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

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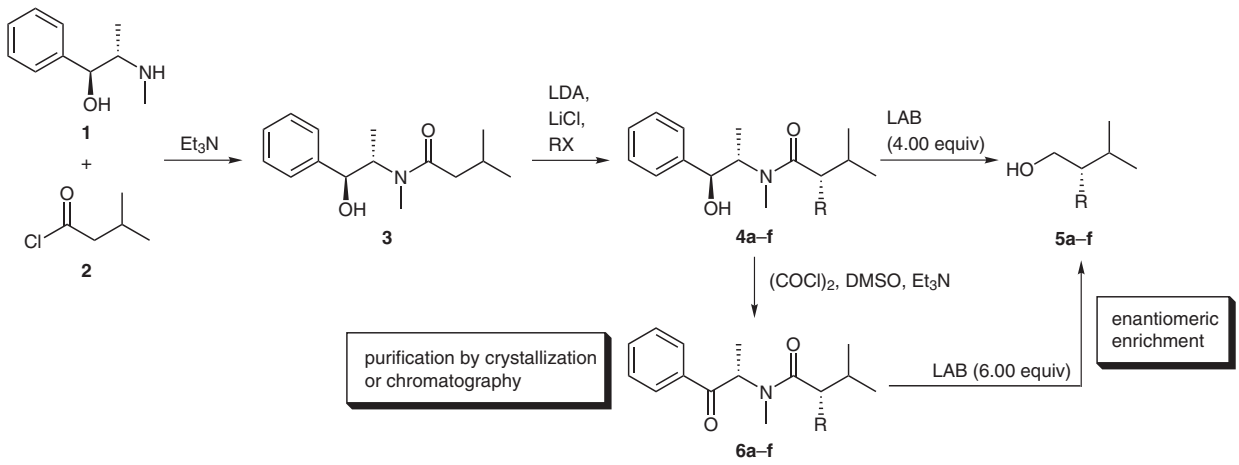
Abstract: An improved method for the selective synthesis of enantiopure 2-substituted alcohols is described. Highly diastereoselective alkylation of pseudoephedrine-derived amides and subsequent oxidation of the hydroxyl group in the amide side chain, leads to oxoamides. These oxoamides can be purified 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 enolates[2] 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 procedure[4] to the new oxoamide procedure

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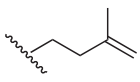
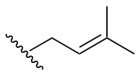
not sufficient for our synthesis.[6] However, oxidation of the hydroxyamide **4a** led to the oxoamide **6a**, which could be purified by recrystallization and also chromatography.[7] Reduction of **6a** after crystallization using LAB, led to alcohol **5a** in a comparable yield (89%) but with a highly 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.

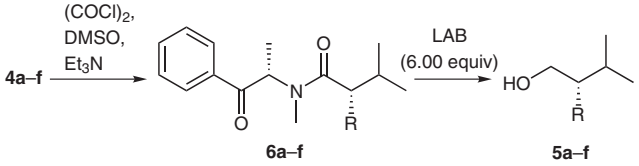
In order to determine the scope and limitations of this method, we prepared a range of 2-substituted alcohols. For this investigation we used pseudoephedrine isovalerylamide (**3**) as substrate, which was synthesized by N-acylation of (+)-(1*S*,2*S*)-pseudoephedrine (**1**) with isovaleryl chloride (**2**) in tetrahydrofuran in the presence of triethylamine. Six different hydroxyamides **4a–f** were synthesized by diastereoselective alkylation of the lithium enolate of **3** according to the protocol of Myers.[4b] The alkylation reactions proceeded in good to excellent yields (71–92%) and the hydroxyamides **4a–f** were converted to the 2-substituted alcohols by reductive cleavage with LAB (Table 1).[4b] **4f** was a crystalline solid, which after recrystallization and reduction with LAB, provided alcohol **5f** in 80% yield (69% over two steps) and >99% ee as determined by capillary GC on chiral stationary phases. However, none of the remaining five hydroxyamides **4a–e** could be purified and the diastereomeric ratio of the formed mixture of diastereomers could not be determined using HPLC.[8] In our experience, reduction of the hydroxyamides **4a–e** with LAB is difficult and leads to the alcohols **5a–e** in low to moderate yields with selectivities from 90% to 96% ee (Table 1). It can be assumed that the ee values of the alcohols **5a–f** correspond to the ratio of the diastereomeric hydroxyamides **4a–e**, since racemization during the reductive cleavage seems not to occur; this can be deduced from the reaction of **4f**, which leads to enantiopure **5f**.

Oxidation of **4a–f** using 2-iodoxybenzoic acid, permanganate or the Swern procedure, gave the oxoamides **6a–f**, which could then be purified by recrystallization or chromatography. We preferred the Swern protocol,[10] as no epimerization using triethylamine as base occurred and the transformation was fast, simple and efficient.

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

Entry	Alcohol	R	ee (%)[a]	Yield [two steps[9] (%)]
1	**5a**		90	63
2	**5b**		96	56
3	**5c**	Me	90	43
4	**5d**	Et	96	26
5	**5e**	Pr	94	37
6	**5f**	Bn	>98	69

[a] The ee values were determined by chiral capillary GC.

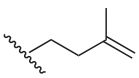
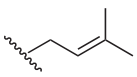


Scheme 2 Synthesis of 2-substituted alcohols **5a–f** via oxoamides **6a–f**

Oxoamides **6a–b** and **6d–f** are crystalline solids with melting points between 39 °C and 70 °C, but **6c** was formed as a yellow oil. The absolute configuration of **6a** was determined by X-ray diffraction considering the known configuration of the amide side chain at the remaining 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 colum. The resulting epimerically enriched oxoamides were reduced with LAB to give the desired alcohols **5a–c** and **5e** with highly increased enantiopurity compared to the direct cleavage of the hydroxyamides **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

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

Entry	Alcohol	R	ee[a]	Yield [three steps (%)]
1	**5a**		90[b] 97[c] >99.9[d]	58
2	**5b**		96[b] >99.9[d]	70
3	**5c**	Me	90[b] >99.9[d]	71
4	**5d**	Et	96[b]	39
5	**5e**	Pr	95[b] >99[d]	72
6	**5f**	Bn	>99[b]	67

[a] 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).
[b] Without enrichment.
[c] After recrystallization from EtOH–H_2O.
[d] After preparative HPLC (entries 1–3, Daicel Chiralpak® IA; entry 5, Daicel Chiralpak® IB).

can be greatly improved in many cases by the intermediate oxidation of the hydroxyamide intermediate **4** to an oxoamide **6**, which can be purified either by crystallization or chromatography before reductive cleavage to give the desired chiral alcohols **5**. The procedure works extremely well for compounds with longer and branched side chains at the 2-position such as **5a** and **5b**.

