 1, entry 5, Table 16). Presumably, as the distance between the negative charges shrank (going from n = 3 to n = 1), the formation of the tetraanionic intermediate leading to the diketone product became more difficult. By contrast, in the addition of alkyllithium reagents to the dimethylated diamides (Table 17),

Table 17. Reaction of Dimethylated Pseudoephedrine Bis-amides with Organolithium Reagents to Form Ketoamides and Diketones



entry	n	R	equiv of RLi	ketoamide yield (%)	diketone yield (%)
1[a]	3	CH_3	10	–	83
2[a]	3	CH_3	3.0	68	27
3	3	C_6H_5	10	16	60
4	3	C_6H_5	3.1	70	14
5	3	CH_3CH_2	4.5	–	63
6	1	CH_3CH_2	4.1	–	68
7[b]	1	CH_3CH_2	3.0	–	–
8	1	C_6H_5	7.5	–	58
9	1	C_6H_5	3.2	46	15

[a] The reaction mixture was warmed to 0 °C. [b] Only the diketone and starting material were detected by thin layer chromatography. [c] Only the ketoamide was detected by thin layer chromatography.

diketones were easily formed and it was the ketoamides that were difficult to obtain in good yield due to competitive overaddition (entries 2, 4, 7, and 9, Table 17).

Experimental Section

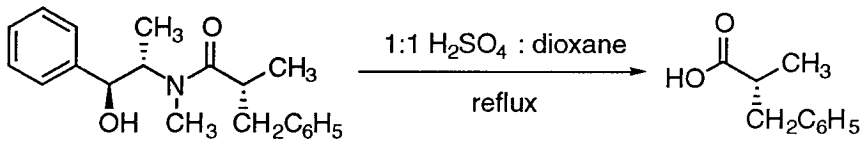
General Procedures. All non-aqueous reactions were performed in flame-dried, round-bottomed flasks, equipped with a magnetic stirring bar and fitted with a rubber septum under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation at ~25 Torr. Flash column chromatography was performed as described by Still et al.[12] employing 230–400 mesh silica gel. Analytical thin-layer chromatography was performed using glass plates precoated with 0.25-mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm).

Materials. Commercial reagents and solvents were used as received with the following exceptions. Tetrahydrofuran and ether were distilled under nitrogen from sodium benzophenone ketyl. Dichloromethane, diisopropylamine, triethylamine, chlorotrimethylsilane, and toluene were distilled under nitrogen from calcium hydride. The molarity of *n*-butyllithium, methyllithium, phenyllithium, and ethyllithium was determined by titration against diphenylacetic acid as an indicator (average of three determinations).[13] Solvents used for flash column chromatography were reagent-grade. The amide substrates **17-21** and the diamide substrates of Tables 16 and 17 were prepared as described in Bryant H. Yang's thesis.[22]

Instrumentation. Infrared data are presented as follows: frequency of absorption (cm^{-1}), intensity of absorption (br = broad, s = strong, m = medium). ^1H NMR spectra were recorded at 400 or 300 MHz, and ^{13}C NMR spectra were recorded at 100 or 75 MHz; chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane. ^1H NMR chemical shifts are referenced to the signal for residual hydrogen in the NMR solvent ($CHCl_3$: δ 7.26, C_6HD_5: δ 7.15). Data are presented as

follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sx = sextet, m = multiplet), integration, and coupling constant in Hertz. ^{13}C NMR chemical shifts are referenced to the carbon signal for the solvent ($CDCl_3$: δ 77.0, C_6D_6: δ 128.0). Mass spectrometry was performed at the University of Nebraska at Lincoln, at the California Institute of Technology, or the University of California at Irvine. Combustion analyses were performed by Quantitative Technologies Incorporated. Chiral capillary gas chromatography (GC) analysis was carried out using a 25 m × 0.25 mm ID Alltech Chirasil-Val chiral fused silica capillary column, under isothermal conditions, with a column head pressure of 17 psi.

Hydrolysis of Pseudoephedrine Amides to Form Carboxylic Acids



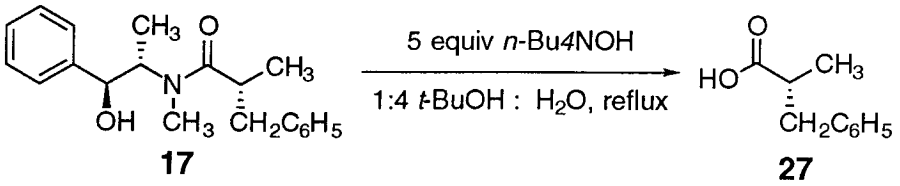
17 **27**

(*R*)-α-Methyl benzenepropionic acid **27**: Hydrolysis of Pseudoephedrine Amides with H_2SO_4 in 1:1 Aqueous Dioxane.

A 250-mL round-bottomed flask was charged with amide **17** (10.0 g, 32.1 mmol, 1 equiv), dioxane (50 mL), and 9 N aqueous sulfuric acid solution (50 mL). The biphasic mixture was heated at reflux for 6 h, then was cooled to 0 °C. The pH of the mixture was adjusted to pH ≥ 10 by the slow addition of 50% (w/w) aqueous sodium hydroxide solution and the resulting mixture was partitioned between water (100 mL) and dichloromethane (200 mL). The aqueous layer was separated and extracted with dichloromethane (200 mL). The aqueous layer was acidified to pH ≤ 2 by the slow addition of 6 N aqueous sulfuric acid solution, then was extracted with dichloromethane (3 × 200 mL). The latter organic extracts were combined and concentrated to a volume of ca. 50 mL and the concentrate was then washed with 1 N aqueous hydrochloric acid solution to remove residual dioxane. The resulting organic layer was dried over sodium sulfate and was concentrated to afford acid **27** as a clear liquid (5.07 g, 95%). Coupling of acid **27** (25 mg, 0.15 mmol, 1 equiv) with (*R*)-α-methylbenzylamine (24 μL, 0.19 mmol, 1.2 equiv) in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (44 mg, 0.23 mmol, 1.5 equiv), 1-hydroxybenzotriazole hydrate (31 mg, 0.23 mmol, 1.5 equiv), and triethylamine (86 μL, 0.62 mmol, 4.0 equiv) in *N*,*N*-dimethylformamide (0.5 mL) at 23 °C for 20 h gave the corresponding (*R*)-α-methylbenzyl amide[23] which was analyzed by chiral capillary GC to establish an ee of 97% for acid **27**.

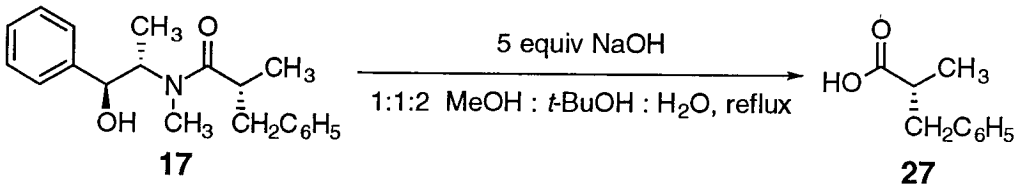
^{1}H NMR (300 MHz, $CDCl_3$) δ:	7.25 (m, 5H, **H**-Ar), 3.09 (dd, 1H, J_1 = 13.1 Hz, J_2 = 6.1 Hz, one of $C_6H_5C\mathbf{H}_2$), 2.75 (m, 2H, one of $C_6H_5C\mathbf{H}_2$, $C_6H_5CH_2C\mathbf{H}$), 1.18 (d, 3H, J = 6.8 Hz, $C\mathbf{H}_3$).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	182.5, 139.0, 129.0, 128.4, 126.4, 41.2, 39.3, 16.5.
FTIR (neat, cm^{-1}):	2976 (br, s, OH), 1707 (s, C=O).
HRMS (FAB):	Calcd for $C_{10}H_{12}O_2$ $(M)^+$: 164.0838. Found: 164.0832.
Analysis:	Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.23; H, 7.30.

The carboxylic acids of entries 2–7 (Table 4) were prepared analogously except that 18 N H_2SO_4 was employed and the reaction time was reduced to 1–2 h at reflux.



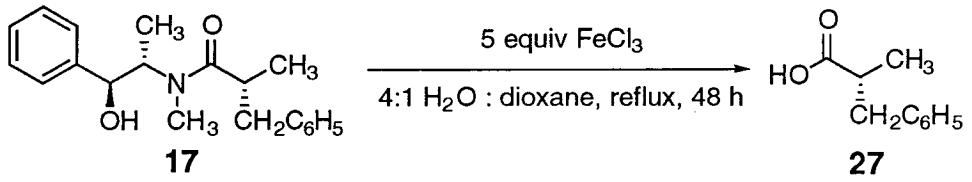
(*R*)-α-Methyl benzenepropionic acid **27**: Hydrolysis of Pseudoephedrine Amides with *n*-Bu_4NOH in 4:1 Aqueous *tert*-Butyl Alcohol.

A 100-mL round-bottomed flask was charged with amide **17** (0.500 g, 1.61 mmol, 1 equiv), aqueous tetra-*n*-butylammonium hydroxide solution (40% w/w, 5.21 g, 8.03 mmol, 5.00 equiv), *tert*-butyl alcohol (5 mL), and water (15 mL) and the biphasic mixture was heated at reflux for 24 h. The mixture was cooled to 23 °C, then was partitioned between 0.5 N aqueous sodium hydroxide solution (200 mL) and ether (25 mL). The aqueous layer was separated and extracted with two 25-mL portions of ether, then was brought to pH ≤ 1 by the addition of 3 N aqueous hydrochloric acid solution. The acidified solution was saturated with sodium chloride and extracted with three 35-mL portions of ether. The combined ether extracts were washed with water (10 mL), then were dried over sodium sulfate and were concentrated to afford acid **27** as a clear liquid (0.245 g, 93%) with spectroscopic data identical to those obtained from **27** prepared above. Chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide,[23] prepared as described above, established that **27** prepared by this method was of 94% ee. The purity of **27** was estimated to be ≥95% by ^1H and ^{13}C NMR spectroscopic data.



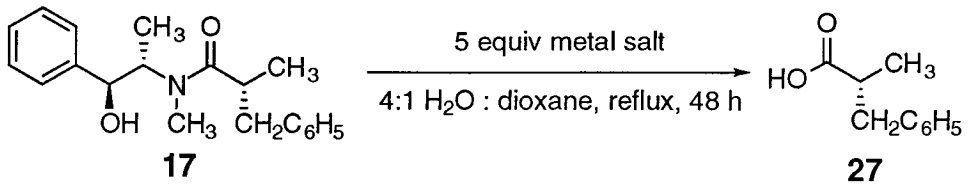
(*R*)-α-Methyl benzenepropionic acid **27**: Hydrolysis of Pseudoephedrine Amides with NaOH in 2:1:1 Water:*tert*-Butyl Alcohol:Methanol.

A 250-mL round-bottomed flask was charged with amide **17** (10.0 g, 32.1 mmol, 1 equiv), *tert*-butyl alcohol (25 mL), methanol (25 mL), and 3.22 N aqueous sodium hydroxide solution (50 mL, 161 mmol, 5.01 equiv). The mixture was heated at reflux for 24 h, then was cooled to 23 °C. The mixture was concentrated to remove the organic solvents and the resulting aqueous solution was partitioned between water (200 mL) and dichloromethane (200 mL). The aqueous layer was separated, extracted with dichloromethane (200 mL), then was acidified to pH ≤ 2 by the slow addition of 6 N aqueous sulfuric acid solution. The acidified aqueous solution was extracted with dichloromethane (3 × 200 mL) and the combined organic extracts were dried over sodium sulfate and were concentrated to afford acid **27** as a clear liquid (5.18 g, 98%) with spectroscopic data identical to those obtained from **27** prepared above. Chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide,[23] prepared as described above, established that **27** prepared by this method was of 92% ee: Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37; found: C, 72.79; H, 7.09.



(*R*)-α-Methyl benzenepropionic acid **27**: Hydrolysis of Pseudoephedrine Amides with $FeCl_3$ in 4:1 Aqueous Dioxane.

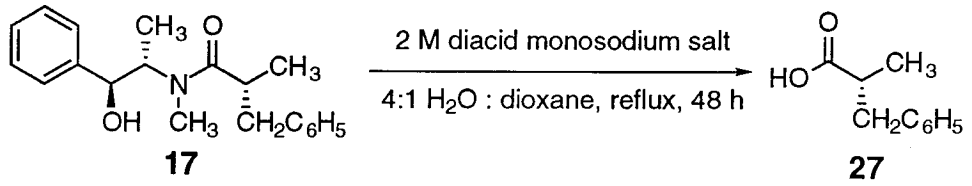
A 10-mL round-bottomed flask was charged with amide **17** (157 mg, 0.505 mmol, 1 equiv), iron(III) chloride hexahydrate (676 mg, 2.50 mmol, 4.95 equiv), water (4 mL), and dioxane (1 mL). The biphasic mixture was heated at reflux for 48 h, then was cooled to 23 °C. The pH of the mixture was adjusted to ≥ 10 by the dropwise addition of 50% (w/w) aqueous sodium hydroxide solution and the resulting mixture was partitioned beween water (10 mL) and dichloromethane (10 mL). The aqueous layer was separated, extracted with dichloromethane (10 mL), then was acidified to pH ≤ 2 by the dropwise addition of 6 N aqueous sulfuric acid solution. The resulting aqueous solution was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over sodium sulfate and were concentrated to afford acid **27** as a clear liquid (78.2 mg, 94%) with spectroscopic data identical to those obtained from **27** prepared above. Chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide,[23] prepared as described above, established that **27** prepared by this method was of 98% ee. The purity of **27** was estimated to be ≥95% by ^1H and ^{13}C NMR spectroscopic data.



(*R*)-α-Methyl benzenepropionic acid **27**: Hydrolysis of Pseudoephedrine Amides with $Yb(OTf)_3$ or $ZrOCl_2$ in 4:1 Aqueous Dioxane.

These hydrolyses were performed in a manner analogous to the hydrolysis with $FeCl_3$, substituting zirconyl chloride or ytterbium triflate (5 equiv) for iron (III) chloride.

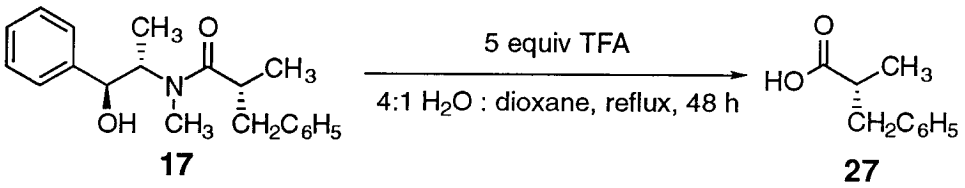
Likewise, the hydrolyses of amide **17** in the presence of the metal salts described in Table 8 were conducted employing a procedure analogous to the hydrolysis with $FeCl_3$ described above, substituting the metal salt (5 equiv) for iron (III) chloride.



(*R*)-α-Methyl benzenepropionic acid **27**: Hydrolysis of Amide **17** with the Monosodium Salt of Organic Diacids in 4:1 Aqueous Dioxane.

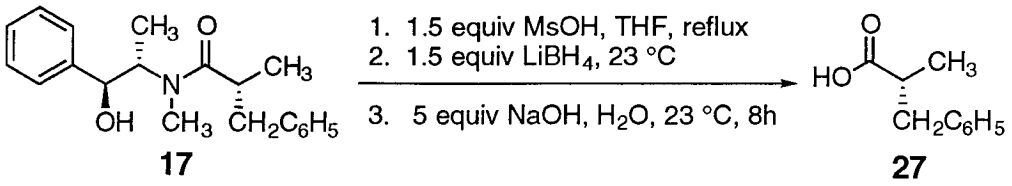
A 10-mL round-bottomed flask was charged with amide **17** (158 mg, 0.51 mmol, 1 equiv), oxalic acid dihydrate (1.26 g, 10.0 mmol, 20 equiv), aqueous sodium hydroxide solution (2.5 M, 4 mL, 10 mmol, 20 equiv), and dioxane (1 mL). The biphasic mixture was heated at reflux for 48 h, then was cooled to 23 °C. The pH of the mixture was adjusted to ≥ 10 by the dropwise addition of 50% (w/w) aqueous sodium hydroxide solution and the resulting mixture was partitioned beween water (10 mL) and dichloromethane (10 mL). The aqueous layer was separated, extracted with dichloromethane (10 mL), then was acidified to pH ≤ 2 by the dropwise addition of 6 N aqueous sulfuric acid solution. The resulting aqueous solution was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over sodium sulfate and were concentrated to afford acid **27** as a clear liquid (12.1 mg, 14%) with spectroscopic data identical to those obtained from **27** prepared above. Chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide,[23] prepared as described above, established that **27** prepared by this method was of 73% ee.

The hydrolyses of amide **17** with the other diacid monosodium salts described in Table 10 were conducted employing a procedure analogous to that described above, substituting the diacid (10 mmol) for oxalic acid.



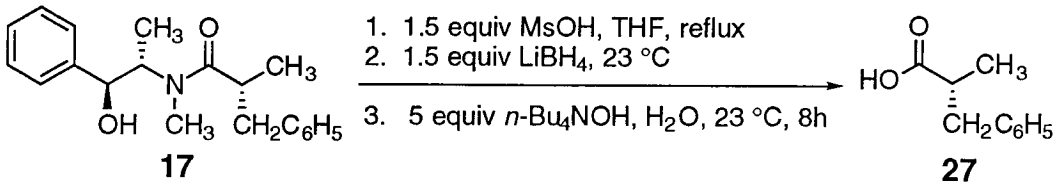
(*R*)-α-Methyl benzenepropionic acid **27**: Hydrolysis of Pseudoephedrine Amides with Trifluoroacetic acid in 4:1 Aqueous Dioxane.

A 10-mL round-bottomed flask was charged with amide **17** (157 mg, 0.51 mmol, 1 equiv), trifluoroacetic acid (193 μL, 2.51 mmol, 5.0 equiv), water (4 mL), and dioxane (1 mL). The biphasic mixture was heated at reflux for 48 h, then was cooled to 23 °C. The pH of the mixture was adjusted to ≥ 10 by the dropwise addition of 50% (w/w) aqueous sodium hydroxide solution and the resulting mixture was partitioned beween water (10 mL) and dichloromethane (10 mL). The aqueous layer was separated, extracted with dichloromethane (10 mL), then was acidified to pH ≤ 2 by the dropwise addition of 6 N aqueous sulfuric acid solution. The resulting aqueous solution was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over sodium sulfate and were concentrated to afford acid **27** as a clear liquid (73.9 mg, 89%) with spectroscopic data identical to those obtained from **27** prepared above. Chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide,[23] prepared as described above, established that **27** prepared by this method was of 95% ee. The purity of **27** was estimated to be ≥95% by ^{1}H and ^{13}C NMR spectroscopic data.



(*R*)-α-Methyl benzenepropionic acid **27**: Hydrolysis of Pseudoephedrine Amides Involving in situ Borane-Amine Complexation (Sodium Hydroxide).

A 10-mL round-bottomed flask was charged with amide **17** (160 mg, 0.513 mmol, 1 equiv), tetrahydrofuran (2.0 mL), and methanesulfonic acid (48 μL, 0.74 mmol, 1.44 equiv). This mixture was heated at reflux for 1 h, then was cooled to 23 °C. A solution of lithium borohydride (2.0 M, 0.38 mL, 0.76 mmol, 1.5 equiv) in tetrahydrofuran was cautiously added to the mixture, leading to significant gas evolution. A solution of aqueous sodium hydroxide (1.25 N, 2.0 mL, 2.5 mmol, 4.9 equiv) was then cautiously added and the resulting mixture was stirred for 8 h at 23 °C. The reaction mixture was partitioned between water (10 mL) and dichloromethane (10 mL). The aqueous layer was separated and extracted with dichloromethane (10 mL), then was acidified to pH ≤ 2 by the slow addition of 3 N aqueous hydrochloric acid solution. The resulting acidified solution was extracted with dichloromethane (3 × 10 mL). The latter extracts were combined, dried over sodium sulfate, and were concentrated to afford acid **27** as a clear liquid (79.5 mg, 94%) with spectroscopic data identical to those obtained from **27** prepared above. Chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide,[23] prepared as described above, established that **27** prepared by this method was of 98% ee. The purity of **27** was estimated to be ≥95% by ^{1}H and ^{13}C NMR spectroscopic data.

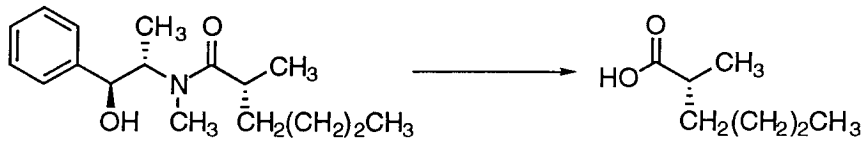


17 **27**

(*R*)-α-Methyl benzenepropionic acid **27**: Hydrolysis of Pseudoephedrine Amides Involving in situ Borane Amine Complexation (*n*-Bu_4NOH).

A flame-dried 10-mL round-bottomed flask was charged with amide **17** (158 mg, 0.508 mmol, 1 equiv), tetrahydrofuran (2.0 mL), and methanesulfonic acid (48 μL, 0.74 mmol, 1.46 equiv). The mixture was heated at reflux for 1 h, then was cooled to 23 °C. A solution of lithium borohydride (2.0 M, 0.38 mL, 0.76 mmol, 1.5 equiv) in tetrahydrofuran was cautiously added to the mixture, leading to significant gas evolution. Water (1.0 mL) and an aqueous solution of tetra-*n*-butylammonium hydroxide (40% w/w, 1.62 g, 2.50 mmol, 4.92 equiv) were then cautiously added and the mixture was stirred at 23 °C for 1 h. The reaction mixture was partitioned between 0.5 N aqueous sodium hydroxide solution (50 mL) and ether (10 mL). The aqueous phase was separated and extracted with ether (2 × 10 mL), then was acidified to pH ≤ 2 by the slow addition of 3 N aqueous hydrochloric acid solution and was extracted with ether (3 × 10 mL). The latter organic extracts were combined and washed sequentially with 1 N aqueous hydrochloric acid solution (10 mL) and brine (10 mL) to remove residual tetra-*n*-butylammonium salts, then were dried over sodium sulfate and concentrated to afford acid **27** as a clear liquid (75.4 mg, 91%) with spectroscopic data identical to those obtained from **27** prepared above. Chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide,[23] prepared as described above, established that **27** prepared by this method was of 94% ee. The purity of **27** was estimated to be ≥95% by ^1H and ^{13}C NMR spectroscopic data.

The following carboxylic acids (≥95% purity) were prepared by the methods described above, as summarized within Tables 1–14, with yields and enantiomeric excesses listed therein.



18 **28**

(*R*)-2-Methylhexanoic Acid **28**

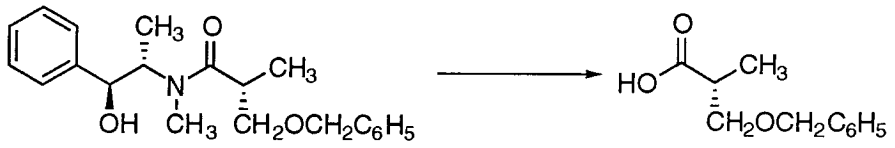
Hydrolysis of amide **18** afforded acid **28** as a clear liquid:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.44 (sx, 1H, J = 6.9 Hz, C**H**CO_2H), 1.70 (m, 1H, one of CHC**H**$_2$CH$_2$), 1.45 (m, 1H, one of CHC**H**$_2$CH$_2$), 1.35 (m, 4H, C**H**$_2$CH$_2$CH$_3$, CH$_2$C**H**$_2$CH$_3$), 1.17 (d, 3H, J = 7.0 Hz, CHC**H**$_3$),.0.90 (m, 3H, CH$_2$CH$_2$C**H**$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 183.9, 39.4, 33.2, 29.3, 22.6, 16.8, 13.9.

FTIR (neat, cm^{-1}): 3028 (br, s, OH), 1712 (s, C=O).

LRMS (EI): *m/z* (relative intensity) 101 (5), 87 (28), 74 (100), 55 (11).



19 **29**

(*R*)-3-Benzyloxy-2-methylpropionic Acid **29**

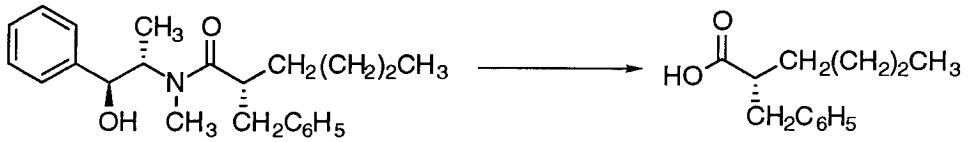
Hydrolysis of amide **19** afforded acid **29** as a clear liquid:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.8–9.2 (br, 1H, $CO_2\mathbf{H}$), 7.25–7.37 (m, 5H, **H**-Ar), 4.55 (s, 2H, $OC\mathbf{H}_2C_6H_5$), 3.66 (dd, 1H, J_1 = 9.1 Hz, J_2 = 7.4 Hz, one of $CHC\mathbf{H}_2O$), 3.54 (dd, 1H, J_1 = 9.1 Hz, J_2 = 5.6 Hz, one of $CHC\mathbf{H}_2O$), 2.81 (m, 1H, one of $C\mathbf{H}CO_2H$), 1.22 (d, 3H, J = 7.1 Hz, $C\mathbf{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 180.0, 137.9, 128.5, 127.8, 127.7, 73.3, 71.6, 40.1, 13.7.

FTIR (neat, cm^{-1}): 2800–3400 (br, s, OH), 1711 (s, C=O).

HRMS (EI): Calcd for $C_{11}H_{14}O_3$ $(M)^+$: 194.0943.
Found: 194.0946.



20 **30**

(*R*)-α-Butyl benzenepropionic acid **30**

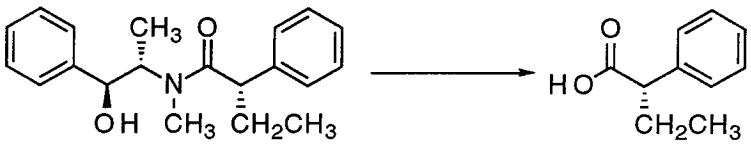
Hydrolysis of amide **20** afforded acid **30** as a clear liquid:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.30 (m, 5H, **H**-Ar), 2.98 (dd, 1H, J_1 = 7.8 Hz, J_2 = 13.5 Hz, one of $C_6H_5C\mathbf{H}_2$), 2.70 (m, 2H, one of $C_6H_5C\mathbf{H}_2$, $C\mathbf{H}CO_2H$), 1.65 (m, 1H, one of $CHC\mathbf{H}_2CH_2$), 1.55 (m, 1H, one of $CHC\mathbf{H}_2CH_2$), 1.30 (m, 4H, $C\mathbf{H}_2CH_2CH_3$, $CH_2C\mathbf{H}_2CH_3$), 0.85 (m, 3H, $CH_2CH_2C\mathbf{H}_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 181.8, 139.1, 128.9, 128.4, 126.4, 47.3, 38.1, 31.4, 29.3, 22.5, 13.9.

FTIR (neat, cm^{-1}): 3028 (br, s, OH), 1711 (s, C=O).

HRMS (EI): Calcd for $C_{13}H_{18}O_2$ $(M)^+$: 206.1307.
Found: 206.1314.



21 **31**

(*S*)-α-Ethyl benzeneacetic acid **31**

Hydrolysis of amide **21** afforded acid **31** as a clear liquid:

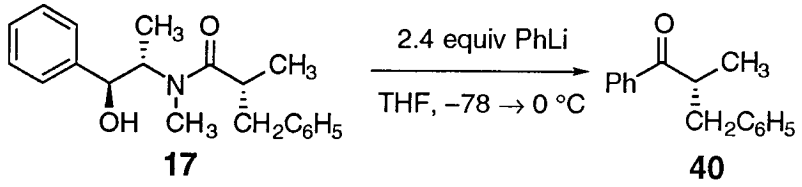
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.25 (m, 5H, **H**-Ar), 3.41 (t, 1H, *J* = 7.7 Hz, $CHCO_2H$), 2.05 (m, 1H, one of CH_2CH_3), 1.76 (m, 1H, one of CH_2CH_3), 0.86 (t, 3H, *J* = 7.4 Hz, CH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 180.5, 138.3, 128.6, 128.1, 127.4, 53.3, 26.3, 12.1.

FTIR (neat, cm^{-1}): 2967 (br, s, OH), 1712 (s, C=O).

HRMS (EI): Calcd for $C_{10}H_{12}O_2$ $(M)^+$: 164.0837.
Found: 164.0839.

Reaction of Pseudoephedrine Amides with Organolithium Reagents to Form Ketones.

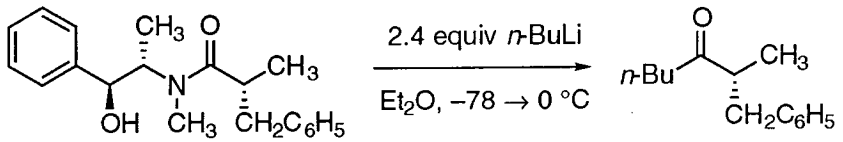


17 **40**

(*R*)-2-Methyl-1,3-diphenyl-1-propanone **40**

Amide **17** (261 mg, 0.839 mmol, 1 equiv) was suspended in toluene (5 mL) in a 25-mL rounded-bottomed flask. The suspension was warmed to 70 °C to dissolve the amide and the resulting solution was cooled to 23 °C, then was concentrated under reduced pressure. The reaction flask was flushed with dry argon, tetrahydrofuran (10 mL) was added, and the resulting slurry was cooled to –78 °C. A solution of phenyllithium in 70% cyclohexane–ether (1.94 M, 1.04 mL, 2.02 mmol, 2.41 equiv) was added via syringe and the mixture was then warmed to 0 °C and was held at that temperature for 5 min. Excess phenyllithium was quenched at 0 °C by the addition of diisopropylamine (0.12 mL, 0.84 mmol, 1 equiv). After 15 min, a solution of acetic acid in ether (10% v/v, 10 mL) was added. The mixture was partitioned between ethyl acetate (40 mL) and saturated aqueous sodium bicarbonate solution (50 mL), and the organic phase was separated and extracted with saturated aqueous sodium bicarbonate solution (50 mL) and water (50 mL). The organic phase was dried over sodium sulfate and was concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (3 → 10%) afforded ketone **40** as a clear liquid (176 mg, 94% yield). High resolution ^{1}H NMR analysis (300 MHz, C_6D_6) of the Mosher ester derivatives[24,25] of the diastereomeric alcohol mixture obtained by the reduction of ketone **40** with lithium aluminum hydride (as described for ketone **41** below) established that ketone **40** was of ≥95% ee.

^{1}H NMR (300 MHz, $CDCl_3$) δ:	7.1–7.8 (m, 10H, **H**-Ar), 3.79 (sx, 1H, J = 6.9 Hz, COC**H**), 3.22 (dd, 1H, J_1 = 13.7 Hz, J_2 = 6.3 Hz, one of $C_6H_5CH_2$), 2.74 (dd, 1H, J_1 = 13.7 Hz, J_2 = 7.9 Hz, one of $C_6H_5CH_2$), 1.25 (d, 3H, J = 6.9 Hz, CH_3).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	203.7, 139.9, 136.4, 132.9, 129.1, 128.6, 128.3, 128.2, 126.2, 42.7, 39.3, 17.4.
FTIR (neat, cm^{-1}):	1679 (s, C=O).
HRMS (EI):	Calcd for $C_{16}H_{16}O$, $(M)^+$: 224.1201. Found: 224.1201.



17 **41**

(*R*)-2-Methyl-1-phenyl-3-heptanone **41**

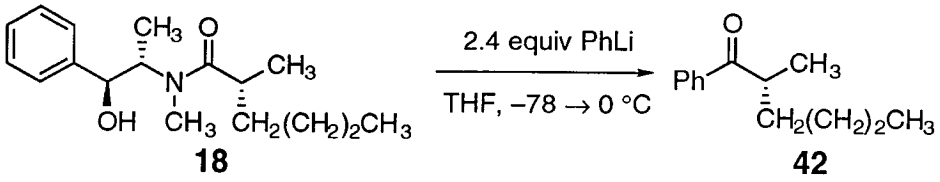
Amide **17** (10.0 g, 32.1 mmol, 1 equiv) was suspended in toluene (50 mL) in a 500-mL round-bottomed flask. The suspension was warmed to 70 °C to dissolve the amide and the resulting solution was cooled to 23 °C, then was concentrated under reduced pressure. The reaction flask was then flushed with dry argon, ether (250 mL) was added, and the resulting slurry was cooled to –78 °C. A solution of *n*-butyllithium in hexanes (2.39 M, 32.3 mL, 77.2 mmol, 2.40 equiv) was added via syringe and the mixture was then warmed to 0 °C and was held at that temperature for 15 min. Excess *n*-butyllithium was quenched at 0 °C by the addition of diisopropylamine (4.5 mL, 32 mmol, 1 equiv). After 15 min, a solution of acetic acid in ether (20% v/v, 100 mL) was added. The mixture was partitioned between ethyl acetate (300 mL) and water (300 mL), and the aqueous phase was separated and extracted with dichloromethane (2 × 300 mL). The combined organic extracts were dried over anhydrous sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (2 → 5%) afforded ketone **41** as a clear liquid (5.80 g, 88% yield). A solution of lithium aluminum hydride in ether (1.0 M, 0.75 mL, 0.75 mmol, 1.5 equiv) was added to a solution of ketone **41** (102 mg, 0.50 mmol, 1 equiv) in ether (1 mL) at 0 °C to afford a mixture of diastereomeric alcohols. High resolution ^{1}H NMR analysis (400 MHz, C_6D_6) of the corresponding Mosher ester derivatives[24,25] of this mixture of diastereomeric alcohols established that ketone **41** was of ≥95% ee.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.20 (m, 5H, **H**-Ar), 2.97 (dd, 1H, J_1 = 13.2 Hz, J_2 = 7.1 Hz, one of $C\mathbf{H}_2C_6H_5$), 2.83 (sx, 1H, J = 7.0 Hz, $COC\mathbf{H}C_6H_5$), 2.55 (dd, 1H, J_1 = 13.2 Hz, J_2 = 7.3 Hz, one of $C\mathbf{H}_2C_6H_5$), 2.39 (dt, 1H, J_1 = 16.9 Hz, J_2 = 7.3 Hz, one of $COC\mathbf{H}_2$), 2.25 (dt, 1H, J_1 = 16.9 Hz, J_2 = 7.3 Hz, one of $COC\mathbf{H}_2$), 1.45 (m, 2H, $C\mathbf{H}_2CH_2CH_3$), 1.23 (sx, 2H, J = 7.4 Hz, $C\mathbf{H}_2CH_2CH_3$), 1.07 (d, 3H, J = 6.9 Hz, $CHC\mathbf{H}_3$), 0.85 (t, 3H, J = 7.3 Hz, $CH_2CH_2C\mathbf{H}_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 214.4, 139.8, 128.9, 128.3, 126.2, 48.1, 41.7, 39.1, 25.6, 22.3, 16.5, 13.9.

FTIR (neat, cm^{-1}): 1712 (s, C=O).

HRMS (EI): Calcd for $C_{14}H_{20}O$ $(M)^+$: 204.1514.
Found: 204.1517.



(*R*)-2-Methyl-1-phenyl-1-hexanone **42**

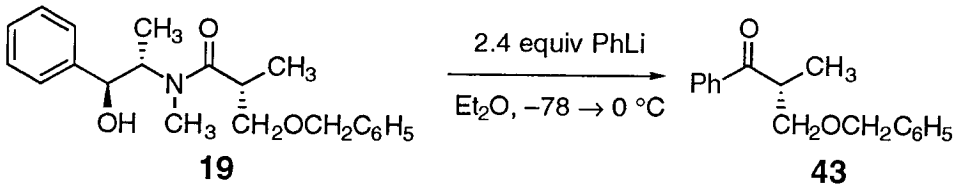
Ketone **42** was prepared by the addition of phenyllithium to amide **18** using a procedure analogous to that described above for the preparation of ketone **40**. Thus, a solution of phenyllithium in 70% cyclohexane–ether (1.94 M, 1.20 mL, 2.33 mmol, 2.44 equiv) was added to a suspension of amide **18** (264 mg, 0.953 mmol, 1 equiv) in tetrahydrofuran (10 mL) to afford ketone **42** as a clear liquid (168 mg, 93%) after purification by flash column chromatography (gradient elution of ethyl acetate–hexanes, 2 → 10%). High resolution ^{1}H NMR analysis (400 MHz, C_6D_6) of the Mosher ester derivatives[24,25] of the diastereomeric alcohol mixture obtained by the reduction of ketone **42** with lithium aluminum hydride (as described for ketone **41** above) established that ketone **42** was of ≥95% ee.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.95 (m, 2H, **H**-Ar), 7.50 (m, 3H, **H**-Ar), 3.46 (sx, 1H, J = 6.8 Hz, COC**H**), 1.80 (m, 1H, one of COCHC**H**$_2$), 1.45 (m, 1H, one of COCHC**H**$_2$), 1.30 (m, 4H, C**H**$_2$CH$_2$CH$_3$, CH$_2$C**H**$_2$CH$_3$), 1.19 (d, 3H, J = 6.9 Hz, CHC**H**$_3$), 0.87 (m, 3H, CH$_2$CH$_2$C**H**$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 204.5, 136.7, 132.7, 128.6, 128.2, 40.5, 33.4, 29.6, 22.8, 17.2, 13.9.

FTIR (neat, cm^{-1}): 1682 (s, C=O).

HRMS (EI): Calcd for $C_{13}H_{18}O$ $(M)^+$: 190.1358.
Found: 190.1363.

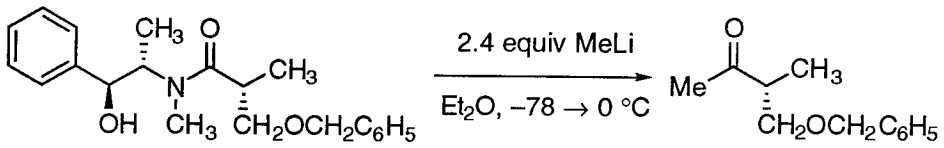


19 **43**

(R)-2-(Benzyloxymethyl)-1-phenyl-1-propanone **43**

Ketone **43** was prepared by the addition of phenyllithium to amide **19** using a procedure analogous to that described above for the preparation of ketone **40**. Thus, a solution of phenyllithium in 70% cyclohexane–ether (1.94 M, 0.910 mL, 1.77 mmol, 2.40 equiv) was added to a suspension of amide **19** (251 mg, 0.736 mmol, 1 equiv) in ether (7 mL) to afford ketone **43** as a clear liquid (119 mg, 64%) after purification by flash column chromatography (gradient elution of ethyl acetate–hexanes, 7.5 → 30%). High resolution ^{1}H NMR analysis (400 MHz, C_6D_6) of the Mosher ester derivatives[24,25] of the diastereomeric alcohol mixture obtained by the reduction of ketone **43** with lithium aluminum hydride (as described for ketone **41** above) established that ketone **43** was of ≥95% ee.

^{1}H NMR (300 MHz, $CDCl_3$) δ:	8.0 (m, 2H, **H**-Ar), 7.55 (m, 1H, **H**-Ar), 7.45 (m, 2H, **H**-Ar), 7.3 (m, 5H, **H**-Ar), 4.51 (dd, 2H, J_1 = 17.6 Hz, J_2 = 12.1 Hz, $CH_2C_6H_5$), 3.85 (m, 2H, $CHCH_2O$), 3.55 (m, 1H, $CHCH_2O$), 1.23 (d, 3H, J = 6.8 Hz, CH_3).
^{13}C NMR (100 MHz, $CDCl_3$) δ:	202.8, 138.3 136.9, 133.0, 128.6, 128.5, 128.4, 73.4, 72.5, 41.6, 15.0.
FTIR (neat, cm^{-1}):	1682 (s, C=O).
HRMS (EI):	Calcd for $C_{17}H_{19}O_2$ $(MH)^+$: 255.1385. Found: 255.1383.



19 **44**

(R)-3-(Benzyloxymethyl)-2-butanone **44**

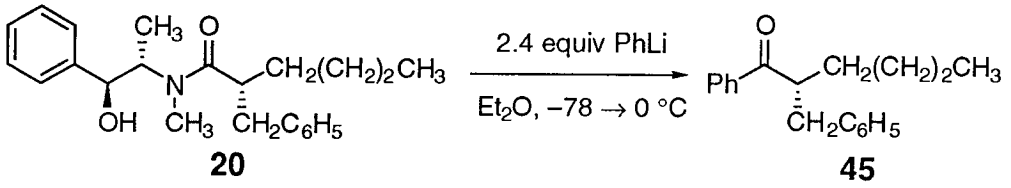
Ketone **44** was prepared by the addition of methyllithium to amide **19** using a procedure analogous to that described above for the preparation of ketone **40**. Thus, a solution of methyllithium in ether (1.25 M, 1.65 mL, 2.06 mmol, 2.39 equiv) was added to a suspension of amide **19** (294 mg, 0.862 mmol, 1 equiv) in ether (10 mL) to afford ketone **44** as a clear liquid (112 mg, 68%) after purification by flash column chromatography (gradient elution of ethyl acetate–hexanes, 15 → 50%). High resolution ^{1}H NMR analysis (400 MHz, $CDCl_3$) of the Mosher ester derivatives[24,25] of the diastereomeric alcohol mixture obtained by the reduction of ketone **44** with lithium aluminum hydride (as described for ketone **41** above) established that ketone **44** was of 95% ee.

^{1}H NMR (300 MHz, C_6D_6) δ: 7.05–7.25 (m, 5H, **H**-Ar), 4.20 (dd, 2H, J_1 = 16.1 Hz, J_2 = 12.0 Hz, C**H**$_2$C$_6$H$_5$), 3.39 (dd, 1H, J_1 = 9.0 Hz, J_2 = 7.3 Hz, one of CHC**H**$_2$O), 3.18 (dd, 1H, J_1 = 9.0 Hz, J_2 = 5.4 Hz, one of CHC**H**$_2$O), 2.47 (m, 1H, C**H**CH$_2$O), 1.80 (s, 3H, C**H**$_3$CO), 0.85 (d, 3H, J = 7.1 Hz, CHC**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.1, 138.2, 128.4, 127.7, 73.3, 72.2, 47.3, 29.1, 13.4.

FTIR (neat, cm^{-1}): 1715 (s, C=O).

HRMS (EI): Calcd for $C_{12}H_{16}O_2$ $(M)^+$: 192.1150.
Found: 192.1149.



