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Synthesis and elucidation of absolute stereochemistry of salaprinol, another thiosugar sulfonium sulfate from the ayurvedic traditional medicine *Salacia prinoides*

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ABSTRACT

Synthesis and elucidation of absolute stereochemistry of salaprinol (**3**) isolated from the root and stems of *Salacia prinoides*, which has been used for the treatment of diabetes in India, Sri Lanka, and Southeast Asia countries, is described. Compound **3** and its 2′-epimer, *epi*-salaprinol (***epi*-3**) were synthesized via the coupling reaction of a cyclic sulfate, 2-*O*-benzylglycerol 1,3-cyclic sulfate (**5**), with a thiosugar, 1,4-dideoxy-1,4-epithio-D-arabinitol (**6**), as the key reaction, and *S* configuration of the asymmetric center in the side chain of **3** was elucidated by the X-ray crystallographic analysis.

1. Introduction

In the course of our studies on the antidiabetogenic compounds from natural medicines,[1] we have isolated two potent α-glucosidase inhibitors, salacinol (**1**) and kotalanol (**2**), with unique thiosugar sulfonium sulfate inner salt structure from the roots, stems, and leaves of *Salacia reticulata*,[2] *Salacia oblonga*,[3] and *Salacia chinensis*,[4] which have traditionally been used for the treatment of diabetes in Sri Lanka, India, and Thailand. Their α-glucosidase inhibitory activities are potent, and have been revealed to be as high as those of voglibose and acarbose, which are widely used clinically these days. Owing to both the high inhibitory activity and the intriguing structure, much attention has been focused on **1** and related compounds, intensive studies on the structure–activity relationships (SAR) on **1** and heterocyclic analogs having been reported.[5] In addition, clinical evaluation[6] of the safety of the extract has also been intensively carried out with a view to develop the *Salacia* extract as an effective functional foods for slight degree of diabetics. In our continuous studies on exploring the active constituents in *Salacia* species, we recently isolated two new thiosugar derivatives named salaprinol (**3**) and ponkoranol (**4**) from the methanolic extract of roots and stems of Indian *S. prinoides*, which are also used for the treatment of diabetes.[7]

In our previous SAR studies,[5e] the authors have briefly commented the synthesis of the diastereomeric mixture of **3** and its 2′-epimer (***epi*-3**). Careful reexamination on the synthesis enabled us to isolate each isomer as single crystals. In this paper we describe full details of the synthesis of **3** and ***epi*-3**, and unambiguous elucidation of the absolute stereostructure of both isomers on the basis of the single crystal X-ray analysis.

2. Synthesis of salaprinol (3) and *epi*-salaprinol (*epi*-3)

Firstly, glycerol (**7**) was derived into 2-*O*-benzylglycerol[8] (**8**). When **7** was treated with trityl chloride according to the literature,[8] formation of considerable amount of 1,2,3-tri-*O*-tritylglycerol[9] (**9**) was observed. Furthermore, undesirable acetylation forming mono- and diacetates[10a,b,11] (**10** and **11**) was found to occur on detritylation to **8**. Thus, the reaction condition of these two steps were modified and optimized in this study. Thus, selective tritylation of the primary hydroxyl of **7** was performed when the reaction was conducted in pyridine at room temperature, to give 1,3-di-*O*-tritylglycerol[8] (**12**) predominantly (**12**/**9**=ca. 20:1), although prolonged reaction time was required (24 h). The carbinol moiety of **12** was then protected with benzyl bromide in the presence of sodium

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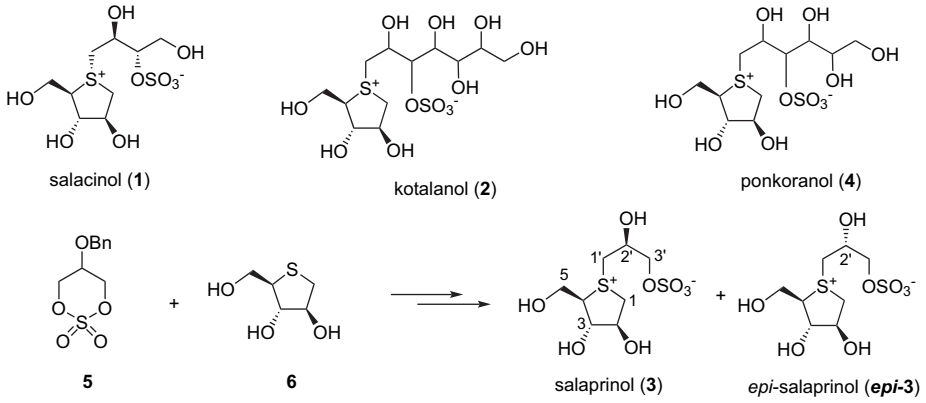


Scheme 1.

hydride to give 2-*O*-benzyl-1,3-di-*O*-tritylglycerol[8] (**13**) in good yield. Hydrolysis of **13** was successfully performed by refluxing a mixture of 10% sulfuric acid and 1,4-dioxane to give **8** in 95% yield. Thus, the yield of **8** from **7** was improved to ca. 90% from 50% reported.[8] Finally, the diol **8** was converted into the desired 2-benzyloxy cyclic sulfate **5** according to the conditions reported previously by the authors (Scheme 1).[5e]

