# Carbocyclic Sugar Amines: Synthesis and Stereochemistry of Racemic α- and β-Carbocyclic Ribofuranosylamine, Carbocyclic Lyxofuranosylamine, and Related Compounds

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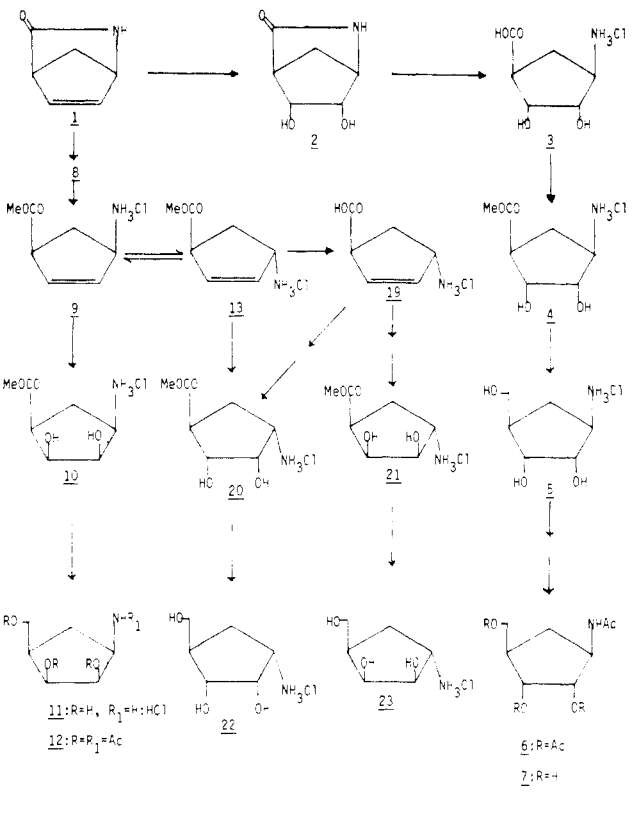
The facile and stereoselective synthesis of racemic carbocyclic β-ribofuranosylamine, carbocyclic β-lyxofuranosylamine, and related 2,3-*cis*-dihydroxy carbocyclic pentofuranosylamines is reported. In addition, the synthesis, isolation, and base-catalyzed epimerization of methyl *cis*-4-aminocyclopent-2-enecarboxylate are described. The epimerization at C(1) followed by stereoselective cis hydroxylation provides for the first time access to the racemic carbocyclic α-pentofuranosylamines.

The increasing interest in the incorporation of carbocyclic sugars, especially the 2,3-*cis*-dihydroxy derivatives, into nucleoside analogues has prompted us to investigate a more efficient and stereoselective route for the synthesis of analogues of carbocyclic sugar amines. Current procedures for their synthesis are relatively tedious and often require separation of stereoisomers. For example, 4β-amino-2α,3α-dihydroxy-1β-cyclopentanemethanol (carbocyclic β-D,L-ribofuranosylamine) can be obtained either stereoselectively[1] or as a mixture of isomers,[2,3] but in either case the procedure is lengthy. The 4α-amino-2α,3α-dihydroxy-1α-cyclopentanemethanol (carbocyclic β-D,L-lyxofuranosylamine) has also been isolated as a byproduct from a mixture of isomers.[4] A major obstacle to a simplified synthesis of these carbocyclic pentofuranoses has been stereocontrol of cis-dihydroxylation. Shealy and Clayton[1b] have demonstrated that cis-dihydroxylation of norbornadiene with potassium permanganate leads to an *exo-cis*-dihydroxy derivative, as expected from the rule of exo addition.[5] We have successfully applied permanganate oxidation to the structurally analogous compound, 2-azabicyclo[2.2.1]hept-5-en-3-one[4,6] (1) and other cyclopentenes and report the stereoselectivity of their facile conversion to 2,3-*cis*-dihydroxy derivatives.

Potassium permanganate was chosen as the cis-hydroxylating reagent for the following reasons: (1) the reaction could be followed colorimetrically, (2) the alternative reagent, osmium tetroxide, is highly toxic, and (3) the reaction is found to be highly stereoselective. Treatment of an acetone solution of the lactam 1[4,6] with an aqueous solution of potassium permanganate leads to a single product **2**, whose geometry (see Scheme I) can be readily demonstrated from analysis of the $^1$H NMR spectrum. First, the lactam ring can be shown to remain intact by observation of a single amide NH resonance at 7.47 ppm in $Me_2SO$-$d_6$. In norbornenediol-like systems the 4,5,6,1 carbon atoms are coplanar; therefore the values of $J_{1,6}$ and $J_{4,5}$ should be nearly equal. If cis-hydroxylation were endo then all the protons should have dihedral angles ca. 0°; hence all the vicinal coupling constants should be about 5–6 Hz, similar to that for the cis 5,6 protons ($J_{5,6}$ = 5.7 Hz). An exo cis-hydroxylation would lead to a trans orientation for the 1,6 and 4,5 protons, corresponding to a dihedral angle of ca. 120°, hence a small, <2 Hz, coupling. The observed values of $J_{1,6}$ and $J_{4,5}$ are <2 Hz, consistent with the report by Shealy and Clayton[1b] that cis-hydroxylation of norbornadiene systems goes exo. The *exo-cis*-5,6-dihydroxy-2-azabicyclo[2.2.1]heptan-3-one (**2**)

Scheme I



is a crystalline solid, mp 169–170 °C, and readily hydrolyzed in dilute acid. The resulting amino acid (**3**) gave the corresponding methyl ester (**4**) after reflux in methanolic HCl. Direct reduction of the dihydroxy methyl ester **4** with lithium triethylborohydride gave a quantitative yield of the triol **5**. Since this free carbocyclic ribofuranosylamine has not been previously characterized, a sample was acetylated to the peracetylated derivative **6** which upon selective deacetylation in methanolic ammonia gave the previously characterized 4β-acetamido-2α,3α-dihydroxy-1β-cyclopentanemethanol (**7**).[1] The sequence from compounds **1**–**5** therefore represents a high-yield, stereose-

