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New Route to Enantiomers of Cyclic β-Hydroxyethers. The Crystal Structure of (S)-(+)-Tetrahydrofurfuryl-O,O'-Diacetyl-(2R,3R)-Hydrogentartrate.

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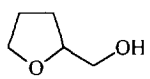
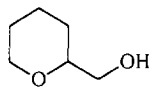
Abstract: Title compounds **1-2** were readily resolved into their enantiomers by crystallizing their half esters formed with O,O'-diacetyl-(2R,3R)-tartaric acid. An intermolecular H-bond between the free carboxyl group and the ring oxygen, determined by single crystal X-ray study of (S)-(+)-tetrahydrofurfuryl-O,O'-diacetyl-(2R,3R)-hydrogentartrate, enhances the selectivity and the crystallizing ability itself. Copyright © 1996 Elsevier Science Ltd

β-Hydroxyethers, especially enantiomers of the tetrahydrofurfuryl-alcohol **1** are important chiral intermediates in organic syntheses. Enantiomeric tetrahydrofurfuryl alcohol was used in the synthesis of (-)-normetazocine derivatives having differentiated opioid action profiles[1], for the preparation of strong analgesics with non-morphine-like action profile[2], for the preparation of the stereoisomers of furnidipine[3a,b], which exhibit either calcium channel antagonist or agonist properties[3a,c], furthermore optically active **1** was used for the preparation of enantiomers of hexanolide and dodecanolide[4,5], the enantiomers of naftidrofuryl[11], for preparation of chiral ligands employed in the asymmetric addition of organometallic compounds to ketones and aldehydes[6]. Enantiomers of 3-hydroxytetrahydrofuran, 3-hydroxytetrahydropyran and 1,2-pentanediol as well as enantiomers of 2-methyltetrahydrofuran and 2-pentanol can also be prepared starting from the acetate or tosylate of the enantiomeric tetrahydrofurfuryl alcohol[7,8].



1



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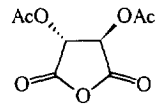

3

Despite the great importance of the enantiomerically pure β-hydroxyethers, they are available on the preparative scale only with difficulty, even though there are a number of methods that can be applied for

preparation of the enantiomers. There are stereoselective syntheses as well as resolution methods available. The application of the former provides (S)-(+)-**1** in a multistep procedure starting from L-glutamic acid with an overall yield not exceeding 5% and with an ee. of about 90%[12]. (R)-(-)-**1** was also prepared from the dibutylacetal of the corresponding aldehyde[23]. (S)-(+)-**2** was prepared from its acetate obtained by hydrogenation (Pd) of tri-O-acetyl-D-galactal[16]. On the one hand the enantiomer obtained is determined by the availability of its chiral precursor taken mostly from natural sources, on the other hand the enantiomeric mixtures need further purifications when e.g. racemization occurs in the reaction. The enantiomeric enrichment in the case of **1** is really difficult[10,8,12].

Preparative scale resolutions have recently incorporated three major areas: a) classical methods based on crystallization of diastereoisomers and less frequently based on kinetic resolution and on the preferential crystallization of enantiomers; b) host-guest complexation and c) enzyme catalyzed reactions (those are enzyme catalyzed kinetic resolutions).

Since racemic hydroxyethers are now readily available, they can serve as a source of either enantiomer by resolution. Applications of any of the methods mentioned above can be found in the literature. Racemic **1** was resolved first by a traditional method[9] generally applicable for alcohols. Crystallization of the acid phthalate salt formed with brucine[10,8] yields optically active acid phthalates with an ee. of about 30%[8]. The number (3-4[10], 5-6[8]) of recrystallizations that were needed to obtain pure isomers results in a drastic decrease in yields. Analogously, racemic **2** was resolved with brucine[21]. Oxidation of racemic **1** to tetrahydrofuroic acid (45%), followed by resolution of the acid with brucine and (+)-ephedrine (24-24%), esterification with diazomethane (89%) and reduction (74%) afforded the enantiomers of **1** with an overall yield of 7% with respect to half the amount of the starting racemic **1**[3a,b]. Analogously, the methylester of the non-racemic tetrahydrofuroic acid obtained by resolution with quinine was reduced to tetrahydrofurfuryl alcohol[13].

