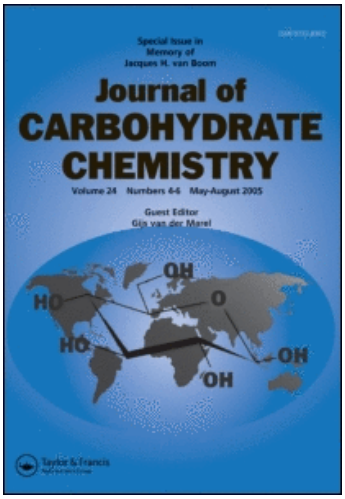

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Highly Regioselective Ring Opening of Five-Membered Cyclic Sulfates with Lithium Azide: Synthesis of Azido Sugars

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HIGHLY REGIOSELECTIVE RING OPENING OF FIVE-MEMBERED CYCLIC SULFATES WITH LITHIUM AZIDE: SYNTHESIS OF AZIDO SUGARS

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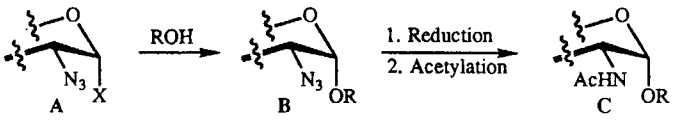
ABSTRACT

Cyclic sulfates of sugar pyranoses are easily prepared from their corresponding diol derivatives by treatment with thionyl chloride and subsequent oxidation of the resulting cyclic sulfites. Ring opening of these cyclic sulfates with lithium azide proceeds smoothly and in a highly regioselective fashion to give, after mild acid hydrolysis of the generated sulfate group, valuable azido sugars.

INTRODUCTION

It is well established, due to the pioneering work of Paulsen,[1-3] that an azido function plays a pivotal role in the synthesis of oligosaccharides containing 1,2-*cis* linked amino sugars. For example (see Scheme 1), the presence of the non-participating azido group at C-2 in sugar moiety **A** is an essential prerogative for the stereoselective introduction of a 1,2-*cis* glycosidic linkage between donor **A** (X = leaving group) and the hydroxyl group of an aglycon (ROH). Mild reduction of the azido group in the glycosylation product **B** followed by acetylation of the free amino group gives an easy access to the *N*-acetylated and 1,2-*cis* linked derivative **C**.

Scheme 1



The importance of the azido approach was *inter alia* nicely illustrated in the preparation of well-defined heparin fragments[4] and the antifungal agent amphotericin B.[5] At present three main procedures have been developed for the introduction of the versatile azido group in sugars. For instance, azidonitration[6,7] of the double bond in D-glucal or D-galactal is limited to the preparation of 2-azido-2-deoxysugars (*i.e.* **A**, $X=NO_2$). On the other hand, Walden inversion of a triflate group[8-11] or the regioselective ring opening of an epoxide by an azide nucleophile[12-14] gives access to azido sugars having an azido function at almost any position of the sugar skeleton.

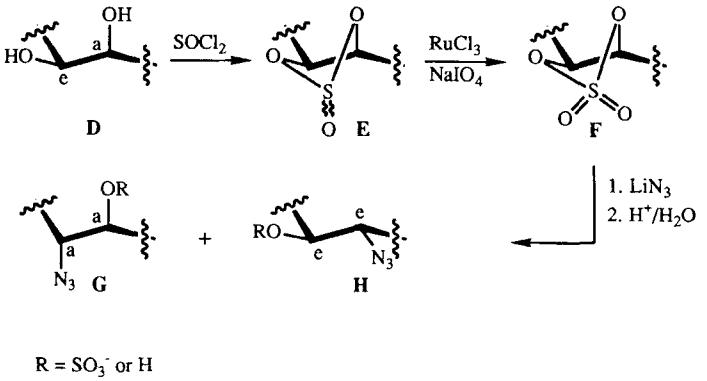
Earlier studies from this laboratory revealed that cyclic sulfate functions are very prone to ring opening by carbon[15-18] and nitrogen[15,19] nucleophiles. We report here the preparation and use of five-membered cyclic sulfates in the synthesis of azido sugars.

RESULTS AND DISCUSSION

The requisite five-membered cyclic sulfates (*i.e.* compounds **11** - **17** in Table 1) were readily accessible by converting the individual diol function in the corresponding sugars (*i.e.* compounds **1** - **7** in Table 1) following a synthetic route described earlier (see Scheme 2) for the preparation of similar sugar cyclic sulfates.[18] Thus, reaction of the diol function in **D** with thionyl chloride in the solvent system pyridine - ethyl acetate gives the cyclic sulfite **E**. Oxidation of **E** with sodium periodate in the presence of a catalytic amount of ruthenium (III) chloride hydrate, according to Sharpless,[20] affords the key cyclic sulfate **F**.

