The synthesis of 1,4-anhydro-α-D-mannopyranose

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Abstract

We report the first synthesis of 1,4-anhydro-α-D-mannopyranose. Several unsuccessful approaches were attempted, including azide-mediated cyclization of a 1-*O*-acetyl-4-*O*-mesyl derivatives of α-D-talopyranose, and *N*-iodosuccinimide/triflic acid cyclization of a 4-hydroxy thiomannoside. Ultimately, base-mediated intramolecular nucleophilic substitution of 2,3,6-tri-O-benzyl-α-D-mannopyranosyl chloride successfully provided the cyclized product in low yield, which could be deprotected by hydrogenolysis to afford the title 1,4-anhydrosugar.

Keywords 1,4-anhydrosugar; 1,4-anhydromannose; 2,7-dioxabicyclo[2.2.1]heptanes; 1,5-anhydro-α-D-mannofuranose; chemical synthesis

INTRODUCTION

Anomeric anhydrosugars are intramolecular acetals formally derived by the loss of a water molecule from the parent sugar.[1,2] 1,2-Anhydropyranoses have been widely exploited in glycosylation chemistry[3] and have been implicated as intermediates in enzyme-catalyzed reactions.[4] 1,6-Anhydropyranoses occur in nature both as products of enzymatic reactions and through pyrolysis of cellulose.[2] These compounds have been widely studied owing to their interesting and useful attributes in synthetic carbohydrate chemistry.[2,5-7]

1,4-Anhydropyranoses (which may be considered 1,5-anhydrofuranoses) have received relatively less attention, although have been proposed as intermediates in enzymatic transformations,[8] and have had only sporadic investigations into their synthesis and transformations.[9-13] Studies on this class of sugars experienced an inauspicious start when in 1928, Freudenberg and Braun reported that treatment of 2,3,6-tri-*O*-methyl-α-D-glucosyl chloride **1** with sodium in ether afforded the protected 1,4-anhydro-α-D-glucopyranose **2** (Figure 1, *Method A*),[14] a result that could not be replicated by Hess and Littmann in 1933.[15] Instead, Hess and Littmann,[15] and later Kops and Schuerch[16] reported that treatment of 2,3,6-tri-*O*-methyl-4-*O*-tosyl-α-D-glucose **3** with sodium isopropoxide afforded the protected 1,4-anhydro-β-D-galactopyranose **4** (Figure 1, *Method B*). These two studies illustrate two of the main approaches used for the synthesis of this class of compounds, namely base-promoted intramolecular nucleophilic substitution by the 4-hydroxyl on an anomeric halide, or base-promoted intramolecular nucleophilic substitution by the anomeric hydroxyl on a sugar bearing a suitable leaving group at the 4-position.[17,18] A third approach, related to the first, involves Lewis acid-catalyzed transacetalization of a 4-hydroxy glycoside[9] or Lewis acid-catalyzed intramolecular glycosylation reactions, as exemplified by Thiem and Weisner through the BF₃.Et₂O-catalyzed reaction of 2,3,6-tri-*O*-benzoyl-α-D-galactopyranosyl fluoride **5** to afford the protected 1,4-anhydro-β-D-galactopyranose **6** (Figure 1, *Method C*).[19] A fourth approach involves the intramolecular addition of the 4-hydroxy group to a glycal, promoted by a suitable electrophile, such as in the transformation of **7** to **8** (Figure 1, *Method D*).[20,21] As the electrophile adds the alkene, this method yields a 2-substituted 1,4-anhydro-2-deoxy sugar, and is not suitable for the synthesis of 1,4-anhydro sugars that are oxygenated at C2.
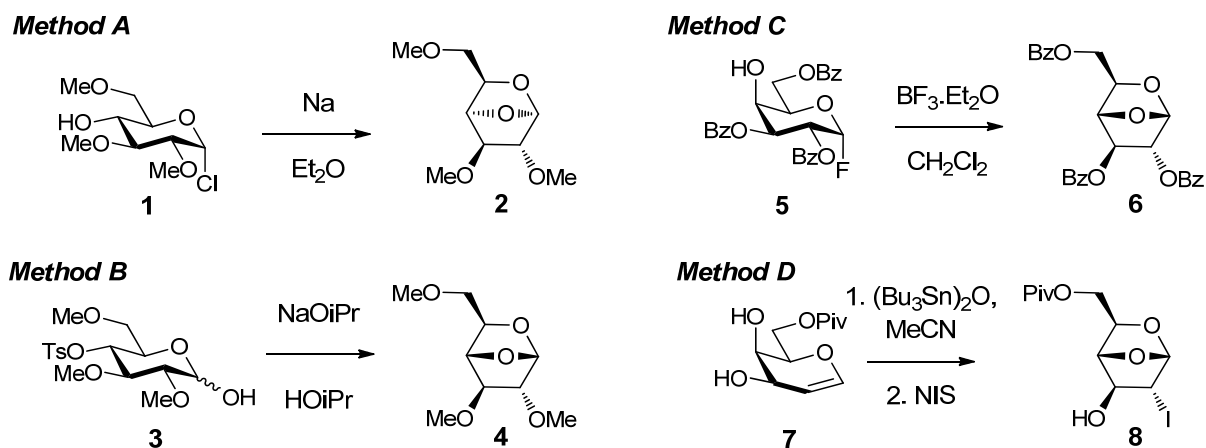
Figure 1: Summary of approaches used for the targeted synthesis of 1,4-anhydro sugars.

In this work we report efforts, which were ultimately successful, to prepare 1,4-anhydro-α-D-mannopyranose **9** (Figure 2). The synthesis of this anhydro sugar has not been reported previously, although it has been invoked as an intermediate in the solvolysis of α-D-mannopyranosyl fluoride.[22]
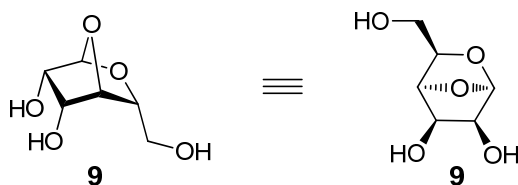

Figure 2: 1,4-Anhydro-α-D-mannopyranose

RESULTS AND DISCUSSION

Brimacombe and co-workers[23] reported the synthesis of 1,4-anhydro-2,3-*O*-isopropylidene-α-L-rhamnopyranose **10**, which was prepared by utilizing an approach based on that outlined in *Method B* of Scheme 1, however they used sodium azide[24,25] to displace the anomeric acetyl group of **11** to generate an anomeric alkoxide (Figure 3). As this represents the only literature example of a 1,4-anhydrosugar bearing exclusively *endo* substituents our initial efforts towards 1,4-anhydro-α-D-mannopyranose were dedicated to a similar approach. As it is unlikely that the 1,4-anhydro system would survive the conditions needed for isopropylidene deprotection,[12] and as it has been shown that non-anomeric ester groups are stable to the reaction conditions,[24] we chose to employ ester protecting groups.
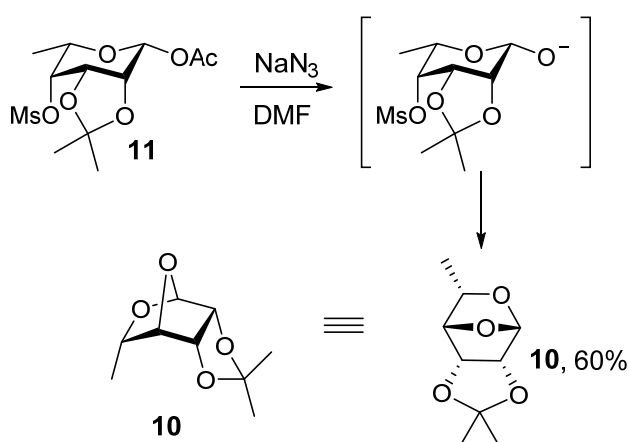

