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Synthesis of unnatural pentahydroxylated pyrrolizidines: 5-*epi*- and 5,7a-di-*epi*-hyacinthacine C_1

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ABSTRACT

Stereocontrolled synthesis of 5-*epi*- and 5,7a-di-*epi*-hyacinthacine C_1 (**7** and **8**), two potential glycosidase inhibitors are described using α,β-unsaturated ketone **9** as homochiral starting material. The key step in the synthesis is the highly diastereoselective dihydroxylation reaction of **9**, that allows the obtention of a single bis-hydroxylated ketone (**10**). Further derivatization into two epimeric mesylate esters followed by internal cyclization form the pyrrolizidinic compounds **7** and **8**. This type of compounds can be useful in glycobiology due to their ability to inhibit carbohydrate-processing enzymes.

1. Introduction

Glycosidases are enzymes involved in different and important biological processes ,such as intestinal digestion, lysosomal catabolism and post-translational modification.[1] These processes are closely related to the endoplasmic reticulum (ER) quality control and ER-associated degradation of glycoproteins and in this respect, variation of the glycosidase activity by inhibitors such as azasugars has enormous applications in glycobiology and drug therapy.[2] Examples of these types of compounds are isofagomine and some of its derivatives,[3] α-1-*C*-nonyl-1,5-dideoxy-1,5-iminoxylitol,[4] and α-1-*C*-octyl-1-deoxynojirimycin,[5] which are promising candidates in pharmacological chaperone therapy for the treatment of Gaucher disease and Pompe disease.

Naturally occurring iminosugars are classified into five structural classes: polyhydroxylated pyrrolidines, piperidines, indolizidines, pyrrolizidines and nortropanes. Among them, Hyacinthacine C_1 (**1**) and C_5 (**2**) together with Casuarine (**3**) and its 3-*epi*- and 6-*epi*-isomers (**4** and **5**, respectively) are the most polyhydroxylated pyrrolizidine alkaloids (PHPAs) bearing hydroxymethyl and methyl groups adjacent to the ring nitrogen (C-3 and C-5, Fig. 1). They are relatively uncommon in nature, where only the five compounds described below (**1**–**5**) have been identified so far from natural sources. The first described, PHPA **1**, was isolated by Asano et al.[6] from the immature fruits and stalks of *Hyacinthoides* non-script and later,[7] from the bulbs of *Muscari Armeniacum* (Hyacinthaceae). On the other hand, PHPA **2**, has

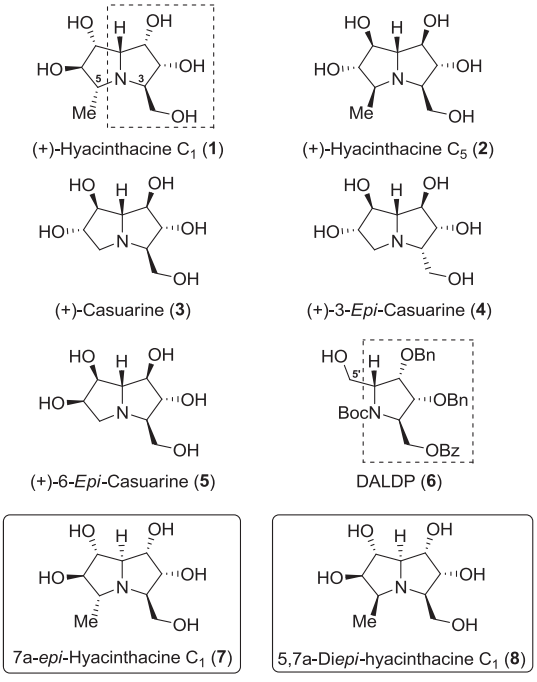

Figure 1. Some natural (**1**–**5**) and unnatural (**7**,**8**) pentahydroxylated pyrrolizidine alkaloids and DALDP-derivative **6**.

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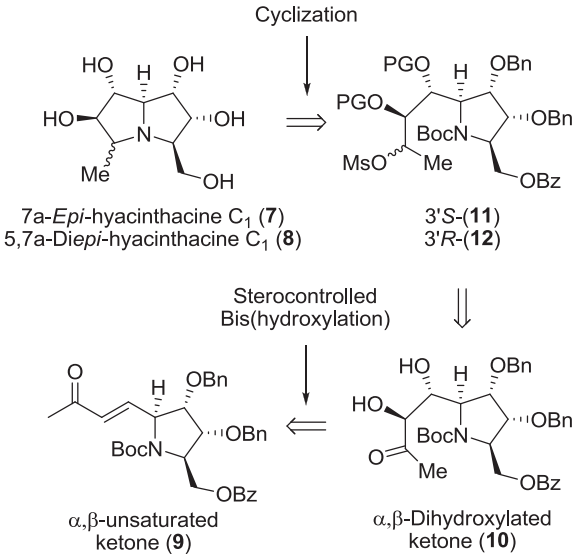
been recently isolated, by Kato et al.,[8] from the bulbs of *Scilla socialis* (Hyacinthaceae). Compounds **1** and **2** have shown a potent inhibition activity versus *Aspergillus niger* amyloglucosidase with a IC_{50} of 84 and 57 μM, respectively. Moreover PHPA **2** has also showed a strong inhibitory activity against intestinal rat maltase (IC_{50}=77 μM) and *Caldocellum saccharolyticum* β-glucosidase (IC_{50}=48 μM). These activities make both compounds potential candidates for the development of new drugs against viral infections, cancer and diabetes.[9]

From a chemical point of view, absolute configurations of **1** and **2** have not been disclosed so far, this fact, together with some discrepancies on the actual structure of **1**,[10] make highly desirable the total stereoselective syntheses of **1** and **2**. Moreover, Pyne et al. have recently reassigned the structure of uniflorine B as the known pyrrolizidine alkaloid (+)-casuarine (**3**), while the structure of (−)-uniflorine A was suggested to be that of (+)-6-*epi*-casuarine (**5**).[11] At the same time, stereocontrolled syntheses of new and related PHPAs are also needed to study their potential as glycosidase inhibitors and their possible application as therapeutical agents.

Most of the synthetic routes to these iminosugars start with a carbohydrate analogue resembling, if possible, the majority of its stereocenters. However, non-carbohydrate approaches, such as ring closing metathesis,[11a,12] cyclization of acetylenic sulfones with chloroamines,[13] tandem inter [4+2]/inter [3+2] cycloaddition process,[14] cuprate chemistry[15] and diastereoselective *syn*-dihydroxylation[11a,16] are becoming more popular. Supporters of non-carbohydrate synthetic strategy claim that these routes are superior because they exhibit increased stereoselectivity and are more efficient at introducing the amine moiety. On the other hand, some carbohydrate-derivatives like polyhydroxylated pyrrolidines and piperidines combine two desirable qualities: the presence of the amino group and of several stereogenic centres. For these reasons, these compounds can be considered as valuable starting material for the synthesis of more elaborated iminosugars.