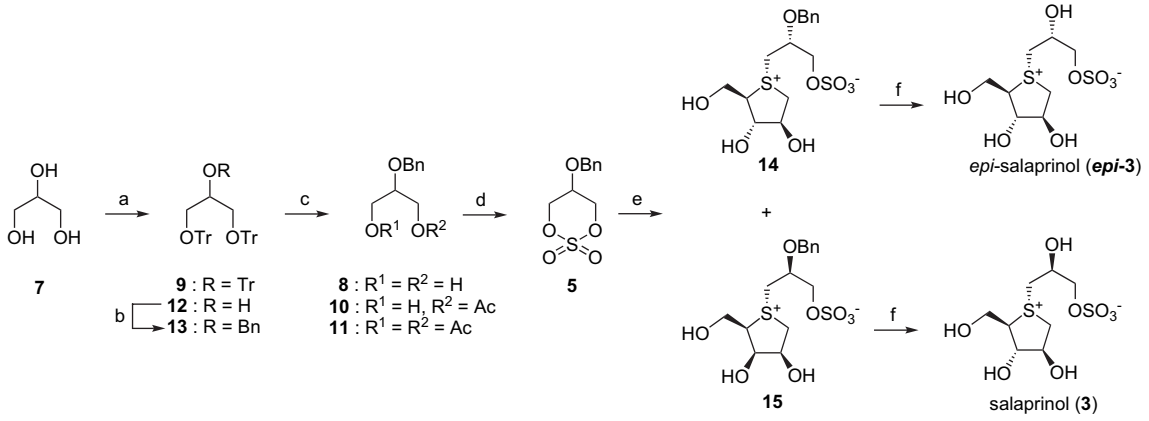
The cyclic sulfate (**5**) was subjected to the coupling reaction with a thiosugar[5e] (**6**) in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) at 65–70 °C. When the reaction was carried out in relatively large scale (4 mmol), one of the epimers (**14**) deposited fortunately in the reaction mixture and pure **14** was obtained in 16% yield after recrystallization. In addition, careful column chromatography of the condensed filtrate afforded a fraction composed of ca. 10:1 epimeric mixture of **15** and **14**, although these two epimers were hardly separable by TLC analysis. ^{1}H and ^{13}C NMR spectroscopic properties of **14** and **15** were quite similar with each other. Downfield shift with respect to the signals due to C-1 methylene (**14**: δ_C 50.8, **15**: δ_C 51.5), C-4 methine (**14**: δ_C 73.4, **15**: δ_C 73.6), and C-1′ methylene (**14**: δ_C 49.6, **15**: δ_C 49.9) carbons supported their sulfonium ion structure.

Hydrogenolysis of **14** with palladium on carbon in 80% aqueous acetic acid gave *epi*-salaprinol (***epi*-3**) in good yield. The ca. 10:1 mixture of **15** and **14** was also hydrogenated to give a mixture of **3** and ***epi*-3**, and exclusive crystallization of the major product (**3**) from the mixture was successfully conducted by the use of methanol as the solvent, affording pure **3** as colorless crystals (Scheme 2). Although their ^{13}C NMR spectroscopic properties were quite similar with each other, discrimination of each isomer was possible on the basis of ^{1}H NMR spectra, some signals due to α-protons to the sulfonium center (H-4, H-1a, H-1′a, H-1′b) of ***epi*-3** being observed at lower field than those of **3** as shown in Figure 1 and Table 1. Coupling patterns of all the proton signals of both **3** and ***epi*-3** were unambiguously resolved in the present study by the use of a 700 MHz ^{1}H NMR spectrometer (Table 1). ^{1}H NMR and ^{13}C NMR spectroscopic properties of **3** were completely in accord with those of authentic salaprinol isolated from *S. prinoides* (Tables 1 and 2).[7]

3. X-ray crystallographic analysis of salaprinol (3) and *epi*-salaprinol (*epi*-3)

Single crystals of **3** were obtained as colorless prisms from a methanol solution, and the stereochemistry of both the sulfonium center and C-2′ were established on the basis of the X-ray crystallographic analysis. Compound **3** was found to be packed to form $P2_12_12_1$ type orthorhombic crystals, and the sulfonium and C-2′ was proved to be both in *S* configuration as shown in Figure 2. On the other hand, single crystals of *epi*-salaprinol (***epi*-3**) were obtained from an aqueous methanol solution as colorless prisms, and were found to be $P2_1$ type monoclinic crystals. The absolute stereochemistry of the epimeric center (C-2′) was proved to be *R* configuration. Unlike salacinol (**1**), which forms characteristic spirobicyclic-like inner salt structure, both compounds were found to be packed to form salts intermolecularly between the sulfonium cation and sulfate anion at the solid state, as shown in the packing diagram (Fig. 3).

In summary, salaprinol (**3**), another sulfonium sulfate from the *Salacia* species, and its epimer (***epi*-3**) were synthesized by the coupling reaction of a cyclic sulfate (**5**) and a thiosugar (**6**). Each of the epimers was successfully recrystallized to give single crystals. Absolute stereochemistry of both epimers was unambiguously elucidated by the X-ray crystallographic analysis. These two twitter



Scheme 2. Reagents and conditions: (a) TrCl, py, rt; (b) BnBr, NaH, DMF, 0 °C to rt or BnCl, KOH, toluene, reflux; (c) 10% aq H_2SO_4, 1,4-dioxane, reflux; (d) (1) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C, then (2) $NaIO_4$, $RuCl_3$, $NaHCO_3$, CCl_4, CH_3CN, H_2O, 0 °C to rt; (e) thiosugar **6**, K_2CO_3, HFIP, 65–70 °C; (f) H_2, Pd–C, 80% AcOH, 50 °C.

