A Highly Diastereoselective Synthesis of New Polyhydroxy 2-Aminonorbornanecarboxylic Acids

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Our recent research is directed toward the synthesis of β-heterosubstituted carbocyclic amino acids[1−4] in which the skeleton of natural amino acid is included. For this reason and for their rigidity, they appear to be interesting compounds as biological targets. In particular, the 2-aminonorbornanecarboxylic acid derivatives, because of the bulkiness and apolarity of the ring and the metabolic stability, are characterized by different biological activities.[5]

As evidenced by recent literature, a new and very promising research field is related to the preparation of hydroxy- and polyhydroxycarbocyclic amino acids, which are considered mimetic of carbohydrates but are characterized by a greater metabolic stability.[4,6] In continuing our research in this area, we now report on the highly diastereoselective synthesis of 2-amino-3,6-dihydroxynorbornanecarboxylic acid **14** and of 2-amino-3,5,6-trihydroxynorbornanecarboxylic acids **15**−**18**. Our purpose in the synthesis of the polyhydroxylated norbornanecarboxylic acid derivatives is related to the possibility to change the polarity of this nucleus and their biological properties. As known, in many cases, polar substituents are responsible for the interactions between the substrate and the enzymatic receptor and their spatial arrangement is determinant to realize those interactions. So, the preparation of compounds **14**−**18** having several hydroxy groups in a specific position and in a controlled spatial arrangement represents an important goal. The key starting materials for the preparation of these compounds are the *exo*- and *endo*-2-amino-3-hydroxynorbornenecarboxylic acid derivatives **3** and **4**, including the serine skeleton, which were synthesized recently in our laboratory.[3]

The cycloaddition reaction between oxazolone (*Z*)-**1** and cyclopentadiene (**2**) was carried out using litium perchlorate as the catalyst, giving a mixture of cycloadducts *exo*-**3** and *endo*-**4**. After the addition of anhydrous ethanol to the crude reaction mixture, cycloadducts **3** and **4** were transformed into the corresponding esters *exo*-**5** and *endo*-**6** (70:30 ratio), which were isolated in a 70% overall yield (Scheme 1). Esters **5** and **6** were the key starting materials for the preparation of the 5,6-dihydroxy derivatives in which the cis or trans relationship between the two hydroxy groups exists (Scheme 1). Treatment of ester *exo*-**5** with a catalytic amount of osmium tetraoxide in the presence of an excess of *N*-methylmorpholine *N*-oxide in a mixture of acetone/water allowed the formation of the *cis*-dihydroxy derivative *exo*-**7**, as a single diastereoisomer, in 74% yield. The derivative *endo*-**8** was isolated in 80% yield when starting from *endo*-**6** and operating under the same conditions.

The synthesis of the *trans*-5,6-dihydroxy derivatives was achieved using an epoxide as the key intermediate (Scheme 2). When the ester *exo*-**5** was treated with *m*-chloroperbenzoic acid at room temperature, the epoxide *exo*-**9** was isolated in quantitative yield as a single diastereoisomer. When the reaction was performed starting from the ester *endo*-**6**, the epoxide *endo*-**10** was isolated in 67% yield in addition to the lactone derivative *endo*-**11** (22%). This latter probably derives from an intramolecular reaction of the carboxyl acid group, formed by partial hydrolysis of the ester function, with the epoxide giving the lactone **11** in which the trans stereochemistry between the two oxygen atoms is assured.

It was observed that, on prolonging the reaction time (96 h instead of 24 h), the formation of the lactone derivative was increased (1:3 with respect to 3:1). Also starting from the ester *endo*-**6** a single diastereoisomeric epoxide was isolated. It is possible to obtain the same lactone *endo*-**11** in 75% yield starting from the epoxide *endo*-**10** by reacting it with titanium tetrachloride in a dichloromethane solution according to the mechanism reported in the literature.[7] Instead, the use of titanium tetrachloride gave the oxazine derivative *exo*-**12** in 66% yield when starting from the epoxide *exo*-**9**. For its formation it may be assumed that the Lewis acid favors the enolization of the amide function, which reacts intramolecularly with the oxirane ring giving the same trans stereochemical result at C-4 and C-5 observed for the endo derivative. Interestingly, it is possible to obtain directly a mixture of oxazine derivative **12** and lactone **11** when starting from a mixture of esters *exo*-**5** and *endo*-**6** that were transformed into epoxides *exo*-**9** and *endo*-**10**, as reported above, and subsequent reaction with titanium tetrachloride.

