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Kinetic resolution of racemic (cyclohexyl)(geranyl)acetic acid

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General methods

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument [300.13 MHz (^{1}H), 75.47 MHz (^{13}C), respectively] in $CDCl_3$. The chemical shifts of ^{1}H and ^{13}C were measured relative to Me_4Si or $CDCl_3$ respectively. Mass spectra were obtained on a Kratos MS-30 (70 ev, direct inlet probe). The high-resolution mass spectra (HRMS) were measured with a Bruker microTOF II spectrometer using electrospray ionization (ESI). The measurements were taken in the positive ion mode (interface capillary voltage 4500 V) in the mass range *m/z* = 50-3000 Da; external or internal calibration was done with an electrospray calibrant solution (Agilent). Syringe injection was used for the solution in MeCN or MeCN−H_2O (flow rate 3 μL/min). The reactions were monitored by TLC (Silufol, toluene/EtOAc 95:5) using visualization by UV or I_2. Specific optical rotations $[\alpha]_D^{20}$ were measured with a Jasco DIP-360 instrument at 589 nm. Silica gel 0.060 – 0.200 (Acros) was used for column chromatography. Compounds **4**,[S1,S2] **5**,[S3] and **12**[S4] were synthesized by known procedures. Bromocyclohexane, diethylmalonate, linalool, 2-methyl-3-butene-2-ol, (*S*)- or (*R*)-BINOLs and $BnNEt_3Cl$ were purchased from Aldrich and used without purification. The solvents were purified by standard procedures.

Diethyl malonate derivatives 4 and 9 (general procedure). A mixture of diethyl cyclohexylmalonate (**2**) (24.2 g, 0.1 mol) and corresponding alkylating agent **3** or **8** (0.1 mol) was gradually added to a suspension of powdered KOH (5.6 g, 0.1 mol) and $BnNEt_3Cl$ (5 mmol) in DMF (30 ml) at 80-85°C with stirring. The reaction mixture was stirred for additional 5-6 h at 95-100°C and cooled to ambient temperature (TLC-monitoring). The precipitate was filtered off and washed with diethyl ether (2×20 ml). The combined filtrates were evaporated under reduced pressure (40 torr, 40°C) to a minimum volume and the residue was diluted with Et_2O (50 mL). The ether solution was washed with water (3×30 ml) and dried over anhydrous $MgSO_4$. The solvent was evaporated (40 torr, 40°C) and the remaining oil was distilled *in vacuo* (0.5 torr) to afford compound **4** or **9** and unchanged starting compounds **2** and **3**.

Diethyl [(2*E*)-3,7-dimethylocta-2,6-dien-1-yl](cyclohexyl)malonate (**4**). A colourless oil, 21.3 g, yield 56% (86% calculated on the consumed starting materials), b.p. 175-180°C (0.5 torr); n_D^{20} 1.4790 [Lit.[S1]: b.p. 161-169°C (0.3 torr); n_D^{25} 1.4795]. ^{1}H-NMR: δ 0.85-1.00 (m, 4H, $2CH_2$);1.25 (t, 6H, 2Me, *J* 7.1 Hz); 1.30-1.40 (m, 2H, CH_2); 1.55-1.75 (m, 4H, $2CH_2$); 1.60, 1.62, 1.68 (all s, 3H each, Me); 1.90-2.10 (m, 6H, $3CH_2$); 2.64 (m, H, CH); 4.12 (q, 4H, $2CH_2$, *J* 7.1 Hz); 5.06 (m, 1H, CH=); 5.08 (m, 1H, CH=) (see ref.[S5]).

Diethyl (3-methylbut-2-en-1-yl)(cyclohexyl)malonate (**9**). A colourless oil, 2.02 g, yield 65%, b.p. 120-125°C (0.5 torr); n_D^{20} 1.4670 [Lit.[S6]: b.p. 151-165°C (6.5 torr); n_D^{25} 1. 1.4680]. ^{1}H-NMR: δ 0.87-1.23 (m, 4H, $2CH_2$);1.25 (t, 6H, 2Me, *J* 7.0 Hz); 1.41-1.69 (m, 6H, $3CH_2$); 1.63 (s, 3H, Me); 1.72 (s, 3H, Me); 2.63 (m, H, CH); 4.18 (q, 4H, $2CH_2$, *J* 7.0 Hz); 5.05 (t, 1H, CH=, *J* 7.0 Hz).

