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Synthesis of 2,4-Dimethylglutaric Acid Monoesters via Enzyme-catalyzed Asymmetric Alcoholysis of *meso*-2,4-Dimethylglutaric Anhydride[1]

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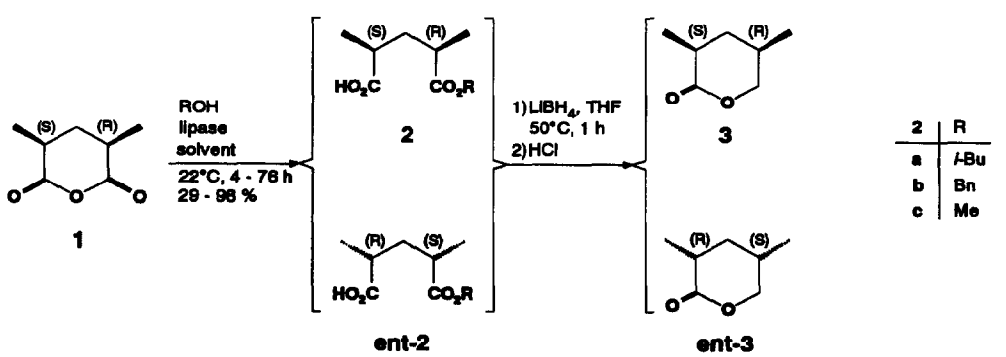
Abstract: 1-(2-Methylpropyl) 5-hydrogen (2*R*,4*S*)-2,4-dimethylpentanedioate with an enantiomeric excess of 90 % was obtained in a yield of 72 % from *meso*-2,4-dimethylpentanedioic anhydride and 2-methylpropanol by an asymmetric alcoholysis catalyzed by the lipase from *Candida sp. 382*.

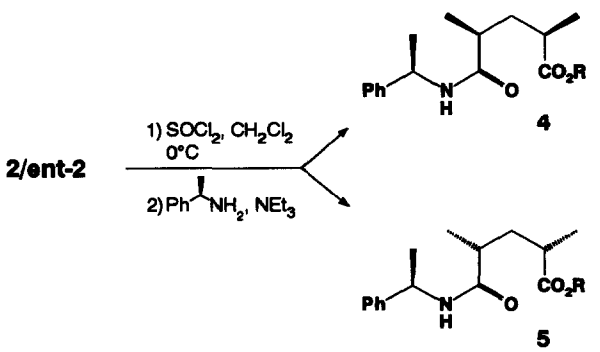
The homochiral monoesters **2** and *ent*-**2** are useful intermediates for the synthesis of various natural products possessing carbon chains with methyl groups in *a syn*-1,3-relationship. The versatility of these esters is based on the possibility of converting them into (2*R*,4*S*)- and (2*S*,4*R*)-2,4-dimethyl-5-oxopentanoates[2] or the lactones **3** and *ent*-**3**.[3] Thus, the (2*R*,4*S*)-monoester **2c** has been used for syntheses of the Prelog-Djerassi lactonic acid,[4] the macrolide (+)-conglobatin,[5] and intermediates of the biosynthesis of polyether antibiotics.[6] The monoester **2c** should also be useful for the synthesis of the pheromone (-)-α-multistriatin, which so far has been prepared from *rac*-**2c** only in racemic form.[2] *ent*-**2c** has served as starting material for the antibiotic ionomycin,[7] whereas the (2*R*,4*S*)-lactone *ent*-**3** has also been used for the synthesis of the Prelog-Djerassi lactonic acid.[8]

All of the above mentioned homochiral starting products are available by asymmetrization of *meso*-2,4-dimethylpentanedioic anhydride (**1**) or dialkyl *meso*-2,4-dimethylpentanedioates. Reaction of **1** with (*R*)-1-phenylethylamine affords the diastereomeric monoamides **4** and **5** (R = H), which can be converted into the lactones **3** and *ent*-**3**, respectively.[8] Enantioselective hemihydrolysis of dimethyl *meso*-2,4-dimethylpentanedioate in the presence of α-chymotrypsin[5,9] provides the monoester **2c**, whereas incubation with *Gliocladium roseum*[10] gives rise to *ent*-**2c**.



The ability of enzymes to act even in organic solvents as effective chiral catalysts[11] has also enabled the asymmetric alcoholysis of cyclic *meso*-dicarboxylic anhydrides.[12,13] Although the enantiomeric excess (e.e.) reported for the butanolysis of **1** with a lipase from *Pseudomonas fluorescens* (Amano P) did not exceed 8 %,[12] the encouraging results obtained with other *meso*-dicarboxylic anhydrides[14] caused us to reinvestigate the possibility of obtaining the monoesters **2** or *ent*-**2** by an enzyme-catalyzed asymmetric alcoholysis of **1**.

