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SYNTHESIS OF 1S,2R,3S,4R,5R-METHYL[2,3,4-TRIHYDROXY-5-(HYDROXYMETHYL)CYCLOPENTYL]AMINE: A POTENT α-MANNOSIDASE INHIBITOR

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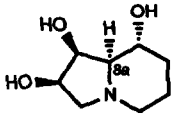
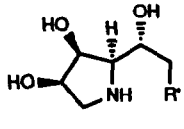
Summary: The title carbocyclic amine 15, prepared in high yield from isoxazolidine 8 using an efficient oxidation-epimerization-reduction sequence, is an inhibitor of mung bean α-mannosidase II and a potent inhibitor of jack bean α-mannosidase.

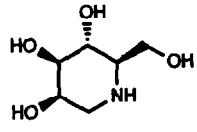
Inhibitors of the glycoprotein processing enzyme α-D-mannosidase II, such as swainsonine (1),[1] have potential therapeutic use as antimetastatic,[2,3] and immunomodulatory agents.[4] Synthetic hydroxylated pyrrolidines such as 1,4-dideoxy- and 1,4,6-trideoxy-1,4-imino-D-mannitol (2[5] and 3[6]) have shown potent α-mannosidase inhibitory activity. A recent molecular orbital and molecular graphics study[7] concluded that 1-3, as well as 8a-epi 1 are more potent α-mannosidase inhibitors than the more mannose-like deoxymannojirimycin (4) because of a better superimposition of their heteroatoms with the corresponding heteroatoms of the lowest energy "flap up" half chair form of the mannosyl cation 6,[7] the presumed



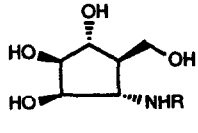
(-) - Swainsonine
1



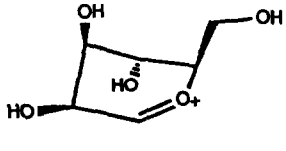
2 R'= OH
3 R'= H



Deoxymannojirimycin
4

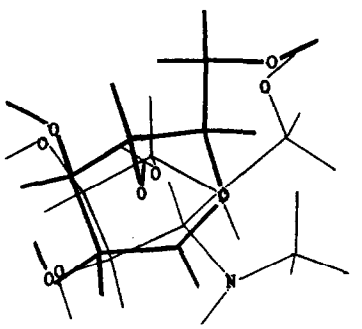


5



mannosyl cation
6

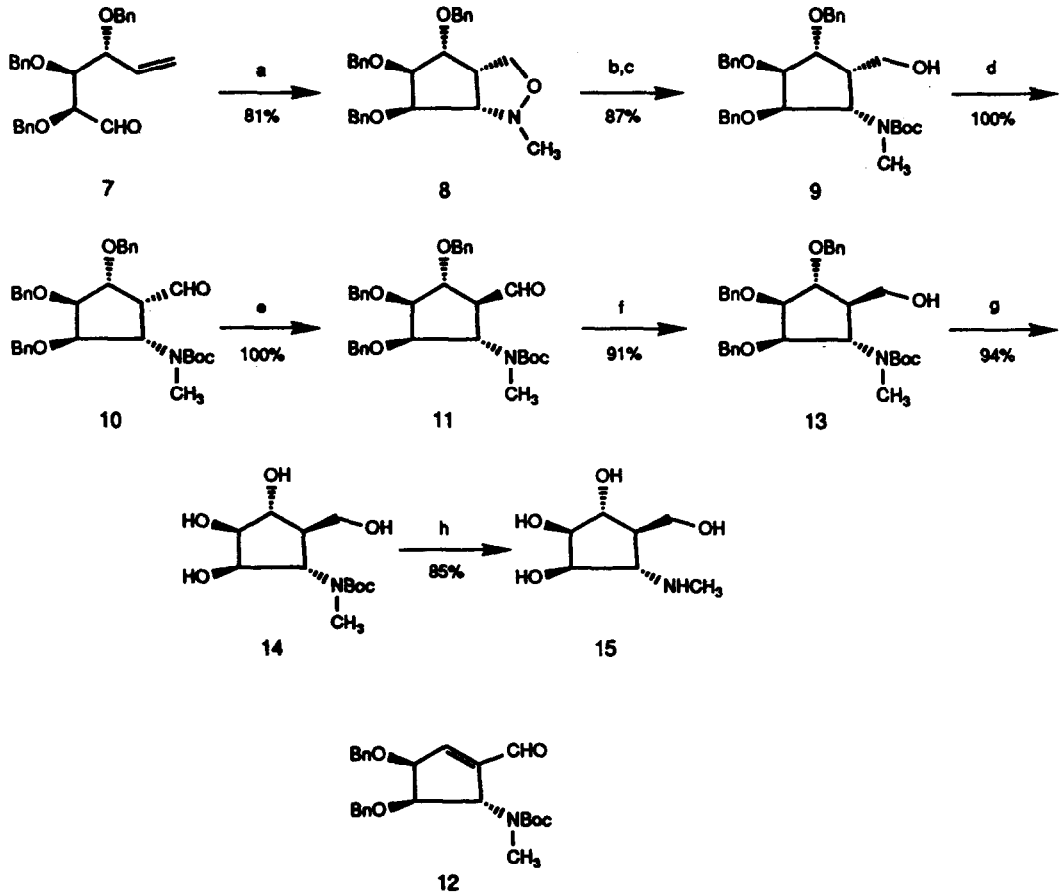
intermediate in the hydrolysis of mannopyranosides. We proposed the hydroxylated cyclopentylamines 5 as potential α-mannosidase inhibitors based on the following: a) the α-amino function is appropriately positioned to be protonated in the enzyme active site by an α-oriented carboxylic acid, and b) four hydroxy groups, which are ideally oriented because of the geometry of the five-membered ring, are present, as in the mannosyl cation 6. Molecular modeling studies of N-methyl analog 15 vs the MO-optimized "flap up" half chair form of the mannopyranosyl cation 6[7] show good overlap of the hydroxy groups. The N-methylamino moiety is located on the α-face between the ring oxygen and C-1 of the mannosyl cation, with a closer proximity to C-1. Consequently, cyclopentylamines 5 could mimic either the mannosyl cation or its protonated polysaccharide precursor.



