Asymmetric α-Amination of Ketone Enolates by Chiral α-Chloro-α-nitroso Reagents: a New Approach to Optically pure Erythro-β-Amino Alcohols

Von Oppolzer, Wolfgang; Tamura, Osamu; Sundarababu, Gajendran; Signer, Marcel Jacques

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Supporting Information for *J. Am. Chem. Soc.*, **1992**, 114(14), 5900-5902, DOI: 10.1021/ja00040a086

OPPOLZER
5900-5902

JA920920K J-5902-m1

Asymmetric "α-Amination" of Ketone Enolates by Chiral α-Chloronitroso Reagents: A New Approach to Optically Pure Erythro β-Amino Alcohols

Wolfgang Oppolzer*, Osamu Tamura, Gajendran Sundarababu and Marcel Signer

Département de Chimie Organique, Université de Genève, CH-1211 Genève 4, Switzerland

SUPPLEMENTARY MATERIAL

General.

Preparations and reactions of enolates were carried out under Ar atmosphere. Solvents were dried by distillation from drying agents as follows: Et_2O, THF and toluene (Na-metal); CH_2Cl_2 (CaH_2). 'Workup' denotes extraction with Et_2O or CH_2Cl_2, washing of the organic phase with sat. aq. NH_4Cl soln., drying ($MgSO_4$), and evaporation *in vacuo*. Flash chromatography (FC): SiO_2 *Merck 9385*. GC: *Hewlett-Packard 5790 A*, integrator *HP 3390*, capillary column, retention time in min (area-%). M.p.: Kofler hot stage, uncorrected. IR: *Polaris/Matteson*, in $CHCl_3$, unless otherwise specified. ^{1}H-NMR at 400 or 200 MHz, ^{13}C-NMR at 100 MHz, in $CDCl_3$, unless otherwise specified, standard $CDCl_3$ (δ = 7.27 ppm), J in Hz. MS: m/z (rel.-%).

1-{[(Dicyclohexylamino)sulfonyl]methyl}-7,7-dimethylbicyclo[2.2.1]heptan-2-one (**1a**).

A soln. of (+)- camphorsulphonyl chloride (7.52 g, 30 mmol) in DMF (30 ml) was added over 2 h to a solution of dicyclohexylamine, (12 ml, 60 mmol), isoquinoline (7.04 ml, 60 mmol), and DMAP (0.73 g, 6 mmol) in dry DMF (30 ml) at 0°C. After stirring at 0°C for further 1h, the reaction mixture was poured into 10% aq. citric acid (200 ml), extracted with CH_2Cl_2. Drying, and evaporation of the extracts and chromatography of the residue (EtOAc/hexane, 1:3) afforded **1a** (8.8 g, 74%) which was recrystallized from hexane. M.p.: 140-142°C. $[\alpha]_D^{20}$ = +25.3° ($CHCl_3$, c = 3.5). IR: 2940, 1750, 1300, 1170, 1140. ^{1}H-NMR: 0.90 *(s, 3H)*; 1.18 (*s, 3H*) 1.82 - 1.05 (*m, 22H*); 1.92 (*d, J= 18 ,1H*); 1.95 -2.1 (*m, 2H*); 2.41

-2.33 (*m, 1H*) ; 2.66- 2.57 (*m, 1H*), 2.79 (*d, J = 14, 1H*); 3.32 (*d, J = 14, 1H*); 3.26 - 3.25 (*m, 2H*). ^{13}C-NMR: 215.7, 59.1, 57.72, 52.28, 47.53, 43.06, 42.63, 33.0, 32.62, 26.90, 26.50, 25.37, 25.24, 20.36, 19.91 MS (M-1, 314, 0.8 %) 215 (20.1), 181 (25.2), 180 (13), 179 (12.3), 151 (21.7), 138 (28.7) 123 (29.5) 109 (45), 107 (12.6), 100 (16.4), 98 (26.1), 93 (12.3), 83 (27.4), 81 (45.8), 79 (14), 67 (35.3), 56 (30.4), 55 (100), 54 (11.4), 53 (14.7). Anal. Calcd. for $C_{22}H_{37}NO_3S$: C,66.79; H,9.43; N, 3.54. Found: C, 66.74; H, 9.47; N, 3.67.

1-{[(Diisopropylamino)sulfonyl]methyl}-7,7-dimethylbicyclo[2.2.1]heptan-2-one **(1b).**

Following the above described protocol for the preparation of **1a**, (+)-camphorsulphonyl chloride (7.52 g, 30 mmol), was reacted with diisopropylamine (8.4 ml, 60 mmol) to give **1b** (6.6 g, 78%) which was recrystallized from hexane. M.p. 83-84°C. $[\alpha]_D^{20}$ = +30.4° ($CHCl_3$, *c*= 1). IR: 2900, 1750, 1330, 1135. ^{1}H-NMR: 0.89 (*s, 3H*); 1.17 (*s, 3H*); 1.33(*d, J = 7, 6H*); 1.35 (*d, J= 7, 6H*) ;1.40 (*m, 1H*); 1.68- 1.57 (*m, 1H*); 1.93 (*d, J = 18, 1H*); 2.11-1.99 (*m, 2H*); 2.37(*td, J. = 4,18, 1H*); 2.6 (*m, 1H*); 2.79 (*d, J=14, 1H*); 3.33 (*d, J=14, 1H*); 3.79 (*septet, J=7, 2H*). ^{13}C-NMR: 215.51, 58.91, 51.33, 48.41, 47.49, 42.99, 42.60, 26.86, 25.31, 22.55, 22.12, 20.24, 19.83. MS: M-15,300(15); 215(40); 151(40); 123(50); 109(60); 99(40); 86(100); 81(85); 67(30); 58(20); 53(10). Anal. calcd. for $C_{16}H_{29}NO_3S$: C, 60.92; H, 9.27; N,4.44. Found: C, 60.90; H, 9.45; N,4.48.

