Use of Pseudoephedrine as a Practical Chiral Auxiliary for Asymmetric Synthesis

Thesis by

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In Partial Fulfillment of the Requirements

for the Degree of

Doctor of Philosophy

California Institute of Technology

Pasadena, California

1997

(Submitted March 3, 1997)

Acknowledgments

I am indebted to a great many people who were instrumental in the completion of this thesis. Great thanks go to Professor Andy Myers for the professionalism, enthusiasm, advice, and encouragement he provided as my mentor, and for the creativity, knowledge, and scholarship he offered as my research director. I am also grateful for the chance to work on a methodology project which has been challenging and instructive, yet is practical and broadly useful. I know that not everyone gets a second chance, and I feel fortunate for the opportunity I was given.

It has been an honor to work alongside a number of talented co-workers. I especially must thank my classmate Tommy Chen, who has worked closely with me for over four years. Apart from his invaluable collaborative assistance, I have also benefited from the good cheer he maintains through even the worst of times, as well as all the times he willingly helped me carry solvents. I benefited from many stimulating discussions with Steve Goldberg during our two plus years of working back-to-back. I also thank Jim Gleason and Mike Kort for being excellent instructors at our problem sessions, and Steve Arvedson for the great times we had both in lab and with CBB. Special thanks also go to former Myers group members Brad, Dave Madar, Shin, Kevin, Pete, Elaine, Nat, Mark, Dave Gin, Marlys, and Susan, as well as to present group members Lydia, Norma, Cindy, Mike, Dave, Dan, Mo and Jun for their advice and friendship over the years. I also thank Erick Carreira and his research group for many helpful discussions, and Mike Abrams and Professor John Bercaw for providing us with the neopentyllithium used in our studies of LAB.

Professor Charles L. Perrin was my first organic chemistry professor, and I'm grateful for the chance I had to work in his lab at UCSD. His scholarship and enthusiasm for chemistry remains an inspiration to me. I thank his former students Tammy, John, Kathy, Rich, Miles, Jennifer, Marcey, and Lee. I also thank Erik Sorensen for sharing with me his passion for organic synthesis.

This work would not have been completed without the love and support provided by my mother, father, and brother, and so it is to them that I dedicate this work.

I thank God for my close friends Chris Lee and Mark Yee, who were like brothers to me through thick and thin, and for other AACFers Ed, Naoki, Eileen, and Angela for their encouragement that helped me reach this point.

Finally, I would like to thank the NSF for a predoctoral fellowship.

Abstract

The use of pseudoephedrine as a practical chiral auxiliary for asymmetric synthesis is described. Both enantiomers of pseudoephedrine are inexpensive commodity chemicals and can be *N*-acylated in high yields to form tertiary amides. In the presence of lithium chloride, the enolates of the corresponding pseudoephedrine amides undergo highly diastereoselective alkylations with a wide range of alkyl halides to afford α-substituted products in high yields. These products can then be transformed in a single operation into highly enantiomerically enriched carboxylic acids, alcohols, and aldehydes. Lithium amidotrihydroborate (LAB) is shown to be a powerful reductant for the selective reduction of tertiary amides in general and pseudoephedrine amides in particular to form primary alcohols.

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List of Abbreviations

Bn	benzyl
BOC	butyloxycarbonyl
BOM	benzyloxymethyl
Bu	butyl
calcd	calculated
℃	degrees Celsius
CI	chemical ionization
cm^{-1}	reciprocal centimeters
COSY	correlated spectroscopy
δ	chemical shift (parts per million)
de	diastereomeric excess
2-D	two-dimensional
DIBAL-H	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMSO	dimethyl sulfoxide
E	entgegen
ee	enantiomeric excess
EI	electron impact
ent	enantiomer of
equiv	equivalent(s)
EtOAc	ethyl acetate
FAB	fast atom bombardment
FTIR	Fourier transform infrared
g	gram(s)
GC	gas chromatography

h	hour(s)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	Hertz
i	iso
J	coupling constant
L	liter(s)
LDA	lithium diisopropylamide
LiTMP	lithium 2,2,6,6-tetramethylpiperidide
M	molar (concentration)
$(M)^+$	molecular ion
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mm Hg	millimeters of mercury
mmol	millimole(s)
mp	melting point
μL	microliter(s)
m/z	mass to charge ratio
n	normal
N	normal (concentration)
nm	nanometers
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser enhancement
Ph	phenyl

pH	power of hydrogen (concentration)
Piv	pivaloyl
PMA	phosphomolybdic acid reagent, 20 wt. % solution in ethyl alcohol
ppm	parts per million
Pr	propyl
R	rectus
R_f	retention factor
S	sinister
S_N1	nucleophilic substitution, first order
t	tertiary
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin-layer chromatography
UV	ultraviolet
v/v	volume to volume ratio
wt %	weight percent
w/w	weight-to-weight ratio
Z	zusammen

Chapter 1

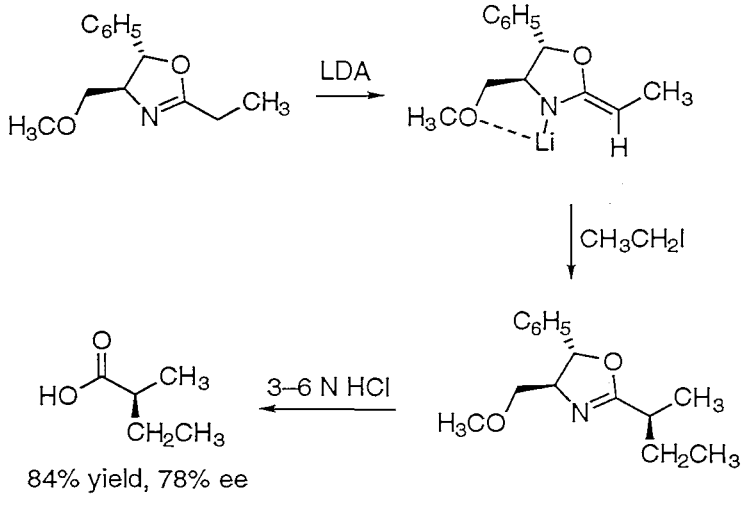
Synthesis and Diastereoselective Alkylation of Pseudoephedrine Amides

Introduction

The asymmetric alkylation of the α-carbon of carboxylic acid derivatives is a reaction of fundamental importance in modern synthetic organic chemistry.[1] With few exceptions, this type of transformation is accomplished using a chiral auxiliary, a molecule that can control the stereochemistry of the alkylation step in such a way as to give product of the desired configuration. For the application at hand, the chiral auxiliary is typically covalently attached to a carboxylic acid equivalent, and once it has achieved its purpose, it is cleaved from the substrate. Because chiral auxiliaries are required in stoichiometric amounts, it is advantageous that they be inexpensive and/or recoverable. In order to be able to access both enantiomers of a given product, it is also useful if both antipodes (or the synthetic equivalent) are readily available.

The first practical demonstration of the use of a chiral auxiliary for the asymmetric alkylation of a carboxylic acid enolate equivalent was reported by Meyers and co-workers in 1976.[2] In this pioneering work, it was shown that oxazoline anions derived from chiral β-amino alcohols were alkylated by a range of alkyl halides with high diastereoselectivities

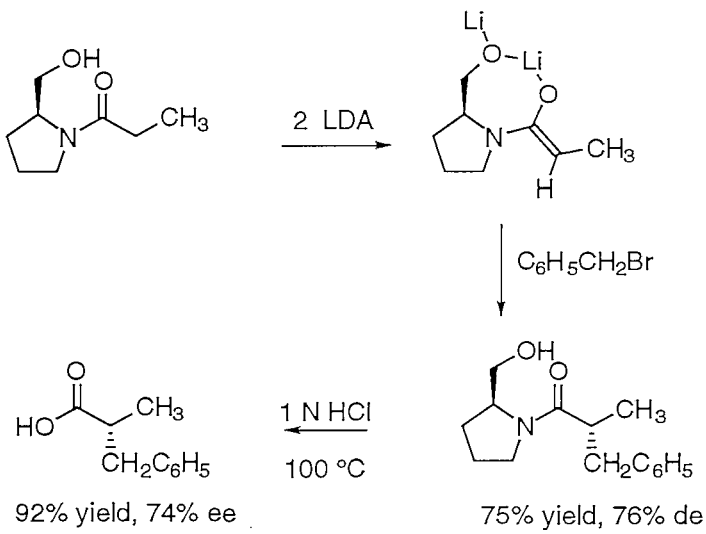
Scheme I



(Scheme I). These alkylation products were then transformed into chiral carboxylic acids with synthetically useful optical purities (51–86% ee).

Later, Evans and Takacs[3a] and Sonnet and Heath[3b] independently demonstrated that alkylations of enolates of tertiary amides derived from the amino alcohol prolinol occurred with higher diastereoselectivities (Scheme II, 76–94% de). Although a limitation of this methodology is the expense of the chiral auxiliary, particularly in the less readily available enantiomeric form (entry 2, Table 1), this work was influential not only as a practical

Scheme II



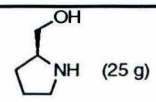
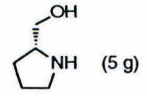
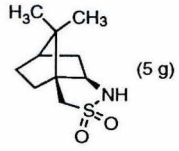
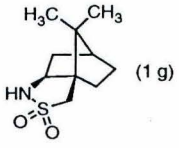
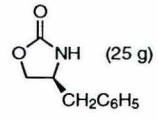
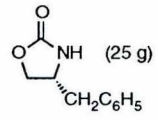
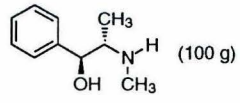
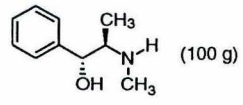
92% yield, 74% ee

75% yield, 76% de

addition to synthetic methodology, but also as a paradigm for the design of new chiral auxiliaries employing rigid cyclic platforms with well defined conformational preferences.

The C_2-symmetric bis(methoxymethoxymethyl)pyrrolidine auxiliary of Yamaguchi et al. exemplifies the degree to which this paradigm has evolved (Scheme III). Alkylation diastereoselectivities of 97–>98% de are possible with this auxiliary, but a major drawback of this methodology is the difficulty in preparing the chiral auxiliary. From commercial

Table 1. Cost of the Chiral Auxiliaries Prolinol, 2,10-Camphorsultam, 4-Benzyl-2-oxazolidinone, and Pseudoephedrine

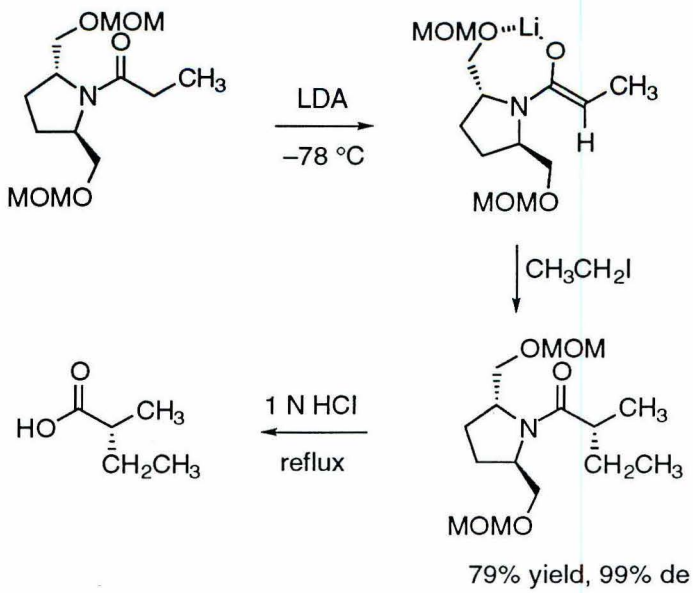
entry	chiral auxiliary (grams)[a]	cost (dollars per gram)[a]	cost (dollars per mole)[a]
1	 (25 g)	6.7	677
2	 (5 g)	31.1	3149
3	 (5 g)	23.7	5105
4	 (1 g)	48.2	10378
5	 (25 g)	7.4	1705
6	 (25 g)	9.6	1311
7	 (100 g)	1.0	172
8	 (100 g)	1.2	198

[a] Calculated from the price of the largest quantity available from Aldrich Chemical Company, Inc., (1997).

materials, the preparation of the auxiliary requires six linear steps and a resolution.[4] Like the alkylation products of prolinol amide enolate alkylations, difficulties were encountered in transforming the amide alkylation products into useful synthetic intermediates. For the

latter reason, subsequent developments in chiral auxiliary-based alkylation methodology have focused primarily on the alkylation of acyl derivatives that are more readily cleaved than amides.[5]

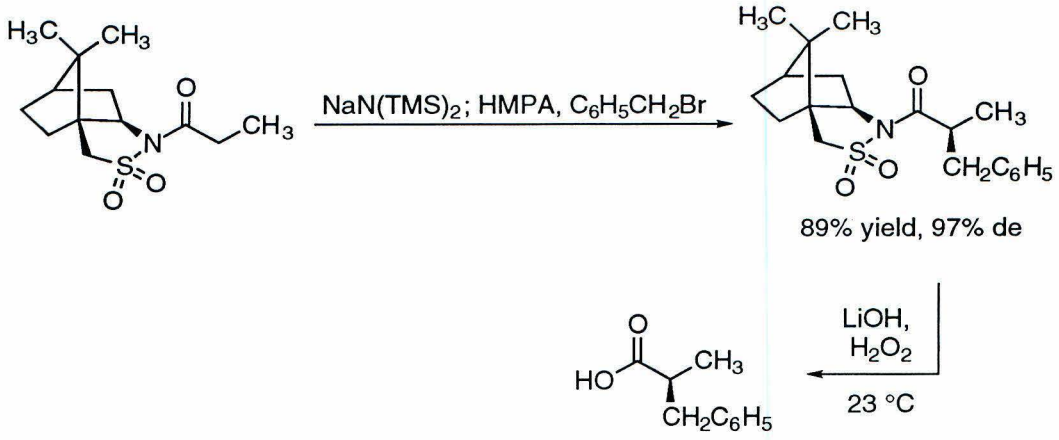
Scheme III



79% yield, 99% de

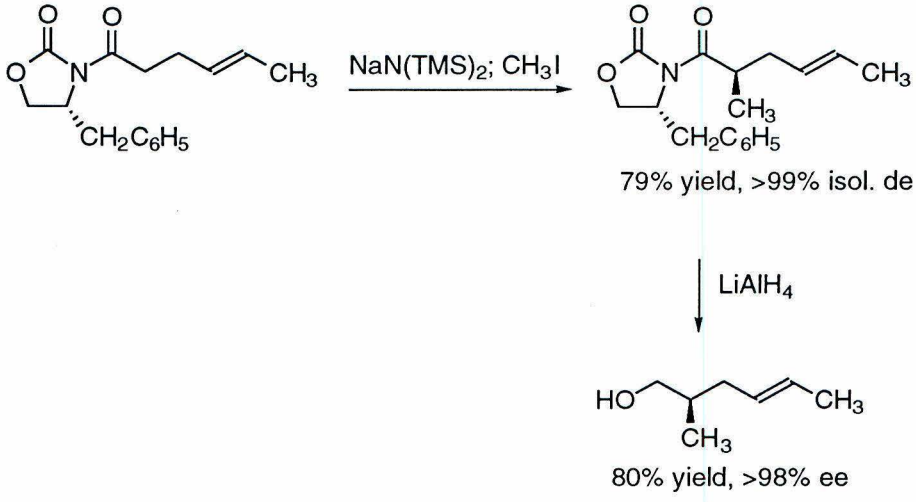
An important contribution in this area is the development of the camphor-derived sultam auxiliaries by Oppolzer and co-workers.[6] In addition to the practical feature that the auxiliary can be readily cleaved under mild conditions (Scheme IV), the alkylation reactions are typically highly diastereoselective, and many of the alkylation products are crystalline and are easily enriched to ≥99% de. Two limitations of this technology are the comparatively high cost of both enantiomeric forms of the auxiliary (entries 3 and 4, Table 1), and the necessity of using the reactivity-enhancing ligand hexamethylphosphoric triamide (HMPA) for efficient alkylation.

Scheme IV



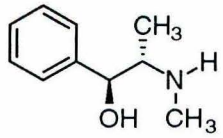
The chiral auxiliaries that have defined the standard in the field for over a decade have been the oxazolidinone auxiliaries of Evans and co-workers.[7] They are commercially available at a reasonable cost (entries 5 and 6, Table 1), their imide derivatives are alkylated with predictable and high diastereoselectivity, and the latter products are readily transformed into carboxylic acids, esters, and primary alcohols (Scheme V). As a

Scheme V



limitation in these alkylation reactions, the oxazolidinone-derived enolates react efficiently only with reactive halides (e.g., allylic halides), and they do not react at all with *n*-alkyl iodides such as *n*-butyl iodide.[7b]

Described herein is the use of the amino alcohol pseudoephedrine as a highly practical chiral auxiliary for asymmetric alkylation reactions.[8,9] Both enantiomers of



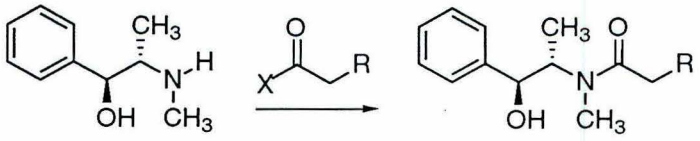
(*S*,*S*)-(+)-pseudoephedrine

pseudoephedrine are readily available and are inexpensive (the hydrochloride salt of *d*-pseudoephedrine, for example, is a commodity chemical employed in over-the-counter medications (Sudafed®, Suphedrine®, etc.) with annual worldwide production in excess of 300 metric tons). As is evident from entries 7 and 8 of Table 1, pseudoephedrine is less expensive per gram and per mole than the other commercially available chiral auxiliaries mentioned above. Pseudoephedrine amides are also easily prepared and are frequently crystalline. They undergo efficient and highly diastereoselective alkylation reactions with a wide range of alkyl halides, to include less reactive substrates such as β-branched alkyl iodides, and these alkylation reactions do not require the presence of carcinogenic co-solvents such as HMPA. Like the starting materials, the alkylated products are frequently crystalline and are easily enriched to ≥99% de upon recrystallization. The scope of this methodology is defined and possible factors responsible for the exceptionally high levels of diastereoselectivity observed with this nonconventional, acyclic auxiliary are discussed.[10] Extensive developmental work on the transformation of the alkylation products into highly enantiomerically enriched carboxylic acids, alcohols, and aldehydes is described in subsequent chapters.

Synthesis of Pseudoephedrine Amides

Amide bond formation is one of the most highly developed and efficient transformations in organic chemistry. Acylation reactions of the amino alcohol pseudoephedrine provide no exceptions to this generalization. As shown by the examples of Table 2, pseudoephedrine is acylated in high yield by a variety of activated carboxylic acid derivatives, to include symmetrical and mixed anhydrides and carboxylic acid chlorides.[11,12] Acylation reactions with carboxylic acid anhydrides proceed efficiently in dichloromethane or tetrahydrofuran (THF) as solvent and do not require the presence of an external base, although the reactions are much more rapid if a base such as triethylamine

Table 2. Selective *N*-Acylation of Pseudoephedrine



entry	R	method (X)[a]	product	yield (%)	mp (°C)
1	CH_3	A	**1**	95[b]	114–115
2	*n*-Bu	A	**2**	91[b]	62–63
3	Bn	B	**3**	83[b]	102–104
4	Ph	B	**4**	88[b]	145–146
5	*i*-Pr	B	**5**	92[b]	73–74
6	*t*-Bu	B	**6**	88[b]	68–69
7	CH_2Bn	B	**7**	81[b]	100–102
8	2-thiophene	B[c]	**8**	87	110–111
9	3-pyridyl	C	**9**	97, 72[b]	117.5–118.5
10	OH	D	**10**	93	61–63

[a] Method A: Acylation with the symmetrical carboxylic acid anhydride (X = RCH_2CO_2). Method B: Acylation with the carboxylic acid chloride (X = Cl). Method C: Acylation with the mixed anhydride derived from pivaloyl chloride (X = *t*-$BuCO_2$). Method D: Acylation with the methyl ester (X = CH_3O). [b] Values for products isolated by a single recrystallization of the crude product. [c] Acylation of (1*R*,2*R*)-(–)-pseudoephedrine.

(1.2 equiv) is added. Acylation reactions with carboxylic acid chlorides require the presence of a slight excess of a base (e.g., Et_3N) and occur readily at 0 °C in most organic solvents.[13] In cases where neither the anhydride nor the acid chloride derivative of a carboxylic acid is readily available, acylation using the mixed anhydride formed from the carboxylic acid, pivaloyl chloride, and triethylamine is found to be a convenient preparative method (entry 9). Each of the amide products of Table 2 is a non-hydrated, air-stable, free-flowing crystalline solid and can be isolated by direct recrystallization of the crude acylation product (entries 1–7, and 9) or by flash column chromatography (entries 8–10). In most cases, the only by-product in the acylation reactions is a small amount (≤5%) of the *N*,*O*-diacylated product, which is easily separated by recrystallization or flash column chromatography. Because intramolecular $O \rightarrow N$ acyl transfer within pseudoephedrine β-amino esters occurs rapidly, and because the *N*-acyl form is strongly favored under neutral or basic conditions,[11c] products arising from (mono) acylation on oxygen rather than nitrogen, are not observed.

The latter feature of pseudoephedrine chemistry makes available yet another procedure for *N*-acylation that has been developed for α-heteroacetamide derivatives such as pseudoephedrine α-hydroxyacetamide (entry 10, Table 2) and pseudoephedrine glycinamide.[14] This procedure takes advantage of the intramolecular $O \rightarrow N$ acyl transfer reaction that follows *O*-acylation, and employs an α-hetero acetate ester as an *O*-acyl transfer agent in the presence of substoichiometric quantities of a base such as lithium methoxide or *n*-butyllithium. The formation of oligomeric by-products is found to be reduced, though not completely suppressed, if the reaction is conducted in the presence of lithium chloride (2 equiv) as an addition. In the case of entry 10, product yields can be increased by saponifying the crude acylation product with 1 N aqueous sodium hydroxide solution at 23 °C. Under these conditions, the α-hydroxy amide functionality is stable, while the α-hydroxy ester functionalities of the oligomeric by-products are saponified. The scope of this reaction methodology has been expanded to include the preparation of

non-heteroacetamide derivatives, such as pseudoephedrine propionamide.[8b] These reactions proceed optimally using sodium methoxide (0.5 equiv) as base.[8b]

Alkylation of Pseudoephedrine Amide Enolates

Two general procedures for the diastereoselective alkylation of pseudoephedrine amides have been developed. In the first, the alkylation is conducted using excess alkyl halide (procedure A, yield based on enolate), and in the second, excess enolate is used (procedure B, yield based on alkyl halide). Alkylation reactions using the alkyl halide as the limiting reagent are slightly higher yielding than those based on limiting enolate, but the difference is sufficiently minor that the primary consideration in choosing a procedure is the expense and/or availability of the alkyl halide relative to that of the pseudoephedrine amide.

In a typical protocol employing excess alkylating agent (procedure A), a suspension of anhydrous lithium chloride (6.0–7.0 equiv) in THF containing diisopropylamine (2.25 equiv) is treated at –78 °C with a solution of *n*-butyllithium in hexanes (2.1 equiv). The resulting suspension is held at –78 °C for 5 min, the reaction flask is briefly transferred to an ice bath (5 min), then is cooled to –78 °C. A solution of the pseudoephedrine amide substrate (1 equiv) in THF is added to the cold suspension of lithium diisopropylamide-lithium chloride and the mixture is held at –78 °C for 30–60 min, then is warmed to 0 °C and is held at that temperature for 10–15 min. The enolate suspension is stirred briefly at 23 °C (3–5 min), then is cooled to 0 °C and is treated with an alkylating agent (1.5–4.0 equiv). For most substrates, enolization is rapid at 0 °C and further warming to 23 °C is probably unnecessary, although innocuous, because pseudoephedrine amide enolates generally exhibit good thermal stability at 23 °C ($t_{1/2}$ > 12 h).

Reactions employing excess enolate (procedure B) are conducted similarly, but with 1.3–1.8 equiv of enolate and 1 equiv of electrophile. It is important in these reactions

that excess base (LDA) not be used, for many electrophiles are destroyed by the excess base. Typically, we employ 1.90–1.95 moles of LDA per mole of amide substrate in reactions with excess enolate.

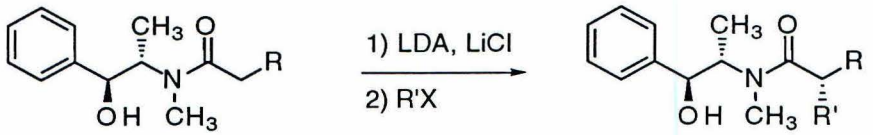
The presence of lithium chloride in the reaction is essential to accelerate the rate of alkylation. In addition, *O*-alkylation of the secondary hydroxyl group of the pseudoephedrine auxiliary is suppressed in the presence of lithium chloride. At the concentrations of a typical alkylation reaction (~0.2 M in enolate), the solubility limit of lithium chloride is reached at approximately 5 equiv at 0 °C and 6 equiv at 23 °C. Thus, typical reactions conducted with the recommended 6.0–7.0 equiv of lithium chloride are saturated; use of more than 7 equiv of lithium chloride in the reaction produces no discernible differences in the reaction rate, yield, or diastereoselectivity. Alkylation reactions conducted in the presence of fewer than ~4 equiv of lithium chloride are markedly slower and typically do not proceed to completion. For example, in the absence of lithium chloride, the reaction of *n*-butyl iodide with the enolate derived from pseudoephedrine propionamide proceeds to the extent of only 32% within 5 h at 0 °C, whereas in the presence of 6 equiv of lithium chloride the alkylation reaction is complete within 1.5 h at 0 °C (80% yield of recrystallized product). Trapping of the same enolate with benzyl bromide proceeds to only 60% completion in the absence of lithium chloride, but affords a 90% yield of recrystallized product in its presence (6 equiv). In neither case was the diastereoselectivity of the alkylation reaction influenced by the presence of lithium chloride in the medium.[15]

It is important to ensure that rigorously anhydrous lithium chloride is employed in the alkylation reaction, for any water of hydration will quench the strong base used in the enolization step. It is recommended that the (highly hygroscopic) anhydrous reagent be flame-dried immediately prior to use followed by cooling under an inert atmosphere at 23 °C.

The role of lithium chloride in the reaction is not known. There is ample precedent in the literature, notably in the work of Seebach and co-workers, documenting the beneficial influence of lithium chloride in enolate alkylation reactions. It has been proposed in these studies that lithium chloride may modify the aggregation state, and thereby the reactivity of an enolate in solution.[16]

Alkylation with Primary Alkyl Halides. Pseudoephedrine amide enolates react efficiently (80–99% yields of purified alkylation products) and highly diastereoselectively (94–98% crude de, 95–≥99% isolated de) with a wide variety of primary alkyl halides (Table 3). Each of the examples in Table 3 involves a readily available and/or inexpensive alkyl halide and therefore was conducted with limiting enolate (procedure A). Because pseudoephedrine amide enolates are highly nucleophilic, many primary alkyl halides react readily even at –78 °C (e.g., entries 8 and 11). Reactions conducted at –78 °C display slightly enhanced diastereoselectivities versus the same reactions conducted at 0 °C (entries 7 and 10), but reactions conducted at 0 °C are nevertheless highly diastereoselective. Notably, even poorly reactive substrates such as *n*-alkyl iodides (entries 2, 5, and 9) react efficiently and highly selectively with pseudoephedrine amide enolates at 0 °C.[17] Elimination-prone substrates such as (2-iodoethyl)benzene (entry 5) react efficiently, showing little evidence of elimination. Similarly, the potentially enolizable substrate *tert*-butyl bromoacetate (entry 6) is found to alkylate the enolate derived from pseudoephedrine propionamide in good yield. The electrophile benzyloxymethyl chloride (BOM chloride, entry 3) is singular in that it is found to alkylate pseudoephedrine amide enolates with poor diastereoselectivity (33% de). This poor selectivity is thus far unique to this substrate and may reflect a change in the reaction mechanism, perhaps toward an S_N1-type transition state. The use of BOM bromide as substrate (entry 4) obviates this problem, returning the high diastereoselectivity found with all other alkyl halides used in this study. In every case studied, the major

Table 3. Diastereoselective Alkylation of Pseudoephedrine Amides



Entry	R	R'X[a]	temp (°C)	prod.	crude de (%)	isol de (%)	isol yield (%)	mp (°C)
1	CH_3	BnBr	0	**11**	94	≥99[b]	90[b]	136–137
2	CH_3	*n*-BuI	0	**12**	98	≥99[b]	80[b]	66–67
3	CH_3	BOMCl	0	**13**	33	33	77	–
4	CH_3	BOMBr	–78	**13**	98	98	80	65–66
5	CH_3	$C_6H_5(CH_2)_2I$	0	**14**	95	95	86	–
6	CH_3	$BrCH_2CO_2t$-Bu	–78	**15**	94	96	78	–
7	Bn	CH_3I	0	**16**	94	94	99	79–81
8	Bn	CH_3I	–78	**16**	97	97	95	79–81
9	Bn	*n*-BuI	0	**17**	98	98	90	–
10	*n*-Bu	CH_3I	0	**18**	94	94	94	–
11	*n*-Bu	CH_3I	–78	**18**	96	96	89	–
12	*n*-Bu	BnBr	0	**19**	98	≥99[b]	87[b]	120–121
13	Ph	EtI	0	**20**	96	≥99	92	65–66
14	CH_2Bn	CH_3I	0	**21**	95	≥99[b]	92[c]	89–90
15	*i*-Pr	BnBr	0	**22**	98	≥99[b]	83[b]	118–119
16	*t*-Bu	BnBr	0	**23**	98	≥99[b]	84[b]	125–127
17	3-pyridyl	$CH_2{=}CHCH_2I$	–78	**24**	98	98	83	109–110
18	2-thiophene[d]	CH_3I	–78	**25**	95	95	88	–

[a] All reactions were conducted with excess alkyl halide (1.5–4.0 equiv). [b] Values for products isolated by a single recrystallization of the crude reaction mixture. [c] Two recrystallizations were conducted. [d] Alkylation of (1*R*,2*R*)-pseudoephedrine-2-thiopheneacetamide.

product arises 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 is drawn in a planar, extended conformation (see Figure 1).

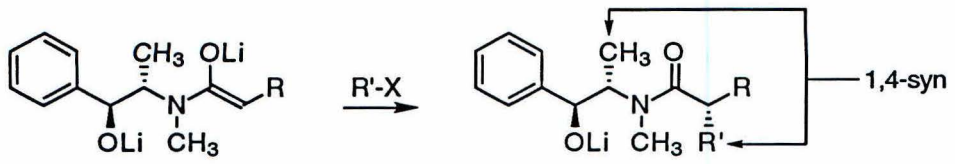
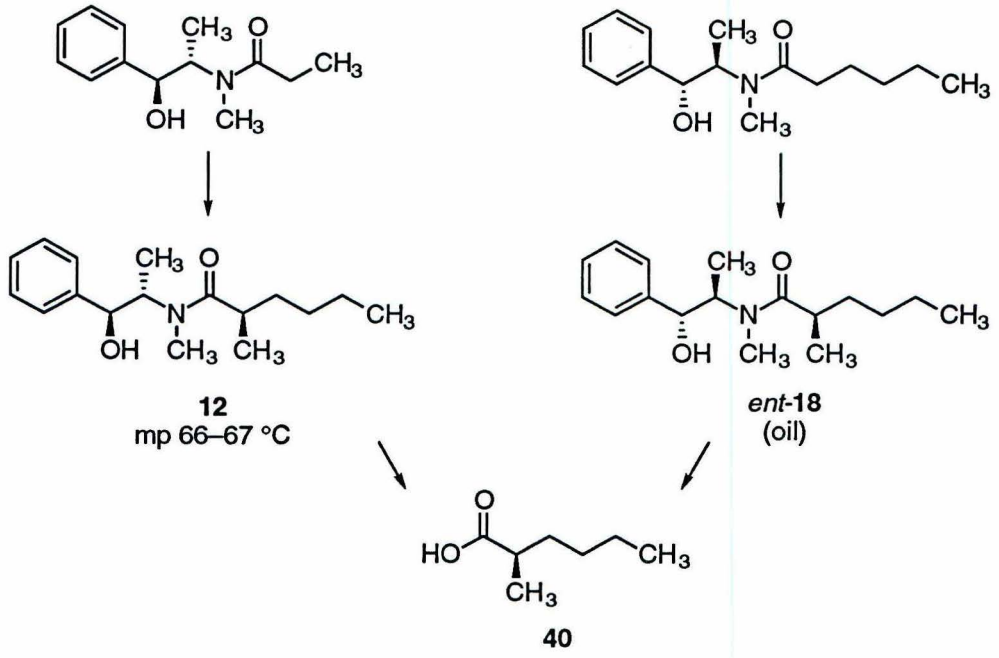


Figure 1. Mnemonic for pseudoephedrine amide enolate alkylation.

A particularly valuable feature of pseudoephedrine as a chiral auxiliary from the standpoint of process chemistry is the crystallinity of its *N*-acyl derivatives; many of the alkylation products are crystalline materials and can be isolated in ≥99% de and >80% yield after recrystallization of the crude reaction products (entries 1–2, 12, and 14–16). Typically, at least one diastereomer within a given diastereomeric pair of alkylation products is crystalline. Thus, by proper choice of the *N*-acyl group, alkyl halide, and the configuration of the pseudoephedrine auxiliary (*d* or *l*), a crystalline product can often be

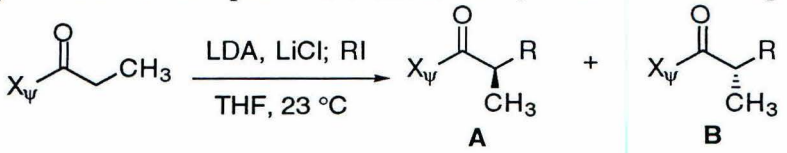
Scheme VI

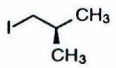
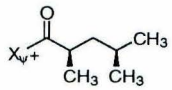
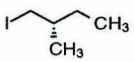
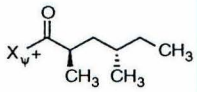
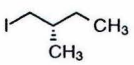
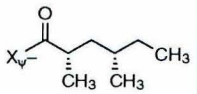
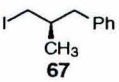
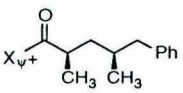
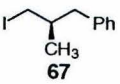
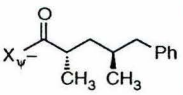
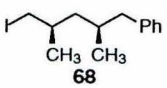
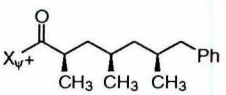
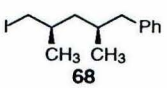
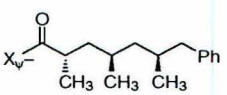
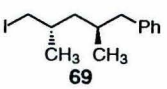
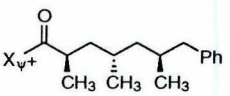
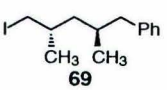
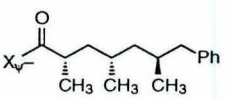


obtained. For example, (*R*)-2-methylhexanoic acid **40** is obtained by the hydrolysis of either diastereomer **12** or *ent*-**18**; however, only **12** is crystalline (Scheme VI). To obtain (*R*)-2-methylhexanoic acid from the crystalline intermediate **12**, (*S*,*S*)-pseudoephedrine propionamide is alkylated with *n*-butyl iodide, followed by hydrolysis (vide infra) of the product **12**.

Alkylation with β-Branched Primary Alkyl Iodides. The superior nucleophilicity and excellent thermal stability of pseudoephedrine amide enolates make possible alkylation reactions at 23 °C with ordinarily unreactive substrates such as β-branched primary alkyl iodides. This is a valuable transformation for it provides a concise route to "skipped" or 1,3-dialkyl-substituted carbon chains, found within many natural products. With chiral β-branched primary iodides, an important issue concerns the degree to which the existing stereocenter within the electrophile will influence the stereoselectivity of the alkylation reaction. In initial studies, the alkylation of both enantiomers of pseudoephedrine propionamide with (*S*)-1-iodo-2-methylbutane was examined. Each reaction was conducted using excess enolate (1.8 equiv)[18] and limiting alkyl iodide (procedure B). As shown by entries 2 and 3 of Table 4, both alkylation reactions were highly selective and efficient, although that producing the 1,3-syn product (entry 3) proceeded with slightly higher diastereoselectivity, suggesting that this represents a "matched" case. These and other findings within Table 4 represent significant advances over existing asymmetric alkylation methodology. For example, alkylation of the enolate derived from (*S*)-prolinol propionamide with (*S*)-1-iodo-2-methylbutane in the presence of HMPA is reported to proceed in 49% yield and 90% de.[19] In addition, the selectivity of the latter reaction was found to be reduced on larger scale (~80% de, 10 mmol).[19a] By contrast, in no case have we observed a variation in product de as a function of scale in the alkylation of a pseudoephedrine amide enolate.[20] Use of Enders' chiral hydrazone methodology[21] in the synthesis of 1,3-dimethyl-substituted carbon chains has been

Table 4. Alkylation of Pseudoephedrine Amides with β-Branched Electrophiles



entry	RI[a]	time (h)	product	isol yield (%)	ratio of **A** : **B**
1		6	 **26**	89	86 : 1
2		20	 **27**	94	62 : 1
3		18	 **28**	94	1 : 89
4	 **67**	6	 **29**	97	>99 : 1
5	 **67**	7	 **30**	95	1 : 58
6	 **68**	18	 **31**	93	142 : 1
7	 **68**	18	 **32**	96	1 : 70
8	 **69**	12	 **33**	93	66 : 1
9	 **69**	18	 **34**	94	1 : 199

[a] Except in entry 1 where 4 equiv of iodide were used (yield based on pseudoephedrine amide), and the alkylation was conducted at 0 °C, all alkylations were conducted at 23 °C using excess enolate (1.8–2.0 equiv, yield based on alkyl iodide).

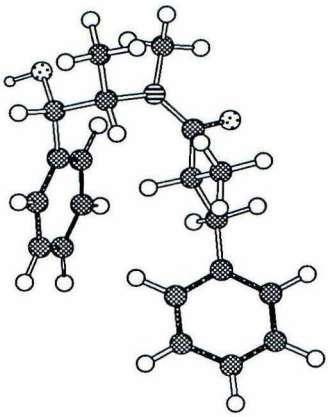
successfully implemented by Nicolaou et al.[22] in their synthesis of the sidechain of zaragozic acid A, but the expense of the auxiliary makes the large-scale applications of this methodology impractical. Similarly, use of Evans' chiral imide enolate methodology[7] in the synthesis of 1,3-dimethyl-substituted fragments was described recently by Decicco and Grover in synthetic studies of microcolin A, but the alkylation required the use of a large excess (25 equiv) of the alkylating agent.[23] This is an undesirable feature in any reaction, but particularly in an iterative sequence (vide infra) where the electrophilic component becomes successively more valuable with each iteration.

In their asymmetric synthesis of ionomycin, Evans et al. pointed out that a sequence involving the asymmetric alkylation of a chiral propionate-derived enolate, reduction of the alkylation product to a primary alcohol and alcohol activation (e.g., $RCH_2OH \rightarrow RCH_2I$), followed by a second alkylation reaction with a chiral propionate-derived enolate would provide an iterable approach to the synthesis of 1,3,5,n-polymethyl-substituted chains.[24] This strategy was adopted in order to illustrate the application of pseudoephedrine amide enolate alkylation chemistry to the iterative synthesis of 1,3,5,n(odd)-polymethyl-substituted carbon chains of any configuration, and results are shown in Table 4.[25] Thus, treatment of the iodide **67**[26] with 1.8 equiv of the enolate derived from (*S*,*S*)-pseudoephedrine propionamide (**1**) at 23 °C for 6 h afforded the 1,3-syn alkylation product **29** with >99:1 diastereoselectivity and in 97% yield whereas use of the enolate derived from (*R*,*R*)-pseudoephedrine propionamide (*ent*-**1**) under identical conditions provided the 1,3-anti product **30** with 58:1 diastereoselectivity and in 95% yield (entries 4 and 5).[18,27] As before, the reaction producing the syn stereochemistry appears to represent a matched case while that producing the anti diastereomer represents a mismatched case, although even the mismatched alkylation reaction is highly selective.

Alkylation products **29** and **30** were transformed into the corresponding alcohols by LAB reduction (vide infra), and then to the corresponding iodides in an aggregate yield in excess of 91%. Iodides **68** and **69** were felt to provide a more stringent test of

secondary diastereodifferentiating effects in the alkylation reactions. Reaction of the syn iodide **68** (1 equiv) with 1.8 equiv of the enolate derived from **1** afforded the syn,syn alkylation product **31** with 142:1 selectivity and in 93% yield, whereas the enolate derived from *ent*-**1** produced the anti,syn product **32** with only slightly lower selectivity (70:1, 96% yield). Reaction of the anti iodide **69** with 1.8 equiv of the enolate derived from **1** produced the anti,anti amide **33** with 66:1 selectivity and in 93% yield, whereas the alkylation of the enolate derived from *ent*-**1** proceeded with higher selectivity (199:1) to form the syn,anti product **34** in 94% yield. These results again support the idea that 1,3-syn products represent matched cases and demonstrate convincingly that the high diastereofacial bias of pseudoephedrine amide enolates overrides secondary effects due to the stereocenter within the alkyl iodide. The diastereoselectivities of the alkylation reactions can be seen to increase with the steric bulk of the alkyl iodide. In addition, the results of Table 4 illustrate the exceptional efficiency of the alkylation reactions when limiting iodide is employed (procedure B), with chemical yields typically exceeding 93%.

Concerning Rotamers and Diastereomeric Ratios. Like most tertiary amides, pseudoephedrine amides exhibit rotational isomerism about the N-C(O) bond and interconversion of isomers is slow on the NMR (^{1}H and ^{13}C) time scale. In one case (substrate **11**), we observed a coalescence temperature of 120 °C (^{1}H NMR at 400 MHz, DMSO) for rotamer interconversion. In solution, the ratio of rotational isomers of pseudoephedrine amides typically varies from 1:1 to 7:1. In all cases, the major rotamer in solution is assigned as that with the *N*-methyl group anti to the carbonyl group on the basis of its shielding relative to the minor isomer.[28] Interestingly, in solid state structures of three pseudoephedrine amides (**11**, **12**, and **16** below)[8] a single rotameric form is present wherein the *N*-methyl group is syn to the carbonyl group, the minor isomer in solution. However, in a fourth structure (pseudoephedrine glycinamide monohydrate, vide infra)[14]



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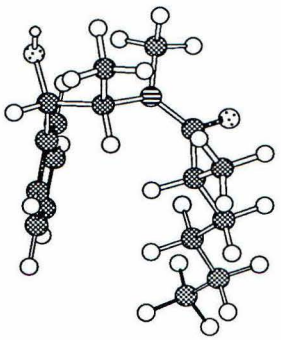
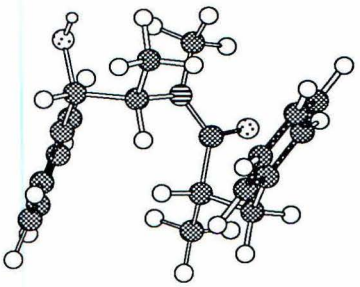


12



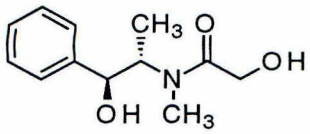
16

the amide crystallized exclusively as the rotamer with the *N*-methyl group anti to the amide carbonyl. These data reveal the fine balance in energetics between isomers, and the importance of crystal packing forces on the distribution.

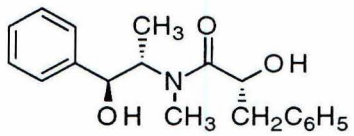
From a practical standpoint, the ^{1}H NMR spectrum of a given pseudoephedrine amide will be complicated by the presence of rotamers and for this reason diastereomeric ratios are best assigned by capillary GC analysis. Typically, the corresponding trimethylsilyl ether or acetate ester is prepared and analyzed using a Chirasil Val column (Alltech).

Limitations of the Alkylation Methodology. In testing the limits of pseudoephedrine amide enolate alkylations, we have found that the alkylation of pseudoephedrine amide enolates with secondary alkyl halides such as cyclohexyl bromide and cyclohexyl iodide is exceedingly slow and does not provide a viable route to products of this type.[29]

Another problematic case we have encountered is the alkylation of pseudoephedrine α-hydroxyacetamide **10** and its protected derivatives. Enolization of **10** using 3.2 equiv of LDA at –78 °C was accompanied by partial decomposition of the starting material. By using excess pseudoephedrine α-hydroxyacetamide (1.65 equiv) and limiting benzyl bromide the *C*-alkylated product **35** was formed in 84% yield and 82% de. This diastereo-



10

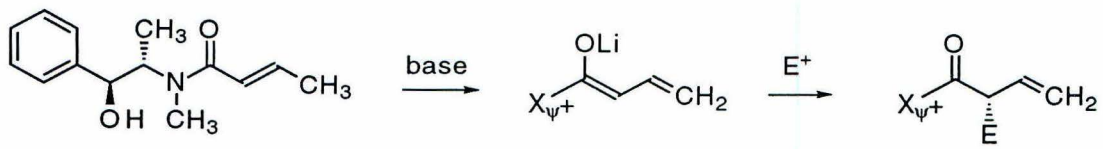


35

selectivity is lower than that obtained in benzylations of other pseudoephedrine amide enolates, including the α-heterosubstituted enolates derived from pseudoephedrine glycinamide,[9] chloroacetamide,[8] and fluoroacetamide[30] and may be related to the fact that the pseudoephedrine α-hydroxyacetamide enolate is a presumed trianion whereas the latter enolates are all dianions. Alkylation reactions of an extensive series of *O*-protected derivatives of pseudoephedrine α-hydroxyacetamide were also examined, but the alkylation reactions were either unselective (protecting group = TBS, TBDPS, THP, BOM, Piv, and methyl-1-methoxyethyl), or the enolate was unstable (protecting group = Bn). Consequently, none of these offered any improvement over pseudoephedrine α-hydroxyacetamide itself.

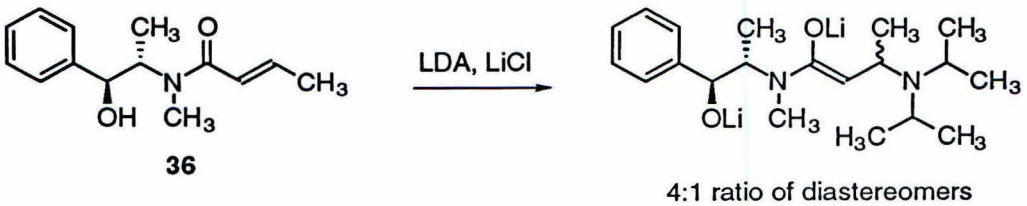
We also encountered difficulties when we attempted to extend our alkylation studies to pseudoephedrine crotonamide (**36**). It was anticipated that alkylation of the lithium enolate of **36** with a suitable electrophile (E^+) would occur at the α position to yield a β,γ-unsaturated amide (Scheme VII). When amide **36** was subjected to standard enolization conditions (LDA, LiCl, THF), followed by quenching with benzyl bromide at

Scheme VII



36

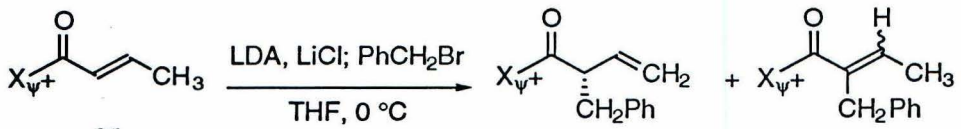
0 °C, a substantial (>50%) quantity of a by-product arising from the 1,4-conjugate addition product of LDA with pseudoephedrine crotonamide was isolated (4:1 ratio of diastereomers). Although the desired β,γ-unsaturated alkylation product (**37**) could be



36

4:1 ratio of diastereomers

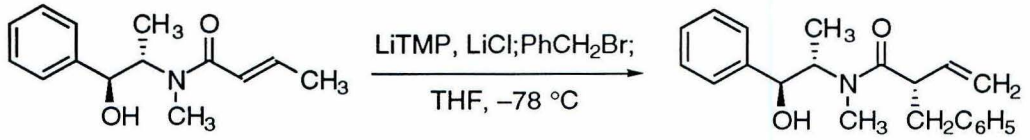
recovered from the reaction mixture, it was contaminated with an approximately equal quantity of the α,β-unsaturated isomer **38**. Presumably, the β,γ-unsaturated amide is the kinetic alkylation product, but it undergoes base-catalyzed isomerization at 0 °C to afford the corresponding α,β-unsaturated isomer.



36 **37** **38**

Use of the more hindered base lithium 2,2,6,6-tetramethylpiperidide (LiTMP) gave reduced yields of the corresponding conjugate addition by-product, though a minor amount of a dimeric product, resulting from conjugate addition of the pseudoephedrine crotonamide enolate with unreacted pseudoephedrine crotonamide (or its alkoxide), was also detected. Optimal results were achieved when an ice-cooled solution of pseudoephedrine crotonamide in tetrahydrofuran was added to a suspension of LiTMP and lithium chloride in tetrahydrofuran at 0 °C. At 0 °C the enolization of pseudoephedrine crotonamide is thought to be nearly instantaneous, thus the conjugate addition of pseudoephedrine crotonamide enolate with unreacted pseudoephedrine crotonamide does not occur. The enolate was then cooled to –78 °C (a necessary modification to prevent

double bond migration following the alkylation step), and benzyl bromide was added. The reaction mixture was stirred for 2 hours at –78 °C, and afforded a 72% yield of the desired product **37** after purification by flash column chromatography, with none of the α,β-unsaturated compound **38**. The crude de was 93%, and the minor diastereomer could be removed efficiently by recrystallizing the chromatographed material from ethyl acetate.



36 **37**: 72% yield, 93% de

One limitation about carrying out the alkylation reaction at –78 °C is that pseudoephedrine amide enolate alkylations do not proceed efficiently at –78 °C with less reactive electrophiles, such as 1-iodobutane. The alkylation reaction with 1-iodobutane at –78 °C proceeds in only 33% yield, but in 97% de.

The Basis for Selectivity in Pseudoephedrine Amide Enolate Alkylations. In an effort to obtain structural information concerning the conformations of pseudoephedrine amide enolates, we attempted to crystallize a pseudoephedrine amide enolate. Despite extensive efforts over a wide range of pseudoephedrine amide substrates (e.g., pseudoephedrine propionamide, chloroacetamide,[8] phenylacetamide, and the C_2 symmetric bis-amides, vide infra), in no case have we been successful in obtaining an X-ray quality crystal of a pseudoephedrine amide enolate.

The structural similarity between pseudoephedrine amides and prolinol amides (both are amides of 2-amino alcohols) and the observation that, in both systems, alkyl halides and epoxides exhibit opposite diastereoselectivity in alkylation reactions[31,32] suggest that the origin of selectivity in the two systems may be similar. Askin et al. have suggested that the alkoxy group of prolinol amide enolates may direct the alkylation reaction in the case of epoxide electrophiles, and provide a steric blockade in reactions with

alkyl halides.[32] A similar rationale may explain the selectivity of pseudoephedrine amide enolate alkylations if a reactive conformer such as that shown in Figure 2 is invoked. In this conformation, the lithium alkoxide, and perhaps more importantly, the solvent

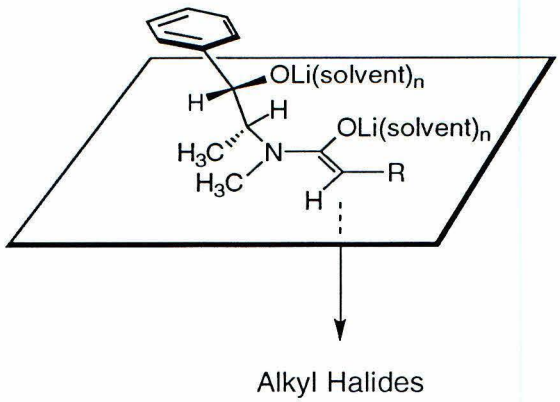


Figure 2. Proposed reactive conformation of pseudoephedrine amide enolates.

molecules (tetrahydrofuran and possibly diisopropylamine) associated with the lithium cation are proposed to block the β-face of the *Z*-enolate, forcing the alkylation to occur from the α-face. In this model, the pseudoephedrine side chain adopts a staggered conformation in which the C–H bond α to nitrogen lies in-plane with the enolate oxygen, in accord with predictions based on allylic strain arguments.[33] The positioning of the secondary alkoxide on the β-face of the enolate may also benefit from extended coordination of the oxyanions with one or more lithium cations. The feasibility of such a

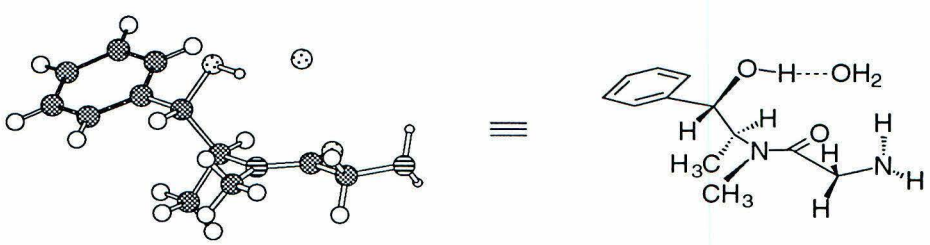
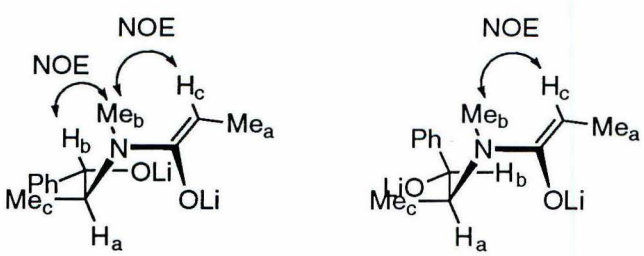


Figure 3. Crystal structure of pseudoephedrine glycinamide monohydrate.

staggered conformer is supported by a similar conformer depicted in the X-ray crystal structure of pseudoephedrine glycinamide monohydrate (Figure 3),[14] wherein allylic and torsional strain is minimized, and the secondary hydroxyl group is disposed on the β-face of the plane defined by the amide bond linkage. Although the proposed model provides a rationale for the observed selectivity, it should be noted that several important features of the actual transition structure of the enolate have been neglected such as its aggregation state, rotameric distribution, state of ionization, and the degree of pyramidalization of nitrogen, as well as the bond-breaking and bond-forming trajectories.

Attempts to corroborate the proposed structure in Figure 2 with ^{1}H NMR data have been complicated by poor line shape or highly complex spectra. When the lithium enolate of pseudoephedrine propionamide is generated in the presence of lithium chloride, the ^{1}H NMR spectrum in THF-d_8 shows a single species, but the signals are too broad to allow for the determination of any coupling constants, or to conduct any NOE (nuclear Overhauser enhancement) studies. When the enolate is generated in the absence of lithium chloride, the ^{1}H NMR spectrum shows two separate species with sharply defined signals. Through 2-D correlated spectroscopy (COSY) studies and differential NOE measurements, we were able to assign each peak to its respective structure and to assign a reasonable conformation to each structure (structure X and structure Y, Figure 4).[34]



structure X
J (H_a-H_b) = 8.0 Hz
δ (Me_c): 0.60 ppm

structure Y
J (H_a-H_b) = 0 Hz
δ (Me_b): 1.82 ppm

Figure 4. Proposed conformations of the lithium enolate of pseudoephedrine propionamide in THF, in the absence of lithium chloride.

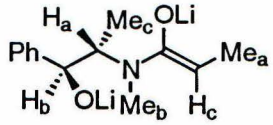
For structure X, the NOE between protons of the *N*-methyl group (Me_b) and the enolate proton (H_c) establishes the enolate is of the *Z*-configuration and is in the anti conformer (*N*-methyl group is anti to the enolate oxygen). The 8.0 Hz coupling constant between H_a and H_b is consistent with a dihedral angle of 150° to 180° or 0° to 20°,[35] but the NOE between the protons of the *N*-methyl group (Me_b) and H_b virtually rules out the latter possibility. The steric interaction between the phenyl ring and Me_c can be minimized by turning the face of the aromatic ring toward Me_c, which may explain the upfield shift (δ = 0.60 ppm) for the protons of Me_c. It is interesting to note that the conformer of structure X is essentially that shown in Figure 2 for R = Me. As drawn, the oxyanions of structure X are in close proximity, and thus an extended coordination of the oxyanions with one or more lithium cations is possible.

Structure Y also displays an NOE between protons of the *N*-methyl group (Me_b) and the enolate proton (H_c), suggesting that structure Y is a *Z*-enolate, and that the *N*-methyl group is anti to the enolate oxygen. However, the absence of coupling between H_a and H_b, and an upfield shift of the *N*-methyl group (Me_b) protons suggest the structure shown above. The 1,3-diaxial interaction between the phenyl ring and the *N*-methyl group can be minimized by turning the face of the aromatic ring toward the *N*-methyl group, which would explain the upfield shift for Me_b (δ = 1.82, cf. δ = 2.52 for structure X).

A comparison of the chemical shifts of structure X and structure Y with that of the enolate generated in the presence of lithium chloride (structure Z) suggests that structure Z may be similar to that of structure X, and hence, to the conformer proposed in Figure 2 (Table 5). In all cases, the chemical shifts of structure Z resemble those of structure X more closely than those of structure Y. In particular, the upfield shift of Me_c in structure Z suggests that the phenyl ring is opening its face to Me_c, as in structure X.

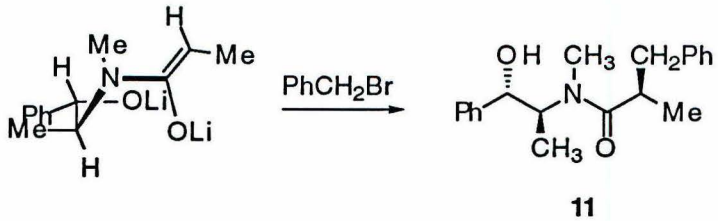
It is not clear at present why the selectivity of the asymmetric alkylation reaction is relatively unaffected by the concentration of lithium chloride. In the absence of lithium

Table 5. ^{1}H NMR Data for the Lithium Enolate of Pseudoephedrine Propionamide



resonance	structure X (δ)	structure Y (δ)	structure Z (δ)
H_a	3.50	2.96	too broad to find
H_b	4.56	4.83	4.4
H_c	3.34	3.19	3.3
Me_a	1.43	1.28	1.45
Me_b	2.52	1.82	2.35
Me_c	0.60	1.70	0.4

chloride, structure X and structure Y are present in equimolar amounts. While it would be expected that the alkylation of structure X will occur almost exclusively from the front face to afford the observed product (Figure 5), both of the enolate π-faces of structure Y appear to be accessible. It is possible that in the absence of lithium chloride, structure Y is in an unreactive aggregation state.



11

Figure 5. Predicted facial selectivity in the alkylation of structure X with benzyl bromide.

In the context of this discussion of the diastereoselectivity of pseudoephedrine amide enolate alkylations, it is interesting to note that the use of ephedrine, the diastereomer of pseudoephedrine, as a chiral auxiliary in amide enolate alkylations proved

markedly inferior from a number of standpoints. The use of ephedrine as a chiral auxiliary was described more than 15 years ago and, as outlined in that work, entailed the use of the carcinogenic co-solvent HMPA in the alkylation reactions.[36] In addition, difficulties in transforming the alkylated ephedrine amides into useful products were reported. We have reinvestigated the alkylation of ephedrine amides using the protocol described above for pseudoephedrine amide enolate alkylations (employing lithium chloride as an additive) and have found these alkylations to exhibit only modest diastereoselectivity.[37] In addition, ephedrine amides lack the desirable process features of pseudoephedrine amides – they are typically oils.

Conclusion

Pseudoephedrine has been documented to be a highly practical chiral auxiliary for asymmetric alkylation reactions. The enolates of pseudoephedrine amides undergo efficient and highly diastereoselective alkylation reactions with a wide variety of alkyl halides. In addition, the low cost of the auxiliary, the crystallinity of many of the starting materials and products, and the fact that carcinogenic co-solvents are not required make the reported procedures amenable to large scale and process applications.

Experimental Section

General Procedures. All non-aqueous reactions were performed in flame-dried round-bottomed or modified Schlenk (Kjeldahl shape) 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 unless otherwise noted. Organic solutions were concentrated by rotary evaporation at ~25 Torr. Flash column chromatography was performed as described by Still et al.[38] 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). All recrystallization mixtures were cooled gradually to –20 °C prior to harvesting the product by filtration.

Materials. BOMBr and BOMCl were prepared according to the literature procedure.[39] 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, acetonitrile, and toluene were distilled under nitrogen from calcium hydride. Lithium chloride was dried under vacuum at 150 °C for 24 h, then stored under a nitrogen atmosphere, or alternatively was flame-dried under vacuum immediately prior to use. Benzyl bromide, iodomethane, isobutyl iodide, and (2-iodoethyl)benzene were passed through basic alumina immediately prior to use. Allyl iodide and ethyl were washed with aqueous sodium thiosulfate solution, dried over potassium carbonate, and passed through basic alumina immediately prior to use. The molarity of *n*-butyllithium was determined by titration against diphenylacetic acid as an indicator (average of three determinations).[40]

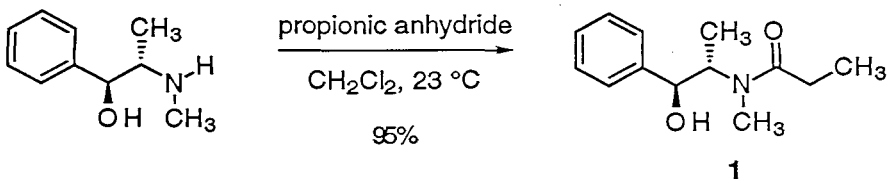
Instrumentation. Melting points are uncorrected. Infrared data are presented as follows: frequency of absorption (cm^{-1}), intensity of absorption (br = broad, s = strong, m

= medium). ^{1}H 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. ^{1}H 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) or to tetramethylsilane. 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. Correlated spectroscopy (COSY) experiments were performed on a GE QE-300 MHz instrument at 23 °C using the following parameters: P2 = 7.00 μsec, D5 = 200 msec, D8 = 10.00 μsec, I8 = 312 μsec, acquisition time = 159.74 msec, recycle time = 0.47 sec. Nuclear Overhauser enhancement (NOE) experiments were performed on the same instrument at 23 °C using the following parameters: P2 = 8 msec, D4 = 1 msec, D5 = 1 sec, D6 = 5 sec, L1 = 3075. ^{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-Lincoln, at the California Institute of Technology, or at the University of California at Irvine. Crystal structures were obtained by Dr. Joseph Ziller (University of California at Irvine). Combustion analyses were performed by Mr. Fenton Harvey (California Institute of Technology), or by Quantitative Technologies Incorporated.

Chiral capillary gas chromatography (GC) analysis was carried out using an Alltech Chirasil-Val chiral fused silica capillary column, under isothermal conditions, with a column head pressure of 17 psi.

Determination of Absolute Stereochemistry of Alkylation Products: The structures of alkylation products **11**, **12**, and **16** were determined by X-ray crystallographic analysis. Product **13** was transformed by LAB (vide infra) to the known (*S*)-2-methyl-1,3-propanediol benzyl ether in good yield.[7b] Both (*R*)- and (*S*)- Mosher ester derivatives[41] of this alcohol were prepared and were identified conclusively by comparison with ^{1}H NMR data from authentic materials).[7b] Products **17** and **19** form a

diastereomeric pair. Their hydrolysis (vide infra) produces enantiomeric acids whose configuration was established by comparison of the respective optical rotations to literature values of the known (*R*)-2-benzylhexanoic acid.[42] Products **12** and **18** form a diastereomeric pair; since the configuration of **12** was secured by X-ray analysis, that of **18** is defined unambiguously. Acidic hydrolysis of product **20** produces 2-phenylbutyric acid, which was coupled with (*R*)-α-methylbenzylamine as described for acid **39** (vide infra). The resulting (*R*)-α-methylbenzyl amide was shown to be identical to the (*R*)-α-methylbenzyl amide of commercially available (*S*)-2-phenylbutyric acid by chiral capillary GC analysis. In every case studied, the major pseudoephedrine alkylation product results from electrophilic attack on the putative *Z*-enolate (R syn to the enolate oxygen) from the same face as the carbon-bound methyl group of pseudoephedrine when it is drawn in its extended conformation (Figure 1). The remaining alkylations were assumed to proceed analogously.

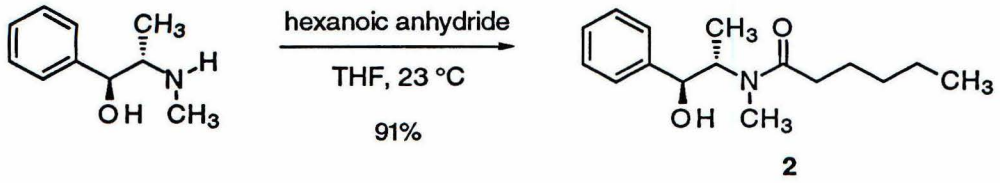


1

(*S*,*S*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methyl Propionamide **1**

A 1-L flask was charged with (+)-pseudoephedrine (21.0 g, 127 mmol, 1 equiv), triethylamine (21.3 mL, 153 mmol, 1.20 equiv) and dichloromethane (250 mL). The flask was placed in a water bath at 23 °C, and propionic anhydride (17.4 mL, 136 mmol, 1.07 equiv) was added to the solution in 1-mL portions over several minutes. The reaction mixture was stirred for 30 min at 23 °C, then excess anhydride was quenched by the addition of water (40 mL). The organic layer was separated and extracted with half-saturated aqueous sodium bicarbonate solution (2 × 40 mL) and 1 N aqueous hydrochloric acid solution (2 × 40 mL). The organic extract was dried over sodium sulfate and was concentrated in vacuo to furnish a white solid. Recrystallization of the product from hot toluene (110 °C, 85 mL) furnished amide **1** as a white crystalline solid (26.9 g, 95%): mp 114–115 °C.

^{1}H NMR (300 MHz, C_6D_6) δ:	(3:1 rotamer ratio, * denotes minor rotamer peaks) 6.95–7.45 (m, 5H, Ar**H**), 4.83 (br, 1H, O**H**), 4.51 (t, 1H, J = 7.2 Hz, C**H**OH), 4.10 (m, 2H, C**H**OH, NCHC**H**$_3$), 3.68* (m, 1H, NC**H**CH$_3$), 2.77* (s, 3H, NC**H**$_3$), 2.40* (m, 2H, C**H**$_2$), 2.06 (s, 3H, NC**H**$_3$), 1.73 (m, 2H, C**H**$_2$), 1.22* (t, 3H, J = 7.3 Hz, CH$_2$C**H**$_3$), 0.9–1.1 (m, 6H, C**H**$_3$CHN, CH$_2$C**H**$_3$), 0.53* (d, 3H, J = 6.7 Hz, C**H**$_3$CHN).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	(2:1 rotamer ratio, * denotes minor rotamer peaks) 175.8, 174.8*, 142.2, 141.5*, 128.3*, 128.1, 127.9*, 127.4, 126.7*, 126.3, 76.1, 75.0*, 58.1, 57.7*, 32.1, 27.3, 26.6*, 15.2*, 14.2, 9.4*, 9.0.
FTIR (neat, cm^{-1}):	3380 (br, m, OH), 1621 (s, C=O).
HRMS (FAB):	Calcd for $C_{13}H_{20}NO_2$ $(MH)^+$: 222.1495 Found: 222.1490.
Analysis:	Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33 Found: C, 70.62; H, 8.36; N, 6.34.
TLC (15% MeOH–CH_2Cl_2), R_f:	**1**: 0.61 (UV, PMA). pseudoephedrine: 0.05 (UV, PMA).

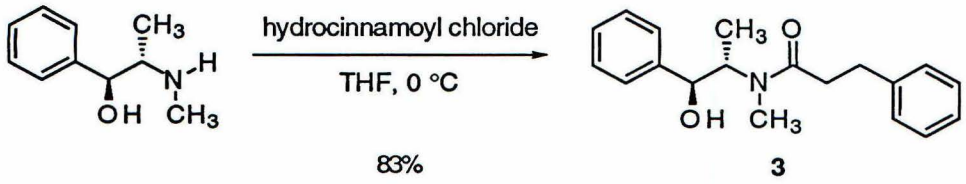


2

(*S*,*S*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methyl Hexanamide **2**

A 2-L flask was charged with (+)-pseudoephedrine (40.0 g, 242 mmol, 1 equiv) and tetrahydrofuran (500 mL). The flask was placed in a water bath at 23 °C, and hexanoic anhydride (55.5 g, 259 mmol, 1.07 equiv) was added to the solution via cannula over 10 min. The reaction mixture was stirred for 25 min at 23 °C, then the hexanoic acid was quenched by the cautious addition of saturated aqueous sodium bicarbonate solution (300 mL). Tetrahydrofuran was removed under reduced pressure, and the resulting aqueous solution was partitioned between water (500 mL) and ethyl acetate (250 mL). The aqueous layer was separated and extracted with ethyl acetate (2 × 250 mL). The combined organic extracts were dried over sodium sulfate and were concentrated to furnish a white solid. The solid was dissolved in a warm solution of ether (35 °C, 100 mL), and the solution was diluted with hot hexanes (69 °C, 100 mL). Recrystallization of the product from this 1:1 mixture of ether and hexanes afforded amide **2** as a white crystalline solid (58.2 g, 91%): mp 62–63 °C.

^{1}H NMR (300 MHz, C_6D_6) δ:	(7:1 rotamer ratio, * denotes minor rotamer peaks) 7.0–7.4 (m, 5H, aromatic), 4.9 (br, 1H, **OH**), 4.52 (d, 1H, J = 6.9 Hz, **CHOH**), 4.14 (m, 2H, **CHOH**, **NCHCH$_3$**), 3.77* (m, 1H, NCHCH$_3$), 2.79* (s, 3H, **NCH$_3$**), 2.42* (m, 2H, **COCH$_2$**), 2.13 (s, 3H, **NCH$_3$**), 1.83 (m, 2H, **COCH$_2$**), 1.59 (qn, 2H, J = 7.6 Hz, **COCH$_2$CH$_2$**), 1.1–1.4 (m, 4H, **CH$_2$CH$_2$CH$_3$**), 0.99 (d, 3H, J = 7.0 Hz, **CH$_3$CHN**), 0.86 (t, 3H, J = 7.0 Hz, **CH$_2$CH$_3$**), 0.59* (d, 3H, J = 6.8 Hz, **CH$_3$CHN**).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	(2:1 rotamer ratio, * denotes minor rotamer peaks) 175.2, 174.2*, 142.3, 141.6*, 128.3*, 128.0, 127.8*, 127.3, 126.7*, 126.2, 76.1, 75.1*, 58.2, 57.0*, 34.1, 33.4*, 32.4*, 31.5*, 31.3, 26.6, 24.9*, 24.5, 22.31*, 22.29, 15.2*, 14.2, 13.82*, 13.79.
FTIR (neat, cm^{-1}):	3378 (br, m, OH), 1618 (s, C=O).
HRMS (FAB):	Calcd for $C_{16}H_{26}NO_2$ $(MH)^+$: 264.1965. Found: 264.1966.
Analysis:	Calcd for $C_{16}H_{25}NO_2$: C, 72.97; H, 9.57; N, 5.32. Found: C, 73.07; H, 9.30; N, 5.27.
TLC (15% MeOH–CH_2Cl_2), R_f:	**2**: 0.71 (UV, PMA). pseudoephedrine: 0.05 (UV, PMA).

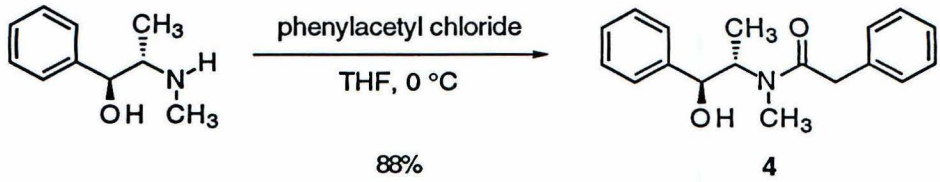


3

(*S*,*S*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methyl Benzenepropionamide **3**

A solution of hydrocinnamoyl chloride (24.4 g, 145 mmol, 1.15 equiv) in tetrahydrofuran (50 mL) was added via cannula over 10 min to an ice-cooled solution of (+)-pseudoephedrine (20.8 g, 126 mmol, 1 equiv) and triethylamine (22.8 mL, 164 mmol, 1.30 equiv) in tetrahydrofuran (300 mL). After 10 minutes, excess acid chloride was quenched by the addition of water (10 mL). The mixture was partitioned between ethyl acetate (500 mL) and brine (40 mL), and the organic layer was separated and extracted with brine (2 × 40 mL). The organic layer was dried over sodium sulfate and was concentrated. Recrystallization of the crude reaction product from hot toluene (110 °C, 125 mL) afforded amide **3** as a white crystalline solid (31.2 g, 83%): mp 102–104 °C.

^{1}H NMR (300 MHz, C_6D_6) δ:	(3:1 rotamer ratio, * denotes minor rotamer peaks) 7.0–7.4 (m, 10H, aromatic), 4.59 (br, 1H, **OH**), 4.48 (t, 1H, *J* = 7.1 Hz, **CH**OH), 4.20 (m, 1H, NC**H**CH$_3$), 4.01* (dd, 1H, *J* = 8.4 Hz, 2.4 Hz, **CH**OH), 3.66* (m, 1H, NC**H**CH$_3$), 3.15* (m, 2H, **CH$_2$**Ph), 2.93 (t, 2H, *J* = 7.7 Hz, C**H$_2$**Ph), 2.79* (s, 3H, NC**H$_3$**), 2.49* (m, 2H, COC**H$_2$**), 2.13 (m, 2H, COC**H$_2$**), 2.02 (s, 3H, NC**H$_3$**), 0.92 (d, 3H, *J* = 7.0 Hz, C**H$_3$**CHN), 0.49* (d, 3H, *J* = 6.8 Hz, C**H$_3$**CHN).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	(3:1 rotamer ratio, * denotes minor rotamer peaks) 174.3, 173.2*, 142.2, 141.5*, 141.3*, 141.1, 128.6*, 128.39, 128.36, 128.31, 128.29, 128.2*, 127.6*, 126.8*, 126.4, 126.1, 125.9*, 76.3, 75.3*, 58.2, 58.0*, 36.1, 35.4*, 32.3*, 31.5*, 31.1, 26.9, 15.2*, 14.3.
FTIR (neat, cm^{-1}):	3374 (br, m, OH), 1621 (s, C=O).
HRMS (FAB):	Calcd for $C_{19}H_{24}NO_2$ $(MH)^+$: 298.1808.
	Found: 298.1806.
Analysis:	Calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71.
	Found: C, 76.45; H, 8.00; N, 4.40.
TLC (15% MeOH–CH_2Cl_2), R_f:	**3**: 0.71 (UV, PMA).
	pseudoephedrine: 0.05 (UV, PMA).

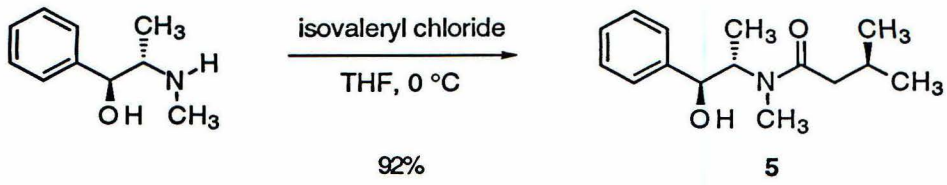


4

(*S*,*S*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methyl Benzeneacetamide **4**

An ice-cooled solution of phenylacetyl chloride (21.1 g, 137 mmol, 1.10 equiv) in tetrahydrofuran (100 mL) was added via cannula over 15 min to a solution of (+)-pseudoephedrine (20.5 g, 124 mmol, 1 equiv) and triethylamine (19.7 mL, 142 mmol, 1.14 equiv) in tetrahydrofuran (500 mL) at 0 °C. The resulting suspension was stirred for 30 min at 0 °C, then excess acid chloride was quenched by the addition of saturated aqueous sodium bicarbonate solution (10 mL). Volatile solvents were removed under reduced pressure, and the resulting aqueous solution was partitioned between dichloromethane (600 mL) and water (100 mL). The organic layer was separated and extracted sequentially with water (100 mL), 1 N aqueous hydrochloric acid solution (100 mL), and brine (60 mL). The organic layer was dried over sodium sulfate and was concentrated. Recrystallization of the crude reaction product from hot toluene (110 °C, 200 mL) afforded amide **4** as a white crystalline solid (30.9 g, 88%): mp 145–146 °C.

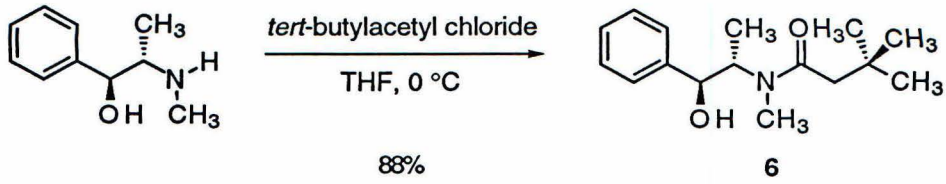
^{1}H NMR (*300 MHz*, C_6D_6) δ:	(2:1 rotamer ratio, * denotes minor rotamer peaks) 6.9–7.5 (m, 10H, aromatic), 4.65 (br, 1H, **OH**), 4.48 (t, 1H, *J* = 7.1 Hz, **CH**OH), 4.22 (m, 1H, NC**H**CH$_3$), 4.17* (m, 1H, **CH**OH), 3.90* (m, 1H, NC**H**CH$_3$), 3.78* (s, 2H, C**H**$_2$Ph), 3.31 (d, 2H, *J* = 1.3 Hz, C**H**$_2$Ph), 2.76* (s, 3H, NC**H**$_3$), 2.12 (s, 3H, NC**H**$_3$), 0.95 (d, 3H, *J* = 7.0 Hz, C**H**$_3$CHN), 0.42* (d, 3H, *J* = 6.7 Hz, C**H**$_3$CHN).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	(2:1 rotamer ratio, * denotes minor rotamer peaks) 173.1, 172.2*, 142.2, 141.4*, 135.5*, 134.5, 128.7, 128.64, 128.58, 128.3, 128.1*, 127.5*, 126.73*, 126.68*, 126.6*, 126.3, 76.2, 75.3*, 58.6, 41.8, 41.4*, 33.3*, 27.0, 15.0*, 14.3.
FTIR (neat, cm^{-1}):	3393 (br, m, OH), 1618 (s, C=O).
HRMS (FAB):	Calcd for $C_{18}H_{22}NO_2$ $(MH)^+$: 284.1652.
	Found: 284.1646.
Analysis:	Calcd for $C_{18}H_{21}NO_2$: C, 76.30; H, 7.47; N, 4.94.
	Found: C, 76.07; H, 7.40; N, 4.86.
TLC (15% MeOH–CH_2Cl_2), R_f:	**4**: 0.69 (UV, PMA).
	pseudoephedrine: 0.05 (UV, PMA).



(*S*,*S*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*,3-dimethyl Butanamide **5**

An ice-cooled solution of isovaleryl chloride (8.47 g, 70.3 mmol, 1.10 equiv) in tetrahydrofuran (50 mL) was added via cannula over 15 min to a solution of (+)-pseudoephedrine (10.6 g, 63.9 mL, 1 equiv) and triethylamine (10.7 mL, 76.7 mmol, 1.2 equiv) in tetrahydrofuran (200 mL) at 0 °C. After 30 min, excess acid chloride was quenched by the addition of saturated aqueous sodium bicarbonate solution (5 mL). The mixture was partitioned between half-saturated aqueous sodium bicarbonate solution (80 mL) and ethyl acetate (200 mL). The organic layer was separated and extracted sequentially with half saturated aqueous sodium bicarbonate solution (25 mL), two 25-mL portions of 3 N aqueous hydrochloric acid solution, and two 20-mL portions of brine. The organic layer was dried over sodium sulfate and was concentrated. Recrystallization of the crude reaction product from hot hexanes (69 °C, 25 mL) afforded amide **5** as a white crystalline solid (14.6 g, 92%): mp 73–74 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ:	(4:1 rotamer ratio, * denotes minor rotamer peaks) 7.20–7.45 (m, 5H, aromatic), 4.6 (m, 1H, **CH**OH), 4.42 (m, 1H, NC**H**CH_3), 4.01* (m, 1H, NC**H**CH_3), 2.91* (s, 3H, NCH_3), 2.81 (s, 3H, NCH_3), 2.05–2.30 (m, 3H, COCH_2**C**H), 1.13 (d, 3H, J = 7.0 Hz, CHNCH_3), 0.96 (m, 6H, $CH_2CH(CH_3)_2$).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	(4:1 rotamer ratio, * denotes minor rotamer peaks) 174.9, 173.6*, 142.5, 141.3*, 128.7*, 128.3, 127.5, 126.9*, 126.3, 76.5, 75.5*, 58.7, 58.3*, 43.1, 42.5*, 33.2, 26.7*, 25.5, 22.8*, 22.7, 22.6, 22.4*, 22.3*, 15.3*, 14.5.
FTIR (neat, cm^{-1}):	3380 (br, s, OH), 1614 (s, C=O).
HRMS (FAB):	Calcd for $C_{15}H_{24}NO_2$ $(MH)^+$: 250.1807.
	Found: 250.1816.
Analysis:	Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62.
	Found: C, 72.02; H, 9.58; N, 5.43.
TLC (80% EtOAc–hexanes), R_f:	**5**: 0.71 (UV, PMA).
	pseudoephedrine: 0.04 (UV, PMA).

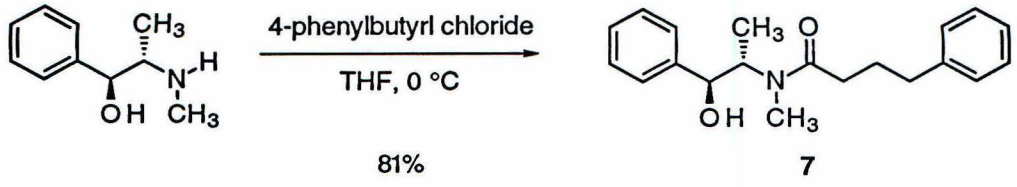


6

(*S*,*S*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*,3,3-trimethyl Butanamide **6**

An ice-cooled solution of *tert*-butylacetyl chloride (7.33 g, 54.4 mmol, 1.05 equiv) in tetrahydrofuran (50 mL) was transferred via cannula over 5 min to a solution of (+)-pseudoephedrine (8.56 g, 51.8 g, 1 equiv) and triethylamine (8.67 mL, 62.2 mL, 1.20 equiv) in tetrahydrofuran (200 mL) at 0 °C. The resulting thick white suspension was stirred at 0 °C for 65 min, then excess acid chloride was quenched by the sequential addition of saturated aqueous sodium bicarbonate solution (5 mL) and 0.5 N aqueous sodium hydroxide solution (30 mL). Tetrahydrofuran was removed under reduced pressure, and the resulting aqueous solution was extracted with dichloromethane (200 mL). The organic layer was separated and extracted sequentially with three 20-mL portions of 0.5 N aqueous sodium hydroxide solution and three 20-mL portions of 1 N aqueous hydrochloric acid solution. The organic layer was dried over sodium sulfate and was concentrated. Recrystallization of the crude reaction product from hot hexanes (69 °C, 40 mL) afforded amide **6** as a white crystalline solid (12.0 g, 88%): mp 68–69 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ:	(5:1 rotamer ratio, * denotes minor rotamer peaks) 7.2–7.4 (m, 5H, aromatic), 4.59 (m, 1H, **CH**OH), 4.44 (br, m, 1H, NC**H**CH_3), 4.09* (m, 1H, NC**H**CH_3), 2.90* (s, 3H, NCH_3), 2.84 (s, 3H, NCH_3), 2.23 (d, 2H, J = 1.4 Hz, CH_2), 1.12 (d, 3H, J = 7.0 Hz, CH_3CHN), 1.06* (s, 9H, $CH_2C(CH_3)_3$), 1.01 (s, 9H, $CH_2C(CH_3)_3$).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	(5:1 rotamer ratio, * denotes minor rotamer peaks) 174.4, 173.0*, 142.6, 141.2*, 128.6*, 128.3, 127.5, 126.9*, 126.3, 76.4, 75.6*, 58.7, 45.8, 45.1*, 34.1, 31.6*, 30.1*, 29.9, 15.4*, 14.5.
FTIR (neat, cm^{-1}):	3382 (br, s, OH), 1614 (s, C=O).
HRMS (FAB)	Calcd for $C_{16}H_{26}NO_2$ $(MH)^+$: 264.1964.
	Found: 264.1971.
Analysis:	Calcd for $C_{16}H_{25}NO_2$: C, 72.97; H, 9.57; N, 5.32.
	Found: C, 72.73; H, 9.74; N, 5.21.
TLC (80% EtOAc–hexanes), R_f:	**6**: 0.66 (UV, PMA).
	pseudoephedrine: 0.04 (UV, PMA).

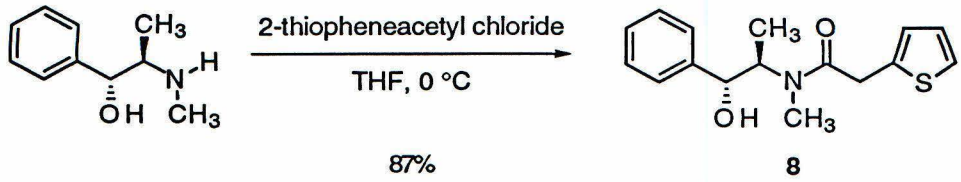


7

(*S*,*S*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methyl Benzenebutanamide **7**

A solution of 4-phenylbutyric acid (4.57 g, 29.1 mmol, 1.20 equiv) in dichloromethane (15 mL) was charged sequentially with oxalyl chloride (2.53 mL, 29.1 mmol, 1.20 equiv) and *N*,*N*-dimethylformamide (10 μL, 0.13 mmol, 0.005 equiv). The latter addition resulted in vigorous bubbling, and the resulting mixture was stirred at 23 °C for 1 hour, during which time the bubbling ceased. The reaction mixture was cooled to 0 °C and was transferred via cannula to a solution of (+)-pseudoephedrine (4.00 g, 24.2 g, 1 equiv) and triethylamine (4.72 mL, 33.9 mmol, 1.40 equiv) in tetrahydrofuran (50 mL) at 0 °C. After 1 h, unreacted acid chloride was quenched by the addition of water (5 mL). The mixture was partitioned between ethyl acetate (400 mL) and half-saturated aqueous sodium bicarbonate solution (25 mL), and the organic layer was separated and extracted sequentially with half-saturated aqueous sodium bicarbonate solution (25 mL), two 25-mL portions of 2 N aqueous hydrochloric acid solution, and brine (25 mL). The organic layer was dried over sodium sulfate and was concentrated. Recrystallization of the crude reaction product from hot toluene (110 °C, 15 mL) afforded amide **7** as a white crystalline solid (6.08 g, 81%): mp 100–102 °C.

^{1}H NMR (*300 MHz*, $CDCl_3$) δ:	(3:1 rotamer ratio, * denotes minor rotamer peaks) 7.1–7.4 (m, 10H, aromatic), 4.60 (m, 1H, **CH**OH), 4.53* (m, 1H, **CH**OH), 4.45 (m, 1H, NC**H**CH_3), 4.33 (br, 1H, **OH**), 3.90* (m, 1H, NC**H**CH_3), 2.92* (s, 3H, NC**H**$_3$), 2.75 (s, 3H, NC**H**$_3$), 2.64–2.69 (m, 2H, COC**H**$_2$), 2.35 (m, 2H, PhC**H**$_2$), 2.00 (m, 2H, PhCH_2C**H**$_2$), 1.10 (d, 3H, J = 6.9 Hz, **CH**$_3$CHN), 0.95* (d, 3H, J = 6.8 Hz, **CH**$_3$CHN).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	(3:1 rotamer ratio, * denotes minor rotamer peaks) 175.0, 174.0*, 142.4, 141.9*, 141.6, 141.2*, 128.6*, 128.5, 128.3, 127.6, 126.8*, 126.4, 125.9*, 76.5, 75.5*, 58.5, 58.2*, 35.4*, 35.1, 33.3, 32.8*, 26.8*, 26.3, 15.3*, 14.4.
FTIR (neat, cm^{-1}):	3374 (br, m, OH), 1620 (s, C=O).
HRMS (FAB):	Calcd for $C_{20}H_{26}NO_2$ $(MH)^+$: 312.1964.
	Found: 312.1974.
Analysis:	Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50.
	Found: C, 77.06; H, 7.94; N, 4.62.
TLC (15% MeOH–CH_2Cl_2), R_f:	**7**: 0.67 (UV, PMA).
	4-phenylbutyric acid: 0.60 (UV).

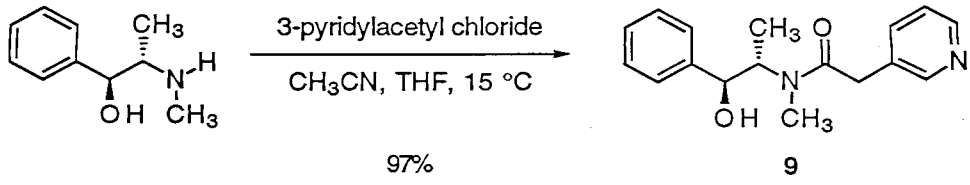


8

(*R*,*R*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methyl 2-Thiopheneacetamide **8**

A solution of 2-thiopheneacetyl chloride (3.89 g, 24.2 mmol, 1.05 equiv) in tetrahydrofuran (10 mL, followed by a 10-mL rinse) was added via cannula to a solution of (–)-pseudoephedrine (3.81 g, 23.1 mmol, 1 equiv) and triethylamine (3.86 mL, 27.7 mmol, 1.20 equiv) in tetrahydrofuran (100 mL) at 0 °C. The resulting thick suspension was stirred for 30 min at 0 °C, then excess acid chloride was quenched by the addition of water (20 mL). Tetrahydrofuran was removed under reduced pressure, and the resulting aqueous solution was partitioned between water (20 mL) and ethyl acetate (300 mL). The organic layer was separated and extracted sequentially with 80% saturated aqueous sodium bicarbonate solution (25 mL), 2 N aqueous hydrochloric acid solution (25 mL) and brine (25 mL). The organic layer was dried over sodium sulfate and was concentrated. The crude reaction product was purified by flash column chromatography (60% ethyl acetate–hexanes) affording the amide **8** as a yellow crystalline solid (5.29 g, 87%): mp 110–111 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ:	(2:1 rotamer ratio, * denotes minor rotamer peaks) 7.2–7.4 (m, 5H, aromatic), 6.9–7.0 (m, 3H, thiophene), 4.50–4.62 (m, 2H, CHOH, $NCHCH_3$), 3.91–4.12* (m, 2H, CHOH, $NCHCH_3$), 3.96* (s, 2H, CH_2), 3.88 (s, 2H, CH_2), 2.96* (s, 3H, NCH_3), 2.88 (s, 3H, NCH_3), 1.11 (d, 3H, J = 6.9 Hz, CH_3CHN), 0.90* (d, 3H, J = 6.8 Hz, CH_3CHN).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	(2:1 rotamer ratio, * denotes minor rotamer peaks) 172.0, 171.1*, 142.1, 141.3*, 137.0*, 136.1, 128.7*, 128.4, 127.7, 126.8, 126.4, 126.1*, 126.0*, 124.7, 124.6*, 76.3, 75.5, 58.8, 58.4, 36.0, 35.5, 32.9, 27.1, 15.1, 14.2.
FTIR (neat, cm^{-1}):	3384 (br, m, OH), 1624 (s, C=O).
HRMS (FAB):	Calcd for $C_{16}H_{20}NO_2S$ $(MH)^+$: 290.1215. Found: 290.1229.
Analysis:	Calcd for $C_{16}H_{19}NO_2S$: C, 66.41; H, 6.62; N, 4.84. Found:C, 66.18; H, 6.64; N, 4.64.
TLC (15% MeOH–CH_2Cl_2), R_f:	**8**: 0.59 (UV, PMA). pseudoephedrine: 0.05 (UV, PMA).

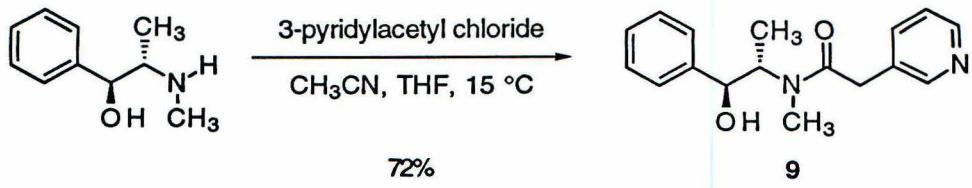


9

(*S*,*S*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methyl 3-Pyridineacetamide **9**

Triethylamine (3.34 mL, 24.0 mmol, 3.00 equiv) was added to a suspension of 3-pyridylacetic acid hydrochloride (2.08 g, 12.0 mmol, 1.50 equiv) in acetonitrile (60 mL). The resulting suspension was stirred at 23 °C for 10 min, then was cooled to 0 °C. Pivaloyl chloride (1.48 mL, 12.0 mmol, 1.50 equiv) was added followed by tetrahydrofuran (10 mL) to improve stirring of the thick suspension. A solution of (+)-pseudoephedrine (1.32 g, 7.99 mmol, 1 equiv) and triethylamine (1.11 mL, 7.99 mmol, 1 equiv) in tetrahydrofuran (20 mL, followed by a 3-mL rinse) was added rapidly via cannula. The mixture was warmed slowly to 15 °C over one hour, and excess anhydride was quenched by the addition of water (10 mL). Volatile solvents were removed under reduced pressure, and the resulting aqueous solution was suspended between 0.5 N aqueous sodium hydroxide solution and 10% methanol–dichloromethane (50 mL). The aqueous layer was separated and extracted with 10% methanol–dichloromethane (4 × 50 mL). The combined organic layers were washed with 1 N aqueous sodium hydroxide solution (15 mL), then were dried over sodium sulfate and were concentrated. Purification of the product by flash column chromatography, eluting with a gradient of ethyl acetate–methanol–triethylamine [(90:8:2) → (88:10:2)] afforded amide **9** as a white crystalline solid (2.21 g, 93%): mp 117.5–118.5 °C.

^{1}H NMR (*300 MHz*, $CDCl_3$) δ:	(2:1 rotamer ratio, * denotes minor rotamer peaks) 8.2–8.6 (m, 2H, two of $C_5\mathbf{H}_4N$), 7.6–7.7 (m, 1H, one of $C_5\mathbf{H}_4N$), 7.1–7.4 (m, 6H, one of $C_5\mathbf{H}_4N$, phenyl), 4.4–4.7 (m, 2H, CHOH, $NC\mathbf{H}CH_3$), 4.0–4.3* (m, 2H, CHOH, $NC\mathbf{H}CH_3$), 3.80* (d, 2H, J = 1.8 Hz, $C\mathbf{H}_2$), 3.67 (s, 2H, $C\mathbf{H}_2$), 2.96* (s, 3H, $NC\mathbf{H}_3$), 2.89 (s, 3H, $NC\mathbf{H}_3$), 1.13 (d, 3H, J = 6.8 Hz, $C\mathbf{H}_3CHN$), 0.93* (d, 3H, J = 6.8 Hz, $C\mathbf{H}_3CHN$).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	(2:1 rotamer ratio, * denotes minor rotamer peaks) 171.0, 170.8*, 149.8*, 149.6, 147.4, 147.2*, 142.1, 142.0*, 136.9*, 136.6, 131.5*, 130.6, 128.3*, 128.0, 127.7*, 127.3, 126.5*, 126.3, 123.2, 123.0*, 75.3, 74.8*, 58.4, 56.5*, 38.0, 37.4*, 31.8*, 27.1, 15.2*, 14.0.
FTIR (neat, cm^{-1}):	3385 (br, m, OH), 1626 (s, C=O).
HRMS (FAB):	Calcd for $C_{17}H_{21}N_2O_2$ $(MH)^+$: 285.1603.
	Found: 285.1596.
Analysis:	Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85.
	Found: C, 71.77; H, 7.08; N, 9.81.
TLC (Et_3N-pretreated plate, 10% MeOH–CH_2Cl_2), R_f:	**9**: 0.40 (UV, PMA).
	pseudoephedrine: 0.14 (UV, PMA).

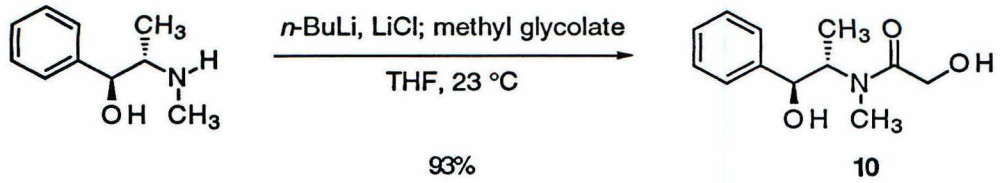


9

(*S*,*S*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methyl 3-Pyridineacetamide **9**

Amide **9** could also be purified by recrystallization. Following a procedure similar to that described above, using (+)-pseudoephedrine (1.49 g, 8.99 mmol, 1 equiv), triethylamine (3.38 mL, 24.3 mmol, 3.00 equiv), 3-pyridylacetic acid hydrochloride (2.11 g, 12.1 mmol, 1.35 equiv), and pivaloyl chloride (1.50 mL, 12.1 mmol, 1.35 equiv), the crude reaction product was recrystallized from hot toluene (110 °C, 8 mL) furnishing the amide **9** as a crystalline solid (1.83 g, 72%). Spectroscopic data were identical to those listed above: mp 117.5–118.5 °C.

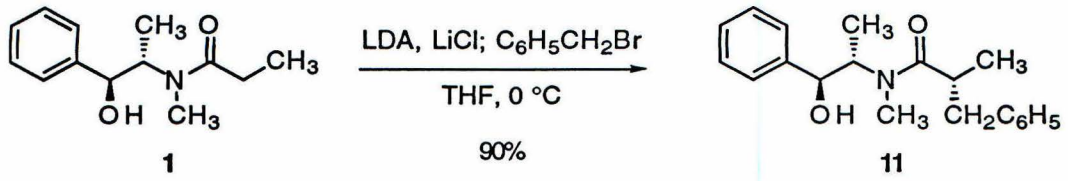
Analysis: Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85.
Found: C, 71.60; H, 7.18; N, 9.73.



(*S*,*S*)-α-Hydroxy-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methyl Acetamide **10**

A solution of *n*-butyllithium in hexanes (2.37 M, 5.62 mL, 13.3 mmol, 0.5 equiv) was added to an ice-cooled suspension of lithium chloride (3.39 g, 79.9 mmol, 3.00 equiv) and (+)-pseudoephedrine (4.40 g, 26.6 mmol, 1 equiv) in tetrahydrofuran (200 mL), and the suspension was stirred at 0 °C for 30 min. Methyl glycolate (4.11 mL, 53.3 mmol, 2.00 equiv) was added via syringe over 5 min, and the mixture was warmed to 23 °C and stirred at that temperature for 3 h. A solution of 0.5 N aqueous sodium hydroxide (100 mL) was added, and the biphasic mixture was stirred at 23 °C for 1 h. Volatile organic solvents were removed under reduced pressure, and the resulting aqueous solution was extracted with five 50-mL portions of 10% methanol–dichloromethane. The combined organic extracts were dried over sodium sulfate and were concentrated. Purification of the product by flash column chromatography eluting with a gradient of methanol–dichloromethane (6 → 10%) afforded amide **10** as a colorless oil which slowly solidified (5.55 g, 93%): mp 61–63 °C.

^{1}H NMR (*300 MHz*, $CDCl_3$) δ:	(2:1 rotamer ratio, * denotes minor rotamer peaks) 7.20–7.45 (m, 5H, aromatic), 4.60 (m, 2H, CH_2OH), 4.36* (m, 2H, CH_2OH), 4.10–4.20 (m, 2H, CHOH, $NCHCH_3$), 3.75* (br, 1H, OH), 3.65 (br, 1H, OH), 3.55–3.65* (m, 2H, CHOH, $NCHCH_3$), 3.20 (br, 1H, OH), 3.01* (s, 3H, NCH_3), 2.75 (s, 3H, NCH_3), 2.40* (br, 1H, OH), 1.08 (d, 3H, J = 6.6 Hz, CH_3CHN), 0.99* (d, 3H, J = 6.8 Hz, CH_3CHN).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	(2:1 rotamer ratio, * denotes minor rotamer peaks) 172.9, 172.6*, 141.6, 141.1*, 128.7*, 128.4, 127.9*, 126.7, 126.5, 75.6, 74.9*, 60.1, 60.0*, 57.3*, 56.7, 29.0, 27.1*, 15.0*, 14.0.
FTIR (neat, cm^{-1}):	3390 (br, s, OH), 1634 (s, C=O).
HRMS (EI):	Calcd for $C_{12}H_{18}NO_3$ $(MH)^+$: 224.1287.
	Found: 224.1289.
Analysis:	Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27.
	Found: C, 64.53; H, 7.58; N, 6.20.
TLC (Et_3N-pretreated plate,	
10% MeOH–CH_2Cl_2), R_f:	**10**: 0.44 (UV, PMA).
	pseudoephedrine: 0.11 (UV, PMA).

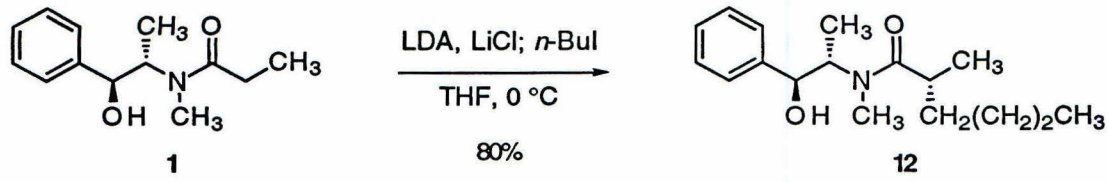


1 11

[1*S*(*R*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*,2-dimethyl Benzenepropionamide **11**

A 3-necked, 2-L flask equipped with a mechanical stirrer was charged with lithium chloride (25.0 g, 596 mmol, 6.00 equiv), diisopropylamine (31.3 mL, 224 mmol, 2.25 equiv) and tetrahydrofuran (120 mL). The resulting suspension was cooled to –78 °C and a solution of *n*-butyllithium in hexanes (2.43 M, 85.1 mL, 207 mmol, 2.08 equiv) was added via cannula. The suspension was warmed briefly to 0 °C, then was cooled to –78 °C. An ice-cooled solution of amide **1** (22.0 g, 99.4 mmol, 1 equiv) in tetrahydrofuran (300 mL) was added to the reaction flask via cannula. The reaction mixture was stirred at –78 °C for 1 h, at 0° C for 15 min, at 23 °C for 5 min, and finally was cooled to 0 °C, whereupon benzyl bromide (17.7 mL, 149 mmol, 1.50 equiv) was added. The mixture was stirred at 0 °C for 15 min then was quenched by the addition of saturated aqueous ammonium chloride solution (10 mL). The mixture was partitioned between saturated aqueous ammonium chloride solution (800 mL) and ethyl acetate (500 mL), and the aqueous layer was separated and extracted with two 150-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate and were concentrated to afford a yellow solid. Recrystallization of the product from hot toluene (110 °C, 100 mL) afforded amide **11** as a white crystalline solid (27.8 g, 90%): mp 136–137 °C. Amide **11** (30 mg, 0.096 mmol, 1 equiv) was silylated with chlorotrimethylsilane (34 μL, 0.27 mmol, 2.8 equiv) and triethylamine (49 μL, 0.35 mmol, 3.6 equiv) in dichloromethane (1 mL) at 23 °C for 10 min, and chiral capillary GC analysis[43] of the resulting trimethylsilyl ether established that amide **11** was of ≥99% de.

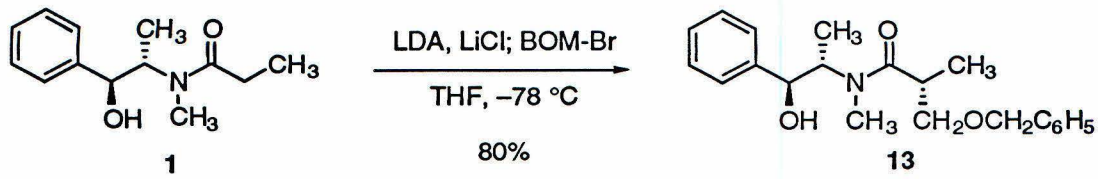
^{1}H NMR (300 MHz, C_6D_6) δ:	(3:1 rotamer ratio, * denotes minor rotamer peaks) 6.9–7.4 (m, 10H, aromatic), 4.45 (m, 1H, **CH**OH), 4.25 (br, 1H, **OH**), 3.96* (m, 1H, **CH**OH), 3.80* (m, 1H, NC**H**CH$_3$), 3.36* (dd, 1H, J_1 = 13.1 Hz, J_2 = 6.92 Hz, **CH**Ph), 3.01 (m, 1H, NC**H**CH$_3$), 2.75* (m, 1H, COC**H**), 2.70* (s, 3H, NC**H**$_3$), 2.45–2.59 (m, 3H, COC**H**, C**H**$_2$Ph), 2.08 (s, 3H, NC**H**$_3$), 1.05* (d, 3H, J = 7.0 Hz, COCHC**H**$_3$), 1.02 (d, 3H, J = 6.5 Hz, C**H**$_3$CHN), 0.83 (d, 3H, J = 7.0 Hz, COCHC**H**$_3$), 0.59* (d, 3H, J = 6.8 Hz, C**H**$_3$CHN).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	(3:1 rotamer ratio, * denotes minor rotamer peaks) 178.2, 177.2*, 142.3, 141.1*, 140.5*, 139.9, 129.2*, 128.9, 128.6*, 128.31*, 128.26, 127.5*, 126.8*, 126.4, 126.2, 76.4, 75.2*, 58.0, 40.3, 40.0*, 38.9, 38.1*, 32.3, 27.1*, 17.7*, 17.4, 15.5*, 14.3.
FTIR (neat, cm^{-1}):	3384 (br, m, OH), 1617 (s, C=O).
HRMS (FAB):	Calcd for $C_{20}H_{26}NO_2$ $(MH)^+$: 312.1965. Found: 312.1972.
Analysis:	Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 76.87; H, 8.06; N, 4.50.
TLC (80% EtOAc–hexanes), R_f:	**11**: 0.46 (UV, PMA). **1**: 0.24 (UV, PMA). benzyl bromide: 0.70 (UV, PMA).



[(1*S*(*R*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*,2-dimethyl Hexanamide **12**

A 3-necked, 2-L flask equipped with a mechanical stirrer was charged with lithium chloride (16.8 g, 396 mmol, 6.00 equiv), diisopropylamine (20.8 mL, 149 mmol, 2.25 equiv), and tetrahydrofuran (175 mL). The resulting suspension was cooled to –78 °C, and a solution of *n*-butyllithium in hexanes (1.73 M, 79.4 mL, 137.4 mmol, 2.08 equiv) was added via cannula. The suspension was warmed briefly to 0 °C, then was cooled to –78 °C. An ice-cooled solution of amide **1** (14.6 g, 66.1 mmol, 1 equiv) in tetrahydrofuran (150 mL) was added to the reaction flask by cannula, and the reaction was stirred at –78 °C for 1 h, at 0 °C for 15 min, at 23 °C for 5 min, and finally was cooled to 0 °C, whereupon 1-iodobutane (22.6 mL, 198 mmol, 3.00 equiv) was added. The mixture was stirred at 0 °C for 1.5 h then was quenched by the addition of saturated aqueous ammonium chloride solution (10 mL). The mixture was partitioned between saturated aqueous ammonium chloride solution (800 mL) and ethyl acetate (500 mL). The aqueous layer was separated and extracted with two 150-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate and were concentrated. Recrystallization of the product from hot hexanes (69 °C, 100 mL) afforded amide **12** as a white crystalline solid (14.8 g, 80%): mp 65.5–66.5 °C. Chiral capillary GC analysis[43] of the corresponding trimethylsilyl ether, prepared as described above for amide **11**, established that amide **12** was of ≥99% de.

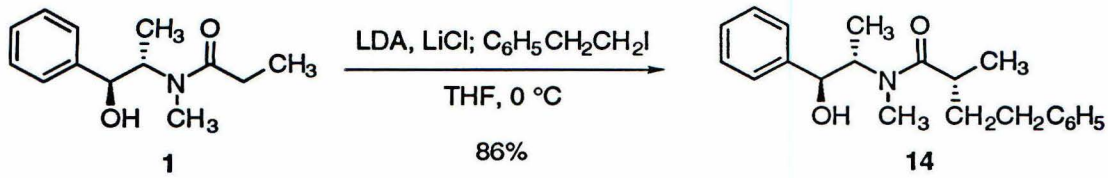
^{1}H NMR (300 MHz, C_6D_6) δ:	(3:1 rotamer ratio, * denotes minor rotamer peaks) 7.00–7.45 (m, 5H, aromatic), 5.17 (br, 1H, **OH**), 4.55 (t, 1H, J = 7.2 Hz, **CH**OH), 4.06 (m, 1H, NC**H**CH$_3$), 3.90* (m, 1H, NC**H**CH$_3$), 2.77 (s, 3H, NC**H**$_3$), 2.70* (m, 1H, COC**H**CH$_3$), 2.22 (s, 3H, NC**H**$_3$), 2.17 (m, 1H, COC**H**CH$_3$), 1.70 (m, 2H, COCHC**H**$_2$), 1.40* (m, 2H, COCHC**H**$_2$), 1.02 (d, 3H, J = 7.2 Hz, C**H**$_3$CHN), 0.99 (d, 3H, J = 6.8 Hz, COCHC**H**$_3$), 0.90–1.25 (m, 4H, CH$_3$C**H**$_2$C**H**$_2$), 0.85 (t, 3H, J = 7.0 Hz, CH$_2$C**H**$_3$), 0.62* (d, 3H, J = 6.8 Hz, C**H**$_3$CHN).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	(5:1 rotamer ratio, * denotes minor peaks) 179.2, 177.8*, 142.6, 141.2*, 128.6*, 128.3*, 128.2, 127.4, 126.8*, 126.2, 76.4, 75.4*, 59.1, 57.8*, 36.5, 35.8*, 33.7, 33.4, 29.7*, 29.5, 27.0*, 22.9*, 22.7, 18.0*, 17.3, 15.3*, 14.5, 14.1*, 14.0.
FTIR (neat, cm^{-1}):	3382 (br, m, OH), 1614 (s, C=O).
HRMS (FAB):	Calcd for $C_{17}H_{28}NO_2$ $(MH)^+$: 278.2121. Found: 278.2124.
Analysis:	Calcd for $C_{17}H_{27}NO_2$: C, 73.61; H, 9.81; N, 5.05. Found: C, 73.40; H, 9.71; N, 5.11.
TLC (80% EtOAc–hexanes), R_f:	**12**: 0.61 (UV, PMA). **1**: 0.24 (UV, PMA).



[1*S*(*R*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*,2-dimethyl-3-benzyloxy Propionamide **13**

A solution of *n*-butyllithium in hexanes (2.37 M, 1.53 mL, 3.62 mmol, 2.08 equiv) was added to a suspension of lithium chloride (516 mg, 12.2 mmol, 7.00 equiv) and diisopropylamine (0.549 mL, 3.92 mmol, 2.25 equiv) in tetrahydrofuran (7 mL) at –78 °C. The suspension was warmed briefly to 0 °C, then was cooled to –78 °C. An ice-cooled solution of amide **1** (385 mg, 1.74 mmol, 1 equiv) in tetrahydrofuran (6 mL, followed by a 1-mL rinse) was added via cannula. The mixture was stirred at –78 °C for 1 h, at 0 °C for 15 min, at 23 °C for 5 min, and finally was cooled to –78 °C, whereupon benzyloxymethyl bromide (0.378 mL, 2.96 mmol, 1.70 equiv) was added. The reaction mixture was stirred at –78 °C for 1 h 25 min, then was quenched at –78 °C by the addition of methanol (0.6 mL). The mixture was warmed to 23 °C and partitioned between saturated aqueous ammonium chloride solution (200 mL) and ethyl acetate (30 mL). The aqueous layer was separated and extracted with two 30-mL portions of ethyl acetate. The combined organic extracts were dried over sodium sulfate and were concentrated. Purification of the product by flash column chromatography (55% ethyl acetate–hexanes) afforded amide **13** as a colorless oil which slowly solidified (477 mg, 80%): mp 65–66 °C. Chiral capillary GC analysis[43] of the corresponding trimethylsilyl ether, prepared as described above for amide **11**, established that amide **13** was of 98% de.

^{1}H NMR (300 MHz, C_6D_6) δ:	(3:2 rotamer ratio, * denotes minor rotamer peaks) 7.0–7.4 (m, 10H, aromatic), 4.54 (m, 1H, **CH**OH), 4.18–4.4.4 (m, 3H, NC**H**CH_3, PhCH_2O), 4.03* (m, 1H, NC**H**CH_3), 3.70 (m, 2H, PhCH_2OCH_2), 3.25* (m, 2H, PhCH_2OCH_2), 3.02* (m, 1H, COC**H**CH_3), 2.84 (s, 3H, NCH_3), 2.72 (m, 1H, COC**H**CH_3), 2.31 (s, 3H, NCH_3), 0.98* (d, 3H, J = 6.6 Hz, COCHCH_3), 0.97 (d, 3H, J = 6.6 Hz, CH_3CHN), 0.96 (d, 3H, J = 6.8 Hz, COCHCH_3), 0.59* (d, 3H, J = 6.7 Hz, CH_3CHN).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	(1:1 rotamer ratio) 177.0, 175.5, 142.3, 141.8, 138.2, 137.1, 128.4, 128.3, 128.2, 128.0, 127.5, 126.9, 126.4, 76.3, 75.4, 73.9, 73.5, 73.3, 73.0, 58.4, 37.4, 35.8, 33.0, 27.0, 15.8, 14.7, 14.4, 14.2.
FTIR (neat, cm^{-1}):	3386 (br, m, OH), 1618 (s, C=O).
HRMS (FAB):	Calcd for $C_{21}H_{27}NO_3$ $(M)^+$: 341.1991.
	Found: 341.2006.
Analysis:	Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10.
	Found: C, 73.99; H, 8.15; N, 4.02.
TLC (80% EtOAc–hexanes), R_f:	**13**: 0.44 (UV, PMA).
	1: 0.31 (UV, PMA).

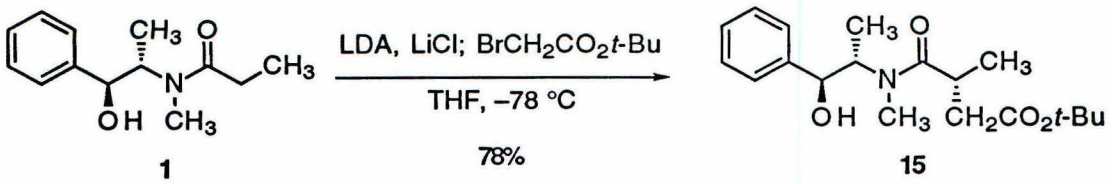


1 14

[1*S*(*R*),2*S*)]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*,2-dimethyl Benzenebutanamide **14**

A solution of *n*-butyllithium in hexanes (2.37 M, 10.7 mL, 25.4 mmol, 2.08 equiv) was added dropwise to a suspension of lithium chloride (3.10 g, 73.2 mmol, 6.00 equiv) and diisopropylamine (3.90 mL, 27.8 mmol, 2.28 equiv) in tetrahydrofuran (50 mL) at –78 °C. The suspension was warmed briefly to 0 °C, then was cooled to –78 °C. An ice-cooled solution of amide **1** (2.70 g, 12.2 mmol, 1 equiv) in tetrahydrofuran (40 mL, followed by a 2-mL rinse) was added via cannula over 4 min. The mixture was stirred at –78 °C for 1 h, at 0 °C for 10 min, at 23 °C for 3 minutes, and finally was cooled to 0 °C, whereupon (2-iodoethyl)benzene (4.42 mL, 30.5 mmol, 2.50 equiv) was added. The reaction mixture was stirred at 0 °C for 1.5 h, then was quenched by the addition of saturated aqueous ammonium chloride solution (10 mL). The mixture was partitioned between half-saturated brine (200 mL) and ethyl acetate (30 mL). The aqueous layer was separated and extracted with two 75-mL portions of ethyl acetate. The combined organic fractions were washed with two 5-mL portions of brine, then were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (15 → 52%) afforded amide **14** as a colorless oil (3.43 g, 86%). Chiral capillary GC analysis[43] of the corresponding trimethylsilyl ether, prepared as described above for amide **11**, established that amide **14** was of 95% de.

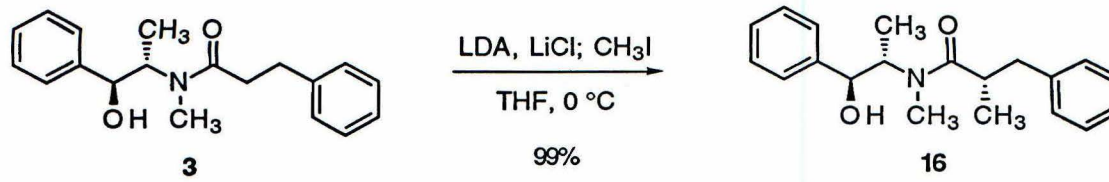
^{1}H NMR (*300 MHz*, $CDCl_3$) δ:	(3:1 rotamer ratio, * denotes minor rotamer peaks) 7.0–7.4 (m, 10 H, aromatic), 4.63 (d, 1H, J = 7.6 Hz, **CH**OH), 4.54* (d, 1H, J = 8.7 Hz, **CH**OH), 4.42 (br, m, 1H, **CH**NCH_3), 3.99* (m, 1H, **CH**NCH_3), 2.93* (s, 3H, NCH_3), 2.72 (s, 3H, NCH_3), 2.40–2.65 (m, 3H, $PhCH_2CH_2CH$), 2.18* (m, 1H, one of $PhCH_2CH_2$), 1.99 (m, 1H, one of $PhCH_2CH_2$), 1.73* (m, 1H, one of $PhCH_2CH_2$), 1.62 (m, 1H, one of $PhCH_2CH_2$), 1.15 (d, 3H, J = 7.0 Hz, CH_3CHCH_2), 1.10 (d, 3H, J = 6.8 Hz, CH_3CHN), 0.99* (d, 3H, J = 6.9 Hz, CH_3CHN).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	(3:1 rotamer ratio, * denotes minor rotamer peaks) 178.4, 177.1*, 142.6, 141.8, 141.4*, 128.6*, 128.4, 128.3, 127.5, 126.9*, 126.3, 125.8, 76.3, 75.4*, 58.8, 57.8*, 35.6, 35.3, 35.2*, 33.4, 32.9, 27.0*, 17.9*, 17.3, 17.2*, 15.4.
FTIR (neat, cm^{-1}):	3381 (br, s, OH), 1621 (s, C=O).
HRMS (FAB):	Calcd for $C_{21}H_{28}NO_2$ $(MH)^+$: 326.2120.
	Found: 326.2099.
TLC (80% EtOAc–hexanes), R_f:	**14**: 0.49 (UV, PMA).
	1: 0.27 (UV, PMA).



