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Stereoselective Synthesis of Polyoxamic Acid from (*R*)-Phenylglycine

G. Veeresa and Apurba Datta*

Organic III, Indian Institute of Chemical Technology, Hyderabad - 500 007, India

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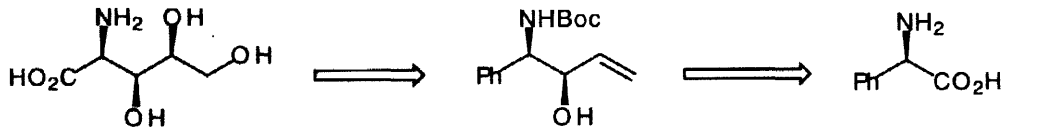
Abstract : An efficient route for the synthesis of the biologically important amino acid, polyoxamic acid (**1**) has been developed *via* a *syn* selective Grignard reaction of vinylmagnesium bromide on (*R*)-*N*-Boc-phenylglycinal and utilization of the phenyl group as a masked carboxyl synthon.

The 1,2-amino alcohol fragment is found in many natural products, in particular as a central moiety of non-proteinogenic amino acids and amino polyols. An important example of the above class of compounds is polyoxamic acid (**1**), component amino acid of the polyoxin group of nucleoside antibiotics.[1] As a consequence of the potent biological activity associated with these compounds[2], a variety of chemical syntheses of polyoxamic acid have been developed over the past several years.[3] However, considering the biological importance of **1** and related compounds, development of new methods for synthesizing this amino acid still remains challenging and worthwhile. Thus, in continuation of our studies on the synthesis of non-proteinogenic hydroxy amino acids of pharmaceutical interest[4] we decided to investigate the synthesis of polyoxamic acid starting from commercially available (*R*)-phenylglycine (**3**). It has been shown that chelation controlled addition of Grignard reagents to *N*-Boc-α-amino aldehydes results in the formation of the corresponding 1,2-amino alcohols with good *syn* diastereoselection.[4b,5,6] Accordingly, the key features of our proposed synthesis involve i) *syn* selective addition of vinylmagnesium bromide to (*R*)-phenylglycinal, affording the amino alcohol **2** (Scheme 1) with required stereochemistry, and ii) utilization of the phenyl group as a carboxylic acid synthon and the vinyl group as a precursor for the *vicinal* diol. The results of the studies are described herein.



1 (Polyoxamic acid) **2** **3** (*R*-Phenylglycine)

Scheme 1

N-Boc-phenylglycinol (**4**) was prepared in a one-pot reaction by lithium aluminium hydride reduction and derivatization of (*R*)-phenylglycine (**3**, Scheme 2). Swern oxidation of **4** followed by *in-situ* reaction of the resulting aldehyde with vinylmagnesium bromide yielded the corresponding allylic alcohol **2** with good

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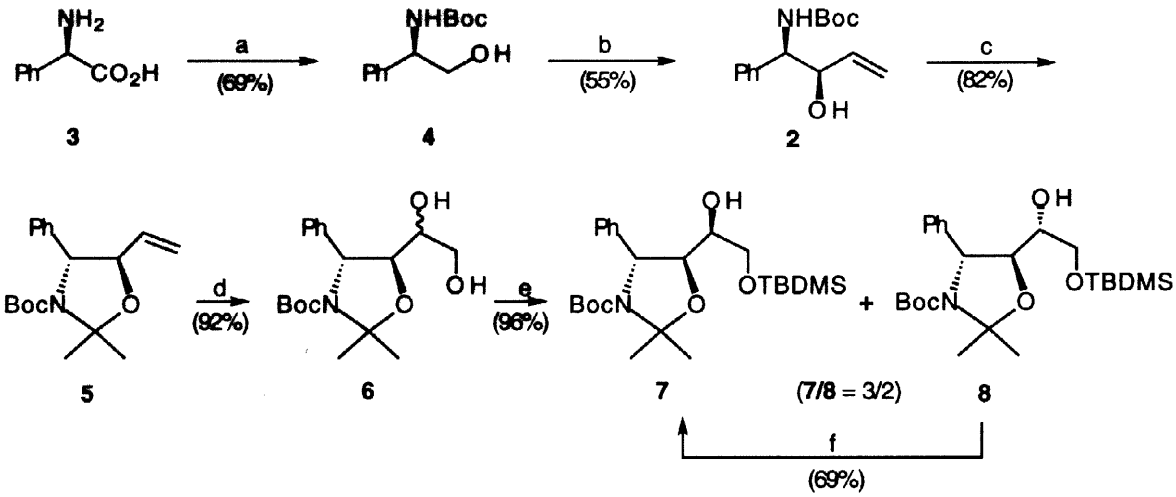
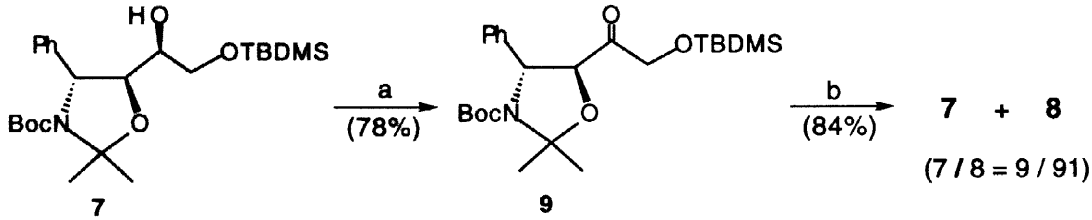
diastereoselection (9:1, diastereoisomers separated by column chromatography) in favour of the *syn* isomer, which is in accordance with the earlier reported observation.[6] The pivotal intermediate **2** with the required *syn*-β-amino alcohol framework and two differential functional groups in phenyl and the terminal olefin thus represents a convenient launching pad for the proposed synthesis.



