SULFONIUM-ION GLYCOSIDASE INHIBITORS ISOLATED FROM *Salacia* SPECIES USED IN TRADITIONAL MEDICINE, AND RELATED COMPOUNDS

Sankar MOHAN[1] and B. Mario PINTO[2,*]

Department of Chemistry, Simon Fraser University, Burnaby, B.C., Canada, V5A 1S6; e-mail: [1] sankarm@sfu.ca, [2] bpinto@sfu.ca

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This article is dedicated, with respect, to Dr. Alfred Bader on the occasion of his 85th birthday.

A novel class of naturally-occurring glycosidase inhibitors, having sulfonium sulfate structures, has been isolated as bioactive components from Indian plants, belonging to the *Salacia* genus in the family *Celastraceae*, and used in Ayurvedic medicine for the treatment of type-2 diabetes. Thus far, five such sulfonium salts, namely, salacinol, kotalanol, salaprinol, ponkoranol and de-*O*-sulfonated kotalanol, have been isolated from this plant species. These structurally unique zwitterionic glycosidase inhibitors have received much attention due to their therapeutic potential in the treatment of type-2 diabetes. We recently reported a review article which focused mainly on salacinol and related analogues. The present review presents an update on the remaining four compounds from this class of glycosidase inhibitors, with respect to their isolation, glucosidase inhibitory activities, and synthesis. In addition, progress towards the stereochemical structure elucidation of kotalanol, through synthesis of analogues, is described. Review with 42 references.

Keywords: Glycosidase inhibitors; Carbohydrates; Thiasugars; Sulfonium sulfates; Salacinol; Salaprinol; Natural products.

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1. INTRODUCTION

In the drug discovery program, the process of isolation and characterization of bioactive components from medicinal plants, used in traditional medicine or folk medicine, is a proven strategy for identifying lead drug candidates for modern therapeutic use[1]. Indeed, the therapeutic effects of many of the bioactive compounds isolated from plants correlate with their traditional use in herbal extracts[1].

Salacia reticulata, also known as Kothalahimbutu in Singhalese, is the medicinal plant used in traditional medicine in Sri Lanka and South India for the treatment of type-2 diabetes. *S. reticulata* is a large woody, climbing plant found widely in Sri Lanka and southern parts of India. Ayurvedic medicine, the ancient art of treatment with Indian herbal remedies, prescribes this herbal extract, obtained by storing water overnight in a mug carved from Kothalahimbutu wood, as a remedy for type-2 diabetes[2–4]. Clinical evaluations of the aqueous extract of *S. reticulata* have also shown direct correlation to their antidiabetic properties observed in the traditional use. Administration of the herbal extract of *S. reticulata* to rats, after a carbohydrate meal, significantly reduced blood glucose levels[5]. Most importantly, no serious acute toxicity or mutagenicity was observed in rats after the oral ingestion of the extracts at a dose of 5000 mg/kg [6]. The *Salacia* extract was also tested in a double-blind study involving human patients with type-2 diabetes and a placebo-control group[7]. These studies showed that the extract is an effective treatment for type-2 diabetes, with side effects comparable to the placebo control group. Pre-treatment with *Salacia* extract prior to sucrose loading significantly suppressed postprandial hyperglycemia in human volunteers[8]. The herbal extract was also found to be successful in lowering acute glycemia and insulinemia in type-2 diabetic patients after a high-carbohydrate meal[9]. A recent study showed that the *Salacia* extract is also effective in reducing body weight gain in mice on a normal and high-fat diet and could potentially reduce the risk of obesity-associated complications, including type-2 diabetes[10]. Of note, food supplements and herbal teas containing *Salacia* roots have been used extensively in the United States and Japan as a preventive measure for diabetes and obesity[10].

2. ISOLATION OF SULFONIUM SALTS AS BIOACTIVE COMPONENTS FROM PLANTS BELONGING TO THE *Salacia* GENUS

Yoshikawa et al.[11] attributed the antidiabetic properties of *Salacia* extract to intestinal α-glucosidase inhibitory activity based on the glucosidase inhibi-

tion results obtained *in vivo* and *in vitro* assays. Thus, *S. reticulata* extract strongly inhibited the increase in serum glucose level in rats after the administration of sucrose and maltose, but not glucose[11]; a strong inhibition profile *in vitro* was observed against rat intestinal sucrase and maltase with IC_{50} values of 35 and 26 μg/ml, respectively[11]. The approach to identify the active components of the aqueous extract employed a bioassay-guided separation using intestinal α-glucosidase inhibitory activity. This resulted in the isolation of two naturally occurring glycosidase inhibitors from *S. reticulata*, namely salacinol (**1**)[11] and kotalanol (**2**)[12] (Fig. 1). Later, both salacinol (**1**) and kotalanol (**2**) were isolated from other *Salacia* plants such as *S. oblonga*[13] and *S. chinensis*[14]. Both of these compounds share a common structural motif, a zwitterionic sulfonium sulfate structure, that comprises a 1,4-anhydro-1,4-thio-D-arabinitol core **3** (Fig. 1) and a polyhydroxylated acyclic side chain. The length of the polyhydroxylated side chain differs in salacinol and kotalanol; salacinol has a four-carbon chain whereas kotalanol has a seven-carbon chain. The initial stereostructure of salacinol (**4**; Fig. 1) reported by Yoshikawa et al.[11] was revised and the absolute stereostructure of salacinol (**1**) was unambiguously determined by its total synthesis, achieved independently by our group[15] and Yuasa et al.[16], Later on, the crystal structure obtained by Yoshikawa et al.[17] also confirmed the revised structure **1**. Various structure–activity relationship studies of salacinol (**1**) indicated the importance of the 1,4-anhydro-4-thio-D-arabinitol core and the stereochemical requirements on the side chain; however, the

