

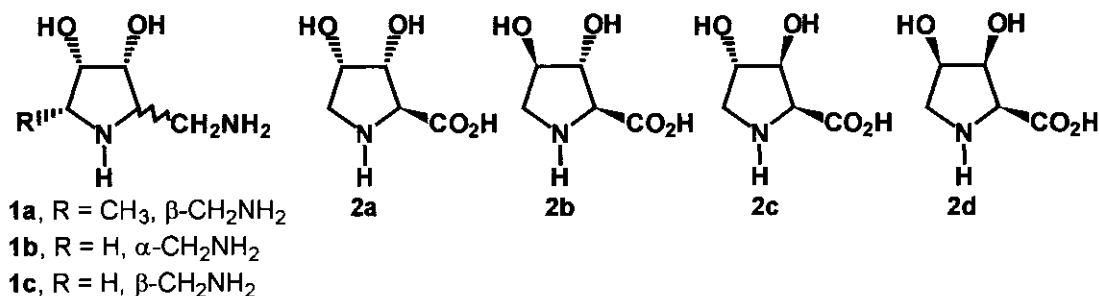
EFFICIENT SYNTHESIS OF A NEW AMINOAZASUGAR AND DIHYDROXYPROLINES FROM AN ENDOCYCLIC ENECARBAMATE

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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 enecarbamate 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}



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 tandemly 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

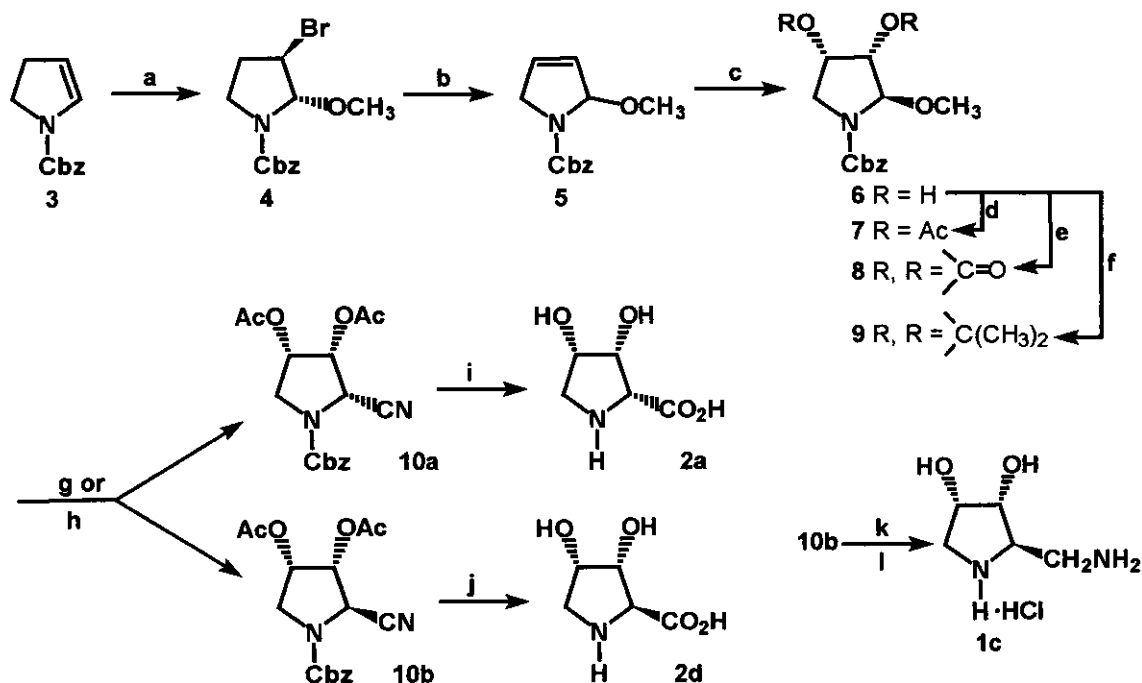
In the work presented below, we describe efficient methodology for the synthesis of racemic aminoazasugar (**1c**) as well as *cis*-3,4-dihydroxyprolines (**2a**) and (**2d**), from the known endocyclic enecarbamate (**3**) (Scheme).

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 ¹H-NMR due to rotamers at room temperature, in CCl₄ / 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 Et₃N 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 (¹H-NMR / CDCl₃). When compound (**7**) was allowed to react with trimethylsilyl

cyanide and boron trifluoride etherate at room temperature¹² 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) chloride¹² 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** (¹H-NMR / 65 °C / CCl₄).



Scheme. Reagents and Conditions: a) NBS, CH₃OH, CH₂Cl₂, -20 °C to rt, overnight, then "flash" chromatography (81%), b) *t*-C₄H₉OK, 18-C-6, C₆H₅CH₃, rt, 1.5 h, then filtration through basic alumina (87%), c) cat. OsO₄, NMO, H₂O, (CH₃)₂CO, *t*-C₄H₉OH, rt, overnight (91%), d) Ac₂O, C₅H₅N, rt, 24 h (88%), e) (CCl₃)₂CO, CH₂Cl₂ (quant.), f) (CH₃)₂C(OCH₃)₂, cat. *p*-TsOH, (CH₃)₂CO (76%), g) (CH₃)₃SiCN (1.5 equiv.), BF₃·(C₂H₅)₂O (2 equiv.), CH₂Cl₂, rt, then "flash" chromatography (74%), h) (CH₃)₃SiCN (1.5 equiv.), TiCl₄ (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) H₂, PtO₂, EtOH, 12 N HCl, 6 h, l) 12 N HCl, CH₃OH, 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 ¹H-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 ¹H-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.

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