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HIGHLY STEREOSELECTIVE APPROACH FOR β-HYDROXY-α-AMINO ACIDS FROM D-GLUCOSE : THE SYNTHESIS OF MeBmt

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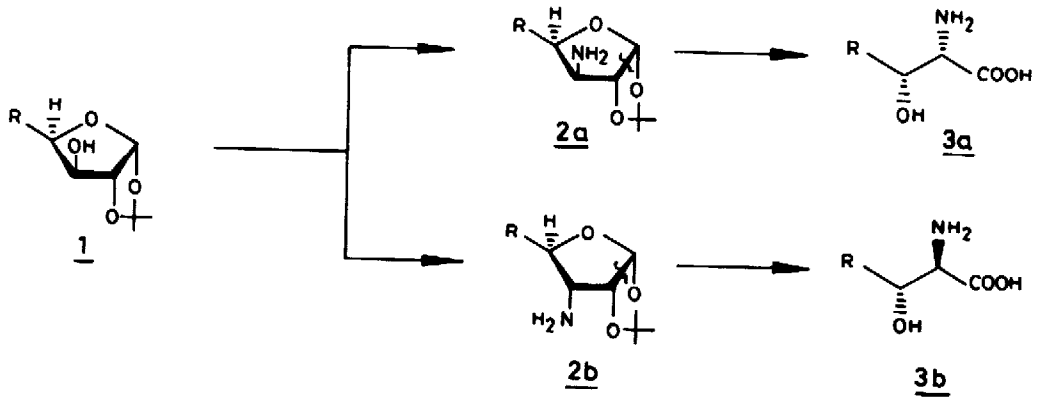
Abstract: A highly stereoselective protocol for the synthesis of β-hydroxy-α-amino acids from glucofuranose has been developed which has culminated in stereospecific synthesis of MeBmt - an unusual aminoacid component of immunosuppressive peptide cyclosporin.

β-Hydroxy-α-amino acids are part of the structure of several biologically active natural peptides such as cyclosporin[1] and echinocandins[2]. Recently we[3] and several others[2,4] have developed elegant approaches for their synthesis which are mainly based on the preparation and hydrolysis of 4-carboxy-5-alkyl oxazolidone derivatives obtainable from epoxide opening[3] or aldol condensation[4], most of which require separation of diastereomers at some stages during the synthesis. Surprisingly, carbohydrates which are available abundantly in enantiomerically pure form have not yet been taken advantage of, for the synthesis of these important class of compounds. We wish to describe for the first time the strategy for stereospecific synthesis of β-hydroxy-α-amino acids from cheaply available D-glucose, which is demonstrated in the total synthesis of MeBmt[(4R)-4-{(E)-2-butenyl}-4,N-dimethyl-L-threonine][3,4].

Our strategy for the β-hydroxy-α-amino acid is based on the synthesis of 3-amino-3-deoxy-1,2-O-isopropylidene glucofuranose derivatives (**2**) having desired alkyl chain at C-4, followed by oxidative cleavage of the resulting diol-derived from deprotection of the 1,2-O-isopropylidene- to carboxylic acid as depicted in scheme I. It can be seen that the configurations of the amino

Scheme I - A strategy

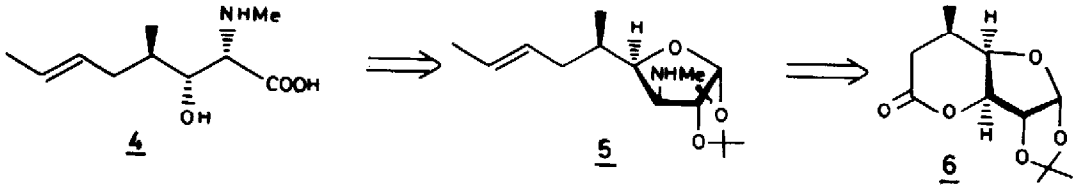


and hydroxy groups in the target **3** are derived from those at C-3 and C-4 of glucofuranose respectively. Thus, it is possible to prepare stereochemically defined **3** from a single chiral progenitor **1** by applying highly predictive transformations[5].

MeBmt (**4**) was selected as a representative example to demonstrate the utility of the above strategy for the synthesis of such class of compounds. MeBmt is present in the backbone of clinically used immunosuppressive cyclic undecapeptide cyclosporin[1] and has been found[6] to play a very critical role in the chemotherapeutic action of the drug. An efficient synthesis of **4**, therefore, would facilitate preparation of large number of analogues to study their structure -activity relationship, which would in turn help in improving the therapeutic index of the drug.

