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Potent Glucosidase Inhibitors: De-*O*-sulfonated Ponkoranol and Its Stereoisomer

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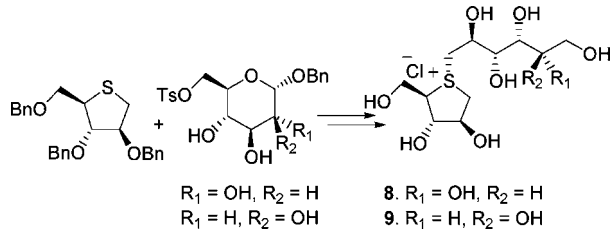
ABSTRACT



Ponkoranol, a glucosidase inhibitor isolated from the plant *Salacia reticulata*, comprises a sulfonium ion with an internal sulfate counterion. An efficient synthetic route to de-*O*-sulfonated ponkoranol and its 5′-stereoisomer is reported, and it is shown that these compounds are potent glucosidase inhibitors that inhibit a key intestinal human glucosidase, the *N*-terminal catalytic domain of maltase glucoamylase, with K_i values of 43 ± 3 and 15 ± 1 nM, respectively.

Compounds isolated from medicinal plants can provide the lead structures for drug development programs.[1,2] For example, the aqueous extracts of the roots and stems of the large woody climbing plant *Salacia reticulata*, known as Kothalahimbutu in Singhalese, have been used in the Ayurvedic system of Indian medicine in Sri Lanka and Southern India for the treatment of Type-2 diabetes.[3,4] Several glucosidase inhibitors have been isolated from the water-soluble fraction of this plant extract and also other plants that belong to the *Salacia* genus such as *Salacia chinensis*, *Salacia prinoides*, and *Salacia oblonga* which explain, at least in part, the antidiabetic property of the aqueous extracts of these plants.[5−7] Thus far, six components have been isolated from the plant *S. reticulata*, namely salaprinol (**1**),[7] salacinol (**2**),[6] ponkoranol (**3**),[7] kotalanol (**4**),[5] de-*O*-sulfonated kotalanol (**5**),[8] and de-*O*-sulfonated salacinol (**6**)[9] (Figure 1), all of which possess a common structural motif that comprises a 1,4-anhydro-4-thio-D-arabinitol and

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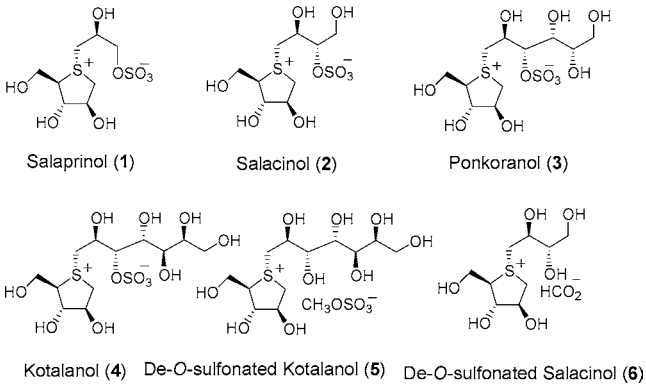

Figure 1. Components isolated from *Salacia* species.

a polyhydroxylated side chain. We have carried out extensive research on the synthesis of higher homologues of salacinol (**2**) which has led to the stereochemical structure elucidation of compounds **3**−**5**.[10−12] Interestingly, ponkoranol (**3**), the recently isolated[7] six-carbon-chain homologue of salacinol, was synthesized by us several years earlier with the expectation that it would be an effective glucosidase inhibitor.[13]

Recently, Minami et al.[9] reported the isolation of a thiosugar sulfonium−alkoxide inner salt (**7**), neosalacinol (Figure 2), from *S. reticulata*; however, Tanabe et al.[14] have

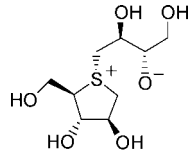

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Figure 2. Proposed structure of neosalacinol.

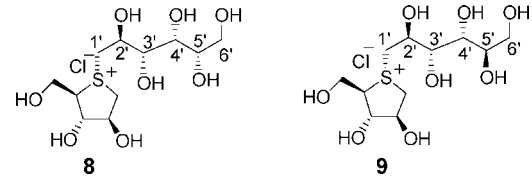
shown that this compound is de-*O*-sulfonated salacinol (**6**). Comparison of the inhibitory activities of de-*O*-sulfonated salacinol (**6**) vs salacinol (**2**) and de-*O*-sulfonated kotalanol (**5**) vs kotalanol (**4**) against rat intestinal α-glucosidases (maltase, sucrase, and isomaltase) revealed that the desulfonated analogues were either equivalent or better inhibitors than the parent compounds.[7,15,16] Furthermore, we have shown recently that de-*O*-sulfonated kotalanol (**5**) ($K_i = 0.03 \pm 0.01$ μM) is more potent an inhibitor of the *N*-terminal catalytic domain of human intestinal maltase glucoamylase (ntMGAM) than kotalanol (**4**) itself ($K_i = 0.19 \pm 0.03$ μM) (Table 1).[17]

Table 1. Experimentally Determined K_i Values[a]

Inhibitor	Ki (nM)
2	190 ± 20[19]
3	170 ± 30[19]
4	190 ± 30[17]
5	30 ± 10[17]
8	43 ± 1
9	15 ± 1

[a] Analysis of ntMGAM inhibition was performed using maltose as the substrate.

