# Stereocontrolled Synthesis of 5α- and 5*β*-Substituted Kainic Acids

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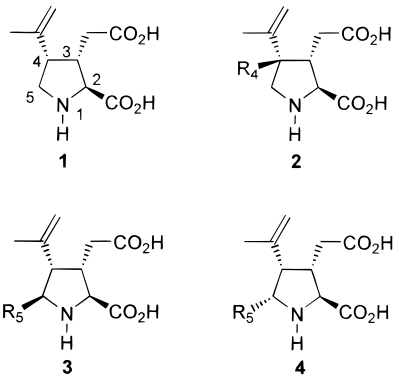
A general and efficient method for the stereoselective synthesis of racemic 5*β*- and 5α-substituted kainic acids **3** and **4** has been developed starting from the bicyclic pyroglutamate derivative **6**, readily available on a large scale. Compound **6** proved to be a versatile synthon from which straightforward functionalizations at both C-5*β* and C-5α were accomplished in a stereoselective manner without compromising the stereogenic integrity of the potentially labile C-2 center. The key steps involved the stereoselective nucleophilic addition of organocopper reagents to the *N*-acyliminium ion **I**, and the stereoselective hydrogenation of the cyclic imine **9** derived from **6**. Transformations of the bicyclic intermediates **7** and **8** into the final substituted kainic acids **3** and **4** were accomplished via stepwise sequences that avoid the facile and undesirable intramolecular Claisen and epimerization reactions. Compounds **3** and **4** have shown no significant binding affinity for the kainate receptors, which reflects the sensitivity of the recognition site to steric and conformational factors.

## Introduction

Kainic acid[1] (**1**) and its analogues have attracted considerable interest due to their potent and specific neuroexcitatory activity at the glutamate receptors.[2] This important property along with its unique structure has motivated the development of stereocontrolled approaches for the synthesis of either the naturally occurring kainoids[3] or their chemically modified analogues.[4] Although a number of structure−activity relationship studies on kainic acid have revealed that the unsaturation at C-4 as well as the relative stereochemistry of the three stereocenters are crucial for the high affinity to the kainate receptor,[5] little was known on the structural modification at the pyrrolidine core. Recently we have reported an efficient stereocontrolled route to 4-substituted kainic acids **2**.[6] To provide further information regarding the structural requirements for activating kainate receptors and with the ultimate goal of discovering potent and selective kainate receptor antagonists, we have developed a novel and general approach to the stereocontrolled introduction of substituents at positions 5*β* and 5α in the pyrrolidine ring system of kainic acid that culminated in the total synthesis of 5*β*- and 5α-substituted kainic acids (**3** and **4**).




## Results and Discussion

In light of our synthetic approach to the 4-substituted kainic acids **2** (Scheme 1) based on the stereocontrolled C-4 alkylation on the pyroglutamate derivative **6**, the most notable difficulty of achieving our targets resided in the stereoselective functionalization of C-5 on the same bicyclic pyroglutamate **6**. Recently, we[7] and others[8,9] have reported on the stereoselective functionalization of N−BOC ethyl pyroglutamate as one of the most useful routes to the synthesis of 5-substituted prolines. On the basis of these results and taking into account the high degree of stereocontrol exercised by the 3-azabicyclo[3.3.0]octane nucleus, it was argued that bicyclic pyroglutamate **6** could be transformed into the 5*β*-substituted prolinate **7** by diastereoselective addition of organocopper reagents to the *N*-acyliminium ion **I** whereas the 5α epimer **8**

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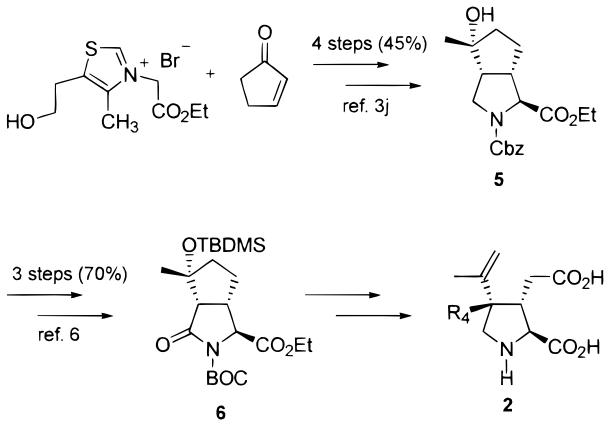
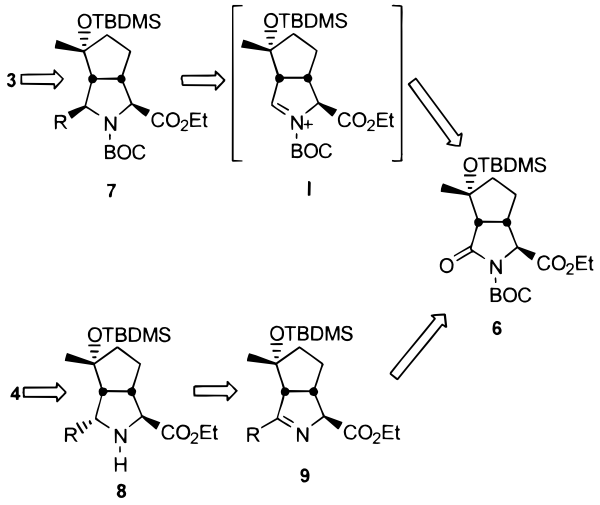
**Scheme 1**

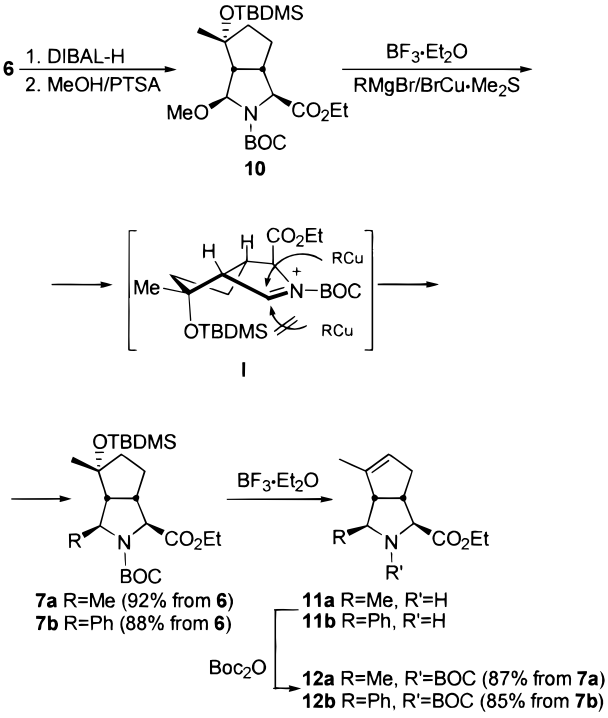



would be the result of the hydrogenation of the cyclic imine **9** (Scheme 2). After the stereoselective introduction of the substituent in the desired position, the side chains at C-3 and C-4 would be generated by dehydration of the tertiary alcohol followed by oxidative cleavage of the double bond. Methyl and phenyl substituents at C-5 were chosen on the basis of their distinctive size and properties compared with a hydrogen atom.

**Scheme 2**




**Scheme 3**




The key bicyclic intermediate **6** was obtained from the azabicyclooctanone derivative **5** in 70% yield after protecting group exchange, C-4 oxidation, and further protection of the hydroxyl group.[6] Compound **5**, in turn, was prepared via a [3 + 2] cycloaddition reaction of a thiazolium ylide with 2-cyclopentenone in a four-step sequence in 45% overall yield as reported by Monn and Valli[3j] (Scheme 1). The synthesis of the 5β-substituted kainic acids **3** is shown in Scheme 3. Partial reduction with DIBAL[10] of the lactam carbonyl on **6**, followed by treatment of the resulting hemiaminal with PTSA in MeOH resulted in the formation of **10** as a single diastereomer. The stereochemistry of the newly generated center is not relevant, but it was presumably assigned as 5β on the basis of the steric hindrance imposed by the 3-azabicyclo[3.3.0]octane nucleus. The generation of the *N*-acyliminium ion intermediate **I** by

(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) Goldberg, O.; Teichberg, V. I. *J. Med. Chem.* **1985**, *28*, 1957. (d) Yanagida, M.; Hashimoto, K.; Ishida, M.; Shinozaki, H.; Shirahama, H. *Tetrahedron Lett.* **1989**, *30*, 3799. (e) Hashimoto, K.; Horikawa, M.; Shirahama, H. *Tetrahedron Lett.* **1990**, *31*, 7047. (f) Kozikowski, A. P.; Fauq, A. H. *Tetrahedron Lett.* **1990**, *31*, 2967. (g) Hanssen, J. J.; Krogsgaard-Larsen, P. *Med. Res. Rev.* **1990**, *10*, 55. (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) Tabcheh, M.; Pappalardo, L.; Roumestant, M. L.; Viallefont, P. *Amino Acids* **1992**, *2*, 191. (l) Baldwin, J. E.; MacKenzie T. S. C.; Moloney, M. G. *Synlett* **1994**, 925. (m) Baldwin, J. E.; Rudolph, M. *Tetrahedron Lett.* **1994**, *35*, 6163. (n) Baldwin, J. E.; Bamford, S. J.; Fryer, A. M.; Wood, M. E. *Tetrahedron Lett.* **1995**, *36*, 4869. (o) Gill, P.; Lubell, W. D. *J. Org. Chem.* **1995**, *60*, 2658. (p) Ezquerra, J.; Escribano, A.; Rubio, A.; Remuiñán, M. J.; Vaquero, J. J. *Tetrahedron Lett.* **1995**, *36*, 6149. (q) Hashimoto, K.; Ofhune, Y.; Shirahama, H. *Tetrahedron Lett.* **1995**, *36*, 6235. (r) Horikawa, M.; Shima, Y.; Hashimoto, K.; Shirahama, H. *Heterocycles* **1995**, *40*, 1009. (s) Hashimoto, K.; Hashimoto, M.; Shirahama, H. *Tetrahedron* **1996**, *52*, 1931. (t) Hanessian, S.; Ninkovic, S.; Reinhold: U. *Tetrahedron Lett.* **1996**, *37*, 8971. (u) 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. (v) Ezquerra, J.; Escribano, A.; Rubio, A.; Remuiñán, M. J.; Vaquero, J. J. *Tetrahedron Asymmetry* **1996**, *7*, 2613. (w) Maeda, H.; Kraus, G. A. *J. Org. Chem.* **1997**, *62*, 2314.