1-{[(Dicyclohexylamino)sulfonyl]methyl}-7,7-dimethylbicyclo[2.2.1]heptan-2-one oxime.

A mixture of **1a** (8.5 g, 21.5 mmol), $NH_2OH.HCl$ (3 g, 43 mmol) and $NaOAc.3H_2O$ (5.85 g, 43 mmol) in EtOH-H_2O (10:1, 70 ml) was heated under reflux. After 72 h, the solvent was removed, the residue partitioned between CH_2Cl_2 and aq.$NaHCO_3$ and the organic phase was dried and evaporated. Crystallization of the solid residue (MeOH) afforded 1-{[(dicyclohexylamino)sulfonyl]methyl}-7,7-dimethylbicyclo[2.2.1]heptan-2-one oxime (8.5 g, 96%) M.p.178-181°C. $[\alpha]_D^{20}$ = -1.23° ($CHCl_3$, c = 1.465). IR: 3550 3350, 2950, ,1320, 1140, 975. ^{1}H-NMR: 0.85 (*s, 3H*); 1.10 (*s, 3H*); 1.17-1.05 (*m, 2H*); 1.24-1.40 (*m, 5H*); 1.60 (*br.d, J=12, 2H*); 1.68-1.85 (*m, 13H*) ;1.86-1.97 (*m, 2H*); 2.09 (*d, J=18, 1H*) ; 2.49-2.62 (*m, 2H*); 2.88 (*d, J=14, 1H*); 3.30 (*m, 2 H*); 3.34 (*d, J=14, 1H*); 8.70 (*s, 1H*). ^{13}C-NMR: 168.05, 57.56, 54.02, 52.90 49.43, 43.73, 33.15, 32.89, 32.50, 28.24, 27.14, 26.51, 26.48, 25.26 19.51, 19.41. MS: $C_{22}H_{38}N_2O_3S^+$ not found, 411(25), 392(25), 367(15), 353(15), 327(10), 230

(40), 180(85), 167(15), 138(100), 108(20), 98(20) 83(20), 67(15), 56(25). Anal.Calcd.for $C_{22}H_{38}N_2O_3S$: C,64.35; H, 9.33; N,6.82. Found: C,64.33; H,9.39; N,6.88.

1-{[(Diisopropylamino)sulfonyl]methyl}-7,7-dimethylbicyclo[2.2.1]heptan-2-one oxime.

Following the above described procedure, diisopropylsulfonamide **1b** (5.6 g, 17.7 mmol) was reacted with $NH_2OH.HCl$ (2.46 g, 35.4 mmol) to give 1-{[(diisopropylamino)sulfonyl]methyl}-7,7-dimethylbicyclo[2.2.1]heptan-2-one oxime which was crystallised from MeOH (5 g, 85%). M.p.: 155-156°C. $[\alpha]_D^{20}$ = +10.5° ($CHCl_3$, *c*= 1.02). IR: 3580, 3340, 2970, 1330, 1135, 980. ^{1}H-NMR: 0.86 (*s, 3H*); 1.11 (*s, 3H*) ; 1.32 (*d, J = 7, 6H*); 1.34 (*d, J=7, 6H*); 1.25 -1.35 (*m, 1H*); 1.69 -1.76 (*m, 1H*); 1.88 -1.97 (*m, 2H*); 2.07 (*d, J = 18, 1H*); 2.5 - 2.62 (*m, 2H*); 2.9 (*d, J = 14, 1H*); 3.38 (*d, J = 14, 1H*); 3.77 (*septet, J = 7, 2H*); 7.91 (*s, 1H*). ^{13}C-NMR: 168.14, 53.13, 52.82, 49.38, 48.30, 43.69, 32.70, 28.19, 27.12, 22.63, 22.04, 19.46, 19.39. MS: $C_{16}H_{30}N_2O_3S^+$ not found 166(10.0), 107 (16.22), 100 (67.71) 86 (100), 79 (13.83), 70 (10.29), 67 (12.56), 58 (44.86), 55 (16.15), 53 (10.51) Anal. Calcd. for $C_{16}H_{30}N_2O_3S$: C, 58.15; H, 9.15; N, 8.48. Found : C,58.13; H, 9.36; N, 8.50.

2-Chloro-2-nitroso-1-{[(dicyclohexylamino)sulfonyl]methyl}-7,7-dimethylbicyclo[2.2.1]heptane (**2a**).

