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Carbohydrate Research 340 (2005) 2612–2619
Carbohydrate RESEARCH

Synthesis of D-lyxitol and D-ribitol analogues of the naturally occurring glycosidase inhibitor salacinol

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Received 2 August 2005; received in revised form 4 September 2005; accepted 5 September 2005
Available online 29 September 2005

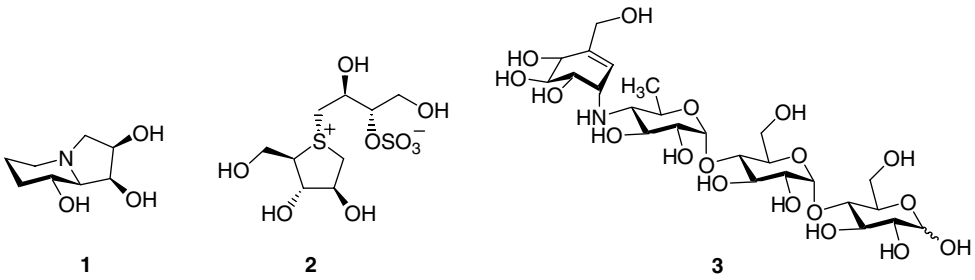
Abstract—The synthesis of analogues of the naturally occurring glycosidase inhibitor, salacinol, in which the D-arabinitol ring has been replaced by D-lyxitol or D-ribitol, is described. Salacinol is one of the active principles in the aqueous extracts of *Salacia reticulata*, which are traditionally used in India and Sri Lanka for the treatment of Type II diabetes. The synthetic strategy relies on the nucleophilic attack of 1,4-anhydro-2,3,5-tri-*O*-*p*-methoxybenzyl-4-thio-D-lyxitol or 1,4-anhydro-2,3,5-tri-*O*-*p*-methoxybenzyl-4-thio-D-ribitol at the least hindered carbon of the benzylidene-protected L-cyclic sulfate derived from L-erythritol. Screening of these compounds against recombinant human maltase glucoamylase (MGA), a critical intestinal glucosidase involved in the processing of oligosaccharides of glucose into glucose itself, shows that they are not effective inhibitors of MGA and demonstrates the importance of the D-arabinitol configuration in the heterocyclic ring for effective inhibition.

Keywords: Glycosidase inhibitors, Salacinol analogues; Synthesis; Sulfonium salts

1. Introduction

Modification of cell surface oligosaccharides can lead to disease states such as diabetes and cancer.[1–3] This suggests that the oligosaccharides play important roles in multi-cellular systems and that inhibition of the glycosidase enzymes involved in oligosaccharide processing on glycoproteins might lead to therapeutic strategies. For example, swainsonine (**1**), a plant derived alkaloid, is a good inhibitor of Golgi α-mannosidase II.[4] Treatment with swainsonine (**1**) has led to a significant reduction of tumor mass in human patients suffering from breast, liver, lung cancer, and other malignancies.[5,6] The bridgehead nitrogen atom of swainsonine (**1**) is known to be protonated at physiological pH and it is believed that this provides stabilizing electrostatic interactions between the inhibitor and a carboxylate residue in the enzyme active site.[7]

Recently, Yoshikawa et al.[8,9] described a new class of a naturally occurring glycosidase inhibitor, salacinol (**2**),



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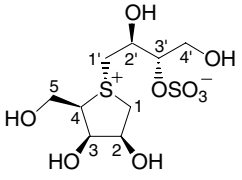
doi:10.1016/j.carres.2005.09.004

isolated from *Salacia reticulata* Wight (known as kothalahimbutu in Singhalese), a plant used in Ayurvedic medicine for the treatment of Type II diabetes mellitus. The structure of salacinol (**2**) possesses an unusual zwitterion consisting of a sulfonium ion with an internal sulfate counterion. The 1,4-anhydro-4-thio-D-arabinitol moiety with the permanent positive charge at the sulfur atom is postulated to bind to glycosidase enzymes by mimicry of the shape and charge of the oxacarbenium-ion intermediate in the glycosidase-mediated hydrolysis reaction. The inhibitory activities of salacinol (**2**) against sucrase and maltase are nearly equivalent to acarbose (**3**), which is clinically used for the treatment of diabetes. However, the inhibitory activity of salacinol (**2**) against isomaltase is greater than that of acarbose (**3**).[9] We[10,11] and others[12] have reported the synthesis of salacinol (**2**), and we have also reported the synthesis and glycosidase inhibitory properties of the heteroatom congeners of salacinol (**2**) in which the ring sulfur atom is replaced by nitrogen[13] and selenium,[14,15] and analogues in which the stereochemistry of the heteroalditol ring was changed from D-arabinitol to D-xylitol.[16]

We now report the total synthesis of the corresponding analogues in which the heteroalditol ring is D-lyxitol (**4**) and D-ribitol (**5**), and in which the stereochemistry at C-3 and C-2, respectively, is inverted. These compounds were required for the study of structure–activity relationships with glycosidase enzymes.