[1*S*(*R*),2*S*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*,2-dimethyl *tert*-Butyloxycarbonyl-propionamide **15**

A solution of *n*-butyllithium in hexanes (2.37 M, 10.7 mL, 25.4 mmol, 2.08 equiv) was added to a suspension of lithium chloride (3.10 g, 73.2 mmol, 6.00 equiv) and diisopropylamine (3.90 mL, 27.8 mmol, 2.28 equiv) in tetrahydrofuran (50 mL) at –78 °C. The suspension was warmed briefly to 0 °C, then was cooled to –78 °C. An ice-cooled solution of amide **1** (2.70 g, 12.2 mmol, 1 equiv) in tetrahydrofuran (40 mL, followed by a 2-mL rinse) was added via cannula. The resulting mixture was stirred at –78 °C for 30 min, at 0 °C for 10 min, at 23 °C for 3 min, and finally was cooled to –78 °C whereupon *tert*-butyl bromoacetate (3.60 mL, 24.4 mmol, 2.00 equiv) was added. The reaction mixture was stirred at –78 °C for 3.9 h, then was quenched at –78 °C by the addition of methanol (2 mL). The mixture was warmed to 0 °C, then was quenched further with saturated aqueous ammonium chloride solution (15 mL). The mixture was warmed to 23 °C, then was partitioned between half-saturated brine (200 mL) and ethyl acetate (30 mL), and the aqueous layer was separated. The aqueous layer was extracted with two 75-mL portions of ethyl acetate. The combined organic extracts were washed with brine (2 × 15 mL), then were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (30 → 53%) afforded amide **15** as a colorless oil (3.20 g, 78%). Chiral capillary GC analysis[43] of the corresponding trimethylsilyl ether, prepared as described above for amide **11**, established that amide **15** was of 96% de.

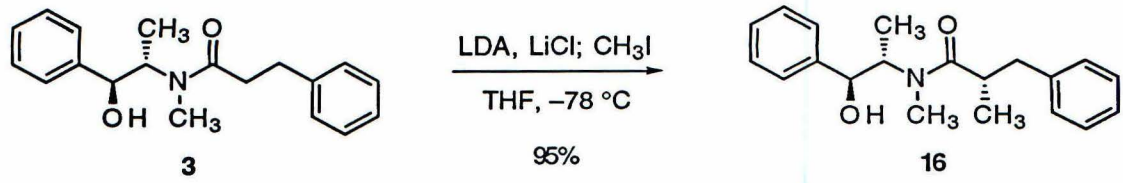
^{1}H NMR (300 MHz, $CDCl_3$) δ:	(1:1 rotamer mixture) 7.20–7.45 (m, 5H, aromatic), 4.73 (m, 1H, CHOH), 4.59 (m, 1H, CHOH), 4.20 (m, 2H, $CHNCH_3$), 2.98 (s, 3H, NCH_3), 2.93 (s, 3H, NCH_3), 2.74 (dd, 1H, J_1 = 16.7 Hz, J_2 = 9.1 Hz, one of CH_2), 2.30 (m, 1H, one of CH_2), 1.43 (s, 9H, $C(CH_3)_3$), 1.10 (d, 3H, J = 7.0 Hz, CH_3), 0.97 (d, 3H, J = 6.8 Hz, CH_3).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	(1:1 rotamer mixture) 177.3, 176.3, 173.3, 172.0, 142.3, 141.6, 128.5, 128.3, 128.0, 127.6, 127.1, 126.6, 80.5, 76.2, 75.8, 59.5, 58.7, 39.8, 39.5, 33.3, 32.0, 28.1, 27.0, 17.5, 16.9, 15.9, 14.3.
FTIR (neat, cm^{-1}):	3417 (br, m, OH), 1731 (s, C=O), 1622 (s, C=O).
HRMS (FAB):	Calcd for $C_{19}H_{30}NO_4$ $(MH)^+$: 336.2175.
	Found: 336.2176.
TLC (80% EtOAc–hexanes), R_f:	**15**: 0.56 (UV, PMA).
	1: 0.29 (UV, PMA).
	tert–butylbromoacetate: 0.17 (PMA).



[1*S*(*S*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*,2-dimethyl Benzenepropionamide **16**

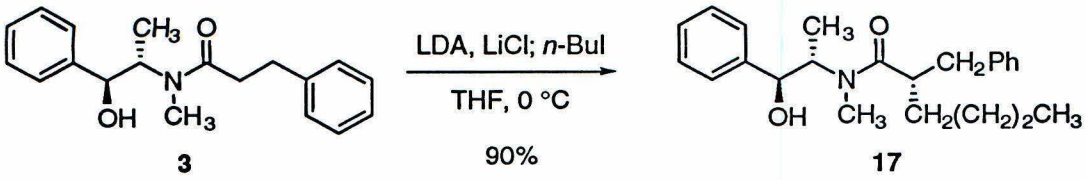
A solution of *n*-butyllithium in hexanes (1.39 M, 7.48 mL, 10.4 mmol, 2.08 equiv) was added to a suspension of lithium chloride (2.12 g, 50.0 mmol, 10.0 equiv) and diisopropylamine (1.55 mL, 11.1 mmol, 2.21 equiv) in tetrahydrofuran (18 mL) at –78 °C. The resulting suspension was warmed briefly to 0 °C, then was cooled to –78 °C. A solution of amide **3** (1.49 g, 5.00 mmol, 1 equiv) in tetrahydrofuran (20 mL) was added dropwise via cannula. The reaction mixture was stirred at –78 °C for 1.3 h, at 0 °C for 15 min, at 23 °C for 5 min, and finally was cooled to 0 °C, whereupon iodomethane (1.24 mL, 20.0 mmol, 4.00 equiv) was added. The reaction mixture was stirred at 0 °C for 55 min, then was quenched by the addition of saturated aqueous ammonium chloride solution (10 mL). The mixture was partitioned between saturated aqueous ammonium chloride solution (150 mL) and ethyl acetate (100 mL), and the layers were separated. The aqueous layer was extracted with two 50-mL portions of ethyl acetate, and the combined organic extracts were dried over sodium sulfate and were concentrated. Purification of the residue by flash chromatography (55% ethyl acetate–hexanes) afforded amide **16** as an oil which slowly solidified (1.54 g, 99%): mp 79–81 °C. Chiral capillary GC analysis[43] of the corresponding trimethylsilyl ether, prepared as described above for amide **11**, established that amide **16** was of 94% de.

^{1}H NMR (300 MHz, C_6D_6) δ:	(3:1 rotamer ratio, * denotes minor rotamer peaks) 6.95–7.4 (m, 10H, aromatic), 5.25 (br, 1H, **OH**), 4.51 (t, 1H, *J* = 7.0 Hz, **CH**OH), 3.97* (m, 1H, **CH**OH), 3.75 (m, 1H, NC**H**CH$_3$), 3.15* (m, 1H, NC**H**CH$_3$), 3.06 (m, 1H, COC**H**CH$_3$), 2.71* (s, 3H, NC**H**$_3$), 2.58* (m, 2H, C**H**$_2$Ph), 2.45 (m, 2H, C**H**$_2$Ph), 1.93 (s, 3H, NC**H**$_3$), 1.34* (d, 3H, *J* = 6.3 Hz, COCHC**H**$_3$), 1.00 (d, 3H, *J* =7.0 Hz, C**H**$_3$CHN), 0.93 (d, 3H, *J* = 6.4 Hz, COCHC**H**$_3$), 0.30* (d, 3H, *J* =6.8 Hz, C**H**$_3$CHN).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	(3:1 rotamer ratio, * denotes minor rotamer peaks) 178.1, 177.0*, 142.3, 141.3*, 140.2*, 139.9, 128.94, 128.86*, 128.6*, 128.34, 128.29*, 128.2, 127.4, 126.7*, 126.3, 126.2, 126.1*, 76.1, 75.4*, 60.3, 58.1*, 41.2*, 40.3, 39.0, 38.2*, 33.9, 27.0*, 18.2*, 17.6, 14.8*, 14.2.
FTIR (neat, cm^{-1}):	3374 (br, m, OH), 1614 (s, C=O).
HRMS (FAB):	Calcd for $C_{20}H_{26}NO_2$ $(MH)^+$: 312.1965.
	Found: 312.1965.
Analysis:	Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50.
	Found: C, 76.86; H, 8.31; N, 4.41.
TLC (80% EtOAc–hexanes), R_f:	**16**: 0.53 (UV, PMA).
	3: 0.45 (UV, PMA).



[1*S*(*S*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*,2-dimethyl Benzenepropionamide **16**

A solution of *n*-butyllithium in hexanes (2.37 M, 7.38 mL, 17.5 mmol, 2.08 equiv) was added to a suspension of lithium chloride (2.14 g, 50.4 mmol, 6.00 equiv) and diisopropylamine (2.65 mL, 18.9 mmol, 2.25 equiv) in tetrahydrofuran (25 mL) at –78 °C. The resulting suspension was warmed briefly to 0 °C, then was cooled to –78 °C. A solution of amide **3** (2.50 g, 8.41 mmol, 1 equiv) in tetrahydrofuran (30 mL, followed by a 3-mL rinse) was added dropwise via cannula. The reaction mixture was stirred at –78 °C for 1 h, at 0 °C for 15 min, at 23 °C for 5 min, and finally was cooled to –78 °C, whereupon iodomethane (2.00 mL, 32.1 mmol, 3.80 equiv) was added. The reaction mixture was stirred at –78 °C for 8 h then was quenched at –78 °C by the addition of methanol (1.65 mL). The mixture was warmed to 23 °C and was treated with half-saturated aqueous ammonium chloride solution (10 mL). Volatile solvents were removed under reduced pressure, and the resulting aqueous solution was partitioned between saturated aqueous ammonium chloride solution (200 mL) and ethyl acetate (40 mL). The aqueous layer was separated and extracted with two 40-mL portions of ethyl acetate. The combined organic fractions were dried over sodium sulfate and were concentrated. Purification of the product by flash chromatography (50% ethyl acetate–hexanes) afforded amide **16** as a white crystalline solid (2.49 g, 95%). Spectroscopic data were identical to those listed above. Chiral capillary GC analysis[43] of the corresponding trimethylsilyl ether, prepared as described above for amide **11**, established that amide **16** was of 97% de.

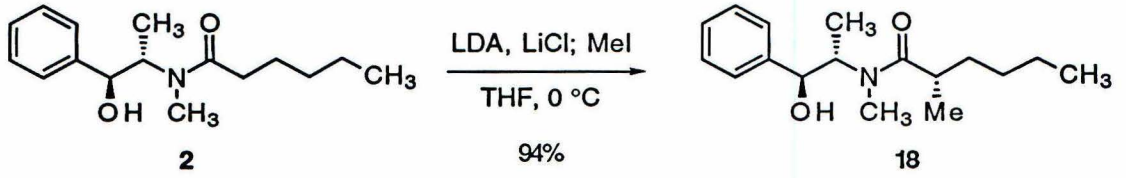


3 17

[1*S*(*S*),2*S*]-α-Butyl-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methyl Benzenepropionamide **17**

A solution of *n*-butyllithium in hexanes (2.37 M, 17.0 mL, 40.3 mmol, 2.08 equiv) was added to a suspension of lithium chloride (4.94 g, 117 mmol, 6.00 equiv) and diisopropylamine (6.12 mL, 43.7 mmol, 2.25 equiv) in tetrahydrofuran (40 mL) at –78 °C. The resulting suspension was warmed briefly to 0 °C, then was cooled to –78 °C. A solution of amide **3** (5.50 g, 19.4 mmol, 1 equiv) in tetrahydrofuran (35 mL, followed by a 5-mL rinse) was added dropwise via cannula. The reaction mixture was stirred at –78 °C for 50 min, at 0 °C for 13 min, at 23 °C for 4 min, and finally was cooled to 0 °C, whereupon 1-iodobutane (5.52 mL, 48.5 mmol, 2.50 equiv) was added. The mixture was stirred at 0° C for 1 h, then was quenched by the addition of saturated aqueous ammonium chloride solution (10 mL). The mixture was partitioned between saturated aqueous ammonium chloride solution (400 mL) and ethyl acetate (150 mL). The aqueous layer was separated and extracted with two 150-mL portions of ethyl acetate. The combined organic fractions were washed with brine (25 mL), then were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (45 → 60%) afforded amide **17** as a yellow oil (6.14 g, 90%). Chiral capillary GC analysis[43] of the corresponding trimethylsilyl ether, prepared as described above for amide **11**, established that amide **17** was of 98% de.

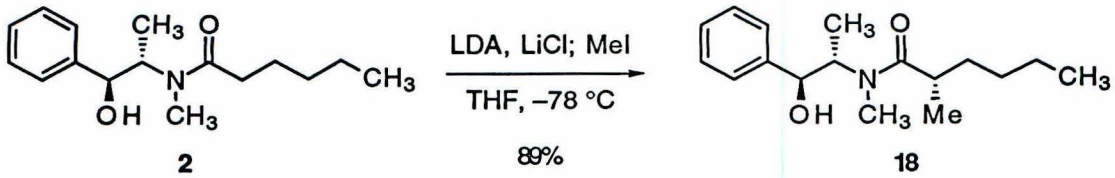
^{1}H NMR (300 MHz, C_6D_6) δ:	(3:1 rotamer ratio, * denotes minor rotamer peaks) 7.0–7.4 (m, 10H, aromatic), 5.2 (br, 1H, OH), 4.49 (t, 1H, J = 6.9 Hz, CHOH), 4.02* (m, 1H, CHOH), 3.90 (m, 1H, $NCHCH_3$), 3.78* (m, 1H, $NCHCH_3$), 3.03 (m, 1H, COCH), 2.70* (s, 3H, NCH_3), 2.57 (m, 2H, CH_2Ph), 2.02 (s, 3H, NCH_3), 0.93–1.9 (m, 6H, $CH_3CH_2CH_2CH_2$), 0.92 (d, 3H, J = 7.0 Hz, CH_3CHN), 0.84 (t, 3H, J = 7.2 Hz, CH_3CH_2), 0.16* (d, 3H, J = 6.7 Hz, CH_3CHN).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	(4:1 rotamer ratio, * denotes minor rotamer peaks) 177.7, 176.7*, 142.2, 141.1*, 140.2*, 139.8, 128.9, 128.6*, 128.4, 128.3*, 128.24*, 128.16, 127.4, 126.8*, 126.32, 126.29, 126.1*, 75.8, 75.3*, 60.0, 58.2*, 44.9, 44.2*, 39.8*, 39.5, 33.6, 33.1, 29.9*, 29.5, 27.0*, 22.9*, 22.8, 14.4*, 14.3, 14.0*, 13.9.
FTIR (neat, cm^{-1}):	3404 (s, br, OH), 1624 (m, C=O).
HRMS (FAB):	Calcd for $C_{23}H_{29}NO$ $(M–H_2O)^+$: 335.2251. Found: 335.2234.
TLC (60% EtOAc–hexanes), R_f:	**17**: 0.42 (UV, PMA). **3**: 0.28 (UV, PMA).



[1*S*(*S*),2*S*)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*,2-dimethyl Hexanamide **18**

A solution of *n*-butyllithium in hexanes (1.39 M, 7.48 mL, 10.4 mmol, 2.08 equiv) was added to a suspension of lithium chloride (2.12 g, 50.0 mmol, 10.0 equiv) and diisopropylamine (1.55 mL, 11.1 mmol, 2.21 equiv) in tetrahydrofuran (18 mL) at –78 °C. The resulting suspension was warmed briefly to 0 °C, then was cooled to –78 °C. A solution of amide **2** (1.32 g, 5.00 mmol, 1 equiv) in tetrahydrofuran (15 mL, followed by a 5-mL rinse) was added dropwise to the reaction flask via cannula. The reaction mixture was stirred at –78 °C for 50 min, at 0 °C for 15 min, at 23 °C for 5 min, and finally was cooled to 0 °C, whereupon iodomethane (1.24 mL, 20.0 mmol, 4.00 equiv) was added. The mixture was stirred at 0 °C for 55 min, then was quenched by the addition of saturated aqueous ammonium chloride solution (10 mL). The reaction mixture was partitioned between saturated aqueous ammonium chloride solution (150 mL) and ethyl acetate (100 mL). The aqueous layer was separated and extracted with two 50-mL portions of ethyl acetate. The combined organic fractions were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (50% ethyl acetate–hexanes) furnished amide **18** as a yellow oil (1.30 g, 94%). Chiral capillary GC analysis[43] of the corresponding trimethylsilyl ether, prepared as described above for amide **11**, established that amide **18** was of 94% de.

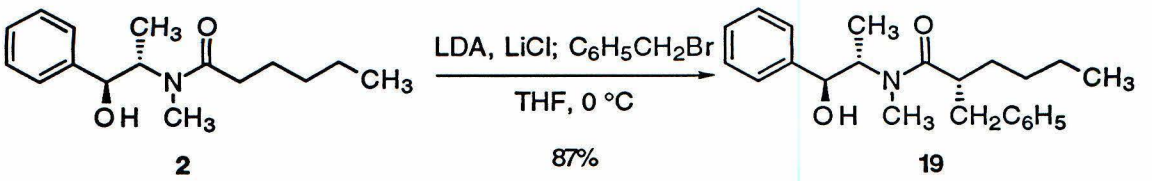
^{1}H NMR (300 MHz, C_6D_6) δ:	(3:1 rotamer ratio, * denotes minor rotamer peaks) 7.0–7.4 (m, 5H, aromatic), 5.30 (br, 1H, **OH**), 4.56 (t, 1H, J = 6.8 Hz, **CH**OH), 4.16* (d, 1H, J = 8.6 Hz, **CH**OH), 3.95 (m, 1H, NC**H**CH$_3$), 2.82* (s, 3H, NC**H**$_3$), 2.70 (m, 1H, COC**H**CH$_3$), 2.18 (s, 3H, NC**H**$_3$), 2.15* (m, 1H, COC**H**CH$_3$), 1.78 (m, 2H, COCHC**H**$_2$), 1.0–1.4 (m, 4H, CH$_3$C**H**$_2$C**H**$_2$), 1.33* (d, 3H, J = 6.7 Hz, COCHC**H**$_3$), 1.08 (d, 3H, J = 7.0 Hz, C**H**$_3$CHN), 0.92 (d, 3H, J = 6.8 Hz, COCHC**H**$_3$), 0.87 (t, 3H, J = 6.9 Hz, **CH**$_3$CH$_2$), 0.69* (d, 3H, J = 6.7 Hz, C**H**$_3$CHN).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	(3:1 rotamer ratio, * denotes minor rotamer ratio) 178.9, 177.9*, 142.5, 141.5*, 128.5*, 128.0, 127.3, 126.8*, 126.1, 76.3, 75.2*, 59.8, 57.9*, 36.4, 35.5*, 34.2*, 33.9, 33.6, 29.5, 27.0*, 22.7, 17.6*. 17.3, 15.5*, 14.3, 13.9.
FTIR (neat, cm^{-1}):	3382 (br, m, OH), 1614 (s, C=O).
HRMS (FAB):	Calcd for $C_{17}H_{28}NO_2$ $(MH)^+$: 278.2121.
	Found: 278.2119.
TLC (80% EtOAc–hexanes), R_f:	**18**: 0.56 (UV, PMA).
	2: 0.37 (UV, PMA).



2 18

[1*S*(*S*),2*S*)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*,2-dimethyl Hexanamide **18**

A 3-necked, 1-L flask equipped with a mechanical stirrer was charged with lithium chloride (7.73 g, 182 mmol, 6.00 equiv), diisopropylamine (9.58 mL, 68.3 mmol, 2.25 equiv), and tetrahydrofuran (75 mL). The resulting suspension was cooled to –78 °C, and a solution of *n*-butyllithium in hexanes (1.71 M, 36.9 mL, 63.2 mmol, 2.08 equiv) was added via cannula. The suspension was warmed briefly to 0 °C, then was cooled to –78 °C. An ice-cooled solution of amide **2** (8.00 g, 30.4 mmol, 1 equiv) in tetrahydrofuran (50 mL) was added to the reaction flask via cannula. The reaction mixture was stirred at –78 °C for 1 h, at 0 °C for 15 min, at 23 °C for 5 min, and finally was cooled to –78 °C, whereupon iodomethane (5.67 mL, 91.1 mmol, 3.00 equiv) was added. The mixture was stirred at –78 °C for 6 h, then was quenched by the addition of methanol (7.0 mL). The mixture was warmed to 23 °C and was treated with saturated aqueous ammonium chloride solution (10 mL). Volatile organic solvents were removed by rotary evaporation, and the resulting aqueous solution was partitioned between saturated aqueous ammonium chloride solution (400 mL) and ethyl acetate (130 mL). The aqueous layer was separated and extracted with two 130-mL portions of ethyl acetate. The combined organic fractions were dried over sodium sulfate and were concentrated. Purification of the residue by flash chromatography (50% ethyl acetate–hexanes) afforded amide **18** as a yellow oil (7.49 g, 89%). Spectroscopic data were identical to those listed above. Chiral capillary GC analysis[43] of the corresponding trimethylsilyl ether, prepared as described above for amide **11**, established that amide **18** was of 96% de.



2 19

[1*S*(*R*),2*S*]-α-Butyl-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methyl Benzenepropionamide **19**

A 3-necked, 2-L flask equipped with a mechanical stirrer was charged with lithium chloride (19.3 g, 456 mmol, 6.00 equiv), diisopropylamine (23.9 mL, 170.8 mmol, 2.25 equiv), and tetrahydrofuran (200 mL). The resulting suspension was cooled to –78 °C, and a solution of *n*-butyllithium in hexanes (2.43 M, 65.0 mL, 158 mmol, 2.08 equiv) was added via cannula. The suspension was warmed briefly to 0 °C, then was cooled to –78 °C. An ice-cooled solution of amide **2** (20.0 g, 75.9 mmol, 1 equiv) in tetrahydrofuran (150 mL) was added to the reaction flask via cannula. The reaction mixture was stirred at –78 °C for 50 min, at 0 °C for 15 min, at 23 °C for 5 min, and finally was cooled to 0 °C, whereupon benzyl bromide (13.6 mL, 113.9 mmol, 1.50 equiv) was added. The mixture was stirred at 0 °C for 40 min, then was quenched by the addition of saturated aqueous ammonium chloride solution (10 mL). Volatile organic solvents were removed by rotary evaporation, and the resulting aqueous solution was partitioned between saturated aqueous ammonium chloride solution (700 mL) and ethyl acetate (150 mL). The aqueous layer was separated and extracted with three 150-mL portions of ethyl acetate. The combined organic fractions were dried over sodium sulfate and were concentrated. Recrystallization of the crude product from hot toluene (110 °C, 100 mL) afforded amide **19** as white crystals (23.3 g, 87%): mp 120–121 °C. Chiral capillary GC analysis[43] of the corresponding trimethylsilyl ether, prepared as described above for amide **11**, established that amide **19** was of ≥99% de.

^{1}H NMR (300 MHz, C_6D_6) δ: (6:1 rotamer ratio, * denotes minor rotamer peaks) 7.0–7.45 (m, 10H, aromatic), 4.36 (m, 1H, **CH**OH), 4.15 (br, 1H, O**H**), 3.98* (m, 1H, **CH**OH), 3.35* (m, 1H, NC**H**CH$_3$), 2.99 (m, 1H, NC**H**CH$_3$), 2.72* (s, 3H, NC**H**$_3$), 2.53–2.67 (m, 3H, COC**H**, COCH**CH**$_2$Ph), 2.12 (s, 3H, NC**H**$_3$), 1.9 (m, 2H, PhC**H**$_2$CHC**H**$_2$), 1.1–1.4 (m, 4H, CH$_3$C**H**$_2$C**H**$_2$), 0.87 (t, 3H, J = 7.0 Hz, C**H**$_3$CH$_2$), 0.77 (m, 3H, C**H**$_3$CHN), 0.64* (d, 3H, J = 6.2 Hz, C**H**$_3$CHN).

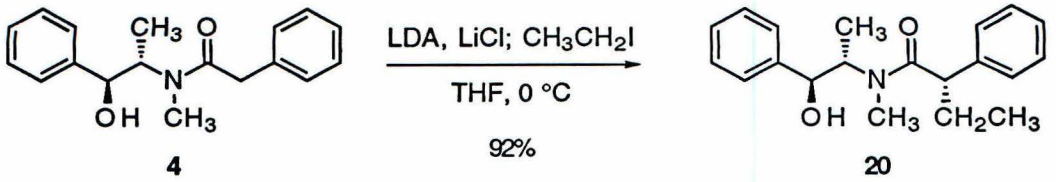
^{13}C NMR (75 MHz, $CDCl_3$) δ: (4:1 rotamer ratio, * denotes minor rotamer peaks) 177.9, 176.6*, 142.2, 141.0*, 140.5*, 139.9, 129.2, 128.9, 128.6*, 128.5*, 128.3, 128.2, 127.6, 126.9*, 126.5, 126.3*, 126.2, 76.4, 75.1*, 58.2*, 57.9, 44.8, 44.0*, 39.6, 39.3*, 32.9*, 32.8, 32.1, 29.8*, 29.6, 27.0*, 22.8, 15.5*, 14.2, 13.9.

FTIR (neat, cm^{-1}): 3369 (br, m, OH), 1614 (s, C=O).

HRMS (FAB): Calcd for $C_{23}H_{29}NO$ $(M–H_2O)^+$: 335.2251.
Found: 335.2257.

Analysis: Calcd for $C_{23}H_{31}NO_2$: C, 78.15; H, 8.84; N, 3.96.
Found: C, 78.12; H, 9.08; N, 3.81.

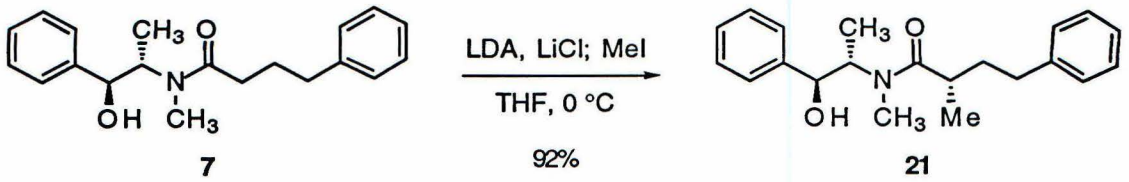
TLC (80% EtOAc–hexanes), R_f: **19**: 0.60 (UV, PMA).
2: 0.38 (UV, PMA).
benzyl bromide: 0.76 (UV, PMA).



[1*S*(*S*),2*S*]-α-Ethyl-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methyl Benzeneacetamide **20**

A solution of *n*-butyllithium in hexanes (2.04 M, 10.2 mL, 20.8 mmol, 2.08 equiv) was added via cannula to a suspension of lithium chloride (4.24 g, 100 mmol, 10.0 equiv) and diisopropylamine (3.10 mL, 22.1 mmol, 2.21 equiv) in tetrahydrofuran (35 mL) at –78 °C. The resulting suspension was warmed briefly to 0 °C then was cooled to –78 °C. A solution of amide **4** (2.83 g, 10.0 mmol, 1 equiv) in tetrahydrofuran (50 mL) was added dropwise to the reaction flask via cannula. The reaction mixture was stirred at –78 °C for 1 h, at 0 °C for 10 min, at 23 °C for 4 minutes, and finally was cooled to 0 °C, whereupon ethyl iodide (3.20 mL, 40.0 mmol, 4.00 equiv) was added. The mixture was stirred at 0 °C for 40 min then was quenched by the addition of saturated aqueous ammonium chloride (10 mL). The mixture was partitioned between saturated aqueous ammonium chloride solution (800 mL) and ethyl acetate (100 mL). The aqueous layer was separated and extracted with two 100-mL portions of ethyl acetate. The combined organic fractions were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (50% ethyl acetate–hexanes) furnished amide **20** as a colorless oil which slowly solidified (2.85 g, 92%): mp 65–66 °C. Chiral capillary GC analysis[43] of the corresponding trimethylsilyl ether, prepared as described above for amide **11**, established that amide **20** was of ≥99% de.

^{1}H NMR (300 MHz, C_6D_6) δ:	(3:1 rotamer ratio, * denotes minor rotamer peaks) 6.9–7.4 (m, 10H, aromatic), 4.95 (br, 1H, **OH**), 4.51 (t, 1H, *J* = 6.9 Hz, **CHOH**), 4.10 (m, 1H, $NCHCH_3$), 4.03* (m, 1H, **CHOH**), 3.82* (m, 1H, $NCHCH_3$), 3.11 (dd, 1H, *J* = 7.5 Hz, 7.0 Hz, CH_3CH_2CH), 2.78* (s, 3H, NCH_3), 2.48* (m, 1H, CH_3CH_2CH), 2.25 (m, 1H, one of CH_3CH_2), 2.12 (s, 3H, NCH_3), 1.90* (m, 2H, CH_3CH_2), 1.73 (m, 1H, one of CH_3CH_2), 0.98 (d, 3H, *J* = 6.8 Hz, CH_3CHN), 0.97* (m, 3H, CH_3CH_2), 0.82 (t, 3H, *J* = 7.3 Hz, CH_3CH_2), 0.30* (d, 3H, *J* = 6.5 Hz, CH_3CHN).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	(2:1 rotamer ratio, * denotes minor rotamer peaks) 175.4, 174.2*, 142.3, 141.3*, 140.5*, 139.6, 128.8, 128.71, 128.68*, 128.3*, 128.2, 127.8, 127.7*, 127.4*, 126.9, 126.7*, 126.6*, 126.3; 76.3, 75.6*, 72.7*, 57.6, 51.8, 51.1*, 28.2, 28.1, 27.4*, 14.4*, 14.0, 12.4, 12.3*.
FTIR (neat, cm^{-1}):	3384 (br, m, OH), 1620 (s, C=O).
HRMS (FAB):	Calcd for $C_{20}H_{26}NO_2$ $(MH)^+$: 312.1965.
	Found: 312.1962.
Analysis:	Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50.
	Found: C, 77.10; H, 8.19; N, 4.44.
TLC (80% EtOAc–hexanes), R_f:	**20**: 0.56 (UV, PMA).
	4: 0.44 (UV, PMA).

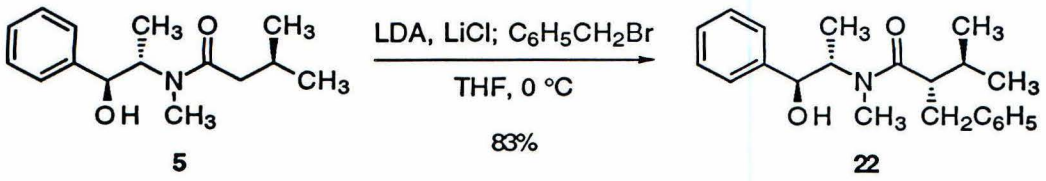


7 21

[1*S*(*S*),2*S*)]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*,2-dimethyl Benzenebutanamide **21**

A solution of *n*-butyllithium in hexanes (2.37 M, 13.3 mL, 31.4 mmol, 2.08 equiv) was added to a suspension of lithium chloride (3.84 g, 90.6 mmol, 6.00 equiv) and diisopropylamine (4.82 mL, 34.4 mmol, 2.28 equiv) in tetrahydrofuran (50 mL) at –78 °C. The suspension was warmed briefly to 0 °C, then was cooled to –78 °C. An ice-cooled solution of amide **7** (4.70 g, 15.1 mmol, 1 equiv) in tetrahydrofuran (40 mL, followed by a 2-mL rinse) was added via cannula over 4 min. The reaction mixture was stirred at –78 °C for 30 min, at 0 °C for 10 min, at 23 °C for 3 min, and finally was cooled to 0 °C, whereupon iodomethane (1.88 mL, 30.2 mmol, 2.00 equiv) was added. The mixture was stirred at 0 °C for 20 min, then was quenched by the addition of saturated aqueous ammonium chloride solution (15 mL) and half-saturated brine (150 mL). The layers were separated, and the aqueous layer was extracted with two 60-mL portions of ethyl acetate. The combined organic extracts were washed with brine (2 × 15 mL), then were dried over sodium sulfate and were concentrated. Recrystallization of the crude product from hot toluene (110 °C, 13 mL) afforded amide **21** as white crystals (2.76 g, 56%). The mother liquor was concentrated to afford a solid residue, and the solid was recrystallized from hot hexanes (69 °C, 5 mL) to afford additional product as an off-white solid (1.78 g, 36%): mp 89–90 °C. Chiral capillary GC analysis[43] of the corresponding trimethylsilyl ether, prepared as described above for amide **11**, established that amide **21** was of ≥99% de.

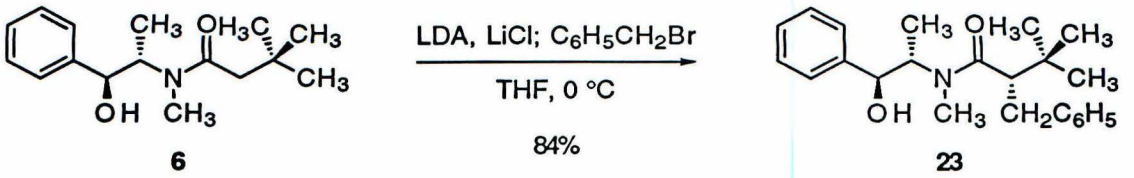
^{1}H NMR (300 MHz, $CDCl_3$) δ:	(4:1 rotamer ratio, * denotes minor rotamer peaks) 7.0–7.4 (m, 10H, aromatic), 4.70 (br, 1H, **OH**), 4.65 (m, 1H, **CHOH**), 4.50* (m, 1H, **CHOH**), 4.30 (m, 1H, $NCHCH_3$), 3.85* (m, 1H, $NCHCH_3$), 2.93* (s, 3H, NCH_3), 2.65 (s, 3H, NCH_3), 2.5–2.8 (m, 3H, COCH, $PhCH_2$), 2.05 (m, 1H, one of $PhCH_2CH_2$), 1.65 (m, 1H, one of $PhCH_2CH_2$), 1.21 (d, 3H, J = 7.0 Hz, CH_3CHCO), 1.03 (d, 3H, J = 6.8 Hz, CH_3CHN), 0.94* (d, 3H, J = 6.8 Hz, CH_3CHN).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	(4:1 rotamer ratio, * denotes minor rotamer peaks) 178.5, 142.6, 141.9, 128.7*, 128.6*, 128.4, 128.3, 128.2*, 127.5, 126.9*, 126.2, 125.8, 76.5, 75.6*, 59.7, 57.7*, 48.2*, 35.9*, 35.6, 35.4, 34.6, 33.4, 27.1*, 19.1*, 17.3, 15.5*, 14.4.
FTIR (neat, cm^{-1}):	3374 (br, m, OH), 1614 (s, C=O).
HRMS (FAB):	Calcd for $C_{21}H_{28}NO_2$ $(MH)^+$: 326.2120.
	Found: 326.2104.
Analysis:	Calcd for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.30.
	Found: C, 77.20; H, 8.47; N, 4.19.
TLC (80% EtOAc–hexanes), R_f:	**21**: 0.47 (UV, PMA).
	7: 0.39 (UV, PMA).



[1*S*(*S*),2*S*]-α-(1-Methylethyl)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methyl Benzenepropionamide **22**

A solution of *n*-butyllithium in hexanes (2.37 M, 16.6 mL, 39.4 mmol, 2.08 equiv) was added to a suspension of lithium chloride (4.82 g, 114 mmol, 6.00 equiv) and diisopropylamine (6.06 mL, 43.2 mL, 2.28 equiv) in tetrahydrofuran (50 mL) at –78 °C. The suspension was warmed briefly to 0 °C, then was cooled to –78 °C. An ice-cooled solution of amide **5** (4.73 g, 19.0 mmol, 1 equiv) in tetrahydrofuran (30 mL, followed by a 3-mL rinse) was added via cannula. The reaction mixture was stirred at –78 °C for 40 min, at 0 °C for 10 min, at 23 °C for 3 min, and finally was cooled to 0 °C, whereupon benzyl bromide (4.06 mL, 34.1 mmol, 1.80 equiv) was added. The mixture was stirred at 0 °C for 1 h then was quenched by the addition of saturated aqueous ammonium chloride solution (10 mL). The mixture was partitioned between half-saturated brine (200 mL) and ethyl acetate (30 mL). The aqueous layer was separated and extracted with two 75-mL portions of ethyl acetate. The combined organic extracts were washed with two 15-mL portions of brine, then were dried over sodium sulfate and were concentrated. The residue was dissolved in hot ethyl acetate (77 °C, 8 mL), and the solution was diluted with hot hexanes (69 °C, 8 mL). Recrystallization of the product from this 1:1 mixture of ethyl acetate and hexanes afforded amide **22** as white crystals (5.36 g, 83%): mp 118–119 °C. Chiral capillary GC analysis[43] of the corresponding trimethylsilyl ether, prepared as described above for amide **11**, established that amide **22** was of ≥99% de.

^{1}H NMR (300 MHz, $CDCl_3$) δ:	(6:1 rotamer ratio, * denotes minor rotamer peaks) 7.0–7.4 (m, 10H, aromatic), 4.40–4.52 (m, 2H, **CH**OH, NC**H**CH_3), 4.15* (m, 1H, **CH**OH), 3.85* (m, 1H, NC**H**CH_3), 3.63 (m, 1H, CHO**H**), 2.86 (m, 2H, CHC**H**$_2$Ph), 2.76* (s, 2H, C**H**$_2$Ph), 2.74* (s, 3H, NC**H**$_3$) 2.66 (m, 1H, C**H**CH_2Ph), 2.49 (s, 3H, NC**H**$_3$), 2.01 (m, 1H, C**H**$(CH_3)_2$), 1.09 (d, 3H, J = 6.7, one of CH(C**H**$_3)_2$), 1.08* (d, 3H, J = 6.7 Hz, one of CH(C**H**$_3)_2$), 0.97 (d, 3H, J = 6.7 Hz, one of CH(C**H**$_3)_2$), 0.88* (d, 3H, J = 6.7 Hz, one of CH(C**H**$_3)_2$), 0.63 (d, 3H, J = 6.5 Hz, C**H**$_3$CHN).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	(6:1 rotamer ratio, * denotes minor rotamer peaks) 177.6, 142.2, 141.0*, 140.2, 129.2*, 128.9, 128.6*, 128.5*, 128.3, 128.2, 127.6, 127.0*, 126.6, 126.5*, 126.1, 76.5, 75.0*, 58.2*, 57.1, 52.2, 51.0*, 37.1, 36.8*, 31.6, 31.5*, 31.2, 27.0*, 21.3, 20.3*, 20.1, 15.2*, 14.1.
FTIR (neat, cm^{-1}):	3381 (br, s, OH), 1614 (s, C=O).
HRMS (FAB):	Calcd for $C_{22}H_{30}NO_2$ $(MH)^+$: 340.2277.
	Found: 340.2292.
Analysis:	Calcd for $C_{22}H_{29}NO_2$: C, 77.84; H, 8.61; N, 4.13;
	Found: C, 77.49; H, 8.81; N, 4.03.
TLC (60% EtOAc–hexanes), R_f:	**22**: 0.41 (UV, PMA).
	5: 0.23 (UV, PMA).
	benzyl bromide: 0.64 (UV, PMA).

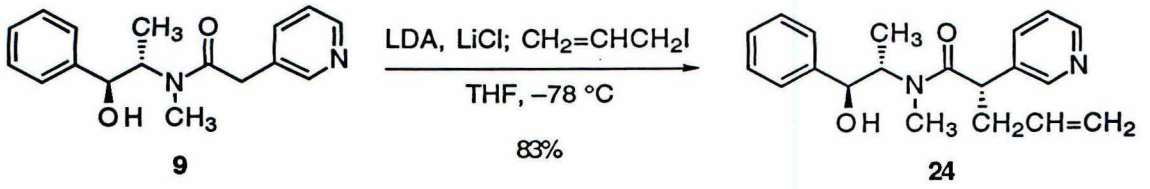


6 23

[1*S*(*S*),2*S*]-α-(1,1-Dimethylethyl)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methyl Benzenepropionamide **23**

A solution of *n*-butyllithium in hexanes (2.37 M, 15.4 mL, 36.6 mmol, 2.08 equiv) was added to a suspension of lithium chloride (4.47 g, 106 mmol, 6.00 equiv) and diisopropylamine (5.62 mL, 40.1 mmol, 2.28 equiv) in tetrahydrofuran (60 mL) at –78 °C. The suspension was warmed briefly to 0 °C, then was cooled to –78 °C. An ice-cooled solution of amide **6** (4.63 g, 17.6 mmol, 1 equiv) in tetrahydrofuran (30 mL, followed by a 3-mL rinse) was added via cannula over 4 min. The resulting mixture was stirred at –78 °C for 30 min, at 0 °C for 10 min, at 23 °C for 3 min, and finally was cooled to 0 °C whereupon benzyl bromide (4.60 mL, 38.7 mmol, 2.20 equiv) was added. The mixture was stirred at 0 °C for 2.8 h, then was quenched by the addition of saturated aqueous ammonium chloride solution (10 mL). The mixture was partitioned between half-saturated brine (200 mL) and ethyl acetate (30 mL), and the aqueous layer was separated and extracted with two 75-mL portions of ethyl acetate. The combined organic extracts were washed with two 15-mL portions of brine, then were dried over sodium sulfate and were concentrated. Recrystallization of the crude product from hot toluene (110 °C, 25 mL) afforded amide **23** as white crystals (5.24 g, 84%): mp 125–127 °C. Chiral capillary GC analysis[43] of the corresponding trimethylsilyl ether, prepared as described above for amide **11**, established that amide **23** was of ≥99% de.

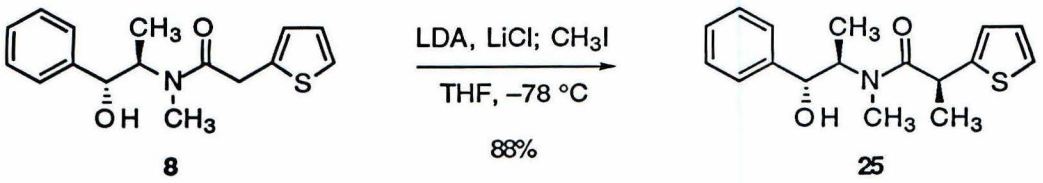
^{1}H NMR (300 MHz, $CDCl_3$) δ:	(7:1 rotamer ratio, * denote minor rotamer peaks) 7.15–7.35 (m, 10H, aromatic), 4.40–4.52 (m, 2H, **CH**OH, NC**H**CH_3), 3.9–4.1* (m, 2H, **CH**OH, NC**H**CH_3), 2.75–3.0 (m, 3H, PhCH_2**CH**), 2.69* (s, 3H, NCH_3), 2.48 (s, 3H, NCH_3), 1.11 (s, 9H, C(CH_3)$_3$), 1.08* (s, 9H, C(CH_3)$_3$), 0.86* (d, 3H, J = 6.6 Hz, CH_3CHN), 0.60 (d, 3H, J = 6.4 Hz, CH_3CHN).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	(7:1 rotamer ratio, * denotes minor rotamer peaks) 177.1, 142.1, 140.6, 129.2*, 128.8, 128.7*, 128.3, 128.2, 128.1*, 127.6, 127.0*, 126.7, 126.1, 76.4, 74.9*, 58.5*, 57.0, 54.2, 53.8*, 35.6*, 35.2, 33.8*, 31.8, 28.1*, 27.0, 26.8, 19.2*, 15.0*, 14.2.
FTIR (neat, cm^{-1}):	3393 (br, m, OH), 1615 (s, C=O).
HRMS (FAB):	Calcd for $C_{23}H_{32}NO_2$ $(MH)^+$: 354.2433.
	Found: 354.2439.
Analysis:	Calcd for $C_{23}H_{31}NO_2$: C, 78.15; H, 8.84; N, 3.96.
	Found: C, 78.08; H, 8.90; N, 3.85.
TLC (60% EtOAc–hexanes), R_f:	**23**: 0.52 (UV, PMA).
	6: 0.33 (UV, PMA).
	benzyl bromide: 0.69 (UV, PMA).



[1*S*(*S*),2*S*]-α-Allyl-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methyl 3-Pyridineacetamide **24**

A solution of *n*-butyllithium in hexanes (2.34 M, 0.890 mL, 2.08 mmol, 2.08 equiv) was added to a suspension of lithium chloride (254 mg, 6.00 mmol, 6.00 equiv) and diisopropylamine (0.320 mL, 2.28 mmol, 2.28 equiv) in tetrahydrofuran (3.0 mL) at –78 °C. The resulting suspension was warmed briefly to 0 °C, then was cooled to –78 °C. A solution of amide **9** (284 mg, 1.00 mmol, 1 equiv) in tetrahydrofuran (5.0 mL, followed by a 0.5 mL rinse) was added dropwise via cannula. The reaction mixture was stirred at –78 °C for 30 min, at 0 °C for 10 min, then was cooled to –78 °C, whereupon allyl iodide (0.229 mL, 2.50 mmol, 2.50 equiv) was added. The mixture was stirred at –78 °C for 3.8 h then was quenched by the addition of a solution of acetic acid in methanol (40% v/v, 0.7 mL). The mixture was warmed to 23 °C, and traces of iodine were removed by the addition of 2 M aqueous sodium thiosulfate solution (5 mL). The mixture was partitioned between half-saturated sodium bicarbonate solution (50 mL) and ethyl acetate (15 mL). The aqueous layer was separated and extracted with two 15-mL portions of ethyl acetate. The combined organic fractions were washed with brine (5 mL), then were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes–triethylamine [(85:15:2) → (95:5:2)] afforded amide **24** as a yellow solid (268 mg, 83%). Chiral capillary GC analysis[43] of the corresponding trimethylsilyl ether, prepared as described above for amide **11**, established that amide **24** was of 98% de.

^{1}H NMR (300 MHz, $CDCl_3$) δ:	(2:1 rotamer ratio, * denotes minor rotamer peaks) 8.4–8.6 (m, 2H, two of $C_5\mathbf{H}_4N$), 7.65 (m, 1H, one of $C_5\mathbf{H}_4N$), 7.15–7.4 (m, 6H, one of $C_5\mathbf{H}_4N$, phenyl), 5.70 (m, 1H, $\mathbf{CH}$=CH_2), 5.00 (m, 2H, CH=$\mathbf{CH}_2$), 4.6–4.8 (m, 2H, $\mathbf{CH}$OH, NC$\mathbf{H}$$CH_3$), 4.03 (m, 1H, COC$\mathbf{H}$), 3.74* (t, 1H, J = 7.3 Hz, COC$\mathbf{H}$), 2.92 (s, 3H, N$\mathbf{CH}_3$), 2.83 (m, 2H, $\mathbf{CH}_2$CH=CH_2), 2.77 (s, 3H, N$\mathbf{CH}_3$), 2.38* (m, 2H, $\mathbf{CH}_2$CH=CH_2), 1.10 (d, 3H, J = 6.6 Hz, $\mathbf{CH}_3$), 0.60* (d, 3H, J = 6.7 Hz, $\mathbf{CH}_3$).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	(2:1 rotamer ratio, * denotes minor rotameric peaks) 173.4, 172.7*, 149.5, 149.4*, 148.4, 148.2*, 142.1, 141.5*, 135.61*, 135.58*, 135.3, 135.2, 135.1*, 134.7, 128.8, 128.34*, 128.27, 127.6, 126.6, 126.2, 123.9, 123.7*, 117.2, 117.0*, 76.1, 75.3*, 57.9, 46.8, 46.2*, 39.0, 38.8*, 27.6, 14.9*, 14.1.
FTIR (neat, cm^{-1}):	3388 (br, m, OH), 1633 (s, C=O).
HRMS (FAB)	Calcd for $C_{20}H_{25}N_2O_2$ $(MH)^+$: 325.1916.
	Found: 325.1918.
Analysis:	Calcd for $C_{20}H_{24}N_2O_2$: C, 74.05; H, 7.46; N, 8.63.
	Found: C, 73.91; H, 7.34; N, 8.58.
TLC (Et_3N-pretreated plate, 80% EtOAc–hexanes), R_f:	**24**: 0.57 (UV, PMA).
	9: 0.36 (UV, PMA).
	allyl iodide: 0.09 (PMA).

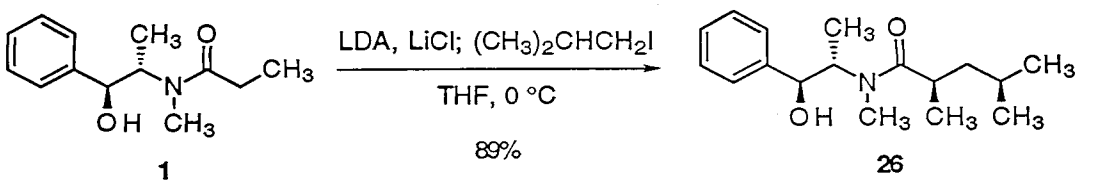


8 **25**

[1*R*(*R*),2*R*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*,2-dimethyl 2-Thiopheneacetamide **25**

A solution of *n*-butyllithium in hexanes (2.34 M, 6.31 mL, 14.8 mmol, 2.08 equiv) was added to a suspension of lithium chloride (1.96 g, 46.2 mmol, 6.50 equiv) and diisopropylamine (2.27 mL, 16.2 mmol, 2.28 equiv) in tetrahydrofuran (15 mL) at –78 °C. The suspension was warmed briefly to 0 °C, then was cooled to –78 °C. An ice-cooled solution of amide **8** (2.06 g, 7.10 mmol, 1 equiv) in tetrahydrofuran (15 mL, followed by a 3-mL rinse) was added via cannula. The resulting mixture was stirred at –78 °C for 30 min, at 0 °C for 10 min, and finally was cooled to –78 °C, whereupon iodomethane (1.55 mL, 24.9 mmol, 3.50 equiv) was added. The reaction mixture was stirred at –78 °C for 7.7 h then was quenched by the addition of a solution of acetic acid in ether (30% v/v, 4.4 mL). The mixture was warmed to 23 °C, then was diluted with 2 M aqueous sodium thiosulfate solution (5 mL) and was partitioned between 2 M aqueous sodium thiosulfate solution (150 mL) and ethyl acetate (50 mL). The aqueous layer was separated and extracted with two 75-mL portions of ethyl acetate. The combined organic extracts were washed with brine (10 mL), then were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (50% ethyl acetate–hexanes) afforded amide **25** as a yellow oil (1.90 g, 88%). Chiral capillary GC analysis[43] of the corresponding trimethylsilyl ether, prepared as described above for amide **11**, established that amide **25** was of 95% de.

^{1}H NMR (*300 MHz*, $CDCl_3$) δ:	(2:1 rotamer ratio, * denotes minor rotamer peaks) 7.10–7.42 (m, 5H, phenyl), 6.8–7.0 (m, 3H, thiophene), 4.57 (m, 1H, CHOH), 4.44 (m, 1H, $NCHCH_3$), 4.16 (m, 1H, COCH), 2.95* (s, 3H, NCH_3), 2.82 (s, 3H, NCH_3), 1.49 (d, 3H, J = 6.8 Hz, CH_3), 1.49* (d, 3H, CH_3), 1.33 (d, 3H, J = 6.9 Hz, CH_3), 0.76* (d, 3H, J = 6.7 Hz, CH_3CHN).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	(2:1 rotamer ratio, * denotes rotamer peaks) 175.1, 144.0*, 142.3, 128.8, 128.3, 128.1*, 127.6, 127.1*, 126.7, 126.4, 124.6*, 124.4*, 124.2, 124.0*, 123.9*, 76.4, 75.7*, 59.2, 58.1*, 39.0, 38.1*, 33.1, 27.5*, 21.2, 14.9*, 14.0.
FTIR (neat, cm^{-1}):	3386 (br, m, OH), 1625 (s, C=O).
HRMS (FAB):	Calcd for $C_{17}H_{22}NO_2S$ $(MH)^+$: 304.1371. Found: 304.1368.
TLC (80% EtOAc–hexanes), R_f:	**25**: 0.48 (UV, PMA). **8**: 0.39 (UV, PMA).

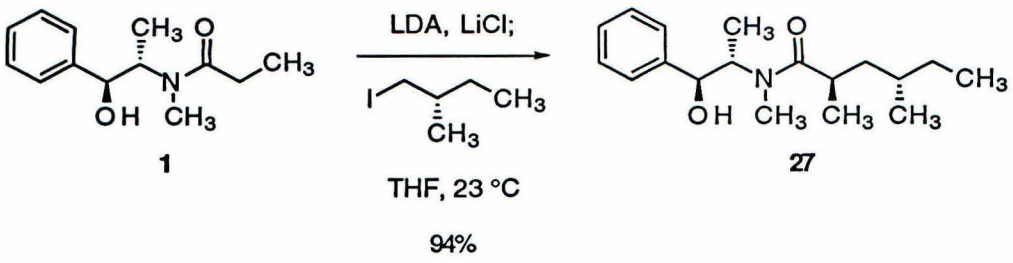


1 26

[1*S*(*R*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*,2,4-trimethyl Pentanamide **26**

A solution of *n*-butyllithium in hexanes (2.37 M, 10.7 mL, 25.4 mmol, 2.08 equiv) was added to a suspension of lithium chloride (3.10 g, 73.2 mmol, 6.00 equiv) and diisopropylamine (3.90 mL, 27.8 mmol, 2.28 equiv) in tetrahydrofuran (50 mL) at –78 °C. The suspension was warmed briefly to 0 °C, then was cooled to –78 °C. An ice-cooled solution of amide **1** (2.70 g, 12.2 mmol, 1 equiv) in tetrahydrofuran (40 mL, followed by a 2-mL rinse) was added via cannula over 4 min. The resulting mixture was stirred at –78 °C for 1 h, at 0 °C for 10 min, at 23 °C for 3 min, and finally was cooled to 0 °C whereupon isobutyl iodide (5.62 mL, 48.8 mmol, 4.00 equiv) was added. After 6 h, the reaction was quenched by the sequential addition of saturated aqueous ammonium chloride solution (15 mL) and 2 M aqueous sodium thiosulfate solution (5 mL). The mixture was partitioned between half-saturated brine (150 mL) and ethyl acetate (30 mL), and the aqueous layer was separated and extracted with two 60-mL portions of ethyl acetate. The combined organic fractions were washed with two 15-mL portions of brine, then were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (25 → 47%) afforded amide **26** as a white solid (2.99 g, 89%). Chiral capillary GC analysis[43] of the corresponding trimethylsilyl ether, prepared as described above for amide **11**, established that amide **26** was of 98% de. A portion of the recovered solid (2.93 g) was recrystallized from hot hexanes (69 °C, 8 mL) to afford amide **26** as white crystals (2.16 g, 74% recovery, 65% overall yield): mp 59–60 °C.

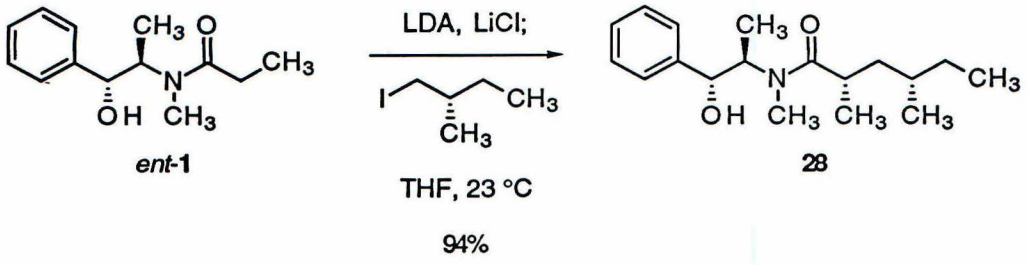
^{1}H NMR (300 MHz, $CDCl_3$) δ:	(4:1 rotamer ratio, * denotes minor rotamer peaks) 7.2–7.4 (m, 5H, aromatic), 4.60 (m, 1H, CHOH), 4.38 (br, 1H, $NCHCH_3$), 4.10* (m, 1H, $NCHCH_3$), 2.93* (m, 1H, $COCHCH_3$), 2.91* (s, 3H, NCH_3), 2.85 (s, 3H, NCH_3), 2.67 (sx, 1H, J = 6.8 Hz, $COCHCH_3$), 1.77 (m, 1H, $CH(CH_3)_2$), 1.5 (m, 2H, CH_2), 1.15 (d, 3H, J = 7.0 Hz, CH_3), 1.07 (d, 3H, J = 6.7 Hz, CH_3), 0.88–1.02* (m, 6H, $CH(CH_3)_2$), 0.85 (d, 3H, J = 6.2 Hz, CH_3), 0.82 (d, 3H, J = 6.5 Hz, CH_3).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	(4:1 rotamer ratio, * denotes minor rotamer peaks) 179.3, 142.6, 128.7*, 128.2, 127.4, 126.9*, 126.3, 76.5, 75.3*, 59.2, 58.0*, 43.1, 34.4, 33.5*, 33.2, 26.2*, 25.6, 23.0*, 22.7, 22.5, 18.1*, 17.4, 15.4*, 14.4.
FTIR (neat, cm^{-1}):	3385 (br, s, OH), 1619 (s, C=O).
HRMS (FAB):	Calcd for $C_{17}H_{28}NO_2$ $(MH)^+$: 278.2120.
	Found: 278.2109.
Analysis:	Calcd for $C_{17}H_{27}NO_2$: C, 73.61; H, 9.81; N, 5.05.
	Found: C, 73.65; H, 10.02; N, 4.94.
TLC (80% EtOAc–hexanes), R_f:	**26**: 0.54 (UV, PMA).
	1: 0.27 (UV, PMA).



[1*S*(2*R*,4*S*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*,2,4-trimethyl Hexanamideamide **27**

A solution of *n*-butyllithium in hexanes (2.44 M, 7.54 mL, 18.4 mmol, 3.67 equiv) was added via cannula to a suspension of lithium chloride (2.81 g, 66.2 mmol, 13.2 equiv) and diisopropylamine (2.72 mL, 19.4 mmol, 3.86 equiv) in tetrahydrofuran (15 mL) at –78 °C. The resulting suspension was warmed briefly to 0 °C, then was cooled to –78 °C. An ice-cooled solution of amide **1** (2.09 g, 9.45 mmol, 1.88 equiv) in tetrahydrofuran (30 mL, followed by a 3-mL rinse) was added dropwise via cannula. The reaction mixture was stirred at –78 °C for 30 min, at 0 °C for 10 min, and at 23 °C for 3 minutes, whereupon (*S*)-1-iodo-2-methylbutane (994 mg, 5.02 mmol, 1 equiv) was added. The mixture was stirred for 20 h at 23 °C then was quenched with half-saturated aqueous ammonium chloride solution (40 mL). Organic solvents were removed in vacuo, and the resulting aqueous solution was extracted with ethyl acetate (3 × 25 mL). The combined organic fractions were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (25 → 47%) furnished amide **27** as an oil which slowly solidified (1.38 g, 94%): mp 49–51 °C. Chiral capillary GC analysis[43] of the corresponding trimethylsilyl ether, prepared as described above for amide **11**, established that the ratio of the (2*R*,4*S*) diastereomer to the (2*S*,4*S*) diastereomer was 62:1.

^{1}H NMR (300 MHz, C_6D_6) δ:	(5:1 rotamer ratio, * denotes minor rotamer peaks) 7.0–7.4 (m, 5H, aromatic), 4.55 (t, 1H, J = 7.3 Hz, **CH**OH), 4.13 (m, 1H, NC**H**CH_3), 3.94* (m, 1H, NC**H**CH_3), 2.99* (m, 1H, COC**H**), 2.75* (s, 3H, N**C**H_3), 2.35 (m, 1H, COC**H**), 2.23 (s, 3H, N**C**H_3), 1.98* (m, 1H, CH_3CH_2**CH**), 1.50 (m, 3H, COCH**C**H_2, CH_3CH_2**C**H), 1.20 (m, 2H, CH_3**C**H_2), 0.90–1.04 (m, 6H, COCH**C**H_3, CH_3CH_2CH**C**H_3), 0.74–0.82 (m, 6H, **C**H_3CH_2, **C**H_3CHN), 0.62* (d, 3H, J = 6.7 Hz, **C**H_3CHN).
^{13}C NMR (100 MHz, $CDCl_3$) δ:	(5:1 rotamer ratio, * denotes minor rotamer peaks) 178.3, 177.1*, 141.5, 140.2*, 127.6*, 127.1, 126.3, 125.8*, 125.2, 75.4, 74.2*, 58.2, 57.0*, 39.6, 33.1, 32.1, 30.9, 28.9*, 28.5, 25.8*, 17.9, 16.5*, 15.9, 14.4*, 13.3, 10.1.
FTIR (neat, cm^{-1})	3385 (br, m, OH), 1618 (s, C=O).
HRMS (EI):	Calcd for $C_{18}H_{30}NO_2$ $(MH)^+$: 292.2277. Found: 292.2272.
Analysis:	Calcd for $C_{18}H_{29}NO_2$: C, 74.18; H, 10.03; N, 4.81. Found: C, 74.22; H, 9.75; N, 4.80.
TLC (80% EtOAc–hexanes), R_f:	**27**: 0.50 (UV, PMA). **1**: 0.33 (UV, PMA).



ent-**1**

28

[1*R*(2*S*,4*S*),2*R*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*,2,4-trimethyl Hexanamide **28**

A solution of *n*-butyllithium in hexanes (2.44 M, 7.40 mL, 18.1 mmol, 3.64 equiv) was added via cannula to a suspension of lithium chloride (2.75 g, 64.9 mmol, 13.1 equiv) and diisopropylamine (2.67 mL, 19.0 mmol, 3.84 equiv) in tetrahydrofuran (15 mL) at –78 °C. The suspension was warmed briefly to 0 °C, then was cooled to –78 °C. An ice-cooled solution of *ent*-**1** (2.09 g, 9.45 mmol, 1.88 equiv) in tetrahydrofuran (30 mL, followed by a 2-mL rinse) was added dropwise via cannula. The reaction mixture was stirred at –78 °C for 30 min, at 0 °C for 10 min, and at 23 °C for 3 minutes, whereupon (*S*)-1-iodo-2-methylbutane (983 mg, 4.96 mmol, 1 equiv) was added. The mixture was stirred at 23 °C for 18 h then was quenched by the addition of half-saturated aqueous ammonium chloride solution (40 mL). Organic solvents were removed in vacuo, and the resulting aqueous solution was extracted with ethyl acetate (3 × 25 mL). The combined organic fractions were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (25 → 47%) furnished amide **28** as a viscous oil (1.35 g, 94%). Amide **28** (16 mg, 0.055 mmol, 1 equiv) was acetylated with acetic anhydride (18 μL, 0.19 mmol, 3.5 equiv) and 4-dimethylaminopyridine (24 mg, 0.19 mmol, 3.5 equiv) in dichloromethane (1 mL) at 23 °C for 1 h. Chiral capillary GC analysis[43] of the resulting acetate ester established that the ratio of the (2*S*,4*S*) diastereomer to the (2*R*,4*S*) diastereomer was 89:1.

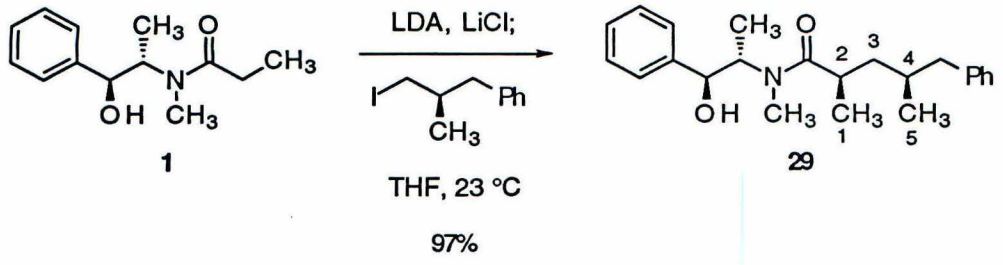
^{1}H NMR (400 MHz, C_6D_6) δ: (4:1 rotamer ratio, * denotes minor rotamer peaks) 7.0–7.4 (m, 5H, aromatic), 5.2 (br, 1H, OH), 4.54 (t, 1H, J = 7.2 Hz, CHOH), 4.15 (m, 1H, $NCHCH_3$), 3.95* (m, 1H, $NCHCH_3$), 3.05* (m, 1H, COCH), 2.74* (s, 3H, NCH_3), 2.45 (m, 1H, COCH), 2.25 (s, 3H, NCH_3), 1.89 (m, 1H, CH_3CH_2CH), 1.62* (m, 1H, CH_3CH_2CH), 1.48* (m, 2H, $CH_3CH_2CHCH_2$), 1.28 (m, 2H, $CH_3CH_2CHCH_2$), 1.08* (d, 3H, J = 9.2 Hz, $COCHCH_3$), 1.04* (d, 3H, J = 6.4 Hz, $CH_3CH_2CHCH_3$), 1.01 (d, 3H, J = 6.5 Hz, $COCHCH_3$), 0.97 (d, 3H, J = 7.1 Hz, CH_3CHN), 0.88 (t, 3H, J = 7.2 Hz, CH_3CH_2), 0.70 (d, 3H, J = 6.8 Hz, $CH_3CH_2CHCH_3$), 0.63* (d, 3H, J = 6.4 Hz, CH_3CHN).

^{13}C NMR (100 MHz, $CDCl_3$) δ: (4:1 rotamer ratio, * denotes minor rotamer peaks) 179.3, 177.9*, 142.7, 141.3*, 128.8*, 128.3, 128.1, 127.6, 127.0*, 126.3, 76.6, 75.3*, 59.2, 58.1*, 41.3, 34.3, 33.8*, 33.4, 32.1, 29.7, 26.9*, 19.5*, 19.2, 18.8*, 18.0, 15.5*, 14.5, 11.2.

FTIR (neat, cm^{-1}): 3384 (br, m, OH), 1618 (s, C=O).

HRMS (EI): Calcd for $C_{18}H_{30}NO_2$ $(MH)^+$: 292.2277.
Found: 292.2268.

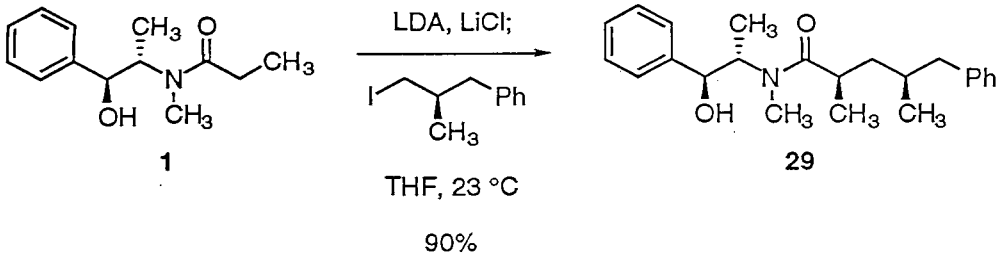
TLC (80% EtOAc–hexanes), R_f: **28**: 0.50 (UV, PMA).
ent-**1**: 0.33 (UV, PMA).



[1*S*(2*R*,4*S*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*,2,4-trimethyl Benzene-pentanamide **29**

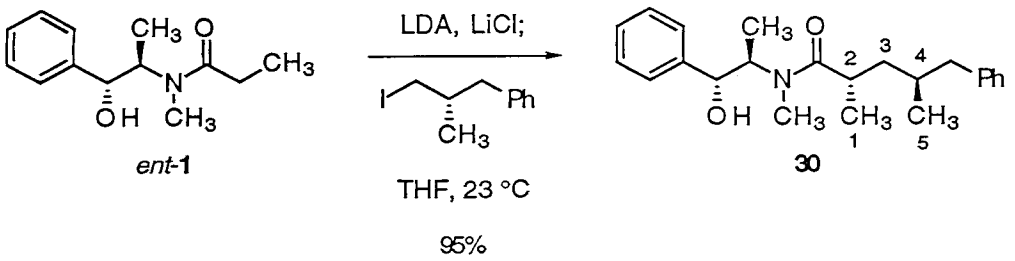
A solution of *n*-butyllithium in hexanes (2.33 M, 28.8 mL, 67.1 mmol, 3.90 equiv) was added via cannula to a suspension of lithium chloride (9.20 g, 217 mmol, 12.6 equiv) and diisopropylamine (10.6 mL, 75.7 mmol, 4.40 equiv) in tetrahydrofuran (45 mL) at –78 °C. The suspension was warmed briefly to 0 °C, then was cooled to –78 °C. An ice-cooled solution of amide **1** (8.00 g, 36.2 mmol, 2.10 equiv) in tetrahydrofuran (115 mL, followed by a 5-mL rinse) was added dropwise via cannula. The mixture was stirred at –78 °C for 40 min, at 0 °C for 10 min, and at 23 °C for 3 minutes, whereupon a solution of the iodide **67** (4.48 g, 17.2 mmol, 1 equiv) in tetrahydrofuran (3 mL, followed by a 3-mL rinse) was added via cannula. The mixture was stirred at 23 °C for 6 h then was quenched by the addition of 75% saturated aqueous ammonium chloride solution (200 mL). Organic solvents were removed in vacuo, and the resulting aqueous solution was extracted with ethyl acetate (3 × 100 mL). The combined organic fractions were washed with brine (30 mL), then were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (48% ethyl acetate–hexanes) furnished amide **29** as a viscous oil (5.89 g, 94%). The ratio of the (2*R*,4*S*) diastereomer to the (2*S*,4*S*) diastereomer was estimated to be ≥99:1 based on the crude de of the reduction product **61** (vide infra).

^{1}H NMR (400 MHz, $CDCl_3$) δ:	(4:1 rotamer ratio, * denotes minor rotamer peaks) 7.0–7.4 (m, 10H, aromatic), 4.95 (br, 1H, OH), 4.57 (m, 1H, CHOH), 4.51* (m, 1H, CHOH), 4.39 (br, 1H, $NCHCH_3$), 4.1* (m, 1H, $NCHCH_3$), 3.34 (br, 1H, H2), 3.04* (m, 1H, H2), 2.86* (s, 3H, NCH_3), 2.76 (s, 3H, NCH_3), 2.66 (m, 2H, $PhCH_2$), 2.25 (m, 1H, H4), 1.97* (m, 2H, $PhCH_2$), 1.78 (m, 1H, one of H3), 1.71 (m, 1H, one of H3), 1.21* (m, 2H, H3), 1.10 (d, 3H, J = 7.0 Hz, H1), 1.06* (d, 3H, J = 7.0 Hz, H1), 1.02 (d, 3H, J = 7.0 Hz, CH_3CHN), 0.97* (d, 3H, J = 6.6 Hz, H5), 0.83* (d, 3H, J = 6.6 Hz, CH_3CHN), 0.70 (d, 3H, J = 6.6 Hz, H5).
^{13}C NMR (100 MHz, $CDCl_3$) δ:	(4:1 rotamer ratio, * denotes minor rotamer peaks) 178.4, 177.2*, 142.5, 141.6*, 141.1*, 140.8, 129.1*, 129.0, 128.4*, 128.0, 127.9, 127.2, 126.7*, 126.3*, 126.1, 125.6, 125.4*, 76.1, 75.0*, 58.7, 57.8*, 43.7, 43.5*, 41.5*, 41.2, 34.1, 33.2*, 33.0, 32.4, 26.9*, 19,3*, 19.2, 18.6*, 17.7, 15.4*, 14.1.
FTIR (neat, cm^{-1}):	3384 (br, m, OH), 1620 (s, C=O).
Analysis:	Calcd for $C_{23}H_{31}NO_2$: C, 78.15; H, 8.84; N, 3.96. Found: C, 77.99; H, 9.00; N, 3.91.
TLC (30% EtOAc–hexanes), R_f:	**29**: 0.14 (UV, PMA). **67**: 0.68 (UV, PMA).



[1*S*(2*R*,4*S*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*,2,4-trimethyl Benzene-pentanamide **29**

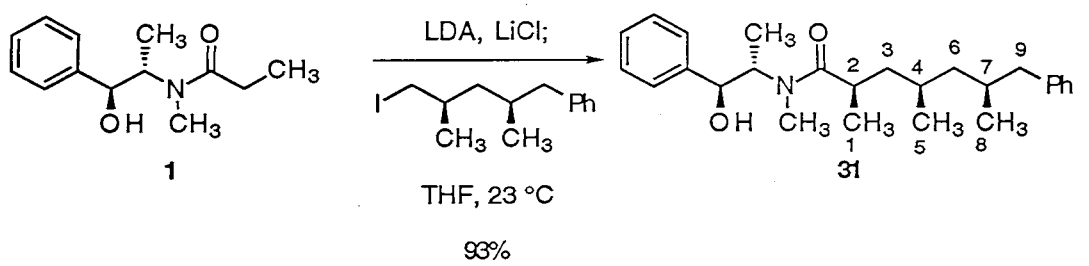
Amide **29** could also be prepared using fewer equivalents of enolate. Thus a solution of *n*-butyllithium in hexanes (0.933 mL, 2.27 mmol, 2.65 equiv) was added via cannula to a suspension of lithium chloride (343 mg, 8.09 mmol, 9.45 equiv) and diisopropylamine (0.342 mL, 2.44 mmol, 2.85 equiv) in tetrahydrofuran (1.5 mL) at –78 °C. The suspension was warmed briefly to 0 °C, then was cooled to –78 °C. An ice-cooled solution of amide **1** (256 mg, 1.15 mmol, 1.35 equiv) in tetrahydrofuran (3 mL, followed by a 1-mL rinse) was added dropwise via cannula. The mixture was stirred at –78 °C for 40 min, at 0 °C for 10 min, and at 23 °C for 3 minutes, whereupon a solution of the iodide **67** (223 mg, 0.855 mmol, 1 equiv) in tetrahydrofuran (1 mL, followed by a 1-mL rinse) was added via cannula. The mixture was stirred at 23 °C for 21 h then was quenched by the addition of 75% saturated aqueous ammonium chloride solution (20 mL). The mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic fractions were washed with brine (5 mL), then were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (48% ethyl acetate–hexanes) furnished amide **29** as a viscous oil (272 mg, 90%). The ratio of the (2*R*,4*S*) diastereomer to the (2*S*,4*S*) diastereomer was estimated to be 99:1 based on the crude de of the reduction product **61** (vide infra). Spectroscopic data were identical to those listed above.



[1*R*(2*S*,4*S*),2*R*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*,2,4-trimethyl Benzene-pentanamide **30**

A solution of *n*-butyllithium in hexanes (2.33 M, 26.2 mL, 60.9 mmol, 4.05 equiv) was added via cannula to a suspension of lithium chloride (9.20 g, 217 mmol, 14.4 equiv) and diisopropylamine (9.56 mL, 68.2 mmol, 4.53 equiv) in tetrahydrofuran (40 mL) at –78 °C. The suspension was warmed briefly to 0 °C, then was cooled to –78 °C. An ice-cooled solution of *ent*-**1** (6.89 g, 31.1 mmol, 2.07 equiv) in tetrahydrofuran (115 mL, followed by a 3 mL rinse) was added dropwise via cannula. The reaction mixture was stirred at –78 °C for 40 min, at 0 °C for 10 min, and at 23 °C for 3 minutes, whereupon a solution of the iodide **67** (3.92 g, 15.1 mmol, 1 equiv) in tetrahydrofuran (4 mL, followed by a 2-mL rinse) was added via cannula. The mixture was stirred at 23 °C for 7 h then was quenched by the addition of 75% saturated aqueous ammonium chloride solution (200 mL). Organic solvents were removed in vacuo, and the resulting aqueous solution was extracted with ethyl acetate (3 × 120 mL). The combined organic fractions were washed with brine (40 mL), then were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (47 → 51%) furnished amide **30** as a viscous oil (5.05 g, 95%). Chiral capillary GC analysis[43] of the corresponding trimethylsilyl ether, prepared as described above for amide **11**, established that the ratio of the (2*S*,4*S*) diastereomer to the (2*R*,4*S*) diastereomer was 58:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ:	(4:1 rotamer ratio, * denotes minor rotamer peaks) 7.0–7.4 (m, 10H, aromatic), 4.79 (br, 1H, OH), 4.54 (m, 1H, CHOH), 4.50* (m, 1H, CHOH), 4.45 (m, 1H, $NCHCH_3$), 4.05* (m, 1H, $NCHCH_3$), 3.36 (br, 1H, H2), 2.96* (m, 1H, H2), 2.87* (s, 3H, NCH_3), 2.75 (s, 3H, NCH_3), 2.58 (m, 2H, one of $PhCH_2$), 2.33 (dd, 1H, J_1 = 13.2 Hz, J_2 = 8.1 Hz, one of $PhCH_2$), 1.79* (m, 1H, H4), 1.67 (m, 1H, H4), 1.46 (m, 1H, one of H3), 1.33 (m, 1H, one of H3), 1.08 (d, 3H, J = 6.6 Hz, H1), 1.02* (d, 3H, J = 6.6 Hz, H1), 0.97 (d, 3H, J = 6.6 Hz, CH_3CHN), 0.81 (d, 3H, J = 6.6 Hz, H5).
^{13}C NMR (100 MHz, $CDCl_3$) δ:	(4:1 rotamer ratio, * denotes minor rotamer peaks) 178.6, 177.6*, 142.5, 141.6*, 141.1*, 140.8, 129.1*, 128.9, 128.4*, 128.03, 128.00, 127.3, 126.7*, 126.2, 125.6, 125.4*, 76.1, 75.1*, 58.2, 57.8*, 43.8, 40.8, 40.5, 34.2, 33.1*, 32.7, 32.4*, 26.9*, 19.6, 19.1*, 17.5*, 17.0, 15.4*, 14.2.
FTIR (neat, cm^{-1}):	3385 (br, m, OH), 1618 (s, C=O).
Analysis:	Calcd for $C_{23}H_{31}NO_2$: C, 78.15; H, 8.84; N, 3.96. Found: C, 78.27; H, 8.94, N, 3.97.
TLC (30% EtOAc–hexanes), R_f:	**30**: 0.18 (UV, PMA). **67**: 0.72 (UV, PMA).



[1*S*(2*R*,4*R*,6*S*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*,2,4,6-tetramethyl Benzeneheptanamide **31**

A solution of *n*-butyllithium in hexanes (2.43 M, 5.30 mL, 12.9 mmol, 3.88 equiv) was added via cannula to a suspension of lithium chloride (1.77 g, 41.7 mmol, 12.5 equiv) and diisopropylamine (2.04 mL, 14.6 mmol, 4.38 equiv) in tetrahydrofuran (9 mL) at –78 °C. The suspension was warmed briefly to 0 °C then was cooled to –78 °C. An ice-cooled solution of amide **1** (1.47 g, 6.65 mmol, 2.00 equiv) in tetrahydrofuran (25 mL, followed by a 3-mL rinse) was added dropwise via cannula. The reaction mixture was stirred at –78 °C for 40 min, at 0 °C for 10 min, and at 23 °C for 3 minutes, whereupon a solution of the iodide **68** (1.00 g, 3.32 mmol, 1 equiv) in tetrahydrofuran (2 mL, followed by a 3-mL rinse) was added. The mixture was stirred at 23 °C for 18 h then was quenched by the addition of half-saturated aqueous ammonium chloride solution (50 mL). Organic solvents were removed in vacuo, and the resulting aqueous solution was extracted with ethyl acetate (3 × 25 mL). The combined organic fractions were washed with brine (7 mL), then were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (39% ethyl acetate–hexanes) furnished amide **31** as a viscous oil (1.22 g, 93%). Chiral capillary GC analysis[43] of the corresponding trimethylsilyl ether, prepared as described above for amide **11**, established that the ratio of the (2*R*,4*R*,6*S*) diastereomer to the (2*S*,4*R*,6*S*) diastereomer was 142:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ: (3:1 rotamer ratio, * denotes minor rotamer peaks) 7.0–7.4 (m, 10H, aromatic), 4.97 (br, 1H, **OH**), 4.49 (m, 1H, **CH**OH), 4.46 (m, 1H, NC**H**CH_3), 4.02* (m, 1H, **CH**OH), 3.82* (m, 1H, NC**H**CH_3), 2.94* (m, 1H, H2), 2.81* (s, 3H, NC**H**$_3$), 2.73 (s, 3H, NC**H**$_3$), 2.65 (m, 1H, H2), 2.59 (m, 1H, one of H9), 2.28 (m, 1H, one of H9), 1.85 (m, 2H, H7, H4), 1.75 (m, 1H, one of H3), 1.59* (m, 2H, H3), 1.47 (m, 1H, one of H3), 1.29* (m, 2H, H6), 1.20 (m, 2H, H6), 1.04 (d, 3H, J = 6.2 Hz, H1), 1.00* (d, 3H, J = 6.6 Hz, H1), 0.94 (d, 3H, J = 6.6 Hz, CHNC**H**$_3$), 0.83 (d, 3H, J = 6.2 Hz, H8), 0.76 (d, 3H, J = 6.6 Hz, H5).

^{13}C NMR (100 MHz, $CDCl_3$) δ: (3:1 rotamer ratio, * denotes minor rotamer peaks) 178.2, 177.2*, 142.4, 141.7*, 141.2*, 141.0, 128.9, 128.2*, 127.8, 127.7, 127.0, 126.6*, 126.0, 125.3, 75.7, 74.8*, 57.6, 44.9*, 44.6, 43.3, 43.1, 41.2*, 40.8, 33.5, 32.8*, 32.3*, 31.9, 27.8, 26.8*, 20.5*, 20.3, 20.0*, 19.8, 18.5*, 17.8, 15.2*, 14.0.

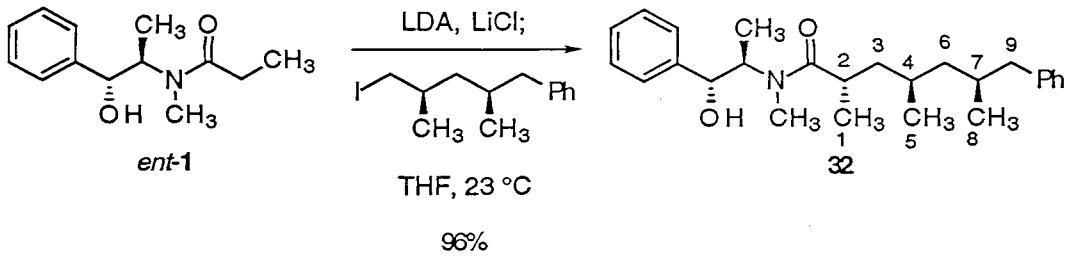
FTIR (neat, cm^{-1}): 3383 (br, m, OH), 1621 (s, C=O).

HRMS (FAB): Calcd for $C_{26}H_{38}NO_2$ $(MH)^+$: 396.2903.

Found: 396.2897.

TLC (30% EtOAc–hexanes), R_f: **31**: 0.17 (UV, PMA).

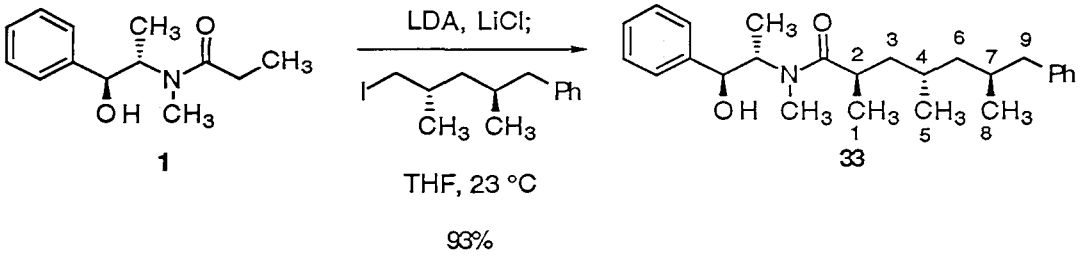
68: 0.66 (UV, PMA).



[1*R*(2*S*,4*R*,6*S*),2*R*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*,2,4,6-tetramethyl Benzeneheptanamide **32**

A solution of *n*-butyllithium in hexanes (2.43 M, 5.31 mL, 12.9 mmol, 3.87 equiv) was added via cannula to a suspension of lithium chloride (1.77 g, 41.7 mmol, 12.5 equiv) and diisopropylamine (2.04 mL, 14.6 mmol, 4.37 equiv) in tetrahydrofuran (9 mL) at –78 °C. The suspension was warmed briefly to 0 °C, then was cooled to –78 °C. An ice-cooled solution of *ent*-**1** (1.47 g, 6.66 mmol, 2.00 equiv) in tetrahydrofuran (25 mL, followed by a 3-mL rinse) was added dropwise via cannula. The reaction mixture was stirred at –78 °C for 40 min, at 0 °C for 10 min, and at 23 °C for 3 minutes, whereupon a solution of the iodide **68** (1.01 g, 3.33 mmol, 1 equiv) in tetrahydrofuran (2 mL, followed by a 3-mL rinse) was added. The mixture was stirred at 23 °C for 18 h then was quenched by the addition of half-saturated aqueous ammonium chloride solution (50 mL). Organic solvents were removed in vacuo, and the resulting aqueous solution was extracted with ethyl acetate (3 × 25 mL). The combined organic fractions were washed with brine (7 mL), then were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (39% ethyl acetate–hexanes) furnished amide **32** as a viscous oil (1.27 g, 96%). Chiral capillary GC analysis[43] of the corresponding trimethylsilyl ether, prepared as described above for amide **11**, established that the ratio of the (2*S*,4*R*,6*S*) diastereomer to the (2*R*,4*R*,6*S*) diastereomer was 70:1.

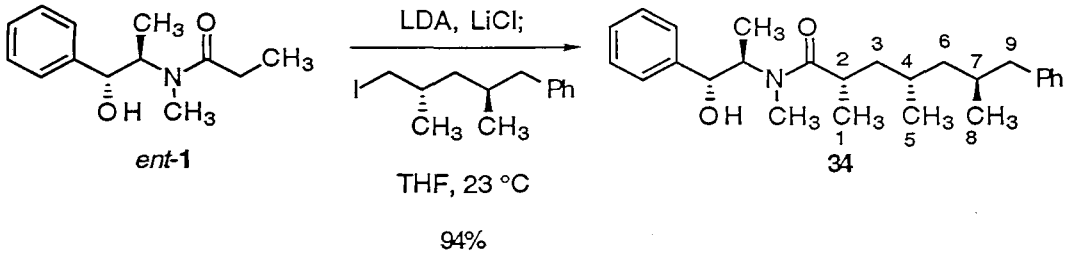
^{1}H NMR (400 MHz, $CDCl_3$) δ:	(3:1 rotamer ratio, * denotes minor rotamer peaks) 7.0–7.4 (m, 10H, aromatic), 4.83 (br, 1H, **OH**), 4.53 (m, 1H, **CH**OH), 4.47 (m, 1H, NC**H**CH_3), 4.03* (m, 1H, **CH**OH), 3.62* (m, 1H, NC**H**CH_3), 2.94* (s, 3H, NC**H**$_3$), 2.85 (s, 3H, NC**H**$_3$), 2.62 (m, 1H, H2), 2.23 (m, 2H, H9), 1.79 (m, 2H, H7, H4), 1.62* (m, 2H, H7, H4), 1.51 (m, 2H, H3), 1.33* (m, 2H, H3), 1.20 (m, 2H, H6), 1.05 (d, 3H, J = 7.0 Hz, H1), 0.98 (d, 3H, J = 6.6 Hz, **CH**$_3$CHN), 0.89* (d, 3H, J = 6.2 Hz, H1), 0.83 (d, 3H, J = 6.6 Hz, H8), 0.80 (d, 3H, J = 6.6 Hz, H5).
^{13}C NMR (100 MHz, $CDCl_3$) δ:	(3:1 rotamer ratio, * denotes minor rotamer peaks) 178.7, 177.8*, 142.3, 141.7*, 141.2*, 141.0, 128.9, 128.3*, 127.9, 127.8, 127.1, 126.6*, 126.1, 125.4, 125.3*, 75.9, 75.0*, 57.7, 45.3*, 44.9, 43.4, 40.5, 40.0*, 33.8, 32.7*, 32.3, 32.0, 31.8*, 27.6, 27.2*, 26.9*, 20.0, 19.7, 19.5*, 16.5, 15.3*, 14.1.
FTIR (neat, cm^{-1}):	3382 (br, m, OH), 1620 (s, C=O).
HRMS (FAB):	Calcd for $C_{26}H_{38}NO_2$ $(MH)^+$: 396.2903. Found: 396.2890.
TLC (30% EtOAc–hexanes), R_f:	**32**: 0.17 (UV, PMA). **68**: 0.71 (UV, PMA).



[1*S*(2*R*,4*S*,6*S*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*,2,4,6-tetramethyl Benzeneheptanamide **33**

A solution of *n*-butyllithium in hexanes (2.33 M, 5.53 mL, 12.9 mmol, 3.62 equiv) was added via cannula to a suspension of lithium chloride (1.76 g, 41.6 mmol, 11.7 equiv) and diisopropylamine (2.04 mL, 14.5 mmol, 4.09 equiv) in tetrahydrofuran (9 mL) at –78 °C. The suspension was warmed briefly to 0 °C, then was cooled to –78 °C. An ice-cooled solution of amide **1** (1.53 g, 6.93 mmol, 1.95 equiv) in tetrahydrofuran (24 mL, followed by a 5-mL rinse) was added dropwise via cannula. The reaction mixture was stirred at –78 °C for 40 min, at 0 °C for 10 min, and at 23 °C for 3 minutes, whereupon a solution of the iodide **69** (1.07 g, 3.56 mmol, 1 equiv) in tetrahydrofuran (3 mL, followed by a 2-mL rinse) was added. The mixture was stirred at 23 °C for 12 h then was quenched by the addition of half-saturated aqueous ammonium chloride solution (30 mL). Organic solvents were removed in vacuo, and the resulting aqueous solution was extracted with ethyl acetate (3 × 25 mL). The combined organic fractions were washed with brine (7 mL), then were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (44% ethyl acetate–hexanes) furnished amide **33** as a white solid (1.30 g, 96%): mp 73–74 °C. Chiral capillary GC analysis[43] of the corresponding trimethylsilyl ether, prepared as described above for amide **11**, established that the ratio of the (2*R*,4*S*,6*S*) diastereomer to the (2*S*,4*S*,6*S*) diastereomer was 66:1.

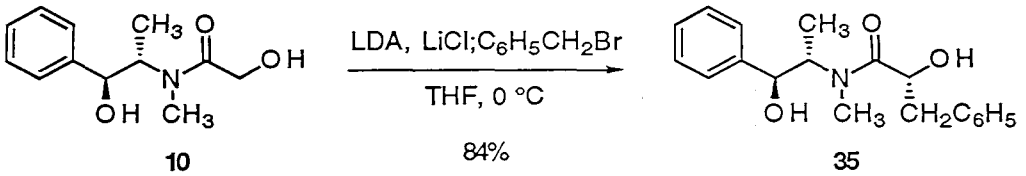
^{1}H NMR (400 MHz, $CDCl_3$) δ:	(3:1 rotamer ratio, * denotes minor rotamer peaks) 7.0–7.4 (m, 10H, aromatic), 4.58 (m, 1H, CHOH), 4.54* (m, 1H, CHOH), 4.48* (m, 1H, $NCHCH_3$), 4.50* (m, 1H, $NCHCH_3$), 2.92* (m, 1H, H2), 2.88* (s, 3H, NCH_3), 2.82 (s, 3H, NCH_3), 2.78 (m, 1H, H2), 2.68 (m, 1H, one of H9), 2.55 (m, 1H, one of H9), 2.38 (m, 1H, H7), 2.21 (br, s, OH), 1.80 (m, 1H, H4), 1.58* (m, 1H, H4), 1.46 (m, 1H, one of H3), 1.38 (m, 1H, one of H3), 1.23 (m, 2H, H6), 1.05 (m, 9H, H1, CH_3CHN, H8), 0.98* (d, 3H, J = 6.6 Hz, H1), 0.82* (m, 6H, CH_3CHN, H8), 0.77 (d, 3H, J = 6.6 Hz, H5).
^{13}C NMR (100 MHz, $CDCl_3$) δ:	(3:1 rotamer ratio, * denotes minor rotamer peaks) 179.1, 177.9*, 142.5, 141.4*, 141.1, 129.4*, 129.1, 128.6*, 128.2, 128.0, 127.4, 126.8*, 126.3, 125.6; 76.4, 75.2*, 57.9, 44.7*, 44.4, 41.9, 41.6*, 34.0, 33.0*, 32.4, 32.0, 27.9, 27.6*, 26.9*, 19.3, 19.2, 17.6*, 17.1, 15.4*, 14.3.
FTIR (neat, cm^{-1}):	3383 (br, m, OH), 1618 (s, C=O).
Analysis:	Calcd for $C_{26}H_{37}NO_2$: C, 78.94; H, 9.43, N, 3.54. Found: C, 78.74; H, 9.16; N, 3.47.
TLC (30% EtOAc–hexanes), R_f:	**33**: 0.13 (UV, PMA). **69**: 0.66 (UV, PMA).



[1*R*(2*S*,4*S*,6*S*),2*R*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*,2,4,6-tetramethyl Benzeneheptanamide **34**

A solution of *n*-butyllithium in hexanes (2.33 M, 5.55 mL, 12.9 mmol, 3.86 equiv) was added via cannula to a suspension of lithium chloride (1.77 g, 41.7 mmol, 12.5 equiv) and diisopropylamine (2.04 mL, 14.6 mmol, 4.36 equiv) in tetrahydrofuran (9 mL) at –78 °C. The suspension was warmed briefly to 0 °C, then was cooled to –78 °C. An ice-cooled solution of *ent*-**1** (1.48 g, 6.70 mmol, 2.00 equiv) in tetrahydrofuran (24 mL, followed by a 5-mL rinse) was added dropwise via cannula. The reaction mixture was stirred at –78 °C for 40 min, at 0 °C for 10 min, and at 23 °C for 3 minutes, whereupon a solution of the iodide **69** (1.01 g, 3.35 mmol, 1 equiv) in tetrahydrofuran (3 mL, followed by a 2-mL rinse) was added. The mixture was stirred at 23 °C for 18 h then was quenched by the addition of 75% saturated aqueous ammonium chloride solution (40 mL). Organic solvents were removed in vacuo, and the resulting aqueous solution was extracted with ethyl acetate (3 × 25 mL). The combined organic fractions were washed with brine (7 mL), then were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (40% ethyl acetate–hexanes) furnished amide **34** as a viscous oil (1.25 g, 94%). Chiral capillary GC analysis[43] of the corresponding acetate ester, prepared as described above for amide **28**, established that the ratio of the (2*S*,4*S*,6*S*) diastereomer to the (2*S*,4*S*,6*S*) diastereomer was 199:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ:	(3:1 rotamer ratio, * denotes minor rotamer peaks) 7.0–7.4 (m, 10H, aromatic), 4.60 (m, 1H, CHOH), 4.57* (m, 1H, CHOH), 4.40* (m, 1H, $NCHCH_3$), 4.09* (m, 1H, $NCHCH_3$), 3.01* (m, 1H, H2), 2.90* (s, 3H, NCH_3), 2.84 (s, 3H, NCH_3), 2.69 (sx, 1H, J = 6.6 Hz, H2), 2.59 (dd, 1H, J_1 = 13.2 Hz, J_2 = 5.9 Hz, one of H9), 2.35 (dd, 1H, J_1 = 13.2 Hz, J_2 = 8.6 Hz, one of H9), 1.85 (m, 2H, H7, H4), 1.65 (m, 2H, H3), 1.52 (m, 2H, H6), 1.12 (d, 3H, J = 6.6 Hz, H1), 1.09* (d, 3H, H1), 1.06 (d, 3H, J = 6.6 Hz, H8), 0.99* (d, 3H, J = 7.0 Hz, H8), 0.87* (d, 3H, J = 6.6 Hz, H5), 0.82 (d, 3H, J = 6.6 Hz, H5), 0.73 (d, 3H, J = 6.2 Hz, CH_3CHN).
^{13}C NMR (100 MHz, $CDCl_3$) δ:	(3:1 rotamer ratio, * denotes minor rotamer peaks) 178.4, 177.3*, 142.4, 141.7*, 141.3*, 141.1, 128.9, 128.2*, 127.9, 127.8, 127.1, 126.7*, 126.1, 125.3, 75.9, 74.9*, 57.9, 57.6*, 44.2, 44.1, 41.9, 33.7, 32.8*, 32.5, 32.0, 27.7, 26.9*, 19.8*, 19.4, 19.0, 18.2*, 17.6, 15.3*, 14.1.
FTIR (neat, cm^{-1}):	3384 (br, m, OH), 1620 (s, C=O).
HRMS (FAB):	Calcd for $C_{26}H_{38}NO_2$ $(MH)^+$: 396.2903.
	Found: 396.2894.
TLC (30% EtOAc–hexanes), R_f:	**34**: 0.16 (UV, PMA).
	69: 0.66 (UV, PMA).

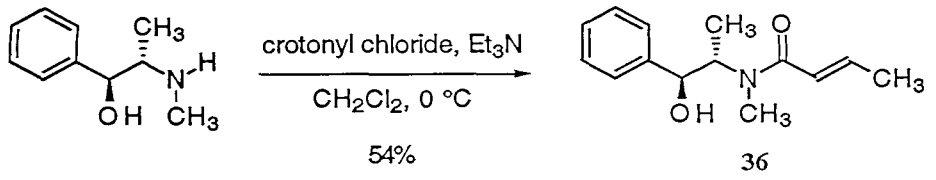


10 35

[1*S*(*R*),2*S*)-α-Hydroxy-*N*-(2hydroxy-1-methyl-2-phenylethyl)-*N*-methyl Benzene-propionamide **35**

A solution of *n*-butyllithium in hexanes (2.36 M, 1.20 mL, 2.83 mmol, 6.05 equiv) was added to a suspension of lithium chloride (262 mg, 6.18 mmol, 13.2 equiv) and diisopropylamine (0.433 mL, 3.09 mmol, 6.60 equiv) in tetrahydrofuran (3 mL) at –78 °C. The suspension was warmed briefly to 0 °C then was cooled to –78 °C. A solution of amide **10** (230 mg, 1.03 mmol, 2.20 equiv) in tetrahydrofuran (2 mL, followed by a 1-mL rinse) was added dropwise via cannula. The reaction mixture was stirred at –78 °C for 30 min, at 0 °C for 10 min, then was cooled to –78 °C. Benzyl bromide (56.0 μL, 0.468 mmol, 1 equiv) was added, and the mixture was warmed to 0 °C. The mixture was stirred at 0 °C for 4 h then was quenched by the sequential addition of half-saturated aqueous ammonium chloride solution (5 mL) and half-saturated brine (5 mL). The mixture was extracted with ethyl acetate (3 × 20 mL), and the combined organic fractions were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (72% ethyl acetate–hexanes) afforded amide **35** as a viscous oil (124 mg, 84%). Analysis by ^{1}H NMR spectroscopy (300 MHz, C_6D_6) established that amide **35** was of 82% de.

^{1}H NMR (300 MHz, C_6D_6) δ:	7.0–7.6 (m, 10 H, aromatic), 4.65 (br, s, 2H, OH), 4.55 (m, 1H, NCHCH$_3$), 4.44* (m, 1H, COCH), 4.38 (m, 1H, COCH), 4.24 (m, 1H, PhCHOH), 3.98* (m, 1H, PhCHOH), 3.84* (m, 1H, CHNCH$_3$), 3.53* (m, 1H, one of PhCH$_2$), 3.10* (m, 1H, one of PhCH$_2$), 2.84 (s, 1H, one of PhCH$_2$), 2.82 (s, 1H, one of PhCH$_2$), 2.81* (s, 3H, NCH$_3$), 2.16 (s, 3H, NCH$_3$), 0.63 (d, 3H, J = 6.9 Hz, CH$_3$CHN), 0.41* (d, 3H, J = 6.7 Hz, CH$_3$CHN).
FTIR (neat, cm^{-1}):	3382 (br, s, OH), 3029 (w), 1627 (s, C=O), 1495 (m), 1455 (m), 1392 (m), 1079 (m), 1052 (m), 753 (m), 701 (s)
HRMS (FAB):	Calcd for $C_{19}H_{24}NO_3$ $(MH)^+$: 314.1756. Found: 314.1761.
TLC (10% MeOH–CH_2Cl_2), R_f:	**35**: 0.41 (UV, PMA). **10**: 0.31 (UV, PMA).

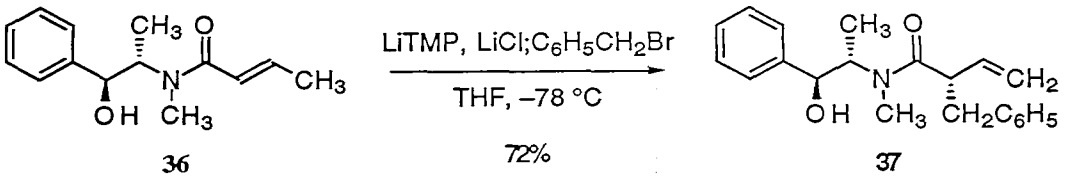


36

(*S*,*S*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*-methyl Crotonamide **36**

An ice-cooled solution of crotonyl chloride (14.5 g, 138 mmol, 1 equiv) in dichloromethane (70 mL) was added via cannula over 5 min to a solution of pseudoephedrine (23.5 g, 142 mmol, 1 equiv) and triethylamine (25.7 mL, 185 mmol, 1.30 equiv) in dichloromethane (300 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min then excess acid chloride was quenched by the addition of saturated aqueous sodium bicarbonate solution (5 mL). The mixture was partitioned between dichloromethane (300 mL) and saturated aqueous sodium bicarbonate solution (40 mL). The organic layer was separated and extracted sequentially with saturated aqueous sodium bicarbonate solution (2 × 40 mL) and 3 N aqueous hydrochloric acid solution (3 × 40 mL). The organic layer was dried over sodium sulfate and was concentrated. Recrystallization of the crude product from hot toluene (110 °C, 70 mL) afforded amide **36** as a yellow crystalline solid (18.5 g, 54% yield): mp 91–93 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ:	(4:1 rotamer ratio, * denotes minor rotamer peaks) 7.2–7.4 (m, 5H, aromatic), 6.85–7.00 (m, 1H, CH_3**C**H=CH), 6.37* (d, 1H, J = 15.1 Hz, CH_3CH=**C**H), 6.20 (d, 1H, J = 14.4 Hz, CH_3CH=**C**H), 4.59 (d, 1H, J = 8.2 Hz, **C**HOH), 4.47 (m, 1H, NC**H**CH_3), 4.15 (br, 1H, O**H**), 2.94* (s, 3H, NC**H**$_3$), 2.87 (s, 3H, NC**H**$_3$), 1.89 (dd, 3H, J_1 = 6.8 Hz, J_2 = 1.5 Hz, **C**H_3CH=CH), 1.10 (d, 3H, J = 6.9 Hz, **C**H_3CHN), 0.98* (d, 3H, J = 6.8 Hz, **C**H_3CHN).
FTIR (neat, cm^{-1}):	3368 (br, m, OH), 1659 (s), 1596 (s), 1452 (m), 1406 (m), 1050 (m), 762 (m), 703 (m).
HRMS (FAB):	Calcd for $C_{14}H_{20}NO_2$ $(MH)^+$: 234.1494. Found: 234.1503.
TLC (15% MeOH–CH_2Cl_2), R_f:	**36**: 0.57 (UV, PMA). pseudoephedrine: 0.05 (UV, PMA).



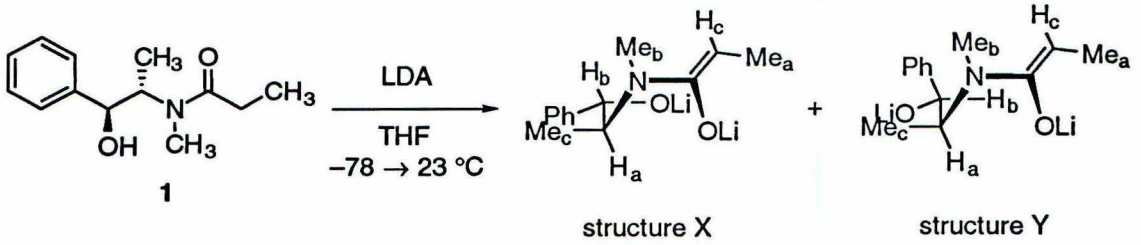
36 37

[1*S*(*S*),2*S*]-α-Vinyl-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methyl Benzenepropionamide **37**

A solution of *n*-butyllithium in hexanes (2.25 M, 1.02 mL, 2.30 mmol, 2.30 equiv) was added to a suspension of lithium chloride (254 mg, 6.00 mmol, 6.00 equiv) and 2,2,6,6-tetramethylpiperidine (0.422 mL, 2.50 mmol, 2.50 equiv) in tetrahydrofuran (3 mL) at –78 °C. The suspension was stirred at –78 °C for 5 minutes then was warmed to 0 °C and held at that temperature for 20 minutes. An ice-cooled solution of amide **36** (233 mg, 1.00 mmol, 1 equiv) in tetrahydrofuran (2.5 mL, followed by a 0.5-mL rinse) was added via cannula. The reaction mixture was cooled to –78 °C and maintained at that temperature for 10 minutes, whereupon benzyl bromide (0.420 mL, 3.50 mmol, 3.50 equiv) was added dropwise via syringe. The mixture was stirred at –78 °C for 5 h, then was treated with a solution of acetic acid and ether (50% v/v, 2 mL). The mixture was warmed to 23 °C and was partitioned between half-saturated aqueous sodium bicarbonate solution (75 mL) and ethyl acetate (15 mL). The aqueous layer was separated and extracted with ethyl acetate (2 × 15 mL). The combined organic fractions were washed with brine (5 mL), then were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (35 → 55%) afforded amide **37** as a white crystalline solid (232 mg, 72%). ^{1}H NMR analysis (300 MHz, C_6D_6) and chiral capillary GC analysis[43] of the corresponding trimethylsilyl ether, prepared as described above for amide **11**, established that amide **36** was of 93% de. Recrystallization of the solid (1.0 g, obtained from the combined yields of several of the above-mentioned reactions) from hot ethyl acetate (70 °C, 10 mL) afforded

white crystals (520 mg, 52% recovery, 36% overall yield). Chiral capillary GC analysis, as described above, established that amide **37** was of ≥99% de: mp 114–116 °C.

^{1}H NMR (300 MHz, $CDCl_3$), δ:	(3:1 rotamer ratio, * denotes minor rotamer peaks) 7.15–7.40 (m, 10H, aromatic), 5.87 (m, 1H, C**H**=CH_2), 5.04 (m, 2H, CH=C**H**$_2$), 4.55 (dd, 1H, J_1 = 7.6 Hz, J_2 = 6.7 Hz, C**H**OH), 4.45 (dd, 1H, J_1= 8.6 Hz, J_2 = 2.5 Hz, C**H**OH), 4.38 (br, 1H, NC**H**CH_3), 3.76* (m, 1H, C**H**CH_2Ph), 3.48 (m, 1H, C**H**CH_2Ph), 3.17 (m, 2H, one of Ph**CH**$_2$), 2.87* (s, 3H, NC**H**$_3$), 2.80 (m, 2H, one of Ph**CH**$_2$), 2.69 (s, 3H, NC**H**$_3$), 0.99 (d, 3H, J = 6.9 Hz, CH_3), 0.93* (d, 3H, J = 6.8 Hz, C**H**$_3$).
FTIR (neat, cm^{-1}):	3378 (br, m, OH), 3027 (m), 2977 (m), 1618 (s, C=O), 1493 (m), 1453 (m), 1406 (m), 1115 (m), 1049 (m), 919 (m), 752 (m), 700 (s).
HRMS (FAB):	Calcd for $C_{21}H_{26}NO_2$ $(MH)^+$: 324.1964. Found: 324.1960.
TLC (80% EtOAc–hexanes), R_f:	**37**: 0.57 (UV, PMA). **36**: 0.30 (UV, PMA).



Pseudoephedrine Propionamide Enolate

A solution of *n*-butyllithium in hexanes (2.42 M, 0.860 mL, 2.08 mmol, 2.08 equiv) was added to a solution of diisopropylamine (0.320 mmol, 2.28 mmol, 2.28 equiv) in tetrahydrofuran (2.5 mL) at –78 °C. The solution was warmed briefly to 0 °C, then was cooled to –78 °C. An ice-cooled solution of amide **1** (221 mg, 1.00 mmol, 1 equiv) in tetrahydrofuran (2.5 mL, followed by a 0.5-mL rinse) was added via cannula. The reaction mixture was stirred at –78 °C for 1 h, at 0 °C for 11 min, and at 23 °C for 3 min. An aliquot from the reaction mixture (700 μL) was withdrawn by microliter syringe and was transferred to a 5-mL flask. Volatile solvents were removed under vacuum (0.5 mm Hg for 1 h). The residue was dissolved in d_8-tetrahydrofuran (700 μL), and the solvent was removed under vacuum (0.5 mm Hg for 10 min). The residue was dissolved in d_8-tetrahydrofuran (700 μL) and the solution was transferred to an NMR tube.

^{1}H NMR (300 MHz, THF-d_8) δ: (1:1 mixture of structure X and structure Y) 6.9–7.8 (m, 5H, aromatic), 4.83 (s, 0.5H, H_b of Y), 4.56 (d, 0.5H, J = 8.0 Hz, H_b of X), 3.58 (obscured by THF-d_8, m, 0.5H, C**H**NCH$_3$ of X), 3.34 (qt, 0.5H, J = 6.3 Hz, H_c of X), 3.19 (qt, 0.5H, J = 6.4 Hz, H_c of Y), 2.97 (m, 0.5H, C**H**NCH$_3$ of Y), 2.82 {residual HN[C**H**(CH$_3$)$_2$]$_2$}, 2.52 (s, 1.5H, NC**H**$_3$ of X), 1.82 (s, 1.5H, NC**H**$_3$ of Y), 1.73 (obscured by THF-d_8, 1.5H, C**H**$_3$CHN of Y), 1.43 (d, 1.5H, J = 6.3 Hz, C**H**$_3$C=COLi of X), 1.28 (d, 1.5H, J = 6.4 Hz, C**H**$_3$C=COLi of Y), 0.93 {residual HN[CH(C**H**$_3$)$_2$]$_2$}, 0.60 (d, 1.5H, J = 7.2 Hz, C**H**$_3$CHN of X).

Chapter 2

Hydrolysis of Pseudoephedrine Amides to Form Highly Enantiomerically Enriched Carboxylic Acids

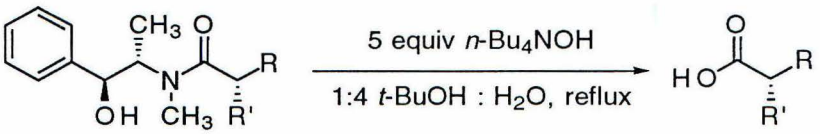
Introduction

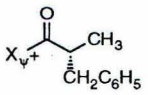
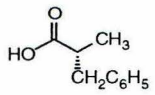
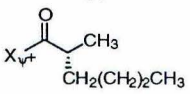
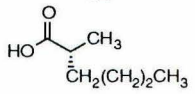
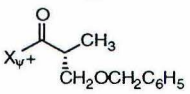
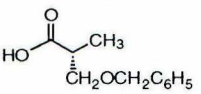
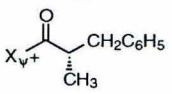
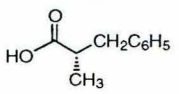
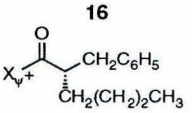
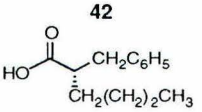
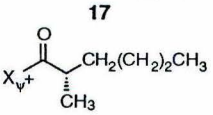
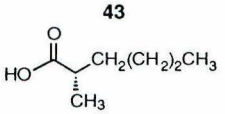
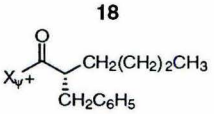
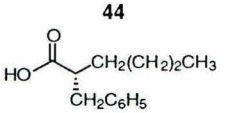
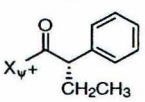
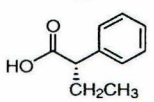
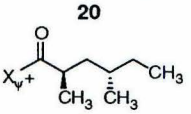
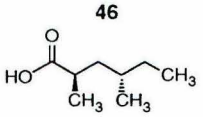
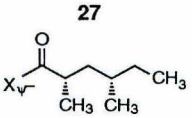
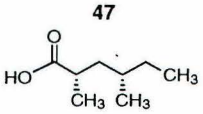
The diastereoselective alkylation of pseudoephedrine amide enolates does not in and of itself constitute a valuable addition to synthetic methodology unless the alkylation products can be transformed into useful materials. For this reason, much effort has focused on the development of methods to transform the alkylated amides of Tables 3 and 4 into useful products. Conditions were developed to transform these alkylated pseudoephedrine amides directly into chiral carboxylic acids, alcohols, aldehydes, and ketones[44] of high enantiomeric excess (ee).[45] Of these, the most challenging transformation was the simple hydrolysis reaction, for which basic and acidic conditions have been developed. The choice of a hydrolysis method will be dictated by the substrate and then by consideration of cost and convenience, as outlined below.

Basic Hydrolysis of Alkylated Pseudoephedrine Amides to Form Carboxylic Acids

Conditions for the base-promoted hydrolysis of pseudoephedrine amides[11b,c] were developed in conjunction with a protocol for the acid-promoted hydrolysis of pseudoephedrine amides (vide infra).[44] The procedure was optimized for the highly epimerizable phenylacetamide substrate **20**,[44] and the use of 5 equiv of tetra-*n*-butylammonium hydroxide in a mixture of water and *tert*-butyl alcohol (4:1, respectively) at reflux proved to be optimal with respect to reaction time, yield, and product ee. When these conditions were employed for the basic hydrolysis of other alkylated pseudoephedrine amides, results were generally far superior to those observed with the epimerizable substrate **20** (Table 6). 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-

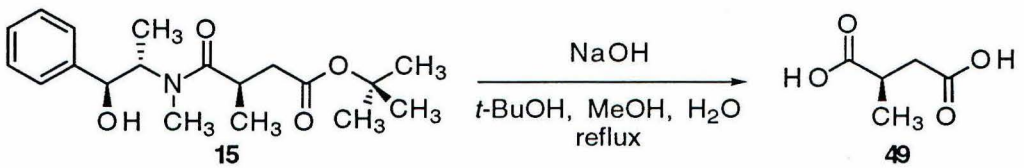
Table 6. Basic Hydrolysis of Pseudoephedrine Amides



entry	substrate[a]	product	isol yield (%)	isol ee or de (%)
1	 **11**	 **39**	93	94
2	 **12**	 **40**	93	97
3	 **13**	 **41**	92	69
4	 **16**	 **42**	91	94
5	 **17**	 **43**	89	82
6	 **18**	 **44**	88	93
7	 **19**	 **45**	90	84
8	 **20**	 **46**	82	64
9	 **27**	 **47**	86	95
10	 **28**	 **48**	84	95

[a] Substrates **11**, **12**, **19**, and **20** were of ≥99% de. Substrates **13**, **17**, and **28** were of 98% de, substrates **16** and **27** were of 97% de, and substrate **18** was of 96% de.

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 is an excellent alternative method and was employed, for example, for the hydrolysis of the 2-methyl succinic acid derivative **15** (74% yield, 94% ee), where the poor ether solubility of the product, 2-methyl succinic acid, precluded the use of tetra-*n*-



15 **49**

74% yield, 94% ee

butylammonium hydroxide as base. For other substrates, this alternative hydrolysis procedure affords products of slightly lower ee as compared to the method employing tetra-*n*-butylammonium hydroxide as base. For example, hydrolysis of substrate **11** with sodium hydroxide in a 2:1:1 mixture of water, methanol and *tert*-butyl alcohol affords the corresponding acid **39** in 98% yield and 92% ee[44] whereas hydrolysis of **11** with tetra-*n*-butylammonium hydroxide affords acid **39** in 93% yield and 94% ee (entry 1, Table 6).

Although the base-promoted hydrolysis of pseudoephedrine amides typically affords products in lower ee than does the acid-promoted hydrolysis, these procedures offer viable alternatives for the hydrolysis of acid-sensitive substrates. Though a substantial degradation in ee occurs for certain substrates (e.g., substrates **13**, **17**, **19**, and **20**, Table 6), in at least one case (entry 10, Table 6), basic hydrolysis proceeds with less epimerization than the acidic hydrolysis method (95% de versus 93% de, respectively).

The mechanism of both of the base-promoted hydrolysis reactions is believed to involve initial rate-limiting intramolecular $N \rightarrow O$ acyl transfer followed by rapid saponification of the resulting β-amino ester intermediate. 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.

Acidic Hydrolysis of Alkylated Pseudoephedrine Amides to Form Carboxylic Acids

For alkylation products that are not acid-sensitive, hydrolysis[11b,c] to the corresponding carboxylic acid can generally be effected in excellent chemical yield.[8,44] When the pseudoephedrine amide substrate is heated at reflux in a 1:1 mixture of sulfuric acid (9–18 N) and dioxane, the substrate initially undergoes a rapid intramolecular $N \rightarrow O$ acyl transfer reaction followed by rate-limiting hydrolysis of the resulting ammonium ester intermediate to the carboxylic acid (Figure 6). Although this protocol typically affords

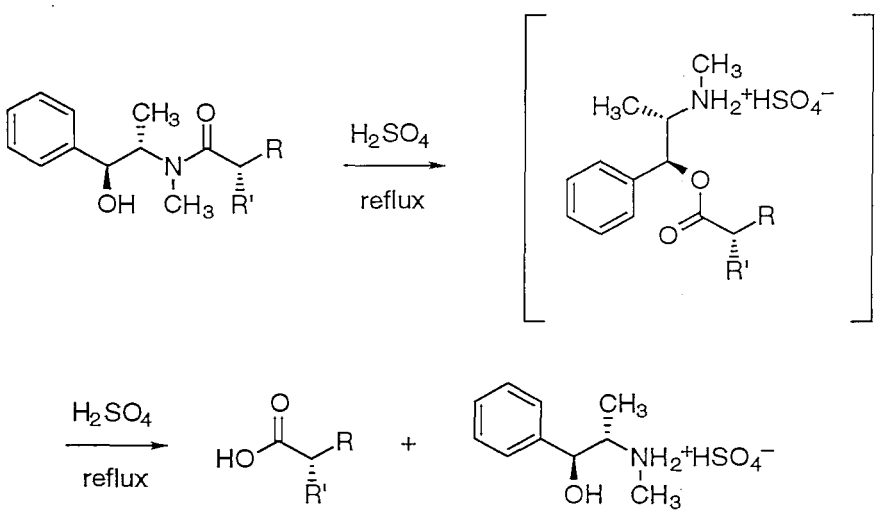
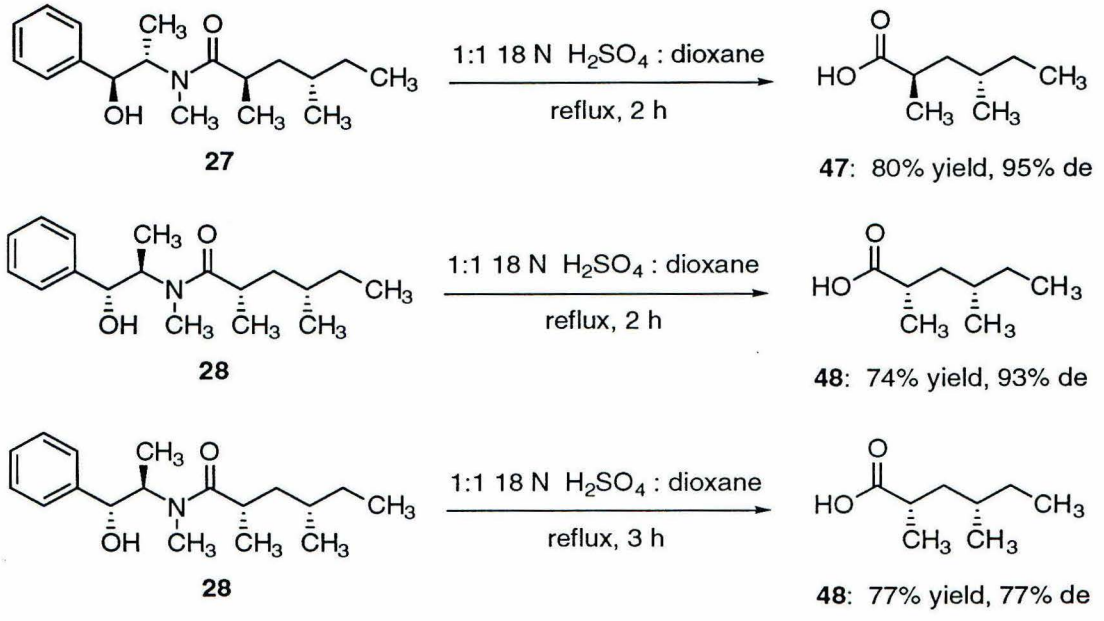


Figure 6. Sulfuric acid-promoted hydrolysis of pseudoephedrine amides.

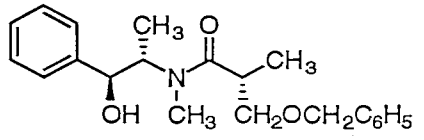
carboxylic acids with virtually complete preservation of stereochemical integrity, in one case (acid **48**), prolonged exposure to the reaction conditions has been found lower the de of the product acid (Scheme VIII).

