Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 9035–9038

Synthesis of chiral non-proteinogenic 4,5-dihydroxytetrahydropyran derived α-amino acids from D-mannitol

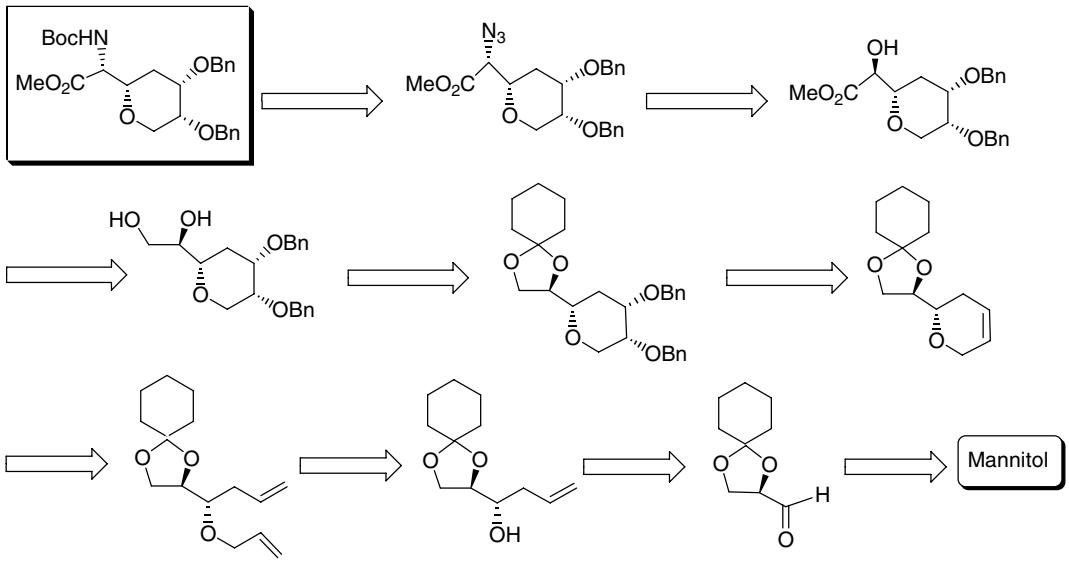
Anita Brar and Yashwant D. Vankar*

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

Received 5 September 2006; revised 10 October 2006; accepted 19 October 2006

Abstract—Starting from *R*-2,3-*O*-cyclohexylideneglyceraldehyde, which was obtained from D-mannitol, four tetrahydropyran derived chiral, non-proteinogenic α-amino acids have been synthesized. The key step in these syntheses is the ring closing metathesis using the first generation Grubbs' catalyst.

Alpha-amino acids are the fundamental building blocks of proteins as well as peptides which carry out various biological processes including catalysis, gene regulation, signal transduction and immune response.[1] In order to modify and improve the physical properties such as stability and bioavailability, and biological properties such as receptor affinity, DNA-binding specificity, antibiotic and antitumour activity of peptides, there have been many reports[2] in the literature on the use of non-proteinogenic α-amino acids.[3,4] Additionally, non-proteinogenic