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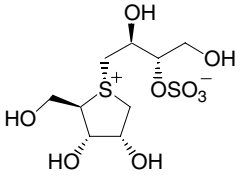

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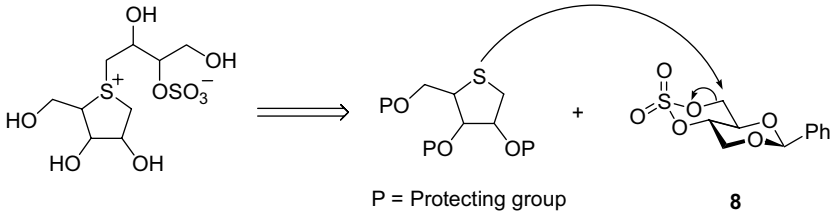
2. Results and discussion

The target compounds **4** and **5** could be synthesized by alkylating the anhydro-alditol derivatives at the ring sulfur atom (Scheme 1). This route was chosen to provide flexibility in synthesizing compounds having different configurations of the sugar rings. The alkylation of 1,4-anhydro-2,3,5-tri-*O*-*p*-methoxybenzyl-4-thio-D-lyxitol (**6**) and 1,4-anhydro-2,3,5-tri-*O*-*p*-methoxybenzyl-4-thio-D-ribitol (**7**) with 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic sulfate (**8**), previously synthesized in our laboratory,[10,11] should afford compounds **4** and **5**, respectively.

The required compound **6** was prepared from commercially available D-lyxose as shown in Scheme 2. The starting material, 2,3,5-tri-*O*-benzyl-D-lyxofuranoside (**9**), was prepared in three steps starting from D-lyxose, as described by Postema et al.[17] Reduction of **9** with sodium borohydride afforded the diol **10** in 91% yield. Selective protection of the primary hydroxyl group using *tert*-butyldimethylsilylchloride gave **11** in 93% yield. The D-lyxitol derivative **11** was converted to the L-ribitol derivative **12** by a Mitsunobu reaction using *p*-nitrobenzoic acid. Deprotection of the *p*-nitrobenzoyl and *tert*-butyldimethylsilyl groups using sodium methoxide and tetrabutylammonium fluoride, respectively, gave the diol **13**. Although the preparation of **13** from L-ribose was reported by Elie et al.,[18] the method was not practical for large scale synthesis because L-ribose is very expensive. Hence, we started with less expensive D-lyxose to synthesize **13** by inverting the configuration at C-4 using a Mitsunobu reaction. Compound **13** was converted to the dimesylate using methanesulfonyl chloride in pyridine and the dimesylate was treated with sodium sulfide to give **14** in 87% yield. To eliminate the problematic hydrogenolysis step of removing the benzyl ether groups after the coupling reaction between benzyl-protected thio-D-lyxitol and **8**, we decided to use *p*-methoxybenzyl (PMB) protecting groups. The acid-sensitive PMB group is a suitable choice because the benzylidene group from the L-cyclic sulfate is also acid labile and both could be cleaved in one pot by acid hydrolysis after the coupling reaction between **8** and **6**.[11] Hence, the benzyl protecting group was cleaved using Birch reduction to give the triol **15** in 86% yield. Reprotection of triol **15** with PMB groups afforded the required compound **6** in 94% yield.

The required compound **7** was synthesized from commercially available D-ribose (Scheme 3). Methyl 2,3,5-tri-*O*-benzyl-D-ribofuranoside (**16**) was prepared in two steps starting from D-ribose, as described by Barker and Fletcher.[19] With **16** in hand, 1,4-anhydro-4-thio-D-ribitol



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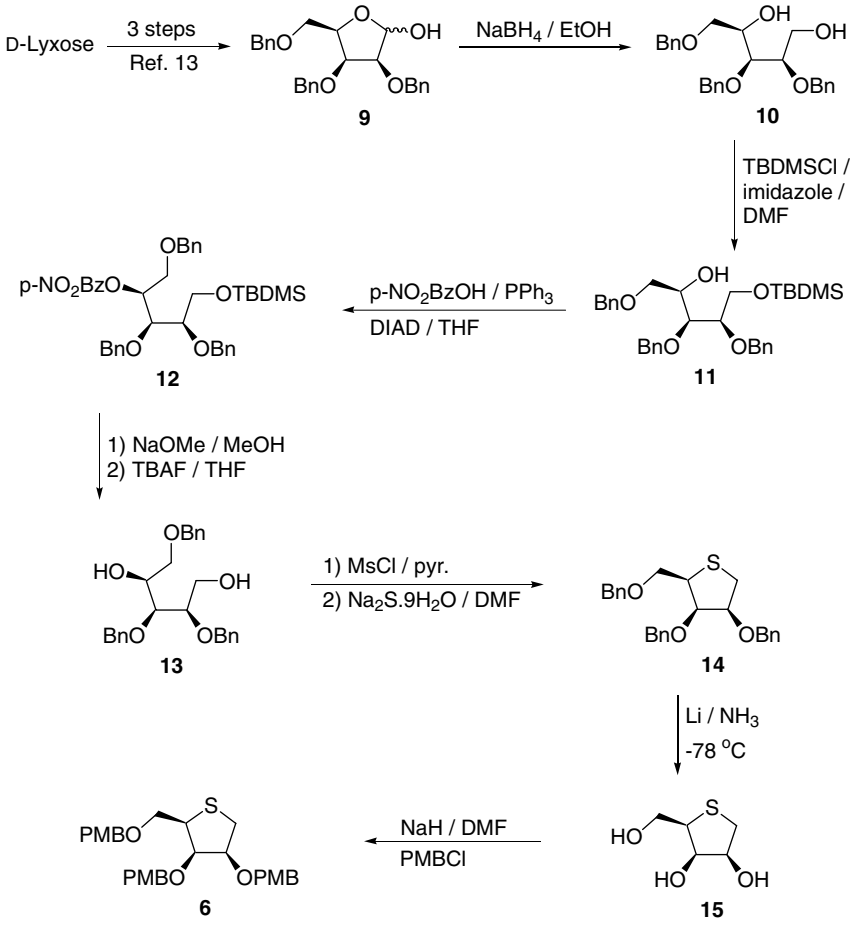
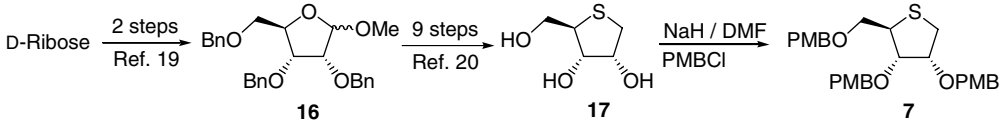
Scheme 1.