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(1) (a) Y. F. Shealy and A. M. Clayton, *J. Am. Chem. Soc.*, 88, 3885 (1966); (b) *ibid.*, **91**, 3075 (1969); (c) A. K. Saksena, *Tetrahedron Lett.*, 133 (1980).
(2) A. Holy, *Collect. Czech. Chem. Commun.*, **41**, 647, 1096 (1976).
(3) R. Vince and S. Daluge, *J. Org. Chem.* **45**, 531 (1980).
(4) S. Daluge and R. Vince, *J. Org. Chem.*, **43**, 2311 (1978).
(5) (a) K. Adler and G. Stein, *Justus Liebigs Ann. Chem.*, **515**, 185 (1935); (b) *ibid.*, **525**, 183 (1936); (c) K. Adler, J. Moneh, and H. Wirtz, *ibid.*, **627**, 47 (1959).
(6) J. C. Jagt and A. M. van Leusen, *J. Org. Chem.* **39**, 564 (1974).

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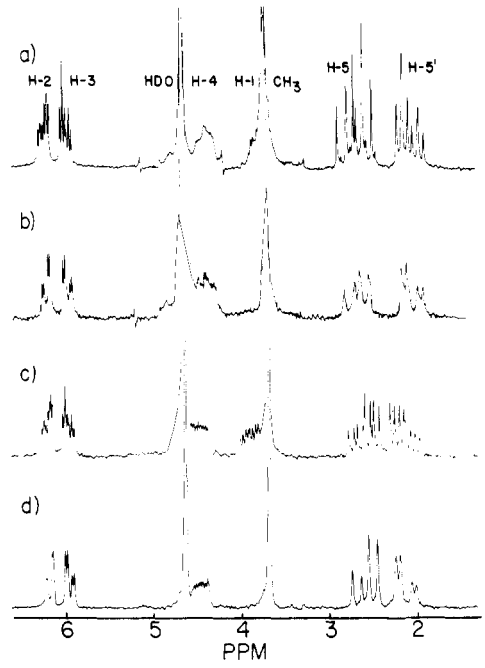



**Figure 1.** $^1$H NMR spectra of methyl *cis*- and *trans*-4-aminocyclopent-2-enecarboxylate hydrochlorides (**9** and **13**) recorded at 80 MHz in $D_2O$ as solvent with sodium 3-(trimethylsilyl)-propionate-*2,2,3,3-d*$_4$ as the internal reference standard. Spectra a and c represent the $\beta$ and $\alpha$ anomers, respectively. Spectra b and d are the corresponding C(1) deuterium-labeled derivatives.

lective route to the free carbocyclic $\beta$-D,L-ribofuranosylamine (**5**). More importantly, compound **5** can be used directly, i.e., without blocking of the hydroxyl groups, for many chemical elaborations.[7]

The stereoselectivity of permanganate cis-hydroxylation was also studied on substituted cyclopentenes since considerable amounts of the amino acid **8** were recovered in the workup of **1**. In contrast to the stereospecificity observed with the lactam **1**, cis-hydroxylation of **8** afforded a 1:1 mixture of the previously characterized **4** and a new compound, **10**. This was an unexpected result, considering the steric hindrance to endo cis-hydroxylation that would be expected in the zwitterionic amino acid. Even more surprising was the result that treatment of the methyl ester **9** with permanganate gave a quantitative yield of compound **10**. Reduction of the dihydroxy methyl ester **10** to the corresponding triol **11** gave an $^1$H NMR spectrum consistent with all substituents cis as expected for carbocyclic $\beta$-D,L-lyxofuranosylamine. The all-cis structure was confirmed by acetylation of **11** to the previously characterized 4$\alpha$-acetamido-2$\alpha$,3$\alpha$-diacetoxy-1$\alpha$-cyclopentanemethylacetate (**12**).[3,4] Therefore permanganate cis-hydroxylation of the readily available methyl ester **9** affords a direct and stereoselective route to carbocyclic $\beta$-D,L-lyxofuranosylamines without necessity for separation of stereoisomers as required for the published procedures using osmium tetroxide.[2,3]

In order to pursue the orgins of the stereocontrol of permanganate cis-hydroxylation we attempted to reduce the methyl ester **9** to the 2,3-unsaturated carbocyclic $\beta$-D,L-pentofuranosylamine (**15**), thus decreasing the steric bulk at C(1). Treatment of **9** with triethylamine followed by reduction with lithium borohydride or triethylborohydride, however, led to a 1:1 mixture of compounds. Analysis of the $^1$H NMR spectra indicated that the compounds represented cis and trans isomers of the 1 and 4 substituents, **15** and **16**, and an uncharacterized compound(s) that no longer contained the 2,3 double bond. Reduction of the methyl ester **9** with triethylborohydride in the absence of triethylamine gave only **15**.

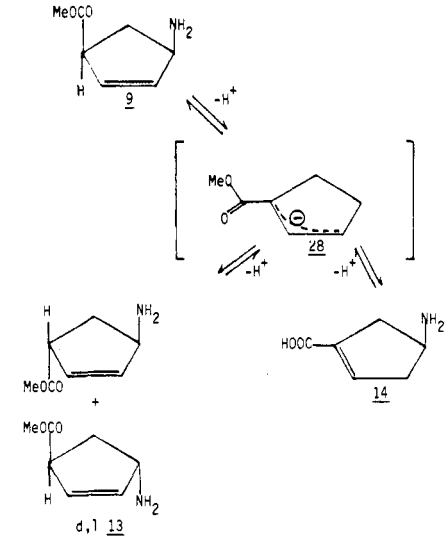



**Figure 2.** Proposed mechanism for the epimerization of **9**. Note that the initial reactant, **9**, is a D,L mixture; thus the product **13** is also a D,L mixture. Inversion at C(1) therefore has the same effect as inversion at C(4); i.e., the product **13** can be drawn as the $\alpha$ anomer.

