Improved Syntheses of the Naturally Occurring Glycosidase Inhibitor Salacinol

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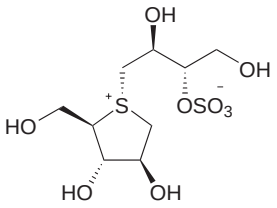
This work is dedicated, with respect, to the memory of Raymond U. Lemieux.

Abstract: Improved syntheses of the naturally occurring sulfonium ion, salacinol are described. Salacinol is one of the active principles in the aqueous extracts of *Salacia reticulata* that are traditionally used in Sri Lanka and India for the treatment of Type 2 Diabetes. The synthetic strategy relies on the nucleophilic attack of 2,3,5-tri-*O*-benzyl- or 2,3,5-tri-*O*-*p*-methoxybenzyl-1,4-anhydro-4-thio-D-arabinitol at the least hindered carbon of benzylidene-protected L-erythritol-1,3-cyclic sulfate in 1,1,1,3,3,3-hexafluoro-2-propanol as solvent. The reactions are compared to those with the benzyl-protected L-erythritol-1,3-cyclic sulfate and also to those in acetone and 2-propanol. Excellent yields are obtained for the reactions with the benzylidene-protected cyclic sulfate. The synthetic route employing *p*-methoxybenzyl ether protecting groups is advantageous since all protecting groups in the adduct may be removed with trifluoroacetic acid to yield salacinol, thereby obviating the problematic deprotection of benzyl ethers by hydrogenolysis.

Key words: glycosidase inhibitors, salacinol, efficient synthesis, sulfonium salt, cyclic sulfate

Salacinol (**1**) is a potent glycosidase inhibitor isolated from the aqueous extracts of *Salacia reticulata* that are used in Sri Lanka and India for the treatment of diabetes.[1–3] The molecular structure of this inhibitor is unique in that it contains a sulfonium ion (1,4-anhydro-4-thio-D-pentitol cation) stabilized by an internal sulfate counterion (1′-deoxy-L-erythrosyl-3′-sulfate anion). Glycosidase inhibitors containing sulfonium ions are of interest as mimics of oxacarbenium intermediates in glycosidase hydrolysis reactions.[4–6] In this regard, we[5,7] and others[6] have previously reported the syntheses of salacinol (**1**) and its stereoisomers. In the search for novel glycosidase inhibitors, we have also reported the synthesis and glycosidase inhibitory properties of the heteroatom congeners of salacinol in which the ring sulfur atom has been substituted by the cognate atoms nitrogen[8] and selenium.[9] We report here an improved method for the synthesis of the natural product salacinol (**1**) that exploits an unusual solvent effect provided by 1,1,1,3,3,3-hexafluoroisopropanol (HFIP). The previous syntheses of salacinol and its stereoisomers employed either acetone[5,7] or DMF[6] as solvents.



Salacinol **1**

Figure 1

The key step in the published syntheses of salacinol (**1**)[5,6] is the ring opening reaction of a cyclic sulfate by nucleophilic attack of the ring sulfur atom of 1,4-anhydro-4-thio-D-pentitol (**2**) (Scheme 1). The alkylation reaction involving these partners is critically dependent on the protecting groups on the cyclic sulfate. Thus, the unoptimized reaction of the per-benzylated thioether **2** with benzylidene-protected cyclic sulfate **3** in acetone, containing potassium carbonate, proceeded in 33% yield (Scheme 1).[5] A similar yield was obtained in the reaction with the monobenzylated thioether **5**.[5] Reaction of the unprotected thioether **7** with the isopropylidenated-cyclic sulfate **8** in DMF proceeded in 61% yield to give **9**, although its reaction with the corresponding benzylated-cyclic sulfate **10** did not proceed.[6] The latter derivative **10** is clearly a much less reactive alkylating agent than **8**. Significant decomposition of the cyclic sulfates **8** and **10** at temperatures of 60–70 ºC in DMF was also observed.[6] Deprotection of **9** proceeded in 75% yield to afford salacinol **1** in 46% overall yield.[6]

