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

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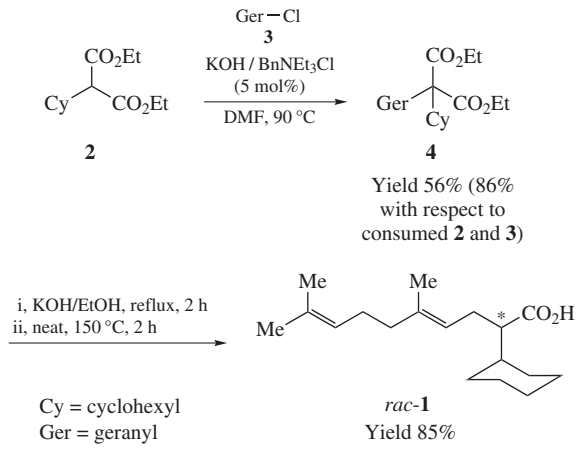
A kinetic resolution of racemic (cyclohexyl)(geranyl)acetic acid, the active ingredient of wound-curing medication Cygerol, to (*S*)- and (*R*)-enantiomers was achieved by diastereoselective esterification with (*S*)- or (*R*)-BINOL.

(Cyclohexyl)(geranyl)acetic acid **1** is the active substance of Cygerol® that was manufactured in Russia and used for curing of wounds, in particular surgery wounds, radiation or trophic ulcers and burns.[1–7] Being structurally similar to natural isoprenoids, in particular to vitamins of group A, compound **1** exhibits antibacterial activity and has an extremely low toxicity. Furthermore, isoprenoid acids turned to be promising as tracking drugs for cell therapy of various human diseases and injuries of vital organs and tissues with mesenchymal stem cell (MSC) and MSC-derived cardiomyoblasts.[8] Molecule of **1** contains a stereocenter, however, just racemic form of **1** is known so far. Taking into account that biological activities of enantiomers may be different[9] we decided to prepare both enantiomers of compound **1**. Diastereoselective crystallization of *rac*-**1** derivatives (esters, amides, *etc*.) is not applicable in this case as most of them are liquids[6] due to the presence of long-chained geranyl group. Therefore, we have selected a kinetic resolution method assuming that enantiomers of **1** should react with chiral alcohols with different rates. This method is commonly used for the resolution of dicarboxylic acids *via* diastereoselective reaction of cyclic *meso*-anhydrides with chiral alcohols.[10] However, a few examples of diastereoselective esterification of prochiral monocarboxylic acids have been reported up to now, enantiomeric excesses of the products having been commonly modest.[11]

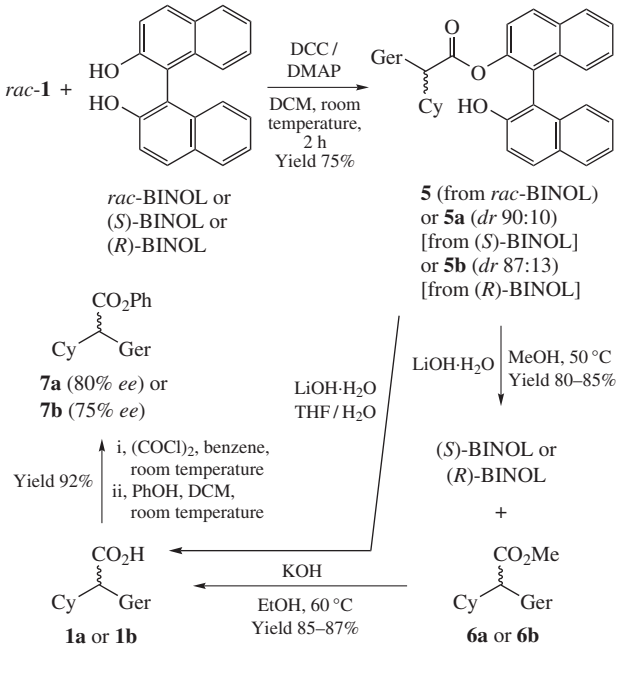
We synthesized racemic compound **1** by a modified synthetic scheme[1,4–6] that included alkylation of diethyl cyclohexylmalonate **2** with geranyl chloride **3** followed by a one-pot hydrolysis–decarboxylation sequence starting from compound **4** (Scheme 1). We managed to improve the yield of diester **4** from 65[6] to 86% with respect to consumed starting compounds **2** and **3** by carrying out the alkylation in the phase-transfer catalytic system KOH–DMF–$BnNEt_3Cl$ instead of Na–toluene,[1] NaH–DMF[6] or NaOEt–EtOH[6] systems. Furthermore, a change of the solvent at the hydrolysis step (EtOH instead of water) allowed us to significantly accelerate the reaction which simplified the procedure.

