Tetrahedron Letters 50 (2009) 2249–2251

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Lipase-catalysed synthesis of homotartaric acid enantiomers

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ARTICLE INFO

Article history:
Received 23 January 2009
Revised 23 February 2009
Accepted 25 February 2009
Available online 1 March 2009

Keywords:
Lipases
Enzyme catalysis
Kinetic resolution
Desymmetrisation
Enantiomer
1,3-Diols
Homotartaric acid

ABSTRACT

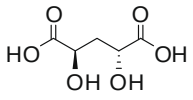
The investigation of lipase-catalysed kinetic resolution of diol *anti*-**2** and desymmetrisation of diol meso *syn*-**2** allowed the development of a new procedure to synthesise optically active (*R*,*R*)-homotartaric acid.

Optically active 2,4-dihydroxyglutaric acid (**1**, homotartaric acid, Chart 1), showing a C2 symmetry in a rather flexible structural backbone, could be a useful alternative to tartaric acid as an optical resolution agent or as a chiral ligand in stereoselective syntheses. The diisopropyl ester of (2*S*,4*S*)-**1** has been employed by Sharpless[1] as a ligand in the asymmetric epoxidation of prochiral allylic alcohols by alkyl hydroperoxides. The titanium complex of derivative (2*S*,4*S*)-**1** was found to mimic titanium tartrate in the epoxidation of primary alcohols. The application of diacid **1** has been limited so far by the lack of efficient methods for the preparation of the two enantiomeric forms.

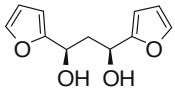
(−)-*threo*-2,4-Dihydroxyglutaric acid was first described by Nef[2] as the product of nitric acid oxidation of (−)-L-*threo*-3-deoxy-pentonic acid lactone.[3] (*R*,*R*) and (*S*,*S*)-**1** have been also prepared by nitrous acid deamination of the corresponding γ-hydroxy glutamic acid enantiomers, obtained by enzymic resolution.[4] The work was aimed to establish the absolute configuration of the starting hydroxy glutamic acid stereoisomers. Classical resolution of racemic homotartaric acid by fractional crystallisation of the monobrucine salt was reported[1] with 4% yields. In 2001 a Japanese patent[5] described the preparation of (*S*,*S*)- and (*R*,*R*)-**1** by asymmetric hydrogenation of 1,3-diphenyl-1,3-propandione, using ultrasonicated (*R*,*R*)- and (*S*,*S*)-tartaric acid-modified Ni Raney catalysts, respectively. Protection of the OH groups as dodecanoyloxy derivatives, oxidation by reaction with H_5IO_6 and $RuCl_3$ in CCl_4/MeCN/H_2O, followed by treatment with sodium methylate in methanol afforded the corresponding sodium salt of homotartaric acid enantiomers.

Our experience in the field of the enzymatic resolution of 1,3-diols[6] allowed us to optimise a new and efficient procedure for the preparation of the two enantiomers of chiral homotartaric acid in satisfactory yields, starting from racemic diol *anti*-**2**, and meso diol *syn*-**2** (Chart 1).

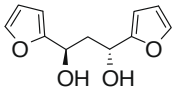
Aldolic condensation of 1-(furan-2-yl)ethanone with furan-2-carbaldehyde afforded hydroxy ketone **3** (Scheme 1). Interestingly, treatment of **3** with $NaBH_4$ in isopropanol at 0 °C gave a 1:0.2 mixture of diols *anti* and *syn*-**2**, while reduction of the acetate



rac-(2*RS*,4*RS*)-**1**



syn-**2**



anti-**2**

Chart 1.

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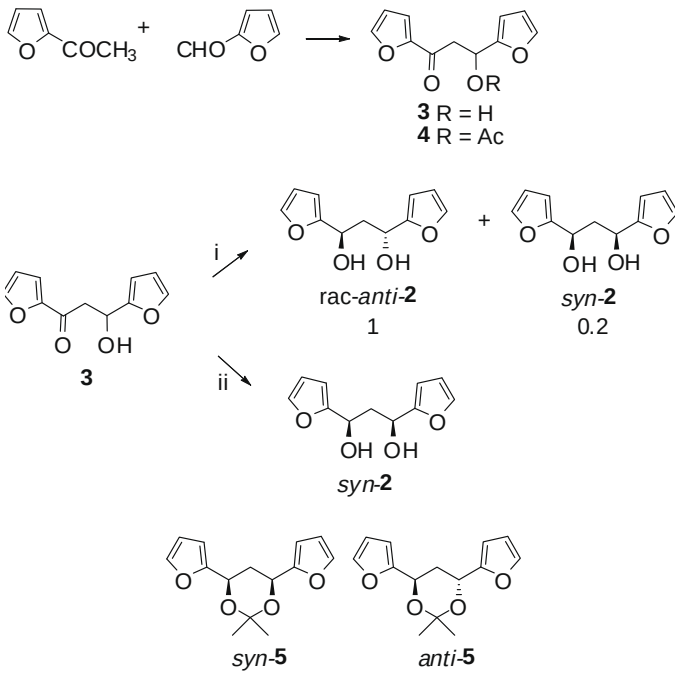
doi:10.1016/j.tetlet.2009.02.192