The biological importance of salacinol (**1**)[1–3] prompted us to investigate a more efficient method for its synthesis. The Hughes–Ingold rules indicate that the S_N2 reaction between a neutral nucleophile, such as **2** or **5**, and a neutral electrophile, such as **3**, **8** or **10**, should show a large increase in rate on increasing solvent polarity.[10] 1,1,1,3,3,3-Hexafluoroisopropanol (HFIP) has a higher normalized Dimroth–Reichardt solvent polarity parameter, $E_T^N = 1.068$, than water, $E_T^N = 1.00$.[10] In contrast, the E_T^N values for acetone and DMF are only 0.355 and 0.404, respectively. Furthermore, HFIP is volatile (bp = 59 °C), thus facilitating product purification. Preliminary studies indicated that tetrahydrothiophene reacted cleanly with **3** and **10** in HFIP at 45 °C for 2 days to give the desired alkylation products in >90% yield.[11]

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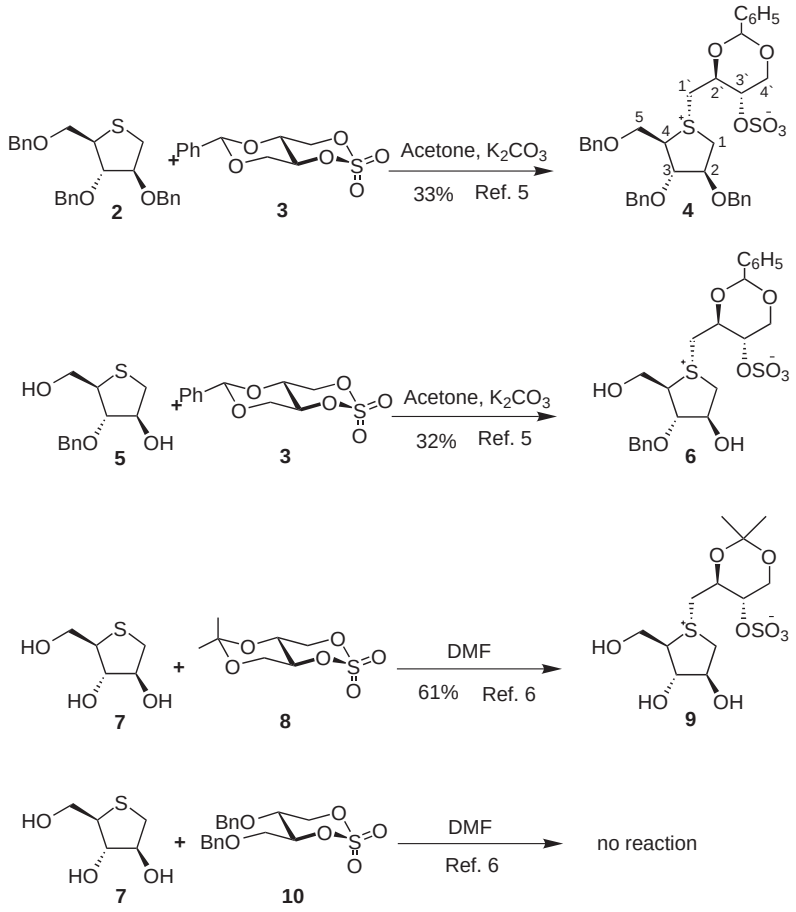


