Stereocontrolled Synthesis of 4-Substituted (±)-Kainic Acids

Iván Collado, Jesús Ezquerra, Ana I. Mateo, and Almudena Rubio*

Centro de Investigación Lilly, S. A. Av. de la Industria, 30. 28108-Alcobendas, Madrid, Spain

Received November 19, 1997

Racemic 4-substituted kainic acids **4a**,**b** have been synthesized from ethyl (1*SR*,2*SR*,5*RS*,6*RS*)-*N*-(benzyloxycarbonyl)-3-aza-6-hydroxy-6-methylbicyclo[3.3.0]octane-2-carboxylate (**7**) after its transformation in the pyroglutamate derivative **6**. The key step in the synthesis has been the regioselective alkylation of **6** to obtain **11a**,**b**, without compromising the stereogenic integrity of the potentially labile C-2 center. The elaboration of the C-3 and C-4 substituents of kainic acid over **11** was achieved after double bond isomerization of **11**, oxidative double bond cleavage of **5**, and chemoselective aldehyde reduction of **16** followed by Wittig olefination reaction of **17** and final alcohol oxidation and hydrolysis over **18** to the corresponding 4-methyl kainic acid **4a** and 4-benzyl kainic acid **4b**. The relatively small changes introduced in the structure of kainic acid **1** have been found to lead to a loss of affinity for kainate receptors.

Introduction

Since its first isolation from the marine alga *Digenea simplex*,[1] kainic acid (**1**) (Figure 1) has attracted a considerable attention in the scientific community. Owing to its marked neuroexcitatory activity[2] and unique structure, a number of stereoselective syntheses have been described over the last 15 years.[3] Furthermore, with the aim of modifying its pharmacological profile, there has been much interest in synthesizing unnatural analogues of this important substance.[4] From these reports, it has become apparent that the isopropenyl appendage at C-4 plays a key role in binding at the kainic acid recognition site.[5] Hence, the exploration in the vicinity of this group became highly desirable. However, with the exception of Kozikowski's examination of the conformationally rigid 4-spiro kainic acid **2**,[4e] structural modifications at the pyrrolidine core are still lacking. The difficulties of exploring the substitution effects at C-4 reside on the deficiency of synthetic strategies that allow the general and stereocontrolled functionalization of this position.

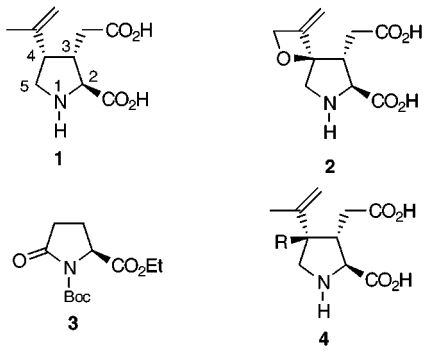


Figure 1.

Results and Discussion

Our synthetic strategy, is outlined in Scheme 1. The C-4 isopropenyl and the C-3 acetate group of kainic acid would be the result of selective lactam reduction of the bicyclic pyroglutamate derivative **5**, followed by oxidative

(1) Murukami, S.; Takemoto, T.; Shimizu, Z. *J. Pharm. Soc. Jpn.* **1953**, *73*, 1026.

(2) (a) McGeer, E. G.; Olney, J. W.; McGeer, P. L., Eds. *Kainic acid as a Tool in Neurobiology*; Raven Press: New York, 1978. (b) Watkins, J. C.; Krogsgaard-Larsen, P.; Honoré, T. *Trends Pharmacol. Sci.* **1990**, *11*, 25. (c) Lodge, D., Ed. *Excitatory Amino Acids in Health and Disease*; John Wiley & Sons: New York, 1988. (d) Krogsgaard-Larsen, P.; Hansen, J. J., Eds. *Excitatory Amino Acids Receptors*; Ellis Horwood: New York, 1992.

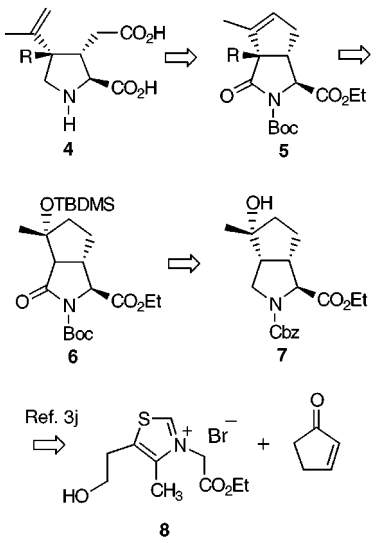
(3) For some leading references to synthesis of kainic acid, see: (a) Oppolzer, W.; Thirring, K. *J. Am. Chem. Soc.* **1982**, *104*, 4978. (b) Baldwin, J. E.; Li, C.-S. *J. Chem. Soc., Chem. Commun.* **1987**, 166. (c) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1204. (d) Takano, S.; Sugihara, T.; Sotoh, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1988**, *110*, 6467. (e) Cooper, J.; Knight, D. W.; Gallagher, P. T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 553. (f) Barco, A.; Benetti, S.; Spalluto, G.; Casolari, A.; Pollini, G. P.; Zanirato, V. *J. Org. Chem.* **1992**, *57*, 6279. (g) Takano, S.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1992**, 169. (h) Hatakeyama, S.; Sugawara, K.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1993**, 125. (i) Yoo, S−e.; Lee, S. H. *J. Org. Chem.* **1994**, *59*, 6968. (j) Monn, J. A.; Valli, M. J. *J. Org. Chem.* **1994**, *59*, 2773. (k) Bachi, M. D.; Melman, A. *Synlett* **1996**, 60. (l) Bachi, M. D.; Bar-Ner, N.; Melman, A. *J. Org. Chem.* **1996**, *61*, 7116. (m) Hanessian, S.; Ninkovic, S. *J. Org. Chem.* **1996**, *61*, 5418. (n) Bachi, M. D.; Melman, A. *J. Org. Chem.* **1997**, *62*, 1896. (o) Nakada, Y.; Sugahara, T.; Ogasawara, K. *Tetrahedron Lett.*, **1997**, *38*, 857. For reviews see: Synthesis of Optically Active α-Amino Acids: Williams, R. M., Ed.; Pergamon Press: New York, 1989; p 305. Parsons, A. F. *Tetrahedron* **1996**, *52*, 4145.

