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Attempted Synthesis of 2-Acetamido and 2-Amino Derivatives of Salacinol. Ring Opening Reactions

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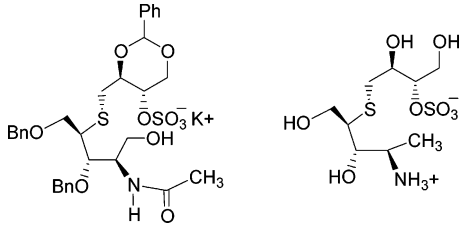
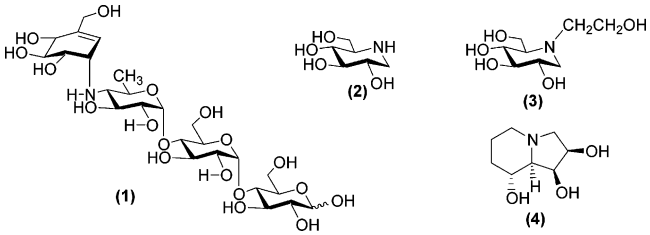
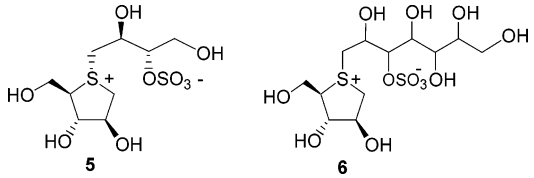


The attempted synthesis of the 2-acetamido and 2-amino derivatives of salacinol, a naturally occurring glycosidase inhibitor, is described. Reaction of the protected acetamidothioarabinitol unit with the cyclic sulfate derived from L-erythritol gave the corresponding sulfonium sulfate, which underwent ring opening to give an acyclic amido sulfate. The corresponding reaction of the protected azidothioarabinitol unit with the cyclic sulfate proceeded to give the sulfonium sulfate. However, upon reduction of the azido function to an amine it formed an acyclic ammonium sulfate.

Glycosidase enzymes are involved in many important biological processes such as digestion, the biosynthesis of glycoproteins, and the catabolism of glycoconjugates.[1−5] Inhibition of glycosidases has potential as a means of therapy for diseases such as type II diabetes, cancer, and infectious diseases.[6] For example, acarbose (**1**) and 1-deoxynojirimycin (DNJ, **2**) are two naturally occurring glycosidase inhibitors, of which **1** has been used for the oral treatment of type II diabetes.[7−10] Miglitol (**3**), a synthetic α-glycosidase inhibitor, has also been approved by the Food and Drug Administration for use in the treatment of type II diabetes.[11,12] Swainsonine (**4**), an inhibitor of Golgi α-mannosidase II (GMII), a key enzyme in the *N*-glycosylation pathway, reduces tumor cell metastasis, enhances cellular immune responses, and slows tumor cell growth.[13]



Salacinol (**5**) and kotalanol (**6**) are two naturally occurring glycosidase inhibitors which have been extracted from the roots and stems of the Sri Lankan plant, *Salacia reticulata*.[14−17] The extracts from this plant have been traditionally used for the treatment of the type II diabetes in Sri Lanka and India.[18] The permanent positive charge of the sulfur atom on salacinol and kotalanol and the shape of the ring are thought to mimic the oxacarbenium ion transition state in glycosidase-mediated hydrolysis reactions.[19]



We and others have reported the synthesis of salacinol and its diastereomers,[6,20−26] the nitrogen and selenium analogues

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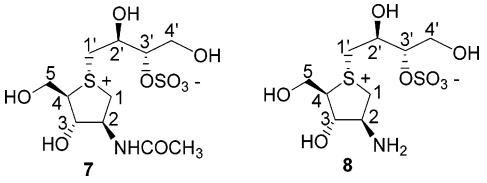
of salacinol,[27−33] chain-extended analogues, [34−38] and other analogues.[34−38] Some of these derivatives exhibited interesting biological properties.[34,35,39,40]

