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Isolation, structure identification and SAR studies on thiosugar sulfonium salts, neosalaprinol and neoponkoranol, as potent α-glucosidase inhibitors

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ABSTRACT

Two hitherto missing members of sulfonium salts family in Salacia genus plants as a new class of α-glucosidase inhibitors, neoponkoranol (**7**) and neosalaprinol (**8**), were isolated from the water extracts, and their structures were unambiguously identified. For further SAR studies on this series of sulfonium salts, several epimers of **7** and **8** were synthesized, and their inhibitory activities against rat small intestinal α-glucosidases were evaluated. Among them, 3′-epimer of **7** was found most potent in this class of molecules, and revealed as potent as currently used antidiabetics, voglibose and acarbose.

1. Introduction

Glucosidases are largely involved in the human metabolic system. Thus, the inhibition of glucosidases is considered to be an efficient way to treat diseases such as diabetes,[1] cancers,[2] viral infections[3] and Gaucher's disease.[4] Many naturally occurring and synthesized azasugars, which are believed to carry a positive charge at physiological pH and hence are postulated to bind in the active sites of glucosidase enzymes, are effective inhibitors of various glucosidases.[5] These evidences indicated that a potent glucosidase inhibitor might include an atom that carries a permanent positive charge at a suitable position that mimic the oxacarbenium ion-like transition state of the enzyme-catalyzed reaction.[6]

In late 1990s, salacinol (**1**) was isolated by us as a potent α-glucosidases inhibitor from an Ayurvedic medicinal plant *Salacia reticulata*,[7] which have been traditionally used for the treatment of diabetes in Sri Lanka and south region of India. The structure of **1** was quite unique, bearing the permanent positive charge as the thiosugar sulfonium sulfate inner salt comprised of 1-deoxy-4-thio-D-arabinofranosyl cation and 3′-sulfate anion as shown in Figure 1.[7] Its α-glucosidase inhibitory activity was revealed to be as potent as those of voglibose and acarbose which are widely used clinically these days.[7] The mode of action of salacinol (**1**) was also proved to be the competitive inhibition against α-glucosidase, and K_i values against rat intestinal α-glucosidases, that is, maltase, sucrase, and isomaltase were revealed as 0.31, 0.32, and 0.47 μg/mL, respectively.[7b] Since the discovery of **1**, related sulfonium sulfates, kotalanol[8] (**2**), ponkoranol[9] (**3**) and salaprinol[9] (**4**) were subsequently isolated, and the stereostructure of these sulfonium sulfates (**2**, **3**, **4**) were elucidated by the total synthesis or other means[10] (Fig. 1).

Other than **4**, all these sulfonium sulfates showed potent α-glucosidase inhibitory activities, composing a new class of naturally occurring α-glycosidase inhibitors. Because of both the intriguing structure and high α-glucosidase inhibitory activities, much attention has been focused on **1**, and intensive studies on the structure–activity relationships (SAR) have been reported.[11]

In 2008, another two compounds termed neosalacinol[12] (**5′**) and 13-membered cyclic sulfoxide[13] (**6′**) were reported, by Minami and Ozaki, respectively, as the constituents responsible for the α-glucosidase inhibitory activities of *Salacia* genus plants (Fig. 2). Shortly thereafter, these two compounds were revised to be de-*O*-sulfonates (**5**[14] and **6**[15]) of **1** and **2**, respectively, as shown in Figure 1. It was interesting to note that desulfonated kotalanol (**6**) showed higher α-glucosidase inhibitory activities than the original sulfate (**2**).[9] Ever since the discovery of the existence of **5** and **6** in *Salacia* genus plants, intensive exploratory study on water extracts of *Salacia chinensis* originated from Thailand have been conducted by us in order to isolate other minor sulfoniums. In this paper, full

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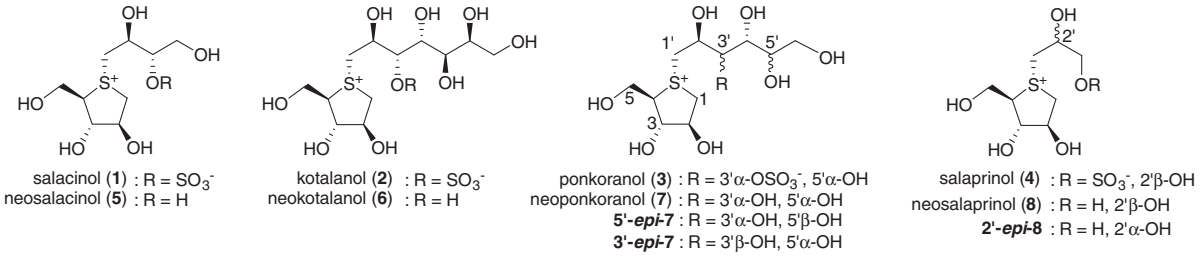


Figure 1. Sulfonium salts isolated from *Salacia* species and related sulfonium salts as a new class of α-glucosidase inhibitors.

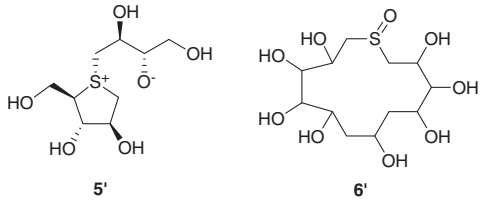


Figure 2. Proposed structures of neosalacinol (**5′**) and neokotalanol (**6′**).

details of isolation and identification of desulfonates of **3** and **4**, neoponkoranol (**7**) and neosalaprinol (**8**), respectively, the existence of which in the plants has been strongly expected, are described. In addition, syntheses of their epimers (**3′-*epi*-7**, **5′-*epi*-7**, and **2′-*epi*-8**) and SAR studies on this neo-series of compounds against rat small intestinal α-glucosidases are also presented.[16]

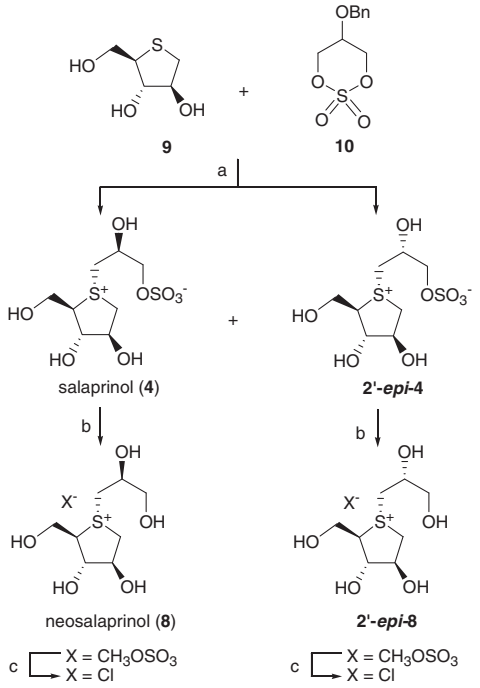
2. Results and discussion

2.1. Isolation and Identification of Neoponkolanol (7) and Neosalaprinol (8)

A water extract was prepared in 9.87% yield in a usual manner from dried stems of *S. chinensis* originated from Thailand. The extract was then dissolved in water, and centrifuged. The supernatant was subjected to Diaion HP-20 column chromatography to give a water-eluted fraction (4.00%) and a MeOH-eluted fraction (1.95%). An aliquot of the H_2O-eluted fraction was dissolved in MeCN/H_2O (50:50, v/v) and centrifuged one more time, then the supernatant was subjected to column chromatography [Chromatorex NH, MeCN/H_2O (50:50 → 20:80, v/v) → H_2O] to give eight fractions. The second fraction (Fr. 2) was purified by means of HPLC [Daisopak-SP-120-5-ODS-BP (20 mm id × 250 mm), mobile phase: 0.1% (v/v) aqueous AcOH] to give neosalaprinol (**8**, 0.00096%) as a colorless oil. According to the same procedure, neoponkoranol (**7**, 0.0016%) was isolated as a colorless solid from the fifth fraction (Fr. 5). The ^{1}H and ^{13}C NMR spectral properties of **7** and **8** were in good accord with those of authentic specimens synthesized alternatively.