All chemicals were obtained from commercial suppliers and used without further purification. Melting points were determined with a Mettler FP 61 apparatus and are uncorrected. Flash chromatography was performed on silica gel 60 (Merck, 40–63 μm). Analytical 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-Cyclodextrin-B-2,2,6-M-19 columns were used. ^{1}H and ^{13}C 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-[(1*S*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl]-3-*N*-dimethylbutyramide (3)

To a solution of (+)-(1*S*,2*S*)-pseudoephedrine (**1**; 3.62 g, 21.9 mmol) and Et_3N (3.60 g, 26.3 mmol) in THF (50 mL) at 0 °C, a solution of isovaleryl chloride (**2**; 2.89 g, 2.94 mL, 24.0 mmol) in THF (1 mL) was added within 15 min. After an additional 15 min, the reaction mixture was quenched with H_2O (10 mL). EtOAc (50 mL) was added and the organic phase was separated, washed with brine (2 × 40 mL) and dried with Na_2SO_4. 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; $[\alpha]_D^{20}$ +104.0 (*c* 1.00, $CHCl_3$); R_f = 0.3 (Et_2O).

IR (KBr): 3321, 2958, 2880, 1611 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (major rotamer) = 0.89–0.94 (m, 6 H, C*H*$_3$CHC*H*$_3$), 1.09 (d, *J* = 6.6 Hz, 3 H, CH_3), 2.05–2.28 (m, 3 H, H-2, H-3), 2.78 (s, 3 H, NCH_3), 4.41 (m_c, 1 H, NCH), 4.56 (m_c, 2 H, C*H*OH, O*H*), 7.20–7.36 (m, 5 H); δ (minor rotamer) = 0.96 (d, *J* = 3.3 Hz, 3 H, CH_3), 2.88 (s, 3 H, NCH_3), 3.99 (dq, *J* = 8.1, 6.6 Hz, 1 H, NCH).

^{13}C NMR (75 MHz, $CDCl_3$): 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, NH_3): *m*/*z* (%) = 250.3 (100) $[M + H]^+$, 499.6 (19) $[2 \times M + H]^+$.

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{24}NO_2$: 250.1802; found: 250.1802.

UV/Vis (MeCN): λ_{max} (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 (2.35 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 alkylating 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 NH_4Cl (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 Na_2SO_4, concentrated in vacuo and the residue was purified by flash chromatography.

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

A solution of triflic anhydride (2.40 mmol) in CH_2Cl_2 (3 mL) was added to a solution of 3-methylbut-3-en-1-ol (2.40 mmol) and pyridine (2.88 mmol) in CH_2Cl_2 (3 mL) at –78 °C. The reaction mixture was stirred for 2 h at 0 °C, poured on crushed ice, diluted with CH_2Cl_2 (20 mL), extracted with cold aq HCl (1 M, 3 × 15 mL) and washed with cold H_2O (15 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed in vacuo at 0 °C. The triflate 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 diisopropyl amine (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 triflate (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 NH_4Cl (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 Na_2SO_4, concentrated in vacuo and the residue was purified by flash chromatography.

Yield: 83%; $[\alpha]_D^{20}$ +85.2 (*c* 1.00, $CHCl_3$); R_f = 0.2 (*n*-pentane–Et_2O, 1:1).

IR (film): 3385, 2963, 1616, 1452, 1051, 701 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (major rotamer) = 0.92 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$CHCH$_3$), 0.94 (d, *J* = 6.6 Hz, 3 H, CH$_3$CHC*H*$_3$), 1.16 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.67 (s, 3 H, C=CC*H*$_3$), 1.59–1.95 (m, 5 H, CH$_3$C*H*CH$_3$, C*H*$_2$C*H*$_2$), 2.24–2.27 (m, 1 H, H-2), 2.86 (s, 3 H, NCH_3), 4.38–4.54 (m, 1 H, NCH), 4.54 (s, 1 H, C=CH*H*), 4.61 (dd, *J* = 7.2, 7.2 Hz, 1 H, C*H*OH), 4.68 (s, 1 H, C=C*H*H), 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, C*H*$_3$CHCH$_3$), 2.92 (s, 3 H, NCH_3), 4.11 (q, *J* = 6.8 Hz, 1 H, NCH), 4.57 (m, 1 H, C=CH*H*), 4.72 (s, 1 H, C=C*H*H).

^{13}C NMR (75 MHz, DMSO-d_6, 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, NH_3): *m*/*z* (%) = 318.5 (100) $[M + H]^+$, 636.1 (23) $[2 \times M + H]^+$.

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{32}NO_2$: 318.243; found: 318.243.

Anal. Calcd for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84. Found: C, 75.41; H, 9.64.

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

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

Yield: 92%; $[\alpha]_D^{20}$ +69.6 (*c* 0.50, $CHCl_3$); R_f = 0.7 (Et_2O).