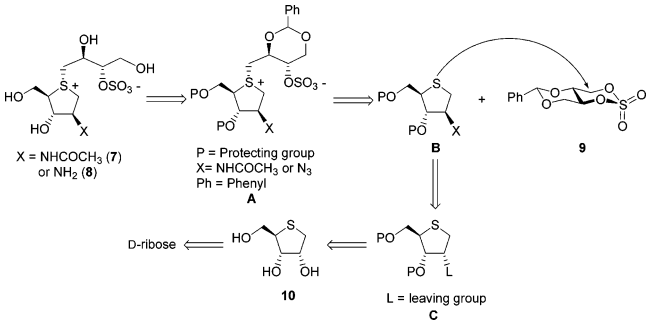
It was of interest to investigate the effect of introducing an acetamido or an amine function at the C-2 position of salacinol to broaden the scope of glycosidase inhibitory activities, in particular, to target the hexosaminidase enzymes. Therefore, we report herein the attempted synthesis of the 2-acetamido- (**7**) and 2-amino- (**8**) substituted analogues of salacinol. These derivatives were found to undergo ring opening reactions by nucleophilic participation of the amide or amine moieties to give acyclic amido or ammonium sulfates, respectively.



The target compounds **7** and **8** could be obtained by hydrogenolysis of the coupled product **A**, which has an acetamide or an azide group at C-2 (Scheme 1). Compound **A** could be synthesized, in turn, by the alkylation of a 2-azido- or 2-acetamido-1,4-anhydro-4-thio-D-arabinitol derivative (**B**) with 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic sulfate (**9**). Compound **B** could, in turn, be synthesized from the reaction of sodium azide with a selectively protected 1,4-anhydro-4-thio-D-ribose (**C**) unit in which C-2 bears a good leaving group. Compound **C** could be obtained from 1,4-anhydro-4-thio-D-ribose (**10**), which could be synthesized, in turn, from commercially available D-ribose.[41]

1,4-Anhydro-4-thio-D-ribose (**10**) was synthesized from commercially available D-ribose in 11 steps according to a literature procedure.[41] To introduce an azide group selectively at C-2 of compound **10**, the 3-OH and 5-OH groups were first protected by using 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane in pyridine

SCHEME 1



to give **11**, and the 2-OH group of compound **11** was then mesylated (**12**). The substitution of the mesylate in **12** by an azide group did not proceed in MeOH; however, at 75 °C in DMF, the substitution proceeded with inversion of configuration at C-2 (**13**). The azide group in compound **13** was then reduced to an amine by using triphenylphosphine (PPh_3) in dioxane: MeOH:H_2O (10:3:1) to afford compound **14** in 70% yield; acetylation then afforded compound **15** in 77% yield. The alkylation reaction of compound **15** with 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic sulfate (**9**) did not proceed as expected. Instead, the silyl protecting group was removed under the reaction conditions. Therefore, we chose to replace this group by benzyl ethers. The silyl protecting group in **15** was thus removed, using tetra-*n*-butylammonium fluoride (TBAF), and the crude product obtained was then subjected to benzylation by using benzyl bromide and a mixture of BaO and $Ba(OH)_2 \cdot 8H_2O$ to afford compound **16** in 78% yield. A 1D-NOESY experiment performed on compound **16** confirmed the stereochemistry at C-2 by showing a correlation between H-2 and H-4 of the five-membered ring. The alkylation reaction between compound **16** and 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic sulfate (**9**) gave compound **18c** in 87% yield. A 1D-NOESY experiment performed on the coupled product showed no correlation between H-1′ and H-1 (as would be expected for the target compound **17**); the latter result also confirms that the five-membered ring had been opened to give an acyclic thioether. The ^{13}C NMR spectrum of the coupled product indicated the presence of a carbonyl group, and a g-HMBC spectrum showed a correlation between this carbonyl carbon and H-2, and no correlation between the carbonyl carbon and H-1, thus suggesting **18c** as the product of the reaction. The IR spectrum of this product suggested the presence of an OH group as well as an amide carbonyl group, further corroboration of the structure of **18c**. The high-resolution mass spectrum confirmed the molecular formula of compound **18c**. The microanalysis of compound **18c** also confirmed the presence of potassium as the counterion (Scheme 2).

Scheme 3 shows the proposed mechanism for the formation of **18c**. Nucleophilic attack of the amide oxygen on C-1 of compound **17** would result in opening of the five-membered ring to give (**18a**), which could then react with water during the processing and purification to give **18b**. Further rearrangement of the orthoaminal (**18b**) would result in **18c**.