1 was resolved via host-guest complexation (15% yield)[14] as well as via its carbonate ester by enzymic hydrolysis[22]. In contrast with 2-hydroxymethyltetrahydropyran **2** the kinetic resolution of **1** via lipase catalyzed hydrolysis of the butyric esters was unsuccessful[15].

Currently we are interested in the development of new applications of tartaric acid derivatives in resolutions. Since tartaric acid and its derivatives are available in both enantiomeric forms, during the course of a resolution either of the enantiomers can be prepared in the same manner. We have successfully applied O,O'-dibenzoyltartaric acid for resolution of carboxylic acids and carboxylic acid derivatives[17], moreover the O,O'-dibenzoyltartaric acid enantiomers themselves are now readily available by resolution via preferential crystallization starting from the racemic form[18].

As part of our extended study, we found that diacetyltartaric acid forms crystalline half esters with β-hydroxyethers, thus facilitating the separation of the stereoisomers of the latter type of compounds by fractional crystallization. The limited use of **3** in resolutions is due to the fact that acid diacetyltartrates exhibit a low tendency toward crystallization. There were only a few examples reported as crystalline solid, e.g. methyl[19a] and tert-butyl[19b] ester, whilst half esters with (-)-borneol[24a], benzyl alcohol[24b], ethyl, isopropyl and isobutyl alcohol[19a] were obtained as oily products.

Half esters with O,O'-diacetyl-(2R,3R)-tartaric acid were applied to the resolution of pantolactone by crystallizing the pyridine salt[25], and to the resolution of timolol[26]. As the half ester formed with timolol has

basic groups, internal salt formation is possible. Diacetyltartaric anhydride was used in the kinetic acylation of various racemic alcohols[20a], alcohols and amines[20b] as well as 1-phenylethanol in the presence of a number of bases as catalysts[20c].

In accordance with the results obtained for primary alcohols[20a,b], kinetic resolution of racemic **1** with **3** in the presence of pyridine resulted in an enantiomeric excess of less than 4%, crystallization of the half ester obtained allows, however, optional separation of the enantiomers.

In our procedure racemic alcohols **1-2** were acylated with **3** using 5-10% pyridine as a catalyst in ethyl acetate, from which the product was obtained as a crystalline mass. Crude esters were purified further by recrystallizing them from the usual organic solvents such as benzene, acetone, ethanol and ethyl acetate. Of a number of solvents investigated ethyl acetate was found to be the best. The pure ester was hydrolysed under mild conditions, in dilute aqueous NaOH solution at room temperature.

An X-ray crystallographic study was performed on (S)-**1-3** in order to see if any reasoning can be found as to what interactions cause the excellent crystallizing ability in this case. It seems that the H-bonding network linking the carboxylic group and the ether oxygen of a second molecule plays the most important role in the crystallization and in the arrangement of the molecules. In Figure 1. an ORTEP drawing of (S)-(+)-tetrahydrofurfuryl-O,O'-diacetyl-(2R,3R)-hydrogentartrate with the atomic numbering is reported. Table 1. lists the atomic coordinates with e.s.d.'s. In Figure 2. a packing diagram of (S)-**1-3** is shown. Table 2. lists the bond length, Table 3. lists the bond angles with e.s.d.'s.

