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(3*R*,4*S*,5*R*,6*R*,7*S*)-3,4,5,7-Tetrahydroxyconidine, an azetidine analogue of 6,7-diepicastanospermine and a conformationally constrained D-deoxyaltronojirimycin, from L-arabinose

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ABSTRACT

The synthesis from L-arabinose of an azetidine analogue of 6,7-diepicastanospermine and its glycosidase inhibition profile are described.

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1. Introduction

Iminosugars,[1] where the oxygen of the sugar ring is replaced by nitrogen, are carbohydrate mimics; their interactions with enzymes and other receptors indicate their promise as chemotherapeutic agents.[2] Many hundreds of pyrrolidine, piperidine and azepane monosaccharide analogues have been studied. In contrast, there are few examples of carbohydrate-derived azetidines,[3] although the properties of hydroxyazetidines are of current interest.[4] *N*-Alkyl hydroxyazetidines are potent inhibitors of purine nucleoside phosphorylase with sub-nanomolar K_i.[5] Azetidine iminosugar analogues of pentoses have been found to be specific inhibitors of non-mammalian glycosidases,[6,7] and *N*-nonyl trihydroxy-azetidines are specific inhibitors of some ceramide-specific glucosyl transferases and glucosidases.[8] Bicyclic trihydroxy azetidines with no hydroxyl group in the azetidine ring show no significant glycosidase inhibition;[9] an azetidine analogue of swainsonine showed no significant inhibition of α-mannosidases.[10]

This paper reports the synthesis of tetrahydroxyconidine **2**,[11] an azetidine analogue of 6,7-diepicastanospermine **1**, via hydroxylation of the key intermediate **3** derived from L-arabinose **4** (Fig. 1); it was not possible to achieve the alternative hydroxylation that would lead to the azetidine **6** as the corresponding analogue of castanospermine **5**. The azetidine **2** can also be considered as a conformationally restricted equivalent of 1-deoxyaltronojirimycin (*altro*-DNJ) **7**. *altro*-DNJ **7** has been isolated from *Scilla sibirica*,[12] *Angylcalyx pyrnaertii*,[13] and from a Thai medicinal plant (*Connarus ferrugineus*).[14] Azet-LAB **8**, which has recently been shown to be a good inhibitor of some non-mammalian glycosidases,[6] has the same aminotriol motif. Several stereoisomers of castanospermine have been isolated from *Castanospermum australe*,[15,16] including 6,7-diepicastanospermine.[17] Many syntheses of *altro*-DNJ **7** have been reported,[18] but only one synthesis of 6,7-diepicastanospermine **1** has been described.[19] Inhibition of α-glucosidases of *N*-linked glycoprotein processing by castanospermine has led to strategies for the chemotherapy of viral diseases.[20] Celgosivir, the 6-*O*-butyryl ester of castanospermine, is in clinical trials as a chemotherapeutic agent for hepatitis C.[21] Synthesis of many castanospermine analogues[22] have allowed the structural basis of the inhibition of human glycosidases by castanospermines to be delineated.[23] This paper provides the first synthesis of a tetrahydroxyazetidine analogue **2** of indolizidine iminosugars, together with other conidines, and reports on the effects of **2** and related compounds on a panel of glycosidases.

2. Results and discussion

2.1. Synthesis

For the synthesis of the conidine **2**, the protected azetidine **9**,[6,24] derived from L-arabinose **4**, underwent acid catalyzed hydrolysis

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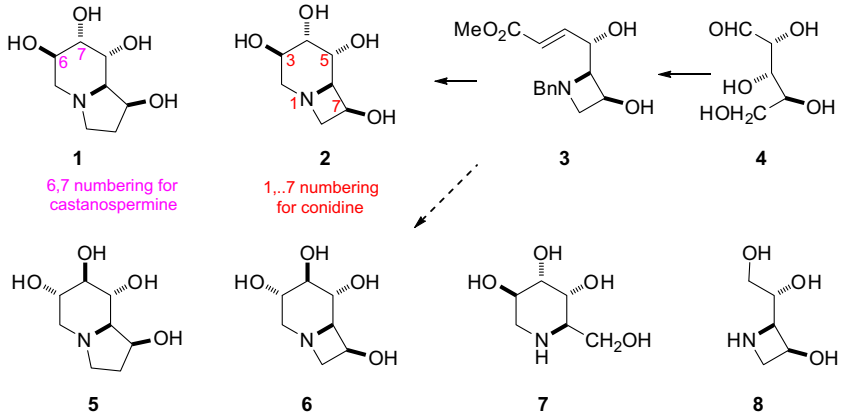
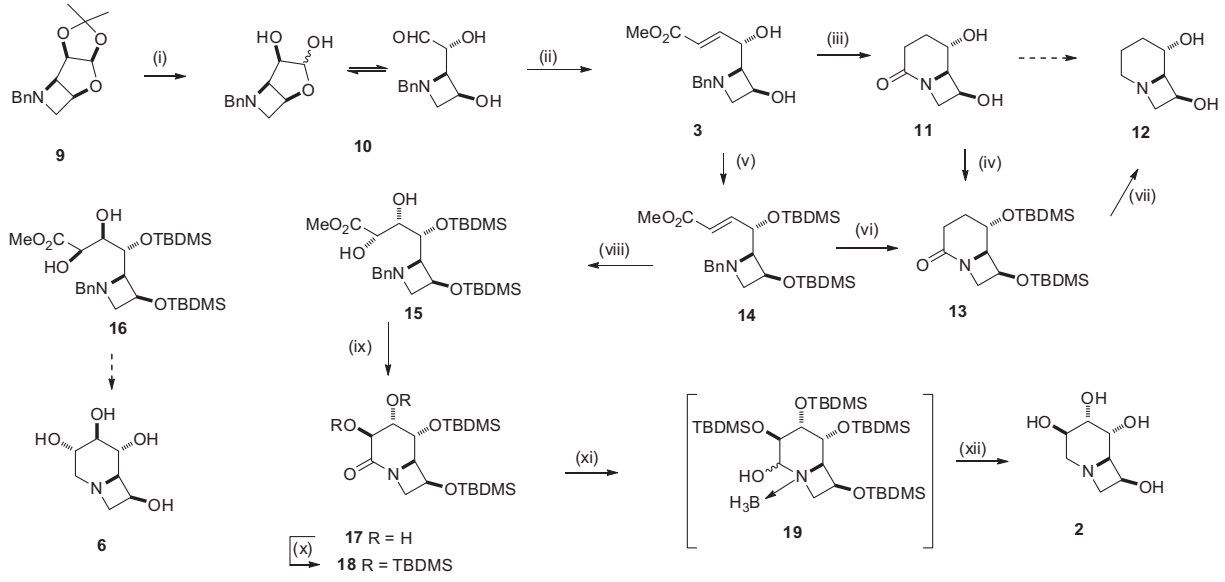