The structure and the stereochemistry of all compounds were assigned by analytical and spectroscopic

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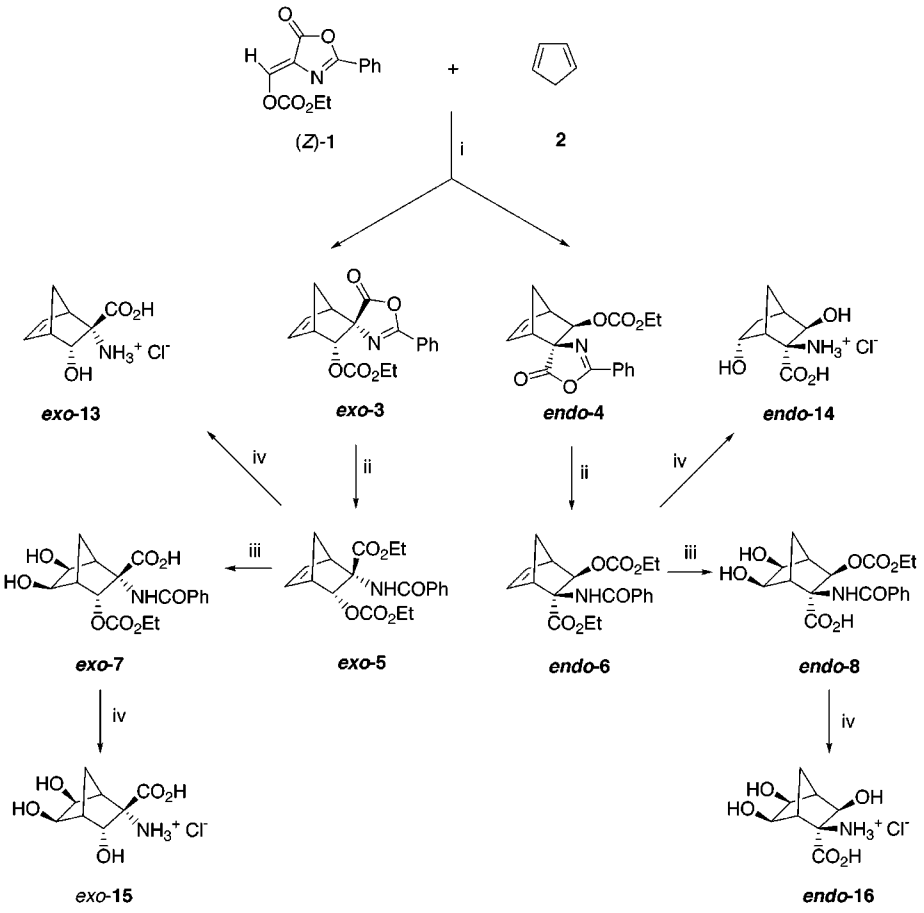
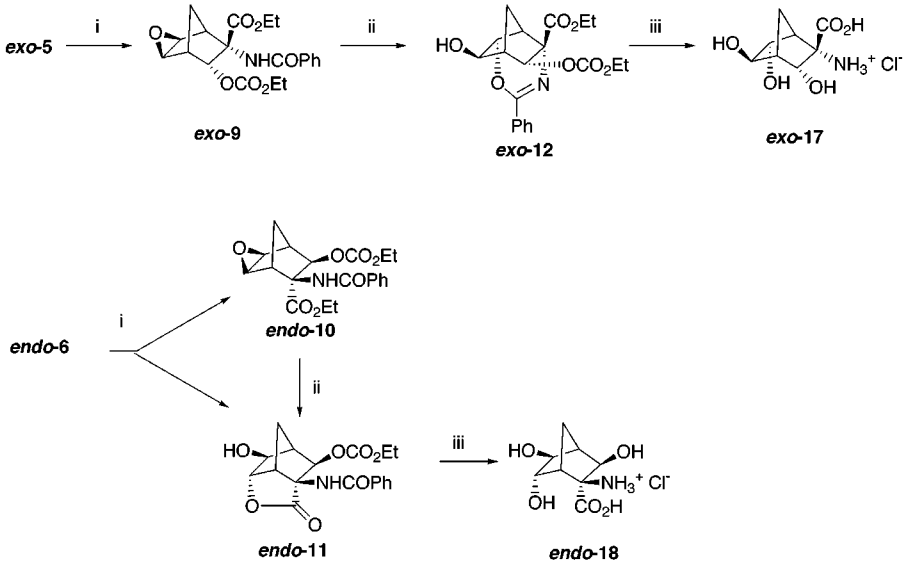
Scheme 1[a]



[a] Reagents and conditions: (i) $LiClO_4$, CH_2Cl_2; (ii) EtOH; (iii) OsO_4, NMO, acetone/H_2O; (iv) HCl (20 °C), 100 °C.