Freshly prepared t-BuOCl (530 mg, 4.9 mmol) was added over 2 min. to a cold (-10°C) solution of 1-{[(dicyclohexylamino)sulfonyl]methyl}-7,7-dimethylbicyclo[2.2.1]heptan-2-one oxime (1.6 g, 3.9 mmol) in CH_2Cl_2 (30) ml. Stirring for 15 min, evaporation and crystallization of the blue residue from hexane/CH_2Cl_2 gave pure **2a** (1.4 g, 81%). M.p.: 145-150°C (dec.). $[\alpha]_D^{20}$ = -346° ($CHCl_3$, *c* = 0.87). IR ($CHCl_3$): 2950, 1590, 1320,1140, 1050, 980. ^{1}H-NMR: 1.16 (*s, 3H*); 1.23 (*s, 3H*); 1.0-1.95 (*m, 22H*); 2.12-2.28 (*m, 3H*); 2.45-2.57 (*m, 1H*); 2.78 (*d, J=14, 1H*); 3.07-3.21 (*m, 2H*); 3.22-3.34 (*m 1H*); 3.38 (*d, J=14, 1H*). ^{13}C-NMR: 123.61, 58.35, 57.48, 54.37, 53.74, 45.99, 43.69, 33.15, 32.39, 28.41, 27.37, 26.48, 26.44, 25.20, 20.87, 20.36. MS: $C_{22}H_{37}ClN_2O_3S^+$ not found, 415(50), 395(20), 370(15), 314(10), 244(20), 181(50), 164(15), 138(99), 83(80), 55(100). HR-MS: Mass calcd. for $C_{22}H_3ClNO_2S$: 413.2155; Found: 413.2139. Anal.Found: C,59.00; H,8.47; N,6.13; Cl,8.19; S,7.41; $C_{22}H_{37}ClN_2O_3S$ requires: C,59.37; H,8.38; N,6.30; Cl,7.97; S,7.20.

2-Chloro-2-nitroso-1-{[(diisopropylamino)sulfonyl]methyl}-7,7-dimethylbicyclo[2.2.1]heptane (**2b**).

Following the protocol, described above for the preparation of **2a**, 1-{[(diisopropylamino)sulfonyl]methyl}-7,7-dimethylbicyclo[2.2.1]heptan-2-one oxime (2 g, 6.06 mmol) and t-BuOCl (724 mg, 6.67 mmol) furnished (after crystallization from hexane/CH_2Cl_2) **2b** (1.82 g, 82.4%). M.p.: 124-127°. $[\alpha]_D^{20}$ = -329° ($CHCl_3$, *c*= 1). IR: 2980, 1580, 1335, 1120, 980. ^{1}H-NMR : 1.17 (*s, 3H*); 1.23 (*s, 3H*); 1.24 (*d, J = 7, 6H*); 1.26 (*d, J = 7, 6H*); 1.87 -1.96 (*m, 2H*); 2.14 -2.29 (*m 3H*); 2.48 -2.58 (*m, 1H*); 2.79 (*d, J = 14, 1H*); 3.24 -3.32 (*m, 1H*); 3.39 (*d, J = 14, 1H*), 3.63 (*septet, J = 7, 2H*). ^{13}C-NMR: 123.72, 58.23, 53.76, 53.45, 48.24, 45.93, 43.71, 28.49, 27.39, 22.66, 21.89, 20.86, 20.31. Anal.Cald. for $C_{16}H_{29}ClN_2O_3S$: C,52.66; H,8.01; N,7.68; S,8.79; Cl,9.72. Found: C,52.48; H,7.91; N,7.65; S,8.96; Cl,9.85.

Nitrone **6a** *(R = Ph).*

A 1 M soln. of LiHMDS (THF, 0.88 ml), was added at -78°C to a soln. of propiophenone (108 mg, 0.8 mmol) in THF (8 ml). Stirring for 30 min., addition of a 1 M soln. of $ZnCl_2$ (Et_2O, 0.96 ml) over 10 min, stirring for 1.5 h, dropwise addition of a 0.5 M soln. of the chloronitrosocompound **2a** (THF, 2 ml), warming of the reaction mixture to -30°C over 1.5 h, quenching with aq. phosphate buffer (pH = 7, 8 ml), extraction (CH_2Cl_2) and flash chromatography (FC, hexane/EtOAc 3:2) furnished unstable nitrone **6a** (colorless solid, 260 mg, 64%). M.p.:90°C dec. IR:($CHCl_3$): 2950, 1700, 1450, 1320, 1170, 1150, 1050, 980. ^{1}H-NMR: 1.01-2.03 (*m 27H*),1.09 (*s, 3H*), 1.20 (*s, 3H*), 1.75 (*d, J=7, 3H*), 2.83-2.92 (*m, 1H*), 3.49 (*br.d., J=14, 2H*), 4.66 (*d, J=14, 1H*), 5.34 (*q, J=7, 1H*), 7.47 (*t, J=8, 2H*), 7.55-7.64 (*m, 1H*), 7.89 (*d, J=8*, 2H). MS: $C_{31}H_{46}N_2O_4S^+$·not found, 181(27.9),180(15),148(16), 138(26.9), 81(26.2), 79(16.2), 77(37.9), 69(13.9), 67(24.5), 56(28.3), 55(100), 54(10.8), 53(14.5), 51(11.2). For the preparative conversion of propiophenone **3a** into (-)-norephedrine **9a** (*vide infra*) the nitrone **6a** was hydrolyzed *in situ.*

Epimerization of Nitrone **6a** *to Nitrone* **5a.**

Et_3N (726 mg, 7.2 mmol) was added to a soln. of nitrone **6a** (1.084 g, 2 mmol) in CH_2Cl_2 (20 ml) at r.t. Stirring the mixture for 3 h, evaporation and immediate ^{1}H-NMR analysis showed a 1:1-ratio of **6a**/**5a**. FC (hexane/EtOAc 1:1) afforded the more polar nitrone **5a** (150 mg, 15%) IR: 2940 ,1700, 1600, 1470, 1330, 1170, 1140, 910. ^{1}H- NMR: 1.15 (*s, 3H*); 1.23 (*s, 3H*); 1.68 (*d, J=7, 3H*); 2.24 - 0.6 (*m, 26H*); 3.03, (*br.d, J=15, 1H*); 3.76

