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Confirmation of the structure of a glucono-1,4-lactone derivative obtained from silylation of glucono-1,5-lactone

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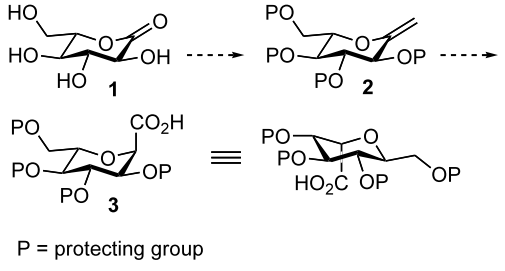
Abstract—Silylation reactions of glucono-1,5-lactone can give the persilylated glucono-1,5-lactone or the persilylated 1,4-lactone depending on the reaction conditions employed. The structure of 2,3,5,6-tetra-*O*-(*tert*-butyldimethylsilyl)-D-glucono-1,4-lactone, obtained in 84% yield from the reaction of glucono-1,5-lactone with TBSOTf and lutidine in dichloromethane, has been confirmed by X-ray crystallography. Formation of the glucono-1,5-lactone and manno-1,5-lactone derivatives and other possible products has also been ruled out by synthesis of possible *exo*-glycal derivatives of these lactones using the Ramberg–Bäcklund rearrangement of the corresponding sulfones.

1. Introduction

We have been interested in developing routes to intermediates that will be useful for the synthesis of analogues of L-idose and L-iduronic acid (e.g. **3**). This work forms part of a project aimed at the synthesis and biological evaluation of hexuronic acid conjugates; we have recently shown that glucuronic acid-containing glycoconjugates are inhibitors of heparin binding to FGF and also inhibitors of endothelial cell survival pathways.[1] It would be interesting to compare the biological activity of L-iduronic acid containing analogues in these assays. L-Iduronic acid is the C-5 epimer of D-glucuronic acid and is an important structural component of heparin and related oligosaccharides[2] and synthetic routes to these derivatives are often long. Our proposed synthesis (Scheme 1) of the *C*-glycosyl derivative **3** from commercially available L-glucono-1,5-lactone **1** prompted us to investigate the silylation reactions of **1** or alternatively its less expensive enantiomer, D-glucono-1,5-lactone **4**.

The silylation of D-glucono-1,5-lactone **4** has been investigated previously. Collins and Jones[3] have described the use of TBSCl and imidazole in DMF and they obtained a product with $[\alpha]_D^{20}$ +17.2 (*c* 0.97, $CHCl_3$) and mp 99.5–100°C; Fang et al.[4] have used DMAP, 2,6-lutidine and TBSCl and they obtained a product with $[\alpha]_D^{25}$ +55 (*c* 5.4, $CHCl_3$);[5] the NMR spectroscopic data for the major product isolated in these two cases differed considerably. More recently, Yang et al.[6] suggested that the reaction of **4** with TBSOTf in the presence of pyridine in DMF gives the 1,5-lactone **6a**, whereas a similar reaction in dichloromethane gives the 1,4-lactone **5a**; their assignment was based on ^{13}C NMR and IR data (for example **5a** had a higher stretching frequency than **6a**; 1794 versus 1769 cm^{-1}).

We could not introduce silyl groups on to all of the hydroxyl groups of **4** using the method described by



Scheme 1. Proposed synthesis of L-iduronic acid analogues.

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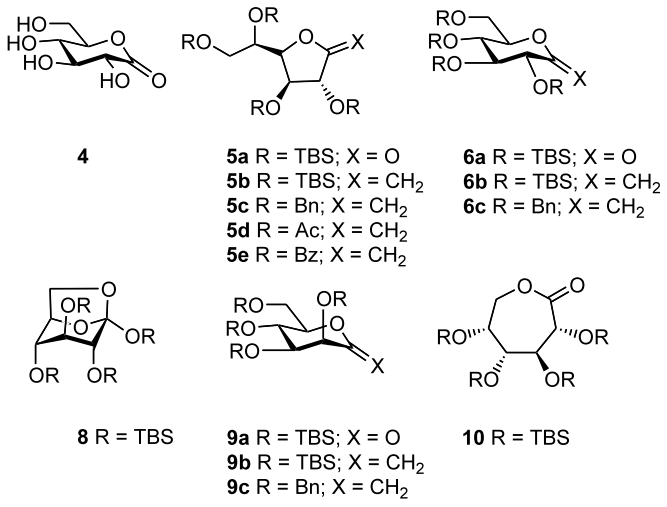
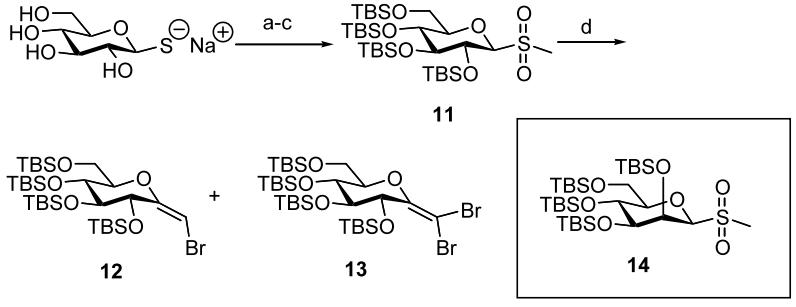


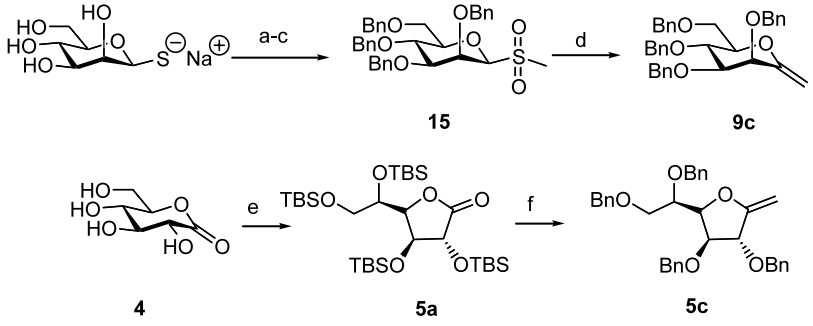
Collins and Jones but the silylation of **4** with TBSOTf and 2,6-lutidine in dichloromethane gave a compound (86%; mp 92–96°C; $[\alpha]_D$ +36.1 (*c* 1.0, $CHCl_3$)) which had spectroscopic data similar to that obtained by these workers; a minor amount of **8** was also observed in the product mixture; support for formation of **8** was obtained from the ^{13}C NMR spectrum which had a signal at δ 118.0 ppm consistent with the *ortho* ester.[7] The IR spectrum of the major product had a band at 1785 cm^{-1} indicating that it was the γ-lactone **5a**. Epimerisation of the lactone to give **9a** could also explain the observations by different workers (although this is less likely), as could the formation of the seven-membered lactone **10**, possibly from **8**.

