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Synthesis of 2-amido, 2-amino, and 2-azido derivatives of the nitrogen analogue of the naturally occurring glycosidase inhibitor salacinol and their inhibitory activities against *O*-GlcNAcase and NagZ enzymes

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Abstract—Seven 2-substituted derivatives of the nitrogen analogue of salacinol, a naturally occurring glycosidase inhibitor, were synthesized for structure–activity studies with hexosaminidase enzymes. The target zwitterionic compounds were synthesized by means of nucleophilic attack of the 2-azido-1,4-dideoxy-1,4-imino-D-arabinitol at the least hindered carbon atom of 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic sulfate. Hydrogenation of the azido zwitterionic compound in methanol resulted in the reduction of the azide and subsequent methylation of the resulting amine in one pot. A similar reaction, with ethanol as the solvent, gave the *N*-ethyl derivative. The 2-amino analogues were finally obtained by the reduction of the azide function using triphenylphosphine. Acylation of the amine using acetic, propionic, or valeric anhydride afforded the corresponding 2-amido derivatives. Deprotection of the acylated, coupled products using 80% trifluoroacetic acid proceeded smoothly. Unlike their sulfonium ion counterparts, these compounds were stable and did not undergo ring opening. We also report the synthesis of the parent nitrogen heterocycles, *N*-Boc-1,2,4-trideoxy-2-amino-1,4-imino-D-arabinitol, and 1,2,4-trideoxy-2-acetamido-1,4-imino-D-arabinitol and its corresponding *N*-Boc protected compound. The 2-substituted analogues and the parent iminoalditol showed marginal activity (<33% at 250 μM) against human *O*-GlcNAcase and *Vibrio cholerae* NagZ enzymes.

Keywords: Glycosidase inhibitors; Salacinol; 1,2,4-Trideoxy-2-amido-1,4-imino-D-arabinitol derivatives; Ammonium sulfates; Cyclic sulfates; *O*-GlcNAcase and NagZ inhibition

1. Introduction

Glycosidases are involved in many biological processes such as cell–cell or cell–virus recognition, immune responses, cell growth, and viral and parasitic infections.[1,2] The controlled inhibition of glycosidases has potential for the treatment of many diseases such as diabetes, viral infections, and cancer.[3–5]

There are several naturally occurring glycosidase enzyme inhibitors such as acarbose **1**, swainsonine **2**, and 1-deoxynojirimycin **3**, of which **1** has been used for the oral treatment of type II diabetes.[6–9] Swainsonine **2** is an inhibitor of Golgi α-mannosidase II (GMII), which is a key enzyme in the N-glycosylation pathway.[10] Deoxynojirimycin **3** is a powerful glucosidase inhibitor and its derivatives have been used in the treatment of diabetes, Gaucher's disease, and viral infections.[11–16]

Salacinol **4** and kotalanol **5** are two naturally occurring glycosidase inhibitors which are extracted from roots and stems of a Sri Lankan plant, *Salacia reticulata*.[17–24] These compounds are unique in having a sulfonium salt along with a sulfate counter ion. The permanent positive charge on the sulfur atom is thought to mimic the oxacarbenium ion-like transition state for

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the glycosidase-mediated hydrolysis reactions.[25–27] It has been suggested that the counterion sulfate is important for the interaction of this compound with the active site of the enzyme,[25,28,29] although this conclusion has been brought into question recently.[30]

It was of interest to design compounds that might function as inhibitors of the hexosaminidase enzymes that cleave the β-glycosidic linkage of 2-acetamido-2-deoxy-β-D-glycopyranosides. Our initial foray into this area involved the attempted synthesis of 2-acetamido- and 2-amino derivatives of salacinol **4**. The benzylidene-protected 3,5-*O*-benzyl-2-acetamido- **6** and the 2-amino- **7** substituted analogues of salacinol were found to undergo ring opening reactions by nucleophilic participation of the amide or amine moieties to give acyclic amido **8** or ammonium sulfates **9**, respectively (Scheme 1).[31] We were intrigued by this result because it seemed to suggest that irreversible inhibition of enzymes might occur through nucleophilic participation of active-site residues. We further questioned whether this type of reactivity would be general with the 2-amino and 2-amido compounds, and whether the corresponding *nitrogen* analogues of salacinol containing such functionalities at C-2 would be stable. We report herein the synthesis of seven target compounds **10**–**16** containing acetamido, amino, azido, and longer-chain amido substituents at C-2.

A very recent report describing the activity of the parent iminoalditol **17**, its enantiomer **18**, and the corresponding *N*-benzyl derivatives **19**, **20** against a D-hexosaminidase enzyme indicated that whereas the D-isomers are weak competitive inhibitors, the L-isomers are potent, non-competitive inhibitors.[32] Accordingly, we report also our own syntheses of the parent compounds, the iminoarabinitol **17**, *N*-Boc-1,2,4-trideoxy-2-amino-1,4-imino-D-arabinitol **21**, and *N*-Boc-1,2,4-trideoxy-2-acetamido-1,4-imino-D-arabinitol **22**.

Finally, we report the enzyme inhibitory activities of compounds **10**–**16** (Scheme 2), their parent 2-acetamido (**17**) and 2-azido (**24**) iminoalditols, *N*-Boc protected 2-acetamido (**22**) and 2-amino (**21**) compounds against two enzymes that cleave the β-glycosidic linkage of 2-acetamido-2-deoxy-β-D-glycopyranosides.

2. Results and discussion

Retrosynthetic analysis indicated that the target compounds **10**–**16** could be synthesized by the reduction of the 2-azido function, its subsequent acylation, and the removal of the benzylidene protecting group in compound **23**. Compound **23** could be synthesized, in turn, by nucleophilic attack of the azido compound **24** at the less hindered carbon of 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic sulfate (**25**). Compound **24** could be synthesized from the epoxide **26** that could be synthesized, in turn, from the commercially available L-glutamic acid (Scheme 2).

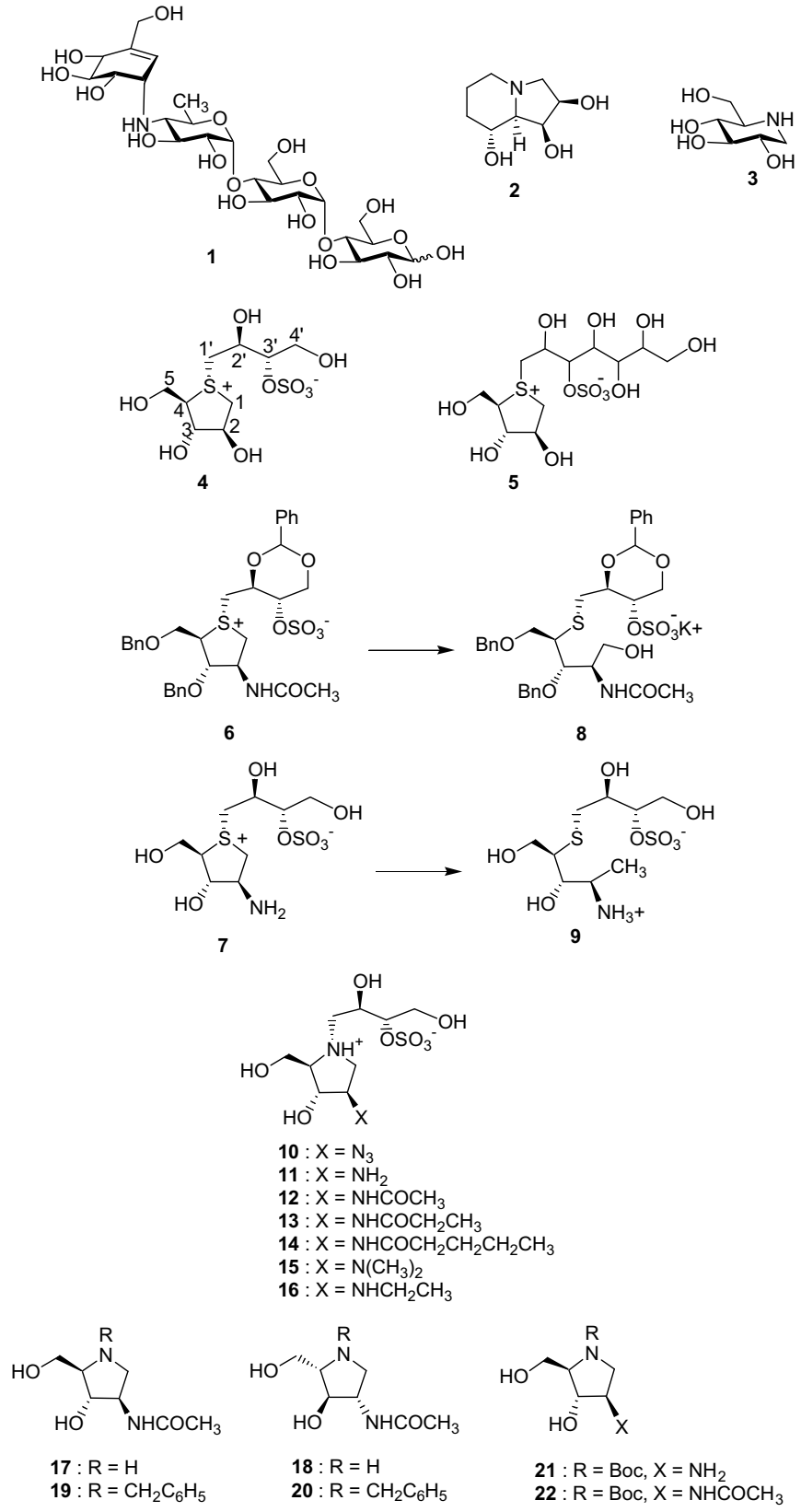
N-Boc-1,2,4-trideoxy-2-azido-1,4-imino-D-arabinitol **29** was synthesized from L-glutamic acid in 8 steps according to a literature procedure.[33–35] The Boc protecting group was then removed under acidic conditions to give the desired azido iminoalditol **24** in 72% yield (Scheme 3).