(*d, J=15, 1H*) *3.98 (d, J=14, 1H*); 5.22 (*q, J=7, 1H*); 7.44 (*m, 2H*); *7.52 (m 1H*); 7.92 (*m 2H*). MS: 543 (M+1, 0.12); 194 (20.3); 181 (12.9); 180 (33.6); 138 (15.6); 107 (10); 106 (11.4); 105 (100); 98 (13.6); 93 (11.9); 91 (12.6); 83 (33); 81 (17.9); 79 (15.8); 77 (14.3); 69 (13.8); 67 (16.8); 56 (21.5); 55 (84.9). The nitrone **5a** was subjected to the hydrolysis/C=O-reduction/*N,O*-hydrogenolysis/*N,O*-diacetylation sequence as described below for the conversion **3a** → **9a** to give the *N,O*-diacetyl derivative of (+)-norephedrine. ^{1}H-NMR identical to that of a sample obtained from (-)-norephedrine. $[\alpha]_D^{20}$ = +61.3° ($CHCl_3$, *c* = 0.364).

(1R,2S)-2-(N-Hydroxyamino)-1-phenyl-1-propanol (**8a**).

A 0.92 M soln. of LiHMDS (THF, 3.6 ml), was added at -78°C to a soln. of freshly distilled propiophenone (402 mg, 3 mmol) in THF (30 ml). Stirring for 30 min., addition of a 1.34 M soln. of $ZnCl_2$ (Et_2O, 4.5 ml) over 10 min, stirring for 1.5 h, dropwise addition of a 0.5 M soln. of the chloronitroso compound **2a** (THF, 6 ml), warming of the reaction mixture to -30°C over 1.5 h, addition of 1 N aq. HCl (45 ml), stirring for 12 h at r.t., evaporation *in vacuo*, shaking with Et_2O/1 N aq. HCl, evaporation of the dried Et_2O layer and crystallization of the residue yielded ketone **1a** (1.009 g, 85%). The aq. layer was evaporated and the residue was dissolved in MeOH (15 ml). Addition of $NaBH_4$ (250 mg, 6.6 mmol) over 15 min. at 0°C, stirring at 0°C for 1 h, addition of 1 N aq. HCl (→ pH = 1), evaporation, successive addition of water, 25% aq. NaOH (→ pH = 12) and solid NaCl and extraction with Et_2O yielded crude hydroxylamine **8a** which was directly converted to (-)norephedrine (**9a**, *vide infra*). For spectral characterization a sample of crude **8a** was chromatographed (MeOH/CH_2Cl_2 1:10) to afford pure **8a**. M.p.: 86-87°. $[\alpha]_D^{20}$ = -25.4° ($CHCl_3$, *c* = 1.08). IR ($CHCl_3$): 3640, 3570, 3320, 3000, 1450, 1025, 910 ^{1}H-NMR; 0.87(*d, J=7, 3H*), 3.27(*dq, J= 7,3, 1H*), 4.95-5.35 (*br, 3H*), 5.16(*d, J=3, 1H*), 7.24-7.38(*m, 5H*). ^{13}C-NMR: 141.24, 128.27, 127.26, 125.95, 72.30, 62.65,10.42. M.S: 79 (17.3); 77(26.9); 60(100); 51(18.2). HRMS: Calcd.for $C_9H_{11}NO$ (M-18): 149.0887; Found: 149.0855.

(1R,2S)-2-Amino-1-phenyl-1-propanol ((-)-Norephedrine, **9a**).

Crude hydroxylamine **8a** (*vide supra*) was stirred with 1N aq. HCl/AcOH (2:1, 15 ml) and zinc dust (1.96 g, 30 mmol) at 0°C for 3 days. Filtration, basification of the filtrate with 50% aq. NaOH to pH = 14, addition of solid NaCl, extraction with Et_2O and distillation of

the dried and evaporated extracts (100°C / 0.2 Torr) afforded (-)-norephedrine **9a** (310 mg, 68% from propiophenone, *erythro/threo* = 95:5, e.e. = 96% by GC of bis(trifluoroacetyl) derivative). Addition of a 1 M soln. of maleic acid (EtOH, 2.46 ml) to a soln. of distilled **9a** in EtOH (1 ml), precipitation of the salt with ether and crystallization of the precipitate from isopropanol/Et_2O gave the hydrogen maleate of **9a** (345 mg, 43% from propiophenone). M.p.: 129-133°C. A sample was converted to the *N,O*-bis(trifluoroacetyl) derivative which was found to be >99% pure by chiral GC analysis (*vide infra*).

GC Analysis of 2-Amino-1-phenyl-1-propanol Stereoisomers.

The aminol sample (2 mg) was heated in EtOAc/$(CF_3CO)_2O$ (1:1, 0.2 ml) at 100°C for 10 min. After evaporation, the residue was analyzed by using a *Lipodex-D* capillary column, 140°C and H_2 as a carrier gas. With reference samples, obtained from (-)-norephedrine, (+)-norephedrine and (-)-norpseudoephedrine, baseline separations were achieved.

(-)-N,O-Diacetyl norephedrine

A mixture of crude hydroxylamine **8a** (40 mg, 0.24 mmol) and zinc powder (500 mg, 7.7 mmol) in 1N HCl-AcOH (2:1, 3 ml) was stirred at 0^0 for 72 h. Filtration and co-evaporation of the filtrate with toluene gave a residue which was stirred with a mixture of Ac_2O (6 ml) and pyridine (6 ml) at r.t. for 48h.