Figure 3: Synthesis of 1,4-anhydro-2,3-*O*-isopropylidene-α-L-rhamnopyranose, by Brimacombe and co-workers.[23]

Methyl talopyranoside **12** was prepared in 5 steps from methyl α-D-mannopyranoside (Figure 4).[26,27] Acetylation with Ac$_2$O and pyridine afforded diacetate **13**, which was subjected to acetolysis (2% H$_2$SO$_4$, Ac$_2$O) to afford the triacetate **14**. Compound **14** was treated with sodium azide in DMF or DMSO; however, under a range of temperatures up to reflux the desired intramolecular substitution to afford **15** did not occur. Instead, only deacetylated talose mesylates were obtained after extended reaction times. In order to prevent cleavage of the acetates at the 2- and 3-positions, more robust benzoate protecting groups were installed by treatment of **12** with BzCl and pyridine, to afford the dibenzoate **16**. Acetolysis of **16** (4% H$_2$SO$_4$, Ac$_2$O) afforded the anomeric acetate **17** in 85% yield. Treatment of **17** with sodium azide in DMF or DMSO at a range of temperatures for extended periods gave no evidence of the 1,4-anhydrosugar **18**, and resulted in only decomposition of

the starting material. For example, trace amounts of tetrabenzoate **19** were isolated, formed by intermolecular transesterification.
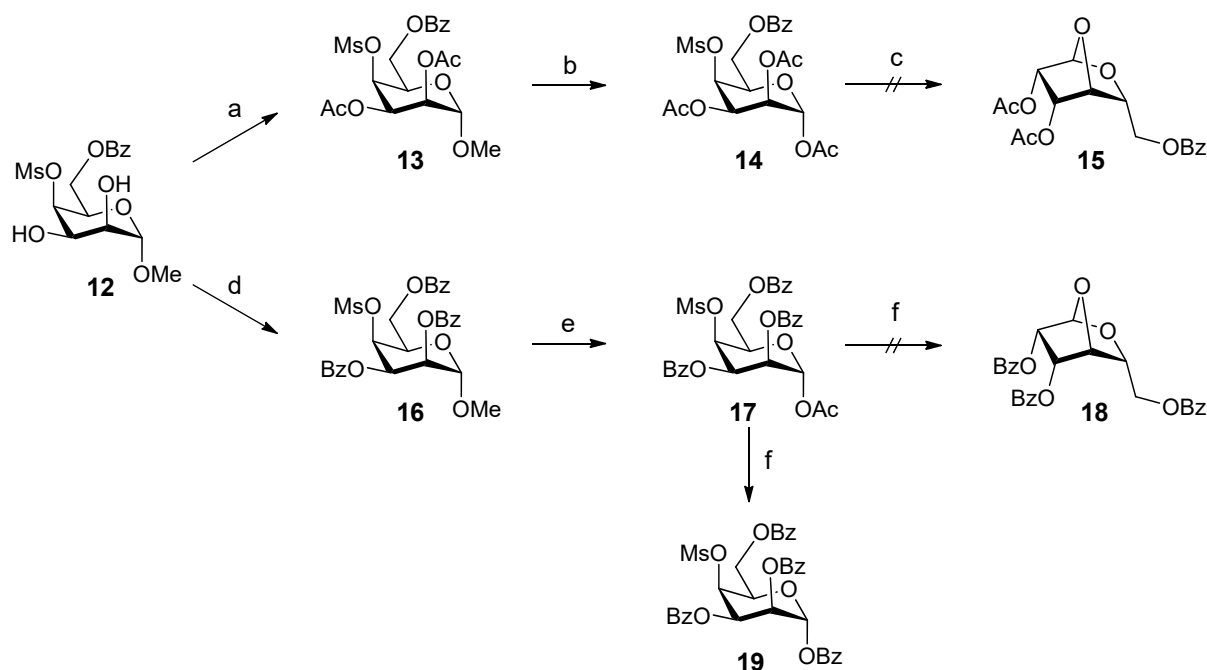

Figure 4: Attempted preparation of 1,4-anhydromannose **15** and **18** by intramolecular substitution of a 4-mesylate by an anomeric alkoxide. *Reagents and conditions:* a) Ac₂O, pyr, 99%. b) 2% H₂SO₄, Ac₂O, 71%. c) NaN₃ in DMF or DMSO. d) BzCl, pyr, 100%. e) 2% H₂SO₄, Ac₂O, 85%. f) NaN₃, DMF or DMSO, traces only of **19**.

Achieving no success in our attempts to generate the desired 1,4-anhydro bridge by *Method B*, which involves reaction of O1 with C4, we sought to reverse the approach and use O4 as nucleophile to react with C1 under Lewis acidic conditions as outlined in *Method C* in Figure 1. Accordingly, the thiotolyl α-D-mannoside **20**[28] was treated with 3.3 equivalents of BzCl at 0 °C in pyridine and allowed to warm to room temperature to afford the tribenzoate **21** in 85% yield (Figure 5). Disappointingly, activation of thiomannoside **21** with *N*-iodosuccinimide and triflic acid at a variety of temperature in a range of different solvents failed to form the 1,4-anhydrosugar **22**. We speculate that the deactivating benzoate protecting groups render the 4-hydroxyl insufficiently nucleophilic to effect the cyclization.
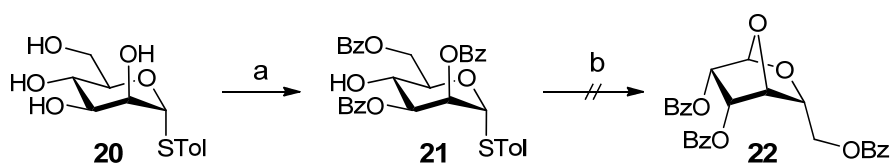
Figure 5: Attempted preparation of 1,4-anhydromannose **22** by intramolecular substitution of C1 by the 4-hydroxyl. *Reagents and conditions:* a) BzCl, pyr, −50 °C, 65%. b) NIS, TfOH, CH$_2$Cl$_2$.