The alkylation reaction of **24** with 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic sulfate (**25**) in acetonitrile in a sealed tube afforded the desired coupled product **23** in 68% yield. The benzylidene protecting group was then removed using trifluoroacetic acid (TFA, 80%) to afford the desired product **10** in 73% yield (Scheme 4).

Hydrogenation of compound **23** in methanol at 70 psi did not yield the expected compound **11** (Scheme 5). Instead, we observed a very interesting result, namely the one-pot reduction of the azide to the amine followed by *N*,*N*-dimethylation, while the benzylidene protecting group remained intact (see **30**, Scheme 6). A 1D-NOESY experiment of compound **30** showed correlations between $N(CH_3)_2$ and H-2 and H-3 which confirmed that methylation of the amine had occurred. Also, correlations were observed between the H-1b resonance and H-1′b and H-4. Treatment of this compound with trifluoroacetic acid (80%) afforded the 2-*N*,*N*-dimethylamino analogue **15**. To explore this chemistry further, the hydrogenation reaction was then performed at 70 psi H_2 in the presence of Pd/C in ethanol; the *N*-ethylamino derivative **31** was isolated. Treatment of this compound with trifluoroacetic acid (80%) afforded the 2-*N*-ethylamino analogue (**16**) (Scheme 6). These compounds presumably result from the formation of formaldehyde or acetaldehyde on the catalyst surface. Reaction with the amines, after hydrogenation of the azides, would then give the imines which undergo further hydrogenation to yield the *N*-alkylamino derivatives.

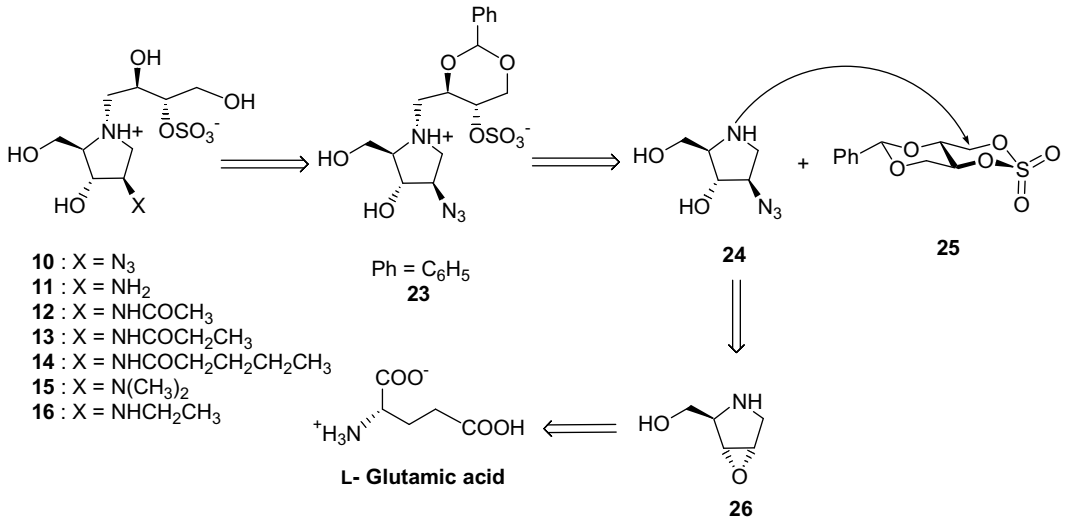
Reduction of the azido compound **23** to the amine **32** was accomplished using PPh_3, following a literature procedure.[36,37] Deprotection of the benzylidene protecting group afforded the desired 2-amino derivative **11** in 76% yield (Scheme 7). The stereochemistry at the ring nitrogen center of **11** was confirmed by means of a 1D-NOESY experiment. Thus, irradiation of the H-1′b resonance showed correlations to H-4, H-1b, and H-1a, and irradiation of H-4 showed correlations to H-1′b, H-1b, and H-1′a. Correlations between H-1′ and H-4 indicated that H-1′ and H-4 are on the same face, and correlations between H-1 and H-4 indicated that the ring was intact and had not opened.

Treatment of compound **32** with acetic, propionic, or valeric anhydride in methanol afforded the corresponding amides **33**–**35** in 54–89% yield. Removal of the benzylidene group in each of these compounds then afforded the corresponding ammonium salts **12**–**14** (Scheme 8).

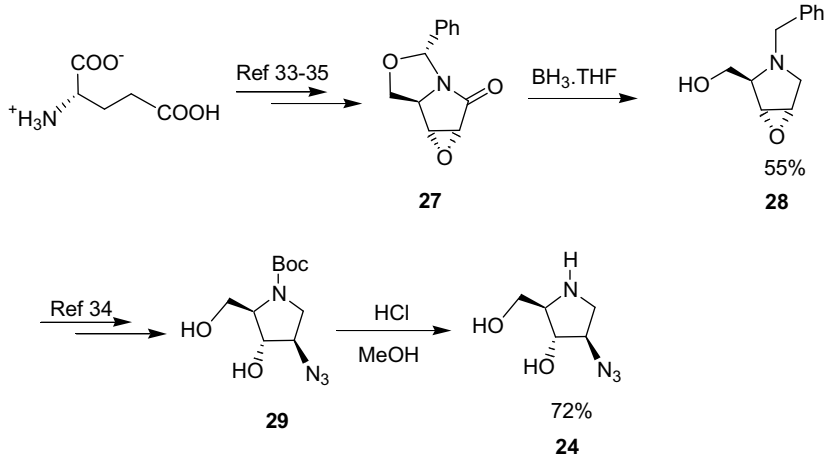


Scheme 1.

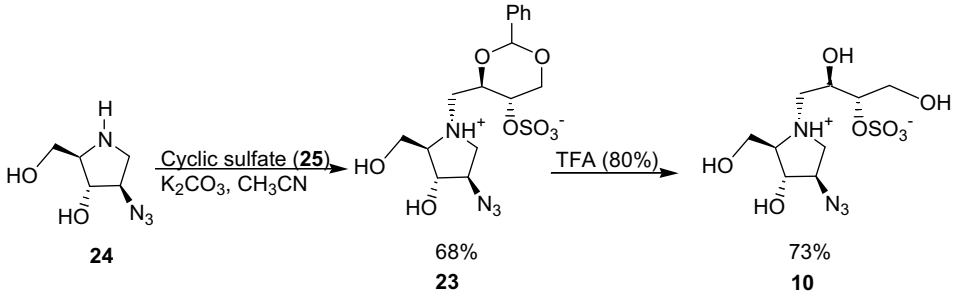
To obtain the parent iminoarabinitol, the azide **29** was first reduced using triphenylphosphine to afford the amine **21** in 92% yield. The ^{13}C NMR spectrum of this compound at ambient temperature showed two sets of



Scheme 2.



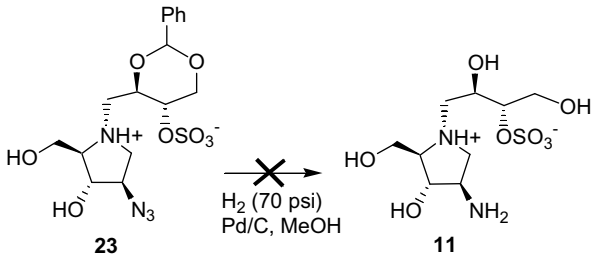
Scheme 3.



Scheme 4.

peaks due to restricted rotation about the carbamate; the ^{13}C NMR spectrum at 70 °C using D_2O as the solvent revealed one set of peaks above coalescence. The amine **21** was then acetylated using acetic anhydride in methanol to afford the corresponding amide **22** in 90% yield; the ^{13}C NMR spectrum of this compound was also obtained at 70 °C in D_2O. Deprotection of **22** with HCl afforded, after neutralization, the desired 1,2,4-trideoxy-2-acetamido-1,4-imino-D-arabinitol (**17**) in 84% yield (Scheme 9).

