Enantioselective Synthesis of 2-Substituted Alcohols Using (+)-(1S,2S)-Pseudoephedrine as Chiral Auxiliary

Lutz F. Tietze,*a Christian Raith,a C. Christian Brazel,a Sören Hölsken,a Jörg Magullb

a Institut für Organische und Biomolekulare Chemie, Georg-August-Universität, Tammannstraße 2, 37077 Göttingen, Germany
Fax +49(551)399476; E-mail: ltietze@gwdg.de
b Institut für Anorganische Chemie, Georg-August-Universität, Tammannstraße 4, 37077 Göttingen, Germany

Received 10 August 2007; revised 26 October 2007

Abstract: An improved method for the selective synthesis of enantiopure 2-substituted alcohols is described. Highly diastereoselective alkylation of pseudoephedrine-derived amides and subsequent oxidation of the hydroxyl group in the amide side chain, leads to oxoamides. These oxoamides can be purified by crystallization or preparative HPLC to obtain diastereomeric ratios of >99:1. The following reductive cleavage of the modified auxiliary allows the epimerization-free formation of enantiopure 2-substituted alcohols with up to 99.9% ee.

Key words: alcohols, auxiliary, asymmetric synthesis, reduction, alkylation

Chiral alcohols with a stereogenic center in the 2-position are versatile building blocks for natural product synthesis. On the one hand, they can be transformed into chiral electrophiles e.g. aldehydes, activated esters as triflates, tosylates or iodides and, on the other hand, they can be used as nucleophiles. A variety of methods for the enantioselective synthesis of 2-substituted alcohols has been developed,1 most of which are related to a diastereoselective alkylation of chiral enolates2 or enamines.3 A general problem of these methods is the separation of the mixtures of stereoisomers usually obtained to afford pure diastereomers, which can then be converted into enantiopure alcohols. The well known and most widely applied alkylation of N-acyl pseudoephedrine derivatives, developed by Myers,4 often fails to yield crystalline compounds amenable to purification by recrystallization. In the case of non-crystalline compounds, separation of the diastereomeric products by chromatography is seldom successful even using HPLC as we have observed. Nevertheless, the procedure is very useful since, even in those cases where an enrichment is not possible, high selectivities can be obtained with an ee of over 90% in most cases. However, we have recently found that by a slight change of the protocol, the desired alkylated alcohols can be formed with up to 99.9% ee and, moreover, the liberation of the alcohols is highly improved. Thus, before reductive cleavage to give the alcohols, we have incorporated an oxidation of the primarily formed hydroxyamides 4 to give the corresponding oxoamides 6, which are nearly always crystalline and can therefore be purified by recrystallization (Scheme 1). Moreover, in almost all cases, the formed diastereomers can also be separated by chromatography.

For the total synthesis of polyoxygenated cembranoids, we needed alcohol (S)-5a.5 Alkylation of pseudoephedrine isovalerylamide (3) with 3-methylbut-3-enyl triflate led to the formation of hydroxyamide 4a as an oil, which could not be further purified. Reduction of 4a applying lithium aminotrihydroborate (LAB) gave the alcohol 5a in good yield (89%) but with an ee of only 90%, which was

Scheme 1

Comparison of the Myers procedure4 to the new oxoamide procedure

SYNTHESIS 2008, No. 2, pp 0229–0236
Advanced online publication: 18.12.2008
DOI: 10.1055/s-2008-1000851; Art ID: T12807SS
© Georg Thieme Verlag Stuttgart · New York
not sufficient for our synthesis. However, oxidation of the hydroxamide 4a led to the oxoamide 6a, which could be purified by recrystallization and also chromatography. Reduction of 6a after crystallization using LAB, led to alcohol 5a in a comparable yield (89%) but with a highly increased optical purity of 97% ee. After chromatographic purification of 6a followed by reductive cleavage, the alcohol 5a was even obtained with 99.9% ee.

