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Synthesis of orthogonally protected D-olivoside, 1,3-di-*O*-acetyl-4-*O*-benzyl-2,6-dideoxy-D-arabinopyranose, as a *C*-glycosyl donor

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ABSTRACT

1,3-Di-*O*-acetyl-4-*O*-benzyl-2,6-dideoxy-D-arabinopyranose (**11**) was synthesised from thiophenyl α-D-mannopyranoside (**21**) in an eight-step sequence. Tosylation of **21** and subsequent reaction with 2,2-dimethoxypropane gave tosylate **22**, which upon treatment with lithium aluminium hydride furnished 6-deoxy glycoside **24** and by-product thiophenyl 6-deoxy-2-*O*-isopropyl-α-D-arabinopyranoside. The X-ray crystal structure of the latter was determined. Benzylation of the 4-hydroxyl group of **24** and subsequent protecting group manipulation gave D-rhamnosyl bromide **29**, which on treatment with zinc–copper couple gave the orthogonally protected D-rhamnal **30**. Triphenylphosphine hydrogen bromide catalysed addition of acetic acid to **30** furnished the target molecule **11**. The scandium(III) triflate promoted reaction of **11** and 2-naphthol gave the corresponding C-glycoside **36** in 86% yield.

1. Introduction

The angucycline family of antibiotics is secondary metabolites produced by microorganisms[1,2] of which the first member was discovered in 1965.[3,4] These antibiotics have attracted much attention due to the wide range of biological activities that they exhibit, which include antibacterial,[5–7] antiviral,[8] antitumour[9–11] and enzyme inhibition properties.[12] 2,6-Dideoxy- and 2,3,6-trideoxy-sugars such as D-olivose (**1**) and L-rhodinose (**2**) are present in many of these antibiotics and may be attached at different positions of the angucycline framework either by *C*- or *O*-glycosidic linkages.[1] Urdamycin B (**3**), a secondary metabolite of *Streptomyces fradiae*, shows glycosylation typical of the *C*-glycosyl angucycline subgroup.[13] The oligosaccharide moiety of **3** consists of a trisaccharide containing two D-olivose (**1**) and one L-rhodinose (**2**) residues. A β-D-olivose residue is attached to C-9 of the benzo[*a*]anthraquinone ring system by a *C*-glycosidic linkage. The oligosaccharide chain then extends from O-3 of this sugar.[1]

In an ongoing synthetic programme we have developed a Diels–Alder strategy to access certain members of the angucycline antibiotics. The key part of the strategy involves the reaction of substituted naphthoquinones with dienes resulting in the formation of a functionalised benzo[*a*]anthraquinone ring system. Further modifications to the tetracyclic core has resulted in the syntheses of (±)-rubiginone B1[14] and B2,[15] emycin A,[14,16] (+)-ochromycinone[16] and (−)-tetrangomycin.[17–19] Furthermore, the reaction of *C*-glycosyl-napthoquinone **5** and diene (±)-**6** provided, after further modification, *C*-glycosidic angucycline **7**.[20] Other groups have utilised *C*-glycosidic naphthoquinones as dienophiles for the synthesis of angucycline antibiotics. Sulikowski et al.[21,22] used *C*-glycosyl dienophile **8** in their elegant synthesis of urdamycinone B (**4**), while Matsuo et al.[23,24] used the unprotected C-glycoside **9** as a dienophile in their approach to **4**.

Given the success of these C-glycosides as dienophiles for the synthesis of **4**, we reasoned that orthogonally protected *C*-glycosyl-naphthoquinone **10** would expedite the synthesis of more highly glycosylated angucyclines such as urdamycin B (**3**). Given this, we focussed on the preparation of the corresponding *C*-glycosyl donor,

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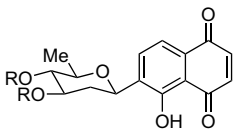
1,3-di-*O*-acetyl-4-*O*-benzyl-2,6-dideoxy-D-arabinopyranose **11**. Not only would this compound allow access to *C*-glycosyl-naphthoquinones, it would also serve as a precursor to 2,6-dideoxyglycosyl trichloroacetimidates.[25] Tanaka et al. have shown that this latter class of glycosyl donor can be used for the direct synthesis of β-2,6-dideoxyoligosaccharides.



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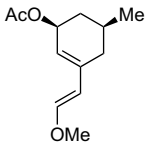
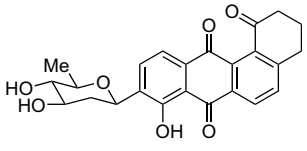
9 R = H



(±)-**6**



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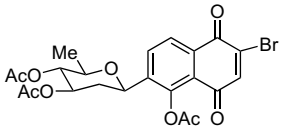

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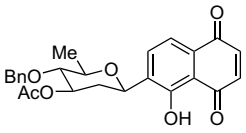

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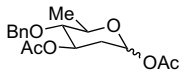

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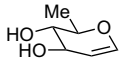
2. Result and discussion

Our initial approach to **11** was based upon modification of 6-deoxy-D-glucal **12**, which can be prepared from 6-*O*-tosyl-D-glucal **13** by treatment with lithium aluminium hydride.[26,27]



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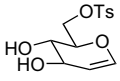

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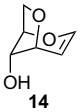

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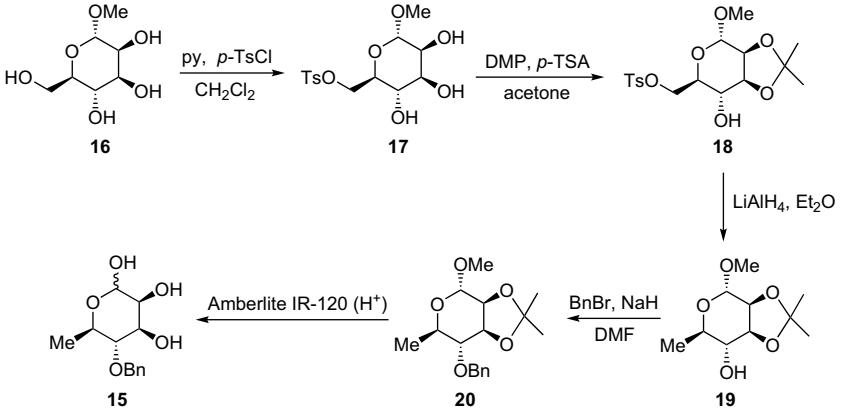
We found this reaction to be very variable, especially on larger scale where a significant quantity of the anhydro-sugar **14** was formed. It was envisaged that **11** could be synthesised from methyl 4-*O*-benzyl-D-rhamnose **15**. A strategy was devised to access **15** starting from methyl α-D-mannopyrannoside **16** (Scheme 1).

