JOC The Journal of Organic Chemistry

Article

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b02566 • Publication Date (Web): 30 Nov 2017

Just Accepted

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Diastereoselective synthesis of salacinol-type α-glucosidase inhibitors

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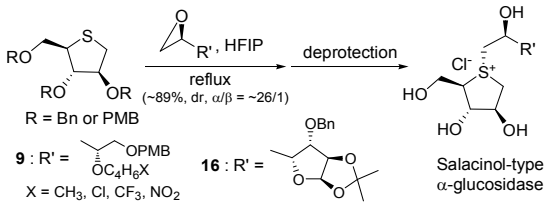


Abstract

A facile and highly diastereoselective approach towards the synthesis of potent salacinol-type α-glucosidase inhibitors, originally isolated from plants of the genus "*Salacia*", was developed using the *S*-alkylation of thiosugars with epoxides in HFIP (~90%, dr, α/β = ~26/1). The dr ratio of the product was significantly improved by the protocol as compared to that of the conventional *S*-alkylation of thiosugars (dr, α/β = ~8/1). The protocol could be used for gram scale synthesis of the desired compounds. The 3'-*O*-benzylated salacinol analogs, which are the most potent *in vitro* inhibitors to date, were synthesized and evaluated *in vivo*; all analogs suppressed blood glucose levels in maltose–loaded mice, at levels comparable to those of the anti-diabetic agent, voglibose.

Introduction

At the end of 1990s, salacinol (**1**) was isolated from the roots and stems of *Salacia reticulata*, a plant that has been used for treating diabetes in Ayurvedic medicine. The α-glucosidase inhibitory activity of **1** was as strong as those of current antidiabetics, such as voglibose and acarbose.[1] Following the discovery of **1**, the side chain extended homologs, kotalanol (**2**)[2] and ponkoranol (**3**)[3] as well as their de-*O*-sulfonated versions neosalacinol (**4**),[4] neokotalanol (**5**),[5] and neoponkoranol (**6**)[6] were isolated from plants in the same genus in the form of sulfonium salts, and these compounds also exhibited antidiabetic activities (Fig. 1).

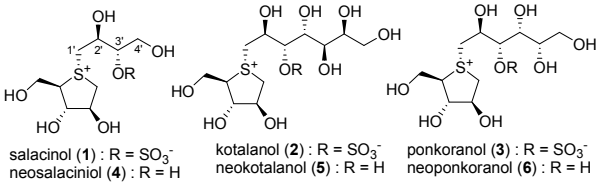
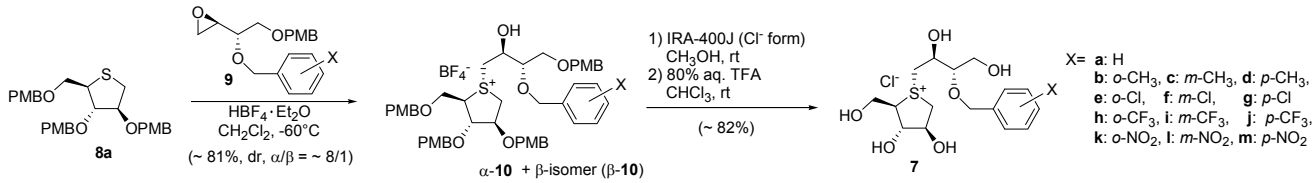


Figure 1. A new class of natural α-glucosidase inhibitors

Towards that end, human clinical trials revealed the efficacy of extracts from *Salacia reticulata* as a potential treatments for type 2 diabetes mellitus with minimal side effects.[7] Owing to the high inhibitory activities and intriguing structures of **1**–**6**, they have garnered considerable attention, and their total syntheses[8] as well as intensive structure-activity relationship (SAR) studies[9] have been carried out worldwide on this class of α-glucosidase inhibitors; numerous analogs have been synthesized to date, and structural determinants of the glycosidase inhibitory activities have been clarified to some extent. However, no candidates with superior inhibitory activities to those of the original sulfonium salts **1**–**6** were developed until a series of neosalacinols (**7a**–**7m**) with 3'-*O*-(mono-substituted benzyl) groups were synthesized recently.[9b] Among them, *ortho*-substituted derivatives **7b**, **7e**, **7h**, and **7k** were found to be stronger inhibitors than the corresponding *meta*- and *para*-substituted ones, and their *in vitro* inhibitory activities (IC_{50} = 0.13–0.66 μM against rat intestinal maltase) were

significantly superior to those of parent compounds **1** and **4** [IC_{50} (μM): **1**, 5.2, **4**, 8.0], indicating that they are the most potent compounds among cyclic sulfonium species synthesized to date (Scheme 1).[9b]

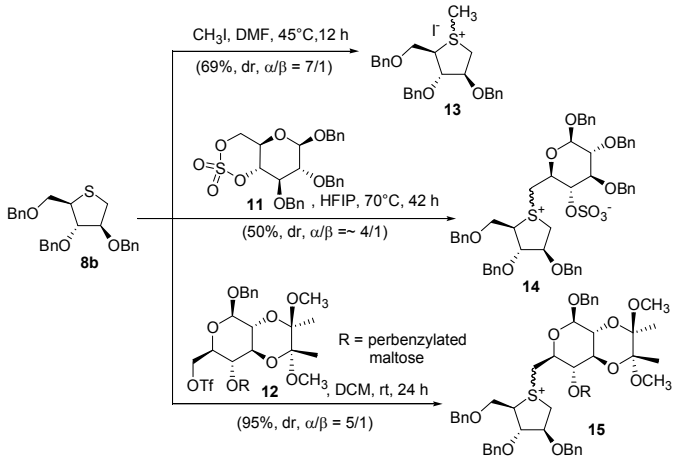
Scheme 1. Previous synthetic protocol for 7a–7m



Despite their potent inhibitory activities, synthetic issues associated with the originally reported synthesis of **7a**–**7m** severely limited access to these molecules, precluding the assessment of their effects *in vivo*. Specifically, the original synthesis of **7a**–**7m** utilized the acid mediated *S*-alkylation of thiosugars (**8a**) with epoxides (**9a**–**9m**) as a key reaction. However, the reaction exhibited a low diastereoselectivity, albeit good yields, and the diastereomeric ratio of the products **10** never exceed α/β = ~8/1. Separation of the α- and β-stereoisomers of **10** was quite difficult because of their extremely similar polarity, and repeated separations were required to obtain sufficient amounts of the desired α-isomer. As shown in Scheme 2, poor diastereoselectivity in the *S*-alkylation process in the conventional synthesis of salacinol analogs was also reported,[8c,10] in which both α- and β-stereoisomers were obtained as either a poorly separable or an inseparable mixture. This is a significant drawback of the thiosugar-*S*-alkylation-based approach toward salacinol-type sulfonium salts. Thus, a facile and effective protocol is required for these compounds, for which the conventional protocol is inefficient. In the course of our independent efforts to synthesize natural α-glucosidase inhibitor neoponkoranol (**6**), we discovered the unique reactivity of **8b** with epoxide **16** in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), in which the key sulfonium salt **α-17** was formed with excellent diastereoselectivity [dr, α/β = ~26/1, Scheme 3]. Herein, we describe a protocol that highlights the surprises associated with the highly

diastereoselective synthesis of α-isomer of sulfonium salt in HFIP. Additionally, the protocol successfully yielded potent *in vitro* inhibitors **7b**, **7e**, **7h**, and **7k** in good yields. Based on the evaluation of their activity in mice, **7b**, **7e**, **7h**, and **7k** were revealed to be stronger *in vivo* than natural seeds **1**–**6**.

Scheme 2. The key reaction in conventional synthesis of salacinol-analogues



Results and Discussion

Strong Brønsted acids such as CF_3SO_3H and HBF_4 are known to be good proton sources for the *S*-alkylation of sulfides with epoxides, and the anions function as counter anions for the sulfonium cation.[11] Due to the excellent proton-donating ability, the reaction rapidly (~2 h) proceeded to give the β-hydroxylated sulfonium salts in good yields. However, HFIP has not been used as an acid in *S*-alkylation to date because of its weak acidity (p*K*a = 9.3). Therefore, we set out to determine whether HFIP would function as an acid in the *S*-alkylation, and if the resultant sulfonium salts with $(CF_3)_2CHO^-$, which is a significantly stronger base than $CF_3SO_3^-$ or BF_4^-, could be isolated. Thus, the *S*-alkylation of **8b** (1.3 eq.) with **16** (1.0 eq.) was conducted in HFIP (Scheme 3). The reaction proceeded slowly under reflux; after 18 h, the nearly complete consumption of **16** was observed by TLC. After the removal of HFIP *in vacuo*, a mixture of **α-** and **β-17** (~26:1 ratio) was observed, as judged by the integration of the individual C6′ methine doublets in the ^{1}H NMR spectrum of the crude reaction mixture [Supporting Information (SI)-Fig. 1]. The ^{13}C NMR spectrum of the reaction mixture

