Tetrahedron Letters 50 (2009) 5827–5830

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Intramolecular ketonitrone-olefin cycloaddition reaction: direct and stereocontrolled synthesis of nitrogenated quaternary centered aminocyclopentitols as galactosidase inhibitors

Y. Suman Reddy, P. Kadigachalam, Venkata Ramana Doddi, Yashwant D. Vankar *

Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur 208 016, India

ARTICLE INFO

Article history:
Received 8 July 2009
Revised 29 July 2009
Accepted 31 July 2009
Available online 9 August 2009

Keywords:
Ketonitrone
Cycloaddition
Aminocyclopentitol
Glycosidase inhibitors

ABSTRACT

Synthesis of nitrogenated quaternary centered polyhydroxylated aminocyclopentanes by implementation of ketonitrone-olefin cycloaddition reaction as a key step has been accomplished in a stereocontrolled manner. The target molecules were found to be moderate but selective inhibitors of galactosidases.

Synthesis of novel heterocyclic ring systems and polyhydroxylated carbocycles from sugars by using intramolecular nitrone-alkene cycloaddition (INAC) reaction[1] has gained importance in recent times. The derived cycloadducts bearing an amino functionality emanating due to INAC reactions can serve as excellent precursors for the synthesis of carbamino sugars, some natural products, and their analogs.[2] In INAC reactions, ketonitrone-olefin cycloaddition reaction is particularly useful for the synthesis of nitrogenated quaternary centered molecules.[3,4] Inspite of its synthetic potential it has received little attention,[4] as compared to reactions of nitrones derived from aldehydes.[1a,5]

Over the last few years, synthesis of glycosidase inhibitors has become one of the promising areas of research in organic chemistry.[6] Because of their crucial role in biological events, glycosidase inhibitors are used in the treatment and study of a wide range of diseases such as diabetes,[7] viral infections,[8] and cancer.[9] Amongst glycosidase inhibitors, aminocyclopentitols are an important class of compounds and their chemistry is of significance in medicinal chemistry as well as natural products chemistry.[10] Aminocyclopentitols are structurally similar to sugars and therefore they are also called as aminocarbasugars.[11] These contain three hydroxy groups along with one free or substituted amino group.[12] The core structure of aminocyclopentitol system is present in a growing number of natural products. For example, an important group of naturally occurring glycosidase inhibitors (Fig. 1) bearing aminocyclopentitol moiety includes mannosidase inhibitor mannostatin A **1**, the carbocyclic nucleosides viz. aristeromycin **2**, neplanocin A **3**, and analogs such as *epi*-5′-nor-aristeromycin **4** and the selective trehalase inhibitor trehazolin **5**. Another important aminocyclopentitol BCX-1812 **6** is a neuraminidase inhibitor and it is in clinical development to treat influenza.[13] Besides these, many other polyhydroxylated five- and six-membered and bicyclic aza heterocycles and their analogs are potent glycosidase inhibitors.[14a] Because of their remarkable structural features and ability to act as carbohydrate mimics,[14b] there has been an explosive growth in design, synthesis and biological evaluation of new glycosidase inhibitors.[15]

In conjunction with our interest toward the synthesis of natural and unnatural azasugars, carbasugars, and hybrid sugars as glycosidase inhibitors[16] and in view of the potential of the intramolecular ketonitrone-olefin cycloaddition reaction, we hereby report on the synthesis of nitrogenated quaternary centered polyhydroxylated aminocyclopentanes (aminocyclopentitols) from commercially available *tetra-O*-benzyl-D-glucopyranose. Retrosynthetic analysis for our approach is shown in Scheme 1 which indicates the implementation of intramolecular ketonitrone-olefin cycloaddition reaction as a key step.

Our synthesis of the target aminocyclopentitol system began with the Wittig methylenation of commercially available *tetra-O*-benzyl-D-glucopyranose **7** (Scheme 2) by Martin's modified procedure[17] to give the corresponding heptenitol **8** in high yield. This secondary alcohol was subjected to oxidation by pyridinium chlorochromate (PCC) which produced the ketone **9**.