IR (film): 3328, 2959, 2872, 1601, 1054, 754, 704 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (major rotamer) = 0.88 (d, *J* = 6.8 Hz, 3 H, C*H*$_3$CHCH$_3$), 0.94 (d, *J* = 6.8 Hz, 3 H, CH$_3$CHC*H*$_3$), 1.07 (d, *J* = 6.6 Hz, 3 H, CH$_3$), 1.58 (m$_c$, 3 H, C=CCH$_3$), 1.61 (m$_c$, 3 H, C=CCH$_3$), 1.81 (dqq, *J* = 7.5, 6.8, 6.8 Hz, 1 H, CH$_3$C*H*CH$_3$), 2.16–2.40 (m, 3 H, H-2, CH$_2$), 2.80 (s, 3 H, NCH$_3$), 4.41 (m$_c$, 1 H, NCH), 4.59 (m$_c$, 1 H, C*H*OH), 4.93 (m$_c$, 1 H, HC=C), 7.20–7.39 (m, 5 H); δ (minor rotamer) = 0.86 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$CHCH$_3$), 0.93 (d, *J* = 6.6 Hz, 3 H, CH$_3$CHC*H*$_3$), 0.96 (d, *J* = 6.2 Hz, 3 H, CH$_3$), 1.66 (s, 3 H, C=CCH$_3$), 1.68 (s, 3 H, C=CCH$_3$), 2.61 (m$_c$, 1 H, H-2), 2.86 (s, 3 H, NCH$_3$), 4.11 (dq, *J* = 9.2, 6.8 Hz, 1 H, NCH), 4.50 (dd, *J* = 9.2, 2.1 Hz, 1 H, C*H*OH), 5.22 (m$_c$, 1 H, HC=C).

^{13}C NMR (75 MHz, $CDCl_3$): δ (major rotamer) = 14.6, 17.6, 19.9, 21.2, 25.7, 29.0, 30.8, 33.6, 49.4, 59.1, 76.4, 121.7, 126.4, 127.5, 128.3, 132.9, 142.5, 178.2; δ (minor rotamer) = 15.3, 17.7, 20.1, 21.3, 25.8, 26.8, 29.2, 48.2, 58.5, 75.2, 122.4, 127.5, 128.2, 128.6, 134.2, 141.0, 176.7.

MS (DCI, NH_3): *m*/*z* (%) = 318.4 (100) [M + H]$^+$, 635.7 (24) [2 × M + H]$^+$.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{32}NO_2$: 318.2428; found: 318.2428.

UV/Vis (MeCN): λ_{max} (log ε) = 192 (4.70), 248 (2.36), 254 (2.38), 258 nm (3.30).

(*S*)-*N*-[(1*S*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl]-2,3,*N*-trimethylbutyramide (4c)

Amide **3** was alkylated with iodomethane.

Yield: 92%; $[\alpha]_D^{20}$ +143.0 (*c* 0.50, $CHCl_3$); R_f = 0.3 (Et_2O–*n*-pentane, 5:1).

IR (film): 3379, 2965, 1611, 1453, 702 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (major rotamer) = 0.85 (d, *J* = 6.6 Hz, 3 H, CH$_3$CHC*H*$_3$), 0.87 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$CHCH$_3$), 0.97 (d, *J* = 6.8 Hz, 3 H, CH$_3$), 1.18 (d, *J* = 7.2 Hz, 3 H, CH$_3$), 1.85 (dqq, *J* = 8.1, 6.6, 6.6 Hz, 1 H, CH$_3$C*H*CH$_3$), 2.26 (dq, *J* = 8.1, 6.8 Hz, 1 H, H-2), 2.75 (s, 3 H, NCH$_3$), 4.25 (m$_c$, 1 H, NCH), 4.61 (dd, *J* = 7.0, 7.0 Hz, 1 H, C*H*OH), 5.01 (br s, 1 H, OH), 7.19–7.38 (m, 5 H); δ (minor rotamer) = 0.98 (d, *J* = 7.2 Hz, 3 H, CH$_3$CHC*H*$_3$), 1.06 (d, *J* = 6.6 Hz, 3 H, CH$_3$), 2.53 (dq, *J* = 7.2, 7.2 Hz, 1 H, H-2), 2.88 (s, 3 H, NCH$_3$), 4.10 (dq, *J* = 8.4, 7.2 Hz, 1 H, NCH), 4.54 (d, *J* = 8.4 Hz, 1 H, C*H*OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ (major rotamer) = 14.4, 14.8, 19.2, 21.4, 31.0, 34.4, 43.4, 60.2, 76.4, 126.1, 127.4, 128.1, 142.6, 179.1; δ (minor rotamer) = 15.5, 19.3, 21.5, 26.9, 31.4, 42.5, 58.1, 75.3, 126.8, 128.2, 128.6, 141.4, 178.0.

MS (DCI, NH_3): *m*/*z* (%) = 264.3 (100) [M + H]$^+$, 527.7 (32) [2 × M + H]$^+$.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{26}NO_2$: 264.1958; found: 264.1958.

UV/Vis (MeCN): λ_{max} (log ε) = 248 (2.36), 254 (2.39), 258 (2.39), 264 nm (2.23).

(*S*)-2-Ethyl-*N*-[(1*S*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*,3-dimethylbutyramide (4d)

Amide **3** was alkylated with iodoethane.

Yield: 80%; $[\alpha]_D^{20}$ +92.8 (*c* 0.50, $CHCl_3$); R_f = 0.4 (Et_2O–*n*-pentane, 5:1).

IR (film): 3383, 2963, 2873, 1615, 1454, 701 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (major rotamer) = 0.72 (t, *J* = 7.1 Hz, 3 H, CH$_2$C*H*$_3$), 0.89 (d, *J* = 7.1 Hz, 3 H, CH$_3$CHC*H*$_3$), 0.91 (d, *J* = 6.9 Hz, 3 H, C*H*$_3$CHCH$_3$), 1.12 (d, *J* = 6.9 Hz, 3 H, CH$_3$), 1.55 (m$_c$, 2 H, H-6), 1.86 (dqq, *J* = 8.1, 6.9, 6.9 Hz, 1 H, CH$_3$C*H*CH$_3$), 2.24 (m$_c$, 1 H, H-2), 2.86 (s, 3 H, NCH$_3$), 4.48 (m$_c$, 1 H, NCH), 4.60 (m$_c$, 1 H, C*H*OH), 7.20–7.37 (m, 5 H); δ (minor rotamer) = 0.97 (d, *J* = 7.1 Hz, 3 H, CH$_3$), 2.53 (m$_c$, 1 H, H-2), 2.89 (s, 3 H, NCH$_3$), 4.14 (dq, *J* = 9.0, 7.0 Hz, 1 H, NCH), 4.56 (m$_c$, 1 H, C*H*OH).