Scheme VIII



Hydrolysis of Pseudoephedrine Amides Involving In Situ Borane-Amine Complexation

One of the problematic substrates for both the basic and acidic hydrolyses was the α-benzyloxymethyl-substituted substrate **13**. Basic hydrolysis (tetra-*n*-butylammonium hydroxide, water-*tert*-butyl alcohol, reflux) of amide **13** resulted in a 92% yield of the corresponding acid, but the ee was only 64%. Acidic hydrolysis (18 N sulfuric acid, dioxane, reflux) resulted in the complete decomposition of amide **13**.[8a]

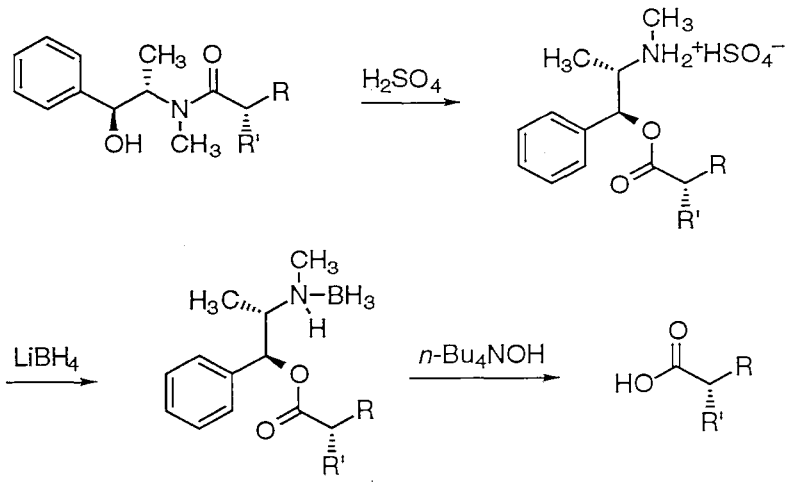


13

It was known for the acidic hydrolysis of alkylated pseudoephedrine amides that the reaction proceeds via rapid $N \rightarrow O$ acyl transfer (forming a hydrosulfate ester) followed by rate-limiting hydrolysis (Figure 6, above). Although amide **13** decomposes in a 1:1 mixture of 18 N sulfuric acid and dioxane at reflux, it undergoes clean $N \rightarrow O$ acyl transfer at 23 °C in 2–5 hours under otherwise identical reaction conditions to furnish the corresponding hydrosulfate salt in approximately 95% de. Though water-soluble, this hydrosulfate salt can be salted out of the aqueous phase with sodium chloride and extracted with ethyl acetate. Attempts to hydrolyze the hydrosulfate salt under basic conditions (sodium hydroxide or tetra-*n*-butylammonium hydroxide, 23 °C) resulted primarily instead in reversion to amide **13**. Attempts to protect the nitrogen as the corresponding trifluoroacetamide, acetamide, or priopionamide (to prevent $O \rightarrow N$ acyl transfer), followed by alkaline hydrolysis of the ester functionality, gave only fair yields of the desired acid. Competitive hydrolysis of the amide functionality, followed by reversion to amide **13** also occurred. Though ester functionalities are typically more susceptible to hydrolysis than amide functionalities, the rate of hydrolysis of the ester functionality was probably retarded due to increased steric hindrance. We therefore required a nitrogen protecting group that would be stable to alkaline conditions. While *N-tert*-butyloxycarbonyl (*N*-BOC) carbamates are stable to basic conditions, the BOC group was deemed undesirable because it costs more per mole than does pseudoephedrine itself.

The key to achieving hydrolysis involved the formation of a stable amine-borane complex in situ by the addition of lithium borohydride to the $N \rightarrow O$ acyl transfer intermediate (Scheme IX). The sequence of $N \rightarrow O$ acyl transfer, amine-borane complex formation, and saponification was thus accomplished as follows. A solution of the

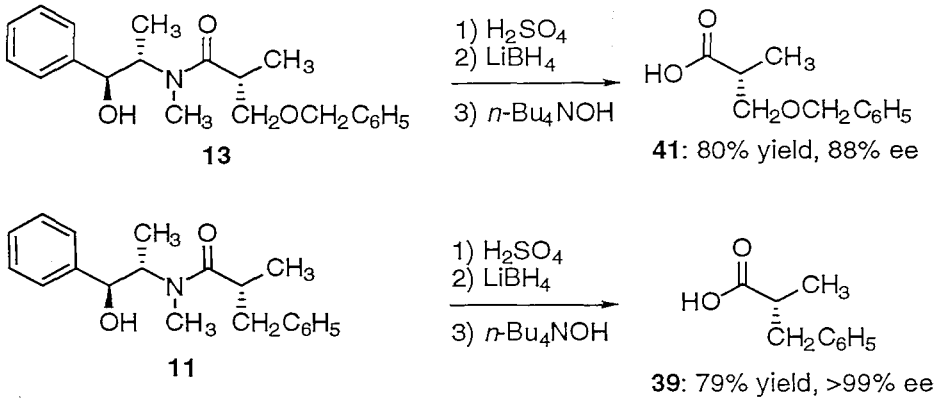
Scheme IX



pseudoephedrine amide substrate in THF was stirred in a 1:1 mixture of 18 N H_2SO_4 and dioxane for 2–5 h at 23 °C to furnish the *N* → *O* acyl transfer hydrosulfate salt. After an extractive work-up, deprotonation of the hydrosulfate salt with lithium borohydride (2.0 M in THF, 1.2 equiv) in THF at 23 °C afforded an amine-borane complex which did not undergo reduction. After another extractive work-up, subjection of the amine-borane complex to aqueous tetra-*n*-butylammonium hydroxide (5 equiv) at 23 °C effected ester hydrolysis to liberate the desired carboxylate product.

Application of this methodology to the hydrolysis of the α-benzyloxymethyl-substituted-amide **13** afforded acid **41** in 80% yield and 88% ee, and hydrolysis of the benzylated pseudoephedrine propionamide (**11**) afforded acid **39** in 79% yield and >99% ee (Scheme X).[44] Although labor-intensive, this method afforded acid **39** in higher ee (99%) than the one-step hydrolysis protocols discussed above. For instance, the use of H_2SO_4 in dioxane afforded acid **39** in 97% ee, *n*-Bu_4NOH in water and *tert*-butyl alcohol afforded **39** in 94% ee, and NaOH in water–*tert*-butyl alcohol–methanol afforded **39** in 92% ee. This general procedure (*N* → *O* acyl transfer, amine-borane complex formation,

Scheme X



and saponification) has been subsequently modified so that it can be carried out as a one-pot procedure.[8b,44]

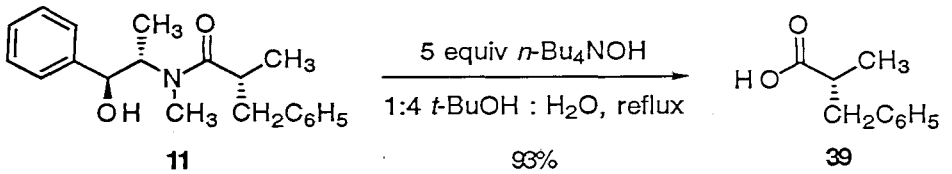
Experimental Section

General Procedures. All non-aqueous reactions were performed in flame-dried round-bottomed or modified Schlenk (Kjeldahl shape) 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 unless otherwise noted. Organic solutions were concentrated by rotary evaporation at ~25 Torr. 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 was distilled under nitrogen from sodium benzophenone ketyl. Dichloromethane and triethylamine were distilled under nitrogen from calcium hydride.

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) or to tetramethylsilane. 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 California Institute of Technology or at the University of California at Irvine. Combustion analyses were performed by Quantitative Technologies Incorporated.

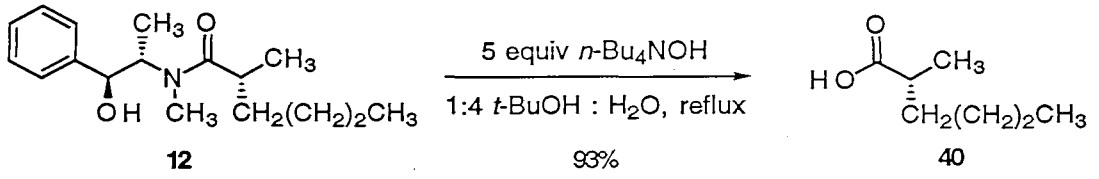
Chiral capillary gas chromatography (GC) analysis was carried out using an Alltech Chirasil-Val chiral fused silica capillary column, under isothermal conditions, with a column head pressure of 17 psi.



(*R*)-α-Methyl Benzenepropionic Acid **39**

A 100-mL round-bottomed flask equipped with a reflux condenser was charged with amide **11** (500 mg, 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 was 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 **39** as a clear liquid (245 mg, 93%). Coupling of acid **39** (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[46] which was analyzed by chiral capillary GC to establish an ee of 94% for acid **39**. The purity of acid **39** was estimated to be ≥95% by ^{1}H and ^{13}C NMR spectroscopic data.

^{1}H NMR (300 MHz, $CDCl_3$) δ:	7.25 (m, 5H, aromatic), 3.09 (dd, 1H, J_1 = 13.1 Hz, J_2 = 6.1 Hz, one of PhC**H**$_2$), 2.75 (m, 2H, one of PhC**H**$_2$, CH_3C**H**), 1.18 (d, 3H, J = 6.8 Hz, C**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.
TLC (7.5% MeOH–CH_2Cl_2), R_f:	**39**: 0.29–0.51 streak (UV, PMA). **11**: 0.65 (UV, PMA).

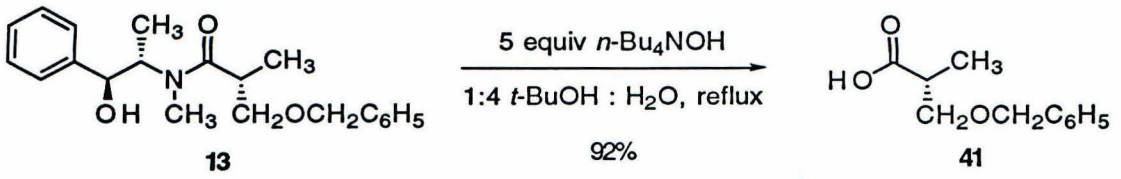


12 93% **40**

(*R*)-2-Methyl Hexanoic Acid **40**

A 10-mL round-bottomed flask equipped with a reflux condenser was charged with amide **12** (80.0 mg, 0.288 mmol, 1 equiv), aqueous tetra-*n*-butylammonium hydroxide solution (40% w/w, 0.930 g, 1.44 mmol, 5.00 equiv), *tert*-butyl alcohol (1 mL), and water (3.1 mL) and the biphasic mixture was heated at reflux for 22 h. The mixture was cooled to 23 °C, then was partitioned between 1 N aqueous sodium hydroxide solution (100 mL) and ether (10 mL). The aqueous layer was separated and extracted with two 10-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 was extracted with three 15-mL portions of ether. The combined ether extracts were washed with water (5 mL), then were dried over sodium sulfate and were concentrated to afford acid **40** as a clear liquid (35 mg, 93%). Chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide,[46] prepared as described above for acid **39**, established that acid **40** was of 97% ee. The purity of acid **40** was estimated to be ≥95% by ^{1}H and ^{13}C NMR spectroscopic data.

^{1}H NMR (300 MHz, $CDCl_3$) δ:	2.44 (sx, 1H, J = 6.9 Hz, COC**H**), 1.70 (m, 1H, one of COCHC**H**$_2$), 1.45 (m, 1H, one of COCHC**H**$_2$), 1.35 (m, 4H, CH_3**CH**$_2$**CH**$_2$), 1.17 (d, 3H, J = 7.0 Hz, **CH**$_3$CHCOOH), 0.90 (m, 3H, **CH**$_3$).
^{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).
TLC (80% EtOAc–hexanes), R_f:	**40**: 0.61 (UV, PMA).

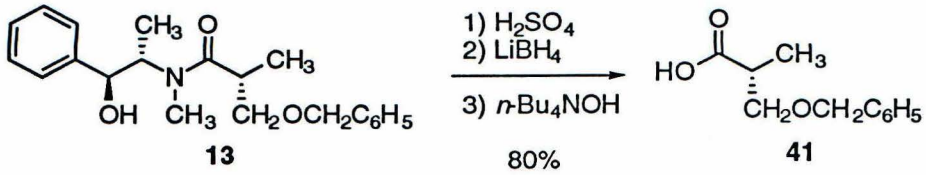


13 41

(*R*)-3-Benzyloxy-2-methylpropionic Acid **41**

A 25-mL round-bottomed flask equipped with a reflux condenser was charged with amide **13** (0.262 g, 0.767 mmol, 1 equiv), aqueous tetra-*n*-butylammonium hydroxide solution (40% w/w, 2.49 g, 3.83 mmol, 5.00 equiv), *tert*-butyl alcohol (2.7 mL), and water (8 mL) and the biphasic mixture was heated at reflux for 26 h. The mixture was cooled to 23 °C, then was partitioned between 1.5 N aqueous sodium hydroxide solution (100 mL) and ether (20 mL). The aqueous layer was separated and extracted with two 20-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 was 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 **41** as a clear liquid (138 mg, 92%). Chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide,[46] prepared as described above for acid **39**, established that acid **41** was of 69% ee. The purity of acid **41** was estimated to be ≥95% by ^{1}H and ^{13}C NMR spectroscopic data.

^{1}H NMR (300 MHz, $CDCl_3$) δ:	8.8–9.2 (br, 1H, **H**OOC), 7.25–7.37 (m, 5H, aromatic), 4.55 (s, 2H, Ph**C**H_2), 3.66 (dd, 1H, J_1 = 9.1 Hz, J_2 = 7.4 Hz, one of CH_3CHC**H**$_2$), 3.54 (dd, 1H, J_1 = 9.1 Hz, J_2 = 5.6 Hz, one of CH_3CHC**H**$_2$), 2.77–2.84 (m, 1H, CH_3C**H**), 1.22 (d, 3H, J = 7.1 Hz, **C**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.
TLC (7.5% MeOH–CH_2Cl_2), R_f:	**41**: 0.07–0.33 streak (UV, PMA).
	13: 0.38 (UV, PMA).
	benzyl alcohol: 0.64 (UV, PMA).



13 **41**

(*R*)-3-Benzyloxy-2-methylpropionic Acid **41**

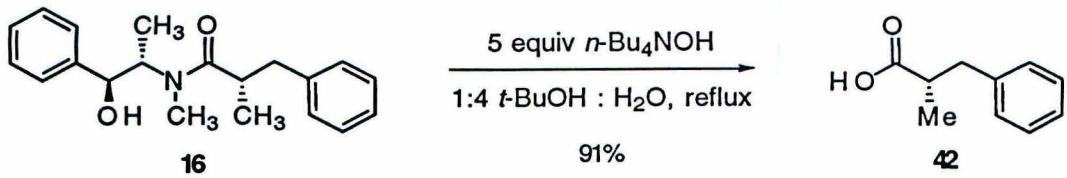
An ice-cooled solution of 18 N sulfuric acid (2.5 mL) was added to a solution of amide **13** (600 mg, 1.76 mmol, 1 equiv) in dioxane (2.5 mL) at 10 °C. The biphasic mixture was warmed to 23 °C and was held at that temperature for 3 h. The mixture was partitioned between brine (35 mL) and ethyl acetate (35 mL). The aqueous layer was separated and saturated with sodium chloride, then was extracted with ethyl acetate (3 × 35 mL). The combined organic fractions were dried over sodium sulfate and were concentrated to yield a fine white powder (610 mg). A portion (10.3% of recovered material, 64 mg) of the powder was dissolved in tetrahydrofuran (1 mL) and was cooled to 0 °C. A solution of lithium borohydride in tetrahydrofuran (2.0 M, 0.109 mL, 0.218 mmol, 1.20 equiv) was added slowly via syringe, resulting in vigorous gas evolution. The mixture was stirred at 0 °C for 5 minutes, after which time bubbling had ceased, then excess hydride was quenched by the slow addition of 0.1 N aqueous hydrochloric acid solution (1 mL). The mixture was partitioned between 0.1 N aqueous hydrochloric acid solution (80 mL) and ethyl acetate (20 mL), and the aqueous layer was separated. The aqueous layer was extracted with ethyl acetate (2 × 20 mL), and the combined organic fractions were washed with brine (5 mL), then were dried over sodium sulfate and were concentrated. The residue was dissolved in *tert*-butyl alcohol (0.7 mL) and water (1 mL), and the biphasic mixture was cooled to 0 °C. An aqueous solution of tetra-*n*-butylammonium hydroxide (0.500 M, 1.80 mL, 0.905 mmol, 5.00 equiv) was added and the reaction mixture was warmed to 23 °C and held at that temperature for 10 h. The reaction mixture was partitioned between 1 N aqueous sodium hydroxide solution (100

mL) and ether (12 mL). The aqueous layer was separated and extracted with ether (2 × 12 mL). The aqueous layer was acidified to pH ≤ 2 by the careful addition of 3 N aqueous hydrochloric acid solution, then was saturated with sodium chloride and was extracted with ether (3 × 30 mL). The combined organic fractions were washed with brine (5 mL), then were dried over sodium sulfate and were concentrated to give the desired acid (28 mg, 80% from **1**). Chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide,[46] prepared as described above for acid **39**, established that acid **41** was of 88% ee. Spectroscopic data were identical to those listed above. The purity of acid **41** was estimated to be ≥95% by ^{1}H and ^{13}C NMR spectroscopic data.

TLC (7.5% MeOH–CH_2Cl_2), R_f: **53**: 0.07–0.33 streak (UV, PMA).

$N \rightarrow O$ acyl transfer: 0.13–0.26 streak (UV, PMA).

14: 0.38 (UV, PMA).

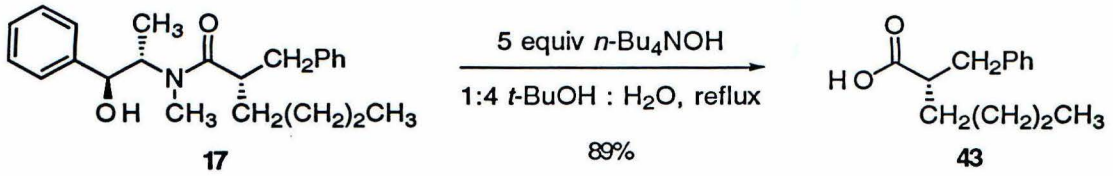


(*S*)-α-Methyl Benzenepropionic Acid **42**

A 10-mL round-bottomed flask equipped with a reflux condenser was charged with amide **16** (77.0 mg, 0.248 mmol, 1 equiv), aqueous tetra-*n*-butylammonium hydroxide solution (40% w/w, 0.803 g, 1.24 mmol, 5.00 equiv), *tert*-butyl alcohol (1 mL), and water (3.2 mL) and the biphasic mixture was heated at reflux for 22 h. The mixture was cooled to 23 °C, then was partitioned between 1 N aqueous sodium hydroxide solution (100 mL) and ether (10 mL). The aqueous layer was separated and extracted with two 10-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 was extracted with four 15-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 **42** as a clear liquid (37 mg, 93%). Chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide,[46] prepared as described above for acid **39**, established that acid **42** was of 94% ee. The purity of acid **42** was estimated to be ≥95% by ^{1}H and ^{13}C NMR spectroscopic data. Spectroscopic data were identical to those of its enantiomer, (*R*)-α-methyl benzenepropionic acid (**39**).

TLC (7.5% MeOH–CH_2Cl_2), R_f: **42**: 0.24–0.60 streak (UV, PMA).

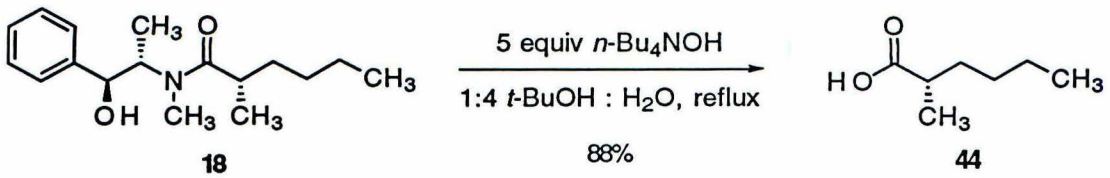
16: 0.67 (UV, PMA).



(*S*)-α-Butyl Benzenepropionic Acid **43**

A 25-mL round-bottomed flask equipped with a reflux condenser was charged with amide **17** (275 mg, 0.778 mmol, 1 equiv), aqueous tetra-*n*-butylammonium hydroxide solution (40% w/w, 2.52 g, 3.89 mmol, 5.00 equiv), *tert*-butyl alcohol (2.7 mL), and water (8 mL) and the biphasic mixture was heated at reflux for 24 h. The mixture was cooled to 23 °C, then was partitioned between 1 N aqueous sodium hydroxide solution (100 mL) and ether (20 mL). The aqueous layer was separated and extracted with two 20-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 was 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 **43** as a clear liquid (143 mg, 89%). Chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide,[46] prepared as described above for acid **39**, established that acid **43** was of 82% ee. The purity of acid **43** was estimated to be ≥95% by ^{1}H and ^{13}C NMR spectroscopic data.

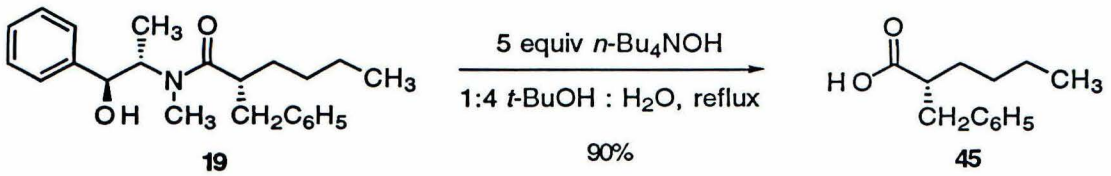
^{1}H NMR (300 MHz, $CDCl_3$) δ:	7.30 (m, 5H, aromatic), 2.98 (dd, 1H, J_1 = 7.8 Hz, J_2 = 13.5 Hz, one of $PhCH_2$), 2.70 (m, 2H, one of $PhCH_2$, HOOCCH), 1.65 (m, 1H, one of $HOOCCHCH_2$), 1.55 (m, 1H, one of $HOOCCHCH_2$), 1.30 (m, 4H, $CH_3CH_2CH_2$), 0.85 (m, 3H, CH_3).
^{13}C NMR (75 MHz, $CDCl_3$) 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.
TLC (7.5% MeOH–CH_2Cl_2), R_f:	**43**: 0.30–0.57 streak (UV, PMA). **17**: 0.61 (UV, PMA).



(*S*)-2-Methylhexanoic Acid **44**

A 10-mL round-bottomed flask equipped with a reflux condenser was charged with amide **18** (80.0 mg, 0.288 mmol, 1 equiv), aqueous tetra-*n*-butylammonium hydroxide solution (40% w/w, 0.930 g, 1.44 mmol, 5.00 equiv), *tert*-butyl alcohol (1 mL), and water (3.1 mL) and the biphasic mixture was heated at reflux for 23 h. The mixture was cooled to 23 °C, then was partitioned between 1 N aqueous sodium hydroxide solution (100 mL) and ether (10 mL). The aqueous layer was separated and extracted with two 10-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 was extracted with three 15-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 **44** as a clear liquid (33.0 mg, 88%). Chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide,[46] prepared as described above for acid **39**, established that acid **44** was of 93% ee. The purity of acid **44** was estimated to be ≥95% by ^{1}H and ^{13}C NMR spectroscopic data. Spectroscopic data were identical to those of its enantiomer, (*R*)-2-methylhexanoic acid (**40**).

TLC (80% EtOAc–hexanes), R_f: **18**: 0.56 (UV, PMA).

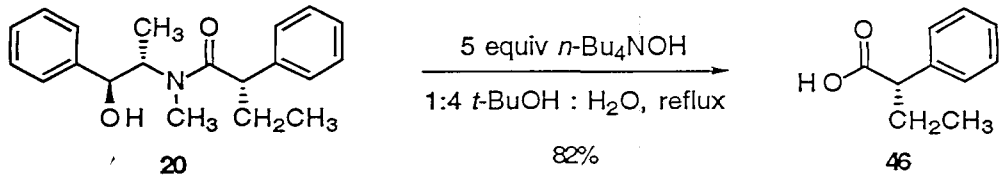


(*R*)-α-Butyl Benzenepropionic Acid **45**

A 50-mL round-bottomed flask equipped with a reflux condenser was charged with amide **19** (580 mg, 1.64 mmol, 1 equiv), aqueous tetra-*n*-butylammonium hydroxide solution (40% w/w, 5.70 g, 8.79 mmol, 5.36 equiv), *tert*-butyl alcohol (5 mL), and water (14 mL) and the biphasic mixture was heated at reflux for 21 h. The mixture was cooled to 23 °C, then was partitioned between 1 N aqueous sodium hydroxide solution (120 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 6 N aqueous hydrochloric acid solution. The acidified solution was saturated with sodium chloride and was 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 **45** as a clear liquid (305 mg, 90%). Chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide,[46] prepared as described above for acid **39**, established that acid **45** was of 84% ee. The purity of acid **45** was estimated to be ≥95% by ^{1}H and ^{13}C NMR spectroscopic data. Spectroscopic data were identical to those of its enantiomer, (*S*)-α-butyl benzenepropionic acid (**43**).

TLC (7.5% MeOH–CH_2Cl_2), R_f: **45**: 0.58 (UV, PMA).

19: 0.75 (UV, PMA).

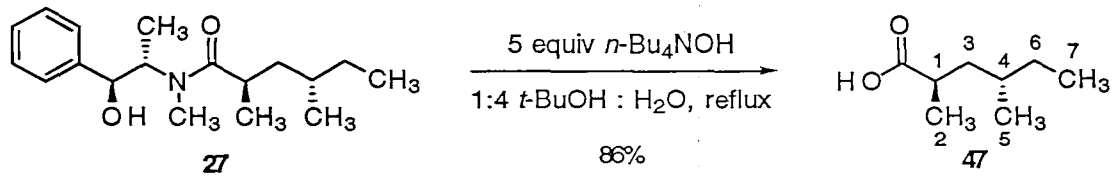


20 46

(*S*)-α-Ethyl Benzeneacetic Acid **46**

A 10-mL round-bottomed flask equipped with a reflux condenser was charged with amide **20** (86.0 mg, 0.276 mmol, 1 equiv), aqueous tetra-*n*-butylammonium hydroxide solution (40% w/w, 0.810 g, 1.25 mmol, 4.50 equiv), *tert*-butyl alcohol (1 mL), and water (3.2 mL) and the biphasic mixture was heated at reflux for 20 h. The mixture was cooled to 23 °C, then was partitioned between 1 N aqueous sodium hydroxide solution (100 mL) and ether (10 mL). The aqueous layer was separated and extracted with two 10-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 was extracted with three 15-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 **46** as a clear liquid (37.4 mg, 82%). Chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide,[46] prepared as described above for acid **39**, established that acid **46** was of 64% ee. The purity of acid **46** was estimated to be ≥95% by ^{1}H and ^{13}C NMR spectroscopic data.

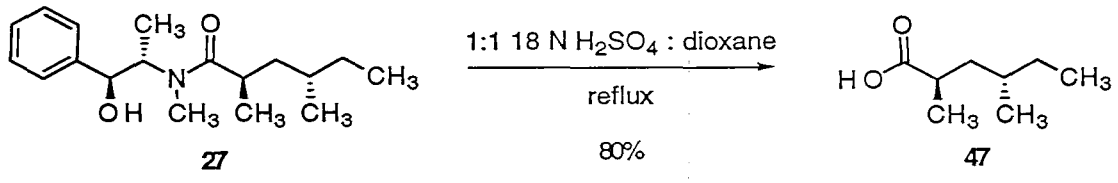
^{1}H NMR (300 MHz, $CDCl_3$) δ:	7.25 (m, 5H, aromatic), 3.41 (t, 1H, J = 7.7 Hz, PhC**H**), 2.05 (m, 1H, one of CH_3CH_2), 1.76 (m, 1H, one of CH_3CH_2), 0.86 (t, 3H, J = 7.4 Hz, CH_3).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	180.5, 138.3, 128.6, 128.1, 127.4, 53.3, 26.3, 12.1.
FTIR (neat, cm^{-1}):	2967 (br, s, OH), 1712 (s, C=O).
HRMS (EI):	Calcd for $C_{10}H_{12}O_2$ $(M)^+$: 164.0837. Found: 164.0839.
TLC (7.5% MeOH–CH_2Cl_2), R_f:	**46**: 0.24–0.45 streak (UV, PMA). **20**: 0.75 (UV, PMA).



(2*R*,4*S*)-2,4-Dimethylhexanoic Acid **47**

A 25-mL round-bottomed flask equipped with a reflux condenser was charged with amide **27** (197 mg, 0.674 mmol, 1 equiv), aqueous tetra-*n*-butylammonium hydroxide solution (0.560 M, 6.00 mL, 3.37 mmol, 5.0 equiv), and *tert*-butyl alcohol (1.5 mL) and the biphasic mixture was heated at reflux for 24 h. The mixture was cooled to 23 °C, then was partitioned between 1 N aqueous sodium hydroxide solution (40 mL) and ether (5 mL). The aqueous layer was separated and extracted with three 5-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 was extracted with three 20-mL portions of ether. The combined ether extracts were washed with half-saturated brine (5 mL), then were dried over magnesium sulfate and were concentrated to afford acid **47** as a clear liquid (83.6 mg, 86%). The de of acid **47** was determined to be 95% by comparison of the ^{1}H NMR spectrum with that of acid **48**. The purity of acid **47** was estimated to be ≥95% by ^{1}H and ^{13}C NMR spectroscopic data.

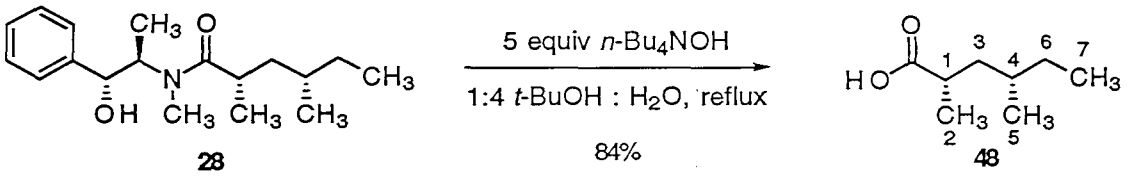
^{1}H NMR (300 MHz, $CDCl_3$) δ:	2.55 (m, 1H, H1), 1.55 (m, 1H, H4), 1.39 (m, 3H, H3, one of H6), 1.17 (m, 1H, one of H6), 1.16 (d, 3H, J = 6.9 Hz, H2), 0.87 (m, 6H, H7, H5).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	184.1, 40.5, 37.3, 32.1, 29.5, 18.8, 16.9, 11.2.
FTIR (neat, cm^{-1}):	2800–3400 (br, m, OH), 1712 (s, C=O).
HRMS (CI):	Calcd for $C_8H_{15}O_2Na_2$ $(MNa_2–H)^+$: 189.0867. Found: 189.0869.
TLC (10% MeOH–CH_2Cl_2), R_f:	**47**: 0.44 (PMA).
	27: 0.57 (UV, PMA).



27 47

(2*R*,4*S*)-2,4-Dimethylhexanoic Acid **47**

A 10-mL round-bottomed flask equipped with a reflux condenser was charged with amide **27** (114 mg, 0.391 mmol, 1 equiv), dioxane (0.7 mL), and 18 N aqueous sulfuric acid (0.7 mL). The biphasic mixture was heated at reflux for 2.8 h, then was cooled to 23 °C. The pH of the mixture was adjusted to pH ≥ 10 by the slow addition of 2 N aqueous sodium hydroxide solution (40 mL) and the resulting mixture was extracted with ether (3 × 7 mL). The aqueous phase was acidified to pH ≤ 2 by the cautious addition of 3 N aqueous hydrochloric acid solution (40 mL). The acidified solution was saturated with sodium chloride and was extracted with ethyl acetate (3 × 30 mL). The combined ethyl acetate extracts were washed sequentially with 3 N aqueous hydrochloric acid solution (5 mL) and brine (5 mL), then were dried over sodium sulfate and were concentrated to afford acid **47** as a clear liquid (45.0 mg, 80%). The de was determined to be 95% by comparison of the ^{1}H NMR spectrum with that of acid **48**. The purity of acid **47** was estimated to be ≥95% by ^{1}H and ^{13}C NMR spectroscopic data. Spectroscopic and TLC data were identical to those listed above.

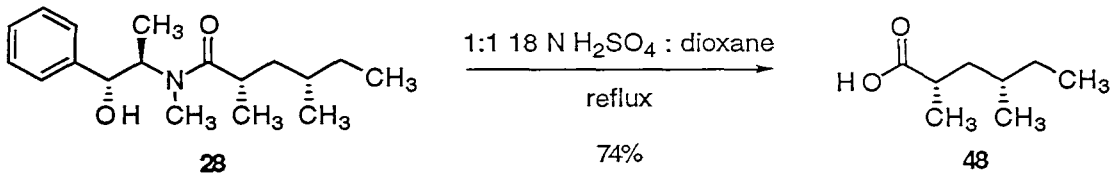


28 48

(2*S*,4*S*)-2,4-Dimethylhexanoic Acid **48**

A 25-mL round-bottomed flask equipped with a reflux condenser was charged with amide **28** (186 mg, 0.639 mmol, 1 equiv), aqueous tetra-*n*-butylammonium hydroxide solution (0.530 M, 6.00 mL, 3.2 mmol, 5.0 equiv), and *tert*-butyl alcohol (1.5 mL) and the biphasic mixture was heated at reflux for 24 h. The mixture was cooled to 23 °C, then was partitioned between 1 N aqueous sodium hydroxide solution (40 mL) and ether (5 mL). The aqueous layer was separated and extracted with three 5-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 was extracted with three 20-mL portions of ether. The combined ether extracts were washed with half-saturated brine (5 mL), then were dried over magnesium sulfate and were concentrated to afford acid **48** as a clear liquid (77.9 mg, 84%). The de of acid **48** was determined to be 95% by comparison of the ^{1}H NMR spectrum with that of acid **47**. The purity of acid **48** was estimated to be ≥95% by ^{1}H and ^{13}C NMR spectroscopic data.

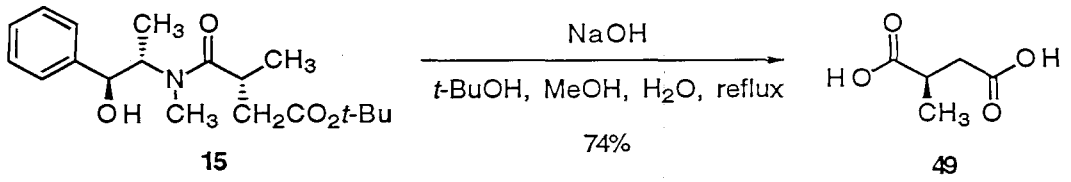
^{1}H NMR (300 MHz, $CDCl_3$) δ:	2.50–2.62 (m, 1H, H1), 1.68–1.78 (m, 1H, H4), 1.29–1.45 (m, 2H, H3), 1.18 (d, 3H, J = 7.0 Hz, H2), 1.08–1.15 (m, 2H, H6), 0.89 (d, 3H, J = 6.5 Hz, H5), 0.86 (t, 3H, J = 7.3 Hz, H6).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	183.8, 40.9, 37,5, 32.3, 29.5, 19.0, 17.9, 11.1.
FTIR (neat, cm^{-1}):	3000–3400 (br, m, OH), 1708 (s, C=O).
HRMS (CI):	Calcd for $C_8H_{15}O_2Na_2$ $(MNa_2–H)^+$: 189.0867. Found: 189.0871.
TLC (10% MeOH–CH_2Cl_2), R_f:	**48**: 0.57 (PMA). **28**: 0.72 (UV, PMA).



28 48

(2*S*,4*S*)-2,4-Dimethylhexanoic Acid **48**

A 10-mL round-bottomed flask equipped with a reflux condenser was charged with amide **28** (109 mg, 0.375 mmol, 1 equiv), dioxane (0.6 mL), and 18 N aqueous sulfuric acid (0.6 mL). The biphasic mixture was heated at reflux for 2 h, then was cooled to 23 °C. The pH of the mixture was adjusted to pH ≥ 10 by the slow addition of 2 N aqueous sodium hydroxide solution (40 mL) and the resulting mixture was extracted with ether (3 × 7 mL). The aqueous phase was acidified to pH ≤ 2 by the cautious addition of 3 N aqueous hydrochloric acid solution (40 mL). The acidified solution was saturated with sodium chloride and was extracted with ethyl acetate (3 × 30 mL). The combined ethyl acetate extracts were washed sequentially with 3 N aqueous hydrochloric acid solution (5 mL) and brine (5 mL), then were dried over sodium sulfate and were concentrated to afford acid **48** as a clear liquid (39.8 mg, 74%). The de was determined to be 93% by comparison of the ^{1}H NMR spectrum with that of acid **47**. The purity of acid **48** was estimated to be ≥95% by ^{1}H and ^{13}C NMR spectroscopic data. Spectroscopic and TLC data were identical to those listed above.



15 49

(*R*)-α-Methyl Butanedioic Acid **49**

A 25-mL round-bottomed flask equipped with a reflux condenser was charged with amide **15** (563 mg, 1.76 mmol, 1 equiv), *tert*-butyl alcohol (3 mL), methanol (3 mL), and 1 N aqueous sodium hydroxide solution (12.0 mL, 12.0 mmol, 6.80 equiv). The mixture was heated at reflux for 24 h, then was cooled to 23 °C. The mixture was partitioned between 0.5 N aqueous sodium hydroxide solution (100 mL) and dichloromethane (10 mL). The aqueous layer was separated, then was extracted with dichloromethane (2 × 10 mL) and was acidified to pH ≤ 2 by the slow addition of 3 N aqueous hydrochloric acid solution (40 mL). The acidified aqueous layer was saturated with sodium chloride, then was extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were dried over sodium sulfate and were concentrated to afford diacid **49** as a white solid (173 mg, 74%). Diacid **49** was reduced with lithium aluminum hydride (3 equiv) in THF at 0 °C to the corresponding diol, and ^{1}H NMR analysis (400 MHz, $CDCl_3$) of the corresponding bis-Mosher esters[58] derived from both (*R*)- and (*S*)-Mosher's acid established that diacid **49** was of 94% ee: mp 104–106 °C.

^{1}H NMR (300 MHz, CD_3OD) δ:	5.03 (br, 1H, HOOC), 2.82 (m, 1H, CH_3CH), 2.65 (dd, 1H, J_1 = 16.7 Hz, J_2 = 8.3 Hz, one of $HOOCCH_2$), 2.38 (dd, 1H, J_1 = 16.7 Hz, J_2 = 5.8 Hz, one of $HOOCCH_2$), 1.20 (d, 3H, J = 7.2 Hz, CH_3CH).
^{13}C NMR (100 MHz, CD_3OD) δ:	179.2, 175.6, 38.5, 37.0, 17.4.
HRMS (EI):	Calcd for $C_5H_9O_4$ $(MH)^+$: 133.0501.
	Found: 133.0504.
Analysis:	Calcd for $C_5H_8O_4$: C, 45.46; H, 6.10; N, 0.
	Found: C, 45.86; H, 5.93; N, 0.14.
TLC (80% EtOAc–hexanes), R_f:	**49**: 0 (PMA).
	15: 0.56 (UV, PMA).

Chapter 3

Reduction of Pseudoephedrine Amides to Form Highly Enantiomerically Enriched Primary Alcohols

Introduction

In general, the addition of hydride to the carbonyl group of a tertiary amide affords a tetrahedral intermediate that partitions between CN bond cleavage (leading to the primary alcohol via the aldehyde) and CO bond cleavage (leading to the formation of a tertiary amine by-product via an imminium intermediate, Figure 7). This partitioning is highly

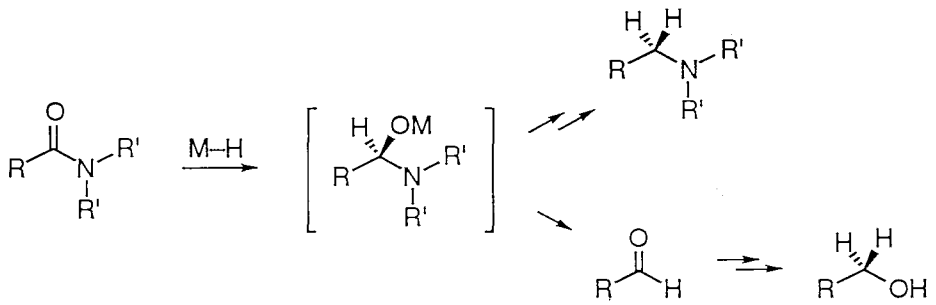
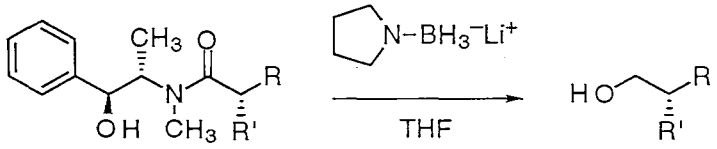


Figure 7. Divergent pathways for tertiary amide reductions.

sensitive to the reaction medium and the nature of the counterion "M." Typical metal hydride reagents such as lithium aluminum hydride[47] and diborane[48] favor the formation of the tertiary amine by-product. For this reason, it is often difficult to convert a tertiary amide into the corresponding primary alcohol, a useful synthetic transformation. Important exceptions to this trend include the reagents lithium triethylborohydride ($LiBHEt_3$, "superhydride")[49] and 9-BBN,[50] developed by Brown and co-workers, and metal amide-borane complexes, introduced by Hutchins et al.[51] and extensively developed by Singaram and co-workers.[52]

Table 7. Reduction with Borane-Lithium Pyrrolidide (LPT) to Form Primary Alcohols



entry	substrate[a]	R	R'	prod	temp (°C)	time (h)	isol yield (%)	isol ee (%)
1	**11**	CH_3	Bn	**50**	23	6.0	84	≥95
2	**12**	CH_3	*n*-Bu	**51**	23	10.0	81	≥95
3	**13**	CH_3	BOM	**52**	0	3.0	45	91
4	**16**	Bn	CH_3	**53**	23	10.3	87	≥95
5	**17**	Bn	*n*-Bu	**54**	23	3.1	88	≥95
6	**19**	*n*-Bu	Bn	**55**	23	5.8	89	≥95
7	**20**	Ph	Et	**56**	23	14.0	87	33[b]
8	**22**	*i*-Pr	Bn	**57**	66	11.0	80	≥95
9	**23**	*t*-Bu	Bn	**58**	66	12.0	5	–

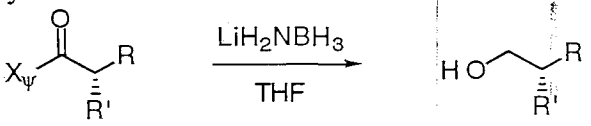
[a] The starting material was in all cases of ≥99% de except **13** and **17** were of 98% de, and **16** which was of 97% de. [b] The predominating enantiomer had inverted configuration relative to the starting material (**20**).

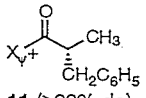
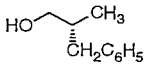
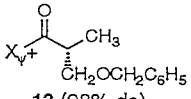
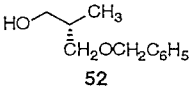
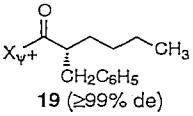
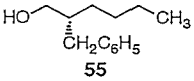
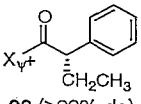
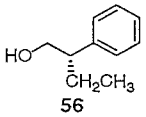
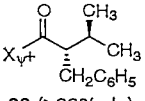
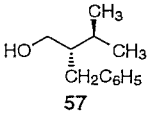
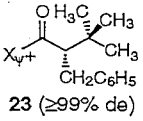
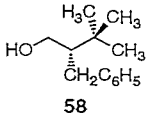
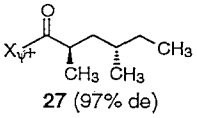
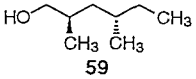
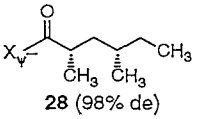
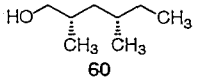
Reduction of Pseudoephedrine Amides with LAB to Form Primary Alcohols

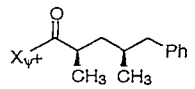
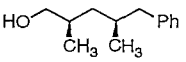
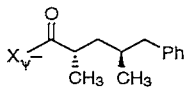
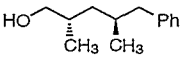
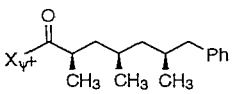
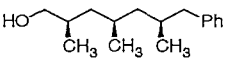
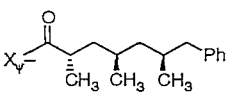
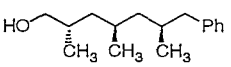
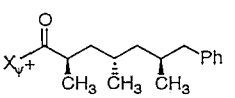
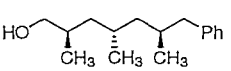
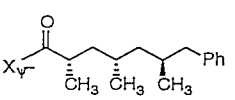
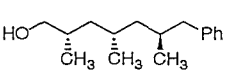
The transformation of pseudoephedrine amides into the corresponding primary alcohols may be considered as a special case within the broader problem of the selective reduction of tertiary amides. Pseudoephedrine amides were found to be inert toward superhydride and 9-BBN. As we reported earlier,[8] the lithium pyrrolidide-borane reagent (lithium pyrrolididotrihydroborate, $Li(CH_2)_4NBH_3$, LPT) of Singaram et al.[52] is effective in transforming certain pseudoephedrine amides into the corresponding primary alcohols selectively and in high yield (Table 7). Subsequently, however, we have encountered difficulties with this reagent in several problematic cases (e.g., entries 3, 7, and 9 within Table 7). For example, the α-benzyloxymethyl-substituted amide **13** suffered partial

decomposition during the reduction and the α-ethyl phenylacetamide substrate **20** provided the primary alcohol **56** in only 33% ee, with inverted configuration! In both cases, the problems encountered were attributed to base-induced epimerization (decomposition) of the intermediate aldehydes. The inverted configuration of the product **56** is believed to arise from enolization of the intermediate aldehyde by a chiral, pseudoephedrine-derived base, followed by enantioselective protonation and reduction. In addition to these examples, highly sterically hindered substrates such as **23** were found to be essentially inert to LPT. We have since reported the development of a new reagent, lithium amidotrihydroborate (LiH_2NBH_3, LAB), that lacks the problematic features of LPT.[53] In our initial report, LAB was prepared by the deprotonation of the commercial solid reagent, borane-ammonia complex,[54] using slightly less than 1 equiv of *n*-butyllithium as base at 0 °C. In more recent work, we have substantially improved the reagent preparation by the use of 1 equiv of lithium diisopropylamide (LDA) as the base in the reaction.[25] The efficiency of the reduction is greater using LDA as the base and, notably, the product is isolated with much greater facility. Difficulties encountered when *n*-butyllithium was used as base were traced to the formation of butylboron intermediates in the reaction (particularly in large-scale experiments) and, ultimately, butylboron alkoxide products that were difficult to hydrolyze. This problem could be largely circumvented by conducting the deprotonation with *n*-butyllithium at –78 °C or, preferably, could be completely avoided by deprotonation with LDA at 0 °C followed by warming to 23 °C. In the optimized procedure, solid ammonia-borane complex (4.0 equiv) is added to a solution of LDA (3.9 equiv) in THF at 0 °C, and the resulting suspension is warmed to 23 °C and is held at that temperature for 15–20 min. The cloudy suspension of LAB is then cooled to 0 °C and a solution of the pseudoephedrine amide substrate (1 equiv) in THF is added. Typical reductions proceed to completion within a few hours at 23 °C, although more hindered substrates (entry 6, Table 8) may require heating to reflux (66 °C). When the reduction is complete, an acidic

Table 8. Reduction of Pseudoephedrine Amides with Lithium Amidotrihydroborate (LAB) to Form Primary Alcohols



entry	substrate	product	temp (°C)	time (h)	isol yield (%)	isol ee (%)
1	 **11** (≥99% de)	 **50**	23	1.0	90	≥99
2	 **13** (98% de)	 **52**	0	1.3	86	95
3	 **19** (≥99% de)	 **55**	23	2.5	92	≥95
4	 **20** (≥99% de)	 **56**	23	1.9	83	92
5	 **22** (≥99% de)	 **57**	23	18	86	≥95
6	 **23** (≥99% de)	 **58**	66	10	92	≥95
7	 **27** (97% de)	 **59**	23	2	78[a]	97
8	 **28** (98% de)	 **60**	23	2	79[a]	98

9	 **29** (98% de)	 **61**	23	2	95	98
10	 **30** (97% de)	 **62**	23	2	96	96
11	 **31** (99% de)	 **63**	23	2	93	99
12	 **32** (97% de)	 **64**	23	2	93	97
13	 **33** (97% de)	 **65**	23	2	91	97
14	 **34** (99% de)	 **66**	23	2	89	99

[a] The yield was lowered due to the volatility of the product.

aqueous work-up procedure provides a mixture of the desired alcohol and a (different) alkoxy boron species. Fortunately, this alkoxy boron species is exceedingly labile toward silica gel and undergoes quantitative cleavage to the alcohol during flash column chromatographic purification. Where flash column chromatography is not an acceptable means of purification (e.g., on large scale, where distillation of the alcohol might be preferable), the alkoxy boron species can be cleaved rapidly and quantitatively by treatment with 1 N aqueous sodium hydroxide solution at 23 °C for 30–60 min.

This modified LAB reduction procedure has proven to be highly effective for the synthesis of a wide variety of highly enantiomerically enriched primary alcohols from the corresponding pseudoephedrine amide precursors. As evident from the examples of Table

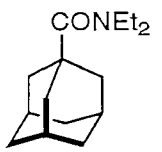
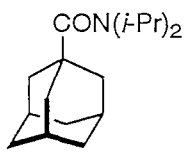
8, little to no epimerization of the α-stereocenter is observed. Generally, <4% of the tertiary amine by-product is produced if care is taken to use at least 4 molar equiv of LAB in the reaction. Tertiary amine formation can be more extensive if less reductant is employed.[53] The tertiary amine generally exhibits an R_f value comparable to that of the product alcohol, and is most conveniently removed by extraction with aqueous acid. When an acid wash is not desirable (for acid-sensitive substrates or for tertiary amine hydrochlorides that are not water soluble), the tertiary amine by-product can be readily separated by flash column chromatography using triethylamine-pretreated silica gel.

Reductions of pseudoephedrine amides with LAB are much more rapid than reductions with LPT. For example, LAB reduction of substrate **11** occurs in 1 h at 23 °C (90% yield) whereas LPT reduction of **11** requires 6 h at 23 °C (84% yield). In addition, LAB appears to have a lesser tendency to effect base-induced side reactions compared to LPT. As a result, highly epimerizable aldehyde intermediates can be traversed without substantial loss of stereochemical integrity. For example, reduction of the α-benzyloxymethyl-substituted amide **13** (98% de) with LAB formed the corresponding alcohol in 86% yield and 95% ee and reduction of the phenylacetamide **20** (≥99% de) with LAB provided (*S*)-2-phenyl-1-butanol in 83% yield and 92% ee. In addition, LAB is found to be far superior to LPT for the reduction of sterically hindered amides. Thus, the substrate **22** was found to be inert to LPT at 23 °C but was cleanly reduced with LAB at 23 °C (entry 5, Table 8, 86% yield of alcohol, ≥95% ee). More dramatically, the highly hindered substrate **23** proved to be virtually inert toward LPT, even in refluxing THF (Table 7, entry 9, 12 h, 5% yield), but was readily reduced with LAB (Table 8, entry 6, 10 h, 66 °C, 91% yield, ≥95% ee).

Reduction of Tertiary Amides with LAB to Form Primary Alcohols

Our success with LAB in the reduction of pseudoephedrine amides prompted us to

Table 9. Use of LAB for the Reduction of Tertiary Amides to Primary Alcohols

entry	substrate	temp (°C)	time (h)	isol yield alcohol (%)	isol yield 3° amine (%)
1	$CH_3(CH_2)_{10}CONEt_2$	23	1.3	94	<5
2		23	16.0	87	8
3	$CH_3(CH_2)_{10}CON(i\text{-}Pr)_2$	23	6.0	68	28
4		66	1.7	47	51

investigate whether LAB was a superior reagent for the reduction of tertiary amides in general (Table 9).[53] *N*,*N*-Diethyldodecanamide formed 1-dodecanol in 94% yield (1.3 h at 23 °C) with LAB (4.0 equiv), whereas LPT is reported to give the tertiary amine, *N*,*N*-diethyldodecanamine, in 71% yield.[52b] The reduction of *N*,*N*-diethyldodecanamide with lithium triethylborohydride is not reported, but reduction of *N*,*N*-diethylbutanamide, a substrate of similar steric and electronic character, is reported to proceed in only 50% yield at 25 °C (2.2 equiv of hydride).[49] Even the hindered 1-adamantanecarboxylic acid *N*,*N*-diethylamide (entry 2) is reduced to the primary alcohol (88%) with LAB. In exploring the limits of tertiary amide reductions with LAB, we find that substantial amounts of tertiary amine by-products are formed with *N*,*N*-diisopropylamides as substrates (entries 3 and 4, Table 9). This is in keeping with Hutchins' observations that substrates with *N*-substituents of increasing steric demand tend to favor formation of the tertiary amine with

sodium dimethylamidotrihydroborate as reductant.[51] The fact that the *N*,*N*-diisopropylamides of entries 3 and 4 are reduced at all with LAB is testimony to the high nucleophilicity of this reagent; lithium triethylborohydride, for example, does not react with *N*,*N*-diisopropylamides.[49] It should be noted that while the modified procedure for the preparation of LAB (deprotonation of borane-ammonia complex with LDA instead of *n*-butyllithium) results in a cleaner reduction and a more facile work-up procedure, the modified procedure is less effective in the conversion of *N*,*N*-diisopropylamides to primary alcohols. Reduction of the *N*,*N*-diisopropylamide of entry 4, Table 9, using the modified procedure for the preparation of LAB, afforded a 37% yield of 1-adamantanemethanol (cf. 47% yield when using *n*-butyllithium as the deprotonating agent), with a corresponding increase in the yield of the tertiary amine by-product. The decreased yield of primary alcohol may be due simply to product inhibition. Diisopropylamine is the stoichiometric by-product of the deprotonation of borane-ammonia complex with LDA, and it is also the stoichiometric by-product in the transformation of an *N*,*N*-diisopropylamide to the corresponding primary alcohol.

^{11}B NMR Studies of LAB

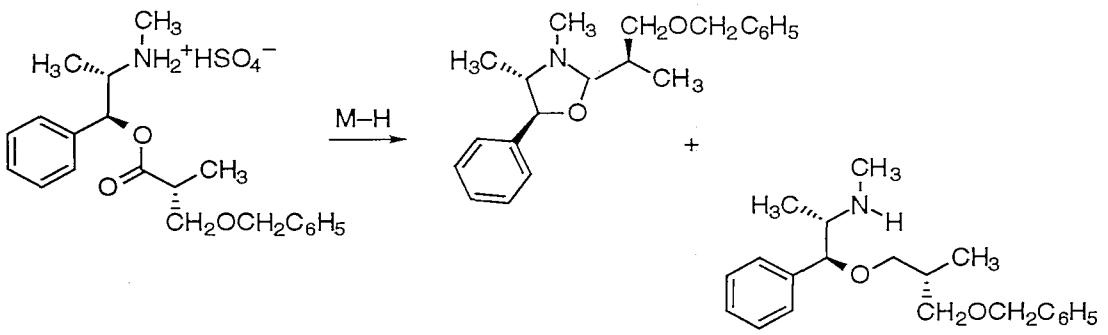
To our knowledge, though LAB has been the subject of two computational studies,[55] it had not been prepared in the laboratory prior to our initial report. Evidence that the reaction of *n*-butyllithium with borane-ammonia complex forms LAB comes from ^{1}H-decoupled ^{11}B NMR spectroscopy, where a sharp singlet resonating at –22 ppm (BF_3•OEt_2 reference) is observed. This value corresponds well with known amide-borane complexes[52a] (but not, e.g., with $LiBuBH_3$, which resonates at –29 ppm).[56] In addition, when the solid borane-ammonia reagent and neopentyllithium were combined in THF-d_8 at 23 °C, the same singlet at –22 ppm was observed in the ^{11}B NMR spectrum and neopentane was formed cleanly (^{13}C NMR). Evidence that using the modified LAB preparation (LDA as the deprotonating agent in lieu of *n*-butyllithium) does not produce

lithium diisopropylamidotrihydroborate (LDT) comes from comparative studies of the reactivity of the two metal amide borane complexes. LDT was prepared by the literature procedure:[52b] borane-tetrahydrofuran complex was complexed with diisopropylamine to form a stable amine-borane complex, and deprotonation of this amine-borane complex with *n*-butyllithium formed LDT. Pseudoephedrine amide **23** was inert to LDT even in refluxing THF (isolated yield of alcohol **58** was <5%). However, the reducing agent formed in situ by combining borane-ammonia complex with LDA does reduce amide **23** (Table 6, entry 6). Furthermore, this species reverts on silica gel to borane-ammonia complex, and not, e.g., to borane-diisopropylamine complex (as determined by TLC analysis).

Reduction of Pseudoephedrine Amides Involving In Situ Borane-Amine Complexation

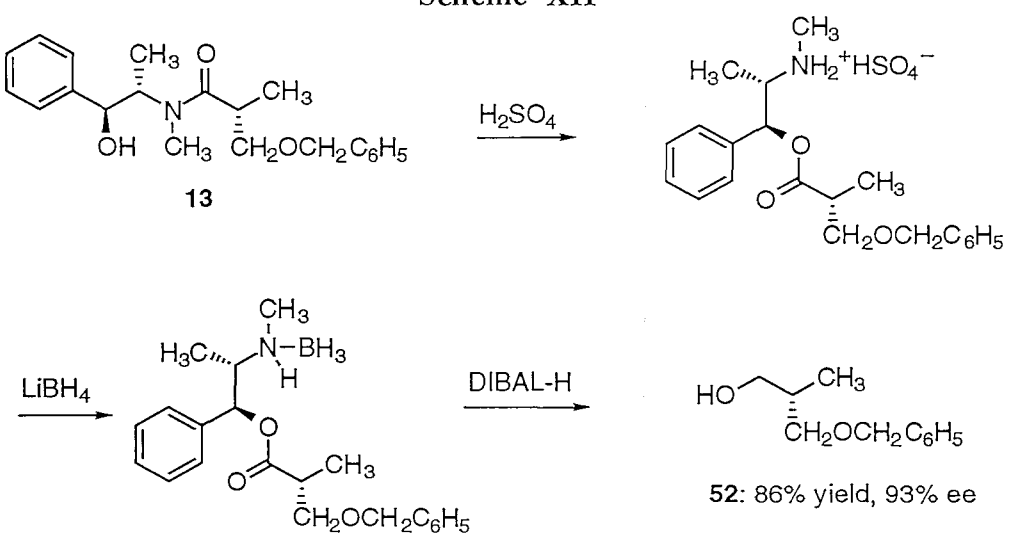
The hydrosulfate salt formed by $N \rightarrow O$ acyl transfer under acidic conditions was also investigated as an intermediate in a procedure to form highly enantiomerically enriched primary alcohols. Using the α-benzyloxymethyl-substituted amide **13** as a model substrate, attempts to reduce its corresponding $N \rightarrow O$ acyl transfer hydrosulfate salt using a variety of metal-hydride reducing agents (lithium aluminum hydride, diisobutylaluminum hydride, sodium bis(2-methoxyethoxy)aluminum hydride, lithium triethylborohydride) all gave significant quantities of a pseudoephedrine aminal by-product or an ether by-product (Scheme XI), both of which result from either $O \rightarrow N$ acyl transfer or the tetrahedral intermediate that would lead to $O \rightarrow N$ acyl transfer. The first step to either of these by-products is probably metal hydride-induced deprotonation of the ammonium terminus to generate a free (nucleophilic) amine.

Scheme XI



Using a procedure analogous to the hydrolysis of pseudoephedrine amides involving in situ borane-amine complexation (pp. 116–119), the amine-borane complex was reduced with diisobutylaluminum hydride to afford the alcohol **52** in 86% yield and 93% ee (Scheme XII, cf. 86% yield, 95% ee with LAB). This same sequence of steps was used to transform phenylacetamide **20** to alcohol **56** in 95% ee (cf. 90% ee with LAB). In the case of amide **20**, the product alcohol (**56**) had the same R_f as the pseudoephedrine-borane complex which was liberated during the reaction, rendering flash column chromatographic purification ineffective. Pseudoephedrine-borane complex

Scheme XII



52: 86% yield, 93% ee

can be decomposed with trifluoroacetic acid in methanol to allow for flash column chromatographic purification, but this was not conducted for alcohol **56**, since the higher ee observed with this procedure (than with LAB) did not offset the much more arduous procedures required to effect this reductive transformation.

Conclusion

In summary, we have demonstrated that LAB is a highly nucleophilic hydride source that is easily prepared from readily available, commercial materials. Its efficacy for the particular application at hand, the selective reduction of a tertiary amide to the corresponding alcohol, appears to be superior to any existing reagent.

Experimental Section

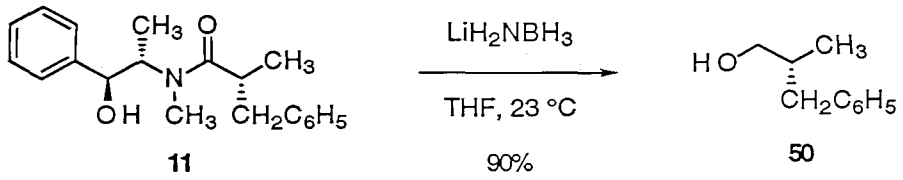
General Procedures. All non-aqueous reactions were performed in flame-dried round-bottomed or modified Schlenk (Kjeldahl shape) flasks, equipped with a magnetic stirring bar and fitted with a rubber septum under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula unless otherwise noted. Organic solutions were concentrated by rotary evaporation at ~25 Torr. Flash column chromatography was performed as described by Still et al.[38] 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 was distilled under nitrogen from sodium benzophenone ketyl. Dichloromethane, diisopropylamine, triethylamine, and pyrrolidine 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).[40] Borane-ammonia complex and neopentyllithium were stored and transferred under nitrogen. Solvents used for flash column chromatography were reagent-grade.

Instrumentation. Melting points are uncorrected. 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) or to tetramethylsilane. Data are presented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sx = sextet, sp = septet, 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). ^{11}B spectra were recorded at 128 MHz and the chemical shifts are expressed in parts per million (δ scale) downfield from both trimethylborate and boron trifluoride etherate. Mass spectrometry was performed at the California Institute of Technology or at the University of California at Irvine. Combustion analyses were performed by Quantitative Technologies Incorporated.

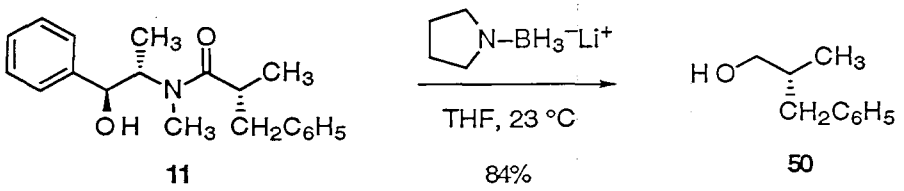
Chiral capillary gas chromatography (GC) analysis was carried out using an Alltech Chirasil-Val chiral fused silica capillary column, under isothermal conditions, with a column head pressure of 17 psi. High performance liquid chromatography (HPLC) was conducted using a Chiralcel OD column.



(*R*)-β-Methyl Benzenepropanol **50**

A solution of *n*-butyllithium in hexanes (2.34 M, 53.5 mL, 125 mmol, 3.90 equiv) was added to a solution of diisopropylamine (18.9 mL, 125 mmol, 4.20 equiv) in tetrahydrofuran (150 mL) at –78 °C. The resulting solution was stirred at –78 °C for 10 min, at 0 °C for 5 min, then was cooled to –78 °C. Borane-ammonia complex (90%, 4.41 g, 129 mmol, 4.00 equiv) was added in one portion, and the suspension was warmed to 0 °C. The mixture was stirred at 0 °C for 20 min, at 23 °C for 20 min, then was cooled to 0 °C. A solution of amide **11** (10.0 g, 32.1 mmol, 1 equiv) in tetrahydrofuran (150 mL, followed by a 5-mL rinse) was added via cannula over ~4 min. The reaction mixture was warmed to 23 °C and was held at that temperature for 50 min, then was cooled to 0 °C where excess hydride was quenched by the careful addition of 3 N aqueous hydrochloric acid solution (350 mL). The biphasic mixture was stirred at 23 °C for 30 min, then was extracted with three 150-mL portions of ether. The combined organic extracts were washed sequentially with 3 N aqueous hydrochloric acid solution (50 mL) and brine (50 mL), then were dried over magnesium sulfate and were concentrated. Purification of the residue by flash column chromatography (43% ether–petroleum ether) afforded alcohol **50** as a colorless liquid (4.35 g, 90%). Chiral HPLC analysis[57] (Chiralcel OD) of alcohol **50** established that alcohol **50** was of ≥99% ee.

^{1}H NMR (300 MHz, C_6D_6) δ:	7.0–7.2 (m, 5H, aromatic), 3.15 (m, 2H, HOC**H**$_2$), 2.62 (dd, 1H, J_1 = 13.3 Hz, J_2 = 6.2 Hz, one of PhC**H**$_2$), 2.22 (dd, 1H, J_1 = 13.3 Hz, J_2 = 8.0 Hz, one of PhC**H**$_2$), 1.70 (m, 1H, C**H**$_3$CH), 0.77 (d, 3H, J = 6.7 Hz, CH_3), 0.62 (t, 1H, J = 5.2 Hz, **OH**).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	140.6, 129.0, 128.2, 125.7, 67.4, 39.6, 37.7, 16.4.
FTIR (neat, cm^{-1}):	3332 (br, s, OH).
Analysis:	Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39; N, 0.
	Found: C, 79.67; H, 9.05; N, <0.05.
TLC (60% EtOAc–hexanes), R_f:	**50**: 0.56 (UV, PMA).
	11: 0.21 (UV, PMA).

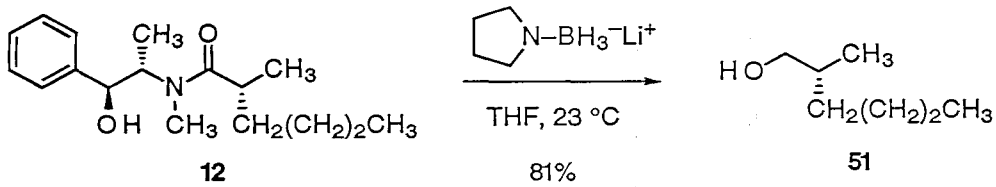


(*R*)-β-Methyl Benzenepropanol **50**

A 100-mL flask was immersed in an ice bath and was charged sequentially with pyrrolidine (0.800 mL, 9.63 mmol, 3.00 equiv) and borane-tetrahydrofuran complex (1.0 M in THF, 9.63 mL, 9.63 mmol, 3.00 equiv). The solution was warmed to 23 °C, and was held at that temperature for 1 h, then was cooled to 0 °C. A solution of *n*-butyllithium in hexanes (1.71 M, 5.63 mL, 9.63 mmol, 3.00 equiv) was added to the cold solution of borane-pyrrolidine complex, and the resulting solution was stirred at 0 °C for 30 min. A solution of amide **11** (1.00 g, 3.21 mmol, 1 equiv) in tetrahydrofuran (9 mL, followed by a 1-mL rinse) was added via cannula. The reaction mixture was stirred at 23 °C for 6 h before excess hydride was quenched by the addition of 3 N aqueous hydrochloric acid solution (15 mL). The mixture was partitioned between aqueous 1 N hydrochloric acid solution (350 mL) and ether (50 mL). The aqueous layer was separated and extracted with three 50-mL portions of ether. The combined ether extracts were washed with two 25-mL portions of a 1:1 mixture of brine and 1 N aqueous hydrochloric acid solution, then were concentrated. The residue was stirred with 1 N aqueous sodium hydroxide solution (100 mL) at 23 °C for 30 min and the mixture was extracted with ether (3 × 30 mL). The combined ether extracts were washed with two 10-mL portions of a 1:1 mixture of brine and 1 N aqueous sodium hydroxide solution, then were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (35% ether–petroleum ether) afforded alcohol **50** as a colorless liquid (405 mg, 84%). Acylation of alcohol **50** (9.0 mg, 0.060 mmol, 1 equiv) with the Mosher acid chloride (~0.17 mmol,

~2.8 equiv) and triethylamine (42 μL, 0.30 mmol, 5.0 equiv) in dichloromethane (1.5 mL) at 23 °C for 10 h, followed by ^{1}H NMR analysis (300 MHz, C_6D_6) of the resulting Mosher ester derivative[53] established that alcohol **50** was of ≥95% ee.[58] The Mosher chloride (~0.17 mmol, ~2.8 equiv) was prepared in situ by stirring Mosher's acid (40 mg, 0.17 mmol, 2.8 equiv), oxalyl chloride (19 μL, 0.22 mmol, 3.7 equiv), and *N*,*N*-dimethylformamide (2.0 μL, 0.026 mmol, 0.43 equiv) in dichloromethane (1 mL) at 23 °C for 30 min, followed by removal of dichloromethane and excess oxalyl chloride under reduced pressure (0.5 mm Hg) at 0 °C for 30 min. Spectroscopic data of alcohol **50** were identical to those listed above.

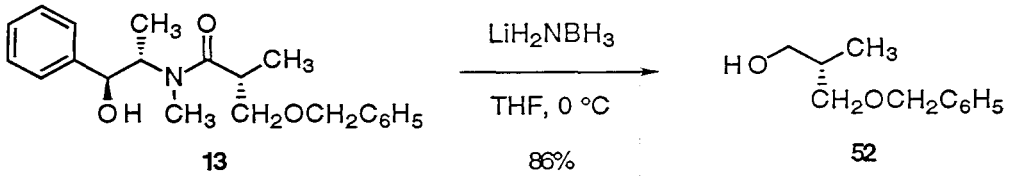
HRMS (FAB):	Calcd for $C_{10}H_{14}O$ $(M)^+$: 150.1045.
	Found: 150.1047.
TLC (60% EtOAc–hexanes), R_f:	**50**: 0.56 (UV, PMA).
	11: 0.21 (UV, PMA).



(*R*)-2-Methyl-1-hexanol **51**

Alcohol **51** was prepared by the reduction of amide **12** with LPT, as described above for the alcohol **50**. Thus, treatment of amide **12** (2.00 g, 7.21 mmol, 1 equiv) with LPT (5.41 mmol, 3.00 equiv) at 23 °C for 10 h afforded alcohol **51** as a colorless liquid (170 mg, 81%) after purification by flash column chromatography (40% ether-petroleum ether). High resolution ^{1}H NMR analysis (300 MHz, C_6D_6) of the corresponding Mosher ester derivative,[58] prepared as described above for alcohol **50**, established that alcohol **51** was of ≥95% ee.

^{1}H NMR (300 MHz, C_6D_6) δ:	3.19 (m, 2H, $HOCH_2$), 0.92–1.44 (m, 7H, $CH_3CH_2CH_2CH_2CH$), 0.87 (t, 3H, J = 6.9 Hz, CH_3CH_2), 0.83 (d, 3H, J = 6.6 Hz, CH_3CH), 0.69 (s, 1H, OH).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	68.0, 36.0, 33.2, 29.6, 23.4, 16.8, 14.3.
FTIR (neat, cm^{-1}):	3339 (br, s, OH).
HRMS (FAB):	Calcd for C_7H_{14} $(M–H_2O)^+$: 98.1096. Found: 98.1099.
TLC (60% ether–pet ether), R_f:	**51**: 0.43 (PMA). **12**: 0.32 (UV, PMA).

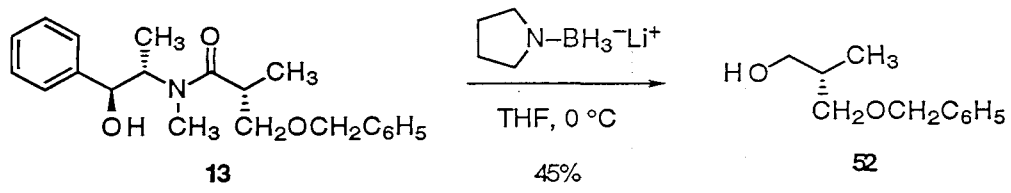


13 86% **52**

(*S*)-3-Benzyloxy-2-methylpropanol **52**

A solution of *n*-butyllithium in hexanes (2.38 M, 1.22 mL, 2.90 mmol, 3.90 equiv) was added to a solution of diisopropylamine (0.439 mL, 3.13 mmol, 4.20 equiv) in tetrahydrofuran (2.5 mL) at –78 °C. The resulting solution was stirred at –78 °C for 10 min, at 0 °C for 5 min, then was cooled to –78 °C. Borane-ammonia complex (90%, 102 mg, 2.98 mmol, 4.00 equiv) was added in one portion, and the suspension was warmed to 0 °C. The mixture was stirred at 0 °C for 20 min, at 23 °C for 20 min, then was cooled to 0 °C. A solution of amide **13** (255 mg, 0.746 mmol, 1 equiv) in tetrahydrofuran (2 mL, followed by a 0.5-mL rinse) was added via cannula. The reaction mixture was stirred at 0 °C for 1.3 h, then excess hydride was quenched by the careful addition of 3 N aqueous hydrochloric acid solution (10 mL). The mixture was extracted with four 9-mL portions of ether. The combined organic extracts were washed sequentially with 3 N aqueous hydrochloric acid solution (3 mL) and brine (3 mL), then were dried over magnesium sulfate and were concentrated. Purification of the residue by flash column chromatography (gradient elution of ether–petroleum ether, 40 → 50%) afforded alcohol **52** as a colorless liquid (116 mg, 86%). High resolution ^{1}H NMR analysis (400 MHz, $CDCl_3$) of the corresponding Mosher ester derivative,[58] prepared as described above for alcohol **50**, established that alcohol **52** was of 95% ee.

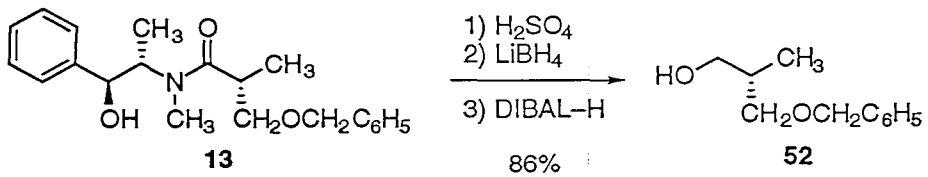
^{1}H NMR (300 MHz, C_6D_6) δ:	7.0–7.25 (m, 5H, aromatic), 4.21 (s, 2H, PhC**H**$_2$), 3.46 (d, 2H, J = 8.9 Hz, CH_3CHCH_2O), 3.20 (m, 2H, HOC**H**$_2$), 1.86 (m, 1H, CH_3CH), 0.73 (d, 3H, J = 6.9 Hz, CH_3).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	138.0, 128.4, 127.6, 127.5, 75.2, 73.3, 67.6, 35.6, 13.4.
FTIR (neat, cm^{-1}):	3388 (br, s, OH).
HRMS (EI):	Calcd for $C_{11}H_{16}O_2$ $(M)^+$: 180.1150.
	Found: 180.1155.
TLC (60% EtOAc–hexanes), R_f:	**52**: 0.43 (UV, PMA).
	13: 0.19 (UV, PMA).



(*S*)-3-Benzyloxy-2-methylpropanol **52**

Alcohol **52** was prepared by the reduction of amide **13** with LPT, as described above for the alcohol **50**. Thus, treatment of amide **13** (100 mg, 0.293 mmol, 1 equiv) with LPT (1.17 mmol, 4.20 equiv) at 0 °C for 3 h afforded alcohol **52** as a colorless liquid (23.5 mg, 45%) after purification by flash column chromatography (gradient elution of ether-petroleum ether, 40 → 50%). High resolution ^{1}H NMR analysis (300 MHz, $CDCl_3$) of the corresponding Mosher ester derivative,[58] prepared as described above for alcohol **50**, established that alcohol **52** was of 91% ee. Spectroscopic data of alcohol **52** were identical to those listed above.

TLC (60% EtOAc–hexanes), R_f: **52**: 0.43 (UV, PMA).
13: 0.19 (UV, PMA).
benzyl alcohol: 0.48 (UV, PMA).



(*S*)-3-Benzyloxy-2-methylpropanol **52**

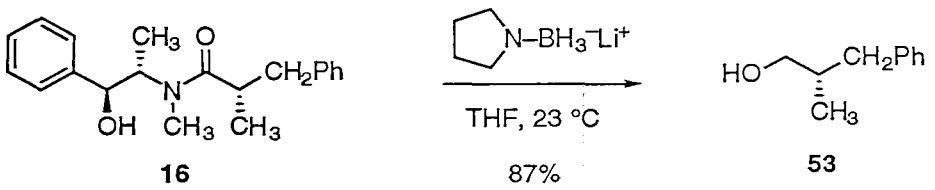
An ice-cooled solution of 18 N aqueous sulfuric acid (2 mL) was added to a solution of amide **13** (500 mg, 1.46 mmol, 1 equiv) in dioxane (2 mL) at 10 °C. The biphasic mixture was warmed to 23 °C and held at that temperature for 2 hours. The mixture was partitioned between brine (35 mL) and ethyl acetate (35 mL). The aqueous layer was separated and saturated with sodium chloride, then was extracted with ethyl acetate (3 × 35 mL). The combined organic fractions were dried over sodium sulfate and were concentrated to yield a fine white powder. The powder was dissolved in tetrahydrofuran (8 mL) and cooled to 0 °C. A solution of lithium borohydride in tetrahydrofuran (2.0 M, 0.880 mL, 1.75 mmol, 1.20 equiv) was added slowly via syringe, resulting in vigorous gas evolution. The reaction mixture was stirred at 0 °C for 5 min, after which time bubbling had ceased, and a solution of diisobutylaluminum hydride in toluene (1.0 M, 4.38 mL, 4.38 mmol, 3.00 equiv) was added dropwise via syringe. The mixture was stirred at 0 °C for 15 min, then excess hydride was quenched by the slow addition of 3 N aqueous hydrochloric acid solution (5 mL). The mixture was partitioned between 1 N aqueous hydrochloric acid solution (100 mL) and ethyl acetate (35 mL). The aqueous layer was separated and extracted with ethyl acetate (2 × 35 mL). The combined organic fractions were dried over sodium sulfate and were concentrated. The residue was dissolved in a solution of methanol (12 mL) and trifluoroacetic acid (2.8 mL, 36 mmol, 25 equiv), and the mixture was stirred overnight at 23 °C. The reaction mixture was partitioned between ethyl acetate (200 mL) and saturated aqueous sodium bicarbonate solution (20 mL). The organic layer was separated and extracted sequentially with

saturated aqueous sodium bicarbonate solution (2 × 20 mL), 3 N aqueous hydrochloric acid solution (2 × 20 mL), and brine (10 mL), then was dried over sodium sulfate and was concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ether–petroleum ether (40 → 50%) afforded alcohol **52** as a colorless liquid (225 mg, 86% yield from **13**). High resolution ^{1}H NMR spectroscopy (300 MHz, $CDCl_3$) of the corresponding Mosher ester derivative,[58] prepared as described above for alcohol **50**, established that alcohol **52** was of 93% ee. Spectroscopic data of alcohol **52** were identical to those listed above.

TLC (7.5% MeOH–CH_2Cl_2), R_f: **52**: 0.58 (UV, PMA).

N → *O* acyl transfer: 0.13–0.26 streak (UV, PMA).

13: 0.38 (UV, PMA).

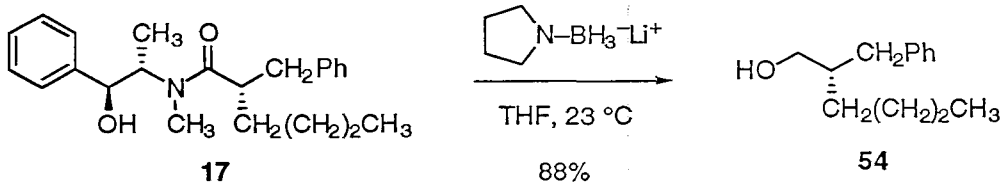


16 87% **53**

(*S*)-β-Methyl Benzenepropanol **53**

Alcohol **53** was prepared by the reduction of amide **16** with LPT, as described above for the alcohol **50**. Thus, treatment of amide **16** (500 mg, 1.61 mmol, 1 equiv) with LPT (4.82 mmol, 3.00 equiv) at 23 °C for 10.3 h afforded alcohol **53** as a colorless liquid (210 mg, 87%) after purification by flash column chromatography (35% ether-petroleum ether). High resolution ^{1}H NMR analysis (300 MHz, C_6D_6) of the corresponding Mosher ester derivative,[58] prepared as described above for alcohol **50**, established that alcohol **53** was of ≥95% ee. Spectroscopic data of alcohol **53** were identical to those of its enantiomer, (*R*)-β-methyl benzenepropanol (**50**).

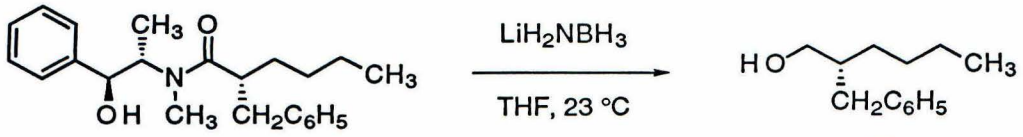
HRMS (FAB):	Calcd for $C_{10}H_{14}O$ $(M)^+$: 150.1045.
	Found: 150.1046.
TLC (50% EtOAc–hexanes), R_f:	**53**: 0.51 (UV, PMA).
	16: 0.24 (UV, PMA).



(*S*)-β-Butyl Benzenepropanol **54**

Alcohol **54** was prepared by the reduction of amide **17** with LPT, as described above for the alcohol **50**. Thus, treatment of amide **17** (201 mg, 0.569 mmol, 1 equiv) with LPT (1.71 mmol, 3.00 equiv) at 23 °C for 3.1 h afforded alcohol **54** as a colorless liquid (96 mg, 88% yield) after purification by flash column chromatography (25% ethyl acetate–hexanes). High resolution ^{1}H NMR analysis (300 MHz, $CDCl_3$) of the corresponding Mosher ester derivative,[58] prepared as described above for alcohol **50**, established that alcohol **54** was of ≥95% ee.

^{1}H NMR (300 MHz, C_6D_6) δ:	7.0–7.3 (m, 5H, aromatic), 3.25 (d, 2H, J = 5.1 Hz, $HOCH_2$), 2.59 (dd, 1H, J = 13.5 Hz, 7.6 Hz, one of $PhCH_2$), 2.48 (dd, 1H, J = 13.5 Hz, 6.5 Hz, one of $PhCH_2$), 1.60 (m, 1H, one of $HOCH_2CHCH_2$), 1.31 (m, 1H, one of $HOCH_2CHCH_2$), 1.20 (m, 4H, $CH_3CH_2CH_2$), 0.84 (m, 3H, CH_3).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	140.8, 129.1, 128.1, 125.7, 64.6, 42.4, 37.5, 30.3, 29.0, 22.9, 14.0.
FTIR (neat, cm^{-1}):	3342 (br, m, OH).
HRMS (FAB):	Calcd for $C_{13}H_{20}O$ $(M)^+$: 192.1515.
	Found: 192.1508.
TLC (40% EtOAc–hexanes), R_f:	**54**: 0.47 (UV, PMA).
	17: 0.22 (UV, PMA).



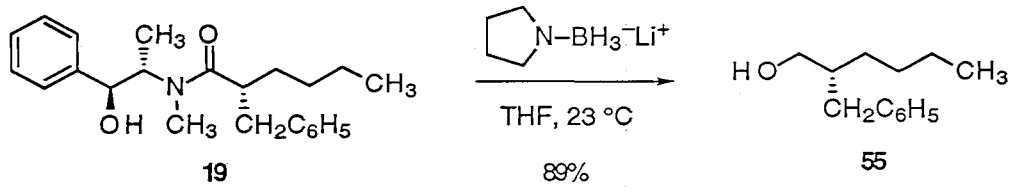
19 **55**

(*R*)-β-Butyl Benzenepropanol **55**

A solution of *n*-butyllithium in hexanes (2.37 M, 4.78 mL, 11.3 mmol, 4.00 equiv) was added to a suspension of borane-ammonia complex (90%, 408 mg, 11.9 mmol, 4.20 equiv) in tetrahydrofuran (10 mL) at 0 °C. The suspension was warmed briefly to 23 °C, then was cooled to 0 °C. A solution of amide **19** (1.00 g, 2.83 mmol, 1 equiv) in tetrahydrofuran (10 mL, followed by a 2-mL rinse) was added via cannula, and the mixture was warmed to 23 °C. The mixture was stirred at 23 °C for 2.5 h, then excess hydride was quenched by the cautious addition of 1 N aqueous hydrochloric acid solution (120 mL). The mixture was extracted with four 40-mL portions of ether. The combined ether extracts were washed with 1 N aqueous hydrochloric acid solution (10 mL), then were dried over sodium sulfate and were concentrated. The residue was stirred in 1 N aqueous sodium hydroxide solution (150 mL) at 23 °C for 1 h. The mixture was extracted with ether (40 mL), then was saturated with sodium chloride and was extracted with two 40-mL portions of ether. The combined ether extracts were washed sequentially with 1 N aqueous hydrochloric acid solution (2 × 40 mL) and brine (10 mL), then were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ether–petroleum ether (30 → 35%) afforded alcohol **55** as a colorless liquid (500 mg, 92%). High resolution ^{1}H NMR analysis (400 MHz, $CDCl_3$) of the corresponding Mosher ester derivative,[58] prepared as described above for alcohol **50**, established that alcohol **55** was of ≥95% ee. Spectroscopic data of alcohol **55** were identical to those of its enantiomer, (*S*)-β-butyl benzenepropanol (**54**).

TLC (50% EtOAc–hexanes), R_f: **55**: 0.55 (UV, PMA).

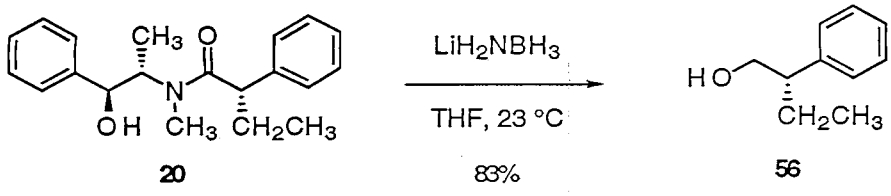
19: 0.38 (UV, PMA).



(*R*)-β-Butyl Benzenepropanol **55**

Alcohol **55** was prepared by the reduction of amide **19** with LPT, as described above for the alcohol **50**. Thus, treatment of amide **19** (500 mg, 1.41 mmol, 1 equiv) with LPT (4.24 mmol, 3.00 equiv) at 23 °C for 5.8 h afforded alcohol **55** as a colorless liquid (243 mg, 89%) after purification by flash column chromatography (25% ethyl acetate–hexanes). High resolution ^{1}H NMR analysis (300 MHz, $CDCl_3$) of the corresponding Mosher ester derivative,[58] prepared as described above for alcohol **50**, established that alcohol **55** was of ≥95% ee. Spectroscopic data were identical to those of its enantiomer, (*S*)-β-butyl benzenepropanol (**54**).

HRMS (FAB):	Calcd for $C_{13}H_{20}O$ $(M)^+$: 192.1515.
	Found: 192.1508.
TLC (50% EtOAc–hexanes), R_f:	**55**: 0.55 (UV, PMA).
	19: 0.38 (UV, PMA).



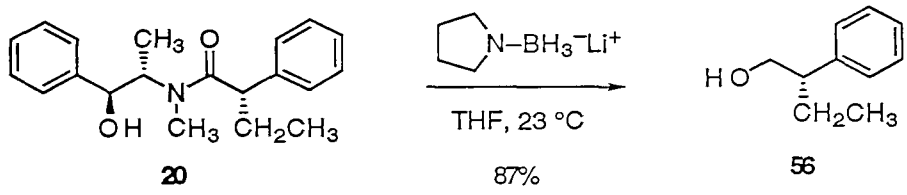
20 83% **56**

(*S*)-β-Ethyl Benzeneethanol **56**

A solution of *n*-butyllithium in hexanes (2.39 M, 0.880 mL, 2.10 mmol, 3.90 equiv) was added to a solution of diisopropylamine (0.317 mL, 2.26 mmol, 4.20 equiv) in tetrahydrofuran (2 mL) at –78 °C. The resulting solution was stirred at –78 °C for 10 min, at 0 °C for 5 min, then was cooled to –78 °C. Borane-ammonia complex (90%, 74 mg, 2.16 mmol, 4.00 equiv) was added in one portion, and the suspension was warmed to 0 °C. The mixture was stirred at 0 °C for 20 min, at 23 °C for 20 min, then was cooled to 0 °C. A solution of amide **20** (168 mg, 0.539 mmol, 1 equiv) in tetrahydrofuran (1.5 mL, followed by a 0.5-mL rinse) was added via cannula. The reaction mixture was warmed to 23 °C and was held at that temperature for 1.9 h, then was cooled to 0 °C where excess hydride was quenched by the careful addition of 3 N aqueous hydrochloric acid solution (8 mL). The mixture was extracted with four 7-mL portions of ether. The combined ether extracts were washed sequentially with 3 N aqueous hydrochloric acid solution (3 mL) and brine (3 mL), then were dried over magnesium sulfate and were concentrated. Purification of the residue by flash column chromatography (40% ether–petroleum ether) afforded alcohol **56** as a colorless liquid (67 mg, 83%). Acylation of the product with the (*R*)-Mosher acid chloride according to the method described above for alcohol **50** afforded a mixture of Mosher ester derivatives in 92% de as determined by ^{1}H NMR analysis, establishing that alcohol **56** was of 92% ee.[58] The major diastereomer was shown to be identical to the Mosher ester derivative prepared from the acylation of authentic (*S*)-β-ethyl benzeneethanol by high resolution ^{1}H NMR analysis (400 MHz, C_6D_6). An authentic

sample of (*S*)-β-ethyl benzeneethanol was prepared by reduction of (*S*)-2-phenylbutyric acid with lithium aluminum hydride in THF at 0 °C.

^{1}H NMR (300 MHz, C_6D_6) δ:	7.0–7.2 (m, 5H, aromatic), 3.48 (m, 2H, HOC**H**$_2$), 2.44 (m, 1H, PhC**H**), 1.62 (m, 1H, one of $CH_3C\mathbf{H}_2$), 1.41 (m, 1H, one of $CH_3C\mathbf{H}_2$), 0.91 (t, 1H, O**H**), 0.72 (t, 3H, J = 7.4 Hz, C**H**$_3$).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	142.2, 128.6, 128.1, 126.6, 67.3, 50.4, 24.9, 11.9.
FTIR (neat, cm^{-1}):	3354 (br, s, OH).
HRMS (FAB):	Calcd for $C_{10}H_{14}O$ $(M)^+$: 150.1045.
	Found: 150.1047.
TLC (50% EtOAc–hexanes), R_f:	**56**: 0.52 (UV, PMA).
	20: 0.33 (UV, PMA).

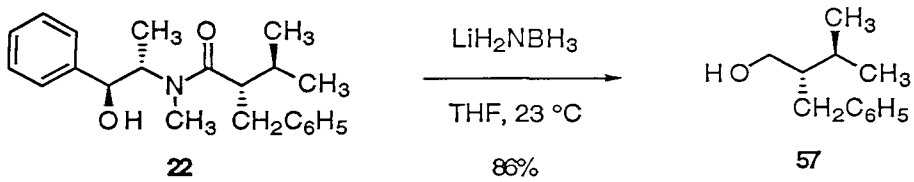


20 **56**

(*S*)-β-Ethyl Benzeneethanol **56**

Alcohol **56** was prepared by the reduction of amide **20** with LPT, as described above for the alcohol **50**. Thus, treatment of amide **20** (500 mg, 1.61 mmol, 1 equiv) with LPT (4.82 mmol, 3.00 equiv) at 23 °C for 14 h afforded alcohol **56** as a colorless liquid (210 mg, 87%) after purification by flash column chromatography (40% ether–petroleum ether). High resolution ^{1}H NMR analysis (400 MHz, C_6D_6) of the corresponding Mosher ester derivative, as described in the preceding procedure, established that the reduction of amide **20** with LPT afforded (*R*)-β-ethyl benzeneethanol in 33% ee. Spectroscopic data of alcohol **56** were identical to those listed above.

TLC (50% EtOAc–hexanes), R_f: **56**: 0.52 (UV, PMA).
20: 0.33 (UV, PMA).

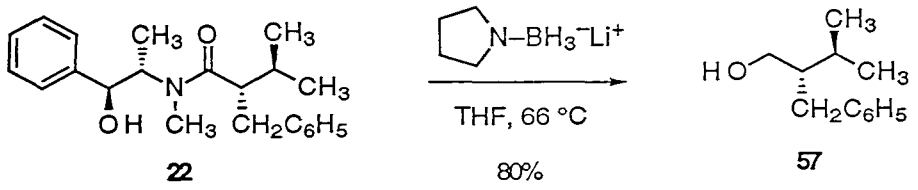


22 57

(*S*)-β-(1-Methylethyl)benzenepropanol **57**

A solution of *n*-butyllithium in hexanes (2.34 M, 1.48 mL, 3.47 mmol, 3.90 equiv) was added to a solution of diisopropylamine (0.523 mL, 3.73 mmol, 4.20 equiv) in tetrahydrofuran (4 mL) at –78 °C. The resulting solution was stirred at –78 °C for 10 min, at 0 °C for 5 min, then was cooled to –78 °C. Borane-ammonia complex (90%, 122 mg, 3.56 mmol, 4.00 equiv) was added in one portion, and the suspension was warmed to 0 °C. The mixture was stirred at 0 °C for 20 min, at 23 °C for 20 min, then was cooled to 0 °C. A solution of amide **22** (302 mg, 0.890 mmol, 1 equiv) in tetrahydrofuran (3 mL, followed by a 0.5-mL rinse) was added via cannula. The reaction mixture was warmed to 23 °C and was held at that temperature for 18 h, then was cooled to 0 °C where excess hydride was quenched by the careful addition of 3 N aqueous hydrochloric acid solution (10 mL). The mixture was extracted with four 9-mL portions of ether. The combined organic extracts were washed sequentially with 3 N aqueous hydrochloric acid solution (3 mL) and brine (3 mL), then were dried over magnesium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ether–petroleum ether (20 → 40%) afforded alcohol **57** as a colorless liquid (137 mg, 86%). High resolution ^{1}H NMR analysis (400 MHz, $CDCl_3$) of the corresponding Mosher ester derivative,[58] prepared as described above for alcohol **50**, established that alcohol **57** was of ≥95% ee.

^{1}H NMR (300 MHz, $CDCl_3$) δ:	7.1–7.4 (m, 5H, aromatic), 3.55 (d, 3H, J = 5.6 Hz, $HOC\mathbf{H}_2$), 2.71 (dd, J = 13.7, 5.5 Hz, one of $PhC\mathbf{H}_2$), 2.51 (dd, 1H, J = 13.7, 9.1 Hz, one of $PhC\mathbf{H}_2$), 1.86 (m, 1H, $HOCH_2C\mathbf{H}$), 1.67 (m, 1H, $C\mathbf{H}(CH_3)_2$), 0.98 (d, 3H, J = 5.6 Hz, $C\mathbf{H}_3$), 0.96 (d, 3H, J = 5.6 Hz, $C\mathbf{H}_3$).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	141.4, 129.0, 128.3, 125.8, 62.9, 48.8, 34.4, 27.8, 19.7, 19.4.
FTIR (neat, cm^{-1}):	3354 (br, m, OH).
HRMS (EI):	Calcd for $C_{12}H_{18}O$ $(M)^+$: 178.1358.
	Found: 178.1357.
TLC (50% EtOAc–hexanes), R_f:	**57**: 0.52 (UV, PMA).
	22: 0.33 (UV, PMA).

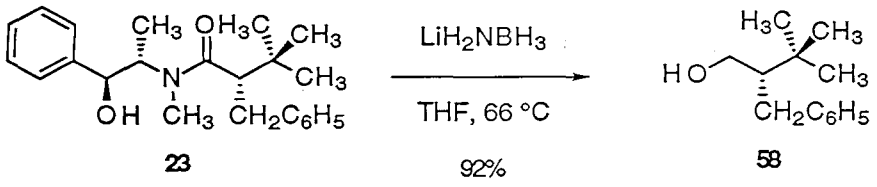


(*S*)-β-(1-Methylethyl)benzenepropanol **57**

Alcohol **57** was prepared by the reduction of amide **22** with LPT, as described above for the alcohol **50**. Thus, treatment of amide **22** (100 mg, 0.295 mmol, 1 equiv) with LPT (1.18 mmol, 4.00 equiv) at 66 °C for 11 h afforded alcohol **57** as a colorless liquid (42.0 mg, 80%) after purification by flash column chromatography (gradient elution of ether–petroleum ether, 20 → 40%). High resolution ^{1}H NMR analysis (300 MHz, $CDCl_3$) of the corresponding Mosher ester derivative,[58] prepared as described above for alcohol **50**, established that alcohol **57** was of ≥95% ee. Spectroscopic data of alcohol **57** were identical to those listed above.

TLC (50% EtOAc–hexanes), R_f: **57**: 0.52 (UV, PMA).

22: 0.33 (UV, PMA).

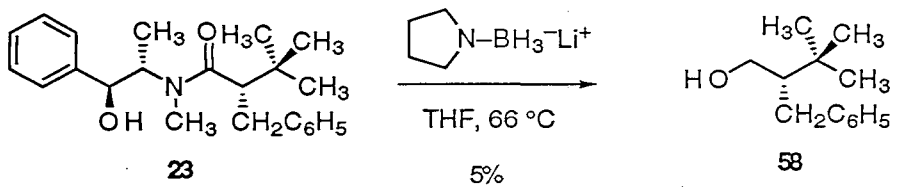


23 58

(*S*)-β-(1,1-Dimethylethyl)benzenepropanol **58**

A solution of *n*-butyllithium in hexanes (2.31 M, 4.78 mL, 11.0 mmol, 3.90 equiv) was added to a solution of diisopropylamine (1.67 mL, 11.9 mmol, 4.20 equiv) in tetrahydrofuran (11 mL) at –78 °C. The resulting solution was stirred at –78 °C for 10 min, at 0 °C for 5 min, then was cooled to –78 °C. Borane-ammonia complex (90%, 388 mg, 11.3 mmol, 4.00 equiv) was added in one portion, and the suspension was warmed to 0 °C. The mixture was stirred at 0 °C for 20 min, at 23 °C for 20 min, then was cooled to 0 °C. A solution of amide **23** (1.00 g, 2.83 mmol, 1 equiv) in tetrahydrofuran (9 mL, followed by a 2-mL rinse) was added via cannula. The reaction mixture was warmed to 66 °C and was held at that temperature for 10 h, then was cooled to 0 °C where excess hydride was quenched by the careful addition of 3 N aqueous hydrochloric acid solution (30 mL). The mixture was extracted with four 15-mL portions of ether. The combined organic extracts were washed sequentially with 3 N aqueous hydrochloric acid solution (5 mL) and brine (5 mL), then were dried over magnesium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ether–petroleum ether (20 → 30%) afforded alcohol **58** as a white solid (500 mg, 92%): mp 30–31 °C. High resolution ^{1}H NMR analysis (400 MHz, $CDCl_3$) of the corresponding Mosher ester derivative,[58] prepared as described above for alcohol **50**, established that alcohol **58** was of ≥95% ee.

^{1}H NMR (300 MHz, $CDCl_3$) δ:	7.15–7.35 (m, 5H, aromatic), 3.61 (m, 2H, $HOCH_2$), 2.89 (dd, 1H, J_1 = 13.6 Hz, J_2 = 3.3 Hz, one of $PhCH_2$), 2.47 (dd, 1H, J_1 = 13.6 Hz, J_2 = 10.9 Hz, one of $PhCH_2$), 1.54 (m, 1H, $HOCH_2CH$), 1.02 (s, 9H, $C(CH_3)_3$).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	142.2, 129.0, 128.4, 125.8, 62.7, 53.0, 34.0, 33.0, 28.4.
FTIR (neat, cm^{-1}):	3385 (br, m, OH).
HRMS (EI):	Calcd for $C_{13}H_{20}O$ $(M)^+$: 192.1514.
	Found: 192.1513.
TLC (50% EtOAc–hexanes), R_f:	**58**: 0.60 (UV, PMA).
	23: 0.50 (UV, PMA).

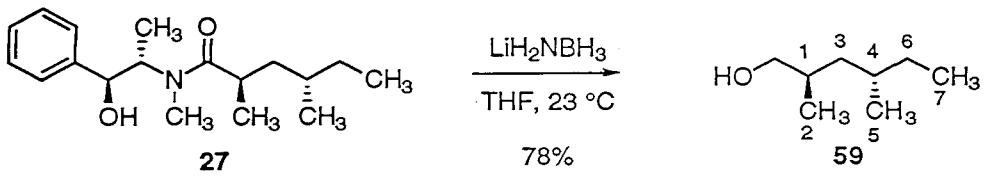


(*S*)-β-(1,1-Dimethylethyl)benzenepropanol **58**

Alcohol **58** was prepared by the reduction of amide **23** with LPT, as described above for the alcohol **50**. Thus, treatment of amide **23** (100 mg, 0.283 mmol, 1 equiv) with LPT (1.13 mmol, 4.00 equiv) at 66 °C for 12 h afforded alcohol **58** as a colorless liquid (2.9 mg, 5%) after purification by flash column chromatography (gradient elution of ether–petroleum ether, 15 → 30%). Spectroscopic data were identical to those listed above.

TLC (50% EtOAc–hexanes), R_f: **58**: 0.60 (UV, PMA).

23: 0.50 (UV, PMA).

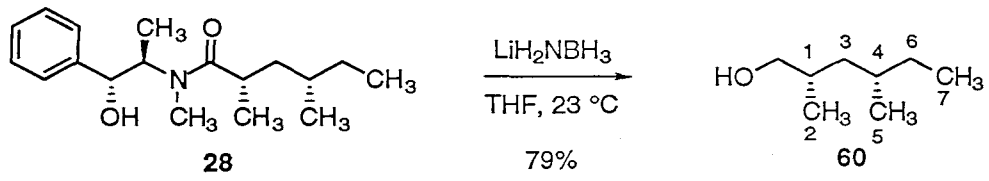


27 59

(2*R*,4*S*)-2,4-Dimethylhexanol **59**

A solution of *n*-butyllithium in hexanes (2.44 M, 5.51 mL, 13.4 mmol, 3.90 equiv) was added to a solution of diisopropylamine (2.03 mL, 14.5 mmol, 4.20 equiv) in tetrahydrofuran (10 mL) at –78 °C. The resulting solution was stirred at –78 °C for 10 min, then was warmed to 0 °C and was held at that temperature for 10 min. Borane-ammonia complex (90%, 473 mg, 13.8 mmol, 4.00 equiv) was added in one portion, and the suspension was stirred at 0 °C for 15 min, then was warmed to 23 °C. After 20 min, the suspension was cooled to 0 °C. A solution of amide **27** (1.00 g, 3.45 mmol, 1 equiv) in tetrahydrofuran (4 mL, followed by a 4-mL rinse) was added via cannula. The reaction mixture was warmed to 23 °C and was held at that temperature for 2 h, then was cooled to 0 °C where excess hydride was quenched by the careful addition of 3 N aqueous hydrochloric acid solution (40 mL). Volatile organic solvents were removed by rotary evaporation, and the resulting aqueous solution was extracted with three 20-mL portions of ether. The combined ether fractions were washed sequentially with 3 N aqueous hydrochloric acid solution (5 mL), 2 N aqueous sodium hydroxide solution (5 mL), and brine (5 mL). The organic layer was dried over magnesium sulfate and was concentrated. Purification of the residue by flash column chromatography (40% ether–petroleum ether) afforded alcohol **59** as a colorless liquid (350 mg, 78%). Acetylation of alcohol **59** (25 mg, 0.19 mmol, 1 equiv) with acetic anhydride (45 μL, 0.48 mmol, 2.5 equiv) and 4-dimethylaminopyridine (59 mg, 0.48 mmol, 2.5 equiv) in dichloromethane (1 mL) at 23 °C for 1 h and chiral capillary GC analysis[59] of the resulting acetate ester established that alcohol **59** was of 97% de.

^{1}H NMR (400 MHz, $CDCl_3$) δ:	3.48 (dd, 1H, J_1 = 10.3 Hz, J_2 = 5.9 Hz, one of $HOCH_2$), 3.40 (dd, 1H, J_1 = 10.3 Hz, J_2 = 6.6 Hz, one of $HOCH_2$), 1.72 (m, 1H, H1), 1.42 (m, 1H, H4), 1.32 (m, 1H, one of H3), 1.18 (m, 1H, one of H3), 1.12 (m, 2H, H6), 0.89 (d, 3H, J = 6.6 Hz, H2), 0.87 (t, 3H, J = 7.3 Hz, H7), 0.84 (d, 3H, J = 6.2 Hz, H5).
^{13}C NMR (100 MHz, $CDCl_3$) δ:	68.9, 40.2, 33.2, 31.5, 30.4, 18.8, 16.3, 11.3.
FTIR (neat, cm^{-1}):	3331 (s, br, OH).
HRMS (EI):	Calcd for C_8H_{16} $(M–H_2O)^+$: 112.1252. Found: 112.1251.
TLC (50% EtOAc–hexanes), R_f:	**59**: 0.54 (PMA). **27**: 0.41 (UV, PMA).

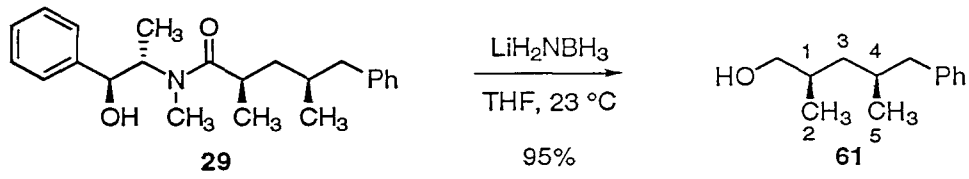


28 60

(2*S*,4*S*)-2,4-Dimethylhexanol **60**

A solution of *n*-butyllithium in hexanes (2.44 M, 5.53 mL, 13.5 mmol, 3.90 equiv) was added to a solution of diisopropylamine ((2.04 mL, 14.6 mmol, 4.20 equiv) in tetrahydrofuran (10 mL) at –78 °C. The resulting solution was stirred at –78 °C for 10 min, then was warmed to 0 °C and was held at that temperature for 10 min. Borane-ammonia complex (90%, 475 mg, 13.8 mmol, 4.00 equiv) was added in one portion, and the suspension was stirred at 0 °C for 15 min, then was warmed to 23 °C. After 20 min, the suspension was cooled to 0 °C. A solution of amide **28** (1.01 g, 3.46 mmol, 1 equiv) in tetrahydrofuran (4 mL, followed by a 4-mL rinse) was added via cannula. The reaction mixture was warmed to 23 °C and was held at that temperature for 2 h, then was cooled to 0 °C where excess hydride was quenched by the careful addition of 3 N aqueous hydrochloric acid solution (40 mL). After an aqueous work-up using the procedure described above for alcohol **59**, purification of the product by flash column chromatography (40% ether–petroleum ether) afforded alcohol **60** as a colorless liquid (357 mg, 79%). Chiral capillary GC analysis[59] of the corresponding acetate ester, prepared as described above for alcohol **59**, established that alcohol **60** was of 98% de.

^{1}H NMR (400 MHz, $CDCl_3$) δ:	3.53 (dd, 1H, J_1 = 10.3 Hz, J_2 = 5.1 Hz, one of $HOCH_2$), 3.38 (dd, 1H, J_1 = 10.3 Hz, J_2 = 7.0 Hz, one of $HOCH_2$), 1.72 (sx, 1H, J = 6.6 Hz, H1), 1.40–1.50 (m, 4H, H3, H4, one of H6), 1.09 (m, 1H, one of H6), 0.92 (d, 3H, J = 7.0 Hz, H2), 0.87 (d, 3H, J = 6.2 Hz, H5), 0.86 (t, 3H, J = 7.3 Hz, H7).
HRMS (EI):	Calcd for C_8H_{16} $(M–H_2O)^+$: 112.1252.
	Found: 112.1249.
^{13}C NMR (100 MHz, $CDCl_3$) δ:	68.2, 40.6, 33.1, 31.5, 28.9, 19.7, 17.2, 11.1.
FTIR (neat, cm^{-1}):	3332 (s, br, OH).
TLC (60% EtOAc–hexanes), R_f:	**60**: 0.59 (PMA).
	28: 0.42 (UV, PMA).

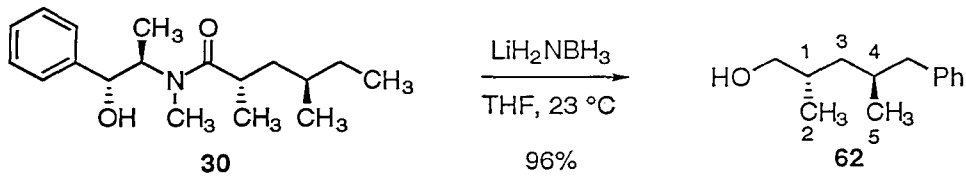


29 61

(2*R*,4*S*)-2,4-Dimethyl-5-phenylpentanol **61**

A solution of *n*-butyllithium in hexanes (2.33 M, 20.0 mL, 46.5 mmol, 3.90 equiv) was added to a solution of diisopropylamine (7.02 mL, 50.1 mmol, 4.20 equiv) in tetrahydrofuran (50 mL) at –78 °C. The resulting solution was stirred at –78 °C for 10 min, then was warmed to 0 °C and was held at that temperature for 10 min. Borane-ammonia complex (90%, 1.64 g, 47.7 mmol, 4.00 equiv) was added in one portion, and the suspension was stirred at 0 °C for 15 min, then was warmed to 23 °C. After 15 min, the suspension was cooled to 0 °C. A solution of amide **29** (4.22 g, 11.9 mmol, 1 equiv) in tetrahydrofuran (30 mL, followed by a 5-mL rinse) was added via cannula over 3 min. The reaction mixture was warmed to 23 °C and was held at that temperature for 2 h, then was cooled to 0 °C where excess hydride was quenched by the careful addition of 3 N aqueous hydrochloric acid solution (120 mL). The mixture was stirred for 30 min at 0 °C then was extracted with four 45-mL portions of ether. The combined organic extracts were washed sequentially with 3 N aqueous hydrochloric acid solution (20 mL), 2 N aqueous sodium hydroxide solution (20 mL), and brine (20 mL). The organic layer was dried over magnesium sulfate and was concentrated. Purification of the residue by flash column chromatography (35% ether–petroleum ether) afforded alcohol **61** as a colorless liquid (2.18 g, 95%). Chiral capillary GC analysis[59] of the corresponding acetate ester, prepared as described above for alcohol **59**, established that alcohol **61** was of 98% de.

^{1}H NMR (400 MHz, $CDCl_3$) δ:	7.1–7.4 (m, 5H, aromatic), 3.52 (dd, 1H, J_1 = 10.5 Hz, J_2 = 5.1 Hz, one of HOC**H**$_2$), 3.38 (dd, 1H, J_1 = 10.5 Hz, J_2 = 6.6 Hz, one of HOC**H**$_2$), 2.68 (dd, 1H, J_1 = 13.3 Hz, J_2 = 5.4 Hz, one of PhC**H**$_2$), 2.28 (dd, 1H, J_1 = 13.3 Hz, J_2 = 8.6 Hz, one of PhC**H**$_2$), 1.80 (m, 2H, H1, H4), 1.37 (dd, 1H, J_1 = 13.7 Hz, J_2 = 6.8 Hz, one of H3), 1.03 (dd, 1H, J_1 = 13.7 Hz, J_2 = 7.3 Hz, one of H3), 0.96 (d, 3H, J = 6.7 Hz, H2), 0.86 (d, 3H, J = 6.6 Hz, H5).
^{13}C NMR (100 MHz, $CDCl_3$) δ:	141.4, 129.2, 128.2, 125.8, 68.2, 43.4, 40.8, 33.3, 32.5, 20.2, 17.4.
FTIR (neat, cm^{-1}):	3346 (br, m, OH).
Analysis:	Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48; N, 0. Found: C, 80.93; H, 10.43; N, <0.05.
TLC (60% EtOAc–hexanes), R_f:	**61**: 0.64 (UV, PMA). **29**: 0.51 (UV, PMA).

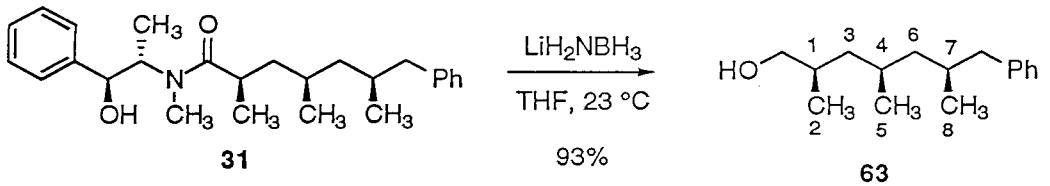


30 62

(2*S*,4*S*)-2,4-Dimethyl-5-phenylpentanol **62**

A solution of *n*-butyllithium in hexanes (2.33 M, 18.9 mL, 44.1 mmol, 3.90 equiv) was added to a solution of diisopropylamine (6.66 mL, 47.5 mmol, 4.20 equiv) in tetrahydrofuran (50 mL) at –78 °C. The resulting solution was stirred at –78 °C for 10 min, then was warmed to 0 °C and was held at that temperature for 10 min. Borane-ammonia complex (90%, 1.55 g, 45.3 mmol, 4.00 equiv) was added in one portion, and the suspension was stirred at 0 °C for 15 min, then was warmed to 23 °C. After 15 min, the suspension was cooled to 0 °C. A solution of amide **30** (4.00 g, 11.3 mmol, 1 equiv) in tetrahydrofuran (30 mL, followed by a 5-mL rinse) was added via cannula over 3 min. The reaction mixture was warmed to 23 °C and was held at that temperature for 2 h, then was cooled to 0 °C where excess hydride was quenched by the careful addition of 3 N aqueous hydrochloric acid solution (120 mL). After an aqueous work-up using the procedure described above for alcohol **61**, purification of the product by flash column chromatography (35% ether–petroleum ether) afforded alcohol **62** as a colorless liquid (2.10 g, 96%). Chiral capillary GC analysis[59] of the corresponding acetate ester, prepared as described above for alcohol **59**, established that alcohol **62** was of 98% de.

^{1}H NMR (400 MHz, C_6D_6) δ:	7.0–7.2 (m, 5H, aromatic), 3.13 (m, 2H, HOC**H**$_2$), 2.48 (dd, 1H, J_1 = 13.2 Hz, J_2 = 6.1 Hz, one of PhC**H**$_2$), 2.27 (dd, 1H, J_1 = 13.2 Hz, J_2 = 7.9 Hz, one of PhC**H**$_2$), 1.75 (m, 1H, H1), 1.52 (m, 1H, H4), 1.11 (m, 1H, one of H3), 0.99 (m, 1H, one of H3); 0.77 (d, 3H, J = 6.6 Hz, H2) , 0.73 (d, 3H, J = 6.6 Hz, H5).
^{13}C NMR (100 MHz, $CDCl_3$) δ:	141.4, 129.2, 128.2, 125.8, 69.1, 44.6, 40.3, 33.3, 32.2, 19.2, 16.2.
FTIR (neat, cm^{-1}):	3346 (br, m, OH).
Analysis:	Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48; N, 0. Found: C, 81.05; H, 10.53; N, <0.05.
TLC (60% EtOAc–hexanes), R_f:	**62**: 0.58 (UV, PMA). **30**: 0.41 (UV, PMA).

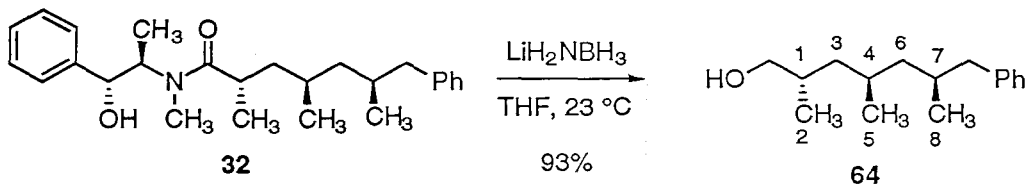


31 63

(2*R*,4*R*,6*S*)-2,4,6-Trimethyl-7-phenylheptanol **63**

A solution of *n*-butyllithium in hexanes (2.43 M, 3.54 mL, 8.60 mmol, 3.90 equiv) was added to a solution of diisopropylamine (1.30 mL, 9.28 mmol, 4.20 equiv) in tetrahydrofuran (7.5 mL) at –78 °C. The resulting solution was stirred at –78 °C for 10 min, then was warmed to 0 °C and was held at that temperature for 10 min. Borane-ammonia complex (90%, 303 mg, 8.82 mmol, 4.00 equiv) was added in one portion, and the suspension was stirred at 0 °C for 15 min, then was warmed to 23 °C. After 15 min, the suspension was cooled to 0 °C. A solution of amide **31** (0.872 g, 2.21 mmol, 1 equiv) in tetrahydrofuran (7.5 mL, followed by a 5-mL rinse) was added via cannula over 3 min. The reaction mixture was warmed to 23 °C and was held at that temperature for 2 h, then was cooled to 0 °C where excess hydride was quenched by the careful addition of 3 N aqueous hydrochloric acid solution (30 mL). The mixture was extracted with four 15-mL portions of ether. The combined organic extracts were washed sequentially with 3 N aqueous hydrochloric acid solution (7 mL), 2 N aqueous sodium hydroxide solution (7 mL), and brine (7 mL). The organic layer was dried over magnesium sulfate and was concentrated. Purification of the residue by flash column chromatography using silica gel packed with 35:63:2 ether–petroleum ether–triethylamine and eluted with 35% ether–petroleum ether afforded alcohol **63** as a colorless liquid (480 mg, 93%). Chiral capillary GC analysis[59] of the corresponding acetate ester, prepared as described above for alcohol **59**, established that alcohol **63** was of 99% de.

^{1}H NMR (400 MHz, $CDCl_3$) δ:	7.1–7.4 (m, 5H, aromatic), 3.52 (dd, 1H, J_1 = 10.5 Hz, J_2 = 5.1 Hz, one of HOC**H**$_2$), 3.37 (dd, 1H, J_1 = 10.5 Hz, J_2 = 6.6 Hz, one of HOC**H**$_2$), 2.70 (dd, 1H, J_1 = 13.2 Hz, J_2 = 5.1 Hz, one of PhC**H**$_2$), 2.23 (dd, 1H, J_1 = 13.2 Hz, J_2 = 8.8 Hz, one of PhC**H**$_2$), 1.81 (m, 1H, H1), 1.60–1.74 (m, 2H, H7, H4), 1.23–1.33 (m, 2H, H3), 0.88–1.14 (m, 2H, H6), 0.92 (d, 3H, J = 6.6 Hz, H2), 0.91 (d, 3H, J = 6.2 Hz, H5), 0.81 (d, 3H, J = 6.6 Hz, H8).
^{13}C NMR (100 MHz, $CDCl_3$) δ:	141.4, 129.1, 128.0, 125.5, 68.8, 45.3, 44.3, 41.4, 33.1, 32.2, 27.2, 19.3, 19.0, 16.4.
FTIR (neat, cm^{-1}):	3331 (br, m, OH).
Analysis:	Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18; N, 0.
	Found: C, 81.85; H, 11.35; N, <0.05.
TLC (40% EtOAc–hexanes), R_f:	**63**: 0.55 (UV, PMA).
	31: 0.33 (UV, PMA).
	tertiary amine by-product: 0.46 (UV, PMA).

