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A new stereoselective approach for *N*-benzyl amino(hydroxymethyl)-cyclopentitols using RCM

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ABSTRACT

A new stereoselective approach for the synthesis of *N*-benzyl amino(hydroxymethyl)cyclopentitols by using stereoselective allylation on lactamine and RCM from D-ribose has been described and the glycosidase inhibitory activities of these amino cyclopentitols have been studied.

Glycosidases are involved in several metabolic pathways. The development of inhibitors for glycosidases is an important challenge toward the treatment of diseases such as diabetes, cancer, and viral infections.[1] Recently aminocyclopentitols have drawn considerable attention as potent glycosidase inhibitors.[2] Aminocyclopentitol substructures (Fig. 1) are found in a number of bioactive natural products such as mannostatin A (**1**), trehazolin (**2**), allosamidin (**3**)[3] and the carbocyclic nucleosides namely aristeromycin (**4**), and neplanocin A (**5**). The neuraminidase inhibitor BCX 1812 (**6**) in clinical development to treat influenza is also an aminocyclopentitol.[4] In the context of glycosidase inhibition, aminocyclopentitols can be considered as structural analogs of monosaccharide containing basic nitrogen function at the anomeric center. Particularly, the amino group mimics the protonated form of the leaving group oxygen atom in α or β orientation in the transition state of glycosidase-catalyzed reaction. Due to interesting biological activity and fascinating structural features, there has been a remarkable growth in design, synthesis, and evaluation of new glycosidase inhibitors, such as Merrell-Dow cyclopentylamine (**7**),[5] α-D-*gluco*, β-D-*gluco*, α-D-*galacto*, β-D-*galacto*, α-D-*manno*, β-D-*manno*, α-L-*fuco*, *and* β-L-*fuco* configured aminocyclopentitols.[6] Recent studies by Reymond and co-workers revealed that the *N*-benzyl derivatives of aminocyclopentitols show an enhanced inhibitory potency.[6d,h] Jager and co-workers reported that the presence of hydroxymethyl functionality in amino cyclopentane skeleton may serve as a general framework to generate a new family of glycosidase inhibitors.[6f] However, glycosidase inhibition by aminocyclopentitols as a function of their structural and stereo chemical features still remains to be fully understood. Hence the synthesis of new analogs can provide not only better understanding of glycosidase functioning but also lead to inhibitors with more therapeutic value.

In connection with our ongoing research in the synthesis of glycosidase inhibitors carbasugars[7] and azasugars,[8] herein we wish to report the stereoselective synthesis of novel *N*-benzyl derivatives of amino(hydroxylmethyl)cyclopentitols, *N*-benzyl α-L-*manno* aminocyclopentitol (**8a**),[9] 4-deoxy-*N*-benzyl-α-L-*manno* aminocyclopentitol (**8b**), and *N*-benzyl 6,7-di-*epi*-trehalamine (**8c**)[10,11] using stereoselective allylation on lactamine and ring-closing metathesis (RCM)[12] as key steps. The retro synthetic analysis of aminocyclopentitol skeletons (**8a–c**) is depicted in Scheme 1 which shows the importance of key intermediate **9** from which a variety of aminocyclopentitols can be prepared. It was further envisaged that the presence of 1,3-dioxalane ring in **9** could be helpful in getting better selectivity during further transformations.

In general the success of the RCM strategy depends on the efficient preparation of diene. In our strategy the RCM precursor **10** required for the construction of aminocyclopentene **9** could be prepared from lactamine **11** by allylation, oxidative cleavage of the double bond followed by condensation with Eschenmoser's salt and subsequent reduction.

