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The Synthesis of Pseudo-Sugar Disaccharides: A Diels–Alder Approach to Monocarba-Disaccharides

David S. Larsen,* and Nicholas S. Trotter

Department of Chemistry, University of Otago, P.O. Box 56, Dunedin, New Zealand

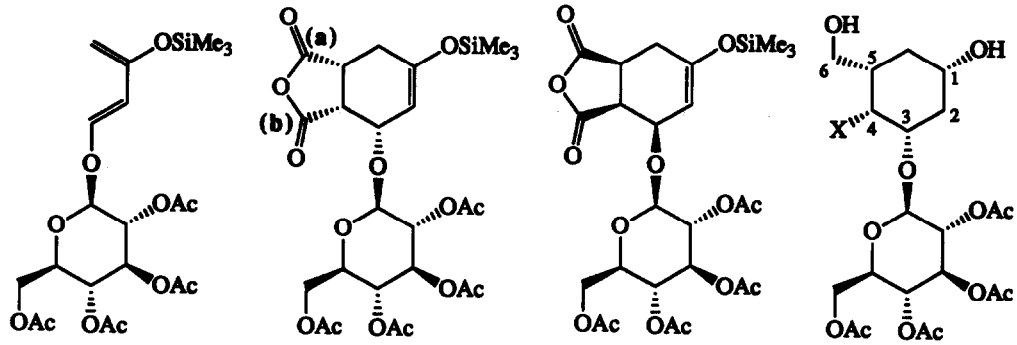
Richard J. Stoodley

Department of Chemistry, UMIST, P.O. Box 88, Manchester M60 1QD, U.K.

Abstract: *A direct approach to the synthesis of pseudo-sugar disaccharides employing the Diels–Alder reaction of a dienyl glycoside and maleic anhydride as a key step is described. Cycloadduct (2), obtained from diene (1), was transformed into the monocarba-disaccharide (11) in 26% overall yield using a seven-step procedure.*

Pseudo-sugars are compounds in which the ring oxygen of a furanoid or pyranoid sugar is replaced by a methylene group.[1] Because of their structural similarity to the parent carbohydrates they have been expected to possess interesting biological activities. Indeed, pseudo-α-D-galactopyranose—a naturally occurring pseudo-monosaccharide—is endowed with antibiotic properties, pseudo-β-DL-glucopyranose is as sweet as D-glucose, and pseudo-α-DL-glucopyranose is effective in inhibiting glucose stimulated release of insulin and has islet glucokinase activity.[1,2] Many synthetic routes have been developed for the synthesis of pseudo-monosaccharides in racemic and enantiomerically pure forms.[1] However, less attention has been focussed on the synthesis of monocarba-disaccharides (disaccharides containing one pseudo-sugar residue). Relatively small numbers of this type of pseudo-oligosaccharide have been synthesised and linear strategies utilising coupling and glycosylation reactions have usually been employed.[1,3] We felt that a direct approach using the asymmetric Diels–Alder reaction of dienyl glycosides with maleic anhydride could lead to an efficient and highly versatile synthesis of such compounds.

Carbohydrate-based diene systems have been shown to exhibit high diastereofacial selectivity in their reactions with cyclic dienophiles.[4] The diene (1) reacted with maleic anhydride in benzene to give a 6:1 mixture of the two cycloadducts (2) and (3). Trituration of the crude mixture with diethyl ether afforded (2) in a 57% yield on an *ca.* 50 mmol scale in this study. It was envisaged that the cycloadduct (2) would serve as a precursor of monocarba-disaccharides. Appropriate functionalisation of the carbocyclic ring could lead to 1,1-, 1,3- and 1,4- glycosidically linked systems. This paper describes our initial efforts which were directed towards the synthesis of a monocarba-disaccharide containing a 4-amino-2,4-dideoxy pseudo-sugar residue coupled to glucose *via* a β-1,3-glucosidic linkage.

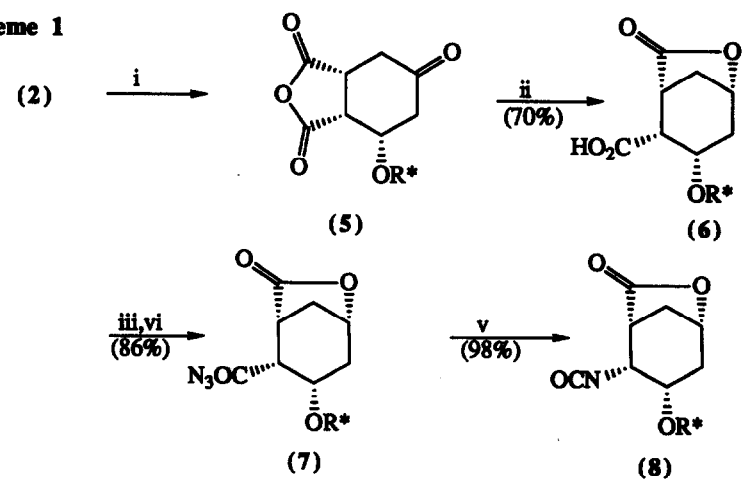


(1) (2) (3) (4)

The strategy employed would depend on the ability to chemically distinguish the two carboxyl groups of the anhydride functionality of (2). Reduction at site (a) followed by a decarboxylative procedure with introduction of heteroatom functionality at site (b) would give rise to a compound of type (4) with the desired carbocyclic skeleton.