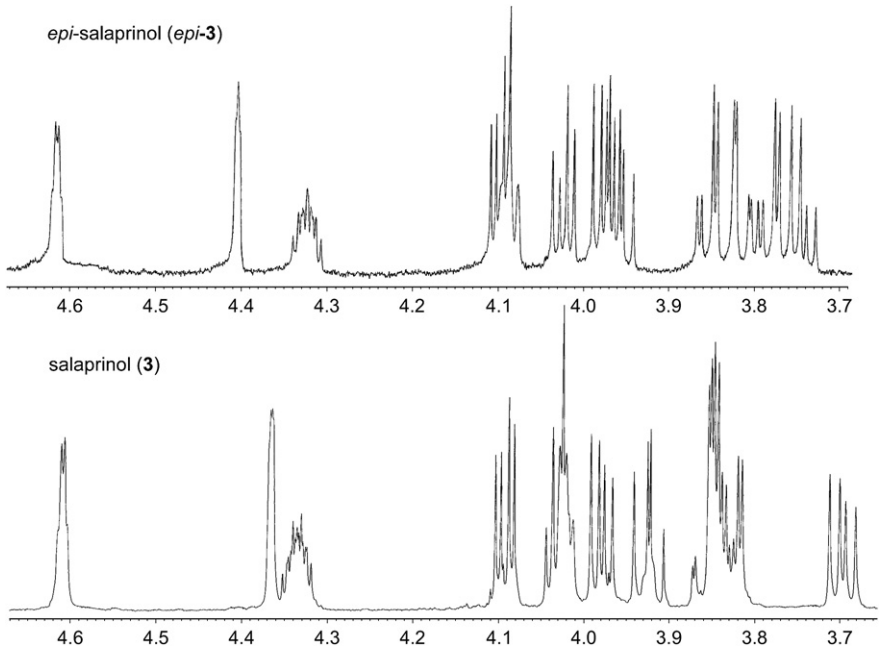


Figure 1. ^{1}H NMR spectra (700 MHz) of salaprinol (**3**) and *epi*-salaprinol (***epi*-3**).

Table 1
^{1}H NMR data for compounds **3** and ***epi*-3** in CD_3OD

	Salaprinol (500 MHz)[7]	**3** (700 MHz)	***epi*-3** (700 MHz)
H-1a	3.85 (dd, *J*=12.4, 3.5)	3.84 (dd, *J*=12.6, 3.4)	3.81 (dd, *J*=12.6, 2.0)
H-1b	3.88 (dd, *J*=12.4, 2.0)	3.86 (dd, *J*=12.6, 2.2)	3.86 (dd, *J*=12.6, 3.4)
H-2	4.63 (ddd-like)	4.61 (dt-like, *J*=ca. 3.4, 2.2)	4.62 (dt-like, *J*=ca. 3.4, 2.0)
H-3	4.38 (br s-like)	4.37 (br dd-like, *J*=ca. 2.2, 1.2)	4.41 (br dd-like, *J*=ca. 2.0, 2.0)
H-4	4.04 (dd-like)	4.02 (br dd like, *J*=ca. 11.2, 5.4)	4.09 (br dd-like, *J*=ca. 8.6, 5.8)
H-5a	3.93 (dd, *J*=13.0, 11.0)	3.92 (dd, *J*=13.5, 11.2)	3.96 (dd, *J*=11.6, 8.6)
H-5b	4.05 (dd, *J*=13.0, 5.5)	4.03 (dd, *J*=13.5, 5.4)	4.03 (dd, *J*=11.6, 5.8)
H-1′a	3.71 (dd, *J*=13.0, 8.2)	3.70 (dd, *J*=13.2, 8.2)	3.74 (dd, *J*=13.2, 7.7)
H-1′b	3.84 (dd, *J*=13.0, 3.4)	3.83 (dd, *J*=13.2, 3.4)	3.78 (dd, *J*=13.2, 3.8)
H-2′	4.35 (m)	4.34 (dddd, *J*=8.2, 6.6, 4.6, 3.4)	4.33 (dddd, *J*=7.7, 6.4, 4.7, 3.8)
H-3′a	4.00 (dd, *J*=11.0, 6.2)	3.98 (dd, *J*=10.9, 6.6)	3.98 (dd, *J*=10.9, 6.4)
H-3′b	4.11 (dd, *J*=11.0, 4.8)	4.09 (dd, *J*=10.9, 4.6)	4.10 (dd, *J*=10.9, 4.7)

Table 2
^{13}C NMR data for compounds **3** and ***epi*-3** in CD_3OD

	C-1	C-2	C-3	C-4	C-5	C-1′	C-2′	C-3′
Salaprinol (125 MHz)[7]	51.7	79.4	79.6	73.7	60.9	51.3	67.4	70.4
3 (125 MHz)	51.7	79.4	79.6	73.7	60.9	51.4	67.3	70.3
***epi*-3** (125 MHz)	50.76	79.4	79.8	73.4	60.9	50.84	67.3	70.2

ionic analogs were found not to form the spirobicyclic-like inner salt structure as salacinol.