Workup, chromatography (EtOAc) and crystallisation (EtOAc-hexane) afforded (-)-*N,O*-diacetyl norephedrine (39 mg, 70% from **8a**). M.p.: 98-99°C. $[\alpha]_D^{20}$ = -79.42°, ($CHCl_3$, *c* = 1.341). IR ($CHCl_3$): 3500, 1740, 1675, 1510, 1240, 1050. ^{1}H-NMR: 1.06 (*d, J=7, 3H*), 1.96 (*s, 3H*), 2.16 (*s, 3H*), 4.41-4.51 (*m, 1H*), 5.50 (*br.d, J =8, 1H*), 5.84 (*d, J = 4, 1H*), 7.26-7.36 (*m, 5H*). ^{13}C-NMR: 170.29, 169.31, 137.01, 128.45, 128.1, 126,44, 77.54, 48.57, 23.45, 21.13, 15.25. MS: $C_{13}H_{17}NO_3^{+\cdot}$ not found, 176(2.2), 107(10), 87(23), 86(100), 45(12). HR-MS: Mass calculated for $C_{11}H_{13}NO$: 175.0997; Found: 175.1006. Analogous acetylation of commercial (-)-norephedrine (*Fluka*, 50 mg) gave the diacetyl derivative (65 mg, 83%), m.p. 98 - 99°C. Mixed m.p. with a sample obtained from propiophenone: 98-99°C. $[\alpha]_D^{20}$ = -79.04° ($CHCl_3$, *c* = 0.645). The IR and NMR spectra are identical to the above described ones.

(1R,2S)-2-Amino-1-(2',5'-dimethoxyphenyl)-1-propanol (Methoxamine, 9b)

A 1 M soln. of NaHMDS (THF, 3.3 ml), was added at -78°C to a soln. of ketone **3b** (580 mg, 3 mmol) in THF (30 ml). Stirring for 30 min., addition of a 0.5 M soln. of the chloronitroso compound **2a** (THF, 6 ml) over 20 min., stirring for 20 min., addition of 1 N aq. HCl (40ml), warming of the reaction mixture to r.t. (9 h), evaporation *in vacuo*, shaking the residue with Et_2O/1 N aq. HCl and evaporation of the dried Et_2O layer yielded ketone **1a** (1.079 g, 90%). The aq. layer was evaporated and the residue was dissolved in MeOH (15 ml). Addition of $NaBH_4$ (227 mg, 6 mmol) over 15 min. at 0°C, stirring at 0°C for 1 h, addition of 1 N aq. HCl (5 ml, → pH = 1), evaporation, successive addition of water, 25% aq. NaOH (→ pH = 12) and solid NaCl and extraction with Et_2O yielded crude hydroxylamine **8b** (455 mg, 67% yield from **3b**, *erythro/threo* = 9:1 by ^{1}H-NMR). Crude **8b** (390 mg, 1.72 mmol) was stirred with zinc dust (1.35 g, 17 mmol) in 1 N aq. HCl/AcOH (2:1, 16 ml) at 0°C for 96 h. Filtration, basification of the filtrate with 50% aq. NaOH (→ pH = 14), extraction with Et_2O, drying and evaporation of the extracts afforded crude methoxamine **9b** (310 mg, 85%, *erythro/threo* = 9:1 by ^{1}H-NMR). Crude **9b** (300 mg, 1.42 mmol) was purified by recrystallization of its hydrogen maleate salt from isopropanol/MeOH/Et_2O giving colorless crystals (297 mg, 39% from ketone **3b**). M.p.: 172 - 175°C. $[\alpha]_D^{20}$ = -38.7° (MeOH, *c* = 1). ^{1}H-NMR(D_2O): 0.98 (*d, J=7, 3H*); 3.53-3.60 (*m, 1H*); 3.6 (*s, 6H*); 5.01 (*d, J= 4.5, 1H*); 6.13 (*s, 2H*); 6.8-6.9 (*m, 3H*). MS: 212 (M-115, 1.44); 168 (25.5); 139 (10.1); 137 (13.6); 72 (56.6); 71 (11); 65 (10); 55(37); 54 (21.4); 53 (35.2).

Methoxamine hydrogen maleate, prepared *via* the approach of Fujita and Hiyama [6] showed an identical ^{1}H-NMR spectrum. M.p.: 171-73°C. Mixed m.p. with a sample obtained from ketone **3b**: 169-171°C. $[\alpha]_D^{20}$: -36.32° (MeOH, *c* = 0.581).

Nitrone 6c (R=t-Bu)

A 1.6 M soln. of buthyllithium (hexane, 732 µl, 1.171 mmol) was added to a soln. of 1,1,3,3-tetramethyl-1,3-diphenyldisilazane (339 µl 1.17 mmol) in THF (10 ml) at 0 °C under N_2. After stirring the soln. for 15 min. it was cooled to -78 °C and 2,2-dimethyl-3-pentanone (**3c**, 150 µl, 1.064 mmol) was added. Stirring the soln for 1 h, addition of a 0.945 M soln. of $ZnCl_2$ (THF, 1.69 ml, 1.597 mmol), stirring for 1.5 h, addition of a soln. of nitrosoreagent **2a** (568 mg, 1.276 mmol) in THF (2 ml), stirring for 4 h, addition of

