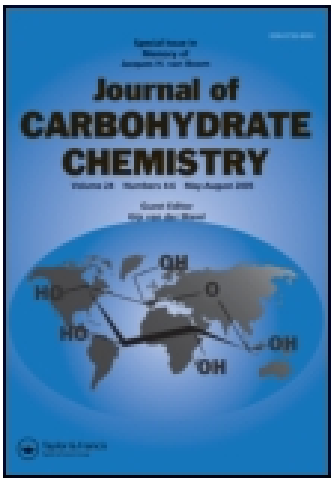

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lcar20

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Published online: 27 Feb 2008.

To cite this article: Franck Dagron & André Lubineau (2000) Ring Opening of Benzyl β-D-Galactoside Cyclic Sulfates into Galactose Monosulfates. New Access to 6-Deoxy-Galacto-Hex-5-Enopyranoside and 4-Deoxy-3-Ketogalactopyranoside., Journal of Carbohydrate Chemistry, 19:3, 311-321, DOI: 10.1080/07328300008544080

To link to this article: http://dx.doi.org/10.1080/07328300008544080

J. CARBOHYDRATE CHEMISTRY, 19(3), 311–321 (2000)

RING OPENING OF BENZYL β-D-GALACTOSIDE CYCLIC SULFATES INTO GALACTOSE MONOSULFATES. NEW ACCESS TO 6-DEOXY-*GALACTO*-HEX-5-ENOPYRANOSIDE AND 4-DEOXY-3-KETOGALACTOPYRANOSIDE.

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Received July 30, 1999 - Final Form February 4, 2000

ABSTRACT

The behavior of 3,4- and 4,6-cyclic sulfates derived from benzyl 2,6- and 2,3-di-*O*-benzyl-β-D-galactopyranosides toward hydrolysis has been studied using aqueous sodium hydroxide under various conditions. Starting from benzyl 2,6-di-*O*-benzyl-3,4-*O*-sulfuryl-β-D-galactopyranoside (**5**), the reaction with aq NaOH in THF gave both 3- and 4-monosulfates **7** and **8** (83%, in 68:32 ratio), while the reaction in DMF led unexpectedly to the 4-deoxy-3-keto derivative **10** in 77% yield after acidic hydrolysis of the intermediate enolester **9**. On the other hand, when benzyl 2,3-di-*O*-benzyl-4,6-*O*-sulfuryl-β-D-galactopyranoside (**6**) was treated with aq NaOH in THF, a mixture of benzyl 2,3-di-*O*-benzyl-6-deoxy-4-*O*-(sodium sulfonato)-α-L-*arabino*-hex-5-enopyranoside (**11**) and benzyl 2,3-di-*O*-benzyl-4-deoxy-6-*O*-(sodium sulfonato)-α-L-*threo*-hex-4-enopyranoside (**12**) (in 65:35 ratio) was obtained in 93% yield, giving a new and rapid access to **11**, a potential precursor of L-sugars derivatives. Alternatively, $BzONBu_4$ gave a regiospecific opening reaction of **6** and led to the 6-*O*-benzoate 4-*O*-sulfate derivative (**13**) in excellent yield.

INTRODUCTION

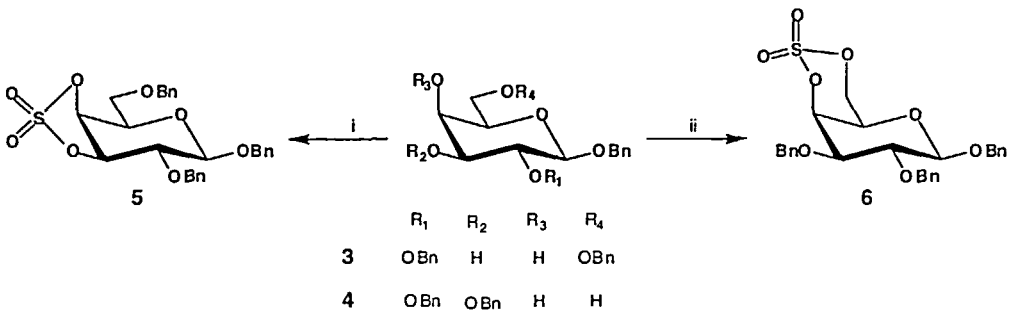
Sulfated oligosaccharides such as glycosaminoglycans or sulfated Lewis antigens play important roles in many recognition processes.[1] They are implied for example in key events in the inflammatory response.[2] As part of our studies on the preparation of a library of sulfated oligosaccharides by combinatorial chemistry,[3] we were interested in a regioselective access to 4-*O*-sulfated galactose derivatives. Indeed, whereas several regioselective sulfation reactions have been reported to give in good yield 3-*O*-sulfated galactose derivatives, using for example the stannylene methodology,[4] none allows the direct preparation of 4-*O*-sulfated compounds.

Formally, 4-*O*-sulfate derivatives can be obtained from regioselective opening reactions of 3,4- or 4,6-cyclic sulfates. However, while cyclic sulfates are well-known for their epoxide-like reactivity and have been usually prepared to introduce various functional groups by nucleophilic attack at the carbon atom which undergoes inversion of configuration,[5] their monohydrolyses were poorly documented. Such a reaction, however, has been described by Brimacombe *et al.*[6] on cyclohexane-*cis*-1,2-diol cyclic sulfate. The reaction was performed in aq sodium hydroxide to give the corresponding *cis*-diol monosulfate with complete retention of configuration. We decided to take advantage of this reactivity and to study the regioselectivity of the opening reaction of carbohydrate cyclic sulfates in aqueous media.