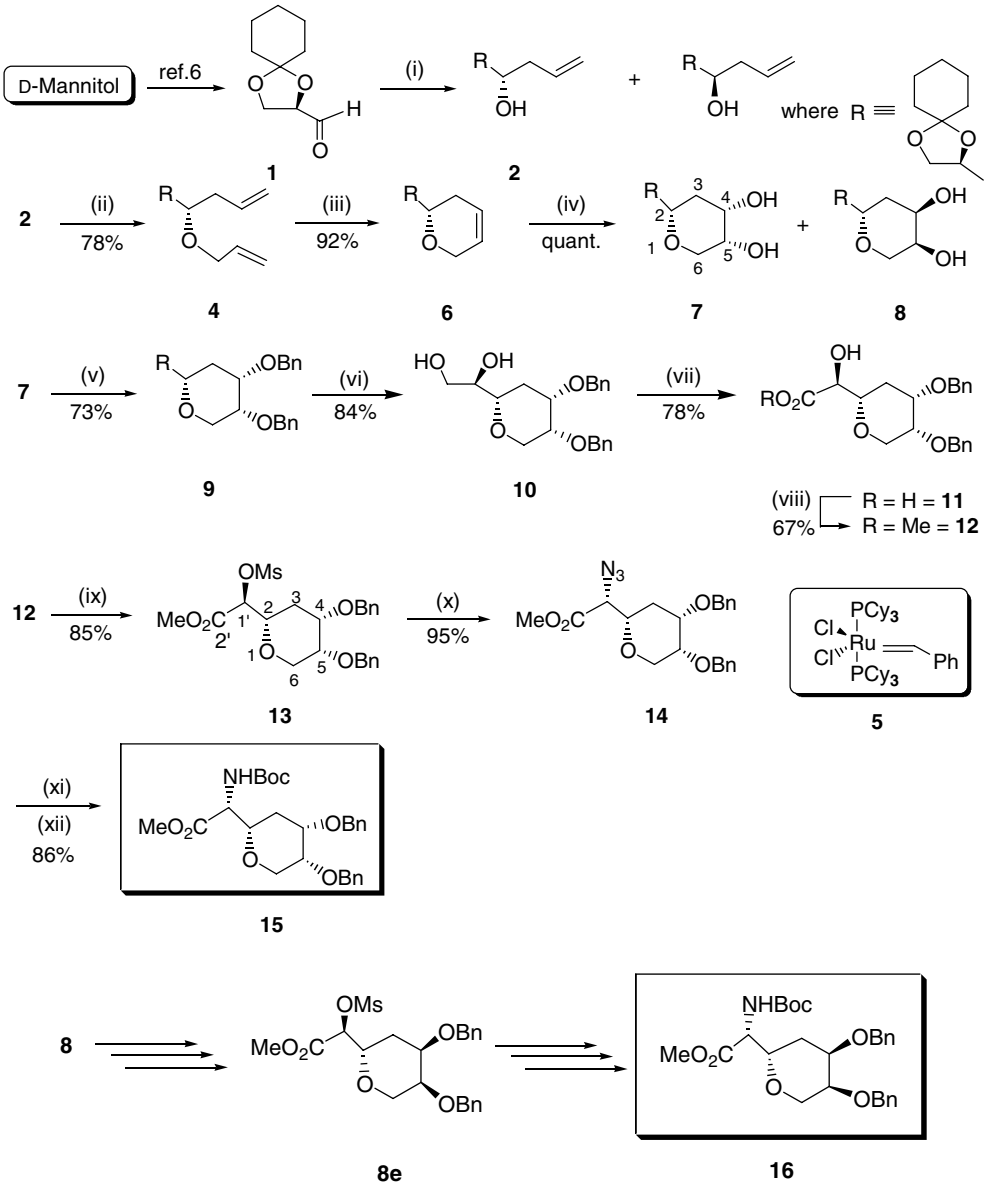
Scheme 1.

Keywords: α-Amino acids; Non-proteinogenic; D-Mannitol; *R*-2,3-*O*-Cyclohexylideneglyceraldehyde.
* Corresponding author. Tel.: +91 512 2597169; fax: +91 512 259 7436; e-mail: vankar@iitk.ac.in

0040-4039/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2006.10.099

amino acids also serve[5] as useful building blocks in the synthesis of alkaloids and other natural products. Clearly, the development of new non-proteinogenic amino acids is important in view of the above described usefulness in organic synthesis. In this letter, we wish to report the synthesis of four new 4,5-dihydroxytetrahydropyran based amino acid analogs starting from *R*-2,3-*O*-cyclohexylideneglyceraldehyde.[6] It was expected that the protected 1,2-diol unit in *R*-2,3-*O*-cyclohexylideneglyceraldehyde would enable the formation of the α-amino acid part. Retrosynthetic analysis towards the synthesis of pyranoid based sugar amino acids is shown in Scheme 1.

