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Total Synthesis of Hyacinthacine A_1, a Glycosidase Inhibitor

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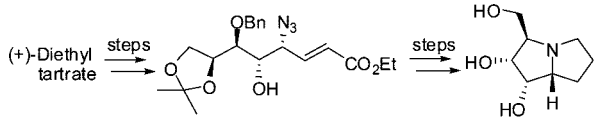

A practical and enantioselective total synthesis of hyacinthacine A_1 is achieved involving syn allylic epoxide opening with retention using Pd catalysis and "domino" hydrogenation (five steps in one pot) sequences.

The carbohydrate-processing enzymes viz. glycosidase play a very important role in AIDS, cancer, malaria, and diabetes.[1] Inhibiting such pathways leads aids in understanding and developing new drug candidates. It has been proven that iminosugars can inhibit these carbohydrate enzymes because of their resemblance to nature.[2] Naturally, these classes of compounds have attracted the attention of researchers engaged in finding remedies for these diseases as biochemical tools in glycolscience.[3] Based on the chemical structure, the naturally occurring iminosugars have been classified into piperidines,[4] indolizidines,[5] pyrrolizidines,[6] pyrrolidines[7] and nortropans.[8] Of these, the polyhydroxylated pyrrolizidine alkaloids (PHPAs) are scarce in nature and also are difficult to purify from their limited sources.[9] This leaves only total synthesis as a choice to explore SAR and for development of therapeutic agents.[10]

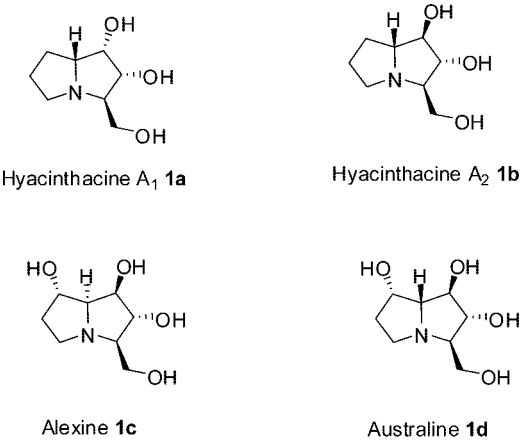

FIGURE 1. Structures of polyhydroxylated pyrrolizidines.

There are quite a few pyrrolizidine classes of iminosugars known, which include hyacinthacine, alexine, australine, etc. (Figure 1). The biological profile offered by these classes of alkaloids attracted organic chemists to explore various synthetic routes to have substantial number of analogues and quantities for further studies. The noteworthy routes are the chiron approaches starting from sugars, amino acids, and asymmetric approaches involving chiral dihydroxylation and epoxidation.[11] All these approaches, while offering advantages, also suffer from a few drawbacks, and more efficient strategies are needed for further exploitation of this rather new research field.

The natural product hyacinthacine A_1 (Figure 1), which is isolated in less than 0.0005% from the bulbs of *Muscari armemiacum* (Hyacinthaceae),[12] needs to be synthesized from

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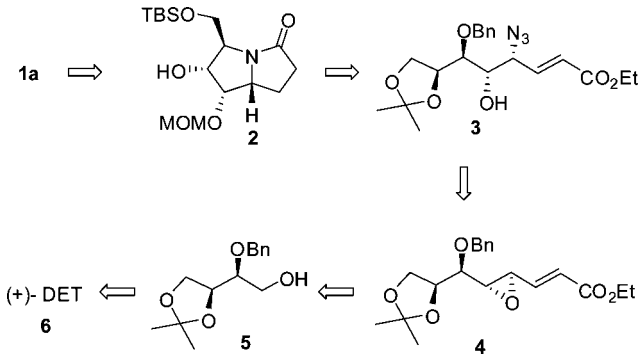
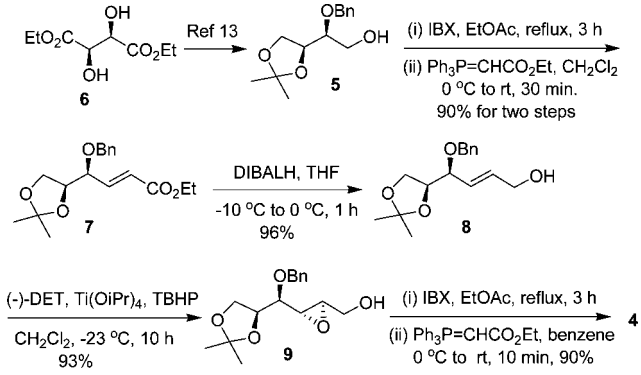
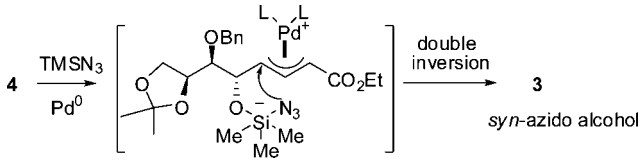
SCHEME 1. Retrosynthesis of Hyacinthacine A_1



