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A Straightforward Preparation of Both Enantiomerically Pure 2-*O*-Benzyl-*erythro*-Butanetetrols

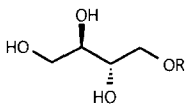
Michael Flasche and Hans-Dieter Scharf*

Dedicated to Hans-Jürgen Bestmann on the occasion of his 65 th birthday

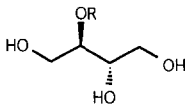
Institut für Organische Chemie, RWTH Aachen, W-52056 Aachen, Germany

Abstract A short and efficient synthesis of both enantiomerically pure 2-*O*-benzyl-*erythro*-butanetetrols **4** and ***ent*-4** from the readily available D-erythronolactone **1** is presented. The synthesis proceeds in a highly efficient manner and is in both cases substrate controlled.

Homochiral *erythro*-butanetetrol derivatives are important building blocks in natural product synthesis[1-4]. Two principal possibilities exist to establish chirality on *meso*-diols: enantioselective differentiation of the primary (type A) or the secondary hydroxyl functions (type B). Whereas the former enantiodifferentiaton is feasible by means of enzymatic hydrolysis and esterification[5] many indirect procedures are described for the latter[6-11]. However only a few methods exist towards the *direct* introduction of protecting groups on an appropriate *erythro*-diol[12].



type A

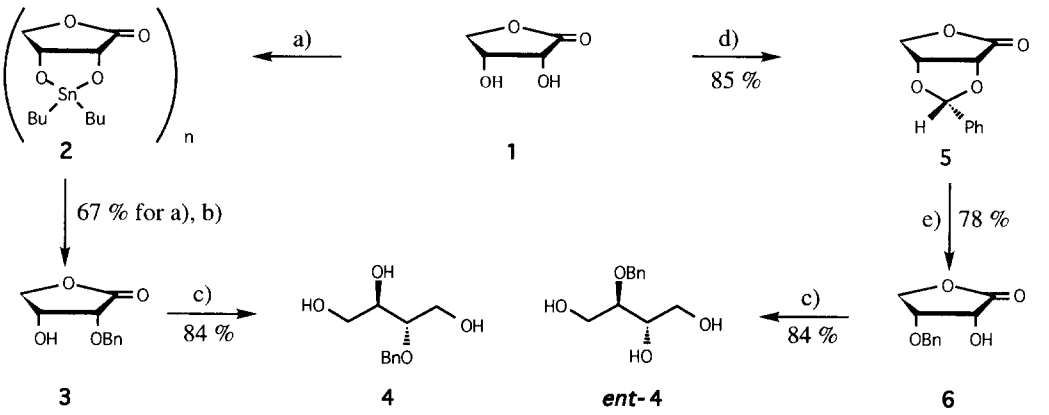


type B

We wish to introduce D-erythronolactone **1** as a suitable chiron for this purpose: its striking feature being its significant reactivity distinction of the hydroxyl functions[13]. Therefore we examined some regioselective benzylation methods[14] to obtain the title compounds.

We have investigated a range of conditions for the regioselective introduction of the benzyl moiety (BnBr, Bu_4NHSO_4 cat., NaOH, CH_2Cl_2/water[15]; NaH/DME, $CuCl_2$, BnI[16]; $Cl_3CC(OBn)=NH$, CF_3SO_3H cat., cyclohexane, EtOAc[17]) but due to solubility problems or fragmentation of the subtrate **1** the desired product could not be detected. In our hands the direct introduction succeeded with the nearly neutral tin-mediated etherification method[18]. The dibutylstannylation/benzylation sequence led to pure 2-*O*-benzyl-D-erythronolactone **3**[19]. The structure was confirmed by NMR measurements and by chemical transformations[20]; subsequent reduction furnished the title compound **4** in 55 % overall yield. The preference for the 2-*O*-

protection can be rationalized on the basis of a postulated dimeric structure of the stannylenacetal[21]: the more basic α–hydroxyl function is two fold coordinated by the tin moiety, whereas the more nucleophilic β–hydroxyl function is three fold coordinated and therefore masked against electrophilic attack. In contrast benzylation using tributylstannylether as intermediate led only to a mixture of chromatographically separable benzyl ethers with the projected 3-*O*-benzyl-D-erythronolactone **6**[19] as the main diastereomer (77 : 23). The low selectivity for 3-*O*-protection is best described by the scrambling of the preformed 3-*O*-tributylstannyl ether before substitution under the specified reaction conditions[22].



conditions: a) Bu_2SnO, toluene, reflux, 6 h; b) 12 eq. BnBr, 1.25 eq N-Methylimidazole, DMF, r. t., 24 h; c) 0.9 eq $LiAlH_4$, CH_2Cl_2/Et_2O, - 20°C - r. t., 6 h; d) I. 1.3 eq. HMDS, 0.66 eq. TMSCl, r. t., 12 h, II. 1.25 eq. $PhCH(OMe)_2$, 10 mol% TMSOTf, CH_2Cl_2, - 78°C, 3 h; e) 1.2 eq. $TiCl_4$, 1.2 eq. $HSiEt_3$, - 78°C, 40 min.