To prevent the intramolecular nucleophilic participation of the amide group observed in compound **18a**, we next examined the alkylation reaction of a 2-azido arabinitol derivative (Scheme 4). Starting from compound **13**, the silyl protecting group was substituted by benzyl protecting groups (**19**). The alkylation reaction of compound **19** with 2,4-*O*-benzylidene-L-erythritol-

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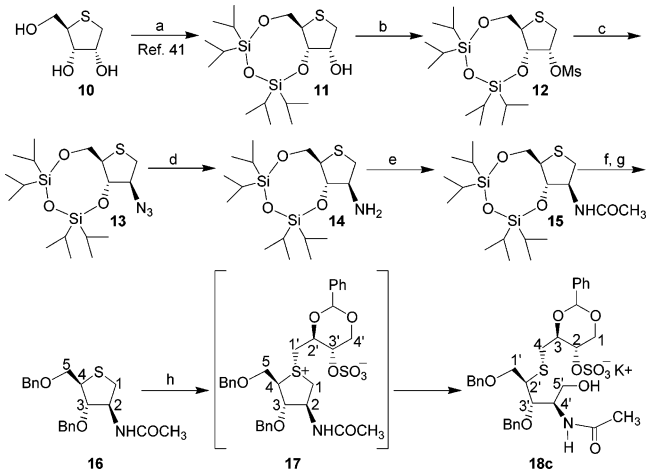
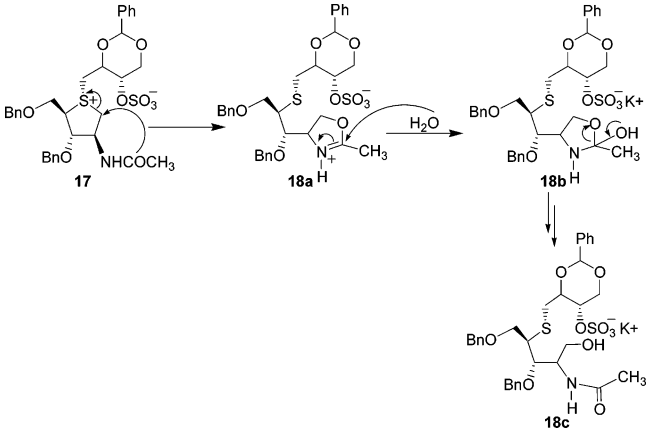
SCHEME 2[a]



[a] Reagents and conditions: (a) 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane, pyridine ($TIPSCl_2$), rt; (b) methanesulfonyl chloride, pyridine; (c) NaN_3, DMF, 85 °C; (d) PPh_3, dioxane:MeOH:H_2O (10:3:1), 55 °C; (e) Ac_2O, pyridine; (f) tetra-*n*-butylammonium fluoride (TBAF), THF; (g) BnBr, BaO (9.3 equiv), $Ba(OH)_2 \cdot 8H_2O$ (1.75 equiv), DMF; (h) 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic sulfate, K_2CO_3, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), 60 °C.

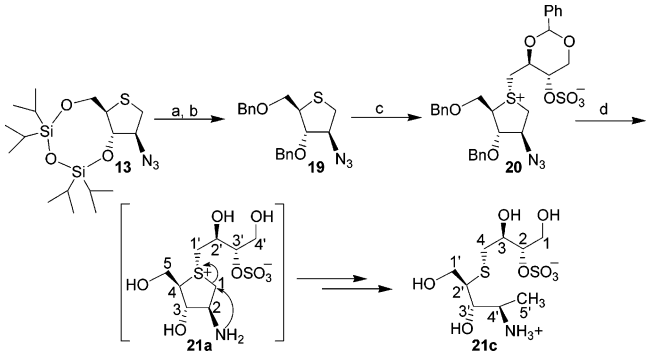
SCHEME 3



1,3-cyclic sulfate (**9**) gave the coupled product **20** in 76% yield. A 1D-NOESY experiment of the coupled product **20** confirmed the formation of the sulfonium salt by showing a correlation between H-1, H-1′, and H-4 in this product. Hydrogenolysis of compound **20** afforded the acyclic thioether **21c** in 53% yield, and not the expected compound **21a** (Scheme 4). A 1D-NOESY experiment showed no correlation between H-1 and H-1′ as one would have expected for compound **21a**. g-HMBC data confirmed that compound **21c** was the likely product of the reaction. Thus, no correlation between H-5′ and C-2′ or between H-5′ and C-4 was observed. In addition, no correlation between H-2′ and C-5′ or H-4 and C-5′ was observed. These results confirm that the ring is opened. Correlations between H-2′ and C-4 and also between H-4 and C-2′ (alternative numbering; see Scheme 4) were observed, indicating that the side chain is on C-2′. A DEPT experiment showed the existence of a CH_3 group, which corroborated the structure **21c**, and the high-resolution mass spectral data were also consistent with the molecular formula of compound **21c**.

