Direct preparation of diacetals from 1,2-diketones and their use as 1,2-diol protecting groups

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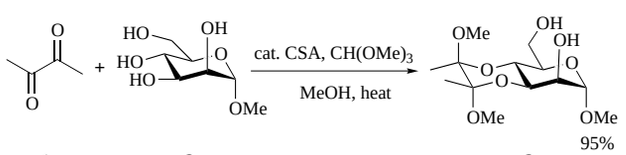
A range of 1,2-diketones have been evaluated as potential protecting groups for *trans*-1,2-diols *via* 1,2-diacetal formation. The procedure is especially useful in oligosaccharide and natural product synthesis.

In a recent communication we illustrated the utility of some 1,2-diketones as highly effective protecting groups for 1,2-diols.[1] Our initial report on the use of the cyclohexane diacetal (CDA) showed it to be especially useful for the protection of the *trans*-diequatorial-1,2-diol functionality in carbohydrate chemistry.[2] Of equal importance is the simultaneous, powerful tuning effect imparted upon the glycosidation reactivity of CDA-protected monosaccharide building blocks, governed by the torsional constraints of the diacetal unit.[3] These CDA-protected units have since proved to be highly compatible with strategies for the concise assembly of complex oligosaccharides.[4] We now report in full our findings on a range of 1,2-diketones screened for application as potential protecting groups for diols and other polyols.

The initial route to CDA-protected structures involved the reaction of preformed 1,1,2,2-tetramethoxycyclohexane with a 1,2-diol in boiling methanol along with three equivalents of trimethyl orthoformate and catalytic camphorsulfonic acid (CSA).[5] However, it was found that the tetramethoxydiacetals of all the 1,2-diketones necessary for this investigation were not readily formed using standard conditions. We therefore speculated that it might be possible to use 1,2-diketones directly with 1,2-diols to yield the desired 1,2-diacetal products. Indeed reaction of commercially available butane-2,3-dione **1** with methyl α-D-mannopyranoside **2** in boiling methanol with catalytic CSA and three equivalents of trimethyl orthoformate for 16 h gave the corresponding butane diacetal (BDA) **3** in 95% yield (Scheme 1). The high selectivity demonstrated in the protection

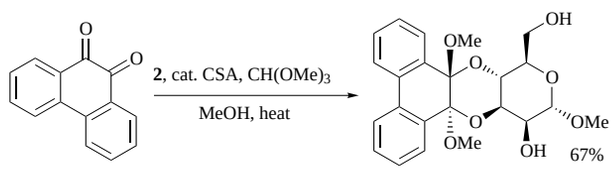


1 **2** **3**

Scheme 1

of *trans*-1,2-diols is attributed to the combination of two factors; firstly, the formation of the sterically less demanding *trans* ring junction and secondly the control of configuration at the two acetal centres by the operation of anomeric effects. This direct reaction of 1,2-diketones avoids the need for the preparation of the tetramethoxydiacetal reagent and represents an overall simplification of the process as a whole compared with other procedures available.[6]

Due to the success of the cyclohexane-1,2-dione based protection reactions it was decided to investigate the potential of several other readily available cyclic and open chain 1,2-diketones as potential protecting group reagents for *trans*-1,2-diols. We were interested in varying both steric and electronic factors in the dione to quantify their effects on the protection reaction of the diol. Many 1,2-diketones were therefore synthesised to probe these effects. Reaction of commercially available phenanthrene-9,10-quinone **4** with methyl α-D-mannopyranoside **2** under the standard reaction conditions yielded the anticipated diacetal **5** in 67% yield as a crystalline product (Scheme 2). Further protection examples of methyl pyranosides



4 **5**

Scheme 2

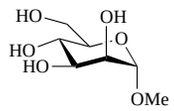
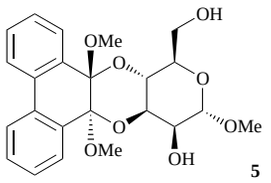
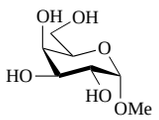
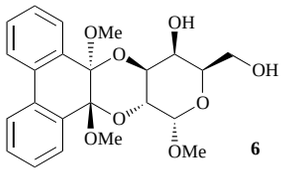
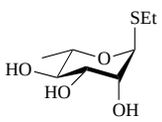
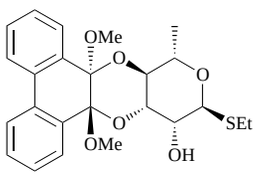
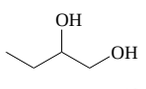
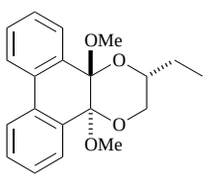
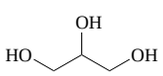
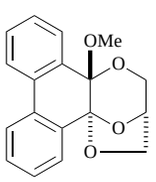
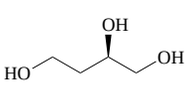
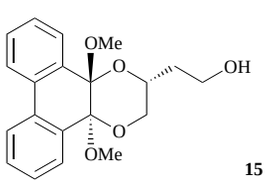
were also successful (Table 1). The procedure was also compatible with thioglycosides, as illustrated by the protection of ethyl 1-thio-α-L-rhamnopyranoside **7** as diacetal **8** in 68% yield. The structure of the phenanthrene-9,10-diacetal **5** was confirmed by the X-ray crystal structure obtained from its bis(*p*-nitrobenzoate) ester **9** (Fig. 1).†

Open chain 1,2-diols were also protected as cyclic diacetals with phenanthrene-9,10-quinone as shown with (±)-butane-1,2-diol **10** (Table 1). The reaction of glycerol **12** provided a useful result in the simultaneous protection of *all three* hydroxy groups. Thus, although the dioxane ring of the cyclic diacetal formed as expected, an intramolecular trap of the 3-hydroxy group occurred in preference to reaction with the solvent methanol to yield the triprotected structure **13**. This reactivity offers an interesting contrast with that of (*R*)-(+)-butane-1,2,4-triol **14** with phenanthrene-9,10-quinone **4** in that the 1,2,4-triol reacts in a more conventional fashion to leave the 1 and 2 positions protected and the 4-hydroxy group free in **15** (Table 1).

The higher yields in the protection reaction, obtained by the use of phenanthrene-9,10-quinone **4** as the 1,2-diketone rather than cyclohexane-1,2-dione based 1,1,2,2-tetramethoxycyclohexane, are attributed to the greater thermodynamic stability of the phenanthrene-9,10-diacetal. It is thought that the lack of any 1,3 steric interactions between the axial methoxy groups of the diacetal and any hydrogen atoms in the cyclohexyl component of the protecting group is a favourable arrangement. These superior yields in the protection reaction are, however, undermined by difficulties in the deprotection of the phenanthrene-9,10-diacetals, in contrast to the CDA products. It was antici-

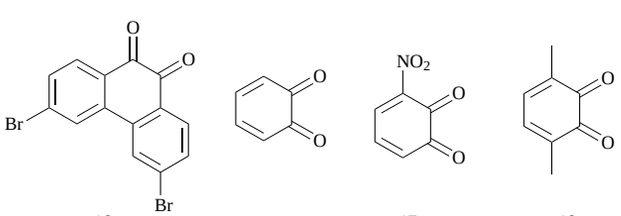
† Full details of this X-ray crystal structure determination are available from the author on request.

Table 1

Substrate	1,2-Diacetal product	
 *manno-* **2**	 **5**	67%
 *galacto-*	 **6**	66%
 *rhamno-* **7**	 **8**	68%
 **10**	 **11**	57%
 **12**	 **13**	69%
 **14**	 **15**	65%

pated that the benzylic nature of the acetal centres in the phenanthrene-9,10-diacetals would facilitate a hydrogenolytic deprotection mechanism. Unfortunately, this proved not to be the case. Use of dissolving-metal reduction in liquid ammonia was similarly ineffective. Protic acid catalysed hydrolysis was also unable to effect a deprotection of these remarkably stable cyclic diacetals in useful yields.

Electronic modification of the phenanthrene-9,10-quinone structure in an effort to try and improve the lability of the diacetal adducts towards deprotection also failed. The di-*o*-bromo-substituted phenanthrene-9,10-quinone **16**[7] was rendered unreactive in the protection reaction by the electron



16 **17** **18**

Unreactive 1,2-diones in diacetal protection reaction

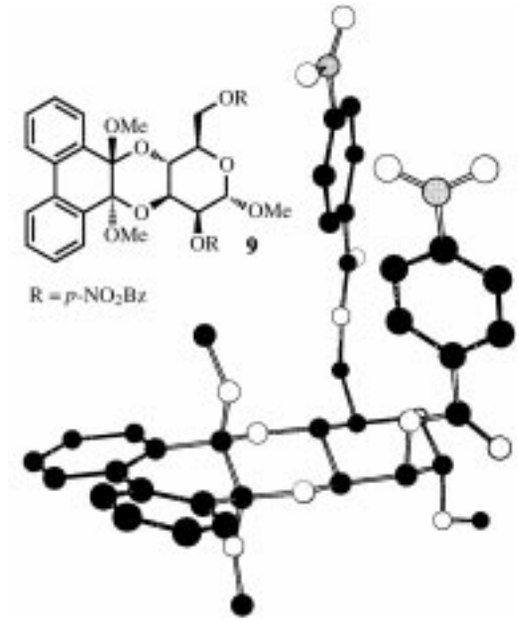
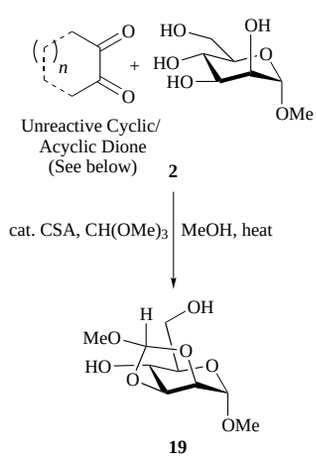