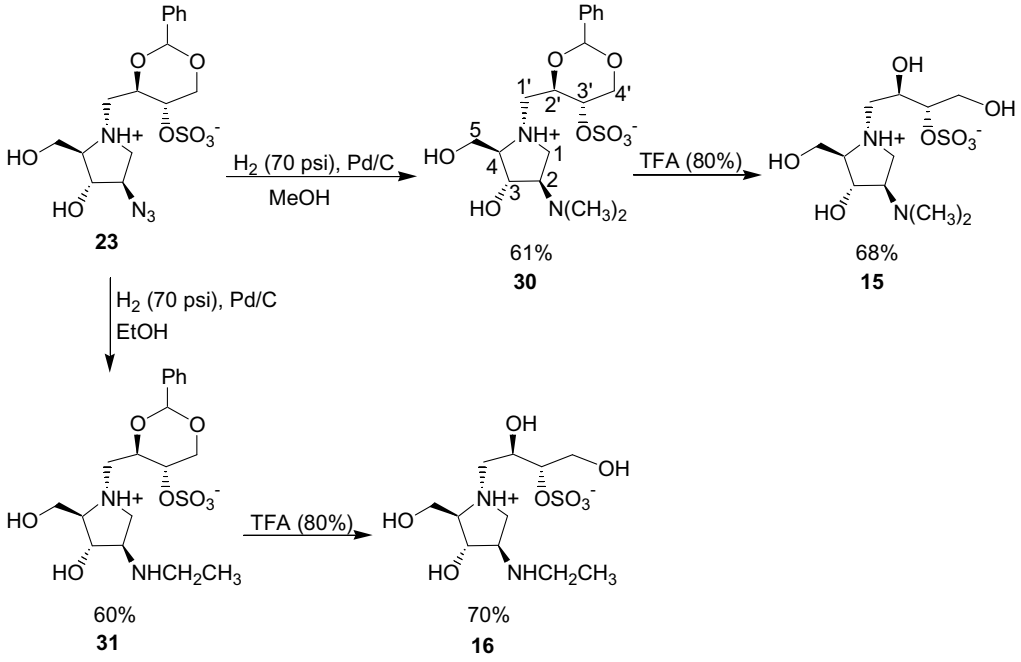
Compounds **10**–**16**, their parent 2-acetamido (**17**) and 2-azido (**24**) iminoalditols, *N*-Boc protected-2-acetamido (**22**) and 2-amino (**21**) compounds were tested against two enzymes that cleave the β-glycosidic linkage



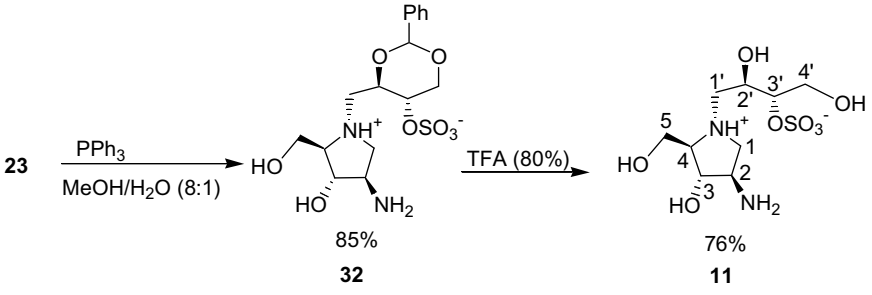
Scheme 5.

of 2-acetamido-2-deoxy-β-D-glycopyranosides. There are two main enzyme-catalyzed hydrolytic mechanisms known for cleaving this linkage. Examples of these two mechanistic classes include the *exo*-β-*N*-acetylglucosaminidases from family 3, and those from families 20 and 84 of the glycoside hydrolases, all of which are functionally related in that they catalyze the release of terminal 2-acetamido-2-deoxy-β-D-glycopyranose residues from glycoconjugates.[38–44] *exo*-β-*N*-Acetylglucosaminidases from family 3, of which *Vibrio cholerae* NagZ (VCNagZ) is a member, uses a catalytic mechanism involving the formation and breakdown of a covalent glycosyl-enzyme intermediate.[41] The enzymes from family 20[38,39] and more recently, 84,[42–44] of which human *O*-GlcNAcase is a member, have been shown to differ in that they use a catalytic mechanism involving assistance from the 2-acetamido group of the substrate.

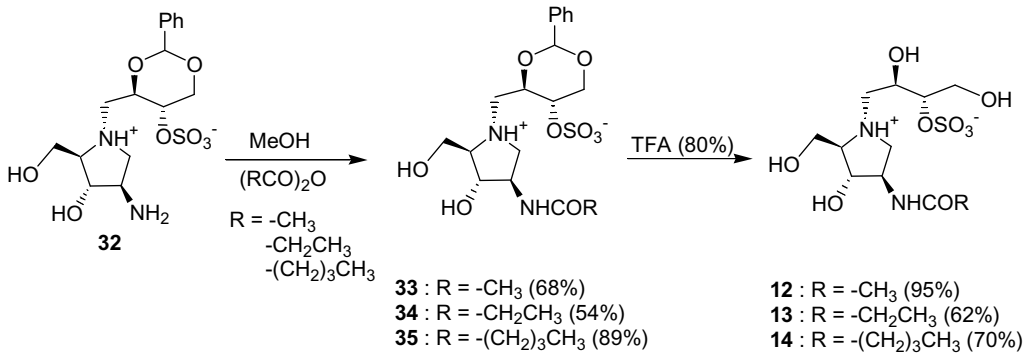
The percent inhibition of enzyme activity in each case, at an inhibitor concentration of 250 μM, is shown in Scheme 10. Among the ammonium ions, compounds **15** and **16** showed the highest activities, with **15** and **16** showing 33% and 27% inhibition of *O*-GlcNAcase, respectively, and 13% and 23% inhibition of NagZ, respectively. These results likely reflect better hydrophobic contacts within the active site of the enzyme by the non-polar methyl and ethyl groups on C-2; compound **11**, with the 2-amino group, showed the lowest (1%)



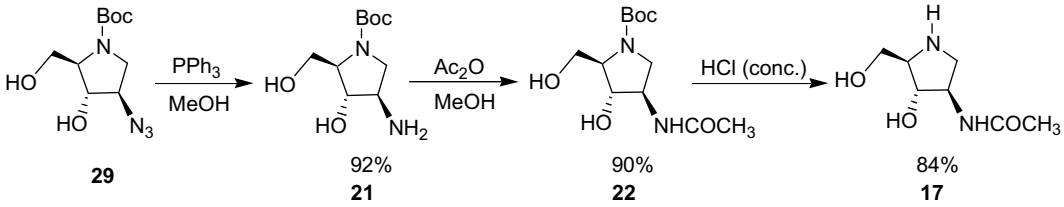
Scheme 6.



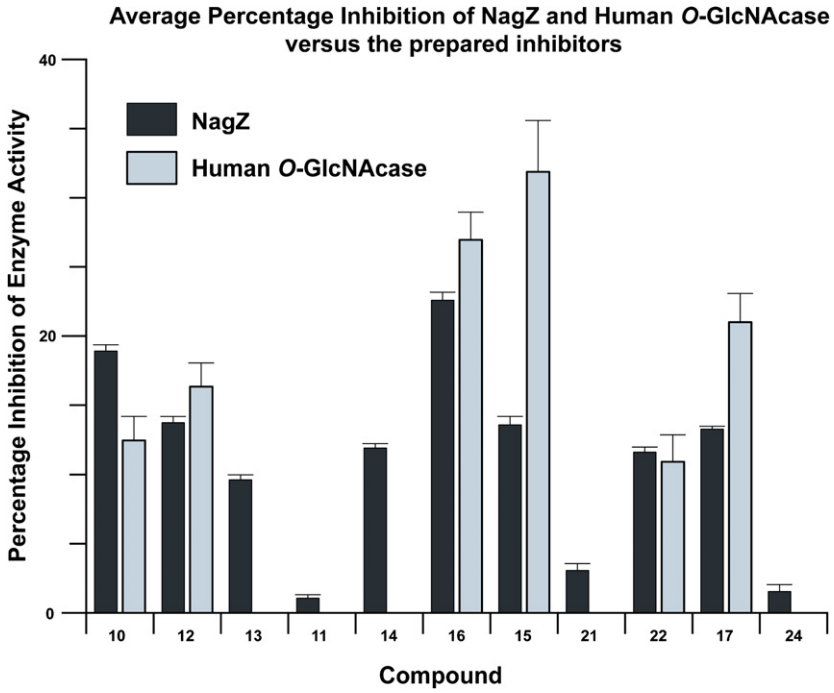
Scheme 7.



Scheme 8.



Scheme 9.



Scheme 10.

activity. Among the parent iminoalditols, the 2-acetamido derivatives **17** and **22** showed the highest inhibition of the enzymes.

3. Conclusions

Seven 2-*N*-substituted derivatives of the nitrogen analogue of the naturally occurring glucosidase inhibitor salacinol were synthesized. Nucleophilic attack of 2-azido-1,4-iminoarabinitol at the less hindered carbon of a benzylidene-protected L-erythritol-1,3-cyclic sulfate proceeded smoothly and afforded the desired coupled products. These compounds are quite stable at room temperature in contrast to their sulfur congeners in which ring opening reactions were observed. The parent compound, 2-acetamido-1,2,4-trideoxy-1,4-imino-

D-arabinitol, was also prepared from the *N*-Boc, 2-azido derivative. A one-pot reduction and alkylation of the coupled azido derivatives was observed in hydrogenation reactions at 70 psi of the azide in methanol or ethanol containing Pd/C as a catalyst. The inhibitory activities of seven 2-substituted analogues of the nitrogen analogue of salacinol along with four of their iminoalditol parent compounds were tested against two enzymes that cleave the β-glycosidic linkage of 2-acetamido-2-deoxy-β-D-glycopyranosides, namely *O*-GlcNAcase and NagZ; the compounds showed marginal inhibitory activity (<33% at 250 μM).