a. LAH, THF then Boc_2O, CH_2Cl_2. **b.** Swern oxidation then $H_2C{=}CHMgBr$, THF. **c.** $Me_2C(OMe)_2$, PPTS, toluene. **d.** AD-mix-β. **e.** TBDMSCl, imidazole, DMAP, CH_2Cl_2. **f.** i) Ph_3P, $EtO_2CN{:}NCO_2Et$, 4-nitrobenzoic acid, THF. ii) K_2CO_3, MeOH.

Scheme 2

Acetonide protection of the amino alcohol functionality of **2** afforded the vinyl oxazolidine **5** (Scheme 2) and the assigned stereochemistry was further verified by NMR studies where the observed coupling constant (J = 8.3 Hz) between the two protons in the oxazolidine ring (C_4-C_5) is indicative of a *trans* relationship. Attempted dihydroxylation of the terminal double bond of **5** using AD-mix-β resulted in an inseparable mixture of alcohols **6**. However, treatment of this mixture with TBDMSCl under standard conditions gave the mono-silylated derivatives **7** and **8** in nearly quantitative yield, which were separated by column chromatography. The poor diastereoselectivity (3:2) in favour of the β-alcohol during dihydroxylation is not very surprising as the chiral olefin and the catalyst represents a mismatched pair. In a separate experiment, oxidation of the alcohol **7** to the corresponding ketone **9** (Scheme 3) followed by reduction of the



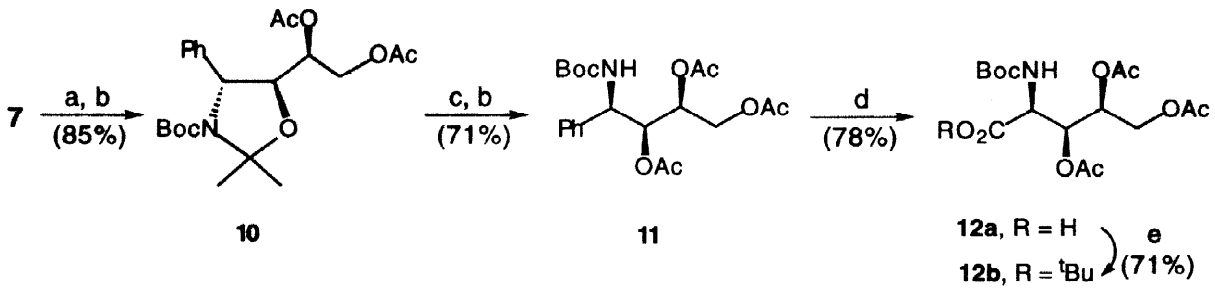
a. 2-Iodoxybenzoic acid, DMSO, THF. **b.** $Zn(BH_4)_2$, THF.

Scheme 3

resulting carbonyl group with $Zn(BH_4)_2$ (*erythro* selective)[7] under standard conditions provided the *anti*-alcohol **8** as the major isomer (>90%), which was found to be similar in all respects to the alcohol **8** as obtained previously (Scheme 2), thereby confirming the stereochemical assignment of the alcohols **7** and **8**. The undesired isomer **8** was next converted to the required β-hydroxy compound **7** via a Mitsunobu protocol

as shown in Scheme 2.

After a few unsuccessful trials, we could find the right combination of reaction sequence and protecting groups for converting the protected amino triol **7** to the target molecule in good overall yield, as depicted in scheme 4. Thus, deprotection of the silylether linkage of **7** and subsequent acetylation of the diol yielded the diacetate **10**. N,O-deprotection of the acetonide linkage followed by acetylation of the resulting hydroxy group formed the *N*-Boc protected triacetate **11**. Finally, degradative oxidation of the phenyl group yielded the corresponding carboxylic acid **12a**, suitably protected for further peptide coupling towards the syntheses of various polyoxins. Also, conversion of the acid **12a** to its *tert*-butyl ester **12b** afforded a known precursor[8] of polyoxamic acid thereby completing a formal synthesis of **1**.[9]



a. Bu_4NF, THF. **b.** Ac_2O, DMAP, py. **c.** 80% AcOH, 50°C. **d.** $RuCl_3.H_2O$, $NaIO_4$, CCl_4, CH_3CN, H_2O. **e.** $Me_2C{=}CH_2$, $BF_3.Et_2O$, CH_2Cl_2.