The initial pathway for these transformations is shown in Scheme 1. Acidic hydrolysis of the silyl enol ether moiety of (2) using a catalytic amount of concentrated hydrochloric acid in chloroform gave the ketone (5). Differentiation of the carboxyl groups of (5) was easily effected by treatment with sodium cyanoborohydride in acetic acid to give the lactonic acid (6)[5] in a 70% yield after recrystallisation. Treatment of the acid chloride derived from (6) with sodium azide in anhydrous THF gave the corresponding acyl azide (7). Subsequent heating at reflux in benzene resulted in a Curtius rearrangement with retention of stereochemistry at C-4 to give the isocyanate (8) in a 98% yield.

Scheme 1

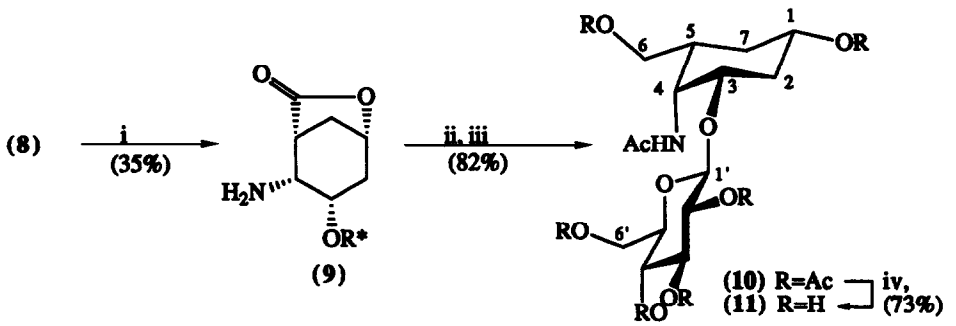


R* =2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl

Reagents: i Ätalytic c HCl, $CHCl_3$; ii, $NaCNBH_3$, HOAc; iii, $(COCl)_2$, DMF, CH_2Cl_2; iv, NaN_3, THF; v, Δ, benzene, 2 h.

It was envisaged that reduction of both the isocyanate and lactone groups of (8) would give after acetylation a protected monocarba-disaccharide. However, treatment of (8) with excess lithium aluminium hydride in refluxing THF followed by acetylation resulted in a low mass recovery of material. An alternative protocol involved hydrolysis of the isocyanate (8) to the amine (9). This also proved problematical and resulted in low yields. The best result was obtained by treatment of (8) with an equimolar amount of triethylamine in aqueous THF which gave the amine (9) in a 35% yield. The problem with the conversion of (8) into (9) appeared to be competing hydrolysis of the acetate and lactone functionalities. Subsequent reduction of (9) with lithium aluminium hydride in refluxing THF followed by acetylation afforded the monocarba-disaccharide (10).[6] Deprotection of (10) using the method of Pathak[7] gave the desired pseudo-disaccharide (11)[8] (Scheme 2).

Scheme 2



Reagents: i, NEt_3, THF, H_2O; ii, $LiAlH_4$, THF, Δ; iii, Ac_2O, pyridine, DMAP;
iv, IRA-400 (OH) resin, MeOH.

In conclusion, we have demonstrated that the asymmetric Diels–Alder reaction using the dienyl glucoside (1) has provided a direct and efficient route to the pseudo-sugar disaccharide (11). The availability of a wide range of dienyl glycosides makes this methodology attractive for the synthesis of pseudo-sugar disaccharides and further work is underway extending the procedure to the synthesis of 1,1- and 1,4-glycosidically linked monocarba-disaccharides. Furthermore, there is a close similarity of the functionality and stereochemistry of the pseudo-sugar residue of (9) to that of kedarosamine[9] (2,4-dideoxy-4-dimethylamino-L-fucopyranose), the amino sugar component of the antitumor antibiotic kedarcidin.[10] Minor modification to our synthetic route is expected to result in an asymmetric synthesis of pseudo-kedarosamine.