SCHEME 2



SCHEME 3. Syn Opening of Epoxide with $TMSN_3$ and $Pd(PPh_3)_4$

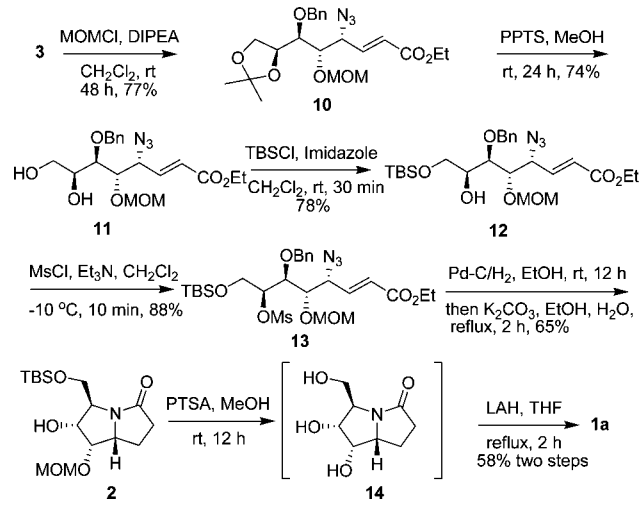


simple and readily accessible chemicals so that analoging can done efficiently for glycosidase inhibition and related studies (Scheme 1).

The known α-benzyloxy alcohol **5** (obtained from (+)-DET **6**)[13] on a very straightforward IBX oxidation followed by Wittig olefination with ethoxycarbonylmethylenetriphenylphosphorane produced the (*E*)-α,*β*-unsaturated ester **7**. This on DIBALH reduction yielded allyl alcohol **8**, which underwent a mismatched Sharpless asymmetric epoxidation with D-(−)-DET to furnish epoxy alcohol **9** in more than 98% de and ee.[14] Further homologation was achieved by a one-pot, two-step protocol (IBX, EtOAc followed by $PPh_3{=}CHCO_2Et$) to furnish α,*β*-unsaturated *γ*,*δ*-epoxy ester **4** in 90% yield for two steps (Scheme 2).[15]

The desired azido group was introduced with retention of configuration taking advantage of the neighboring olefin group via *π*-allyl Pd complex (Scheme 3).[16] This represents first application of this novel methodology in a total synthesis of natural product.

SCHEME 4



The protection of the *syn*-azido alcohol **3** as MOM ether **10** was achieved using MOMCl and diisopropylethylamine (DIPEA), which followed selective acidic hydrolysis of the isopropylidine group in the presence of MOM ether using PPTS in MeOH to realize diol **11**. The selective blocking of the primary alcohol group was rather routine under silylation conditions (TBSCl, imidazole) to obtain **12** in 78% yield. The prerequisite for the most critical domino reaction to generate the bicyclic pyrrolizidone moiety was to make the free secondary alcohol as mesyl ester which was performed by exposing **12** to MsCl and Et_3N at −10 °C for 10 min. The resulting mesylate **13** when subjected to hydrogenation (10% Pd−C/H_2, EtOH) followed by filtration, and the filtrate was refluxed in the presence of K_2CO_3 (diluted with 0.2 mL of H_2O) resulting in a cascade of transformations which include reduction of azide to amine followed by a S_N2 displacement of mesylate to generate the pyrrolidine intermediate, which in turn underwent an intramolecular amidation with the ester to furnish the pyrrolizidone **2** in 65% yield (five steps). The concomitant olefin reduction and hydrogenolysis of benzyl ether were obvious. The resulting **2** on hydrolysis of MOM ether and silyl ether with PTSA and further reduction of amide functionality with LAH completes the total synthesis of hyacinthacine A_1, **1a**, in 58% yield over two steps (Scheme 4).

