Enantioselective Synthesis of Conformationally Restricted Analogs of NMDA: *cis*- and *trans*-Piperidine-2,3-dicarboxylic Acids and Methylated Derivatives

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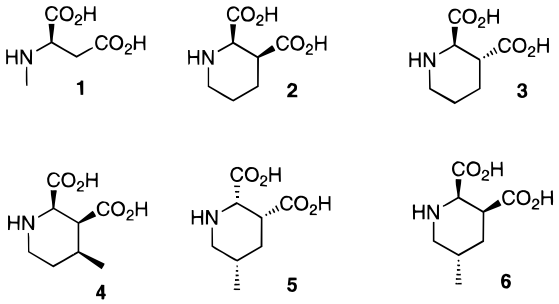
Received April 2, 1996[⊗]

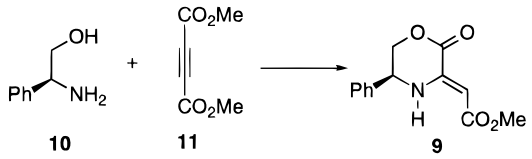
Various enantiopure stereoisomeric cyclic amino diacids belonging to the 2,3-piperidinedicarboxylic acid series were obtained via an aza-annulation reaction between enamino esters and acryloyl, methacryloyl, or crotonyl chloride. Enantioselective syntheses of these conformationnally restricted analogs of *N*-methyl-D-aspartic acid were realized owing to a chiral induction originated from (2*S*)-2-phenylglycinol. New information about the mechanism of the aza-annulation process is inferred from AM1 calculations which were performed in order to explain the steroselectivity displayed during the formation of the C-4 stereocenter in compound **4**.

It is now well established that *N*-methyl-D-aspartic acid (NMDA, **1**) receptors are involved in the neuroexcitatory transmission effects mediated by L-glutamate[1] and that the synthesis of NMDA analogs constitutes an active area of investigation.[2] In order to explore the corresponding structure:activity relationships by using conformationally restricted analogs, 2,3-piperidinedicarboxylic acids **2** and **3** are the most obvious candidates. They both show the same *R* absolute configuration at the center corresponding to the stereogenic center of NMDA and either a *cis* or a *trans* geometry between the two carboxylic functions. Davies et al.[3] synthesized these *cis* and *trans* compounds under their racemic forms by hydrogenating the corresponding pyridinedicarboxylic acid, and this group succeeded in resolving the *cis* isomer but the racemic *trans* compound could not be resolved. The biological activity of the racemic *trans* diacid was tested, and it appeared as an agonist of the NMDA receptor.[3,4] In regard to the *cis* isomer, both enantiomers were studied and the levorotatory displayed a pronounced antagonist activity. Since it was not possible to assign their respective absolute configurations to the resolved *cis* antipodes, it was assumed that the most active enantiomer should have the same absolute configuration at C-2 as NMDA and should therefore present the 2*R*,3*S* structure.[4a]



We report herein the first enantioselective synthesis of *cis*- and *trans*-2,3-piperidinedicarboxylic acids **2** and *ent*-**3** by using a new methodology which provides access to a variety of such conformationally restricted analogs of NMDA[5] such as the methylated derivatives **4**−**6**. As shown in Scheme 1, the retrosynthetic analysis was based on (i) formation of the bicyclic material **8** by condensing enamino ester **9** with the required unsaturated acyl halide[6,7] which allows the construction of the carbon framework and (ii) stereoselective hydrogenation of intermediate **8** which controls the chiral induction during the formation of the carboxyl-bearing stereogenic centers.

The initial source of chirality was supplied by phenylglycinol, which is easily accessible under both enantiomeric forms. Thus oxazinone **9**, which was used as a common chiral substrate for each synthesis reported below, was obtained[8] by condensing (2*S*)-2-phenylglycinol (**10**) with dimethyl acetylenedicarboxylate (**11**).



Results

***cis*- and *trans*-2,3-Piperidinedicarboxylic Acids.** Condensation of oxazinone **9** with acryloyl chloride

[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1996.

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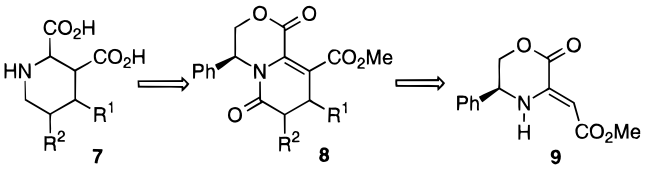
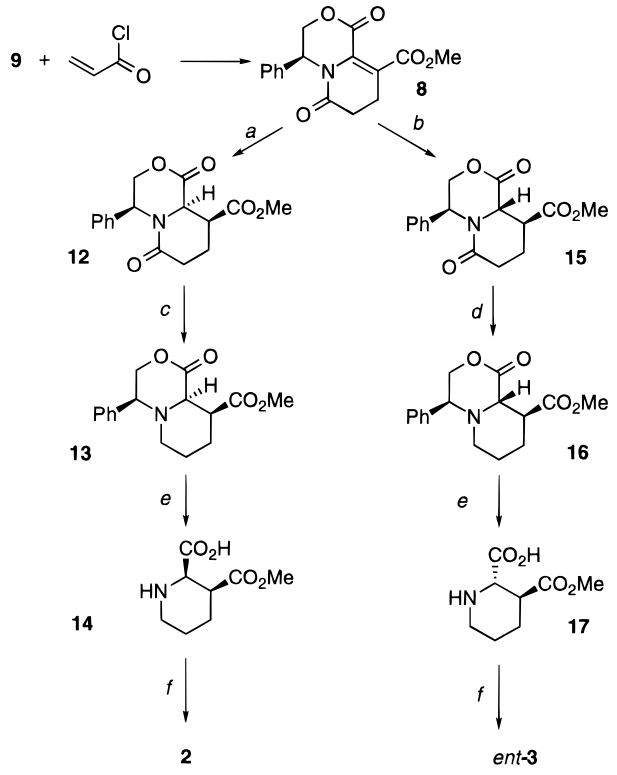
Scheme 1



Scheme 2[a]



[a] Reaction conditions: (a) H_2, 5% Pd/C, EtOH, 93%; (b) H_2, 5% Pd/C, Na_2CO_3 (3.5 equiv), 95%; (c) BH_3-Me_2S (2 equiv), THF, rt, 8%; (d) BH_3-THF (10 equiv), THF, rt, 63%; (e) H_2, 20% $Pd(OH)_2$/C, EtOH, 97% (**14**) and 85% (**17**); (f) 3 N HCl, reflux, 80% (**2**) and 93% (*ent*-**3**).

yielded the bicyclic enamido ester **8** (Scheme 2). The ethylenic double bond of compound **8** was hydrogenated and this reaction led to either the *cis*-hydrogenated, or the *trans*-hydrogenated product **12** or **15**, respectively. The stereoselectivity of this reduction was dramatically affected by the presence of sodium carbonate along with the usual palladium catalyst: whereas hydrogenation with a 5% Pd/C catalyst afforded compound **12** as a pure diastereomer, its epimer **15** was the only product of a hydrogenation performed in the presence of Pd/C and Na_2CO_3.