Scheme 1. Reagents and conditions: (i) $NaBH_4$, isopropanol, 0 °C; (ii) diethylmethoxyborane, THF–CH_3OH, −78 °C; $NaBH_4$.

derivative **4** with $NaBH_4$ in ethanol afforded a 0.5:1 *anti*/*syn*-**2** mixture. Isolation of diol *anti*-**2** was favoured by its almost complete insolubility in chloroform: crystallisation of the 1:0.2 *anti*/*syn*-**2** mixture from $CHCl_3$ allowed us to recover *anti*-**2** as a single pure compound. Reaction of hydroxy ketone **3** with diethylmethoxyborane[7] followed by treatment with $NaBH_4$ allowed us to obtain only diol *syn*-**2**.

The relative configuration of diols **2** was first tentatively assigned on the basis of their NMR spectra and those of the corresponding acetonides **5**: the two hydrogen atoms at C(2) are homotopic in racemic *anti*-**2** and **5**, and diastereotopic in meso *syn*-**2** and **5**. The assignment was then confirmed at the end of the synthetic sequence by the resulting homotartaric acid stereoisomer.

Table 1
Results of the enzyme-catalysed acetylation of diols *anti*- and *syn*-**2**

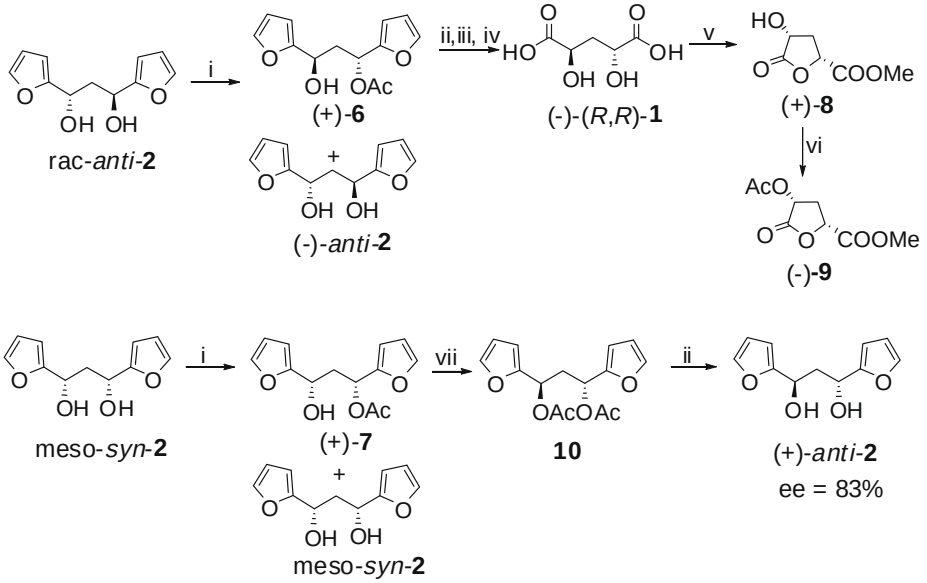
	Enzyme	Product[a] (ee %)	E, c[b] (%)
anti-**2**	PPL[c]	(+)-**6** (95)	77, 41
	CRL[d]	(+)-**6** (95)	206, 51
	PS[e]	(+)-**6** (27)	1.8, 16
syn-**2**	PPL	No reaction	
	CRL	(+)-**7** (83)	
	PS	(+)-**7** (62)	

[a] GC analysis on chiral column of the corresponding acetonides.
[b] Enantiomeric ratio (E) and conversion (c) were determined according to Ref. 9.
[c] *Porcine pancreatic* lipase.
[d] *Candida rugosa* lipase.
[e] *Pseudomonas cepacia* lipase.