Scheme 4

In conclusion, the above method represents a practical and relatively short synthesis of polyoxamic acid and offers a viable alternative to the existing methods for synthesizing the title compound and its analogs.

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References and Notes

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9. All the compounds synthesized were fully characterized by IR, ^1H and ^{13}C NMR and mass spectral data. Characteristic data for some key compounds are given below:

5: light yellow viscous liquid; $[\alpha]_D$ = -32.7 (c=1.4, $CHCl_3$); IR (neat) 1696 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$) δ 1.03 (s, 9H, tBu), 1.72 and 1.74 (2s, 6H, 2xCH_3), 4.25 (br t, *J*= 7.5 Hz, 1H, H-5), 4.36 (br d, *J*= 6.9 Hz, 1H, H-4), 5.19 (m, 2H, C$\underline{H}_2$=CH-), 5.87 (m, 1H, -C$\underline{H}$-CH_2-), 7.32 (m, 5H, Ph); CIMS 304 (MH+).

7: light yellow viscous liquid; $[\alpha]_D$ = -21.2 (c=1.3, $CHCl_3$); IR (neat) 3376, 1696 cm^{-1}; ^{1}HNMR (200 MHz, $CDCl_3$) δ 0.05 and 0.06 (2 s, 6H, tBuSi$\underline{Me}_2$), 0.85 (s, 9H, t$\underline{Bu}$SiMe$_2$), 1.1 (br s, 9H, tBuO), 1.65 and 1.72 (2s, 6H, -C($\underline{Me}$)$_2$), 2.32 (br s, 1H, OH, exchangeable with D_2O), 3.65 (m, 3H), 3.89 (br t, *J*= 7.1 Hz, 1H), 4.85 (br s, 1H, Ph-C$\underline{H}$), 7.26 (m, 5H, Ph); MS (FAB+) 452 (MH+).

11: colourless liquid; $[\alpha]_D$ = +12.9 (c=0.6, $CHCl_3$); IR (neat) 3410, 1746, 1711 (br) cm^{-1}; ^{1}HNMR (200 MHz, $CDCl_3$) δ 1.4 (br s, 9H, tBu), 2.05 (s, 3H, OAc), 2.1 (s, 3H, OAc), 2.15 (s, 3H, OAc), 4.05 (dd, *J*= 4.5 and 11.4 Hz, 1H, C$\underline{H}_2$OAc), 4.26 (br d, *J*= 11.1 Hz, 1H, C$\underline{H}_2$OAc), 5.1 (m, 3H), 5.45 (br d, *J*= 9.0 Hz, 1H, NH), 7.3 (m, 5H, Ph); CIMS 424 (MH+).

12a: colourless liquid; $[\alpha]_D$ = 22.2 (c=1.5, $CHCl_3$); IR (neat) 3360, 1754, 1726 (br) cm^{-1}; ^{1}HNMR (200 MHz, $CDCl_3$) δ 1.4 (s, 9H, tBu), 2.04 (s, 6H, 2 x OAc), 2.13 (s, 3H, OAc), 4.11 (dd, *J* = 4.5 and 11.2 Hz, 1H, C$\underline{H}_2$OAc), 4.29 (br d, *J* = 11.4 Hz, 1H, C$\underline{H}_2$OAc), 4.77 (br d, *J* = 9.4 Hz, 1H, C$\underline{H}$OAc), 4.89 (br s, 1H, CO_2H), 5.08 (m, 1H, C$\underline{H}$OAc), 5.17 (br d, *J* = 9.5 Hz, 1H, C$\underline{H}$-CO_2H), 5.65 (br d, *J* = 9.2 Hz, 1H, N$\underline{H}$); ^{13}CNMR (50 MHz, $CDCl_3$) δ 172.8, 170.8, 169.7, 169.4, 155.4, 80.8, 77.2, 70.2, 68.1, 61.7, 30.8, 29.6, 28.2, 20.8, 20.6, 20.4; CIMS: 392 (MH+).

12b: colourless liquid; $[\alpha]_D$ = 15.6 (c= 0.6, $CHCl_3$) [lit [7]. $[\alpha]_D$ = 14.1 (c= 1.12, $CHCl_3$)]; IR (neat) 3350, 1748, 1690 cm^{-1}; ^{1}HNMR (200 MHz, $CDCl_3$) δ 1.49 (br s, 18H, 2 x tBu), 2.05 (s, 3H, OAc), 2.11 (s, 3H, OAc), 2.16 (s, 3H, OAc), 4.20 (br d, *J* = 3.2 Hz, 2H, C$\underline{H}_2$OAc), 4.97 (br d, *J* = 8.8 Hz, 2H, 2 x C$\underline{H}$OAc), 5.41 (br d, *J* = 8.9 Hz, 1H, C$\underline{H}$-CO_2Bu^t), 6.01 (d, *J* = 9.8 Hz, 1H, N$\underline{H}$). CIMS 448 (MH+).