Use of Pseudoephedrine as a Practical Chiral Auxiliary for Asymmetric Synthesis

Thesis by
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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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<tbody>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>BOC</td>
<td>butyloxycarbonyl</td>
</tr>
<tr>
<td>BOM</td>
<td>benzylxoxymethyl</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>calcd</td>
<td>calculated</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celsius</td>
</tr>
<tr>
<td>CI</td>
<td>chemical ionization</td>
</tr>
<tr>
<td>cm⁻¹</td>
<td>reciprocal centimeters</td>
</tr>
<tr>
<td>COSY</td>
<td>correlated spectroscopy</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift (parts per million)</td>
</tr>
<tr>
<td>de</td>
<td>diastereomeric excess</td>
</tr>
<tr>
<td>2-D</td>
<td>two-dimensional</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>E</td>
<td>entgegen</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact</td>
</tr>
<tr>
<td>ent</td>
<td>enantiomer of</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalent(s)</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>FAB</td>
<td>fast atom bombardment</td>
</tr>
<tr>
<td>FTIR</td>
<td>Fourier transform infrared</td>
</tr>
<tr>
<td>g</td>
<td>gram(s)</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
</tbody>
</table>
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 $\alpha$-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 $\beta$-amino alcohols were alkylated by a range of alkyl halides with high diastereoselectivities.

**Scheme I**

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

Later, Evans and Takacs\textsuperscript{3a} and Sonnet and Heath\textsuperscript{3b} independently demonstrated that alkylation 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

\begin{center}
\textbf{Scheme II}
\end{center}

![Scheme II](image)

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

<table>
<thead>
<tr>
<th>entry</th>
<th>chiral auxiliary (grams)</th>
<th>cost (dollars per gram)</th>
<th>cost (dollars per mole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{Prolinol} ) ((25 \text{ g}))</td>
<td>6.7</td>
<td>677</td>
</tr>
<tr>
<td>2</td>
<td>( \text{2,10-Camphorsultam} ) ((5 \text{ g}))</td>
<td>31.1</td>
<td>3149</td>
</tr>
<tr>
<td>3</td>
<td>( \text{4-Benzyl-2-oxazolidinone} ) ((5 \text{ g}))</td>
<td>23.7</td>
<td>5105</td>
</tr>
<tr>
<td>4</td>
<td>( \text{Pseudoephedrine} ) ((1 \text{ g}))</td>
<td>48.2</td>
<td>10378</td>
</tr>
<tr>
<td>5</td>
<td>( \text{Prolinol amide} ) ((25 \text{ g}))</td>
<td>7.4</td>
<td>1705</td>
</tr>
<tr>
<td>6</td>
<td>( \text{Prolinol amide} ) ((25 \text{ g}))</td>
<td>9.6</td>
<td>1311</td>
</tr>
<tr>
<td>7</td>
<td>( \text{Pseudoephedrine} ) ((100 \text{ g}))</td>
<td>1.0</td>
<td>172</td>
</tr>
<tr>
<td>8</td>
<td>( \text{Pseudoephedrine} ) ((100 \text{ g}))</td>
<td>1.2</td>
<td>198</td>
</tr>
</tbody>
</table>

*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**

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 \(\geq 99\%\) 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.
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. 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
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 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\(^{®} \), Suphadrine\(^{®} \), 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 \( \beta \)-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 \( \geq 99\% \) 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.\textsuperscript{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

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>method (X)\textsuperscript{a}</th>
<th>product</th>
<th>yield (%)</th>
<th>mp (°C)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>CH\textsubscript{3}</td>
<td>A</td>
<td>1</td>
<td>95\textsuperscript{b}</td>
<td>114–115</td>
</tr>
<tr>
<td>2</td>
<td>n-Bu</td>
<td>A</td>
<td>2</td>
<td>91\textsuperscript{b}</td>
<td>62–63</td>
</tr>
<tr>
<td>3</td>
<td>Bn</td>
<td>B</td>
<td>3</td>
<td>83\textsuperscript{b}</td>
<td>102–104</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>B</td>
<td>4</td>
<td>88\textsuperscript{b}</td>
<td>145–146</td>
</tr>
<tr>
<td>5</td>
<td>i-Pr</td>
<td>B</td>
<td>5</td>
<td>92\textsuperscript{b}</td>
<td>73–74</td>
</tr>
<tr>
<td>6</td>
<td>t-Bu</td>
<td>B</td>
<td>6</td>
<td>88\textsuperscript{b}</td>
<td>68–69</td>
</tr>
<tr>
<td>7</td>
<td>CH\textsubscript{2}Bn</td>
<td>B</td>
<td>7</td>
<td>81\textsuperscript{b}</td>
<td>100–102</td>
</tr>
<tr>
<td>8</td>
<td>2-thiophene</td>
<td>B\textsuperscript{c}</td>
<td>8</td>
<td>87</td>
<td>110–111</td>
</tr>
<tr>
<td>9</td>
<td>3-pyridyl</td>
<td>C</td>
<td>9</td>
<td>97, 72\textsuperscript{b}</td>
<td>117.5–118.5</td>
</tr>
<tr>
<td>10</td>
<td>OH</td>
<td>D</td>
<td>10</td>
<td>93</td>
<td>61–63</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Method A: Acylation with the symmetrical carboxylic acid anhydride (X = RCH\textsubscript{2}CO\textsubscript{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\textsubscript{2}). Method D: Acylation with the methyl ester (X = CH\textsubscript{3}O). \textsuperscript{b}Values for products isolated by a single recrystallization of the crude product. \textsuperscript{c} Acylation of (1R,2R)-(-)-pseudoephedrine.
(1.2 equiv) is added. Acylation reactions with carboxylic acid chlorides require the presence of a slight excess of a base (e.g., Et₃N) and occur readily at 0 °C in most organic solvents. 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 → N acyl transfer within pseudoephedrine β-amino esters occurs rapidly, and because the N-acyl form is strongly favored under neutral or basic conditions, 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 glycaminamide. This procedure takes advantage of the intramolecular O → 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. These reactions proceed optimally using sodium methoxide (0.5 equiv) as base.

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.\textsuperscript{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.\textsuperscript{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 benzyloxyethyl 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'X$^a$</th>
<th>temp (°C)</th>
<th>prod.</th>
<th>crude de (%)</th>
<th>isol de (%)</th>
<th>isol yield (%)</th>
<th>mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_3$</td>
<td>BnBr</td>
<td>0</td>
<td>11</td>
<td>94</td>
<td>≥99$^b$</td>
<td>90$^b$</td>
<td>136-137</td>
</tr>
<tr>
<td>2</td>
<td>CH$_3$</td>
<td>n-BuI</td>
<td>0</td>
<td>12</td>
<td>98</td>
<td>≥99$^b$</td>
<td>80$^b$</td>
<td>66-67</td>
</tr>
<tr>
<td>3</td>
<td>CH$_3$</td>
<td>BOMCl</td>
<td>0</td>
<td>13</td>
<td>33</td>
<td>33</td>
<td>77</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>CH$_3$</td>
<td>BOMBr</td>
<td>-78</td>
<td>13</td>
<td>98</td>
<td>98</td>
<td>80</td>
<td>65-66</td>
</tr>
<tr>
<td>5</td>
<td>CH$_3$</td>
<td>C$_6$H$_5$(CH$_2$)$_2$I</td>
<td>0</td>
<td>14</td>
<td>95</td>
<td>95</td>
<td>86</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>CH$_3$</td>
<td>BrCH$_2$CO$_2$t-Bu</td>
<td>-78</td>
<td>15</td>
<td>94</td>
<td>96</td>
<td>78</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Bn</td>
<td>CH$_3$I</td>
<td>0</td>
<td>16</td>
<td>94</td>
<td>94</td>
<td>99</td>
<td>79-81</td>
</tr>
<tr>
<td>8</td>
<td>Bn</td>
<td>CH$_3$I</td>
<td>-78</td>
<td>16</td>
<td>97</td>
<td>97</td>
<td>95</td>
<td>79-81</td>
</tr>
<tr>
<td>9</td>
<td>Bn</td>
<td>n-BuI</td>
<td>0</td>
<td>17</td>
<td>98</td>
<td>98</td>
<td>90</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>n-Bu</td>
<td>CH$_3$I</td>
<td>0</td>
<td>18</td>
<td>94</td>
<td>94</td>
<td>94</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>n-Bu</td>
<td>CH$_3$I</td>
<td>-78</td>
<td>18</td>
<td>96</td>
<td>96</td>
<td>89</td>
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</tr>
<tr>
<td>12</td>
<td>n-Bu</td>
<td>BnBr</td>
<td>0</td>
<td>19</td>
<td>98</td>
<td>≥99$^b$</td>
<td>87$^b$</td>
<td>120-121</td>
</tr>
<tr>
<td>13</td>
<td>Ph</td>
<td>EtI</td>
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<td>20</td>
<td>96</td>
<td>≥99</td>
<td>92</td>
<td>65-66</td>
</tr>
<tr>
<td>14</td>
<td>CH$_2$Bn</td>
<td>CH$_3$I</td>
<td>0</td>
<td>21</td>
<td>95</td>
<td>≥99$^b$</td>
<td>92$^c$</td>
<td>89-90</td>
</tr>
<tr>
<td>15</td>
<td>i-Pr</td>
<td>BnBr</td>
<td>0</td>
<td>22</td>
<td>98</td>
<td>≥99$^b$</td>
<td>83$^b$</td>
<td>118-119</td>
</tr>
<tr>
<td>16</td>
<td>t-Bu</td>
<td>BnBr</td>
<td>0</td>
<td>23</td>
<td>98</td>
<td>≥99$^b$</td>
<td>84$^b$</td>
<td>125-127</td>
</tr>
<tr>
<td>17</td>
<td>3-pyridyl</td>
<td>CH$_2$=CHCH$_2$I</td>
<td>-78</td>
<td>24</td>
<td>98</td>
<td>98</td>
<td>83</td>
<td>109-110</td>
</tr>
<tr>
<td>18</td>
<td>2-thiophene$^d$</td>
<td>CH$_3$I</td>
<td>-78</td>
<td>25</td>
<td>95</td>
<td>95</td>
<td>88</td>
<td>-</td>
</tr>
</tbody>
</table>

$a$ 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 (1R,2R)-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](image-url)

Scheme VI

<table>
<thead>
<tr>
<th>Compound</th>
<th>Formula</th>
<th>mp/Character</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>CH₃CH(NH₂)CH₂CH₂CH₂CH₂CH₃</td>
<td>66–67 °C</td>
</tr>
<tr>
<td>ent-18</td>
<td>CH₃CH(NH₂)CH₂CH₂CH₂CH₂CH₃</td>
<td>(oil)</td>
</tr>
<tr>
<td>40</td>
<td>CH₃CH₂CH(NH₂)CH₂CH₂CH₂CH₃</td>
<td></td>
</tr>
</tbody>
</table>
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) 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. In addition, the selectivity of the latter reaction was found to be reduced on larger scale (~80% de, 10 mmol). 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. Use of Enders’ chiral hydrazone methodology in the synthesis of 1,3-dimethyl-substituted carbon chains has been
Table 4. Alkylation of Pseudoephedrine Amides with β-Branched Electrophiles

<table>
<thead>
<tr>
<th>entry</th>
<th>RI&lt;sup&gt;a&lt;/sup&gt;</th>
<th>time (h)</th>
<th>product</th>
<th>isol yield (%)</th>
<th>ratio of A : B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I&lt;sub&gt;CH₃&lt;/sub&gt;</td>
<td>6</td>
<td>![Image]</td>
<td>89</td>
<td>86 : 1</td>
</tr>
<tr>
<td>2</td>
<td>I&lt;sub&gt;CH₃&lt;/sub&gt;</td>
<td>20</td>
<td>![Image]</td>
<td>94</td>
<td>62 : 1</td>
</tr>
<tr>
<td>3</td>
<td>I&lt;sub&gt;CH₃&lt;/sub&gt;</td>
<td>18</td>
<td>![Image]</td>
<td>94</td>
<td>1 : 89</td>
</tr>
<tr>
<td>4</td>
<td>I&lt;sub&gt;Ph&lt;/sub&gt;</td>
<td>6</td>
<td>![Image]</td>
<td>97</td>
<td>&gt;99 : 1</td>
</tr>
<tr>
<td>5</td>
<td>I&lt;sub&gt;Ph&lt;/sub&gt;</td>
<td>7</td>
<td>![Image]</td>
<td>95</td>
<td>1 : 58</td>
</tr>
<tr>
<td>6</td>
<td>I&lt;sub&gt;CH₃&lt;/sub&gt;</td>
<td>18</td>
<td>![Image]</td>
<td>93</td>
<td>142 : 1</td>
</tr>
<tr>
<td>7</td>
<td>I&lt;sub&gt;Ph&lt;/sub&gt;</td>
<td>18</td>
<td>![Image]</td>
<td>96</td>
<td>1 : 70</td>
</tr>
<tr>
<td>8</td>
<td>I&lt;sub&gt;Ph&lt;/sub&gt;</td>
<td>12</td>
<td>![Image]</td>
<td>93</td>
<td>66 : 1</td>
</tr>
<tr>
<td>9</td>
<td>I&lt;sub&gt;Ph&lt;/sub&gt;</td>
<td>18</td>
<td>![Image]</td>
<td>94</td>
<td>1 : 199</td>
</tr>
</tbody>
</table>

<sup>a</sup> 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.\textsuperscript{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\textsuperscript{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.\textsuperscript{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., $\text{RCH}_2\text{OH} \rightarrow \text{RCH}_2\text{I}$), 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.\textsuperscript{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.\textsuperscript{25} Thus, treatment of the iodide 67\textsuperscript{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).\textsuperscript{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 (1H and 13C) time scale. In one case (substrate 11), we observed a coalescence temperature of 120 °C (1H 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)\(^14\)
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 $\alpha$-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 $\alpha$-hydroxyacetamide (1.65 equiv) and limiting benzyl bromide the C-alkylated product $^{35}$ was formed in 84% yield and 82% de. This diastereo-
selectivity is lower than that obtained in benzylations of other pseudoephedrine amide enolates, including the α-heterosubstituted enolates derived from pseudoephedrine glycinamide,\textsuperscript{9} chloroacetamide,\textsuperscript{8} and fluoroacetamide\textsuperscript{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\textsuperscript{+}) 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

\textbf{Scheme VII}
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 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.