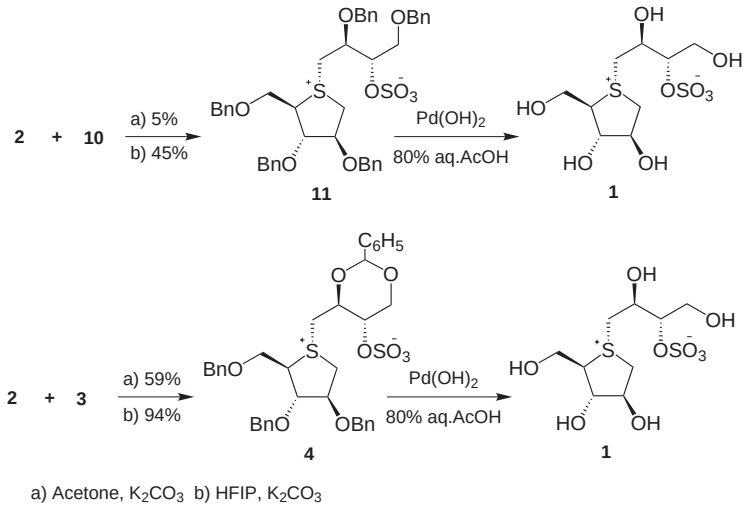
Scheme 1

Therefore, a systematic evaluation of the role of solvent in the alkylation reactions of **2** with benzyl- or benzylidene-protected cyclic sulfates **10** or **3**, respectively was undertaken. The reactions were carried out in acetone and hexafluoroisopropanol (HFIP) concurrently under identical conditions of concentration, temperature, and duration (Scheme 2). Reaction of the thioether **2** (1 equiv) and the cyclic sulfate **10** (1.2 equiv) in acetone containing K_2CO_3 at 75–80 °C in a sealed tube proceeded very slowly and yielded the desired alkylated product **11** in only 5% yield; the remainder of the starting materials was recovered. Prolonged heating and use of excess cyclic sulfate did not improve the yields. In addition, when excess cyclic sulfate **8** was used, its slow decomposition complicated the purification of the product **11** formed. However, the analogous reaction between **2** and the cyclic sulfate **10** in HFIP yielded the adduct **11** in 45% yield, with recovery of the unreacted starting materials (Scheme 2).[12] It is noteworthy that the analogous reaction between **2** and the cyclic sulfate **10** in the polar, protic solvent 2-propanol at 83 °C for 26 h did not yield any desired product, the starting materials being recovered. It would appear, therefore, that it is the highly polar nature of HFIP that is critical in facilitating this reaction.

The previous results of Yuasa et al.[6] had indicated a far lesser reactivity of the benzylated cyclic sulfate relative to the cyclic sulfate containing an acetal protecting group (Scheme 1). Thus, the reactions of the benzylidene-protected cyclic sulfate **3** in acetone and HFIP, containing potassium carbonate, under identical conditions of concentration, temperature, and duration were examined next (Scheme 2). The alkylation reaction of **2** with **3** in acetone proceeded with a dramatic increase in the yield (59%) of the alkylated product **4** relative to the reaction with **10**. The improvement from our earlier reported unoptimized yield of 33%[5] is due to the use of a more concentrated reaction mixture.[13]

More significantly, the desired product **4** was obtained in 94% yield when the reaction was performed in HFIP.[13] Higher temperatures (>80 °C) and prolonged reaction times led to the decomposition of the cyclic sulfate, although the stability of the cyclic sulfate was greater in the presence of K_2CO_3.

The increased yields in HFIP may be accounted for by better solvation of the transition states for the reactions and of the adducts. The increased reactivity of the cyclic sulfate with the benzylidene protecting group (**3**) may be accounted for by the relief of ring strain accompanying the reaction, unlike in the corresponding reaction of the benzyl-protected cyclic sulfate **10**. Finally, the reaction of the thioether **7** (not containing protecting groups) with the benzylidene-protected cyclic sulfate **3** in HFIP was exam-

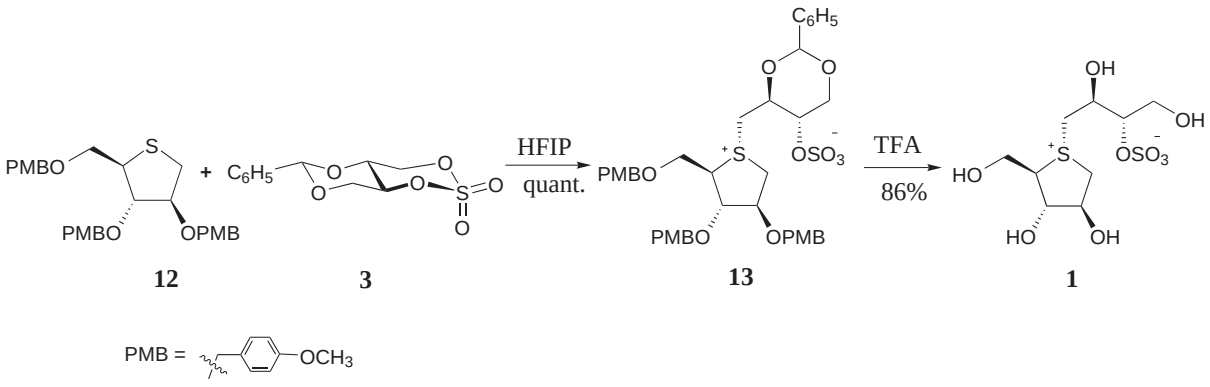


Scheme 2

ined. At 60 °C, decomposition of the cyclic sulfate was observed, with no significant formation of the desired coupled product. Hydrogenolysis of the protected derivatives **4**[5] and **11** afforded salacinol (**1**), although this step was problematic because of poisoning of the catalyst, and only afforded the product in 65% yield.

