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TETRAHEDRON: *ASYMMETRY*

Resolution of methyl nonactate†

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Abstract

A straightforward resolution of racemic methyl nonactate has been achieved by chromatographic separation of the corresponding D-mandelates followed by chemoselective hydrolysis of the mandelate ester function. Baker's yeast reduction of the ketone derived from racemic methyl nonactate proceeded with high enantioselectivity to give (+)-8-*epi*-methyl nonactate and (−)-methyl nonactate as alternative building blocks for macrotetrolide synthesis but was less efficient for the production of the latter compound. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

Using sultone chemistry,[1] we have recently found a short and highly diastereoselective access[2] to the monomeric subunits of the macrotetrolides, also known as actins or nactins. These 32-membered macrocycles display a broad range of interesting biological activities (Fig. 1).[3] A characteristic feature of the structurally elucidated actins is the alternating sequence of (+)- and (−)-enantiomers of the hydroxy acid building blocks. With respect to a stereoselective synthesis

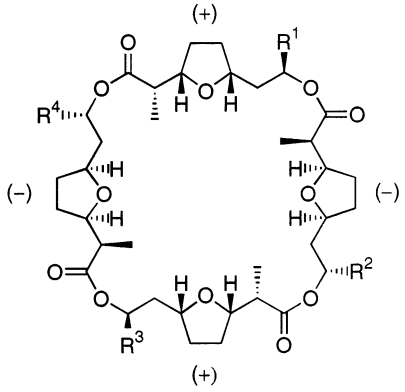

Figure 1. Actins (R^1–R^4 = Me, Et, *i*-Pr)

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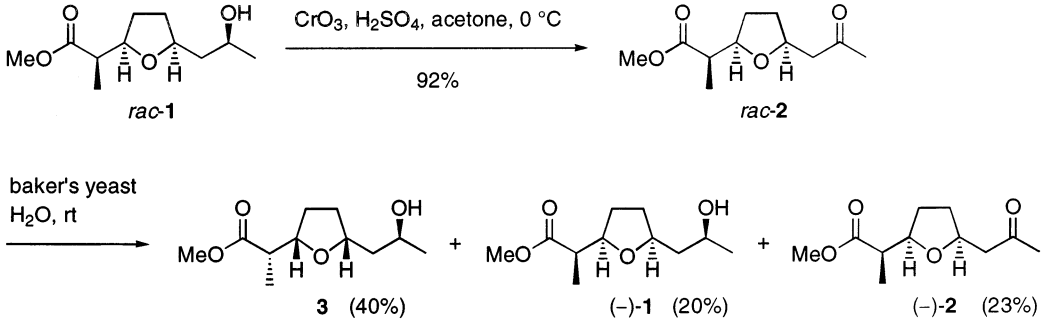
of actins, including the achiral S_4-symmetrical members such as nonactin (R^1–R^4 = Me)[4] and tetranactin (R^1–R^4 = Et),[5] both enantiomers of the hydroxy acid components, termed as actic or nactic acids, thus have to be at hand separately. Our general sultone route to actic acids, first exemplified for racemic nonactic acid,[2,6,7] can easily be used for the enantioselective preparation of either enantiomer.[8] However, a short synthesis of the racemic hydroxy acid followed by an efficient resolution would be more economical if an access to actins incorporating both enantiomers of an actic acid, e.g. nonactin, were desired.