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.

\[
\begin{align*}
\text{36} & \quad \text{LiTMP, LiCl, PhCH}_2\text{Br; THF, -78 °C} \\
\text{37: 72% yield, 93% de}
\end{align*}
\]

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, phenylacetamide, and the C₂ 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 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. 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 molecules (tetrahydrofuran and possibly diisopropylamine) associated with the lithium cation are proposed to block the \( \beta \)-face of the Z-enolate, forcing the alkylation to occur from the \( \alpha \)-face. In this model, the pseudoephedrine side chain adopts a staggered conformation in which the C–H bond \( \alpha \) to nitrogen lies in-plane with the enolate oxygen, in accord with predictions based on allylic strain arguments. The positioning of the secondary alkoxide on the \( \beta \)-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 2.** Proposed reactive conformation of pseudoephedrine amide enolates.

![Proposed reactive conformation of pseudoephedrine amide enolates](image)

**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), wherein allylic and torsional strain is minimized, and the secondary hydroxyl group is disposed on the ω-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).$^{34}$

![Figure 4. Proposed conformations of the lithium enolate of pseudoephedrine propionamide in THF, in the absence of lithium chloride.](image-url)
For structure X, the NOE between protons of the N-methyl group (Me₆) and the enolate proton (Hₑ) 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 Hₐ and Hₖ is consistent with a dihedral angle of 150° to 180° or 0° to 20°, but the NOE between the protons of the N-methyl group (Me₆) and Hₖ virtually rules out the latter possibility. The steric interaction between the phenyl ring and Meₑ can be minimized by turning the face of the aromatic ring toward Meₑ, which may explain the upfield shift (δ = 0.60 ppm) for the protons of Meₑ. 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 (Me₆) and the enolate proton (Hₑ), 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 Hₐ and Hₖ, and an upfield shift of the N-methyl group (Me₆) 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 Meₖ (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 Meₑ in structure Z suggests that the phenyl ring is opening its face to Meₑ, 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

<table>
<thead>
<tr>
<th>resonance</th>
<th>structure X (δ)</th>
<th>structure Y (δ)</th>
<th>structure Z (δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_a$</td>
<td>3.50</td>
<td>2.96</td>
<td>too broad to find</td>
</tr>
<tr>
<td>$H_b$</td>
<td>4.56</td>
<td>4.83</td>
<td>4.4</td>
</tr>
<tr>
<td>$H_c$</td>
<td>3.34</td>
<td>3.19</td>
<td>3.3</td>
</tr>
<tr>
<td>$Me_a$</td>
<td>1.43</td>
<td>1.28</td>
<td>1.45</td>
</tr>
<tr>
<td>$Me_b$</td>
<td>2.52</td>
<td>1.82</td>
<td>2.35</td>
</tr>
<tr>
<td>$Me_c$</td>
<td>0.60</td>
<td>1.70</td>
<td>0.4</td>
</tr>
</tbody>
</table>

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.

![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. 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 alkylation reactions (employing lithium chloride as an additive) and have found these alkylation reactions to exhibit only modest diastereoselectivity. 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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{40}

Instrumentation. Melting points are uncorrected. Infrared data are presented as follows: frequency of absorption (cm\textsuperscript{-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 ($\delta$ scale) downfield from tetramethylsilane. $^1$H NMR chemical shifts are referenced to the signal for residual hydrogen in the NMR solvent (CHCl$_3$: $\delta$ 7.26, C$_6$HD$_5$: $\delta$ 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 $\mu$sec, D5 = 200 msec, D8 = 10.00 $\mu$sec, I8 = 312 $\mu$sec, 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$_3$: $\delta$ 77.0, C$_6$D$_6$: $\delta$ 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. Both (R)- and (S)- Mosher ester derivatives of this alcohol were prepared and were identified conclusively by comparison with $^1$H NMR data from authentic materials. 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.\footnote{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)-\(\alpha\)-methylbenzylamine as described for acid 39 (vide
infra). The resulting (R)-\(\alpha\)-methylbenzyl amide was shown to be identical to the (R)-\(\alpha\)-
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.
(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$_6$D$_6$) $\delta$: (3:1 rotamer ratio, * denotes minor rotamer peaks)
6.95–7.45 (m, 5H, ArH), 4.83 (br, 1H, OH), 4.51 (t, 1H, $J = 7.2$ Hz, CHOH), 4.10 (m, 2H, CHOH, NCHCH$_3$), 3.68* (m, 1H, NCHCH$_3$), 2.77* (s, 3H, NCH$_3$), 2.40* (m, 2H, CH$_2$), 2.06 (s, 3H, NCH$_3$), 1.73 (m, 2H, CH$_2$), 1.22* (t, 3H, $J = 7.3$ Hz, CH$_2$CH$_3$), 0.9–1.1 (m, 6H, CH$_3$CHN, CH$_2$CH$_3$), 0.53* (d, 3H, $J = 6.7$ Hz, CH$_3$CHN).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: (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$_2$Cl$_2$), $R_f$: 1: 0.61 (UV, PMA).
pseudoephedrine: 0.05 (UV, PMA).
(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 x 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, CD\(_2\)Cl\(_2\)) \(\delta\): (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\(_3\)) \(\delta\): (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\(_{25}\)NO\(_2\) (MH\(^+\)): 264.1965.


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\(_2\)Cl\(_2\)), \(R_f\): 2: 0.71 (UV, PMA).

pseudoephedrine: 0.05 (UV, PMA).
(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 x 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, CD$_2$D$_2$) $\delta$: (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, CHOH), 4.20 (m, 1H,
NCHCH$_3$), 4.01* (dd, 1H, $J = 8.4$ Hz, 2.4 Hz,
CHOH), 3.66* (m, 1H, NCHCH$_3$), 3.15* (m, 2H,
CH$_2$Ph), 2.93 (t, 2H, $J = 7.7$ Hz, CH$_2$Ph), 2.79* 
(s, 3H, NCH$_3$), 2.49* (m, 2H, COCH$_2$), 2.13 (m,
2H, COCH$_2$), 2.02 (s, 3H, NCH$_3$), 0.92 (d, 3H, $J$
= 7.0 Hz, CH$_3$CHN), 0.49* (d, 3H, $J = 6.8$ Hz,
CH$_3$CHN).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: (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$_2$Cl$_2$), $R_f$: 3: 0.71 (UV, PMA).

pseudoephedrine: 0.05 (UV, PMA).
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, \(\text{C}_6\text{D}_6\)) \(\delta\):  
(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, \(\text{CHOH}\)), 4.22 (m, 1H, \(\text{NCHCH}_3\)), 4.17* (m, 1H, \(\text{CHOH}\)), 3.90* (m, 1H, \(\text{NCHCH}_3\)), 3.78* (s, 2H, \(\text{CH}_2\text{Ph}\)), 3.31 (d, 2H, \(J = 1.3\) Hz, \(\text{CH}_2\text{Ph}\)), 2.76* (s, 3H, \(\text{NCH}_3\)), 2.12 (s, 3H, \(\text{NCH}_3\)), 0.95 (d, 3H, \(J = 7.0\) Hz, \(\text{CH}_3\text{CHN}\)), 0.42* (d, 3H, \(J = 6.7\) Hz, \(\text{CH}_3\text{CHN}\)).

\(^{13}\)C NMR (75 MHz, \(\text{CDCl}_3\)) \(\delta\):  
(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 \(\text{C}_{18}\text{H}_{22}\text{NO}_2\) (MH)*: 284.1652.  
Found: 284.1646.

Analysis:  
Calcd for \(\text{C}_{18}\text{H}_{21}\text{NO}_2\): C, 76.30; H, 7.47; N, 4.94.  
Found: C, 76.07; H, 7.40; N, 4.86.

TLC (15% MeOH–\(\text{CH}_2\text{Cl}_2\)), \(R_f\):  
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$_3$) $\delta$: (4:1 rotamer ratio, * denotes minor rotamer peaks)
7.20–7.45 (m, 5H, aromatic), 4.6 (m, 1H, CHO\H), 4.42 (m, 1H, NCHCH$_3$), 4.01* (m, 1H, NCHCH$_3$), 2.91* (s, 3H, NCH$_3$), 2.81 (s, 3H, NCH$_3$), 2.05–2.30 (m, 3H, COCH$_2$CH), 1.13 (d, 3H, J = 7.0 Hz, CHNCH$_3$), 0.96 (m, 6H, CH$_2$CH(CH$_3$)$_2$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: (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$_{24}$N\textsubscript{2}O (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).
(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$_3$) $\delta$: (5:1 rotamer ratio, * denotes minor rotamer peaks)
7.2–7.4 (m, 5H, aromatic), 4.59 (m, 1H, CHOH),
4.44 (br, m, 1H, NCHCH$_3$), 4.09* (m, 1H, NCHCH$_3$), 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$_3$CHN), 1.06* (s, 9H, CH$_2$C(CH$_3$)$_3$), 1.01 (s, 9H, CH$_2$C(CH$_3$)$_3$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: (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.

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).
(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$_3$) $\delta$: (3:1 rotamer ratio, * denotes minor rotamer peaks)

7.1–7.4 (m, 10H, aromatic), 4.60 (m, 1H, CHOH),
4.53* (m, 1H, CHOH), 4.45 (m, 1H, NCHCH$_3$),
4.33 (br, 1H, OH), 3.90* (m, 1H, NCHCH$_3$),
2.92* (s, 3H, NCH$_3$), 2.75 (s, 3H, NCH$_3$), 2.64–
2.69 (m, 2H, COCH$_2$), 2.35 (m, 2H, PhCH$_2$), 2.00
(m, 2H, PhCH$_2$CH$_2$), 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$_3$) $\delta$: (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,

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.


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$_2$Cl$_2$), $R_f$: 7: 0.67 (UV, PMA).

4-phenylbutyric acid: 0.60 (UV).
(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$_3$) $\delta$: (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$_3$CHN), 0.90* (d, 3H, $J = 6.8$ Hz, CH$_3$CHN).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: (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$_{20}$N0$_2$S (MH)$^+$: 290.1215.
Found: 290.1229.

Analysis: Calcd for C$_{16}$H$_{19}$N0$_2$S: C, 66.41; H, 6.62; N, 4.84.
Found:C, 66.18; H, 6.64; N, 4.64.

TLC (15% MeOH–CH$_2$Cl$_2$), $R_f$: 8: 0.59 (UV, PMA).
pseudoephedrine: 0.05 (UV, PMA).
(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$_5$H$_4$N), 7.6–7.7 (m, 1H, one of C$_5$H$_4$N), 7.1–7.4 (m, 6H, one of C$_5$H$_4$N, phenyl), 4.4–4.7 (m, 2H, CHOH, NCHCH$_3$), 4.0–4.3* (m, 2H, CHOH, NCHCH$_3$), 3.80* (d, 2H, $J = 1.8$ Hz, CH$_2$), 3.67 (s, 2H, CH$_2$), 2.96* (s, 3H, NCH$_3$), 2.89 (s, 3H, NCH$_3$), 1.13 (d, 3H, $J = 6.8$ Hz, CH$_3$CHN), 0.93* (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)
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$_2$O$_2$ (MH)$^+$: 285.1603. Found: 285.1596.

Analysis: Calcd for C$_{17}$H$_{20}$N$_2$O$_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.77; H, 7.08; N, 9.81.

TLC (Et$_3$N-pretreated plate, 10% MeOH–CH$_2$Cl$_2$), $R_f$: 9: 0.40 (UV, PMA).

pseudoephedrine: 0.14 (UV, PMA).
\[
\begin{align*}
\text{CH}_3
&\quad \text{CH}_3
\quad \text{N}
\quad \text{H}
\quad \text{OH}
\quad \text{CH}_3
\end{align*}
\]

\[3\text{-pyridylacetyl chloride} \quad \text{CH}_3\text{CN, THF, 15 °C} \quad \text{72%} \]

\[\begin{align*}
\text{CH}_3
&\quad \text{N}
\quad \text{H}
\quad \text{OH}
\quad \text{CH}_3
\quad \text{3-pyridylacetamide 9}
\end{align*}\]

\[
(\text{S,S})-\text{N-(2-Hydroxy-1-methyl-2-phenylethyl)-N-methyl 3-Pyridineacetamide 9}
\]

Amide 9 could also be purified by recrystallization. Following a procedure similar to that described above, using (+)-pseudoephephrine (1.49 g, 8.99 mmol, 1 equiv), triethylamine (3.38 mL, 24.3 mmol, 3.00 equiv), 3-pyrindylacetic 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\text{17}H\text{20}N\text{2}O\text{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$_2$OH), 4.36* (m, 2H, CH$_2$OH), 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$_3$CHN), 0.99* (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)
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$_3$N-pretreated plate, 10% MeOH–CH$_2$Cl$_2$), $R_f$: 10: 0.44 (UV, PMA).

pseudoephedrine: 0.11 (UV, PMA).
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 of the resulting trimethylsilyl ether established that amide 11 was of ≥99% de.
**FTIR (neat, cm⁻¹):**

3384 (br, m, OH), 1617 (s, C=O).