(4) (a) Goldberg, O.; Luini, A.; Teichberg, V. I. *Tetrahedron Lett.* **1980**, *21*, 2355 (b) Conway, G. A.; Park, J. S.; Maggiora, L.; Mertes, M. P.; Galton, N.; Michaelis E. K. *J. Med. Chem.* **1984**, *27*, 52. (c) Tsai, C.; Schnider, J. A.; Lehmann, *J. Neurosci. Lett.* **1988**, *92*, 298. (d) Yanagida, M.; Hashimoto, K.; Ishida, M.; Shinozaki, H.; Shirahama, H. *Tetrahedron Lett.* **1989**, *30*, 3799. (e) Kozikowski, A. P.; Fauq, A. H. *Tetrahedron Lett.* **1990**, *31*, 2967. (f) Hashimoto, K.; Horikawa, M.; Shirahama, H. *Tetrahedron Lett.* **1996**, *31*, 7047. (g) Ishida, M.; Shinozaki, H. *Br. J. Pharmacol.* **1991**, *104*, 873. (h) Hashimoto, K.; Shirahama, H. *Tetrahedron Lett.* **1991**, *32*, 2625. (i) Jefferies, I. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1519. (j) Hashimoto, K.; Horikawa, M.; Ishida, M.; Shinozaki, H.; Shirahama, H. *Bioorg. Med. Chem. Lett.*, **1992**, *2*, 743. (k) Baldwin, J. E.; Rudolph, M. *Tetrahedron Lett.* **1994**, *35*, 6163. (l) Baldwin, J. E.; Bamford, S. J.; Fryer, A. M.; Wood, M. E. *Tetrahedron Lett.* **1995**, *36*, 4869. (m) Gill, P.; Lubell, W. D. *J. Org. Chem.* **1995**, *60*, 2658. (n) Ezquerra, J.; Escribano, A.; Rubio, A.; Remuiñán, M. J.; Vaquero, J. J. *Tetrahedron Lett.* **1995**, *36*, 6149. (o) Hashimoto, K.; Ofhune, Y.; Shirahama, H. *Tetrahedron Lett.* **1995**, *36*, 6235. (p) Horikawa, M.; Shima, Y.; Hashimoto, K.; Shirahama, H. *Heterocycles* **1995**, *40*, 1009. (q) Hashimoto, K.; Hashimoto, M.; Shirahama, H. *Tetrahedron* **1996**, *52*, 1931. (r) Hanessian, S.; Ninkovic, S.; Reinhold: U. *Tetrahedron Lett.* **1996**, *37*, 8971. (s) Cantrell, B. E.; Zimmerman, D. M.; Monn, J. A.; Kamboj, R. K.; Hoo, K. H.; Tizzano, J. P.; Pullar, I. A.; Farrell, L. N.; Bleakman, D. *J. Med. Chem.* **1996**, *39*, 3617. (t) Maeda, H.; Kraus, G. A. *J. Org. Chem.* **1997**, *62*, 2314.

(5) (a) Ishida, M.; Shinozaki, H. *Br. J. Pharmacol.* **1991**, *104*, 873. (b) Tsai, C.; Schnider, J. A.; Lehmann, J. *Neurosci. Lett.* **1988**, *92*, 298. (c) Sonnenberg, J. D.; Koch, H. P.; Willis, C. L.; Bradbury, F.; Dauenhauer, D.; Bridges, R.; Chamberlin, A. R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1607.

S0022-3263(97)02123-3 CCC: $15.00
Published on Web 02/24/1998

Scheme 1



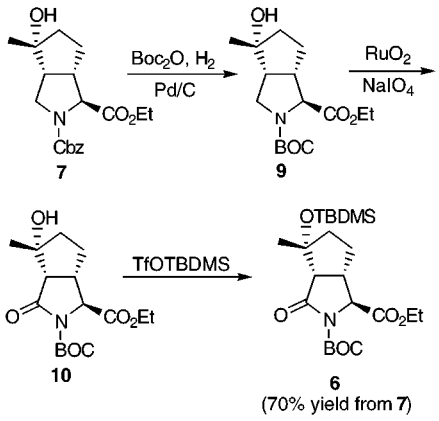
cleavage of the double bond. This intermediate compound **5** would arise from the selective alkylation of the lactam enolate derived from **6**, followed by dehydration of the tertiary alcohol. Finally, **6** could be obtained by oxidation α- to the nitrogen of the bicyclic prolinate **7**, which in turn can be obtained via the [3 + 2] cycloaddition reaction of a thiazolium ylide with 2-cyclopentenone in a four-step sequence as reported by Monn and Valli.[3j] The advantages of this retrosynthetic analysis include: (1) straightforward access to 4-substituted kainic acids, (2) high degree of stereocontrol exercised by the 3-azabicyclo[3.3.0]octane nucleus, and (3) use of the azabicyclooctanol **7**, readily available on a large scale, as starting material.

This retrosynthetic analysis is based on the possibility of selectively alkylate the lactam enolate derived from **6**. To our advantage we took into account our previous experience working with ethyl *N*-BOC pyroglutamate **3**, where we have reported the aldol reaction,[6] mono alkylation[7] and double alkylation[8] of its lactam enolate. During the functionalization step, the pyroglutamate potentially labile C-2 stereogenic center was not affected, resulting in a convenient means to prepare 4-monosubstituted or 4,4-disubstituted prolines, after selective reduction of the pyroglutamate lactam carbonyl group.[9]

On the basis of these preliminary results, we wish to report the first approach to the stereocontrolled introduction of substituents at C-4 in the pyrrolidine ring system of kainic acid that culminated in the stereocontrolled synthesis of 4-substituted kainic acids **4**.

The bicyclic prolinate derivative **7** was prepared on a large scale in 45% overall yield, following the sequence reported by Monn and Valli.[3j] Transformation of **7** into the key pyroglutamate intermediate **6** was accomplished in 70% overall yield after exchange of CBZ nitrogen protecting group by BOC,[10] ruthenium oxidation[11] of C-4, and further protection of the hydroxy group (Scheme 2).

Scheme 2

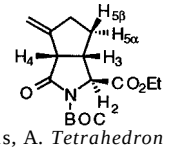


It should be pointed out that the protecting group exchange was necessary in order to carry out the oxidation step.

Reaction of the bicyclic pyroglutamate **6** with 1 equiv of LiHMDS and subsequent trapping of the resulting enolate with electrophiles as previously reported for the alkylation of **3**[8] did not lead to the clean formation of the C-5 alkylated product, affording instead a mixture of C-2 and C-5 alkylation products along with products resulting from the elimination of the OTBDMS group. This result led us to use 2 equiv of base and longer reaction times in order to favor the quantitative formation of the enolate **III** (Scheme 3). This modification resulted in the exclusive formation of **11a**−**c** without any evidence of C-2 alkylation.[12]