Figure 1. Synthetic strategy for azetidine analogue of castanospermine.

by aqueous trifluoroacetic acid to afford a 1:1 mixture of the lactols **10** in 77% yield (Scheme 1). Reduction of the lactol in situ, followed by hydrogenolysis of the benzyl group afforded azet-LAB **8** as previously described.[6] Reaction of the purified lactols **10** with the stabilized ylid $Bu_3P{=}CHCO_2Me$ in 1,4-dioxane gave the *trans*-enoate **3** in 52% yield. Transfer hydrogenation of **3** by ammonium formate in the presence of palladium on carbon caused debenzylation and reduction of the C=C followed by cyclization to the lactam **11** (65%); the very low carbonyl stretch at 1607 cm^{-1} is characteristic of conidine lactams.[25] All attempts to reduce the unprotected lactam directly to the dihydroxy conidine **12** were unsuccessful, so the hydroxyl groups in **11** were protected as their TBDMS ethers by treatment with TBDMS triflate in DMF in the presence of 2,6-lutidine to yield the protected lactam **13** (73%). **13** was formed more efficiently by prior silylation of azetidine enoate **3** to the corresponding bis-TBDMS ether **14** (88%); subsequent transfer hydrogenation of **14** afforded the protected lactam **13** in 99% yield. Higher yields of bicyclic lactam formation are generally formed when the hydroxyl groups are protected (and in particular when such protection precludes the formation of an alternative lactone). Reduction of the protected lactam **13** by borane in THF gave the corresponding protected amine as the borane adduct (79%), treatment of which with aqueous trifluoroacetic acid formed the conidine diol **12** (94%).

The osmium(VIII)-catalyzed hydroxylation of the unprotected **3** and protected **14** enoates by a number of procedures was investigated.[26] All attempts to hydroxylate the unprotected diol **3** were unsuccessful; the reactions were very slow and gave highly polar compounds that were difficult to isolate and purify. Thus, no reaction of **3** with the TMEDA/osmium tetroxide mixture was observed.[27a] A wide variety of conditions for dihydroxylation of the bis-TBDMS ether **14** gave only the diol **15**; the optimum conditions [$K_2OsO_4{\cdot}2H_2O$, $K_3Fe(CN)_6$, K_2CO_3, and $(DHQ)_2PHAL$ in *tert*-BuOH:-H_2O (3:1)] gave the diol **15** as a single stereoisomer in 77% yield. There was no evidence for the formation of the distereoisomer **16** (which would have allowed the synthesis of the castanospermine azetidine analogue **6**) under any of the conditions, including the use of other ligands, and different amounts and sources of



Scheme 1. (i) CF_3COOH/H_2O 1:1, RT, 24 h, 77% (ii) $Bu_3P{=}CHCO_2Me$, 1,4-dioxane, RT, 16 h, 52% (iii) $HCO_2^-NH_4^+$, 10% Pd/C, MeOH, reflux, 1 h, 65% (iv) *tert*-$BuMe_2SiOSO_2CF_3$, 2,6-lutidine, DMF, RT, 16 h, 73% (v) *tert*-$BuMe_2SiOSO_2CF_3$, 2,6-lutidine, DMF, RT, 22 h, 88% (vi) $HCO_2^-NH_4^+$, 10% Pd/C, MeOH, reflux, 45 min, 99% (vii) THF/BH_3, THF, reflux, 3 h, 79%; then $CF_3COOH:H_2O$ 9:1, RT, 3 d, 94% (viii) K_2OsO_4, $K_3Fe(CN)_6$, K_2CO_3, $(DHQ)_2PHAL$, *tert*-$BuOH:H_2O$ 3:1, RT, 24 h, 77% (ix) $HCO_2^-NH_4^+$, 10% Pd/C, MeOH, reflux, 1 h, 57% (x) *tert*-$BuMe_2SiOSO_2CF_3$, 2,6-lutidine, DMF, RT, 16 h, 88% (xi) THF:BH_3, THF, reflux, 1 h, 84% (xii) H_2, 10% Pd/C, CF_3COOH/H_2O 9:1, RT, 4 d, 80% from **18**.

osmium. The dihydroxylation of **14** is an example of the Kishi model[27b] in which the stereoselectivity of the *Z*-substituted alkene is controlled by 1,3-allylic strain.[27c]

Removal of the benzyl group in **15** by transfer hydrogenation resulted in the formation of the hydroxylated lactam **17** (57%). NOE analysis of **17** is consistent with its stereochemistry (Fig. 2). There are significant NOEs from H3 to H4 as well as from H4 to H5. However, there is no evidence of NOEs neither from H6 to H4 nor from H3 to H5, which rules out the presence of the stereoisomer **20**.

Attempts to reduce the diol **17** with a number of hydride reducing agents were unsuccessful; accordingly **17** was protected as the tetrasilyl ether **18** by treatment with treatment with TBDMS triflate in DMF with 2,6-lutidine (88%). Reduction of the lactam **18** did not give the corresponding amine directly; the initial reduction product was consistent with the structure of lactol/borane complex **19** which could be isolated by flash chromatography as an unstable non-polar intermediate. Evidence for the structure of **19** included the low resolution mass spectrum (ESI), the B–H stretch at 2382 cm^{-1} in the infra red, and the HSQC spectrum which showed only one methylene group. Hydrogenation of **19** in aqueous trifluoroacetic acid in the presence of a 10% palladium catalyst removed both the borane and silyl ether protecting groups, and proceeded with intramolecular reductive amination to afford the target tetrahydroxy conidine **2** in 80% yield from the protected amide **18**. Although conidine itself undergoes acid catalyzed polymerization,[28] **2** was stable to acid treatment.