**HRMS (FAB):**

Calcd for C₂₀H₂₆NO₂ (MH)+: 312.1965.


**Analysis:**

Calcd for C₂₀H₂₅NO₂: C, 77.14; H, 8.09; N, 4.50.

Found: C, 76.87; H, 8.06; N, 4.50.

**TLC (80% EtOAc–hexanes), Rf:**

1: 0.46 (UV, PMA).

1: 0.24 (UV, PMA).

benzyl bromide: 0.70 (UV, PMA).
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 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$_6$D$_6$) 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, CHO), 4.06 (m, 1H, NCHCH$_3$), 3.90* (m, 1H, NCHCH$_3$), 2.77 (s, 3H, NCH$_3$), 2.70* (m, 1H, COCHCH$_3$), 2.22 (s, 3H, NCH$_3$), 2.17 (m, 1H, COCHCH$_3$), 1.70 (m, 2H, COCHCH$_2$), 1.40* (m, 2H, COCHCH$_2$), 1.02 (d, 3H, $J = 7.2$ Hz, CH$_3$CHN), 0.99 (d, 3H, $J = 6.8$ Hz, COCHCH$_3$), 0.90–1.25 (m, 4H, CH$_3$CH$_2$CH$_2$), 0.85 (t, 3H, $J = 7.0$ Hz, CH$_2$CH$_3$), 0.62* (d, 3H, $J = 6.8$ Hz, CH$_3$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).
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 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, CD$_3$D$_6$) δ:

(3:2 rotamer ratio, * denotes minor rotamer peaks)
7.0–7.4 (m, 10H, aromatic), 4.54 (m, 1H, CHOH),
4.18–4.4.4 (m, 3H, NCHCH$_3$, PhCH$_2$O), 4.03*
(m, 1H, NCHCH$_3$), 3.70 (m, 2H, PhCH$_2$OCH$_2$),
3.25* (m, 2H, PhCH$_2$OCH$_2$), 3.02* (m, 1H,
COCHCH$_3$), 2.84 (s, 3H, NCH$_3$), 2.72 (m, 1H,
COCHCH$_3$), 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$_3$CHN), 0.96 (d, 3H, J = 6.8 Hz, COCHCH$_3$),
0.59* (d, 3H, J = 6.7 Hz, CH$_3$CHN).

$^{13}$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.

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).
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 $-78^\circ$C. The suspension was warmed briefly to 0 °C, then was cooled to $-78^\circ$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 $-78^\circ$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$_3$) 8: (3:1 rotamer ratio, * denotes minor rotamer peaks)
7.0–7.4 (m, 10 H, aromatic), 4.63 (d, 1H, $J$ = 7.6 Hz, CHOH), 4.54* (d, 1H, $J$ = 8.7 Hz, CHOH), 4.42 (br, m, 1H, CHNCH$_3$), 3.99* (m, 1H, CHNCH$_3$), 2.93* (s, 3H, NCH$_3$), 2.72 (s, 3H, NCH$_3$), 2.40–2.65 (m, 3H, PhCH$_2$CH$_2$CH), 2.18* (m, 1H, one of PhCH$_2$CH$_2$), 1.99 (m, 1H, one of PhCH$_2$CH$_2$), 1.73* (m, 1H, one of PhCH$_2$CH$_2$), 1.62 (m, 1H, one of PhCH$_2$CH$_2$), 1.15 (d, 3H, $J$ = 7.0 Hz, CH$_3$CHCH$_2$), 1.10 (d, 3H, $J$ = 6.8 Hz, CH$_3$CHN), 0.99* (d, 3H, $J$ = 6.9 Hz, CH$_3$CHN).

$^{13}$C NMR (75 MHz, CDCl$_3$) 8: (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).
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 x 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 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, CDCl₃) 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, CHNCH₃), 2.98 (s, 3H, NCH₃), 2.93 (s, 3H, NCH₃), 2.74 (dd, 1H, $J_1 = 16.7$ Hz, $J_2 = 9.1$ Hz, one of CH₂), 2.30 (m, 1H, one of CH₂), 1.43 (s, 9H, C(CH₃)₃), 1.10 (d, 3H, $J = 7.0$ Hz, CH₃), 0.97 (d, 3H, $J = 6.8$ Hz, CH₃).

$^{13}$C NMR (75 MHz, CDCl₃) 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).


TLC (80% EtOAc–hexanes), $R_f$: 15: 0.56 (UV, PMA). 1: 0.29 (UV, PMA). tert-butylbromoacetate: 0.17 (PMA).
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 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$_6$D$_6$) $\delta$: (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, CHOH), 3.97* (m, 1H, CHOH), 3.75 (m, 1H, NCHCH$_3$), 3.15* (m, 1H, NCHCH$_3$), 3.06 (m, 1H, COCHCH$_3$), 2.71* (s, 3H, NCH$_3$), 2.58* (m, 2H, CH$_2$Ph), 2.45 (m, 2H, CH$_2$Ph), 1.93 (s, 3H, NCH$_3$), 1.34* (d, 3H, $J = 6.3$ Hz, COCHCH$_3$), 1.00 (d, 3H, $J = 7.0$ Hz, CH$_3$CHN), 0.93 (d, 3H, $J = 6.4$ Hz, COCHCH$_3$),
0.30* (d, 3H, $J = 6.8$ Hz, CH$_3$CHN).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: (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).
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 of the corresponding trimethylsilyl ether, prepared as described above for amide 11, established that amide 16 was of 97% de.
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 \(-78^\circ C\). The resulting suspension was warmed briefly to 0 \( ^\circ \)C, then was cooled to \(-78^\circ C\). 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 \(-78^\circ C\) for 50 min, at 0 \( ^\circ \)C for 13 min, at 23 \( ^\circ \)C for 4 min, and finally was cooled to 0 \( ^\circ \)C, whereupon 1-iodobutane (5.52 mL, 48.5 mmol, 2.50 equiv) was added. The mixture was stirred at 0 \( ^\circ \)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. 

\[
\text{[1S(S),2S1-\( \beta \)-Butyl-\( \text{N}-(2\text{-hydroxy-1-methyl-2-phenylethyl})\)-\( \text{N} \)-methyl] \text{Benzene-propionamide 17}}
\]
\[^1\text{H NMR (300 MHz, C}_6\text{D}_6) \delta: \]
(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, \(\text{CHOH}\)), 4.02* (m, 1H, \(\text{CHOH}\)), 3.90 (m, 1H, \(\text{NCHCH}_3\)), 3.78* (m, 1H, \(\text{NCHCH}_3\)), 3.03 (m, 1H, \(\text{COCH}\)), 2.70* (s, 3H, \(\text{NCH}_3\)), 2.57 (m, 2H, \(\text{CH}_2\text{Ph}\)), 2.02 (s, 3H, \(\text{NCH}_3\)), 0.93–1.9 (m, 6H, \(\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\)), 0.92 (d, 3H, \(J = 7.0\) Hz, \(\text{CH}_3\text{CHN}\)), 0.84 (t, 3H, \(J = 7.2\) Hz, \(\text{CH}_3\text{CH}_2\)), 0.16* (d, 3H, \(J = 6.7\) Hz, \(\text{CH}_3\text{CHN}\)).

\[^{13}\text{C NMR (75 MHz, CDCl}_3) \delta: \]
(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 \(\text{C}_{23}\text{H}_{29}\text{NO} (\text{M}–\text{H}_2\text{O})^+: 335.2251.

Found: 335.2234.

TLC (60% EtOAc–hexanes), \(R_f\):
17: 0.42 (UV, PMA).
3: 0.28 (UV, PMA).
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 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$_6$D$_6$) $\delta$: (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, CHO), 4.16* (d, 1H, $J = 8.6$ Hz, CHO),
3.95 (m, 1H, NCHCH$_3$), 2.82* (s, 3H, NCH$_3$), 2.70 (m, 1H, COCHCH$_3$), 2.18 (s, 3H, NCH$_3$), 2.15* (m, 1H, COCHCH$_3$), 1.78 (m, 2H, COCHCH$_3$), 1.0–1.4 (m, 4H, CH$_3$CH$_2$CH$_2$),
1.33* (d, 3H, $J = 6.7$ Hz, COCHCH$_3$), 1.08 (d, 3H, $J = 7.0$ Hz, CH$_3$), 0.92 (d, 3H, $J = 6.8$ Hz, COCHCH$_3$), 0.87 (t, 3H, $J = 6.9$ Hz, CH$_3$CH$_2$), 0.69* (d, 3H, $J = 6.7$ Hz, CH$_3$CHN).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: (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).
1S(S,2S)-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 of the corresponding trimethylsilyl ether, prepared as described above for amide 11, established that amide 18 was of 96% de.
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 of the corresponding trimethylsilyl ether, prepared as described above for amide 11, established that amide 19 was of ≥99% de.
\[ ^1\text{H NMR (300 MHz, C}_6\text{D}_6 \] \delta: (6:1 rotamer ratio, * denotes minor rotamer peaks)

7.0–7.45 (m, 10H, aromatic), 4.36 (m, 1H, CHO\text{OH}), 4.15 (br, 1H, OH), 3.98* (m, 1H, CHO\text{OH}), 3.35* (m, 1H, NCHCH\text{3}), 2.99 (m, 1H, NCHCH\text{3}), 2.72* (s, 3H, NCH\text{3}), 2.53–2.67 (m, 3H, COCH, COCHCH\text{2Ph}), 2.12 (s, 3H, NCH\text{3}), 1.9 (m, 2H, PhCH\text{2CHCH\text{2}}), 1.1–1.4 (m, 4H, CH\text{3CH\text{2CH\text{2}}}), 0.87 (t, 3H, J = 7.0 Hz, CH\text{3CH\text{2}}), 0.77 (m, 3H, CH\text{3CHN}), 0.64* (d, 3H, J = 6.2 Hz, CH\text{3CHN}).

\[ ^1\text{C NMR (75 MHz, CDCl}_3 \] \delta: (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\textsuperscript{-1}): 3369 (br, m, OH), 1614 (s, C=O).

HRMS (FAB):

Calcd for C\text{23}H\text{29}NO (M-H\text{2}O\textsuperscript{*}): 335.2251.

Found: 335.2257.

Analysis:

Calcd for C\text{23}H\text{31}NO\textsubscript{2}: C, 78.15; H, 8.84; N, 3.96.

Found: C, 78.12; H, 9.08; N, 3.81.

TLC (80% EtOAc–hexanes), \textit{R}_f:

19: 0.60 (UV, PMA).

2: 0.38 (UV, PMA).

benzyl bromide: 0.76 (UV, PMA).
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 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$_6$D$_6$) $\delta$: (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$_3$CH$_2$CH), 2.78* (s, 3H, NCH$_3$), 2.48* (m, 1H, CH$_3$CH$_2$CH), 2.25 (m, 1H, one of CH$_3$CH$_2$), 2.12 (s, 3H, NCH$_3$), 1.90* (m, 2H, CH$_3$CH$_2$), 1.73 (m, 1H, one of CH$_3$CH$_2$), 0.98 (d, 3H, $J = 6.8$ Hz, CH$_3$CHN), 0.97* (m, 3H, CH$_3$CH$_2$), 0.82 (t, 3H, $J = 7.3$ Hz, CH$_3$CH$_2$), 0.30* (d, 3H, $J = 6.5$ Hz, CH$_3$CHN).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: (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).


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).
[1S(S),2S)]-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 analysis43 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$_3$) $\delta$: (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$_2$CH$_2$), 1.65 (m, 1H, one of PhCH$_2$CH$_2$), 1.21 (d, 3H, $J$ = 7.0 Hz, CH$_3$CHCO), 1.03 (d, 3H, $J$ = 6.8 Hz, CH$_3$CHN), 0.94* (d, 3H, $J$ = 6.8 Hz, CH$_3$CHN).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: (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).
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 \(-78\ \degree\ C\). The suspension was warmed briefly to 0 \degree\ C, then was cooled to \(-78\ \degree\ C\). 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 \(-78\ \degree\ C\) for 40 min, at 0 \degree\ C for 10 min, at 23 \degree\ C for 3 min, and finally was cooled to 0 \degree\ C, whereupon benzyl bromide (4.06 mL, 34.1 mmol, 1.80 equiv) was added. The mixture was stirred at 0 \degree\ 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 \degree\ C, 8 mL), and the solution was diluted with hot hexanes (69 \degree\ 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 \degree\ C.

Chiral capillary GC analysis of the corresponding trimethylsilyl ether, prepared as described above for amide 11, established that amide 22 was of \(\geq 99\%\) de.
1H NMR (300 MHz, CDCl₃) δ: (6:1 rotamer ratio, * denotes minor rotamer peaks)
7.0–7.4 (m, 10H, aromatic), 4.40–4.52 (m, 2H, CHOH, NCHCH₃), 4.15* (m, 1H, CHOH), 3.85* (m, 1H, NCHCH₃), 3.63 (m, 1H, CHOH), 2.86 (m, 2H, CHCH₂Ph), 2.76* (s, 2H, CH₂Ph), 2.74* (s, 3H, NCH₃), 2.66 (m, 1H, CHCH₂Ph), 2.49 (s, 3H, NCH₃), 2.01 (m, 1H, CH(CH₃)₂), 1.09 (d, 3H, J = 6.7, one of CH(CH₃)₂), 1.08* (d, 3H, J = 6.7 Hz, one of CH(CH₃)₂), 0.97 (d, 3H, J = 6.7 Hz, one of CH(CH₃)₂), 0.88* (d, 3H, J = 6.7 Hz, one of CH(CH₃)₂), 0.63 (d, 3H, J = 6.5 Hz, CH₃CHN).