* Corresponding author. Tel.: +91 512 2597169; fax: +91 512 259 0007.
E-mail address: vankar@iitk.ac.in (Y.D. Vankar).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.07.157

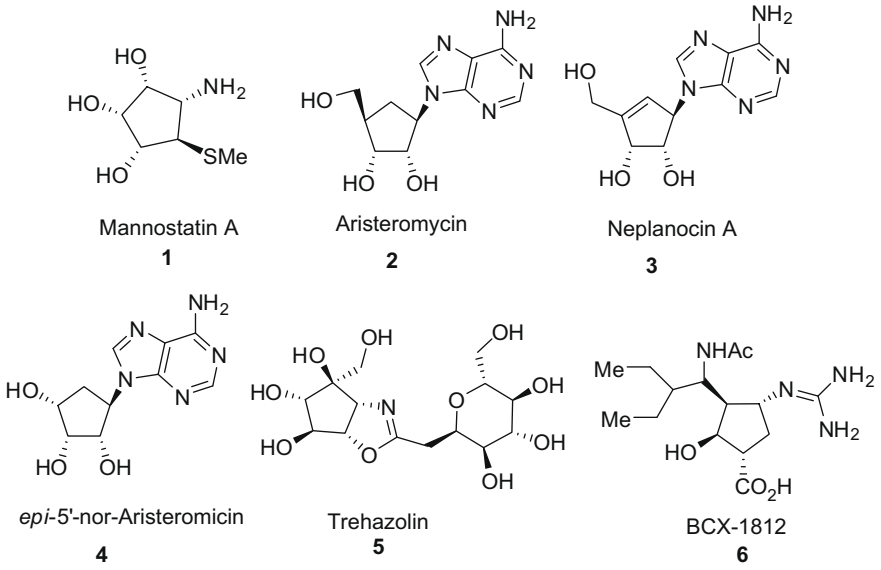
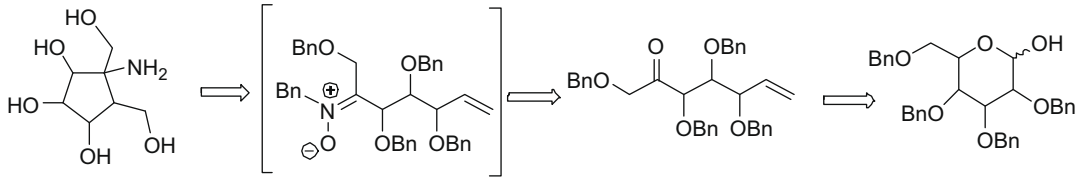
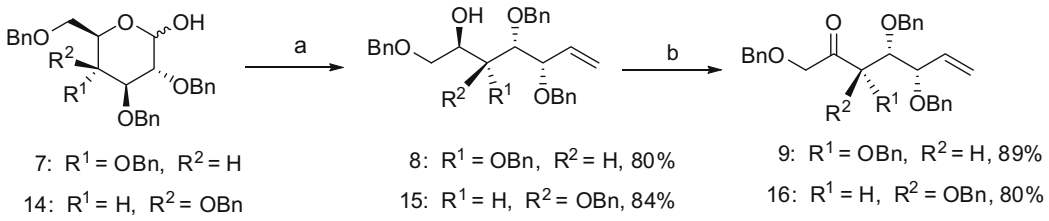


Figure 1. Structures of some biologically important aminocyclopentitols.



Scheme 1. The retrosynthetic analysis of aminocyclopentitols.