4. Experimental

4.1. General

Melting points were determined on a Yanagimoto MP-3S micromelting point apparatus, and mps and bps are uncorrected. IR spectra were measured on either a Shimadzu IR-435 grating spectrophotometer or a Shimadzu FTIR-8600PC spectrophotometer. NMR spectra were recorded on a JEOL AL 400 (400 MHz ^{1}H, 100 MHz ^{13}C), a JEOL JNM-ECA 500 (500 MHz ^{1}H, 125 MHz ^{13}C), a JEOL JNM-ECA 600 (600 MHz ^{1}H, 150 MHz ^{13}C) or a JEOL JNM-ECA 700 (700 MHz ^{1}H, 175 MHz ^{13}C) spectrometer. Chemical shifts (δ) and coupling constants (J) are given in parts per million and hertz, respectively. Low-resolution and high-resolution mass spectra were recorded on a JEOL JMS-HX 100 spectrometer. Optical rotations were determined with a JASCODIP-370 digital polarimeter. Column chromatography was effected over Fuji Silysia Chemical silica gel BW-200. All the organic extracts were dried over anhydrous sodium sulfate prior to evaporation.

4.2. 3.1.2-*O*-Benzyl-1,3-tri-*O*-tritylglycerol (13)

4.2.1. Method A

According to the method reported,[8] a mixture of glycerol (**7**, 3.3 g, 35.9 mmol), trityl chloride (25 g, 89.6 mmol), and pyridine (30 ml) was heated at 100 °C for 1 h. After being cooled, the reaction mixture was poured into ice-cooled water (150 ml) and extracted with ethyl acetate. The extract was subsequently washed by water and brine. After removal of the ethyl acetate in vacuo, the remaining pyridine was co-evaporated with *n*-hexane to give a ca. 3.3:1 mixture of 1,3-di-*O*-tritylglycerol[8] (**12**) and 1,2,3-tri-*O*-tritylglycerol[9] (**9**) as a colorless solid (25.7 g). When glycerol (**7**, 1.0 g, 10.9 mmol) was treated with trityl chloride (7.4 g, 26.5 mmol) in pyridine (20 ml) at 50 °C, a ca. 10:1 mixture of **12** and **9** was obtained.

A suspension of a ca. 3.3:1 mixture of **12** and **9** (25.6 g), benzyl chloride (20 ml, 174 mmol), and crushed potassium hydroxide (18 g, 321 mmol) in toluene (100 ml) was heated under reflux for

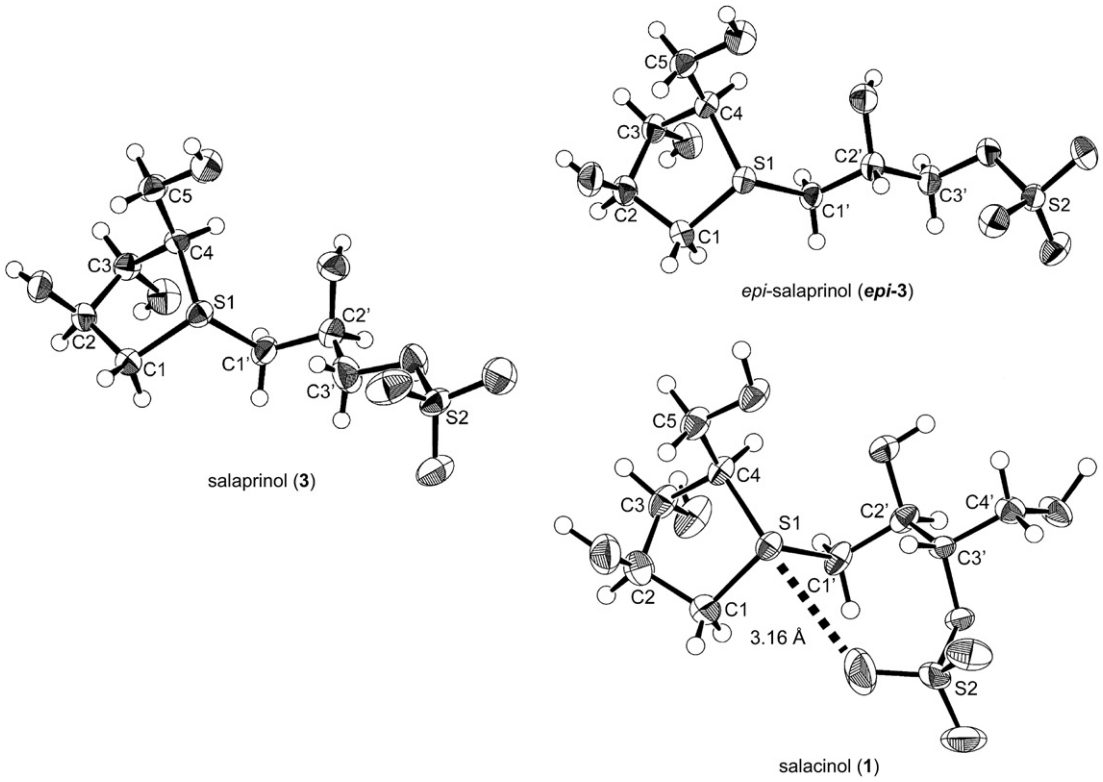


Figure 2. Perspective views of salacinol (**1**), salaprinol (**3**), and *epi*-salaprinol (***epi*-3**).