In conclusion, the synthesis of hyacinthacine A_1 is achieved starting from L-(+)-DET. The key steps are the azido group introduction with retention of configuration while opening epoxide and the domino-pyrrolizidone construction in one stroke. Also, the appropriate choice of Sharpless asymmetric epoxidation and chiral synthon and epoxide opening will provide various stereo analogs which is a noteworthy feature of present strategy.

Experimental Section

(4*R*,5*S*,6*S*,*E*)-Ethyl 4-Azido-6-(benzyloxy)-6-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-5-hydroxyhex-2-enoate (3). To a stirred solution of (*E*)-α,*β*-unsaturated *γ*,*δ*-epoxy ester **4** (4.34 g, 11.98 mmol) in THF (60 mL) were added $TMSN_3$ (3.2 mL, 23.97 mmol) and $Pd(PPh_3)_4$ (1.38 g, 1.19 mmol) under N_2 atmosphere, and the mixture was stirred for 12 h at rt. Then 10% citric acid in methanol (10 mL) was added to the reaction mixture, which was stirred at 0 °C for 1 h, solid $NaHCO_3$ (10 g) was added and the mixture stirred for 15 min and filtered, methanol was completely removed in vacuo at 30 °C, and the mixture was purified through silica gel chroma-

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tography (12% EtOAc/petroleum ether) to yield *syn*-azido alcohol **3** (4.85 g, 80%): $[\alpha]^{25}_D = -47.6$ (*c* 1.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ_H (ppm) 7.38−7.34 (m, 5H), 6.95 (dd, *J* = 15.1, 6.7 Hz, 1H), 6.07 (d, *J* = 15.1 Hz, 1H), 4.75 (d, *J* = 11.3 Hz, 1H), 4.61 (d, *J* = 11.3 Hz, 1H), 4.38−4.29 (m, 1H), 4.24−4.14 (m, 3H), 4.02 (dd, *J* = 8.3, 6.0 Hz, 1H), 3.85 (t, *J* = 8.3 Hz, 1H), 3.81−3.72 (m, 1H), 3.62 (dd, *J* = 8.3, 5.2 Hz, 1H), 2.74 (d, *J* = 5.2 Hz, 1H), 1.44 (s, 3H), 1.34 (s, 3H), 1.30 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm) 165.7, 141.9, 137.7, 128.7, 128.4, 128.3, 125.0, 109.5, 77.7, 76.7, 74.4, 73.2, 66.0, 62.7, 61.0, 26.4, 25.2, 14.3; IR (neat) ν_{max} 3450, 2985, 2932, 2104, 1720, 1656, 1455, 1373, 1249, 1180, 1064, 984 cm^{-1}; MS (ESI) *m*/*z* 428 (100) $[M + Na]^+$; HRMS (ESI) $[M + Na]^+$ $C_{20}H_{27}N_3O_6Na$ calcd 428.1797, found 428.1795.

