EFFICIENT SYNTHESIS OF A NEW AMINOAZASUGAR AND DIHYDROXYPROLINES FROM AN ENDOCYCLIC ENECARBAMATE

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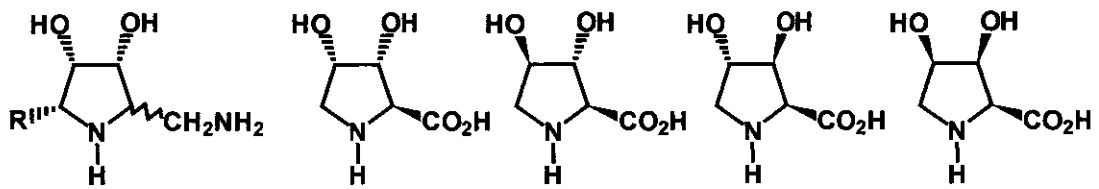
Abstract – A novel procedure for the synthesis of *trans*-2,3-(2-aminomethyl)-*cis*-3,4-dihydroxypyrrolidine (a new aminoazasugar) and *cis*-2,3- and *trans*-2,3-*cis*-3,4-dihydroxyprolines is presented. Starting from the known endocyclic ene-carbamate 1-carbobenzyloxy-2-pyrroline, the above compounds were efficiently synthesized in 6 or 7 steps in good overall yields. In the key step, *trans*-2,3-(1-carbobenzyloxy)-*cis*-3,4-diacetyloxy-2-methoxypyrrolidine underwent Lewis acid promoted cyanation, presumably *via* the corresponding *N*-acyliminium ion.

Numerous recent publications testify to the great interest in new synthetic procedures giving access to polyhydroxylated pyrrolidines[1a-1c] and piperidines[1a,1d] (often denominated *azasugars*). These compounds are of current interest for their intriguing and manifold biological properties. For example, homoaminoazasugar (**1a**) was recently synthesized from D-ribose and revealed by Wong *et al.* to be a potent α-fucosidase inhibitor.[2a] Also, Kim *et al.* have synthesized (**1b**) and its acetonide (dioxolane) and shown that both compounds form stable platinum(II) chloride complexes which exhibit levels of *in vitro* cytotoxicity to human cancer cells comparable to those of cisplatin and carboplatin.[2b]



1a, R = CH_3, β-CH_2NH_2
1b, R = H, α-CH_2NH_2
1c, R = H, β-CH_2NH_2

2a **2b** **2c** **2d**

Figure

Meanwhile, 3,4-dihydroxyprolines (**2a-2d**) are interesting for their potential as glycosidase inhibitors.[3] For example, Wong *et al.* have incorporated **2a** as one of the amino acids in a glycosylated dipeptide derivative and shown that this derivative has ten times the activity of SLe^x as an E-selectin inhibitor[4a] while **2b** has been shown to be an active β-D-glucuronidase inhibitor.[4b] Also, three of the eight possible stereoisomers of 3,4-dihydroxyproline, all of L-configuration, have been isolated from natural sources: **2a** is the sixth amino acid residue in the tandomly repeated consensus decapeptides of an adhesive (foot) protein from the marine mussel species *Mytilus edulis*,[5] **2b** was isolated from the hydrolysate of the toxic peptides (virotoxins) of the mushroom species *Amanita virosa*,[6] and **2c** was obtained from the cell walls of the diatom species *Navicula pelliculosa*.[7] A 3,4-dihydroxy-L-proline of unspecified relative configuration was produced by the diatom species *Nitzschia angularia* in Si-starvation synchrony.[8] Syntheses of all of the eight possible 3,4-dihydroxyproline stereoisomers have been reported.[9]