Cyclohexylacetic acid derivatives *rac*-1 and 10 (g**eneral procedure**). A diethyl malonate derivative **4** or **9** (0.02 mol) was added in one portion to a vigorously stirred solution of KOH (6,0 g, 0.11 mol) in EtOH (9 ml) at 70^{o}C (an intensive foaming was observed) and the reaction mixture was refluxed with stirring for 2-3 h (TLC-monitoring). The solvent was evaporated under reduced pressure (40 torr, 40°C), water (20 ml) was added to the residue and the resulting aqueous solution was extracted with diethyl ether (2×5 ml) to remove neutral components. The remaining aqueous solution was acidified to pH ~2 with a 15% aqueous HCl and extracted with Et_2O (3×15 ml). The combined ether extracts were washed with water (3×30 ml) and dried over anhydrous $MgSO_4$. The ether was evaporated under reduced pressure (40 torr, 40°C), the residue was heated at 150°C until evolution of CO_2 ceased (2-3 h) and the residual oil was distilled *in vacuo* (0.5 torr) to afford compounds ***rac*-1** or **10**.

(Cyclohexyl)(geranyl)acetic acid (***rac*-1**). A pale-yellow oil, 4.76 g, yield 85%, b.p. 165-170°C (0.2 torr); n_D^{20} 1.4890 [Lit.[S1]: b.p. 160-165°C (0.14 Topp); n_D^{25} 1.4910]. ^{1}H-NMR: δ 0.97-1.31 (m, 6H, $3CH_2$); 1.56 (s, 6H, 2Me); 1.67 (s, 3H, Me); 1.46-1.83 (m, 5H, CH, $2CH_2$); 1.93-2.06 (m, 4H, $2CH_2$); 2.15-2.31 (m, 3H, CH, CH_2); 5.06-5.13 (m, 2H, 2CH=), 10.5 (br. s, 1H, CO_2H).

(Cyclohexyl)(prenyl)acetic acid (**10**). A colourless oil, 3.4 g, yield 81%, b.p. 120-125°C (0.5 torr); n_D^{20} 1.4780. ^{1}H-NMR: δ 0.98-1.32 (m, 6H, $3CH_2$); 1.62 (s, 3H, Me); 1.69 (s, 3H, Me); 1.74-1.85 (m, 4H, $2CH_2$); 2.15-2.31 (m, 3H, CH, CH_2); 5.10 (t, 1H, CH=, *J* 6.5 Hz); 11.5 (br. s,

1H, CO_2H). ^{13}C-NMR: δ: 17.8, 25.9, 26.3, 26.4, 30.6, 30.9, 39.8, 52.5, 52.2, 121.4, 133.6, 181.7. EI-MS *m/z* 210 $[M]^+$.

BINOL esters 5, 5a, 5b, 11 and 12 (**general procedure**). A mixture of acid ***rac*-1** or **10** (195 mg, 0.7 mmol), *rac*- or (*S*)- or (*R*)-BINOL (100 mg, 0.35 mmol), DCC (144 mg, 0.7 mmol) and DMAP (8.0 mg) in CH_2Cl_2 (7.0 ml) was stirred at ambient temperature for 2 h (TLC-monitoring). The precipitate was filtered off, the filtrate was washed successively with 10% HCl (2×4 ml), water (2×5 ml) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure (40 torr, 40°C) and the residue was purified by column chromatography (SiO_2, *n*-hexane/toluene 1:1) to afford compounds **5, 5a, 5b, 11** or **12**.