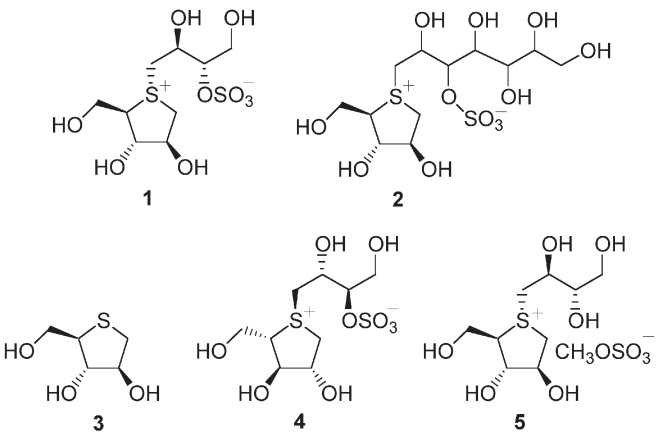


FIG. 1
Structure of salacinol and kotalanol isolated from *Salacia* species and related analogues

sulfate group at C-3′ was found to be unimportant. In fact, the synthetic compound, de-*O*-sulfonated salacinol **5** (Fig. 1) was found to retain its inhibitory activity compared to salacinol (**1**)[18]. These results are summarized in a review article which focused on salacinol and related analogues[19].

Unlike salacinol, since its isolation in 1998, the absolute stereostructure of kotalanol (**2**) has not yet been determined[12]. The presence of the 1,4-anhydro-1,4-thio-D-arabinitol core **3** was confirmed by degradation studies by Yoshikawa et al.[12]; alkaline treatment of kotalanol with 1% CH_3ONa in MeOH yielded 1,4-anhydro-1,4-thio-D-arabinitol (**3**) as the degradation product. However, the configurations of the stereogenic centers in the heptitol side chain and the configuration at the stereogenic sulfonium-ion center were left undetermined.

Recently, Yoshikawa et al.[20] isolated two additional structurally similar zwitterionic sulfonium sulfates having three- and six-carbon polyhydroxylated side chains, namely salaprinol (**6**) and ponkoranol (**7**) (Fig. 2) from the roots and stems of *Salacia prinoides* (also known as Kushan in Sanskrit), another plant in the *Salacia* genus also used for the treatment of type-2 diabetes in Indian traditional medicine. In addition, they have also isolated salacinol (**1**) and kotalanol (**2**) from this plant. Detailed spectral analysis and degradation studies of these compounds led to their overall structural assignments as **6** and **7**; however, once again, the configurations at the stereogenic centers in the side chain and at the stereogenic sulfonium cen-

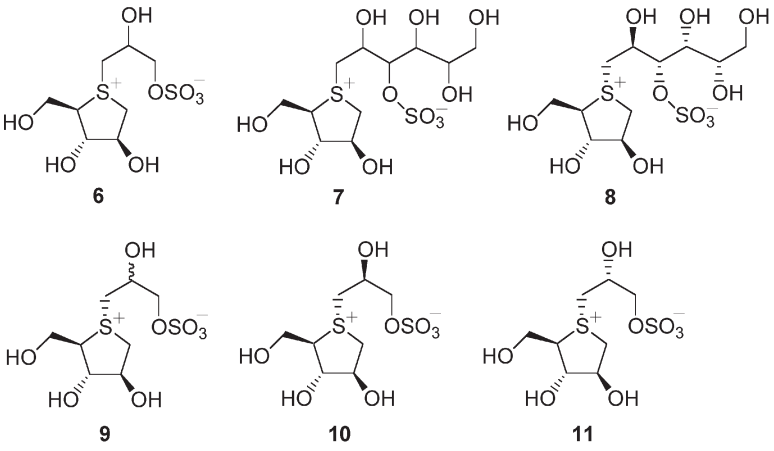
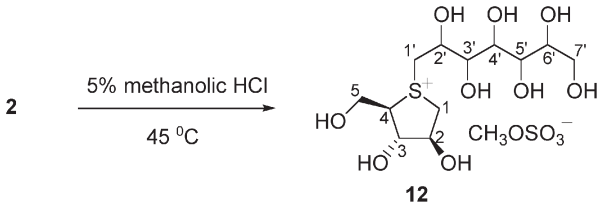


FIG. 2
Structure of salaprinol and ponkoranol isolated from *S. prinoides* and related analogues

ter were left undetermined owing to the presence of non-crystalline material[20]. Interestingly, these two natural compounds were synthesized in the laboratory, prior to their isolation. Comparison of physical data of the natural compound, ponkoranol (**7**), with those of synthetic six-carbon chain-extended analogues of salacinol[21–24] confirmed that ponkoranol is indeed compound **8** [21] (Fig. 2). Similarly, prior to its isolation, salaprinol (**6**) was synthesized as a diastereomeric mixture (**9**; Fig. 2), with respect to the C-2′ configuration, by Muraoka et al.[25] as a deoxy analogue of salacinol. Very recently, the same group reported the synthesis and absolute stereostructure of salaprinol (**10**; Fig. 2), having the *S*-configuration at C-2′; slight modifications in the earlier synthetic route of **9** enabled them to isolate each diastereomer, salaprinol (**10**) and 2′-*epi*-salaprinol (**11**; Fig. 2), as single crystals (details of the synthesis will be discussed later)[26].

In addition to the isolation of salaprinol (**10**) and ponkoranol (**7**), the synthesis of a de-*O*-sulfonated analogue (**12**) of kotalanol was also reported by Yoshikawa et al.[20]; the same procedure used for the synthesis of de-*O*-sulfonated salacinol (**5**)[17] was also applied here (Scheme 1). The α-glucosidase inhibitory activities of the compound **12** against rat intestinal α-glucosidases, maltase and isomaltase, *in vitro*, were found to be similar to



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SCHEME 1

those of salacinol (**1**) and kotalanol (**2**); however, its sucrase inhibitory activity was weaker when compared to salacinol (**1**) and kotalanol (**2**) (Table I)[20]. The inhibition assay indicated that salaprinol (**10**) was the least active natural compound in this class of inhibitors, which corroborates the earlier data obtained with the synthetic diastereomeric mixture **9** [25]. Comparison of the inhibitory activities of ponkoranol (**7**) against intestinal α-glucosidases (maltase, sucrase and isomaltase) with those of salacinol, kotalanol and their respective desulfonated analogues (**5** and **12**) revealed that the inhibitory activities of ponkoranol (**7**) were either equivalent or stronger than those of salacinol (**1**) and kotalanol (**2**) (Table I)[20].