showed 11 resonances likely related to the 11 carbons (C1–C5 and C1′–C6′) of the sulfonium moiety of **α-17**, along with two peaks corresponding to the 2 carbons of $(CF_3)_2CHO^-$, indicating the successful sulfonium ion formation (Table 1). Thus, HFIP was confirmed to function as an acid for the *S*-alkylation of **8b** and the conjugate anion of HFIP [$(CF_3)_2CHO^-$] could play the role as the counter anion for sulfonium ions; however, sulfonium salts **17** free from HFIP gradually decomposed into starting materials **8b** and **16** in $CDCl_3$ upon standing at room temperature, according to the NMR analysis. This suggested that purification of the sulfonium salts **17** by column chromatography would be impossible. As expected, attempts to purify the sulfonium salts resulted in unsuccessful recovery of the starting materials **8b** and **16**. The lability of intermediates **17** could be attributed to the proton abstraction from the hydroxyl at C2' by $(CF_3)_2CHO^-$, because the corresponding sulfonium salts with Cl^- are known to be stable. Thus, we abandoned the purification of **17** and tried to exchange $(CF_3)_2CHO^-$ with Cl^-. An attempt to exchange $(CF_3)_2CHO^-$ with Cl^- by IRA-400J (Cl^- form) resin led to the complete decomposition to the starting materials, whereas $(CF_3)_2CHO^-$ could be replaced with Cl^- by *in situ* treatment with methanolic HCl. Following the neutralization of excess HCl with $NaHCO_3$, separable chlorides **18** were obtained in good yields without significant loss in the diastereomeric ratio (dr, α/β = ~23/1). Notably, the analogous reaction between **8b** and **16** in the refluxing 2-propanol over 18 h left the starting materials unchanged, instead of yielding the desired product. Thereby, the acidity of HFIP was suggested to play a critical role in promoting this reaction. The FAB-MS spectrum of **α-18** obtained in positive mode showed peaks at *m/z* 713 due to the sulfonium cation moiety, and the compound exhibited a positive reaction in the Beilstein test, indicating the presence of chlorine in the compound. As all of the ^{13}C NMR data for **α-18** and **α-17** agreed well with each other (Table 1), the structure of **α-18** was confirmed by direct comparison with an authentic sample synthesized according to the procedure reported previously.[8f] Briefly, **8b** was subjected to HBF_4•$(C_2H_5)_2O$ mediated *S*-alkylation with **16** to give a ~7/1 diastereomeric mixture of **α-** and **β-19** in 85% combined yield. After

purification, the BF_4^- anion of **α-19** was exchanged with Cl^- using IRA-400J (Cl^- form) resin to produce **α-18** in 96% yield. Finally, the stereoconfiguration of the side chain of **α-18** relative to the $BnOCH_2$ moiety at C-4 was confirmed to be anti on the basis of NOE spectroscopy experiments (Scheme 3), indicating that α-facial *S*-alkylation exclusively took place on the sulfur atom.

Scheme 3. Synthesis of neoponkoranol (6) via the *S*-alkylation of 8b with 16

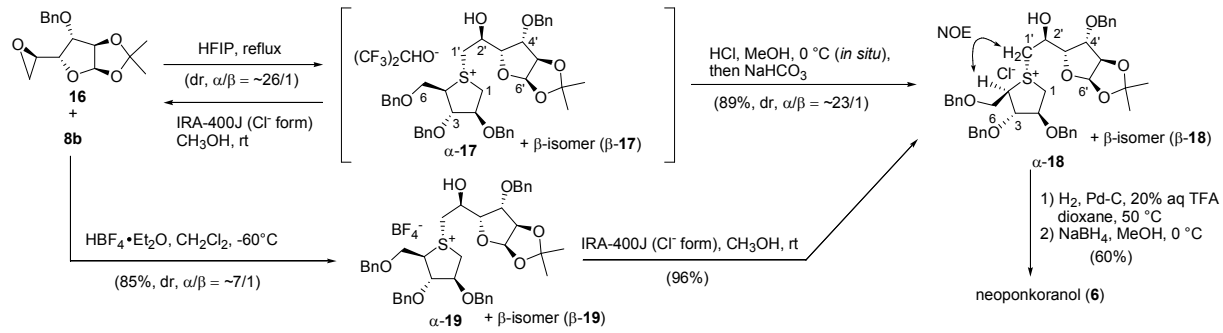


Table 1. ^{13}C NMR data (125 MHz, $CDCl_3$) for eleven carbons (C1–C5 and C1'–C6') of sulfonium salts α-17, α-18, and α-19

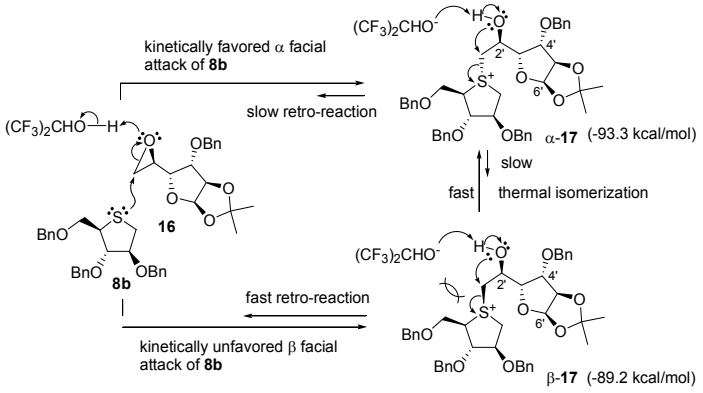
	C1	C2	C3	C4	C5	C1'	C2'	C3'	C4'	C5'	C6'
α-17[a]	48.3	82.3	81.9	66.9	66.5	51.6	65.0	82.4	81.3	82.1	105.1
α-18	48.3	82.3	82.2	66.5	66.8	52.1	64.9	82.1	81.0	82.8	105.0
α-19	48.0	82.4	82.2	67.1	66.6	51.3	65.4	81.9	81.0	82.4	105.1

[a]Two signal due to two carbons of $(CF_3)_2CHO^-$ moiety were also observed at δ_C 122.7 (q, J = 283 Hz) and 69.5 (hept, J = 28 Hz) (see SI-Fig. 1-2).

Next, we attempted to elucidate the mechanistic details behind the high diastereoselectivity in HFIP. The reaction between **8b** (1.3 eq.) and **16** (1.0 eq.) was conducted in HFIP-d_2 at 30 °C in a sealed tube. ^1H NMR indicated that the reaction was complete in ~42 h, giving a ~9/1 diastereomeric mixture of **α-** and **β-17**. The ratio of **α-** and **β-17** in the mixture was nearly unchanged at 30 °C after 6 h (SI-Fig. 2, 3), whereas the ratio dramatically increased and reached ~24/1 upon heating at 55–60 °C for 13 h. Notably, the re-formation of a small amount of **16** was detected after heating for 3 h, and to our surprise, the amount of re-formed **16** was nearly unchanged at around 2% during the last 6 h (SI-Fig. 4, 5). This

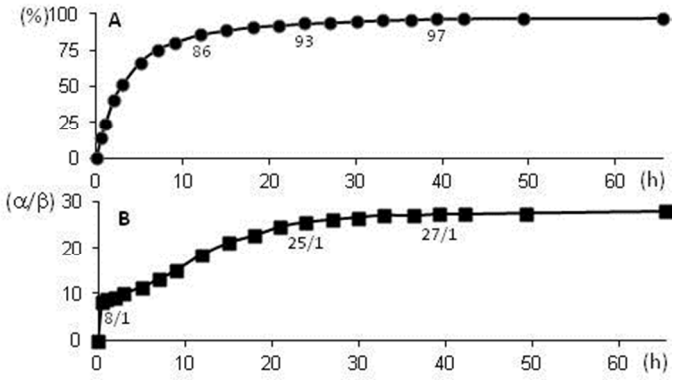
suggested that the *S*-alkylation and retro-reaction were at equilibrium at this temperature. On the basis of these results, we surmised that three pathways contributed to the highly diastereoselective formation of **α-17** in HFIP (Scheme 4): (1) *S*-alkylation would proceed with ~9/1 face-selectivity, mainly giving **α-17**; (2) the retro-reaction of **β-17** to starting materials **8b** and **16** was approximately four times faster than that of **α-17** (SI-Fig. 1). The reaction would lead to the hydrogen abstraction of the hydroxyl at the C2′ position by $(CF_3)_2CHO^-$, and the resulting alkoxide at C2′ would participate in an intramolecular S_N2 attack on the C1′ carbon to give **8b** and **16**, which would subsequently react with each other. (3) The isomerization of the sulfonium center[12] from thermodynamically less stable **β-17** (–89.2 kcal/mol) to more stable **α-17** (–93.3 kcal/mol) was accelerated upon heating at 55–60 °C, increasing the α/β ratio. The proposed stability of the sulfonium structure was supported by the isomerization experiment of the corresponding chloride **β-18** to **α-18**, in which the ratio of α/β = ~9/1 increased to ~24/1 after heating at 55–60 °C in HFIP-d_2 for 14 h (SI-Fig. 6, 7). Thus, the reaction cycle consisting of the reversible *S*-alkylation and isomerization would be repeated until the highly diastereoselective formation of **α-17** was complete.