As Figure 1 shows, PHPA **1** bears hydroxymethyl and methyl substituents at C-3 and C-5, respectively. Moreover, the stereochemistry and functionalization at the indicated ring (dashed line) totally match that existing in the protected DALDP-derivative **6**. In this respect, our group has been engaged in the total syntheses of different PHPAs[17] by using appropriately functionalized tetrahydroxypyrrolidines as key intermediates[18] and recently, we have described[17j] the use of **6** in the synthesis of (+)-hyacinthacine A_6, (+)-5,7a-di-*epi*-hyacinthacine A_6 and (+)-7a-*epi*-hyacinthacine A_1 by means of the appropriately functionalized α,β-unsaturated ketone **9** (see Scheme 1). Given the chemical nature of **9**, we envisaged its potential use as starting material for the preparation of pentahydroxylated pyrrolizidines through stereoselective bis-hydroxylation of its conjugated double bond. In this article, we describe our studies towards the synthesis of unnatural 7a-*epi*-hyacinthacine C_1 (**7**) and 5,7a-di-*epi*-hyacinthacine C_1 (**8**).

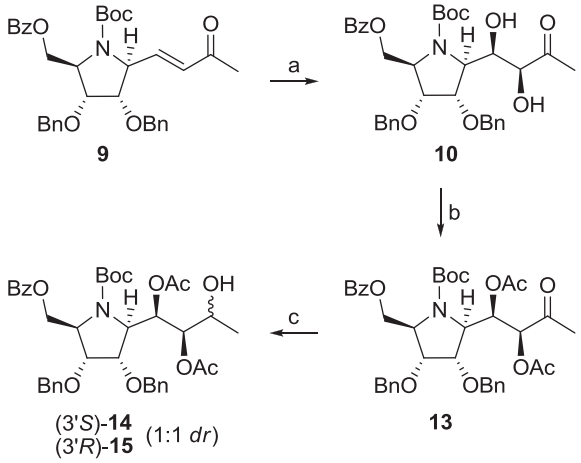


Scheme 1. Retrosynthetic analysis for the synthesis of 7a-*epi*-hyacinthacine C_1 (**7**) and 5,7a-di-*epi*-hyacinthacine C_1 (**8**) from α,β-unsaturated ketone **9**.

2. Results and discussion

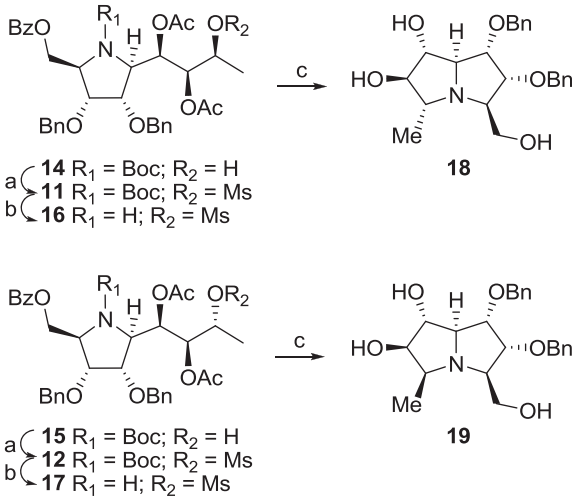
The retrosynthetic analysis for the synthesis of pyrrolizidines **7** and **8**, (Scheme 1) focuses on the preparation of α,β-dihydroxylated ketone **10** as the key intermediate. Hence, with α,β-unsaturated ketone **9**[17j] as starting material, stereocontrolled dihydroxylation will allow to obtain the desired bis-hydroxy intermediate **10**. Selective ketone reduction in **10**, followed by cyclization to the pyrrolizidine skeleton through the corresponding mesylate derivatives **11** and **12**, and final protecting groups removal, will render the proposed unnatural 7a-*epi*-hyacinthacine C_1 (**7**) and 5,7a-di-*epi*-hyacinthacine C_1 (**8**).

As described in the retrosynthetic analysis, α,β-unsaturated ketone **9** was used as starting material. Catalytic dihydroxylation (DH) of **9** with OsO_4 yielded (1′*R*,2′*S*)-**10** as a single product (Scheme 2). The absolute configuration of the new stereogenic centres in **10** was determined later in the synthesis. It is worth mention here the high diastereoselectivity achieved is this reaction since, with a analogous compound presenting a Cbz-protecting group at the amino moiety and a benzyl group at C-5′, the DH reaction in similar conditions, leads to the obtention of a compound with (1′*S*,2′*R*)-configurations.[19] According to the retrosynthetic plan, and in order to obtain the mesylate intermediates **11** and **12**, chemical protection of the newly generated hydroxyl groups in derivative **10** was attempted. Several protecting groups (BnBr, TESCl, TMSCl, TBDMSCl) were tried, resulting in low yields or inseparable mixture of compounds. Only acetylation with Ac_2O/Py proved successful, affording di-*O*-acetylated **13** with high yield. Reduction of **13** with $NaBH_4$ yielded a resolvable mixture of alcohols **14** and **15** (1:1 dr). As before, the absolute configuration of the new quiral centres in **14** and **15** was not determined at this point but later in the synthesis.



Scheme 2. Reagents and conditions: (a) OsO_4, NMO, Me_2CO, rt; (b) Ac_2O, Py, rt; (c) $NaBH_4$, MeOH, 0 °C.

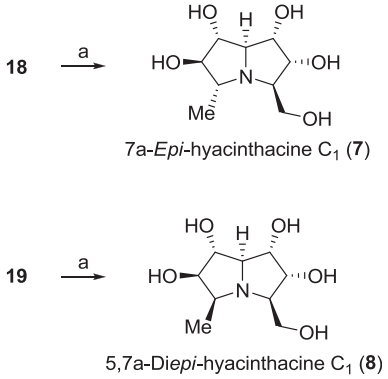
In order to build the pyrrolizidinic skeleton, alcohols **14** and **15** were separately reacted with MsCl and converted into the corresponding mesylate derivatives **11** and **12**, respectively. Acid-catalyzed *N*-Boc deprotection reaction on **11** and **12** yielded pyrrolidines **16** and **17** as shown in Scheme 3. Both amines were refluxed with NEt_3 in MeOH to obtain the pyrrolizidine skeleton through internal nucleophilic substitution, and in situ reacted with 2 M MeONa to remove the acetyl and benzyl protecting groups and to afford pyrrolizidines **18** and **19**, respectively. The absolute



Scheme 3. Reagents and conditions: (a) MsCl, TEA, CH_2Cl_2, rt; (b) TFA, CH_2Cl_2, rt.; (c) NEt_3, THF reflux, then NaOMe, rt.

configuration for **18** and **19** were established on the basis of their spectroscopic data, and their proposed structures were confirmed by extensive NOE experiments.