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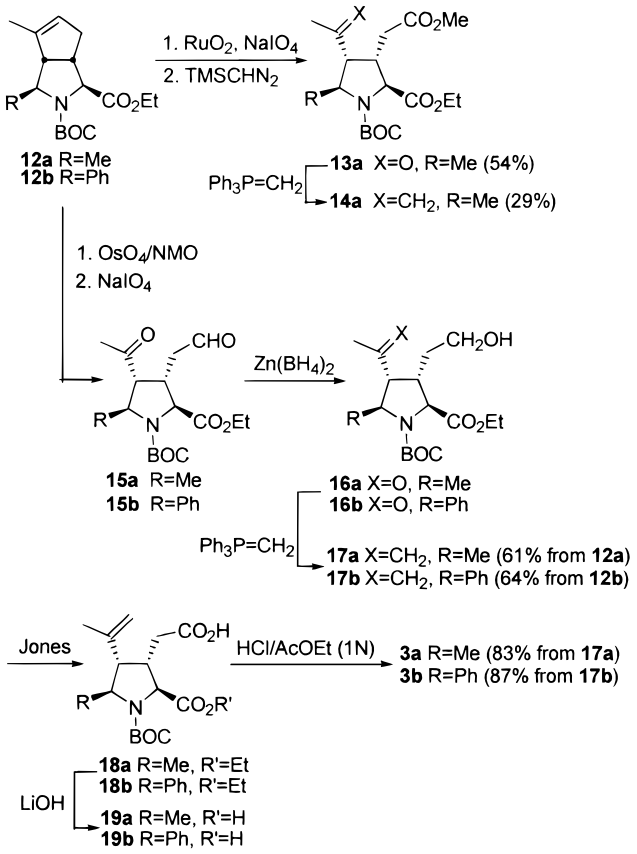
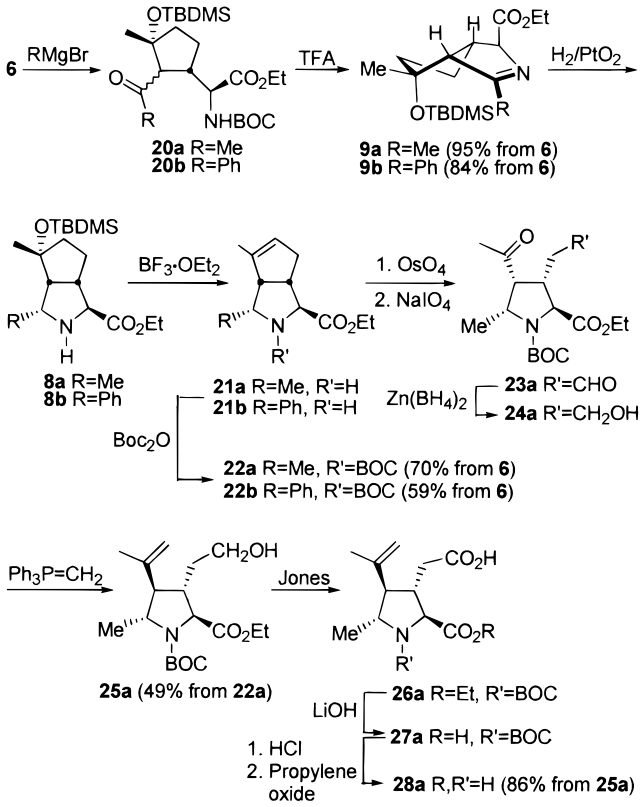
(10) Langlois, N.; Rojas, A. *Tetrahedron Lett.* **1993**, *34*, 2477.

**Scheme 4**




treatment of the aminal **10** with $BF_3{\cdot}OEt_2$, and its reaction with 2 equiv of a Grignard-derived organocopper reagent[7d] $RCu{\cdot}MgBr_2$ gave rise to the single diastereomers **7a**,**b** in excellent yields (92% for **7a** and 88% for **7b** for the three steps from **6**). The stereochemistry of **7a**,**b** could not be deduced unambiguously at this stage due to the presence of rotamers that highly complicates the NMR spectra. Treatment of **7a**,**b** with $BF_3{\cdot}OEt_2$ resulted in the alcohol deprotection and elimination with simultaneous removal of the *N*-BOC protecting group giving **11a**,**b** (96% for **11a** and 94% for **11b**). NOE experiments recorded on compounds **11** allowed us to firmly establish the stereochemistry as 5$\beta$,[11] confirming that the stereochemical outcome of the organocopper addition is governed by the steric congestion imposed by the bicyclic system and the OTBDMS group. Nitrogen protection in **11a**,**b** gave **12a**,**b** (91% for **12a** and 90% for **12b**). Noteworthy, all the chemical transformations from **6** to **12a**,**b** were performed without further purification of the intermediates.

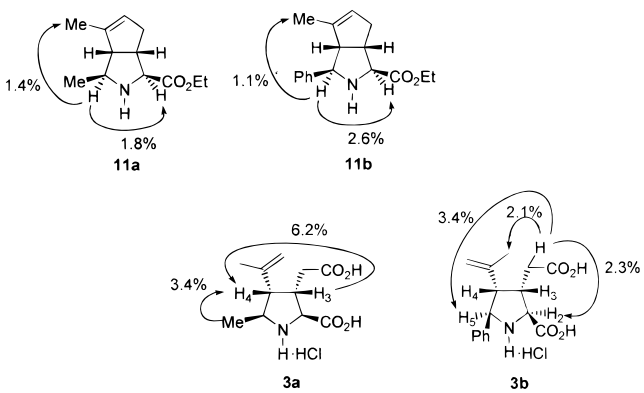
**Scheme 5**



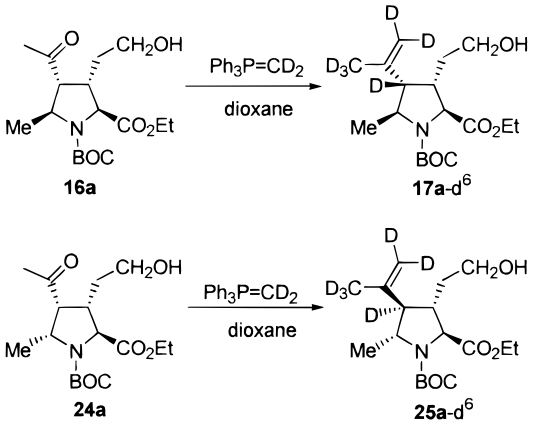

Once the desired functionalization at C-5 was achieved, the next steps in the synthesis were directed to the elaboration of the side chains at C-3 and C-4 (Scheme 4). Keto ester **13a** was prepared from **12a** by ruthenium oxidation followed by esterification with (trimethylsilyl)-diazomethane (54% for the two steps). The Wittig reaction on **13a** was shown to compete with the intramolecular Claisen cyclization resulting in a low yield of the corresponding olefin **14a**. Since other methylenation methods were unsuccessful, we explored the route previously reported for the synthesis of 4-substituted kainic acids.[6] Thus, osmylation of **12a**,**b** followed by periodate cleavage gave the keto aldehydes **15a**,**b** which were chemoselectively reduced with $Zn(BH_4)_2$ to the keto alcohols **16a**,**b**. Characterization of **16a** and **16b** was not possible since they exist as an equilibrium mixture with their corresponding lactols. The Wittig methylenation on **16a**,**b** gave the desired olefins **17a**,**b** in good overall yields and without purification of the intermediates (61% for **17a** and 64% for **17b**). It is noteworthy that no evidence of epimerization at C-4 was observed under these basic conditions. The synthesis of **3** was then completed after Jones oxidation and hydrolysis of the ester and BOC groups. The stereochemistry of the final amino acids **3a**,**b** was unambiguously confirmed by NOE experiments performed on the hydrochlorides.[11]

The synthesis of the 5$\alpha$-substituted kainic acids started from the same common intermediate **6**. In this case, the stereoselective introduction of substituents at C-5 required the nucleophilic ring opening[7d] of the pyroglutamate derivative **6** with a suitable Grignard reagent and further cyclization of the resulting keto *N*-BOC derivative to the imines **9a**,**b**. The $\alpha$-configuration of the

(11) The NOEs observed in **11** and **3** are shown below:



**Scheme 6**

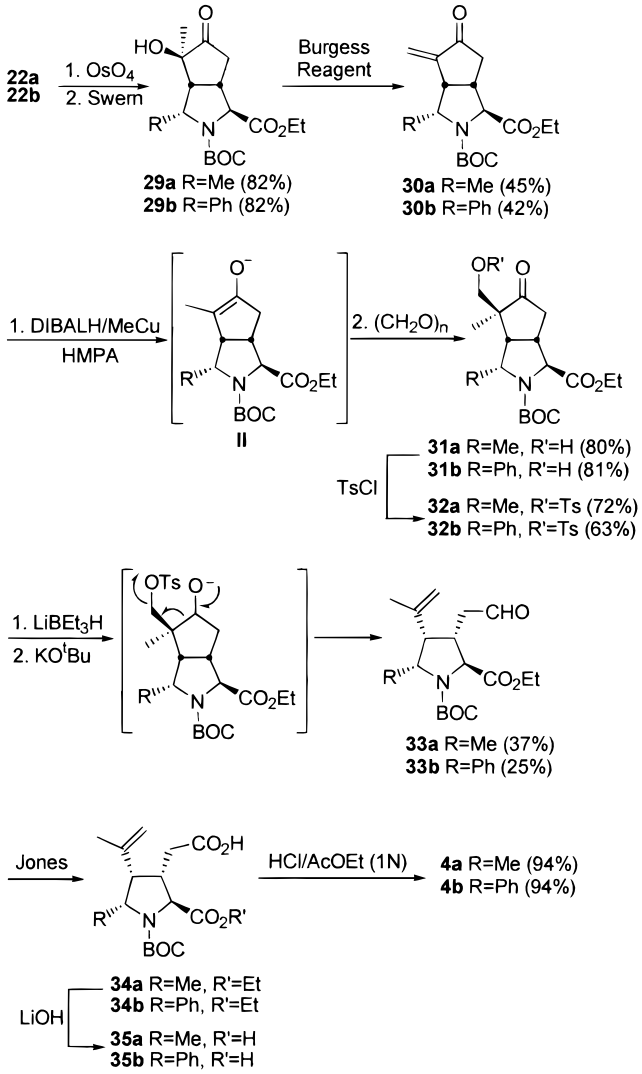



C-5 substituent would then be the result of the hydrogenation of **9** from the less-hindered face. Reaction of **6** with a Grignard reagent (R = $CH_3$, $C_6H_5$) took place exclusively at the lactam carbonyl group giving the ketones **20a**,**b** in quantitative yield (Scheme 5). Surprisingly, the conditions for the isolation of the intermediates **20a**,**b** greatly influence the ratio of the two epimeric ketones. Thus, when the reactions were quenched with a saturated ammonium chloride solution, the nonepimerized ketones were isolated as single products, whereas quenching the reaction mixture with a MeOH/AcOH (1:1) solution gave rise to an equimolecular mixture of epimeric ketones. In both cases, further treatment with trifluoroacetic acid gave exclusively the cyclic imines **9a**,**b**. This transformation proceeded in excellent yields (95% for **9a** and 84% for **9b**), but only when the reaction was carried out with a large excess (30 equiv) of trifluoroacetic acid. These conditions were determined after it was realized that smaller excess of trifluoroacetic acid retards the removal of the BOC group and favors the α,β-elimination of the OTBDMS group giving mixtures of the desired imines **9a**,**b** along with varying amounts of side products resulting from the elimination of the OTBDMS group.