phosphate buffer (pH = 7), workup and chromatography (hexane/EtOAc 7:3) gave nitrone **6c** (colorless solid, 373 mg, 67%). HPLC (*Merck, LiChrosorb Si60*, hexane/isopropanol 96:4): 4.9 (100%). $[\alpha]_D$= -89.5°, $[\alpha]_{578}$= -94.2°, $[\alpha]_{546}$= -109.5°, $[\alpha]_{436}$= -214.2°, $[\alpha]_{365}$= -428.8°, ($CHCl_3$, c = 1.08, T = 19.6 °C). IR ($CHCl_3$): 3025, 2935, 2856, 1723, 1604, 1453, 1384, 1319, 1257, 1195, 1166, 1141, 1108, 1048, 1024, 983, 908, 855. ^{1}H-NMR ($CDCl_3$): 1.20(*m*, 7H); 1.11(*s*, 3H); 1.21(*s*, 9H); 1.22(s, 3H); 1.55(*d*, *J* = 6.8, 3H); 1.75(*m*, 17H); 2.01(*d*, *J* = 16, 1H); 2.09(*m*, 1H); 2.87(*m*, 1H); 3.49(*br*, 2H); 3.69(*d*, *J* =14, 1H); 4.44(*d*, *J* = 14, 1H); 4.87(*q*, *J* = 6.8, 1H). ^{13}C-NMR ($CDCl_3$): 206.93(*s*), 150.30(*s*), 68.92(*d*), 57.12(*d*), 55.53(*t*), 55.43(*s*), 49.31(*s*), 46.27(*d*), 43.95(*s*), 38.79(*t*), 33.62(*t*), 32.27(*t*), 30.46(*t*), 26.92(*q*), 26.56(*t*), 26.41(*t*), 26.19(*t*), 25.42(*t*), 21.34(*q*), 18.78(*q*), 15.02(*q*). MS: (6,$C_{29}H_{50}N_2O_4S^{+\cdot}$ +1), 505(5), 342(17), 194(32), 180(39), 176(11), 138(12), 98(12), 93(14), 83(29), 81(15), 79(12), 69(18), 67(15), 57(100).

Nitrone **6d** *(R=i-Pr)*

Following the protocol, described above for the preparation of **6c**, 2-methyl-3-pentanone (**3d**, 300 µl, 2.41 mmol) and nitroso reagent **2a** (1.12 g, 2.52 mmol) gave nitrone **6d** (colorless solid, 985 mg, 81%). HPLC (*Merck, LiChrosorb Si60*, hexane/isopropanol 96:4): 5.84 (99.8%). $[\alpha]_D$= -119.6°, $[\alpha]_{578}$= -125.9°, $[\alpha]_{546}$= -146.2°, $[\alpha]_{436}$= -281.7°, $[\alpha]_{365}$= -536.0°, ($CHCl_3$, c = 1.26, T = 19.8 °C). IR ($CHCl_3$): 3018, 2935, 2855, 1723, 1600, 1453, 1319, 1224, 1220, 1141, 1108, 983, 572. ^{1}H-NMR ($CDCl_3$): 1.09(*m*, 2H); 1.10(*d*, *J* = 6.6, 3H); 1.11(*s*, 3H); 1.14(*d*, *J* = 6.6, 3H); 1.27(*s*, 3H); 1.30(*m*, 5H); 1.65(*d*, *J* = 7, 3H); 1.75(*m*, 19H); 2.88(*m*, 1H); 2.98(*hept*, *J* = 7, 1H); 3.51(*br*, 2H); 3.51(*d*, *J* = 14, 1H); 4.65(*q*, *J* = 7, 1H); 4.7(*d*, *J* = 14.3, 1H). ^{13}C-NMR ($CDCl_3$): 208.25(*s*), 152.47(*s*), 71.12(*d*), 57.08(*d*), 55.9(*t*), 55.49(*s*), 48.79(*s*), 46.57(*d*), 38.74(*t*), 36.42(*d*), 33.8(*t*), 32.11(*t*), 31.36(*t*), 26.59(*t*), 26.46(*t*), 25.93(*t*), 25.39(*t*), 21.52(*q*), 18.72(*q*), 18.7(*q*), 18.55(*q*), 14.06(*q*). MS: (2, $C_{28}H_{48}N_2O_4S^{+\cdot}$), 491(17), 421(24), 328(68), 264(52), 246(100), 194(64), 180(93), 138(70), 83(41).

Nitrone **6e** *(R=Et)*

Following the protocol, described above for the preparation of **6c**, 3-pentanone (**3e**, 100 µl, 0.944 mmol) and nitroso reagent **2a** (504 mg, 1.132 mmol) gave nitrone **6e** (357 mg, 76%). HPLC (*Merck, LiChrosorb Si60*, hexane/isopropanol 96:4): 8.51 (99.6%). $[\alpha]_D$= -121.0°, $[\alpha]_{578}$= -127.4°, $[\alpha]_{546}$= -148.7°, $[\alpha]_{436}$= -289.7°, $[\alpha]_{365}$=-567.4°, ($CHCl_3$, c = 0.39, T = 19.8 °C). IR ($CHCl_3$): 2935, 2856, 1725, 1604, 1453, 1383, 1319, 1257, 1223, 1166, 1141, 1108, 1048, 1036, 983, 895, 855, 722, 663, 572. ^{1}H-NMR ($CDCl_3$): 1.08(*t*, *J* = 7.2, 3H); 1.09(*m*, 1H); 1.11(*s*, 3H); 1.29(*s*, 3H); 1.30(*m*, 6H); 1.72(*m*, 14H); 1.64(*d*, *J* =6.8, 3H); 1.95(*m*, 4H);

2.08(*d*, *J* = 16, 1H); 2.44(*dq*, *J* = 18.5, *J* = 7.2, 1H); 2.75(*dq*, *J* = 18.5, 7.2, 1H); 2.93(*m*, 1H); 3.45(*d*, *J* = 14, 1H); 3.50(*br*, 2H); 4.47(*q*, *J* = 6.8, 1H); 4.75(*d*, *J* = 14, 1H). ^{13}C-NMR ($CDCl_3$): 205.29(*s*), 153.05(*s*), 72.30(*d*), 57.12(*d*), 55.86(*t*), 55.45(*s*), 48.79(*s*), 46.65(*d*), 39.16(*t*), 33.87(*t*), 32.15(*t*), 32.09(*t*), 31.23(*t*), 26.60(*t*), 26.50(*t*), 25.89(*t*), 25.39(*t*), 21.58(*q*), 18.51(*q*), 14.14(*q*), 7.32(*q*). MS: 314(9), 250(6), 234(7), 194(17), 181(16), 180(24), 138(24), 83(28), 55(100).