^{13}C NMR (75 Hz, $CDCl_3$): δ (major rotamer) = 11.7, 14.7, 19.9, 21.3, 23.2, 30.7, 33.5, 50.7, 59.2, 76.3, 126.3, 127.4, 128.2, 142.5, 178.4; δ (minor rotamer) = 12.4, 15.2, 19.6, 21.5, 22.5, 26.7, 49.3, 58.1, 75.3, 127.0, 128.6, 141.2, 176.8.

MS (DCI, NH_3): *m*/*z* (%) = 278.0 (100) [M + H]$^+$, 295.4 (10) [M + NH$_4$]$^+$, 555.7 (36) [2 × M + H]$^+$.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{28}NO_2$: 278.2115; found: 278.2120.

UV/Vis (MeCN): λ_{max} (log ε) = 252 (2.31), 258 (2.33), 264 nm (2.26).

(*S*)-2-Isopropylpentanoic Acid *N*-[(1*S*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl]-*N*-methyl Amide (4e)

Amide **3** was alkylated with 1-iodopropane.

Yield: 85%; $[\alpha]_D^{20}$ +92.8 (*c* 0.50, $CHCl_3$); R_f = 0.6 (Et_2O).

IR (film): 3383, 2459, 1616, 1454, 761 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (major rotamer) = 0.80 (t, *J* = 7.2 Hz, 3 H, CH$_3$), 0.87 (d, *J* = 6.8 Hz, 3 H, C*H*$_3$CHCH$_3$), 0.90 (d, *J* = 6.8 Hz, 3 Hz, CH$_3$CHC*H*$_3$), 0.93–1.09 (m, 2 H, C*H*$_2$CH$_3$), 1.11 (d, *J* = 7.0 Hz, 3 H, CH$_3$), 1.35 (m$_c$, 1 H, H-3), 1.49–1.63 (m, 1 H, H-3), 1.82 (dqq, *J* = 8.2, 6.8, 6.8 Hz, 1 H, CH$_3$C*H*CH$_3$), 2.28 (ddd, *J* = 8.2, 8.2, 3.5 Hz, 1 H, H-2), 2.84 (s, 3 H, NCH$_3$), 4.43 (m$_c$, 1 H, NCH), 4.58 (d, *J* = 7.3 Hz, 1 H, C*H*OH), 7.18–7.35 (m, 5 H); δ (minor rotamer) = 0.95 (d, *J* = 6.6 Hz, 3 H, CH$_3$), 2.63 (m$_c$, 1 H, H-2), 2.86 (s, 3 H, NCH$_3$), 4.12 (dq, *J* = 9.1, 6.6 Hz, 1 H, NCH), 4.53 (d, *J* = 9.1 Hz, 1 H, C*H*OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ (major rotamer) = 14.3, 14.6, 19.9, 20.6, 21.2, 31.0, 32.5, 34.5, 49.0, 59.5, 76.3, 126.2, 127.4, 128.2, 142.6, 178.6; δ (minor rotamer) = 15.2, 19.6, 21.5, 26.8, 31.8, 47.8, 75.3, 127.0, 128.3, 128.6, 141.2, 177.0.

MS (DCI, NH_3): *m*/*z* (%) = 292.4 (100) [M + H]$^+$, 583.7 (22) [2 × M + H]$^+$.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{30}NO_2$: 292.2271; found: 292.2271.

UV/Vis (MeCN): λ_{max} (log ε) = 252 (2.31), 258 (2.33), 264 nm (2.26).

(*S*)-2-Benzyl-*N*-[(1*S*,2*S*)-2-hydroxy-1-methyl-2-phenylethyl]-3,*N*-dimethylbutyramide (4f)

Amide **3** was alkylated with benzyl bromide.

Yield: 85%; mp 121–122 °C; $[\alpha]_D^{20}$ –35.0 (*c* 0.50, $CHCl_3$); R_f = 0.6 (Et_2O).

IR (KBr): 3332, 2965, 1611, 696 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (major rotamer) = 0.61 (d, *J* = 6.6 Hz, 3 H, CH$_3$), 0.95 (d, *J* = 6.3 Hz, 3 H, C*H*$_3$CHCH$_3$), 1.06 (d, *J* = 6.3 Hz, 3 H, CH$_3$CHC*H*$_3$), 2.00 (m$_c$, 1 H, CH$_3$C*H*CH$_3$), 2.46 (s, 3 H, NCH$_3$), 2.64 (m$_c$, 1 H, H-2), 2.76–2.93 (m, 2 H, CH$_2$), 3.69 (m$_c$, 1 H, NCH), 4.38–4.48 (m, 2 H, C*H*OH, OH), 7.13–7.28 (m, 10 H); δ (minor rotamer) = 0.86 (d, *J* = 6.9 Hz, 3 H, CH$_3$), 2.72 (s, 3 H, NCH$_3$), 3.85 (dq, *J* = 8.7, 6.6 Hz, 1 H, NCH), 4.13 (dd, *J* = 8.7, 3.6 Hz, 1 H, C*H*OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ (major rotamer) = 14.2, 20.2, 21.3, 31.2, 31.5, 37.1, 52.2, 57.1, 76.5, 126.1, 126.5, 126.6, 126.9, 127.6, 128.2, 128.3, 128.5, 128.6, 128.9, 129.2, 140.2, 142.2, 177.7; δ (minor rotamer) = 15.2, 26.9, 36.8, 51.1, 58.2, 74.9, 140.8.

MS (DCI, NH_3): *m*/*z* (%) = 340.3 (100) [M + H]$^+$, 679.8 (18) [2 × M + H]$^+$.

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{22}H_{30}NO_2$: 340.2271; found: 340.2271.

UV/Vis (MeCN): λ_{max} (log ε) = 192 (4.64), 252 (4.01), 258 (4.59), 264 nm (3.90).