RESULTS AND DISCUSSION

We present here the results of the monohydrolysis assays of benzyl 2,6-di-*O*-benzyl-3,4-*O*-sulfuryl-β-D-galactopyranoside (**5**) and that of benzyl 2,3-di-*O*-benzyl-4,6-*O*-sulfuryl-β-D-galactopyranoside (**6**). These cyclic sulfates were readily available following the procedure described by Gao and Sharpless[7] (Scheme 1) using the oxidation system $NaIO_4$-$RuCl_3.H_2O$ to oxidize the cyclic sulfites (as a mixture of diastereoisomers) prepared in excellent yields from the corresponding diols. Thus, the 3,4-cyclic sulfate **5** was prepared in 91% overall yield from the benzyl 2,6-di-*O*-benzyl-β-D-galactopyranoside[8] (**3**) using first $SOCl_2$ (1.5 eq) in CH_2Cl_2 in the presence of triethylamine (4 eq) followed by oxidation. The 4,6-cyclic sulfate **6** was prepared in the same way from the benzyl 2,3-di-*O*-benzyl-β-D-galactopyranoside[9] (**4**) in 75% overall yield.

We then tested the ring opening reactions of these cyclic sulfates. Treatment of the cyclic sulfate **5** with aqueous sodium hydroxide (10 M, 25 eq) in refluxing THF gave a mixture of monosulfates **7** and **8** in 83% isolated yield in a 68/32 ratio as shown by NMR (Scheme 2). The influence of temperature (0 °C, 25 °C, 66 °C), by varying at the same time



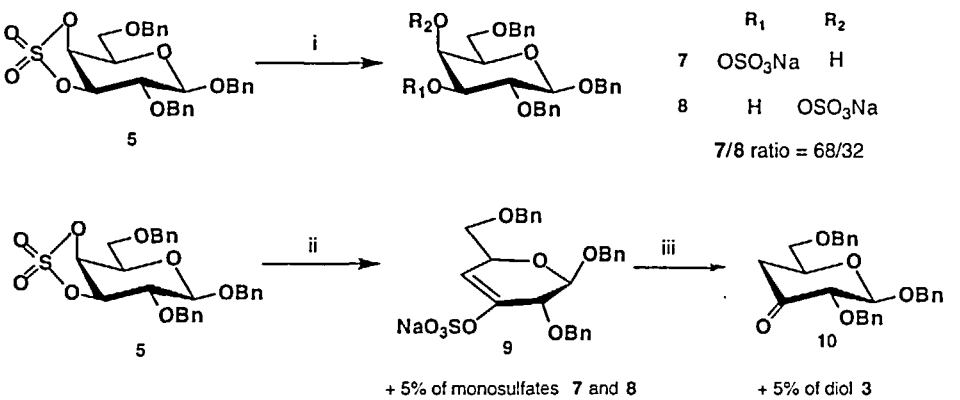
Reagents and conditions: i) a) $SOCl_2$, NEt_3, CH_2Cl_2, 20 min, 0 °C. b) $RuCl_3$ (cat.), $NaIO_4$, $CCl_4/CH_3CN/H_2O$ (2/2/3), 1 h, 0 °C, 91% (2 steps). ii) $SOCl_2$, NEt_3, CH_2Cl_2, 30 min, 0 °C. b) $RuCl_3$ (cat.), $NaIO_4$, $CCl_4/CH_3CN/H_2O$ (2/2/3), 4 h, 0 °C, 75% (2 steps).

Scheme 1

the number of equivalents of NaOH (25, 5 and 2 eq), on the ratio of the two isomers, was studied by following the anomeric C-1 signals of both monosulfates using ^{13}C NMR. The ratio of **7** and **8** was found to be constant between 65-70/30-35 (data not shown).

However, when the cyclic sulfate **5** was treated with 10 M aqueous sodium hydroxide in DMF in place of THF, compounds **7** and **8** were obtained in only 5% total yield. The major compound obtained in that case resulted from deprotonation at C-3 to give the vinylic sulfate **9** which was hydrolyzed to the corresponding ketone **10** (77% overall yield).

The regioselectivity of the elimination process is both due to the acidic H-3 proton and to a *trans*-diaxial orientation between H-3/C-3 and C-4/O-4 bonds allowing an E_2 *anti*

