Available online at www.sciencedirect.com

SCIENCE @ DIRECT®

Carbohydrate Research 338 (2003) 369–373

CARBOHYDRATE RESEARCH

www.elsevier.com/locate/carres

Note

Remote site bromination via a cascade rearrangement involving two bridging dioxonium species during oxidative cleavage of a benzylidene acetal

Xuezheng Song,[a] Rawle I. Hollingsworth[a,b,*]

[a]*Department of Chemistry, Michigan State University, East Lansing, MI 48824, USA*
[b]*Department of Biochemistry and Molecular Biology, Michigan State University, East Lansing, MI 48824, USA*

Received 7 January 2002; accepted 28 October 2002

Abstract

Attempted cleavage of the benzylidene group of 3,5-*O*-benzylidene-2,6,7-tri-*O*-trimethylacetyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone with *N*-bromosuccinimide led to the formation of a 7-bromo derivative with a benzoyl group in the 3-position and trimethylacetyl groups in the 5 and 6 positions. Analysis of the coupling constants in the proton NMR spectra indicated that both trimethylacetyl groups had participated to shift the crowded electron-deficient center formed at the 5-position by the decomposition of the bromobenzylidene group to the much more accessible 7-position. The net result of this cascade rearrangement was retention at both the C-5 and C-6 positions. This is an interesting example of a cascade rearrangement under strict entropic and stereo control the synthetic utility of which is being investigated. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Bromination; Acetal-cleavage; Rearrangement; Aldonolactone

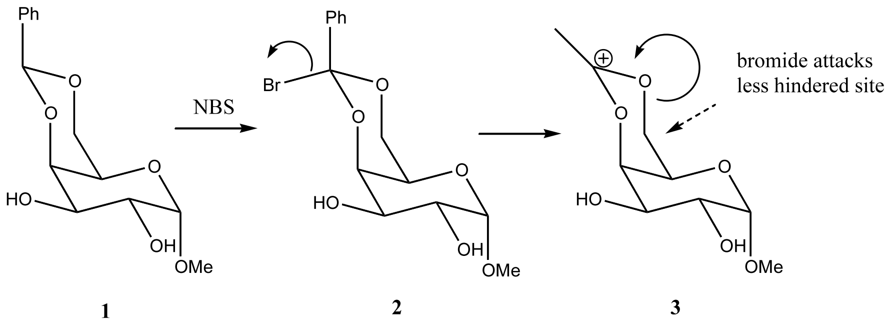
Ever since its introduction,[1,2] the oxidative cleavage of benzylidene acetals of carbohydrates to yield benzoylated bromo derivatives has been of key synthetic utility. One feature of the reaction is the extent to which its outcome is dominated by steric rather than by electronic considerations. In the cleavage of 4,6-benzylidene acetals of a typical hexopyranoside **1** (Scheme 1), the product formed is not the 4-bromo-6-benzoate (via the more stable secondary carbocation). The 6-bromo 4-benzoate is formed instead because attack from the primary position is more favored. The formation of a cyclic 1,3-dioxonium species **3** is the key feature of the NBS oxidation of acetals.

During the course of our work on the synthetic applications of carbohydrate lactones, we explored the oxidative cleavage of the acetal ring of 3,5-*O*-benzylidene-2,6,7-tri-*O*-trimethylacetyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone (**4**). Our primary goal was to develop a way of introducing a bromo group at the 5-position of the carbon skeleton to form **5** by NBS cleavage of the benzylidene ring. We anticipated (Scheme 2) formation of the 3-bromo derivative **6** or elimination to yield the α,β-unsaturated lactone **7** to be the main competing processes. The latter elimination pathway was expected to dominate if the system was too sterically crowded to allow bromination. The proton NMR spectrum of the main product from the NBS oxidation of **4** indicated that the benzylidene ring had undergone the expected rearrangement to form a benzoate ester (signals at 7.45 ppm, 7.59 ppm and 7.93 ppm) but it also indicated that the position of bromination was the 7 (primary) position. The product featured a bromo group two carbon atoms away from the intended site. None of the desired product **5** was obtained. This very unexpected result was confirmed by DEPT, HMQC and DQF-COSY NMR experiments. These NMR spectroscopy methods were used to confirm the identity of the primary carbon (DEPT) and that it was the site of bromination by virtue of the connectivity (HMQC) of the C-13 signal for the primary carbon at 28.8 ppm to two distinct proton signals. Both proton and ^{13}C NMR spectroscopy indicated that all three trimethylacetyl groups

