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Diastereoselective Synthesis of *cis*-4-Hydroxypipecolic Acid from D-Glucosamine.

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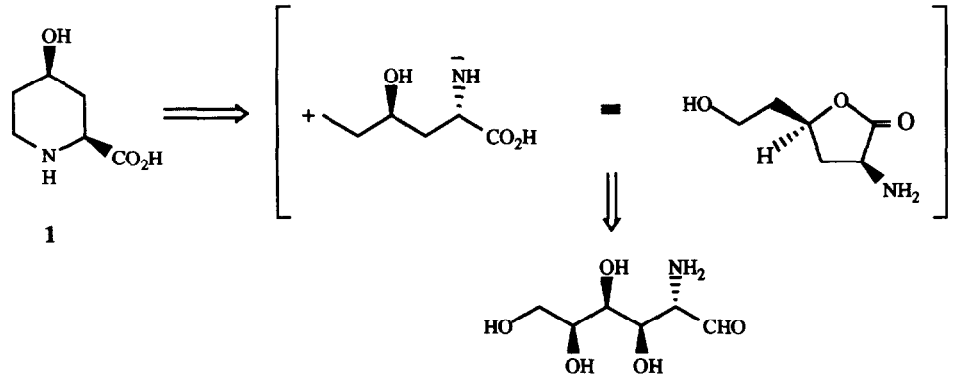
Abstract: An expeditious synthesis of *cis*-4-hydroxypipecolic acid (**1**) is described. The key step was diastereoselective hydrogenation of 2-acetamido-6-*O*-acetyl-2,3,5-trideoxy-hex-2-enono-1,4-lactone (**3**), obtained in three high yielding steps from D-glucosamine. The formation of the piperidine ring from 2-amino-2,3,5-trideoxy-*threo*-hexono-1,4-lactone derivative (**10**) was achieved by intramolecular nucleophilic displacement of the C-6 sulfonate by the C-2 amino group.

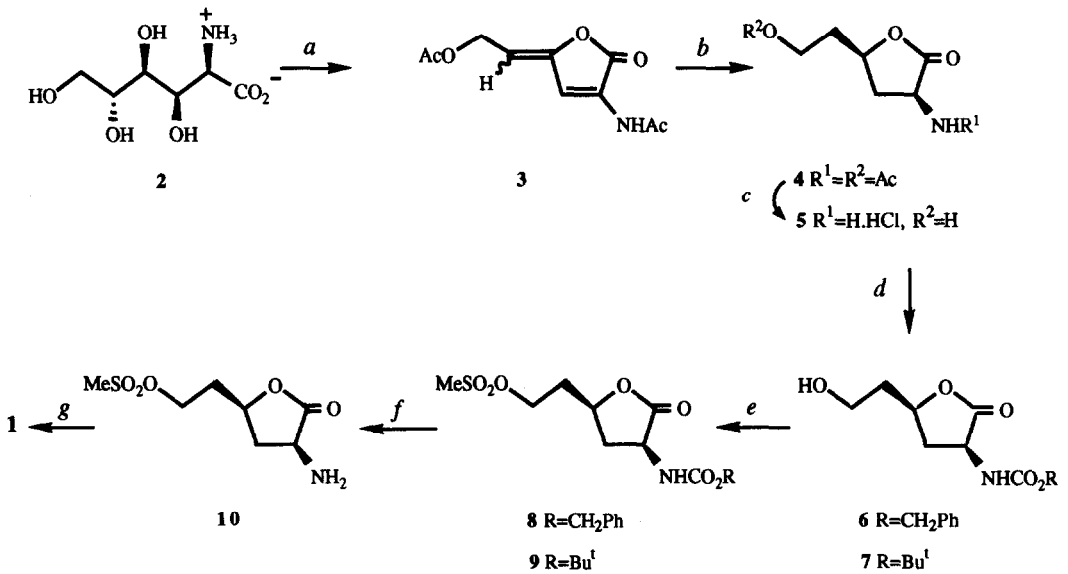
Because of the varied biological activities displayed by hydroxylated amino acids, their synthesis from carbohydrate precursors have received a great deal of attention during the last years.[1] As part of our project on the synthesis of hydroxy amino acids we were interested in a direct route for the preparation of *cis*-4-hydroxypipecolic acid (*cis*-4-hydroxy-2-piperidinecarboxylic acid, **1**). The 4-phosphonooxy derivative of **1** has been recently synthesized,[2] and it showed activity as an *N*-methyl-D-aspartate (NMDA) antagonist. The NMDA subtype of excitatory amino acids receptors are probably involved in a variety of neuropathologies,[3] and the search for competitive NMDA antagonists has been the focus of considerable investigation.[2,4,5] We trust that the introduction of different substituents on the HO-4 of **1** would lead to a variety of potential antagonist at the NMDA site.