2.2. Synthesis of Neosalaprinol (8)

Syntheses of salaprinol (**4**) and its 2′-epimer (**2′-*epi*-4**) had already been established by a coupling reaction of thiosugar, 1,4-dideoxy-1,4-epithio-D-arabinitol (**9**) with cyclic sulfate (**10**)[10c] (Scheme 1). As the first attempt, acid catalyzed hydrolysis of **4**–**8** was conducted. Thus, a synthesized authentic sample of **4** was treated with 5% methanolic hydrogen chloride at 50 °C to give the desired degradation product (**8**, X = CH_3OSO_3). The ^{13}C NMR spectrum showed a peak at δ_c 55.1 corresponding to $CH_3OSO_3^-$ as the counter anion, which was exchanged to the chloride (**8**, X = Cl) by the treatment with IRA 400J (Cl^- form). The exchange

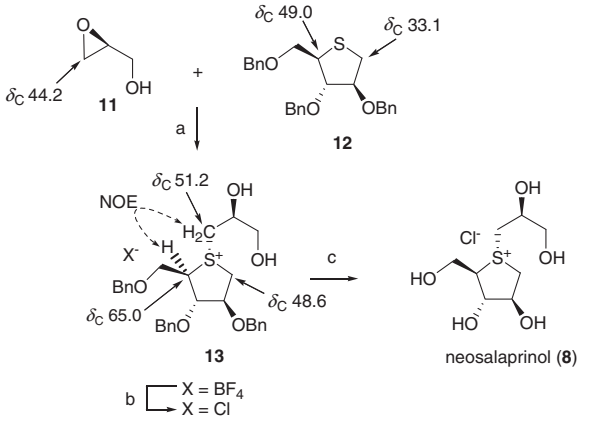


Scheme 1. Reagents and conditions: (a) K_2CO_3, HFIP, 65–70 °C; (b) 5% methanolic HCl, 50 °C; (c) IRA 400J (Cl^- form), CH_3OH, rt.

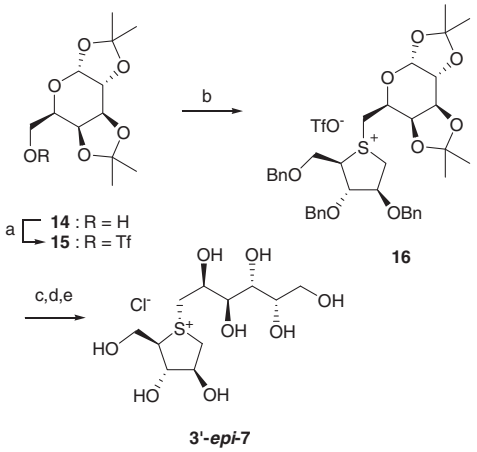
of the anion from $CH_3OSO_3^-$ to Cl^- could be unambiguously confirmed by the complete disappearance of the signals due to $CH_3OSO_3^-$ in the ^{1}H and ^{13}C NMR spectra of **8** (X = Cl). Except for proton and carbon signals corresponding to the $CH_3OSO_3^-$ moiety, NMR spectral properties of these two sulfomium salts (X = CH_3OSO_3 and Cl) were in good accord with each other. Their FAB mass spectra run in a positive ion mode showed a peak at *m/z* 225 due to the sulfonium cation moiety corresponding to the desulfonated structure.

Under similar conditions, **2′-*epi*-4** was also converted to the corresponding sulfonium chloride (**2′-*epi*-8**) in 88% yield. The ^{1}H and ^{13}C NMR spectral properties were quite similar with those of **8** (Scheme 1).

In the coupling reaction of thiosugar (**9**) and cyclic sulfate (**10**), formation of a 1:1 mixture of **4** and **2′-*epi*-4** is inevitable because of the *meso* structure of **10**, and each isomer (**4** and **2′-*epi*-4**) could be obtained only by exclusive recrystallization and subsequent careful column chromatography.[10c] Therefore, an asymmetric synthetic route to **8** has been developed in the present study by employing the regioselective coupling reaction of an epoxide with a thiosugar. Thus (*S*)-glycidol (**11**) was treated with thiosugar, 2,3,5-tri-*O*-benzyl-1,4-dideoxy-1,4-epithio-D-arabinitol (**12**) in the presence of tetrafluoroboric acid dimethyl ether complex. The crude product was then treated with IRA 400J (Cl^- form) to provide the sulfonium



Scheme 2. Reagents and conditions: (a) $HBF_4{\cdot}(CH_3)_2O$, CH_2Cl_2, −45 °C–rt; K_2CO_3, HFIP, 65–70 °C; (b) IRA 400J (Cl^- form), CH_3OH, rt; (c) H_2, 10% Pd-C, 80% AcOH, 50 °C.



Scheme 3. Reagents and conditions: (a) Tf_2O, 2,6-lutidine, −20–0 °C; (b) thiosugar **12**, THF, 40 °C; (c) H_2, 10% Pd-C, 30% aq TFA, 1,4-dioxane, 50 °C; (d) IRA 400J (Cl^- form), CH_3OH, rt; (e) $NaBH_4$, H_2O, 0 °C.

chloride, 2,3,5-tri-*O*-benzyl-1,4-dideoxy-1,4-{(*R*)-[(2*S*)-2,3-dihydroxypropyl]episulfoniumylidene}-D-arabinitol chloride (**13**) in 44% yield. Its FAB mass spectrum run in a positive ion mode showed a peak at *m/z* 495 corresponding to the desired sulfonium cation moiety. As shown in Scheme 2, observed low field shift of ^{13}C NMR signals due to α carbons to the sulfur supported the sulfonium salt formation. The absolute stereochemistry at the stereogenic sulfur center was determined by means of nuclear Overhauser effect (NOE) experiments, which showed H-4 to H-1′ correlations, implying that these atoms are *syn*-facial with respect to the sulfonium ring as shown in Scheme 2. Hydrogenolysis of sulfonium chloride (**13**) thus obtained was carried out over 10% Pd-C at 60 °C in 80% acetic acid to give **8** in 85% yield (Scheme 2).

2.3. Synthesis of 3′-*epi*-Neoponkolanol (3′-*epi*-7)

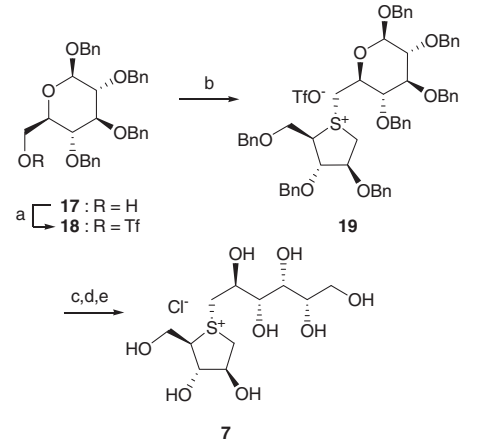
Syntheses of **7** and its 5′-epimer (**5′-*epi*-7**) have been reported very recently by Eskandari et al.[11h] They commented that **5′-*epi*-7** was more active than **7** itself, and that the compound (**5′-*epi*-7**) was the most active inhibitor to date in this class of molecules. As 3′-epimer of ponkoranol (**7**) had been found also active against α-glucosidases,[10b] 3′-epimer of **7** (**3′-*epi*-7**) was synthesized and evaluated in the present study. Thus, commercially available 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**14**) was treated with trifluoromethanesulfonic anhydride (Tf_2O) in dichloromethane in the presence of 2,6-lutidine to give 1,2:3,4-di-*O*-isopropylidene-6-*O*-trifluoromethanesulfonyl-α-D-galactopyranose (**15**) in 94% yield. The triflate (**15**) was then treated with thiosugar (**12**) in THF at 40 °C for 15 h to give the desired coupled product, 2,3,5-tri-*O*-benzyl-1,4-dideoxy-1,4-[(*S*)-(1,2:3,4-di-*O*-isopropylidene-6-deoxy-α-D-galactopyranos-6-yl)episulfoniumylidene]-D-arabinitol trifluoromethanesulfonate (**16**) in 76% yield. The FAB mass spectrum run in a positive ion mode showed a peak at *m/z* 663 due to the sulfonium cation moiety, while in a negative ion mode, a peak due to the TfO^- ion was observed at *m/z* 149. The sulfonium salt **16** was then converted to **3′-*epi*-7** by hydrogenolysis over Pd-C, followed by the treatment with IRA 400J (Cl^- form) and finally by $NaBH_4$ reduction in 50% overall yields from **16**. The positive ion FAB mass spectrum showed a peak at *m/z* 315 corresponding to the desired sulfonium moiety of **3′-*epi*-7** (Scheme 3).