Methyl α-D-mannopyranoside (**16**) was converted, via tosylate **17** and acetonide **18**, into D-rhamnoside **19** in 41% overall yield using the chemistry of Nishio et al.[28] Benzylation of **19** under standard conditions gave **20** in good yield (65%). The next step in the synthetic sequence was the hydrolysis of the isopropylidene group and methyl glycoside of **20** using aqueous acetic acid and ion exchange resin to give 4-*O*-benzyl-D-rhamnopyranose (**15**). The reaction was monitored by TLC and after a few hours a new compound was formed. A preliminary examination of the reaction mixture by ^{1}H NMR spectroscopy showed that the isopropylidene group had been hydrolysed but not the methyl glycoside. The mixture was heated at reflux and monitored by TLC. After 72 h the intermediary methyl glycoside had been consumed. Unfortunately, analysis of the crude reaction product showed that it was a complex mixture of products.

Given the problem associated with the hydrolysis of **20**, an alternative route to 4-*O*-benzyl-D-rhamnal derivatives was developed (Scheme 2).

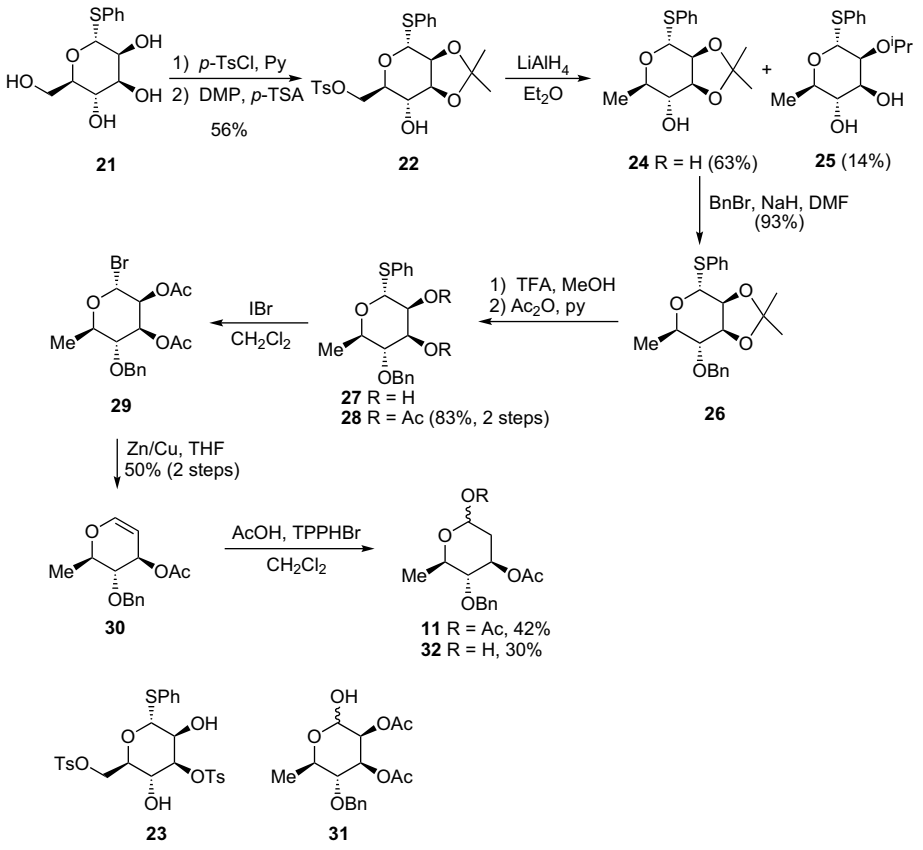
Tosylation and subsequent treatment of thiophenyl glycoside **21**[29] with dimethoxypropane under acidic conditions gave acetonide **22** in 56% yield. A by-product, thiophenyl 3,6-di-*O*-tosyl-α-D-mannopyranoside (**23**), was also isolated in 7% yield from the reaction. Reduction of **22** was achieved with lithium aluminium hydride in dry ether to give **24** in 63% yield. The spectroscopic data were in good agreement with those reported for *ent*-**24**, which has been prepared previously from L-rhamnose by Crich and Picione[30] and also by Zegelaar-Jaarsveld et al.[31] An unexpected by-product, isopropyl ether **25** was also isolated from the reduction. The analytical and spectroscopic data were consistent with the structure of **25**. A strong HMBC correlation between the isopropyl methine-proton and C-2 indicated that the isopropyl group was attached to O-2 of the sugar. Furthermore, the molecular structure of **25** was confirmed from a single X-ray crystal diffraction study and is shown in Figure 1.[32]

Benzylation of **24** using benzyl bromide and sodium hydride in DMF afforded **26** in 93% yield. The spectroscopic data of **26** were consistent with those of its enantiomer.[30,31] Hydrolysis of **26** was effected using trifluoroacetic acid in methanol to give **27**, which on subsequent acetylation furnished **28** in 83% yield for the two steps. Rhamnoside **28** has been previously reported by Yu and Wang,[33] however, no details of the synthesis or data were given. Reaction of **28** with iodine monobromide gave rhamnosyl bromide **29**, which proved extremely labile. To circumvent this, the crude reaction product was immediately treated with zinc–copper couple using the



16 **17** **18** **19** **20** **15**

Scheme 1.