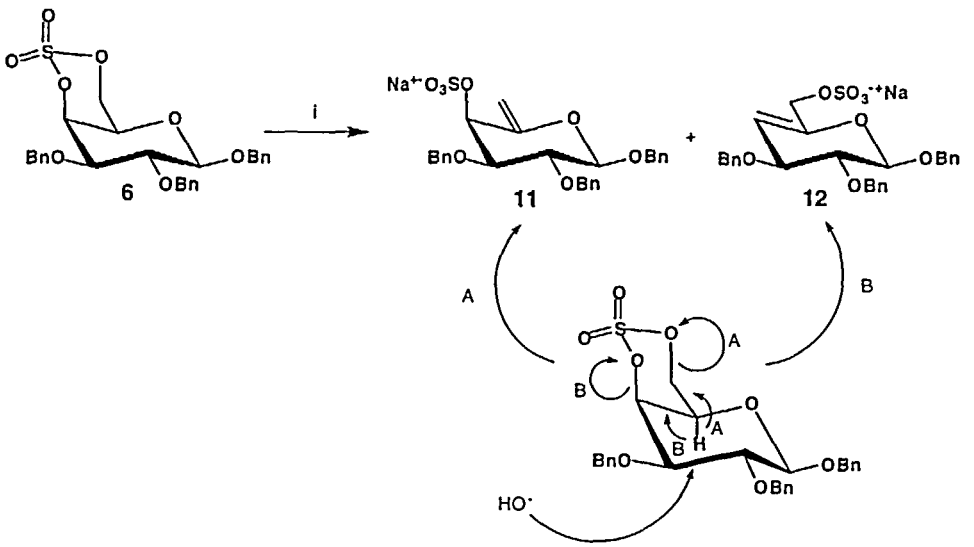


Reagents and conditions: i) NaOH 10 M (25 eq), THF, 1.5 h, 70 °C, mixture of **7** and **8** (68/32), 83%. ii) NaOH 10 M (10 eq), DMF, 2 h, 70 °C iii) THF, H_2O cat., H_2SO_4 cat., 0 °C, 77% yield over 2 steps.

Scheme 2

elimination in a polar and non protic solvent such as DMF as compared to THF. This reaction constitutes a new useful way to 4-deoxy-3-ketosugars, precursors of 4-deoxy 4-C branched-chain sugars.[10] (Scheme 2)

In contrast, ring opening of the 4,6-cyclic sulfate **6** by aqueous sodium hydroxide in THF or in DMF did not give monohydrolysis of the cyclic sulfate as expected. This treatment led in 93% total yield to the exocyclic and endocyclic elimination products, both resulting from deprotonation at C-5 of the acidic proton to give a mixture of benzyl 2,3-di-*O*-benzyl-6-deoxy-4-*O*-(sodium sulfonato)-α-L-*arabino*-hex-5-enopyranoside (**11**), and benzyl 2,3-di-*O*-benzyl-4-deoxy-6-*O*-(sodium sulfonato)-α-L-*threo*-hex-4-enopyranoside (**12**) in a 65/35 ratio (Scheme 3). The *anti* elimination can occur following two routes (A and B) with cyclic sulfate acting like a very good leaving group.



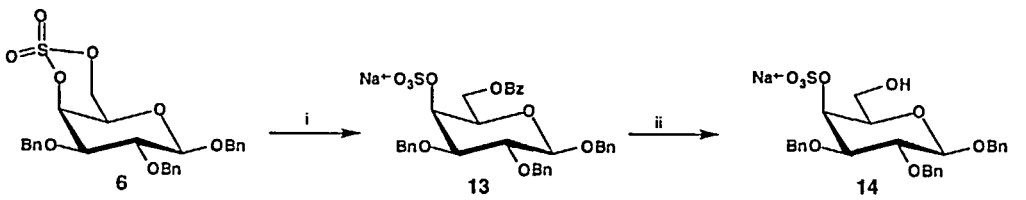
Reagents and conditions : i) NaOH 10 M (25 eq), THF, 3.5 h, 70 °C, mixture of **11/12** (65/35), 93%.

Scheme 3

This new access to a 6-deoxy-hex-5-enopyranoside derivative, obtained in 60% yield by 4,6-cyclic sulfate ring opening constitutes a new interesting route to this type of unsaturated compounds, potential precursors of L-sugars derivatives through hydroboration[11] and of carbocyclic sugars through the Ferrier rearrangement.[12]

In the case of 4,6-cyclic sulfate **6**, the mono 4-*O*-sulfate derivative **13** could be obtained in near quantitative yield through nucleophilic attack at the primary carbon atom of **6**

using $BzONBu_4$ in DMF.[13] Compound **13** was then debenzoylated with MeONa to afforded **14** in 95% yield (Scheme 4).



Reagents and conditions: i) a) $BzO^-NBu_4^+$ (1.1 eq), DMF, 2 h, rt, 97%. b) Biorad AG50WX8-Na^+. ii) MeONa/MeOH, rt, overnight, 95% isolated.

Scheme 4

In conclusion, we describe here, along with a synthesis of a 4-sulfate galactoside derivative (**14**), a facile access to a 6-deoxyhex-5-enopyranoside derivative (**11**) and a 4-deoxy-3-ketogalactopyranoside derivative (**10**), potential precursors of various natural products.

EXPERIMENTAL

General procedures. NMR spectra were recorded with Brücker AM250, AC200 and AC250 spectrometers. ^1H and ^{13}C chemical shifts (δ) for NMR spectra are reported relative to tetramethylsilane (0 ppm) and internal chloroform (77 ppm); signal multiplicity is indicated as follow: s for singlet, sb for broad singlet, d for doublet, t for triplet, q for quadruplet, m for multiplet. IR spectra were recorded on a FT-IR Brücker IFS 66 spectrometer. Optical rotations were determined using a Jasco DIP-370 digital polarimeter. Flash chromatography was performed using 6-35 μ silica gel (60) purchased from S.D.S. Company. TLC was run using Merck 60 F254 plates, and visualized first with UV light and second by heating after alcoholic sulfuric acid treatment. Melting points were measured with a Reichert apparatus and are uncorrected. Elemental analyses were performed at the Service Central de Microanalyses, CNRS, Gif sur Yvette, France.

