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The Different Behaviour of *syn*- and *anti*-2,3-Dimethylbutanedioic Anhydride in the Lipase-catalyzed Enantioselective Alcoholysis[1]

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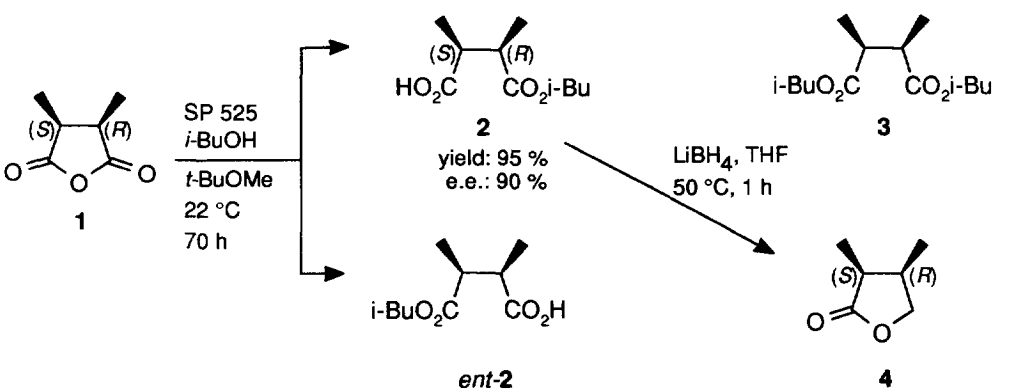
Abstract: The *syn*- and *anti*-relationship of the vicinal methyl groups in the 2,3-dimethylbutanedioic anhydrides **1** and *rac*-**5** has a significant influence on the lipase-catalyzed enantioselective alcoholysis with 2-methylpropanol. For their conversion into the enantiomerically highly enriched monoesters **2** and *ent*-**6** different enzymes are required. Lipase SP 525 (Novo Nordisk) and lipase Amano PS from *Pseudomonas cepacia* turned out to be the most suitable ones. Remarkably, the (2*S*,3*S*)-*anti*-anhydride *ent*-**5** is alcoholysed with high enantioselectivity to the monoester *ent*-**6**, the other enantiomer (**5**) remains almost unattacked and can be isolated with an e.e. of 96 %.

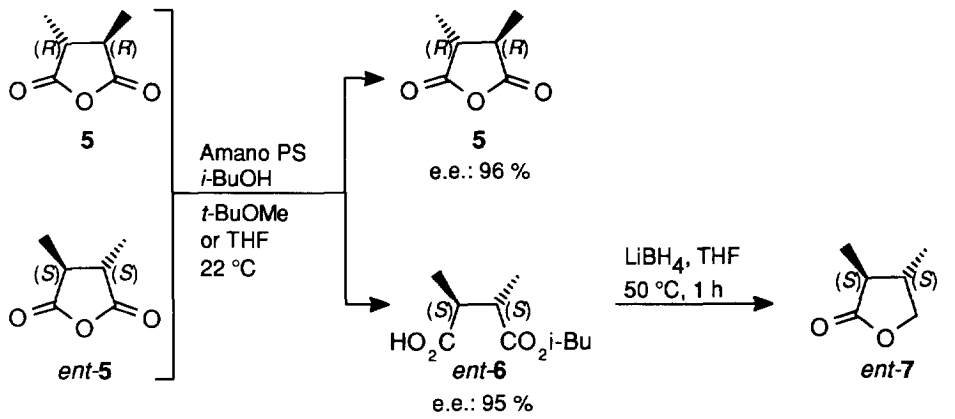
Enantiomerically pure monoalkyl esters of *syn*- and *anti*-2,3-dimethylbutanedioic acid, such as **2**, *ent*-**2**, **6**, and *ent*-**6** may be regarded as versatile intermediates for compounds with vicinal methyl groups in *syn*- or *anti*-relationships.[2–4] Such compounds are available by anionic oxy-Cope[3] and aza-Claisen[5] rearrangements, by asymmetric hydrogenation of 2-methyl-3-methylene- and 2,3-dimethylenebutanedioic acid derivatives,[6,7] or by an enantioselective Michael addition.[8] A promising alternative approach to the above mentioned monoalkyl esters is the enzyme-catalyzed enantioselective alcoholysis of the cyclic carboxylic anhydrides **1** and *rac*-**5** in analogy with the corresponding 2,4-dimethylpentanedioic anhydrides.[9,10] To our knowledge this procedure has so far not been applied to prochiral or racemic butanedioic anhydrides.