Scheme 2.

method of Bredenkamp et al.[34] to give the target rhamnal **30** in 50% yield for the two steps along with hydrolysis product **31** in 36% yield. The stability of bromide **29** is in contrast to that of **34** (Scheme 3). The reaction of thiophenyl glycoside **33** with iodine monobromide gave **34**, which upon subsequent treatment with zinc–copper couple furnished tri-*O*-acetyl-D-rhamnal **35** in 72% yield for the two steps.

The last step in the sequence to **11** (Scheme 2) was the triphenylphosphine hydrogen bromide catalysed addition of acetic acid to glycal **30**. The expected 2-deoxy glycosyl acetate **11** was obtained in 42% yield as a 4:1 mixture of α- and β-anomers, along with a 30% yield of a 4.5:1 mixture of α- and β-anomers the corresponding pyranose **32** and starting material (17%) was also recovered from the reaction. Olivose **32** presumably arises from addition of adventitious water to **30** or by hydrolysis of **11**. Acetylation of **32** under standard conditions gave the target compound **11** in quantitative yield. Olivoside **11** was then tested as a glycosyl donor

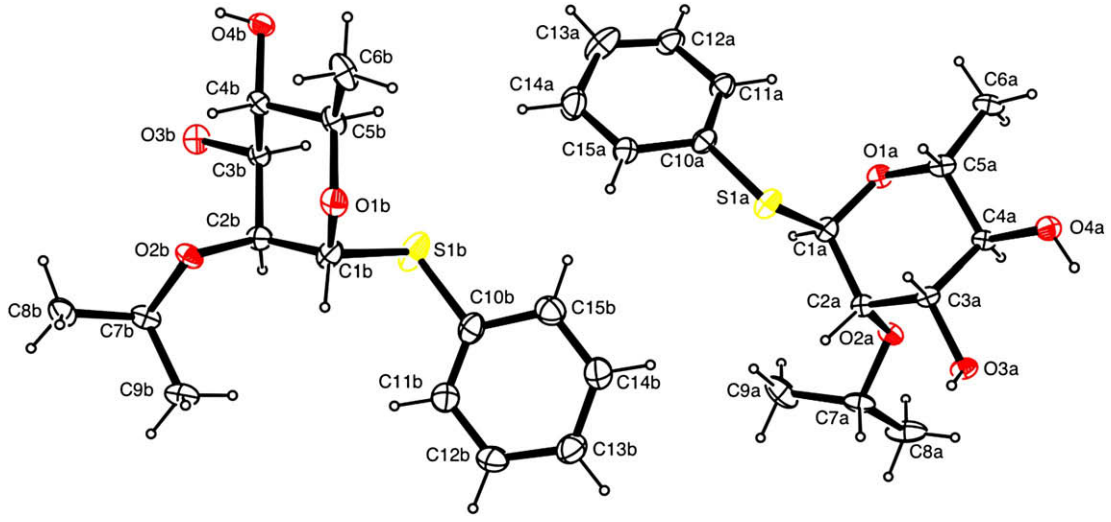
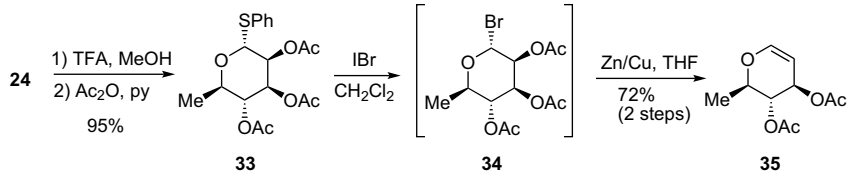
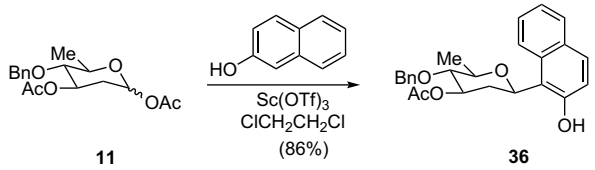


Figure 1. The asymmetric unit of **25** showing the atom numbering scheme for the two unique molecules with ellipsoids drawn at the 50% probability level. For clarity only the major disorder components of the phenyl rings are shown.



Scheme 3.



Scheme 4.

(Scheme 4). Gratifyingly, reaction of **11** and 2-naphthol in 1,2-dichloroethane catalysed by scandium(III) triflate[35,36] proceeded smoothly and gave β-C-glycoside **36** in 86% yield.

3. Conclusions

In conclusion, we have developed a reliable eight-step synthesis of the orthogonally protected *C*-glycosyl donor, 1,3-di-*O*-acetyl-4-*O*-benzyl-2,6-dideoxy-D-arabinopyranose (**11**) from thiophenyl α-D-mannopyranoside. This strategy also provides an alternative synthesis of 3,4-di-*O*-acetyl-D-rhamnal (**35**) a key intermediate for the synthesis of D-olivosides. Olivoside **11** proved to be an effective *C*-glycosyl donor in its scandium(III) triflate promoted glycosylation of 2-naphthol.

4. Experimental

4.1. General

Melting points were recorded on a Gallenkamp capillary melting point apparatus or a Mettler Toledo FP62 automatic melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR assignments were made on the basis of chemical shift and the coupling information obtained from one or two-dimensional experiments (e.g., COSY, HSQC, HMBC, DEPT and NOESY). Infrared (IR) spectra were recorded on a Perkin Elmer 1600 series FTIR spectrophotometer. Low resolution mass spectra were run on a Shimadzu QP8000 alpha mass detector with APCI or ESI probes using a manual Rheodyne injector and a Shimadzu LC10AD HPLC pump to provide direct sample injection. High resolution mass spectra were recorded by Bruce Clark using a Kratos MSORF mass spectrometer. Elemental analyses were carried out using a Carlo Erba 1108 CHNS combustion analyser. Polarimetry was performed using a Jasco DIP1000 Digital polarimeter with a cell of 10 cm in length and 3.5 mm internal diameter and the observed rotation was measured at 589 nm (sodium D line). Thin-layer chromatography (TLC) was performed on Merck silica gel (DC Alurolle Kieselgel 60 F_{254}, 0.2 mm layer) plates in the solvent system indicated. Organic reagents for moisture sensitive reactions were distilled from the following drying agents: tetrahydrofuran and ether (sodium-benzophenone ketyl), dichloromethane and triethylamine (calcium hydride). All moisture sensitive reactions were performed under a nitrogen atmosphere.