Removal of the remaining *O*-benzyl protecting groups on intermediates **18** and **19** completed the synthesis and yielded the desired (+)-7a-*epi*-hyacinthacine C_1 (**7**) and (−)-5,7a-di-*epi*-hyacinthacine C_1 (**8**) (Scheme 4). Their analytical and spectroscopic data were in accordance with those proposed and were confirmed by NOE experiments.



Scheme 4. Reagents and conditions: (a) H_2, 10% Pd/C, HCl, MeOH, rt, then Amberlite IRA-400 (OH^- form).

3. Conclusions

We describe herein the synthesis of two new pentahydroxylated pyrrolizydines: (+)-7a-*epi*-hyacinthacine C_1 (**7**) and (−)-5,7a-di-*epi*-hyacinthacine C_1 (**8**). The feasibility of the methodology employed relies on a highly diastereoselective DH reaction that allows the obtention of a single bis-hydroxylated ketone. In general, this is an effective methodology for the preparation of analogues of hyacinthacines C. This type of compounds can be useful in glycobiology due to their ability to inhibit carbohydrate-processing enzymes and hence their potential as glycosidase inhibitors and therapeutical agents.

4. Experimental section

4.1. General remarks

Solutions were dried over $MgSO_4$ before concentration under reduced pressure. The ^1H and ^{13}C NMR spectra were recorded with Bruker AMX-300, AM-300 and ARX-400 spectrometers for solutions in $CDCl_3$ (internal Me_4Si). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and br, broad. IR spectra were recorded with a Perkin–Elmer FT-IR Spectrum One instrument and mass spectra were recorded with a Hewlett–Packard HP-5988-A and Fisons mod. Platform II and VG Autospec-Q mass spectrometers or a NALDI ionization-time of flight (NALDI-TOF) mass spectrometer and EI mass spectrometer. Optical rotations were measured for solutions in $CHCl_3$ (1-dm tube) with a Jasco DIP-370 polarimeter. TLC was performed on precoated silica gel 60 F_{254} aluminium sheets and detection by employing a mixture of 10% ammonium molybdate (w/v) in 10% aqueous sulfuric acid containing 0.8% cerium sulfate (w/v) and heating. Column chromatography was performed on silica gel (Merck, 7734). All compounds were shown to be homogeneous by chromatographic methods and characterized by NMR, MS and HRMS.

4.2. Synthesis and characterization

*4.2.1. (2S,3S,4R,5R)-2-[(1′R,2′S)-1′,2′-Dihydroxy-3′-oxobutyl]-5-(benzoyloxymethyl)-3,4-dibenzyloxy-N-tert-butyloxycarbonylpyrrolidine (**10**).* To a stirred solution of **9** (663 mg, 1.13 mmol) in acetone/water 8:1 v/v (13.5 mL) were added NMO (266 mg, 2.27 mmol) and aqueous 1% OsO_4 (1.5 mL). The mixture was left at room temperature 7 h. TLC (Et_2O/hexane, 4:1) then revealed the presence of a new product of lower mobility. The mixture was concentrated to a residue that was submitted to chromatography (Et_2O/hexane, 2:3→3:1) to afford syrupy **10**. Yield: 498 mg (71%); $[\alpha]^{25}_D$ +50 (*c* 1, $CHCl_3$); IR (KBr, neat) 3378 (OH), 1720 and 1666 cm^{-1} (C=O); ^1H NMR (400 MHz): δ=7.93–7.23 (m, 15H, 3Ph), 5.30 (br s, 1H, OH), 4.87 and 4.76 (2d, 2H, *J*=12.2 Hz, CH_2Ph), 4.61 and 4.56 (2d, 2H, *J*=12.1 Hz, CH_2Ph), 4.40–4.30 (m, 3H), 4.23–4.19 (m, 2H), 4.15–4.10 (m, 2H), 3.67 (m, 1H), 3.25 (br s, 1H, OH), 2.13, (s, 3H, *Me*CO) and 1.52 (s, 9H, CMe_3); ^{13}C NMR (100 MHz): δ=209.97 (C-3′), 166.52 (C=O, Bz), 157.31 (C=O, Boc), 137.85, 137.39, 133.53, 129.92, 128.68, 128.16 (Ph), 82.82 (CMe_3), 76.77 and 76.24 (C-3,4), 75.21 and 72.01, (C-1′,2′), 64.79 and 60.62 (C-2,5), 72.11 and 71.36 ($2CH_2Ph$), 62.00 (CH_2OBz), 28.53 (CMe_3) and 27.49 (C-4′); HRMS (NALDI-TOF) calcd for $C_{35}H_{41}NNaO_9$ $[M+Na]^+$ 642.2679, found 642.2684 (deviation 0.8 ppm).

*4.2.2. (2S,3S,4R,5R)-2-[(1′R,2′S)-1′,2′-Diacetyloxy-3′-oxobutyl]-5-(benzoyloxymethyl)-3,4-dibenzyloxy-N-tert-butyloxycarbonylpyrrolidine (**13**).* Compound **10** (450 mg, 0.727 mmol) was acetylated in dry pyridine (7.0 mL), acetic anhydride (0.275 mL, 2.91 mmol) and DMAP (cat.) at room temperature for 3 h. TLC (Et_2O/hexane, 4:1) then showed a faster-running compound. MeOH (2 mL) was added, stirred for 10 min and the reaction mixture was supported on silica gel and chromatographed (Et_2O/hexane, 1:2→4:1) to afford pure **13** as a colourless syrup (440 mg, 86%); $[\alpha]^{25}_D$ +46 (*c* 1, $CHCl_3$); IR (KBr, neat) 1749, 1722 and 1666 cm^{-1} (C=O); ^1H NMR (400 MHz): δ=8.01–7.22 (m, 15H, 3Ph), 5.27 and 5.06 (H-1′,2′), 4.73 (m, 2H), 4.53–4.50 (m, 3H), 4.36 (m, 3H), 4.15 and 3.76 (2 m, 2H), 2.23, 1.99 and 1.82 (3s, 9H, 3*Me*CO) and 1.48 (s, 9H, CMe_3); ^{13}C NMR (100 MHz): δ=202.64 (C-3′), 173.17 and 172.52 (2C=O, Ac), 166.52 (C=O, Bz), 156.01 (C=O, Boc), 137.85, 137.39, 133.53, 129.92, 128.68, 128.16 (Ph), 82.82 (CMe_3), 76.77, 76.24, 75.21 and 72.01 (C-3,4,1′,2′), 64.79 and 60.62 (C-2,5), 72.11 and 71.36 ($2CH_2Ph$), 62.00 (CH_2OBz), 28.53 (CMe_3), 27.49 (C-4′), 20.68 and 20.49 ($2CH_3CO_2$); HRMS (NALDI-TOF) calcd for $C_{39}H_{45}NNaO_{11}$ $[M+Na]^+$ 726.2890, found 726.2885 (deviation −0.7 ppm).