13C NMR (75 MHz, CDCl₃) 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 C₂₂H₃₀N₂O₂ (MH)⁺: 340.2277.
Found: 340.2292.

Analysis:
Calcd for C₂₂H₂₉N₂O₂: C, 77.84; H, 8.61; N, 4.13; Found: C, 77.49; H, 8.81; N, 4.03.

TLC (60% EtOAc–hexanes), Rₜ:
22: 0.41 (UV, PMA).
5: 0.23 (UV, PMA).
benzyl bromide: 0.64 (UV, PMA).
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 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, CHOH, NCHCH$_3$), 3.9–4.1* (m, 2H, CHOH, NCHCH$_3$), 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$_3$CHN), 0.60 (d, 3H, J = 6.4 Hz, CH$_3$CHN).

$^{13}$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).
(1S(S),2S)-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 of the corresponding trimethylsilyl ether, prepared as described above for amide 11, established that amide 24 was of 98% de.
\(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \(\delta\): (2:1 rotamer ratio, * denotes minor rotamer peaks)
8.4–8.6 (m, 2H, two of C\(_5\)H\(_4\)N), 7.65 (m, 1H, one of C\(_5\)H\(_4\)N), 7.15–7.4 (m, 6H, one of C\(_5\)H\(_4\)N, phenyl), 5.70 (m, 1H, CH=CH\(_2\)), 5.00 (m, 2H, CH=CH\(_2\)), 4.6–4.8 (m, 2H, CHOH, NCHCH\(_3\)), 4.03 (m, 1H, COCH), 3.74* (t, 1H, \(J = 7.3\) Hz, COCH), 2.92 (s, 3H, NCH\(_3\)), 2.83 (m, 2H, CH\(_2\)CH=CH\(_2\)), 2.77 (s, 3H, NCH\(_3\)), 2.38* (m, 2H, CH\(_2\)CH=CH\(_2\)), 1.10 (d, 3H, \(J = 6.6\) Hz, CH\(_3\)), 0.60* (d, 3H, \(J = 6.7\) Hz, CH\(_3\)).

\(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)) \(\delta\): (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\(_2\)O\(_2\): MH\(^+\): 325.1916.
Found: 325.1918.

Analysis:
Calcd for C\(_{20}\)H\(_{24}\)N\(_2\)O\(_2\): C, 74.05; H, 7.46; N, 8.63.
Found: C, 73.91; H, 7.34; N, 8.58.

TLC (Et\(_3\)N-pretreated plate, 80% EtOAc–hexanes), \(R_f\): 24: 0.57 (UV, PMA).
9: 0.36 (UV, PMA).
allyl iodide: 0.09 (PMA).
(1R(R),2R)-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 analysis⁴³ 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$_3$) $\delta$: 
(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, CHO), 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$_3$CHN).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 
(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$_2$S (MH)$^+$: 304.1371.
Found: 304.1368.

TLC (80% EtOAc–hexanes), $R_f$: 25: 0.48 (UV, PMA).
8: 0.39 (UV, PMA).
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 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\(_3\)) \(\delta\): (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\(_3\)).

\(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): (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).
[1S(2R,4S),2S]-N-(2-Hydroxy-1-methyl-2-phenylethyl)-N,2,4-trimethylhexanamide

**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 of the corresponding trimethylsilyl ether, prepared as described above for amide 11, established that the ratio of the (2R,4S) diastereomer to the (2S,4S) diastereomer was 62:1.
\( ^1H \text{ NMR (300 MHz, } CD_{3}D_{6}) \delta: \) (5:1 rotamer ratio, * denotes minor rotamer peaks)

- 7.0–7.4 (m, 5H, aromatic)
- 4.55 (t, 1H, \( J = 7.3 \text{ Hz, } \text{CHOH} \))
- 4.13 (m, 1H, \( \text{NCH}_{2} \))
- 3.94* (m, 1H, \( \text{NCHCH}_{3} \))
- 2.99* (m, 1H, \( \text{COCH} \))
- 2.75* (s, 3H, \( \text{NCH}_{3} \))
- 2.35 (m, 1H, \( \text{COCH} \))
- 2.23 (s, 3H, \( \text{NCH}_{3} \))
- 1.98* (m, 1H, \( \text{CH}_{3}\text{CH}_{2} \))
- 1.50 (m, 3H, \( \text{COCHCH}_{2}, \text{CH}_{3}\text{CH}_{2} \))
- 0.90–1.04 (m, 6H, \( \text{COCHCH}_{3}, \text{CH}_{3}\text{CH}_{2}\text{CHCH}_{3} \))
- 0.74–0.82 (m, 6H, \( \text{CH}_{3}\text{CH}_{2}, \text{CH}_{3}\text{CHN} \))
- 0.62* (d, 3H, \( \text{CH}_{3}\text{CHN} \))

\( ^{13}C \text{ NMR (100 MHz, } CDCl_{3}) \delta: \) (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.

\( \text{FTIR (neat, cm}^{-1}\) \)

- 3385 (br, m, OH)
- 1618 (s, C=O)

\( \text{HRMS (EI)}: \)

Calcd for \( \text{C}_{18}\text{H}_{30}\text{NO}_{2} \) (MH\(^+\)): 292.2277.

Found: 292.2272.

\( \text{Analysis}: \)

Calcd for \( \text{C}_{18}\text{H}_{29}\text{NO}_{2} \): C, 74.18; H, 10.03; N, 4.81.

Found: C, 74.22; H, 9.75; N, 4.80.

\( \text{TLC (80\% } \text{EtOAc–hexanes), } R_{f}: \)

- 27: 0.50 (UV, PMA).
- 1: 0.33 (UV, PMA).
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 of the resulting acetate ester established that the ratio of the (2S,4S) diastereomer to the (2R,4S) diastereomer was 89:1.
$^{1}H\text{ NMR}\text{ (}400\text{ MHz, } C_{6}D_{6}\text{)} \delta$: 

(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$_3$CH$_2$CH), 1.62* (m, 1H, CH$_3$CH$_2$CH), 1.48* (m, 2H, CH$_3$CH$_2$CHCH$_2$), 1.28 (m, 2H, CH$_3$CH$_2$CHCH$_2$), 1.08* (d, 3H, $J = 9.2$ Hz, COCHCH$_3$), 1.04* (d, 3H, $J = 6.4$ Hz, CH$_3$CH$_2$CHCH$_3$), 1.01 (d, 3H, $J = 6.5$ Hz, COCHCH$_3$), 0.97 (d, 3H, $J = 7.1$ Hz, CH$_3$CH$_3$), 0.88 (t, 3H, $J = 7.2$ Hz, CH$_3$CH$_2$), 0.70 (d, 3H, $J = 6.8$ Hz, CH$_3$CH$_2$CHCH$_3$), 0.63* (d, 3H, $J = 6.4$ Hz, CH$_3$CH$_3$).

$^{13}C\text{ NMR}\text{ (}100\text{ MHz, } CDCl$_3\text{)} \delta$: 

(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$_{30}$N$_{2}$O (MH)$^+$: 292.2277. Found: 292.2268.

TLC (80% EtOAc–hexanes), $R_f$: 28: 0.50 (UV, PMA).

ent-1: 0.33 (UV, PMA).
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 (2R,4S) diastereomer to the (2S,4S) 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\(_3\)) \(\delta\): (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, \(J = 6.6\) Hz, CH\(_3\)CHN), 0.97* (d, 3H, \(J = 6.6\) Hz, CH\(_3\)CHN), 0.70 (d, 3H, \(J = 6.6\) Hz, H5).

\(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): (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\(_{31}\)N\(_2\)O: 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).
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 $-78 \degree C$. The suspension was warmed briefly to 0 $\degree C$, then was cooled to $-78 \degree C$. 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 $-78 \degree C$ for 40 min, at 0 $\degree C$ for 10 min, and at 23 $\degree C$ 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 $\degree C$ 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 ($3 \times 10$ 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 $(2R,4S)$ diastereomer to the $(2S,4S)$ 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.
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 x 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 analysis43 of the corresponding trimethylsilyl ether, prepared as described above for amide 11, established that the ratio of the (2S,4S) diastereomer to the (2R,4S) 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$_3$CHN), 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).
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 of the corresponding trimethylsilyl ether, prepared as described above for amide 11, established that the ratio of the (2R,4R,6S) diastereomer to the (2S,4R,6S) 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, CHOH), 4.46 (m, 1H, NCHCH$_3$), 4.02* (m, 1H, CHOH), 3.82* (m, 1H, NCHCH$_3$), 2.94* (m, 1H, H2), 2.81* (s, 3H, NCH$_3$), 2.73 (s, 3H, NCH$_3$), 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, CHNCH$_3$), 0.83 (d, 3H, J = 6.2 Hz, H8), 0.76 (d, 3H, J = 6.6 Hz, H5). 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.

$^{13}$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).
[1R(2S,4R,6S),2R]-N-(2-Hydroxy-1-methyl-2-phenylethyl)-N,2,4,6-tetramethylbenzeneheptanamide 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 of the corresponding trimethylsilyl ether, prepared as described above for amide 11, established that the ratio of the (2S,4R,6S) diastereomer to the (2R,4R,6S) 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, CHOH), 4.47 (m, 1H, NCHCH$_3$),
4.03* (m, 1H, CHOH), 3.62* (m, 1H, NCHCH$_3$),
2.94* (s, 3H, NCH$_2$), 2.85 (s, 3H, NCH$_3$), 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).
[1S(2R,4S,6S),2S]-N-(2-Hydroxy-1-methyl-2-phenylethyl)-N,2,4,6-tetramethylbenzeneheptanamide 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 of the corresponding trimethylsilyl ether, prepared as described above for amide 11, established that the ratio of the (2R,4S,6S) diastereomer to the (2S,4S,6S) 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$_3$CHN, H8),  
0.98* (d, 3H, J = 6.6 Hz, H1), 0.82* (m, 6H,  
CH$_3$CHN, 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*,  

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).
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\(^\text{43}\) 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$_3$) $\delta$: (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, NCH$_2$CH$_3$), 4.09* (m, 1H, NCH$_2$CH$_3$), 3.01* (m, 1H, H2), 2.90* (s, 3H, NCH$_3$), 2.84 (s, 3H, NCH$_3$), 2.69 (sx, 1H, $J_1 = 6.6$ 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$_3$CHN).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: (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).
[(RS)-α-Hydroxy-N-(2-hydroxy-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 1H NMR spectroscopy (300 MHz, C6D6) established that amide 35 was of 82% de.
$^1$H NMR (300 MHz, $C_6D_6$) $\delta$: 7.0–7.6 (m, 10 H, aromatic), 4.65 (br, s, 2H, OH), 4.55 (m, 1H, NCH$_2$), 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$_2$), 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$_{24}$N$_2$O$_3$ (MH)$^+$: 314.1756.

Found: 314.1761.

TLC (10% MeOH–CH$_2$Cl$_2$), $R_f$: 35: 0.41 (UV, PMA).

10: 0.31 (UV, PMA).
(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\(_3\)) \(\delta\):  
(4:1 rotamer ratio, * denotes minor rotamer peaks)
7.2–7.4 (m, 5H, aromatic), 6.85–7.00 (m, 1H, CH\(_3\)CH=CH), 6.37* (d, 1H, \(J = 15.1\) Hz, CH\(_3\)CH=CH), 6.20 (d, 1H, \(J = 14.4\) Hz, CH\(_3\)CH=CH), 4.59 (d, 1H, \(J = 8.2\) Hz, CHO\(_\text{OH}\)), 4.47 (m, 1H, NCH\(_2\)CH\(_3\)), 4.15 (br, 1H, OH), 2.94* (s, 3H, NCH\(_3\)), 2.87 (s, 3H, NCH\(_3\)), 1.89 (dd, 3H, \(J_1 = 6.8\) Hz, \(J_2 = 1.5\) Hz, CH\(_3\)CH=CH), 1.10 (d, 3H, \(J = 6.9\) Hz, CH\(_3\)CHN), 0.98* (d, 3H, \(J = 6.8\) Hz, CH\(_3\)CHN).

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\(_2\)Cl\(_2\)), \(R_f\):
36: 0.57 (UV, PMA).

pseudoephedrine: 0.05 (UV, PMA).
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%). ¹H NMR analysis (300 MHz, C₆D₆) and chiral capillary GC analysis 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, CH=CH$_2$), 5.04 (m, 2H, CH=CH$_2$), 4.55 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 6.7$ Hz, CHO), 4.45 (dd, 1H, $J_1 = 8.6$ Hz, $J_2 = 2.5$ Hz, CHO), 4.38 (br, 1H, NCHCH$_3$), 3.76* (m, 1H, CHCH$_2$Ph), 3.48 (m, 1H, CHCH$_2$Ph), 3.17 (m, 2H, one of PhCH$_2$), 2.87* (s, 3H, NCH$_3$), 2.80 (m, 2H, one of PhCH$_2$), 2.69 (s, 3H, NCH$_3$), 0.99 (d, 3H, $J = 6.9$ Hz, CH$_3$), 0.93* (d, 3H, $J = 6.8$ Hz, CH$_3$).

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.