All data were collected on a Rigaku AFC6S single crystal diffractometer, using Cu-K_α radiation (λ =1.5418 Å), ω-2θ scans, with 4 < 2θ < 150 . $C_{13}H_{18}O_9$, M=318.27, monoclinic, a=9.309(7) Å b=9.891(5) Å c=9.619(8) Å β=115.54(6) , V=799(1) Å^3, space group $P2_1$, Z=2, D_{calc} =1.32 gcm^{-3} , μ= 0.98 mm^{-1}. 1732 reflections were measured of which 1626 were independent and 1348 was considered as observed ($F>4\sigma(F)$). All data were corrected for Lorentz and polar factors. Computations were carried out using the teXsan package[27], but final refinement was done with SHELXL-93[28]. The non-hydrogen atoms were refined anisotropically, the hydrogen atom positions were generated via geometric evidences and the isotropic thermal motion parameters were refined, but were allowed the ride on their parent atoms. Refinement was done by full-matrix least squares to give R_1=0.054 for the observed data , wR_2= 0.2002 for all the independent reflections $\{(w=1/[\sigma^2(F_o^2)+(0.0982*p)^2+0.29*p]$ where $p=[max(F_o^2,0)+2F_c^2)]/3\}$. The maximum and minimum residual electron densities in the final ΔF map were 0.23 and -0.24e$^-$/Å^3 respectively. The maximum and mean shift/error ratios in the final refinement cycle were 0.00 and 0.00 respectively.

Hydrogen bond geometry
Distance O1...O13_$1 2.603(5) Å
Angle O1...H13_$1-O13_$1
$1: -x, y-0.5, -z