The starting material 5-*O*-*tert*-butyl dimethylsilyl-2,3-*O*-isopropylidene-D-ribofuranose **12**, required for our synthesis was prepared from D-ribose using reported procedure (Scheme 2).[13] Reaction on **12** with benzylamine gave ribosylamine **13**. Treatment of crude **13** with allylbromide and zinc furnished amino alcohol **14** exclusively as a single isomer. The absolute configuration of the newly generated stereo center was not confirmed at this stage, but it was done at the later stages by NOE correlations, which indicated the formation of *erythro* isomer. Previously there are some reports on the stereoselective nucleophilic addition on lactamine, Wilcox and co-workers[14] reported that the Grignard addition on *N,N*-dibenzyl ribosylamine having 2,3-*O*-isopropylidene unit gave *threo* amino ethers where the nucleophilic addition is taking place on non-chelated iminium ion. Later Nicotra and co-workers[15] reported that the nucleophilic addition on *N*-benzyl-tri-*O*-benzyl glucosamine also gave *threo* amino ethers. Here the selectivity was due to the chelation between imine and α-benzyloxy group whereas in the case of compound **13**, allylation gave exclusively *erythro* isomer which presumably proceeded via seven-membered

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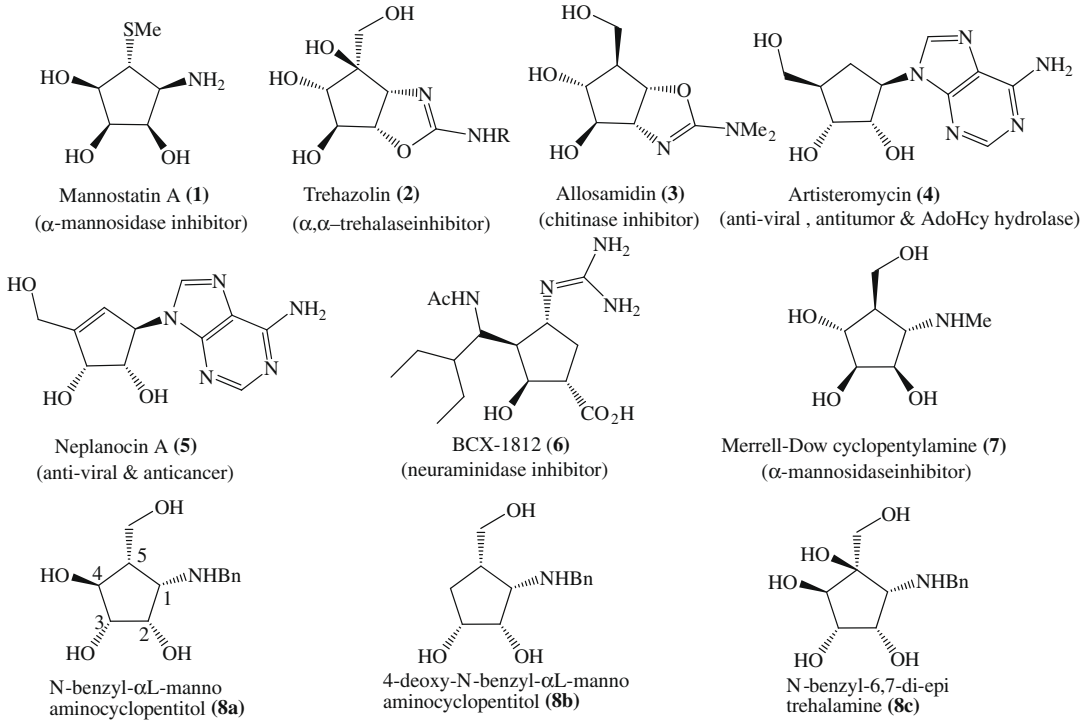
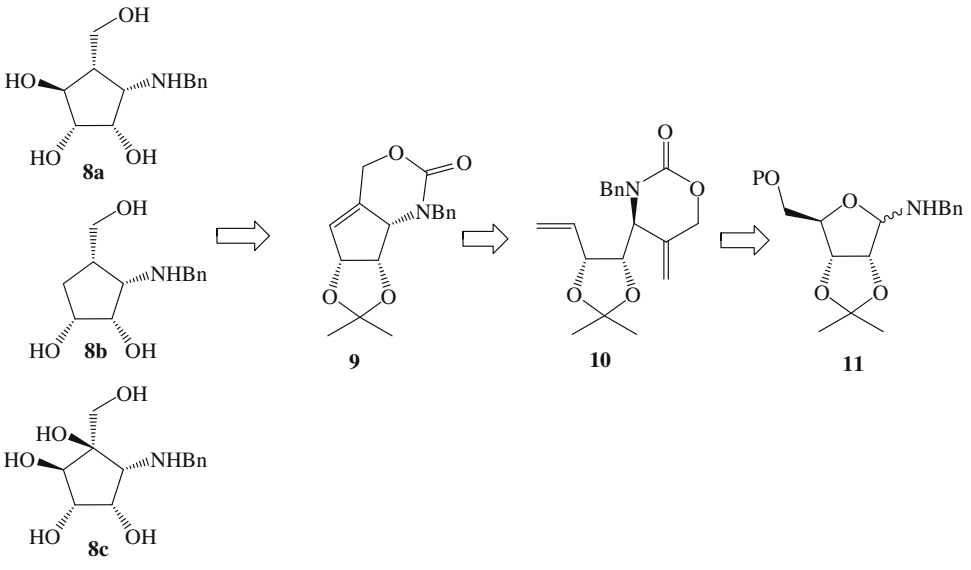