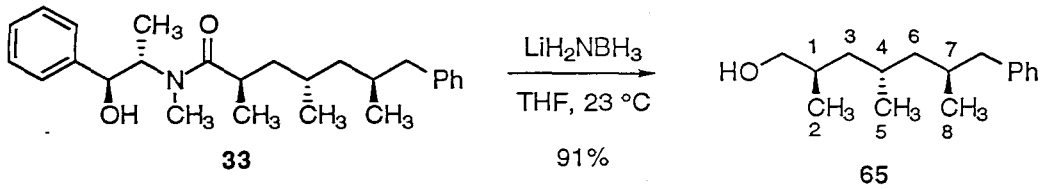


32 **64**

(2*S*,4*R*,6*S*)-2,4,6-Trimethyl-7-phenylheptanol **64**

A solution of *n*-butyllithium in hexanes (2.43 M, 3.61 mL, 8.77 mmol, 3.90 equiv) was added to a solution of diisopropylamine (1.32 mL, 9.44 mmol, 4.20 equiv) in tetrahydrofuran (7.5 mL) at –78 °C. The resulting solution was stirred at –78 °C for 10 min, then was warmed to 0 °C and was held at that temperature for 10 min. Borane-ammonia complex (90%, 308 mg, 8.99 mmol, 4.00 equiv) was added in one portion, and the suspension was stirred at 0 °C for 15 min, then was warmed to 23 °C. After 15 min, the suspension was cooled to 0 °C. A solution of amide **32** (889 mg, 2.25 mmol, 1 equiv) in tetrahydrofuran (7.5 mL, followed by a 5-mL rinse) was added via cannula over 3 min. The reaction mixture was warmed to 23 °C and was held at that temperature for 2 h, then was cooled to 0 °C where excess hydride was quenched by the careful addition of 3 N aqueous hydrochloric acid solution (30 mL). After an aqueous work-up using the procedure described above for alcohol **63**, purification of the product by flash column chromatography using silica gel packed with 38:60:2 ether–petroleum ether–triethylamine and eluted with 38% ether–petroleum ether afforded alcohol **64** as a colorless liquid (488 mg, 93%). Chiral capillary GC analysis[59] of the corresponding acetate ester, prepared as described above for alcohol **59**, established that alcohol **64** was of 97% de.

^{1}H NMR (400 MHz, $CDCl_3$) δ:	7.1–7.4 (m, 5H, aromatic), 3.43 (dd, 1H, J_1 = 10.5 Hz, J_2 = 5.9 Hz, one of HOC**H**$_2$), 3.37 (dd, 1H, J_1 = 10.5 Hz, J_2 = 6.6 Hz, one of HOC**H**$_2$); 2.65 (dd, 1H, J_1 = 13.2 Hz, J_2 = 5.5 Hz, one of PhC**H**$_2$), 2.28 (dd, 1H, J_1 = 13.2 Hz, J_2 = 8.8 Hz, one of PhC**H**$_2$), 1.82 (m, 1H, H1), 1.55–1.75 (m, 2H, H7, H4), 1.25 (m, 1H, one of H3), 1.00–1.12 (m, 3H, one of H3, H6), 0.87 (d, 3H, J = 7.0 Hz, H2), 0.86 (d, 3H, J = 6.6 Hz, H5), 0.81 (d, 3H, J = 6.6 Hz, H8).
^{13}C NMR (100 MHz, $CDCl_3$) δ:	141.4, 129.1, 128.0, 125.5, 69.1, 45.7, 43.7, 40.1, 33.1, 32.2, 27.2, 20.0, 19.8, 16.1.
FTIR (neat, cm^{-1}):	3332 (br, m, OH).
Analysis:	Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18; N, 0.
	Found: C, 81.74; H, 11.34; N, <0.05.
TLC (40% EtOAc–hexanes), R_f:	**64**: 0.53 (UV, PMA).
	32: 0.33 (UV, PMA).
	tertiary amine by-product: 0.43 (UV, PMA).

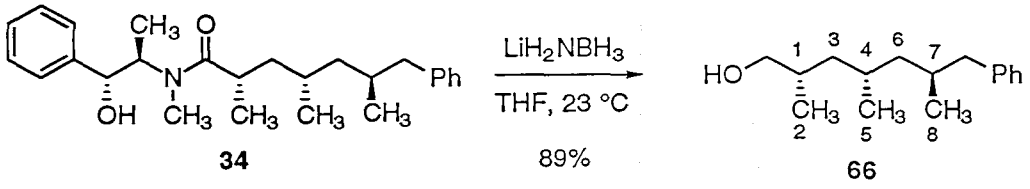


33 65

(2*R*,4*S*,6*S*)-2,4,6-Trimethyl-7-phenylheptanol **65**

A solution of *n*-butyllithium in hexanes (2.43 M, 3.49 mL, 8.49 mmol, 3.90 equiv) was added to a solution of diisopropylamine (1.28 mL, 9.14 mmol, 4.20 equiv) in tetrahydrofuran (7.5 mL) at –78 °C. The resulting solution was stirred at –78 °C for 10 min, then was warmed to 0 °C and was held at that temperature for 10 min. Borane-ammonia complex (90%, 299 mg, 8.71 mmol, 4.00 equiv) was added in one portion, and the suspension was stirred at 0 °C for 15 min, then was warmed to 23 °C. After 15 min, the suspension was cooled to 0 °C. A solution of amide **33** (861 mg, 2.18 mmol, 1 equiv) in tetrahydrofuran (7.5 mL, followed by a 5-mL rinse) was added via cannula over 3 min. The reaction mixture was warmed to 23 °C and was held at that temperature for 2 h, then was cooled to 0 °C where excess hydride was quenched by the careful addition of 3 N aqueous hydrochloric acid solution (30 mL). After an aqueous work-up using the procedure described above for alcohol **63**, purification of the product by flash column chromatography using silica gel packed with 35:63:2 ether–petroleum ether–triethylamine and eluted with 35% ether–petroleum ether afforded alcohol **65** as a colorless liquid (463 mg, 91%). Chiral capillary GC analysis[59] of the corresponding acetate ester, prepared as described above for alcohol **59**, established that alcohol **65** was of 97% de.

^{1}H NMR (400 MHz, $CDCl_3$) δ:	7.1–7.4 (m, 5H, aromatic), 3.48 (dd, 1H, J_1 = 12.0 Hz, J_2 = 6.2 Hz, one of HOC**H**$_2$), 3.42 (dd, 1H, J_1 = 12.0 Hz, J_2 = 6.6 Hz, one of HOC**H**$_2$), 2.59 (dd, 1H, J_1 = 13.4 Hz, J_2 = 6.2 Hz, one of PhC**H**$_2$), 2.36 (dd, 1H, J_1 = 13.4 Hz, J_2 = 8.1 Hz, one of PhC**H**$_2$), 1.84 (m, 1H, H1), 1.72 (m, 1H, H7), 1.61 (m, 1H, H4), 1.24 (m, 1H, one of H3), 1.02–1.18 (m, 3H, one of H3, H6), 0.90 (d, 3H, J = 6.6 Hz, H2), 0.82 (d, 3H, J = 6.6 Hz, H5), 0.79 (d, 3H, J = 6.6 Hz, H8).
^{13}C NMR (100 MHz, $CDCl_3$) δ:	141.4, 129.1, 128.0, 125.5, 68.8, 45.3, 44.3, 41.4, 33.1, 32.2, 27.2, 19.2, 19.0, 16.3.
FTIR (neat, cm^{-1}):	3332 (br, m, OH).
Analysis:	Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18; N, 0.
	Found: C, 82.03; H, 11.23; N, <0.05.
TLC (50% EtOAc–hexanes), R_f:	**65**: 0.58 (UV, PMA).
	33: 0.40 (UV, PMA).
	tertiary amine by-product: 0.49 (UV, PMA).

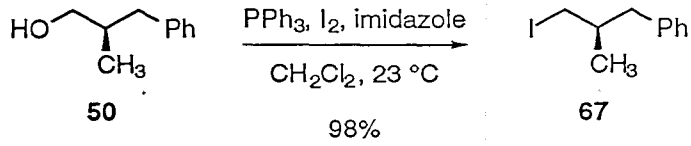


34 **66**

(2*S*,4*S*,6*S*)-2,4,6-Trimethyl-7-phenylheptanol **66**

A solution of *n*-butyllithium in hexanes (2.43 M, 3.58 mL, 8.70 mmol, 3.90 equiv) was added to a solution of diisopropylamine (1.31 mL, 9.35 mmol, 4.20 equiv) in tetrahydrofuran (7.5 mL) at –78 °C. The resulting solution was stirred at –78 °C for 10 min, then was warmed to 0 °C and was held at that temperature for 10 min. Borane-ammonia complex (90%, 303 mg, 8.82 mmol, 4.00 equiv) was added in one portion, and the suspension was stirred at 0 °C for 15 min, then was warmed to 23 °C. After 15 min, the suspension was cooled to 0 °C. A solution of amide **34** (872 mg, 2.21 mmol, 1 equiv) in tetrahydrofuran (7.5 mL, followed by a 5-mL rinse) was added via cannula over 3 min. The reaction mixture was warmed to 23 °C and was held at that temperature for 2 h, then was cooled to 0 °C where excess hydride was quenched by the careful addition of 3 N aqueous hydrochloric acid solution (30 mL). After an aqueous work-up using the procedure described above for alcohol **63**, purification of the product by flash column chromatography using silica gel packed with 35:63:2 ether–petroleum ether–triethylamine and eluted with 35% ether–petroleum ether afforded alcohol **66** as a colorless liquid (467 mg, 89%). Chiral capillary GC analysis[59] of the corresponding acetate ester, prepared as described above for alcohol **59**, established that alcohol **66** was of 99% de.

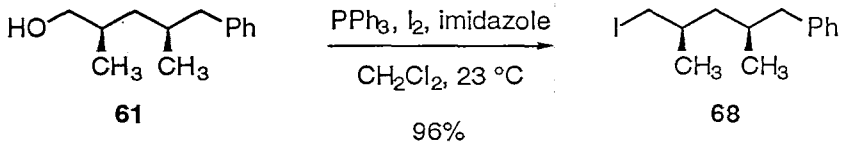
^{1}H NMR (400 MHz, $CDCl_3$) δ:	7.1–7.4 (m, 5H, aromatic), 3.51 (dd, 1H, J_1 = 11.7 Hz, J_2 = 5.1 Hz, one of HOC**H**$_2$), 3.38 (dd, 1H, J_1 = 11.7 Hz, J_2 = 7.0 Hz, one of HOC**H**$_2$), 2.56 (dd, 1H, J_1 = 13.2 Hz, J_2 = 6.2 Hz, one of PhC**H**$_2$), 2.39 (dd, 1H, J_1 = 13.2 Hz, J_2 = 8.1 Hz, one of PhC**H**$_2$), 1.82 (m, 1H, H1), 1.73 (m, 1H, H7), 1.61 (m, 1H, H4), 1.24 (m, 1H, one of H3), 1.13 (m, 1H, one of H3), 1.06 (m, 1H, one of H6), 0.98 (m, 1H, one of H6), 0.91 (d, 3H, J = 6.6 Hz, H2), 0.83 (d, 3H, J = 7.3 Hz, H5), 0.82 (d, 3H, J = 7.5 Hz, H8).
^{13}C NMR (100 MHz, $CDCl_3$) δ:	141.5, 129.1, 128.0, 125.6, 68.4, 44.7, 44.0, 41.8, 33.0, 32.3, 27.4, 20.1, 19.1, 17.1.
FTIR (neat, cm^{-1}):	3345 (br, m, OH).
Analysis:	Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18; N, 0.
	Found: C, 81.71; H, 11.39; N, <0.05.
TLC (40% EtOAc–hexanes), R_f:	**66**: 0.55 (UV, PMA).
	34: 0.34 (UV, PMA).
	tertiary amine by-product: 0.45 (UV, PMA).



(*R*)-1-Iodo-2-methyl-3-phenylpropane **67**

Imidazole (6.86 g, 101 mmol, 1.50 equiv) and iodine (23.0 g, 90.7 mmol, 1.35 equiv) were added sequentially to a solution of triphenylphosphine (21.1 g, 80.6 mmol, 1.20 equiv) in dichloromethane (250 mL) at 23 °C. A solution of alcohol **50** (10.1 g, 67.2 mmol, 1 equiv) in dichloromethane (30 mL) was added to the resulting fine suspension via cannula. After 2 h, dichloromethane was removed in vacuo. The solid residue was suspended in a minimal amount of dichloromethane (30 mL), and the suspension was loaded onto a column of silica gel eluting with 10% ether–petroleum ether to afford the iodide **67** as a colorless liquid (17.1 g, 98%).

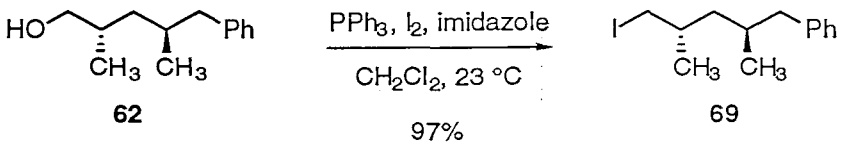
^{1}H NMR (400 MHz, C_6D_6) δ:	6.9–7.2 (m, 5H, aromatic), 2.73 (dd, 1H, J_1 = 9.7 Hz, J_2 = 4.9 Hz, one of ICH_2), 2.70 (dd, 1H, J_1 = 9.7 Hz, J_2 = 5.5 Hz, one of ICH_2), 2.43 (dd, 1H, J_1 = 13.5 Hz, J_2 = 7.0 Hz, one of $PhCH_2$), 2.18 (dd, 1H, J_1 = 13.5 Hz, J_2 = 7.1 Hz, one of $PhCH_2$), 1.33 (m, 1H, CH_3CH), 0.72 (d, 3H, J = 6.8 Hz, CH_3).
^{13}C NMR (100 MHz, $CDCl_3$) δ:	140.8, 129.0, 128.3, 126.2, 42.5, 36.7, 20.7, 17.0.
FTIR (neat, cm^{-1}):	2958 (s), 1494 (s), 1453 (s), 1194 (s).
HRMS (EI):	Calcd for $C_{10}H_{13}I$ $(M)^+$: 260.0062.
	Found: 260.0057.
Analysis:	Calcd for $C_{10}H_{13}I$: C, 46.18; H, 5.04.
	Found: C, 46.34, H, 5.20.
TLC (40% EtOAc–hexanes), R_f:	**67**: 0.69 (UV, PMA).
	50: 0.38 (UV, PMA).



(2*R*,4*S*)-1-Iodo-2,4-dimethyl-5-phenylpentane **68**

Imidazole (1.08 g, 15.8 mmol, 1.60 equiv) and iodine (3.51 g, 13.8 mmol, 1.40 equiv) were added sequentially to a solution of triphenylphosphine (3.11 g, 11.9 mmol, 1.20 equiv) in dichloromethane (50 mL) at 23 °C. A solution of alcohol **61** (1.90 g, 9.88 mmol, 1 equiv) in dichloromethane (5 mL, followed by a 4-mL rinse) was added to the resulting fine suspension via cannula. After 4 h, dichloromethane was removed in vacuo. The solid residue was suspended in a minimal amount of dichloromethane (5 mL), and the suspension was loaded onto a column of silica gel eluting with 10% ether–petroleum ether. The combined fractions containing the iodide **68** were washed with saturated aqueous sodium thiosulfate solution (10 mL), then were dried over sodium sulfate and were concentrated to afford the iodide **68** as a clear red liquid (2.87 g, 96%).

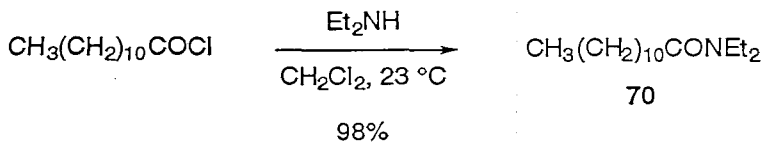
^{1}H NMR (400 MHz, $CDCl_3$) δ:	7.1–7.4 (m, 5H, aromatic), 3.24 (dd, 1H, J_1 = 9.6 Hz, J_2 = 4.0 Hz, one of ICH_2), 3.11 (dd, 1H, J_1 = 9.6 Hz, J_2 = 6.0 Hz, one of ICH_2), 2.66 (dd, 1H, J_1 = 13.3 Hz, J_2 = 5.7 Hz, one of $PhCH_2$), 2.32 (dd, 1H, J_1 = 13.3 Hz, J_2 = 8.5 Hz, one of $PhCH_2$), 1.77 (m, 1H, ICH_2CH), 1.54 (m, 1H, $PhCH_2CH$), 1.37 (m, 1H, one of $PhCH_2CHCH_2$), 1.10 (m, 1H, one of $PhCH_2CHCH_2$), 0.99 (d, 3H, J = 6.5 Hz, ICH_2CHCH_3), 0.85 (d, 3H, J = 6.6 Hz, $PhCH_2CHCH_3$).
^{13}C NMR (100 MHz, $CDCl_3$) δ:	140.9, 129.2, 128.1, 125.7, 43.8, 43.5, 32.3, 31.9, 21.4, 19.5, 17.7.
FTIR (neat, cm^{-1}):	2957 (s), 1494 (s), 1454 (s).
HRMS (FAB):	Calcd for $C_{13}H_{19}I$ $(M)^+$: 302.0533.
	Found: 302.0520.
Analysis:	Calcd for $C_{13}H_{19}I$: C, 51.67; H, 6.34.
	Found: C, 51.69, H, 6.44.
TLC (40% EtOAc–hexanes), R_f:	**68**: 0.74 (UV, PMA).
	61: 0.46 (UV, PMA).



(2*S*,4*S*)-1-Iodo-2,4-dimethyl-5-phenylpentane **69**

Imidazole (975 mg, 14.3 mmol, 1.45 equiv) and iodine (3.26 g, 12.8 mmol, 1.30 equiv) were added sequentially to a solution of triphenylphosphine (2.98 g, 11.4 mmol, 1.15 equiv) in dichloromethane (50 mL) at 23 °C. A solution of alcohol **62** (1.90 g, 9.88 mmol, 1 equiv) in dichloromethane (5 mL, followed by two 2.5-mL rinses) was added to the resulting fine suspension via cannula. After 3.2 h, dichloromethane was removed in vacuo. The solid residue was suspended in a minimal amount of dichloromethane (5 mL), and the suspension was loaded onto a column of silica gel eluting with 10% ether–petroleum ether. The combined fractions containing the iodide **69** were washed with saturated aqueous sodium thiosulfate solution (10 mL), then were dried over sodium sulfate and were concentrated to afford the iodide **69** as a clear red liquid (2.90 g, 97%).

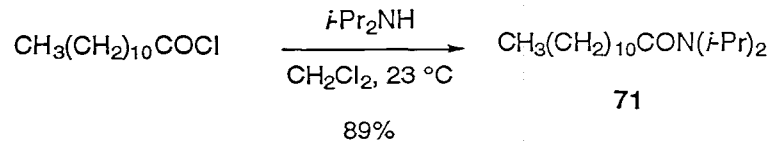
^{1}H NMR (400 MHz, $CDCl_3$) δ:	7.1–7.4 (m, 5H, aromatic), 3.19 (dd, 1H, J_1 = 9.5 Hz, J_2 = 5.1 Hz, one of CH_2I), 3.12 (dd, 1H, J_1 = 9.5 Hz, J_2 = 6.2 Hz, one of CH_2I), 2.61 (dd, 1H, J_1 = 13.4 Hz, J_2 = 6.1 Hz, one of $PhCH_2$), 2.40 (dd, 1H, J_1 = 13.4 Hz, J_2 = 8.1 Hz, one of $PhCH_2$), 1.78 (m, 1H, ICH_2CH), 1.62 (m, 1H, $PhCH_2CH$), 1.20–1.27 (m, 2H, $PhCH_2CHCH_2$), 0.93 (d, 3H, J = 6.5 Hz, ICH_2CHCH_3), 0.84 (d, 3H, J = 6.6 Hz, $PhCH_2CHCH_3$).
^{13}C NMR (100 MHz, $CDCl_3$) δ:	141.0, 129.1, 128.1, 125.7, 44.1, 43.8, 32.54, 32.45, 20.1, 19.2, 18.1.
FTIR (neat, cm^{-1}):	2979 (s), 2957 (s), 2918 (s), 1494 (s), 1454 (s), 1378 (s); 742 (s).
HRMS (FAB):	Calcd for $C_{13}H_{20}I$ $(MH)^+$: 303.0610. Found: 303.0601.
Analysis:	Calcd for $C_{13}H_{19}I$: C, 51.67; H, 6.34. Found: C, 51.67, H, 6.46.
TLC (40% EtOAc–hexanes), R_f:	**69**: 0.77 (UV, PMA). **62**: 0.51 (UV, PMA).



N,*N*-Diethyldodecanamide **70**

Diethylamine (5.30 mL, 51.3 mmol, 2.50 equiv) was added quickly in 1-mL portions to a well-stirred solution of dodecanoyl chloride (4.49 g, 20.5 mmol, 1 equiv) in dichloromethane (120 mL) at 23 °C. After stirring for 10 h at 23 °C, the reaction mixture was diluted with dichloromethane (300 mL), and the solution was extracted sequentially with 1 N aqueous sodium hydroxide solution (2 × 50 mL) and 1 N aqueous hydrochloric acid solution (2 × 50 mL). The organic layer was dried over sodium sulfate and was concentrated. Purification of the residue by flash column chromatography (40% ethyl acetate–hexanes) afforded amide **70** as a colorless oil (5.15 g, 98%).

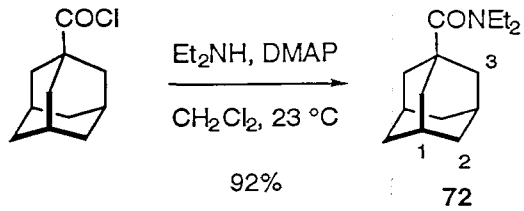
^{1}H NMR (300 MHz, $CDCl_3$) δ:	3.27–3.41 (m, 4H, NCH_2CH_3), 2.28 (t, 2H, J = 7.7 Hz, CH_2CO), 1.26–1.84 [m, 18H, $(CH_2)_9CH_2CO$], 1.17 (t, 3H, J = 7.1 Hz, one of NCH_2CH_3), 1.11 (t, 3H, J = 7.1 Hz, one of NCH_2CH_3), 0.88 [t, 3H, J = 6.6 Hz, $CH_3(CH_2)_9$].
FTIR (neat, cm^{-1}):	2924 (s), 2853 (m), 1644 (s, C=O), 1462 (m), 1427 (m).
HRMS (FAB):	Calcd for $C_{16}H_{34}NO$ $(MH)^+$: 256.2640. Found: 256.2644.
TLC (50% EtOAc–hexanes) R_f:	**70**: 0.45 (PMA).



N,*N*-Diisopropyldodecanamide **71**

Diisopropylamine (7.22 mL, 51.5 mmol, 2.50 equiv) was added quickly in 1-mL portions to a well-stirred solution of dodecanoyl chloride (4.51 g, 20.6 mmol, 1 equiv) in dichloromethane (100 mL) at 23 °C. After stirring for 10 h at 23 °C, the reaction mixture was diluted with dichloromethane (300 mL), and the mixture was extracted successively with 1 N aqueous sodium hydroxide solution (2 × 50 mL) and 1 N aqueous hydrochloric acid solution (2 × 50 mL). The organic layer was dried over sodium sulfate and was concentrated. Purification of the residue by flash column chromatography (15% ethyl acetate–hexanes) afforded amide **71** as a colorless oil (5.16 g, 89%).

^{1}H NMR (300 MHz, $CDCl_3$) δ:	3.97 (sp, 1H, J = 6.7 Hz, one of NC**H**, 3.47 (br, 1H, one of NC**H**), 2.27 (t, 2H, J = 7.7 Hz, CH_2CO), 1.36–1.81 [m, 18H, $(CH_2)_9CH_2CO$], 1.27 [d, 6H, J = 10.6 Hz, one of $CH(CH_3)_2$], 1.19 [d, 6H, J = 6.7 Hz, one of $CH(CH_3)_2$], 0.88 (t, 3H, J = 6.6 Hz, CH_3CH_2).
FTIR (neat, cm^{-1}):	3002 (m), 2962 (s), 2925 (s), 2854 (s), 1646 (s), 1463 (m), 1440 (m), 1369 (m), 1336 (m), 1304 (m), 1216 (m), 1135 (m), 1044 (m).
HRMS (FAB)	Calcd for $C_{18}H_{38}NO$ $(MH)^+$: 284.2953. Found: 284.953.
TLC (50% EtOAc–hexanes) R_f:	**71**: 0.66 (PMA).

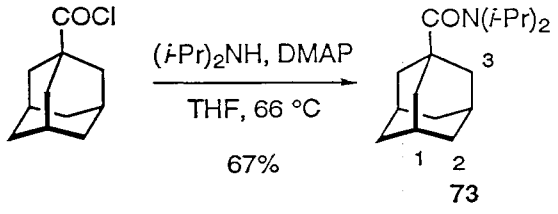


72

1-Adamantanecarboxylic Acid *N*,*N*-Diethylamide **72**

Diethylamine (1.55 mL, 15.0 mmol, 3.00 equiv) was added to a well-stirred solution of 1-adamantanecarbonyl chloride (0.990 g, 4.98 mmol, 1 equiv) and 4-dimethylaminopyridine (18.0 mg, 0.149 mmol, 0.03 equiv) in dichloromethane (20 mL) at 0 °C. The reaction mixture was warmed to 23 °C and held at that temperature for 2.5 h. Excess anhydride was quenched by the addition of 0.5 N aqueous sodium hydroxide solution (10 mL). The mixture was diluted with dichloromethane (200 mL) and the resulting mixture was extracted sequentially with 0.5 N aqueous sodium hydroxide solution (3 × 25 mL) and 3 N aqueous hydrochloric acid solution (3 × 25 mL). The organic layer was dried over sodium sulfate and was concentrated. Purification of the residue by flash column chromatography (32% ethyl acetate–hexanes) afforded amide **72** as a white solid (1.07 g, 92%): mp: 61–63 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ:	3.42 (m, 4H, NCH_2CH_3), 2.04 (s, 3H, H1), 2.00 (s, 6H, H3), 1.72 (s, 6H, H2), 1.13 (t, 6H, $J = 7.6$ Hz, NCH_2CH_3).
FTIR (neat, cm^{-1}):	2970 (m), 2904 (s), 2850 (m), 1621 (s, C=O), 1614 (s, C=O), 1454 (m), 1446 (m), 1409 (m), 1282 (m), 1250 (m), 1061 (m).
HRMS (FAB)	Calcd for $C_{15}H_{26}NO$ $(MH)^+$: 236.2014. Found: 236.2007.
TLC (50% EtOAc–hexanes) R_f:	**72**: 0.51 (PMA). 1-adamantanecarboxylic acid: 0.38 (PMA).

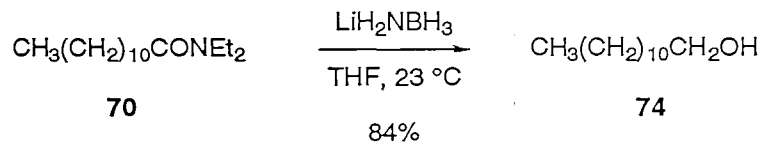


73

1-Adamantanecarboxylic Acid *N*,*N*-Diisopropylamide **73**

Diisopropylamine (1.58 mL, 11.3 mmol, 3.00 equiv) was added to a solution of 1-adamantanecarbonyl chloride (750 mg, 3.78 mmol, 1 equiv) and 4-dimethylaminopyridine (14 mg, 0.11 mmol, 0.03 equiv) in tetrahydrofuran (9 mL) at 23 °C. The mixture was heated to reflux and held at that state for 24 h. The reaction mixture was cooled to 23 °C, and unreacted acid chloride was quenched by the addition of 1 N aqueous sodium hydroxide solution (5 mL). The mixture was partitioned between dichloromethane (150 mL) and 1 N aqueous sodium hydroxide solution (50 mL). The organic layer was separated and extracted with 3 N aqueous hydrochloric acid solution (3 × 25 mL), then was dried over sodium sulfate and was concentrated. Purification of the residue by flash column chromatography (10% ethyl acetate–hexanes) afforded amide **73** as a white solid (666 mg, 67%): mp 149-152 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ:	4.54 [br, s, 1H, C**H**$(CH_3)_2$], 3.24 [br, s, 1H, C**H**$(CH_3)_2$], 2.03 (s, 3H, H1), 1.98 (s, 6H, H3), 1.71 (s, 6H, H2), 1.36 (br, s, 6H, two C**H**$_3$ groups), 1.20 (br, s, 6H, two C**H**$_3$ groups).
FTIR (neat, cm^{-1}):	2961 (m), 2910 (m), 2848 (m), 1609 (s, C=O), 1438 (m), 1369 (m), 1325 (m), 1301 (m), 1210 (m), 1026 (m).
HRMS (FAB):	Calcd for $C_{17}H_{30}NO$ $(MH)^+$: 264.2327. Found: 264.2328.
TLC (40% EtOAc–hexanes) R_f:	**73**: 0.49 (PMA). 1-adamantanecarboxylic acid: 0.35 (PMA).

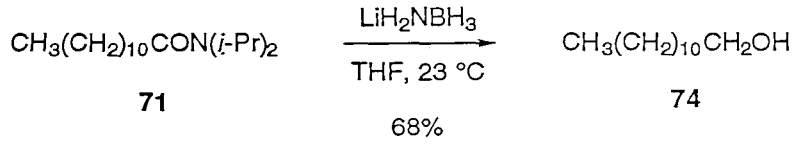


70 84% **74**

1-Dodecanol **74**

A solution of *n*-butyllithium in hexanes (2.37 M, 0.681 mL, 1.61 mmol, 4.00 equiv) was added to an ice-cooled suspension of borane-ammonia complex (90%, 0.0580 g, 1.69 mmol, 4.20 equiv) in tetrahydrofuran (1.5 mL). The resulting suspension was warmed briefly to 23 °C, then was cooled to 0 °C. A solution of amide **70** (103 mg, 0.403 mmol, 1 equiv) in tetrahydrofuran (1.5 mL, followed by a 0.5-mL rinse) was added via cannula. The reaction mixture was warmed to 23 °C and held at that temperature for 1.3 h. Excess hydride was quenched by the dropwise addition of 1 N aqueous hydrochloric acid solution (3 mL) at 0 °C. The mixture was partitioned between 1 N aqueous hydrochloric acid solution (50 mL) and ether (15 mL). The aqueous layer was separated and extracted with three 15-mL portions of ether. The combined organic extracts were washed with 1 N aqueous hydrochloric acid solution (5 mL) and were concentrated. The residue was stirred in 1 N aqueous sodium hydroxide solution (50 mL) for 20 min, and the mixture was extracted with ether (20 mL). The aqueous layer was separated, then was saturated with sodium chloride and was extracted with ether (2 × 20 mL). The combined ether extracts were washed sequentially with 1 N aqueous hydrochloric acid solution (5 mL) and brine (5 mL), then were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ether-petroleum ether (30 → 40%) afforded alcohol **74** as a low-melting solid (70.7 mg, 94%): mp 24-26 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ:	3.62 (t, 3H, J = 6.6 Hz, $HOCH_2$), 1.58 (m, 2H, $HOCH_2CH_2$), 1.25 [m, 18H, $(CH_2)_9CH_2CH_2OH$], 0.86 (m, 3H, CH_3).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	63.0, 32.8, 31.9, 29.6, 29.4, 29.3, 25.7, 22.7, 14.1.
FTIR (neat, cm^{-1}):	3332 (br, m, OH), 2922 (s), 2853 (s), 1464 (m), 1057 (m).
TLC (50% EtOAc–hexanes) R_f:	**74**: 0.53 (PMA).
	70: 0.49 (PMA).



71 68% **74**

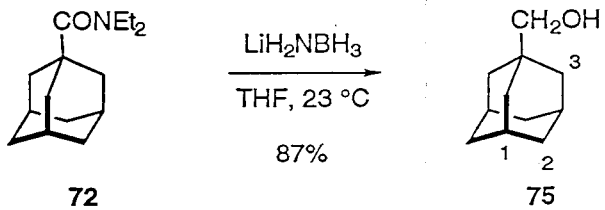
1-Dodecanol **74**

A solution of *n*-butyllithium in hexanes (2.47 M, 1.84 mL, 4.55 mmol, 4.00 equiv) was added to a suspension of borane-ammonia complex (90%, 0.160 g, 4.66 mmol, 4.10 equiv) in tetrahydrofuran (5 mL) at 0 °C. The suspension was warmed briefly to 23 °C, then was cooled to 0 °C. A solution of amide **71** (322 mg, 1.14 mmol, 1 equiv) in tetrahydrofuran (2 mL, followed by a 1.5-mL rinse) was added via cannula. The reaction mixture was warmed to 23 °C and held at that temperature for 6 h. Excess hydride was quenched at 0 °C by the dropwise addition of 3 N aqueous hydrochloric acid solution (3 mL). The mixture was partitioned between 1 N aqueous hydrochloric acid solution (9 mL) and ether (15 mL). The aqueous layer was separated and extracted with three 15-mL portions of ether. The combined organic extracts were washed with 1 N aqueous hydrochloric acid solution (5 mL) and were concentrated. The residue was stirred in 1 N aqueous sodium hydroxide solution (60 mL) for 1 h, and the mixture was extracted with ether (20 mL). The aqueous layer was separated and saturated with sodium chloride, then was extracted with ether (3 × 20 mL). The combined ether extracts were washed sequentially with 1 N aqueous hydrochloric acid solution (5 mL) and brine (5 mL), then were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (35:65:2 ether-petroleum ether-triethylamine) afforded alcohol **74** as a low-melting solid (143 mg, 68%): mp 24–26 °C. Spectroscopic data were identical to those listed above.

TLC (50% EtOAc–hexanes) R_f: **74**: 0.58 (PMA).

71: 0.70 (PMA).

tertiary amine by-product: 0.25 (PMA).

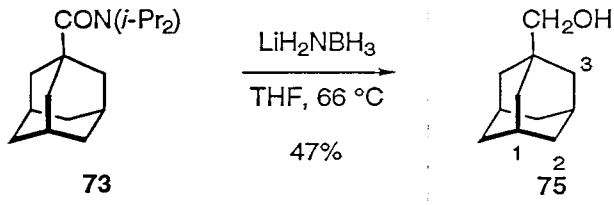


72 **75**

1-Adamantanemethanol **75**

A solution of *n*-butyllithium in hexanes (2.34 M, 1.41 mL, 3.30 mmol, 3.90 equiv) was added to solution of diisopropylamine (0.498 mL, 3.55 mmol, 4.20 equiv) in tetrahydrofuran (3 mL) at –78 °C. The resulting solution was stirred at –78 °C for 10 min, then was warmed to 0 °C and held at that temperature for 5 min. Borane-ammonia complex (90%, 116 mg, 3.38 mmol, 4.00 equiv) was added in one portion, and the suspension was stirred at 0 °C for 20 min, then was warmed to 23 °C. After 20 min, the suspension was cooled to 0 °C, and a solution of amide **72** (199 mg, 0.845 mmol, 1 equiv) in tetrahydrofuran (3 mL, followed by a 0.5-mL rinse) was added via cannula. The reaction mixture was warmed to 23 °C and held at that temperature for 16 h, then excess hydride was quenched by the addition of 3 N aqueous hydrochloric acid solution (10 mL). The mixture was extracted with four 9-mL portions of ether. The combined ether fractions were washed sequentially with 3 N aqueous hydrochloric acid solution (3 mL) and brine (3 mL), then were dried over magnesium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ether-petroleum ether (30 → 40%) afforded alcohol **75** as a crystalline solid (122 mg, 87%): mp 114–115 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ:	3.20 (d, 2H, J = 6.2 Hz, CH_2OH), 2.00 (m, 3H, H1), 1.69 (m. 6H, H3), 1.51 (d, 6H, J = 2.3 Hz, H2), 1.24 (t, 1H, J = 6.2 Hz, OH).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	73.6, 38.9, 37.1, 34.4, 28.1.
FTIR (neat, cm^{-1})	3216 (br, m, OH), 2896 (s), 2844 (m), 1052 (m).
Analysis:	Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91.
	Found: C, 79.61; H, 10.85.
TLC (3.5% MeOH–CH_2Cl_2) R_f:	**75**: 0.50 (PMA).
	72: 0.56 (PMA).



73 75

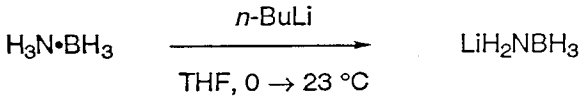
1-Adamantanemethanol **75**

A solution of *n*-butyllithium in hexanes (2.47 M, 0.970 mL, 2.39 mmol, 4.00 equiv) was added to a suspension of borane-ammonia complex (90%, 86 mg, 2.51 mmol, 4.20 equiv) in tetrahydrofuran (2 mL) at 0 °C. The resulting suspension was warmed briefly to 23 °C, then was cooled to 0 °C. A solution of the amide **73** (158 mg, 0.598 mmol, 1 equiv) in tetrahydrofuran (1 mL, followed by a 1-mL rinse) was added via cannula. The reaction mixture was heated to reflux and held at that state for 1.7 h. The reaction mixture was cooled to 0 °C and excess hydride was quenched by the dropwise addition of 1 N aqueous hydrochloric acid solution (3 mL). The mixture was partitioned between brine (50 mL) and ether (20 mL). The aqueous layer was separated and extracted with three 20-mL portions of ether. The combined organic extracts were washed with 1 N aqueous hydrochloric acid solution (5 mL), then were concentrated. The residue was stirred in 2 N aqueous sodium hydroxide solution (50 mL) for 30 min, and the mixture was extracted with ether (20 mL). The aqueous layer was separated and saturated with sodium chloride, then was extracted with ether (2 × 20 mL). The combined ether extracts were washed sequentially with 1 N aqueous hydrochloric acid solution (5 mL) and brine (5 mL), then were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ether-petroleum ether (25 → 40%) afforded alcohol **75** as a white solid (47.2 mg, 47%) with the same melting point and spectroscopic data as those listed above.

TLC (40% EtOAc–hexanes) R_f: **75**: 0.42 (PMA).

73: 0.59 (PMA).

tertiary amine by-product: 0.71 (PMA).



Lithium Amidotrihydroborate

Borane-ammonia complex (90%, 9.60 mg, 0.311 mmol, 1 equiv) was suspended in tetrahydrofuran (1 mL). The solution was cooled to 0 °C, and a solution of *n*-butyllithium in hexanes (2.49 M, 0.125 mL, 0.311 mmol, 1 equiv) was added via syringe. The mixture was stirred at 0 °C for 3 min, at 23 °C for 3 min, then was cooled to 0 °C. Organic solvents were removed under vacuum (0.5 mm Hg) for 1 h, and the residue was suspended in THF-d_8. The cloudy suspension was transferred into an NMR tube.

^{11}B NMR (32 MHz, THF-d_8, $B(OMe)_3$ reference) δ: –40.5 (LiH_2NBH_3).

^{11}B NMR (32 MHz, THF-d_8, BF_3•OEt_2 reference) δ: –22.2 (LiH_2NBH_3).

$$H_3N{\bullet}BH_3 \xrightarrow[THF,\ 0 \rightarrow 23\ ^\circ C]{(CH_3)_3CCH_2Li} LiH_2NBH_3 + C(CH_3)_4$$

Lithium Amidotrihydroborate

Neopentyllithium (21.4 mg, 0.274 mmol, 0.950 equiv) was transferred under a nitrogen atmosphere to a suspension of borane-ammonia complex (90%, 9.9 mg, 0.29 mmol, 1 equiv) in THF-d_8 (850 μL) at 23 °C. The resulting clear solution was transferred into an NMR tube.

^{11}B NMR (32 MHz, THF-d_8, $B(OMe)_3$ reference) δ:	–40.5 (LiH_2NBH_3).
^{11}B NMR (32 MHz, THF-d_8, $BF_3{\bullet}OEt_2$ reference) δ:	–22.2 (LiH_2NBH_3).
^{13}C NMR (100 MHz, THF-d_8) δ:	31.6 (CH_3).

Chapter 4

Reduction of Pseudoephedrine Amides to Form Highly Enantiomerically Enriched Aldehydes

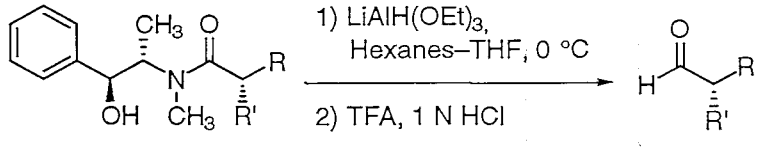
Introduction

The direct conversion of alkylated carboxylic acid equivalents to highly enantiomerically enriched α-substituted aldehydes is a valuable transformation in organic synthesis. Although there are isolated instances in the literature where such a transformation could be carried out in a single step,[60] there was at the time of our initial report no general procedure for the direct conversion of an alkylation product to the corresponding aldehyde.[61]

Reduction of Pseudoephedrine Amides to Form Aldehydes

Pseudoephedrine amides can be converted directly to highly enantiomerically enriched aldehydes using Brown and Tsukamoto's lithium triethoxyaluminum hydride reagent.[62] This reagent is produced in situ from the reaction of 1 molar equivalent of lithium aluminum hydride with 1.5 molar equivalents of ethyl acetate and affords aldehydes of 90–98% ee (75–82% yield, Table 10) from the corresponding pseudoephedrine amides.

Table 10. Reduction of Pseudoephedrine Amides with $LiAlH(OEt)_3$ to Form Aldehydes



entry	substrate[a]	R	R'	prod	time (h)	isol yield (%)	isol ee (%)
1	**11**	CH_3	Bn	**76**	1.0	76	95
2	**12**	CH_3	*n*-Bu	**77**	1.1	75[b]	98
3	**16**	Bn	CH_3	**78**	1.2	77	94
4	**17**	Bn	*n*-Bu	**79**	1.0	80	97
5	**19**	*n*-Bu	Bn	**80**	0.8	82	97
6	**20**	Ph	Et	**81**	0.9	80	90

[a] The starting material was in all cases of ≥99% de except **16** which was of 97% de, and **17** which was of 98% de. [b] Yield based on capillary GC analysis.

In the optimum procedure, 1 equiv of a pseudoephedrine amide is added as a solution in THF to a cold (–78 °C) suspension of the lithium triethoxyaluminum hydride reagent (2.3 equiv) in hexanes. The reaction mixture is warmed to 0 °C and stirred at that temperature for 0.8–1.2 h followed by quenching. The ratio of the solvents hexanes and THF was found to be an important variable; mixtures containing less than 60% by volume of hexanes led to greater degrees of over-reduction (to the primary alcohol and to the tertiary amine). In addition, the successful generation of the alkoxyaluminum hydride reagent was found to be quite sensitive to the quality of the lithium aluminum hydride reagent. According to the reaction stoichiometry, a 10% underestimation of the content of lithium aluminum hydride results in a 40% decrease in the amount of active hydride produced. Commercial stock solutions of lithium aluminum hydride proved to be unreliable for the preparation of lithium triethoxyaluminum hydride. Optimal results were achieved when anhydrous ethyl acetate was added slowly (ca. 1–2 h) to an ice-cooled suspension of solid lithium aluminum hydride (stored and transferred under nitrogen) in anhydrous hexanes.

Quenching of the reaction mixture with a dilute solution of aqueous acid (e.g., 0.5 N aqueous hydrochloric acid solution) afforded a mixture of the desired aldehyde and a pseudoephedrine aminal by-product in a ratio ranging from 1:1 to 5:1, respectively,

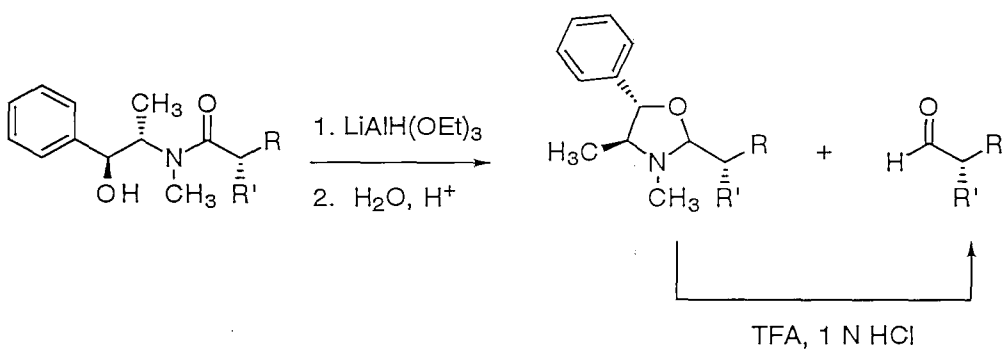


Figure 8. Generation and cleavage of pseudoephedrine aminals.

depending upon the substrate (Figure 8).[63] By quenching the reaction with stronger acid (10 equiv of trifluoroacetic acid in 1 N aqueous hydrochloric acid solution), complete conversion of the aminal by-product to the desired aldehyde was achieved. Only in rare instances did trace amounts of aminal (1–2%) remain after this work-up procedure. Although inappropriate for acid-sensitive substrates, this protocol was nevertheless quite effective for the preparation of a number of highly enantiomerically enriched aldehydes. Ee's of 94–98% are possible, and even the highly racemization-prone aldehyde **81** was isolated in 90% ee.

Experimental Section

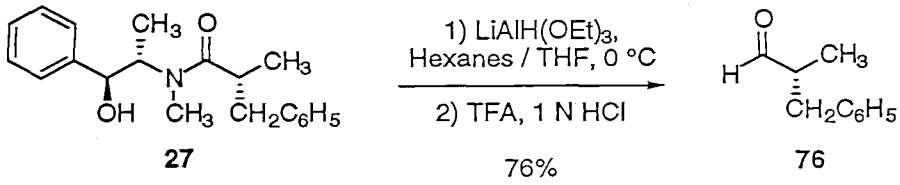
General Procedures. All non-aqueous reactions were performed in flame-dried round-bottomed or modified Schlenk (Kjeldahl shape) flasks, equipped with a magnetic stirring bar and fitted with a rubber septum under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula unless otherwise noted. Organic solutions were concentrated by rotary evaporation at ~25 Torr. Flash column chromatography was performed as described by Still et al.[38] 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 was distilled under nitrogen from sodium benzophenone ketyl. Dichloromethane and triethylamine were distilled under nitrogen from calcium hydride. Ethyl acetate and hexanes used in the generation of lithium triethoxyaluminum hydride were distilled from calcium hydride at 760 torr. 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 300 MHz, and ^{13}C NMR spectra were recorded at 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) or to tetramethylsilane. 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 California Institute of Technology.

Chiral capillary gas chromatography (GC) analysis was carried out using an Alltech Chirasil-Val chiral fused silica capillary column, under isothermal conditions, with a column head pressure of 17 psi.



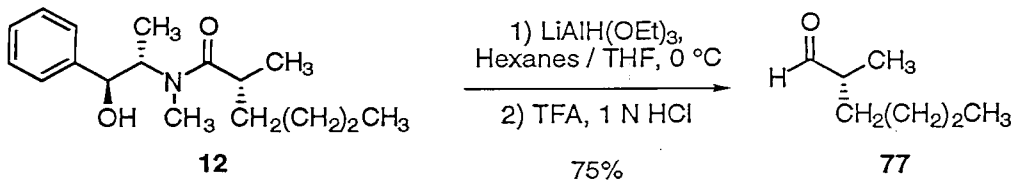
27 76

(*R*)-α-Methyl Benzenepropanal **76**

A 1-L round-bottomed flask was charged with solid lithium aluminum hydride (95%, 2.95 g, 73.9 mmol, 2.30 equiv) under a nitrogen atmosphere. The hydride was suspended in hexanes (170 mL) and the flask was immersed in an ice bath. Ethyl acetate (10.7 mL, 110 mmol, 3.41 equiv) was added by addition funnel over a period of 1.5 h, and the resulting suspension was cooled to –78 °C. A solution of amide **11** (10.0 g, 32.1 mmol, 1 equiv) in tetrahydrofuran (110 mL) was added via cannula over 5 min and the reaction mixture was warmed to 0 °C. After stirring for 1 h at 0 °C, the reaction mixture was transferred by cannula to a solution of trifluoroacetic acid (25 mL, 325 mmol, 10 equiv) in 1 N aqueous hydrochloric acid solution (400 mL) and the transfer was quantitated with an additional portion of tetrahydrofuran (10 mL). The resulting biphasic mixture was stirred at 23 °C for 5 min, then was diluted with 1 N aqueous hydrochloric acid solution (700 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 150 mL) and the combined organic layers were neutralized by the cautious addition of saturated aqueous sodium bicarbonate solution (250 mL). The latter addition sometimes produced an emulsion that could be cleared by filtration through a coarse frit loaded with a 1-cm pad of Celite. The aqueous layer (pH 7–8) was separated and extracted with ethyl acetate (100 mL). The combined organic extracts were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (7.5% ethyl acetate–hexanes) afforded the aldehyde **76** as a colorless liquid (3.64 g, 76%). Aldehyde **76** was oxidized[64] to the corresponding carboxylic acid (**39**) and chiral capillary

GC analysis of the corresponding (*R*)-α-methylbenzyl amide, as described for acid **39**, established that aldehyde **76** was of 95% ee.

^{1}H NMR (300 MHz, C_6D_6) δ:	9.29 (d, 1H, J = 1.2 Hz, CHO), 6.80–7.12 (m, 5H, aromatic), 2.72 (dd, 1H, J_1 = 13.2 Hz, J_2 = 5.4 Hz, one of PhC**H**$_2$), 2.0–2.2 (m, 2H, one of PhC**H**$_2$, C**H**CHO), 0.69 (d, 3H, J = 6.9 Hz, C**H**$_3$).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	204.3, 138.7, 128.9, 128.4, 126.3, 48.0, 36.5, 13.1.
FTIR (neat, cm^{-1}):	1723 (s, C=O).
HRMS (FAB):	Calcd for $C_{10}H_{13}O$ $(MH)^+$: 149.0966.
	Found: 149.0965.
TLC (50% EtOAc–hexanes), R_f:	**76**: 0.63 (UV, PMA).
	11: 0.22 (UV, PMA).
	aminal by-product: 0.70 (UV, PMA).



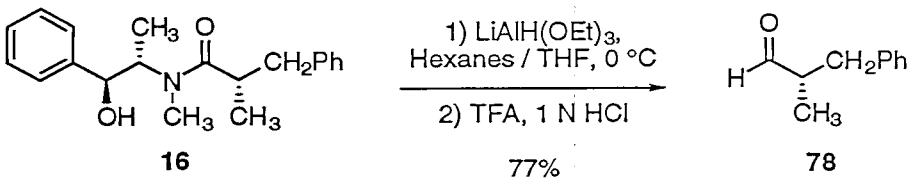
12 75% **77**

(*R*)-2-Methylhexanal **77**

A 100-mL round-bottomed flask was charged with solid lithium aluminum hydride (95%, 328 mg, 8.21 mmol, 2.30 equiv) under a nitrogen atmosphere. The hydride was suspended in hexanes (16 mL) and the flask was immersed in an ice bath. Ethyl acetate (1.17 mL, 12.1 mmol, 3.38 equiv) was added by syringe pump over a period of 1.5 h, and the resulting suspension was cooled to –78 °C. A solution of amide **12** (990 mg, 3.57 mmol, 1 equiv) in tetrahydrofuran (8 mL, followed by a 1-mL rinse) was added via cannula over 3 min and the reaction mixture was warmed to 0 °C. After stirring for 1.1 h at 0 °C, the reaction mixture was transferred by cannula to a solution of trifluoroacetic acid (2.75 mL, 36 mmol, 10 equiv) in 1 N aqueous hydrochloric acid solution (45 mL) and the transfer was quantitated with an additional portion of tetrahydrofuran (2 mL). The resulting biphasic mixture was stirred at 23 °C for 5 min, then was diluted with 1 N aqueous hydrochloric acid solution (100 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were neutralized by the cautious addition of saturated aqueous sodium bicarbonate solution (30 mL). The latter addition sometimes produced an emulsion that could be cleared by filtration through a coarse frit loaded with a 1-cm pad of Celite. The aqueous layer (pH 7–8) was separated and extracted with ethyl acetate (15 mL). The organic layers were combined and the resulting solution was diluted to a total volume of 200 mL with ethyl acetate. Capillary GC analysis, using the (*R*)-(+)-α-methylbenzyl amide of (*R*)-2-methylhexanoic acid as an internal standard, indicated the amount of aldehyde **77** produced was (318 mg ± 3%, 78 ±

3% yield). Oxidation of aldehyde **77** to the corresponding carboxylic acid (**40**), as described above for aldehyde **76**, and chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide, as described for acid **39**, established that aldehyde **77** was of 98% ee.

^{1}H NMR (300 MHz, C_6D_6) δ:	9.27 (d, 1H, J = 1.8 Hz, CHO), 1.83 (m, 1H, COCH), 0.85–1.15 (m, 6H, $CH_2CH_2CH_2$), 0.78 (t, 3H, J = 7.0 Hz, CH_3CHCO), 0.75 (d, 3H, J = 7.0 Hz, CH_3CH_2).
FTIR (neat, cm^{-1}):	1729 (s, C=O).
HRMS (FAB):	Calcd for $C_7H_{14}O$ $(M)^+$: 114.1045.
	Found: 114.1047.
TLC (50% EtOAc–hexanes), R_f:	**77**: 0.78 (PMA).
	12: 0.33 (UV, PMA).



16 **78**

(*S*)-α-Methyl Benzenepropanal **78**

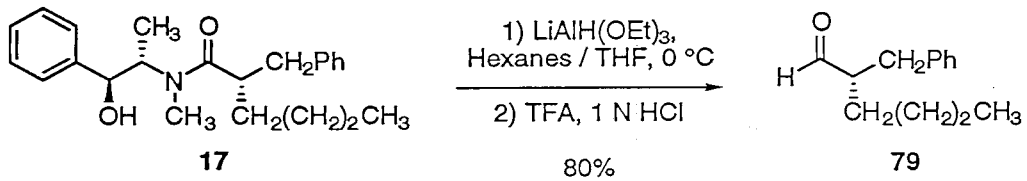
A 100-mL round-bottomed flask was charged with solid lithium aluminum hydride (95%, 213 mg, 5.33 mmol, 2.30 equiv) under a nitrogen atmosphere. The hydride was suspended in hexanes (13 mL) and the flask was immersed in an ice bath. Ethyl acetate (0.765 mL, 7.83 mmol, 3.38 equiv) was added by syringe pump over a period of 1.5 h, and the resulting suspension was cooled to –78 °C. A solution of amide **16** (721 mg, 2.32 mmol, 1 equiv) in tetrahydrofuran (6 mL, followed by a 1-mL rinse) was added via cannula over 3 min and the reaction mixture was warmed to 0 °C. After stirring for 1.2 h at 0 °C, the reaction mixture was transferred by cannula to a solution of trifluoroacetic acid (1.8 mL, 23.3 mmol, 10 equiv) in 1 N aqueous hydrochloric acid solution (30 mL) and the transfer was quantitated with an additional portion of tetrahydrofuran (2 mL). The resulting biphasic mixture was stirred at 23 °C for 5 min, then was diluted with 1 N aqueous hydrochloric acid solution (100 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were neutralized by the cautious addition of saturated aqueous sodium bicarbonate solution (19 mL). The latter addition sometimes produced an emulsion that could be cleared by filtration through a coarse frit loaded with a 1-cm pad of Celite. The aqueous layer (pH 7–8) was separated and extracted with ethyl acetate (10 mL). The combined organic extracts were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (10% ethyl acetate–hexanes) afforded the aldehyde **78** as a colorless liquid (263 mg, 77%). Oxidation of aldehyde **78** to the corresponding carboxylic

acid (**42**), as described above for aldehyde **76**, and chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide, as described for acid **39**, established that aldehyde **78** was of 94% ee. Spectroscopic data were identical to those of its enantiomer, (*R*)-α-methyl benzenepropanal **76**.

TLC (50% EtOAc–hexanes), R_f: **78**: 0.68 (UV, PMA).

16: 0.24 (UV, PMA).

aminal by-product: 0.76 (UV, PMA).



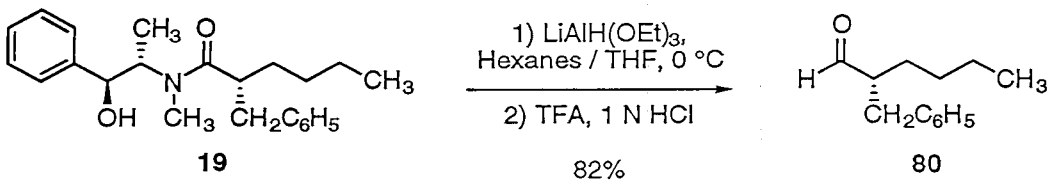
17 80% **79**

(*S*)-α-Butyl Benzenepropanal **79**

A 100-mL round-bottomed flask was charged with solid lithium aluminum hydride (95%, 256 mg, 6.41 mmol, 2.30 equiv) under a nitrogen atmosphere. The hydride was suspended in hexanes (18 mL) and the flask was immersed in an ice bath. Ethyl acetate (0.920 mL, 9.42 mmol, 3.38 equiv) was added by syringe pump over a period of 1.5 h, and the resulting suspension was cooled to –78 °C. A solution of amide **17** (985 mg, 2.79 mmol, 1 equiv) in tetrahydrofuran (7 mL, followed by a 2-mL rinse) was added via cannula over 3 min and the reaction mixture was warmed to 0 °C. After stirring for 45 min at 0 °C, the reaction mixture was transferred by cannula to a solution of trifluoroacetic acid (2.1 mL, 28 mmol, 10 equiv) in 1 N aqueous hydrochloric acid solution (40 mL) and the transfer was quantitated with an additional portion of hexanes (5 mL). The resulting biphasic mixture was stirred at 23 °C for 5 min, then was diluted with 1 N aqueous hydrochloric acid solution (150 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were neutralized by the cautious addition of saturated aqueous sodium bicarbonate solution (25 mL). The latter addition sometimes produced an emulsion that could be cleared by filtration through a coarse frit loaded with a 1-cm pad of Celite. The aqueous layer (pH 7–8) was separated and extracted with ethyl acetate (10 mL). The combined organic extracts were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (100% hexanes → 9% ethyl acetate–hexanes) afforded the aldehyde **79** as a colorless liquid (427 mg, 80%).

Oxidation of aldehyde **79** to the corresponding carboxylic acid (**43**), as described above for aldehyde **76**, and chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide, as described for acid **39**, established that aldehyde **79** was of 97% ee.

^{1}H NMR (300 MHz, C_6D_6) δ:	9.34 (d, 1H, J = 2.3 Hz, C**H**O), 6.9–7.3 (m, 5H, aromatic), 2.71 (dd, 1H, J_1 =13.9 Hz, J_2 = 7.2 Hz, one of PhC**H**$_2$), 2.36 (dd, 1H, J_1 =13.9 Hz, J_2 = 7.0 Hz, one of PhC**H**$_2$), 2.22 (m, 1H, COC**H**), 1.31 (m, 1H, one of COCHC**H**$_2$CH$_2$), 0.9–1.2 (m, 5H, one of COCHC**H**$_2$CH$_2$, CH$_3$C**H**$_2$C**H**$_2$), 0.74 (t, 3H, J = 6.7 Hz, C**H**$_3$).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	204.7, 138.9, 128.9, 128.5, 126.3, 53.4, 35.0, 29.0, 28.3, 22.7, 13.8.
FTIR (neat, cm^{-1}):	1726 (s, C=O).
HRMS (FAB):	Calcd for $C_{13}H_{18}O$ $(M)^+$: 190.1358.
	Found: 190.1346.
TLC (50% EtOAc–hexanes), R_f:	**79**: 0.73 (UV, PMA).
	17: 0.42 (UV, PMA).
	aminal by-product: 0.76 (UV, PMA).



19 82% **80**

(*R*)-α-Butyl Benzenepropanal **80**

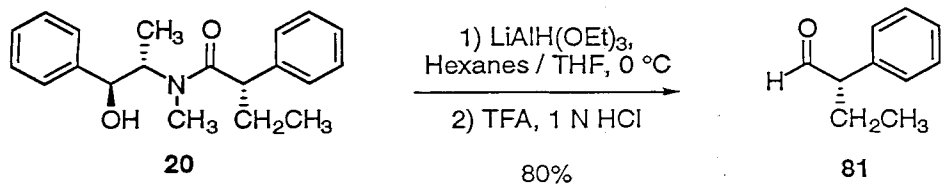
A 100-mL round-bottomed flask was charged with solid lithium aluminum hydride (95%, 259 mg, 6.48 mmol, 2.30 equiv) under a nitrogen atmosphere. The hydride was suspended in hexanes (12 mL) and the flask was immersed in an ice bath. Ethyl acetate (0.931 mL, 9.53 mmol, 3.38 equiv) was added by syringe pump over a period of 1.5 h, and the resulting suspension was cooled to –78 °C. A solution of amide **19** (996 mg, 2.82 mmol, 1 equiv) in tetrahydrofuran (6.5 mL, followed by a 1.5-mL rinse) was added via cannula over 3 min and the reaction mixture was warmed to 0 °C. After stirring for 45 min at 0 °C, the reaction mixture was transferred by cannula to a solution of trifluoroacetic acid (2.2 mL, 28 mmol, 10 equiv) in 1 N aqueous hydrochloric acid solution (40 mL) and the transfer was quantitated with an additional portion of hexanes (2 mL). The resulting biphasic mixture was stirred at 23 °C for 5 min, then was diluted with 1 N aqueous hydrochloric acid solution (150 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 25 mL) and the combined organic layers were neutralized by the cautious addition of saturated aqueous sodium bicarbonate solution (25 mL). The latter addition sometimes produced an emulsion that could be cleared by filtration through a coarse frit loaded with a 1-cm pad of Celite. The aqueous layer (pH 7–8) was separated and extracted with ethyl acetate (10 mL). The combined organic extracts were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (100% hexanes → 9% ethyl acetate–hexanes) afforded the aldehyde **80** as a colorless liquid (441 mg, 82%).

Oxidation of aldehyde **80** to the corresponding carboxylic acid (**45**), as described above for aldehyde **76**, and chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide, as described for acid **39**, established that aldehyde **80** was of 97% ee. Spectroscopic data were identical to those of its enantiomer, (*S*)-α-butyl benzenepropanal **79**.

TLC (40% EtOAc–hexanes), R_f: **80**: 0.73 (UV, PMA).

19: 0.27 (UV, PMA).

aminal by-product: 0.79 (UV, PMA).



20 **81**

(*S*)-α-Ethyl Benzeneacetaldehyde **81**

A 100-mL round-bottomed flask was charged with solid lithium aluminum hydride (95%, 441 mg, 11.0 mmol, 2.30 equiv) under a nitrogen atmosphere. The hydride was suspended in hexanes (21 mL) and the flask was immersed in an ice bath. Ethyl acetate (1.59 mL, 16.2 mmol, 3.38 equiv) was added by syringe pump over a period of 1.5 h, and the resulting suspension was cooled to –78 °C. A solution of amide **20** (1.50 g, 4.80 mmol, 1 equiv) in tetrahydrofuran (11 mL, followed by a 3-mL rinse) was added via cannula over 3 min and the reaction mixture was warmed to 0 °C. After stirring for 55 min at 0 °C, the reaction mixture was transferred by cannula to a solution of trifluoroacetic acid (3.7 mL, 48 mmol, 10 equiv) in 1 N aqueous hydrochloric acid solution (60 mL) and the transfer was quantitated with an additional portion of hexanes (3 mL). The resulting biphasic mixture was stirred at 23 °C for 5 min, then was diluted with 1 N aqueous hydrochloric acid solution (100 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were neutralized by the cautious addition of saturated aqueous sodium bicarbonate solution (40 mL). The latter addition sometimes produced an emulsion that could be cleared by filtration through a coarse frit loaded with a 1-cm pad of Celite. The aqueous layer (pH 7–8) was separated and extracted with ethyl acetate (10 mL). The combined organic extracts were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (10% ethyl acetate–hexanes) afforded the aldehyde **81** as a colorless liquid (569 mg, 80%). Oxidation of aldehyde **81** to the corresponding carboxylic acid (**46**), as

described above for aldehyde **76**, and chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzyl amide, as described for acid **39**, established that aldehyde **81** was of 90% ee.

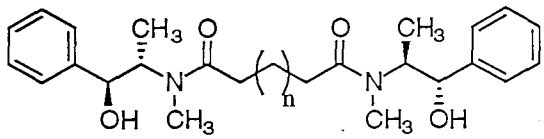
^{1}H NMR (300 MHz, C_6D_6) δ:	9.34 (d, 1H, J = 1.8 Hz, C**H**O), 6.8–7.15 (m, 5H, aromatic), 2.87 (m, 1H, PhC**H**), 1.82–1.91 (m, 1H, one of $CH_3C\mathbf{H}_2$), 1.48 (m, 1H, one of $CH_3C\mathbf{H}_2$), 0.66 (t, 3H, J = 7.4 Hz, $C\mathbf{H}_3$).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	200.9, 136.2, 128.9, 128.7, 127.4, 60.7, 22.8, 11.6.
FTIR (neat, cm^{-1}):	1727 (s, C=O).
HRMS (FAB):	Calcd for $C_{10}H_{13}O$ $(MH)^+$: 149.0966.
	Found: 149.0972.
TLC (60% EtOAc–hexanes), R_f:	**81**: 0.79 (UV, PMA).
	20: 0.45 (UV, PMA).
	aminal by-product: 0.82 (UV, PMA).

Chapter 5

Synthesis and Diastereoselective Alkylation of C_2-Symmetric Bis-amides Derived from Pseudoephedrine and a Dicarboxylic Acid

Synthesis and Alkylation

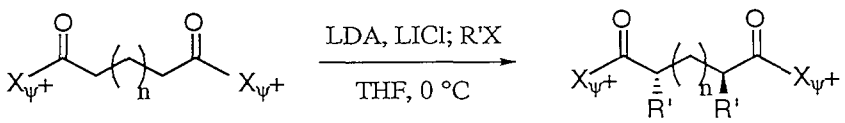
C_2-symmetric pseudoephedrine bis-amides were prepared from the commercial carboxylic acid dichlorides succinyl chloride, glutaryl chloride, adipoyl chloride, and pimeloyl chloride. Unlike the pseudoephedrine amides derived from monocarboxylic acids, these bis-amides were foams rather than crystalline solids.



n = 0 Pseudoephedrine succinamide (82)
n = 1 Pseudoephedrine glutaramide (83)
n = 2 Pseudoephedrine adipamide (84)
n = 3 Pseudoephedrine pimelamide (85)

The protocol for the alkylation of these pseudoephedrine bis-amides was similar to that for pseudoephedrine amides. The bis-amide was enolized using lithium diisopropylamide (4.2 equiv, –78 °C for 40 minutes, 0 °C for 10 minutes, and 23 °C for 3 minutes) in tetrahydrofuran in the presence of 10–12 equivalents of lithium chloride. Except for the special case where n = 2, alkylation reactions of pseudoephedrine bis-amides proceeded in good yield at 0 °C with both benzyl bromide and methyl iodide to yield C_2-symmetric bis-alkylated products (Table 11). In each of these cases, the isolated product was found to be almost exclusively (>95%) a single species. It was not determined, however, whether the minor species was a minor diastereomer or a minor rotamer. That the alkylation product was in all cases essentially a single rotamer was surprising in that each of the starting materials exists as a complex mixture of 3 or 4 rotamers, depending on the substrate. In contrast, the alkylation of pseudoephedrine (mono) amide derivatives causes only a minor perturbation on the rotamer distribution.

Table 11. Alkylation of Pseudoephedrine Bis-amides



n	R'X	product	yield (%)	de (%)
0	MeI	**86**	74	>90
1	MeI	**87**	78	>90
1	$PhCH_2Br$	**88**	81	>90
3	MeI	**89**	90	>90
3	$PhCH_2Br$	**90**	86	>90

In the case of pseudoephedrine adipamide (n = 2), enolization was clean (by TLC) yet the alkylation reaction at 0 °C produced a number of products which could not be separated. The most likely explanation for the problematic alkylation reaction is that one of the enolate functionalities is alkylated, generating an electrophilic amide carbonyl group. Before a second alkylation can occur at the other enolate functionality, a Dieckmann-type

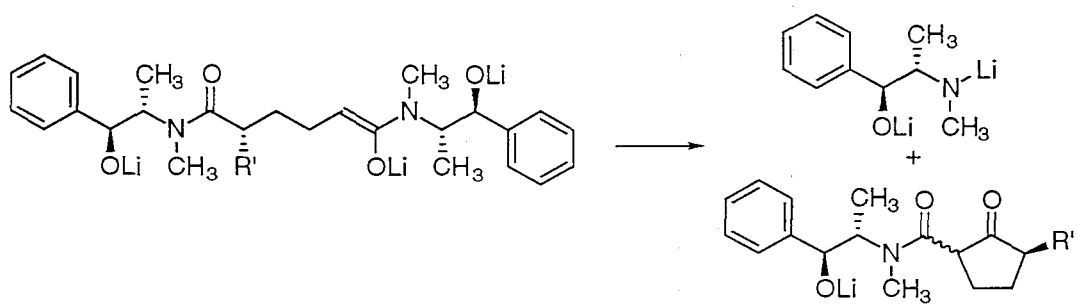


Figure 9. Dieckmann cyclization following the mono-alkylation of pseudoephedrine adipamide.

cyclization[65] occurs to produce a cyclopentanone derivative (Figure 9). Dieckmann cyclization does not occur for the other pseudoephedrine bis-amides because ring closure would form a 3, 4, or 6 membered ring for n = 0, 1, or 3, respectively.

It is interesting to note that the alkylation diastereoselectivity does not seem to depend greatly on the length of the diacid precursor. Assuming that the basis of the selectivity in the alkylation of these C_2-symmetric bis-amides is the same as that in the alkylation of pseudoephedrine (mono) amides, the alkylation of pseudoephedrine succinamide might be anticipated to occur with higher selectivity than the alkylation of pseudoephedrine glutaramide. When drawn in the extended conformation, the alkylation product of pseudoephedrine succinamide is predicted to be the 1,2-syn product. The steric bias at one enolate π-face might mutually reinforce the steric bias at the other enolate π-face (matched case). When drawn in the extended conformation, the alkylation product of pseudoephedrine glutaramide, in contrast, is predicted to be the 1,3-anti product. The steric bias at one enolate π-face might counteract the steric bias at the other enolate π-face (mismatched case). Thus the selectivity of alkylations where n is even should be higher than the selectivity of alkylations where n is odd, though it would be predicted that as n increases, the magnitude of matched or mismatched effects will diminish as more intervening methylene groups are placed between the two enolate functionalities. The magnitude of these effects does not appear to be large, for all the alkylation reactions studied appear to proceed in greater than 90% de.

Cleavage of Alkylated C_2-Symmetric Bis-amides

Though the most useful C_2-symmetric products would likely be the products derived from the bis-methylated succinamide, preliminary studies have focused on the cleavage of bis-benzylated compounds because the resulting products are much less water soluble compared to the bis-methylated compounds. Cleavage experiments have been unsuccessful, and so far no reliable protocol has been found. Base-promoted hydrolysis

led to the formation of the monocarboxylic acid after approximately one day, but prolonged reaction times (two additional days) did not drive the reaction to the diacid.

Acidic hydrolysis (18 N sulfuric acid, dioxane, reflux, one day) of the bis-methylated pseudoephedrine pimelamide (**83**) led to hydrolysis at one terminus, and $N \rightarrow O$ acyl transfer at the other terminus. Prolonged heating led only to decomposition. Attempted reduction of the bis-benzylated pseudoephedrine glutaramide (**82**) to the corresponding diol with LPT or LAB also failed, instead affording tertiary amine at one terminus and unreacted amide at the other. Prolonged reaction time drove the reaction primarily to the bis-tertiary amine by-product.

Experimental Section

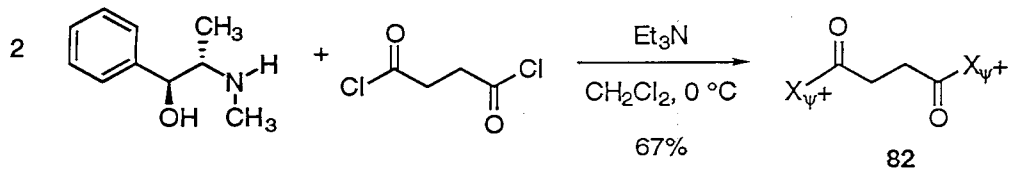
General Procedures. All non-aqueous reactions were performed in flame-dried round-bottomed or modified Schlenk (Kjeldahl shape) flasks, equipped with a magnetic stirring bar and fitted with a rubber septum under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula unless otherwise noted. Organic solutions were concentrated by rotary evaporation at ~25 Torr. Flash column chromatography was performed as described by Still et al.[38] 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 was distilled under nitrogen from sodium benzophenone ketyl. Dichloromethane, diisopropylamine, and triethylamine were distilled under nitrogen from calcium hydride. Lithium chloride was dried under vacuum at 150 °C for 24 h, then stored under a nitrogen atmosphere, or alternatively was flame-dried under vacuum immediately prior to use. Benzyl bromide and iodomethane were passed through basic alumina immediately prior to use. The molarity of *n*-butyllithium was determined by titration against diphenylacetic acid as an indicator (average of three determinations).[40] 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 300 MHz and ^{13}C NMR spectra were recorded at 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) or to tetramethylsilane (δ = 0). 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 California Institute of Technology.

Determination of Absolute Stereochemistry of Alkylation Products: The alkylation of C_2-symmetric pseudoephedrine bis-amides was assumed to proceed analogously to the alkylation of pseudoephedrine amide enolates, wherein the major pseudoephedrine alkylation product results from electrophilic attack on the putative *Z*-enolate functionalities (R syn to the enolate oxygen) from the same face as the carbon-bound methyl group of the nearer pseudoephedrine moiety when it is drawn in its extended conformation (see Figure 1, p. 14).

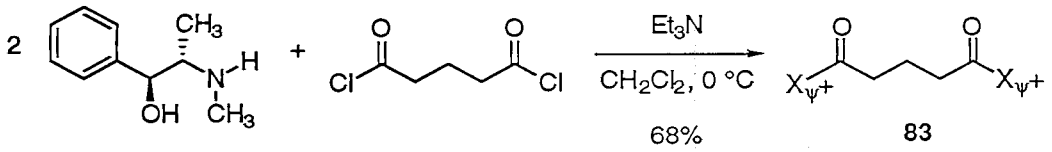


82

(1*S*,2*S*)-Pseudoephedrine Succinamide **82**

An ice-cooled solution of succinyl chloride (4.18 g, 27.0 mmol, 1 equiv) in dichloromethane (40 mL, followed by a 5-mL rinse) was added via cannula over 3 min to a solution of (+)-pseudoephedrine (9.58 g, 58.0 mmol, 2.15 equiv) and triethylamine (9.02 mL, 64.7 mmol, 2.40 equiv) in dichloromethane (130 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, then unreacted acid chloride was quenched by the addition of saturated aqueous sodium bicarbonate solution (5 mL). The resulting mixture was partitioned between half-saturated aqueous sodium bicarbonate solution (30 mL) and dichloromethane (300 mL). The organic layer was separated and extracted sequentially with half-saturated aqueous sodium bicarbonate solution (30 mL) and 3 N aqueous hydrochloric acid solution (2 × 50 mL), then was dried over sodium sulfate and was concentrated. Purification of the residue by flash column chromatography (5.5% methanol–dichloromethane) furnished pseudoephedrine succinamide **82** as a light brown foam (7.45 g, 67%).

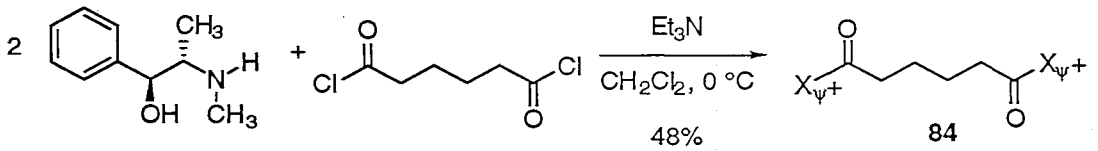
^{1}H NMR (300 MHz, $CDCl_3$) δ:	(4:3:3:2 rotamer ratio) 7.2–7.5 (m, 10H, aromatic), 4.57 (m, 2H, CHOH), 4.24 (m, 2H, $NCHCH_3$), 2.98 (s, 6H, NCH_3), 2.97 (s, 6H, NCH_3), 2.94 (s, 6H, NCH_3), 2.93 (s, 6H, NCH_3), 2.70 (m, 4H, CH_2CH_2), 0.98 (m, 6H, CH_3CHN).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	174.5, 174.2, 173.5, 173.2, 141.9, 141.8, 141.7, 141.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.7, 127.6, 127.1, 127.0, 126.8, 75.94, 75.87, 75.6, 75.5, 58.6, 58.3, 57.1, 56.9, 31.2, 29.5, 29.3, 28.6, 28.4, 26.89, 26.86, 15.5, 14.4.
FTIR (neat, cm^{-1}):	3389 (br, m, OH), 1621 (s, C=O), 1484 (m), 1454 (m), 1407 (m), 1116 (m) 1049 (m), 735 (m), 702 (m).
HRMS (FAB):	Calcd for $C_{24}H_{33}N_2O_4$ $(MH)^+$: 413.2440. Found: 413.2434.
TLC (7.5% MeOH–CH_2Cl_2), R_f:	**82**: 0.27 (UV, PMA). pseudoephedrine: 0.03 (UV, PMA).



(1*S*,2*S*)-Pseudoephedrine Glutaramide **83**

An ice-cooled solution of glutaryl chloride (4.59 g, 27.2 mmol, 1 equiv) in dichloromethane (40 mL, followed by a 10-mL rinse) was added via cannula over 3 min to a solution of (+)-pseudoephedrine (9.65 g, 58.4 mmol, 2.15 equiv) and triethylamine (9.08 mL, 65.2 mmol, 2.40 equiv) in dichloromethane (160 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, then unreacted acid chloride was quenched by the addition of saturated aqueous sodium bicarbonate solution (5 mL). The resulting mixture was partitioned between half-saturated aqueous sodium bicarbonate solution (30 mL) and dichloromethane (300 mL). The organic layer was separated and extracted sequentially with half-saturated aqueous sodium bicarbonate solution (2 × 35 mL) and 3 N aqueous hydrochloric acid solution (3 × 35 mL), then was dried over sodium sulfate and was concentrated. Purification of the residue by flash column chromatography (5.5% methanol–dichloromethane) furnished pseudoephedrine glutaramide **83** as a light brown foam (7.82 g, 68%).

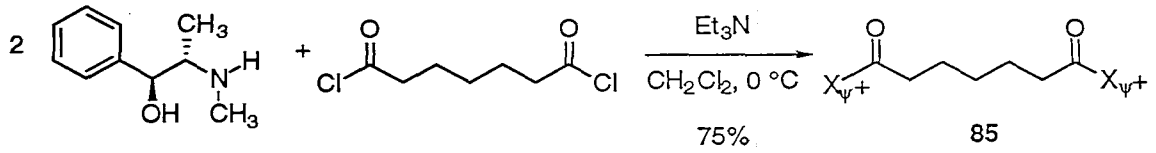
^{1}H NMR (300 MHz, C_6D_6) δ:	(4:3:2:1 rotamer ratio) 7.0–7.6 (m, 10H, aromatic), 4.8–5.5 (m, 2H, OH), 4.52 (d, 2H, J = 8.9 Hz, CHOH), 4.41 (d, 2H, J = 8.9 Hz, CHOH), 3.82–3.94 (m, 2H, $NCHCH_3$), 2.83 (s, 3H, NCH_3), 2.77 (s, 3H, NCH_3), 2.54 (s, 3H, NCH_3), 2.45 (s, 3H, NCH_3), 1.9–2.4 (m, 6H, $CH_2CH_2CH_2$), 0.99 (d, 6H, J = 6.9 Hz, CH_3CHN), 0.69 (d, 6H, J = 6.9 Hz, CH_3CHN), 0.56 (d, 6H, J = 6.7 Hz, CH_3CHN), 0.51 (d, 6H, J = 6.8 Hz, CH_3CHN).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	174.52, 174.47, 173.9, 173.7, 142.3, 142.0, 141.4, 128.5, 128.4, 128.2, 128.0, 127.9, 127.6, 127.5, 127.1, 127.0, 126.9, 126.7, 76.0, 75.5, 75.4, 59.4, 58.8, 56.6, 56.5, 33.7, 33.3, 32.3, 31.2, 31.13, 31.10, 26.9, 21.2, 20.5, 19.9, 15.8, 15.6, 14.5, 14.3.
FTIR (neat, cm^{-1}):	3380 (br, m, OH), 2979 (m), 2936 (m), 1618 (s, C=O), 1483 (m), 1453 (m), 1406 (m), 1265 (s), 1119 (m), 1049 (m), 1026 (m), 762 (m), 733 (m), 702 (m).
HRMS (FAB):	Calcd for $C_{25}H_{35}N_2O_4$ $(MH)^+$: 427.2597. Found: 427.2612.
TLC (7.5% MeOH–CH_2Cl_2), R_f:	**83**: 0.20 (UV, PMA). pseudoephedrine: 0.03 (UV, PMA).



(1*S*,2*S*)-Pseudoephedrine Adipamide **84**

An ice-cooled solution of adipoyl chloride (1.82 g, 9.44 mmol, 1 equiv) in dichloromethane (30 mL, followed by a 5-mL rinse) was added via cannula over 3 min to a solution of (+)-pseudoephedrine (3.94 g, 23.9 mmol, 2.40 equiv), 4-dimethylaminopyridine (12.0 mg, 0.098 mmol, 0.01 equiv), and triethylamine (4.15 mL, 29.8 mmol, 3.00 equiv) in dichloromethane (60 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour, then unreacted acid chloride was quenched by the addition of saturated aqueous sodium bicarbonate solution (10 mL). The resulting mixture was partitioned between half-saturated aqueous sodium bicarbonate solution (30 mL) and dichloromethane (100 mL). The organic layer was separated and extracted sequentially with half-saturated aqueous sodium bicarbonate solution (10 mL) and 3 N aqueous hydrochloric acid solution (3 × 10 mL), then was dried over sodium sulfate and was concentrated. Purification of the residue by flash column chromatography (4% methanol–dichloromethane) furnished pseudoephedrine adipamide **84** as a colorless foam (2.12 g, 48%).

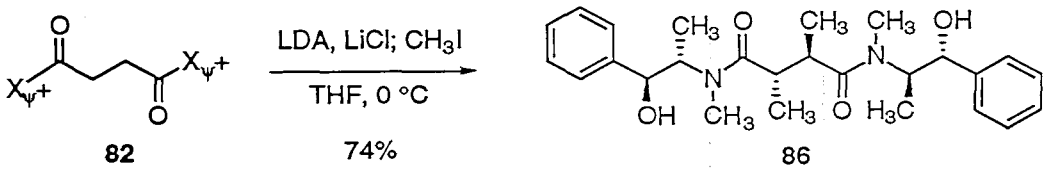
^{1}H NMR (300 MHz, $CDCl_3$), δ:	(4:2:1 mixture of rotamers) 7.2–7.4 (m, 10H, aromatic), 4.00–4.58 (m, 4H, CHOH, $NCHCH_3$), 2.91 (s, 6H, NCH_3), 2.89 (s, 6H, NCH_3), 2.83 (s, 6H, NCH_3), 2.2–2.4, 1.6–1.8 (m, 8H, $CH_2CH_2CH_2CH_2$), 1.07 (d, 6H, J = 6.8 Hz, CH_3CHN), 1.00 (m, 6H, CH_3CHN).
FTIR (neat, cm^{-1}):	3406 (br, s, OH), 1619 (s, C=O), 1483 (m), 1453 (m), 1407 (m), 1118 (m), 1050 (m), 702 (m).
HRMS (FAB):	Calcd for $C_{26}H_{37}N_2O_4$ $(MH)^+$: 441.2753. Found: 441.2763.
TLC (15% MeOH–CH_2Cl_2), R_f:	**84**: 0.68 (UV, PMA). pseudoephedrine: 0.05 (UV, PMA).



(1*S*,2*S*)-Pseudoephedrine Pimelamide **85**

An ice-cooled solution of pimeloyl chloride (2.32 g, 11.8 mmol, 1 equiv) in dichloromethane (30 mL, followed by a 5-mL rinse) was added via cannula over 3 min to a solution of (+)-pseudoephedrine (4.28 g, 25,9 mmol, 2.20 equiv) and triethylamine (3.94 mL, 65.2 mmol, 2.40 equiv) in dichloromethane (80 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1.3 h, then unreacted acid chloride was quenched by the addition of saturated aqueous sodium bicarbonate solution (5 mL). The mixture was partitioned between half-saturated aqueous sodium bicarbonate solution (10 mL) and dichloromethane (120 mL). The organic layer was separated and extracted sequentially with half-saturated aqueous sodium bicarbonate solution (10 mL) and 3 N aqueous hydrochloric acid solution (2 × 10 mL), then was dried over sodium sulfate and was concentrated. Purification of the residue was purified by flash column chromatography (4.5% methanol–dichloromethane) furnished pseudoephedrine pimelamide **85** as a white foam (4.00 g, 75%).

^{1}H NMR (300 MHz, $CDCl_3$) δ:	(2:1:1 rotamer ratio) 7.2–7.4 (m, 10H, aromatic), 4.58 (m, 2H, CHOH), 4.41 (m, 2H, $NCHCH_3$), 4.03 (m, 2H, $NCHCH_3$), 2.90 (s, 6H, NCH_3), 2.86 (s, 6H, NCH_3), 2.83 (s, 6H, NCH_3), 2.40 (m, 4H, CH_2CO), 1.60 (m, 4H, $COCH_2CH_2$), 1.38 (m, 2H, $COCH_2CH_2CH_2$), 1.04 (d, 6H, J = 6.8 Hz, CH_3CHN), 0.95 (d, 6H, J = 6.8 Hz, CH_3CHN).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	175.2, 142.2, 128.6, 128.3, 127.6, 126.9, 126.5, 126.4, 76.4, 76.3, 75.3, 58.4, 57.8, 33.9, 33.6, 33.1, 28.8, 28.5, 24.8, 24.6, 24.4, 15.4, 14.5.
FTIR (neat, cm^{-1}):	3372 (br, m, OH), 2936 (m), 1618 (s, C=O), 1482 (m), 1452 (m), 1406 (m), 1119 (m), 1052 (m), 760 (m), 733 (m), 702 (m).
HRMS (FAB):	Calcd for $C_{27}H_{39}N_2O_4$ $(MH)^+$: 455.2910. Found: 455.2904.
TLC (15% MeOH–CH_2Cl_2), R_f:	**85**: 0.57 (UV, PMA). pseudoephedrine: 0.05 (UV, PMA).

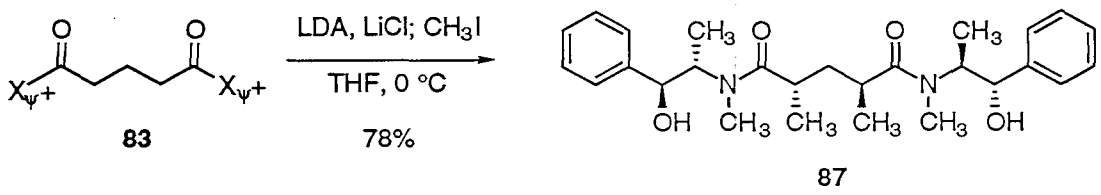


82 86

Bis-methylated Pseudoephedrine Succinamide **86**

A solution of *n*-butyllithium in hexanes (2.33 M, 0.890 mL, 2.08 mmol, 4.16 equiv) was added to a suspension of lithium chloride (254 mg, 6.00 mmol, 12.0 equiv) and diisopropylamine (0.319 mL, 2.28 mmol, 4.56 equiv) in tetrahydrofuran (3 mL) at –78 °C. The suspension was warmed briefly to 0 °C, then was cooled to –78 °C. A solution of succinamide **82** (206 mg, 0.500 mmol, 1 equiv) in tetrahydrofuran (2 mL, followed by a 0.5-mL rinse) was added via cannula. The reaction mixture was stirred at –78 °C for 45 min, at 0 °C for 10 min, at 23 °C for 3 min, and finally was cooled to 0 °C, whereupon iodomethane (0.125 mL, 2.00 mmol, 4.00 equiv) was added via syringe. The mixture was stirred at 0 °C for 15 minutes then was quenched by the addition of saturated aqueous ammonium chloride solution (1 mL). The mixture was partitioned between dichloromethane (20 mL) and water (90 mL). The aqueous layer was separated and extracted with dichloromethane (2 × 15 mL). The combined organic fractions were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (70 → 90%) afforded bis-amide **86** as a white foam (162 mg, 74%). High resolution ^{1}H NMR analysis established that bis-amide **86** was of >90% de.

^{1}H NMR (300 MHz, C_6D_6) δ:	(20:1:1 ratio of species, * denotes minor species) 7.55 (m, 4H, aromatic), 7.0–7.3 (m, 6H, aromatic), 5.10 (br, 2H, OH), 4.80 (m, 2H, NCHCH$_3$), 4.42 (m, 2H, CHOH), 3.00 (m, 2H, COCH), 2.91* (s, 6H, NCH$_3$), 2.62* (s, 6H, NCH$_3$), 2.60 (s, 6H, NCH$_3$), 1.33* (d, 6H, J = 7.0 Hz, CH$_3$CHN), 0.97 (d, 6H, J = 6.4 Hz, COCHCH$_3$), 0.74* (d, 6H, J = 6.7 Hz, CH$_3$CHN), 0.62 (d, 6H, J = 6.8 Hz, CH$_3$CHN).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	178.6, 141.4, 128.5, 128.1, 127.5, 127.2, 127.0, 75.8, 55.0, 41.4, 29.2, 14.5, 14.3.
FTIR (neat, cm^{-1}):	3412 (br, m, OH), 2980 (m), 1618 (s, C=O), 1483 (m), 1452 (m), 1413 (m), 1279 (m), 1110 (m), 1050 (m), 757 (m), 731 (m), 702 (m).
HRMS (FAB):	Calcd for $C_{26}H_{37}N_2O_4$ $(MH)^+$: 441.2753. Found: 441.2750.
TLC (EtOAc), R_f:	**86**: 0.33 (UV, PMA). **82**: 0.13 (UV, PMA).

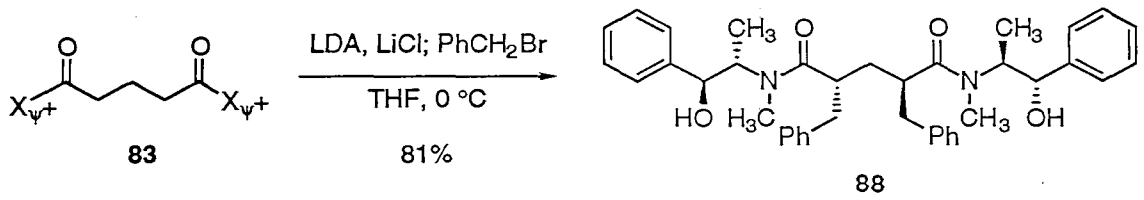


83 87

Bis-methylated Pseudoephedrine Glutaramide **87**

A solution of *n*-butyllithium in hexanes (2.33 M, 0.890 mL, 2.08 mmol, 4.16 equiv) was added to a suspension of lithium chloride (254 mg, 6.00 mmol, 12.0 equiv) and diisopropylamine (0.319 mL, 2.28 mmol, 4.56 equiv) in tetrahydrofuran (3 mL) at –78 °C. The suspension was warmed briefly to 0 °C, then was cooled to –78 °C. A solution of glutaramide **83** (214 mg, 0.500 mmol, 1 equiv) in tetrahydrofuran (2 mL, followed by a 0.5-mL rinse) was added via cannula. The reaction mixture was stirred at –78 °C for 45 min, at 0 °C for 10 min, at 23 °C for 3 min, and finally was cooled to 0 °C whereupon iodomethane (0.125 mL, 2.00 mmol, 4.00 equiv) was added via syringe. The mixture was stirred at 0 °C for 10 minutes, then was quenched by the addition of saturated aqueous ammonium chloride solution (2 mL). The mixture was partitioned between ethyl acetate (15 mL) and water (90 mL). The aqueous layer was separated and extracted with dichloromethane (3 × 15 mL). The combined organic fractions were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (80% ethyl acetate–hexanes) afforded bis-amide **87** as a white foam (177 mg, 78%). High resolution ^{1}H NMR analysis established that bis-amide **87** was of >90% de.

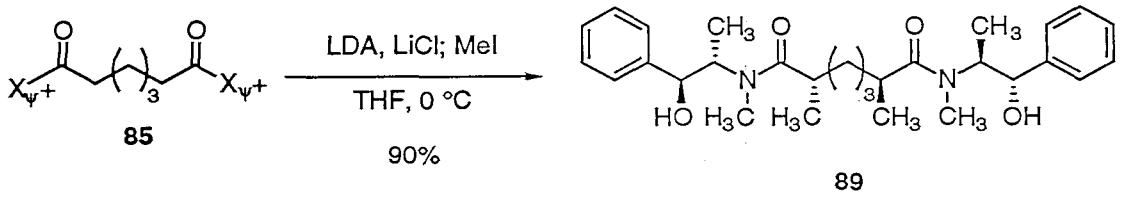
^{1}H NMR (300 MHz, C_6D_6) δ:	(30:1:1 ratio of species, * denotes minor species) 7.6 (m, 4H, aromatic), 7.0–7.4 (m, 6H, aromatic), 5.32 (br, 2H, OH), 5.11 (m, 2H, $NCHCH_3$), 4.51 (m, 2H, CHOH), 3.00* (s, 6H, NCH_3), 2.77 (m, 2H, COCH), 2.56 (s, 6H, NCH_3), 1.82 (dd, 2H, J_1 = 6.1 Hz, J_2 = 5.5 Hz, $COCHCH_2$), 1.28* (d, 6H, J = 6.8 Hz, CH_3), 1.13* (d, 6H, J = 6.6 Hz, CH_3), 0.99 (d, 6H, J = 6.9 Hz, CH_3), 0.90* (d, 6H, J = 7.0 Hz, CH_3), 0.69* (d, 6H, J = 6.9 Hz, CH_3), 0.59 (d, 6H, J = 6.9 Hz, CH_3).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	177.0, 142.3, 128.2, 127.6, 127.2, 75.6, 55.9, 36.6, 33.1, 29.4, 17.9, 14.6.
FTIR (neat, cm^{-1}):	3399 (br, m, OH), 2971 (m), 1617 (s, C=O), 1452 (m), 1315 (m), 1078 (m), 1049 (m), 912 (m), 730 (m), 702 (m).
HRMS (FAB):	Calcd for $C_{27}H_{39}N_2O_4$ $(MH)^+$: 455.2910. Found: 455.2914.
TLC (EtOAc), R_f:	**87**: 0.32 (UV, PMA). **83**: 0.10 (UV, PMA).



Bis-benzylated Pseudoephedrine Glutaramide 88

A solution of *n*-butyllithium in hexanes (2.33 M, 4.19 mL, 9.73 mmol, 4.16 equiv) was added to a suspension of lithium chloride (1.19 g, 28.1 mmol, 12.0 equiv) and diisopropylamine (1.50 mL, 10.7 mmol, 4.56 equiv) at –78 °C. The suspension was warmed briefly to 0 °C, then was cooled to –78 °C. A solution of glutaramide **83** (1.00 g, 2.34 mmol, 1 equiv) in tetrahydrofuran (8 mL, followed by a 1-mL rinse) was added via cannula. The reaction mixture was stirred at –78 °C for 45 min and at 0 °C for 10 min. Tetrahydrofuran (10 mL) was added to improve stirring of the thick suspension. Benzyl bromide (0.970 mL, 8.20 mmol, 3.50 equiv) was added via syringe, and the reaction mixture slowly thinned. The mixture was stirred at 0 °C for 50 min, then was quenched by the addition of saturated aqueous ammonium chloride solution (2 mL). The mixture was partitioned between ethyl acetate (40 mL) and water (200 mL). The aqueous layer was separated and extracted with ethyl acetate (2 × 40 mL). The combined organic fractions were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (48% ethyl acetate–hexanes) afforded bis-amide **88** as a white foam (1.15 g, 81%). High resolution ^{1}H NMR analysis established that bis-amide **88** was of >90% de.

^{1}H NMR (300 MHz, C_6D_6) δ:	7.6 (m, 4H, aromatic), 7.0–7.3 (m, 16H, aromatic), 5.37 (d, 2H, *J* = 4.4 Hz, OH), 5.20 (m, 2H, NCHCH$_3$), 4.48 (m, 2H, CHOH), 3.03 (m, 4H, PhCH$_2$), 2.51 (m, 2H, COCH), 2.49 (s, 6H, NCH$_3$), 2.03 (m, 2H, COCHCH$_2$), 0.47 (d, 6H, *J* = 6.9 Hz, CH$_3$CHN).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	176.1, 141.9, 139.2, 129.0, 128.4, 128.3, 127.7. 127.5, 126.4, 75.9, 55.0, 40.9, 39.4, 33.2, 29.1, 14.5.
FTIR (neat, cm^{-1}):	3406 (br, s, OH), 3062 (m), 3028 (m), 2981 (m), 2930 (m), 1623 (s, C=O), 1493 (m), 1454 (m), 1414 (m), 1312 (m), 1118 (m), 1078 (m), 1051 (m), 1027 (m), 911 (m), 758 (m), 733 (s), 701 (s).
HRMS (FAB):	Calcd for $C_{39}H_{47}N_2O_4$ $(MH)^+$: 607.3536 Found: 607.3527.
TLC (EtOAc), R_f:	**88**: 0.54 (UV, PMA). **83**: 0.13 (UV, PMA).



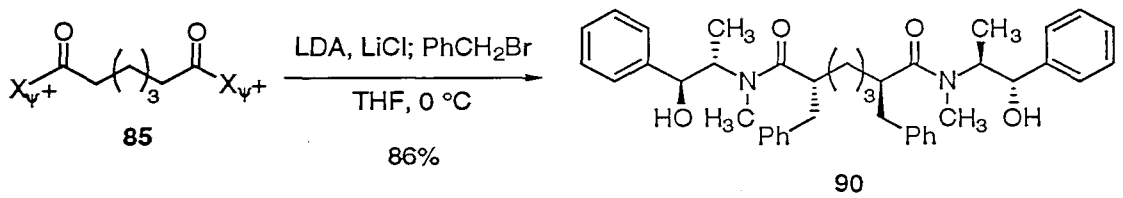
85

89

Bis-methylated Pseudoephedrine Pimelamide **89**

A solution of *n*-butyllithium in hexanes (2.33 M, 0.89 mL, 2.08 mmol, 4.16 equiv) was added to a suspension of lithium chloride (254 mg, 6.00 mmol, 12.0 equiv) and diisopropylamine (0.319 mL, 2.28 mmol, 4.56 equiv) in tetrahydrofuran (3 mL) at –78 °C. The suspension was warmed briefly to 0 °C, then was cooled to –78 °C. A solution of pimelamide **85** (227 mg, 0.500 mmol, 1 equiv) in tetrahydrofuran (2.5 mL, followed by a 0.5-mL rinse) was added via cannula. The reaction mixture was stirred at –78 °C for 35 min, at 0 °C for 10 min, at 23 °C for 3 min, and finally was cooled to 0 °C, whereupon iodomethane (0.125 mL, 2.00 mmol, 4.00 equiv) was added via syringe. The mixture was stirred at 0 °C for 20 min then was quenched by the addition of saturated aqueous ammonium chloride solution (1 mL). The mixture was partitioned between dichloromethane (15 mL) and water (75 mL). The aqueous layer was separated and extracted with dichloromethane (2 × 15 mL). The combined organic fractions were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (3.5% methanol–dichloromethane) afforded bis-amide **89** as a white foam (217 mg, 90%). High resolution ^{1}H NMR analysis established that bis-amide **89** was of >90% de.

^{1}H NMR (300 MHz, $CDCl_3$) δ:	7.10–7.40 (m, 10 H, aromatic), 4.82 (m, 2H, $NCHCH_3$), 4.43 (d, 2H, J = 7.4 Hz, CHOH), 3.03 (s, 6H, NCH_3), 2.86 (m, 2H, COCH), 1.96 (m, 4H, $COCHCH_2$), 1.36 (m, 2H, $COCHCH_2CH_2$), 1.10 (d, 6H, J = 6.8 Hz, CH_3), 0.83 (d, 6H, J = 6.9 Hz, CH_3).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	178.3, 141.8, 128.5, 128.2, 128.1, 127.5, 127.3, 127.0, 126.8, 126.3, 75.5, 55.5, 35.8, 34.1, 29.8, 25.5, 18.5, 14.7.
FTIR (neat, cm^{-1}):	3384 (br, m, OH), 2933 (m), 1615 (s, C=O), 1452 (m), 1410 (m), 1085 (m), 1049 (m), 701 (m).
HRMS (FAB):	Calcd for $C_{29}H_{43}N_2O_4$ $(MH)^+$: 483.3223. Found: 483.3209.
TLC (EtOAc), R_f:	**89**: 0.32 (UV, PMA). **85**: 0.10 (UV, PMA).



Bis-benzylated Pseudoephedrine Pimelamide **90**

A solution of *n*-butyllithium in hexanes (2.33 M, 0.89 mL, 2.08 mmol, 4.16 equiv) was added to a suspension of lithium chloride (0.212 g, 5.00 mmol, 10.0 equiv) and diisopropylamine (0.319 mL, 2.28 mmol, 4.56 equiv) in tetrahydrofuran (3 mL) at –78 °C. The suspension was warmed briefly to 0 °C, then was cooled to –78 °C. A solution of pseudoephedrine pimelamide **85** (227 mg, 0.500 mmol, 1 equiv) in tetrahydrofuran (2.5 mL, followed by a 0.5-mL rinse) was added via cannula. The reaction mixture was stirred at –78 °C for 30 min, at 0 °C for 10 min, at 23 °C for 3 min, and finally was cooled to 0 °C whereupon benzyl bromide (0.208 mL, 1.75 mmol, 3.50 equiv) was added via syringe. The mixture was stirred at 0 °C for 10 min then was quenched by the addition of saturated aqueous ammonium chloride solution (1 mL). The mixture was partitioned between dichloromethane (15 mL) and water (75 mL). The aqueous layer was separated and extracted with dichloromethane (2 × 15 mL). The combined organic fractions were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography eluting with a gradient of ethyl acetate–hexanes (60 → 65%) afforded bis-amide **90** as a white foam (273 mg, 86%). High resolution ^{1}H NMR analysis established that bis-amide **90** was of >90% de.

^{1}H NMR (300 MHz, C_6D_6) δ:	6.9–7.4 (m, 20H, aromatic), 5.18–5.28 (m, 4H, OH, NC**H**CH_3), 4.24 (m, 2H, C**H**OH), 3.00 (m, 4H, PhCH_2), 2.63 (m, 2H, COC**H**), 2.37 (s, 6H, NCH_3), 2.27 (m, 4H, COCHCH_2), 1.39 (m, 2H, COCHCH$_2$$CH_2$), 0.38 (d, 6H, J = 6.9 Hz, CH_3CHN).
^{13}C NMR (75 MHz, $CDCl_3$) δ:	176.8, 141.5, 139.6, 129.0, 128.2, 127.5, 127.2, 126.3, 75.3, 54.4, 43.9, 40.9, 33.5, 28.8, 24.8, 14.3.
FTIR (neat, cm^{-1}):	3402 (br, m, OH), 3027 (m), 2977 (m), 2929 (m), 1613 (s, C=O), 1493 (m), 1454 (m), 1414 (m), 1308 (m), 1266 (m), 1119 (m), 1046 (m), 757 (m), 740 (m), 701 (s).
HRMS (FAB):	Calcd for $C_{41}H_{51}N_2O_4$ $(MH)^+$: 635.3845. Found: 635.3839.
TLC (7.5% MeOH–CH_2Cl_2), R_f:	**90**: 0.62 (UV, PMA). **85**: 0.25 (UV, PMA).

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(4) Kawanami, Y.; Ito, Y.; Kitagawa, T.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 857.

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(9) For the specific case of the alkylation of pseudoephedrine glycinamide and its application to the preparation of highly enantiomerically enriched α-amino acids, see: (a)

Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656. (b) Myers, A. G.; Gleason, J. L.; Yoon, T. *J. Am. Chem. Soc.* **1995**, *117*, 8488.

(10) For the use of the acyclic amino alcohol phenylglycinol as a chiral auxiliary, see: (a) Micouin, L.; Schanen, V.; Riche, C.; Chiaroni, A.; Quirion, J-C.; Husson, H-P. *Tetrahedron Lett.* **1994**, *35*, 7223. (b) Micouin, L.; Jullian, V.; Quirion, J-C.; Husson, H-P. *Tetrahedron: Asymmetry*, **1996**, *7*, 2839.

(11) (a) Schmidt, E.; Calliess, F. W. *Arch. Pharm.* **1912**, *250*, 154. (b) Mitchell, W. *J. Chem. Soc.* **1940**, 1153. (c) Brenner, M.; Huber, W. *Helv. Chem. Acta* **1953**, *36*, 1109.

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(13) By contrast, *N*-acylation of oxazolidinones with carboxylic acid chlorides or anhydrides requires the use of the more pyrophoric reagent *n*-butyllithium. See: Gage, J. R.; Evans, D. A. *Org. Synth., Coll. Vol. VIII* **1993**, 339.

(14) Myers, A. G.; Yoon, T.; Gleason, J. L. *Tetrahedron Lett.* **1995**, *36*, 4555.

(15) This stands in contrast to the alkylation of the enolate derived from pseudoephedrine glycinamide (reference 9), where the selectivity of the alkylation with ethyl iodide was diminished in the absence of lithium chloride (97% de with lithium chloride versus 82% de without lithium chloride).

(16) (a) Seebach, D.; Bossler, H.; Gründler, H.; Shoda, S.-I. *Helv. Chim. Acta* **1991**, *74*, 197. (b) Miller, S. A.; Griffiths, S. L.; Seebach, D. *Helv. Chim. Acta* **1993**, *76*, 563. (c) Bossler, H. G.; Seebach, D. *Helv. Chim. Acta* **1994**, *77*, 1124.

(17) (a) Imide enolates, by contrast, are essentially inert toward these same substrates (reference 7b). (b) The presence of lithium chloride in the reaction medium did not alter this outcome. Thus, the lithium enolate derived from the imide *N*-propionyl benzyloxazolidinone was found not to react with *n*-butyl iodide at 0 °C in the presence of 10 equiv of lithium chloride after 16 h (Myers, A. G.; Chen, H., California Institute of Technology, unpublished results).

(18) Fewer equivalents of the enolate can be employed. For example, alkylation of 1.3 equiv of the enolate derived from **1** with the iodide **67** at 23 °C for 21 h afforded the 1,3-syn alkylatin product **29** in 90% yield with 99:1 selectivity (cf. entry 4, Table 4).

(19) (a) White, J. D.; Johnson, A. T. *J. Org. Chem.* **1994**, *59*, 3347. (b) A similar observation was made by Heathcock and co-workers: Stoermer, D.; Caron, S.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9115.

(20) Using procedure A, the alkylation product **11** was obtained in the same yield and with the same selectivity on both small scale (0.1 mmol of amide 1) and large scale (99 mmol of amide 1). Similarly, using procedure B, the alkylation product **29** was obtained in the same yield and with the same selectivity on both small scale (1.9 mmol of the iodide **67**) and large scale (17 mmol of the iodide **67**).

(21) Enders, D.; Tiebes, J.; DeKimpe, N.; Keppens, M.; Stevens, C.; Smagghe, G.; Betz, O. *J. Org. Chem.* **1993**, *58*, 4881.

(22) Nicolaou, K. C.; Yue, E. W.; La Greca, S.; Nadin, A.; Yang, Z.; Leresche, J. E.; Tsuri, T.; Naniwa, Y.; De Riccardis, F. *Chem. Eur. J.*, **1995**, *1*, 467.

(23) Decicco, C. P.; Grover, P. *J. Org. Chem.* **1996**, *61*, 3534.

(24) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290.

(25) Myers, A. G.; Yang, B. H.; Chen, H.; Kopecky, D. J. *Synlett*, in press.

(26) The iodide **67** was prepared by iodination of the corresponding alcohol, prepared in ≥99% ee and 90% yield by LAB reduction (see text) of the alkylation product **11**. For iodination of alcohols, see: (a) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. I* **1980**, 2866. (b) Lange, G. L.; Gottardo, C. *Synth. Commun.* **1990**, *20*, 1473.

(27) In these and all subsequent alkylation reactions, care was taken to avoid adventitious diastereomeric enrichment upon purification and de values reported reflect those of the crude reaction mixtures.

(28) It has been noted previously that ^{1}H NMR resonances for protons on the *N*-methyl group anti to the carbonyl oxygen of *N,N*-dimethylformamides are shifted upfield of resonances corresponding to the protons of the *N*-methyl group syn to the carbonyl oxygen in benzene-d_6 as solvent: (a) Hatton, J. V.; Richards, R. E.; *Mol. Phys.*, **1960**, *3*, 253. (b) Hatton, J. V.; Richards, R. E. *Mol. Phys.*, **1962**, *5*, 139. (c) Stewart, W. E.; Siddall, T. H. III. *Chem. Rev.* **1970**, *5*, 517.

(29) Similarly problematic are the reactions with electrophiles that are both β-alkyl branched and β-alkoxy substituted. These reactions are extremely slow, even at 45 °C (see ref. 8b).

(30) Myers, A. G.; McKinstry, L.; Barbay, J. K., manuscript in preparation.

(31) Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996**, *61*, 2428.

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(34) In order to arrive at these conformations, it was assumed that each observed NOE was intramolecular, and that the observed enhancement was not a composite of NOE's from two or more rapidly equilibrating conformers.

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(37) For example, enolization of ephedrine propionamide (1 equiv) with LDA (2.1 equiv) in the presence of lithium chloride (6 equiv), as described for pseudoephedrine propionamide, and addition of *n*-butyl iodide at 0 °C afforded a diastereomeric mixture of alkylation products (70% de, configuration not determined) in 90% yield after purification by flash column chromatography.

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

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(42) Watson, M. B.; Youngson, G. W. *J. Chem. Soc., (c)*, **1968**, 258.

(43) In each case, an authentic sample of the minor diastereomeric alkylation product was prepared for comparative analysis (chiral capillary GC analysis of the corresponding trimethylsilyl ether or acetate ester). In the case of amides **15**, **20**, **24**, and **25**, diastereomeric mixtures of α-epimers were obtained by epimerization with LDA (5 equiv) or lithium 2,2,6,6-tetramethylpiperidide (5 equiv) in THF for 5 h at 23 °C followed by quenching with aqueous ammonium chloride solution. Each of the remaining alkylation products in Tables 3 and 4 was epimerized by stirring the substrate with trifluoroacetic acid (10 equiv) in THF at reflux for 1 h (effecting $N \rightarrow O$ acyl transfer as well as α-epimerization), followed by neutralization with aqueous sodium bicarbonate solution at 23 °C for 24 h (causing $O \rightarrow N$ acyl transfer).

(44) This work was conducted by Hou Chen. For details, see: Chen, H. Ph.D. Thesis, California Institute of Technology, 1997.

(45) Myers, A. G.; Yang, B. H.; Chen, H., submitted for publication in *Org. Synth.*

(46) In each case, an authentic sample of the minor diastereomeric (*R*)-α-methylbenzyl amide was prepared for comparative analysis.

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(57) Alcohol **53** was used for comparative analysis.

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

(59) Acetate esters of the diastereomeric alcohol pairs **59** and **60**, **61** and **62**, **63** and **64**, and **65** and **66** were separated with baseline resolution when assayed by chiral capillary GC analysis.

(60) For examples, see: (a) Meyers, A. I.; Spohn, R. F.; Linderman, R. J. *J. Org. Chem.* **1985**, *50*, 3633. (b) Chibale, K.; Warren, S. *Tetrahedron Lett.* **1994**, *35*, 3991.

(61) Recently, Masamune and co-workers reported a general method for this type of transformation: see ref. 5c.

(62) Brown, H. C.; Tsukamoto, A. *J. Am. Chem. Soc.* **1964**, *86*, 1089.

(63) Kraus, G. A.; Taschner, J. *J. Org. Chem.* **1980**, *45*, 1175, and references therein.

(64) In all cases, the pseudoephedrine aminal was found to be a single diastereomer, of undetermined stereochemistry.