Formation of Oxoamides 6a–f; General Procedure

To a stirred solution of oxalyl chloride (938 mg, 7.24 mmol) in CH_2Cl_2 (16 mL) at –78 °C, dimethyl sulfoxide (1.03 g, 14.5 mmol) in CH_2Cl_2 (3 mL) was added. After 5 min, the hydroxyamide (6.58 mmol) was added dropwise as a solution in CH_2Cl_2 (7 mL) over a period of 5 min. The solution was stirred for 15 min and Et_3N (3.33 g, 32.9 mmol) was added dropwise. After 10 min, the reaction mixture was warmed to r.t. and the reaction was quenched with H_2O (50 mL). The phases were separated and the organic phase was extracted with CH_2Cl_2 (50 mL). The combined organic phases were washed with aq HCl (2 N, 50 mL), aq NaOH (2 M, 50 mL), H_2O (50 mL), brine (50 mL) and dried with Na_2SO_4. The solvent was evaporated in vacuo and the residue was purified by flash chromatography. Crystalline products were crystallized from EtOH–H_2O. **6a–c** and **6e** were purified by semi-preparative HPLC, using Daicel Chiralpak® IA or IB columns.

(*S*)-2-Isopropyl-5-methylhex-5-enoic Acid *N*-[(*S*)-1-Methyl-2-oxophenylethyl]-*N*-methyl Amide (6a)

Yield: 79%; mp 53–54 °C; $[\alpha]_D^{20}$ –228.0 (*c* 1.00, $CHCl_3$); R_f = 0.4 (Et_2O–*n*-pentane, 1:2).

IR (KBr): 2963, 1692, 1625, 1448, 693 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.81 (d, *J* = 6.6 Hz, 3 H, CH_3CHCH$_3$), 0.87 (d, *J* = 6.6 Hz, 3 H, CH$_3$CHCH_3), 1.35 (d, *J* = 6.7 Hz, 3 H, CH$_3$), 1.42–1.71 (m, 5 H, CH_2CH_2, CH$_3$C*H*CH$_3$), 1.64 (s, 3 H, C=CCH$_3$), 2.46 (m$_c$, 1 H, H-2), 2.97 (s, 3 H, NCH$_3$), 4.59 (s, 1 H, C=C*H*H), 4.69 (s, 1 H, C=CH*H*), 5.63 (q, *J* = 6.7 Hz, 1 H, NCH), 7.46–7.62 (m, 3 H), 7.87 (d, *J* = 7.2 Hz, 2 H).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 12.1, 18.6, 19.8, 21.2, 26.6, 29.6, 31.7, 34.3, 45.5, 55.1, 109.2, 127.1, 127.7, 131.8, 136.0, 144.7, 173.7, 198.2.

MS (ESI): *m/z* (%) = 338.2 (16) [M + Na]$^+$, 653.1 (100) [2 × M + Na]$^+$.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd for $C_{20}H_{29}NNaO_2$: 338.210; found: 338.209.

UV/Vis (MeCN): λ_{max} (log ε) = 196 (4.55), 240 nm (4.04).

HPLC (IA; flow 0.8 mL/min; *n*-hexane–2-propanol, 99:1; 245 nm): t_R [(2*S*)-**6a**] = 18.9 min, t_R [(2*R*)-**6a**] = 20.9 min; dr >99:1.

(*S*)-2-Isopropyl-5-methylhex-4-enoic Acid *N*-[(*S*)-1-Methyl-2-oxo-2-phenylethyl]-*N*-methyl Amide (6b)

Yield: 80%; mp 39–40 °C; $[\alpha]_D^{20}$ –175.3 (*c* 4.00, $CHCl_3$); R_f = 0.3 (Et_2O–*n*-pentane, 1:5).

IR (KBr): 2962, 1684, 1639, 1449, 702 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.66 (d, *J* = 6.8 Hz, 3 H, CH_3CHCH$_3$), 0.85 (d, *J* = 6.8 Hz, 3 H, CH$_3$CHCH_3), 1.25 (d, *J* = 6.6 Hz, 3 H, CH$_3$), 1.58 (s, 3 H, C=CCH$_3$), 1.61 (s, 3 H, C=CCH$_3$), 1.83 (m$_c$, 1 H, CH$_3$C*H*CH$_3$), 2.15–2.35 (m, 3 H, H-2, H-6), 2.70 (s, 3 H, NCH$_3$), 4.97 (m$_c$, 1 H, HC=C), 6.20 (q, *J* = 6.7 Hz, 1 H, NCH), 7.37 (m$_c$, 2 H), 7.49 (m$_c$, 1 H), 7.95 (m$_c$, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.9, 17.6, 19.9, 21.0, 25.7, 29.3, 30.8, 30.9, 48.3, 52.9, 121.4, 128.4, 128.5, 133.2, 133.3, 135.2, 175.5, 199.8.

MS (EI, 70 eV): *m/z* (%) = 125.2 (8), 210.3 (24), 272.3 (6), 315.4 (8) [M]$^+$.

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{20}H_{30}NO_2$: 316.2271; found: 316.2271.

UV/Vis (MeCN): λ_{max} (log ε) = 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 [(2*S*)-**6b**] = 15.0 min, t_R [(2*R*)-**6b**] = 21.7 min; dr >99:1.

(*S*)-2,3,*N*-Trimethyl-*N*-[(*S*)-1-methyl-2-oxo-2-phenylethyl]-*N*-butyramide (6c)

Yield: 90%; $[\alpha]_D^{20}$ –195.7 (*c* 3.00, $CHCl_3$); R_f = 0.3 (Et_2O–*n*-pentane, 1:2).

IR (film): 2963, 2348, 1690, 1640, 1449, 1237, 749 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.72 (d, *J* = 6.8 Hz, 3 H, CH_3CHCH$_3$), 0.82 (d, *J* = 6.8 Hz, 3 H, CH$_3$), 1.00 (d, *J* = 6.8 Hz, 3 H, CH$_3$CHCH_3), 1.30 (d, *J* = 7.1 Hz, 3 H, CH$_3$), 1.77 (m$_c$, 1 H, CH$_3$C*H*CH$_3$), 2.31 (m$_c$, 1 H, H-2), 2.76 (s, 3 H, NCH$_3$), 6.12 (q, *J* = 6.8 Hz, 1 H, NCH), 7.37 (m$_c$, 2 H), 7.50 (m$_c$, 1 H), 7.93 (m$_c$, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.9, 14.3, 19.0, 21.4, 30.6, 30.7, 42.4, 53.1, 128.4, 128.5, 133.2, 135.2, 176.2, 199.7.