A retrosynthetic analysis of MeBmt (**4**) is represented in scheme II. Therefore, our first concern was to prepare **6** where the critical chirality of the C-5 methyl group corresponding to C-4 methyl in the target molecule **4** can be fixed - and it has been shown how this can be

Scheme II

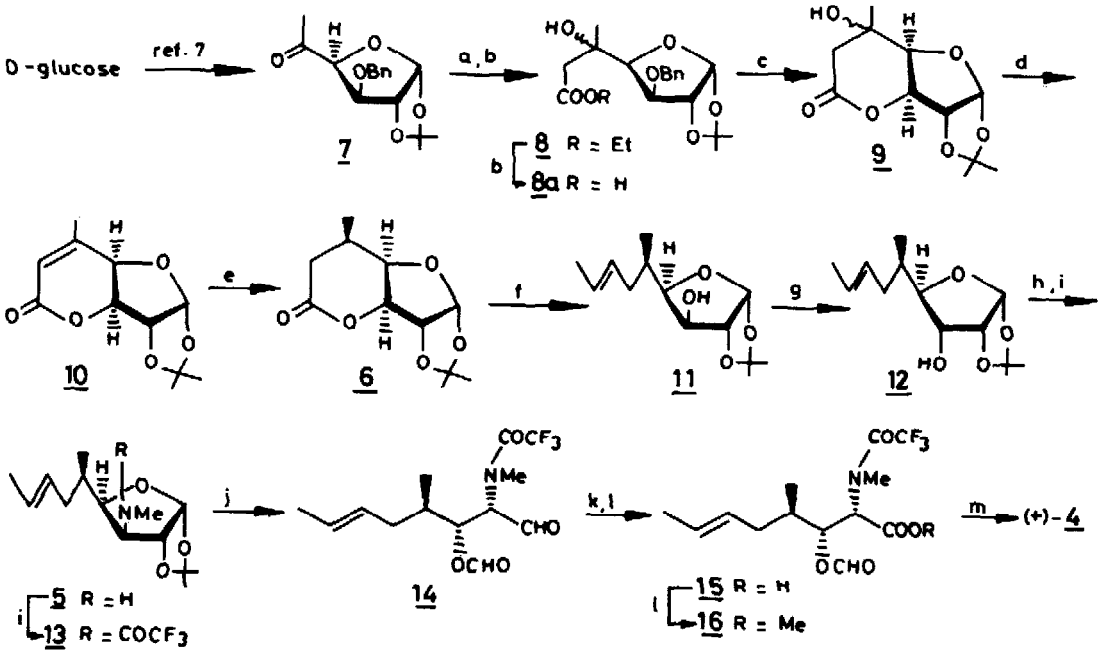


effected using D-glucose (scheme III). Thus, Reformatsky reaction with Zn and ethylbromoacetate on **7**, a known ketone[7] derived from D-glucose, in refluxing benzene gave rise to tertiary carbinol **8** as a mixture of diastereomers which was used as such for the next step, as this newly created centre has to be destroyed later to generate the key olefin **10**. Ester **8** on hydrolysis with alc. KOH to corresponding acid **8a**, followed by catalytic hydrogenolysis of the benzyl group produced the hydroxy lactone **9** in excellent yield. The tertiary alcohol **9** was dehydrated to α,β-unsaturated lactone **10** using MsCl-Et_3N and DMAP (cat) by a procedure devised recently by us[8]. Careful study of the molecular model of **10** clearly indicated that hydrogenation would occur from its less congested α-side, thereby, creating the desired chirality of the methyl group needed in the target molecule (**4**). Hydrogenation of **10** over Rh-Al_2O_3 in ethylacetate at 50 psi afforded **6** $[\alpha]_D$-7.2° (c 0.83, $CHCl_3$) as a sole product as expected, in excellent yield.

Having secured the desired configuration of the methyl group, our next task was to complete the synthesis. Thus, controlled reduction of lactone **6** with DIBAL-H at -78° afforded corresponding lactol which on Wittig olefination with $Ph_3P{=}CHCH_3$ under Schlosser's conditions[9] furnished **11**. Having assembled the required side chain, the pivotal chiron **11**, there remained for us to replace the hydroxyl group at C-3 with N-methylamino group by the retention of the configuration which was achieved successfully by applying double inversion method. For instance, oxidation of alcohol functionality in **11** followed by the reduction of the resulting ketone with sodium borohydride afforded D-allofuranose **12** which was converted into **5** by displacement of the 3-O-triflate of the former, by methylamine in DMF with concomitant inversion of its configuration, in almost quantitative yield. For the purpose of operational convenience the N-methylamino group was protected as trifluoroacetamide (**13**) using $(CF_3CO)_2O$, and Na_2CO_3. The deprotection of the 1,2-O-isopropylidene group with 80% aq. CF_3COOH followed by the cleavage of the diol thus obtained with Lead tetraacetate afforded rather unstable aldehyde **14**, with secondary hydroxyl group already in protected form as formate to our advantage, which circumvented the problem of over oxidation, when we followed the subsequent oxidation of the aldehyde

functionality immediately with Jones' reagent to get acid **15. 15** was characterised as its Methyl ester (**16**) prepared by diazomethane and treated with 2N KOH, when three reactions viz., hydrolysis of ester, formate and trifluoroacetamide occurred simultaneously, to furnish, after usual work up, MeBmt (m.p.238-9°; $[\alpha]_D$ + 12.4 (c 0.32, H_2O, pH 7, phosphate buffer), lit[4c].m.p.240° $[\alpha]_D$+13° (c 0.46, H_2O, pH 7, phosphate buffer).