Scheme 2.



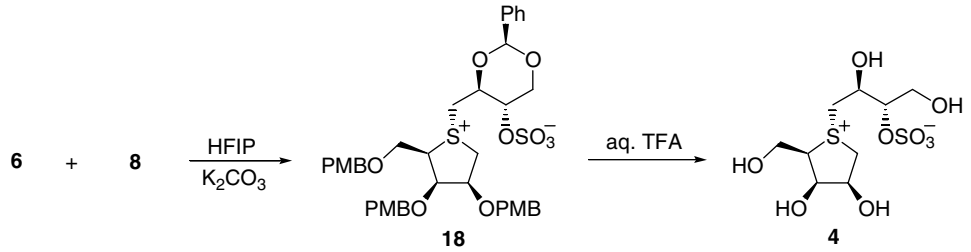
Scheme 3.

(**17**) was prepared in nine steps as described by Naka et al.[20] PMB protection of **17** afforded the desired compound **7** in 91% yield. Although the synthesis of **7** was reported earlier by Minakawa et al.,[21] we employed an alternative route (Scheme 3) similar to that described above for the preparation of **6**.

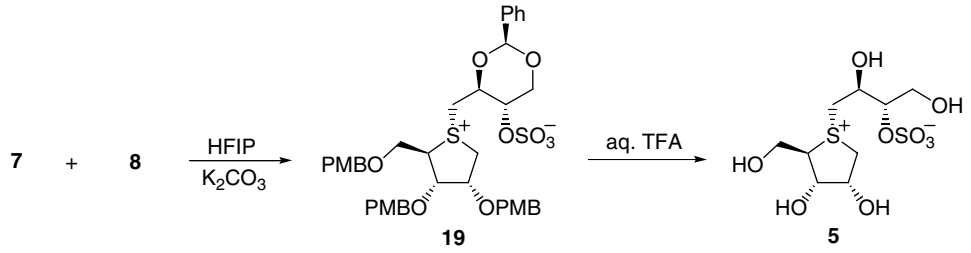
We next turned our attention to the coupling reaction. Thus, compound **18** was prepared by alkylation of PMB-protected anhydro-4-thio-D-lyxitol **6** with the benzylidene-protected L-cyclic sulfate **8** in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) containing K_2CO_3 at 70 °C in 90% yield (Scheme 4). The choice of HFIP as a solvent was based on our previous work where the yield of the coupling reaction was highest when HFIP was used as a solvent.[11] Potassium carbonate was used to prevent the hydrolysis of the cyclic sulfate.[10] The stereochemistry at the sulfur center was assigned with the aid of a NOESY experiment, which showed a correlation between H-4 and H-1′, suggesting that the L-erythritol side chain and the C-4 substituent were trans to each other. Deprotection of **18** proceeded smoothly in aqueous trifluoroacetic acid (TFA) to give the final compound **4** in 78% yield.

Compound **5** was obtained in a similar manner by coupling of **7** with the L-cyclic sulfate **8** to produce the sulfonium salt **19** in 92% yield (Scheme 5). Deprotection with aqueous TFA produced compound **5** in 81% yield. Proof of stereochemistry at the stereogenic sulfur atom was established as before with a NOESY experiment.

As a final point of interest, we comment on the screening of the compounds synthesized in this study against recombinant human maltase glucoamylase (MGA), a



Scheme 4.



Scheme 5.

critical intestinal glucosidase involved in the processing of oligosaccharides of glucose into glucose itself. Compounds **4** and **5** were not effective inhibitors of MGA, whereas salacinol **2** inhibited this enzyme with a K_i value of 0.19 μM.[22] Thus, it would appear that the D-arabinitol configuration in the heterocyclic ring displayed by salacinol **2** is critical for activity, and the design of new agents for the treatment of Type 2 diabetes should incorporate this feature.

3. Experimental

3.1. General

Optical rotations were measured at 23 °C using a Rudolph Research Autopol II polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova spectrometer at frequencies of 500 and 125 MHz, respectively. All assignments were confirmed with the aid of two-dimensional ^{1}H, ^{1}H (gCOSY) or ^{1}H, ^{13}C (gHMQC) experiments using standard Varian pulse programs. Processing of the spectra was performed with MesRec software. Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectra were obtained using 2,5-dihydroxybenzoic acid as a matrix on a PerSeptive Biosystems Voyager-DE spectrometer. Column chromatography was performed with Merck Silica gel 60 (230–400 mesh).