4. Experimental

4.1. General methods

Optical rotations were measured at 21 °C. ^{1}H and ^{13}C NMR were recorded with frequencies of 500 and 125 MHz, respectively. All assignments were confirmed with the aid of two-dimensional ^{1}H, ^{1}H (gCOSY) and ^{1}H, ^{13}C (gHMQC) experiments using standard Varian pulse programs. Processing of the data was performed with MestRec software. 1D-NOESY experiments were recorded at 295 K on a 500 MHz spectrometer. For each 1D-NOESY spectrum, 512 scans were acquired with Q3 Gaussian Cascade pulse. A mixing time of 800 ms was used in all the 1D-NOESY experiments. Analytical thin-layer chromatography (TLC) was performed on aluminum plates precoated with Silica Gel 60F-254 as the adsorbent. The developed plates were air-dried, exposed to UV light, and/or sprayed with a solution containing 3% ninhydrin in EtOH and heated. Column chromatography was performed with Silica Gel 60 (230–400 mesh). High resolution mass spectra were obtained by the electrospray ionization (ESI) technique, using a ZabSpec OA TOF mass spectrometer at 10,000 RP.

4.2. Kinetic analysis of *O*-GlcNAcase and NagZ

All assays were carried out in triplicate at 37 °C for 30 min by using a stopped assay procedure in which the enzymatic reactions (50 μL) were quenched by the addition of a 4-fold excess (200 μL) of quenching buffer (200 mM glycine, pH 10.75). Assays were initiated by the addition, via syringe, of enzyme (5 μL), and in all cases the final pH of the resulting quenched solution was greater than 10. The time-dependent assay of human *O*-GlcNAcase[45] and *V. cholerae* (VC) NagZ[46] enzymes revealed that both enzymes were stable over this period in the assay buffer: 50 mM NaH_2PO_4, 100 mM NaCl, 0.1% BSA, pH 7.4. The enzymes *O*-GlcNAcase and VCNagZ were used at a concentration of 0.16 μg μL^{-1} and 0.053 μg μL^{-1}, respectively, in the assays using *p*-nitrophenyl GlcNAc as a substrate (0.25 mM for *O*-GlcNAcase, 0.5 mM for VCNagZ). All inhibitors were tested at a concentration of 250 μM. The progress of the reaction at the end of 30 min was determined by measuring the extent of 4-nitrophenolate liberated, as determined by absorbance measurements at 400 nm. The absorbance measurements were averaged to give a final result.

4.3. General procedure for trifluoroacetic acid treatment

The coupled compound (0.1 mmol) was dissolved in trifluoroacetic acid (2 mL, 80%) and the solution was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the crude product was collected.

4.4. General procedure for amide formation

To a solution of amine **32** (0.1 mmol) in MeOH (10 mL), the desired anhydride (acetic, propionic, or valeric) (1.5 equiv) was added. The mixture was stirred at room temperature for 4 h and the solvent was removed under reduced pressure to afford the crude product.

4.5. 1′-((2-Azido-1,4-imino-1,2,4-trideoxy-D-arabinitol)-4-*N*-ammonium)-2′,4′-*O*-benzylidene-1′-deoxy-L-erythritol-3′-sulfate (23)

Compound **24** (200 mg, 1.0 mmol), 2,4-benzylidene-L-erythritol-1,3-cyclic sulfate (**25**) (413 mg, 1.2 equiv), and K_2CO_3 (80 mg) were dissolved in CH_3CN–MeOH (5:1). The mixture was stirred in a sealed tube in an oil bath at 78 °C for 16 h. K_2CO_3 was removed by filtration and the solvent was removed under reduced pressure. Flash chromatography of the crude product [EtOAc–MeOH, 10:1] afforded compound **23** as a solid (374 mg, 68%). Mp 110–112 °C; $[\alpha]_D$ +93 (*c* 0.3, MeOH); ^{1}H NMR (CD_3OD) δ 7.41–7.30 (5H, m, Ar), 5.58 (1H, s, CHPh), 4.39 (1H, dd, $J_{4'b,4'a} = 11.0$, $J_{3',4'a} = 5.4$ Hz, H-4′a), 4.09 (1H, ddd, $J_{2',3'} = 9.9$ Hz, H-3′), 3.95 (1H, ddd, $J_{1'b,2'} = 8.4$ Hz, H-2′), 3.84 (1H, dd, $J_{2,3} = 2.8$ Hz, H-3), 3.82 (1H, ddd, $J_{1a,2} = 1.4$, $J_{1b,2} = 5.8$ Hz, H-2), 3.78 (1H, dd, $J_{3',4'} = 10.6$ Hz, H-4′b), 3.58 (1H, dd, $J_{5b,5a} = 9.1$, $J_{4,5a} = 7.2$ Hz, H-5a), 3.57 (1H, dd, $J_{4,5b} = 6.4$ Hz, H-5b), 3.29 (1H, dd, $J_{1'b,1'a} = 14.2$ Hz, H-1′a), 3.08 (1H, dd, $J_{2,1a} = 1.4$, $J_{1b,1a} = 11.6$ Hz, H-1a), 2.79 (1H, dd, $J_{2,1b} = 5.8$ Hz, H-1b), 2.54 (1H, dd, H-1′b), 2.50 (1H, ddd, $J_{3,4} =$ 3.4 Hz, H-4); ^{13}C NMR (CD_3OD) δ 138.0, 128.7, 127.9, 126.1 (6C, Ph), 100.9 (CHPh), 80.0 (C-3), 76.6 (C-2′), 73.3 (C-4), 69.3 (C-4′), 68.3 (C-3′), 66.2 (C-2), 59.7 (C-5), 57.7 (C-1), 54.9 (C-1′). Anal. Calcd for $C_{16}H_{22}N_4O_8S$: C, 44.65; H, 5.15; N, 13.02. Found: C, 44.28; H, 4.94; N, 12.72.

4.6. 1′-((2-Azido-1,4-imino-1,2,4-trideoxy-D-arabinitol)-4-*N*-ammonium)-1′-deoxy-L-erythritol-3′-sulfate (10)

Compound **23** (50 mg, 0.1 mmol) was subjected to trifluoroacetic acid treatment and the crude product was purified by flash chromatography [EtOAc–MeOH, 7:1] to afford compound **10** as a syrup (29 mg, 73%). $[\alpha]_D$ +50 (*c* 0.02, MeOH); ^{1}H NMR (CD_3OD) δ 4.35 (1H, ddd, $J_{2',3'} = 9.4$, $J_{4'a,3'} = 4.65$ Hz, H-3′), 3.99 (1H, ddd, $J_{1'a,2'} = 5.5$ Hz, H-2′), 3.98 (1H, dd, $J_{3,2} = 5.1$ Hz, H-2), 3.91 (1H, dd, $J_{4'b,4'a} = 12.0$ Hz, H-4′a), 3.81 (1H, dd, $J_{4,3} = 2.2$ Hz, H-3), 3.80 (1H, dd, $J_{3',4'b} = 5.0$ Hz, H-4′b), 3.71 (1H, dd, $J_{5b,5a} = 11.7$, $J_{4,5a} = 4.6$ Hz, H-5a), 3.66 (1H, dd, $J_{4,5b} = 4.0$ Hz, H-5b), 3.28 (1H, dd, $J_{1b,1a} = 11.1$, $J_{2,1a} = 2.6$ Hz, H-1a), 3.21 (1H, dd, $J_{1'b,1'a} = 13.2$ Hz, H-1′a), 2.95 (1H, dd, $J_{2,1b} = 6.6$ Hz, H-1b), 2.57 (1H, m, H-4), 2.56 (1H, dd, $J_{2',1'b} = 6.9$ Hz, H-1′b); ^{13}C NMR (CD_3OD) δ 80.8 (C-3′), 76.8 (C-3), 73.3 (C-4), 69.8 (C-2′), 66.3 (C-2), 60.9 (C-5), 60.2 (C-4), 57.4 (C-1), 57.2 (C-1′). HRMS: $[M+H]^+$ calcd for $C_9H_{19}O_8N_4S$, 343.0924; found, 343.0972.

4.7. 1′-((2-Amino-1,4-imino-1,2,4-trideoxy-D-arabinitol)-4-*N*-ammonium)-2′,4′-*O*-benzylidene-1′-deoxy-L-erythritol-3′-sulfate (32)

To a solution of **23** (100 mg, 0.2 mmol) in MeOH–H_2O (15:1, 15 mL) was added PPh_3 (63 mg, 1.2 equiv). The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography [EtOAc–MeOH, 3:1] to afford **32** as a syrup (80 mg, 85%). $[\alpha]_D$ +21 (*c* 0.1, MeOH); ^{1}H NMR (D_2O) δ 7.41–7.29 (5H, m, Ar), 5.61 (1H, s, CHPh), 4.39 (1H, dd, $J_{3',4'a} = 5.4$, $J_{4'b,4'a} = 11.0$ Hz, H-4′a), 4.16 (1H, ddd, $J_{2',3'} = 9.8$, $J_{4'b,3'} = 9.9$ Hz, H-3′), 3.99 (1H, dd, $J_{2,3} = 2.8$, $J_{4,3} = 4.8$ Hz, H-3), 3.95 (1H, ddd, $J_{1'a,2'} = 1.9$ Hz, H-2′), 3.77 (1H, dd, H-4′b), 3.67 (1H, dd, $J_{4,5a} = 3.1$, $J_{5b,5a} = 12.3$ Hz, H-5a), 3.55 (1H, dd, $J_{4,5b} = 2.4$ Hz, H-5b), 3.43 (1H, m, H-2), 3.16 (1H, dd, $J_{1'b,1'a} = 14.4$ Hz, H-1′a), 3.11 (1H, dd, $J_{2,1a} = 0.8$, $J_{1b,1a} = 11.7$ Hz, H-1a), 2.93 (1H, dd, $J_{2,1b} = 6.2$ Hz, H-1b), 2.64 (1H, dd, $J_{2',1'b} = 7.5$ Hz, H-1′b), 2.56 (1H, ddd, H-4); ^{13}C NMR (D_2O) δ 136.4, 129.9, 128.9, 126.2 (6C, Ph), 101.1 (CHPh), 79.0 (C-2′), 75.1 (C-3), 71.9 (C-4), 68.9 (C-3′), 68.6 (C-4′), 58.7 (C-5), 56.0 (C-1), 55.8 (C-2), 53.4 (C-1′). HRMS: $[M+H]^+$ calcd for $C_{16}H_{25}O_8N_2S$, 405.1331; found, 405.1337.