References and Notes:

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3. For examples of the synthesis of monocarba-disaccharides see: (a) Paulsen, H.; von Deyn, W.; *Justus Leibigs Ann. Chem.* **1987**, 141–152; (b) Ogawa, S.; Yokoi, N.; Shibata, Y.; Chida, N.; *Carbohydr. Res.* **1988**, *181*, 57–66; (c) Ogawa, S.; Shibata, Y. *Carbohydr. Res.* **1987**, *176*, 309–315; (c) Ogawa, S.; Shibata, Y. *Carbohydr. Res.* **1987**, *170*, 116–123.

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5. The structures of new compounds were assigned on the basis of 300 MHz ^{1}H NMR, 50 or 75 MHz ^{13}C NMR, infrared and mass spectral data. All new compounds gave satisfactory elemental analyses and/or parent ion identification by high resolution mass spectrometry.

6. Selected data for (**10**):$[\alpha]_D$ = -23 (0.2%, CH_2Cl_2); δ_H ($CDCl_3$, 300 MHz) 1.12br (1 H, q, *J* 13, 13, and 13 Hz, 7-H_{ax}), 1.53br (1 H, q, *J* 12, 12, and 12 Hz, 2-H_{ax}), 1.80–1.95 (2 H, m, 5- and 7-H_{eq}), 1.97, 1.98, 2.01, 2.03, 2.04, 2.05, and 2.08 (each 3 H, 7 x s, 6 x OAc and NHAc), 2.22–2.33 (1 H, m, 2-H_{eq}), 3.70 (1 H, ddd, *J* 2.5, 5, and 10 Hz, 5'-H), 3.74–3.87 (2 H, m, 3- and 6-H), 4.06–4.16 (3 H, m, 6'- and 6-H), 4.26 (1 H, dd, *J* 5 and 12 Hz, 6'-H), 4.55br (1 H, dt, *J* 10, 4, and 4 Hz, 4-H), 4.62 (1 H, d, *J* 8 Hz, 1'-H), 4.76br (1 H, tt, *J* 11, 11, 4, and 4 Hz, 1-H), 4.91 (1 H, dd, *J* 8 and 10 Hz, 2'-H), 5.02 (1 H, t, *J* 10 and 10 Hz, 4'-H), 5.17 (1 H, t, *J* 10 and 10 Hz, 3'-H), and 5.40br (1 H, d, *J* 10 Hz, NHAc); δ_C ($CDCl_3$, 50 MHz) 20.6, 20.7, 20.9, 21.1 (6 x $OCOCH_3$), 23.2 $NHCOCH_3$), 28.6 (C-7), 34.0 (C-2), 35.8 (C-5), 46.0 (C-4), 62.0 (C-6'), 64.5 (C-6), 68.4 (C-4'), 68.6 (C-1), 71.0 (C-2'), 71.7 (C-5'), 72.6 (C-3'), 75.0 (C-3), 99.8 (C-1'), 169.5, 169.6, 170.1, 170.5, 170.7, and 171.0 (7 x CO); FABMS m/z 618 (MH^+, 25%), 307 (100%) ; Found: C, 52.23 ; H, 6.41; N, 2.20; $C_{27}H_{39}NO_{15}$ requires C, 52.51 ; H, 6.36; N, 2.27%.

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8. Selected data for (**11**):$[\alpha]_D$ = -24 (0.1%, H_2O); δ_H (D_2O, 300 MHz) 1.10br (1 H, dt, *J* 11, 14, and 14 Hz, 7-H_{ax}), 1.56 (1 H, q, *J* 12, 12, and 12 Hz, 2-H_{ax}), 1.75–1.89 (2 H, m, 5- and 7-H_{eq}), 2.07 (3 H, s, NHAc), 2.16—2.27 (1 H, m, 2-H_{eq}), 3.19 (1 H, dd, *J* 8 and 9 Hz, 2'-H), 3.31–3.52 (5 H, m, 3'-, 4'-, 5'-H and 6-H_2), 3.70 (1 H, dd, *J* 12 and 6 Hz, 6'-H), 3.79br (1 H, tt, *J* 11, 11, 4, and 4 Hz, 1-H), 3.91 (1 H, dd, *J* 12 and 2 Hz, 6'-H), 4.06 (1 H, dt, *J* 13, 4, and 4 Hz, 3-H), 4.53 and 4.56 (2 H, ovelapping t and d, *J* 4 and 4, *J* 8 Hz, 4- and 1'-H); FABMS m/z 366 (MH^+, 2%), 154 (100%); Found: C, 46.57 ; H, 7.59; N, 3.46; $C_{15}H_{27}NO_9.H_2O$ requires C, 47.11 ; H, 7.38; N, 3.66%. Reacetylation of (**11**) using pyridine and acetic anhydride gave (**10**) in a quantitative yield.

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10. Leet, J. E.; Schroeder, D. R.; Hofstead, S. J.; Matson, J. A.; Golik, J; Colson, K. L.; Klohr, S. E.; Doyle, T. W.; Matson J. A. *J. Am. Chem. Soc.*, **1992**, *114*, 7946–7948.

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