In 2008, Ozaki et al.[27] reported the isolation of compound **13** from the aqueous extract of *S. reticulata* using the bioassay-guided isolation tech-

nique similar to the one used by Yoshikawa et al. The compound **13** was assigned the structure of a 13-membered cyclic sulfoxide (**13**; Fig. 3), and was reported to be a more potent α-glucosidase inhibitor than salacinol (**1**) or kotalanol (**2**)[27]. The reported structure of compound **13** was clearly different from the zwitterionic glycosidase inhibitors. However, careful examination by Muraoka et al.[28], of the reported spectral data of the natural compound **13** and their comparison with those of the synthetic de-*O*-sulfonated kotalanol (**12**), led to the revision of the structure **13**. The major mistakes in the structure assignment of this natural compound, as pointed out by Muraoka et al.[28], were the assignment of two of the four methylene carbon resonances in the ^{13}C NMR spectrum of the natural compound;

TABLE I
Comparison of inhibitory activities (IC_{50}, μmol/l) of zwitterionic glycosidase inhibitors **1**, **2**, **7**, **10** and **12** and related analogues **5** and **9** against rat intestinal α-glucosidases[a]

Inhibitor	Maltase	Sucrase	Isomaltase	Ref.
Salacinol (**1**)	5.2 (0.97)	1.6 (0.2)	1.3 (1.1)	20, 29
Kotalanol (**2**)	7.2 (0.54)	0.75 (0.42)	5.7 (4.2)	20, 29
De-*O*-sulfonated salacinol (**5**)	8.0	1.3	0.30	20
Ponkoranol (**7**)	3.2	0.29	2.6	20
Diastereomeric mixture of salaprinol (**9**)	>1390	780	–	20
Salaprinol (**10**)	>100	>100	–	20
Synthetic de-*O*-sulfonated kotalanol (**12**)	4.8	4.5	1.8	20
Natural de-*O*-sulfonated kotalanol	0.227 (0.11)	0.186 (0.052)	0.099 (0.42)	27

[a] Values in parentheses indicate K_i values (μmol/l).

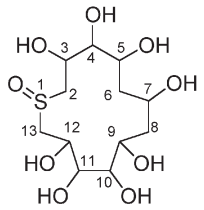

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FIG. 3
Proposed 13-membered cyclic sulfoxide isolated by Ozaki et al.[27]

peaks at 58.0 and 62.0 ppm were assigned to carbons C-6 and C-8, respectively, in the structure **13**. Very good agreement was obtained when the reported ^{1}H and ^{13}C NMR data of the isolated natural compound were compared with those of the de-*O*-sulfonated analogue (**12**) of kotalanol; hence Muraoka et al.[28] reassigned these two peaks to C-5 (58.0 ppm) and C-7′ (62.0 ppm) in **12** [20], and confirmed that the natural compound isolated by Ozaki et al.[27] was indeed de-*O*-sulfonated kotalanol **12** and not the 13-membered sulfoxide **13**. However, the counter-anion for the natural de-*O*-sulfonated kotalanol is not the same as in the synthetic **12** as there were no signals corresponding to the counter-anion in the reported ^{1}H and ^{13}C NMR data of the natural compound[27]. For the synthetic **12**, the proton signal at 3.71 ppm and carbon signal at 58.1 ppm, corresponding to the methyl sulfate counter-anion, were observed in the ^{1}H and ^{13}C NMR spectra, respectively[20]. It was concluded, therefore, that the counter-anion for the natural de-*O*-sulfonated kotalanol would have to be a non-protic counter-anion such as Cl^{-} and SO_4^{2-}, which might arise from the ion exchange reaction or hydrolysis of methyl sulfate anion during the isolation process[28].

The inhibitory activities of the zwitterionic sulfonium sulfates **1**, **2**, **7**, **10** and **12** isolated from *Salacia* species and closely related analogues **5** and **9** against rat intestinal α-glucosidase are summarized in Table I for comparison.

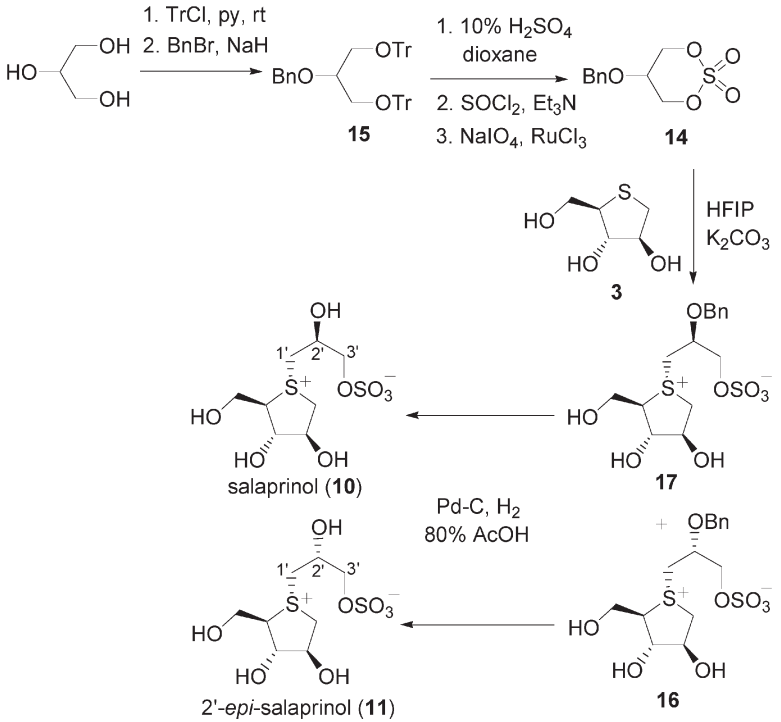
Although the exact mechanism of inhibition of α-glucosidases exhibited by these zwitterionic compounds has yet to be elucidated, a mechanism similar to that of the amine-based glycosidase inhibitors was proposed by us; the presence of a permanent positive charge on the sulfur atom of these compounds is thought to be the functional mimic of the protonated ammonium center when binding to active-site carboxylate residues[19]. The critical interactions observed between the sulfonium-ion center and an active site carboxylate Asp 204 in the crystal structure of the salacinol–Golgi α-mannosidase II (GM II) complex[30], as also seen between the nitrogen atom of swainsonine, a naturally-occurring GM II inhibitor, and Asp 204 in the crystal structure of the swainsonine–GM II complex, provides further validation of this proposal.