MS (DCI, NH_3): *m/z* (%) = 276.4 (100) [M + H]$^+$, 551.8 (1) [2 × M + H]$^+$.

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{16}H_{24}NO_2$: 262.1802; found: 262.1802.

UV/Vis (MeCN): λ_{max} (log ε) = 197 (4.46), 240 (4.00), 324 nm (2.19).

HPLC (IA; flow 0.8 mL/min; *n*-hexane–2-propanol, 99:1; 245 nm): t_R (2*S*)-**6c** = 18.9 min, t_R (2*R*)-**6c** = 20.9 min; dr >99:1.

(*S*)-2-Ethyl-3,*N*-dimethyl-*N*-[(*S*)-1-methyl-2-oxo-2-phenylethyl]butyramide (6d)

Yield: 86%; mp 63–64 °C; $[\alpha]_D^{20}$ –242.2 (*c* 5.00, $CHCl_3$); R_f = 0.2 (Et_2O–*n*-pentane. 1:5).

IR (KBr): 2968, 2871, 1685, 1624, 1324, 750 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.70 (d, *J* = 6.8 Hz, 3 H, CH_3CHCH$_3$), 0.84 (d, *J* = 6.8 Hz, 3 H, CH$_3$CHCH_3), 0.78 (t, *J* = 7.3 Hz, 3 H, CH$_3$), 1.34 (d, *J* = 6.8 Hz, 3 H, CH$_3$), 1.47–1.69 (m, 2 H, CH$_2$), 1.79 (m$_c$, 1 H, CH$_3$C*H*CH$_3$), 2.27 (ddd, *J* = 7.7, 7.7, 4.0 Hz, 1 H, H-2), 2.81 (s, 3 H, NCH$_3$), 6.21 (q, *J* = 6.8 Hz, 1 H, NCH), 7.40 (m$_c$, 2 H), 7.52 (m$_c$, 1 H), 7.96 (m$_c$, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.8, 13.3, 19.7, 21.1, 23.1, 30.7, 31.0, 49.6, 53.2, 128.4, 128.5, 133.2, 135.3, 175.6, 199.8.

MS (DCI, NH_3): *m/z* (%) = 267.4 (100) [M + H]$^+$, 551.8 (1) [2 × M + H]$^+$.

HRMS-ESI: *m/z* [M + H]$^+$ calcd for $C_{17}H_{26}NO_2$: 276.1958; found: 276.1958.

UV/Vis (MeCN): λ_{max} (log ε) = 198 (4.49), 240 (4.01), 322 nm (2.23).

(*S*)-2-Isopropylpentanoic Acid *N*-[(*S*)-1-Methyl-2-oxo-2-phenylethyl]-*N*-methyl Amide (6e)

Yield: 92%; mp 64–65 °C; $[\alpha]_D^{20}$ –224.0 (*c* 4.00, $CHCl_3$); R_f = 0.3 (Et_2O–*n*-pentane, 1:5).

IR (KBr): 2959, 2872, 1691, 1638, 1449, 1237, 813 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.68 (d, *J* = 6.9 Hz, 3 H, CH_3CHCH$_3$), 0.82 (d, *J* = 6.6 Hz, 3 H, CH$_3$CHCH_3), 0.83 (t, *J* = 7.1 Hz, 3 H, CH$_3$), 0.98–1.23 (m, 2 H, CH$_2$), 1.32 (d, *J* = 6.9 Hz, 3 H, CH$_3$), 1.34–1.43 (m, 1 H, H-6), 1.50–1.64 (m, 1 H, H-6), 1.73 (m$_c$, 1 H, CH$_3$C*H*CH$_3$), 2.31 (ddd, *J* = 7.6, 7.3, 3.5 Hz, 1 H, H-2), 2.80 (s, 3 H, NCH$_3$), 6.14 (q, *J* = 6.8 Hz, 1 H, NCH), 7.38 (m$_c$, 2 H), 7.50 (m$_c$, 1 H), 7.94 (m$_c$, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.2, 14.4, 19.7, 20.8, 21.0, 30.8, 31.1, 32.3, 47.9, 53.3, 128.4, 128.5, 133.2, 135.4, 175.7, 199.8.

MS (DCI, NH_3): *m/z* (%) = 290.2 (100) $[M + H]^+$, 581.4 (1) $[2 \times M + H]^+$.

HRMS-ESI: *m/z* $[M + H]^+$ calcd for $C_{18}H_{28}NO_2$: 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 [(2*S*)-**6e**] = 5.7 min, t_R [(2*R*)-**6e**] = 6.4 min; dr >99:1.

(*S*)-2-Benzyl-3,*N*-dimethyl-*N*-[(*S*)-1-methyl-2-oxomethyl-2-phenylethyl]butyramide (6f)

Yield: 82%; mp 70–71 °C; $[\alpha]_D^{20}$ –210.6 (*c* 5.00, $CHCl_3$); R_f = 0.2 (Et_2O–*n*-pentane, 5:1).

IR (KBr): 2962, 1691, 1627, 1454, 963.3, 750.0, 521 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.70 (d, *J* = 6.7 Hz, 3 H, CH_3CHCH_3), 0.91 (d, *J* = 6.8 Hz, 3 H, CH_3), 0.99 (d, *J* = 6.7 Hz, 3 H, CH_3CHCH_3), 1.95 (dqq, *J* = 8.2, 6.8, 6.8 Hz, 1 H, CH_3CHCH_3), 2.31 (s, 3 H, NCH_3), 2.60 (m_c, 1 H, H-2), 2.87 (m_c, 2 H, CH_2), 6.15 (q, *J* = 6.8 Hz, 1 H, NCH), 7.15–7.27 (m, 5 H), 7.39 (m_c, 2 H), 7.51 (m_c, 1 H), 7.96 (m_c, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.6, 20.2, 20.9, 30.2, 31.3, 37.1, 51.1, 52.4, 126.2, 128.2, 128.5, 128.6, 129.0, 133.3, 135.2, 140.0, 174.9, 199.7.