Scheme 2[a]



[a] Reagents and conditions: (i) *m*-$ClC_6H_5CO_3H$; (ii) $TiCl_4$, CH_2Cl_2; (iii) HCl (20%), 100 °C.

data ($^1H-\ ^{13}C$ NMR, COSY, HETCOR, and NOESY experiments). The ^1H NMR spectrum of compound *exo*-**7** showed the typical signal associated with H-3 ($\delta = 5.07$), an AB system associated with H-5 and H-6 ($\delta = 4.10$, 4.17, respectively) for which the cis stereochemistry was assigned considering the *J* values (5.8 Hz). The NOESY experiment allowed the observation of the spatial proximity between the NH proton ($\delta = 6.86$) and H-6 and this last with H-5. Furthermore, the Overhauser effect was detected between H-3 and one of the methylene bridge protons ($\delta = 1.77$). The NOESY experiment on the *endo*-**8** compound showed the cis relationship between the H-3 ($\delta = 5.67$) and H-5 ($\delta = 4.14$) and between the latter and H-6 ($\delta = 3.92$). Spatial proximity between one of the two

methylene bridge protons (δ = 1.95) and NH (δ = 6.37) was confirmed. The ^{1}H NMR spectra of compounds *exo*-**9** and *endo*-**10** revealed the presence of an oxirane ring (AB systems: δ = 3.42, 3.27, J = 3.3 Hz; δ = 3.39, 3.34, J = 3.7 Hz, respectively). The H-3 proton is present as a doublet at δ = 5.22 (J = 4.0 Hz) and 5.53 (J = 2.2 Hz), respectively. The stereochemistry assigned to compound *exo*-**9** was confirmed by a NOESY experiment that showed evidence of spatial proximity between NH proton (6.94 δ) and the oxirane proton at δ = 3.27. These data confirm that the oxygen bridge is cis in respect to the methylene bridge. Spatial proximity was also observed between H-3 and the methylene proton at δ = 1.40. The cis relationship between the methylene bridge and the oxirane was also confirmed in compound *endo*-**10**, by the same experiment showing spatial proximity between the H-3 (δ = 5.52) and the H-5 (δ = 3.34). Furthermore, the same effect was observed between the NH proton (δ = 6.54) and one of the methylene bridge protons (δ = 1.48), thus confirming the endo stereochemistry of the adduct. The ^{1}H NMR spectrum of lactone **11** showed two signals associated with H-3 (δ = 4.63) and H-2 (δ = 3.86). This last is present as a singlet, thus demonstrating the trans relationship between these protons. The H-7 proton is deshielded (3.76 δ), whereas the H-9 is shifted at δ 4.77. The NOESY experiment revealed a positive Overhauser effect between H-9 and H-1 and H-2 (δ = 2.73). Spatial proximity was observed between H-3 and the proton of the methylenic bridge (δ =2.2) confirming the assigned stereochemistry to H-3. In the oxazine derivative **12** the H-10 proton is in the usual range at 5.61 δ, as well as the H-8 (δ = 2.60).

Finally, compounds **5** and **6** and the polyhydroxylated compounds **7**, **8** and **11**, **12** were hydrolyzed with hydrogen chloride (20%) at 100 °C. The hydrolysis of compound *exo*-**5** gave the expected amino acid *exo*-**13** in satisfactory yield (88%) (Scheme 1). A different result was observed when the endo derivative **6** was treated under the same reaction conditions (Scheme 1). In fact, the 2-amino-3,6-dihydroxy amino acid **14** was isolated in 80% yield. To our knowledge, this result was never observed when endo amino acidic derivatives with a structure analogous to **6** were hydrolyzed. In fact, the functionalization of a double bond with an hydroxy group, via carboxylate, is usually pursued using the iodo-lactonization reaction.[8] For its formation we assumed that the carboxylic group adds to the double bond giving the lactone intermediate that was hydrolyzed to compound **14**. The hydrolysis of compounds **7**, **8** and **11**, **12** was successfully carried out under the same reaction conditions giving the trihydroxyamino acids **15**, **16** and **17**, **18**, respectively, in very good yields (80−90%).

