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Synthesis of (2*S*,4*R*,5*R*)-4,5,6-Trihydroxynorleucine and 5-Hydroxynorvaline from precursors obtained by an unusual rearrangement in a 5,6-dihydro-2-pyrone

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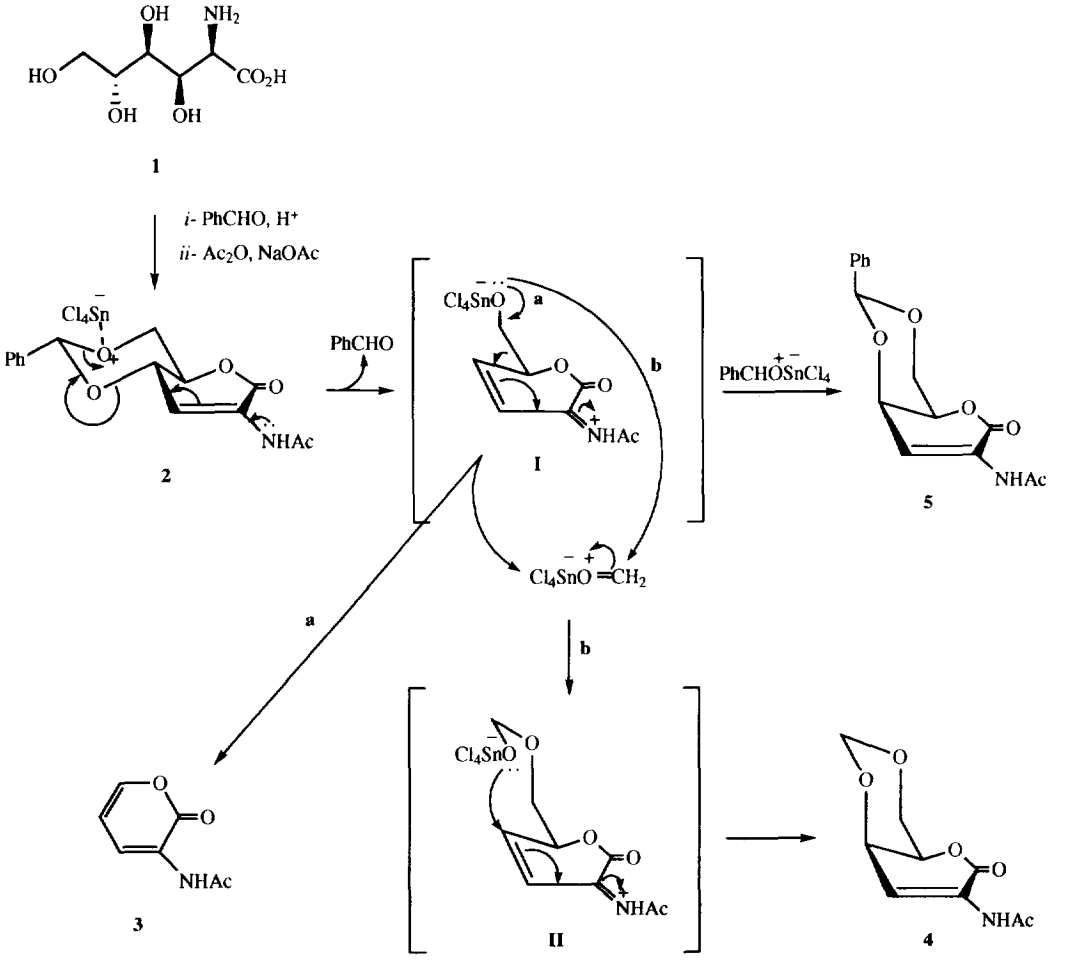
Abstract. 2-Acetamido-4,6-*O*-benzylidene-2,3-dideoxy-D-*erythro*-hex-2-enono-1,5-lactone (**2**), readily prepared from D-glucosamine, undergoes a rearrangement on treatment with tin(IV) chloride which leads to 3-acetamido-2-pyrone (**3**) and 2-acetamido-2,3-dideoxy-4,6-*O*-formylidene-D-*threo*-hex-2-enono-1,5-lactone (**4**). A mechanism is proposed for this unusual rearrangement, which was not observed for other analogous hex-2-enono-1,5-lactones. For example, the 2-acetoxy analog of **2** (2-acetoxy-4,6-*O*-benzylidene-3-deoxy-D-*erythro*-hex-2-enono-1,5-lactone, **7**) was synthesized and treated with tin(IV) chloride affording 3-acetoxy-6-chloromethyl-2-pyrone (**8**) as main product. The 2-pyrone derivatives **3** and **4** are convenient precursors for the synthesis of 5-hydroxynorvaline (**12**) and (2*S*,4*R*,5*R*,)-4,5,6-trihydroxynorleucine (**14**), respectively. The latter was prepared by diastereoselective hydrogenation of **4**, followed by deprotection.