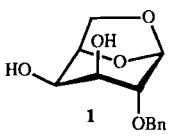
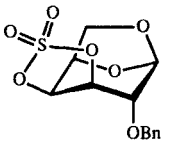
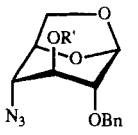
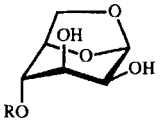
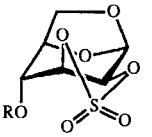
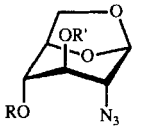
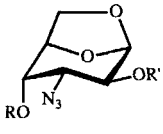
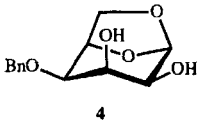
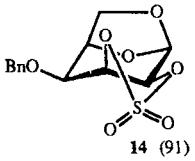
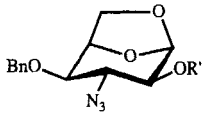
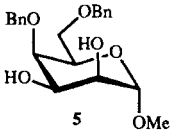
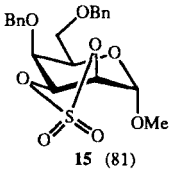
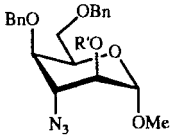
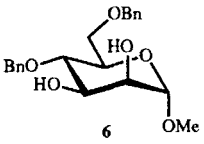
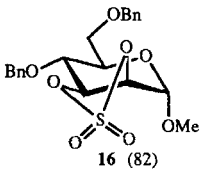
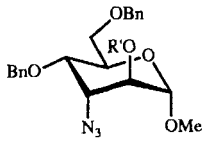
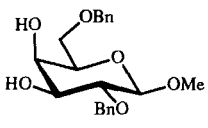
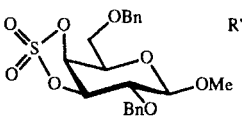
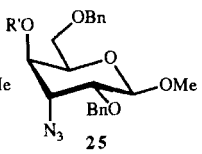
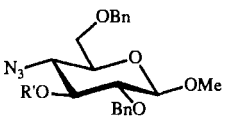
It can be seen in Table 1 that the conversion of the diol function in the known 1,6-anhydro-derivatives of D-*galacto*-(**1**),[21] D-*manno*-(**2**, **3**),[9,22] and D-*talo*-(**4**)[23] pyranose into the respective cyclic sulfates is a high yielding process. In a similar fashion, the conformationally less rigid cyclic sulfates **15** - **17** were obtained in a good yield (Table 1) starting with the methyl D-*manno*-(**6**),[24] D-*galacto*-(**7**)[25] pyranosides and the unknown D-*talo*-(**5**) pyranoside which

Scheme 2



R = SO_3^- or H

Table 1 Ring opening of cyclic sulfates **11** - **17** with lithium azide to give azido sugars **18** -**26** (R′ = H)

Entry	Diol	Cyclic sulfates Yield (%)	Azido sugars Yield (%)	
1	 **1**	 **11** (84)	 **18** (96)	
2	 **2** R = Bn **3** R = TBDPS	 **12** R = Bn (90) **13** R = TBDPS (92)	 **19** R = Bn (82) **21** R = TBDPS (89)	 **20** R = Bn (10)
3	 **4**	 **14** (91)	 **22** (92)	
4	 **5**	 **15** (81)	 **23** (90)	
5	 **6**	 **16** (82)	 **24** (90)	
6	 **7**	 **17** (87)	 **25**	 **26** (94)[a]

a. Compounds **25** and **26** were isolated in a combined yield of 94% in a ratio of 6:1.

Scheme 3

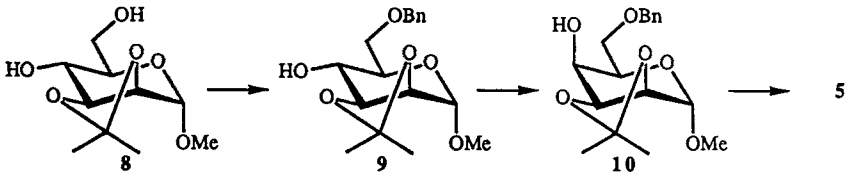


Table 2 ^{1}H NMR data for cyclic sulfates **11** - **17**

Compound	Solvent	H-1	H-2	H-3	H-4	H-5	H-6	H-6′
		($J_{1,2}$)	($J_{2,3}$)	($J_{3,4}$)	($J_{4,5}$)	($J_{5,6}$)	($J_{6,6'}$)	($J_{5,6'}$)
11	$(CD_3)_2SO$	5.60	3.87	5.32	5.61	4.96	4.07	3.72
				(6.1)	(5.3)	(5.1)	(8.7)	
12	$(CD_3)_2SO$	5.65	5.22	5.29	4.06	4.86	3.74	3.86
		(2.6)	(6.2)	(1.3)		(6.0)	(8.1)	(1.3)
13	$(CD_3)_2SO$	5.57	4.80	4.87	4.04	4.39	3.68	3.78
		(1.5)	(6.0)			(5.9)	(8.1)	(1.2)
14	$(CD_3)_2SO$	5.51	4.64	5.24	3.96	4.52	3.81	4.41
		(2.4)	(8.4)	(4.9)	(5.1)	(6.3)	(7.9)	(0.9)
15	$CDCl_3$	5.10	4.82	5.01	3.91	3.86	3.37	3.56
			(5.6)	(4.8)		(2.4)	(9.5)	(6.2)
16	$(CD_3)_2SO$	5.18	5.28	5.54	4.05	3.72	3.72	3.72
			(5.2)	(7.7)	(7.9)			
17	$CDCl_3$	4.28	3.88	4.83	5.11	3.90	3.68	3.76
		(7.7)	(7.5)	(5.4)	(1.5)	(7.6)	(9.4)	(5.8)