Benzyl 2,6-di-*O*-benzyl-3,4-*O*-sulfuryl-β-D-galactopyranoside (5). To a solution of benzyl 2,6-di-*O*-benzyl-β-D-galactopyranoside[8] (**3**) (2 g, 4.44 mmol) in dichloromethane (9 mL) under nitrogen was added triethylamine (2.48 mL, 17.7 mmol). The mixture was then cooled (0 °C) and a solution of thionyl choride (0.49 mL, 6.7 mmol) in dichloromethane (2.9 mL) was added dropwise over a period of 10 min. After stirring at 0 °C for 20 min, the mixture was diluted with dichloromethane (50 mL) and washed with water

(50 mL). The aqueous layer was extracted with dichloromethane (2 x 50 mL). The organic phases were pooled and filtered using silicon treated paper. The filtrate was then concentrated and coevaporated twice with toluene to give a yellow syrup containing the mixture of diastereoisomeric cyclic sulfites. This syrup was dissolved in a mixture of CCl_4, CH_3CN and H_2O (2/2/3, 21 mL). The solution was stirred at 0 °C and $NaIO_4$ (1.81 g, 8.5 mmol) was then added, followed by a solution of $RuCl_3.H_2O$ in water (67.5 mM, 314 µL, 0.02 mmol). The mixture was stirred at 0 °C for 1 h, and then diluted with dichloromethane (50 mL) and washed with 5% aq $KHCO_3$. The aqueous layer was then extracted with dichloromethane (2 x 50 mL). The organic phases were pooled and filtered using silicon treated paper and the filtrate concentrated. Flash chromatography (EtOAc-hexane 15:85) of the residue gave **5** (2.08 g, 91% over the 2 steps) as a white powder : $[\alpha_D]$ +17° (*c* 2.11, CH_2Cl_2); ^1H NMR 250 MHz ($CDCl_3$) δ 7.35 ppm (m, 15 H, Ph), 5.12 (dd, 1 H, $J_{3,4}$ = 5.5 Hz, $J_{4,5}$ = 1.5 Hz, H-4), 4.94 (d, 1 H, J_{gem} = 12.0 Hz, *H*CHPh), 4.88 (d, 1 H, J_{gem} = 11.0 Hz, *H*CHPh), 4.83 (dd, 1 H, $J_{2,3}$ = 8.0 Hz, H-3), 4.73 (d, 1 H, *H*CHPh), 4.65 (d, 1 H, *H*CHPh), 4.58 (s, 2H, *H*CHPh), 4.45 (d, 1 H, $J_{1,2}$ = 8.0 Hz, H-1), 3.98 (t, 1 H, H-2), 3.89 (ddd, $J_{5,6}$ = 6.0 Hz, $J_{5,6'}$ = 8.0 Hz, H-5), 3.79 (dd, 1 H, J_{gem} = 9.5 Hz, H-6), 3.71 (dd, 1 H, H-6'); ^{13}C NMR ($CDCl_3$) δ 137.2, 137.1, 136.4 (C_q Bn), 128.5, 128.4, 128.2, 128.1, 128.0, 127.9 (CH_{arom}), 100.7 (C-1), 85.1, 79.4, 77.5, 70.8 (C-2, C-3, C-4, C-5), 75.0, 73.8, 71.0 (3 x CH_2Ph), 67.4 (C-6); IR (cm^{-1}) 2892, 1451, 1383, 1211, 1099, 1068, 977, 927, 868, 824, 757, 732, 696.

Anal. Calcd for $C_{27}H_{28}O_8S$ (512.6): C, 63.27; H, 5.51; O, 24.97; S, 6.25. Found: C, 63.48; H, 5.58; O, 24.61; S, 6.24.