A synthetic approach was adopted to provide confirmation that the structure of the product obtained from this reaction was neither that of the δ-lactone **6b** nor that of **9a**. In order to obtain structural clarification we decided to convert **5a** into an *exo*-glycal methylene derivative such as **5b–e**, and then to prepare an authentic sample of **6b** or **6c** using Ramberg–Bäcklund chemistry.[8] We were unable to prepare the *exo*-glycal derivative **6b** by Ramberg–Bäcklund reaction of **11**, which can be prepared in three steps from sodium thioglucose (Scheme 2); this reaction gave instead the monobromide **12** and the dibromide **13**. A similar approach using the mannose derivative **14** was also unsuccessful and did not provide **9b**.

The synthesis of **9c** was instead achieved using the Ramberg–Bäcklund reaction of **15** (Scheme 3), prepared from sodium 1-thio-D-mannose,[9] and we found that this compound had spectroscopic data identical with that reported previously.[10] The *exo*-glycal derivative **6c** has been prepared previously using this methodology and its spectroscopic data was available to us for comparison purposes.[11] Reaction of **5a**, obtained from reaction of **4** with TBSOTf/lutidine/CH_2Cl_2, with Cp_2TiMe_2, followed by removal of the silyl groups using TBAF and subsequent benzylation gave a product **5c** where the bulk material had spectroscopic data different to both **6c** and **9c**.



Scheme 2. *Reagents and conditions*: (a) MeI, MeOH; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2; (c) MCPBA, CH_2Cl_2; (d) KOH–Al_2O_3, CF_2Br_2, CH_2Cl_2, *t*-BuOH.



Scheme 3. *Reagents and conditions*: (a) MeI, MeOH; (b) NaH, BnBr, DMF; (c) MCPBA, CH_2Cl_2; (d) KOH–Al_2O_3, CF_2Br_2, CH_2Cl_2, *t*-BuOH; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2; (f) Cp_2TiMe_2, then TBAF, THF, then NaH, BnBr, DMF.

We obtained single crystals of **5a** and determined the structure of the major product from this reaction by X-ray crystallography (Fig. 1); this confirmed that the γ-lactone is the major product of the reaction obtained from silylation of the lactone using TBSOTf in dichloromethane. X-Ray powder diffraction techniques, together with the synthetic work, confirmed that the product obtained from the silylation reaction of **4** was the same as that used for single crystal analysis. The synthesis of **5d** and **5e** was also carried out from **5b** using standard reaction sequences.

2. Summary

Silylation reactions of glucono-1,5-lactone can afford the protected glucono-1,4-lactone or the protected 1,5-lactone depending on the reaction conditions employed. The structure of 2,3,5,6-tetra-*O*-(*tert*-butyldimethylsilyl)-γ-D-gluconolactone, obtained from the reaction of δ-gluconolactone with TBSOTf and lutidine in dichloromethane has been confirmed by X-ray crystallography; the presence of the glucono-1,5-lactone was ruled out by synthesis of *exo*-glycal derivatives using the Ramberg–Bäcklund reaction. This rearrangement is interesting and gives useful yields of the five-membered lactone. Thus, the method should have good potential utility in synthesis.

3. Experimental

3.1. General methods

Optical rotations were determined with a Perkin–Elmer 241 model polarimeter at the sodium D line at 23°C. NMR spectra were recorded with JEOL JNM-GX270 and Varian Inova 300 spectrometers. Chemical shifts are reported relative to internal tetramethylsilane in chloroform (δ 0.0), deuterium oxide (δ 4.80) for ^{1}H and either chloroform (δ 77.0), deuterium oxide (with acetonitrile as reference; δ 119.2), for ^{13}C. Multiplicity (in parentheses) in ^{13}C NMR was determined by DEPT. Coupling constants are reported in hertz. IR spectra were recorded with a Mattson Galaxy Series FTIR 3000 using either thin film between NaCl plates or KBr discs as specified. Melting points were measured on a Gallenkamp Melting Point apparatus. Elemental analysis was performed on an Exeter Analytical CE440 elemental analyser. Low and high resolution mass spectra were measured on either a VG micromass 70/70H or VG ZAB-E spectrophotometer or autospec spectrometers and were measured in ES positive mode unless otherwise indicated. TLC was performed on aluminium sheets precoated with silica gel 60 (HF_{254}, E. Merck) and spots visualized by UV and charring with sulphuric acid–ethanol (1:20). Flash column chromatography was carried out with silica gel 60 (0.040–0.630 mm, Merck) and employed a stepwise solvent polarity gradient correlated with TLC mobility. Chromatography solvents used were EtOAc (Riedel–deHaen) and petroleum ether (BDH laboratory supplies) with the fraction of light petroleum ether with boiling point 40–60°C. Toluene and dichloromethane reaction solvents were freshly distilled from calcium hydride.

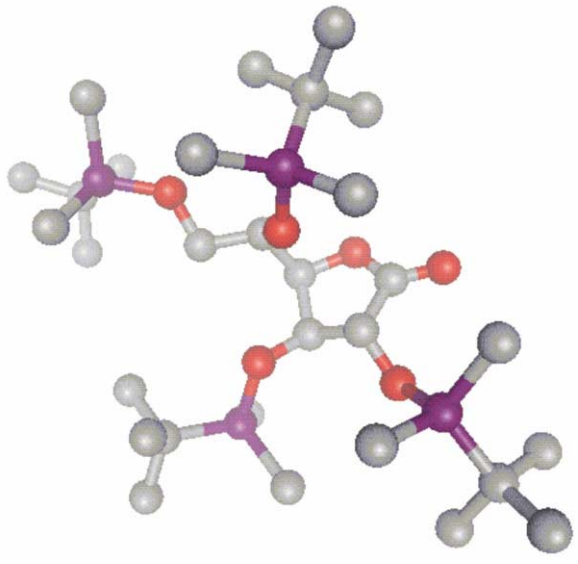


Figure 1. X-Ray structure of 2,3,5,6-tetra-*O*-(*tert*-butyldimethysilyl)-D-glucono-1,4-lactone **5a** (H atoms not shown).