*4.2.3. (2R,3S,4R,5R)-2-[(1′R,2′R,3′S)-1′,2′-Diacetyloxy-3′-hydroxybutyl]-5-(benzoyloxymethyl)-3,4-dibenzyloxy-N-tert-butyloxycarbonylpyrrolidine (**14**) and (2R,3S,4R,5R)-2-[(1′R,2′R,3′R)-1′,2′-diacetyloxy-3′-hydroxybutyl]-5-(benzoyloxymethyl)-3,4-dibenzyloxy-*

*N-tert-butyloxycarbonylpyrrolidine (**15**).* To an ice-water cooled solution of **13** (895 mg, 1.27 mmol) in anhydrous MeOH (6 mL), $NaBH_4$ (57.7 mg, 1.53 mmol) was added portionwise and the mixture was stirred for 1.5 h. TLC (ether/hexane, 7:1) then showed the presence of two more polar products. The reaction mixture was neutralized with AcOH, and the mixture was supported on silica gel and chromatographed (Et_2O/hexane, 1:1) to afford first **14** (220 mg, 25%) as a thick syrup; $[\alpha]_D^{25}$ +54 (*c* 1, $CHCl_3$); IR (KBr, neat) 3407 (OH), 1738, 1722 and 1673 cm^{-1} (C=O); ^1H NMR (400 MHz): δ=7.88–7.17 (m, 15H, 3Ph), 4.98–4.92 (m, 2H), 4.70 and 4.47 (2d, 2H, *J*=12.5 Hz, CH_2Ph), 4.61–4.55 (m, 2H), 4.56 and 4.34 (2d, 2H, *J*=11.3 Hz, CH_2Ph), 4.41–4.37 (m, 1H), 4.12–4.07 (m, 2H), 3.66 (br d, 1H), 3.36 (m, 1H), 1.98 (s, 6H, 2*Me*CO), 1.51 (s, 9H, CMe_3), 0.60 (d, 3H, *J*=6.5 Hz, H-4′,4′,4′); ^{13}C NMR (100 MHz): δ=170.77 and 170.30 (2C=O, Ac), 166.10 (C=O, Bz), 157.64 (C=O, Boc), 137.33, 137.14, 133.34, 129.66, 128.41, 128.37, 128.14, 128.05 (Ph), 82.53 (*C*Me_3), 76.58, 73.48, 71.77, 71.02, 70.48 (C-1′,2′,3′,3,4), 72.31 and 70.76 (2*C*H_2Ph), 61.48 and 60.40 (C-2,5), 61.62 (*C*H_2OBz), 28.17 (C*Me*$_3$), 21.25 and 20.84 (2*C*H_3CO_2) and 16.40 (C-4′); HRMS (NALDI-TOF) calcd for $C_{39}H_{47}NNaO_{11}$ $[M+Na]^+$ 728.3047, found 728.3043 (deviation −0.5 ppm).

Eluted second was **15** (198 mg, 22%) as a syrup.

$[\alpha]_D^{26}$ −12 (*c* 1, $CHCl_3$); IR (KBr, neat) 3474 (OH), 1750, 1724 and 1701 cm^{-1} (C=O); ^1H NMR (400 MHz): δ=7.93–7.19 (m, 15H, 3Ph), 5.67 (br d, 1H), 5.38 (m, 1H), 5.18 (br d, 1H), 4.93 (m, 1H), 4.69–3.84 (m, 9H), 1.99, 1.97, 1.91 and 1.89 (4s, 6H, 2*Me*CO, 2 rotamers), 1.44 and 1.34 (2s, 9H, CMe_3, 2 rotamers), 1.08 (m, 3H, H-4′,4′,4′; 2 rotamers); ^{13}C NMR (100 MHz): δ=170.77 and 169.53 (2C=O, Ac), 166.23 (C=O, Bz), 155.48 and 154.72 (C=O, Boc, 2 rotamers), 136.93, 133.28, 129.80, 129.72, 128.47, 128.34, 128.14, 128.05 (Ph), 81.77 (*C*Me_3), 78.17, 75.05, 73.91, 70.03, 66.03 (C-1′,2′,3′,3,4), 72.41, 71.86, 71.79 and 71.02 (2*C*H_2Ph, 2 rotamers), 63.12, 62.97 (*C*H_2OBz, 2 rotamers), 62.98 and 60.03 (C-2,5), 28.25 and 28.16 (C*Me*$_3$, 2 rotamers), 20.73 (2*C*H_3CO_2) and 16.83 (C-4′); HRMS (NALDI-TOF) calcd for $C_{39}H_{47}NNaO_{11}$ $[M+Na]^+$ 728.3047, found 728.3054 (deviation 1.0 ppm).

*4.2.4. (2R,3S,4R,5R)-2-[(1′R,2′S,3′S)-1′,2′-Diacetyloxy-3′-(methanesulfonyloxy)butyl]-5-(benzoyloxymethyl)-3,4-dibenzyloxy-N-tert-butyloxycarbonylpyrrolidine (**11**).* To an ice-water cooled and stirred solution of **14** (0.204 g, 0.29 mmol) in dry Cl_2CH_2 (7 mL) were added TEA (81 μL, 0.58 mmol) and MsCl (33 μL, 0.43 mmol) and the mixture was left at room temperature for 3 h. TLC (ether/hexane, 7:1) then showed a faster-running compound. MeOH (1 mL) was added and after 15 min the reaction mixture was supported on silica gel and chromatographed (ether/hexane, 2:3→1:1→ether) to afford syrupy **11** (171 mg, 75%) as a colourless syrup. $[\alpha]_D^{25}$ −39 (*c* 1, $CHCl_3$); IR (KBr, neat) 1744, 1723 and 1701 cm^{-1} (C=O); ^1H NMR (400 MHz): δ=8.01–7.25 (m, 15H, 3Ph), 6.01, 5.25, 5.14 and 4.93 (4 m, 4H), 4.71–3.93 (m, 9H), 3.05 (s, 3H, OMs), 2.19, 2.14, 2.11, 2.02 (4s, 6H, 2*Me*CO, 2 rotamers), 1.48 and 1.38 (2s, 9H, CMe_3, 2 rotamers), 1.20 and 1.04 (2 m, 3H, H-4′,4′,4′, 2 rotamers); ^{13}C NMR (100 MHz): δ=170.85 and 169.57 (2C=O, Ac), 166.12 (C=O, Bz), 158.67 and 154.66 (C=O, Boc, 2 rotamers), 137.41, 137.02, 133.28, 129.72, 128.49, 128.28, 128.07 (Ph), 81.67 (*C*Me_3), 81.35, 80.71, 76.90, 75.48, 75.20, 73.71, 68.51, 68.12, 67.66 (C-1′,2′,3′,3,4, 2 rotamers), 72.28 and 71.42 (2*C*H_2Ph), 63.28 (*C*H_2OBz), 60.73 and 59.80 (C-2,5), 38.77 (OMs), 28.17 (C*Me*$_3$), 21.08 (2*C*H_3CO_2) and 16.41 (C-4′); HRMS (NALDI-TOF) calcd for $C_{40}H_{49}NNaO_{13}S$ $[M+Na]^+$ 806.2822, found 806.2820 (deviation −0.2 ppm).

