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EXPERIMENTAL

Materials and Methods

Phenylselenyl chloride, 4-*tert*-butylcyclohexanone, 4-methylcyclohexanone, 3,5-dimethylcyclohexanol, (*R*)- and (*S*)-1-phenylethylamine, (*R*)-1-(1-naphthyl)ethylamine, (-)-sparteine (**4**), (*S*, *S*)-(-)-bis[1-(phenyl)ethyl]amine hydrochloride, (+)-Ipc_2BCl , (-)-Ipc_2BCl, and (-)-Ipc_2Br were commercially available. (*Cis*)-3,5-dimethylcyclohexanone (**13**) was obtained by Jones' oxidation of *trans-meso*-3,5-dimethylcyclohexanol obtained by fractionation (SiO_2, PhH:EtOAc, 4:1) of the commercially available mixture.[1] The boron reagent **2**,[2] (2*S*, 5*S*)-2,5-dimethylpyrrolidine,[3] (*R*)-*N*,*N*-dimethyl-1-(1-naphthyl)ethylamine,[4] (*R*)- and (*S*)-*N*,*N*,-dimethyl-1-phenylethylamine,[5] (1*R*, 2*R*)- and (1*S*, 2*S*)-*N*,*N*,*N'*,*N'*-tetramethyl-1,2-diphenyl-1,2-ethanediamine (**3**)[6,7] were prepared according to known procedures. The *N*-methylamines (*S*, *S*)-*N*-methylbis[1-(phenyl)ethyl]amine and (2*S*, 5*S*)-*N*,2,5-trimethylpyrrolidine,[8] was prepared by Eshweiler-Clarke methylation[5] of the corresponding secondary amine. Ozone was generated by a Welsbach model T-408 ozonator operating at an oxygen pressure of 8 psi and a flow rate of 0.2 ft^3/min. Reaction temperatures refer to the bath: ice/water (0 °C), $CO_{2(s)}$/acetone (-78 °C), $N_{2(l)}$/diethyl ether (-116 °C) and $N_{2(l)}$/pentane (-131 °C).

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[1] Gleave, D. M. Ph.D. Thesis, University of Saskatchewan, 1993.

[2] Corey, E. J.; Yu, C. M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495-5496.

[3] Beak, P.; Kerrick, S. T.; Wu, S. D.; Chu, J. X. *J. Am. Chem. Soc.* **1994**, *116*, 3231-3239.

[4] Yamamoto, K.; Ikeda, K.; Yin, L. K. *J. Organomet. Chem.* **1989**, *370*, 319-332.

[5] Cope, A. C.; Ciganek, E.; Fleckenstein, L. J.; Meisinger, M. A. P. *J. Am. Chem. Soc.* **1960**, *82*, 4651-4655.

[6] Pikul, S.; Corey, E. J. *Org. Synth.* **1993**, *71*, 22-28.

[7] Horner, L.; Dickerhof, K. *Liebigs Ann. Chem.* **1984**, 1240-1257.

[8] Tokuda, M.; Yamada, Y.; Takagi, T.; Suginome, H. *Tetrahedron* **1987**, *43*, 281-296.

Spectral Data

Optical rotations were determined at ambient temperature on a Perkin-Elmer 141 polarimeter using a 1 mL, 10 dm cell; concentrations (*c*) are reported in g/100 mL. Mass spectra were obtained on a VG 70E double focussing high resolution spectrometer. Infrared spectra were recorded on a Biorad FTS-40 fourier transform interferometer using a diffuse reflectance cell (DRIFT). Only diagnostic peaks are reported. Unless otherwise noted, nuclear magnetic resonance (NMR) spectra were measured in $CDCl_3$ solution on a Bruker AM-300 spectrometer. For ^1H NMR, residual $CHCl_3$ in $CDCl_3$ was employed as the internal standard and assigned as 7.26 ppm downfield (δ) from tetramethylsilane (TMS). For ^{13}C NMR, $CDCl_3$ was employed as the internal standard and assigned as 77.0 δ relative to TMS. ^1H NMR spectra were normally obtained with a digital resolution of 0.25 Hz/pt (sweep width=4000 Hz, FID=32 K data points) and coupling constants are reported to the nearest 0.5 Hz.