2. Results and discussion

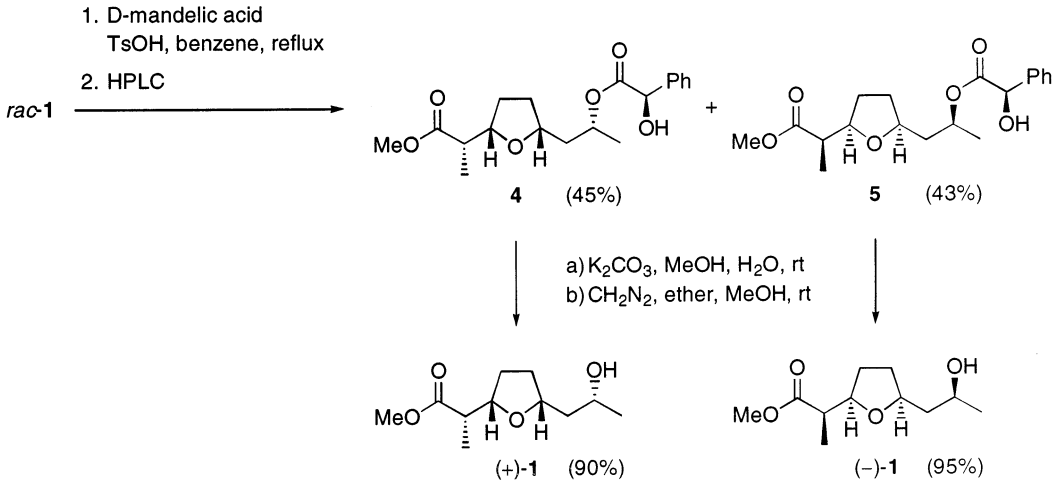
To this end, we first investigated a reagent controlled enantioselective reduction of ketone *rac*-**2**[9] readily available from racemic methyl nonactate *rac*-**1**[2] (Scheme 1). Whereas the (+)-enantiomer of **2** underwent a smooth reduction with baker's yeast[10] to provide (+)-8-*epi*-methyl nonactate **3**[4e,6,10] with 94.5% *ee* determined by capillary GC, the (–)-enantiomer of **2** was only partially reduced. Nevertheless, (–)-methyl nonactate (–)-**1**[6,10] as well as recovered (–)-**2**[11] were isolated with high enantiomeric purity (94.3 and 97% *ee* by capillary GC), respectively. While the efficacy in the production of (–)-**1** was not satisfactory, the simultaneous generation of both **3** and (–)-**1** with high *ee* from *rac*-**2** is noteworthy in view of the reported successful coupling of these compounds[4b] or their enantiomers,[4c,e] respectively, to nonactin.



Scheme 1. Reduction of ketone *rac*-**2** with baker's yeast

As an alternative, we studied the conversion of *rac*-**1** to diastereomeric derivatives that would allow a complete separation by liquid chromatography. In this context, the resolution of racemic alcohols via their *O*-methylmandelates has proven to be a valuable method on several occasions.[12] However, with the *O*-methylmandelic esters derived from *rac*-**1** no baseline separation could be achieved. In contrast, the corresponding D-mandelates **4** and **5** prepared by direct esterification of *rac*-**1** with D-mandelic acid[13] could be separated well by HPLC (Scheme 2; Fig. 2). Solvolysis[13] of **4** and **5** to give the methyl nonactates (+)-**1**[6,7] and (–)-**1**, respectively, turned out to be highly chemoselective for the mandelic ester function and delivers either enantiomer with 97% *ee* according to capillary GC. A subsequent treatment of the crude products with diazomethane is not strictly required to secure a high yield of the desired methyl esters[‡] but is now routinely used in our laboratories in order to maximize the production of (+)-**1** and (–)-**1**.

[‡] Solvolysis of D-mandelate **4** with K_2CO_3 in MeOH/H_2O at rt without subsequent diazomethane treatment led to (+)-**1** in 83% isolated yield.



Scheme 2. Resolution of racemic methyl nonactate (*rac*-**1**)