*4.2.5. (2R,3S,4R,5R)-2-[(1′R,2′S,3′S)-1′,2′-Diacetyloxy-3′-(methanesulfonyloxy)butyl]-5-(benzoyloxymethyl)-3,4-dibenzyloxypyrrolidine (**16**).* To an ice-water cooled and stirred solution of **11** (180 mg, 0.23 mmol) in dry Cl_2CH_2 (3.5 mL) were added slowly TFA (3.5 mL) and the mixture was left at room temperature for 60 min TLC (ether/hexane, 7:1) then showed a slower-running compound. The solvent was eliminated and the residue co-distilled with toluene to a new residue that was supported on silica gel and chromatographed (ether/hexane, 2:1) to afford **16** (130 mg, 83%). $[\alpha]_D^{29}$ +39 (*c* 1, $CHCl_3$); IR (KBr, neat) 3381 (NH), 1743 and 1721 cm^{-1} (C=O); ^1H NMR (500 MHz): δ=7.98–7.23 (m, 15H, 3Ph), 5.04–4.98 (m, 2H, H-2′,3′), 4.88 (br d, 1H, $J_{2,1'}$=8.4 Hz, H-1′), 4.53 (s, 2H, CH_2Ph), 4.47 and 4.45 (2d, 2H, *J*=11.6 Hz, CH_2Ph), 4.37 (dd, 1H, $J_{5'a,5'b}$=11.4, $J_{5,5'a}$=5.2 Hz, H-5′a), 4.17 (dd, 1H, $J_{5,5'b}$=5.1 Hz, H-5′b), 3.92 (t, 1H, $J_{3,4}$=$J_{2,3}$=4.8 Hz, H-3), 3.82 (m, 2H, H-4,5), 3.63 (dd, 1H, H-2), 3.07 (s, 3H, OMs), 2.04 and 1.92 (2s, 6H, 2*Me*CO) and 1.06 (d, 3H, $J_{3',4'}$=6.0 Hz, H-4′,4′,4′); ^{13}C NMR (125 MHz): δ=170.48 and 169.98 (2C=O, Ac), 166.30 (C=O, Bz), 137.67, 137.55, 132.96, 130.00, 129.60, 128.35, 128.12, 128.00, 127.83 (Ph), 81.11, 78.49 and 78.08 (C-3′,3,4), 72.77 (C-2′), 68.82 (C-1′), 71.90 and 71.53 (2CH_2Ph), 66.06 (*C*H_2OBz), 58.66 and 58.54 (C-2,5), 38.71 (OMs), 21.17 and 20.81 (2*C*H_3CO_2) and 16.93 (C-4′); HRMS (NALDI-TOF) calcd for $C_{35}H_{41}NNaO_{11}S$ $[M+Na]^+$ 706.2298, found 706.2304 (deviation 0.8 ppm).

*4.2.6. (1S,2R,3R,5R,6R,7R,7aS)-1,2-Dibenzyloxy-6,7-dihydroxy-3-hydroxymethyl-5-methylpyrrolizidine (**18**).* To a solution of **16** (120 mg, 0.17 mmol) in anhydrous THF (6 mL) was added NEt_3 (0.1 mL) and the reaction mixture was refluxed for 7 h, and then treated with 2 M NaOMe in methanol (1 mL) for 1 h. TLC (ether/MeOH, 10:1) revealed a new compound. The reaction mixture was supported on silica gel and chromatographed (ether/MeOH, 8:1) to afford syrupy **18** (42 mg, 60%), $[\alpha]_D^{26}$ +25 (*c* 1, $CHCl_3$); IR (KBr, neat) 3378 (OH); ^1H NMR (500 MHz): δ=7.36–7.26 (m, 10H, 2Ph), 4.63 and 4.49 (2d, 2H, *J*=11.70 Hz, CH_2Ph), 4.58 and 4.52 (2d, 2H, *J*=11.8 Hz, CH_2Ph), 3.98 (t, $J_{1,2}$=$J_{1,7a}$=4.2 Hz, H-1), 3.92 (dd, 1H, $J_{2,3}$=7.0 Hz, H-2), 3.81 (dd, 1H, $J_{8a,8b}$=12.0, $J_{3,8a}$=4.2 Hz, H-8a), 3.74 (dd, 1H, $J_{3,8b}$=6.2 Hz, H-8b), 3.56 (t, 1H, $J_{6,7}$=$J_{7,7a}$=8.2 Hz, H-7), 3.47 (t, 1H, $J_{5,6}$=8.2 Hz, H-6), 3.42–3.36 (m, 2H, H-3,7a), 3.06 (m, 1H, H-5), 1.21 (d, 3H, $J_{5,Me}$=6.1 Hz, Me); ^{13}C NMR (125 MHz): δ=139.57, 129.30, 129.16, 128.66 (Ph), 83.79 (C-6), 81.10 (C-1), 80.01 (C-2,7), 73.00 and 72.27 (2CH_2Ph), 71.69 (C-7a), 65.23 (C-3), 59.58 (C-8), 58.53 (C-5) and 19.33 (Me); HRMS (NALDI-TOF) calcd for $C_{23}H_{29}NNaO_5$ $[M+Na]^+$ 422.1943, found 422.1949 (deviation 1.4 ppm).

*4.2.7. (1S,2R,3R,5R,6R,7R,7aS)-1,2,6,7-Tetrahydroxy-3-hydroxymethyl-5-methylpyrrolizidine (**7**).* Compound **18** (40 mg, 0.10 mmol) in MeOH (10 mL) and conc. HCl (five drops) was hydrogenated (70 psi H_2) in the presence of 10% Pd/C (50 mg) for 24 h. The catalyst was filtered off, washed with MeOH, and the combined filtrate and washings were treated with Amberlite IRA-400 resin (OH^- form). Evaporation of the solvent afforded a residue that was retained on a column of Dowex 50Wx8 (200–400 mesh). The column was thoroughly washed with MeOH, water and then with 1 N NH_4OH to afford pure **7** (15 mg, 68%) as a colourless viscous syrup; $[\alpha]_D^{29}$ +7 (*c* 1, MeOH); IR (KBr, neat) 3384 (OH); ^1H NMR (500 MHz): δ=4.04 (dd, $J_{1,2}$=4.7, $J_{1,7a}$=2.7 Hz, H-1), 3.95 (dd, 1H, $J_{2,3}$=7.9 Hz, H-2), 3.86 (dd, 1H, $J_{8a,8b}$=12.1, $J_{3,8a}$=3.7 Hz, H-8a), 3.82 (dd, 1H, $J_{3,8a}$=6.0 Hz, H-8b), 3.61 (t, 1H, $J_{6,7}$=$J_{7,7a}$=8.1 Hz, H-7), 3.46 (t, 1H, $J_{5,6}$=8.1 Hz, H-6), 3.20 (dd, 1H, H-7a), 3.18 (m, 1H, H-3), 3.06 (m, 1H, H-5), 1.24 (d, 3H, $J_{5,Me}$=6.1 Hz, Me); ^{13}C NMR (125 MHz): δ=83.60 (C-6), 80.06 (C-7), 75.58 (C-1), 73.89 (C-7a), 73.51 (C-2), 66.42 (C-3), 59.78 (C-8), 58.56 (C-5) and 19.50 (Me); HRMS (NALDI-TOF) calcd for $C_9H_{18}NO_5$ $[M+H]^+$ 220.1185, found 220.1186 (deviation 0.5 ppm).

