Stereocontrolled Synthesis of 1,3-Amino Alcohols by Reduction of Substituted 2-{1-[(*tert*-Butylsulfinyl)amino]alkyl}cyclohexanones

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Dedicated to Professor Yoshinori Yamamoto on the occasion of his 65th birthday

Abstract: Assembly of diethylzinc, cyclohex-2-en-1-one, and a chiral *N*-*tert*-butylsulfinyl imine in the presence of an appropriate phosphoramidite ligand yields a β-sulfinylamino cyclohexanone, which on reduction with sodium borohydride or lithium triethylborohydride provides access to a wide range of enantiomerically pure *N*-*tert*-butylsulfinyl 1,3-amino alcohols with five stereogenic centers.

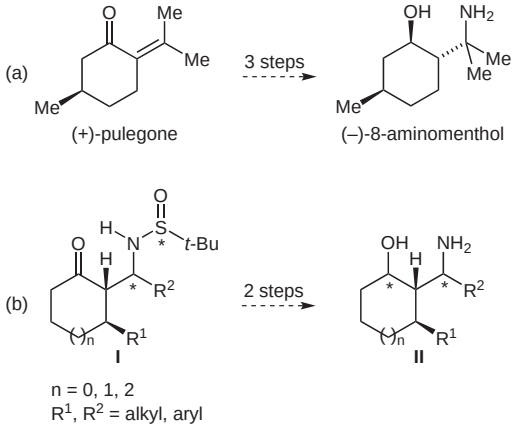
Key words: amino alcohols, ketones, reduction, phosphoramidites, multicomponent reaction, stereoselectivity

Chiral amino alcohols are useful as building blocks in asymmetric synthesis, where they can function as ligands or auxiliaries. Although less common than 1,2-amino alcohols, 1,3-amino alcohols have been used extensively in asymmetric synthesis.[1]

After the seminal contribution of He and Eliel in 1987,[2] more work has been published on the chemistry of (–)-8-aminomenthol [(1*S*,2*S*,5*R*)-2-(2-aminopropan-2-yl)-5-methylcyclohexanol] and its derivatives than on any other single 1,3-amino alcohol.[3] This is probably because such compounds can be readily prepared in three steps from natural (+)-pulegone (Scheme 1, a). To the best of our knowledge, and despite the prevalence of (–)-8-aminomenthol as a source of chirality in asymmetric synthesis, no work on any other stereoisomer has been reported. Undoubtedly, this is because of the lack of affordable enantiomerically pure precursors and routes for the efficient syntheses of these chiral building blocks.[4]

We have recently reported that enantiomerically pure β-amino cycloalkanones can be readily prepared by trapping by chiral *N*-*tert*-butylsulfinyl imines of the chiral enolates formed by asymmetric conjugate addition of dialkylzinc reagents to cycloalkanones.[5] These enantiomerically pure β-amino cycloalkanones, which contain three consecutive stereogenic centers, offer a good platform for the stereoselective synthesis of *syn*- and *anti*-1,3-amino alcohols (Scheme 1, b).

Although a broad range of substrates could be used for the preparation of β-aminocycloalkanones by our tandem procedure, we selected diethylzinc, cyclohex-2-en-1-one,



Scheme 1 Stereoselective synthesis of β-amino cycloalkanols

and sulfinimine **2** (or its enantiomer *ent*-**2**) for the sake of simplicity in this study. In our previous study, we used the phosphoramidite ligand **L2**, because it permits the generation of highly enantioenriched enolates (ee > 98%) through a copper-catalyzed addition of dialkylzinc reagents to cyclic enones.[6] We decided to re-examine the tandem reaction by using phosphoramidite ligand **L1**, in which the binaphthyl moiety is the sole source of chirality, and which has been reported to afford only modest enantioselectivity (60% ee) in the conjugate addition.[7]

Our studies in which we used ligand **L1** in the tandem copper-catalyzed addition of diethylzinc to cyclohex-2-en-1-one and Mannich reaction with sulfinimine **2** (or *ent*-**2**) are summarized in Table 1. Interestingly, better diastereoselection was obtained when the (R_S)-sulfinimine **2** was added before the conjugate addition occurred (entries 1 and 3), and the opposite was observed with *ent*-**2** (entries 2 and 4). A greater excess of the enolate afforded similar results, suggesting that kinetic resolution of the homochiral enolate is not a good explanation for this matched/mismatched combination. It is more likely that the (R_S)-sulfinimine **2** cooperates with phosphoramidite *Sa*-**L1** in the copper-catalyzed addition of diethylzinc; however, we lack firm evidence to support this hypothesis. Importantly, diastereoisomers **3a** and **3b** could be easily separated by normal flash chromatography (FC). Nevertheless, the use of the phosphoramidite ligand **L2** is still more practical, because compound **3a** is obtained as a single isomer (entry 5). Unfortunately, a rather low selectivity was observed when the combination of ligand **L2**