cyclopentylamine 15 ——

mannosyl cation 6 ▬▬

The known isoxazolidine 8[9] was prepared in 81% yield via the intramolecular cycloaddition of the N-methyl nitrone derived from aldehyde 7. Reductive cleavage of the isoxazolidine ring (Zn dust, aq 85% HOAc, 50-55°C, 1 h) followed by acylation of the crude amino alcohol [$(BOC)_2O$, THF, 50°C] gave α-hydroxymethyl carbamate 9.[10] Swern oxidation [2.7 equiv DMSO, 2.3 equiv $(COCl)_2$, 5.1 equiv DBU, -78°C] gave a mixture of products, including 43% of the epimerized β-carboxaldehyde 11 and 10% of the α,β-unsaturated aldehyde 12; no 10 was detected. However, oxidation of 9 with the Dess-Martin periodinane[11] (1.5 equiv, CH_2Cl_2, 30 min) cleanly gave the α-carboxaldehyde 10 in quantitative yield (crude). Treatment of 10 with 0.25 equiv DBU at -78°C (CH_2Cl_2, 1 h, quench with HOAc at -78°C) led to clean epimerization to 11 without any concomitant elimination. Reduction of 11 with $NaBH_4$ in EtOH gave the β-hydroxymethyl carbamate 13 in 91% overall yield from 9. Debenzylation (H_2, Pd black, CH_3OH, 4 days) to 14 followed by cleavage of the t-Boc group [HCl(g), ether/CH_3OH] and flash chromatography[12] on silica gel (3:1:2 CH_3OH:conc NH_4OH:CH_2Cl_2) gave 15. Further purification by ion exchange chromatography (Bio-Rad AG 50W-X8, 0.5 M NH_4OH) and crystallization from i-PrOH at -78°C gave 15 as an extremely hygroscopic white solid.



(a) CH_3NHOH, CH_3OH, Δ; (b) Zn, HOAc; (c) $(Boc)_2O$; (d) Dess-Martin periodinane; (e) DBU, -78°C; (f) $NaBH_4$; (g) H_2, Pd; (h) HCl(g).