We have recently described a strategy for the synthesis of hydroxy amino acids using D-glucosamine as a convenient chiral template.[1,2] Hydroxy amino acids are biologically interesting molecules, as they can act as antimetabolites and enzyme inhibitors.[3] For this reason, many elegant procedures for their synthesis have been described employing carbohydrates,[4] and particularly aldonolactones,[5] as starting materials. In our strategy, D-glucosamine is oxidized to 2-amino-2-deoxy-D-gluconic acid (**1**), which yields unsaturated aldonolactones on acylation.[6] These 2-enonolactones, having the amino group properly located at C-2, are the key precursors of the hydroxy amino acid derivatives, as on hydrogenation of the C-2–C-3 double bond, the configuration of C-2 is inverted leading to an amino acid in the L-series, generally found in nature. For example, enantiomerically pure (2*S*,4*S*,5*R*)-4,5,6-trihydroxynorleucine was obtained in high yield from **1**, by the procedure described above.[1] We wish to report now the synthesis of a diastereomeric norleucine isolated as the lactone **14** from 2-acetamido-4,6-*O*-benzylidene-2,3-dideoxy-D-*erythro*-hex-2-enono-1,5-lactone (**2**).

Compound **2** was prepared[6] by benzylidenation of **1**, followed by high temperature acetylation. We have previously observed[6] that attempted removal of the benzylidene group of **2** under acid conditions, promotes a further elimination to give the 6-hydroxymethyl-2-pyrone. We have also described[7] that Lewis acids, such as tin(IV) chloride, promote the 5,6-insaturation of peracylated 5,6-

dihydro-2-pyrone derivatives, to give the corresponding 2-pyrones in excellent yields. However, treatment of **2** with tin(IV) chloride gave two products, which were separated by column chromatography. The less polar one was obtained crystalline in 53% yield. Its ^{1}H NMR spectrum (Table 1) showed, besides the acetyl and N*H* singlets, only three mutually coupled double doblets due to three vinylic protons. The ^{13}C NMR spectrum (Table 2) showed five resonances characteristic of a 2-pyrone ring.[7] The structure of the product was then established as 3-acetamido-2-pyrone (**3**).

The other component of the mixture was also isolated crystalline in 30% yield. The ^{1}H NMR spectrum of this product gave a pattern of signals typical of a 2-substituted-2-enono-1,5-lactone system,[6] similar to that of **2**, although no signals due to aromatic protons were observed. The small values for the coupling constants $J_{4,5}$ (2.0 Hz), $J_{5,6}$ (<1 Hz) and $J_{5,6'}$ (1 Hz) when compared with those of the analog *erythro* pyranone **2** (9.6, 7.0, and 11.2 Hz, respectively) indicated a *gauche* relationship



