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EFFICIENT SYNTHESIS OF (S)-5-HYDROXYMETHYL-5(H)-FURAN-2-ONE FROM D-MANNITOL

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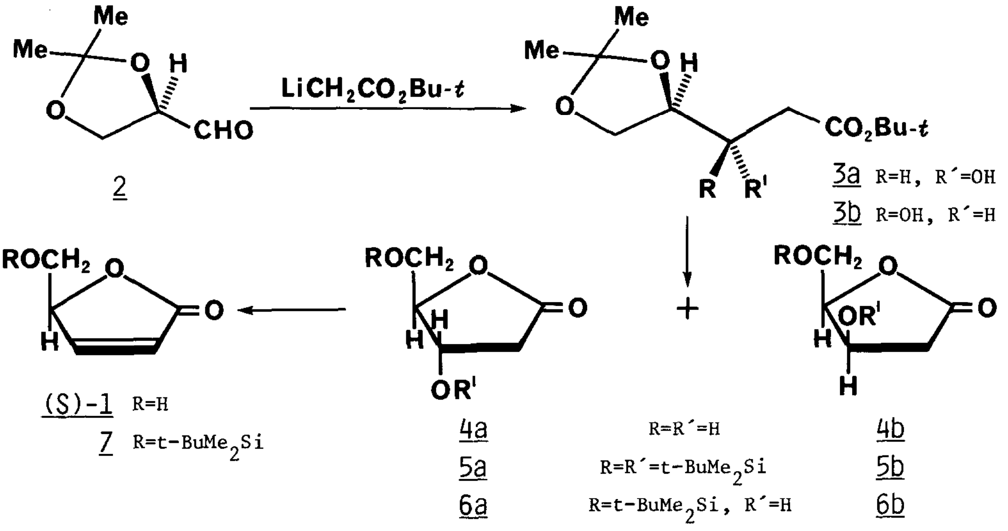
Abstract: Chiral synthons - (S)-5-hydroxymethyl-5(H)-furan-2-one and its t-butyldimethylsilyl ether - were synthesized from D-mannitol in 6-7 steps via 2-desoxy-D-ribonolactone derivatives.

Chiral 5-hydroxymethyl-5(H)-furan-2-ones (1, γ-hydroxymethyl-α,β-butenolides) as well as their O-derivatives and saturated congeners are widely used for the asymmetric total synthesis of various natural products[1]. For similar purposes we were in need of multigram quantities of (S)-1 or its O-derivative. This chiral synthon had been reported to be effectively synthesized in two steps from D-ribonolactone in 68% total yield[2a,b] which however declined on scaling the synthesis up to 2 g level.[2a] More complicated syntheses of (S)-1 benzyl and trityl ethers were published.[2c,d] We present here a preparative synthesis of synthon (S)-1 and its t-butyldimethylsilyl (BDMS) ether from cheap and available D-mannitol.

2,3-O-Isopropylidene-D-glyceraldehyde, 2, is readily available from D-mannitol in high yield.[3] Condensation of aldehyde 2 with $LiCH_2CO_2Bu$-t[4] in THF-hexane (8:5) at -78° gave rise to a mixture (ratio 79:21 by GLC[5]) of epimeric t-butyl (3S,4R)- and (3R,4R)-4,5-O-isopropylidene-3,4,5-trihydroxypentanoates, 3a,b[6], $[\alpha]_D^{25}$ -12° (c 1.075, $CHCl_3$), in 72% yield. Treatment of this mixture with 50% aqueous CF_3CO_2H (90-95°, 2 hr) quantitatively produced a mixture of (4S,5R)- and (4R,5R)-4-hydroxymethyltetrahydrofuran-2-ones, 4a,b,[6] of the same composition.[5] The silylation of 4a,b as a mixture[7] with 1.4 equiv of $t\text{-}BuMe_2SiCl$ and 1.82 equiv of Py in CH_2Cl_2 (20°, 16 hr) proceeded mainly at primary hydroxyl groups producing a mixture of bis-BDMS ethers 5a,b and mono-BDMS ethers 6a,b, R_f 0.63 and 0.27 (SiO_2, hexane-EtOAc, 6:4, diastereomers in each pair having the same R_f). The mixture was easily separated by flash chromatography giving diastereomeric pairs 5a,b (9%) and 6a,b (67%). The pair 6a,b had a diastereoisomeric ratio of 75:25.[5] Main (4S,5R)-isomer 6a (5-O-BDMS ether of 2-desoxy-D-ribonolactone),[6] m.p. 65.5-67°, $[\alpha]_D^{25}$ -4° (c 0.911, $CHCl_3$) could be isolated in 35% total yield by crystallization from hexane.

