Carbohydrate Research, 158 (1986) c1–c4
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

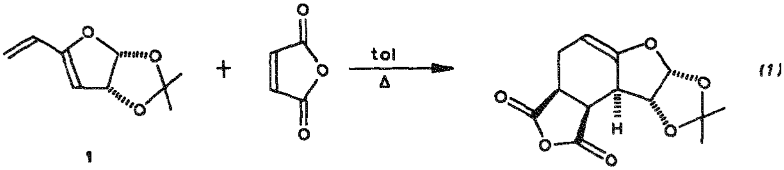
Preliminary communication

Synthesis and Diels–Alder reactions of dieno-pyranosides

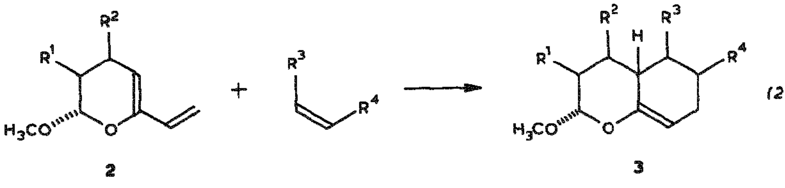
ROBERT M. GIULIANO AND JOHN H. BUZBY
Department of Chemistry, Villanova University, Villanova, PA 19085 (U.S.A.)

(Received June 9th, 1986; accepted for publication in revised form, August 1st, 1986)

The use of carbohydrates and their derivatives as starting materials for the synthesis of enantiomerically pure, non-carbohydrate compounds continues to be an area of active investigation. In most applications of the Diels–Alder reaction to carbohydrate substrates, it is the dienophile which is derived from the carbohydrate, and the so-called annulated sugars obtained are suitable precursors to a variety of carbocyclic compounds[1]. Recent studies have shown that dienes derived from carbohydrates can undergo the Diels–Alder reaction with high stereoselectivity, as exemplified by the reactions of dieno-furanoside[2] **1** and related systems[3] with maleic anhydride (Eq. *1*).



Diels–Alder reactions of analogous, six-membered dieno-pyranosides **2**, a logical extension of the five-membered-ring cases, have not been reported, and we decided to investigate the synthesis and Diels–Alder reactions of dienes of this type. The depth of existing methodology for the synthesis of carbohydrate derivatives in their pyranose form, and the variety of potential dienophiles, suggested that a versatile route to annulated pyranosides of general structure **3** could be developed by using Diels–Alder reactions of **2** (Eq. *2*). In addition, functionalized

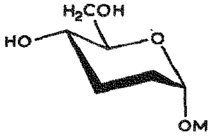


0008-6215/86/$ 03.50

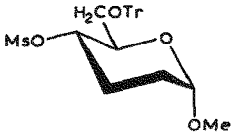
decalones might be derivable from the Diels–Alder adducts by a reaction sequence consisting of oxidation of **3** to the enol lactone followed by transformation of the pyranoid ring into a carbocyclic ring by nucleophilic ring-opening–ring-closure[4].

We now describe the synthesis and Diels–Alder reactions of dienopyranosides **8** and **9**.

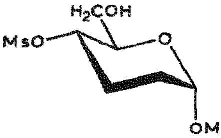
Methyl 2,3-dideoxy-α-D-*erythro*-hexopyranoside[5] **4** was prepared in 80% overall yield from tri-*O*-acetyl-D-glucal by the Ferrier reaction followed by de-esterification (triethylamine–methanol–water) and hydrogenation (10% Pd–C, methanol). Successive treatment of **4** with chlorotriphenylmethane and methanesulfonyl chloride in pyridine gave **5**, from which the trityl group was removed by hydrolysis with 0.175% sulfuric acid in 1:1 methanol–dichloromethane