3.2. 2,3,5,6-Tetra-*O*-(*tert*-butyldimethysilyl)-L-glucono-1,4-lactone (enantiomer of 5a) and 1-(*tert*-butyldimethylsilyloxy)-2,3,4-tri-*O*-(*tert*-butyldimethylsilyl)-1,6-anhydro-L-glucopyranose (enantiomer of 8)

To L-gluconolactone **1** (0.25 g, 1.40 mmol) in dichloromethane (10 mL) at 0°C under N_2, 2,6-lutidine (1.30 mL, 11.2 mmol) and *tert*-butyldimethylsilyl triflate (1.93 mL, 8.43 mmol) were added. The solution was allowed to stir at 0°C for 2 h, then warmed to room temperature. The reaction was quenched with the addition of water (10 mL). The organic layer was further washed with 5% aqueous $CuSO_4$ solution (3×10 mL) and water (3×10 mL), dried with Na_2SO_4, filtered and the dichloromethane was removed in vacuo. Chromatography (20:1 petroleum spirits–diethyl ether) gave 2,3,5,6-tetra-*O*-(*tert*-butyldimethysilyl)-L-glucono-1,4-lactone as a white solid (0.77 g, 86%) and 1-(*tert*-butyldimethylsilyloxy)-2,3,4-tri-*O*-(*tert*-butyldimethylsilyl)-1,6-anhydro-L-glucopyranose, as a clear oil, that was crystallised from ethanol to give clear crystals (0.06 g, 6%).

3.2.1. Analytical data for 2,3,5,6-tetra-*O*-(*tert*-butyldimethysilyl)-L-glucono-1,4-lactone. R_f 0.56 (9:1 petroleum spirits–diethyl ether); mp 92–96°C; $[\alpha]_D$ −36.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.58 (d, 1H, *J* 6.8 H-2), 4.58 (apt t, 1H, *J* 7.0 H-4), 4.43 (apt t, 1H, *J* 6.8, H-3), 4.03 (ddd, 1H, *J* 5.5, 3.0, H-5), 3.94 (dd, 1H, *J* 6.6, 10.1, H-6a), 3.34 (dd, 1H, H-6b), 0.92, 0.92, 0.90, 0.89 (4s, 36H, 4×$Si(CH_3)_2C(CH_3)_3$), 0.19, 0.14, 0.12, 0.11, 0.06, 0.05 (6s, 24H, 4×$Si(CH_3)_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 174.6 (s, C-1), 80.8, 76.3, 74.4, 73.5 (4d, C-2–5), 63.8, 25.9, 25.8, 25.7,

25.5 (each q, $Si(CH_3)_2C(CH_3)_3$), 18.2, 18.1, 18.0, 17.9 (4s, 4×$Si(CH_3)_2C(CH_3)_3$), −4.11, −4.4, −4.5, −4.5, −4.8, −5.1, −5.1, −5.7, −5.8 (each q, $Si(CH_3)_2C(CH_3)_3$); IR (KBr): 2961, 1786 (C=O), 1463, 1258, 1119, 1003, 835, 773 cm^{-1}. Anal. calcd for $C_{30}H_{66}O_6Si_4$: C, 56.73; H, 10.47. Found: C, 56.45; H, 10.42%. CI-HRMS: Found 635.4007, required 635.4015 $[M+H]^+$.

3.2.2. Analytical data for 1-(*tert*-butyldimethylsilyloxy)-2,3,4-tri-*O*-(*tert*-butyldimethylsilyl)-1,6-anhydro-L-gluco-pyranose. R_f 0.64 (9:1 petroleum spirits–EtOAc); mp 78–81°C; $[\alpha]_D$ +15.4 (*c* 0.9 $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): δ 4.40–4.42 (m, 1H), 3.89–3.92 (m, 1H), 3.76–3.81 (m, 3H), 3.44–3.46 (m, 2H), 0.92, 0.92, 0.91, 0.90 (4s, 36H, 4×$Si(CH_3)_2C(CH_3)_3$), 0.19, 0.14, 0.13, 0.11, 0.10, 0.10, 0.09, 0.09 (each s, 24H, 4×$Si(CH_3)_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$) δ 118.0 (s, C-1), 78.9, 78.4, 74.6, 73.0 (each d, C-2–5), 63.8 (t, C-6), 26.3, 26.0, 26.0, 25.8, 25.7, 25.6, 25.4 (each q, 4×$Si(CH_3)_2C(CH_3)_3$), 18.4, 18.1, 18.1, 17.8 (each s, 4×$Si(CH_3)_2C(CH_3)_3$), −2.9, −2.9, −3.2, −3.5, −4.4, −4.7, −4.7 (each q, 4×$Si(CH_3)_2C(CH_3)_3$); IR (film): *v* 2928, 1463, 1257, 1003 cm^{-1}; CI-HRMS. Found 635.4009, required 635.4015 $[M+H]^+$.