Scheme 1

Table 1. ^{1}H-NMR Data for Compounds **3-5, 7,8** and **10-14.***#

Compound	H-2 ($J_{2,3}$)	H-3 ($J_{2,3'}$)	H-3' ($J_{3,3'}$)($J_{3',4}$)	H-4 ($J_{3,4}$)	H-5 ($J_{4,5}$)	H-6 ($J_{5,6}$)	H-6' ($J_{5,6'}$)	N*H* ($J_{6,6'}$)
3		8.23 ($J_{3,5}$ 1.8 Hz)		6.29 (7.2)	7.25 (5.1)			8.02
4[a]		7.55		4.39 (6.7)	4.26 (2.0)	4.34 (<1)	3.96 (1.0)	7.94 (13.3)
5[b]		7.60		4.62 (6.8)	4.30 (2.0)	4.51 (<1)	4.18 (1.8)	8.00 (13.2)
7[c]		6.64		4.74 (1.7)	4.55 (10.3)	4.46 (4.8)	4.01 (10.5)	(10.7)
8		7.09		6.31 (7.2)		4.31		
10	4.64 (12.0)	2.57 (7.9)	1.60	2.06[d]	4.40[e]			6.42
11[f,g]	3.70	1.85		3.58[d,e]				
12[g]	3.78	1.95		1.68[d]	3.66[e]			
13[h,i]	4.68 (12.8)	2.64 (8.7)	1.47 (14.2)(2.4)	4.30 (9.0)	4.53 (<1)	4.06 (<1)	3.91 (1.7)	8.20 (13.0)
14[g]	4.52	2.63		4.93	3.77	3.58		

* For comparison, the 2-pyrone ring was numbered as a lactone derivative. # For compounds **6** and **9** see Ref 6 and 9. [a] OCH_2O: 5.08, 4.79 ppm (J 6.4 Hz). [b] PhC*H*: 5.61 ppm. [c] PhC*H*: 5.54 ppm. [d,e] Centers of H-4,4' and H- 5,5' multiplets, respectively. [f] For the acid form. [g] In D_2O. [h] OCH_2O: 4.90 and 4.74 ppm (J 6.4 Hz). [i] In $(CD_3)_2SO$.

for H-4, H-5 and H-5, H-6,6', and hence a *threo* relationship for the chiral centers at C-4 and C-5. Furthermore, in agreement with the Garbish equation,[8] the value for the coupling constant between the allylic and vinylic protons ($J_{3,4}$) showed by the product (6.7 Hz) and by its precursor **2** (1.2 Hz) were also indicative that a configurational inversion took place at C-4. A distinctive feature in the spectrum was the presence of two doublets at low field, due to an isolated AB system (J 6.4 Hz), which suggested the presence of a formylidene group. This was confirmed by the ^{13}C NMR spectrum of the product which showed the ketal carbon resonance at 92.7 ppm. On the basis of the spectral data the structure of the compound was therefore established as 2-acetamido-2,3-dideoxy-4,6-*O*-formylidene-D-*threo*-hex-2-enono-1,5-lactone (**4**). Also, from the reaction of **2** with $SnCl_4$ a minor product (**5**) was isolated. Its ^{1}H NMR spectrum showed a pattern of signals similar to that of the 4,6-*O*-benzylidene-2-enonolactone **2** but, as in **4**, the $J_{4,5}$, $J_{5,6}$ and $J_{5,6'}$ values were all smaller, and that of $J_{3,4}$ was larger, indicating that **5** was in fact the isomer of **2** having inverted configuration at C-4 (D-*threo*).

Compound **3** arises from the unexpected breaking of the C-5–C-6 bond, and compound **4** results from a ketal interchange with inversion of the C-4 configuration. The mechanism depicted in Scheme **1** would explain the formation of compounds **3**, **4** and **5**. Coordination of the $SnCl_4$ with

Table 2. ^{13}C-NMR Data for Compounds[§#] **3-5, 7, 8** and **10-14.**

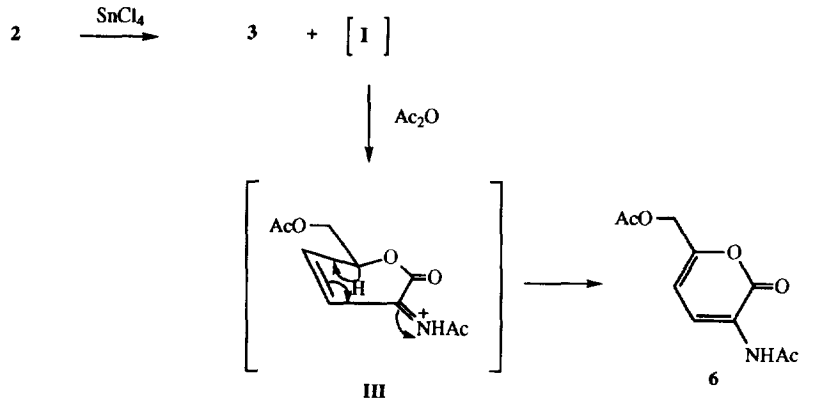
Compound	C-1	C-2	C-3	C-4	C-5	C-6
3	159.3	125.8	122.7	107.0	144.0	
4[a]	161.7	128.3	116.4	67.8	71.9	66.4
5[b]	162.5	126.4	116.9	69.1	72.1	68.0
7[c]	157.8	137.1	130.9	73.3*	72.8*	67.7
8	156.8	136.7	130.3	103.7	155.7	40.5
10	172.0	47.8	21.0*	25.0*	67.5	
11[de]	175.0	53.7	28.6*	28.1*	61.9	
12[d]	175.6	55.5	28.1*	28.0*	61.8	
13[f]	171.2	44.8	31.5	69.8*	71.0*	66.6
14[d]	175.1	49.0	29.8	80.1	73.6	62.6