With these disappointing results, we reconsidered our approach and decided to pursue *Method A* in Figure 1, in which the nucleophilicity of the O4 can be assured. When investigating the conversion of 2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl chloride **23** to the 1,4-anhydro sugar **24** using sodium hydride, Sato and co-workers identified a remarkable solvent dependence (Figure 6A).[29] Upon performing the reaction in DMSO mainly 2-benzyloxy-3,6-di-*O*-benzyl-D-glucal **25** was obtained with the desired anhydro sugar **24** isolated in only 8% yield. However, using THF, an impressive 93% yield of **24** resulted. Accordingly, we set about the preparation of the equivalent D-*manno* configured precursor. Acetolysis of methyl 2,3,6-tri-*O*-benzyl-α-D-mannoside **26**[30] afforded the anomeric acetate **27** in an unoptimized 26% yield (Figure 6B). Treatment of **26** with HCl in Et$_2$O gave the anomeric chloride **28** in good yield; however all attempts to obtain the 4-hydroxy chloride **29** through deacetylation were hampered by significant decomposition. Given that hemiacetals may also be converted to glycosyl chlorides by ethereal HCl, **27** was deacetylated by treatment with NaOMe in MeOH, affording an inseparable 7:1 mixture of the D-mannose and D-glucose epimers, **30** and **31**, respectively, the latter arising from Lobry de Bruyn-Alberda van Ekenstein reaction. Treatment of this mixture with HCl in Et$_2$O afforded a 7:1 epimeric mixture of D-mannosyl chloride **29** and D-glucosyl chloride **23**. To effect the cyclization, treatment of the epimeric mixture of glycosyl chlorides **29**/**23** with NaH in THF at reflux for 2 days gave clean conversion to two compounds, in a 7:1 ratio as assessed by ^{1}H NMR analysis. The major product was isolated in 75% yield and was assigned as the elimination product **25**. The less abundant material was isolated in a 15% yield and was assigned as a 1,4-anhydro sugar based on the distinctive signal in the ^{1}H NMR spectrum at δ 5.45 ppm. However, careful analysis of this material revealed it to be the 1,4-anhydro glucopyranose **24**. This disappointing result suggested that the D-*gluco*-configured chloride cyclized essentially quantitatively to the 1,4-anhydro glucopyranose **24**, whereas the more abundant D-*manno*-configured chloride appears to be converted smoothly to the elimination product **25**.
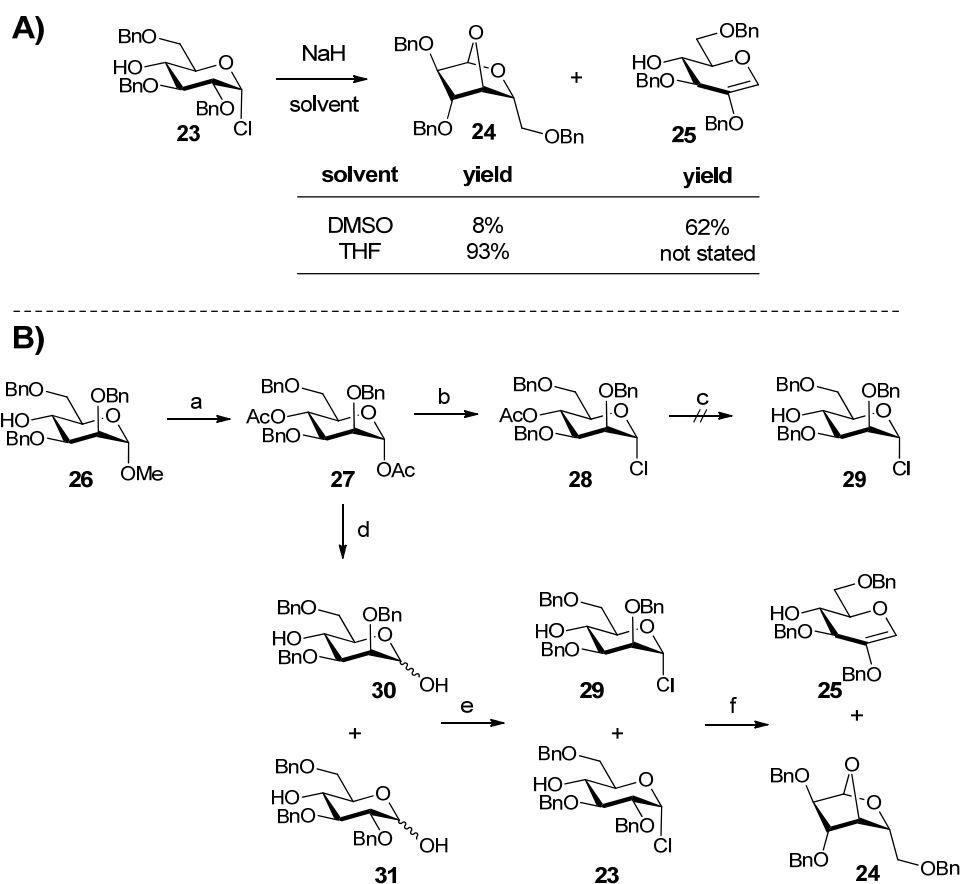
Figure 6: A) Summary of solvent dependence of substitution/elimination reactions of glucosyl chloride **31**, reported by Sato *et al.*[29] **B)** Attempted preparation of 1,4-anhydromannose **22** by intramolecular substitution of C1 by the 4-hydroxyl. *Reagents and conditions:* a) 0.2% H_2SO_4, Ac_2O, 26%. b) HCl in Et_2O, 93%. c) NaOMe, MeOH. d) NaOMe, MeOH, 91%, 7:1 **30/31**. e) HCl in Et_2O, 62%, 7:1 **29/23**. f) NaH, THF, reflux, 90%, 6:1 **25/24**.

To more carefully investigate this reaction, we developed an alternative synthesis of the chloride **29** (Figure 7). Thus acidic hydrolysis of **26** afforded the pure hemiacetal **30**. Treatment of **30** with ethereal HCl afforded a pure sample of the chloride **29**. Overnight reflux of a mixture of **29** and NaH in THF afforded a mixture of 2 compounds in a 13:1 ratio. After purification, the major compound was identified as **25**. Analysis of the minor component **32** led to its assignment as 1,4-anhydro-2,3,6-tri-*O*-benzyl-α-D-mannopyranose, albeit in a yield of 5%. Figure 8 shows a comparison of the ^{1}H NMR spectra of 1,4-anhydro-2,3,6-tri-*O*-benzyl-α-D-glucopyranose **(24)** and 1,4-anhydro-2,3,6-tri-*O*-benzyl-α-D-mannopyranose **32**. Characteristic features of the two 1,4-anhydro sugars are down-field signals for H1 (**24**: δ 5.45, s; **32**: δ 5.59, d, $J_{1,2}$ 2.5 Hz), extensive long range "W" couplings,

particularly in the case of **24**, and upfield signals for H2 (**24**: 3.69, d, $J_{2,3}$ 2.5 Hz; **32**: 3.81, ddd, $J_{1,2}$ 2.5, $J_{2,3}$ 8.3, $J_{2,4}$ 0.9 Hz). Finally, compound **32** was deprotected using H_2 and Pd(OH)$_2$-C to yield 1,4-anhydro-α-D-mannopyranose **9** in 75% yield.
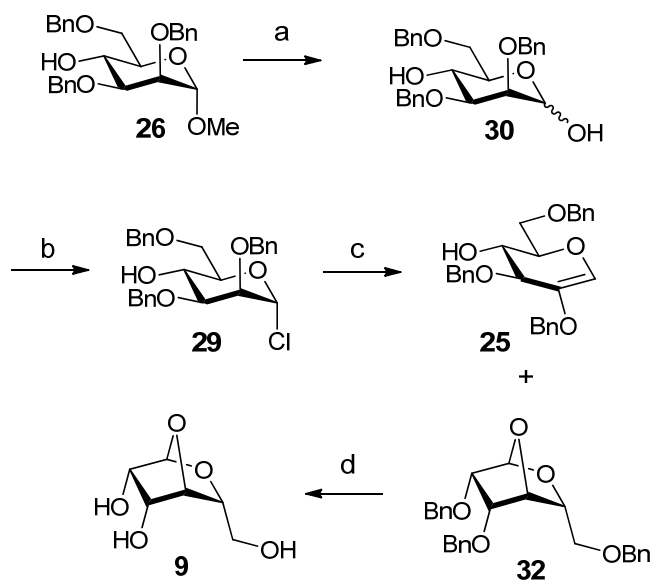