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and sulfinimine *ent*-**2** was used, compounds *ent*-**3b** and *ent*-**3c** being obtained as an inseparable 71:29 mixture (entry 6).[8]

The stereochemical information present in cyclohexanones **3** suggests that a stereoselective reduction is possible. However, because control can be exerted by the cyclohexanone moiety as well as by the sulfinylamino group, the stereochemical outcome was not completely apparent at the outset of this work. Moreover, the repulsive gauche interaction between the C(2) and C(3) substituents of the cyclohexanone moiety could favor the diaxial conformer over the usual diequatorial one, further complicating the result.[9]

Reduction of compound **3a** with sodium borohydride gave the crystalline amino alcohol **4a** exclusively in almost quantitative yield. When the 71:29 mixture of compounds **3b** and **3c** was reduced by sodium borohydride, diastereoisomers **4c** and **4d** were isolated as pure compounds after FC. To confirm the stereochemical assignment, the sulfinyl group in compounds **4a** and **4d** was oxidized with 3-chloroperoxybenzoic acid to give the sulfonamides **4f** and *ent*-**4f**, respectively. This result clearly supports the view that the formation of the minor β-amino cycloalkanone **3c** is a consequence of poor diastereocontrol in the reaction of the chiral enolate with the chiral sulfinimine (Scheme 2).

Interestingly, reduction of **3a** with lithium triethylborohydride at –78 °C gave the *syn*-amino alcohol **4b**, whereas *anti*-amino alcohols are formed preferentially by reduction of acyclic *N*-sulfinyl β-amino ketones.[10] More surprisingly, when the mixture of compounds **3b** + **3c** was submitted to reduction under the same conditions, *syn*-amino alcohols **4c** and **4e** were isolated after FC (Scheme 2).

The absolute configuration of compound **4a** was determined by single-crystal X-ray analysis. The observed stereochemistry was consistent with an axial hydride delivery from sodium borohydride to the diequatorial conformer of cyclohexanone **3a** (Figure 1).

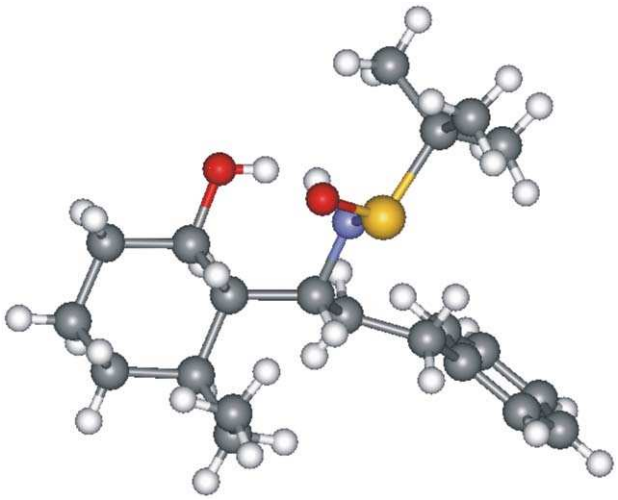
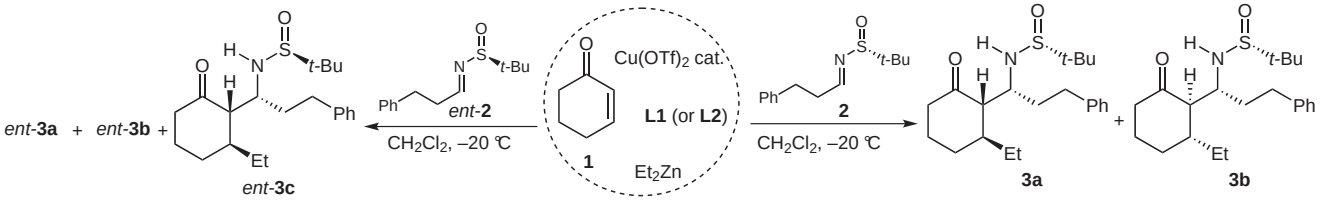
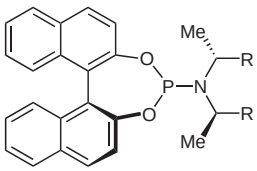


