Available online at www.sciencedirect.com

Tetrahedron Letters 45 (2004) 835–837

Tetrahedron Letters

Evidence on the structure of coyolosa. Synthesis of 6,6′-ether linked hexoses

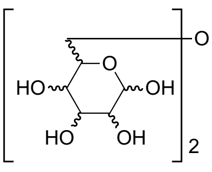
Alan H. Haines*

Centre for Carbohydrate Chemistry, School of Chemical Sciences and Pharmacy, University of East Anglia, Norwich NR4 7TJ, UK

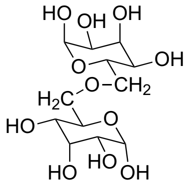
Received 29 September 2003; revised 21 October 2003; accepted 6 November 2003

Abstract—The structure previously reported for coyolosa, a hypoglycemic substance isolated from natural sources, as a 6,6′-ether linked pseudo-disaccharide derived from allose, is incorrect since 6-*O*-(6-deoxy-D-allos-6-yl)-D-allose **10**, synthesised by an unequivocal route, and its derived peracetate **11**, both have spectral properties, which differ from those reported for coyolosa and its peracetate. A versatile synthesis has been developed for this type of compound, containing two carbohydrate moieties joined through an ether linkage at their primary centres, which involves the displacement of a primary carbohydrate triflate with a carbohydrate alkoxide, and it allows the preparation of both symmetrical and unsymmetrical representatives of this class of compound.

Considerable interest has been raised by the report[1] of a new hypoglycemic compound that was isolated by methanol extraction of the *Acrocomia mexicana* root. The active compound was termed 'coyolosa' and on the basis of elemental and spectral analysis a structure was suggested as comprising two hexopyranose units joined through an ether link at their 6-positions, which can be represented by the general formula **1**. Only one set of signals for H-1 to H-6 and C-1 to C-6 were observed in the ^{1}H and ^{13}C NMR spectra, respectively, indicating either identical or enantiomeric related sub-units. The structure **2** drawn in the original publication depicts the ether-linked pseudo-disaccharide with D- and L-allopyranose moieties, an unusual combination, but a D- and D- or an L- and L-combination would also satisfy the NMR data in a nonchiral solvent. Unfortunately, no optical rotation data were given for coyolosa, measurements which would have ruled out the D- and L-combination if optical activity had been observed. Furthermore, there is some confusion in the report[1] regarding the solvent used for measurement of the NMR spectrum of coyolosa (DMSO being given in the text and $CDCl_3$ in Table 1), and in the reporting of the chemical shifts and coupling constants in the ^{1}H NMR spectrum. Therefore, in order to confirm the proposed structure of coyolosa, or to throw light on alternatives, a synthesis of the 6,6′-ether linked *allo*-isomer was undertaken; the availability of the synthetic compound should allow a direct comparison with the natural material.[2]



1



2

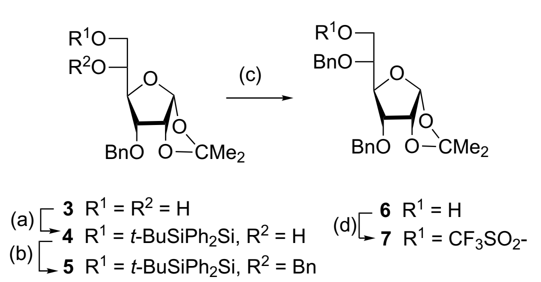
The most direct method for forging the 6,6′-linkage is direct displacement of a suitably protected 6-triflate of D-allose with the alkoxide of the corresponding alcohol. 3-*O*-Benzyl-1,2-di-*O*-isopropylidene-α-D-allofuranose (Scheme 1, **3**)[3] was prepared from 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose[4] by sequential *O*-benzylation and partial hydrolysis. Treatment of **3** with *tert*-butyldiphenylsilyl chloride gave the 6-*O*-silyl derivative **4**,[5] benzylation of which gave the 3,5-di-*O*-benzyl derivative **5**. Removal of the silyl protecting group in **5** afforded the 6-hydroxy compound **6**, which gave the 6-triflate **7** on treatment with triflic anhydride. Reaction of the sodium

---

Keywords: Coyolosa; *Acrocomia mexicana*; Ether-linked sugars; Hypoglycemic.