*4.1.1. Thiophenyl 2,3-O-isopropylidene-6-O-p-toluenesulfonyl-α-D-mannopyranoside (**22**)*

p-Toluenesulfonyl chloride (8.66 g, 45.4 mmol) was added to a mixture of thioglycoside (**21**) (9.90 g, 36.0 mmol) in dichloromethane (75 mL) and pyridine (75 mL) at 0 °C. The mixture was slowly warmed to room temperature and stirred overnight. The solvent was removed in vacuo and the residue was dissolved in dichloromethane. The solution was washed with 1.0 M HCl (150 mL), saturated aqueous sodium hydrogen carbonate solution (2×100 mL), water (2×100 mL) and brine (50 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was dissolved in dichloromethane (50 mL), *p*-toluenesulfonic acid (1.00 g, 5.26 mmol) and 2,2-dimethoxypropane (50 mL) were added. The pH of the mixture was tested with indicator paper to ensure that the solution was acidic. The mixture was stirred for 17 h at room temperature then diluted with dichloromethane, washed with saturated aqueous sodium hydrogen carbonate solution (2×100 mL), water (2×100 mL) and brine (50 mL). The organic layer was separated and dried over anhydrous magnesium sulfate and the solvent removed. Purification of the residue by column chromatography [hexane/diethyl ether 1:1 to 1:3 as eluant] gave two fractions. The higher R_f fraction gave the *title compound* **22** (9.50 g, 56%) as a white foam. ν_{max} (KBr): 3693, 3599, 1594, 1386, 1370, 1063 cm^{-1}; $[\alpha]_D$ +114.7 (*c* 0.2, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$): 1.36 (3H, s, CH_3), 1.58 (3H, s, CH_3), 2.43 (3H, s, Ts-CH_3), 3.73 (1H, m, H-4), 4.11–4.21 (3H, m, H-2, H-3, H-5), 4.32 (2H, ddd, *J*=9.0, 6.9, 4.5 Hz, H-6), 5.70 (1H, s, H-1), 7.27–7.43 (7H, m, Ph-H), 7.71 (2H, d, *J*=9.0 Hz, Ph-H) ppm; δ_C (125 MHz, $CDCl_3$): 21.75, 26.39, 28.16, 68.54, 69.06, 69.25, 76.20, 78.08, 84.14, 110.10, 127.97, 128.07, 129.21, 129.88, 132.18, 132.72, 144.99 ppm. Found: C, 56.28; H, 5.61; S, 13.48%. $C_{22}H_{26}O_7S_2$ requires: C, 56.63; H, 5.62; S, 13.75%. The lower R_f fraction gave *thiophenyl 3,6-di-O-p-toluenesulfonyl-α-D-mannopyranoside* (**23**) (1.56 g, 7%) as a white foam. ν_{max} (KBr): 3594, 1594, 1371, 1077 cm^{-1}; $[\alpha]_D$ +109.1 (*c* 0.2, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$): 2.43 (3H, s, Ts-CH_3), 2.48 (3H, s, Ts-CH_3), 4.01–4.04 (1H, m, H-5), 4.23–4.31 (2H, m, H-6), 4.21–4.28 (3H, m, H-4, H-6), 4.33 (1H, d, *J*=4.8 Hz, H-2), 4.62 (1H, dd, *J*=9.6, 3.0 Hz, H-3), 5.39 (1H, s, H-1), 7.27–7.41 (9H, m, Ph-H), 7.73 (2H, d, *J*=8.1 Hz, Ph-H), 7.86 (2H, d, *J*=8.1 Hz, Ph-H) ppm; δ_C (125 MHz, $CDCl_3$): 21.72, 21.83, 64.52, 68.41, 70.93, 71.34, 81.93, 87.52, 127.95, 128.13, 128.17, 129.25, 129.87, 130.19, 131.74, 132.62, 132.71, 132.77, 145.05, 145.70 ppm. Found: C, 53.93; H, 5.14; S, 16.26%. $C_{26}H_{28}O_9S_3$ requires: C, 53.78; H, 4.86; S, 16.57%.

*4.1.2. Thiophenyl 2,3-O-isopropylidene-6-deoxy-α-D-mannopyranoside (**24**)*

$LiAlH_4$ (0.590 g, 15.6 mmol) was added to a solution of tosylate **22** (2.00 g, 4.30 mmol) in diethyl ether (100 mL) cooled in an ice-salt bath. The ice bath was removed and the mixture was stirred under nitrogen for 12 h. The reaction mixture was cooled in an ice bath and the reaction quenched by the addition of 1 M sodium hydroxide (5 mL). The mixture was diluted with diethyl ether, washed with brine (50 mL) and water (2×100 mL). The organic layer was separated and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo. Purification of the residue by silica gel column chromatography [hexane/diethyl ether 1:1 to 2:1 as eluant] afforded two fractions. The higher R_f fraction gave the *title compound* **24** (0.800 g, 63%) as a white crystalline solid. Mp 76 °C (diethyl ether/hexane); ν_{max} (KBr): 3597, 2938, 2923, 1603, 1382, 1214, 1062 cm^{-1}; $[\alpha]_D$ +199.3 (*c* 0.6, CH_2Cl_2); δ_H (300 MHz,

$CDCl_3$): 1.26 (3H, d, J=6.0 Hz, H-6), 1.39 (3H, s, CH_3), 1.56 (3H, s, CH_3), 2.2 (1H, OH), 3.50 (1H, m, H-5), 4.10 (1H, d, J=6.4 Hz, H-2), 4.17 (1H, t, J=7.1 Hz, H-4), 4.37 (1H, d, J=0.9 Hz, H-3), 5.76 (1H, s, H-1), 7.32–7.50 (5H, m, Ph-H) ppm; δ_C (125 MHz, $CDCl_3$): 17.13, 26.47, 28.22, 67.02, 75.32, 76.66, 77.50, 78.41, 88.31, 109.84, 127.67, 129.11, 131.93, 133.47 ppm. Found: C, 60.57; H, 6.80; S, 10.65%. $C_{15}H_{20}O_4S$ requires: C, 60.79; H, 6.80; S, 10.82%.