Figure 7: Preparation of 1,4-anhydromannose **9**. *Reagents and conditions:* a) 1 M HCl, AcOH, 51%. b) HCl in Et$_2$O, 51%. c) NaH, THF, reflux, 71% of **25**, 5% of **32**. d) H$_2$, Pd(OH)$_2$/C, EtOAc/EtOH, 67%.
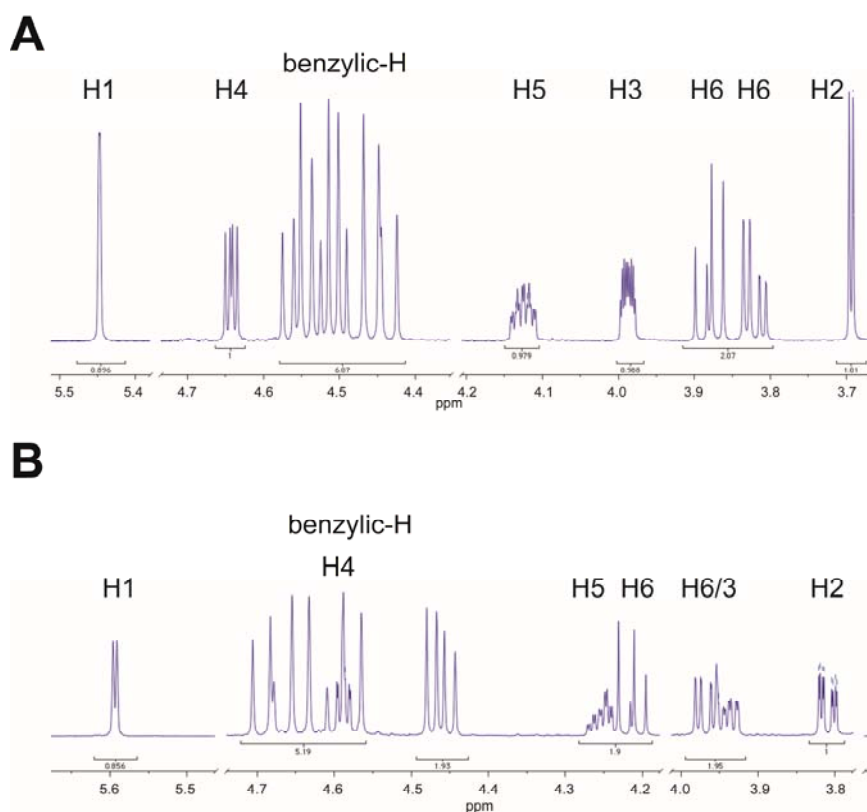
Figure 8: Excerpts of the ^{1}H NMR spectra (500 MHz, CDCl$_3$) of A) 1,4-anhydro-2,3,6-tri-*O*-benzyl-α-D-glucopyranose (**24**) and B) 1,4-anhydro-2,3,6-tri-*O*-benzyl-α-D-mannopyranose (**32**).

CONCLUSION

In summary, we report the first synthesis of the previously unreported 'all *endo*' 1,4-anhydro sugar, 1,4-anhydro-α-D-mannopyranose. This work is significant as it highlights several unsuccessful approaches to this compound and reveals that conditions suitable for cyclization of 2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl chloride **23** to the corresponding 1,4-anhydroglucose derivative **24** in high yield,[29] give predominantly the elimination product **25** when applied to the D-*manno*-configured epimer **29**. Nonetheless, this approach does provide small amounts of the desired 1,4-anhydro mannose derivative, which could be deprotected to yield the parent 1,4-anhydro-α-D-mannopyranose **9**.

EXPERIMENTAL

General methods

^{1}H and ^{13}C NMR were recorded using Inova 400 or Inova 500 instruments (Melbourne). All signals were referenced to TMS (0.00 ppm), or solvent peaks (CDCl$_3$: δ 7.26 ppm for ^{1}H or 77.16 ppm for ^{13}C; D$_2$O: δ 4.80 ppm for ^{1}H or TMS 0.00 ppm for ^{13}C; d$_4$-MeOH: δ 3.49 ppm for ^{1}H or 49.0 ppm for ^{13}C). Melting points were obtained using a Reichert-Jung hot-stage apparatus. TLC analysis used-aluminium backed Merck Silica Gel 60 F$_{254}$ sheets, detection was achieved using UV light, 5% H$_2$SO$_4$ in MeOH, or cerium molybdate ("Hanessian's stain") with charring as necessary. Flash chromatography was performed using Geduran silica gel according to the method of Still *et al.*[31] Dry CH$_2$Cl$_2$, THF, and Et$_2$O were obtained from a dry solvent apparatus (Glass Contour of SG Water, Nashua, U.S.A.).[32] DMF and DMSO were dried over 4 Å molecular sieves. Elemental analyses were performed by C.M.A.S. (Belmont, Victoria).

1,2,3-Tri-*O*-acetyl-6-*O*-benzoyl-4-*O*-methanesulfonyl-α-D-talopyranoside (14)

(i) Methyl 2,3-di-O-acetyl-6-O-benzoyl-4-O-methanesulfonyl-α-D-talopyranoside (**13**)

A solution of methyl 6-*O*-benzoyl-4-*O*-methanesulfonyl-α-D-talopyranoside **12**[26,27] (180 mg, 0.478 mmol) was dissolved in a mixture of acetic anhydride and pyridine (3 mL, 1:2) was stirred for 24 h. The solvent was evaporated under reduced pressure and the residue was dissolved in EtOAc. The organic phase was sequentially washed with 2 M aq. HCl (3×), sat. aq. NaHCO$_3$, water, and sat. aq. NaCl, before being dried (MgSO$_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (acetone/PhMe 1:4) to give the diacetate **13** as a colourless oil (198 mg, 99%), ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.11, 2.17 (6 H, 2 × s, 2 × COCH$_3$), 3.13 (3 H, s, Ms), 3.42 (3 H, s, OCH$_3$), 4.38 (1 H, dt, $J_{4,5}$ 1.1, $J_{5,6}$ 7.0, $J_{5,6'}$ 6.5 Hz, H5), 4.44 (1 H, dd, $J_{5,6}$ 7.0, $J_{6,6'}$ 11.1 Hz, H6), 4.67 (1 H, dd, $J_{5,6}$ 6.6, $J_{6,6'}$ 11.1 Hz, H6'), 4.81 (1 H, dd, $J_{1,2}$ 1.4 Hz, H1), 5.12-5.14 (1 H, m, H4), 5.15 (1 H, ddd, $J_{1,2}$ 1.4, $J_{2,3}$ 3.7, $J_{2,4}$ 1.1 Hz, H2), 5.30 (1 H, t, $J_{2,3}$ $J_{3,4}$ 3.7 Hz, H3), 7.42-7.48 (2 H, m, Ar), 7.55-7.61 (1 H, m, Ar), 8.02-8.08 (2 H, m, Ar); ^{13}C NMR (125 MHz, CDCl$_3$) δ 20.9, 21.1 (2 C, COCH$_3$), 39.0 (1 C, Ms), 55.7 (1 C, OCH$_3$), 62.3, 65.4, 65.5, 67.5, 74.0 (5 C, C2,3,4,5,6), 99.5 (1 C, C1), 128.7, 129.4, 129.9, 133.6 (6 C, Ar), 166.1, 169.6, 170.3 (3 C, C=O).

