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Preliminary communication

Geminal alkylation in carbohydrate chemistry. Conversion of L-glutamic acid into *gem*-di-*C*-methyl carbohydrate derivatives, and synthesis of 6-chloro-9-(5,5-dimethylfuran-2-yl)purine

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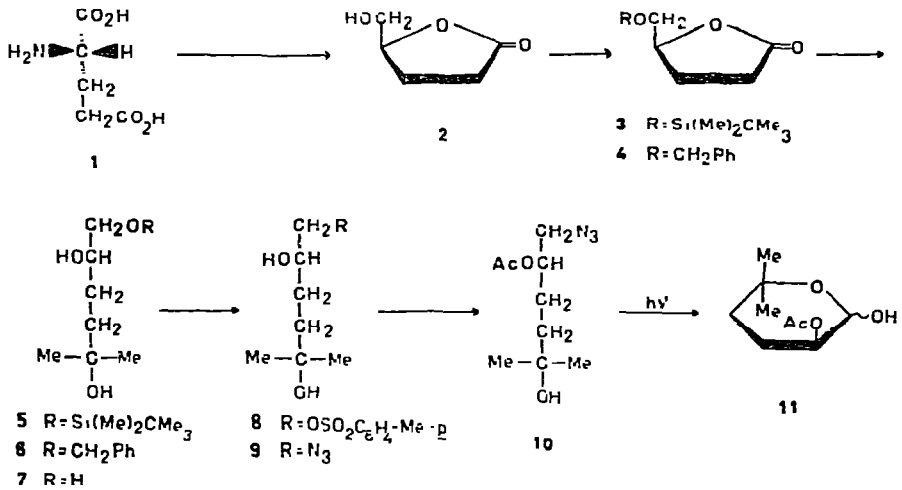
During the past two decades, the synthetic chemistry of branched-chain sugars has developed very rapidly[1]; many of these sugars have been found in antibiotics[1a], and some nucleoside derivatives[2] have exhibited biological activity. A few naturally occurring antibiotics contain components which belong to a special and rare class of branched-chain sugars, namely, that of *gem*-di-*C*-alkyl derivatives; these antibiotics include novobiocin[3] and chlorobiocin, coumermycin A-1 (ref. 5) and coumermycin A-2 (ref. 6), antibiotic X-5108 (goldinomycin)[7], mocimycin (kirromycin)[8], and efrotomycin[9]. Recently, the synthesis of a nucleoside in which the carbohydrate moiety contains a *gem*-di-*C*-(hydroxymethyl) grouping was reported[10]. At the present time, there is a dearth of examples of the synthesis[11] of *gem*-di-*C*-alkyl carbohydrate derivatives. However, in recent years, several elegant synthetic methods for geminal alkylation at a carbonyl carbon atom have been developed[12]; these are of potential utility in the carbohydrate field. Here, we describe the conversion of L-glutamic acid into *gem*-di-*C*-methyl carbohydrate derivatives, and the synthesis, from one of them, of a nucleoside, namely, 6-chloro-9-(5,5-dimethylfuran-2-yl)purine (**13**).

The lactone alcohol **2** was prepared from L-glutamic acid (2-amino-2,3,4-trideoxy-L-*glycero*-pentaric acid; **1**) by the method described by Taniguchi *et al.*[13], which involves deamination of the amino acid to give, after esterification, 2,3-dideoxy-D-*glycero*-pentaro-1,4-lactone 5-ethyl ester, which was reduced with sodium borohydride in ethanol to afford 2,3-dideoxy-D-*glycero*-pentono-1,4-lactone (**2**) (see Scheme 1). The hydroxyl group in **2** could be protected by conversion of **2** into the known[13] benzyl ether **4** or the *tert*-butyldimethylsilyl[14] derivative **3**. Compound **3** had b.p. 80°/1.0 torr and $[\alpha]_D^{23}$ +5.2° (*c* 2.1, chloroform). Treatment of **3** with methylmagnesium iodide in diethyl ether for 1 h at room temperature gave the monosilylated triol **5** in 70% yield; m.p. 65–67°, $[\alpha]_D^{23}$ +2.8° (*c* 2.5, chloroform); ν_{max}^{Nujol} 3333 cm^{-1} (OH), no C=O absorption. Similarly, treatment of **4** under the same Grignard conditions afforded the corresponding monobenzylated triol **6** in 74% yield; b.p. 83°/~1.0 torr, $[\alpha]_D^{23}$ –4.6° (*c* 2.8, methanol); ν_{max}^{film} 3430 cm^{-1} (OH), no C=O absorption. Removal of the protecting group in **5** by the use of tetrabutylammonium fluoride in tetra-