The next step of each synthesis was to reduce the amido moiety of compounds **12** and **15**. It appeared that the reactivities of these molecules were very different: reduction of amide **12** was effected very smoothly by using BH_3-Me_2S complex[9] whereas its stereoisomer **15** was not reduced under these conditions. The reduction of compound **15** required a large excess of the BH_3-THF complex with an inverse mode of addition.[10] X-ray analysis[5] was performed on compounds **13** and **16**, whose structures were thus established.

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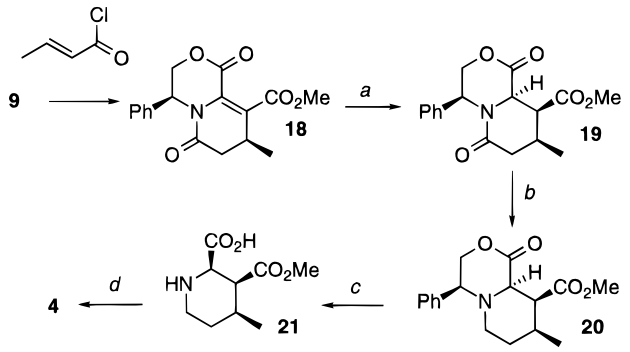
Scheme 3[a]



[a] Reaction conditions: (a) H_2, 5% Pd/C, EtOH, 85%; (b) BH_3-THF (2 equiv), THF, rt, 91%; (c) H_2, 20% $Pd(OH)_2$/C, EtOH, 94%; (d) 3.5 N NaOH, rt, 94%.

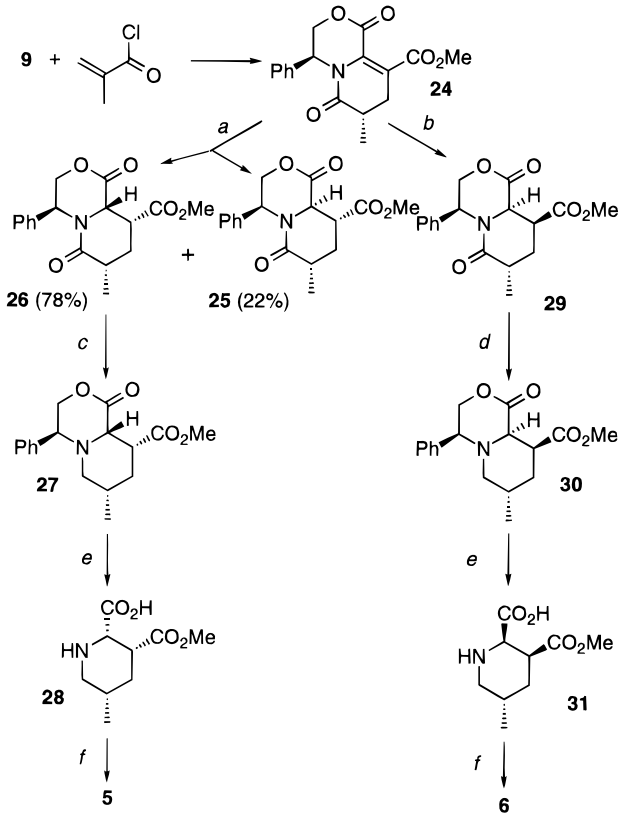
These syntheses were completed in two steps: first, hydrogenolysis of the benzylic amines in the presence of palladium hydroxide which also gave rise to the saponification of the lactone moiety and second, acidic hydrolysis of the esters which afforded the desired amino diacids. The produced (2*R*,3*S*)-*cis* stereoisomer **2** was levorotatory in agreement with the hypothesis made by Olverman et al.[4a] Therefore, these amino diacids were synthesized in six steps, from (2*S*)-2-phenylglycinol, in 46% and 37% overall yields, respectively.

***cis*-2,3-Piperidinedicarboxylic Acid, Methylated Derivatives.** The scope of the present methodology can be extended by using substituted unsaturated acyl chlorides since in such a case a third stereogenic center is generated. As shown above, with acryloyl chloride as the starting material, the two final stereocenters were created during the hydrogenation step. On the other hand, with either crotonyl chloride or methacryloyl chloride, a supplementary stereocenter is created during the annulation step and this procedure leads to the methylated amino diacids **4**−**6**.

The above procedure, detailed in the case of compounds **2** and *ent*-**3**, was followed for the synthesis of amino diacid **4** (overall yield: 46% from chiral amino alcohol **10**). The cyclization step was achieved by condensing enamino ester **9** with crotonyl chloride or crotonic anhydride, the yield being slightly higher in the latter case, and afforded the bicyclic enamido ester **18** as a diastereomerically pure compound (Scheme 3). The relative configuration of this molecule was determined from NMR measurements effected on the following products of this synthesis. Compounds **20** and **21**: (i) irradiation of the H nucleus at C-9a in compound **20** shows that the coupling constant between the nuclei at C-9 and C-8 corresponds to a *cis* relationship ($J = 3.7$ Hz), (ii) a NOE experiment demonstrates that in compound **21** the three H nuclei at C-2, C-3, and C-4 are located in the same half-space.

Methylated amino diacids **5** and **6** were synthesized by the same procedure starting from methacryloyl chloride (Scheme 4). In this case too, the global stereoselectivity of the hydrogenation of enamino ester **24** was strongly dependent on the nature of the catalyst. When catalyzed by palladium, the hydrogenation produced a diastereomeric mixture of *cis*- and *trans*-hydrogenated compounds **25** and **26**, in a respective 1:3.5 ratio. On the other hand, compound **29** was obtained as a single stereoisomer when Raney nickel was used as a catalyst (an identical result was observed when this reaction was

Scheme 4[a]



[a] Reaction conditions: (a) H_2, 5% Pd/C, EtOH:AcOEt (1:1), 77%; (b) H_2, Raney Ni, EtOH:AcOEt (1:1), 79%; (c) BH_3−THF (10 equiv), THF, 0 °C, 80%; (d) BH_3−THF (10 equiv), THF, −30 °C, 85%; (e) H_2, 20% $Pd(OH)_2$/C, EtOH, 87% (**28**) and 88% (**31**); (f) 3 N HCl, reflux, 90% (**5**) and 97% (**6**).

catalyzed with 5% Rh on alumina). Target molecule **5** was obtained from amido ester **26** by the usual amide reduction−debenzylation−hydrolysis sequence of reactions. The relative configuration of compound **27** was assigned from an X-ray analysis.[11]

Similarly, amino diacid **6** was derived from amido ester **29**. Intermediate **30** has a *cis* ring junction as shown by a NMR comparison with compound **13**, whose structure was proved by an X-ray analysis (see above). The *trans* relationship between the methyl group and the carboxylic moieties can be deduced from the diastereomeric relation between compounds **6** and **5** which would have appeared as enantiomers in the opposite case. Finally, amino diacids **5** and **6** were obtained with 29% and 44% overall yields, respectively, from chiral amino alcohol **10**.

Discussion

Chiral Induction during the Hydrogenation Step. The formation of compound **15**, formally resulting from an *anti*-addition of hydrogen on the enamide **8**, can be attributed to an epimerization provoked by the presence of sodium carbonate acting as a base on the relatively acidic hydrogen atom located at the ring junction. It was checked that the *trans* compound was the thermodynamic isomer by treating compound **12** with sodium carbonate, and this experiment yielded compound **15**. It could be noted that the use of sodium carbonate during hydrogenations of unsaturated ketones was first reported by Paquette[12] who have recommended this procedure in order to enhance the *syn*-stereoselectivity of the hydrogenation of electrophilic olefinic double bonds. However, the substrates studied by Paquette[12] and others[7d,13] were substantially different from the one at hand because they had only one electron-attracting group linked to the ethylenic double bond. In the case of compound **12**, the lactone moiety is responsible for the acidity of the ring-junction hydrogen atom which is adjacent to this function and epimerization at the C-9a center is thus favored.