MS (DCI, NH_3): *m/z* (%) = 338.4 (100) $[M + H]^+$, 675.7 (1) $[2 \times M + H]^+$.

HRMS-ESI: *m/z* $[M + H]^+$ calcd for $C_{22}H_{28}NO_2$: 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 [(2*S*)-**6f**] = 20.9 min, t_R [(2*R*)-**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 (4 mL) at –78 °C, *n*-BuLi (2.5 M in hexanes, 1.1 mL, 2.81 mmol, 5.85 equiv) was added. The solution was stirred for 10 min at –78 °C and for another 10 min at 0 °C. Borane-ammonia complex (90%, 98.8 mg, 2.88 mmol, 6.00 equiv) was added at 0 °C and the resulting suspension was stirred at 0 °C for 15 min and at r.t. for 15 min. The mixture was cooled to 0 °C and a solution of the oxoamide (0.480 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 of aq HCl (2 M, 10 mL) and then stirred for 30 min. The organic phase was separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with aq HCl (2 M, 10 mL), aq NaOH (2 M, 10 mL), brine (10 mL) and dried with Na_2SO_4. The solvent was evaporated in vacuo (200 mbar) and the product was purified by flash chromatography.

(*S*)-2-Isopropyl-5-methylhex-5-en-1-ol (5a)

Yield: 89%; $[\alpha]_D^{20}$ –11.8 (*c* 1.00, $CHCl_3$); [lit.[15] (*R*)-**5a**: $[\alpha]_D^{24}$ +9.04 (*c* 1.2, $CHCl_3$)]; R_f = 0.4 (Et_2O–*n*-pentane, 2:1).

IR (film): 3344, 2958, 1650, 1454, 1370, 1036 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.9 Hz, 3 H, CH_3CHCH_3), 0.92 (d, *J* = 6.9 Hz, 3 H, CH_3CHCH_3), 1.21–2.15 (m, 3 H, H-2, $CHCH_2$), 1.74 (s, 3 H, $C{=}CCH_3$), 1.78–1.89 (m, 1 H, CH_3CHCH_3), 1.97–2.15 (m, 2 H, $CH_2C{=}C$), 3.62 (m_c, 2 H, CH_2O), 4.70 (s, 1 H, C = C*H*H), 4.71 (s, 1 H, C = CH*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3, 19.8, 22.4, 25.7, 27.9, 36.0, 46.1, 63.6, 109.9, 146.

MS (EI, 70 eV): *m/z* (%) = 69 (100), 156 (10) $[M]^+$.

HRMS-EI: *m/z* $[M]^+$ calcd for $C_{10}H_{20}O$: 156.151; found: 156.151.

UV/Vis (MeCN): λ_{max} (log ε) = 192 nm (3.90).

GC [120 °C; $p(H_2)$ = 3 psi; *n*-hexane]: t_R [(*S*)-**5a**] = 16.29 min, t_R [(*R*)-**5a**] = 16.66 min; ≥99.9% ee.

(*S*)-2-Isopropyl-5-methylhex-4-en-1-ol (5b)

Yield: 95%; $[\alpha]_D^{20}$ –7.5 (*c* 1.00, $CHCl_3$); R_f = 0.4 (Et_2O–*n*-pentane, 1:2).

IR (film): 3356, 2954, 1451, 1378, 1042 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.9 Hz, 3 H, CH_3CHCH_3), 0.89 (d, *J* = 6.9 Hz, 3 H, CH_3CHCH_3), 1.31–1.42 (m, 1 H, H-2), 1.60 (s, 3 H, $C{=}CCH_3$), 1.68 (s, 3 H, $C{=}CCH_3$), 1.77 (dqq, *J* = 6.9, 6.9, 5.0 Hz, 1 H, CH_3CHCH_3), 1.89–2.08 (m, 2 H, CH_2), 3.56 (m_c, 2 H, CH_2OH), 5.14 (m_c, 1 H, HC=C).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.7, 19.4, 19.9, 25.8, 26.8, 28.0, 47.3, 64.2, 123.4, 132.6.

MS (EI, 70 eV): *m/z* (%) = 69.1 (100), 82.1 (40), 156.3 (22) $[M]^+$.

HRMS-ESI: *m/z* $[M + H]^+$ calcd for $C_{12}H_{21}O$: 157.1587; found: 157.1587.

UV/Vis (MeCN): λ_{max} (log ε) = 192 nm (3.90).

GC [120 °C; $p(H_2)$ = 3 psi; *n*-hexane]: t_R [(*S*)-**5b**] = 16.29 min, t_R [(*R*)-**5b**] = 16.74 min; ≥99.9% ee.

(*S*)-2,3-Dimethylbutan-1-ol (5c)

Yield: 85%; $[\alpha]_D^{20}$ +4.6 (*c* 1.00, $CHCl_3$) [lit.[16] $[\alpha]_D^{20}$ +5.0 (*c* 3.0, CH_2Cl_2)]; R_f = 0.4 (Et_2O–*n*-pentane, 1:2).

IR (film): 3345, 2959, 2876, 1464, 1036 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.79 (d, *J* = 7.2 Hz, 3 H, CH_3CHCH_3), 0.82 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.87 (d, *J* = 6.9 Hz, 3 H, CH_3CHCH_3), 1.46 (m_c, 1 H, H-2), 1.66 (dqq, *J* = 6.9, 6.9, 5.1 Hz, 1 H, CH_3CHCH_3), 1.83 (br s, 1 H, OH), 3.39 (dd, *J* = 10.5, 6.9 Hz, 1 H, H-1), 3.54 (dd, *J* = 10.5, 6.0 Hz, 1 H, H-1).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.4, 17.9, 20.6, 28.8, 41.3, 66.4.

MS (DCI, NH_3): *m/z* (%) = 120.2 (84) $[M + NH_4]^+$, 137.2 (24) $[M + NH_3 + NH_4]^+$.

HRMS-ESI: *m/z* $[M + H]^+$ calcd for $C_6H_{15}O$: 103.1117; found: 103.1117.

UV/Vis (MeCN): λ_{max} (log ε) = 255 nm (1.45).