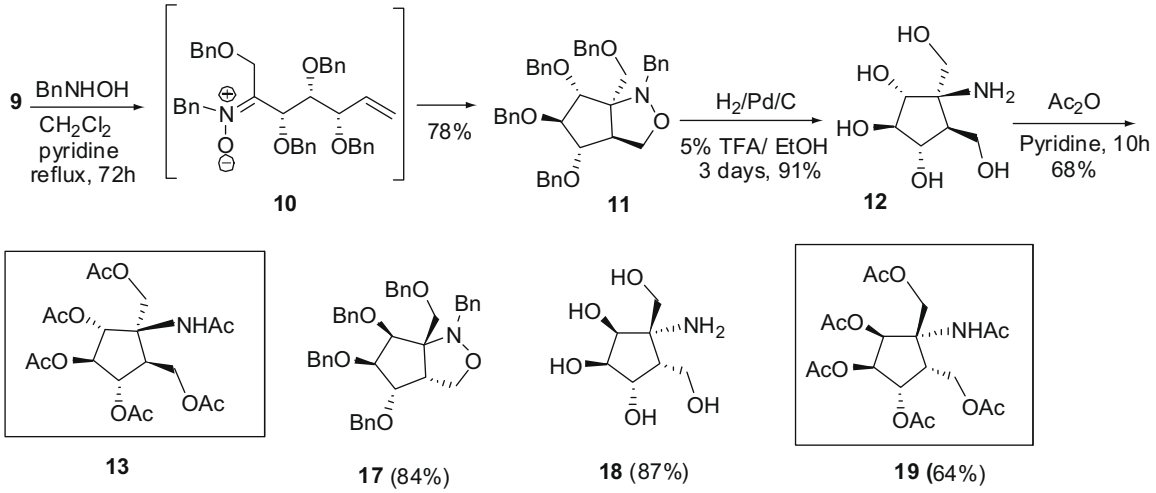


Scheme 2. Reagents and conditions: (a) $Ph_3P^+CH_3\ Br^-$ (3 equiv), *n*-BuLi (6 equiv), toluene, rt, 48 h; (b) PCC (1.8 equiv), molecular sieves 3 Å, CH_2Cl_2, 1 h.

Intramolecular ketonitrone-olefin cycloaddition reaction on ketone **9** upon treatment with *N*-benzylhydroxylamine in methylene chloride in the presence of dry pyridine readily led to the formation of *bis*-isoxazolidine **11** in 78% yield via intermediate **10** (Scheme 3). In order to obtain the target aminocyclopentitol system, global deprotection was carried out by catalytic hydrogenation in 5% TFA/EtOH with 6 bars of H_2 for 3 days, which resulted in cleavage of the N–O bond and removal of all the benzyl protecting groups. The product **12** was isolated in 91% yield by passing over a column of Dowex 50 resin. This compound was characterized as its acetate **13** which was obtained in 68% yield upon acetylation of **12** using Ac_2O/pyridine. The structure and stereochemical outcome of the aminocyclopentitol was deduced from COSY, NOE, and other spectral data[18] of its peracetylated derivative **13**. In an NOE experiment, irradiation of the signal for H-5 led to the enhancement (Fig. 2) of the signal for H-2, H-7, and H-7′ and there was no enhancement of the signals for N–H and H-3. This suggested that H-2, H-5, carbon side chain containing H-7 and H-7′ are in cis relationship. Therefore it was concluded that the two carbon side chains are trans to each other whereas the acetoxy groups at C-1 and C-3 are α-oriented, and the acetoxy groups at C-2 and NHAc are β-oriented. These NOE observations confirm the absolute stereochemistry of newly generated chiral centers as 4*R* and 5*S*, respectively.

Further investigations on the intramolecular ketonitrone-olefin cycloaddition were undertaken using ketone **16**, which was prepared from D-galactose using the same synthetic sequence and reaction conditions as shown in Scheme 3 for the conversion of **9** to **13**.

The stereochemical outcome of compound **18**, obtained from **16**, was confirmed from the COSY and NOE (Fig. 2) spectral data of the corresponding peracetylated derivative **19.** In an NOE experiment the irradiation of the signal for H-5 led to the enhancement of the signal for H-7 and H-7′ and there was no enhancement of the signals for H-3 and H-2. This indicated that H-5, H-7, and H-7′ are in cis relationship. Thus, it was concluded that the two carbon side chains are trans to each other, whereas the acetoxy groups at C-2 and C-3 are β-oriented. This confirmed the absolute stereochemistry of the newly generated chiral centers as 4*S* and 5*R*, respectively.



Scheme 3. The stereocontrolled synthesis of aminocyclopentitols.