Fig. 1 Representation of the structure of compound **9** as determined by X-ray crystal structure analysis

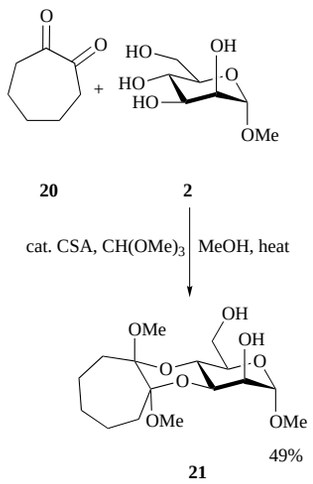
withdrawing groups. Other quinone based 1,2-diketones with nitro and alkyl substituents such as **17** and **18**, mainly prepared by oxidation of the corresponding phenol,[8] proved unreactive as potential protecting groups. Any formation of 1,2-diacetal structures was slower than reaction of the monosaccharide with the trimethyl orthoformate dehydrating agent to yield the exchanged orthoformate **19** (Scheme 3). Other dehydrating



Scheme 3

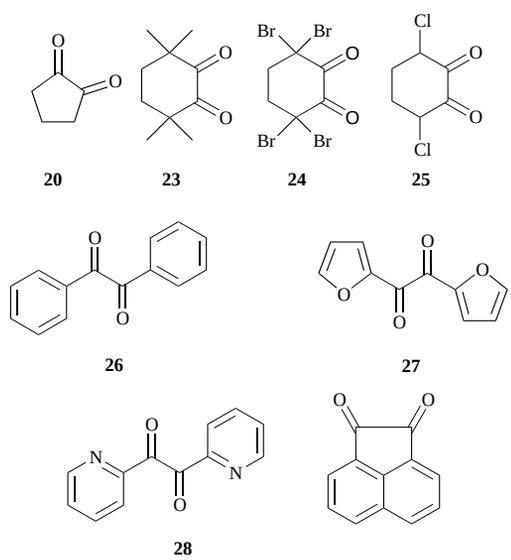
agents of comparable efficacy could not be found for the reaction.

Variations of the cyclohexane-1,2-dione by ring expansion or contraction of the reagent illustrated that ring sizes below six were not suitable as cyclic 1,2-diketone protecting groups. For example, cyclopentane-1,2-dione[9] **22** proved unreactive with the substrate giving only reaction of the monosaccharide with the trimethyl orthoformate (Scheme 3). In contrast, synthesis of cycloheptanedione **20** by oxidation of the corresponding 1,2-diol[10] provided a reactive 1,2-diketone that gave comparable yields of protection to cyclohexane-1,2-dione (used as its tetramethoxydiacetal)[2] in the protection reaction (Scheme 4). A competition reaction between equimolar amounts of cycloheptane-1,2-dione and cyclohexane-1,2-dione with methyl α-D-mannopyranoside **2** showed that rates of protection by both reagents were very similar. Deprotection of a cycloheptane-1,2-diacetal protected monosaccharide proceeded



Scheme 4

smoothly with a trifluoroacetic acid–H_2O (4:6) mixture at a similar rate to that for CDA protected adducts. Of greatest interest were competition glycosidation reactions of cycloheptane and cyclohexane diacetal protected glycosyl donor units. Once again the reactivity was identical, indicating that the reactivity tuning of the cycloheptyl protecting group was equivalent to that of the original CDA unit. Due to the similar reactivity of cycloheptane-1,2-dione, compared to the well understood reactivity of CDA based upon cyclohexane-1,2-dione, this was not pursued any further as a potential protecting group.



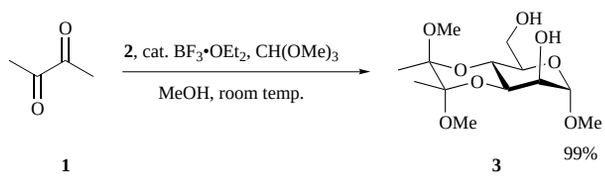
Unreactive 1,2-diones in diacetal protection reaction

Steric and electronic variants of the cyclohexane-1,2-dione reagent all proved to be unreactive. 3,3,6,6-Tetramethylcyclohexane-1,2-dione **23**,[11] 3,3,6,6-tetrabromocyclohexane-1,2-dione **24**[12] and 3,6-dichlorocyclohexane-1,2-dione **25**[13] gave no reaction with our model diol, methyl α-D-mannopyranoside **2**. It appears that any steric congestion of the sites α to the reacting carbonyl groups prevents the desired reaction taking place.

Open chain diones were also considered due to the commercial availability of several examples. Initial studies with benzil **26** proved unsatisfactory. This was somewhat surprising given the success of phenanthrene-9,10-quinone **4** in the protection reaction. This could be explained by considering the disadvantage of bringing two relatively bulky phenyl groups into close proximity in the proposed benzil-1,2-diacetal. This once again supports the theory that diones with *α*-steric congestion suffer from low reactivity in the protection process. The furan and pyridine variants **27** and **28** were similarly unreactive.

Given that steric constraints appear to inhibit the reaction, the use of the much less hindered butane-2,3-dione **1** was investigated next. This dione reagent gave outstanding results with a range of diol substrates. Reaction of 1.1 equivalents of the 1,2-diketone with the 1,2-diol, catalytic CSA and three equivalents of trimethyl orthoformate in boiling methanol overnight gave high yields of the protected monosaccharide units. Protection of the disaccharide ethyl 1-thio-β-D-lactose **29** to give protected structure **30** in moderate yield was also achieved (Table 2). However, it was observed that extension of the reagent to all mono- and di-saccharide units was not possible. Studies with disaccharides such as maltose and sucrose only gave products consistent with cleavage of the glycosidic bond under the strongly acidic conditions required to effect efficient protection.

Use of Lewis acid catalysis in these reactions was also investigated (Scheme 5). It was found that reaction of butane-



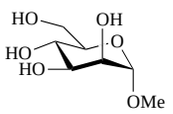
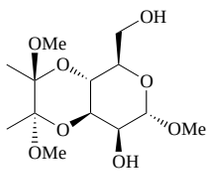
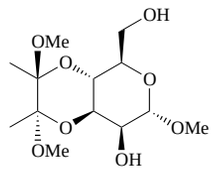
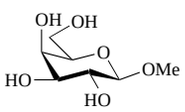
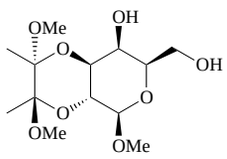
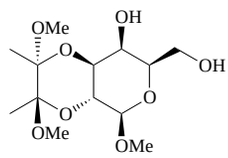
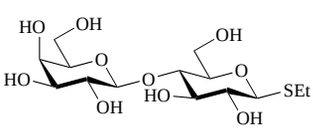
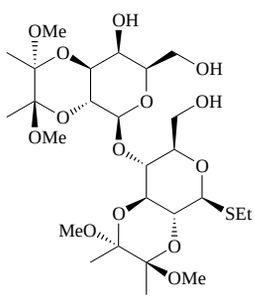
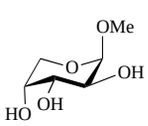
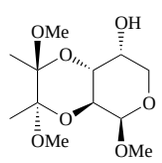
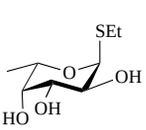
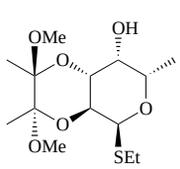
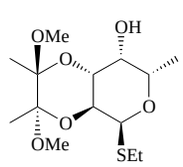
Scheme 5

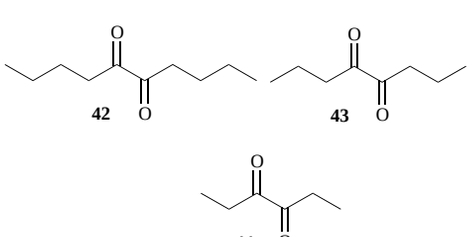
2,3-dione **1** with methyl α-D-mannopyranoside **2** occurred at room temperature in the presence of $BF_3{\cdot}OEt_2$ to yield the butane diacetal **3** (BDA) in near quantitative yield after 17 h. The temperature of the reaction is of importance as heating the reaction to reflux reduces the yield of the methyl mannopyranoside protection to 62%. Previous work with Lewis acid catalysis for this process showed lack of full equilibration to anomerically stabilised products and gave mixtures of fusion products.[6] Reaction with ethyl 1-thio-α-D-mannopyranoside under these conditions illustrates this lack of full equilibration as reaction at the 2,3-diol pair is observed as a significant competing process for the desired 3,4-protection. Interestingly, yields for all the monosaccharide units screened were not universally high. As was observed with previous dispiroketal and CDA protections, the protecting groups appeared to favour certain monosaccharide configurations over others.[2,14] For example the relatively poor yields for the protection of *arabino* and *fuco* substrates **32** and **34** with butane-2,3-dione and Lewis acid are in strong contrast to the near quantitative yields obtained with mannose. Despite the significant contributions of others in quantifying hydroxy group reactivity in carbohydrates,[15] it remains difficult to define the cause of the obvious differences in the protection behaviour of the substrates addressed in this study and others.