The alcoholysis of the prochiral anhydride **1** with 2-methylpropanol was performed with several lipases. Best results were obtained with the lipase SP 525 (Novo Nordisk) in *tert*-butyl methyl ether. In this case the

monoester **2** was achieved in a yield of 95 % with an enantiomeric excess (e.e.) of 90 %. The enantiomeric purity of **2** was determined by GLC analysis of the diastereomeric (*R*)-1-phenylethylamides obtained by treatment of **2** with thionyl chloride and (*R*)-1-phenylethylamine.[11] The absolute configuration of **2** was ascertained by its reduction with lithium borohydride to (2*S*,3*R*)-2,3-dimethylbutan-4-olide (**4**), a compound of known absolute configuration.[12]

For the preparation of enantiomerically pure bifunctional compounds with vicinal methyl groups in the epimeric series the racemic anhydride *rac*-**5** was alcoholysed with 2-methylpropanol in the presence of various lipases. In this case, best results were obtained with the lipase Amano PS from *Pseudomonas cepacia*. When the alcoholysis of *rac*-**5** in THF was stopped after a conversion of 40 %, the monoester *ent*-**6** was obtained in a yield of 38 % with an e.e. of 95 % after distillative separation from the unreacted anhydride. After a 60 % conversion in a 1:1 mixture of *tert*-butyl methyl ether and cyclohexane the unsolvolysed anhydride **5** was isolated by a fractional distillation in a yield of 38 % with an e.e. of 96 %. The enantiomeric purity of the anhydride **5** was determined by comparison with data published for the specific rotation of this compound.[13] The enantiomeric purity of the monoester *ent*-**6** was determined by HPLC after reaction with thionyl chloride and (*R*)-1-phenylethylamine.[11] The absolute configuration of *ent*-**6** resulted from the fact that the configuration of **5** is known.[13]



A comparison of these two lipase-catalyzed reactions discloses significant differences in the enantioselectivity of the alcoholysis. The *meso*-anhydride **1** is alcoholysed with a high enantioselectivity at the carbonyl group proximal to the (*R*)-configurated stereogenic centre, if SP 525 is used as catalyst. The same enzyme, however, catalyses the alcoholysis of the (*R*,*R*)-configurated anhydride **5** with a more diminished enantioselectivity than the (*S*,*S*)-configurated anhydride *ent*-**5**. In contrast, lipase PS catalyses the alcoholysis of anhydride *ent*-**5** with (*S*)-configurated stereogenic centres attached to both carbonyl groups with a high enantioselectivity. This enzyme, however, does not favour the alcoholysis of anhydride **1** at the carbonyl group proximal to the (*S*)-configurated stereogenic centre. These observations reveal that minor structural differences may be of unpredictable influence on the enantioselectivity of lipase-catalyzed reactions.

1-(2-Methylpropyl) 4-Hydrogen (2*R*,3*S*)-2,3-Dimethylbutanedioate (2): Lipase SP 525 (Novo Nordisk) (150 mg), calcium sulfate hemihydrate (200 mg), and 2-methylpropanol (148 mg, 2.0 mmol) were suspended in a solution of the anhydride **1** (128 mg, 10 mmol) in *tert*-butyl methyl ether (15 mL). The suspension was stirred at 22 °C for 70 h. After filtration the solvent was evaporated under reduced pressure. Kugelrohr distillation of the residue (oven temp. 165 °C/0.67 mbar) afforded the monoester **2** (192 mg, 95 %): $[\alpha]^{20}_D$ = −2.7 (c = 2.0 in EtOH); e.e. = 90 %; ^{1}H NMR (200 MHz): δ = 0.87 [d, 6 H, *J* = 6.7 Hz, $CH(CH_3)_2$], 1.12–1.18 (m, 6 H, 2-CH_3, 3-CH_3), 1.87 (sept, 1 H, *J* = 6.7 Hz, $CHMe_2$), 2.71–2.80 (m, 2 H, 2-H, 3-H), 3.82 (d, 2 H, *J* = 6.5 Hz, OCH_2), 9.90 (s, 1 H, CO_2H); ^{13}C NMR: δ = 14.26 (3-CH_3), 14.92 (2-CH_3) 19.05 [$C(CH_3)_2$], 27.67 (CMe_2), 42.30 (C-2), 42.39 (C-3), 70.91 (O-CH_2), 174.50 (C-1), 181.01 (C-4); Anal. calcd. for ($C_{10}H_{18}O_4$): C, 59.38; H, 8.97. Found: C, 59.27; H, 9.07.