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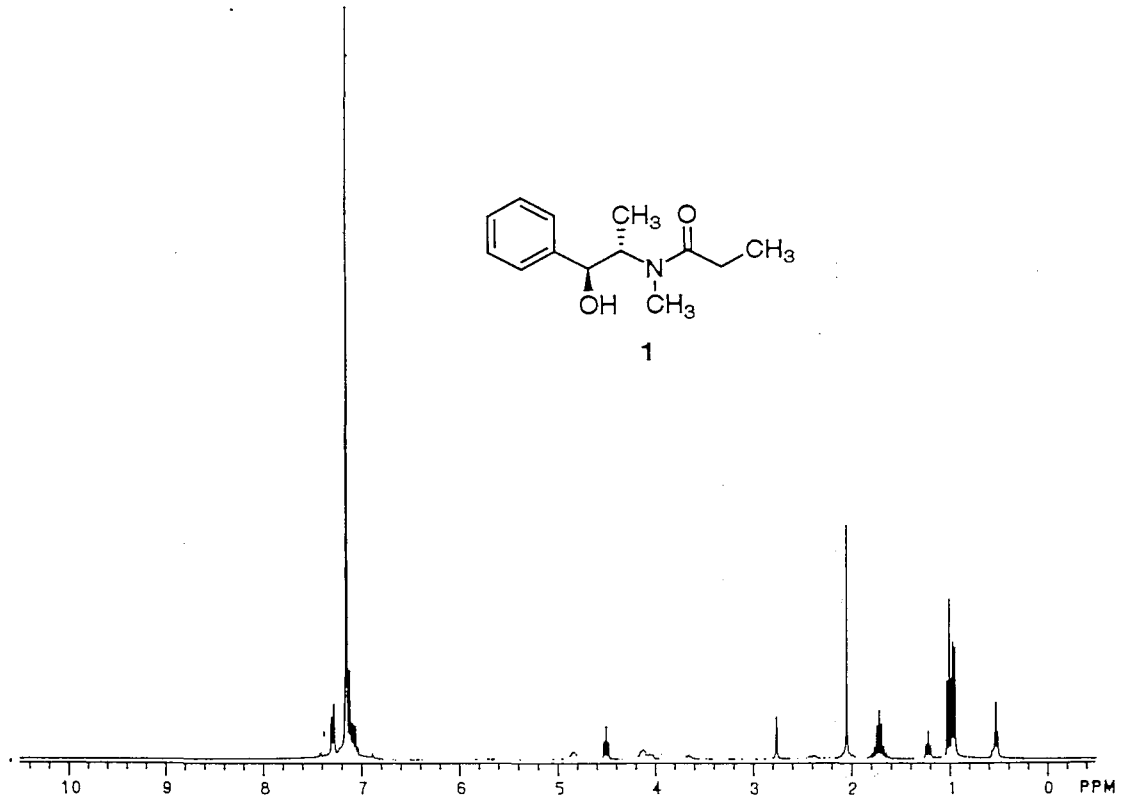
Appendix. Catalog of Spectra

Spectroscopic Data of Compounds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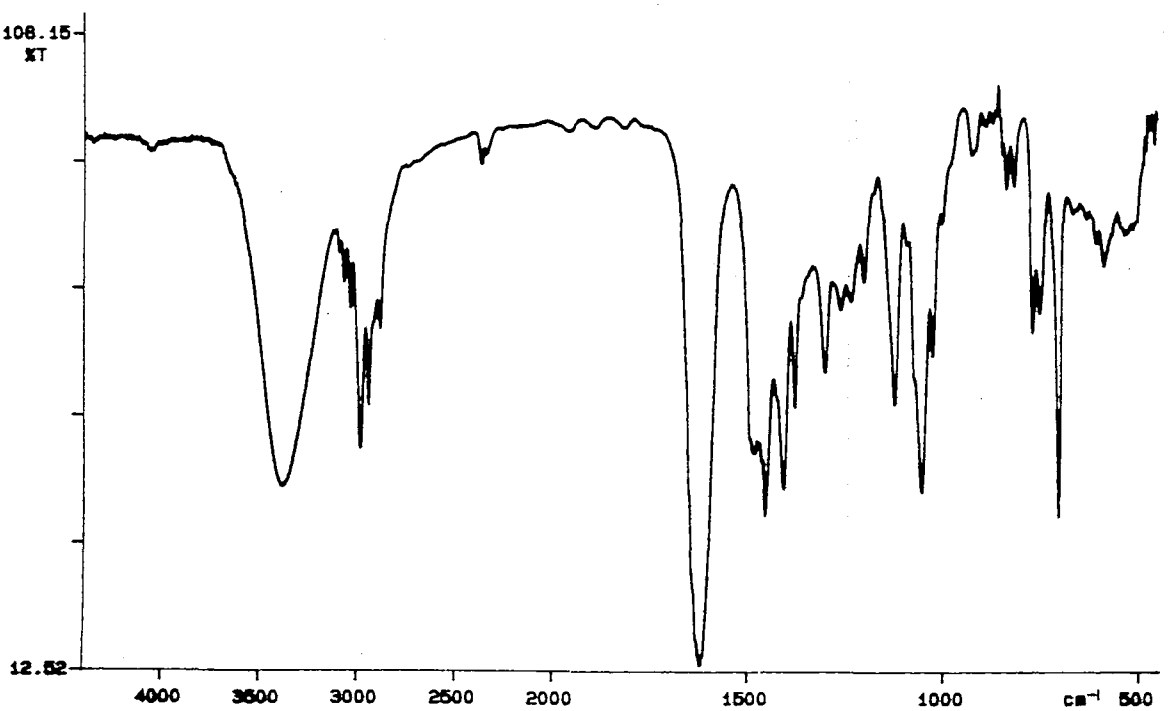
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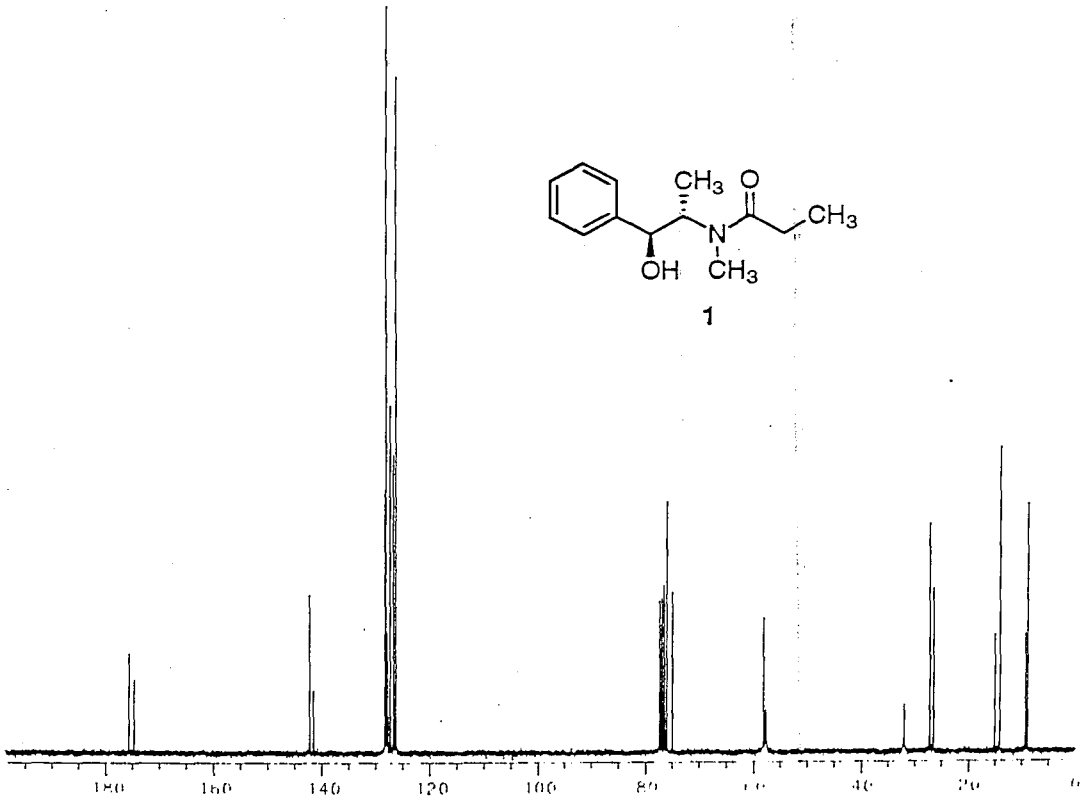

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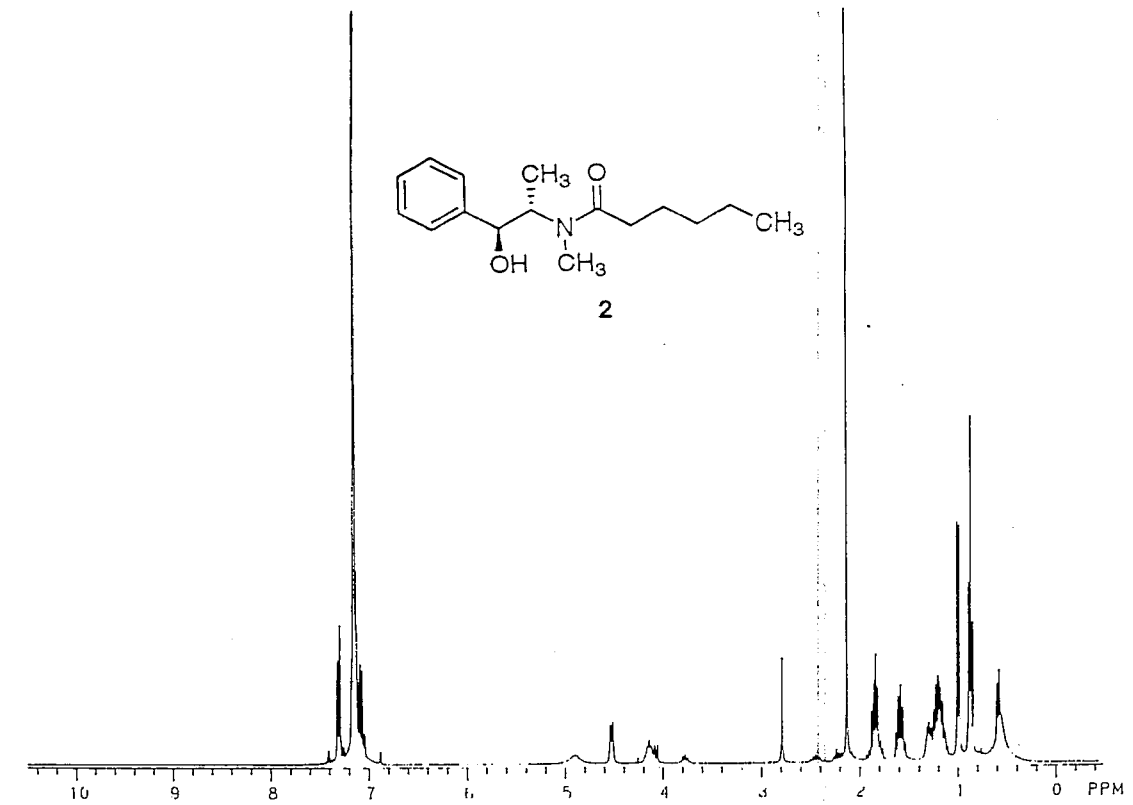
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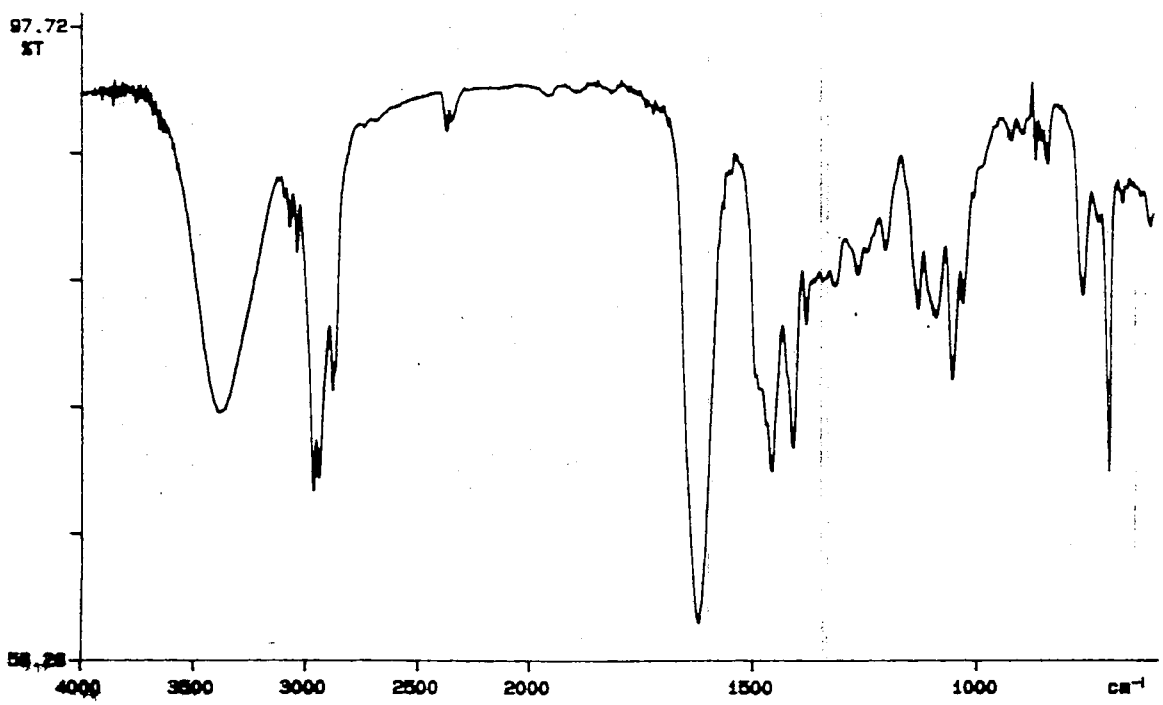
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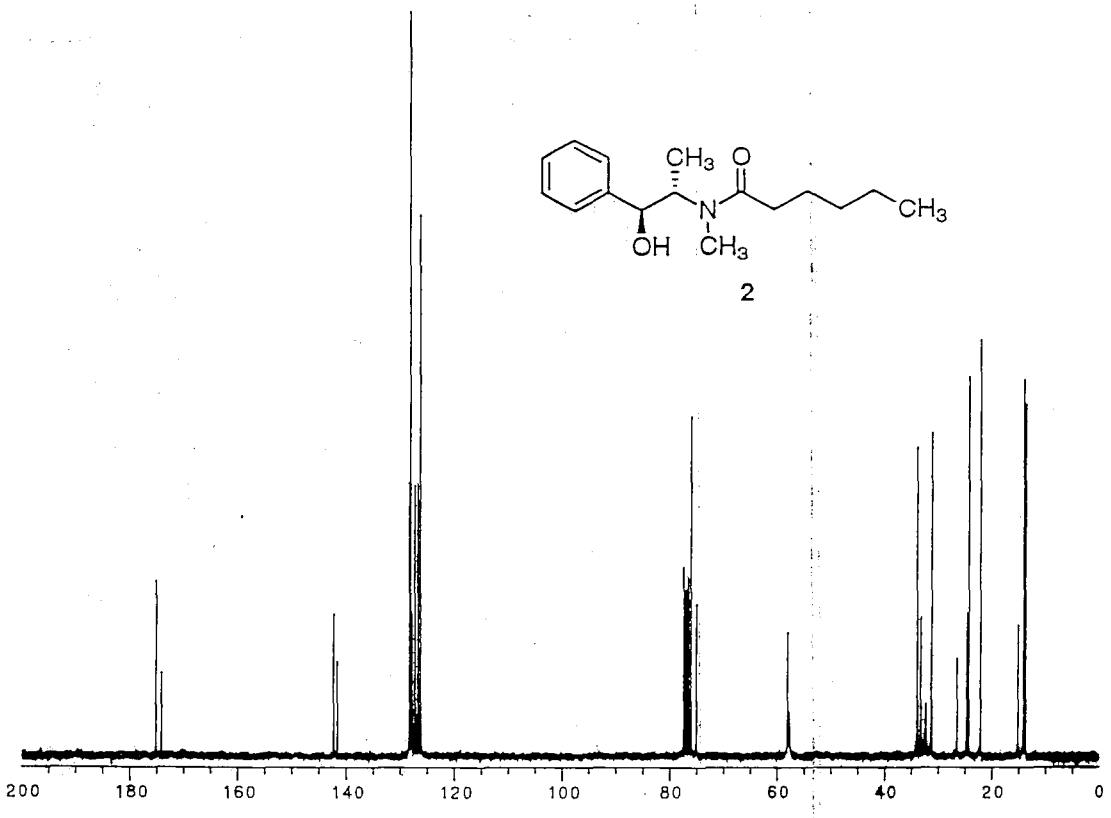
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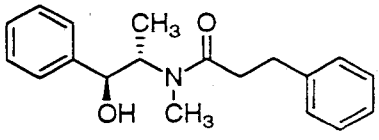
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OH
CH3

3

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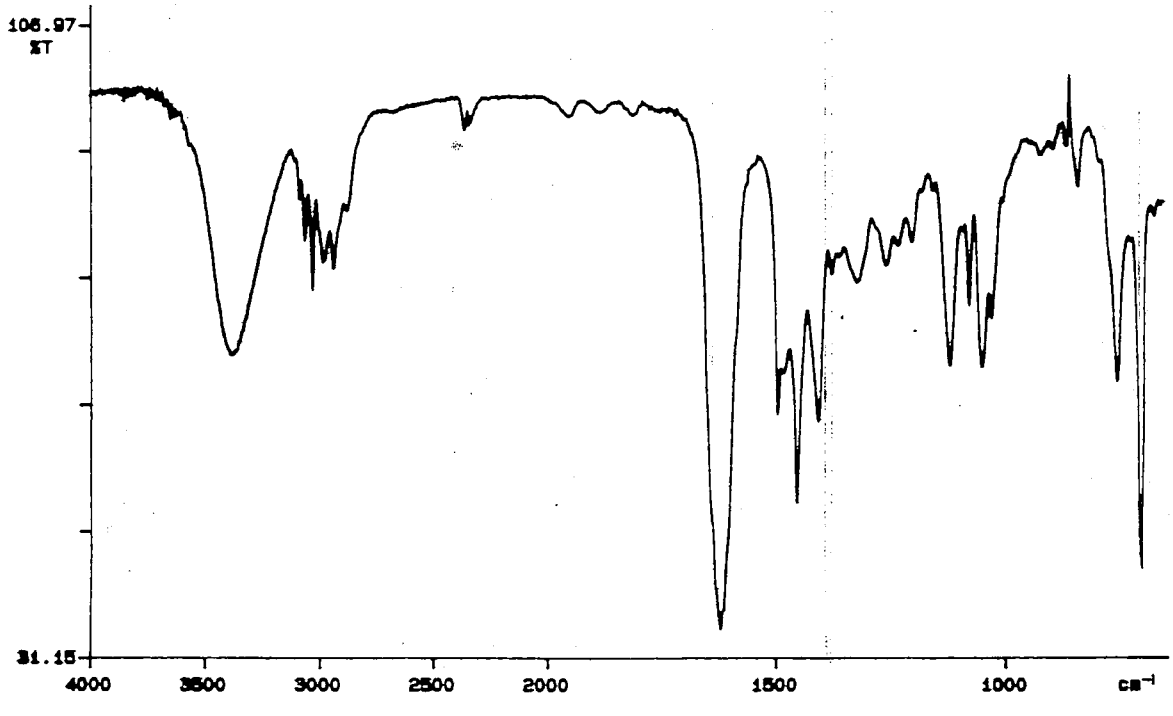
PPM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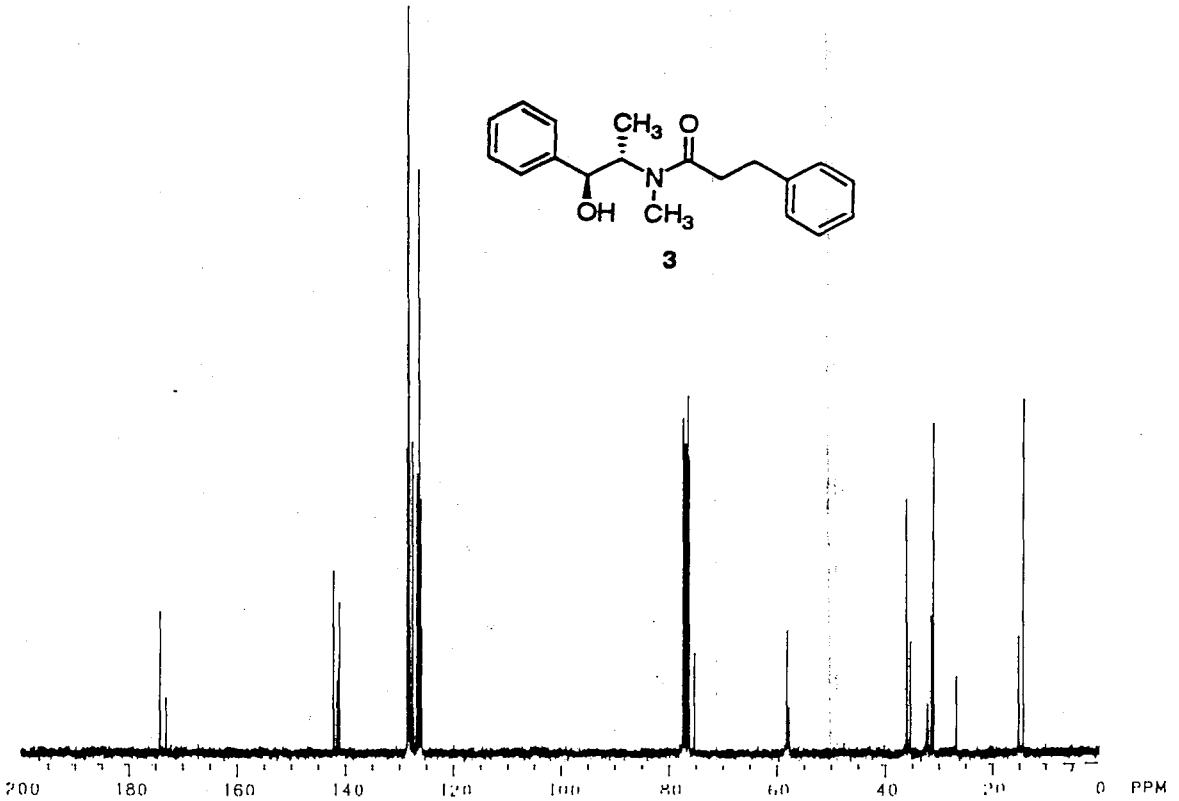

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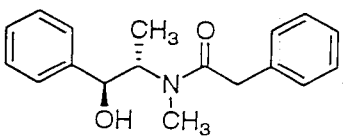
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OH
CH3

4

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5
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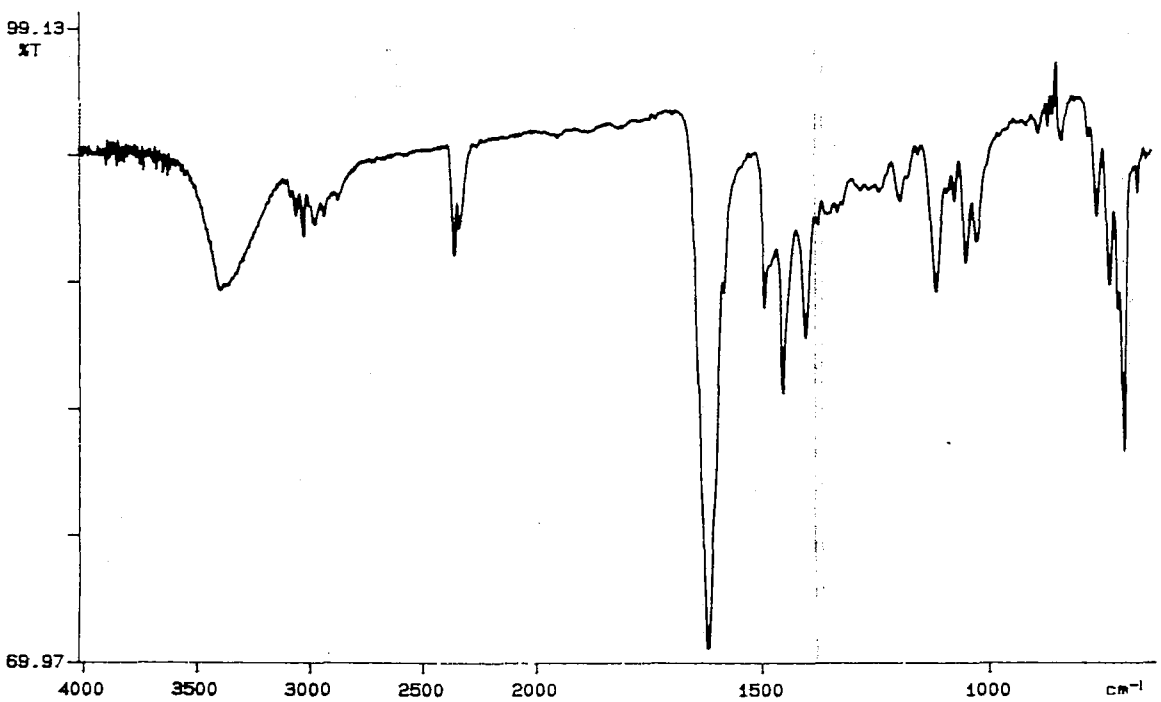
PPM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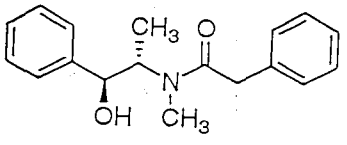
cm-1



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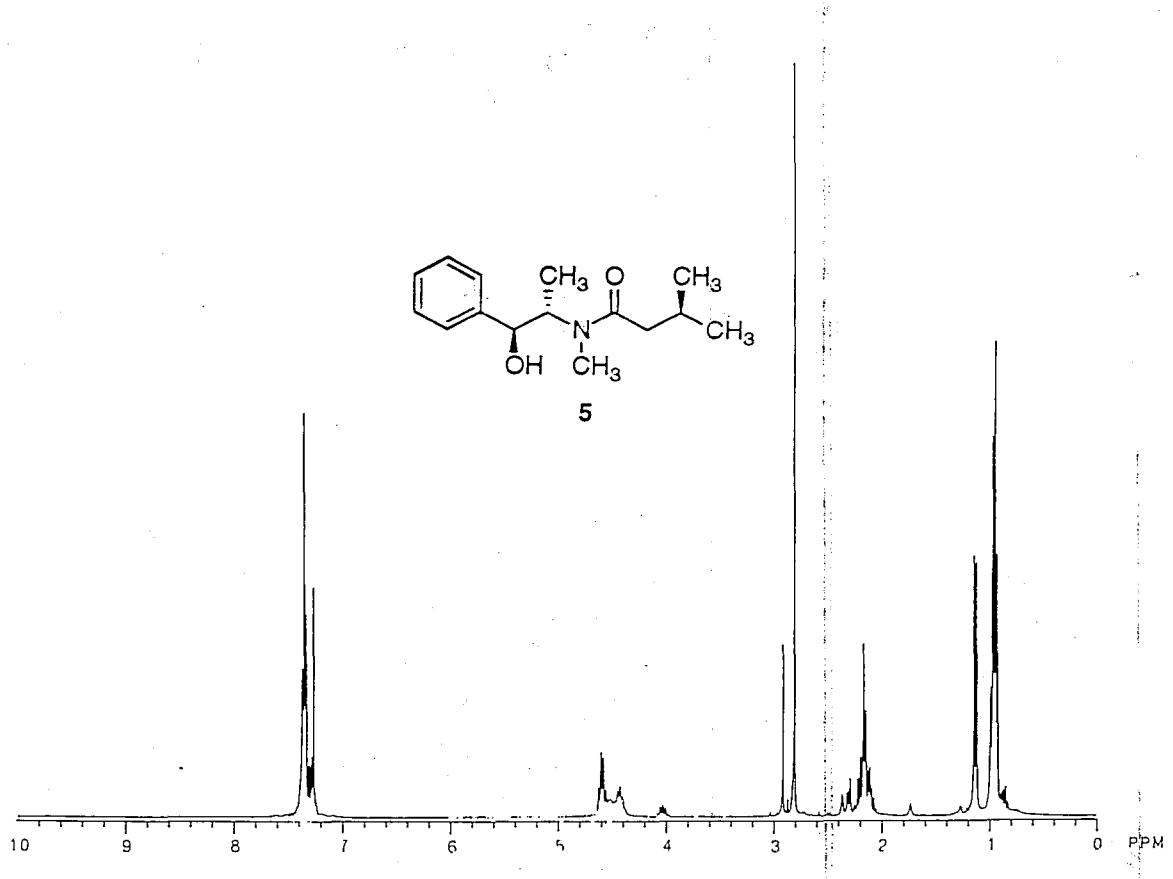
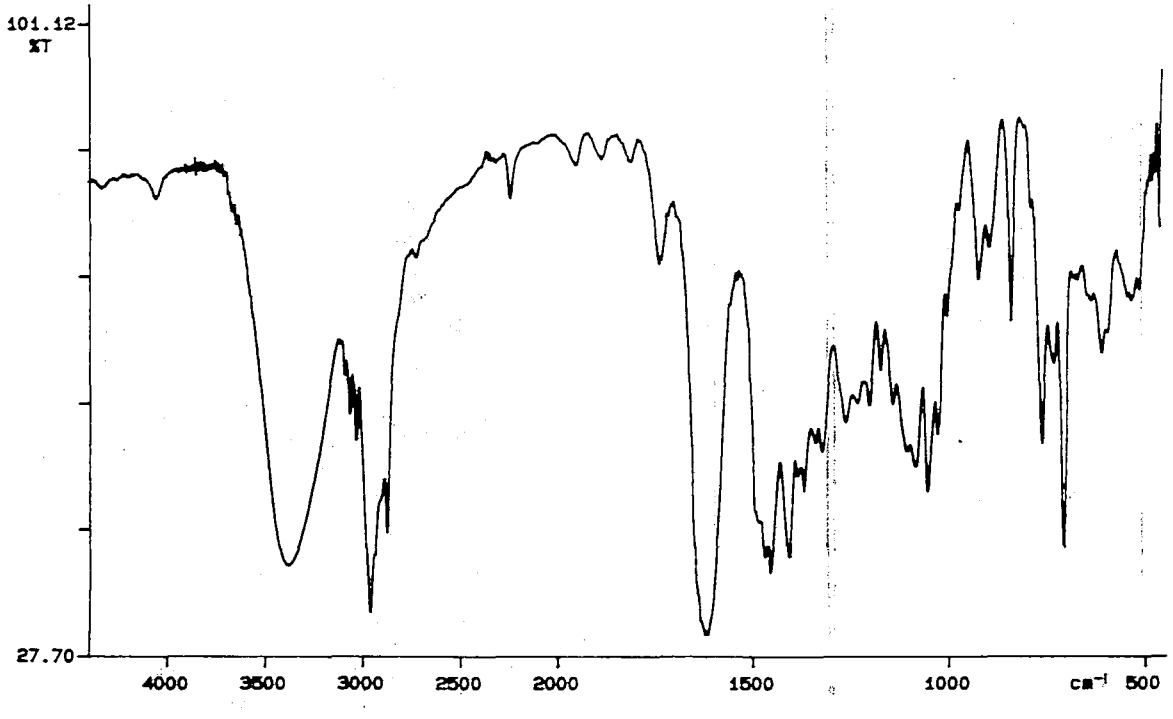

CH3
O
CH3
N
CH3
OH
CH3
10
9
8
7
6
5
4
3
2
1
0
PPM

5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cm-1
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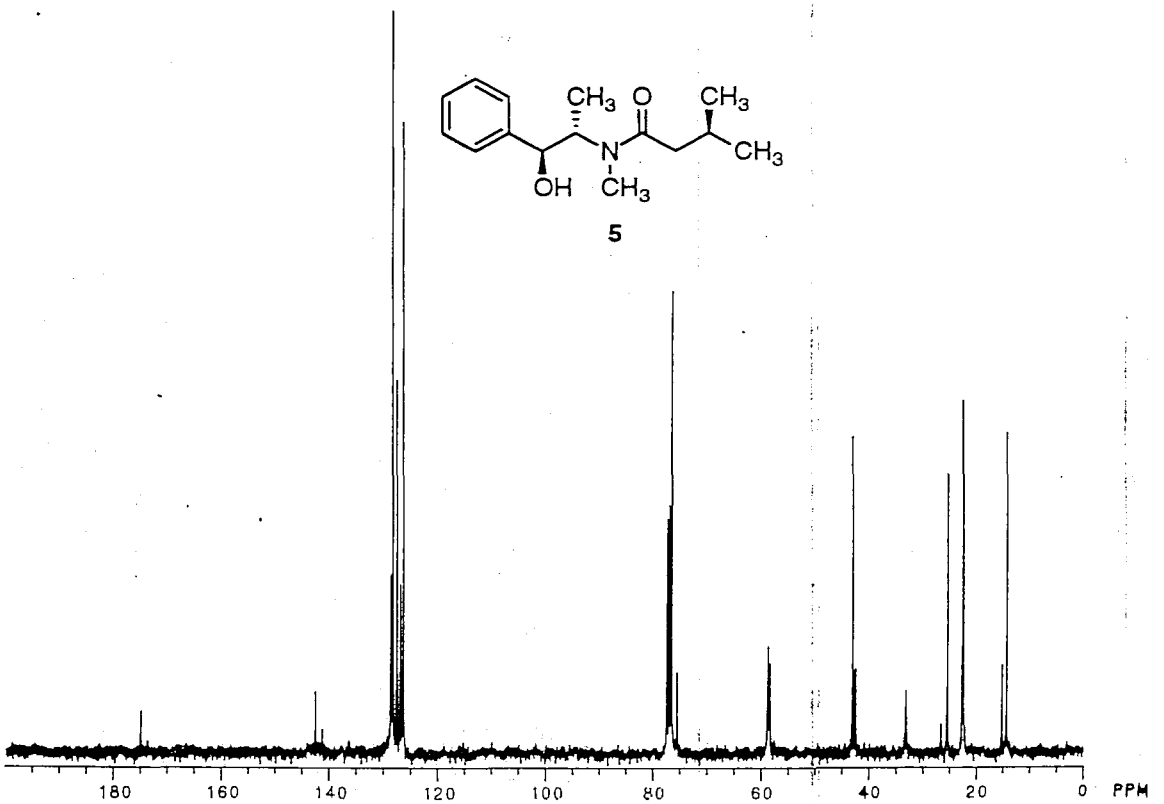

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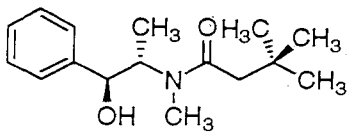
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O
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CH3
CH3
N
OH
CH3

6

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8
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5
4
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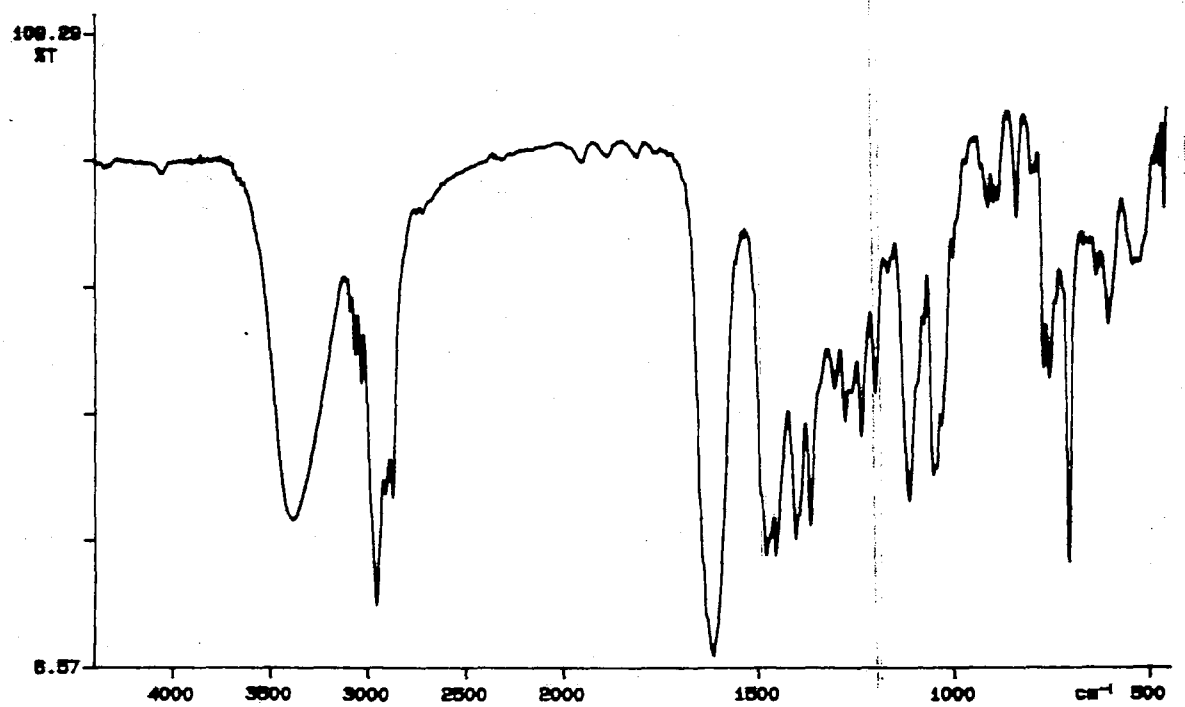
2
1
0
PPM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1000
cm-1
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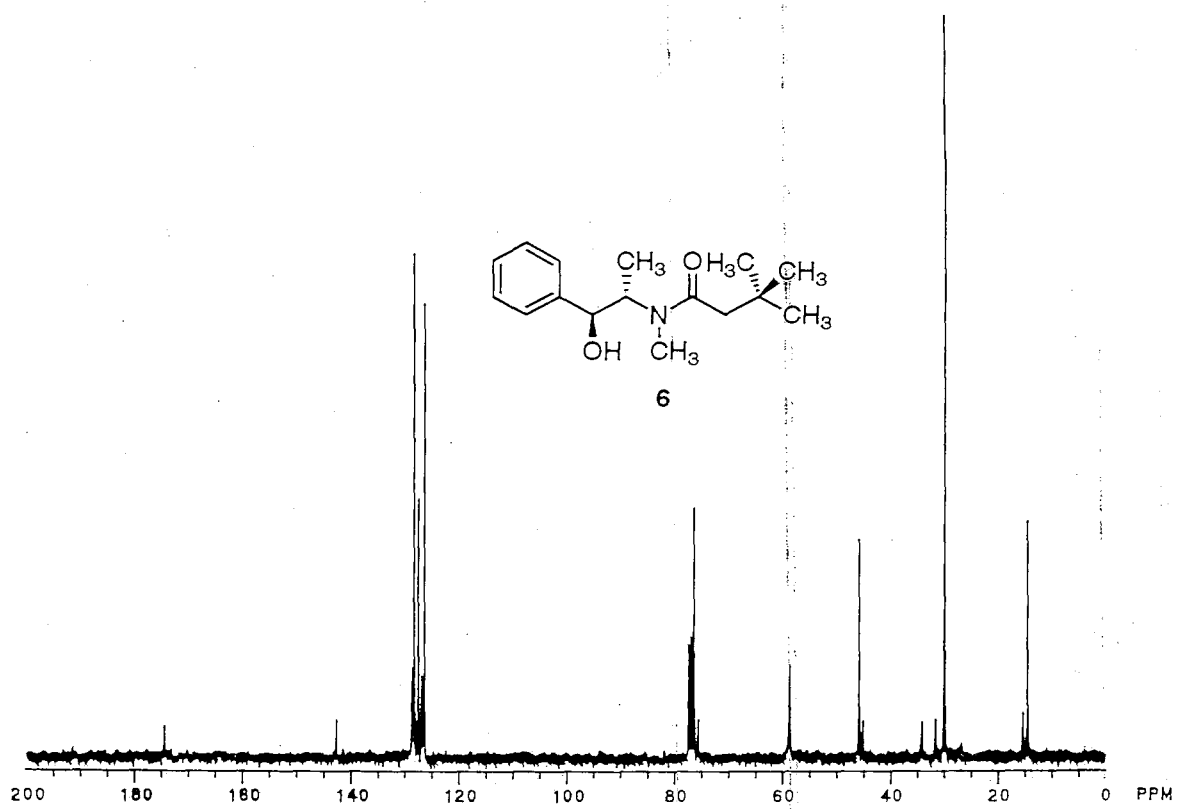

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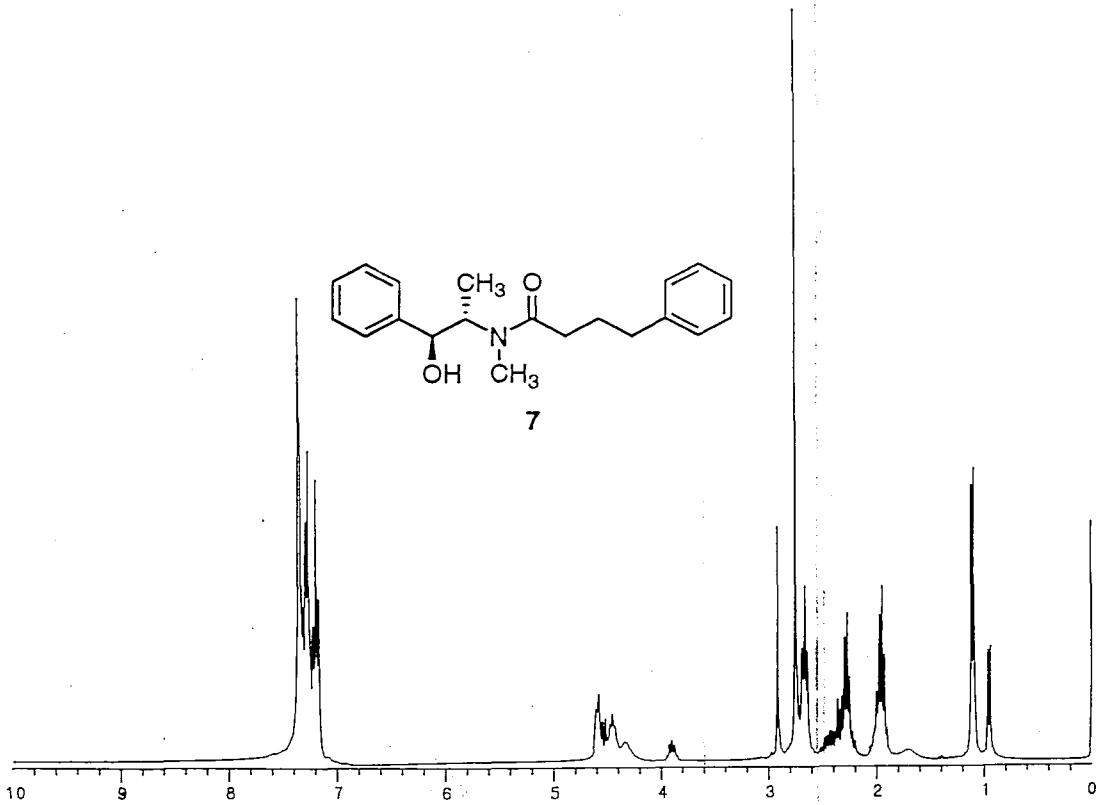
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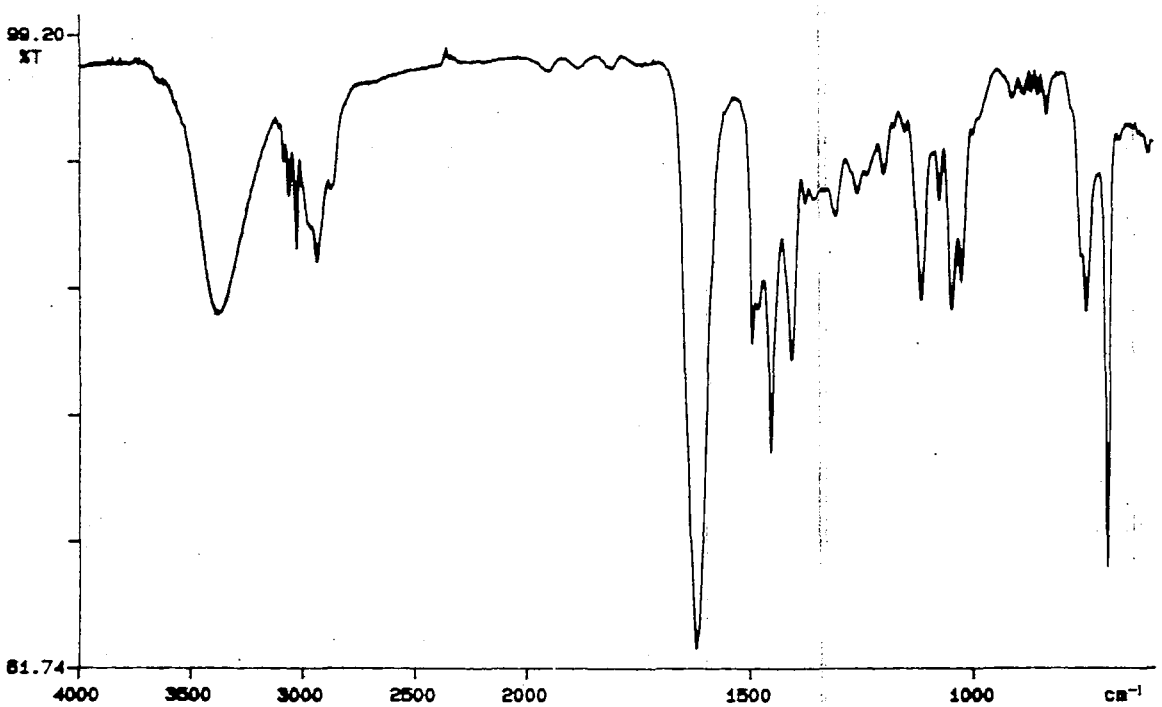
O
N
OH
CH3
10
9
8
7
6
5
4
3
2
1
0

7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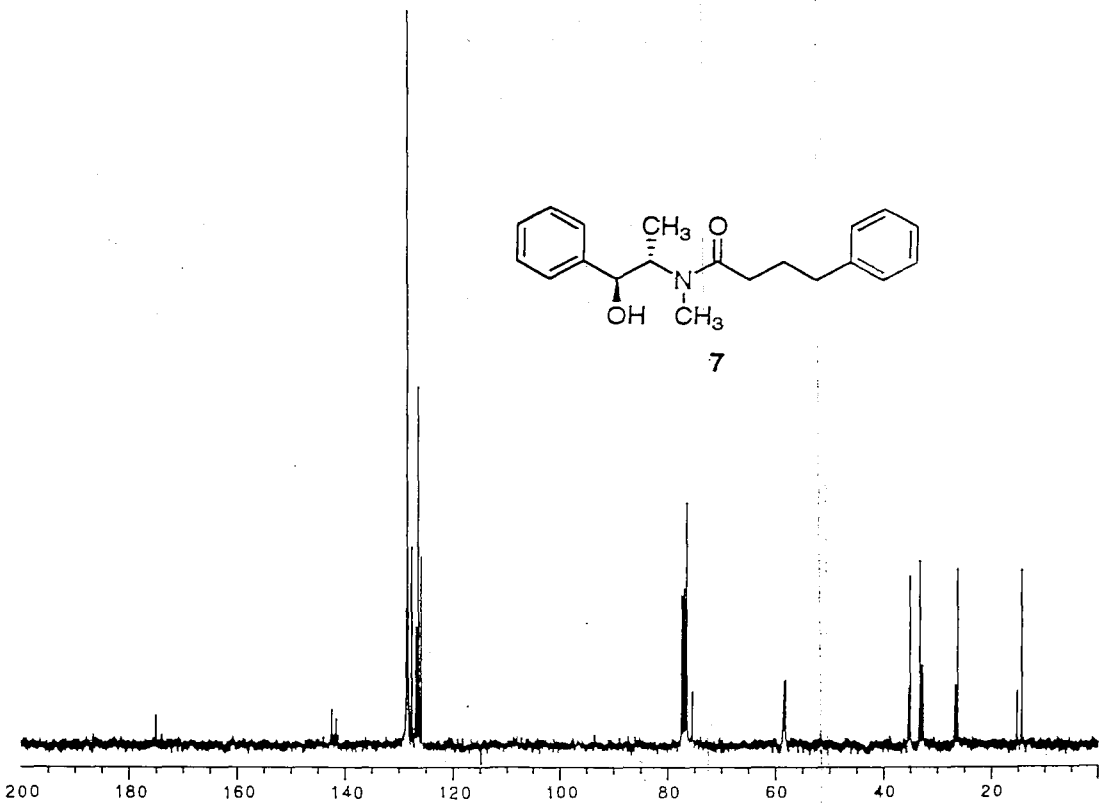
1000
cm-1



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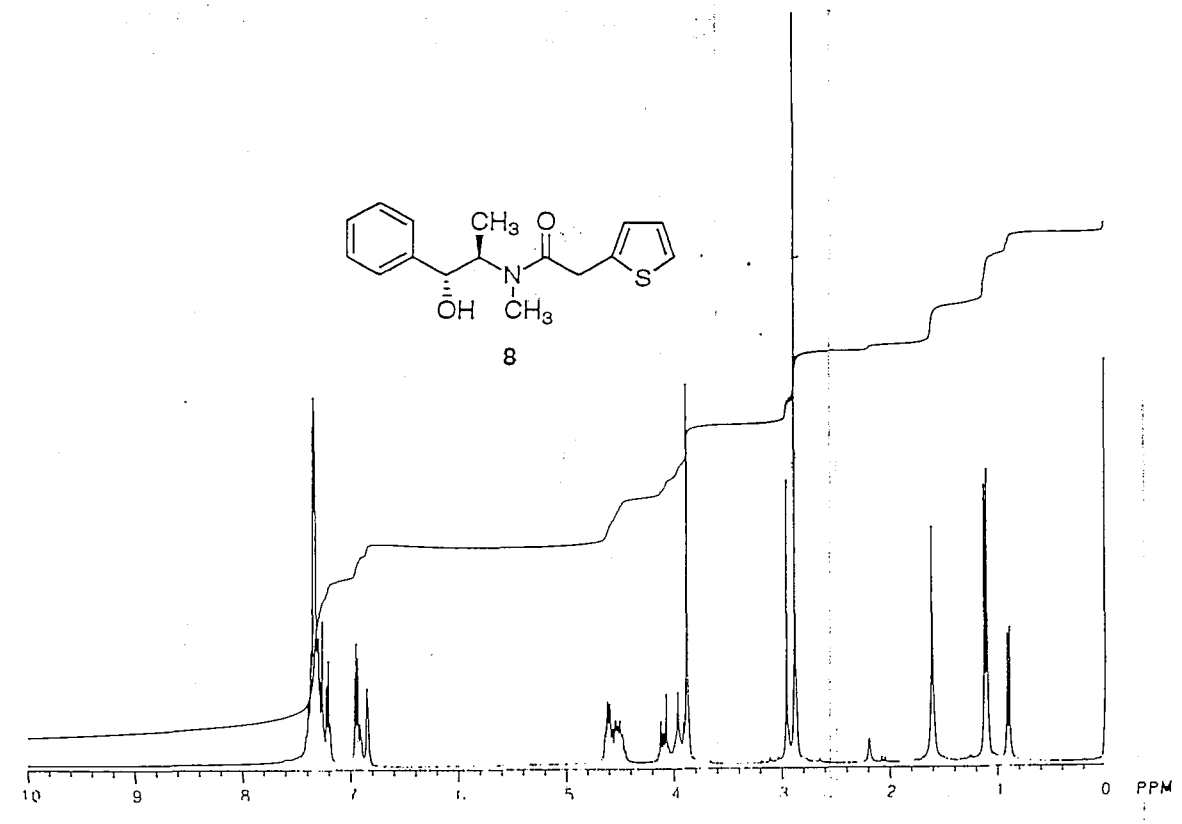
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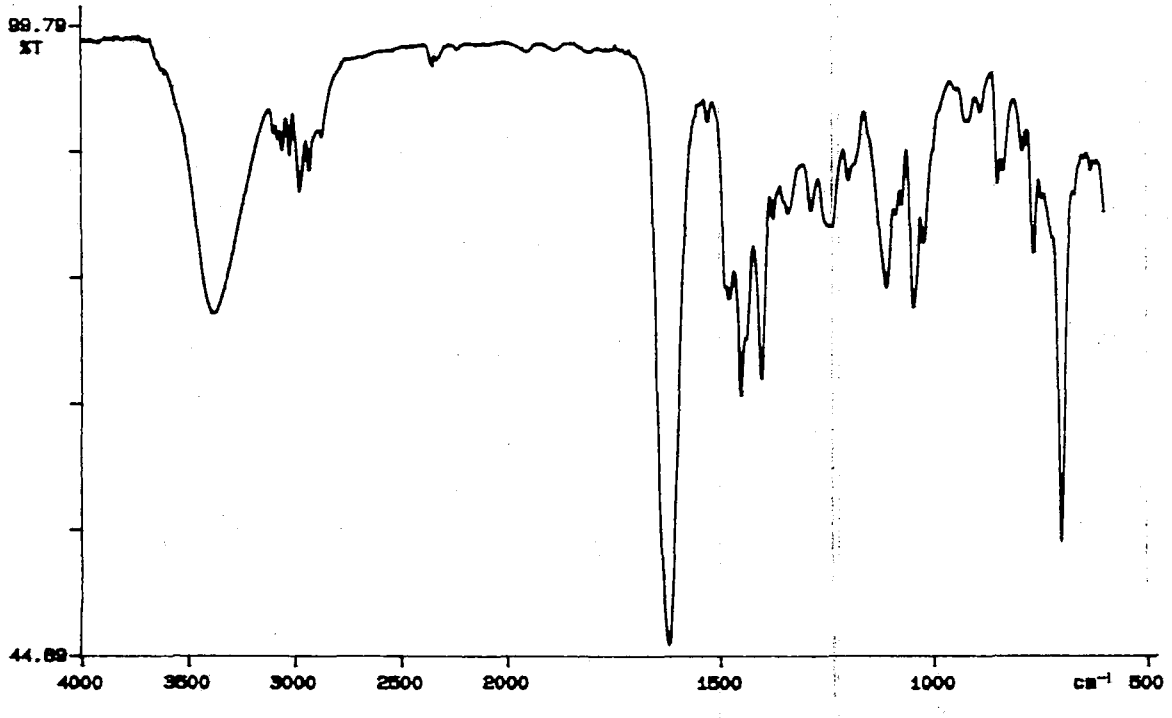
O
N
S
OH
CH3
10
9
8
7
6
5
4
3
2
1
0
PPM

8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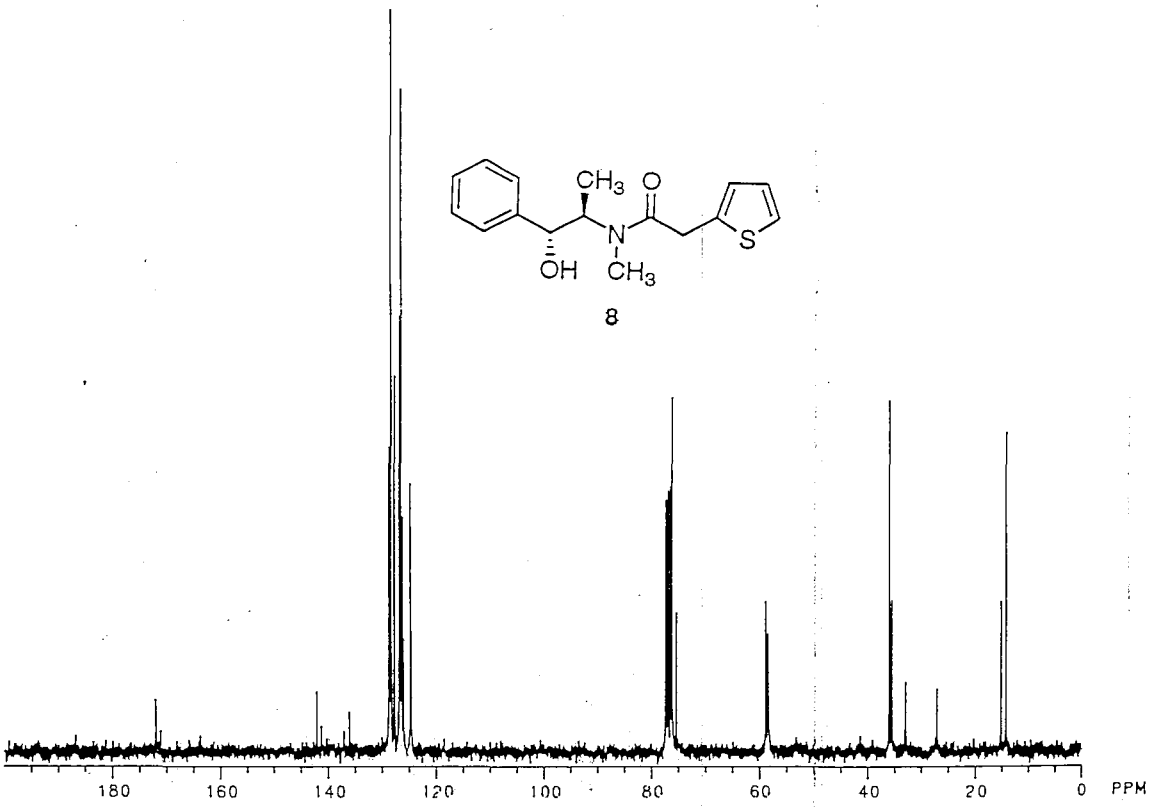
2500
2000
1500
1000
cm-1
500



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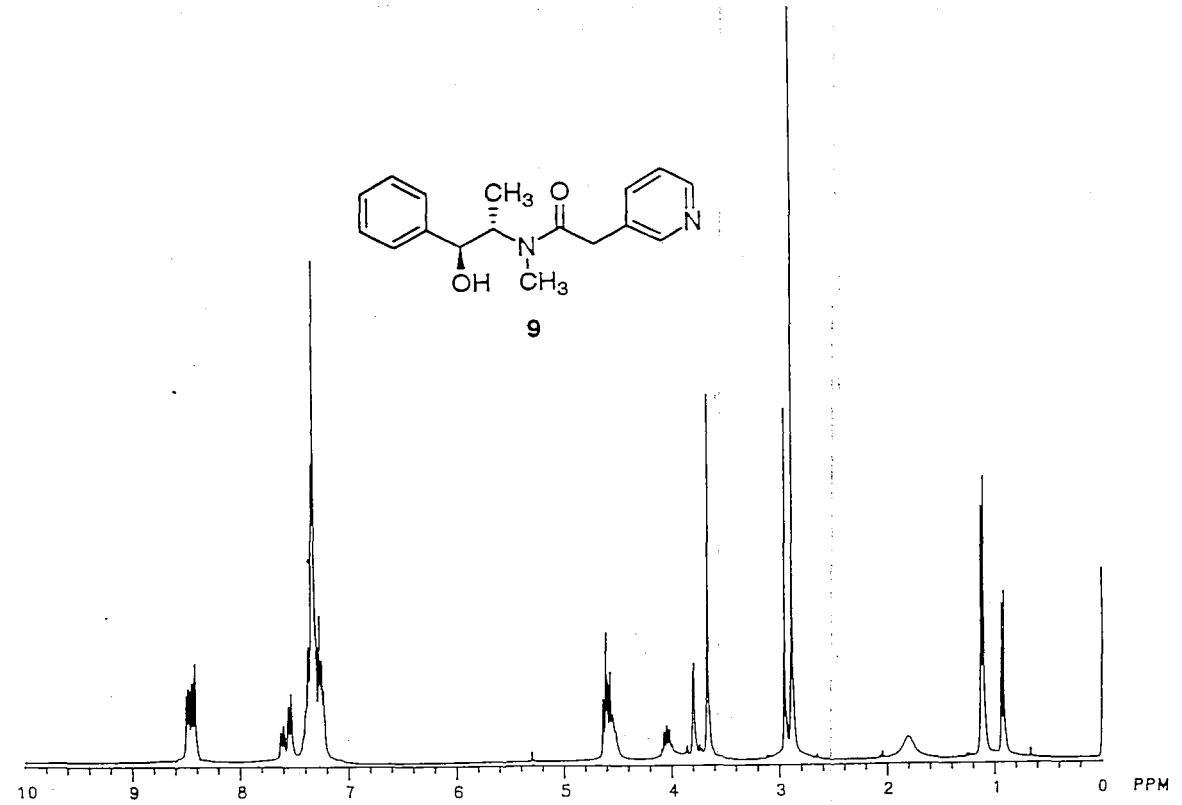
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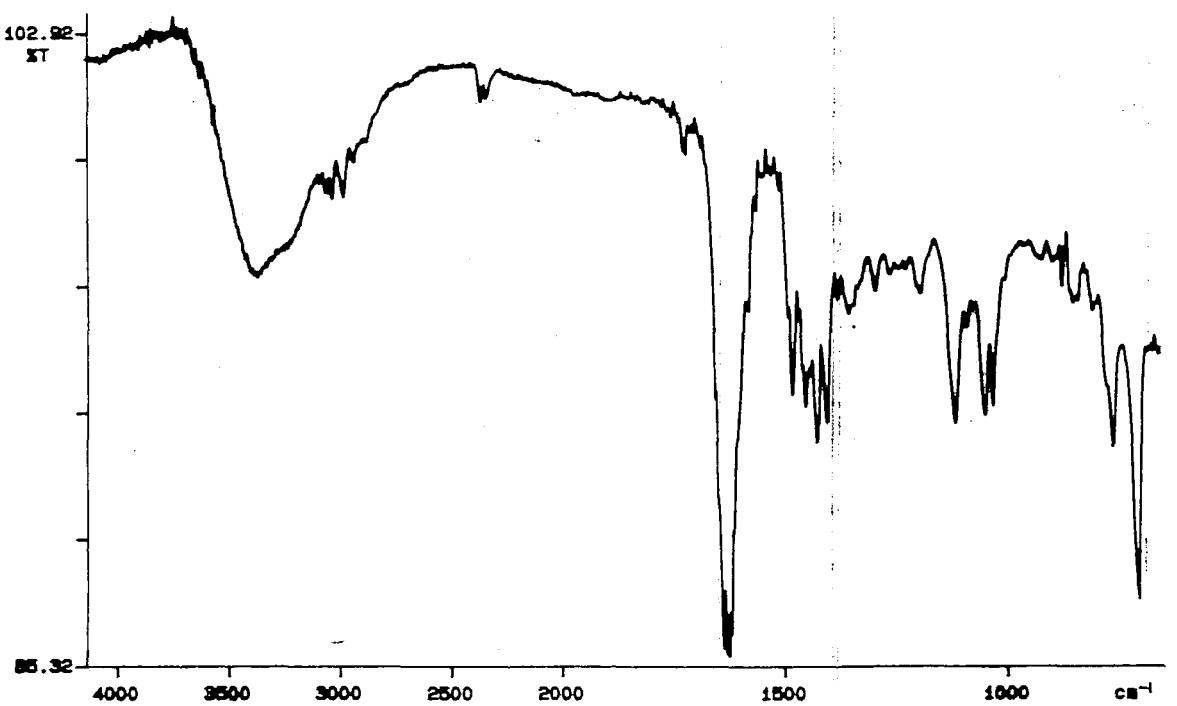
N
OH
CH3
10
9
8
7
6
5
4
3
2
1
0
PPM

9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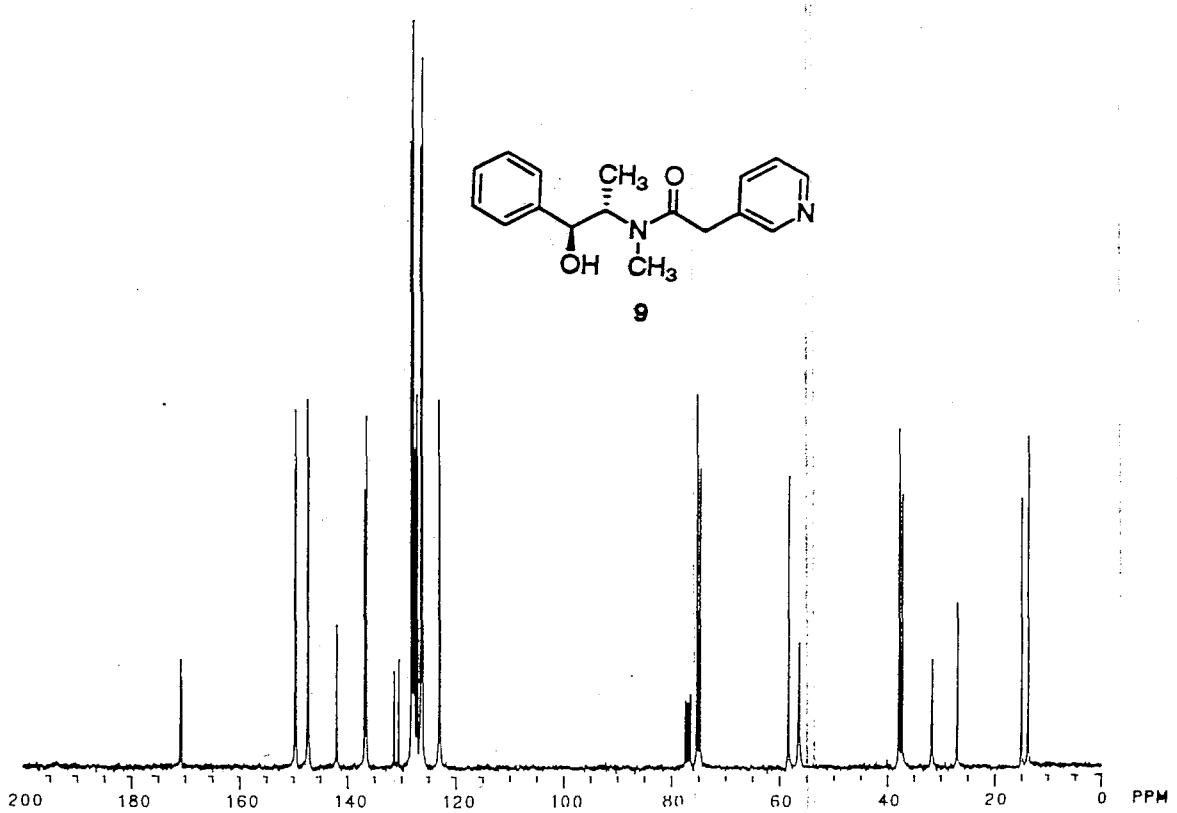
1000
cm-1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O
N
OH
CH3
N
9
200
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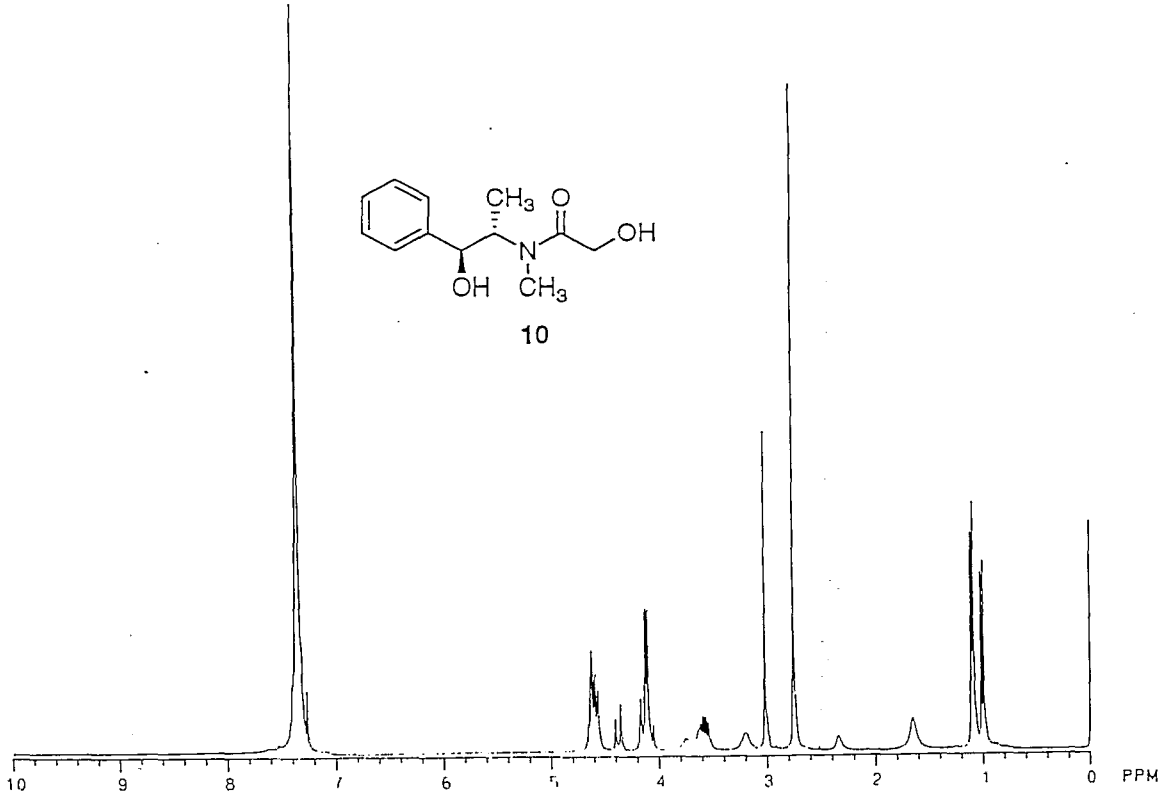
160
140
120
100
80
60
40
20
0
PPM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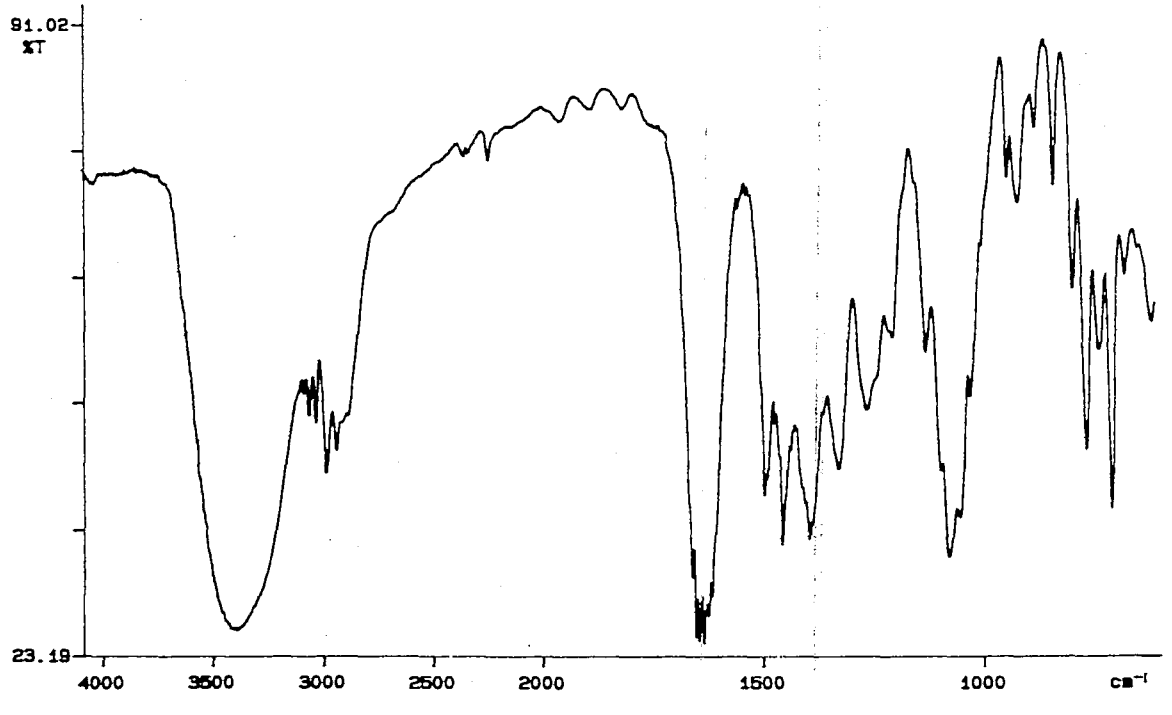
OH
N
OH
CH3
10
10
9
8
7
6
5
4
3
2
1
0
PPM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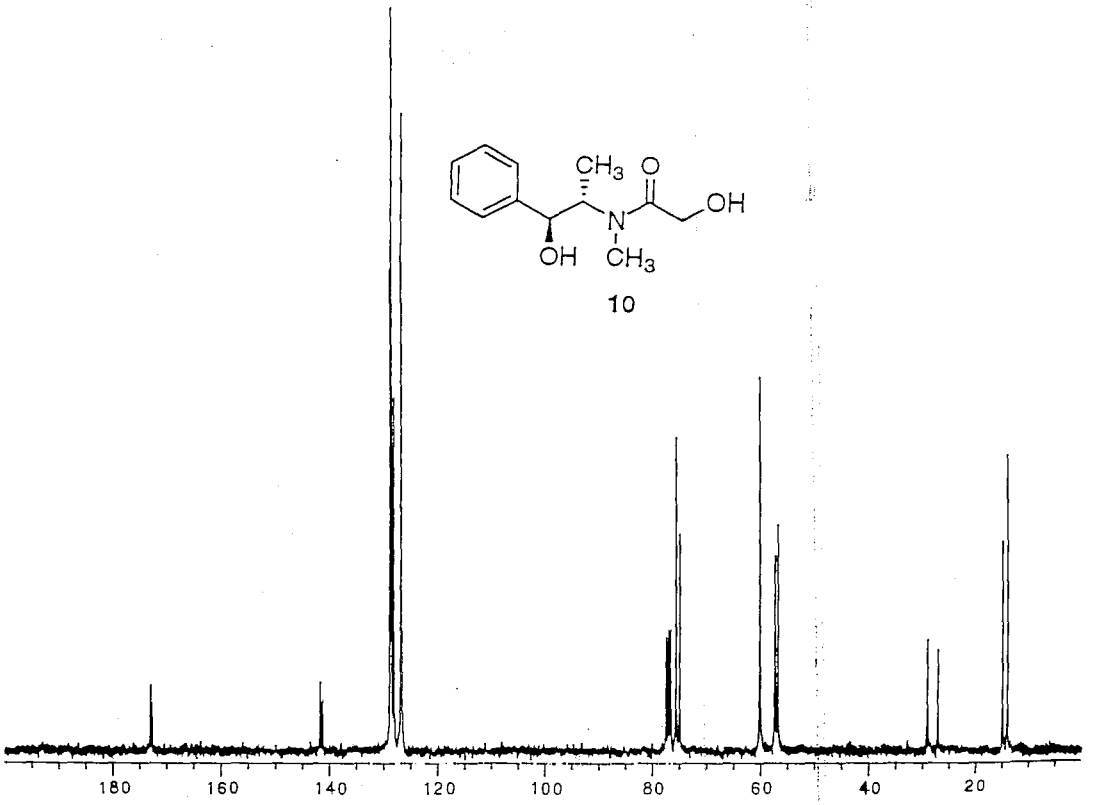
1000
cm-1



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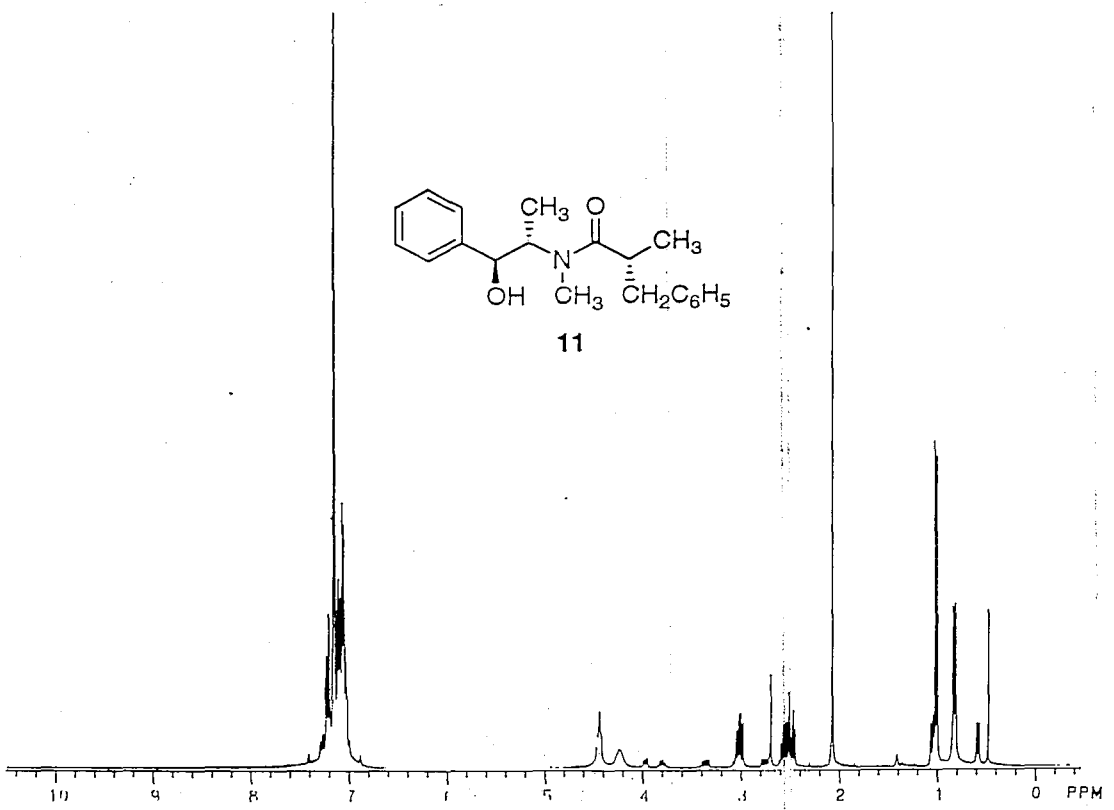
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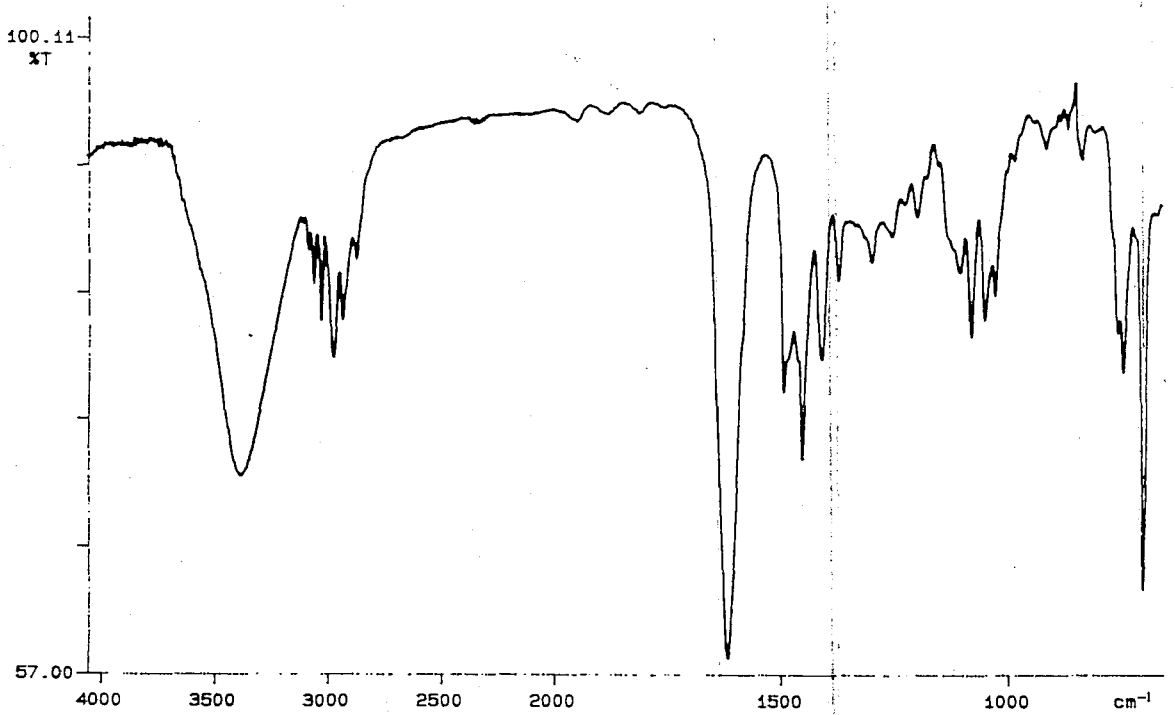
O
CH3
N
OH
CH3
CH2C6H5
11
10
9
8
7
6
5
4
3
2
1
0
PPM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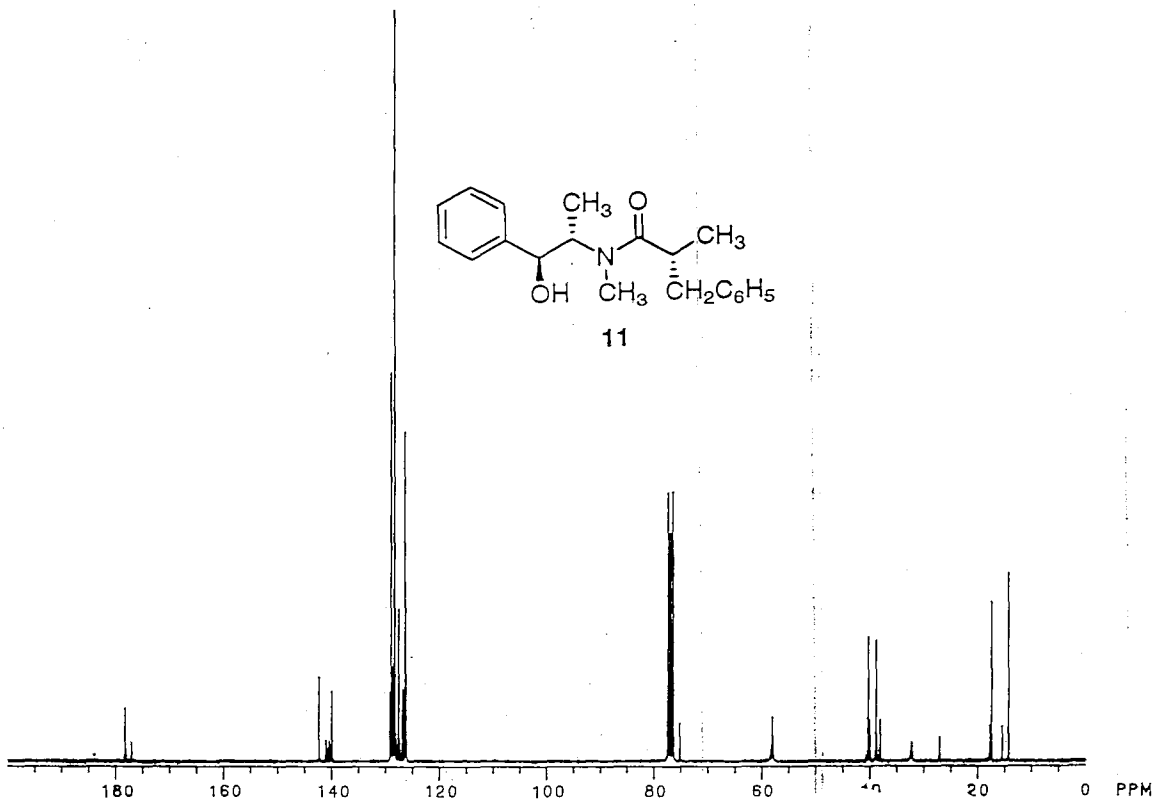
1000
cm-1



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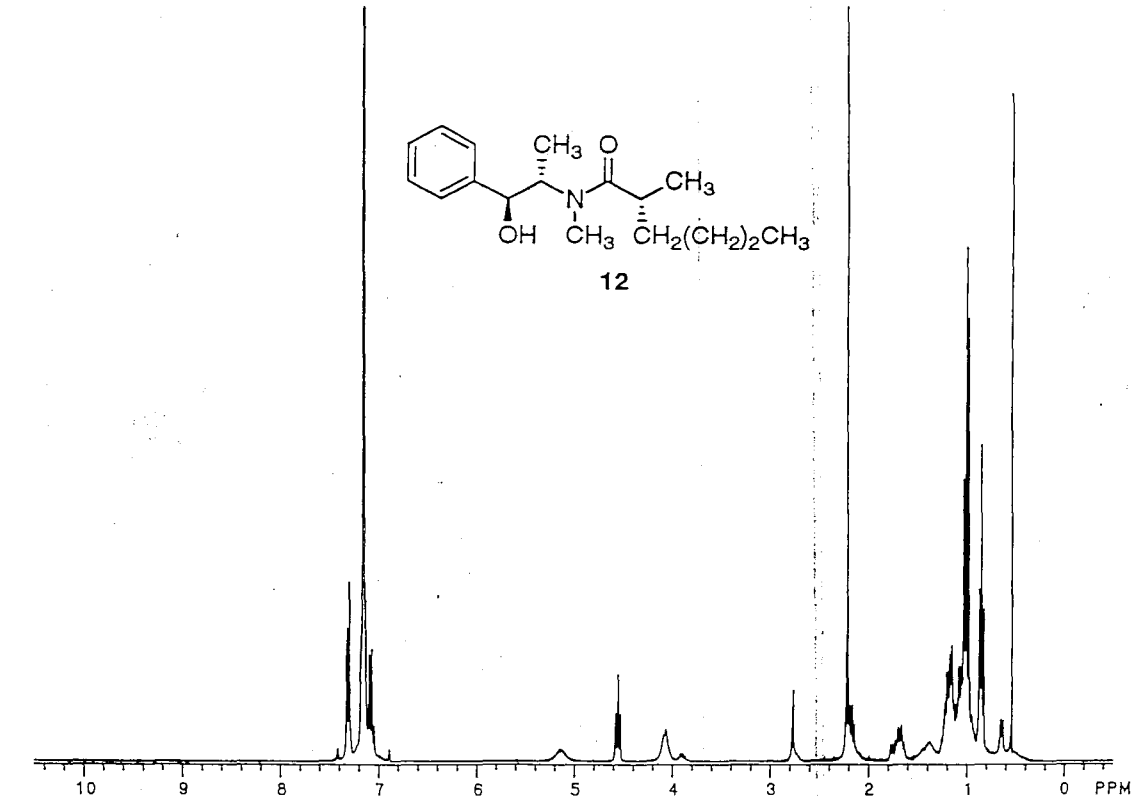
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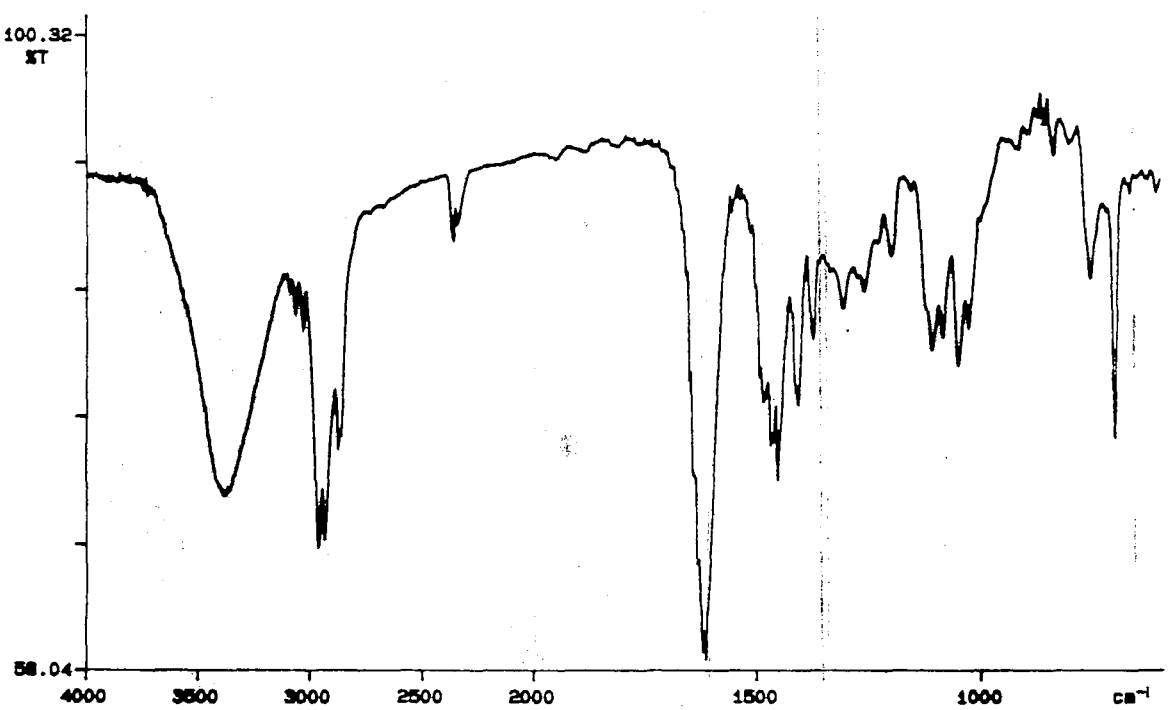
O
CH3
N
OH
CH3
CH2(CH2)2CH3
10
9
8
7
6
5
4
3
2
1
0
PPM

12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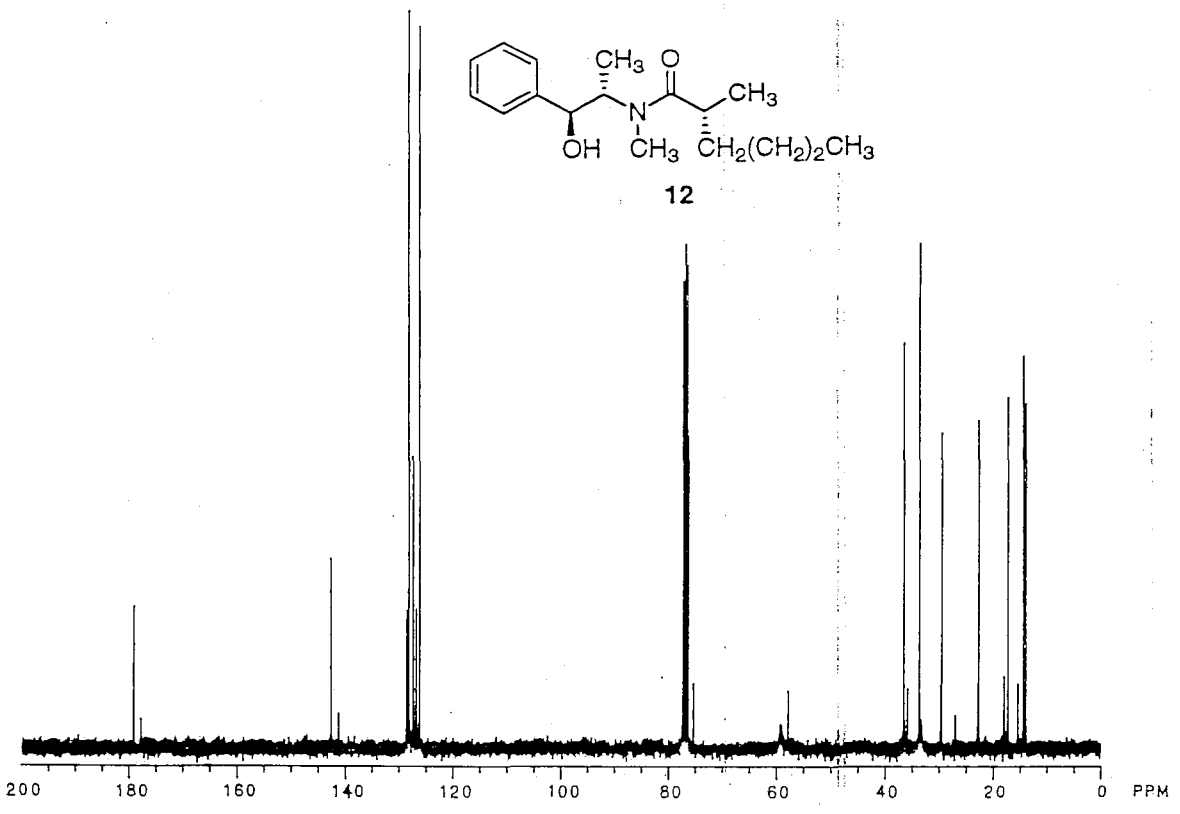
2500
2000
1500
1000
cm-1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O
CH3
N
OH
CH3
CH2(CH2)2CH3
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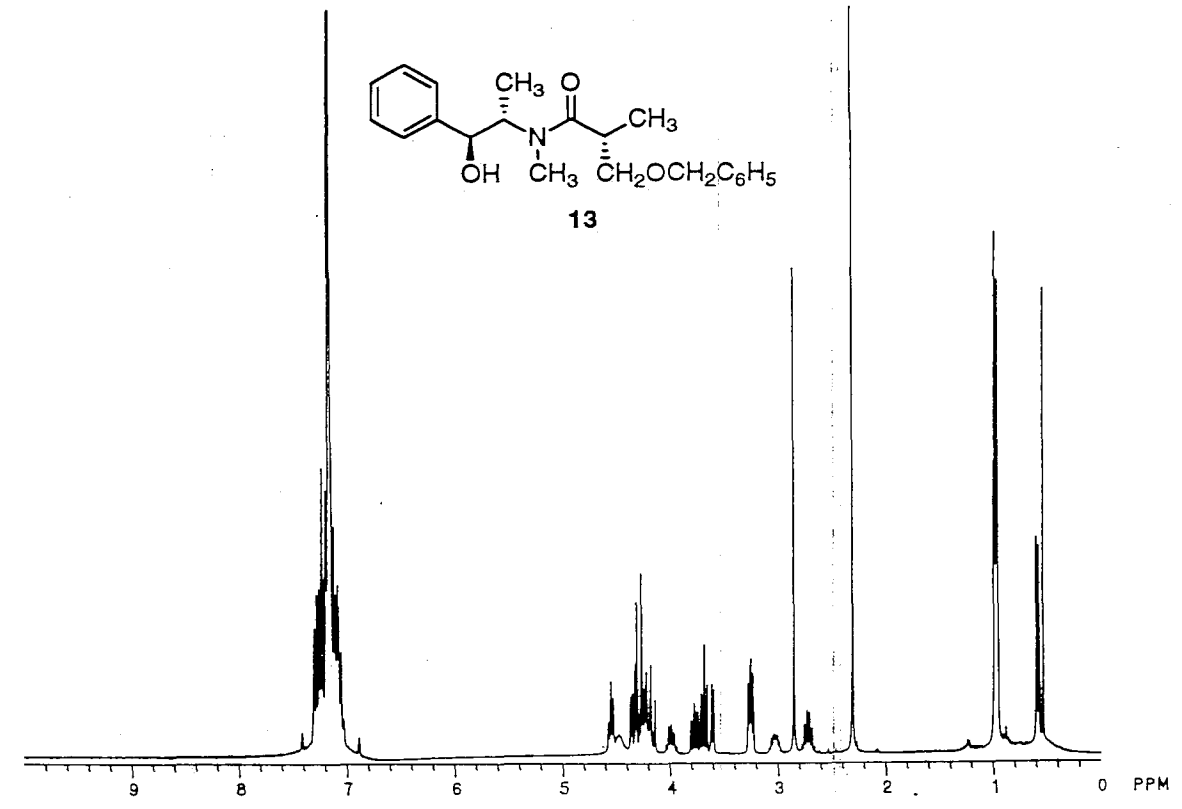
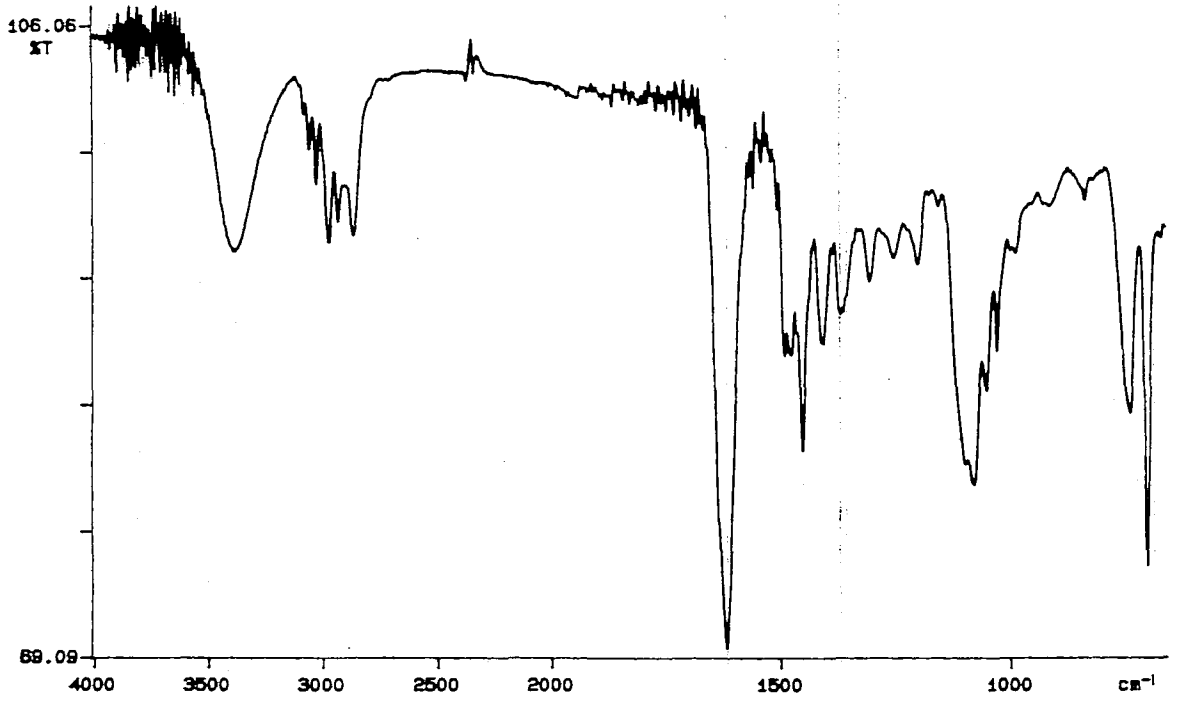
180
160
140
120
100
80
60
40
20
0
PPM

12


CH3 O
CH3
N
OH CH3 CH2OCH2C6H5
13
9
8
7
6
5
4
3
2
1
0
PPM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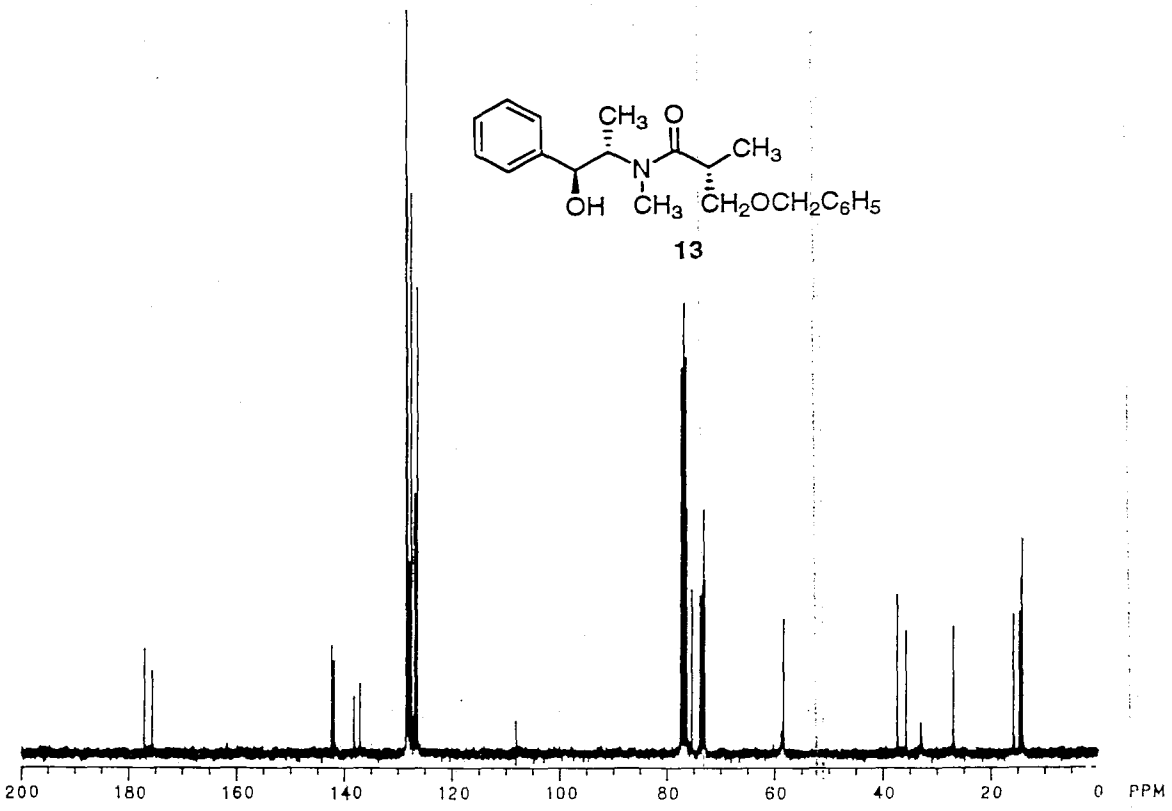
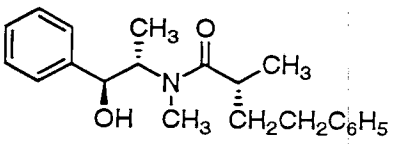
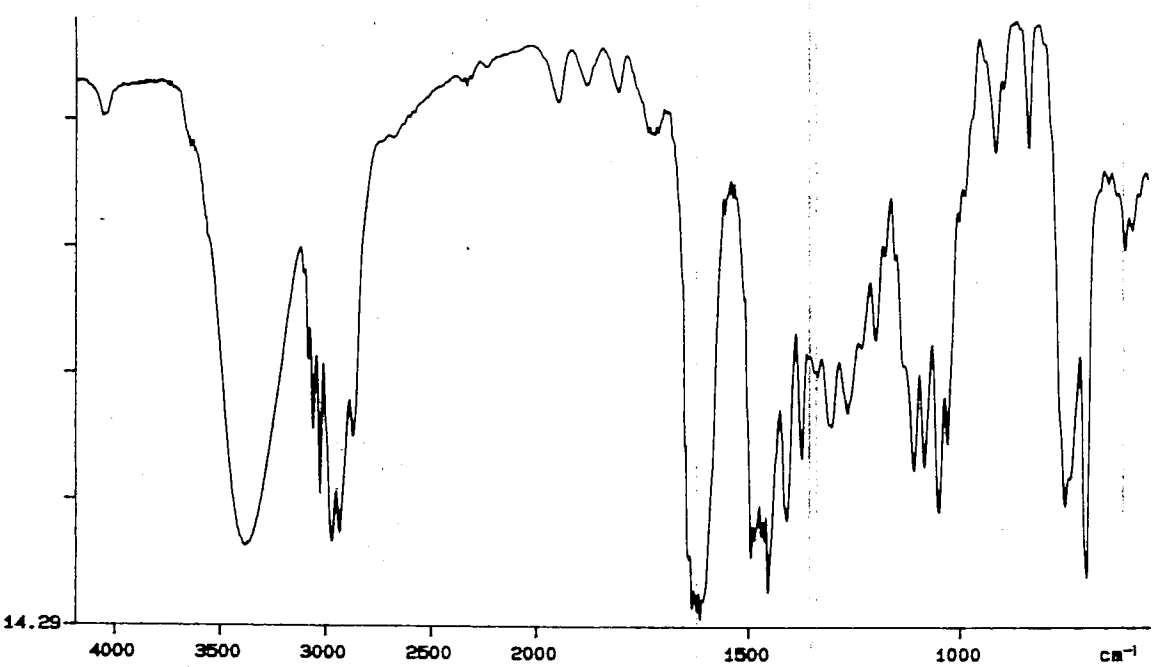
1000
cm-1


CH3
O
CH3
N
OH
CH3
CH2OCH2C6H5
13
200
180
160
140
120
100
80
60
40
20
0
PPM


CH3
O
CH3
N
OH
CH3
CH2CH2C6H5

14

9
8
7
6
5
4
3
2
1
0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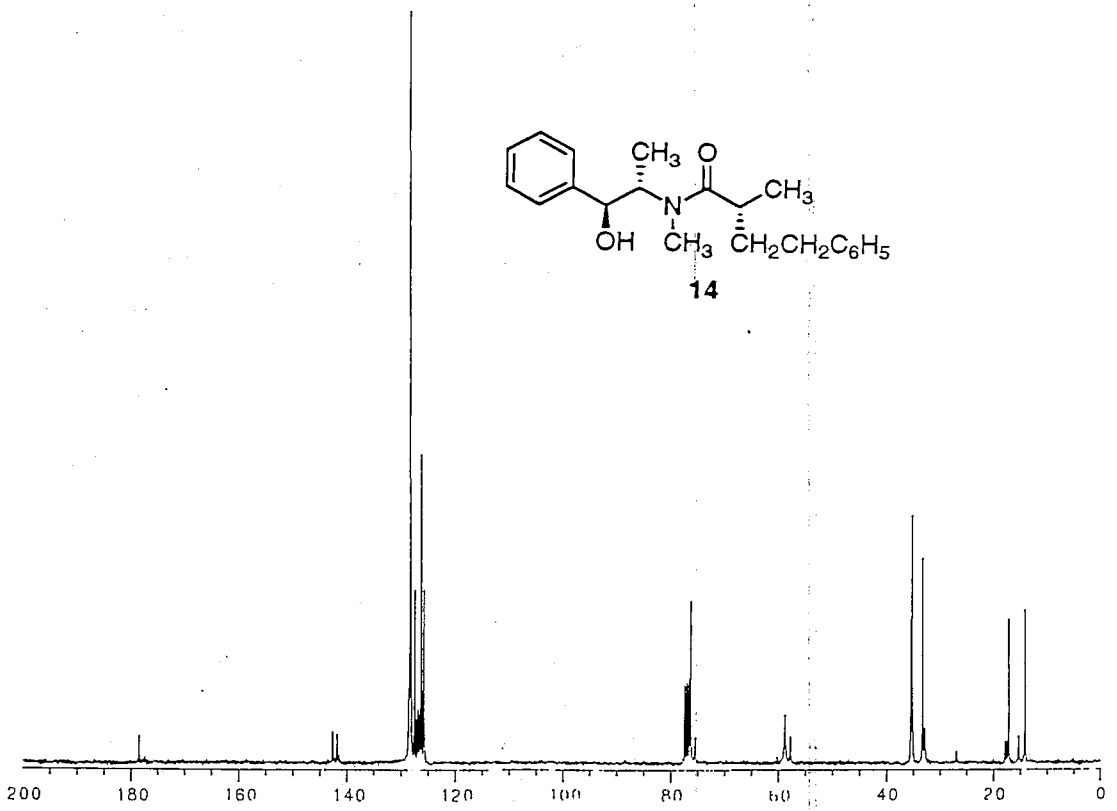
1000
cm-1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O
CH3
N
OH
CH3
CH2CH2C6H5
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180
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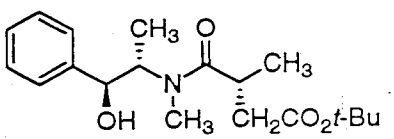
140
120
100
80
60
40
20
0

14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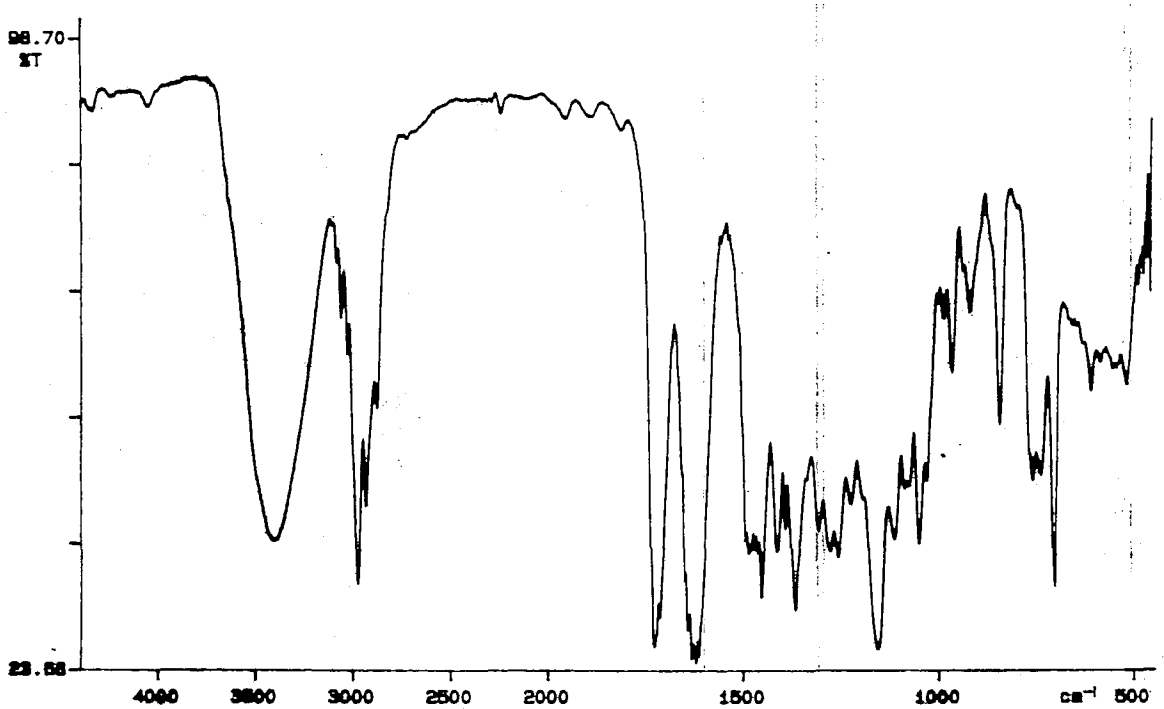
O
CH3
N
OH
CH3
CH2CO2t-Bu

15

10
9
8
7
6
5
4
3
2
1
0
PPM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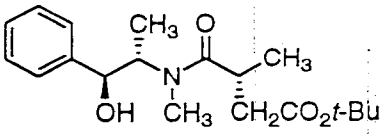
1000
cm-1
500



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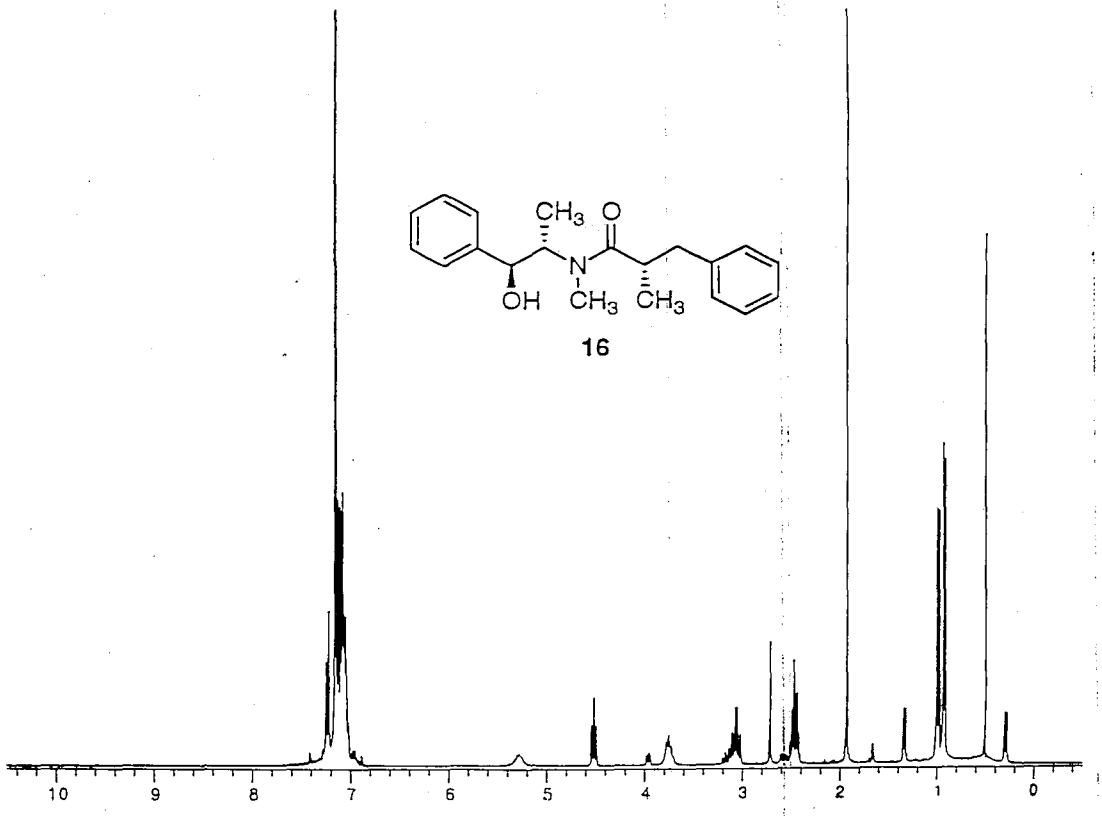
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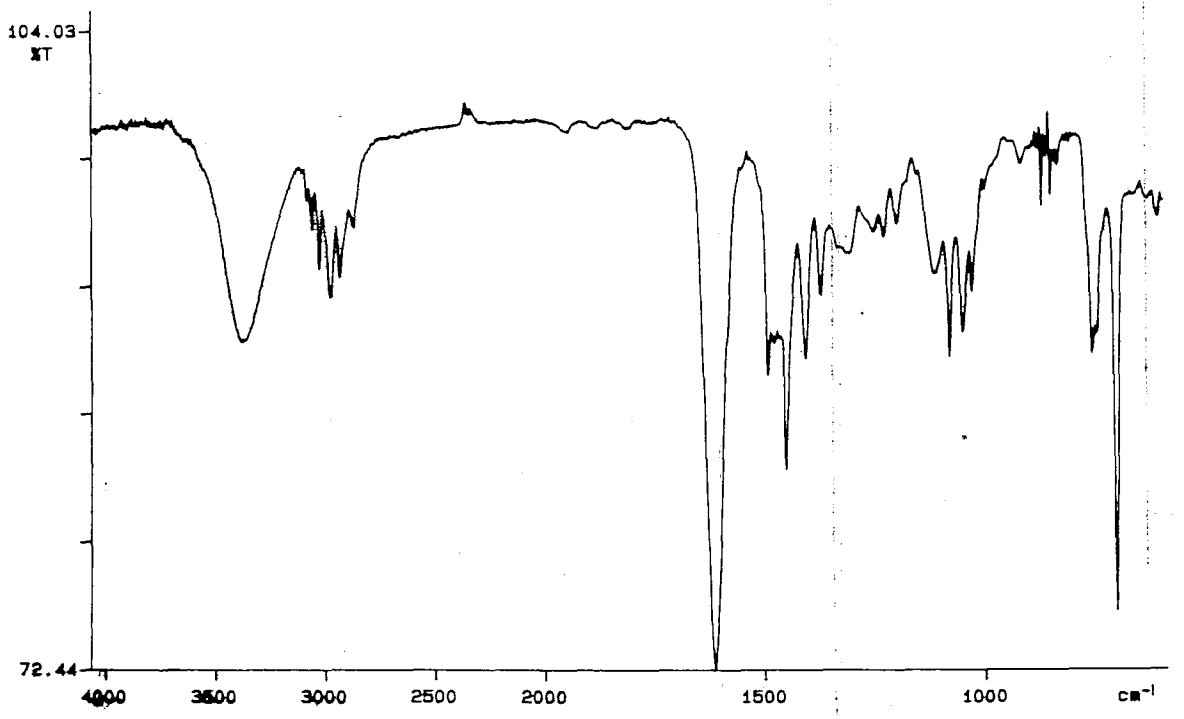
N
OH CH3 CH3
16
10 9 8 7 6 5 4 3 2 1 0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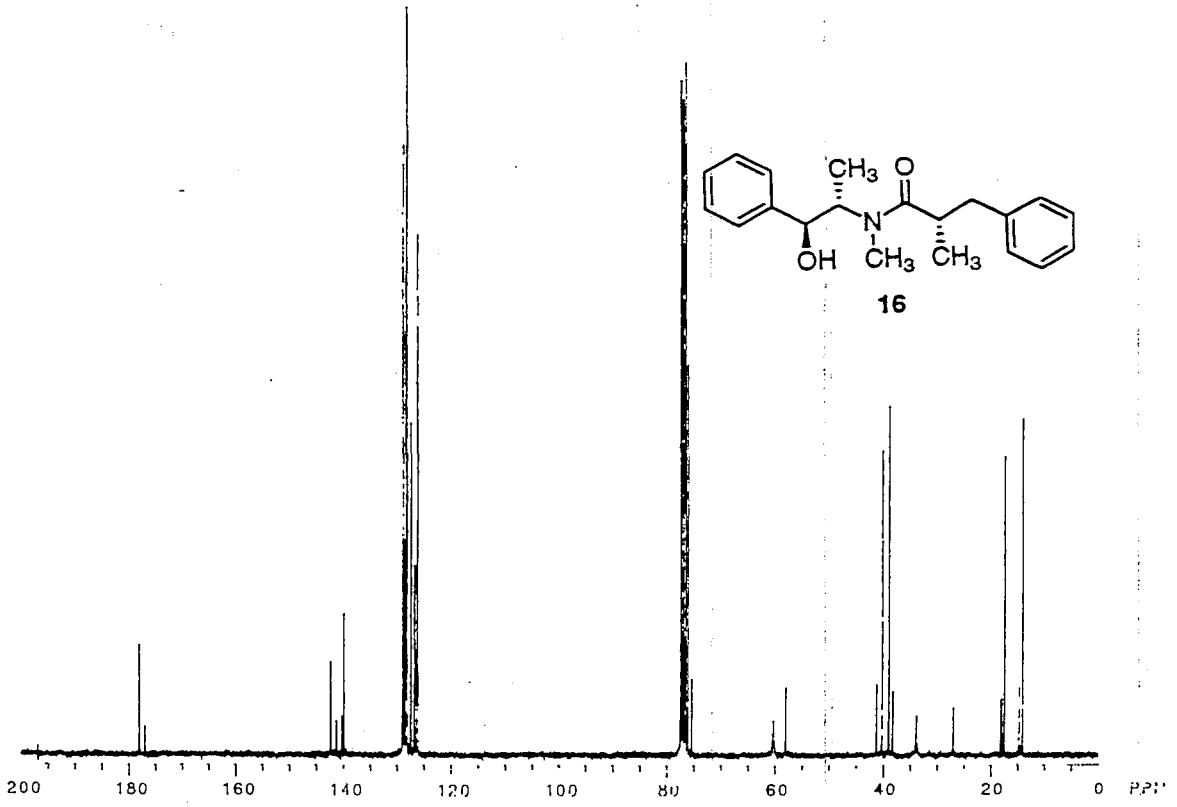
72.44
4000 3500 3000 2500 2000 1500 1000
cm-1



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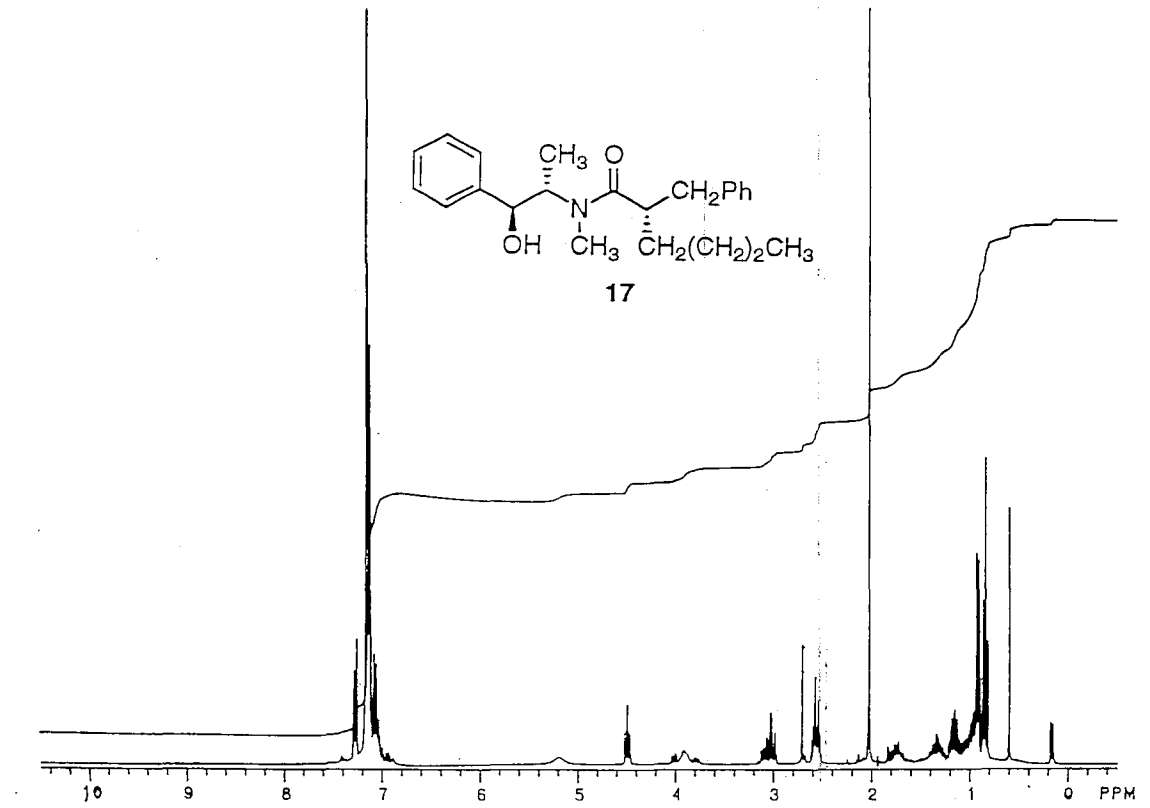
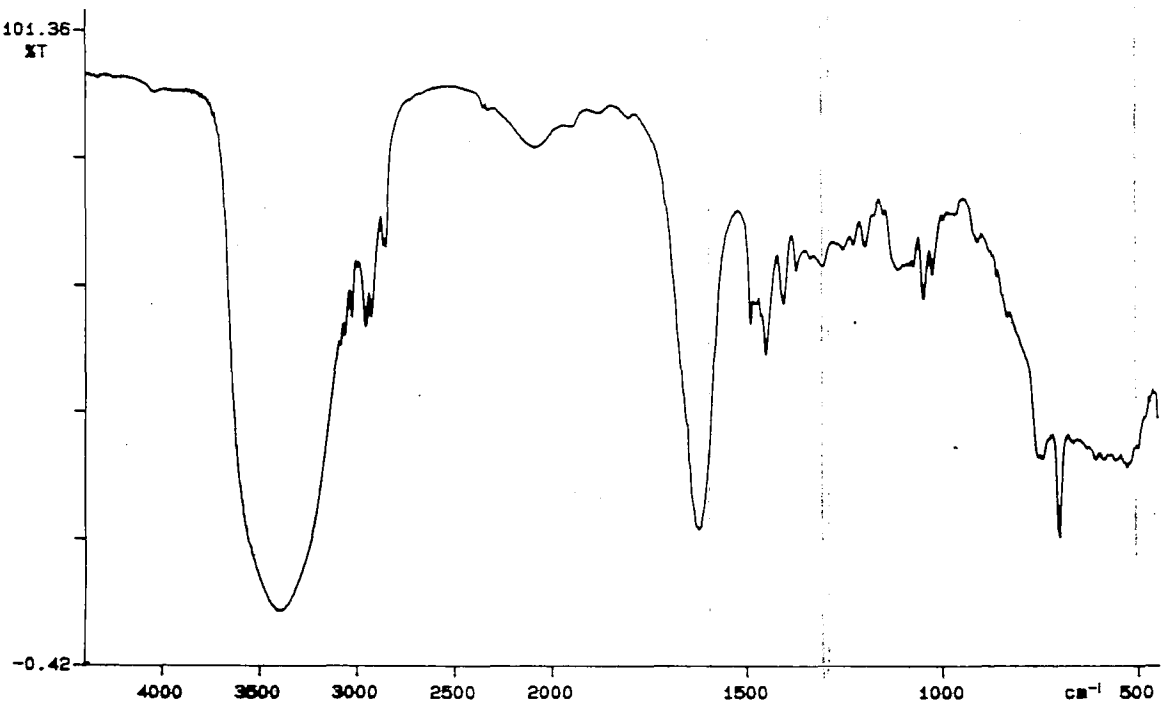
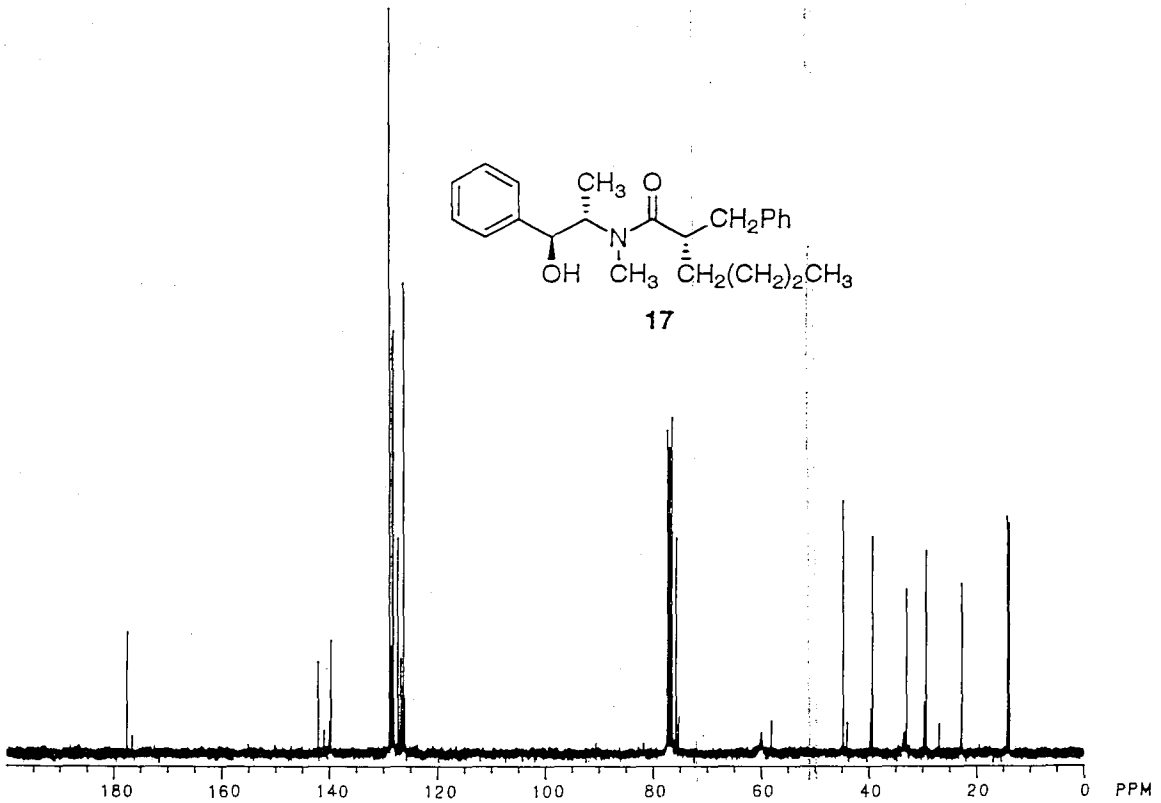
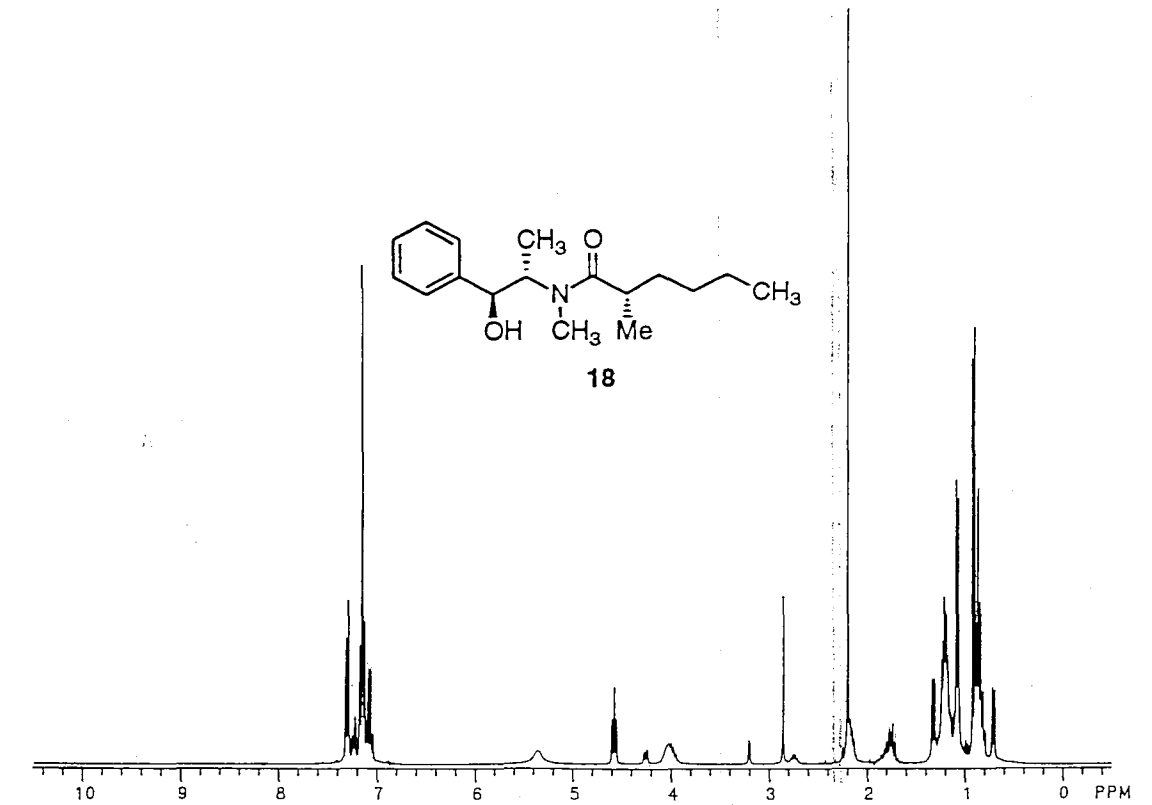
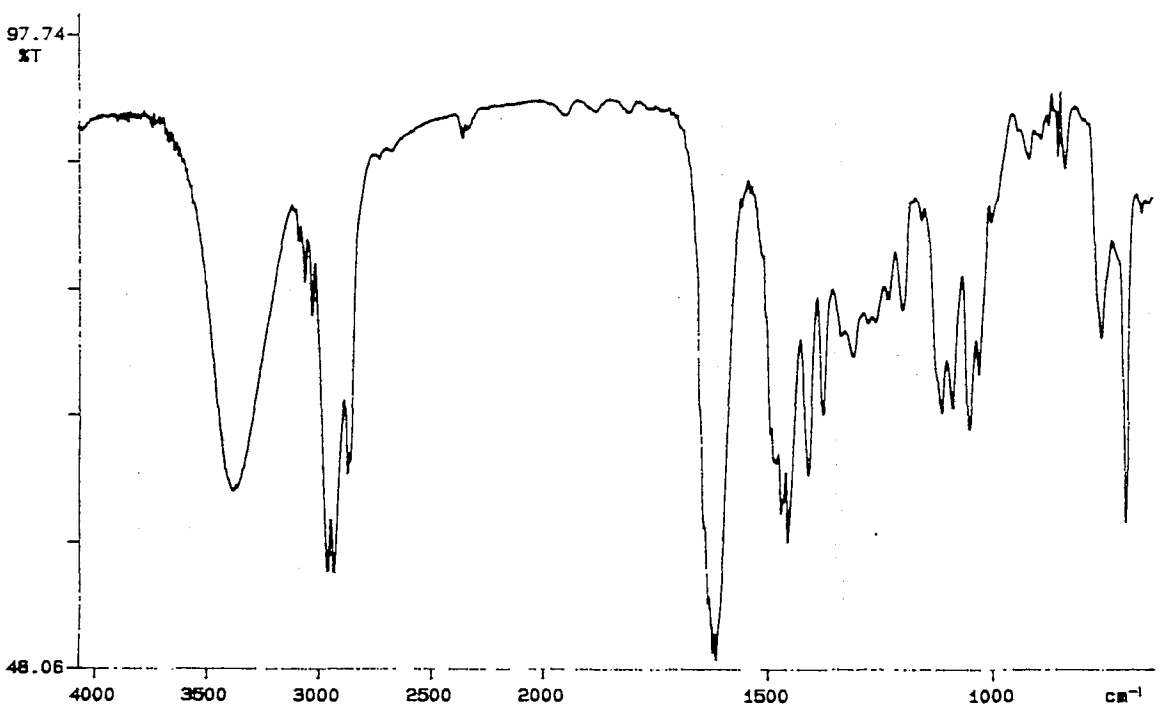