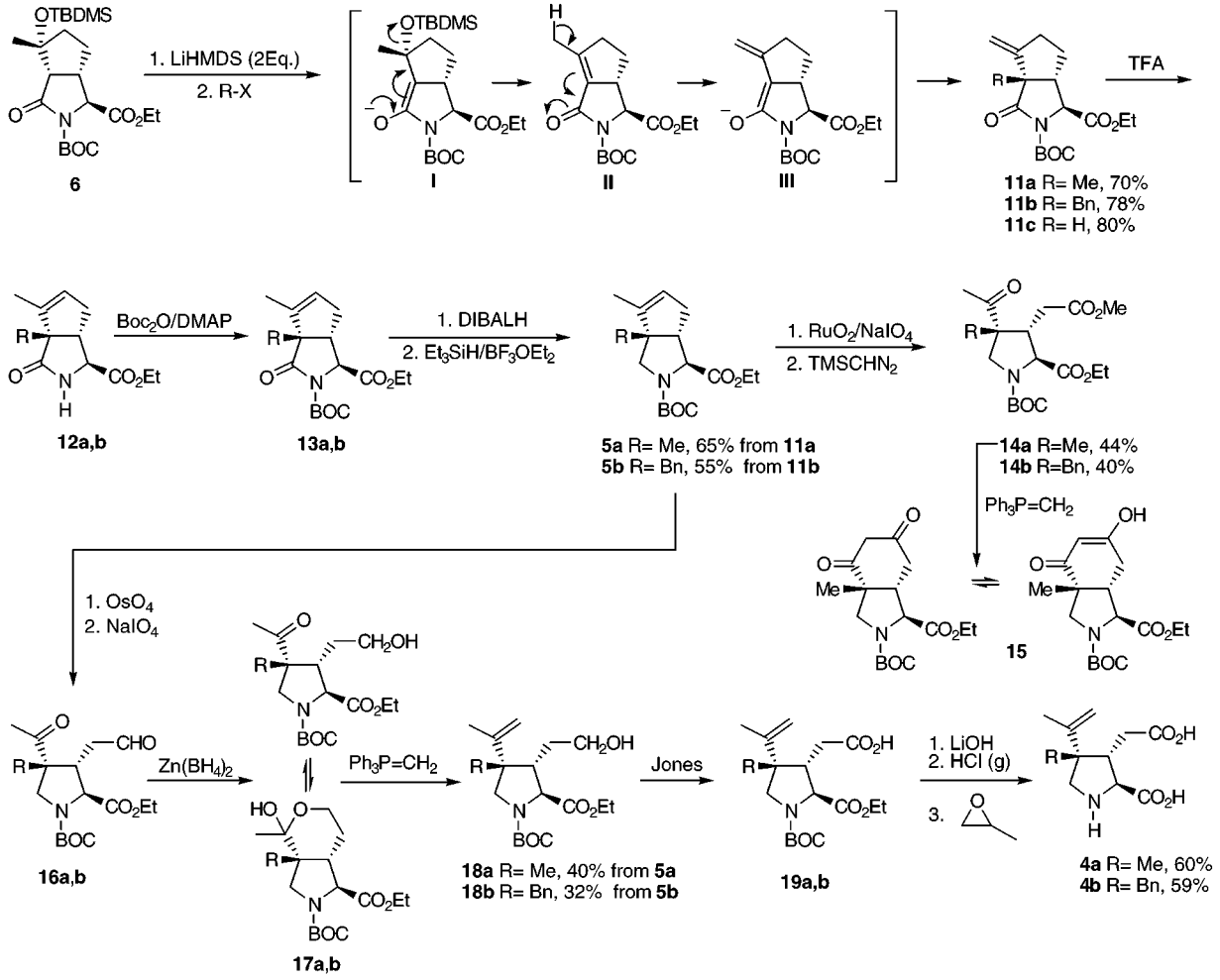
With compounds **11** in hands, the next steps of the synthesis were directed to the generation of the side chains at C-3 and C-4. Accordingly, when **11a** or **11b** were treated with TFA in a sealed tube at 140 °C, double bond isomerization occurred with simultaneous cleavage of the BOC group, which was introduced again under standard conditions to give **13a** or **13b**. Reduction of the lactam carbonyl moiety to **5a** or **5b** was performed in a two-step sequence: (1) partial reduction of the lactam carbonyl moiety into the corresponding hemiaminal with DIBALH[13] and (2) further reduction of this intermediate with Et_3SiH in the presence of $BF_3{\cdot}Et_2O$ via an *N*-acyliminium ion,[9] which led to the isolation of **5a** or **5b** in 65% and 55% yields from **11a** or **11b**, respectively. It is important to mention that, in contrast with our previously reported results,[9] repeated attempts to use $LiEt_3BH$ instead of DIBALH led only to 25% conversion recovering most of the unchanged starting material. Oxidative ring opening of **5a** or **5b** under Sharpless conditions,[14] followed by esterification of the carboxylic acid with $TMSCHN_2$, furnished the keto diesters **14a** or

(6) Ezquerra, J.; Pedregal, C.; Yruretagoyena, B.; Rubio, A.; Carreño, M. C.; Escribano, A.; García Ruano, J. L. *J. Org. Chem.* **1995**, *60*, 2925.
(7) Ezquerra, J.; Pedregal, C.;.Rubio, A.; Yruretagoyena, B.; Escribano, A.; Sánchez-Ferrando, F. *Tetrahedron* **1993**, *49*, 8665.
(8) Ezquerra, J.; Pedregal, C.; Rubio, A.; Vaquero, J. J.; Matía, M. P.; Martín, J.; Diaz, A.; Navío, J. L.; Deeter, J. B. *J. Org. Chem.* **1994**, *59*, 4327.
(9) Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreño, M. C.; García Ruano, J. L. *Tetrahedron Lett.* **1994**, *35*, 2053.
(10) Sakaitani, M.; Hori, K.; Ohfune, Y. *Tetrahedron Lett.* **1988**, *29*, 2983.
(11) Yoshifuji, S.; Tanaka, K.-I.; Kawai, T.; Nitta, Y. *Chem. Pharm. Bull.* **1986**, *34*, 3873.
(12) That the stereochemistry at C-2 stereogenic center was preserved was ascertained on the basis of the observed NOEs. Thus, for **11c**, irradiation of H_2 (arbitrary numbering) shows NOEs at $H_{5\alpha}$, indicating that they are on the same face of the molecule.



(13) Langlois, N.; Rojas, A. *Tetrahedron Lett.* **1993**, *34*, 2477.

Scheme 3



14b in a modest yield (44% and 40%, respectively). Methylenation reaction on **14a** or **14b** would complete the elaboration of the side chains. Wittig reactions on analogous ketones in which R = H are known to proceed in good yield but the significant epimerization that was produced[3j,m] precluded its use on those enolizable ketones. Since C-4 substitution prevents such epimerization, Wittig reaction appeared to be suitable for the methylenation of ketones **14a** or **14b**. However, reaction of **14a** with triphenylphosphonium methylide did not give the required product, affording instead the diketone **15** resulting from an intramolecular Claisen reaction. Other nonbasic methylenation reagents[3j,15] such as $CH_2I_2-Zn-TiCl_4$ turned out to be equally ineffective. Therefore, an alternative route to the elaboration of the side chains was sought. Osmylation of **5a** or **5b** followed by periodate cleavage gave the keto aldehydes **16a** or **16b** which were chemoselectively reduced with $Zn(BH_4)_2$ to the keto alcohols **17a** or **17b**. The Wittig reaction of **17a** or **17b** proceeded smoothly to give **18a** or **18b** in 40% and 32% yield, respectively, for the four steps from **5a** or **5b** and without purification of the intermediates. Finally, the synthesis of the 4-substituted kainic acids[16] was completed after Jones oxidation followed by basic hydrolysis of the ethyl ester, acidic *N*-BOC deprotection, and final isolation of the zwitterions by treatment with propylene oxide, yielding **4a** in 60% yield and **4b** in a 59% isolated yield from **18a** and **18b**, respectively.

Biological Properties of 4a and 4b. Compounds **4a** and **4b** were evaluated for their binding as agonists and antagonists in cells expressing hum-GluR5 and 6 kainate receptors and in the rat forebrain kainate receptors. Unfortunately, no significant binding affinity was found compared with kainic acid itself. This lack of activity reflects the sensitivity of the kainate receptors' recognition site to the steric congestion imposed by the substituent attached to the pyrrolidine core.

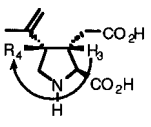
Summary

We have described in this paper a highly efficient route to the synthesis of 4-substituted kainic acids. The key functionalization step comprised regioselective alkylation of **6** without compromising the stereogenic integrity of the potentially labile C-2 center. Transformations of the

(14) Carlsen, P. H. J.; Katsuki, T.; Martin V. S.; Sharpless, K. B. *J. Org. Chem.* **1991**, *46*, 3936.

(15) (a) Hibino, J.-I.; Okazoe, T.; Kazuhiko, T.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5579. (b) Takai, K.; Hotta, y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, *27*, 2417.

(16) The structural assignments for compounds **4a** and **4b** were confirmed on the basis of the observed NOEs. Thus, for **4a,** irradiation of H_3 shows NOE at the methyl on C_4.



4

bicyclic intermediate **11** into the final substituted kainic acids were accomplished via stepwise sequences that avoid the undesirable facile intramolecular Claisen and epimerization reactions. Thus, 4-methyl kainic acid **4a** and 4-benzyl kainic acid **4b** were obtained in 16 steps from **7** in an 8% yield and 6% yield, respectively.

Experimental Part

All solvents and reagents were purchased from commercial sources and used as received, unless otherwise indicated. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl prior to use. ^{1}H NMR and ^{13}C NMR data were recorded on a Bruker AC-200P (200 MHz). IR spectra were obtained on Nicolet 510 P-FT (film and KBr). High-resolution mass spectra (HRMS) were measured on a VG-Autospec spectrometer. Melting points were determined on a Büchi apparatus and are not corrected. Analytical TLC was performed on Merck TLC glass plates precoated with F_{254} silica gel 60 (UV, 254 nm, and iodine). Chromatographic separations were performed by using 230−400 mesh silica gel (Merck). Elemental analyses were performed by the Universidad de Alcalá de Henares de Madrid.