---

[*] Corresponding author. Tel.: +1-517-353-0613; fax: +1-517-353-9334
E-mail address: rih@cem.msu.edu (R.I. Hollingsworth).

PII: S0008-6215(02)00463-9

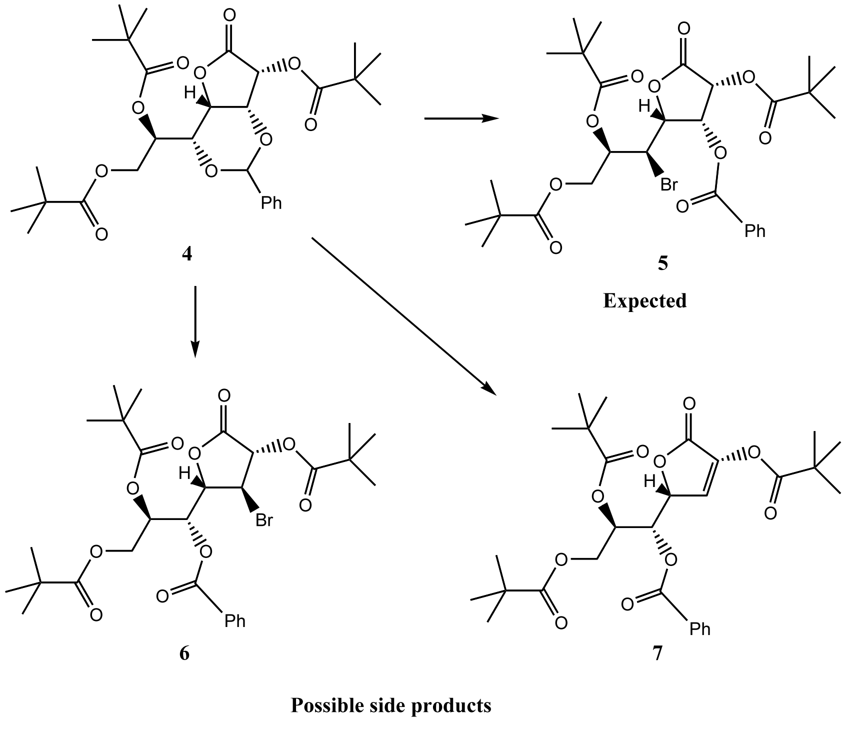


Scheme 1. Mechanism of NBS cleavage of acetals showing the formation of a 2-phenyl-1,3-dioxonium species.