2.4. Synthesis of Neoponkoranol (7)

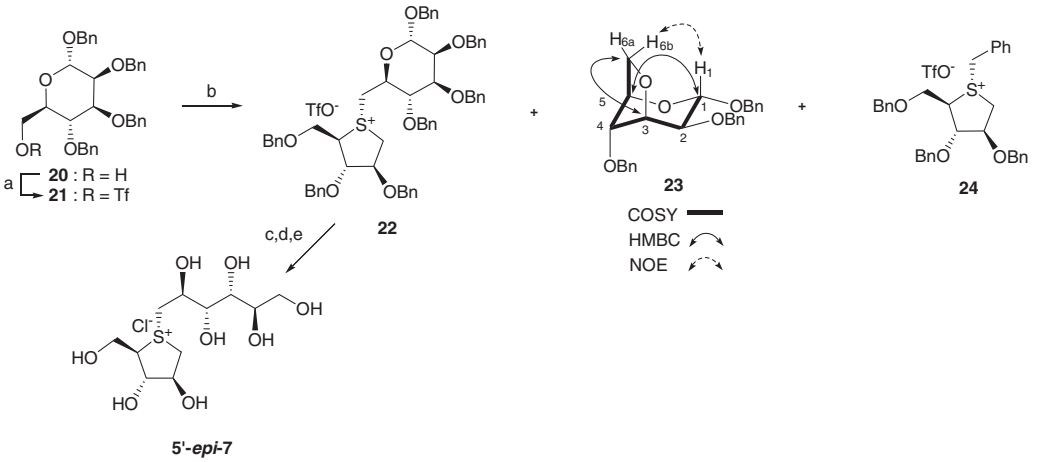
Neoponkoranol (**7**) was also synthesized in order to evaluate simultaneously with other specimens. In the present study, a triflate of glucopyranoside, benzyl 2,3,4-tri-*O*-benzyl-6-*O*-trifluoromethanesulfonyl-β-D-glucopyranoside (**18**) was employed as a coupling partner with thiosugar (**12**).[16] Thus, benzyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranoside[17] (**17**), derived from D-glucose, was treated with Tf_2O in dichloromethane in the presence of 2,6-lutidine to give **18** in 91% yield. The coupling reaction of triflate (**18**) with thiosugar (**12**) completed in 7 h at 40 °C, to give the desired sulfonium salt, 2,3,5-tri-*O*-benzyl-1,4-dideoxy-1,4-[(*S*)-(1,2,3,4-tetra-*O*-benzyl-6-deoxy-β-D-glucopyranos-6-yl)episulfoniumylidene]-D-arabinitol trifluoromethanesulfonate (**19**), in 64% yield. The sulfonium salt **19** was then converted to **7** in 45% overall yields via 3 steps in a similar manner described above for the preparation of **3′-*epi*-7** (Scheme 4).

2.5. Characteristic cyclization of mannose derivative leading to 3,6-anhydromannopyranoside

The protocol was also applied for the synthesis of 5′-epimer (**5′-*epi*-7**) of **7**. Thus, benzyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside[18] (**20**) was converted to its triflate, benzyl 2,3,4-tri-*O*-benzyl-6-*O*-trifluoromethanesulfonyl-α-D-mannopyranoside (**21**), in 80% yield. The first trial of the coupling reaction performed at 40 °C resulted in a complex mixture, in which no formation of the desired sulfonium salt, 2,3,5-tri-*O*-benzyl-1,4-dideoxy-1,4-



Scheme 4. Reagents and conditions: (a) Tf_2O, 2,6-lutidine, −20–0 °C; (b) thiosugar **12**, THF, 40 °C; (c) H_2, 10% Pd-C, 80% aq AcOH, 60 °C; (d) IRA 400J (Cl^- form), CH_3OH, rt; (e) $NaBH_4$, H_2O, 0 °C.



Scheme 5. Reagents and conditions: (a) Tf_2O, 2,6-lutidine, −20–0 °C; (b) thiosugar **12**, THF, 40 °C; (c) H_2, Pd-C, 80% aq AcOH, 60 °C; (d) IRA 400J (Cl^- form), CH_3OH, rt; (e) $NaBH_4$, H_2O, 0 °C.

[(*S*)-(1,2,3,4-tetra-*O*-benzyl-6-deoxy-α-D-mannopyranos-6-yl)-episulfoniumylidene]-D-arabinitol trifluoromethanesulfonate (**22**) was detected. At 0 °C, the desired sulfonium salt (**22**) was obtained in 37% yield accompanied by two side products, benzyl 2,4-di-*O*-benzyl-3,6-anhydro-α-D-mannopyranoside (**23**) and 1,4-dideoxy-1,4-[(*R*)-benzylepisulfoniumylidene]-D-arabinitol trifluoromethanesulfonate (**24**) in 40% and 48% yield, respectively. At −20 °C, no progress of the reaction could be observed, and the starting materials were recovered. The FAB mass spectrum of **23** showed a peak at *m*/*z* 455 corresponding to the sodium adduct ion to the molecule, which lost one benzyl moiety from the reactant (**20**). Its NMR spectra showed signals at δ_C 100.9 and δ_H 5.06 characteristic of the acetal moiety. A NOE correlation between H-6b and H-1 as well as HMBC correlations between positions 3 and 6, and also those between positions 5 and 1, well supported the depicted structure **23**. On the other hand, FAB mass spectrum of **24** in the positive ion mode showed a peak at *m*/*z* 511, which indicated the introduction of one more benzyl moiety to the reactant (**12**). The negative-ion FAB mass spectrum showed a peak at *m*/*z* 149 corresponded to the triflate anion moiety (Scheme 5). The formation of **23** and **24** was ascribable to an intramolecular cyclization[19] arising from an attack of **12** to the methylene carbon at the C3-benzyloxy moiety as shown in Scheme 6. Finally, the sulfonium salt **22** was transformed into the target compound (**5′-*epi*-7**) in a similar manner used for the preparation of **7** in 42% yield from **22**.

2.6. α-Glucosidase inhibitory activities of sulfonium salts

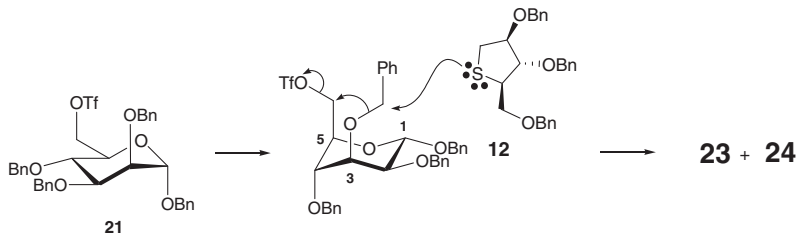
Inhibitory activities of these six compounds synthesized (**2′-*epi*-4**, **7**, **3′-*epi*-7**, **5′-*epi*-7**, **8** and **2′-*epi*-8**) were tested for rat small intestinal α-glucosidases in vitro, and compared with those of other sulfoniums (**1–6**) or clinically used antidiabetics, voglibose and acarbose (Table 1). One of the two newly isolated sulfonium salts (**7**) showed potent inhibitory activity against three enzymes tested, while the other (**8**) inhibited both sucrase and isomaltase more effectively than its sulfate (**4**). It is interesting to note that upon de-*O*-sulfonation, all the resulting sulfonium salts (**5**, **6**, **7**, **8**, and **2′-*epi*-8**) showed improved inhibitory activities against isomaltase. Even 2′-episalaprinol (**2′-*epi*-4**), which lost its characteristic selectivity against isomaltase upon 2′-epimerization, was activated moderately against the enzyme.