This result indicated that epimerization was not caused by the reductant but instead was base catalyzed, occurring when triethylamine was added to the suspension of **9** in THF in order to generate the soluble free amine. The site of inversion was determined by incubating **9** with sodium deuteroxide in $CD_3OD$. The spectra of the isolated anomers **9** and **13**, shown in Figure 1, clearly demonstrate that the proton at C(1) exchanges with deuterium. This proton is expected to be the most acidic since it is $\alpha$ to both the ester and the olefin. Note that although epimerization takes place at C(1), the reactant **9** is a D,L mixture; hence the product can be formally drawn as the $\alpha$ anomer, i.e., *as if* epimerization had occurred at C(4) (see Figure 2). The third compound that was recovered in trace amounts from the epimerization reaction was isolated as the amino acid. It is tentatively assigned structure **14** based on its $^1$H NMR spectra which show a single olefin CH resonance and two methylene groups. Daluge and Vince[4] have also noted that reduction of a compound similar to **9** by lithium borohydride gave an unexpected cyclopentanemethanol derivative corresponding to reduction of the carbon–carbon double bond. Both observations are consistent with the reduction of an $\alpha,\beta$-unsaturated ester[8] similar to **14**.

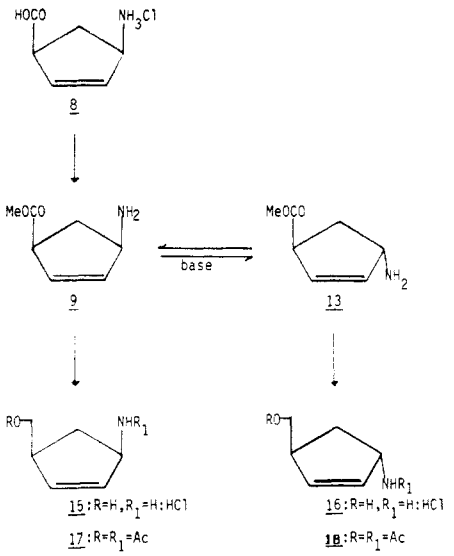
The mixture of cis and trans isomers **9** and **13** was separated by HPLC, using a C-18 reverse-phase column. The recovered cis isomer **9** was identical with the starting material. Reduction of each isomer followed by acetylation of the resulting compounds, **15** and **16**, led to the corresponding acetamido acetates **17** and **18**, respectively (see Scheme II). Compound **17** was identical with the previously reported *cis*-4-acetamidocyclopent-2-enemethyl acetate,[4,9] and **18** was clearly an acetamido acetate with little perturbation in coupling constants from the unacetylated compound. The 1,4 cis isomer was identified

(7) (a) N. J. Cusack, B. J. Hildick, D. H. Robinson, P. W. Rugg, and G. Shaw, *J. Chem. Soc., Perkin Trans. 1*, 1720 (1973); (b) N. J. Cusack, D. H. Robinson, P. W. Rugg, and G. Shaw, *ibid.*, 73 (1974).

(8) (a) Y. Pepin, H. Nazemi, and D. Payette, *Can. J. Chem.*, **56**, 41 (1978); (b) I. Kompis and P. Schonholzer, *Helv. Chim. Acta*, **60**, 518 (1977).

(9) S. Daluge and R. Vince, *Tetrahedron Lett.*, 3005 (1976).

Scheme II




by the similarity in the coupling constants between the protons at C(1) and C(4) and the corresponding protons of the C(5) methylene, as expected from their similar geometry ($J_{1,5}$ = 4.6, $J_{1,5'}$ = 8.3, $J_{4,5}$ = 4.6, and $J_{4,5'}$ = 8.3 Hz). In **16** the values differ as would be expected for an inversion of configuration at either C(1) or C(4) ($J_{1,5}$ = 5.2, $J_{1,5'}$ = 8.1 Hz, whereas $J_{4,5}$ = 8.1 and $J_{4,5'}$ = 3.9 Hz). Consequently it is apparent that by a single treatment of the cis-carbocyclic olefin ester **9** in base a 1:1 mixture of cis and trans isomers can be obtained. Subsequent separation of the isomers provides a facile route to the $\alpha$ configuration.

The isolation of the trans isomers of the carbocyclic D,L-olefins **13** and **19** allowed further study of the stereochemistry of permanganate cis-hydroxylation. As found for **9**, the methyl ester **13** gave a quantitative yield of a single *cis*-diol, **20**. In contrast, treatment of the amino acid **19** with permanganate followed by esterification in methanolic HCl led to a 1:1 mixture of **20** and a second compound **21**. The stereochemistry of the reaction was determined by analysis of the $^1$H NMR spectra. The primary criterion for the assignment of configuration in the anomeric aldopentofuranose series is the chemical shift of the anomeric protons. In the trans-1,2 configuration the resonance on C(1) is more shielded.[10,11] The shielding is attributed to the proximity of the hydroxyl at C(2). As can be seen in Scheme I, the carbocyclic 2,3-*cis*-dihydroxy derivatives are structurally analogous to the corresponding aldopentofuranoses and therefore they should follow the same rules. Accordingly, the chemical shift of the anomeric C-4 proton (3.78 ppm) of **20** has been compared to those of compounds **4** (3.54 ppm) and **10** (3.75 ppm). The similarity of the chemical shift of the C-4 proton in **20** and **10** argues for the same cis configuration, establishing **20** as the carbocyclic $\alpha$-D,L-ribofuranosylamine analogue, methyl 4$\alpha$-amino-2$\alpha$,3$\alpha$-dihydroxy-1$\beta$-cyclopentanecarboxylate. Compound **21**, where the C-4 proton resonates at 3.66 ppm, is then identified as the corresponding $\alpha$-lyxofuranosylamine analogue, methyl 4$\alpha$-amino-2$\beta$,3$\beta$-dihydroxy-1$\beta$-cyclopentanecarboxylate. These results are in accord with comparison of the vicinal coupling constant

