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L-(S)-ERYTHRULOSE : THE SYNTHESIS OF (R)-1,2,4-BUTANETRIOL AND OF SOME RELATED C_4 CHIRONS.

E. Van der Eycken[1], H. De Wilde, L. Deprez and M. Vandewalle*
State University of Ghent, Department of Organic Chemistry,
Laboratory for Organic Synthesis,
Krijgslaan, 281 (S.4), B-9000 GENT (Belgium)

Abstract : L-(S)-Erythrulose can easily be transformed into (R)-1,2,4-butanetriol and related C_4 chiral building blocks. A formal synthesis of (-)GABOB is presented. Also the formation of 3-methylene-1,2,4-butanetriol derivatives is described.

Because L-(S)-erythrulose 1 recently became more readily available[2] it can be considered as a valuable new "chiral pool" compound. In the preceeding publication[3] 1 has been used as a precursor for the more difficultly accessible S-enantiomer of the glyceraldehyde acetonides[4].

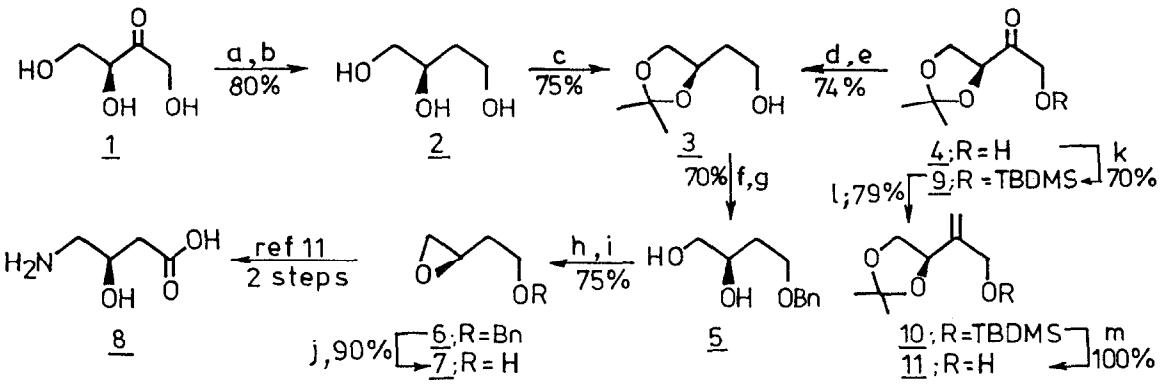
However, the most salient feature of 1 undoubtedly consists of its potential as a C_4-chiral building block. In the present paper emphasis is put on some transformations of the carbonyl group in 1, with the central formation of (R)-1,2,4-butanetriol 2, which has previously been obtained from unnatural D-malic acid[5]. Some derivatives, well-known in the racemic or enantiomeric series, are shown in the scheme. An illustrative example is epoxide 7, which is an intermediate in the total synthesis of the antiepileptic and hypotensive drug (-)-γ-amino-β-hydroxy butyric acid (8; GABOB)[6]. Related C_4 chiral templates with R configuration have until now been prepared from D-malic acid[7], from (R,R)-tartaric acid[8], by yeast reduction of an appropriate -keto ester[9,10] or from 3-butene-1-ol (vide infra)[11].

The best results for the reductive removal of the keto function in 1 were obtained via the tosylhydrazone. Treatment of anhydrous 1[3] with tosylhydrazine afforded the crude hydrazone (oil). The subsequent reduction and column chromatography on aluminum oxide ($CHCl_3$-MeOH; 10:3) gave pure 2, $|\alpha|_D^{20}$ = +25° (c = 2.01, MeOH), the S enantiomer[12] has $|\alpha|_D$ = -24.6° (c = 3.32, MeOH). Acetal formation of 2 gave 3 next to 7 % of the corresponding 1,3-dioxolane (see ref. 14 for a pertinent observation). An alternative procedure for the formation of 3 consists of reductive removal of the carbonyl function in 4[3,13]; no byproduct could be detected in the ^1H NMR spectrum. 3 has $|\alpha|_D^{20}$ = +2.1° (c = 2.5, MeOH); enantiomeric 3 has $|\alpha|_D$ = -2.23° (c = 9.8, MeOH)[14].

Protection of the hydroxyl function in (R)-3 as the benzyl ether and hydrolysis of the acetonide led to (R)-5; $|\alpha|_D^{22}$ = -5.09° (c = 1.97, $CHCl_3$) and $|\alpha|_{365}^{22}$ = -14.96° (c = 1.97, $CHCl_3$). Diol 5 was converted into epoxide 6 via the mesylate of the primary alcohol; (R)-6 has $|\alpha|_D^{22}$ = +12.86° (c = 2.41, $CHCl_3$) and $|\alpha|_{365}^{22}$ = +34.19° (c = 2.41, $CHCl_3$). Enantiomeric (S)-6 has $|\alpha|_D^{26}$ = -13.4° (c = 0.39, EtOH)[15].

Hydrogenolysis of 6 and HPLC purification (50 x 0.7 cm column RSiL 10; pentane/ether 1:9; 40 ml/min) afforded 7; $|\alpha|_D^{23}$ = +23.42° (c = 1.58, CH_2Cl_2) and $|\alpha|_{365}^{23}$ = +63.35° (c = 1.58, CH_2Cl_2). (R)-4-hydroxy-1,2-epoxybutane (7) has already been obtained[16] from L-malic acid, $|\alpha|_D^{23}$ = +23.42° (c = 5.00, CH_2Cl_2) was reported. Rossiter and Sharpless[11] prepared 7.

in 55 % ee, via asymmetric epoxidation of 3-butene-1-ol and subsequently transformed it into GABOB (8).



a) $TsNHNH_2$, MeOH, r.t., 30 min; b) $NaBH_4$, MeOH, r.t. 30 min; c) acetone, 1,4-dioxane, MeOH (7.5/15/1), $ZnCl_2$, Na_2SO_4, 0°C - r.t.; d) $TsNHNH_2$, MeOH, 50°C, 10 min; e) $NaBH_4$, i.PrOH, reflux, 3 h; f) NaOH (50 %) BnCl, TBAB, r.t., 21 h; g) HOAc, r.t., 10 h; h) MesCl, py, 0°C, 20 min; i) NaOH, H_2O, DMSO, 0°C, 15 min; j) H_2, Pd-C, EtOH, r.t., 1 atm, 9 h; k) TBMSCl, imidazole, DMF, r.t., 1 h; l) $Ph_3P{=}CH_2$, Et_2O, 20°C, 1 h; m) Bu_4NF, THF.

The carbonyl group in 4 can also easily be converted into a methylene unit. Subsequent to protection of the hydroxyl function, a Wittig reaction on 9 afforded 10; $|\alpha|_D^{20}$ = -33.9° (c = 20 in $CHCl_3$). 10 and 11 ($|\alpha|_D^{20}$ = -45.5° (c = 20 in $CHCl_3$)) and derivatives thereof are substrates for the study of selected reactions, e.g. epoxidation, hydroxylation and reduction, which could provide chiral building blocks for polypropionate-derived natural products[17]. This work is presently in progress.

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