R-2,3-*O*-Cyclohexylideneglyceraldehyde **1** (Scheme 2), obtained[6] from D-mannitol, was reacted with allyl zinc bromide to give a 7:3 diastereomeric mixture of *anti*–*syn* allylic alcohols **2** and **3** in a 78% yield. The two diastereomers were separated and allylic alcohol **2** was reacted with allyl bromide in the presence of NaH to afford diene **4** (Scheme 2) in a 78% yield. Ring closing metathesis of diene **4** using 2 mol % of the first generation Grubbs' catalyst[7] **5** led to the formation of the corresponding dihydropyran derivative **6** in a 92% yield. Dihydroxylation of **6** with OsO_4/NMO gave a 1:1.6 mixture of diols **7** and **8** in a quantitative yield, which were readily separated by column chromatography. Attempts to improve the diastereoselectivity using ADmix-β did not lead to positive results. The indicated stereochemistry of **7** at C-4 and C-5 was assigned on the basis of ^{1}H NMR spectral analysis, and COSY and NOE data of mesylate **13**, obtained later (vide infra). At this stage,



Scheme 2. Reagents and conditions: (i) allyl bromide, Zn dust, aq NH_4Cl, THF, rt, 4 h; (ii) allyl bromide, NaH, THF, rt, 1.5 h; (iii) 2 mol % Grubbs' catalyst **5**, rt, 20 min; (iv) OsO_4, NMO, $(CH_3)_2CO/H_2O/t$-BuOH (1:1:0.5), $Na_2S_2O_5$, quantitative yield, 2 h; (v) NaH, BnBr, DMSO, rt, 7 h; (vi) MeOH/HCl, rt, 1 h; (vii) TEMPO, NaOCl, $NaHCO_3$, KBr, $(CH_3)_2CO$, 0 °C, 2 h; (viii) CH_2N_2, THF, rt, 20 min; (ix) MsCl, pyridine, CH_2Cl_2, rt, 1 h; (x) NaN_3, DMF, rt, 4 h; (xi) PPh_3, H_2O, THF, rt, 1.5 h; (xii) $(Boc)_2O$, Et_3N, DCM, rt, 5 h.

however, diol **7** was protected as the corresponding dibenzyl ether **9** followed by the cleavage of the cyclohexylidene unit with MeOH/HCl to form diol **10** in an 84% yield. The primary hydroxyl group was oxidized with NaOCl/TEMPO[8] and the corresponding α-hydroxy acid **11**, obtained in a 78% yield, was then esterified with diazomethane to give methyl ester **12** in a 67% yield. In order to introduce an amino functionality, the hydroxyl group was mesylated in a 85% yield with methanesulfonyl chloride in the presence of pyridine. Mesylate **13** was used for establishing the stereochemistry since the stereochemistry at C-2 was not expected to change during the course of these reactions. COSY data was used to assign the proton chemical shifts following which NOE experiments and homonuclear decoupling permitted the absolute stereochemical assignments (Fig. 1). The homonuclear decoupling of H-1′ at δ 5.18 converted a triplet of doublets for H-2 at δ 3.89 to a doublet of doublets ($J = 11.7$ and 2.7 Hz) indicating that H-2 was axially oriented. In the NOE experiment, irradiation of the signal as peak at δ 3.51 for H-4 led to the enhancement of the signals for H-2 at δ 3.89 and for H-5 at δ 3.68, thereby establishing the cis relationship between H-2, H-4 and H-5. Further, in this NOE experiment, resonances corresponding to one of the two methylene protons at C-3 and C-6 at δ 1.70 and 3.36, respectively, were also enhanced. In addition, the irradiation of H-2 at δ 3.89 led to the enhancement of the signals at δ 3.51 for H-4 and resonances corresponding to one of the two methylene protons at C-3 and C-6 at δ 1.70 and 3.36, respectively. These data favour the structure indicated for compound **13**. Treatment of mesylate **13** with NaN_3 in DMF at room temperature gave azido ester **14** in a 95% yield.