Scheme III



a) Zn, $BrCH_2COOEt$, C_6H_6, reflux, 95% b) alc.KOH c) Pd-C, H_2, EtOH, 50 psi d) MsCl, Et_3N, DMAP (cat), CH_2Cl_2 e) Rh-Al_2O_3, H_2, EtOAc, 50 psi, 70% from **8a** f) i. DIBAL-H, CH_2Cl_2, -78°, ii. $Ph_3P{=}CHCH_3$, 65% g) i. PDC, Ac_2O, CH_2Cl_2, ii. $NaBH_4$, MeOH, h) i. $(CF_3SO_2)_2O$, pyr. DMAP, CH_2Cl_2, 0°, ii. $MeNH_2$, DMF, 80°, sealed tube, i) $(CF_3CO)_2O$, Na_2CO_3, Ether, 0°, 72% from **11**, j) i. 80:20 CF_3COOH:H_2O, 0°, ii. $Pb(OAc)_4$, CH_2Cl_2, k) Jones' oxidation, -15°, l) CH_2N_2, Ether, m) 2N.KOH, Dowex H^+, 45% from **13**.

It is pertinent to mention here that the configuration of the methyl group at C-5 during hydrogenation step was correctly predicted as 'R'. Thus we have presented a new strategy and operationally novel approach for the stereospecific and expedient synthesis of β-hydroxy-α-amino acids. Thus this strategy should find widespread applications for the synthesis of several other natural products[10].

References and Notes:

1. D.J.G. White (Ed), "Cyclosporin A", Elsevier, Biomedical, Amsterdam, 1982.
2. a) V.R. Traber, C. Keller-Juslen, H.R. Loosli and M. Kuhn, Helv. Chim. Acta., **62**, 1252 (1979); b) D.A. Evans and A.E. Weber, J. Am. Chem. Soc., **109**, 7151 (1987) and references cited therein; c) N. Kurokawa and Y. Ohfune, J. Am. Chem. Soc., **108**, 6041 (1986).
3. A.V. Rama Rao, T.G. Murali Dhar, T.K. Chakraborty and M.K. Gurjar, Tetrahedron Lett., **29**, 2069 (1988).
4. a) J.D. Aebi, M.K. Dhaon and D.H. Rich, J. Org. Chem., **52**, 2881 (1987); b) R.T. Tung and D.H. Rich, Tetrahedron Lett., **28**, 1139 (1987); c) R.M. Wenger, Helv. Chim. Acta., **66**, 2308 (1983); d) D.A. Evans and A.E. Weber, J. Am. Chem. Soc., **108**, 6757 (1986); e) D. Seebach, E. Juaristi, D.D. Miller, C. Schickli and T. Weber, Helv. Chim. Acta., **70**, 237 (1987); f) U. Schmidt and W. Siegel, Tetrahedron Lett., **28**, 2849 (1987).
5. a) S. Hanessian, "Total synthesis of Natural Products: The chiron Approach" Pergamon Press. Oxford (1983); b) A Vasella, 'Chiral Building blocks in enantiomer synthesis - Ex sugars' in "Modern synthetic methods" Ed. R. Scheffold, Salle and Sauerlander, Frankfurt am p.173(1980).
6. a) R.M. Wenger, Angew.Chem., Int. Ed. Engl., **24**, 77 (1985); b) D.H. Rich, M.K. Dhaon, B. Dunlap and S.P.F. Miller., J. Med. Chem., **29**, 978 (1986). c) D.H. Rich, C.Q. Sun, D. Guillavme, B. Dunlap, D.A. Evans, A.E. Weber, J. Med. Chem., **32**, 1982 (1989).
7. a) T.D. Inch, Carbohydrate Research, **5**, 45 (1967); b) D.E. Kiely, J. Walls and R.L. Black, Carbohydrate Research, **31**, 387 (1973).
8. J.S. Yadav and S.V. Mysorekar, Syn. Commun., **19**, 1057 (1989).
9. M. Schlosser and K.F. Christmann, Justus Liebigs Ann. Chem., **708**, 1 (1967).
10. All the compounds gave expected spectroscopic data and exact high resolution mass.

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