Figure 1. Some of the natural and unnatural aminocyclopentitols.

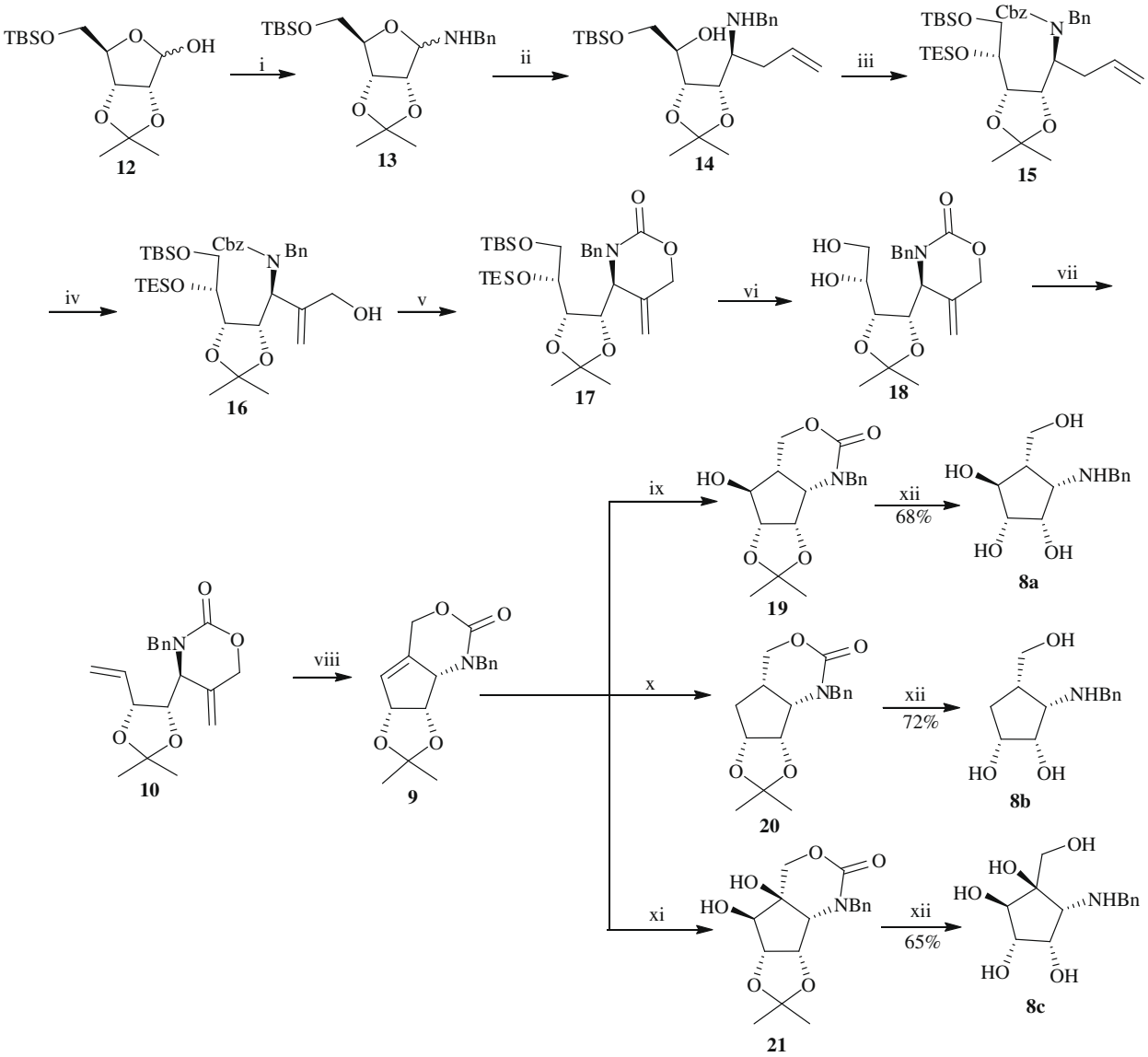


Scheme 1. Retrosynthetic analysis of aminocyclopentitols.

transition state[16] or Felkin-Anh model (Fig. 2). In fact the formation of *erythro* isomer shows that chelation between imine and isopropylidene group has not taken place due to steric strain.

Having the amino compound **14** in hand we proceeded to the next stage. Secondary hydroxyl group of compound **14** was protected as its triethylsilyl ether and then amino functionality was converted to carbamate with CbzCl to give **15**. The next step is the introduction of 1,1-disubstituted olefin required for RCM. Oxidative cleavage of terminal double bond in **15** with OsO_4/$NaIO_4$ produced aldehyde which on treatment with Eschenmoser's salt yielded α-methylene aldehyde.[17] The crude aldehyde was further reduced to alcohol **16** under Luche condition at −78 °C, yielding the required olefin without any α-elimination. In order to protect the primary hydroxyl group, compound **16** was treated with sodium hydride to give the cyclic carbamate **17**. Global deprotection of *bis*-silylether in **17** with TBAF gave diol **18**. Diol functionality of **18** was converted to olefin using I_2/TPP to give diene **10**. The diene **10** was subjected to ring-closing metathesis using Grubb's second generation catalyst[18] in toluene under reflux conditions produced the key intermediate aminocyclopentene **9** in 75% yield.