was prepared as outlined in Scheme 3. Thus, regioselective benzylation[26] of methyl 2,3-*O*-isopropylidene-α-D-mannopyranoside (**8**)[27] to give **9** was effected by reaction of the 4,6-dibutylstannylene derivative of **8** with benzyl bromide in the presence of tetrabutylammonium iodide. Swern oxidation of **9** followed by reduction of the ketone function with sodium borohydride gave the D-*talo*-pyranoside **10**. Subsequent benzylation of **10** and acidic hydrolysis of the acetonide function furnished the target compound **5** in 35% yield (over the four steps). The identity of compounds **11** - **17** was firmly established by ^{1}H NMR spectroscopy (see Table 2).

At this stage, having the requisite cyclic sulfates in hand, we turned our attention to the stereochemical outcome of the ring opening of the cyclic sulfates **11** - **17** by azide ions. To this end, the cyclic sulfates were first treated, as illustrated in Scheme 2, with lithium azide in *N,N*-dimethylformamide for 2-3 h at 80 °C followed by *in situ* removal of the generated sulfate group under mild acidic conditions [*i.e.* sulfuric acid (1 equiv)/ water (1 equiv)/ tetrahydrofuran]. It was expected, in analogy with the well-documented[28,29] ring opening of

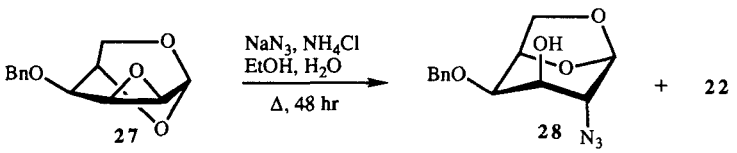
sugar epoxides by nucleophiles, that the above two-step process would follow a similar course. Thus, attack of the azide ion on the cyclic sulfate **F**, containing an equatorially-axially fused sulfate function, and subsequent acid hydrolysis will give predominantly the diaxial product **G** (R = H) instead of the diequatorial product **H** (R = H). Indeed, the 3,4-cyclic sulfate of the 1,6-anhydro-D-galactose derivative **11** yielded exclusively (see entry 1 in Table 1) the 1,6-anhydro-4-azido-4-deoxy-D-glucopyranose **18**. On the other hand, nucleophilic attack on the corresponding D-mannose 2,3-cyclic sulfate **12** was accompanied (entry 2) by the formation of a small quantity of the 1,6-anhydro-3-azido-3-deoxy-D-altropyranose **20**. However, regiospecific ring opening could be effected giving the 1,6-anhydro-2-azido-2-deoxy-D-glucopyranose **21** (entry 2) by replacing the benzyl group at the C-4 position in **12** by the rather bulky *tert*-butyldiphenylsilyl (TBDPS) group. In contrast, ring opening of the D-*talo*-2,3-cyclic sulfate **14** proceeded regiospecifically (entry 3) giving the diequatorial D-idopyranose **22**. However, the conformationally less rigid D-*talo*-2,3-cyclic sulfate **15** (entry 4) afforded solely the diaxial methyl 3-azido-3-deoxy-α-D-idopyranoside **23**. The same regiospecific ring opening was observed for the D-manno-2,3-cyclic sulfate **16** (entry 5). Finally, it can be seen in entry 6 that the azide ion-mediated ring opening of the less rigid D-galacto-3,4-cyclic sulfate **17** did not proceed regiospecifically (*cf.* entry 1). Analysis of the crude reaction mixture revealed the presence of the methyl 3-azido-3-deoxy-ß-D-gulo- and methyl 4-azido-4-deoxy-ß-D-glucopyranoside **25** and **26**, respectively, in a ratio of 6:1. The structure of the azido products **18** - **26** could be unambiguously ascertained after acetylation. The ^{1}H NMR data of the acetylated products are compiled in Table 3 and are in excellent agreement with the proposed structures of the azido derivatives **18** - **26**.