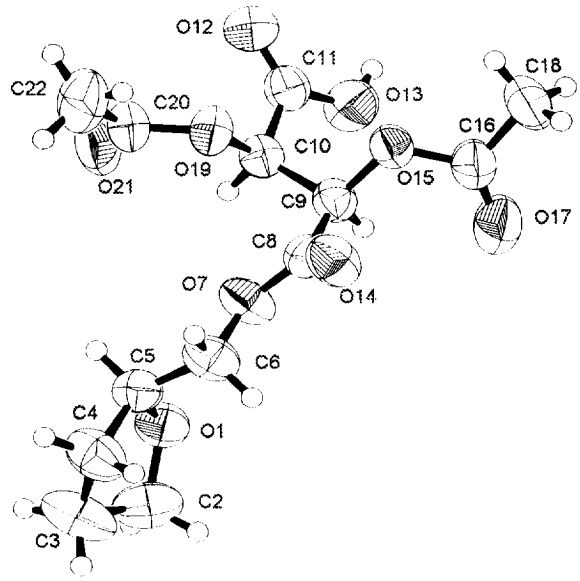

Figure 1. ORTEP drawing of (S)-**1-3**

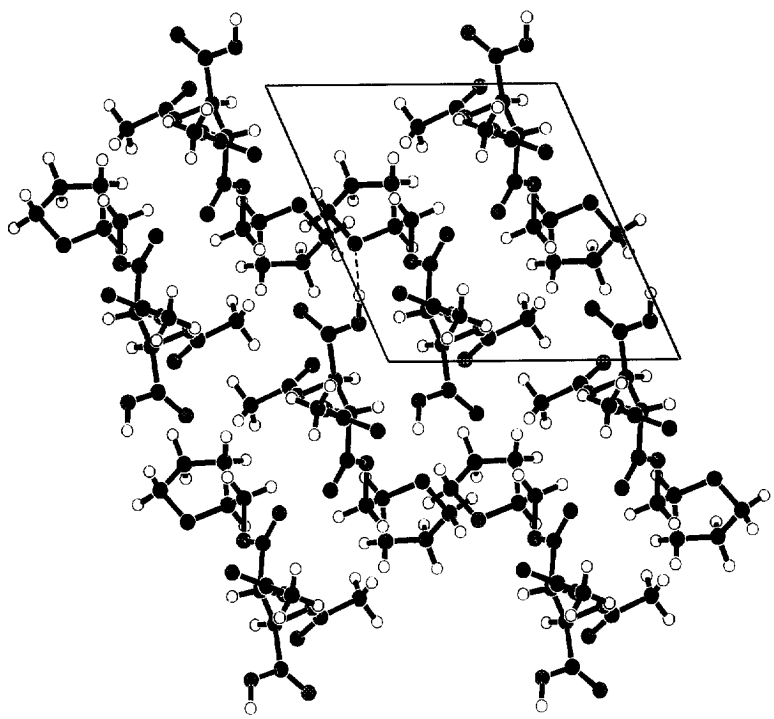

Figure 2. Packing diagram of (S)-**1-3** along the b axis

Table 1. Fractional Atomic Coordinates with e.s.d.'s

		x/a	y/b	z/c	U(eq)
1.	O1	0.4298(4)	0.3394	0.0660(4)	0.0699(9)
2.	O7	0.3617(4)	0.5382(6)	0.2310(4)	0.0720(10)
3.	O12	-0.1870(5)	0.6339(7)	0.2225(5)	0.0816(11)
4.	O13	-0.1403(4)	0.7461(7)	0.0441(4)	0.0808(11)
5.	H13	-0.2406(4)	0.7858(7)	-0.0002(4)	0.118(27)
6.	O14	0.4603(4)	0.7111(6)	0.3954(5)	0.0804(11)
7.	O15	0.1679(4)	0.8288(6)	0.2891(4)	0.0606(8)
8.	O17	0.2472(10)	0.9531(8)	0.1426(9)	0.136(2)
9.	O19	0.1192(4)	0.5545(6)	0.3645(4)	0.0666(9)
10.	O21	0.0079(8)	0.3558(6)	0.2657(7)	0.111(2)
11.	C2	0.5446(7)	0.2835(11)	0.0210(8)	0.097(2)
12.	H2A	0.6128(7)	0.3540(11)	0.0124(8)	0.136(12)
13.	H2B	0.4923(7)	0.2381(11)	-0.0777(8)	0.136(12)
14.	C3	0.6383(10)	0.1864(11)	0.1429(9)	0.114(3)
15.	H3A	0.7441(10)	0.1743(11)	0.1484(9)	0.136(12)
16.	H3B	0.5856(10)	0.0993(11)	0.1260(9)	0.136(12)
17.	C4	0.6451(8)	0.2521(10)	0.2838(8)	0.093(2)
18.	H4A	0.7364(8)	0.3118(10)	0.3285(8)	0.136(12)
19.	H4B	0.6516(8)	0.1851(10)	0.3600(8)	0.136(12)
20.	C5	0.4896(6)	0.3322(8)	0.2289(6)	0.0657(12)
21.	H5	0.4138(6)	0.2831(8)	0.2561(6)	0.079(10)
22.	C6	0.5145(6)	0.4700(8)	0.2961(6)	0.0727(14)
23.	H6A	0.5554(6)	0.4649(8)	0.4073(6)	0.136(12)
24.	H6B	0.5906(6)	0.5190(8)	0.2711(6)	0.136(12)
25.	C8	0.3515(5)	0.6561(7)	0.2922(6)	0.0592(11)
26.	C9	0.1840(6)	0.7097(7)	0.2120(5)	0.0591(11)
27.	H9	0.1609(6)	0.7324(7)	0.1053(5)	0.079(10)
28.	C10	0.0637(5)	0.6070(7)	0.2123(5)	0.0573(11)
29.	H10	0.0582(5)	0.5329(7)	0.1425(5)	0.079(10)
30.	C11	-0.1028(6)	0.6642(7)	0.1631(6)	0.0624(11)
31.	C16	0.1992(8)	0.9474(8)	0.2399(7)	0.0769(15)
32.	C18	0.1644(9)	1.0650(8)	0.3140(9)	0.092(2)
33.	H18A	0.1276(9)	1.0345(8)	0.3878(9)	0.195(21)
34.	H18B	0.0837(9)	1.1194(8)	0.2372(9)	0.195(21)
35.	H18C	0.2594(9)	1.1178(8)	0.3654(9)	0.195(21)
36.	C20	0.0850(8)	0.4245(7)	0.3780(8)	0.079(2)
37.	C22	0.1514(12)	0.3811(11)	0.5401(10)	0.120(3)
38.	H22A	0.2071(12)	0.4553(11)	0.6055(10)	0.195(21)
39.	H22B	0.2238(12)	0.3074(11)	0.5557(10)	0.195(21)
40.	H22C	0.0665(12)	0.3524(11)	0.5647(10)	0.195(21)