Figure 1 X-ray crystal structure of compound **4a**

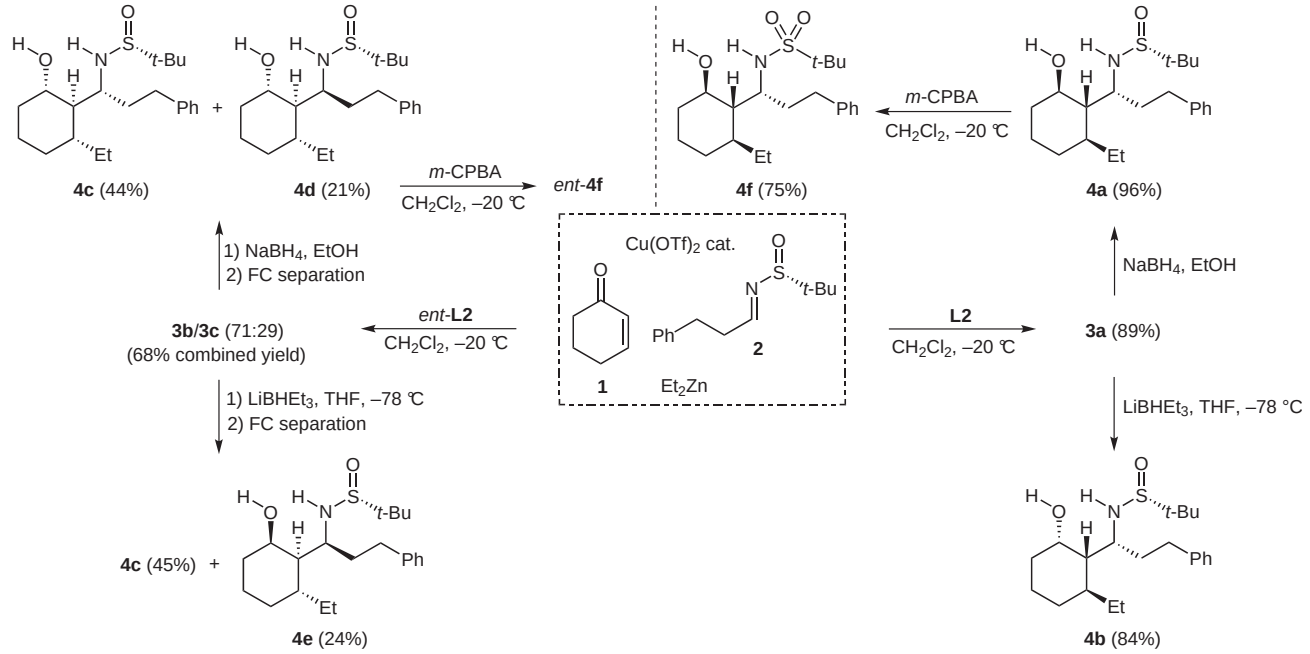
Importantly, because both enantiomers of the phosphoramidite ligand and *tert*-butylsulfinamides were available, enantiomers of amino alcohols **4a**–**e** were also prepared from *ent*-**L2** and *ent*-**2** (see below). Moreover, the *N*-sulfinyl group can be easily oxidized to a sulphonamide group (e.g., **4f**) or removed with methanolic hydrogen chloride to give the free amine, which can be further alkylated. We hope that this ability to modify the electronic nature of the amino group could be useful in finding future applications

Table 1 Syntheses of 2-{[(*tert*-Butylsulfinyl)amino]methyl}cyclohexanone **3a**–**c**



	Entry	Ligand	Method	Imine	Products (ratio)[c]
 **L1** (R = Me) **L2** (R = Ph)	1	**L1**	A[a]	**2**	**3a** + **3b** (77:23)
	2	**L1**	A	*ent*-**2**	*ent*-**3a** + *ent*-**3b** + *ent*-**3c** (27:67:6)
	3	**L1**	B[b]	**2**	**3a** + **3b** (86:14)
	4	**L1**	B	*ent*-**2**	*ent*-**3a**, *ent*-**3b**, *ent*-**3c** (49:48:3)
	5	**L2**	B	**2**	**3a** (>98)
	6	**L2**	B	*ent*-**2**	*ent*-**3b** + *ent*-**3c** (71:29)

[a] Method A: The sulfinimine (**2** or *ent*-**2**) was added 5 h after the addition of Et_2Zn.
[b] Method B: Et_2Zn was added to the mixture of cyclohex-2-en-1-one, ligand, $Cu(OTf)_2$, and sulfinimine **2**.
[c] Relative amounts of each diasteromeric product as determined by ^1H NMR of the crude reaction mixture.



Scheme 2 Synthesis of N-protected 1,3-amino alcohols **4a**–**f**

for these chiral 1,3-amino alcohols in asymmetric synthesis.