Although 2′-epimerization caused drastic decrease in its inhibitory activity against isomaltase, the configuration of the chiral center at C′3 and/or C′5 positions showed no significant influence

Table 1
IC_{50} Values (μM) of thiosugar sulfonium salts and related compounds against disaccharidases

Compound	Maltase	Sucrase	Isomaltase
Salacinol (**1**)	5.2[a]	1.6[a] /1.5[b]	1.3[a] /1.5[b]
Neosalacinol (**5**)	8.0[a]	1.3[a]	0.3[a]
Kotalanol (**2**)	7.2[a]	0.75[a]	5.7[a]
Neokotalanol (**6**)	4.8[a]	4.5[a]	1.8[a]
Salaprinol (**4**)	>329(23)[c]	>329(42)[c]	15
Neosalaprinol (**8**)	>384(35) [c]	90	6.5
2′-*epi*-salaprinol (**2′-*epi*-4**)	>329(12.6) [c]	>329(0.5)[c]	>329(18.4)[c]
2′-*epi*-neosalaprinol (**2′-*epi*-8**)	105	>384(34.5)[c]	52.9
Ponkoranol (**3**)	3.2[a]	0.29[a]	2.6[a]
Neoponkoranol (**7**)	5.1	1.0	1.4
5′-*epi*-neoponkoranol (**5′-*epi*-7**)	4.3	2.9	1.0
3′-*epi*-neoponkoranol (**3′-*epi*-7**)	1.3	0.3	1.0
Voglibose	1.2[a]	0.2[a]	2.1[a]
Acarbose	2.0[a]	1.7[a]	155[a]

[a] Lit. 9.
[b] Inhibitory activities of **1** against sucrase and isomaltase were re-examined in this study as references.
[c] Values in parentheses indicate inhibition (%) at the corresponding concentrations (μM).



Scheme 6. Plausible mechanism for formation of **23** and 24.

on the inhibitory activity. Thus, in ponkoranol series, all the four compounds (**3**, **7**, **3′-*epi*-7**, and **5′-*epi*-7**) showed potent inhibitory activities irrespective of existence of the sulfate moiety at C3′ and also of stereochemistry at 3′ and/or 5′. Of the four, **3′-*epi*-7** was most potent, and showed almost the same inhibitory abilities as voglibose against all enzymes. Thus, we comment **3′-*epi*-7** is the most potent inhibitor in this class of molecules to date.

3. Conclusions

In conclusion, by intensive exploratory studies on *Salacia* extracts, two prognosticated constituents, neoponkoranol (**7**) and neosalaprinol (**8**), have been isolated. The structures of **7** and **8** were unambiguously identified by comparison of their physical and spectral data with those reported or with authentic specimens alternatively synthesized. Thus, all the predicted or speculated neo-type members of the sulfonium salt so far were finally extracted out successively. One of the two newly isolated sulfonium salts (**7**) showed potent inhibitory activity against three enzymes, and its 3′-epimer (**3′-*epi*-7**) was found to be the most potent inhibitor against rat small intestinal α-glucosidases so far in this class of molecules. Epimerization at C′2-position resulted in losing completely the activity even against isomaltase. Further SAR studies on this series of compounds for the stronger α-glucosidase inhibitory activity and selectivity to glucosidases are in progress.

4. Experimental

4.1. General experimental procedures

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 JNM-ECA 500 (500 MHz ^{1}H, 125 MHz ^{13}C) or 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) spectrometers. Chemical shifts (δ) and coupling constants (J) are given in ppm and Hz, respectively. DSS was used as an internal standard in the measurement of NMR spectra in D_2O, and TMS was used otherwise mentioned. 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 silica gel BW-200. All the organic extracts were dried over anhydrous sodium sulfate prior to evaporation.

4.2. Isolation of Neoponkoranol (7) and Neosalaprinol (8)

Dried stems of *S. chinensis* (15.0 kg) originated from Thailand were extracted twice with water (150 L) under reflux for 2 h. Evaporation of the water under reduced pressure provided a extract (1.48 kg), which (1.00 kg) was then dissolved in water (10 L) and centrifuged at 3000 rpm for 10 min. The supernatant was subjected to Diaion HP-20 column chromatography (4.0 kg, $H_2O \rightarrow$ MeOH, twice) to give a water-eluted fraction (405.6 g) and a methanol-eluted fraction (197.8 g). An aliquot of the H_2O-eluted fraction (25.0 g) was dissolved in MeCN/H_2O (50:50, v/v, 500 mL) and centrifuged at 3000 rpm for 10 min, then the supernatant was subjected to column chromatography [Chromatorex NH, 2.0 kg, MeCN/H_2O (50:50 → 20:80, v/v) → H_2O] to give eight fractions [Fr. 1 (5.91 g), Fr. 2 (2.84 g), Fr. 3 (0.88 g), Fr. 4 (0.90 g), Fr. 5 (0.29 g), Fr. 6 (1.22 g), Fr. 7 (0.68 g), and Fr. 8 (6.28 g)]. The fraction 2 (0.80 g) was purified by HPLC [detection: RI, column: Daisopak-SP-120–5-ODS-BP (20 mm id × 250 mm), mobile phase: H_2O and 0.1% (v/v) aqueous AcOH] to give neosalaprinol (**8**, 1.7 mg, 0.00096%), the ^{1}H and ^{13}C NMR spectral properties of which were in accord with those of an authentic specimen synthesized alternatively. The fraction 5 (0.28 g) was purified by HPLC [detection: RI, column: Daisopak-SP-120-5-ODS-BP (20 mm id × 250 mm), mobile phase: H_2O and 0.1% (v/v) aqueous AcOH] to give neoponkoranol (**7**, 10.1 mg), the ^{1}H and ^{13}C NMR spectral properties of which were in accord with those of an authentic specimen synthesized alternatively.

4.3. Synthesis of 1,4-dideoxy-1,4-{(*R*)-[(2*S*)-2,3-dihydro- xypropyl]episulfoniumylidene}-D-arabinitol Chloride (Neosalaprinol 8) and its 2′-epimer (2′-*epi*-8)

4.3.1. Acidic methanolysis of salaprinol (4) and 2′-epimer of salaprinol (2′-*epi*-4)

A mixture of salaprinol[10c] (**4**, 2 mg, 0.0066 mmol) and 5% methanolic hydrogen chloride (1 mL) was stirred at 50 °C for 2 h. The mixture was condensed to give a colorless oil (2.1 mg), which was then treated with ion exchange resin IRA 400J (Cl^- form, 20 mg) in methanol (1 mL) at room temperature for 1 h. The resins were filtered off and washed with methanol. The combined filtrate and the washings were condensed to give neosalaprinol (**8**) as a colorless oil (1.5 mg, 87%), $[\alpha]_D^{25}$ +18.0 (c 0.1, CH_3OH). IR (neat): 3302, 1072, 1063, 1020 cm^{-1}. ^{1}H NMR (700 MHz, CD_3OD) δ: 3.57 (1H, dd, J = 11.4, 5.8, H-3′a), 3.64 (1H, dd, J = 11.4, 4.6, H-3′b), 3.65 (1H, dd, J = 13.0, 8.9, H-1′a), 3.75 (1H, dd, J = 13.0, 3.2, H-1′b), 3.84 (1H, dd, J = 12.8, 3.4, H-1a), 3.87 (1H, dd, J = 12.8, 1.8, H-1b), 3.93 (1H, dd, J = 11.1, 9.2, H-5a), 4.01 (1H, br s dd, J = ca. 9.2, 5.4, H-4), 4.04 (1H, dd, J = 11.1, 5.4, H-5b), 4.11 (1H, dddd, J = 8.9, 5.8, 4.6, 3.2, H-2′), 4.37 (1H, dd, J = ca. 1.5, 1.5, H-3), 4.62 (1H, ddd, J = ca. 3.4, 1.8, 1.5, H-2), ^{13}C NMR (175 MHz, CD_3OD) δ: 51.5 (C-1′), 52.0 (C-1), 61.0 (C-5), 65.6 (C-3′), 69.6 (C-2′), 73.7(C-4), 79.5(C-2), 79.6 (C-3). FABMS m/z: 225 $[M-Cl^-]^+$ (pos). FAB-HRMS m/z: 225.0758 ($C_8H_{17}O_5S$ requires 225.0796).