2.2. Biological activity

Inhibition by the iminosugars **2**, **7**, **8**, **11**, and **12** of the following glycosidases was studied (Fig. 3):[29] α-glucosidases (rice, yeast, rat intestinal maltase, *Aspergillus niger*), β-glucosidases (almond, bovine liver, *A. niger*), α-galactosidase (coffee beans), β-galactosidases (bovine liver, rat intestinal lactase), α-mannosidase (Jack beans), β-mannosidase (snail), α-L-rhamnosidase (*Penicillium decumbens*), α-L-fucosidase (bovine kidney), β-glucuronidases (*Escherichia coli*, bovine liver), trehalase (porcine kidney), and amyloglucosidases (*A. niger*, *Rhizopus sp.*). The indolizidine alkaloid 6,7-diepicastanospermine **1** has been reported as moderate but specific inhibitor of the fungal α-glucosidase, amyloglucosidase (*A. niger*) (IC_{50} 84 μM)[30] in comparison with castanospermine **5** (IC_{50} 8 μM).

This study (Table 1) revealed that the tetrahydroxyconidine **2** showed no inhibition of amyloglucosidase from *A. niger* (31% inhibition at 1 mM); **2** was a weak inhibitor of amyloglucosidase from *Rhizopus sp.* and rat intestinal lactase, with IC_{50} values of 532 and 418 μM, respectively. **2** can be regarded as a conformationally restricted bicyclic amine, which combines the stereochemical motifs of both *altro*-DNJ **7** (piperidine-ring) and the azet-LAB **8** (azetidine-ring). The monocyclic azetidine, azet-LAB **8** is a good inhibitor of *A. niger* α-glucosidase, rat intestinal lactase, and *Rhizopus sp.* amyloglucosidase, with IC_{50} 39, 70 and 19 μM, respectively.[6] In contrast, *altro*-DNJ **7** showed no inhibition against these enzymes but does inhibit bovine kidney α-L-fucosidase with IC_{50} value of 194 μM. Furthermore, this study revealed that the less oxygenated indolizidine alkaloid conidine diol **12** was much better and specific fungal glycosidase inhibitors than tetrahydroxyconidine **2**: α-glucosidase (*A. niger*) (IC_{50} 307 μM) and amyloglucosidases (IC_{50} 930 μM from *A. niger*, IC_{50} 243 μM from *Rhizopus sp.*), and α-L-rhamnosidase (*P. decumbens*) (IC_{50} 117 μM); similarly, the less oxygenated indolizidine alkaloid lentiginosine **21** also specifically inhibits fungal amyloglucosidase (*A. niger*) (IC_{50} 32 μM).[31] The lactam **11** showed no inhibition of any glycosidase.

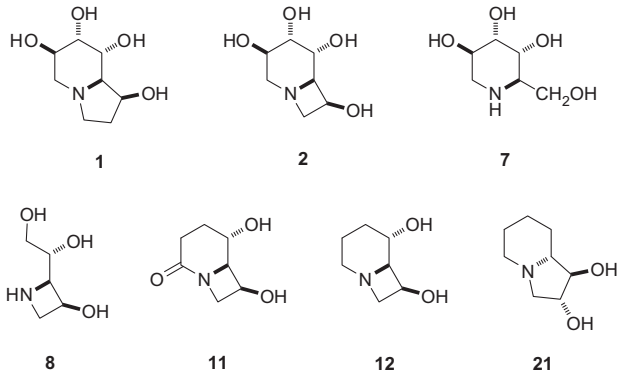


Figure 3. Glycosidase inhibition discussion.

3. Conclusion

In summary, the synthesis of the first tetrahydroxyazetidine analogue of castanospermine from arabinose demonstrates that such structures are stable. Lentiginosine **21**, although only a weak glycosidase inhibitor, inhibits ATPase and chaperone activity of Hsp90,[32] where its enantiomer and a further hydroxylated derivative show a novel mechanism for apoptosis.[33] It is likely that azetidine analogues such as **2** and **12** may have interesting biological properties other than glycosidase inhibition. A different approach is necessary for the synthesis of the azetidine castanospermine analogue **6**.

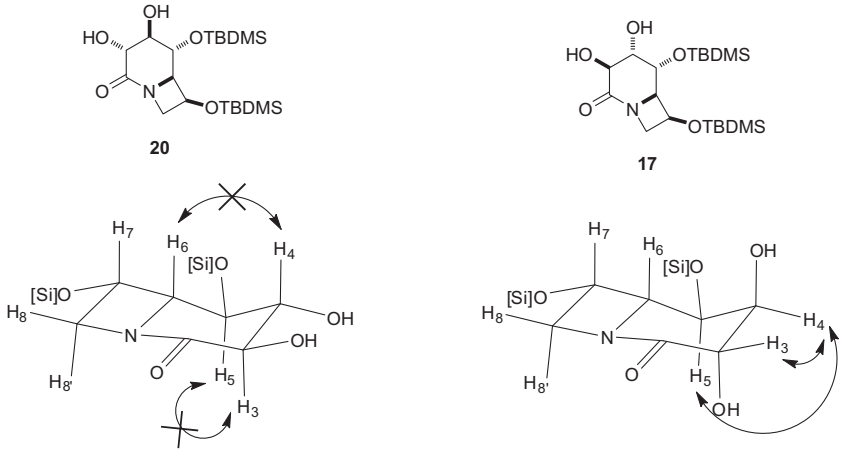
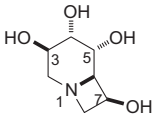
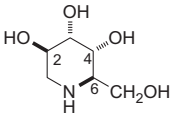
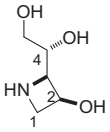
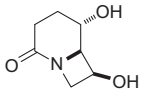
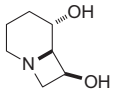


Figure 2. NOE enhancements on **20** and **17**.

