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Enantiomerically Pure (*R*)- and (*S*)-3-Benzyloxy-2,3-dihydrofuran: Versatile Precursors for the Synthesis of Protected Glycerinaldehydes

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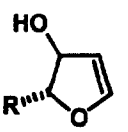
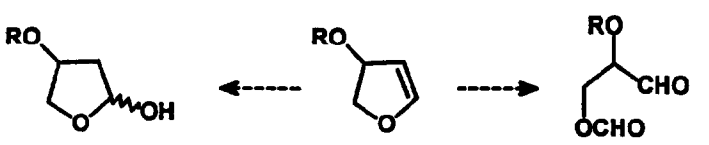
Abstract: Pure enantiomers of 3-benzyloxy-2,3-dihydrofuran were prepared and converted into 2-*O*-benzyl-3-*O*-formyl-glycerinaldehyde.

Furanoid glycals (**1**) or (**2**) in contrast to the corresponding pyranoid systems -although readily accessable from the "chiral pool" of carbohydrates by the same methodologies [1-3]- have found only limited use in synthesis [2,4,5] due to their tendency of undergoing elimination to form furans. The free alcohol systems are sensitive to acids; when substituted with good leaving groups like acyloxy furanoid glycals have only be prepared and used *in situ*. Especially the parent compound 3-hydroxy-2,3-dihydrofuran (**1a**) is very labile and could not be obtained in pure form [2].



1a: R = H
2: R = CH_2OR'

On the other hand, if an enantioselective synthesis of a properly protected 3-hydroxy-2,3-dihydrofuran could be achieved avoiding the problem of aromatisation this would open up an interesting entry into valuable C_3- and C_4-building blocks. For example 2,3-protected glycerinaldehyde (**3**) should be accessible by ozonolysis, hydration should lead to 3-*O*-protected 2-desoxy-threose.

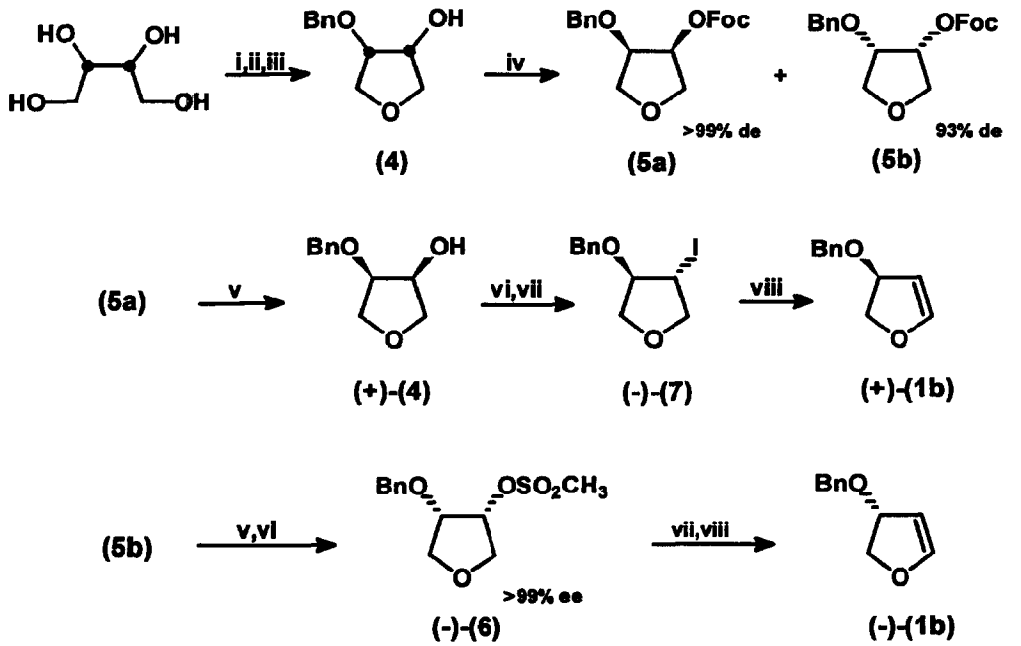


1 **3**

a: R = H
b: R = CH_2Ph

Now we would like to describe an efficient synthesis of the pure enantiomers of title compound 3-benzyloxy-2,3-dihydrofuran **(1b)** [3], which is stable for months under nonacidic conditions, and its conversion into 2-*O*-benzyl-3-*O*-formyl-glycerinaldehyde **(3b)**.