The use of open-chain substrates was also addressed with butane-2,3-dione **1** (Table 3). 1-Phenylethane-1,2-diol **36** reacted as anticipated to give the butane diacetal **37**. The interchange of protic for Lewis acid catalysis with accompanying temperature changes has revealed an interesting and potentially useful selectivity for the protection of triols as diacetals. As with phenanthrene-9,10-quinone, butane-2,3-dione reacts with glycerol **12** to give a triprotected structure **38** under CSA catalysis at reflux. However, $BF_3{\cdot}OEt_2$ catalysis at room temperature facilitates only a diprotection of the glycerol as a diacetal, leaving the 3-hydroxy group free and unprotected in **39**. A similar contrast is observed in the case of (*R*)-(+)-butane-1,2,4-triol giving **40** and **41** (Table 3). This interesting selectivity offers a useful addition to protecting group strategy for such small carbon building block units.

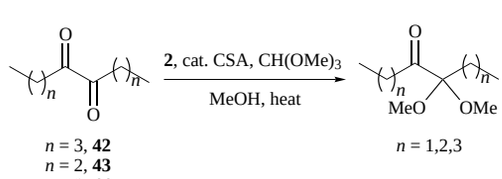
As a final probe into the structural limitations on 1,2-diketones as potential 1,2-diol protecting groups, chain exten-

Table 2

Substrate	Acid catalyst: CSA		Acid catalyst: $BF_3 \cdot OEt_2$	
 *manno-* **2**	 **3**	95%	 **3**	99%
 *galacto-*	 **31**	80%	 **31**	85%
 *lacto-* **29**	 **30**	31%	—	
 *arabino-* **32**	—		 **33**	42%
 *fuco-* **34**	 **35**	80%	 **35**	14%



Unreactive 1,2-diones in diacetal protection reaction

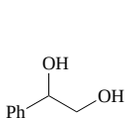
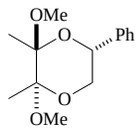
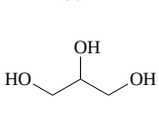
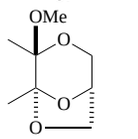
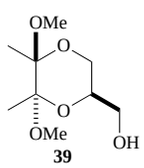
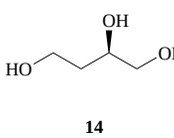
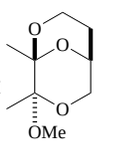
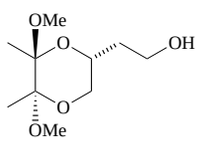


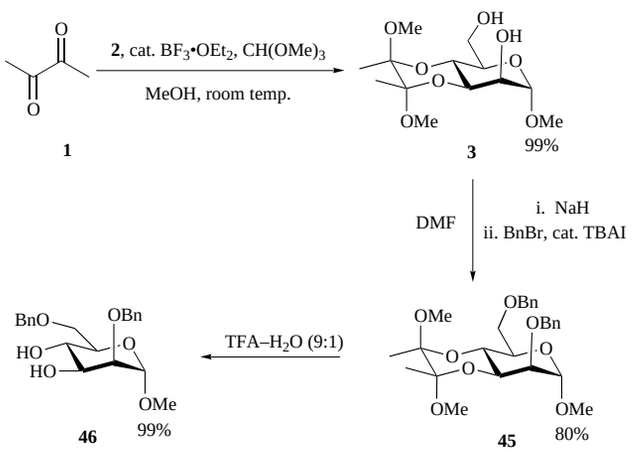
Scheme 6

sion of the successful butane-2,3-dione **1** was investigated. Decane-5,6-dione **42** and octane-4,5-dione **43** were synthesised by the method of Mueller-Westerhoff and Zhou,[16] while hexane-3,4-dione **44** was commercially available. Use of these 1,2-diketones under the standard reaction conditions yielded the dimethoxyacetal of the starting diketone as the only recovered material from the reaction in each case (Scheme 6). From this evidence it appears that only a methyl group (as seen in the BDA examples) or a methylene constrained in a cyclic 1,2-diketone of ring size greater than five can be tolerated next to the ketone in the basic structure of the protecting reagent.

Reaction of diones with other 1,2-related heteroatom based functionality gave little success in obtaining diacetal-like products. Glycolic acid reacted giving acetalisation of the hydroxy group and methyl esterification of the carboxylic acid under the reaction conditions when reacted with phenanthrene-9,10-quinone or butane-2,3-dione. These diones also failed to react with α-amino acids, 1,2-amino alcohols and 1,2-related hydroxy/thiol functionality combinations. Most products in these reactions are variants of the competing spirocyclisation reaction of the 1,2-related functionality onto a single carbonyl group of the 1,2-diketone. Unfortunately these could not be readily equilibrated to cyclic diacetal-like structures using acceptable reaction conditions.

Table 3

Substrate	Acid catalyst: CSA	Acid catalyst: $BF_3{\cdot}OEt_2$
 **36**	 **37** 94%	—
 **12**	 **38** 98%	 **39** 62%
 **14**	 **40** 65%	 **41** 64%



Scheme 7

The BDA-protected moiety **3** has proved compatible with standard synthetic manipulations common to oligosaccharide synthesis (Scheme 7). This sequence also addresses the deprotection of BDA protected building blocks. The high yielding protection reaction has already been illustrated and benzylation of the 2,6-positions is readily achieved to yield the fully protected monosaccharide **45**. Selective, further manipulations of both 2 and 6 positions in mannopyranosides have also been achieved using this diacetal methodology.[5] Deprotection of the diacetal unit was carried out using 9:1 TFA–H_2O at room temperature yielding diol **46**. The reaction was complete within one minute and analysis of the crude material showed very clean deprotected material. Furthermore the volatility of the dione liberated allowed evaporation as a purification process and avoided the use of column chromatography. The success of this process now gives a highly efficient procedure for the preparation of these valuable building blocks under very straightforward reaction conditions.

In conclusion, it has been established that the reaction of 1,2-diketones with 1,2-diols to give the corresponding diacetal structures, which serve as valuable protecting groups for diols, is not general for all 1,2-diketones. These results have established some of the parameters for the design and exploitation of 1,2-diketones as protecting groups in oligosaccharide and other natural product synthesis programmes.

Experimental

General procedures

^{1}H NMR spectra were recorded on a Bruker DRX-600, a Bruker DRX-500, a Bruker AM-400, a Bruker AC-250 or a Bruker AC-200 spectrometer as solutions in deuteriochloroform ($CDCl_3$) using the residual $CHCl_3$ as reference (7.26 ppm) unless otherwise stated. All multiplets were analysed as first order couplings. ^{13}C spectra were recorded on a Bruker AC-200, a Bruker AC-250 or a Bruker AM-400 spectrometer and chemical shifts are quoted relative to the middle peak of $CDCl_3$ (77 ppm). Coupling constants (J) are quoted in Hz. Low and high resolution mass spectra were recorded under EI or positive FAB conditions using a Kratos MS 890 spectrometer. Microanalyses were performed in the University of Cambridge microanalyses laboratory. Optical rotations were measured using an Optical Activity AA-1000 polarimeter and are quoted in units of 10^{-1} deg cm^2 g^{-1}. Ether refers to diethyl ether and petrol refers to light petroleum (bp 40–60 °C). All solvents were purified before use: light petroleum was redistilled, *N*,*N*-dimethylformamide (DMF) and dichloromethane (DCM) were distilled from calcium hydride, ether was distilled from sodium–benzophenone ketyl and methanol was distilled from magnesium. Where appropriate, reactions were carried out under an argon atmosphere in oven dried glassware (150 °C overnight). Reagents were either dried by standard procedures or used as purchased. Flash chromatography was carried out using Merck–Kieselgel 60 (0.040–0.063 mm) under pressure. Thin layer chromatography was visualised with UV light (254 nm) and either acidified ammonium molybdate(IV) or 10% concentrated sulfuric acid in methanol as appropriate.

(9′*S*,10′*S*)-Methyl 3,4-*O*-(9′,10′-dimethoxyphenanthrene-9′,10′-diyl)-α-D-mannopyranoside 5

(±)-Camphorsulfonic acid (657 mg, 2.83 mmol) was added to a solution of methyl α-D-mannopyranoside (5 g, 25.7 mmol), phenanthrene-9,10-quinone **4** (5.9 g, 28.3 mmol) and trimethyl orthoformate (9.3 ml, 84.9 mmol) in dry methanol (50 ml). The mixture was heated under reflux for 72 h. The reaction was neutralised with triethylamine (0.5 ml) and the solvents removed under reduced pressure. The residue was purified by flash column chromatography (gradient elution: ether to ethanol–ether 5:95) to give the diacetal **5** as a white solid (6.55 g, 67%), $[a]_D^{30}$ +53.1 (*c* 1.16, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3448, 1452, 1234, 1089, 1037, 741; δ_H(400 MHz, $CDCl_3$) 1.76 (1H, br s, 2-OH), 2.26 (1H, br s, 6-OH), 2.91 and 2.94 (2 × 3H, 2 × s, 2 × OMe), 3.40 (3H, s, 1-OMe), 3.97–4.00 (3H, m, H-5, H-6$_a$, H-6$_b$), 4.16 (1H, br s, H-2), 4.46 (1H, dd, *J* 2.8, 10.5, H-3), 4.54 (1H, t, *J* 10.5, H-4), 4.83 (1H, s, H-1), 7.30–7.34 (2H, m, H-2′, H-7′), 7.37–7.43 (2H, m, H-3′, H-6′), 7.58 (1H, dd, *J* 0.8, 7.5, H-1′), 7.66 (1H, dd, *J* 1.1, 7.5, H-8′), 7.74 (2H, d, *J* 7.7, H-5′, H-4′); δ_C(100 MHz, $CDCl_3$) [49.3 and 49.6 (2 × OMe)], 55.0 (1-OMe), 61.3 (C-6), [63.8, 69.3, 70.2 and 70.9 (C-2, C-3, C-4, C-5)], [97.3 and 97.8 (C-9′, C-10′)], 101.1 (C-1), [124.3 × 2, 125.0, 125.3, 127.3 × 2, 129.1, 129.2, 132.9, 133.0, 133.1, 133.2 (Ar-C)]; *m/z* (EI) 430 (8%, M$^+$), 399 (9), 368 (4), 271 (6), 239 (40), 180 (100), 152 (65) (Found: M$^+$, 430.1627. $C_{23}H_{26}O_8$ requires *M*, 430.1628).