Table 1
Concentration of azetidine analogues of 6,7-diepicastanospermine and related compounds giving 50% inhibition of various glycosidases

			IC$_{50}$ (μM) 		
Enzyme	**2**	**7**	**8**	**11**	**12**
α-Glucosidase					
Rice	NI (13.8%)	NI (7.2%)	NI (12.1%)	NI (2.7%)	NI[a] (0%)[b]
Yeast	NI (0%)	NI (1.4%)	NI (16.0%)	NI (3.1%)	NI (1.6%)
Rat intestinal maltase	NI (30.3%)	NI (24.2%)	**607**	NI (25.2%)	NI (14.3%)
Aspergillus niger	NI (47.3%)	NI (19.1%)	**39**	NI (0%)	**307**
β-Glucosidase					
Almond	NI (31.1%)	NI (18.8%)	**347**	NI (0%)	NI (0%)
Bovine liver	NI (18.9%)	NI (10.9%)	**997**	NI (14.9%)	NI (9.7%)
Aspergillus niger	NI (1.8%)	NI (1.8%)	NI (0.4%)	NI (1.2%)	NI (0%)
α-Galactosidase					
Coffee beans	NI (3.5%)	NI (20.5%)	NI (7.6%)	NI (0%)	NI (8.4%)
β-Galactosidase					
Bovine liver	NI (43.4%)	NI (19.9%)	NI (25.2%)	NI (13.4%)	NI (14.0%)
Rat intestinal lactase	**418**	NI (44.6%)	**70**	NI (0%)	NI (32.2%)
β-Mannosidase					
Snail	NI (0%)	NI (0%)	NI (0%)	NI (0%)	NI (0%)
α-L-Rhamnosidase					
Penicillium decumbens	NI (2.0%)	NI (2.1%)	**634**	NI (11.1%)	**117**
α-L-Fucosidase					
Bovine kidney	NI (2.0%)	**194**	NI (4.6%)	NI (0%)	NI (0%)
β-Glucuronidase					
Escherichia coli	NI (0%)	NI (0%)	NI (0%)	NI (8.9%)	NI (13.2%)
Bovine liver	NI (7.8%)	NI (7.4%)	NI (7.4%)	NI (4.2%)	NI (0%)
α,α-Trehalase					
Porcine kidney	NI (9.0%)	NI (2.1%)	NI (5.8%)	NI (5.2%)	NI (1.0%)
Amyloglucosidase					
Aspergillus niger	NI (31.3%)	NI (5.0%)	**105**	NI (3.0%)	**930**
Rhizopus sp.	**532**	NI (7.0%)	**19**	NI (3.8%)	**243**

[a] NI–no inhibition (less than 50% inhibition at 1000 μM).
[b] (–): inhibition% at 1000 μM.

4. Experimental

4.1. Materials and methods

All commercial reagents were used as supplied. THF and DMF were purchased dry from the Aldrich chemical company in sure-seal bottles. Methanol and pyridine were purchased dry from the Aldrich chemical company in sure-seal bottles over molecular sieves. All other solvents were used as supplied (Analytical or HPLC grade), without prior purification. Thin layer chromatography (TLC) was performed on aluminum sheets coated with 60 F254 silica. Plates were visualized using a spray of 1% w/v potassium permanganate in 1 M sodium hydroxide, or a 0.2% w/v cerium (IV) sulfate and 5% ammonium molybdate solution in 2 M sulfuric acid. Flash column chromatography was performed on Sorbsil C60 40/60 silica. Melting points were recorded on a Kofler hot block and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 341 polarimeter with a path length of 1 dm. Concentrations are quoted in g 100 ml^{-1}. Infrared spectra were recorded on a Perkin–Elmer 1750 IR Fourier Transform spectrophotometer. Only the characteristic peaks are quoted. Low resolution mass spectra (m/z) were recorded on a Waters LCT Premier spectrometer, and high resolution mass spectra (HRMS m/z) on a Waters ZMD spectrometer. The technique used was electrospray ionization (ESI). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVII500 (^{1}H: 500 MHz and ^{13}C: 125.7 MHz) and Bruker DPX400 and AV400 spectrometers (^{1}H: 400 MHz and ^{13}C: 100.6 MHz) in the deuterated solvent stated. All chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz. Residual signals from the solvents were used as an internal reference, except in the case of deuterium oxide, where acetonitrile was used as the reference.

4.1.1. (2*E*)-Methyl-(4*S*,5*S*,6*S*)-*N*-benzyl-4,6-dihydroxy-5,7-iminohept-2-enoate (3)

Compound **9** (970 mg, 3.71 mmol) was dissolved in a mixture of trifluoroacetic acid (2.5 mL) and water (2.5 mL) and the resulting solution was stirred at room temperature. After 24 h, TLC analysis (2:1 cyclohexane/ethyl acetate) showed the complete consumption of starting material and the formation of a major product (R_f 0.10). The solvents were removed in vacuo. Purification by flash column chromatography (EtOAc/NEt$_3$, 99:1) afforded the corresponding lactol **10** (631 mg, 77%) as a yellow oil in a 1:1 mixture of anomers.

Bu$_3$PCH$_2$CO$_2$MeBr (1.12 g, 3.16 mmol) was dissolved in dichloromethane (20 mL) and washed with sodium hydroxide (1 M aq, 20 mL) for 15 min. The aqueous layer was then washed with dichloromethane (2 × 15 mL). The combined organics were dried (MgSO$_4$), filtered and concentrated in vacuo. The resulting ylid was added to a solution of **10** (582 mg, 2.63 mmol) in 1,4-dioxane (10 mL) and the reaction mixture stirred at room temperature for 16 h. After this time, TLC analysis (ethyl acetate) showed the complete consumption of starting material (R_f 0.50) and the formation of a major product (R_f 0.38). The reaction mixture was concentrated and the residue purified by flash column chromatography on silica gel (1:1 cyclohexane/ethyl acetate) to afford **3** as a pale yellow solid (380 mg, 52%); $[\alpha]_D^{25}$ +23.4 (c 0.36 in CHCl$_3$); ν_{max} (film, cm^{-1}): 3403 (s, br s, OH), 1721 (CO), 1658 (C=C); mp 108–110 °C; δ_H (CDCl$_3$, 400 MHz): 3.28–3.31 (1H, dd, H7, $J_{7,6}$ 6.4, $J_{7,7'}$ 9.2), 3.40–3.44 (2H, m, H7′ and H5), 3.69 (2H, s, CH_2Ph), 3.73 (3H, s, CH_3),

4.08–4.10 (1H, dt, H4, $J_{4,2}$ 2.0, $J_{4,5}$/$J_{4,3}$ 4.4), 4.47–4.51 (1H, dd, H6, $J_{6,5}$ 1.6, $J_{6,7'}$ 6.4), 6.08–6.12 (1H, dd, H2, $J_{2,4}$ 2.0, $J_{2,3}$ 16), 6.91–6.96 (1H, dd, H3, $J_{3,4}$ 4.4, $J_{3,2}$ 16), 7.27–7.35 (5H, m, 5 × ArH); δ_C ($CDCl_3$, 100 MHz): 51.7 (CH_3), 61.2, 61.4 (CH_2Ph and C7), 65.9 (C6), 70.3 (C4), 71.3 (C5), 121.2 (C2), 127.6 (*p*-ArCH), 128.6, 128.8 (2 × *o*-ArCH and 2 × *m*-ArCH), 137.3 ppm (*ipso*-ArC), 146.4 (C3), 166.9 (C1); *m*/*z* (ESI+ve): 278 ([M+H]$^+$, 69%), 300 ([M+Na]$^+$, 64%), 577 ([2M+Na]$^+$, 100%); HRMS *m*/*z* (ESI+ve): found 278.1385 ([M+H]$^+$); $C_{15}H_{20}NO_4$ requires 278.1387.