3.2. 2,3,5-Tri-*O*-benzyl-D-lyxitol (10)

To a stirred solution of 2,3,5-tri-*O*-benzyl-D-lyxofuranoside **9** (5.64 g, 13.4 mmol) in EtOH (150 mL) at 0 °C was added sodium borohydride (0.215 g, 6.72 mmol) gradually. After stirring for 1.5 h at 0 °C, the reaction was quenched by the addition of AcOH and the reaction mixture was concentrated. The residue was diluted with EtOAc (200 mL) and washed with H_2O (2 × 100 mL) and brine (100 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc, 1:3–1:1) to give a colorless oil **10** (5.50 g, 97%); $[\alpha]_D$ −20.5 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.38–7.25 (m, 15H, Ar), 4.74 and 4.54 (2H, 2d, $J_{a,b} = 11.5$ Hz, CH_2Ph), 4.63 (s, 2H, CH_2Ph), 4.53 and 4.48 (2d, each 1H, $J_{a,b} = 12.5$ Hz, CH_2Ph), 4.01 (1H, ddd, $J_{3,4} = 1.8$ Hz, $J_{4,5a} = J_{4,5b} = 6.1$ Hz, H-4), 3.88 (1H, dd, $J_{1a,1b} = 11.7$ Hz, $J_{1a,2} = 4.1$ Hz, H-1a), 3.81 (1H, dd, $J_{2,3} = 5.9$ Hz, H-3), 3.75 (1H, dd, $J_{1b,2} = 3.7$ Hz, H-1b), 3.72 (1H, ddd, H-2), 3.55 (1H, dd, $J_{5a,5b} = 9.9$ Hz, H-5a), 3.47 (1H, dd, H-5b); ^{13}C NMR ($CDCl_3$): δ 137.84, 137.80, 137.75 (3C$_{ipso}$), 128.52–127.79 (15C, Ar), 79.48 (C-2), 77.00 (C-3), 74.37, 73.44, 72.38 (3CH_2Ph), 71.22 (C-5), 69.67 (C-4), 60.47 (C-1); MALDI-TOF MS: *m/e* 423.07 (M^++H), 445.12 (M^++Na), 4.61.11 (M^++K). Anal. Calcd for $C_{26}H_{30}O_5$: C, 73.91; H, 7.16. Found: C, 74.05; H, 7.21.

3.3. 2,3,5-Tri-*O*-benzyl-1-*O*-*tert*-butyldimethylsilyl-D-lyxitol (11)

A mixture of **10** (5.24 g, 12.4 mmol), imidazole (3.72 g, 54.6 mmol), and TBDMSCl (2.07 g, 13.6 mmol) in dry DMF (50 mL) was stirred at 0 °C under N_2 for 30 min. The reaction was quenched by the addition of ice (20 mL), and the reaction mixture was partitioned

between Et_2O (200 mL) and H_2O (100 mL). The separated organic phase was washed with H_2O (100 mL) and brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc, 3:1) to give a colorless oil **11** (6.164 g, 93%); $[\alpha]_D$ −14.4 (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.35–7.25 (15H, m, Ar), 4.74 and 4.60 (2H, 2d, $J_{a,b} = 11.7$ Hz, CH_2Ph), 4.69 and 4.51 (2H, 2d, $J_{a,b} = 11.9$ Hz, CH_2Ph), 4.51 and 4.45 (2H, 2d, $J_{a,b} = 11.6$ Hz, CH_2Ph), 4.05 (1H, dddd, $J_{3,4} = 2.3$ Hz, $J_{4,5a} = J_{4,5b} = 5.9$ Hz, $J_{4,OH} = 5.9$ Hz, H-4), 3.88 (1H, dd, $J_{1a,1b} = 11.0$ Hz, $J_{1a,2} = 4.2$ Hz, H-1a), 3.78 (1H, dd, $J_{1b,2} = 4.9$ Hz, H-1b), 3.77 (1H, dd, $J_{2,3} = 4.1$ Hz, H-3), 3.73 (1H, ddd, H-2), 3.54 (1H, dd, H-5a), 3.49 (1H, dd, H-5b), 3.02 (1H, d, OH), 0.89 (9H, s, (CH_3)$_3$CSi), 0.05 (6H, s, (CH_3)$_2$Si); ^{13}C NMR ($CDCl_3$): δ 149.11, 145.62, 140.95 (3C$_{ipso}$), 128.35–127.60 (15C, Ar), 80.25 (C-2), 77.25 (C-3), 73.65, 73.26, 72.84 (3*C*H$_2$Ph), 71.16 (C-5), 69.75 (C-4), 62.04 (C-1), 25.88 (3C, (*C*H$_3$)$_3$CSi) 18.23 (1C, *C*Si), −5.40, −5.44 (2C, (*C*H$_3$)$_2$Si); MALDI-TOF MS: *m*/*e* 537.89 (M^++H), 559.33 (M^++Na). Anal. Calcd for $C_{32}H_{44}O_5Si$: C, 71.60; H, 8.26. Found: C, 71.44; H, 8.34.

