Supporting Information

Toward the Creation of NMR Databases in Chiral Solvents: Bidentate Chiral NMR Solvents for Assignment of the Absolute Configuration of Acyclic Secondary Alcohols

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Synthesis of chiral NMR solvents 1a~d

Chiral NMR solvents **1a**, **1b** and **1d** were prepared, with small modifications of the literature known methods [(a) Horner, L.; Dickerhof, K. *Liebigs Ann. Chem.* **1984**, 1240-1258; (b) Mimoun, H.; Laumer, J. Y. S.; Giannini, L.; Scopelliti, R.; Floriani, C. *J. Am. Chem. Soc.* **1999**, *121*, 6158-6166].

General procedure for **1a**, **1b** and **1d**: Dibromopropane (2.08 g, 10.3 mmol, 1equiv.) was added dropwise over 5 min to (*R*)-α-phenetylamine (5.00g, 41.3 mmol, 4 equiv.) at 130 °C. After stirring for 30 min, the mixture was cooled to 80 °C and then poured into aqueous 50 % NaOH solution (300 mL). The resulting free amines were extracted with EtOAc (300 mL) and the organic layer was washed with brine, dried over anhydrous K_2CO_3, filtered and evaporated to give the crude oil. The crude product was distilled by Kugelrohr to give pure **1a** (2.56 g 82%).

Dibromoethane (1.94 g) was used for synthesis of **1b** (2.39g, 86%) according to the procedure shown above.

1,3-Dibromo-2-methylpropane used for synthesis of **1d** was prepared, according to the procedure reported by B. Török and Á. Molnár (*J. Chem. Soc. Perkin Trans. 1* **1993**, 801-804).

Chiral NMR solvent **1c** was prepared by LAH-reduction of the literature known amide *N,N'*-bis-(1-phenylethyl)-succinamide (Potapov, V. M.; Koval', G. N.; Solov'eva, L. D. *J. Org. Chem. USSR* **1985**, *21*, 705-708).

For spectroscopic data of **1a,b**, see: Hulst, R.; de Vries, N. K.; Feringa, B. L. *Tetrahedron:Asymmetry* **1994**, *5*, 699-708.

Spectroscopic data of chiral NMR solvents **1c,d**:

1c ($[\alpha]_D^{25}$ = +60 (*c* 1.1 $CHCl_3$)): 145.7 (x2), 128.3 (x4), 126.8 (x2), 126.5 (x4), 58.3 (x2), 47.6 (x2), 28.0 (x2), 24.3 (x2).

1d ($[\alpha]_D^{25}$ = +68 (*c* 1.0 $CHCl_3$)): 146.0, 145.9, 128.3 (x4), 126.7 (x2), 126.5 (x4), 58.6, 58.4, 53.9, 53.8, 33.8, 24.5, 24.4, 17.3.

^{13}C NMR Data of 2, 3, 6, 8a and 8b (100 MHz, $CDCl_3$)

2: 72.0, 37.2 (x2), 27.8 (x2), 22.8 (x2), 14.1 (x2).

3: 72.8, 41.6 (x2), 27.0, 26.1 (x2), 23.3 (x2), 14.1 (x2).

6: 74.6, 29.8 (x2), 9.8 (x2).

8a: 82.2, 46.8, 39.7 (x2), 35.1 (x2), 32.1, 27.5 (x3), 19.0 (x2).

8b: 74.5, 47.6, 37.4 (x2), 32.3, 28.4 (x2), 27.6 (x3), 18.7 (x2).

Synthesis of alcohols 9, 10, 13 and 14

The alcohol **10** was obtained from valeraldehyde by Brown's asymmetric allylation (Jadhav, P. K.; Bhat, K. S.; Perumal, T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432-439). Hydrogenation (H_2/Pd on C/MeOH) of **10** gave the alcohol **9**.

^{13}C NMR (100 MHz, $CDCl_3$) of **9**: 71.7, 39.6, 37.2, 27.8, 22.7, 18.8, 14.10, 14.06.

^{13}C NMR (100 MHz, $CDCl_3$) of **10**: 134.9, 118.0, 70.6, 41.9, 36.5, 27.8, 22.7, 14.0.