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 $-78 \, ^\circ\mathrm{C}$. The solution was warmed briefly to 0 °C, then was cooled to $-78 \, ^\circ\mathrm{C}$. An ice-cooled solution of amide I (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 $-78 \, ^\circ\mathrm{C}$ 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-$d_8$) $\delta$: (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 (observed by THF-$d_8$, m, 0.5H, CHNCH$_3$ 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, CHNCH$_3$ of Y), 2.82 (residual HN[CH(CH$_3$)$_2$]), 2.52 (s, 1.5H, NCH$_3$ of X), 1.82 (s, 1.5H, NCH$_3$ of Y), 1.73 (observed by THF-$d_8$, 1.5H, CH$_3$CHN of Y), 1.43 (d, 1.5H, $J = 6.3$ Hz, CH$_3$=C=OLi of X), 1.28 (d, 1.5H, $J = 6.4$ Hz, CH$_3$=C=OLi of Y), 0.93 (residual HN[CH(CH$_3$)$_2$]), 0.60 (d, 1.5H, $J = 7.2$ Hz, CH$_3$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 of high enantiomeric excess (ee). 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 were developed in conjunction with a protocol for the acid-promoted hydrolysis of pseudoephedrine amides (vide infra). The procedure was optimized for the highly epimerizable phenylacetamide substrate 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

<table>
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<tr>
<th>entry</th>
<th>substrate&lt;sup&gt;a&lt;/sup&gt;</th>
<th>product</th>
<th>isol yield (%)</th>
<th>isol ee or de (%)</th>
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<td>84</td>
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</tbody>
</table>

<sup>a</sup> 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-

![Chemical structure of 15 and 39](image)

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% ee⁴⁴ 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 $\beta$-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\textsuperscript{11b,c} to the corresponding carboxylic acid can generally be effected in excellent chemical yield.\textsuperscript{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

![Chemical Structures](image)

**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-benzylxoymethyl-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
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 $N$-$n$-tert-butylxycarbonyl ($N$-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
pseudoephedrine amide substrate in THF was stirred in a 1:1 mixture of 18 N H₂SO₄ 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-benzzyloxymethyl-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). 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 H₂SO₄ in dioxane afforded acid 39 in 97% ee, n-Bu₄NOH 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,
and saponification) has been subsequently modified so that it can be carried out as a one-pot procedure.
**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). \(^1\)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 (\(\delta\) scale) downfield from tetramethylsilane. \(^1\)H NMR chemical shifts are referenced to the signal for residual hydrogen in the NMR solvent (CHCl\(_3\): \(\delta\) 7.26, C\(_6\)H\(_5\)D\(_2\): \(\delta\) 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\(_3\): \(\delta\) 77.0, C\(_6\)D\(_6\): \(\delta\) 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 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 1H and 13C NMR spectroscopic data.
$^{1}$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.25 (m, 5H, aromatic), 3.09 (dd, 1H, $J_1 = 13.1$ Hz, $J_2 = 6.1$ Hz, one of PhCH$_2$), 2.75 (m, 2H, one of PhCH$_2$, CH$_3$CH), 1.18 (d, 3H, $J = 6.8$ Hz, CH$_3$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 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$_2$Cl$_2$), $R_f$: 39: 0.29–0.51 streak (UV, PMA). 11: 0.65 (UV, PMA).
(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, 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 1H and 13C NMR spectroscopic data.
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 2.44 (sx, 1H, $J = 6.9$ Hz, COCH), 1.70 (m, 1H, one of COCHCH$_2$), 1.45 (m, 1H, one of COCHCH$_2$), 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$_3$) $\delta$: 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).
(R)-3-Benzylxyo-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, 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 ¹H and ¹³C NMR spectroscopic data.
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 8.8–9.2 (br, 1H, HOOC), 7.25–7.37 (m, 5H, aromatic), 4.55 (s, 2H, PhCH$_2$), 3.66 (dd, 1H, $J_1 = 9.1$ Hz, $J_2 = 7.4$ Hz, one of CH$_3$CHCH$_2$), 3.54 (dd, 1H, $J_1 = 9.1$ Hz, $J_2 = 5.6$ Hz, one of CH$_3$CHCH$_2$), 2.77–2.84 (m, 1H, CH$_3$CH), 1.22 (d, 3H, $J = 7.1$ Hz, CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 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$_2$Cl$_2$), $R_f$: 41: 0.07–0.33 streak (UV, PMA).
13: 0.38 (UV, PMA).

benzyl alcohol: 0.64 (UV, PMA).
(R)-3-Benzyl oxy-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 x 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 x 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, 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 1H and 13C NMR spectroscopic data.

TLC (7.5% MeOH–CH₂Cl₂), Rf: 53: 0.07–0.33 streak (UV, PMA).
N → O acyl transfer: 0.13–0.26 streak (UV, PMA).
14: 0.38 (UV, PMA).
**5 equiv n-Bu₄NOH**

1:4 t-BuOH : H₂O, reflux

91%

[(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, 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 ¹H and ¹³C NMR spectroscopic data. Spectroscopic data were identical to those of its enantiomer, (R)-α-methyl benzenepropionic acid (39).

TLC (7.5% MeOH–CH₂Cl₂), Rf: 42: 0.24–0.60 streak (UV, PMA).
16: 0.67 (UV, PMA).
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, 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 1H and 13C 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$_3$CH$_2$CH$_2$), 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$_2$Cl$_2$), $R_f$: 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 1H and 13C NMR spectroscopic data. Spectroscopic data were identical to those of its enantiomer, (R)-2-methylhexanoic acid (40).

TLC (80% EtOAc–hexanes), Rf: 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, 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 1H and 13C NMR spectroscopic data. Spectroscopic data were identical to those of its enantiomer, (S)-α-butyl benzenepropionic acid (43).

TLC (7.5% MeOH−CH2Cl2), \( R_f \): 45: 0.58 (UV, PMA).
19: 0.75 (UV, PMA).
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 1H and 13C NMR spectroscopic data.
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.25 (m, 5H, aromatic), 3.41 (t, 1H, $J = 7.7$ Hz, PhCH), 2.05 (m, 1H, one of CH$_3$CH$_2$), 1.76 (m, 1H, one of CH$_3$CH$_2$), 0.86 (t, 3H, $J = 7.4$ Hz, CH$_3$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 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$_2$Cl$_2$), $R_f$: 46: 0.24–0.45 streak (UV, PMA). 20: 0.75 (UV, PMA).
(2R,4S)-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 1H NMR spectrum with that of acid 48. The purity of acid 47 was estimated to be ≥95% by 1H and 13C 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 (Cl): Calcd for C$_8$H$_{15}$O$_2$Na$_2$ (MNa$_2$-H)$^+$: 189.0867. Found: 189.0869.

TLC (10% MeOH–CH$_2$Cl$_2$), $R_f$: 47: 0.44 (PMA).

27: 0.57 (UV, PMA).
(2R,4S)-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.
(2S,4S)-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 (Cl): Calcd for C$_8$H$_{15}$O$_2$N$_2$ (M$^+$): 189.0867. Found: 189.0871.

TLC (10% MeOH–CH$_2$Cl$_2$), $R_f$: 48: 0.57 (PMA). 28: 0.72 (UV, PMA).
(2S,4S)-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.
(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 ¹H NMR analysis (400 MHz, CDCl₃) of the corresponding bis-Mosher esters 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$_3$OD) $\delta$: 5.03 (br, 1H, HOOC), 2.82 (m, 1H, CH$_3$CH), 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$_3$CH).

$^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$: 179.2, 175.6, 38.5, 37.0, 17.4.

HRMS (EI):
Calcd for C$_5$H$_9$O$_4$ (MH)$^+$: 133.0501.
Found: 133.0504.

Analysis:
Calcd for C$_5$H$_9$O$_4$: 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 sensitive to the reaction medium and the nature of the counterion “M.” Typical metal hydride reagents such as lithium aluminum hydride and diborane 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 (LiBHEt₃, “superhydride”) and 9-BBN, developed by Brown and co-workers, and metal amide-borane complexes, introduced by Hutchins et al. and extensively developed by Singaram and co-workers.

\[ R\text{--N}\text{--R'} \quad \xrightarrow{M-H} \quad [\text{tetrahedral intermediate}] \quad \xrightarrow{CN\text{ bond cleavage}} \quad R\text{--OH} \quad \xrightarrow{CO\text{ bond cleavage}} \quad R\text{--NR'}\text{--R'} \]

Figure 7. Divergent pathways for tertiary amide reductions.
Table 7. Reduction with Borane-Lithium Pyrrolidide (LPT) to Form Primary Alcohols