4.8. 1′-((2-Amino-1,4-imino-1,2,4-trideoxy-D-arabinitol)-4-*N*-ammonium)-1′-deoxy-L-erythritol -3′-sulfate (11)

Compound **32** (130 mg, 0.3 mmol) was subjected to trifluoroacetic acid treatment and the crude product was purified by flash chromatography [EtOAc–MeOH–H_2O, 5:3:1] to afford compound **11** as a white solid (77 mg, 76%). Mp 210–212 °C (dec); $[\alpha]_D$ +40 (*c* 0.1, MeOH); ^{1}H NMR (D_2O) δ 4.27 (1H, ddd, $J_{2',3'} = 5.2$ Hz, H-3′), 4.02 (1H, ddd, $J_{1'b,2'} = 6.9$, $J_{1'a,2'} = 6.6$ Hz, H-2′), 4.01 (1H, dd, $J_{4,3} = 4.6$ Hz, H-3), 3.74 (1H, dd, $J_{4'b,4'a} = 12.6$, $J_{3',4'a} = 3.4$ Hz, H-4′a), 3.67 (1H, dd, $J_{3',4'b} = 5.6$ Hz, H-4′b), 3.64 (1H, dd, $J_{5b,5a} = 12.2$, $J_{4,5a} = 3.1$ Hz, H-5a), 3.58 (1H, dd, $J_{4,5b} = 2.7$ Hz, H-5b), 3.47 (1H, ddd, $J_{1a,2} = 2.0$, $J_{3,2} = 2.0$ Hz, H-2), 3.14 (1H, dd, $J_{1b,1a} = 11.5$ Hz, H-1a), 2.92 (1H, dd, $J_{1'b,1'a} = 13.2$ Hz, H-1′a), 2.83 (1H, dd, $J_{2,1b} = 5.9$ Hz, H-1b), 2.51 (1H, ddd, H-4), 2.42 (1H, dd, H-1′b); ^{13}C NMR (D_2O) δ 81.2 (C-3′), 75.0 (C-3), 72.3 (C-4), 69.4 (C-2′), 59.5 (C-4′), 58.9 (C-5), 55.8 (C-2), 55.3 (C-1), 55.0 (C-1′). Anal. Calcd for $C_9H_{20}N_2O_8S$: C, 34.17; H, 6.37; N, 8.86. Found: C, 34.38; H, 6.41; N, 8.75.

4.9. 1′-((2-Acetamido-1,4-imino-1,2,4-trideoxy-D-arabinitol)-4-*N*-ammonium)-2′,4′-*O*-benzylidene-1′-deoxy-L-erythritol-3′-sulfate (33)

Compound **32** (34 mg, 0.08 mmol) was subjected to the amidation conditions using Ac_2O and the crude product was purified by flash chromatography [EtOAc–MeOH, 3:1] to afford **33** as a syrup (25 mg, 68%). $[\alpha]_D$ −17 (*c* 0.1, MeOH); ^{1}H NMR (CD_3OD) δ 7.48–7.29 (5H, m, Ar), 5.58 (1H, s, CHPh), 4.52 (1H, dd, $J_{4'b,4'a} = 10.9$, $J_{3',4'a} = 5.4$ Hz, H-4′a), 4.24 (1H, ddd, $J_{4'b,3'} = 9.8$, $J_{2',3'} = 9.7$ Hz, H-3′), 4.07 (1H, ddd, $J_{1'b,2'} = 7.6$, $J_{1'a,2'} = 3.3$ Hz, H-2′), 4.03 (1H, dd, $J_{4,3} = 8.5$, $J_{2,3} = 3.1$ Hz, H-3), 4.01 (1H, ddd, $J_{1a,2} = 3.0$ Hz, H-2), 3.83 (1H, dd, $J_{5b,5a} = 12.1$, $J_{4,5a} = 3.3$ Hz, H-5a), 3.77 (1H, dd, H-4′b), 3.69 (1H, dd, $J_{4,5b} = 2.8$ Hz, H-5b), 3.58 (1H, dd, $J_{1'b,1'a} = 12.4$ Hz, H-1′a), 3.31 (1H, dd, H-1a), 3.21 (1H, dd, $J_{1a,1b} = 11.9$, $J_{2,1b} = 6.2$ Hz, H-1b), 2.92 (1H, dd, H-1′b), 2.80 (1H, dd, H-4), 1.96 (1H, s, CH_3); ^{13}C NMR (D_2O) δ 174.8 (CO), 136.0, 130.1, 128.9, 126.3 (6C, Ph), 101.0 (CHPh), 75.3 (C-3′), 73.6 (C-3), 72.5 (C-4), 68.4 (C-4′), 68.1 (C-2′), 57.8 (C-1), 56.1 (C-5), 54.7 (C-1′), 54.3 (C-2). Anal. Calcd for $C_{18}H_{26}N_2O_9S$: C, 48.42; H, 5.87; N, 6.27. Found: C, 48.20; H, 5.96; N, 6.19.

4.10. 1′-((2-Acetamido-1,4-imino-1,2,4-trideoxy-D-arabinitol)-4-*N*-ammonium)-1′-deoxy-L-erythritol-3′-sulfate (12)

Compound **33** (26 mg, 0.06 mmol) was subjected to trifluoroacetic acid treatment and the crude product was purified by flash chromatography [EtOAc–MeOH, 2:1] to afford compound **12** as a syrup (20 mg, 95%). $[\alpha]_D$ +50 (*c* 0.1, MeOH); ^{1}H NMR (CD_3OD) δ 4.48 (1H, ddd, $J_{2',3'} = 4.6$ Hz, H-3′), 4.06 (1H, ddd, $J_{1'b,2'} = 6.3$ Hz, H-2′), 3.96 (1H, ddd, $J_{3,2} = 4.9$ Hz, H-2), 3.93 (1H, dd, $J_{3',4'a} = 4.1$ Hz, H-4′a), 3.91 (1H, dd, $J_{4,3} =$

3.4 Hz, H-3), 3.82 (1H, dd, $J_{4'a,4'b} = 12.0$, $J_{3',4'b} = 5.1$ Hz, H-4′b), 3.72 (1H, dd, $J_{5b,5a} = 11.8$, $J_{4,5a} = 3.9$ Hz, H-5a), 3.63 (1H, dd, $J_{4,5b} = 3.3$ Hz, H-5b), 3.15 (1H, dd, $J_{1b,1a} = 10.1$ Hz, H-1a), 3.11 (1H, dd, $J_{1'b,1'a} = 12.7$, $J_{2',1'a} = 7.5$ Hz, H-1′a), 2.85 (1H, dd, $J_{2,1b} = 6.1$ Hz, H-1b), 2.53 (1H, dd, H-1′b), 2.45 (1H, ddd, H-4), 1.96 (3H, s, CH_3); ^{13}C NMR (CD_3OD) δ 172.0 (CO), 80.9 (C-3′), 78.0 (C-3), 73.7 (C-1′), 69.7 (C-2′), 60.9 (C-4′), 60.5 (C-5), 57.3 (C-4), 57.1 (C-1), 56.5 (C-2), 21.4 (CH_3). HRMS: $[M+H]^+$ calcd for $C_{11}H_{23}O_9N_2S$, 359.1124; found, 359.1122.