In view of these findings, it was of interest to question whether de-*O*-sulfonated ponkoranol **8** and its 5′-stereoisomer **9** (Figure 3) would be more potent inhibitors than ponkoranol itself.



8 **9**

Figure 3. De-*O*-sulfonated ponkoranol and its 5′-stereoisomer.

Our previous work with kotalanol analogues had suggested that the configuration at C-5′ was not critical for inhibitory

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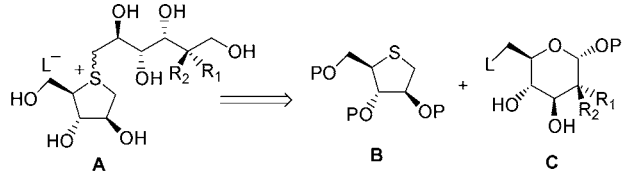
activity.[17,18] We report here an efficient synthetic route to de-*O*-sulfonated ponkoranol **8** and its 5′-stereoisomer **9** and show that they are very potent inhibitors of the amino terminal catalytic domain of human maltase glucoamylase (ntMGAM).[19]

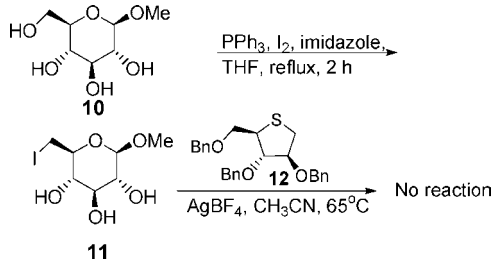
The sulfonium ions **A** could be synthesized by alkylation of an appropriately protected 1,4-anhydro-4-thio-D-arabinitol **B** at the ring sulfur atom with agent **C**. The desired stereochemistry at C-5′ could be readily obtained by choice of either D-glucose or D-mannose as starting material (Scheme 1).

Scheme 1. Retrosynthetic Analysis



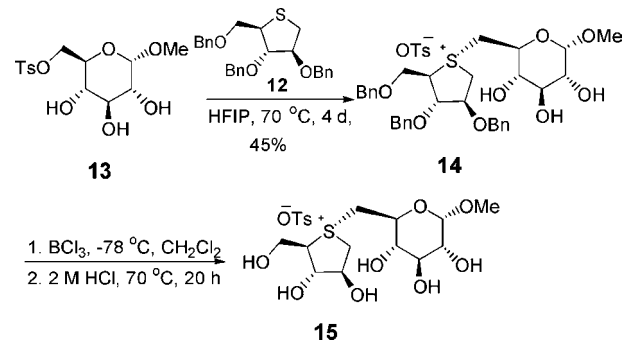
Initially, the S-alkylation of thioarabinitol **12**[20] with methyl 6-iodo-β-D-glucopyranoside **11**[21] in CH_3CN using $AgBF_4$ at 65 °C was examined, based on the procedure that has been reported for S-alkylation with simple alkyl halides (Scheme 2).[22] No product formation and decomposition of the starting

Scheme 2. First Attempted Synthesis of **8**



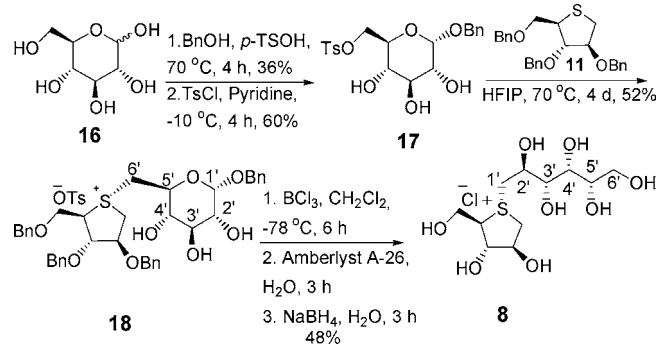
material were observed by TLC; the reaction in 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HFIP)[23] as a solvent was also unsuccessful. In contrast, the coupling reaction with the *p*-toluenesulfonyl ester **13**[24] in HFIP at 70 °C proceeded smoothly and yielded the sulfonium ion **14** (Scheme 3). The