3.3. 2,3,5,6-Tetra-*O*-(*tert*-butyldimethysilyl)-D-glucono-1,4-lactone 5a

An identical procedure for D-gluconolactone **4** as described above for L-gluconolactone gave **5a**: $[\alpha]_D$ +36.1 (*c* 1.0, $CHCl_3$); the spectroscopic data for **5a** was identical to that of its enantiomer. Crystals of **5a** were obtained (from ethanol, crystals were twinned) and the structure confirmed by X-ray crystallography. Crystallographic data (excluding structure factors) for **5a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 196326. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]. Crystal data and structure refinement for **5a**: empirical formula $C_{30}H_{66}O_6Si_4$; formula weight 635.19; temperature 363(2) K; wavelength 71.073 pm; crystal system monoclinic; space group *P*2(1); unit cell dimensions $a=$ 1263.45(18) pm, $\alpha=90°$, $b=2112.3(3)$ pm, $\beta=96.096(4)°$, $c=1487.1(2)$ pm, $\gamma=90°$, volume 3.9463(10) nm^3, $Z=4$; density (calculated 1.069 Mg/m^3; absorption coefficient 0.185 mm^{-1}; $F(000)$ 1400; crystal size 0.32×0.16×0.08 mm^3; theta range for data collection 1.38–8.55°; index ranges $-16\le h\le 16$, $-28\le k\le 28$, $0\le l\le 19$; reflections collected 21639; independent reflections 21639 [R(int) = 0.0000]; completeness to theta = 28.55°, 91.5%; absorption correction none; max. and min. transmission 0.9854 and 0.9433; refinement method full-matrix least-squares on F^2; data/restraints/parameters 21639/1/762; goodness-of-fit on F^2 0.965; final R indices [$I>2\sigma(I)$], $R_1=0.0758$, $wR_2=0.1807$; R indices (all data) $R_1=0.1242$, $wR_2=0.2176$; absolute structure parameter, −0.01(15); largest diff. peak and hole, 0.615 and −0.629 e $Å^{-3}$.

3.4. 2,5-Anhydro-3,4,6,7-tetra-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-D-gluco-hept-1-enitol, 5b

To a stirred solution of **5a** (1.80 g, 2.84 mmol) in dry toluene (50 mL), dimethyl-bis-cyclopentadiene titanium (1.40 g, 7.62 mmol) was added. The resulting solution was stirred for 20 h at 70°C, cooled and toluene removed in vacuo. Chromatography of the resulting residue (petroleum spirits as eluant; silica prewashed with 1% triethylamine in petroleum spirits) gave the title compound as a clear oil (1.25 g, 87%); R_f 0.66 (20:1 petroleum spirits–EtOAc); $[\alpha]_D$ +14.3 (*c* 1.5, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 4.30–4.34 (m, 2H, H-4, H-3), 4.24 (d, 1H, *J* 1.8, H-1a), 4.02–4.08 (m, 2H, H-5, H-6), 3.98 (d, 1H, *J* 1.8, H-1b), 3.87, 3.73 (2H, $J_{7a,7b}$ 11.0, $J_{7,6}$ 5.5 and 2.6 H-7a, H-7b), 0.89, 0.88, 0.88, 0.87 (each s, 36H, $Si(CH_3)_2C(CH_3)_3$), 0.12, 0.11, 0.10, 0.10, 0.09, 0.08, 0.07, 0.06 (each s, 24H, $Si(CH_3)_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$), δ: 163.1 (s, C2), 89.7 (t, C1), 83.6 (d, C3), 77.2, 76.7, 71.8 (3d, C-4–6), 65.0 (t, C-7), 26.0, 25.9, 25.8, 25.7, 25.6, 25.5, 25.4 (each q, $Si(CH_3)_2C(CH_3)_3$), 18.4, 18.3, 18.0, 18.0, 17.9 (each s, $Si(CH_3)_2C(CH_3)_3$), −3.6, −3.8, −4.0, −4.1, −4.2, −4.3, −4.5, −4.6, −4.8, 4.9 (each q, $Si(CH_3)_2C(CH_3)_3$); IR (film): *v* 2957, 2887, 2860, 1682 (C=C), 1473, 1255, 1096, 835, 777 cm^{-1}; CI-HRMS. Found 633.4218, required 633.4222 $[M+H]^+$.

3.5. 2,5-Anhydro-1-deoxy-D-gluco-hept-1-enitol

To **5b** (0.59 g, 0.93 mmol) in THF (10 mL), TBAF (3.72 mL, 1 M in THF) was added and the resulting solution was stirred for 2 h. THF was removed in vacuo. Chromatography (12:1 EtOAc–MeOH as eluant, silica prewashed with 1% triethylamine in MeOH) gave the title compound as a clear oil (0.15 g, 95%); R_f 0.51 (3:1 EtOAc–MeOH); ^1H NMR (300 MHz D_2O) δ 4.61 (dd, 1H, *J* 1.5, 0.7), 4.37 (br s, 1H), 4.31 (d, 1H, *J* 2.2), 4.22–4.26 (m, 2H), 3.90 (apt ddd, 1H, *J* 5.7, 3.1, 2.9), 3.80 (dd, 1H, *J* 12.1, 2.9), 3.65 (dd, 1H, *J* 12.1, 5.7).

3.6. 2,5-Anhydro-3,4,6,7-tetra-*O*-benzyl-1-deoxy-D-gluco-hept-1-enitol, 5c

A solution of 2,5-anhydro-1-deoxy-D-gluco-hept-1-enitol (0.14 g, 0.80 mmol), sodium hydride (0.13 g, 3.20 mmol) in dry DMF (5 mL) and benzyl bromide (0.38 mL, 3.20 mmol) under N_2 at room temperature was stirred for 2 h. Methanol (10 mL) was added and water (5 mL) and the mixture was extracted with EtOAc (3×20 mL). The combined organic extracts were dried (Na_2SO_4) filtered and the solvent was removed in vacuo to give the title compound as a yellow oil (0.35 g, 82%); R_f 0.75 (10:1 petroleum spirits–EtOAc); $[\alpha]_D$ +17.0 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.20–7.37 (m, 20H, aromatic H), 4.78 (d, 2H, *J* 12.0, OCH_2Ph), 4.67 (d, 1H, *J* 12.0, OCH_2Ph), 4.08 (ddd, 1H, *J* 8.8, 5.5, 2.0), 3.91 (dd, 1H, *J* 10.8), 3.72 (dd, 1H, *J* 5.5); ^{13}C NMR ($CDCl_3$): δ 159.6 (s, C-2), 138.8, 138.6, 137.7, 137.6 (each s, each *ipso* C), 128.5, 128.4, 128.3, 128.2, 128.0, 127.8, 127.8, 127.7, 127.6, 127.6, 127.5, 127.4 (each d, each aromatic C), 87.0 (t, C-1), 81.9, 80.9, 79.8,

76.6 (each d, C-3–6), 73.5, 72.5, 72.1, 70.7, 69.9 (each t, C-6 and OCH_2Ph); IR (film) 3029, 2864, 1676 (C=C), 1453, 1067, 739, 713 cm^{-1}; LR-ESMS: 559.4 $[M+Na]^+$. Anal. calcd for $C_{35}H_{36}O_5$: C, 78.33; H, 6.76. Found: C, 78.16; H, 6.72%.