(2S,3R)-2-Amino-4,4-dimethyl-3-pentanol (**9c**)

Stirring a soln. of nitrone **6c** (344 mg, 0.685 mmol) in 2N HCl /THF (1:2, 6 ml) for 24 h, evaporation of the THF, extraction of the aq. phase with ether, drying and evaporation of the extracts gave ketone **1a** (255 mg, 98%). Evaporation of the aq. phase, addition of toluene and evaporation (3x) gave a residue which was dissolved in ethanol (5 ml). Addition of $NaBH_4$ (50 mg, 1.322 mmol) at -78°C, stirring of the mixture for 30 min., warming to 0°C, addition of 2N aq. HCl and evaporation furnished a residue which was dissolved in 1N aq.HCl/AcOH (2:1, 6 ml). Addition of zinc powder (500 mg) at 0°C, stirring for 3 days, filtration through Celite, basification with aq. NaOH to pH = 14, extraction with Et_2O, drying, evaporation of the organic extracts and distillation of the residue afforded aminol **9c** (colorless solid, 69 mg, 80%). M.p.= 69-71°C. $[\alpha]_D$= -29.6°, $[\alpha]_{578}$= -31.2°, $[\alpha]_{546}$= -35.4°, $[\alpha]_{436}$= -57.9°, $[\alpha]_{365}$= -86.3°, ($CHCl_3$, c= 0.52, T = 19.8 °C). IR ($CHCl_3$): 3630, 3600-3000, 2983, 2872, 1583, 1479, 1365, 1300, 1240, 1107, 987, 884, 662. ^{1}H-NMR ($CDCl_3$): 0.96(*s*, 9H); 1.06(*d*, *J* = 6.2, 3H); 1.78(*br*, 3H); 3.18(*d*, *J* = 2.6, 1H); 3.21(*dq*, *J* = 6.2, 2.6, 1H). ^{13}C-NMR ($CDCl_3$): 82.42(*d*), 47.70(*d*), 34.33(*s*), 26.89(*q*), 17.57(*q*). MS: (10, $C_7H_{17}NO^{+\cdot}$), 116(49), 98(3), 87(9), 74(100), 56(59). To determine the stereochemical purity a soln. of aminol **9c** (2 mg) in $(CF_3CO)_2O$/EtOAc (1:1) was stirred at r.t. for 10 min., then heated to 100°C for 1 min and evaporated giving the corresponding *N,O*-bistrifluoracetyl derivative (oil). GC (Chirasil-Val III: 60°C/14 min.; 5°C/min. → 150°C): 18.22(100%).

(2S,3R)-2-Amino-4-methyl-3-pentanol (**9d**)

Following the protocol, described above for the conversion **6c** → **9c**, nitrone **9d** (700 mg, 1.376 mmol) gave ketone **1a** (605 mg, 95%) and aminol **9d** (colorless solid, 130 mg, 81%) which was recrystallized from hexane (119 mg, 74%). M.p.= 87-88 °C. $[\alpha]_D$= -8.6°, $[\alpha]_{578}$= -8.9°, $[\alpha]_{546}$= -10.1°, $[\alpha]_{436}$= -16.5°, $[\alpha]_{365}$= -23.2°, ($CHCl_3$, c= 0.655, T = 19.6°C). IR ($CHCl_3$): 3640, 3750-3000, 2966, 1588, 1471, 1384, 1312, 1225, 1082, 990, 888, 848, 666. ^{1}H-NMR ($CDCl_3$): 0.86(*d*, *J* = 6.6, 3H); 1.00(*d*, *J* = 6.3, 3H); 1.02(*d*, *J* = 6.3, 3H); 1.65(*m*, 1H); 1.70(*br*, 3H); 3.04(*dd*, *J* = 8.1, 3.7, 1H); 3.13(*dq*, *J* = 6.3, 3.7, 1H). ^{13}C-NMR ($CDCl_3$): 79.93(*d*), 47.65(*d*), 30.42(*d*), 19.42(*q*), 18.58(*q*), 15.83(*q*). MS: (61, $C_6H_{15}NO^{+\cdot}$ +1), 100(9), 84(7), 74(73), 73(13), 56(100). Anal. Calcd. for $C_6H_{15}NO$: C, 61.50; H, 12.90; N, 11.95. Found: C, 61.48; H, 12.82; N, 11.97.

To determine the stereochemical purity a soln. of aminol **9d** (2 mg) in $(CF_3CO)_2O$/EtOAc was stirred at r.t. for 10 min., then heated to 100°C for 1 min and evaporated giving the corresponding *N,O*-bistrifluoracetyl derivative (oil). GC (Chirasil-Val III: 60°C/5 min.; 5°C/min. → 100°C): 11.38 (99.7%).