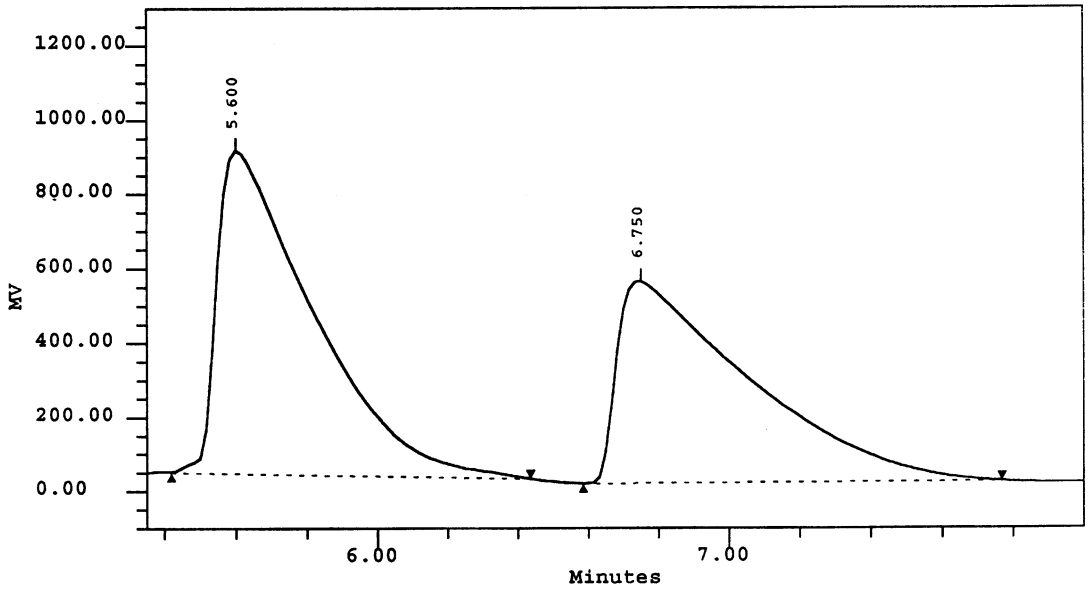


Figure 2. HPLC separation of D-mandelates **4** (5.60 min) and **5** (6.75 min)

3. Experimental

3.1. General experimental information

Flash chromatography was performed on Merck silica gel 60 (40–63 μm). Chiral capillary GC analyses were performed with a Shimadzu GC-9A and a Shimadzu integrator C-R3A on a Macherey–Nagel HYDRODEX®-β-6-TBDM column (50 m length, 0.25 mm i.d.). HPLC separations were performed with a Waters 600 pump, a Knauer K-2400 RI detector and a Nucleosil 100-5 (5 μm, 250 mm length, 20 mm i.d.) column. All reported R_f values refer to

CH_2Cl_2/ethyl acetate/diethyl ether, 4:1:1, if not mentioned otherwise. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. FT-IR spectra were obtained on a Nicolet 205. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker ASP-300 (^{1}H: 300 MHz, ^{13}C: 75.47 MHz). ^{13}C multiplicities were determined using DEPT pulse sequences. ESI-MS were measured with a Bruker Esquire LC integrated with a Hewlett Packard 1100 LC system. Microanalyses were performed by the analytical laboratory of the Institut für Organische Chemie, Technische Universität Dresden. D-Mandelic acid (D:L $\geq$ 99:1) was purchased from Fluka.

3.2. Preparation of ketone rac-**2**

Racemic methyl nonactate (*rac*-**1**, 430 mg, 1.99 mmol) was oxidized with chromium trioxide in acetone/10% aqueous sulfuric acid according to Ref. 9 to give *rac*-**2** (390 mg, 92%).

3.3. Reduction of ketone rac-**2** with baker's yeast

Ketone *rac*-**2** (200 mg, 0.935 mmol) was added to a mixture of baker's yeast (35 g) and glucose (3.2 g) in water (210 ml). After stirring the resultant suspension at rt for 3 days, the yeast was removed by centrifugation, and the aqueous solution was extracted six times with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, the solvent was removed in vacuo, and the residue was subjected to flash chromatography (CH_2Cl_2/ethyl acetate/diethyl ether, 4:1:1) to give (–)-**2** (45 mg, 23%), **3** (80 mg, 40%), and (–)-**1** (40 mg, 20%). Ketone (–)-**2**: R_f 0.59; $[\alpha]_D^{25} = -19.5$ (*c* 0.81, $CHCl_3$), 97% *ee* (GC). (+)-8-*epi*-Methyl nonactate (**3**): R_f 0.35; $[\alpha]_D^{25} = +31.5$ (*c* 1.27, $CHCl_3$), 94.5% *ee* (GC). (–)-Methyl nonactate ((–)-**1**): R_f 0.25; $[\alpha]_D^{25} = -17.2$ (*c* 1.12, $CHCl_3$), 94.3% *ee* (GC).