Scheme 4. Plausible mechanism for the diastereoselective formation of α-17 in HFIP



Given the reactivity observed in HFIP-d_2, we set out to develop a rapid and highly diastereoselective approach toward **α-17**. Thus, the reaction between **8b** (1.3 eq.) and **16** (1.0 eq.) in HFIP-d_2 was monitored by NMR spectroscopy. As shown in Fig. 2, after heating at 55–60 °C for 42 h, ~97% of **16** was consumed, and **α-17** (α/β = ~27/1) was formed exclusively. The conversion of **16** was nearly unchanged upon heating for another 23 h. On the contrary, the α/β ratio dramatically increased upon heating for 24 h (30 min: ~8/1→24 h: ~25/1), and was nearly unchanged after 41 h (65 h: ~28/1) (SI-Fig. 8, 9). Finally, in order to accelerate the *S*-alkylation rate, a mixture of **16** was treated with five equivalents of **8b** in non-deuterated HFIP. Heating the reaction mixture at reflux for 6 h followed by the usual work-up gave a ~23/1 mixture of **α-** and **β-18** in 89% yield. After chromatographic separation, the benzyl moieties of **α-18** were removed by hydrogenolysis, and the resulting crude hemiacetal was reduced with $NaBH_4$ to give neoponkoranol (**6**) in 60% yield (Scheme 3).

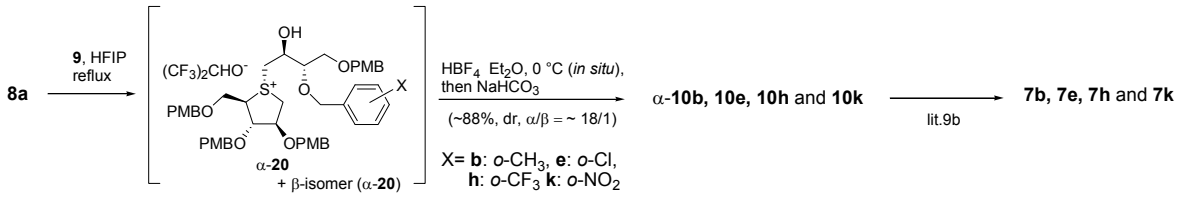
Figure 2. (A) Conversion % of 16 in the *S*-alkylation in HFIP-d_2 at 55–60°C, and (B) diastereomeric ratio of α- and β-isomer. Conversion % and dr ratio (α/β) were estimated by 500 MHz ^{1}H NMR spectrum (Time interval NMR spectra were given in SI-Fig. 8, 9)



With the conditions for the one-pot highly diastereoselective synthesis of the α-isomer in hand, we applied the reaction to the gram-scale production of intermediates for **7b**, **7e**, **7h**, and **7k** in order to evaluate the *in vivo* activity (Scheme 5). From epoxides **9b**, **9e**, **9h**, and **9k** (1.0–1.3 g), **α-20b**, **α-20e**,

α-20h, and **α-20k** were obtained predominantly with $(CF_3)_2CHO^-$ as the counter anion; the counter anion was then exchanged to BF_4^- by treating *in situ* with $HBF_4•(C_2H_5)_2O$ at 0 °C to give the corresponding sulfonium salts **α-10b**, **α-10e**, **α-10h**, and **α-10k** in good yields and good diastereoselectivities. After purification, they were converted to **7b**, **7e**, **7h**, and **7k** in around 80% yields (~800–950 mg) according to a previously reported method.[9b]

Scheme 5. Synthesis of 7a, 7b, 7e, 7h and 7k *via* the *S*-alkylation in HFIP



With suitable amounts of **7b**, **7e**, **7h**, and **7k** in hand, their α-glucosidase inhibitory activities were tested against human small intestinal maltase *in vitro*, and their potencies as inhibitors were compared with those of several reference standards, such as salacinol (**1**), neosalacinol (**4**), and three currently used antidiabetics (voglibose, acarbose, and miglitol). The synthesized analogs inhibited human small intestinal maltase more potently than **1**, **4**, and three commonly used antidiabetics (Table 2).

Table 2. E_{bind} (kcal/mol) to hNtMGAM, and IC_{50} and K_i values (μM) values against human intestinal maltase

Entry	Compound	E_{bind}[a]	IC_{50}	K_i
1	**7b** (*o*-CH_3)	–37.2	0.58	0.073
2	**7e** (*o*-Cl)	–41.6	0.11	0.023
3	**7h**(*o*-CF_3)	–37.5	0.22	0.035
4	**7k** (*o*-NO_2)	–38.9	0.15	0.015
5	Salacinol (**1**)	–37.0	4.9	0.44
6	Neosalacinol (**4**)	–36.4	9.0	1.2
7	Voglibose	–	1.3	0.17
8	Acarbose	–	16.7	2.6
9	miglitol	–	3.7	0.57

[a]lit[9b].

Among them, **7e**, **7h**, and **7k** showed strong *in vitro* inhibitory activities (IC_{50}: 0.11-0.22 μM), and were approximately 20–45 times more active than salacinol (**1**, IC_{50}: 4.9 μM), although their potency was weaker than the previously reported E_{bind} values[9b] of these molecules to hNtMGAM. The discrepancies between the predicted and obtained experimental results obtained in this study might be related to the existence of other catalytic domains such as sucrase-isomaltase (CtSI) and/or *C*-terminal maltase-glucoamylase (CtMGAM), which have been proven to affect the maltose hydrolysis.[13] On the contrary, the inhibition mode of these analogs was revealed to be competitive by Lineweaver-Burk plots of inhibition kinetics against human small intestinal maltase (SI-Fig. 10). The *K*i values were in the range of 15–73 nM, indicating that all 3′-*O*-benzylated analogs could function as superior competitive inhibitors against human small intestinal maltase. Next, the activities of the analogs were examined *in vivo* in mice. Following the oral administration of maltose, mice in the control group showed a maximum blood glucose levels after 30 min. On the contrary, oral administration (0.3 mg/kg) of **7b**, **7e**, **7h**, and **7k** prior to maltose loading significantly suppressed the blood glucose levels, indicating that these compounds are good *in vivo* α-glucosidase inhibitors. The degree of suppression by **7b**, **7e**, **7h**, and **7k** was superior to that of salacinol (**1**) (Table 3). Notably, **7b**, which was a weaker inhibitor than **7e**, **7h**, and **7k** *in vitro*, showed a nearly equal suppression of blood glucose levels *in vivo* to that of **7e**, **7h**, and **7k**. On the contrary, examination of dose-dependent effects indicated that the elevation in blood glucose levels in maltose-loaded mice was effectively suppressed by 0.1 mg/kg dose of **7k** and the potency was nearly equivalent to that of the antidiabetic, voglibose (Table 4). Thus, the 3'-*O*-sulfonium salts **7b**, **7e**, **7h**, and **7k** were revealed, for the first time, to be highly potent *in vivo* α-glucosidase inhibitors.

Table 3. Inhibitory effects of 7b, 7e, 7h, 7k and salacinol (1) on blood glucose levels in mice

Treatment	Dose (mg/kg, *po*)	N	Blood glucose (mg/dL)					
			0 min	15 min	30 min	60 min	120 min	180 min
Normal	—	4	77.8±5.0	99.0±6.2$^{\#\#}$	99.0±2.1$^{\#\#}$	98.3±2.8$^{\#\#}$	90.3±5.1	82.8±4.1
Control	—	8	70.8±5.5	195.5±10.0	196.3±10.7	158.1±9.8	100.6±4.3	90.4±6.1
Salacinol (**1**)	0.3	6	74.0±5.6	158.0±9.3**	165.8±5.8*	143.0±8.1	95.8±4.6	84.0±2.8
7b (*o*-CH_3)	0.3	6	72.7±3.7	124.8±3.2**	128.2±3.2**	127.5±6.6*	102.5±4.1	91.5±4.1
7e (*o*-Cl)	0.3	6	70.0±3.2	118.3±4.4**	130.3±4.9**	123.0±6.5**	96.2±4.9	82.2±5.4
7h (*o*-CF_3)	0.3	6	74.7±4.2	119.2±6.4**	130.5±9.0**	134.0±8.8	107.5±5.9	82.3±3.5
7k (*o*-NO_2)	0.3	6	77.8±3.0	116.5±2.7**	127.0±6.4**	125.8±4.3*	106.8±6.7	96.5±7.3

Each value represents the mean±SEM. Significantly different from the control: $^{*}p<0.05$, $^{**}p<0.01$, $^{\#}p<0.05$, $^{\#\#}p<0.01$. Normal group: administrated a distilled water; Control group: administrated a 10% (w/v) maltose solution (1 g/kg).