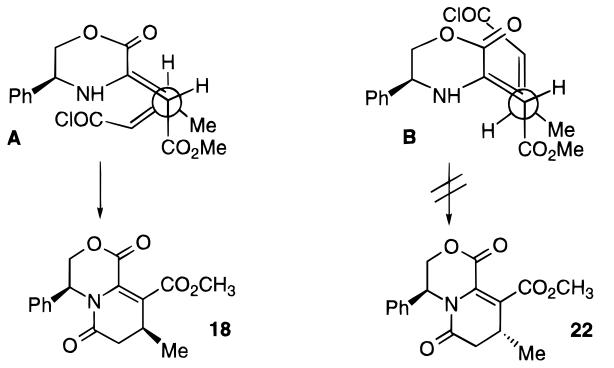


Figure 1. Synclinal geometries of the interacting double bonds involved in the annulation reaction.

The steric course of hydrogenations leading to compounds **12**, **19**, and **29** can be simply dictated by a steric effect: addition of hydrogen occurred onto substrates **8**, **18**, and **24**, respectively, with the usual *syn*-stereoselectivity from the less hindered face of the double bond, i.e., *anti* with respect to the phenyl substituent: the equatorial methyl group seems to reverse the face selectivity. However, the stereochemistry of the palladium-catalyzed hydrogenation of enamido ester **24**, affording the **25**:**26** mixture, cannot be explained by such a simple effect, and this result is still unanswered.

Chiral Induction during the Annulation Step. From a mechanistic point of view, nothing definite can be deduced from the stereoselective creation of the 7*S* stereogenic center during the synthesis starting from substrate **24** (cf. Scheme 4). The crystallographic data, performed on compound **27**, showed that the 7*S* methyl substituent is equatorial; however, if the aza-anulation step follows either a Michael addition or a hetero-Diels−Alder process, the creation of this stereogenic center should not result from the condensation step but later on during a protonation step.

Much more meaningful is the stereoselectivity of the cyclization that afforded enamino ester **18** (Scheme 3). The stereoselective creation of the C-4 stereocenter in compound **4** is clearly relevant to the hitherto nonelucidated mechanism of such reactions since it is created during the keystep. Stille[7f] recently suggested that three different concerted sigmatropic processes might be involved in the first step. Actually the present result is compatible with a simple Michael addition of the enamine moiety onto crotonyl chloride followed by the formation of the amido group. As shown in Figure 1, two acyclic transition states can be considered: both of them have the favored synclinal disposition of the double bonds as

(11) The X-ray analysis was performed by Dr. J. Vaissermann at the Laboratoire de Chimie des Métaux de Transition (Université P. et M. Curie).

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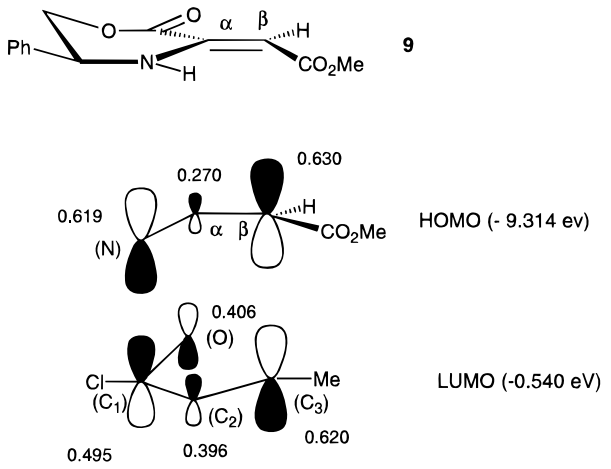

Figure 2. HOMO−LUMO interactions between enamino ester **9** and crotonyl halide.

initially suggested by Seebach and Golinsky,[14] which has found a wide scope of application;[15] these two situations can be considered as nearly equivalent in regard to steric hindrance. Arrangement **A** is consistent with the stereochemical outcome of the condensation, and this conclusion was substantiated by the following theoretical analysis.

We performed AM1 calculations of the orbital factors which come into play during the first step of the reaction between enamino ester **9** and crotonyl chloride in order to discriminate between a hetero-Diels−Alder condensation and a Michael addition. Examination of the frontier orbital interactions (enamino ester HOMO and acyl halide LUMO, cf. Figure 2) reveals that (i) the best overlap occurs between the C_β and C_3 centers in agreement with both processes; (ii) there is not an alike favorable overlap between the enamino ester C_α center and the oxygen atom of the acyl halide, which should occur in the case of a hetero-Diels−Alder mechanism; and (iii) there is a secondary favorable interaction between the orbitals located on the nitrogen of enamino ester **9** and the C_1 center of the acyl halide. The third observation suggests that the amino and the acyl moieties should be as close as possible and explains the preferred formation of product **18** via arrangement **A** (cf. Figure 1). Similar considerations were presented by Sevin et al.[16] to rationalize the asymmetric alkylation of chiral ketone enamines by electron-deficient alkenes.

Calculations on the hetero-Diels−Alder condensation and the Michael addition approaches have been performed, and both transition states were optimized. There is a strong energetical discrimination (8.85 kcal) between these processes, the Michael addition being favored, as suggested by the above examination of the reagents frontier orbitals. Moreover, in the transition state of the Michael addition the only salient bond order refers to the incipient $C_\beta-C_3$ bond (cf. Figure 2) in a disposition similar to arrangement **A** (cf. Figure 1). Therefore, this theoretical analysis clearly discards the hypothesis of a hetero-Diels−Alder mechanism.

In summary, homochiral compounds related to the 2,3-piperidinedicarboxylic acid family have been prepared in six steps from (2*S*)-phenylglycinol using the aza-annulation−hydrogenation strategy. From a mechanistic point of view, MO calculations are consistent with a process involving a Michael addition as a stereodirecting key step.

Experimental Section

General Methods. ^{1}H NMR spectra ($CDCl_3$ solutions unless otherwise stated) were carried out at 250 or 400 MHz and ^{13}C NMR spectra ($CDCl_3$ solutions unless otherwise stated) at 62.9 or 100 MHz. MS and HRMS were measured in the EI mode with an ionization potential of 70 eV; the accurate mass measurements were done with a resolving power of 10 000. Melting points are uncorrected. Column chromatography was performed on silica gel 230−400 mesh with various mixtures of diethyl ether (E) and petroleum ether (PE). Tetrahydrofuran (THF) was distilled from benzophenone ketyl.