3. SYNTHESIS OF SALAPRINOL

Previously, Muraoka et al.[25] reported the synthesis of a diastereomeric mixture **9** of salaprinol, with respect to the C-2′ configuration. Optimization of the earlier synthetic route enabled them to obtain each diastereomer, **10** and **11**, as single crystals[26]. Spectroscopic properties of **10** were found to be

completely in accord with those of authentic salaprinol isolated from *S. prinoides*. Hence, the absolute stereostructure of salaprinol was assigned as **10**, having the *S*-configuration at C-2′ [26].

The general synthetic strategy for the preparation of sulfonium sulfates involves nucleophilic ring opening of a cyclic sulfate by the sulfur atom of a thioether[19]. Hence, the starting point in the synthesis of any such sulfonium sulfate would be to synthesize a suitable cyclic sulfate. The required cyclic sulfate **14** for the synthesis of salaprinol was synthesized from glycerol (Scheme 2). Thus, 2-*O*-benzyl-1,3-di-*O*-tritylglycerol (**15**) was obtained in two steps starting from glycerol. In the first step, the selective tritylation of the primary hydroxy groups was optimized by conducting the reaction at room temperature instead of running the reaction at 100 °C as done in the previous synthetic route, which gave a considerable amount of 1,2,3-tri-*O*-tritylglycerol. Benzylation, followed by removal of trityl groups by treatment with 10% sulfuric acid yielded the diol which was then converted into the required cyclic sulfate **14**. Use of 10% sulfuric acid for the removal



SCHEME 2

of trityl protecting groups significantly improved the yield of the corresponding diol compared to the conditions (80% acetic acid) used in the earlier synthetic route, which resulted in undesirable acetylation of the corresponding diol. During the coupling reaction of the cyclic sulfate **14** with thioarabinitol (**3**) in 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP), one of the epimers deposited in the reaction mixture, which was filtered, recrystallized, and characterized as **16**. Chromatographic separation of the condensed filtrate gave a 10:1 epimeric mixture of **17** and **16**. Pure 2′-*epi*-salaprinol (**11**) was obtained from **16** by hydrogenolysis using 10% Pd-C and H_2 (Scheme 2). Hydrogenolysis of a 10:1 epimeric mixture of **17** and **16** followed by crystallization yielded pure salaprinol (**10**).

4. SYNTHESIS OF KOTALANOL ANALOGUES

The absolute stereostructure of kotalanol (**2**) could be one of 32 possible stereoisomers, with respect to the undefined configurations at the five stereogenic centers of the acyclic side chain. In order to determine the absolute stereochemical structure of kotalanol, we relied on our previous data on the inhibitory activities of the lower 5- and 6-carbon chain homologues and related heteroatom analogues **8** and **18**–**26** (Fig. 4) against recombinant human maltase glucoamylase (MGA), a critical intestinal glucosidase in-

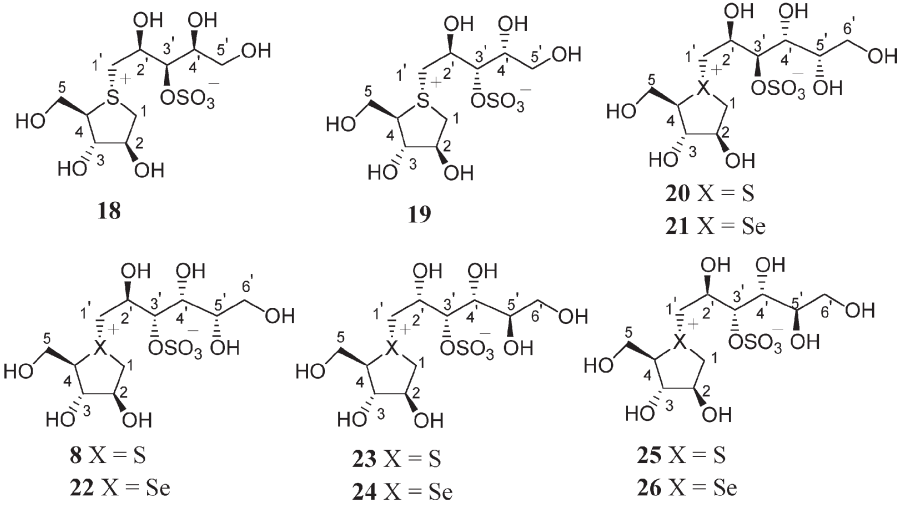


FIG. 4
Five- and six-carbon chain-extended analogues of salacinol synthesized by our group[21–24]

volved in the breakdown of glucose oligomers into glucose[21–24]. The inhibitory activities show a strong dependence on a particular stereochemical pattern with respect to each stereogenic center in the acyclic side chains (Table II). For example, the inhibitory activity of compound **25** was found to be 0.65 μmol/l [24], whereas compound **23**, having the same configurations as compound **25** at all of the stereogenic centers except C-2′, was found to be inactive (Table II)[23].