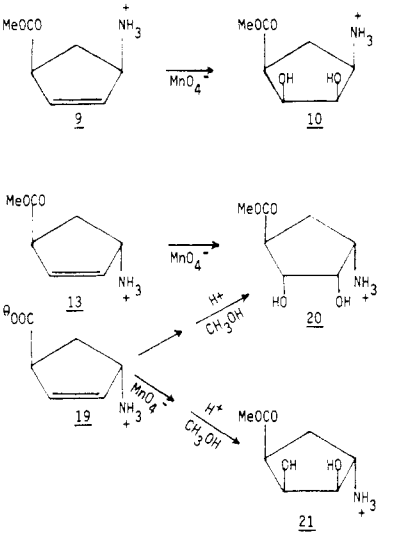



**Figure 3.** 2,3-Cis-dihydroxylation of compounds **9**, **13**, and **19** with potassium permanganate.

$J_{3,4}$ in **20** and **21** and the corresponding values in the carbocyclic $\beta$-D,L-ribo and carbocyclic $\beta$-D,L-lyxo structures of **4** and **10**. Subsequent reduction of the esters with triethylborohydride gave the corresponding $\alpha$-carbocyclic sugar amines **22** and **23**. Compound **22** is of particular interest since this method is the first report of the synthesis of carbocyclic sugars with an $\alpha$ configuration.

The stereochemistry of the cis-hydroxylation reaction is summarized in Figure 3. In the 1-methyl ester, cis-hydroxylation by permanganate occurs cis to the 4-ammonium group regardless of the configuration at C(1), whereas in the unesterified carbocyclic olefin **19** or **8**, cis-hydroxylation occurs both cis and trans to the 4-ammonium. The stereochemical determinants for the reaction are obscure. Electrostatics alone do not seem to explain the stereochemistry. For example, in **19** there is attack by the anionic permanganate cis to the anionic carboxylate and trans to the C(4) ammonium, whereas no attack is observed cis to the neutral ester in **13**. Further investigations of the stereochemistry of the cis-hydroxylation reaction should clarify this point. The procedures outlined, however, provide a simple route to the stereoselective synthesis of a series of important carbocyclic sugar amine analogues.

## Experimental Section

**General Methods.** Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The NMR spectra were recorded either at 80 MHz on a Varian FT-80A Fourier transform NMR spectrometer or at 360 MHz on a Bruker HXS-360 NMR spectrometer equipped with a Nicolet Technologies 1180/Fourier transform system and a computer-controlled homonuclear decoupling accessory; $D_2O$ was used as solvent with sodium 3-(trimethylsilyl)propionate-2,2,3,3-$d_4$ as the internal standard; the chemical shifts are reported in parts per million (ppm). The IR spectra were recorded on a Perkin-Elmer 337 spectrophotometer and mass spectra with an AEI-MS 9 high-resolution mass spectrometer. Silica gel (Baker-flex) eluted with a mixture of solvent, *n*-butyl alcohol–acetic acid–water (5:2:3), was used for TLC and spots were detected with a 0.2% ninhydrin aerosol spray in ethanol. In the absence of crystallization or to obtain material for seed crystals, compounds were purified by HPLC, using a C-18 reverse-phase preparative column eluted with water. A Waters Associate R401 differential refractometer was used for detection.

**General Procedure for Reduction with Lithium Triethylborohydride.** The methyl ester derivative, suspended in dry tetrahydrofuran (20 mL/mmol), was cooled to 0 °C in an ice bath and a 1.5-fold excess of 1 M lithium triethylborohydride in

(10) (a) J. D. Stevens, R. K. Ness and H. G. Fletcher, Jr., *J. Org. Chem.*, **33**, 1806 (1968); (b) J. D. Stevens and H. G. Fletcher, Jr., *ibid.*, **33**, 1799 (1968).

(11) (a) R. U. Lemieux and D. R. Linebach, *Ann. Rev. Biochem.*, **32**, 156 (1963); (b) B. L. Kam, J.-L. Barascut and J.-L. Imbach, *Carbohydr. Res.*, **69**, 135 (1979).

tetrahydrofuran was added with stirring. After 30 min the solvent was removed under vacuum and the residue was dissolved in methanol and treated with 0.1 N HCl at 0 °C to destroy any remaining lithium triethylborohydride. Methanol and the resulting trichloroborane were removed by rotary evaporation, and the lithium chloride was removed by washing the dry residue with acetone.

**2-Azabicyclo[2.2.1]hept-5-en-3-one (1).** The lactam 1 was synthesized according to the literature procedure[4] except that pyridine was added to neutralize the acetic acid. After extraction, the organic phase was rotary evaporated to dryness and the resulting oil was crystallized in ethyl ether–hexane to give the lactam 1 as needles (70% yield): mp 58–59 °C; IR and $^1$H NMR spectra were identical with those reported.

The mother liquors and aqueous phase of the extraction were combined, treated with charcoal, and filtered. The resulting mixture was rotary evaporated to dryness and excess pyridine removed by coevaporation with a mixture of ethanol–toluene (1:4 v/v). The residue was refluxed in 6 N aqueous HCl for 30 min and treated as described below to give the amino acid 8 (20% yield).