(4*S*)-1,6-Dioxo-4-phenyl-1,3,4,6,7,8-hexahydropyrido-[2,1-*c*][1,4]oxazine-9-carboxylic Acid Methyl Ester (8). Compound **9** was obtained by the procedure described by Tamura and Harada[8] for the synthesis of *ent*-**9** (88%, $[\alpha]^{20}_D$: +258 (*c* 0.5, $CHCl_3$) [lit.[8] $[\alpha]^{20}_D$: −259 (*c* 1.1, $CHCl_3$) for *ent*-**9**]. Acryloyl chloride (0.75 g, 6.5 mmol) was added to a solution of compound **9** (1.6 g, 6.5 mmol) in tetrahydrofuran (45 mL) at rt. The reaction mixture was refluxed over a 2.5 h period. The mixture was cooled to rt, poured into 30 mL of saturated aqueous sodium hydrogen carbonate solution, and extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The resulting oil was chromatographed over silica gel (E/PE: 80/20, then pure ether) to give compound **8** (1.7 g 89%): mp 128 °C. ^{1}H NMR: 2.56−2.82 (m, 4H), 3.74 (s, 3H), 4.53−4.58 (ABX system, J_{AB} = 11.8, J_{AX} = 2.8, J_{BX} = 2.0 Hz, 2H), 5.65 (bs, 1H), 7.10−7.31 (m, 5H). ^{13}C NMR: 22.8, 29.2, 51.1, 53.0, 70.1, 122.7, 125.9, 127.5, 128.4, 129.2, 135.8, 158.8, 166.8, 167.7. IR ($CHCl_3$): 1635, 1685, 1720, 1735 cm^{-1}. $[\alpha]^{20}_D$: +102 (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.67; H, 4.98; N, 4.71.

[4*S*-4α,9α,9aα]-1,6-Dioxo-4-phenyloctahydropyrido[2,1-*c*][1,4]oxazine-9-carboxylic acid Methyl Ester (12). A solution of lactam **8** (1.5 g, 5 mmol) and 5% Pd/C (0.5 g) in 100 mL of absolute EtOH was placed under hydrogen (1 atm) for 1.5 h. The catalyst was removed by filtration on Celite. After evaporation, compound **12** was isolated as a white solid (1.4 g, 93%) and used crude for the next step. An analytical sample was recrystallized from absolute EtOH: mp 108 °C. ^{1}H NMR: 1.91−2.32 (m, 4H), 3.32−3.38 (m, 1H), 3.65 (s, 3H), 4.26−4.35 (m, 2H), 4.54 (dd, *J* = 3.3 and 12.2 Hz, 1H), 5.18 (d, *J* = 2.7 Hz, 1H), 7.17−7.43 (m, 5H). ^{13}C NMR: 22.2, 28.7, 39.1, 52.2, 54.7, 56.6, 69.5, 126.4, 127.5, 128.5, 139.3, 168.1, 168.2, 171.4. IR ($CHCl_3$): 1685, 1720, 1735 cm^{-1}. $[\alpha]^{20}_D$: +118 (*c* 1.05, $CHCl_3$). HRMS: calcd for $C_{16}H_{17}NO_5$ *m*/*z* = 303.1106, obsd *m*/*z* = 303.1105.

[4*S*-4α,9α,9a*β*]-1,6-Dioxo-4-phenyloctahydropyrido[2,1-*c*][1,4]oxazine-9-carboxylic Acid Methyl Ester (15). To a solution of compound **8** (0.5 g, 1.66 mmol) in absolute ethanol (50 mL) were added 5% Pd/C (0.2 g) and sodium carbonate (0.6 g). This mixture was submitted to the action of hydrogen for 2 h; then the catalyst and Na_2CO_3 were removed by filtration. After evaporation, the crude solid (0.48 g, 95%) was used without further purification in the next step. An analytical sample was purified by recrystallization in absolute EtOH: mp 196 °C. ^{1}H NMR: 2.08−2.15 (m, 2H), 2.33−2.39 (m, 2H), 3.37−3.44 (m, 1H), 3.76 (s, 3H), 4.33 (t, *J* = 12 Hz, 1H), 4.50 (dd, *J* = 6.5 and 12.5 Hz, 1H), 5.00 (d, *J* = 5 Hz, 1H), 5.38 (dd, *J* = 6.5 and 11.2 Hz, 1H) 7.23−7.33 (m, 5H).

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^{13}C NMR: 21.4, 30.4, 39.8, 52.9, 54.8, 55.4, 68.4, 126.0, 128.5, 129.2, 136.4, 168.3, 168.7, 172.4. IR ($CHCl_3$): 1650, 1730, 1760 cm^{-1}. $[\alpha]^{20}_D$: −27.6 (*c* 0.74, $CHCl_3$). HRMS: calcd for $C_{16}H_{17}NO_5$ *m*/*z* = 303.1106, obsd *m*/*z* = 303.1108.

Na_2CO_3-Mediated Epimerization of Compound 12. A solution of compound **12** (0.1 g, 3.3 mmol) in abolute ethanol (10 mL) was stirred at rt during 3 h in the presence of Na_2CO_3 (0.11 g). The mixture was then filtrated and the solvent was evaporated. NMR of the crude product corresponded to compound **15**.

[4*S*-4α,9α,9aα]-1-Oxo-4-phenyloctahydropyrido[2,1-*c*]-[1,4]oxazine-9-carboxylic Acid Methyl Ester (13). A solution of compound **12** (0.26 g, 0.85 mmol) in THF (7 mL) was added dropwise to a 10 M THF solution of BH_3/Me_2S (0.2 mL, 1.9 mmol). The mixture was stirred for 2 h at rt. Water was then added, and the aqueous solution was extracted with dichloromethane. After evaporation, the residue was chromatographed (E/PE 50/50) to furnish compound **13** as a white solid (0.20 g, 82%): mp 124 °C. ^{1}H NMR: 1.36−1.56 (m, 3H), 1.72 (td, *J* = 3.4 and 10.7 Hz, 1H), 2.35−2.39 (m, 1H), 2.65−2.79 (m, 1H), 3.10 (d, *J* = 2.3 Hz, 1H), 3.47−3.48 (m, 1H), 3.55 (dd, *J* = 3.1 and 10.6 Hz, 1H), 3.74 (s, 3H), 4.10 (dd, *J* = 3.1 and 10.8 Hz, 1H), 4.29 (t, *J* = 10.7 Hz, 1H), 7.21−7.31 (m, 5H). ^{13}C NMR: 22.3, 26.5, 43.3, 51.9, 52.0, 63.1, 65.4, 72.6, 128.1, 128.6, 128.9, 136.2, 169.1, 172.3. IR ($CHCl_3$): 1725, 1735 cm^{-1}. $[\alpha]^{20}_D$: +66 (*c* 0.3, $CHCl_3$). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.41; H, 6.61; N, 4.84. Found: C, 66.31; H, 6.54; N, 4.81.