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<td>3</td>
<td>13</td>
<td>CH₃</td>
<td>BOM</td>
<td>52</td>
<td>0</td>
<td>3.0</td>
<td>45</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>Bn</td>
<td>CH₃</td>
<td>53</td>
<td>23</td>
<td>10.3</td>
<td>87</td>
<td>≥95</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>Bn</td>
<td>n-Bu</td>
<td>54</td>
<td>23</td>
<td>3.1</td>
<td>88</td>
<td>≥95</td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>n-Bu</td>
<td>Bn</td>
<td>55</td>
<td>23</td>
<td>5.8</td>
<td>89</td>
<td>≥95</td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>Ph</td>
<td>Et</td>
<td>56</td>
<td>23</td>
<td>14.0</td>
<td>87</td>
<td>33b</td>
</tr>
<tr>
<td>8</td>
<td>22</td>
<td>i-Pr</td>
<td>Bn</td>
<td>57</td>
<td>66</td>
<td>11.0</td>
<td>80</td>
<td>≥95</td>
</tr>
<tr>
<td>9</td>
<td>23</td>
<td>t-Bu</td>
<td>Bn</td>
<td>58</td>
<td>66</td>
<td>12.0</td>
<td>5</td>
<td>-</td>
</tr>
</tbody>
</table>
```

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. 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, the lithium pyrrolidide-borane reagent (lithium pyrroloididotrihydroborate, Li(CH₂)₄NBH₃, LPT) of Singaram et al. 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 \(\alpha\)-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\(_2\)NBH\(_3\), 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 \(\degree\)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 \(-78\) \(\degree\)C or, preferably, could be completely avoided by deprotonation with LDA at 0 \(\degree\)C followed by warming to 23 \(\degree\)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 \(\degree\)C, and the resulting suspension is warmed to 23 \(\degree\)C and is held at that temperature for 15–20 min. The cloudy suspension of LAB is then cooled to 0 \(\degree\)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 \(\degree\)C, although more hindered substrates (entry 6, Table 8) may require heating to reflux (66 \(\degree\)C). When the reduction is complete, an acidic
Table 8. Reduction of Pseudoephedrine Amides with Lithium Amidotrihydroborate (LAB) to Form Primary Alcohols

\[
\begin{align*}
\text{entry} & \quad \text{substrate} & \quad \text{product} & \quad \text{temp} & \quad \text{time} & \quad \text{isol} & \quad \text{isol} \\
1 & \quad X_4+ \quad \begin{array}{c} \text{O} \\ \text{CH}_3
\end{array} & \quad \begin{array}{c} \text{O} \\ \text{CH}_2\text{C}_6\text{H}_5
\end{array} \\ & \quad \text{11 (≥99% de)} & \quad \begin{array}{c} \text{OH} \\ \text{CH}_3
\end{array} & \quad \begin{array}{c} \text{O} \\ \text{CH}_2\text{C}_6\text{H}_5
\end{array} \\ & \quad \text{50} & \quad 23 & \quad 1.0 & \quad 90 & \geq 99 \\
2 & \quad X_4+ \quad \begin{array}{c} \text{O} \\ \text{CH}_3
\end{array} & \quad \begin{array}{c} \text{O} \\ \text{CH}_2\text{OCH}_2\text{C}_6\text{H}_5
\end{array} \\ & \quad \text{13 (98% de)} & \quad \begin{array}{c} \text{OH} \\ \text{CH}_3
\end{array} & \quad \begin{array}{c} \text{O} \\ \text{CH}_2\text{OCH}_2\text{C}_6\text{H}_5
\end{array} \\ & \quad \text{52} & \quad 0 & \quad 1.3 & \quad 86 & \quad 95 \\
3 & \quad X_4+ \quad \begin{array}{c} \text{O} \\ \text{CH}_3
\end{array} & \quad \begin{array}{c} \text{O} \\ \text{CH}_2\text{C}_6\text{H}_5
\end{array} \\ & \quad \text{19 (≥99% de)} & \quad \begin{array}{c} \text{OH} \\ \text{CH}_3
\end{array} & \quad \begin{array}{c} \text{O} \\ \text{CH}_2\text{C}_6\text{H}_5
\end{array} \\ & \quad \text{55} & \quad 23 & \quad 2.5 & \quad 92 & \geq 95 \\
4 & \quad X_4+ \quad \begin{array}{c} \text{O} \\ \text{CH}_3
\end{array} & \quad \begin{array}{c} \text{O} \\ \text{CH}_2\text{CH}_3
\end{array} \\ & \quad \text{20 (≥99% de)} & \quad \begin{array}{c} \text{OH} \\ \text{CH}_3
\end{array} & \quad \begin{array}{c} \text{O} \\ \text{CH}_2\text{CH}_3
\end{array} \\ & \quad \text{56} & \quad 23 & \quad 1.9 & \quad 83 & \quad 92 \\
5 & \quad X_4+ \quad \begin{array}{c} \text{O} \\ \text{CH}_3
\end{array} & \quad \begin{array}{c} \text{O} \\ \text{CH}_2\text{C}_6\text{H}_5
\end{array} \\ & \quad \text{22 (≥99% de)} & \quad \begin{array}{c} \text{OH} \\ \text{CH}_3
\end{array} & \quad \begin{array}{c} \text{O} \\ \text{CH}_2\text{C}_6\text{H}_5
\end{array} \\ & \quad \text{57} & \quad 23 & \quad 18 & \quad 86 & \geq 95 \\
6 & \quad X_4+ \quad \begin{array}{c} \text{O} \\ \text{CH}_3
\end{array} & \quad \begin{array}{c} \text{O} \\ \text{CH}_2\text{C}_6\text{H}_5
\end{array} \\ & \quad \text{23 (≥99% de)} & \quad \begin{array}{c} \text{OH} \\ \text{CH}_3
\end{array} & \quad \begin{array}{c} \text{O} \\ \text{CH}_2\text{C}_6\text{H}_5
\end{array} \\ & \quad \text{58} & \quad 66 & \quad 10 & \quad 92 & \geq 95 \\
7 & \quad X_4+ \quad \begin{array}{c} \text{O} \\ \text{CH}_3
\end{array} & \quad \begin{array}{c} \text{O} \\ \text{CH}_3
\end{array} \\ & \quad \text{27 (97% de)} & \quad \begin{array}{c} \text{OH} \\ \text{CH}_3
\end{array} & \quad \begin{array}{c} \text{O} \\ \text{CH}_3
\end{array} \\ & \quad \text{59} & \quad 23 & \quad 2 & \quad 78^a & \quad 97 \\
8 & \quad X_4+ \quad \begin{array}{c} \text{O} \\ \text{CH}_3
\end{array} & \quad \begin{array}{c} \text{O} \\ \text{CH}_3
\end{array} \\ & \quad \text{28 (98% de)} & \quad \begin{array}{c} \text{OH} \\ \text{CH}_3
\end{array} & \quad \begin{array}{c} \text{O} \\ \text{CH}_3
\end{array} \\ & \quad \text{60} & \quad 23 & \quad 2 & \quad 79^a & \quad 98
\end{align*}
\]
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

\*The yield was lowered due to the volatility of the product.
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. 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-benzylxoxymethyl-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

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>isol yield alcohol (%)</th>
<th>isol yield 3° amine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\text{CH}_3(\text{CH}<em>2)</em>{10}\text{CONEt}_2$</td>
<td>23</td>
<td>1.3</td>
<td>94</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="amide structure" /></td>
<td>23</td>
<td>16.0</td>
<td>87</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>$\text{CH}_3(\text{CH}<em>2)</em>{10}\text{CON(Pr)}_2$</td>
<td>23</td>
<td>6.0</td>
<td>68</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="amide structure" /></td>
<td>66</td>
<td>1.7</td>
<td>47</td>
<td>51</td>
</tr>
</tbody>
</table>

investigate whether LAB was a superior reagent for the reduction of tertiary amides in general (Table 9).\textsuperscript{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.\textsuperscript{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).\textsuperscript{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. 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. 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.

\[ \text{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.} \]

\( ^{11} \text{B NMR Studies of LAB} \)

To our knowledge, though LAB has been the subject of two computational studies, 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 \( ^1 \text{H} \)-decoupled \( ^{11} \text{B} \) NMR spectroscopy, where a sharp singlet resonating at -22 ppm (\( \text{BF}_3 \cdot \text{OEt}_2 \) reference) is observed. This value corresponds well with known amide-borane complexes (but not, e.g., with \( \text{LiBuBH}_3 \), which resonates at -29 ppm). 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 \( ^{11} \text{B} \) NMR spectrum and neopentane was formed cleanly (\( ^{13} \text{C} \) 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: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 $N \to O$ acyl transfer under acidic conditions was also investigated as an intermediate in a procedure to form highly enantiomerically enriched primary alcohols. Using the $\alpha$-benzyloxyethyl-substituted amide 13 as a model substrate, attempts to reduce its corresponding $N \to O$ 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 $O \to N$ acyl transfer or the tetrahedral intermediate that would lead to $O \to N$ 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.
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
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.
**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). \(^1\)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 (\(\delta\) scale) downfield from tetramethylsilane. \(^1\)H NMR chemical shifts are referenced to the signal for residual hydrogen in the NMR solvent (CHCl\(_3\): \(\delta\) 7.26, C\(_6\)H\(_5\): \(\delta\) 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$_3$: $\delta$ 77.0, C$_6$D$_6$: $\delta$ 128.0). $^{11}$B spectra were recorded at 128 MHz and the chemical shifts are expressed in parts per million ($\delta$ 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 of alcohol 50 established that alcohol 50 was of ≥99% ee.
\(^1\)H NMR (300 MHz, C\(_6\)D\(_6\)) \(\delta\): 7.0–7.2 (m, 5H, aromatic), 3.15 (m, 2H, HOCH\(_2\)), 2.62 (dd, 1H, \(J_1 = 13.3\) Hz, \(J_2 = 6.2\) Hz, one of PhCH\(_2\)), 2.22 (dd, 1H, \(J_1 = 13.3\) Hz, \(J_2 = 8.0\) Hz, one of PhCH\(_2\)), 1.70 (m, 1H, CH\(_3\)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\(_3\)) \(\delta\): 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).
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 x 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 ¹H NMR analysis (300 MHz, C₆D₆) of the resulting Mosher ester derivative⁵³ 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 C₁₀H₁₄O (M⁺): 150.1045.
Found: 150.1047.

TLC (60% EtOAc–hexanes), Rf: 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$_6$D$_6$) of the corresponding Mosher ester derivative,$^8$ prepared as described above for alcohol 50, established that alcohol 51 was of ≥95% ee.

$^1$H NMR (300 MHz, C$_6$D$_6$) δ: 3.19 (m, 2H, HOCH$_2$), 0.92–1.44 (m, 7H, CH$_3$CH$_2$CH$_2$CH$_2$CH), 0.87 (t, 3H, $J = 6.9$ Hz, CH$_3$CH$_2$), 0.83 (d, 3H, $J = 6.6$ Hz, CH$_3$CH), 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$_7$H$_{14}$ (M–H$_2$O)$^+$: 98.1096.

TLC (60% ether–pet ether), $R_f$: 51: 0.43 (PMA).

12: 0.32 (UV, PMA).
(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 1H NMR analysis (400 MHz, CDCl₃) of the corresponding Mosher ester derivative, prepared as described above for alcohol 50, established that alcohol 52 was of 95% ee.
$^1$H NMR (300 MHz, C$_6$D$_6$) $\delta$: 7.0–7.25 (m, 5H, aromatic), 4.21 (s, 2H, PhCH$_2$), 3.46 (d, 2H, $J = 8.9$ Hz, CH$_3$CHCH$_2$O), 3.20 (m, 2H, HOCH$_2$), 1.86 (m, 1H, CH$_3$CH), 0.73 (d, 3H, $J = 6.9$ Hz, CH$_3$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 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, 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).
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,$^5$ 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$_2$Cl$_2$), $R_f$: 52: 0.58 (UV, PMA).

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

13: 0.38 (UV, PMA).
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$_6$D$_6$) of the corresponding Mosher ester derivative, prepared as described above for alcohol 50, established that alcohol 53 was of $\geq$95% ee. Spectroscopic data of alcohol 53 were identical to those of its enantiomer, (R)-$\beta$-methyl benzene propanol (50).

HRMS (FAB): Calcd for C$_{10}$H$_{14}$O (M$^+$): 150.1045.

TLC (50% EtOAc–hexanes), $R_r$: 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 ¹H NMR analysis (300 MHz, CDCl₃) of the corresponding Mosher ester derivative,⁵⁸ prepared as described above for alcohol 50, established that alcohol 54 was of ≥95% ee.
\(^1\text{H NMR (300 MHz, C}_{6}\text{D}_{6}) \delta:\) 7.0–7.3 (m, 5H, aromatic), 3.25 (d, 2H, \(J = 5.1\) Hz, \(\text{HOCH}_2\)), 2.59 (dd, 1H, \(J = 13.5\) Hz, 7.6 Hz, one of \(\text{PhCH}_2\)), 2.48 (dd, 1H, \(J = 13.5\) Hz, 6.5 Hz, one of \(\text{PhCH}_2\)), 1.60 (m, 1H, one of \(\text{HOCH}_2\text{CHCH}_2\)), 1.31 (m, 1H, one of \(\text{HOCH}_2\text{CHCH}_2\)), 1.20 (m, 4H, \(\text{CH}_3\text{CH}_2\text{CH}_2\)), 0.84 (m, 3H, \(\text{CH}_3\)).

\(^{13}\text{C NMR (75 MHz, CDCl}_3) \delta:\) 140.8, 129.1, 128.1, 125.7, 64.6, 42.4, 37.5, 30.3, 29.0, 22.9, 14.0.

\(\text{FTIR (neat, cm}^{-1}\)): 3342 (br, m, \(\text{OH}\)).

\(\text{HRMS (FAB)}:\) Calcd for \(\text{C}_{13}\text{H}_{20}\text{O} (\text{M}^+: 192.1515).\)

\(\text{Found: 192.1508.}\)

\(\text{TLC (40\% EtOAc–hexanes), } R_f:\) 54: 0.47 (UV, PMA).

17: 0.22 (UV, PMA).
(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 \times 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, CDCl₃) 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 1H NMR analysis (300 MHz, CDCl3) 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).

Found: 192.1508.

TLC (50% EtOAc–hexanes), Rf: 55: 0.55 (UV, PMA).
19: 0.38 (UV, PMA).
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 1H NMR analysis, establishing that alcohol 56 was of 92% ee. 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 1H NMR analysis (400 MHz, C6D6). 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$_6$D$_6$) $\delta$: 7.0–7.2 (m, 5H, aromatic), 3.48 (m, 2H, HOCH$_2$), 2.44 (m, 1H, PhCH), 1.62 (m, 1H, one of CH$_3$CH$_2$), 1.41 (m, 1H, one of CH$_3$CH$_2$), 0.91 (t, 1H, OH), 0.72 (t, 3H, $J = 7.4$ Hz, CH$_3$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 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).
