A New Asymmetric Synthesis of trans-Hydroisoquinolones

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Supporting Information

A. Representative Experimental Procedures[1]

Preparation of Benzyl 2-[(6'*R*)-(*tert*-Butyldiphenylsiloxy)cyclohex-1-enyl]ethylcarbamate (17). This compound was prepared from **13** (16.7 g, 36.1 mmol, 91% *ee*)[2] according to the general Suzuki coupling procedure we described earlier[3] to give **17** (15.6 g, 84%) as a pale yellow oil: $[\alpha]^{25}_{D}$ +18.2, $[\alpha]^{25}_{577}$ +18.6, $[\alpha]^{25}_{546}$ +21.7, $[\alpha]^{25}_{435}$ +39.2, $[\alpha]^{25}_{405}$ +48.4 (*c* 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68–7.72 (m, 4H), 7.25–7.44 (m, 11H), 5.52 (s, 1H), 5.07 (s, 2H), 4.09 (br s, 1H), 2.97–3.10 (m, 2H), 2.21–2.24 (m, 1H), 2.02–2.10 (m, 3H), 1.85–1.89 (m, 1H), 1.70–1.76 (m, 2H), 1.38–1.52 (m, 2H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 136.7, 136.6, 136.0, 135.9, 134.5, 133.9, 129.7, 129.5, 129.0, 128.5, 128.2, 128.1, 128.0, 127.6, 127.4, 126.7, 68.3, 66.5, 39.2, 33.7, 32.3, 27.1, 25.4, 19.4, 18.5; IR (film) 3336, 2932, 1715, 1513, 1251, 1069, 703 cm^{-1}; MS (CI, isobutane) *m/e* 513.2691 (M, 513.2699 calcd for $C_{32}H_{39}NO_3Si$), 456, 199. Anal. Calcd for $C_{32}H_{39}NO_3Si$: C, 74.81; H, 7.65; N, 2.73. Found: C, 74.68; H, 7.60; N, 2.69.

Preparation of (*R*)-2-[6'-(*tert*-Butyldiphenylsiloxy)-1'-cyclohexen-1'-yl]ethylamine (23). A mixture of **17** (1.54 g, 3.00 mmol), Pd on carbon (10% Pd by weight, 80 mg), NH_4HCO_2 (2 g), MeOH (100 mL) and AcOH (20 mL) was stirred at rt for 1h. The mixture then was filtered through Celite and the eluent was concentrated. The residue was diluted with $CHCl_3$ (20 mL), and this solution was washed with saturated aqueous Na_2CO_3 (20 mL), dried (Na_2SO_4) and

[1] General experimental details have been described: Metais, E.; Overman, L. E.; Rodriguez, M. I.; Stearns, B. A. *J. Org. Chem.* **1997**, *62*, 9210–9216.

[2] The enantiomeric purity of **13** was determined to be 91% *ee* by HPLC analysis (Daicel Chiralcel OB-H column, 85:15 hexanes–*i*-PrOH, 0.8 mL/min, λ = 254 nm) of the corresponding alcohol, which was prepared by the treatment of **13** with TBAF.

[3] Kamatani, A.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 8743–8744.

filtered. The filtrate was concentrated to give **23** (1.14 g, ~100%) as a pale yellow oil: $[\alpha]^{25}_{D}$ +14.0, $[\alpha]^{25}_{577}$ +13.8, $[\alpha]^{25}_{546}$ +16.3, $[\alpha]^{25}_{435}$ +30.2, $[\alpha]^{25}_{405}$ +36.6 (*c* 1.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54–7.73 (m, 4H), 7.34–7.47 (m, 6H), 5.52 (t, *J* = 3.5 Hz, 1H), 4.07 (t, *J* = 4.6 Hz, 1H), 2.41–2.55 (m, 2H), 2.23–2.29 (m, 1H), 1.87–2.08 (m, 3H), 1.65–1.80 (m, 2H), 1.37–1.52 (m, 2H), 1.37 (br s, 2H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 136.0, 134.6, 134.0, 129.6, 129.5, 127.5, 127.4, 126.2, 68.2, 40.2, 38.2, 32.4, 27.0, 25.5, 19.4, 18.5; IR (film) 2933, 2857, 1428, 1111, 1069, 1016, 703 cm^{-1}; MS (FAB) *m*/*e* 380.2418 (MH, 380.2410 calcd for $C_{24}H_{34}NOSi$), 307, 199, 154, 135, 124.