[4*S*-4α,9α,9a*β*]-1-Oxo-4-phenyloctahydropyrido[2,1-*c*]-[1,4]oxazine-9-carboxylic Acid Methyl Ester (16). A solution of compound **15** (0.1 g, 0.33 mmol) in THF (5 mL) was dropped into a 1 M solution of BH_3/THF complex (3.3 mL, 3.3 mmol) in THF and cooled to 0 °C. Once the addition was over, the mixture was hydrolyzed with water and then extracted with dichloromethane. Evaporation of the combined organic layers gave an oily residue which was chromatographed on silica gel (E/PE 50/50) Compound **16** was isolated as a white solid (0.6 g, 63%): mp 108 °C. ^{1}H NMR: 1.55−1.91 (m, 4H), 2.55−2.57 (m, 1H), 2.72−2.74 (m, 1H), 3.00−3.02 (m, 1H), 3.77 (s, 3H), 3.95 (dd, *J* = 5.7 and 6.1 Hz, 1H), 4.06 (d, *J* = 6.6 Hz, 1H), 4.37 (dd, *J* = 7.2 and 11.6 Hz, 1H), 4.65 (dd, *J* = 5.6 and 11.6 Hz, 1H), 7.20−7.43 (m, 5H). ^{13}C NMR: 22.6, 25.1, 41.8, 52.0, 52.2, 57.8, 61.7, 71.5, 127.9, 128.3, 128.9, 136.4, 170.2, 173.5. IR ($CHCl_3$): 1725, 1735 cm^{-1}. $[\alpha]^{20}_D$: −41 (*c* 0.6 $CHCl_3$). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.41; H, 6.61; N, 4.84. Found: C, 66.38; H, 6.76; N, 4.88.

[4*S*-4α,8α]-1,6-Dioxo-8-methyl-4-phenyl-1,3,4,6,7,8-hexahydropyrido[2,1-*c*][1,4]oxazine-9-carboxylic Acid Methyl Ester (18). Crotonic anhydride (1.7 mL, 11.6 mmol) was added to a solution of compound **9** (2.2 g, 8.9 mmol) in THF (50 mL). The black solution was refluxed for 10 days. After cooling, the mixture was poured into a saturated aqueous solution of sodium hydrogen carbonate. The aqueous layer was extracted with dichloromethane, and the combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (E/PE 80/20). Compound **18** was obtained as a yellow solid (2.1 g, 76%): mp 57 °C. ^{1}H NMR: 1.28 (d, *J* = 7.0 Hz, 3H), 2.57 (dd, *J* = 3.4 and 15.5 Hz, 1H), 2.81−2.88 (m, 2H), 3.86 (s, 3H), 4.68−4.71 (ABX system J_{AB} = 12, J_{AX} = 1.8, and J_{BX} = 2.8 Hz, 2H), 5.87 (bs, 1H), 7.28−7.41 (m, 5H). ^{13}C NMR: 17.7, 29.5, 36.9, 49.9, 52.8, 69.9, 124.8, 126.2, 128.5, 128.9, 129.2, 136.0, 158.1, 166.7, 167.8. IR ($CHCl_3$): 1635, 1685, 1720, 1735 cm^{-1}. $[\alpha]^{20}_D$: +95.9 (*c* 1.1 $CHCl_3$). HRMS: calcd for $C_{17}H_{17}NO_5$ *m*/*z* = 315.1106, obsd *m*/*z* = 315.1105.

[4*S*-4α,8α,9α,9aα]-1,6-Dioxo-8-methyl-4-phenyloctahydropyrido[2,1-*c*][1,4]oxazine-9-carboxylic Acid Methyl Ester 19. A solution of compound **18** (1.3 g, 4.1 mmol) in absolute ethanol (70 mL) was placed with 5% palladium on carbon (0.37 g) under an atmosphere of hydrogen for 2.5 h. The mixture was filtered on Celite and then evaporated. Compound **19** was obtained as a white solid (1.1 g, 85%): mp 129 °C. ^{1}H NMR: 1.07 (d, *J* = 6.1 Hz, 3H), 2.25−2.44 (m, 3H), 3.28−3.32 (m, 1H), 3.74 (s, 3H), 4.44 (d, *J* = 12.1 Hz, 1H), 4.50 (d, *J* = 4.6 Hz, 1H), 4.68 (dd, *J* = 3.4 and 12.2 Hz, 1H), 5.29 (d, *J* = 3 Hz, 1H), 7.12−7.41 (m, 5H). ^{13}C NMR: 19.1, 28.7, 36.5, 44.7, 52.0, 55.1, 57.7, 69.9, 126.2, 127.7, 128.7, 138.9, 168.2, 170.8. IR ($CHCl_3$): 1660, 1730, 1760 cm^{-1}. $[\alpha]^{20}_D$: +76.4 (*c* 1.2 $CHCl_3$). HRMS: calcd for $C_{17}H_{19}NO_5$ *m*/*z* = 317.1263, obsd *m*/*z* = 317.1263.

[4*S*-4α,8α,9α,9aα]-1-Oxo-8-methyl-4-phenyloctahydropyrido[2,1-*c*][1,4]oxazine-9-carboxylic Acid Methyl Ester (20). A 1 M solution of BH_3/THF complex in THF (3.2 mL, 3.2 mmol) was added at 0 °C to a solution of compound **19** (0.5 g, 1.6 mmol) in THF (25 mL). The mixture was stirred at room temperature for 1.5 h and then hydrolyzed by water (15 mL). The reaction mixture was extracted with dichloromethane, and evaporation of the organic layers gave a residue which was submitted to flash chromatography (E/PE 40/60). Compound **20** was obtained as a yellow oil (0.43 g, 91%). ^{1}H NMR: 1.24 (d, *J* = 6.9 Hz, 3H), 1.42−1.43 (m, 1H), 1.66 (dq, *J* = 4.4 and 12.4 Hz, 1H), 1.81−1.88 (m, 2H), 2.76−2.80 (m, 1H), 3.14 (d, *J* = 2 Hz, 1H), 3.40−3.42 (m, 1H), 3.60 (dd, *J* = 3.2 and 10.6 Hz, 1H), 3.75 (s, 3H), 4.15 (dd, *J* = 3.4 and 10.9 Hz, 1H), 4.24 (t, *J* = 10.7 Hz, 1H), 7.28−7.38 (m, 5H). Irradiation of the ^{1}H NMR 3.14 signal (H-9a) causes the 3.42 resonance (H-9) to change to a doublet (*J* = 3.7 Hz). ^{13}C NMR: 19.7, 29.5, 35.1, 48.3, 51.4, 52.2, 62.9, 66.9, 72.7, 128.1, 128.7, 129.0, 136.1, 168.9, 171.5. IR ($CHCl_3$): 1720, 1730 cm^{-1}. $[\alpha]^{20}_D$: +43 (*c* 0.96, $CHCl_3$). MS *m*/*e* 303 (31) (M^+), 186 (46), 104 (100), 96 (38), 84 (74). HRMS: calcd for $C_{17}H_{21}NO_4$ *m*/*z* = 303.1470, obsd *m*/*z* = 303.1471.

[4*S*-4α,7*β*]-1,6-Dioxo-7-methyl-4-phenyl-1,3,4,6,7,8-hexahydropyrido[2,1-*c*][1,4]oxazine-9-carboxylic Acid Methyl Ester 24. A solution of compound **9** (1.9 g, 7.7 mmol) in THF (30 mL) and methacryloyl chloride (3 mL, 31 mmol) was refluxed with stirring for 24 h. After cooling, the reaction mixture was poured into an aqueous solution saturated with sodium hydrogen carbonate, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The crude residue was obtained as a solid (an epimeric mixture at C7, 90/10) which was recrystallized in absolute ethanol to give pure compound **24** (2.1 g, 87%): mp 96 °C. ^{1}H NMR: 1.30 (d, *J* = 6.9 Hz, 3H), 2.47 (dd, *J* = 12.8 and 17.7 Hz, 1H), 2.73−2.79 (m, 1H), 2.96 (dd, *J* = 6.9 and 17.7 Hz, 1H), 3.85 (s, 3H), 4.62 (dd, *J* = 1.6 and 11.8 Hz, 1H), 4.74 (dd, *J* = 2.9 and 11.8 Hz, 1H), 5.68 (s, 1H), 7.17−7.39 (m, 5H). ^{13}C NMR: 15.1, 30.4, 33.9, 52.1, 53.1, 70.2, 121.5,125.9, 128.1, 128.5, 129.2, 136.1, 159.4, 167.6, 169.9. IR ($CHCl_3$): 1640, 1690, 1720, 1740 cm^{-1}. $[\alpha]^{20}_D$: +54.8 (*c* 1.1, $CHCl_3$). HRMS: calcd for $C_{17}H_{17}NO_5$ *m*/*z* = 315.1106, obsd *m*/*z* = 315.1106.