4.11. 1′-((1,4-Imino-2-propionamido-1,2,4-trideoxy-D-arabinitol)-4-*N*-ammonium)-2′,4′-*O*-benzylidene-1′-deoxy-L-erythritol-3′-sulfate (34)

Compound **32** (65 mg, 0.16 mmol) was subjected to the amidation conditions using propionic anhydride and the crude product was purified by flash chromatography [EtOAc–MeOH, 3:1] to afford **34** as a syrup (40 mg, 54%). $[\alpha]_D$ +250 (*c* 0.1, MeOH); ^{1}H NMR (CD_3OD) δ 7.51–7.31 (5H, m, Ar), 5.58 (1H, s, CHPh), 4.57 (1H, dd, $J_{4'b,4'a} = 10.9$, $J_{3',4'a} = 5.4$ Hz, H-4′a), 4.27 (1H, ddd, $J_{4'b,3'} = 9.8$, $J_{2',3'} = 9.7$ Hz, H-3′), 4.01 (1H, ddd, $J_{1'b,2'} = 6.7$ Hz, H-2′), 3.98 (1H, ddd, $J_{3,2} = 5.4$ Hz, H-2), 3.95 (1H, dd, $J_{4,3} = 3.8$ Hz, H-3), 3.79 (1H, dd, H-4′b), 3.76 (1H, dd, $J_{5b,5a} = 11.5$, $J_{4,5a} = 3.8$ Hz, H-5a), 3.64 (1H, dd, $J_{4,5b} = 2.6$ Hz, H-5b), 3.37 (1H, dd, $J_{1b,1a} = 13.6$, $J_{2,1a} = 4.1$ Hz, H-1a), 3.16 (1H, dd, $J_{1'b,1'a} = 10.2$ Hz, H-1′a), 2.92 (1H, dd, H-1′b), 2.68 (1H, dd, $J_{2,1b} = 6.7$ Hz, H-1b), 2.49 (1H, ddd, H-4), 2.22 (2H, q, $J_{CH_3,CH_2} = 7.6$ Hz, CH_2), 1.11 (3H, t, CH_3); ^{13}C NMR (CD_3OD) δ 175.7 (CO), 138.0, 128.7, 127.9, 126.1 (6C, Ph), 100.9 (CHPh), 78.7 (C-2′), 77.9 (C-3), 73.9 (C-4), 69.4 (C-3′), 69.2 (C-4′), 59.5 (C-5), 57.9 (C-1′), 56.3 (C-2), 55.8 (C-1), 28.9 (CH_2), 9.2 (CH_3). HRMS: $[M+H]^+$ calcd for $C_{19}H_{29}O_9N_2S$, 461.1594; found, 461.1599.

4.12. 1′-((1,4-Imino-2-propionamido-1,2,4-trideoxy-D-arabinitol)-4-*N*-ammonium)-1′-deoxy-L-erythritol-3′-sulfate (13)

Compound **34** (20 mg, 0.08 mmol) was subjected to trifluoroacetic acid treatment and the crude product was purified by flash chromatography [EtOAc–MeOH, 3:1] to afford compound **13** as a syrup (10 mg, 62%). $[\alpha]_D$ +100 (*c* 0.02, MeOH); ^{1}H NMR (CD_3OD) δ 4.49 (1H, ddd, $J_{2',3'} = 4.7$ Hz, H-3′), 4.05 (1H, ddd, H-2′), 3.95 (1H, ddd, H-2), 3.92 (1H, dd, $J_{4'b,4'a} = 11.9$, $J_{3',4'a} = 4.2$ Hz, H-4′a), 3.89 (1H, dd, $J_{4,3} = 3.5$ Hz, H-3), 3.82 (1H, dd, $J_{3',4'b} = 5.1$ Hz, H-4′b), 3.69 (1H, dd, $J_{5b,5a} = 11.7$, $J_{4,5a} = 4.1$ Hz, H-5a), 3.61 (1H, dd, $J_{4,5b} = 3.5$ Hz, H-5b), 3.13 (1H, dd, $J_{1b,1a} = 10.0$ Hz, H-1a), 3.08 (1H, dd, $J_{1'b,1'a} = 12.8$, $J_{2',1'a} = 7.8$ Hz, H-1′a), 2.81 (1H, dd, $J_{2,1b} = 5.9$ Hz, H-1b), 2.49 (1H, dd, $J_{2',1'b} = 5.9$ Hz, H-1′b), 2.39 (1H, ddd, H-4), 2.23 (2H, q, $J_{CH_3,CH_2} = 7.6$ Hz, CH_2), 1.12 (3H, t, CH_3); ^{13}C NMR (CD_3OD) δ 175.7 (CO), 80.9 (C-3′), 78.2 (C-3), 73.8 (C-4), 69.9 (C-2′), 60.9 (C-4′), 60.7 (C-5), 57.3 (C-1), 57.2 (C-1′), 56.4 (C-2), 28.9 (CH_2), 9.3 (CH_3). HRMS: $[M+H]^+$ calcd for $C_{12}H_{25}O_9N_2S$, 373.1281; found, 373.1295.

4.13. 1′-((1,4-Imino-2-pentanamido-1,2,4-trideoxy-D-arabinitol)-4-*N*-ammonium)-2′,4′-*O*-benzylidene-1′-deoxy-L-erythritol-3′-sulfate (35)

Compound **32** (13 mg, 0.03 mmol) was subjected to the amidation conditions using valeric anhydride and the crude product was purified by flash chromatography [EtOAc–MeOH, 6:1] to afford **35** as a syrup (14 mg, 89%). $[\alpha]_D$ +85 (*c* 0.04, MeOH); ^{1}H NMR (CD_3OD) δ 7.39–7.20 (5H, m, Ar), 5.47 (1H, s, CHPh), 4.46 (1H, dd, $J_{4'b,4'a} = 10.9$, $J_{3',4'a} = 5.4$ Hz, H-4′a), 4.16 (1H, ddd, $J_{4'b,3'} = 9.8$, $J_{2',3'} = 5.5$ Hz, H-3′), 3.89 (1H, ddd, H-2′), 3.86 (1H, ddd, $J_{3,2} = 5.5$ Hz, H-2), 3.83 (1H, dd, H-3), 3.68 (1H, dd, H-4′b), 3.64 (1H, dd, $J_{5b,5a} = 11.7$, $J_{4,5a} = 6.1$ Hz, H-5a), 3.52 (1H, dd, $J_{4,5b} = 1.5$ Hz, H-5b), 3.24 (1H, dd, $J_{1'b,1'a} = 13.7$, $J_{2',1'a} = 5.1$ Hz, H-1′a), 3.04 (1H, dd, $J_{1b,1a} = 9.8$ Hz, H-1a), 2.79 (1H, dd, $J_{2,1b} = 5.9$ Hz, H-1b), 2.54 (1H, dd, $J_{2',1'b} = 6.8$ Hz, H-1′b), 2.34 (1H, ddd, $J_{3,4} = 2.0$ Hz, H-4), 2.10 (2H, dt, $J_{CH_2,CH_2} = 7.3$, $J_{NH,CH_2} = 2.6$ Hz, CH_2), 1.47 (2H, m, CH_2), 1.23 (2H, m, CH_2), 0.82 (3H, t, $J_{CH_2,CH_3} = 7.3$ Hz, CH_3); ^{13}C NMR (CD_3OD) δ 174.9 (CO), 138.1, 128.6, 127.9, 126.1 (4C, Ph), 100.9 (CHPh), 78.9 (C-2′), 78.0 (C-3), 73.9 (C-4), 69.4 (C-3′), 69.2 (C-4′), 59.7 (C-5), 58.1 (C-1), 56.4 (C-2), 55.8 (C-4′), 35.5, 28.0, 22.2 (3 × CH_2), 12.9 (CH_3). HRMS: $[M+H]^+$ calcd for $C_{21}H_{33}O_9N_2S$, 489.1907; found, 489.1923.

4.14. 1′-((1,4-Imino-2-pentanamido-1,2,4-trideoxy-D-arabinitol)-4-*N*-ammonium)-1′-deoxy-L-erythritol-3′-sulfate (14)

Compound **35** (14 mg, 0.03 mmol) was subjected to trifluoroacetic acid treatment and the crude product was purified by flash chromatography [EtOAc–MeOH, 3:1] to afford compound **14** as a syrup (8 mg, 70%). $[\alpha]_D$ +60 (*c* 0.05, MeOH); ^{1}H NMR (CD_3OD) δ 4.47 (1H, ddd, $J_{2',3'} = 9.3$ Hz, H-3′), 4.05 (1H, ddd, H-2′), 3.97 (1H, ddd, $J_{1b,2} = 6.0$ Hz, H-2), 3.92 (1H, dd, $J_{4'b,4'a} = 12.0$, $J_{3',4'a} = 4.2$ Hz, H-4′a), 3.90 (1H, dd, $J_{4,3} = 3.6$, $J_{2,3} = 1.9$ Hz, H-3), 3.82 (1H, dd, $J_{3',4'b} = 5.1$ Hz, H-4′b), 3.71 (1H, dd, $J_{5b,5a} = 11.7$, $J_{4,5a} = 4.2$ Hz, H-5a), 3.63 (1H, dd, $J_{4,5b} = 3.6$ Hz, H-5b), 3.15 (1H, dd, $J_{1b,1a} = 10.0$ Hz, H-1a), 3.12 (1H, dd, $J_{1'b,1'a} = 12.9$, $J_{2',1'a} = 7.3$ Hz, H-1′a), 2.87 (1H, dd, H-1b), 2.54 (1H, dd, $J_{2',1'b} = 6.2$ Hz, H-1′b), 2.46 (1H, ddd, H-4), 2.22 (2H, dt, $J_{CH_2,CH_2} = 7.3$, $J_{NH,CH_2} = 0.8$ Hz, CH_2), 1.59

(2H, m, CH_2), 1.36 (2H, m, CH_2), 0.93 (3H, t, $J_{CH_2,CH_3} = 7.3$ Hz, CH_3); ^{13}C NMR (CD_3OD) δ 175.0 (CO), 80.9 (C-3′), 78.1 (C-3), 73.8 (C-4), 69.7 (C-2′), 60.9 (C-4′), 60.6 (C-5), 57.4 (C-1′), 57.2 (C-1), 56.4 (C-2), 35.6, 28.0, 22.2 ($3 \times CH_2$), 12.9 (CH_3). HRMS: [M+H] calcd for $C_{14}H_{29}O_9N_2S$, 401.1594; found, 401.1617.