Based on these results, it appeared to us that the four possible stereochemical patterns for the stereogenic centers in the acyclic side chain of kotalanol are as shown in compound **27** (Fig. 5), with the *S*-configuration at C-2′ and C-3′, *R*-configuration at C-4′, and *R*- or *S*-configurations at C-5′ and C-6′. Although our results indicated that the configuration at C-3′ is unimportant (Table II), we chose the *S*-configuration at C-3′ to reflect a presumed common biosynthetic pathway for salacinol and kotalanol. This approach led us to narrow down the possible stereoisomers of kotalanol from

TABLE II

Experimentally determined K_i values against MGA for compounds **8** [21] and **18**–**26** [22–24] and salacinol (**1**)[32] with an identical 1,4-anhydro-4-thio-D-arabinitol configuration in the heteroalditol ring and acyclic chains of 5 and 6 carbons with different configurations at the stereogenic centers[a]

Inhibitor	Configurations at the stereogenic centers				K_i, μmol/l
	C-2′	C-3′	C-4′	C-5′	
Salacinol	*S*	*S*	–	–	0.19 ± 0.02 [32]
18	*S*	*R*	*S*	–	NA[b,21]
19	*S*	*S*	*R*	–	0.26 ± 0.02 [21]
20	*S*	*R*	*R*	*S*	0.25 ± 0.02 [21]
21	*S*	*R*	*R*	*S*	0.10 ± 0.02 [22]
8	*S*	*S*	*R*	*S*	0.17 ± 0.03 [21]
22	*S*	*S*	*R*	*S*	0.10 ± 0.02 [22]
23	*R*	*S*	*R*	*R*	NA[b,23]
24	*R*	*S*	*R*	*R*	41.0 ± 7.0 [23]
25	*S*	*S*	*R*	*R*	0.65 ± 0.10 [24]
26	*S*	*S*	*R*	*R*	0.14 ± 0.03 [24]

[a] Analysis of MGA inhibition was performed using maltose as the substrate, and measuring the release of glucose. Absorbance measurements were averaged to give a final result. [b] NA: not active.

32 to 4. The synthesis of the first two candidates, **28** and **29**, and their inhibitory activities against MGA were reported by us recently (Fig. 5)[31]. In these compounds, the choice of the *S*-configuration at C-5′ was based on the lower K_i value of **8** vs **25**.

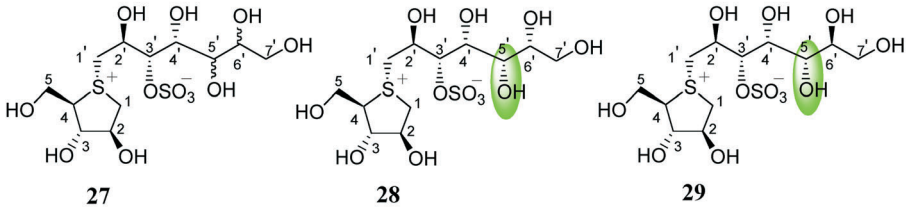
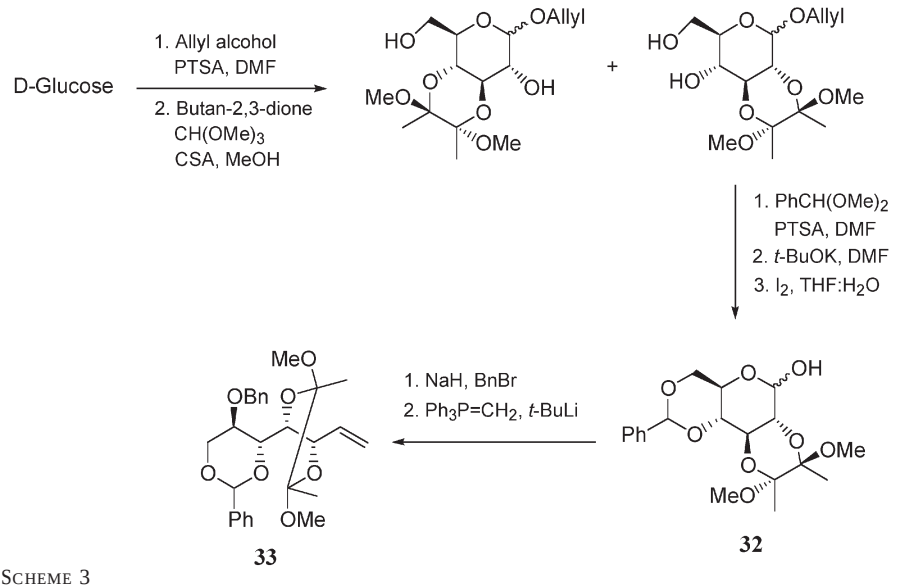


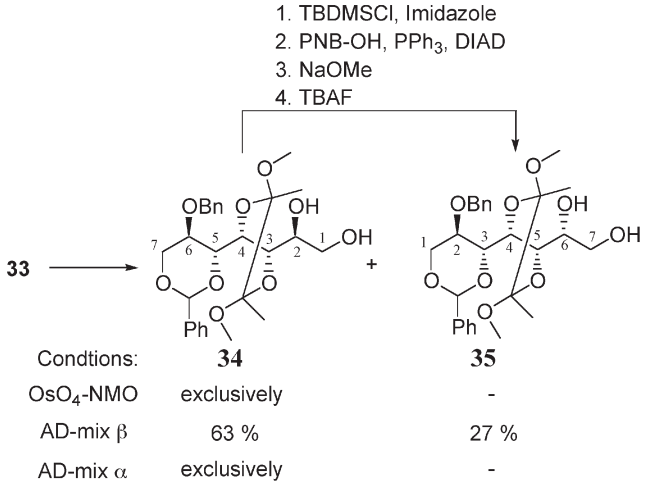
FIG. 5
Proposed stereochemical pattern for the side chain of kotalanol and initial candidates

The synthesis of compounds **28** and **29** started with the cyclic sulfates **30** and **31**, which were obtained in turn, by homologation of a suitably protected hexose sugar via sequential Wittig and dihydroxylation reactions as shown in Schemes 3 and 4. Thus, compound **32** was synthesized in four steps starting from D-glucose, its benzylation, followed by Wittig reaction yielded alkene **33**.