(9′*R*,10′*R*)-Methyl 2,3-*O*-(9′,10′-dimethoxyphenanthrene-9′,10′-diyl)-α-D-galactopyranoside 6

(±)-Camphorsulfonic acid (58 mg, 0.25 mmol) was added to a solution of methyl α-D-galactopyranoside (0.5 g, 2.5 mmol), phenanthrene-9,10-quinone (0.52 g, 2.5 mmol) and trimethyl orthoformate (1.1 ml, 10 mmol) in dry methanol (10 ml). The mixture was heated under reflux for 48 h. The reaction was neutralised with triethylamine (0.5 ml) and the solvents removed under reduced pressure. The residue was purified by flash column chromatography (gradient elution: ether to ethanol–ether 5:95) to give the diacetal **6** as a white solid (671

mg, 66%), $[\alpha]_D^{26}$ +87.9 (*c* 1.56, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3503, 1662, 1453, 1233, 1200, 1152, 1082, 986, 970, 802, 771, 746, 629; δ_H(400 MHz, $CDCl_3$) 1.82 (1H, br s, 4-OH), 2.56 (1H, br d, 6-OH), 2.89 and 2.90 (2 × 3H, 2 × s, 2 × OMe), 3.49 (3H, s, 1-OMe), 3.84–3.92 (1H, m, H-5), 3.97–4.02 (2H, m, H-6_a, H-6_b), 4.29 (1H, d, *J* 2.7, H-4), 4.53 (1H, dd, *J* 2.7, 10.9, H-3), 4.61 (1H, dd, *J* 3.3, 10.9, H-2), 5.50 (1H, d, *J* 3.3, H-1), [7.28–7.43 (4H, m), 7.65 (2H, app. dt, *J* 1.3, 8.7) and 7.72 (2H, app. t, *J* 8.2) (Ar-H)]; δ_C(100 MHz, $CDCl_3$) [49.38 and 49.45 (2 × OMe)], 55.4 (1-OMe), 62.9 (C-6), [66.1, 67.5, 69.7 and 70.6 (C-2, C-3, C-4, C-5)], [97.5 and 97.7 (C-9′, C-10′)], 98.8 (C-1), [124.1, 124.3, 125.6, 126.3, 127.2, 127.5, 129.0, 129.2, 132.7, 132.9, 133.0 and 133.1 (Ar-C)]; *m/z* (EI) 430 (20%, M^+), 415 (5), 399 (20), 368 (10), 271 (20), 239 (75), 223 (65), 211 (90), 195 (100), 180 (70), 165 (40), 125 (50), 100 (100) (Found: M^+, 430.1626. $C_{23}H_{26}O_8$ requires *M*, 430.1628).

(9′*R*,10′*R*)-Ethyl 3,4-*O*-(9′,10′-dimethoxyphenanthrene-9′,10′-diyl)-1-thio-α-L-rhamnopyranoside 8

(±)-Camphorsulfonic acid (56 mg, 0.24 mmol) was added to a solution of ethyl 1-thio-α-L-rhamnopyranoside **7** (1.07 g, 2.4 mmol), phenanthrene-9,10-quinone **4** (0.5 g, 3.6 mmol) and trimethyl orthoformate (1.1 ml, 10 mmol) in dry methanol (10 ml). The mixture was heated under reflux for 48 h. The reaction was neutralised with triethylamine (0.5 ml) and the solvents removed under reduced pressure. The residue was purified by flash column chromatography (eluent: petrol–ether 1:3) to give the diacetal **8** as a white solid (725 mg, 68%), $[\alpha]_D^{26}$ −155.9 (*c* 0.81, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3454, 1449, 1234, 1091, 1035, 981, 960, 914, 768, 741; δ_H(400 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.4, SCH_2CH_3), 1.48 (3H, d, *J* 6.2, H-6), 2.55–2.75 (2H, m, SCH_a-$H_b CH_3$), 2.80 (1H, br s, OH), 2.910 and 2.913 (2 × 3H, 2 × s, 2 × OMe), 4.18 (1H, app. t, *J* 10.4, H-4), 4.26 (1H, d, *J* 1.8, H-2), 4.35–4.45 (2H, m, H-3, H-5), 5.34 (1H, s, 1-H), [7.32 (2H, app. t, *J* 7.4), 7.42 (2H, app. t, *J* 7.6), 7.63 (2H, app. t, *J* 7.8), 7.74 (2H, d, *J* 7.7) (Ar-H)]; δ_C(100 MHz, $CDCl_3$) 10.8 (C-6), 15.0 (SCH_2CH_3), 25.3 (SCH_2CH_3), [49.1 and 49.5 (2 × OMe)], [67.2, 69.7, 70.0 and 72.0 (C-2, C-3, C-4, C-5)], 84.3 (C-1), [97.2 and 97.7 (C-9′, C-10′)], [124.30, 124.33, 125.1, 125.3, 127.3, 129.1, 129.2, 132.92, 132.97, 133.0 and 133.2 (Ar-C) overlapping signals]; *m/z* (EI) 444 (M^+, 25%), 413 (20), 382 (5), 351 (12), 271 (10), 239 (100), 223 (75), 211 (25), 195 (60), 180 (50) (Found: M^+, 444.1587. $C_{24}H_{28}O_6S$ requires *M*, 444.1606).

(9′*S*,10′*S*)-Methyl 2,6-di-*O*-(*p*-nitrobenzoyl)-3,4-*O*-(9′,10′-dimethoxyphenanthrene-9′,10′-diyl)-α-D-mannopyranoside 9

A solution of *p*-nitrobenzoyl chloride (1.3 g, 6.9 mmol) in DCM (5 ml) was added to a cooled solution of protected mannoside **5** (1.0 g, 2.3 mmol) in pyridine (10 ml). The mixture was allowed to warm to room temperature over 16 h. The mixture was poured onto ice and the ice allowed to melt. Sodium hydrogen carbonate (0.6 g) was added and the mixture extracted with DCM (2 × 30 ml) and the combined organic fractions were washed with saturated aqueous sodium hydrogen carbonate (2 × 30 ml), saturated aqueous copper sulfate (40 ml) and dried ($MgSO_4$). The solvents were removed under reduced pressure and the residue purified by column chromatography (eluent: ether–petrol 1:1). The material was further purified by crystallisation from DCM–petrol to give the diester **9** as colourless needles (1.06 g, 63%) (Found: C, 58.77; H, 4.48; N, 3.52. $C_{37}H_{32}N_2O_{14}$·$0.5CH_2Cl_2$ requires C, 58.41; H, 4.31; N, 3.63%); $[\alpha]_D^{30}$ +29.3 (*c* 0.83, $CHCl_3$); mp 211–212 °C; ν_{max}($CHCl_3$)/cm^{-1} 1728, 1609, 1529, 1453, 1349, 1280, 1230, 1086, 1051, 958, 770, 742, 719; δ_H(400 MHz, $CDCl_3$) 2.89 and 2.93 (2 × 3H, 2 × s, 2 × OMe), 3.49 (3H, s, 1-OMe), 4.43–4.46 (1H, m, H-5), 4.65 (1H, app. t, *J* 10.3, H-4), 4.75–4.82 (2H, m, H-3, H-6_a), 4.93 (1H, *J* 1.7, 11.9, H-6_b), 4.96 (1H, s, H-1), 5.60 (1H, dd, *J* 1.3, 2.7, H-2), [7.24 (1H, app. dt, *J* 0.8, 7.5), 7.31 (1H, app. dt, *J* 0.8, 7.4), 7.37 (1H, app. dt, *J* 1.1, 7.7), 7.42 (1H, app. dt, *J* 1.1, 7.5), 7.50 (1H, dd, *J* 0.9, 7.5), 7.59 (1H, dd, *J* 0.9, 7.5), 7.70 (1H, d, *J* 7.7), 7.73 (1H, d, *J* 7.7), 8.21 (4H, s) and 8.25 (4H, s) (Ar-H)]; δ_C(100 MHz, $CDCl_3$) [49.6 and 49.7 (2 × OMe)], 55.4 (1-OMe), 63.9 (C-6), [65.1, 67.3, 69.0 and 72.1 (C-2, C-3, C-4, C-5)], [97.7 and 97.9 (C-9′, C-10′)], 99.2 (C-1), [123.6, 123.7, 124.2, 124.5, 125.0, 125.5, 127.4, 127.5, 129.4, 130.7, 131.0, 131.8, 132.8, 133.0, 135.2, 135.3 and 150.8 (Ar-C) overlapping signals], 164.2 and 164.4 (2 × C=O); *m/z* (FAB) 729 (5%, M + H^+), 697 (100), 307 (100), 289 (50), 223 (50), 195 (50) (Found: $[M + H]^+$, 729.1932. $C_{37}H_{33}N_2O_{14}$ requires *M* + H, 729.1971).