§ For comparison, the 2-pyrone ring was numbered as a lactone derivative. # For compounds **6** and **9** see Ref 6 and 9. * Signals may be interchanged. [a] OCH_2O 92.7 ppm. [b] In $(CD_3)_2CO$, PhCH: 100.9 ppm. [c] PhCH: 100,0 ppm. [d] In D_2O. [e] The signals reported correspond to the acid form. [f] In DMSO-d_6, OCH_2O: 92.0 ppm.

the benzylidene oxygen atom could promote the electronic displacement of the non-bonding pair of the nitrogen with fragmentation of the C-4–O bond, loss of benzaldehyde and formation of the ionic intermediate **I**. The pool of electrons by the positive charge on nitrogen induces the electronic rearrangement which results in the breaking of the C-5–C-6 bond (route **a**) to give **3**. In this process, a molecule of formaldehyde activated by $SnCl_4$ is produced. Such a molecule is susceptible of the nucleophilic attack by the oxygen atom of **I** (route **b**) leading to the ionic intermediate **II**. Attack of the activated oxygen atom of **II** to the α,β-unsaturated imine system from above of the molecular plane leads to **4**. The participation of the reaction solvent (dichloromethane) as methylene donor in the formation of **4** was excluded, as **3** and **4** were also obtained when other reaction solvents, such as acetonitrile or 1,2-dichloroethane, were used. Compound **5** would arise from the benzylidenation of the intermediate **I** by a process similar to that depicted in route **b**.

The mechanism proposed (Scheme 1) is supported by the results obtained when the reaction of **2** with $SnCl_4$, was conducted in the presence of an excess of acetic anhydride. In this case, together with **3** the 3-acetamido-6-acetoxymethyl-2-pyrone (**6**) was formed (Scheme 2). This fact suggests the conversion of the intermediate **I** into **III** by acetylation of the activated oxygen. The formation of **6** from **III** is expected, as this species is analogous to those suggested as intermediates in the elimination of peracylated 3-acetamido-5,6-dihydro-2-pyrones,[7] which also rearrange with loss of H-6 to give the corresponding 2-pyrone.

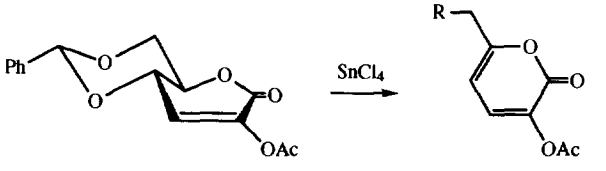
For comparative purposes, it was interesting to examine the reaction of the 2-acetoxy analog of **2** with $SnCl_4$. Such a compound was synthesized by benzylidenation of D-glucono-1,5-lactone with α,α-dimethoxytoluene. The crude 4,6-*O*-benzylidene derivative was acetylated under conditions which promote β-elimination, affording crystalline 2-acetoxy-4,6-*O*-benzylidene-3-deoxy-D-*erythro*-hex-2-enono-1,5-lactone (**7**) in 76% overall yield. Treatment of **7** with $SnCl_4$, under reaction conditions identical to those employed with **2**, led to a main product, which was spectroscopically identified as 3-ace-