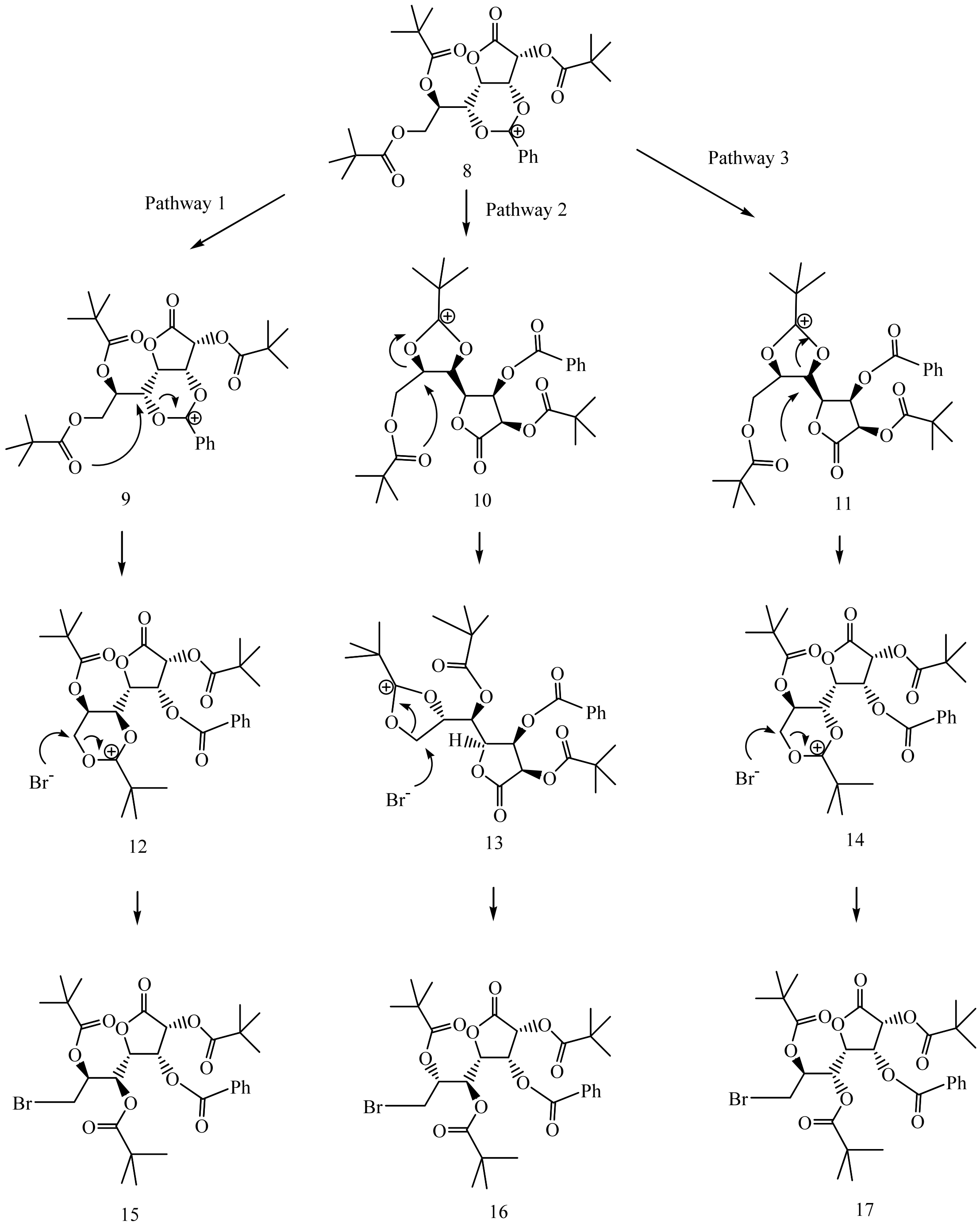
were still present. High-resolution-fast-atom-bombardment mass spectrometry also confirmed the formula containing one benzoate, one bromo and three trimethylacetyl groups (*m*/*z* 627.1799).

There are three possible rearrangement modes (Scheme 3, pathways 1, 2 and 3) that could result in 7-bromination of **4**. The 7-trimethylacetoxy group could have migrated to the 5 position (pathway 1) inverting that center. Alternatively the 6-trimethylacetoxy group could have migrated to the 5 position and the 7-group could have migrated to the 6 position inverting both the 5 and 6 positions (pathway 2). In the third scenario (pathway 3), the trimethylacetoxy group in the C-6 position could participate in the phenyldioxolonium ring cleavage to form a new cylic dioxonium species with inversion at C-5. This species is then ring-opened by the C-7 trimethylacetoxy group with a second inversion (net retention) at C-5 to form a 1,3-dioxonium species between C-5 and C-7. This is then cleaved at the unhindered 7-position by bromide to give the 7-bromo product. In this pathway, neither the 5 nor 6 center is inverted.