20 **45**

(R)-2-Butyl-1,3-diphenyl-1-propanone **45**

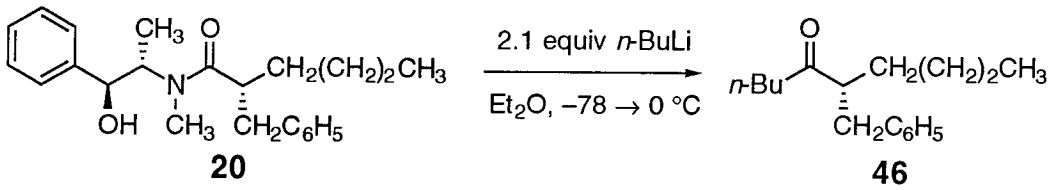
Ketone **45** was prepared by the addition of phenyllithium to amide **20** using a procedure analogous to that described above for the preparation of ketone **40**. Thus, a solution of phenyllithium in 70% cyclohexane–ether (1.94 M, 0.91 mL, 1.77 mmol, 2.41 equiv) was added to a suspension of amide **20** (259 mg, 0.733 mmol, 1 equiv) in ether (8 mL) to afford ketone **45** as a clear liquid (186 mg, 96%) after purification by flash column chromatography (gradient elution of ethyl acetate–hexanes, 3 → 5%). High resolution ^{1}H NMR analysis (400 MHz, $CDCl_3$) of the Mosher ester derivatives[24,25] of the diastereomeric alcohol mixture obtained by the reduction of ketone **45** with lithium aluminum hydride (as described for ketone **41** above) established that ketone **45** was of ≥95% ee.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.1–7.9 (m, 10H, **H**-Ar), 3.74 (m, 1H, COC**H**), 3.10 (dd, 1H, J_1 = 13.6 Hz, J_2 = 7.7 Hz, one of $\mathbf{CH_2}C_6H_5$), 2.78 (dd, 1H, J_1 = 13.6 Hz, J_2 = 6.5 Hz, one of $\mathbf{CH_2}C_6H_5$), 1.80 (m, 1H, one of $CHCH_2CH_2$), 1.55 (m, 1H, one of $CHCH_2CH_2$), 1.25 (m, 4H, $CH_2CH_2CH_3$, $CH_2CH_2CH_3$), 0.80 (m, 3H, $CH_2CH_2CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 204.0, 140.0, 137.5, 132.8, 129.0, 128.5, 128.3, 128.1, 126.1, 48.3, 38.2, 32.1, 29.5, 22.8, 13.9.

FTIR (neat, cm^{-1}): 1679 (s, C=O).

HRMS (EI): Calcd for $C_{19}H_{22}O$ $(M)^+$: 266.1671.
Found: 266.1673.



20 **46**

(R)-2-Butyl-1-phenyl-3-heptanone **46**

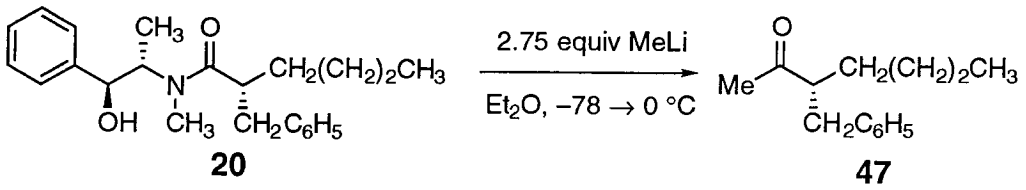
Ketone **46** was prepared by the addition of *n*-butyllithium to amide **20** using a procedure analogous to that described above for the preparation of ketone **41**. Thus, a solution of *n*-butyllithium in hexanes (1.71 M, 3.50 mL, 5.99 mmol, 2.11 equiv) was added to a suspension of amide **20** (1.00 g, 2.83 mmol, 1 equiv) in ether (30 mL) to afford ketone **46** as a clear liquid (652 mg, 94%) after purification by flash column chromatography (gradient elution of ethyl acetate–hexanes, 2.5 → 10%). High resolution ^{1}H NMR analysis (400 MHz, C_6D_6) of the Mosher ester derivatives[24,25] of the diastereomeric alcohol mixture obtained by the reduction of ketone **46** with lithium aluminum hydride (as described for ketone **41** above) established that ketone **46** was of ≥95% ee.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.20 (m, 5H, **H**-Ar), 2.80 (m, 2H, COC**H**, one of $C\mathbf{H}_2C_6H_5$), 2.65 (dd, 1H, J_1 = 12.0 Hz, J_2 = 5.0 Hz, one of $C\mathbf{H}_2C_6H_5$), 2.28 (dt, 1H, J_1 = 17.2 Hz, J_2 = 7.3 Hz, one of $COC\mathbf{H}_2$), 2.11 (dt, 1H, J_1 = 17.2 Hz, J_2 = 7.3 Hz, one of $COC\mathbf{H}_2$), 1.65 (m, 1H, one of $CHC\mathbf{H}_2CH_2$), 1.40 (m, 3H, one of $C\mathbf{H}_2$), 1.25 (m, 6H, one of $C\mathbf{H}_2$), 0.87 (t, 3H, J = 7.0 Hz, one of $C\mathbf{H}_3$), 0.81 (t, 3H, J = 7.3 Hz, one of $C\mathbf{H}_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 214.6, 139.9, 128.9, 126.1, 54.0, 43.4, 38.2, 31.6, 29.5, 25.2, 22.8, 22.2, 13.9, 13.8.

FTIR (neat, cm^{-1}): 1712 (s, C=O).

HRMS (EI): Calcd for $C_{17}H_{26}O$ $(M)^+$: 246.1984.
Found: 246.1995.



20 **47**

(R)-3-(Phenylmethyl)-2-heptanone **47**

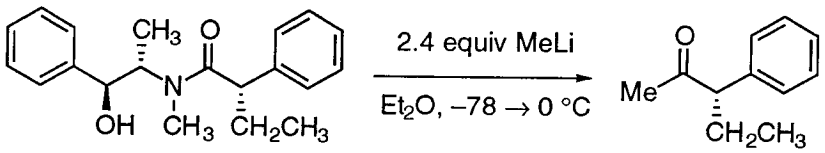
Ketone **47** was prepared by the addition of methyllithium to amide **20** using a procedure analogous to that described above for the preparation of ketone **41**. Thus, a solution of methyllithium in ether (1.30 M, 6.20 mL, 8.06 mmol, 2.76 equiv) was added to a suspension of amide **20** (1.03 g, 2.92 mmol, 1 equiv) in ether (30 mL) to afford ketone **47** as a clear liquid (582 mg, 98%) after purification by flash column chromatography (15% ethyl acetate–hexanes). High resolution ^{1}H NMR analysis (400 MHz, C_6D_6) of the Mosher ester derivatives[24,25] of the diastereomeric alcohol mixture obtained by the reduction of ketone **47** with lithium aluminum hydride (as described for ketone **41** above) established that ketone **47** was of ≥95% ee.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.2 (m, 5H, **H**-Ar), 2.85 (m, 2H, COC**H**, one of $C\mathbf{H}_2C_6H_5$), 2.69 (dd, 1H, J_1 = 12.1 Hz, J_2 = 5.1 Hz, one of $C\mathbf{H}_2C_6H_5$), 2.00 (s, 3H, $COC\mathbf{H}_3$), 1.65 (m, 1H, one of $CHC\mathbf{H}_2CH_2$), 1.45 (m, 1H, $CHC\mathbf{H}_2CH_2$), 1.27 (m, 4H, $C\mathbf{H}_2CH_2CH_3$, $CH_2C\mathbf{H}_2CH_3$), 0.88 (t, 3H, J = 6.9 Hz, $CH_2CH_2C\mathbf{H}_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 212.5, 139.6, 128.8, 128.4, 126.2, 54.7, 37.9, 31.4, 30.2, 29.4, 22.7, 13.9.

FTIR (neat, cm^{-1}): 1713 (s, C=O).

HRMS (EI): Calcd for $C_{14}H_{20}O$ $(M)^+$: 204.1514.
Found: 204.1521.

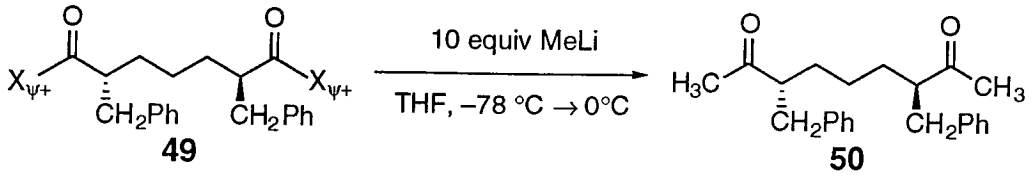


21 **48**

(*S*)-3-Phenyl-2-pentanone **48**

Ketone **48** was prepared by the addition of methyllithium to amide **21** using a procedure analogous to that described above for the preparation of ketone **40**. Thus, a solution of methyllithium in ether (1.40 M, 1.40 mL, 1.96 mmol, 2.38 equiv) was added to a solution of amide **21** (256 mg, 0.823 mmol, 1 equiv) in ether (8 mL) to afford ketone **48** as a clear liquid (72 mg, 54%) after purification by flash column chromatography (gradient elution of ethyl acetate–hexanes, 15 → 40%). High resolution ^{1}H NMR analysis (400 MHz, C_6D_6) of the Mosher ester derivatives[24,25] of the diastereomeric alcohol mixture obtained by the reduction of ketone **48** with lithium aluminum hydride (as described for ketone **41** above) established that ketone **48** was of 88% ee.

^{1}H NMR (300 MHz, C_6D_6) δ:	6.9–7.1 (m, 5H, **H**-Ar), 3.08 (t, 1H, J = 7.3 Hz, COC**H**), 2.03 (m, 1H, one of CHC$\mathbf{H}_2$), 1.66 (s, 3H, COC$\mathbf{H}_3$), 1.66 (m, 1H, one of CHC$\mathbf{H}_2$), 0.71 (t, 3H, J = 7.6 Hz, $CH_2C\mathbf{H}_3$).
^{13}C NMR (100 MHz, $CDCl_3$) δ:	208.5, 139.0, 128.9, 128.3, 127.2, 61.6, 29.1, 25.0, 12.0.
FTIR (neat, cm^{-1}):	1708 (s, C=O).
HRMS (EI):	Calcd for $C_{11}H_{14}O$ $(M)^+$: 162.1045. Found: 162.1052.



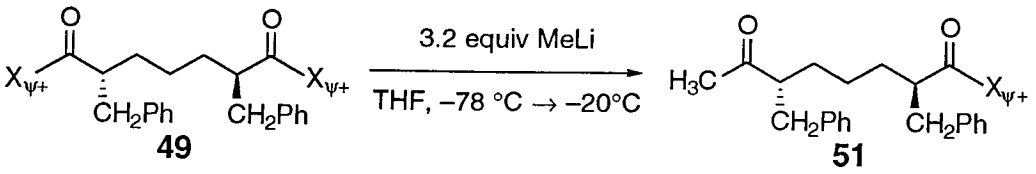
49 50

Diketone **50** (Entry 1, Table 16)

A 10-mL round-bottomed flask equipped with a magnetic stir bar was charged with diamide **49** (135 mg, 0.21 mmol, 1 equiv) and toluene (2 mL). This solution was concentrated under reduced pressure, affording a sticky foam. The reaction flask was flushed with dry argon, tetrahydrofuran (4 mL) was added, and the resulting solution was cooled to –78 °C. A solution of methyllithium in ether (1.30 M, 1.64 mL, 2.13 mmol, 10.0 equiv) was added via syringe and the mixture was warmed to –20 °C and was held at that temperature for 30 min. To ensure complete reaction, the reaction mixture was warmed to 0 °C and was held at that temperature for 30 min. Excess methyllithium was quenched at 0 °C by the addition of diisopropylamine (280 μL, 2.13 mmol, 10 equiv). After 15 min, a solution of acetic acid in ether (10% v/v, 2 mL) was added and the mixture was partitioned between dichloromethane (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was separated and extracted with dichloromethane (2 × 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (15 → 50%) afforded diketone **50** as a clear liquid (63 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.0–7.3 (m, 10H, **H**-Ar), 2.83 (dd, 2H, J_1 = 13 Hz, J_2 = 8 Hz, one of $C_6H_5C\mathbf{H}_2$), 2.77 (m, 2H, COC**H**), 2.60 (dd, 2H, J_1 = 10 Hz, J_2 = 6 Hz, one of $C_6H_5C\mathbf{H}_2$), 1.95 (s, 6H, $C\mathbf{H}_3$), 1.60 (m, 2H, one of $CHC\mathbf{H}_2CH_2$), 1.37 (m, 2H, one of $CHC\mathbf{H}_2CH_2$), 1.14 (m, 2H, one of $CHCH_2C\mathbf{H}_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.2, 139.4, 128.9, 128.6, 126.4, 54.5, 38.2, 31.5, 30.4, 25.1.



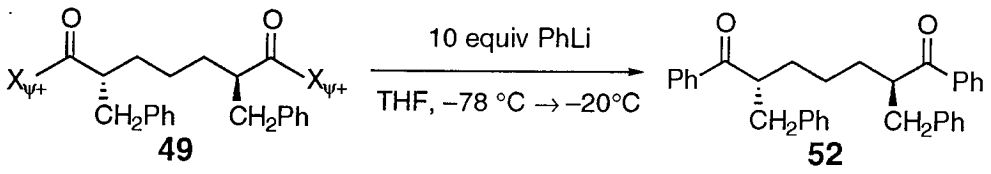
49 51

Ketoamide **51** (Entry 2, Table 16)

A 10-mL round-bottomed flask equipped with a magnetic stir bar was charged with diamide **49** (64 mg, 0.10 mmol, 1 equiv) and toluene (2 mL). This solution was concentrated under reduced pressure, affording a sticky foam. The reaction flask was flushed with dry argon, tetrahydrofuran (2 mL) was added, and the resulting solution was cooled to –78 °C. A solution of methyllithium in ether (1.27 M, 0.26 mL, 0.32 mmol, 3.2 equiv) was added via syringe and the mixture was warmed to –20 °C and was held at that temperature for 15 min. Excess methyllithium was quenched at –20 °C by the addition of diisopropylamine (39 μL, 2.13 mmol, 3 equiv). After 15 min, a solution of acetic acid in ether (10% v/v, 2 mL) was added and the mixture was partitioned between dichloromethane (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was separated and extracted with dichloromethane (2 × 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (15 → 50%) afforded ketoamide **51** as a clear oil (41 mg, 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.0–7.4 (m, 15H, **H**-Ar), 4.52 (m, 1H, O**H**), 4.45 (dd, 1H, J_1 = 8 Hz, J_2 = 6 Hz, $C_6H_5C\mathbf{H}$), 4.36 (dd, 1H, J_1 = 9 Hz, J_2 = 3 Hz, $C_6H_5C\mathbf{H}$'), 3.97 (m, 1H, NC**H**'), 3.83 (m, 1H, NC**H**), 2.55–3.10 (m, 6H, $C_6H_5C\mathbf{H}_2$, $CH_3COC\mathbf{H}$, NCOC**H**), 2.83 (s, 3H, $NC\mathbf{H}_3$'), 2.52 (s, 3H, $NC\mathbf{H}_3$), 1.95 (s, 3H, $C\mathbf{H}_3CO$), 1.90 (s, 3H, $C\mathbf{H}_3CO$'), 1.0–1.8 (m, 6H, $C\mathbf{H}_2CH_2CH_2$, $CH_2C\mathbf{H}_2CH_2$, $CH_2CH_2C\mathbf{H}_2$), 0.89 (d, 3H, J = 7 Hz, $NCHC\mathbf{H}_3$'), 0.76 (d, 3H, J = 7 Hz, $NCHC\mathbf{H}_3$)

^{13}C NMR (100 MHz, $CDCl_3$) δ:

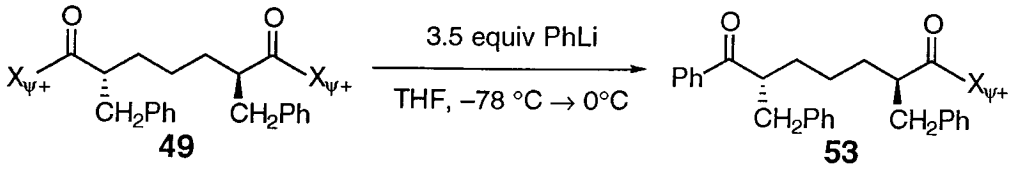


Diketone **52** (Entry 3, Table 16)

A 10-mL round-bottomed flask equipped with a magnetic stir bar was charged with diamide **49** (67 mg, 0.10 mmol, 1 equiv) and toluene (2 mL). This solution was concentrated under reduced pressure, affording a sticky foam. The reaction flask was flushed with dry argon, tetrahydrofuran (2 mL) was added, and the resulting solution was cooled to –78 °C. A solution of phenyllithium in cyclohexane–ether (0.91 M, 1.15 mL, 1.05 mmol, 10 equiv) was added via syringe and the mixture was warmed to –20 °C and was held at that temperature for 15 min. To ensure complete reaction, the reaction mixture was warmed to 0 °C and was held at that temperature for 1h. Excess phenyllithium was quenched at 0 °C by the addition of diisopropylamine (138 μL, 1.05 mmol, 10 equiv). After 15 min, a solution of acetic acid in ether (10% v/v, 2 mL) was added and the mixture was partitioned between dichloromethane (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was separated and extracted with dichloromethane (2 × 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (7.5 → 50%) afforded diketone **52** as a clear liquid (9 mg, 18%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.0–8.0 (m, 20 H, **H**-Ar), 3.58 (m, 2H, COC**H**), 3.00 (dd, 2H, J_1 = 14 Hz, J_2 = 7 Hz, one of $C_6H_5CH_2$), 2.63 (dd, 2H, J_1 = 14 Hz, J_2 = 7 Hz, one of $C_6H_5CH_2$), 1.70 (m, 2H, one $CHCH_2CH_2$), 1.46 (m, 2H, one of $CHCH_2CH_2$), 1.19 (m, 2H, $CHCH_2CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.7, 139.7, 137.4, 132.9, 129.0, 128.6, 128.4, 128.2, 126.3, 47.9, 38.5, 32.0, 25.2.

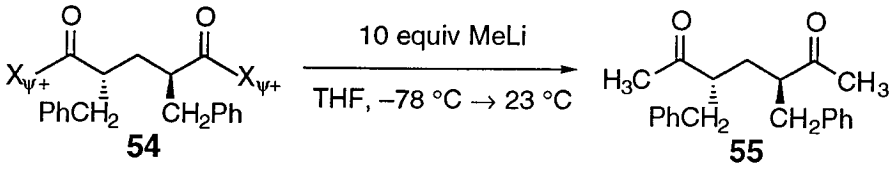


49 53

Ketoamide **53** (Entry 4, Table 16)

A 10-mL round-bottomed flask equipped with a magnetic stir bar was charged with diamide **49** (127.2 mg, 0.20 mmol, 1 equiv) and toluene (2 mL). This solution was concentrated under reduced pressure, affording a sticky foam. The reaction flask was flushed with dry argon, tetrahydrofuran (4 mL) was added, and the resulting solution was cooled to –78 °C. A solution of phenyllithium in cyclohexane–ether (1.72 M, 0.41 mL, 0.70 mmol, 3.5 equiv) was added via syringe and the mixture was warmed to –20 °C and was held at that temperature for 30 min. To ensure complete reaction, the reaction mixture was warmed to 0 °C and was held at that temperature for 15 min. Excess phenyllithium was quenched at 0 °C by the addition of diisopropylamine (105 μL, 0.80 mmol, 4.0 equiv). After 15 min, a solution of acetic acid in ether (10% v/v, 2 mL) was added and the mixture was partitioned between dichloromethane (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was separated and extracted with dichloromethane (2 × 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (7.5 → 50%) afforded ketoamide **53** as a clear oil (85 mg, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.0–7.9 (m, 20H, **H**-Ar), 4.42 (m, br, 2H, **OH**, C_6H_5CH), 4.30 (dd, 1H, J_1 = 9 Hz, J_2 = 2 Hz, C_6H_5CH'), 3.87 (m, 1H, NC**H**), 3.67 (m, 2H, NC**H**', C_6H_5COCH), 2.55–3.10 (m, 5H, NCOC**H**, $C_6H_5CH_2$), 2.75 (s, 3H, NCH_3'), 2.42 (s, 3H, NCH_3), 1.0–1.9 (m, 6H, CH_2), 0.75 (d, 3H, J = 6 Hz, $NCHCH_3$), 0.63 (d, 3H, J = 6 Hz, $NCHCH_3$).

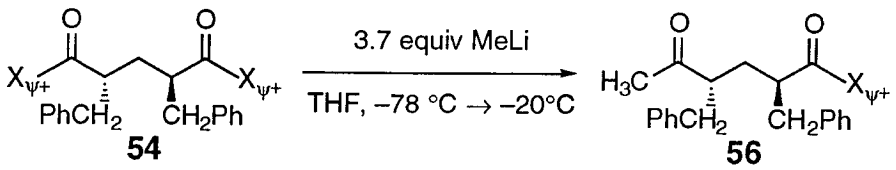


54 55

Diketone **55** (Entry 5, Table 16)

A 10-mL round-bottomed flask equipped with a magnetic stir bar was charged with diamide **54** (62 mg, 0.10 mmol, 1 equiv) and toluene (2 mL). This solution was concentrated under reduced pressure, affording a sticky foam. The reaction flask was flushed with dry argon, tetrahydrofuran (2 mL) was added, and the resulting solution was cooled to –78 °C. A solution of methyllithium in ether (1.27 M, 0.80 mL, 1.01 mmol, 10.0 equiv) was added via syringe and the mixture was warmed to 0 °C and was held at that temperature for 1 h. To ensure complete reaction, the reaction mixture was warmed to 23 °C and was held at that temperature for 1 h. In the course of warming to 23 °C, the mixture became yellow. Excess methyllithium was quenched at 23 °C by the addition of diisopropylamine (133 μL, 1.01 mmol, 10.0 equiv). After 15 min, a solution of acetic acid in ether (10% v/v, 2 mL) was added and the mixture was partitioned between dichloromethane (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was separated and extracted with dichloromethane (2 × 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (10 → 40%) afforded diketone **55** as a clear liquid (18 mg, 57%).

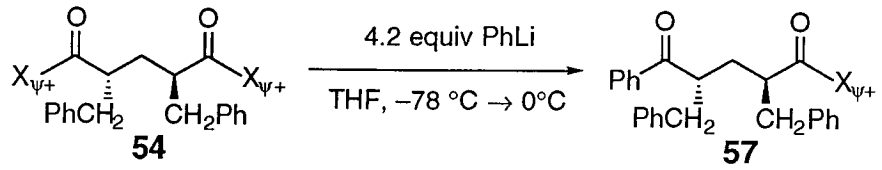
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.0–7.3 (m, 10H, **H**-Ar), 2.78 (m, 4H, one of $C_6H_5C\mathbf{H}_2$, COC**H**), 1.03 (dd, 2H, J_1 = 9 Hz, J_2 = 6 Hz, one of $C_6H_5C\mathbf{H}_2$), 1.91 (s, 6H, $C\mathbf{H}_3$), 1.79 (t, 2 H, J = 7 Hz, $CHC\mathbf{H}_2CH$).



Ketoamide **56** (Entry 6, Table 16)

A 10-mL round-bottomed flask equipped with a magnetic stir bar was charged with diamide **54** (60 mg, 0.10 mmol, 1 equiv) and toluene (2 mL). This solution was concentrated under reduced pressure, affording a sticky foam. The reaction flask was flushed with dry argon, tetrahydrofuran (2 mL) was added, and the resulting solution was cooled to –78 °C. A solution of methyllithium in ether (1.27 M, 0.25 mL, 0.32 mmol, 3.2 equiv) was added via syringe and the mixture was warmed to –20 °C and was held at that temperature for 30 min. As diamide **54** was detected by thin layer chromatographic analysis of the reaction mixture at this point, a solution of methyllithium in ether (1.27 M, 0.04 mL, 0.05 mmol, 0.5 equiv) was added and the mixture was stirred at –20 °C for an additional 15 min. Excess methyllithium was quenched at –20 °C by the addition of diisopropylamine (39 μL, 0.30 mmol, 3.0 equiv). After 15 min, a solution of acetic acid in ether (10% v/v, 2 mL) was added and the mixture was partitioned between dichloromethane (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was separated and extracted with dichloromethane (2 × 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with 40% ethyl acetate–hexanes afforded ketoamide **56** as a clear oil (34 mg, 76%).

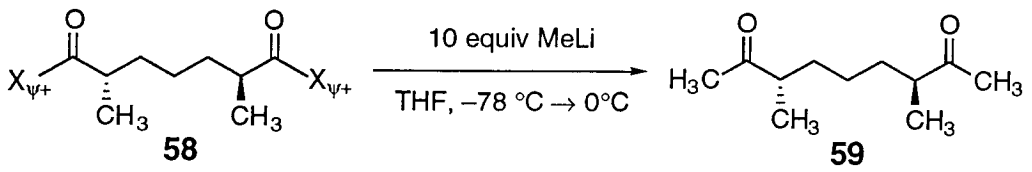
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.0–7.4 (m, 15H, **H**-Ar), 4.69 (m, 1H, O**H**), 4.41 (d, 1H, J = 9 Hz, $C_6H_5C\mathbf{H}$), 4.00 (m, 1H, NC**H**), 2.60–3.00 (m, 6H, $C_6H_5C\mathbf{H}_2$, NCOC**H**, $CH_3COC\mathbf{H}$), 2.45 (s, 3H, $NC\mathbf{H}_3$), 2.10 (m, 1H, one of $CHCH_2C\mathbf{H}$), 2.00 (s, 3H, $C\mathbf{H}_3CO$), 1.81 (m, 1H, one of $CHCH_2C\mathbf{H}$), 0.67 (d, J = 7 Hz, $NCHC\mathbf{H}_3$).



Ketoamide **57** (Entry 7, Table 16)

A 10-mL round-bottomed flask equipped with a magnetic stir bar was charged with diamide **54** (123 mg, 0.20 mmol, 1 equiv) and toluene (2 mL). This solution was concentrated under reduced pressure, affording a sticky foam. The reaction flask was flushed with dry argon, tetrahydrofuran (4 mL) was added, and the resulting solution was cooled to –78 °C. A solution of phenyllithium in cyclohexane–ether (1.72 M, 0.38 mL, 0.65 mmol, 3.2 equiv) was added via syringe and the mixture was warmed to –20 °C and was held at that temperature for 30 min. The reaction mixture then was warmed to 0 °C and was held at that temperature for 30 min. As a small amount of diamide **54** was detected by thin layer chromatographic (TLC) analysis at this point, the reaction mixture was cooled to –78°C and a solution of phenyllithium in cyclohexane–ether (1.72 M, 0.12 mL, 0.21 mmol, 1 equiv) was added via syringe. The mixture was warmed to 0 °C and was held at that temperature for 30 min, but no significant change was noted by TLC analysis. Excess phenyllithium was quenched at 0 °C by the addition of diisopropylamine (107 μL, 0.81 mmol, 4.0 equiv). After 15 min, a solution of acetic acid in ether (10% v/v, 2 mL) was added and the mixture was partitioned between dichloromethane (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was separated and extracted with dichloromethane (2 × 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (5 → 50%) afforded ketoamide **57** as a clear oil (66 mg, 63%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.0–8.0 (m, 20H, **H**-Ar), 4.53 (m, 1H, NC**H**), 4.23 (d, 1H, J = 9 Hz, $C_6H_5C\mathbf{H}$), 3.88 (qn, 1H, J = 7Hz, $C_6H_5COC\mathbf{H}$), 3.01 (dd, 1H, J_1 = 14 Hz, J_2 = 7 Hz, one of $C_6H_5C\mathbf{H}_2$), 2.95 (m, 1H, NCOC**H**), 2.73 (m, 3H, 3 of $C_6H_5C\mathbf{H}_2$), 2.11 (dd, 2H, J_1 = 7 Hz, J_2 = 6 Hz, $CHC\mathbf{H}_2CH$), 2.03 (s, 3H, $NC\mathbf{H}_3$), 0.51 (d, 3H, J = 7 Hz, $NCHC\mathbf{H}_3$).



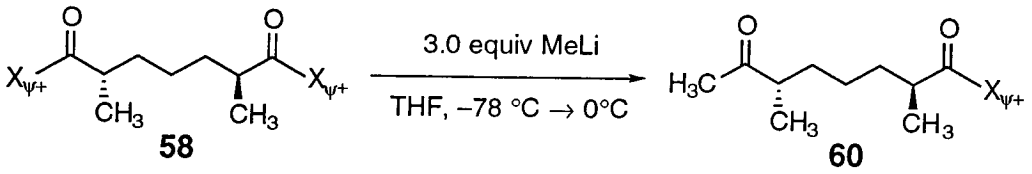
58 59

Diketone **59** (Entry 1, Table 17)

A 10-mL round-bottomed flask equipped with a magnetic stir bar was charged with diamide **58** (101 mg, 0.21 mmol, 1 equiv) and toluene (2 mL). This solution was concentrated under reduced pressure, affording a sticky foam. The reaction flask was flushed with dry argon, tetrahydrofuran (4 mL) was added, and the resulting solution was cooled to –78 °C. A solution of methyllithium in ether (1.30 M, 1.62 mL, 2.10 mmol, 10 equiv) was added via syringe and the mixture was warmed to –20 °C and was held at that temperature for 30 min. To ensure complete reaction, the mixture was warmed to 0 °C and was held at that temperature for 30 min. Excess methyllithium was quenched at 0 °C by the addition of diisopropylamine (106 μL, 0.81 mmol, 4.0 equiv). After 15 min, a solution of acetic acid in ether (10% v/v, 2 mL) was added and the mixture was partitioned between dichloromethane (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was separated and extracted with dichloromethane (2 × 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (25 → 40%) afforded diketone **59** as a clear liquid (32.2 mg, 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.48 (sx, 2H, J = 7 Hz, COC**H**), 2.11 (s, 6H, $COC\mathbf{H}_3$), 1.62 (m, 2H, one of $CHC\mathbf{H}_2CH_2$), 1.31 (m, 2H, one of $CHC\mathbf{H}_2CH_2$), 1.20 (m, 2H, $CHCH_2C\mathbf{H}_2$), 1.06 (d, 6H, J = 8 Hz, $CHC\mathbf{H}_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 47.0, 32.8, 28.0, 24.9, 16.3.

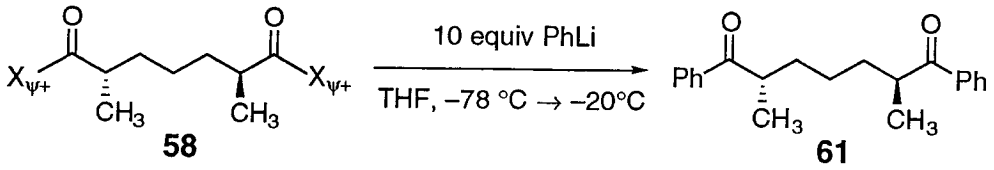


58 60

Ketoamide **60** (Entry 2, Table 17)

A 10-mL round-bottomed flask equipped with a magnetic stir bar was charged with diamide **58** (97.9 mg, 0.20 mmol, 1 equiv) and toluene (2 mL). This solution was concentrated under reduced pressure, affording a sticky foam. The reaction flask was flushed with dry argon, tetrahydrofuran (4 mL) was added, and the resulting solution was cooled to –78 °C. A solution of methyllithium in ether (1.36 M, 0.45 mL, 0.61 mmol, 3.0 equiv) was added via syringe and the mixture was warmed to –20 °C and was held at that temperature for 30 min. To ensure complete reaction, the mixture was warmed to 0 °C and was held at that temperature for 30 min. Excess methyllithium was quenched at 0 °C by the addition of diisopropylamine (106 μL, 0.81 mmol, 4.0 equiv). After 15 min, a solution of acetic acid in ether (10% v/v, 2 mL) was added and the mixture was partitioned between dichloromethane (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was separated and extracted with dichloromethane (2 × 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (30 → 100%) afforded ketoamide **60** as a clear oil (46 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.2–7.4 (m, 5H, **H**-Ar), 4.60 (d, 1H, J = 7 Hz, $C_6H_5C\mathbf{H}$), 4.56 (d, 1H, J = 8 Hz, $C_6H_5C\mathbf{H}$'), 4.30 (m, 1H, NC**H**), 4.05 (m, 1H, NC**H**'), 2.90 (s, 3H, $NC\mathbf{H}_3$'), 2.79 (s, 3H, $NC\mathbf{H}_3$), 2.58 (m, 1H, NCOC**H**), 2.48 (m, 1H, $CH_3COC\mathbf{H}$), 2.10 (s, 3H, $COC\mathbf{H}_3$), 2.08 (s, 3H, $COC\mathbf{H}_3$'), 1.65 (m, 2H, one of $NCOCHC\mathbf{H}_2$, one of $CH_3COCHC\mathbf{H}_2$), 1.30 (m, 2H, one of $NCOCHC\mathbf{H}_2$, one of $CH_3COCHC\mathbf{H}_2$), 1.18 (m, 2H, $CH_2C\mathbf{H}_2CH_2$), 1.14 (d, 3H, J = 7 Hz, $C\mathbf{H}_3CHN$), 1.04 (d, 3H, J = 7 Hz, $NCOCHC\mathbf{H}_3$), 1.03 (d, 3H, J = 7 Hz, $C\mathbf{H}_3CHN$'), 0.98 (d, 3H, J = 7 Hz, $CH_3COCHC\mathbf{H}_3$).



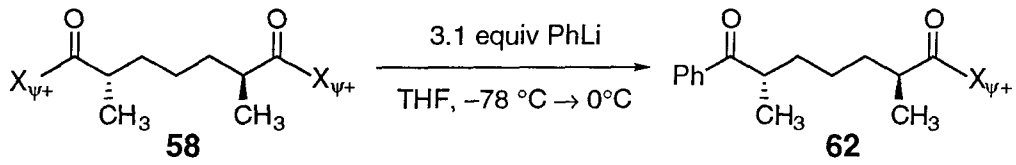
58 61

Diketone **61** (Entry 3, Table 17)

A 10-mL round-bottomed flask equipped with a magnetic stir bar was charged with diamide **58** (51 mg, 0.11 mmol, 1 equiv) and toluene (2 mL). This solution was concentrated under reduced pressure, affording a sticky foam. The reaction flask was flushed with dry argon, tetrahydrofuran (2 mL) was added, and the resulting solution was cooled to –78 °C. A solution of phenyllithium in cyclohexane–ether (0.91 M, 1.16 mL, 1.06 mmol, 10 equiv) was added via syringe and the mixture was warmed to –20 °C and was held at that temperature for 2 h. Excess phenyllithium was quenched at –20 °C by the addition of diisopropylamine (140 μL, 1.06 mmol, 10 equiv). After 15 min, a solution of acetic acid in ether (10% v/v, 2 mL) was added and the mixture was partitioned between dichloromethane (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was separated and extracted with dichloromethane (2 × 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (10 → 60%) afforded diketone **61** as a clear oil (20 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.90 (m, 4H, **H**-Ar), 7.53 (m, 2H, **H**-Ar), 7.43 (m, 4H, **H**-Ar), 3.42 (sx, 2H, J = 7 Hz, COC**H**), 1.80 (m, 2H, one of $CHC\mathbf{H}_2CH_2$), 1.44 (m, 2H, one of $CHC\mathbf{H}_2CH_2$), 1.32 (m, 2H, $CHCH_2C\mathbf{H}_2$), 1.16 (d, 6H, J = 7 Hz, $C\mathbf{H}_3$).

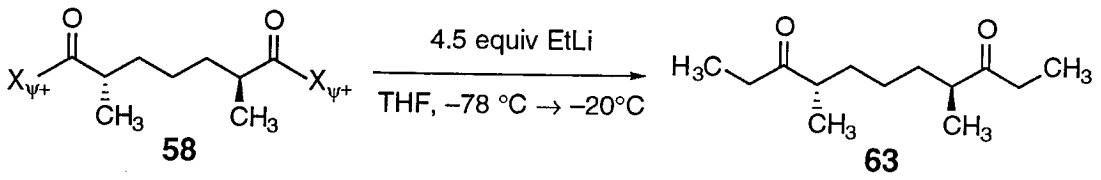
^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.3, 136.8, 132.9, 128.7, 128.3, 40.5, 33.6, 25.3, 17.5.



Ketoamide **62** (Entry 4, Table 17)

A 10-mL round-bottomed flask equipped with a magnetic stir bar was charged with diamide **58** (97.2 mg, 0.20 mmol, 1 equiv) and toluene (2 mL). This solution was concentrated under reduced pressure, affording a sticky foam. The reaction flask was flushed with dry argon, tetrahydrofuran (4 mL) was added, and the resulting solution was cooled to –78 °C. A solution of phenyllithium in cyclohexane–ether (1.72 M, 0.36 mL, 0.62 mmol, 3.1 equiv) was added via syringe and the mixture was warmed to –20 °C and was held at that temperature for 30 min. Excess phenyllithium was quenched at –20 °C by the addition of diisopropylamine (106 μL, 0.81 mmol, 4.0 equiv). After 15 min, a solution of acetic acid in ether (10% v/v, 2 mL) was added and the mixture was partitioned between dichloromethane (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was separated and extracted with dichloromethane (2 × 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (5 → 100%) afforded ketoamide **62** as a clear oil (56 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.2–8.0 (m, 10H, **H**-Ar), 4.80 (m, br, 1H, O**H**), 4.58 (t, 1H, J = 7 Hz, $C_6H_5C\mathbf{H}$), 4.51 (dd, J_1 = 8 Hz, J_2 = 6 Hz, $C_6H_5C\mathbf{H}$'), 4.24 (m, 1H, NC**H**), 4.00 (m, 1H, NC**H**'), 3.44 (m, 1H, $C_6H_5COC\mathbf{H}$), 2.86 (s, 3H, $NC\mathbf{H}_3$'), 2.72 (s, 3H, $NC\mathbf{H}_3$), 2.55 (m, 1H, NCOC**H**), 1.77 (m, 1H, one of $C_6H_5COCHC\mathbf{H}_2$), 1.66 (m, 1H, one of $NCOCHC\mathbf{H}_2$), 1.05–1.45 (m, 4H, one of $C_6H_5COCHC\mathbf{H}_2$, one of $NCOCHC\mathbf{H}_2$, $CH_2C\mathbf{H}_2CH_2$), 1.15 (d, 3H, J = 7 Hz, $C_6H_5COCHC\mathbf{H}_3$), 1.11 (d, 3H, J = 7 Hz, $NCHC\mathbf{H}_3$), 0.97 (d, 3H, J = 7 Hz, $NCOCHC\mathbf{H}_3$), 0.88 (d, 3H, J = 7 Hz, $NCHC\mathbf{H}_3$').



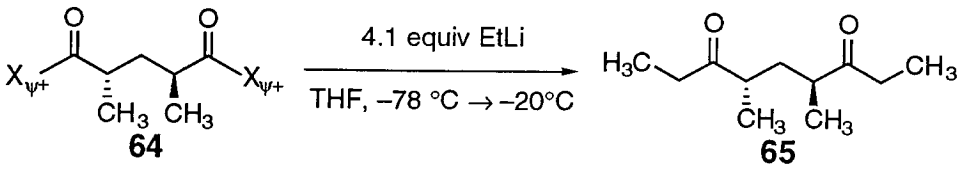
58 63

Diketone **63** (Entry 5, Table 17)

A 10-mL round-bottomed flask equipped with a magnetic stir bar was charged with diamide **58** (50.5 mg, 0.10 mmol, 1 equiv) and toluene (2 mL). This solution was concentrated under reduced pressure, affording a sticky foam. The reaction flask was flushed with dry argon, tetrahydrofuran (2 mL) was added, and the resulting solution was cooled to –78 °C. A solution of ethyllithium in ether (0.69 M, 0.68 mL, 0.47 mmol, 4.5 equiv) was added via syringe and the mixture was warmed to –20 °C and was held at that temperature for 1 h. Excess ethyllithium was quenched at –20 °C by the addition of diisopropylamine (69 μL, 0.52 mmol, 5.0 equiv). After 15 min, a solution of acetic acid in ether (10% v/v, 2 mL) was added and the mixture was partitioned between dichloromethane (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was separated and extracted with dichloromethane (2 × 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with 10% ethyl acetate–hexanes afforded diketone **63** as a clear oil (14 mg, 63%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.33–2.54 (m, 6H, COC**H**, COC**H**$_2$), 1.60 (m, 2H, one of CHC**H**$_2$CH$_2$), 1.27 (m, 2H, one of CHC**H**$_2$CH$_2$), 1.16 (m, 2H, CHCH$_2$C**H**$_2$), 1.03 (d, 6H, J = 7 Hz, CHC**H**$_3$), 1.01 (t, 6H, J = 7 Hz, CH$_2$C**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 215.2, 45.9, 34.3, 33.1, 25.2, 16.6, 7.8.



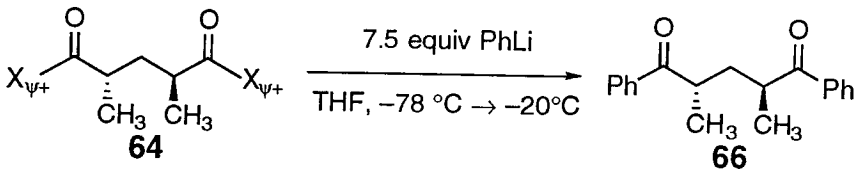
64 65

Diketone **65** (Entry 5, Table 17)

A 50-mL round-bottomed flask equipped with a magnetic stir bar was charged with diamide **64** (227 mg, 0.50 mmol, 1 equiv) and toluene (5 mL). This solution was concentrated under reduced pressure, affording a sticky foam. The reaction flask was flushed with dry argon, tetrahydrofuran (10 mL) was added, and the resulting solution was cooled to –78 °C. A solution of ethyllithium in ether (0.70 M, 2.90 mL, 2.05 mmol, 4.1 equiv) was added via syringe and the mixture was warmed to –20 °C and was held at that temperature for 15 min. Excess ethyllithium was quenched at –20 °C by the addition of diisopropylamine (328 μL, 2.50 mmol, 5.0 equiv). After 15 min, a solution of acetic acid in ether (10% v/v, 10 mL) was added and the mixture was partitioned between dichloromethane (50 mL) and saturated aqueous sodium bicarbonate solution (50 mL). The aqueous phase was separated and extracted with dichloromethane (2 × 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with 10% ethyl acetate–hexanes afforded diketone **65** as a clear oil (62 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.3–2.6 (m, 6H, COC**H**, $COCH_2$), 1.66 (t, 2H, J = 7 Hz, $COCHCH_2$), 1.04 (d, 6H, J = 7 Hz, $CHCH_3$), 1.01 (t, 6H, J = 7 Hz, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 214.8, 43.8, 35.9, 34.3, 17.3, 7.8.