In order to determine the scope and limitations of this method, we prepared a range of 2-substituted alcohols. For this investigation we used pseudoephedrine isovaleramide (3) as substrate, which was synthesized by N-acylation of (+)-(1S,2S)-pseudoephedrine (1) with isovaleryl chloride (2) in tetrahydrofuran in the presence of triethylamine. Six different hydroxamides 4a–f were synthesized by diastereoselective alkylation of the lithium enolate of 3 according to the protocol of Myers. The enantiopure alcohols were obtained from the diastereomeric hydroxyamides 4a–f by diastereoselective alkylation of the lithium enolate of 3 with moderate to excellent diastereomeric excess (Table 1).4b The diastereomeric ratio could be determined by capillary GC on chiral stationary phases. They correspond to the dr values of the oxoamides, which remain 1'-position.11–13 The diastereomeric ratio could be determined by HPLC using Daicel Chiralpak® IA and IB analytical columns and n-hexane–2-propanol as mobile phase. However, oxoamide 6d could not be separated on these columns even using different mobile phases.14 Oxoamides 6a–c were purified using a preparative HPLC Daicel Chiralpak® IA column, 6e was purified by using a Daicel Chiralpak® IB column. The resulting epimerically enriched oxoamides were reduced with LAB to give the desired alcohols 5a–e and 5f with highly increased enantiopurity compared to the direct cleavage of the hydroxamides 4.

Moreover, since the liberation of the alcohols was much easier, the yields for the three-step procedure were improved (Table 2).

The described examples show that the original Myers procedure for the synthesis of 2-substituted chiral alcohols could be improved, the yields for the three-step procedure were improved (Table 2).

Scheme 2 Synthesis of 2-substituted alcohols 5a–f via oxoamides 6a–f

Table 1 Synthesis of 2-Substituted Alcohols 5a–f Starting from 3 using the Myers Protocol

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>R</th>
<th>ee (%)</th>
<th>Yield [two steps (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td></td>
<td>90</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>5b</td>
<td></td>
<td>96</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>5c</td>
<td>Me</td>
<td>90</td>
<td>43</td>
</tr>
<tr>
<td>4</td>
<td>5d</td>
<td>Et</td>
<td>96</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>5e</td>
<td>Pr</td>
<td>94</td>
<td>37</td>
</tr>
<tr>
<td>6</td>
<td>5f</td>
<td>Bn</td>
<td>&gt;98</td>
<td>69</td>
</tr>
</tbody>
</table>

* The ee values were determined by chiral capillary GC.

Table 2 Oxidation of Hydroxamides 4a–f and Reductive Cleavage of the Resulting Oxoamides to Alcohols 5a–f

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>R</th>
<th>ee*</th>
<th>Yield [three steps (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td></td>
<td>90*</td>
<td>97* 58</td>
</tr>
<tr>
<td>2</td>
<td>5b</td>
<td></td>
<td>96*</td>
<td>&gt;99.9d 70</td>
</tr>
<tr>
<td>3</td>
<td>5c</td>
<td>Me</td>
<td>90*</td>
<td>&gt;99.9d 71</td>
</tr>
<tr>
<td>4</td>
<td>5d</td>
<td>Et</td>
<td>96*</td>
<td>39</td>
</tr>
<tr>
<td>5</td>
<td>5e</td>
<td>Pr</td>
<td>95*</td>
<td>&gt;99.9d 72</td>
</tr>
<tr>
<td>6</td>
<td>5f</td>
<td>Bn</td>
<td>&gt;98</td>
<td>67</td>
</tr>
</tbody>
</table>

* The ee values of the alcohols 5a–f were determined by chiral capillary GC. They correspond to the dr values of the oxoamides, which were determined by HPLC on chiral stationary phases (Daicel Chiralpak® IA, IB).

* Without enrichment.

* After recrystallization from EtOH–H2O.

* After preparative HPLC (entries 1–3, Daicel Chiralpak® IA; entry 5, Daicel Chiralpak® IB).
HPLC experiments were performed on Daicel Chiralpak® IA (250 × 4.6 mm) and IB (250 × 4.6 mm) columns. Semi-preparative HPLC separations were performed on semi-preparative Daicel Chiralpak® IA (250 × 20 mm) and IB (250 × 10 mm) columns. For chiral capillary GC analysis CP-Chirasil-DEX-CB and CP-Cyclohexane-B-2,2,6-M-19 columns were used. 1H and 13C NMR spectra were measured on Mercury 300 and Unity 300 spectrometers (300 MHz) with TMS as internal standard. IR spectra were measured on a Bruker Vector 22 spectrometer. Mass spectra were recorded with a Finnigan MAT 95 (EI), TSQ 7000 or LCQ (ESI), ESI-HRMS were recorded on a Bruker APEX IV spectrometer. UV/Vis spectra were measured using a Perkin-Elmer Lambda 2 spectrometer.