(ii) 1,2,3-Tri-O-acetyl-6-O-benzoyl-4-O-methanesulfonyl-α-D-talopyranoside (**14**)

A solution of the diacetate **13** (170 mg, 0.408 mmol) in a 2% solution of H_2SO_4 in acetic anhydride (2 mL) was stirred overnight then poured onto ice and extracted with EtOAc. The organic phase was sequentially washed with sat. aq. $NaHCO_3$, H_2O and sat. aq. NaCl, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. The oil was purified by flash chromatography (acetone/PhMe 1:4) to give the α-anomer **14** contaminated with 5% β-anomer, as a colourless oil (143 mg, 71%, 95% α-anomer by ^{1}H NMR), $[\alpha]_D^{19}$ 87 ° (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.11, 2.14, 2.18 (9 H, 3 × s, 3 × $COCH_3$), 3.12 (3 H, s, Ms), 4.40 (1 H, dd, $J_{5,6}$ 8.0, $J_{6,6'}$ 10.8 Hz, H6), 4.45-4.49 (1 H, m H5), 4.64 (1 H, dd, $J_{5,6'}$ 5.8, $J_{6,6'}$ 10.8 Hz, H6'), 5.15-5.16 (1 H, m, H4), 5.18 (1 H, ddd, $J_{1,2}$ 1.6, $J_{2,3}$ 3.7, $J_{2,4}$ 1.1 Hz, H2), 5.34 (1 H, t, $J_{2,3} = J_{3,4}$ 3.7 Hz, H3), 6.18 (1H, d, $J_{1,2}$ 1.6 Hz, H1), 7.43-7.47 (2 H, m, Ar), 7.56-7.60 (1 H, m, Ar), 8.00-8.03 (2 H, m, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.85, 20.94, 20.97 (3 C, 3 × $COCH_3$), 39.0 (1 C, Ms), 61.5, 65.0, 66.3, 68.6, 73.2 (5 C, C2,3,4,5,6), 91.5 (1 C, C1), 128.7, 129.2, 129.9, 133.7 (6 C, Ar), 166.0, 168.0, 169.7, 170.0 (4 C, C=O); HRMS (ESI[+]): m/z 511.0879 [M+Na][+] (calcd. $[C_{20}H_{24}O_{12}S+Na]^+$ 511.0880).

Methyl 2,3,6-tri-*O*-benzoyl-4-*O*-methanesulfonyl-α-D-talopyranoside (16)

Benzoyl chloride (94 μL, 0.810 mmol) was added dropwise to a stirred solution of methyl 6-*O*-benzoyl-4-*O*-methanesulfonyl-α-D-talopyranoside **12**[26,27] (152 mg, 0.404 mmol) in dry pyridine (3.0 mL) under N_2 atmosphere. After 2 h at r.t. the mixture was poured into water (20 mL) and extracted with EtOAc. The organic phase was washed sequentially with 1 M aq. HCl, sat. aq. $NaHCO_3$, H_2O, and sat. aq. NaCl then dried over $MgSO_4$, filtered and evaporated to dryness under reduced pressure. Flash chromatography (30% EtOAc/pet. sp.) of the residue afforded the tribenzoate **16** as colourless oil (236 mg, 100%), $[\alpha]_D^{19}$ -78 ° (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.88 (3 H, s, SCH_3), 3.49 (3 H, s, CH_3), 4.52-4.57 (2 H, m, H5,6), 4.75 (1 H, dd, $J_{5,6'}$ 9.5, $J_{6,6'}$ 14.0 Hz, H6'), 5.02 (1 H, d, $J_{1,2}$ 1.5 Hz, H1), 5.36-5.38 (1 H, m, H4), 5.53 (1 H, ddd, $J_{1,2}$ 1.5, $J_{2,3}$ 3.7, $J_{2,4}$ 1.0 Hz, H2), 5.69 (1 H, t, $J_{2,3} = J_{3,4}$ 3.7 Hz, H3), 7.35-7.65 (9 H, m, Ar), 7.95-7.98 (2 H, m, Ar), 8.06-8.12 (2 H, m, Ar), 8.22-8.25 (2 H, m, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.0 (1 C, Ms), 55.8 (1 C, OCH_3), 62.5, 66.3, 66.7, 68.2, 74.4 (5 C, C2,3,4,5,6), 99.5 (1 C, C1), 128.61, 128.64, 128.69, 128.74, 129.1, 129.5, 129.6, 130.1, 130.3, 130.3 133.5, 133.7, 133.8 (18 C, Ar), 165.4, 165.9, 166.2 (3 C, C=O).

1-*O*-Acetyl-2,3,6-tri-*O*-benzoyl-4-*O*-methanesulfonyl-α-D-talopyranose (17)

A solution of the methyl talopyranoside **16** (195 mg, 0.336 mmol) in 4% H_2SO_4/Ac_2O (5.0 mL) was stirred at r.t. for 5 h then ice-water was added and stirring continued for 30 min. The mixture was extracted with EtOAc (5 × 5 mL) and the organic phase sequentially washed with sat. aq. $NaHCO_3$ (5 ×), H_2O, and sat. aq. NaCl. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a residue that was purified by flash chromatography (30 % EtOAc/pet. sp.) affording **17** as a clear oil (173 mg, 85%). $[\alpha]_D^{19}$ -71 ° (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.21 (3 H, s, $COCH_3$), 2.89 (3 H, s, Ms), 4.51 (1 H, dd, $J_{5,6}$ 7.7, $J_{6,6'}$ 11.1 Hz, H6), 4.61-4.65 (1 H, m, H5), 4.73 (1 H, dd, $J_{5,6'}$ 6.1, $J_{6,6'}$ 11.1 Hz, H6'), 5.41-5.43 (1 H, m, H4), 5.56 (1 H, ddd, $J_{1,2}$ 1.7, $J_{2,3}$ 3.8, $J_{2,4}$ 1.1 Hz, H2), 5.72 (1 H, t, $J_{2,3} = J_{3,4}$ 3.8 Hz, H3), 6.39 (1 H, d, $J_{1,2}$ 1.7 Hz), 7.36-7.65 (9 H, m, Ar), 7.94-7.99 (2 H, m, Ar), 8.04-8.08 (2 H, m, Ar), 8.21-8.24 (2 H, m, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0 (1 C, $COCH_3$), 39.0 (1 C, Ms), 61.7, 66.0, 67.0, 68.8, 73.5 (5 C, C2,3,4,5,6), 91.6 (1 C, C1), 128.7, 128.8, 128.9, 129.3, 129.4, 130.1, 130.3, 133.6, 133.8, 133.9 (18 C, Ar), 165.5, 165.6, 166.1 (3 C, 3 × **C**OPh), 168.10 (1 C, **C**OCH$_3$); HRMS (ESI[+]): *m/z* 635.1192 [M+Na][+] (calcd. [$C_{38}H_{28}O_{12}S$+Na][+] 635.1194).

Attempted formation of 18; Preparation of 1,2,3,6-tetra-*O*-benzoyl-4-*O*-methanesulfonyl-α-D-talopyranose (19)

Reaction of the tribenzoate **17** with NaN_3 in DMF or DMSO at temperatures above 80 °C afforded only decomposed materials and traces of the tetrabenzoate **19**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.91 (3 H, s, Ms), 4.53 (1 H, dd, $J_{5,6}$ 10.4, $J_{6,6'}$ 13.9 Hz, H6), 4.70-4.75 (2 H, m, H5,6'), 5.49-5.51 (1 H, m, H4), 5.74 (1 H, ddd, $J_{1,2}$ 1.7, $J_{2,3}$ 3.7, $J_{2,4}$ 1.1 Hz, H2), 5.86 (1 H, t, $J_{2,3} = J_{3,4}$ 3.7 Hz, H3), 6.64 (1 H, d, $J_{1,2}$ 1.7 Hz, H1), 7.37-7.56 (10 H, m, Ar), 7.63-7.67 (2 H, m, Ar), 7.99-8.03 (2 H, m, Ar), 8.08-8.11 (4 H, m, Ar), 8.24-8.27 (2 H, m, Ar); HRMS (ESI[+]): *m/z* 692.1798 [M+NH$_4$][+] (calcd. [$C_{35}H_{30}O_{12}$+NH$_4$][+] 692.1796). [13]C data was not obtained.