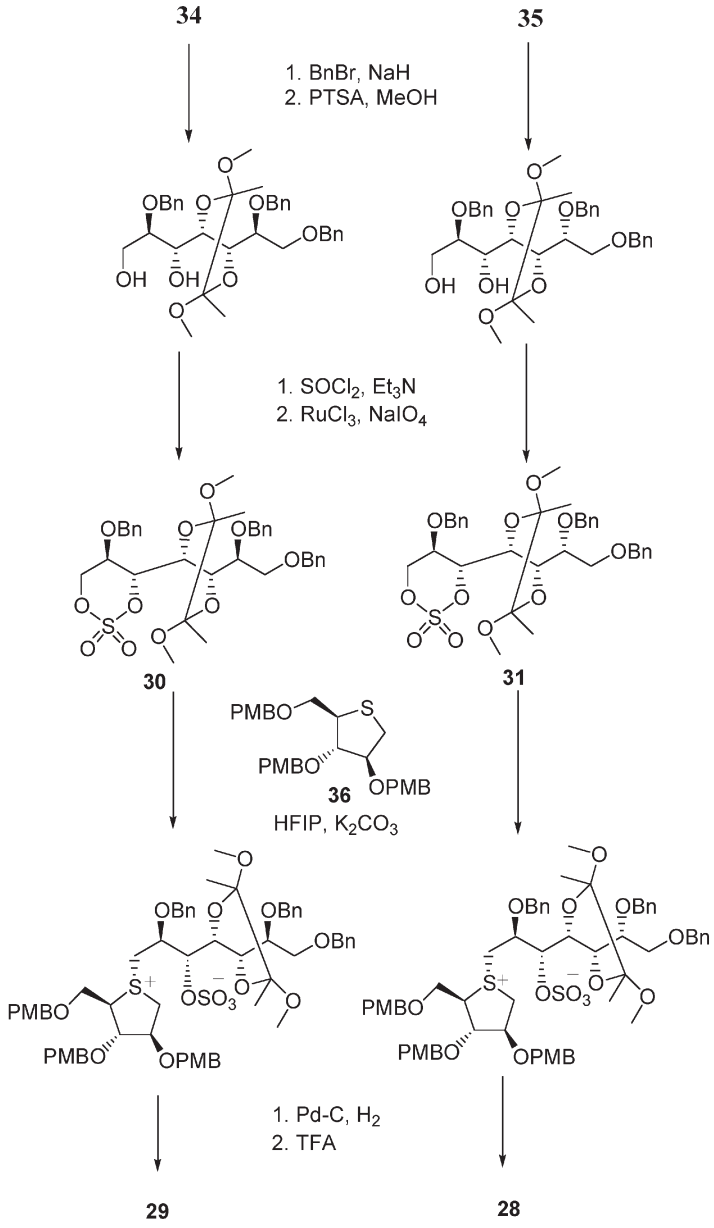
SCHEME 3

Dihydroxylation of compound **33** under OsO_4-*N*-methylmorpholine-*N*-oxide (NMO) conditions yielded one diastereomer **34** exclusively (Scheme 4). The stereochemical outcome of this reaction was assigned by Kishi's empirical rule for dihydroxylation[33], which predicts that in the *syn*-hydroxylation of acyclic allylic alcohols the relative configuration of the pre-existing hydroxy group and the adjacent newly introduced hydroxyl group in the major product is *erythro*. Unfortunately, efforts to obtain the other diastereomer **35** using AD-mix β or AD-mix α resulted in the formation of diastereomer **34** as the major product. Hence, the desired diastereomer **35** was obtained through a Mitsunobu protocol from diastereomer **34**, as shown in Scheme 4.



SCHEME 4

Compounds **34** and **35** were converted into the required cyclic sulfates, **30** and **31**, respectively, as shown in Scheme 5. The coupling reaction of thioether **36** with **31** and **30** using our optimized reaction conditions (HFIP, K_2CO_3, sealed tube) gave the corresponding sulfonium sulfates which, upon deprotection, yielded the desired candidates **28** and **29**, respectively (Scheme 5). Comparison of the physical data of **28** and **29** with those reported for kotalanol (**2**)[12] revealed discrepancies with respect to some of the chemical shift values in the ^1H and ^{13}C NMR spectra taken in pyridine-d_5. The most notable difference was the chemical shift value of H-5′, reported at 5.86 ppm in kotalanol (**2**)[12], which appeared at 4.94 and 4.65 ppm, for **28** and **29**, respectively. In fact, compounds **28** and **29** had


34
35
1. BnBr, NaH
2. PTSA, MeOH
1. SOCl2, Et3N
2. RuCl3, NaIO4
30
31
36
HFIP, K2CO3
1. Pd-C, H2
2. TFA
29
28

SCHEME 5

no signal appearing below 5.47 and 5.34 ppm, respectively. Similarly, the most notable difference in the ^{13}C NMR was the chemical shift value of C-3′; compared to compounds **28** and **29** (for C-3′ δ 80.5 and 81.8 ppm, respectively), C-3′ is shielded in kotalanol (for C-3′ δ 77.9 ppm). Comparison of accumulated data to date for related analogues indicates that C-3′ exhibits an upfield shift when the sulfate moiety at C-3′ and the hydroxy group at C-5′ are *anti* to each other. Thus, in kotalanol (**2**), C-3′ resonates at 77.9 ppm; the corresponding shifts in **20**, **23** and **25** are 78.9 [21], 77.6 [23b] and 78.3 ppm [24], respectively. This leads us to speculate that kotalanol (**2**) has the opposite configuration at C-5′ to **28** and **29**, with an *anti* relationship between the substituents at C-3′ and C-5′, as shown in Fig. 6 for compound **37**. This still leaves the configuration at C-6′ unspecified (Fig. 6).