***exo-cis*-5,6-Dihydroxy-2-azabicyclo[2.2.1]heptan-3-one (2).** The lactam 1[4,6] (3.27 g, 30 mmol) was dissolved in acetone, and 1 M aqueous potassium permanganate was added dropwise with stirring (about 35 mL) over a period of about 1 h at room temperature until the purple color persisted. The resulting precipitate was filtered off over Celite and washed with more acetone. The filtrates were combined and rotary evaporated to dryness. The residue was then dissolved in ethanol and any further manganese dioxide was allowed to precipitate overnight at 0 °C. Filtration followed by removal of the ethanol under vacuum gave the dihydroxy lactam 2 (3.95 g, 27.5 mmol, 91%): crystallized from methanol–ethyl ether; mp 169–170 °C; IR (neat, NaCl) 3320 (br, OH, NH), 1690 (C=O), 1580 (lactam 2); mass spectrum, *m/e* 143; NMR ($D_2O$) $\delta$ 4.08 [d, 1 H, $J$ = 5.7 Hz, C(5)], 4.04 [d, 1 H, $J$ = 5.7 Hz, C(6)], 3.80 [m, 1 H, C(4)], 2.54 [m, 1 H, C(1)], 2.10 [br s, 2 H, C(7,7′)]. Anal. Calcd for $C_6H_9O_3N$: C, 50.35; H, 6.29; N, 9.79. Found: C, 50.40; H, 6.21; N, 9.70.

**Methyl 4$\beta$-Amino-2$\alpha$,3$\alpha$-dihydroxy-1$\beta$-cyclopentanecarboxylate Hydrochloride (4).** The dihydroxy lactam 2 (5.7 g, 40 mmol) was refluxed in 3 N aqueous HCl (25 mL) for 3 h followed by rotary evaporation to dryness to give 3 (not isolated): $R_f$ 0.50; NMR ($D_2O$) $\delta$ 4.20 [dd, 1 H, $J_{1,2}$ = 4.5, $J_{2,3}$ = 5.7 Hz, C(2)], 3.71 [dd, 1 H, $J_{3,4}$ = 7.0 Hz, C(3)], 3.20 [m, 1 H, C(4)], 2.65 [m, 1 H, C(1)], 2.35 [dq, 1 H, $J_{1,5}$ = 9.1, $J_{4,5}$ = 7.8, $J_{5,5'}$ = 13.2 Hz, C(5)], 1.42 [dt, 1 H, $J_{1,5'} = J_{4,5'}$ = 9.3 Hz, C(5′)]. The amino acid 3 was refluxed in 1 N methanolic HCl for 2 h, and the solution was rotary evaporated to dryness to an oil. Tituration of the residue in ethyl ether gave the methyl ester 4 (8.2 g, 38.8 mmol, 97%) as a white powder which was recrystallized from methanol–ethyl ether: mp 146–147 °C; $R_f$ 0.54; IR (KBr) 3350–2950 (v/br, OH, NH), 1735 (C=O), 1625 (amine 2); NMR ($D_2O$) $\delta$ 4.30 [dd, 1 H, $J$ = 5.5, 7.0 Hz, C(2)], 4.08 [dd, 1 H, $J$ = 5.5, 5.1 Hz, C(3)], 3.54 [m, 1 H, C(4)], 2.96 [m, 1 H, C(1)], 2.53 [dt, 1 H, $J$ = 8.5, 13.8 Hz, C(5)], 1.84 [dt, 1 H, $J$ = 9.2, 13.8 Hz, C(5′)], 3.75 (s, 3 H, $OCH_3$). Anal. Calcd for $C_7H_{14}O_4NCl$: C, 39.71; H, 6.62; N, 6.62; Cl, 16.78. Found: C, 39.82; H, 6.54; N, 6.62; Cl, 16.83.

**4$\beta$-Amino-2$\alpha$,3$\alpha$-dihydroxy-1$\beta$-cyclopentanemethanol Hydrochloride (5).** The methyl ester 4 (3.49 g, 16.5 mmol), suspended in tetrahydrofuran (100 mL), was reduced with triethylborohydride at 0 °C, as described above. The solvent was removed under vacuum and the resulting residue was treated as described in the general procedure to give 5 (2.75 g, 15 mmol, 91%) as an oil: $R_f$ 0.44; IR (neat, NaCl) 3300 (br, OH, NH), 1635 (amine 2); mass spectrum, *m/e* 183; NMR ($D_2O$) $\delta$ 4.00 [dd, 1 H, $J$ = 5.7, 8.0 Hz, C(2)], 3.92 [dd, 1 H, $J$ = 4.2, 5.7 Hz, C(3)], 3.54 [m, 1 H, C(6)], 2.34 [dt, 1 H, $J$ = 8.3, 8.3, 13.3 Hz, C(5)], 2.17 [m, 1 H, C(1)], 1.34 [dt, 1 H, $J$ = 9.6, 9.6, 13.3 Hz, C(5′)], 3.63 [dd, 1 H, $J$ = 5.6, 11.3 Hz, C(6)], 3.58 [dd, 1 H, $J$ = 6.0, 11.3 Hz, C(6′)].

A sample of 5 (0.25 g, 1.36 mmol) was acetylated in pyridine with acetic anhydride to give the 4$\beta$-acetamido-2$\alpha$,3$\alpha$-diacetoxy-1$\beta$-cyclopentanemethyl acetate (6, not isolated) as an oil: IR (neat, NaCl) 3200 (br, NH), 1735 (OAc), 1646 (amide 1), 1560 (amide 2); NMR ($D_2O$) $\delta$ 5.05 [m, 2 H, C(2), C(3)], 4.14 [m, partially overlapped, 1 H, C(4)], 4.08 [d, 2 H, $J$ = 5.2 Hz, C(6,6′)], 2.45 [m, 2 H, C(1,5)], 1.22 [m, 1 H, C(5′)], 2.05 (s, 9 H, OAc), 1.96 (s, 3 H, NHAc). Compound 6 was partially deacetylated by treatment with methanolic ammonia overnight at 0 °C to give 7 (0.38 g, 1.2 mmol, 88%), identical with the known 4$\beta$-acetamido-2$\alpha$,3$\alpha$-dihydroxy-1$\beta$-cyclopentanemethanol:[1] NMR ($D_2O$) $\delta$ 4.10 [m, 1 H, C(4)], 3.87 [dd, 1 H, $J$ = 5.0, 5.7 Hz, C(2)], 3.80 [dd, 1 H, $J$ = 5.7, 7.5 Hz, C(3)], 3.63 and 3.58 [2 dd, 1 H each, $J$ = 6.1, 11.0 Hz, C(6,6′)], 2.27 [dt, 1 H, $J$ = 8.5, 8.5, 13.5 Hz, C(5)], 2.13 [m, 1 H, C(1)], 1.13 [dt, 1 H, $J$ = 8.8, 8.8, 13.5 Hz, C(5′)], 1.97 (s, 3 H, NHAc).