N-[(1S,2S)-2-Hydroxy-1-methyl-2-phenylethyl]-3-N-dimethylbutyramide (3)

To a solution of (+)-(1S,2S)-pseudopephedrine (1; 3.62 g, 21.9 mmol) and EtN (3.60 g, 26.3 mmol) in THF (50 ml) at 0 °C, a solution of isovaleryl chloride (2; 2.89 g, 29.4 mL, 24.0 mmol) in THF (1 mL) was added within 15 min. After an additional 15 min, the reaction mixture was quenched with H2O (10 mL). EtOAc (50 mL) was added and the organic phase was washed with brine (2 × 40 mL) and dried with Na2SO4. The solvent was evaporated in vacuo and the residue was purified by crystallization from n-hexane to afford 3.

Yield: 5.30 g (97%); colorless crystals; mp 75–76 °C; [α]D 20 +104.0 (c 1.00, CHCl3); Rf 0.3 (EtOAc).

IR (KBr): 3328, 2959, 2872, 1601, 1054, 754, 704 cm–1.

1H NMR (300 MHz, CDCl3): δ (major rotamer) = 0.98–0.94 (m, 6 H, CH3(CH2)3), 0.99 (d, J = 6.6 Hz, 3 H, CH3), 2.05–2.28 (m, 3 H, H-2, H-3), 2.78 (s, 3 H, NCH3), 4.41 (m, 1 H, NCH), 4.56 (m, 2 H, CHOH, OH), 7.20–7.36 (m, 5 H). δ (minor rotamer) = 0.96 (d, J = 3.3 Hz, 3 H, CH3), 2.88 (s, 3 H, NCH3), 3.99 (dq, J = 8.1, 6.6 Hz, 1 H, NCH).

13C NMR (75 MHz, CDCl3): δ (major rotamer) = 14.5, 22.6, 22.7, 25.5, 33.3, 43.1, 58.8, 76.5, 126.3, 127.5, 128.3, 142.5, 175.0; δ (minor rotamer) = 15.3, 26.7, 42.5, 58.3, 75.5, 126.9, 128.7, 141.1, 173.6.

MS (DCI, NH3): m/z (%) = 250.3 (100) [M + H]+, 499.6 (19) [2 × M + H]+.


UV/Vis (MeCN): λmax (log ε) = 252 (2.34), 257 (2.41), 264 nm (2.33).

Alkylation of 3, General Procedure

To a stirred suspension of anhydrous LiCl (6.00 mmol) and diisopropylamine (2.55 mmol) in THF (3 mL) at –78 °C, n-BuLi (2.5 M in hexanes, 2.10 mmol) was added. The resulting suspension was stirred at 0 °C for 5 min, cooled to –78 °C and treated with an ice-cold solution of 3 (1.00 mmol) in THF (3 mL). The reaction mixture was stirred at –78 °C for 1 h, at 0 °C for 15 min and at r.t. for 5 min. The alkylation agent (1.50 mmol) was added at 0 °C and the reaction was stirred at this temperature, whilst monitoring the conversion by TLC. The reaction was quenched with sat. aq NH4Cl (16 mL); EtOAc (10 mL) was added, the organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried with Na2SO4, concentrated in vacuo and the residue was purified by flash chromatography.

(5)-2-Isopropyl-5-methylhex-5-enoic Acid N-[(1S,2S)-2-Hydroxy-1-methyl-2-phenylethyl]-N-methyl Amide (4a)

A solution of triflic anhydride (2.40 mmol) in CH2Cl2 (3 mL) was added to a solution of 3-methylbut-3-en-1-ol (2.40 mmol) and pyridine (2.88 mmol) in CH2Cl2 (3 mL) at –78 °C. The reaction mixture was stirred for 2 h at 0 °C, poured on crushed ice, diluted with CH2Cl2 (20 mL), extracted with cold aq HCl (1 M, 5 × 15 mL) and washed with cold H2O (15 mL). The organic phase was dried over MgSO4 and the solvent was removed in vacuo at 0 °C. The trflate was obtained as a dark-purple liquid and used directly for the alkylation reaction.