The structure assigned to the amino acids **13**, **14**, and **15**−**18** is in agreement with analytical and spectroscopical data. The ^{1}H NMR of compounds *endo*-**14** revealed the presence of two deshielded protons, H-6 (δ = 4.92) and H-3 (δ = 4.04), respectively. Two methylene groups are present, the methylene bridge one at δ = 2.03, 1.58 and the CH_2-5 one (δ = 1.80, 1.38). This has been confirmed by ^{13}C NMR in which signals at δ = 33.6 (C-7), 34.5 (C-5), as well as two signals at low field at δ = 75.5 (C-3), 80.9 (C-6) are present. The NOESY experiment confirmed the stereochemistry assigned. Positive Overhauser effects were observed between H-3 and H-5 (δ = 1.59) and between H-6 and the proton of the bridge at δ = 2.23. Interestingly, compound **14** was transformed spontaneously into its lactone as demonstrated by IR spectroscopy (1789 cm^{-1}). The same transformation was observed for compound **18** (1786 cm^{-1}). As in the its precursor **11**, the H-1 protons is deshielded at δ = 3.69.

Considering the results reported, we can conclude that the goal of our syntheses has been the control of the stereochemistry of six centers. Four diastereoisomeric 2-amino-3,5,6-trihydroxynorbornanecarboxylic acids were prepared in which the trans−cis (compound **15**), cis−cis (compound **16**), trans−trans (compound **17**), and cis−trans (compound **18**) relationships between OH-3 and OH-5 and between the latter and OH-6 exist.

Experimental Section

General Methods. Melting points are uncorrected. IR spectra using the Nujol method were measured using NaCl plates. ^{1}H and ^{13}C NMR were recorded in $CDCl_3$ at 200, 300 and 50, 75 MHz, respectively, with $CHCl_3$ as internal standard. J values are given in hertz. Ethanol-free CH_2Cl_2 was used in all experiments. Oxazolone **1** and spirocompounds **3** and **4** are known compounds.[3] Freshly distilled cyclopentadiene was used.

General Procedure for the Cycloaddition Reaction. To a stirred solution of oxazolone (*Z*)-**1** (522 mg, 2 mmol) and cyclopentadiene (528 mg, 8 mmol) in anhydrous CH_2Cl_2 (10 mL) under nitrogen at 25 °C was added $LiClO_4$ (1.06 g, 10 mmol). After 24 h, anhydrous EtOH (2 mL) was added and the stirring was continued for 16 h. The solvent was evaporated, and the crude reaction mixture was purified by chromatography [2-cm width plate; silica gel Kieselgel 60 (Merck); 230−400-mesh ASTM; cyclohexane/AcOEt (65:35) eluent; 7 mL/min] to give two fractions, the first containing pure ester *exo*-**5** (370 mg, 50%) and the second pure ester *endo*-**6** (220 mg, 30%).

Ethyl (1*R,2*S**,3*R**,4*S**)-2-benzoylamino-3-ethoxycarbonyloxybicyclo[2.2.1]hept-5-ene-2-carboxylate 5:** mp 102 °C (CH_2Cl_2/*i*-Pr_2O); IR ν_{max} 3300, 1730, 1700, 1640 cm^{-1}; ^{1}H NMR δ 1.26 (t, J = 6.9, 3 H), 1.31 (t, J = 7.0, 3 H), 1.71, 1.96 (AB system, J = 10.2, 2 H), 3.27 (bs, 1 H), 3.76 (bs, 1 H), 4.18−4.32 (m, 4 H), 5.61 (d, J = 3.7, 1 H), 6.33 (bs, 2 H), 6.55 (s, 1 H, exch), 7.41−7.75 (m, 5 H); ^{13}C NMR δ 14.2, 43.9, 46.1, 49.8, 61.8, 64.6, 65.4, 80.5, 127.1, 128.6, 131.7, 133.9, 136.5, 153.8, 166.9, 172.0. Anal. Calcd: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.30; H, 6.18; N, 3.50.