X-Ray structure determination of compound 9.† $C_{37}H_{32}N_2O_{14}$·$0.5CH_2Cl_2$, *M* 770.10, orthorhombic, space group $P2_12_12$, *a* = 17.334(3), *b* = 27.100(5), *c* = 7.868(2) Å, *U* = 3696.0(13) $Å^3$, *F*(000) = 1600, D_c = 1.384 Mg m^{-3}, *Z* = 4, μ(Mo-Kα) = 1.540 mm^{-1}, final *wR*(F^2) = 0.1621 on 7248 independent reflections, *R*(*F*) = 0.0564 for 5155 independent reflections [$I > \sigma(I)$].

(2*R,4a*S**,12b*S**)-2-Ethyl-2,3,4a,12b-tetrahydro-4a,12b-dimethoxyphenanthreno[9,10-*b*][1,4]dioxine 11**

(±)-Camphorsulfonic acid (70 mg, 0.3 mmol) was added to a solution of (±)-butane-1,2-diol **10** (225 mg, 2.5 mmol), phenanthrene-9,10-quinone **4** (626 mg, 3.0 mmol) and trimethyl orthoformate (0.8 ml, 7.2 mmol) in dry methanol (10 ml). The mixture was heated under reflux for 72 h. The reaction was neutralised with triethylamine (0.5 ml) and the solvents removed under reduced pressure. The residue was purified by flash column chromatography (eluent: petrol–ether 4:1) to give the diacetal **11** (560 mg, 57%) which was further recrystallised from hexane to give a white solid, mp 95–96 °C; ν_{max}(KBr disc)/cm^{-1} 2294, 1449, 1236, 1059, 1013, 765; δ_H(250 MHz, $CDCl_3$) 1.13 (3H, t, *J* 7.4, CH_2CH_3), 1.65 (2H, m, CH_2CH_3), 2.91 and 2.93 (2 × 3H, 2 × s, 2 × OMe), 3.78 (1H, dd, *J* 3.8, 11.2, H-3_{eq}), 3.89 (1H, t, *J* 11.2, H-3_{ax}), 4.15 (1H, m, H-2), [7.31 (1H, dt, *J* 1.5, 7.5), 7.36 (2H, dt, *J* 1.5, 7.5), 7.41 (1H, dt, *J* 1.5, 7.5), 7.64 (1H, dd, *J* 1.5, 7.5), 7.69 (1H, dd, *J* 1.5, 7.5), 7.74 (2H, dd, *J* 1.5, 7.5) (Ar-H)]; δ_C(62.5 MHz, $CDCl_3$) 9.7 (Me), 24.3 (CH_2Me), [49.1 and 49.3 (2 × OMe)], 64.1 (C-2), 69.4 (C-3), [95.6 and 96.2 (C-4a, C-12b)], [124.0, 124.1, 125.3, 125.4, 127.3, 128.8, 128.9, 130.4, 133.0, 133.1, 133.6, 133.8 (Ar-C)]; *m/z* (EI) 326 (9%, M^+) 311 (4), 295 (8), 270 (4), 264 (5), 239 (10), 223 (5), 211 (100), 195 (30), 180 (25) (Found: M^+, 326.1517. $C_{20}H_{22}O_4$ requires *M*, 326.1509).

(3*R,5a*S**,13b*S**)-3,4,5a,13b-Tetrahydro-5a-methoxy-2*H*-3,13b-epoxyphenanthro[9,10-*b*][1,4]dioxepine 13**

(±)-Camphorsulfonic acid (70 mg, 0.3 mmol) was added to a solution of glycerol (230 mg, 2.5 mmol), phenanthrene-9,10-quinone **4** (626 mg, 3.0 mmol) and trimethyl orthoformate (0.8 ml, 7.2 mmol) in dry methanol (10 ml). The mixture was heated under reflux for 72 h. The reaction was neutralised with triethylamine (0.5 ml) and the solvents removed under reduced pressure. The residue was purified by flash column chromatography (eluent: petrol–ether 3:2) to give the diacetal **13** (511 mg, 69%) which was further recrystallised from hexane to give a white solid, mp 178–180 °C; ν_{max}(KBr disc)/cm^{-1} 2920, 1454, 1236, 1072, 1024, 746; δ_H(250 MHz, $CDCl_3$) 3.02 (3H, s, OMe), 3.73 (1H, dd, *J* 1.3, 11.4, H-4_{eq}), 4.00 (1H, dd, *J* 1.3, 6.0, H-2_{exo}), 4.23 (1H, d, *J* 6.0, H-2_{endo}), 4.45 (1H, dt, *J* 1.3, 11.4, H-4_{ax}), 4.77 (1H, dd, *J* 1.3, 6.0, H-3), [7.30–7.48 (4H, m), 7.65 (1H, dd, *J* 1.5, 7.4), 7.76 (3H, m) (Ar-H)]; δ_C (62.5 MHz, $CDCl_3$), 49.6 (OMe), 65.2 (C-4), 67.1 (C-2), 74.9 (C-3), 95.7 (C-5a), 103.5 (C-13b), [124.3, 124.4, 126.7, 127.3, 128.3, 129.3, 130.0, 130.4, 131.5, 132.4, 132.8 and 133.3 (Ar-C)]; *m/z* (EI) 296 (35%, M^+), 281 (10), 265 (30), 237 (56), 211 (100), 195 (32), 180 (50) (Found: M^+, 296.1052. $C_{18}H_{16}O_4$ requires *M*, 296.1054).

(2*R*,4a*S*,12b*S*)-2,3,4a,12b-Tetrahydro-4a,12b-dimethoxyphenanthreno[9,10-*b*][1,4]dioxine-2-ethanol 15

(±)-Camphorsulfonic acid (70 mg, 0.3 mmol) was added to a solution of (*R*)-(+)-butane-1,2,4-triol **14** (266 mg, 2.5 mmol),

phenanthrene-9,10-quinone **4** (626 mg, 3.0 mmol) and trimethyl orthoformate (0.8 ml, 7.2 mmol) in dry methanol (10 ml). The mixture was heated under reflux for 72 h. The reaction was neutralised with triethylamine (0.5 ml) and the solvents removed under reduced pressure. The residue was purified by flash column chromatography (gradient elution: petrol–ether 3:7 to petrol–ether 1:9) to give the diacetal **15** (554 mg, 65%) which was further recrystallised from ethyl acetate to give a white solid, $[\alpha]_D^{25}$ −45.0 (*c* 1.00, $CHCl_3$); mp 138–141 °C; ν_{max}(KBr disc)/cm^{-1} 3416, 2941, 1452, 1444, 1056, 1031, 864; δ_H(200 MHz, $CDCl_3$) 1.85 (3H, m, CH_2CH_2OH), 2.92 and 2.95 (2 × 3H, 2 × s, 2 × OMe), 3.78 (1H, dd, *J* 3.7, 11.4, H-3$_{ax}$), 3.95 (3H, m, H-3$_{eq}$, CH_2OH), 4.51 (1H, m, H-2), [7.28–7.77 (8H, m) (Ar-H)]; δ_C(62.5 MHz, $CDCl_3$) 33.6 (*C*H_2CH_2OH), [49.3 and 49.4 (2 × OMe)], 59.7 (CH_2OH), 63.8 (C-3), 66.4 (C-2), [95.7 and 96.5 (C-4a, C-12b)], [124.1, 124.2, 125.1, 125.4, 127.3, 129.0, 132.9, 133.0, 133.3 and 133.4 (Ar-C) overlapping signals]; *m/z* (EI) 342 (9%, M$^+$), 327 (3), 299 (6), 279 (8), 270 (5), 239 (23), 211 (100), 195 (38), 180 (35), 152 (20) (Found: M$^+$, 342.1470. $C_{20}H_{22}O_5$ requires *M*, 342.1456).

(1′*S*,2′*S*)-Methyl 3,4-*O*-(1′,2′-dimethoxycycloheptane-1′,2′-diyl)-α-D-mannopyranoside 21

Cycloheptane-1,2-dione **20** (70 mg, 0.56 mmol), (±)-camphorsulfonic acid (11 mg, 0.05 mmol), methyl α-D-mannopyranoside **2** (100 mg, 0.52 mmol) and trimethyl orthoformate (0.28 ml, 2.6 mmol) were heated at 70 °C for 16 h in dry methanol (15 ml). The reaction was neutralised with triethylamine (0.1 ml) and the solvents removed under reduced pressure. The residue was purified by flash column chromatography (eluent: ether–methanol 24:1) to give the diacetal **21** (90 mg, 49%) as a clear oil, $[\alpha]_D^{23}$ +185 (*c* 0.5, $CHCl_3$); ν_{max}(film)/cm^{-1} 3440, 2935, 2834, 1201, 1122, 1063, 923, 737; δ_H(500 MHz, $CDCl_3$) 1.31–1.62 and 1.71–1.95 (10H, m, 2 × H-3′, 2 × H-4′, 2 × H-5′, 2 × H-6′, 2 × H-7′), 2.25–2.51 (2H, br, 2-OH, 6-OH), 3.20 (6H, s, 2 × OMe), 3.42 (1H, s, H-2), 3.72–3.86 (3H, m, H-5, H-6$_a$, H-6$_b$), 3.92 (1H, dd, *J* 10.0, 3.0, H-3), 4.01 (1H, t, *J* 10.0, H-4), 4.72 (1H, d, *J* 1.0, H-1); δ_C(100 MHz, $CDCl_3$) [21.6, 24.6, 28.8 and 29.2 (C-3′, C-4′, C-5′, C-6′, C-7′) overlapping signals], [47.3 and 47.6 (2 × OMe)], 53.5 (1-OMe), 61.4 (C-6), [62.4, 67.6, 69.6 and 70.5 (C-2, C-3, C-4, C-5)], [101.1, 101.3 and 101.8 (C-1, C-1′, C-2′)]; *m/z* (EI) 348 (20%, M$^+$), 333 (80), 101 (100) (Found: M$^+$, 348.1791. $C_{16}H_{28}O_8$ requires *M*, 348.1784).