The results thus far obtained indicate that the azide ion-mediated ring opening of the equatorially-axially locked five-membered cyclic sulfates **11** - **17** is a highly regioselective process. Furthermore, the rigid cyclic sulfates **11** and **13** (entries 1 and 2) afford exclusively the respective diaxial products **18** and **21**. The latter result is in good agreement with the Fürst-Plattner[30] rule of *trans*-diaxial opening of steroid epoxides and pyranose epoxides which are held in a rigid conformation by a 4,6-acetal group or by a 1,6-anhydro bridge. It can also be seen (entry 3) that the rigid cyclic sulfate **14** did not afford the expected Fürst-Plattner product, but instead the diequatorial product **22**. In this respect, it is of interest to note ring opening of the 2,3-anhydro function in the 1,6-anhydro-4-*O*-benzyl-D-talopyranose **27**[13,31] with azide ions obeys the Fürst-Plattner rule giving the minor product **22** and the major 2,3-diaxial 2-azido-2-deoxy-D-galactopyranose **28** (see Scheme 4). In contrast, axial attack of an azide ion on the relatively more flexible cyclic sulfates in entries 4-6 may result, as observed earlier[28,29] for structurally related pyranose epoxides, in the formation of two products, one arising from each of the possible chair conformations. The latter mode of ring opening is consistent with the products **25** and **26** in entry 6. In the light of these results it was rather unexpected to find that the ring opening of the 2,3-cyclic sulfates in entries 4 and 5 proceeded regiospecifically.

Table 3 ^{1}H NMR ($CDCl_3$) data for the acetylated azido products **18** - **26**

Compound	H-1	H-2	H-3	H-4	H-5	H-6	H-6′
R′ = Ac	($J_{1,2}$)	($J_{2,3}$)	($J_{3,4}$)	($J_{4,5}$)	($J_{5,6}$)	($J_{6,6'}$)	($J_{5,6'}$)
18	5.41	3.25	5.00	3.27	4.67	3.80	4.03
	(1.6)	(3.0)	(1.5)		(5,6)	(7.6)	(1.0)
19	5.51	3.28	5.05	3.21	4.61	3.75	3.94
					(5.9)	(7.4)	(1.0)
20	5.49	5.16	3.49	3.76	4.58	3.67	3.77
	(1.6)	(9.8)	(4.4)		(1.0)	(8.0)	
21	4.89	3.11	5.47	3.52	4.34	3.52	3.69
					(7.6)	(1.0)	
22	5.38	4.60	3.72	3.61	4.42	3.71	4.15
	(1.8)	(9.0)	(8.9)	(4.0)	(4.4)	(8.0)	
23	4.77	4.77	3.92	3.54	4.14	3.72	3.72
		(6.1)	(5.9)	(3.8)	(5.2)	(10.0)	(5.6)
24	4.59	4.91	3.85	3.98	4.13	3.70	3.80
	(1.2)	(3.4)	(3.6)	(9.5)	(2.2)	(10.7)	(3.8)
25	4.68	3.56	3.91	4.87	4.03	3.48	3.48
	(7.9)	(3.6)	(3.7)	(1.4)	(6.6)		(6.3)
26	4.32	3.32	5.09	3.63	3.34	3.69	3.69
	(7.7)	(9.5)	(9.7)				

Scheme 4



In conclusion the results presented in this paper show that the effective introduction and highly regioselective ring opening of five-membered cyclic sulfates is a convenient and promising route to valuable azido sugars. Apart from this it is also worthwhile to mention that the opening of the five-membered cyclic sulfates is a much faster process than the opening of epoxides[2-4] in closely related sugars (*e.g.* see Scheme 4). Finally, it has to be mentioned that the ring opening of cyclic sulfites **E** of compounds **1** - **7** (experimental details not given here) was, in sharp contrast with the results of Guiller *et al.*,[32] extremely slow and accompanied with the formation of several unwanted products.

EXPERIMENTAL

General methods and materials - Pyridine was dried by refluxing with CaH_2 (5 g/L) and then distilled. Dichloromethane, 1,2-dichloroethane and toluene were distilled from P_2O_5. *N,N*-

dimethylformamide was stirred with CaH_2 at room temperature and distilled under reduced pressure. Diethyl ether was distilled from $LiAlH_4$. Pyridine and *N,N*-dimethylformamide were stored over molecular sieves 4Å (Aldrich), toluene and diethyl ether over sodium wire and dichloromethane and 1,2-dichloroethane were stored over alumina. Reactions were performed at ambient temperature unless noted otherwise. Column chromatography was performed on columns of silica gel 60 (Merck 230-400 mesh). TLC was conducted on DC Fertigfolien (Schleicher & Schüll F1500 LS254). Compounds were detected by charring with 20% sulfuric acid in methanol. Optical rotations were determined with a Perkin-Elmer Model 241 polarimeter, for solutions in $CHCl_3$ unless stated otherwise. ^{13}C NMR spectra were recorded at 50.1 MHz with a Jeol JNM-FX200 spectrometer. ^1H NMR spectra were recorded on a Bruker WM-300 spectrometer equipped with an ASPECT 2000 computer. Chemical shifts are given in ppm (δ) relative to TMS as internal reference, unless stated otherwise.