As depicted retrosynthetically in Scheme 1, disconnection of the C-6–N bond of **1** produces a synthon equivalent to an aminolactone, which may be obtained from D-glucosamine. This sugar provides the correct functionalization at C-2, 4 and 6, and can be readily oxidize[6] (HgO) to 2-amino-2-deoxy-D-gluconic acid (**2**, D-glucosaminic acid) and converted into an aldono-1,4-lactone derivative.[7] Fleet and co-workers[8] have synthesized a number of hydroxy amino acids from conveniently protected sugar lactones. They usually



Scheme 1

incorporate the amino function by nucleophilic substitution of a sulfonylated hydroxyl group of the sugar lactone by azide, followed by reduction. The advantage of our strategy is that the amino group is properly located in the starting sugar (**2**), hence the synthesis is shorter. Furthermore, the required stereochemistry for the chiral centers of **1** was readily generated from **2**, in two high yielding steps: the β-elimination process, which takes place during the acetylation[7] (acetic anhydride, sodium acetate, 100°C, 1 min) of **2**, and then catalytic hydrogenation. Previous work from our laboratory[9] has shown that hydrogenation of unsaturated aldono-1,4-lactones leads diastereoselectively to a *cis* relationship for the C-2 and C-4 substituents of the resulting saturated lactone. Thus, hydrogenation (10% Pd on charcoal) of furanone **3**, took



(*a*) Ac_2O, NaOAc, 100°C, 1 min; (*b*) H_2, Pd/C (15 psi); (*c*) aq. HCl; (*d*) $PhCH_2CO_2Cl$ (or BOC-ON); (*e*) MsCl-pyridine in $CHCl_3$; (*f*) H_2, Pd/C (or $(CH_3)_3SiI$); (*g*) aq KOH.

place with an excellent diastereofacial selectivity to give a 3,5-dideoxylactone **4** (90% yield from **2**), bearing a *threo* relationship for their chiral centers.[7] Diastereomerically pure compound **4** has the appropriate stereochemistry for the synthesis of **1**. Therefore, **4** was *N*- and *O*-deacetylated in acidic medium to afford (87% yield) the dideoxylactone **5** (hydrochloride derivative), which is identical to the lactone precursor formulated in Scheme 1.

The synthetic strategy proposed involves the nucleophilic displacement of conveniently substituted HO-6 by the amino function attached to C-2. Protection of the latter was required, prior to the conversion of HO-6 into a good leaving group by sulfonylation. Thus, treatment of **5** with benzyl chloroformate in Et_3N-CH_2Cl_2, afforded crystalline 2-(*N*-benzyloxycarbonyl)amino-2,3,5-trideoxy-D,L-*threo*-hexono-1,4-lactone (**6**) in 68% yield. Alternatively, protection of NH_2 of **5** with 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON) in water- dioxane- Et_3N led to syrupy **7** in 54% yield. Mesylation of **6** or **7** with methanesulfonyl chloride (mesyl chloride) in pyridine, led to mixtures from which the corresponding mesylates (**8** or **9**, respectively) were difficult to isolate. However, high yields of **8** and **9** (~80%) were obtained when the mesylation was conducted employing 1.3 molar equivalents of mesyl chloride-pyridine in dichloromethane, conditions which had been successful for the preparation of tosylates.[10]

Attempted removal of the BOC *N*-protecting group with $(CH_3)_3SiI$ in $CHCl_3$ and further addition of CH_3OH,[11] gave the amino-mesylate **10**, which was isolated from the reaction mixture in poor yield. However, removal of the carbobenzoxy group of **8** was readily accomplished, by hydrogenolysis with 10% Pd/C as catalyst, to give **10** in 98% yield. Since compound **10** rapidly decomposes on storage, it was generated by hydrogenation of **8** and immediately used for the cyclization step, which was achieved by nucleophilic displacement of the mesylate by the amino group, with 2M aq KOH. The resulting *cis*-4-hydroxypipecolic acid (**1**) was purified by ion exchange column chromatography with Dowex 50W (H^+) resin and isolated as the hydrochloride derivative in 55% yield from **8**.