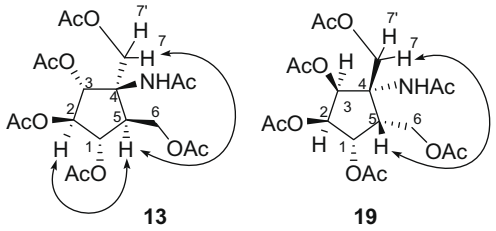
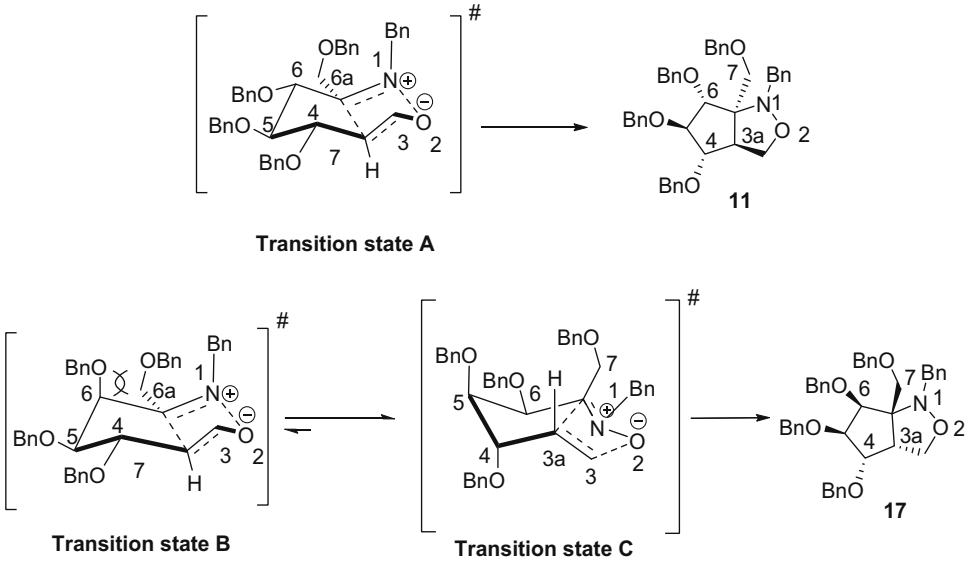


Figure 2. The NOE analysis of compounds **13** and **19**.

The obtained stereochemistry of these molecules can be explained by the following transition state analysis. During the conversion of D-glucose-derived ketone into the corresponding cycloadduct, the transition state **A** in which nitrone and olefin could orient in *exo* manner and then the formation of the 5-membered ring occur in such a way that –H and the $-CH_2OBn$ group are cis to each other at the ring junction (Scheme 4). In D-galactose-derived case, a closely related transition state **C** is favored, in which $-CH_2OBn$ and the C-6 OBn group avoid repulsive interactions present in transition state **B** as was evident by the inspection of molecular models. These transition state analyses support the stereochemical outcome proved by NOE experiments of the final acetate derivatives **13** and **19**.

Enzyme inhibition studies: The inhibitory activity of aminocyclopentitols **12** and **18** were tested against five commercially available glycosidases. Thus, aminocyclopentitol **12** was active only against β-galactosidase (bovine liver) (IC_{50} = 0.4 mM), while aminocyclopentitol **18** was active against α-galactosidase (coffee beans) (IC_{50} = 0.2 mM); otherwise compounds were inactive up to 3 mM. Although these compounds are not as strongly active as mannostatin A, an α-mannosidase inhibitor[19] with IC_{50} = 160 nm, and trehazolin, a trehalase inhibitor[20] with IC_{50} = 27 nm, they are specific galactosidase inhibitors. It is expected that further structural modifications may lead to improved inhibitions.

In conclusion, we have developed a direct and efficient route to the synthesis of nitrogenated quaternary centered polyhydroxylated aminocyclopentanes (aminocyclopentitols) with full stereochemical control by using intramolecular ketonitrone-olefin cycloaddition as a key step. To the best of our knowledge, these are the first examples of aminocyclopentitols bearing an amino group at the quaternary center that act as galactosidase inhibitors. Compounds **12** and **18** showed specific inhibition toward β-galactosidase and α-galactosidase, respectively.



Scheme 4. Proposed transition states of intramolecular ketonitrone-olefin cycloaddition reaction

Acknowledgments

We thank the Department of Science and Technology, New Delhi, for financial support to one of us (Y.D.V.) in the form of Ramanna Fellowship (Grant No. SR/S1/RFOC-04/2006). Y.S.R. thanks CSIR, New Delhi, for a senior research fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.157.