Methyl 4,6-Di-*O*-benzyl-α-D-talopyranoside (5). To a stirred solution of **10** (0.57 g, 1.75 mmol) was added NaH (63 mg, 80%, 1.2 eq) and benzyl bromide (0.27 mL, 1.3 eq). After stirring for 2 h, methanol (5 mL) was added and the reaction mixture concentrated. The residue was redissolved in dichloromethane (75 mL) and extracted twice with water, dried ($MgSO_4$) and concentrated. The residue was dissolved in acetic acid-H_2O (8:2, 10 mL) and stirred for 16 h at 75 °C. The reaction mixture was concentrated followed by evaporation of the residual oil with toluene (2x25 mL). The residue was chromatographed on silica gel with dichloromethane-methanol (1/0 to 95/5, v/v) to furnish pure **5** (0.52 g, 80%): $[\alpha]_D^{20}$ +28.1° (*c* 1); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 55.5 (OCH_3), 67.7, 70.6, 72.6, 79.5 (C-2, C-3, C-4 and C-5), 70.2 (C-6), 74.4, 76.7 (CH_2Ph), 103.6 (C-1), 128.7-129.4 ($CH_{arom.}$ phenyl), 139.3, 139.4 ($C_{arom.}$ phenyl).

Anal. Calcd for $C_{21}H_{26}O_6$: C, 67.3; H, 7.0. Found: C, 67.4; H, 7.0.

Methyl 6-*O*-Benzyl-2,3-*O*-isopropylidene-α-D-mannopyranoside (9). A solution of **8**[27] (1.17 g, 5 mmol) and dibutyltin oxide (1.3 g, 5.2 mmol) in dry methanol (30 mL) was refluxed for 2.5 h and subsequently concentrated. The residue was co-evaporated with toluene (2x10 mL). The resulting oil was dissolved in toluene (30 mL) to which was added tetrabutylammonium iodide (1.6 g, 5 mmol) and benzyl bromide (0.94 g, 5.5 mmol). After stirring for 24 h at 50 °C the reaction mixture was concentrated and applied to a column of silica gel. Elution was effected with dichloromethane/acetone (1/0 to 97/3, v/v) and concentration of the appropiate fractions gave **9** (1.3 g, 80%): $[\alpha]_D^{20}$ +8.2° (*c* 1); ^1H NMR ($CDCl_3$) δ 1.36, 1.55 (2xs, 6 H, $C(CH_3)_2$), 3.39 (s, 3 H, OCH_3), 3.69-3.78 (m, 4 H, H-4, H-5, H-6, H-6'), 4.07-4.15 (m, 2 H, H-2, H-3), 4.60 (q, 2 H, CH_2Ph), 4.90 (s, 1 H, H-1), 7.25-7.38 (m, 5 H, $H_{arom.}$ phenyl). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 25.6, 27.4 ($C(CH_3)_2$), 54.2 (OCH_3), 68.5, 69.0, 75.0, 78.2 (C-2, C-3, C-4 and /C-5), 69.2 (C-6), 72.9 (CH_2Ph), 97.6 (C-1), 108.9 ($C(CH_3)_2$), 126.8-127.9 ($CH_{arom.}$ phenyl), 137.7 ($C_{arom.}$ phenyl).

Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.9; H, 7.4. Found: C, 62.8; H, 7.3.

Methyl 6-*O*-Benzyl-2,3-*O*-isopropylidene-α-D-talopyranoside (10). To a cooled (-78 °C) solution of oxalyl chloride (0.35 mL, 4 mmol) in dichloromethane (6 mL) was added a

solution of dimethylsulfoxide (0.57 mL, 8 mmol) in dichloromethane (2 mL). The mixture was stirred for 5 min at -78 °C under a nitrogen atmosphere, after which a suspension of **9** (1.13 g, 3.5 mmol) in dichloromethane (3 mL) was injected slowly. The temperature was kept at -78 °C for 30 min and triethylamine (2.3 mL) was added. After 30 min the mixture was diluted with dichloromethane (40 mL) and extracted twice with brine (2x10 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was dissolved in 1,2-dimethoxyethane and reduced with sodium borohydride (0.13 g, 3.5 mmol). After 30 min acetone was added and the mixture was concentrated. Chromatography of the residue on silica gel with dichloromethane/acetone (1/0 to 95/5, v/v) afforded **10** (0.62 g, 55%): $[\alpha]_D^{20}$ +14.9° (*c* 1); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 24.8, 25.4 ($C(CH_3)_2$), 54.7 (OCH_3), 64.0, 67.6, 72.1, 73.2 (C-2, C-3, C-4 and C-5), 69.5 (C-6), 73.1 (CH_2Ph), 98.1 (C-1), 109.0 ($C(CH_3)_2$), 126.5-128.0 ($CH_{arom.}$ phenyl), 137.8 ($C_{arom.}$ phenyl).

Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.9; H, 7.4. Found: C, 63.0; H, 7.4.