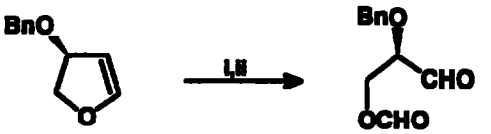
Key compound for the synthesis of the enol ether **(1b)** is 4-benzyloxy-tetrahydrofuran-3-ol **(4)**. Its racemate was synthesized in 88 % yield from erythritol following literature procedures [6, 7, 8]. The resolution of the enantiomers by an enzymatic saponification of the corresponding acetate with crude SAM II- lipase has been described by Seemayer and Schneider [9] to yield (-)-(4) (92 % ee) and the corresponding acetate of its enantiomer (> 98 % ee). In our hand it turned out to be more practicable for the separation of larger amounts of optically pure material to use a classical resolution of diastereomeric esters. The derived (*S*)-furan-5-oxy-2-carboxylic acid esters [10] (Foc-esters) **(5a)** and **(5b)** could be easily separated by crystallisation of **(5a)** from dichloromethane/diethylether (1:20). X-ray analysis of the Foc-ester **(5a)** allowed to establish the absolute configuration [11]. After hydrolysis of the Foc-esters (3*S*,4*R*)-4-benzyloxy-tetrahydrofuran-3-ol (+)-(4) was obtained enantiomerically pure (> 99 % ee, GLC of **(5a)**) whereas its antipode (-)-(4) had an optical purity of 93 % ee.



Scheme: i: Dowex 50 W 4, 150 °C, 95 % [6]; ii: PhCHO, p-TosOH, 92 %; iii: LAH, $AlCl_3$, Et_2O/CH_2Cl_2, 100 %; iv: FocCl, NEt_3, DMAP, **(5a)**: 89 %, **(5b)**: 94 % [12]; v: KOH, $MeOH/CH_2Cl_2$, 95 % [13]; vi: MesCl, NEt_3, Et_2O, rt, (+)-(6): 97 %, (-)-(6): 70 % [14]; vii: KI, 18-C6, toluene, reflux, 5d, 78 % [15]; viii: DBU, ether, 5d, rt, 61 % [16,17].

In this case, however, the purity of its corresponding highly crystalline mesylate (-)-(6) could be raised to > 99 % by recrystallisation from hexane. After nucleophilic substitution of methanesulfonate by iodide and elimination of hydrogen iodide by DBU in diethylether optically pure (+)-(1b) and (-)-(1b) were obtained in 34 % and 28 % overall yield, respectively. Syn-elimination leading to 3-benzyloxy-2,5-dihydrofuran was only observed using more drastic conditions and turned out to be no problem [17].

Ozonolysis of the title compound (+)-(1b) [18] followed by reductive workup with dimethylsulfide and subsequent kugelrohr distillation readily afforded (*R*)-2-*O*-benzyl-3-*O*-formyl-glycerinaldehyde (+)-(3b) in 53 % yield [19] as a colourless liquid (bp: 110 °C/0.1 mbar). (+)-(3b) has two remarkable properties which makes it useful as a glycerinaldehyde system with different protecting groups at the hydroxyl-functions [20]: in chloroform solution oligomerisation was not observed even at room temperature (monitored by NMR) and racemisation was very slow (< 5 % within one week, monitored by optical rotation).



(+)-(1b) (+)-(3b)

Scheme: i: O_3, CH_2Cl_2, -78 °C; ii: DMS, 12h, -78 °C-rt

Conclusions: 3-Benzyloxy-2,3-dihydrofuran is highly interesting not only because large amounts are easily available in enantiomerically pure form but also because it is stable enough to be used as a chiral building block.