4.1.2. (5*S*,6*S*,7*S*)-5,7-Dihydroxy-1-azabicyclo[4.2.0]octane-2-one (11)

Compound **3** (100 mg, 0.36 mmol), 10% Pd on carbon (115 mg) and ammonium formate (341 mg, 5.40 mmol) were suspended in anhydrous methanol (10 mL) and the mixture was refluxed under argon. After 1 h, TLC analysis (3:7 methanol/ethyl acetate) showed no-remaining starting material (R_f 0.74) and formation of the product (R_f 0.38). The mixture was filtered through Celite and washed with methanol. The solvent was concentrated in vacuo and the residue purified by flash column chromatography on silica gel (2:8 methanol/ethyl acetate) to afford **11** as a white solid (37.1 mg, 65%); $[\alpha]_D^{25}$ −42.0 (*c* 0.48 in methanol); ν_{max} (film, cm^{-1}): 3363 (s, br s, OH), 1607 (CO); mp 164–166 °C; δ_H (CD_3OD, 400 MHz): 1.86–1.93 (1H, m, H4), 2.03–2.10 (1H, m, H4′), 2.33–2.42 (1H, ddd, H3, $J_{3,4}$ 7.2, $J_{3,4'}$ 10.8, $J_{3,3}$ 18), 2.45–2.52 (1H, ddd, H3′, $J_{3',4}$ 1.6, $J_{3',4'}$ 7.2, $J_{3',3}$ 18), 3.75–3.78 (1H, dt, H8, $J_{8,8'}$ 10.8, $J_{8,6}$/$J_{8,7}$ 1.6), 4.16–4.24 (2H, m, H5 and H8′), 4.33–4.36 (1H, dd, H6, $J_{6,7}$ 5.2, $J_{6,5}$ 8.4), 4.55–4.58 (1H, td, H7, $J_{7,8}$ 2.0, $J_{7,6}$/$J_{7,8'}$ 5.2); δ_C (CD_3OD, 100 MHz): 29.5, 29.6 (C3 and C4), 59.4 (C8), 62.2 (C5), 66.6 (C7), 73.2 (C6), 172.7 (CO); *m*/*z* (ESI+ve): 158 ([M+H]$^+$, 16%), 180 ([M+Na]$^+$, 45%), 337 ([2 M+Na]$^+$, 100%); HRMS *m*/*z* (ESI+ve): found 180.0631 ([M+Na]$^+$); $C_{17}H_{11}NNaO_3$ requires 180.0631.

4.1.3. (2*E*)-Methyl-(4*S*,5*S*,6*S*)-*N*-benzyl-4,6-bis(*tert*-butyldimethylsilyloxy)-5,7-iminohept-2-enoate (14)

tert-Butyldimethylsilyl trifluoromethanesulfonate (0.21 mL, 0.91 mmol) and 2,6-lutidine (0.14 mL, 1.21 mmol) were added to a solution of **3** (84 mg, 0.30 mmol) in dimethylformamide (6 mL) and the resulting solution was stirred at room temperature. After 22 h, TLC analysis (2:1 cyclohexane/ethyl acetate) showed the complete consumption of starting material and the formation of a major product (R_f 0.85). The mixture was diluted with ethyl acetate (10 mL), washed with 1:1 water/brine (3 × 10 mL) and the organic layer dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (5:1 cyclohexane/ethyl acetate) afforded **14** (135 mg, 88%) as a yellow oil; $[\alpha]_D^{25}$ −1.6 (*c* 0.32 in $CHCl_3$); ν_{max} (film, cm^{-1}): 1727 (CO), 1472 (arom); δ_H ($CDCl_3$, 400 MHz): 0.03–0.08 (4 × 3H, m, 4 × CH_3), 0.92–0.93 (2 × 9H, m, 2 × C(CH_3)$_3$), 2.92–2.96 (1H, m, H7, $J_{7,5}$ 2.4, $J_{7,6}$ 6.0, $J_{7,7'}$ 8.8), 3.15–3.17 (1H, d, H7′, $J_{7',7}$ 8.8), 3.23–3.30 (2H, m, CH_2Ph and H5), 3.74 (3H, s, OCH_3), 3.82–3.85 (1H, d, CH_2Ph, J_{gem} 13.2), 4.49–4.52 (1H, t, H6, $J_{6,5}$ 6.0, $J_{6,7}$ 6.0), 4.78–4.81 (1H, m, H4), 6.09–6.13 (1H, dd, H2, $J_{2,4}$ 1.6, $J_{2,3}$ 15.6), 7.23–7.30 (5H, m, 5 × Ar*H*), 7.30–7.38 (1H, ddd, H3, $J_{3,5}$ 2.8, $J_{3,4}$ 4.8, $J_{3,2}$ 15.6); δ_C ($CDCl_3$, 100 MHz): −4.5, −4.4, −4.3, −4.1 (4 × CH_3), 18.2 (2 × *C*(CH$_3$)$_3$), 26.0 (2 × C(*C*H$_3$)$_3$), 51.5 (O*C*H$_3$), 60.5 (C7), 62.1 (*C*H$_2$Ph), 65.2 (C6), 70.4 (C4), 74.9 (C5), 120.1 (C2), 127.0 (*p*-Ar*C*H), 128.2, 128.9 (2 × *o*-Ar*C*H and 2 × *m*-Ar*C*H), 138.3 ppm (*ipso*-Ar*C*), 151.1 (C3), 167.2 (C1); *m*/*z* (ESI+ve): 506 ([M+H]$^+$, 100%), 528 ([M+Na]$^+$, 36%); HRMS *m*/*z* (ESI+ve): found 506.3124 ([M+H]$^+$); $C_{27}H_{48}NO_4Si_2$ requires 506.3116.