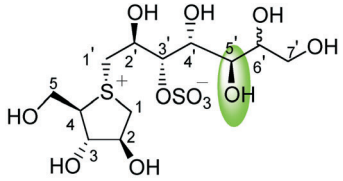


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FIG. 6
Proposed stereostructure for kotalanol by Nasi et al.[31]

Compounds **28** and **29** inhibited MGA with K_i values of 0.10 and 0.13 μmol/l, respectively, and they constitute the most active compounds in this class of glucosidase inhibitors to date[31].

Recently, Muraoka and co-workers[34] also reported the synthesis of four kotalanol analogues (**38**–**41**; Fig. 7) with the *S*-configuration at C-4′ and have compared their inhibitory activities with that of natural kotalanol (**2**). It is noteworthy that all four compounds showed less inhibitory activity than kotalanol (Table III)[34], also suggesting that the configuration at C-4′ in kotalanol is *R*.

The required cyclic sulfates **42**–**45** for the synthesis of compounds **38**–**41** were synthesized by homologation of a suitably protected intermediate **46** via sequential Wittig and dihydroxylation reactions, as shown in Scheme 6 [34].

Thus, the acetonide intermediate **46**, obtained from D-xylose in several steps[34], was deprotected using 0.5% H_2SO_4 and subjected to Wittig reaction which gave a mixture of *cis*- and *trans*-olefins **47**. *Cis*- and *trans*-**47** were separated by column chromatography. The ester group of *trans*-**47** was then

reduced using diisobutylaluminium hydride (DIBAL) to give the allylic alcohol **48**. Dihydroxylation of **48** using OsO_4 and NMO gave a mixture of isomeric triols **49** and **50** which were separated by column chromatography and converted into the corresponding cyclic sulfates **42** and **43**, respectively, as shown in Scheme 6. Finally, coupling of the cyclic sulfates **42** and **43** with the thioether **3**, followed by deprotection using 30% aqueous

TABLE III
Inhibitory activities of compounds **38**–**41**[34]

Compound	IC_{50}, μmol/l		
	maltase	sucrase	isomaltase
38	235	136	11
39	49	67	1.6
40	235	214	16
41	58	32	6.5

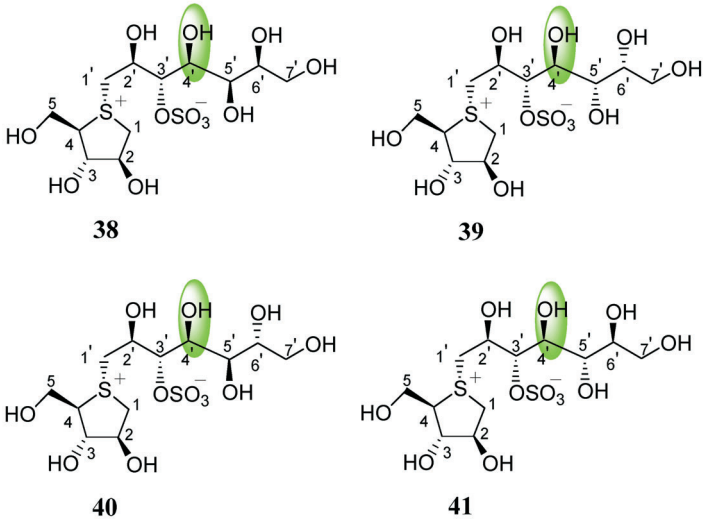
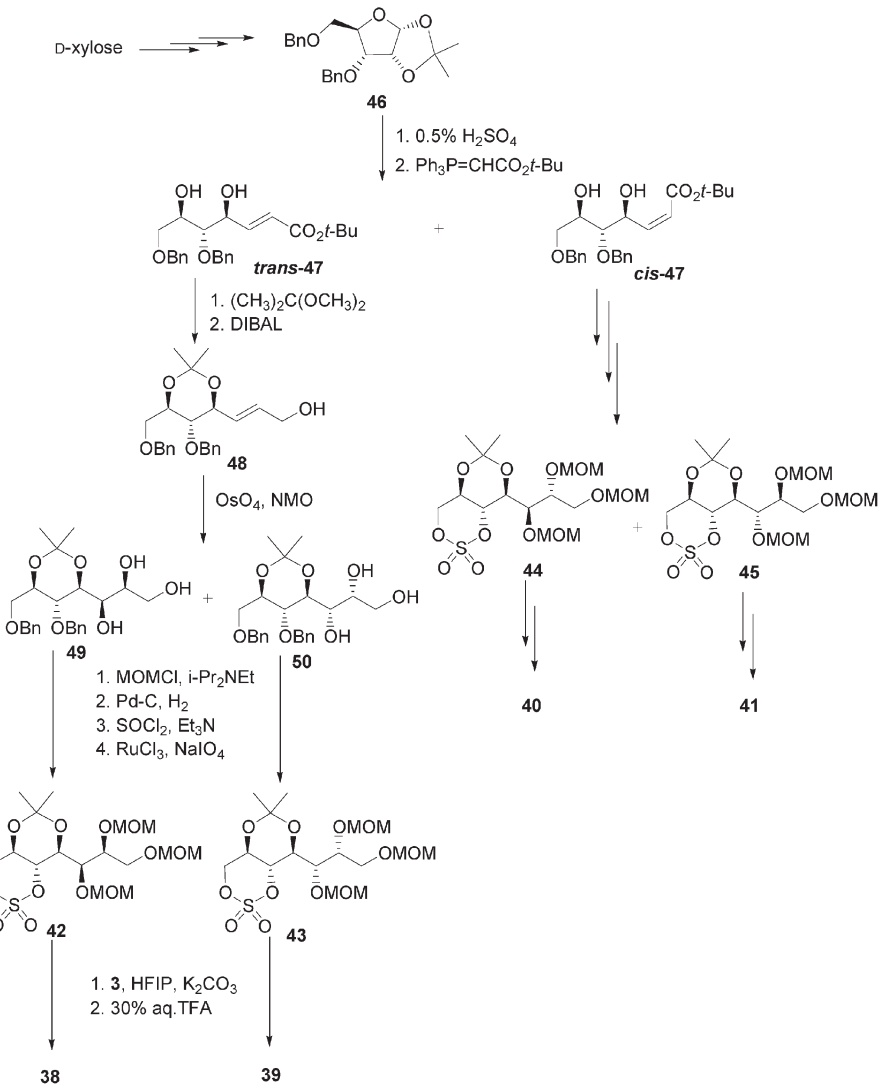