(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 ¹H NMR analysis (400 MHz, C₆D₆) 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:  
56: 0.52 (UV, PMA).
20: 0.33 (UV, PMA).
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 1H NMR analysis (400 MHz, CDCl3) of the corresponding Mosher ester derivative, prepared as described above for alcohol 50, established that alcohol 57 was of ≥95% ee.
\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 7.1–7.4 (m, 5H, aromatic), 3.55 (d, 3H, \(J = 5.6\) Hz, HOCH\(_2\)), 2.71 (dd, \(J = 13.7, 5.5\) Hz, one of PhCH\(_2\)), 2.51 (dd, 1H, \(J = 13.7, 9.1\) Hz, one of PhCH\(_2\)), 1.86 (m, 1H, HOCH\(_2\)CH), 1.67 (m, 1H, CH(CH\(_3\))\(_2\)), 0.98 (d, 3H, \(J = 5.6\) Hz, CH\(_3\)), 0.96 (d, 3H, \(J = 5.6\) Hz, CH\(_3\)).

\(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 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).
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).
(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 1H NMR analysis (400 MHz, CDCl3) of the corresponding Mosher ester derivative, prepared as described above for alcohol 50, established that alcohol 58 was of ≥95% ee.
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 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$_2$CH), 1.02 (s, 9H, C(CH$_3$)$_3$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 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).
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).
(2R,4S)-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 of the resulting acetate ester established that alcohol 59 was of 97% de.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 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$_3$) $\delta$: 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$_8$H$_{16}$ (M-H$_2$O)$^+$; 112.1252. Found: 112.1251.

TLC (50% EtOAc–hexanes), $R_f$:

59: 0.54 (PMA).

27: 0.41 (UV, PMA).
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 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$_3$) $\delta$: 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).


$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 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).
(2R,4S)-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 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$_3$): 7.1-7.4 (m, 5H, aromatic), 3.52 (dd, 1H, $J_1 = 10.5$ Hz, $J_2 = 5.1$ Hz, one of HOCH$_2$), 3.38 (dd, 1H, $J_1 = 10.5$ Hz, $J_2 = 6.6$ Hz, one of HOCH$_2$), 2.68 (dd, 1H, $J_1 = 13.3$ Hz, $J_2 = 5.4$ Hz, one of PhCH$_2$), 2.28 (dd, 1H, $J_1 = 13.3$ Hz, $J_2 = 8.6$ Hz, one of PhCH$_2$), 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$_3$): 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).
(2S,4S)-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 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$_6$D$_{12}$) δ: 7.0–7.2 (m, 5H, aromatic), 3.13 (m, 2H, HOCH$_2$), 2.48 (dd, 1H, $J_1 = 13.2$ Hz, $J_2 = 6.1$ Hz, one of PhCH$_2$), 2.27 (dd, 1H, $J_1 = 13.2$ Hz, $J_2 = 7.9$ Hz, one of PhCH$_2$), 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).
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 of the corresponding acetate ester, prepared as described above for alcohol 59, established that alcohol 63 was of 99% de.
\[^{1}\text{H NMR (400 MHz, CDCl}_3\text{) } \delta: \]
7.1–7.4 (m, 5H, aromatic), 3.52 (dd, 1H, \(J_1 = 10.5\) Hz, \(J_2 = 5.1\) Hz, one of HOCH\(_2\)), 3.37 (dd, 1H, \(J_1 = 10.5\) Hz, \(J_2 = 6.6\) Hz, one of HOCH\(_2\)), 2.70 (dd, 1H, \(J_1 = 13.2\) Hz, \(J_2 = 5.1\) Hz, one of PhCH\(_2\)), 2.23 (dd, 1H, \(J_1 = 13.2\) Hz, \(J_2 = 8.8\) Hz, one of PhCH\(_2\)), 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).

\[^{13}\text{C NMR (100 MHz, CDCl}_3\text{) } \delta: \]
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.

\text{FTIR (neat, cm\(^{-1}\):) } 3331 (br, m, OH).

\text{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.

\text{TLC (40\% EtOAc–hexanes), } \(R_f\): 63: 0.55 (UV, PMA).
31: 0.33 (UV, PMA).

tertiary amine by-product: 0.46 (UV, PMA).
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 of the corresponding acetate ester, prepared as described above for alcohol 59, established that alcohol 64 was of 97% de.

(2S,4R,6S)-2,4,6-Trimethyl-7-phenylheptanol 64
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.1–7.4 (m, 5H, aromatic), 3.43 (dd, 1H, $J_1 = 10.5$ Hz, $J_2 = 5.9$ Hz, one of HOCH$_2$), 3.37 (dd, 1H, $J_1 = 10.5$ Hz, $J_2 = 6.6$ Hz, one of HOCH$_2$); 2.65 (dd, 1H, $J_1 = 13.2$ Hz, $J_2 = 5.5$ Hz, one of PhCH$_2$), 2.28 (dd, 1H, $J_1 = 13.2$ Hz, $J_2 = 8.8$ Hz, one of PhCH$_2$), 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$_3$) $\delta$: 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).
(2R, 4S, 6S)-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 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$_3$) $\delta$: 7.1–7.4 (m, 5H, aromatic), 3.48 (dd, 1H, $J_1 = 12.0$ Hz, $J_2 = 6.2$ Hz, one of HOCH$_2$), 3.42 (dd, 1H, $J_1 = 12.0$ Hz, $J_2 = 6.6$ Hz, one of HOCH$_2$), 2.59 (dd, 1H, $J_1 = 13.4$ Hz, $J_2 = 6.2$ Hz, one of PhCH$_2$), 2.36 (dd, 1H, $J_1 = 13.4$ Hz, $J_2 = 8.1$ Hz, one of PhCH$_2$), 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$_3$) $\delta$: 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).
(2S,4S,6S)-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 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$_3$) $\delta$: 7.1–7.4 (m, 5H, aromatic), 3.51 (dd, 1H, $J_1 = 11.7$ Hz, $J_2 = 5.1$ Hz, one of HOCH$_2$), 3.38 (dd, 1H, $J_1 = 11.7$ Hz, $J_2 = 7.0$ Hz, one of HOCH$_2$), 2.56 (dd, 1H, $J_1 = 13.2$ Hz, $J_2 = 6.2$ Hz, one of PhCH$_2$), 2.39 (dd, 1H, $J_1 = 13.2$ Hz, $J_2 = 8.1$ Hz, one of PhCH$_2$), 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$_3$) $\delta$: 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, CD$_2$Cl$_2$) $\delta$: 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$_3$CH), 0.72 (d, 3H, $J = 6.8$ Hz, CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 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).
(2R,4S)-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\(_3\)) \(\delta\): 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\(_2\)CH), 1.54 (m, 1H, PhCH\(_2\)CH), 1.37 (m, 1H, one of PhCH\(_2\)CHCH\(_3\)), 1.10 (m, 1H, one of PhCH\(_2\)CHCH\(_3\)), 0.99 (d, 3H, \(J = 6.5\) Hz, ICH\(_2\)CHCH\(_3\)), 0.85 (d, 3H, \(J = 6.6\) Hz, PhCH\(_2\)CHCH\(_3\)).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 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).
(2S,4S)-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$_2$I), 3.12 (dd, 1H, $J_1 = 9.5$ Hz, $J_2 = 6.2$ Hz, one of CH$_2$I), 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$_2$CH), 1.62 (m, 1H, PhCH$_2$CH), 1.20–1.27 (m, 2H, PhCH$_2$CHCH$_2$), 0.93 (d, 3H, $J = 6.5$ Hz, ICH$_2$CHCH$_3$), 0.84 (d, 3H, $J = 6.6$ Hz, PhCH$_2$CHCH$_3$).

$^{13}$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).


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).
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%).

\[ \text{CH}_3(\text{CH}_2)_{10}\text{COCl} \xrightarrow{\text{Et}_2\text{NH}} \text{CH}_3(\text{CH}_2)_{10}\text{CONEt}_2 \]

\[ \text{CH}_2\text{Cl}_2, 23 \degree \text{C} \]

98%

\[ \text{N,N-Diethyldodecanamide 70} \]

1H NMR (300 MHz, CDCl₃) δ: 3.27–3.41 (m, 4H, NCH₂CH₃), 2.28 (t, 2H, J = 7.7 Hz, CH₂CO), 1.26–1.84 [m, 18H, (CH₂)₉CH₂CO], 1.17 (t, 3H, J = 7.1 Hz, one of NCH₂CH₃), 1.11 (t, 3H, J = 7.1 Hz, one of NCH₂CH₃), 0.88 [t, 3H, J = 6.6 Hz, CH₃(CH₂)₉].

FTIR (neat, cm⁻¹): 2924 (s), 2853 (m), 1644 (s, C=O), 1462 (m), 1427 (m).


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%).

**1H NMR (300 MHz, CDCl₃):**
- 3.97 (sp, 1H, J = 6.7 Hz, one of NCH), 3.47 (br, 1H, one of NCH), 2.27 (t, 2H, J = 7.7 Hz, CH₂CO), 1.36–1.81 [m, 18H, (CH₂)₉CH₂CO], 1.27 [d, 6H, J = 10.6 Hz, one of CH(CH₃)₂], 1.19 [d, 6H, J = 6.7 Hz, one of CH(CH₃)₂], 0.88 (t, 3H, J = 6.6 Hz, CH₃CH₂).

**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 C₁₈H₃₈NO (MH⁺): 284.2953.
- Found: 284.953.

**TLC (50% EtOAc–hexanes) Rf:**
- 71: 0.66 (PMA).
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-adamantancarbonyl 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$_3$) $\delta$: 3.42 (m, 4H, NCH$_2$CH$_3$), 2.04 (s, 3H, H1), 2.00 (s, 6H, H3), 1.72 (s, 6H, H2), 1.13 (t, 6H, $J = 7.6$ Hz, NCH$_2$CH$_3$).

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).


TLC (50% EtOAc–hexanes) $R_f$: 72: 0.51 (PMA).

1-adamantanecarboxylic acid: 0.38 (PMA).
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, CH$(OCH_3)_2$], 3.24 [br, s, 1H, CH$(CH_3)_2$], 2.03 (s, 3H, H1), 1.98 (s, 6H, H3), 1.71 (s, 6H, H2), 1.36 (br, s, 6H, two CH$_3$ groups), 1.20 (br, s, 6H, two CH$_3$ 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).
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 x 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$_2$CH$_2$), 1.25 [m, 18H, (CH$_2$)$_9$CH$_2$CH$_2$OH], 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).
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) Rf:  
74: 0.58 (PMA).
71: 0.70 (PMA).

tertiary amine by-product: 0.25 (PMA).
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$_3$) $\delta$: 3.20 (d, 2H, $J = 6.2$ Hz, CH$_2$OH), 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$_3$) $\delta$: 73.6, 38.9, 37.1, 34.4, 28.1.

FTIR (neat, cm$^{-1}$) Analysis: 3216 (br, m, OH), 2896 (s), 2844 (m), 1052 (m). 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$_2$Cl$_2$) $R_f$: 75: 0.50 (PMA). 72: 0.56 (PMA).
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.

\[
\text{TLC (40\% EtOAc–hexanes) } R_f: \quad 75: 0.42 \text{ (PMA)}. \quad 73: 0.59 \text{ (PMA)}. \quad \text{tertiary amine by-product: } 0.71 \text{ (PMA)}.\]
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 \textit{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-\textit{d}_8. The cloudy suspension was transferred into an NMR tube.

\textsuperscript{11}B NMR (32 MHz, THF-\textit{d}_8, B(OMe)\textsubscript{3} reference) \(\delta\): 
-40.5 (LiH\textsubscript{2}NBH\textsubscript{3}).

\textsuperscript{11}B NMR (32 MHz, THF-\textit{d}_8, BF\textsubscript{3}\cdot\text{OEt}_2 reference) \(\delta\): 
-22.2 (LiH\textsubscript{2}NBH\textsubscript{3}).
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 \(\mu\)L) at 23 °C. The resulting clear solution was transferred into an NMR tube.

\[ ^{11}\text{B NMR (32 MHz, THF-\(d_8\), B(OMe)_3 reference)} \delta: \text{−40.5 (LiH}_2\text{NBH}_3\text{).} \]

\[ ^{11}\text{B NMR (32 MHz, THF-\(d_8\), BF}_3\text{•OEt}_3\text{ reference)} \delta: \text{−22.2 (LiH}_2\text{NBH}_3\text{).} \]

\[ ^{13}\text{C NMR (100 MHz, THF-\(d_8\)) \delta: 31.6 (CH}_3\text{).} \]
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 $\alpha$-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, there was at the time of our initial report no general procedure for the direct conversion of an alkylation product to the corresponding aldehyde.

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. 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

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate$^a$</th>
<th>R</th>
<th>R'</th>
<th>prod</th>
<th>time (h)</th>
<th>isol yield (%)</th>
<th>isol ee (%)</th>
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<td>Bn</td>
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<td>1.0</td>
<td>76</td>
<td>95</td>
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<td>n-Bu</td>
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<td>1.1</td>
<td>75$^b$</td>
<td>98</td>
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<tr>
<td>3</td>
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<td>Bn</td>
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<td>1.2</td>
<td>77</td>
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<tr>
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<td>0.9</td>
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<td>90</td>
</tr>
</tbody>
</table>

$^a$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). 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.
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.\textsuperscript{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\textsuperscript{-1}), intensity of absorption (br = broad, s = strong, m = medium). \textsuperscript{1}H NMR spectra were recorded at 300 MHz, and \textsuperscript{13}C NMR spectra were recorded at 75 MHz; chemical shifts are expressed in parts per million (\delta scale) downfield from tetramethylsilane. \textsuperscript{1}H NMR chemical shifts are referenced to the signal for residual hydrogen in the NMR solvent (CHCl\textsubscript{3}: \delta 7.26, C\textsubscript{6}HD\textsubscript{3}: \delta 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. \textsuperscript{13}C NMR chemical shifts are referenced to the carbon signal
for the solvent (CDCl₃: δ 77.0, C₆D₆: 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.
(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 oxidized64 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.

\[^1\text{H NMR (300 MHz, C}_6\text{D}_6)\delta:\]

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 PhCH\(_2\)), 2.0–2.2 (m, 2H, one of PhCH\(_2\), CHCHO), 0.69 (d, 3H, \(J = 6.9\) Hz, CH\(_3\)).