Ethyl (1*SR*,2*SR*,5*RS*,6*RS*)-*N*-(*tert*-Butoxycarbonyl)-3-aza-6-hydroxy-6-methylbicyclo[3.3.0]octan-2-carboxylate (9). To a solution of **7**[3j] (10.5 g, 30.2 mmol) and di-*tert*-butyl dicarbonate (8.6 g, 39.3 mmol) in methanol (300 mL) was added 850 mg of Pd/C (10%). The reaction mixture was hydrogenated at atmospheric pressure until completion (24 h), and the suspension was filtered through a pad of Celite. After evaporation to dryness **9** was obtained (8.2 g, 87% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$, doubling due to amide rotamers) δ 4.19−3.98 (m, 3H), 3.74−3.42 (m, 2H), 2.78−2.59 (m, 1H), 2.44−2.30 (m, 1H), 2.10−1.53 (m, 5H), 1.42−1.20 (m, 15H); ^{13}C NMR ($CDCl_3$, doubling due to amide rotamers) δ 173.3, 172.8, 154.7, 154.0, 79.9, 79.5, 67.6, 66.9, 60.7, 52.5, 51.9, 47.9, 46.8, 46.4, 40.6, 40.1, 29.7, 28.3 y 28.2, 27.9, 27.3, 14.2; IR (film) 3440, 1744, 1703, 1397, 1368, 1186 cm^{-1}. Anal. Calcd for $C_{16}H_{27}NO_5$: C, 61.32; H, 8.68; N, 4.47. Found: C, 61.28; H, 8.76; N, 4.40.

Ethyl (1*SR*,2*SR*,5*SR*,6*RS*)-*N*-(*tert*-Butoxycarbonyl)-3-aza-6-hydroxy-6-methyl-4-oxobicyclo[3.3.0]octane-2-carboxylate (10). To a solution of $NaIO_4$ (28.0 g, 131 mmol) in H_2O (250 mL) was added 520 mg (3.9 mmol) of $RuO_2 \cdot H_2O$. The resulting suspension was stirred until it was transformed into a yellow solution. A solution of **9** (8.2 g, 26.2 mmol) in ethyl acetate (90 mL) was added, and the mixture was stirred overnight. The aqueous phase was extracted with ethyl acetate (2 × 100 mL), and the combined organic phases were treated with 2-propanol (20 mL) and stirred for 2 h. The resulting black suspension was filtered through Celite, dried (Na_2SO_4), filtered, and evaporated to dryness to afford compound **10** (8.6 g) as a white solid, which was used without further purification: mp 107−108 °C; ^{1}H NMR ($CDCl_3$) δ 4.32 (d, J = 2.6 Hz, 1H), 4.20 (c, J = 7.1 Hz, 2H), 2.97 (s, 1H), 2.83 (d, J = 9.8 Hz, 1H), 2.67−2.53 (m, 1H), 2.25−2.09 (m, 1H), 1.94−1.74 (m, 2H), 1.65−1.36 (m, 1H), 1.46 (s, 9H), 1.43 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.0, 171.2, 149.0, 83.7, 80.1, 64.7, 61.6, 56.7, 40.8, 38.7, 31.4, 28.1, 27.8, 14.1; IR (KBr) 3490, 1786, 1736, 1346, 1323, 1294 cm^{-1}. Anal. Calcd for $C_{16}H_{25}NO_6$: C, 58.70; H, 7.70; N, 4.28. Found: C, 58.71; H, 7.95; N, 4.16.

Ethyl (1*SR*,2*SR*,5*SR*,6*RS*)-*N*-(*tert*-Butoxycarbonyl)-3-aza-6-[(*tert*-butyldimethylsilyl)oxy]-6-methyl-4-oxobicyclo[3.3.0]octane-2-carboxylate (6). To a solution of **10** (8.6 g, 26.2 mmol) in CH_2Cl_2 (45 mL) were added 2,6-lutidine (9.1 mL, 78.6 mmol) and *tert*-butyldimethylsilyl triflate (6.6 mL, 28.8 mmol). After the reaction mixture was stirred at room temperature for 4 h, an additional 1.5 mL (6.5 mmol) of *tert*-butyldimethylsilyl triflate was added, and the resulting solution was stirred overnight at room temperature. A 10% citric acid solution (400 mL) was added, and the product was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated in vacuo. The reaction crude was purified by flash chromatography (hexane/ethyl acetate 5:1) to afford compound **6** as a white solid (9.2 g, 80% overall yield from **9**): mp 70−72 °C; ^{1}H NMR ($CDCl_3$) δ 4.22 (d, J = 5.7 Hz, 1H), 4.17 (c, J = 7.1 Hz, 2H), 2.68 (d, J = 10.8 Hz, 1H), 2.70−2.50 (m, 1H), 2.26−1.84 (m, 3H), 1.60−1.50 (m, 1H), 1.54 (s, 3H), 1.42 (s, 9H), 1.24 (t, J = 7.1 Hz, 3H), 0.78 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 171.6, 171.4, 148.9, 84.2, 82.6, 66.8, 61.0, 59.9, 43.0, 38.7, 31.2, 27.6, 25.7, 25.6, 17.7, 14.0, −2.5, −2.6; IR (KBr) 1794, 1740, 1310, 1252, 1159 cm^{-1}. Anal. Calcd for $C_{22}H_{39}NO_6Si$: C, 59.83; H, 8.90; N, 3.17. Found: C, 59.95; H, 8.84; N, 3.24.