In a similar manner, 2′-epimer of salaprinol[10c] (**2′-*epi*-4**, 2 mg, 0.0066 mmol) was derived to the corresponding sulfonium chloride (**2′-*epi*-8**, 1.6 mg, 88%) as a colorless oil, $[\alpha]_D^{23}$ −11.4 (c 0.83, CH_3OH). IR (neat): 3385, 1641, 1456, 1417, 1258, 1067, 1047 cm^{-1}. ^{1}H NMR (700 MHz, CD_3OD) δ: 3.58 (1H, dd, J = 11.4, 5.8, H-3′a), 3.64 (1H, dd, J = 11.4, 4.6, H-3′b), 3.70 (1H, dd, J = 13.0, 7.4, H-1′a), 3.72 (1H, dd, J = 13.0, 4.4, H-1′b), 3.82 (1H, dd, J = ca. 12.8, 2.5, H-1a), 3.85 (1H, dd, J = ca. 12.8, 3.0, H-1b), 3.95 (1H, dd, J = 11.6, 9.0, H-5a), 4.04 (1H, dd, J = 11.6, 5.8, H-5b), 4.07–4.10 (1H, m, H-4), 4.08–4.13 (1H, m, H-2′), 4.40 (1H, dd, J = ca. 2.5, 1.5, H-3), 4.62 (1H, ddd, J = ca. 3.0, 2.5, 2.5, H-2). ^{13}C NMR (175 MHz, CD_3OD) δ: 50.8 (C-1), 50.9 (C-1′), 61.1 (C-5), 65.5 (C-3′), 69.4 (C-2′), 73.5 (C-4), 79.4 (C-2), 79.8 (C-3). FABMS m/z: 225 $[M-Cl^-]^+$ (pos). FAB-HRMS m/z: 225.0759 ($C_8H_{17}O_5S$ requires 225.0796).

4.3.2. 2,3,5-Tri-*O*-benzyl-1,4-dideoxy-1,4-{(*R*)-[(2*S*)-2,3-dihydroxypropyl]episulfoniumylidene}-D-arabinitol chloride (13)

To a solution of (*S*)-glycidol (**11**, 35 mg, 0.47 mmol) and thiosugar (**12**, 100 mg, 0.24 mmol) in dichloromethane (2 mL) was added tetrafluoroboric acid dimethyl ether complex (64 μL, 0.53 mmol), and the mixture was stirred at −45 °C for 2 h, and then at room temperature for another 14 h. The reaction mixture was condensed under reduced pressure to give a colorless oil (195 mg), which was used in the next step without purification. The oil (190 mg) was treated with IRA 400J (Cl^- form, 2.10 g) in methanol (7 mL) at room temperature for 1 h. The resins were filtered off and washed with methanol. The combined filtrate and the washings were condensed to give a colorless oil (170 mg), which on column chromatography ($CHCl_3 \rightarrow CHCl_3$/MeOH, 50/1 → 20/1 → 10/1) gave title compound (**13**) as a colorless oil (56.0 mg, 44%), $[\alpha]_D^{23}$ +14.8 (c 0.65, $CHCl_3$). IR (neat): 3312, 1497, 1456, 1398, 1364, 1094, 1072 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 1.98 (1H, br s, OH), 3.73 (1H, dd, J = 12.0, 3.2, H-3′a), 3.78 (1H, dd,

J = 10.0, 7.2, H-5a), 3.83 (1H, dd, *J* = 10.0, 6.4, H-5b), 3.84 (1H, dd, *J* = 12.0, 5.2, H-3′b), 3.90 (1H, br d, *J* = ca. 12.4, H-1′a), 3.97 (1H, br dd, *J* = ca. 13.2, 2.0, H-1a), 4.11 (1H, br d, *J* = ca. 12.4, H-1′b), 4.23 (1H, br d, *J* = ca. 13.2, H-1b), 4.27 (1H, br s, H-3), 4.27–4.31 (1H, br m, H-2′), 4.31–4.36 (1H, br m, H-4), 4.40/4.50 (each 1H, d, *J* = 11.6, PhC*H*$_2$), 4.45–4.47 (1H, br m, H-2), 4.48/4.57 (each 1H, d, *J* = 12.0, PhC*H*$_2$), 4.57/4.62 (each 1H, d, *J* = 12.0, PhC*H*$_2$), 5.97 (1H, br, OH), 7.13–7.35 (15H, m, arom.). ^{13}C NMR (175 MHz, $CDCl_3$) δ: 48.6 (C-1), 51.2 (C-1′), 64.2 (C-3′), 65.0 (C-4), 67.0 (C-5), 68.7 (C-2′), 71.9/72.3/73.6 (PhCH_2), 82.4 (C-2), 82.6 (C-3), 127.96/127.98/128.1/128.3/128.4/128.5/128.6/128.7/128.8 (d, arom.), 135.9/136.1/136.9 (s, arom.). FABMS *m/z*: 495 $[M-Cl^-]^+$ (pos.).

4.3.3. Hydrogenolysis of 13 (Neosalaprinol 8)

A suspension of 10% Pd-C (50 mg) in 80% aqueous acetic acid (1.0 mL) was pre-equilibrated with hydrogen. To the suspension was added a solution of sulfonium salt (**13**, 35.0 mg, 0.066 mmol) in 80% aqueous acetic acid (1.0 mL), and the mixture was hydrogenated at 60 °C under atmospheric pressure for 6 h until uptake of hydrogen ceased. The catalysts were filtered off and washed with methanol. The combined filtrate and the washings were evaporated, and co-evaporated with benzene to give a colorless oil (16.5 mg), which on column chromatography (AcOEt/MeOH, 10:1 → AcOEt/MeOH/H_2O, 20:4:1 → 10:4:1) gave title compound (**8**) as a colorless oil (14.6 mg, 85%), the ^{1}H and ^{13}C NMR spectroscopic properties of which were in accord with those of a specimen synthesized by acidic methanolysis of **4**.

4.4. Syntheses of Neoponkoranol (7) and its 3′- and 5′-epimers

4.4.1. 1,2:3,4-Di-*O*-isopropylidene-6-*O*-trifluoromethanesulfonyl-α-D-galactopyranose (15)

Under argon atmosphere, to a solution of 2,6-lutidine (1.1 mL, 4.5 mmol) in dry dichloromethane (35 mL) was added trifluoromethanesulfonic anhydride (Tf_2O, 1.8 mL, 4.5 mmol) at −20 °C. After 5 min, a solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**14**, 780 mg, 3.0 mmol) in dichloromethane (40 mL) was added dropwise to the solution at −20 °C. The resulting solution was stirred at −20 °C for 5 min, and then at 0 °C for another 30 min. The mixture was poured into ice-cooled water and extracted with dichloromethane. The extract was condensed under reduced pressure to give a pale yellow oil (1.9 g), which on column chromatography (*n*-hexane/AcOEt, 20:1) gave title compound (**15**) as a colorless oil (1.10 g, 94%), $[\alpha]_D^{25}$ −44.6 (*c* 1.8, $CHCl_3$). IR (neat): 1416, 1385, 1250, 1211, 1150, 1119, 1073, 1015 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.337/1.343/1.45/1.53 [each 3H, s, (CH_3)$_2$C], 4.11 (1H, ddd, *J* = 7.2, 4.7, 2.0, H-5), 4.25 (1H, dd, *J* = 8.0, 2.0, H-4), 4.36 (1H, dd, *J* = 5.0, 2.6, H-2), 4.58 (1H, dd, *J* = 10.5, 7.2, H-6a), 4.64 (1H, dd, *J* = 10.5, 4.7, H-6b), 4.66 (1H, dd, *J* = 8.0, 2.6, H-3), 5.54 (1H, d, *J* = 5.0, H-1). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.4/24.8/25.8/25.9 [(*C*H_3)$_2$C], 66.0 (C-5), 70.2 (C-2), 70.4 (C-4), 70.6 (C-3), 74.6 (C-6), 96.1 (C-1), 109.1/110.1 [(CH$_3$)$_2$*C*], 118.6 (q, *J* = 318, *C*$F_3SO_3^-$). FABMS *m/z*: 393 $[M+H]^+$ (pos).