For a kinetic resolution of *rac*-**1** we have chosen (*S*)- and (*R*)-BINOLs as we expected that the presence of bulky C_2-symmetric binaphthyl fragment in these chiral auxiliaries[12] would enhance diastereoselectivity of the esterification reaction. First of all, we studied the model reaction between *rac*-**1** and *rac*-BINOL in the presence of DCC–DMAP at ambient temperature (Scheme 2). We were pleased to find out that even in the presence of 2 equiv. of acid *rac*-**1** only monoester **5** was formed within 2 h from the reaction start. The absence of the double-esterification product may be attributed to a shielding of the hydroxyl group in compound **5** by the geranyl and cyclohexyl fragments. This finding was unexpected and useful for a success of kinetic resolution as stereochemical outcomes of the first and second esterification steps might be different.

Next, we carried out the esterification of *rac*-**1** with (*S*)-BINOL under the same conditions to obtain compound **5a** in 75% yield and with *dr* 90:10 (HPLC data, see Scheme 2). Ester **5a** was hydrolyzed to acid **1a** by $LiOH·H_2O$ in the THF–H_2O solvent



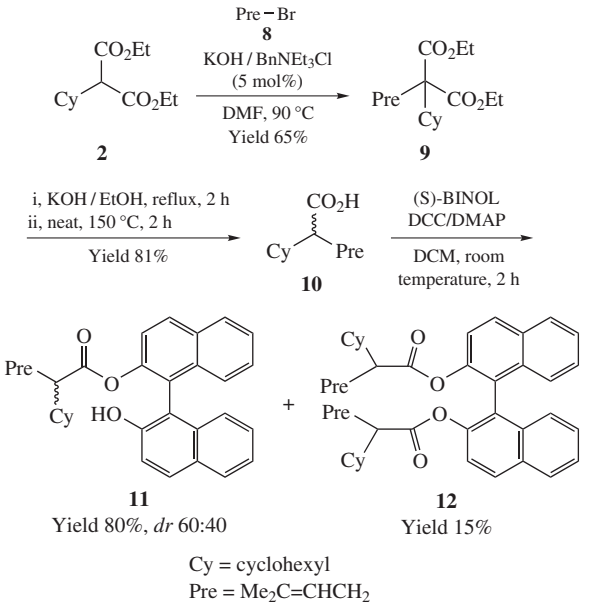
Scheme 1



Scheme 2

system. Unfortunately, the liberated acid **1a** and (*S*)-BINOL were found to have similar retention times and our attempts to separate them by column chromatography on silica gel failed. Therefore, we included a step of LiOH-promoted trans-esterification of compound **5a** with MeOH followed by hydrolysis of methyl ester **6a** with KOH–EtOH system. Products **6a** and **1** could be easily purified by column chromatography. Since acid **1a** does not contain a chromophoric group, we converted it to suitable for UV detection phenyl ester **7a**. The *ee* value of the latter (HPLC data, Chiralcel AD-H) and consequently of original acid **1a** was 80%.†

Our efforts to isolate antipode **1b** that remained unchanged during the esterification of *rac*-**1** with (*S*)-BINOL were unsuccessful as chromatographic characteristics of these compounds are similar. However, we synthesized enantiomer **1b** *via* a diastereoselective reaction of *rac*-**1** with (*R*)-BINOL followed by LiOH-promoted trans-esterification of (*R*)-BINOL ester **5b** (*dr* 87:13) and basic hydrolysis of methyl ester **6b** to target acid **1b** (see Scheme 2). According to HPLC data for corresponding phenyl ester **7b**, the enantiomeric excess of product **1b** was 75%. Unfortunately, we were not able to determine absolute configurations of oily enantiomers **1a** and **1b** because the results of their CD-analysis were not interpretable.