As the starting dideoxylactone **5** is easily prepared, with excellent yield (~83% from **2**), and the

Table 1. ^{13}C NMR Data for Compounds **1**, **5-10**:

COMPOUND	C-1	C-2	C-3	C-4	C-5	C-6	~$NHCO_2$	~OSO_2CH_3
1[a]	171.6	56.0	30.4*	65.3	34.1*	41.9		
5[a]	175.3	51.4	34.7*	79.4	38.3*	59.5		
6[b]	174.6	51.8	36.2	75.7	37.7	58.6		
7[c]	174.9	51.6	36.5	75.6	37.8	58.6	155.4	
8[b]	174.1	51.6	35.6	73.9	34.8	65.8	156.0	37.4
9[d]	174.4	51.3	35.7	73.8	34.9	66.0	155.2	37.4
10[e]	173.4	51.1	35.9	76.9	34.9	67.9		37.9

[a]Recorded in D_2O, [b]$PhCH_2$ δ: 128.2, 128.4, 128.7 and 67.4, [c]$C(CH_3)_3$ δ: 78.4 and 28.4, [d]$C(CH_3)_3$ δ: 80.6 and 28.4, [e]recorded in CD_3OD, *signals may be interchanged.

following steps are simple and can be readily accomplished, the synthesis of **1** here described compares favourably with recent procedures described in the literature for the preparation of derivatives of **1**. These procedures include: hydrogenation of 2-cyano-4-methoxy-pyridines at high pressures[12] (1000 psi, with Rh/Al_2O_3, 100 °C), low temperature Lewis acid catalyzed cyclization of a glycine cation equivalent,[13] or condensation (and olefin-iminium ion cyclization) of *N*-3-butenyl-benzenemethamine with glyoxylic acid.[2]

EXPERIMENTAL

General methods: Melting points (mp) were determined with a Thomas-Hoover capillary mp apparatus, and are uncorrected. ^1H NMR spectra were obtained on either a Bruker AC 200 spectrometer (200 MHz) or a Varian Gemini 300 (300 MHz) for solutions in $CDCl_3$, unless otherwise noted, with Me_4Si as internal standard (δ, 0.00 ppm). ^{13}C NMR spectra were recorded in a Varian XL 100 spectrometer (25.2 MHz), with the solvent used for the proton spectrum. Analytical thin layer chromatography (TLC) was performed on silica gel (Merck 60 F 254) precoated plates (0.25 mm). Visualization was effected with anisaldehyde (5% v/v) in 95% ethanol containing 5% sulfuric acid or phosphomolybdic acid (7% w/v) in 95% ethanol. Column chromatography was carried out on silica gel 60 (Merck, 240-400 mesh).

2-Amino-2,3,5-trideoxy-D,L-*threo*-hexono-1,4-lactone hydrochloride (5).

A suspension of **4**[7] (1.0 g, 0.44 mmol) in 5N HCl (25 mL) was heated at 65 ± 5 °C for 18 h. The solution was concentrated at reduced pressure. In order to remove the aq. HCl, methanol was added to the residue, followed by evaporation. The operation was repeated several times, affording a white solid, which was dried overnight in vacuum. The solid was suspended in absolute ethanol (3 mL) and filtered to give crystalline **5** (0.69 g, 87%), mp 173-174 °C. (lit.[7] mp 173-174 °C).

2-(*N*-Benzyloxycarbonyl)amino-2,3,5-trideoxy-D,L-*threo*-hexono-1,4-lactone (6).