To a stirred suspension of anhydrous LiCl (6.00 mmol) and diisopropylamine (2.35 mmol) in THF (3 mL) at –78 °C, n-BuLi (2.5 M in hexanes, 2.10 mmol) was added. The resulting suspension was stirred at 0 °C for 5 min, cooled to –78 °C and treated with an ice-cold solution of 3 (1.00 mmol) in THF (3 mL). The reaction mixture was stirred at –78 °C for 1 h, at 0 °C for 15 min and at r.t. for 5 min. The previously synthesized 3-methylbut-3-enyl trflate (2.40 mmol) was added at –78 °C and the reaction mixture was allowed to warm to –20 °C, while monitoring the conversion by TLC. The reaction was quenched with sat. aq NH4Cl (16 mL). EtOAc (10 mL) was added, the organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried with Na2SO4, concentrated in vacuo and the residue was purified by flash chromatography.

Yield: 83%; [α]D 20 +85.2 (c 1.00, CHCl3); Rs 0.2 (n-pentane–EtOAc, 1:1).

IR (film): 3385, 2963, 1616, 1452, 1051, 701 cm–1.

1H NMR (300 MHz, CDCl3): δ (major rotamer) = 0.92 (d, J = 6.6 Hz, 3 H, CH3(CH2)3), 0.94 (d, J = 6.6 Hz, 3 H, CH3(CH2)3), 1.16 (d, J = 6.8 Hz, 3 H, CH3), 1.67 (s, 3 H, C=CH2), 1.59–1.95 (m, 5 H, CH3CH2), 2.24–2.27 (m, 1 H, H-2), 2.86 (s, 3 H, NCH3), 4.38–4.54 (m, 1 H, NCH), 4.54 (s, 1 H, C=CH2), 4.61 (dd, J = 7.2, 7.2 Hz, 1 H, CHOH), 4.68 (s, 1 H, C=CH2), 4.85 (br s, 1 H, OH), 7.20–7.34 (m, 5 H). δ (minor rotamer) = 0.98 (d, J = 6.6 Hz, 3 H, CH3(CH2)3), 2.92 (s, 3 H, NCH3), 4.11 (q, J = 6.8 Hz, 1 H, NCH), 4.57 (m, 1 H, C=CH2), 4.72 (s, 1 H, C=CH2).

13C NMR (75 MHz, DMSO-d6, 100 °C): δ = 13.6, 18.7, 20.1, 21.4, 26.9, 29.6, 30.6, 34.6, 46.1, 54.0, 73.8, 109.2, 126.1, 126.3, 127.2, 143.2, 144.9, 147.3.

MS (DCI, NH3): m/z (%) = 318.5 (100) [M + H]+, 636.1 (23) [2 × M + H]+.


Anal. Calc. for C25H37NO3: C 75.67; H 9.84. Found: C 75.41; H 9.64.

(S)-2-Isopropyl-5-methylhex-5-enoic Acid N-[(1S,2S)-2-Hydroxy-1-methyl-2-phenylethyl]-N-methyl Amide (4b)

Amide 3 was alkylated with 3,3-dimethylallyl bromide.

Yield: 92%; [α]D 20 +69.6 (c 0.50, CHCl3); Rs 0.7 (EtOAc).

IR (film): 3328, 2959, 2872, 1601, 1054, 754, 704 cm–1.
Yield: 92%; methylbutyramide (4c)

IR (film): 3383, 2963, 2873, 1615, 1454, 701 cm⁻¹.

UV/Vis (MeCN): λmax (log ε) = 278.0 (100) [M + H]+, 295.4 (10) [M + H]+, 557.5 (36) [2 × M + H]+.

HRMS-ESI: m/z [M + H]+ calculated for C₁₉H₂₃N₂O₂: 340.3 (100) [M + H]+, 679.8 (18) [2 × M + H]+.