References and notes

1. (a) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990–2016; (b) Koumbis, A. E.; Gallos, J. K. *Curr. Org. Chem.* **2003**, *7*, 585–628; (c) Osborn, H. M. I.; Gemmell, N.; Harwood, L. M. *J. Chem. Soc., Perkin Trans 1* **2002**, 2419–2438; (d) Shing, T. K. M.; Wong, A. W. F.; Ikeno, T.; Yamada, T. *J. Org. Chem.* **2006**, *71*, 3253–3263.
2. (a) Tufariello, J. J.. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, pp 83–168; (b) Shing, T. K. M.; Wong, A. W. F.; Ikeno, T.; Yamada, T. *Org. Lett.* **2007**, *9*, 207–209.
3. (a) Torrente, S.; Noya, B.; Branchadell, V.; Alonso, R. *J. Org. Chem.* **2003**, *68*, 4772–4783; (b) Torrente, S.; Noya, B.; Paredes, M. D.; Alonso, R. *J. Org. Chem.* **1997**, *62*, 6710–6711.
4. (a) White, J. D.; Blakemore, P. R.; Korf, E. A.; Yokochi, A. F. T. *Org. Lett.* **2001**, *3*, 413–415; (b) Snider, B. B.; Lin, H. *Org. Lett.* **2000**, *2*, 643–646; (c) Williams, G. M.; Roughley, S. D.; Davies, J. E.; Holmes, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 4900–4901; (d) Werner, K. M.; de los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1999**, *64*, 686–687. 4865–4873; (e) Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778–7786; (f) Marotta, E.; Righi, P.; Rosini, G. *Tetrahedron Lett.* **1998**, *39*, 1041–1044.
5. For the 1,3-dipolar cycloaddition of glycosyl aldonitrones, see: (a) Fisera, L.; Al-Timari, V. A. R.; Ertl, P. In *Cycloaddition Reactions in Carbohydrate Chemistry*; Giuliano, R. M., Ed.; ACS Symposium Series No. 494; American Chemical Society: Washington, DC, 1992. Chapter 11; For the intramolecular cycloaddition of sugar-derived aldonitrones, see: (b) Sharma, G. V. M.; Reddy, K. R.; Sankar, A. R.; Kunwar, A. C. *Tetrahedron Lett.* **2001**, *42*, 8893–8896; (c) Shing, T. K. M.; Zhong, Y.-L. *Tetrahedron* **2001**, *57*, 1573–1579; (d) Pal, A.; Bhattacharjya, A.; Mukhopadhyay, R. *Tetrahedron Lett.* **2000**, *41*, 10135–10139; (e) Collins, P. M.; Ashwood, M. S.; Eder, H.; Wright, S. H. B.; Kennedy, D. J. *Tetrahedron Lett.* **1990**, *31*, 2055–2058; (f) Ferrier, R. J.; Prasit, P. *J. Chem. Soc., Chem. Commun.* **1981**, 983–985; (g) Borrachero, P.; Cabrera-Escribano, F.; Dianez, M. J. *Tetrahedron: Asymmetry* **2002**, *13*, 2025–2038; (h) Kuban, J.; Kolarovic, A.; Fisera, L.; Jager, V.; Humpa, O.; Pronayova, N.; Ertl, P. *Synlett* **2001**, 1862–1865; (i) Silva, A. M. G.; Tome, A. C.; Neves, M. B. P. M. S.; Silva, A. M. S.; Cavaleiro, J. A. S.; Perrone, D.; Dondoni, A. *Tetrahedron Lett.* **2002**, *43*, 603–605; For transformations of carbohydrate derivatives into functionalized cyclohexanes and cyclopentanes, see: (j) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779–2831; For the conversion of sugar aldonitrones to cycloheptane derivatives, see: (k) Bar, N. C.; Roy, A.; Achari, B.; Mandal, S. B. *J. Org. Chem.* **1997**, *62*, 8948–8951; (l) Marco-Contelles, J.; De Opazo, E. *J. Carbohydr. Chem.* **2002**, *21*, 201–218.
6. (a) Ganem, B. *Acc. Chem. Res.* **1996**, *29*, 340–347; (b) Bols, M. *Acc. Chem. Res.* **1998**, *31*, 1–8; (c) Asano, N. *Glycobiology* **2003**, *13*, 93R–104R.
7. (a) Treadway, J. L.; Mendys, P.; Hoover, D. J. *Exp. Opin. Invest. Drugs* **2001**, *10*, 439–454; (b) Jacob, G. S. *Curr. Opin. Struct. Biol.* **1995**, *5*, 605–611.
8. (a) Chand, P.; Kotian, P. L.; Dehghani, A.; El-Kattan, Y.; Lin, T.-H.; Hutchison, T. L.; Sudhakar Babu, Y.; Bantia, S.; Elliott, A. J.; Montgomery, J. A. *J. Med. Chem.* **2001**, *44*, 4379–4392; (b) Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofbergen, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, W. G.; Stevens, R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681–690.