***cis*-4-Aminocyclopent-2-enecarboxylate Hydrochloride (8).** The lactam 1 (4.8 g, 44 mmol) was readily hydrolyzed in 1 N aqueous HCl at reflux for 1 h. The solution was rotary evaporated to dryness and the residue was freed from excess HCl by shaking with ethyl ether or acetone to give 8 (6.47 g, 39.6 mmol, 90%) as a white powder that was recrystallized from ethanol–ethyl acetate: mp 175–176 °C; IR (KBr) 3200–2900 (v/br, OH, NH), 2860 (HC=CH), 1710 (C=O), 1570 (C=C); NMR ($D_2O$) $\delta$ 6.24 [dq, 1 H, $J$ = 2.3, 1.5, 5.7 Hz, C(2)], 5.98 [dq, 1 H, $J$ = 1.6, 2.0, 5.7 Hz, C(3)], 4.39 [m, 1 H, C(4)], 3.79 [m, 1 H, C(1)], 2.68 [dt, 1 H, $J$ = 8.2, 14.5 Hz, C(5)], 2.06 [dt, 1 H, $J$ = 4.2, 4.2, 14.5 Hz, C(5′)], 3.74 (s, 3 H, $OCH_3$). Anal. Calcd for $C_6H_{10}O_2NCl$: C, 44.04; H, 6.11; N, 8.56; Cl, 27.71. Found: C, 44.03; H, 6.25; N, 8.54; Cl, 27.48.

**Methyl *cis*-4-Aminocyclopent-2-enecarboxylate Hydrochloride (9).** The amino acid 8 (5 g, 30.6 mmol) was refluxed in 1 N methanolic HCl (100 mL) for 1 h. The solvent was removed under vacuum and the resulting oil was precipitated with ethyl ether. The precipitate (6.4 g, 36 mmol, 98%) was recrystallized from methanol–ethyl acetate: mp 82–83 °C; $R_f$ 0.47; IR (KBr) 3390 (br, OH, NH), 2950 (HC=CH), 1725 (C=O), 1595 (C=C); NMR ($D_2O$) $\delta$ 6.22 [dq, 1 H, $J$ = 1.5, 5.7 Hz, C(2)], 5.98 [dt, 1 H, $J$ = 2.0, 5.7 Hz, C(3)], 4.46 [m, 1 H, C(4)], 3.81 [m, 1 H, C(1)], 2.72 [dt, 1 H, $J$ = 4.7, 4.7, 14.5 Hz, C(5)], 2.08 [dt, 1 H, $J$ = 8.2, 8.2, 14.5 Hz, C(5′)], 3.75 (s, 3 H, $OCH_3$). Anal. Calcd for $C_7H_{12}O_2NCl$: C, 47.32; H, 6.76; N, 7.89; Cl, 20.0. Found: C, 47.27; H, 6.71; N, 7.96; Cl, 20.10.

**Methyl 4$\alpha$-Amino-2$\alpha$,3$\alpha$-dihydroxy-1$\alpha$-cyclopentanecarboxylate Hydrochloride (10).** The methyl ester 9 (3.5 g, 20 mmol) was dissolved in water (10 mL) and then 1 M aqueous potassium permanganate (22 mL) was added dropwise at room temperature over a period of 30 min. The precipitate was filtered off over Celite and the solvent was removed under vacuum. The resulting oil was refluxed in 1 N methanolic HCl for 30 min. The solution was rotary evaporated to dryness and the residue purified by HPLC, using a C-18 reverse-phase column eluted with water. Removal of the water, followed by tituration with ethyl ether, gave the methyl ester 10 (3.5 g, 17 mmol, 85%), which crystallized from methanol–ethyl ether as needles: mp 149–150 °C; $R_f$ 0.51; IR (KBr) 3325–2950 (v/br, OH, NH), 1740 (C=O), 1625 (amine 2); NMR ($D_2O$) $\delta$ 4.43 [t, 1 H, $J$ = 4.2 Hz, C(2)], 4.25 [dd, 1 H, $J$ = 3.7, 6.7 Hz, C(3)], 3.75 [m, 1 H, C(4)], 3.15 [m, 1 H, C(1)], 2.41 [dq, 1 H, $J$ = 5.0, 8.2, 14.6 Hz, C(5)], 2.28 [dq, 1 H, $J$ = 8.8, 9.5, 14.6 Hz, C(5′)], 3.75 (s, 3 H, $OCH_3$). Anal. Calcd for $C_7H_{14}O_4NCl$: C, 39.71; H, 6.62; N, 6.62; Cl, 16.78. Found: C, 39.56; H, 6.54; N, 6.49; Cl, 16.72.

**4$\alpha$-Amino-2$\alpha$,3$\alpha$-dihydroxy-1$\alpha$-cyclopentanemethanol Hydrochloride (11).** The methyl ester 10 (3.5 g, 16.6 mmol) was reduced with lithium triethylborohydride and purified as described above for compound 4 to give 11 (2.5 g, 14.0 mmol, 85%) as an oil: $R_f$ 0.40; the IR spectrum was identical with that of 5; mass spectrum, *m/e* 183; NMR ($D_2O$) $\delta$ 4.22 [t, 1 H, $J$ = 5.0, 5.0 Hz, C(2)], 4.20 [dd, 1 H, $J$ = 4.9, 5.0 Hz, C(3)], 3.70 [m, 1 H, C(4)], 2.36 [dt, 1 H, $J$ = 8.6, 8.6, 14.3 Hz, C(5)], 2.22 [m, 1 H, C(1)], 1.60 [dq, 1 H, $J$ = 5.0, 9.7, 14.3 Hz, C(5′)], 3.80 [dd, 1 H, $J$ = 7.4, 11.0 Hz, C(6)], 3.65 [dd, 1 H, $J$ = 6.1, 11.0 Hz, C(6′)].