4.4.2. 2,3,5-Tri-*O*-benzyl-1,4-dideoxy-1,4-[(*S*)-(1,2:3,4-di-*O*-isopropylidene-6-deoxy-α-D-galactopyranos-6-yl)episulfoniumylidene]-D-arabinitol trifluoromethanesulfonate (16)

Under argon atmosphere, a mixture of triflate (**15**, 1.0 g, 2.55 mmol), thiosugar (**12**, 710 mg, 1.69 mmol), and THF (10 mL) was stirred at 40 °C for 15 h. The reaction mixture was condensed under reduced pressure to give a pale yellow oil (1.7 g), which on column chromatography ($CHCl_3$/MeOH, 200:1) gave title compound (**16**) as a colorless oil (1.05 g, 76%), $[\alpha]_D^{25}$ −71.2 (*c* 1.96, $CHCl_3$). IR (neat): 1454, 1385, 1262, 1215, 1157, 1069, 1030, 1003 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 1.31 [6H, s, (CH_3)$_2$C], 1.35/1.56 [each 3H, s, (CH_3)$_2$C], 3.77 (1H, dd, *J* = 13.4, 4.2, H-1a), 3.78 (1H, dd, *J* = 13.4, 9.0, H-6′a), 3.82 (1H, dd, *J* = 13.4, 2.6, H-1b), 3.86 (1H, dd, *J* = 10.0, 8.3, H-5a), 3.94 (1H, dd, *J* = 10.0, 6.6, H-5b), 4.14 (1H, dd, *J* = 13.4, 3.0, H-6′b), 4.31 (1H, dd, *J* = 5.0, 2.6, H-2′), 4.32–4.35 (1H, m, H-4), 4.34 (1H, dd, *J* = 7.8, 1.8, H-4′), 4.38 (1H, ddd, *J* = 9.0, 3.0, 1.8, H-5′), 4.43/4.45 (each 1H, d, *J* = 11.8, PhC*H*$_2$), 4.44 (1H, m, H-3), 4.50–4.52 (1H, m, H-2), 4.51/4.63 (each 1H, d, *J* = 11.8, PhC*H*$_2$), 4.62 (1H, dd, *J* = 7.8, 2.6, H-3′), 4.55/4.58 (each 1H, d, *J* = 11.8, PhC*H*$_2$), 5.42 (1H, d, *J* = 5.0, H-1′), 7.16–7.34 (15H, m, arom.). ^{13}C NMR (175 MHz, $CDCl_3$) δ: 24.1/24.8/25.77/25.83 [CH_3]$_2$C], 47.4 (C-6′), 48.6 (C-1), 64.7 (C-4), 65.3 (C-5′), 66.9 (C-5), 70.3 (C-2′), 70.6 (C-3′), 71.1 (C-4′), 72.2/72.3/73.6 (PhCH_2), 82.4 (C-3), 83.3 (C-2), 96.1 (C-1′), 109.6/109.8 [(CH$_3$)$_2$*C*], 120.7 (q, *J* = 319, *C*$F_3SO_3^-$), 127.96/128.06/128.3/128.45/128.49/128.52/128.7(2xC)/128.72 (d, arom.), 135.9/136.1/137.0 (s, arom.). FABMS *m/z*: 663 $[M-CF_3SO_3^-]^+$ (pos.), 149 $[CF_3SO_3]^-$ (neg.)

4.4.3. 1,4-Dideoxy-1,4-{(*R*)-[(2*S*,3*R*,4*R*,5*S*)-2,3,4,5,6-pentahydroxyhexyl]episulfoniumylidene}-D-arabinitol chloride (3′-*epi*-7)

A suspension of 10% Pd-C (600 mg) in 30% aqueous TFA solution (15 mL) was pre-equilibrated with hydrogen. To the suspension was added a mixture of compound **16** (340 mg, 0.42 mmol), TFA (5 mL) and 1,4-dioxane (10 mL). The resulted mixture was hydrogenated at 50 °C under atmospheric pressure until uptake of hydrogen ceased. The catalyst was filtered off and washed with a mixture of methanol and water. After the combined filtrate and the washings were condensed under reduced pressure, the residue (245 mg) was washed with dichloromethane to give a colorless oil (230 mg), which was treated with IRA 400J (Cl^- form, 2.5 g) in methanol (3 mL) at room temperature for 3 h. The resins were filtered off and washed with methanol. The filtrate and the washings were combined and condensed under reduced pressure to give a colorless oil (200 mg), which was treated with $NaBH_4$ (130 mg, 3.4 mmol) in water (15 mL) at 0 °C for 20 min. The mixture was acidified with 2 M hydrochloric acid to pH ca. 4, and condensed under reduced pressure to give a white solid (320 mg), which on column chromatography ($CHCl_3$/MeOH, 10:1 → 4:1) gave title compound (**3′-*epi*-7**) as colorless amorphous (74.0 mg, 50% yield from **16**), $[\alpha]_D^{25}$ −38.6 (*c* 1.13, CH_3OH). IR (neat): 3383, 1669, 1418, 1317, 1204, 1140, 1074, 1046, 1030, 843, 802, 723, 666 cm^{-1}. ^{1}H NMR (700 MHz, D_2O) δ: 3.66–3.70 (2H, m, H-3′ and H-4′), 3.69 (2H, d, *J* = ca. 6.4, H-6′a and H-6′b), 3.79 (1H, dd, *J* = 13.5, 3.0, H-1′a), 3.89 (1H, dd, *J* = 13.5, 9.4, H-1′b), 3.90 (1H, dd, *J* = 13.3, 4.0, H-1a), 3.92 (1H, dd, *J* = 13.3, 3.2, H-1b), 3.960 (1H, td, *J* = 6.4, 0.8, H-5′), 3.962 (1H, dd, *J* = 12.5, 9.4, H-5a), 4.09 (1H, ddd, *J* = 9.4, 5.0, 3.2, H-4), 4.15 (1H, dd, *J* = 12.5, 5.0, H-5b), 4.45 (1H, dd, *J* = 3.2, 3.2, H-3), 4.48 (1H, ddd, *J* = 9.4, 3.0, 1.0, H-2′), 4.76 (1H, ddd, *J* = ca. 4.0, 3.2, 3.2, H-2). ^{13}C NMR (175 MHz, D_2O) δ: 50.7 (C-1), 53.2 (C-1′), 61.9 (C-5), 65.7 (C-6′), 68.8 (C-2′), 72.0 (C-4′), 72.3 (C-4), 72.5 (C-5′), 73.6 (C-3′), 79.5 (C-2), 80.1 (C-3). FAB-MS *m/z*: 315 $[M-Cl^-]^+$ (pos). FAB-HRMS *m/z*: 315.1129 ($C_{11}H_{23}O_8S$ requires 315.1114).

4.4.4. Benzyl 2,3,4-tri-*O*-benzyl-6-*O*-trifluoromethanesulfonyl-β-D-glucopyranoside (18)

In a manner similar to that used for the synthesis of triflate (**15**: **4.4.1.**), benzyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranoside[17] (**17**, 250 mg, 0.46 mmol) was derived to the corresponding triflate (**18**, 282 mg, 91%) as a colorless oil, $[\alpha]_D^{24}$ +11.0 (*c* 1.13, $CHCl_3$). IR (neat): 1456, 1377, 1308, 1213, 1148, 1073, 963 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 3.44 (1H, dd, *J* = 10.0, 9.0, H-4), 3.52 (1H, dd, *J* = 9.0, 7.6, H-2), 3.56 (1H, ddd, *J* = 10.0, 6.2, 2.0, H-5), 3.67 (1H, dd, *J* = 9.0, 9.0, H-3), 4.41 (1H, dd, *J* = 10.6, 6.2, H-6a), 4.52 (1H, d, *J* = 7.6, H-1), 4.56/4.71 (each 1H, d, *J* = 11.0, PhC*H*$_2$), 4.58 (1H, dd, *J* = 10.6, 2.0, H-6b), 4.66/4.92 (each 1H, d, *J* = 11.7, PhC*H*$_2$), 4.77/4.952 (each 1H, d, *J* = 11.0, PhC*H*$_2$), 4.89/4.956 (each 1H, d, *J* = 11.0, PhC*H*$_2$), 7.23–7.37 (20H, m, arom.). ^{13}C NMR (175 MHz,

$CDCl_3$) δ: 71.1 (PhCH$_2$), 72.3 (C-5), 74.7 (C-6), 74.9/75.0/75.7 (PhCH$_2$), 76.3 (C-4), 82.0 (C-2), 84.4 (C-3), 102.0 (C-1), 118.6 (q, J = 317, CF_3SO_3), 127.8/127.9/128.0/128.1/128.16/128.23/128.3/128.39(2xC)/ 128.44/128.5/128.7 (d, arom.), 136.9/137.2/138.12/138.16 (s, arom.). FABMS m/z: 695 $[M+Na]^+$ (pos.).