1 h. After being cooled, the reaction mixture was washed subsequently with water and brine. Removal of the solvent left an orange oil (33.1 g), which on column chromatography ($CHCl_3$–*n*-hexane, 1:2→1:1) gave 2-*O*-benzyl-1,3-di-*O*-tritylglycerol[8] (**13**, 16.8 g, 70% from **7**) and **9** (6.2 g, 21% from **7**).

4.2.2. Method B

A mixture of glycerol (**7**, 1.0 g, 10.9 mmol), trityl chloride (7.4 g, 26.5 mmol), and pyridine (20 ml) was stirred at room temperature for 24 h. Work-up in a manner similar to that used in method A gave a ca. 20:1 mixture of **12** and **9** as a colorless solid (9.0 g), which was used in the next step without purification.

The solid (9.0 g) was added in small portions to a mixture of benzyl bromide (2.7 ml, 22.7 mmol) and sodium hydride (1.0 g, 25 mmol, 60% in mineral oil) in DMF (40 ml) with vigorous stirring at 0 °C, and the resulting mixture was stirred at 0 °C for 1.5 h. The mixture was allowed to warm to room temperature and was stirred for another 2 h. The reaction mixture was poured into ice-water (150 ml), and the deposited brown solid was filtered and washed with water to give a brown solid (10.3 g), which on column

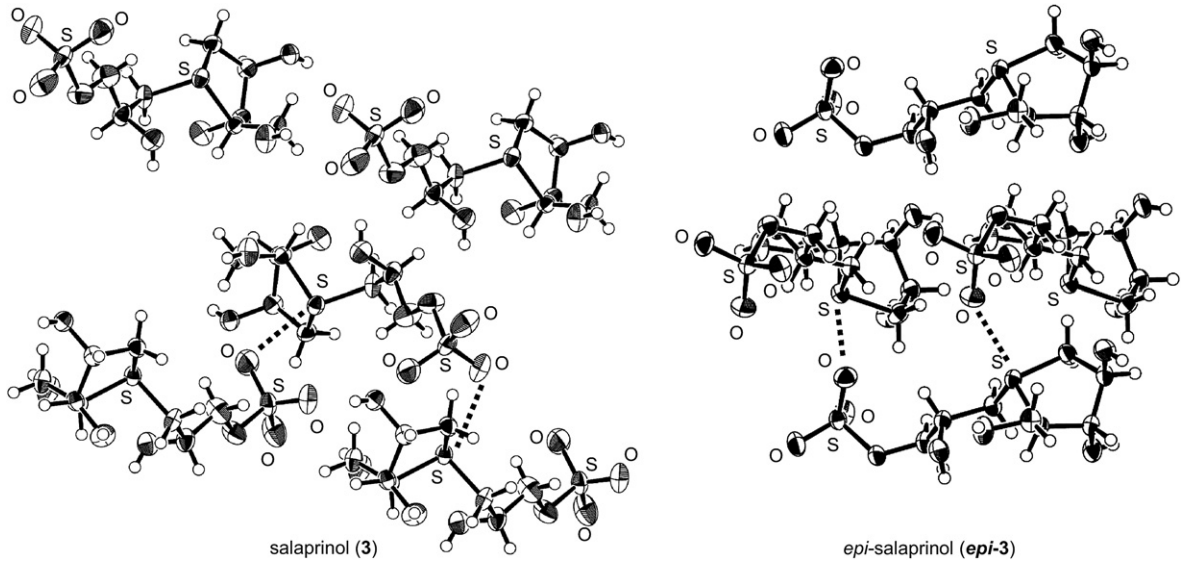


Figure 3. Packing diagrams of salaprinol (**3**) and *epi*-salaprinol (***epi*-3**).

chromatography ($CHCl_3$–*n*-hexane, 1:2→1:1) gave **13** (6.7 g, 93% from **7**) and **9** (230 mg, 5% from **7**).

*4.2.2.1. Compound **13**.* Colorless needles, mp 155–158 °C (from EtOH–AcOEt), lit.[8] solid (no mp). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.27 (2H, dd, J=9.6, 5.6 Hz, H-1a and H-3a), 3.32 (2H, dd, J=9.6, 4.8 Hz, H-1b and H-3b), 3.74 (1H, tt, J=5.6, 4.8 Hz, H-2), 4.60 (2H, s, PhCH_2), 7.18–7.42 (35H, m, arom.). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 63.4 (C-1 and C-3), 72.1 (Ph*C*H_2), 77.7 (C-2), 86.6 (Ph$_3$*C*), 126.8/127.4/127.6/127.7/128.3/128.7 (d, arom.), 138.7/144.1 (s, arom.).

*4.2.2.2. Compound **9**.* Colorless moss-like solid, mp 197–199 °C, lit.[9a,b] 196–197 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.99 (2H, dd, J=9.6, 4.4 Hz, H-1a and H-3a), 3.19 (2H, dd, J=9.6, 6.0 Hz, H-1b and H-3b), 3.70 (1H, tt, J=6.0, 4.4 Hz, H-2), 7.08–7.34 (45H, m, arom.). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 63.4 (C-1 and C-3), 72.7 (C-2), 86.3/86.8 (Ph$_3$*C*), 126.6/126.8/127.5/127.6/128.9/129.0 (d, arom.), 144.2/144.8 (s, arom.).