3.7. 3,4,6,7-Tetra-*O*-acetyl-2,5-anhydro-1-deoxy-D-gluco-hept-1-enitol, 5d

To 2,5-anhydro-1-deoxy-D-gluco-hept-1-enitol (0.18 g, 1.02 mmol) in pyridine (4 mL), acetic anhydride (4 mL) and DMAP (cat.) were added at room temperature for 24 h. Water (4 mL) was added and the mixture was extracted with EtOAc (2×10 mL), dried (Na_2SO_4) filtered and the solvents was removed in vacuo. Chromatography (4:1 petroleum spirits–EtOAc) gave the title compound as an oil (0.17 g, 49%); R_f 0.22 (4:1 petroleum spirits–EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 5.30 (s, 1H), 5.39 (d, 1H, J 3.4, H-1a), 5.26 (ddd, 1H, $J_{6,5}$ 9.3, $J_{6,7a}$ 4.9, $J_{6,7b}$ 2.4, H-6), 4.57–4.64 (m, 3H, H-3, H-4, H-7a), 4.43 (d, 1H, J 2.2, H-1b), 4.17 (dd, 1H, $J_{7a,7b}$ 12.4, $J_{7a,6}$ 4.9, H-7b), 2.11, 2.10, 2.08, 2.02 (each s, 12H, C(O)CH_3); ^{13}C NMR ($CDCl_3$): δ 170.6, 169.6, 169.3, 169.1 (s, 4×C(O)CH_3), 158.2 (s, C-2), 89.3 (t, C-1), 79.0, 74.9, 73.3, 67.3 (d, C-3–6), 63.0 (C-7), 20.9, 20.8, 20.6 (each q, C(O)CH_3); IR (film) 2937, 1751 (C=O), 1671 (C=C), 1437, 1371, 1225, 1050, 931; HRMS-CI. Found 345.1185; required 345.1182 $[M+H]^+$.

3.8. 2,5-Anhydro-3,4,6,7-tetra-*O*-benzoyl-1-deoxy-D-gluco-hept-1-enitol, 5e

To a stirred solution of 2,5-anhydro-1-deoxy-D-gluco-hept-1-enitol (0.15 g, 0.85 mmol) in dry pyridine (8 mL) at 0°C under N_2, benzoyl chloride (0.59 mL, 5.11 mmol) was added. The resulting solution was stirred at 0°C for 3 h and warmed up to room temperature and water was added (10 mL). The mixture was extracted with EtOAc (3×20 mL) and the combined organic layers were washed with 5% aqueous $CuSO_4$ (2×40 mL) and water (2×40 mL), dried with Na_2SO_4, filtered and the solvent was removed in vacuo. Chromatography (silica prewashed and with 1% triethyamine in 6:1 petroleum spirits–EtOAc which was also eluant) gave **5e** as a white solid (0.26 g, 52%); R_f 0.42 (4:1 petroleum spirits–EtOAc); mp 52–56°C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.84–8.10 (m, 8H, aromatic H), 7.24–7.63 (m, 12H, aromatic H), 5.92 (d, 1H, J 1.0, H-3), 5.87 (ddd, 1H, $J_{6,5}$ 9.1, $J_{6,7a}$ 5.5 $J_{6,7b}$ 2.8, H-6), 5.83 (dd, 1H, $J_{4,5}$ 3.8, $J_{4,3}$ 1.0), 5.09 (dd, 1H, $J_{5,4}$ 3.6, $J_{5,6}$ 9.1, H-5), 5.00 (dd, 1H, $J_{7b,7a}$ 12.3, $J_{7b,6}$ 2.8, H-7b), 4.72 (dd, 1H, $J_{7a,7b}$ 12.3, $J_{7a,6}$ 5.5), 4.71 (d, $J_{1a,1b}$ 2.2, H-1a), 4.56 (d, 1H, $J_{1b,1a}$ 2.2); ^{13}C NMR ($CDCl_3$): δ 166.4, 165.3, 165.2, 165.1 (each s, C(O)Ph), 158.2 (s, C-2), 133.9, 133.8, 133.5, 133.4, 130.2, 130.0, 130.0, 129.9, 129.5, 128.8, 128.7, 128.7, 128.6 (aromatic C), 89.8 (t, C-1), 79.7, 75.7, 74.9, 68.9 (each d, C-3–6), 64.0 (t, C-7); IR (KBr): ν 3069, 1725 (C=O), 1451, 1281 (C=C), 1106 cm^{-1}.

3.9. Methyl 1-thio-β-D-glucopyranoside

A suspension of sodium 1-thio-D-glucose (10 g, 45.8 mmol), iodomethane (2.85 mL, 45.8 mmol) and MeOH (100 mL) was stirred until a clear solution resulted. The MeOH was then removed in vacuo and chromatography gave the title compound as a yellow solid (8.75 g, 91%); R_f 0.49 (3:1 EtOAc–MeOH); ^1H NMR (300 MHz, D_2O): δ 4.42 (d, 1H, J 9.7, H-1), 3.87 (dd, J 12.3, 2.1, H-6a), 3.68 (dd, J 12.3, H-6b), 3.48 (dd, J 0.9, 15.5, H-3), 3.45 (m, H5), 3.35 (dd, 1H, J 15.5, 0.9, H-4) 3.33 (apt. t, J 9.7, H-2), 2.20 (s, 3H, SCH_3); ^{13}C NMR ($CDCl_3$), 85.8 (d, C-1), 80.1, 77.4, 71.9, 69.8 (d, C-2—5), 61.2 (t, C-6), 11.7 (q, SCH_3); IR (KBr): ν 3441 (O-H), 2928, 1633, 1021 cm^{-1}.