The carbocyclic amine 15 is a potent inhibitor of jack bean α-mannosidase,[13] with an IC_{50} of 62 nM vs an IC_{50} of 87 nM for swainsonine (1). However, against the purified mung bean glycoprotein processing enzyme α-mannosidase II[14], 15 has an IC_{50} of 1.0 μM as compared to swainsonine which has an IC_{50} of 40 nM. The potent activity of 15 is exceptional in that recent reports show that N-methylation of monocyclic analogues of swainsonine markedly decreases α-mannosidase inhibitory activity.[15]

Acknowledgments

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10. Physical data for new compounds: 9, white solid: mp 74.5-77°C; IR (KBr) ν_{max} 3512, 1682 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.4-7.2 (m, 15 H), 4.72-4.42 (m, 7 H), 4.52 (d, J=12 Hz), 4.44 (d, J=12 Hz), 4.32-4.17 (m, 1 H), 4.01 (d, 0.5 H, J=2 Hz), 3.99 (d, 0.5 H, J=2 Hz), 3.96-3.86 (m, 1 H), 3.63-3.54 (m, 2 H), 2.8 (m, 1 H), 2.79 and 2.74 (2s, 3 H), 2.63 (m, 0.5 H), 2.17 (m, 0.5 H), 1.47 (s, 9 H); mass spectrum, m/z 548 (M^++1), 448 (100); $[\alpha]_D^{25}$ + 56° (c 0.27, $CHCl_3$). Anal. ($C_{33}H_{41}NO_6$) C,H,N. 10, colorless oil: ^1H NMR ($CDCl_3$) δ 9.68 (bs, 1 H), 7.4-7.1 (m, 15 H), 4.75-4.35 (m, 8 H), 4.19-3.86 (m, 2 H), 3.30 (bs, 1 H), 2.78 and 2.72 (2s, 3 H), 1.45 (s, 9 H). 11, colorless oil: ^1H NMR ($CDCl_3$) δ 9.69 (s, 1 H), 7.4-7.23 (m, 15 H), 4.86 (t, 1 H, J=8.4 Hz), 4.6-4.4 (m, 6 H), 4.15-4.05 (m, 2 H), 3.87 (bs, 1 H), 2.74 (bs, 4 H), 1.45 (s, 9 H). 12, ^1H NMR ($CDCl_3$) δ 9.75 (s, 1 H), 7.4-7.28 (m, 10 H), 6.79 (bs, 1 H), 5.18 (bs, 0.4 H), 4.85 (d, 0.6 H, J=1.0 Hz), 4.80-4.52 (m, 6 H), 4.23 and 4.07 (2 m in 3:2 ratio, 1 H), 2.80 and 2.67 (2 s in 3:2 ratio, 3 H), 1.43 (s, 9 H). 13, colorless oil: IR (neat) ν_{max} 3458, 1692, 1668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38-7.25 (m, 15 H), 4.65-4.37 (m, 7 H), 3.98 (dd, 1 H, J=8.9, 5 Hz), 3.84 (dd, 1 H, J=5, 2.5 Hz), 3.81-3.54 (m, 4 H), 2.70 and 2.64 (2 s in 1:2.5 ratio, 3 H), 1.98 and 1.88 (2 bs in 3:8 ratio, 1 H), 1.48 (s, 9 H); mass spectrum, m/z 548 (M^++1), 492 (100); $[\alpha]_D^{25}$ + 44.8° (c 1.02, $CHCl_3$). Anal. ($C_{33}H_{41}NO_6$) C,H,N. 14, white crystals: mp 81-83°C; IR (KBr) ν_{max} 3420, 1690, 1666 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.22 (bd, 2 H, J=5.6 Hz), 4.64 (bs, 1 H), 4.58 (bs, 1 H), 4.15 (bs, 2 H), 3.94 (bs, 1 H), 3.73 (bs, 1 H), 3.54 (bs, 1 H), 2.81 (s, 3 H), 1.78 (bs, 1 H), 1.44 (s, 9 H); FABMS (glycerol), m/z 278 (M^++1, 100), 222 (100); $[\alpha]_D^{25}$ + 30.8° (c 1.06, $CHCl_3$). Anal. ($C_{12}H_{23}NO_6$) C,H,N. 15: ^1H NMR (D_2O) δ 3.86-3.59 (m, 5 H), 2.61 (dd, 1 H, J=7.3, 2.9 Hz), 2.31 (s, 3 H), 1.55 (m, 1 H); ^{13}C NMR (D_2O) δ 79.34, 78.16, 75.94, 67.98, 64.28, 52.10, 35.92; $[\alpha]_D^{20}$ + 8.5° (c 1.07, CH_3OH). Anal. ($C_7H_{15}NO_4$) H,N; C: calcd, 47.45; found 46.58.
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