Scheme 2

toxy-6-chloromethyl-2-pyrone (**8**). Compound **8** instead of the expected[9] 6-acetoxymethyl analog **9**, was also obtained when the reaction was conducted in the presence of acetic anhydride. The ^1H NMR spectrum of **8** differs from that of **9** in the upfield shift for the 6-methylene group signal (~0.5 ppm). The ^{13}C NMR spectrum of **8** showed also the resonance for the methylene carbon at a δ value (40.5 ppm) similar to that reported for 6-chloromethyl-2-pyrones.[7] The fact that no compounds arising from the breaking of the C-5–C-6 bond of **7** were produced, suggests that no ionic species such as **I** or **III** are involved in the formation of **8**. The influence of the replacement of the NHAc group by AcO at C-3 on the course of the reaction may be interpreted in terms of the electron-donating ability of nitrogen, which being stronger than that of oxygen, can effectively stabilize the carbocations produced by cleavage of the C-4–O bond.

The 2-pyrone derivatives **3** and **4** are suitable precursors of hydroxy α-amino acids, that could be prepared by a sequence of hydrogenation and deprotection reactions. Thus, catalytic hydrogenation of **3** gave the *N*-acetyl-5-hydroxynorvaline-1,5-lactone (**10**), which on treatment with 2N HCl afforded the crystalline hydrochloride derivative **11**. The ammonium salt of 5-hydroxynorvaline (**12**) was also prepared.

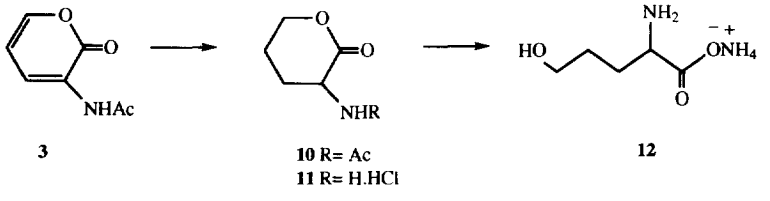


7

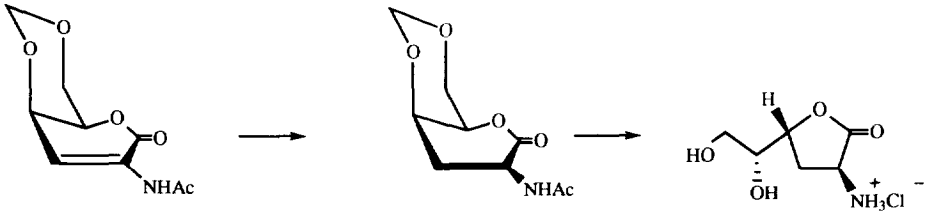
8 R= Cl
[**9** R= OAc]

On the other hand, hydrogenation of **4** took place with excellent diastereofacial selectivity to give exclusivelly the isomer of *S* configuration at C-2, as indicated by the large values for $J_{2,3}$ and $J_{2,3'}$.[1] The high stereoselectivity may be explained assuming that hydrogenation takes place in the preferred

$^{O}H_5$ conformation of the enonolactone ring of **4**. In this conformation, which is constrained by the *cis*-fused dioxane ring, the axially oriented allylic substituent would induce the approach of hydrogen from the opposite face of the double bond, leading to the dideoxylactone **13**, having the D-*lyxo* configuration. Removal of the formylidene and *N*-acetyl groups of **13**, under acidic conditions, led to the 1,4-lactone form of the 4,5,6-trihydroxynorleucine (**14**) having 2*S*,4*R*,5*R* absolute configuration.



3 **10** R= Ac, **11** R= H.HCl **12**



4 **13** **14**

EXPERIMENTAL

General Methods. Melting points (mp) were determined with a Thomas-Hoover capillary mp apparatus, and are uncorrected. NMR spectra were obtained for solutions in $CDCl_3$, unless otherwise noted. 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. Column chromatography was carried out on silica gel (Merck, 240-400 mesh). CH_2Cl_2 was refluxed over P_2O_5, distilled and stored over 4Å molecular sieves.