Hydrogenation of the cyclic imines **9a**,**b** proceeded quantitatively to give, as expected, the prolinate derivatives **8a**,**b** as single isomers. The stereochemistry of C-5 was confirmed by NOE experiments performed on the elimination products **21a**,**b** resulting from the treatment of **8a**,**b** with $BF_3$·$OEt_2$. Nitrogen protection on **21a**,**b** allowed us to isolate the *N*-BOC derivatives **22a**,**b** in excellent overall yields for the five steps from **6** (70% for **22a** and 59% for **22b**). Oxidative ring opening of **22a** followed by chemoselective reduction of the resulting keto aldehyde **23a** afforded the keto alcohol **24a**. Owing to the lability of the C-4 stereocenter of **24a**, it was not surprising that attempts to apply the same synthetic route as described above for the elaboration of the side chains resulted in the exclusive formation of the allokainic acid derivative **28a**.

At this point, there was an intriguing aspect to the Wittig reaction. The fact that no evidence of C-4 epimerization was observed when the Wittig reaction was carried out on **16a**, whereas such epimerization on the isomer **24a** was complete, led us to study in more detail these reactions. There were two possible explanations to this different behavior: (a) the substituent at C-5β was preventing the enolization of the ketone **16a** or (b) enolization occurred but, the result of the equilibration

**Scheme 7**




was the thermodynamically more stable **16a**. These assumptions were discerned by performing the Wittig reactions with dideuterated triphenylphosphonium methylide (Scheme 6). In both cases, introduction of deuterium at C-4 indicated that ketone enolization occurred prior to the Wittig reaction and therefore the more stable *trans*-C4/C5 olefins **17a** and **25a** were obtained.

Since the Wittig reaction proceeded with epimerization at C-4 and other nonbasic methylenation reagents proved to be ineffective, an alternative approach was devised for the conversion of **22a**,**b** into the α-substituted kainic acids **4** (Scheme 7). Hydroxylation of the double bond followed by Swern oxidation afforded the hydroxy ketones **29a**,**b**, which were dehydrated with the Burgess reagent[12] to give the unsaturated ketones **30a**,**b**. Several attempts to generate the thermodynamic enolate **II** by treatment of the enones **30a**,**b** with a complex prepared from diisobutylaluminum hydride and copper iodide in a mixture of THF and HMPA,[3g,13] resulted in the recovery of the unreacted enone. However, when the copper iodide

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was replaced by methyl copper (prepared from methyllithium and copper bromide dimethyl sulfide complex), the enolate **II** was formed, and, after addition of an excess of paraformaldehyde, the hydroxy ketones **31a**,**b** were isolated in very good yields. The alcohols **31a**,**b** were tosylated and further reduced with lithium triethylborohydride. Treatment of the resulting monotosylated diols with potassium *tert*-butoxide[14] gave the Wharton fragmentation's products **33a**,**b** in moderate yields. Finally, Jones oxidation followed by ester hydrolysis and BOC removal allowed to isolate the 5α-substituted kainic acids **4a**,**b**. The stereochemistry of **4a**,**b** was ascertained by comparison of their NMR spectra[15] with those of **3a**,**b** and by the NOE results.[16]

Compounds **3** and **4** were evaluated for their binding as agonists and antagonists in cells expressing hum-GluR6 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 steric and conformational factors.

## Summary

We have described in this paper highly efficient routes to the synthesis of 5*β*- and 5α-substituted kainic acids. The introduction of substituents at C-5*β* and C-5α, and the elaboration of the stereogenic centers to the final kainoids can be accomplished with full control over its relative configuration from the common intermediate **6**. The key functionalization steps comprised organocopper addition to the *N*-acyliminium ion **I** and hydrogenation of the cyclic imine **9**, both of which proceeded with excellent yields and diastereoselectivities. Transformations of the bicyclic intermediates **7** and **8** into the final substituted kainic acids were accomplished via stepwise sequences that avoid the undesirable facile intramolecular Claisen and epimerization reactions. In summary, pyroglutamate derivative **6** proved to be a versatile synthon from which straightforward access to both 4-,[6] 5*β*-, and 5α-substituted kainic acids could be achieved with complete stereocontrol.

## Experimental Section

**Materials and Methods.** All solvents and reagents were purchased from commercial sources and used as received, unless otherwise indicated. Tetrahydrofuran, dioxane, and diethyl ether were distilled from sodium/benzophenone ketyl prior to use. HMPA was distilled under $CaH_2$ and collected over 4 Å molecular sieves. $^1$H NMR and $^{13}$C NMR data were recorded at 200 and 50 MHz, respectively. Analytical TLC was performed on Merck TLC glass plates precoated with F254 silica gel 60 (UV (254 nm), PMA and iodine). Chromatographic separations were performed by using 230−400 mesh silica gel (Merck).

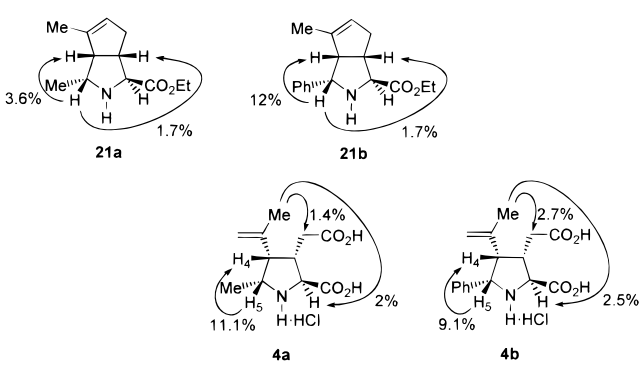
**Ethyl (1*SR*,2*SR*,4*SR*,5*SR*,6*RS*)-*N*-(*tert*-Butoxycarbonyl)-3-aza-6-[(*tert*-butyldimethylsilyl)oxy]-6-methyl-4-methoxybicyclo[3.3.0]octane-2-carboxylate (10).** To a solution of **6** (3.0 g, 6.8 mmol) in 50 mL of THF at −78 °C was added 10.2 mL (10.2 mmol) of a 1 M solution of diisobutylaluminum hydride in THF. The mixture was stirred at −78 °C for 30 min and then quenched with methanol (15 mL). The reaction mixture was poured into a mixture of ethyl acetate (50 mL) and a sodium tartrate solution (40 mL) and stirred at room temperature for 1 h. The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the organic phase was dried ($Na_2SO_4$) and evaporated to dryness. The residue was dissolved in methanol (25 mL), and 130 mg (0.68 mmol) of *p*-toluenesulfonic acid was added. After the solution was stirred at room-temperature overnight, a saturated $NaHCO_3$ solution (10 mL) was added. The methanol was evaporated in vacuo, and the aqueous phase was extracted with ether (3 × 25 mL). The organic phase was dried ($Na_2SO_4$) and concentrated to dryness to give 3.1 g of **10** which was used in subsequent reaction without further purification: $^1$H NMR ($CDCl_3$, doubling due to rotamers) *δ* 5.29 and 5.28 (2s, 1H), 4.22−4.02 (m, 3H), 3.40 and 3.35 (2s, 3H), 2.96−2.82 (m, 1H), 2.29−2.19 (m, 1H), 2.05−1.53 (m, 4H), 1.46−1.20 (m, 15H), 0.86 and 0.83 (2s, 9H), 0.09 and 0.06 (2s, 6H); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) *δ* 173.0, 172.4, 153.6, 153.4, 90.3, 90.0, 81.4, 81.3, 80.6, 80.1, 68.3, 67.7, 62.9, 62.0, 60.8, 60.7, 55.2, 55.1, 45.8, 43.9, 41.9, 40.8, 30.8, 30.7, 28.6, 28.1, 28.3, 28.2, 26.0, 18.0, 14.2, 14.1, −2.2, −2.3; IR (film) 2957, 1709, 1390, 1367, 1179 cm$^{-1}$; HRMS (*m*/*z*): calcd for $C_{23}H_{43}NO_6Si$ ($M^+$): 457.2860, found: 457.2861.