It is relatively easy to differentiate between these three scenarios by a consideration of the coupling constants of the H-4, H-5, and H-6 proton signals in the NMR spectrum. The coupling constants observed in the reference spectrum of *per*-trimethylacetyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone **18** (Fig. 1A). The coupling constants observed reflect the conformation shown which is largely in agreement with published studies on acyclic carbohydrate esters and aldonolactone side chains[3,4] except that in this case, the terminal dihedral



Scheme 2. Expected pathways for NBS cleavage of 3,5-(*R*)-*O*-benzylidene-2,6,7-tri-*O*-trimethylacetyl-D-*gluco*-D-*glycero*-heptono-1,4-lactone.



Scheme 3. Three possible pathways that could lead to 7-bromination of **4**. The third scenario is the only one that leads to net retention.

is a sickle conformation. In the first scenario, if the C-5 position alone had been inverted, both the H-4/H-5 splitting and the H-5/H-6 splitting should be affected (Fig. 1B). The change in the splitting pattern for H-4 should be quite dramatic since it should go from a doublet of doublets ($J = \sim 10 + 3$ Hz) to a narrow triplet ($J = \sim 3$ Hz). The changes in splittings expected in the second scenario where both the C-5 and C-6 positions are inverted are even more dramatic and are shown in Fig. 1C. In this case both H-4 and H-5 should be narrow triplets ($J = \sim 3$ Hz). The actual splittings that were observed are shown in Fig. 1D. It is clear from this that none of the coupling constants have changed indicating that scenario 3 was the one that had taken place to give product **17**.

The sensitivity to steric constraints of the oxidative cleavage of acetals with bromine is a hallmark of that reaction. In this study we observed that rather involved rearrangement can occur in order to mitigate these steric constraints. The process is characterized by a very high level of stereocontrol and its synthetic utility in obtaining access to currently inaccessible molecules with contiguous hydroxyl groups such as L sugars and other rare carbohydrates and related compounds is being evaluated. Similar participation of the ester groups of dioxonium species from polyesters is a well known phenomenon.[5]