3.4. 2,3,5-Tri-*O*-benzyl-D-ribitol (13)

A solution of **11** (6.50 g, 12.1 mmol) in THF (60 mL) containing *p*-nitrobenzoic acid (4.06 g, 24.2 mmol) and triphenylphosphine (6.36 g, 24.2 mmol) was cooled to 0 °C. A solution of diisopropylazodicarboxylate (4.8 mL, 24.2 mmol) in THF (30 mL) was added to the mixture over 2 h. After stirring for 20 h at ambient temperature, the reaction mixture was concentrated and then partitioned between Et_2O (200 mL) and H_2O (100 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (3 × 50 mL), followed by brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was dissolved in MeOH (50 mL) and 1 N NaOMe/MeOH (1.0 mL) was added. The mixture was stirred at room temperature for 1 h and concentrated. The residue was partitioned between Et_2O (150 mL) and H_2O (100 mL). The organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was re-dissolved in THF (50 mL) and a solution of tetrabutylammonium fluoride (1 M in THF, 13.0 mL, 13.0 mmol) was added. The mixture was stirred at room temperature for 1.5 h and partitioned between Et_2O (150 mL) and H_2O (50 mL). The organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc, 4:1–1:1) to give a colorless oil **13** (2.80 g, 57%). See Ref. 18 for experimental data.

3.5. 1,4-Anhydro-2,3,5-tri-*O*-benzyl-4-thio-D-lyxitol (14)

To a stirred solution of **13** (6.01 g, 14.2 mmol) in pyridine (60 mL) at 0 °C under N_2 was added methanesulfonyl chloride (2.70 mL, 2.5 equiv) dropwise. The mixture was stirred at 0 °C for 2 h and concentrated under high vacuum. The residue was diluted with EtOAc (200 mL) and the organic phase was washed with H_2O (100 mL), 1 M HCl (100 mL), saturated aqueous $NaHCO_3$ (2 × 100 mL), and brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was dissolved in dry DMF (60 mL) together with $Na_2S{\cdot}9H_2O$ (4.61 g, 1.3 equiv). The mixture was stirred at 105 °C for 2 h. After cooling to room temperature, the mixture was diluted with Et_2O (200 mL) and washed with H_2O (3 × 100 mL), followed by brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by a flash chromatography (hexanes/EtOAc, 5:1) to give a colorless oil **14** (5.20 g, 87%); $[\alpha]_D$ +94.0 (*c* 0.93, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.38–7.22 (15H, m, Ar), 4.88 and 4.78 (2H, 2d, $J_{a,b} = 11.6$ Hz, CH_2Ph), 4.68 (2H, s, CH_2Ph) 4.49 (2H, s, CH_2Ph), 4.20 (1H, dd, $J_{2,3} = 3.1$ Hz, $J_{3,4} = 3.8$ Hz, H-3), 4.04 (1H, ddd, $J_{1a,2} = 9.2$ Hz, $J_{1b,2} = 6.3$ Hz, H-2), 3.89 (1H, dd, $J_{4,5a} = 7.3$ Hz, $J_{5a,5b} = 8.7$ Hz, H-5a), 3.58 (1H, m, H-4), 3.54 (1H, dd, $J_{4,5b} = 6.6$ Hz, H-5b), 3.07 (1H, dd, $J_{1a,1b} = 9.2$ Hz, H-1a), 2.92 (1H, dd, H-1b); ^{13}C NMR ($CDCl_3$): δ 138.85, 138.33, 138.27 (3C$_{ipso}$), 128.68–127.64 (15C, Ar), 83.71 (C-2), 78.99 (C-3), 73.81, 73.56, 72.37 (3*C*H$_2$Ph), 70.42 (C-5), 40.92 (C-4), 30.56 (C-1); MALDI-TOF MS: *m*/*e* 421.29 (M^++H), 443.29 (M^++Na), 459.29 (M^++K), 511.32 (M^++Bn), 313.28 (M^+−OBn). Anal. Calcd for $C_{26}H_{28}O_3S$: C, 74.25; H, 6.71. Found: C, 74.02; H, 6.73.

3.6. 1,4-Anhydro-4-thio-D-lyxitol (15)

To condensed NH_3 (~30 mL) at −78 °C was added lithium metal (four small pieces) gradually. A solution of **14** (0.70 g, 1.7 mmol) in Et_2O (5 mL) was then added to the mixture dropwise. The mixture was stirred at −78 °C to ambient temperature for 5 h. The reaction was quenched by the addition of MeOH (5 mL) and concentrated. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 1:10–1:8) to give a colorless oil **15** (0.215 g, 86%); $[\alpha]_D$ +4.0 (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 4.38 (1H, dd, $J_{2,3} = 4.3$ Hz, $J_{3,4} = 6.7$ Hz, H-3), 4.26 (1H, ddd, $J_{1a,2} = 5.9$ Hz, $J_{1b,2} = 5.2$ Hz, H-2), 4.01 (1H, dd, $J_{4,5a} = 2.6$ Hz, $J_{5a,5b} = 11.9$ Hz, H-5a), 3.69 (1H, dd, $J_{4,5b} = 5.0$ Hz, H-5b), 3.56 (1H, ddd, H-4), 3.04 (1H, dd, $J_{1a,1b} = 11.5$ Hz, H-1a), 2.89 (1H, dd, H-1b); ^{13}C NMR ($CDCl_3$): δ 76.62 (C-2), 74.23 (C-3), 60.16 (C-5), 55.70 (C-4), 37.43 (C-1). Anal. Calcd for $C_5H_{10}O_3S$: C, 39.98; H, 6.71. Found: C, 39.62; H, 6.65.