Ethyl (1*SR*,2*SR*,5*SR*)-*N*-(*tert*-Butoxycarbonyl)-3-aza-5-methyl-6-methylidene-4-oxobicyclo[3.3.0]octane-2-carboxylate (11a), Ethyl (1*SR*,2*SR*,5*SR*)-*N*-(*tert*-Butoxycarbonyl)-3-aza-5-benzyl-6-methylidene-4-oxobicyclo[3.3.0]octane-2-carboxylate (11b), and Ethyl (1*SR*,2*SR*,5*SR*)-*N*-(*tert*-Butoxycarbonyl)-3-aza-6-methylidene-4-oxobicyclo[3.3.0]octane-2-carboxylate (11c). To a solution of **6** (8.20 g, 18.6 mmol) in dry THF (90 mL) stirred at −78 °C under nitrogen was added a 1 M solution of lithium hexamethyldisilazide in THF (37.2 mL, 37.2 mmol). The reaction mixture was allowed to stir at −78 °C for 30 min and then warmed to −20 °C. After 30 min at −20 °C, the electrophile (20.5 mmol) was added, and the mixture was then stirred for 2 h at this temperature. The resulting solution was poured into saturated NH_4Cl solution (100 mL) and extracted with ethyl acetate (3 × 200 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (hexane/ethyl acetate 7:1). **11a**: 4.2 g (70% yield), colorless oil; ^{1}H NMR ($CDCl_3$) δ 5.27 (m, 1H), 5.08 (m, 1H), 4.25 (q, J = 7.1 Hz, 2H), 4.19 (d, J = 4.3 Hz, 1H), 2.51−2.35 (m, 3H), 2.20−2.05 (m, 1H), 1.84−1.66 (m, 1H), 1.50 (s, 9H), 1.36 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 175.2, 171.1, 152.2, 149.5, 109.1, 83.4, 61.8, 61.4, 55.2, 47.5, 31.9, 30.1, 27.7, 23.7, 14.0; IR (film) 2980, 1790, 1748, 1721, 1372, 1312, 1256, 1200, 1154 cm^{-1}. Anal. Calcd for $C_{17}H_{25}NO_5$: C, 63.12; H, 7.80; N, 4.33. Found: C, 63.01; H, 7.83; N, 4.25. **11b**: 5.8 g (78% yield), colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.25−7.11 (m, 5H), 5.52 (m, 1H), 5.24 (m, 1H), 4.21−4.09 (m, 2H), 4.11 (d, J = 4.7 Hz, 1H), 3.09 (AB system, J = 13.6 Hz, 2H), 2.53−2.02 (m, 3H), 1.80−1.59 (m, 2H), 1.49 (s, 9H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.4, 170.8, 150.9, 149.2, 136.7, 129.9, 128.1, 126.6, 110.0, 83.3, 61.7, 61.2, 60.3, 43.0, 41.7, 32.5, 29.8, 27.6, 13.8; IR (film) 2980, 1790, 1748, 1717, 1456, 1370, 1312, 1152 cm^{-1}; HRMS (*m*/*z*) calcd for $C_{19}H_{21}NO_5$ ($M^+ - {}^t$Bu + H): 343.1420. Found 343.1435. **11c**: 4.6 g (80% yield), colorless oil; ^{1}H NMR ($CDCl_3$) δ 5.36 (m, 1H), 5.12 (m, 1H), 4.31 (d, J = 2.5 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.44 (d, J = 8 Hz, 1H), 2.80−2.67 (m, 1H), 2.47−2.09 (m, 3H), 1.88−1.57 (m, 1H), 1.50 (s, 9H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.3, 170.8, 149.3, 145.8, 110.1, 83.3, 62.5, 61.4, 51.3, 39.8, 32.4, 31.4, 27.6, 14.0; IR (film) 2980, 1790, 1748, 1717, 1370 cm^{-1}; HRMS (*m*/*z*) calcd for $C_{16}H_{23}NO_5$ (M^+): 309.1576. Found 309.1580.

Ethyl (1*SR*,2*SR*,5*SR*)-3-Aza-5,6-dimethyl-4-oxobicyclo[3.3.0]oct-6-ene-2-carboxylate (12a) and Ethyl (1*SR*,2*SR*,5*SR*)-3-Aza-5-benzyl-6-methyl-4-oxobicyclo[3.3.0]oct-6-ene-2-carboxylate (12b). To a solution of **11a** or **11b** (10 mmol) in CH_2Cl_2 (21 mL), in a sealed tube, was added TFA (21 mL, 298 mmol). The resulting solution was stirred for 5 h at 140 °C. After cooling to room temperature, the reaction mixture was neutralized with a saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated to dryness, affording **12a** or **12b** which were used in next reaction without further purification. **12a**: white solid, mp 93−95 °C; ^{1}H NMR ($CDCl_3$) δ 6.42 (s, 1H), 5.27 (m, 1 H), 4.14 (q, J = 7.1 Hz, 2H), 3.68 (d, J = 5.8 Hz, 1 H), 2.70−2.54 (m, 2H), 2.37−2.20 (m, 1H), 1.66 (m, 3H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 171.5, 140.2, 124.9, 62.1, 61.8, 60.2, 49.8, 36.2, 18.7, 13.8, 12.2; IR (KBr) 1744, 1694, 1206 cm^{-1}. Anal. Calcd for $C_{12}H_{17}NO_3 \cdot {}^1/_9H_2O$: C, 63.99; H, 7.71; N, 6.22. Found: C, 64.00; H, 7.60; N, 5.87. **12b**: white solid, mp 118−

119 °C; ^{1}H NMR ($CDCl_3$) δ 7.39−7.16 (m, 5H), 6.16 (s, 1H), 5.43 (m, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.72 (d, J = 6.5 Hz, 1H), 3.04 (AB system, J = 13.6 Hz, 2H), 2.94−2.83 (m, 1H), 2.28−2.04 (m, 2H), 1.95 (m, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 177.2, 171.7, 139.4, 137.1, 129.8, 128.0, 126.4, 126.1, 64.4, 61.5, 60.5, 46.3, 38.0, 36.9, 14.0, 12.9. IR (KBr) 1747, 1694, 1217 cm^{-1}. Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.20; H, 7.07; N, 4.68. Found: C, 71.98; H, 7.15; N, 4.34.

Ethyl (1*SR*,2*SR*,5*SR*)-*N*-(*tert*-Butoxycarbonyl)-3-aza-5,6-dimethyl-4-oxobicyclo[3.3.0]oct-6-ene-2-carboxylate (13a) and Ethyl (1*SR*,2*SR*,5*SR*)- N-**(*tert*-Butoxycarbonyl)-3-aza-5-benzyl-6-methyl-4-oxobicyclo[3.3.0]oct-6-ene-2-carboxylate (13b).** To a stirred solution of **12a** or **12b** (9 mmol) in CH_3CN (60 mL) were added di-*tert*-butyl dicarbonate (2.2 g, 9.9 mmol) and DMPA (110 mg, 0.9 mmol) at room temperature. After stirring overnight, the solvent was evaporated, and the residue was dissolved in ether and then treated with 0.5 N HCl (10 mL). The layers were separated, and the aqueous phase was extracted with ether (3 × 100 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, and filtered, and the solvent was removed in vacuo to give **13a** or **13b** which were used without further purification. **13a**: colorless oil; ^{1}H NMR ($CDCl_3$) δ 5.39 (m, 1H), 4.24 (q, J = 7.1 Hz, 2H), 4.12 (d, J = 5.1 Hz, 1H), 2.86−2.68 (m, 1H), 2.48−2.32 (m, 2H), 1.76 (m, 3H), 1.49 (s, 9H),1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.6, 171.5, 149.4, 141.2, 124.5, 83.4, 64.2, 61.4, 60.5, 45.6, 37.3, 27.8, 19.9, 14.1, 12.2; IR (film) 2977, 1790, 1748, 1717, 1314 cm^{-1}. Anal. Calcd for $C_{17}H_{25}NO_5 \cdot {}^1/_5H_2O$: C, 62.45; H, 7.83; N, 4.28. Found: C, 62.35; H, 7.78; N, 4.11. **13b**: white solid, mp 103−104 °C; ^{1}H NMR ($CDCl_3$) δ 7.24−7.06 (m, 5H), 5.38 (s, 1H), 4.08 (q, J = 7.1 Hz, 2H), 3.95 (d, J = 6.2 Hz, 1H), 3.01 (AB system, J = 13.9 Hz, 2H), 2.54−2.46 (m, 1H), 2.16−2.04 (m, 2H), 1.87 (m, 3H), 1.45 (s, 9H), 1.17 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 173.9, 171.4, 149.2, 139.4, 136.7, 129.8, 128.2, 126.9, 126.6, 83.5, 66.0, 64.7, 61.3, 41.9, 38.1, 37.5, 27.8, 14.0, 12.7. IR (KBr) 1786, 1738, 1282, 1148 cm^{-1}. HRMS (m/z) calcd for $C_{19}H_{21}NO_5$ ($M^+ - {}^t$Bu + H): 343.1420. Found 343.1422.