General procedure for the synthesis of cyclic sulfates 11 - 17. To a solution of diol (1.00 mmol) and thionyl chloride (1.05 mmol) in ethyl acetate (5 mL) was added a solution of pyridine (2.1 mmol) in ethyl acetate (1 mL). The mixture was stirred and the temperature was not allowed to raise above r.t.. When TLC analysis (dichloromethane/acetone, 97/3, v/v) showed complete conversion of the starting material into cyclic sulfite, the mixture was diluted with ethyl acetate (25 mL) and extracted with water (5 mL). The organic phase was dried ($NaSO_4$) and concentrated. The residue was dissolved in a mixture of dichloromethane (2 mL), acetonitrile (2 mL) and water (3 mL), sodium periodate (2 equiv) and $RuCl_3xH_2O$ (2 mg) were added and the mixture was stirred for 1 h at 20 °C. The mixture was filtered and the filtrate was diluted with dichloromethane (20 mL); the organic layer was separated and washed with water (5 mL), dried ($MgSO_4$) and concentrated. The residue was applied to a column of silica gel suspended in dichloromethane. Elution was effected with dichloromethane/acetone (1/0 to 97/3, v/v).

1,6-Anhydro-2-*O*-benzyl-ß-D-galactopyranose 3,4-sulfate (11). Prepared as described above, starting from 1,6-anhydro-2-*O*-benzyl-ß-D-galactopyranose[21] in a yield of 84%: $[\alpha]_D^{20}$ -93.4° (*c* 1); ^1H NMR (see Table 2); $13C\{^1H\}$ NMR ($CDCl_3$) δ 63.1 (C-6), 70.3, 74.1, 74.6, 76.6 (C-2, C-3, C-4 and C-5), 72.6 (CH_2Ph), 99.5 (C-1), 127.8-128.5 ($CH_{arom.}$ phenyl), 135.9 ($C_{arom.}$ phenyl).

Anal. Calcd for $C_{13}H_{14}O_7S$: C, 49.6; H, 4.4. Found: C, 49.6; H, 4.4.

1,6-Anhydro-4-*O*-benzyl-ß-D-mannopyranose 2,3-sulfate (12). Prepared as descibed above, starting from 1,6-Anhydro-4-*O*-benzyl-ß-D-mannopyranose[9] in a yield of 90%: $[\alpha]_D^{20}$ -1.5° (*c* 1); ^1H NMR (see Table 2); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 65.0 (C-6), 71.8 (CH_2Ph), 73.4, 73.6, 76.5, 76.8 (C-2, C-3, C-4 and C-5), 96.5 (C-1), 127.7-128.5 ($CH_{arom.}$ phenyl), 136.0 ($C_{arom.}$ phenyl).

Anal. Calcd for $C_{13}H_{14}O_7S$: C, 49.6; H, 4.4. Found: C, 49.7; H, 4.4.

1,6-Anhydro-4-*O*-*tert*-butyldiphenylsilyl-ß-D-mannopyranose 2,3-sulfate (13). Prepared as descibed above, starting from 1,6-anhydro-4-*O*-*tert*-butyldiphenylsilyl-ß-D-mannopyranose[22]

in a yield of 92%: $[\alpha]_D^{20}$ -7.0° (*c* 1); ^{1}H NMR (see Table 2); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 18.9 ($(CH_3)_3C$), 26.5 ($(CH_3)_3C$), 64.6 (C-6), 69.2, 75.5, 76.5, 79.1 (C-2, C-3, C-4, C-5), 96.5 (C-1), 127.9-135.3 ($CH_{arom.}$ phenyl), 131.4, 131.8 ($C_{arom.}$ phenyl).

Anal. Calcd for $C_{22}H_{26}O_7SSi$: C, 57.1; H, 5.7. Found: C, 57.1; H, 5.6.

1,6-Anhydro-4-*O*-benzyl-ß-D-talopyranose 2,3-sulfate (14). Prepared as descibed above, starting from 1,6-anhydro-4-*O*-benzyl-ß-D-talopyranose[23] in a yield of 91%: $[\alpha]_D^{20}$ -63.7° (*c* 1); ^{1}H NMR (see Table 2); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 65.0 (C-6), 70.8, 71.8, 76.7, 78.8 (C-2, C-3, C-4 and C-5), 71.8 (CH_2Ph), 96.9 (C-1), 128.0-128.7 ($CH_{arom.}$ phenyl), 136.6 ($C_{arom.}$ phenyl).

Anal. Calcd for $C_{13}H_{14}O_7S$: C, 49.6; H, 4.4. Found: C, 49.6; H, 4.4.