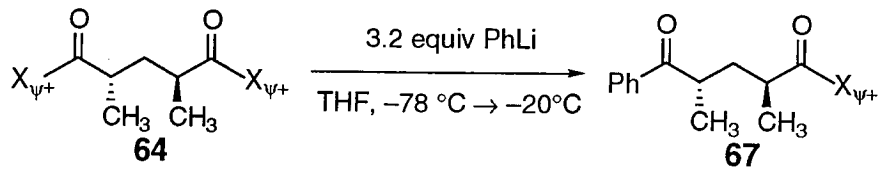


Diketone **66** (Entry 8, Table 17)

A 10-mL round-bottomed flask equipped with a magnetic stir bar was charged with diamide **64** (48 mg, 0.11 mmol, 1 equiv) and toluene (2 mL). This solution was concentrated under reduced pressure, affording a sticky foam. The reaction flask was flushed with dry argon, tetrahydrofuran (2 mL) was added, and the resulting solution was cooled to –78 °C. A solution of phenyllithium in cyclohexane–ether (1.72 M, 0.31 mL, 0.53 mmol, 5.0 equiv) was added via syringe and the mixture was warmed to –20 °C and was held at that temperature for 1 h. As a small amount of the intermediate ketoamide was detected by thin layer chromatographic (TLC) analysis at this point, the reaction mixture was cooled again to –78°C and a solution of phenyllithium in cyclohexane–ether (1.72 M, 0.16 mL, 0.27 mmol, 2.5 equiv) was added via syringe. The mixture was warmed to –20 °C and was held at that temperature for 15 min, but no significant change was noted by TLC analysis. Excess phenyllithium was quenched at –20 °C by the addition of diisopropylamine (84 μL, 0.64 mmol, 6 equiv). After 15 min, a solution of acetic acid in ether (10% v/v, 2 mL) was added and the mixture was partitioned between dichloromethane (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was separated and extracted with dichloromethane (2 × 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (10 → 75%) afforded diketone **66** as a clear liquid (17 mg, 58%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75 (m, 4H, **H**-Ar), 7.43 (m, 2H, **H**-Ar), 7.30 (m, 4H, **H**-Ar), 3.49 (sx, 2H, J = 7 Hz, COC**H**), 2.00 (t, 2H, J = 7 Hz, CHC**H**$_2$), 1.20 (d, 6H, J = 7 Hz, C**H**$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.4, 136.6, 133.0, 128.6,. 128.2, 38.6, 37.4, 18.7.



Ketoamide **67** (Entry 9, Table 17)

A 10-mL round-bottomed flask equipped with a magnetic stir bar was charged with diamide **64** (48 mg, 0.11 mmol, 1 equiv) and toluene (2 mL). This solution was concentrated under reduced pressure, affording a sticky foam. The reaction flask was flushed with dry argon, tetrahydrofuran (2 mL) was added, and the resulting solution was cooled to –78 °C. A solution of phenyllithium in cyclohexane–ether (1.72 M, 0.20 mL, 0.34 mmol, 3.2 equiv) was added via syringe and the mixture was warmed to –20 °C and was held at that temperature for 15 min. Excess phenyllithium was quenched at –20 °C by the addition of diisopropylamine (55 μL, 0.42 mmol, 4.0 equiv). After 15 min, a solution of acetic acid in ether (10% v/v, 2 mL) was added and the mixture was partitioned between dichloromethane (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was separated and extracted with dichloromethane (2 × 15 mL). The combined organic extracts were dried over anhydrous sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (10 → 100%) afforded ketoamide **67** as a clear oil (18 mg, 46%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.2–7.9 (m, 10 H, **H**-Ar), 4.76 (m, br, 1H, O**H**), 4.51 (d, 1H, J = 9 Hz, C_6H_5CH), 4.41 (d, 1H, J = , C_6H_5CH'), 4.21 (m, 1H, NC**H**), 3.80 (m, 1H, NC**H**'), 3.55 (sx, 1H, J = 7 Hz C_6H_5COCH), 2.80 (s, 3H, NCH_3'), 2.64 (sx, 1H, J = 7 Hz, NCOC**H**), 2.47 (s, 3H, NCH_3), 1.90 (t, 2H, J = 7 Hz, $CHCH_2CH$), 1.22 (d, 3H, J = 7 Hz, CH_3CHN'), 1.16 (d, 3H, J = 7 Hz, $C_6H_5COCHCH_3$), 1.04 (d, 3H, J = 7 Hz, CH_3CHN), 0.98 (d, 3H, J = 7 Hz, $NCOCHCH_3$), 0.37 (d, 3H, J = 7 Hz, $NCOCHCH_3$').

References and Notes

(1) Aldol reviews:(a) Evans, D.A.; Nelson, J.V.; Taber, T.R. *Top. in Stereochem.* **1982**, *13*, 1. (b) Heathcock, Clayton *Asymmetric Synthesis* **1984**, *3*, 111.

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(15) For reviews of asymmetric enolate alkylations see: (a) Evans, D. A. in *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol 3, pp. 1–110. (b) Lutomski, K. A.; Meyers, A. I.; in *Asymmetric Synthesis*; Morrison, J. D.; Ed.; Academic Press: New York, 1984; Vol 3, pp. 213–274. (c) Seebach, D.; Imwinkelried, R.; Weber, T. in *Modern Synthetic Synthesis*, Scheffold, R., Ed.; Springer, Berlin-Heidelberg, 1986; Vol 4, pp. 125–259. (d) Crosby, J. *Tetrahedron* **1991**, *47*, 4789. (e) Caine, D. in *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: New York, 1991, Vol 3, pp. 1–63.

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(20) The mechanism shown in Figure 7 was further supported by the observation that the mesylate of amide **17** also decomposes to ephedrine ester **39**.

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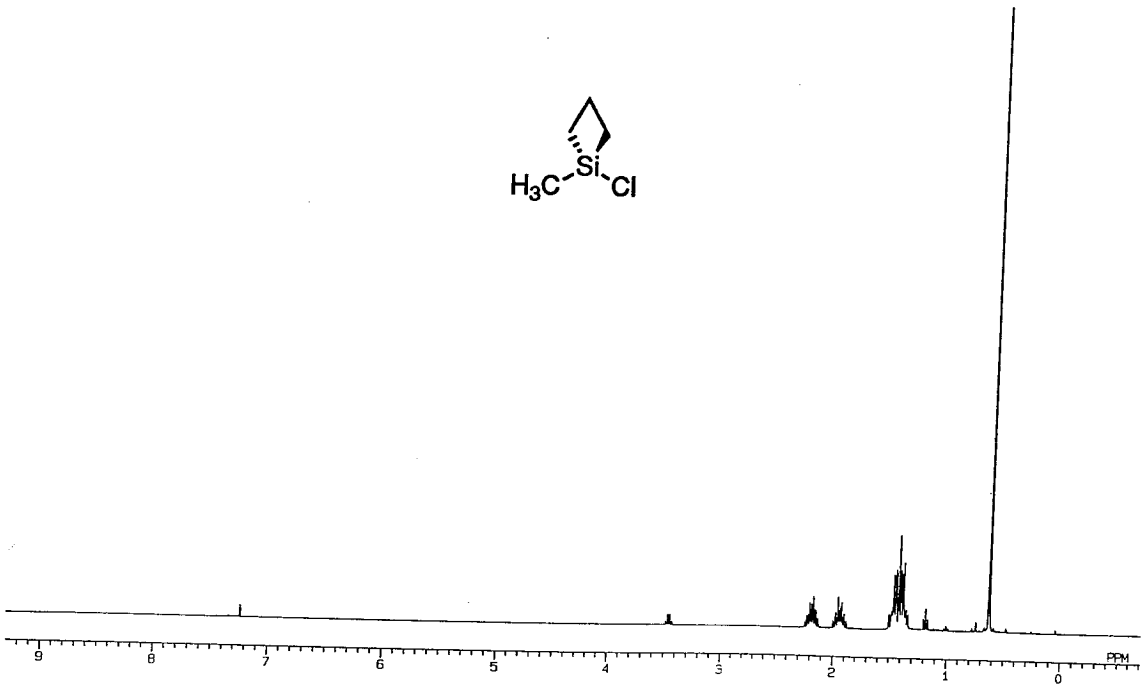
(25) Both (*R*)- and (*S*)-Mosher ester derivatives were prepared for comparative analysis.

Appendix. Catalog of Spectra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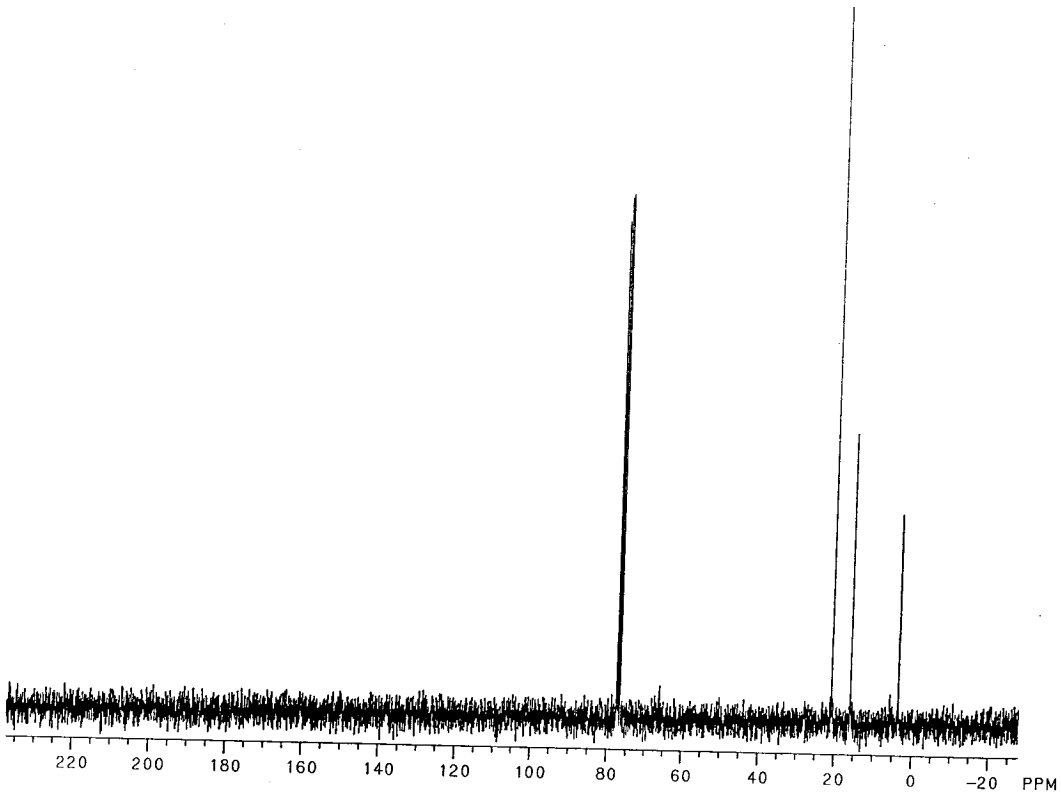
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140
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20
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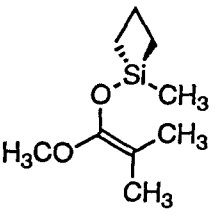
−20
PPM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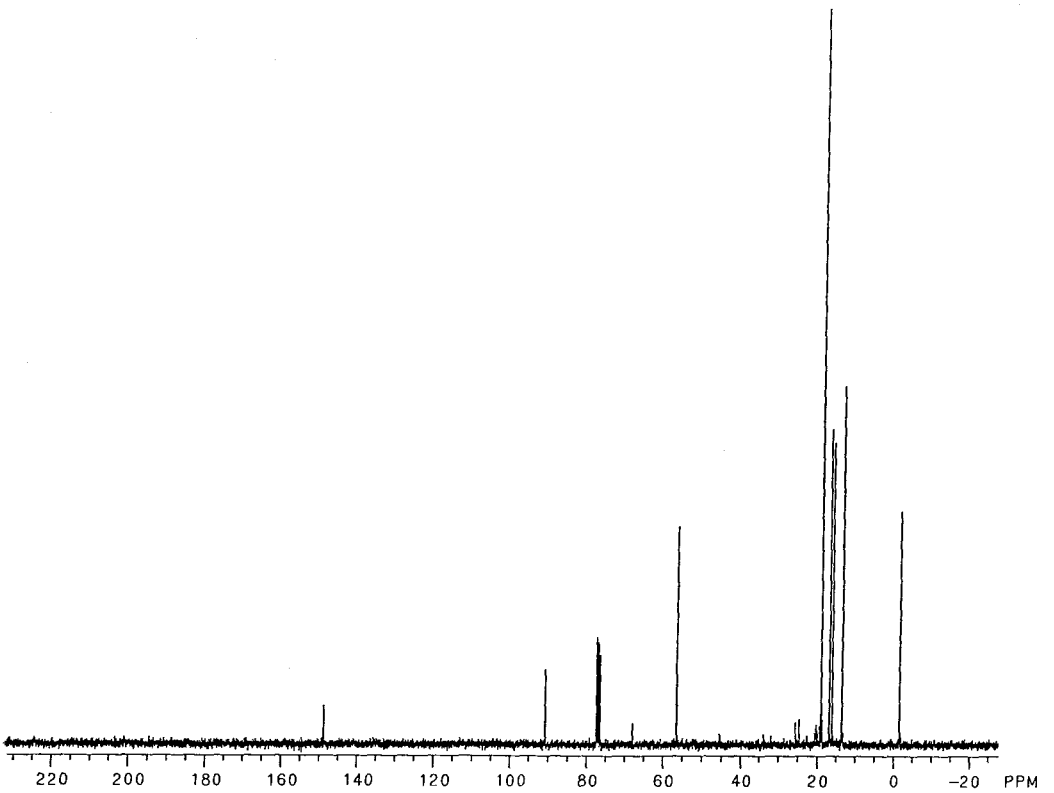
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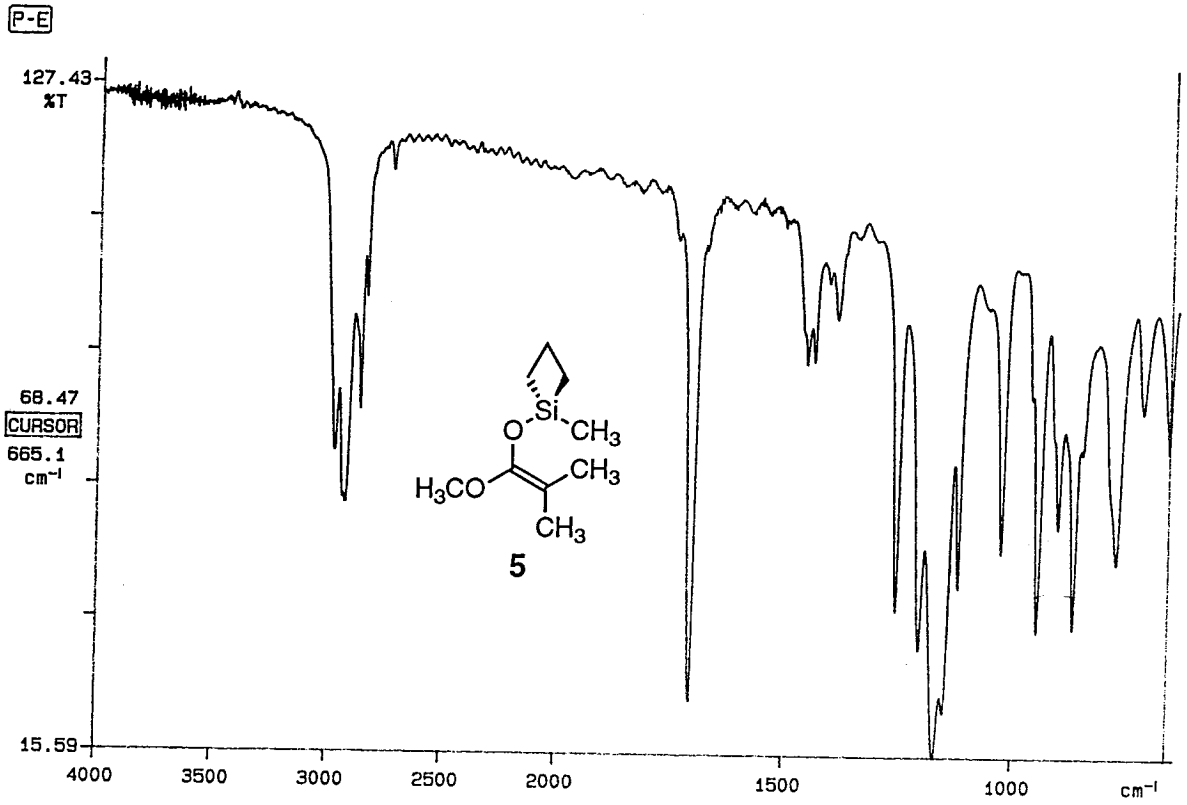
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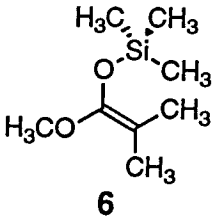
CH3

5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CH3
CH3

6

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2
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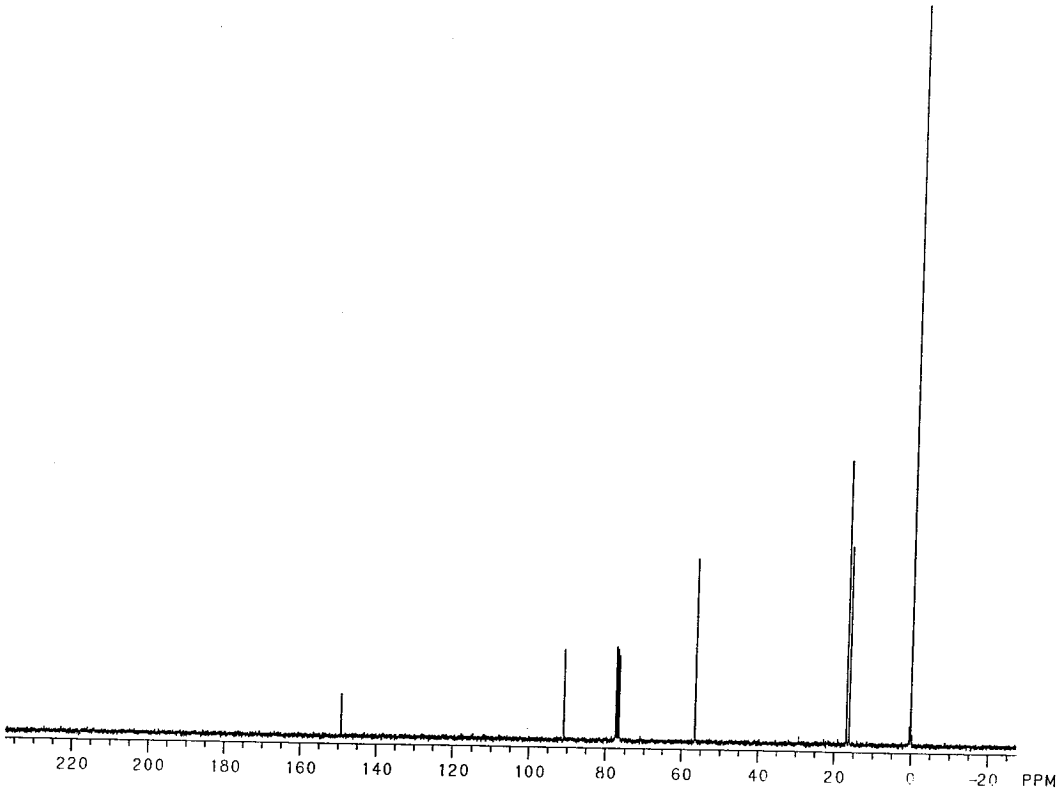
PPM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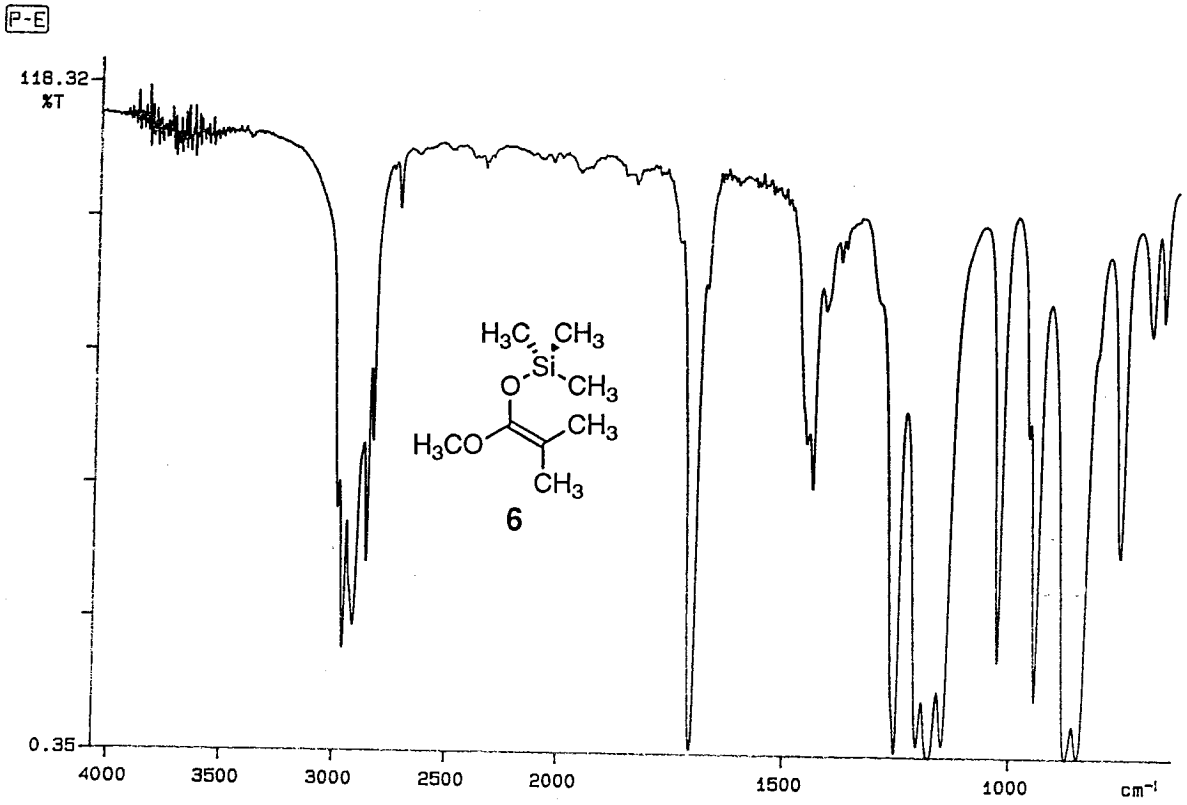
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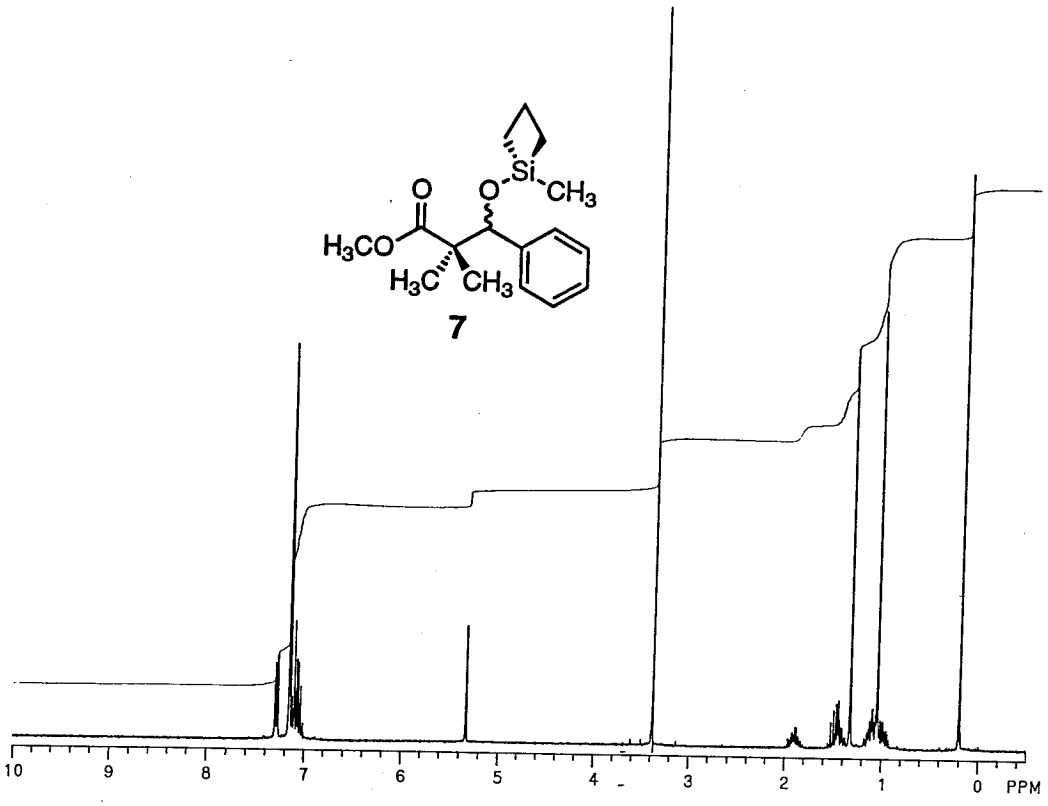
CH3
CH3

6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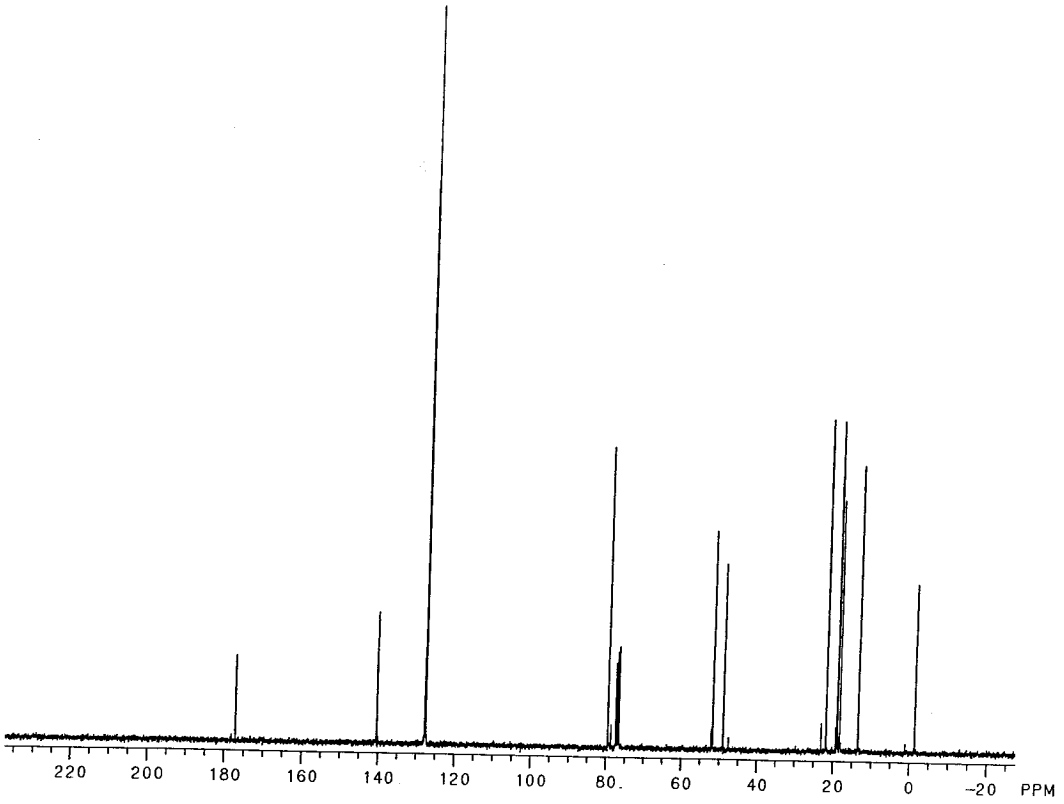
PPM

7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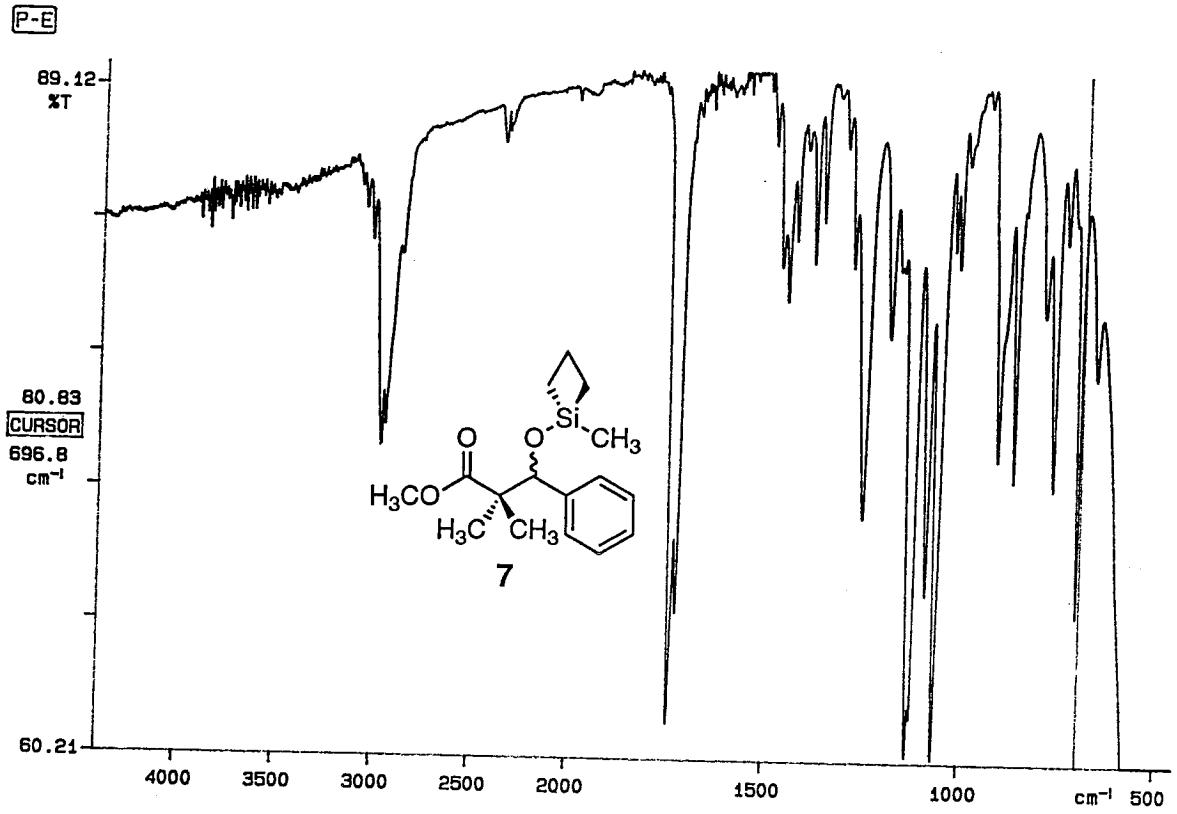
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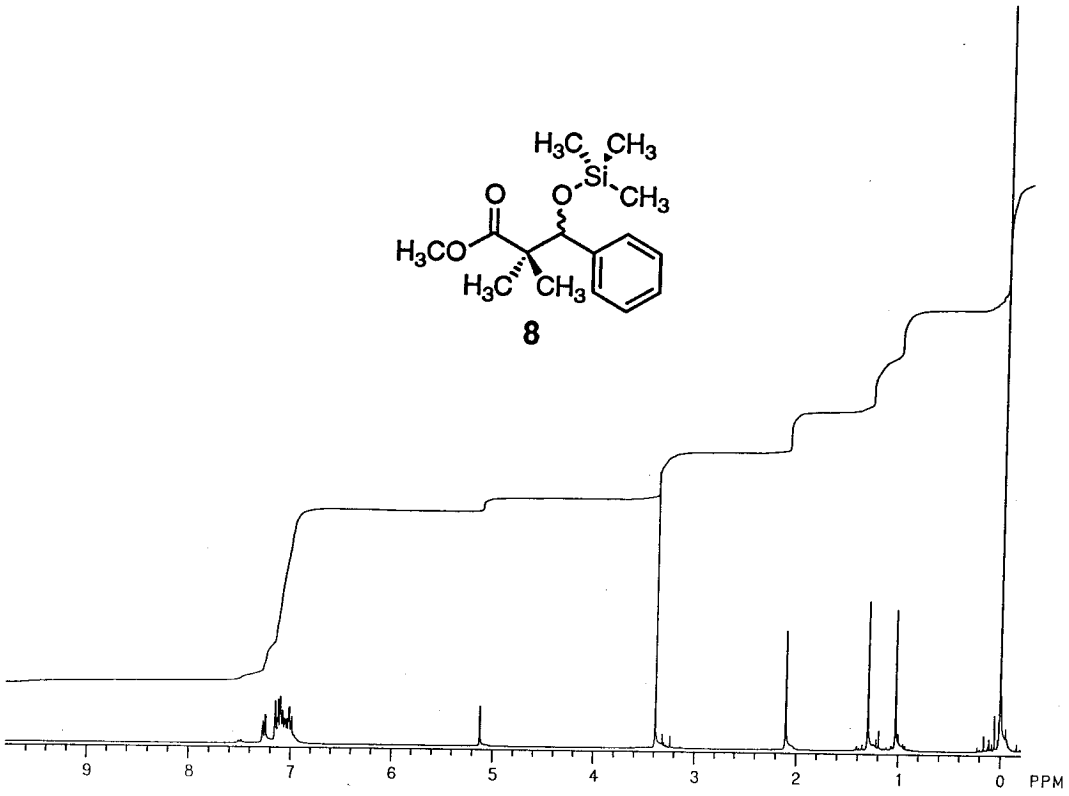