3.10. Methyl 2,3,5,6-tetra-*O*-(*tert*-butyldimethylsilyl)-1-thio-β-D-glucopyranoside

To a solution of methyl 1-thio-β-D-glucopyranoside (4.0 g, 19.0 mmol), CH_2Cl_2 (50 mL) and 2,6-lutidine (17.7 mL, 152.2 mmol) at 0°C, under a N_2 atmosphere, *tert*-butyldimethylsilyl triflate (26.2 mL, 114.2 mmol) was added dropwise over 10 min and the mixture then was stirred for 3 h. Water was added (20 mL) and stirring continued for 10 min. The product was then diluted with CH_2Cl_2 (20 mL), washed with 5% aq. $CuSO_4$ (3×60 mL), dried (Na_2SO_4) filtered and the solvent was removed. Chromatography (75:1 petroleum spirits:EtOAc) gave the title compound as a clear oil (10.58 g, 83.4%); R_f 0.81 (24:1 petroleum spirits–EtOAc); $[\alpha]_D$ −18.5 (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.58 (d, 1H, J 8.0, H-1), 3.96 (dt, 1H, J 3.1, 1.2), 3.81 (dd, 1H, J 8.0, 3.1), 3.70–3.79 (m, 3H), 3.64 (dt, 1H, J 1.0, 7.8), 2.16 (s, 3H, CH_3), 0.90, 0.89, 0.89 (each s, 36H, Si$(CH_3)_2$C$(CH_3)_3$), 0.14, 0.11, 0.10, 0.08, 0.05, 0.02 (each s, 24H, Si$(CH_3)_2$C$(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 84.3, 83.4, 78.0, 76.3, 70.0 (each d, C-1–5), 64.3 (t, C-6), 26.1, 26.0, 25.9 (each q, Si$(CH_3)_2$C$(CH_3)_3$), 18.4, 18.1, 18.0, 17.9 (each s, Si$(CH_3)_2C(CH_3)_3$), 12.9 (q, SCH_3), −4.1, −4.2, −4.3, −4.4, −4.7, −5.2 (each q, Si$(CH_3)_2$C$(CH_3)_3$); IR (film) ν 2964, 1462, 1250, 923, 777, 642 cm^{-1}; LRMS-ES: 689.4 $[M+Na]^+$. Anal. calcd for $C_{31}H_{70}O_5Si_4S$: C, 55.80; H, 10.57; S, 4.80. Found: C, 55.80; H, 10.71; S, 5.21%.

3.11. 2,3,5,6-Tetra-*O*-(*tert*-butyldimethylsilyl)-1-β-D-glucopyranosyl methyl sulfone, 11

A solution of methyl 2,3,5,6-tetra-*O*-(*tert*-butyldimethylsilyl)-1-thio-β-D-glucopyranoside (3.88 g, 5.8 mmol), MCPBA (6.05 g, 17.5 mmol) and CH_2Cl_2 (50 mL), were stirred at 0°C, under a N_2 atmosphere for 4 h. The mixture was washed with 10% aqueous sodium thiosulphate (3×50 mL), saturated $NaHCO_3$ solution (2×50 mL), dried ($MgSO_4$), filtered and the solvent was removed in vacuo. Chromatography (40:1 petroleum spirits–EtOAc) gave the title compound as a white crystalline solid (2.37 g, 58.6%); R_f 0.51 (10:1 petroleum spirits–EtOAc); mp 38–42°C; ^1H NMR (300 MHz, $CDCl_3$): δ 4.55 (d, 1H, J 5.3, H-1), 4.28 (dt, 1H, J 5.0, 1.5), 3.98 (br m, 1H), 3.88 (apt t, 1H, J 1.8), 3.74–3.80 (m, 3H), 2.88 (s, 3H, SCH_3), 0.91, 0.90, 0.89, 0.88 (each

s, 36H, $Si(CH_3)_2C(CH_3)_3$), 0.17, 0.16, 0.14, 0.13, 0.11, 0.10, 0.07, 0.01 (each s, 24H, $Si(CH_3)_2C(CH_3)_3$), ^{13}C NMR ($CDCl_3$): δ 94.7 (d, C1), 82.5, 75.5, 70.6, 69.9 (each d, C-2–5), 63.4 (t, C-6), 37.3 (q, $S(O)_2CH_3$, 25.9, 25.8 (each q, $Si(CH_3)_2C(CH_3)_3$), 18.3, 18.0, 18.0, 17.9 (each s, $Si(CH_3)_2C(CH_3)_3$), −5.3, −5.0, −4.8, −4.3, −4.3, −4.1, −3.9 (each q, $4\times Si(CH_3)_2C(CH_3)_3$); IR (KBr): ν 2957, 2658, 1453, 1255, 1101, 938, 811, 756 cm^{-1}; LRMS-ES: 721.3 $[M+Na]^+$. Anal. calcd for $C_{31}H_{70}O_7Si_4S$: C, 53.24; H, 10.09; S, 4.60. Found: C, 52.99; H, 10.00; S, 4.73%.

3.12. 2,6-Anhydro-3,4,6,7-tetra-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-1-bromo-D-gluco-1-enitol, 12 and 2,6-anhydro-3,4,6,7-tetra-*O*-(*tert*-butyldimethylsilyl)-1-deoxy-1,1-dibromo-D-gluco-1-enitol, 13

To a stirred solution of **11** (0.23 g, 0.33 mmol), KOH supported on neutral alumina (0.75 g) and *tert*-butanol (10 mL) at 5–10°C, dibromodifluromethane (0.32 g, 1.32 mmol) from a pre-cooled syringe was added dropwise over 10 min. The solution was stirred for 30 min and then filtered through a pad of Celite, washing with dichloromethane (15 mL). The combined organic extracts were washed with brine (1×20 mL) and water (1×20 mL) successively, dried ($MgSO_4$) filtered and the solvent was removed in vacuo. Chromatography (silica prewashed with 1% triethylamine in petroleum spirits; eluted with same mixture), gave **12** (0.025 g, 11%) and **13** (0.05 g, 19%).