4.4.5. 2,3,5-Tri-*O*-benzyl-1,4-dideoxy-1,4-[(*S*)-(1,2,3,4-tetra-*O*-benzyl-6-deoxy-β-D-glucopyranos-6-yl)episulfoniumylidene]-D-arabinitol trifluoromethanesulfonate (19)

Under argon atmosphere, a mixture of triflate (**18**, 230 mg, 0.34 mmol), thiosugar (**12**, 95 mg, 0.23 mmol) and THF (0.5 mL) was stirred at 40 °C for 7 h. The reaction mixture was condensed under reduced pressure to give a pale yellow oil (325 mg), which on column chromatography ($CHCl_3$/MeOH, 200:1) gave title compound (**19**) as a colorless oil (161 mg, 64%), $[\alpha]_D^{24}$ +9.9 (c 1.63, $CHCl_3$). IR (neat): 1589, 1497, 1454, 1362, 1250, 1223, 1153, 1100, 1030 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 3.364 (1H, dd, J = 8.8, 8.8, H-4′), 3.366 (1H, dd, J = 8.8, 7.8, H-2′), 3.43 (1H, dd, J = 13.0, 7.2, H-6′a), 3.61–3.64 (1H, m, H-1a), 3.636 (1H, dd, J = 8.8, 8.8, H-3′), 3.642 (1H, dd, J = 10.4, 8.8, H-5a), 3.69–3.73 (1H, m, H-1b), 3.70 (1H, dd, J = 10.4, 6.0, H-5b), 3.75 (1H, dd, J = 13.0, 2.8, H-6′b), 3.76 (1H, ddd, J = 8.8, 7.2, 2.8, H-5′), 4.04 (1H, br dd, J = ca. 8.8, 6.0, H-4), 4.18 (1H, dd, J = ca. 1.8, 1.8, H-3), 4.42/4.43/4.47 (each 1H, d, J = ca. 12.0, PhCH_2), 4.48 (1H, d, J = 7.8, H-1′), 4.49–4.51 (1H, m, H-2), 4.49/4.50/4.56/4.58/4.63/4.64/4.772/4.776/4.83/4.86/4.93 (each 1H, d, J = ca. 12.0, PhCH_2), 7.16–7.35 (35H, m, arom.). ^{13}C NMR (175 MHz, $CDCl_3$) δ: 47.2 (C-6′), 47.5 (C-1), 66.5 (C-5), 66.9 (C-4), 70.7 (C-5′), 72.0/72.2/72.4/73.6/74.3/74.8/75.7 (PhCH$_2$), 77.5 (C-4′), 81.7 (C-2′), 82.3 (C-2), 82.5 (C-3), 83.9 (C-3′), 103.1 (C-1′), 120.8 (q, J = 318, $CF_3SO_3^-$), 127.6/127.76/127.82/127.9/128.0/128.1/128.3(2xC)/128.37/128.44/128.49(2xC)/128.51(2xC)/128.59(2xC)/128.68/128.73/128.79/128.82/129.1 (d, arom.), 135.95/135.99/136.6/137.1/137.4/ 138.0(2xC) (s, arom.). FABMS m/z: 943 $[M-CF_3SO_3^-]^+$ (pos).

4.4.6. 1,4-Dideoxy-1,4-{(*R*)-[(2*S*,3*S*,4*R*,5*S*)-2,3,4,5,6-pentahydroxyhexyl]episulfoniumylidene}-D-arabinitol chloride (Neoponkoranol 7)

Hydrogenolysis of **19** (96 mg, 0.088 mmol) was conducted by employing 80% aqueous acetic acid (10 mL) as the solvent to give the de-benzylated intermediate, which was derived to title compound (**7**, 14 mg, 45% from **19**) by a similar manner used for the synthesis of **3′-*epi*-7** (**4.4.3.**) as a colorless solid, $[\alpha]_D^{23}$ +4.3 (c 0.60, H_2O), lit.[11h] $[\alpha]_D^{23}$ +4.0 (c 0.50, H_2O). ^{1}H NMR (700 MHz, D_2O) δ: 3.51 (1H, dd, J = 11.7, 5.6, H-6′a), 3.62 (1H, dd, J = 11.7, 3.6, H-6′b), 3.63 (1H, dd, J = 7.8, 1.8, H-3′), 3.68 (1H, dd, J = 13.2, 9.2, H-1′a), 3.71 (1H, ddd, J = ca. 5.6, 5.6, 3.6, H-5′), 3.73 (1H, dd, J = ca. 5.6, 1.8, H-4′), 3.79 (1H, dd, J = 13.0, 4.0, H-1a), 3.83 (1H, dd, J = 13.0, 3.0, H-1b), 3.850 (1H, dd, J = 11.0, 8.2, H-5a), 3.854 (1H, dd, J = 13.2, 3.2, H-1′b), 4.02 (1H, ddd, J = ca. 8.2, 4.8, 3.0, H-4), 4.04 (1H, dd, J = 11.0, 4.8, H-5b), 4.15 (1H, ddd, J = 9.2, 7.8, 3.2, H-2′), 4.36 (1H, dd, J = ca. 3.0, 3.0, H-3), 4.66 (1H, ddd, J = ca. 4.0, 3.0, 3.0, H-2). ^{13}C NMR (175 MHz, D_2O) δ: 50.9 (C-1), 52.7 (C-1′), 61.9 (C-5), 65.0 (C-6′), 70.2 (C-2′), 72.0 (C-4′), 72.7 (C-4), 75.4 (C-5′), 75.8 (C-3′), 79.7 (C-2), 80.3 (C-3).

4.4.7. Benzyl 2,3,4-tri-*O*-benzyl-6-*O*-trifluoromethanesulfonyl-α-D-mannopyranoside (21)

In a manner similar to that used for the synthesis of triflate (**15**: **4.4.1.**), benzyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside[18] (**20**, 1.0 g, 1.8 mmol) was derived to the corresponding triflate (**21**, 967 mg, 80%) as a colorless oil, $[\alpha]_D^{24}$ +43.6 (c 1.40, $CHCl_3$). IR (neat): 1454, 1416, 1246, 1208, 1146, 1115, 1030 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 3.80 (1H, dd, J = 3.1, 1.8, H-2), 3.85–3.90 (2H, m, H-4 and H-5), 3.97 (1H, dd, J = ca. 9.2, 3.1, H-3), 4.46/4.648 (each 1H, d, J = 12.0, PhCH_2), 4.57/4.59 (each 1H, d, J = ca. 11.6, PhCH_2), 4.58/4.97 (each 1H, d, J = 11.0, PhCH_2), 4.60 (1H, d, J = ca. 11.6, H-6a), 4.62 (1H, d, J = ca. 11.6, H-6b), 4.648/4.70 (each 1H, d, J = 12.4, PhCH_2), 4.91, (1H, d, J = 1.8, H-1), 7.37–7.24 (20H, m, arom.). ^{13}C NMR (175 MHz, $CDCl_3$) δ: 69.4/72.7/75.2/75.4 (PhCH$_2$), 70.0 (C-5), 72.1 (C-6), 73.6 (C-4), 74.3 (C-2), 80.0 (C-3), 97.0 (C-1), 118.6 (q, J = 319, $CF_3SO_3^-$), 127.6/127.7(3xC)/127.8/127.9/128.0/128.1/128.36/128.41/128.5/128.6 (d, arom.) 136.8/137.7/137.9/138.0 (s, arom.). FABMS m/z: 695 $[M + Na]^+$ (pos.).

4.4.8. 2,3,5-Tri-*O*-benzyl-1,4-dideoxy-1,4-[(*S*)-(1,2,3,4-tetra-*O*-benzyl-6-deoxy-α-D-mannopyranos-6-yl)episulfoniumylidene]-D-arabinitol Trifluoromethanesulfonate (22)

Under argon atmosphere, a mixture of triflate (**21**, 900 mg, 1.34 mmol), thiosugar (**12**, 370 mg, 0.88 mmol) and THF (2 mL) was stirred at 0 °C for 17 h. The reaction mixture was condensed under reduced pressure to give a pale yellow oil (1.25 g), which on column chromatography ($CHCl_3$/MeOH, 200:1) gave title compound (**22**, 364 mg, 37% from **12**), benzyl 2,4-di-*O*-benzyl-3,6-anhydro-α-D-mannopyranoside (**23**, 230 mg, 40% from **21**), and 1,4-dideoxy-1,4-[(*R*)-benzylepisulfoniumylidene]-D-arabinitol trifluoromethanesulfonate (**24**, 283 mg, 48% from **12**).