General procedure for determination of the selectivity of enolborination

A saturated ozone solution in 15 mL of dichloromethane was added rapidly via syringe to the enolborination reaction mixture (0.1-0.2 mmol scale). The ozone solution was prepared by bubbling ozone into 50 mL of dry dichloromethane at -94 °C until saturated (as indicated by a deep blue color; the concentration of a saturated ozone solution in dichloromethane at -94 °C is reportedly[9] 0.062 M). Excess ozone was removed by bubbling argon through the reaction solution. The mixture was allowed to warm to room temperature and was concentrated. The resulting crude ozonide was dissolved in 2 mL of acetone and cooled to 0 °C. Jones' reagent was added dropwise under vigorous stirring until the red-brown color persisted. Sufficient 2-propanol was added to destroy the excess oxidant and the mixture was filtered through celite and the solid was washed three times with acetone. The combined filtrate and washings were concentrated, and the residue was triturated with ether (3 × 5 mL). The combined ether layers were dried over Na_2SO_4, concentrated, and fractionated (SiO_2, 6% $MeOH/CH_2Cl_2$) to obtain the diacids. The enantiomeric purity of each diacid was determined by ^1H NMR (in $CDCl_3$) in the presence of *ca.* 10 equiv. of (*R*)-1-phenylethylamine (for **9** and **15**) or (*R*)-1-(1-naphthyl)ethylamine (for **10** and **18**) based on integration of the well-separated *t*-butyl or methyl signals. The downfield signals were due to the (3*R*) isomers of **9** and **10**, to the (2*R*)-isomer of **15** and to the (2*S*)-isomer of **18**. The absolute configurations of the major enantiomers of the diacids **9**, **10**, and **18** were determined by comparison of the observed

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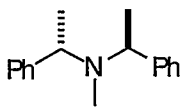
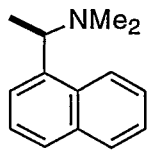
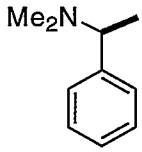
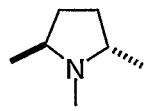
[9] Mei, Y. H.; Mendenhall, G. D. *Anal. Chem.* **1997**, *69*, 1019-1022.

optical rotation with that reported for the known compounds: (*S*)-(+)-**9** ($[\alpha]_D$ 17.2, *c* 1.0, acetone);[10] (*R*)-(+)-**10** ($[\alpha]_D$ 11.5, *c* 9.3, $CHCl_3$);[11] (*S*)-(-)-**18** ($[\alpha]_D$ -13.4, *c* 2.15, EtOH).[12] The absolute configuration for **15** was assigned assuming enolborination occured with the same sense of enantioselectivity as observed for **9**, **10** and **13**.

Table 1. Selectivity of enolborination of 4-*tert*-butylcyclohexanone using enantiopure monoamines.[a]

entry	amine	boron reagent	% yield[b]	selectivity (**7a**:**7b**)[c]
1.	Et_3N	(-)-Ipc_2BCl	85	1.7:1
2.		Chx_2BCl	N.R.	
3.		(-)-Ipc_2BCl	N.R.	
4.		Chx_2BCl	55	1.1:1
5.		(-)-Ipc_2BCl	50	1.2:1
6.		(+)-Ipc_2BCl	40	1:1
7.		Chx_2BCl	65	1:1.3
8.		(-)-Ipc_2BCl	55	1.2:1
9.		(+)-Ipc_2BCl	55	1:2.2
10.		Chx_2BCl	65	2.0:1
11.		(-)-Ipc_2BCl	60	2.6:1
12.		(+)-Ipc_2BCl	60	1.1:1

[a] Reaction in pentane (0.06 M in ketone, 1.5 equiv. each of boron reagent and amine) at -78 °C for 6 h (incomplete reaction) using. [b] Isolated yield of the diacid(s) obtained after oxidation of the enolborinate. [c] Measured by ^1H NMR of the derived diacid(s) in the presence of (*R*)-1-phenylethylamine or (*R*)-1-(1-naphthyl)ethylamine.

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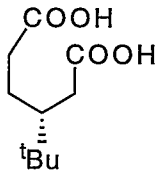
[10] Tichy, M.; Malon, P.; Fric, I.; Blaha, K. *Collect. Czech. Chem. Commun.* **1977**, *42*, 3591-3604

[11] Shirai, R.; Tanaka, M.; Koga, K. *J. Am. Chem. Soc.* **1986**, *108*, 543-545.

[12] Wong, C. H.; Auer, E.; LaLonde, R. T. *J. Org. Chem.* **1970**, *35*, 517-519.