Methyl 4,6-Di-*O*-benzyl-α-D-talopyranoside 2,3-sulfate (15). Prepared as described above, starting from **5** in a yield of 81%: $[\alpha]_D^{20}$ -57.9° (*c* 1); ^{1}H NMR (see Table 2); 13C{^{1}H} NMR ($CDCl_3$) δ 55.3 (OCH_3), 67.0, 69.5, 76.2, 79.5 (C-2, C-3, C-4 and C-5), 68.4 (C-6), 73.3, 75.8 (CH_2Ph), 95.5 (C-1), 127.5-129.6 ($CH_{arom.}$ phenyl), 136.8, 137.5 ($C_{arom.}$ phenyl).

Anal. Calcd for $C_{21}H_{24}O_8S$: C, 57.7; H, 5.5. Found: C, 57.8; H, 5.5.

Methyl 4,6-Di-*O*-benzyl-α-D-mannopyranoside 2,3-sulfate (16). Prepared as described above, starting from methyl 4,6-di-*O*-benzyl-α-D-mannopyranoside[24] in a yield of 82%: $[\alpha]_D^{20}$ +15.8° (*c* 1); ^{1}H NMR (see Table 2); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 55.0 (OCH_3), 67.8 (C-6), 67.9, 72.9, 79.4, 85.9, (C-2, C-3, C-4 and C-5), 73.3, 74.0 (CH_2Ph), 95.1 (C-1), 127.5-129.4 ($CH_{arom.}$ phenyl), 136.8, 137.5 ($C_{arom.}$ phenyl).

Anal. Calcd for $C_{21}H_{24}O_8S$: C, 57.7; H, 5.5. Found: C, 57.6; H, 5.5.

Methyl 2,6-Di-*O*-benzyl-ß-D-galactopyranoside 3,4-sulfate (17). Prepared as described above, starting from methyl 2,6-di-*O*-benzyl-ß-D-galactopyranoside[25]. Yield 87%; $[\alpha]_D^{20}$ +18.1° (*c* 1); ^{1}H NMR (see Table 2); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 56.8 (OCH_3), 67.3 (C-6), 70.4, 77.4, 79.5, 84.9 (C-2, C-3, C-4 and C-5), 73.4, 74.6 (CH_2Ph), 102.7 (C-1), 127.5-128.3 ($CH_{arom.}$ phenyl), 137.2 ($C_{arom.}$ phenyl).

Anal. Calcd for $C_{21}H_{24}O_8S$: C, 57.7; H, 5.5. Found: C, 57.7; H, 5.5.

General procedure for the synthesis of azido sugars 18 - 26. To a solution of cyclic sulfate (1 mmol) in DMF (5 mL) was added LiN_3 (2 equiv). The mixture was stirred at 80 °C until (2-3 h) TLC analysis (dichloromethane/acetone, 97/3, v/v) showed complete conversion of the cyclic sulfate into baseline material. The mixture was concentrated and dissolved in THF (5 mL). Concentrated sulfuric acid (50 µL) and water (18 µL) were added and the mixture was stirred for 0.5 h at ambient temperature. The mixture was diluted with ethyl acetate (20 mL) and washed twice with a saturated aqueous sodium bicarbonate solution (5 mL). The organic layer was dried ($MgSO_4$), concentated and applied to a column of silica gel and eluted with dichloromethane/acetone (1/0 to 95/5, v/v).

1,6-Anhydro-4-azido-2-*O*-benzyl-4-deoxy-ß-D-glucopyranose (18). Yield: 96%; $[\alpha]_D^{20}$ -71.3° (*c* 1); IR (neat): 2110 cm^{-1} (N_3); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 62.6 (C-4), 62.1, 69.2, 74.2 (C-2, C-3 and C-5), 66.1 (C-6), 71.8 (CH_2Ph), 100.6 (C-1), 127.6-128.2 ($CH_{arom.}$ phenyl), 137.2 ($C_{arom.}$ phenyl).

Anal. Calcd for $C_{13}H_{15}N_3O_4$: C, 56.3; H, 5.4. Found: C, 56.4; H, 5.5.

1,6-Anhydro-2-azido-4-*O*-benzyl-2-deoxy-ß-D-glucopyranose (19). Yield: 82%; $[\alpha]_D^{20}$ -4.4° (*c* 1); IR (neat): 2120 cm^{-1} (N_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 62.6 (C-2), 65.9 (C-6), 70.1, 74.7, 78.5 (C-3, C-4 and C-5), 71.6 (*C*H_2Ph), 100.7 (C-1), 127.7-128.5 ($CH_{arom.}$ phenyl), 137.2 ($C_{arom.}$ phenyl).

Anal. Calcd for $C_{13}H_{15}N_3O_4$: C, 56.3; H, 5.4. Found: C, 56.3; H, 5.4.

1,6-Anhydro-3-azido-4-*O*-benzyl-3-deoxy-ß-D-altropyranose (20). Yield:10%; $[\alpha]_D^{20}$ +79.3° (*c* 1); IR (neat): 2110 cm^{-1} (N_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 61.4 (C-3), 65.5 (C-6), 71.0, 74.2, 76.1 (C-2, C-4 and C-5), 72.5 (*C*H_2Ph), 101.6 (C-1), 127.9-128.5 ($CH_{arom.}$ phenyl), 137.1 ($C_{arom.}$ phenyl).