Benzyl 2,3-di-*O*-benzyl-4,6-*O*-sulfuryl-β-D-galactopyranoside (6). The same procedure as for the cyclic sulfate **5** was followed. A solution of **4**[9] (1.74 g, 3.87 mmol) in CH_2Cl_2 (5 mL) was treated with $SOCl_2$ (564 µL, 7.73 mmol) and NEt_3 (2.7 mL, 19.3 mmol) for 30 min at 0 °C. The crude mixture of diastereoisomeric cyclic sulfites was then oxidized by the system $NaIO_4$ (2.48 g, 11.58 mmol) and $RuCl_3.H_2O$ (0.08 mmol) in a mixture of $CCl_4/CH_3CN/H_2O$ (2:2:3, 14 mL). After 4 h at 0 °C the same work-up as above gave **6** (1.48 g, 75%) after flash chromatography (EtOAc - hexane 25:75). $[\alpha_D]$ -12° (*c* 2.39, CH_2Cl_2); ^1H NMR 250 MHz ($CDCl_3$) δ 7.35 ppm (m, 15 H, Ph), 5.04 (d, 1 H, $J_{3,4}$ = 3.5 Hz, H-4), 4.96 (d, 1 H, J_{gem} = 12.0 Hz, *H*CHPh), 4.88 (d, 1 H, J_{gem} = 11.0 Hz, *H*CHPh), 4.81 (dd, 1 H, $J_{5,6}$ = 1.5 Hz, J_{gem} = 12.5 Hz, H-6), 4.75 (d, 1 H, *H*CHPh), 4.70 (s, 2 H, C*H*$_2$Ph), 4.64 (d, 1 H, *H*CHPh), 4.62 (dd, 1 H, $J_{5,6'}$ = 1.5 Hz, H-6'), 4.51 (d, 1 H, $J_{1,2}$ = 8.0 Hz, H-1), 3.78 (dd, 1 H, $J_{2,3}$ = 10.0 Hz, H-2), 3.63 (d, 1 H, H-3), 3,50 (m, 1 H, H-5); ^{13}C NMR ($CDCl_3$) δ 138.0, 137.0, 136.7 (C_q Bn), 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8 (CH_{arom}), 101.9 (C-1), 80.7, 77.6, 76.8 (C-2, C-3, C-5), 75.5, 74.3, 72.5, 71.2 (3 x CH_2Ph, C-6), 63.8 (C-4); IR (cm^{-1}) 2868, 1498, 1455, 1404, 1203, 1091, 993, 901, 877, 838, 792, 696, 527.

Anal. Calcd for $C_{27}H_{28}O_8S$ (512.6): C, 63.27; H, 5.51; O, 24.97; S, 6.25. Found: C, 63.53; H, 5.57; O, 24.73; S, 5.98.

Benzyl 2,6-di-*O*-benzyl-3-*O*-(sodium sulfonato)-β-D-galactopyranoside (7) and Benzyl 2,6-di-*O*-benzyl-4-*O*-(sodium sulfonato)-β-D-galactopyranoside (8). Aqueous sodium hydroxide (10 M, 1.49 mL, 25 eq) was added to a solution of cyclic sulfate **5** (305 mg, 0.596 mmol) in THF (1.49 mL),. The mixture was then strongly stirred and refluxed at 70 °C. When the starting material was consumed after 1.5 h, the mixture was cooled to room temperature then diluted with ethyl acetate (30 mL) and washed with water (2 x 30 mL). The aqueous layer was extracted with ethyl acetate (3 x 20 mL). The organic phases were pooled, dried (sodium sulfate), filtered and concentrated. Flash chromatography (ethyl acetate/propan-2-ol/water 95/4/2) of the residue followed by cation exchange chromatography (Biorad AG50WX8-Na^+) gave **7** (52 mg) and **8** (eluted first, 23 mg) along with a mixture of **7** and **8** (2:1, 60 mg). Total yield 83% (**7**/**8** 68:32). Data for benzyl 2,6-di-*O*-benzyl-3-*O*-(sodium sulfonato)-β-D-galactopyranoside (**7**): $[\alpha_D]$ -11° (*c* 1.25, MeOH); ^{1}H NMR 250 MHz ($CDCl_3/CD_3OD$ = 8/2) δ 7.30 ppm (m, 15 H, Ph), 4.93 (d, 1 H, J_{gem} = 12.0 Hz, *H*CHPh), 4.78 (s, 2 H, C*H*$_2$Ph), 4.62 (d, 1 H, *H*CHPh), 4.55 (s, 2 H, C*H*$_2$Ph), 4.52 (d, 1 H, $J_{1,2}$ = 8.0 Hz, H-1), 4.41 (dd, 1 H, $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 2.5 Hz, H-3), 4.38 (sb, 1 H, H-4), 3.65 to 3.80 (m, 4 H, H-2, H-5, H-6, H-6'); ^{13}C NMR ($CDCl_3/CD_3OD$ = 8/2) δ 138.3, 138.0, 137.5 (C_q Bn), 128.6, 128.5, 128.3, 128.1, 127.9, 127.7 (C_{arom}), 102.3 (C-1), 80.4, 77.3, 73.3, 69.9 (C-2, C-3, C-4, C-5), 75.0, 73.7, 71.2 (3 x *C*H$_2$Ph), 67.6 (C-6); IR (cm^{-1}) 3448, 3030, 2874, 1635, 1497, 1454, 1367, 1257, 1063, 999, 814, 734, 696.

Anal. Calcd for $C_{27}H_{29}O_9SNa$, 0.25 H_2O: C, 58.21; H, 5.35; S, 5.76. Found: C, 58.12; H, 5.35; S, 5.74.