Optimized procedure for the enantioselective enolborination: Preparation of (*R*)-3-*tert*-butylhexanedioic acid



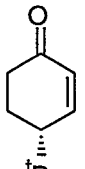
(*R*)-**9**

A solution of 4-*tert*-butylcyclohexanone (**5**) in a 3.5:6.5 mixture of pentane and ether (0.59 M; 0.22 mL, 0.13 mmol) was added dropwise via syringe to a stirred solution of (+)-Ipc_2BCl (86 mg, 0.27 mmol) and (*S,S*)-(-)-**3** (36 mg, 0.13 mmol) in a 3.5:6.5 mixture of pentane and ether (2.0 mL) at -131 °C. After 24 h., oxidation of the reacton mixure with O_3 and then with Jones' reagent according to the general procedure gave (*R*)-(-)**9** (21 mg, 76%) of 88% ee (a 16.5:1 mixture of enantiomers by ^1H NMR in the presence of (*R*)-1-phenylethylamine). Optical rotation indicated 89.4% ee (corresponding to a 17.8:1 mixture of enantiomers). A similar experiment for 10 h using (-)-Ipc_2BCl and sparteine (**4**) gave (*S*)-(+)-**9** (80%) of 90% ee (a 19:1 mixture of enantiomers by ^1H NMR)

$[\alpha]_D$ -15.4 (c 0.99, acetone) [lit:[10] +17.2° (c 1.0, acetone) for the (*S*) enantiomer]

^1H-NMR (300 MHz, $CDCl_3$) δ: 10.4 (brs, 2H), 2.57-2.35 (m, 3H), 2.10 (dd, 1H, *J* = 15.5, 7.5 Hz), 1.95 (m, 1H), 1.75 (m, 1H), 1.43 (m, 1H), 0.92 (s, 9H).

Preparation of (*R*)-4-*tert*-butylcyclohex-2-en-1-one[13]



11

A solution of the enolborinate from **5** (0.020 g, 0.13 mmol) and (+)-Ipc_2BCl/(*S,S*)-(-)-**3** was obtained according to the optimized procedure. A solution of PhSeCl (0.026 g, 0.14 mmol) in of CH_2Cl_2 (1 mL) was added dropwise via syringe to above enolate solution at -131 °C. After 10 min., 1 mL of methanol was added and the reaction mixture was allowed to warm to room temperature. The mixture was

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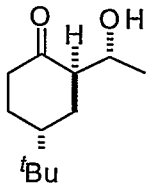
[13] Cain, C. M.; Cousins, R. P. C.; Coumbarides, G.; Simpkins, N. S. *Tetrahedron* **1990**, *46*, 523-544.

diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ solution and with brine (20 mL), dried over Na_2SO_4, and concentrated. The crude selenide was dissolved in CH_2Cl_2 (30 mL) and the solution was cooled to -78 °C. Ozone was very slowly bubbled through the solution (1 bubble per second) until a pale blue color persisted (ca. 0.75 h). The excess ozone was removed by bubbling argon through the solution and then diisopropylamine (1.7 mL, precooled to -78 C) was added and the cold reaction mixture was transferred by a double-ended needle to a refluxing CCl_4 solution (50 mL) containing diisopropylamine (0.85 mL). After 5 min, the cooled (room temperature) solution was washed sequentially with 10% HCl, saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The residue was fractionated (SiO_2, 10% EtOAc/hexane) to afford known enone (+)-**11** (0.011 g, 54%; 89.1% ee by optical rotation).

$[\alpha]_D$ 49.4 (*c* 1.07, benzene) [lit:[14] 51.0 (benzene) for the 4-*R* enantiomer of 92% ee]

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.03 (dt, 1H, *J* = 10, 2.5 Hz), 6.04 (ddd, 1H, *J* = 10, 2.5, 1.5 Hz), 2.53 (m, 1H), 2.41-2.05 (m, 3H), 1.75 (m, 1H) and 0.98 (s, 9H)

Preparation of (1'*R* ,2*R*, 4*R*)-4-*tert*-butyl-2-(1'-hydroxyethyl)cyclohexanone