3-Acetamido-2-pyrone (3) and 2-acetamido-2,3-dideoxy-4,6-*O*-formylidene-D-*threo*-hex-2-enono-1,5-lactone (4). To a solution of 2-acetamido-4,6-*O*-benzylidene-2,3-dideoxy-D-*erythro*-hex-2-enono-1,5-lactone[1] (**2**, 0.455 g, 1.56 mmol) in dry CH_2Cl_2 (5 mL) and acetonitrile (0.5 mL), tin(IV) chloride (0.2 mL, 1.56 mmol) was added. The solution was stirred, under nitrogen, for 1 h at room temperature. TLC monitoring of the reaction mixture revealed two main spots having Rf 0.49 and 0.25 (1:1 PhMe-EtOAc), and no remaining starting **2** was detected. The mixture was diluted with CH_2Cl_2 (30 mL), and washed with saturated aqueous $NaHCO_3$ (20 mL), and water (20 mL), dried ($MgSO_4$) and concentrated. The syrupy residue was chromatographed on a silicagel column using 4:1 PhMe-EtOAc as eluent. The faster migrating product (Rf 0.49) was isolated (0.13g, 53%) and characterized as 3-acetamido-2-pyrone (**3**). Recrystallized from EtOH it gave mp 144-147 °C. Anal. Calcd for $C_7H_7NO_3$: C, 54.90; H, 4.61; N, 9.19. Found: C, 55.16; H, 4.81; N, 9.20.

Further fractions from the column afforded the product of Rf 0.25, which was identified as **4** (0.10 g, 30%). Recrystallized from ethanol **4** gave mp 169 °C (dec); $|\alpha|_D$ +62.6° (*c* 1, $CHCl_3$). Anal. Calcd for $C_9H_{11}NO_5$: C, 50.71; H, 5.20; N, 6.57. Found: C, 50.76; H, 5.24; N, 6.84.

From intermediate fractions of the column a small amount (24 mg) of a by product (Rf 0.35), characterized as 2-acetamido-4,6-*O*-benzylidene-2,3-dideoxy-D-*threo*-hex-2-enono-1,5-lactone (**5**), was isolated crystalline. Recrystallized from ethanol it gave mp 178 °C (dec); $|\alpha|_D$ +12,6° (*c* 1, $CHCl_3$).

3-Acetamido-6-acetoxymethyl-2-pyrone (6). To a cooled (0 °C) solution of **2** (70 mg, 0.24 mmol) in CH_2Cl_2 (1.2 mL) and acetonitrile (0.4 mL), acetic anhydride (0.4 mL, 4.2 mmol) and $SnCl_4$ (35 μL, 0.27 mmol) were added, under nitrogen. After 1h of stirring at room temperature, the mixture showed by TLC two main spots having Rf 0.49 and 0.40 (1:1 PhMe-EtOAc). The reaction mixture was processed as described above, and the products purified by column chromatography. Compound **3** (21 mg, 56.8%) was isolated first, and it had the same physical and spectroscopic properties as the product already described. The next chromatographic fraction (Rf 0.40) afforded, upon evaporation of the solvent and recrystallization from ethanol, 3-acetamido-6-acetoxymethyl-2-pyrone (**6**, 12 mg, 21 %); mp 116-118 °C. Lit[6] mp 116-117 °C.

2-Acetoxy-4,6-*O*-benzylidene-3-deoxy-D-*erythro*-hex-2-enono-1,5-lactone (7). The procedure described by Evans[10] was employed for the benzylidenation. D-Glucono-1,5-lactone (2.0 g, 11.2 mmol), anhydrous DMF (10 mL), α,α-dimethoxytoluene (1.71 g, 12.4 mmol) and *p*-toluenesulfonic acid (6 mg) were placed in a round-bottomed flask. This was attached to a rotatory evaporator and the bath temperature was maintained at 60 ± 5 °C. The pressure was adjusted to produce a gentle reflux of the DMF in the vapor duct. After 1.5 h the temperature was raised to 85 °C, and the liquids were distilled under vacuum. The residue was dissolved in acetic anhydride (10 mL) and sodium acetate (0.5 g) was added. The mixture was heated under reflux for 3 min, and poured into ice-water to yield a solid, which by recrystallization from EtOH afforded compound **7** (2.47 g, 76%) as white needles; mp 146-147 °C; $|\alpha|_D$ +61.4° (*c* 2.5, $CHCl_3$). Anal. Calcd for $C_{15}H_{14}O_6$: C, 62.07; H, 4.87. Found: C, 62.36; H, 4.73.