3.12.1. Analytical data for 12. R_f 0.94 (10:1 petroleum spirits–EtOAc); mp 82–84°C; ^1H NMR (300 MHz, $CDCl_3$) δ 5.02 (s, 1H, H-1), 4.19 (ddd, 1H, $J_{6,7a}$ 1.9, $J_{6,7b}$ 2.9, $J_{6,5}$ 9.1, H-6), 4.04 (dd, 1H, J 3.4, 1.0, H-3), 4.01 (dd, 1H, $J_{5,6}$ 9.1, $J_{5,4}$ 0.7, H-4), 3.93 (dd, 1H, $J_{7a,7b}$ 12.0, $J_{7a,6}$ 1.9, H-7a), 3.82 (dd, 1H, $J_{7b,7a}$ 12.0, $J_{7b,6}$ 2.9, H-7b), 3.78 (overlapping dd, 1H, $J_{4,5}$ 0.7, $J_{4,3}$ 3.4), 0.91, 0.90, 0.89, 0.89, 0.88, 0.88, 0.87, 0.86, 0.85, 0.84 (each s, $Si(CH_3)_2C(CH_3)_3$), 0.13, 0.13, 0.11, 0.10, 0.09, 0.07, 0.06 (each s, $Si(CH_3)_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 153.2 (s, C-2), 81.3, 78.1, 76.7, 72.6, 72.0 (all d, C-1, C3–6), 61.6 (t, C-7), 25.9, 25.8, 25.6 (each q, $Si(CH_3)_2C(CH_3)_3$), 18.3, 18.0, 17.8 (each s, $Si(CH_3)_2C(CH_3)_3$), −0.0, −4.0, −4.1, −4.6, −4.6, −4.8, −5.0, −5.0, −5.4 (each q, $Si(CH_3)_2C(CH_3)_3$); IR (KBr): ν 2957, 2856, 1259, 1098, 1020, 836 cm^{-1}; HRMS-ES. Found 733.3147, required 733.3147 $[M+Na]^+$.

3.12.2. Analytical data for 13. R_f 0.86 (10:1 petroleum spirits–EtOAc); mp 68–70°C; ^1H NMR (300 MHz, $CDCl_3$) δ 4.72 (dd, 1H, J 3.5, 1.0, H-5), 4.23 (ddd, 1H, J 9.1, 2.6, 1.9, H-4), 4.05 (d, 1H, J 9.1, H-3), 3.92 (dd, 1H, J 12.1, 1.7 H-7a), 3.79–3.84 (m, 2H, H-6, H-7b), 0.82, 0.89, 0.89, 0.88 0.87, 0.86, 0.85 (each s, 36H) (each s, $Si(CH_3)_2C(CH_3)_3$), 0.17, 0.16, 0.16, 0.13, 0.11, 0.11, 0.10 (each s, 24H, $Si(CH_3)_2C(CH_3)_3$); ^{13}C NMR ($CDCl_3$): δ 152.2 (s, C-2), 78.8, 76.5 71.6, 71.0 (each d, C-3–6), 70.1 (s, C-1), 61.6 (t, C-7), 25.9, 25.7, 25.6 (each q, $Si(CH_3)_2C(CH_3)_3$), 18.3, 18.0, 17.8 (each s, $Si(CH_3)_2C(CH_3)_3$), −4.0, −4.0, −4.3, −4.6, −4.7, −4.9, −5.0, −5.4 (each q, $Si(CH_3)_2C(CH_3)_3$); IR (KBr): ν 2928, 2858, 1257, 1089, 837 cm^{-1}; HRMS-ES. Found 811.2252; required 811.2252 $[M+Na]^+$.

3.13. Methyl 1-thio-β-D-mannopyranoside[12]

To a suspension of sodium 1-thio-D-mannose[9] (3.25 g, 14.9 mmol) in MeOH (40 mL), iodomethane (1.38 mL, 22.3 mmol) was added. The suspension was stirred until a clear solution was observed. The MeOH was removed in vacuo and residue applied to a column packed and eluted with 3:1 EtOAc–MeOH to give the product as a yellow solid (2.99 g, 95%); R_f 0.39 3:1 EtOAc–MeOH; $[\alpha]_D$ −115° (*c* 1.0 MeOH) $[\alpha]_D$ −129.2 (*c* 1.1, MeOH); ^1H NMR (300 MHz, D_2O): δ 4.78 (d, 1H, J 0.9, H-1), 4.04 (dd, 1H, J 3.5, H-2), 3.92 (dd, 1H, J 2.4, 12.3, H-6a), 3.73 (dd, 1H, J 6.2, H-6b), 3.66 (dd, 1H, J 3.5, H-3), 3.60 (t, 1H, J 9.7, H-4), 3.41 (ddd, 1H, J 6.2, H-5), 2.27 (s, 3H, OMe); ^{13}C NMR (D_2O): δ 86.9 (d, C-1), 81.4, 75.1, 72.8, 67.5 (d,C-2–5) 62.4 (t, C-6).

3.14. Methyl 2,3,5,6-tetra-*O*-benzyl-1-thio-β-D-mannopyranoside

To a stirred solution of methyl 1-thio-β-D-mannopyranoside (2.10 g, 10.0 mmol) and sodium hydride (1.6 g, 40.0 mmol) in dry DMF (40 mL) under N_2 at room temperature, benzyl bromide was added. The mixture was stirred for 4 h and MeOH (45 mL) was then added followed by water (45 mL). The mixture was extracted with EtOAc (3×50 mL), dried (Na_2SO_4), filtered, and the solvent was removed in vacuo. Chromatography (4:1 petroleum spirits–EtOAc) gave the title compound as a yellow oil (3.86 g, 67%); R_f 0.54 (4:1 petroleum spirits:EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 7.18–7.46 (m, 20H, $4\times OCH_2C_6H_5$), 4.95 (d, 1H, J 11.6 OCH_2Ph), 4.87 (d, 1H, J 10.7, OCH_2Ph), 4.82 (d, 1H, J 11.8, OCH_2Ph), 4.70 (d, 1H, J 11.6, OCH_2Ph), 4.65 (d, 1H, J 11.6, OCH_2Ph), 4.58 (m, 2H, OCH_2Ph), 4.45 (s, 1H, H-1), 3.97 (d, $J_{2,3}$ 2.9, H-2), 3.93 (apt t, 1H, $J_{3,4}$ 9.5, H-4), 3.81 (dd, 1H, $J_{6a,5}$ 1.8, $J_{6a,6b}$ 11.0, H-6a), 3.72 (dd, 1H, $J_{6b,5}$ 5.9, $J_{6b,6a}$ 11.0, H-6b), 3.60 (dd, 1H, $J_{3,2}$ 2.9 $J_{3,4}$ 9.5, H-3), 3.48 (ddd, 1H, $J_{5,6a}$ 1.8, $J_{5,6b}$ 5.9, $J_{5,4}$ 9.5, H-5), 2.24 (s, 3H, SCH_3); ^{13}C NMR ($CDCl_3$) δ 139.6, 138.7, 138.4, 137.6 (each s, *ipso* C), 128.7, 128.6, 128.5, 128.5, 128.4, 128.0, 127.9, 127.8, 127.7 (each d, aromatic C), 86.0, 84.7, 80.6, 77.1, 75.3 (each d, C-1–5), 75.5, 75.1, 73.7, 72.7, 70.1 (each t, C-6 and CH_2Ph), 14.9 (q, SCH_3); LRMS-ES: 593.4 $[M+Na]^+$.