Data for benzyl 2,6-di-*O*-benzyl-4-*O*-(sodium sulfonato)-β-D-galactopyranoside (**8**): $[\alpha_D]$ -18° (*c* 1.01, MeOH); ^{1}H NMR 250 MHz ($CDCl_3/CD_3OD$ = 8/2) δ 7.30 ppm (m, 15 H, Ph), 4.90 (d, 1 H, J_{gem} = 11.0 Hz, *H*CHPh), 4.87 (d, 1 H, J_{gem} = 12.0 Hz, *H*CHPh), 4.72 (d, 1 H, *H*CHPh), 4.71 (d, 1 H, $J_{3,4}$ = 3.0 Hz, H-4), 4.59 (d, 1 H, *H*CHPh), 4.54 (s, 2 H, C*H*$_2$Ph), 4.42 (d, 1 H, $J_{1,2}$ = 7.5 Hz, H-1), 3.92 (dd, 1 H, $J_{5,6}$ = 4.5 Hz, J_{gem} = 11.0 Hz, H-6), 3.78 (dd, 1 H, $J_{5,6'}$ = 7.0 Hz, H-6'), 3.70 (dd, 1 H, $J_{2,3}$ = 10.0 Hz, H-3), 3.66 (m, 1 H, H-5), 3.58 (dd, 1 H, H-2); ^{13}C NMR ($CDCl_3/CD_3OD$ = 8/2) δ 138.7, 138.3, 137.3 (C_q Bn), 128.6, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8 (CH_{arom}), 102.6 (C-1), 79.9, 76.6, 73.6, 71.2 (C-2, C-3, C-4, C-5), 75.0, 73.7, 71.2 (3 x *C*H$_2$Ph), 69.9 (C-6); IR (cm^{-1}) 3449, 3030, 2872, 1585, 1497, 1454, 1366, 1249, 1109, 1061, 926, 862, 733, 695, 628.

Anal. Calcd for $C_{27}H_{29}O_9SNa$, 0.5 H_2O: C, 57.75; H, 5.38; S, 5.71. Found: C, 57.69; H, 5.37; S, 5.42.

Benzyl 2,3-di-*O*-benzyl-6-deoxy-4-*O*-(sodium sulfonato)-α-L-*arabino*-hex-5-enopyranoside (11) and Benzyl 2,3-di-*O*-benzyl-4-deoxy-6-*O*-(sodium

sulfonato)-α-L-*threo*-hex-4-enopyranoside (12). Aqueous sodium hydroxide (10 M, 0.73mL, 25 eq) was added to a solution of cyclic sulfate **6** (148 mg, 0.289 mmol) in THF (0.72 mL). The mixture was strongly stirred and refluxed at 70 °C. When the starting material was consumed after 3.5 h, the mixture was cooled to room temperature then diluted with ethyl acetate (20 mL) and washed with water (2 x 20 mL). The aqueous layer was extracted with ethyl acetate (3 x 15 mL). The organic phases were pooled, dried (Na_2SO_4), filtered and concentrated. Flash chromatography (ethyl acetate/propan-2-ol/water/NEt_3 94:4:2:0.5) of the residue followed by cation exchange chromatography (Biorad AG50WX8-Na^+) gave **11** (73 mg) and **12** (45 mg) along with a mixture of **11** and **12** (3:1, 25 mg). Total yield 93% (**11/12** 65:35). Data for benzyl 2,3-di-*O*-benzyl-6-deoxy-4-*O*-(sodium sulfonato)-α-L-*arabino*-hex-5-enopyranoside (**11**): $[\alpha_D]$ -47° (*c* 1.27, MeOH); ^1H NMR 250 MHz ($CDCl_3/CD_3OD$ = 8/2) δ 7.30 ppm (m, 15 H, Ph), 5.16 (d, 1 H, $J_{3,4}$ = 3.0 Hz, H-4), 4.95 (d, 1 H, J_{gem} = 12.0 Hz, *H*CHPh), 4.90 (d, 1 H, J_{gem} = 11.0 Hz, *H*CHPh), 4.87 (s, 2 H, C*H*$_2$Ph), 4.74 (d, 1 H, *H*CHPh), 4.69 (d, 1 H, $J_{6,6'}$ = 10.5 Hz, H-6), 4.65 (d, 1 H, *H*CHPh), 4.62 (d, 1 H, $J_{1,2}$ = 6.0 Hz, H-1), 4.59 (d, 1 H, H-6'), 3.70 to 3.80 (m, 2 H, H-2, H-3); ^{13}C NMR ($CDCl_3/CD_3OD$ = 8/2) δ 151.2 (C-5), 137.7, 137.2, 136.6 (C_q Bn), 128.3, 128.1, 128.0, 127.7, 127.6, 127.5, 127.4 (C_{arom}), 102.3 (C-1), 101.0 (C-6), 77.4, 77.2, 72.5 (C-2, C-3, C-4), 74.4, 71.7, 70.9 (3 x *C*H$_2$Ph); IR (cm^{-1}) : 3478, 3088, 3063, 3032, 2876, 1667, 1617, 1497, 1453, 1394, 1363, 1265, 1156, 1100, 1071, 1040, 1027, 935, 855, 731, 698.

Anal. Calcd for $C_{27}H_{27}O_8SNa$, 0.25 H_2O: C, 60.16; H, 5.14; S, 5.95. Found: C, 60.01; H, 5.37; S, 5.59.