Preparation of Ethyl (1*R*,4a*S*,8a*S*)-5-Oxo-1-isopropyloctahydroisoquinoline-2-carboxylate (26). A mixture of **23** (130 mg, 0.35 mmol), isobutyraldehyde (36 μL, 0.40 mmol), $MgSO_4$ (20 mg), K_2CO_3 (20 mg) and CH_2Cl_2 (2 mL) was stirred at rt for 5–10 min, filtered, and the filtrate was concentrated using a rotary evaporator to give the corresponding crude imine: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67–7.73 (m, 4H), 7.35–7.43 (m, 6H), 7.12 (app d, *J* = 5.2 Hz, 1H), 5.47 (br s, 1H), 4.03 (br s, 1H), 3.02–3.34 (m, 2H), 2.27–2.38 (m, 2H), 2.20–2.29 (m, 2H), 1.79–2.00 (m, 2H), 1.72–1.75 (m, 3H), 1.35–1.49 (m, 3H), 1.05 (br s, 9H), 0.98 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 137.2, 136.0, 129.5, 129.4, 127.7, 127.5, 127.3, 126.3, 68.7, 59.2, 34.9, 33.9, 32.3, 27.1, 26.5, 25.4, 19.4, 18.6.

This imine intermediate was immediately converted to the corresponding α-ethoxy carbamate using a modification of a procedure of Speckamp.[4] Diethyl pyrocarbonate (60 μL, 1.2 equiv) was added to a solution of the imine and anhydrous EtOH (1 mL). The resulting solution was maintained at rt for 1 d, the solution was concentrated, and the residue was purified on silica gel (10:1 hexanes–EtOAc) to afford 165 mg (85%) of α-ethoxycarbamate **27** (R = *i*-Pr), a yellow oil that was a ~1:1 mixture of epimers: ^{1}H NMR (500 MHz, $C_6D_5CD_3$, 70 °C) δ (selected signals) 5.54–5.59 (m, 1H), 4.31 (br s, 1H), 4.04–4.09 (m, 2H).

Freshly distilled $BF_3{\cdot}OEt_2$ (26 μL, 2 equiv) was added dropwise to a solution of a portion **27** (R = *i*-Pr, 55 mg, 0.10 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (70 μL, 3 equiv) and CH_2Cl_2 (1 mL) at 0 °C. The resulting yellow-orange solution was maintained at 0 °C for 2 h, at which time TLC analysis showed that the starting material had been consumed. Triethylamine (140 μL, 10 equiv) and MeOH (40 μL, 10 equiv) were added successively and the resulting mixture was allowed to warm to rt. This mixture was washed with saturated aqueous Na_2CO_3, and the organic layer was dried (Na_2SO_4) and filtered. The filtrate was concentrated and the resulting residue was purified on silica gel gel (5:1 hexanes–EtOAc) to give 24 mg (77% overall from **23**) of **26** as a pale yellow oil: 88% *ee* (Daicel Chiralcel AS, 95:5 hexanes–*i*-PrOH, 1 mL/min, λ = 208 nm);

[4] Hiemstra, H.; Fortgens, H. P.; Speckamp, W. N. *Tetrahedron Lett*. **1985**, *26*, 3155–3158.

