Synthesis of polyfunctional quinolizidine alkaloids: development towards selective glycosidase inhibitors†

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A highly divergent route to a variety of quinolizidine alkaloids is described. The enantiomeric precursors **22a** and **22b** utilized for the synthesis of these alkaloids were constructed stereospecifically from the PET cyclization of the corresponding acetylene tethered α-trimethylsilyl amine moieties **21a** and **21b**, respectively, both of which were synthesised from D-ribose. The polyhydroxy quinolizidine alkaloid **7** was found to be a selective inhibitor of α-galactosidase with *Ki* 83.9 μM. The amine analogs **18**, **12** and **10** are found to be selective and potent inhibitors of α-glucosidase with *Ki* 28, 120 and 140 μM, respectively.

Introduction

Polyhydroxy azabicyclic alkaloids like castanospermine[1] (**1**) and swainsonine[2] (**2**) have emerged as an important family of glycosidase inhibitors having chemotherapeutic potential[3] for a variety of diseases such as HIV,[4] cancer[5] and several viral infections such as influenza (Fig. 1).[6] Despite their therapeutic potential, these molecules have not had a full clinical evaluation, largely due to their low natural abundance and the difficulty in preparing a comprehensive array of variant structures. In addition, many of these molecules exhibit superfluous toxic effects *e.g.* castanospermine, although known to display potent inhibitory activity against glucosidases and antiviral properties against a number of viruses[6], is also found to inhibit intestinal sucrases causing osmic diarrhea[7] resulting in its withdrawal from use as a clinical therapeutic. Thus, there is a need to synthesize a palette of polyhydroxylated analogs of these molecules to allow a better understanding of the structural requirements for a glycosidase inhibitor and to develop more potent, selective and less toxic drugs.

As a result, considerable efforts have been directed towards the development of ring expansion analogs[8] and stereoisomers[9] of **1** and **2**. By contrast, examples involving ring expansion analogs of 1-deoxycastanospermine (**4**), which can also be visualized as a bicyclic analog of the potent glycosidase inhibitor 1-deoxynojirimycine (**3**), are scarce in literature.[10]

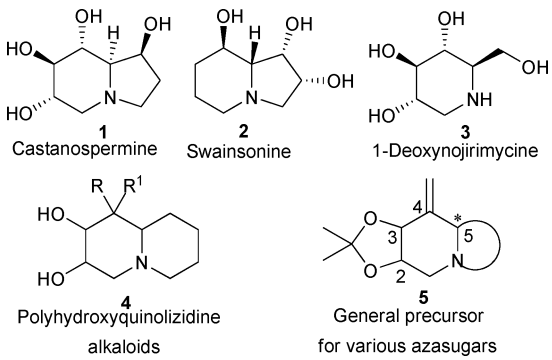

Fig. 1

In connection with this, intense research has also been done on changing the lipophilicity of **3** by attaching a hydrophobic group to its nitrogen atom, resulting in interesting inhibitory activities.[11] All these facts, coupled with our continuing interest in this area,[12] spurred us to synthesize azasugars of general structure **4**. The known synthetic efforts towards molecules of type **4** have involved a chiron approach with long reaction sequences producing a maximum of two analogs. In some cases, a key reaction produces two diastereomers which were further reacted to get different analogs indicating a difficulty in getting a single required product in an appreciable yield.[10b,c] Recently, we have demonstrated the construction of azabicyclic system **5** where the bridge head stereocentre is constructed in a stereospecific manner along with subsequent application to the syntheses of various classes of azasugars.[12e–g] Thus, we envisaged the synthesis of azasugars **6–12** from a common intermediate **22a** and similarly azasugars **13–18** from **22b**. Both **22a** and **22b** were traced back to a common starting material, D-ribose, through **21a** and **21b**, respectively (Scheme 1). We wish to report herein the synthesis of a variety of quinolizidine alkaloids having general structure **4** along with their enzyme inhibition study.

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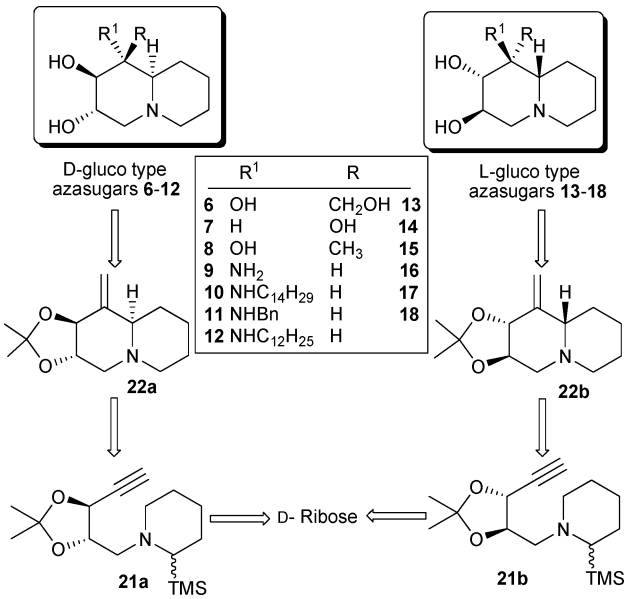
† Electronic supplementary information (ESI) available: Experimental and spectroscopic data of compounds **7**·HCl, **8**·HCl, **9**·2HCl, **10**·2HCl, **11**·2HCl, **12**·2HCl and **29**, X-ray crystal structure analysis of **23** and **25**, optical rotation data for all enantiomeric compounds, copies of ^{1}H and ^{13}C-NMR spectra for compounds **6–12**, **21a**, **22a** and **23–31**, COSY, NOESY, HETCOR spectra for **22a**, **23**, **25** and **28**, general procedure for the enzyme inhibition assay, Lineweaver–Burke plots for selected compounds. CCDC reference numbers 726211 and 726212. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b907007a

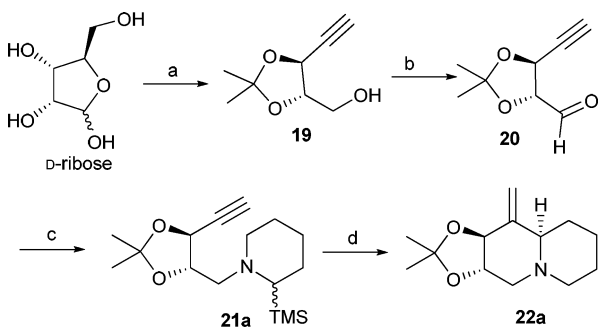


Scheme 1 Retrosynthetic plan.

Results and discussion

Stereospecific synthesis of azabicyclic template 22a

The synthesis of azasugars **6–12** began with the preparation of the key precursor **21a** (72% yield), which was achieved by the reductive amination[13] of aldehyde **20** in the presence of 2-(trimethylsilyl)piperidine.[14] The aldehyde **20** was obtained by the IBX oxidation[15] of **19** (85% yield) synthesized from D-ribose by following literature procedures.[12h,16] The photoinduced electron transfer (PET) mediated cyclization[17] of **21a** (3.38 mmol) was carried out by irradiating its dilute solution containing 1,4-dicyanonaphthalene (DCN) (0.67 mmol) in isopropanol (200 ml) in a pyrex vessel using a 450 W Honovia medium pressure lamp as the light source. Usual workup and purification of the photolysate by column chromatography gave **22a** as a single diastereomer in 65% yield (Scheme 2).