We investigated the role of lipases in the kinetic resolution of racemic *anti*-**2** and in the desymmetrisation of meso *syn*-**2**[8] (Scheme 2): the results are collected in Table 1. Monoacetate (+)-**6** was obtained with high enantiomeric excess and optimal conversion when *Candida rugosa* lipase (CRL) was employed as a catalyst. The same enzyme was found to be the most efficient in the desymmetrisation reaction of diol *syn*-**2** to afford optically active monoacetate (+)-**7** (ee = 83%).

Diol (+)-*anti*-**2**, recovered from the saponification of (+)-*anti*-**6** and showing ee = 95%, was treated with ozone in $MeOH/CH_2Cl_2$/HCOOH solution, followed by performic acid treatment at 90 °C.[10] Isolation of homotartaric acid was carried out through the intermediate preparation of the barium salt, which crystallised from acetone-water solution. The salt was converted into the corresponding diacid by treatment with acid ion-exchange resin (Scheme 2).[11]

Diacid (−)-(*R*,*R*)-**1** was obtained as a white solid which crystallised from acetone, and showed $[\alpha]_D = -2.71$ (*c* 3.3, H_2O) ($[\alpha]_D = -2.61$ (*c* 4.1, H_2O) for L-*threo*-**1**).[2,3] The absolute configuration of this homotartaric acid enantiomer was in agreement with the known preference of lipase for the acetylation of (*R*) secondary alcohols.[6] Treatment of diacid (−)-**1** with diazomethane led to the isolation of a compound which resulted to be mainly lactone (+)-**8**.



Scheme 2. Reagents: (i) CRL, vinyl acetate, *t*-butylmethylether; (ii) NaOH in MeOH; (iii) O_3, CH_2Cl_2, MeOH, HCOOH; then H_2O_2 and HCOOH; (iv) $Ba(OH)_2$; acid ion-exchange resin, crystallisation from acetone; (v) CH_2N_2; (vi) Ac_2O, pyridine; (vii) PPh_3, diisopropyl azodicarboxylate, CH_3COOH, THF;

Acetylation of (+)-**8** gave derivative (−)-**9**, which showed ee = 97% by GC analysis on a chiral column (See 'Supplementary data' for details). The enantiomeric purity of diacid (−)-**1** could be derived from that of the precursor (+)-**6** and from that of the reaction product (−)-**9**.

Compound (+)-**7** was converted into diacetate *anti*-**10** by Mitsunobu's esterification (Scheme 2). Saponification of **10** gave *anti* diol (+)-**2** with ee = 83% (GC analysis of the corresponding acetonide on a chiral column). Thus, CRL showed preference for the acetylation of the (*R*)-stereogenic centre also in the desymmetrisation protocol.

In summary, we prepared optically active homotartaric acid in satisfactory yields taking advantage of enzyme catalysis. Previous methods based on classical resolution and metal catalysis were not so efficient for this kind of substrate. We showed the possibility either of resolving racemic *anti*-**2** diol, or of performing a desymmetrisation of meso diol *syn*-**2**. This latter meso diol was obtained with 100% diastereoselectivity by reduction of hydroxy ketone **3** by reaction with diethylmethoxyborane followed by $NaBH_4$ treatment.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.192.