Acetylation of a sample of 11 gave the known 4$\alpha$-acetamido-2$\alpha$,3$\alpha$-diacetoxy-1$\alpha$-cyclopentanemethyl acetate (12):[3,4] NMR ($D_2O$) $\delta$ 5.38 [dd, 1 H, $J$ = 4.2, 5.2 Hz, C(2)], 5.23 [dd, 1 H, $J$ = 4.2, 6.2 Hz, C(3)], 4.48 [m, 1 H, partially overlapped by HOD, C(4)], 4.28 [dd, 1 H, $J$ = 10.9, 8.1 Hz, C(6)], 4.10 [dd, 1 H, $J$ = 10.9, 5.9 Hz, C(6′)], 2.70–2.30 [m, 2 H, C(1,5)], 1.72 [m, 1 H, C(5′)], 2.09 (s, 3 H, OAc), 2.07 (s, 6 H, 2-OAc), 2.00 (s, 3 H, NAc).

**Epimerization of Methyl Ester 9.** The methyl ester 9 (1.52 g, 8.6 mmol) was dissolved in methanol (20 mL) and incubated for 30 min at pH ~10–11. The solvent was then removed by rotary evaporation, the resulting oil was dissolved in methanol,

and the NaCl precipitate was removed by filtration. The solution was refluxed with methanolic HCl for 30 min, and then the solvent was removed. The resulting products were separated by HPLC, using a C-18 reverse-phase column eluted with water. The amino acid **14**, 4-aminocyclopent-1-enecarboxylic acid, eluted first, with a relative integrated area corresponding to about 5%, followed by **13**, methyl *trans*-4-aminocyclopent-2-enecarboxylate, and then **9** in a ratio of 1:1.

**Compound 13**: crystallized from methanol–ethyl acetate; mp 108–110 °C; $R_f$ 0.48; the IR spectrum was almost identical with that of compound **9**; NMR ($D_2O$) $\delta$ 6.22 [dq, 1 H, $J$ = 1.5, 1.8, 5.7 Hz, C(2)], 5.98 [dt, 1 H, $J$ = 2.0, 5.7 Hz, C(3)], 4.51 [m, 1 H, C(4)], 3.88 [m, 1 H, C(1)], 2.64 [dq, 1 H, $J$ = 8.1, 5.2, 14.7 Hz, C(5)], 2.16 [dq, 1 H, $J$ = 4.2, 8.7, 14.7 Hz, C(5′)], 3.72 (s, 3 H, $OCH_3$). Anal. Calcd for $C_7H_{12}O_2NCl$: C, 47.32; H, 6.76; N, 7.89; Cl, 20.0. Found: C, 47.27; H, 6.80; N, 7.83; Cl, 19.89.

**Compound 14**: obtained as an oil; $R_f$ 0.55; IR (neat, NaCl) 3250 (br, OH, NH), 2900 (C=CH), 1680 (C=O), 1580 (C=C); NMR ($D_2O$) $\delta$ 6.59 [br s, 1 H, C(2)], 4.07 [m, 1 H, C(4)], 3.05, 3.00, 2.64, and 2.58 [m, 1 H each, C(5), C(5′), C(3), and C(3′)].

***cis*- and *trans*-4-Aminocyclopent-2-enemethanol Hydrochlorides (15 and 16).** The methyl ester **9** (2.5 g, 14 mmol) or **13** (0.28 g, 1.58 mmol) suspended in dry tetrahydrofuran was cooled at 0 °C in an ice bath and then was treated with lithium triethylborohydride, as described in the general procedure, to give **15** (1.97 g, 13.2 mmol) and **16** (0.22 g, 1.47 mmol) as oils.

**Compound 15**: 95% yield; $R_f$ 0.46; mass spectrum, $m/e$ 149; IR (neat, NaCl) 3395 (br, OH, NH), 2950 (HC=CH), 1640 (C=C); NMR ($D_2O$) $\delta$ 6.10 [dt, 1 H, $J$ = 1.8, 5.7 Hz, C(2)], 5.80 [dt, 1 H, $J$ = 2.0, 5.7 Hz, C(3)], 4.33 [m, 1 H, C(4)], 3.00 [m, 1 H, C(1)], 2.57 [dt, 1 H, $J$ = 4.6, 15.0 Hz, C(5)], 1.57 [dt, 1 H, $J$ = 8.3, 15.0 Hz, C(5′)], 3.63 [d, 2 H, $J$ = 4.6 Hz, C(6,6′)].

**Compound 16**: 93% yield; IR and mass spectra identical with those of **15**; $R_f$ 0.41; NMR ($D_2O$) $\delta$ 6.22 [dt, 1 H, $J$ = 1.7, 5.7 Hz, C(2)], 5.90 [dt, 1 H, $J$ = 2.3, 5.7 Hz, C(3)], 4.42 [m, 1 H, C(6)], 3.18 [m, 1 H, C(1)], 2.13 [dq, 1 H, $J$ = 8.1, 5.2 Hz, 14.6 Hz, C(5)], 2.03 [dq, 1 H, $J$ = 3.9, 8.1, 14.6 Hz, C(5′)], 3.61 [dd, 1 H, $J$ = 5.5, 11.3 Hz, C(6)], 3.58 [dd, 1 H, $J$ = 6.0, 11.5 Hz, C(6′)].