Table 4. Dose-dependent effect of 7k, salacinol (1) and voglibose on blood glucose levels in mice

Treatment	Dose (mg/kg, *po*)	N	Blood glucose (mg/dL)					
			0 min	15 min	30 min	60 min	120 min	180 min
Normal	—	4	53.3±3.6	71.0±3.7$^{\#\#}$	73.3±7.3$^{\#\#}$	80.3±8.4$^{\#\#}$	65.8±8.0$^{\#}$	63.0±5.4
Control	—	8	59.4±2.0	166.5±6.4	163.4±6.6	135.6±8.0	85.5±4.5	82.3±3.3
Voglibose	0.1	6	63.2±4.8	130.8±4.3**	135.3±8.9	124.0±9.6	80.3±3.3	73.0±5.0
	0.3	6	61.7±3.8	108.5±7.1**	119.2±10.4**	113.5±6.6	82.2±5.5	74.2±3.4
Salacinol (**1**)	0.3	6	63.5±5.4	137.8±11.8*	155.5±8.9	140.8±12.4	93.5±11.1	79.2±4.3
7k (*o*-NO_2)	0.03	6	62.5±2.8	161.8±5.9	162.3±8.2	131.0±6.2	81.3±6.1	74.5±3.6
	0.1	6	62.8±7.9	138.3±4.6*	142.5±7.9	127.5±3.5	85.8±4.0	79.2±4.4
	0.3	6	59.0±5.7	107.2±6.9**	98.5±7.1**	94.5±6.4**	71.3±5.0	67.8±3.9

Each value represents the mean±SEM. Significantly different from the control: $^{*}p<0.05$, $^{**}p<0.01$, $^{\#}p<0.05$, $^{\#\#}p<0.01$. Normal group: administrated a distilled water; Control group: administrated a 10% (w/v) maltose solution (1 g/kg).

In conclusion, we have developed an easy and highly diastereoselective synthetic protocol toward salacinol-type α-glucosidase inhibitors via the *S*-alkylation of thiosugars with epoxides in HFIP. Compared to the conventional protocol[9] for the *S*-alkylation of thiosugars, this method proved far more amenable to scale-up, enabling the preparation of large amounts of the key intermediates required to produce the desired inhibitors. During these studies, a cooperative mechanism consisting of reversible *S*-alkylation and thermal isomerization of the sulfonium salts was found to contribute to the highly diastereoselective formation of the intermediates. We have also established that sulfonium salts **7** are the most potent *in vivo* inhibitors among salacinol analogs synthesized to date. We have also proved that a series of sulfonium salts **7** are more potent *in vivo* inhibitors than the parent sulfonium salts **1**, and the potency was nearly equivalent to that of the antidiabetic agent voglibose.

EXPERIMENTAL SECTION

General Experimental Details. IR spectra were measured on a FT-IR spectrophotometer. NMR spectra were recorded on a FT-NMR spectrometers (^{1}H, 500 or 800 MHz; ^{13}C, 125 or 200 MHz). Chemical shifts (δ) and coupling constants (J) are given in ppm and Hz, respectively. TMS was used as an internal standard in the measurement of NMR spectra in $CDCl_3$, CD_3OD or HFIP-d_2. 1D NMR peak assignments were confirmed by COSY and HSQC spectra. Low-resolution and high-resolution mass spectra were recorded on a double-focusing mass spectrometer (FAB). Optical rotations were determined with a digital polarimeter. Column chromatography was performed over silica gel (45–106 μM). HPLC was performed on a DAISOPAK-SP120-5-ODS-BP (20x250 mm) with a refractive index detector. All the organic extracts were dried over anhydrous Na_2SO_4 prior to evaporation. Conformational energies of sulfonium structure of **α-** and **β-1**7 were calculated using MOPAC7 with AM1 Hamiltonian.

***S*-Alkylation of Thiosugar (8b, 1.3 eq.) with Epoxide (16) in HFIP.** A mixture of thiosugar (**8b**, 374 mg, 0.89 mmol), epoxide (**16**, 200 mg, 0.68 mmol), and HFIP (4 mL) was heated under reflux for 12 h. Removal of the solvent *in vacuo* left a colorless oil (580 mg). ^{1}H NMR spectrum of the crude mixture, which was immediately measured in $CDCl_3$ after evaporation of HFIP, indicated that the *S*-alkylation gave a ca. *ca*. 26/1 mixture of 1,4-dideoxy-1,4-[(*R*)-(6-deoxy-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranos-6-yl)episulfoniumylidene]-2,3,5-tri-*O*-benzyl-D-arabinitol 1,1,1,3,3,3-hexafluoroisopropoxide (**α-17**) and its β-isomer (**β-17**). After the crude mixture was allowed to stand at room temperature for 12 h in $CDCl_3$ in the NMR tube, the NMR spectrum of the resulting mixture indicated that the ratio of two isomers **α-17**/**β-17** changed to *ca*. 39/1 by decomposition of **α-17** and **β-17** to starting materials **8b** and **16.** ^{1}H- and ^{13}C-NMR spectra were

depicted in Supporing information Figures [(SI)-Figures 1-1 and 1-2]. ^{13}C NMR data for the major isomer **α-18** extracted from the spectrum of the crude mixture in $CDCl_3$ was summarized in Table 1.

NMR Monitoring Experiment.

*S-Alkylation of **8b** with **16** in HFIP-d_2 at 30 °C.* A mixture of **8b** (93.6 mg, 0.22 mmol), **16** (50 mmol, 0.17 mmol) and HFIP-d_2 (0.1 mL) was kept on standing at 30 °C in a test tube with tight cap. The reaction mixture, which was picked up (5 μL) at certain intervals (12 h, 24 h, 36 h, 42 h, 48 h), was diluted with HFIP-d_2 (0.6 mL), and ^1H NMR spectrum of the resulting solution was immediately measured by a 500 MHz NMR spectrometer. Time interval ^1H-NMR spectra were depicted in SI-Figures 2 and 3.

*Thermal Isomerisation of Sulfonium 1,1,1,3,3,3-Hexafluoroisopropoxide-d_1 (**17**) in HFIP-d_2.* In a sealed NMR test tube, a *ca*. 9/1 mixture of **α-17** and **β-17**, which was obtained by the aforementioned *S*-alkylation of **8b** with **16** (after 48 h at 30 °C in HFIP-d_2), was heated at 55–60 °C, and time interval ^1H NMR spectra (1 h, 3 h, 5 h, 7 h, 9 h, 13 h) were measured by a 500 MHz NMR spectrometer. Time interval ^1H-NMR spectra were depicted in SI-Figures 4 and 5.

*Thermal isomerisation of Sulfonium Cloride (**18**) in HFIP-d_2.* In a sealed NMR test tube, a *ca*. 9/1 mixture of 1,4-dideoxy-1,4-[(*R*)-(6-deoxy-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranos-6-yl)episulfoniumylidene]-2,3,5-tri-*O*-benzyl-D-arabinitol chloride (**α-18** and **β-18**, 55 mg) and HFIP-d_2 (0.6 mL) was heated at 55–60 °C, and time interval ^1H NMR spectra (2 h, 4 h, 5 h, 6 h, 8h, 11 h, 14 h) were measured by a 500 MHz NMR spectrometer. Time interval ^1H-NMR spectra were depicted in SI-Figures 6 and 7.

*S-Alkylation of **8b** with **16** in HFIP-d_2 at 60 °C.* In a sealed NMR test tube, a mixture of **8b** (46.8 mg, 0.11 mmol), **16** (25 mg, 0.085 mmol) and HFIP-d_2 (0.6 mL) was heated at 55–60 °C, and time

interval ^{1}H NMR spectra (0.5 h, 1 h, 2 h, 3 h, 5 h, 9 h, 12 h, 15 h, 18 h, 21 h, 24 h, 27 h, 33 h, 42 h, 65 h) were measured by a 500 MHz NMR spectrometer. Time interval ^{1}H-NMR spectra were depicted in SI-Figures 8 and 9.

*Synthesis of Sulfonium Chloride (**18**) through S-Alkylation of Thiosugar (**8b**, 5 eq) with Epoxide (**16**) in HFIP.* A mixture of thiosugar (**8b**, 1.44 g, 3.43 mmol), epoxide (**16**, 200 mg, 0.68 mmol), and HFIP (5 mL) was heated under reflux for 6 h. After being cooled with cold water, the reaction mixture was acidified with 5% methanolic hydrogen chloride to pH 3. The mixture was immediately neutralized with $NaHCO_3$ with ice cooling. The resulting suspension was filtered by suction, and the filter cake was washed with CH_2Cl_2. The combined filtrate and washings were condensed *in vacuo* to give a colorless oil (1.85 g), which on column chromatography ($CHCl_3$/MeOH = 100/1→30/1→10/1) gave **α-18** (391 mg, 76%), a *ca*. 2.5:1 mixture of **α-18** and **β-18** (67 mg, 13%), and thiosugar (**8b**, 1.1 g).