Dehydration of the 6a,b mixture with $SOCl_2$ (5 equiv) and Py (10 equiv) in CH_2Cl_2 (24°, 22 hr) produced the single compound, BDMS ether of (S)-1, 7,[6] m.p. 31-32°, $[\alpha]_D^{25}$ -141°, (c 0.937, $CHCl_3$), in a yield amounting to 75% after Kugelrohr distillation. The 100% enan-



tiomeric purity of 7 as well as its ability to be converted to other synthon (S)-1 derivatives was demonstrated by the hydrolysis with AcOH-THF-H$_2$O[8] (6:2:2, 24°, 22 hr), which afforded synthon (S)-1[6] (82%), m.p. 36.5-38.5°, $[\alpha]_D^{25}$ -145° (c 1.132, H$_2$O) [Lit.[2b]: m.p. 37-39°, $[\alpha]_D^{25}$ -143° (c 1.14, H$_2$O)].

Compound 7 is a conveniently protected form of synthon (S)-1. It is available now in a four-step sequence from aldehyde 2 in 36% unoptimized total yield which shows no tendency to decrease on scaling up the synthesis.

References and Notes

1. N.K.Kochetkov, A.F.Sviridov, M.S.Ermolenko, D.V.Jashunskii, O.S.Chizhov. Carbohydrates in the Synthesis of Natural Products, Moscow, "Nauka", 1984, p.260.
2. a) P.Camps, J.Font, O.Ponsati, Tetrahedron Letters, 1981, 22, 1471; b) P.Camps, J.Cardelliach, J.Font, R.M.Ortuno, O.Ponsati, Tetrahedron, 1982, 38, 2395; c) M.Tanoguchi, K.Koga, S.Yamada, Tetrahedron, 1974, 30, 3547; K.Tamioka, T.Ishiguro, K.Koga, J.Chem.Soc.Chem. Comm., 1979, 652; d) R.E.Ireland, R.C.Anderson, R.Badoud, B.J.Fitzsimmons, G.McGarvey, S.Thaisrivongs, C.S.Wilcox, J.Am.Chem.Soc., 1983, 105, 1988.
3. The best procedures for conversion of D-mannitol into 1,2;5,6-di-O-isopropylidene-D-mannitol (92% yield) (J.L.Debost, J.Gelas, D.Horton, J.Org.Chem., 1983, 48, 1381) and the latter into aldehyde 2 (81% yield) (R.Dumont, H.Pfauder, Helv., 1983, 66, 814) were described recently. In the present work crude undestilled aldehyde 2 available in quantitative yield was used.
4. M.W.Ratneke, D.F.Sullivan, J.Am.Chem.Soc., 1973, 95, 305.
5. GLC analyses were carried out for corresponding TMS ether on packed columns with 1% XE-60 (for 3a,b) or SE-30 phases.
6. The compound (or mixture) had all chromatographic and spectral data (TLC, GLC, IR, ^{1}H-NMR, MS) in accord with the structure (or composition).
7. The erythro- and threo-diastereomers in the pairs 3a,b or 4a,b were indistinguishable by TCL but they had not to be separated. Pure bis-BDMS ether of 2-desoxy-D-ribonolactone, 5a[6], m.p. 80-82°, $[\alpha]_D^{25}$ +13° (c 0.9, CHCl$_3$), could be secured in 67% isolated yield by the silylation of 4a,b with excess of t-BuMe$_2$SiCl-imidazole in Py (20°, 22 hr) and crystallization of crude product (5a,b mixture) from hexane at -78°. It was found to be identical to the sample prepared by bromine oxidation of 2-desoxy-D-ribose (A.M.Gakhokidze, J.Gen.Chem.(U.S.S.R.), 1945, 15, 539; R.E.Deriaz, W.G.Overend, M.Stacey, E.G.Teece, L.F. Wiggins, J.Chem.Soc., 1949, 1879) with subsequent silylation.
8. The desilylation of 7 with n-Bu$_4$NF in THF (22°, 2.5 hr) (E.J.Corey, A.Venkateswarlu, J.Am. Chem.Soc., 1972, 94, 6190) produced racemic 1.

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