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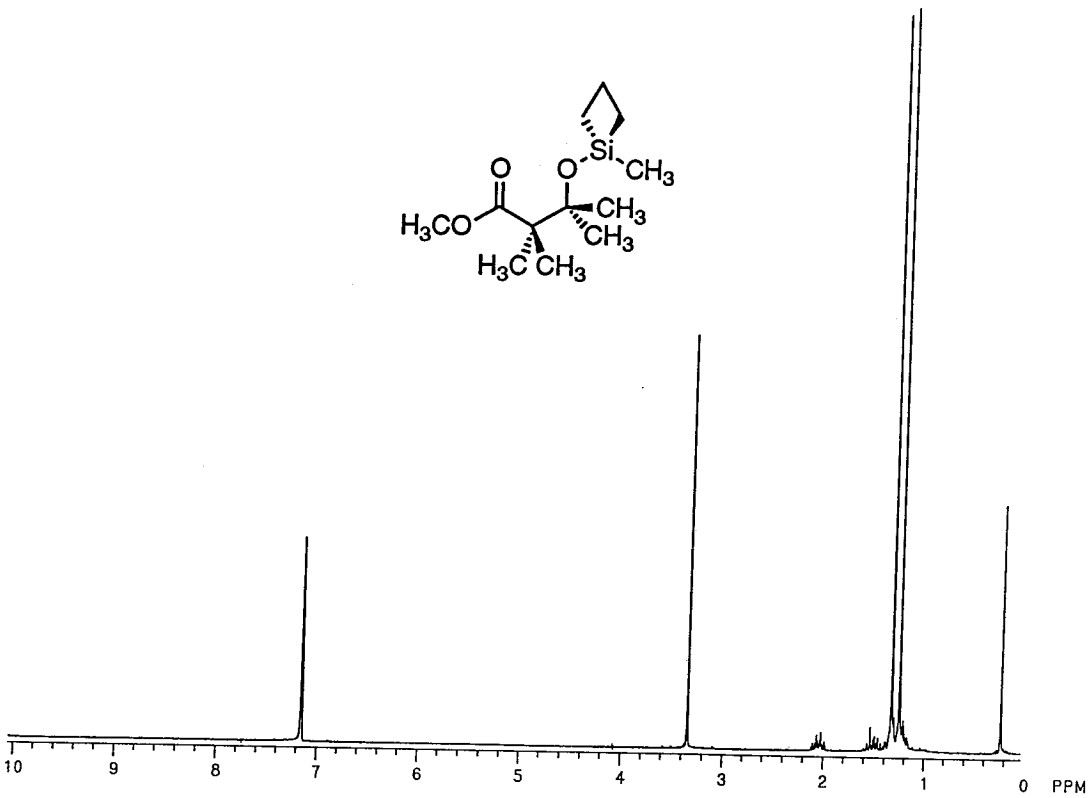
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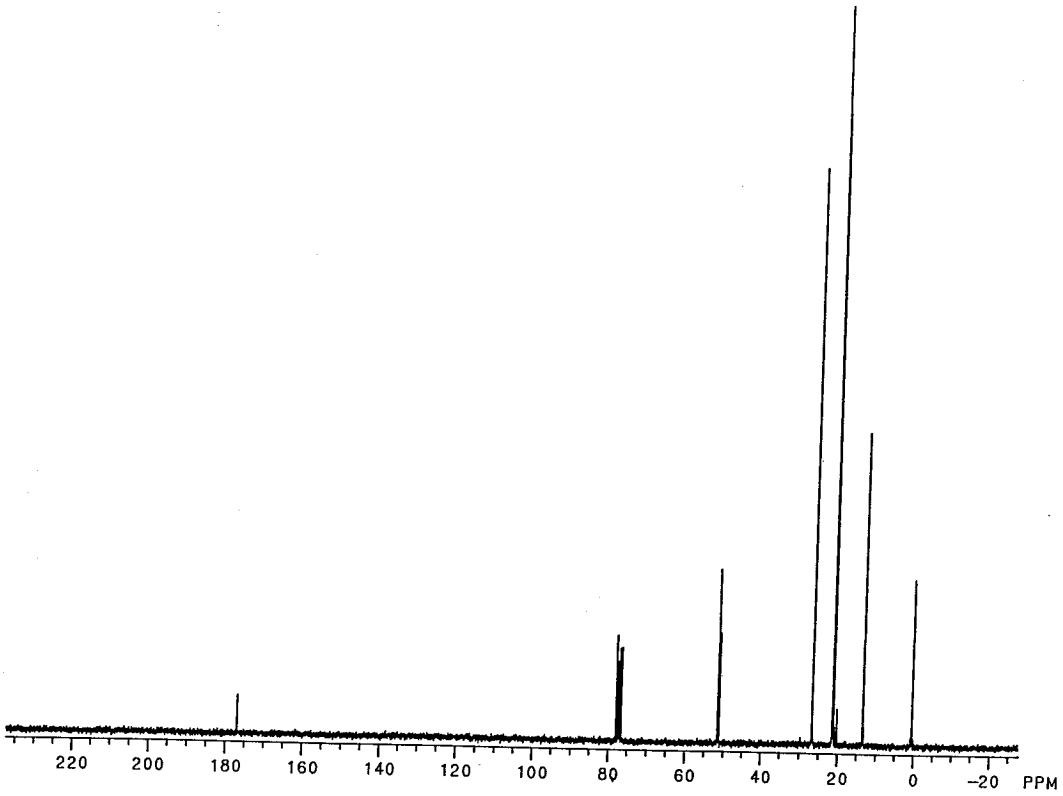
PPM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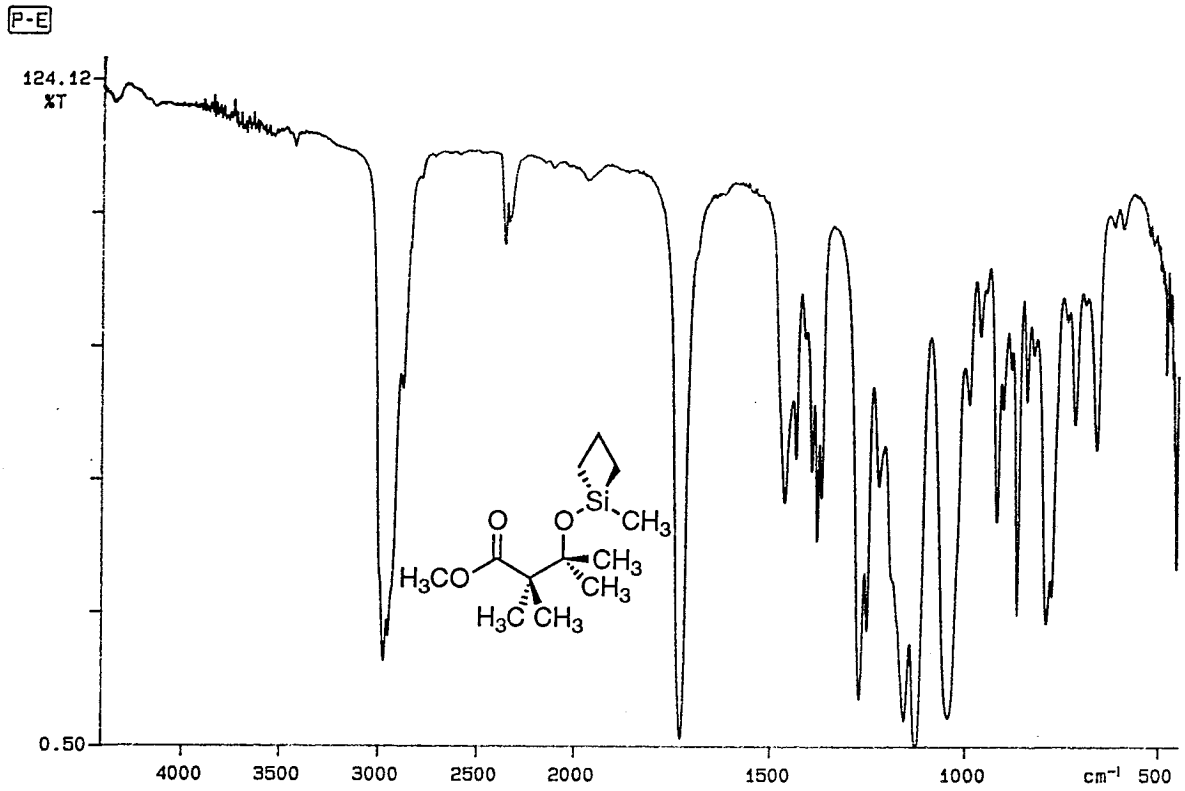
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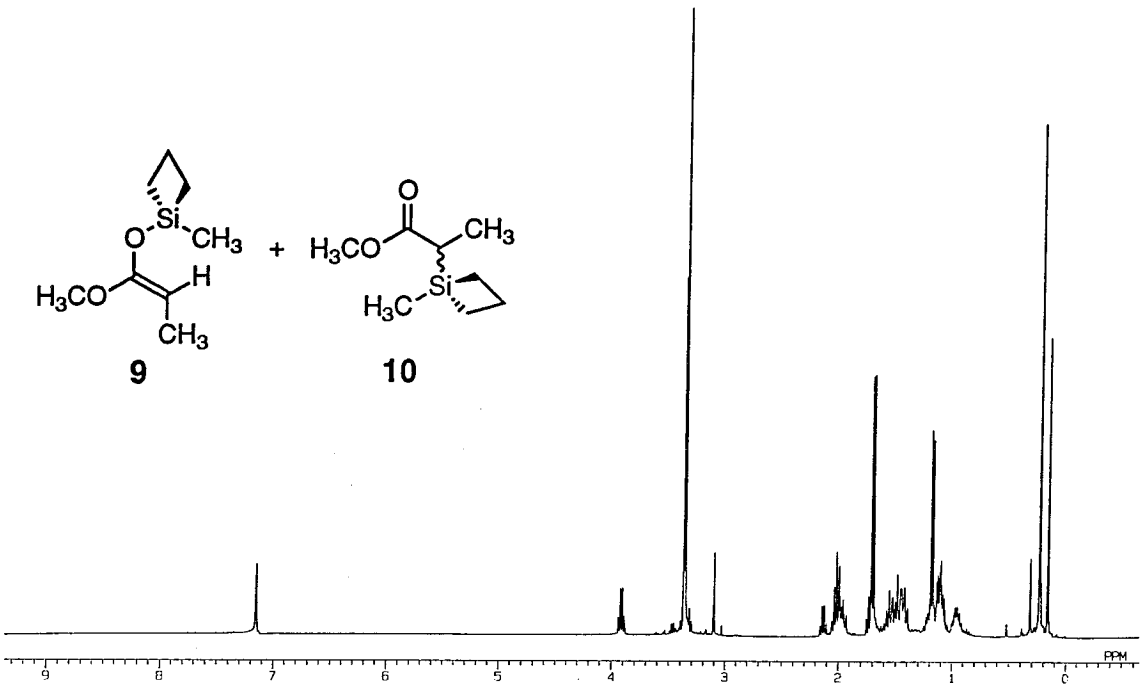
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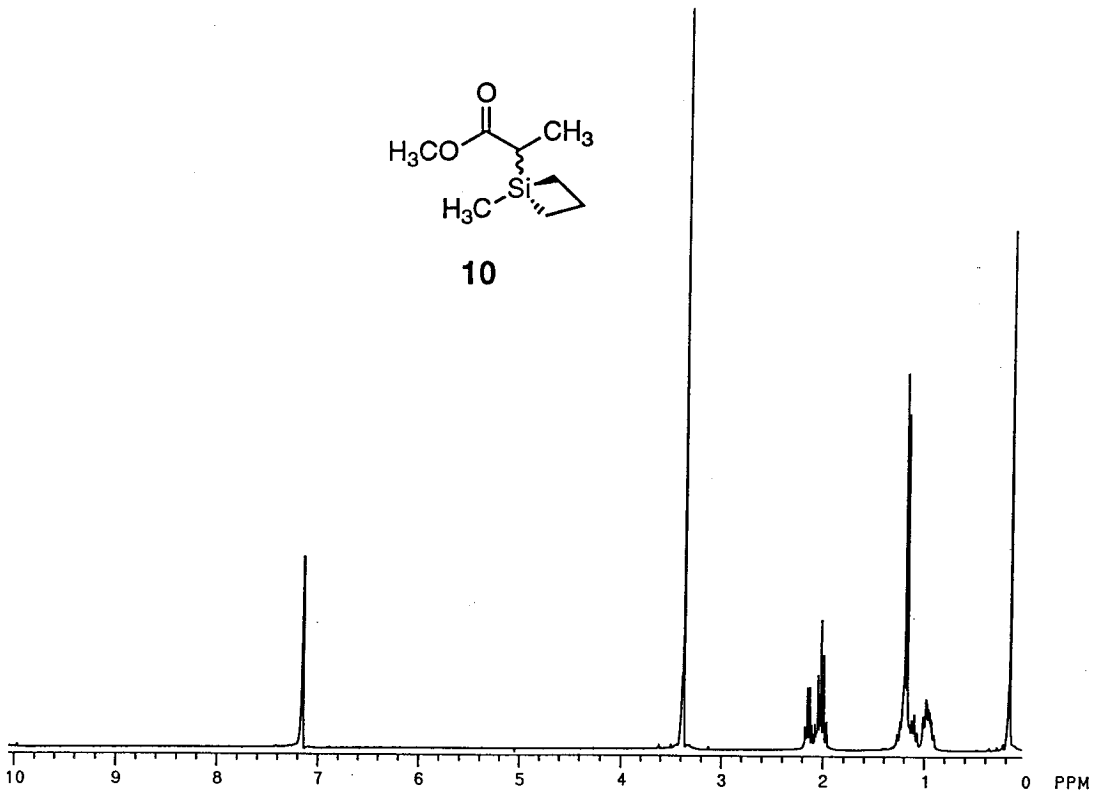
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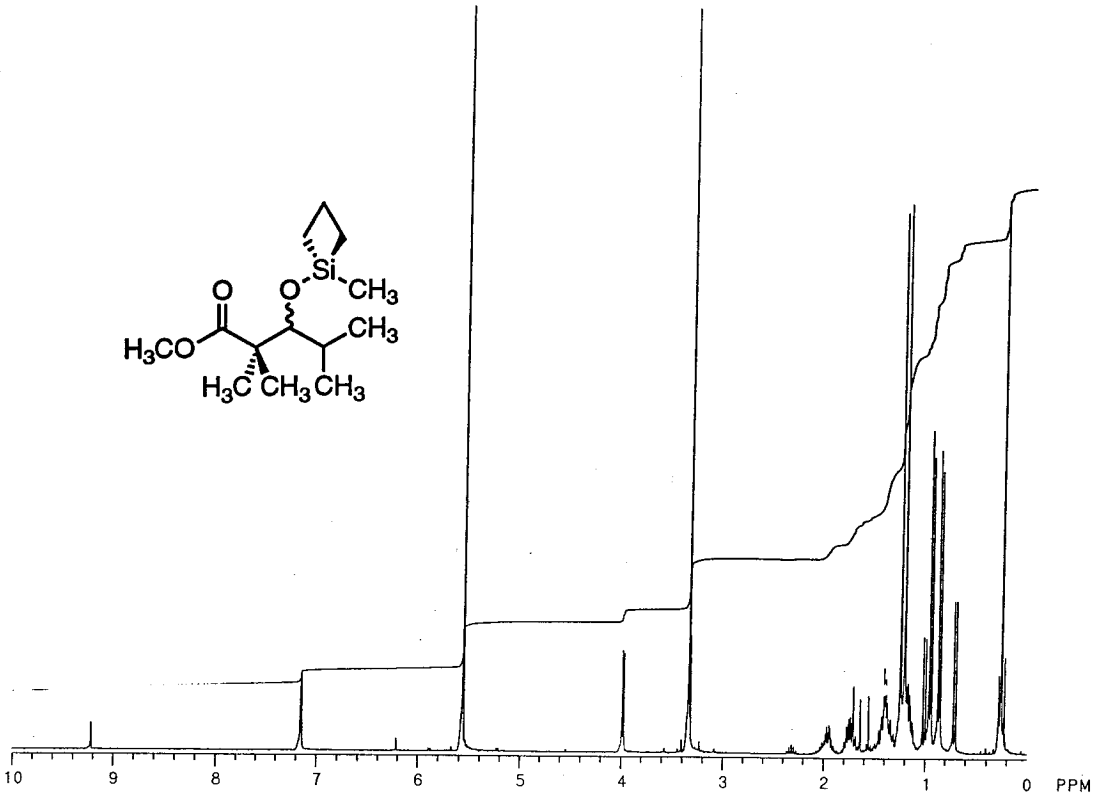
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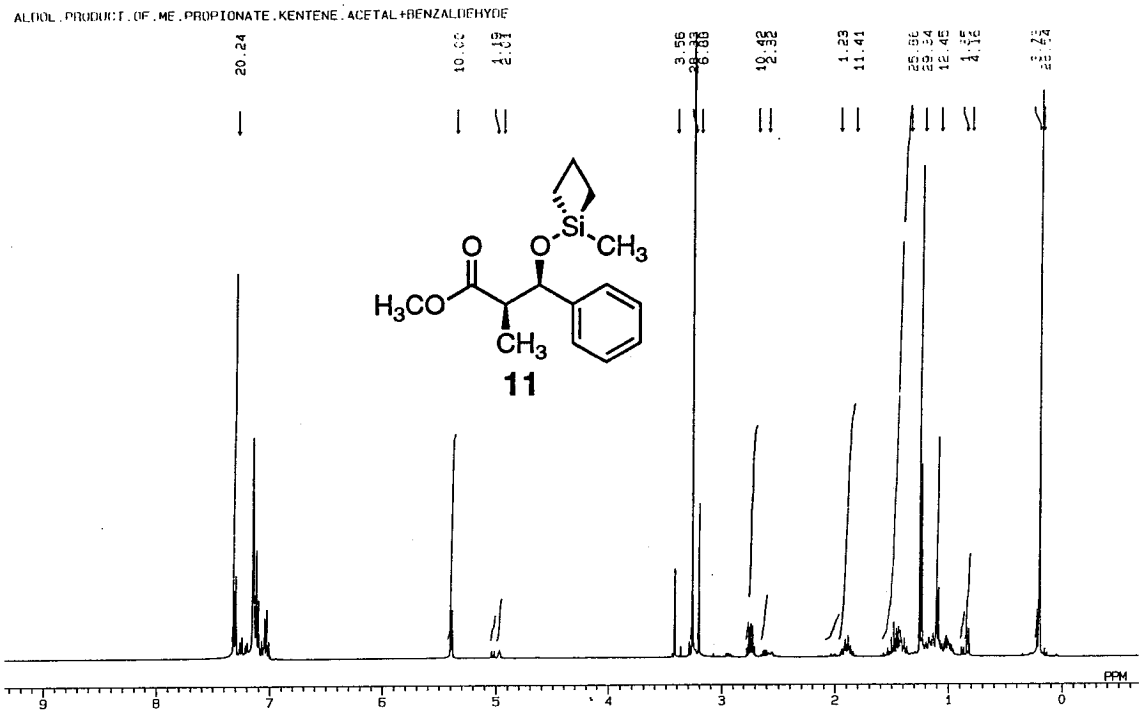
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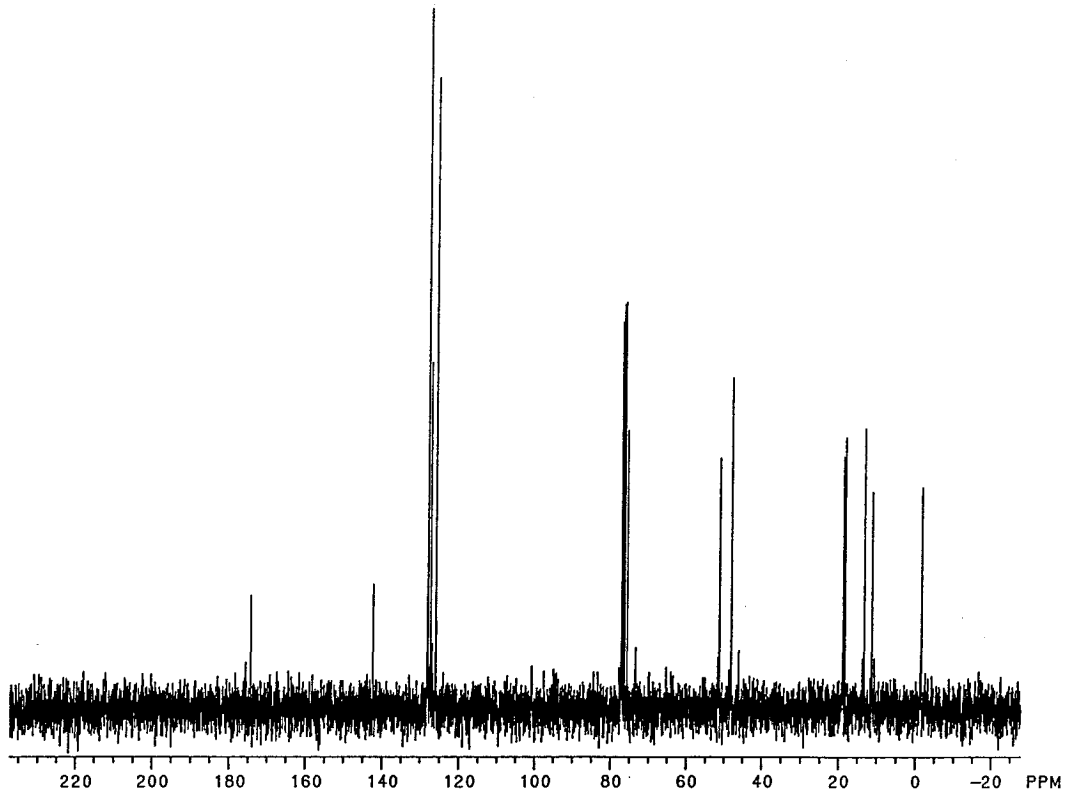
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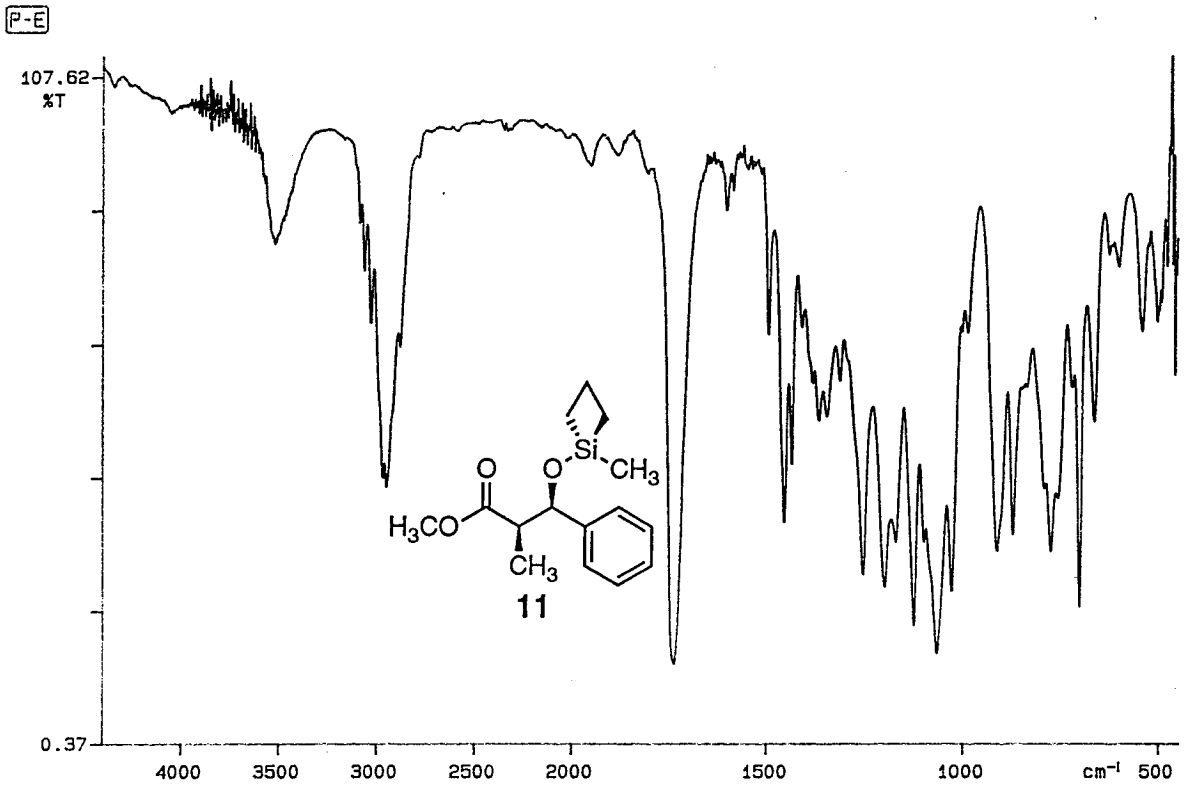
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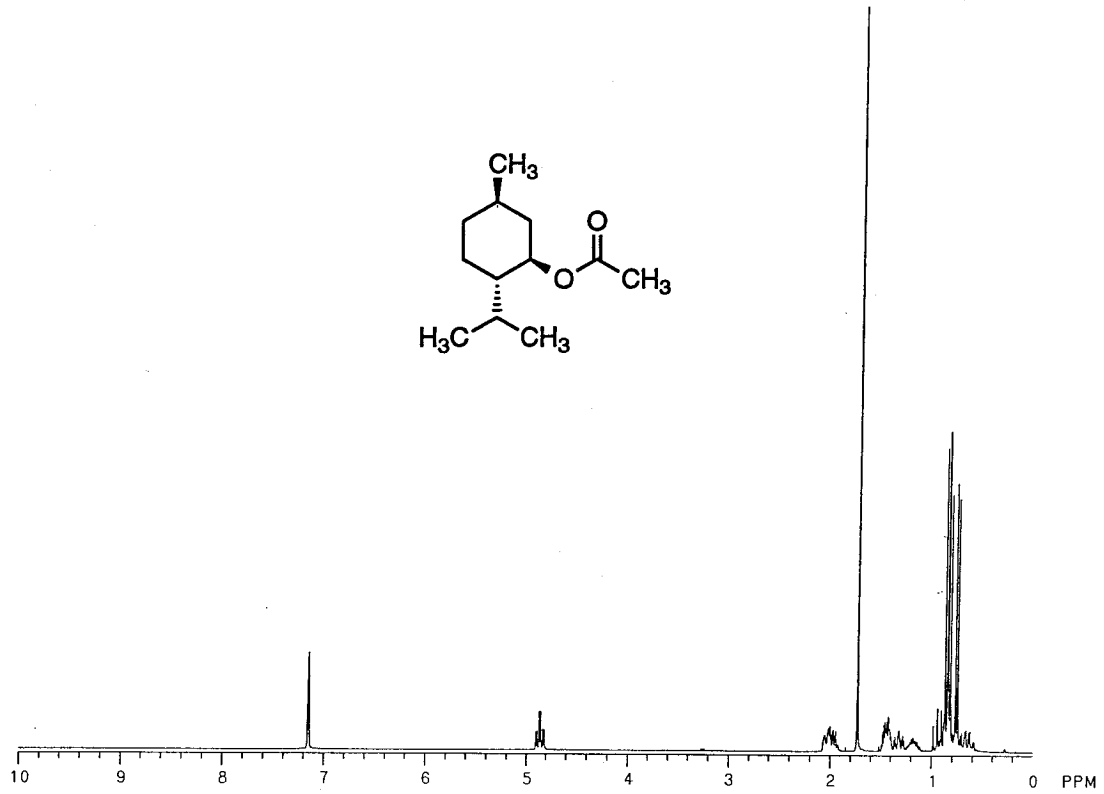
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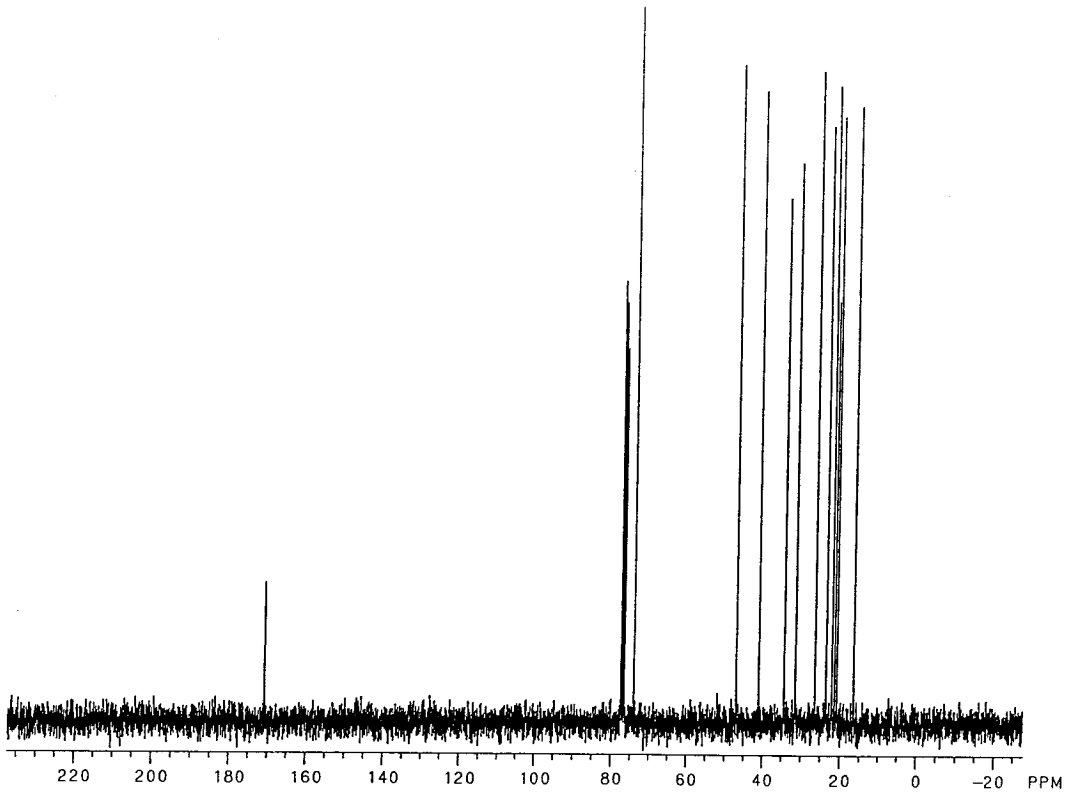
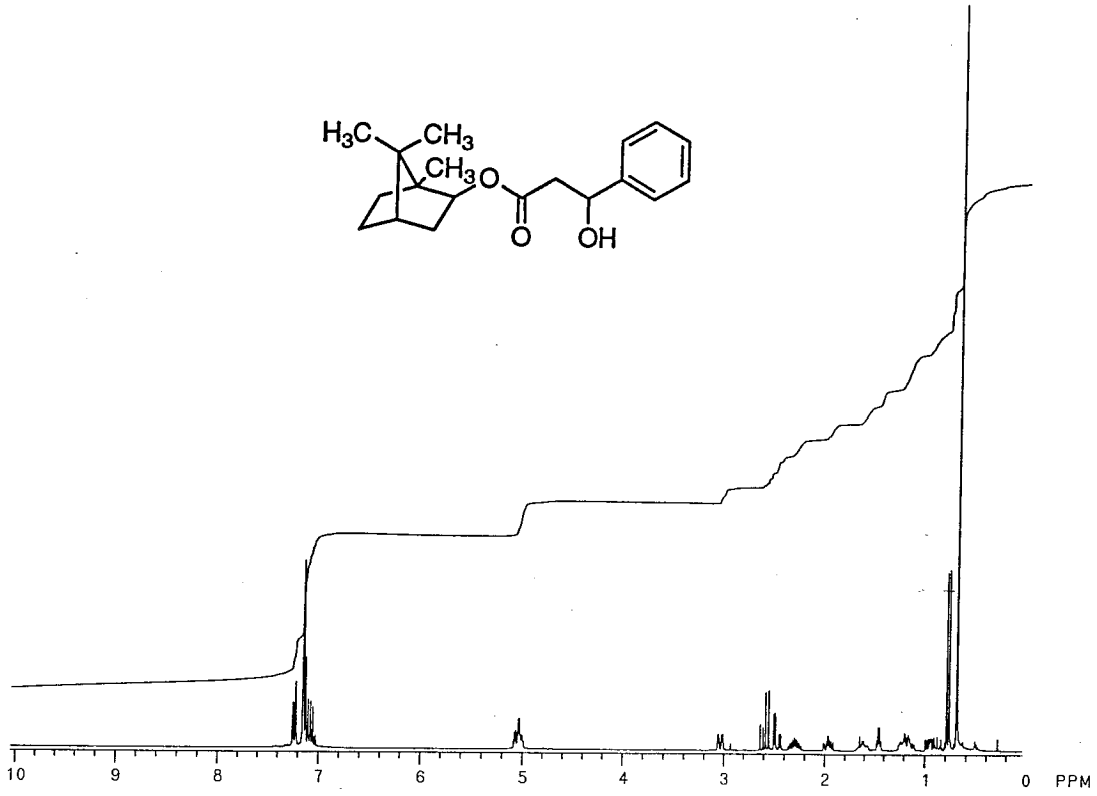
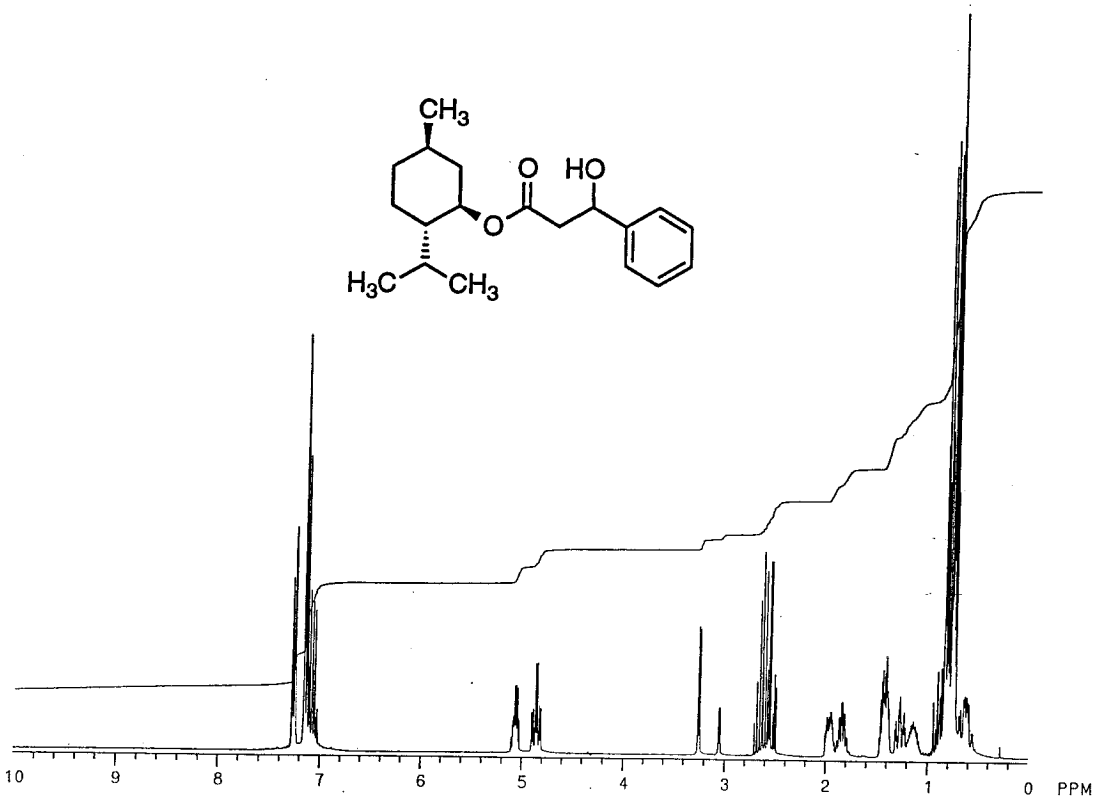
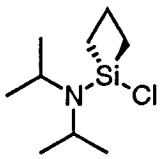
0
PPM

