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TWO COMPLEMENTARY METHODS FOR INTRODUCTION OF *gem*-DIMETHYL GROUP IN HEXOPYRANOSIDE RING

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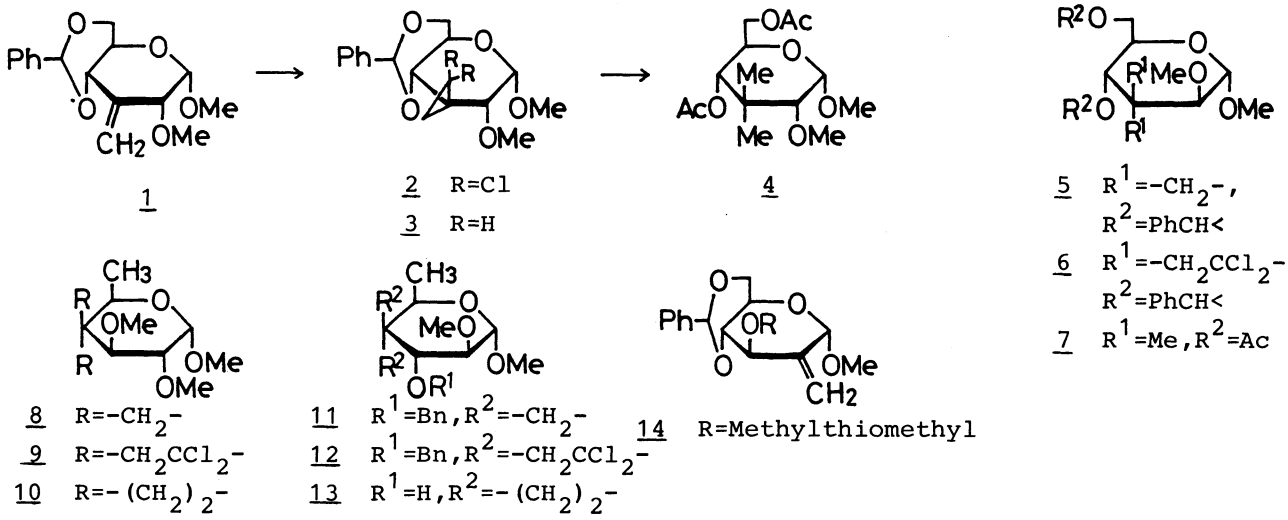
Hexopyranosides having a *gem*-dimethyl group in the pyranose ring were synthesized by reductive cleavage of spiro-cyclopropane derivatives and by addition of methyl cuprates to methyl-branched enolone derivatives.

Quaternization[1] of carbon is one of the challenging subject in the field of organic synthesis. Although a few methods for synthesis of *gem*-dialkyl derivatives of carbohydrates were developed,[2] pyranoside derivative having quaternized *gem*-dimethyl group in the ring has not been reported until quite recently.[3] We would like to report two different and complementary methods for the synthesis of *gem*-di-*C*-methyl hexopyranosides, which could well be of application in chiral synthesis of natural products like terpenoids.

gem-Dimethyl group on C-3 position of hexopyranoside could be introduced *via* spiro-cyclopropane derivative (2, 3, and 6). Dichlorocyclopropanation of methyl 4,6-*O*-benzylidene-2-*O*-methyl-3-*C*-methylene-α-D-*ribo*-hexopyranoside (1)[4] ($CHCl_3$, 50% aqueous sodium hydroxide-benzene, benzyltriethylammonium chloride, room temperature, overnight) gave a single product (2)[5] quantitatively, ^{1}H NMR($CDCl_3$):δ 1.86 and 2.04(each 1H, d, *J* 7.6Hz, H-3'a and H-3'b), ^{13}C NMR($CDCl_3$):ppm 33.92(C-3), 22.45(C-3':CH_2), and 62.37(C-3':CCl_2). Hydrogenolysis of 2[H_2 100 atom, Raney-Ni(W-7), butanol-ethanol (5:2), room temperature, 5 days] followed by acetylation gave a desired 3,3-di-*C*-methyl derivative (4) in 70% yield, $[\alpha]_D$ +28.0° ($CHCl_3$), ^{1}H NMR($CDCl_3$):δ 4.90(d, *J* 4.0Hz, H-1), 3.06(d, H-2), 4.84(d, *J* 9.8Hz, H-4), 1.00 and 1.12(each s, CMe). Furthermore, spiro-cyclopropane (3) obtained by cyclopropanation of 1 [CH_2N_2, bis(*N*-*(RS)*-phenethylsalicylaldiminato)copper(II), hexane-benzene (1:1), room