(S)-2-Isopropylpentanoic Acid N-{(1S,2S)-2-Hydroxy-1-methyl-2-phenylethyl}-N-methyl Amide (4e)

Amide 3 was alkylated with iodoethane.

Yield: 85%; [α]D²₀ +92.8 (c 0.50, CHCl₃); Rf = 0.6 (Et₂O).

IR (film): 3383, 2459, 1614, 1454, 761 cm⁻¹.

UV/Vis (MeCN): λmax (log ε) = 278.0 (100) [M + H]+, 295.4 (10) [M + H]+, 557.5 (36) [2 × M + H]+.

HRMS-ESI: m/z [M + H]+ calculated for C₁₉H₂₃N₂O₂: 340.3 (100) [M + H]+, 679.8 (18) [2 × M + H]+.

(S)-2-Ethyl-N-{(1S,2S)-2-hydroxy-1-methyl-2-phenylethyl}-N₃₃-dimethylbutyramide (4d)

Amide 3 was alkylated with iodoethane.

Yield: 80%; [α]D²₀ +92.8 (c 0.50, CHCl₃); Rf = 0.4 (Et₂O–n-pentane, 5:1).

IR (film): 3383, 2963, 2873, 1615, 1454, 701 cm⁻¹.

UV/Vis (MeCN): λmax (log ε) = 248 (2.36), 254 (2.39), 264 nm (2.25).

(5)-2-Benzyl-N-{(1S,2S)-2-hydroxy-1-methyl-2-phenylethyl}-3-N₃₃-dimethylbutyramide (4f)

Amide 3 was alkylated with benzyl bromide.

Yield: 85%; mp 121–122 °C; [α]D²₀ +35.0 (c 0.50, CHCl₃); Rf = 0.6 (Et₂O).

IR (KBr): 3332, 2965, 1611, 696 cm⁻¹.

UV/Vis (MeCN): λmax (log ε) = 252 (2.31), 258 (2.33), 264 nm (2.26).

HRMS-ESI: m/z [M + H]+ calc'd for C_{12}H_{14}NO_{2}: 242.27; found: 242.27.

UV/Vis (MeCN): \( \lambda_{\text{max}} \) (log \( \varepsilon \)) = 196 (4.54), 241 (3.99), 322 nm (4.15).

HPLC (IA; flow 0.8 mL/min; n-hexane–2-propanol, 99:1; 245 nm): \( t_{R} \) ([2S]-6b) = 13.3 min, \( t_{R} \) ([2R]-6b) = 14.7 min; \( \text{dr} \) = 99:1.

(5)-2,3,6-Trimethyl-1-ethoxycarbonyl-2-phenyl)-N-methyl amide (6c)
Yield: 92%; mp 64–65 °C; \([\alpha]_{D}^{20} = -224.0 \pm 0.24\) (4.00, CHCl_{3}); \( R_{f} \) = 0.3 (Et_{2}O–n-pentane, 1:5).

HRMS-ESI: m/z [M + H]+ calc'd for C_{12}H_{14}NO_{2}: 242.27; found: 242.27.

UV/Vis (MeCN): \( \lambda_{\text{max}} \) (log \( \varepsilon \)) = 196 (4.56), 241 (3.99), 322 nm (4.15).

HPLC (IA; flow 0.8 mL/min; n-hexane–2-propanol, 99:1; 245 nm): \( t_{R} \) ([2S]-6b) = 13.3 min, \( t_{R} \) ([2R]-6b) = 14.7 min; \( \text{dr} \) = 99:1.

(5)-2,3,6-Trimethyl-1-ethoxycarbonyl-2-phenyl)-N-methyl amide (6d)
Yield: 92%; mp 64–65 °C; \([\alpha]_{D}^{20} = -224.0 \pm 0.24\) (4.00, CHCl_{3}); \( R_{f} \) = 0.3 (Et_{2}O–n-pentane, 1:5).

HRMS-ESI: m/z [M + H]+ calc'd for C_{12}H_{14}NO_{2}: 242.27; found: 242.27.

UV/Vis (MeCN): \( \lambda_{\text{max}} \) (log \( \varepsilon \)) = 196 (4.56), 241 (3.99), 322 nm (4.15).