Data for benzyl 2,3-di-*O*-benzyl-4-deoxy-6-*O*-(sodium sulfonato)-α-L-*threo*-hex-4-enopyranoside (**12**): $[\alpha_D]$ -17° (*c* 1.07, MeOH); ^1H NMR 250 MHz ($CDCl_3/CD_3OD$ = 8/2) δ 7.30 ppm (m, 15 H, Ph), 5.19 (d, 1 H, $J_{3,4}$ = 3.5 Hz, H-4), 5.03 (d, 1 H, $J_{1,2}$ = 5.0 Hz, H-1), 4.93 (d, 1 H, J_{gem} = 12.0 Hz, *H*CHPh), 4.76 (d, 1 H, J_{gem} = 11.5 Hz, *H*CHPh), 4.67 (d, 1 H, *H*CHPh), 4.61 (d, 1 H, *H*CHPh), 4.58 (s, 2 H, C*H*$_2$Ph), 4.40 (s, 2 H, H-6, H-6'), 4.08 (dd, 1 H, $J_{2,3}$ = 5.0 Hz, H-3), 3.72 (t, 1 H, H-2); ^{13}C NMR ($CDCl_3/CD_3OD$ = 8/2) δ 147.8 (C-5), 137.6, 137.4, 136.6 (C_q Bn), 128.1, 127.7, 128.6, 127.5 (CH_{arom}), 100.0 (C-4), 98.9 (C-1), 76.5, 73.2 (C-2, C-3), 70.8, 70.6, 66.3, 63.3 (3 x *C*H$_2$Ph, C-6); IR (cm^{-1}) 3449, 3064, 3031, 2876, 1606, 1497, 1454, 1368, 1247, 1166, 1104, 1071, 1028, 983, 834, 733, 691.

Anal. Calcd for $C_{27}H_{27}O_8SNa$, 1.25 H_2O: C, 58.21; H, 5.34; S, 5.76. Found: C, 58.31; H, 5.16; S, 5.38.

Benzyl 6-*O*-benzoate-2,3-di-*O*-benzyl-4-*O*-(sodium sulfonato)-β-D-galactopyranoside (13). A solution of compound **6** (202 mg, 0.395 mmol) and tetrabutylammonium benzoate (158 mg, 0.434 mmol, 1.1 eq) in anhydrous DMF (1.3 mL)

was stirred at room temperature for 2 h and then diluted with ethyl acetate (25 mL), washed with brine then with water. The aqueous layer was extracted with ethyl acetate (3 x 25 mL). The organic phases were pooled, dried (Na_2SO_4), filtered then concentrated. Flash chromatography (ethyl acetate / propan-2-ol / water 94:4:2) of the residue followed by cation exchange chromatography (Biorad AG50WX8-Na^+) gave **13** (252 mg, 97%) as a white powder. $[\alpha_D]$ +47° (*c* 1.17, DMF); ^1H NMR 250 MHz ($CDCl_3/CD_3OD$ = 8/2) δ 7.40 to 7.60 ppm (m, 5 H, Bz), 7.20 to 7.30 (m, 15 H, Ph), 5.01 (d, 1 H, J_{gem} = 11.5 Hz, *H*CHPh), 4.97 (d, 1 H, $J_{3,4}$ = 3.0 Hz, H-4), 4.85 (d, 1 H, J_{gem} = 10.5 Hz, *H*CHPh), 4.84 (d, 1 H, *H*CHPh), 4.78 (dd, 1 H, $J_{5,6}$ = 8.5 Hz, $J_{6,6'}$ = 12.0 Hz, H-6), 4.71 (d, 1 H, *H*CHPh), 4.67 (dd, 1 H, $J_{5,6'}$ = 4.5 Hz, H-6'), 4.61 (d, 1 H, J_{gem} = 11.5 Hz, *H*CHPh), 4.55 (d, 1 H, *H*CHPh), 4.45 (d, 1 H, $J_{1,2}$ = 7.5 Hz, H-1), 3.83 (dd, 1 H, H-5), 3.63 (d, 1 H, $J_{2,3}$ = 9.5 Hz, H-2), 3.61 (dd, 1 H, H-3); ^{13}C NMR ($CDCl_3/CD_3OD$ = 8/2) δ 166.4 (C=O), 138.3, 138.1, 136.9 (C_q Bn), 132.8 (C_qBz), 129.3, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 127.3, 127.2 (CH_{arom}), 101.5 (C-1), 79.1, 78.2, 72.1, 66.1 (C-2, C-3, C-4, C-5), 75.0, 71.6, 70.5 (3 x CH_2Ph), 64.1 (C-6); IR (cm^{-1}) 3492, 3031, 1707, 1496, 1453, 1318, 1252, 1114, 1041, 918, 864, 732, 710, 696.

Anal. Calcd for $C_{34}H_{33}O_{10}SNa$, H_2O: C, 60.53; H, 5.23; S, 4.75. Found: C, 60.67; H, 5.31; S, 4.67.