9. (a) Nishimura, Y.; Satoh, T.; Adachi, H.; Kondo, S.; Takeuchi, T.; Azetaka, M.; Fukuyasu, H.; Iizuka, Y. *J. Med. Chem.* **1997**, *40*, 2626–2633; (b) Zitzmann, N.; Mehta, A. S.; Carrouée, S.; Butters, T. D.; Platt, F. M.; McCauley, J.; Blumberg, B. S.; Dwek, R. A.; Block, T. M. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 11878–11882.
10. Antonio, D. *Eur. J. Org. Chem.* **2008**, 3893–3906.
11. Arjona, O.; Gomez, A. M.; Lopez, J. C.; Plumet, J. *Chem. Rev.* **2007**, *107*, 1919–2036.
12. For recommendations on the nomenclature of cyclitols, see: http://www.chem.qmul.ac.uk/iupac/cyclitol.
13. Smith, B. J.; McKimm-Breshkin, J. L.; McDonald, M.; Fernley, R. T.; Varghese, J. N.; Colman, P. M. *J. Med. Chem.* **2002**, *45*, 2207–2212.
14. (a) De Melo, E. B.; Gomes, A. D. S.; Carvalho, I. *Tetrahedron* **2006**, *62*, 10277–10302; (b) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515–553.
15. Berecibar, A.; Grandjean, C.; Siriwardena, A. *Chem. Rev.* **1999**, *99*, 779–844.
16. (a) Kumar, A.; Rawal, G. K.; Vankar, Y. D. *Tetrahedron* **2008**, *64*, 2379–2390; (b) Ramana, D. V.; Vankar, Y. D. *Eur. J. Org. Chem.* **2007**, *33*, 5583–5589; (c) Reddy, B. G.; Vankar, Y. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 2001–2004; (d) Jayakanthan, K.; Vankar, Y. D. *Org. Lett.* **2005**, *7*, 5441–5444; (e) Jayakanthan, K.; Vankar, Y. D. *Tetrahedron Lett.* **2006**, *49*, 8667–8671; (f) Rawal, G. K.; Rani, S.; Kumar, A.; Vankar, Y. D. *Tetrahedron Lett.* **2006**, *47*, 9117–9120; (g) Rani, S.; Agarwal, A.; Vankar, Y. D. *Tetrahedron Lett.* **2003**, *44*, 5001–5004.
17. Martin, O. R.; Saavedra, O. M.; Xie, F.; Liu, L.; Picasso, S.; Vogel, P.; Kizu, H. *Bioorg. Med. Chem.* **2001**, *9*, 1269–1278.
18. Experimental data of selected compounds: (3a*S*,4*S*,5*R*,6*R*,6a*R*)-1-benzyl-4,5,6-tris(benzyloxy)-6a-(benzyloxymethyl)hexahydro-1*H*-cyclopenta[*c*]isoxazole (**11**): To a stirred solution of the requisite ketone **9** (536 mg, 1 mmol) in methylene chloride (9 mL), benzylhydroxylamine (369 mg, 3 mmol) and pyridine (242 μL, 3 mmol) were added. The reaction mixture was heated to reflux for 72 h. On cooling, the reaction mixture was poured into water and extracted with dichloromethane (3 × 8 mL). Usual work-up thereafter gave a crude product whose purification gave bis-isoxazolidine **11** (517 mg) as a colorless thick liquid. Yield: 78%. R_f: 0.40 (hexane:ethyl acetate, 9:1), $[\alpha]_D^{28}$ +25 (*c* 0.85, CH_2Cl_2). IR (neat) ν_{max}: 3086, 3062, 3029, 2865, 1604, 1495, 1453, 1361, 1308, 1207, 1092, 1027, 909, 807, 734, 697, 602 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34–7.21 (m, 25H, Ar–H), 4.93 (d, 1H, *J* = 11.7 Hz, O–CH_2Ph), 4.88 (d, 1H, *J* = 11.4 Hz, O–CH_2Ph), 4.75 (d, 1H, *J* = 11.4 Hz, O–CH_2Ph), 4.73 (d, 1H, *J* = 11.7 Hz, O–CH_2Ph), 4.64–4.52 (m, 4H, O–CH_2Ph), 4.30 (overlapping dd, 1H, *J* = 8.8 Hz, H-5), 4.13 (d, 1H, *J* = 9.2 Hz, H-6), 3.94 (d, 1H, *J* = 14.8 Hz, N–CH_2Ph), 3.83 (d, 2H, *J* = 10.2 Hz, H-7, H-3), 3.68 (dd, 2H, *J* = 15.1, 8.8 Hz, H-4, N–CH_2Ph), 3.57 (d, 1H, *J* = 10.2 Hz, H-7′), 3.50 (d, 1H, *J* = 8.8 Hz, H-3′), 3.03–3.01 (m, 1H, H-3a). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7–138.1 (m), 128.4–126.9 (m), 87.39, 86.03, 80.33, 73. 190, 73.62, 72.94, 72.58, 71.81, 71.25, 69.34, 54.49, 52.26. ESMS: *m*/*z* 664.303 $[M+Na]^+$. Anal. Calcd for $C_{42}H_{43}NO_5$: C, 78.60; H, 6.75; N, 2.18; O, 12.46. Found: C, 78.62; H, 6.69; N, 2.23.