The compound **9** was transformed to various aminocyclopentitol derivatives with high stereoselectivity as follows. Hydroboration of aminocyclopentene **9** with BH_3–DMS complex gave hydroxy product **19**. Chemoselective hydrogenation of aminocyclopentene **9** using Pd/C afforded **20** and dihydroxylation of **9** with



Scheme 2. Synthesis of *N*-benzyl aminocyclopentitols **8a–c**. Reagents and conditions: (i) $BnNH_2$, MeOH, reflux, 12 h; (ii) allylbromide, Zn, THF, 0 °C to rt, 4 h, 70% (over two steps); (iii) (a) TES-Cl, imidazole, DCM, 0 °C, 10 min, 93%; (b) NaH, CbzCl, THF, 0 °C, 1 h, 85%; (iv) (a) OsO_4/NaIO4, acetone/water 4:1, 0 °C to rt, 3 h; (b) Et_3N, Eschenmoser's salt, DCM, 0 °C to rt, 4 h; (c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −78 °C, 30 min, 70% (over three steps); (v) NaH, THF, 0 °C to rt, 2 h, 85%; (vi) TBAF, THF, rt, 5 h, 92%; (vii) TPP, I_2, imidazole, toluene, reflux, 3 h, 83%; (viii) Grubb's second generation catalyst, toluene, reflux, 18 h, 75%; (ix) $BH_3{\cdot}DMS$, H_2O_2, NaOH, THF, −15 °C to rt, 3 h, 50%; (x) Pd/C, H_2, MeOH, 30 min, 90%; (xi) OsO_4, NMO, acetone/water, 4:1, rt, 3 h, 85%; (xii) 6 N HCl, reflux, 12 h.