$[\alpha]^{25}_{D}$ +10.1, $[\alpha]^{25}_{577}$ +11.4, $[\alpha]^{25}_{546}$ +13.4, $[\alpha]^{25}_{435}$ +31.3, $[\alpha]^{25}_{405}$ +44.2 (*c* 1.3, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 3.99–4.04 (m, 3H, H-3eq, OCH_2), 3.90 (br s, 1H, H-1), 2.71 (br t, *J* = 12.9 Hz, 1H, H-3ax), 2.48–2.52 (m, 1H, H-4a), 2.41 (td, *J* = 13.9, 6.2 Hz, 1H, H-6ax), 2.22 (br d, *J* = 13.9 Hz, 1H, H-6eq), 2.11–2.18 (m, 1H, C*H*Me_2), 2.02–2.06 (m, 1H, H-7eq), 1.70–1.77 (m, 4H, H-4eq, 7ax, 8ax, 8a), 1.47–1.54 (m, 1H, H-8eq), 1.27 (qd, *J* = 13.6, 5.2 Hz, 1H, H-4ax), 1.18 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 1.08 (d, *J* = 6.4 Hz, 3H, $CHCH_3$), 0.84 (d, *J* = 6.8 Hz, 3H, $CHCH_3$); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 209.6, 154.6, 59.9, 46.2, 46.0, 40.4, 38.8, 28.7, 25.3, 25.2, 24.3, 22.6, 19.3, 13.9 (one carbon is buried under $CDCl_3$); IR (film) 2955, 1694, 1428, 1102, 1025, 768 cm^{-1}; MS (CI, isobutane) *m/e* 268.1917 (MH, 268.1913 calcd for $C_{15}H_{26}NO_3$), 224, 152, 123.

B. Determination of the Absolute Configuration of 28.

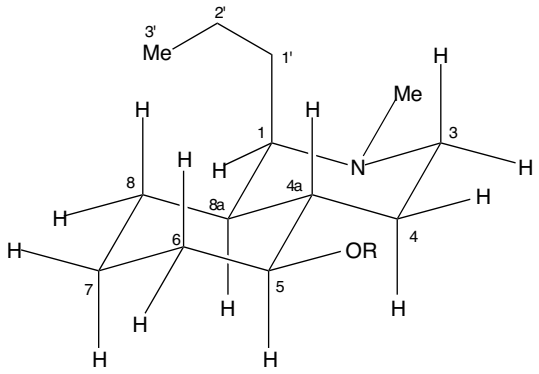
Preparation of (1*R*,4a*S*,5*S*,8a*S*)-2-Methyl-1-propyldecahydroisoquinolin-5-yl (2*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropionate. A solution of sodium borohydride (11 mg, 0.28 mmol) and ethanol (3 mL) was added to a solution of **28** (56 mg, 0.21 mmol) and ethanol (1 mL) at –30 °C. The resulting solution was stirred for 10 min at –30 °C, then at 0 °C for 30 min, and finally at rt for 2 h. The reaction mixture was quenched with water (50 μL) and concentrated. The residue was diluted with $CHCl_3$, dried (Na_2SO_4) and filtered. The filtrate was concentrated, and the residue was dissolved in dry THF (5 mL). Lithium aluminum hydride (1 M in THF, 0.9 mL) was then added dropwise to this solution at 0 °C, and the resulting solution was heated at reflux for 3.5 h. After cooling to rt, H_2O (30 μL), 15% NaOH (30 μL) and H_2O (90 μL) were added sequentially. After stirring for 5 min, the mixture was filtered, the filtrate was concentrated, the residue was diluted with $CHCl_3$, and this solution was dried (Na_2SO_4) and filtered, and the filtrate was concentrated. The resulting residue was purified on silica gel (9:1:0.02 $CHCl_3$–*i*-PrOH–NH_4OH) to afford a pale yellow oil (48 mg, ~100%) that was a ~3:1 mixture of the desired equatorial alcohol [^{1}H NMR (500 MHz, $CDCl_3$) δ 3.25 (H-5)] and its axial epimer. This mixture was converted to the corresponding mixture of Mosher esters without further purification.