Therefore, this anhydride was treated at 22°C with molecular sieve 4Å and 2-methylpropanol, benzyl alcohol, and methanol, respectively, in the presence of pig liver esterase (PLE), pancreatin and the lipases from *Yarrovia lipolytica* (YLL), *Candida cylindracea* (CCL), and *Candida sp. 382* (CSL). Diethyl ether, *tert*-butyl methyl ether, toluene, cyclohexane, and hexane were used as solvents. Pancreatin and the lipase from *Candida cylindracea* did not catalyze the alcoholysis of **1**. Pig liver esterase and the lipases from *Yarrovia lipolytica* and *Candida sp. 382*, however, exhibited a good catalytic activity. For these enzymes the reaction rate was faster than that observed for the alcoholysis of 3-substituted glutaric anhydrides.[14] Although an e.e. of 60 % could be achieved with pig liver esterase in the hemihydrolysis of dimethyl *meso*-2,4-dimethylpentanedioate,[9] this enzyme did not exhibit any enantioselectivity in the alcoholysis of **1** (Table, entry 3). The lipase from *Yarrovia lipolytica* provided *ent*-**2** with an e.e. of 51-55 % (entries 1 and 2). The lipase from *Candida sp. 382*, however, yielded the enantiomeric monoester **2** with an e.e. of 60-90 % (entries 4-11). The alcohol applied to the ring opening seemed to have only a minor influence on the enantiodifferentiation (entries 1 and 2; entries 4, 5 and 6). In agreement with other reported observations,[15] in unpolar solvents like cyclohexane or hexane, higher e.e.'s were achieved than in the more polar ethers. The addition of molecular sieve 4Å proved to be important, as in the absence of molecular sieve, yield and e.e. decreased (entry 8). It is worth mentioning that the lipase from *Candida sp. 382* catalyzed not only the alcoholysis of **1**, but also the esterification of the formed monoester **2a** to the corresponding dialkyl ester, which could be isolated in a yield of 7 %. Despite this undesired side reaction, under optimal conditions the monoester **2a** could be obtained from **1** in a yield of 72 % with an e.e. of 90 % (entry 9).



4, 5	R
a	*i*-Bu
b	Bn
c	Me

Since the specific rotations of the monoesters **2** and *ent*-**2** are small,[4,7] the absolute configuration and the e.e. were determined in two independent ways. In the first, the esters **2a-c**/*ent*-**2a-c** were converted via the ester chlorides into the diastereomeric (*R*)-1-phenylethylamides **4a-c** and **5a-c** and then analyzed by HPLC. In the second, the monoesters were reduced by lithium borohydride to the corresponding hydroxy acids and cyclized to the lactones **3**/*ent*-**3**.[3] Then the e.e.'s were determined by HPLC on a chiral phase.

Table. Enzyme-catalyzed Alcoholysis of *meso*-2,4-Dimethylpentanedioic Anhydride (**1**) to the 2,4-Dimethylpentanedioic Acid Monoesters **2**/*ent*-**2**[a]

Entry	Enzyme	Alcohol	Solvent	Reaction time (h)	Monoester **2**/*ent*-**2**		
					Yield (%)	E.e. (%)	Main enantiomer
1	YLL	*i*-BuOH	Et_2O	5	98	51	*ent*-**2a**
2	YLL	BnOH	Et_2O	48	63	55	*ent*-**2b**
3	PLE	MeOH	Et_2O	5.5	81	0	–
4	CSL	MeOH	Et_2O	20	92	60	**2c**
5	CSL	BnOH	Et_2O	42.5	76	70	**2b**
6	CSL	*i*-BuOH	Et_2O	20	89	72	**2a**
7	CSL	*i*-BuOH	*t*-BuOMe	4.5	98	73	**2a**
8[b]	CSL	*i*-BuOH	*c*-C_6H_{12}	32	29	78	**2a**
9	CSL	*i*-BuOH	*c*-C_6H_{12}	6	72	90	**2a**
10	CSL	*i*-BuOH	*n*-C_6H_{14}	76	78	87	**2a**
11[c]	CSL	*i*-BuOH	*n*-C_6H_{14}	68	55	80	**2a**

[a] **1** (1 mmol) was stirred at 22°C in the solvent (10 mL) with the alcohol (2 mmol), the molecular sieve 4Å (0.2 g), and the enzymes (0.5 g of YLL, 0.1 g of PLE, and 0.1 g of CSL, respectively). [b] Without molecular sieve 4Å. [c] In 5 mL of solvent.