CH3 O
CH2Ph
N
OH CH3 CH2(CH2)2CH3
17
10 9 8 7 6 5 4 3 2 1 0 PPM

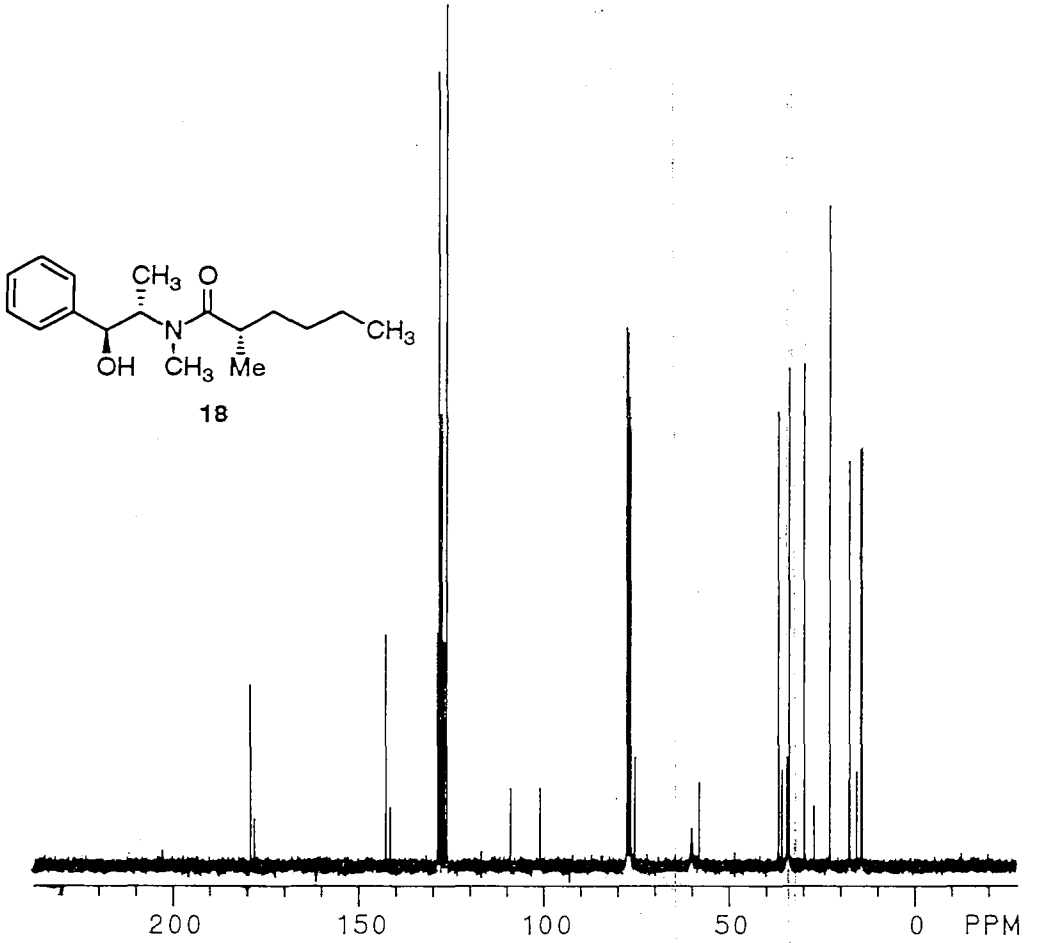

101.36
%T
-0.42
4000 3500 3000 2500 2000 1500 1000 cm-1 500

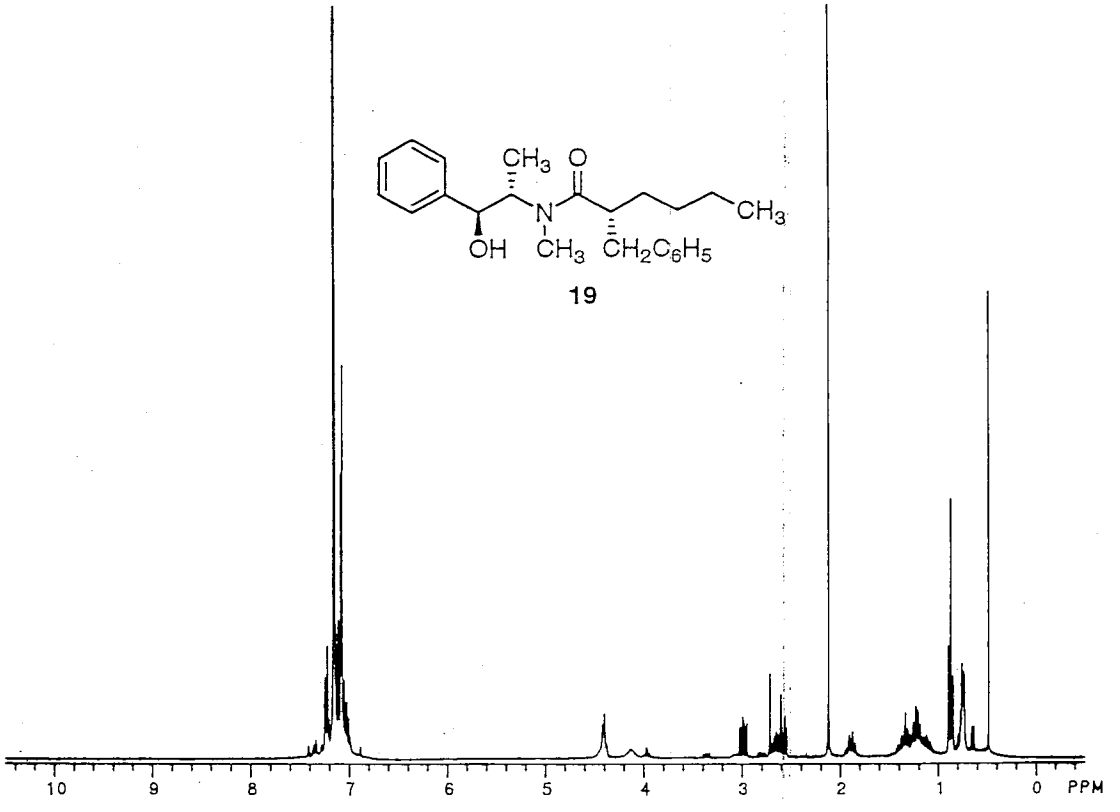

CH3
O
CH2Ph
N
OH
CH3
CH2(CH2)2CH3
17
180
160
140
120
100
80
60
40
20
0
PPM

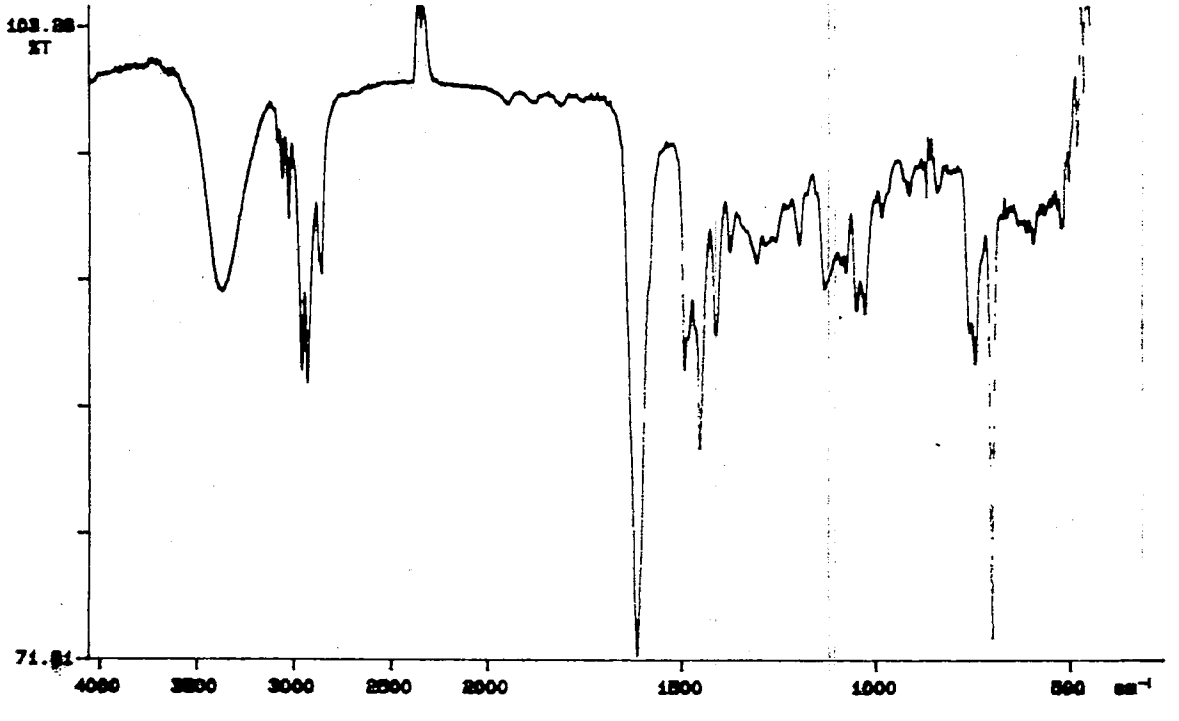

CH3
O
N
CH3
OH
CH3
Me
CH3
10
9
8
7
6
5
4
3
2
1
0
PPM

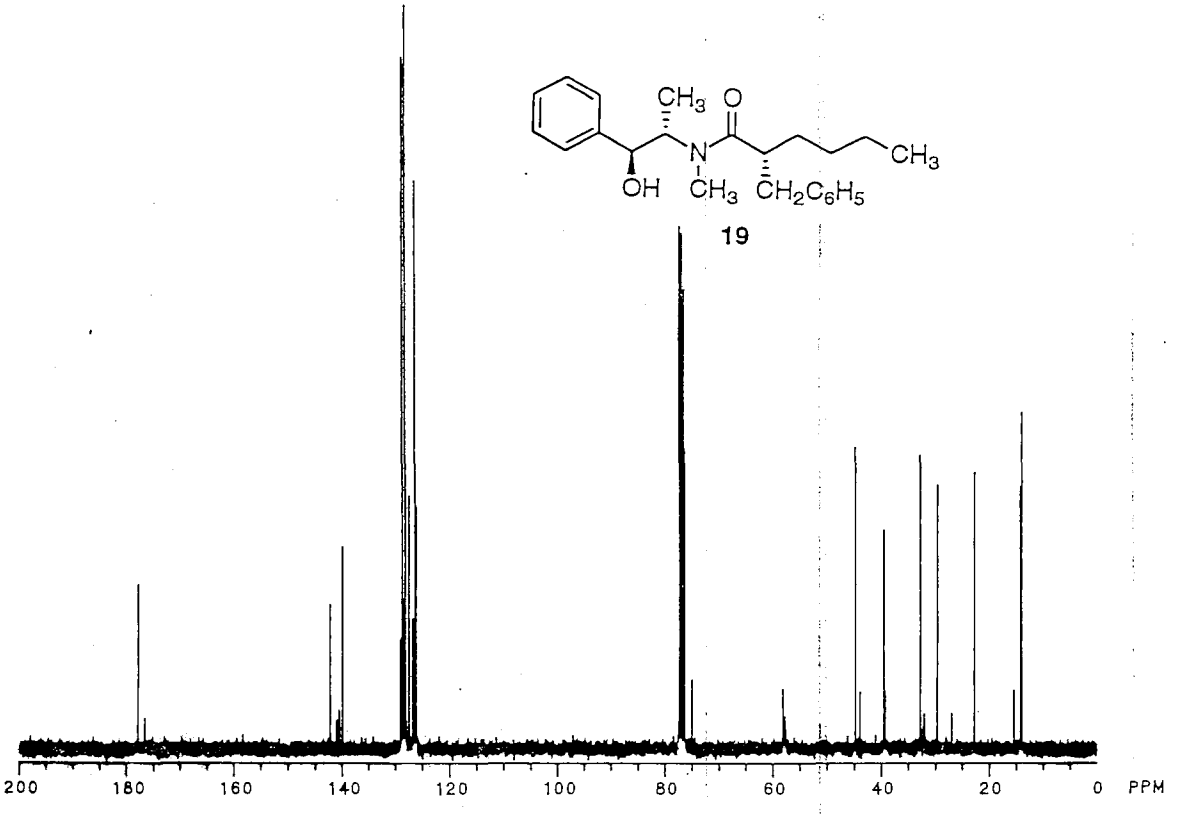
18

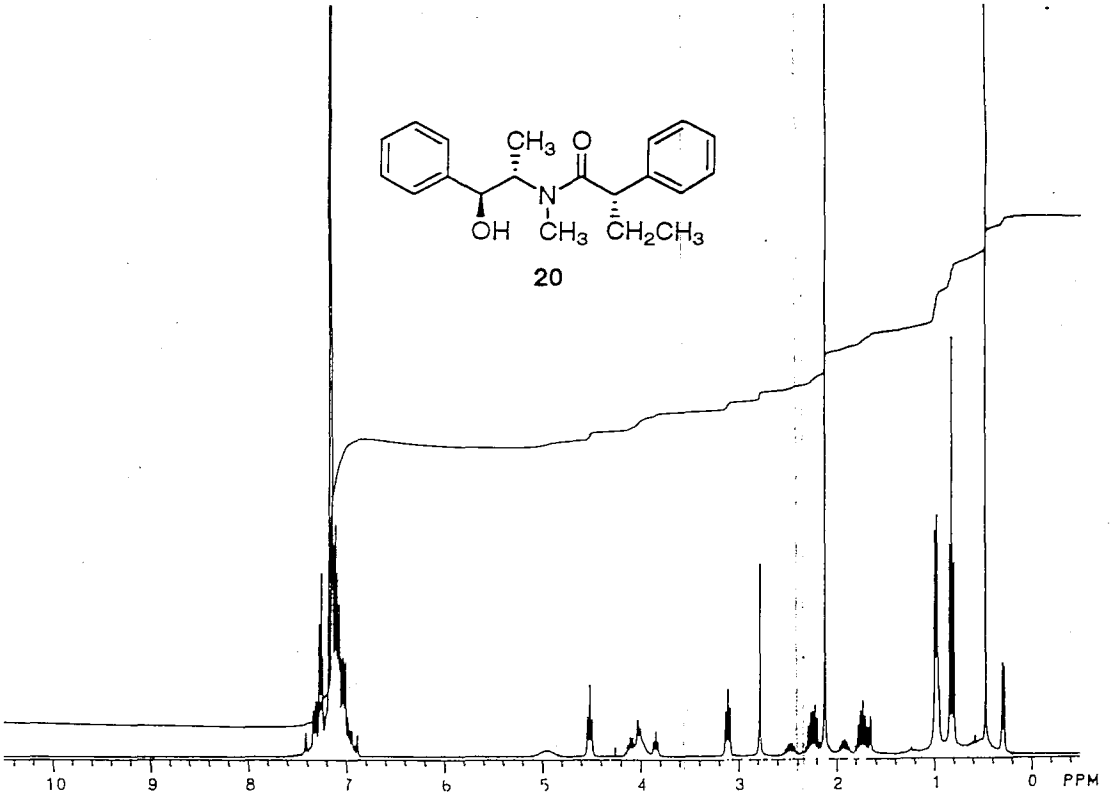

97.74
%T
48.06
4000
3500
3000
2500
2000
1500
1000
cm-1


CH3
O
N
CH3
OH
CH3
Me
18
200
150
100
50
0
PPM

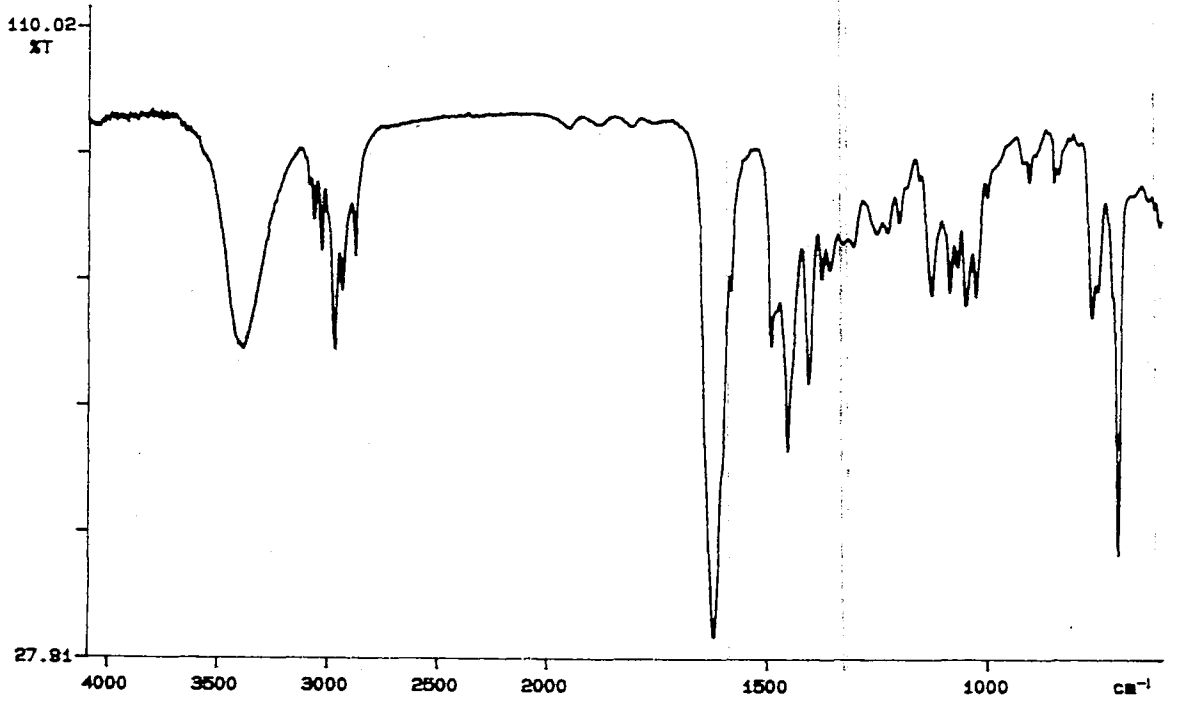

CH3
O
N
CH3
OH
CH3
CH2C6H5
19
10
9
8
7
6
5
4
3
2
1
0
PPM

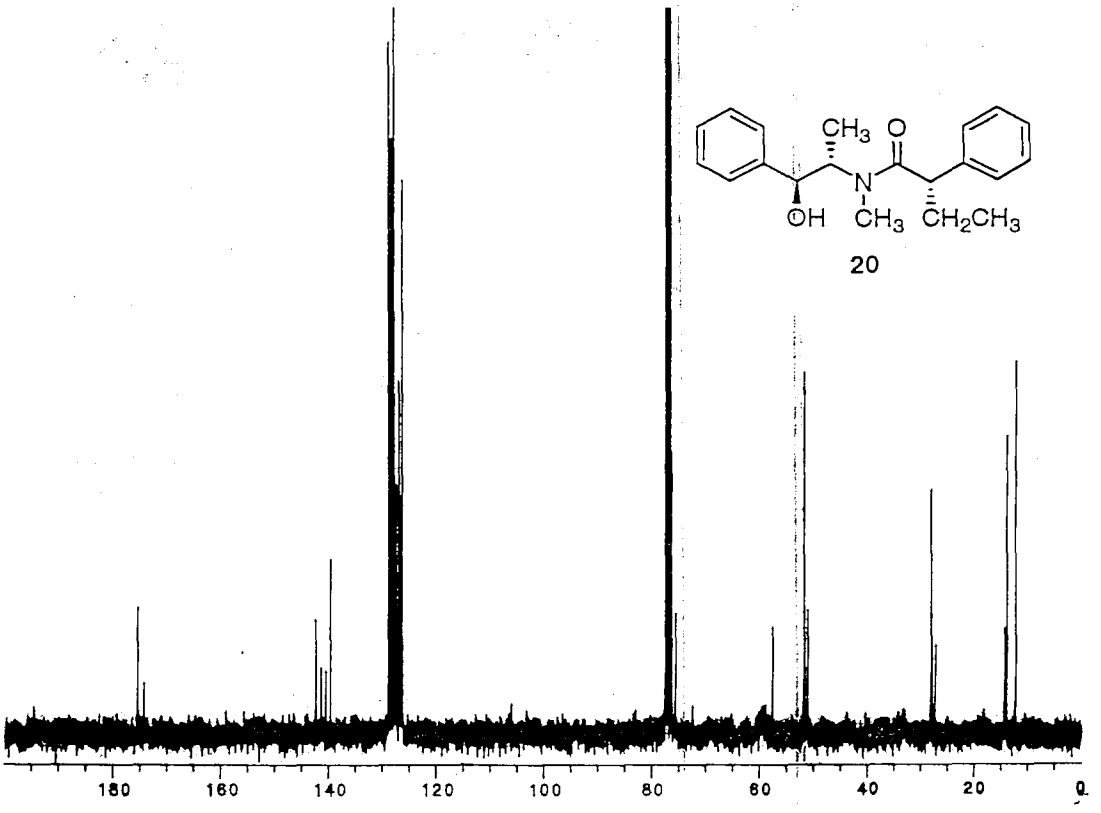

%T
4000
3500
3000
2500
2000
1500
1000
500
cm-1


CH3
O
N
CH3
OH
CH3
CH2C6H5
19
200
180
160
140
120
100
80
60
40
20
0
PPM


CH3
O
N
OH
CH3
CH2CH3
10
9
8
7
6
5
4
3
2
1
0
PPM

20


110.02
%T
27.81
4000
3500
3000
2500
2000
1500
1000
cm-1



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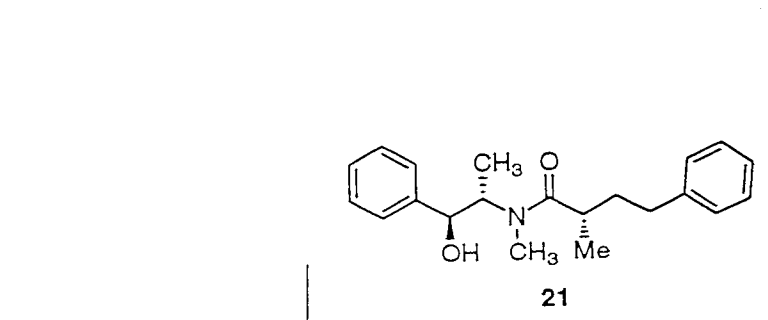
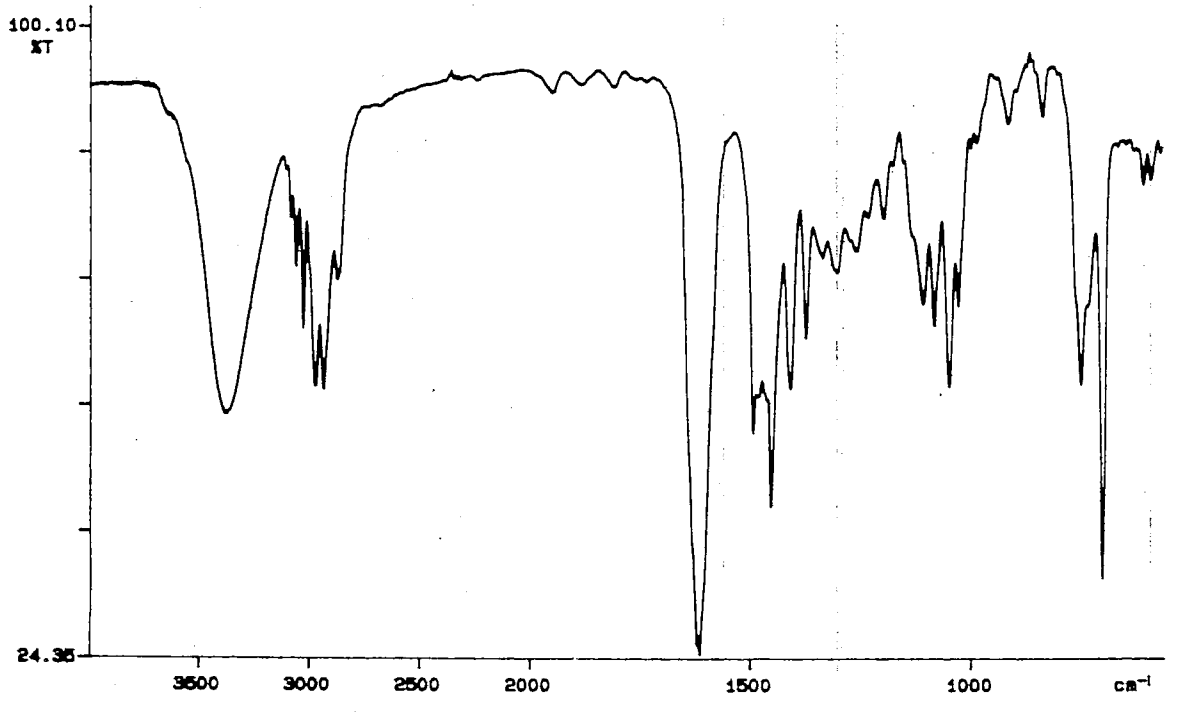
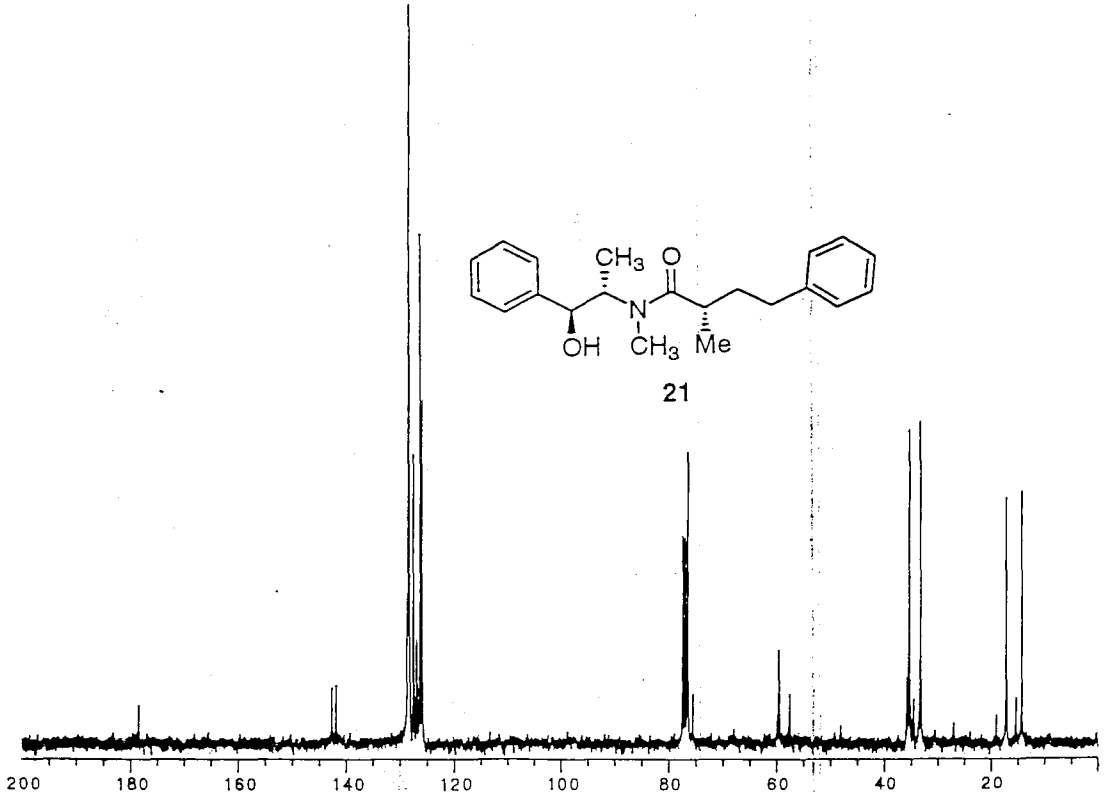

CH3
O
N
OH
CH3
Me

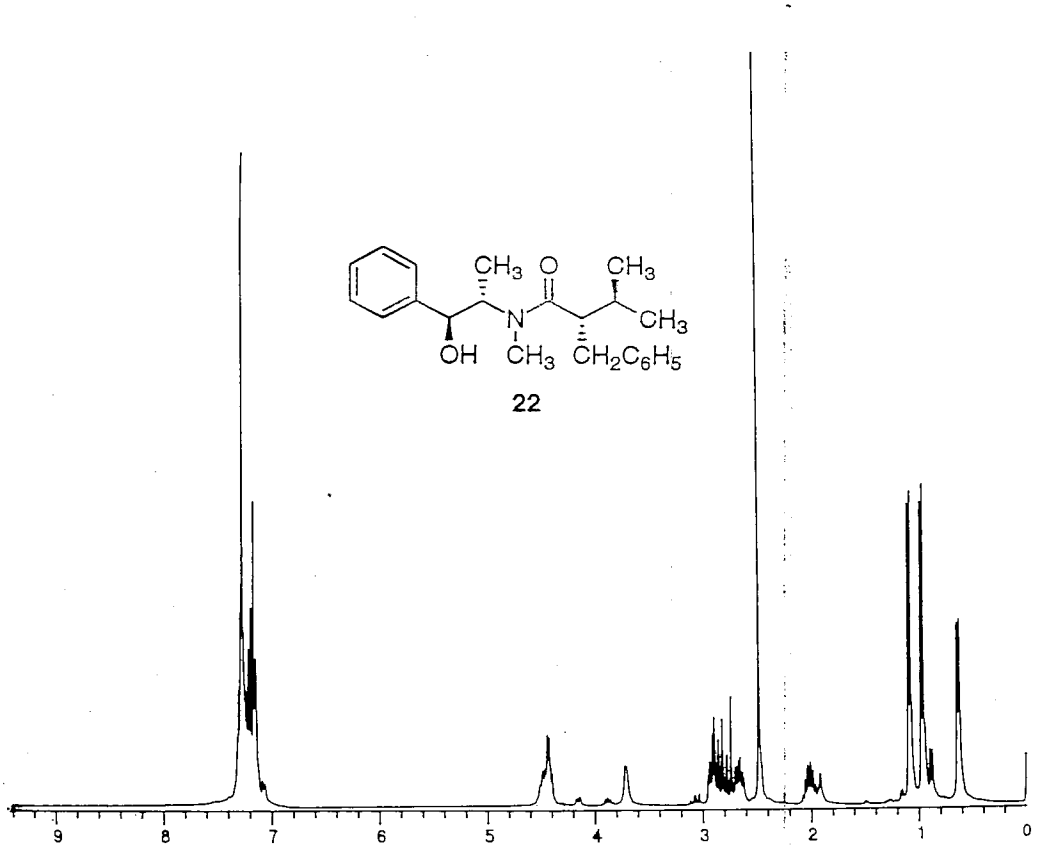
21

9
8
7
6
5
4
3
2
1
0

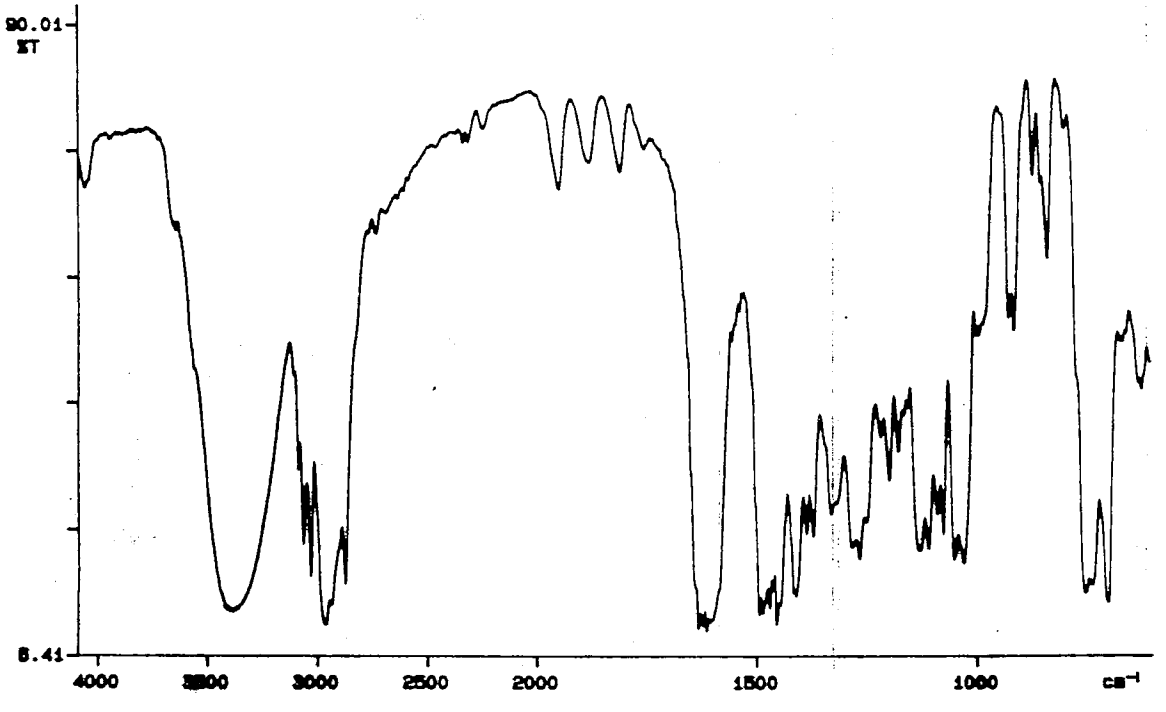

100.10
%T
24.35
3500
3000
2500
2000
1500
1000
cm-1

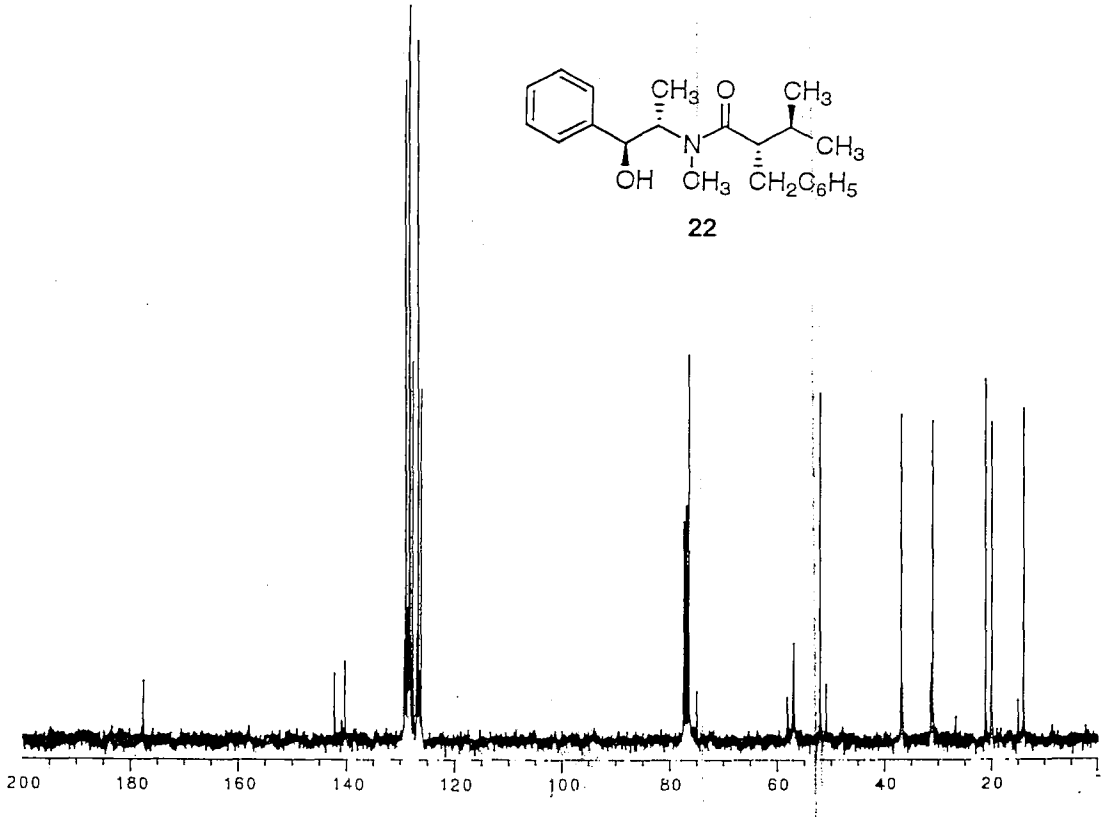


21

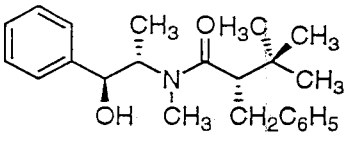

CH3 O CH3
N
CH3
OH CH3 CH2C6H5
9
8
7
6
5
4
3
2
1
0

22


90.01
%T
8.41
4000
3500
3000
2500
2000
1500
1000
cm-1

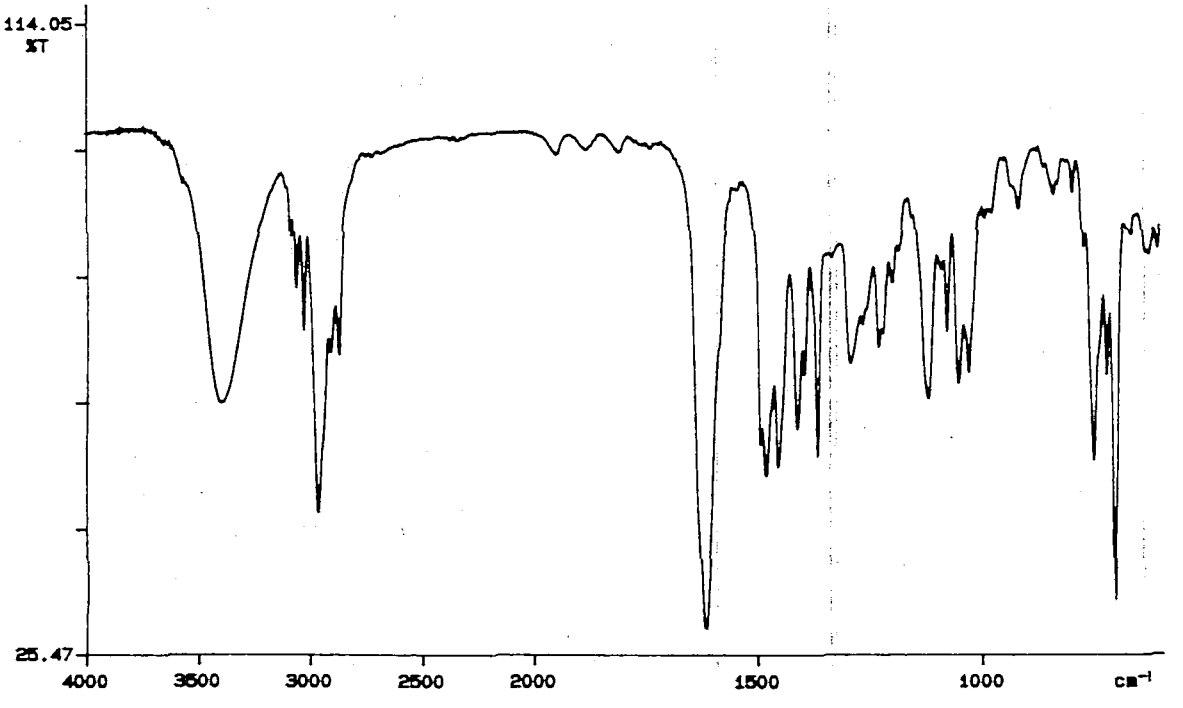


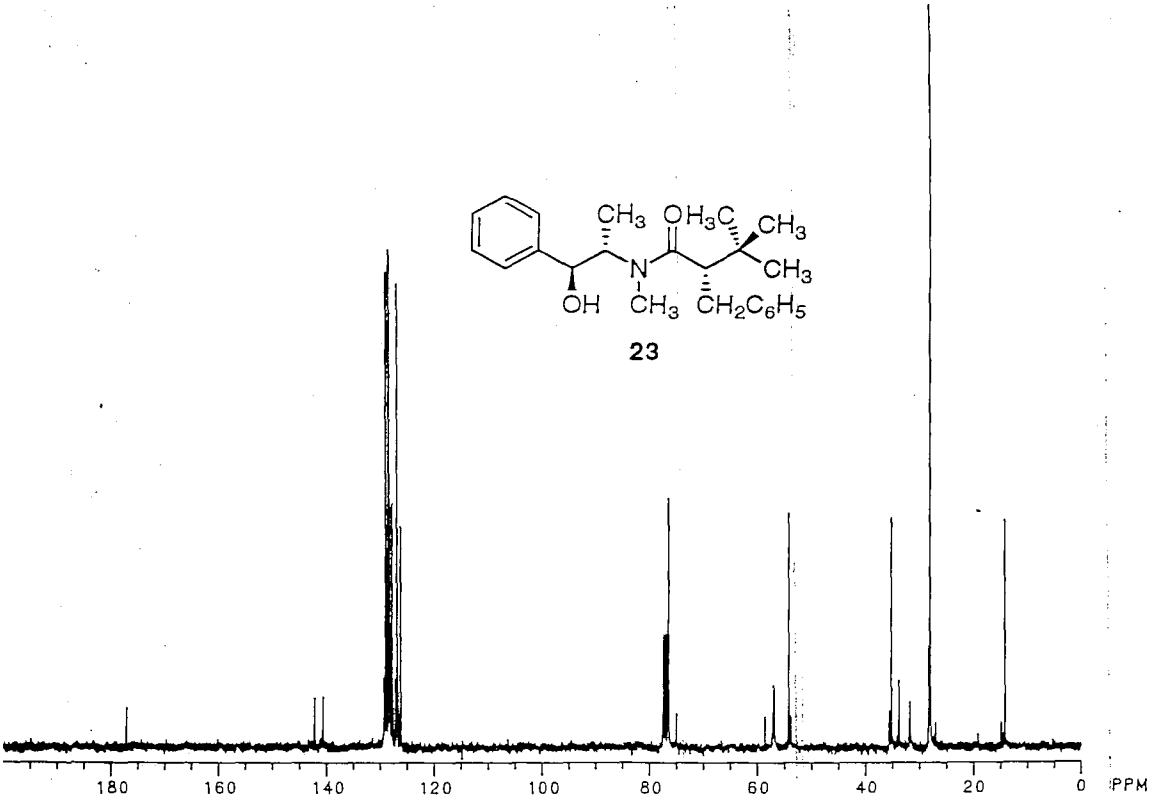
22


CH3
OH3C
CH3
CH3
N
OH
CH3
CH2C6H5

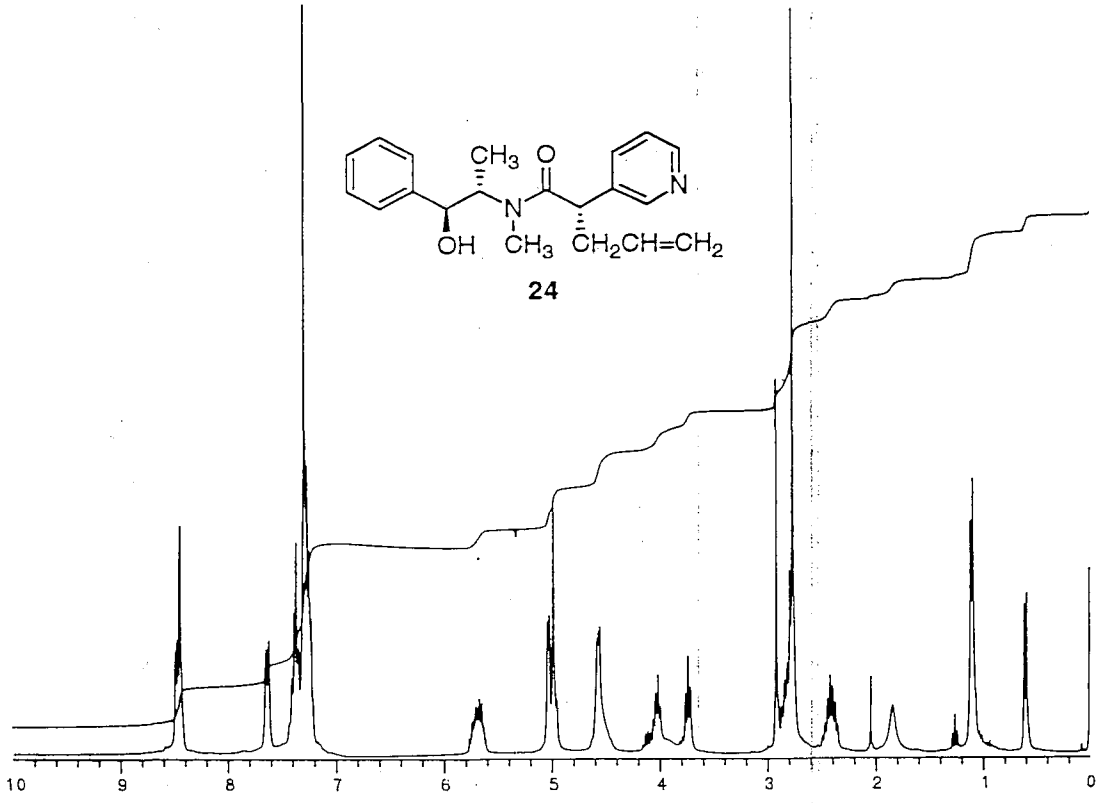
23

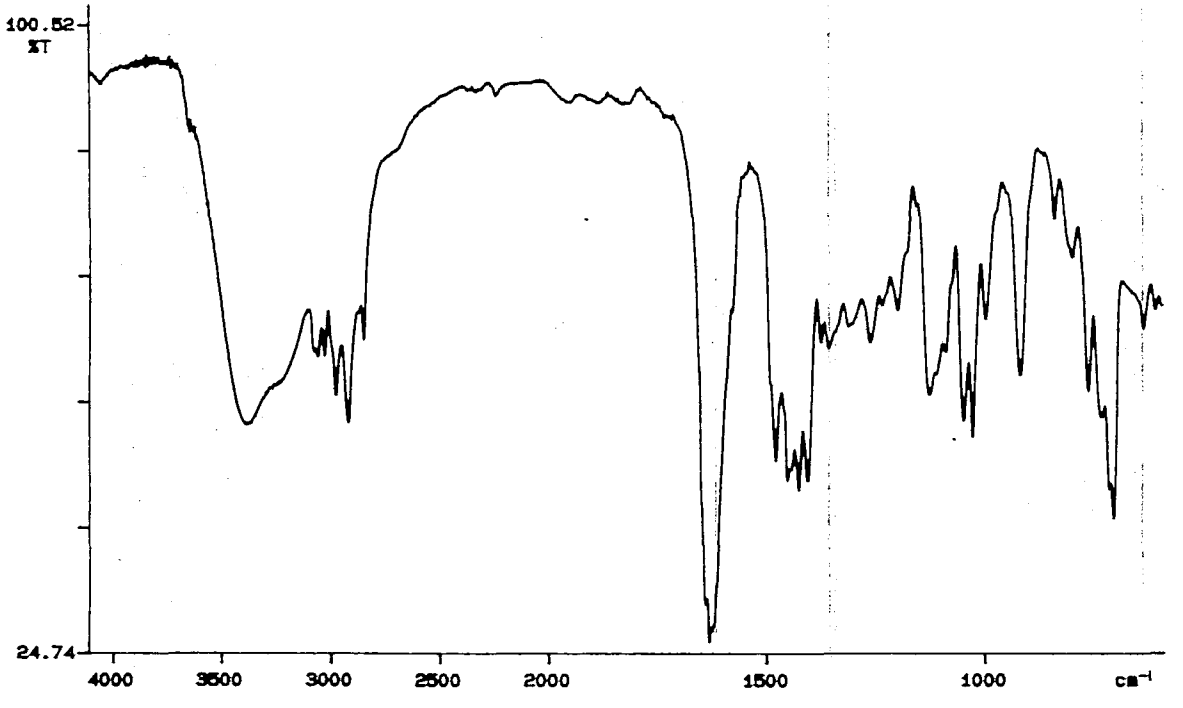
10
9
8
7
6
5
4
3
2
1

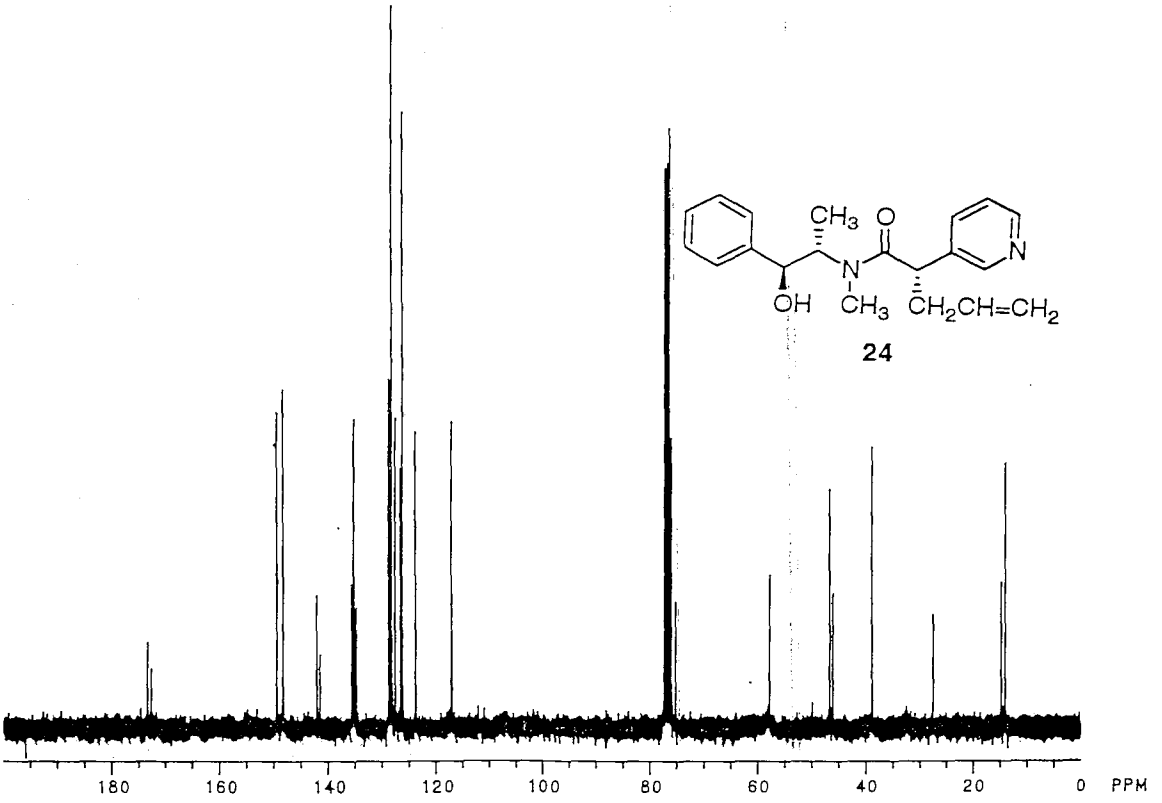

114.05
%T
25.47
4000
3500
3000
2500
2000
1500
1000
cm-1

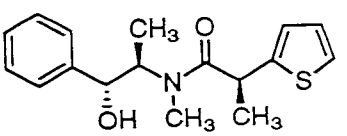

CH3
OH3C
CH3
CH3
N
OH
CH3
CH2C6H5
180
160
140
120
100
80
60
40
20
0
PPM

23


CH3 O
N
N
OH CH3 CH2CH=CH2
24
10
9
8
7
6
5
4
3
2
1
0

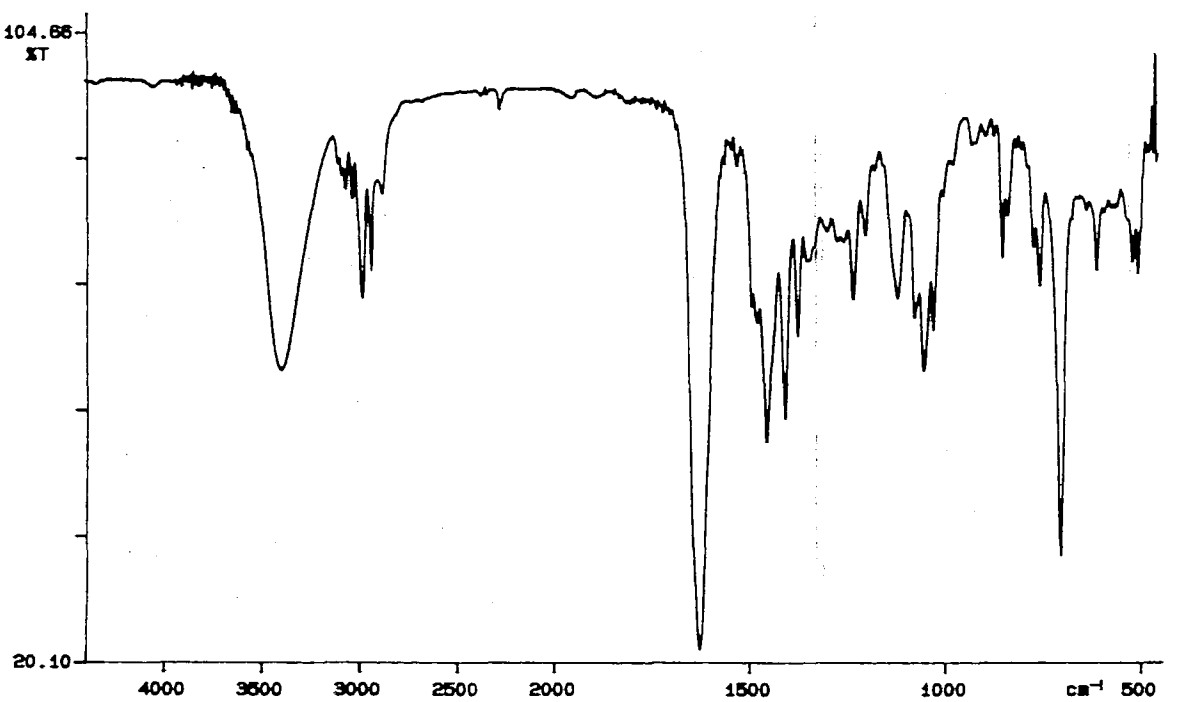

100.52
%T
24.74
4000
3500
3000
2500
2000
1500
1000
cm-1

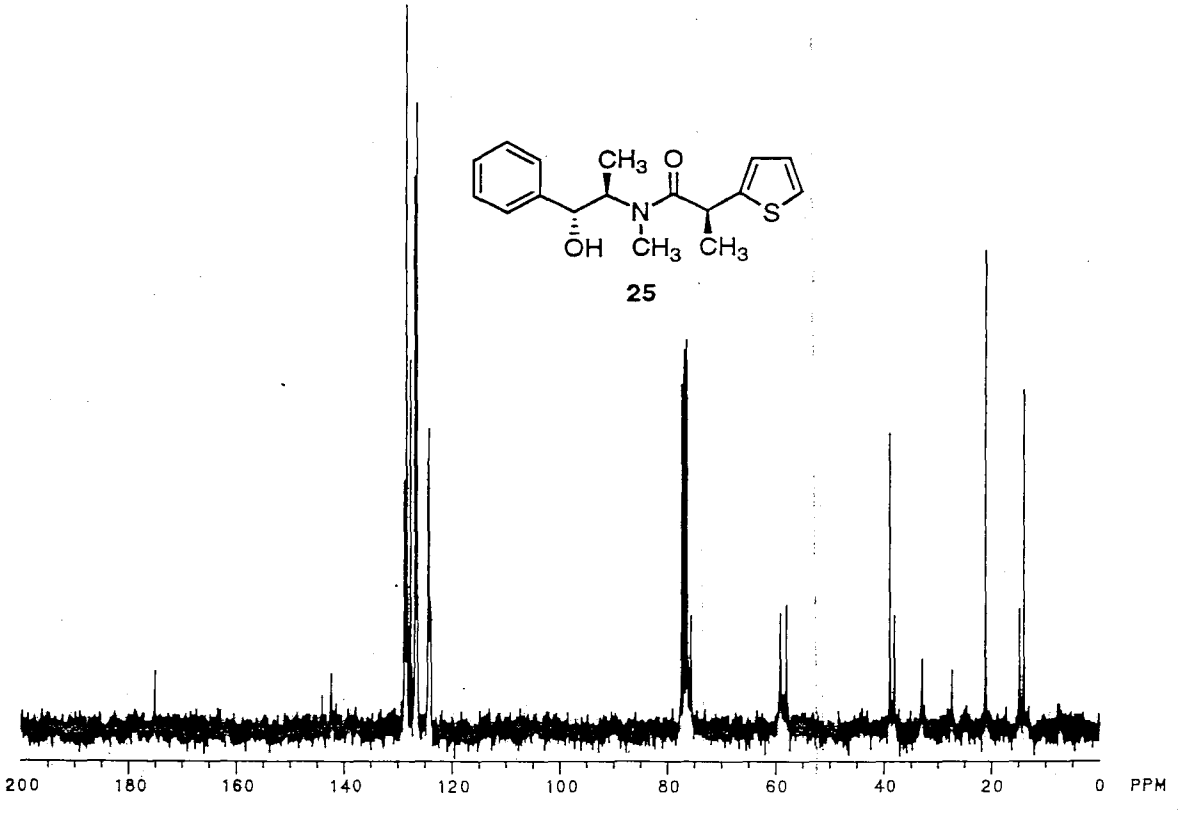

CH3
O
N
OH
CH3
CH2CH=CH2
24
180
160
140
120
100
80
60
40
20
0
PPM


CH3
O
N
S
OH
CH3
CH3

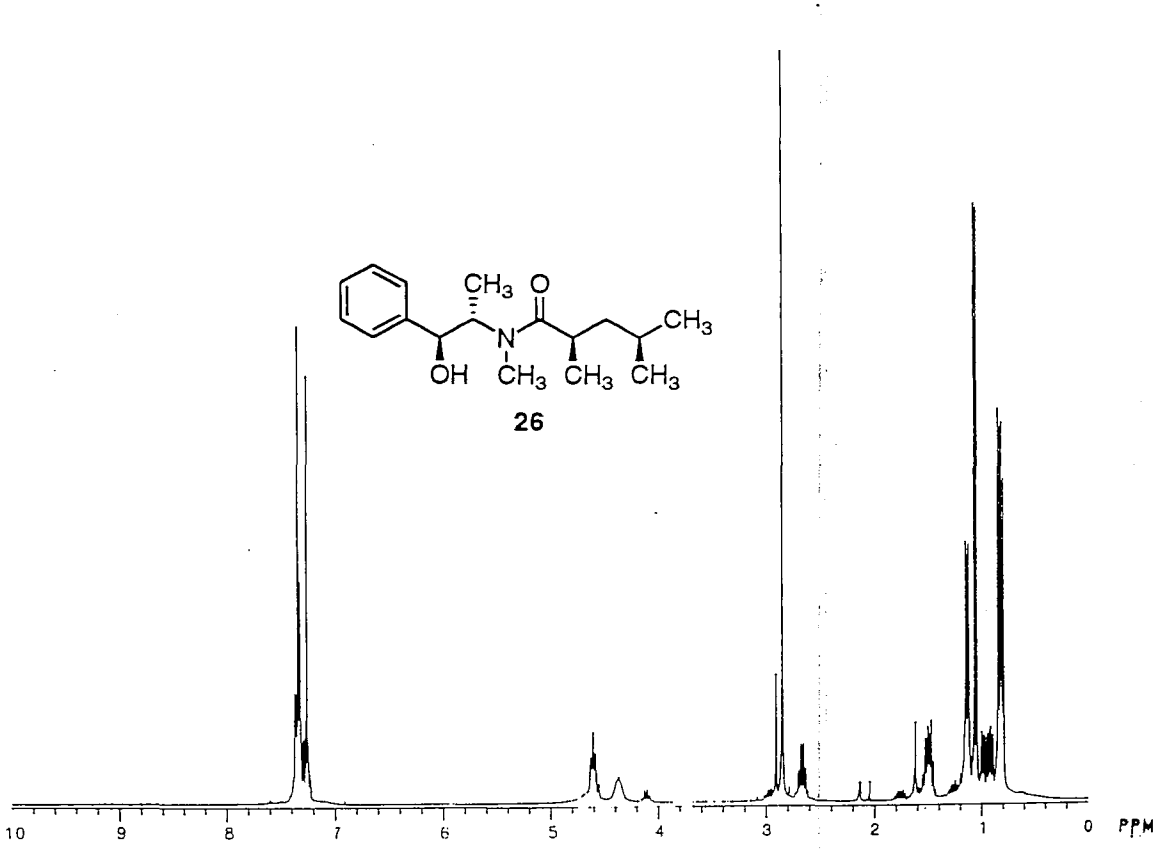
25

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

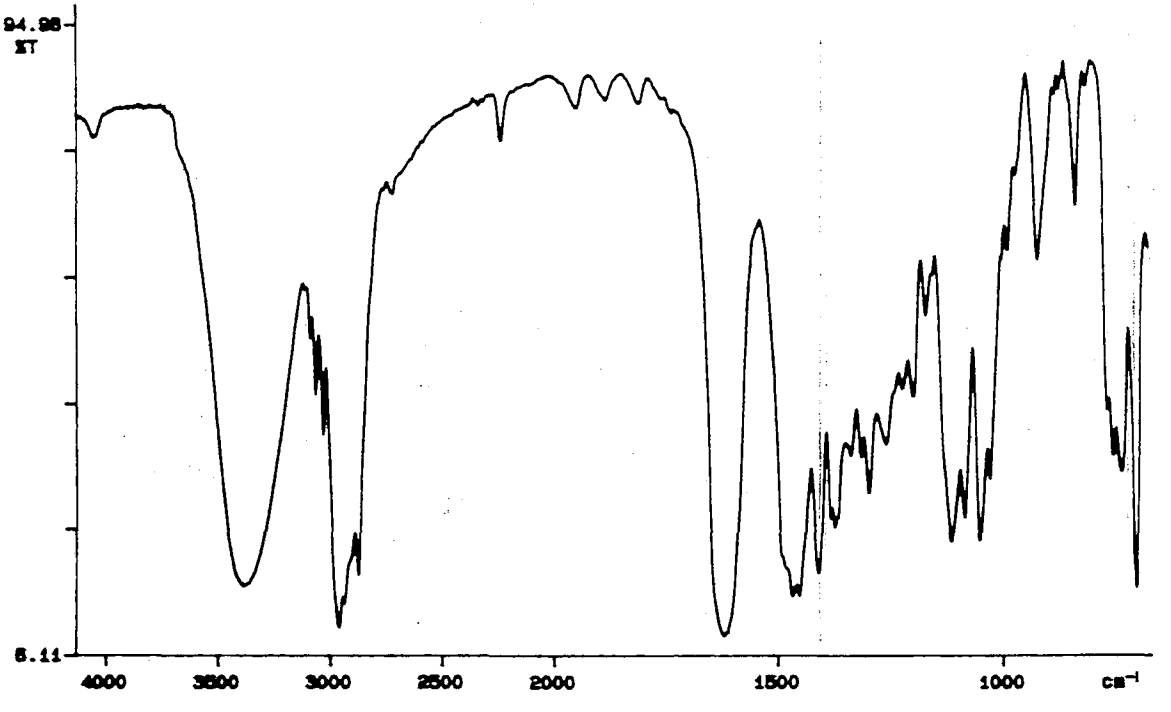

104.66
%T
20.10
4000
3500
3000
2500
2000
1500
1000
cm-1
500

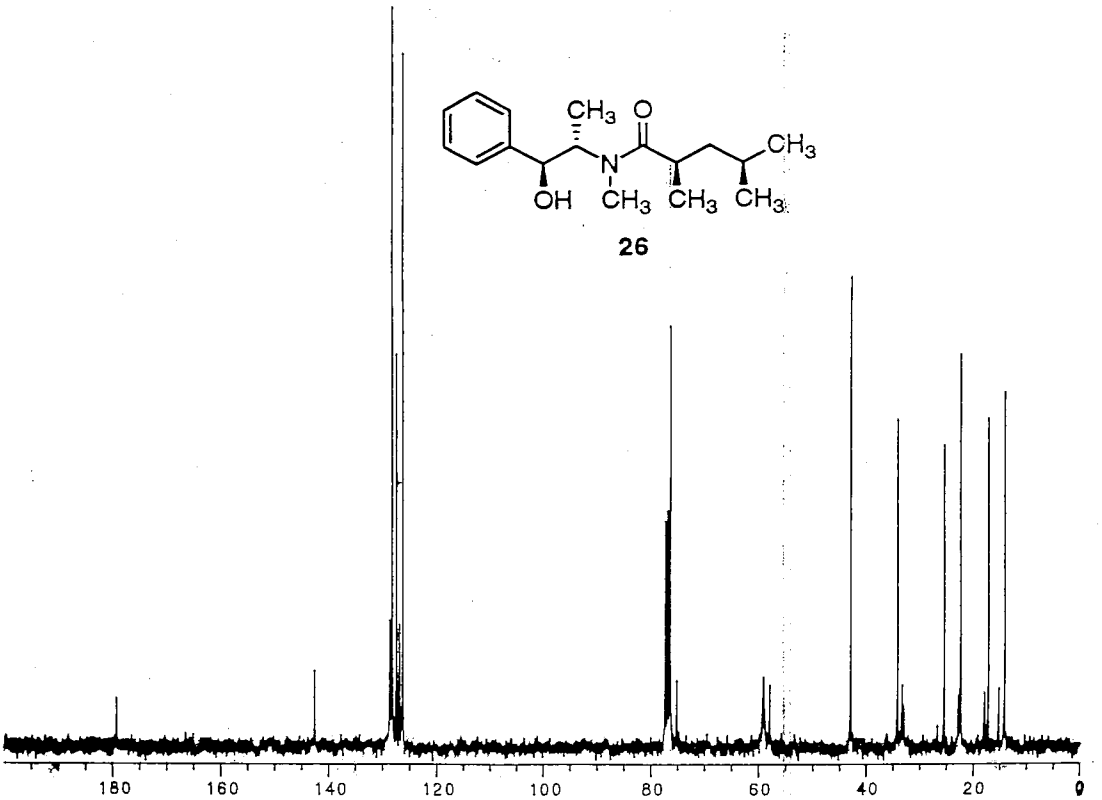


25

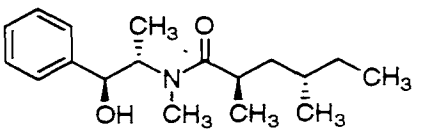

CH3
O
CH3
N
OH
CH3
CH3
CH3
10
9
8
7
6
5
4
3
2
1
0
PPM

26

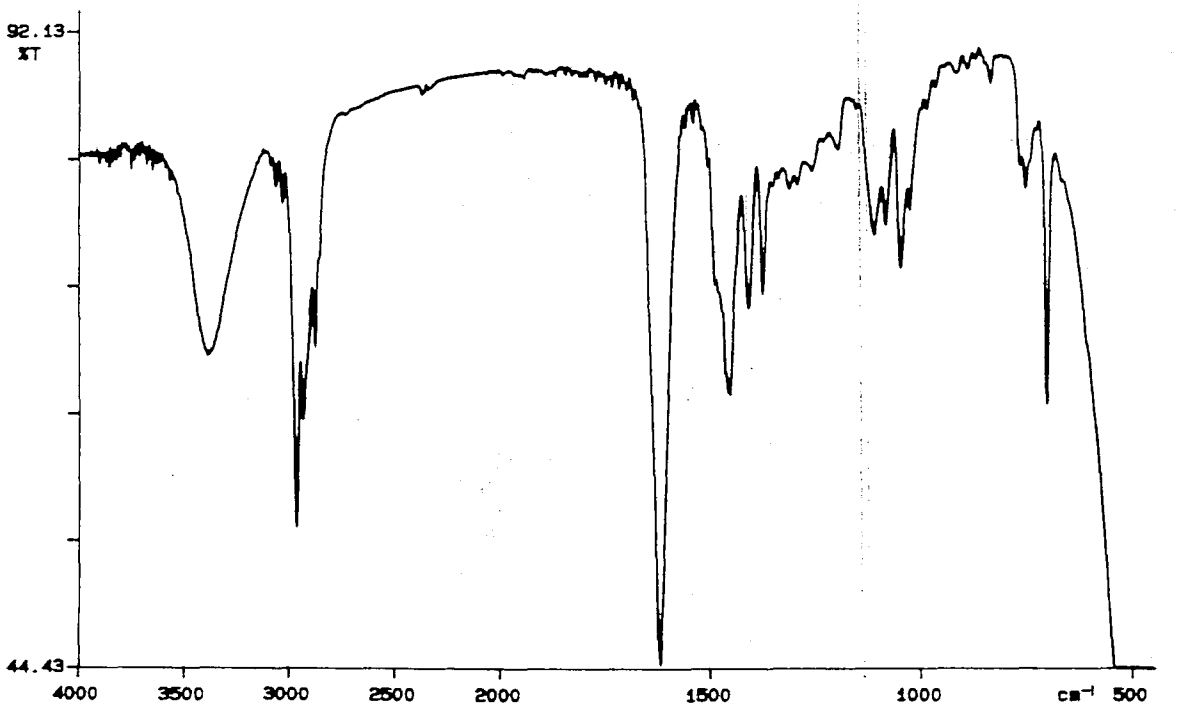

94.26
%T
5.11
4000
3500
3000
2500
2000
1500
1000
cm-1

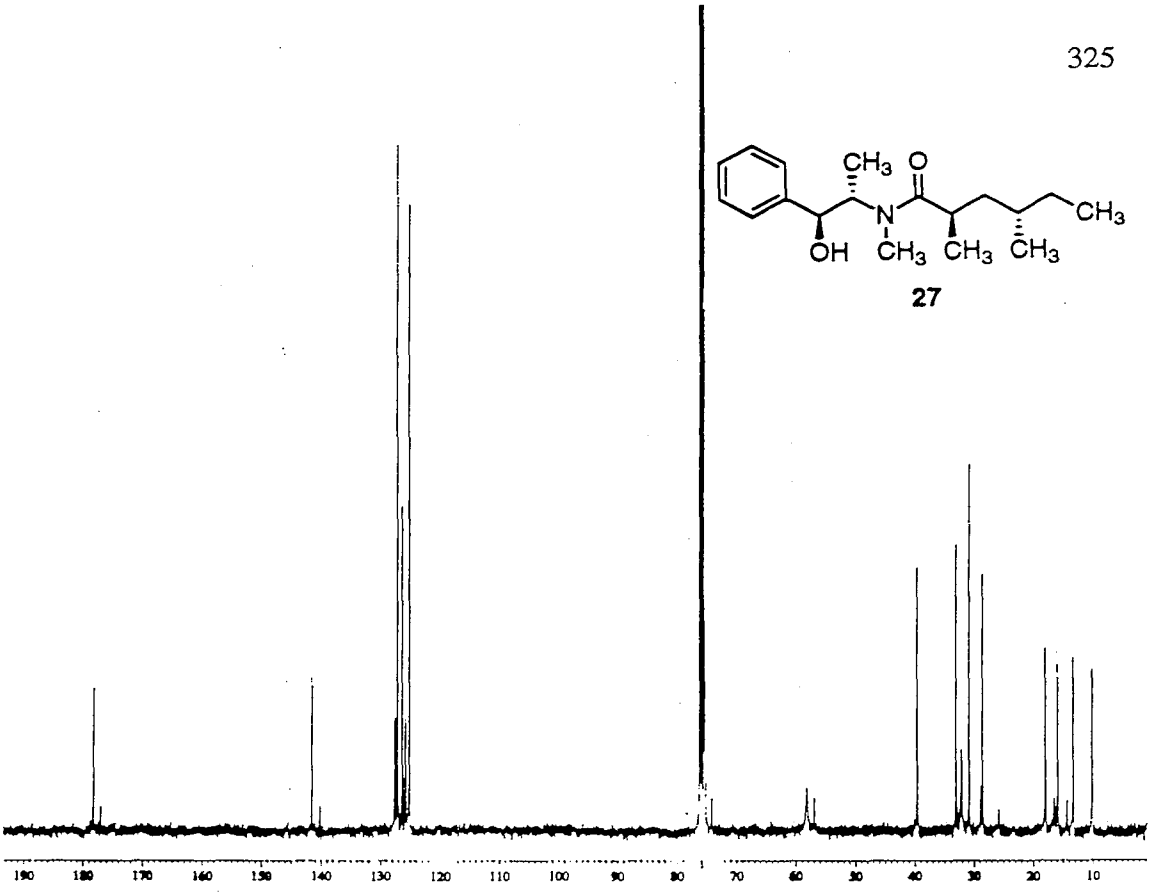


26

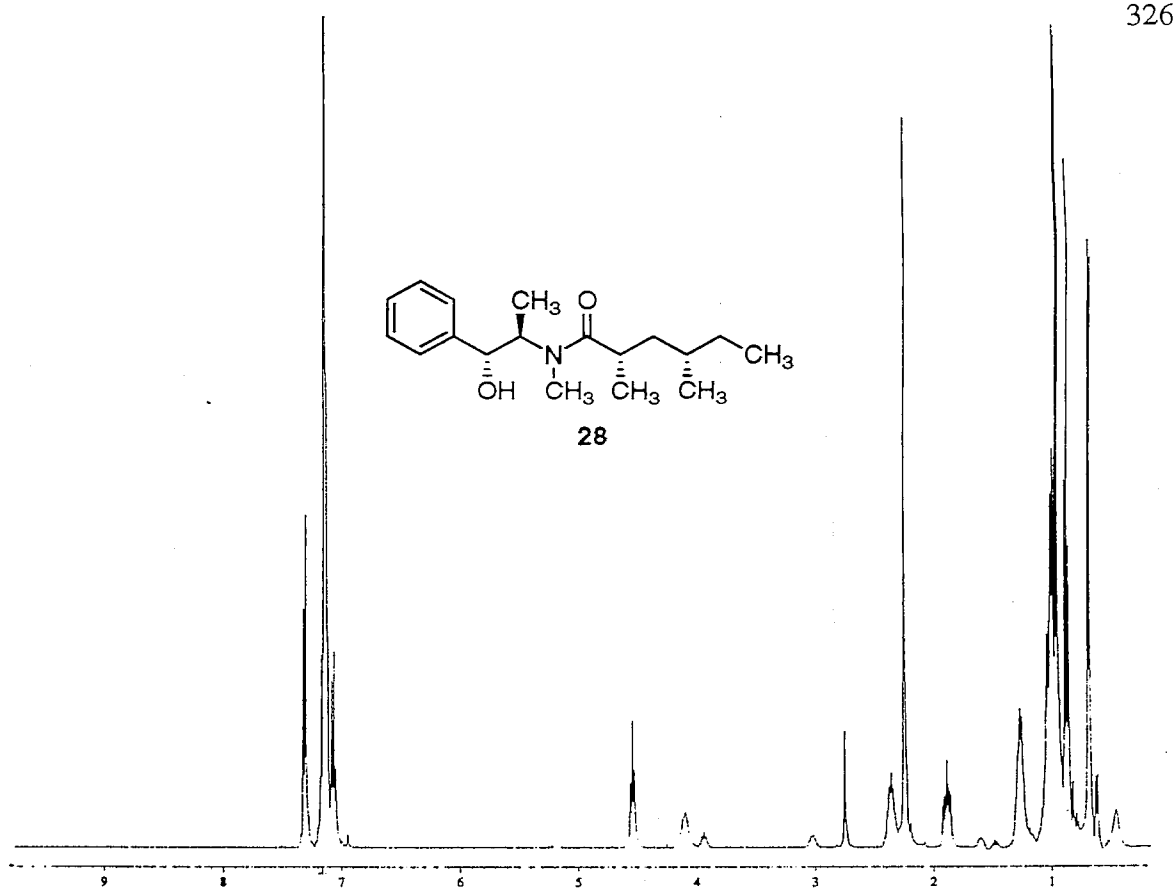

CH3
O
N
CH3
OH
CH3
CH3
CH3

27

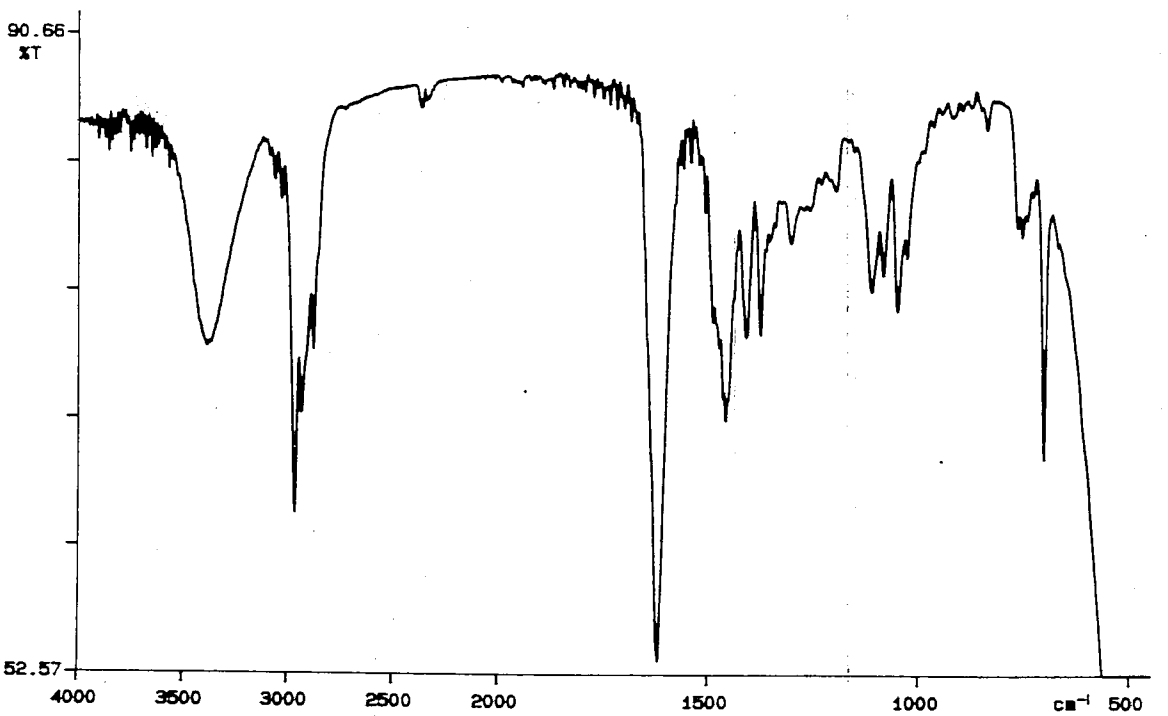

92.13
%T
44.43
4000
3500
3000
2500
2000
1500
1000
cm-1
500

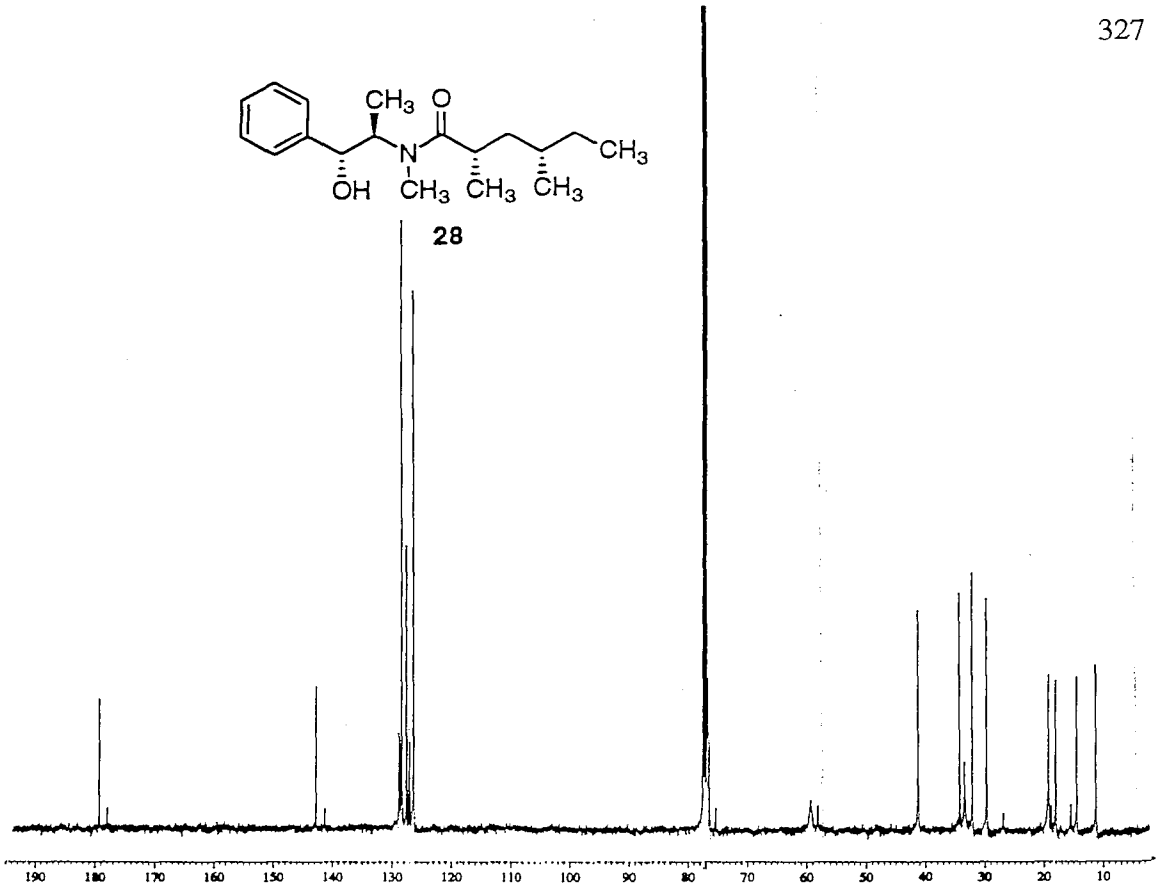

CH3
O
N
CH3
OH
CH3
CH3
CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

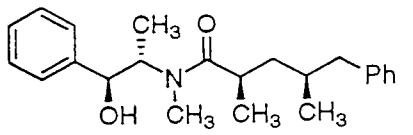
27


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

28

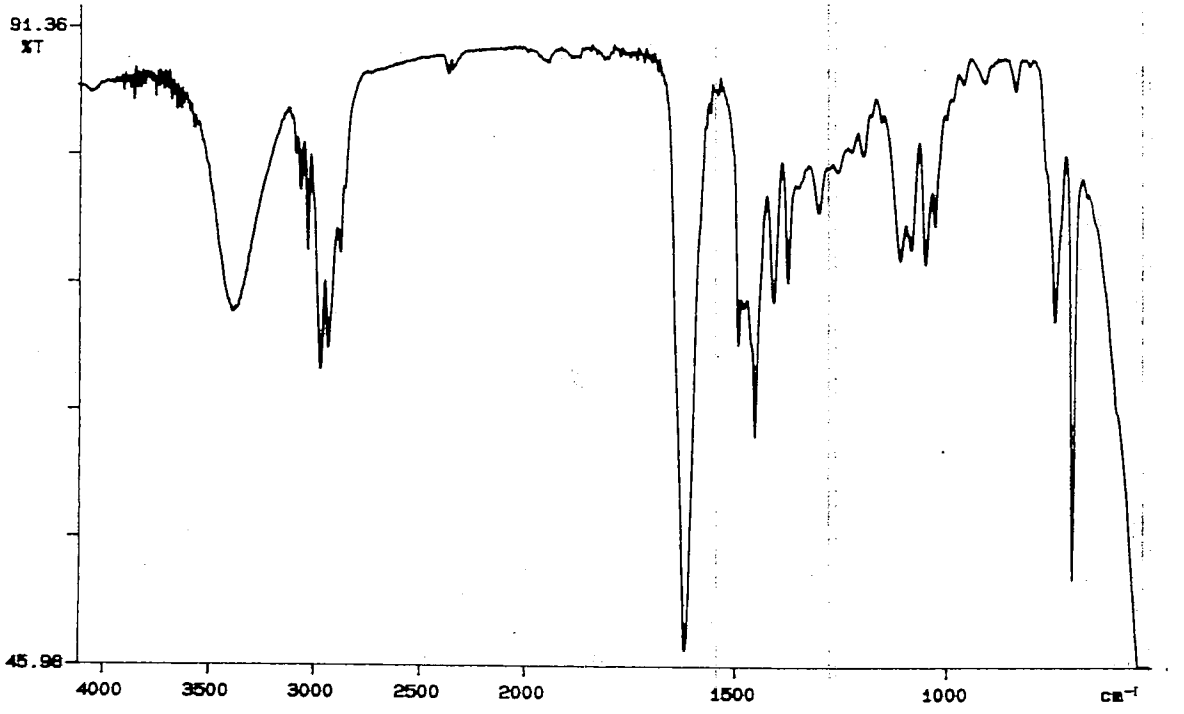

90.66
%T
52.57
4000
3500
3000
2500
2000
1500
1000
cm-1
500

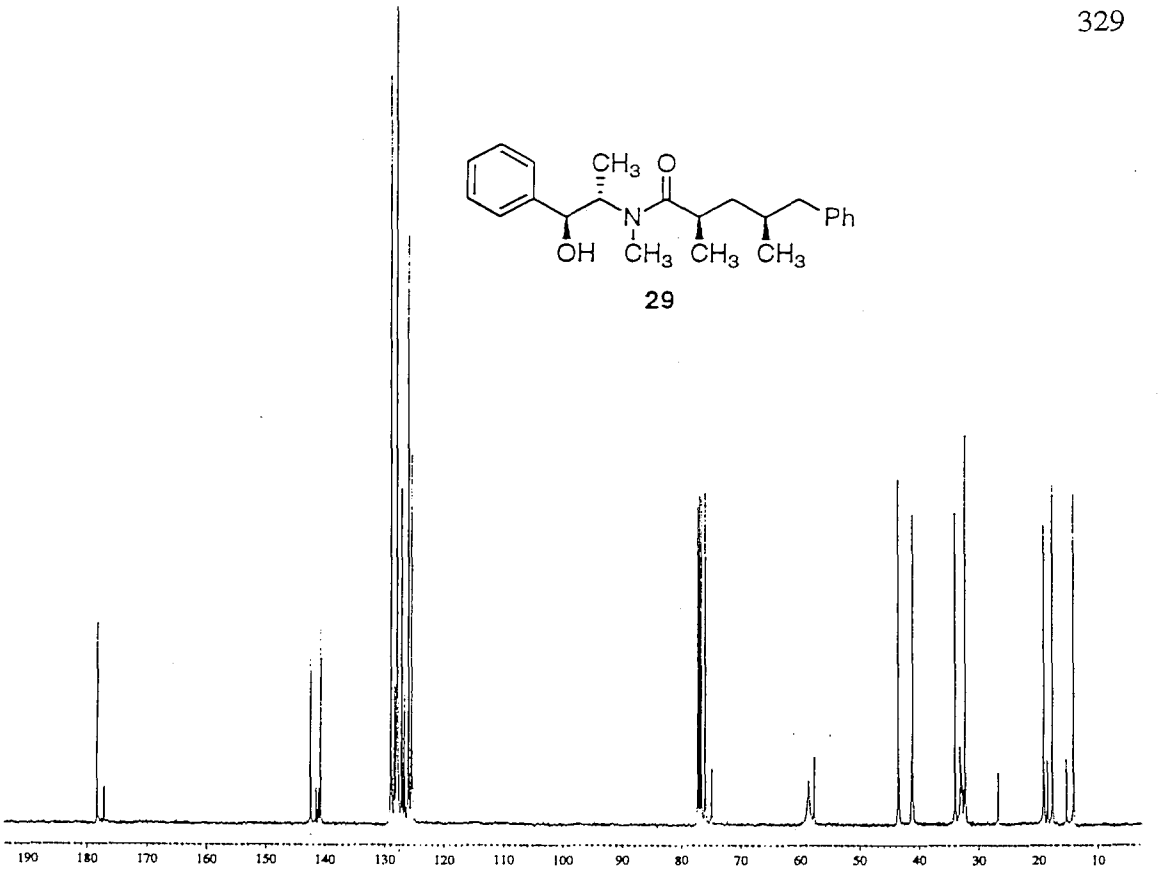

CH3
O
N
CH3
OH
CH3
CH3
CH3
28
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


CH3
O
N
Ph
OH
CH3
CH3
CH3

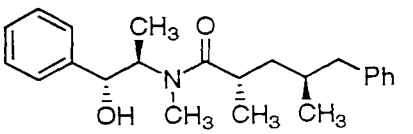
29

9
8
7
6
5
4
3
2
1


91.36
%T
45.98
4000
3500
3000
2500
2000
1500
1000
cm-1


CH3
O
N
Ph
OH
CH3
CH3
CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

29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N
Ph
OH
CH3
CH3
CH3

30

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4
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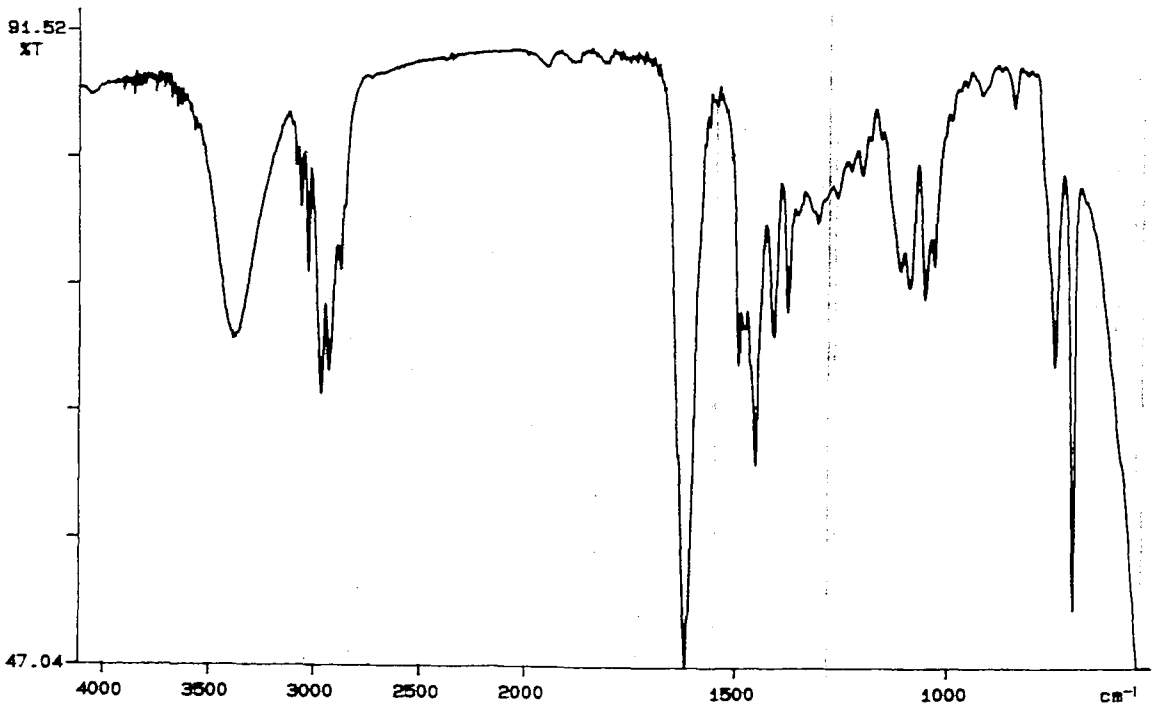
1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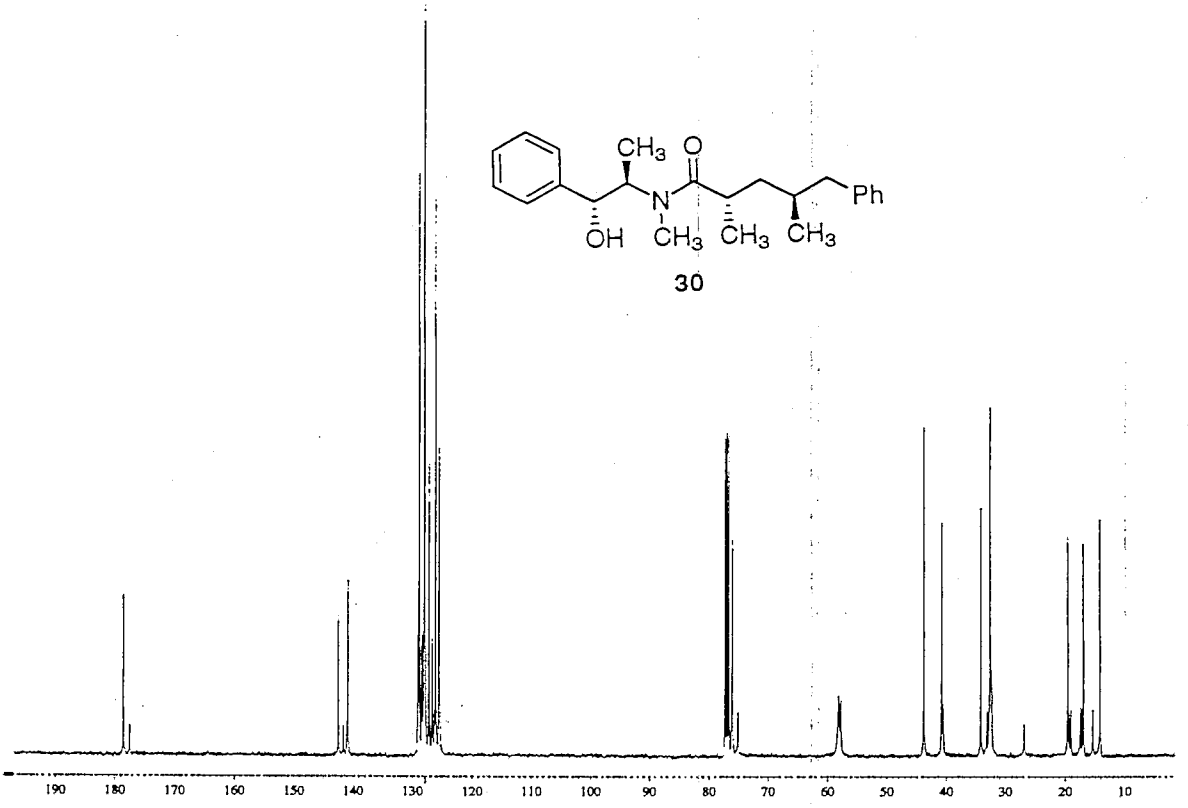
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Ph
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CH3
CH3
CH3
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70
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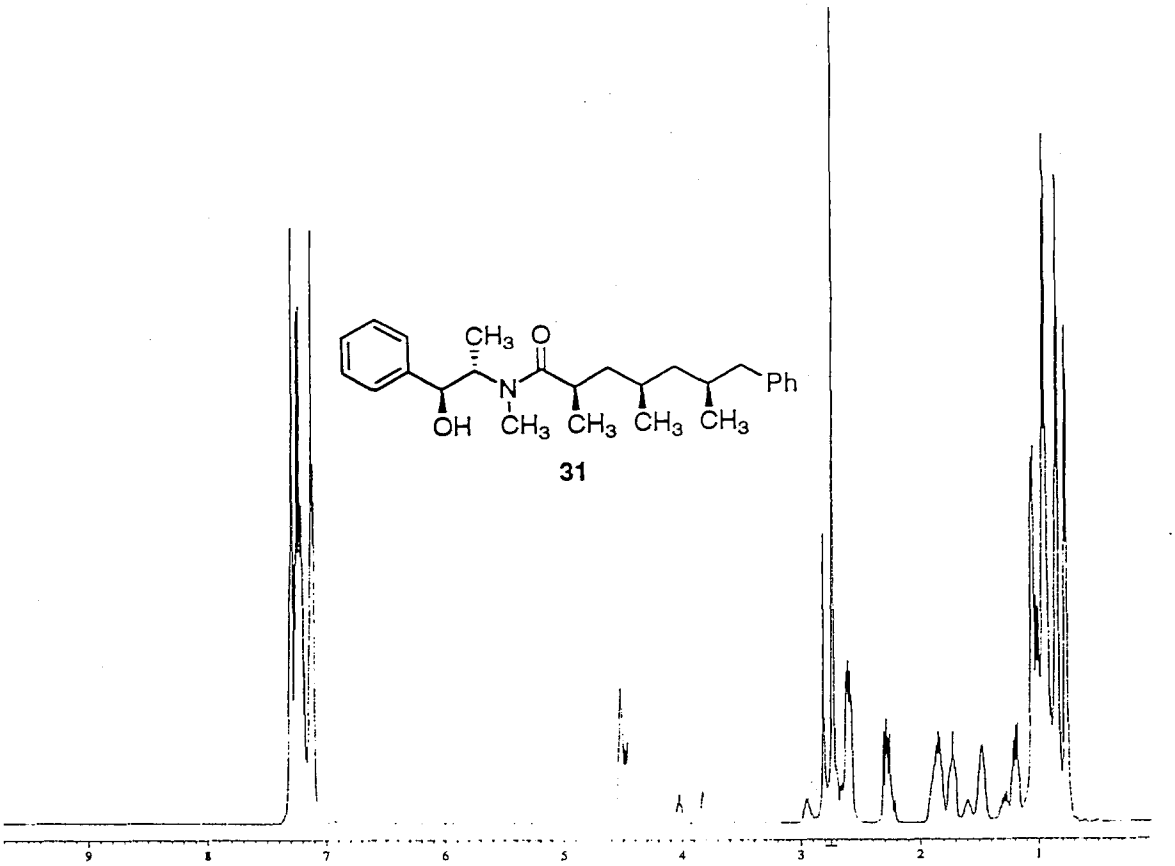
30
20
10

30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CH3
CH3
CH3
CH3
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7
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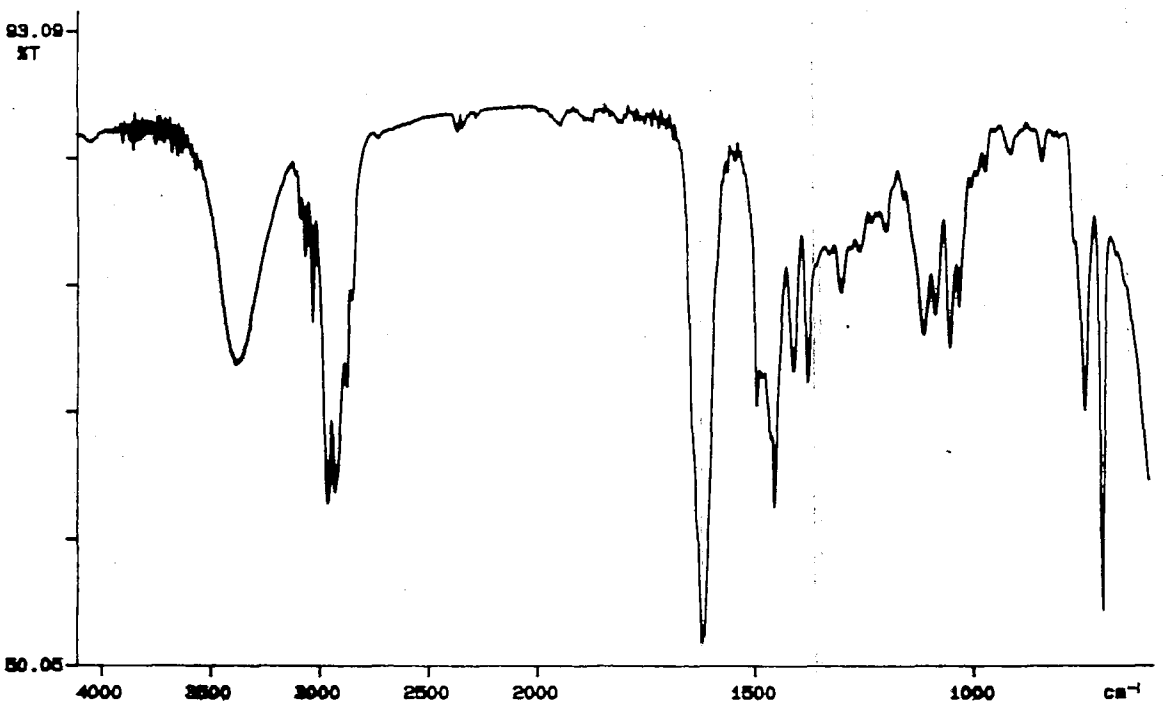
4
3
2
1

31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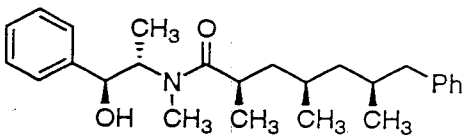
cm-1


CH3
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N
Ph
OH
CH3
CH3
CH3
CH3

31

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100
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30
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10
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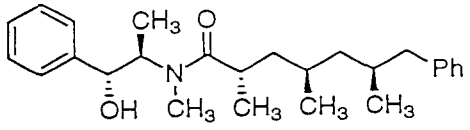
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OH
CH3
CH3
CH3
CH3

32

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8
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4
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2
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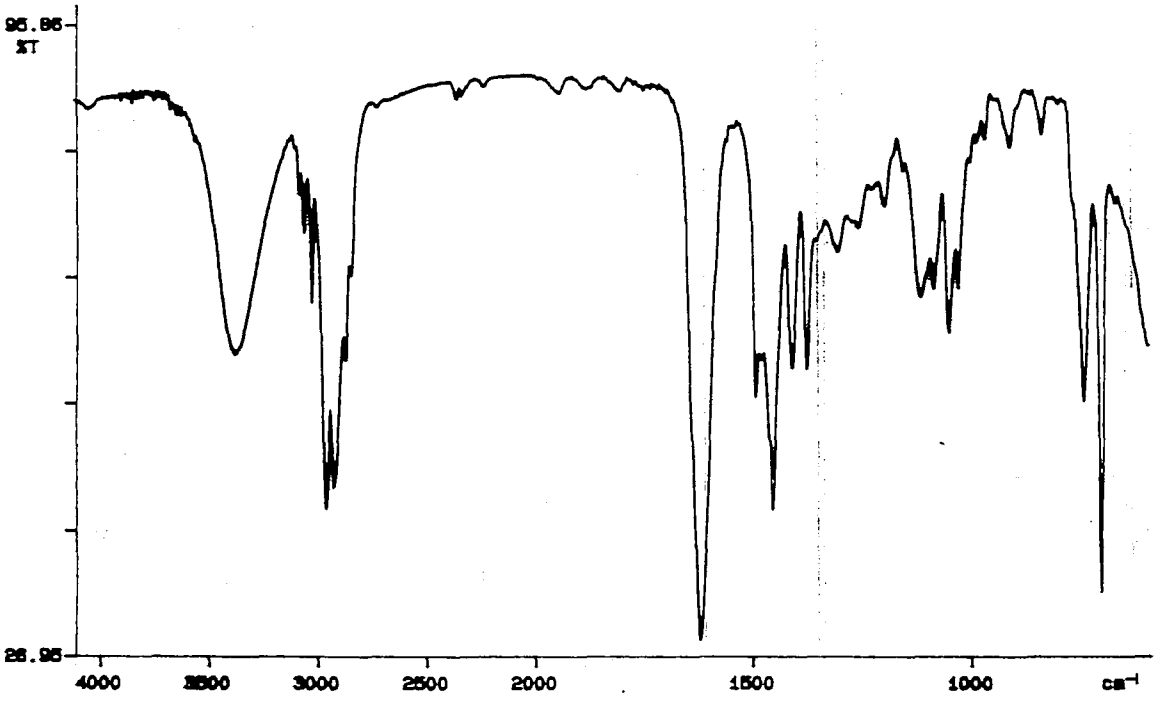
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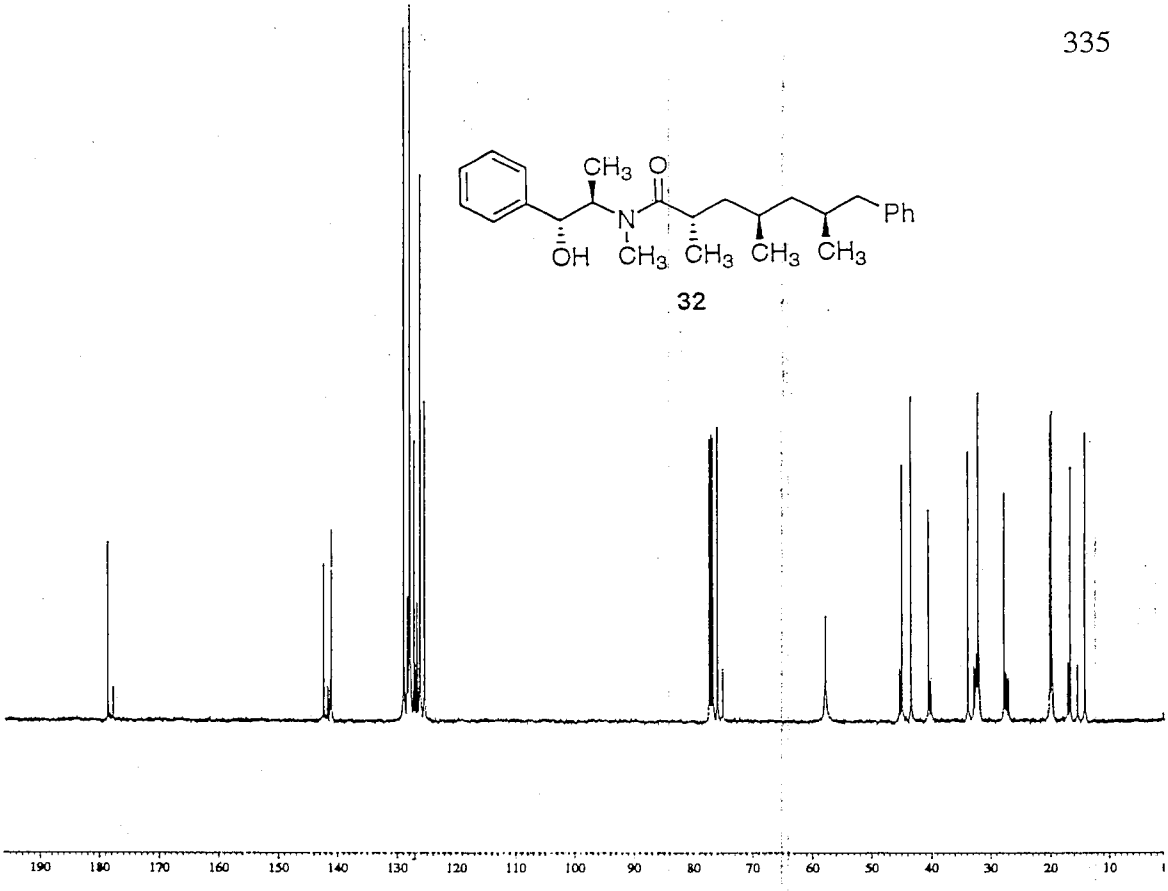
CH3
O
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Ph
OH
CH3
CH3
CH3
CH3
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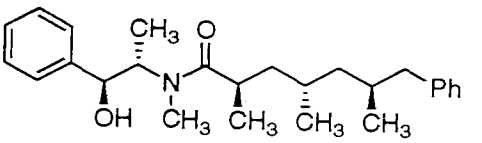
30
20
10

32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Ph
OH
CH3
CH3
CH3
CH3

33

9
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6
5
4
3
2
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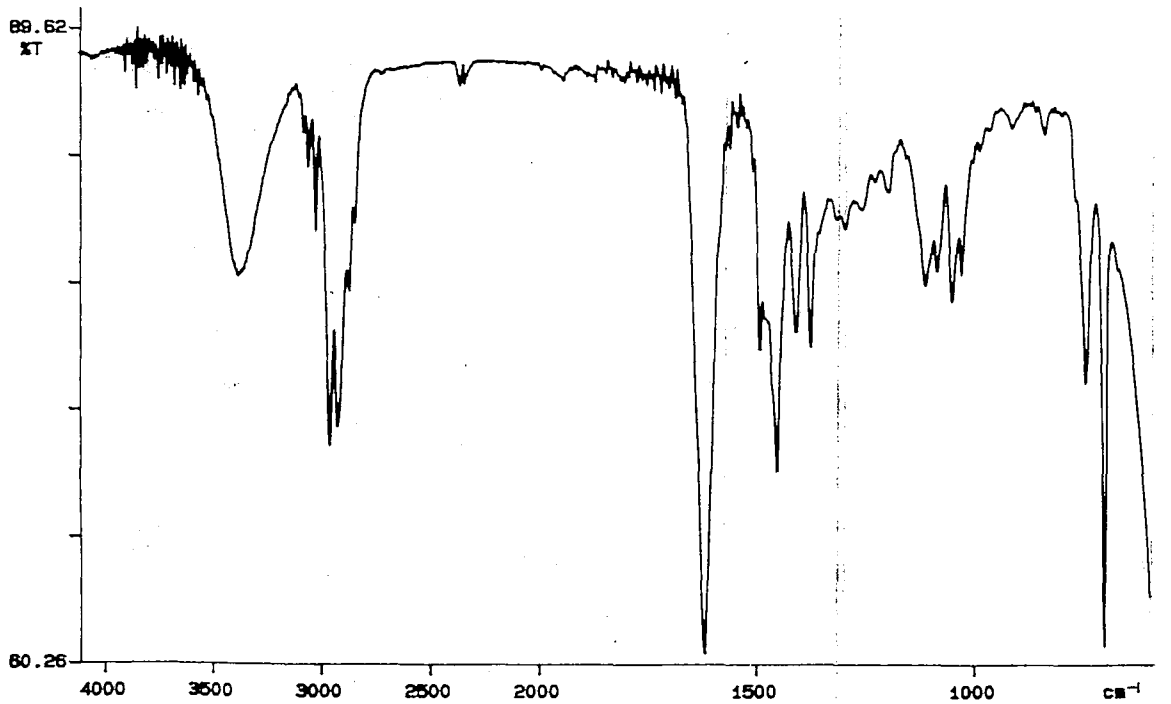
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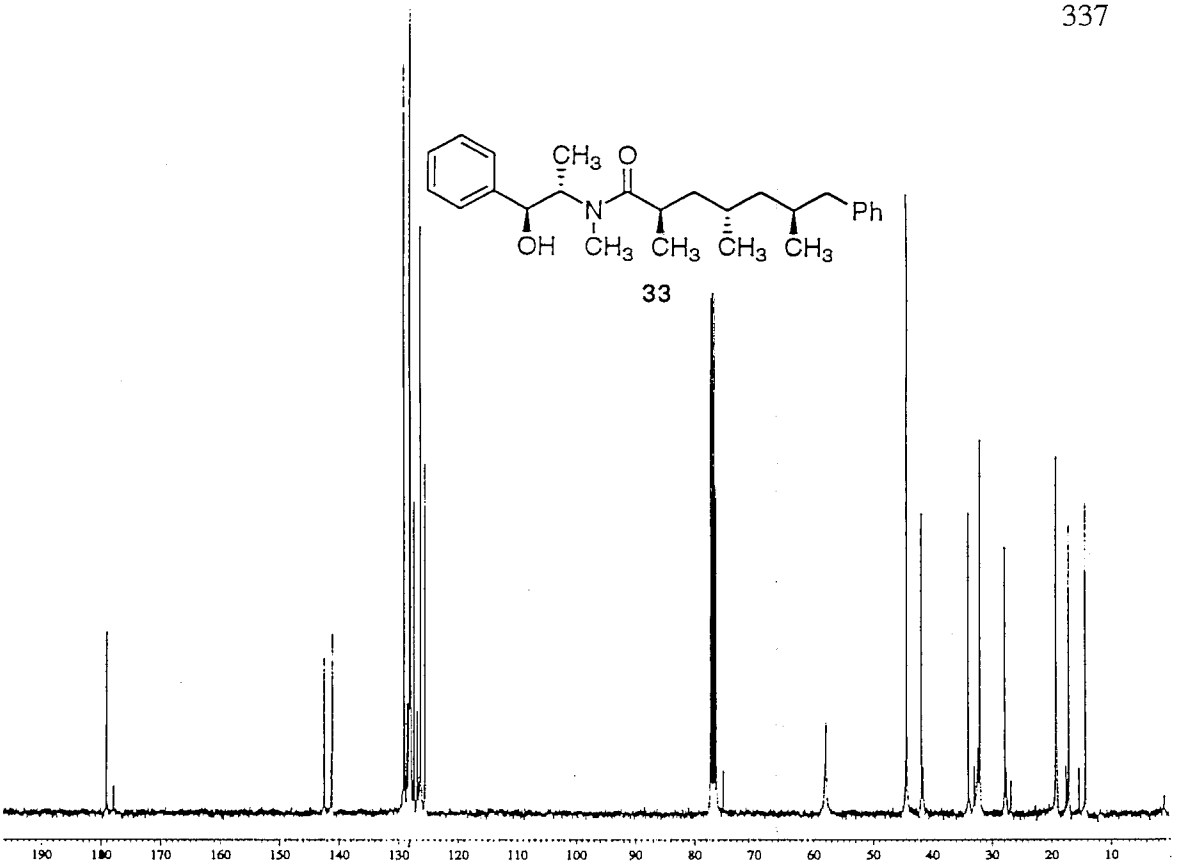
cm-1


CH3
O
N
Ph
OH
CH3
CH3
CH3
CH3
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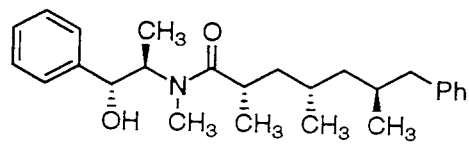
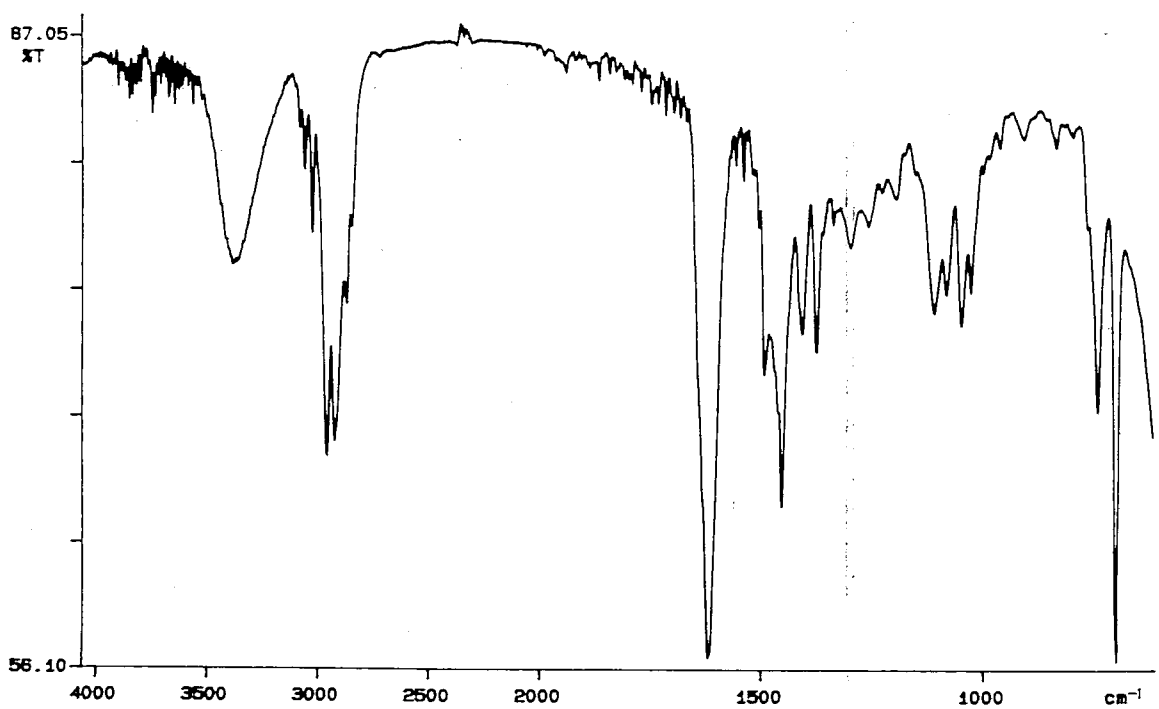
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