**Ethyl (1*SR*,2*SR*,4*SR*,5*RS*,6*RS*)-*N*-(*tert*-Butoxycarbonyl)-3-aza-6-[(*tert*-butyldimethylsilyl)oxy]-4,6-dimethylbicyclo[3.3.0]octane-2-carboxylate (7a) and Ethyl (1*SR*,2*SR*,4*RS*,5*RS*,6*RS*)-*N*-(*tert*-Butoxycarbonyl)-3-aza-6-[(*tert*-butyldimethylsilyl)oxy]-4-phenyl-6-methylbicyclo[3.3.0]octane-2-carboxylate (7b).** To a suspension of CuBr·$Me_2S$ (3.0 g, 14.6 mmol) in 30 mL of diethyl ether at −40 °C was added a solution of the Grignard reagent (MeMgBr or PhMgBr) (14.6 mmol). The reaction mixture was stirred at −40 °C for 30 min and then cooled to −78 °C prior to the addition of 1.8 mL (14.6 mmol) of boron trifluoride etherate. After the mixture was stirred for 15 min, a solution of **10** (3.0 g, 6.6 mmol) in diethyl ether (15 mL) was added. The reaction mixture was stirred at −78 °C for 15 min and then allowed to warm to room temperature and remain there for 1 h at which time TLC analysis (hexane/ethyl acetate 7:1) revealed complete consumption of **10**. The reaction mixture was quenched with 30 mL of a (1:1) mixture of a saturated $NH_4OH$ solution and a saturated solution of $NH_4Cl$. After stirring for 1 h, the layers were separated and the aqueous layer was extracted with diethyl ether (3 × 25 mL). The combined organic phases were washed with a saturated $NaHCO_3$ solution, dried ($Na_2SO_4$) and concentrated in vacuo to give **7a**,**b**, which were purified by chromatography (**7a**: hexane/ethyl acetate 7:1; **7b**: hexane/ethyl acetate 8:1) **7a**: 2.7 g (92% yield from **6**); colorless oil; $^1$H NMR ($CDCl_3$, doubling due to rotamers) *δ* 4.16−3.91 (m, 4H), 2.78−2.62 (m, 1H), 2.04−1.11 (m, 23H), 0.81 (s, 9H), 0.05 (s, 6H); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) *δ* 173.8, 173.3, 153.7, 152.7, 82.0, 79.2, 68.9, 68.4, 63.4, 63.1, 60.5, 54.6, 46.0, 44.8, 41.5, 40.7, 29.9, 28.3, 27.9, 27.2, 25.9, 22.1, 21.4, 18.0, 14.1, −2.2, −2.4; IR (film) 2963, 2932, 1699, 1391, 1182 cm$^{-1}$. Anal. Calcd for $C_{23}H_{43}NO_5Si$: C, 62.54; H, 9.81; N, 3.17. Found: C, 62.90; H, 9.98; N, 3.52. **7b**: 2.92 g (88% yield from **6**); colorless oil; $^1$H NMR ($CDCl_3$, doubling due to rotamers) *δ* 7.55−7.50 (m, 2H), 7.32−7.12 (m, 3H), 4.96 and 4.92 (2s, 1H), 4.36−4.06 (m, 3H), 2.96−2.81 (m, 1H), 2.23−1.83 (m, 4H), 1.68−1.47 (m, 1H), 1.42−1.19 (m, 6H), 1.32 and 1.11 (2s, 9H), 0.88 (s, 9H), 0.17 and 0.15 (2s, 6H); $^{13}$C NMR ($CDCl_3$, doubling

(14) (a) Wharton, P. S.; Hiegel, G. A.; Coombs, R. V. *J. Org. Chem.* **1963**, *28*, 3217. (b) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535. (c) Caine, D. *Org. Prep. Proced. Int.* **1988**, *25*, 3.

(15) Hashimoto, K.; Konno, K.; Shirahama, H. *J. Org. Chem.* **1996**, *61*, 4685.

(16) The NOEs observed in **21** and **4** are shown below:



due to rotamers) δ 173.8, 173.4, 153.5, 152.8, 146.0, 145.2, 128.3, 128.0, 126.2, 126.1, 125.9, 125.6, 82.2, 79.8, 79.4, 69.5, 69.2, 65.9, 65.5, 62.5, 62.4, 60.7, 60.6, 46.5, 45.7, 42.2, 42.1, 28.7, 28.4, 28.1, 27.9, 26.7, 26.5, 26.1, 25.9, 18.0, −2.0, −2.1, −2.2, −2.3; IR (film) 1750, 1699, 1391, 1256, 1181 $cm^{-1}$. Anal. Calcd for $C_{28}H_{45}NO_5Si$: C, 66.76; H, 9.00; N, 2.78. Found: C, 66.68; H, 8.92; N, 2.58.

**Ethyl (1*SR*,2*SR*,4*SR*,5*SR*)-3-Aza-4,6-dimethylbicyclo-[3.3.0]oct-6-ene-2-carboxylate(11a)andEthyl(1*SR*,2*SR*,4*RS*,5*SR*)-3-Aza-4-phenyl-6-methylbicyclo[3.3.0]oct-6-ene-2-carboxylate (11b).** To a solution of **7a**,**b** (6.5 mmol) in $CHCl_3$ (35 mL) was added 16.0 mL (130 mmol) of boron trifluoride etherate. The mixture was heated in a sealed tube at 100−110 °C for 24 h, and then it was quenched with a saturated solution of $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (2 × 50 mL). The combined organic phases were washed with a saturated solution of $NaHCO_3$ (25 mL), dried ($Na_2SO_4$), and concentrated in vacuo to give **11a**,**b** which were used in subsequent reaction without further purification. **11a**: colorless oil; $^1$H NMR ($CDCl_3$) δ 5.13 (s, 1H), 4.18 (c, 2H, $J$ = 7.1 Hz), 3.22 (d, 1H, $J$ = 8.5 Hz), 2.95−2.82 (m, 1H), 2.79−2.58 (m, 2H), 2.51−2.17 (m, 2H), 2.04 (s broad, 1H), 1.64 (s, 3H), 1.27 (d, 3H, $J$ = 6.4 Hz), 1.24 (t, 3H, $J$ = 7.1 Hz); $^{13}$C NMR ($CDCl_3$) δ 173.8, 140.5, 122.8, 67.8, 62.7, 60.7, 60.0, 48.9, 35.8, 21.3, 14.7, 14.2; IR (film) 2963, 2928, 2855, 1736, 1200 $cm^{-1}$; HRMS (*m*/*z*): calcd for $C_{12}H_{18}NO_2$: ($M^+$ − 1): 208.1338, found: 208.1343. **11b**: colorless oil; $^1$H NMR ($CDCl_3$) δ 7.47−7.21 (m, 5H), 5.24 (s, 1H), 4.22 (c, 2H,$J$ = 7.1 Hz), 3.93 (d, 1H, $J$ = 5.8 Hz), 3.43 (d, 1H, $J$ = 8.7 Hz), 3.20−3.13 (m, 1H), 3.03−2.89 (m, 1H), 2.62−2.30 (m, 2H), 2.36 (s broad, 1H), 1.67 (s, 3H), 1.28 (t, 3H, $J$ = 7.1 Hz); $^{13}$C NMR ($CDCl_3$) δ 173.5, 143.6, 140.5, 128.5, 127.2, 123.1, 68.1, 67.8, 63.0, 60.7, 48.3, 35.6, 15.0, 14.1. IR (film) 2924, 1738, 1194 $cm^{-1}$. HRMS (*m*/*z*): calcd for $C_{17}H_{21}NO_2$: ($M^+$): 271.1572, found: 271.1575.

**Ethyl (1*SR*,2*SR*,4*SR*,5*SR*)-*N*-(*tert*-Butoxycarbonyl)-3-aza-4,6-dimethylbicyclo[3.3.0]oct-6-ene-2-carboxylate (12a) and Ethyl (1*SR*,2*SR*,4*RS*,5*SR*)-*N*-(*tert*-Butoxycarbonyl)-3-aza-4-phenyl-6-methylbicyclo[3.3.0]oct-6-ene-2-carboxylate (12b).** To a solution of **11a**,**b** (6 mmol), $Et_3N$ (2.19 mL, 15 mmol) and DMAP (732 mg, 6 mmol) in $CH_2Cl_2$ (15 mL) was added a solution of di-*tert*-butyl dicarbonate (2.64 g, 12 mmol) in $CH_2Cl_2$ (5 mL). The reaction mixture was stirred at room temperature until completion. The mixture was then poured into a 1:1 mixture of $CH_2Cl_2$ and a 1 N solution of HCl. The organic phase was separated, washed several times with 1 N HCl, dried ($Na_2SO_4$), and evaporated to dryness. The crude was purified by chromatography (hexane/ethyl acetate 8:1) to give **12a**,**b** (1.75 g of **12a**, 87% yield from **7a**; 2.05 g of **12b**, 85% yield from **7b**). **12a**: colorless oil; $^1$H NMR ($CDCl_3$, doubling due to rotamers) δ 5.29 (s, 1H), 4.21−3.76 (m, 4H), 2.93−2.83 (m, 1H), 2.72−2.69 (m, 1H), 2.57−2.29 (m, 2H), 1.69 (s, 3H), 1.51−1.21 (m, 15H); $^{13}$C NMR ($CDCl_3$, 333 K) δ 173.1, 153.2, 140.1, 123.8, 79.2, 67.2, 60.2, 60.1, 56.5, 45.6, 37.6, 28.1, 21.0, 14.1, 13.9; IR (film) 2976, 1751, 1696, 1451, 1392, 1257, 1186 $cm^{-1}$. Anal. Calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.79; N, 4.53. Found: C, 65.62; H, 9.07; N, 4.67. **12b**: white solid, mp 92−94 °C (hexane); $^1$H NMR ($CDCl_3$, doubling due to rotamers) δ 7.57−7.53 (m, 2H), 7.36−7.16 (m, 3H), 5.35 (s, 1H), 5.05 and 4.84 (2s, 1H), 4.24 (c, 2H, $J$ = 7.1 Hz), 4.00 and 3.92 (2d, 1H, $^1J$ = 6.3 Hz, $^2J$ = 6.6 Hz), 2.99−2.90 (m, 2H), 2.52−2.32 (m, 2H), 1.87 (s, 3H), 1.36−1.16 (m, 12H); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) δ 173.4, 172.9, 153.9, 153.3, 144.6, 143.9, 139.8, 128.2, 128.0, 126.4, 125.8, 125.6, 123.9, 80.1, 79.9, 67.2, 66.9, 65.0, 64.4, 62.6, 62.2, 60.7, 45.7, 45.1, 36.4, 36.1, 27.9, 14.7, 14.1; IR (KBr) 1752, 1699, 1385, 1368, 1181 $cm^{-1}$. Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77. Found: C, 71.22; H, 7.83; N, 3.55.

**Methyl (2*SR*,3*SR*,4*RS*,5*SR*)-*N*-(*tert*-Butoxycarbonyl)-4-acetyl-2-(ethoxycarbonyl)-5-methylpyrrolidine-3-acetate (13a).** A mixture consisting of $RuO_2$·$H_2O$ (97 mg, 0.73 mmol) and $NaIO_4$ (3.2 g, 15.0 mmol) in $CH_3CN$ (6.5 mL), $CCl_4$ (6.5 mL), and $H_2O$ (9.5 mL) was vigorously stirred at room temperature for 15 min. To this mixture was added a solution of **12a** (1.11 g, 3.6 mmol) in $CH_3CN$ (5 mL) and $CCl_4$ (5 mL). The black-colored mixture was stirred at room temperature for 4 h and then partitioned between ether (20 mL) and $H_2O$ (20 mL). The layers were separated, and the aqueous phase was extracted with ether (2 × 20 mL). The combined organic phases were washed with $H_2O$ (10 mL), dried ($Na_2SO_4$), filtered through Celite, and concentrated in vacuo. The crude carboxylic acid was dissolved in ether (100 mL) and treated sequentially with EtOH (3.6 mL) and a 2 M solution of (trimethylsilyl)diazomethane in hexane (3.6 mL, 7.2 mmol). The reaction mixture was stirred at room temperature for 30 min, and then the solvents were evaporated in vacuo. The reaction crude was purified by chromatography (hexane/ethyl acetate 2:1) to afford 0.68 g of **13a** (54% yield) colorless oil; $^1$H NMR ($CDCl_3$, doubling due to rotamers) δ 4.23−3.96 (m, 4H), 3.64 (s, 3H), 3.19−3.14 (m, 1H), 2.92−2.49 (m, 3H), 2.17 (s, 3H), 1.47−1.19 (m, 15H); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) δ 207.2, 172.3, 172.0, 172.1, 171.9, 153.7, 153.0, 80.2, 64.6, 64.3, 61.1, 60.3, 58.9, 57.4, 55.8, 55.0, 51.7, 40.1, 39.3, 32.8, 32.2, 30.9, 30.6, 28.2, 28.1, 20.6, 20.3, 14.1; IR (film) 1747, 1720, 1699, 1684 $cm^{-1}$.