4.3. Detritylation of 2-*O*-benzyl-1,3-di-*O*-tritylglycerol (13)

4.3.1. Method A

According to the method reported,[8] **13** (1.0 g, 1.5 mmol) was treated in refluxing 80% aqueous acetic acid (5 ml) for 1 h to give a ca. 4.7:1 mixture of 2-*O*-benzylglycerol[8,10] (**8**) and 2-*O*-benzylglycerol 1-acetate[10a,b,11] (**10**) contaminated with a trace amount of 2-*O*-benzylglycerol 1,3-diacetate[10a] (**11**) as a colorless oil (396 mg). The crude oil was heated under reflux in a mixture of 10% hydrochloric acid (1 ml) and methanol (3 ml) for 1 h. Removal of the solvent in vacuo left a colorless oil (366 mg), which on column chromatography ($CHCl_3$→$CHCl_3$–MeOH, 30:1) gave **8** (232 mg, 85% from **13**) as a colorless oil. Analytical sample of the side product **10** was obtained by means of column chromatography ($CHCl_3$→$CHCl_3$–MeOH, 30:1) of a small portion of the crude hydrolyzed products from **13**.

4.3.2. Method B

A mixture of **13** (11.6 g, 17.4 mmol), 10% aqueous sulfuric acid (15 ml), and 1,4-dioxane (40 ml) was heated under reflux for 3 h. After being cooled, the reaction mixture was diluted with water and the resulting mixture was neutralized with sodium hydrogen carbonate. The deposited trityl alcohol (9.1 g) was filtered and washed with water. The combined filtrate and the washings were saturated with sodium chloride, and the resulting mixture was extracted with ethyl acetate. Removal of the solvent left practically pure **8** (2.93 g, 92%) as a colorless oil, which on distillation at reduced pressure gave **8** (2.9 g, 91%). The oil solidified on standing at room temperature.

*4.3.2.1. Compound **8**.* Mp 34–36 °C, lit.[8] 35–36 °C, lit.[10d] 35–37 °C; bp 150–152 °C/0.1 mmHg, lit.[10b] 180 °C/3 mmHg, lit.[10d] 149 °C/0.2 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.10 (2H, br s, OH), 3.60 (1H, tt, J=4.8, 4.4 Hz, H-2), 3.72 (2H, dd, J=11.6, 4.8 Hz, H-1a and H-3a), 3.79 (2H, dd, J=11.6, 4.4 Hz, H-1b and H-3b), 4.66 (2H, s, PhCH_2), 7.23–7.40 (5H, m, arom.). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 62.1 (C-1 and C-3), 79.1 (C-2), 71.9 (PhCH_2), 127.8/127.9/128.5 (d, arom.), 137.9 (s, arom.).

*4.3.2.2. Compound **10**.* Colorless oil. The closed signals due to two methylene carbons C-1 and C-3 were unambiguously assigned on the basis of two dimensional NMR studies. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.02 (1H, br s, OH), 2.08 (3H, s CH_3C=O), 3.61–3.67 (1H, br m, H-3a), 3.69–3.75 (2H, br m, H-2 and H-3b), 4.23 (2H, d, J=4.9 Hz, H-1a and H-1b), 4.61/4.71 (each d, J=11.7 Hz) 7.27–7.39 (5H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.8 (O=CCH_3), 62.0 (C-3), 62.9 (C-1), 72.2 (PhCH_2), 77.6 (C-2), 127.9/128.0/128.5 (d, arom.), 137.8 (s, arom.), 171.0 (O=*C*CH_3).

4.4. Preparation of diol 8 from glycerol (7) without isolation of the intermediates 12 and 13

Following the method B described above for the preparation of **13**, a mixture of **7** (2.05 g, 22.3 mmol), trityl chloride (15.0 g, 53.8 mmol), and pyridine (40 ml) was stirred at room temperature for 24 h. Work-up gave a ca. 20:1 mixture of **12** and **9** (17.5 g), which was treated with benzyl bromide (7.5 ml, 63.2 mmol) in DMF (100 ml) in the presence of sodium hydride (2.5 g, 62.5 mmol, 60% in mineral oil). After being stirred at room temperature for 2 h, the reaction mixture was poured into ice-cooled water (300 ml), and the separated paste-like material was taken up in ethyl acetate. The organic layer was washed successively with water and brine, and evaporated to give a brown oil (22.6 g), which on trituration with hot methanol gave a pale yellow solid (17.3 g). The solid (17.3 g) was then heated under reflux in a mixture of 10% sulfuric acid (30 ml) and 1,4-dioxane (90 ml) for 2 h. The reaction mixture was diluted with water (500 ml) and the resulting mixture was neutralized with sodium hydrogen carbonate. The deposited trityl alcohol (13.8 g) was filtered and washed with water. The combined filtrate and the washings were then washed with diethyl ether, and the organic layer was reextracted with water. All the aqueous layers were combined and saturated with sodium chloride, then extracted with ethyl acetate. The extracts were evaporated to give a brown oil (4.28 g), which on distillation at reduced pressure gave **8** (3.63 g, 90% from **7**) as a colorless oil, which solidified when seeded with the authentic sample **8** obtained by the above experimental section.