3.7. 1,4-Anhydro-2,3,5-tri-*O*-*p*-methoxybenzyl-4-thio-D-lyxitol (6)

A solution of **15** (0.201 g, 1.33 mmol) in DMF (20 mL) was added to a suspension of NaH (60% in oil, 175 mg, 3.3 equiv) in DMF (30 mL) at 0 °C under N_2. After stirring at 0 °C for 45 min, *p*-methoxybenzyl chloride (0.687 g, 3.3 equiv) was added dropwise. The reaction mixture was stirred at room temperature for 2 h and then quenched by the addition of ice (20 mL). The mixture was diluted with H_2O (50 mL) and extracted with Et_2O (3 × 100 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc, 8:1–5:1) to give a colorless oil **6** (0.640 g, 94%): $[\alpha]_D$ −2.08 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.28–7.19 (6H, m, Ar), 6.90–6.79 (6H, m, Ar), 4.76 and 4.59 (2H, 2d, $J_{a,b} = 11.4$ Hz, CH_2Ar), 4.48 (2H, s, CH_2Ar), 4.43 and 4.42 (2H, 2d, $J_{a,b} = 11.4$ Hz CH_2Ar), 4.14 (1H, dd, $J_{2,3} = 3.1$ Hz, $J_{3,4} = 4.0$, H-3), 3.98 (1H, ddd, $J_{1a,2} = 9.2$ Hz, $J_{1b,2} = 6.1$ Hz, H-2), 3.82 (1H, dd, $J_{4,5a} = 7.2$ Hz, $J_{5a,5b} = 8.7$ Hz, H-5a), 3.81 (3H, s, CH_3OAr), 3.80 (3H, s, CH_3OAr), 3.79 (3H, s, CH_3OAr), 3.53 (1H, ddd, $J_{4,5b} = 6.6$ Hz H-4), 3.47 (1H, dd, H-5b), 3.01 (1H, dd, $J_{1a,1b} = 9.3$ Hz, H-1a), 2.86 (1H, dd, H-1b); ^{13}C NMR ($CDCl_3$): δ 159.45, 159.42, 159.32 (3C$_{ipso}$), 131.01–113.84 (15C, Ar), 83.41 (C-2), 78.38 (C-3), 73.34, 73.20, 72.03 (3*C*H$_2$Ar), 70.08 (C-5), 55.52, 55.49, 55.47 (3*C*H$_3$OAr), 45.98 (C-4), 30.59 (C-1); MALDI-TOF MS: *m*/*e* 511.28 (M^++H), 533.26 (M^++Na), 549.21 (M^++K). Anal. Calcd for $C_{29}H_{34}O_6S$: C, 68.21; H, 6.71. Found: C, 67.90; H, 7.09.

3.8. 1,4-Anhydro-2,3,5-tri-*O*-*p*-methoxybenzyl-4-thio-D-ribitol (7)

A solution of **17** (0.510 g, 3.4 mmol) in DMF (30 mL) was added to a suspension of NaH (60% in oil, 0.449 g, 3.3 equiv) in DMF (50 mL) at 0 °C under N_2. After stirring at 0 °C for 45 min, *p*-methoxybenzyl bromide (1.74 g, 3.3 equiv) was added dropwise. The reaction mixture was stirred at room temperature for 2 h and then quenched by the addition of ice (20 mL). The mixture was diluted with H_2O (100 mL) and extracted with Et_2O (3 × 100 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (hexanes/EtOAc, 8:1–5:1) to give a white solid **7** (1.58 g, 91%). See Ref. 21 for experimental data.

3.9. 2,3,5-Tri-*O*-*p*-methoxybenzyl-1,4-dideoxy-1,4-[[(2*S*,3*S*)-2,4-*O*-benzylidene-3-(sulfooxy)butyl]-(*S*)-epi-sulfoniumylidene]-D-lyxitol inner salt (18)