3.4. Preparation of D-mandelates **4** and **5**

A solution of *rac*-**1** (3.22 g, 14.9 mmol) and D-mandelic acid (2.72 g, 17.9 mmol) in benzene (150 ml) was treated with $TsOH \cdot H_2O$ (10 mol%), and the resultant mixture was heated to reflux for 4 h using a Dean–Stark trap. After usual workup, the crude product was purified by HPLC (20 ml/min flow; CH_2Cl_2/ethyl acetate/diethyl ether, 8:1:1, rt) in 100 mg portions to give **4** (2.32 g, 45%) and **5** (2.24 g, 43%). D-Mandelate **4**: R_f 0.58 (CH_2Cl_2/ethyl acetate/diethyl ether, 8:1:1); $[\alpha]_D^{25} = -39.8$ (*c* 0.95, $CHCl_3$); IR (neat): 3474, 1738 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.05 (d, $J = 7.0$ Hz, 3 H), 1.11–1.23 (m, 1 H), 1.28 (d, $J = 6.3$ Hz, 3 H), 1.40–1.65 (m, 3 H), 1.71–1.80 (m, 2 H), 2.42 (dq, $J_d = 8.1$ Hz, $J_q = 7.0$ Hz, 1 H), 3.23–3.34 (m, 1 H), 3.58 (d, $J = 5.6$ Hz, 1 H), 3.68 (s, 3 H), 3.72–3.80 (m, 1 H), 5.00–5.10 (m, 2 H), 7.30–7.41 (m, 5 H); ^{13}C NMR ($CDCl_3$): δ 175.3 (s), 173.1 (s), 138.5 (s), 128.5 (d), 128.3 (d), 126.5 (d), 80.6 (d), 75.9 (d), 72.9 (d), 71.4 (d), 51.6 (q), 45.4 (d), 42.1 (t), 31.3 (t), 28.5 (t), 20.1 (q), 13.4 (q); MS (ESI) *m*/*z*: 368 [M+NH_4^+], 351 [M+H^+], 333 [M+H^+–H_2O]; Anal. calcd for $C_{19}H_{26}O_6$: C, 65.14; H, 7.43. Found C, 64.85; H, 7.63. D-Mandelate **5**: R_f 0.52 (CH_2Cl_2/ethyl acetate/diethyl ether, 8:1:1); $[\alpha]_D^{25} = -67.3$ (*c* 1.00, $CHCl_3$); IR (neat): 3473, 1738 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.09 (d, $J = 6.1$ Hz, 3 H), 1.16 (d, $J = 6.9$ Hz, 3 H), 1.43–1.83 (m, 4 H), 1.91–2.01 (m, 2 H), 2.50 (dq, $J_d = 8.2$ Hz, $J_q = 7.0$ Hz, 1 H), 3.56 (d, $J = 5.7$ Hz, 1 H), 3.7 (s, 3 H), 3.85–4.02 (m, 2 H), 5.05–5.13 (m, 2 H), 7.30–7.42 (m, 5 H); ^{13}C NMR ($CDCl_3$): δ 175.2 (s), 173.1 (s), 138.6 (s), 128.5 (d), 128.3 (d), 126.8 (d), 80.1 (d), 75.7 (d), 73.1 (d), 71.6 (d), 51.6 (q), 45.2 (d), 42.0 (t), 30.9 (t), 28.3 (t), 20.6 (q), 13.2 (q); MS (ESI) *m*/*z*: 368 [M+NH_4^+], 351 [M+H^+], 333 [M+H^+–H_2O]; Anal. calcd for $C_{19}H_{26}O_6$: C, 65.14; H, 7.43. Found C, 65.12; H, 7.71.

3.5. Hydrolysis of D-mandelates **4** and **5**

To a mixture of D-mandelate **4** (2.20 g, 6.28 mmol) and K_2CO_3 (4 equiv.) in MeOH (25 ml) was added water until a clear solution resulted. The mixture was stirred at rt for 8 h, neutralized with 2N HCl, and extracted with ethyl acetate. After removing the solvent in vacuo, the residue was dissolved in MeOH and treated with a solution of diazomethane in diethyl ether. The crude product was purified by flash chromatography (CH_2Cl_2/diethyl ether/ethyl acetate, 4:1:1) to give (+)-**1** (1.22 g, 90%). R_f 0.25; $[\alpha]_D^{25} = +19.2$ (*c* 0.93, $CHCl_3$), 97% *ee* (GC).

Following the procedure described above, D-mandelate **5** (2.24 g, 6.4 mmol) was converted to (−)-**1** (1.25 g, 95%). R_f 0.25; $[\alpha]_D^{25} = -19.2$ (*c* 1.02, $CHCl_3$); 97% *ee* (GC).

Acknowledgements

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