Scheme 2 *Reagents and conditions:* (a) Ref. 12h; (b) IBX, EtOAc, reflux, 8 h, 85%; (c) 2-(trimethylsilyl)piperidine, $NaBH(OAc)_3$, 1,2-dichloroethane (DCE), rt, 3 h, 72%; (d) hv, DCN, 2-PrOH, 1 h, 60%.

The cyclized product **22a** was fully characterized by extensive ^{1}H NMR, ^{13}C NMR, COSY, NOESY and HETCOR spectral analyses.

Transformation of 22a to various polyhydroxy quinolizidine alkaloids 6, 7 and 8

The olefinic moiety of **22a** upon dihydroxylation with OsO_4 in the presence of 50% aqueous NMO using acetone as a solvent produced **23** in 90% yield (crystalline solid, m.p. 135–136 °C) as a single diastereomer. X-Ray diffraction analysis unambiguously confirmed the relative stereochemistry of the newly generated stereocentre (Fig. 2).[18] Acetonide deprotection from **23** using 1 N HCl gave **6**·HCl in quantitative yield.

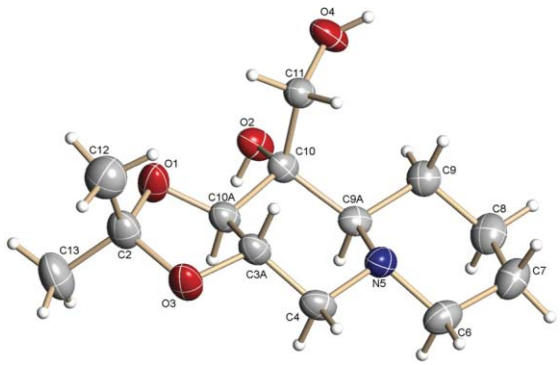


Fig. 2 ORTEP diagram of **23**.[18] Ellipsoids are drawn at 50% probability.

$NaIO_4$ cleavage of **23** afforded the corresponding ketone **24**, which on sodium borohydride reduction provided **25** in 82% yield as an exclusive diastereomer (Scheme 3). The stereochemistry of **25** was ascertained from its ^{1}H NMR coupling constants, in addition to COSY, NOESY and HETCOR spectral analyses. The relative stereochemical outcome was further confirmed by X-ray crystallography (Fig. 3).[18] The acetonide moiety was removed to give **7**·HCl in quantitative yield.

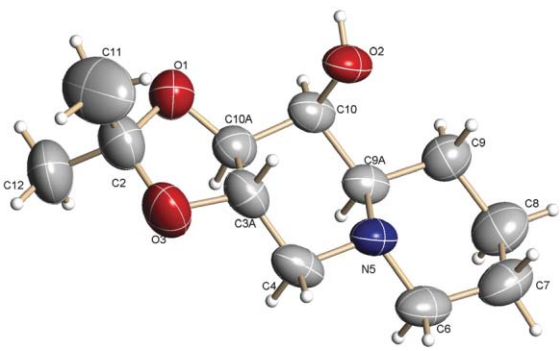
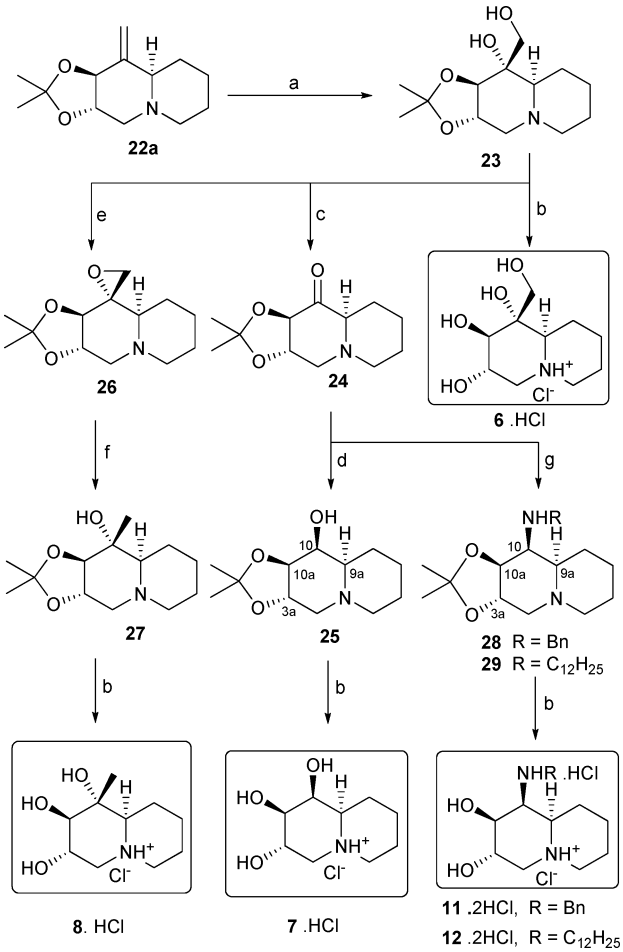


Fig. 3 ORTEP diagram of **25**.[18] Ellipsoids are drawn at 50% probability.

At this stage, we also synthesized 1-deoxy-8-methylhomocastanospermine (**8**) from **23** and studied its potential as a glycosidase inhibitor. In this context, the diol **23** was converted to the corresponding epoxide **26** (via its primary mesylate) in 90% yield using mesylchloride and triethylamine. The regioselective reductive opening of the epoxide ring using $LiAlH_4$ gave **27** as an exclusive product in 90% yield, which upon acetonide removal furnished **8**·HCl quantitatively.



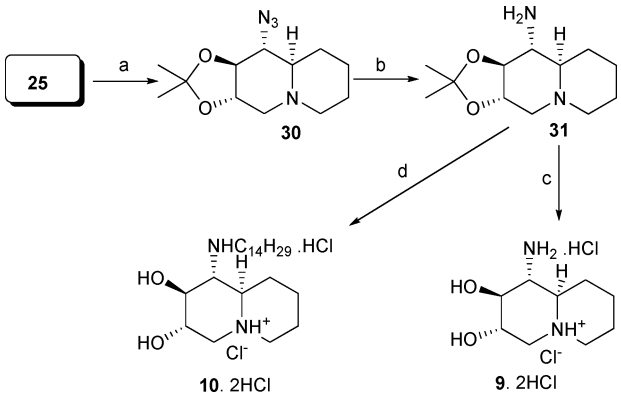
Scheme 3 *Reagents and conditions:* (a) OsO_4, NMO (50% aq. solution), acetone, rt, 12 h, 90%; (b) 1 N HCl, rt, 4 h, 100%; (c) $NaIO_4$, silica gel, DCM, 10 min; (d) $NaBH_4$, MeOH, rt, 6 h, 80% over two steps; (e) $MeSO_2Cl$, Et_3N, DCM, 0 °C to rt, 12 h, 90%; (f) $LiAlH_4$, THF, 12 h, 90%; (g) $NaB(OAc)_3H$, EDC, R NH_2, rt, 3 h, 65–75%.