* Fax: +44-1603-592-015; e-mail: a.haines@uea.ac.uk

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.11.033

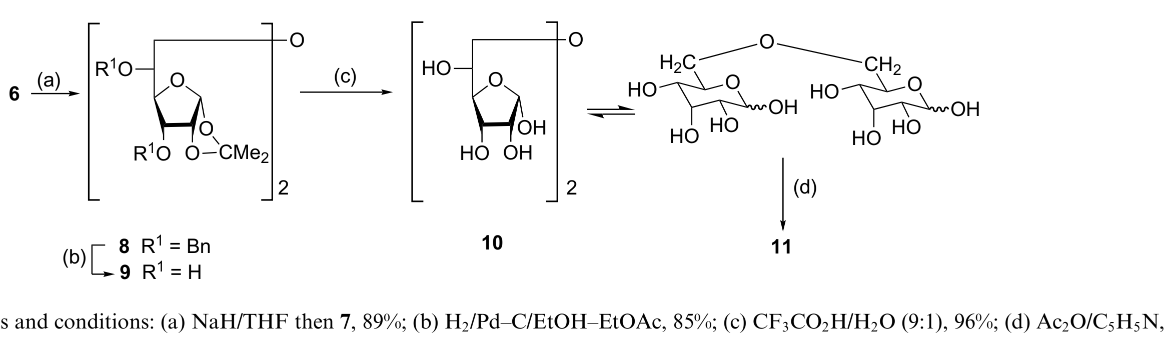


Scheme 1. Reagents and conditions: (a) *t*-$BuSiPh_2Cl/C_5H_5N$, 94%; (b) $NaH/PhCH_2Br/DME$, 68%; (c) Bu_4NF/THF, 91%; (d) $Tf_2O/Et_3N/CH_2Cl_2$, 80%.

alkoxide of **6** with triflate **7** in THF (Scheme 2) gave the dimeric structure **8**, hydrogenation of which gave the 6,6′-ether **9**, which on acidic hydrolysis gave the 6,6′-ether linked D-allose **10** as a hygroscopic solid that could exist, presumably, in the di-furanose, di-pyranose, or a furanose–pyranose form. Coyolosa has a reported[1] mp of 170–172 °C. The ^1H NMR spectrum of **10** in D_2O suggested that the β,β-pyranose form was predominant (~80%, δ_H 4.88, $J_{1,2}$ 8.2 Hz, H-1) with a minor signal (13% of the total anomeric signal) for an α-pyranose anomeric form (δ_H 5.13, $J_{1,2}$ 3.4 Hz) and two small signals (7% of total) at δ_H 5.23 and 5.36. These values for the anomer ratios agree well with those reported[6] for the composition of D-allose in aqueous solution of 77.5% β-pyranose, 14% α-pyranose and 8.5% furanose forms. Although individual hydroxy proton resonances could be observed in the ^1H NMR spectrum of **10** in DMSO-d_6 as reported,[1] the separate C–H proton resonances were generally uninformative due to signal overlap and increased complexity due to coupling with the hydroxy protons. The ^{13}C NMR spectrum of **10** showed two anomeric signals at δ_C 94.19 (major) and 93.57 (minor), which are in close agreement with those for β- and α-D-allose at 94.3 and 93.7, respectively.[7]