Ethyl (1*R,2*R**,3*S**,4*S**)-2-benzoylamino-3-ethoxycarbonyloxybicyclo[2.2.1]hept-5-ene-2-carboxylate 6:** mp 118 °C (CH_2Cl_2/*i*-Pr_2O); IR ν_{max} 3300, 1730, 1700, 1640 cm^{-1}; ^{1}H NMR δ 1.21 (t, J = 7.3, 3 H), 1.29 (t, J = 7.4, 3 H), 1.82, 2.04 (AB system, J = 9.5, 2 H), 2.97 (bs, 1 H), 3.37 (bs, 1 H), 4.13−4.30 (m, 4 H), 5.15 (d, J = 1.8, 1 H), 6.17−6.22 (m, 1 H), 6.36−6.40 (m, 1 H), 6.92 (s, 1 H, exch), 7.43−7.83 (m, 5 H); ^{13}C NMR δ 14.3, 45.7, 47.9, 49.5, 61.4, 64.5, 65.5, 78.9, 127.1, 128.7, 131.7, 133.8, 134.1, 138.0, 153.8, 166.9, 170.8. Anal. Calcd: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.29; H, 6.22; N, 3.78.

General Procedure for the *cis*-Diol Synthesis. Ester **5** or **6** (1.5 g, 4 mmol) was suspended in a mixture of acetone/H_2O (25 mL, 10:1). After the addition of *N*-methylmorpholine *N*-oxide (703 mg, 6 mmol) and OsO_4 (5 mg, 0.012 mmol) the solution turned brown. The reaction mixture was stirred at room temperature for 50 min, after which time the solvent was evaporated. The crude reaction mixture was taken up with a solution of $Na_2S_2O_4$ (20 mL, 20%) and extracted with AcOEt (40 mL). The organic layer was then washed with a solution of HCl (2 × 30 mL, 10%) and dried over Na_2SO_4. After recrystallization from Et_2O, pure compound **7** or **8** was obtained. A further amount of compound **7** or **8** was obtained after chromatography (CH_2Cl_2/Et_2O, 1:0 to 0:1) on silica gel column.

Ethyl (1*S,2*S**,3*R**,4*R**,5*R**,6*S**)-2-benzoylamino-3-ethoxycarbonyloxy-5,6-dihydroxybicyclo[2.2.1]heptane-2-carboxylate 7:** yield 1.2 g, 74%; mp 174 °C (Et_2O); IR ν_{max} 3430−3200, 1720, 1625 cm^{-1}; ^{1}H NMR δ 1.22 (t, J = 7.3, 3 H), 1.36 (t, J = 6.9, 3 H), 1.77, 2.08 (AB system, J = 12.1, 2 H), 2.60 (bs, 1 H), 3.27 (bs, 1 H), 2.60−3.00 (bs, 2 H, exch), 4.09 (d, J = 5.8, 1

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H), 4.16−4.33 (m, 5 H), 5.07 (d, J = 4.4, 1 H), 6.86 (s, 1 H, exch), 7.40−7.75 (m, 5 H); ^{13}C NMR δ 14.1, 14.2, 28.2, 47.3, 50.5, 61.5, 61.9, 65.1, 67.4, 69.1, 77.4, 127.1, 128.8, 132.2, 133.4, 153.4, 167.9, 171.4. Anal. Calcd: C, 58.96; H, 6.18; N, 3.44. Found: C, 58.75; H, 6.18; N, 3.45.

Ethyl (1*S,2*R**,3*S**,4*R**,5*R**,6*S**)-2-benzoylamino-3-ethoxycarbonyloxy-5,6-dihydroxybicyclo[2.2.1]heptane-2-carboxylate 8:** yield 1.3 g, 80%; mp 85 °C (CH_2Cl_2/*i*-Pr_2O); IR ν_{max} 3600−3100, 1730, 1640 cm^{-1}; ^{1}H NMR δ 1.17 (t, J = 6.6, 3 H), 1.26 (t, J = 7.3, 3 H), 1.95, 2.12 (AB system, J = 11.4, 2 H), 2.41 (bs, 1 H), 2.53 (bs, 1 H), 2.40−3.40 (bs, 1 H, exch), 3.92 (d, J = 5.1, 1 H), 4.00−4.40 (m, 5 H), 5.67 (bs, 1 H), 6.37 (s, 1 H, exch), 7.40−7.78 (m, 5 H); ^{13}C NMR δ 14.5, 23.2.2, 30.6, 51.1, 52.4, 62.3, 64.6, 65.4, 69.3, 69.6, 77.4, 127.4, 128.9, 132.2, 133.8, 153.4, 168.4, 170.5. Anal. Calcd: C, 58.96; H, 6.18; N, 3.44. Found: C, 58.60; H, 6.00; N, 3.21.