Synthesis of amine analogs 9, 10, 11 and 12

At this juncture, we also visualized the creation of another class of azasugars with an additional basic site[12h,19] for binding to the enzyme. In this regard, a hydroxyl moiety at C-10 was converted to corresponding amine functionality. The mesylate obtained from alcohol **25** was directly subjected to S_N2 displacement with LiN_3 to produce azide **30** in 72% yield, which on catalytic hydrogenation over 10% Pd/C furnished the corresponding free amine in 85% yield. Removal of the acetonide group gave **9**·2 HCl in quantitative yield (Scheme 4).

Based on our previous research experiences regarding structure activity relationships among glycosidase inhibitors,[12e–h] we intended to increase the lipophilicity of amine functionalities by attaching a long hydrocarbon chain[20] and evaluating its role in enzyme inhibition. Towards this end, *N*-alkylation of **31** was carried out by refluxing with tetradecyl bromide in the presence of K_2CO_3 in CH_3CN–THF (3:1) to furnish the corresponding alkylated product in 65% yield which, upon acetonide removal, produced **10**·2 HCl quantitatively (Scheme 4).

Since it was not possible at this stage to predict which diastereomer would be the most biologically active, we felt that



Scheme 4 *Reagents and conditions:* (a) (i) $MeSO_2Cl$, Et_3N, DCM, 0 °C to rt, 6 h, (ii) LiN_3, DMF, 110 °C, 20 h, 72% over two steps; (b) H_2, 10% Pd/C, MeOH, 2 h, 85%; (d) 1 N HCl, rt, 4 h, 100%; (d) (i) $C_{14}H_{29}Br$, K_2CO_3, CH_3CN–THF (3:1), reflux, 6 h, 65%, (ii) 1 N HCl, rt, 4 h, 100%.

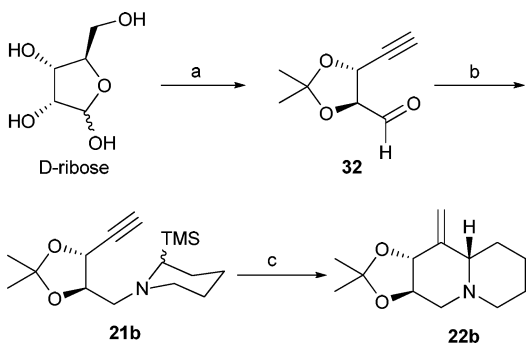
it would not be a disadvantage to make two other new analogs **11** and **12**. In this regard, ketone **24**, upon reductive amination with benzyl amine, furnished **28** as a single diastereomer in 75% yield.

The stereochemistry at C-10 of **28** was ascertained by analyzing coupling constants for 3a-H (δ_H 3.98, dt, J = 10.07, 4.10 Hz), 10a-H (δ_H 3.38, dd, J = 9.45, 3.63 Hz), 10-H (δ_H 3.04, t, J = 2.91 Hz) and 9a-H (δ_H 1.97, td, J = 11.14, 2.34 Hz) suggesting the orientations for 3a-H-axial, 10a-H-axial, 10-H-equatorial and 9a-H-axial, respectively. This stereochemical outcome was further confirmed from COSY, NOESY and HETCOR experiments. Amine **28** upon acetonide deprotection gave **11**·2 HCl in quantitative yield.

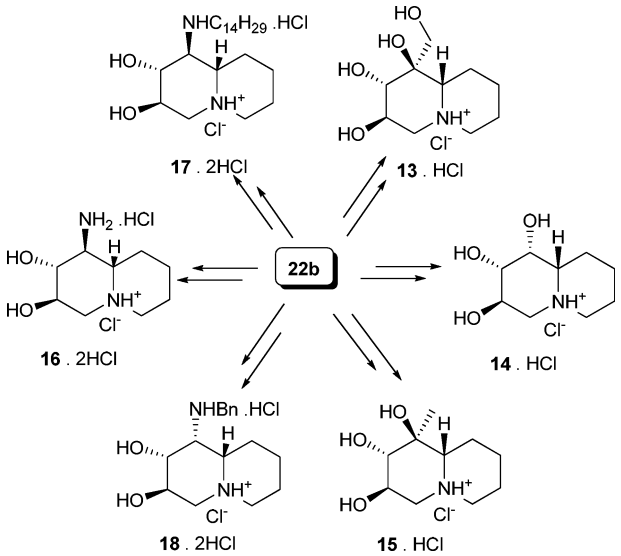
Similarly, **12**·2 HCl was obtained as a single diastereomer by reductive amination of keto **24** with dodecyl amine (65% yield) followed by acetonide removal (Scheme 3).

Synthesis of enantiomers 13–18. The syntheses of **13–18** were envisaged from synthon **22b** which in turn we planned to obtain from **21b** in a similar manner to that discussed in Scheme 2. Synthon **21b** was obtained by the reductive amination of aldehyde[12h] **32** with 2-(trimethylsilyl)piperidine[14] in 65% yield.

Following similar steps as described above, the enantiomeric template **22b** was obtained (Scheme 5), which was transformed to hydrochloride salts of **13–18** (Scheme 6) in a parallel manner as described for **6–12**.



Scheme 5 *Reagents and conditions:* (a) Ref. 12h; (b) 2-(trimethylsilyl)-piperidine, $NaBH(OAc)_3$, 1,2-dichloroethane, rt, 3 h; (c) hν, DCN, 2-PrOH, 1 h, 60%.



Scheme 6 Syntheses of **13–18**.

Enzyme inhibition studies

The enzyme inhibitory activities of all the final molecules **6–18** were tested against various enzymes and the results are summarized in Table 1. Compound **12** and **17** were found to be anomer specific inhibitors of α-mannosidase (*Ki* = 293 μM and 650 μM, respectively). The other compounds **9**, **11**, **14**, **16** and **18** were found to be anomer specific inhibitors of α-glucosidase with *Ki* values (in μM) of 675, 278, 450, 258 and 28, respectively.

Compound **18** in particular was found to be a very selective potent inhibitor of α-glucosidase (*Ki* = 28 μM) as it did not show any inhibition against other enzymes under investigation.