To a mixture of **6** (90 mg, 0.176 mmol) and the L-cyclic sulfate **8** (57 mg, 1.2 equiv) in HFIP (0.5 mL) was added K_2CO_3 (5 mg). The mixture was stirred in a sealed tube at 70 °C for 16 h. The reaction mixture was concentrated and the crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 1:0–15:1) to give an amorphous solid **18** (124 mg, 90%): $[\alpha]_D$ −11.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.46–6.84 (17H, m, Ar), 5.36 (1H, s, CH_2Ph), 4.85 (1H, ddd, $J_{1a,2} = 6.1$ Hz, $J_{1b,2} = 8.6$ Hz, $J_{2,3} = 2.5$ Hz, H-2), 4.70 and 4.45 (2H, 2d, $J_{a,b} = 11.0$ Hz, CH_2Ar), 4.60 (2H, s, CH_2Ar), 4.57 (1H, dd, $J_{3',4a'} = 5.5$ Hz, $J_{4a'4b'} = 11.0$ Hz, H-4a′), 4.53 (1H, dd, $J_{3,4} = 3.9$ Hz, H-3), 4.44 (1H, m, H-3′), 4.33 (1H, m, H-4), 4.30 and 4.26 (2H, 2d, $J_{a,b} = 11.7$ Hz, CH_2Ar), 4.26–4.21 (2H, m, H-2′, H-1a′), 4.19 (1H, dd, $J_{1a'1b'} = 13.6$ Hz, H-1b′), 3.91 (1H, dd, $J_{1a,1b} = 12.9$ Hz, H-1a), 3.81 (1H, dd, $J_{4,5a} = 4.6$ Hz, $J_{5a,5b} = 9.8$ Hz, H-5a), 3.80 (3H, s, CH_3OAr), 3.79 (3H, s, CH_3OAr), 3.76 (3H, s, CH_3OAr), 3.74 (1H, dd, $J_{3'4b'} = 3.9$ Hz, H-4b′), 3.71 (1H, dd, $J_{4,5b} = 4.6$ Hz, H-5b), 3.54 (1H, dd, H-1b); ^{13}C NMR ($CDCl_3$): δ 159.86, 159.81, 159.77 (3C$_{ipso}$, PMB), 137.04 (1C$_{ipso}$, Ph), 130.32–113.98 (20C, Ar), 101.50 (1C, *C*H$_2$Ph), 81.51 (C-2), 78.33 (C-3), 76.01 (C-2′), 74.24, 73.38, and 73.29 (3*C*H$_2$Ar), 69.54 (C-4′), 67.72 (C-3′), 65.41 (C-5), 62.55 (C-4), 54.15–53.29 (3C, *C*H$_3$OAr), 47.63 (C-1′), 41.40 (C-1); MALDI-TOF MS: *m*/*e* 783.45 (M^++H), 805.21 (M^++Na), 821.84 (M^++K). Anal. Calcd for $C_{40}H_{46}O_{12}S_2$: C, 61.36; H, 5.92. Found: C, 61.61; H, 6.04.

3.10. 2,3,5-Tri-*O*-*p*-methoxybenzyl-1,4-dideoxy-1,4-[[(2*S*,3*S*)-2,4-*O*-benzylidene-3-(sulfooxy)butyl]-(*R*)-epi-sulfoniumylidene]-D-ribitol inner salt (19)

To a solution of 1,4-anhydro-2,3,5-tri-*O*-*p*-methoxybenzyl-4-thio-D-ribitol (**7**) (300 mg, 588 mmol) and the L-cyclic sulfate **8** (192 mg, 1.2 equiv) in HFIP (1.5 mL) was added K_2CO_3 (20 mg). The mixture was stirred in a sealed tube at 70 °C for 16 h. The reaction mixture was concentrated and the crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 1:0–20:1) to give a white foam **19** (425 mg, 92%): $[\alpha]_D$ +64.2 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.42–6.84 (17H, m, Ar), 5.53 (1H, s, CH_2Ph), 4.66 and 4.54 (2H, 2d, $J_{a,b} = 11.3$ Hz, CH_2Ar), 4.53 (1H, ddd, $J_{2'3'} = J_{3',4a'} = 9.8$ Hz, $J_{3',4b'} = 5.3$ Hz, H-3′), 4.48 (1H, dd, $J_{4a'4b'} = 10.8$ Hz, H-4a′), 4.45 (1H, d, $J_{1a',1b'} = 13.9$ Hz, H-1a′), 4.85 (1H, dd, $J_{1a,2} = J_{2,3} = 2.6$ Hz, H-2), 4.44 and 4.27 (2H, 2d, $J_{a,b} = 11.2$ Hz, CH_2Ar), 4.34 and 4.19 (2H, 2d, $J_{a,b} = 11.9$ Hz, CH_2Ar), 4.23 (1H, dd, $J_{1b',2b'} = 2.9$ Hz, H-2′), 4.15 (1H, dd, $J_{3,4} = 9.5$ Hz, H-3), 4.01 (1H, dd, H-1b′), 3.82 (3H, s, CH_3OAr), 3.81 (3H, s, CH_3OAr), 3.80 (3H, s, CH_3OAr), 3.76 (1H, dd, H-4b′), 3.68 (1H, ddd, $J_{4,5a} = J_{4,5b} = 2.0$ Hz, H-4), 3.58 (2H, br s, H-1a, H-1b), 3.34 (1H, dd, $J_{5a,5b} = 10.9$ Hz, H-5a), 3.29 (1H, dd, H-5b); ^{13}C NMR ($CDCl_3$): δ 160.08, 160.05, 159.95 (3C$_{ipso}$, PMB), 136.82 (1C$_{ipso}$, Ph),

136.82–114.09 (20C, Ar), 101.44 (1C, CH$_2$Ph), 81.66 (C-3), 76.64 (C-2′), 76.34 (C-2), 73.64, 73.10, 72.51 (3CH$_2$Ar), 69.16 (C-4′), 65.68 (C-3′), 64.09 (C-4), 62.17 (C-5), 55.50–55.46 (3CH$_3$OAr), 51.34 (C-1′), 43.68 (C-1); MALDI-TOF MS: *m/e* 783.31 (M^++H), 805.34 (M^++Na), 821.87 (M^++K). Anal. Calcd for $C_{40}H_{46}O_{12}S_2$: C, 61.36; H, 5.92. Found: C, 61.19; H, 5.98.