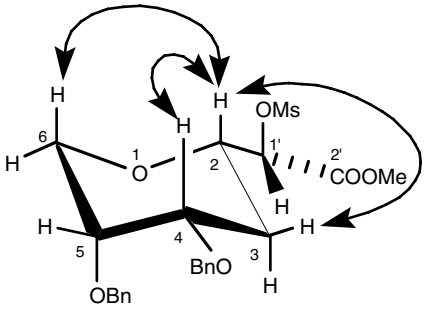
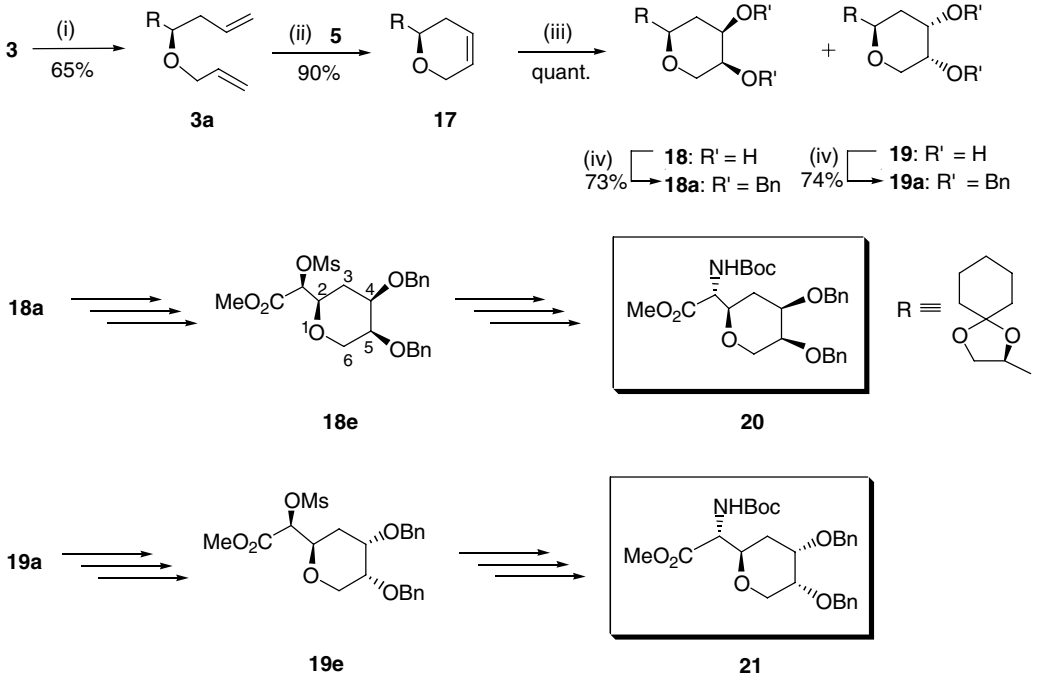


Figure 1. NOE correlations for compound **13**.

Reduction of the azido moiety with Ph_3P–H_2O followed by the protection of the amino group as –NHBoc eventually gave the desired α-amino acid derivative **15** in an 86% yield.

Likewise, isomeric diol **8** was transformed into Boc protected α-amino acid **16** using an analogous sequence of reactions (Scheme 2). The spectroscopic and analytical data for all the compounds in this sequence of reactions (**8** to **16**) are given in the Supplementary data. The absolute stereochemistry of mesylate **8e** was confirmed by NOESY data, which showed that H-2 and H-4, as well as H-2 and H-5 were *anti* to each other.

Allylic alcohol **3** was converted to dihydropyran derivatives **18** and **19** via *syn* diastereomeric diene **3a** using allylation and subsequent ring closing metathesis (Scheme 3) in an analogous manner to compounds **7** and **8**. Dihydroxylation of compound **17** with OsO_4/NMO led to formation of the two diastereomers **18** and **19** in a 1.3:1 ratio and in a quantitative yield. These



Scheme 3. Reagents and conditions: (i) allyl bromide, NaH, THF; (ii) 2 mol % Grubbs' catalyst **5**, rt; (iii) OsO_4, NMO, $(CH_3)_2CO/H_2O/t$-BuOH (1:1:0.5), $Na_2S_2O_5$, quantitative yield; (iv) NaH, BnBr, DMSO, rt.

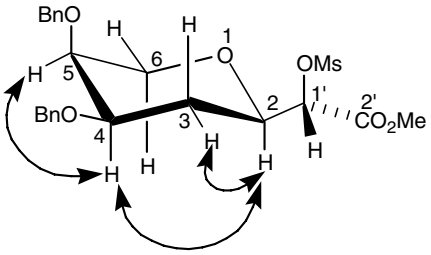


Figure 2. NOE correlations for compound **18e**.