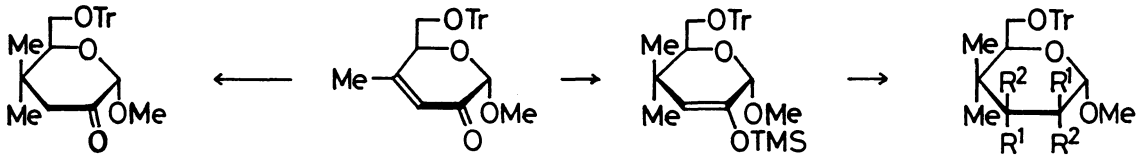
temperature, 2 h, 87%] could be also converted into 4 by the same procedure (62%).



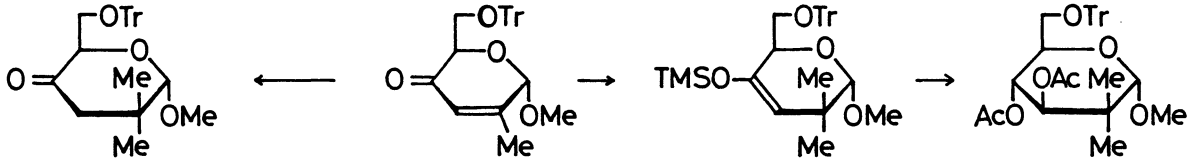
This method seems to be sensitive to stereochemical circumstance. The C-2 epimer (5) of 1 resisted to dichlorocyclopropanation and gave 6 in 54% yield even at 60 °C. Moreover, the corresponding 3,3-*gem*-dimethyl derivative 7[6] was obtained in only 16% yield under the same procedure as described above. On the other hand, 4-*C*-methylene hexopyranosides (8[7] and 11[8]) were converted into epimeric mixtures of spiro-dichlorocyclopranes (9 and 12) in 49% and 48% yields, respectively. Attempt at hydrogenolytic cleavage of carbon-carbon bond of the cyclopropane ring in 9 and 12 gave dechlorinated spiro-cyclopropanes (10[9] and 13[10]). A 2-*C*-methylenehexopyranoside 14[11] gave the spiro-dichlorocyclopropane but it could not be converted into the di-*C*-methyl derivative. Thus the hydrogenolytic cleavage of spiro-cyclopropane derivatives was especially sensitive to steric factor.

Introduction of *gem*-dimethyl group to C-4 and C-2 positions of hexopyranosides was achieved by the Michael addition of lithium dimethylcuprate[12] to the methyl branched enolones. Methyl 3,4-dideoxy-4-*C*-methyl-6-*O*-trityl-α-D-*glycero*-hex-3-enopyranosid-2-ulose (15)[13] was treated with lithium dimethylcuprate (diethyl ether, 0 °C, 4 h) or mixed lithium dimethyl cyanocuprate (diethyl ether, -78 °C, 4 h) to give 4,4-di-*C*-methyl-2-ulose (16) in 82% or 93% yield, respectively, ^{1}H NMR($CDCl_3$):δ 4.58(s, H-1), 1.96(dd, *J* 1.0 and 14.2 Hz, H-3a), 2.64(d, H-3e), 1.76 and 1.78(each broad s, CMe). Recovery of asymmetric carbons lost during formation of the enolones was also achieved by

hydroboration reaction of its silyl enolate. Addition of cholorotrimethylsilane (hexamethylphosphoric triamide, triethylamine, -50-0 °C)[14] directly to the reaction solution of 15 with lithium dimethylcuprate gave the silyl enolate (17). Hydroboration[15] [sodium borohydride, cobalt(II) chloride, tetrahydrofuran, room temperature, overnight] of 17 followed by oxidation (30% H_2O_2, 15% aqueous sodium hydroxide, dichloromethane-methanol, reflux, 1 h) and acetylation gave the corresponding D-*xylo* (18) and D-*arabino* (19) isomers in the ratio of 2:1 (55%), 18: $[\alpha]_D$ +91.5° ($CHCl_3$), ^1H NMR($CDCl_3$):δ 4.42(d, *J* 4.0 Hz, H-1), 0.88 and 0.90(each s, CMe), 3.60(s, OMe); 19: $[\alpha]_D$ +113° ($CHCl_3$), ^1H NMR($CDCl_3$):δ 4.60(d, *J* 1.2 Hz, H-1), 0.82 and 0.86(each s, CMe), 3.64(s, OMe).