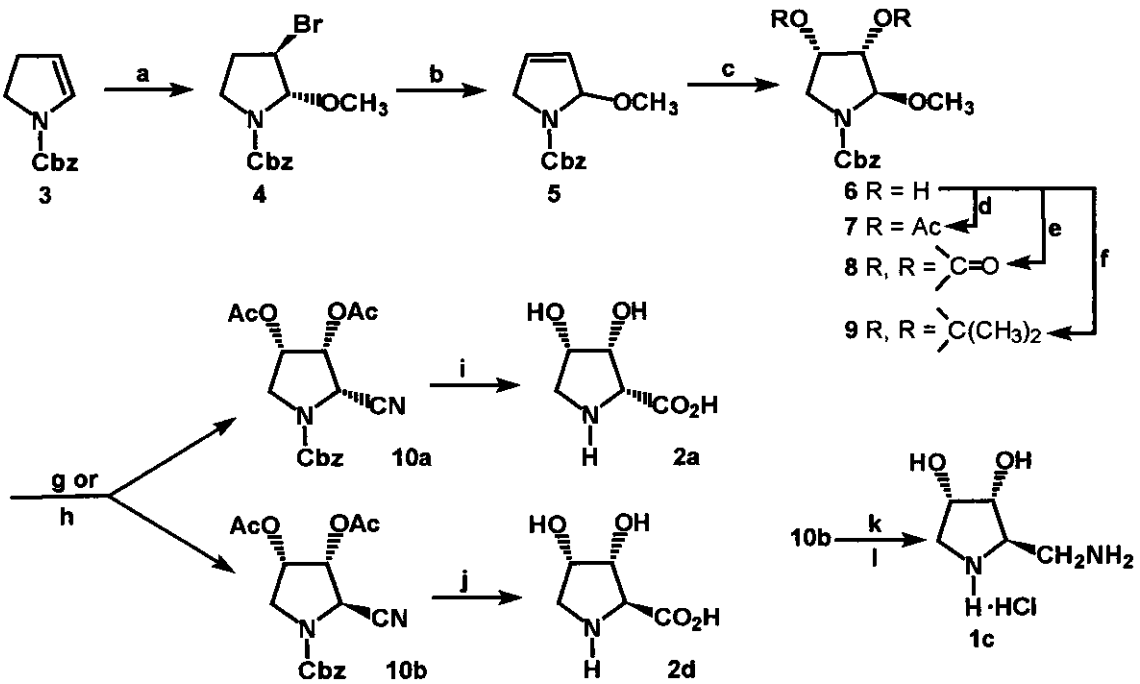
In the work presented below, we describe efficient methodology for the synthesis of racemic aminoazasugar (**1c**) as well as *cis*-3,4-dihydroxyprolines (**2a**) and (**2d**), from the known endocyclic enecarbamate (**3**) (Scheme).

Enecarbamate (**3**) was prepared in accordance with Kraus and Neuenschwander's procedure.[10] When compound (**3**) was treated with *N*-bromosuccinimide (NBS) in the presence of excess methanol, regio- and stereoselective methoxybromination occurred yielding *trans*-bromomethoxypyrrolidine (**4**) in good yield after chromatography (81%). Stereochemical assignment at this point was made based on the observed coupling constant of 4.8 Hz between H-2 and H-3 (65 °C ^{1}H-NMR due to rotamers at room temperature, in CCl_4 / TMS). Next, treatment of **4** with potassium *tert*-butoxide in the presence of a catalytic amount of crown ether furnished Δ^3-pyrroline (**5**).[11] Formation of the Δ^2-regioisomeric product was not observed presumably due to the *syn*-relationship of the C-2 hydrogen and bromine atom in compound (**4**).

Δ^3-Pyrroline (**5**) proved to be a highly labile compound. It underwent dehydromethoxylation to *N*-carbobenzyloxypyrrole over a short period of time even at low temperature. We found filtration of the dehydrobromination reaction mixture through a plug of *basic* alumina (silica or neutral alumina should *not* be used), followed by evaporation of volatiles *in vacuo*, to be an efficient work-up procedure. Also, addition of Et_3N to solvents used for washing and transfer decreased decomposition during handling. By observing the above precautions, compound (**5**) could be isolated in good yield and was immediately used in the next step.

Reaction of **5** with catalytic osmium tetroxide and *N*-methylmorpholine *N*-oxide (NMO) yielded diol (**6**) in high yield (91%). Next, the hydroxyl groups were protected by conversion of **6** to diacetyl derivative (**7**). The 2,3-*trans* relationship in compound (**7**) was apparent from the absence of coupling (0 Hz) between H-2 and H-3 (^{1}H-NMR / $CDCl_3$). When compound (**7**) was allowed to react with trimethylsilyl

cyanide and boron trifluoride etherate at room temperature[12] a 2 : 1 mixture of cyanation products (**10a**) and (**10b**) was obtained in moderate yield, presumably *via* an *N*-acyliminium ion intermediate. Changing the Lewis acid to titanium(IV) chloride[12] marginally increased the ratio of **10a** to **10b** (3:1) although the yield was lower. The epimeric nature of the nitriles was confirmed by the H-2 – H-3 coupling constants of 7.3 Hz for **10a** and 4.4 Hz for **10b** (^{1}H-NMR / 65 °C / CCl_4).