two diastereomers were separated by column chromatography and the hydroxyl groups of the diols were protected as benzyl ethers to form **18a** and **19a**, respectively, which were subsequently converted to the desired amino acid derivatives **20** and **21** following a similar sequence of reactions as followed for converting compound **12**–**15**. The analytical and spectroscopic data for all the intermediate compounds are given in the Supplementary data. In order to assign the absolute stereochemistry of the newly generated stereogenic centres, mesylates **18e** and **19e** were analyzed spectroscopically using COSY, NOESY, and homonuclear decoupling data. Thus, homonuclear decoupling of H-1′ in compound **18e** at δ 5.00 converted the triplet of doublets for H-2 at δ 3.86 to a doublet of doublets ($J = 12.0$ and 1.9 Hz) indicating that H-2 was axially oriented with a diaxial coupling of 12.0 Hz. Further, the NOESY data suggested a cis relationship between H-2, H-4 and H-5. Clearly, the other diastereomer **19e** will have H-2 and H-4, as well as H-2 and H-5 trans to each other; this was also confirmed from the NOESY data. These are in accordance with structure **18e** (Fig. 2) with $^4C_1$ conformation. Thus, in all the structures, it appears that the group at C-2 prefers to occupy an equatorial position.

In summary, D-mannitol, a cheap and commercially available chiral compound can be readily transformed into four different tetrahydropyran derived α-amino acid derivatives of non-proteinogenic origin. These molecules could also be regarded as *C*-glycosyl amino acid derivatives of non-natural origin considering that the sugar moiety is a 5-nor-2-deoxy sugar. While our work was in progress, a report on converting D-serine to glycosyl nucleoside amino acid cores appeared[9] in the literature with the stereochemistry of the serine dictating the stereochemistry of the final products. However, the present approach leads to the formation of stereochemically different amino acids from D-mannitol.

Acknowledgements

We thank the Council of Scientific and Industrial Research, New Delhi, for financial support through a project [01(1892)/03/EMR-II]. One of us (A.B.) thanks the Centre for Development of Technical Education for a Research Scholarship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.10.099.

References and notes

1. (a) Wang, L.; Schultz, P. G. *Chem. Commun.* **2002**, 1; (b) Cornish, V. W.; Mendel, D.; Schultz, P. G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 621.
2. (a) Wang, L.; Brock, A.; Herbereich, B.; Schultz, P. G. *Science* **2002**, *292*, 498; (b) Mendel, D.; Ellman, J. A.; Chang, Z.; Veenstra, D. L.; Kollman, P. A.; Schultz, P. G. *Science* **1992**, *256*, 1798; (c) Isono, K.; Asahi, K.; Suzuki, S. *J. Am. Chem. Soc.* **1969**, *91*, 7490; (d) Lichtenthaler, F. W.; Morino, T.; Menzel, H. M. *Tetrahedron Lett.* **1975**, *9*, 665; (e) Waltho, J. P.; Williams, D. H.; Selva, E.; Ferrar, P. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2263; (f) Lindberg, B. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 279.
3. (a) Seitz, O. *ChemBioChem.* **2000**, *1*, 214; (b) Hilaire, P. M. S.; Lowary, T. L.; Meldal, M.; Bock, K. *J. Am. Chem. Soc.* **1998**, *120*, 13312; (c) Varki, A. *Glycobiology* **1993**, *3*, 97; (d) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683; (e) Imperiali, B. *Acc. Chem. Res.* **1997**, *30*, 452.
4. (a) Dondoni, A.; Marioti, G.; Marra, A. *J. Org. Chem.* **2002**, *67*, 4475; (b) Davis, B. G. *Chem. Rev.* **2002**, *102*, 579; (c) Schweizer, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 230; (d) Dondoni, A.; Marra, A. *Chem. Rev.* **2000**, *100*, 4395.
5. (a) Beck, G. *Synlett* **2002**, 837; (b) Boto, A.; Hernandez, R.; Montoya, A.; Suarez, E. *Tetrahedron Lett.* **2002**, *43*, 8269; (c) O'Donnel, M. J. *Aldrichim. Acta* **2001**, *34*, 3; (d) Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S. *Tetrahedron Lett.* **2002**, *43*, 4495.
6. (a) Chattopadhyay, A. *J. Org. Chem.* **1996**, *61*, 6104; (b) Mamdapur, V. R.; Chattopadhyay, A. *J. Org. Chem.* **1995**, *60*, 585; (c) Suzuki, T.; Sato, E.; Unno, K. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2263.
7. *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH, 2003; vol. 2.
8. Pais, G. C. G.; Maier, M. E. *J. Org. Chem.* **1999**, *64*, 4551.
9. Bhaket, P.; Stauffer, C. S.; Datta, A. *J. Org. Chem.* **2004**, *69*, 8594.