4-Methylphenyl 2,3,6-tri-*O*-benzoyl-1-thio-α-D-mannopyranoside (21)

4-Methylphenyl 1-thio-α-D-mannopyranoside **20**[28] (503 mg, 1.76 mmol) was dissolved in dry pyridine (20 mL) and concentrated to dryness under reduced pressure, this process was repeated twice leaving a small volume of pyridine (10 mL) on the last cycle. The dried solution was cooled to -40 °C and benzoyl chloride (673 μL, 5.80 mmol) was added dropwise over a period of 1 h with stirring. The solvent was evaporated under reduced pressure (50

°C), the residue dissolved in CH_2Cl_2, and the mixture extracted sequentially with 1 M aq. HCl (2 ×), sat. aq. $NaHCO_3$ (2 ×), H_2O and finally sat. aq. NaCl. The organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil which was purified flash chromatography to afford mostly pure tribenzoate **21** (95% by ^{1}H NMR) as a clear oil (280 mg, 65%), $[\alpha]_D^{19}$ 51 ° (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.30 (3 H, s, CH_3), 4.31 (1 H, t, $J_{3,4}$ = $J_{4,5}$ 9.8 Hz, H4), 4.65 (1 H, dd, $J_{5,6}$ 2.0, $J_{6,6'}$ 12.0 Hz, H6), 4.69 (1 H, ddd, $J_{4,5}$ 9.8, $J_{5,6}$ 2.0, $J_{5,6'}$ 4.6 Hz, H5), 4.91 (1 H, dd, $J_{5,6}$ 4.6, $J_{6,6'}$ 12.0 Hz, H6'), 5.61 (1 H, dd, $J_{2,3}$ 3.2, $J_{3,4}$ 9.8 Hz, H3), 5.63 (1 H, d, $J_{1,2}$ 1.6 Hz, H1), 5.89 (1 H, dd, $J_{1,2}$ 1.6, $J_{2,3}$ 3.2 Hz, H2), 7.06 (2 H, d, Ar), 7.32-7.63 (11 H, m, Ar), 7.92-7.99 (4 H, m, Ar), 8.10 (1 H, dd, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3 (1 C, CH_3), 63.8, 68.9, 72.1, 72.4, 73.1 (5 C, C2,3,4,5,6), 86.6 (1 C, C1), 128.6, 128.6, 128.7, 129.2, 129.3, 129.6, 129.88, 129.97, 130.04, 130.05, 130.1, 132.8, 133.4, 133.58, 133.60, 138.5 (24 C, Ar), 165.4, 166.7, 167.1 (3 C, C=O); HRMS (ESI[+]): *m/z* 599.1742 [M+H][+] (calcd. [$C_{34}H_{30}O_8S$+H][+] 599.1734), 616.2009 [M+NH_4][+] (calcd. [$C_{34}H_{30}O_8S$+NH_4][+] 616.2000), 621.1564 [M+Na][+] calcd. [$C_{34}H_{30}O_8S$+Na][+] 621.1554).

Methyl 2,3,6-tri-*O*-benzyl-α-D-mannopyranoside (26)

CF_3CO_2H (2.25 mL, 30.3 mmol) was added dropwise to a cold (0 °C) stirred mixture of methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside[30] (2.80 g, 6.06 mmol) and triethylsilane (4.84 mL, 30.3 mmol) in CH_2Cl_2 (25 mL). After 30 min the mixture was allowed to warm to r.t. and stirred for a further 4 h before being diluted with EtOAc (100 mL). The mixture was washed with sat. aq. $NaHCO_3$, then sat. aq. NaCl, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography (20% EtOAc/pet. sp.) of the resultant crude material gave the tribenzyl ether **26** as a clear oil (2.13 g, 76%), $[\alpha]_D^{19}$ -3° (c 1.00, $CHCl_3$), lit.[33] $[\alpha]_D^{25}$ 0° (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.52 (1 H, d, $J_{4,OH}$ 2.0 Hz, OH), 3.36 (3 H, s, CH_3), 3.68-3.84 (5 H, m, H2,3,5,6,6'), 4.05 (1 H, dt, $J_{3,4}$ = $J_{4,5}$ 9.4, $J_{4,OH}$ 2.0 Hz, H4), 4.49-4.69 (6 H, m, 3 × C**H**$_2$Ph), 4.79 (1 H, d, $J_{1,2}$ 1.7 Hz, H1), 7.25-7.38 (15 H, m, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.0 (1 C, CH_3), 68.0, 70.6, 71.5, 71.9, 72.8, 73.7, 74.0, 79.8 (8 C, 3 × C**H**$_2$Ph, C2,3,4,5,6), 99.3 (1 C, C1), 127.64, 127.72, 127.78, 127.85, 127.90, 128.0, 128.4, 128.5, 128.6, 138.33, 138.35, 138.41 (18 C, Ar).

1,4-Di-*O*-acetyl-2,3,6-tri-*O*-benzyl-α-D-mannopyranose (27)

A solution of mannoside **26** (402 mg, 0.865 mmol) in 0.2% H_2SO_4 in Ac_2O (1 mL) was stirred at r.t. for 45 min then cold sat. aq. $NaHCO_3$ was added. The mixture was diluted with EtOAc and sequentially washed with sat. aq. $NaHCO_3$ (3 ×), water, and sat. aq. NaCl, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was subjected to flash chromatography (30% EtOAc/pet. sp.) to give the diacetate **27** as white needles (120 mg, 26%), m.p. 102-103 °C. $[\alpha]_D^{20}$ 23 ° (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.93, 2.05 (6 H, 2 × s, 2 × CH_3), 3.55 (1 H, dd, $J_{5,6}$ 3.6, $J_{6,6'}$ 10.8 Hz, H6), 3.59 (1 H, dd, $J_{5,6'}$ 5.5, $J_{6,6'}$ 10.8 Hz, H6'), 3.73 (1 H, dd, $J_{1,2}$ 2.2, $J_{2,3}$ 3.1 Hz, H2), 3.77 (1 H, dd, $J_{3,4}$ 3.1, $J_{4,5}$ 9.6 Hz, H3), 3.87-3.95 (1 H, m, $J_{4,5}$ 9.5, $J_{5,6}$ 3.6, $J_{5,6'}$ 5.5 Hz, H5), 4.44 (1 H, d, ^2J 12.1 Hz, C**H**$_2$Ph), 4.50-4.54 (3 H, m, 3 × C**H**$_2$Ph), 4.72 (2 H, s, C**H**$_2$Ph), 5.43 (1 H, t, $J_{3,4}$ = $J_{4,5}$ 9.6 Hz, H4), 6.18 (1 H, d, $J_{1,2}$ 2.2 Hz, H1), 7.23-7.37 (15 H, m, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 21.2 (2 C, 2 × CH_3), 68.7, 70.0, 72.0, 72.8, 73.1, 73.2, 73.8, 76.3 (8 C, 3 × **C**H$_2$Ph, C2,3,4,5,6), 92.1 (1 C, C1), 127.67, 127.76, 127.89, 127.93, 128.1, 128.2, 128.46, 128.51, 137.8, 138.1 (18 C, Ar), 168.9, 169.9 (2 C, 2 × **C**OCH$_3$); Anal. Calcd for $C_{31}H_{34}O_8$: C, 69.65; H, 6.41. Found: C, 69.71; H, 6.33.