*4.2.8. (2R,3S,4R,5R)-2-[(1′R,2′S,3′R)-1′,2′-Diacetyloxy-3′-(methanesulfonyloxy)butyl]-5-(benzoyloxymethyl)-3,4-dibenzyloxy-N-tert-butyloxycarbonylpyrrolidine (**12**).* To an ice-water cooled and stirred solution of **15** (0.19 g, 0.27 mmol) in dry Cl_2CH_2 (4 mL) were added TEA (75 μL, 0.54 mmol) and MsCl (31 μL, 0.40 mmol) and the mixture was left at room temperature for 3 h. TLC (ether/hexane,7:1) then showed a faster-running compound. MeOH (1 mL) was added and after 15 min the reaction mixture was supported on silica gel and chromatographed (ether/hexane, 2:3→3:1) to afford syrupy **12**

(176 mg, 83%) as a colourless syrup. $[\alpha]_D^{25}$ −6 (*c* 1, $CHCl_3$); IR (KBr, neat) 1753, 1721 and 1701 cm^{-1} (C=O); ^1H NMR (400 MHz): δ=7.92–7.18 (m, 15H, 3Ph), 5.76, 5.51, 5.27 and 4.96 (4 br s, 4H), 4.69–3.96 (m, 9H), 2.59 and 2.45 (2s, 3H, OMs, 2 rotamers), 2.10, 2.07, 2.04 and 2.02 (4s, 6H, 2*Me*CO, 2 rotamers), 1.52 and 1.40 (2s, 9H, CMe_3, 2 rotamers), 0.87 (m, 3H, H-4′,4′,4′, 2 rotamers); ^{13}C NMR (100 MHz): δ=170.13 and 169.76 (2C=O, Ac), 166.21 (C=O, Bz), 155.38 and 154.62 (C=O, Boc, 2 rotamers), 137.16, 137.04, 136.67, 133.32, 129.72, 128.42, 128.12 (Ph), 82.17 and 81.18 (*C*Me$_3$, 2 rotamers), 77.42, 76.73, 76.25, 75.63, 73.63 (C-1′,2′,3′,3,4), 71.82 and 71.09 (2*C*H$_2$Ph), 68.63 and 60.20 (C-2,5), 63.18 and 62.91 (*C*H$_2$OBz, 2 rotamers), 37.68 (OMs), 28.33 and 28.17 (C*Me*$_3$, 2 rotamers), 20.74 and 20.64 (2*C*H$_3$CO$_2$) and 16.20 (C-4′); HRMS (NALDI-TOF) calcd for $C_{40}H_{49}NNaO_{13}S$ $[M+Na]^+$ 806.2822, found 806.2817 (deviation −0.6 ppm).

*4.2.9. (2R,3S,4R,5R)-2-[(1′R,2′S,3′R)-1′,2′-Diacetyloxy-3′-(methanesulfonyloxy)butyl]-5-(benzoyloxymethyl)-3,4-dibenzyloxypyrrolidine (**17**).* To an ice-water cooled and stirred solution of **12** (160 mg, 0.20 mmol) in dry Cl_2CH_2 (3 mL) was added slowly TFA (3 mL) and the mixture was left at room temperature for 45 min. TLC (ether) then showed a slower-running compound. The solvent was eliminated and the residue co-distilled with toluene to a new residue that was supported on silica gel and chromatographed (ether/hexane, 2:1) to afford **17** (126 mg, 90%); $[\alpha]_D^{27}$ +22 (*c* 1, $CHCl_3$); IR (KBr, neat) 3379 (NH), 1742 and 1721 cm^{-1} (C=O); ^1H NMR (400 MHz): δ=7.92–7.15 (m, 15H, 3Ph), 5.20 (dd, 1H, $J_{2',3'}$=6.5, $J_{1',2'}$=2.4 Hz, H-2′), 5.08 (br d, 1H, $J_{2,1'}$=8.0 Hz, H-1′), 4.78 (quint, 1H, $J_{3',4'}$=6.5 Hz, H-3′), 4.47 and 4.40 (2d, 2H, J=12.0 Hz, CH_2Ph), 4.38 and 4.31 (2d, 2H, J=11.4 Hz, CH_2Ph), 4.30 (m, 1H, H-5′a), 4.20 (br dd, 1H, $J_{5'a,5'b}$=7.9, $J_{5,5'b}$=5.9 Hz, H-5′b), 3.90 (br t, 1H, $J_{3,4}$=$J_{4,5}$=6.2 Hz, H-4), 3.84 (m, 2H, H-3,5), 2.80 (s, 3H, OMs), 2.05 and 1.81 (2s, 6H, 2*Me*CO) and 1.28 (d, 3H, H-4′,4′,4′); ^{13}C NMR (100 MHz): δ=170.80 and 170.66 (2C=O, Ac), 166.22 (C=O, Bz), 137.37, 137.14, 133.15, 129.17, 128.44, 128.07, 127.91 (Ph), 78.97 (C-4), 77.53 (C-3), 77.48 (C-3′), 74.82 (C-2′), 72.47 (C-1′), 72.03 and 71.85 (2*C*H$_2$Ph), 64.91 (*C*H$_2$OBz), 58.99 and 58.83 (C-2,5), 38.47 (OMs), 20.95 and 20.88 (2*C*H$_3$CO$_2$) and 17.49 (C-4′); HRMS (NALDI-TOF) calcd for $C_{35}H_{41}NNaO_{11}S$ $[M+Na]^+$ 706.2298, found 706.2300 (deviation 0.3 ppm).