Scheme 3. Second Attempted Synthesis of **8**



benzyl groups of compound **14** were removed by treatment with boron trichloride at −78 °C in CH_2Cl_2. However, attempts to hydrolyze the methyl glycoside **15** with 2 M HCl were not successful, and decomposition of the product was observed. Therefore, a benzyl glycoside was chosen as a protecting group at the anomeric position to ensure its facile removal after the coupling reaction. Thus, benzyl 6-*O*-*p*-toluenesulfonyl-α-D-gluco **17** or mannopyranoside **20** were readily prepared from D-glucose and D-Mannose, respectively, according to literature procedures.[25−27] The thioether **12** was reacted with **17** in HFIP containing K_2CO_3[23] to give the protected sulfonium ion **18** in 52% yield (Scheme 4).

Scheme 4. Synthesis of Compound **8**



The benzyl groups were then removed by treatment with boron trichloride at −78 °C in CH_2Cl_2. During the course of deprotection, the *p*-toluenesulfonate counterion was

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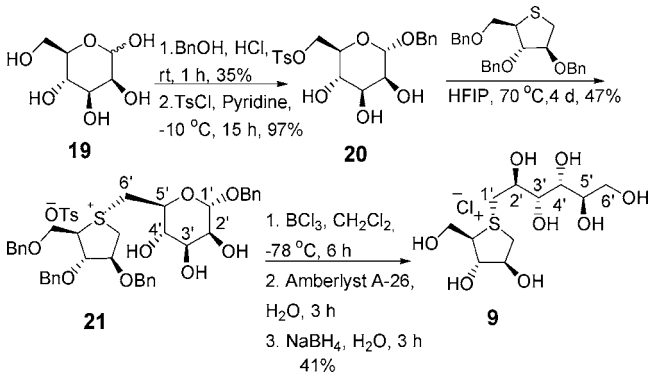
partially exchanged with chloride ion. Similar results were observed in previous work from our laboratory.[22] Hence, after removal of the benzyl groups, the product was subsequently treated with Amberlyst A-26 resin (chloride form) to completely exchange the *p*-toluenesulfonate counterion with chloride ion. Finally, the crude product was reduced with $NaBH_4$ to provide the desired de-*O*-sulfonated ponkoranol **8** in 48% yield over three steps (Scheme 4). The other diastereomer was obtained similarly. Thus, compound **20** was reacted with the thioether **12** to give the protected sulfonium ion **21** in 47% yield which was converted, as before, to the desired compound **9** in 41% yield over three steps (Scheme 5).

Scheme 5. Synthesis of Compound **9**



The absolute stereochemistry at the stereogenic sulfur center in **18** and **21** was established by means of 1D-NOESY experiments (Figure 4) which showed H-4 to H-6′ correlations, implying that these atoms are syn-facial with respect to the sulfonium salt ring.

Finally, we comment on the inhibitory activities of compounds **8** and **9** against the *N*-terminus of recombinant human maltase glucoamylase (ntMGAM),[19] a critical intestinal glucosidase for postamylase processing of starch-derived oligosaccharides into glucose. The de-*O*-sulfonated ponkoranol **8** and its 5′-stereoisomer **9** inhibited ntMGAM with K_i values of 43 ± 3 and 15 ± 1 nM, respectively, both significantly lower than that (170 ± 30[19]) for ponkoranol (**3**) itself (Table 1). Thus, it would appear that de-*O*-sulfonation is beneficial. We have attributed this fact previously to alleviation of steric compression of the sulfate anion in a hydrophobic pocket within the active site of ntMGAM.[18] The K_i values for **8** and **9** compare to a K_i value for de-*O*-sulfonated kotalanol of 30 ± 1 nM.[17] It would appear, therefore, that the configuration at C-5′ is not critical for dictating enzyme inhibitory activity against ntMGAM and, furthermore, that extension of the acyclic carbon chain beyond six carbons is not essential. We note that **9** is the most potent compound to date in this class of molecules.

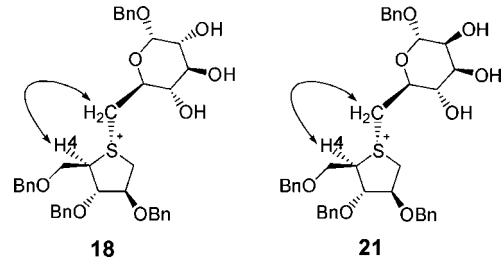


Figure 4. 1D-NOESY correlations of selected protons in compounds **18** and **21**.

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Supporting Information Available: Experimental procedures, characterization data, ^1H and ^{13}C NMR spectra of compounds **8**, **9**, **14**, **18**, and **21**, and 1D-NOESY spectra of compounds **18** and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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