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8. *General procedure for enzyme-catalysed acetylation*: In a typical experiment, a solution of diol **2** (2.08 g, 0.01 mol) in vinyl acetate/*tert*-butyl methyl ether (1:4, 50 mL), was stirred with lipase (PPL, or CRL, or Lipase PS, 2.0 g) at room temperature, and the formation of the corresponding monoacetate was monitored by TLC analysis. The filtered solution was concentrated, and the residue was chromatographed with increasing amounts of ethyl acetate in hexane (see Table 1 for the details regarding the enantiomeric excess values of the transformed monoacetates, the conversion and enantiomeric ratio).
   *From racemic anti-**2*** (10.0 g, 0.048 mol): monoacetate (+)-**6** (4.57 g, 38%) and (−)-*anti*-**2** (3.49 g, 35%) were obtained. 1,3-Di(furan-2-yl)-3-hydroxypropyl acetate ((+)-**6**): $[\alpha]_D^{20}$ + 128.5 (*c* 1, $CHCl_3$), obtained by CRL-catalysed acetylation with 95% ee by GC analysis on chiral column of the corresponding acetonide. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36 (m, 2H, 2α furane H), 6.32 (m, 3H, 3β furane H), 6.25 (d, *J* = 3.3, 1H, 1β furane H), 6.10 (dd, *J* = 9.8, 4.1 Hz, 1H, *CH*OAc), 4.72 (dd, *J* = 9.5, 4.1 Hz, 1H, *CH*OH), 2.54 (ddd, *J* = 14.1, 9.8, 4.1 Hz, *CH*H), 2.37 (ddd, *J* = 14.1, 9.5, 4.1 Hz, *CH*H), 2.05 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.7, 155.6, 152.1, 142.0, 142.5, 110.2, 110.1, 108.5, 106.0, 65.6, 63.9, 38.3, 20.9. GC/MS: t_R 21.47 min *m/z* (% relative intensity) = 232 (M^+ - 18, 5), 190 (95), 95 (100).
   *1,3-Di(furan-2-yl)propane-1,3-diol ((−)-anti-**2**)*: $[\alpha]_D^{20}$ −27.7 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 (m, 2H, 2α furane H), 6.34 (dd, *J* = 3.3, 1.9 Hz, 2H, 2β furane H), 6.28 (d, *J* = 3.3, 2H, 2β furane H), 5.03 (q, *J* = 5.7 Hz, 2H, 2*CH*OH), 2.68 (d, *J* = 5.3 Hz, 2H, 2OH), 2.36 (t, *J* = 5.7 Hz, CH_2); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 156.2, 142.0, 110.2, 105.9, 65.3, 39.8. GC/MS: t_R = 20.39 min, *m/z* (% relative intensity) = 208 (M^+, 2), 190 (35), 94 (100).
   *From meso syn-**2*** (5.0 g, 0.024 mol): monoacetate (+)-**7** (4.74 g, 79%) and unreacted *syn*-**2** (0.60 g, 12%) were obtained. 1,3-Di(furan-2-yl)-3-hydroxypropyl acetate ((+)-**7**): $[\alpha]_D^{20}$: +97 (*c* 3, $CHCl_3$) (obtained by CRL-catalysed acetylation with 83% ee by HPLC analysis on chiral column). ^{1}H NMR ($CDCl_3$, 400 MHz,): δ 7.39 (m, 1H, 1α furane H), 7.35 (m, 1H, 1α furane H), 6.37 (d, 1H, *J* = 3.2 Hz, 1β furane H), 6.34 (dd, 1H, *J* = 3.2 and 1.8 Hz, 1β furane H), 6.31 (dd, 1H, *J* = 3.2 and 1.8 Hz, 1β furane H), 6.23 (d, 1H, *J* = 3.2 Hz, 1β furane H), 6.03 (t, 1H, *J* = 7.3 Hz, *CH*OAc), 4.65 (t, 1H, *J* = 6.3 Hz, *CH*OH), 2.60–2.44 (m, 2H, CH_2), 2.01 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$, 100.6 MHz,): δ 170.1, 155.7, 151.7, 142.7, 142.2, 110.3, 110.2, 109.1, 106.1, 66.2, 64.8, 38.2, 21.0; MS (EI): t_R = 21.43 min, *m/z* (% relative intensity) = 250 (M^+, <1), 232 (3), 190 (100), 95 (91).
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11. *(2R,4R)-(−)-2,4-dihydroxyglutaric acid* (**1**). Diol (+)-*anti*-**2** (3.20 g, 0,0154 mol) was treated with ozone at −60 °C in methanol/dichloromethane/formic acid solution (0.5:0.5:1, 300 mL). When all the starting material had reacted (TLC), the ozonisation was stopped, the mixture was brought to −10 °C, formic acid was added again (50 mL) and the ozonisation was continued for a further hour at this temperature. The solution was slowly heated at 90 °C, to remove methanol and dichloromethane by distillation. After cooling and addition of hydrogen peroxide (30%, 2 mL), the mixture was slowly heated at 90 °C. After cooling, Pd/C (10%, 20 mg) was added and the mixture was heated again to 90 °C. After cooling and filtration on a Celite cake, formic acid was removed by distillation. The residue was diluted with water, $Ba(OH)_2$ was added to basic pH, and the mixture was heated on a steam bath. Acetone was added, and after cooling the barium salt was filtered. This latter was dissolved in the minimum amount of water and eluted through an acid ion-exchange resin column till neutrality of the eluate. Removal of water under reduced pressure afforded a solid residue which was crystallised from acetone to yield diacid **1** (1.06 g, 42%). Mp 132 °C. $[\alpha]_D$ = −2.71 (*c* 3.3, H_2O) ($[\alpha]_D$ = −2.61 (*c* 4.1, H_2O) for (*R,R*)-**1** Ref. 2). ^{1}H NMR (DMSO-d_6, 400 MHz,): δ 4.10 (dd, *J* = 7.7, 5.7 Hz, 2H, 2*CH*COOH), 1.79 (dd, *J* = 7.7, 5.7 Hz, 2H, CH_2); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 175.7, 68.2, 38.6.