Benzyl 2,3-di-*O*-benzyl-4-*O*-(sodium sulfonato)-β-D-galactopyranoside (14). To a solution of compound **13** (111 mg, 0.178 mmol) in dry MeOH (600 µL) was added a solution of MeONa in MeOH (0.25 M, 144 µL). The mixture was stirred for 48 h until the starting material was totally consumed, then neutralized with Dowex 50WX8-H^+, filtered and concentrated. Flash chromatography (ethyl acetate/propan-2-ol/water 85/10/5) of the residue followed by cation exchange chromatography (Biorad AG50WX8-Na^+) gave **14** (94 mg, 95% yield). $[\alpha_D]$ +14° (*c* 1.30, MeOH); ^1H NMR 250 MHz ($CDCl_3/CD_3OD$ = 8/2) δ 7.20 to 7.30 ppm (m, 15 H, Ph), 5.01 (d, 1 H, J_{gem} = 11.5 Hz, *H*CHPh), 5.00 (d, 1 H, $J_{3,4}$ = 1.5 Hz, H-4), 4.89 (d, 1 H, J_{gem} = 12.0 Hz, *H*CHPh), 4.84 (d, 1 H, J_{gem} = 11.0 Hz, *H*CHPh), 4.78 (d, 1 H, *H*CHPh), 4.62 (d, 1 H, *H*CHPh), 4.54 (d, 1 H, *H*CHPh), 4.48 (d, 1 H, $J_{1,2}$ = 7.5 Hz, H-1), 3.91 (dd, 1 H, $J_{5,6}$ = 9.0 Hz, $J_{6,6'}$ = 11.5 Hz, H-6), 3.76 (dd, 1 H, $J_{5,6'}$ = 5.5 Hz, H-6'), 3.60 (m, 2 H, H-2, H-3), 3.48 (d, 1 H, H-5); ^{13}C NMR ($CDCl_3/CD_3OD$ = 8/2) δ 138.1, 137.3, 136.8 (C_q Bn), 128.3, 128.1, 128.0, 127.7, 127.4 (C_{arom}), 102.3 (C-1), 79.3, 78.4, 73.2, 71.0 (C-2, C-3, C-4, C-5), 75.0, 71.8, 70.9 (3 x CH_2Ph), 59.3 (C-6); IR (cm^{-1}) 3467, 3063, 3031, 2876, 1734, 1635, 1497, 1454, 1365, 1255, 1071, 981, 927, 854, 734, 710, 696.

Anal. Calcd for $C_{34}H_{33}O_{10}SNa$, 0.5 H_2O: C, 57.75; H, 5.38; S, 5.71. Found: C, 57.87; H, 5.41; S, 5.69.

Benzyl 2,6-di-*O*-benzyl-4-deoxy-β-D-*erythro*-hexopyranosid-3-ulose (10). Aqueous sodium hydroxide (10 M, 0.1 mL, 10 eq) was added to a solution of cyclic

sulfate **5** (51 mg, 0.1 mmol) in DMF (1.8 mL). The mixture was then strongly stirred and refluxed at 70 °C. After 2 h, when the starting material was totally consumed (as shown by TLC), the mixture was cooled to room temperature, diluted with ethyl acetate (30 mL) and washed with water (2 x 30 mL). The aqueous layer was extracted with ethyl acetate (3 x 20 mL). The organic phases were pooled, dried (Na_2SO_4), filtered and concentrated. The resulting yellow syrup containing the vinylic sulfate **9** was then dissolved in THF (1 mL), cooled to 0 °C and then, water (2 µL) and concentrated H_2SO_4 (2 µL) were added.[12] The mixture was then diluted with CH_2Cl_2 (15 mL), washed with saturated aqueous $NaHCO_3$ then with water. The aqueous layers were extracted with CH_2Cl_2 (2 x 10 mL). The organic phases were pooled, filtered using silicon treated paper and the filtrate concentrated. Flash chromatography (EtOAc-hexane = 15 : 85) of the residue gave **10** (33 mg, 77% over 2 steps). $[\alpha_D]$ -86° (*c* 2.5, CH_2Cl_2); ^{1}H NMR 250 MHz ($CDCl_3$) δ 7.30 to 7.50 ppm (m, 15 H, Ph), 4.98 (d, 1 H, J_{gem} = 12.0 Hz, *H*CHPh), 4.88 (d, 1 H, J_{gem} = 12.0 Hz, *H*CHPh), 4.74 (d, 1 H, J_{gem} = 12.0 Hz, *H*CHPh), 4.71 (d, 1 H, *H*CHPh), 4.69 (d, 1 H, $J_{1,2}$ = 7.5 Hz, H-1), 4.60 (s, 2 H, C*H*$_2$Ph), 3.93 (dd, 1 H, $J_{2,4}$ = 1.0 Hz, H-2), 3.81 (ddd, 1 H, $J_{4,5}$ = 10.5 Hz, $J_{4',5}$ = 4.0 Hz, $J_{5,6}$ = 5.0 Hz, H-5), 3.61 (m, 2 H, H-6, H-6'), 2.58 (ddd, 1 H, $J_{4,4'}$ = 14.5 Hz, H-4), 2.49 (dd, 1 H, H-4'); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 203.3 (C-3), 137.8, 137.4, 137.0 (C_q Bn), 128.4, 128.3, 128.0, 127.8, 127.6 (CH_{arom}), 102.7 (C-1), 83.4, 73.7, 73.5, 71.5, 71.2, 70.9 (C-2, C-5, C-6, *C*H$_2$Ph), 43.9 (C-4); IR (cm^{-1}) 3088, 3063, 3031, 2921, 2865, 1955, 1732, 1605, 1497, 1454, 1362, 1307, 1210, 1131, 1100, 912, 821, 736, 698.

Anal. Calcd for $C_{27}H_{28}O_5$ (432.5): C, 74.98; H, 6.53; O, 18.50. Found: C, 75.74; H, 6.84; O, 18.02.

ACKNOWLEDGMENTS

University of Paris-Sud and CNRS are acknowledged for their financial support and the Ministère de l'éducation Nationale de la Recherche et de la Technologie for a fellowship to FD.

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