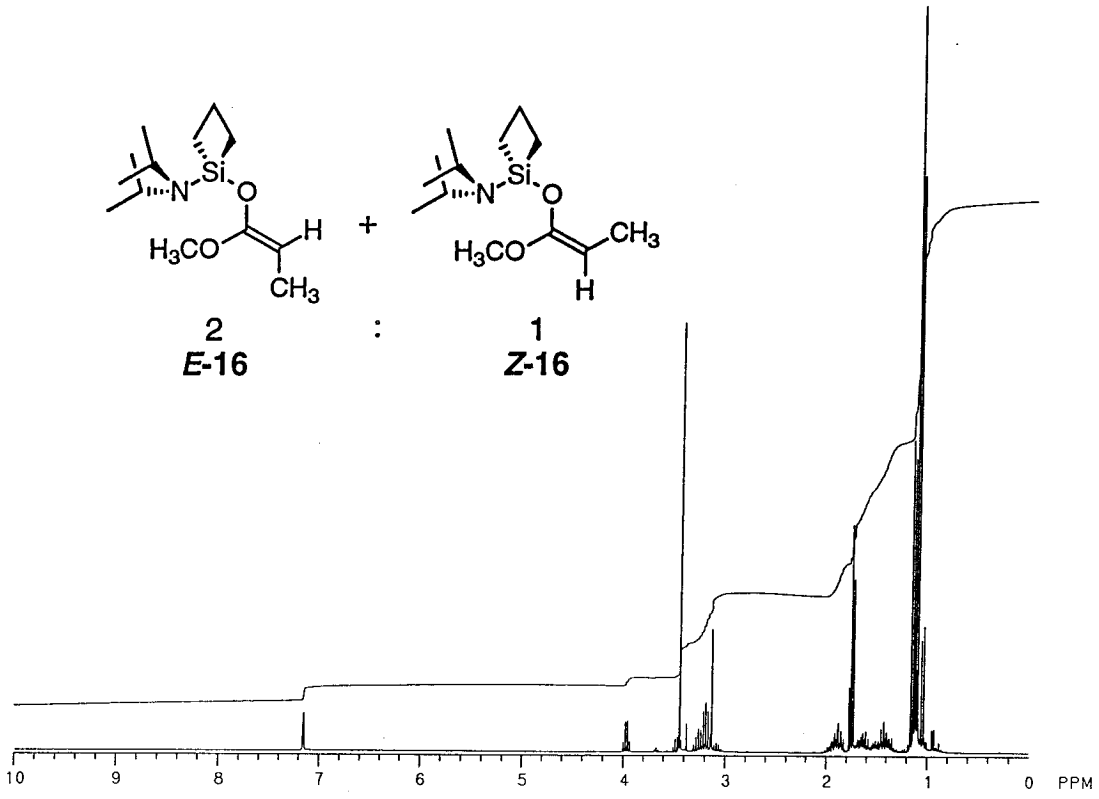

220
200
180
160
140
120
100
80
60
40
20
0
-20
PPM

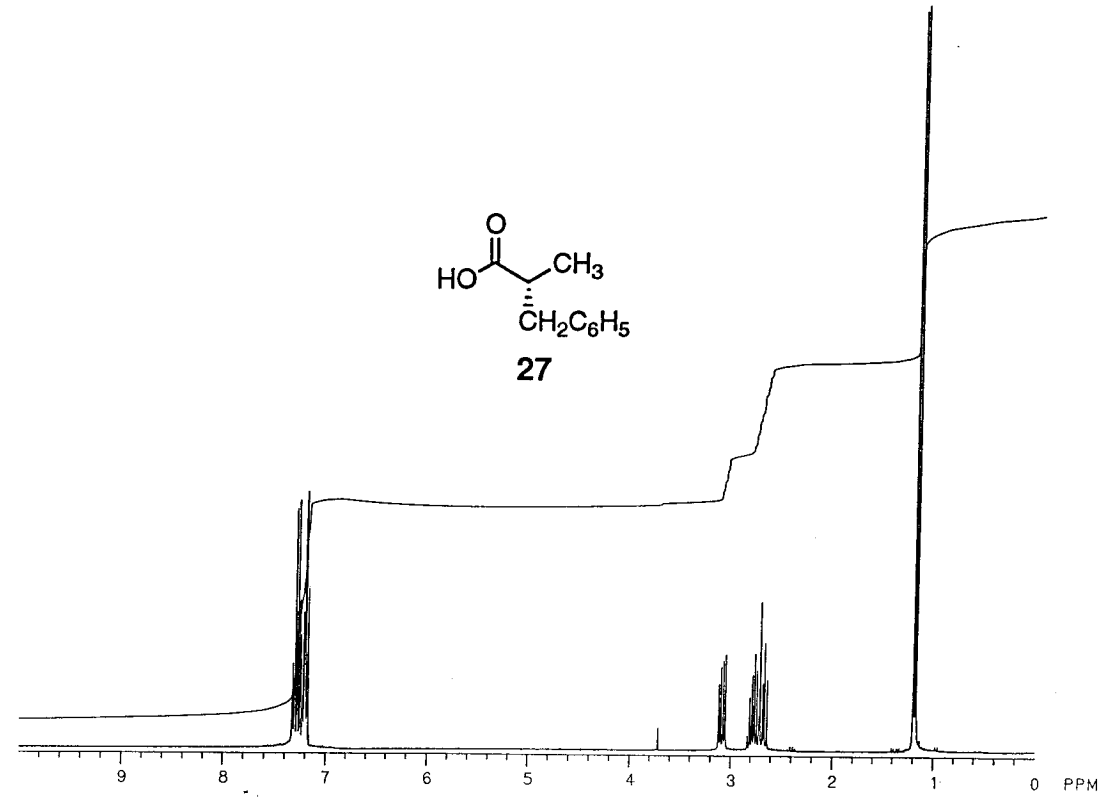

H3C
CH3
CH3
O
O
OH
10
9
8
7
6
5
4
3
2
1
0
PPM


CH3
O
HO
O
H3C
CH3
10
9
8
7
6
5
4
3
2
1
0
PPM

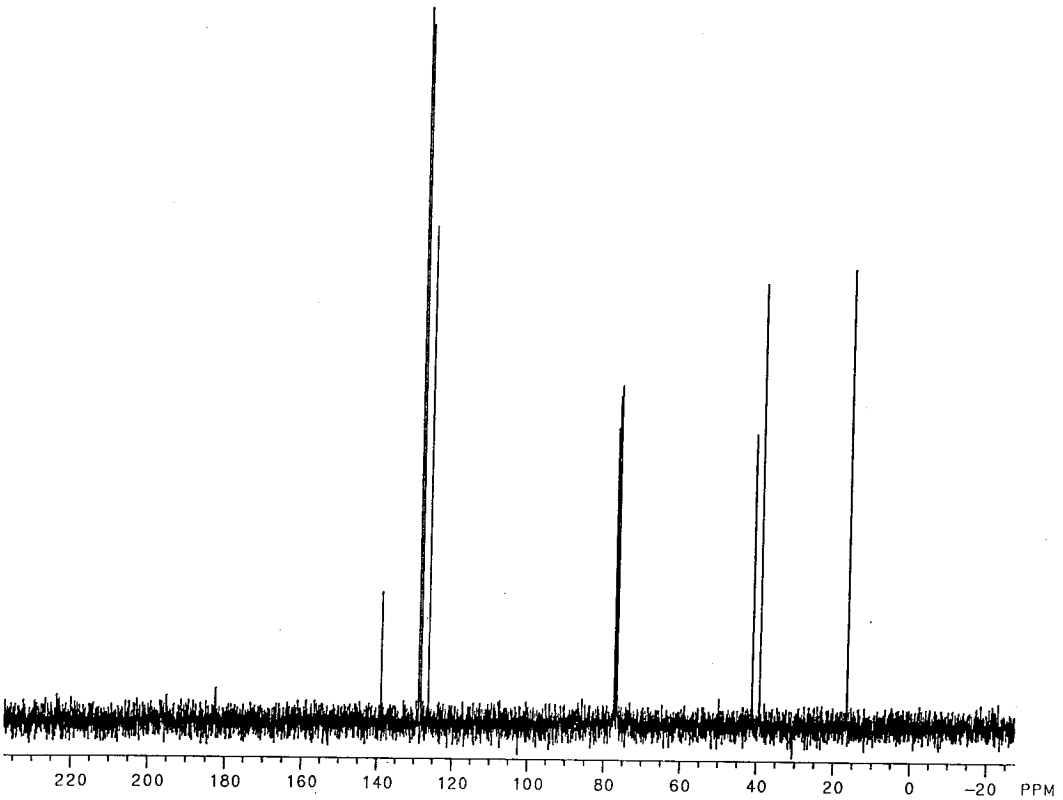


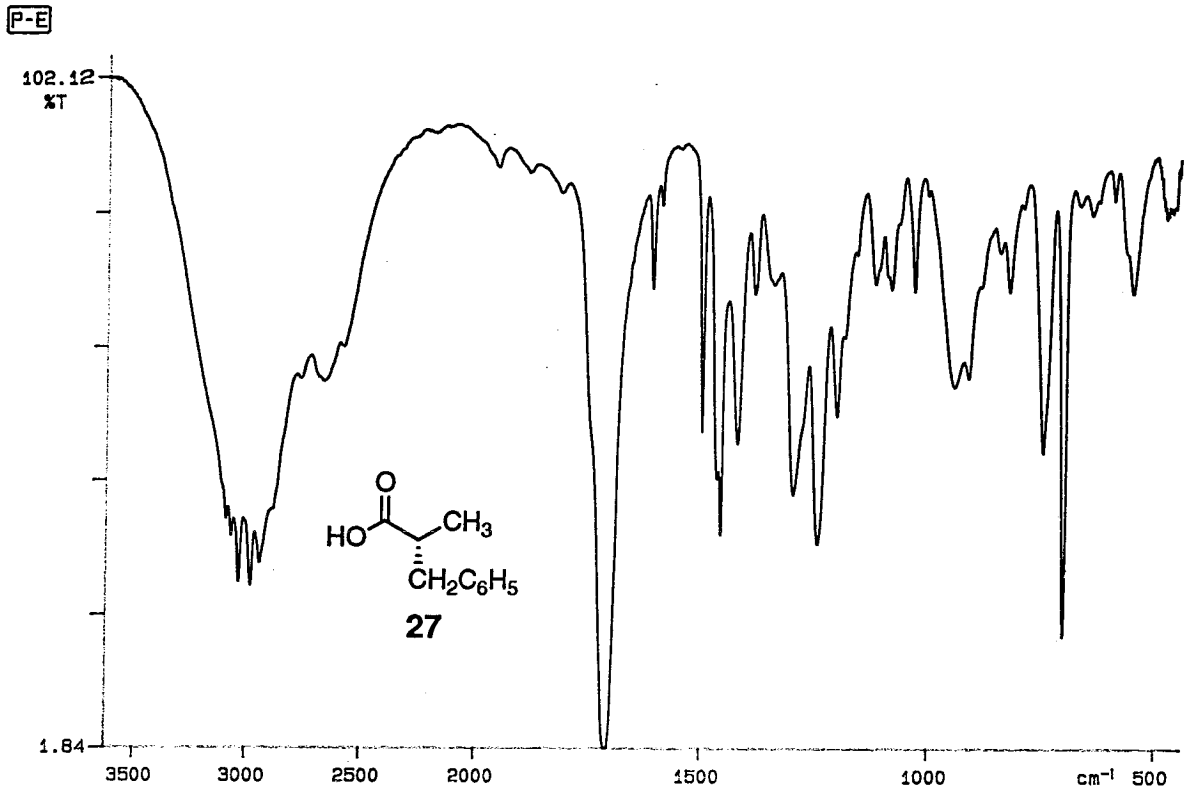
15

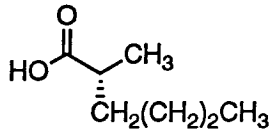

Si
N
O
H
H3CO
CH3
+
Si
N
O
CH3
H3CO
H
2
E-16
:
1
Z-16
10
9
8
7
6
5
4
3
2
1
0
PPM


HO
O
CH3
CH2C6H5
9
8
7
6
5
4
3
2
1
0
PPM

27

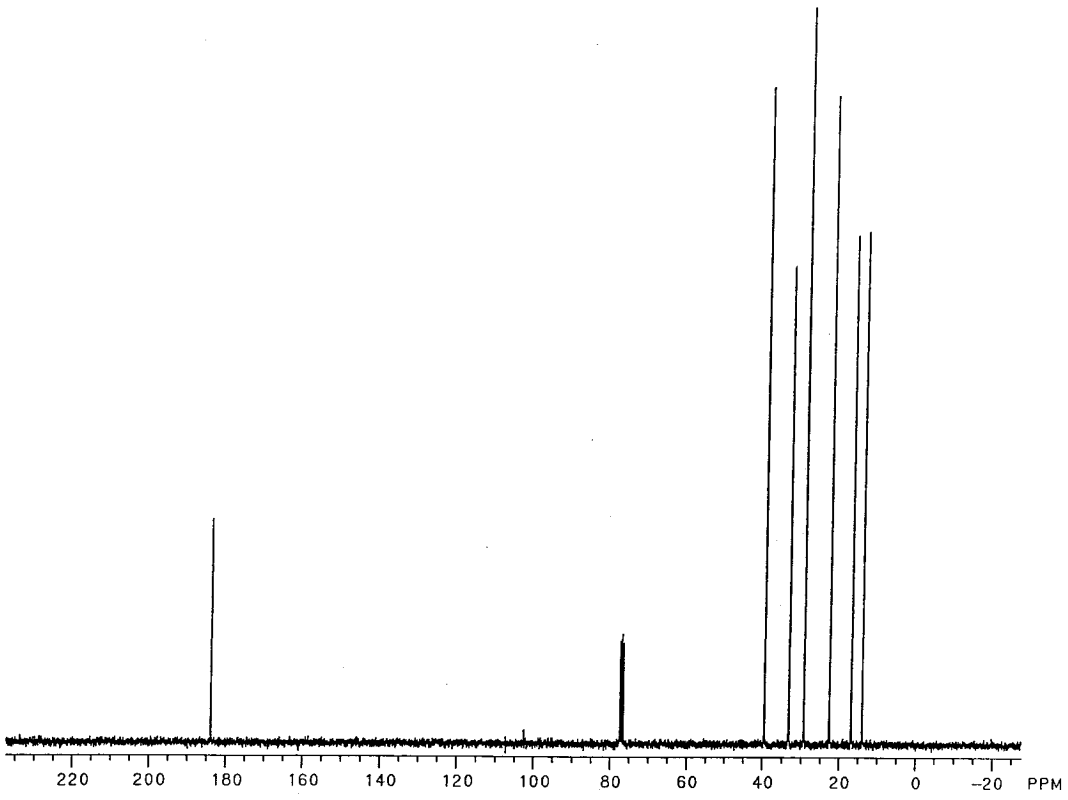

220
200
180
160
140
120
100
80
60
40
20
0
−20
PPM

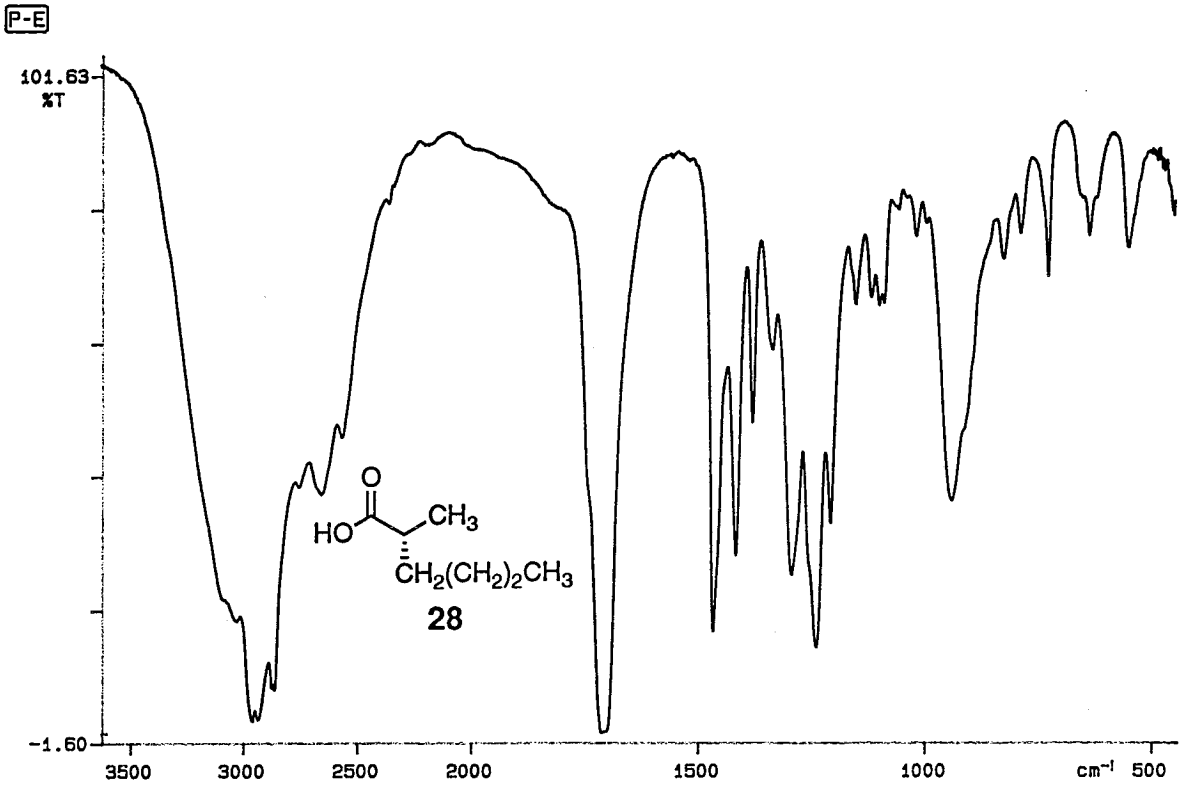

P-E
102.12
%T
1.84
3500
3000
2500
2000
1500
1000
cm-1
500
HO
O
CH3
CH2C6H5
27

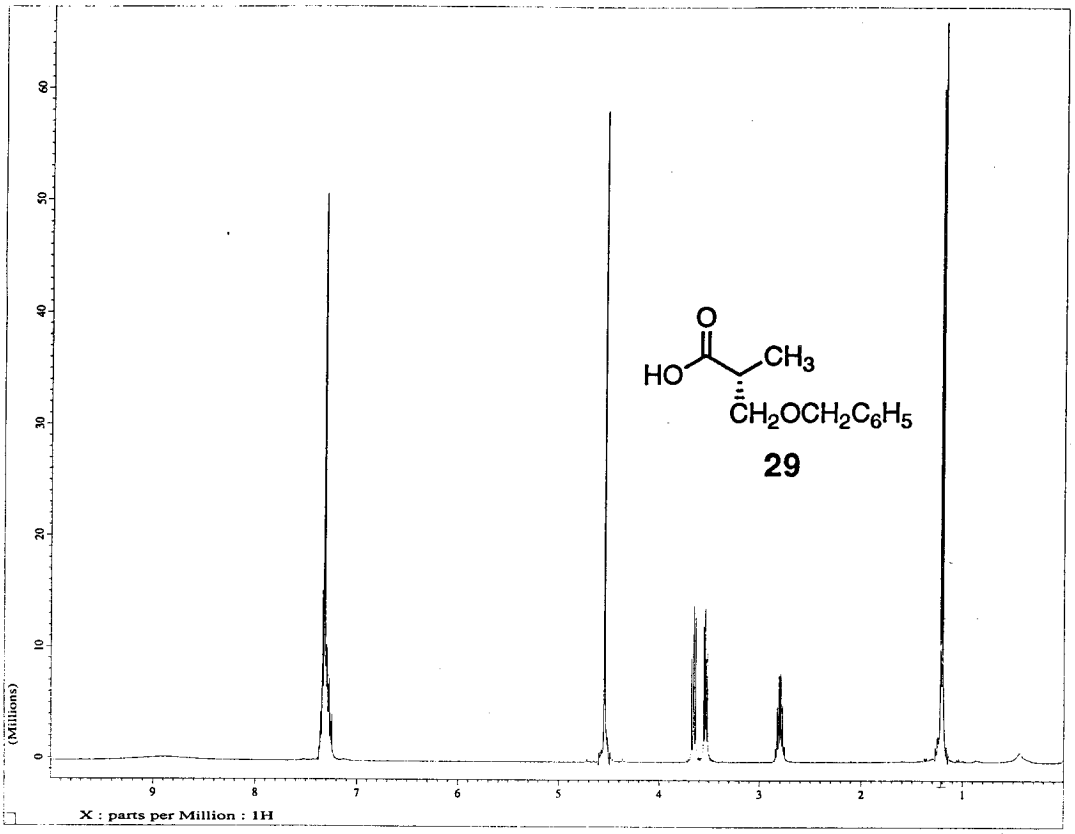

O
HO
CH3
CH2(CH2)2CH3

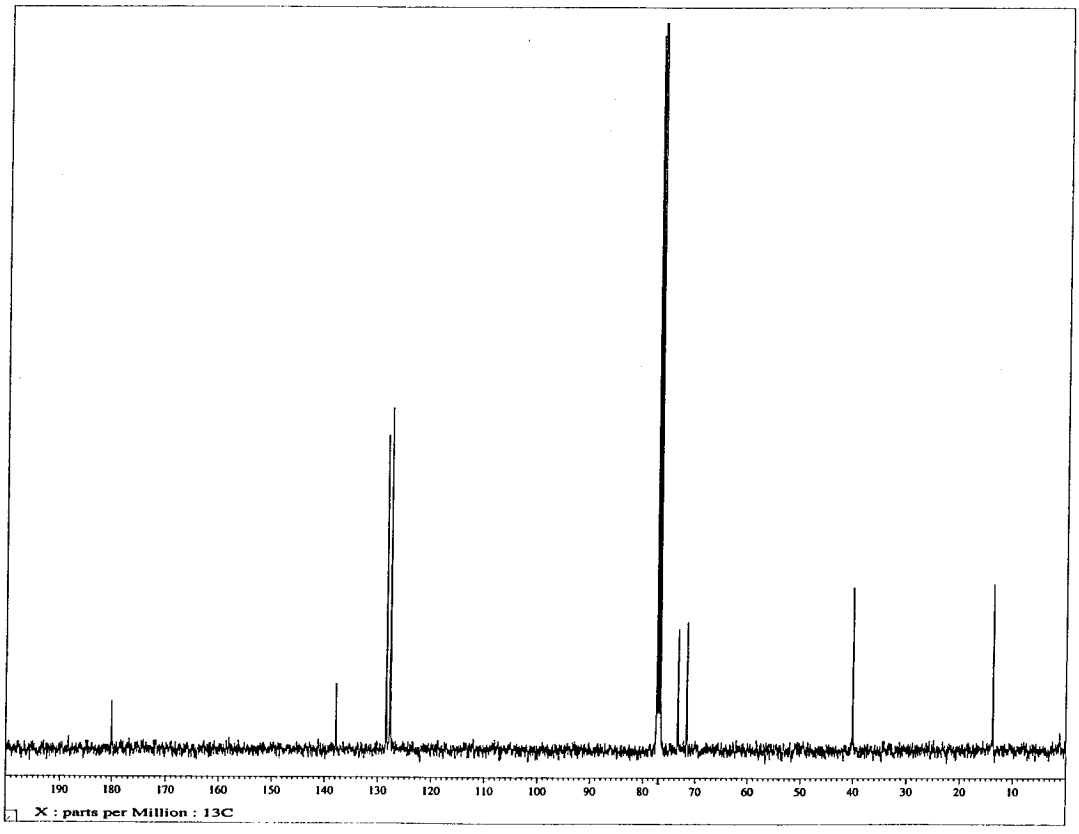
28

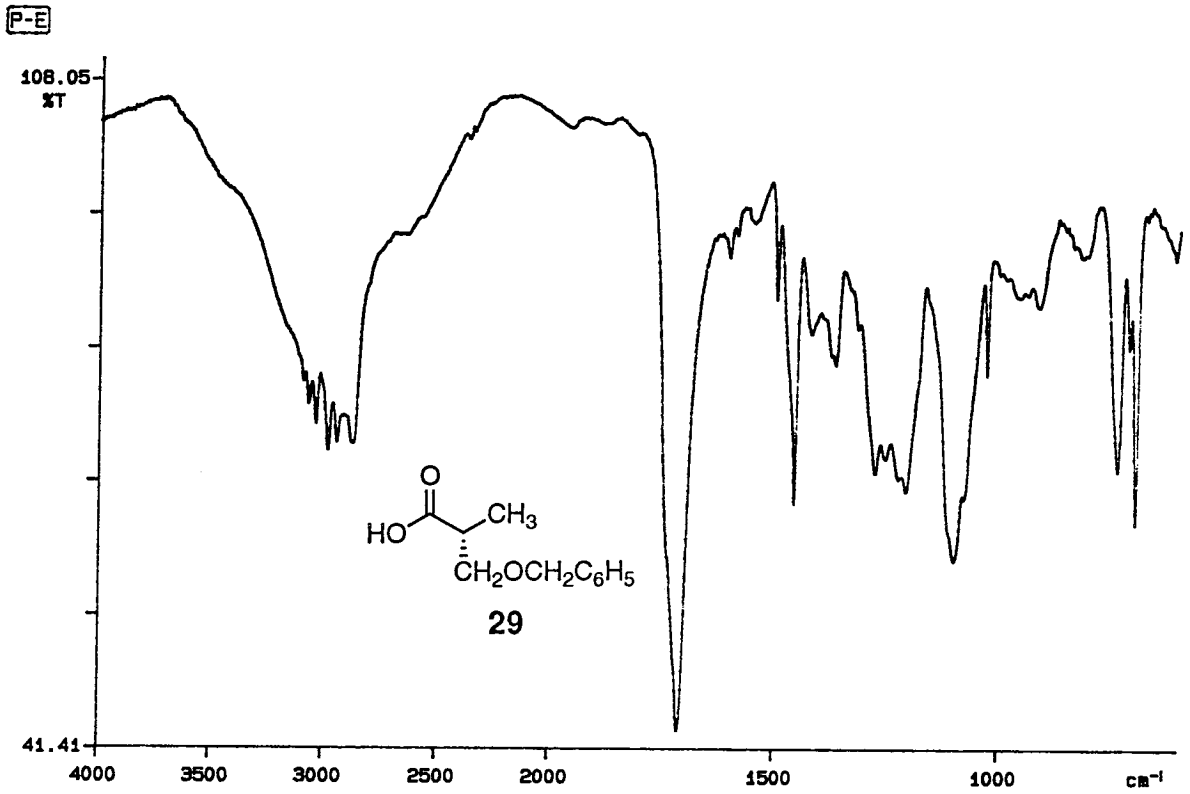
10
9
8
7
6
5
4
3
2
1
0
PPM


220
200
180
160
140
120
100
80
60
40
20
0
-20
PPM

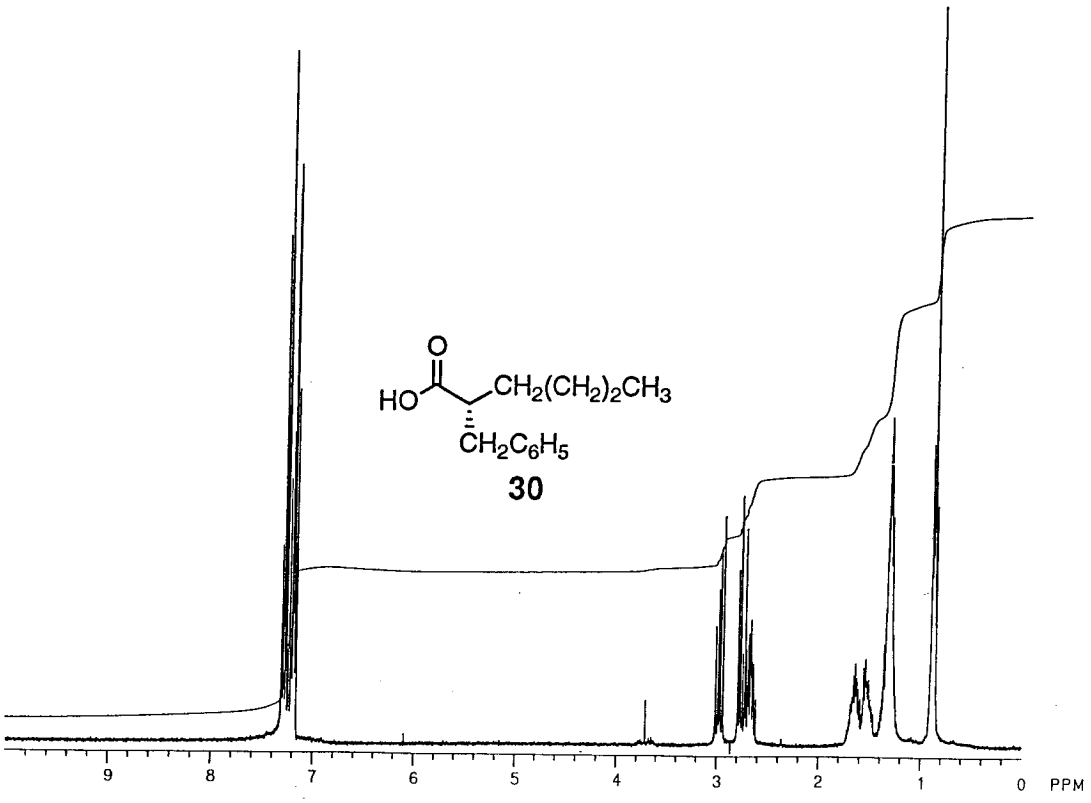

P-E
101.63
%T
-1.60
3500
3000
2500
2000
1500
1000
cm-1
500
O
HO
CH3
CH2(CH2)2CH3
28


O
HO
CH3
CH2OCH2C6H5
29
(Millions)
X : parts per Million : 1H

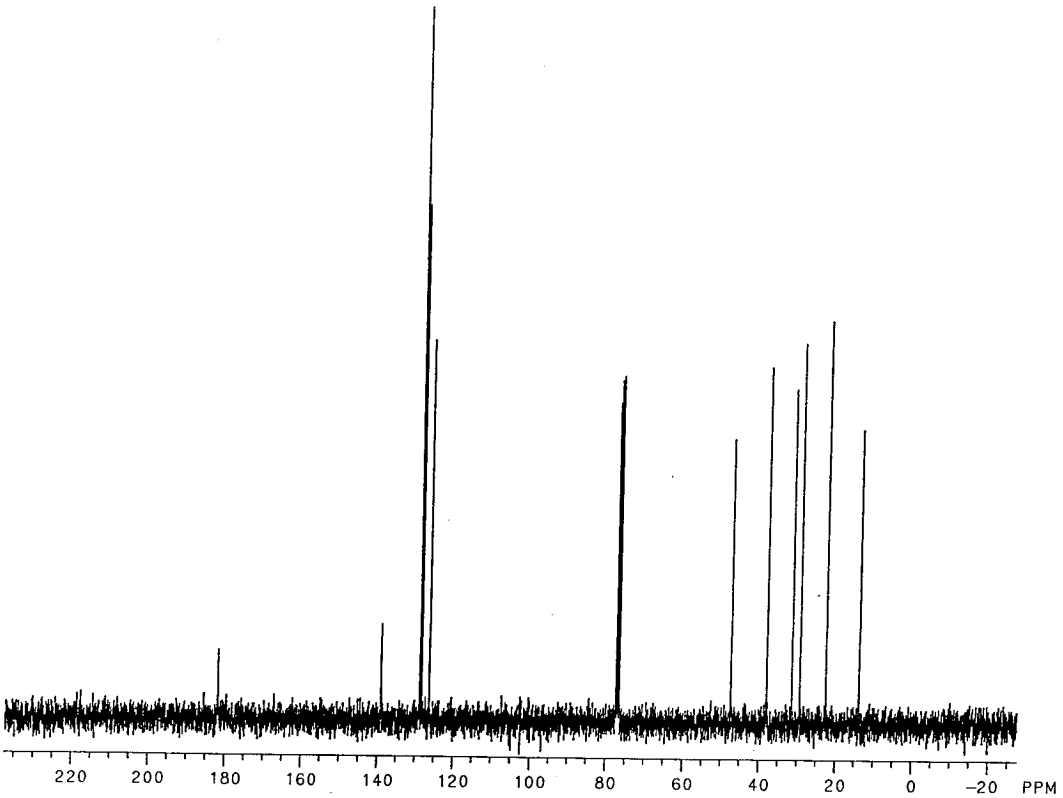

X : parts per Million : 13C

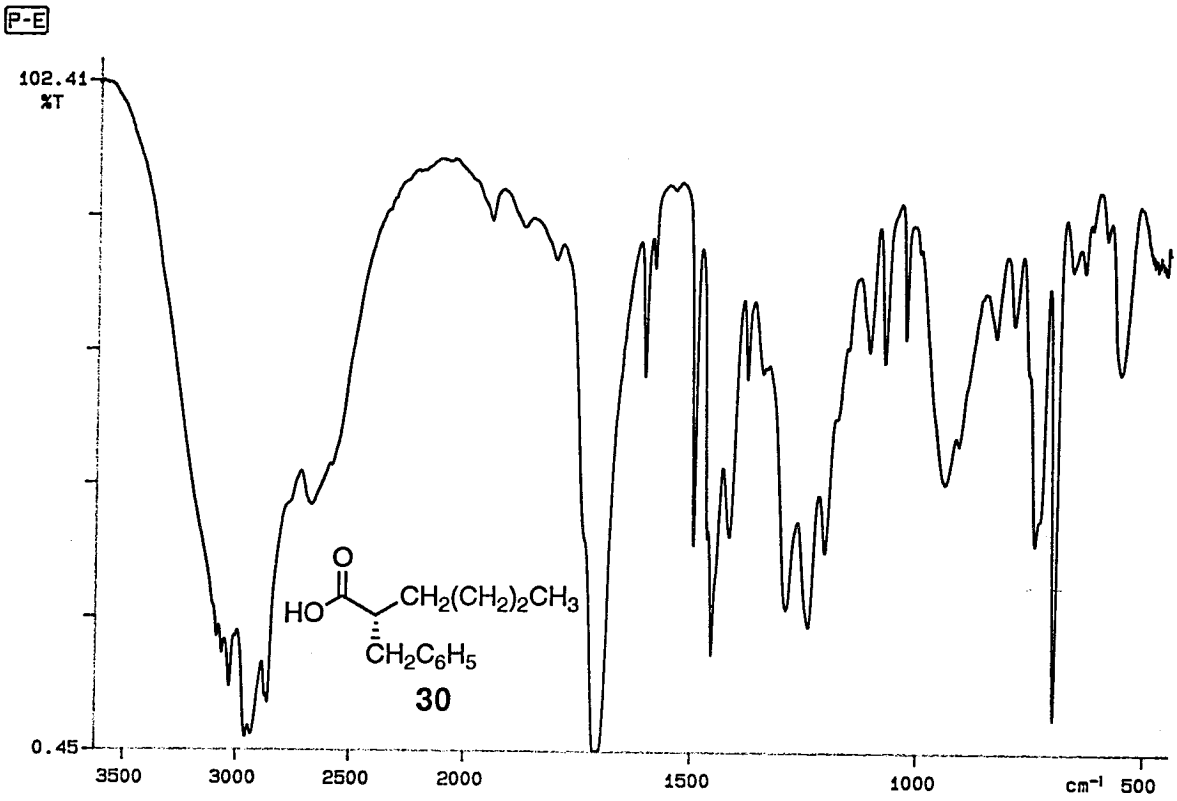

P-E
108.05
%T
41.41
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
HO
O
CH3
CH2OCH2C6H5