3.11. 1,4-Dideoxy-1,4-[[(2*S*,3*S*)-2,4-dihydroxy-3-(sulfooxy)butyl]-(*S*)-episulfoniumylidene]-D-lyxitol inner salt (4)

To a stirred solution of **18** (120 mg, 0.153 mmol) in TFA (10 mL) was added H_2O (1 mL) and the reaction mixture was stirred at ambient temperature for 2 h. The reaction mixture was concentrated and the crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 3:1 to EtOAc/MeOH/H_2O, 6:3:1) to give an amorphous solid **4** (30 mg, 78%); $[\alpha]_D$ +8.2 (*c* 0.2, H_2O); ^{1}H NMR (H_2O): δ 4.85 (1H, ddd, $J_{1a,2}$ = 6.8 Hz, $J_{1b,2}$ = 9.6 Hz, $J_{2,3}$ = 3.0 Hz, H-2), 4.61 (1H, dd, $J_{3,4}$ = 3.2 Hz, H-3), 4.38 (1H, ddd, $J_{2'3'}$ = 7.4 Hz, $J_{3'4a'}$ = 2.9 Hz, $J_{3'4b'}$ = 9.6 Hz, H-3′), 4.34–4.26 (2H, m, H-2′, H-4), 4.18 (1H, dd, $J_{4,5a}$ = 5.1 Hz, $J_{5a,5b}$ = 12.3 Hz, H-5a), 4.02 (1H, dd, $J_{4,5b}$ = 9.4 Hz, H-5b), 3.94 (1H, dd, $J_{1a',1b'}$ = 12.6 Hz, $J_{1a',2'}$ = 3.3 Hz, H-1a′), 3.84 (1H, dd, $J_{1b',2'}$ = 3.5 Hz, H-1b′), 3.83 (1H, dd, $J_{4a'4b'}$ = 13.6 Hz, H-4a′), 3.73 (1H, dd, $J_{1a,1b}$ = 13.3 Hz, H-1a), 3.72 (1H, dd, H-4b′), 3.62 (1H, dd, H-1b); ^{13}C NMR (D_2O): δ 82.91 (C-3′), 76.08 (C-2), 75.34 (C-3), 68.79 (C-4), 68.01 (C-2′), 62.06 (C-1′), 60.32 (C-5), 50.91 (C-4′), 43.84 (C-1); MALDI-TOF MS: *m/e* 335.04 (M^++H), 357.11 (M^++Na). Anal. Calcd for $C_9H_{18}O_9S_2$: C, 32.33; H, 5.43. Found: C, 32.02; H, 5.45.

3.12. 1,4-Dideoxy-1,4-[[(2*S*,3*S*)-2,4-dihydroxy-3-(sulfooxy)butyl]-(*R*)-episulfoniumylidene]-D-ribitol inner salt (5)

To a stirred solution of **19** (202 mg, 0.258 mmol) in TFA (20 mL) was added H_2O (2 mL) and the reaction mixture was stirred at ambient temperature for 2 h. The reaction mixture was concentrated and the crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 3:1 to EtOAc/MeOH/H_2O, 6:3:1) to give an amorphous solid **5** (69 mg, 81%); $[\alpha]_D$ +40.9 (*c* 0.3, H_2O); ^{1}H NMR (H_2O): δ 4.57 (1H, ddd, $J_{1a,2} = J_{2,3}$ = 3.3 Hz, $J_{1b,2}$ = 2.0 Hz, H-2), 4.28 (1H, ddd, $J_{1a',2'} = J_{2',3'}$ = 3.6 Hz, $J_{1b',2'}$ = 7.1 Hz, H-2′), 4.26 (1H, dd, $J_{3,4}$ = 8.4 Hz, H-3), 4.22 (1H, ddd, $J_{2'3'} = J_{3',4b'}$ = 3.3 Hz, $J_{3'4a'}$ = 7.5 Hz, H-3′), 4.06 (1H, dd, $J_{4,5a}$ = 3.2 Hz, $J_{5a,5b}$ = 12.4 Hz, H-5a), 4.03 (1H, dd, $J_{1a',1b'}$ = 13.2 Hz, H-1a′), 3.93 (1H, ddd, $J_{4,5b}$ = 5.4 Hz, H-4), 3.84 (1H, dd, H-5b), 3.83 (1H, dd, $J_{4a'4b'}$ = 12.9 Hz, H-4a′), 3.80 (1H, dd, H-1b), 3.72 (1H, dd, H-4b′), 3.65 (1H, dd, $J_{1a,1b}$ = 14.5 Hz, H-1a), 3.40 (1H, dd, H-1b); ^{13}C NMR (D_2O): δ 79.80 (C-3′), 75.19 (C-3), 73.33 (C-2), 65.41 (C-2′), 65.13 (C-4), 59.74 (C-4′), 57.35 (C-5), 51.06 (C-1′), 44.3 (C-1); MALDI-TOF MS: *m/e* 335.07 (M^++H), 357.01 (M^++Na). Anal. Calcd for $C_9H_{18}O_9S_2$: C, 32.33; H, 5.43. Found: C, 32.12; H, 5.67.

Acknowledgments

We thank K. S. Sadalapure for his initial work on the ribitol analogue (**5**) of salacinol and B. D. Johnston for helpful discussion. We also thank the Natural Sciences and Engineering Research Council of Canada for financial support and the Michael Smith Foundation for Health Research for a trainee fellowship (to N.S.K.).

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