In conclusion, the stereoselective reduction of easily available 2-{1-[(*tert*-butylsulfinyl)amino]alkyl}cyclohexanones with sodium borohydride or lithium triethylborohydride gives access to a wide range of enantiomerically pure 1,3-amino alcohols. Only two synthetic operations are required to build these amino alcohols, which have five stereogenic centers.

TLC was performed on Merck silica gel 60 F_{254}, using aluminum plates and visualized by staining with phosphomolybdic acid. Flash chromatography (FC) was carried out on hand-packed columns of Merck silica gel 60 (0.040–0.063 mm) with hexane–EtOAc as the eluent. IR spectra were recorded on a Nicolet Impact 510 P-FT Spectrometer. Melting points were recorded on an OptiMelt (Stanford Research Systems) apparatus using open glass capillaries and are reported without corrections. ^{1}H NMR spectra were recorded with a Bruker AC-300 using $CDCl_3$ (δ = 7.27) or CD_3OD (δ = 4.84) as the solvent and internal standard. ^{13}C NMR spectra were recorded with ^{1}H-decoupling on a BRUKER 75-MHz spectrometer, and DEPT-135 experiments were performed to assign the CH, CH_2 and CH_3 protons. Optical rotations were measured on a Perkin Elmer 341 polarimeter. HRMS (EI) were recorded on a Finnigan MAT 95S. *N*-Sulfinyl imine **2**[11] and phosphoramidite ligands **L1** and **L2**[12] were prepared according to the reported procedures. The properties of known compounds matched those reported in the corresponding references.

(R_S)-*N*-{(1*R*)-1-[(1*R*,2*S*)-2-Ethyl-6-oxocyclohexyl]-3-phenylpropyl}-2-methylpropane-2-sulfinamide (3a) and (R_S)-*N*-{(1*R*)-1-[(1*R*,2*R*)-2-Ethyl-6-oxocyclohexyl]-3-phenylpropyl}-2-methylpropane-2-sulfinamide (3b); Typical Procedure A

$Cu(OTf)_2$ (22 mg, 0.06 mmol), phosphoramidite **L1** (66 mg, 0.12 mmol), and enone **1** (230 mg, 240 μL, 2.40 mmol) were suspended in CH_2Cl_2 (8.0 mL) and stirred at r.t. for 15 min before cooling to –40 °C. A 1.0 M soln of Et_2Zn in toluene (9.0 mL, 9 mmol) was added dropwise and the mixture was allowed to reach –20 °C while being stirred for 5 h. A soln of sulfinimine **2** (482 mg, 2.00 mmol) in CH_2Cl_2 (6.0 mL) was then added dropwise, and the mixture was stirred overnight at –20 °C. The reaction was quenched at –20 °C by addition of a sat. soln of NH_4Cl in 1:1 H_2O–MeOH (3.0 mL), and the mixture was stirred for 15 min at r.t.. The resulting precipitate was filtered off on a short pad of Celite and, after evaporation of solvents, the crude sample was analyzed by ^{1}H NMR spectroscopy to determine the imine conversion and the diastereomeric ratio of the products. The sample was then purified by column chromatography (silica gel, EtOAc–hexane, 75:25 to 70:30) to give pure **3a**[5b] and **3b** as colorless oils; yield: **3a**: 474 mg (66%); **3b**: 144 mg (20%).

Compound **3b**: $[\alpha]_D^{20}$ –30.7 (*c* 2.5, $CHCl_3$).

IR (KBr): 2957, 2868, 1698, 1454, 1069 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (m, 2 H), 7.15 (m, 3 H), 4.71 (d, *J* = 7.2 Hz, 1 H), 3.40 (m, 1 H), 2.83 (m, 1 H), 2.55 (m, 1 H), 2.30 (m, 4 H), 2.10 (m, 1 H), 1.92 (m, 1 H), 1.80–1.60 (m, 3 H), 1.40 (m, 2 H), 1.26 (s, 9 H), 0.87 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.46 (CH_3), 23.1 (CH_3), 25.1 (CH_2), 25.6 (CH_2), 26.4 (CH_2), 33.1 (CH_2), 38.5 (CH_2), 41.4 (CH), 43.0 (CH_2), 55.2 (CH), 56.4 (q), 58.8 (CH), 125.9 (CH), 128.3 (CH), 128.4 (CH), 141.6 (q), 215.0 (q).

HRMS–MALDI: *m/z* $[M + Na]^+$ calcd for $C_{21}H_{33}NNaO_2S$: 386.2130; found: 386.2139.