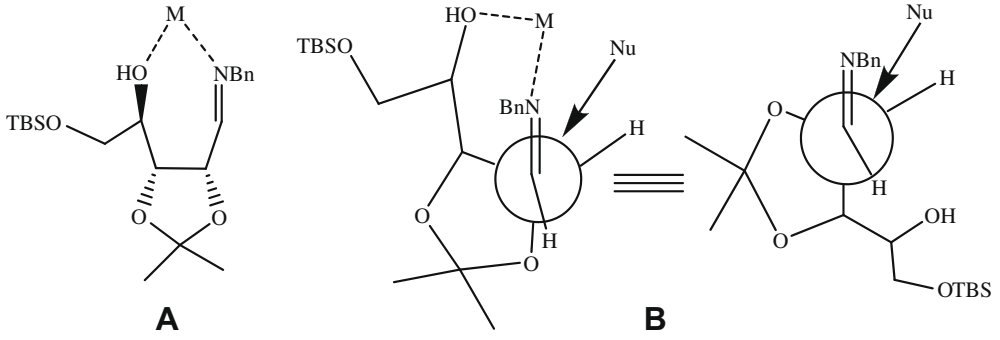


Figure 2. Seven-membered transition state (A) and Felkin-Anh Model (B).

OsO_4 gave dihydroxy compound **21**. The stereochemistry of compounds **19**, **20**, and **21** was established from ^{1}H-NMR couplings[19] and NOE experiments (Fig. 3). Global deprotection of carbamate and 2,3-*O*-isopropylidene group in **19**, **20**, and **21** were achieved with 6 N HCl under reflux to give new *N*-benzyl aminocyclopentitols **8a**, **8b**, and **8c** respectively.[20]

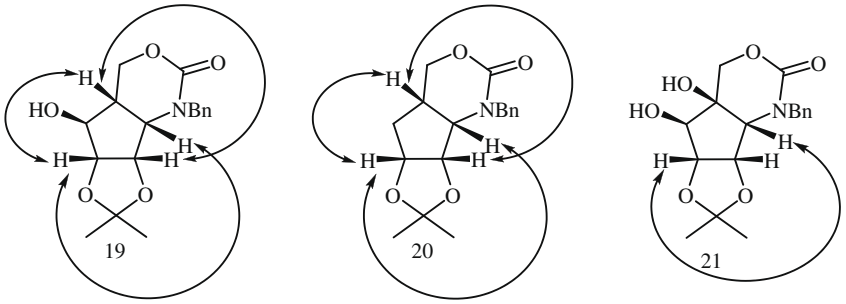


Figure 3. 2D-NOE correlations.

Table 1
Glycosidase inhibitory activity, IC_{50} values in mM

Compounds	α-Glucosidase	β-Glucosidase	α-Galactosidase	β-Galactosidase
8a	0.5	0.41	NI	0.065
8b	0.09	0.21	0.79	0.098
8c	1.0	0.20	NI	NI

NI: no inhibition at 2 mM concentration.

Glycosidase inhibitory study: The glycosidase inhibitory activity against α-glucosidase (yeast), β-glucosidase (almonds), α-galactosidase (green coffee beans), β-galactosidase (*Kluyveromyces lactis*) for compounds **8a–c** was studied and the IC_{50} values are summarized in Table 1. The residual hydrolytic activities of the glycosidases were measured spectrometrically of the corresponding chromogenic nitrophenyl glycosides as substrates in aqueous phosphate buffer at pH 6.8. All the enzymes and substrates were purchased from Sigma–Aldrich Co., U.S.A.