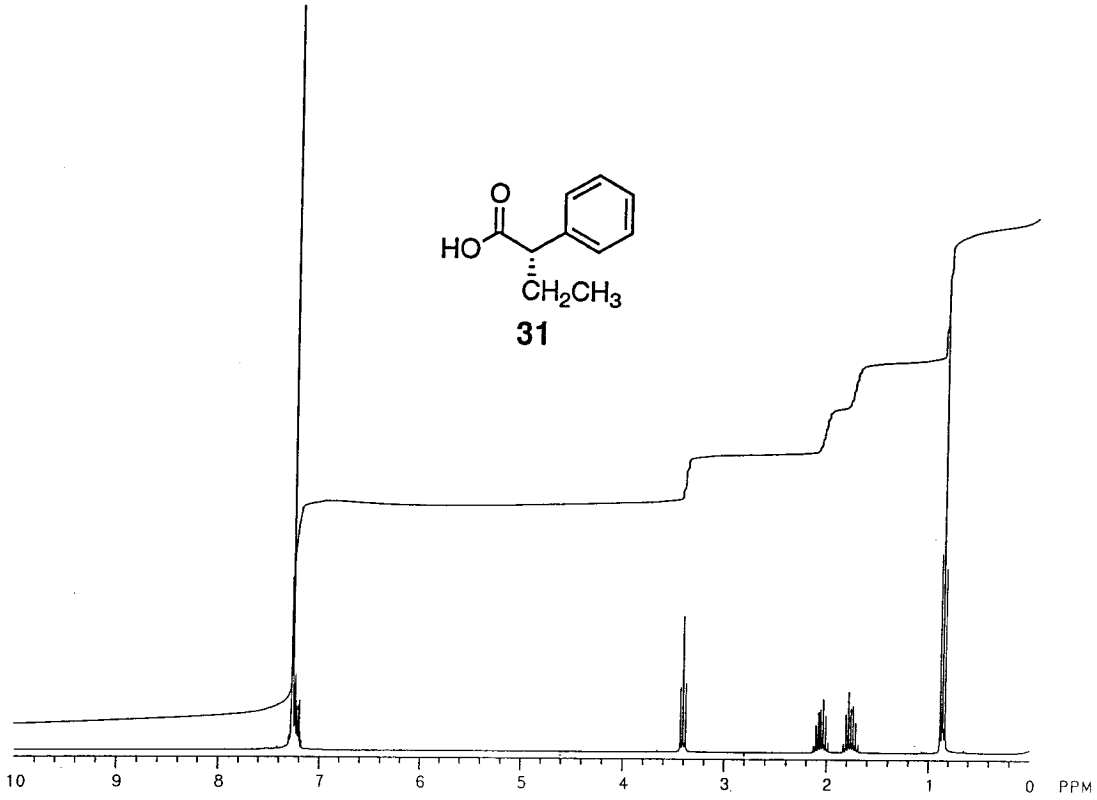
29

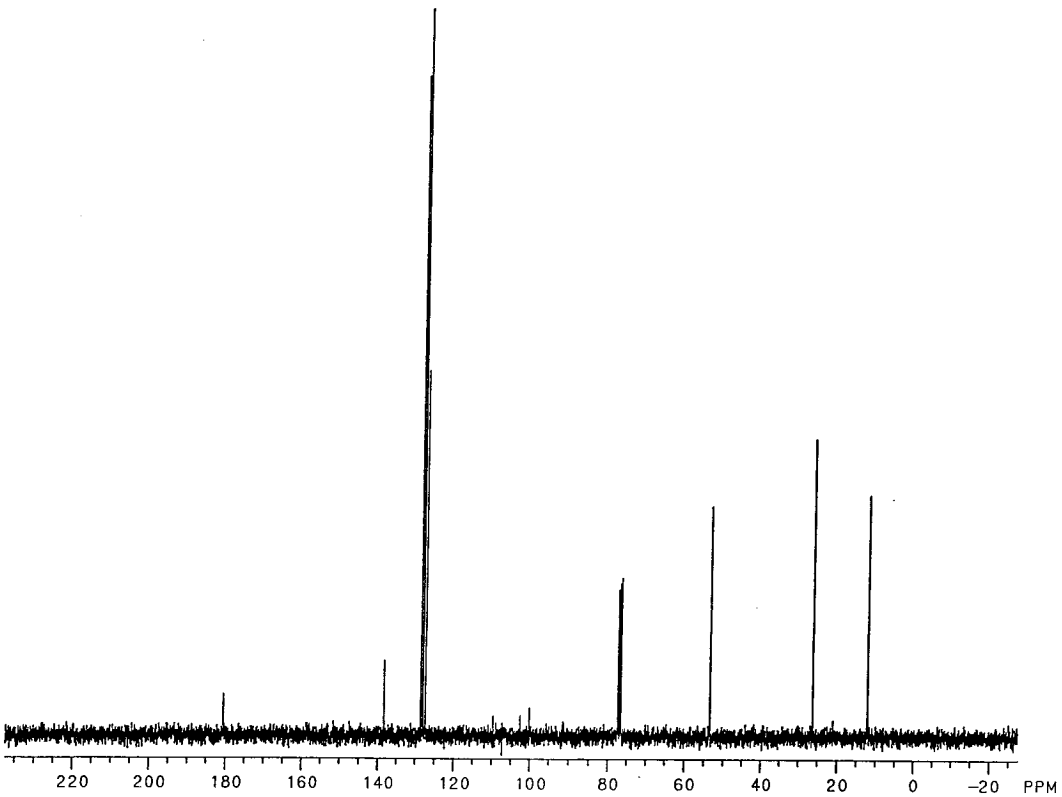

HO
CH2(CH2)2CH3
CH2C6H5
9
8
7
6
5
4
3
2
1
0
PPM

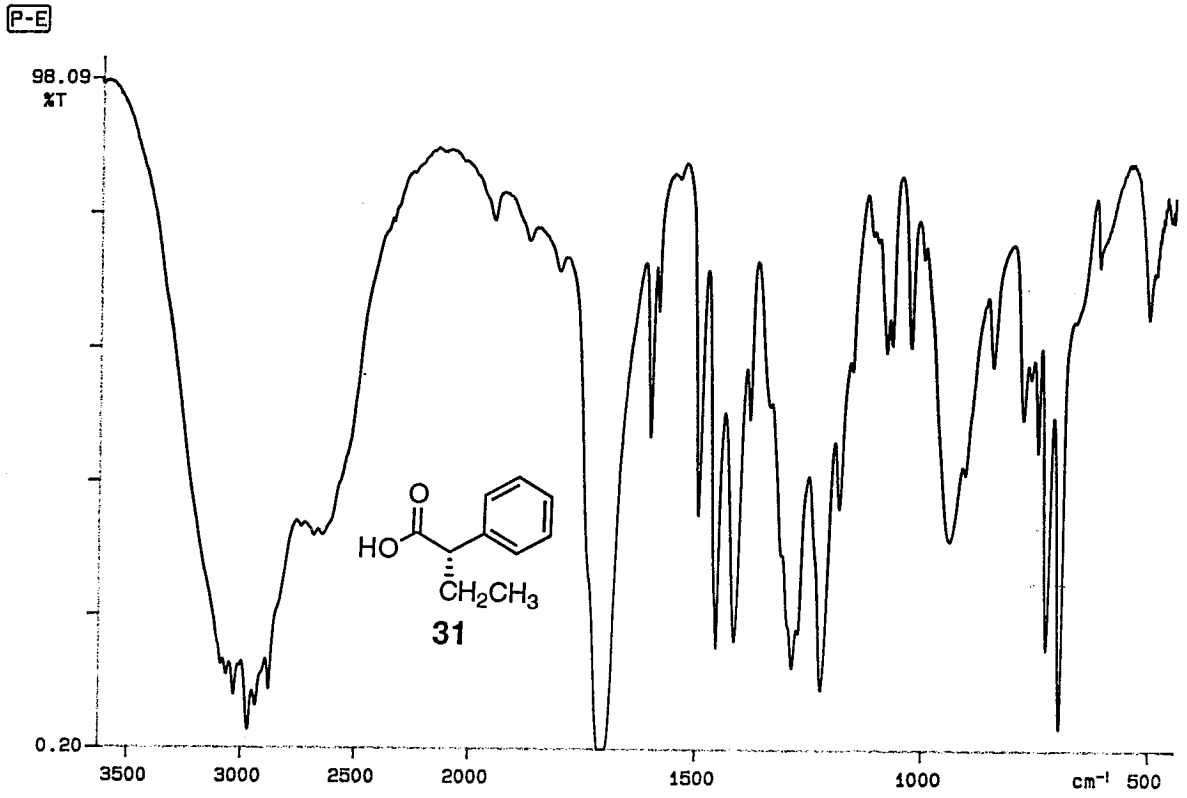
30

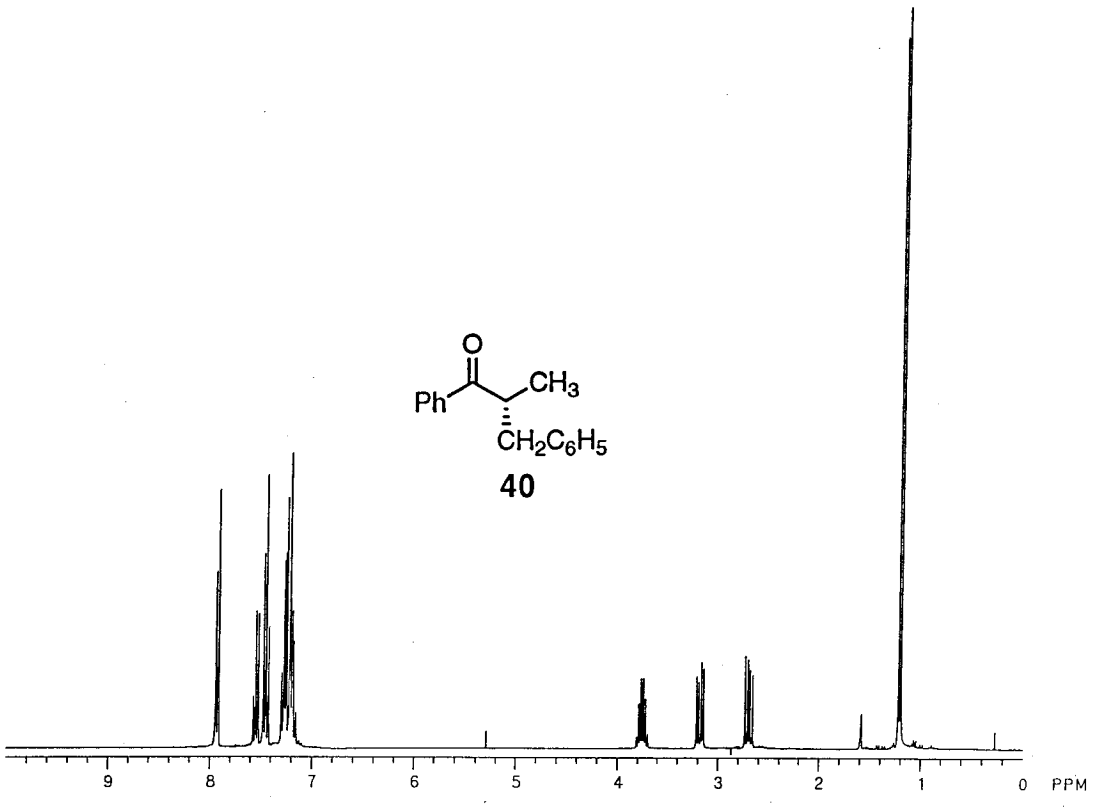

220
200
180
160
140
120
100
80
60
40
20
0
–20
PPM


P-E
102.41
%T
0.45
3500
3000
2500
2000
1500
1000
cm⁻¹
500
HO
O
CH2(CH2)2CH3
CH2C6H5
30

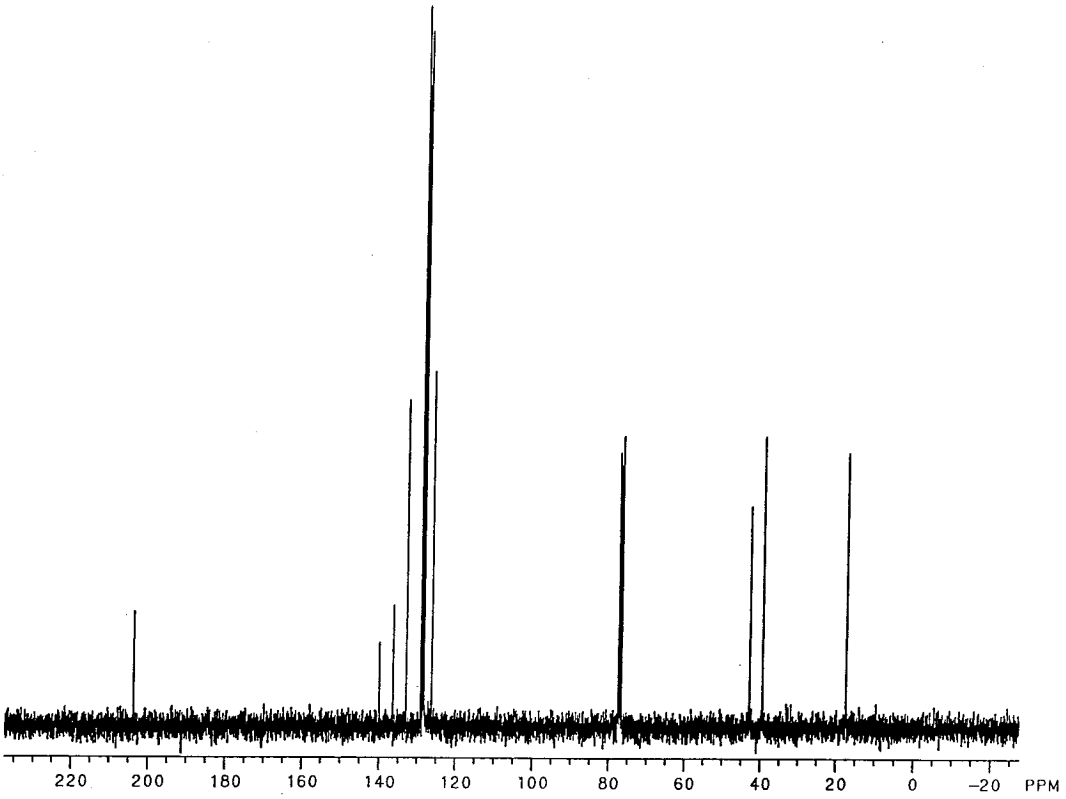

O
HO
CH2CH3
31
10
9
8
7
6
5
4
3
2
1
0
PPM

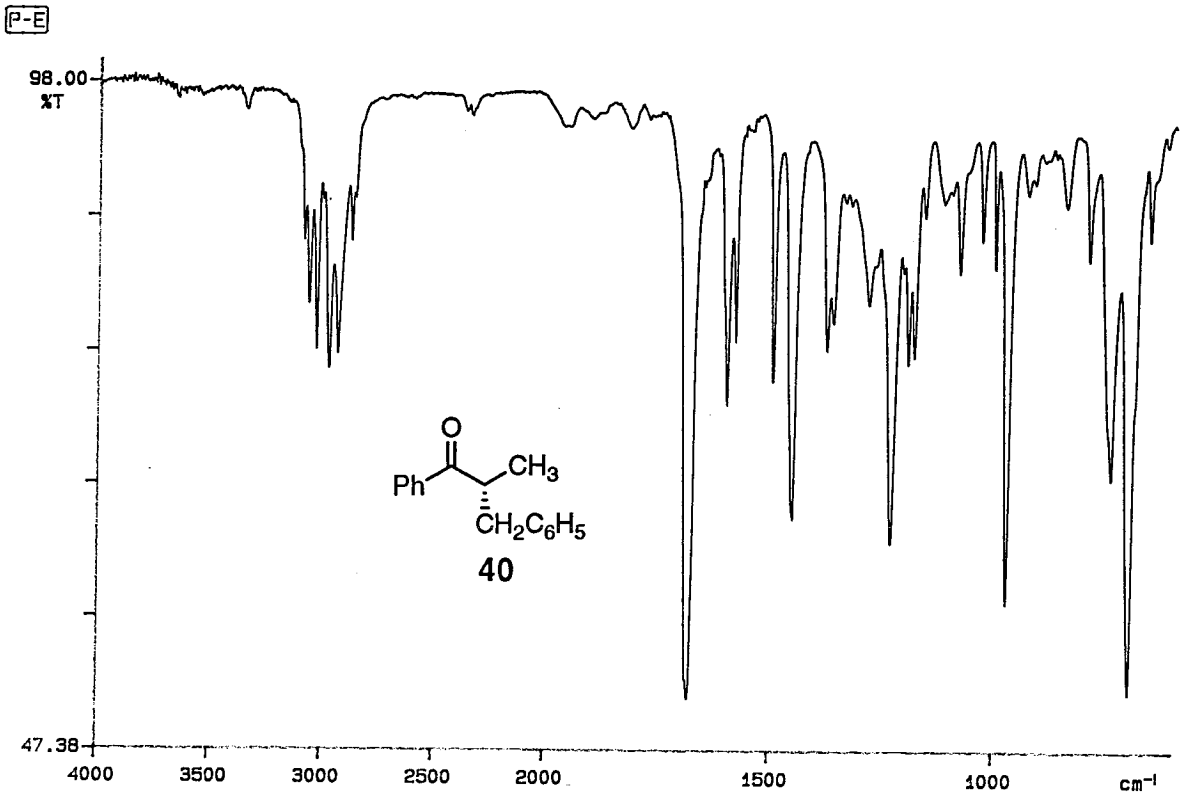

220
200
180
160
140
120
100
80
60
40
20
0
−20
PPM


P-E
98.09
%T
0.20
3500
3000
2500
2000
1500
1000
cm⁻¹
500
HO
O
CH2CH3
31


O
Ph
CH3
CH2C6H5
9
8
7
6
5
4
3
2
1
0
PPM

40


220
200
180
160
140
120
100
80
60
40
20
0
−20
PPM

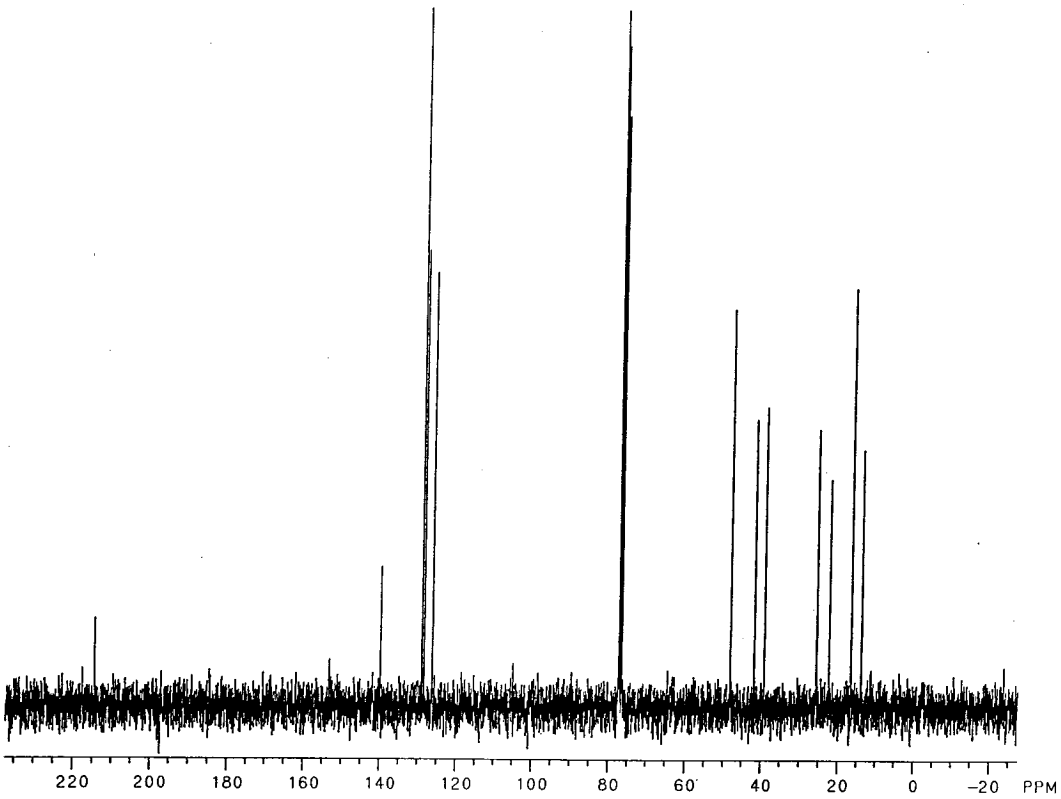

P-E
98.00
%T
47.38
4000
3500
3000
2500
2000
1500
1000
cm-1
O
Ph
CH3
CH2C6H5

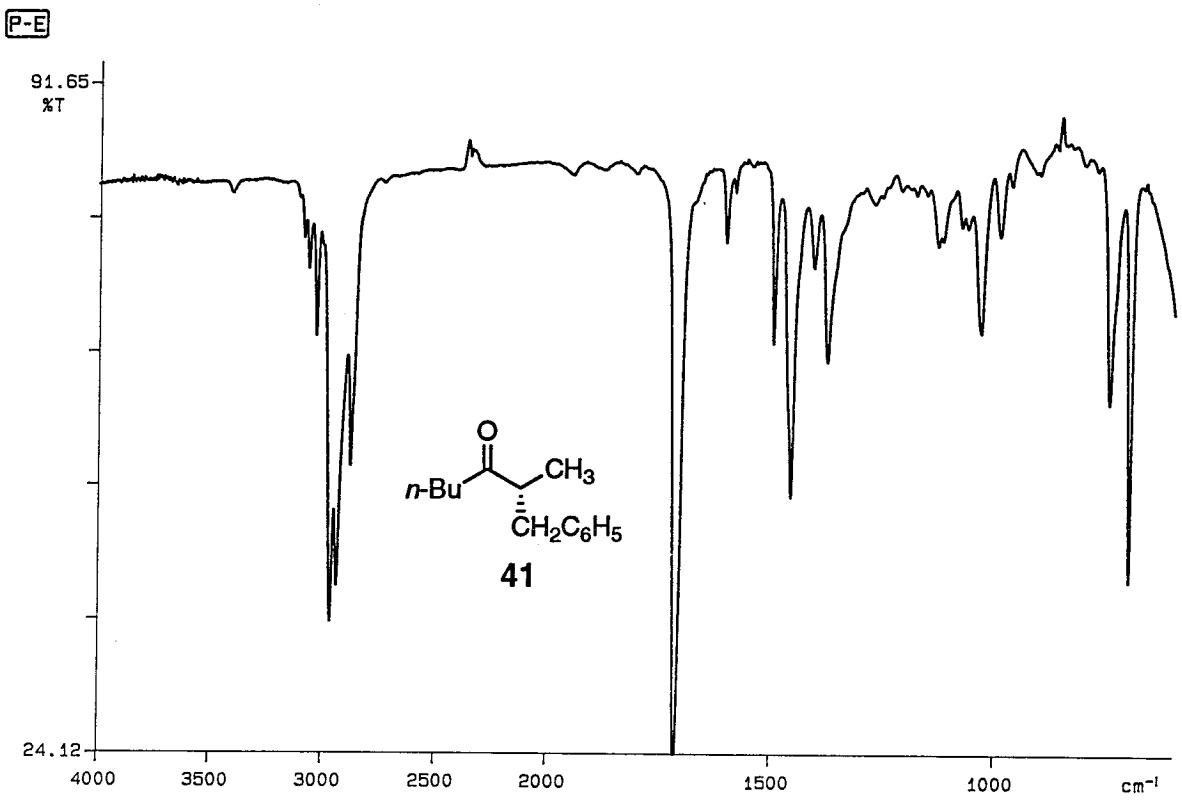
40

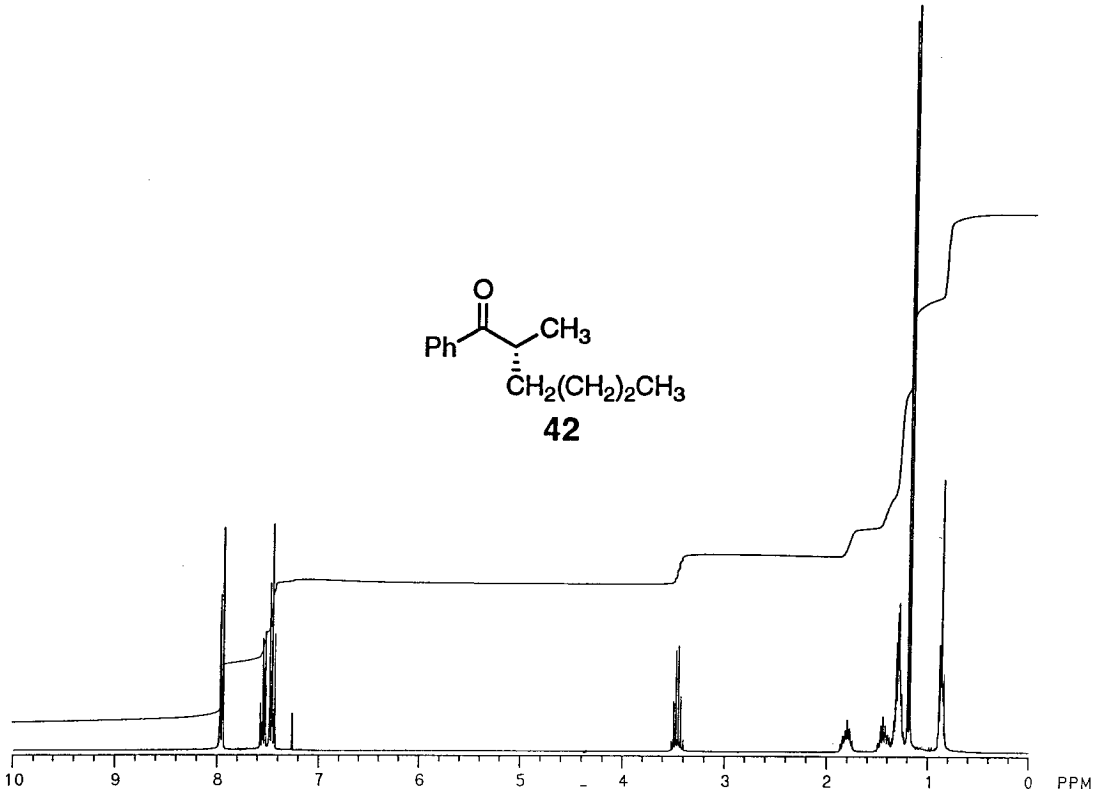

O
n-Bu
CH3
CH2C6H5

41

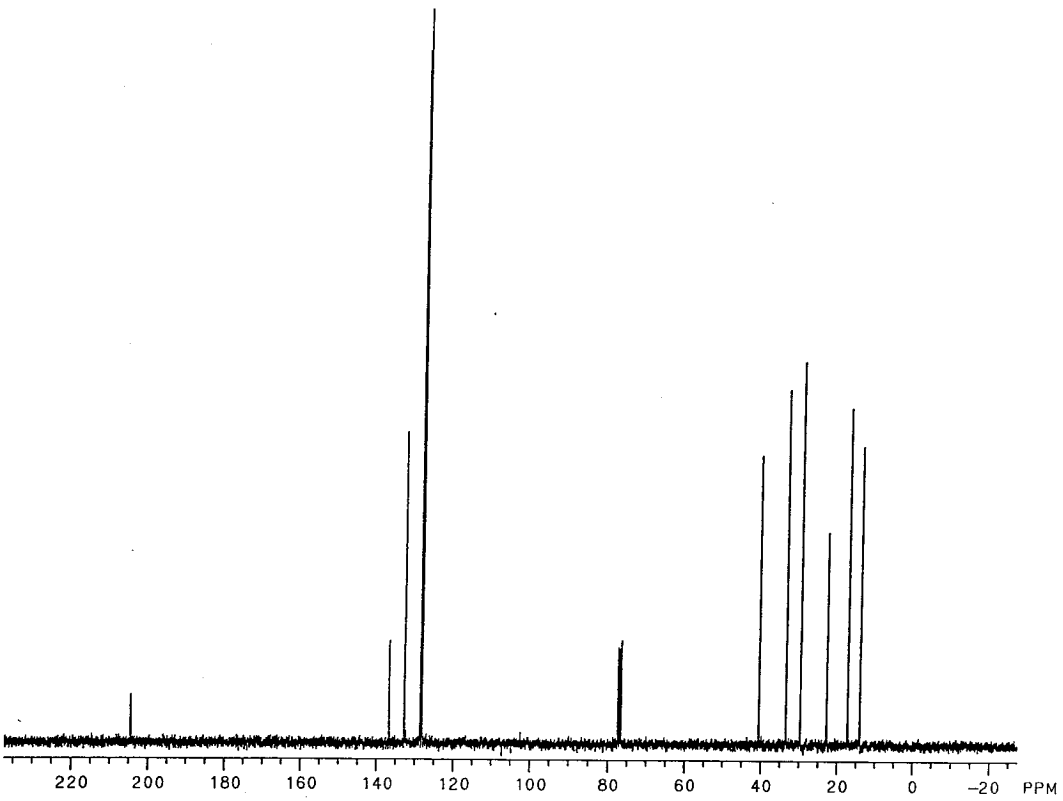
9
8
7
6
5
4
3
2
1
0
PPM

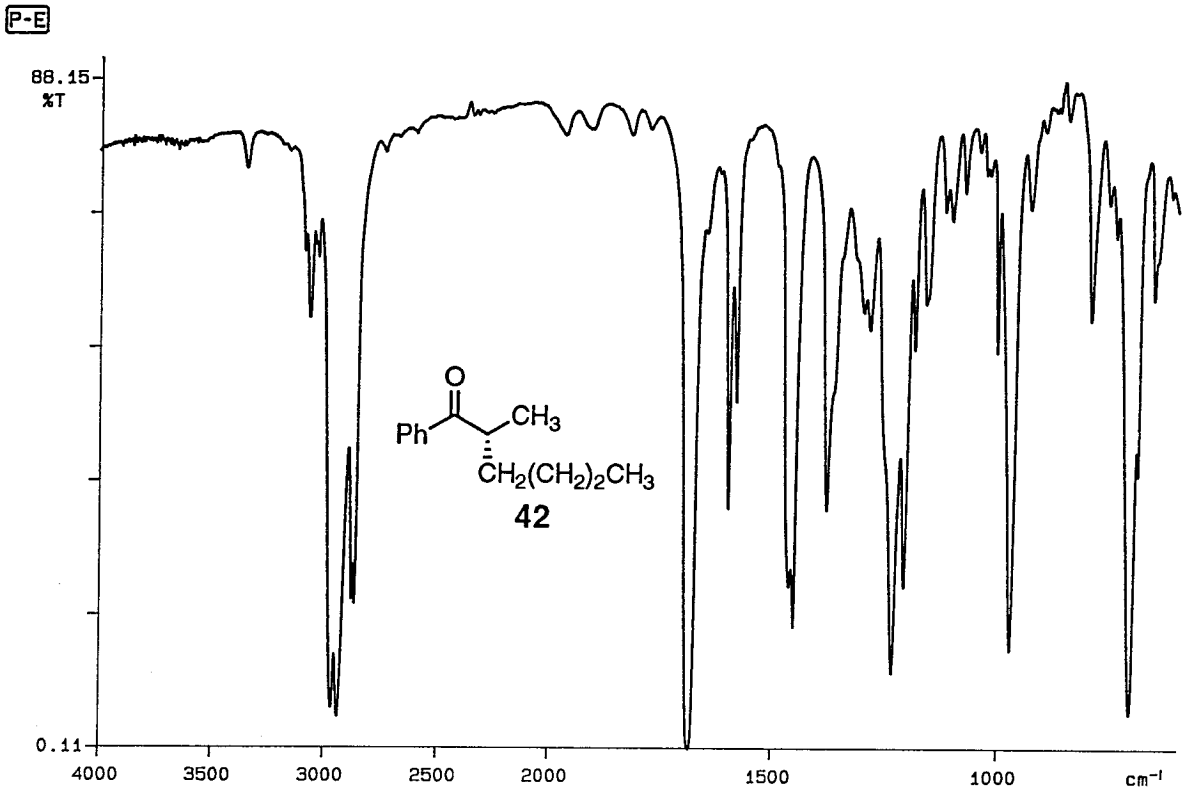

220
200
180
160
140
120
100
80
60
40
20
0
-20
PPM

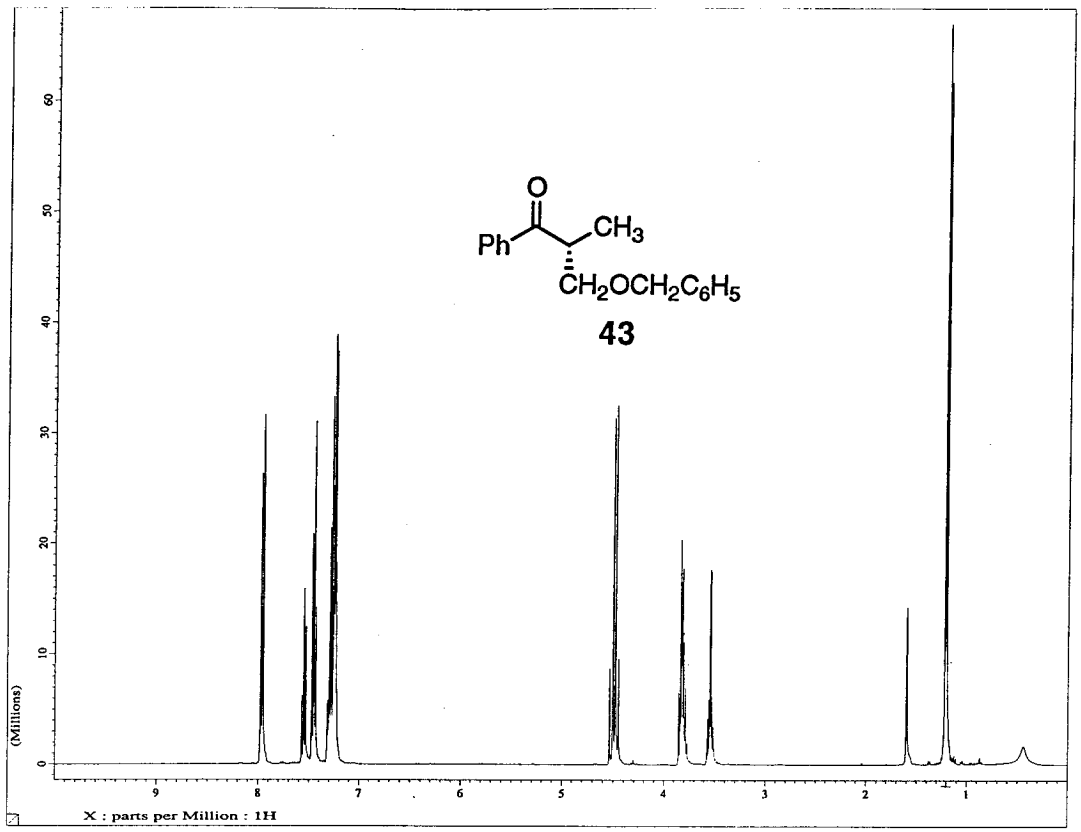

P-E
91.65
%T
24.12
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
O
CH3
n-Bu
CH2C6H5
41

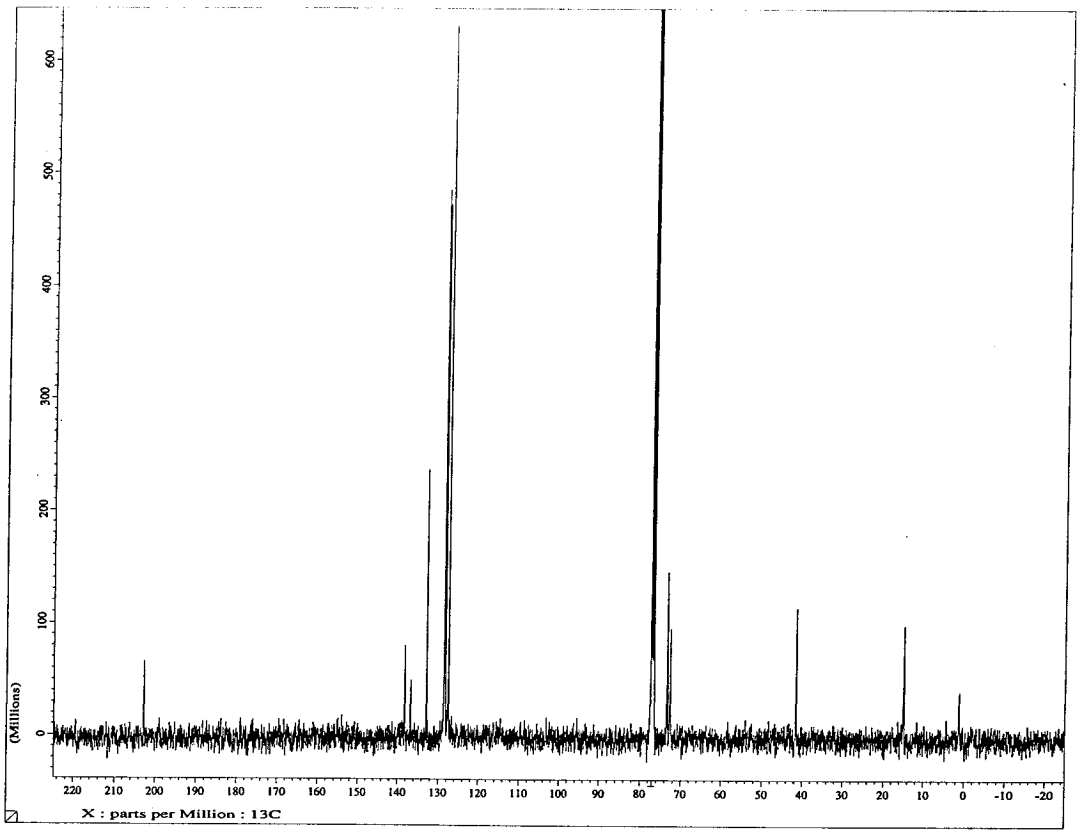

O
Ph
CH3
CH2(CH2)2CH3
10
9
8
7
6
5
4
3
2
1
0
PPM

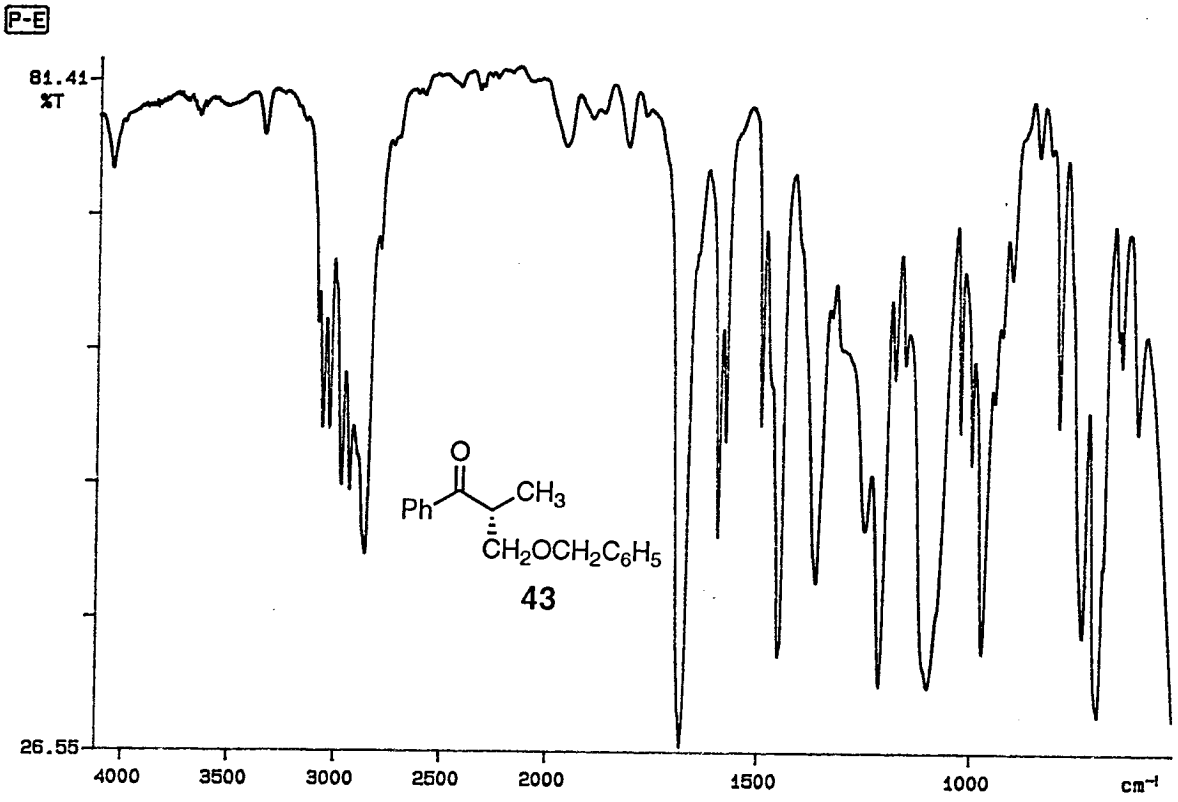
42


220
200
180
160
140
120
100
80
60
40
20
0
–20
PPM

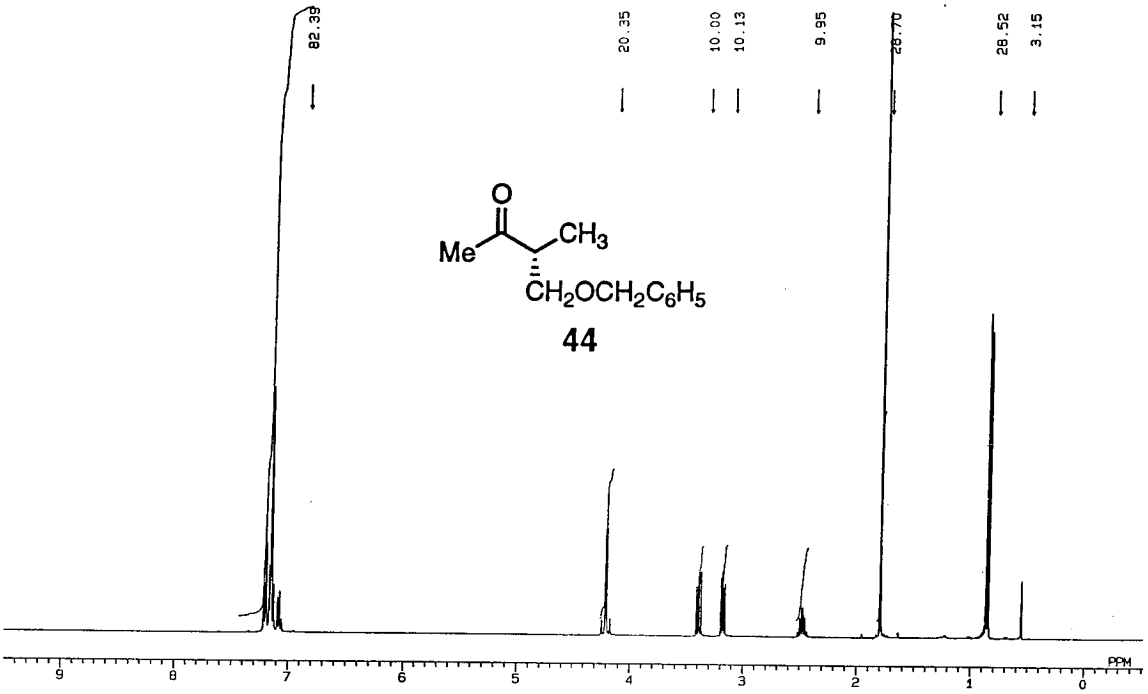

P-E
88.15
%T
0.11
4000
3500
3000
2500
2000
1500
1000
cm-1
O
Ph
CH3
CH2(CH2)2CH3
42

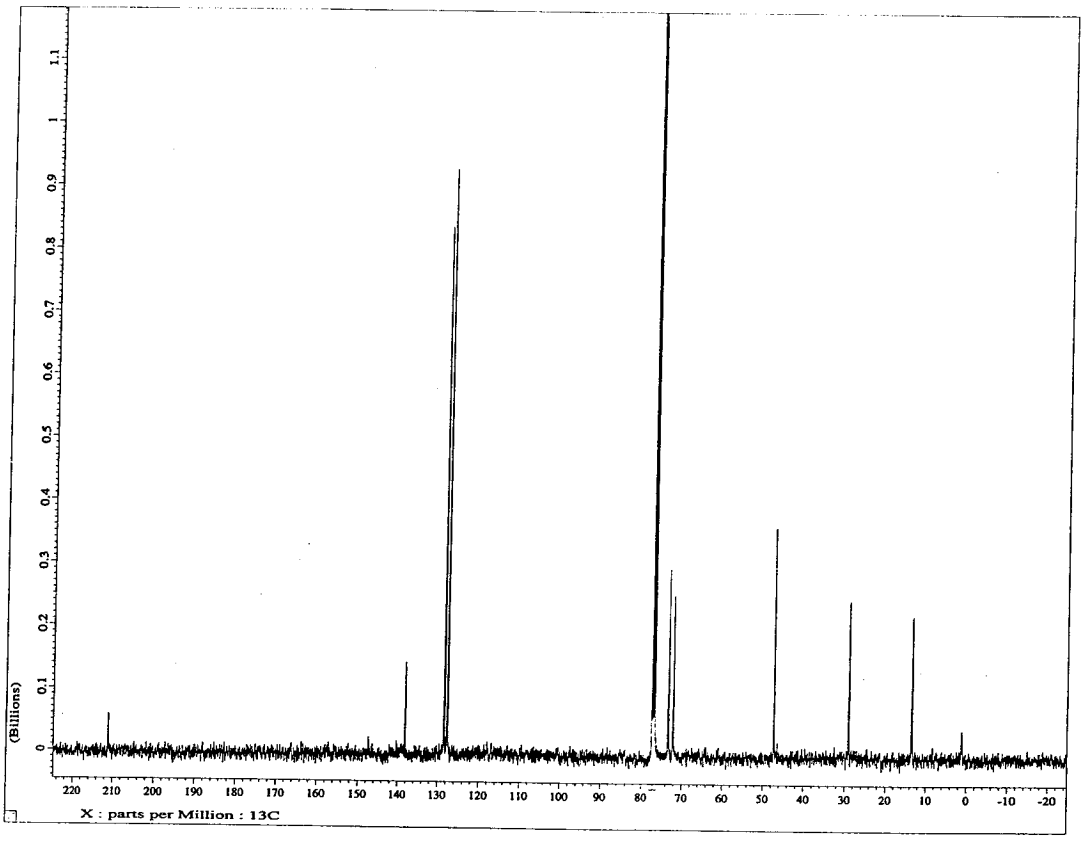

O
Ph
CH3
CH2OCH2C6H5
43
(Millions)
X : parts per Million : 1H


(Millions)
X : parts per Million : 13C


P-E
81.41
%T
26.55
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
O
Ph
CH3
CH2OCH2C6H5