Among the polyhydroxy quinolizidine alkaloids, **7** was found to be a competitive inhibitor for α as well as β-galactosidase with *Ki* values 83.9 μM and 591 μM, respectively, whereas **14** was showing selective inhibitory activity for α-glucosidase, *Ki* = 450 μM. Barring these two cases, none of the polyhydroxy analogs exhibited any significant inhibitions towards the enzymes under study. Introduction of an additional amine functionality was found to be advantageous as all the amine analogs afforded better inhibitory activity against α-glucosidase in general compared with their polyhydroxy analogs. An increase in the inhibitory activity was successfully accomplished by increasing the lipophilicity. For example, **10** (*Ki* = 140 μM) was found to be 5 times more potent against α-glucosidase compared to its free amine counterpart **9** (*Ki* = 675 μM). This increased lipophilicity in compound **10** also exhibited better activity against β-glucosidase, α-mannosidase and β-mannosidase with *Ki* values (in μM) of 524, 805 and 830, respectively, in comparison to no inhibition shown by **9** against these enzymes up to 1 mM concentration. A similar observation was found in the case of alkylated amine **17** with respect to free amine **16**. To our pleasant surprise, the exploratory work to make another diastereomeric amine analog was also fruitful as **12** (*Ki* = 293 μM) was not only anomer specific for α-mannosidase but was also found to be an inhibitor 3 fold stronger than **10** (*Ki* = 805 μM).

Conclusions

In summary, we present a general synthetic route for a variety of enantiopure polyhydoxy quinolizidine alkaloids and some of their amine analogs. Thirteen new azasugars are synthesized and tested against six different enzymes. The simplicity of the steps involved in their syntheses make the route attractive for their preparation. As many of these compounds are selective inhibitors, efficient drug delivery may make them useful therapeutics. Moreover, the enzyme inhibitory study can provide an insight into structure activity relationships for the development of newer analogs as drugs. All the free and alkylated amine analogs produced promising activity, demanding more research in this area.

Experimental section

General experimental methods

Unless mentioned, all reactions were performed under an argon atmosphere. All commercially available reagents were used without further purification unless otherwise noted. Enzymes were purchased from commercial sources. Tetrahydrofuran was freshly distilled from benzophenone ketyl radical under argon prior to

Table 1 Inhibition of glycosidases (*Ki* in μM)[a]: a comparative study

Inhibitor[b]	Enzyme (source)					
	β-Gal. (*Aspergills oryzaie*)	α-Gal. (Green coffee beans)	β-Man. (Snail)	α-Man. (Jack Beans)	β-Glu. (Almond)	α-Glu. (Yeast)
6	33%[c]	NI	NI	11%[c]	NI	NI
7	*591*	*83.9*	NI	18%[c]	NI	NI
8	NI	NI	NI	22%[c]	NI	NI
9	NI	11%[c]	NI	NI	NI	*675*
10	NI	NI	*830*	*805*	*524*	*140*
11	NI	31%[c]	NI	NI	NI	*278*
12	NI	NI	NI	*293*	46%[c]	*120*
13	NI	NI	NI	NI	NI	42%[c]
14	28%[c]	13%[c]	18%[c]	NI	NI	*450*
15	NI	NI	14%[c]	29%[c]	NI	39%[c]
16	NI	NI	13%[c]	22%[c]	NI	*258*
17	NI	NI	NI	*650*	43%[c]	*235*
18	NI	NI	NI	NI	NI	*28*

[a] *Ki in* μM (in italics). [b] Hydrochloride salts of the compounds **6–18** were used for inhibitory activity tests. [c] Percent inhibition at 1 mM; NI, no inhibition up to 1 mM.

use. Column chromatography was performed with silica gel (100–200 and 230–400 mesh). The combined organic layers were dried over $NaSO_4$. Solvents were evaporated under reduced pressure. All yields given refer to isolated yields. Melting points are reported uncorrected. Optical rotations were measured on a precision automated polarimeter JASCO P-1030. NMR spectra were recorded on 200, 400, and 500 MHz spectrometers. Chemical shifts are reported in ppm. Coupling constants (J values) are reported in Hertz. ^{13}C peak multiplicity assignments were made based on DEPT data. IR spectra were recorded on a FT-IR spectrometer. MS experiments were performed on a low resolution magnetic sector mass spectrometer. GC analysis was performed on a Varian CP 3800 GC using a CP-Sil 5CB column. Microanalysis data were obtained using a Carlo-Erba CHNS-O EA 1108 Elemental Analyser. The optical density measurements were carried out on a Varian CARY-50 BIO UV-vis spectrophotometer. The crystal data for compounds **23** and **25** were collected at $T = 296$ K, on SMART APEX CCD Single Crystal X-ray diffractometer using Mo-Kα radiation (λ = 0.7107 Å) to a maximum θ range of 25.00°.

General procedure for the enzyme inhibition assays

Inhibition assays to determine the inhibitory potencies of the azasugars were carried out spectrophotometrically measuring the residual hydrolytic activities of the glycosidases on the corresponding *p*-nitrophenyl glycosides in the presence of the azasugars. The absorbance of the resulting solution was read at 405 nm.

1-(((4*S*,5*S*)-5-Ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2-(trimethylsilyl)piperidine (21a). To a solution of crude aldehyde **20** (5.76 g, 31.82 mmol) (>85% pure by GC) in DCE (90 ml), was added 2-(trimethylsilyl)piperidine (5.24 g, 33.41 mmol) and $NaB(OAc)_3H$ (8.77 g, 41.36 mmol) under argon atmosphere and the mixture was stirred for 3 h. The reaction mixture was cooled in an ice bath and quenched by adding 2 N NaOH until the aqueous layer was basic. After stirring for 0.5 h, the reaction mixture was extracted in DCM. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (pet ether/ethyl acetate, 6:1) to furnish **21a** (6.77 g, 72%). $[\alpha]_D^{26} = -17.20$ (*c* 1.25, $CHCl_3$). Anal. Calcd. for $C_{16}H_{29}NO_2Si$: C, 65.03; H, 9.89; N, 4.74; Si, 9.50; Found: C, 65.12; H, 9.86; N, 4.76, Si, 9.44%. IR ν_{max} cm^{-1} in $CHCl_3$ 3311 (≡C–H), 2933, 2120 (C≡C), 1441, 1381, 1250, 1055. δ_H (400 MHz, $CDCl_3$) 0.6, 0.7 (4.5 H each, 2 s, $Si(CH_3)_3$), 1.21–1.29 (1H, m, 4ax-H), 1.40, 1.41, 1.46 1.46 (1.5H each, 4 s, $C(CH_3)_2$), 1.50–1.63 (4H, m, 3ax-H, 3eq-H, 4eq-H, 5ax-H), 1.71 (1H, dt, $^2J_{H,H}$= 12.51, $^3J_{5eq,6ax}$ = 3.76, 5eq-H), 1.87 (1H, dt, $^3J_{2ax,3ax}$ = 11.54, $^3J_{2ax,3eq}$ = 3.76, 2ax-H), 2.03–2.14 (1H, m, 6ax-H), 2.40–2.46 (1H, m, NCH_2CH), 2.51 (1H, t, $^4J_{H,H}$ = 2.14, C≡C*H*), 2.92–2.97 (1H, m, 6eq-H), 3.12–3.18 (1H, m, NCH_2CH), 4.22–4.32 (2H, m, H-4 dioxolane, H-5 dioxolane). δ_C (50 MHz, $CDCl_3$) −1.1, −1.0 ($Si(CH_3)_3$), 23.8, 24.2 (C-4), 25.7 (C-5), 26.0, 26.09 ($C(CH_3)_2$), 26.03, 26.6 (C-3), 27.06, 27.11 ($C(CH_3)_2$), 54.7, 55.0 (NCH_2CH), 56.0, 56.1 (C-2), 58.1, 58.2 (C-6), 68.6, 68.8 (C-5, dioxolane), 74.4, 74.5 (C≡*C*H), 80.3, 80.9 (C-4, dioxolane), 81.0, 81.1 (*C*≡CH), 110.5, 110.7 ($C(CH_3)_2$). Mass (ESI): *m*/*z* 296 (M^+ + H).