Definition of U(eq.):
U(eq.) = [u11+u22+u33+u23.b*.c*.b.c.cosα+u13.a*.c* a.c.cosβ+u12.a*.b* a.b.cosγ]/3

Table 2. Bond Length (Å) with e.s.d.'s

O1	C5	1.420(6)	O19	C10	1.424(6)
O1	C2	1.426(8)	O21	C20	1.215(8)
O7	C8	1.328(6)	C2	C3	1.476(12)
O7	C6	1.450(6)	C3	C4	1.481(10)
O12	C11	1.191(6)	C4	C5	1.530(8)
O13	C11	1.320(7)	C5	C6	1.483(9)
O14	C8	1.201(6)	C8	C9	1.506(7)
O15	C16	1.343(7)	C9	C10	1.513(7)
O15	C9	1.434(6)	C10	C11	1.520(7)
O17	C16	1.200(8)	C16	C18	1.470(9)
O19	C20	1.344(7)	C20	C22	1.471(9)

Table 3. Bond Angles (degree) with e.s.d.'s

C5	O1	C2	109.1(4)	O15	C9	C10	107.9(4)
C8	O7	C6	117.5(4)	C8	C9	C10	111.5(4)
C16	O15	C9	116.7(4)	O19	C10	C9	107.8(4)
C20	O19	C10	116.9(5)	O19	C10	C11	109.0(4)
O1	C2	C3	105.9(5)	C9	C10	C11	113.9(4)
C2	C3	C4	102.6(6)	O12	C11	O13	126.0(5)
C3	C4	C5	104.5(5)	O12	C11	C10	123.4(5)
O1	C5	C6	110.3(5)	O13	C11	C10	110.6(4)
O1	C5	C4	105.6(4)	O17	C16	O15	121.7(6)
C6	C5	C4	112.2(5)	O17	C16	C18	125.1(6)
O7	C6	C5	107.4(4)	O15	C16	C18	113.2(5)
O14	C8	O7	124.6(5)	O21	C20	O19	121.5(6)
O14	C8	C9	125.6(5)	O21	C20	C22	126.6(6)
O7	C8	C9	109.8(4)	O19	C20	C22	111.9(6)
O15	C9	C8	109.9(4)				

In summary β-hydroxyethers can be resolved by a simple method via their crystalline acid diacetyltartrates. The crystal structure stabilized by a strong H-bond was determined by X-ray crystallographic study.

EXPERIMENTAL

Optical rotations were measured on a Perkin-Elmer polarimeter model No. 241. Infrared spectra were recorded on a Perkin-Elmer FT-IR model No. 1600. Melting points were measured on a Gallenkamp Apparatus and are uncorrected. Racemic alcohols were distilled before use.

O,O'-diacetyl-(2R,3R)-tartaric anhydride 3 was prepared according to the literature procedure[29] using a slight modification. To powdered (R,R)-tartaric acid (250g, 1.67 mol) acetic anhydride (595g, 5.83 mol) and 5 drops of sulfuric acid were added and the mixture was stirred. After the dissolution was complete, the acetic acid formed was distilled off using gentle suction at a temperature high enough to avoid crystallization. To the hot residue toluene (130 ml) was then added, and allowed to stand overnight at room temperature, then cooled to 5 °C. The crystalline anhydride was separated by filtration, washed twice with toluene (30 ml each) and dried. 344 g (1.59 mol, 95%) of **3** was obtained, m.p.: 130-131 °C, $[\alpha]_D$ = +59.6 (c:6,acetone). (Lit.[29]: m.p.: 135 °C, lit.[30]: $[\alpha]_D^{20}$ = +61.97 (c:10,acetone).) This anhydride was used without further purification.