A lower R_f fraction gave *thiophenyl 2-O-isopropyl-6-deoxy-α-D-mannopyranoside* (**25**) (0.200 g, 14%) as white crystals. Mp 79.2 °C (diethyl ether/hexane); ν_{max} (KBr): 3584, 3545, 2988, 2933, 1603, 1476 cm^{-1}; $[\alpha]_D$ +153.0 (*c* 1.2, CH_2Cl_2); δ_H (500 MHz, $CDCl_3$): 1.18 (3H, d, J=6.0 Hz, CH_3), 1.20 (3H, d, J=6.0 Hz, CH_3), 1.32 (3H, d, J=6.0 Hz, H-6), 2.38 (1H, br d, J=10.0 Hz, OH), 2.55 (1H, br s, OH), 3.45 (1H, t, J=9.5 Hz, H-4), 3.68–3.77 (2H, m overlapping a sept, J=6.0 Hz, H-3 and isopropyl CH), 3.91 (1H, dd, J=4.0, 1.0 Hz, H-2), 4.06–4.15 (1H, m, H-5), 5.50 (1H, s, H-1), 7.24–7.46 (5H, m, Ph-H) ppm; δ_C (125 MHz, $CDCl_3$): 17.51, 21.83, 23.31, 68.88, 71.66, 71.78, 74.33, 77.50, 86.16, 127.44, 129.50, 131.52, 134.45 ppm. Found: C, 60.20; H, 7.27; S, 10.56%. $C_{15}H_{22}O_4S$ requires: C, 60.38; H, 7.43; S, 10.75%.

4.1.3. *Thiophenyl 6-deoxy-2,3-O-isopropylidene-4-O-benzyl-α-D-mannopyranoside (**26**)*

Benzyl bromide (2.0 mL, 16.1 mmol) was added to a mixture of thioglycoside **24** (2.40 g, 8.10 mmol) and sodium hydride (0.810 g, 20.0 mmol) in DMF (20 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight. The mixture was quenched by the addition of water (2 mL) and then diluted with diethyl ether (150 mL). The mixture was washed with water (2×100 mL), brine (50 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. Purification of the residue by silica gel column chromatography [hexane/diethyl ether (4:1) as eluant] gave the *title compound* **26** (2.90 g, 93%) as a white crystalline solid. Mp 83 °C (hexane); ν_{max} (KBr): 2936, 2920, 1612, 1379, 1217, 1115 cm^{-1}; $[\alpha]_D$ +220.9 (*c* 0.3, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$): 1.23 (3H, d, J=6.1 Hz, H-6), 1.39 (3H, s, CH_3), 1.52 (3H, s, CH_3), 3.31 (1H, dd, J=9.8, 6.6 Hz, H-4), 4.14 (1H, m, H-5), 4.30–4.38 (2H, m, H-2, H-3), 4.64 (1H, d, J=11.7 Hz, CH_2Ph), 4.92 (1H, d, J=11.7 Hz, CH_2Ph), 5.74 (1H, s, H-1), 7.27–7.46 (10H, m, Ph-H) ppm; δ_C (125 MHz, $CDCl_3$): 17.79, 26.56, 28.10, 66.30, 73.20, 76.79, 78.49, 81.53, 83.90, 109.53, 127.57, 127.56, 127.85, 128.07, 128.37, 129.06, 131.86, 133.63, 138.29 ppm. Found: C, 68.24; H, 6.91; S, 8.20%. $C_{22}H_{26}O_4S$ requires: C, 68.37; H, 6.78; S, 8.30%.

4.1.4. *Thiophenyl 6-deoxy-4-O-benzyl-α-D-mannopyranoside (**27**) and thiophenyl 6-deoxy-1,2-di-O-acetyl-4-O-benzyl-α-D-mannopyranoside (**28**)*