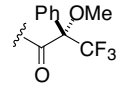
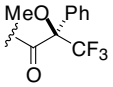
A solution of (*S*)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetic acid (39 mg, 0.17 mmol), thionyl chloride (120 μL, 1.7 mmol), benzene (3 mL) and DMF (1 drop) was heated at 80 °C for 4h, cooled to room temperature and then put under vacuum to remove benzene and residual thionyl chloride. Dry pyridine (0.4 mL) was added to the resulting viscous yellow liquid, followed by a solution of this mixture of epimeric alcohols and CCl_4 (1 mL). The resulting yellow solution was maintained at rt for 17 h, after which time the solution was diluted with EtOAc (10 mL) and washed successively with saturated aqueous Na_2CO_3 (10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4) and filtered, and the filtrate was concentrated. The

residue was purified on silica gel (9:1:0.02 $CHCl_3$–*i*-PrOH–NH_4OH) to provide 25 mg (28% from **28**) of the title *S* Mosher ester: $[\alpha]^{25}_{D}$ –6.9, $[\alpha]^{25}_{577}$ –6.5, $[\alpha]^{25}_{546}$ –7.2, $[\alpha]^{25}_{435}$ –14.9, $[\alpha]^{25}_{405}$ –19.8 (*c* 1.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) see table; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 132.6, 129.5, 128.3, 127.4, 127.2, 123.4 (q, $^1J_{CF}$ = 288.6 Hz), 84.4 (q, $^2J_{CF}$ = 27.4 Hz), 80.8, 63.1, 55.4, 47.0, 42.4, 38.6, 31.6, 28.5, 27.5, 24.6, 23.7, 23.6, 20.0, 14.4; IR (film) 2944, 1747, 1696, 1458, 1272, 1169, 1021 cm^{-1}; MS (CI, isobutane) *m*/*e* calcd for $C_{23}H_{32}NO_3F_3$ 427.2334; found 427.2327 (M), 384, 194, 150.

The corresponding *R* Mosher ester was prepared in identical fashion.

Advanced Mosher Analysis[5]



PROTONS	δ (ppm)		
	R = 	R = 	Δδ (δ_S-δ_R)
1-H	2.53 (m)	2.51 (m)	+ 0.02
N-Me	2.35 (s)	2.32 (s)	+ 0.03
3eq-H	2.49 (app dd, J = 12.6, 3.0 Hz)	2.38 (br d?)	+ 0.11
3ax-H	2.41 (td, J = 12.5, 2.9 Hz)	2.32 (td?)	+ 0.09
4eq-H	1.64 (m)	1.38 (m)	+ 0.26
4ax-H	1.33 (m)	1.19 (m)	+ 0.14
4a-H	1.43 (m)	1.38 (m)	+ 0.05
5-H	4.65 (td, J = 10.6, 4.4 Hz)	4.68 (td, J = 10.4, 4.4 Hz)	– 0.03
6eq-H	2.11 (dd, J = 11.9, 2.9 Hz)	2.17 (m)	– 0.06
6ax-H	1.22 (m)	1.39 (m)	– 0.17
7eq-H	1.80 (app dt, J = 14.2, 3.5 Hz)	1.84 (m)	– 0.04
7ax-H	1.39 (m)	1.40 (m)	– 0.01
8eq-H	1.21-1.33 (m)	1.26 (m)	?
8ax-H	1.05-1.16 (m)	1.07-1.13 (m)	?
8a-H	1.21-1.33 (m)	1.34 (m)	?
1'-H	1.68 (m)	1.64 (br s)	+ 0.04
2'-H	1.29 (m)	1.29 (m)	0
3'-H	0.89 (t, J = 7.2 Hz)	0.90 (t, J = 7.2 Hz)	– 0.01

[5] (a) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096. (b) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.