(5*R*,6*R*,7*S*,7a*R*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-6-hydroxy-7-(methoxymethoxy)hexahydropyrrolizin-3-one (2). To the mesyl ester **13** (300 mg, 0.49 mmol) in EtOH (7 mL) was added 10% Pd/C (50 mg) and the mixture stirred under H_2 (1 atm) at rt for 12 h. Then the reaction mixture was filtered through Celite and washed with EtOH (3−5 mL) and K_2CO_3 (344 mg, 2.49 mmol), water (0.2 mL) was added to the filtrate, and the mixture was refluxed for 2 h. Then it was concentrated in vacuo to remove solvents. The crude mass was chromatographed through silica gel (12% acetone/petroleum ether) to afford bicyclic lactam **2** (111 mg, 65%) as a white solid: mp 90−92 °C; $[\alpha]^{25}_D = -30.1$ (*c* 0.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ_H (ppm) 4.82 (d, *J* = 6.7 Hz, 1H), 4.71 (d, *J* = 6.7 Hz, 1H), 4.57−4.47 (m, 1H), 4.01−3.91 (m, 3H), 3.86 (dd, *J* = 10.5, 2.2 Hz, 1H), 3.54−3.48 (m, 1H), 3.44 (s, 3H), 3.33 (m, 1H), 2.67−2.52 (m, 1H), 2.38 (ddd, *J* = 12.8, 9.8, 3.0 Hz, 1H), 2.26−2.11 (m, 1H), 2.10- 1.97 (m,1H), 0.88 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm) 176.4, 97.7, 79.9, 75.4, 62.8, 61.3, 61.0, 56.2, 32.8, 25.8, 19.1, 18.1, −5.4, −5.5; IR (KBr) ν_{max} 3389, 2927, 2856, 1675, 1436, 1415, 1215, 1121, 1032, 966 cm^{-1}; MS (ESI) *m*/*z* 368 (100) $[M + Na]^+$; HRMS (ESI) $[M + H]^+$ $C_{16}H_{32}NO_5Si$ calcd 346.2049, found 346.2067.

(1*S*,2*R*,3*R*,7a*R*)-3-(Hydroxymethyl)hexahydro-1*H*-pyrrolizine-1,2-diol [(+)-Hyacinthacine A_1] (1a). To bicyclic lactam **2** (40 mg, 0.11mmol) dissolved in MeOH (3 mL) was added PTSA (cat.) and the mixture stirred for overnight at rt. After complete disappearance of the starting material (TLC monitored) and subsequent deprotection of TBS as well as MOM (as evidenced from mass spectum during course of reaction), solid $NaHCO_3$ was added, the mixture stirred for 15 min and filtered, and MeOH was removed from the reaction mixture in vacuo. To that crude mass dissolved in THF (2 mL) was added dropwise a suspension of LAH (13 mg, 0.34 mmol) in THF (1 mL) at 0 °C and the mixture refluxed for 2 h. Then the reaction was quenched with 0.1 mL of water, 0.1 mL of 10% NaOH, and then 0.2 mL of water and stirred for 6 h at rt. The resulting mixture was filtered through Celite and washed with EtOAc (3 × 2 mL). The filtrate was dried over anhydrous Na_2SO_4. Evaporation of solvent in vacuo afforded a residue that was retained on a column packed with Dowex 50W × 8 (200−400 mesh). The column was washed with MeOH, water, and then with 1 N NH_4OH to afford pure **1a** (11.6 mg, 58%): $[\alpha]^{25}_D = +33.5$ (*c* 0.2, CH_3OH) [lit.[12] $[\alpha]^{25}_D = +38.2$, *c* 0.23, H_2O]; ^1H NMR (300 MHz, $CDCl_3 + CD_3OD$) δ_H (ppm) 3.86−3.80 (m, 2H), 3.75−3.64 (m, 2H), 3.57−3.45 (m, 1H), 3.17−3.12 (m, 1H), 2.85 (m, 1H), 2.83−2.75 (m, 1H), 2.10−2.02 (m, 1H), 1.98−1.82 (m, 1H), 1.77−1.61 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3 + CD_3OD$) δ_C (ppm) 75.3, 72.4, 71.5, 70.02, 60.73, 57.27, 27.3, 25.0; IR (neat) ν_{max} 3398, 2932, 2850 cm^{-1}; MS(ESI) *m*/*z* 174 (100) $[M + H]^+$; HRMS (ESI) $[M + H]^+$ $C_8H_{16}NO_3$ calcd 174.1130, found 174.1127.

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Supporting Information Available: Experimental procedures, melting points, specific rotation, spectral data (^1H NMR, ^{13}C NMR, IR, MS, HRMS), and copies of ^1H NMR and ^{13}C NMR for all compounds described in the paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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