Ethyl (1*SR*,2*SR*,5*SR*)-*N*-(*tert*-Butoxycarbonyl)-3-aza-5,6-dimethylbicyclo[3.3.0]oct-6-ene-2-carboxylate (5a) and Ethyl (1*SR*,2*SR*,5*SR*)-*N*-(*tert*-Butoxycarbonyl)-3-aza-5-benzyl-6-methylbicyclo[3.3.0]oct-6-ene-2-carboxylate (5b). To a stirred solution of **13a** or **13b** (5.6 mmol) in THF (54 mL) was added dropwise a 1 M solution of DIBALH in toluene (16.8 mL, 16.8 mmol) at −78 °C under nitrogen. After being stirred at −78 °C for 1 h, the mixture was quenched with methanol (30 mL) and warmed to room temperature. A saturated potassium tartrate solution (50 mL) and ethyl acetate (50 mL) were added. The mixture was stirred for 15 min. The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The crude product was used without further purification. A solution of the reaction crude and triethylsilane (0.87 mL, 5.6 mmol) in CH_2Cl_2 (83 mL) was cooled to −78 °C, and boron trifluoride etherate (0.75 mL, 6.2 mmol) was then added dropwise under a nitrogen atmosphere. After 30 min, 0.87 mL (5.6 mmol) of triethylsilane and 0.75 mL (6.2 mmol) of boron trifluoride etherate were added. After being stirred for 2 h at −78 °C, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL), extracted with CH_2Cl_2 (3 × 100 mL), and dried over $MgSO_4$. Evaporation of the solvent and purification by flash chromatography (hexane/ethyl acetate 4:1) yielded compounds **5a** or **5b** (65% for **5a** and 55% for **5b**, overall yields from **11a** and **11b**, respectively). **5a**: colorless oil; ^{1}H NMR ($CDCl_3$, doubling due to amide rotamers) δ 5.17 (s, 1H), 4.16−4.01 (m 2H), 3.93 and 3.78 (2d, J = 4.9 and 5.6 Hz, 1H), 3.44 and 3.37 (2 AB systems, J = 11.0 Hz, 2H), 2.61−2.45 (m, 1H), 2.35−2.07 (m, 2H), 1.56 (s, 3H), 1.35 and 1.30 (s, 9H), 1.27−1.14 (m, 3H), 1.02 and 1.01 (2s, 3H); ^{13}C NMR ($CDCl_3$, doubling due to amide rotamers) δ 173.4, 173.0, 154.1, 153.4, 144.2, 143.7, 123.0, 122.5, 79.7, 79.5, 67.4, 67.0, 60.6, 57.3, 56.4, 55.0, 54.6, 54.1, 53.1, 36.5, 36.1, 28.2, 28.1, 21.4, 14.2, 14.1, 12.3; IR (film) 2977, 2932, 1748, 1703, 1395, 1368, 1188, 1164 cm^{-1}; HRMS (m/z) calcd for $C_{17}H_{27}NO_4$ (M^+): 309.1940. Found 309.1941. **5b**: white solid, mp 79−80 °C; ^{1}H NMR ($CDCl_3$, doubling due to amide rotamers) δ 7.24−7.06 (m, 5H), 5.28 (s, 1H), 4.22−4.02 (m 2H), 3.96−3.76 (m, 2H), 3.47−3.35 (m, 1H), 2.87−2.56 (m, 3 H), 2.12−1.82 (m, 2H), 1.72 (s, 3H), 1.46 and 1.38 (2s, 9H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, doubling due to amide rotamers) δ 173.4, 173.0, 153.5, 141.8, 137.6, 129.7, 127.8, 126.2, 125.6, 79.8, 67.7, 67.4, 62.2, 61.2, 60.6, 54.2, 53.6, 51.0, 50.0, 40.6, 37.0, 36.7, 28.3, 28.1, 14.1, 12.9; IR (KBr) 1734, 1701, 1393, 1366, 1277 cm^{-1}. Anal. Calcd for $C_{23}H_{31}NO_4$: C, 71.65; H, 8.11; N, 3.64. Found: C, 71.61; H, 8.07; N, 3.52.

Methyl (2*SR*,3*SR*,4*SR*)-*N*-(*tert*-Butoxycarbonyl)-4-acetyl-2-(ethoxycarbonyl)-4-methylpyrrolidine-3-acetate (14a) and Methyl (2*SR*,3*SR*,4*RS*)-*N*-(*tert*-Butoxycarbonyl)-4-acetyl-4-benzyl-2-(ethoxycarbonyl)pyrrolidine-3-acetate (14b). A mixture of $RuO_2 \cdot H_2O$ (53 mg, 0.4 mmol) and $NaIO_4$ (1.75 g, 8.2 mmol) in CH_3CN (3.2 mL), CCl_4 (3.2 mL), and H_2O (2.6 mL) was vigorously stirred at room temperature for 15 min. To this mixture was added a solution of **5a** or **5b** (2 mmol) in CH_3CN (0.6 mL). The reaction mixture was stirred at room temperature for 4 h and then partitioned between ether (10 mL) and H_2O (10 mL). The layers were separated, and the aqueous phase was extracted with ether (3 × 10 mL). The combined organic layers were washed with H_2O (10 mL) and then dried over anhydrous $MgSO_4$, filtered through Celite, and concentrated in vacuo. The crude carboxylic acid was dissolved in ether (50 mL) and treated sequentially with EtOH (2 mL) and a 2 M solution of $TMSCHN_2$ in hexane (2 mL, 4 mmol). The reaction mixture was stirred at room temperature for 30 min. The solvent was eliminated under reduced pressure. The crude residue was purified by flash column chromatography (hexane/ethyl acetate 3:1). **14a**: 337 mg (44% yield); colorless oil; ^{1}H NMR ($CDCl_3$, doubling due to amide rotamers) δ 4.30−4.05 (m, 3H), 3.60 (AB system, J = 11.7 Hz, 2H), 3.54 (s, 3H), 2.71−2.41 (m, 3H), 2.04 (s, 3H), 1.32 and 1.26 (2s, 9H), 1.20−1.11 (m, 6H); ^{13}C NMR ($CDCl_3$, doubling due to amide rotamers) δ 209.2, 209.0, 172.1, 172.0, 171.8, 171.6, 153.3, 153.0, 80.3, 80.2, 64.5, 64.2, 61.0, 60.9, 55.8, 55.0, 54.8, 51.6, 48.8, 47.9, 32.8, 32.2, 28.1, 27.9, 27.0, 26.9, 20.3, 19.7, 13.9, 13.8; IR (film) 1744, 1702, 1400, 1159 cm^{-1}; HRMS (m/z) calcd for $C_{17}H_{29}NO_7$ (M^+): 371.1944. Found 371.1938. **14b**: 358 mg (40% yield); white solid, mp 94−95 °C; ^{1}H NMR ($CDCl_3$, doubling due to amide rotamers) δ 7.24−7.02 (m, 5H), 4.25−3.22 (m, 7H), 2.90−2.39 (m, 3H), 1.96 and 1.94 (2s, 3H), 1.42 and 1.36 (2s, 9H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, doubling due to amide rotamers) δ 210.0, 171.9, 171.6, 152.9, 136.1, 129.6, 128.5 127.0, 80.7, 64.3, 64.0, 61.2, 59.7, 52.7, 51.8, 48.0, 47.2, 40.8, 40.6, 33.4, 33.0, 28.9, 28.3, 28.0, 14.0; IR (KBr) 1761, 1715, 1688, 1410, 1173 cm^{-1}; HRMS (m/z) calcd for $C_{24}H_{33}NO_7$ (M^+): 447.2257. Found 447.2257.