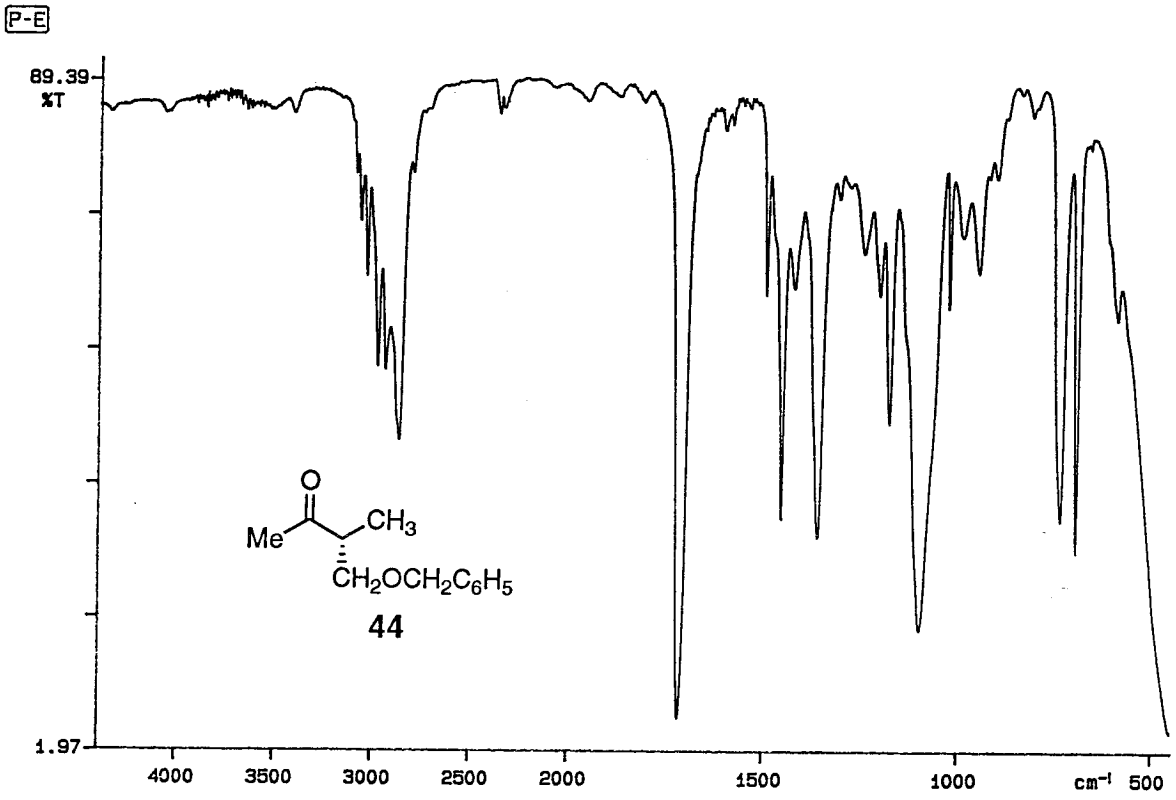
43


82.39
20.35
10.00
10.13
9.95
28.70
28.52
3.15
PPM

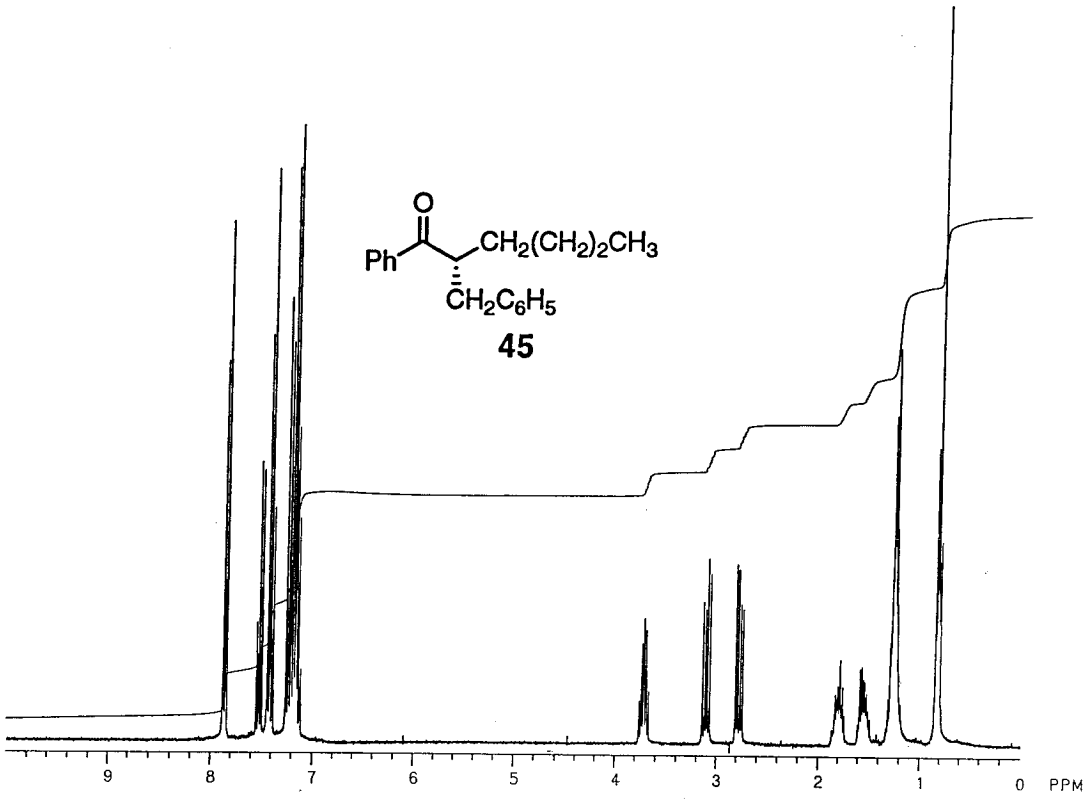

(Billions)
X : parts per Million : 13C

O
Me
CH3
CH2OCH2C6H5

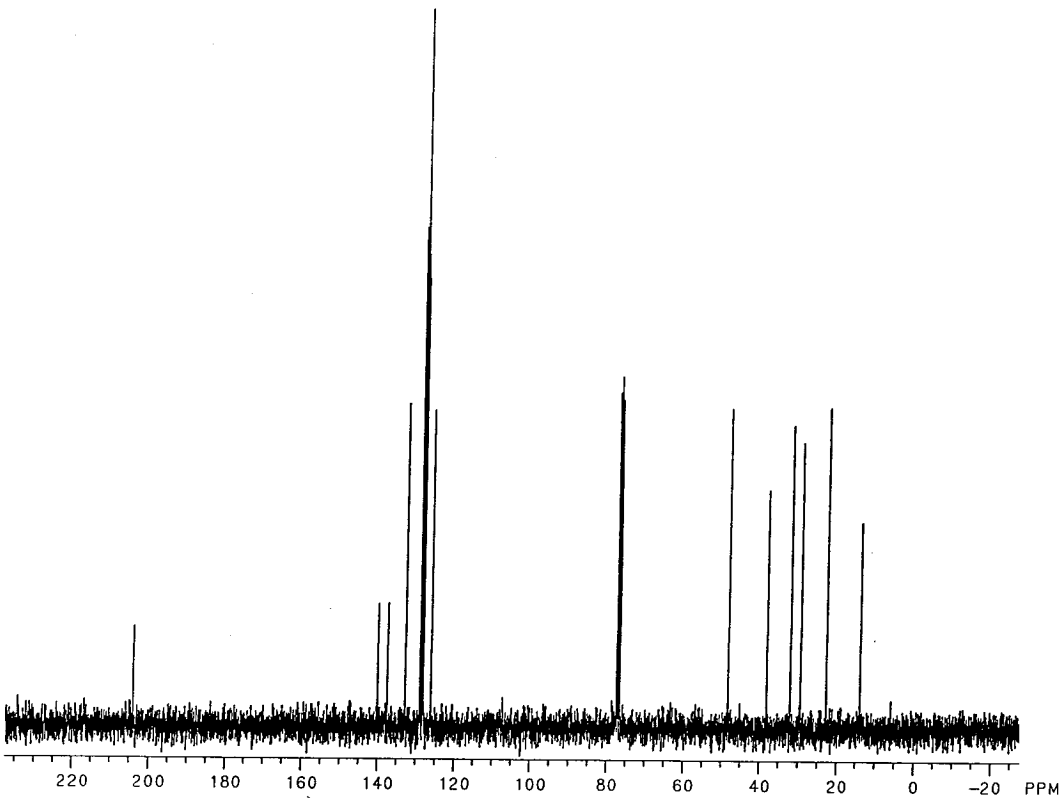
44

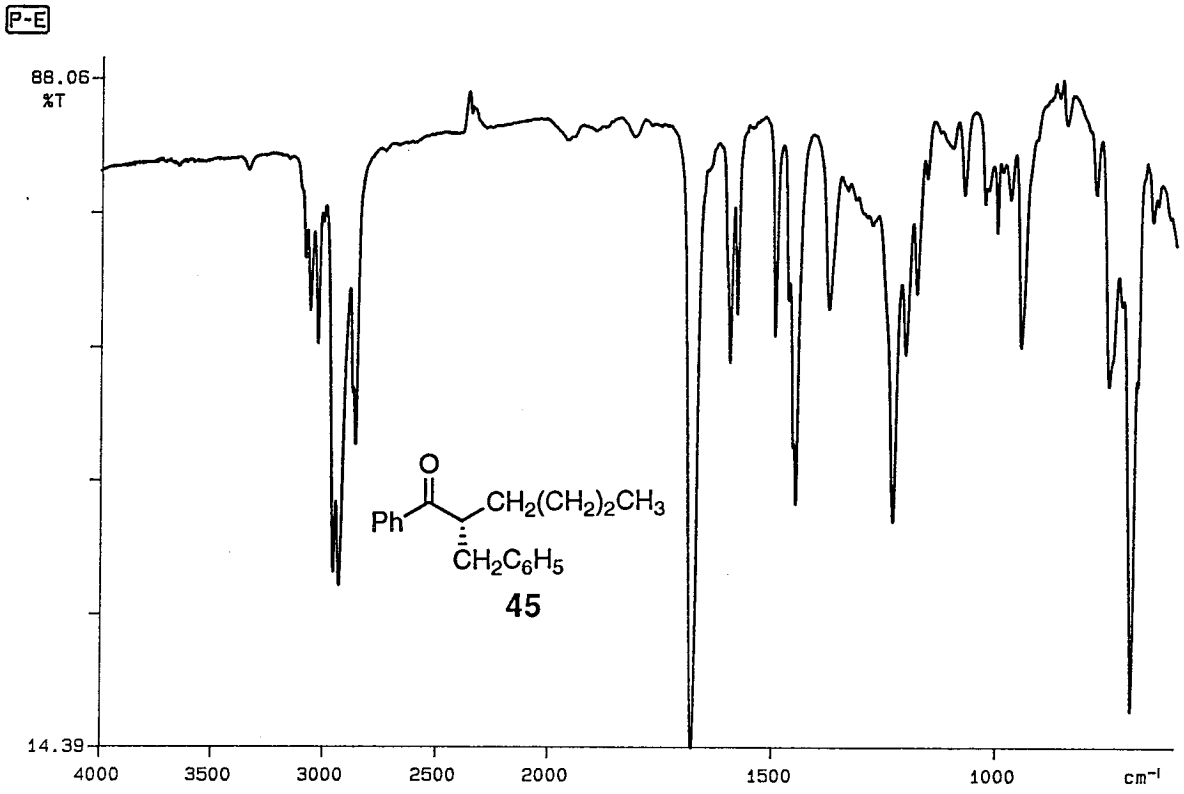

P-E
89.39
%T
1.97
4000
3500
3000
2500
2000
1500
1000
cm-1
500
O
Me
CH3
CH2OCH2C6H5

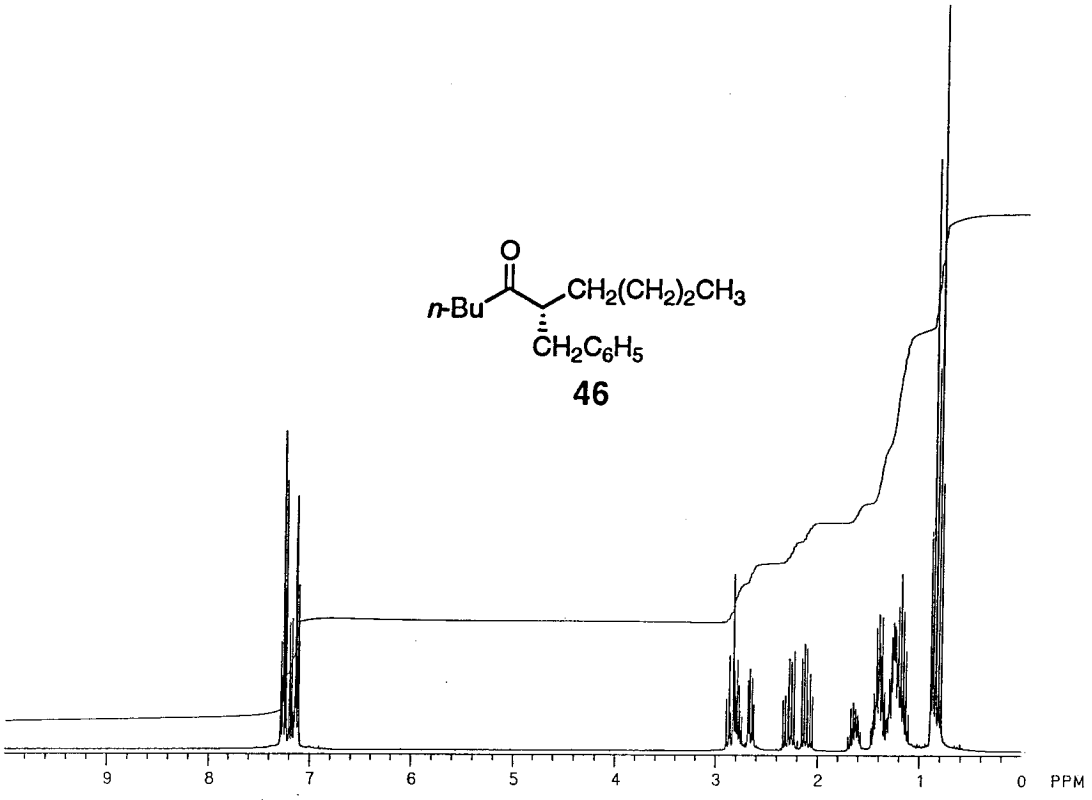
44


O
Ph
CH2(CH2)2CH3
CH2C6H5
9
8
7
6
5
4
3
2
1
0
PPM

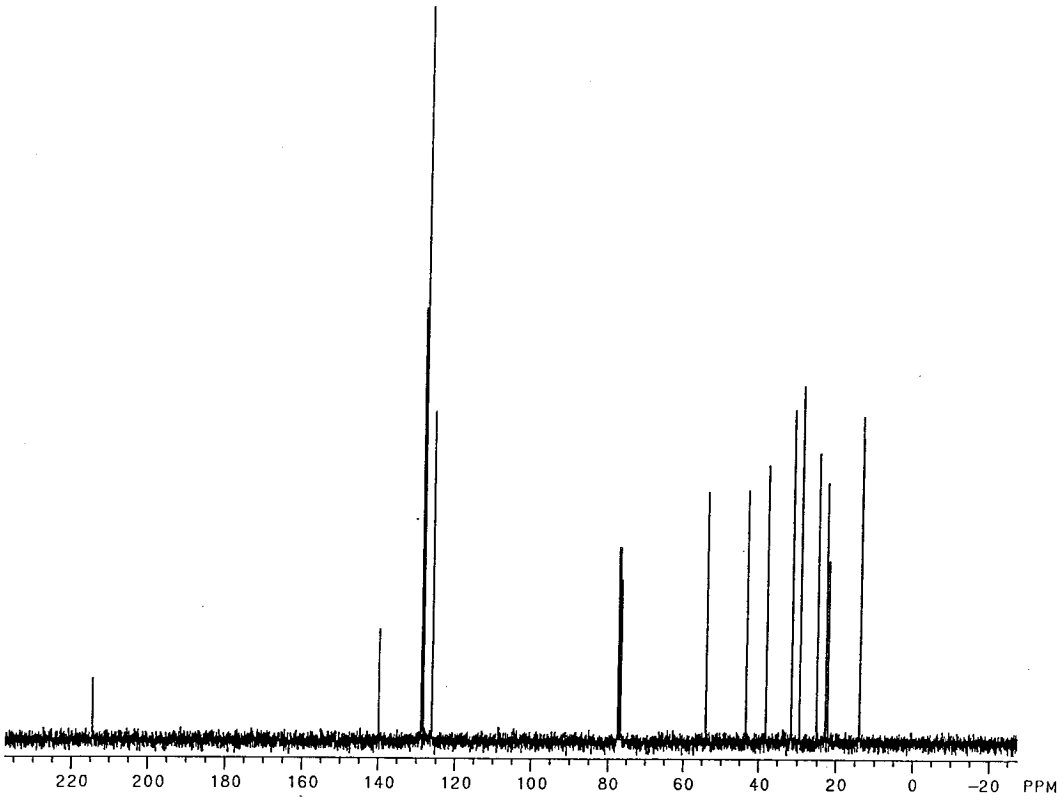
45

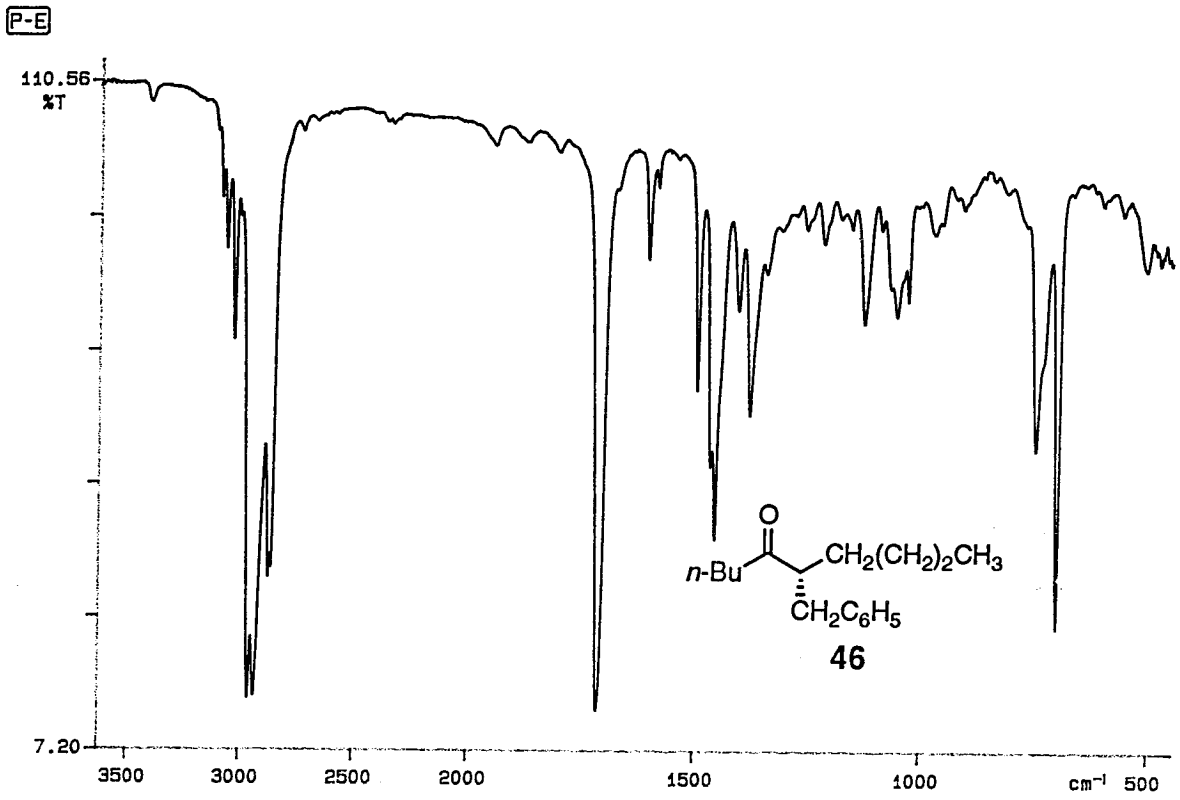

220
200
180
160
140
120
100
80
60
40
20
0
−20
PPM

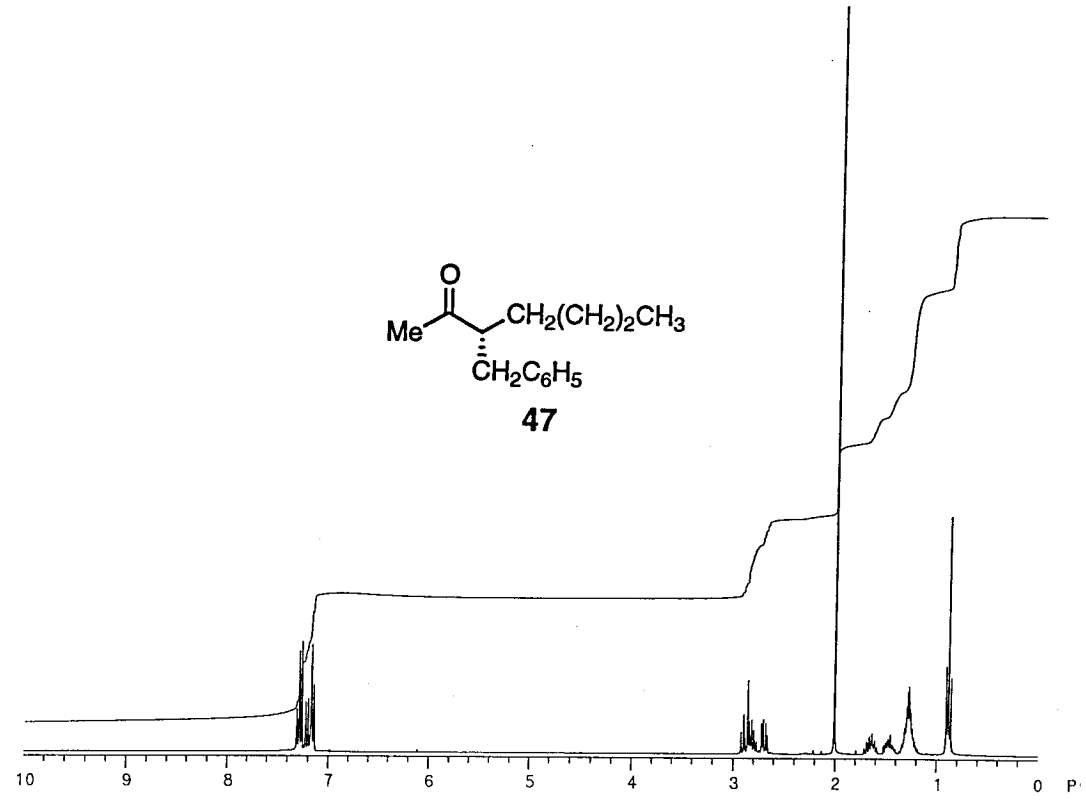

P-E
88.06
%T
14.39
4000
3500
3000
2500
2000
1500
1000
cm-1
O
Ph
CH2(CH2)2CH3
CH2C6H5
45

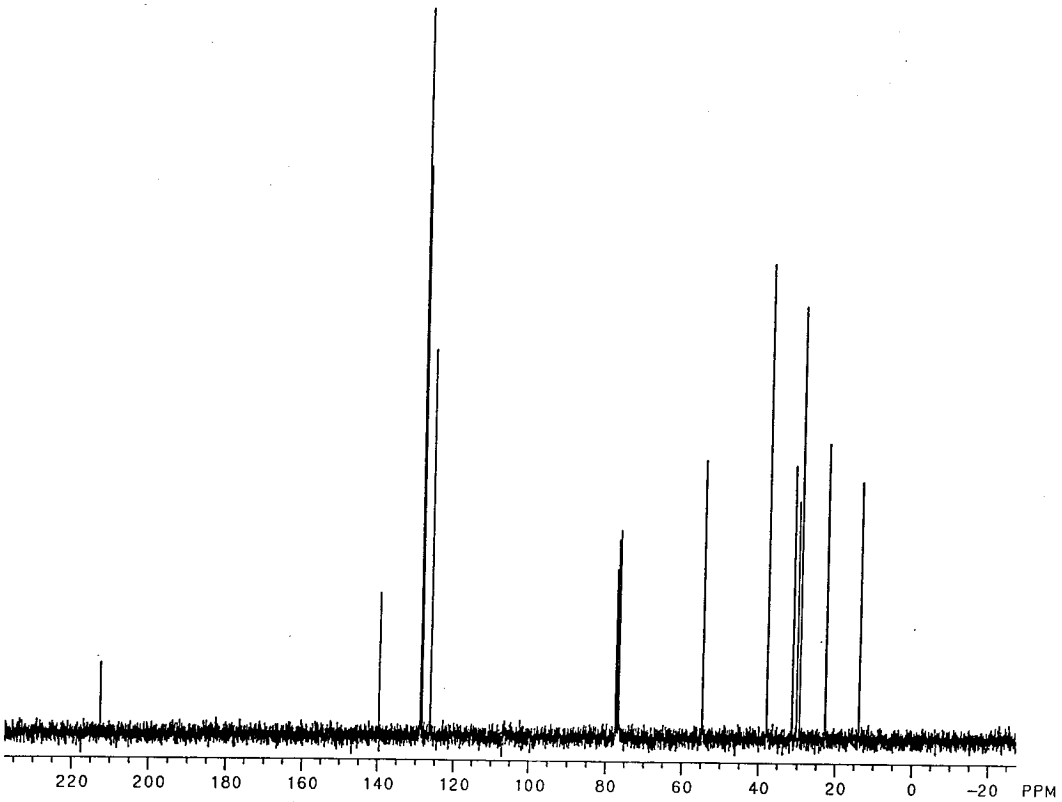

O
n-Bu
CH2(CH2)2CH3
CH2C6H5
9
8
7
6
5
4
3
2
1
0
PPM

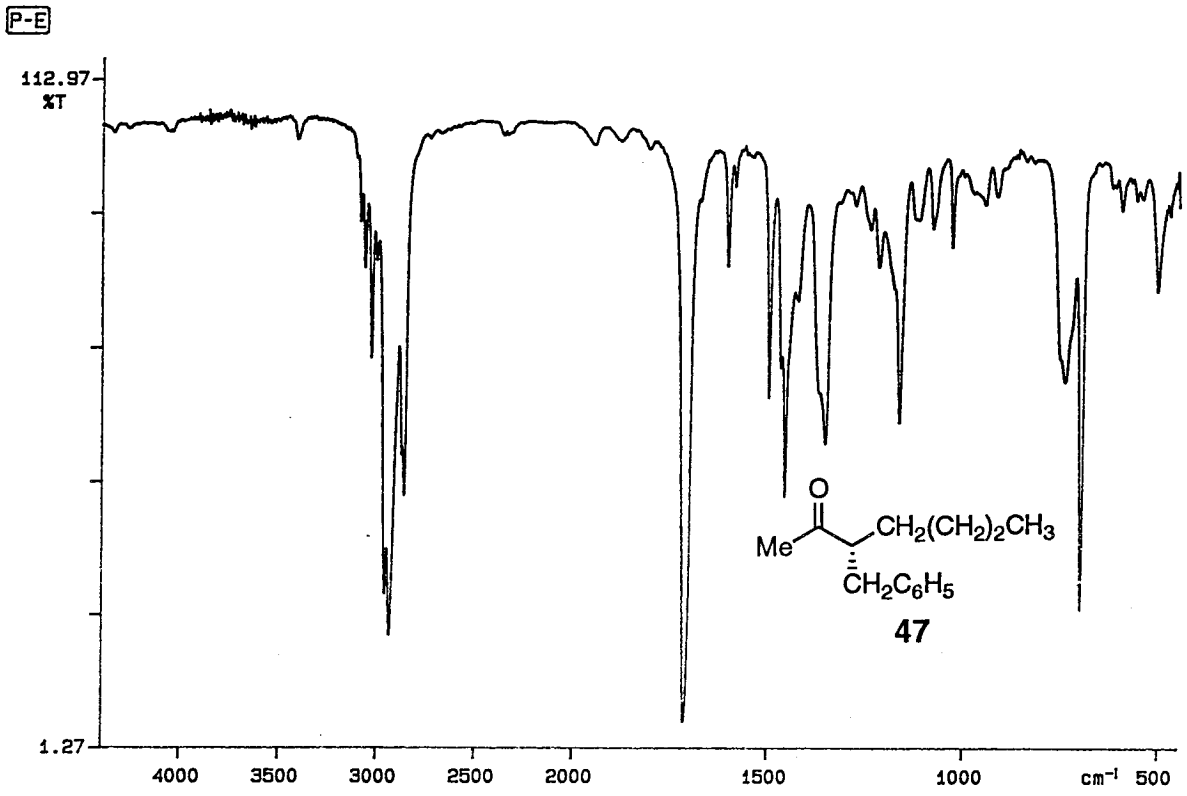
46


220
200
180
160
140
120
100
80
60
40
20
0
−20
PPM

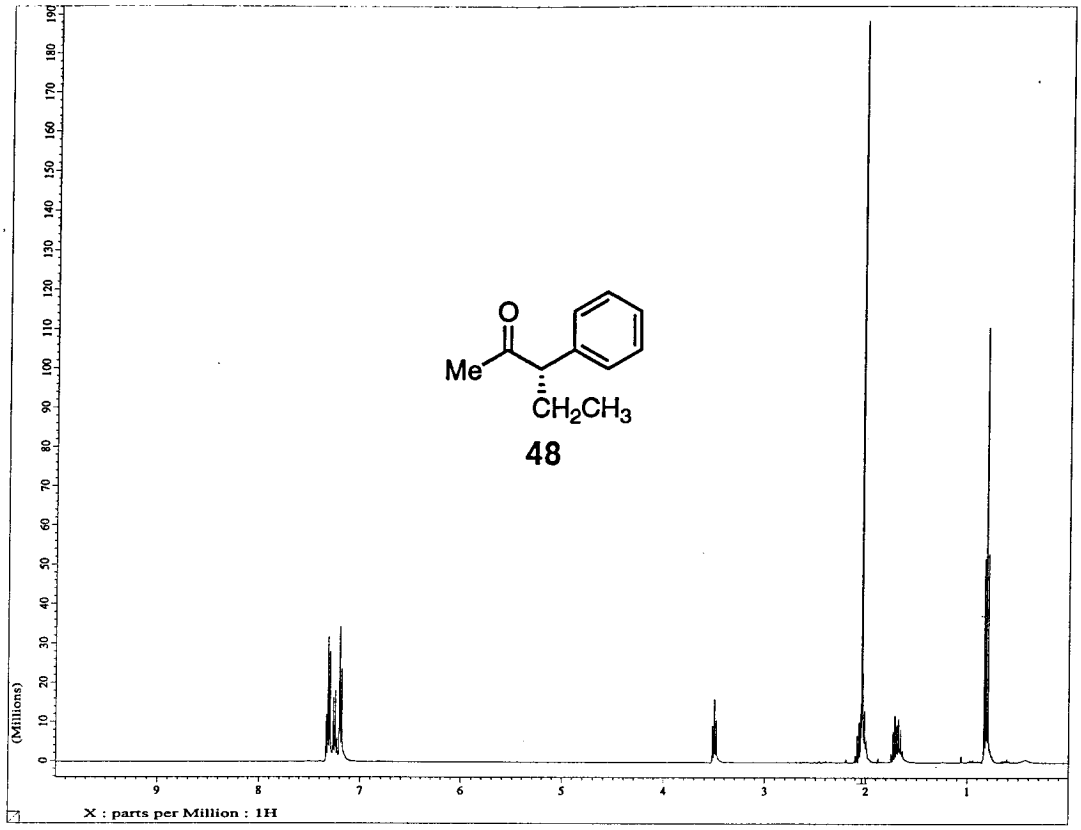

P-E
110.56
%T
7.20
3500
3000
2500
2000
1500
1000
cm⁻¹
500
O
n-Bu
CH2(CH2)2CH3
CH2C6H5
46