**Methyl (2*SR*,3*SR*,4*SR*,5*SR*)-*N*-(*tert*-Butoxycarbonyl)-2-(ethoxycarbonyl)-4-isopropenyl-5-methypyrrolidine-3-acetate (14a).** 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(trimethylsilyl)amide 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 **13a** (740 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 ether (50 mL) and $H_2O$ (50 mL), and the layers were separated. The aqueous phase was extracted with ether (2 × 25 mL), and the combined organic phases were dried ($Na_2SO_4$) and evaporated in vacuo. The crude was purified by chromatography (hexane/ethyl acetate 4:1) affording 214 mg of **14a** as a colorless oil (29% yield): $^1$H NMR ($CDCl_3$, doubling due to rotamers) δ 4.87 (s, 1H), 4.65 (s, 1H), 4.26−3.74 (m, 4H), 3.66 (s, 3H), 2.98−2.82 (m, 1H), 2.68−260 (m, 1H), 2.48−2.25 (m, 2H), 1.64 (s, 3H), 1.45−1.23 (m, 15H); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) δ 172.5, 172.2, 172.3, 154.0, 153.2, 142.3, 142.3, 114.0, 113.9, 80.1, 64.6, 64.3, 61.2, 56.8, 54.4, 53.7, 51.7, 40.5, 39.6, 33.2, 28.4, 28.3, 22.0, 21.8, 20.2, 19.6, 14.2, 14.1.

**(2*SR*,3*SR*,4*SR*,5*SR*)-*N*-(*tert*-Butoxycarbonyl)-2-(ethoxycarbonyl)-4-acetyl-5-methylpyrrolidine-3-acetaldehyde (15a) and (2*SR*,3*SR*,4*SR*,5*RS*)-*N*-(*tert*-Butoxycarbonyl)-2-(ethoxycarbonyl)-4-acetyl-5-phenylpyrrolidine-3-acetaldehyde (15b).** A stirred solution of **12a**,**b** (2 mmol) and *N*-methylmorpholine *N*-oxide (515 mg, 4.4 mmol) in acetone (20 mL) and $H_2O$ (6 mL) was treated with a 4% solution of $OsO_4$ in $H_2O$ (37 mL, 0.003 mmol), and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was partitioned between ether (40 mL) and $H_2O$ (40 mL). The layers were separated, and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic phases were washed with $H_2O$, dried ($Na_2SO_4$), and evaporated to dryness. The crude diols were dissolved in THF (12 mL), and a solution of $NaIO_4$ (642 mg, 3 mmol) in $H_2O$ (8 mL) was added. The mixture was stirred at room temperature for 5 h and then partitioned between ether (40 mL) and $H_2O$ (40 mL). The layers were separated and the aqueous phase was extracted with ether (3 × 40 mL). The combined organic phases were washed with $H_2O$ (20 mL), dried ($Na_2SO_4$) and evaporated to dryness to afford **15a**,**b** which were used without further purification. **15a**: colorless oil; $^1$H NMR ($CDCl_3$, doubling due to rotamers) δ 9.67 (s, 1H), 4.18−3.95 (m, 4H), 3.21−3.18 (m, 1H), 2.95−2.74 (m, 3H), 2.12 (s, 3H), 1.41−1.21 (m, 15H); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) δ 207.7, 207.4, 200.0, 199.7, 172.3, 171.8, 153.7, 153.0, 80.3, 64.7, 64.4, 61.1, 58.9, 57.5, 55.9, 55.3, 43.0, 42.5, 37.6, 36.9, 30.8, 30.5, 28.2, 28.1, 20.6, 20.3, 14.1; IR (film) 2979, 1745, 1711, 1693, 1392, 1257 $cm^{-1}$. Anal. Calcd for $C_{17}H_{27}NO_6.{}^1/_3H_2O$: C, 58.77; H, 8.03; N, 4.03. Found: C, 58.90; H, 8.09; N, 4.39. **15b**: colorless oil; $^1$H

NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 9.68 and 9.66 (2s, 1H), 7.60−7.53 (m, 2H), 7.37−7.21 (m, 3H), 5.07−4.92 (m, 1H), 4.34−4.18 (m, 3H), 3.56−3.49 (m, 1H), 3.20−2.65 (m, 3H), 2.23−2.08 (2s, 3H), 1.38 and 1.09 (2s, 9H), 1.34 (t, 3H, $J$ = 7.1 Hz); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 207.6, 206.8, 199.5, 199.2, 172.0, 171.7, 154.0, 153.5, 141.9, 141.2, 128.6, 128.2, 127.3, 127.1, 126.3, 125.7, 80.9, 80.6, 65.3, 64.9, 63.4, 62.9, 61.5, 61.3, 61.1, 59.8, 43.4, 42.3, 37.1, 31.5, 31.0, 28.1, 27.8, 14.1; IR (film) 2980, 1747, 1700, 1393, 1171 cm$^{-1}$. Anal. Calcd for $C_{22}H_{29}NO_6$: C, 65.49; H, 7.24; N, 3.47. Found: C, 65.18; H, 7.09; N, 3.22.

**Ethyl (2*SR*,3*SR*,4*SR*,5*SR*)-*N*-(*tert*-Butoxycarbonyl)-3-(2-hydroxyethyl)-4-isopropenyl-5-methylpyrrolidine-2-carboxylate (17a) and Ethyl (2*SR*,3*SR*,4*SR*,5*RS*)-*N*-(*tert*-Butoxycarbonyl)-5-phenyl-3-(2-hydroxyethyl)-4-isopropenylpyrrolidine-2-carboxylate (17b).** To a stirred solution of **15a**,**b** (2.0 mmol) in THF (20 mL) at −10 °C and under argon was added 11.0 mL (2.2 mmol) of a 0.2 M solution of $Zn(BH_4)_2$ in THF. The mixture was stirred at −10 °C for 30 min and then quenched with $H_2O$ (5 mL). The THF was eliminated in vacuo, and the aqueous phase was diluted with $H_2O$ (10 mL) and extracted with ether (3 × 20 mL). The combined organic phase was dried ($Na_2SO_4$) and evaporated in vacuo. The crude keto alcohols were dissolved in dioxane (12 mL) and added to a solution of triphenylphosphonium methylide (8 mmol) in dioxane (50 mL). The mixture was stirred until the reaction was judged complete (TLC: hexane/ethyl acetate 2:1). The reaction mixture was partitioned between ether (100 mL) and $H_2O$ (100 mL), and the layers were separated. The aqueous phase was extracted with ether (2 × 50 mL), and the combined organic phases were dried ($Na_2SO_4$) and evaporated in vacuo affording a yellow oil. Flash chromatography (hexane/ethyl acetate 2:1) gave **17a**,**b** (61% for **17a** and 64% for **17b**, overall yields from **12a** and **12b**, respectively). **17a**: $^1$H NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 4.87 (s, 1H), 4.68 (s, 1H), 4.24−4.02 (m, 3H), 3.97−3.75 (m, 1H), 3.71−3.65 (m, 2H), 2.58−2.48 (m, 2H), 1.76−1.49 (m, 2H), 1.65 (s, 3H), 1.44 and 1.39 (2s, 9H), 1.36 and 1.22 (m, 6H); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 173.2, 172.9, 154.2, 153.2, 142.6, 142.4, 113.5, 113.1, 79.8, 64.8, 64.4, 61.0, 60.4, 56.7, 56.3, 55.2, 54.5, 40.9, 40.1, 31.2, 31.1, 28.3, 28.2, 22.0, 21.7, 20.0, 19.4, 14.0, 13.9; IR (film) 3458, 2977, 1747, 1694, 1393, 1258 cm$^{-1}$; HRMS (*m*/*z*): calcd for $C_{18}H_{31}NO_5$ ($M^+$): 341.2202, found: 341.2205. **17b**: colorless oil; $^1$H NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 7.65−7.51 (m, 2H), 7.32−7.14 (m, 3H), 4.92−4.67 (m, 3H), 4.32−4.12 (m, 3H), 3.70−3.52 (m, 2H), 2.92−2.80 (m, 1H), 2.59−2.46 (m, 1H), 1.82 (br s, 1H), 1.71 and 1.65 (2s, 3H), 1.73−1.40 (m, 2H), 1.37 and 1.08 (2s, 9H), 1.34 and 1.32 (2t, 3H, $J$ = 7.1 Hz); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 173.0, 172.8, 154.4, 153.5, 143.1, 142.7, 142.5, 141.2, 128.2, 127.9, 127.1, 126.2, 126.8, 126.7, 114.6, 113.8, 80.6, 80.2, 65.5, 64.3, 65.3, 64.3, 61.2, 60.6, 57.4, 57.0, 40.9, 40.2, 30.9, 28.2, 27.9, 22.8, 22.0, 14.1; IR (film) 3460, 1746, 1694, 1682, 1393, 1368 cm$^{-1}$; HRMS (*m*/*z*): calcd for $C_{23}H_{33}NO_5$ ($M^+$): 403.2359, found: 403. 2360. Deuterated compound **17a**-$d_6$ was prepared from **15a** following the same procedure as for **17a**, but using $Ph_3PCD_3I$ instead of $Ph_3PCH_3I$. The major isolated product in these conditions was **17a**-$d_6$ produced from the equilibrium reactions of the corresponding ketone enolate with $Ph_3PCD_2H^+$. $^1$H NMR ($CDCl_3$, 333 K) $\delta$ 4.87 and 4.68 (residual olefinic protons), 4.24−4.10 (m, 3H), 3.97−3.75 (m, 1H), 3.71−3.65 (m, 2H), 2.58−2.48 (m, 1.3H), 1.76−1.49 (m, 2H), 1.43 (s, 9H), 1.36 (d, $J$ = 6.3 Hz, 3H) and 1.2 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) $\delta$ same as for **17a**, but carbons at 142.6, 142.4, 55.2, 54.5, 22.0, and 21.7 appear as residual signals.