(2′*S*,3′*S*)-Methyl 3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-α-D-mannopyranoside 3

BF_3·OEt_2 (38 μl, 0.3 mmol) was added to a solution of methyl α-D-mannopyranoside **2** (584 mg, 3.0 mmol), butane-2,3-dione **1** (289 μl, 3.3 mmol) and trimethyl orthoformate (1.31 ml, 12.0 mmol) in dry methanol (9 ml). The mixture was stirred at room temperature for 17 h and then neutralised by the addition of five drops of triethylamine. The reaction was concentrated under reduced pressure and purified by flash column chromatography (gradient elution: ether to ether–methanol 95:5) to yield the diacetal **3** (916 mg, 99%) as a white solid (Found: C, 50.64; H, 7.75. $C_{13}H_{24}O_8$ requires C, 50.64; H, 7.85%); $[\alpha]_D^{23}$ +252.4 (*c* 1.05, $CHCl_3$); mp 140 °C; ν_{max}($CHCl_3$)/cm^{-1} 3451, 2949, 1377, 1131, 1037, 974, 848, 732; δ_H(500 MHz, $CDCl_3$) [1.28 and 1.31 (2 × 3H, 2 × s, 2 × CH_3)], 2.18 (1H, br s, OH), 2.65 (1H, s, OH), 3.25 and 3.26 (2 × 3H, 2 × s, 2 × OMe), 3.36 (3H, s, 1-OMe), 3.72–3.85 (3H, m, H-5, H-6$_a$, H-6$_b$), 3.91 (1H, br s, H-2), 3.99 (1H, dd, *J* 3.0, 10.0, H-3), 4.08 (1H, t, *J* 10.0, H-4), 4.74 (1H, s, H-1); δ_C(100 MHz, $CDCl_3$) [17.7 and 17.8 (2 × CH_3)], [47.9 and 48.1 (2 × OMe)], 54.9 (1-OMe), 61.3 (C-6), [63.3, 68.1, 69.7 and 70.5 (C-2, C-3, C-4, C-5)], [99.9 and 100.4 (C-2′, C-3′)], 101.1 (C-1); *m/z* (EI) 293 (2%, M − Me)$^+$, 277 (2), 245 (3), 213 (8), 187 (3), 174 (4), 159 (4), 127 (4), 116 (22), 100 (100) (Found: M − Me$^+$, 293.1234. $C_{12}H_{21}O_8$ requires *M* − Me, 293.1236).

(2′*R*,2‴*R*,3′*R*,3‴*R*)-Ethyl 2,3-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-4-*O*-[2″,3″-*O*-(2‴,3‴-dimethoxybutane-2‴,3‴-diyl)-β-D-galactopyranosyl]-1-thio-β-D-glucopyranoside 30

Butane-2,3-dione **1** (90 μl, 1.0 mmol), (±)-camphorsulfonic acid (11 mg, 0.05 mmol), ethyl 1-thio-β-D-lactoside **29** (150 mg, 0.39 mmol) and trimethyl orthoformate (0.35 ml, 3.2 mmol) were heated at reflux for 11 h in dry methanol (5 ml). The reaction was neutralised with triethylamine (0.1 ml) and the solvents removed under reduced pressure. The residue was purified twice by flash column chromatography (eluent: ether–methanol 99:1) to give the bis-diacetal **30** (74 mg, 31%) as a white solid (Found: C, 50.75; H, 7.59; S, 5.12. $C_{26}H_{46}O_{14}S$ requires C, 50.80; H, 7.54; S, 5.22%); $[\alpha]_D^{21}$ −126.9 (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3486, 2918, 1462, 1377, 1140, 1033, 937, 885, 848; δ_H(600 MHz, $CHCl_3$) [1.26–1.30 (15H, m, SCH_2CH_3, 4 × CH_3)], 1.89 (1H, br s, OH), 2.44 (1H, br s, OH), (2.61, 1H, s, OH), 2.62–2.78 (2H, m, S$CH_aH_bCH_3$), [3.22, 3.25, 3.27, 3.35, (4 × 3H, 4 × s, 4 × OCH_3)], 3.40–3.42 (1H, m H-5), 3.51 (1H, app. t, *J* 9.7, H-2), 3.57 (1H, dd, *J* 4.2, 9.8, H-6$_a$″), 3.61 (1H, app. t, *J* 5.7, H-6$_b$″), 3.68 (1H, dd, *J* 2.9, 10.4, H-3″), 3.78–3.93 (6H, m, H-2″, H-3, H-4, H-5″, H-6$_a$, H-6$_b$), 3.95 (1H, br s, H-4″), 4.55 (1H, d, *J* 9.8, H-1), 4.68 (1H, d, *J* 8.1, H-1″); δ_C(100 MHz, $CDCl_3$) 15.0 (SCH_2CH_3), [17.3, 17.6 × 3 (4 × CH_3)], 24.5 (SCH_2CH_3), [48.0, 48.18 × 2, 48.23 (4 × OMe)], [62.0, 62.3 (C-6, C-6″)], [67.8, 68.1, 69.1, 70.0, 73.7, 75.2, 79.5, 82.7 (C-2, C-2″, C-3, C-3″, C-4, C-4″, C-5, C-5″)], [99.5, 100.0, 100.2 and 100.3 (C-2′, C-2‴, C-3′, C-3‴)], [102.4, 102.7 (C-1, C-1″)]; *m/z* (ESI) 637 (M + Na) (Found: [M + Na]$^+$, 637.2472. $C_{26}H_{46}NaO_{14}S$ requires *M* + Na, 637.2506).

(2′*R*,3′*R*)-Methyl 2,3-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-β-D-galactopyranoside 31

BF_3·OEt_2 (38 μl, 0.3 mmol) was added to a solution of methyl β-D-galactopyranoside (584 mg, 3.0 mmol), butane-2,3-dione **1** (289 μl, 3.3 mmol) and trimethyl orthoformate (1.31 ml, 12.0 mmol) in dry methanol (9 ml). The mixture was stirred at room temperature for 17 h and then neutralised by the addition of five drops of triethylamine. The reaction was concentrated under reduced pressure and purified by flash column chromatography (gradient elution: ether to ether–methanol 95:5) to yield the diacetal **31** (786 mg, 85%) as a white solid (Found: C, 50.80; H, 7.85. $C_{13}H_{24}O_8$ requires C, 50.64; H, 7.85%); $[\alpha]_D^{21}$ −147.6 (*c* 1.13, $CHCl_3$); mp 61 °C; ν_{max}($CHCl_3$)/cm^{-1} 3592, 3501, 3027, 3007, 2947, 1730, 1602, 1449, 1378, 1238, 1143, 1112, 1083, 1050; δ_H(500 MHz, $CHCl_3$) [1.31 and 1.32 (2 × 3H, 2 × s, 2 × CH_3)], 2.31 and 2.66 (2 × 1H, 2 × br s, 2 × OH), 3.26 and 3.27 (2 × 3H, 2 × s, 2 × OMe), 3.54 (3H, s, 1-OMe), 3.59 (1H, t, *J* 6.0, H-5), 3.73 (1H, dd, *J* 3.0, 10.0, H-3), 3.83–3.95 (4H, m, H-2, H-4, H-6$_a$, H-6$_b$), 4.41 (1H, d, *J* 8.0, H-1); δ_C(100 MHz, $CDCl_3$) [17.8 and 17.9 (2 × CH_3)], [48.0 and 48.1 (2 × OMe)], 56.9 (1-OMe), 62.3 (C-6), [68.3, 68.34, 71.7 and 77.4 (C-2, C-3, C-4, C-5)], [100.9 and 101.2 (C-2′, C-3′)], 103.4 (C-1); *m/z* (FAB) 331 (100%, M + Na$^+$), 307 (1), 277 (10), 245 (6), 213 (6), 176 (4), 154 (10), 115 (11) (Found: [M + Na]$^+$, 331.1348. $C_{13}H_{24}NaO_8$ requires *M* + Na, 331.1369).