12

A solution of the enolborinate from **5** (0.029 g, 0.19 mmol) and (+)-Ipc_2BCl and (*S*,*S*)-(-)-**3** was obtained according to the optimized procedure. Freshly-distilled acetaldehyde (0.16 mL, 2.8 mmol) was added dropwise via syringe to above enolate solution at -131 °C. After 5 h., the reaction was quenched by addition of 1 mL of methanol, and allowed to warm to room temperature. Hydrogen peroxide (0.19 mL of a 30% solution) was added dropwise at 0°C and the resulting mixture was stirred at 0° C for 30 min and then at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2, washed with of 2N HCl and saturated $NaHCO_3$, dried over Na_2SO_4, concentrated, and fractionated (SiO_2, 10% ether/CH_2Cl_2) to yield **12** (0.021g, 56%). The *anti* aldol stereochemistry of **12** was assigned based on the characteristic HOC*H*C*H*C=O $^3J_{HH}$ of 8.5 Hz; the *trans* disubstituted cyclohexane stereochemistry was assigned based on comparison of the ^{13}C NMR data with that of the known[15] *cis* and *trans* 2-hydroxymethyl-4-*tert*-butylcyclohexanones. The ee of **12** was determined by ^{1}H NMR of the derived

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[14] Aoki, K.; Nakajima, M.; Tomioka, K.; Koga, K. *Chem. Pharm. Bull.* **1993**, *41*, 994-996.

[15] Wanat, R. A.; Collum, D. B. *J. Am. Chem. Soc.* **1985**, *107*, 2078-2082.

Mosher's ester (*R*-MTPA-Cl, Et_3N, DMAP, 35 °C, 30 min) based on intergration of the well separated ^{t}Bu signals (major: δ 0.87; minor δ 0.81)

IR ν_{max}:3422, 2958, 2864, 1708 cm^{-1}

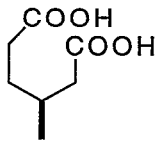
^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.95 (ddq, 1H, *J* = 4, 8.5, 6 Hz), 2.93 (d, 1H, *J* = 4 Hz), 2.41-2.28 (m, 3H), 1.95-1.36 (m, 5H), 1.22 (d, 3H, *J* = 6 Hz), 0.89 (s, 9H).

^{13}C NMR (75 MHz, C_6D_6) δ: 214.9, 68.6, 55.6, 42.7, 39.9, 32.8, 28.1, 27.4, 25.1, 21.3.

LRMS (CI, NH_3), *m/z* (relative intensity): 216 ($[M+18]^+$, 9), 199 ($[M+1]^+$, 100), 181 (11), 172 (9), 154 (9), 123 (5).

HRMS calcd. for $C_{12}H_{23}O_2$: 199.1698; found: 199.1701.

Preparation of (3*S*)-3-methylhexanedioic acid



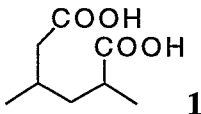
(*S*)-**10**

Enolborination of 4-methylcyclohexanone (**6**) (12 mg, 0.11 mmol) with (-)-Ipc_2BCl (72 mg, 0.22 mmol) and (*R,R*)-(+)-**3** (31 mg, 0.12 mmol) in a 3.5:6.5 mixture of pentane and ether (1.9 mL) at -131 °C for 15 h followed by oxidation of the reaction mixure with O_3 and then with Jones' reagent according to the general procedure gave (*S*)-(-)-**10** (14 mg, 81%; a 22:1 mixture of enantiomers (91.5% ee) by ^{1}H NMR in the presence of (*R*)-1-(1-naphthyl)ethylamine). Optical rotation indicated 95% ee (corresponding to a 39:1 mixture of enantiomers). A similar experiment for 10 h with sparteine (**4**) replacing **3** gave (*S*)-(-)-**10** (80%; a 26:1 mixture of enantiomers by ^{1}H NMR).

$[\alpha]_D$ -11 (*c* 0.92, $CHCl_3$) [lit:[11] 11.5 (*c* 9.3, $CHCl_3$) for the 3*R* enantiomer]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.4 (brs, 2H), 2.50-2.15 (m, 4H), 2.10-1.92 (m, 1H), 1.82-1.68 (m, 1H), 1.61-1.46 (m, 1H), and 1.00 (d, 3H, *J* = 6.7 Hz).