4.5. 2-*O*-Benzylglycerol 1,3-cyclic sulfate (5)

A solution of freshly distilled thionyl chloride (1.04 ml, 14.3 mmol) in dichloromethane (50 ml) was added dropwise to a stirred mixture of **8** (2.0 g, 11 mmol), triethyl amine (4.6 ml, 33.2 mol), and dichloromethane (60 ml) at 0 °C. After being stirred at 0 °C for 10 min, the mixture was poured into ice-cooled and vigorously stirred aqueous sodium hydrogen carbonate (100 ml), and extracted with dichloromethane. The extract was washed with brine and evaporated to give a pale yellow oil (2.53 g), which was used in the next step without purification.

To a well stirred mixture of the oil (2.53 g), sodium hydrogen carbonate (3.3 g, 39.2 mmol), carbon tetrachloride (60 ml), acetonitrile (60 ml), and water (60 ml) was added dropwise a brown mixture of sodium metaperiodate (7.05 g, 32.9 mmol), ruthenium chloride *n*-hydrate (100 mg), and water (60 ml) at 0 °C. After being stirred at room temperature for 30 min, the reaction was quenched by the addition of aqueous sodium thiosulfate-sodium hydrogen carbonate (50 ml). The resulting purple mixture was filtered and the filtrate was extracted with diethyl ether. The extract was washed with brine and evaporated to give a colorless solid (2.66 g), which on column chromatography (*n*-hexane–acetone, 5:1) gave the title compound (**5**, 2.5 g, 93%) as colorless solid. The spectral properties of **5** were in accord with those reported.[5e]

4.6. Coupling reaction between cyclic sulfate 5 and thiosugar 6

A suspension of the cyclic sulfate **5** (1.47 g, 6.0 mmol), a thiosugar[7] **6** (602 mg, 4.0 mmol), potassium carbonate (277 mg, 2 mmol), and HFIP (3 ml) was stirred at 65–70 °C. Potassium carbonate was dissolved in HFIP within 2 h, and the resulting solution was heated at 65–70 °C for another 70 h. In the course of the reaction, precipitates were gradually formed in the reaction mixture, and the precipitates were filtered and washed with a mixture of ethyl acetate and methanol (10:1, v/v) to give a colorless solid (482 mg), which on recrystallization from aqueous methanol gave 1,4-dideoxy-1,4-{(*S*)-[(2*R*)-2-benzyloxy-3-(sulfooxy)propyl]-

episulfoniumylidene}-D-arabinitol inner salt (**14**, 258 mg, 16%) as colorless prisms. The combined filtrate and the washings were evaporated to give a colorless paste (2.88 g), which on column chromatography (AcOEt–MeOH–H_2O, 20:2:1) gave a ca. 10:1 mixture of 1,4-dideoxy-1,4-{(*S*)-[(2*S*)-2-benzyloxy-3-(sulfooxy)-propyl]-episulfoniumylidene}-D-arabinitol inner salt (**15**) and its epimer **14** (103 mg, 6.5%), a ca. 6:1 mixture of **15** and **14** (216 mg, 14%), and a ca. 1.4:1 mixture of **15** and **14** (102 mg, 6.5%).

Compound ***14***: colorless prisms, mp 178.5–180 °C (from aq MeOH), $[\alpha]_D^{23}$ −71.4 (*c* 0.52, H_2O). IR (Nujol): 3344, 1461, 1377, 1273, 1192, 1123, 1088, 1057, 1011 cm^{-1}. ^1H NMR (600 MHz, pyridine-d_5) δ: 4.08 (dd, *J*=12.5, 2.2 Hz, H-1a), 4.25 (dd, *J*=12.5, 3.9 Hz, H-1b), 4.44 (dd, *J*=13.2, 4.3 Hz, H-1′a), 4.48 (dd, *J*=11.6, 7.9 Hz, H-5a), 4.51 (dd, *J*=11.6, 6.0 Hz, H-5b), 4.55 (dd, *J*=13.2, 5.8 Hz, H-1′b), 4.61 (dddd, *J*=6.9, 5.8, 4.3, 4.0 Hz, H-2′), 4.65/4.77 (each 1H, d, *J*=11.7 Hz, PhCH_2), 4.71 (dd, *J*=11.5, 6.9 Hz, H-3′a), 4.75–4.78 (m, H-4), 4.84 (dd, *J*=11.5, 4.0 Hz, H-3′b), 5.01 (br s-like, H-3), 5.10 (br m, H-2), 7.21–7.29 (3H, m, arom.), 7.36–7.39 (2H, m, arom.), 7.60–7.84 (1H, br s, OH), 8.29/8.39 (each 1H, s, OH). ^{13}C NMR (150 MHz, pyridine-d_5) δ: 49.6 (C-1′), 50.8 (C-1), 60.2 (C-5), 65.6 (C-3′), 71.9 (OCH_2Ph), 73.4 (C-4), 74.0 (C-2′), 79.0 (C-2), 79.4 (C-3), 128.3/128.5/128.8 (d, arom.), 138.0 (s, arom.).