4.15. 1′-((2-*N*,*N*-Dimethylamino-1,4-imino-1,2,4-trideoxy-D-arabinitol)-4-*N*-ammonium)-2′,4′-*O*-benzylidene-1′-deoxy-L-erythritol-3′-sulfate (30)

Compound **23** (100 mg, 0.23 mmol) was dissolved in MeOH (20 mL), Pd/C (100 mg) was added, and the mixture was stirred under H_2 (70 psi) overnight. The catalyst was removed by filtration and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography [EtOAc–MeOH, 3:1] to afford compound **30** as a syrup (61 mg, 61%). $[\alpha]_D$ +80 (*c* 0.05, MeOH); ^1H NMR (CD_3OD) δ 7.48–7.32 (5H, m, Ar), 5.59 (1H, s, CHPh), 4.59 (1H, dd, $J_{4'b,4'a} = 10.9$, $J_{3',4'a} = 5.4$ Hz, H-4′a), 4.30 (1H, ddd, $J_{4'b,3'} = 10.0$, $J_{2',3'} = 9.9$ Hz, H-3′), 4.23 (1H, dd, $J_{4,3} = 5.8$, $J_{2,3} = 4.0$ Hz, H-3), 3.94 (1H, ddd, $J_{1'a,2'} = 3.2$ Hz, H-2′), 3.85 (1H, dd, $J_{5b,5a} = 12.1$, $J_{4,5a} = 2.7$ Hz, H-5a), 3.78 (1H, ddd, H-4′b), 3.63 (1H, dd, $J_{4,5b} = 2.2$ Hz, H-5b), 3.49 (1H, dd, $J_{1b,1a} = 11.6$, $J_{2,1a} = 2.2$ Hz, H-1a), 3.30 (1H, dd, H-1′a), 3.18 (1H, ddd, H-2), 2.92 (1H, dd, $J_{2,1b} = 7.3$ Hz, H-1b), 2.72 (6H, s, $2 \times CH_3$), 2.68 (1H, dd, $J_{2',1'b} = 6.1$ Hz, H-1′b), 2.51 (1H, ddd, H-4); ^{13}C NMR (CD_3OD) 137.9, 128.7, 127.9, 126.1 (4C, Ph), 101.1 (CHPh), 79.5 (C-2′), 72.7 (C-3), 72.5 (C-4), 71.5 (C-2), 69.3 (C-3′), 68.7 (C-4′), 58.3 (C-5), 54.9 (C-1), 53.7 (C-1′), 41.3 (CH_3). Anal. Calcd for $C_{18}H_{28}N_2O_8S$: C, 49.99; H, 6.52; N, 6.48. Found: C, 50.35; H, 6.48; N, 6.53. HRMS: $[M+H]^+$ calcd for $C_{18}H_{29}O_8N_2S$, 433.1645; found, 433.1645.

4.16. 1′-((2-*N*,*N*-Dimethylamino-1,4-imino-1,2,4-trideoxy-D-arabinitol)-4-*N*-ammonium)-1′-deoxy-L-erythritol-3′-sulfate (15)

Compound **30** (28 mg, 0.06 mmol) was subjected to trifluoroacetic acid treatment and the crude product was purified by flash chromatography [EtOAc–MeOH, 3:1] to afford compound **15** as a syrup (15 mg, 68%). $[\alpha]_D$ −9 (*c* 0.2, MeOH); ^1H NMR (CD_3OD) δ 4.43 (1H, ddd, $J_{2',3'} = 4.7$ Hz, H-3′), 4.11 (1H, dd, $J_{4,3} = 4.5$ Hz, H-3), 4.06 (1H, ddd, H-2′), 3.94 (1H, dd, $J_{4'b,4'a} = 11.9$, $J_{3',4'a} = 4.5$ Hz, H-4′a), 3.80 (1H, dd, $J_{3',4'b} = 4.6$ Hz, H-4′b), 3.79 (1H, dd, $J_{5b,5a} = 11.7$, $J_{4,5a} = 3.9$ Hz, H-5a), 3.65 (1H,dd, $J_{4,5b} = 3.0$ Hz, H-5b), 3.42 (1H, dd, $J_{1b,1a} = 11.3$, $J_{2,1a} = 3.0$ Hz, H-1a), 3.11 (1H, dd, $J_{2',1'a} = 7.1$ Hz, H-1′a), 2.99 (1H, ddd, $J_{3,2} = 0.3$ Hz, H-2), 2.76 (1H, dd, $J_{2,1b} = 7.9$ Hz, H-1b), 2.56 (6H, s, $2 \times CH_3$), 2.43 (1H, ddd, H-4), 2.42 (1H, dd, $J_{1'a,1'b} = 12.6$, $J_{2',1'b} = 5.9$ Hz, H-1′b); ^{13}C NMR (CD_3OD) 80.2 (C-3′), 73.3 (C-3), 72.9 (C-4), 71.2 (C-2), 69.6 (C-2′), 60.6 (C-4′), 58.9 (C-5), 55.9 (C-1′), 54.7 (C-1), 41.7 (CH_3). HRMS: $[M+Na]^+$ calcd for $C_{11}H_{24}O_8N_2SNa$, 367.1151; found, 367.1152.

4.17. 1′-((2-*N*-Ethylamino-1,4-imino-1,2,4-trideoxy-D-arabinitol)-4-*N*-ammonium)-2′,4′-*O*-benzylidene-1′-deoxy-L-erythritol-3′-sulfate (31)

Compound **23** (16.5 mg, 0.04 mmol) was dissolved in EtOH (15 mL), Pd/C (60 mg) was added, and the mixture was stirred under H_2 (70 psi) overnight. The catalyst was removed by filtration, the solvent was removed under reduced pressure, and the crude product was purified by flash chromatography [EtOAc–MeOH, 3:1] to afford compound **31** as a syrup (10 mg, 60%). $[\alpha]_D$ +43 (*c* 0.1, MeOH); ^1H NMR (CD_3OD) δ 7.56–7.29 (5H, m, Ar), 5.58 (1H, s, CHPh), 4.57 (1H, dd, $J_{4'b,4'a} = 10.9$, $J_{3',4'a} = 5.4$ Hz, H-4′a), 4.37 (1H, ddd, $J_{4'b,3'} = 9.8$, $J_{2',3'} = 9.7$ Hz, H-3′), 4.22 (1H, dd, $J_{4,3} = 3.6$, $J_{2,3} = 1.8$ Hz, H-3), 3.94 (1H, ddd, $J_{1'b,2'} = 5.7$, $J_{1'a,2'} = 4.3$ Hz, H-2′), 3.88 (1H, dd, $J_{5b,5a} = 11.7$, $J_{4,5a} = 2.3$ Hz, H-5a), 3.78 (1H, dd, H-4′b), 3.62 (1H, dd, $J_{4,5b} = 1.9$ Hz, H-5b), 3.41 (1H, dd, $J_{1b,1a} = 11.2$ Hz, H-1a), 3.33 (1H, ddd, $J_{1a,2} = 1.0$ Hz, H-2), 3.26 (1H, dd, $J_{1'b,1'a} = 13.8$ Hz, H-1′a), 3.11 (2H, m, CH_2), 2.97 (1H, dd, $J_{2,1b} = 5.2$ Hz, H-1b), 2.78 (1H, dd, H-1′b), 2.56 (1H, ddd, H-4), 1.29 (3H, t, $J_{CH_2,CH_3} = 7.3$ Hz, CH_3); ^{13}C NMR (CD_3OD) 138.0, 128.7, 127.9, 126.1 (6C, Ph), 101.1 (CHPh), 78.8 (C-2′), 73.8 (C-3), 73.4 (C-4), 69.3 (C-2), 69.2 (C-3′), 62.9 (C-4′), 58.7 (C-1), 55.2 (C-5), 54.4 (C-1′), 41.1 (CH_2), 10.5 (CH_3). HRMS: $[M+H]^+$ calcd for $C_{18}H_{29}O_8N_2S$, 433.1645; found, 433.1638.

4.18. 1′-((2-*N*-Ethylamino-1,4-imino-1,2,4-trideoxy-D-arabinitol)-4-*N*-ammonium)-1′-deoxy-L-erythritol-3′-sulfate (16)

Compound **31** (10 mg, 0.02 mmol) was subjected to trifluoroacetic acid treatment and the crude product was purified by flash chromatography [EtOAc–MeOH, 3:1] to afford compound **16** as a syrup (5.6 mg, 70%). $[\alpha]_D$ +29 (*c* 0.04, MeOH); ^1H NMR (CD_3OD) δ 4.37 (1H, ddd, $J_{2',3'} = 4.7$ Hz, H-3′), 4.04 (1H, dd, H-3), 3.98 (1H, ddd, $J_{1'a,2'} = 8.3$, $J_{1'b,2'} = 5.2$ Hz, H-2′), 3.82 (1H, dd, $J_{4'b,4'a} = 11.9$, $J_{3',4'a} = 4.2$ Hz, H-4′a), 3.71 (1H, dd, $J_{3',4'b} = 5.1$ Hz, H-4′b), 3.69 (1H, dd, $J_{5b,5a} = 11.7$, $J_{4,5a} = 2.4$ Hz, H-5a), 3.54 (1H, dd, $J_{4,5b} = 2.3$ Hz, H-5b), 3.27 (1H, dd, $J_{1b,1a} = 11.0$ Hz, H-1a), 3.18 (1H, ddd, $J_{1b,2} = 5.3$ Hz, H-2), 2.96 (2H, m, CH_2), 2.94 (1H, dd, $J_{1'b,1'a} = 12.7$ Hz, H-1′a), 2.72 (1H,dd, H-1b), 2.41 (1H, dd, H-1′b), 2.36 (1H, ddd, $J_{3,4} = 4.5$ Hz, H-4), 1.19 (3H, t, $J_{CH_2,CH_3} = 7.2$ Hz, CH_3); ^{13}C NMR (CD_3OD) 80.6 (C-3′), 74.3 (C-3), 73.4 (C-4), 69.3

(C-2′), 63.1 (C-2), 60.6 (C-4′), 58.9 (C-5), 55.8 (C-1′), 54.6 (C-1), 41.2 (CH_2), 10.9 (CH_3). HRMS: $[M+Na]^+$ calcd for $C_{11}H_{24}O_8N_2SNa$, 367.1151; found, 367.1193.