FIG. 7
Kotalanol analogues made by Muraoka and co-workers[34]

trifluoroacetic acid (TFA) afforded the kotalanol analogues **38** and **39**. Similarly, analogues **40** and **41** were synthesized from the cyclic sulfates **44** and **45** which were, in turn, synthesized from *cis*-**47**.



SCHEME 6

5. 1,5-ANHYDRO-1,5-IMINO-D-GLUCITOL AND 1,5-ANHYDRO-1,5-IMINO-D-XYLITOL ANALOGUES OF SALACINOL

Previously, we reported the synthesis of 1,5-anhydro-1,5-imino-D-glucitol analogues **51** of salacinol[35]. We found that this compound **51** was inactive against glucoamylase G2 from *Aspergillus niger*[35], as well as recombinant human maltase glucoamylase (MGA) (80% activity remaining at 1 mM inhibitor concentration)[36]. However, the 1,5-anhydro-1,5-imino-D-xylitol analogue **52** (lacking the side chain at C-5; Fig. 8) had some activity against MGA (IC_{50} = 30 μmol/l)[36]; this activity is significantly lower than that of salacinol (K_i = 0.2 μmol/l)[32]. Very recently, Tanabe et al.[37] reported the synthesis of the same compound **51** and its glucosidase inhibitory activity against rat intestinal maltase and sucrase. Surprisingly, compound **51** showed equivalent inhibitory activities (IC_{50} values against maltase and sucrase were 8.8 and 2.5 μmol/l, respectively) to those of salacinol (**1**; Table I). The corresponding de-*O*-sulfonated analogue **53** was also found to be active (IC_{50} values against maltase and sucrase were 45 and 2.1 μmol/l,

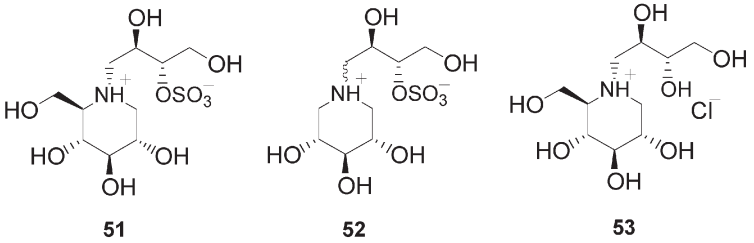
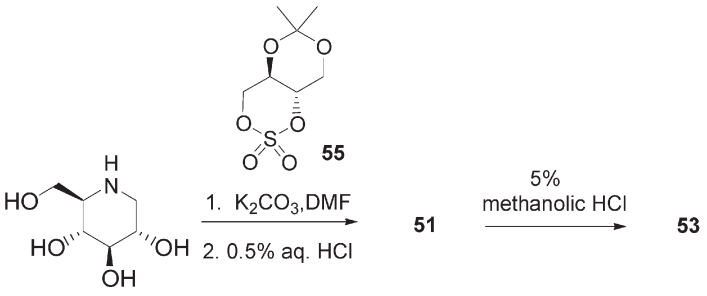


FIG. 8
1,5-Anhydro-1,5-imino-D-glucitol and 1,5-anhydro-1,5-imino-D-xylitol analogues of salacinol



SCHEME 7

respectively). In this report, compound **51** was obtained in two steps from deoxynojirimycin (**54**) and the cyclic sulfate **55**, synthesized from D-glucose, as shown in Scheme 7 [37]. The corresponding de-*O*-sulfonated analogue **53** was obtained by treatment with 5% methanolic HCl.

6. CONCLUSIONS

It is noteworthy that recent pharmacological studies suggest that the *Salacia* extract could be used in a multiple-target strategy for the treatment of obesity and associated disorders, including diabetes[38]. Thus, *Salacia* extract was successful in modulating multiple targets: α-glucosidases[8,9,13], peroxisome proliferator-activated receptor-alpha (PPARα)-mediated lipogenic gene transcription[39], angiotensin II/angiotensin II type I receptor[40], aldose reductase[13,14] and pancreatic lipase[41]. The antidiabetic effects of *Salacia* extract have therefore been attributed to these multi-target actions[38]. However, more rigorous mechanistic studies with the identified bioactive components and structure–activity relationship (SAR) studies would allow a better understanding of these multitarget actions exhibited by the herbal extract. Another study shows that salacinol (**1**) is a potent inhibitor of human lysosomal α-glucosidase, with an IC_{50} value of 0.34 μmol/l and hence could have potential as a pharmacological chaperone in the treatment of glycospingolipid (GSL) storage disorders, such as Pompe's disease[42]. Given these therapeutic indications, the development of efficient synthetic strategies to obtain the bioactive components **1**, **2**, **7**, **10** and **12** isolated from *Salacia* species, in conjunction with their SAR studies, takes on some prominence.

7. ABBREVIATIONS

CSA	camphorsulfonic acid
DIAD	diisopropyl azodicarboxylate
MOM	methoxymethyl
PMB	*para*-methoxybenzyl
PNB-OH	*para*-nitrobenzoic acid
PTSA	*para*-toluenesulfonic acid
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl

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