General Procedure for Epoxidation Reaction. Ester **5** or **6** (373 mg, 1 mmol) was dissolved in $CHCl_3$ (6 mL). *m*-Chloroperbenzoic acid (380 mg, 2.2 mmol) was added, and the mixture was stirred at room temperature for 24 h. The organic layer was washed with a solution of $NaHCO_3$ (5 mL, 5%) and dried over Na_2SO_4. The pure compound **9** (390 mg) was obtained in quantitative yield when starting from **5**. In the case of **6**, the crude reaction mixture was chromatographed (cyclohexane/AcOEt, 1:1) giving a first fraction containing the pure epoxide **10** (261 mg, 67%) and a second fraction containing the lactone **11** (80 mg, 22%). Starting from **6** and prolonging the reaction time (96 h), a mixture of **10** and **11** in a 1:3 ratio was found.

Ethyl (1*R,2*S**,3*R**,4*R**,5*R**,6*S**)-6-benzoylamino-7-ethoxycarbonyloxy-3-oxatricyclo[3.2.1.0^{2,4}]octane-6-carboxylate 9:** mp 122 °C (CH_2Cl_2/*i*-Pr_2O/*n*-pentane); IR ν_{max} 3400−3200, 1710, 1640 cm^{-1}; ^{1}H NMR δ 1.24 (t, J = 7.3, 3 H), 1.38 (t, J = 7.0, 3 H), 1.40,1.54 (AB system, J = 11.7, 2 H), 2.99 (bs, 1 H), 3.27, 3.42 (AB system, J = 3.3, 2 H), 3.64 (bs, 1 H), 4.23 (q, J = 7.3, 2 H), 4.32 (q, J = 7.0, 2 H), 5.22 (d, J = 4.0, 1 H), 6.94 (s, 1 H, exch), 7.44−7.81 (m, 5 H); ^{13}C NMR δ 14.4, 14.6, 21.4, 41.0, 43.1 47.9, 48.9, 62.2, 63.8, 65.5, 80.8 127.4, 129.1, 132.4, 133.8, 153.8, 167.3, 171.6. Anal. Calcd: C, 61.69; H, 5.95; N, 3.60. Found: C, 61.69; H, 5.95; N, 3.60.

Ethyl (1*R,2*R**,4*S**,5*S**,6*R**,7*S**)-6-benzoylamino-7-ethoxycarbonyloxy-3-oxatricyclo[3.2.1.0^{2,4}]octane-6-carboxylate 10:** oil; IR ν_{max} 3400−3200, 1715, 1635 cm^{-1}; ^{1}H NMR δ 1.23 (t, J = 7.0, 3 H), 1.26 (t, J = 7.0, 3 H), 1.48, 1.58 (AB system, J = 10.9, 2 H), 2.71 (bs, 1 H), 2.97 (bs, 1 H), 3.34, 3.39 (AB system, J = 3.7, 2 H), 4.13−4.31 (m, 4 H), 5.53 (d, J = 2.2, 1 H), 6.54 (s, 1 H, exch), 7.41−7.79 (m, 5 H); ^{13}C NMR δ 14.2, 23.7, 44.1, 46.2, 47.5, 48.3, 61.8, 64.5, 68.1, 77.4, 127.2, 128.7, 132.0, 133.7, 153.7, 167.5, 169.9. Anal. Calcd: C, 61.69; H, 5.95; N, 3.60. Found: C, 61.50; H, 5.81; N, 3.48.

Ethyl (1*R,2*R**,3*R**,6*R**,7*S**,9*S**)-6-benzoylamino-2-hydroxy-5-oxo-4-oxatricyclo[4.2.1.0^{3,7}]non-9-yl carbonate 11:** mp 179 °C (Et_2O); IR ν_{max} 3480, 3315, 1760, 1740, 1625 cm^{-1}; ^{1} H NMR δ 1.34 (t, J = 7.2, 3 H), 2.10, 2.21 (AB system, J = 12.1, 2 H), 2.73 (s, 1 H), 3.75 (dd, J = 5.2, 1.5, 1 H), 3.91 (s, 1 H), 4.27 (q, J = 7.0, 2 H), 4.62 (dd, J = 5.3, 1.5, 1 H), 4.77 (s, 1 H), 6.95 (s, 1 H, exch), 7.44−7.82 (m, 5 H); ^{13}C NMR δ 14.6, 30.7, 47.1, 50.1, 64.2, 65.7, 75.5, 78.2, 84.1, 127.6, 129.1, 132.6, 133.4, 153.7, 166.9, 174.0. Anal. Calcd: C, 59.83; H, 5.30; N, 3.88. Found: C, 59.80; H, 5.25; N, 3.86.