***cis*- and *trans*-4-Acetamidocyclopent-2-enemethyl Acetates (17 and 18).** Compounds **15** and **16** (0.15 g, 1 mmol) were acetylated in pyridine–acetic anhydride to give, quantitatively, **17** and **18**, respectively, as oils. Compound **17** was identical with the *cis*-4-acetamidocyclopent-2-enemethyl acetate.[4,9] Compound **18** had IR [(neat, NaCl) 3280 (br, NH), 2945 (HC=CH), 1730 (OAc), 1650 (C=C, amide 1), 1550 (amide 2)] and mass spectra ($m/e$ 197) identical with those of **17**: NMR ($D_2O$) $\delta$ 5.96 [dt, 1 H, $J$ = 1.7, 5.7 Hz, C(2)], 5.79 [dt, 1 H, $J$ = 2.0, 5.7 Hz, C(3)], 4.80 [m, 1 H, C(4)], 3.19 [m, 1 H, C(1)], 2.24–1.90 [m, 2 H, overlapped, C(5,5′)], 4.08 (d, 2 H, $J$ = 6.0 Hz, C(6,6′)], 2.08 (s, 3 H, OAc), 1.95 (s, 3 H, NAc). Anal. Calcd for $C_{10}H_{15}O_3N$: C, 60.89; H, 7.67; N, 7.10. Found for **18**: C, 60.87; H, 7.60; N, 7.14.

**Methyl 4α-Amino-2α,3α-dihydroxy-1β-cyclopentanecarboxylate Hydrochloride (20).** Compound **13** (0.25 g, 1.41 mmol) was hydroxylated with potassium permanganate as described for lactam **1** and methyl ester **9**. Similar treatment of the resulting dihydroxy derivative gave **20** (0.26 g, 1.23 mmol, 87%) as an oil: $R_f$ 0.50; IR spectrum identical with that of **4**; NMR ($D_2O$) $\delta$ 4.31 [dd, 1 H, $J$ = 3.9, 8.3 Hz, C(2)], 4.23 [t, 1 H, $J$ = 4.2 Hz, C(3)], 3.77 [m, 1 H, C(4)], 3.13 [m, 1 H, C(1)], 2.40 [dq, 1 H, $J$ = 6.6, 9.2, 14.5 Hz, C(5)], 2.17 [dq, 1 H, $J$ = 11.2, 7.2, 14.5 Hz, C(5′)], 3.75 (s, 3 H, $OCH_3$).

**Methyl 4α-Amino-2β,3β-dihydroxy-1β-cyclopentanecarboxylate Hydrochloride (21).** The methyl ester **13** (0.25 g, 1.4 mmol) was quantitatively hydrolyzed in dilute HCl to give *trans*-4-aminocyclopent-2-enecarboxylic acid (**19**, see Scheme I). Treatment of **19** in water with aqueous potassium permanganate as described above, followed by esterification of the resulting reaction products, gave a mixture of **20** and methyl 4α-amino-2β,3β-dihydroxy-1β-cyclopentanecarboxylate hydrochloride (**21**) in a ratio of about 1:1 (0.20 g, 0.95 mmol mixture). Compound **21** (not isolated): NMR ($D_2O$) $\delta$ 4.37 [t, 1 H, $J$ = 4.2 Hz, C(2)], 4.12 [dd, 1 H, $J$ = 4.2, 9.0 Hz, C(3)], 3.66 [m, 1 H, C(4)], 3.34 [m, 1 H, C(1)], 2.69 [dq, 1 H, $J$ = 8.2, 10.7, 14.5 Hz, C(5)], 1.86 [dq, 1 H, $J$ = 7.1, 10.5, 14.5 Hz, C(5′)], 3.75 (s, 3 H, $OCH_3$).

**4α-Amino-2α,3α-dihydroxy-1β-cyclopentanemethanol Hydrochloride (22).** The methyl ester **20** (0.2 g, 0.94 mmol) was reduced with lithium triethylborohydride in tetrahydrofuran to give **22** (0.14 g, 0.76 mmol, 81%) as an oil, with an IR spectrum identical with those of **5** and **11**: $R_f$ 0.42; NMR ($D_2O$) $\delta$ 4.18 [t, 1 H, $J$ = 4.1, 4.1 Hz, C(2)], 3.94 [dd, 1 H, $J$ = 4.1, 7.8 Hz, C(3)], 3.68 [m, 1 H, C(4)], 2.34 [m, 1 H, C(1)], 2.00 [dq, 1 H, $J$ = 7.2, 8.9, 14.3 Hz, C(5)], 1.94 [dq, 1 H, $J$ = 10.4, 6.7, 14.3 Hz, C(5′)], 3.70 [dd, 1 H, $J$ = 5.0, 11.2 Hz, C(6)], 3.58 [dd, 1 H, $J$ = 6.0, 11.2 Hz, C(6′)].

**4α-Amino-2β,3β-dihydroxy-1β-cyclopentanemethanol Hydrochloride (23).** The mixture of methyl esters **20** and **21** was treated with triethylborohydride as described above. The resulting triols, **22** and **23**, were obtained as oils. The IR spectrum of the mixture was almost identical with those of the previous triols **5**, **11**, and **22**: NMR ($D_2O$) $\delta$ 4.17 [dd, 1 H, $J$ = 4.0, 4.5 Hz, C(2)], 4.13 [dd, 1 H, $J$ = 4.0, 7.5 Hz, C(3)], 3.60 [m, 1 H, C(4)], 2.41 [m, 1 H, C(1)], 2.04 [dq, 1 H, $J$ = 7.2, 10.4, 14.3 Hz, C(5)], 1.83 [dq, 1 H, $J$ = 7.3, 10.3, 14.3 Hz, C(5′)], 3.76 [dd, 1 H, $J$ = 8.0, 10.9 Hz, C(6)], 3.60 [dd, 1 H, $J$ = 6.9, 10.9 Hz, C(6′)].

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