\[^{13}\text{C NMR (75 MHz, CDCl}_3)\delta:\]

204.3, 138.7, 128.9, 128.4, 126.3, 48.0, 36.5, 13.1.

\text{FTIR (neat, cm}^{-1}):\quad 1723 (s, C=O).

\text{HRMS (FAB):}\quad \text{Calcd for C}_{10}\text{H}_{13}\text{O (MH)}^+: 149.0966.

\text{Found: 149.0965.}

\text{TLC (50% EtOAc–hexanes), } R_f: \quad 76: 0.63 (UV, PMA).

\quad 11: 0.22 (UV, PMA).

\text{aminal by-product: 0.70 (UV, PMA).}
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, CD\(_2\)Cl\(_2\)) \(\delta\):

- 9.27 (d, 1H, \(J = 1.8\) Hz, CHO),
- 1.83 (m, 1H, COCH),
- 0.85–1.15 (m, 6H, CH\(_2\)CH\(_2\)CH\(_2\)),
- 0.78 (t, 3H, \(J = 7.0\) Hz, CH\(_3\)CHCO),
- 0.75 (d, 3H, \(J = 7.0\) Hz, CH\(_3\)CH\(_2\)).

FTIR (neat, cm\(^{-1}\)):

- 1729 (s, C=O).

HRMS (FAB):

- Calcd for C\(_7\)H\(_{14}\)O (M\(^+\)): 114.1045.
- Found: 114.1047.

TLC (50% EtOAc–hexanes), \(R_f\):

- 77: 0.78 (PMA).
- 12: 0.33 (UV, PMA).
(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), Rf:  
78: 0.68 (UV, PMA).  
16: 0.24 (UV, PMA).  
aminal by-product: 0.76 (UV, PMA).
(S)-\(\alpha\)-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\(_6\)D\(_6\)) δ: 9.34 (d, 1H, J = 2.3 Hz, CHO), 6.9-7.3 (m, 5H, aromatic), 2.71 (dd, 1H, \(J_1 = 13.9\) Hz, \(J_2 = 7.2\) Hz, one of PhCH\(_2\)), 2.36 (dd, 1H, \(J_1 = 13.9\) Hz, \(J_2 = 7.0\) Hz, one of PhCH\(_2\)), 2.22 (m, 1H, COCH), 1.31 (m, 1H, one of COCHCH\(_2\)CH\(_2\)), 0.9-1.2 (m, 5H, one of COCHCH\(_2\)CH\(_2\), CH\(_3\)CH\(_2\)CH\(_2\)), 0.74 (t, 3H, \(J = 6.7\) Hz, CH\(_3\)).

\(^{13}\)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).
(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).
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$_6$D$_6$) δ: 9.34 (d, 1H, $J = 1.8$ Hz, CHO), 6.8–7.15 (m, 5H, aromatic), 2.87 (m, 1H, PhCH), 1.82–1.91 (m, 1H, one of CH$_3$CH$_2$), 1.48 (m, 1H, one of CH$_3$CH$_2$), 0.66 (t, 3H, $J = 7.4$ Hz, CH$_3$).

$^{13}$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

C₂-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.

\[
\begin{align*}
\text{n} = 0 & \quad \text{Pseudoephedrine succinamide (82)} \\
\text{n} = 1 & \quad \text{Pseudoephedrine glutaramide (83)} \\
\text{n} = 2 & \quad \text{Pseudoephedrine adipamide (84)} \\
\text{n} = 3 & \quad \text{Pseudoephedrine pimelamide (85)}
\end{align*}
\]

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

<table>
<thead>
<tr>
<th>n</th>
<th>R'X</th>
<th>product</th>
<th>yield (%)</th>
<th>de (%)</th>
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<tr>
<td>0</td>
<td>MeI</td>
<td>86</td>
<td>74</td>
<td>&gt;90</td>
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<tr>
<td>1</td>
<td>MeI</td>
<td>87</td>
<td>78</td>
<td>&gt;90</td>
</tr>
<tr>
<td>1</td>
<td>PhCH₂Br</td>
<td>88</td>
<td>81</td>
<td>&gt;90</td>
</tr>
<tr>
<td>3</td>
<td>MeI</td>
<td>89</td>
<td>90</td>
<td>&gt;90</td>
</tr>
<tr>
<td>3</td>
<td>PhCH₂Br</td>
<td>90</td>
<td>86</td>
<td>&gt;90</td>
</tr>
</tbody>
</table>

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 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 \( \pi \)-face might mutually reinforce the steric bias at the other enolate \( \pi \)-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 \( \pi \)-face might counteract the steric bias at the other enolate \( \pi \)-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.\(^4\) 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).\(^4\)

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). \(^1\)H 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 (\(\delta\) scale) downfield from tetramethylsilane. \(^1\)H NMR chemical shifts are referenced to the signal for residual hydrogen in the NMR solvent (CHCl\(_3\): \(\delta\) 7.26, C\(_6\)H\(_5\)D\(_2\): \(\delta\) 7.15) or to tetramethylsilane (\(\delta\) = 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\(_3\): \( \delta 77.0 \), C\(_6\)D\(_6\): \( \delta 128.0 \)). 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).
(1S,2S)-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%).
1H NMR (300 MHz, CDCl₃) δ: (4:3:3:2 rotamer ratio) 7.2–7.5 (m, 10H, aromatic), 4.57 (m, 2H, CHOH), 4.24 (m, 2H, NCH₂CH₃), 2.98 (s, 6H, NCH₃), 2.97 (s, 6H, NCH₃), 2.94 (s, 6H, NCH₃), 2.93 (s, 6H, NCH₃), 2.70 (m, 4H, CH₂CH₂), 0.98 (m, 6H, CH₃CHN).

13C NMR (75 MHz, CDCl₃) 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).


TLC (7.5% MeOH–CH₂Cl₂), Rf: 82: 0.27 (UV, PMA).

pseudoephedrine: 0.03 (UV, PMA).
(1S,2S)-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\(_2\)D\(_2\)) \(\delta\): (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, CHO\(_2\)), 4.41 (d, 2H, \(J = 8.9\) Hz, CHO\(_2\)), 3.82–3.94 (m, 2H, NCH\(_3\)), 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\(_2\)CH\(_2\)CH\(_2\)), 0.99 (d, 6H, \(J = 6.9\) Hz, CH\(_3\)CHN), 0.69 (d, 6H, \(J = 6.9\) Hz, CH\(_3\)CHN), 0.56 (d, 6H, \(J = 6.7\) Hz, CH\(_3\)CHN), 0.51 (d, 6H, \(J = 6.8\) Hz, CH\(_3\)CHN).

\(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 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, 75.4, 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\(_2\)O\(_4\) (MH\(^+\)): 427.2597.

Found: 427.2612.

TLC (7.5% MeOH–CH\(_2\)Cl\(_2\)), \(R_f\): 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\(_3\)), 8: (4:2:1 mixture of rotamers) 7.2–7.4 (m, 10H, aromatic), 4.00–4.58 (m, 4H, CH\(_2\)OH, 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\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)), 1.07 (d, 6H, \(J = 6.8\) Hz, CH\(_3\)CHN), 1.00 (m, 6H, CH\(_3\)CHN).

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\(_2\)O\(_4\) (MH\(^+\)): 441.2753. Found: 441.2763.

TLC (15% MeOH–CH\(_2\)Cl\(_2\)), \(R_f\): 84: 0.68 (UV, PMA). pseudoephedrine: 0.05 (UV, PMA).
(1S,2S)-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%).
\(^1\text{H}\) NMR (300 MHz, CDCl\(_3\)) \(\delta\): (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\(_2\)CO), 1.60 (m, 4H, COCH\(_2\)CH\(_2\)), 1.38 (m, 2H, COCH\(_2\)CH\(_2\)CH\(_2\)), 1.04 (d, 6H, \(J = 6.8\) Hz, CH\(_3\)CHN), 0.95 (d, 6H, \(J = 6.8\) Hz, CH\(_3\)CHN).

\(^13\text{C}\) NMR (75 MHz, CDCl\(_3\)) \(\delta\): 175.2, 142.2, 128.6, 128.3, 127.6, 126.9, 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\(_2\)O\(_4\) (MH\(^+\)): 455.2910.

Found: 455.2904.

TLC (15% MeOH–CH\(_2\)Cl\(_2\)), \(R_f\): 85: 0.57 (UV, PMA).

pseudoephedrine: 0.05 (UV, PMA).
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 1H NMR analysis established that bis-amide 86 was of >90% de.
**$^{1}$H NMR (300 MHz, C$_6$D$_6$) $\delta$:** (20:1:1 ratio of species, * denotes minor species)

<table>
<thead>
<tr>
<th>Peak</th>
<th>Assignments</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.55 (m)</td>
<td>4H, aromatic</td>
</tr>
<tr>
<td>7.0–7.3 (m)</td>
<td>6H, aromatic</td>
</tr>
<tr>
<td>5.10 (br)</td>
<td>2H, OH</td>
</tr>
<tr>
<td>4.80 (m)</td>
<td>2H, NCHCH$_3$</td>
</tr>
<tr>
<td>4.42 (m)</td>
<td>2H, CHOH</td>
</tr>
<tr>
<td>3.00 (m)</td>
<td>2H, COCH</td>
</tr>
<tr>
<td>2.91* (s)</td>
<td>6H, NCH $_3$</td>
</tr>
<tr>
<td>2.62* (s)</td>
<td>6H, NCH$_3$</td>
</tr>
<tr>
<td>2.60 (s)</td>
<td>6H, NCH$_3$</td>
</tr>
<tr>
<td>1.33* (d)</td>
<td>6H, J = 7.0 Hz, CH$_3$CHN</td>
</tr>
<tr>
<td>0.97 (d)</td>
<td>6H, J = 6.4 Hz, COCH$_3$CHN</td>
</tr>
<tr>
<td>0.74* (d)</td>
<td>6H, J = 6.7 Hz, CH$_3$CHN</td>
</tr>
<tr>
<td>0.62 (d)</td>
<td>6H, J = 6.8 Hz, CH$_3$CHN</td>
</tr>
</tbody>
</table>

**$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$:**

- 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$_2$O$_4$ (MH)$^+$: 441.2753.

Found: 441.2750.

**TLC (EtOAc), $R_f$:**

- 86: 0.33 (UV, PMA).
- 82: 0.13 (UV, PMA).
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 x 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, CD\(_{2}D_{2}\)) \(\delta\): (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, NCH\(_{2}\)CH\(_{3}\)), 4.51 (m, 2H, CHO\(_{2}\)), 3.00* (s, 6H, NCH\(_{3}\)), 2.77 (m, 2H, COCH\(_{3}\)), 1.28* (d, 6H, J = 6.8 Hz, CH\(_{3}\)), 0.99 (d, 6H, J = 6.9 Hz, CH\(_{3}\)), 0.90* (d, 6H, J = 7.0 Hz, CH\(_{3}\)), 0.59 (d, 6H, J = 6.9 Hz, CH\(_{3}\)).

\(^{13}\)C NMR (75 MHz, CDCl\(_{3}\)) \(\delta\): 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\(_{2}\)O\(_{4}\) (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.
1H NMR (300 MHz, CDCl₃) 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, NCH₂CH₃), 4.48 (m, 2H, CHOH), 3.03 (m, 4H, PhCH₂), 2.51 (m, 2H, COCH), 2.49 (s, 6H, NCH₃), 2.03 (m, 2H, COCHCH₂), 0.47 (d, 6H, J = 6.9 Hz, CH₃CHN).

13C NMR (75 MHz, CDCl₃) 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 C₃₉H₄₇N₂O₄ (MH⁺): 607.3536

Found: 607.3527.

TLC (EtOAc), Rf: 88: 0.54 (UV, PMA).

83: 0.13 (UV, PMA).
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 x 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 ¹H NMR analysis established that bis-amide 89 was of >90% de.
{H NMR (300 MHz, CDCl₃) 8: 7.10–7.40 (m, 10 H, aromatic), 4.82 (m, 2H, NCHCH₃), 4.43 (d, 2H, J = 7.4 Hz, CHOH), 3.03 s (6H, NCH₃), 2.86 (m, 2H, COCH), 1.96 (m, 4H, COCHCH₂), 1.36 (m, 2H, COCHCH₂CH₂), 1.10 (d, 6H, J = 6.8 Hz, CH₃), 0.83 (d, 6H, J = 6.9 Hz, CH₃).

{C NMR (75 MHz, CDCl₃) 8: 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 C₂₉H₄₃N₂O₄ (MH)⁺: 483.3223.
Found: 483.3209.

TLC (EtOAc), Rf: 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 x 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 bisamide 90 as a white foam (273 mg, 86%). High resolution ^1H NMR analysis established that bis-amide 90 was of >90% de.
$^1$H NMR (300 MHz, $C_6D_6$) $\delta$: 6.9–7.4 (m, 20H, aromatic), 5.18–5.28 (m, 4H, OH, NCH$_2$CH$_3$), 4.24 (m, 2H, CHOCH), 3.00 (m, 4H, PhCH$_2$), 2.63 (m, 2H, COCH), 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$_3$CHN).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 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$_2$O$_4$ (MH)$^+$: 635.3845. Found: 635.3839.

TLC (7.5% MeOH–CH$_2$Cl$_2$), $R_f$: 90: 0.62 (UV, PMA), 85: 0.25 (UV, PMA).
References and Notes


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


(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).


(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 benzylazoxazolidinone 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 alkylation product 29 in 90% yield with 99:1 selectivity (cf. entry 4, Table 4).


(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).


(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 $\beta$-alkyl branched and $\beta$-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.


(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.


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


(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.

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


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

Appendix. Catalog of Spectra
Spectroscopic Data of Compounds

Amides 1–34: $^1$H NMR, FTIR, $^{13}$C NMR

Amides 35–37: $^1$H NMR, FTIR

structure X and structure Y: $^1$H NMR, 2-D COSY

Acids 39–41, 43, and 46–49: $^1$H NMR, FTIR

Alcohols 50–52, 54, 56–66: $^1$H NMR, FTIR

Iodides 67–69: $^1$H NMR, FTIR

Tertiary Amides 70–73: $^1$H NMR, FTIR

Primary Alcohols 75 and 76: $^1$H NMR, FTIR

Aldehydes 76, 77, 79, and 81: $^1$H NMR, FTIR

Bis-amides 82–90: $^1$H NMR, FTIR
\[
\begin{align*}
\text{CH}_3 & \quad \text{N~CH}_3 \\
\text{OH} & \quad \text{CH}_3
\end{align*}
\]
Chemical structure and spectra.
The image contains a chemical structure and two infrared spectra. The chemical structure is labeled as compound 14. The upper spectrum is labeled as 14.29 cm⁻¹, and the lower spectrum ranges from 4000 to 1000 cm⁻¹.
The image shows a chemical structure labeled as 17 with a corresponding NMR spectrum. The chemical structure includes a phenyl group, an amide bond, and a chain with hydroxyl and methyl groups. The NMR spectrum displays various peaks at different chemical shifts, indicating the presence of different types of hydrogen atoms in the molecule. The spectrum is plotted against ppm on the x-axis and intensity on the y-axis.
The image contains a chemical structure and spectra. The chemical structure is labeled as '26'. The spectra include a nuclear magnetic resonance (NMR) spectrum and an infrared (IR) spectrum.
structure X

structure Y
HO
\begin{center}
\includegraphics[width=\textwidth]{image}
\end{center}

\begin{align*}
\text{CH}_2\text{C}_6\text{H}_5
\end{align*}
HO\text{\scriptsize{\textbackslash CH}}_3
\text{\scriptsize{\textbackslash CH}}_2(\text{\scriptsize{\textbackslash CH}}_2)_2\text{\scriptsize{\textbackslash CH}}_3
40
\[ \text{HO-CH} = \text{CH}_3 \]
\[ \text{CH}_2\text{OCH}_2\text{C}_6\text{H}_5 \]

41

The diagram shows the infrared (IR) spectrum and the NMR spectrum of the compound. The IR spectrum is plotted on the lower graph, with the wavenumbers ranging from 4000 to 1000 cm\(^{-1}\). The NMR spectrum is on the upper graph, showing the chemical shifts in ppm. The compound is identified as 41.
HO\textsuperscript{-}CH\textsubscript{3}CH\textsubscript{3}CH\textsubscript{3} 47

3.12 3500 3000 2500 2000 1500 1000 cm\textsuperscript{-1}

102.45
CH$_3$(CH$_2$)$_{10}$CONEt$_2$

70
$\text{CH}_3(\text{CH}_2)_{10}\text{CON}(\ddot{\text{A}}\text{Pr})_2$
\( \text{CH}_3(\text{CH}_2)_{10}\text{CH}_2\text{OH} \)

74
\begin{align*}
  &\text{H} \quad \text{CH}_3 \\
  &\quad \text{CH}_2 \text{C}_6 \text{H}_5 \\
  &76
\end{align*}