HPLC (IA; flow 0.8 mL/min; n-hexane–2-propanol, 99:1; 245 nm): \( t_{R} \) ([2S]-6b) = 13.3 min, \( t_{R} \) ([2R]-6b) = 14.7 min; \( \text{dr} \) = 99:1.

(5)-2,3,6-Trimethyl-1-ethoxycarbonyl-2-phenyl)-N-methyl amide (6e)
Yield: 92%; mp 64–65 °C; \([\alpha]_{D}^{20} = -224.0 \pm 0.24\) (4.00, CHCl_{3}); \( R_{f} \) = 0.3 (Et_{2}O–n-pentane, 1:5).

HRMS-ESI: m/z [M + H]+ calc'd for C_{12}H_{14}NO_{2}: 242.27; found: 242.27.
MS (DCI, NH₃): m/z (%) = 290.2 (100) [M + H]⁺, 581.4 (1) [2 × M + H]⁺.

HRMS-ESI: m/z [M + H]⁺ calcd for C₁₅H₂₅NO₂: 290.2115; found: 290.2115.

UV/Vis (MeCN): λ_max (log ε) = 198 (4.48), 239 (4.02), 318 nm (3.36).

HPLC (IB: flow 0.8 mL/min; n-hexane–2-propanol, 99:1; 245 nm): t_R ([2S]-6e) = 5.7 min, t_R ([2R]-6e) = 6.4 min; dr = 99:1.

(S)-2-Benzyl-3-N-dimethyl-N-[[(S)-1-methyl-2-oxazolin-2-yl]phenylethyl]butyramide (6f)

Yield: 89%; [α]_D^20 = −7.5 (c 1.00, CHCl₃); R_f = 0.4 (Et₂O–n-pentane, 1:2).

IR (film): 3345, 2959, 2876, 1466, 1036 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 0.88 (d, J = 6.9 Hz, 3 H, CH₂(CH₂)₃), 0.87 (d, J = 6.9 Hz, 3 H, CH₂(CH₂)₃), 0.85 (d, J = 6.9 Hz, 3 H, CH₂(CH₂)₃), 1.46 (m, 4 H, 1 H, 1 H, 2 H), 1.66 (dqq, J = 6.9, 6.9, 5.1 Hz, 1 H, CH₂(CH₂)₃), 1.83 (br s, 1 H, OH), 3.39 (ddq, dd = 10.5, 6.9 Hz, 1 H, 1 H, 1 H, 1 H, 1 H, 1 H, 1 H, 2 H), 3.54 (dd, J = 10.5, 6.0 Hz, 1 H, 1 H-1).

13C NMR (75 MHz, CDCl₃): δ = 12.6, 20.2, 20.9, 30.2, 31.3, 37.1, 51.1, 52.4, 126.2, 128.2, 128.5, 129.0, 133.3, 135.3, 140.0, 174.9, 199.7.

MS (DCI, NH₃): m/z (%) = 338.4 (100) [M + H]⁺, 675.7 (1) [2 × M + H]⁺.

HRMS-ESI: m/z [M + H]⁺ calcd for C₂₀H₃₃NO₂: 338.2115; found: 338.2115.

UV/Vis (MeCN): λ_max (log ε) = 192 (4.80), 242 (4.04), 323 nm (2.21).

HPLC (IA; flow 0.8 mL/min; n-hexane–2-propanol, 99:1; 245 nm): t_R ([2S]-6f) = 20.9 min, t_R ([2R]-6f) = 33.8 min; dr >99:1.