[4*S*-4α,7*β*,9*β*,9aα]-1,6-Dioxo-7-methyl-4-phenyloctahydropyrido[2,1-*c*][1,4]oxazine-9-carboxylic Acid Methyl Ester (25) and [4*S*-4α,7*β*,9*β*,9a*β*]-1,6-Dioxo-7-methyl-4-phenyloctahydropyrido[2,1-*c*][1,4]oxazine-9-carboxylic Acid Methyl Ester (26). A mixture of compound **24** (0.7 g, 2.2 mmol) and 5% Pd on carbon (0.3 g) in ethanol/ethyl acetate (1/1, 80 mL) was stirred under hydrogen (1 atm) for 2 h. The catalyst was filtered on Celite, and the filtrate was evaporated. The residue was chromatographed on silica gel (E/PE 80/20, then Et_2O). The following compounds were obtained by order of elution:

Compound 26: 0.42 g (59.6%), mp 111 °C. ^{1}H NMR: 1.13 (d, *J* = 6.7 Hz, 3H), 1.85−1.92 (m, 1H), 2.29−2.40 (m, 2H), 3.28−3.32 (m, 1H), 3.67 (s, 3H), 4.50 (dd, *J* = 7.5 and 12 Hz, 1H), 4.63 (d, *J* = 5.2 Hz, 1H), 4.69 (dd, *J* = 5.5 and 12 Hz, 1H), 5.60 (dd, *J* = 5.5 and 7.5 Hz, 1H), 7.19−7.27 (m, 5H). ^{13}C NMR: 16.7, 27.8, 35.3, 39.9, 52.3, 52.7, 54.8, 68.4., 126.3, 128.2, 129.0, 136.0, 167.6, 171.2, 172.1. $[\alpha]^{20}_D$: +37 (*c* 1.1, $CHCl_3$). HRMS: calcd for $C_{17}H_{19}NO_5$ *m*/*z* = 317.1263, obsd *m*/*z* = 317.1262.

Compound 25: 0.12 g (17%), mp 185 °C. ^{1}H NMR: 1.17 (d, *J* = 6.9 Hz, 3H), 1.76 (dd, *J* = 12 and 12 Hz, 1H), 2.30 (ddd, *J* = 3.1, 5.8, and 13.1 Hz, 1H), 2.38−2.46 (m, 1H), 3.23 (ddd, *J* = 3.1, 10.6, and 13 Hz, 1H), 3.73 (s, 3H), 4.41 (dd, *J* = 1.2 and 12.2 Hz, 1H), 4.74 (d, *J* = 10.5 Hz, 1H), 4.78 (dd, *J* = 3,1 and 12.1 Hz, 1H), 5.29 (d, *J* = 2.6 Hz, 1H), 6.99−7.28 (m, 5H). ^{13}C NMR: 16.6, 32.3, 36.1, 41.7, 52.7, 55.3, 57.7, 69.6, 125.6, 128.0, 129.0, 138.5, 168.4, 170.7, 172.6. $[\alpha]^{20}_D$: +63 (*c* 0.7, $CHCl_3$). Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 4.41; N, 6.03. Found: C, 64.28; H, 4.33; N, 6.08.

[4*S*-4α,7*β*,9*β*,9a*β*]-1-Oxo-7-methyl-4-phenyloctahydropyrido[2,1-*c*][1,4]oxazine-9-carboxylic Acid Methyl Ester (27). To a 1 M solution of BH_3/THF complex (6.3 mL, 6.3 mmol) in THF, cooled to 0 °C, was added dropwise a THF (2 mL) solution of compound **26** (0.2 g, 0.63 mmol). The reaction was complete at the end of addition, and the mixture was hydrolyzed cautiously with water. The aqueous layer was extracted with dichloromethane, and the organic fractions were combined and dried over $MgSO_4$. After evaporation, the residue was purified by flash chromatography (E/PE 30/70) to give compound **27** as a white solid (0.15 g, 80%). An analytical sample was recrystallized in cyclohexane: mp 92 °C. ^{1}H NMR: 0.83 (d, J = 6.5 Hz, 3H), 1.40−1.54 (m, 1H), 1.63−1.69 (m, 1H), 1.99−2.12 (m, 2H), 2.69 (ddd, J = 1.4, 3.7 and 11.2 Hz, 1H), 2.85 (dt, J = 4.5 and 11.9 Hz, 1H), 3.65 (s, 3H), 3.80 (dd, J = 6.5 and 10.9 Hz, 1H), 4.17 (t, J = 11.3 Hz, 1H), 4.30 (d, J = 4.7 Hz, 1H), 4.51 (dd, J = 6.5 and 10.1 Hz, 1H), 7.19−7.32 (m, 5H). ^{13}C NMR: 18.8, 29.7, 30.8, 41.4, 52.1, 55.1, 60.5, 64.1, 69.9, 126.7, 128.0, 128.9, 138.2, 170.7, 172.3. IR ($CHCl_3$): 1725, 1740 cm^{-1}. $[\alpha]^{20}_D$: −121 (*c* 0.97, $CHCl_3$). Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.18; H, 7.12; N, 4.47.

Crystal Data.[18] $C_{17}H_{21}NO_4$, monoclinic, no centrosymmetric $P2_1$ space group, Z = 2, D_c = 1.27 g cm^{-3}, μ(Mo Kα) = 0.84 cm^{-1}, a = 10.510(2), b = 7.073(1), and c = 10.758(2) Å, β = 96.24(1)°, V = 795(1) Å^3. Data were collected at room temperature on an Enraf-Nonius CAD4 diffractometer. The program used was CRYSTALS. No significant variations were observed in the intensities of two checked reflections during data collection. The structure was solved by use of SHELXS86 program, G. M. Sheldrick, Program for Crystal Structure Solution, University of Göttingen, 1986, and refined by full-matrix least-squares analysis with anisotropic thermal parameters for all non hydrogen atoms. H atoms were introduced in calculated positions in the last refinement. The final refinement of 200 parameters using 837 reflections (with $(F_o)^2 > 2\sigma(F_o)^2$) were used to solve and refine the structure to R = 0.0451 and R_w = 0.0444.