4



5



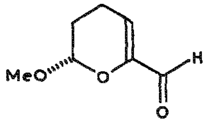
6

at room temperature, to give **6** in 50% overall yield. Oxidation of **6** and elimination were achieved in a single step with the sulfur trioxide–pyridine complex[6] in Me_2SO and triethylamine, to give enal **7*** in 53% yield. (Selective oxidation of the primary hydroxyl group of **4** would shorten the synthesis of **7**; however, we were unable to carry out this transformation successfully.) Wittig alkenation of **7** was conducted in THF, using sodium hexamethyldisilazide as the base and methyltriphenylphosphonium bromide, to give diene **8** in 50% yield after purification by column chromatography (Florisil, petroleum ether). Other bases and solvents (NaH–Me_2SO, BuLi–ether) gave lower yields of **8** in the Wittig reaction. The synthesis of diene **9** was achieved in a similar manner. Methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside[7] was prepared as described, and methylated (methyl iodide, sodium hydride, THF, room temperature), to give **10**. Hydrogenolysis of the benzylidene group gave diol **11**, which was converted into **9** in 30% overall yield, using the sequence described above for the synthesis of **8**.

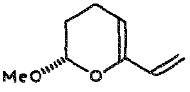
The reaction of **8** with an excess of maleic anhydride in refluxing benzene gave a near-equal mixture of two products which were inseparable by flash chromatography. The vinyl-proton resonance expected was absent from the ^1H-n.m.r. spectrum of the mixture; however, the ^{13}C-n.m.r. spectrum exhibited two sets of alkene-carbon resonances. N.m.r.-spectral data and elemental analysis were consistent with the structure assigned for **12**. Double-bond migration to the more highly substituted position occurred under the conditions of the Diels–Alder reaction. This type of rearrangement has been observed[8] in the intramolecular

---

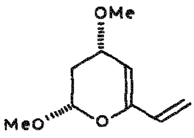
*Compounds **7**, **8**, **9**, and **12** (X=0) gave satisfactory, high-resolution mass spectra. Satisfactory elemental (combustion) analyses were obtained for all other new compounds.



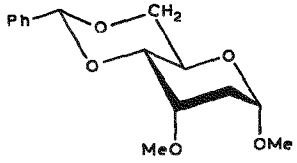
7



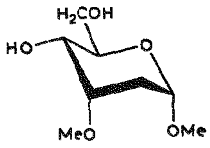
8



9

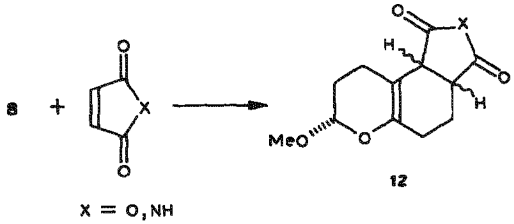


10

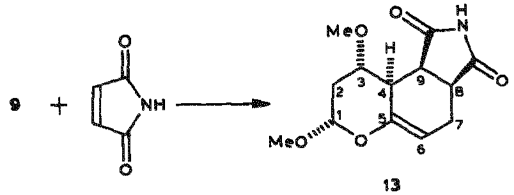


11

Diels–Alder reaction of a carbohydrate derivative. In the case of **8**, facial selectivity in the addition of the dienophiles could not be determined because the stereocenter at C-4 in **12** (carbohydrate numbering) was destroyed in the rearrangement. The same result was obtained when **8** reacted with maleimide; however, treatment of diene **9** with maleimide under identical conditions (3 equiv. in refluxing benzene for 3 h) gave a single crystalline product (**13**); m.p. 121–123°, $[\alpha]_D^{20}$ +207° (c 0.29, benzene); ν_{max}^{KBr} 3160 (NH), 3080, 1774 (C=O), 1712 (C=O), and 1670 cm^{-1} (C=C); ^{1}H-n.m.r. (200 MHz, C_6D_6): δ 7.64 (bs, 1 H, N-*H*), 5.02 (ddd, 1 H, $J_{6,7e}$ 7.8, $J_{6,7a}$ 2.6, $J_{4,6}$ 3.3 Hz, H-6), 4.55 (dd, 1 H, $J_{1,2a}$ 7.8, $J_{1,2e}$ 5.6 Hz, H-1), 4.31 (ddd, 1 H, $J_{2a,3}$ 12.0, $J_{2e,3}$ 4.2, $J_{3,4}$ 10.1 Hz, H-3), 3.29 (s, 3 H, OCH_3-1), 3.17 (s, 3 H, OCH_3-4), 2.90 (dd, 1 H, $J_{8,9}$ 8.8, $J_{4,9}$ 6.2 Hz, H-9), 2.45 (ddd, 1 H, $J_{7a,7e}$ 15.2, H-7*a*), 2.32 (ddd, 1 H, $J_{2a,2e}$ 13.1 Hz, H-2*e*), 2.24 (ddd, 1 H, $J_{7a,8}$ 7.4, $J_{7e,8}$ 1.6 Hz, H-8), 2.08