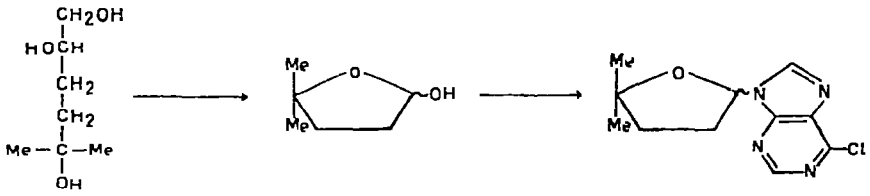
Scheme 1

hydrofuran, or in **6** by hydrogenolysis in methanol over 10% palladium-on-carbon, yielded the free triol **7** as a colorless syrup; $[\alpha]_D^{23}$ −11.6° (*c* 1.7, methanol). Thus, the key intermediate **7** can be conveniently prepared by either of these two routes; however, for large-scale syntheses, that employing the *tert*-butyldimethylsilyl protecting group is more expensive. Treatment of **7** with 1.1 equivalents of *p*-toluenesulfonyl chloride in pyridine for 22 h at room temperature afforded compound **8** as white needles in 40% yield; m.p. 94–95°, $[\alpha]_D^{23}$ −2.2° (*c* 2.2, methanol). Displacement of the *p*-tolylsulfonyloxy group in **8** by treatment with sodium azide in boiling *N,N*-dimethylformamide for 24 h under reflux afforded the azide **9** as a colorless oil in 60% yield; $[\alpha]_D^{23}$ −10° (*c* 2.2, chloroform); R_F 0.43 [t.l.c.* in 2:1 (v/v) ethyl acetate–petroleum ether]. The secondary hydroxyl group in **9** could be selectively acetylated with acetic anhydride–pyridine during 18 h at room temperature, to give 2-*O*-acetyl-1-azido-1,3,4,6-tetradeoxy-5-*C*-methyl-L-*glycero*-hexitol (**10**) as a colorless oil in 87% yield; $[\alpha]_D^{23}$ −8.2° (*c* 3.3, chloroform); R_F 0.56 [3:2 (v/v) ethyl acetate–petroleum ether]; ν_{max}^{film} 3472 (OH), 2105 (N_3), and 1745 cm^{-1} (C=O); p.m.r. data† (chloroform-*d*): δ 6.70 (2-proton, AB portion of ABX pattern, H-1,1′), 5.20–4.70 (m, 1H, H-2), 2.05 (s, 3 H, OAc), 1.75–1.35 (5 H, H-3,3′, H-4,4′, OH), and 1.20 (s, 6 H, 2 Me). Irradiation of a solution of **10** in benzene under nitrogen with u.v. light‡ for 6 h at room temperature afforded 2-*O*-acetyl-3,4,6-trideoxy-5-*C*-methyl-L-*glycero*-hexose (**11**) as a colorless syrup in 51% yield; b.p. 80°/2.0 torr; $[\alpha]_D^{23}$ +17.6° (*c* 2.5, chloroform); R_F 0.21 [1:3 (v/v) ethyl acetate–petroleum ether]; ν_{max}^{film} 3430 (OH) and 1745 cm^{-1} (C=O). A salient feature of the synthesis is that the chirality of the starting material **1** is preserved at C-2 in the final product **11**.

*T.l.c. was performed with Silica Gel G; the term "petroleum ether" refers to the fraction having b.p. 60–80°.

†P.m.r. spectra were recorded at 60 MHz with tetramethylsilane as the internal standard.

‡Irradiation was performed with a 450-W, Hanovia, medium-pressure, mercury-arc lamp (Cat. No. 679A-36) contained in a water-cooled, quartz immersion-well; a Vycor 7010 filter-sleeve was employed. The whole assembly was mounted in a borosilicate glass reaction-vessel.



7 12 13

Scheme 2

The triol **7** was also a key intermediate in the synthesis of a *gem*-di-*C*-methyl derivative resembling a carbohydrate, namely, 5,5-dimethyl-2-furanol (**12**, see Scheme 2). Thus, oxidation of **7** with sodium metaperiodate readily afforded **12** as a colorless liquid; R_F 0.77 (ethyl acetate); ν_{max}^{film} 3448 (OH) and 1739 cm^{-1} (vw, C=O); p.m.r. data (chloroform-*d*): δ 5.10 (bs, 1 H, H-1), 4.20–3.10 (m, 2 H, 2 H-2), 3.40–1.70 (3 H, 2 H-3, OH), and 1.70–1.00 (6 H, CMe_2). The observation of a very weak, C=O absorption in the i.r. spectrum is indicative of the presence of a trace of the acyclic tautomer. Treatment of **12** with 6-chloropurine, diethyl azodicarboxylate, and methyldiphenylphosphine in tetrahydrofuran for 24 h at room temperature gave 6-chloro-9-(5,5-dimethylfuran-2-yl)purine (**13**) as colorless needles in 54% yield, m.p. 62–63°; R_F 0.52 (ethyl acetate); λ_{max}^{EtOH} 263 nm (ϵ_{mM} 7.30); p.m.r. data (chloroform-*d*): δ 8.76 and 8.32 (2 s, 1 H each, H-2 or H-8), 6.40 (1-proton apparent t, H-2′), 3.10–180 (4 H, 2 H-2′, 2 H-3′), 1.47–1.35 (6 H, CMe_2). The conversion of **12** into **13** is another example of the application of the method[15] recently developed for the synthesis of nucleosides by direct replacement of the anomeric hydroxyl group.