In order to obviate the problematic hydrogenolysis step, we next chose to examine the reaction of the thioether containing *p*-methoxybenzyl ether protecting groups with the benzylidene-protected L-erythritol-1,3-cyclic sulfate; we reasoned that the removal of all protecting groups by acid hydrolysis would be facile. Thus, 2,3,5-tri-*O*-*p*-methoxybenzyl-1,4-anhydro-4-thio-D-arabinitol (**12**),[14] synthesized in 87% yield from **7**, was reacted with cyclic sulfate **3** in HFIP to afford the sulfonium salt **13** in quantitative yield (Scheme 3).[15] Deprotection of **13** proceeded smoothly (86%) in aqueous trifluoroacetic acid to afford salacinol **1** in 75% overall yield.[16] The latter sequence represents, therefore, an efficient synthesis of the biologically important natural product salacinol **1**.

As a final point of interest, we comment on the stereochemistry at the stereogenic sulfonium center in **4**, **11**, and **13**. These reactions proceeded stereoselectively irrespective of the solvent used in the reaction. The stereochemistry was confirmed by means of NOESY experiments that showed clear correlations between H-4 and H-1′, thus indicating the presence of the isomer with a *trans* relationship between C-5 and C-1′. The barrier to inversion at the sulfonium ion center must be substantial since no evidence for isomerization in these and related derivatives[7] has been noted.



Scheme 3

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(12) **2,3,5-Tri-*O*-benzyl-1,4-dideoxy-1,4-{[(2S,3S)-2,4-di-(benzyloxy)-3-sulfooxy)butyl]- episulfoniumylidene}-D-arabinitol Inner Salt (11).**
A mixture of the thioether **2**[5] (270 mg, 0.64 mmol)and 2,4-di-*O*-benzyl-1,3-cyclic sulfate(**10**)[6,9] (280 mg, 0.77 mmol) in either acetone or HFIP (0.5 mL), containing anhydrous K_2CO_3 (16 mg, 0.10 mmol) was stirred in a sealed tube in an oil-bath (75–80 °C) for 14h. The solvent was removed under reduced pressure and the residue was purified by column chromatography using (CH_2Cl_2–MeOH, 10:1) as eluant to give the *title compound* **11**, as an amorphous solid (29 mg, 5%) in acetone and (229 mg, 45%) in HFIP. R_f 0.40 (CH_2Cl_2–MeOH, 10:1); $[\alpha]_D$ – 26 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 7.38–7.05 (25 H, m, Ar), 4.67 and 4.45 (2 H, 2d, $J_{A,B}$ = 11.8 Hz, C*H*$_2$Ph), 4.60 and 4.45 (2 H, 2d, $J_{A,B}$ = 9.5 Hz, C*H*$_2$Ph), 4.59 and 4.44 (2 H, 2d, $J_{A,B}$ = 11.2 Hz, C*H*$_2$Ph), 4.58 (1 H, dt, $J_{2',3'}$ = 5.0 Hz, H-3′), 4.42 and 4.28 (2 H, 2d, $J_{A,B}$ = 11.0 Hz, C*H*$_2$Ph), 4.36 (1 H, m, H-2), 4.32 (1 H, ddd, *J* = 1.7, 4.1, 6.3 Hz, H-2′), 4.30 and 4.20 (2 H, 2d, $J_{A,B}$ = 11.7 Hz, C*H*$_2$Ph), 4.23 (1 H, m, H-3), 4.13 (1 H, dd, $J_{1'a,1'b}$ = 13.4, $J_{1'a,2'}$ = 2.0 Hz, H-1′a), 4.05 (1 H, d, $J_{2,3}$ = 13.3 Hz, H-1a), 4.00 (1 H, dd, $J_{4'a,4'b}$ = 11.1, $J_{3',4'a}$ = 2.7 Hz, H-4′a), 3.86 (1 H, dd, $J_{3',4'b}$ = 2.4, $J_{4'a,4'b}$ = 11.3 Hz, H-4′b), 3.71 (1 H, br t, *J* = 9.2 Hz, H-4), 3.69 (1 H, dd, $J_{1'b,2'}$ = 3.8, $J_{1'b,1'a}$ = 9.2 Hz, H-1′b), 3.60 (1 H, dd, $J_{1a,1b}$ = 13.5, $J_{1b,2}$ = 3.8 Hz, H-1b), 3.51 (1 H, dd, $J_{5a,5b}$ = 13.6, $J_{4,5a}$ = 9.7 Hz, H-5a), 3.49 (1 H, dd, $J_{4,5b}$ = 9.7 Hz, H-5b); ^{13}C NMR ($CDCl_3$): δ = 137.97, 136.77, 136.71, 136.05 and 135.77 (5 × C_{ipso} Ph), 128.81–127.66 (25 C, Ph), 83.14 (C-3), 81.65 (C-2), 74.59 (C-3′), 73.81, 73.53, 3.39, 72.12, 71.84 (5 × C*H*$_2$Ph), 73.10 (C-2′), 68.79 (C-4′), 66.62 (C-5), 65.53 (C-4), 50.89 (C-1′), 48.07 (C-1). MALDI–TOF MS: *m*/*z* 785.41 (M^+ + H), 808.32 (M^+ + Na). Anal. Calcd for $C_{44}H_{48}O_9S_2$: C, 67.32; H, 6.16. Found: C, 67.36; H, 6.10.