Optically active **11** and **12** were obtained from Aldrich.

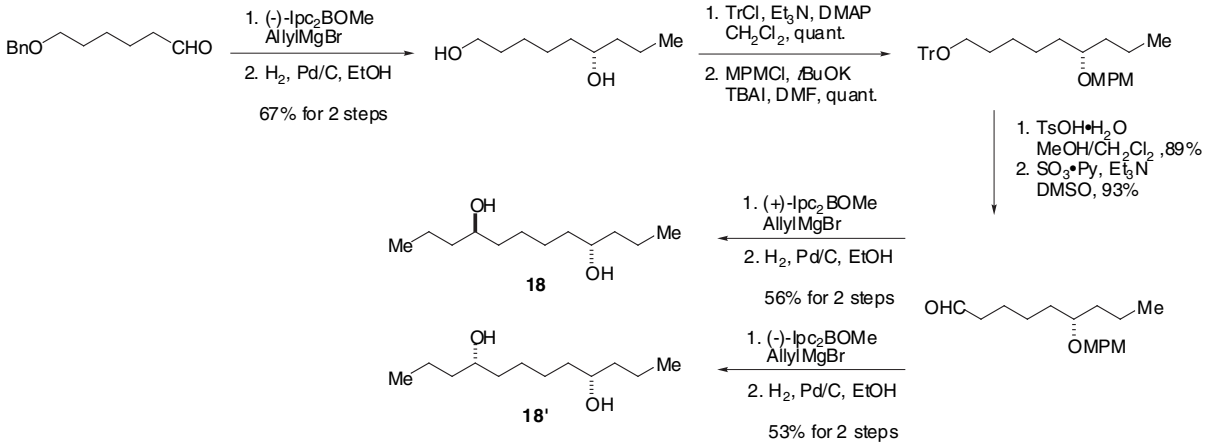
Alcohol **13** was prepared in 2 steps: (1) Jacobsen's hydrolytic kinetic resolution of (±)-isobutyloxirane (Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science*, **1997**, *277*, 936) and (2) LAH/THF.

^{13}C NMR (100 MHz, $CDCl_3$) **13**: 66.1, 48.6, 24.8, 24.0, 23.2, 22.3.

Alcohol **14** was obtained by CBS reduction of pinacolone (Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551-5553).

^{13}C NMR (100 MHz, $CDCl_3$) **14**: 75.6, 34.9, 25.3 (x3), 17.9.

Synthesis of alcohols 16~19 was carried out as summarized below.



Scheme S1. Synthesis of diols **18** and **18'**

The synthesis of *meso*-diols **16**, **17** and **19** and optically active diols **16'**, **17'** and **19'** was carried out under the same conditions given for **18** and **18'**, respectively. Also see Figure 1 and 2 in the Supporting Information.

^{13}C NMR (100 MHz, CD_3OD) of **16**: 72.49 (x2), 40.75 (x2), 34.70 (x2), 19.94 (x2), 14.48 (x2).

^{13}C NMR (100 MHz, CD_3OD) of **17**: 72.12 (x2), 40.68 (x2), 38.51 (x2), 22.95, 19.93 (x2), 14.51 (x2).

^{13}C NMR (100 MHz, $CDCl_3$) of **18**: 71.64 (x2), 39.70 (x2), 37.39 (x2), 25.71 (x2), 18.81 (x2), 14.10 (x2).

^{13}C NMR (100 MHz, $CDCl_3$) of **19**: 71.69 (x2), 39.69 (x2), 37.39 (x2), 29.70, 25.60 (x2), 18.82 (x2), 14.11 (x2).

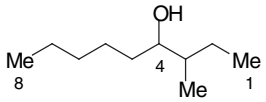
^{13}C NMR (100 MHz, CD_3OD) of **16'**: 72.16 (x2), 40.76 (x2), 34.44 (x2), 19.96 (x2), 14.48 (x2).

^{13}C NMR (100 MHz, CD_3OD) of **17'**:72.10 (x2), 40.71 (x2), 38.48 (x2), 23.00, 19.92 (x2), 14.49 (x2).