*Major isomer **α-18***: colorless amorphous. $[\alpha]^{24}_D$ –38.2 (*c* = 1.17, $CHCl_3$). IR (neat): 3379, 1076, 1115 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) *δ*: 1.29/1.47 [each 3H, s, C(C*H*$_3$)$_2$], 3.74 (2H, d-like, *J* = *ca*. 8.0, H-5a and H-5b), 4.04 (1H, dd, *J* = 12.6, 3.7, H-1'a), 4.08 (1H, dd, *J* = 12.6, 8.0 Hz, H-1'b), 4.17 (1H, br t-like, *J* = *ca*. 8.0, H-4), 4.19 (1H, br s-like, H-3), 4.20 (1H, d, *J* = 3.2 Hz, H-4'), 4.21 (1H, dd-like, *J* = *ca*. 13.0, 3.5, H-1a), 4.33 (1H, dd, *J* = 8.3, 3.2, H-3'), 4.39 (1H, dd d, *J* = 13.0, 1.8, H-1b), 4.43/4.55 (each 1H, d, *J* = 11.7, C*H*$_2$Ph), 4.45 (1H, br s-like, H-2), 4.46/4.58 (each 1H, d, *J* = 12.0, C*H*$_2$Ph), 4.56 (1H, d, *J* = 3.7, H-5'), 4.58 (2H, s, C*H*$_2$Ph), 4.62/4.75 (each 1H, d, *J* = 11.5, C*H*$_2$Ph), 4.63 (1H, ddd-like, *J* = *ca*. 8.3, 8.0, 3.7, H-2'), 5.66 (1H, br s, OH), 5.84 (1H, d, *J* = 3.7, H-6'), 7.13–7.42 (20H, m, arom.). ^{13}C-NMR (125 MHz, $CHCl_3$) *δ*: 26.2/26.8 [C(*C*H$_3$)$_2$], 48.3 (C-1), 52.1 (C-1'), 64.9 (C-2'), 66.5 (C-4), 66.8 (C-5), 71.8/72.3/73.1/73.5 (*C*H$_2$Ph), 81.0 (C-4'), 82.1 (C-3'), 82.2 (C-3), 82.3 (C-2), 82.8 (C-5'), 105.0 (C-6'), 112.1 [*C*(CH$_3$)$_2$], 127.79/127.88/127.93/128.08/128.14/128.2/128.4/128.5/128.6/128.7 (d, arom.),

135.7/135.8/136.6/137.4 (s, arom.). LRMS (FAB) *m/z*: 713 $[M–Cl]^+$. HRMS (FAB) *m/z*: $[M–Cl]^+$ Calcd for $C_{42}H_{49}O_8S$ 713.3148; Found 713.3123.

Minor isomer ***β-18*** *(NMR data extracted from the spectrum of a ca. 2.5:1 mixture)*: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.28/1.47 [each 3H, s, $C(CH_3)_2$], 3.72–3.80 (2H, m, H-1a and H-5a), 3.76–3.88 (2H, m, H-1a'a and H-5a), 4.13–4.24 (4H, m, H-1'b, H-3, H-4 and H-4'), 4.29 (1H, dd, J = 7.2, 2.9, H-3'), 4.37–4.39 (1H, m, H-2), 4.47–4.49 (1H, m, H-5'), 4.70–4.63 (1H, m, H-2'), 4.76–4.79 (1H, m, H-1b), 5.71 (1H, d, J = 3.7, H-6'), 4.37–4.64 (8H, m, CH_2Ph), 7.14–7.43 (20H, m, arom). ^{13}C-NMR (125 MHz, $CHCl_3$) δ: 26.2/29.6 [$C(CH_3)_2$], 43.9 (C-1'), 45.4 (C-1), 61.0 (C-4), 63.3 (C-2'), 65.2 (C-5), 72.3(2C)/73.1/73.4 (CH_2Ph), 81.3 (C-4'), 82.0 (C-3'), 82.6 (C-2), 82.7 (C-5'), 84.6 (C-3), 105.9 (C-6'), 112.0 [$(CH_3)_2C$], 127.9/128.4/128.6/128.74/other signals due to aromatic methine carbons overlapped with those of **α-18** (d, arom.), 135.8/136.0/136.3/137.5 (s, arom.).

Synthesis of Sulfonium Tetrafluoroborate (19) through *S*-Alkylation of Thiosugar (8b) with Epoxide (16) in the presence of HBF_4•Et_2O. To a mixture of **8b** (780 mg, 1.86 mmol), **16** (652 mg, 2.23 mmol) and CH_2Cl_2 (22 mL) was added tetrafluoroboric acid diethyl ether complex (HBF_4•Et_2O, 331 μL, 2.4 mmol) at –60 °C, and the mixture was stirred at –60 °C for 30 min. After the reaction was quenched with $NaHCO_3$, the resulting suspension was filtered by suction, and the filter cake was washed with CH_2Cl_2. The combined filtrate and washings were condensed *in vacuo* to give a colorless oil (1.53 g), which on column chromatography ($CHCl_3$/MeOH = 100/1→30/1→10/1) gave **8b** (1.1 g) and a mixture of 1,4-dideoxy-1,4-{(*R*)-[6-deoxy-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose-6-yl]episulfo-niumylidene}-2,3,5-tri-*O*-benzyl-D-arabinitol tetrafluoroborate (**α-19**, 650 mg, 44%) and a *ca*. 3:1 mixture of **α-19** and **β-19** (617 mg, 41%).

Major isomer ***α-19***: colorless amorphous. $[\alpha]^{23}_D$ –17.5 (c = 0.8, $CHCl_3$). IR (neat): 3480, 1072 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.29/1.47 [each 3H, s, $C(CH_3)_2$], 3.66 (1H, dd, J = 10.0, 10.0, H-5a),

3.73 (1H, dd, *J* = 10.0, 6.0, H-5b), 3.76 (1H, dd-like, *J* = *ca*. 13.5, 3.5, H-1a), 3.77 (1H, dd, *J* = 13.2, 4.0, H-1'a), 3.83 (1H, dd, *J* = 13.2, 3.5, H-1'b), 4.00 (1H, br dd, *J* = 10.0, 6.0, H-4), 4.12 (1H, br d, *J* = *ca*. 13.5, H-1b), 4.13 (1H, d, *J* = 3.2, H-4'), 4.18 (1H, dd, *J* = 7.7, 3.2, H-3'), 4.20 (1H, br s-like, H-3), 4.39/4.51 (each 1H, d, *J* = 11.7, CH_2Ph), 4.45/4.52 (each 1H, d, *J* = 12.0, CH_2Ph), 4.47 (1H, br s-like, H-2), 4.50 (1H, dd, *J* = 7.7, 4.0, H-2'), 4.54/4.56 (each 1H, d-like, *J* = 12.0, OCH_2Ph), 4.57 (1H, d, *J* = 3.7, H-5'), 4.60 (2H, s, CH_2Ph), 5.84 (1H, d, *J* = 3.7, H-6'), 7.13–7.36 (20H, m, arom.). ^{13}C-NMR (125 MHz, $CHCl_3$) δ: 26.2/26.8 [C(*C*H_3)$_2$], 48.0 (C-1), 51.3 (C-1'), 65.4 (C-2'), 66.6 (C-5), 67.1 (C-4), 71.9/72.4/72.7/73.6 (*C*H_2Ph), 81.0 (C-4'), 81.9 (C-3'), 82.2 (C-3), 82.36 (C-5'), 82.41 (C-2), 105.1 (C-6'), 112.3 [*C*(CH$_3$)$_2$], 127.95/128.06/128.10/128.2/128.3/128.4/128.55/128.58/128.7/128.8 (d, arom.), 135.8/135.9/136.6/137.1 (s, arom.). LRMS (FAB) *m/z*: 713 $[M–Cl]^+$. HRMS (FAB) *m/z*: $[M–Cl]^+$ Calcd for $C_{42}H_{49}O_8S$ 713.3148; Found 713.3139.

Minor isomer ***β*-19** *(NMR data extracted from the spectrum of a ca. 3:1 mixture)*: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.29/1.47 [each 3H, s, C(CH_3)$_2$], 3.70–3.85 (4H, m, H-1a, H-1'a, H-5a, and H-5b), 3.94 (1H, dd, *J* = 12.9, 3.4 Hz, H-1'b), 4.00–4.04 (1H, m, H-1b), 4.13–4.23 (4H, m, H-3, H-3', H-4, and H-4'), 4.39–4.41 (1H, m, H-2), 4.52–4.53 (1H, m, H-5'), 4.60–4.64 (1H, m, H-2'), 5.74 (1H, d, *J* = 3.5 Hz, H-6'), 4.37–4.64 (8H, m, CH_2Ph), 7.13–7.36 (20H, m, arom). ^{13}C-NMR (125 MHz, $CHCl_3$) δ: 26.2/26.8 [C(*C*H_3)$_2$], 43.2 (C-1'), 44.9 (C-1), 61.7 (C-4), 64.2 (C-2'), 64.9 (C-5), 72.26/72.33/72.8/73.4 (*C*H_2Ph), 81.1 (C-4'), 81.9 (C-3'), 82.3 (C-2), 82.7 (C-5'), 84.1 (C-3), 105.2 (C-6'), 112.1 [(CH_3)$_2$C], 128.2/128.6/other signals due to aromatic methine carbons overlapped with those of **α-19** (d, arom.), 135.9/136.2/137.0/ a signal due to aromatic quaternary carbon overlapped with those of **α-19** (s, arom.).