Ethyl (1*RS*,6*SR*,7*SR*)-*N*-(*tert*-Butoxycarbonyl)-8-aza-2,4-dioxo-1-methylbicyclo[4.3.0]non-3-ene-7-carboxylate (15). To a suspension of methyltriphenylphosphonium bromide (1.8 g, 5 mmol) in toluene (25 mL) was added, at room temperature under nitrogen, a 0.5 M solution of potassium bis(trimethylsilylamide in toluene (8.8 mL, 4.4 mmol), and the reaction was allowed to continue at room temperature for 1 h. To a stirred solution of **14a** (742 mg, 2 mmol) in toluene (12 mL), at room temperature under nitrogen, was added via cannula the foregoing solution of methyltriphenylphosphonium ylide until the reaction was complete (TLC; hexane/ethyl acetate 2:1). The reaction mixture was partitioned between CH_2Cl_2 (50 mL), and H_2O (50 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL), and the combined organic phases were dried (Na_2SO_4) and evaporated in vacuo affording 652 mg of crude **15**. ^{1}H NMR ($CDCl_3$, doubling due to amide rotamers) δ 5.00 and 4.92 (2s, 1H), 4.36 (m, 1H), 4.20−3.85 (m, 3H), 3.00 (m, 1H), 2.61−2.20 (m, 3H), 1.46−1.20 (m, 15H).

(2*SR*,3*SR*,4*RS*)-*N*-(*tert*-Butoxycarbonyl)-2-(ethoxycarbonyl)-4-acetyl-4-methylpyrrolidine-3-acetaldehyde (16a) and (2*SR*,3*SR*,4*SR*)-*N*-(*tert*-Butoxycarbonyl)-2-(ethoxycarbonyl)-4-acetyl-4-benzylpyrrolidine-3-acetaldehyde

(16b). A vigorously stirred solution of **5a** or **5b** (4 mmol) and *N*-methylmorpholine *N*-oxide (1.0 g, 8.8 mmol) in acetone (40 mL) and H_2O (12 mL) was treated at room temperature with a 4% solution of OsO_4 in water (74 μl, 0.006 mmol), and the resulting mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ether (100 mL) and H_2O (100 mL). The layers were separated, and the aqueous phase was extracted with ether (3 × 100 mL). The combined organic phases were washed with H_2O (100 mL), dried ($MgSO_4$), filtered and, concentrated in vacuo. The crude diols were dissolved in THF (24 mL), and a solution of $NaIO_4$ (1.28 g, 6 mmol) in H_2O (16 mL) was added. The resulting mixture was stirred vigorously at room temperature for 3 h. The mixture was partitioned between ether (100 mL) and H_2O (100 mL), the layers were separated, and the aqueous phase was extracted with ether (3 × 100 mL). The combined organic phases were washed with H_2O (100 mL), dried ($MgSO_4$), filtered, and concentrated to afford **16a** or **16b** which were used in subsequent reactions without further purification. **16a**: colorless oil; ^{1}H NMR ($CDCl_3$, doubling due to amide rotamers) δ 9.73 (s, 1H), 4.24−4.05 (m, 3H), 3.66 and 3.62 (2AB systems, J = 11.7 Hz, 2H), 3.10−2.62 (m, 3H), 2.17 (s, 3H), 1.45−1.21 (m, 15H); ^{13}C NMR ($CDCl_3$, doubling due to amide rotamers) δ 209.5, 209.3, 199.2, 172.1, 171.6, 153.0, 80.4, 80.3, 64.5, 64.3, 61.1, 61.0, 55.9, 55.2, 54.8, 45.7, 45.0, 42.6, 42.3, 28.1, 27.9, 26.9, 26.8, 20.0, 19.6, 13.9, 13.8; IR (film) 2979, 1740, 1703, 1682, 1399, 1368, 1156 cm^{-1}; HRMS (*m*/*z*) calcd for $C_{17}H_{27}NO_6$ (M^+): 341.1838. Found 341.1838. **16b**: colorless oil; ^{1}H NMR ($CDCl_3$, doubling due to amide rotamers) δ 9.74 and 9.71 (2s, 1H), 7.30−7.01 (m, 5H), 4.24−3.56 (m, 5H), 2.95 (AB system, J = 13.4 Hz, 2H), 2.96−2.71 (m, 3H), 1.99 (s, 3H), 1.44 and 1.38 (2s, 9H), 1.34−1.20 (m, 3H). ^{13}C NMR ($CDCl_3$, doubling due to amide rotamers) δ 210.5, 210.0, 199.0, 171.6, 171.2, 153.2, 152.9, 135.9, 129.4, 128.5, 127.8, 127.1, 80.8, 80.7, 64.3, 64.0, 61.2, 60.4, 59.6, 53.1, 52.9, 45.0, 44.3, 42.9, 42.8, 40.9, 40.7, 28.9, 28.8, 28.2, 28.0, 13.9, 13.8; IR (film) 2978, 1748, 1696, 1397, 1370, 1188 cm^{-1}. HRMS (*m*/*z*) calcd for $C_{23}H_{31}NO_6$ (M^+): 417.2151. Found 417.2152.

Ethyl (2*SR*,3*SR*,4*SR*)-*N*-(*tert*-Butoxycarbonyl)-3-(2-hydroxyethyl)-4-isopropenyl-4-methylpyrrolidine-2-carboxylate (18a) and Ethyl (2*SR*,3*SR*,4*RS*)-*N*-(*tert*-Butoxycarbonyl)-4-benzyl-3-(2-hydroxyethyl)-4-isopropenylpyrrolidine-2-carboxylate (18b). To a solution of **16a** or **16b** (3 mmol) in THF (30 mL) under nitrogen at −10 °C was added a 0.2 M solution of zinc borohydride in THF (16.5 mL, 3.3 mmol). After 10 min at this temperature, the reaction mixture was poured into ether (10 mL) and H_2O (10 mL). The layers were separated, and the aqueous phase was extracted with ether (3 × 50 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to yield **17a** or **17b**. To a stirred suspension of methyltriphenylphosphonium bromide (5.9 g, 16.5 mmol) in dioxane (30 mL), at room temperature under nitrogen atmosphere, was added a 0.5 M solution of potassium bis(trimethylsilyl)amide in toluene (30 mL, 15 mmol). The reaction mixture was stirred at room temperature for 60 min, and then a solution of the foregoing keto alcohols **17a** or **17b** in dioxane (10 mL) was added. The reaction was allowed to continue at room temperature overnight. The reaction mixture was partitioned between ether (50 mL) and H_2O (50 mL), and the layers were separated. The aqueous phase was extracted with ether (3 × 50 mL), and the combined organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo. The crude was purified by flash chromatography (hexane/ethyl acetate 1:1). **18a**: 40% overall yield from **5a**; colorless oil; ^{1}H NMR ($CDCl_3$, doubling due to amide rotamers) δ 4.86 (s, 1H), 4.70 (s, 1H), 4.21 (q, J = 7.1 Hz, 2H), 4.11 and 4.05 (2d, J = 6.0 Hz, 1H), 3.77−3.60 (m, 3H), 3.37−3.29 (m, 1H), 2.25−2.14 (m, 2H), 1.94−1.77 (m, 1H), 1.71 (s, 3H), 1.46 and 1.42 (2s, 9H), 1.39−1.23 (m, 3H), 1.24 (s, 3H); ^{13}C NMR ($CDCl_3$, doubling due to amide rotamers) δ 173.5, 173.1, 154.1, 153.5, 147.0, 146.7, 112.2, 112.0, 80.2, 80.0, 64.7, 64.3, 61.2, 60.9, 60.7, 56.8, 56.4, 50.0, 48.9, 48.8, 33.0, 28.4, 28.2, 25.0, 21.1, 14.1, 14.0; IR (film) 3440, 2928, 1746, 1705, 1402 cm^{-1}. Anal. Calcd for $C_{18}H_{31}NO_5 \cdot {}^1/_5H_2O$: C, 62.67; H, 9.17; N, 4.06. Found: C, 62.88; H, 9.13; N, 3.93. **18b**: 32% overall yield from **5b**; colorless oil; ^{1}H NMR ($CDCl_3$, doubling due to amide rotamers) δ 7.26−7.07 (m, 5H), 4.93 and 4.91 (2s, 1H), 4.50 and 4.36 (2s, 1H), 4.29−4.01 (m, 3H), 3.84−3.69 (m, 2H), 3.53−3.20 (m, 2H), 2.99−2.73 (m, 2H), 2.37−2.30 (m, 2H), 2.03−1.74 (m, 1H), 1.83 and 1.79 (2s, 3H), 1.45 and 1.40 (2s, 9H), 1.38−1.20 (m, 3H); ^{13}C NMR ($CDCl_3$, doubling due to amide rotamers) δ 173.1, 172.4, 154.4, 153.6, 143.6, 143.3, 137.4, 137.3, 129.9, 127.7, 127.5, 126.1, 114.8, 80.0, 79.8, 64.0, 63.4, 61.1, 61.0, 60.2, 60.0, 54.0, 52.7, 51.6, 50.9, 48.6, 47.2, 40.3, 39.6, 33.3, 33.0, 28.2, 28.0, 21.3, 20.8, 13.9; IR (film) 3463, 2977, 1748, 1682, 1393 cm^{-1}. Anal. Calcd for $C_{24}H_{35}NO_5$: C, 69.05; H, 8.45; N, 3.36. Found: C, 68.82; H, 8.29; N, 2.96.