Acetylation of **10** gave, after recrystallisation from EtOAc–hexane, a crystalline peracetate **11**, mp 198–199 °C, which contrasts[8] with that for coyolosa peracetate, prepared[1] by acetylation of coyolosa by a similar procedure, which had mp 132–134 °C. The ^1H NMR spectrum of **11** confirmed it as a single isomer with a β-configuration at the anomeric centres (δ_H 5.97, $J_{1,2}$ 8.7 Hz, H-1) and its ^{13}C NMR spectrum had six signals for the carbohydrate carbons, with the value for the anomeric signal (δ_C 90.06) agreeing well with that reported[6] for peracetylated β-D-allopyranose (δ_C 90.1).[7] The reported[1] values for the ^{13}C NMR signals of the carbohydrate carbons of coyolosa peracetate are δ_C 91.77, 89.13, 72.82, 69.90, 67.88 and 61.54 whereas values for compound **11** in the same solvent are at 90.06, 72.90, 70.22, 68.28, 68.03 and 65.90. Thus, it is clear that coyolosa does not possess the structure suggested[1] and in an attempt to identify a possible alternative structure, the 6,6′-ether linked pseudo-disaccharides from D-glucose and D-galactose have also been similarly prepared and full details of their synthesis will be reported elsewhere. However, the spectral characteristics of neither of these compounds, most noticeably the ^{13}C NMR spectra of the peracetates, are in agreement with those reported for coyolosa peracetate and therefore the structure of coyolosa is still an open question.

Despite a report[9] in 1969 that an ether-linked pseudo-disaccharide was a constituent of the exotoxin from *Bacillus thuringiensis*, which has inhibitory action on the de novo synthesis of RNA and the DNA dependent RNA polymerase, this class of carbohydrates has been given relatively little attention to date. Synthesis of the sugar fragment of this endotoxin, which contains a 5 → 4 D-ribose to D-glucose ether link, was reported[10] in 1971, but the first synthesis of this type of compound was by Whistler and Frowein[11] in 1961 who heated together equimolar amounts of 1,2-*O*-isopropylidene-α-D-glucofuranose and 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose at 150 °C, which yielded, after hydrolysis of the product and extensive purification by column chromatography, 6,6′-di-D-glucose anhydride. A related approach has been used by Villa and co-workers[12] to construct an amphiphile containing 6,6′-ether linked D-glucose residues. An attempt to use this type of reaction to prepare **10** in the present work, by fusing together 3,5-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-allofuranose and 5,6-anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-allofuranose[13] was unsuccessful, the reactants showing remarkable stability even at elevated temperatures. A patent[14] records the preparation of the 6,6′-ether linked derivative from 1,2:3,4-di-*O*-isopropylidene-D-galactose, Paulsen and von Deyn[15] have linked some cyclitol derivatives to carbohydrates to produce pseudo-disaccharides with ether linkages using triflate methodology, Schmidt and co-workers[16] introduced a 2 → 6 ether link



Scheme 2. Reagents and conditions: (a) NaH/THF then **7**, 89%; (b) H_2/Pd–C/EtOH–EtOAc, 85%; (c) CF_3CO_2H/H_2O (9:1), 96%; (d) Ac_2O/C_5H_5N, 62%.

between D-gluconolactone and D-glucose residues, and Hodosi and Kovác,[17] in investigating the use of 1,2-stannylene acetals for glycoside synthesis, isolated compounds with $3 \rightarrow 6$, $2 \rightarrow 4$ and $2 \rightarrow 6$ ether links between two carbohydrate residues, in one case as the major product. It would seem that ether-linked pseudo-disaccharides merit further attention, both from the synthetic standpoint and because of their potentially interesting biological properties.

Acknowledgements

I thank the EPSRC Mass Spectrometry Service Centre, Swansea for determination of the high-resolution mass spectra, and Dr. Balaram Mukhopadhyay for helpful discussion and for his measurement of the NMR spectra without which this work would not have been possible.