(3a*S*,9a*R*,10a*S*)-2,2-Dimethyl-10-methyleneoctahydro-3aH-[1,3]dioxolo[4,5-b]quinolizine (22a). A solution containing **21a** (1.0 g, 3.38 mmol) and 1,4-dicyanonaphthalene (0.12 g, 0.67 mmol) in 2-propanol (250 ml) was irradiated in an open vessel using a 450 W Hanovia medium pressure mercury vapor lamp. The lamp was immersed in a Pyrex water-jacketed immersion well to allow only wavelengths greater than 280 nm to pass through. After about 1 h of irradiation, the consumption of the starting material was found to be almost complete (monitored by GC) and at this stage the irradiation was discontinued. The solvent was removed under reduced pressure and the residue was column chromatographed (silica, pet. ether–acetone, 6:1) to afford cyclized product **22a** (0.453 g, 60%) as a yellow liquid. $[\alpha]_D^{29} = +55.80$ (*c* 0.85, CH_2Cl_2). Anal. calcd. for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27; Found: C, 69.98; H, 9.51; N, 6.25%. IR (neat) ν_{max} cm^{-1} 2985(=C–H), 2858, 1806, 1667(C=C), 1370, 1226. δ_H (400 MHz, $CDCl_3$) 1.24–1.33 (1H, m, 8ax-H), 1.44, 1.47 (3H each, 2 s, $C(CH_3)_2$), 1.48–1.65 (3H, m, 7ax-H, 7eq-H, 9ax-H), 1.82–1.92 (2H, m, 8eq-H, 9eq-H), 2.27 (1H, dt, $^3J_{6ax,7ax}$ = 11.79, $^3J_{6ax,7eq}$ = 3.01, 6ax-H), 2.33 (1H, d, $^3J_{9ax,9a\text{-}ax}$ = 11.70, 9a-ax-H), 2.38 (1H, t, $^3J_{4ax,3ax}$ = 10.29, 4ax-H), 2.93 (1H, d, $^2J_{H,H}$ = 11.54, 6eq-H), 3.23 (1H, dd, $J_{4eq,3ax}$ = 3.97, 4eq-H), 3.48 (1H, dt, $^3J_{3a\text{-}ax,10a\text{-}ax}$ = 10.02, 3a-ax-H), 3.74 (1H, dt, $^4J_{H,H}$ = 1.79, 10a-ax-H), 4.89, 5.06 (1H each, 2 s, C=CH_2). δ_C (100 MHz, $CDCl_3$) 24.0 (C-8), 25.7 (C-7), 26.7, 26.9 $C(CH_3)_2$, 27.8 (C-9), 56.8 (C-6), 57.7 (C-4), 61.9 (C-9a), 77.1 (C-3a), 82.2 (C10a), 103.2 (C=*C*H_2), 111.0 ($C(CH_3)_2$), 144.2 (*C*=CH_2). Mass (ESI): *m*/*z* 224 (M^+ + H).

(3a*S*,9a*R*,10*S*,10a*R*)-10-(Hydroxymethyl)-2,2-dimethyloctahydro-3aH-[1,3]dioxolo[4,5-b]quinolizin-10-ol (23). To a solution of **22a** (0.45 g, 2.02 mmol) in acetone (5 ml) was added *N*-methylmorpholine-*N*-oxide (50% aq solution, 1.41 g, 6.06 mmol). The reaction mixture was cooled to 0 °C and to that was added a catalytic amount of osmium tetroxide (1 mL of 1% solution of OsO_4 in *t*-BuOH). The reaction mixture was allowed to come to rt and stirred for 10 h. Solid Na_2SO_3 was added to this reaction mixture. Stirring was continued for 30 min to quench excess *N*-methylmorpholine-*N*-oxide and OsO_4. The mixture was filtered through a short pad of celite and the solvent was evaporated off. The crude reaction mixture upon column chromatography (silica, pet ether–ethyl acetate, 3:2) afforded **23** (0.466 g, 90%) as a colorless solid (mp. 135–136 °C (from ethyl acetate/hexanes)). $[\alpha]_D^{29} = +27.7$(*c* 1.2, DCM). Anal. Calcd. for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44; Found: C, 60.51; H, 9.05; N, 5.45%. IR ν_{max} cm^{-1} in $CHCl_3$ 3432 (OH), 2938, 2306, 2232, 1654, 1265. δ_H (400 MHz, $CDCl_3$, D_2O exchange) 1.13–1.19 (2H, m, 8ax-H, 9ax-H), 1.44 (3H, s, $C(CH_3)_2$), 1.44 (4H, apparent s, $C(CH_3)_2$, 7ax-H), 1.59–1.62 (1H, m, 7eq-H), 1.79–1.80 (1H, m, 8eq-H), 1.93–1.95 (1H, m, 9a-ax-H), 2.01–2.03 (1H, m, 9eq-H), 2.13 (1H, dt, $^3J_{9ax,8ax}$ = 12.55,$^3J_{9ax,8eq}$ = 2.76, 9ax-H), 2.21 (1H, t, $^3J_{4ax,3a\text{-}ax}$ = 10.04, 4ax-H), 2.92 (1H, d, $^2J_{H,H}$ = 11.50, 6eq-H), 3.14 (1H, dd, $^2J_{H,H}$ = 9.88, $^3J_{4eq,3a\text{-}ax}$ = 4.28, 4eq-H), 3.43 (1H, d, $^3J_{10a\text{-}ax,3a\text{-}ax}$ = 9.54, 10a-ax-H), 3.73 (1H, d, $^2J_{H,H}$ = 11.54,CH_2OH), 3.80 (1H, dt, 3a-ax-H), 3.97 (1H, d, CH_2OH). δ_C (50 MHz, $CDCl_3$) 24.2 (C-8), 24.9 (C-9), 25.7 (C-7), 26.6 $C(CH_3)_2$, 56.7 (C-4), 57.9 (C-6), 62.9 (CH_2OH), 68.4 (C-9a), 71.9 (C-3a), 72.4 (C-10), 86.9 (C-10a), 110.6 $C(CH_3)_2$. Mass (ESI): *m*/*z* 257 (M^+ + H), 280 (M^+ + Na).