16 15 17 18 R^1=H,R^2=OAc
19 R^1=OAc,R^2=H



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Furthermore, 2-*C*-methyl-hex-2-enopyranosid-4-ulose analog (20)[16] was converted into 2,2-di-*C*-methyl-4-ulose (21) (75%), ^1H NMR($CDCl_3$):δ 4.36(s, H-1), 2.08(d, *J* 15.4 Hz, H-3a), 2.50(d, H-3e), 0.94 and 1.18(each s, CMe); ^{13}C NMR($CDCl_3$):ppm 103.1(C-1), 23.8 and 25.2(CMe). Hydroboration of its trimethylsilyl enolate (22) followed by acetylation gave D-*arabino* isomer (23) selectively in 51% yield, $[\alpha]_D$ +151° ($CHCl_3$), ^1H NMR ($CDCl_3$): δ 5.16 (s, H-1), 5.22 (d, *J* 8.0 Hz, H-3), 0.96 and 1.12 (each s, CMe), 3.38 (s, OMe). Thus this method proved to be useful as an alternative and complementary one for construction of *gem*-dimethyl group in hexopyranoside ring.

References

1) S. F. Martin, *Tetrahedron*, 36, 419(1980).

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Szarek, *Carbohydr. Res.*, 67, C17(1978).

3) S. Nagarajan and K. L. Rinehart, Jr., *J. Org. Chem.*, 50, 380(1985).

4) Prepared by treatment of the corresponding ulose with Ph_3PMeBr and BuLi in 60% yield. ^1H NMR($CDCl_3$): δ 4.12(d, *J* 3.5 Hz, H-1), 5.26 and 5.32(each dd, *J* 1.5 and 3.3 Hz, H-3'a and H-3'b).

5) The configuration of C-3 was deduced assuming the attack of the carbene from the less sterically hindered site as reported for the reactions of the corresponding ulose: Y. Kondo, *Agr. Biol. Chem.*, 39, 2251 (1975).

6) Syrup, $[\alpha]_D$ +49,9° ($CHCl_3$), ^1H NMR ($CDCl_3$): δ 4.62 (d, *J* 1.8 Hz, H-1), 3.18 (d, H-2), 4.70 (d, *J* 9.2, H-4), 1.04 and 1.24 (each s, CMe).

7) Prepared by the Wittig methylenation of the corresponding ulose in 74% yield.

8) Prepared by the Wittig methylenation of the corresponding ulose in 69% yield. ^1H NMR ($CDCl_3$): δ 4.06 (broad d, *J* 6.2 Hz, H-3), 5.08 and 5.16 (each broad s, H-4'a and H-4'b).

9) ^1H NMR ($CDCl_3$): δ 3.60 (d, *J* 7.2 Hz, H-3), 0.6-1.2 (m, 4 H, CH_2CH_2).

10) ^1H NMR ($CDCl_3$): δ 3.84 (d, *J* 6.0 Hz, H-3), 0.6-1.2 (m, 4 H, CH_2CH_2).

11) Prepared from methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-*arabino*-hexopyranosidulose by methylenation (Ph_3PMeBr, BuLi), de-*O*-benzoylation and methylthiomethylation (DMSO, AcOH) in 35% yield(3 steps). ^1H NMR($CDCl_3$): δ 5.00(s, H-1), 5.16 and 5.32(each dd, *J* 1.6 and 2.2 Hz, H-2'a and H-2'b).

12) M. B. Yunker, D. E. Plaumann, and B. Fraser-Reid, *Can. J. Chem.*, 55, 4002(1977).

13) Prepared from methyl 2,3-dideoxy-6-*O*-trityl-α-D-*glycero*-hex-2-enopyranosid-4-ulose by 1,2-addition of methyl carbanion(MeLi, $CeCl_3$) and successive 1,3-hydroxyl migration(pyridinium chlorochromate). A similar conversion was reported for the corresponding ethyl glycoside: B. J. Fitzsimmons, D. E. Plaumann, and B. Fraser-Reid, *Tetrahedron Lett.*, 1979, 3925.

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16) Prepared from methyl 2,3-dideoxy-2-*C*-methyl-α-D-*erythro*-hex-2-enopyranoside by tritylation and oxidation. A similar conversion was reported for the corresponding de-*O*-tritylated compound: D. R. Hicks and B. Fraser-Reid, *Can. J. Chem.*, 53,2017(1975).

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