A mixture of the acetal **26** (2.75 g, 7.12 mmol) and trifluoroacetic acid (5.00 mL, 35.6 mmol) in methanol (50 mL) was stirred at room temperature for 40 h. The solvent was removed and the residue was diluted with dichloromethane (100 mL). The mixture was washed with water (2×50 mL) and brine (50 mL). The organic layer was separated, dried over anhydrous magnesium sulfate and concentrated in vacuo. A small portion of the solid residue was crystallised from hexane/diethyl ether and gave the *title compound* **27** for characterisation. Mp 106.2 °C (hexane/diethyl ether); ν_{max} (KBr): 3685, 3576, 3089, 2923, 1597, 1382, 1269, 1081 cm^{-1}; $[\alpha]_D$ +232.9 (*c* 0.4, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$): 1.36 (3H, d, J=6.3 Hz, H-6), 2.36–2.42 (1H, br s, OH), 2.28–2.60 (1H, br s, OH), 3.43 (1H, t, J=9.3 Hz, H-4), 3.93 (1H, dd, J=9.3, 3.2 Hz, H-3), 4.18–4.26 (2H, m, H-2, H-5), 4.72 (1H, d, J=11.5 Hz, CH_2Ph), 4.76 (1H, d, J=11.5 Hz, CH_2Ph), 5.48 (1H, d, J=1.5 Hz, H-1), 7.25–7.49 (10H, m, Ph-H) ppm; δ_C (125 MHz, $CDCl_3$): 17.98, 68.69, 71.91, 72.63, 75.15, 81.89, 87.45, 127.47, 128.05, 128.18, 128.77, 129.12, 131.51, 134.17, 138.17 ppm. Found: C, 65.58; H, 6.60; S, 9.35%. $C_{19}H_{22}O_4S$ requires: C, 65.87; H, 6.40; S, 9.26%. The remainder of the residue was dissolved in pyridine (10 mL) at 0 °C and acetic anhydride (10 mL) was added. The mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed in vacuo and the residue was dissolved in dichloromethane. The mixture was washed with 1 M HCl (50 mL) and extracted with dichloromethane (3×50 mL). The extract was washed with saturated aqueous sodium hydrogen carbonate solution (40 mL) and water (100 mL). The phases were separated and the organic phase dried over anhydrous magnesium sulfate. Purification by silica gel column chromatography [hexane/diethyl ether (1:1) as an eluant] afforded the *title compound* **28** (2.54 g, 83%) as a clear syrup. ν_{max} (KBr): 1748, 1374, 1236, 1099, 1079 cm^{-1}; $[\alpha]_D$ +58.9 (*c* 0.4, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$): 1.36 (3H, d, J=6.0 Hz, H-6), 1.99, 2.13 (2×3H, 2×OAc), 3.52 (1H, t, J=9.6 Hz, H-4), 4.25 (1H, dq, J=11.2, 5.6 Hz, H-5), 4.66 (1H, d, J=11.2 Hz, CH_2Ph), 4.72 (1H, d, J=11.2 Hz, CH_2Ph), 5.31 (1H, dd, J=9.5, 3.2 Hz, H-3), 5.37 (1H, d, J=1.7 Hz, H-1), 5.50 (1H, dd, J=3.4, 1.9 Hz, H-2), 7.26–7.47 (10H, m, Ph-H) ppm; δ_C (125 MHz, $CDCl_3$): 17.89, 20.91, 20.98, 69.14, 71.88, 71.91, 75.15, 78.98, 85.72, 127.69, 127.76, 127.92, 128.52, 129.14, 131.96, 133.66, 137.99, 169.83, 169.99 ppm; HRMS-ESI (+): Found m/z 469.1087 (MK^+,100%). $C_{23}H_{26}O_6SK$ requires m/z 469.1087.

4.1.5. *1,5-Anhydro-3-O-acetyl-4-O-benzyl-2,6-dideoxy-D-arabino-hex-1-enitol (**30**)*

A 1 M solution of IBr in dichloromethane (1.72 mL, 1.74 mmol) was added to an ice cold solution of the thioglycoside (**28**) (0.500 g, 1.16 mmol) in dry dichloromethane (10 mL). The mixture was stirred for 8 min and quenched by the addition of aqueous sodium thiosulfate (2 mL). The mixture was diluted with dichloromethane, washed with saturated aqueous sodium thiosulfate solution (50 mL) and water (100 mL). The organic layer was separated, dried over anhydrous magnesium sulfate and the solvent was removed to give thiophenyl 6-deoxy-2,3-di-*O*-acetyl-4-*O*-benzyl-α-D-mannopyranosyl bromide (**29**), which was used without further purification. ν_{max} (KBr): 1757, 1375, 1259, 1236 cm^{-1}; δ_H (300 MHz, $CDCl_3$): inter alia 1.38 (3H, d, J=6.6 Hz, H-6), 1.95, 2.11 (2×3H, s, 2×OAc), 3.62 (1H, t, J=9.9 Hz, H-4), 4.06–4.14 (1H, m, H-5), 4.67 (1H, d, J=11.2 Hz, CH_2Ph), 4.74 (1H, d, J=11.2 Hz, CH_2Ph), 5.49 (1H, dd, J=3.3, 1.5 Hz, H-2), 5.70 (1H, dd, J=9.9, 3.3 Hz, H-3), 6.26 (1H, d, J=1.5 Hz, H-1), 7.28–7.36 (5H, m, Ph-H) ppm. Zinc–copper couple (2.00 g) was added to a cooled (0 °C) solution of bromide (**29**), sodium acetate (116 mg, 1.41 mmol) and acetic acid (127.0 μL, 2.22 mmol) in tetrahydrofuran (30 mL). The mixture was stirred overnight. Sodium carbonate (103 mg, 0.97 mmol) was then added and the mixture was stirred 30 min at room temperature. The solvent was removed in vacuo. Dichloromethane (50 mL) was added and the organic phase was washed with water (3×20 mL) and saturated aqueous sodium hydrogen carbonate solution (30 mL). The organic phase was dried over anhydrous magnesium sulfate and solvent was removed in vacuo. Purification of the residue by silica gel column chromatography [hexane/diethyl ether (1:1)] afforded two fractions. The higher R_f fraction gave the *title compound* (**30**) (152 mg, 50%) as a colourless syrup. HRMS-ESI (+): Found m/z 285.1103 (MNa^+, 100%). $C_{15}H_{18}O_4Na$ requires m/z 285.1103; ν_{max} (KBr): 1730, 1656, 1374, 1234, 1116 cm^{-1}; $[\alpha]_D$ −59.3 (*c* 0.95, $CHCl_3$); δ_H (300 MHz, $CDCl_3$): 1.38 (3H, d, J=6.6 Hz, H-6), 2.03 (3H, s, OAc), 3.50–3.55 (1H, dd, J=8.4, 6.0 Hz, H-4), 3.98–4.06 (1H, m, H-5), 4.71 (1H, d, J=11.7 Hz, CH_2Ph), 4.73 (1H, d, J=11.7 Hz, CH_2Ph), 4.76 (1H, dd, J=6.0, 2.7 Hz, H-2), 5.41 (1H, dddd, J=5.7, 3.0, 1.5, 0.6 Hz, H-3), 6.38 (1H, dd, J=6.0, 1.5 Hz, H-1), 7.28–7.36 (5H, m, Ph-H) ppm; δ_C (125 MHz, $CDCl_3$): 17.29, 21.31, 71.05, 73.67, 74.01, 78.24, 99.22, 127.94 (2C), 128.51, 137.98, 145.87, 170.71 ppm; The lower R_f fraction gave *6-deoxy-2,3-di-O-acetyl-4-O-benzyl-α-D-mannopyranose* (**31**) (118 mg, 30%) (α/β; 1.4:1) as a colourless syrup. HRMS-ESI (+): Found m/z 361.1258 (MNa^+, 100%). $C_{17}H_{22}O_7Na$ requires m/z 361.1263; ν_{max} (KBr): 3589, 2935, 1749, 1369, 1247, 1068 cm^{-1}; Data for α-anomer: δ_H (300 MHz, $CDCl_3$): inter alia 1.33