Preparation of (2*R,4*S**)-2,4-Dimethylhexandioic acid**

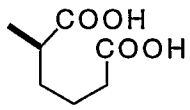


18

Enolborination of (*cis*)-3,5-dimethylcyclohexanone (**16**) (15 mg, 0.12 mmol) with (-)-Ipc_2BCl (77 mg, 0.24 mmol) and (*R,R*)-(+)-**3** (32 mg, 0.12 mmol) in a 3.5:6.5 mixture of pentane and ether (2.0 mL) at -131 °C for 10 h followed by oxidation of the reaction mixure with O_3 and then with Jones' reagent according to the general procedure gave **18**[16] (11 mg, 54%; an 8:1 mixture of enantiomers (77% ee) by ^1H NMR in the presence of (*R*)-1-phenylethylamine). A similar experiment for 10 h with sparteine (**4**) replacing **3** gave **18** (65%; a 23:1 mixture of enantiomers by ^1H NMR).

^1H NMR (300 MHz, $CDCl_3$) δ: 10.4 (br s, 2H), 2.58 (m, 1H), 2.35-2.18 (m, 2H), 2.03 (m, 1H), 1.79 (m, 1H), 1.29-1.17 (m, 1H), 1.20 (d, 3H, J = 7 Hz), 1.06 (d, 3H, J = 6.5 Hz).

Kinetic resolution of (±)-2-methylcyclohexanone: Preparation of (2*R*)-2-methylhexanedioic acid



(*R*)-21

Enolborination of (±)-2-methylcyclohexanone (**16**) (57 mg, 0.51 mmol) with (-)-Ipc_2BCl (65 mg, 0.20 mmol) and (*R,R*)-(+)-**3** (27 mg, 0.10 mmol) in a 3.5:6.5 mixture of pentane and ether (1.7 mL) at -131 °C for 6 h followed by oxidation of the reaction mixure with O_3 and then with Jones' reagent according to the general procedure gave (*R*)-**18** (11 mg, 14% based on **16**, 69% based on **3**; >30:1 mixture of enantiomers (>94% ee, minor isomer not detected) by ^1H NMR in the presence of (*R*)-1-(1-naphthyl)ethylamine). Optical rotation indicated 97% ee (corresponding to a 65:1 mixture of enantiomers). A similar result was obtained using sparteine (**4**) in place of **3**.

$[\alpha]_D$ -13 (*c* 0.6, EtOH) [lit:[12] -13.4 (*c* 2.15, EtOH) for the 2*R* enantiomer]

^1H NMR (300 MHz, $CDCl_3$) δ: 2.55-2.41 (m, 1H), 2.41-2.35 (m, 2H), 1.80-1.62 (m, 3H), 1.58-1.43 (m, 1H), 1.20 (d, 3H, J = 7 Hz).

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[16] Bassi, L.; Joos, B.; Gassmann, P.; Kaiser, H. P.; Leuenberger, H.; Kellerschierlein, W. *Helv. Chim. Acta* **1983**, *66*, 92-117.

Kinetic resolution of (±)-3-methylcyclohexanone: Preparation of (2*S*)-2-methylhexanedioic acid

Enolborination of (±)-3-methylcyclohexanone (**19**) (54 mg, 0.48 mmol) with (-)-Ipc_2BCl (62 mg, 0.19 mmol) and (*R,R*)-(+)-**3** (26 mg, 0.097 mmol) in a 3.5:6.5 mixture of pentane and ether (1.6 mL) at -131 °C for 6 h followed by oxidation of the reaction mixure with O_3 and then with Jones' reagent according to the general procedure gave a 22:1 mixture (by ^1H NMR) of **10** and **18**, respectively (12 mg, 16% based on **19**, 77% based on **3**). ^1H NMR of the mixture in the presence of (*R*)-1-(1-naphthyl)ethylamine) indicated that **10** was ca. a 30:1 mixture of enantiomers in favor of the *S* isomer; there was insufficient **18** (presumably the *R* isomer predominantly) present to determine its ee by this method. The optical rotation of the mixture was consistent with the presence of (*S*)-(-)-**10** as the major isomer ($[\alpha]_D$ -11 (*c* 0.66, $CHCl_3$) [lit:[11] 11.5 (*c* 9.3, $CHCl_3$) for 3*R*-**10**]). A similar result (i.e. a 22:1 mixture of (*S*)-**10** (90% ee) and **18** in 15% combined yield) was obtained at -78 °C using sparteine (**4**) in place of **3**. Only the presence of (*S*)-(-)-**10** (15% yield) could be detected by ^1H NMR of the product from a similar experiment at -131 °C for 4 h using sparteine (**4**) in place of **3**.