Scheme 5 shows the proposed mechanism for the formation of compound **21c** from **21a**. Nucleophilic participation of the

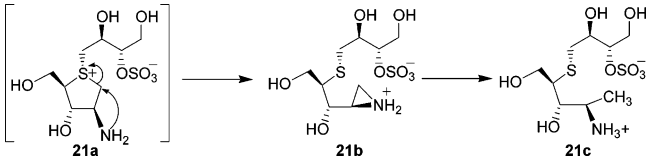
SCHEME 4[a]



[a] Reagents and conditions: (a) tetra-*n*-butylammonium fluoride (TBAF), THF; (b) BnBr, NaH, DMF; (c) 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic sulfate, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), 64 °C; (d) H_2, Pd/C.

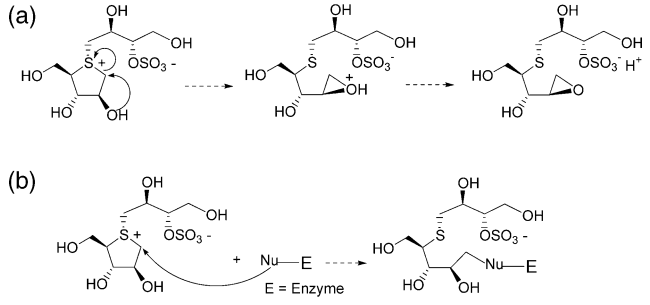
free amine (**21a**) formed during the hydrogenolysis reaction would result in the formation of the aziridinium compound **21b**. Further reduction of compound **21b** during the hydrogenolysis reaction would then afford **21c**.

SCHEME 5



In conclusion, the synthesis of the 2-acetamido and 2-amino derivatives of salacinol was attempted. However, the 2-acetamido analogue underwent ring opening of the five-membered ring by nucleophilic participation of the amide. In the case of the 2-amino derivative, the amine group participated to open the five-membered ring via formation of an aziridinium ion. These are the first examples of which we are aware of the instability of salacinol analogues. Our synthetic efforts to date have not revealed any ring-opened, epoxide products stemming from the participation of O-2 in salacinol analogues (Scheme 6a). Furthermore, enzyme inhibition studies with a variety of glycosidase enzymes have been consistent with a model of reversible, competitive inhibition,[27−32] and have not involved ring-opening reactions by nucleophilic groups in the enzyme active sites (Scheme 6b).

SCHEME 6



Experimental Section

Potassium (2*S*,3*S*)-1,3-Benzylidenedioxy-4-[(2*R*,3*S*,4*R*)-4′-acetamido-1′,3′-bisbenzyloxy-5′-hydroxy-2′-pentylthio]butane-2-sulfate (18c). A mixture of compound **16** (66.6 mg, 0.18 mmol) and 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic sulfate (**9**) (63.5 mg,