General Procedure for the Reaction of Epoxide with $TiCl_4$. Operating under nitrogen atmosphere, the epoxide **9** or **10** (340 mg, 0.89 mmol) was dissolved in CH_2Cl_2 (20 mL) and the solution was cooled at −75 °C. A solution of $TiCl_4$ (106 μL, 1 M in CH_2Cl_2) was added. The reaction mixture was stirred for 15 min at this temperature and then at 25 °C for 45 min. The solvent was evaporated, and the crude reaction mixture was chromatographed on silica gel (CH_2Cl_2/Et_2O, 1:0 to 0:1). Oxazine **12** (230 mg, 66%) was isolated starting from **9**, the lactone **11** (270 mg, 75%) when starting from **10**.

Ethyl (1*R,2*R**,3*R**,7*S**,8*S**,10*R**)-10-ethoxycarbonyloxy-2-hydroxy-5-phenyl-4-oxa-6-azatricyclo[5.2.1.0.^{3,8}]dec-5-ene-7-carboxylate 12:** oil; IR ν_{max} 3400−3350, 1730, 1620 cm^{-1}; ^{1}H NMR δ 1.21 (t, J = 6.9, 3 H), 1.32 (t, J = 7.3, 3 H), 1.85, 1.97 (AB system, J = 13.0, 2 H), 2.31−2.34 (m, 1 H), 2.52 (d, J = 4.1, 1 H), 4.16 (s bs, 1 H), 4.10−4.40 (m, 4 H), 4.57 (d, J = 4.8, 1 H), 4.79 (s, 1 H, exch), 5.61 (d, J = 4.4, 1 H), 7.33−8.02 (m, 5 H); ^{13}C NMR δ 14.5, 38.3, 46.0, 59.7, 62.2, 64.6, 75.2, 77.6, 78.2, 82.4, 127.9, 128.3, 131.3, 133.3, 154.6, 169.2, 173.5. Anal. Calcd: C, 61.69; H, 5.95; N, 3.60. Found: C, 61.53; H, 6.00; N, 3.40.

General Procedure for the Hydrolysis to Amino Acids. Operating in a sealed tube, compounds **5**−**8** and **11**, **12** (1 mmol) were suspended in HCl (5 mL, 20%) and placed in an oven at 100 °C for 15 h. After cooling, the benzoic acid that had separated was filtered. The aqueous layer was washed with Et_2O (5 mL) and then was evaporated to dryness under reduced pressure, affording pure amino acids, as hydrochloric acids, **13**−**16** and **17**, **18**, respectively. Amino acids were dried with P_2O_5 in a vacuum.

(1*R,2*S**,3*R**,4*S**)-2-Amino-3-hydroxybicyclo[2.2.1]hept-5-ene-2-carboxylic acid hydrochloride 13:** yield 90%; mp 200 °C (EtOH, dec); IR ν_{max} 1710 cm^{-1}; ^{1}H NMR (D_2O/CF_3CO_2D) δ 1.50, 1.85 (AB system, J = 10.3, 2 H), 3.05 (bs, 1 H), 3.15 (bs, 1 H), 4.68−4.75 (m, 1 H), 6.18−6.30 (m, 1 H), 6.30−6.48 (m, 1 H); ^{13}C NMR (D_2O/CF_3CO_2D) δ 43.9, 47.7, 50.7, 65.1, 74.7, 133.8, 139.9, 173.5. Anal. Calcd: C, 46.73; H, 5.88; N, 6.81. Found: C, 46.50; H, 6.01; N, 6.60.