2-Cyclohexyl-5,9-dimethyldeca-4,8-dienoic acid 2'-hydroxy[1,1']binaphthalen-2-yl esters 5, 5a and 5b. **5**: a colourless oil, 143 mg, yield 75%. ^{1}H-NMR ($CDCl_3$) δ: 0.80-1.10 (m, 4H), 1.15-1.80 (m, 8H), 1.85-2.25 (m, 6H), 4.90-5.20 (m, 2H, 2CH=), 5.40 (m, 1H, OH), 7.05 (d, 1H, *J* 8.8 Hz), 7.19-7.41 (m, 7H, Ar), 7.50 (t, 1H, *J* 7.7 Hz), 7.80 (d, 1H, *J* 8.0 Hz), 7.88 (d, 1H, *J* 7.7 Hz), 7.95 (d, 1H, *J* 8.0 Hz), 8.10 (d, 1H, *J* 10.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 16.1, 16.2, 26.3, 26.8, 27.9, 29.8, 30.1, 30.3, 39.5, 52.2, 133.7(Ar), 133.8(Ar), 137.2(Ar), 137.4(Ar), 148.3(Ar), 152,1 (Ar), 174.9(C=O). ESI-HRMS: calcd for $C_{38}H_{42}O_3$ $[M+H]^+$ 547.3213; found 547.3207. HPLC data (*Chiralpak AD-H*, *n*-hexane/*i*-PrOH 7/3, 0.7 ml/min, 254 нм): **5a**: t_1 = 5.67 min (minor), t_2 = 6.10 (major), *Dr* = 10:90; **5b**: t_1 = 7.70 min (major), t_2 = 8.45 (minor) *Dr* = 87:13.

2-Cyclohexyl-5-methylhexa-4-enoic acid 2'-hydroxy[1,1']binaphthalen-2-yl ester (**11**). A colourless oil, 134 mg, yield 80%. ^{1}H-NMR δ: 0.36-0.94 (m, 6H), 1.18-1.81 (m, 11H), 2.10-2.15 (m, 3H), 4.93-5.02 (m, 1H), 5.30-5.46 (m, 1H), 7.07-7.09 (m, 1H), 7.27-7.35 (m, 6H), 7.48-7.53 (m, 1H), 7.87 (dd, 2H, *J* 8.8, 16.1 Hz), 8.02 (dd, 2H, *J* 8.8, 27.5 Hz). ^{13}C-NMR δ: 17.7, 17.9, 25.9, 26.1, 26.2, 28.0, 28.2, 29.8, 30.0, 30.3, 39.6, 52.2, 114.8, 118.6, 121.4, 121.8, 123.5, 124.7, 125.8, 126.2, 126.7, 127.4, 128.0, 128.3, 129.2, 130.8, 132.3, 133.4, 133.6, 133.8, 148.3, 152.1, 175.4. IR (KBr) υ, cm^{-1}: 3449 (OH), 2927, 2853, 1741 (C=O), 1210, 1148. ESI-HRMS: calcd for $C_{33}H_{34}O_3$ $[M+H]^+$ 479.2587; found 479.2583. HPLC data (*Chiralpak AD-H*, *n*-hexane/*i*-PrOH 7/3, 0.7 ml/min, 254 нм): **11**: t_1 = 4.45 min (minor), t_2 = 5.12 (major), *Dr* = 40:60.

2,2'-Bis(2-cyclohexyl-5-methylhex-4-enoyloxy)-1,1'-binaphthalene (**12**). A colourless oil, 35 mg, yield 15%. ^{1}H-NMR δ: 0.58-1.86 (m, 34H), 1.86-2.25 (m, 6H), 4.70-5.05 (m, 2H), 7.14-7.50 (m, 8H), 7.78 (dd, 4H *J* 9.2, 23.1 Hz). ^{13}C-NMR δ: 17.8, 17.9, 25.9, 26.3, 28.2, 29.8, 29.9, 30.1,

30.3, 30.4, 39.5, 52.2, 121.9, 123.8, 125.6, 126.4, 126.7, 127.9, 129.4, 131.6, 133.6, 147.3, 173.8. ESI-HRMS calcd for $C_{46}H_{54}O_4$ $[M+H]^+$ 671.4101; found 671.4095.