(13) **2,3,5-Tri-*O*-benzyl-1,4-dideoxy-1,4-{[(2S,3S)-2,4-benzylidenedioxy-3-(sulfooxy)butyl]-episulfoniumylidene}-D-arabinitol Inner Salt (4).**
A mixture of the thioether **2**[5] (260 mg, 0.62 mmol)and 2,4-di-*O*-benzylidene-1,3-cyclic sulfate(**3**)[5] (200 mg, 0.74 mmol) in either acetone or HFIP (0.5 mL) containing K_2CO_3 (13 mg, 0.09 mmol) was treated as described above to yield the *title compound* **4**[5] as an amorphous solid (252 mg, 59% in acetone) and (406 mg, 94% in HFIP).

(14) **1,4-Anhydro-2,3,5-tri-*O*-(*p*-methoxybenzyl)-4-thio-D-arabinitol (12).**
To an ice-cold mixture of 1,4-anhydro-4-thio-D-arabinitol **7**[5] (0.98 g, 6.52 mmol)and 60% NaH (1.56 g, 39.15 mmol, 6 equiv) in THF (15 mL), a solution of *p*-methoxybenzyl chloride (4.59 g, 29.34 mmol, 4.5 equiv) in THF (10 mL) was added over 30 min. The reaction mixture was allowed to attain room temperature and further stirred for 1 h before heating to 55 °C for 12 h. The reaction mixture was cooled and poured in to ice-water (150 mL) and extracted with Et_2O (150 mL). The organic solution was dried (Na_2SO_4) and concentrated. The product was purified by column chromatography [hexanes–EtOAc, 7:3] to give a colorless syrup (2.96 g, 87%). $[\alpha]_D$ +6 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 7.20–6.80 (12 H, m, Ar), 4.55 (2 H, s, C*H*$_2$Ph), 4.48 and 4.45 (2 H, 2d, $J_{A,B}$ = 11.7 Hz, C*H*$_2$Ph), 4.42 and 4.39 (2 H, 2d, $J_{A,B}$ = 12.0 Hz, C*H*$_2$Ph), 4.13 (1 H, dd, $J_{1a,2}$ = 4.6, $J_{2,3}$ = 9.1 Hz, H-2), 4.05 (1 H, dd, $J_{2,3}$ = $J_{3,4}$ = 3.7 Hz, H-3), 3.81 (3 H, s, OC*H*$_3$), 3.79 (3 H, s, OC*H*$_3$), 3.76 (3 H, s, OC*H*$_3$), 3.64 (1 H, dd, $J_{5a,5b}$ = 8.9, $J_{4,5a}$ = 7.5 Hz, H-5a), 3.50 (1 H, ddd, $J_{4,5b}$ = 6.3 Hz, H-4), 3.45 (1 H, dd, H-5b), 3.04 (1 H, dd, $J_{1a,1b}$ = 11.4, $J_{1a,2}$ = 5.2 Hz, H-1a), 2.85 (1 H, dd, H-1b). ^{13}C NMR ($CDCl_3$): δ = 159.24, 159.16 (3 × C_{para}), 130.31, 130.19, 130.01 (3 C_{ipso}), 129.48, 129.28, 129.22 (6 × C_{ortho}), 113.80, 113.74 (6 × C_{meta}), 84.77 (C-3), 84.70 (C-2), 72.66, 71.49, 71.20 (3 × C*H*$_2$Ph), 72.15 (C-5), 55.24 (3 × OC*H*$_3$), 48.96 (C-4), 33.07 (C-1). Anal. Calcd for $C_{29}H_{34}O_6S$: C, 68.21; H, 6.71. Found: C, 67.99; H, 6.69.