Scheme. Reagents and Conditions: a) NBS, CH_3OH, CH_2Cl_2, -20 °C to rt, overnight, then "flash" chromatography (81%), b) *t*-C_4H_9OK, 18-C-6, $C_6H_5CH_3$, rt, 1.5 h, then filtration through basic alumina (87%), c) cat. OsO_4, NMO, H_2O, $(CH_3)_2CO$, *t*-C_4H_9OH, rt, overnight (91%), d) Ac_2O, C_5H_5N, rt, 24 h (88%), e) $(CCl_3)_2CO$, CH_2Cl_2 (quant.), f) $(CH_3)_2C(OCH_3)_2$, cat. *p*-TsOH, $(CH_3)_2CO$ (76%), g) $(CH_3)_3SiCN$ (1.5 equiv.), $BF_3{\cdot}(C_2H_5)_2O$ (2 equiv.), CH_2Cl_2, rt, then "flash" chromatography (74%), h) $(CH_3)_3SiCN$ (1.5 equiv.), $TiCl_4$ (1.1 equiv.), -78 °C to rt, overnight, then "flash" chromatography (44%), i) 12N HCl, reflux, 18 h, then ion-exchange chromatography (71%), j) 6 N HCl, reflux, 18 h, then ion-exchange chromatography (90%), k) H_2, PtO_2, EtOH, 12 N HCl, 6 h, l) 12 N HCl, CH_3OH, reflux, 1 h; then, reverse-phase chromatography (> 50% for steps k and l).

Acetonide and cyclic carbonate derivatives of diol (**6**), compounds (**8**) and (**9**), respectively, were also prepared in moderate yields by the methods indicated in the Scheme. It was hoped that the bicyclic nature of compounds (**8**) and (**9**) might lead predominantly to the formation of the *trans* product in the subsequent cyanation step. Surprisingly, neither **8** nor **9** underwent cyanation with trimethylsilyl cyanide and boron trifluoride etherate under the conditions used with diacetyl derivative (**7**). Diacetyloxyprolinonitrile (**10a**) underwent total hydrolysis in refluxing conc. HCl to the all-*cis* 3,4-

dihydroxyproline (**2a**) whereas **10b** was hydrolyzed to *trans*-2,3-*cis*-3,4-dihydroxyproline (**2d**) in 6 N HCl. Both **2a** and **2d** have ^{1}H-NMR, IR and MS spectral properties in agreement with the literature.[9] Combined hydrogenation-hydrogenolysis was performed on prolinonitrile (**10b**). After reaction, the catalyst was removed by filtration and the volatiles removed *in vacuo*. From the ^{1}H-NMR spectrum of the residue left after evaporation it was concluded that the hydrochloric acid salt of the diacetyl derivative of **1c** was the major product formed together with impurities. The product mixture was then refluxed briefly in acidic methanol to effect ester cleavage which yielded the desired aminoazasugar product (**1c**) as the hydrochloride together with impurities. A pure sample of salt (**1c**)[13] was obtained after semi-preparative reverse-phase HPLC.

In conclusion, the above strategy proved rather efficient for the preparation of the 2-aminomethyl-3,4-dihydroxypyrrolidine and the dihydroxyprolines from an endocyclic enecarbamate. This methodology is presently being applied towards the synthesis of enantiomerically pure compounds.

ACKNOWLEDGMENTS
Support for this research was provided by CNPq, CAPES, FAPESP and FAEP-UNICAMP.

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13. Data for aminoazasugar (**1c**): ^{1}H-NMR (300 MHz, D_2O) δ : 4.25 (br s, 1H, H-4), 4.10 (dd, $J_{3,4}$ = 3.8 Hz, $J_{2,3}$ = 9.3 Hz, 1H, H-3), 3.65 (dt, $J_{2,3}$ = 9.3 Hz, $J_{2,1'}$ = 6.7 Hz, 1H, H-2), 3.48 (dd, $J_{4,5\beta}$ = 3.7 Hz, $J_{5\alpha,5\beta}$ = 13.2 Hz, 1H, H-5β), 3.39 (d, $J_{2,1'}$ = 6.7 Hz, 1H, H-1'), 3.29 (d, $J_{5\alpha,5\beta}$ = 13.2 Hz, 1H, H-5α) ppm; ^{13}C-NMR (75 MHz, D_2O) δ : 73.8 (C-3), 68.6 (C-4), 56.8 (C-2), 50.4 (C-5), 38.7 (C-1') ppm.

Received, 21st August, 1997