(1S,2R,3S,4R,5S)-4-Amino-4,5-bis(hydroxymethyl) cyclopentane-1,2,3-triol (**12**): Compound **11** (332 mg, 0.5 mmol) was dissolved in 5% of TFA/EtOH (8 mL), 10% Pd/C (249 mg) was added and this mixture was hydrogenated under 6 bars H_2 for 3 days at room temperature. The catalyst was filtered off through celite and the filtrate was concentrated in vacuo. Passing over a column of Dowex 50 resin gave **12** (87 mg) as a thick liquid. Yield: 91% R_f = 0.45 (MeOH/EtOAc, 3:7). $[\alpha]_D^{28}$ +4.7 (*c* 1.0, MeOH). ^1H NMR (400 MHz, D_2O): δ 3.57 (m, 3H), 3.46–3.44 (m, 2H), 3.38 (m, 2H), 1.73 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 73.06, 71.56, 71.19, 69.51, 60.51, 54.99, 48.85.

(1S,2R,3R,4R,5S)-4-Acetamido-4,5-bis(acetoxymethyl) cyclopentane-1,2,3-triyl triacetate (**13**): Compound **12** (40 mg, 0.2 mmol) was subjected to acetylation with excess of pyridine and Ac_2O (1:1, 2 mL) at room temperature for 10 h. Usual work-up and purification by column chromatography gave **13** (63 mg) as a colorless oil. Yield: 68% R_f = 0.5 (hexane/EtOAc, 1:1). $[\alpha]_D^{28}$ −20 (*c* 1.0, CH_2Cl_2). IR (neat) ν_{max}: 3358, 2924, 2853, 1744, 1678, 1537, 1463, 1367, 1231, 1030, 896, 722 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.62 (s, N–H), 5.55 (d, 1H, *J* = 8.0 Hz, H-3), 5.44 (dd, 1H, *J* = 8.0, 6.0 Hz, H-2), 5.34 (t, 1H, *J* = 6.0 Hz, H-1), 4.44 (t, 2H, *J* = 12.0 Hz, H-7, H-7′), 4.28 (dd, 1H, *J* = 12.0, 11.5 Hz, H-6), 4.20 (dd, 1H, *J* = 12, 11.5 Hz, H-6′), 2.61–2.58 (m, 1H, H-5), 2.12–2.09 (m, 15H), 1.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.89, 170.81, 170.36, 170.27, 170.13, 79.69, 75.69, 63.90, 62.74, 62.54, 47.51, 23.67, 21.05–20.85 (m). ESMS: *m*/*z* 468.148 $[M+Na]^+$. Anal. Calcd for $C_{19}H_{27}NO_{11}$: C, 51.23; H, 6.11; N, 3.14 O, 39.51. Found: C, 51.20; H, 6.05; N, 3.19.
19. Tropea, J. E.; Kaushal, G. P.; Pastuszak, I.; Mitchell, M.; Aoyagi, T.; Molyneux, R. J.; Elbein, A. D. *Biochemistry* **1990**, *29*, 10062–10069.
20. Ando, O.; Nakajima, M.; Kifune, M.; Fang, H.; Tanzawa, K. *Biochim. Biophys. Acta* **1995**, *1244*, 295–302.