(2′*S*,3′*S*)-Methyl 2,3-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-β-D-arabinopyranoside 33

BF_3·OEt_2 (38 μl, 0.3 mmol) was added to a solution of methyl β-D-arabinopyranoside **32** (492 mg, 3.0 mmol), butane-2,3-dione **1** (289 μl, 3.3 mmol) and trimethyl orthoformate (1.31 ml, 12.0 mmol) in dry methanol (9 ml). The mixture was stirred at room temperature for 17 h and then neutralised by the addition of five drops of triethylamine. The reaction was concentrated under reduced pressure and purified by flash column chromatography (eluent: petrol–ether 2:3) to yield the diacetal **33** (351 mg, 42%) as a white solid, $[\alpha]_D^{22}$ +26.5 (*c* 0.81, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3579, 3032, 2931, 2836, 1449, 1379, 1264, 1240, 1234, 1193, 1144, 1082; δ_H(500 MHz, $CDCl_3$) [1.25 and 1.26 (2 × 3H, 2 × s, 2 × CH_3)], 2.86 (1H, br s, 4-OH), 3.18 and

3.20 (2 × 3H, 2 × s, 2 × OMe), 3.35 (3H, s, 1-OMe), 3.66 (1H, dd, *J* 1.3, 12.5, H-5_{ax}), 3.74 (1H, d, *J* 12.5, H-5_{eq}), 3.88 (1H, br s, H-4), 4.02 (1H, dd, *J* 3.2, 10.5, H-3), 4.13 (1H, dd, *J* 3.4, 10.5, H-2), 4.70 (1H, d, *J* 3.4, H-1); δ_C(100 MHz, $CDCl_3$) [17.6 and 17.7 (2 × CH_3)], [47.8 and 47.9 (2 × OMe)], 55.2 (1-OMe), 62.7 (C-5), [65.2, 65.8 and 68.0 (C-2, C-3, C-4)], 98.54 (C-1), [100.10 and 100.13 (C-2′, C-3′)]; *m/z* (EI) 277 (12%, $M - H)^+$, 247 (56), 215 (50), 187 (17), 154 (23), 145 (26) (Found: $[M - OMe]^+$, 247.1185. $C_{11}H_{19}O_6$ requires *M* − OMe, 247.1185).

(2′*S*,3′*S*)-Ethyl 2,3-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-1-thio-α-D-fucopyranoside 35

(±)-Camphorsulfonic acid (13 mg, 0.05 mmol) was added to a solution of ethyl 1-thio-α-L-fucopyranoside **34** (175 mg, 0.84 mmol), butane-2,3-dione **1** (92 μl, 1.02 mmol) and trimethyl orthoformate (0.35 ml, 3.2 mmol) in dry methanol (10 ml). The mixture was heated under reflux for 16 h. The reaction was neutralised with four drops of triethylamine and the solvents removed under reduced pressure. The residue was purified by flash column chromatography (eluent: petrol–ether 2:3) to give the diacetal **35** (217 mg, 80%) as a white solid (Found: C, 52.12; H, 8.07. $C_{14}H_{26}O_6S$ requires C, 52.15; H, 8.13%); $[\alpha]_D^{20}$ +85.0 (*c* 0.26, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3593, 2928, 2856, 1456, 1384, 1367, 1235, 1230, 1221, 1208, 1198, 1177, 1107, 1082, 1043; δ_H(500 MHz, $CDCl_3$) [1.25 and 1.31 (2 × 3H, 2 × s, 2 × CH_3)], 1.28 (3H, t, *J* 7.5, SCH_2CH_3), 1.33 (3H, d, *J* 6.5, 6-H), 1.99 (1H, br s, 4-OH), 2.72 (2H, m, SCH_2CH_3), 3.30 and 3.42 (2 × 3H, 2 × s, 2 × OMe), 3.69 (1H, q, *J* 6.5, H-5), 3.73–3.80 (3H, m, H-2, H-3, H-4), 4.54 (1H, d, *J* 8.8, H-1); δ_C(100 MHz, $CDCl_3$) [15.1, 16.6, 17.3, 18.6 (4 × CH_3)], 24.0 (SCH_2CH_3), [48.5 and 49.8 (2 × OMe)], [69.5, 70.3, 72.2 and 75.1 (C-2), (C-3), (C-4), (C-5)], 82.9 (C-1), [100.2 and 100.5 (C-2′, C-3′)]; *m/z* (FAB) 307 (15%), 291 (57), 229 (98), 191 (31), 173 (100), 154 (36), 143 (44) (Found: $[M - OMe]^+$, 291.1250. $C_{13}H_{23}O_5S$ requires *M* − OMe, 291.1266).

(2*R,3*R**,5*S**)-2,3-Dimethoxy-2,3-dimethyl-5-phenyl-1,4-dioxane 37**

A solution of (±)-1-phenylethane-1,2-diol **36** (276 mg, 2 mmol), butane-2,3-dione **1** (175 μl, 2 mmol) and trimethyl orthoformate (0.44 ml, 4 mmol) in dry methanol (10 ml) was treated with (±)-camphorsulfonic acid (46 mg, 0.2 mmol). The mixture was heated to reflux for 12 h then neutralised by the addition of five drops of triethylamine. After concentration under reduced pressure, the mixture was purified by flash column chromatography (eluent: petrol–ether 4:1) to yield **37** as a white crystalline solid (474 mg, 94%) (Found: C, 66.95; H, 8.09. $C_{14}H_{20}O_4$ requires C, 66.63; H, 7.99%); mp 54 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 2949, 2918, 1452, 1372, 1213, 1123, 1037, 957, 879, 756, 700; δ_H(400 MHz, $CDCl_3$) [1.34 and 1.37 (2 × 3H, 2 × s, 2 × CH_3)], 3.28 and 3.32 (2 × 3H, 2 × s, 2 × OMe), [3.56 (1H, dd, *J* 3.4, 11.0), 3.73 (1H, dd, *J* 3.4, 11.0) (H-2_a, H-2_b)], 4.92 (1H, dd, *J* 3.4, 11.0, H-1), 7.25–7.45 (5H, m, Ar-H); δ_C(100 MHz, $CDCl_3$) 17.7 and 18.0 (2 × CH_3), 48.0 and 48.2 (2 × OMe), [64.6 and 69.8 (C-1, C-2)], [98.0 and 99.6 (C-2′, C-3′)], [126.6, 128.01, 128.4 and 138.0 (Ar-C)]; *m/z* (EI) 221 (4%, M^+), 189 (1), 163 (3), 135 (6), 104 (100) (Found: $[M - OMe]^+$, 221.1177. $C_{13}H_{17}O_3$ requires *M* − OMe, 221.1177).

(2*R,3*R**,6*S**)-2,3,6,7-Tetrahydro-3-methoxy-2,3-dimethyl-5*H*-2,6-epoxy-1,4-dioxepine 38**

A solution of glycerol **12** (184 mg, 2 mmol), butane-2,3-dione **1** (175 μl, 2 mmol) and trimethyl orthoformate (0.44 ml, 4 mmol) in dry methanol (10 ml) was treated with (±)-camphorsulfonic acid (46 mg, 0.2 mmol). The mixture was heated to reflux for 12 h then neutralised by the addition of five drops of triethylamine. After concentration under reduced pressure, the mixture was purified by flash column chromatography (eluent: petrol–ether 1:1) to yield **38** as a colourless oil (341 mg, 98%), $\nu_{max}(CHCl_3)/cm^{-1}$ 2948, 2855, 1451, 1383, 1373, 1225, 1197, 1166, 1127, 1041, 1012, 867, 754, 643; δ_H(400 MHz, $CDCl_3$) [1.24 and 1.38 (2 × 3H, 2 × s, 2 × CH_3)], 3.28 (3H, s, OMe), 3.38 (1H, dd, *J* 1.3, 11.3, H-5_{eq}), 3.87 (1H, m, H-7_{exo}), 4.04 (1H, ddd, *J* 1.3, 6.6, 11.3, H-5_{ax}), 4.09 (1H, d, *J* 6.6, H-7_{endo}), 4.40 (1H, d, *J* 1.3, H-6); δ_C(100 MHz, $CDCl_3$) [18.3 and 18.6 (2 × CH_3)], 48.4 (OMe), [64.8, 67.1 and 74.4 (C-5, C-6, C-7)], [99.2 and 107.0 (C-2, C-3)]; *m/z* (CI) 192 (10%, $M + NH_4^+$), 160 (100), 143 (95), 100 (15) (Found: $[M + NH_4]^+$, 192.1236. $C_8H_{18}NO_4$ requires $M + NH_4$, 192.1236).

(2*R,5*S**,6*S**)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxane-2-methanol 39**

A solution of glycerol **12** (184 mg, 2 mmol), butane-2,3-dione **1** (175 μl, 2 mmol) and trimethyl orthoformate (0.44 ml, 4 mmol) in dry methanol (10 ml) was treated with $BF_3{\cdot}Et_2O$ (26 μl, 0.2 mmol). The mixture was stirred at room temperature for 12 h then neutralised by the addition of five drops of triethylamine. After concentration under reduced pressure, the mixture was purified by flash column chromatography (eluent: petrol–ether 1:1) to yield **39** as a white solid (254 mg, 62%) (Found: C, 52.36; H, 8.77. $C_9H_{18}O_5$ requires C, 52.41; H, 8.80%); mp 43 °C; $\nu_{max}(CHCl_3)/cm^{-1}$ 3464, 2948, 2832, 1451, 1374, 1209, 1124, 1037, 961, 878; δ_H(400 MHz, $CDCl_3$) [1.18 and 1.20 (2 × 3H, 2 × s, 2 × CH_3)], 2.62 (1H, br s, OH), 3.16 and 3.18 (2 × 3H, 2 × s, 2 × OMe), 3.36 (1H, dd, *J* 3.3, 11.3, H-3_{eq}), 3.49 (2H, m, CH_2OH), 3.60 (1H, dd, *J* 3.3, 11.3, H-3_{ax}), 3.88 (1H, m, H-2); δ_C(100 MHz, $CDCl_3$) [17.5 and 17.7 (2 × CH_3)], [47.9 and 48.0 (2 × OMe)], [60.2, 62.2 and 68.0 (CH_2OH, C-2, C-3)], [98.0 and 99.0 (C-5, C-6)]; *m/z* (CI) 192 (10%, $M - Me^+$), 160 (100), 143 (80), 103 (32), 52 (40) {Found: $[M - (2 \times OMe) - H]^+$, 143.0708. $C_7H_{11}O_3$ requires *M* − (2 × OMe) − H, 143.0708}.