12



13

(dddd, 1 H, $J_{4,7e}$ 1.8 Hz, H-4), 1.54 (dddd, 1 H, H-7*e*), and 1.39 (ddd, 1 H, H-2*a*); ^{13}C-n.m.r. (50.3 MHz, C_6D_6): δ 178.9 (C=O), 177.6 (C=O), 151.0 (C-5), 100.0 (C-6), 99.6 (C-1), 70.8 (C-3), 55.6 (OCH_3), 54.6 (OCH_3), 41.6 (C-4), 41.0 (C-8/9), 40.9 (C-9/8), 34.4 (C-2), and 22.8 (C-7).

Anal. Calc. for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.20; H, 6.33; N, 5.26.

The product was obtained in 53% yield after purification by column chromatography (Florisil, 1:1 ethyl acetate–petroleum ether). Of the four possible products corresponding to *endo vs. exo* addition of the dienophile to the α- or β-face of the diene, the structure of compound **13**, which results from the *endo* addition of maleimide to the β-face of **9**, is most consistent with the ^{1}H-n.m.r. data. The large value (10.1 Hz) of $J_{3,4}$ implies a *trans*-diaxial relationship for H-3 and H-4 which would exist in the two possible products resulting from β-face addition, but not in those produced by addition from the alternative α-face. The value of 6.2 Hz for $J_{4,9}$ is consistent[2] with a *cis* relationship for H-4 and H-9 which results from *endo* addition. Migration of the double bond was not observed during Diels–Alder reactions of **9**, presumably because of the added steric requirement of the 3-substituent, which would encounter an unfavorable interaction with a carbonyl group at C-9 were C-3 and C-9 forced to be coplanar. Selectivity for addition to the β-face of **9** is not surprising, as the α-face is blocked by two axial methoxyl groups. We consider that the chirality of C-3 should have a greater influence on the stereochemical course of the reaction, as C-3 is attached directly to a terminal carbon atom of the diene.

REFERENCES

1 B. Fraser-Reid, *Acc. Chem. Res.*, 18 (1985) 347–354, and references cited therein; D. Horton, T. Machinami, and Y. Takagi, *Carbohydr. Res.*, 121 (1983) 135–161.
2 K. M. Sun, B. Fraser-Reid, and T. F. Tam, *J. Am. Chem. Soc.*, 104 (1982) 367–369.
3 K. M. Sun, R. M. Giuliano, and B. Fraser-Reid, *J. Org. Chem.*, 50 (1985) 4774–4780.
4 C. A. Henrick, E. Bohme, J. A. Edwards, and J. H. Fried, *J. Am. Chem. Soc.*, 90 (1968) 5926–5927; K. R. Becker, *Tetrahedron*, 36 (1980) 1717–1745.
5 R. J. Ferrier and N. Prasad, *J. Chem. Soc. C*, (1969) 570–575.
6 G. M. Cree, D. W. Mackie, and A. S. Perlin, *Can. J. Chem.*, 47 (1969) 511–512.
7 A. Rosenthal and P. Catsoulacos, *Can. J. Chem.*, 46 (1968) 2868–2873.
8 B. Fraser-Reid, Z. Benko, R. Giuliano, K. M. Sun, and N. Taylor, *J. Chem. Soc., Chem. Commun.*, (1984) 1029–1030.