^{13}C NMR (100 MHz, $CDCl_3$) of **18'**: 71.57 (x2), 39.70 (x2), 37.37 (x2), 25.62 (x2), 18.81 (x2), 14.10 (x2)

^{13}C NMR (100 MHz, $CDCl_3$) of **19'**: 71.68 (x2), 39.68 (x2), 37.40 (x2), 29.73, 25.60 (x2), 18.81 (x2), 14.11 (x2).

Synthesis of alcohols 20 and 21 was prepared by Brown's aymmetric crotylboration (Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919-5923) of valeradehyde and hydrogenation (H_2/Pd on C/MeOH)).

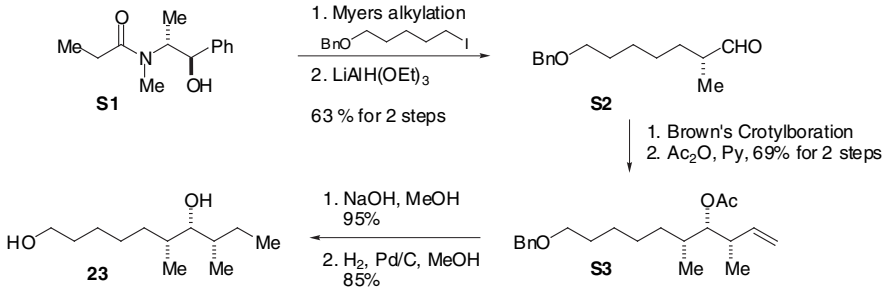


20 and **21**

^{13}C NMR (100 MHz, $CDCl_3$) of **20**: 75.7 (C4), 40.5 (C3), 33.3 (C5), 31.9 (C7), 25.7 (C6), 24.5 (C2), 22.6 (C8), 14.7 (C10), 14.0 (C9), 11.7 (C1).

^{13}C NMR (100 MHz, $CDCl_3$) of **21**: 74.8 (C4), 39.9 (C3), 34.4 (C5), 31.9 (C7), 26.0 (C6), 25.9 (C2), 22.6 (C8), 14.0 (C9), 13.1 (C10), 11.8 (C1).

Synthesis of alcohols 22~25



Scheme S2. Synthesis of alcohol **23**

Aldehyde S2. To a solution of diisopropylamine (5.04 mL, 36.0 mmol) and LiCl (4.07 g, 96.0 mmol) in THF (20 mL) was added n-BuLi (2.5 M in Hexane, 14.8 mL, 33.3 mmol) at -78 °C. The suspension was stirred for 30 min at 0 °C, then recooled to -78 °C. A solution of propionamide **S1** (Myers, A. G.; Yang, B. H.; Chen, H.; Mckinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496-6511) (3.54 g, 16.0 mmol) in THF (40 mL) was added to the reaction flask at -78 °C via cannula. The reaction mixture was stirred at -78 °C for 1 h, at 0 °C for 15 min and at rt for 5 min and finally cooled to 0 °C. A solution of 5-benzyloxy-1-iodopantane (Sargent, M. V.; Wangchareontrakul, S. *J. Chem. Soc. Perkin Trans. 1* **1990**, 129-132) (9.73 g, 32.0 mmol) in THF (20 mL) was added to the reaction flask over 15 min. The mixture was stirred at 0 °C for 1 h and then quenched by the addition of satd aq. NH_4Cl. The resulting mixture was diluted with EtOAc (750 mL) and washed with satd aq. NH_4Cl (250 mL) and brine (250 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by flash chromatography to give amide (6.36 g, >99%).

To a suspension of LAH (118 mg, 3.11 mmol) in hexane (7.2 mL) was added AcOEt (0.45 mL, 4.6 mmol) at 0°C over 2 min. The resulting suspension was cooled to -78 °C. A solution of the amide (537 mg, 1.35 mmol) in THF (4.7 mL) was added to the reaction flask via cannula over 5 min. The reaction mixture was stirred at 0 °C for 1 h, and then 1N HCl was added to the reaction flask at 0 °C. The resulting mixture was diluted with EtOAc (70 mL), and washed with a solution of TFA (1.04 mL) in 1N HCl (17 mL), satd aq. $NaHCO_3$ (30 mL X 2) and brine (30 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by flash chromatography to give aldehyde **S2** (198 mg, 63%).