CH3
O
N
Ph
OH
CH3
CH3
CH3
CH3

34

9
8
7
6
5
4
3
2
1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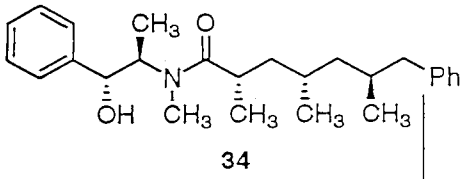
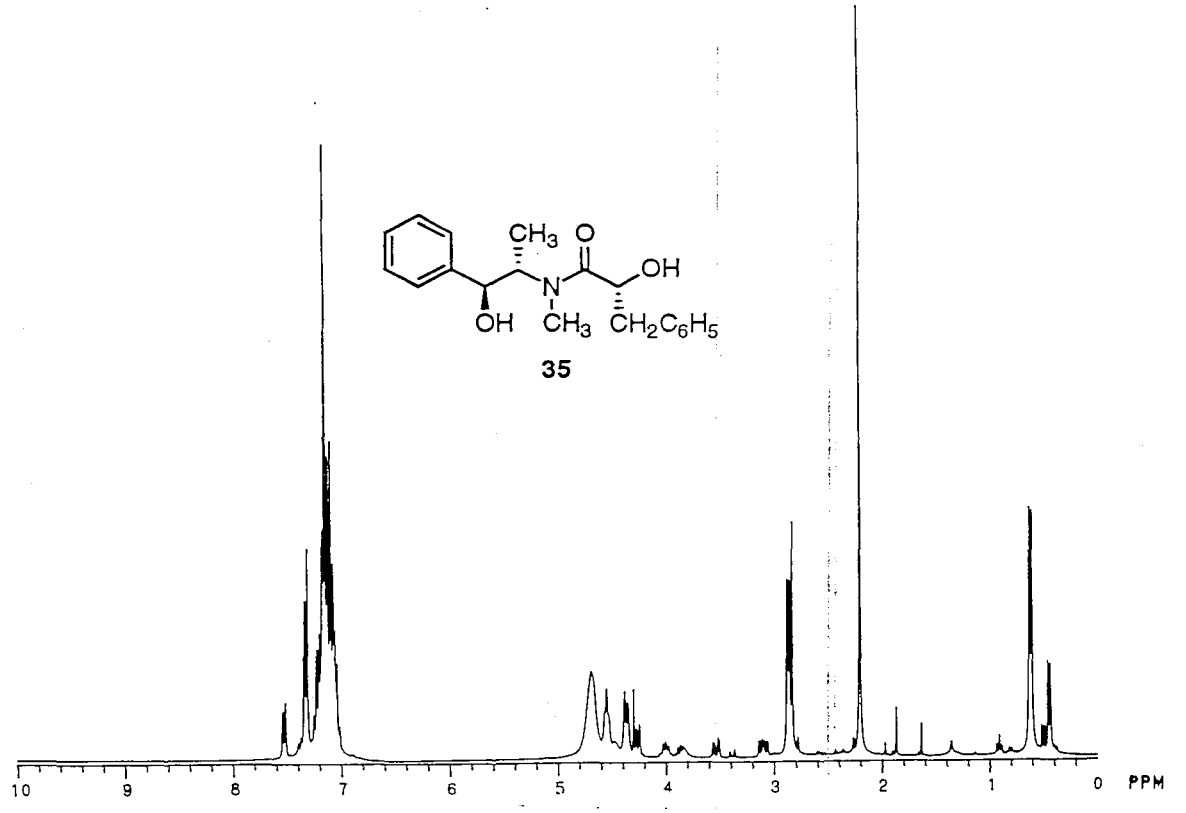
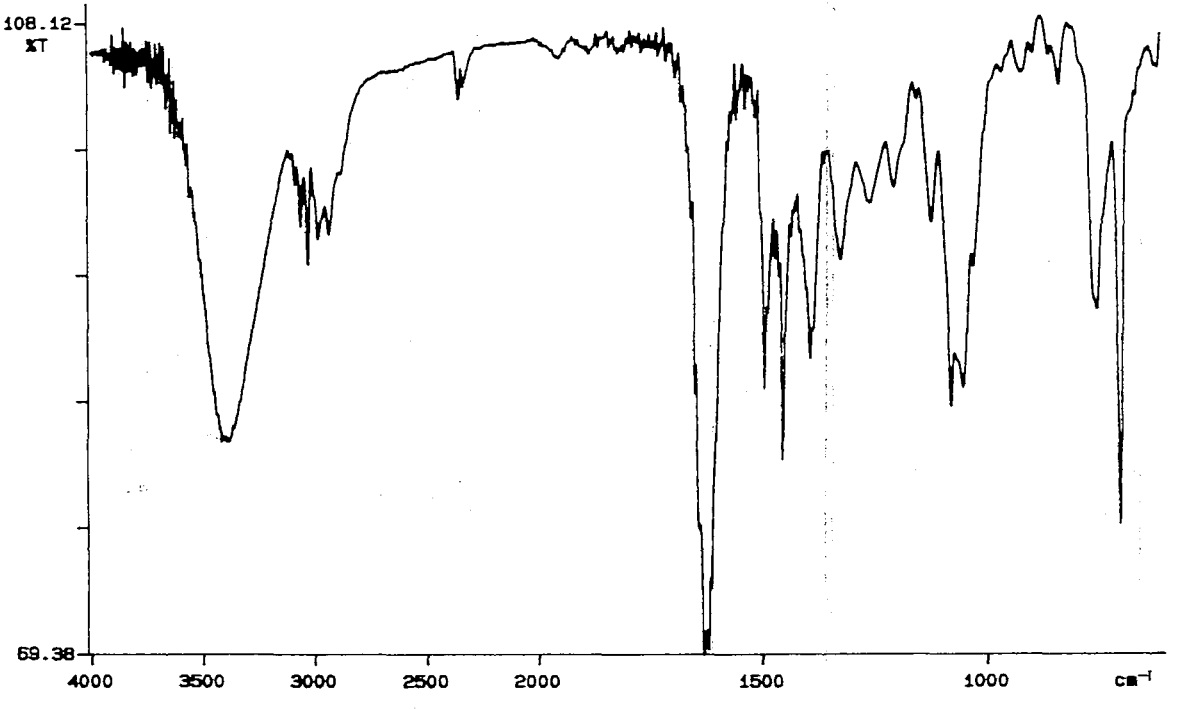
1500
1000
cm-1


CH3
O
N
Ph
OH
CH3
CH3
CH3
CH3

34

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


CH3
O
OH
N
OH
CH3
CH2C6H5
35
10
9
8
7
6
5
4
3
2
1
0
PPM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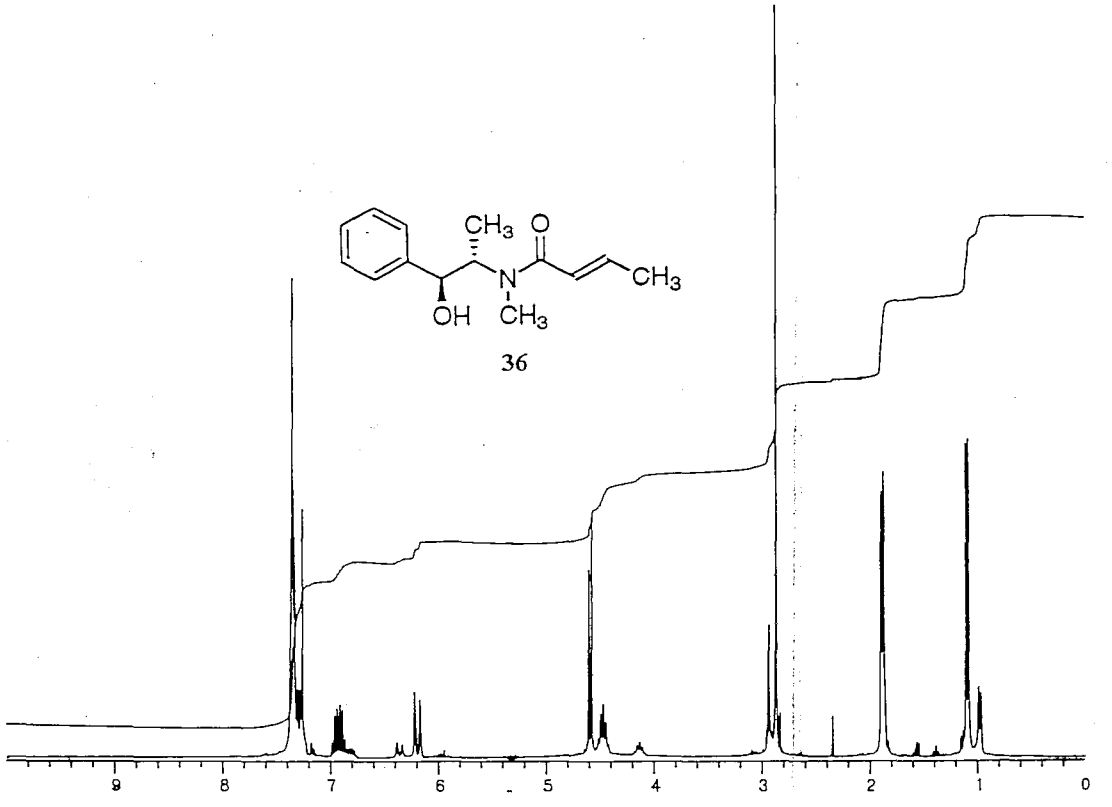
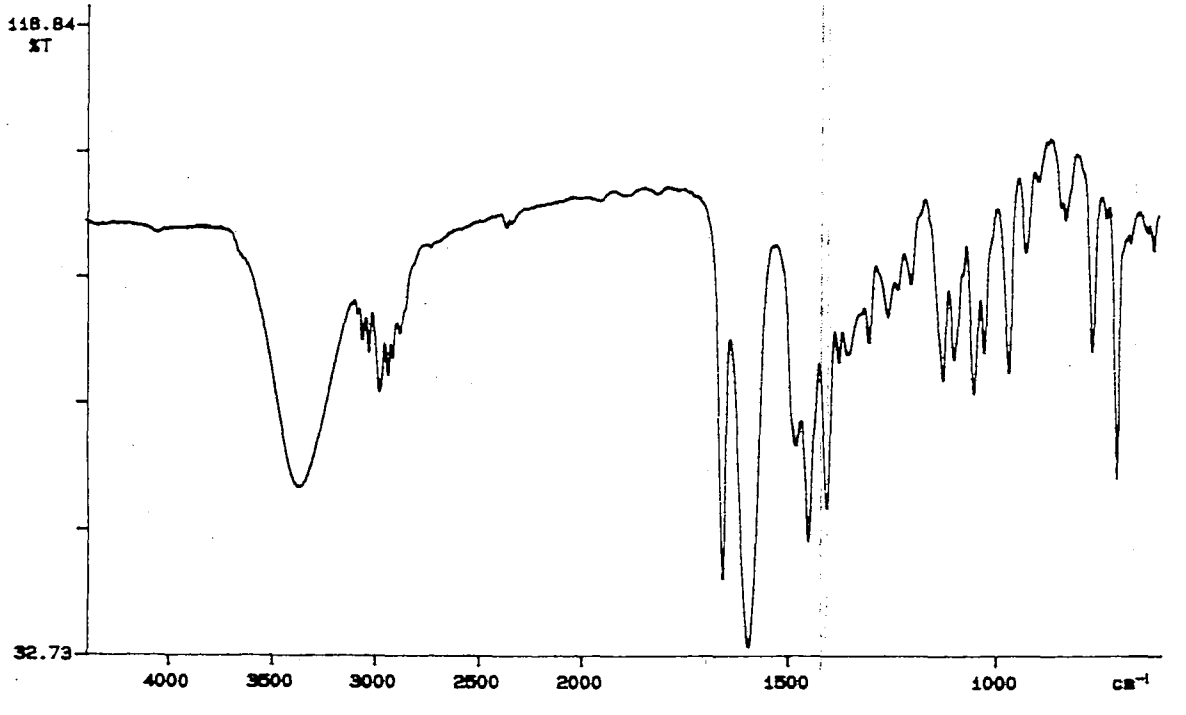
1000
cm-1


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

36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3000
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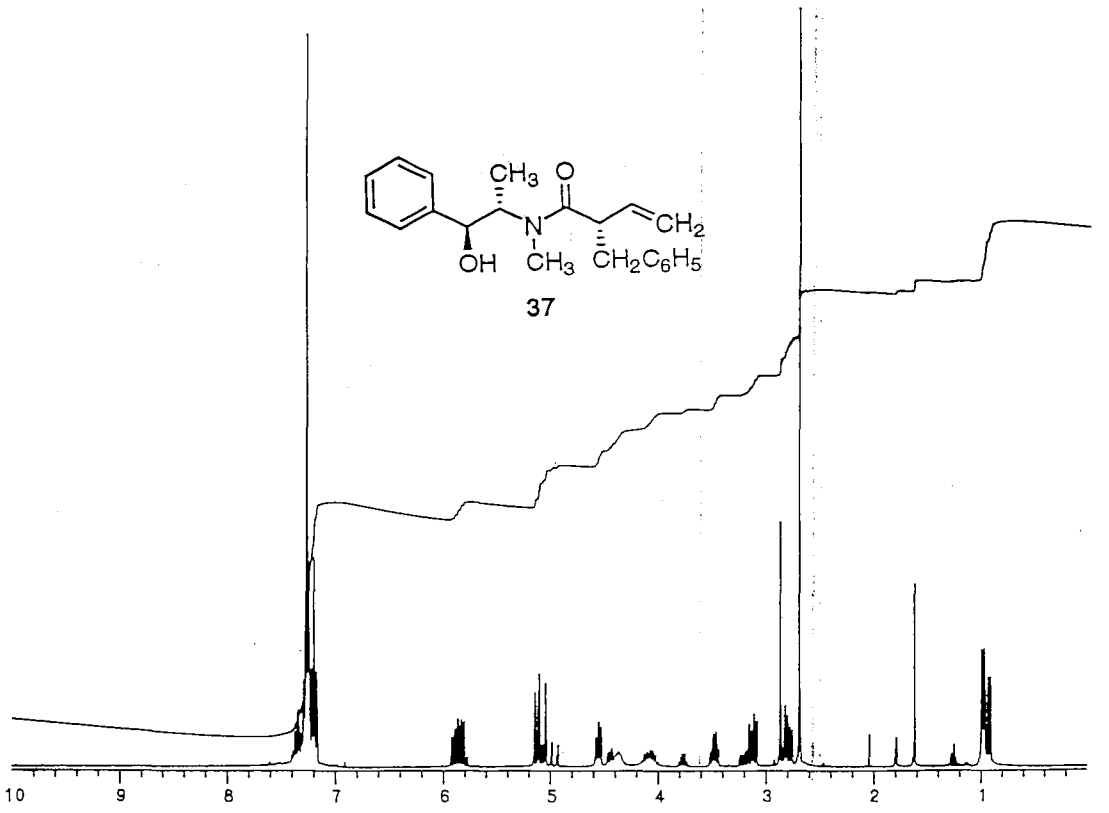
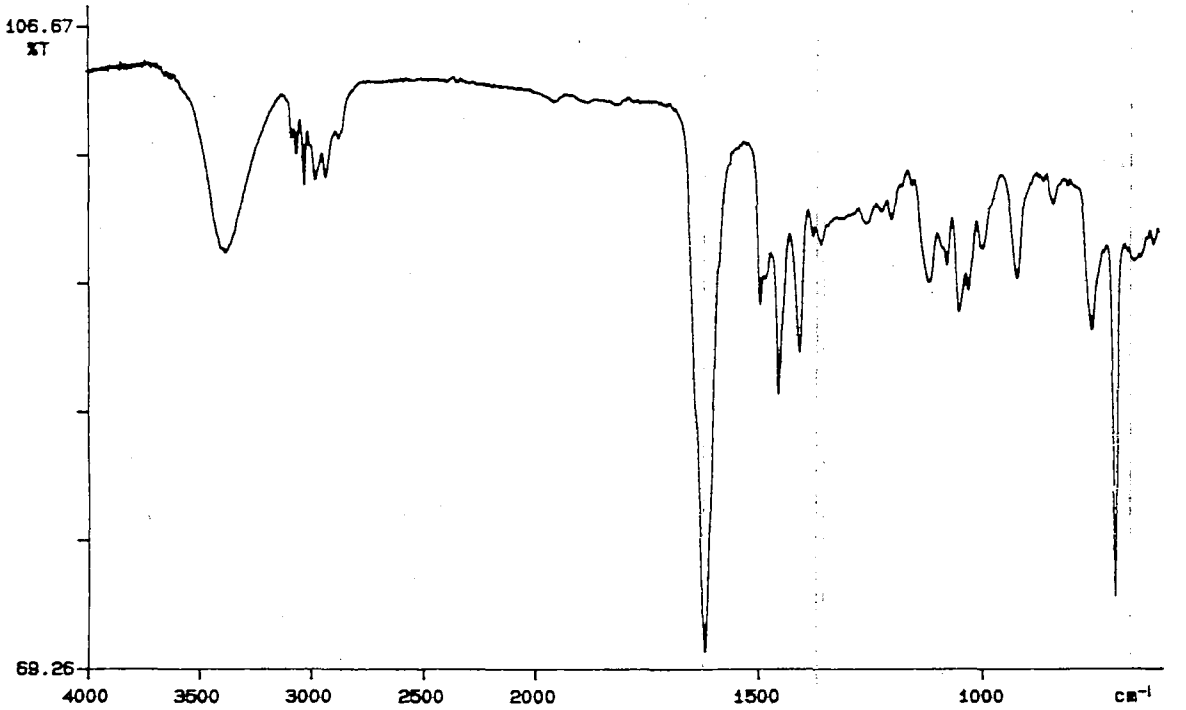
2000
1500
1000
cm-1


CH3
O
N
CH2
OH
CH3
CH2C6H5
10
9
8
7
6
5
4
3
2
1

37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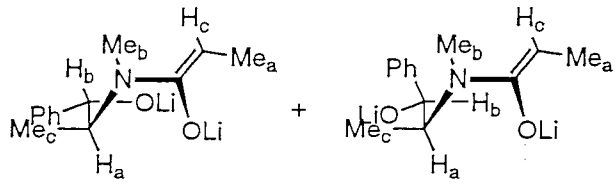
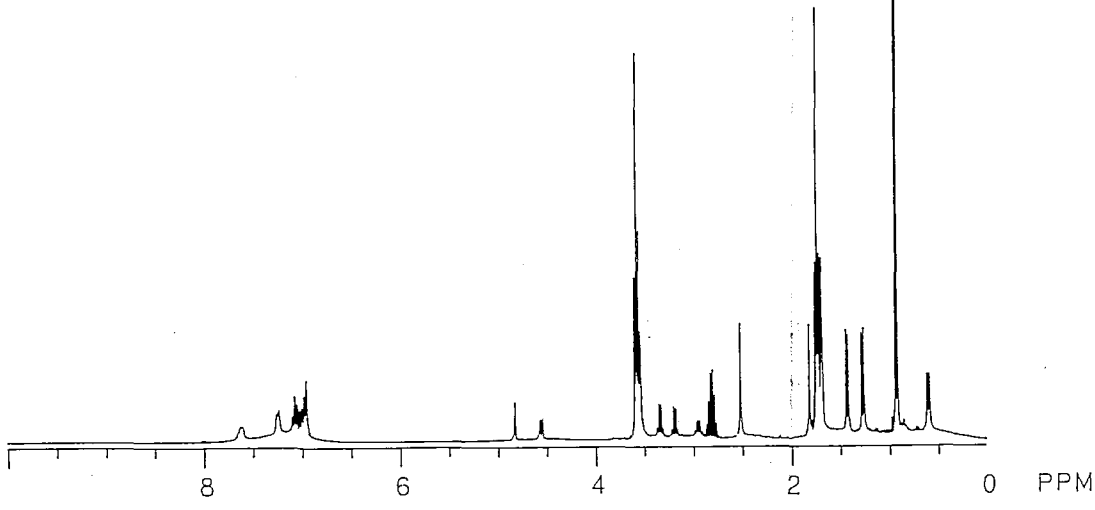
2500
2000
1500
1000
cm-1

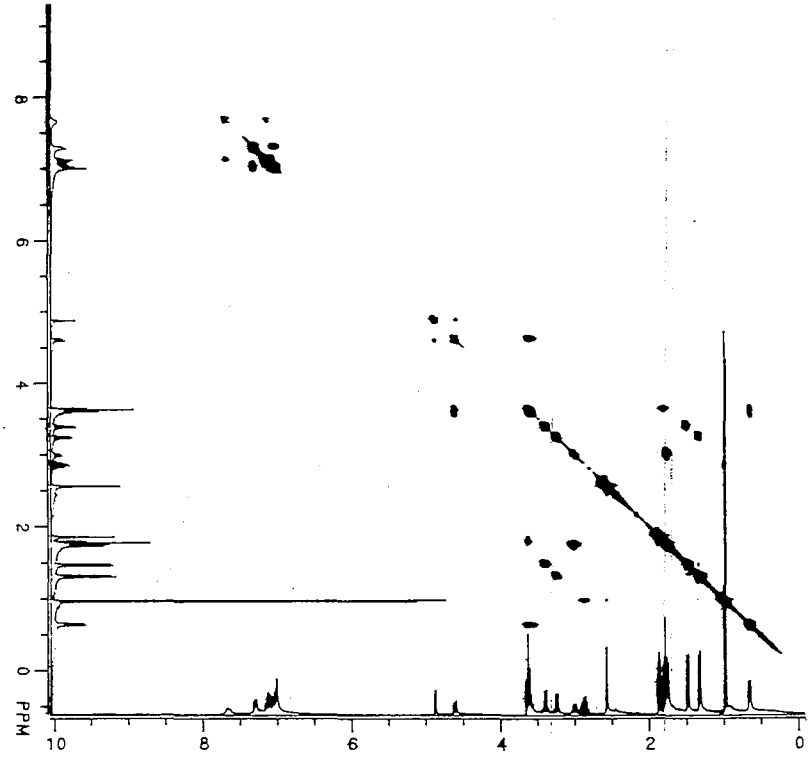


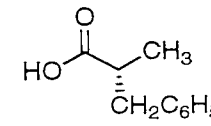
structure X

+

structure Y

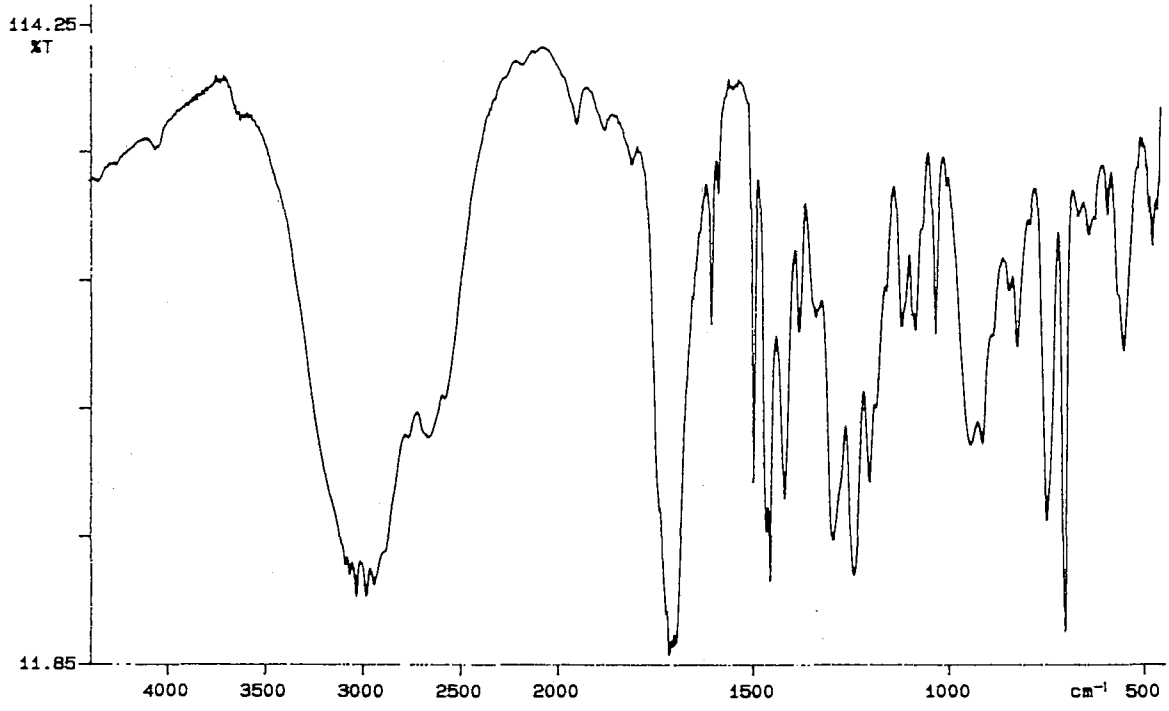





O
HO
CH3
CH2C6H5

39

9
8
7
6
5
4
3
2
1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11.85
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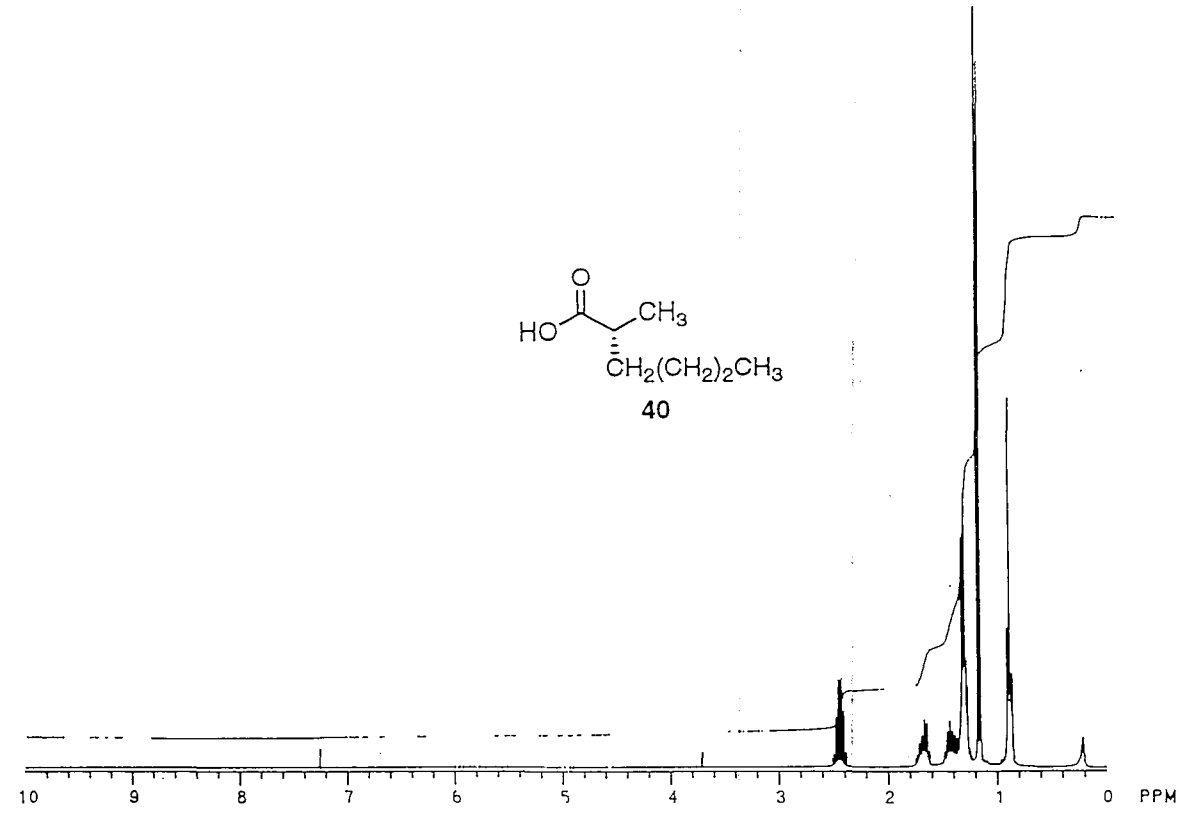
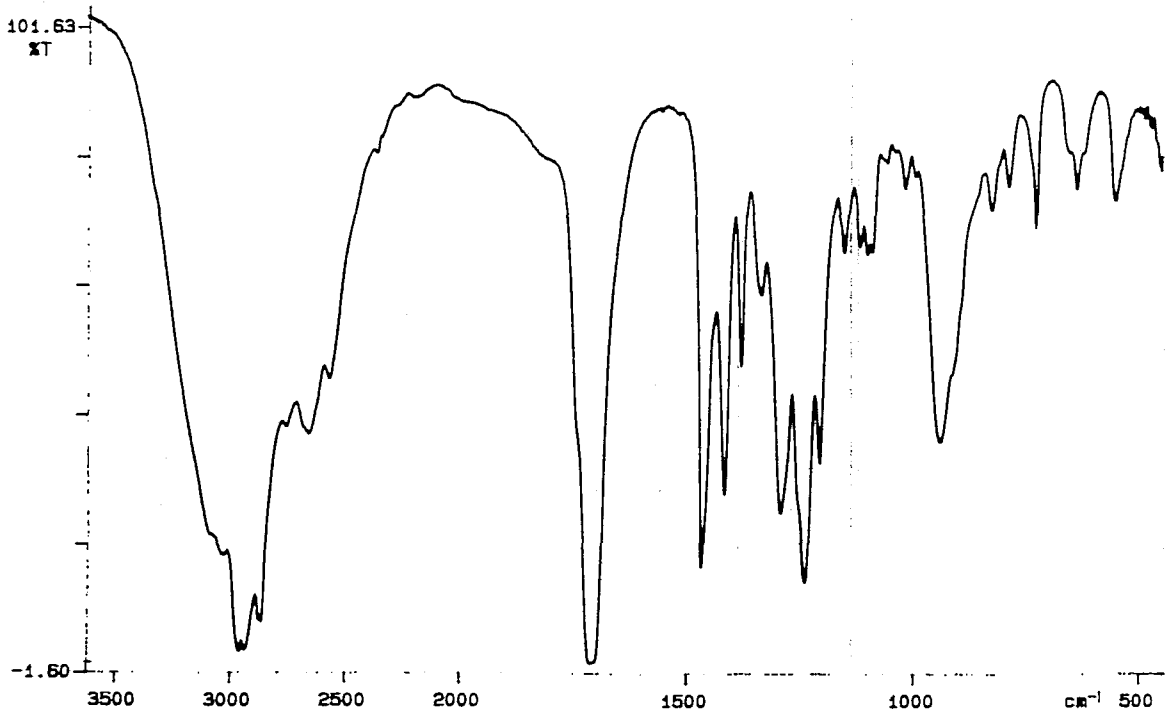
3500
3000
2500
2000
1500
1000
cm-1
500


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

40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-1.60
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3000
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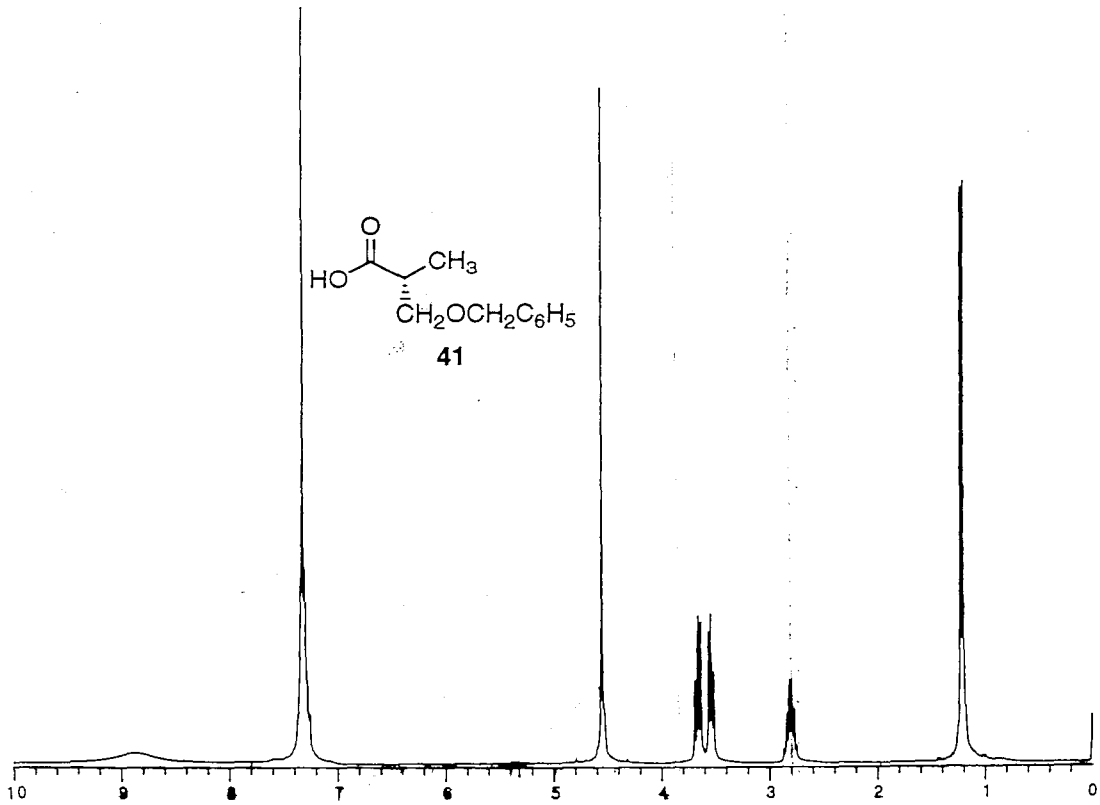
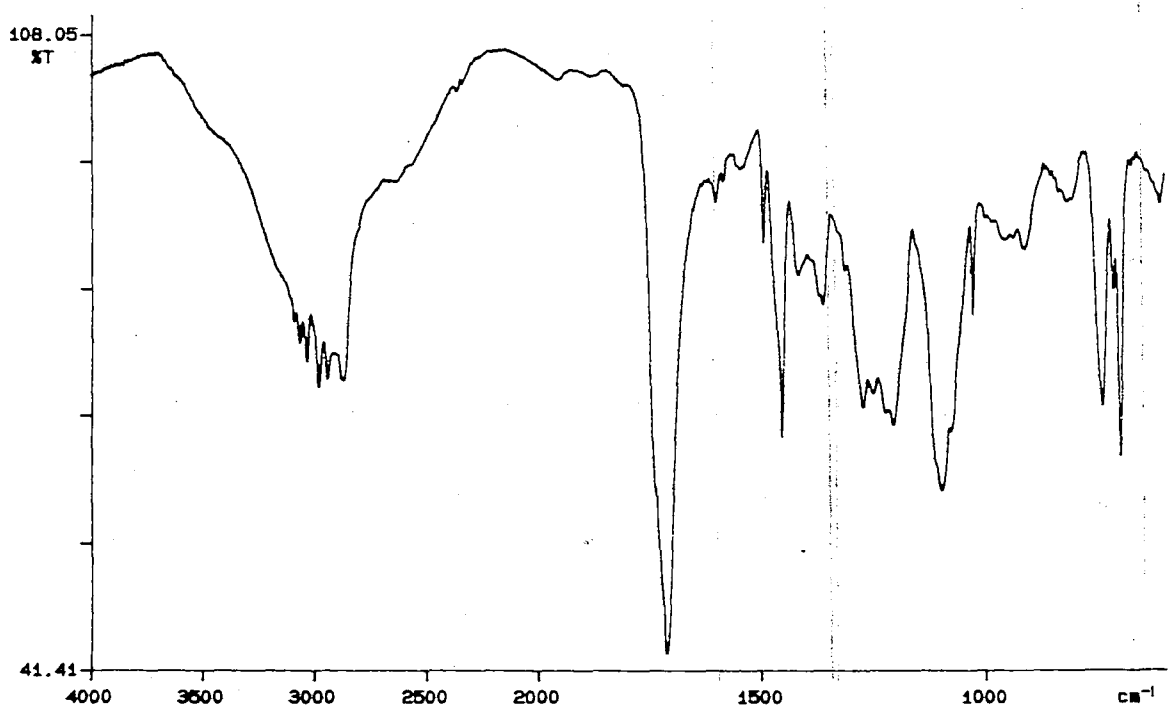
2000
1500
1000
cm-1
500


HO
O
CH3
CH2OCH2C6H5
41
10
9
8
7
6
5
4
3
2
1
0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%T
41.41
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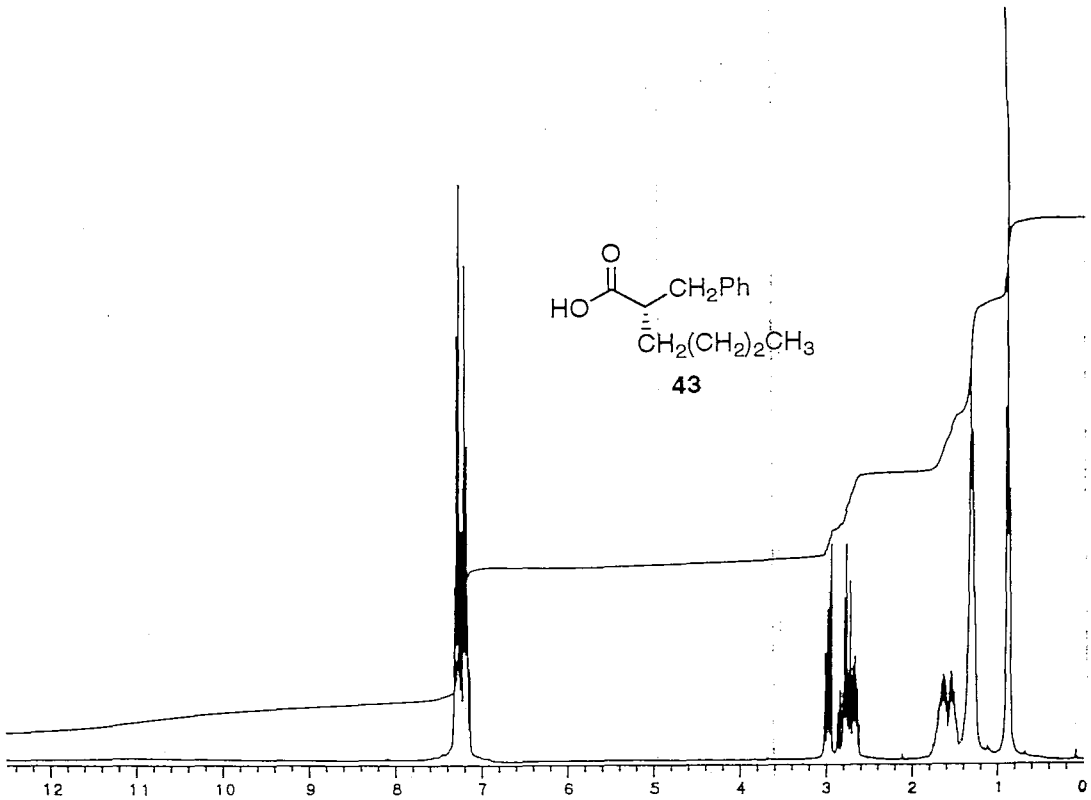
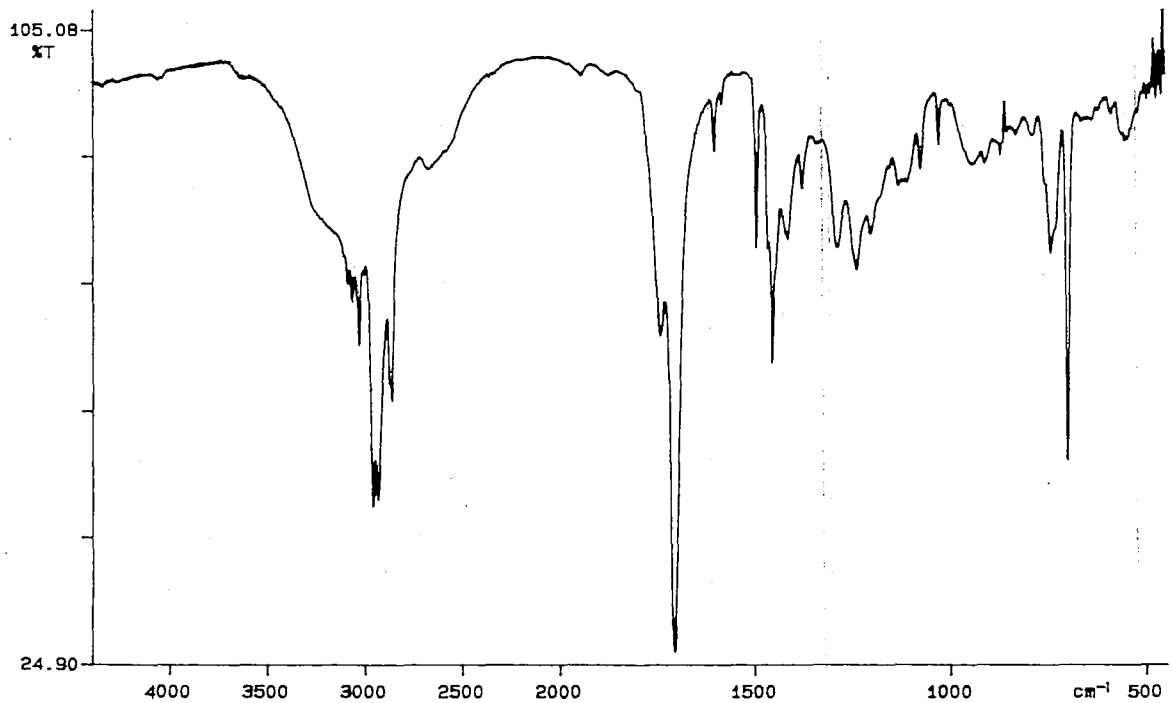
3500
3000
2500
2000
1500
1000
cm-1


O
HO
CH2Ph
CH2(CH2)2CH3
12
11
10
9
8
7
6
5
4
3
2
1
0

43


105.08
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24.90
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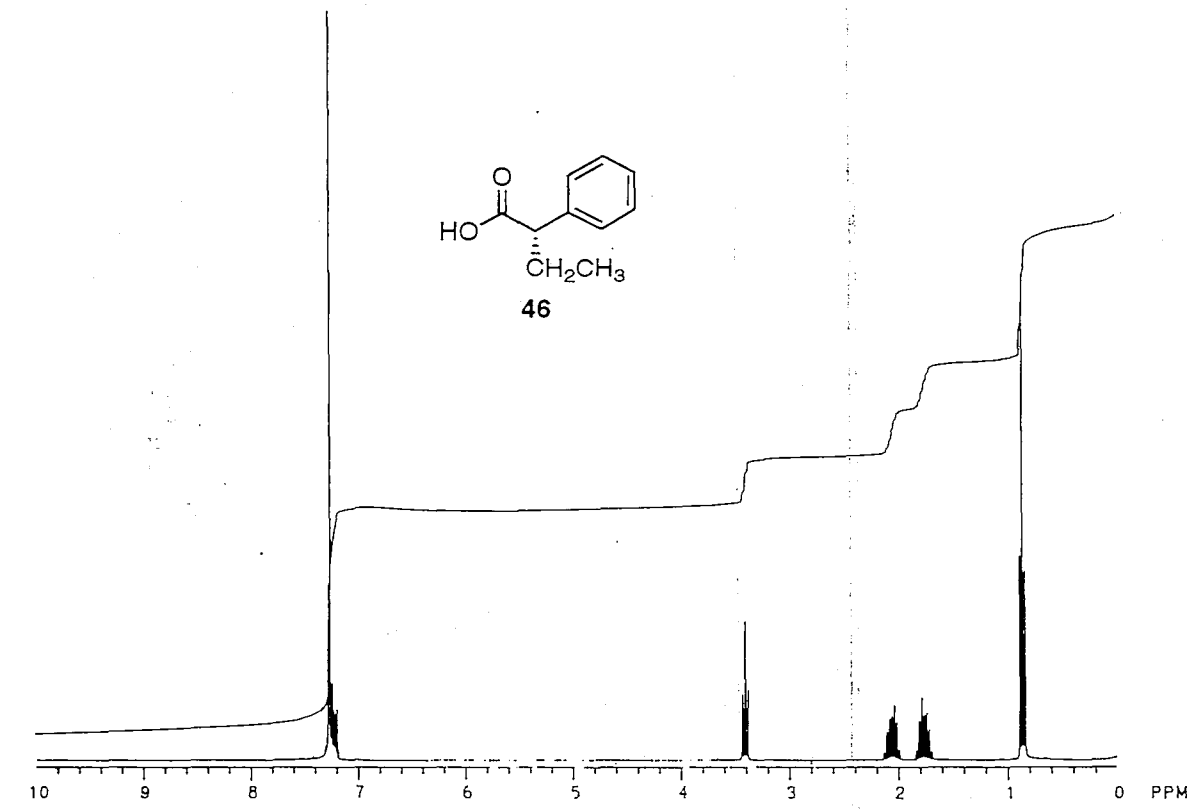
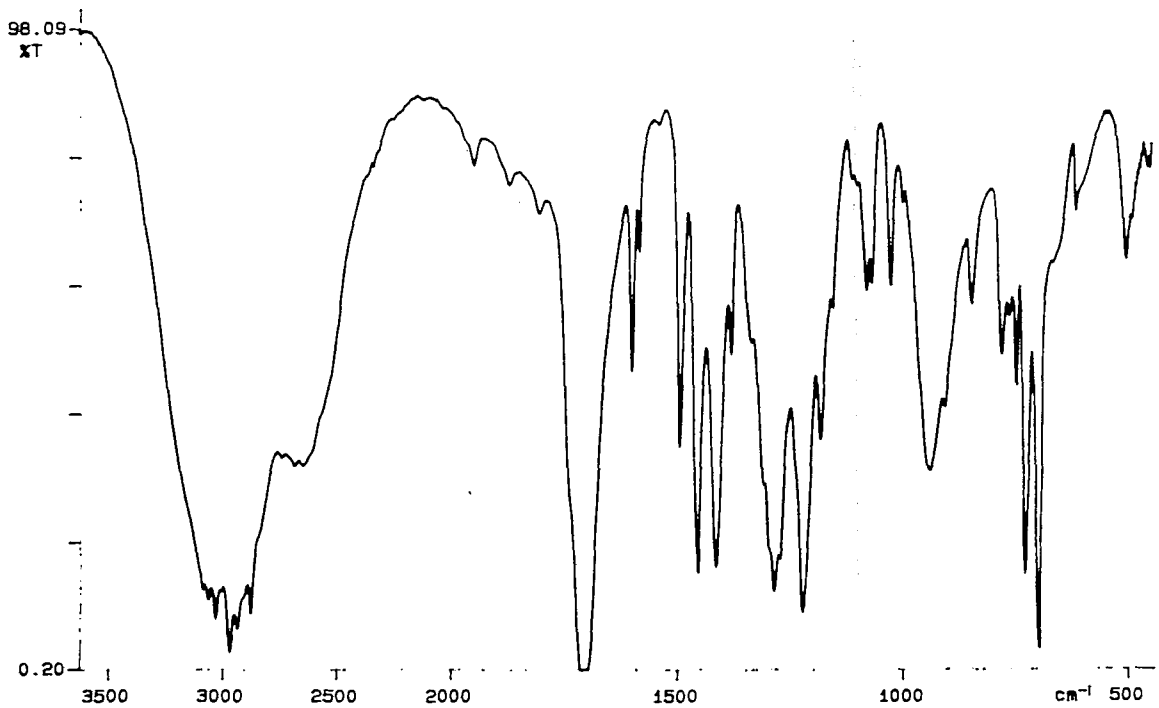
3500
3000
2500
2000
1500
1000
cm-1
500


HO
O
CH2CH3
46
10
9
8
7
6
5
4
3
2
1
0
PPM


98.09
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3000
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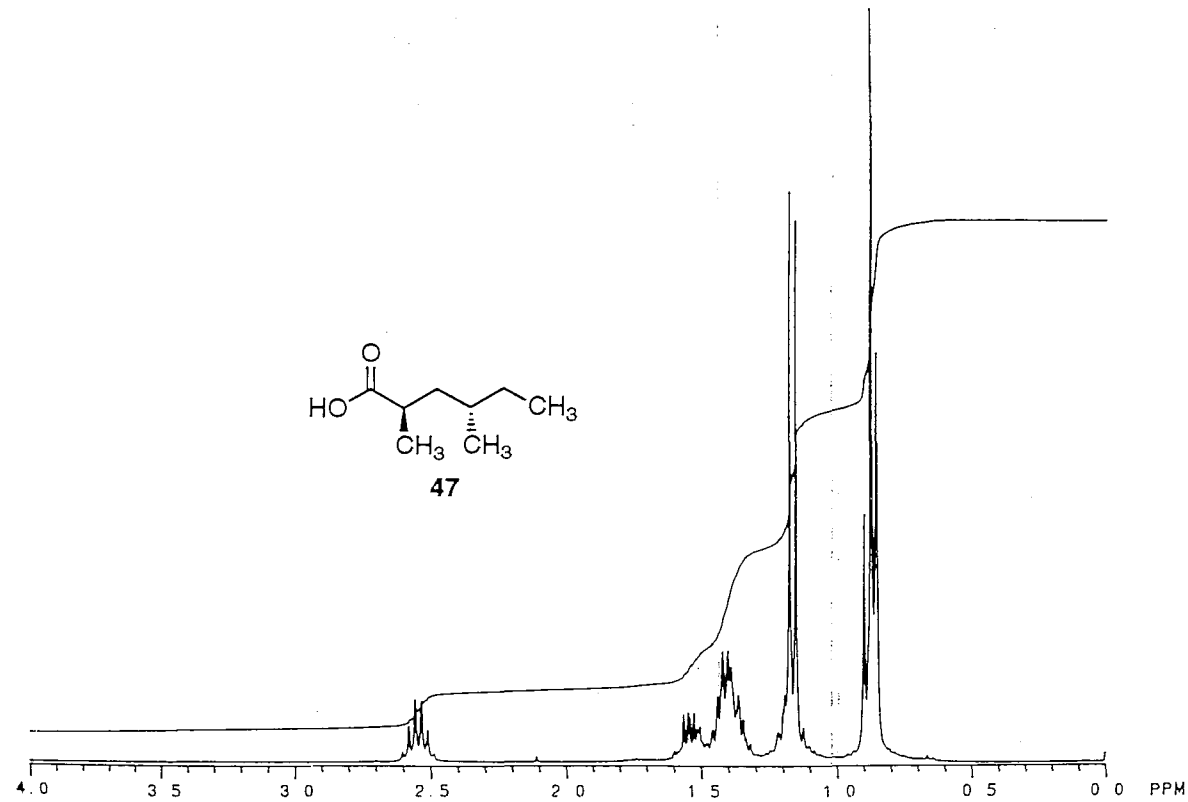
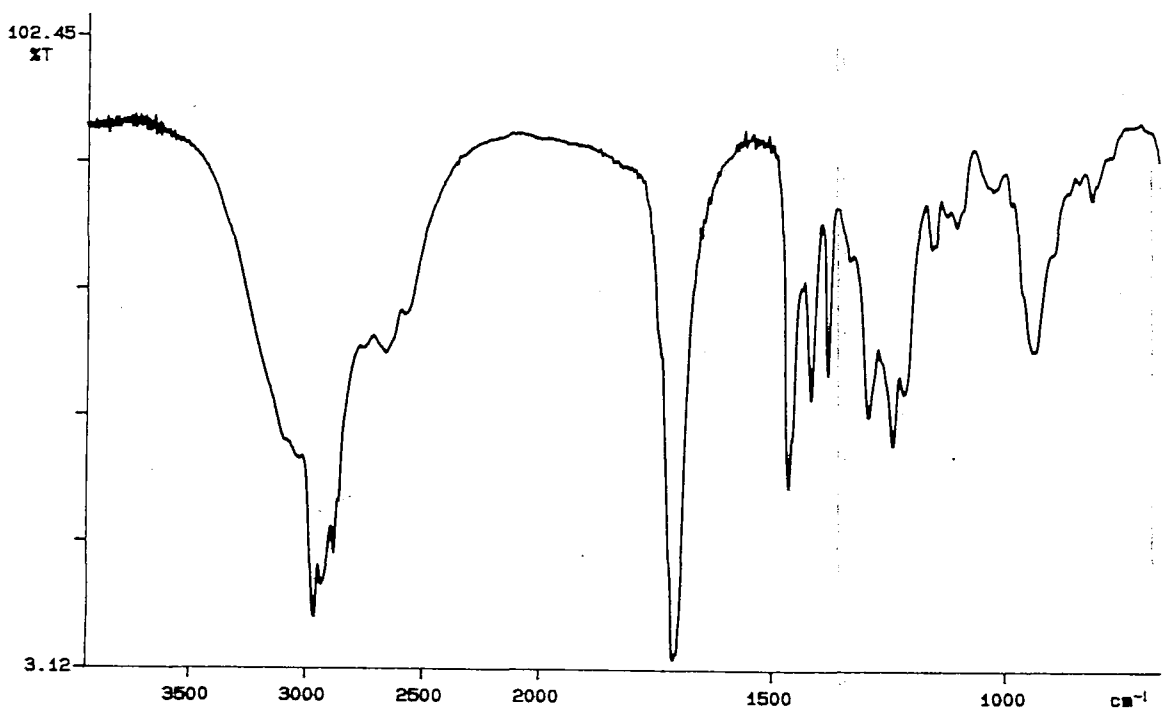
2000
1500
1000
cm-1
500


HO
O
CH3
CH3
CH3
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
PPM

47


102.45
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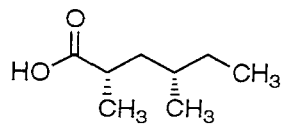
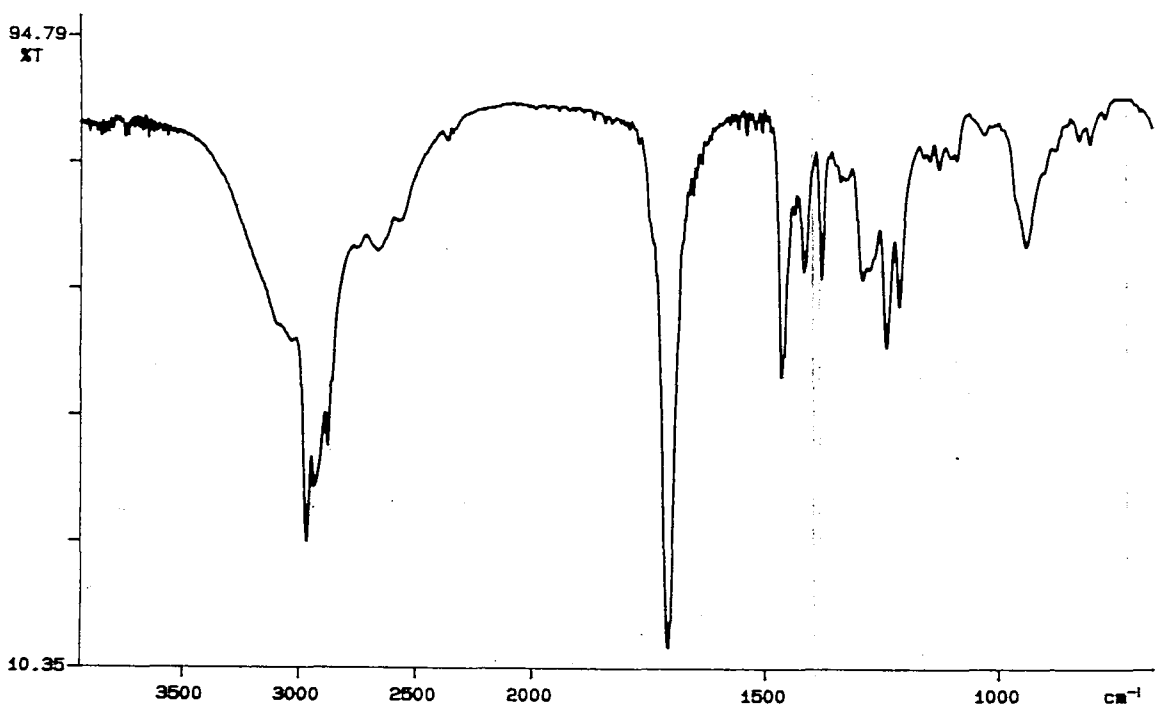
3.12
3500
3000
2500
2000
1500
1000
cm-1


O
HO
CH3
CH3
CH3

48

4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0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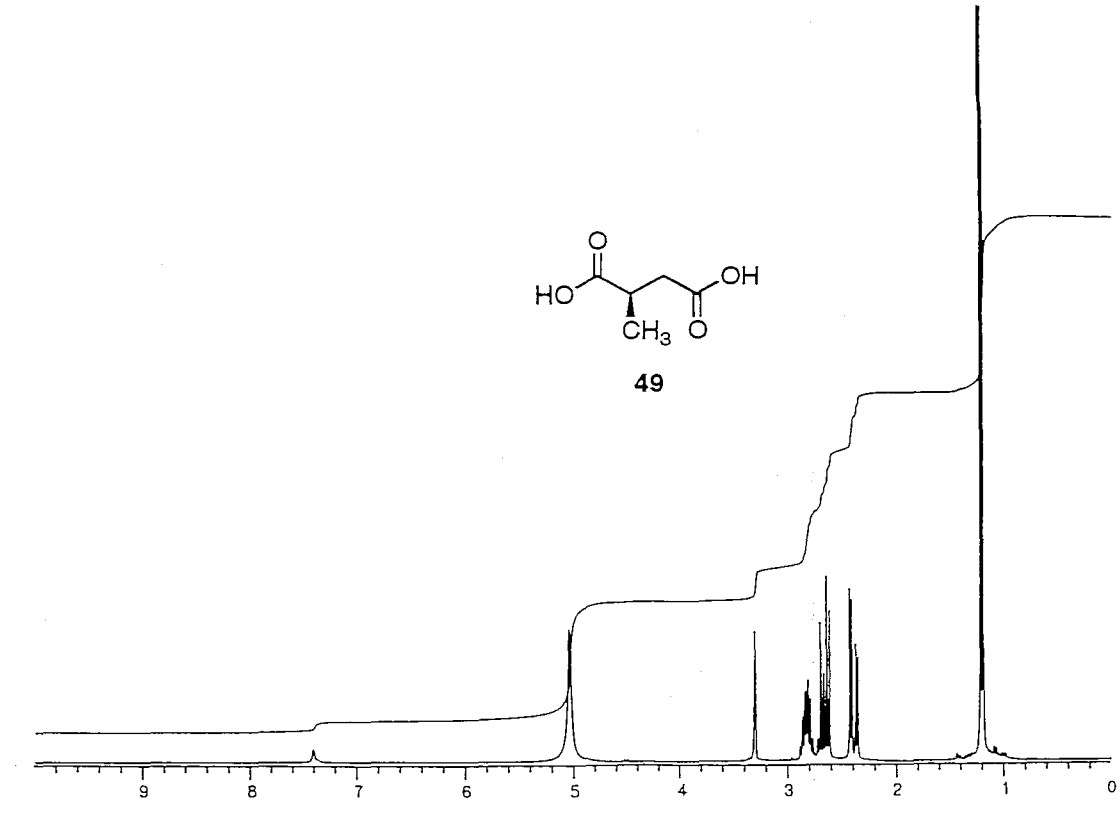
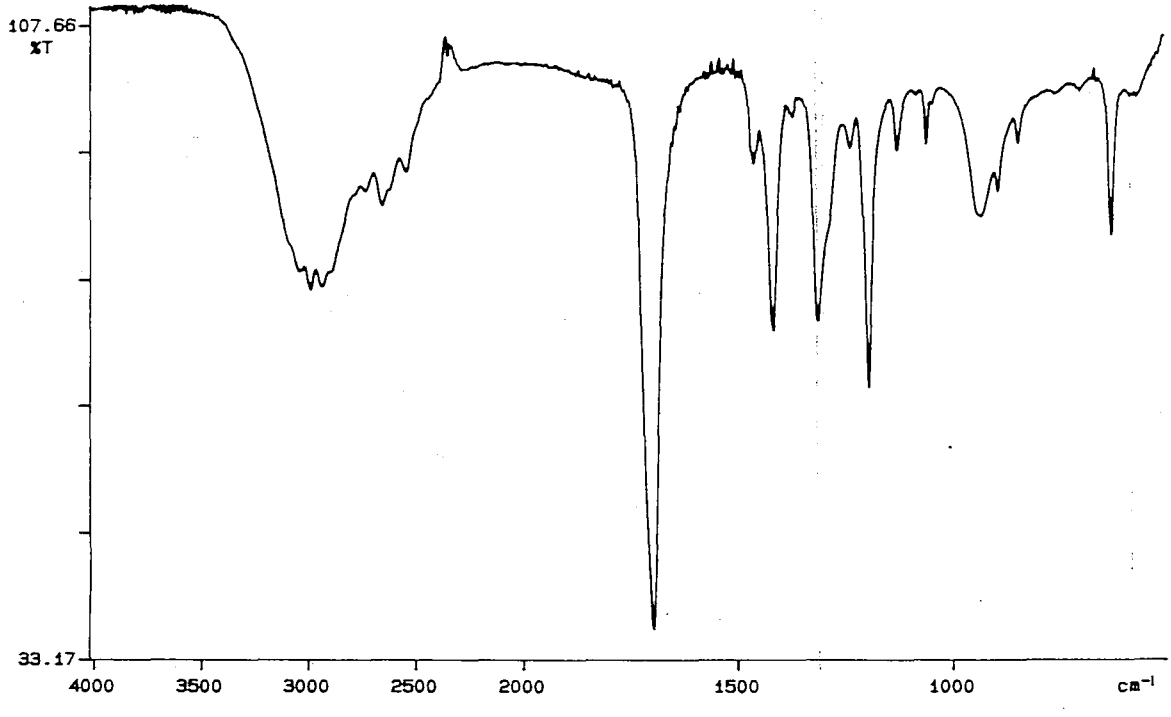
1500
1000
cm-1


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

49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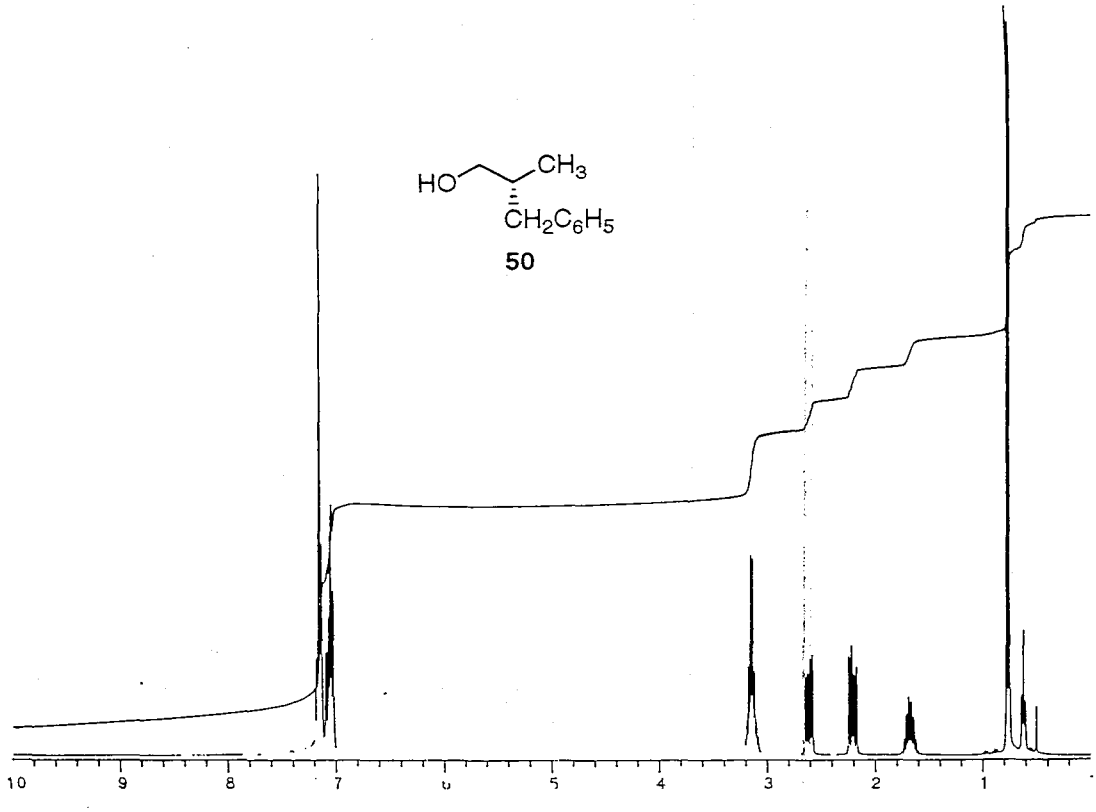
HO
CH3
CH2C6H5
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10
9
8
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4
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2
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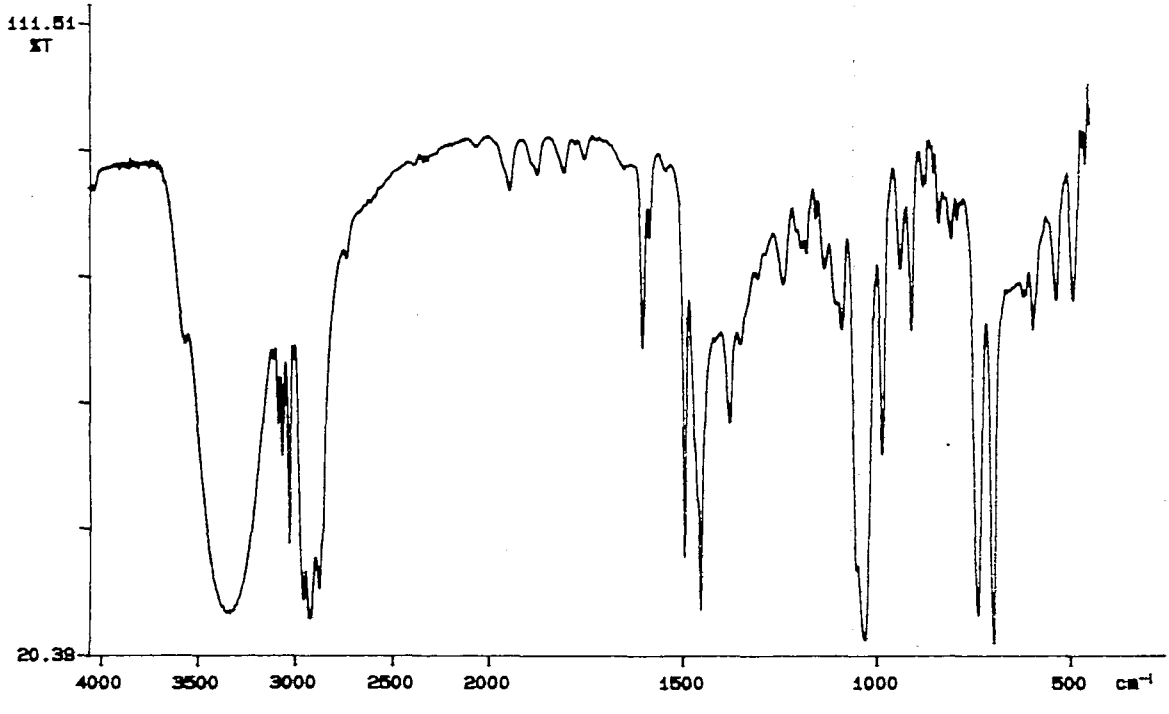
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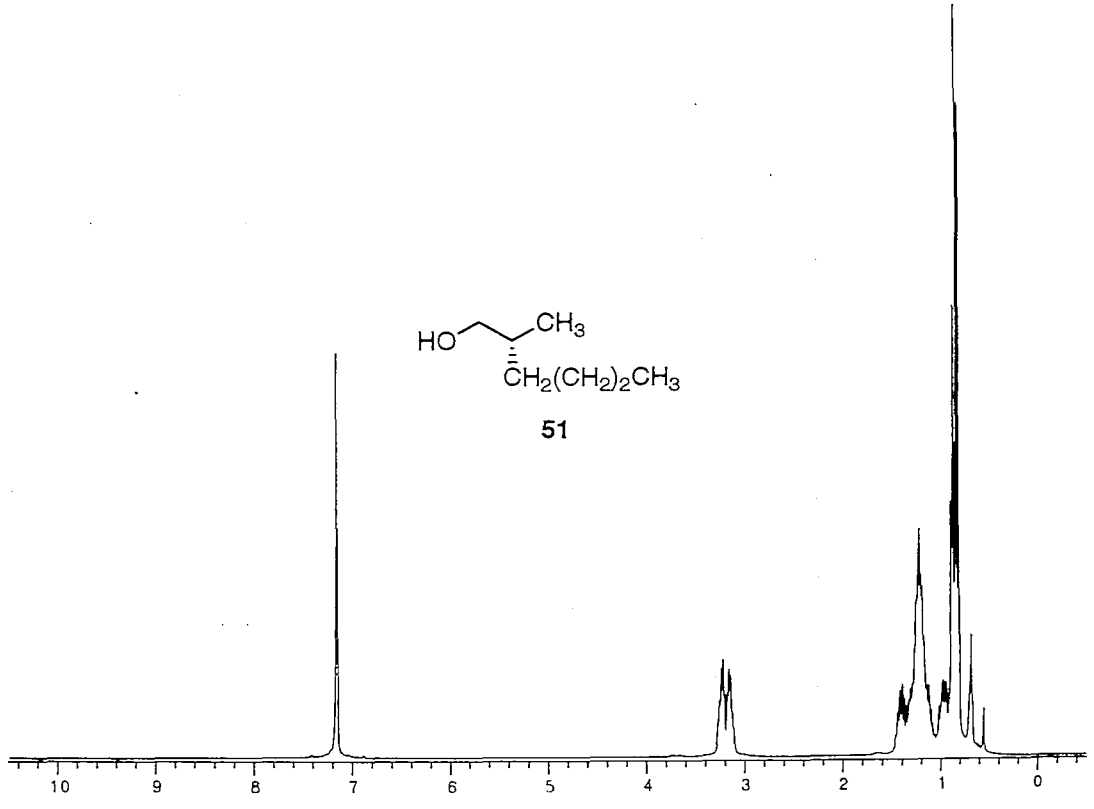
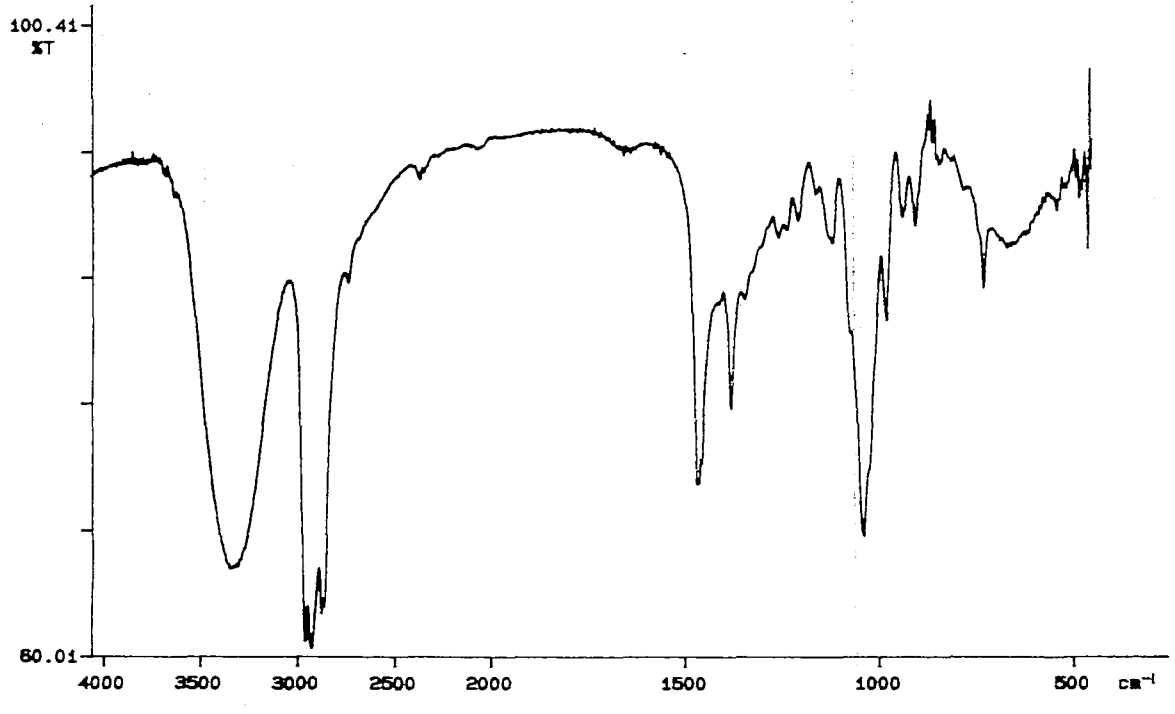

HO
CH3
CH2(CH2)2CH3
51
10
9
8
7
6
5
4
3
2
1
0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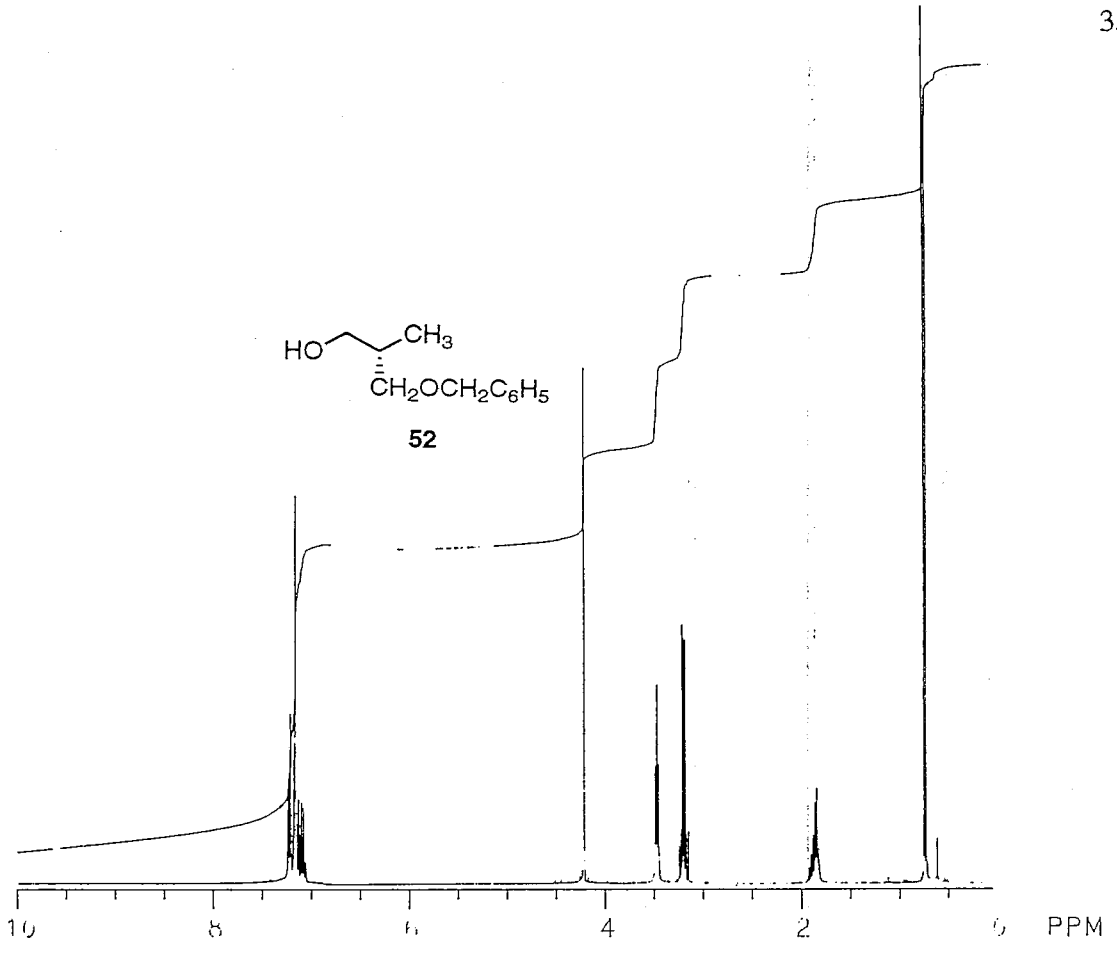
cm-1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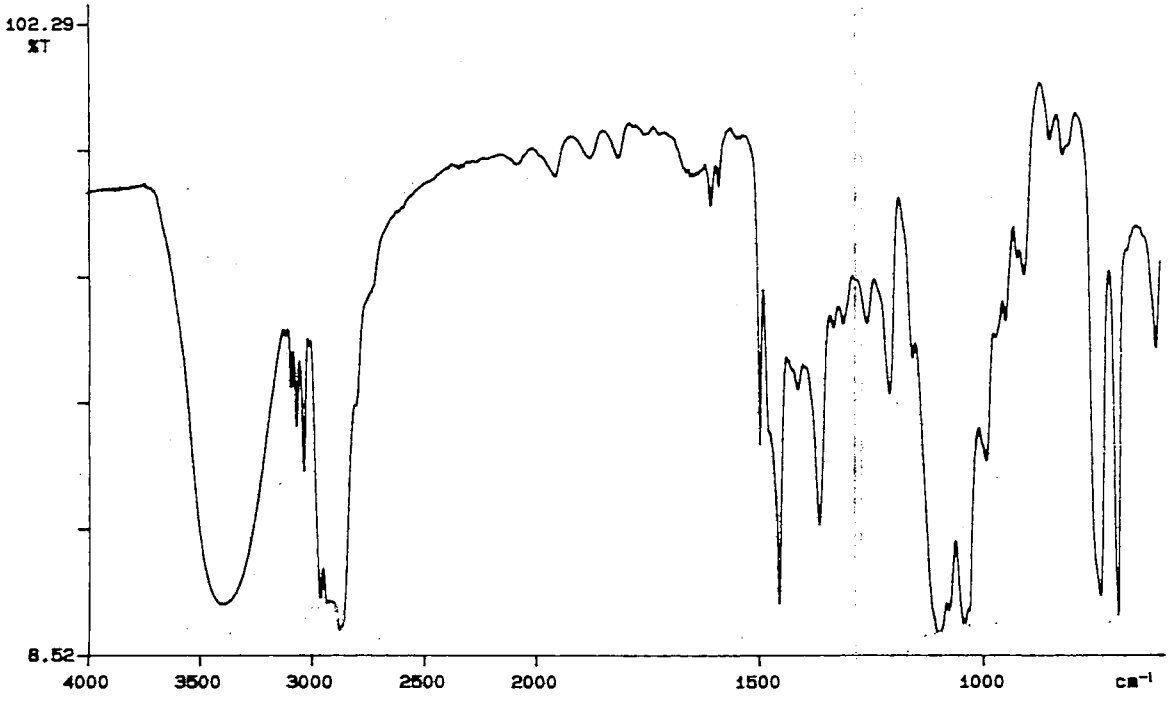
CH3
CH2OCH2C6H5
52
10
8
6
4
2
0
PPM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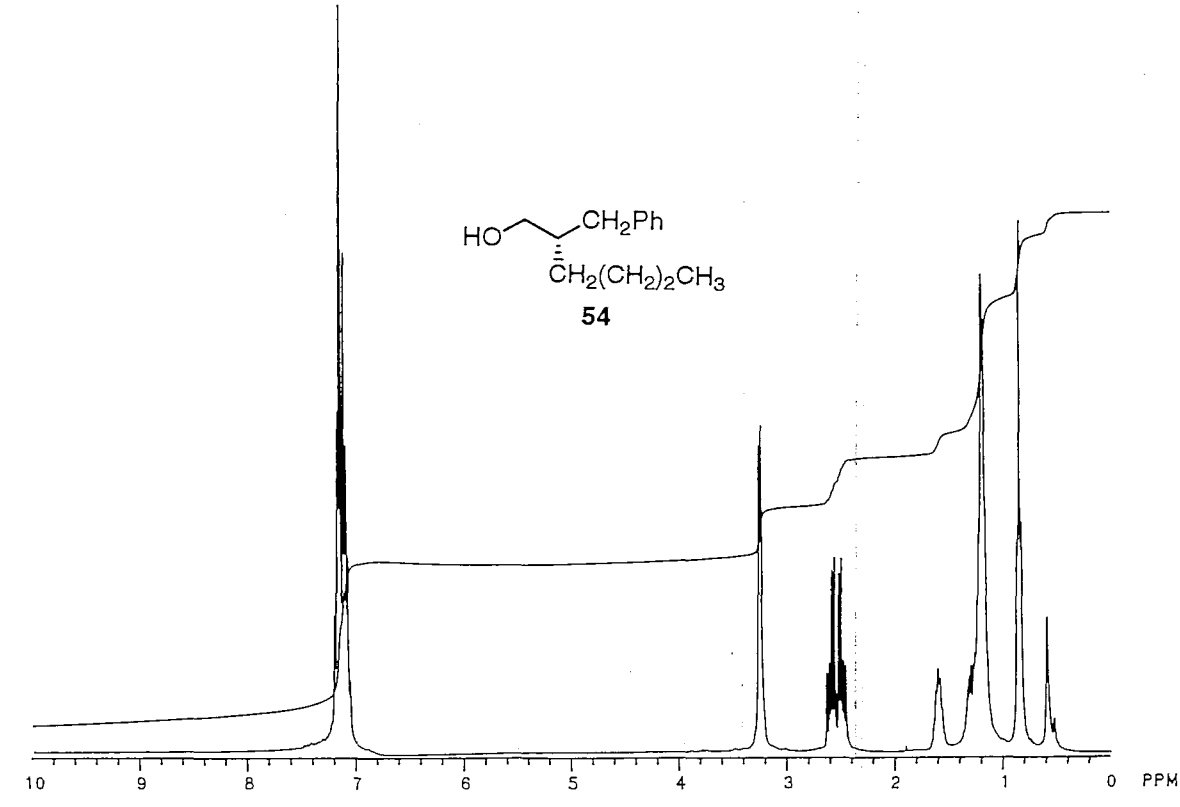
cm-1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CH2Ph
CH2(CH2)2CH3
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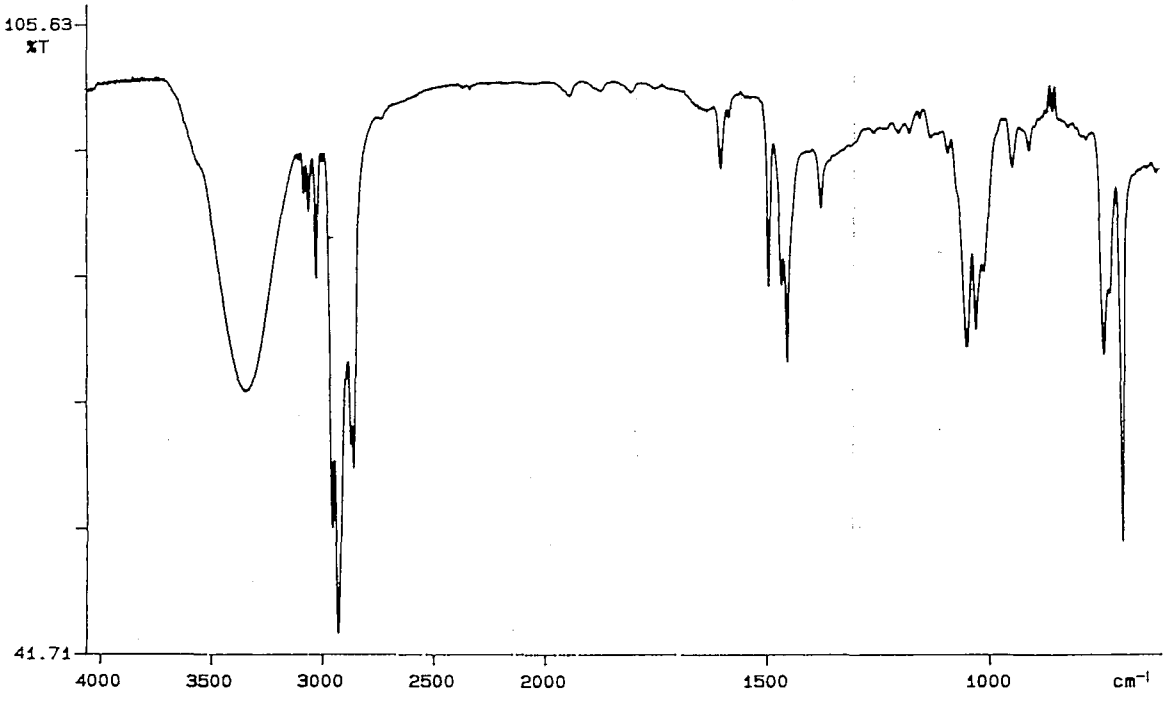
9
8
7
6
5
4
3
2
1
0
PPM

54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41.71
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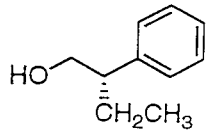
cm-1


HO
CH2CH3

56

10
9
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6
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3
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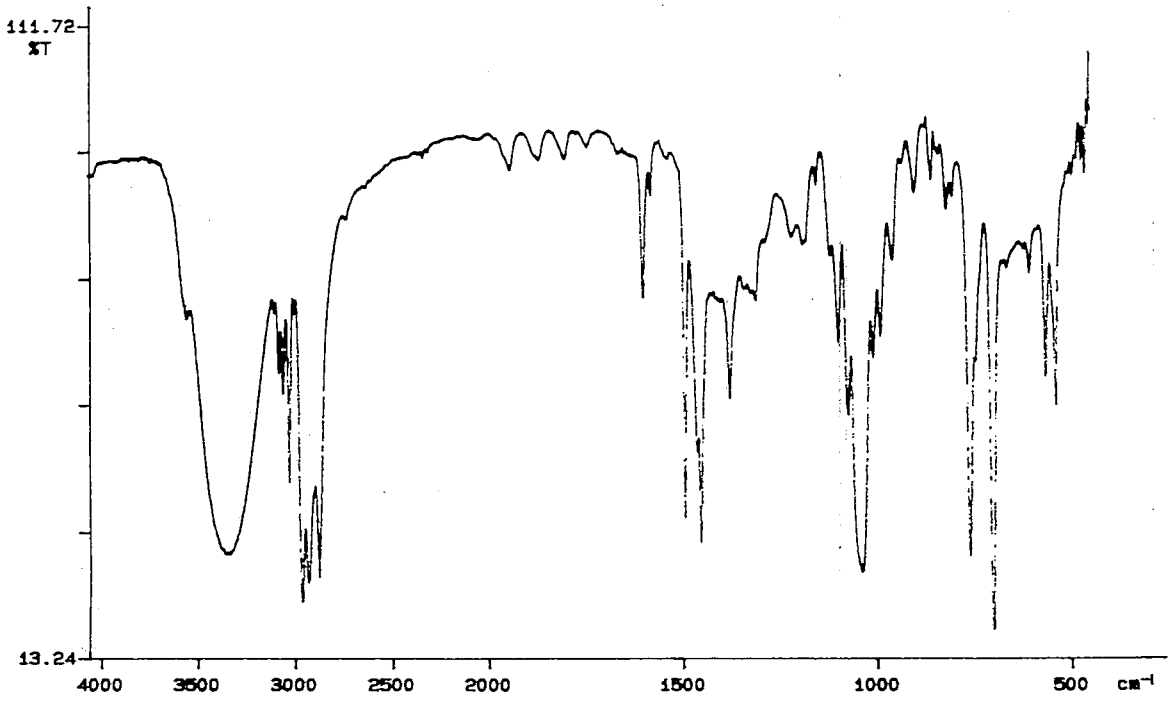
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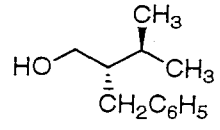
cm-1


CH3
HO
CH3
CH2C6H5

57

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7
6
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1
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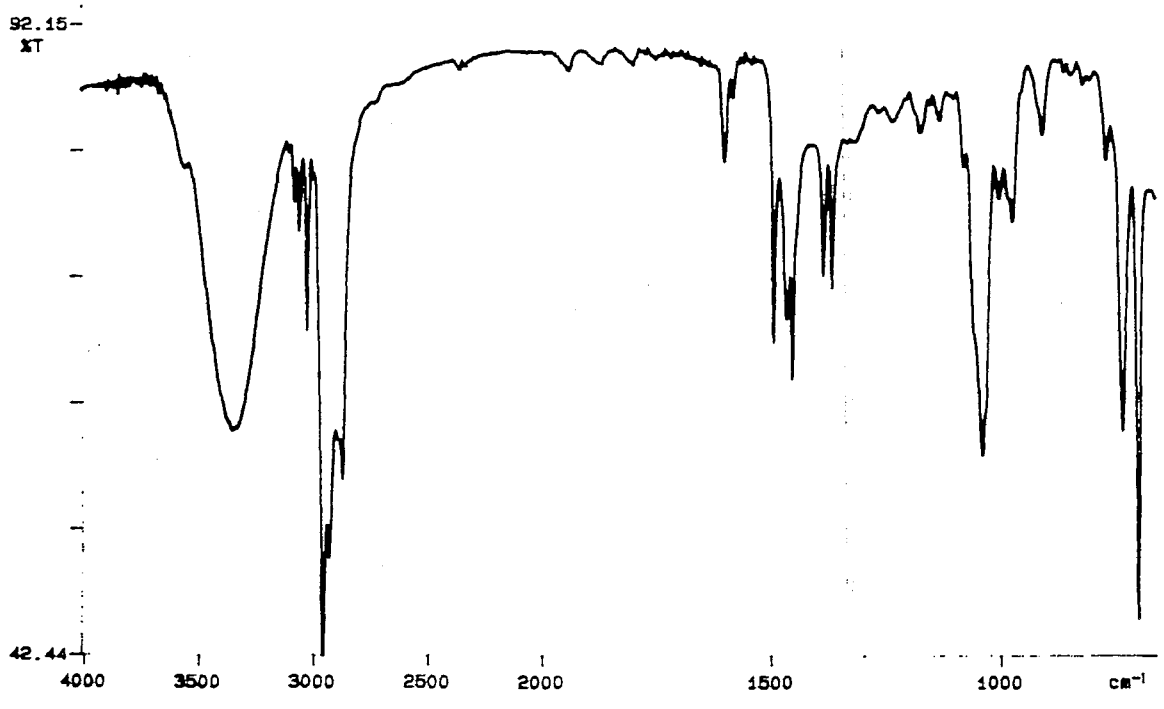
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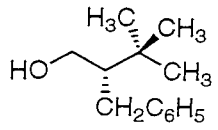
cm-1


H3C
CH3
HO
CH3
CH2C6H5

58

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9
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7
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4
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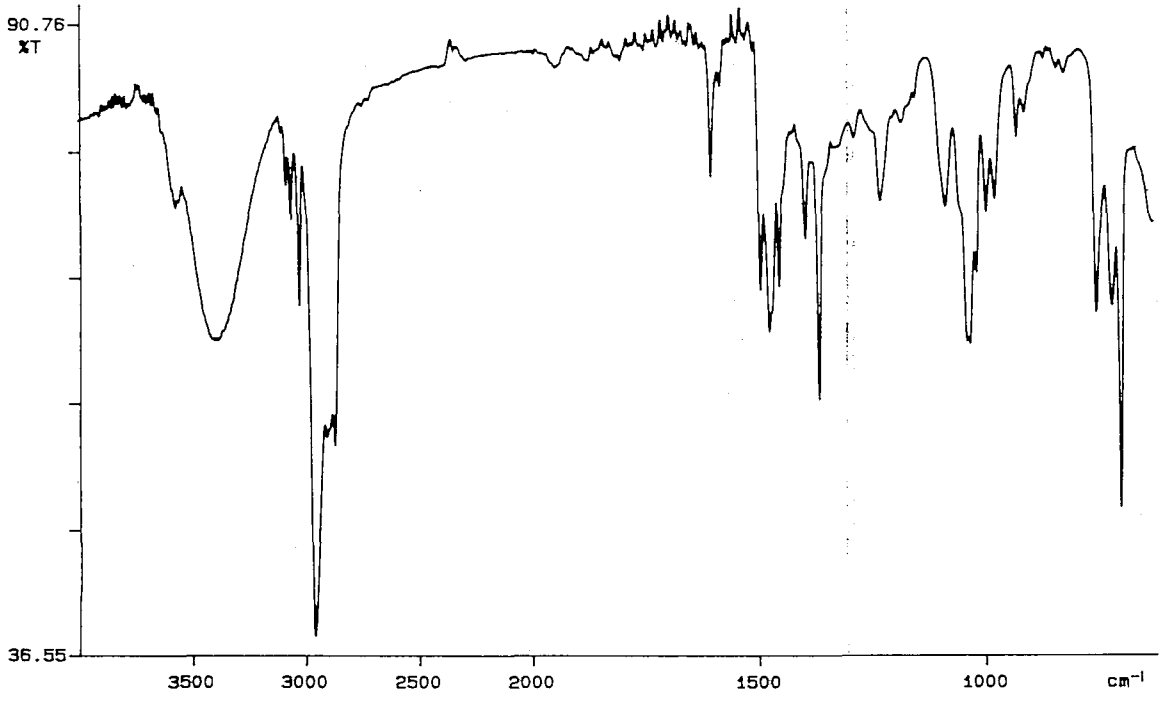
2
1
0
PPM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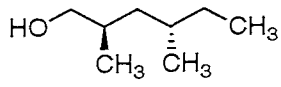
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CH3
CH3
CH3

59

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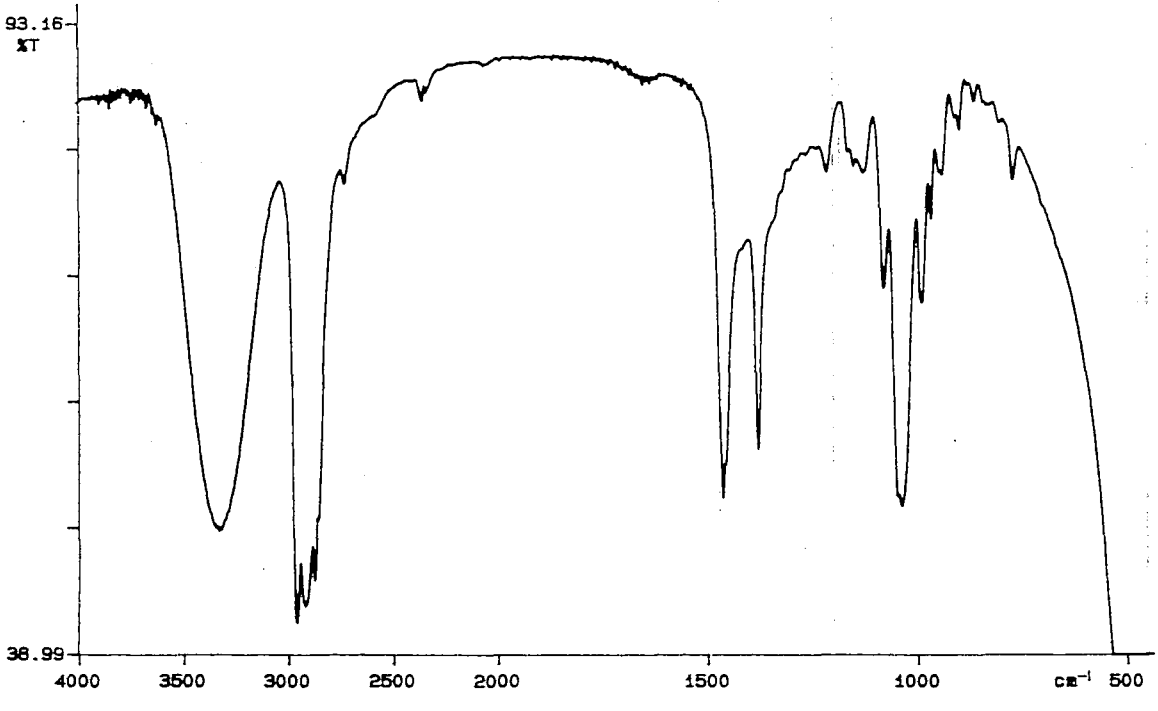
2
1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cm-1
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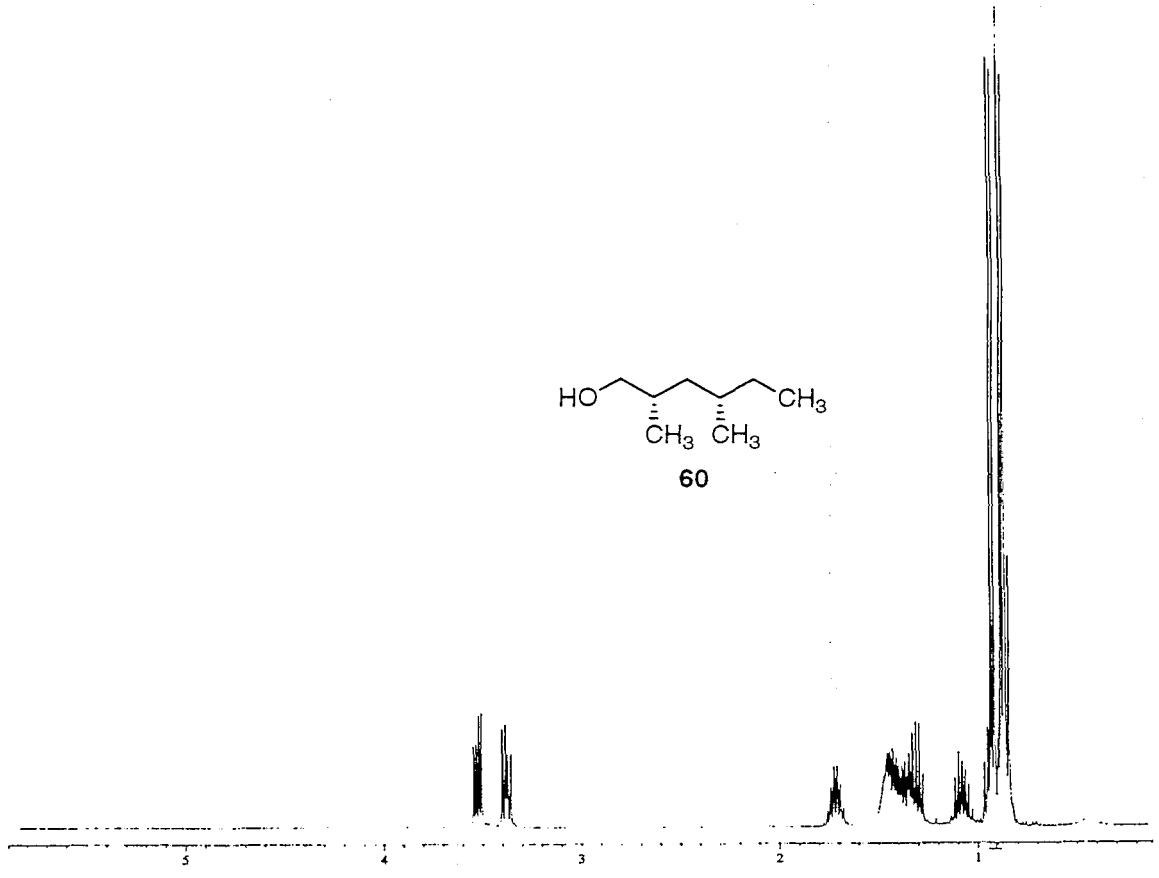
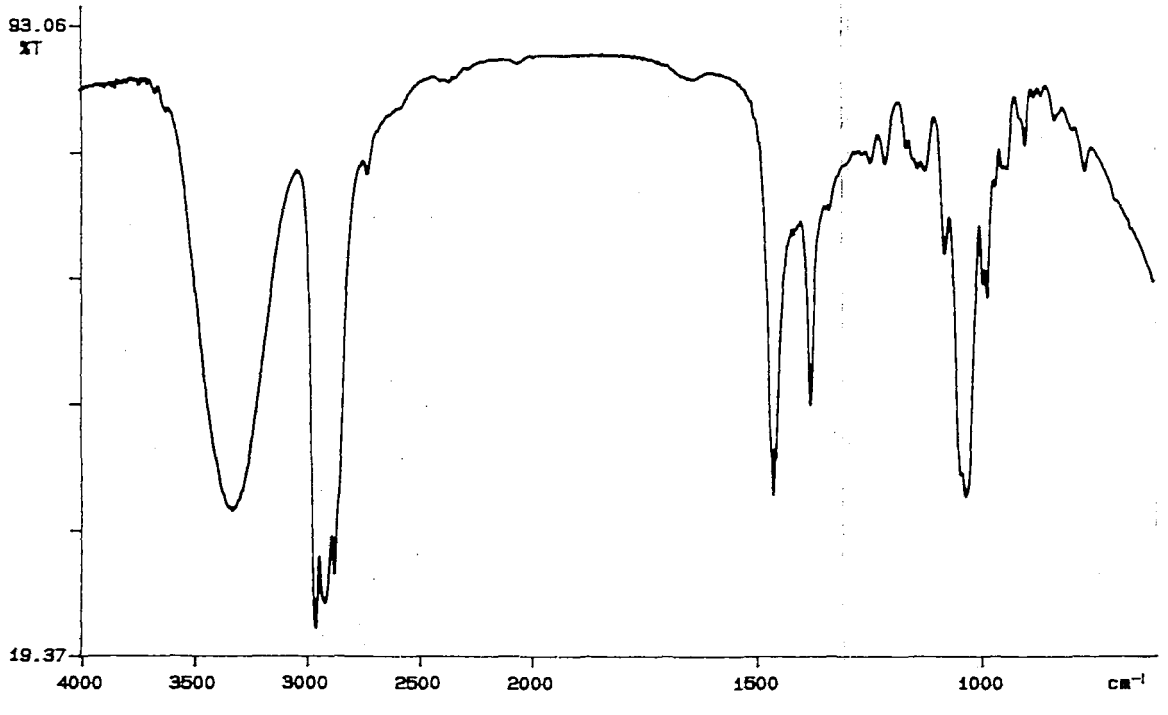

HO
CH3
CH3
CH3
5
4
3
2
1

60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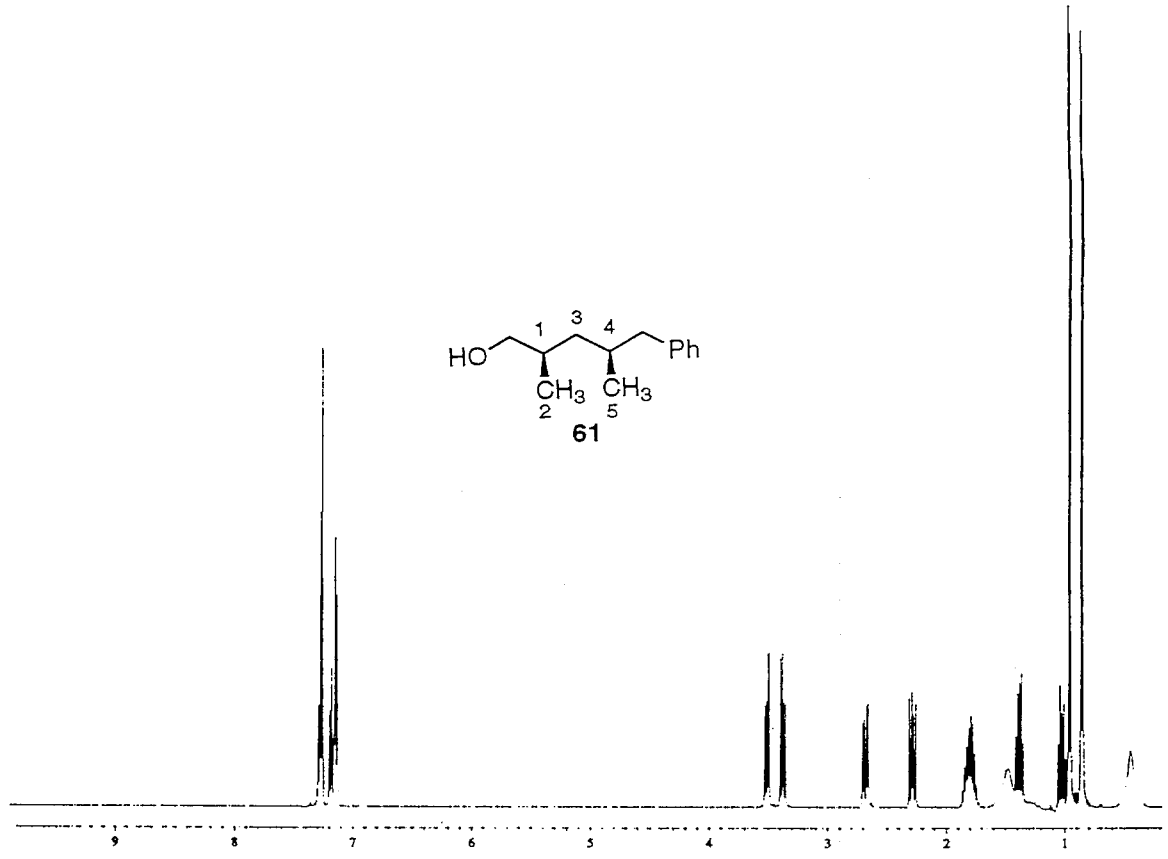
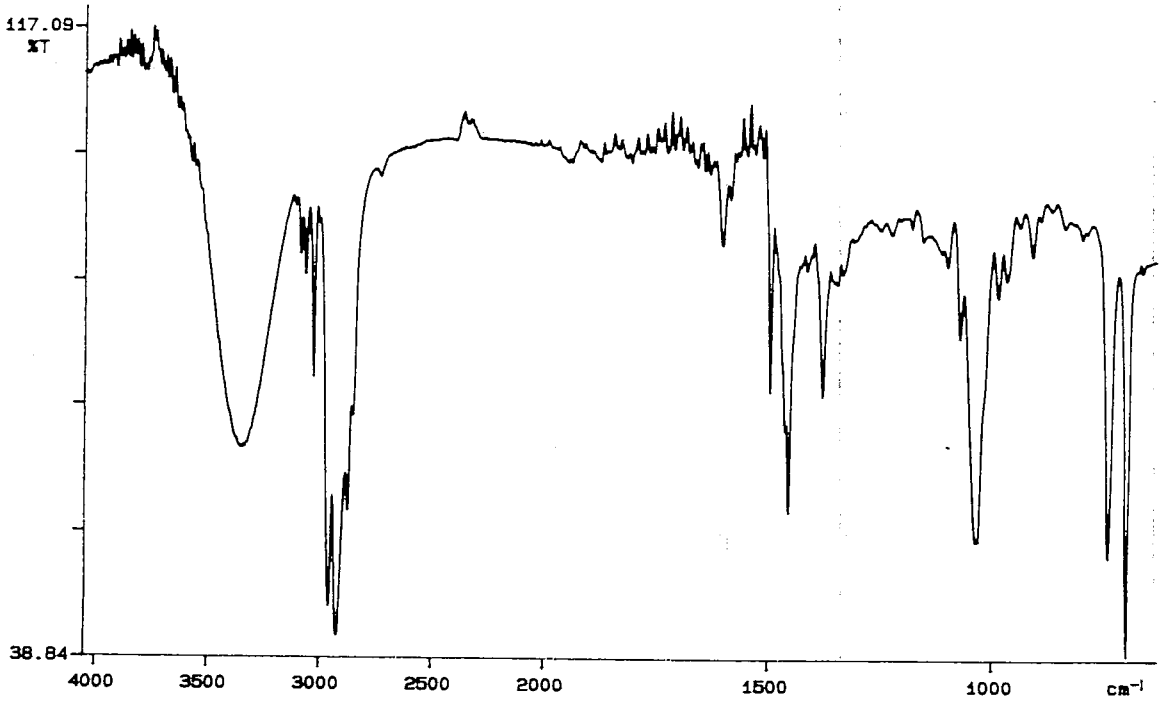

HO
1
3
4
Ph
CH3
2
CH3
5

61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%T
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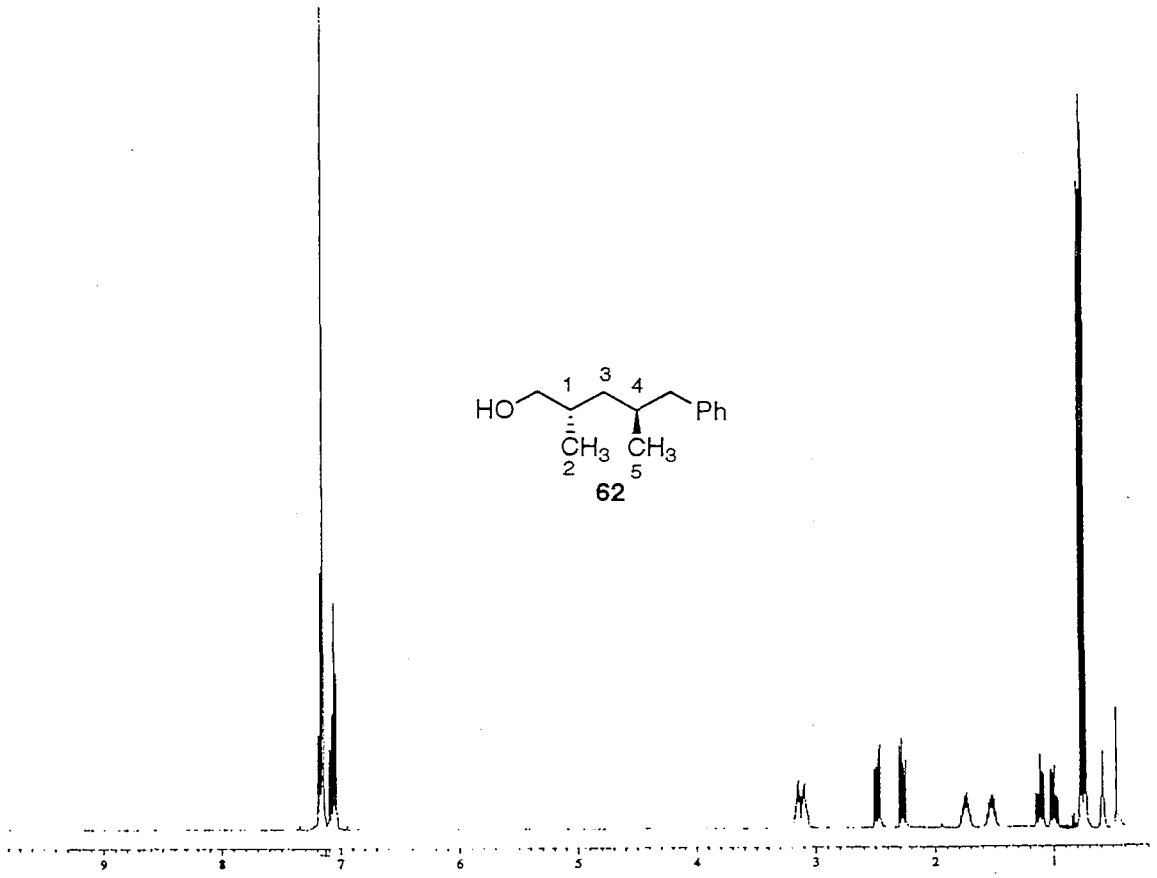
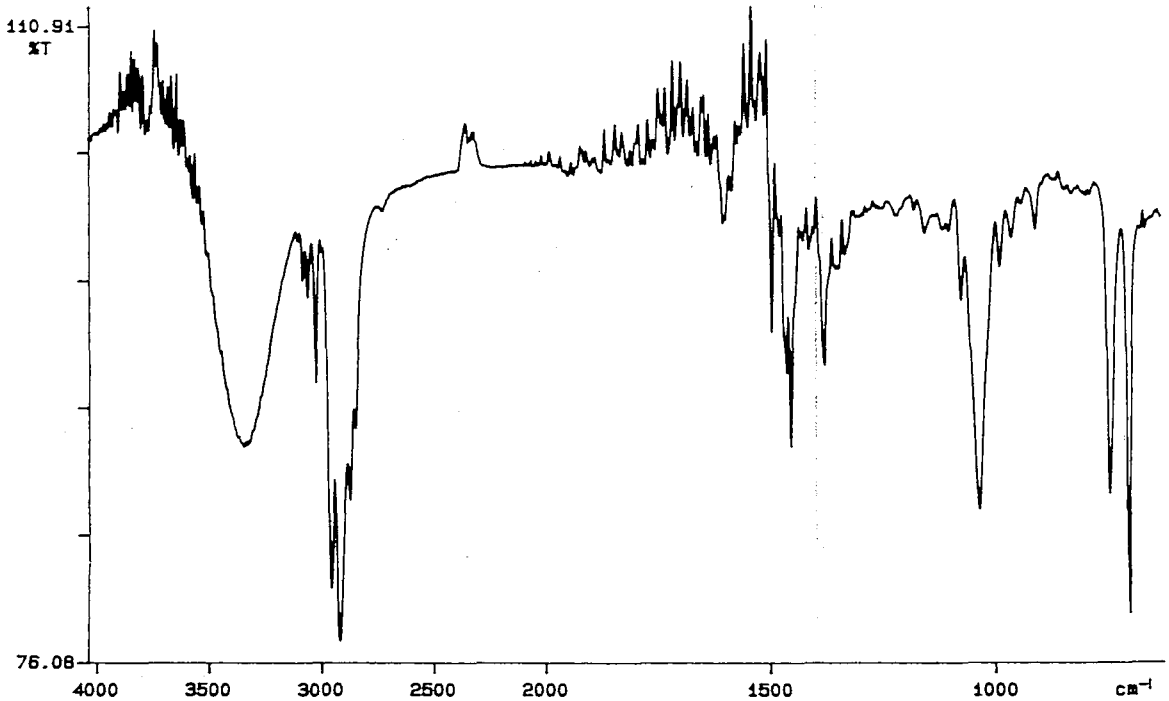
cm-1


HO
1
3
4
Ph
CH3
2
CH3
5

62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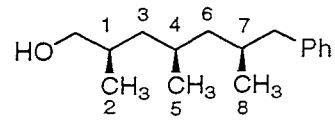
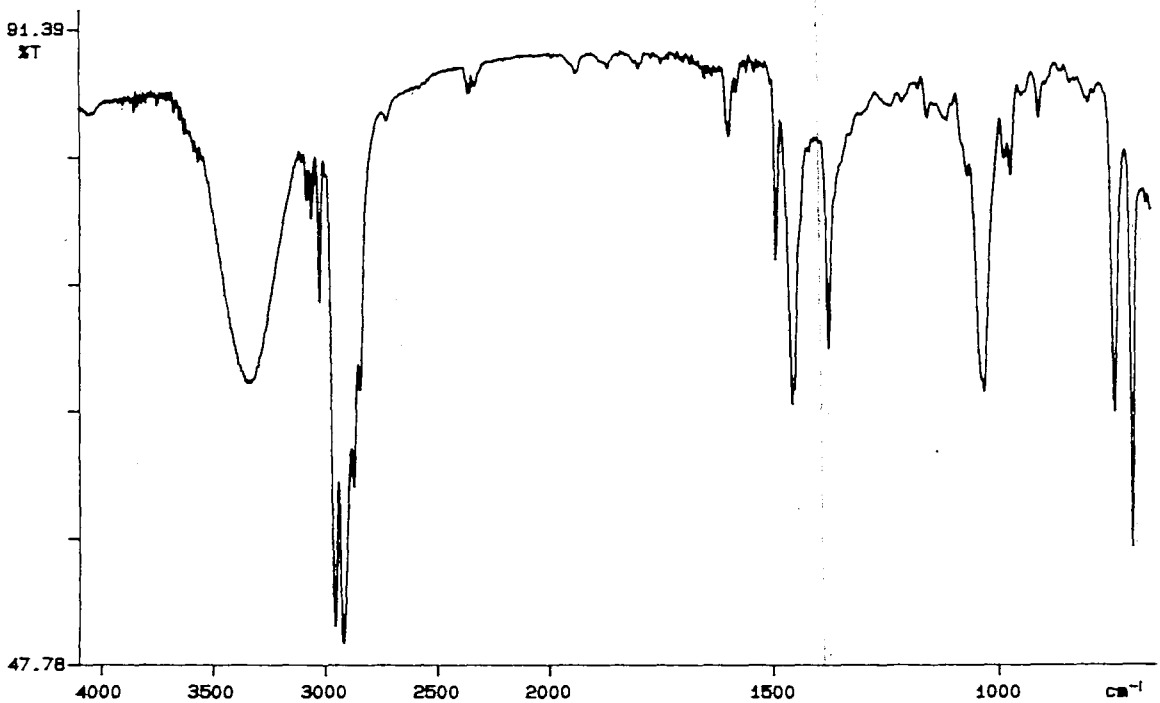
cm-1


HO
1
2
3
4
5
6
7
8
Ph
CH3
CH3
CH3

63

9
8
7
6
5
4
3
2
1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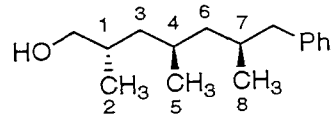
HO
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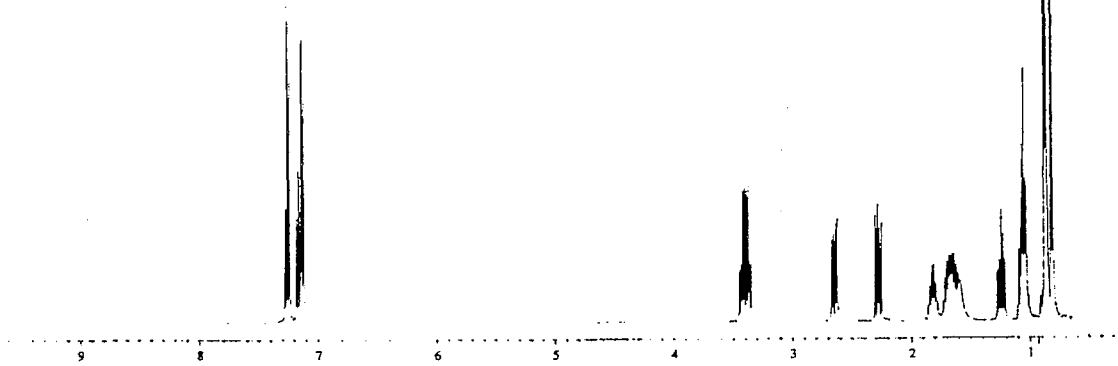
7
8
Ph
CH3
CH3
CH3