Reaction of 7 with $SnCl_4$: Synthesis of 3-acetoxy-6-chloromethyl-2-pyrone (8). Compound **7** (0.59 g, 2.91 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and $SnCl_4$ (0.28 mL, 2.33 mmol) was added at 0°C, under nitrogen. After 1h of stirring at room temperature, the mixture showed a main spot of Rf 0.52 (1:1 hexane-EtOAc). Work up of the reaction mixture in the usual manner, afforded 3-acetoxy-6-chloromethyl-2-pyrone (**8**, 0.18 g, 44%), as a chromatographically homogeneus syrup. Anal. Calcd for $C_8H_7O_4Cl$: C, 47.43; H, 3.48; Cl, 17.50. Found: C, 47.52; H, 3.64; Cl, 17.53.

2-Acetamido-5-hydroxypentanoic acid-1,5-lactone [*N*-Acetyl-5-hydroxynorvaline-1,5-lactone, (10)]. Compound **3** (0.10 g, 0.65 mmol) dissolved in EtOAc (10 mL) was treated with hydrogen (60 psi) in the presence of 10% Pd/C. After 12 h TLC showed a single spot having Rf 0.42 (6.5:1 EtOAc-MeOH). The catalyst was filtered and the filtrate concentrated to afford oily **10** (0.10 g, 97.4%). Anal. calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.35; H, 6.90; N, 8.79.

5-Hydroxynorvaline-1,5-lactone hydrochloride (11). A solution of **10** (0.12 g; 0.76 mmol) in 2N aqueous HCl (25 mL) was heated at 100 °C in a culture tube type with teflon lined screw cap, under a static argon atmosphere. After 1 h of stirring no starting material was detected by TLC (3:1

EtOAc-MeOH). The solvent was evaporated leaving an oil, which crystallized after several evaporations with water using high vacuum. Compound **11** (55 mg; 60 %) was recrystallized from MeOH to give mp 219-223 °C. Anal. Calcd for $C_5H_{10}NO_2Cl$: C, 39.62; H, 6.65; N, 9.24. Found: C, 39.22; H, 6.43; N, 8.91.

5-Hydroxynorvaline ammonium salt (12). A solution of **11** (40 mg, 0.33 mmol) in water was applied to an ion-exchange column of Dowex 50W (H^+) resin. The column was eluted with 1M ammonia to give, after freeze drying, **12** (35 mg; 80%); mp 233-235 °C (decomp). Anal. Calcd for $C_5H_{14}N_2O_3$: C, 45.45; H, 7.63. Found: C, 45.65; H, 7.69.

2-Acetamido-2,3-dideoxy-4,6-*O*-formylidene-D-*lyxo*-hexono-1,5-lactone (13). Compound **4** (0.10 g, 0.47 mmol) dissolved in EtOAc (15 mL) was hydrogenated at 60 psi, in the presence of 10% Pd/C as catalyst. After 20 h, TLC monitoring showed a single spot (Rf 0.22) and no starting material. The catalyst was filtered and the filtrate concentrated to give crystalline **13** (95 mg, 94 %); mp 241°C; $|\alpha|_D$ +116° (*c* 0.6, Me_2SO). Anal. Calcd for $C_9H_{13}NO_5$: C, 50.23; H, 6.09; N, 6.51. Found: C, 50.21; H, 5.85; N, 6.49.

(2*S*,4*R*,5*R*)-4,5,6-Trihydroxynorleucine 1,4-lactone hydrochloride (14). A solution of **13** (0.15 g; 0.7 mmol) in 2N aqueous HCl (30 mL), was heated at 100 °C in a culture tube type with screw cap, under argon atmosphere. After 12 h, no starting material was detected by TLC (3:1 EtOAc-MeOH). The solvent was evaporated and the resulting oil crystallized after freezing overnight. Recrystallized from MeOH, compound **14** (55 mg; 60 %) gave mp 189-191°C. $|\alpha|_D$ -63.3° (*c* 0.5, H_2O). Anal. Calcd for $C_6H_{12}NO_3Cl$: C, 36.47; H, 6.12; Cl, 17.94. Found: C, 36.62; H, 6.43; Cl, 18.12.

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