4.1.4. (5*S*,6*S*,7*S*)-5,7-bis(*tert*-Butyldimethylsilyloxy)-1-azabicyclo[4.2.0]octane-2-one (13)

Compound **14** (130 mg, 0.26 mmol), 10% Pd on carbon (82 mg) and ammonium formate (243 mg, 3.85 mmol) were suspended in anhydrous methanol (10 mL) and the mixture was refluxed under argon. After 45 min, TLC analysis (2:1 cyclohexane/ethyl acetate) showed no-remaining starting material and formation of the product (R_f 0.21). The mixture was filtered through Celite and washed with methanol. The solvent was concentrated in vacuo and the residue purified by flash column chromatography on silica gel (2:1 cyclohexane/ethyl acetate) to afford **13** as a colourless oil (98.4 mg, 99%); $[\alpha]_D^{25}$ +32.7 (*c* 1.25 in $CHCl_3$); ν_{max} (film, cm^{-1}): 1667 (CO); δ_H ($CDCl_3$, 400 MHz): 0.03–0.06 (4 × 3H, m, 4 × CH_3), 0.85–0.88 (2 × 9H, m, 2 × C(CH_3)$_3$), 1.85–2.03 (2H, m, H4), 2.27–2.35 (1H, m, H3), 2.42–2.49 (1H, dt, H3′, $J_{3',4}$ 5.2, $J_{3',4'}$ 5.2, $J_{3',3}$ 17.6), 3.77–3.79 (1H, d, H8, $J_{8,8'}$ 10.5), 4.07–4.11 (1H, dd, H8′, $J_{8',7}$ 4.6, $J_{8',8}$ 10.5), 4.21–4.26 (1H, m, H5), 4.34–4.37 (1H, t, H6, $J_{6,7}$/$J_{6,5}$ 5.6), 4.52–4.54 (1H, m, H7); δ_C ($CDCl_3$, 100 MHz): −4.7, −4.6, −4.3, −4.1 (4× CH_3), 18.0, 18.1 (2 × *C*(CH$_3$)$_3$), 25.9 (2 × C(*C*H$_3$)$_3$), 29.4 (C3), 31.2 (C4), 59.8 (C8), 63.5 (C5), 68.2 (C7), 74.1 (C6), 171.9 (C2); *m*/*z* (ESI+ve): 386 ([M+H]$^+$, 100%), 408 ([M+Na]$^+$, 80%); HRMS *m*/*z* (ESI+ve): found 408.2352 ([M+Na]$^+$); $C_{19}H_{39}NNaO_3Si_2$ requires 408.2361.

4.1.5. (5*S*,6*S*,7*S*)-5,7-Dihydroxy-1-azabicyclo[4.2.0]octane (12)

tert-Butyldimethylsilyl trifluoromethanesulfonate (44 μL, 0.19 mmol) and 2,6-lutidine (30 μL, 0.26 mmol) were added to a solution of **11** (10 mg, 0.06 mmol) in dimethylformamide (1 mL) and the resulting solution was stirred at room temperature. After 16 h, TLC analysis (1:3 cyclohexane/ethyl acetate) showed the complete consumption of starting material and the formation of a major product (R_f 0.51). The mixture was diluted with ethyl acetate (5 mL), washed with 1:1 water/brine (3 × 5 mL), and the organic layer dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (1:1 cyclohexane/ethyl acetate) afforded **13** (18 mg, 73%) as a colourless oil. A solution of borane in tetrahydrofuran (0.44 mL, 1 M) was added to a solution of the protected lactam (17 mg, 0.044 mmol) in anhydrous tetrahydrofuran (1 mL) and the resulting mixture stirred at reflux for 3 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature, and treated with methanol (2 mL). Removal of solvents gave a residue which was purified by chromatography (7:1 cyclohexane/ethyl acetate) to afford the protected amine as a colourless oil (13 mg, 79%). The protected amine (11 mg, 0.03 mmol) was dissolved in a mixture of trifluoroacetic acid (0.9 mL) and water (0.1 mL) and the resulting solution was stirred at room temperature. After 3 days, the solvents were removed in vacuo. The remaining residue was loaded onto a Dowex H$^+$ ion exchange resin. The column was flushed with water and ethanol and then eluted with 2 M aqueous ammonia. The ammoniacal fraction was concentrated in vacuo to afford **12** as white solid (4 mg, 94%); $[\alpha]_D^{25}$ +52.5 (*c* 0.19 in methanol); ν_{max} (film, cm^{-1}): 3315 (s, br s, OH); mp >300 °C; δ_H (CD_3OD, 500 MHz): 1.17–1.25 (1H, dq, H4, $J_{4,5}$ 3.0, $J_{4,3}$/$J_{4,3'}$/$J_{4,4'}$ 12.5), 1.53–1.57 (1H, m, H3), 1.69–1.78 (1H, m, H3′), 1.96–2.01 (1H, m, H4′), 2.51–2.54 (1H, m, H2), 3.26–3.29 (1H, m, H6), 3.33–3.35 (1H, t, H8, $J_{8,7}$/$J_{8,8'}$ 6.8), 3.37–3.40 (1H, td, H8′, $J_{8',6}$ 2.0, $J_{8',7}$/$J_{8',8}$ 6.8), 4.21–4.26 (1H, m, H5), 4.51–4.55 (1H, q, H7, $J_{7,8}$/$J_{7,8'}$/$J_{7,6}$ 6.8); δ_C (CD_3OD, 125 MHz): 20.6 (C3), 31.2 (C4), 46.3 (C2), 58.9 (C8), 63.1 (C5), 63.3 (C7), 71.9 (C6); *m*/*z* (ESI+ve): 144 ([M+H]$^+$, 100%); HRMS *m*/*z* (ESI+ve): found 144.1016 ([M+H]$^+$); $C_7H_{14}NO_2$ requires 144.1019.