(R_S)-*N*-{(1*R*)-1-[(1*R*,2*S*)-2-Ethyl-6-oxocyclohexyl]-3-phenylpropyl}-2-methylpropane-2-sulfinamide (3a); Typical Procedure B

$Cu(OTf)_2$ (22 mg, 0.06 mmol), phosphoramidite **L2** (66 mg, 0.12 mmol), enone **1** (230 mg, 240 μL, 2.40 mmol) and sulfinimine **2** (482 mg, 2.00 mmol) were suspended in CH_2Cl_2 (14.0 mL) and stirred at r.t. for 15 min before cooling to –40 °C. A 1.0 M soln of Et_2Zn in toluene (9.0 mL, 9 mmol) was added dropwise and the mixture was allowed to reach –20 °C while being stirred overnight (12 h). Quenching and purification were carried out as described above to give pure **3a**[5b] as a colorless oil; yield: 640 mg (89%).

(R_S)-*N*-{(1*R*)-1-[(1*R*,2*S*,6*R*)-2-Ethyl-6-hydroxycyclohexyl]-3-phenylpropyl}-2-methylpropane-2-sulfinamide (4a); Typical Procedure for Reduction with $NaBH_4$

$NaBH_4$ (100 mg, 2.6 mmol) was added to a soln of **3a** (492 mg, 1.36 mmol) in 95% EtOH (7 mL) at 0 °C, and the mixture was stirred at 0 °C for 2 h (TLC monitoring; hexane–EtOAc, 1:1). Sat. aq NH_4Cl was then carefully added (5 mL). When gas evolution ceased, the mixture was partitioned between EtOAc (50 mL) and H_2O (20 mL). The aqueous phase was extracted with more EtOAc (2 × 20 mL), and the combined organics extracts were washed with brine (10 mL) and dried ($MgSO_4$). The filtered soln was concentrated in vacuo to give pure **4a** as a colorless solid; yield: 471 mg (96%); mp 175–178 °C; $[\alpha]_D^{20}$ –5.2 (*c* 1.00, EtOH).

IR (KBr): 3374, 3222, 2928, 1455, 1362, 1033 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 7.26 (m, 2 H), 7.15 (m, 3 H), 3.56 (td, *J* = 10.1/3.9 Hz, 1 H), 3.36 (m, 1 H), 2.83 (dt, *J* = 13.3, 5.9 Hz, 1 H), 2.55 (dt, *J* = 13.3, 8.2 Hz, 1 H), 1.75 (m, 3 H), 1.65–1.45 (m, 3 H), 1.27 (m, 2 H), 1.24 (s, 9 H), 1.15–0.80 (m, 4 H), 0.67 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 9.9 (CH_3), 23.5 (CH_3), 25.1 (CH_2), 25.6 (CH_2), 30.7 (CH_2), 31.9 (CH_2), 33.5 (CH_2), 37.5 (CH_2), 40.0 (CH), 53.7 (CH), 57.3 (q), 58.3 (CH), 73.6 (CH), 127.0 (CH), 129.5 (CH), 129.9 (CH), 143.2 (q).

MS (EI, 70 eV): *m/z* (%) = 91.0 (68), 117.0 (100), 181.0 (44), 227 (7), 309 (54) $[M - C_4H_8]^+$.

HRMS–EI: *m/z* $[M - C_4H_8]^+$ calcd for $C_{17}H_{27}NO_2S$: 309.1762; found: 309.1781.

Crystal Structure:[13] $C_{21}H_{35}NO_2S$, *M* = 365.57; triclinic, *a* = 9.5123(11) Å, *b* = 9.7013(11) Å, *c* = 13.3331(15) Å, α = 94.474(2), β = 110.126(2), γ = 105.743(2); *V* = 1091.8(2) $Å^3$; space group *P*1; *Z* = 2; D_c = 1.112 Mg m^{-3}; λ = 0.71073 Å; μ = 0.161 mm^{-1}; *F*(000) = 400; *T* = 23 ± 1 °C. Data collection was performed on a Bruker Smart CCD diffractometer, based on three ω-scan runs (starting = –34°) at values ϕ = 0°, 120°, and 240° with the detector at 2θ = –32°. For each of these runs, 606 frames were collected at 0.3° intervals and 20 s per frame. An additional run at ϕ = 0° of 100 frames was collected to improve redundancy. The diffraction frames were integrated by using the program SAINT,[14a] and the integrated intensities were corrected for Lorentz polarization effects with SADABS.[14b] The structure was solved by direct methods and refined to all 7190 unique F_o^2 by full-matrix least-squares.[14c] All the hydrogen atoms were placed at idealized positions and refined as rigid atoms. Final *wR2* = 0.1448 for all data and 467 parameters; *R*1 = 0.0613 for 4885 $F_o > 4\sigma(F_o)$.