[4*S*-4α,7*β*,9α,9aα]-1,6-Dioxo-7-methyl-4-phenyloctahydropyrido[2,1-*c*][1,4]oxazine-9-carboxylic Acid Methyl Ester (29). To a solution of compound **24** (2 g, 6.3 mmol) in ethyl acetate/ethanol (1/1, 80 mL) was added a suspension of Raney nickel in absolute ethanol (10 mL). The mixture was hydrogenated for 0.5 h, then filtered on Celite, and evaporated under reduced pressure. The crude residue was chromatographed to furnish compound **29** (Et_2O and then Et_2O/MeOH, 90/10) as a white solid (1.6 g, 79%): mp 163 °C. ^{1}H NMR: 1.15 (d, J = 6.6 Hz, 3H), 1.86 (td, J = 4.4 and 14.9 Hz, 1H), 2.31−2.42 (m, 2H), 3.48 (dd, J = 4.1 and 7.5 Hz, 1H), 3.71 (s, 3H), 4.40−4.47 (m, 2H), 4.66 (dd, J = 3.6 and 12.2 Hz, 1H), 5.23 (d, J = 3.3 Hz, 1H), 7.20−7.47 (m, 5H). ^{13}C NMR: 16.6, 30.9, 33.1, 39.6, 52.4, 55.2, 57.0, 69.7, 126.6, 127.7, 128.6, 139.4, 168.4, 171.2, 171.5. $[\alpha]^{20}_D$: +91 (*c* 0.6, $CHCl_3$). Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.16; H, 6.23; N, 4.30.

[4*S*-4α,7*β*,9α,9aα]-1-Oxo-7-methyl-4-phenyloctahydropyrido[2,1-*c*][1,4]oxazine-9-carboxylic Acid Methyl Ester (30). A solution of compound **29** (0.7 g, 2.2 mmol) in THF (10 mL) was added dropwise into a 1 M solution of BH_3/THF complex (22 mL, 22 mmol) at −30 °C with vigorous stirring. The mixture was allowed to reach rt within 3 h. Then, water (15 mL) was slowly added, and the reaction mixture was extracted with dichloromethane. After evaporation, the residue was chromatographed (E/PE 20/80) to give compound **30** as a white solid (0.57 g, 85%). An analytical sample recrystallized from cyclohexane displayed the following data: mp 52 °C. ^{1}H NMR: 0.76 (d, J = 6.6 Hz, 3H), 1.26 (ddd, J = 5.2, 11.1 and 13.5 Hz, 1H), 1.48−1.50 (m, 1H), 1.69−1.77 (m, 1H), 2.42−2.45 (m, 1H), 2.79 (ddd, J = 1.6, 4.2, and 11.1Hz, 1H), 3.13 (d, J = 2.4 Hz, 1H), 3.54−3.56 (m, 1H), 3.63 (dd, J = 3.1 and 10.7 Hz, 1H), 3.80 (s, 3H), 4.19 (dd, J = 3.1 and 10.8 Hz, 1H), 4.36 (t, J = 10.8 Hz, 1H), 7.30−7.40 (m, 5H). ^{13}C NMR: 18.8, 28.1, 34.9, 43.6, 52.1, 59.3, 63.0, 65.1, 72.7, 128.2, 128.7, 129.0, 136.2, 169.1, 172.4. IR ($CHCl_3$): 1710, 1730 cm^{-1}. $[\alpha]^{20}_D$: +66 (*c* 1.3, $CHCl_3$). HRMS: calcd for $C_{17}H_{21}NO_4$ m/z = 303.1470, obsd m/z = 303.1471.

General Procedure for the Hydrogenolysis of Bicyclic Amino Esters. A solution of pyridooxazines (0.7 mmol) in absolute ethanol (10 mL) was injected into a hydrogenation flask containing a prehydrogenated suspension of 20% Pd-$(OH)_2$/C (Pearlman catalyst) (0.4 g) in absolute ethanol (10 mL). The hydrogenation was complete in 4−10 h. The mixture was filtered through Celite 545 and the residue washed with water. The filtrate was evaporated to dryness, leaving the corresponding crude amino acid esters which were crystallized from acetone.

(2*R*,3*S*)-Piperidine-2,3-dicarboxylic acid 3-methyl ester (14): yield 97%, mp (dec) 250 °C. ^{1}H NMR (D_2O): 1.37−1.81 (m, 3H), 1.94−2.03 (m, 1H), 2.83 (td, J = 3.5 and 12.4 Hz, 1H), 3.18−3.25 (m, 2H), 3.54 (s, 3H), 3.64 (d, J = 3.9 Hz, 1H). ^{13}C NMR (D_2O): 19.8, 25.6, 41.3, 45.1, 54.0, 59.3, 173.5, 176.0. $[\alpha]^{20}_D$: +20.3 (*c* 0.54, MeOH). HRMS: calcd for $C_8H_{13}NO_4$ (M - COOH)m/z = 142.0868, obsd m/z = 142.0867.

(2*S*,3*S*)-Piperidine-2,3-dicarboxylic acid 3-methyl ester (17): yield 85%, mp (dec) 250 °C. ^{1}H NMR (D_2O): 1.63−1.71 (m, 2H), 1.79−1.80 (m, 1H), 1.90−1.95 (m, 1H), 2.81 (dt, J = 3.9 and 10.3 Hz, 1H), 2.98 (dt, J = 3.5 and 11.5 Hz, 1H), 3.30−3.34 (m, 1H), 3.65 (s, 3H), 3.76 (d, J = 10.2 Hz, 1H). ^{13}C NMR (D_2O): 21.9, 27.2, 44.7, 44.9, 54.6, 60.5, 173.5, 176.9. $[\alpha]^{20}_D$: +19.4 (*c* 0.5, MeOH). Anal. Calcd for $C_8H_{13}NO_4$: C, 51.32; H, 7.48; N, 6.99. Found: C, 51.22; H, 7.38; N, 6.98.

(2*R*,3*S*,4*S*)-4-Methylpiperidine-2,3-dicarboxylic acid 3-methyl ester (21): yield 94%, mp 168 °C. ^{1}H NMR (D_2O): 0.86 (d, J = 6.9 Hz, 3H), 1.28−1.46 (m, 1H), 1.58−1.65 (m, 1H), 1.90−2.10 (m, 1H), 2.86 (dt, J = 3.4 and 13 Hz, 1H), 3.18 (t, J = 4.6 Hz, 1H), 3.31 (ddd, J = 2, 4.2, and 12.7 Hz, 1H), 3.55 (s, 3H), 3.66 (d, J = 4 Hz, 1H). 1D difference NOE experiment: presaturation of the 3.66 resonance (H-2) resulted in enhancements (7% and 8%, respectively) of the 1.9−2.1 (H-4) and the 3.18 (H-3) signals. ^{13}C NMR (D_2O): 18.9, 25.9, 31.4, 44.1, 45.8, 52.6, 59.5, 172.8, 174.5. $[\alpha]^{20}_D$: +7 (*c* 0.6, MeOH). HRMS: calcd for $C_9H_{15}NO_4$ (M − COOH)m/z = 156.1024, obsd m/z = 156.1023.

(2*S*,3*R*,5*S*)-5-Methylpiperidine-2,3-dicarboxylic acid 3-methyl ester (28): yield 87%, mp (dec) 210 °C. ^{1}H NMR (D_2O): 0.80 (d, J = 6.7 Hz, 3H), 1.10−1.29 (m, 1H), 1.66−1.75 (m, 1H), 1.96 (dt, J = 3.6 and 13.7 Hz, 1H), 2.50 (t, J = 12 Hz, 1H), 2.91 (dt, J = 4.1 and 11.3 Hz, 1H), 3.22 (dd, J = 3.8 and 12.8 Hz, 1H), 3.55 (s, 1H), 4.17 (d, J = 4.1 Hz, 1H). ^{13}C NMR (D_2O): 16.2, 26.1, 27.9, 39.2, 45.7, 51.0, 55.4, 168.5, 172.9. $[\alpha]^{20}_D$: +11.9 (*c* 1.1, MeOH). HRMS: calcd for $C_9H_{15}NO_4$ (M − COOH) m/z = 156.1024, obsd m/z = 156.1023.