*4.2.10. (1S,2R,3R,5S,6R,7R,7aS)-1,2-Dibenzyloxy-6,7-dihydroxy-3-hydroxymethyl-5-methylpyrrolizidine (**19**).* To a solution of **17** (92 mg, 0.135 mmol) in anhydrous THF (6 mL) was added NEt_3 (0.1 mL) and the reaction mixture was refluxed for 7 h. TLC (ether/hexane, 4:1) showed the presence of two new compounds. The reaction was treated with 2 M NaOMe in methanol (1 mL) for 1 h. TLC (ether/MeOH, 10:1) then revealed a new compound. The reaction mixture was supported on silica gel and chromatographed (ether/MeOH, 10:1 →8:1) to afford syrupy **19** (36 mg, 67%), $[\alpha]_D^{28}$ +34 (*c* 1, $CHCl_3$); IR (KBr, neat) 3391 (OH); ^1H NMR (500 MHz): δ=7.36–7.26 (m, 10H, 2Ph), 4.73 and 4.55 (2d, 2H, J=11.90 Hz, CH_2Ph), 4.65 and 4.62 (2d, 2H, J=11.8 Hz, CH_2Ph), 4.11 (dd, $J_{1,2}$=3.2, $J_{2,3}$=6.1 Hz, H-2), 3.95 (dd, 1H, $J_{5,6}$=6.6, $J_{6,7}$=3.1 Hz, H-6), 3.72 (dd, 1H, $J_{7,7a}$=7.8 Hz, H-7), 3.65 (dd, 1H, $J_{1,7a}$=8.2 Hz, H-1), 3.62 (dd, 1H, $J_{3,8}$=3.1, $J_{8,8'}$=11.4 Hz, H-8), 3.47 (br d, 1H, H-8′), 3.02 (t, 1H, H-7a), 2.87 (quint, 1H, $J_{5,Me}$=6.6 Hz, H-5), 2.79 (br s, 1H, H-3), 1.07 (d, 3H, Me); ^{13}C NMR (125 MHz): δ=138.21, 128.49, 127.90, 128.82, (Ph), 84.72 (C-6), 83.48 (C-2), 79.94 (C-7), 79.27 (C-1), 74.31 (C-7a), 72.73 and 71.93 (2*C*H$_2$Ph), 67.07 (C-3), 61.90 (C-8), 59.19 (C-5) and 14.18 (Me); HRMS (NALDI-TOF) calcd for $C_{23}H_{29}NNaO_5$ $[M+Na]^+$ 422.1943, found 422.1946 (deviation 0.7 ppm).

*4.2.11. (1S,2R,3R,5S,6R,7R,7aS)-1,2,6,7-Tetrahydroxy-3-hydroxymethyl-5-methylpyrrolizidine (**8**).* Compound **19** (52 mg, 0.13 mmol) in MeOH (11 mL) and conc. HCl (five drops) was hydrogenated (70 psi H_2) in the presence of 10% Pd/C (50 mg) for 24 h. The catalyst was filtered off, washed with MeOH, and the combined filtrate and washings were treated with Amberlite IRA-400 resin (OH^- form). Evaporation of the solvent afforded a residue that was retained on a column of Dowex 50Wx8 (200–400 mesh). The column was thoroughly washed with MeOH, water and then with 1 N NH_4OH to afford pure **8** (20 mg, 70%) as a colourless viscous syrup; $[\alpha]_D^{26}$ −47 (*c* 1, MeOH); IR (KBr, neat) 3375 (OH); ^1H NMR (500 MHz): δ=4.07 (dd, $J_{1,2}$=6.5, $J_{2,3}$=3.8 Hz, H-2), 3.88 (dd, 1H, $J_{5,6}$=5.9, $J_{6,7}$=3.3 Hz, H-6), 3.71 (m, 2H, H-1,7), 3.65 (d, 2H, $J_{3,8}$=3.5 Hz, H-8,8), 2.77 (quint, 1H, $J_{5,Me}$=$J_{5,6}$=6.4 Hz, H-5), 2.61 (t, 1H, $J_{7,7a}$=$J_{1,7a}$=8.1 Hz, H-7a), 2.48 (br d, 1H, H-3), 0.92 (d, 3H, Me); ^{13}C NMR (125 MHz): δ=85.65 (C-6), 80.86 (C-1), 77.81 (C-2), 77.19 (C-7a), 72.68 (C-7), 70.76 (C-3), 63.10 (C-8), 60.97 (C-5) and 14.77 (Me); HRMS (NALDI-TOF) calcd for $C_9H_{18}NO_5$ $[M+H]^+$ 220.1185, found 220.1188 (deviation 1.4 ppm).

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.07.019.

References and notes

1. (a) Davies, G. J.; Gloster, T. M.; Henrissat, B. *Curr. Opin. Struct. Biol.* **2005**, *15*, 637–645; (b) Herscovics, A. *Biochim. Biophys. Acta* **1999**, *1473*, 96–107; (c) Stütz, A. E. *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Wiley-VCH: Weinheim, 1999; (d) Compain, P.; Martin, O. R. *Iminosugars: From Synthesis to Therapeutic Applications*; Wiley: Chichester, UK, 2007; (e) Rempel, B. P.; Withers, S. G. *Glycobiology* **2008**, *18*, 570–586; (f) Asano, N. In *Modern Alkaloids: Structure, Isolation, Synthesis and Biology*; Fattorusso, E., Taglialatela-Scafati, O., Eds.; Wiley-VCH: Weinheim, 2008; pp 11–138; (g) Asano, N. In *Glycoscience: Chemistry and Chemical Biology*; Fraser-Reid, B. O., Tatsuta, K., Thiem, J., Eds.; Springer: Berlin, 2008; pp 1887–1911.
2. (a) Nash, R. J. In *Bioactive Natural Products*; Colegate, S. M., Molyneux, R. J., Eds.; Summit Wales Limited: Aberystwyth, UK, 2008; p 407; (b) Asano, N. *Mod. Alkaloids* **2008**, 111; Asano, N. *Glycobiology* **2003**, *13*, 93R–104R.
3. (a) Dulsat, C.; Mealy, N. *Drugs Future* **2009**, *34*, 23–25; (b) Zhu, X.; Sheth, K. A.; Li, S.; Chang, H. H.; Fan, J. Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7450–7453.
4. Compain, P.; Martin, O.; Boucheron, C.; Godin, G.; Yu, L.; Ikeda, K.; Asano, N. *ChemBioChem* **2006**, *7*, 1356–1359.
5. (a) Mugrage, B. *PCT Int. Appl.* **2006**, 102; (b) Yu, L.; Ikeda, K.; Kato, A.; Adachi, I.; Godin, G.; Compain, P.; Martin, O.; Asano, N. *Bioorg. Med. Chem.* **2006**, *14*, 7736–7744.
6. Kato, A.; Adachi, I.; Miyauchi, M.; Ikeda, K.; Komae, T.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Wormald, M. R.; Fleet, G. W. J.; Asano, N. *Carbohyr. Res.* **1999**, *316*, 95–103.
7. Asano, N.; Kuroi, H.; Ikeda, K.; Kizu, H.; Kameda, Y.; Kato, A.; Adachi, I.; Waston, A. A.; Nash, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1–8.
8. Kato, A.; Kato, N.; Adachi, I.; Hollinshead, J.; Fleet, G. W. J.; Kuriyama, C.; Ikeda, K.; Asano, N.; Nash, R. J. *J. Nat. Prod.* **2007**, *70*, 993–997.
9. For further reviews on the chemistry and biology of pyrrolizidine alkaloids, see: (a) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680; (b) Compain, P.; Martin, O. R. *Bioorg. Med. Chem.* **2001**, *9*, 3077–3092; (c) Mroczek, T.; Glowniak, K. *Proc. Phytochem. Soc. Eur.* **2002**, *47*, 1–46; (d) Bols, M.; Lillelund, V. H.; Jensen, H. H.; Liang, X. *Chem. Rev.* **2002**, *102*, 515–553; (e) Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773–781; (f) Fu, P. P.; Xia, Q.; Lin, G.; Chou, M. W. *Drug Metab. Rev.* **2004**, *36*, 1–55; (g) Pyne, S. G.; Tang, M. *Curr. Org. Chem.* **2005**, *9*, 1393–1418; (h) Pearson, M. S. M.; Mathé-Allainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, 2159–2191; (i) Stocker, B. L.; Dangerfield, E. M.; Win-Mason, A. L.; Haslett, G. W.; Timmer, M. S. M. *Eur. J. Org. Chem.* **2010**, 1615–1637; (j) Wilson, F. X.; Nash, R. J.; Horne, G.; Storer, R.; Tinsley, J. M.; Roach, A. G. *PCT Int. Appl.* **2010**, 202; (k) Wilson, F. X.; Nash, R. J.; Horne, G.; Storer, R. *PCT Int. Appl.* **2010**, 255; (l) Wilson, F. X.; Nash, R. J.; Horne, G.; Storer, R.; Tinsley, J. M.; Roach, A. G. *PCT Int. Appl.* **2010**, 191; (m) Wilson, F. X.; Nash, R. J.; Horne, G.; Storer, R.; Tinsley, J. M.; Roach, A. G. *PCT Int. Appl.* **2010**, 204.
10. Even though the structure displays for Hyacinthacine C_1 in Fig. 1 was initially reported (see Ref. 6), the same structure has been also assigned to a new hyacinthacine, named as Hyacinthacine C_4 (see Ref. 8).
11. (a) Davis, A. S.; Ritthiwigrom, T.; Pyne, S. G. *Tetrahedron* **2008**, *64*, 4868–4879; (b) Ritthiwigrom, T.; Pyne, S. G. *Org. Lett.* **2008**, *10*, 2769–2771; (c) Pyne, S. *Chem. Aust.* **2008**, *75*, 13–14.