References and notes

1. Pérez, G. S.; Pérez, G. R. M.; Pérez, G. C.; Zavala, S. M. A.; Vargas, S. R. *Pharm. Acta Helv.* **1997**, *72*, 105–111.
2. Unfortunately, the author has not been able to obtain a sample of coyolosa, its peracetate, or original spectra for comparison purposes.
3. Roberts, S. M.; Shoberu, K. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2625–2632.
4. Baker, D. C.; Horton, D.; Tindall, C. G. In *Methods in Carbohydrate Chemistry*; Whistler, R. L., BeMiller, J. N., Eds.; Academic Press: New York, 1976; Vol. 7, pp 3–6.
5. All new compounds gave consistent spectral and high resolution mass spectrometric data. Data are given below for selected compounds; optical rotations were measured at 20 °C and for compounds **8**, **9**, **10** and **11**, in which the two carbohydrate rings are related by symmetry, NMR data are recorded for one ring moiety only.
4 (oil): $[\alpha]_D$ +39° (c 0.6, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.72–7.62, 7.48–7.33, 7.30–7.26 (15H, 3×m, Ar-H), 5.72 (1H, d, $J_{1,2}$ 3.6 Hz, 1-H), 4.67 and 4.50 (each 1H and d, J_{AB} 12 Hz, OCH_2Ph), 4.52 (1H, dd, $J_{2,3}$ 4.2 Hz, 2-H), 4.10 (1H, dd, $J_{3,4}$ 8.7, $J_{4,5}$ 3.9 Hz, 4-H), 4.05 (1H, m, 5-H), 3.93 (1H, dd, 3-H), 3.82–3.72 (2H, complex, 6a- and 6b-H), 1.57 and 1.35 (each 3H, CMe_2), 1.07 (9H, CMe_3); δ_C (75 MHz, $CDCl_3$) 137.55–127.81 (10×s, Ar-C), 112.95 (CMe_2), 104.10 (1-C), 77.88 (4-C), 77.74 (2-C), 77.52 (3-C), 72.05 (CH_2Ph), 71.88 (5-C), 64.47 (6-C), 26.69 (CMe_3, $CMeMe$), 26.51 ($CMeMe$), 19.11 ($SiCMe_3$); m/z (CI): 566.3 $[M+NH_4]^+$. (Found: $[M+NH_4]^+$ 566.2935. $C_{32}H_{44}NO_6Si$ requires m/z 566.2932.)
8 (oil): $[\alpha]_D$ +85.7° (c 0.43, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.38–7.17 (10H, m, Ar-H), 5.65 (1H, d, $J_{1,2}$ 3.3 Hz, 1-H), 4.68 and 4.51 (each 1H and d, J_{AB} 11.8 Hz, OCH_2Ph), 4.63 (2H, s, OCH_2Ph), 4.44 (1H, dd, $J_{2,3}$ 3.7 Hz, 2-H), 4.19 (1H, dd, $J_{3,4}$ 8.5, $J_{4,5}$ 1.6 Hz, 4-H), 4.00 (1H, dd, 3-H), 3.91 (1H, m, 5-H), 3.54 (2H, d, $J_{5,6a}$ and $J_{5,6b}$ 6 Hz, 6a- and 6b-H), 1.56 and 1.33 (each 3H, CMe_2); δ_C (75 MHz, $CDCl_3$) 139.04–127.35 (8×s, Ar-C), 112.98 (CMe_2), 104.15 (1-C), 79.45 (4-C), 77.68 (2-C), 77.43 (5-C), 77.13 (3-C), 73.52 and 72.04 (2×CH_2Ph), 71.41 (6-C), 26.84 and 26.54 (CMe_2); m/z (CI): 800.5 $[M+NH_4]^+$. (Found: $[M+NH_4]^+$ 800.3995. $C_{46}H_{58}NO_{11}$ requires m/z 800.4004.)
9 (oil): $[\alpha]_D$ +56.7° (c 1.33, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 5.71 (1H, d, $J_{1,2}$ 3.7 Hz, 1-H), 4.58 (1H, dd, $J_{2,3}$ 4.3 Hz, 2-H), 4.09 (1H, dd, $J_{3,4}$ 8.6 Hz, 3-H), 4.01 (1H, m, 5-H), 3.85 (1H, dd, $J_{4,5}$ 3.5 Hz, 4-H), 3.68 (1H, dd, $J_{5,6}$ 3.4, $J_{6a,6b}$ 10 Hz, 6a-H), 3.60 (1H, dd, $J_{5,6b}$ 3.9 Hz, 6b-H), 1.51 and 1.29 (each 3H, CMe_2); δ_C (100 MHz, $CDCl_3$) 112.78 (CMe_2), 103.42 (1-C), 81.08 (4-C), 79.75 (2-C), 71.30 (6-C), 69.94 (3-C), 68.88 (5-C), 26.64 and 26.31 (CMe_2); m/z (CI): 440.3 $[M+NH_4]^+$. (Found: $[M+NH_4]^+$ 440.2129. $C_{18}H_{34}NO_{11}$ requires m/z 440.2126.)