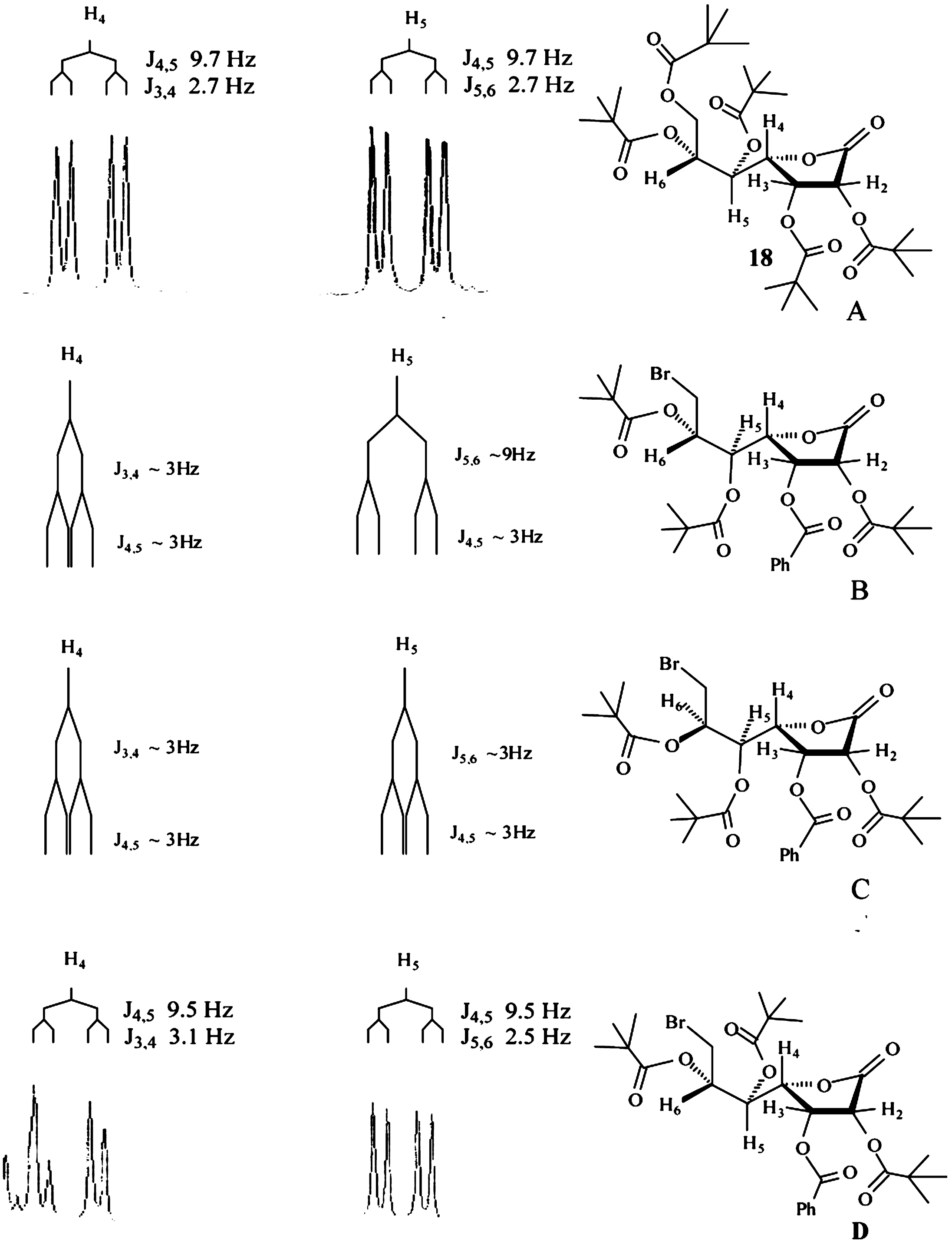


Fig. 1. Evaluation of coupling constants expected for products formed by the 3 possible rearrangement mechanisms. (A) H-4 and H-5 signals from the reference spectrum of 2,3,5,6,7-penta-*O*-trimethylacetyl-D-*gluco*-D-*glycero*-heptono-1,4-lactone (**18**). (B) In the case of inversion at C-5 (Scheme 3 pathway 1) only a narrow triplet ($J = \sim 3$ Hz) is expected for H-4. (C) In the case of inversion at both C-5 and C-6 (Scheme 3 pathway 2) the protons at these two positions should yield narrow triplets. (D) The H-4 and H-5 signals of the product indicating no change in conformation compared to A (Scheme 3 pathway 3).

1. Experimental

1.1. General methods

NMR spectra were obtained on a Varian Inova Spectrometer operating at 300 MHz for protons. Mass spectra were obtained on a Jeol HX-110-HF instrument using fast atom bombardment as the ionization mode. Spectra we recorded in the positive ion mode. IR spectra were obtained on a Nicolet 710 spectrometer in chloroform solution.