To a suspension of 2-amino-2,3,5-trideoxy-D,L-*threo*-hexono-1,4-lactone hydrochloride (**5**, 0.47 g, 2.6 mmol) in dry CH_2Cl_2 (10 mL) triethylamine (0.90 mL, 6.5 mmol) was added. The mixture was cooled in an ice-water bath and benzyl chloroformiate (0.52 mL, 3.6 mmol) was added dropwise, with stirring and under nitrogen. The mixture was left to reach r. t. and the stirring was maintained for 5 h. TLC (Rf 0.15, 1:3, MeOH-EtOAc) showed some remaining starting material; therefore, additional amounts of Et_3N (0.18 mL, 1.3, mmol) and benzylchloroformiate (0.19 mL; 1.3 mmol) were added. After 16 h of stirring at r.t. the solution was concentrated and the residue extracted with CH_2Cl_2 (3 x 50 mL). The organic extract was washed with water, dried ($MgSO_4$), and concentrated. The resulting syrup was purified by flash chromatography (silica gel, 2:1 PhMe-EtOAc) to afford compound **6** as a white solid (0.49 g, 68%); mp 76-77 °C. ^1H NMR (200 MHz): δ= 7.35 (s, 5H aromatic), 5,46 (bs, N*H*), 5.12 (s, 2H, CH_2Ph), 4.62 (m, H-4), 4.47 (m, H-2), 3.75 (m, 2H, H-6,6'), 2.86 (m, H-3), 2.01-1.80 (m, H-3', 5, 5'). Found: C, 60.52; H, 5.70; N, 5.02. $C_{14}H_{17}NO_5$ requires C, 60.21; H, 6.14; N, 5.02.

2-(*N*-*tert*-Butyloxycarbonyl)amino-2,3,5-trideoxy-D,L-*threo*-hexono-1,4-lactone (7):

To a solution of **5** (0.23 g, 1.26 mmol) in 50% aqueous dioxane (4 mL), triethylamine (0.46 mL, 3.3 mmol) and 2-*tert*-butyloxycarbonyloxyimino-2-phenylacetonitrile (BOC-ON, 0.34 g, 1,4 mmol) were added. The solution was stirred for 24 h at r.t. and then concentrated *in vacuo*. Water was added to the residue and evaporated to remove triethylamine. The resulting syrup was

dissolved in a mixture of ether (30 mL) and 0.05 N aq HCl (20 mL). The aqueous layer was separated and extracted again with ether (to remove the by product 2-hydroxyimino-2-phenhylacetonitrile) and then with EtOAc (3 x 30 mL). The EtOAc extracts were pooled, dried ($MgSO_4$) and the solvent evaporated to give oily **7** (0.17 g, 54%). ^1H NMR (300 MHz): δ= 5.18 (bs, N*H*), 4.65 (m, H-4), 4.43 (m, H-2), 3.84 (m, 2H, H-6,6'), 2.87 (m, H-3), 2.05-1.85 (m, H-3',5,5'), 1.47 (s, 9H, (CH_3)$_3$C). Found: C, 53.59; H, 7.58; N, 5.60. $C_{11}H_{19}NO_5$ requires C, 53.87; H,7.81; N, 5.71.

2-(*N*-Benzyloxycarbonyl)amino-6-*O*-methylsulfonyl-2,3,5-trideoxy-D,L-*threo*-hexono-1,4-lactone (8).

To a solution of **7** (0.43 g, 1.5 mmol) and pyridine (0.24 mL, 2 mmol) in dry CH_2Cl_2 (3.5 ml), cooled to -10 °C and under nitrogen, methanesulfonyl chloride (0.17 mL, 2.3 mmol) was slowly added. The mixture was stirred for 1 h at -10 °C, and then was allowed to warm to r.t. After 10 h the solution was diluted with CH_2Cl_2 (50 mL), washed with water, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (silica-gel, 2:1 PhMe-EtOAc), affording crystalline **8** (0.43 g, 78.3%). Recrystallized from hexane-EtOAc, **8** gave mp 92-93 °C. ^1H NMR (200 MHz): δ= 7.35 (s, 5H, *aromatic*), 5.58 (bs, N*H*), 5.12 (s, 2H, C*H*2Ph), 4.60-4.34 (m, 4H, H-2,4,6,6'), 3.02 (s, 3H, CH_3SO_2), 2.81 (m, H-3), 2.17-1.77 (m, H-3,5,5'). Found: C, 50.67; H, 5.24; N, 9.07. $C_{15}H_{19}NO_7S$ requires: C; 50.41; H, 5.36; S, 8.97.

