The Stereoselective Methylations and Hydroxymethylations of 2,8-Dioxabicyclo[3.2.1]octan-3-one Derivatives. Synthesis of Branched-chain Sugars

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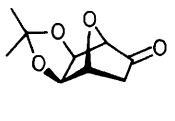
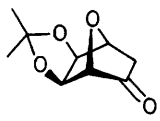
The stereoselective C(4) alkylations of 6-*exo*,7-*exo*-(isopropylidenedioxy)-2,8-dioxabicyclo[3.2.1]octan-3-one with MeI and $PhCH_2OCH_2Br$ are presented; the products so-obtained have been converted to partially protected 5,6-dideoxy-5-*C*-methyl-D,L-*ribo*-hexofuranose and 5-deoxy-5-*C*-methyl-D,L-*talo*-hexofuranose.

The enantiomerically pure ketones (+)-(**1**) and (−)-(**1**) are readily available.[1] Bayer–Villiger oxidation affords the corresponding lactones (−)-(**2**) and (+)-(**2**)[2] which can be transformed in a few synthetic steps into D- and L-ribose derivatives, respectively.[1] Stereospecific hydroxylations at C(3) of (+)-(**1**) and (−)-(**1**) allowed D- and L-allose derivatives, respectively, to be prepared.[3] Because of a recent report by Ager and East[4] on the stereoselective hydroxylation of (±)-(**2**), we report our preliminary results on the stereoselective methylation and hydroxymethylation of the racemic lactone (±)-(**2**) and its derivatives. The results open a new pathway to the total synthesis of rare branched-chain sugars.[5]

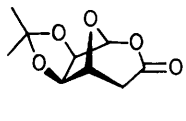
Treatment of (±)-(**2**) with $(Me_3Si)_2NLi$ in tetrahydrofuran (THF) at −65 °C gave a colourless solution of enolate (**3**). Quenching of (**3**) with MeI (19 mol equiv.; −65 to −20 °C) afforded the 4-*exo*-methyl bicyclic lactone (**4**) (m.p. 118—119 °C) in 98% yield. Quenching of (**3**) with $PhCH_2OCH_2Br$ (3.5 mol equiv.; −60 to 0 °C) gave (**5**) (m.p. 97—97.5 °C; 74%). Deprotonation of (**4**) with $(Me_3Si)_2NLi$ in THF at −65 °C followed by quenching with MeOH and then work-up with saturated NH_4Cl (0 °C) led to a 1 : 20 mixture of (**4**) and (**6**) from which the *endo*-isomer (**6**) (m.p. 130—131 °C) could be isolated in 87% yield by crystallization from AcOEt/light petroleum. Quenching with MeI gave (**7**) [m.p. 141—



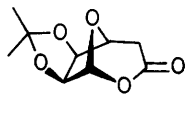
(+)-(1)



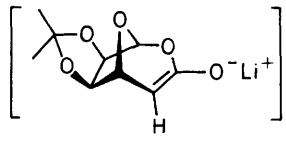
(−)-(1)



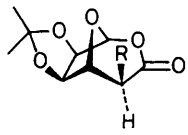
(−)-(2)



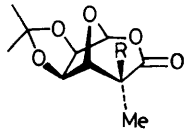
(+)-(2)



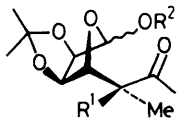
(3)



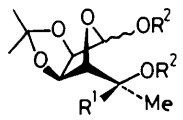
(4) R = Me
(5) R = CH_2OCH_2Ph



(6) R = H
(7) R = Me
(8) R = CH_2OCH_2Ph
(9) R = $CH_2CH{=}CH_2$



(10) R^1 = Me, R^2 = H
(11) R^1 = Me, R^2 = Ac
(14) R^1 = CH_2OCH_2Ph, R^2 = H
(15) R^1 = CH_2OCH_2Ph, R^2 = Ac
(16) R^1 = CH_2OH, R^2 = Ac



(12) R^1 = Me, R^2 = Ac
(13) R^1 = Me, R^2 = H
(17) R^1 = CH_2OH, R^2 = Ac
(18) R^1 = CH_2OH, R^2 = H

141.5 °C; 84% based on (±)-(2)†]; quenching with $BrCH_2OCH_2Ph$ (−60 to −10 °C) afforded (8) (m.p. 71—71.5 °C; 91%) and with $BrCH_2CH{=}CH_2$, (9) (m.p. 132—132.5 °C; 80%). Attempts to deprotonate (5) with $(Me_3Si)_2NLi$ or Pr^i_2NLi in THF followed by quenching with H_2O or MeI led only to products of decomposition.

The relative configuration of C(4) in (4)—(6) was given by the 250 MHz ^1H n.m.r. spectra which showed a typical vicinal coupling constant of *ca.* 0 Hz between H–C(4) and H–C(5) in the cases of the *exo*-derivatives (4) and (5), and of 6.0 Hz in the 4-*endo*-methyl lactone (6).[3] The structures [and relative configuration of C(4)] of (8) and (9) were confirmed by nuclear Overhauser enhancements observed in their ^1H n.m.r. spectra between *exo*-CH_2OCH_2Ph, *exo*-allyl, and H–C(5) protons, and between *endo*-Me and H–C(6) protons. The high *exo*-face selectivity of the quenching reactions (3) → (4), (5) and of transformations (4) → (6), (4) → (8), and (4) → (9) can be attributed to a steric factor, the *endo* faces of the enolate intermediates being less accessible than the *exo* faces.

The usefulness of these reactions is illustrated by the easy transformations of (7) and (8) into partially protected 5,6-dideoxy-5-*C*-methyl-D,L-*ribo*-hexofuranose (13) and 5-deoxy-5-*C*-methyl-D,L-*talo*-hexofuranose (18). Addition of lactone (7) to a solution of trimethylsilylmethyl-lithium[6] in THF (−70 °C; 3 min), followed by treatment with MeOH (−45 °C; 20 min) led, after aqueous work-up, to a mixture of the α- and β-D,L-furanose (10) (m.p. 64—65 °C; 94%). Acetylation (Ac_2O/pyridine/THF; 20 °C; 1 h) gave (11) which was oxidized (20 °C; 4 h) with trifluoroperacetic acid (3 mol equiv.) and Na_2HPO_4 (6 mol equiv.) in CH_2Cl_2 into (12) (95%). Trans-esterification with MeOH and anhydrous K_2CO_3 (20 °C; 5 h) yielded (13) (m.p. 74—75 °C; 98%; mostly the β-anomer by ^1H n.m.r.). In a similar fashion, (8) was transformed into (14) (oil; 95%), and then into (15) (oil; 98%), (16) (oil; 96%), (17) (oil; 50%), and (18) (oil; 98%). Work is underway to apply the reactions described here to optically pure lactones (+)-(2) and (−)-(2) and to other derivatives.[1b] We also plan to convert (13) into 4-*epi*-noviose and noviose.[7]

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† Double methylation of (±)-(2) without isolation of (4) gave a 69% yield of (7). Double methylation of (±)-(1) (KH, MeI) followed by Baeyer–Villiger oxidation (*m*-chloroperbenzoic acid in CH_2Cl_2) gave (7) in 54% yield.

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