64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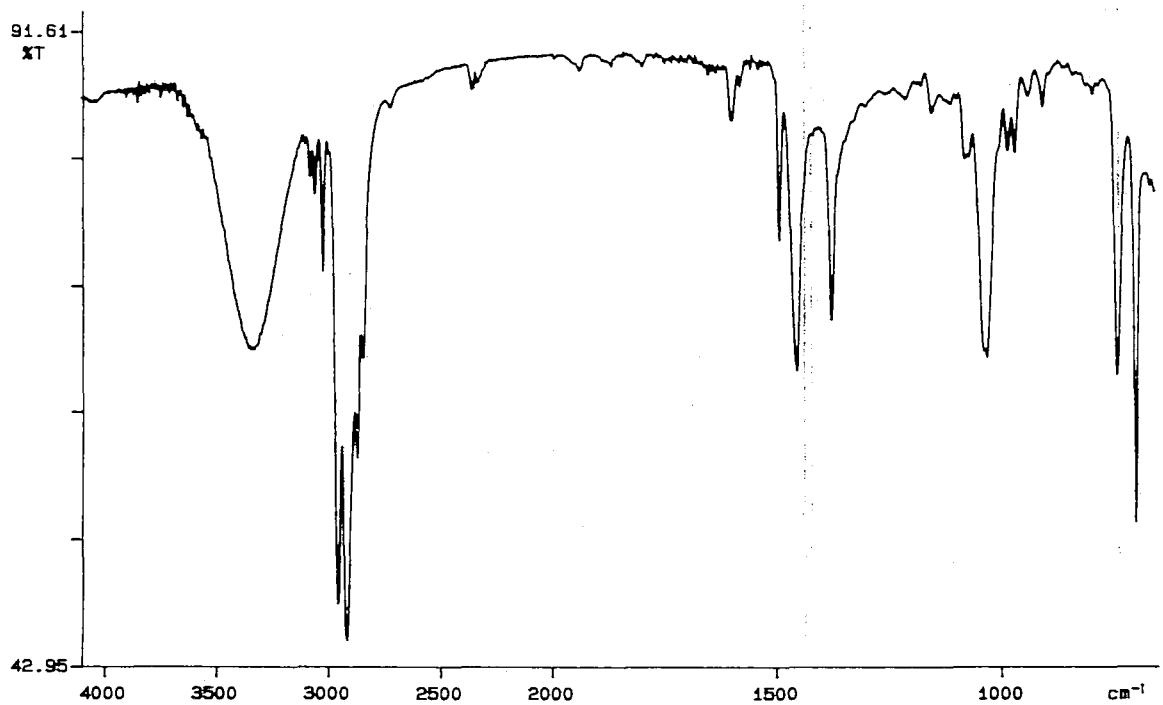
1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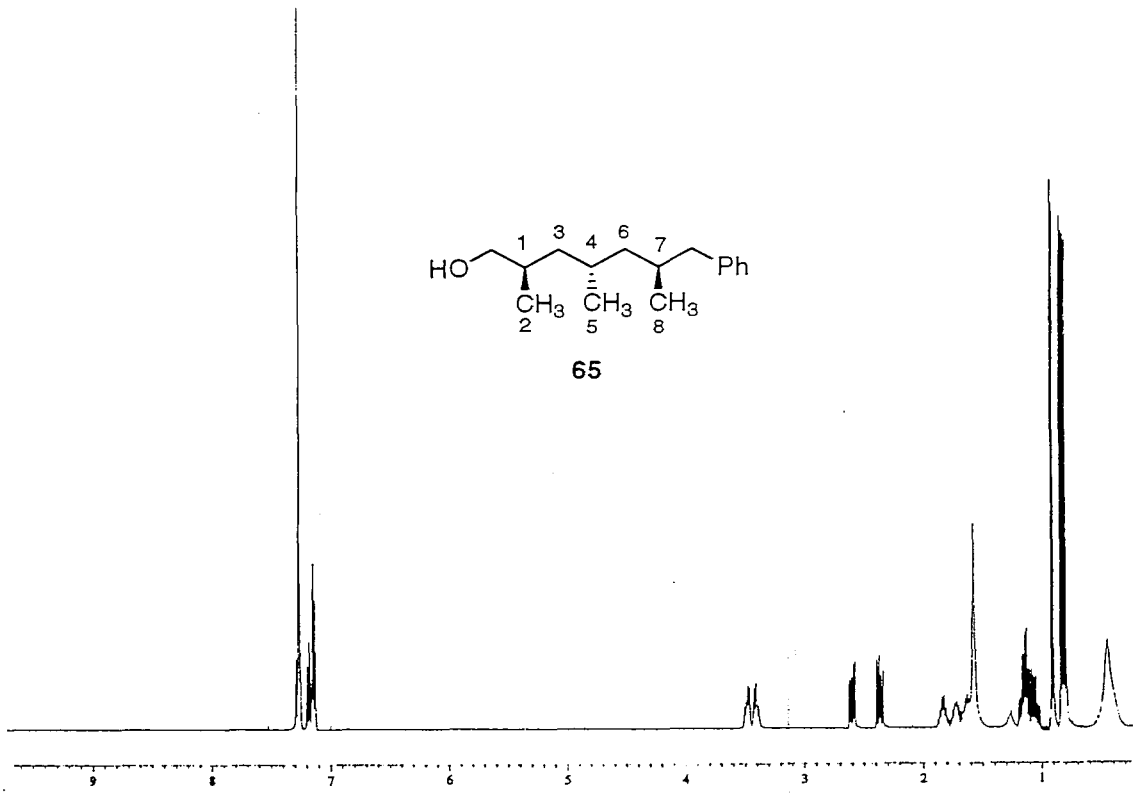
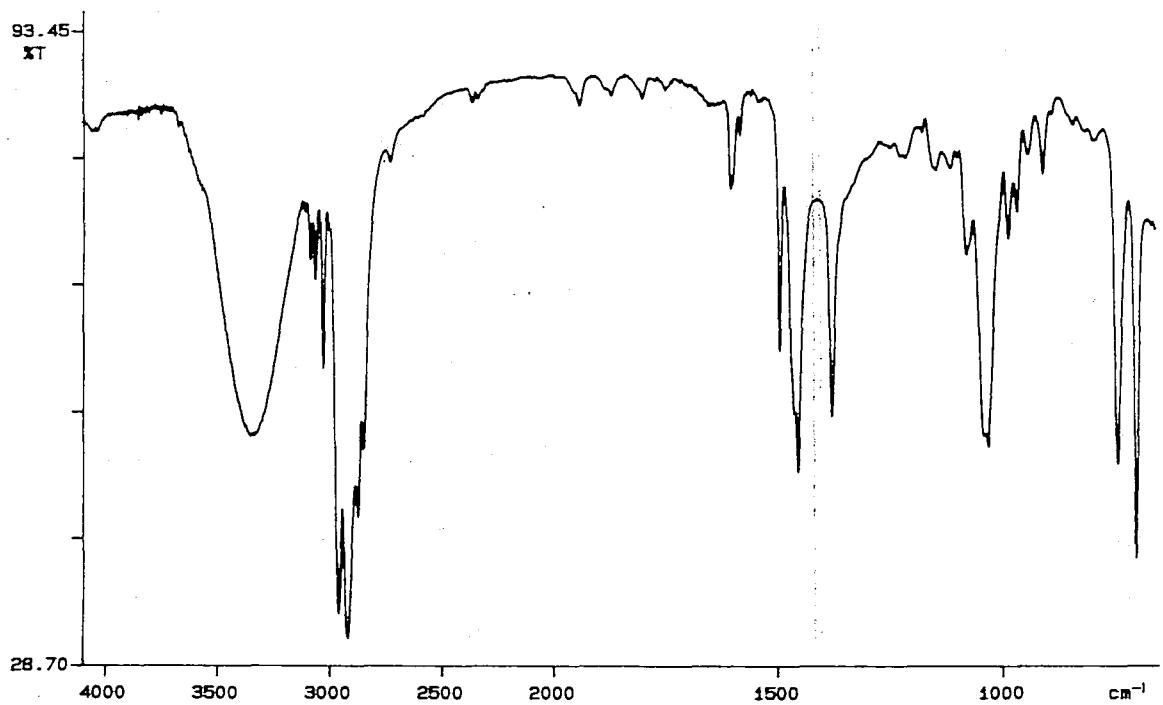
cm-1


HO
1
3
4
6
7
Ph
CH3
2
CH3
5
CH3
8

65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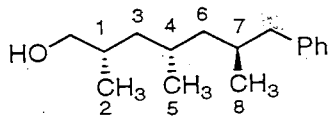
cm-1


HO
1
2
3
4
5
6
7
8
Ph
CH3
CH3
CH3

66

9
8
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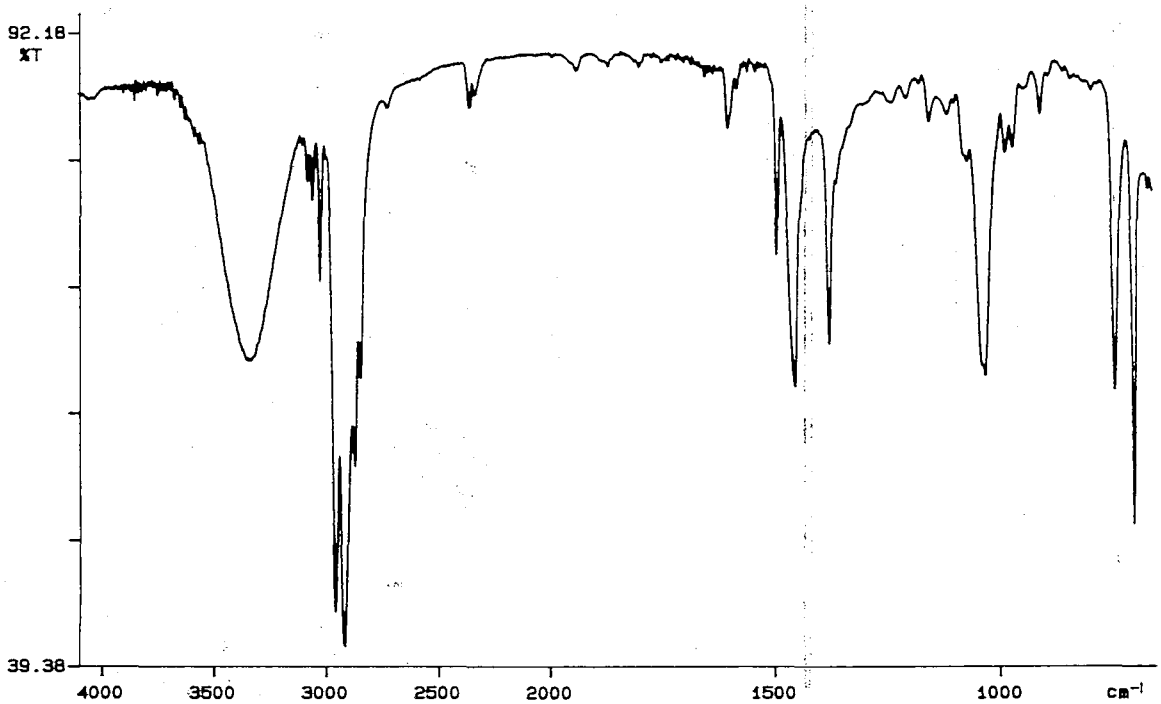
5
4
3
2
1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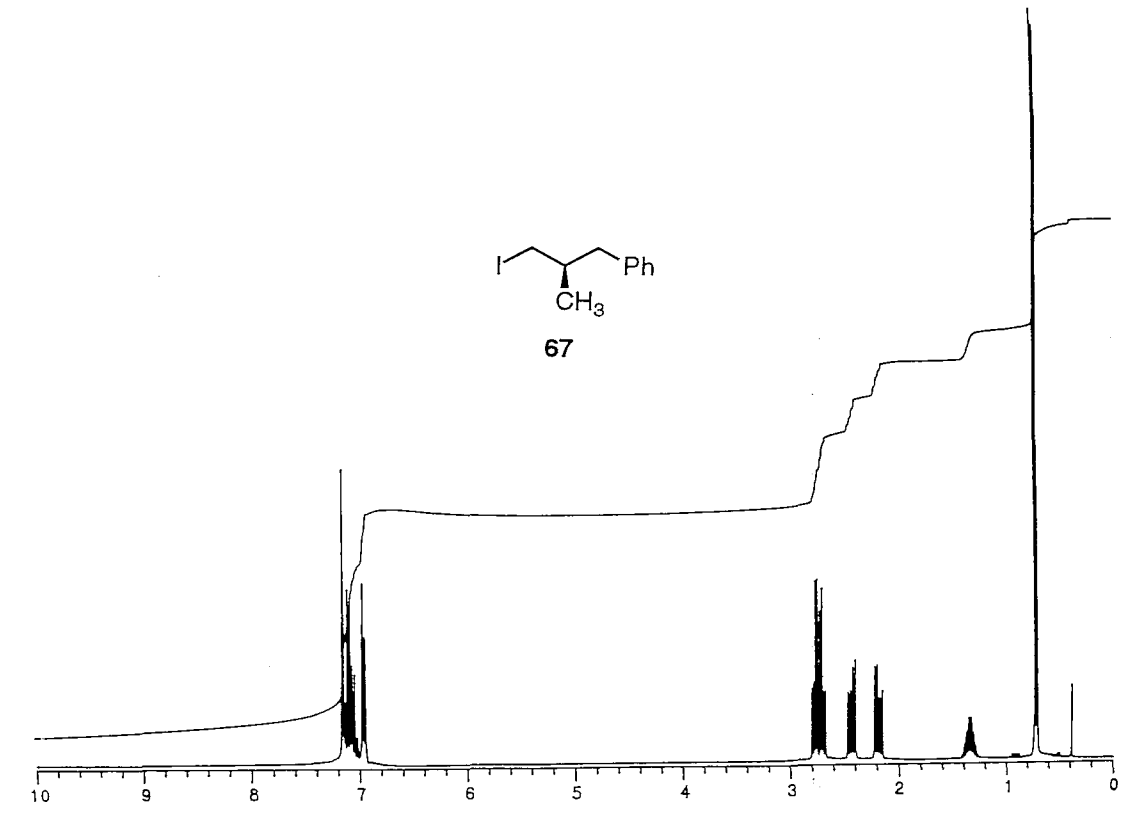
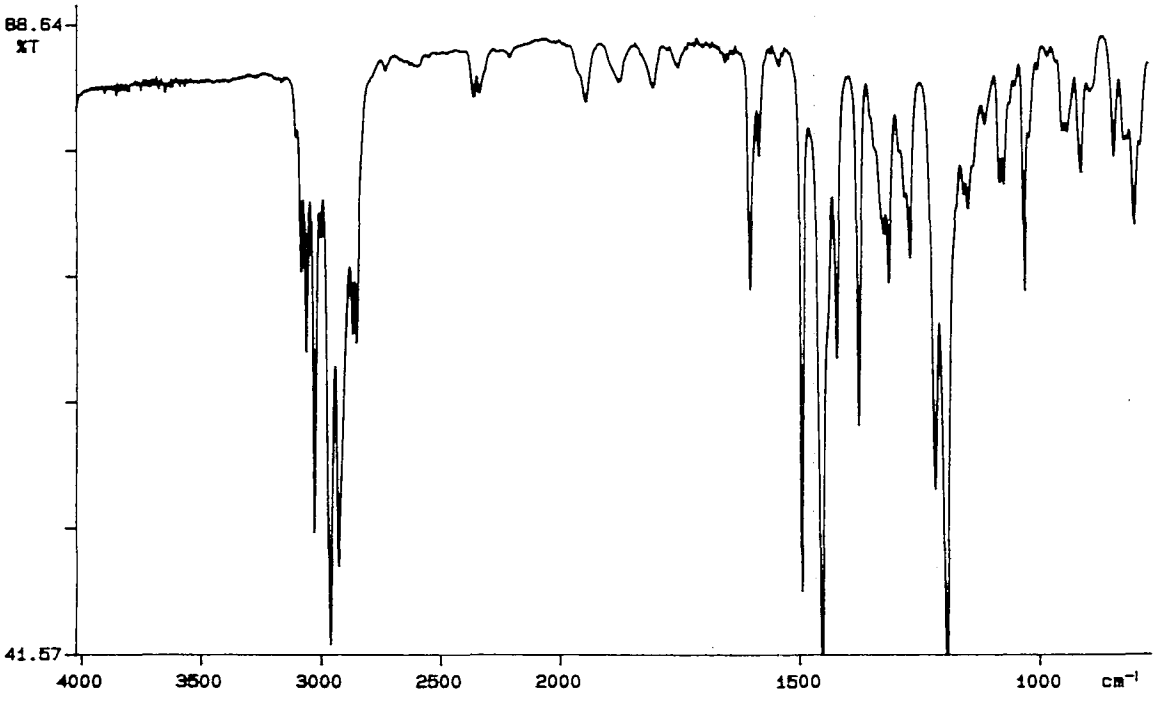
cm-1


I
Ph
CH3
10
9
8
7
6
5
4
3
2
1
0

67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41.57
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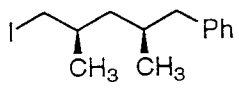
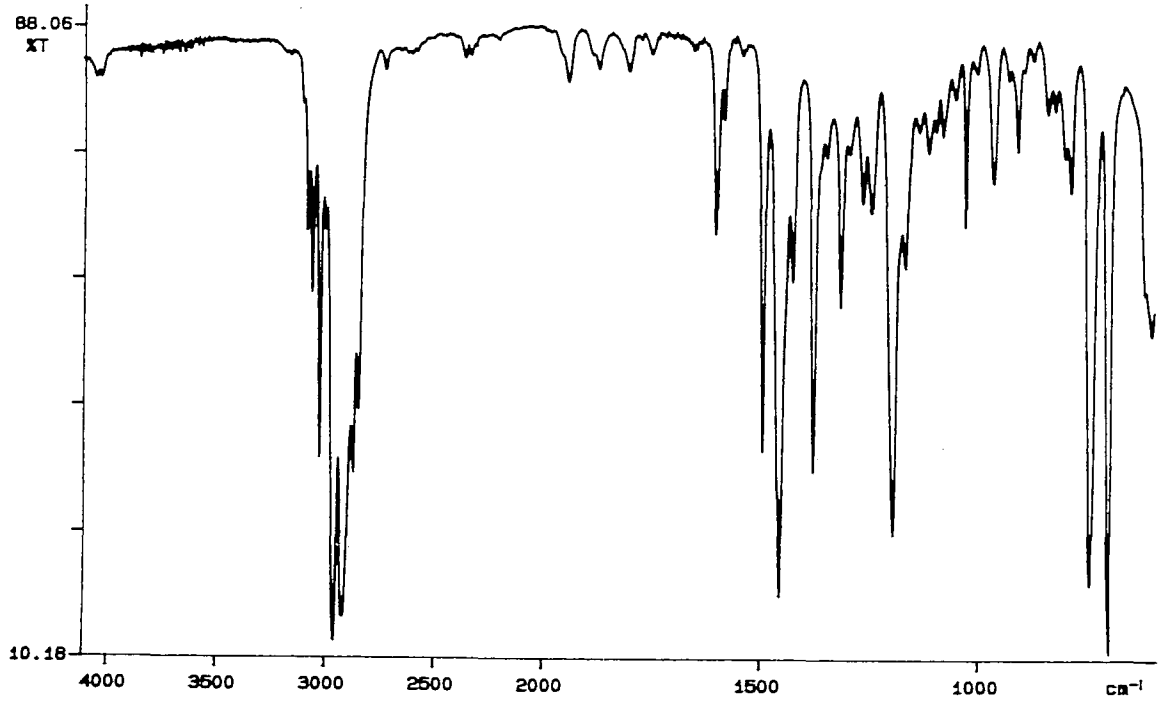
1000
cm-1


I
Ph
CH3
CH3

68

9
8
7
6
5
4
3
2
1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%T
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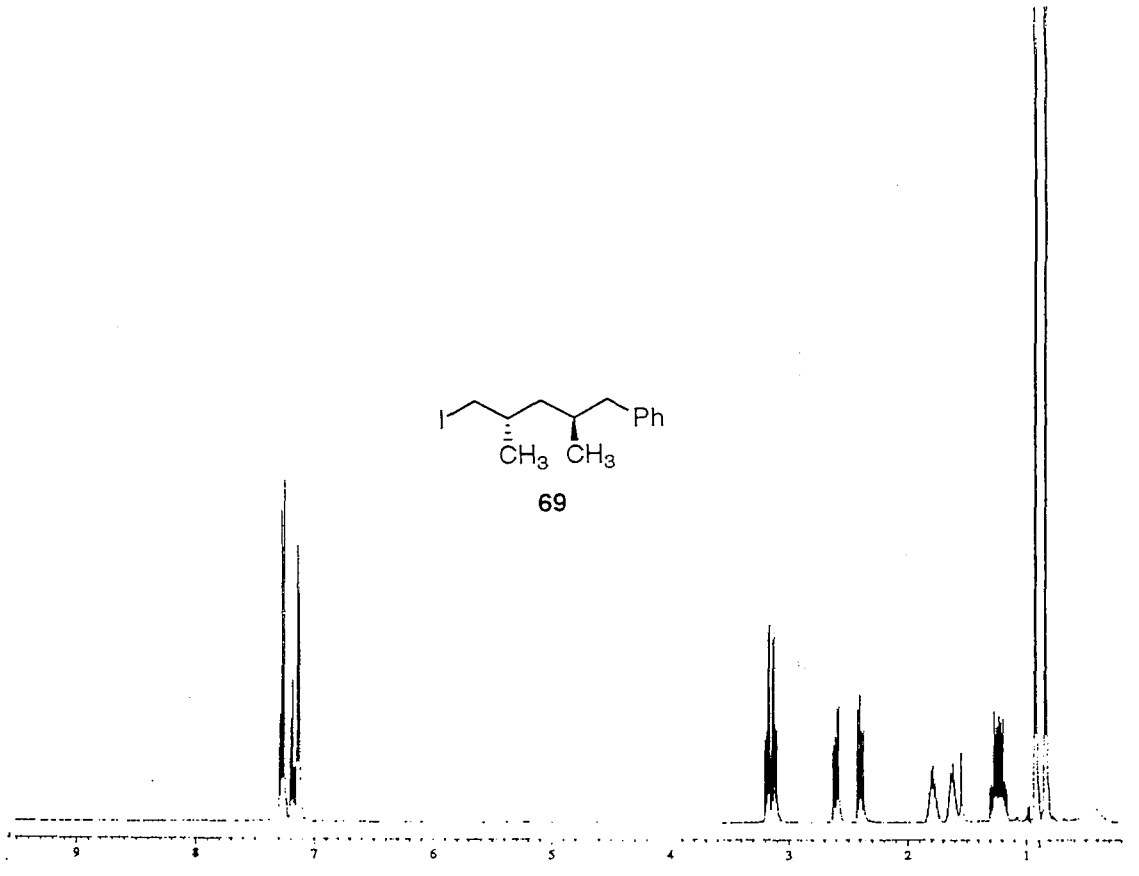
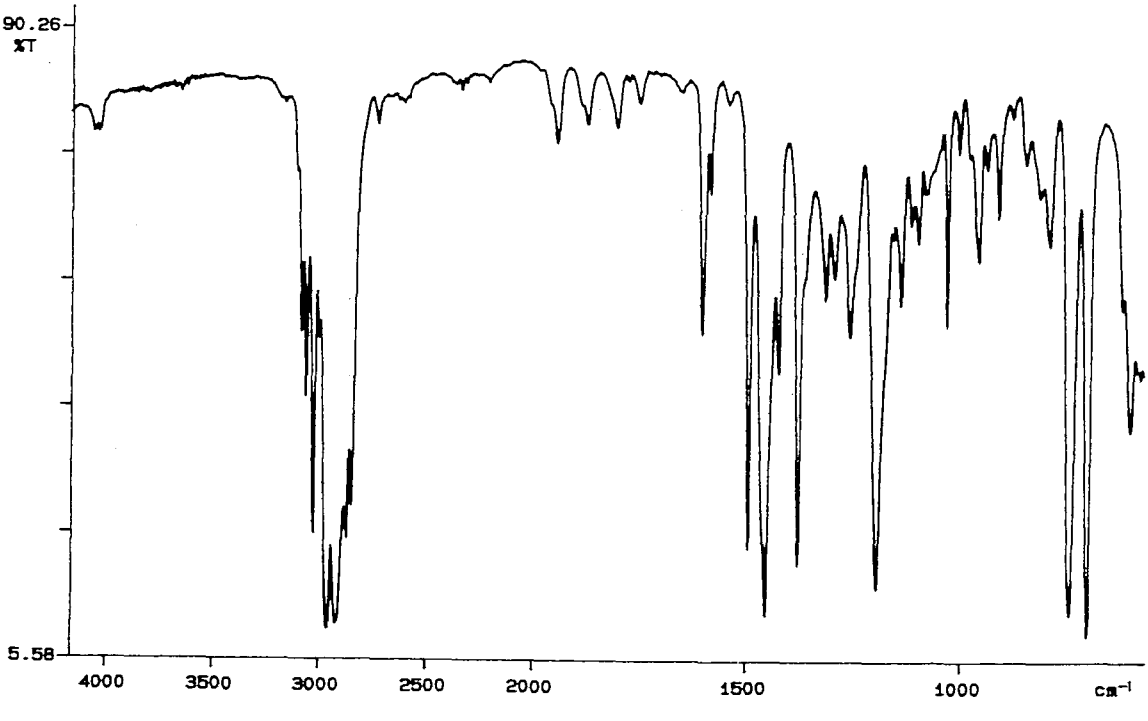
1000
cm-1

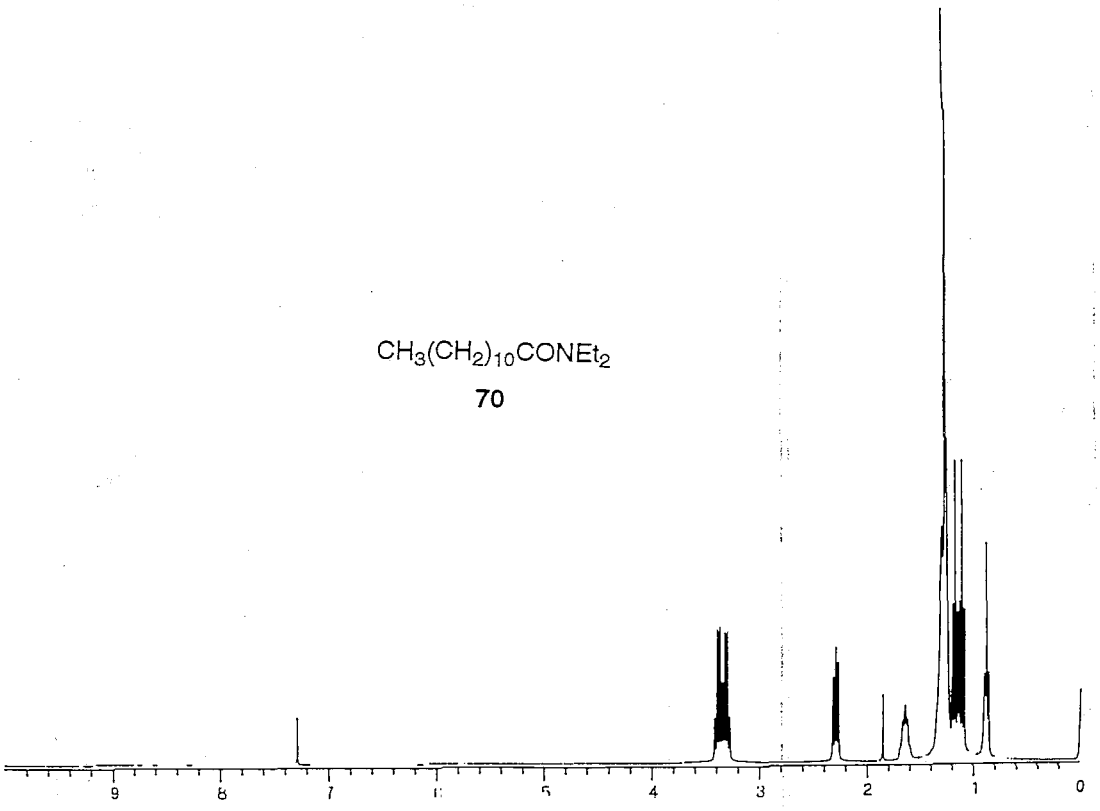

I
Ph
CH3
CH3
9
8
7
6
5
4
3
2
1

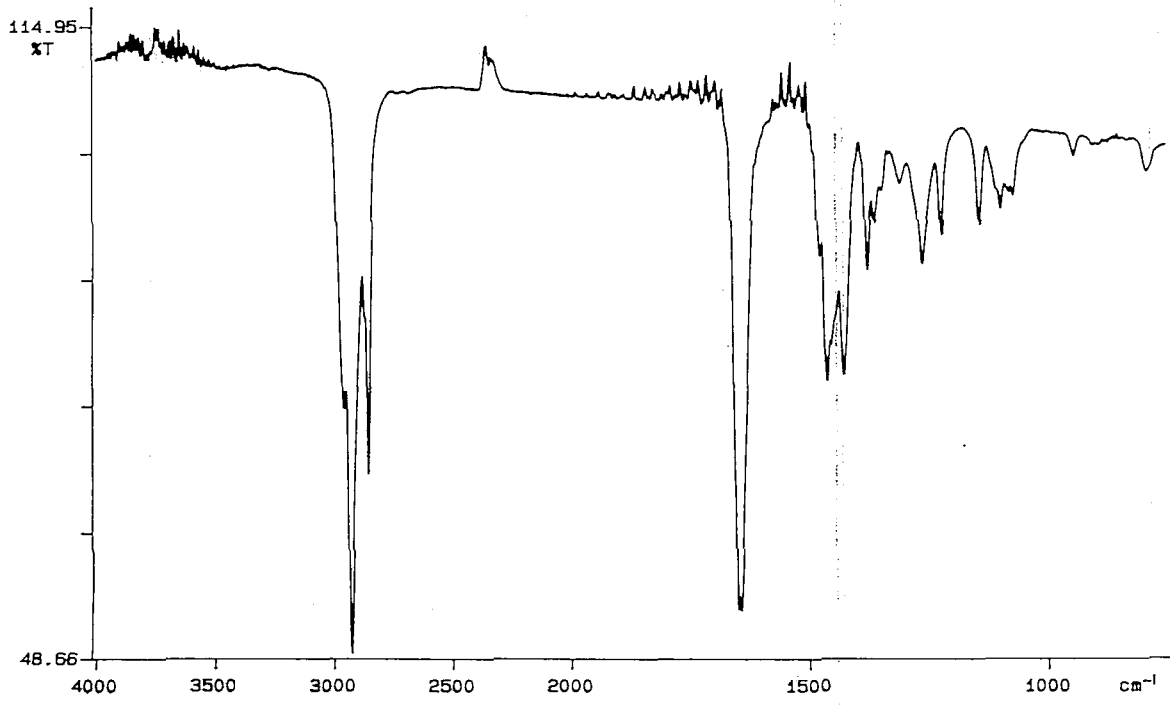
69


90.26
%T
5.58
4000
3500
3000
2500
2000
1500
1000
cm-1

$CH_3(CH_2)_{10}CONEt_2$

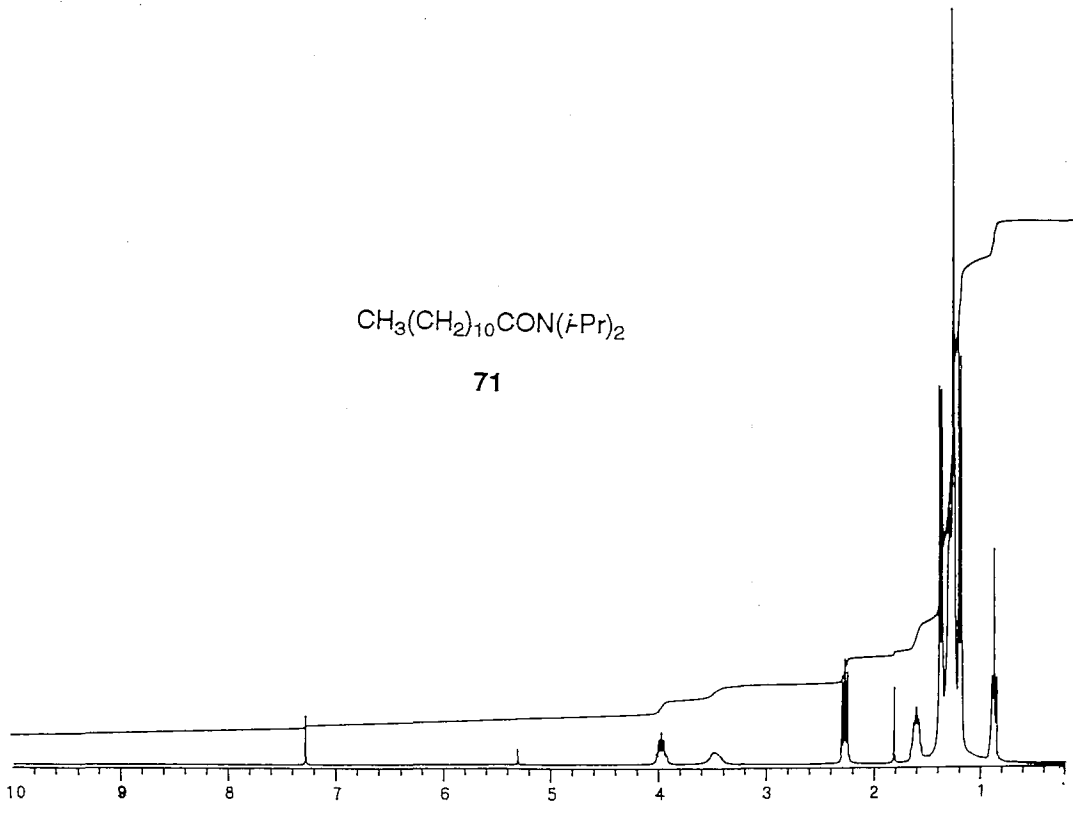
70

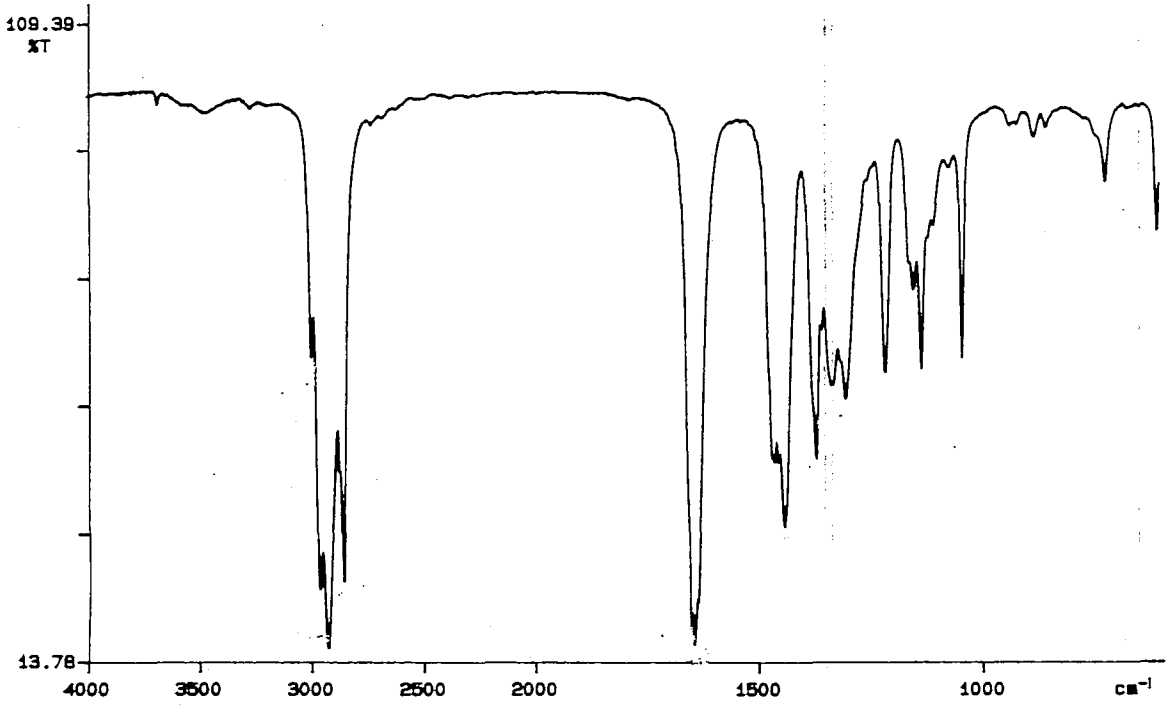


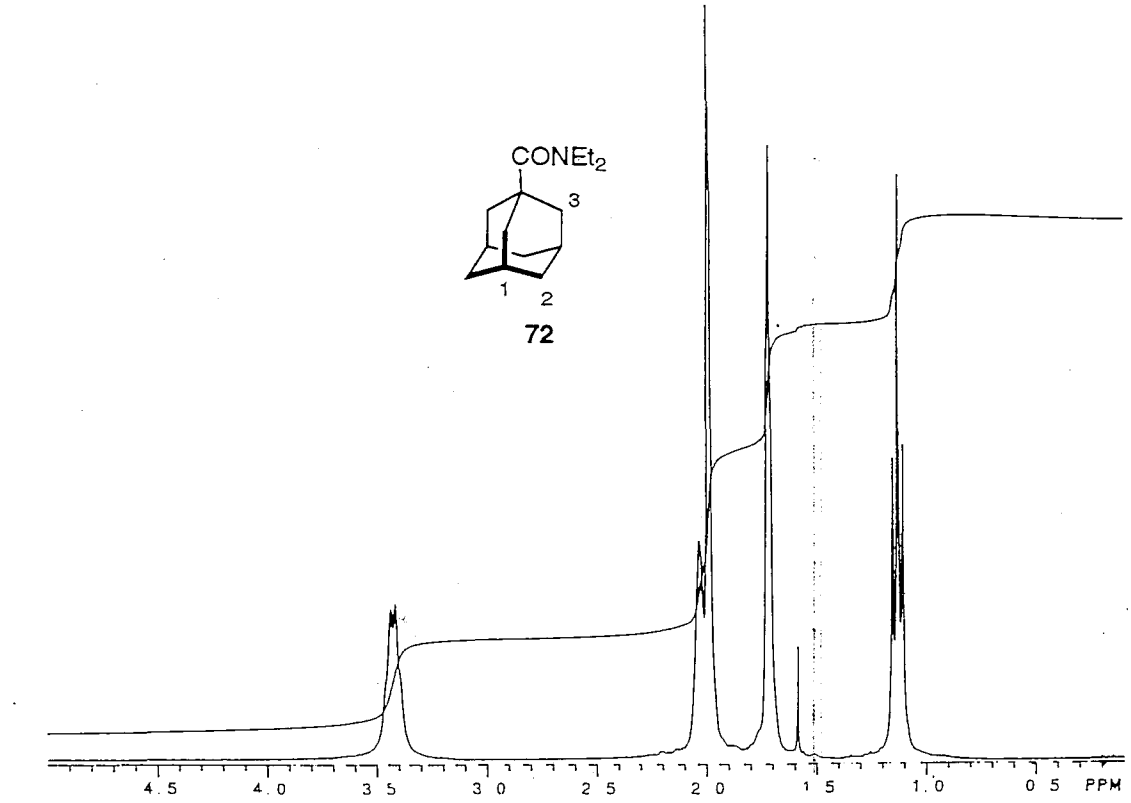


$CH_3(CH_2)_{10}CON(i\text{-}Pr)_2$

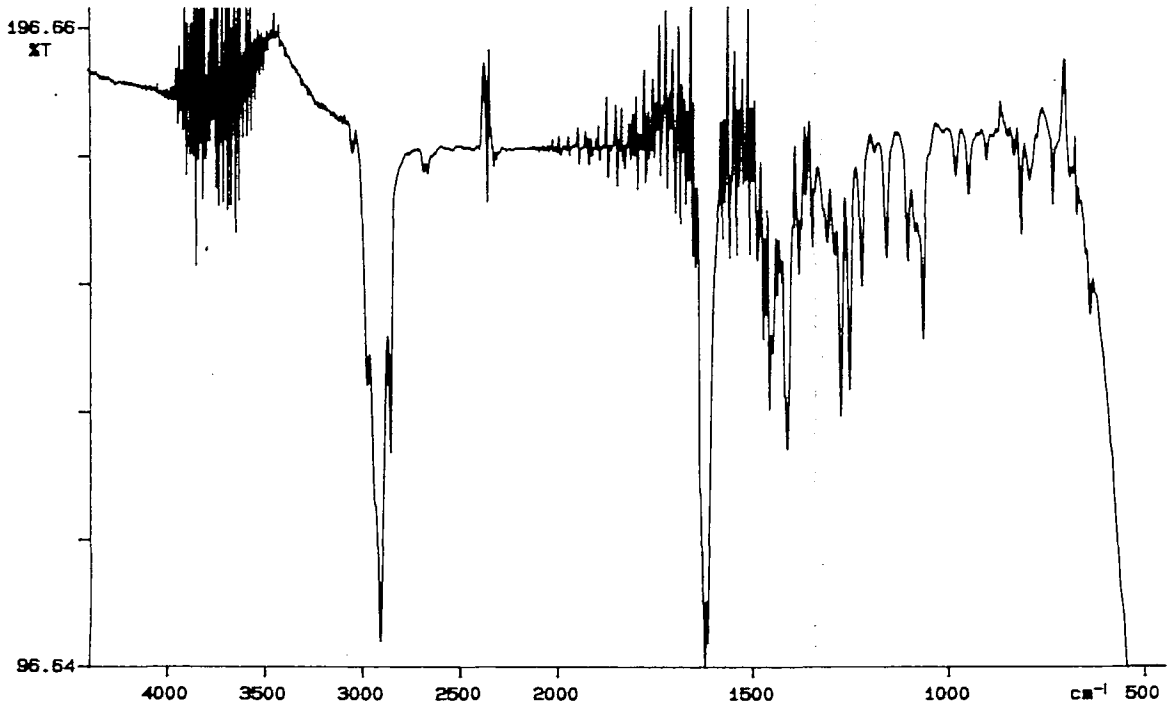
71

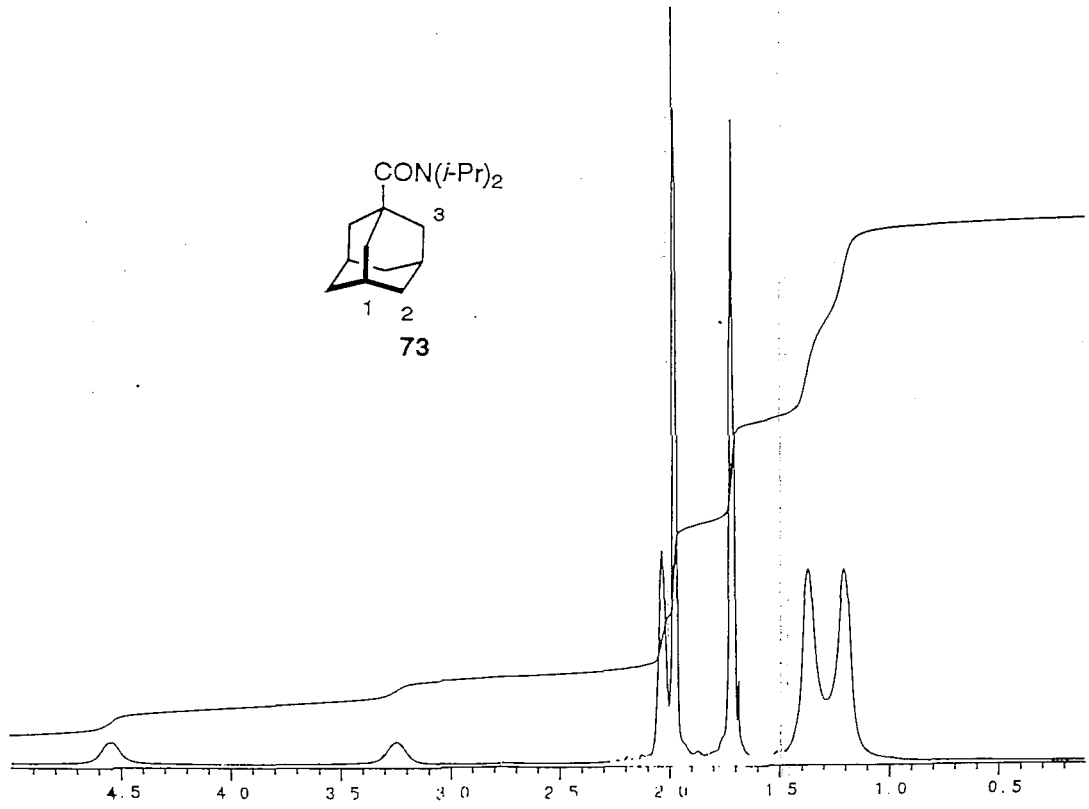




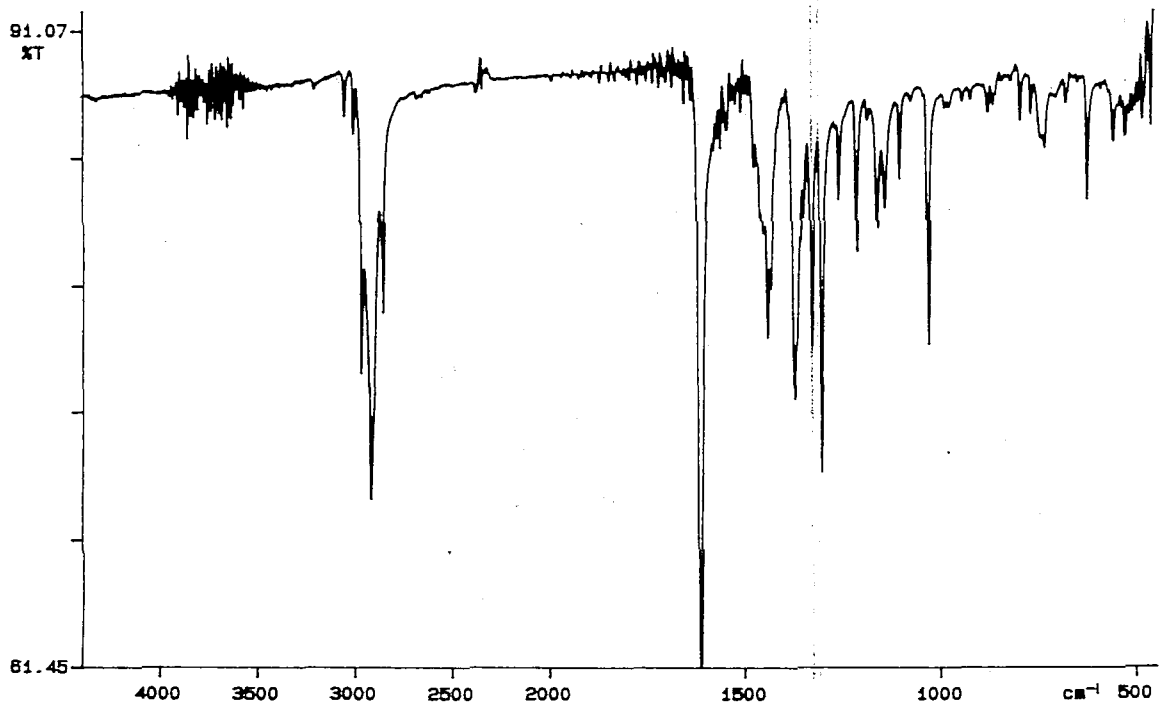

CONEt2
3
1
2
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
PPM

72


196.66
%T
96.64
4000
3500
3000
2500
2000
1500
1000
cm-1
500

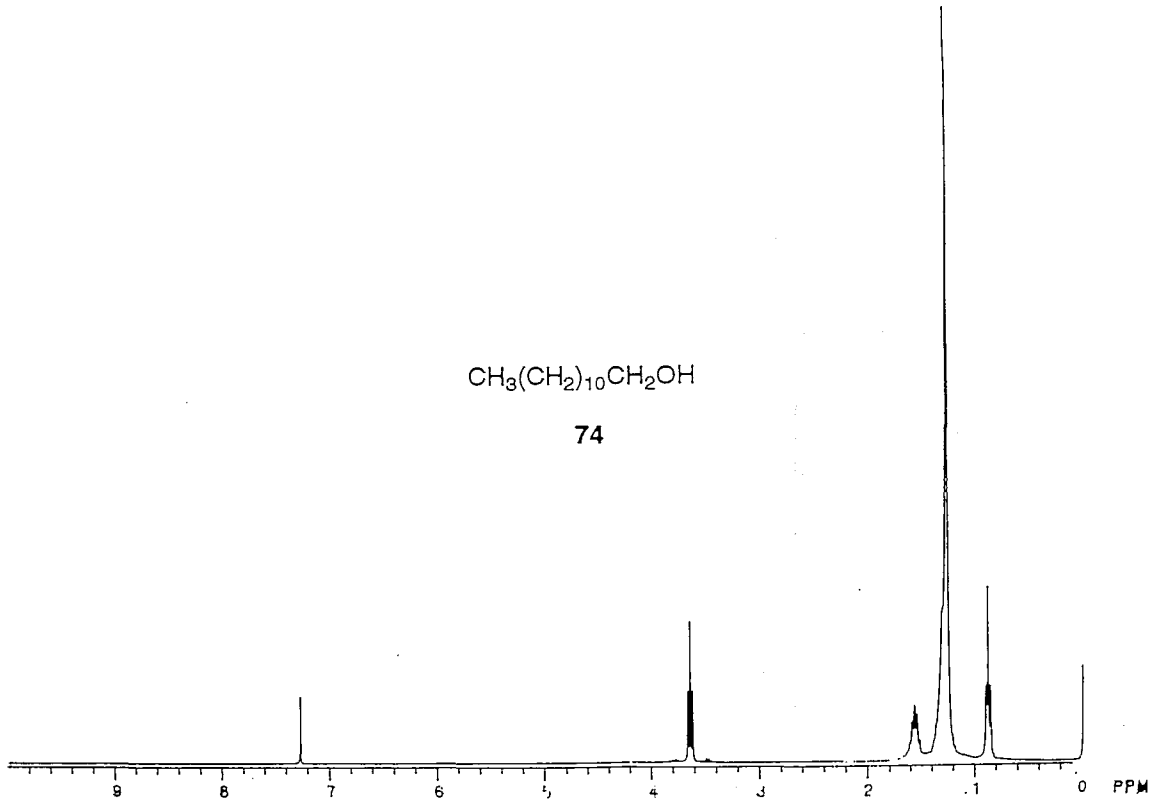

CON(i-Pr)2
3
1
2
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

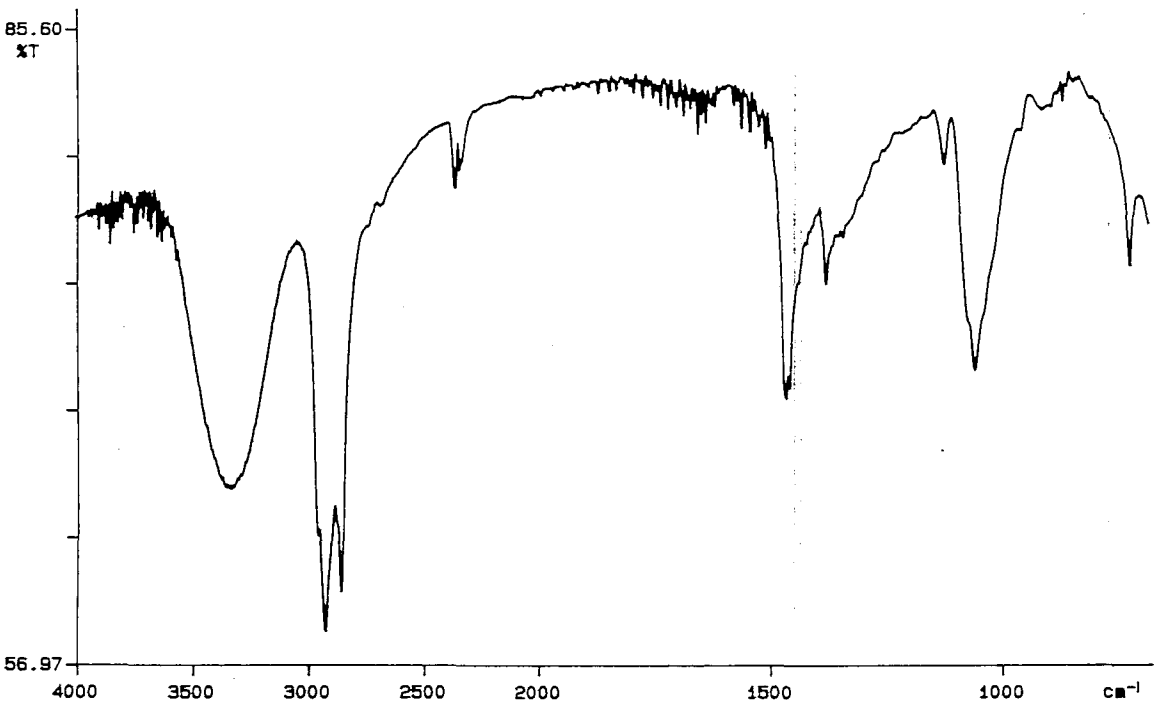
73

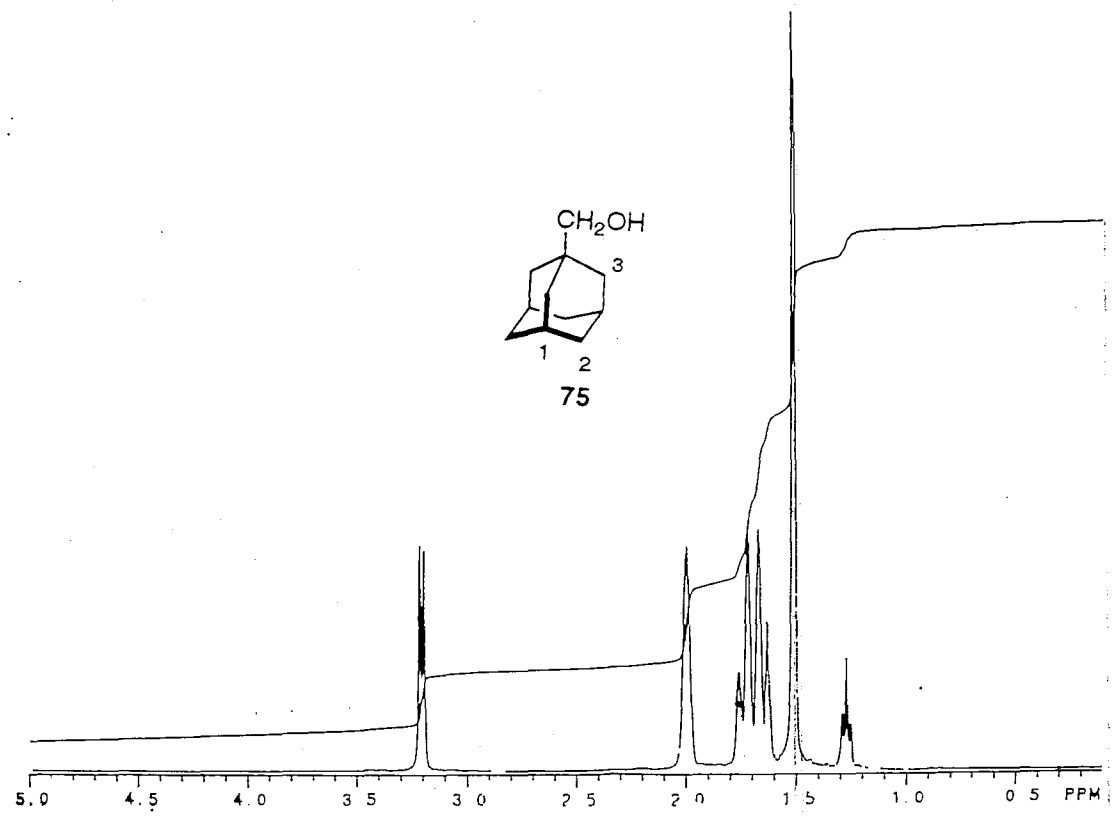

91.07
%T
61.45
4000
3500
3000
2500
2000
1500
1000
cm-1
500

$CH_3(CH_2)_{10}CH_2OH$

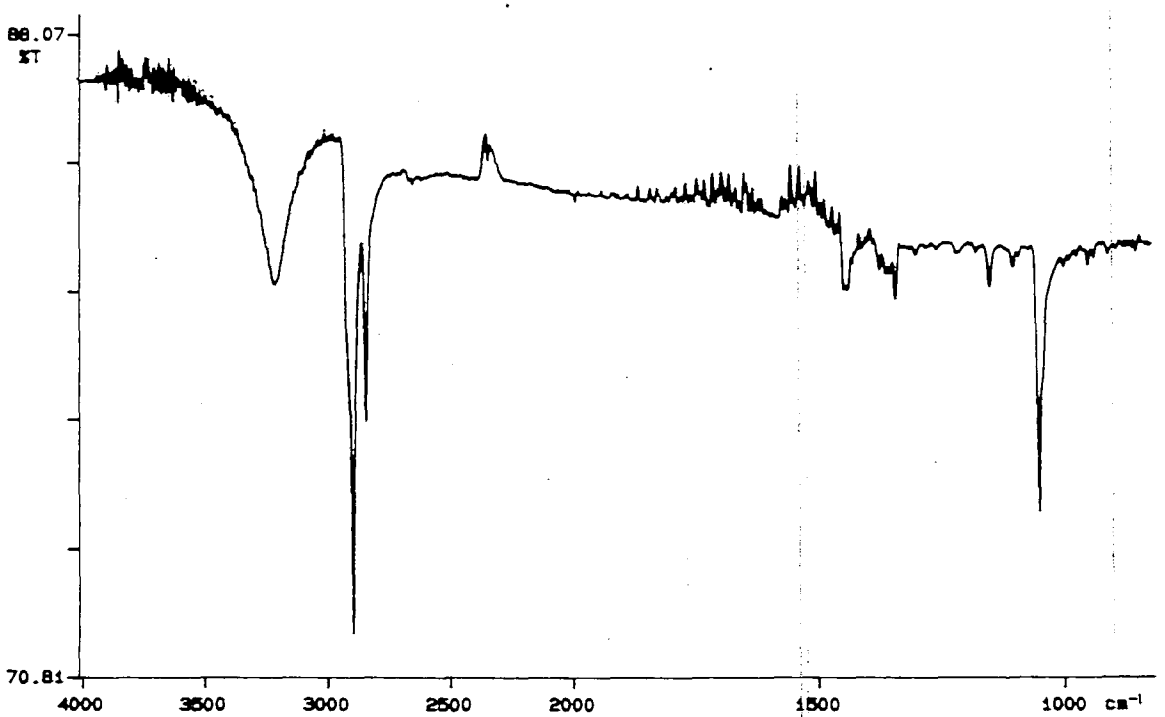
74

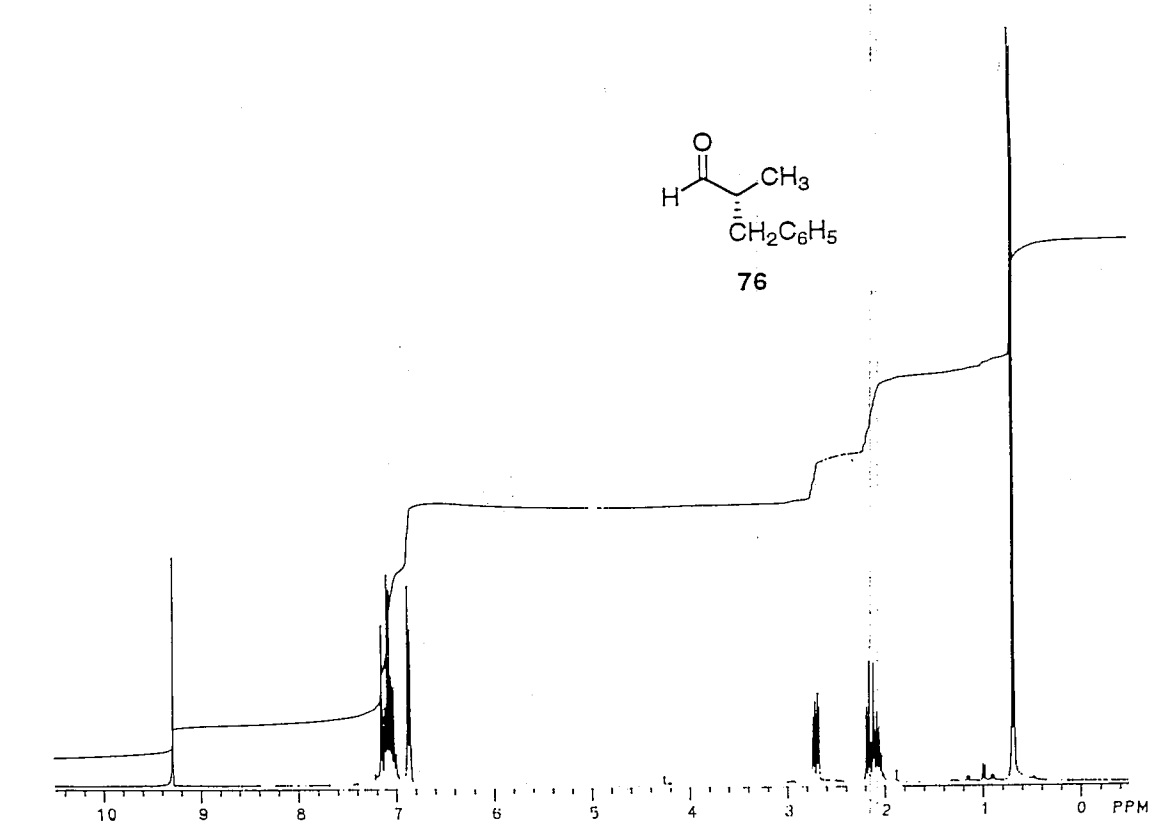




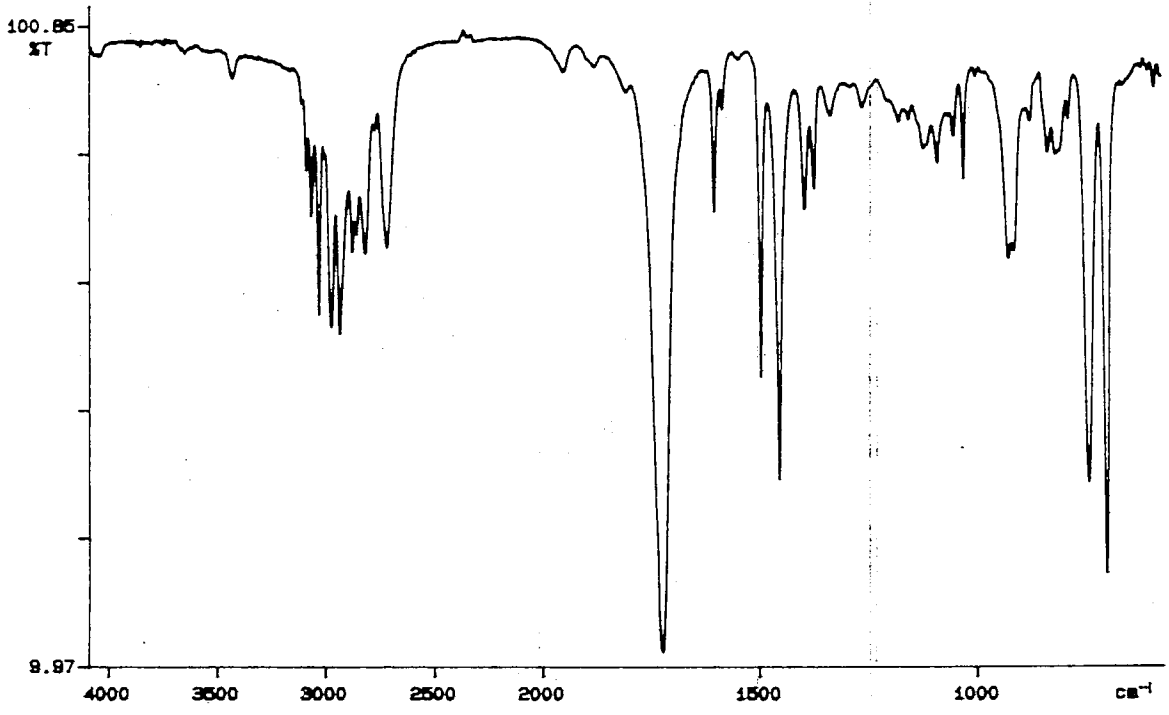

CH2OH
3
1
2
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
PPM

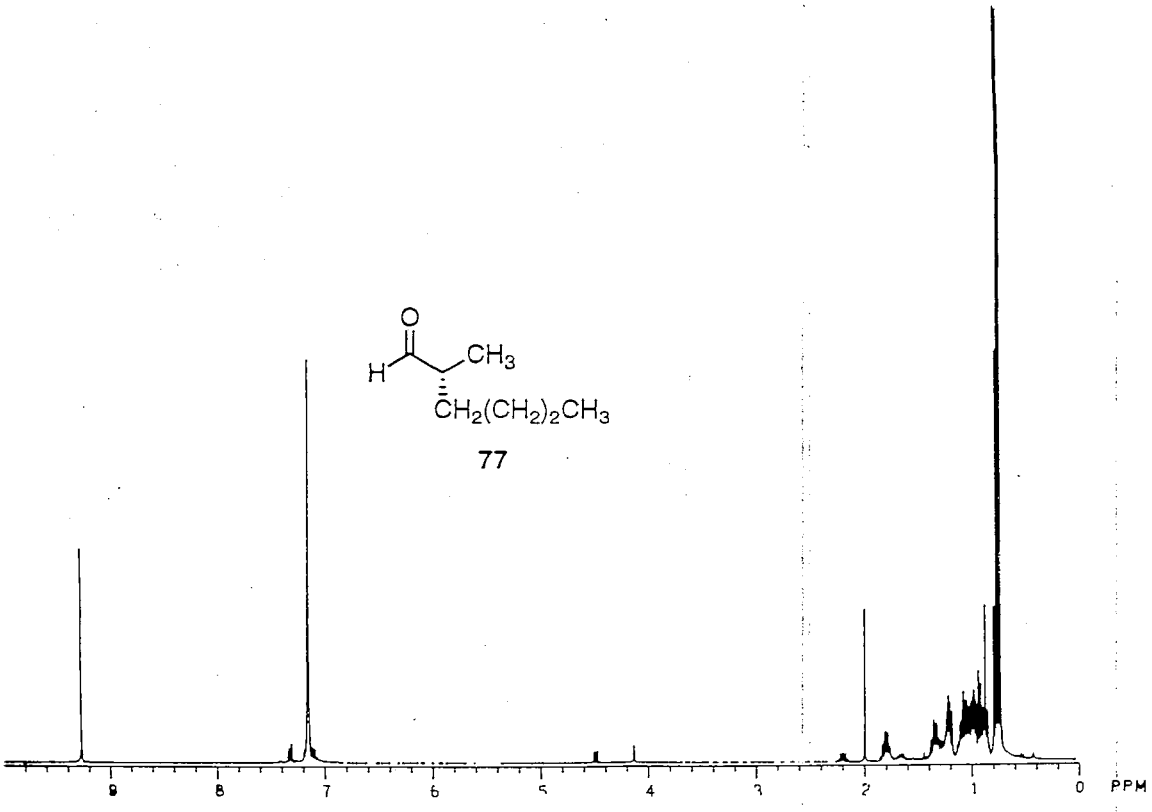
75


88.07
%T
70.81
4000
3500
3000
2500
2000
1500
1000
cm-1

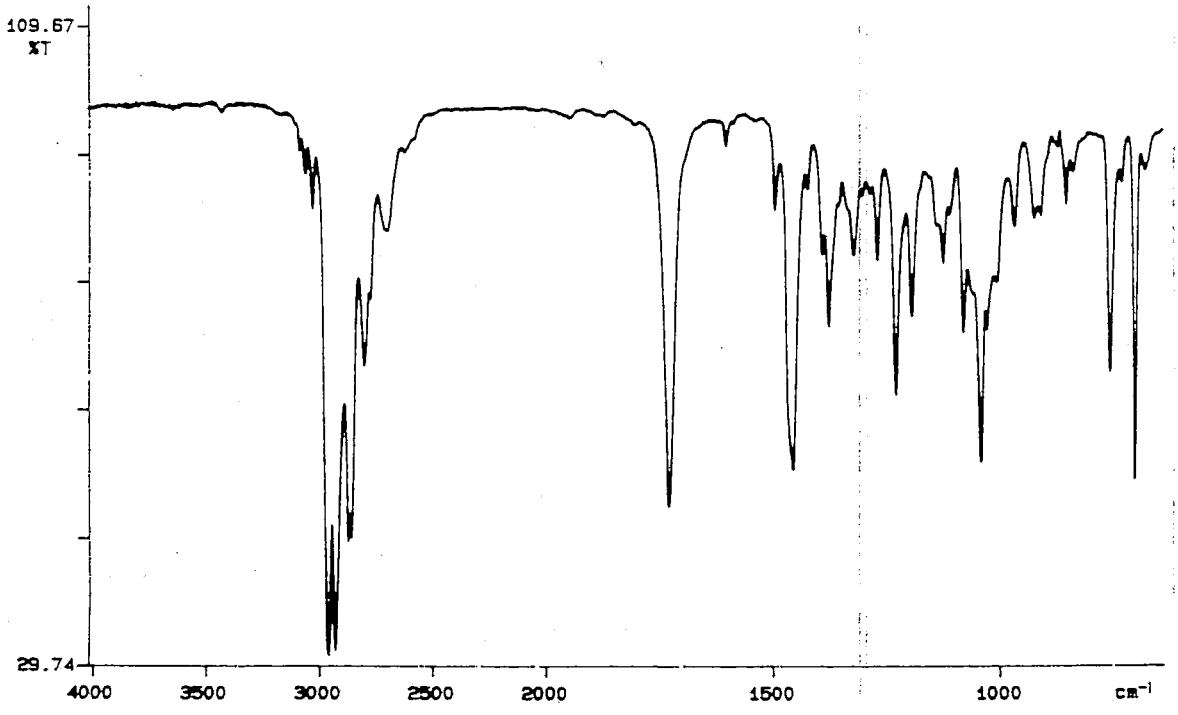

O
H
CH3
CH2C6H5
10
9
8
7
6
5
4
3
2
1
0
PPM

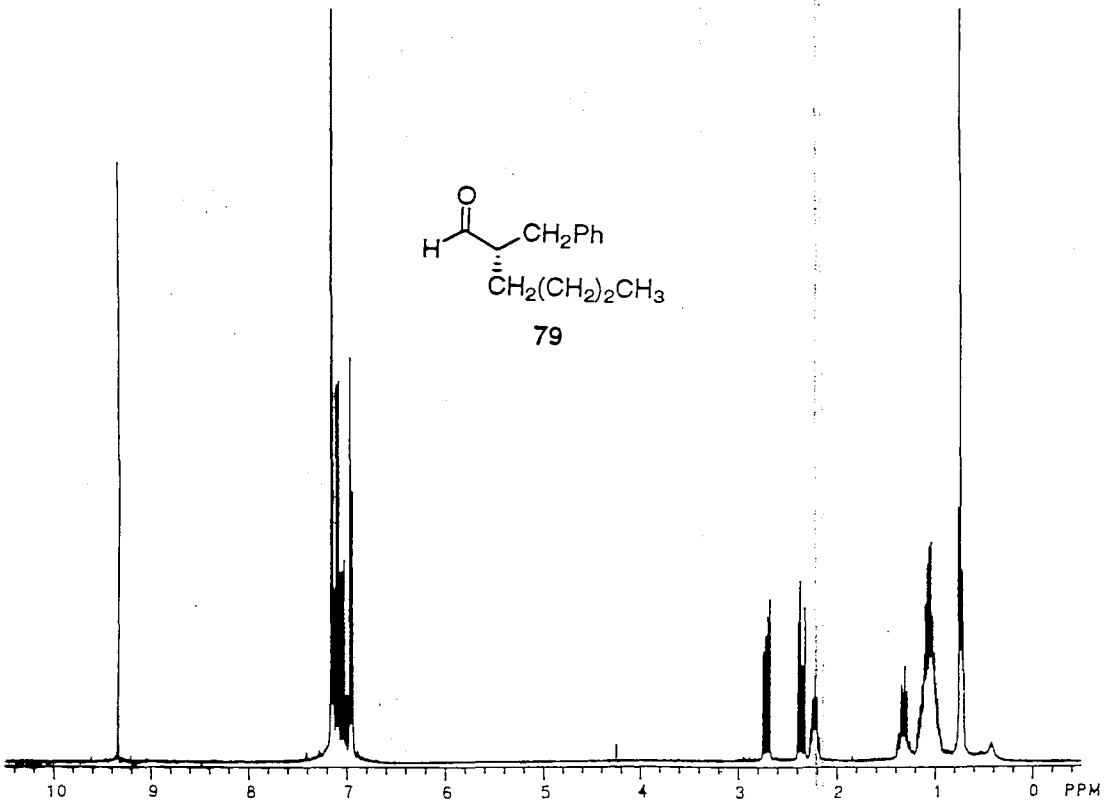
76


100.86
%T
9.97
4000
3500
3000
2500
2000
1500
1000
cm-1

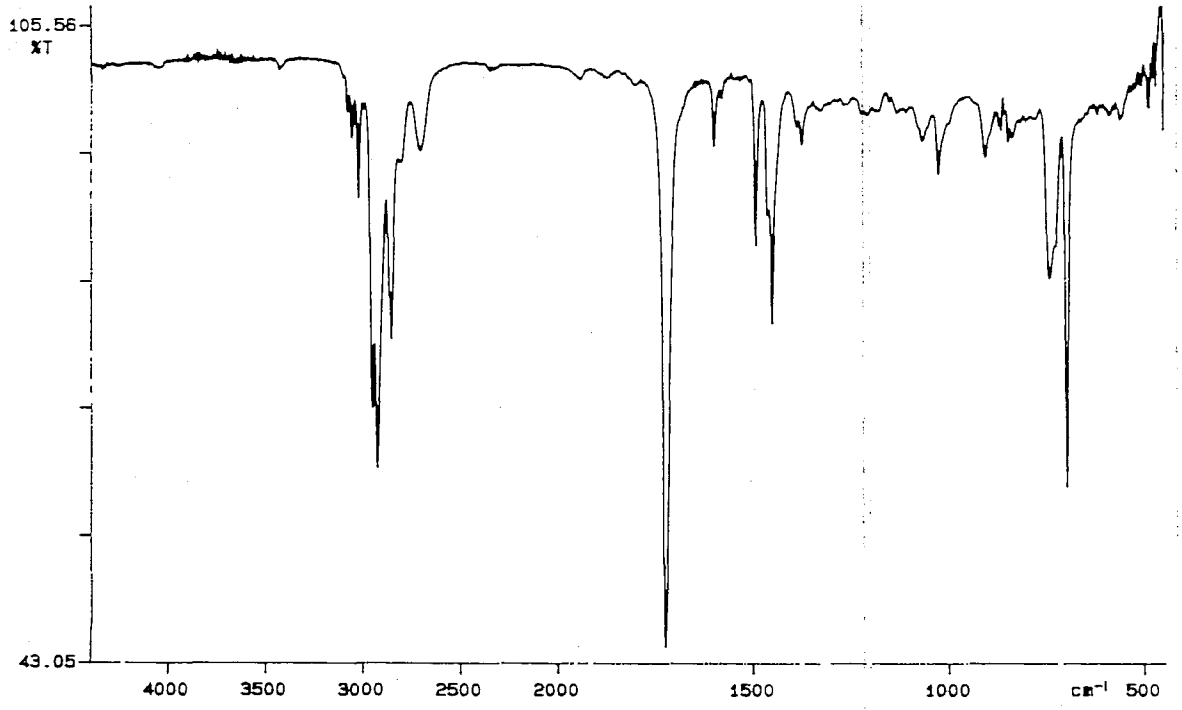

O
H
CH3
CH2(CH2)2CH3
9
8
7
6
5
4
3
2
1
0
PPM

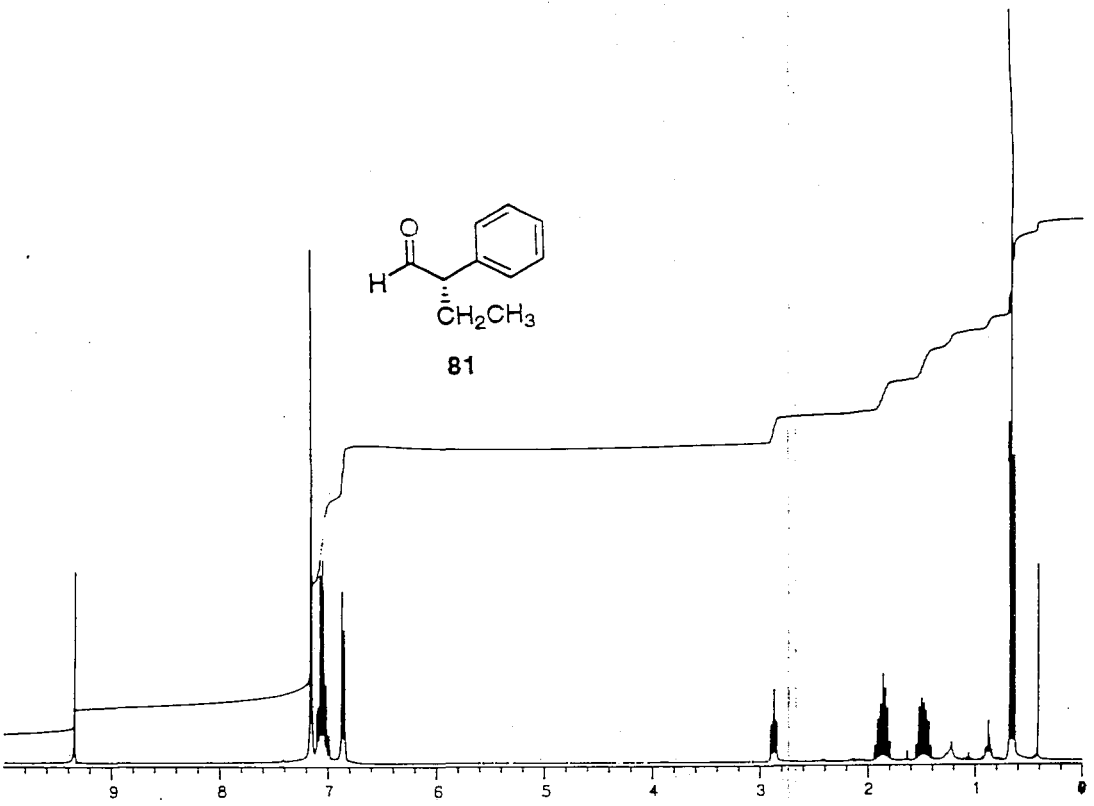
77


109.67
%T
29.74
4000
3500
3000
2500
2000
1500
1000
cm-1

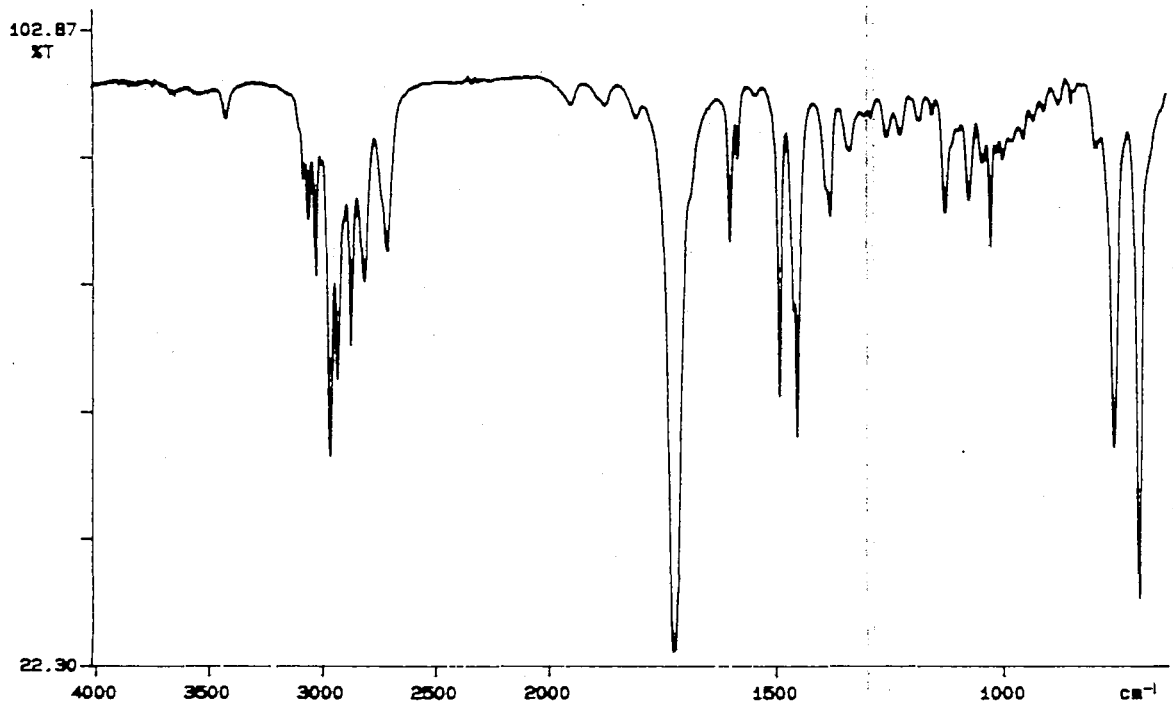

10
9
8
7
6
5
4
3
2
1
0
PPM

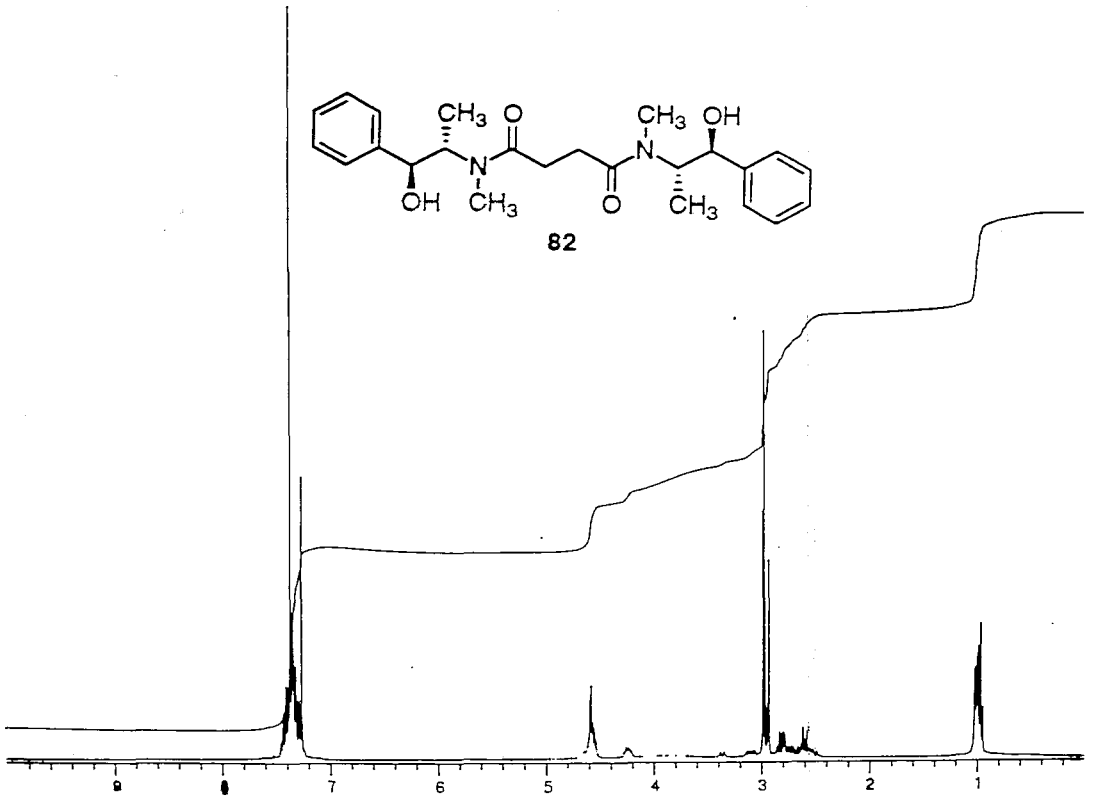
79


105.56
%T
43.05
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500

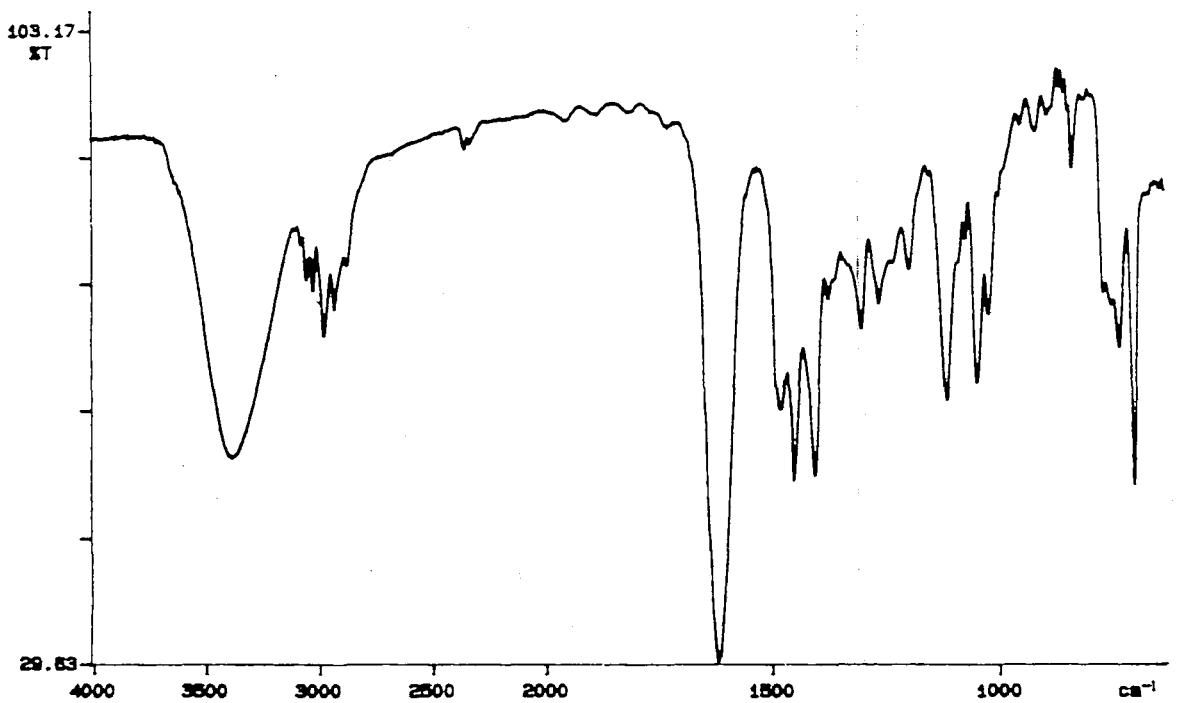

H
O
CH2CH3
9
8
7
6
5
4
3
2
1
0

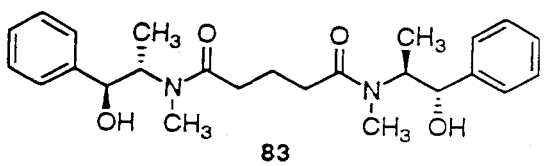
81


102.87
%T
22.30
4000
3500
3000
2500
2000
1500
1000
cm-1


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

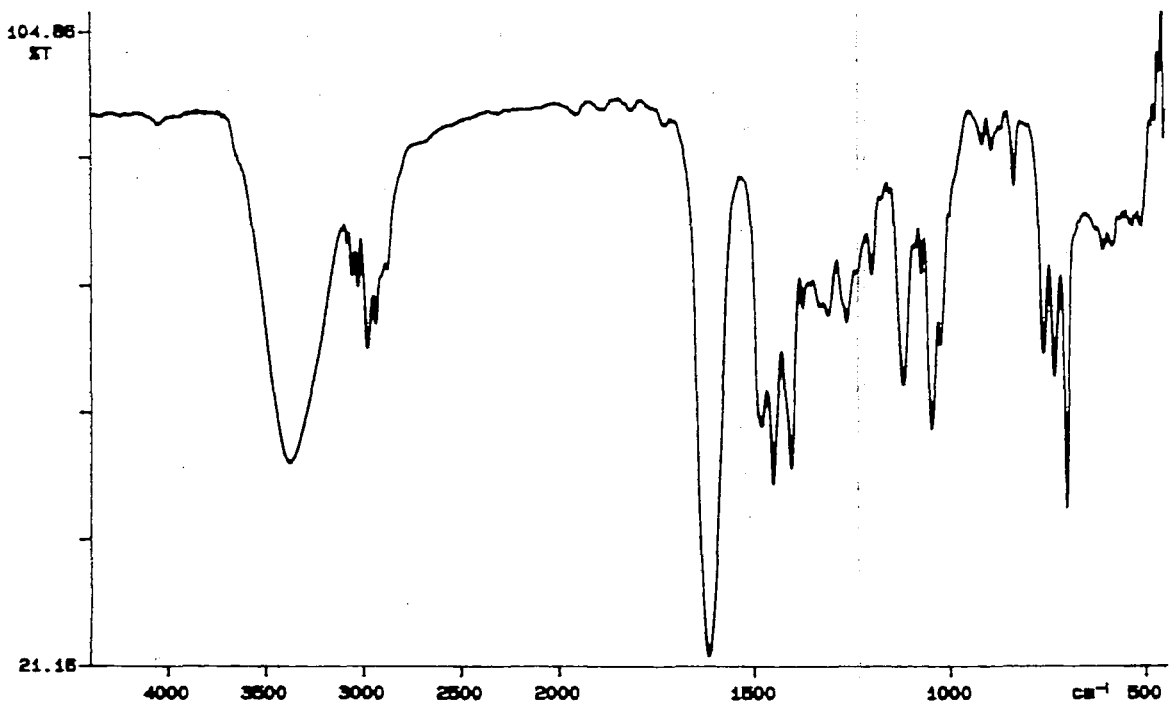
82

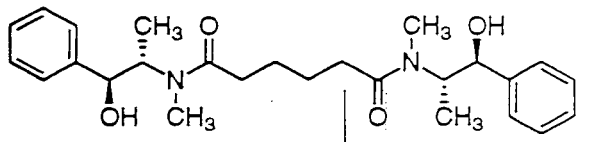

103.17
%T
29.63
4000
3500
3000
2500
2000
1500
1000
cm-1


CH3
O
O
CH3
N
N
OH
CH3
CH3
OH

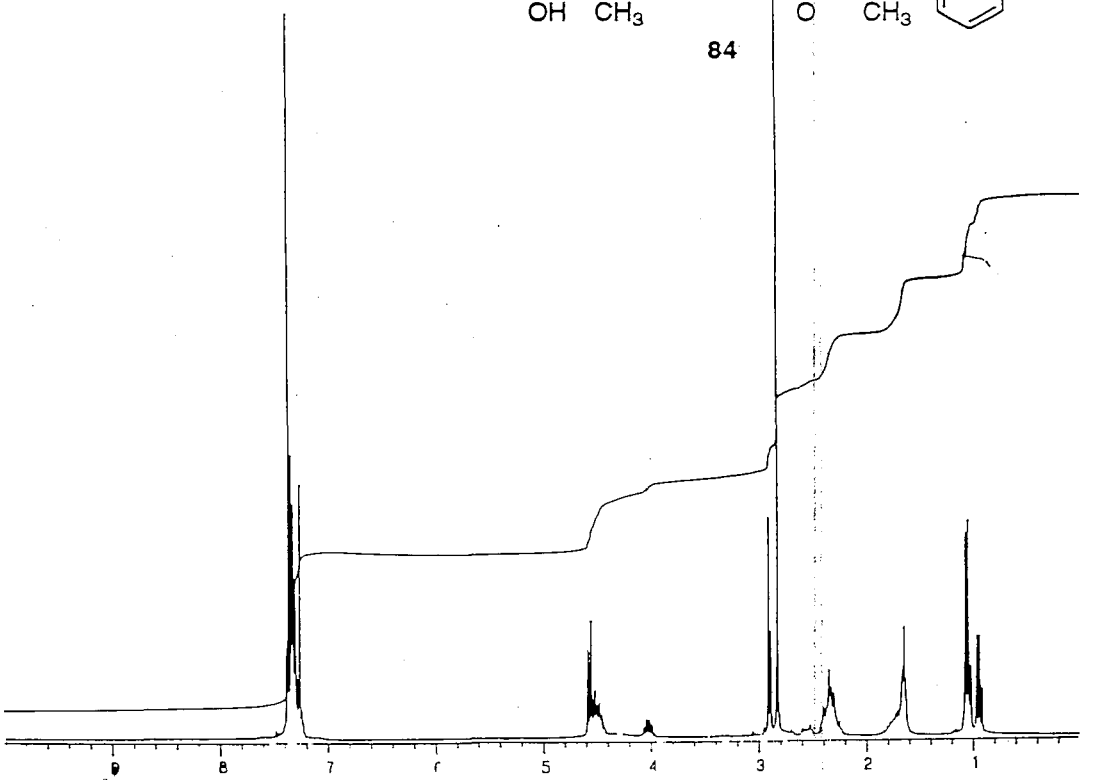
83

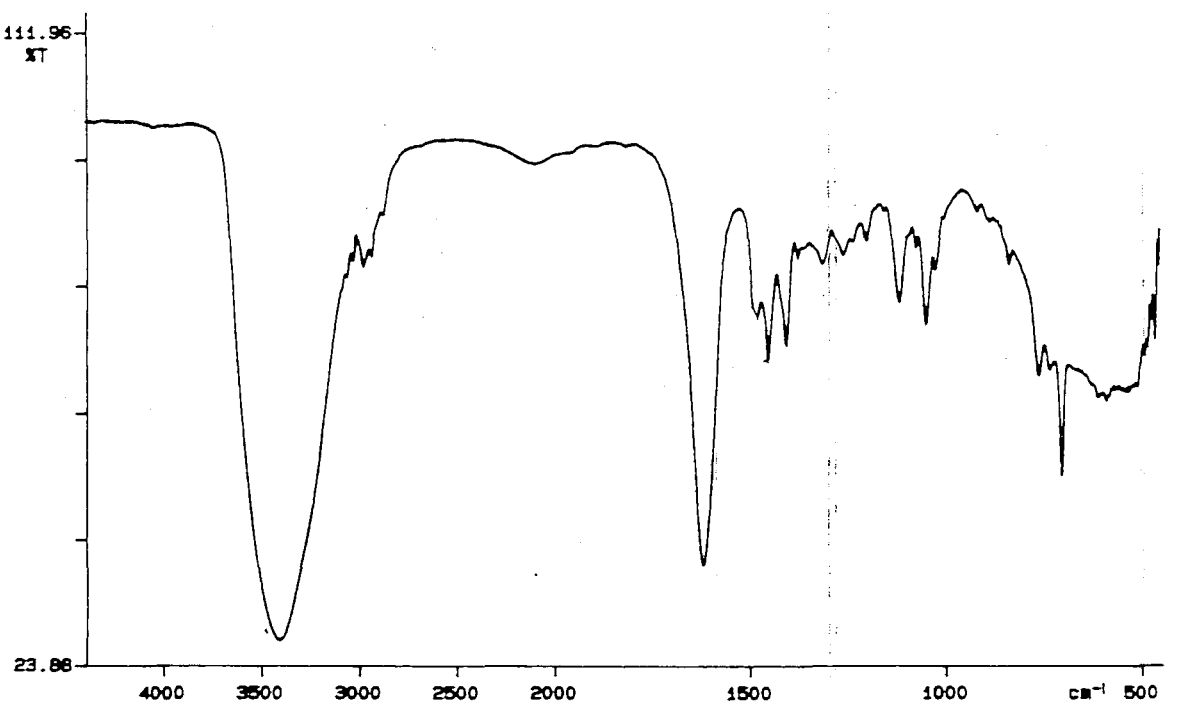
8
6
4
2
0
PPM

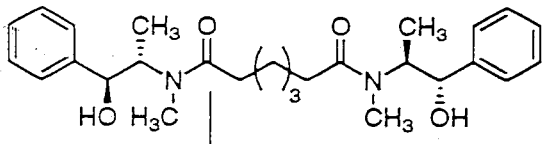

104.86
%T
21.15
4000
3500
3000
2500
2000
1500
1000
cm-1
500


CH3 O
CH3 OH
N
N
OH CH3
O CH3

84

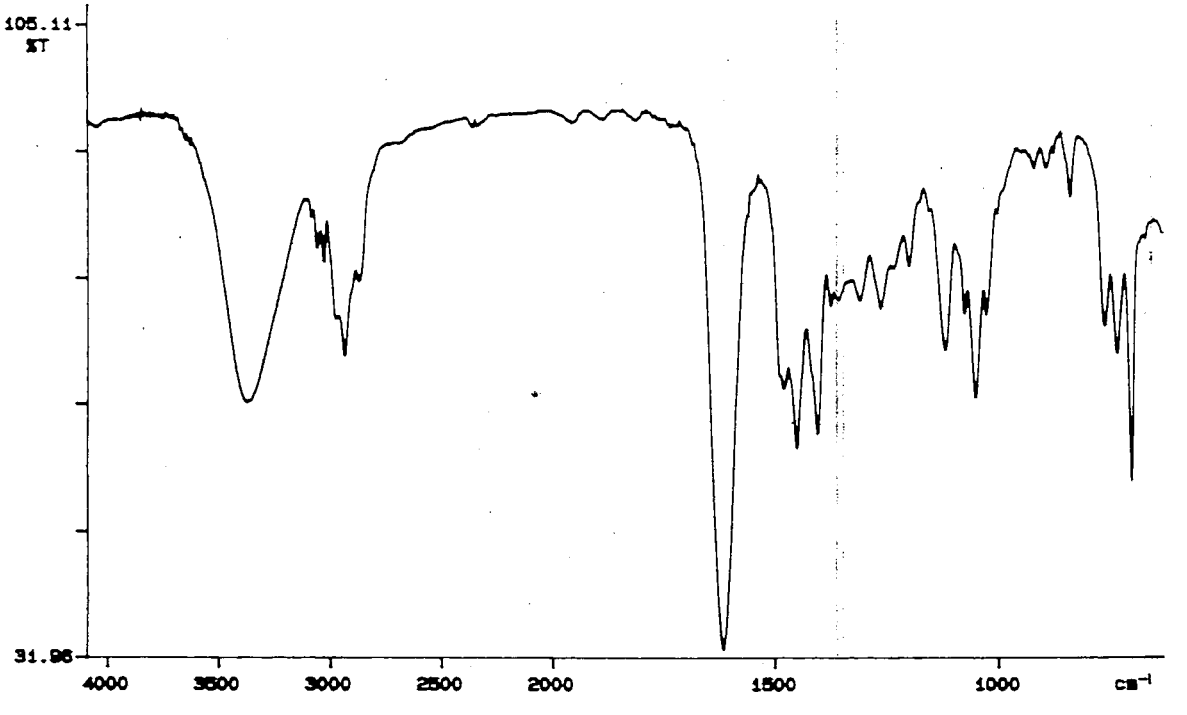

9
8
7
6
5
4
3
2
1

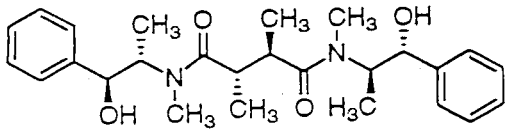

111.96
%T
23.86
4000
3500
3000
2500
2000
1500
1000
cm-1
500


CH3
O
O
CH3
N
N
HO
H3C
CH3
OH
3

85

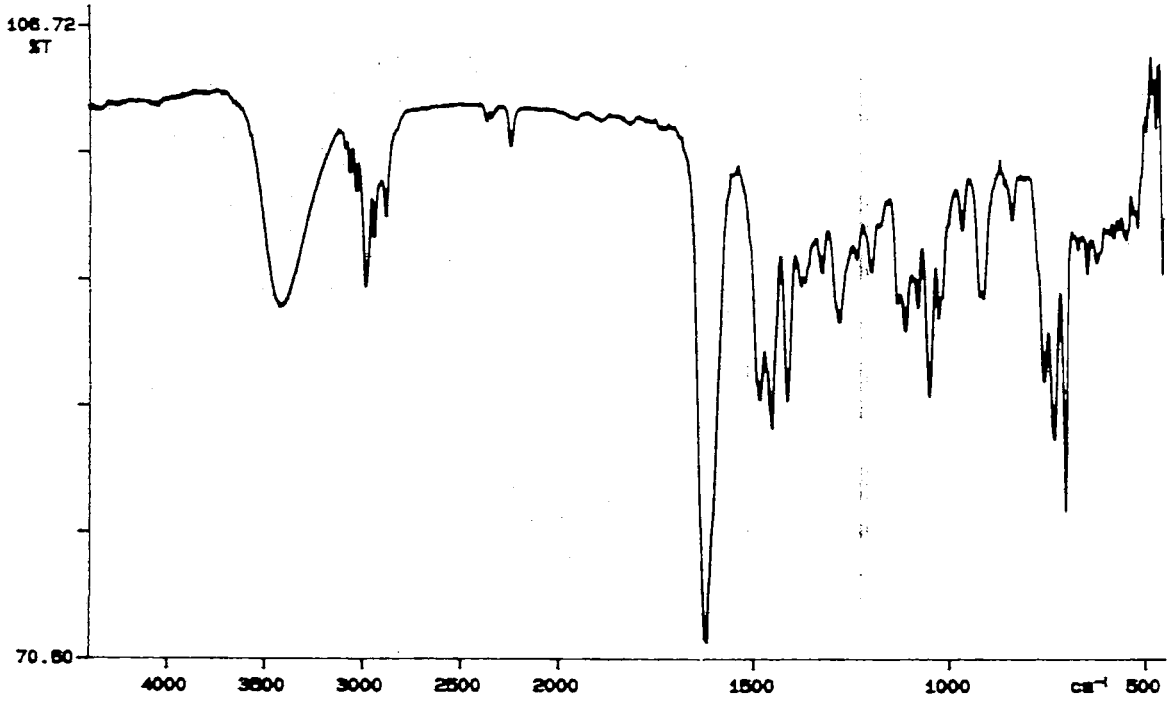
10
9
8
7
4
3
2
1
0

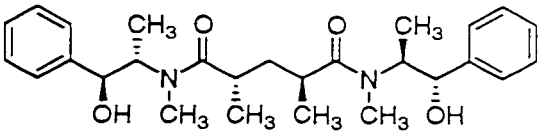

105.11
%T
31.96
4000
3500
3000
2500
2000
1500
1000
cm-1


CH3
O
CH3
CH3
OH
N
N
OH
CH3
CH3
O
H3C

86

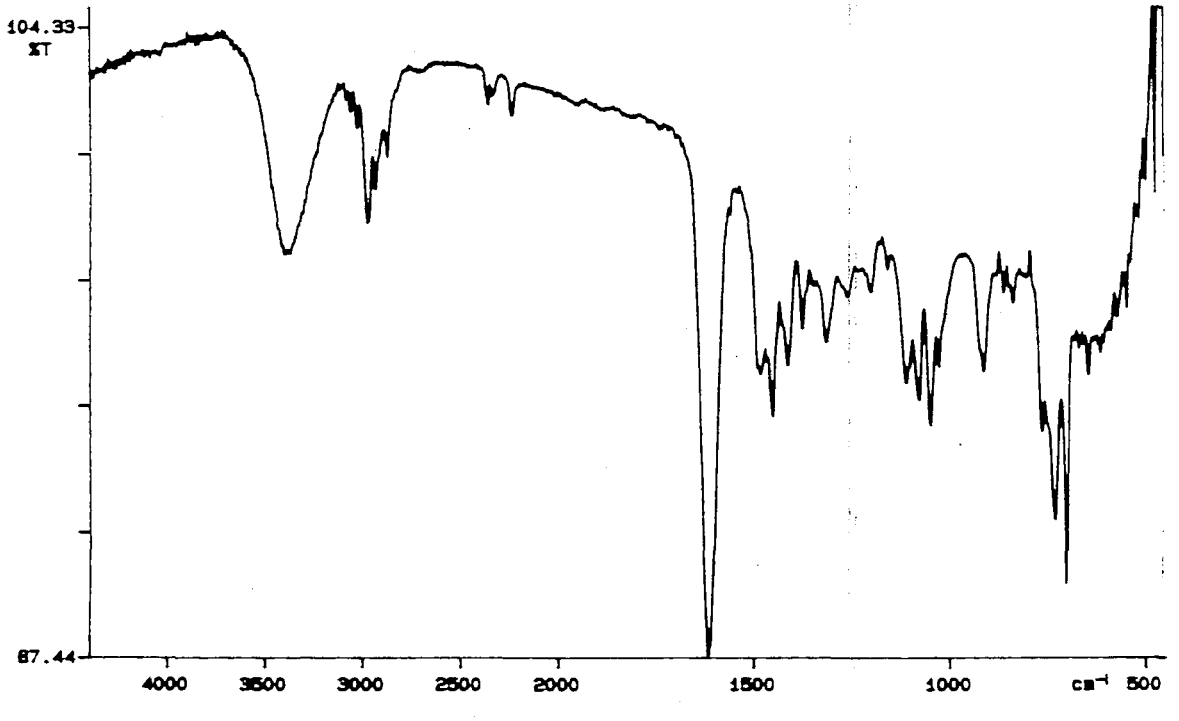
8
6
4
2
0
PPM

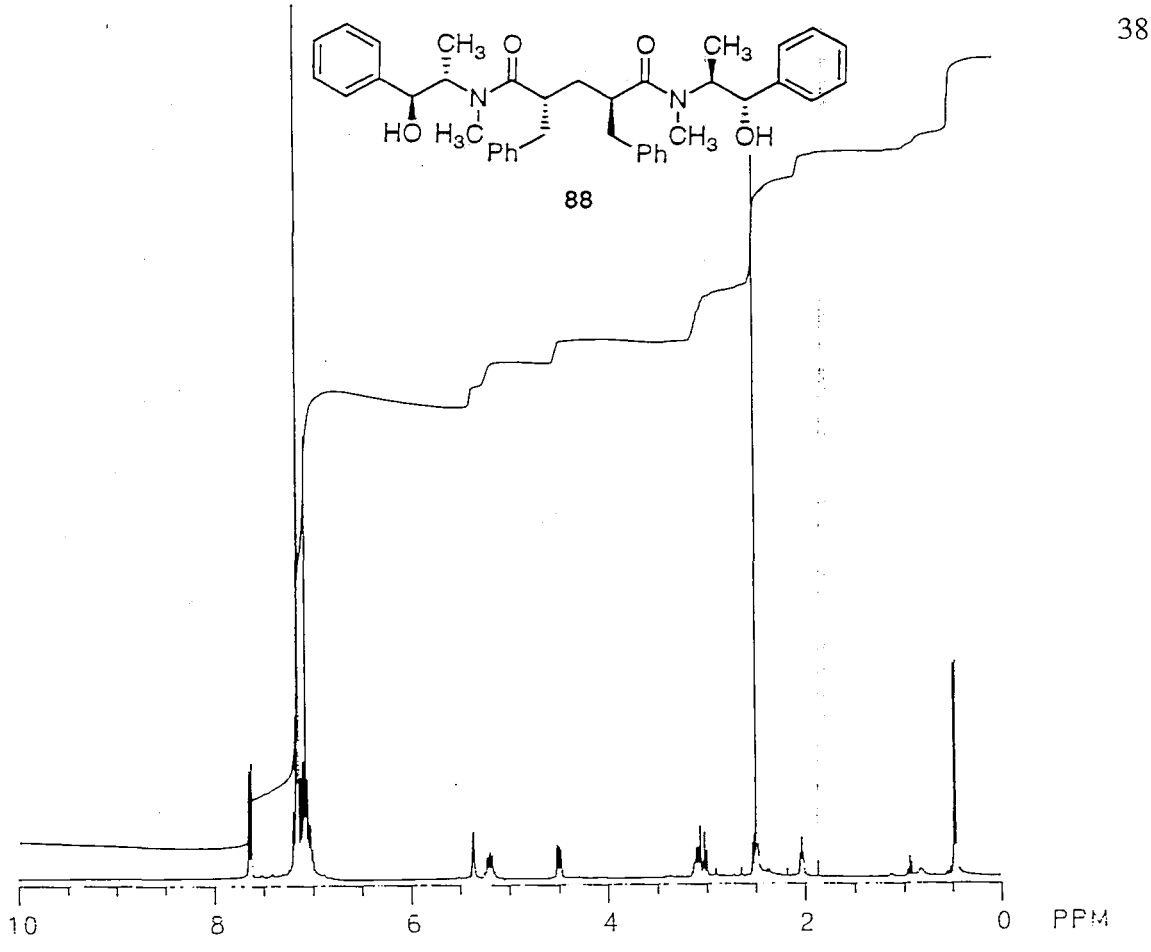

106.72
%T
70.60
4000
3500
3000
2500
2000
1500
1000
cm-1
500


CH3
O
O
CH3
N
N
OH
CH3
CH3
CH3
CH3
OH

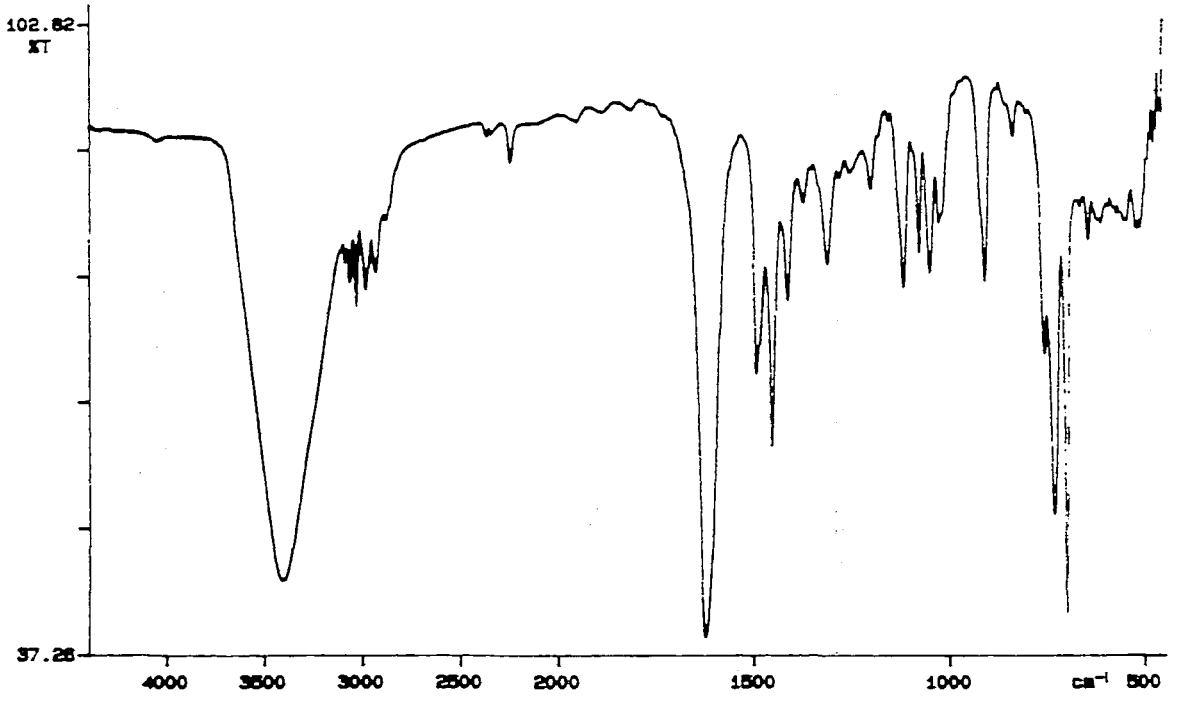
87

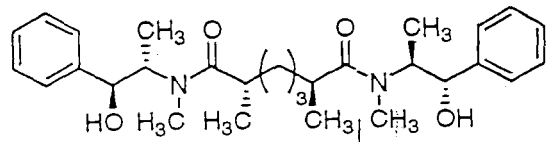
10
8
6
4
0
PPM


104.33
%T
87.44
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500

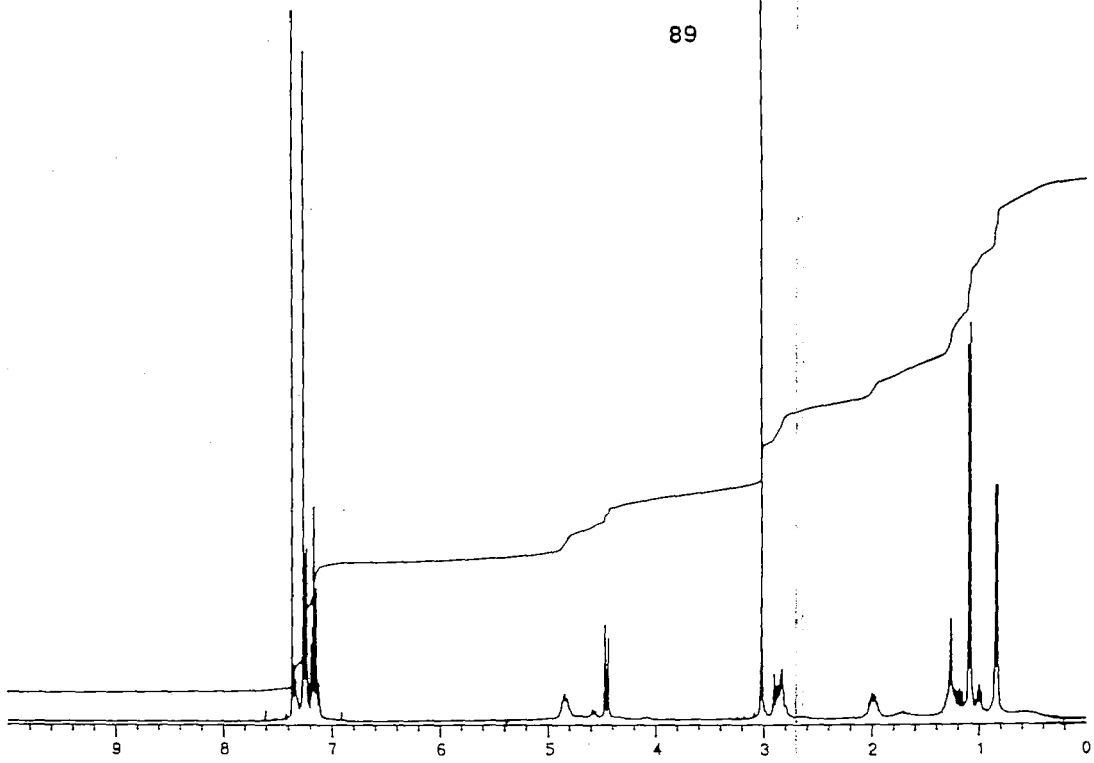

CH3
O
O
CH3
N
N
HO
H3C
Ph
Ph
CH3
OH
10
8
6
4
2
0
PPM

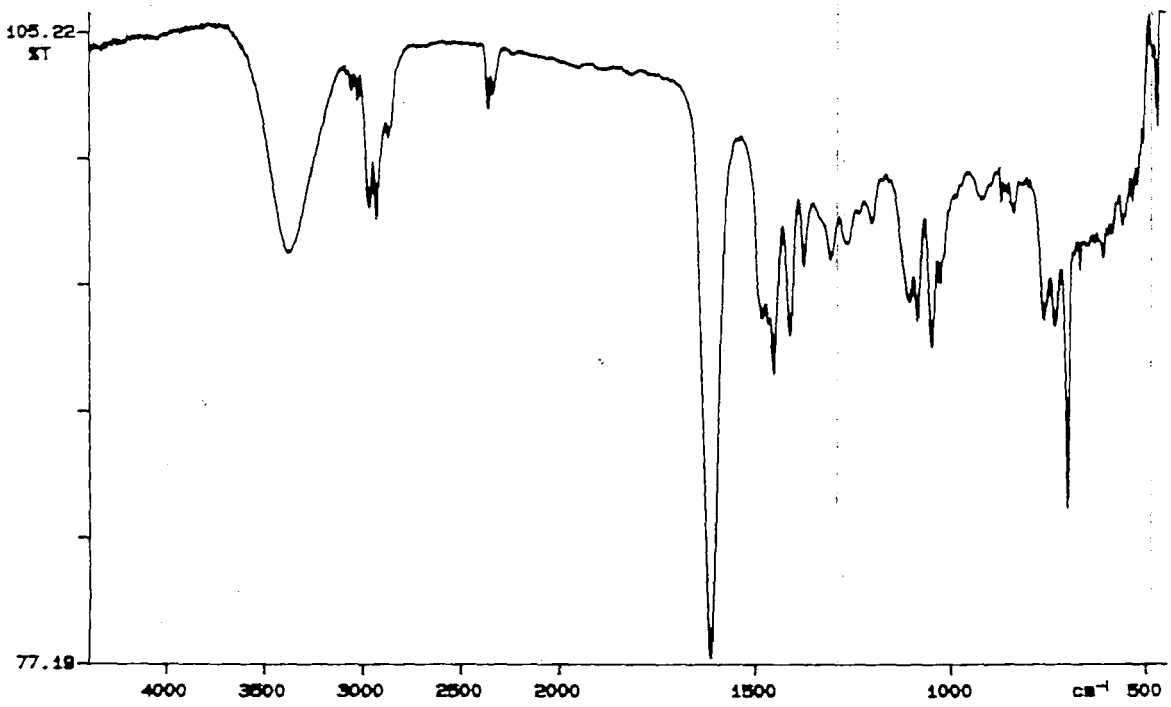
88

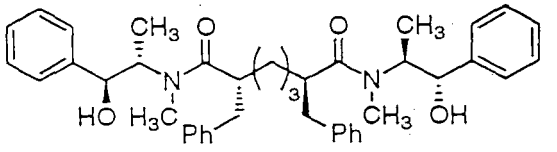

102.82
%T
37.28
4000
3500
3000
2500
2000
1500
1000
cm-1
500


CH3
O
O
CH3
N
N
HO
H3C
H3C
3
CH3
CH3
OH

89

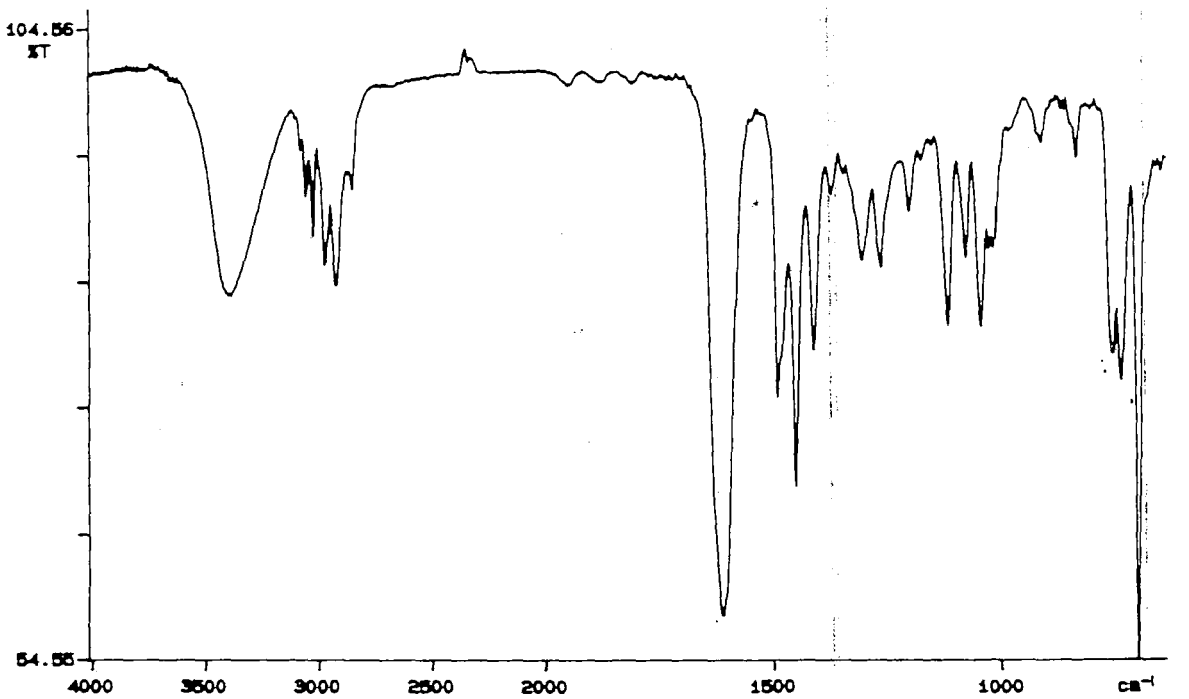

9
8
7
6
5
4
3
2
1
0


105.22
%T
77.19
4000
3500
3000
2500
2000
1500
1000
cm-1
500


CH3
O
O
CH3
N
N
HO
H3C
Ph
3
Ph
CH3
OH

90

10
8
6
4
2
0
PPM


104.56
%T
54.55
4000
3500
3000
2500
2000
1500
1000
cm-1