2-(*N*-*tert*-butyloxycarbonyl)amino-6-*O*-methylsulfonyl-2,3,5-trideoxy-D,L-*threo*-hexono-1,4-lactone (9).

The procedure employed for the preparation of **8** was followed, starting from **7** (0.145 g, 0.64 mmol). The product was purified by column chromatography (silica-gel, 2:1 PhMe-EtOAc) to give oily **9** (Rf 0.57, 1:3, PhMe-EtOAc). ^1H NMR (200 MHz): δ= 5.16 (bs, N*H*), 4.76-4.30 (m, 4H, H-2,4,6,6'), 3.05 (s, 3H, CH_3SO_2), 2.85 (m, H-3), 2.22 (m, 3H, H-3',5,5'), 1.48 (s, 9H, (CH_3)$_3$C).

2-amino-6-*O*-methylsulfonyl-2,3,5-trideoxy-D,L-*threo*-hexono-1,4-lactone (10).

A- From **8**: Compound **8** (0.43 g, 1.2 mmol) dissolved in EtOAc (20 mL) was hydrogenated for 16 h at atmospheric pressure with 10% Pd/C (40 mg) as catalyst. The suspension was filtered and the filtrate concentrated affording compound **10** as an homogeneous oil (Rf 0.34, 1:3, MeOH-EtOAc); yield 0.25 g (98%). ^1H NMR (200 MHz, CD_3OD): δ= 4.95-4.60 (m, 2H, H-2,4), 4.40 (m, 2H, H-6,6'), 3.09 (s, 3H, CH_3SO_2), 2.75 (m, H-3), 2.25-1.80 (m, 3H, H-3,5,5').

B- From **9**; To a solution of compound **9** (75 mg, 0.24 mmol) in dry $CHCl_3$ (1.2 mL) iodotrimethyisilane (59 mg, 0.29 mmol) was added, and the mixture was stirred at r. t. Upon completion (1.5 h) the reaction was quenched by stirring with methanol (47 μL, 1.15 mmol) for 5 min. Concentration of the mixture afforded compound **10** (20 mg, 40 %); ^1H and ^{13}C NMR spectra identical to those of the product obtained as described in *A*.

Compound **10** was unstable and readily decomposes on storage or when chromatographic purification was attempted. Therefore, **10** was used for the next step without further purification.

***cis*-4-Hydroxypipecolic acid hydrochloride (1).**

A solution of compound **10** (68 mg, 0.32 mmol) in 2M KOH (1.2 mL) was stirred at r.t. for 1 h. The solution was made neutral by addition of 0.1 N HCl, and concentrated. The residue was purified by ion exchange column chromatography (Dowex 50, H^+ form). The column was first eluted with water, and then with 1M aq. pyridine. Freeze drying of the fractions which gave a positive ninhydrine test, led to an amorphous, hygroscopic solid. The solid was dissolved in 2M HCl (1 mL), and the solution was

evaporated *in vacuo* to give 1 as a colorless syrup, which crystallized on standing (32 mg, 55%), mp 251-254 °C (lit.[14] mp 253-255 °C); ^{1}H NMR (200 MHz, D_2O): δ= 3.95 ($J_{2,3}$ 11.2, $J_{2,3'}$, 3.5 Hz, H-2), 3.88 ($J_{3,4}$ 4.2, $J_{3',4}$ 10.0 Hz, H-4), 3.42 ($J_{5,6'}$ 12.5, $J_{5',6'}$ 3.3 Hz, H-6'), 2.96 ($J_{5,6}$ 4.0, $J_{5',6}$12.5, $J_{6,6'}$ 13.2 Hz, H-6), 2.01 ($J_{4,5'}$ 10.0, $J_{5,5'}$ 13.7 Hz, H-5'), 2.38 ($J_{3,3'}$ 11.4 Hz, H-3'), 1.63 ($J_{3,5}$ 3.4 Hz, H-3), and 1.51 ($J_{4,5}$ 3.5 Hz, H-5).

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