**(2*SR*,3*SR*,4*SR*,5*SR*)-*N*-(*tert*-Butoxycarbonyl)-2-(ethoxycarbonyl)-4-isopropenyl-5-methylpyrrolidine-3-acetic Acid (18a) and (2*SR*,3*SR*,4*SR*,5*RS*)-*N*-(*tert*-Butoxycarbonyl)-2-(ethoxycarbonyl)-5-phenyl-4-isopropenylpyrrolidine-3-acetic Acid (18b).** To a solution of **17a**,**b** (1.0 mmol) in acetone (7 mL) cooled to 0 °C was added freshly prepared Jones reagent (1.7 mL). After the solution was stirred at 0 °C for 1 h and at room temperature for 2 h, 2-propanol (15 mL) and $H_2O$ (15 mL) were added and the mixture stirred for 15 min. The product was extracted with ethyl acetate (3 × 20 mL), the organic phase was dried ($Na_2SO_4$) and concentrated, affording **18a**,**b** which were used without further purification. **18a**: colorless oil; $^1$H NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 4.88 (s, 1H), 4.66 (s, 1H), 4.22−3.80 (m, 4H), 2.92−2.82 (m, 1H), 2.65−2.28 (m, 3H), 1.63 (s, 3H), 1.43−1.22 (m, 15H); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 176.5, 172.3, 172.0, 154.0, 153.2, 142.1, 114.2, 80.2, 64.5, 64.1, 61.1, 56.9, 54.3, 53.6, 40.2, 39.4, 33.0, 28.2, 28.1, 21.9, 21.7, 20.0, 19.5, 14.0; IR (film) 3230, 2977, 1732, 1682, 1651, 1454, 1392 cm$^{-1}$; HRMS (*m*/*z*): calcd for $C_{18}H_{29}NO_6$ ($M^+$): 355.1995, found: 355.1997. **18a**: white foam; mp 52−54 °C; $^1$H NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 7.65−7.51 (m, 2H), 7.30−7.16 (m, 3H), 4.96−4.71 (m, 3H), 4.32−4.07 (m, 3H), 3.03−2.83 (m, 2H), 2.59−2.31 (m, 2H), 1.71 and 1.66 (2s, 3H), 1.38 and 1.11 (2s, 9H), 1.32 and 1.31 (2t, 3H, $J$ = 7.1 Hz); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 177.2, 172.2, 172.0, 154.2, 153.5, 142.7, 142.3, 142.1, 141.1, 128.3, 128.0, 126.8, 126.1, 126.8, 115.1, 114.5, 80.9, 80.6, 65.4, 64.6, 64.9, 64.5, 61.3, 56.6, 56.3, 39.8 y 39.3, 33.2, 32.9, 28.1, 27.9, 22.8, 22.0, 14.1; IR (KBr) 3210, 1740, 1709, 1393, 1368 cm$^{-1}$. Anal. Calcd for $C_{23}H_{31}NO_6$: C, 66.17; H, 7.48; N, 3.36. Found: C, 65.97; H, 7.31; N, 3.35.

**(2*SR*,3*SR*,4*SR*,5*SR*)-*N*-(*tert*-Butoxycarbonyl)-2-carboxy-4-isopropenyl-5-methylpyrrolidine-3-acetic Acid (19a) and (2*SR*,3*SR*,4*SR*,5*RS*)-*N*-(*tert*-Butoxycarbonyl)-2-carboxy-5-phenyl-4-isopropenylpyrrolidine-3-acetic Acid (19b).** To a solution of **18a**,**b** (1 mmol) in THF (8 mL) was added a 2.5 N solution of LiOH (16 mL, 40 mmol), and the reaction mixture was stirred at room temperature for 48 h. The THF was evaporated in vacuo, and the aqueous phase was washed with ether (2 × 10 mL) prior to the addition of a 1 N solution of HCl until pH 2. The aqueous phase was extracted with ether (3 × 25 mL), dried ($Na_2SO_4$), and evaporated to dryness to afford **19a**,**b**, which were used without further purification. **19a**: colorless oil; $^1$H NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 9.56 (br s, 2H), 4.90 (s, 1H), 4.67 (s, 1H), 4.16−3.69 (m, 2H), 3.04−2.96 (m, 1H), 2.66−2.36 (m, 3H), 1.65 (s, 3H), 1.45−1.29 (m, 12H); $^{13}$C NMR ($CDCl_3$, 333 K) $\delta$ 176.6, 176.1, 154.6, 142.1, 114.0, 81.2, 64.6, 57.2, 54.6, 39.8, 33.2, 28.4, 22.1, 20.0; IR (film) 3410, 1745, 1713, 1655, 1410 cm$^{-1}$. **19b**: mp 196−198 °C; $^1$H NMR (DMSO-$d_6$, doubling due to rotamers) $\delta$ 7.63−7.57 (m, 2H), 7.31−7.19 (m, 3H), 4.93−4.71 (m, 3H), 4.09 and 3.98 (2d, $^1J$ = 8.1 Hz and $^2J$ = 3.9 Hz, 1H), 2.87−2.59 (m, 2H), 2.44−2.16 (m, 2H), 1.66 and 1.60 (2s, 3H), 1.33 and 1.04 (2s, 9H). $^{13}$C NMR (DMSO-$d_6$, doubling due to rotamers) $\delta$ 173.5, 173.3, 173.0, 172.8, 153.6, 153.1, 143.4, 143.2, 142.8, 140.6, 128.1, 127.8, 127.1, 126.2, 126.7, 114.3, 114.1, 79.7, 79.1, 65.0, 64.2, 64.0, 63.5, 56.6, 56.0, 40.6, 40.2, 33.4, 32.5, 27.9, 27.7, 22.9, 21.9; IR (KBr) 3420, 1748, 1713, 1655, 1410 cm$^{-1}$.

**(2*SR*,3*SR*,4*SR*,5*SR*)-2-Carboxy-4-isopropenyl-5-methylpyrrolidine-3-acetic Acid (3a) and (2*SR*,3*SR*,4*SR*,5*RS*)-2-Carboxy-5-phenyl-4-isopropenylpyrrolidine-3-acetic Acid (3b).** A solution of **19a**,**b** (1 mmol) in a 1 N HCl solution in ethyl acetate (5 mL) was stirred at room temperature for 8 h. The solvent was evaporated to dryness, and the resulting precipitate was washed with ether and filtered to afford the hydrochlorides of **3a**,**b** as white solids (83% for **3a** and 87% for **3b**, overall yields from **17a** and **17b**, respectively. **3a**: mp 193 °C; $^1$H NMR ($CD_3OD$) $\delta$ 5.13 (s, 1H), 4.81 (s, 1H), 4.43 (d, 1H, $J$ = 4.0), 3.95−3.79 (m, 1H), 3.23−3.10 (m, 1H), 2.70−2.60 (m, 1H), 2.54−2.31 (m, 2H), 1.78 (s, 3H), 1.43 (d, 3H, $J$ = 6.4 Hz); $^{13}$C NMR ($CD_3OD$) $\delta$ 174.8, 171.2, 140.4, 115.0, 64.2, 58.2, 54.0, 41.5, 34.1, 24.0, 16.5; IR (KBr) 3430, 1740, 1217 cm$^{-1}$. Anal. Calcd for $C_{11}H_{18}NO_4Cl$: C, 50.10; H, 6.89; N, 5.31. Found: C, 50.08; H, 6.67; N, 5.04. **3b**: mp 170−172 °C; $^1$H NMR ($CD_3OD$) $\delta$ 7.57−7.44 (m, 5H), 5.02 (s, 1H), 4.88 (d, 1H, $J$ = 11.6), 4.78 (s, 1H), 4.54 (d, 1H, $J$ = 2.4 Hz), 3.45−3.28 (m, 2H), 2.64−2.42 (m, 2H), 1.75 (s, 3H); $^{13}$C NMR ($CD_3OD$) $\delta$ 174.7, 171.3, 139.4, 134.1, 131.1, 130.4 (2C), 129.9 (2C), 116.2, 65.0, 64.3, 52.1, 41.9, 34.1, 23.8; IR (KBr) 3410, 1759, 1723, 1194 cm$^{-1}$. Anal. Calcd for $C_{16}H_{20}NO_4Cl$: C, 58.99; H, 6.19; N, 4.30. Found: C, 58.90; H, 6.09; N, 4.19.