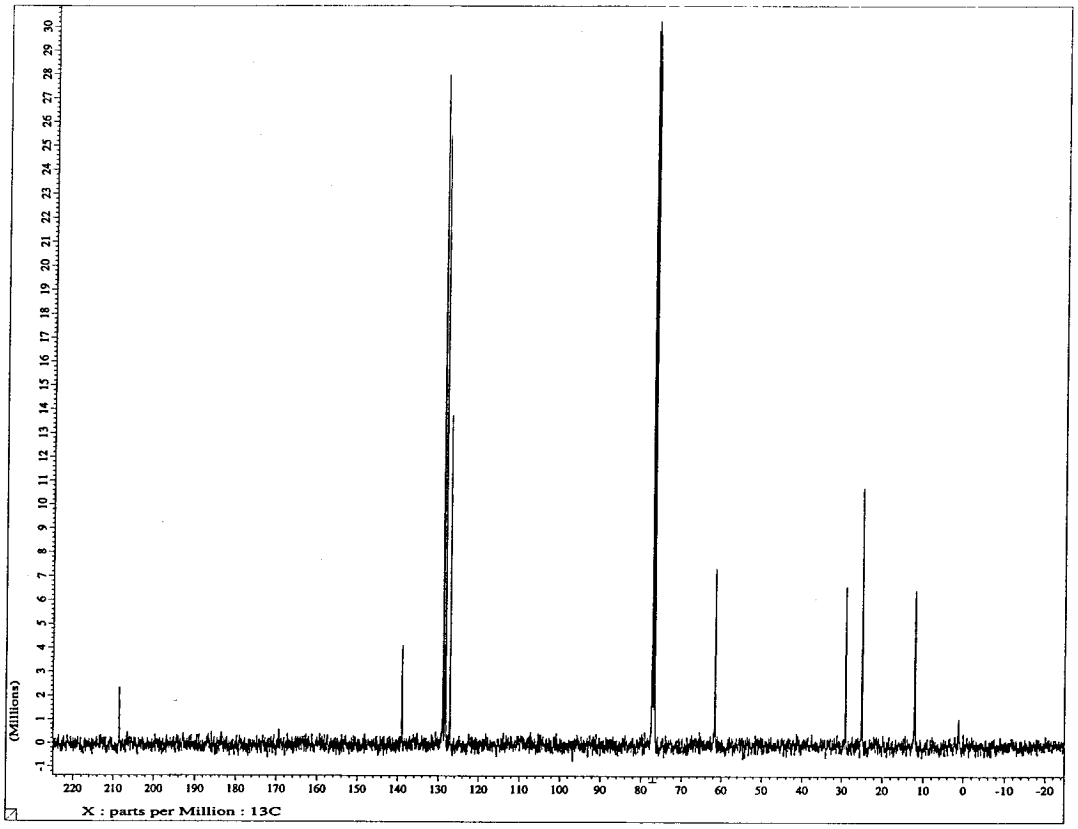

O
Me
CH2(CH2)2CH3
CH2C6H5
47
10
9
8
7
6
5
4
3
2
1
0
P

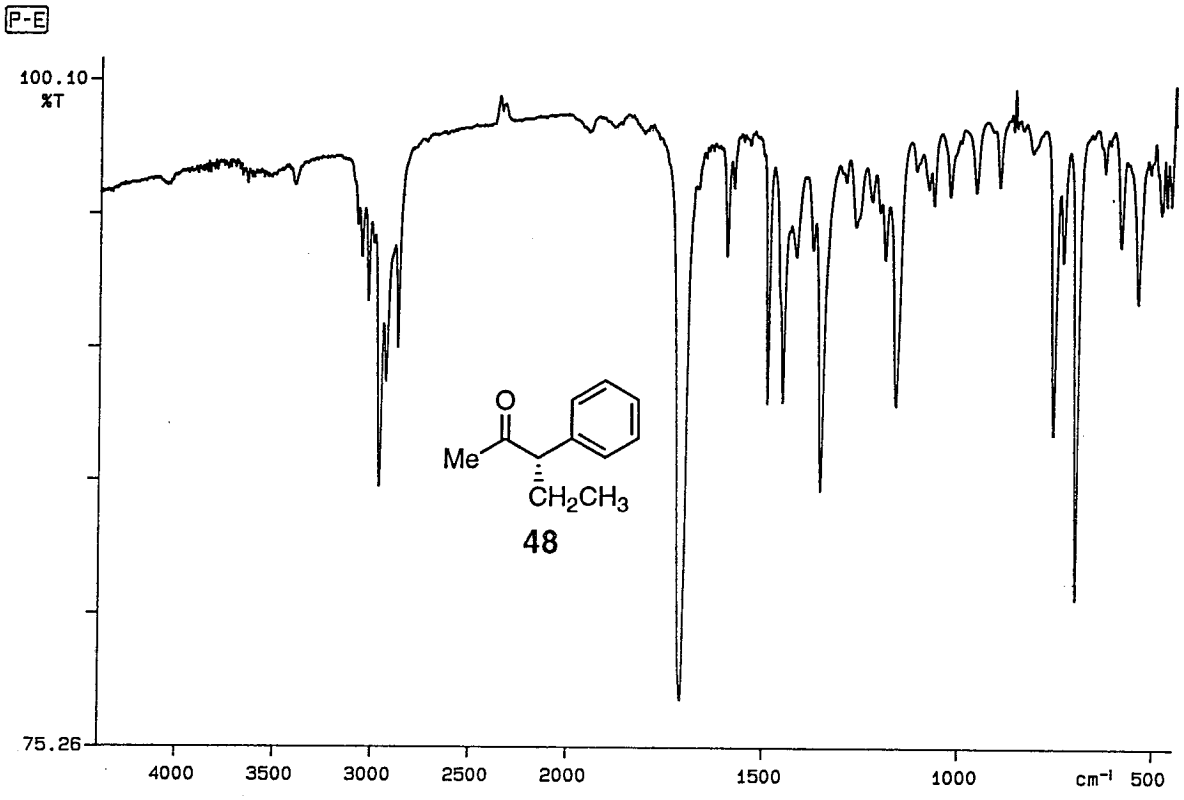

220
200
180
160
140
120
100
80
60
40
20
0
−20
PPM


P-E
112.97
%T
1.27
4000
3500
3000
2500
2000
1500
1000
cm-1
500
O
Me
CH2(CH2)2CH3
CH2C6H5

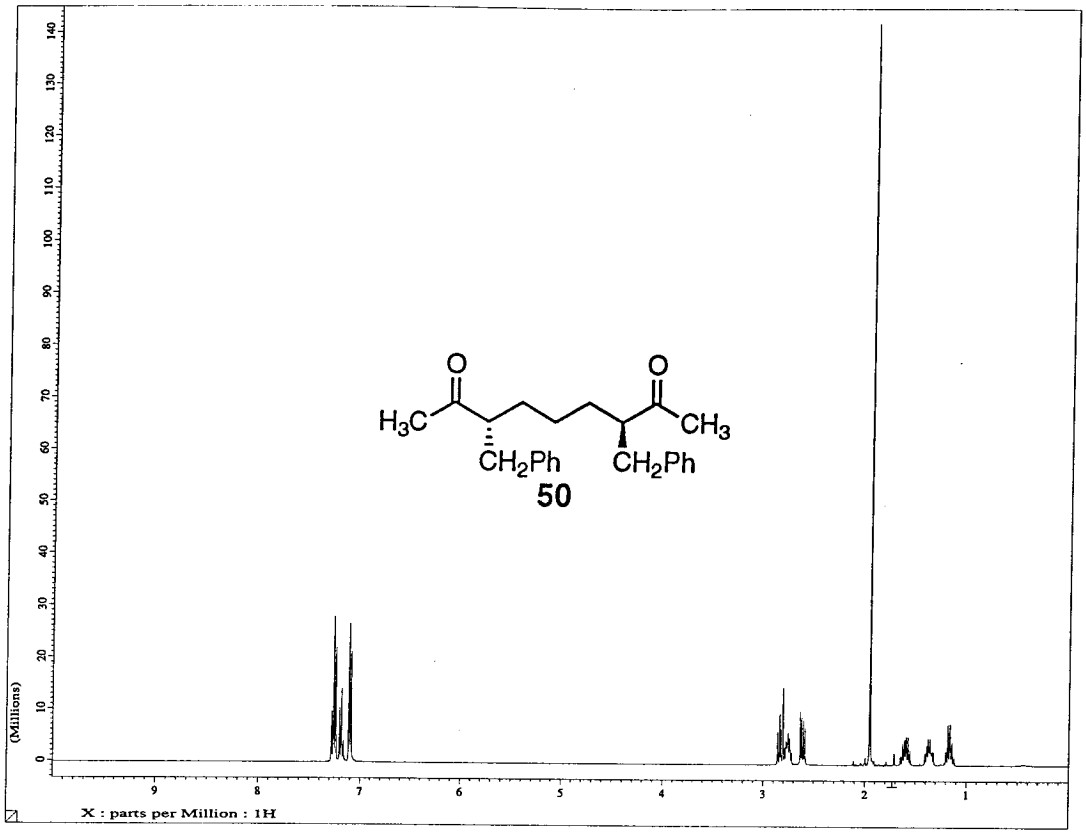
47

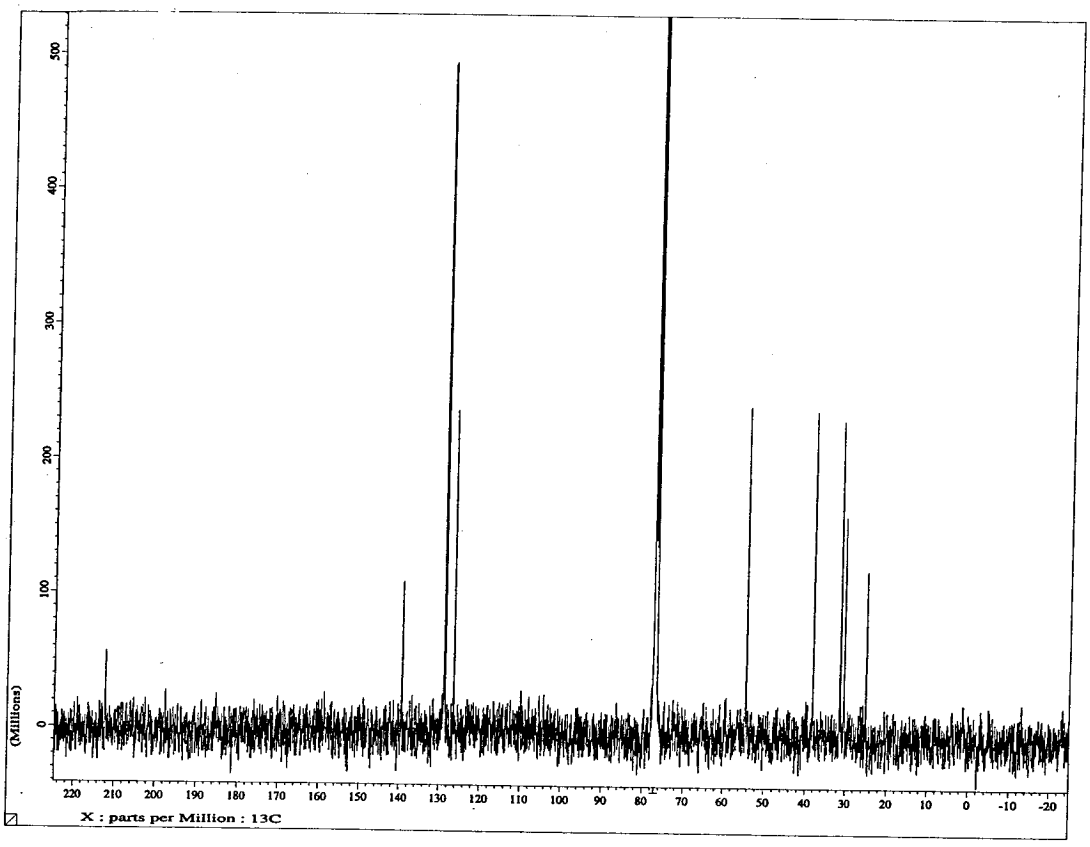

O
Me
CH2CH3
48
(Millions)
X : parts per Million : 1H

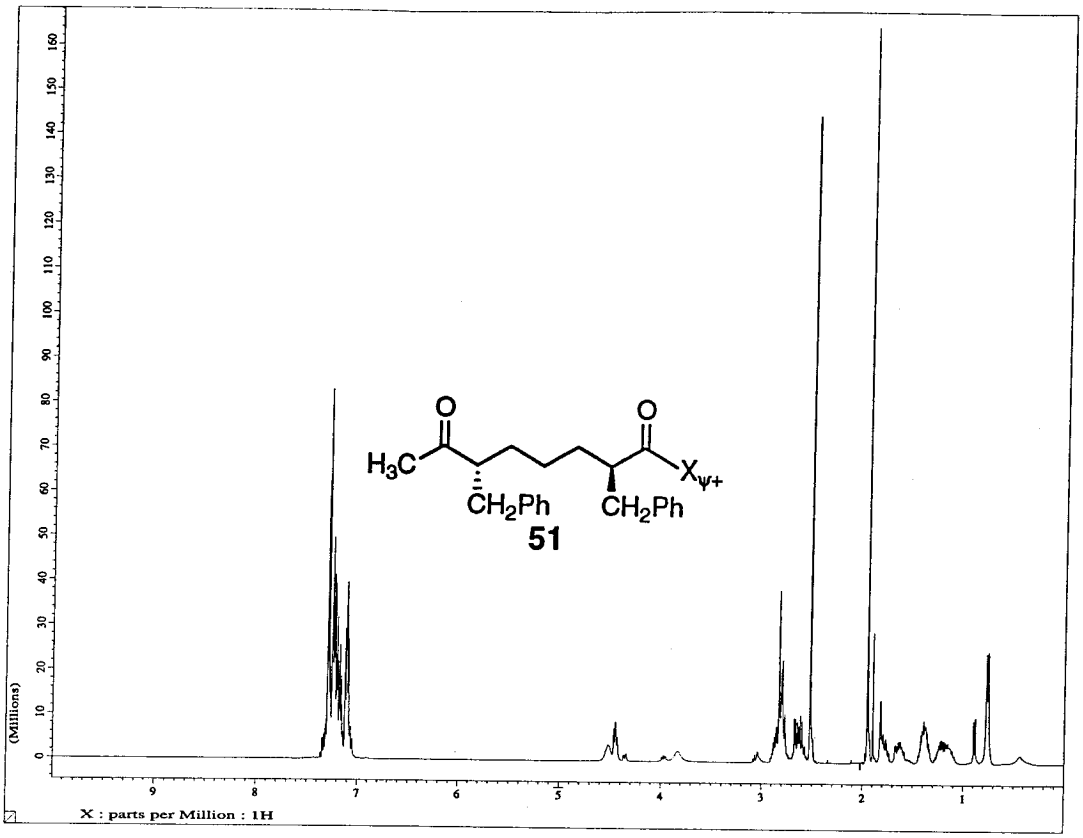

(Millions)
X : parts per Million : 13C

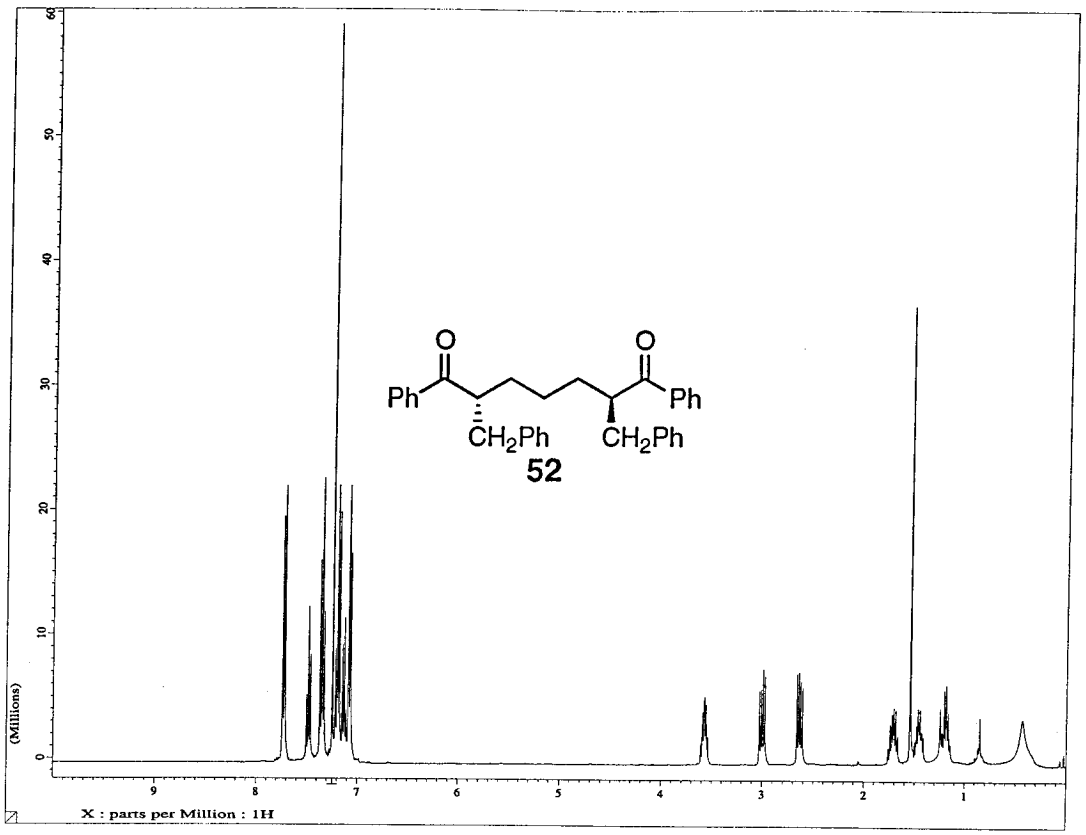

P-E
100.10
%T
75.26
4000
3500
3000
2500
2000
1500
1000
cm-1
500
O
Me
CH2CH3

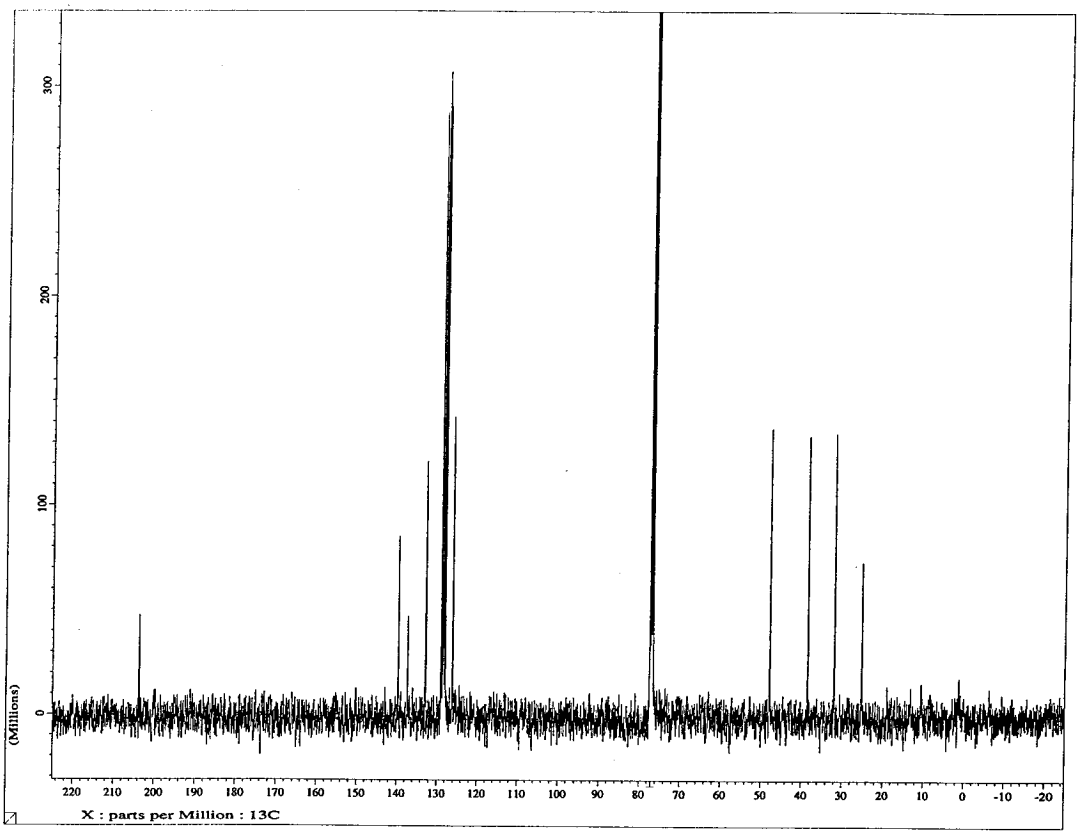
48

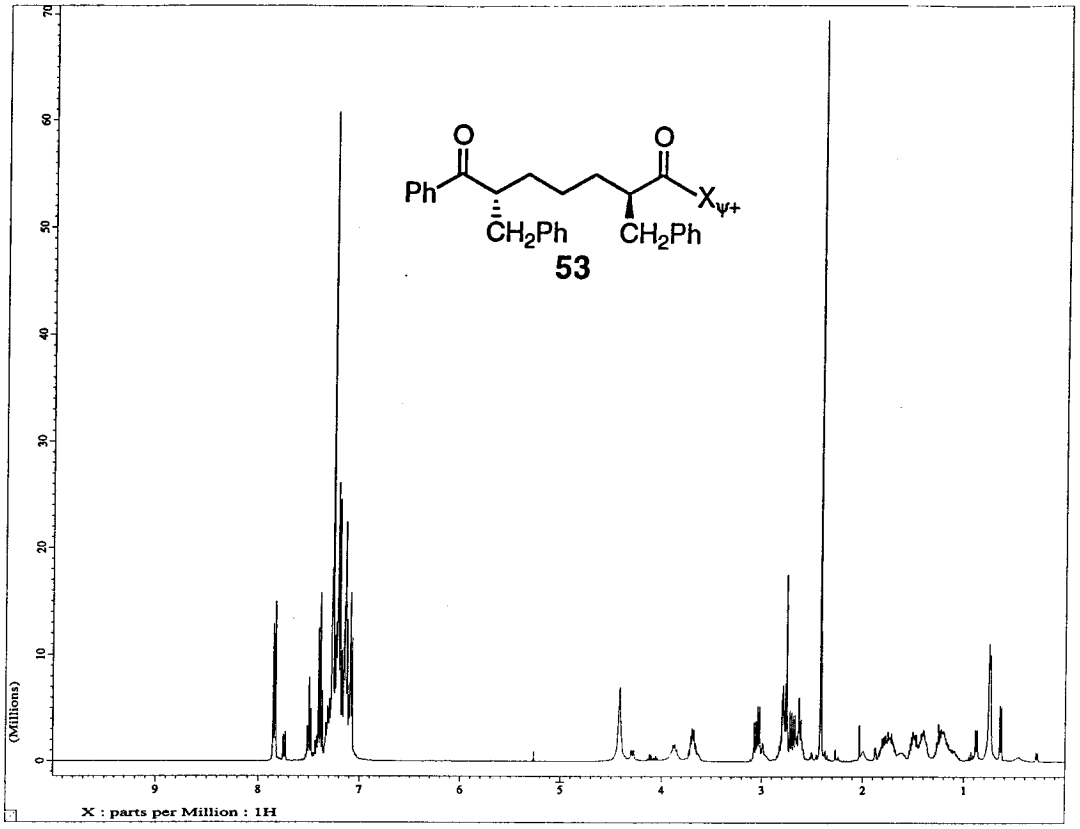

O
O
H3C
CH3
CH2Ph
CH2Ph
50
(Millions)
X : parts per Million : 1H

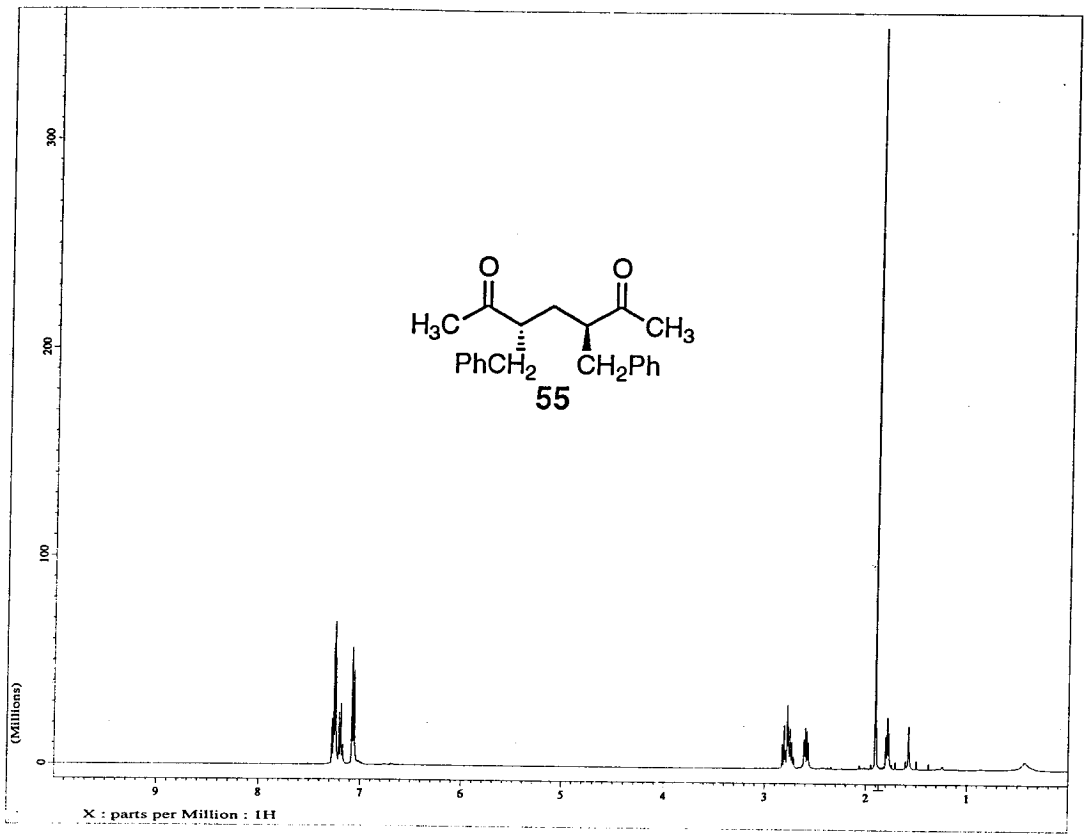

(Millions)
X : parts per Million : 13C

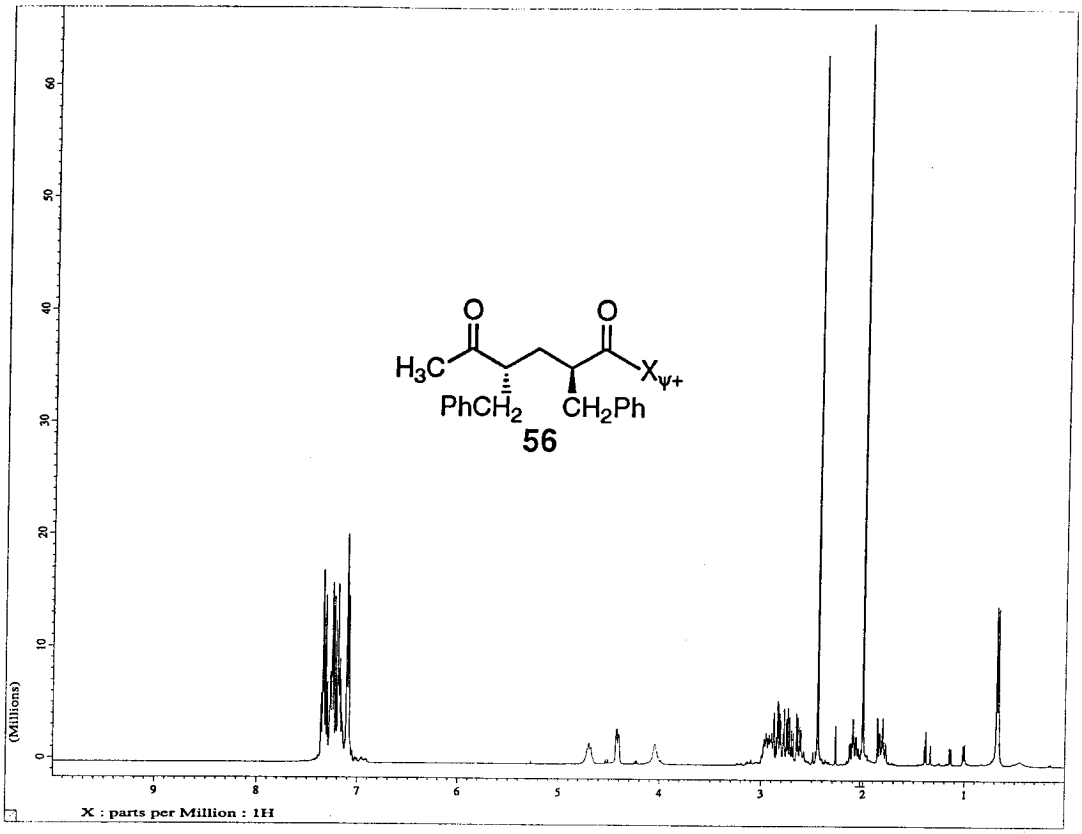

(Millions)
X : parts per Million : 1H
H3C
O
O
CH2Ph
CH2Ph
Xψ+
51

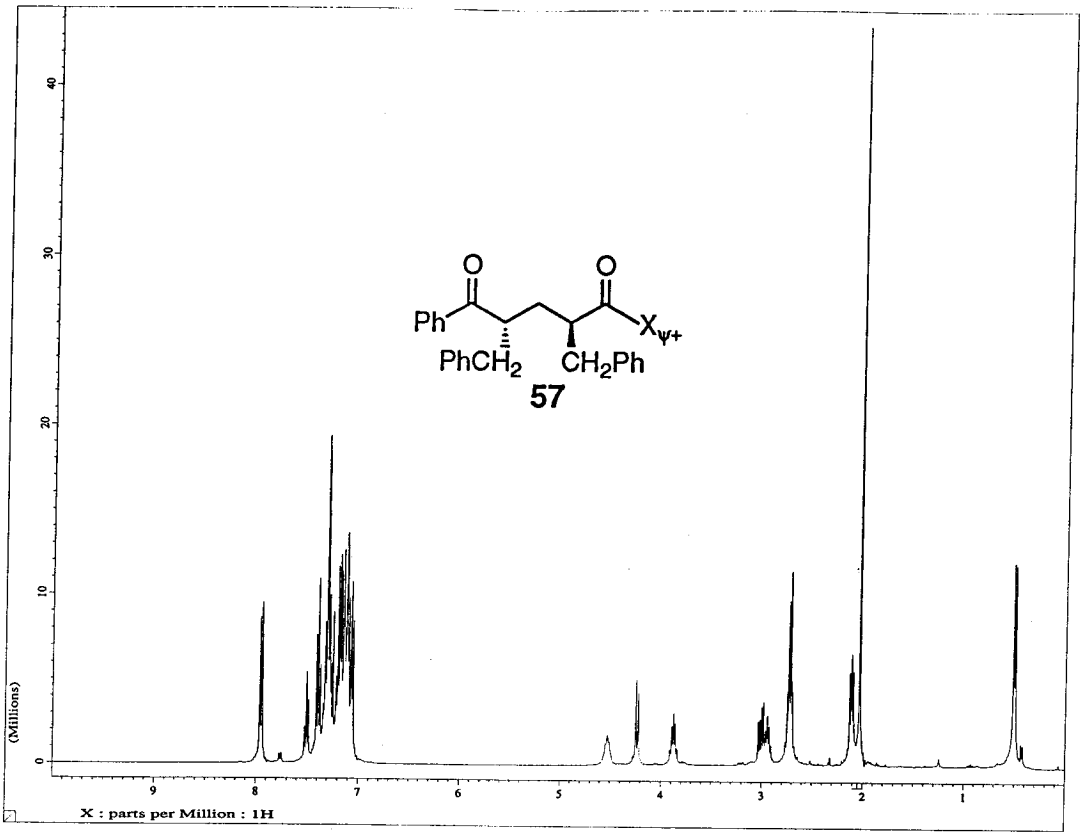

O
O
Ph
Ph
CH2Ph
CH2Ph
52
(Millions)
X : parts per Million : 1H

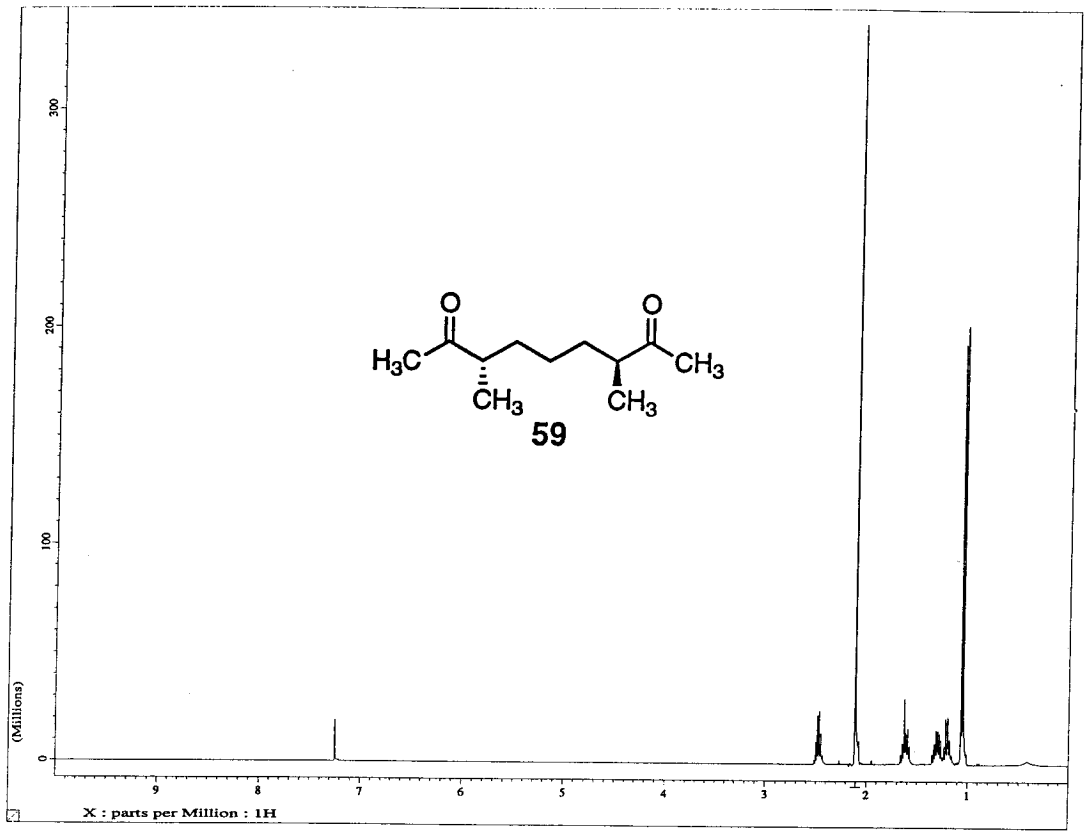

(Millions)
X : parts per Million : 13C

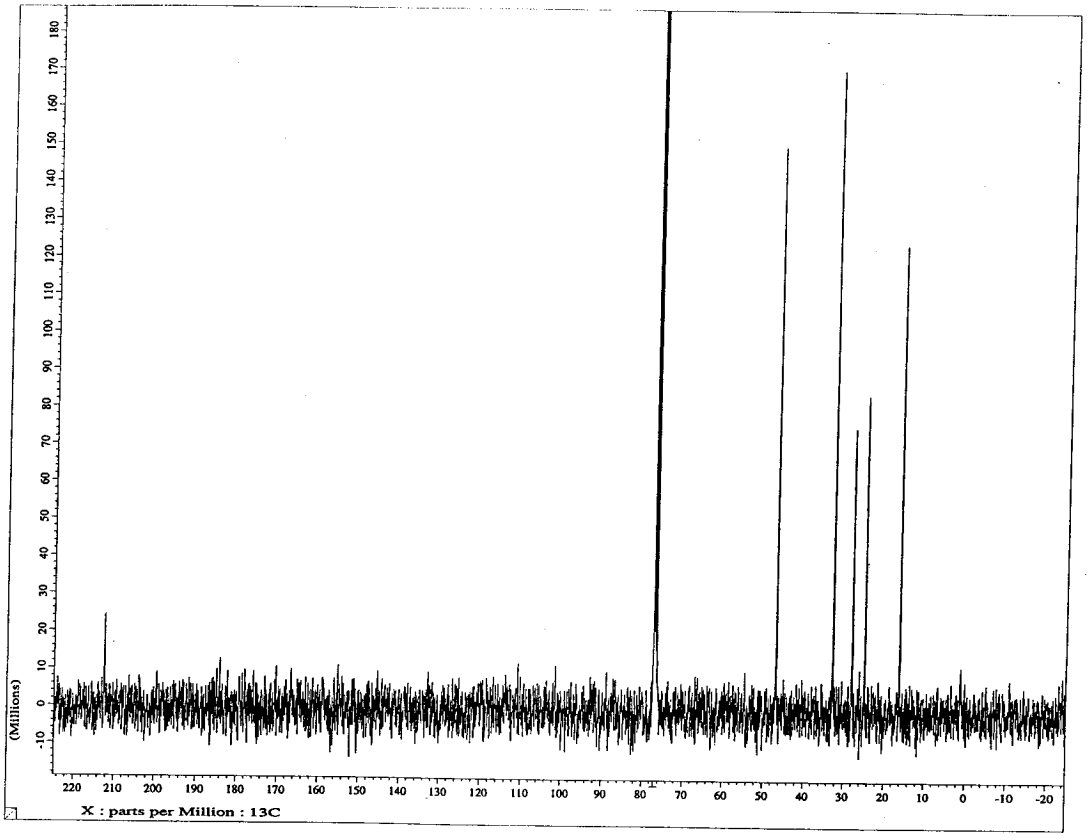

O
O
Ph
X$_{\psi+}$
CH$_2$Ph
CH$_2$Ph
53
(Millions)
X : parts per Million : 1H

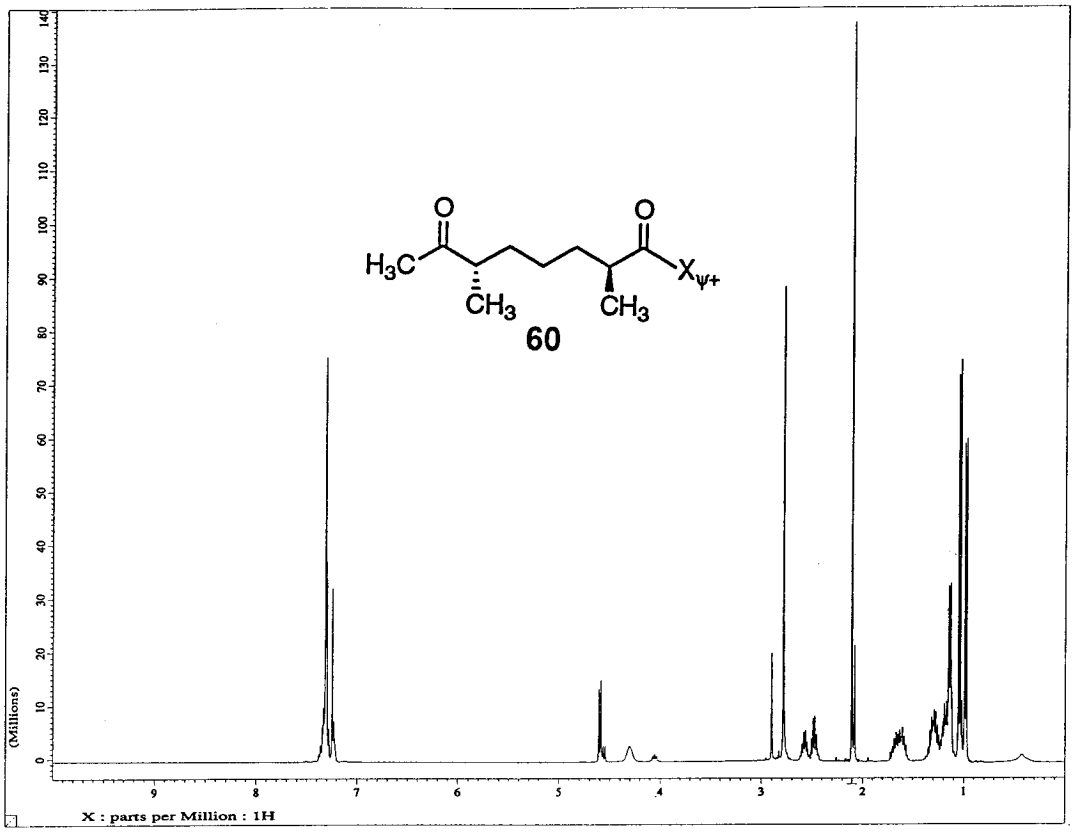

O
O
H3C
CH3
PhCH2
CH2Ph
55
(Millions)
300
200
100
0
9
8
7
6
5
4
3
2
1
X : parts per Million : 1H

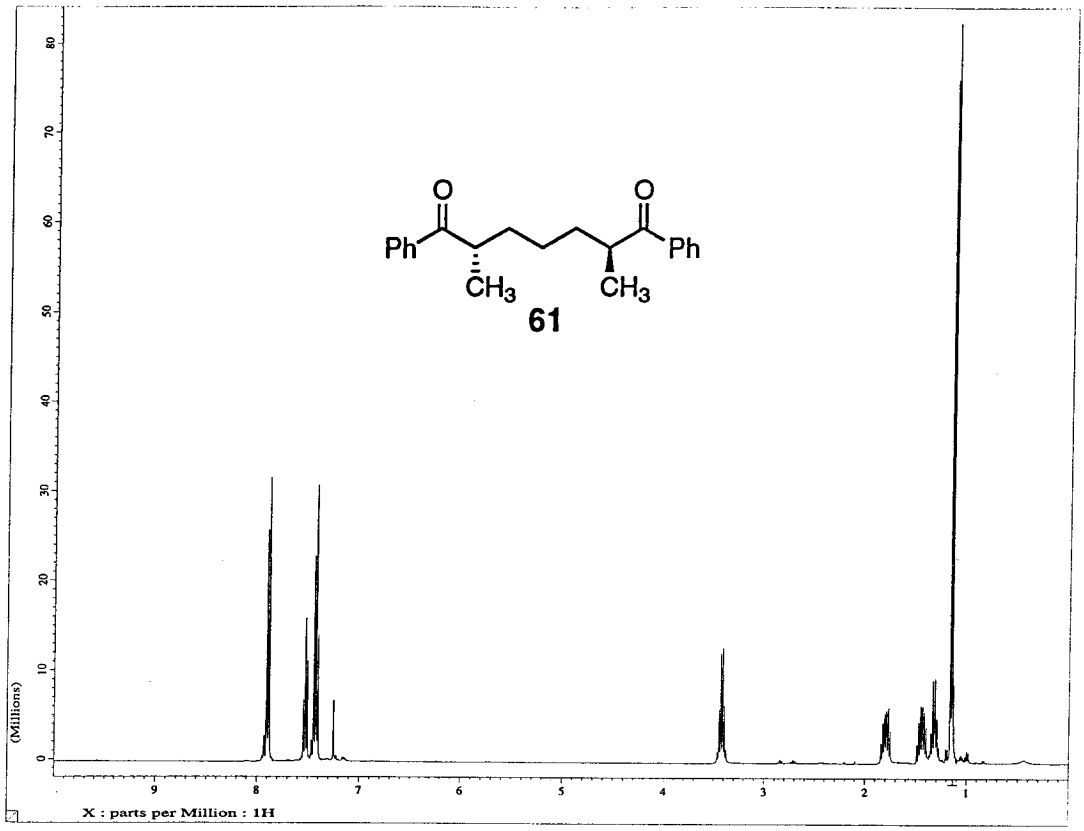

O
O
H3C
Xψ+
PhCH2
CH2Ph
56
(Millions)
60
50
40
30
20
10
0
9
8
7
6
5
4
3
2
1
X : parts per Million : 1H

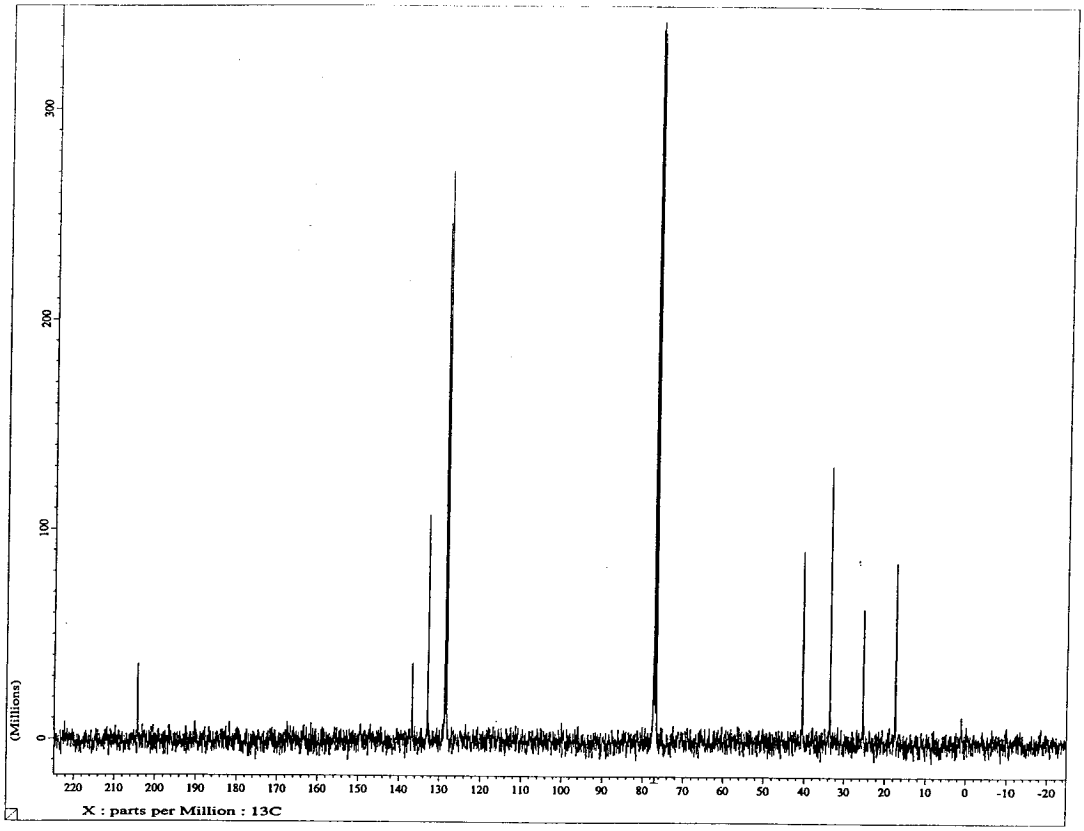

Ph
PhCH2
CH2Ph
Xψ+
57
(Millions)
X : parts per Million : 1H

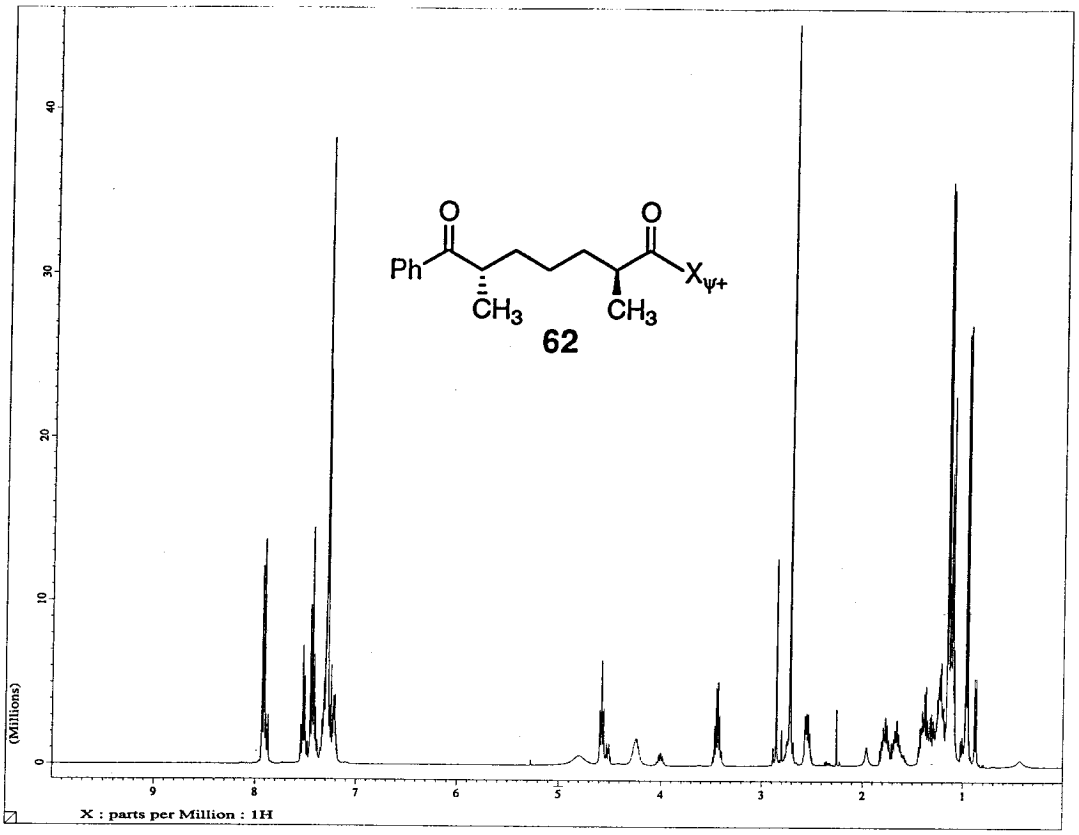

O
O
H3C
CH3
CH3
CH3
59
(Millions)
X : parts per Million : 1H

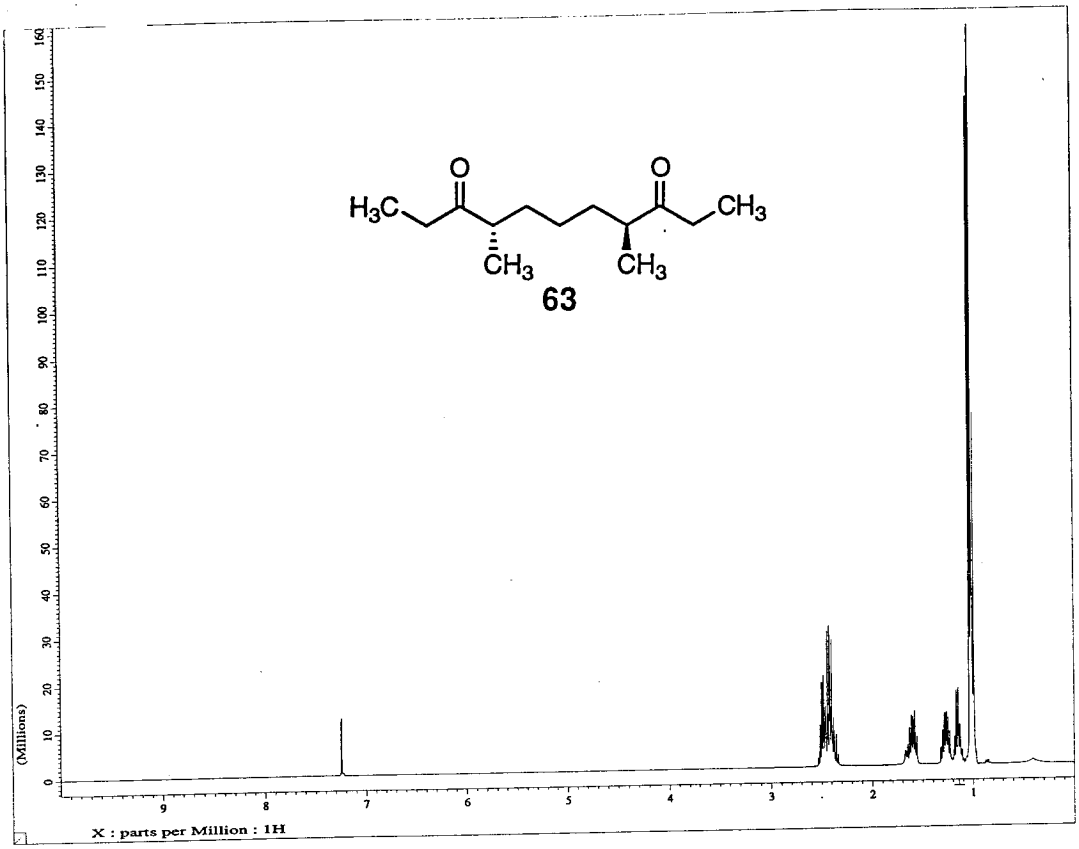

(Millions)
X : parts per Million : 13C


O
O
H3C
CH3
CH3
Xψ+
60
(Millions)
X : parts per Million : 1H

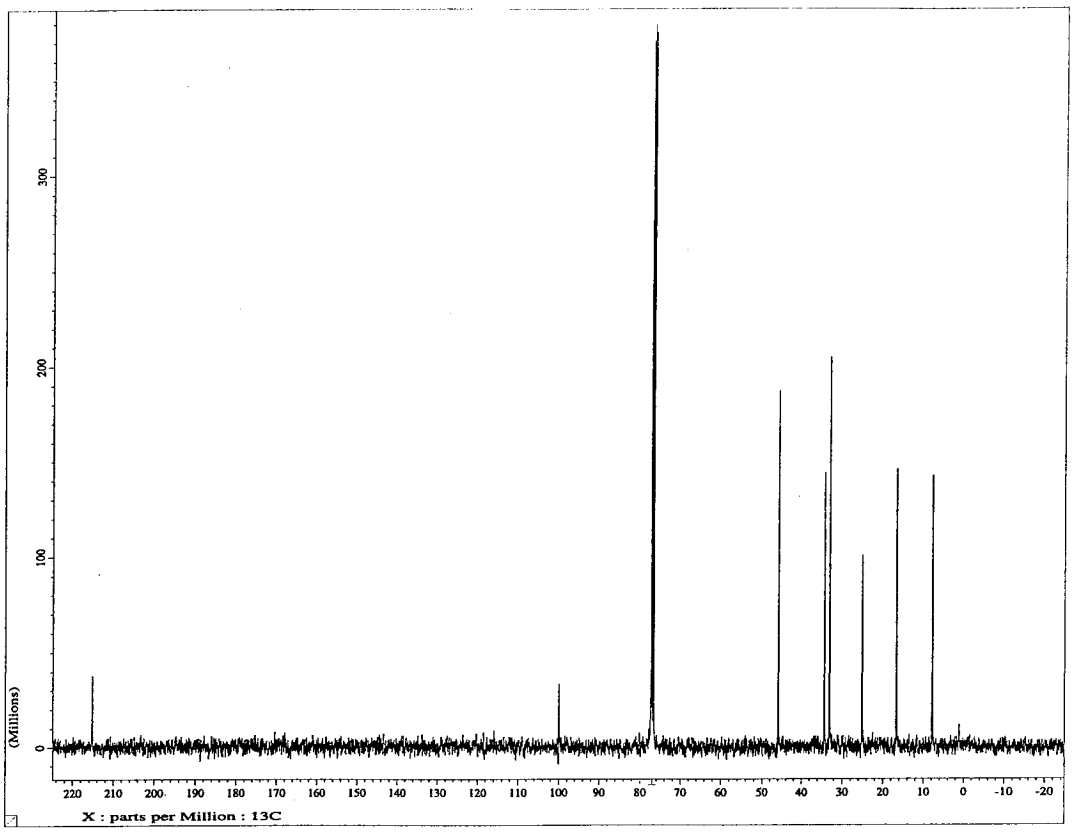

O
O
Ph
Ph
CH3
CH3
61
(Millions)
X : parts per Million : 1H

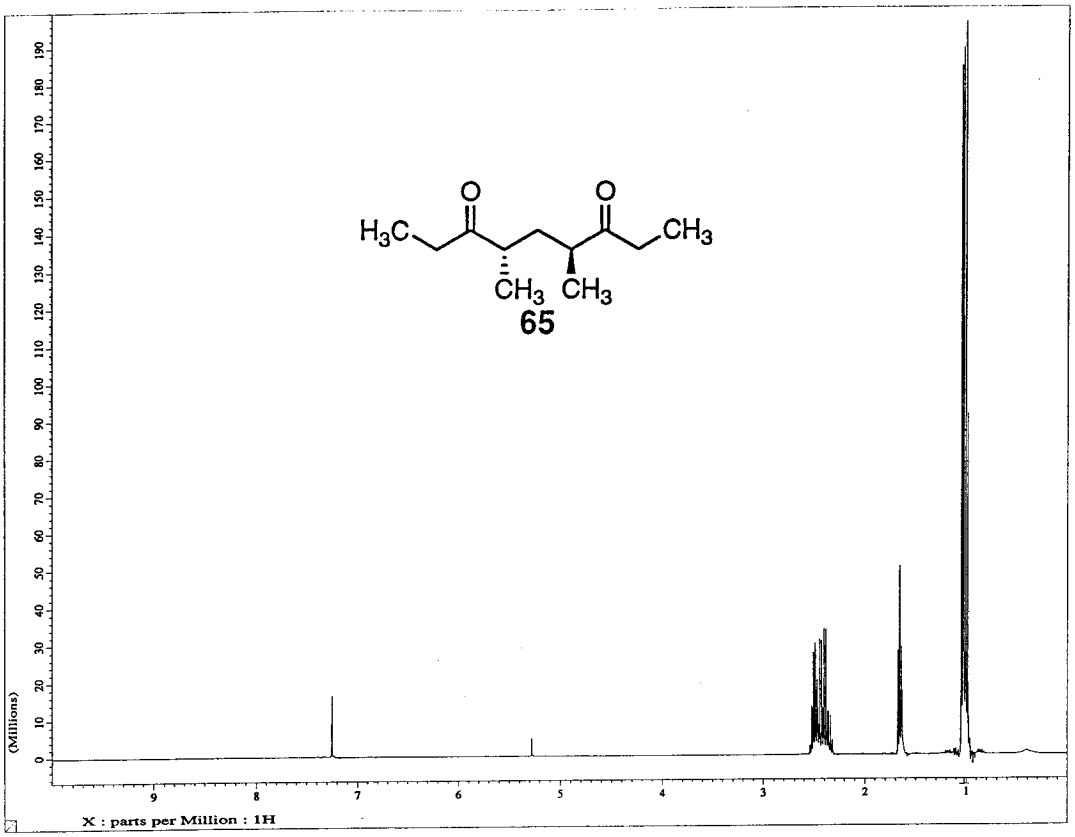

(Millions)
X : parts per Million : 13C

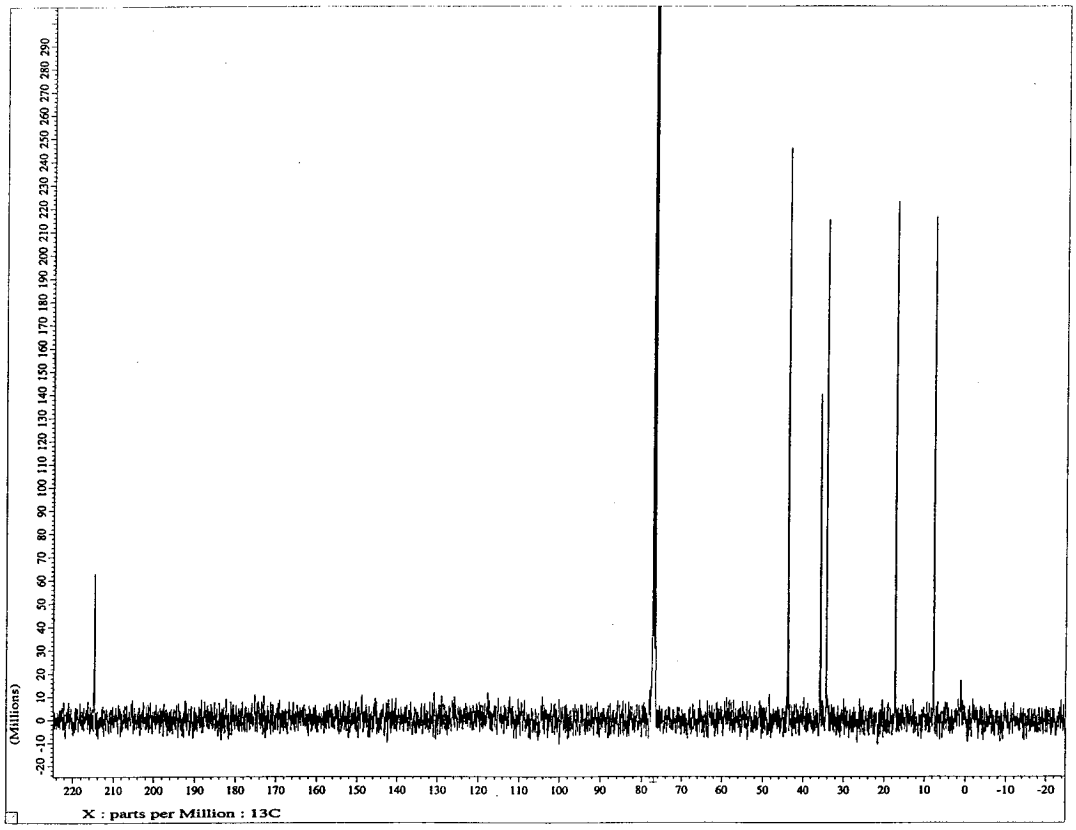

O
O
Ph
CH3
CH3
Xψ+
62
(Millions)
40
30
20
10
0
9
8
7
6
5
4
3
2
1
X : parts per Million : 1H

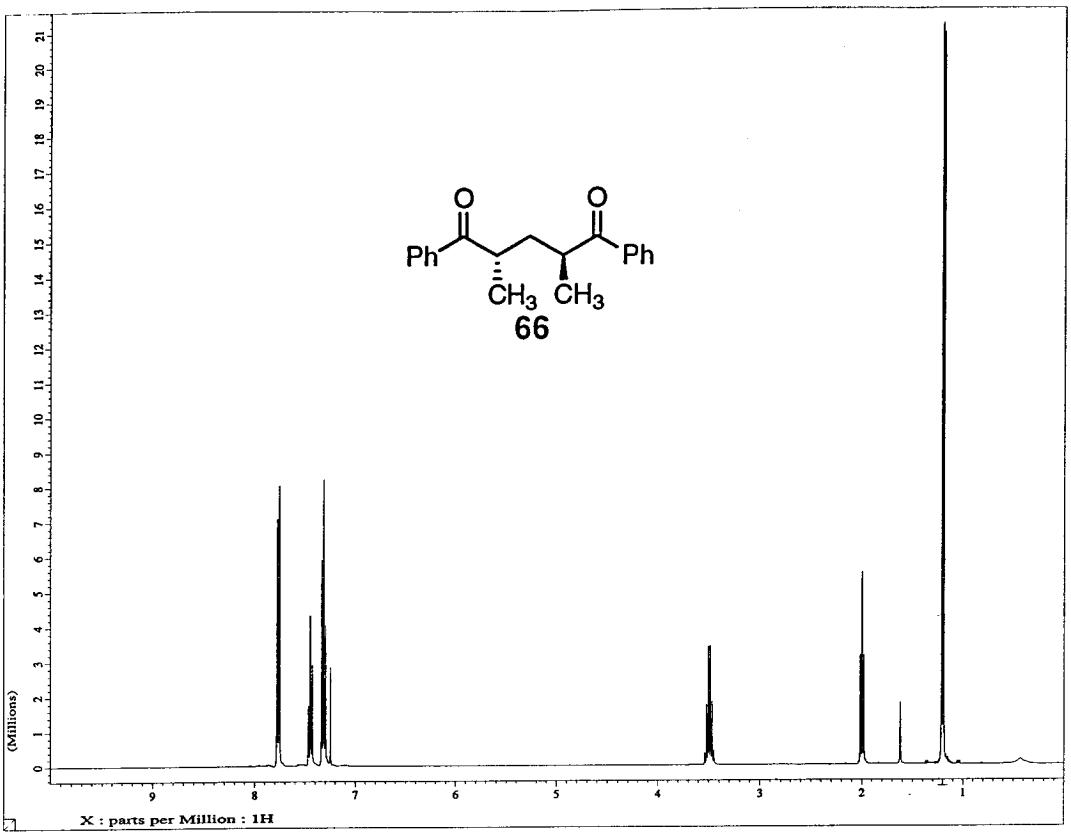

O
O
H3C
CH3
CH3
CH3
(Millions)
X : parts per Million : 1H

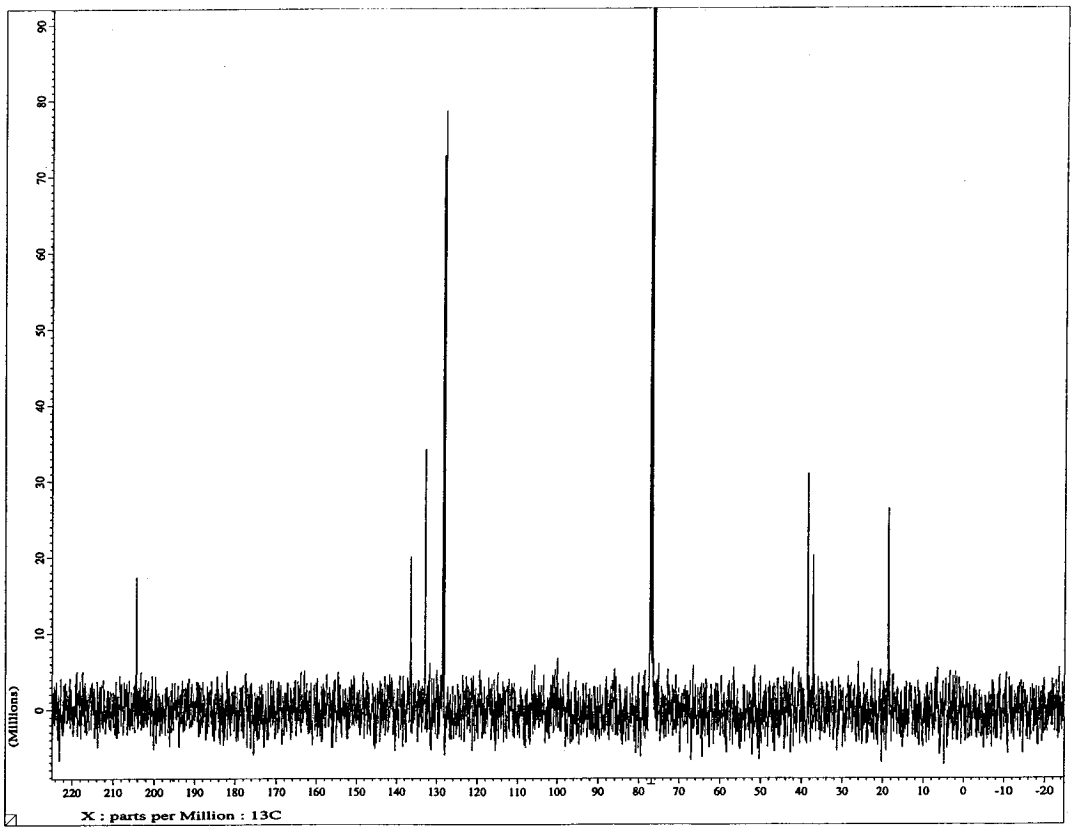
63

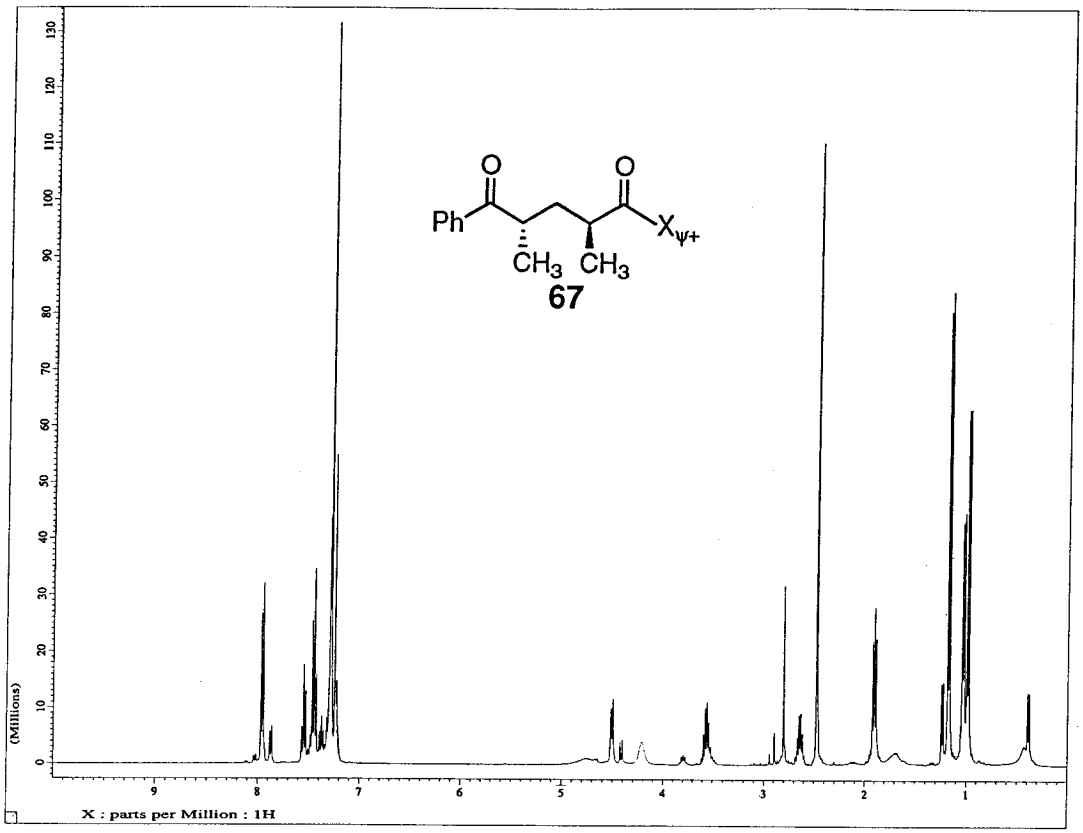

(Millions)
X : parts per Million : 13C


O
O
H3C
CH3
CH3
CH3
65
(Millions)
X : parts per Million : 1H


(Millions)
X : parts per Million : 13C


Ph
Ph
CH3 CH3
66
(Millions)
X : parts per Million : 1H


(Millions)
X : parts per Million : 13C


O
O
Ph
X
CH3 CH3
67
(Millions)
X : parts per Million : 1H