Compound **22**: Colorless oil, $[\alpha]_D^{25}$ +31.1 (c 2.04, $CHCl_3$). IR (neat): 1454, 1366, 1262, 1154, 1111, 1073, 1030 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 3.50 (1H, dd, J = 13.2, 6.0, H-6′a), 3.57 (1H, dd, J = 10.2, 7.6, H-5a), 3.59 (1H, dd, J = 10.2, 7.4, H-5b), 3.62 (1H, dd, J = 13.2, 3.4, H-6′b), 3.69 (1H, dd, J = 13.2, 2.8, H-1a), 3.70 (1H, dd, J = 13.2, 3.5, H-1b), 3.78 (1H, dd, J = 2.6, 2.1, H-2′), 3.80 (1H, dd, J = 9.4, 9.2, H-4′), 3.95 (1H, ddd, J = 9.2, 6.0, 3.4, H-5′), 3.96 (1H, dd, J = 9.4, 2.6, H-3′), 3.98 (1H, br dd, J = ca. 7.6, 7.4, H-4), 4.23–4.25 (1H, m, H-3), 4.46–4.88 (13H, m, PhCH_2), 4.58–4.60 (1H, m, H-2), 4.81 (1H, d, J = 2.1, H-1′), 4.87 (1H, d, J = 11.4, PhCH_2), 7.10–7.36 (35H, m, arom.). ^{13}C-NMR (175 MHz, $CDCl_3$) δ: 47.5 (C-6′), 47.6 (C-1), 66.37 (C-5), 66.41 (C-4), 68.8 (C-5′), 70.5/72.3(2xC)/72.4/73.1/73.3 (PhCH$_2$), 74.2 (C-4′), 74.5 (C-2′/PhCH$_2$), 79.6 (C-3′), 82.2 (C-3), 82.5 (C-2), 98.2 (C-1′), 120.8 (q, J = 318, $CF_3SO_3^-$), 127.7/127.8(2xC)/127.92/128.04(2xC)/128.1/128.2/128.3(2xC)/128.4(2xC)/128.49/128.53(2xC)/128.6(2xC)/128.7(2xC)/ 128.8/129.2 (d, arom.), 136.2/136.3/136.79/136.82/137.6/137.8- (2xC) (s, arom.). FABMS m/z: 943 $[M-CF_3SO_3^-]^+$ (pos.).

Compound **23**: Colorless oil, $[\alpha]_D^{25}$ + 46.8 (c = 1.12, $CHCl_3$). IR (neat): 1497, 1454, 1361, 1331, 1273, 1150, 1111, 1087, 1026 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.76 (1H, dd, J = 6.6, 1.6, H-2), 3.89 (1H, dd, J = 10.6, 2.9, H-6a), 3.91 (1H, dd, J = 6.0, 2.9, H-4), 4.04 (1H, d, J = 10.6, H-6b), 4.20 (1H, dd, J = 6.0, 1.6, H-3), 4.41 (1H, dd, J = 2.9, 2.9, H-5), 4.49/4.64 (each 1H, d, J = 12.0, PhCH_2), 4.57/4.72 (each 1H, d, J = 12.0, PhCH_2), 4.69/4.95 (each 1H, d, J = 12.0, PhCH_2), 5.06 (1H, d, J = 6.6, H-1), 7.24–7.41 (15H, m, arom.). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 69.5 (C-6), 70.9/72.0/72.7 (PhCH$_2$), 73.2 (C-5), 75.4 (C-3), 76.1 (C-2), 77.3 (C-4), 100.9 (C-1), 127.5/127.6/127.86/127.9/ 127.95/127.99/128.2/128.3/128.5 (d, arom.), 137.3/137.7/138.3 (s, arom.). FABMS m/z: 455 $[M + Na]^+$ (pos.).

Compound **24**: Colorless oil, $[\alpha]_D^{25}$ = –1.6 (c = 1.26, $CHCl_3$). IR (neat): 1497, 1454, 1366, 1339, 1273, 1215, 1154, 1088, 1026 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 3.58 (1H, dd, J = 10.2, 10.2, H-5a), 3.66 (1H, dd, J = 13.4, 3.8, H-1a), 3.67 (1H, dd, J = 10.2, 5.8, H-5b), 3.89 (1H, br dd, J = ca. 10.2, 5.8, H-4), 4.17 (1H, dd, J = ca. 1.5, 1.5, H-3), 4.28 (1H, dd, J = 13.4, 1.4, H-1b), 4.30/4.34 (each 1H, d, J = 11.8, PhCH_2), 4.41/4.58 (each 1H, d, J = 11.8, PhCH_2), 4.48–4.50 (1H, m, H-2), 4.49/4.55 (each 1H, d, J = 11.8, PhCH_2), 4.63 (1H, d, J = 12.7, H-1′a), 5.04 (1H, d, J = 12.7, H-1′b), 7.04–7.39 (20H, m, arom.). ^{13}C-NMR (175 MHz, $CDCl_3$) δ: 46.0 (C-1), 49.3 (C-1′), 63.2 (C-4), 66.8 (C-5), 72.0/72.6/73.4 (PhCH$_2$), 82.1 (C-2), 83.2 (C-3), 120.7 (q, J = 320, $CF_3SO_3^-$), 127.6/127.7/128.1/128.50/128.54/128.7/128.8(2xC)/ 128.9/129.7/130.3/130.7 (d, arom.), 135.7/

135.9/136.5(2xC) (s, arom.). FABMS *m/z*: 511 $[M–CF_3SO_3^-]^+$ (pos.), 149 $[CF_3SO_3]^-$ (neg.).

4.4.9. 1,4-Dideoxy-1,4-{(*R*)-[(2*S*,3*S*,4*R*,5*R*)-2,3,4,5,6-pentahydroxyhexyl]episulfoniumylidene}-D-arabinitol Chloride (5′-*epi*-7)

In a manner similar to that used for the synthesis of neoponkoranol (**7**: **4.4.3.**), sulfonium salt (**22**, 200 mg, 0.19 mmol) was derived to title compound (**5′-*epi*-7**, 27.0 mg, 42% from **22**) as a colorless solid, $[\alpha]_D^{24}$ + 9.7 (*c* = 0.30, H_2O), lit[11h] $[\alpha]_D^{23}$ + 11.0 (*c* = 0.3, H_2O). ^{1}H-NMR (700 MHz, D_2O) *δ*: 3.68 (1H, dd, *J* = 12.0, 6.0, H-6′a), 3.75 (1H, ddd, *J* = 9.0, 6.0, 2.8, H-5′), 3.78 (1H, dd, *J* = 9.0, 1.2, H-4′), 3.82 (1H, dd, *J* = 13.4, 9.0, H-1′a), 3.86 (1H, dd, *J* = 12.0, 2.8, H-6′b), 3.89 (1H, dd, *J* = 8.2, 1.2, H-3′), 3.91 (1H, dd, *J* = 13.0, 4.0, H-1a), 3.95 (1H, dd, *J* = 13.0, 3.0, H-1b), 3.97 (1H, dd, *J* = 11.2, 8.2, H-5a), 4.00 (1H, dd, *J* = 13.4, 3.2, H-1′b), 4.14 (1H, ddd, *J* = ca. 8.2, 5.0, 2.6, H-4), 4.16 (1H, dd, *J* = 11.2, 5.0, H-5b), 4.24 (1H, ddd, *J* = 9.0, 8.2, 3.2, H-2′), 4.47 (1H, dd, *J* = ca. 3.0, 2.6, H-3), 4.78 (1H, ddd, *J* = ca. 4.0, 3.0, 3.0, H-2). ^{13}C NMR (175 MHz, D_2O) δ: 50.8 (C-1), 53.1 (C-1′), 61.9 (C-5), 65.7 (C-6′), 70.0 (C-2′), 71.6 (C-4′), 72.7 (C-4), 73.3 (C-5′), 74.3 (C-3′), 79.7 (C-2), 80.2 (C-3).

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