(1*S,2*R**,3*S**,4*S**,6*S**)-2-Amino-3,6-dihydroxybicyclo[2.2.1]-heptane-2-carboxylic acid hydrochloride 14:** yield 90%; mp dec (EtOH); IR ν_{max} 3240, 1610 cm^{-1}; ^{1}H NMR (D_2O) δ 1.38 (dd, J = 15.0, 3.3, 1 H), 1.59 (ddd, J = 12.1, 2.7, 1.3, 1 H), 1.80 (ddd, J = 15.0, 8.0, 1.3, 1 H), 1.99−2.06 (m, 1 H), 2.42 (bs, 1 H), 3.20 (ddd, J = 5.4, 2.7, 1.4, 1 H), 4.04 (s, 1 H), 4.92 (dd, J = 8.0, 5.4, 1 H); ^{13}C NMR (D_2O) δ 33.6, 34.5, 44.7, 49.0, 63.8, 75.4, 80.9, 176.5. Anal. Calcd: C, 42.96; H, 6.31; N, 6.26. Found: C, 42.66; H, 6.03; N, 6.26.

(1*S,2*S**,3*R**,4*R**,5*R**,6*S**)-2-Amino-3,5,6-trihydroxybicyclo[2.2.1]heptane-2-carboxylic acid hydrochloride 15:** yield 89%; mp dec (EtOH); IR ν_{max} 1620 cm^{-1}; ^{1}H NMR (D_2O) δ 1.69−1.84 (m, 2 H), 2.30 (dd, J = 4.4, 1.5, 1 H), 2.48 (bs, 1 H), 3.94, 4.22 (AB system, J = 5.8, 2 H), 4.41 (d, J = 4.4, 1 H); ^{13}C NMR (D_2O) δ 27.8, 48.5, 51.0, 62.6, 66.5, 68.5, 70.5, 173.2. Anal. Calcd: C, 40.09; H, 5.89; N, 5.84. Found: C, 39.94; H, 6.11; N, 5.66.

(1*S,2*R**,3*S**,4*R**,5*R**,6*S**)-2-Amino-3,5,6-trihydroxybicyclo[2.2.1]heptane-2-carboxylic acid hydrochloride 16:** yield 90%; mp dec (EtOH); IR ν_{max} 3400, 1610 cm^{-1}; ^{1}H NMR (D_2O) δ 1.78, 1.93 AB system, J = 12.1, 2 H), 2.12 (bs, 1 H), 2.29 (bs, 1 H), 3.84, 4.57 (AB system, J = 5.9, 2 H), 4.24 (d, J = 1.5, 1 H); ^{13}C NMR (D_2O) δ 29.0, 51.1, 52.0, 66.0, 69.0, 69.7, 72.4, 171.5. Anal. Calcd: C, 40.09; H, 5.89; N, 5.84. Found: C, 40.02; H, 6.00; N 5.74.

(1*S,2*S**,3*R**,4*R**,5*R**,6*R**)-2-Amino-3,5,6-trihydroxybicyclo[2.2.1]heptane-2-carboxylic acid hydrochloride 17:** yield 79%; mp dec (EtOH); IR ν_{max} 3740, 1740 cm^{-1}; ^{1}H NMR (D_2O) δ 1.60 (d, J = 12.1, 1 H), 2.08 (ddd, J = 12.1, 3.6, 1.8, 1 H), 2.32 (d, J = 4.4, 1 H), 2.60 (bs, 1 H), 3.97 (dd, J = 2.6, 2.5, 1 H), 4.07 (dd, J = 3.7, 3.3, 1 H), 4.50 (d, J = 4.4, 1 H); ^{13}C NMR (D_2O) δ 28.9, 46.7, 49.0, 63.2, 71.2, 72.0, 82.9, 173.5. Anal. Calcd: C, 40.09; H, 5.89; N, 5.84. Found: C, 39.99; H, 6.08; N, 5.72.

(1*S,2*R**,3*S**,4*R**,5*R**,6*R**)-2-Amino-3,5,6-trihydroxybicyclo[2.2.1]heptane-2-carboxylic acid hydrochloride 18:** yield 90%; mp dec °C (EtOH); IR ν_{max} 3340, 1786 cm^{-1}; ^{1}H NMR (D_2O) δ 2.00, 2.08 (AB system, J = 12.8, 2 H), 2.47 (bs, 1 H), 3.25 (d, J = 5.5, 1 H), 3.69 (bs, 1 H), 4.03 (bs, 1 H). 4.57 (dd, J = 5.5, 1.8, 1 H); ^{13}C NMR (D_2O) δ 29.8, 51.1, 47.5, 51.7, 66.0, 62.9, 72.5, 73.6, 85.4, 174.9; *m*/*z* 187 (M^+). Anal. Calcd: C, 40.09; H, 5.89; N, 5.84. Found: C, 39.95; H, 5.75; N, 5.80.

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