(2*SR*,3*SR*,4*SR*)-*N*-(*tert*-Butoxycarbonyl)-2-(ethoxycarbonyl)-4-isopropenyl-4-methylpyrrolidin-3-acetic Acid (19a) and (2*SR*,3*SR*,4*RS*)-*N*-(*tert*-Butoxycarbonyl)-4-benzyl-2-(ethoxycarbonyl)-4-isopropenylpyrrolidin-3-acetic Acid (19b). Compounds **18a** or **18b** (0.8 mmol) were dissolved in acetone (5.6 mL), and the solution was cooled to 0 °C prior to the addition of freshly prepared Jones reagent (1.4 mL). The resulting mixture was allowed to stir at 0 °C for 1 h and then allowed to warm to room temperature and stirred for another 2 h. The reaction mixture was poured into H_2O (10 mL) and 2-propanol (10 mL). This mixture was treated with an aqueous 0.1 N solution of KOH until pH ∼ 7, and then it was added to a aqueous 0.5 N solution of HCl until pH ∼ 2. The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with H_2O (10 mL), dried over anhydrous $MgSO_4$, and filtered, and the solvent was evaporated to dryness to afford **19a** or **19b** which were used without further purification. **19a**: colorless oil; ^{1}H NMR ($CDCl_3$, doubling due to amide rotamers) δ 4.89 (s, 1H), 4.70 (s, 1H), 4.19−3.86 (m, 3H), 3.53 and 3.47 (2AB systems, J = 11.0 Hz, 2H), 2.67−2.12 (m, 3H), 1.68 (s, 3H), 1.42 and 1.37 (2s, 9H), 1.27−1.20 (m, 6H); ^{13}C NMR ($CDCl_3$, doubling due to amide rotamers) δ 177.2, 172.3, 172.0, 153.9, 153.3, 146.3, 146.0, 113.3, 113.1, 80.5, 80.3, 64.8, 64.5, 61.2, 57.2, 56.7, 48.8, 48.4, 47.8, 47.5, 34.2, 28.4, 28.2, 24.4, 24.2, 21.3, 14.1, 13.9; IR (film) 3200, 1738, 1703, 1399, 1152; HRMS (*m*/*z*) calcd for $C_{14}H_{21}NO_6$ ($M^+ - {}^t$Bu): 299.1369. Found 299.1367. **19b**: white solid, mp 42−44 °C; ^{1}H NMR ($CDCl_3$, doubling due to amide rotamers) δ 7.29−7.10 (m, 5H), 5.08 and 5.04 (2s, 1H), 4.68 and 4.55 (2s, 1H), 4.23−3.90 (m, 3H), 3.63−3.39 (m, 2H), 3.05−2.28 (m, 5H), 1.83 and 1.80 (2s, 3H), 1.46 and 1.41 (2s, 9H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, doubling due to amide rotamers) δ 176.5, 171.9, 171.5, 154.1, 153.4, 143.2, 143.0, 137.2, 137.1, 129.9, 129.7, 127.9, 127.8, 126.3, 115.7, 80.4, 80.2, 64.1, 63.8, 61.1, 53.2, 52.9, 52.0, 48.1, 46.9, 40.9, 40.2, 35.0, 34.4, 28.2, 28.0, 21.7, 21.3, 13.9, 13.8; IR (KBr) 3448, 1744, 1705, 1402, 1190, 1138; HRMS (*m*/*z*) calcd for $C_{24}H_{33}NO_6$ (M^+): 431.2308. Found 431.2303.

(2*SR*,3*SR*,4*SR*)-2-Carboxy-4-isopropenyl-4-methylpyrrolidine-3-acetic Acid (4a) and (2*SR*,3*SR*,4*RS*)-4-Benzyl-2-carboxy-4-isopropenylpyrrolidine-3-acetic Acid (4b). To a solution of **19a** or **19b** (0.7 mmol) in THF (5 mL) was added a 2.5 N aqueous solution of LiOH (11.2 mL, 28 mmol). The mixture was stirred at room temperature overnight. After the reaction mixture was cooled to 0 °C, a 0.5 N aqueous solution of HCl was added until pH ∼ 2. The diacid was extracted with ethyl ether (3 × 20 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford the diacid which was fully hydrolyzed with a 1 N solution of HCl in ethyl acetate (6 mL) for 6 h at room temperature. The solvent was evaporated to dryness, and the resulting white solid was triturated with ethyl ether. The amino acids **4a** or **4b** were isolated as zwitterions by treatment of a methanolic solution of the hydrochloride with propylene oxide. **4a**: 60% overall yield from **18a**; white solid, mp > 200 °C dec. ^{1}H NMR (D_2O + Py-d_5) δ 5.19 (s, 1H), 4.94 (s, 1H), 4.46 (s, 1H), 3.77 (AB system, J = 11.6 Hz, 2H), 3.26−3.07 (m, 1H), 2.69−2.30 (m, 2H), 2.04 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (D_2O + Py-d_5) δ 182.0, 176.3, 147.3, 113.7, 67.6, 54.8, 52.1, 49.7, 41.7, 25.9, 21.8; IR (KBr) 3420, 1725, 1593, 1393, 1341 cm^{-1}. Anal. Calcd for $C_{11}H_{17}$-

NO_4: C, 58.15%; H, 7.54%; N, 6.16%. Found: C, 57.90%; H, 7.35%; N, 6.44%. **4b**: 59% overall yield from **18b**; white solid, mp > 235 °C dec; ^{1}H NMR (D_2O + KOD) δ 7.05−6.80 (m, 5H), 3.96 (s, 1H), 2.99 (d, J = 2.6 Hz, 1H), 2.51−2.13 (m, 5H), 1.95−1.86 (m, 1H), 1.69−1.57 (m, 1H), 1.50 (s, 3H); ^{13}C NMR (D_2O + Py-d_5) δ 181.7, 176.0, 144.3, 132.0, 130.1, 128.8, 126.1, 117.4, 67.4, 57.7, 50.7, 49.7, 41.6, 41.0, 22.3; IR (KBr) 3434, 1728, 1601, 1397, 1331 cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.32%; H, 6.98%; N, 4.62%. Found: C, 67.30%; H, 6.71%; N, 4.45%.

Acknowledgment. This research was supported by a CDTI program (Plan concertado 94/0036) and the Spanish FARMA III program (Ministerio de Industria y Ministerio de Sanidad). I.C. and A. M. are grateful to the Spanish Ministry of Education for a fellowship.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR of all compounds lacking elemental analyses (**5a**, **11b**,**c**, **13b**, **14a**,**b**, **16a**,**b**, **19a**,**b**) (20 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.

JO972123G