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11) We thank Dr. U. Flörke (Universität-GH Paderborn) for determining the crystal structure.
12) **(5a)**: colourless crystals; m_p = 118 °C; $[\alpha]_D^{22}$ = -8.8 (c = 2.50, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): 7.24-7.37 ppm, 5H, m; 5.47 ppm, 1H, ddd (J = 7.1, 4.8, 2.3 Hz); 4.92 ppm, 2H, s; 4.23 ppm, 1H, ddd (J = 13.3, 7.9, 5.0 Hz), ; 3.68-4.08 ppm, 4H, m; 2.01-2.45 ppm, 4H, m.
(5b): colourless oil; $[\alpha]_D^{22}$ = -14.5 (c = 2.65, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): 7.23-7.37 ppm, 5H, m; 5.40 ppm, 1H, ddd (J = 7.8, 5.1, 2.8 Hz); 4.86-4.95 ppm, 2H, m;4.53 ppm, 1H, d (J = 11.3 Hz); 4.47 ppm, 1H, d (J = 11.3 Hz); 4.15-4.24 ppm, 1H, m; 3.66-4.07 ppm, 4H, m; 2.03-2.59 ppm, 4H, m.
13) **(+)-(4)**: colourless liquid; $[\alpha]_D^{20}$ = +27.52 (c = 1.14, methanol); ^{1}H-NMR ($CDCl_3$): 7.26-7.41 ppm, 5H, m; 4.60 ppm, 2H, s; 4.21-4.26 ppm, 1H, m; 4.00-4.08 ppm, 1H, m, 3.70-3.92 ppm, 4H, m; 2.93 ppm, 1H, s(br).
14) **(+)-(6)**: colourless needles; m_p = 79.9 °C; $[\alpha]_D^{20}$ = +34.4 (c = 2.30, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$): 7.26-7.36 ppm, 5H, m; 5.20 ppm, 1H, dd (J = 8.3, 3.8 Hz); 4.70 ppm, 1H, d (J = 11.5 Hz); 4.55, 1H, d (J = 11.5 Hz); 4.14-4.22 ppm, 1H, m; 4.03-4.05 ppm, 2H, m, 3.69-3.77 ppm, 1H, m; 3.02 ppm, 3H, s.
(-)-(6): m_p = 79.8 °C, $[\alpha]_D^{20}$ = -34.5 (c = 2.35, CH_2Cl_2)
15) **(-)-(7)**: colourless liquid; $[\alpha]_D^{20}$ = -128.0 (c = 2.55, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$): 7.24-7.46 ppm, 5H, m; 4.65 ppm, 1H, d (J = 11.8 Hz); 4.55 ppm, 1H, d (J = 11.8 Hz); 4.45 ppm, 1H, dd (J = 4.9, 1.7 Hz); 4.21-4.39 ppm, 3H, m; 4.07 ppm, 1H, dd (J = 9.3, 1.7 Hz); 3.87 ppm, 1H, dd (J = 10.0, 1.8 Hz).
(+)-(7): $[\alpha]_D^{20}$ = +128.7 (c = 2.45, CH_2Cl_2)
16) 35 % of starting material **(-)-(7)** were recovered.
(+)-(1b): colourless liquid; $[\alpha]_D^{20}$ = +268.8 (c = 2.06, benzene), ^{1}H-NMR (d_6-benzene): 7.01- 7.26 ppm, 5H, m; 6.36 ppm, 1H, d (J = 2.6 Hz); 5.01 ppm, 1H, t (J = 2.6 Hz); 4.40-4.46 ppm, 1H, m; 4.11-4.26 ppm, 1H, m; 4.23ppm, 1H, d (J = 11.6 Hz); 4.16 ppm, 1H, d (J = 11.6 Hz); 3.77-3.80 ppm, 1H, m.
(-)-(1b): $[\alpha]_D^{20}$ = -267.5 (c = 2.10, benzene)
17) Conditions: 7 mL DBU and 5 mmol **(-)-(7)** in 50 mL of ether, rt, 5d. Attempts to accelerate the rate of elimination by an increase of the concentrations lead to 3-benzyloxy-2,5-dihydrofuran (ca. 10 %) as by-product.
18) Recently such cleavage of cyclic enol ethers has been shown to be of general importance for the preparation of aldol and homoaldol compounds: S. Hillers, A. Niklaus and O. Reiser, *J. Org. Chem.* **1993**, *58*, 3169.
19) **(+)-(3b)**: colourless liquid; $[\alpha]_D^{20}$ = +37.9 (c = 2.05, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$): 9.71 ppm, 1H, s; 8.05 ppm, 1H, s; 7.26-7.40 ppm, 5H, m; 4.74 ppm, 2H, s; 4.01-4.69 ppm, 3H, m.
(-)-(3b): $[\alpha]_D^{20}$ = -38.2 (c = 2.15, CH_2Cl_2)
20) For other examples of differently protected glycerinaldehydes see:
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