(S)-(+)-tetrahydrofurfuryl-O,O'-diacetyl-(2R,3R)-hydrogentartrate (S)-1-3. To a stirred mixture of racemic tetrahydrofurfuryl alcohol (47.4 g, 465 mmol) and pyridine (3.70 g, 47 mmol) solid diacetyltartaric anhydride (100 g, 463 mmol) was added. Stirring was continued for 20 minutes at room temperature, then 10 ml of ethyl acetate was added, and the temperature was raised to 80-85 °C. After 1.5 hr heating 60 ml of ethyl acetate was added, and the mixture was allowed to cool to room temperature, then kept for 10 hours at 5 °C. The crystals were filtered off, washed with ethyl acetate (10 ml) and dried. 89.0 g of crude ester was obtained. This crude product was recrystallized three times from ethyl acetate (142, 83 and 39 ml respectively) to yield 19.0 g (59.7 mmol, 26%) of pure **(S)-1-3**. M.p.: 128-130 °C, $[\alpha]_D^{22}$ = +14.9 (c:3,acetone), $[\alpha]_D^{22}$ = -13.6 (c:1.2, chloroform). IR (KBr, cm^{-1}) : 1069, 1212, 1750, 1759, 2605, 2944, 3495.

(S)-(+)-tetrahydrofurfuryl alcohol (S)-**1**. 18.0 g (56.6 mmol) (S)-**1-3** obtained above was slowly added to a stirred solution of 5.0 g NaOH (0.13 mol) in 110 ml of water and allowed to stand for 18 hours at room temperature. The aqueous solution was extracted twice with 100 ml of methylene chloride, 10 g sodium sulfate dissolved in the aqueous phase, and extracted again with 120 ml of methylene chloride. The organic layers were combined and dried over sodium sulfate. The solvent was removed and the residue (6.1 g) was distilled under reduced pressure to give 4.85 g (47.5 mmol, 84%) of (S)-(+)-**1**. $[\alpha]_D^{22}$ = +17.1 (c:5.4,chloroform), $[\alpha]_D^{20}$ = +2.19 (neat). (Lit.[10]: $[\alpha]_D^{20}$ = +17.1 (c:5.34,chloroform), $[\alpha]_D^{20}$ = +2.18 (neat)).

(R)-(-)-tetrahydrofurfuryl alcohol (R)-**1**. To the combined ethyl acetate solutions obtained above 100 ml of ether was added and washed twice with 40 ml of dilute hydrochloric acid and then with 20 ml of water. The solvents were removed and to the residue a solution of 29.7 g (0.75 mol) NaOH in 400 ml of water was added, and the mixture was allowed to stand for 18 hours at room temperature. The aqueous solution was extracted three times with 400 ml portions of methylene chloride, the combined organic layers dried over sodium sulfate and evaporated. Distillation yielded 27.2 g (267 mmol) of (R)-(-)-**2**. $[\alpha]_D^{22}$ = -2.4 (c:5.3, chloroform). (Lit.[10]: $[\alpha]_D^{20}$ = -17.1 (c:5.34,chloroform)).

(R)-(-)-2-hydroxymethyltetrahydropyran (R)-**2**. According to the above procedure, 10.0 g (86 mmol) racemic **2**, 0,34 g (4.3 mmol) pyridine and 18.6 g (86 mmol) diacetyltartaric anhydride were reacted, the crude ester was recrystallized twice from ethyl acetate (10 and 7 ml) to give 5.40 g (16.3 mmol, 38%) of (R)-**2-3**. M.p.: 98-100 °C. IR (KBr, cm^{-1}) : 1082, 1214, 1751, 1760, 2862, 2960, 3413. Hydrolysis and workup as above afforded 1.41 g (12.2 mmol, 75%) of (R)-**2**. $[\alpha]_D^{22}$ = -10.3 (c:1,water), α_D^{20} = +0.69 (neat), α_{436}^{20} = +2.07 (neat). (Lit.[16]: $[\alpha]_D^{25}$ = +19.2 (c:1,water), lit.[21]: $[\alpha]_{436}^{20}$ = +0.69 (neat)).

(S)-(+)-2-hydroxymethyltetrahydropyran (S)-**2**. From the mother liquors 5.1 g (44 mmol) of (S)-**2** was obtained, $[\alpha]_D^{22}$ = +2.8 (c:1,water). (Lit.[16]: $[\alpha]_D^{25}$ = +19.2 (c:1,water)).

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