(2*R*,3*R*,6*R*)-2,3,5,6,7,8-Hexahydro-3-methoxy-2,3-dimethyl-2,6-epoxy-1,4-dioxocine 40

A solution of (*R*)-(+)-butane-1,2,4-triol **14** (212 mg, 2 mmol), butane-2,3-dione **1** (175 μl, 2 mmol) and trimethyl orthoformate (0.44 ml, 4 mmol) in dry methanol (10 ml) was treated with (±)-camphorsulfonic acid (46 mg, 0.2 mmol). The mixture was heated to reflux for 12 h then neutralised by the addition of five drops of triethylamine. After concentration under reduced pressure, the mixture was purified by flash column chromatography (eluent: petrol–ether 1:1) to yield **40** as a colourless oil (242 mg, 65%) (Found: C, 57.41; H, 8.57. $C_9H_{16}O_4$ requires C, 57.24; H, 8.76%); $[\alpha]_D^{20}$ +109.0 (*c* 6.5, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3016, 2963, 1745, 1376, 1215, 1171, 1126, 1034, 990, 940, 868, 766; δ_H(600 MHz, $CDCl_3$) [1.21 and 1.26 (2 × 3H, 2 × s, 2 × CH_3)], 1.52 (1H, dd, *J* 4.2, 13.5, H-7_a), 2.37 (1H, m, H-7_b), 3.24 (3H, s, OMe), 3.52 (1H, d, *J* 11.5, H-5_{eq}), 3.83 (2H, m, H-6, H-8_a), 4.20 (1H, dt, *J* 2.6, 11.5, H-5_{ax}), 4.62 (1H, ddd, *J* 4.2, 10.8, 12.6, H-8_b); δ_C(150 MHz, $CDCl_3$) [18.0 and 23.5 (2 × CH_3)], 27.9 (C-7), 47.8 (OMe), [61.0, 63.6 and 66.4 (C-5, C-6, C-8)], [95.8 and 98.8 (C-2, C-3)]; *m/z* (CI) 206 (10%, $M + NH_4^+$), 175 (10), 174 (95), 158 (25), 157 (100) (Found: $[M + NH_4]^+$, 206.1392. $C_9H_{20}NO_4$ requires $M + NH_4$, 206.1392).

(2*S*,5*S*,6*S*)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxane-2-ethanol 41

A solution of (*R*)-(+)-butane-1,2,4-triol **14** (212 mg, 2 mmol), butane-2,3-dione **1** (175 μl, 2 mmol) and trimethyl orthoformate (0.44 ml, 4 mmol) in dry methanol (10 ml) was treated with $BF_3{\cdot}Et_2O$ (26 μl, 0.2 mmol). The mixture was stirred at room temperature for 12 h then neutralised by the addition of five drops of triethylamine. After concentration under reduced pressure, the mixture was purified by flash column chromatography (eluent: petrol–ether 3:7) to yield **41** as a colourless oil (281 mg, 64%) (Found: C, 54.79; H, 9.21. $C_{10}H_{20}O_5$ requires C, 54.51; H, 9.16%); $[\alpha]_D^{20}$ +194.3 (*c* 0.7, $CHCl_3$); ν_{max}(DCM)/cm^{-1} 3488, 2992, 2948, 2834, 1143, 1125; δ_H(500 MHz, $CDCl_3$) [1.268

and 1.270 (2 × 3H, 2 × s, 2 × CH_3)], 1.57 (1H, m, C$H_a$$H_b$-$CH_2$OH), 1.67 (1H, m, $CH_a$$H_b$$CH_2$OH), 3.25 and 3.27 (2 × 3H, 2 × s, 2 × OMe), 3.38 (1H, dd, *J* 3.1, 11.2, H-3_{eq}), 3.59 (1H, t, *J* 11.2, H-3_{ax}), 3.78 (2H, t, *J* 5.7, CH_2OH), 4.10 (1H, m, H-2); δ_C(100 MHz, $CDCl_3$) [17.6 and 17.9 (2 × CH_3)], 33.1 (CH_2CH_2OH), 48.0 (2 × OMe), [60.3, 63.2 and 66.8 (CH_2OH, C-2, C-3)], [98.0 and 99.0 (C-5, C-6)]; *m/z* (FAB) 189 (5%, M − $MeOH^+$) 157 (100), 136 (25) {Found: [M − (2 × OMe) − H]$^+$, 157.087. $C_8H_{13}O_3$ requires *M* − (2 × OMe) − H, 157.086}.

(2′*S*,3′*S*)-Methyl 2,6-di-*O*-benzyl-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-α-D-mannopyranoside 45

(2′*S*,3′*S*)-Methyl 3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-α-D-mannopyranoside **3** (78 mg, 0.27 mmol) in dry DMF (0.8 ml) was added to a slurry of sodium hydride (60% dispersion in mineral oil) (46 mg, 1.15 mmol) in DMF (0.8 ml) at 0 °C. The suspension was stirred for 1 h. Addition of catalytic tetra-*n*-butylammonium iodide (TBAI) (5 mg) was followed by dropwise addition of benzyl bromide (78 μl, 0.66 mmol). The reaction was left to come to room temperature and stirred for 16 h. Water (4 ml) was added and the mixture extracted with DCM (3 × 10 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography (gradient elution: ether–petrol 1:9 to ether–petrol 2:3) to yield the dibenzylated product **45** (106 mg, 80%) as a colourless oil, $[\alpha]_D^{22}$ +146 (*c* 1.00, $CHCl_3$); ν_{max}(film)/cm^{-1} 3063, 3028, 2922, 2948, 2832, 1497, 1377, 1208, 1128, 1048, 929; δ_H(500 MHz, $CDCl_3$) [1.28 and 1.34 (2 × 3H, 2 × s, 2 × CH_3)], [3.20, 3.28 and 3.34 (3 × 3H, 3 × s, 3 × OMe)], 3.70 (1H, s, H-2), 3.74–3.80 (2H, m, 6-H_a, 6-H_b), 3.89 (1H, ddd, *J* 1.8, 5.3, 7.4, H-5), 4.07 (1H, dd, *J* 2.8, 10.3, H-3), 4.19 (1H, t, *J* 10.3, H-4), [4.60 (1H, d, *J* 12.0), 4.65 (1H, d, *J* 12.0), 4.68 (1H, d, *J* 12.0), 4.94 (1H, d, *J* 12.0) (2 × CH_2Ph)], 4.73 (1H, s, H-1), 7.24–7.35 (8H, m, Ar-H), 7.43 (2H, d, *J* 7.3, Ar-H); δ_C(100 MHz, $CDCl_3$) [17.8 and 17.9 (2 × CH_3)], [47.9 and 48.0 (2 × OMe)], 54.6 (1-OMe), [63.8, 69.0, 70.8 and 75.7 (C-2, C-3, C-4, C-5)], 68.9 (C-6), [73.0, 73.4 (2 × CH_2Ph)], [99.6 and 99.9 (C-2′, C-3′)], 100.3 (C-1), [127.3, 127.4, 127.5, 128.0, 128.2, 128.3, 138.6, 138.8 (12 × Ar-C)]; *m/z* (EI) 473 (1%, M − Me^+), 456 (2), 399 (1), 341 (1), 294 (1), 280 (3), 249 (1), 217 (10), 91 (100) (Found: [M − Me]$^+$, 473.2200. $C_{26}H_{33}O_8$ requires M − Me, 473.2175).

Methyl 2,6-di-*O*-benzyl-α-D-mannopyranoside 46

(2′*S*,3′*S*)-Methyl 2,6-di-*O*-benzyl-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-α-D-mannopyranoside **45** (52 mg, 0.14 mmol) was dissolved in a mixture of trifluoroacetic acid and water (9:1, 1 ml). The reaction was stirred for 2 min then immediately evaporated under reduced pressure. The crude material (42 mg, 99%) gave satisfactory spectral analysis, although some was purified by flash column chromatography to yield a colourless oil **46** for further characterisation, $[\alpha]_D^{30}$ –5.4 (*c* 0.72, $CHCl_3$); ν_{max}(film)/cm^{-1} 3425, 1496, 1453, 1137, 1104, 736, 699; δ_H(400 MHz, $CDCl_3$) 2.60 (1H, br s, OH), 3.02 (1H, br s, OH), 3.35 (3H, s, 1-OMe), 3.66–3.80 (6H, m, H-2, H-3, H-4, H-5, H-6_a, H-6_b), [4.56 (1 H, d, *J* 11.7), 4.58 (1H, d, *J* 10.8), 4.64 (1H, d, *J* 10.8) and 4.71 (1H, d, *J* 11.7) (2 × CH_2Ph)], 4.80 (1H, s, H-1), 7.25–7.40 (10 H, m, Ar-H); δ_C(100 MHz, $CDCl_3$) 54.9 (1-OMe), 70.3 (C-6), [73.0 and 73.6 (2 × CH_2Ph)], [69.7, 70.7, 71.6 and 77.8 (C-2, C-3, C-4, C-5)], 98.2 (1-C), [127.6, 127.9, 128.0, 128.4, 128.6, 137.8, 138.2 (Ar-C)]; *m/z* (EI) 374 (20%, M^+), 373 (20), 343 (30), 283 (45), 163 (50), 107 (60), 91 (100) (Found: M^+, 374.1733. $C_{21}H_{26}O_6$ requires *M*, 374.1729).

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