4.1.6. Methyl-(2*S*,3*S*,4*R*,5*R*,6*S*)-N-Benzyl-4,6-bis(*tert*-butyldimethylsilyloxy)-2,3-dihydroxy-5,7-iminoheptanoate (15)

Potassium ferricyanide (217 mg, 0.66 mmol), potassium carbonate (91 mg, 0.66 mmol), methane sulphonamide (21 mg, 0.22 mmol), potassium osmate dihydrate (2.4 mg, 6.6 μmol) and $(DHQ)_2PHAL$ (26 mg, 0.03 mmol) were dissolved in a mixture of *tert*-butanol (1.7 mL) and water (1.7 mL). This mixture was added to a solution of **14** (111 mg, 0.22 mmol) in *tert*-butanol (3.5 mL) and the resulting solution was stirred at room temperature. After 24 h, TLC analysis (2:1 cyclohexane/ethyl acetate) showed the

formation of a major product (R_f 0.63). Solid Na_2SO_3 was added and the mixture was stirred for a further 15 min. The reaction mixture was concentrated to dryness and the residue was partitioned between ethyl acetate (10 mL) and water (10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (8:1 cyclohexane/ethyl acetate) afforded **15** (91 mg, 77%) as a colourless oil; $[\alpha]_D^{25}$ +28.0 (*c* 0.35 in $CHCl_3$); ν_{max} (film, cm^{-1}): 3563 (OH), 1748 (CO), 1496, 1472 (arom); δ_H ($CDCl_3$, 400 MHz): 0.01–0.11 (4 × 3H, s, 4 × C*H*$_3$), 0.91–0.92 (2 × 9H, s, 2 × C(C*H*$_3$)$_3$), 3.02–3.06 (1H, m, H7, $J_{7,6}$ 6.0, $J_{7,7'}$ 9.2), 3.10–3.12 (1H, d, H7′, $J_{7',7}$ 9.2), 3.45–3.48 (1H, d, C*H*$_2$Ph, J_{gem} 12.8 Hz), 3.57–3.60 (1H, m, H5), 3.81 (3H, s, OC*H*$_3$), 3.94–3.97 (1H, d, H2, $J_{2,3}$ 9.2), 4.06–4.10 (1H, d, C*H*$_2$Ph, J_{gem} 12.8), 4.32–4.34 (1H, dd, H3, $J_{3,4}$ 3.6, $J_{3,2}$ 9.2), 4.35 (1H, m, H4), 4.48–4.51 (1H, t, H6, $J_{6,5}$ 6.0, $J_{6,7}$ 6.0), 7.25-7.34 (5H, m, 5 × Ar*H*); δ_C ($CDCl_3$, 100 MHz): −4.9, −4.8, −4.3, −4.2 (4 × *C*H$_3$), 18.1 (2 × *C*(CH$_3$)$_3$), 25.8, 25.9 (2 × C(*C*H$_3$)$_3$), 52.4 (O*C*H$_3$), 60.4 (C7), 63.6 (*C*H$_2$Ph), 64.9 (C6), 66.2 (C3), 70.7 (C4), 74.5 (C2), 76.7 (C5), 127.6 (*p*-ArCH), 128.6, 128.9 (2 × *o*-Ar*C*H and 2 × *m*-ArCH), 136.9 ppm (*ipso*-ArC), 174.7 (C1); *m*/*z* (ESI+ve): 540 ($[M+H]^+$, 100%), 562 ($[M+Na]^+$, 90%); HRMS *m*/*z* (ESI+ve): found 540.3177 ($[M+H]^+$); $C_{27}H_{50}NO_6Si_2$ requires 540.3171.

4.1.7. (3*S*,4*S*,5*R*,6*R*,7*S*)-5,7-bis(*tert*-Butyldimethylsilyloxy)-3,4-dihydroxy-1-azabicyclo[4.2.0]octane-2-one (17)

Compound **15** (143 mg, 0.26 mmol), 10% Pd on carbon (85 mg) and ammonium formate (251 mg, 3.97 mmol) were suspended in anhydrous methanol (10 mL) and the mixture was refluxed under argon. After 1 hour, TLC analysis (1:2 ethyl acetate/cyclohexane) showed no-remaining starting material and formation of the product (R_f 0.39). The mixture was filtered through Celite and washed with methanol. The solvent was concentrated in vacuo and the residue purified by flash column chromatography on silica gel (1:8 ethyl acetate/cyclohexane) to afford **17** as a white solid (63 mg, 57%); $[\alpha]_D^{25}$ −33.9 (*c* 0.96 in methanol); ν_{max} (film, cm^{-1}): 3200–3300 (OH), 1616 (CO); mp 184–186 °C; δ_H (CD_3OD, 500 MHz): 0.11–0.16 (4 × 3H, s, 4 × C*H*$_3$), 0.92–0.93 (2 × 9H, s, 2 × C(C*H*$_3$)$_3$), 3.76–3.78 (1H, td, H8, $J_{8,6}$ 1.5, $J_{8,7}$ 1.5, $J_{8,8'}$ 10.5), 3.87–3.88 (1H, d, H3, $J_{3,4}$ 3.0), 4.01–4.02 (1H, t, H4, $J_{4,3}$ 3.0 Hz, $J_{4,5}$ 3.0 Hz), 4.22–4.25 (1H, dd, H8′, $J_{8',7}$ 5.0 Hz, $J_{8',8}$ 10.5 Hz), 4.27–4.29 (1H, dd, H5, $J_{5,4}$ 3.0, $J_{5,6}$ 7.5 Hz), 4.63–4.66 (1H, m, H6), 4.67–4.70 (1H, dt, H7, $J_{7,8}$ 1.5, $J_{7,8'}$ 5.0, $J_{7,6}$ 5.0 Hz); δ_C (CD_3OD, 125 MHz): −4.9, −4.8, −4.4 (4 × *C*H$_3$), 18.9, 19.0 (2 × *C*(CH$_3$)$_3$), 26.2, 26.3 (2 × C(*C*H$_3$)$_3$), 61.1 (C8), 64.6 (C5), 68.9 (C7), 70.1 (C6), 73.2 (C3), 78.2 (C4), 173.7 (C2); *m*/*z* (ESI+ve): 418 ($[M+H]^+$, 19%), 440 ($[M+Na]^+$, 37%), 857 ($[2M+Na]^+$, 100%); HRMS *m*/*z* (ESI+ve): found 440.2257 ($[M+Na]^+$); $C_{19}H_{39}NNaO_5Si_2$ requires 440.2259.