Ion Exchange Reaction of Tetrafluoroborate (α-19) to Chloride (α-18). A mixture of **α-19** (625 mg, 0.78 mmol), ion exchange resin [IRA-400J (Cl^- form), 15 g], and MeOH (15 mL) was stirred

at room temperature for 2 h. The reaction mixture was filtered by suction, and the resins were washed with MeOH. The combined filtrate and washings were condensed *in vacuo* to give a colorless amorphous (590 mg), which on column chromatography ($CHCl_3$/MeOH = 30/1→10/1) gave **α-18** (560 mg, 96%) as a colorless amorphous. The ^1H and ^{13}C NMR data agreed well with those obtained by the *S*-alkylation of **8b** with **16** in HFIP.

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)]. A suspension of 10% Pd-C (500 mg) in 80% aqueous AcOH (4 mL) was pre-equilibrated with hydrogen. To the suspension was added a mixture of a solution of **α-18** (532 mg, 0.71 mmol) in 80% aqueous AcOH (6 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 water. The combined filtrate and the washings were condensed *in vacuo* to give a ca. 1:1 amomeric mixture of 1,4-dideoxy-1,4-[(*S*)-(6-deoxy-1-D-glucopyranos-6-yl)episulfoniumylidene]-2,3,5-tri-*O*-benzyl-D-arabinitol chloride containing a small amount of their partially acetylated compounds as a pale yellow amorphous. The amorphous was then treated with 5% hydrochloric acid (5 mL) at 50°C for 4 h, and the reaction mixture was condensed *in vacuo* to give a pale yellow amorphous (214 mg), which was used for the next $NaBH_4$ reduction without further purification.

To a solution of the amorphous (214 mg) in water (5 mL) was added $NaBH_4$ (130 mg, 3.4 mmol) at 0 °C, and the mixture was stirred at 0 °C for 5 h. The reaction mixture was acidified with 1 M HCl to pH 4 at 0 °C. After the reaction mixture was condensed *in vacuo*, the residue was triturated with methanol. The MeOH insoluble material was filtered off, and washed with methanol. The combined filtrate and washings were condensed *in vacuo* to give a colorless solid (278 mg), which on column chromatography ($CHCl_3$/MeOH = 5/1→3/1→3/2) gave a colorless solid (220 mg). Re-purification by

HPLC (H_2O) gave the title compound **7** (129 mg, 52% from **α-18**) as colorless solid. ^{1}H and ^{13}C NMR data of **7** agreed well with those reported.[6]

S-Alkylation of Thiosugar (8a) with Epoxides (9b, 9e, 9h, and 9k) in HFIP.

*1,4-Dideoxy-1,4-{(R)-[4-deoxy-1-O-(p-methoxybenzyl)-2-O-(o-methylbenzyl)-D-erythritol-4-yl]episulfoniumylidene}-2,3,5-tri-O-(p-methoxybenzyl)-D-arabinitol Tetrafluoroborate (**α-10b**)*. According to the method used for the *S*-alkylation of **8b** with **16** in HFIP, a mixture of **8a** (10.2 g, 20 mmol), **9b**[9b] (1.31 g 4.0 mmol), and HFIP (20 mL) was heated under reflux for 4 h. After being cooled with cold water, the reaction was quenched with HBF_4•Et_2O (660 μL, 4.8 mmol), and the resulting mixture was immediately neutralized with $NaHCO_3$ with ice cooling. The resulting suspension was filtered by suction, and the filter cake was washed with CH_2Cl_2. The combined filtrate and washings were condensed *in vacuo* to give a colorless oil (12.5 g), which on column chromatography ($CHCl_3$→$CHCl_3$/MeOH=100/1→30/1→10/1) gave **α-10b** (2.44 g, 66%) and a *ca*. 3:1 mixture of **α-10** and **β-10** (737 mg, 20%).

*Compound **α-10b***: colorless oil. $[\alpha]^{25}_D$ –8.96 (*c* = 1.15, $CHCl_3$). IR (neat): 3499, 1612, 1080 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 2.30 (3H, s, $C_6H_4CH_3$), 3.58 (1H, dd, *J* = 13.2, 2.0, H-1a), 3.60 (1H, dd, *J* = 10.9, 3.5, H-4'a), 3.61 (1H, dd, *J* = 10.3, 8.0, H-5a), 3.64 (1H, d, *J* = 13.2, 3.8, H-1b), 3.66 (1H, dd, *J* = 10.3, 6.9, H-5b), 3.70 (1H, dd, *J* = 10.9, 4.1, H-4'b), 3.73 (1H, dd, *J* = 14.0, 7.5, H-1'a), 3.74–3.77 (1H, m, H-3'), 3.77/3.78/3.79/3.82 (each 3H, s, OCH_3), 3.82 (1H, dd, *J* = 14.0, 3.8, H-1'b), 3.97 (1H, br dd-like, *J* = *ca*. 8.0, 6.9, H-4), 4.11 (1H, br dd-like, *J* = *ca*. 2.0, 1.2, H-3), 4.23 (1H, ddd-like, *J* = *ca*. 3.8, 2.0, 2.0, H-2), 4.21/4.28 (each 1H, d, *J* = 11.5 Hz, OCH_2Ar), 4.23 (1H, br dd-like, *J* = *ca*. 7.5, 3.8, H-2'), 4.36–4.47 (6H, m, OCH_2Ar), 4.57/4.66 (each 1H, d, *J* = 11.2, OCH_2Ar), 6.81–6.88 (8H, m, arom.), 7.02–7.27 (12H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 18.8 ($C_6H_4CH_3$), 48.1 (C-1), 51.1 (C-1'), 55.5 (OCH_3), 66.2 (C-4), 66.4 (C-5), 68.4 (C-4'), 68.7 (C-2'), 71.2/71.4/71.7/73.1/73.3

(O*C*H$_2$Ar), 79.6 (C-3'), 82.0 (C-3), 82.1 (C-2), 113.85/113.93/114.0/114.1/125.9/128.3/129.4/129.6/130.0/130.3 (d, arom.), 127.9/128.0/128.9/ 135.6/137.1/159.3/ 159.5/159.7/159.8 (s, arom.). FABMS (pos.) *m/z*: 839 [M–BF$_4$]$^+$.

*1,4-Dideoxy-1,4-{(R)-[4-deoxy-1-O-(p-methoxybenzyl)-2-O-(o-chlorobenzyl)-D-erythritol-4-yl]episulfoniumylidene}-2,3,5-tri-O-(p-methoxybenzyl)-D-arabinitol Tetrafluoroborate (**α-10e**)*. In a similar manner described above, a mixture of **8a** (7.93 g, 15.5 mmol), **9e**[9b] (1.08 g, 3.1 mmol), and HFIP (20 mL) was heated under reflux for 4 h. Work-up gave a colorless oil (10.0 g), which on column chromatography gave **α-10e** (2.02 g, 69%) and a *ca*. 2:1 mixture of **α-10e** and **β-10e** (463 mg, 16%).

*Compound **α-10e***: colorless oil. $[\alpha]^{23}_{D}$ –3.57 (*c* = 1.26, $CHCl_3$). IR (neat): 3499, 1612, 1072 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 3.636 (1H, dd, *J* = 10.3, 8.9, H-5a), 3.644 (1H, dd, *J* = 10.3, 3.8, H-4'a), 3.68 (1H, dd, *J* = 10.3, 6.9, H-5b), 3.71 (1H, dd, *J* = 13.0, 3.0, H-1a), 3.72 (1H, dd, *J* = 10.3, 3.8, H-4'b), 3.74 (1H, ddd-like, *J* = *ca*. 4.5, 3.8, 3.8, H-3'), 3.77 (3H, s, OC*H*$_3$), 3.78 (1H, dd-like, *J* = 13.2, 7.0, H-1'a), 3.79 (6H, s, OC*H*$_3$), 3.81 (1H, dd-like, *J* = *ca*. 13.0, 4.0, H-1b), 3.81 (3H, s, OC*H*$_3$), 3.87 (1H, dd, *J* = 13.2, 3.4, H-1'b), 4.00 (1H, br dd-like, *J*= *ca*. 8.9, 6.9, H-4), 4.12 (1H, br dd-like, *J* = *ca*. 2.0, 1.2, H-3), 4.27/4.35 (each 1H, d, *J* = 11.5, OC*H*$_2$Ar), 4.30 (1H, ddd-like, *J* = *ca*. 4.0, 3.0, 2.0, H-2), 4.30–4.35 (1H, m, H-2'), 4.38–4.48 (6H, m, OC*H*$_2$Ar), 4.66/4.73 (each 1H, d, *J* = 11.7, OC*H*$_2$Ar), 6.81–6.88 (8H, m, arom.), 7.03–7.43 (12H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 48.1 (C-1), 50.8 (C-1'), 55.26/55.29 (OCH_3), 66.35 (C-4), 66.44 (C-5), 68.3 (C-4'), 68.6 (C-2'), 70.0/71.5/71.8/73.2/73.3 (O*C*H$_2$Ar), 79.7 (C-3'), 81.9 (C-3), 82.1 (C-2), 113.9/114.0/114.08/114.13/127.1/129.4/129.5/129.6/129.65/129.70/130.0/130.7 (d, arom.), 127.8/128.0/128.8/133.6/135.1/159.3/159.6/159.77/159.80 (s, arom.). FABMS (pos.) *m/z*: 859 [M–BF$_4$]$^+$.