(15) **2,3,5-Tri-*O*-*p*-Methoxybenzyl-1,4-dideoxy-1,4-{[(2*S*,3*S*)-2,4-benzylidenedioxy-3-(sulfooxy)butyl]-episulfoniumylidene}-D-arabinitol Inner Salt (13).** A mixture of the thioether **12** (1.50 g, 2.94 mmol), and the cyclic sulfate **3** (0.96 g, 1.2 equiv) in HFIP (2.5 mL) containing anhydrous K_2CO_3 (30 mg) was stirred in a sealed tube in an oil-bath (55°C) overnight. TLC analysis (CH_2Cl_2–MeOH, 10:1) showed that the thioether **12** was completely consumed. The solvent was removed under reduced pressure and the product was purified by column chromatography (gradient of CH_2Cl_2 to CH_2Cl_2–MeOH, 10:1) to give compound **13** (2.3 g, 100%) as a colorless foam. $[\alpha]_D$ –10.5 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (CD_2Cl_2): δ = 7.51–6.81 (17 H, m, Ph), 5.53 (1 H, s, C_6H_5C*H*), 4.57 (1 H, ddd, $J_{2',3'}$ = $J_{3',4'ax}$ = 10.0, $J_{3',4'eq}$ = 5.5 Hz, H-3′), 4.49 (1 H, dd, $J_{4'ax,4'eq}$ = 10.8 Hz, H-4′eq), 4.44 (2 H, s, C*H*$_2$Ph), 4.42–4.39 (1 H, m, H-2), 4.39 and 4.29 (2 H, 2d, $J_{A,B}$ = 11.4 Hz, C*H*$_2$Ph), 4.33 (1 H, dd, $J_{1'a,1'b}$ = 13.4, $J_{1'a,2'}$ = 2.6 Hz, H-1′a), 4.29–4.26 (1 H, m, H-3), 4.26 (1 H, ddd, H-2′), 4.19 and 4.09 (2 H, 2d, $J_{A,B}$ = 11.5 Hz, C*H*$_2$Ph), 4.03 (1 H, br d, $J_{1a,2}$ <1 Hz, H-1a), 3.96–3.89 (2 H, m, H-4, H-1′b), 3.80 (3 H, s, OCH_3), 3.79 (3 H, s, OCH_3), 3.78 (3 H, s, OCH_3), 3.77 (1 H, dd, H-4′ax), 3.63 (1 H, dd, $J_{1a,1b}$ = 13.3, $J_{1b,2}$ = 3.8 Hz, H-1b), 3.58 (1 H, dd, $J_{5a,5b}$ = 9.9, $J_{4,5a}$ = 8.5 Hz, H-5a), 3.49 (1 H, dd, $J_{4,5b}$ = 7.3 Hz, H-5b); ^{13}C NMR (CD_2Cl_2): δ 160.30, 160.23, 159.97, 137.20 and 130.27-126.61 (21 × C, Ph), 114.45, 114.36 and 114.18 (3 × C_{ipso}, OMBn), 101.96 (Ph*C*H), 83.29 (C-3), 82.37 (C-2), 76.76 (C-2′), 73.36, 72.43, and 72.14 (3 × C*H*$_2$Ph), 69.50 (C-4′), 66.71 (C-5), 66.55 (C-4), 66.45 (C-3′), 55.61 (3 C, 3 × OC*H*$_3$), 49.55 (C-1′), 48.48 (C-1). Anal. Calcd for $C_{40}H_{46}O_{12}S_2$: C, 61.36; H, 5.92. Found: C, 61.13; H, 6.00.

(16) **1,4-Dideoxy-1,4-{[(2*S*,3*S*)-2,4-dihydroxy-3-(sulfooxy)butyl]-episulfoniumylidene}-D-arabinitol Inner Salt(1).** Compound **13** (2.30 g, 2.94 mmol) was dissolved in trifluoroacetic acid (24 mL) and while stirring, water (2.4 mL) was added. The mixture was stirred at room temperature for 0.5 h. The solvent was removed under reduced pressure and the gummy residue was washed with CH_2Cl_2 (3 × 20 mL). Water (15 mL) was added to dissolve the crude product, and then evaporated under reduced pressure to remove the traces of remaining acid. Salacinol (**1**) (0.67 g, 68%) was crystallized from MeOH. The mother liquor was concentrated and purified by column chromatography (EtOAc–MeOH–H_2O, 7:3:1) to give more salacinol **1** as a white solid (0.18 g, 18%).