(S_S)-*N*-{(1*R*)-1-[(1*R*,2*S*,6*R*)-2-Ethyl-6-hydroxycyclohexyl]-3-phenylpropyl}-2-methylpropane-2-sulfinamide (*ent*-4a)

By following the typical procedure starting from *ent*-**3a** (616 mg, 1.70 mmol) and $NaBH_4$ (120 mg), pure compound *ent*-**4a** was obtained as a colorless solid; yield: 565 mg (92%); $[\alpha]_D^{20}$ +5.0 (*c* 1.00, EtOH).

(R_S)-*N*-{(1*R*)-1-[(1*R*,2*R*,6*S*)-2-Ethyl-6-hydroxycyclohexyl]-3-phenylpropyl}-2-methylpropane-2-sulfinamide (4c) and (R_S)-*N*-{(1*S*)-1-[(1*R*,2*R*,6*S*)-2-Ethyl-6-hydroxycyclohexyl]-3-phenylpropyl}-2-methylpropane-2-sulfinamide (4d)

By following the typical procedure, a 2.4:1 mixture of **3b** and **3c** (550 mg, 1.50 mmol) was reduced by $NaBH_4$ (110 mg, 2.9 mmol). After solvent evaporation, the residue was purified by FC (hexane–EtOAc, 3:2 to 1:1) to give pure compounds **4c** and **4d** as colorless foams; yield: **4c**: 244 mg (44%); **4d**: 116 mg (21%).

Compound **4c**: $[\alpha]_D^{20}$ –76.5 (*c* 0.65, EtOH).

IR (KBr): 3374, 3222, 2928, 1455, 1362, 1033 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 7.26 (m, 2 H), 7.15 (m, 3 H), 4.23 (m, 1 H), 3.45 (m, 1 H), 2.75 (dt, *J* = 13.3, 5.9 Hz, 1 H), 2.56 (dt, *J* = 13.3, 8.2 Hz, 1 H), 1.85–1.65 (m, 6 H), 1.50 (m, 1 H), 1.40 (m, 2 H), 1.20 (s, 9 H), 1.15–0.80 (m, 3 H), 0.74 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 9.9 (CH_3), 20.5 (CH_2), 23.6 (CH_3), 25.9 (CH_2), 31.6 (CH_2), 33.4 (CH), 33.9 (CH_2), 35.6 (CH_2), 39.7 (CH_2), 47.9 (CH), 57.45 (q), 57.50 (CH), 67.8 (CH), 126.9 (CH), 129.5 (CH), 129.9 (CH), 143.2 (q).

MS (EI, 70 eV): *m/z* (%) = 91.0 (72), 117.0 (100), 181.0 (42), 227 (20), 309 (21) $[M - C_4H_8]^+$.

Compound **4d**: $[\alpha]_D^{20}$ –96.7 (*c* 0.65, EtOH).

IR (KBr): 3374, 3222, 2928, 1455, 1362, 1033 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 7.25 (m, 5 H), 3.56 (td, *J* = 10.3, 4.4 Hz, 1 H), 3.25 (m, 1 H), 2.89 (dt, *J* = 13.8, 6.0 Hz, 1 H), 2.78 (dt, *J* = 13.8, 8.4 Hz, 1 H), 1.80 (m, 3 H), 1.60 (m, 1 H), 1.50 (m, 1 H), 1.25 (m, 4 H), 1.20 (s, 9 H), 1.15–0.80 (m, 4 H), 0.60 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 9.7 (CH_3), 23.2 (CH_3), 25.0 (CH_2), 25.7 (CH_2), 31.8 (CH_2), 33.3 (CH_2), 34.6 (CH_2), 37.6 (CH_2), 39.7 (CH), 54.1 (CH), 57.2 (q), 58.4 (CH), 73.1 (CH), 126.9 (CH), 129.4 (CH), 130.1 (CH), 143.4 (q).

MS (EI, 70 eV): *m/z* (%) = 91.0 (68), 117.0 (100), 181.0 (44), 227 (7), 309 (54) $[M - C_4H_8]^+$.

(S_S)-*N*-{(1*R*)-1-[(1*R*,2*R*,6*S*)-2-Ethyl-6-hydroxycyclohexyl]-3-phenylpropyl}-2-methylpropane-2-sulfinamide (*ent*-4c) and (S_S)-*N*-{(1*S*)-1-[(1*R*,2*R*,6*S*)-2-Ethyl-6-hydroxycyclohexyl]-3-phenylpropyl}-2-methylpropane-2-sulfinamide (*ent*-4d)

By following the typical procedure, a 2.4:1 mixture of *ent*-**3b** and *ent*-**3c** (500 mg) was reduced with $NaBH_4$ (120 mg). After FC (hexane–EtOAc, 3:2 to 1:1), pure *ent*-**4c** and *ent*-**4d** were obtained as colorless foams; *ent*-**4c**; yield: 201 mg (40%); $[\alpha]_D^{20}$ +74.0 (*c* 0.85, MeOH), *ent*-**4d**; yield: 103 mg (20%); $[\alpha]_D^{20}$ +95.0 (*c* 0.65, MeOH).