3.15. 2,3,4,6-Tetra-*O*-benzyl-β-D-mannopyranosyl methyl sulfone, 15

To a solution of methyl 2,3,5,6-tetra-*O*-benzyl-1-thio-β-D-mannopyranoside (1.50 g, 2.63 mmol) in CH_2Cl_2 (20 mL), MCPBA (1.36 g, 7.88 mmol) added and stirring was continued until all the starting material was consumed. The reaction mixture was then diluted with CH_2Cl_2 (20 mL), washed with 5% aqueous sodium thiosulphate (2×50 mL) and a saturated $NaHCO_3$ solution (3×50 mL), dried (Na_2SO_4), filtered and the solvent was removed. This gave the title compound as a clear oil (1.26 g, 80%); R_f 0.88 (10:1 petroleum spirits–EtOAc); ^1H NMR (300 MHz, $CDCl_3$): δ 7.20–7.41 (m, 20H, $4\times OCH_2C_6H_5$), 5.13 (d, 1H J 10.3, OCH_2Ph), 4.88 (d, 1H J 10.8, OCH_2Ph), 4.81 (d, 1H J 11.6, OCH_2Ph), 4.74 (d, 1H J 11.6, OCH_2Ph), 4.67 (d, 1H J 9.9,

OCH_2Ph), 4.64 (d, 1H J 10.8, OCH_2Ph), 4.61 (d, 1H J 11.8, OCH_2Ph), 4.50 (d, 1H J 11.8, OCH_2Ph), 4.50 (apt t, 1H, $J_{2,3}$ 2.6 H-2), 4.25 (s, 1H, H-1), 4.16 (apt t, $J_{4,3}$ 9.7 H-4), 3.84 (dd, 1H, $J_{6a,6b}$ 11.6, $J_{6a,5}$ 3.7, H-6a), 3.78 (dd, 1H, $J_{6b,6a}$ 11.6, $J_{6b,5}$ 1.9, H-6b), 3.66 (dd, 1H, $J_{3,2}$ 2.6, $J_{3,4}$ 9.5, H-3), 3.57 (ddd, 1H, $J_{5,4}$ 9.7, $J_{5,6a}$ 3.7, $J_{5,6b}$ 1.9, H-5), 2.83 (s, 3H, $S(O)_2CH_3$); ^{13}C NMR ($CDCl_3$): δ 138.4, 138.2, 138.1, 137.9 (each s, *ipso* C), 128.4, 128.7, 128.6, 128.5, 128.4, 128.2, 128.2, 128.1, 127.9, 127.8, 127.8 (each d, aromatic C), 92.5 (d, C-1), 83.6, 81.2, 74.5, 74.1 (each d, C-2–5), 75.7, 85.6, 73.7, 73.0, 68.9 (each t, C6 and CH_2Ph), 39.1 (q, SO_2CH_3); IR (KBr) ν 3030, 2872, 1496, 1454, 1361 (S=O), 1316 (S=O), 1115, 963, 740 cm^{-1}.

3.16. 2,6-Anhydro-3,4,6,7-tetra-*O*-benzyl-1-deoxy-D-manno-hept-1-enitol, 9c

To a stirred solution of **15** (1 g, 1.66 mmol), KOH supported on neutral alumina (2.0 g) and *tert*-butanol (20 mL) at <10°C, dibromodifluoromethane (1.38 g, 6.64 mmol) was added dropwise from a pre-cooled syringe over 10 min. The solution was stirred for 30 min until all the starting material was consumed. The solids were filtered off (Celite) and washed with dichloromethane (40 mL). The combined organic portions were washed with satd. brine (1×40 mL) and water (1×40 mL) successively, dried ($MgSO_4$), filtered and the solvent was removed in vacuo. Chromatography (4:1 petroleum spirits–EtOAc as eluant, silica was prewashed with 1% triethylamine in 4:1 petroleum spirits) gave the title compound as a clear oil (0.52 g, 58%); R_f 0.56, 4:1 (petroleum spirits–EtOAc); $[\alpha]_D$ +27.3 (c 1.0, $CHCl_3$) (lit.[10] $[\alpha]_D$ +16.5 (c 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.15–7.46 (m, 20H, $OCH_2C_6H_5$), 4.95 (d, 1H, J 10.8, OCH_2Ph), 4.91 (br s, 1H, H_{1a}-), 4.78 (d, 1H, J 12.4, OCH_2Ph), 4.69 (d, 1H, J 12.4, OCH_2Ph), 4.50–4.65 (m, 4H), 4.44 (d, 1H, J 12.4, OCH_2Ph), 4.39 (bs, 1H, H_{1b}), 4.19 (t, 1H, J 9.0), 4.09 (d, 1H, J 3.2), 3.77–3.89 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 154.9 (s, C-2), 138.4, 138.2, 138.2, 138.0 (each s, *ipso* C), 128.3, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 127.6, 127.5 (each d, aromatic C), 99.5 (t, C-1), 81.5, 80.2, 74.1, 73.7 (each d, C3–6), 75.0, 73.4, 71.4, 69.4, 69.3 (each t, C-7 and CH_2Ph); LRMS-ES: 559.2 $[M+Na]^+$.

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