(1*S*,2*R*,3*S*,9a*R*)-1,2,3-Trihydroxy-1-(hydroxymethyl) decahydroquinolizinium chloride (6·HCl). Compound **23a** (0.025 g, 0.097 mmol) was subjected to acetonide deprotection using aqueous 1 N HCl (1 ml) to provide the hydrochloride salt of **6** quantitatively. $[\alpha]_D^{23} = +24.1$ (*c* 0.95, MeOH). Anal. Calcd. for

$C_{10}H_{20}ClNO_4$: C, 47.34; H, 7.95; N, 5.52; Found: C, 47.44; H, 7.99; N, 5.63%. δ_H (400 MHz, D_2O) 1.36–1.47 (1H, m, 8ax-H), 1.53–1.70 (2H, m, 7ax-H, 9ax-H), 1.82–1.90 (2H, m, 7eq-H, 8eq-H), 2.18 (1H, dt, $^2J_{H,H}$ = 14.38, $^3J_{9eq,8ax}$ = 2.81, 9eq-H), 2.82–2.90 (2H, m, 4ax-H, 6ax-H), 3.01 (1H, dd, $^3J_{9a\text{-}ax,9ax}$ = 12.28, $^3J_{9a\text{-}ax,9eq}$ = 2.03, 9a-ax-H), 3.36–3.41 (2H, m, 4eq-H, 6eq-H), 3.47, 3.52 (1H each, d, $^2J_{H,H}$ = 10.55, CH_2OH), 3.98 (1H, d, $^3J_{2ax,3ax}$ = 10.80, 2ax-H), 4.17 (1H, ddd, $^3J_{4ax,3ax}$ = 10.25, $^3J_{4eq,3ax}$ = 5.30, 3ax-H). δ_C (100 MHz, D_2O) 21.3, 22.9, 23.0 (C-7, C-8, C-9), 56.3, 56.8 (C-4, C-6), 58.7 (CH_2-OH), 64.2 (C-3), 67.9 (C-9a), 72.6 (C-1), 78.0 (C-2). Mass (ESI): *m*/*z* 218 (M^+ + H).

(3a*S*,9a*R*,10*S*,10a*S*)-2,2-Dimethyloctahydro-3aH-[1,3]dioxolo-[4,5-b]quinolizin-10-ol (25). A solution of **23** (0.45 g, 1.75 mmol) in DCM (5 ml) was added to a suspension of silica gel supported sodium periodate [prepared by dissolving $NaIO_4$ (0.53 g, 2.62 mmol) in 1 mL water and 2.77 g of flash silica gel] in DCM (5 ml). The suspension was stirred for 10 min. and filtered. The solvent was evaporated off and the brownish pasty mass was extracted with ethyl acetate (3 × 10 ml). The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. To the solution of that crude ketone (**24**) (0.35 g, 1.55 mmol) in methanol (5 ml) was added $NaBH_4$ (0.118 g, 3.10 mmol). The resulting mixture was stirred at rt for 6 h and then quenched by adding an excess of the saturated solution of NaCl. This brownish suspension was stirred overnight and extracted with ethyl acetate (4 × 5 ml). The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica, pet ether–ethyl acetate, 1:9) to afford **25** (0.282 g, 80%) as a colorless solid (mp 133–134 °C (from ethyl acetate/hexanes)). $[\alpha]_D^{29}$ = +16.77 (*c* 1.2, DCM). Anal. Calcd. for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16; Found: C, 63.44; H, 9.29; N, 6.19%. IR ν_{max} cm^{-1} in $CHCl_3$ 3436 (OH), 2940, 1653, 1265. δ_H (400 MHz, $CDCl_3$, D_2O exchange) 1.23–1.29 (1H, m, 8ax-H), 1.43, 1.43 (3H each, 2 s, C(CH_3)$_2$, 1.56–1.58 (3H, m, 7ax-H, 7eq-H, 9ax-H), 1.77–1.80 (2H, m, 8eq-H, 9eq-H), 1.98 (1H, d, $^3J_{9ax,9a\text{-}ax}$ = 11.04, 9a-ax-H), 2.14–2.23 (2H, m, 6ax-H, 4ax-H), 2.92 (1H, d, $^2J_{H,H}$ = 11.04, 6eq-H), 3.17 (1H, dd, $^2J_{H,H}$ = 9.79, $^3J_{4eq,3a\text{-}ax}$ = 4.02, 4eq-H), 3.29 (1H, dd, $^3J_{3a\text{-}ax,10a\text{-}ax}$ = 9.28, $^3J_{10eq,10a\text{-}ax}$ = 2.51, 10a-ax-H), 3.96 (1H, t, 10-H), 4.00 (1H, dt, 3a-ax-H). δ_C (100 MHz, $CDCl_3$) 24.1 (C-8), 25.4 (C-7), 26.5, 26.8 C(CH_3)$_2$, 28.4 (C-9), 56.4 (C-6), 57.8 (C-4), 63.8 (C-9a), 69.2 (C-10), 70.2 (C-3a), 82.1 (C-10a), 110.2 (*C*(CH_3)$_2$). Mass (ESI): *m*/*z* 228 (M^+ + H), 250 (M^+ + Na).

(2′*S*,3a*S*,9a*R*,10a*R*)-2,2-Dimethyloctahydrospiro[[1,3]dioxolo-[4,5-b]quinolizine-10,2′-oxirane] (26). To a solution of **23** (0.2 g, 0.777 mmol) in dry DCM (3 ml) at 0 °C under argon atmosphere was added triethyl amine (0.22 ml, 1.554 mmol) and methanesulfonyl chloride (0.066 mL, 0.855 mmol). The reaction mixture was stirred at room temperature for 12 h; water was added and extracted with DCM (2 × 5 ml). The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (silica, pet. ether/ethyl acetate, 4:1) to get **26** (0.168 g, 90%) as a white solid. $[\alpha]_D^{26}$ = +49.16 (*c* 1.05, $CHCl_3$). Anal. Calcd. for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85 Found: C, 65.34; H, 8.87; N, 5.83%. IR ν_{max} cm^{-1} in $CHCl_3$ 3054 (C–O epoxide), 1421, 1265. δ_H (500 MHz, $CDCl_3$) 1.01 (1H, ddd, $^2J_{H,H}$ = 15.96, $^3J_{8ax,9ax}$ 3 = 12.66, $^3J_{7eq,8ax}$ = 3.31, 8ax-H), 1.18 (1H, tq, $^3J_{9ax,9a\text{-}ax}$ = 12.9, $^3J_{8eq,9ax}$ = 3.58, 9ax), 1.39, 1.43 (3H each, 2 s, C(CH_3)$_2$), 1.50 (1H, tq, $^3J_{7ax,8ax}$ = 12.93, $^3J_{6eq,7ax}$ = 3.85, 7ax), 1.63–1.69 (2H, m, 7eq, 8eq), 1.77 (1H, d, $^2J_{H,H}$ = 13.2, 9eq), 2.26 (1H, dt, $^3J_{6ax,7ax}$ = 11.83, $^3J_{6ax,7eq}$ = 2.48, 6ax-H), 2.31 (1H, dd, $^3J_{9ax,9a\text{-}ax}$ = 11.22, $^3J_{9eq,9a\text{-}ax}$ = 1.54, 9a-ax-H), 2.37 (1H, t, $^3J_{4ax,3a\text{-}ax}$ = 10.18, 4ax-H), 2.92 (1H, d, $^2J_{H,H}$ = 4.67, 3′-H), 2.99 (1H, br d, $^2J_{H,H}$ = 11.56, 6eq-H), 3.03 (1H, d, 3′-H), 3.23 (1H, dd, $^2J_{H,H}$ = 9.90, $^3J_{4eq,\ 3a\text{-}ax}$ = 3.85, 4eq-H), 3.63 (1H, d, $^3J_{10a\text{-}ax,3a\text{-}ax}$ = 9.08, 10a-H), 3.72 (1H, dt, 3a-ax-H). δ_C (50 MHz, $CDCl_3$) 23.6 (C-8), 24.6 (C-7), 25.8 (C-9), 26.5, 26.7 (C(*C*H_3)$_2$), 45.2 (C-3′), 56.7 (C-6), 57.2 (C-4), 60.3 (C-2′), 62.3 (C-9a), 75.2 (C-3a), 78.4 (C-10a), 111.5 (*C*(CH_3)$_2$). Mass (ESI): *m*/*z* 240 (M^+ + H), 262 (M^+ + Na).