(2S,3R)-2-Amino-3-pentanol (9e)

Following the protocol, described above for the conversion **6c** → **9c**, nitrone **6e** (753 mg, 1.52 mmol) gave ketone **1a** (583 mg, 97%) and, after distillation, crude aminol **9e** (135 mg, 86%, 9:1-*erythro/threo* mixture). A 1 M soln. of maleic acid (EtOH, 814 µl) was added to a soln. of crude **9e** (70 mg, 0.678 mmol) in EtOH (0.3 ml). Addition of Et_2O and crystallization of the precipitate from EtOH/Et_2O gave the hydrogen maleate of **9e** (97mg, 65 %). M.p.= 139.5-141°C. $[\alpha]_D$= -2.4°, $[\alpha]_{578}$= -2.5°, $[\alpha]_{546}$= -2.7°, $[\alpha]_{436}$= -4.°9, $[\alpha]_{365}$= -8.1°. ^{1}H-NMR (CD_3OD): 0.99(*t*, *J* = 7.4, 3H); 1.20(*d*, *J* = 6.6, 3H); 1.47 (*m*, 2H); 3.27(*m*, 1H); 3.59(*m*, 1H); 6.25(*s*, 2H) .^{13}C-NMR (CD_3OD): 170.84(*s*), 136.76(*d*), 73.27(*d*), 52.33(*d*), 26.95(*t*), 11.99(*q*), 10.61(*q*). Anal. Calcd. for $C_9H_{17}NO_5$: C, 49.31; H, 7.82; N, 6.39. Found: C, 49.05; H, 7.72; N, 6.31.

Treatment of this hydrogen maleate (45 mg, 0.205 mmol) with 50% aq. NaOH, workup and distillation gave pure aminol **9e** (oil, 18 mg, 85%). $[\alpha]_D$= +15.1°, $[\alpha]_{578}$= +16.0°, $[\alpha]_{546}$= +18.1°, $[\alpha]_{436}$= +30.4°, $[\alpha]_{365}$= +47.2°. IR ($CHCl_3$): 3700-3000, 2968, 2937, 2878, 1585, 1457, 1379, 1306, 1239, 1083, 969, 955, 892, 672. ^{1}H-NMR ($CDCl_3$): 0.99(*m*, 6H); 1.42(*m*, 2H); 1.83(*br*, 3H); 2.98(*m*, 1H); 3.36(*m*, 1H). ^{13}C-NMR ($CDCl_3$): 76.23(*d*), 50.06(*d*), 25.32(*t*), 16.87(*q*), 10.51(*q*). To determine the stereochemical purity a soln. of aminol **9e** (2 mg) in $(CF_3CO)_2O$/EtOAc was stirred at r.t. for 10 min., then heated to 100°C for 1 min and evaporated giving the corresponding *N,O*-bistrifluoracetyl derivative (oil). GC (Chirasil-Val III: 60°C/ 10 min.; 5°C/min. → 150 °C): 15.82 (100%).

(2S,3R)-2-(N,N-Dibenzylamino)-3-pentanol

Benzyl bromide (304 µl, 2.56 mmol) and triethylamine (357 µl, 2.56 mmol) were added to a soln. of crude aminol **9e** (9:1-*erythro/threo* mixture, 33 mg 0.32 mmol) in CH_3CN (2 ml) and the mixture was stirred at r.t. for 24 h. Addition of water, workup and chromatography (hexane/EtOAc 5:1) gave a colorless oil. (37.5 mg, 0.145 mmol, 45%). ^{1}H-NMR ($CDCl_3$): 0.87(*t*, *J* = 7.4, 3H); 1.11(*d*, *J* = 7, 3H); 1.32 (*m*, 1H); 1.60(*br*, 1H); 1.76(*m*, 1H); 2.72(*m*, 1H); 3.47(*d*, *J* = 14, 2H); 3.52(*m*, 1H); 3.76(*d*, *J* = 13.6, 2H); 7.23(*m*, 2H); 7.32(*m*, 8H). ^{13}C-NMR ($CDCl_3$): 140.14(*s*), 128.75(*d*), 128.24(*d*), 126.88(*d*), 75.24(*d*), 57.08(*d*), 54.77(*t*), 27.15(*t*), 10.34(*q*), 8.65(*q*).

(2S,3R)-2-(N,N-Dibenzylamino)pentan-3-yl (S)-α-methoxy-α-(trifluoromethyl)phenylacetate.

Pyridine (70 μl) and (*R*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride was added to a soln. of (*2S,3R*)-2-(*N,N*-dibenzylamino)-3-pentanol (15 mg, 0.058 mmol) in CH_2Cl_2 (0.5 ml). Shaking of the mixture for 2 days and workup gave a colorless oil (9.5 mg, 0.02 mmol, 35%). GC (OV-1: 150 °C; 10 °C/min.; 270 °C): 12.2 (92%). ^{1}H-NMR ($CDCl_3$): 0.63(*t*, *J* = 7.7, 3H); 0.91(*d*, *J* = 6.6, 3H); 1.64(*m*, 1H); 1.85(*m*, 1H); 2.86(*m*, 1H); 3.37(*d*, *J* = 13.6, 2H); 3.54(*m*, 3H); 3.63(*d*, *J* = 14, 2H); 5.20(*m*, 1H); 7.29(*m*, 13H); 7.53(*m*, 2H). ^{13}C-NMR ($CDCl_3$): 166.32(*s*), 136.69(*s*), 129.5(*d*), 128.84(*d*), 128.30(*d*), 128.24(*d*), 127.29(*d*), 126.97(*d*), 86, 79.57(*d*), 55.46(*d*), 55.0(*s*), 54.09(*t*), 53.69(*q*), 24.78(*t*), 8.92(*q*), 8.63(*q*). The ^{1}H- and ^{13}C-NMR spectra are identical to those provided by Professor M. T. Reetz.