The assays performed with fixed concentration of the substrate (1.6 mM) in phosphate buffer and enzyme concentration is 100 μl (1 mg/ml) in 20 ml of substrate solution. Substrate and compounds were preincubated for 1 min and the reaction was started by the addition of the enzyme. The reaction for enzyme activity was followed for 5 min at 405 nm.

The compounds **8a** and **8b** have shown better inhibition against β-galactosidase and the deoxy compound **8b** also exhibited good inhibition against α-glucosidase.

In conclusion we have successfully demonstrated a general strategy for the synthesis of some novel *N*-benzyl aminocyclopentitols. Also we studied their activity against glycosidases. The salient features of our approach are nucleophilic addition on lactamine for the introduction of chiral amino group and efficient preparation of 1,1-disubstituted olefin for the RCM using Eschenmoser's salt. This strategy is also helpful in designing related skeletons for better activity. Application of this strategy for higher membered amino carbasugars and azasugars is under progress in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.011.

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19. Compounds **19** and **21** were transformed to their acetate derivatives (**21** gave only mono acetylated product). In their ^{1}H NMR spectrum, protons at ***OAc*** bearing carbons appeared as singlets at δ 4.8 and δ 4.7, respectively, thus confirming their orientation as *trans* to adjacent proton.

20. (a) *Data of compound* **8a**: colorless oil $[\alpha]_D^{28}$ −19.5 (*c* 1.8, MeOH); ^{1}H NMR (400 Mhz, D_2O): 7.36 (m, 5H), 4.12 (m, 1H), 4.11 (d, 1H, 13.2 Hz), 3.97 (d, 1H, 13.2 Hz), 3.83 (dd, 1H, 6.6, 8.3 Hz), 3.64–3.74 (m, 4H), 2.11–2.19 (m, 1H); ^{13}C NMR (75 MHz, D_2O): 45.56, 50.99, 57.18, 60.41, 69.66, 76.69, 77.16, 129.93, 130.34, 130.4, 131.1; IR (neat): 3384, 2926, 1641, 1424, 1027 cm^{-1}; HRMS (ESI) for $C_{13}H_{20}NO_4$ calcd: 254.1392, found: 254.1404.
(b) *Data of compound* **8b**: colorless oil $[\alpha]_D^{28}$ −15.8 (*c* 0.3, MeOH); ^{1}H NMR (400 MHz, D_2O): 7.46 (m, 5H), 4.35 (d, 1H, *J* = 12.9 Hz), 4.24 (d, 1H, *J* = 12.9 Hz), 4.18 (t, 1H, *J* = 4.1 Hz), 4.05–4.13 (m, 1H), 3.66–3.73 (m, 3H), 2.46–2.56 (m, 1H), 2.08–2.18 (m, 1H), 1.44–1.53 (m, 1H). ^{13}C NMR (75 MHz, D_2O): 32.72, 37.97, 51.59, 60.27, 62.4, 71.0, 71.38, 129.91, 130.37, 131.23; IR (neat): 3386, 2924, 2854, 1460, 1120 cm^{-1}; HRMS (ESI) for $C_{13}H_{20}NO_3$: calcd: 238.1443, found: 238.1445.
(c) *Data of compound* **8c**: colorless oil $[\alpha]_D^{28}$ −21.0 (*c* 0.6, MeOH), ^{1}H NMR (400 MHz, D_2O): 7.38 (m, 5H), 4.08 (br t, 1H, 3.7 Hz), 3.99 (d, 1H, *J* = 12.5 Hz) 3.87 (d, 1H, *J* = 12.5 Hz), 3.77–3.84 (m, 2H), 3.62 (s, 1H), 3.19 (d, 1H, 3.68). ^{13}C NMR (75 MHz, D_2O): 51.66, 65.6, 66.4, 68.39, 75.91, 76.23, 77.61, 128.83, 129.49, 129.55, 137.03; IR (neat): 3312, 2926, 1600, 1455 cm^{-1}, HRMS (ESI) for $C_{13}H_{20}NO_5$: calcd: 270.1341, found: 270.1337.