*1,4-Dideoxy-1,4-{(R)-[4-deoxy-1-O-(p-methoxybenzyl)-2-O-(o-trifluorobenzyl)-D-erythritol-4-yl]episulfoniumylidene}-2,3,5-tri-O-(p-methoxybenzyl)-D-arabinitol Tetrafluoroborate (**α-10h**)*. In a similar manner described above, a mixture of **8a** (8.65 g, 17.0 mmol), **9h**[9b] (1.30 g, 3.4 mmol), and HFIP (20 mL) was heated under reflux for 4 h. Work-up gave a colorless oil (10.0 g), which on column chromatography gave **α-10h** (2.47 g, 74%) and a *ca*. 2:1 mixture of **α-10h** and **β-10h** (462 mg, 14%).

*Compound **α-10h***: colorless oil. $[\alpha]^{24}_{D}$ –8.1 (*c* = 0.98, $CHCl_3$). IR (neat): 3406, 1612, 1083 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) *δ*: 3.62 (1H, dd, *J* = 10.9, 3.7, H-4'a), 3.64 (1H, dd, *J* = 10.6, 9.0, H-5a), 3.69 (1H, dd, *J* = 10.6, 6.9, H-5b), 3.71 (1H, dd, *J* = 10.9, 4.5, H-4'b), 3.72 (1H, dd, *J* = 13.0, 3.8, H-1a), 3.75–3.83 (3H, m, H-1b, H-1'a and H-3'), 3.85 (1H, dd, *J* = 13.2, 3.7, H-1'b), 3.76/3.77/3.78/3.80 (each 3H, s, OCH_3), 4.01 (1H, br dd-like, *J* = *ca*. 9.0, 6.9, H-4), 4.13 (1H, br s-like, H-3), 4.26/4.34 (each 1H, d, *J* = 11.5, OCH_2Ar), 4.30 (1H, br m, H-2), 4.32–4.34 (1H, m, H-2'), 4.37–4.47 (6H, m, OCH_2Ar), 4.74/4.82 (each 1H, d, *J* = 12.4, OCH_2Ar), 6.80–7.63 (20H, m, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 48.1 (C-1), 50.7 (C-1'), 55.2/55.3 (O*C*H_3), 66.3 (C-4), 66.4 (C-5), 68.2 (C-4'), 68.5 (C-2'), 68.8/71.5/71.7/73.1/73.2 (O*C*H_2Ar), 80.2 (C-3'), 81.9 (C-3), 82.1 (C-2), 113.8/113.9/114.0/114.1/127.9/129.57/129.61/ 129.7/129.9/130.7/132.2 (d, arom.), 124.3 [q, *J* = 272 Hz, *C*F_3,], 125.8 [q, *J* = 5.0 Hz, C_{ortho}-CF_3,], 127.7 [q, *J* = 31.0 Hz, C_{ipso}-CF_3,], 128.1/128.8/130.6/132.2/135.9/159.3/159.5/159.71/159.74 (s, arom.). FABMS (pos.) *m/z*: 893 [M–BF_4]$^+$.

*1,4-Dideoxy-1,4-{(R)-[4-deoxy-1-O-(p-methoxybenzyl)-2-O-(o-nitrobenzyl)-D-erythritol-4-yl]episulfoniumylidene}-2,3,5-tri-O-(p-methoxybenzyl)-D-arabinitol Tetrafluoroborate (**α-10k**)*. In a similar manner described above, a mixture of **8a** (6.83 g, 13.4 mmol), **9k**[b] (1.30 g, 2.7 mmol), and HFIP (20 mL) was heated under reflux for 4 h. Work-up gave a colorless oil (10.0 g), which on

column chromatography gave **α-10k** (1.75 g, 67%) and a *ca*. 1:1.2 mixture of **α-10k** and **β-10k** (220 mg, 9%). ^{1}H and ^{13}C NMR data of **α-10k** agreed well with those reported.[9b]

Synthesis of Sulfonium Salts (7b, 7e, 7h, and 7k).

*1,4-Dideoxy-1,4-{(R)-[4-deoxy-2-O-(o-methylbenzyl)-D-erythritol-4-yl]episulfoniumylidene}-D-arabinitol Chloride (**7b**)*. A mixture of **α-10b** (2.43 g, 2.6 mmol), 80% aqueous TFA (30 mL), and $CHCl_3$ (15 mL) was stirred at room temperature for 5 h. After the reaction mixture was condensed *in vacuo*, the residue was triturated with methanol. The MeOH insoluble material was filtered off, and washed with methanol. The combined filtrate and washings were condensed *in vacuo* to give a colorless oil (1.19 g), which was subsequently stirred with ion exchange resin IRA-400J (50 g) in methanol (100 mL) for 12 h. The resin was filtered off, and washed with methanol. The combined filtrate and washings were condensed *in vacuo* to give colorless oil (888 mg), which on column chromatography ($CHCl_3$/MeOH = 10/1→3/1) gave **7b** (817 mg, 79%) as colorless oil: $[\alpha]^{24}_{D}$ +11.9 (*c* = 1.40, CH_3OH). IR (neat): 3302, 1605, 1076 cm^{-1}. ^{1}H NMR (500 MHz, CD_3OD) *δ*: 2.37 (3H, s, C*H*$_3$), 3.56 (1H, dt, *J* = 5.5, 4.3, H-3'), 3.67 (1H, dd, *J* = 13.2, 8.9, H-1'a), 3.69 (1H, br d-like, *J* = *ca*. 12.6, H-1a), 3.72 (1H, dd, *J* = 11.7, 4.3 Hz, H-4'a), 3.75 (1H, dd, *J* = 12.6, 3.4, H-1b), 3.79 (1H, dd, *J* = 13.2, 3.5, H-1'b), 3.84 (1H, dd, *J* = 11.7, 4.3, H-4'b), 3.89 (1H, dd, *J* = 10.1, 9.8, H-5a), 3.93 (1H, br dd-like, *J* = *ca*. 9.8, 3.8, H-4), 4.02 (1H, dd, *J* = 10.1, 3.8, H-5b), 4.25 (1H, ddd, *J* = 8.9, 5.5, 3.5, H-2'), 4.34 (1H, br d-like, *J* = *ca*. 1.5, H-3), 4.57 (1H, br dd-like, *J* = *ca*. 3.4, 1.5, H-2), 4.63/4.82 (each 1H, d, *J* = 11.5, OC*H*$_2$Ar), 7.13–7.22 (3H, m, arom.), 7.35 (1H, d, *J* = 7.2, arom.). ^{13}C NMR (125 MHz, CD_3OD) *δ*: 19.1 (C*H*$_3$), 51.8 (C-1'), 52.2 (C-1), 60.9 (C-4'), 61.0 (C-5), 68.8 (C-2'), 71.9 (O*C*H$_2$Ar), 73.7 (C-4), 79.4 (C-2), 79.6 (C-3), 83.0 (C-3'), 126.9/129.3/130.4/131.3 (d, arom.), 137.2/138.2 (s, arom.). LRMS (FAB) *m/z*: 359 $[M–Cl]^+$. HRMS (FAB) *m/z*: $[M–Cl]^+$ Calcd for $C_{17}H_{27}O_6S$ 359.1528; Found 359.1560.

*1,4-Dideoxy-1,4-{(R)-[4-deoxy-2-O-(o-chlorobenzyl)-D-erythritol-4-yl]episulfoniumylidene}-D-arabinitol Chloride (**7e**).* In a similar manner described above, from **α-20e** (2.01 g, 2.12 mmol) was preparerd **7e** (704 mg, 80%) as colorless oil: $[\alpha]^{21}_{D}$ +12.6 (*c* = 1.00, CH_3OH). IR (neat): 3302, 1597, 1084 cm^{-1}. ^1H NMR (500 MHz, CD_3OD) *δ*: 3.58 (1H, dt, *J* = 5.8, 4.0, H-3'), 3.74 (1H, dd, *J* = 13.2, 9.2, H-1'a), 3.75 (1H, dd, *J* = 12.0, 4.0, H-4'a), 3.78 (1H, dd, *J* = 12.9, 2.0, H-1a), 3.81 (1H, dd, *J* = 12.9, 3.2, H-1b), 3.87 (1H, dd, *J* = 13.2, 3.5, H-1'b), 3.88 (1H, dd, *J* = 12.0, 4.0, H-4'b), 3.90 (1H, dd, *J* = 10.9, 9.2 Hz, H-5a), 3.97 (1H, br dd-like, *J* = 9.2, 4.9, H-4), 4.03 (1H, dd, *J* = 10.9, 4.9, H-5b), 4.28 (1H, ddd, *J* = 9.2, 5.8, 3.5, H-2'), 4.36 (1H, br d-like, *J* = *ca*. 1.2, H-3), 4.60 (1H, ddd-like, *J* = *ca*. 3.2, 2.0, 1.2, H-2), 4.75/4.85 (each 1H, d, *J* = 12.3, OC*H*$_2$Ar), 7.29 (1H, td, *J* = 7.5, 2.3, arom.), 7.31 (1H, td, *J* = 7.5, 2.3, arom.), 7.39 (1H, dd-like, *J* = 7.5, 2.3, arom.), 7.57 (1H, dd-like, *J* = 7.5, 2.3, arom.). ^{13}C NMR (125 MHz, CD_3OD) *δ*: 51.9 (C-1'), 52.2 (C-1), 60.7 (C-4'), 61.0 (C-5), 68.7 (C-2'), 70.7 (O*C*H_2Ar), 73.8 (C-4), 79.46 (C-2), 79.53 (C-3), 83.5 (C-3'), 128.2/130.4/130.5/131.4 (d, arom.), 134.4/137.0 (s, arom.). LRMS (FAB) *m/z*: 379 $[M–Cl]^+$. HRMS (FAB) *m/z*: $[M–Cl]^+$ Calcd for $C_{16}H_{24}ClO_6S$ 379.0982; Found 379.0989.