(2*S*,3*R*)-2,3-Dimethylbutan-4-olide (4): Lithium borohydride (62 mg, 2.84 mmol) was added under nitrogen at 22 °C during 5 min in 2 portions to a stirred solution of the monoester **2** (143 mg, 0.71 mmol, e.e. = 90 %) in dry THF (10 mL). Then the suspension was stirred at 50 °C for 1 h. The reaction mixture was concentrated under reduced pressure, acidified under ice cooling with 4 N HCl and extracted with ethyl acetate (2 × 10 mL). The combined extracts were washed with a saturated aqueous solution of $NaHCO_3$ (5 mL) and brine (5 mL). After drying ($MgSO_4$) the solvent was removed and the residue was subjected to kugelrohr distillation (oven temp. 141–143 °C/23 mbar) to yield the lactone **4** (51 mg, 45 %): $[\alpha]^{20}_D$ = +39.1 (c = 1.8 in $CHCl_3$); lit.[12]: $[\alpha]^{20}_D$ = + 39.9 (c = 9 in $CHCl_3$); e.e. = 90 % (determined by GC on Lipodex C, temp. 80 °C, hydrogen, column volume 25 m × 0.25 mm, flow rate 0.4 mL/min): R_t = 18.57 min (*ent*-**4**), R_t = 19.35 min (**4**); ^{1}H NMR (200 MHz): δ = 0.97 (d, 3 H, *J* = 6.8 Hz, 2-CH_3), 1.11 (d, 3 H, *J* = 6.9 Hz, 3-CH_3), 2.55–2.67 (m, 2 H, 3-H, 2-H), 3.88 (dd, 1 H, *J* = 8.9 Hz, 3.0 Hz, 5-H), 4.24 (dd, 1 H, *J* = 5.7 Hz, 8.9 Hz, 5 H); ^{13}C NMR: δ = 9.81 (2-CH_3), 13.38 (3-CH_3), 33.83 (C-3), 38.27 (C-2),), 73.11 (C-4), 180.00 (C-1); Anal. calcd. for ($C_6H_{10}O_2$): C, 63.13; H, 8.83. Found: C, 62.85; H, 8.79.

(2*R*,3*R*)-2,3-Dimethylbutanedioic Anhydride (5): Lipase PS from *Pseudomonas cepacia* (100 mg) and 2-methylpropanol (148 mg, 2.0 mmol) were suspended in a solution of the anhydride *rac*-**5**[15] (128 mg, 1.0 mmol) in *tert*-butyl methyl ether (5 mL) and cyclohexane (5 mL). The mixture was stirred at 22 °C for 64 h. After filtration the solvent was evaporated under reduced pressure. Kugelrohr distillation of the residue (oven temp. 115 °C/0.67 mbar) afforded the anhydride **5** (49 mg, 38 %): $[\alpha]^{20}_D$ = +100.6 (c =1 in dioxane); lit:[13]: $[\alpha]^{20}_D$ = +105.2 (c = 8 in dioxane); e.e. = 96 %; ^{1}H NMR (200 MHz): δ = 1.37 (d, 6 H, *J* = 6.8 Hz, 2-CH_3, 3-CH_3), 2.67–2.74 (m, 2 H, 2-H, 3-H); ^{13}C NMR: δ = 14.06 (2-CH_3, 3-CH_3), 43.21 (2-C, 3-C), 173.18 (1-C, 4-C); Anal. calcd. for ($C_6H_8O_3$): C, 56.24; H, 6.29. Found: C, 56.21; H, 6.49.