1.3 equiv) was dissolved in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) (1.5 mL), and K_2CO_3 (40 mg) was added. The mixture was stirred in a sealed tube in an oil bath (60 °C) for 13 h. The solvent was removed under reduced pressure, and flash chromatography [CH_2Cl_2/MeOH, 10:1] of the crude product gave compound **18c** (100 mg, 87%) as an oil. $[\alpha]_D$ −28 (*c* 0.03, MeOH); ^{1}H NMR (CD_3-OD) δ 7.4−7.1 (15H, m, Ar), 5.46 (1H, s, CHPh), 4.58, 4.45 (2H, 2d, $J_{A,B}$ = 10.9 Hz, CH_2Ph), 4.51 (1H, ddd, $J_{5'b,4'}$ = 7.5 Hz, $J_{5'a,4'}$ = 6.8 Hz, $J_{3',4'}$ = 1.5 Hz, H-4′), 4.48 (1H, dd, $J_{2,1}$ = 5.4 Hz, H-1a), 4.42, 4.39 (2H, 2d, $J_{A,B}$ = 11.9 Hz, CH_2Ph), 4.26 (1H, ddd, $J_{3,2}$ = 9.8 Hz, H-2), 3.88 (1H, dd, $J_{2',3'}$ = 8.7 Hz, H-3′), 3.84 (1H, ddd, $J_{4,3}$ = 1.9 Hz, H-3), 3.78 (1H, dd, $J_{1'b,1'a}$ = 9.8 Hz, $J_{2',1'a}$ = 4.1 Hz, H-1′a), 3.70 (1H, dd, $J_{2',1'b}$ = 4.5 Hz, H-1′b), 3.68 (1H, dd, $J_{2,1b}$ = 1.4 Hz, $J_{1a,1b}$ = 10.8 Hz, H-1b), 3.6 (1H, dd, $J_{5'b,5'a}$ = 10.7 Hz, $J_{4',5'a}$ = 6.9 Hz, H-5′a), 3.4 (1H, dd, $J_{4',5'b}$ = 7.6 Hz, H-5′b), 3.2 (1H, ddd, H-2′), 3.16 (1H, dd, $J_{4b,4a}$ = 15.3 Hz, $J_{3,4a}$ = 1.9 Hz, H-4a), 2.93 (1H, s, CH_3), 2.74 (1H, dd, $J_{3,4b}$ = 8.1 Hz, H-4b); ^{13}C NMR (CD_3OD) δ 172.9 (CO), 138.4, 138.3, 137.9, 128.7, 128.2, 128.1, 127.9, 127.8, 127.6, 127.5, 126.2 (18C, Ph), 101.3 (CHPh), 81.6 (C-3), 77.2 (C-3′), 74.4, 73.0 (2 × CH_2Ph), 70.3 (C-1′), 69.9 (C-2), 69.0 (C-1), 61.8 (C-5′), 52.3 (C-4′), 47.9 (C-2′), 34.8 (C-4), 21.8 (CH_3). Anal. Calcd for $C_{32}H_{38}NO_{10}S_2$: C, 54.91; H, 5.48; N, 2.00. Found: C, 54.89; H, 5.50; N, 2.10. HRMS Calcd for $C_{32}H_{38}NO_{10}S_2$ (M − H) 660.19426, found 660.19407.

(2*S*,3*S*)-1,3-dihydroxy-4-[(2*R*,3*S*,4*S*)-4′-amino-1′,3′-dihydroxy-2′-pentylthio]butane-2-sulfate (21c). The protected compound **20** (178 mg, 0.28 mmol) was dissolved in AcOH:H_2O (4:1, 10 mL) and the solution was stirred with palladium hydroxide catalyst on carbon (100 mg) under H_2 (90 psi). After 72 h, the reaction mixture was filtered. The filtrate was concentrated and the residue was purified by column chromatography [EtOAc/MeOH/H_2O, 10:3:1] to give compound **21c** (50 mg, 53%) as a colorless oil. $[\alpha]_D$ −0.05 (*c* 0.22, MeOH); ^{1}H NMR (D_2O) δ 4.23 (1H, ddd, $J_{3,2}$ = 6.9 Hz, H-2), 3.93 (1H, ddd, H-3), 3.80 (1H, dd, $J_{1b,1a}$ = 12.7 Hz, $J_{2,1a}$ = 3.2 Hz, H-1a), 3.74 (1H, dd, $J_{1'b,1'a}$ = 12 Hz, $J_{2',1'a}$ = 5.53 Hz, H-1′a), 3.70 (1H, dd, H-1b), 3.67 (1H, dd, $J_{2',3'}$ = 5.8 Hz, H-3′), 3.63 (1H, dd, $J_{2',1'b}$ = 5.9 Hz, H-1′b), 3.45 (1H, dt, $J_{3',4'}$ = 6.1 Hz, H-4′), 2.92 (1H, ddd, H-2′), 2.88 (1H, dd, $J_{3,4a}$ = 3.8 Hz, H-4a), 2.64 (1H, dd, $J_{4a,4b}$ = 14.0 Hz, $J_{3,4b}$ = 8.2 Hz, H-4b), 1.15 (3H, d, H-5′); ^{13}C NMR (D_2O) δ 81.2 (C-2), 73.7 (C-3′), 69.4 (C-3), 60.4 (C-1′), 59.8 (C-1), 49.8 (C-2′), 49.5 (C-4′), 34.3 (C-4), 16.1 (C-5′). HRMS Calcd for $C_9H_{20}NO_8S_2$ (M − H) 334.06249, found 334.06248.

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Supporting Information Available: General experimental and complete experimental details for the synthesis of **18c** and **21c** from **10** and **13**, respectively, and ^{1}H and ^{13}C NMR spectra for compound **21c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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