GC [80 °C; $p(H_2)$ = 3 psi; *n*-hexane]: t_R [(*S*)-**5c**] = 22.58 min, t_R [(*R*)-**5c**] = 23.05 min; ≥99.9% ee.

(*S*)-2-Ethyl-3-methylbutan-1-ol (5d)

Yield: 57%; $[\alpha]_D^{20}$ –5.8 (*c* 1.00, $CHCl_3$) [lit.[17] $[\alpha]_D^{20}$ –9.47 (neat)]; R_f = 0.4 (Et_2O–*n*-pentane, 1:2).

IR (film): 3345, 2960, 2876, 1466, 1035 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.9 Hz, 3 H, CH_3CHCH_3), 0.85 (d, *J* = 6.9 Hz, 3 H, CH_3CHCH_3), 0.87 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.13–1.45 (m, 3 H, H-2, CH_2), 1.76 (dqq, *J* = 9.0, 6.9, 6.9 Hz, 1 H, CH_3CHCH_3), 1.82 (br s, 1 H, OH), 3.55 (m_c, 2 H, CH_2OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1, 19.3, 19.7, 20.3, 27.5, 48.2, 63.2.

MS (DCI, NH_3): *m/z* (%) = 134.2 (100) $[M + NH_4]^+$, 151.3 (32) $[M + NH_3 + NH_4]^+$, 205.5 (1) $[2 \times M + NH_4]^+$.

HRMS-ESI: *m/z* $[M + H]^+$ calcd for $C_7H_{17}O$: 117.1274; found: 117.1274.

UV/Vis (MeCN): λ_{max} (log ε) = 215 nm (2.27).

GC [80 °C; $p(H_2)$ = 3 psi; *n*-hexane]: t_R [(*S*)-**5d**] = 23.65 min, t_R [(*R*)-**5d**] = 24.41 min; 96% ee.

(*S*)-2-Isopropylpentan-1-ol (5e)
Yield: 92%; R_f = 0.4 (Et_2O–*n*-pentane, 1:2).

IR (film): 3345, 2959, 1466, 1040 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 7.1 Hz, 3 H, CH_3CHCH_3), 0.87 (d, *J* = 6.9 Hz, 3 H, CH_3CHCH_3), 0.88 (t, *J* = 6.5 Hz, 3 H, CH_3), 1.13–1.38 (m, 5 H, H-2, CH_2CH_2), 1.77 (m_c, 1 H, CH_3CHCH_3), 2.46 (br s, 1 H, OH), 3.53 (m_c, 2 H, CH_2OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 19.0, 19.7, 20.9, 27.7, 29.9, 46.2, 63.6.

MS (DCI, NH_3): *m*/*z* (%) = 148.2 (100) $[M + NH_4]^+$, 165.3 (52) $[M + NH_3 + NH_4]^+$, 278.5 (2) $[2 \times M + NH_4]^+$.

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_8H_{19}O$: 131.1430; found: 131.1430.

GC [90 °C; $p(H_2)$ = 3 psi; *n*-hexane]: t_R [(*S*)-**5e**] = 19.51 min, t_R [(*R*)-**5e**] = 20.50 min; >99% ee.

(*S*)-2-Benzyl-3-methylbutan-1-ol (5f)
Yield: 78%; $[\alpha]_D^{20}$ –11.8 (*c* 1.00, $CHCl_3$); R_f = 0.3 (Et_2O–*n*-pentane, 1:2).

IR (film): 3355, 2458, 1451, 1039, 733.7 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.8 Hz, 3 H, CH_3CHCH_3), 0.96 (d, *J* = 6.8 Hz, 3 H, CH_3CHCH_3), 1.47 (br s, 1 H, OH), 1.65 (m_c, 1 H, H-2), 1.85 (dqq, *J* = 9.1, 6.8, 6.8 Hz, 1 H, CH_3CHCH_3), 2.50 (dd, *J* = 13.8, 9.2 Hz, 1 H, CH_2), 2.69 (dd, *J* = 13.7, 5.5 Hz, 1 H, CH_2), 3.52 (d, *J* = 5.7 Hz, 2 H, CH_2OH), 7.14–7.29 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.4, 19.6, 27.6, 34.3, 48.7, 62.8, 125.7, 128.3, 129.0, 141.4.

MS (EI, 70 eV): *m*/*z* (%) = 43.1 (100), 58.1 (55), 91.1 (48), 178.3 (16) $[M]^+$.

HRMS-ESI: *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{19}O$: 179.1430; found: 179.1430.

UV/Vis (MeCN): λ_{max} (log ε) = 194 (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]: t_R [(*R*)-**5f**] = 13.27 min, t_R [(*S*)-**5f**] = 17.12 min; ≥ 99% ee.

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(5) The desired *S*-configuration for alcohol **5a** originates in the alkylation reaction. According to Myers,[4b] 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 $[\alpha]_D^{20}$ –11.8 (*c* 1.00, $CHCl_3$). In the literature the value for the enantiomer (*R*)-**5a** was published as $[\alpha]_D^{24}$ +9.04 (*c* 1.2, $CHCl_3$).[15] 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 (–)-(2*S*),1′*S*)-**6a**, which was converted into alcohol (*S*)-**5a**, was determined by X-ray diffraction.[11]

(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 alkylation of isovaleric acid enolates and reduction of the resulting 2-substituted carboxylic acids by $LiAlH_4$.

(7) The oxoamide **6a** was recrystallized from EtOH–H_2O. 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–H_2O and MeOH–H_2O) and Daicel Chiralpak® IA and IB (*n*-hexane–2-propanol and *n*-hexane–CH_2Cl_2) 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 (+)-(1*S*,2*S*)-pseudoephedrine.

(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).

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monochromated Mo-K_α radiation (λ = 0.71073 Å). The structure was solved by direct methods using SHELXS-97[12] and refined against P^{21} 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 [(–)-(2*S*,1′*S*)-**6a**] contains the supplementary crystallographic data for this article. These data can be obtained free of charge from The Cambridge Cyrstallographic Data Centre via www.ccdc.ac.uk/data_request/cif.

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(14) Mixtures of *n*-hexane–2-propanol and *n*-hexane–CH_2Cl_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.

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