(2*R*,3*S*,5*S*)-5-Methylpiperidine-2,3-dicarboxylic acid 3-methyl ester (31): yield 88%. ^{1}H NMR (D_2O): 0.78 (d, 6.2 Hz, 3H), 1.46 (dt, J = 5.5 and 13 Hz, 1H), 1.54−1.90 (m, 1H), 1.94−2.08 (m, 1H), 2.49 (t, J = 12.2 Hz, 1H), 3.14−3.20 (m, 1H), 3.31−3.35 (m, 1H), 3.56 (s, 3H), 3.59 (d, J = 3.7 Hz, 1H). ^{13}C NMR (D_2O): 17.0, 24.7, 32.7, 40.2, 49.5, 52.7, 57.6, 172.1, 174.7. $[\alpha]^{20}_D$: +15.5 (*c* 1.1, MeOH). HRMS: calcd for $C_8H_{14}NO_2$ (M − COOH) m/z = 156.1024, obsd m/z = 156.1023.

(2*R*,3*S*,4*S*)-4-Methylpiperidine-2,3-dicarboxylic Acid (4). NaOH (0.29 g, 7.2 mmol) was added to an aqueous solution of compound **21** (0.08 g, 0.4 mmol, 0.2 M). The mixture was stirred for 1 h and evaporated. The residue was purified on a cation exchange resin (Dowex 1x2-400). After evaporation, a white solid was obtained (0.7 g, 94%). ^{1}H NMR (D_2O): 0.72 (d, J = 6.7 Hz, 3H), 1.23−1.44 (m, 2H), 1.67−1.74 (m, 1H), 2.60−2.72 (m, 2H), 3.11−3.16 (m, 1H), 3.30−3.40 (m, 1H). ^{13}C NMR (D_2O): 19.4, 26.3, 31.6, 44.1, 48.0, 61.0, 170.9. $[\alpha]^{20}_D$: −11 (*c* 1.1, 6N HCl).

General Procedure for the Hydrolysis of the Amino Acid Esters 14, 17, 28, and 31. A solution of amino acid ester (3.6 mmol) in 3 N hydrochloric acid (8.7 mmol) was refluxed for 8 h and then concentrated under reduced pressure. Chlorhydrates of the amino diacids were obtained as white solids.

(18) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(2*R*,3*S*)-Piperidine-2,3-dicarboxylic acid hydrochloride (2): yield 80%. ^{1}H NMR (D_2O): 1.45−1.55 (m, 1H), 1.74−1.88 (m, 2H), 2.13−2.17 (m, 1H), 2.95 (td, J = 2.7 and 12.8 Hz, 1H), 3.34 (m, 1H), 3.43 (m, 1H), 4.01 (d, J = 3.4 Hz, 1H). ^{13}C NMR (D_2O): 20.4, 25.5, 42.5, 43.5, 57.3, 173.5, 176.2. $[\alpha]^{20}_D$: −4.1 (*c* 1, 6 N HCl) [lit.[3] $[\alpha]^{20}_D$: −4.2 (*c* 1, 6N HCl)].

(2*S*,3*S*)-Piperidine-2,3-dicarboxylic acid hydrochloride (*ent*-3): yield 93%. ^{1}H NMR (D_2O): 1.23−1.85 (m, 3H), 2.01−2.06 (m, 1H), 2.87 (td, J = 4.1 and 9.9 Hz, 1H), 3.01 (td, J = 3.4 and 11.3 Hz, 1H), 3.33−3.38 (m, 1H), 4.09 (d, J = 9.8 Hz, 1H). ^{13}C NMR (D_2O): 20.0, 25.1, 42.0, 43.2, 56.7, 170.0, 175.9. $[\alpha]^{20}_D$: +16.6 (*c* 1, 6 N HCl). HRMS: calcd for $C_7H_{11}NO_4$·HCl (M − COOH,HCl) m/z = 128.0711, obsd m/z = 128.0712.

(2*S*,3*R*,5*S*)-5-Methylpiperidine-2,3-dicarboxylic acid hydrochloride (5): yield 90%. ^{1}H NMR (D_2O): 0.82 (d, J = 6.7 Hz, 3H), 1.12−1.21 (m, 1H), 1.60−1.68 (m, 1H), 1.80−1.83 (m, 1H), 2.50−2.56 (m, 1H), 2.79−2.81 (m, 1H), 2.97 (dd, J = 3.5 and 12.7 Hz, 1H), 4.23 (d, J = 3.2 Hz, 1H). ^{13}C NMR (D_2O): 17.6, 27.3, 29.5, 40.4, 47.6, 56.4, 170.0, 175.5. $[\alpha]^{20}_D$: +12.5 (*c* 1, 6 N HCl). HRMS: calcd for $C_8H_{13}NO_4$·HCl (M − COOH,HCl) m/z = 142.0868, obsd m/z = 142.0867.

(2*R*,3*S*,5*S*)-5-Methylpiperidine-2,3-dicarboxylic acid hydrochloride (6): yield 97%. ^{1}H NMR (D_2O): 0.79 (d, J = 6.3 Hz, 3H), 1.48 (dt, J = 5.1 and 13.4 Hz, 1H), 1.50−1.66 (m, 1H), 2.11 (d, J = 12 Hz, 1H), 2.53 (t, J = 12.2 Hz, 1H), 3.20 (d, J = 13 Hz, 1H), 3.39−3.41 (m, 1H), 3.86 (d, J = 3.5 Hz, 1H). ^{13}C NMR (D_2O): 17.4, 25.1, 32.5, 40.4, 49.9, 56.2, 170.6, 175.9. $[\alpha]^{20}_D$: −9.0 (*c* 1.05, 6 N HCl). HRMS: calcd for $C_8H_{13}NO_4$·HCl (M − COOH,HCl) m/z = 142.0868, obsd m/z = 142.0867.

MO Calculations. The calculations on enamino ester **9** and crotonyl halide were carried out using the AM1 Hamiltonian[16] as implemented in the AMPAC program version 4.0 QCPE No. 527. The geometries were optimized by using the Davidson−Fletcher−Powell algorithm (FLEPO procedure) that minimizes the energy with respect to all internal coordinates. An *s-cis* conformation was optimized for crotonyl chloride. The transition states for the Michael addition and for the hetero-Diels−Alder condensation were optimized by minimizing the energy gradient (NLLSQ procedure): respective energies are −118.30 and −109.40 kcal. Selected bond lengths (and bond order) are (i) C_β−C_3 1.80 Å (0.544), C_α−O 3.20 Å (0.024) for the Michael addition and (ii) C_β−C_3 2.00 Å (0.516), C_α−O 1.92 Å (0.350) for the hetero-Diels−Alder condensation.

Supporting Information Available: ^{1}H and ^{13}C NMR for all new compounds, an ORTEP drawing (X-ray analysis) of compound **27**, and two computerized transition states (53 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9606158