Acetate S3. To a solution of KO*t*Bu (158 g, 1.41 mmol) in THF (10 mL) was added *cis*-2-butene (2 mL) and n-BuLi (2.5 M in hexane, 0.56 mL) at -78 °C. This mixture was stirred for 10 min at -45 °C, and recooled to -78 °C. To this solution was added a solution of (+)-$(Ipc)_2$BOMe in THF (5 mL). After stirring for 30 min at -78 °C, $BF_3{\cdot}Et_2O$ (0.250 mL, 1.92 mmol) and a solution of aldehyde **S2** in THF (2 mL). The solution was stirred for 3 h at -78 °C. After addition of 3N NaOH (1.2 mL) and 30% H_2O_2 aqueous solution (0.5 mL) at rt, the mixture was stirredd overnight at rt, diluted with EtOAc (150 mL), and washed with brine (100 ml). The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give a mixture of alcohol and isopinocampheol. The mixture

was treated with Ac_2O, pyridine, and 4-dimethylaminopyridine. After removing excess reagents in vacuo, the resulting residue was purified by flash chromatography to give acetate **S3** (0.297 g, 69% for 2 steps)

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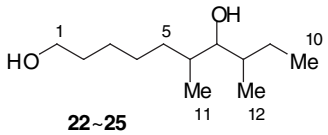
Alcohol 23. To a solution of acetate **S3** (0.283 g, 0.850 mmol) in methanol (4 mL) was added NaOH (one pellet). The mixture was stirred for 7 h at 50 °C, then diluted with EtOAc (100 mL), and washed with 1N HCl (20 mL), satd $NaHCO_3$ (20 mL), and brine (20 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. the resulting residue was purified by flash chromatography to give alcohol (0.200 g, 81%).

To a solution of the alcohol (41.9 mg, 0.144 mmol) in ethanol (3 mL) was added Pd/C (10 wt%, 4.3 mg). The mixture was stirred under hydrogen atmosphere for 7 h at rt, then filtered throuh Celite. The filterate was concentrated in vacuo to give alcohol **23** (24.6 mg, 85%).

The synthesis of **22**, **24** and **25** was carried out under the same conditions given for **23**.

^{13}C NMR (100 MHz, CD_3OD) of **22**: 78.7 (C7), 63.0 (C1), 38.1 (C8), 36.3 (C6), 34.9 (C5), 33.7 (C2), 27.9 (C4), 27.4 (C9), 27.3 (C3), 14.9 (C11), 14.5 (C12), and 11.7 (C10).



22~25

^{13}C NMR (100 MHz, CD_3OD) of **23**: 79.3 (C7), 63.0 (C1), 37.9 (C8), 37.1 (C6), 33.5 (C5), 33.7 (C2), 28.1 (C4), 28.0 (C9), 27.4 (C3), 16.5 (C11), 13.2 (C12), and 12.1 (C10).

^{13}C NMR (100 MHz, CD_3OD) of **24**: 79.1 (C7), 63.0 (C1), 38.7 (C8), 35.9 (C6), 35.6 (C5), 33.7 (C2), 28.2 (C4), 26.0 (C9), 27.3 (C3), 15.9 (C11), 13.4 (C12), and 11.6 (C10).

^{13}C NMR (100 MHz, CD_3OD) of **25**: 81.4 (C7), 63.0 (C1), 38.4 (C8), 36.5 (C6), 31.7 (C5), 33.7 (C2), 28.3 (C4), 24.7 (C9), 27.4 (C3), 17.2 (C11), 16.4 (C12), and 11.9 (C10).

Figure 1. Difference in carbon chemical shifts of *meso*-diols (100 MHz) in between (*R,R*)- and (*S,S*)-chiral solvent (**1a** and **1d**) . The *x*- and *y*-axes represent carbon number and $\delta_{(R,R)}$-$\delta_{(S,S)}$ in ppm, respectively.