Data for **15** extracted from ^1H and ^{13}C NMR spectra of ca. 10:1 mixture of **15** and **14**: ^1H NMR (700 MHz, pyridine-d_5) δ: 4.29 (2H, d-like *J*=2.8 Hz, H-1a and H-1b), 4.39 (dd, *J*=13.2, 7.1 Hz, H-1′a), 4.41 (dd, *J*=11.6, 9.5 Hz, H-5a), 4.47 (dd, *J*=11.6, 5.4 Hz, H-5b), 4.57 (dd, *J*=13.2, 2.9 Hz, H-1′b), 4.67–4.72 (m, H-2′), 4.70–4.73 (m, H-3′a), 4.74/4.85 (each 1H, d, *J*=11.2 Hz, PhCH_2), 4.80 (br dd, *J*=9.5, 5.4 Hz, H-4), 4.84 (dd, *J*=13.8, 6.2 Hz, H-3′b), 4.95 (br dd-like, *J*=ca. 2.8 Hz, H-3), 5.11 (br td-like, *J*=ca., 2.8, 2.8 Hz, H-2), 7.19–7.29 (3H, m, arom.), 7.39–7.42 (2H, m, arom.), 7.77/8.19/8.27 (each 1H, br s, OH). ^{13}C NMR (175 MHz, pyridine-d_5) δ: 49.9 (C-1′), 51.5 (C-1), 60.2 (C-5), 66.3 (C-3′), 72.2 (OCH_2Ph), 73.6 (C-4), 74.4 (C-2′), 78.7 (C-2), 79.2 (C-3), 128.1/128.5/128.8 (d, arom.), 138.2 (s, arom.).

4.7. Salaprinol (3)

A suspension of 10% palladium on carbon (50 mg) in 80% aqueous acetic acid (1 ml) was pre-equilibrated with hydrogen. To the suspension was added a solution of a ca. 10:1 mixture of **15** and **14** (36 mg, 0.09 mmol) in 80% aqueous acetic acid (2 ml), and the mixture was hydrogenated at room temperature under atmospheric pressure until the uptake of hydrogen ceased. The catalyst was filtered and washed with a mixture of methanol and water. The combined filtrate and the washings were evaporated to give a colorless viscous oil (31 mg), which on column chromatography ($CHCl_3$–MeOH–H_2O, 10:5:1) gave a solid (23.8 mg, 86%). The solid was recrystallized from MeOH to give **3** as colorless prisms. Mp 159–161 °C, $[\alpha]_D^{23}$ +10.7 (*c* 0.63, MeOH), lit.[7] +10.3 (*c* 1.30, MeOH). ^1H (700 MHz) and ^{13}C (175 MHz) NMR spectroscopic properties were completely in accord with those reported (500 MHz and 125 MHz),[7] and summarized in Tables 1 and 2.

4.8. *epi*-Salaprinol (*epi*-3)

A solution of **14** (100 mg, 0.25 mmol) in 80% aqueous acetic acid (10 ml) was hydrogenated in a similar manner to that used for above hydrogenation. Work-up gave a colorless solid (76.9 mg), which on recrystallization from aqueous methanol gave the title compound ***epi*-3** (67 mg, 87%) as colorless prisms. Mp 168–170 °C, $[\alpha]_D^{23}$ −59.5 (*c* 0.56, MeOH). IR (Nujol): 3522, 3402, 3283, 1377, 1246, 1207, 1165, 1115, 1072, 1057, 1026, 988 cm^{-1}. ^1H and ^{13}C NMR spectral data are summarized in Tables 1 and 2.

4.9. X-ray crystallographic analysis

Data of both compounds **3** and ***epi*-3** were taken on Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo Kα radiation (λ=0.71075 Å). The structures of **3** and ***epi*-3** were solved by direct methods with SIR97 and SHELX97, respectively. Full-matrix least-squares refinement was employed with anisotropic thermal parameters for all non-hydrogen atoms. All calculations were performed using the CrystalStructure 3.8 crystal structure analysis package, Rigaku and Rigaku/MSC. ORTEP drawings of compounds **3** and ***epi*-3** are shown in Figure 2. The data of **3** and ***epi*-3** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 683290 and CCDC 683289, respectively.

*Crystal data for salaprinol (**3**).* Orthorhombic, space group $P2_12_12_1$, *a*=6.8882(4), *b*=9.6565(7), *c*=18.1174(4) Å, *V*=1205.10(14) $Å^3$, *Z*=4, μ(Mo Kα)=4.73 cm^{-1}, *F*(000)=640, D_c=1.677 g/cm^3, crystal dimensions: 0.20×0.20×0.10 mm. A total of 11,878 reflections (2758 unique) were collected at a temperature of 23 °C to a maximum 2θ value of 55°. Final *R* and R_w values were 0.040 and 0.115, respectively. The maximum and minimum peaks in the difference map were 0.40 e^- $Å^{-3}$ and −0.22 e^- $Å^{-3}$, respectively.

*Crystal data for epi-salaprinol (**epi-3**).* Monoclinic, space group $P2_1$, *a*=8.9887(14), *b*=6.9476(10), *c*=9.9149(13) Å, β=91.543(4)°, *V*=618.96(15) $Å^3$, *Z*=2, μ(Mo Kα)=4.604 cm^{-1}, *F*(000)=320, D_c=1.633 g/cm^3, crystal dimensions: 0.35×0.32×0.20 mm. A total of 5957 reflections (2661 unique) were collected at a temperature of 23 °C to a maximum 2θ value of 55°. Final *R* and R_w values were 0.040 and 0.093, respectively. The maximum and minimum peaks in the difference map were 0.44 e^- $Å^{-3}$ and −0.37 e^- $Å^{-3}$, respectively.

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