Synthesis of 2-Substituted Alcohols 5a–f; General Procedure

To a solution of diisopropylamine (306 mg, 3.02 mmol, 6.30 equiv) in THF (1 mL) was added dropwise a solution of the oxoamide (0.48 mmol, 1.00 equiv) in THF (1 mL) at 0 °C. Borane-ammonia complex (60 mg, 0.88 mmol) was added at 0 °C and the resulting suspension was stirred at 0 °C for 30 min. The mixture was cooled to -78 °C and for another 10 min at 0 °C. The solution was warmed to 0 °C and for another 10 min at 0 °C. Borane-ammonia complex (60 mg, 0.88 mmol) was added at 0 °C and the resulting suspension was stirred at 0 °C for 10 min and at r.t. for 15 min. The mixture was cooled to 0 °C and a solution of the oxoamide (0.48 mmol, 1.00 equiv) in THF (1 mL) was added dropwise over a period of 3 min. The resulting mixture was stirred at r.t. and the conversion was monitored by TLC. The reaction was quenched by addition ofaq HCl (2 M, 10 mL) and then stirred for 30 min. The organic phase was separated and the aq phase was washed withaq HCl (2 M, 10 mL),aq NaOH (2 M, 10 mL), brine (10 mL) and dried with Na₂SO₄. The solvent was evaporated in vacuo (200 mbar) and the product was purified by flash chromatography.
GC [80 °C; p(H2) = 3 psi; n-hexane]: tR ([S]-5d) = 23.65 min, tR ([R]-5d) = 24.41 min; 96% ee.

(S)-2-Isopropylpentan-1-ol (5e)

Yield: 92%; Rf = 0.4 (EtO–n-pentane, 1:2).

IR (film): 3345, 2959, 1466, 1040 cm–1.

UV/Vis (MeCN): λmax (log ε) = 19.4 (4.45), 207 (3.92), 209 (3.91), 262 (2.36), 269 nm (2.25).

HPLC [IA; flow 0.8 mL/min; n-hexane–2-propanol, 97:3; 210 nm]: tR ([S]-5f) = 13.27 min, tR ([R]-5f) = 17.12 min; ≥99% ee.

Acknowledgment

We thank BASF, Bayer and Degussa for gifts of chemicals. C.R. thanks the Fonds der Chemischen Industrie for the granting of a scholarship.

References


(5) The desired S-configuration for alcohol 5a originates in the alkyl migration. According to Myers, the newly introduced alkyl chain is attached from the side which comprises the methyl substituent of the pseudoephedrine side chain. We measured the optical rotation for (S)-5a to be [α]D20 –11.8 (c 1.00, CHCl3). In the literature the value for the enantiomer (R)-5a was published as [α]D20 +4.94 (c 1.2, CHCl3). The opposite signs illustrate that these compounds are enantiomers and the higher value for our compound is due to its higher optical purity. Additionally, the absolute configuration of the oxoamide precursor (–)-(2S,5R)-6a, which was converted into alcohol (S)-5a, was determined by X-ray diffraction.

(6) For determination of ee values by chiral capillary GC or chiral HPLC, racemic mixtures of the alcohols were used as standards. These were synthesized by activation of isovaleric acid enolates and reduction of the resulting 2-substituted carboxylic acids by LiAlH4.

(7) The oxoamide 6a was recrystallized from EtOH–H2O. Daicel Chiralpak® IA columns (n-hexane–2-propanol, 99:1) were used for the analytical and semi-preparative HPLC separation.

(8) HPLC experiments were performed on Jasco Kromasil® RP-18 (MeCN–H2O and MeOH–H2O) and Daicel Chiralpak® IA and IB (n-hexane–2-propanol and n-hexane–CH2Cl2) columns. Epimeric mixtures of the hydroxyamides were used as standards; they were synthesized from racemic 2-substituted carboxylic acids, activated as acid chlorides, and reacted with (+)-[(3S,5S)-6a, which was converted into alcohol (S)-5a, was determined by X-ray diffraction.

(9) Yields for the alkylation correspond to those published in the experimental section. The yields for the reduction of hydroxyamides 4a-f directly to the alcohols originate in unpublished results (L. F. Tietze, C. Raith).


(11) (11) X-ray crystallography: Data were collected on a Stoe IPDS II-ary detector system instrument with graphite-
monochromated Mo-K$_\alpha$ radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods using SHELXS-97$^{12}$ and refined against $P^2_1$ on all data by full-matrix least-squares with SHELXS-97.$^{13}$ All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in the model. CCDC-664393 [(–)-(2S,1’S)-6a] contains the supplementary crystallographic data for this article. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.ac.uk/data_request/cif.


(14) Mixtures of n-hexane–2-propanol and n-hexane–CH$_2$Cl$_2$ in different compositions were tried. Epimeric mixtures of the oxoamides were used as standards for HPLC separation. These mixtures were obtained from oxidation of the epimeric mixtures of the corresponding hydroxyamides.