Besides the tin mediated introduction of benzyl ethers, another principal route for selective derivatisation is the chemo- and regioselective reductive cleavage of the correspondending benzylidene acetal **5**[19] *via* Lewis acid complexation/silane reduction[23]. In our hands the system $TiCl_4/HSiEt_3$[24] worked most successfully. Independent of the acetal configuration the attack of the nucleophile takes place from the β–site and hence the 3-*O*-benzyl-D-erythronolactone **6** (mp 87-88°, $[\alpha]_D^{25}$ - 43.2 (EtOH, c 0.25); Lit [6b]: mp 89°, $[\alpha]_D^{25}$ - 44.2 (EtOH, c 1.13)) is the exclusive product. In this case the carbonyl moiety complexes the Lewis acid of the reducing system and the neighbouring C-O bond is labilized, so that the regioselectivity of benzylidene opening is predetermined ; saturation of the intermediate carboxonium ion led after protic work up to the monoprotected lactone **6**. The title compound ***ent*-4**[19] was obtained after reduction with $LiAlH_4$ in THF in 55 % overall yield.

In this paper we described a procedure for the preparation of both enantiomerically pure 2-benzyloxy-1,3,4-butanetriol **4** and ***ent*-4** from their precursors benzyl-D-erythronolactones **3** and **6** by selective manipulation of D-erythronolactone **1**. In both cases we observed a substrate controlled interaction with the chosen reagent.

The extension of this methodology to related aldonolactones and with other protecting groups is currently under investigation.

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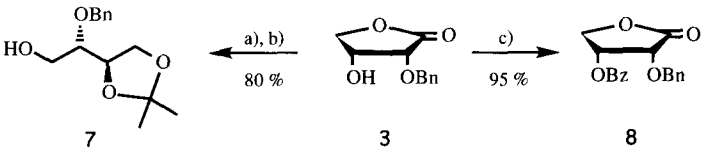
19 Selected physical and spectral data of the new compounds:
3:$[\alpha]_D^{25}$ = - 8.1 (EtOH, c 0.58). m. p. = 125°C; ^{1}H NMR ($CDCl_3$, 300 MHz): 3.06 (s, 1H); 4.13 (d, 1H, J = 4.70 Hz); 4.17 (dd, 1H, J = 10.41 Hz, J = 3.03 Hz, 4'-H); 4.27 (d, 1H, J = 10.41 Hz, 4-H); 4.34 (dd, 1H, J = 4.7 Hz, J = 3.03 Hz, 3-H); 4.97, 4.78 (d, 2H, J = 11.75 Hz); 7.4-7.26 (m, 5H).^{13}C NMR: 67.67 (C2); 71.44 (C4); 72.93 ($\underline{C}H_2Ar$); 74.54 (C3); 128.37, 128.55, 128.73, 136.28 (Ar); 173.68 (C1).Anal. calc. for $C_{11}H_{12}O_4$: C, 63.5; H, 5.77; Found: C, 63.1 H, 5.77.
4:$[\alpha]_D^{25}$ = 21.30 (EtOH, c 1.12).^{1}H-NMR (DMSO-d^6, 300 MHz): 3.32 (dt, 1H, J = 7.08 Hz, J = 3.5 Hz, 2-H); 3.49 (dt, 1H, J = 6.40 Hz, J = 5.0 Hz, 3-H); 3.7 - 3.8 (m, 4-H); 4.2 - 4.3 (bs, 3H, OH-protons); 4.42, 4.53 (d, 2H, J = 11.47 Hz, benzylic protons); 7.18-7.23 (aromatic H). ^{13}C-NMR: 60.77 (C1); 62.94

(C4); 71.35 (C2); 71.42 (benzylic C); 80.93 (C3); 127.1, 127.4, 128.0, 139.16 (aromatic C).IR (Film) in cm^{-1}: 3380, 3085, 3040, 2940, 2880, 1500, 1460, 1400, 1210, 950, 880, 740, 700. MS: 212,1 (1,64 %; Molpeak); 134; 107; 92; 91 (100 %); 70; 61; 43.

***ent*-4:** $[\alpha]_D^{25}$ = - 20.56 (EtOH, c 0.14).

5:$[\alpha]_D^{25}$ = - 115.3 (EtOH, c 1.21). m. p. = 140°C; ^1H NMR ($CDCl_3$, 300 MHz): 4.48 (dd, 1H, 4'-H, J = 11.13 Hz, J = 4.05 Hz); 4.60 (d, 1H, 4-H, J = 11.13 Hz); 4.89 (d, 1H, 2-H, J = 5.74 Hz); 5.00 (dd, 1H, 3-H, J = 5.74 Hz, J = 4.05 Hz); 6.03 (s, 1H); 7.38-7.48 (m, 5H); ^{13}C-NMR: 69.44 (C4); 74.73 (C2); 77.29 (C3); 107.54 (acetal); 126.79, 128.53, 130.13 and 135.10 (aromatic); 173.03 (C1). Anal. calcd. for $C_{11}H_{10}O_4$ (207.4): C, 64.08, H, 4.85; found C, 63.94, H, 4.83.

20 Acetalisation with acetone provided the well known dioxolane **7** (94 %, bp = 120°C/0,1 mm, $[\alpha]_D^{25}$ = + 35.4 ($CHCl_3$, c 1.01); ref. 11: $[\alpha]_D^{25}$ = + 33.4 ($CHCl_3$, c 0.70)) and benzoylation of the lactone **3** led to the ester **8**.



7 3 8

conditions: a) $LiAlH_4$, CH_2Cl_2/Et_2O; b) acetone, p-TsOH; c) BzCl, py.

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22 Benzylation was performed using Bu_4NF on silica gel as catalyst in DMF at 25°C for 3 d; the related uncatalyzed benzoylation led to 3-*O*-benzoyl-D-erythronolactone **9** as the sole product: Flasche, M. *Thesis*, RWTH Aachen 1995.

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