1.1.1. 3,5(R)-*O*-Benzylidene-2,6,7-tri-*O*-trimethylacetyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone (4). 3,5(*R*)-*O*-Benzylidene-D-*glycero*-D-*gulo*-heptonolactone[6] (3.0 g, 10.1 mmol) was dissolved in pyridine (30 mL). The solution was cooled to 0 °C and trimethylacetyl chloride (6.2 mL, 50.3 mmol) was added dropwise. The mixture was protected from moisture and stirred for 24 h. It was then poured into saturated $NaHCO_3$ solution containing crushed ice and extracted twice with CH_2Cl_2. The organic layer was collected, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica using $CHCl_3$ as the elutant. The colorless solid remaining after removing the solvent afforded compound **4** in 92% yield; m.p. 173–176 °C; FAB-MS: m/z calcd. for $C_{29}H_{40}O_{10}$ 548.63, found 549.2699 (MH^+); δ_H(500 MHz; $CDCl_3$): 1.18, 1.19, 1.23 (3 × 9 H, 3 × s, 3 × C(CH_3)$_3$) 4.29 (1 H, dd, $J_{7,7'}$ 12.6, $J_{6,7'}$ 4.1 Hz, H-7′) 4.31 (1 H, dd, $J_{4,5}$ 2.0, $J_{5,6}$ 8.5 Hz, H-5) 4.34 (1 H dd, $J_{3,4}$ 2.2 Hz, H-4) 4.57 (1 H, dd, $J_{6,7}$ 2.4 Hz, H-7) 4.95 (1 H, dd, $J_{2,3}$ 4.2, $J_{3,4}$ 2.2 Hz, H-3) 5.30 (1 H, ddd, H-6) 5.42 (1 H, d, H-2) 5.55 (1 H, s, C*H*Ph) 7.32–7.40 (5 H, m, Ar*H*) d_C ($CDCl_3$): 26.93, 27.13 (OCC(*C*H$_3$)$_3$) 38.77, 38.87 (OC*C*(CH$_3$)$_3$) 61.22 (C-7) 68.96, 70.50, 72.64, 73.52 (C-2, C-3, C-4, C-5, C-6) 98.86 (*C*HPh) 125.81, 128.19, 129.28, 136.10 (Ar*C*) 169.97(O=*C* of lactone) 176.36, 177.55, 177.71 (O*C*C(*C*H$_3$)$_3$) FT-IR: 2975 cm^{-1} (C–H stretch) 1809 cm^{-1} (lactone C=O stretch) 1738 cm^{-1}(trimethylacetyl C=O stretch).

1.1.2. 3-*O*-Benzoyl-7-bromo-7-deoxy-2,5,6-tri-*O*-trimethylacetyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone (17). Compound **4** (3 g, 5.47 mmol) was dissolved in CCl_4 (50 mL) at 60 °C and *N*-bromosuccinimide (1.5 g, 8.43 mmol) was added. The mixture was refluxed at 80 °C in an oil bath for 12 h whereupon TLC ($CHCl_3$) indicated that no starting material remained. The mixture was filtered and washed with saturated $NaHCO_3$ solution. The crude product was purified by flash column chromatography (chloroform) and the major fraction afforded compound **17** in 75% yield. mp 138–140 °C; FAB-MS(MH^+): m/z calcd. for $C_{29}H_{39}BrO_{10}$ 627.53, found 627.1799(MH^+); d_H(500 MHz; $CDCl_3$): 0.99, 1.08, 1.24, (27 H, 3 × s, 3 × C(C*H*$_3$)$_3$) 3.58 (1 H, dd, $J_{7,7'}$ 11.1, $J_{6,7'}$ 9.0 Hz, H-7′) 3.64 (1 H, dd, $J_{6,7}$ 4.5 Hz, H-7) 4.94 (1 H dd, $J_{3,4}$ 3.1, $J_{4,5}$ 9.5 Hz, H-4) 5.51 (1 H, dd, $J_{5,6}$ 2.5 Hz, H-5) 5.54 (1 H, ddd, H-6) 5.78 (1 H, d, $J_{2,3}$ 4.9 Hz, H-2) 5.92 (1 H, dd, H-3) 7.41–7.48 (2 H, m, Ar*H*) 7.56–7.62 (2 H, m, Ar*H*) 7.91–7.95 (1 H, m, Ar*H*) d_C (75.5 MHz; $CDCl_3$): 26.61, 26.64, 26.83, 27.00 (OCC(*C*H$_3$)$_3$) 28.77 (C-7) 38.57, 38.65, 38.81 (OC*C*(CH$_3$)$_3$) 67.48, 68.12, 69.34, 71.27, 74.44 (C-2, 3, 4, 5, 6) 127.92, 128.54, 129.67, 133.88 (Ar*C*) 164.70 (O*C*Ph) 168.89 (O=*C* in lactone) 176.36, 177.55, 177.71 (O*C*C(CH$_3$)$_3$) FT-IR: 2975cm^{-1} (C–H stretch) 1818 cm^{-1}(C=O lactone stretch) 1743cm^{-1}(C=O stretch in O*O*CC(CH$_3$)$_3$).