The second fraction of the kugelrohr distillation (oven temp. 165 °C, 0.67 mbar) provided the monoester *ent*-**6** (123 mg, 61 %, e.e. = 65 %).

1-(2-Methylpropyl) 4-Hydrogen (2*S*,3*S*)-2,3-Dimethylbutanedioate (*ent*-6): The foregoing procedure was repeated with tetrahydrofuran (10 mL) as solvent. After stirring for 270 h at 22 °C the enzyme was filtered off and the filtrate was elaborated as described. Kugelrohr distillation (oven temp. 115 °C, 0.67 mbar) afforded the anhydride **5**/*ent*-**5** (63 mg, 49 %): $[\alpha]^{20}_D$ = +26.3 (c = 1.1 in dioxane); lit.[13]: $[\alpha]^{20}_D$ = +105.2 (c = 8 in dioxane); e.e. = 25 %. The next fraction (oven temp. 165 °C, 0.67 mbar) gave the monoester (*ent*-**6**) (76 mg, 38 %): $[\alpha]^{20}_D$ = −4.2 (c = 3 in $CHCl_3$); e.e. = 95 %;[14] ^{1}H NMR (200 MHz): δ = 0.88 [d, 6 H, *J* = 6.6 Hz, $CH(CH_3)_2$], 1.13–1.20 (m, 6 H, 2-CH_3, 3-CH_3), 1.88 (sept, 1 H, *J* = 6.7 Hz, $CHMe_2$), 2.75–2.86 (m, 2 H, 2-H, 3-H), 3.83 (d, 2 H, *J* = 6.5 Hz, OCH_2), 10.81 (s, 1 H, CO_2H); ^{13}C NMR: δ = 13.55 (2-CH_3), 13.65 (3-

CH_3), 19.04 [$CH(CH_3)_2$], 27.71($CHMe_2$), 41.48 (C-3, C-2), 70.91 (OCH_2), 175.16 (C-1), 181.70 (C-4); Anal. calcd. for ($C_{10}H_{18}O_4$): C, 59.38; H, 8.97. Found: C, 59.31; H, 9.32.

(2*S*,3*S*)-2,3-Dimethylbutan-4-olide (*ent*-7): Reduction of the monoester *ent*-**6** (153 mg, 0.76 mmol, e.e. = 96 %) with lithium borohydride (66 mg, 3.02 mmol) according to the procedure given for **4** afforded the lactone *ent*-**7** (32 mg, 37 %): $[\alpha]^{20}_D = -50.9$ (c = 0.9 in $CHCl_3$); e.e. = 96 % [determined by GC on Lipodex C, column volume 10 m × 0.25 mm, flow rate 0.2 mL/min: R_t = 7.43 min (**7**), R_t = 7.88 min (*ent*-**7**)]; ^1H NMR (200 MHz): δ = 1.16 (d, 3 H, *J* = 6.0 Hz, 3-CH_3), 1.24 (d, 3 H, *J* = 6.6 Hz, 2-CH_3), 1.90–2.28 (m, 2 H, 2-H, 3-H), 3.73 (t, 1 H, *J* = 9.2 Hz, 4-H), 4.37 (t, 1 H, *J* = 9.2 Hz, 4-H); ^{13}C NMR: δ = 13.41 (3-CH_3), 15.90 (2-CH_3), 39.08 (C-3), 42.19 (C-2), 72.88 (C-4), 180.17 (C-1); Anal. calcd. for ($C_6H_{10}O_2$): C, 63.13; H, 8.83. Found: C, 62.85; H, 8.87.

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14 The e.e. was determined by HPLC analysis of the diastereomeric (*R*)-1-phenylethylamides[11] of the monoesters **2**/*ent*-**2** and **6**/*ent*-**6**, respectively, on silica gel with hexane/2-propanol (95:5) as eluant. R_t = 2.50 min (amide of **2**), 3.19 min (amide of *ent*-**2**), 2.14 min (amide of *ent*-**6**), and 3.05 min (amide of **6**).

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