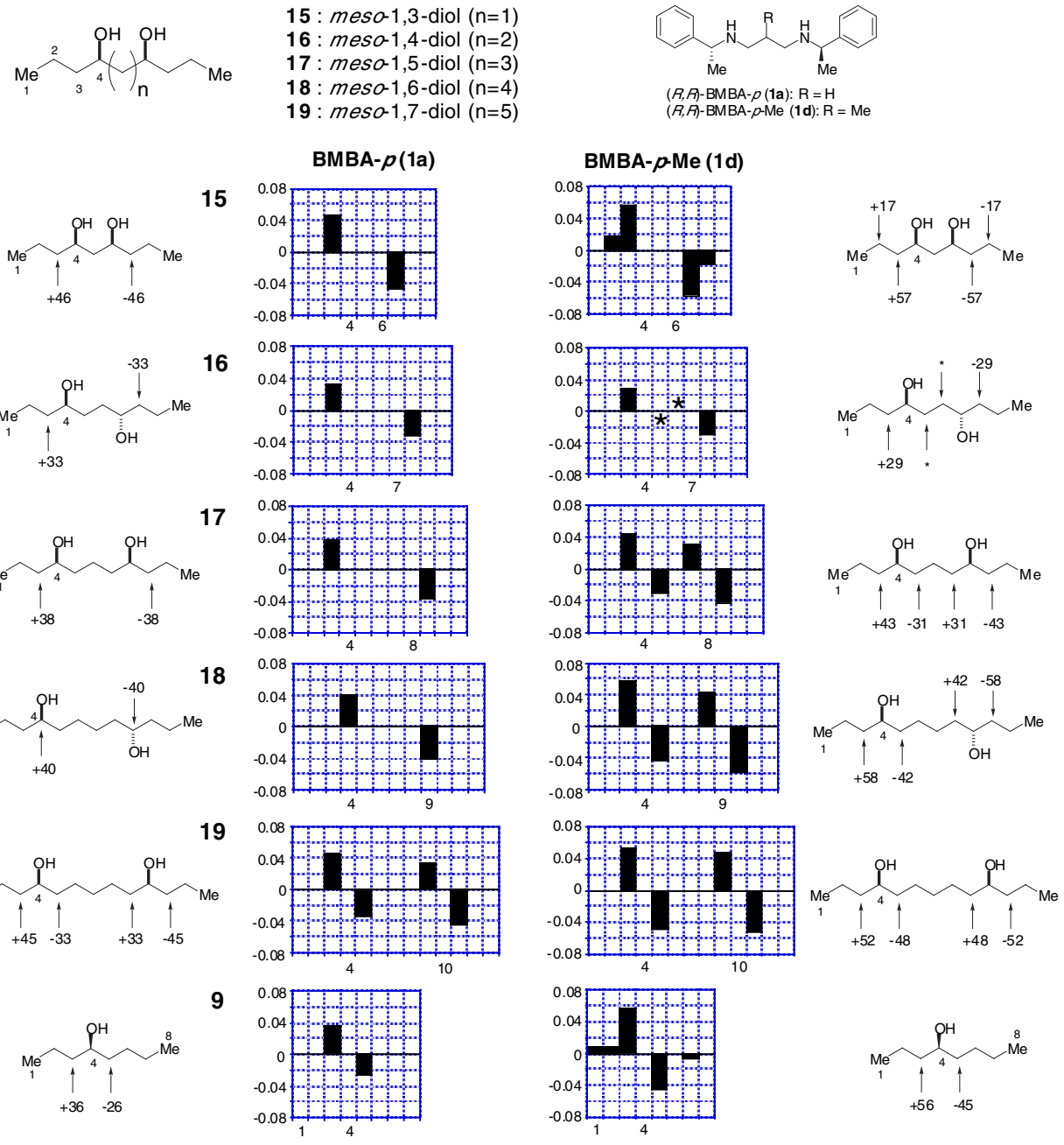


Figure 2. Difference in carbon chemical shifts of optically active diols (100 MHz) in between (*R,R*)- and (*S,S*)-chiral solvent (**1a** and **1d**) . The *x*- and *y*-axes represent carbon number and $\delta_{(R,R)}$-$\delta_{(S,S)}$ in ppm, respectively.