Anal. Calcd for $C_{13}H_{15}N_3O_4$: C, 56.3; H, 5.4. Found: C, 56.4; H, 5.4.

1,6-Anhydro-2-azido-4-*O*-*tert*-butyldiphenylsilyl-2-deoxy-ß-D-glucopyranose (21). Yield: 89%; $[\alpha]_D^{20}$ -25.3° (*c* 1); IR (neat): 2120 cm^{-1} (N_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 19.1 ($(CH_3)_3C$), 26.8 ($(CH_3)_3C$), 62.3 (C-2), 65.7 (C-6), 72.8, 73.6, 77.1 (C-3, C-4, C-5), 100.7 (C-1), 127.8-135.7 ($CH_{arom.}$ phenyl), 131.5, 131.8 ($C_{arom.}$ phenyl).

Anal. Calcd for $C_{22}H_{27}N_3O_4Si$: C, 62.1; H, 6.4. Found: C, 62.0; H, 6.4.

1,6-Anhydro-3-azido-4-*O*-benzyl-3-deoxy-ß-D-idopyranose (22). Yield: 92%; $[\alpha]_D^{20}$ -100.8° (*c* 1); IR (neat): 2110 cm^{-1} (N_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 65.0 (C-6), 66.1 (C-3), 72.7, 73.6, 77.3 (C-2, C-4 and C-5), 72.8 (*C*H_2Ph), 101.3 (C-1), 127.6-129.5 ($CH_{arom.}$ phenyl), 137.2 ($C_{arom.}$ phenyl).

Anal. Calcd for $C_{13}H_{15}N_3O_4$: C, 56.3; H, 5.4. Found: C, 56.3; H, 5.4.

Methyl 3-Azido-4,6-di-*O*-benzyl-3-deoxy-α-D-idopyranoside (23). Yield: 90%; $[\alpha]_D^{20}$ +5.3° (*c* 1); IR (neat): 2120 cm^{-1} (N_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 55.7 (O*C*H_3), 59.1 (C-3), 66.7, 68.5, 74.6 (C-2, C-4 and C-5), 68.2 (C-6), 73.0, 73.2 (*C*H_2Ph), 101.0 (C-1), 127.5-128.4 ($CH_{arom.}$ phenyl), 136.6, 137.7 ($C_{arom.}$ phenyl).

Anal. Calcd for $C_{21}H_{25}N_3O_5$: C, 63.1; H, 6.3. Found: C, 63.1; H, 6.3.

Methyl 3-Azido-4,6-di-*O*-benzyl-α-D-altropyranoside (24). Yield: 90%; $[\alpha]_D^{20}$ +98.5° (*c* 1); IR (neat): 2120 cm^{-1} (N_3); ^1H NMR ($CDCl_3$) δ 2.94 (d, 1 H, 2-OH), 3.46 (s, 3 H, OC*H*$_3$), 3.59-4.18 (m, 6 H, H-2, H-3, H-4, H-5, H-6, H-6'), 4.43-4.85 (m, 5 H, H-1, C*H*$_2$Ph), 7.28-7.61 (m, 10 H, $H_{arom.}$ phenyl). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 55.4 (O*C*H_3), 60.2 (C-3), 67.5, 69.2, 71.9 (C-2, C-4 and C-5), 68.9 (C-6), 71.8, 73.3 (*C*H_2Ph), 101.1 (C-1), 127.6-129.4 ($CH_{arom.}$ phenyl), 137.2, 137.5 ($C_{arom.}$ phenyl).

Anal. Calcd for $C_{21}H_{25}N_3O_5$: C, 63.1; H, 6.3. Found: C, 63.0; H, 6.3.

Methyl 4-Azido-2,6-di-*O*-benzyl-4-deoxy-ß-D-glucopyranoside (25) and Methyl 3-Azido-2,6-di-*O*-benzyl-3-deoxy-ß-D-gulopyranoside (26). Yield: 94% (6:1); Compound **25**: $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 56.8 (O*C*H_3), 61.3 (C-4), 68.8 (C-6), 73.8,75.0, 80.8 (C-2, C-3 and C-5), 73.4, 74.2 (*C*H_2Ph), 104.1 (C-1), 127.4-128.4 ($CH_{arom.}$ phenyl), 137.2, 138.0 ($C_{arom.}$ phenyl), Compound **26**: $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 56.7 (O*C*H_3), 63.0 (C-3), 70.1, 70.6, 75.4 (C-2, C-4 and C-5), 70.2 (C-6), 73.4, 73.7 (*C*H_2Ph), 102.3 (C-1), 127.4-128.4 ($CH_{arom.}$ phenyl), 137.2, 138.1 ($C_{arom.}$ phenyl).

Anal. Calcd for $C_{21}H_{25}N_3O_5$: C, 63.1; H, 6.3. Found: C, 63.1; H, 6.3.

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