(3H, d, *J*=6.3 Hz, H-6), 1.98, 2.14 (2×3H, 2×OAc), 3.08 (1H, OH), 3.48 (1H, t, *J*=9.9 Hz, H-4), 4.04–4.14 (1H, m, H-5), 4.63 (1H, d, *J*=11.4 Hz, CH_2Ph), 4.70 (1H, d, *J*=11.4 Hz, CH_2Ph), 5.11 (1H, d, *J*=3.2 Hz, H-1), 5.28 (1H, d, *J*=1.7 Hz, H-2), 5.37 (1H, dd, *J*=3.4, 1.9 Hz, H-3), 7.32–7.36 (5H, m, Ph-H) ppm; δ_C (125 MHz, $CDCl_3$): inter alia 17.93, 20.95, 20.98, 67.79, 70.80, 71.34, 75.00, 78.81, 92.20, 127.67, 127.85, 127.96, 128.47, 129.49, 138.07, 170.04, 170.24 ppm; Data for β-anomer: δ_H (300 MHz, $CDCl_3$): inter alia 1.39 (3H, d, *J*=6.3 Hz, H-6) ppm; δ_C (125 MHz, $CDCl_3$): inter alia 17.93, 20.95, 70.98, 71.89, 73.69, 75.22, 77.99, 92.21, 127.85, 127.86, 128.49, 137.86, 170.04, 170.24 ppm.

4.1.6. 1,3-Di-O-acetyl-4-O-benzyl-2,6-dideoxy-D-arabino-pyranose (*11*)

Glacial acetic acid (45 μL, 0.79 mmol) was added to a stirred solution of 1,5-anhydro-3-*O*-acetyl-4-*O*-benzyl-2,6-dideoxy-D-*arabino*-hex-1-enitol (**30**) (118 mg, 0.45 mmol) and triphenylphosphine hydrogen bromide (10 mg, 0.03 mmol) in anhydrous dichloromethane (5 mL). The mixture was stirred overnight at room temperature. Removal of the solvent under reduced pressure and purification by silica gel column chromatography [diethyl ether/hexane (1:2)] as eluant gave two fractions. The higher R_f fraction gave recovered starting material **30** (20 mg, 17%). The next fraction gave the title compound **11** (51 mg, 42%) (α/β; 4.5:1) as a colourless syrup. HRMS-ESI (+): Found *m*/*z* 345.1314 (MNa^+, 100%). $C_{17}H_{22}O_6Na$ requires *m*/*z* 345.1314; ν_{max} (KBr): 1747, 1367, 1237, 1103 cm^{-1}; Data for α-anomer: δ_H (500 MHz, $CDCl_3$): inter alia 1.30 (3H, d, *J*=6.3 Hz, H-6), 1.81 (1H, ddd, *J*=13.5, 11.4, 3.9 Hz, H-2ax), 2.01, 2.09 (2×3H, s, 2×OAc), 2.36 (1H, ddd, *J*=13.5, 11.7, 5.1 Hz, H-2eq), 3.23 (1H, t, *J*=9.6 Hz, H-4), 3.89 (1H, m, H-5), 4.67 (1H, d, *J*=11.3 Hz, CH_2Ph), 4.73 (1H, d, *J*=11.3 Hz, CH_2Ph), 5.27 (1H, ddd, *J*=11.4, 9.0, 5.2 Hz, H-3), 6.14 (1H, dd, *J*=3.7, 1.8 Hz, H-1), 7.28–7.37 (5H, m, Ph-H) ppm; δ_C (125 MHz, $CDCl_3$): inter alia 18.28, 21.19, 21.26, 34.36, 69.69, 71.22, 75.12, 82.09, 91.05, 127.85, 127.98, 128.55, 138.01, 169.57, 170.22 ppm; Data for β-anomer: δ_H (500 MHz, $CDCl_3$): inter alia 1.32 (3H, d, *J*=6.3 Hz, H-6), 1.64–1.73 (1H, m, H-2ax), 2.00, 2.09 (2×3H, s, 2×OAc), 2.36 (1H, ddd, *J*=12.0, 9.9, 5.4 Hz, H-2eq), 3.21 (1H, t, *J*=9.6 Hz, H-4), 3.56 (1H, m, H-5), 4.65 (1H, d, *J*=11.3 Hz, CH_2Ph), 4.67 (1H, d, *J*=11.3 Hz, CH_2Ph), 5.01 (1H, ddd, *J*=11.6, 9.2, 5.2 Hz, H-3), 5.75 (1H, dd, *J*=9.9, 2.1 Hz, H-1), 7.28–7.37 (5H, m, Ph-H) ppm; δ_C (125 MHz, $CDCl_3$): inter alia 35.65, 67.32, 72.36, 72.98, 97.10, 138.01, 169.61 ppm; The lower R_f fraction gave *3-O-acetyl-4-O-benzyl-2,6-dideoxy-D-mannopyranose* (**32**), which crystallised from diethyl ether/hexane (38 mg, 30%) (α/β; 2:1). Mp 139.2 °C (diethyl ether/hexane); HRMS-ESI (+): Found *m*/*z* 303.1207 (MNa^+, 100%). $C_{15}H_{20}O_5Na$ requires *m*/*z* 303.1208; ν_{max} (KBr): 3680, 2986, 1741, 1604, 1369, 1239, 1099 cm^{-1}; Data for α-anomer: δ_H (300 MHz, $CDCl_3$): inter alia 1.29 (3H, d, *J*=6.3 Hz, H-6), 1.70 (1H, m, H-2ax), 2.00 (3H, s, OAc), 2.28 (1H, ddd, *J*=13.1, 5.4, 1.8 Hz, H-2eq), 2.49 (1H, dd, *J*=3.3, 2.1 Hz, OH), 3.20 (1H, t, *J*=9.3 Hz, H-4), 4.15 (1H, m, H-5), 4.65 (1H, d, *J*=11.1 Hz, CH_2Ph), 4.71 (1H, d, *J*=11.1 Hz, CH_2Ph), 5.29–5.35 (2H, m, H-1, H-3), 7.28–7.36 (5H, m, Ph-H) ppm; δ_C (125 MHz, $CDCl_3$): inter alia 17.83, 17.86, 35.20, 66.84, 70.94, 74.32, 81.45, 91.18, 127.39, 127.49, 128.05, 128.09, 137.85, 170.22 ppm; Data for β-anomer: δ_H (300 MHz, $CDCl_3$): inter alia 1.34 (3H, d, *J*=6.3 Hz, H-6), 1.65 (1H, q, *J*=12.0, 12.0, 9.5 Hz, H-2ax), 2.01 (3H, s, OAc), 2.40 (1H, ddd, *J*=12.0, 5.2, 2.1 Hz, H-2eq), 2.97 (1H, d, *J*=6.0 Hz, OH), 3.19 (1H, t, *J*=9.3 Hz, H-4), 3.44 (1H, m, H-5), 4.64 (1H, d, *J*=11.1 Hz, CH_2Ph), 4.65 (1H, d, *J*=11.1 Hz, CH_2Ph), 4.85 (1H, ddd, *J*=9.3, 6.0, 2.0 Hz, H-1), 4.89 (1H, ddd, *J*=11.7, 9.0, 5.0 Hz, H-3), 7.28–7.36 (5H, m, Ph-H) ppm; δ_C (125 MHz, $CDCl_3$): inter alia 20.87, 37.74, 72.86, 74.62, 81.45, 93.04, 127.75, 137.85, 170.32 ppm.