1.1.3. 2,3,5,6,7-Penta-*O*-trimethylacetyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone (18). D-*glycero*-D-*gulo*-Heptono-1,4-lactone (4 g, 19.2 mmol) was dissolved in pyridine (100 mL) and the solution cooled to 0 °C. Trimethylacetyl chloride (30 mL, 243.6 mmol) was slowly added and the mixture was stirred at room temperature for 24 h. It was then poured into cold saturated $NaHCO_3$ solution and then extracted with CH_2Cl_2. The organic layer was collected and dried (Na_2CO_3) and the solvent evaporated to yield compound **18** as a colorless oil in 91% yield. d_H(500 MHz; $CDCl_3$): 1.13, 1.17, 1.21 (3 × 9H, s, 3 × C(C*H*$_3$)$_3$) 1.23 (18 H, s, 2 × C(C*H*$_3$)$_3$) 4.03 (1 H, dd, $J_{6,7'}$7.2, $J_{7,7'}$ 12.0 Hz, H-7′) 4.36 (1 H, dd, $J_{6,7}$ 4.4 Hz, H-7) 4.71 (1 H, dd, $J_{3,4}$ 2.7, $J_{4,5}$ 9.7 Hz, H-4) 5.08 (1 H, m, $J_{5,6}$ 2.7 Hz, H-6) 5.64 (1 H, dd, H-5) 5.72 (1 H, d, $J_{2,3}$ 4.5 Hz, H-2) 5.82 (1 H, dd, H-3) d_C (75.5 MHz; $CDCl_3$): 26.68, 26.81, 26.88, 26.92, 26.97 (OCC(*C*H$_3$)$_3$) 38.53, 38.63, 38.72, 38.88, 39.16 (OC*C*(CH$_3$)$_3$) 61.73 (C-7) 68.46, 68.70, 68.97, 75.96 (C-2, 3, 4, 5, 6) 168.46 (O=*C* in lactone) 176.15, 176.23, 176.40, 176.46, 177.91 (O*C*C(CH$_3$)$_3$) FT-IR: 2976 cm^{-1} (C–H stretch) 1817 cm^{-1} (C=O stretch in lactone) 1741 cm^{-1}(C=O stretch in O*O*CC(CH$_3$)$_3$).

References

1. Hanessian, S. *Carbohydr. Res.* **1966**, *2*, 86–88.
2. Hanessian, S.; Pleassas, N. R. *J. Org. Chem.* **1969**, *34*, 1035–1044, 1045–1053 and 1053–1058.
3. Horton, D.; Wander, J. D. *Carbohydr. Res.* **1969**, *10* (2), 279–288.
4. Walaszek, Z.; Horton, D. *Carbohydr. Res.* **1982**, *105* (1), 131–143.
5. Paulsen, H. *Adv. Carbohydr. Chem. Biochem.* **1971**, 127–195.
6. Bichard, C. J. F.; Bruce, I.; Hughes, D. J.; Girdhar, A.; Fleet, G. W. J.; Watkin, D. J. *Tetrahedron: Asymmetry* **1993**, *4*, 1579–1589.