Methyl (cyclohexyl)(geranyl)acetates 6a or 6b (g**eneral procedure**). Solid $LiOH \cdot H_2O$ (13 mg, 3.0 mmol) was added to a solution of **5a** or **5b** (415 mg, 0.76 mmol) in MeOH (2 ml). The reaction mixture was stirred at 50°C for 7 h (TLC-monitoring) and acidified with TFA (0.35 mg). The solvent was evaporated under reduced pressure (40 torr, 40°C) and the residue was purified by column chromatography (SiO_2, *n*-hexane/toluene 3:1) to afford compounds **6a** or **6b**. Colourless oils, 178 mg or 189 mg, yield 80% or 85%, respectively, n_D^{20} 1.4793, *Rf* = 0.65. ^{1}H-NMR ($CDCl_3$) δ: 0.90-1.31 (m, 6H, $3CH_2$), 1.60 (s, 6H, 2Me), 1.68 (s, 3H, Me), 1.90-2.10 (m, 4H, $2CH_2$), 2.16-2.30 (m, 3H, CH, CH_2), 3.63 (s, 3H, Me), 5.05-5.15 (m, 2H, 2CH=). ^{13}C-NMR ($CDCl_3$) δ: 15.9, 17.7, 25.9, 26.3, 26.4, 26.7, 28.1, 30.8, 30.9, 39.9, 51.0, 52.2, 121.7, 124.3, 131.3, 136.9, 176.0. Corresponding (*S*)-BINOL (196 mg, 90%) or (*R*)-BINOL (184 mg, 85%) were recovered by column chromatography as colourless solids, mp 206-208°C (Lit.[7] mp 206-210°C), *Rf* = 0.25.

(Cyclohexyl)(geranyl)acetic acid 1a or 1b (**general procedure**). A solution of KOH (100 mg, 1.8 mmol) in EtOH (2 ml) was added to a solution of **6a** or **6b** (175 mg, 0.6 mmol) in the same solvent (2 ml) and the reaction mixture was stirred at 60°C for 20 h (TLC-monitoring). The solvent was evaporated under reduced pressure (40 torr, 40°C) and water (2 ml) was added to the residue. The resulting mixture was acidified to pH ~2 with 15% HCl and extracted with diethyl ether (3×2 ml). The combined organic extract was dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure (40 torr, 40°C) to afford pure (^{1}H NMR data) acid **1a**, $[\alpha]_D^{25}$ = +3.89 (c = 0.36, MeOH) or **1b**, $[\alpha]_D^{25}$ = −3.1 (c = 0.48, MeOH). Colourless oils, 145 or 142 mg, yield 87% or 85%, respectively.

Phenyl (cyclohexyl)(geranyl)acetates 7a or 7b (g**eneral procedure**). Oxalyl chloride (0.19 ml, 2.2 mmol) was added to a solution of **1a** or **1b** (278 mg, 1.0 mmol) in dry benzene (1.0 ml) and the reaction mixture was stirred at ambient temperature for 2 h. The solvent was evaporated under reduced pressure (40 torr, 40°C), then THF (1.0 ml) and Et_3N (1.0 mmol) were successively added to the residue. The resulting solution was gradually added to a solution of PhOH (94 mg, 1.0 mmol) in THF (1.0 ml) at 0°C and the mixture was stirred at ambient temperature for 5 h. Afterwards, the precipitate was filtered off and washed with THF (2×1 ml). The combined filtrates were concentrated under reduced pressure (40 torr, 40°C) and the residue

was purified by column chromatography (SiO_2, *n*-hexane/toluene 9:1) to afford compound **7a** or **7b**. Colourless oils, 326 mg, yield 92%, n_D^{20} 1.5112. ^{1}H-NMR ($CDCl_3$) δ: 1.00-1.41 (m, 5H, CH, $2CH_2$), 1.60 (s, 6H, 2Me), 1.68 (s, 3H, Me), 1.55-1.98 (m, 5H, CH, $2CH_2$), 2.00-2.18 (m, 4H, $2CH_2$), 2.33-2.50 (m, 3H, CH, CH_2), 5.08-5.18 (m, 2H, 2CH=), 7.00-7.43 (m, 5H, Ar). ^{13}C-NMR ($CDCl_3$) δ: 16.1, 17.7, 25.7, 26.3, 26.4, 26.7, 28.2, 30.7, 31.0, 40.1, 52.3, 121.8, 122.0, 124.2, 125.6, 129.3 (Ar), 131.5(Ar), 137.3 (Ar), 150.9 (Ar), 174.0 (C=O). EI-MS *m/z* 354 $[M]^+$. HPLC data (*Chiralpak AD-H*, *n*-hexane/*i*-PrOH 7/3, 0.7 ml/min, 254 нм): **7a**: t_R = 4.83 min, **7b**: t_R = 6.45 min.

References for Supporting Information

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