4.1.7. 2-Hydroxy-1-[3′-O-acetyl-4′-O-benzyl-2,6-dideoxy-β-D-manno-hexopyranosyl]-naphthalene (*36*)

3-*O*-Acetyl-4-*O*-benzyl-2,6-dideoxy-D-mannopyranose (**11**) (14 mg 0.043 mmol) in dichloroethane (1.0 mL), $Sc(OTf)_3$ (12 mg, 0.024 mmol), 2-naphthol (8 mg, 0.055 mmol) and Drierite (200 mg) in dichloroethane (1.0 mL) and a reaction time of 5 h gave, after purification by silica gel column chromatography [hexane/ethyl acetate (2:1) as eluant], the *title compound* (**36**) (15 mg, 86%) as a white solid.

HRMS-ESI (+): Found *m*/*z* 429.1678 (MNa^+, 100%). $C_{25}H_{26}O_5Na$ requires *m*/*z* 429.1678. ν_{max} (neat): 3702, 2961, 1748, 1602, 1468, 1379, 1233, 1099 cm^{-1}; $[\alpha]_D$ +53 (*c* 0.4, CH_2Cl_2); δ_H (500 MHz, $CDCl_3$): inter alia 1.29 (3H, d, *J*=6.5 Hz, H-6′), 1.98 (3H, s, 1×OAc), 1.95–2.04 (1H, m, H-2′ax), 2.51 (1H, ddd, *J*=13.5, 5.0, 2.0 Hz, H-2′eq), 3.41 (1H, t, *J*=9.5 Hz, H-4′), 3.75 (1H, m, H-5′), 4.74 (1H, d, *J*=11.5 Hz, CH_2Ph), 4.77 (1H, d, *J*=11.5 Hz, CH_2Ph), 5.26 (1H, m, H-3′), 5.52 (1H, dd, *J*=12.0, 2.0 Hz, H-1′), 7.08–7.79 (11H, m, Ph-H, Ar-H), 8.85 (1H, s, OH) ppm; δ_C (125 MHz, $CDCl_3$): 18.69 ($C_{6'}$), 21.18 (OAc), 36.47 ($C_{2'}$), 74.35 ($C_{3'}$), 75.27 (CH_2Ph), 75.95 ($C_{1'}$), 76.90 ($C_{5'}$), 82.10 ($C_{4'}$), 109.54, 114.47, 117.80, 119.78, 120.78, 123.07, 127.83, 127.92, 128.05, 128.61, 128.76, 128.91, 129.91 (C_1), 134.67 (2 *ipso* Ph), 137.98 (2 *ipso* Ph), 153.61 (C_2), 170.31 (OAc) ppm.

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33. Crystallographic data for **25**: $C_{15}H_{22}O_4S$, M_w=298.39, monoclinic, C centred, *a*=18.8001(8), *b*=5.0848(2), *c*=33.1695(13) Å, β=106.036(2)°, *V*=3047.4(2) $Å^3$, space group C2 (# 5), *Z*=8, D_c=1.301 g cm^{-3}, Bruker APEXII diffractometer, Radiation Mo Kα (λ=0.71073, *T*=293(2)K), *R*=0.0518, *Rw*=0.1387, R_1=0.0416,

GOF=1.000 for 8613 reflections with $I>2\sigma(I)$ out of 9533 reflections collected, Flack parameter 0.03(6) with 4096 Friedel pairs. CCDC 704190 contains the supplementary crystallographic data for **25**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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