4-*O*-Acetyl-2,3,6-tri-*O*-benzyl-α-D-mannopyranosyl chloride (28)

A solution of the diacetate **27** (10.0 mg, 18.7 mmol) in ether saturated with HCl (5 mL) was stirred for 30 min at 0 °C under N_2. The mixture was warmed to r.t. and stirred for a further 30 min. The solvent was evaporated under a stream of N_2 and Et_2O (10 mL) was added. This process was repeated five times, and the dried residue was subjected to flash chromatography (15% EtOAc/pet. sp.) giving the chloride **28** (8.9 mg, 93%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.86, 1.98 (6 H, 2 × s, 2 × CH_3), 3.47 (1 H, dd, $J_{5,6}$ 3.5, $J_{6,6'}$ 10.8 Hz, H6), 3.47 (1 H, dd, $J_{5,6'}$ 5.5, $J_{6,6'}$ 10.8 Hz, H6'); 3.66 (1 H, overlapping dd, $J_{1,2}$ 2.6, $J_{2,3}$ 2.8 Hz, H2), 3.70 (1 H, dd, $J_{2,3}$ 2.8, $J_{3,4}$ 9.7 Hz, H3), 3.82-3.86 (1 H, m, H5), 4.36-4.48 (4 H, m, C**H**$_2$Bn), 4.66 (2 H, s, C**H**$_2$Bn), 5.36 (1 H, t, $J_{3,4}$ = $J_{4,5}$ 9.7 Hz, H4), 6.11 (1 H, d, $J_{1,2}$ Hz, H1), 7.16-7.31 (15 H, Ar). Owing to the instability of this compound it was not further characterized.

2,3,6-Tri-*O*-benzyl-α-D-mannopyranose (30)

(i) From mannoside (26)

A solution of the mannoside **26** (2.00 g, 4.31 mmol), AcOH (20 mL) and 1 M aq. HCl (5 mL) was heated in an oil bath at 105 °C for 2.5 h then poured into ice-water and extracted with EtOAc. The organic phase was washed with sat. aq. $NaHCO_3$ then sat. aq. NaCl, dried

(MgSO$_4$), filtered, and concentrated under reduced pressure. Flash chromatography (30% EtOAc/pet. sp.) of the residue gave the title compound **30** as a clear oil, which was used for subsequent reactions without further purification (710 mg, 37%), $[\alpha]_D^{19}$ -20° (c 1.00, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.49 (1 H, d, $J_{1,OH}$ 2.0 Hz, OH), 3.45 (1 H, d, $J_{4,OH}$ 2.0 Hz, OH), 3.69 (1 H, dd, $J_{5,6}$ 7.0, $J_{6,6'}$ 10.3 Hz, H6), 3.76 (1 H, dd, $J_{2,3}$ 3.1, $J_{3,4}$ 9.5 Hz, H3), 3.79 (1 H, dd, $J_{1,2}$ 1.8, $J_{2,3}$ 3.1 Hz, H2), 3.81 (1 H, dd, $J_{5,6'}$ 2.8, $J_{6,6'}$ 10.3 Hz, H6'), 3.93 (1 H, dt, $J_{3,4}$ = $J_{4,5}$ 9.5, $J_{4,OH}$ 2.0 Hz, H4), 4.48 (1 H, d, ^2J 11.7 Hz, C**H**$_2$Ph), 4.55-4.60 (3 H, m, 3 × C**H**$_2$Ph), 4.64 (1 H, d, ^2J 12.4 Hz, C**H**$_2$Ph), 4.68 (1 H, d, ^2J 12.4 Hz, C**H**$_2$Ph), 5.28 (1 H, br s, H1), 7.25-7.38 (15 H, m, Ar); ^{13}C NMR (125 MHz, CDCl$_3$) δ 67.8, 70.7, 71.5, 71.9, 72.8, 73.6, 74.2, 79.4 (8 C, 3 × **C**H$_2$Ph, C2,3,4,5,6), 92.9 (1 C, C1), 127.80, 127.88, 127.93, 128.0, 128.3, 128.47, 128.52, 128.6, 128.7, 138.00, 138.2, 138.3 (18 C, Ar); HRMS (ESI$^+$): *m/z* 451.2127 [M+H]$^+$ (calcd. [C$_{27}$H$_{30}$O$_6$+H]$^+$ 451.2115), 468.2383 [M+NH$_4$]$^+$ (calcd. [C$_{27}$H$_{30}$O$_6$+NH$_4$]$^+$ 468.2381), 473.1934 [M+Na]$^+$ calcd. [C$_{27}$H$_{30}$O$_6$+Na]$^+$ 473.1935).

(ii) From diacetate (27)

A small piece of sodium metal was added to a stirring solution of diacetate **27** (63.5 mg, 0.12 mmol) in MeOH (5 mL). After stirring for 1 h at r.t. the mixture was neutralized by the addition of Amberlite IR-120 (H$^+$), filtered and concentrated to an oil. Chromatography of the mixture as per above afforded the mannose derivative **30** as a mixture with the glucose epimer **31** (48.5 mg, 91%, 7:1 D-*manno*/D-*gluco* by ^{1}H NMR).

*2,3,6-Tri-*O*-benzyl-α-D-glucopyranose* **31**: Partial ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.23 (1 H, t, $J_{1,2} \approx J_{1,OH}$ 2.8 Hz, H1).

1,4-Anhydro-2,3,6-tri-*O*-benzyl-α-D-mannopyranose (32) and 3,6-di-*O*-benzyl-2-benzyloxy-D-glucal (25)

*(i) 2,3,6-Tri-*O*-benzyl-α-D-mannopyranosyl chloride (29)*

The crude hemiacetal **30** (250 mg, 0.555 mmol) was dissolved in dry Et$_2$O (10 mL) under an inert (N$_2$) atmosphere and the solution was saturated with HCl gas. After stirring for 72 h at r.t. the solvent was evaporated under a stream of N$_2$ and Et$_2$O (10 mL) was added. This process was repeated five times and the dried residue was subjected to flash chromatography (15% EtOAc/pet. sp.) giving the chloride **29** as a clear oil (133 mg, 51%), $[\alpha]_D^{19}$ 53 ° (c 1.00, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.76 (1 H, dd, $J_{5,6}$ 3.5, $J_{6,6'}$ 10.9 Hz, H6), 3.80 (1 H, dd, $J_{5,6'}$ 4.8, $J_{6,6'}$ 10.9 Hz, H6'), 3.89 (1 H, dd, $J_{1,2}$ 1.7, $J_{2,3}$ 3.1 Hz, H2), 3.99-4.04 (2 H, m, H3,5), 4.15 (1 H, t, $J_{3,4}$ = $J_{4,5}$ 9.5 Hz, H4), 4.54-4.71 (6 H, m, 3 × C**H**$_2$Ph), 6.12 (1 H, dd, $J_{1,2}$

1.7 Hz, H1), 7.25-7.38 (15 H, m, Ar); ^{13}C NMR (125 MHz, CDCl$_3$) δ 67.2, 69.4, 72.4, 73.1, 73.7, 74.4, 77.2, 77.8 (8 C, 3 × **CH$_2$**Ph, C2,3,4,5,6), 91.6 (1 C, C1), 127.78, 127.85, 128.05, 128.08, 128.13, 128.16, 128.51, 128.64, 128.71, 137.6, 137.9, 138.1 (18 C, Ar); HRMS (ESI$^+$): *m/z* 433.20074 [M-Cl]$^+$ (calcd. [C$_{27}$H$_{29}$O$_5$Cl-Cl]$^+$ 433.20095).