4.1.8. (3*S*,4*R*,5*R*,6*R*,7*S*)-3,4,5,7-Tetrakis(tert-butyldimethylsilyloxy)-1-azabicyclo[4.2.0]octane-2-one (18)

tert-Butyldimethylsilyl trifluoromethanesulfonate (0.07 mL, 0.3 mmol) and 2,6-lutidine (0.05 mL, 0.4 mmol) were added to a solution of **17** (42 mg, 0.1 mmol) in dimethylformamide (4 mL) and the resulting solution was stirred at room temperature. After 16 h, TLC analysis (2:1 cyclohexane/ethyl acetate) showed the complete consumption of starting material and the formation of a major product (R_f 0.79). The mixture was diluted with ethyl acetate (10 mL), washed with 1:1 water/brine (3 × 10 mL) and the organic layer dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (95:5 cyclohexane/ethyl acetate) afforded **18** (57 mg, 88%) as a colourless oil; $[\alpha]_D^{25}$ −8.1 (*c* 0.6 in methanol); ν_{max} (film, cm^{-1}): 1677 (CO); δ_H (CD_3OD, 500 MHz): 0.10–0.19 (8 x 3H, s, 8 × C*H*$_3$), 0.91–0.95 (4 × 9H, s, 4 × C(C*H*$_3$)$_3$), 3.72–3.74 (1H, d, H8′, $J_{8,8'}$ 10.5), 3.86–3.87 (1H, d, H3, $J_{3,4}$ 2.0), 3.96–3.97 (1H, dd, H4, $J_{4,3}$ 2.0 Hz, $J_{4,5}$ 3.0 Hz), 4.17–4.20 (1H, dd, H8́, $J_{8',7}$ 3.5 Hz, $J_{8',8}$ 10.5 Hz), 4.58–4.60 (1H, d, H5, $J_{5,6}$ 8.0 Hz), 4.64–4.68 (2H, m, H6 and H7); δ_C (CD_3OD, 125 MHz): −5.1, −4.6, −4.2, −4.1, −3.8, −3.3 (8 × *C*H$_3$), 18.9, 19.0, 19.1 (4 × *C*(CH$_3$)$_3$), 26.2, 26.3, 26.4, 26.5, 26.7 (4 × C(*C*H$_3$)$_3$), 60.9 (C8), 64.6 (C5), 70.5, 70.9 (C6 and C7), 74.5 (C3), 78.9 (C4), 170.8 (C2); *m*/*z* (ESI+ve): 646 ($[M+H]^+$, 76%), 668 ($[M+Na]^+$, 100%); HRMS *m*/*z* (ESI+ve): found 668.3983 ($[M + Na]^+$); $C_{31}H_{67}NNaO_5Si_4$ requires 668.3989.

4.1.9. (3*R*,4*S*,5*R*,6*R*,7*S*)-3,4,5,7-Tetrahydroxyconidine (2)

A solution of borane in tetrahydrofuran (1.42 mL, 1 M) was added to a solution of **18** (46 mg, 0.071 mmol) in anhydrous tetrahydrofuran (4 mL) and the resulting mixture stirred at reflux for 1 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature, and treated with methanol (2 mL). Removal of solvents gave a residue which was purified by flash column chromatography (50:1 cyclohexane/ethyl acetate) to afford **19** as a colourless oil (39.4 mg, 84%). *Selected data for* **19**: ν_{max} (film, cm^{-1}): 2382 (BH); δ_H ($CDCl_3$, 400 MHz): 0.05–0.16 (8 × 3H, s, 8 × C*H*$_3$), 0.87–0.96 (4 × 9H, s, 4 × C(C*H*$_3$)$_3$), 3.30–3.35 (2H, m, H8 and OH), 3.98–4.00 (3H, m, H3, H6 and H4), 4.05–4.09 (1H, t, H8′, $J_{8,8}/J_{8,7}$ 8.0 Hz), 4.59-4.60 (1H, dd, H2, $J_{2,3}$ 2.0 Hz, $J_{2,OH}$ 4.4 Hz), 4.82–4.84 (1H, m, H5), 5.08–5.13 (1H, q, H7, $J_{7,8'}/J_{7,6}/J_{7,8}$ 7.2 Hz); δ_C ($CDCl_3$, 100 MHz): −5.4, −5.0, −4.7, −4.6, −4.2, −4.1, −3.9, −2.6 (8 × *C*H$_3$), 17.9, 18.0, 18.1, 18.5 (4 × *C*(CH$_3$)$_3$), 25.7, 25.8, 25.9 (4 × C(*C*H$_3$)$_3$), 61.9 (C5), 62.9 (C7), 63.3 (C8), 72.3, 73.5 (C3 and C6), 75.4 (C4), 80.9 (C2); *m*/*z* (ESI+ve): 662 ($[M+H]^+$, 100%), 684 ($[M+Na]^+$, 80%), 1345 ($[2\ M+Na]^+$, 54%).

10% Pd on carbon (16 mg) was added to a degassed solution of **19** in trifluoroacetic acid (1.8 mL) and water (0.2 mL) and the resulting solution was stirred at room temperature under hydrogen. After 4 days, the reaction mixture was filtered through glass microfibre (GF/C), the solvents were removed in vacuo, and the remaining residue was loaded onto a Dowex H^+ ion exchange resin. The column was flushed with water, ethanol, more water, and then eluted with 2 M aqueous ammonia. The ammoniacal fraction was concentrated in vacuo to afford **2** as a brown oil (10.0 mg, 80% from **19**). $[\alpha]_D^{25}$ −26.4 (*c* 0.15 in water); ν_{max} (film, cm^{-1}): 3283 (OH); δ_H (D_2O, 500 MHz): 2.58–2.61 (1H, d, H2, $J_{2,2'}$ 15.0 Hz), 2.93–2.96 (1H, d, H2′, $J_{2',2}$ 15.0), 3.70–3.72 (1H, m, H6), 3.76 (1H, m, H8), 3.83–3.86 (1H, t, H8′, $J_{8',8}/J_{8',7}$ 7.0 Hz), 4.08 (2H, m, H3 and H4), 4.66–4.70 (2H, m, H7 and H5); δ_C (D_2O, 125 MHz): 45.0 (C2), 60.7 (C5), 61.8 (C8), 62.4 (C7), 65.9 (C6), 69.6, 70.7 (C3 and C4); *m*/*z* (ESI+ve): 176 ($[M + H]^+$, 37%); HRMS *m*/*z* (ESI+ve): found 176.0915 ($[M + H]^+$); $C_7H_{14}NO_4$ requires 176.0917.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2013.03.004.

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