**Ethyl (1*SR*,2*SR*,5*RS*,6*RS*)-3-Aza-6-(*tert*-butyldimethylsilyloxy)-4,6-dimethylbicyclo[3.3.0]oct-3-ene-2-carbox-**

**ylate (9a) and Ethyl (1*SR*,2*SR*,5*RS*,6*RS*)-3-Aza-6-(*tert*-butyldimethylsilyloxy)-4-phenyl-6-methylbicyclo[3.3.0]oct-3-ene-2-carboxylate (9b).** To a solution of **6** (3 g, 6.8 mmol) in THF (50 mL) at −40 °C and under argon was added an ether solution of the corresponding Grignard reagent (8.1 mmol). The reaction mixture was stirred at −40 °C for 2 h and then partitioned between a saturated $NH_4Cl$ solution (30 mL) and ether (50 mL). The aqueous phase was extracted with ether (3 × 25 mL), and the combined organic phases were washed with $H_2O$, dried ($Na_2SO_4$), and evaporated to dryness. The crude ketones were dissolved in $CH_2Cl_2$ (35 mL) and added dropwise to 15.6 mL (204 mmol) of TFA. The reaction mixture was stirred at room temperature for 1−2 h and then quenched with a saturated $NaHCO_3$ solution till pH ∼ 8. The layers were separated, and the aqueous phase was extracted with $CH_2Cl_2$ (2 × 25 mL). The combined organic phases were washed with a saturated $NaHCO_3$ solution (25 mL), dried ($Na_2SO_4$), and evaporated in vacuo. Flash chromatography (hexane/ethyl acetate 4:1) afforded **9a**,**b** (95% for **9a** and 84% for **9b**). **9a**: $^1$H NMR ($CDCl_3$) $\delta$ 4.33−4.28 (m, 1H), 4.17 (dc, 2H, $J$ = 7.1 Hz), 3.09−2.87 (m, 2H), 2.07 (d, $J$ = 1.9 Hz, 3H), 2.02−1.53 (m, 4H), 1.48 (s, 3H), 1.25 (t, 3H, $J$ = 7.1 Hz), 0.79 (s, 9H), 0.07 and 0.06 (2s, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 176.2, 173.5, 82.2, 81.2, 69.9, 60.8, 46.6, 43.8, 30.4, 27.7, 25.6, 20.1, 17.9, 14.1, −2.3, −2.6; IR (film) 2957, 2932, 1740, 1173 cm$^{-1}$. Anal. Calcd for $C_{18}H_{33}NO_3Si$: C, 63.67; H, 9.79; N, 4.13. Found: C, 63.48; H, 9.61; N, 4.36. **9b**: mp 52−54 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.83−7.78 (m, 2H), 7.38−7.28 (m, 3H), 4.51 (dd, 1H, $J$ = 6.6 and 2.1 Hz), 4.20 (c, 2H, $J$ = 7.1 Hz), 3.71 (dd, 1H, $J$ = 10.1 y 2.1 Hz), 3.21−3.06 (m, 1H), 2.11−1.69 (m, 4H), 1.42 (s, 3H), 1.27 (t, 3H, $J$ = 7.1 Hz), 0.64 (s, 9H), −0.05 and −0.37 (2s, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 175.4, 173.6, 135.0, 130.2, 128.9 (2C), 127.9 (2C), 82.7, 81.7, 66.0, 61.0, 47.7, 44.2, 29.6, 27.9, 25.6, 17.9, 14.2, −2.6, −2.7; IR (KBr) 2955, 2939, 1736, 1256, 1175 cm$^{-1}$. Anal. Calcd for $C_{23}H_{35}NO_3Si$: C, 68.78; H, 8.78; N, 3.49. Found: C, 68.81; H, 8.82; N, 3.36.

**Ethyl (1*SR*,2*SR*,4*RS*,5*RS*,6*RS*)-3-Aza-6-(*tert*-butyldimethylsilyloxy)-4,6-dimethylbicyclo[3.3.0]octane-2-carboxylate (8a) and Ethyl (1*SR*,2*SR*,4*SR*,5*RS*,6*RS*)-3-Aza-6-(*tert*-butyldimethylsilyloxy)-4-phenyl-6-methylbicyclo-[3.3.0]octane-2-carboxylate (8b).** To a solution of **9a**,**b** (5 mmol) in EtOH (30 mL) was added 110 mg (0.5 mmol) of $PtO_2$, and the mixture was stirred at room temperature under $H_2$ overnight. The suspension was filtered off through a pad of Celite, and the solvent was evaporated in vacuo to give **8a**,**b** which were used without further purification. **8a**: colorless oil; $^1$H NMR ($CDCl_3$) $\delta$ 4.12 (c, 2H, $J$ = 7.1 Hz), 3.48 (d, 1H, $J$ = 3.8 Hz), 3.30−3.15 (m, 1H), 2.98−2.83 (m, 1H), 2.39 (br s, 1H), 2.18−1.97 (m, 2H), 1.86−1.38 (m, 3H), 1.43 (d, 3H, $J$ = 6.9 Hz), 1.42 (s, 3H), 1.23 (t, 3H, $J$ = 7.1 Hz), 0.85 (s, 9H), 0.11 and 0.10 (2s, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 175.2, 84.9, 68.7, 60.5, 59.2, 57.5, 50.6, 44.6, 31.5, 27.2, 26.2, 18.0, 14.4, 14.2, −1.8, −2.0; IR (film) 2957, 2932, 1732 cm$^{-1}$; HRMS (*m*/*z*): calcd for $C_{18}H_{35}NO_3Si$: ($M^+$): 341.2386. Found: 341.2383. **8b**: mp 62−64 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.41−7.38 (m, 2H), 7.30−7.12 (m, 3H), 4.52 (d, 1H, $J$ = 6.2 Hz), 4.16 (c, 2H, $J$ = 7.1 Hz), 3.71 (d, 1H, $J$ = 4.1 Hz), 3.11−2.97 (m, 1H), 2.53 (dd, 1H, $J$ = 6.2 and 9.2 Hz), 2.22−2.07 (m, 1H), 1.86−1.67 (m, 2H), 1.54−1.35 (m, 1H), 1.25 (t, 3H, $J$ = 7.1 Hz), 0.99 (s, 3H), 0.86 (s, 9H), −0.02 and −0.40 (2s, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 175.1, 139.0, 127.5 (2C, 127.4 (2C), 125.9, 84.7, 68.1, 64.1, 60.9, 59.5, 50.5, 44.7, 30.7, 26.9, 26.5, 18.1, 14.2, −1.8, −2.3; IR (KBr) 2957, 2930, 1732, 1256, 1204 cm$^{-1}$. Anal. Calcd for $C_{23}H_{37}NO_3Si$: C, 68.44; H, 9.24; N, 3.47. Found: C, 68.08; H, 9.08; N, 3.37.

**Ethyl (1*SR*,2*SR*,4*RS*,5*SR*)-3-Aza-4,6-dimethylbicyclo-[3.3.0]oct-6-ene-2-carboxylate (21a) and Ethyl (1*SR*,2*SR*,4*SR*,5*SR*)-3-Aza-4-phenyl-6-methylbicyclo[3.3.0]oct-6-ene-2-carboxylate (21b).** To a solution of **8a**,**b** (5 mmol) in $CHCl_3$ (25 mL) was added 12.3 mL (100 mmol) of boron trifluoride etherate. The reaction mixture was heated at 100 °C in a sealed tube for 24 h. The reaction was quenched with a saturated $NaHCO_3$ solution till pH ∼ 8, and the layers were separated. The aqueous phase was extracted with $CH_2Cl_2$ (2 × 40 mL), and the combined organic phases were washed with a saturated $NaHCO_3$ solution (20 mL), dried ($Na_2SO_4$), and evaporated in vacuo to give **21a**,**b** which were used without further purification. **21a**: colorless oil; $^1$H NMR ($CDCl_3$) $\delta$ 5.35 (s, 1H), 4.16 (c, 2H, $J$ = 7.1 Hz), 3.53 (d, 1H, $J$ = 3.1 Hz), 3.51−3.38 (m, 1H), 3.16−2.93 (m, 2H), 2.73−2.58 (m, 1H), 2.28−2.14 (m, 1H), 1.99 (br s, 1H), 1.71 (s, 3H), 1.25 (t, 3H, $J$ = 7.1 Hz), 1.11 (d, 3H, $J$ = 6.6 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 174.9, 138.8, 127.3, 66.7, 60.7, 57.1, 56.0, 47.6, 39.9, 17.7, 17.0, 14.2; IR (film) 2967, 2924, 1732, 1194, 1179 cm$^{-1}$; HRMS (*m*/*z*): calcd for $C_{12}H_{19}NO_2$: ($M^+$): 209.1416. Found: 209.1414. **21b**: colorless oil; $^1$H NMR ($CDCl_3$) $\delta$ 7.38−7.14 (m, 5H), 5.27 (s, 1H), 5.51 (d, 1H, $J$ = 7.2 Hz), 4.18 (c, 2H, $J$ = 7.1 Hz), 3.71 (s, 1H), 3.28−3.13 (m, 2H), 2.82−2.64 (m, 1H), 2.44−2.30 (m, 1H), 2.42 (br s, 1H), 1.27 (t, 3H, $J$ = 7.1 Hz), 0.74 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 175.2, 141.2, 139.5, 127.8 (2C), 127.5 (2C), 126.9, 126.7, 66.3, 63.8, 60.7, 57.5, 46.1, 40.2, 15.8, 14.2; IR (film) 2912, 1732, 1198, 1179 cm$^{-1}$; HRMS (*m*/*z*): calcd for $C_{17}H_{21}NO_2$: ($M^+$): 271.1572, found: 271.1566.

**Ethyl (1*SR*,2*SR*,4*RS*,5*SR*)-*N*-(*tert*-Butoxycarbonyl)-3-aza-4,6-dimethylbicyclo[3.3.0]oct-6-ene-2-carboxylate (22a) and Ethyl (1*SR*,2*SR*,4*SR*,5*SR*)-*N*-(*tert*-Butoxycarbonyl)-3-aza-4-phenyl-6-methylbicyclo[3.3.0]oct-6-ene-2-carboxylate (22b).** To a solution of **21a**,**b** (5 mmol), $Et_3N$ (1.75 mL,12.5 mmol), and DMAP (610 mg, 5 mmol) in $CH_2Cl_2$ (15 mL) was added a solution of di-*tert*-butyl dicarbonate (2.2 g, 10 mmol) in $CH_2Cl_2$ (5 mL). The reaction mixture was stirred at room temperature until completion. The mixture was then poured into a 1:1 mixture of $CH_2Cl_2$ and a 1 N solution of HCl. The organic phase was separated, washed several times with 1N HCl, dried ($Na_2SO_4$), and evaporated to dryness. The crude was purified by chromatography (hexane/ethyl acetate 7:1) to give **22a**,**b** (70% yield for **22a** and 59% yield for **22b**, overall yields from **6**). **22a**: colorless oil; $^1$H NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 5.37 (s, 1H), 4.23−4.04 (m, 4H), 3.24−3.10 (m, 1H), 2.94−2.80 (m, 1H), 2.64−2.51 (m, 1H), 2.23−2.11 (m, 1H), 1.68 (s, 3H), 1.44 and 1.37 (2s, 9H), 1.25 and 1.23 (2t, 3H, $J$ = 7.1 Hz), 1.06 and 1.00 (2d, 3H, $J$ = 6.6 Hz); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 173.4, 173.0, 154.6, 153.9, 139.2, 139.0, 126.5 126.2, 79.7, 64.1, 63.7, 60.7, 55.1, 54.0, 55.0, 54.7, 49.6, 48.6, 38.7, 28.3, 28.2, 17.4, 16.9, 16.8, 16.7, 14.2, 14.1; IR (film) 2978, 1746, 1705, 1366, 1188 cm$^{-1}$. Anal. Calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.79; N, 4.53. Found: C, 65.79; H, 9.14; N, 4.76. **22b**: mp 85−87 °C (hexane); $^1$H NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 7.26−7.07 (m, 5H), 5.18−5.02 (m, 2H), 4.50 and 4.41 (m, 1H), 4.28−4.13 (m, 2H), 3.48−3.39 (m, 1H), 3.10−2.96 (m, 1H), 2.76−2.63 (m, 1H), 2.45−2.34 (m, 1H), 1.35−0.94 (m, 15H); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 173.5, 173.1, 155.1, 154.1, 141.5, 140.5, 140.3, 127.6, 127.3 (2C), 127.3, 127.0 (2C), 126.6, 126.4, 126.1, 79.8, 66.0, 65.7, 65.2, 65.0, 60.9, 57.2, 56.1, 48.3, 47.0, 39.0, 28.1, 27.7, 15.9, 14.1; IR (KBr) 2978, 1744, 1696, 1379, 1186 cm$^{-1}$. Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77. Found: C, 71.48; H, 8.19; N, 3.62.