4.19. *N*-Benzyl-2,3-epoxy-1,4-imino-1,2,3,4-tetradeoxy-D-ribitol (28)

To a solution of compound **27** (16.7 g, 76.7 mmol) in dry THF (100 mL) was added BH_3·THF (160 mL, 1 M solution) at 0 °C. The mixture was stirred under N_2 overnight. The reaction was quenched by slowly adding MeOH until gas evolution had stopped. Additional MeOH (50 mL) was added and the solvents were removed under reduced pressure. The residue was dissolved in MeOH (200 mL), the mixture was heated to reflux for 1 h, and the solvent was removed under reduced pressure. MeOH (100 mL) was added and evaporated under reduced pressure. This procedure was repeated twice. Diethyl ether (250 mL) and HCl (250 mL, 0.5 M) were added and the layers were separated. The organic layer was extracted with HCl (250 mL, 0.5 M). The aqueous layers were combined and adjusted to pH 11–12 with NaOH (10 M), and extracted with dichloromethane (300 mL). The organic phase was dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography [hexanes–EtOAc, 2:1] to afford **28** as a syrup (11.0 g, 70%). $[\alpha]_D$ −18 (*c* 2.9, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.34–7.22 (5H, m, Ph), 3.86, 3.79 (2H, d, $J_{gem} = 13.4$ Hz, CH_2Ph), 3.65 (1H, dd, $J_{2,3} = 2.8$, $J_{2,1b} = 0.5$ Hz, H-2), 3.57 (1H, ddd, H-3), 3.48 (1H, dd, $J_{5b,5a} = 10.8$, $J_{4,5a} = 5.1$ Hz, H-5a), 3.37 (1H, dd, $J_{4,5b} = 6.1$ Hz, H-5b), 3.24 (1H, ddd, H-4), 3.15 (1H, dd, $J_{1b,1a} = 13.2$, $J_{2,1a} = 1.2$ Hz, H-1a), 2.93 (1H, dd, H-1b); ^{13}C NMR ($CDCl_3$) 140.0, 128.76, 128.72, 127.4 (6C, Ph), 66.8 (C-4), 63.1 (CH_2Ph), 61.5 (C-5), 60.2 (C-3), 57.9 (C-2), 54.4 (C-1). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.99; H, 7.33; N, 6.65.

4.20. 2-Azido-1,4-imino-1,2,4-trideoxy-D-arabinitol (24)

To a solution of compound **29** (1.67 g, 6.5 mmol) in MeOH (100 mL) was added concentrated HCl (1.2 mL). The mixture was stirred overnight. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography [EtOAc–MeOH, 3:1] to afford compound **24** as a syrup (0.73 g, 72%). $[\alpha]_D$ +1 (*c* 0.7, MeOH); ^{1}H NMR (CD_3OD) δ 4.23 (1H, ddd, $J_{3,2} = 4.5$ Hz, H-2), 4.12 (1H, dd, H-3), 3.89 (1H, dd, $J_{5b,5a} = 11.8$, $J_{4,5a} = 4.2$ Hz, H-5a), 3.76 (1H, dd, $J_{4,5b} = 7.5$ Hz, H-5b), 3.64 (1H, dd, $J_{1b,1a} = 12.4$, $J_{2,1a} = 6.5$ Hz, H-1a), 3.52 (1H, ddd, $J_{3,4} = 5.4$ Hz, H-4), 3.25 (1H, dd, $J_{2,1b} = 4.6$ Hz, H-1b); ^{13}C NMR (CD_3OD) δ 74.5 (C-3), 66.7 (C-4), 65.3 (C-2), 58.4 (C-5), 47.2 (C-1). HRMS: $[M+H]^+$ calcd for $C_5H_{11}N_4O_2$, 159.0882; found, 159.0884.

4.21. *N*-Boc-2-amino-1,4-imino-1,2,4-trideoxy-D-arabinitol (21)

To a solution of **29** (270 mg, 1.0 mmol) in MeOH–H_2O (20:1, 30 mL) was added triphenylphosphine (329 mg, 1.25 mmol). The mixture was stirred at room temperature overnight, the solvent was removed under reduced pressure, and the crude product was purified by flash chromatography [EtOAc–MeOH–H_2O, 5:3:1] to afford **21** as an amorphous solid (223 mg, 92%). $[\alpha]_D$ −58.82 (*c* 2.55, H_2O); ^{1}H NMR (CD_3OD) δ 4.01–3.95 (1H, m, H-5a), 3.95–3.85 (1H, m, H-3), 3.77 (1H, m, H-1a), 3.67–3.60 (2H, m, H-5b, H-4), 3.26 (1H, m, H-2), 3.14 (1H, dd, $J_{1b,1a} = 11.4$, $J_{2,1b} = 4.4$ Hz, H-1b), 1.48 (9H, s, $C(CH_3)_3$); ^{13}C NMR (at 70 °C, D_2O) δ 156.8 (CO), 82.4 ($C(CH_3)_3$), 79.5 (C-3), 66.1 (C-4), 60.9 (C-5), 55.6 (C-5), 52.3 (C-2), 52.3 (C-1), 28.5 (CH_3). HRMS: $[M+H]^+$ calcd for $C_{10}H_{21}O_4N_2$, 233.1501; found, 233.1490.

4.22. *N*-Boc-2-acetamido-1,4-imino-1,2,4-trideoxy-D-arabinitol (22)

To a solution of **21** (50 mg, 0.2 mmol) in MeOH (15 mL) was added Ac_2O (0.2 mL, 10 equiv) and the mixture was stirred for 2 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography [EtOAc–MeOH, 5:1] to afford **22** as a syrup (53 mg, 90%). $[\alpha]_D$ +320 (*c* 0.125, H_2O); ^{1}H NMR (CD_3OD) δ 4.26–4.06 (1H, m, H-3), 4.11 (1H, m, H-2), 3.92–3.79 (2H, m, H-1a, H-5a), 3.72 (1H, dd, $J_{5a,5b} = 11.0$ Hz, H-5b), 3.57 (1H, m, H-4), 3.12 (1H, dd, $J_{1a,1b} = 11.7$, $J_{2,1b} = 4.6$ Hz, H-1b), 1.95 (3H, s, CH_3), 1.48 (9H, s, $C(CH_3)_3$); ^{13}C NMR (at 70 °C, D_2O) δ 174.9 (CO), 156.8 (CO), 82.7 ($C(CH_3)_3$), 76.6 (C-3), 65.5 (C-4), 60.8 (C-5), 54.9 (C-2), 49.9 (C-1), 28.4 (CH_3), 22.7 (CH_3). HRMS: $[M+H]^+$ calcd for $C_{12}H_{23}O_5N_2$, 275.1607; found, 275.1610.

4.23. 2-Acetamido-1,4-imino-1,2,4-trideoxy-D-arabinitol (17)

To a solution of **22** (37 mg, 0.1 mmol) in MeOH (5 mL) was added HCl (0.03 mL) and the mixture was stirred for 3.5 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography [EtOAc–MeOH, 2:1] to afford **17** as a syrup (24 mg, 84%). $[\alpha]_D$ +4 (*c* 0.17, MeOH); ^{1}H NMR (D_2O) δ 4.15 (1H, ddd, H-2), 4.07 (1H, dd, $J_{2,3} = 7.7$ Hz, H-3), 3.81 (1H, dd, $J_{5b,5a} = 12.7$, $J_{4,5a} = 3.2$ Hz, H-5a), 3.71 (1H, dd, $J_{4,5b} = 5.7$ Hz, H-5b), 3.60 (1H, dd, $J_{1b,1a} = 12.3$, $J_{2,1a} = 8.6$ Hz, H-1a), 3.45 (1H, ddd, $J_{3,4} = 8.1$ Hz, H-4), 3.09 (1H, dd, $J_{2,1b} =$

7.6 Hz, H-1b), 1.86 (3H, s, CH_3); ^{13}C NMR (D_2O) δ 174.8 (CO), 73.1 (C-3), 63.9 (C-4), 57.7 (C-5), 54.5 (C-2), 46.4 (C-1), 22.0 (CH_3). HRMS: $[M+H]^+$ calcd for $C_7H_{15}O_3N_2$, 175.1083; found, 175.1081.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2008.02.027.

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