12. For selected syntheses see: (a) White, J. D.; Hrnciar, P.; Yokochi, A. F. T. *J. Am. Chem. Soc.* **1998**, *120*, 7359–7360; (b) Koch, D.; Maechling, S.; Blechert, S. *Tetrahedron* **2007**, *63*, 7112–7119; (c) Muroni, D.; Mucedda, M.; Saba, A. *Tetrahedron Lett.* **2008**, *49*, 2373–2376; (d) Lesma, G.; Colombo, A.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2009**, *74*, 590–596.
13. (a) Back, T. G.; Nakajima, K. *Org. Lett.* **1999**, *1*, 261–263; (b) Back, T. G.; Nakajima, K. *J. Org. Chem.* **2000**, *65*, 4543–4552.
14. (a) Denmark, S. E.; Parker, D. L., Jr.; Dixon, J. A. *J. Org. Chem.* **1997**, *62*, 435–436; (b) Denmark, S. E.; Herbert, B. *J. Org. Chem.* **2000**, *65*, 2887–2896; (c) Denmark, S. E.; Cottell, J. J. *J. Org. Chem.* **2001**, *66*, 4276–4284.
15. (a) Dieter, K. R.; Lu, K. *J. Org. Chem.* **2002**, *67*, 847–855; (b) Dieter, R. K.; Chen, N.; Watson, R. T. *Tetrahedron* **2005**, *61*, 3221–3230.
16. (a) Tang, M.; Pyne, S. G. *Tetrahedron* **2004**, *60*, 5759–5767; (b) Ritthiwigrom, T.; Willis, A. C.; Pyne, S. G. *J. Org. Chem.* **2010**, *75*, 815–824.
17. (a) Izquierdo, I.; Plaza, M.-T.; Robles, R.; Franco, F. *Tetrahedron: Asymmetry* **2001**, *12*, 2481–2487; (b) Izquierdo, I.; Plaza, M.-T.; Franco, F. *Tetrahedron: Asymmetry* **2002**, *13*, 1581–1585; (c) Izquierdo, I.; Plaza, M.-T.; Franco, F. *Tetrahedron: Asymmetry* **2003**, *14*, 3933–3935; (d) Izquierdo, I.; Plaza, M.-T.; Franco, F. *Tetrahedron: Asymmetry* **2004**, *15*, 1465–1469; (e) Izquierdo, I.; Plaza, M.-T.; Tamayo, J. A. *Tetrahedron* **2005**, *61*, 6527–6533; (f) Izquierdo, I.; Plaza, M.-T.; Yáñez, V. *Tetrahedron: Asymmetry* **2005**, *16*, 3887–3891; (g) Izquierdo, I.; Plaza, M.-T.; Tamayo, J. A. *J. Carbohydr. Chem.* **2006**, *25*, 281–295; (h) Izquierdo, I.; Plaza, M.-T.; Tamayo, J. A.; Rodríguez, M.; Martos, A. *Tetrahedron* **2006**, *62*, 6006–6011; (i) Izquierdo, I.; Plaza, M.-T.; Tamayo, J. A.; Sánchez-Cantalejo, F. *Eur. J. Org. Chem.* **2007**, 6078–6083; (j) Izquierdo, I.; Plaza, M.-T.; Tamayo, J. A.; Franco, F.; Sánchez-Cantalejo, F. *Tetrahedron* **2010**, *66*, 3788–3794.
18. (a) Izquierdo, I.; Plaza, M.-T.; Robles, R.; Franco, F. *Carbohydr. Res.* **2001**, *330*, 401–408; (b) Izquierdo, I.; Plaza, M.-T.; Franco, F. *Tetrahedron: Asymmetry* **2002**, *13*, 1503–1508; (c) Izquierdo, I.; Plaza, M.-T.; Rodríguez, M.; Franco, F.; Martos, A. *Tetrahedron* **2005**, *61*, 11697–11704; (d) Izquierdo, I.; Plaza, M.-T.; Rodríguez, M.; Franco, F.; Martos, A. *Tetrahedron* **2006**, *62*, 1904; (e) Izquierdo, I.; Plaza, M.-T.; Rodríguez, M.; Tamayo, J. A.; Martos, A. *Tetrahedron* **2006**, *62*, 2693–2697; (f) Izquierdo, I.; Plaza, M.-T.; Yáñez, V. *Tetrahedron* **2007**, *63*, 1440–1447.
19. Yu, C.; Gao, H. *Faming Zhuanli Shenqing Gongkai Shuomingshu* **2008**, 18.