*1,4-Dideoxy-1,4-{(R)-[4-deoxy-2-O-(o-trifluorobenzyl)-D-erythritol-4-yl]episulfoniumylidene}-D-arabinitol Chloride (**7h**).* In a similar manner described above, from **α-20h** (2.46 g, 2.5 mmol) was preparerd **7h** (918 mg, 82%) as colorless oil: $[\alpha]_D^{24}$ +12.3 (*c* = 2.0, CH_3OH). IR (neat): 3286, 1612, 1115 cm^{-1}. ^1H NMR (800 MHz, CD_3OD) *δ*: 3.62 (1H, ddd, *J* = 4.8, 4.0, 4.0, H-3'), 3.74 (1H, dd, *J* = 12.0, 4.0, H-4'a), 3.77 (1H, dd, *J* = 13.6, 8.8 H-1'a), 3.79 (1H, dd, *J* = 12.8, 1.6, H-1a), 3.81 (1H, dd, *J* = 12.8, 3.2, H-1b), 3.85 (1H, dd, *J* = 12.0, 4.8, H-4'b), 3.87 (1H, dd, *J* = 13.6, 3.2, H-1'b), 3.91 (1H, dd, *J* = 11.2, 9.6, H-5a), 3.98 (1H, br dd, *J* = *ca*. 9.6, 4.8, H-4), 4.03 (1H, dd, *J* = 11.2, 4.8, H-5b), 4.30 (1H, ddd, *J* = 8.8, 4.0, 3.2, H-2'), 4.36 (1H, dd-like, *J* = *ca*. 2.0, 1.6, H-3), 4.59 (1H, ddd-like, *J* = 3.2, 2.0, 1.6, H-2), 4.86/4.96 (each 1H, d, *J* = 12.8, OC*H*$_2$Ar), 7.46/7.63 (each 1H, br t, *J* = *ca*. 8.0, arom.), 7.67/7.82 (each 1H, br d, *J* = *ca*. 8.0, arom.). ^{13}C NMR (200 MHz, CD_3OD) *δ*: 51.6 (C-1'), 52.3 (C-1),

60.9 (C-4'), 61.0 (C-5), 68.9 (C-2'), 69.7 [br q-like, J = 1.9 Hz, CH$_2$C$_6$H$_4$-(o-CF$_3$)], 73.7 (C-4), 79.6 (C-2), 79.6 (C-3), 84.0 (C-3'), 125.9 [q, J = 272 Hz, CF$_3$,], 126.7 [q, J = 5.8 Hz, C_{ortho}-CF$_3$,], 128.6 [q, J = 31.0 Hz, C_{ipso}-CF$_3$,], 129.0/131.2/133.4 (d, arom.), 138.0 (s, arom.). LRMS (FAB) *m/z*: 413 [M–Cl]$^+$. HRMS (FAB) *m/z*: [M–Cl]$^+$ Calcd for $C_{17}H_{24}O_6F_3S$ 413.1246; Found 413.1220.

*1,4-Dideoxy-1,4-{(R)-[4-deoxy-2-O-(o-nitrobenzyl)-D-erythritol-4-yl]episulfoniumylidene}-D-arabinitol chloride (**7k**)*. In a similar manner described above, from **α-20k** (1.69 g, 1.8 mmol) was preparerd **7k** (586 mg, 78%). ^{1}H and ^{13}C NMR data of **7k** agreed well with those reported.[9b]

Bioassay.

Effects on Human Intestinal α-Glucosidase. The experiment was performed according to the method as described in our previous report.[14] A human small intestinal microsome (batch MIC318017, purchased from BIOPREDIC International, Rennes, France) in 0.1 M maleate buffer (pH 6.0) was used to determine the activity of maltase, a small intestinal α-glucosidase. A test sample was dissolved in dimethyl sulfoxide (DMSO) and the resulting solution was diluted with 0.1 M maleate buffer to prepare the test sample solution (concentration of DMSO: 10%). A substrate solution in the maleate buffer (maltose: 74 mM, 50 μL), the test sample solution (25 μL), and the enzyme solution (25 μL) were mixed at 37°C for 30 min and then immediately heated in boiling water for 2 min to stop the reaction. The glucose concentrations were determined using the glucose-oxidase method. The final concentration of DMSO in the test solution was 2.5% and no influence of DMSO on the inhibitory activity was detected. The IC$_{50}$ was determined graphically (N = 2–4). The intestinal α-glucosidase inhibitors (acarbose, voglibose, and miglitol) were used as reference compounds. For kinetic analysis of the inhibitory activity on human maltase by salacinol (**1**), neosalacinol (**4**), and the 3'-*O*-benzylated analogues (**7b**, **7e**, **7h**, and **7k**), the enzyme solution (25 μL) and each test sample solution (**1**: 0.50, 1.0, and 2.0 μM; **4**: 0.50, 1.0, and 2.0 μM; **7b**: 0.05, 0.10, and 0.20 μM; **7e**: 0.01, 0.04, and 0.08 μM;

7h: 0.02, 0.04, and 0.08 μM; and **7k**: 0.01, 0.02, and 0.04 μM, 25 μL) were incubated with increasing concentrations of the substrate solution (1.5–5.3 mM, 50 μL). The typical competitive inhibitors, acarbose (1.0, 2.0, and 4.0 μM, 25 μL), voglibose (0.10, 0.20, and 0.40 μM, 25 μL), and miglitol (0.25, 0.50, and 1.0 μM, 25 μL), were used as reference compounds. Lineweaver–Burk plots of the inhibition of human intestinal maltase activities by compounds **7b**, **7e**, **7h**, **7k**, salacinol (**1**), neosalacinol (**4**), voglibose, acarbose, and miglitol were depicted in SI-Figure 10.

Animals. Male ddY mice (6-weeks-old) were purchased from Kiwa Laboratory Animal Co., Ltd., Wakayama, Japan. The animals were housed at a constant temperature of 23 ± 2°C, and were then fed a standard laboratory chow (MF, Oriental Yeast Co., Ltd., Tokyo, Japan). The animals were fasted for 20–24 h prior to the beginning of the experiment, but were allowed free access to tap water. All of the experiments were performed on conscious mice unless otherwise noted. The experimental protocol was approved by the Experimental Animal Research Committee at Kindai University.

Effects on Blood Glucose Levels in Maltose-loaded Mice. The experiments were performed according to the method as described in our previous reports with a slight modification.[14] After fasting, the mice were orally administrated a 10% (w/v) maltose solution (1 g/kg) with or without a test sample. At 0, 15, 30, 60, 120, and 180 min after the administration, blood samples were taken from the tail vein and immediately subjected to the measurement of blood glucose using the glucose oxidase method. As a baseline, distilled water was administrated to rats as a normal group. An intestinal α-glucosidase inhibitor voglibose was used as a reference compound.

Statistics. Values are expressed as the mean ± S.E.M. One-way analysis of variance (ANOVA) followed by Dunnett's test was used for statistical analyses. Probability (p) values less than 0.05 were considered significant.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

A new synthetic protocol for the known epoxide **16**, time interval NMR spectra in HFIP-d_2, ^{1}H and ^{13}C NMR spectra for isolated compounds, and Lineweaver–Burk plots of the inhibition of human intestinal maltase activities by compounds **7b**, **7c**, **7d**, **7e**, salacinol (**1**) (PDF).

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This study was supported by a grant from the Houansha Foundation, 2017–2020 and by a Grant-in-Aid for scientific research from the Japan Society for the Promotion of Science [JSPS (KAKENHI), 15K08008, 15K08009, 16K08313, 17K08377 and 17H05438]. We are also thankful for the financial support extended by the MEXT-Supported Program for the Strategic Research Foundation at Private Universities, 2014–2018, the Antiaging Project for Private Universities, and Kobayashi International Scholarship Foundation. We thank Prof. Isao Nakanishi (Kindai University) for kindly calculating the conformational energy of reaction intermediates.

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