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REFERENCES

1 (*a*) J. S. Brimacombe, *Angew. Chem. Int. Ed. Engl.*, 10 (1971) 236–248; (*b*) H. Grisebach and R. Schmid, *ibid.*, 11 (1972) 159–173; (*c*) W. A. Szarek, *MTP Int. Rev. Sci. Org. Chem. Ser. One*, 7 (1973) 85–90; (*d*) W. A. Szarek and D. M. Vyas, *ibid.*, 7 (1976) 105–108.
2 E. Walton, S. R. Jenkins, R. F. Nutt, M. Zimmerman, and F. W. Holly, *J. Am. Chem. Soc.*, 88 (1966) 4524–4525; J. M. J. Tronchet, J. Tronchet, and R. Graf, *J. Med. Chem.*, 17 (1974) 1055–1059.
3 C. H. Shunk, C. H. Stammer, E. A. Kaczka, E. Walton, C. F. Spencer, A. N. Wilson, J. W. Richter, F. W. Holly, and K. Folkers, *J. Am. Chem. Soc.*, 78 (1956) 1770–1771.
4 L. Ninet, F. Benazet, Y. Charpenite, M. Dubost, J. Florent, D. Mancy, J. Preud'Homme, T. L. Threfall, B. Vuillemin, D. E. Wright, A. Abraham, M. Cartier, N. de Chezelles, C. Godard, and J. Theilleux, *C. R. Acad. Sci., Ser. C*, 275 (1972) 455–458; L. Dolak, *J. Antibiot.*, 26 (1973) 121–125.

5 H. Kawaguchi, T. Naito, and H. Tsukiura, *J. Antibiot. Ser. A*, 18 (1965) 11–25.
6 H. Kawaguchi, T. Miyaki, and H. Tsukiura, *J. Antibiot. Ser. A*, 18 (1965) 220–222.
7 H. Maehr, T. H. Williams, M. Leach, and A. Stempel, *Helv. Chim. Acta*, 57 (1974) 212–213; H. Maehr, M. Leach, T. H. Williams, W. Benz, J. F. Blount, and A. Stempel, *J. Am Chem. Soc.*, 95 (1973) 8448–8449; H. Maehr, J. F. Blount, R. H. Evans, Jr., M. Leach, J. W. Westley, T. H. Williams, A. Stempel, and G. Buechi, *Helv. Chim. Acta*, 55 (1972) 3051–3054.
8 H. Maehr, M. Leach, L. Yarmchuk, and A. Stempel, *J. Am. Chem. Soc.*, 95 (1973) 8449–8450.
9 R. Wax, W. Malese, R. Weston, and J. Birnbaum, *J. Antibiot.*, 29 (1976) 670–673.
10 D. L. Leland and M. P. Kotick, *Carbohydr. Res.*, 38 (1974) C9–C11.
11 B. P. Vaterlus, J. Kiss, and H. Spiegelberg, *Helv. Chim. Acta*, 47 (1964) 381–390; R. Kuhn and D. Weiser, *Justus Liebigs Ann. Chem.*, 602 (1957) 208–217; O. Achmatowicz, Jr., P. Bukowski, B. Szechner, Z. Zwierzchowska, and A. Zamojski, *Tetrahedron*, 27 (1971) 1973–1996; O. Achmatowicz, Jr., G. Grynkiewicz, and B. Szechner, *ibid.*, 32 (1976) 1051–1054; D. J. Ward, Ph.D. Thesis, Queen's University, Kingston, 1976.
12 E. J. Corey and J. I. Shulman, *J. Am. Chem. Soc.*, 92 (1970) 5522–5523; G. Andrews and D. A. Evans, *Tetrahedron Lett.*, (1972) 5121–5124; B. M. Trost and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, 95 (1973) 2038–2040; B. M. Trost and M. Preckel, *ibid.*, 95 (1973) 7862–7864; G. H. Posner and D. J. Brunelle, *J. Org. Chem.*, 38 (1973) 2747–2756; J. P. Nallet, R. Barret, C. Aranaud, and J. Huet, *Tetrahedron Lett.*, (1975) 1843–1844.
13 M. Taniguchi, K. Koga, and S. Yamada, *Tetrahedron*, 30 (1974) 3547–3552.
14 E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 94 (1972) 6190–6191.
15 W. A. Szarek, C. Depew, H. C. Jarrell, and J. K. N. Jones, *J. Chem. Soc. Chem. Commun.*, (1975) 648–649.