10 (oil): $[\alpha]_D$ +19.1° (c 0.83, H_2O); δ_H (400 MHz, D_2O) (major isomer) 4.88 (d, $J_{1,2}$ 8.2 Hz, 1-H), 4.16 (br s, 3-H), 3.95–3.86 (complex, 5-H), 3.82 (br d, $J_{6a,6b}$ 11 Hz, 6a-H), 3.77–3.61 (complex, 4- and 6b-H), 3.41 (br d, 2-H)); δ_C (100 MHz, H_2O) 94.19 (major anomer 1-C), 93.57 (minor anomer 1-C), 73.10, 71.86, 71.81, 71.30, 67.55 (2-C to 6-C); m/z (ES): 365.2 $[M+Na]^+$. (Found: $[M+Na]^+$ 365.1059. $C_{12}H_{22}O_{11}Na$ requires m/z 365.1054.)
11, mp 132–134 °C: $[\alpha]_D$ −4° (c 0.45, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 5.97 (1H, d, $J_{1,2}$ 8.7 Hz, 1-H), 5.70 (1H, dd, $J_{2,3}$ 3, $J_{3,4}$ 3 Hz, 3-H), 4.98 (1H, dd, $J_{4,5}$ 8.4 Hz, 4-H), 4.97 (1H, dd, 2-H), 4.10 (1H, ddd, $J_{5,6a}$ 3, $J_{5,6b}$ 4.8 Hz, 5-H), 3.67 (1H, dd, $J_{6a,6b}$ 11.8 Hz, 6a-H), 3.56 (1H, dd, 6b-H), 2.15, 2.11, 2.01, 2.00 (each 3H, CH_3CO); δ_C (100 MHz, $CDCl_3$) 169.95, 169.34, 169.13, 169.09 (4× –CO–), 90.06 (1-C), 72.90 (5-C), 70.22 (6-C), 68.28 (3-C), 68.03 (2- or 4-C), 65.90 (4- or 2-C), 20.76, 20.52, 20.38 (×2) (CH_3CO); m/z (CI): 696.3 $[M+NH_4]^+$. (Found: $[M+NH_4]^+$ 696.2348. $C_{28}H_{42}NO_{19}$ requires m/z 696.2346.)
6. Collins, P. M.; Ferrier, R. J. *Monosaccharides*; Wiley: Chichester, 1995. p 41.
7. Collins, P. M.; Ferrier, R. J. *Monosaccharides*; Wiley: Chichester, 1995; p 535.
8. Disagreement in the mp of the two peracetates could be explained by the seemingly unlikely occurrence of the natural material as the 6,6′-ether derived from D- and L-allose, but the NMR spectra of such an unsymmetrical dimer would be identical to that of the symmetrical D,D- or L,L-compound with the very reasonable assumption that there is no internuclear coupling across the ether link.
9. Farkaš, J.; Šebesta, K.; Horská, K.; Samek, Z.; Dolejš, L.; Šorm, F. *Collect. Czech. Chem. Commun.* **1969**, *34*, 1118–1120.
10. Prystaš, M.; Šorm, F. *Collect. Czech. Chem. Commun.* **1971**, *36*, 1448–1471.
11. Whistler, R. L.; Frowein, A. *J. Org. Chem.* **1961**, *26*, 3947–3948.
12. Vanbaelinghem, L.; Godé, P.; Goethals, G.; Martin, P.; Ronoco, G.; Villa, P. *Carbohydr. Res.* **1998**, *311*, 89–94.
13. Rauter, A. P.; Figueiredo, J.; Ismael, M.; Canda, T.; Font, J.; Figueredo, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1131–1146.
14. Rkagaku Konkjuse. JP 50128024, 1977; RU 9N112P, 1978.
15. Paulsen, H.; von Deyn, W. *Liebigs Ann. Chem.* **1987**, 141–152.
16. Vlahov, I. R.; Valhova, P. I.; Schmidt, R. R. *Tetrahedron Lett.* **1992**, *33*, 7503–7506.
17. Hodosi, G.; Kovác, P. *Carbohydr. Res.* **1998**, *308*, 63–75.