(ii) *1,4-Anhydro-2,3,6-tri-O-benzyl-α-D-mannopyranose* *(32)* *and* *3,6-di-O-benzyl-2-benzyloxy-D-glucal (25)*

Chloride **29** (30.0 mg, 0.064 mmol) was dissolved in dry THF (15 mL) under an N$_2$ atmosphere and an excess of NaH (20 mg) was added with stirring. The mixture was heated to reflux and stirred overnight. The reaction was quenched by the addition of MeOH (1 mL) and the mixture was poured into water and extracted three times with CHCl$_3$. The CHCl$_3$ extract was washed with 0.5 M HCl and sat. aq. NaHCO$_3$, dried (MgSO$_4$), filtered, and concentrated under reduced pressure. The resultant oil was subjected to flash chromatography on silica gel (15% EtOAc/pet. sp.) to afford the anhydro sugar **32** as a white solid (1.3 mg, 5%), m.p. 71-73 °C (CHCl$_3$; [α]$_D$^{18} -45 ° (c 0.415, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.81 (1 H, ddd, $J_{1,2}$ 2.5, $J_{2,3}$ 8.3, $J_{2,4}$ 0.9 Hz, H2), 3.94 (1 H, ddd, $J_{2,3}$ 8.3, $J_{3,4}$ 4.6, $J_{3,5}$ 1.0 Hz, H3), 3.97 (1 H, dd, $J_{5,6}$ 3.7, $J_{6,6'}$ 10.1 Hz, H6), 4.21 (1 H, dd, $J_{5,6'}$ 7.7, $J_{6,6'}$ 10.1 Hz, H6'), 4.25 (1 H, dp, $J_{3,5}$ 1.0, $J_{4,5}$ 3.7, $J_{5,6}$ 3.7, $J_{5,6'}$ 7.7 Hz, H5), 4.46 (2 H, 2 × d, 2 × **CH$_2$**Ph), 4.56-4.71 (5 H, m, 2 × **CH$_2$**Ph, H4), 5.59 (1 H, d, $J_{1,2}$ 2.5 Hz, H1), 7.23-7.39 (15 H, m, Ar); ^{13}C NMR (125 MHz, CDCl$_3$) δ 69.1, 72.2, 73.0, 73.4, 74.6, 74.7, 78.3, 79.5 (8 C, 3 × **CH$_2$**Ph, C2,3,4,5,6), 101.9 (1 C, C1), 127.6, 127.78, 127.86, 127.89, 127.92, 127.97, 128.4, 128.5, 138.0, 138.2, 138.6 (18 C, Ar); HRMS (ESI$^+$): *m/z* 455.1828 [M+Na]$^+$ (calcd. [C$_{27}$H$_{28}$O$_5$+Na]$^+$ 455.1829).

Also obtained was compound **25**, colourless oil (19.3 mg, 71%), [α]$_D$^{18} -25° (CHCl$_3$; lit.[29] -22°); ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.28 (1 H, d, $J_{4,OH}$ 5.5 Hz, OH), 3.71 (1 H, dd, $J_{5,6}$ 3.7, $J_{6,6'}$ 10.7 Hz, H6), 3.79 (1 H, dd, $J_{5,6'}$ 5.9, $J_{6,6'}$ 10.7 Hz, H6'), 3.95 (1 H, m, H5), 4.06 (1 H, overlapping dt, $J_{3,4}$ 5.6, $J_{4,5}$ 7.5, $J_{4,OH}$ 5.5 Hz, H4), 4.15 (1 H, d, $J_{3,4}$ 5.6 Hz, H3), 4.57 (2 H, d, **CH$_2$**Ph), 4.67-4.74 (3 H, m, 3 × **CH$_2$**Ph), 4.84 (1 H, d, ^2J 11.7 Hz, **CH$_2$**Ph), 6.27 (1 H, d, H1), 7.25-7.38 (15 H, m, Ar); ^{13}C NMR (125 MHz, CDCl$_3$) δ 68.83, 68.87, 71.3, 72.7, 73.7, 77.0, 77.3 (7 C, 3 × **CH$_2$**Ph, C3,4,5,6), 127.66, 127.85, 127.90, 127.93, 127.96, 128.04, 128.08, 128.55, 128.57, 128.59 (16 C, 15 × Ar, C1), 137.2, 138.0, 138.6, 139.0 (4 C, 3 × Ar, C2). The NMR data was consistent with literature.[29]

1,4-Anhydro-2,3,6-tri-*O*-benzyl-α-D-glucopyranose (24)[34]

Reaction of the mixed chlorides **29** and **23** according to the protocol described for the synthesis of the anhydro mannose derivative **32** afforded a mixture of the anhydro glucopyranose **24** and the alkene **25** by (10.0 mg, 90%, 6:1 alkene **25**/1,4-anhydroglucose **24**), ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.69 (1 H, d, $J_{2,3}$ 2.5 Hz, H2), 3.82 (1 H, dd, $J_{5,6}$ 4.2, $J_{5,6'}$ 10.6 Hz, H6), 3.88 (1 H, dd, $J_{5,6'}$ 7.7, $J_{5,6'}$ 10.6 Hz, H6'), 3.99 (1 H, m, H3), 4.13 (1 H, m, H5), 4.42-4.58 (6 H, m, 3 × C**H$_2$**Ph), 4.64 (1 H, dd, $J_{3,4}$ 4.7, $J_{4,5}$ 3.1 Hz, H4), 5.45 (1 H, s, H1), 7.21-7.37 (15 H, m, Ar).

1,4-Anhydro-α-D-mannopyranose (9)

The protected anhydro sugar **32** (6.0 mg, 0.014 mmol) was dissolved in a mixture of EtOAc/EtOH (3 mL, 9:1) and Pd(OH)$_2$/C (3 mg) was added. The mixture was stirred under H$_2$ for 70 h then filtered through Celite and concentrated under reduced pressure. The crude residue was purified by flash chromatography (97:2:1 EtOAc:MeOH:H$_2$O) and reverse phase chromatography (H$_2$O, C$_{18}$) to give 1,4-anhydro-α-D-mannopyranose **9** as a colourless gum (1.5 mg, 67%), [α]$_D^{19}$ -54 ° (c 0.10, MeOH); ^{1}H NMR (500 MHz, d$_4$-methanol) δ 3.85 (1 H, dd, $J_{1,2}$ 2.6, $J_{2,3}$ 8.7, $J_{2,4}$ 0.8 Hz, H2), 3.95 (1 H, dd $J_{5,6}$ 2.9, $J_{6,6'}$ 11.4 Hz, H6), 3.99-4.07 (3 H, m, H3,5,6'), 4.54 (1 H, ddd, $J_{2,4}$ 0.8, $J_{3,4}$ 3.2, $J_{4,5}$ 4.8 Hz, H4), 5.45 (1 H, d, $J_{1,2}$ 2.6 Hz, H1); ^{13}C NMR (125 MHz, d$_4$-methanol) δ 60.7, 67.8, 70.2, 81.3, 82.4 (5 C, C2,3,4,5,6), 103.7 (1 C, C1); HRMS (ESI$^+$): m/z 185.0420 [M+Na]$^+$ (calcd. [C$_{27}$H$_{28}$O$_5$+Na]$^+$ 185.0420).

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1,4-Anhydro-α-D-mannopyranoside