(3a*S*,9a*R*,10*R*,10a*R*)-2,2,10-Trimethyloctahydro-3aH-[1,3]dioxolo[4,5-b]quinolizin-10-ol (27). To a solution of **26** (0.1 g, 0.42 mmol) in dry THF (2 ml) at 0 °C was added $LiAlH_4$ (0.031 g, 0.84 mmol), which was allowed to come to rt and stirred overnight. After recooling to 0 °C the reaction mixture was quenched by drop wise addition of 2 N NaOH solution. It was dried with Na_2SO_4 and was filtered through a short celite pad. The reaction mixture was concentrated and purified by column chromatography (pet. ether/ethyl acetate, 3:2) to give corresponding alcohol **27** (0.091 g, 90%) as a white solid. $[\alpha]_D^{25}$ = +38.1 (*c* 1.0, $CHCl_3$). Anal. Calcd. for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.75; H, 9.63; N, 5.75%. IR ν_{max} cm^{-1} in $CHCl_3$ 3442 (OH), 2366, 1631, 1259. δ_H (500 MHz, $CDCl_3$, D_2O exchange) 1.15–1.21 (1H, m, 8ax-H), 1.23 (3H, s, 10-Me), 1.24–1.27 (1H, m, 9ax-H), 1.42, 1.44 (3H each, 2 s, C(CH_3)$_2$), 1.46–1.52 (1H, m, 7ax-H), 1.61 (1H, br d, $^2J_{H,H}$ = 13.07, 7eq-H), 1.76–1.81 (2H, m, 8eq-H, 9eq-H), 1.89–1.91 (1H, m, 9a-ax), 2.18 (1H, dt, $^3J_{6ax,7ax}$ = 12.38, $^3J_{6ax,7eq}$ = 2.89, 6ax-H), 2.21 (1H, t, $^3J_{4ax,3a\text{-}ax}$ = 10.18, 4ax-H), 2.93 (1H, br d, $^2J_{H,H}$ = 11.50, 6eq-H), 3.12 (1H, dd, $^2J_{H,H}$ = 9.81, $^3J_{3a\text{-}ax,4eq}$ = 3.96, 4eq-H), 3.28 (1H, d, $^3J_{3a\text{-}ax,10a\text{-}ax}$ = 9.43, 10a-ax-H), 3.53 (1H, ddd, 3a-ax-H). δ_C (125 MHz, $CDCl_3$) 16.2 (10-Me), 24.0, 24.3, 25.8 (C-7, C-8, C-9), 26.5, 26.8 (C(*C*H_3)$_2$), 56.8 (C-6), 58.1 (C-4), 69.4 (C-9a), 72.3 (C-10), 72.5 (C-3a), 86.9 (C-10a), 110.4 (*C*(CH_3)$_2$). Mass (ESI): *m*/*z* 242 (M^+ + H).

(3a*S*,9a*R*,10*S*,10a*S*)-*N*-Benzyl-2,2-dimethyloctahydro-3aH-[1,3]dioxolo[4,5-b]quinolizin-10-amine (28). The reductive amination procedure used for synthesizing **21a** was applied to ketone **24** (0.078 g, 0.345 mmol) in the presence of benzyl amine (0.045 g, 0.415 mmol) to produce **28** (0.082 g, 75%) as a faint yellow solid. $[\alpha]_D^{26}$ = +18.41 (*c* 1.2, $CHCl_3$). Anal. Calcd. for $C_{19}H_{28}N_2O_2$: C, 72.12; H, 8.92; N, 8.85; Found: C, 71.99; H, 8.97; N, 8.81%. IR ν_{max} cm^{-1} in $CHCl_3$ 3351 (NH), 2984 (C–H arom), 1604 (C=C arom), 1453, 1370, 1235. δ_H (500 MHz, $CDCl_3$) 1.20–1.27 (1H, m, 8ax-H), 1.44, 1.45 (3H, 2 s, C(CH_3)$_2$), 1.48–1.59 (3H, m, 7ax-H, 7eq-H, 9ax-H), 1.76–1.84 (2H, m, 8eq-H, 9eq-H), 1.97 (1H, td, $^3J_{9ax,9a\text{-}ax}$ = 11.14, $^3J_{9eq,9a\text{-}ax}$ = 2.38, 9a-ax-H), 2.11 (1H, dt, $^2J_{H,H}$ = 11.72, $^3J_{6ax,7eq}$ = 3.53, 6ax-H), 2.14 (1H, t, $^3J_{3a\text{-}ax,4ax}$ = 10.24 Hz, 4ax-H), 2.91 (1H, d, 6eq-H), 3.04 (1H, t, $^3J_{10eq,10a\text{-}ax}$ = $^3J_{10eq,9a\text{-}ax}$ = 2.91 Hz, 10eq-H), 3.17 (1H, dd, $^3J_{3a\text{-}ax,4eq}$ = 4.10, 4eq-H), 3.38 (1H, dd, $^3J_{10a\text{-}ax,3a\text{-}ax}$ = 9.45, $^3J_{10a\text{-}ax,10eq}$ = 3.63, 10a-ax-H), 3.88 (1H, d, $^2J_{H,H}$ = 13.11, CH_2Ph), 3.98 (1H, dt, 3a-ax-H), 4.01 (1H, d, CH_2Ph), 7.19–7.22 (1H, m, H-arom), 7.27–7.30 (2H, m, H-arom), 7.35–7.36 (2H, m, H-arom). δ_C (125 MHz, $CDCl_3$) 24.3 (C-8), 25.4 (C-7), 26.6, 26.9 (C(*C*H_3)$_2$), 29.5 (C-9), 54.4 (*C*H_2Ph), 56.8

(C-6), 58.3 (C-10), 58.4 (C-4), 64.9 (C-9a), 70.8 (C-3a), 82.9 (C-10a), 109.8 ($C(CH_3)_2$), 126.7, 128.1, 128.1, 140.9 (4 C-arom). Mass (ESI): m/z 317 (M^+ + H), 339 (M^+ + Na).