(R_S)-*N*-{(1*R*)-1-[(1*S*,2*S*,6*S*)-2-Ethyl-6-hydroxycyclohexyl]-3-phenylpropyl}-2-methylpropane-2-sulfinamide (4b); Typical Procedure for Reduction with $LiBHEt_3$

A 1 M soln of $LiBHEt_3$ in THF (9 mL, 9 mmol) was added dropwise from a syringe to a soln of **3a** (530 mg, 1.50 mmol) in anhyd THF (24 mL) at –78 °C under argon, and the mixture was stirred for 3 h at –78 °C (TLC monitoring; hexane–EtOAc, 1:2). 1:1 MeOH–aq NH_4Cl (10 mL) was added and the mixture was stirred for an additional 15 min while the temperature increased to r.t. and gas evolution ceased. The mixture was partitioned between EtOAc (50 mL) and H_2O (20 mL), and the aqueous phase was extracted with additional EtOAc (2 × 20 mL). The combined organics extracts were washed with brine (10 mL) and dried ($MgSO_4$). The filtered soln was concentrated in vacuo to give crude **4b**, which was triturated with hexane (10 mL) to give a precipitate that was filtered off to give pure **4b** as a colorless solid; yield: 445 mg (82%); mp 152–155 °C; $[\alpha]_D^{20}$ +51.0 (*c* 0.60, EtOH).

IR (KBr): 3208 (br), 2956, 1456, 1355, 1025 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 7.26 (m, 2 H), 7.15 (m, 3 H), 4.20 (m, 1 H), 3.38 (m, 1 H), 2.75 (dt, *J* = 13.3, 5.9 Hz, 1 H), 2.53 (dt, *J* = 13.3, 8.2 Hz, 1 H), 1.90 (m, 1 H), 1.80 (m, 1 H), 1.60 (m, 2 H), 1.50 (m, 2 H), 1.40 (m, 2 H), 1.23 (s, 9 H), 1.15 (m, 1 H), 0.80 (m, 3H), 0.64 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 10.3 (CH_3), 20.9 (CH_2), 23.4 (CH_3), 25.5 (CH_2), 32.2 (CH_2), 34.7 (CH_2), 34.8 (CH_2), 35.2 (CH), 51.2 (CH), 57.8 (q), 59.9 (CH), 67.2 (CH), 126.9 (CH), 129.4 (CH), 129.8 (CH), 143.3 (q).

MS (EI, 70 eV): *m/z* (%) = 91.0 (72), 117.0 (100), 181.0 (42), 227 (20), 309 (21) $[M - C_4H_8]^+$.

HRMS–EI: *m/z* calcd for $C_{17}H_{27}NO_2S$ [M – C_4H_8]$^+$: 309.1762; found: 309.1780.

(S_S)-*N*-{(1*R*)-1-[(1*S*,2*S*,6*S*)-2-Ethyl-6-hydroxycyclohexyl]-3-phenylpropyl}-2-methylpropane-2-sulfinamide (*ent*-4b)

By following the typical procedure, *ent*-**3a** (556 mg, 1.53 mmol) was reduced by a 1 M soln of $LiBHEt_3$ in THF (9 mL, 9 mmol) to give pure *ent*-**4b**; yield: 444 mg (80%); $[\alpha]_D^{20}$ –55.0 (*c* 0.90, MeOH).

(R_S)-*N*-{(1*S*)-1-[(1*R*,2*R*,6*R*)-2-Ethyl-6-hydroxycyclohexyl]-3-phenylpropyl}-2-methylpropane-2-sulfinamide (4e)

By following the typical procedure, a 2.4:1 mixture of **3b** and **3c** (570 mg, 1.57 mmol) was reduced with a 1 M soln of $LiBHEt_3$ in THF (10 mL, 10 mmol). After aqueous workup and solvent evaporation, the residue was purified by FC (hexane–EtOAc, 3:2 to 1:1) to give pure **4c** and **4e** as colorless foams; yield: **4c**: 256 mg (45%); **4e**: 139 mg (24%).

Compound **4e**: $[\alpha]_D^{20}$ –124.0 (*c* 0.50, EtOH).