Scheme 3

The presence of the long-chained geranyl group in compound *rac*-**1** appeared to be a principal stereocontrolling factor for a successful kinetic resolution of *rac*-**1**. Indeed, similarly prepared from diethyl cyclohexylmalonate **2** and prenyl bromide **8** compound **10** bearing the prenyl group instead of the geranyl unit at the stereogenic carbon atom exhibited much worse diastereoselectivity in the reaction with (*S*)-BINOL to afford corresponding ester **11** (*dr* 60:40) along with the exhaustive esterification product **12** (Scheme 3).

In summary, we have prepared for the first time enantiomerically enriched samples of 2-cyclohexyl-2-geranylacetic acids **1a** and **1b**. Further biological studies will show whether pharmacological properties of enantiomers are influenced by their optical configurations.

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Online Supplementary Materials

Supplementary data associated with this article (synthetic details and characteristics of the compounds obtained) can be found in the online version at doi:10.1016/j.mencom.2014.09.002.

† *2-Cyclohexyl-5,9-dimethyldeca-4,8-dienoic acid 2'-hydroxy[1,1']binaphthalen-2-yl esters* **5**, **5a**, **5b** *(general procedure)*. The mixture of *rac*-**1** (195 mg, 0.7 mmol), *rac*-, (*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). A 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, hexane–toluene, 1:1) to afford the BINOL ester **5**, **5a**, or **5b** as colourless oils, 140 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, 2HC=), 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, *m*/*z*: 547.3207 $[M+H]^+$ (calc. for $C_{38}H_{42}O_3$, *m*/*z*: 547.3213). HPLC data (Chiralpak AD-H, hexane–Pr^{i}OH, 7:3, 30 °C, 0.7 ml min^{-1}, 254 nm): **5a**, t_1 = 5.67 min (minor), t_2 = 6.10 (major), *dr* 90:10; **5b**, t_1 = 7.70 min (major), t_2 = 8.45 (minor), *dr* 87:13.

Methyl (cyclohexyl)(geranyl)acetates **6a** *or* **6b**. Solid LiOH·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 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, hexane–toluene, 3:1) to afford the corresponding methyl esters **6a** or **6b**. Colourless oils, 189 or 178 mg, yield 85 or 80%, respectively, n_D^{20} 1.4793, R_f 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, 2HC=). ^{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. Chiral auxiliaries (*S*)-BINOL (196 mg, 90%) or (*R*)-BINOL (184 mg, 85%) were recovered by column chromatography as colourless solids, mp 206–208 °C (lit.,[13] mp 206–210 °C), R_f = 0.25.

(Cyclohexyl)(geranyl)acetic acids **1a** *or* **1b**. The 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 the corresponding acid **1a**, $[\alpha]_D^{25}$ = +3.89 (*c* 0.36, MeOH), or **1b**, $[\alpha]_D^{25}$ = −3.1 (*c* 0.48, MeOH) as colourless oils, 145 mg (87%) or 142 mg (85%), respectively.

Phenyl (cyclohexyl)(geranyl)acetates **7a** *or* **7b**. 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. The precipitate was filtered off and washed with THF (2×1 ml). The combined extracts were concentrated under reduced pressure (40 Torr, 40 °C) and the residue was purified by column chromatography (SiO_2, hexane–toluene, 9:1) to afford the products **7a** $[\alpha]_D^{25}$ = +4.80 (*c* 0.1, CH_2Cl_2), or **7b** $[\alpha]_D^{25}$ = −4.30 (*c* 0.1, CH_2Cl_2). 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, 2HC=), 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, hexane–Pr^{i}OH, 7:3, 30 °C, 0.7 ml min^{-1}, 254 nm): **7a**, t_R (major) = = 4.83 min, *ee* 80%; **7b**, t_R (major) = 6.45 min, *ee* 75%.

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