1-(2-Methylpropyl) 5-Hydrogen (2*R*,4*S*)-2,4-Dimethylpentanedioate (2a): Lipase from *Candida sp. 382* (1g), 2-methylpropanol (1.8 mL, 20 mmol), and molecular sieve 4Å (2 g) were added to a solution of the anhydride **1**[16] (1.42 g, 10 mmol) in hexane (100 mL). The mixture was stirred at 22°C for 76 h. Then the enzyme and the molecular sieve were removed by filtration. The solvent was distilled off under reduced pressure and the residue was chromatographed on silica gel 60 (0.040-0.063 mm) with hexane/diethyl ether/acetic acid (6:1:0.5). Thus, di(2-methylpropyl) *meso*-2,4-dimethylpentanedioate (0.18 g, 7 %) was obtained as the less polar component and the monoester **2a** (1.69 g, 78 %, e.e. 87 %) as more polar component. Both compounds were colourless oils. **2a**: $[\alpha]_D^{20}$ -1.9 (c 2.2, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 0.87 [6 H, d, J = 6.8 Hz, $CH(CH_3)_2$], 1.13-1.19 (6 H, m, 2-CH_3 and 4-CH_3), 1.43 (1 H, m, 3-H), 1.80-2.11 (2 H, m, 3-H and $CHMe_2$), 2.42-2.52 (2 H, m, 2-H and 4-H), 3.79 (2 H, d, J = 6.7 Hz, OCH_2), 9.30 (1 H, s, COOH); Anal. calcd. for ($C_{11}H_{20}O_4$): C, 61.09; H, 9.32. Found: C, 60.55; H, 9.31.

Determination of the e.e. of the monoesters 2a/*ent*-2a by HPLC after Conversion into 4a/5a. - Typical Procedure: Thionyl chloride (48 mg, 0.4 mmol) was added at 0°C to a stirred solution of the monoesters **2a**/*ent*-**2a** (72 mg, 0.33 mmol) in dichloromethane (10 mL). After 10 min (*R*)-1-phenylethylamine (42 µL, 0.33 mmol) and triethylamine (120 µL) were added. The mixture was stirred for 1 h, diluted with EtOAc (20 mL), and washed with 1N HCl (5 mL), saturated aqueous $NaHCO_3$ (5 mL), and brine (5 mL). The organic phase was dried with $MgSO_4$ and evaporated under reduced pressure. The resulting mixture of the phenylethylamides **4** and **5** (75 mg, 71 %) was analyzed by HPLC on silica gel 60 (0.007 mm) with hexane/2-propanol (95:5) as eluant (R_t 3.42 min (**4a**) and 4.58 min (**5a**). **4a**: ^1H NMR (200 MHz, $CDCl_3$) δ 0.87 [6 H, d, J = 6.7 Hz, $(CH_3)_2CH$] 1.05 (3 H, d, J = 6.7 Hz, 4-CH_3), 1.13 (3 H, J = 7.1 Hz, 2-CH_3), 1.41 (3 H, d, J = 6.7 Hz, PhCH_3CH), 1.43 (1 H, m, 3-H), 1.80-2.19 (2 H, m, 3-H and $CHMe_2$), 2.47 (2 H, m, 2-H and 4-H)

3.79 (2 H, d, J = 6.6 Hz, OCH_2), 5.04 (1 H, m, PhMeCH), 5.98 (1 H, m, NH), 7.18-7.24 (5 H, m, C_6H_5); Anal. calcd. for ($C_{19}H_{29}NO_3$: C, 71.44; H, 9.15; N, 4.39. Found: C, 71.39; H, 9.28; N, 4.43.

Determination of the e.e. of the Monoesters 2a/*ent*-2a by HPLC after Conversion into the Lactones 3/ent-3 - Typical Procedure: Lithium borohydride (0.218g, 10 mmol) was added under nitrogen at 22°C during a period of 5 min to a stirred solution of the monoesters **2a**/*ent*-**2a** (0.345g, 1.60 mmol) in dry THF (10 mL). The solution was stirred at 50°C for a period of 1 h. Then the solvent was distilled off. The residue was treated with 2N HCl (20 mL) and extracted with Et_2O (3 x 20 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). After drying of the organic phase ($MgSO_4$) the solvent was evaporated. The residue was subjected to kugelrohr distillation at a bath temperature of 160-165°C and a pressure of 23.7 kPa to yield the lactones **3**/*ent*-**3** (0.097g, 47%) as white prisms: Mp. 41-46°C; $[\alpha]_D^{20}$ +41.9 (c 0.93, $CHCl_3$) (Lit.:[17] $[\alpha]_D^{20}$ = +39.1 (c 10, $CHCl_3$); e.e. >99 % [determined by HPLC on Chiralpak AD with hexane/EtOH (95:5); R_t = 13.25 min (**3**) and 10.56 min (*ent*-**3**)]; ^1H NMR (300 MHz, $CDCl_3$): δ 0.92 (d, J = 6.6 Hz, 3 H, CH_3), 1.20 (d, J = 6.9 Hz, 3 H, CH_3), 1.11-1.26 (m, 1 H, 3-H), 1.9-2.2 (m, 2 H, 3-H and 4-H], 2.4-2.6 (m, 1 H, 2-H), 3.83 (m, 1 H, 5-H), 4.28 (m, 1 H, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.96 (2-CH_3), 17.38 (4-CH_3), 28.60 (C-4), 35.33 (C-2), 36.76 (C-3), 74.91 (C-5), 174.60 (C-1); Anal. calcd. for ($C_7H_{12}O_2$): C, 65.60; H, 9.44. Found: C, 65.57; H, 9.20.

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