(3a*S*,9a*R*,10*R*,10a*S*)-10-Azido-2,2-dimethyloctahydro-3aH-[1,3]dioxolo[4,5-b]quinolizine (30). To a solution of **26** (70 mg, 0.309 mmol) in pyridine (2 ml) at 0 °C was added mesyl chloride (42 mg, 0.371 mmol, in 1 mL DCM). The reaction mixture was stirred at room temperature for 6 h. When TLC revealed no starting material, the solution was diluted with dichloromethane (10 ml) and washed with water (3 × 5 ml) followed by brine solution (5 ml). It was then dried over anhydrous Na_2SO_4. After removal of solvent the crude mesylate (77 mg, 0.251 mmol) was taken up in DMF (2 ml). LiN_3 (123 mg, 2.51 mmol) was added and the mixture was heated at 110 °C for 12 h. The reaction mixture was diluted with water (10 ml) and extracted with ethyl acetate (3 × 10 ml). The ethyl acetate layer was washed with water and dried over anhydrous Na_2SO_4. Solvent removal followed by column chromatography (silica, pet. ether/ethyl acetate, 6:1) gave **30** (56 mg, 72%) as a colorless liquid. $[\alpha]_D^{25}$ = +60.19 (*c* 1.1, $CHCl_3$). Anal. Calcd. for $C_{12}H_{20}N_4O_2$: C, 57.12; H, 7.99; N, 22.21; Found: C, 57.01; H, 7.90; N, 22.05%. IR ν_{max} cm^{-1} in $CHCl_3$ 2936, 2208 (N_3), 2107, 1654, 1446, 1229. δ_H (400 MHz, $CDCl_3$) 1.19–1.25 (2H, m, 8ax-H, 9ax-H), 1.44, 1.45 (3H each, 2 s, C(CH_3)$_2$), 1.48–1.54 (1H, m, 7ax-H), 1.61–1.64 (1H, m, 8eq-H), 1.74–1.81 (2H, m, 7eq-H, 9eq-H), 2.07–2.11 (1H, m, 9a-ax-H), 2.22 (1H, dt, $^3J_{6ax,7ax}$ = 11.83, $^3J_{6ax,7eq}$ = 2.76, 6ax-H), 2.25 (1H, t, $^3J_{3a\text{-}ax,4ax}$ = 10.17, 4ax-H), 2.90 (1H, d, $^2J_{H,H}$ = 11.28, 6eq-H), 3.10 (1H, dd, $^2J_{H,H}$ = 9.90, $^3J_{3a\text{-}ax,4eq}$ = 3.85, 4eq-H), 3.20–3.28 (2H, m, 10ax-H, 10a-ax-H), 3.58 (1H, ddd, 3a-ax-H). δ_C (50 MHz, $CDCl_3$) 23.8 (C-8), 25.6 (C-7), 26.7 (C(CH_3)$_2$), 29.4 (C-9), 56.0 (C-6), 56.9 (C-4), 64.6, 65.2 (C-9a, C-10), 74.2 (C-3a), 81.9 (C-10a), 111.1 ($C(CH_3)_2$). Mass (ESI): m/z 253 (M^+ + H), 275 (M^+ + Na).

(3a*S*,9a*R*,10*R*,10a*S*)-2,2-Dimethyloctahydro-3aH-[1,3]dioxolo-[4,5-b]quinolizin-10-amine (31). The azide **30** (43 mg, 0.172 mmol) in methanol (2 ml) was hydrogenated for 7 h at atmospheric pressure in the presence of 10% Pd on charcoal (4 mg). The reaction mixture was passed through a short pad of celite. Solvent removal followed by column chromatography (silica, $CHCl_3$/MeOH, 24:1) afforded **31** (39 mg, 85%) as a white solid. $[\alpha]_D^{25}$ = +39.43 (*c* 0.7, $CHCl_3$). Anal. Calcd. for $C_{12}H_{22}N_2O_4$: C, 63.68; H, 9.80; N, 12.38; Found: C, 64.80; H, 9.85; N, 12.35%. IR ν_{max} cm^{-1} in $CHCl_3$ 3396 (NH), 3054, 2305, 1598, 1265. δ_H (500 MHz, $CDCl_3$, D_2O exchange) 1.13–1.23 (2H, m, 8ax-H, 9ax-H), 1.42 (6H, s, C(CH_3)$_2$), 1.50–1.56 (1H, m, 7ax-H), 1.58–1.64 (2H, m, 7eq-H, 8eq-H), 1.80 (1H, br d, $^2J_{H,H}$ = 12.9, 9eq-H), 2.04–2.07 (1H, m, 9a-ax-H), 2.21 (1H, dt, $^3J_{6ax,7ax}$ = 11.83, $^3J_{6ax,7eq}$ = 3.03, 6ax-H), 2.27 (1H, t, $^3J_{3a\text{-}ax,4ax}$ = 10.18, 4ax-H), 2.66 (1H, dd, $^3J_{10ax,10a\text{-}ax}$ = 10.18, $^3J_{10ax,9a\text{-}ax}$ = 8.53, 10ax-H), 2.89 (1H, br d, $^2J_{H,H}$ = 11.56, 6eq-H), 3.10 (1H, dd, $^3J_{3a\text{-}ax,10a\text{-}ax}$ = 9.07, 10a-ax-H), 3.13 (1H, dd, $^3J_{4eq,3a\text{-}ax}$ = 4.01, 4eq-H), 3.58 (1H, ddd, 3a-H). δ_C (100 MHz, $CDCl_3$) 24.1 (C-8), 25.8 (C-7), 26.7, 26.8 (C(CH_3)$_2$), 28.6 (C-9), 55.7 (C-9a), 56.2 (C-6), 57.5 (C-4), 67.6 (C-10), 74.3 (C-3a), 84.4 (C-10a), 110.4 ($C(CH_3)_2$). Mass (ESI): m/z 227 (M^+ + H), 249 (M^+ + Na).

Crystal structure determination of compound 23

Crystal data

$C_{13}H_{23}NO_4$, M = 257.32, orthorhombic, a = 5.3743(4), b = 10.2506 (7), c = 24.311(2) Å, V = 1339.27(16) Å^3, space group $P2_12_12_1$, Z = 4, D_c = 1.276 g/cc, μ (Mo–Kα) = 0.094 mm^{-1}, 12741 reflections measured, 2369 unique (R_{int} = 0.0398) [$I>2\sigma(I)$], R value 0.0358, the final w$R(F_2)$ = 0.0823 [$I>2\sigma(I)$].

Crystal structure determination of compound 25

Crystal data

$C_{12}H_{21}NO_3$, M = 227.30, orthorhombic, a = 9.725 (1), b = 6.4790(7), c = 20.325(2) Å, V = 1280.6(2) Å^3, space group $P2_12_12_1$, Z = 4, D_c = 1.179 g/cc, μ (Mo–Kα) = 0.084 mm^{-1}, 10685 reflections measured, 2250 unique (R_{int} = 0.0745) [$I>2\sigma(I)$], R value 0.0480, the final w$R(F_2)$ = 0.0864 [$I>2\sigma(I)$].

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