IR (KBr): 3471, 3415, 2927, 1454, 1362, 1035 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 7.26 (m, 4 H), 4.19 (m, 1 H), 3.37 (m, 1 H), 2.85 (m, 1 H), 2.58 (m, 1 H), 1.90 (m, 2 H), 1.75–1.35 (m, 5 H), 1.30 (m, 1 H), 1.20 (s, 9 H), 0.90 (m, 3 H), 0.70 (m, 1 H), 0.65 (m, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 10.2 (CH_3), 20.9 (CH_2), 23.3 (CH_3), 25.3 (CH_2), 32.1 (CH_2), 33.9 (CH_2), 34.7 (CH_2), 34.8 (CH), 35.5 (CH_2), 52.4 (CH), 57.0 (q), 58.6 (CH), 66.7 (CH), 126.8 (CH), 129.3 (CH), 130.0 (CH), 143.6 (q).

MS (EI, 70 eV): *m/z* (%) = 91.0 (72), 117.0 (100), 181.0 (42), 227 (20), 309 (21) [M – C_4H_8]$^+$.

(S_S)-*N*-{(1*S*)-1-[(1*R*,2*R*,6*R*)-2-Ethyl-6-hydroxycyclohexyl]-3-phenylpropyl}-2-methylpropane-2-sulfinamide (*ent*-4e)

By following the typical procedure, a 2.4:1 mixture of *ent*-**3b** and *ent*-**3c** (489 mg, 1.35 mmol) was reduced with a 1 M soln of $LiBHEt_3$ in THF (9 mL, 9 mmol). After aqueous workup and solvent evaporation, the residue was purified by FC (hexane–EtOAc, 3:2 to 1:1) to give pure *ent*-**4c** and *ent*-**4e** as colorless foams; yield: *ent*-**4c**: 280 mg (57%); *ent*-**4e**: 180 mg (36%); $[\alpha]_D^{20}$ +115.0 (*c* 1.00, MeOH).

***N*-{(1*R*)-1-[(1*S*,2*S*,6*R*)-2-Ethyl-6-hydroxycyclohexyl]-3-phenylpropyl}-2-methylpropane-2-sulfonamide (4f); Typical Procedure for Oxidation of the *tert*-Butylsulfinyl Group**

MCPBA (70%, 55 mg, 0.23 mmol) was add at 0 °C to a soln of compound **4a** (55 mg, 0.15 mmol) in CH_2Cl_2 (2 mL), and the mixture was stirred for 30 min at 0 °C until the starting material was consumed (TLC; hexane–EtOAc, 3:1). A soln of Na_2SO_3 (600 mg) in H_2O (10 mL) was added and the mixture was stirred for 10 min more. The mixture was then extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed with sat. aq $NaHCO_3$ and brine, then dried ($MgSO_4$). The filtered soln was concentrated in vacuo, and the residue was purified by FC (hexane–EtOAc, 4:1) to give **4f** as a colorless foam; yield: 41 mg (75%); $[\alpha]_D^{20}$ +31.0 (*c* 2.7, CH_2Cl_2).

IR (KBr): 3522 (br), 2922, 1459, 1306, 1122 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (m, 5 H), 5.79 (br s, 1 H, NH), 3.79 (m, 1 H, CHN), 3.70 (td, *J* = 10.4, 4.1 Hz, 1 H, CHO), 3.03 (m, 1 H), 2.66 (m, 1 H), 2.00–1.60 (m, 7 H), 1.43 (s, 9 H), 1.30–0.90 (m, 5 H), 0.82 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.4 (CH_3), 23.8 (CH_2), 24.4 (CH_3), 24.9 (CH_2), 30.6 (CH_2), 32.9 (CH_2), 33.3 (CH_2), 36.9 (CH_2), 39.2 (CH), 53.2 (CH), 54.4 (CH), 59.3 (q), 73.2 (CH), 125.8 (CH), 128.3 (CH), 128.5 (CH), 142.3 (q).

MS (EI, 70 eV): *m/z* (%) = 57.1 (24), 91.1 (25), 134.1 (100), 156.1 (23), 254.1 (24) [M – $C_8H_{15}O$]$^+$, 381.2 (1) [M]$^+$.

HRMS–EI: *m/z* [M – $C_8H_{15}O$]$^+$ calcd for $C_{13}H_{20}NO_2S$: 254.1215; found: 254.1211.

***N*-{(1*S*)-1-[(1*R*,2*R*,6*S*)-2-Ethyl-6-hydroxycyclohexyl]-3-phenylpropyl}-2-methylpropane-2-sulfonamide (*ent*-4f)**

By following the typical procedure from **4d** (55 mg, 0.15 mmol) and MCPBA (70%, 55 mg, 0.23 mmol), pure *ent*-**4f** was isolated as a colorless foam; yield: 39 mg (71%); $[\alpha]_D^{20}$ –29.0 (*c* 2.5, CH_2Cl_2).

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