**(2*SR*,3*SR*,4*RS*,5*RS*)-*N*-(*tert*-Butoxycarbonyl)-2-(ethoxycarbonyl)-4-acetyl-5-methylpyrrolidine-3-acetaldehyde (23a).** Compound **23a** was obtained **22a** following the same procedure as for **15a**: $^1$H NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 9.74 (s, 1H), 4.43−4.03 (m, 4H), 3.64−3.55 (m, 1H), 3.27−3.13 (m, 1H), 2.93−2.56 (m, 2H), 2.15 (s, 3H), 1.63−1.22 (m, 15H); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 207.6, 206.9, 199.9, 119.7, 172.5, 172.0, 154.2, 153.5, 80.7, 80.5, 65.7, 61.4, 61.3, 55.4, 54.6, 54.9, 54.5, 44.4, 44.1, 37.7, 36.7, 32.5, 32.2, 28.3, 28.2, 18.1, 17.1, 14.2, 14.1; IR (film) 1744, 1709, 1393, 13681173 cm$^{-1}$; HRMS (*m*/*z*): calcd for $C_{17}H_{27}NO_6$ ($M^+$): 341.1838; Found: 341.1839.

**Ethyl (2*SR*,3*SR*,4*SR*,5*RS*)-*N*-(*tert*-Butoxycarbonyl)-3-(2-hydroxyethyl)-4-isopropenyl-5-methylpyrrolidine-2-carboxylate (25a).** Compound **25a** was obtained from **23a** following the same procedure as for **17a**. Flash chromatography (hexane/ethyl acetate 2:1) afforded **25a** (49% yield from **22a**). $^1$H NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 4.88 (s, 1H), 4.84 (s, 1H), 4.28−3.98 (m, 3H), 3.73−3.55 (m, 3H), 2.19−1.98 (m, 3H), 1.78−1.50 (m, 2H), 1.69 (s, 3H), 1.43−1.21 (m, 15H); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 173.7, 173.1, 154.3, 153.4, 141.5, 115.7, 79.9, 79.8, 65.8, 62.1, 61.5,

60.9, 59.8, 56.8, 56.2, 41.8, 41.0, 35.3, 35.0, 28.1, 28.0, 19.4, 18.2, 17.7, 13.8; IR (film) 3490, 1744, 1694, 1393, 1368 $cm^{-1}$; HRMS (*m*/*z*): calcd for $C_{18}H_{31}NO_5$ ($M^+$): 341.2202, found: 341.2203. Deuterated compound **25a**-$d_6$ was prepared from **22a** following the same procedure as for **25a** using $Ph_3PCD_3I$ instead of $Ph_3PCH_3I$. The major isolated product in these conditions was **25a**-$d_6$ produced from the equilibrium reactions of the corresponding ketone enolate with $Ph_3PCD_2H^+$. $^1H$ NMR ($CDCl_3$, 333 K) $\delta$ 4.8 and 4.84 (residual olefinic protons), 4.19 (m, 2H), 4.01 (d, $J$ = 7.7 Hz, 1H), 3.73−3.55 (m, 3H), 2.25−2.00 (m, 1.3H), 1.80−1.55 (m, 2H), 1.69 (s, 3H), 1. 40 (s, 9H), 1.32−1.22 (m, 6H); $^{13}C$ NMR ($CDCl_3$, doubling due to rotamers) $\delta$ same as for 25a but carbons at 141.5, 62.1, 61.5, and 17.7 appear as residual signals.

**(2*SR*,3*SR*,4*RS*,5*RS*)-*N*-(*tert*-Butoxycarbonyl)-2-(ethoxycarbonyl)-4-isopropenyl-5-methylpyrrolidine-3-acetic Acid (26a).** Compound **26a** was obtained from **25a** following the same procedure as for **18a** and was used in the subsequent reaction without further purification: $^1H$ NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 4.89 (s, 1H), 4.85 (s, 1H), 4.26−3.86 (m, 3H), 3.79−3.61 (m, 1H), 2.61−2.34 (m, 3H), 2.18−2.02 (m, 1H), 1.65 (s, 3H), 1.43−1.20 (m, 15H); $^{13}C$ NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 176.0, 172.6, 171.8, 154.1, 153.2, 140.4, 116.7, 80.1, 65.3, 61.0, 61.0, 60.4, 56.4, 56.0, 40.6, 39.8, 35.2, 28.0, 19.3, 18.1, 17.4, 13.8; IR (film) 3190, 1748, 1713, 1699, 1395, 1370 $cm^{-1}$; HRMS (*m*/*z*): calcd for $C_{18}H_{29}NO_6$ ($M^+$): 355.1995, found: 355.1980.

**(2*SR*,3*SR*,4*RS*,5*RS*)-*N*-(*tert*-Butoxycarbonyl)-2-carboxy-4-isopropenyl-5-methylpyrrolidine-3-acetic Acid (27a).** Compound **27a** was obtained from **26a** following the same procedure as for **19a** and was used without further purification: $^1H$ NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 8.59 (br s, 2H), 4.97 (s, 1H), 4.88 (s, 1H), 3.92−3.64 (m, 2H), 2.74−2.50 (m, 2H), 2.32−1.97 (m, 2H), 1.68 (s, 3H), 1.44−1.24 (m, 12H); $^{13}C$ NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 178.4, 177.2, 177.1, 176.9, 154.3, 153.0, 140.1, 117.3, 80.9, 65.8, 65.3, 60.9, 60.3, 56.3, 56.0, 41.1, 40.5, 35.3, 35.0, 28.3, 28.1, 19.3, 18.1, 17.5; IR (film) 1715,1410 $cm^{-1}$.

**(2*SR*,3*SR*,4*RS*,5*RS*)-2-Carboxy-4-isopropenyl-5-methylpyrrolidine-3-acetic Acid (28a).** Compound **28a** was obtained from **27a** following the same procedure as for **3a**. The hydrochloride was dissolved in the minimum amount of methanol and was added the same volume of propylene oxide. After stirring overnight at room temperature the white precipitate was filtered and washed with ether affording compound **28a** (86% from **25a**) as the zwitterion: mp > 200 °C; $^1H$ NMR ($D_2O$/KOD) $\delta$ 4.83 (s, 1H), 4.80 (s, 1H), 3.23 (dc, $J$ = 6.2 and 10.0 Hz, 1H), 3.17 (d, $J$ = 7.2 Hz, 1H), 2.58 (dd, $J$ = 4.2 and 13.1 Hz, 1H), 2.48−2.37 (m, 1H), 2.15 (dd, $J$ = 9.2 and 13.1 Hz, 1H), 1.99−1.94 (m, 1H), 1.66 (s, 3H), 1.03 (d, $J$ = 6.2 Hz, 3H); $^{13}C$ NMR ($D_2O$/KOD) $\delta$ 183.2, 182.0, 145.1, 114.7, 67.1, 63.5, 57.6, 45.9, 43.7, 19.4, 18.7; IR (KBr) 3420, 1716, 1617, 1389, 1321 $cm^{-1}$. Anal. Calcd for $C_{11}H_{17}NO_4 \cdot {}^1/_3CH_3OH$: C, 56.78; H, 7.87; N, 5.76. Found: C, 56.59; H, 8.08; N, 6.09.

**Ethyl (1*SR*,2*SR*,4*RS*,5*RS*,6*RS*)-*N*-(*tert*-Butoxycarbonyl)-3-aza-4,6-dimethyl-6-hydroxy-7-oxobicyclo[3.3.0]octane-2-carboxylate (29a) and Ethyl (1*SR*,2*SR*,4*SR*,5*RS*,6*RS*)-*N*-(*tert*-Butoxycarbonyl)-3-aza-4-phenyl-6-hydroxy-6-methyl-7-oxobicyclo[3.3.0]octane-2-carboxylate (29b).** To a solution of **22a**,**b** (2 mmol) and *N*-methylmorpholine *N*-oxide (515 mg, 4.4 mmol) in acetone (20 mL) and $H_2O$ (6 mL) were added 37 mL (0.003 mmol) of a 4% solution of $OsO_4$ in $H_2O$. The reaction mixture was stirred at room temperature for 48 h and then partitioned between ether (40 mL) and $H_2O$ (40 mL). The layers were separated, and the aqueous phase was extracted with ether (3 × 20 mL). The combined organic phases were dried ($Na_2SO_4$) and evaporated to dryness. To a solution of oxalyl chloride (206 $\mu$L, 2.4 mmol) in $CH_2Cl_2$ (6 mL) at −78 °C and under argon were added 355 $\mu$L of DMSO (5 mmol). This mixture was stirred at −78 °C for 30 min and then was added a solution of the foregoing crude diol (2 mmol) in $CH_2Cl_2$ (2 mL). After stirring at −78 °C for 45 min, $Et_3N$ (1.4 mL, 10 mmol) was added and the reaction was allowed to reach rt. The reaction mixture was stirred for 30 min and then quenched with $H_2O$ (15 mL). The aqueous phase was extracted with $CH_2Cl_2$ (2 × 5 mL), and the combined organic phases were washed with brine, dried ($Na_2SO_4$), and evaporated to dryness. Flash chromatography (hexane/ethyl acetate 1:1) gave the keto alcohols **29a**,**b** (82% for both **29a** and **29b**). **29a**: colorless oil; $^1H$ NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 4.32−4.01 (m, 4H), 3.08−2.75 (m, 4H), 2.26−2.13 (m, 1H), 1.41 and 1.34 (2s, 9H), 1.40 and 1.39 (2s, 3H), 1.28−1.10 (m, 6H); $^{13}C$ NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 214.3, 214.1, 172.5, 172.1, 154.1, 153.3, 80.6, 80.5, 77.7, 64.5, 61.3, 53.8, 53.5, 52.5, 41.0, 39.8, 39.7, 28.3, 28.2, 18.7, 17.8, 17.1, 14.2, 14.1; IR (film) 3410, 1748, 1693, 1682, 1393, 1192 $cm^{-1}$. Anal. Calcd for $C_{17}H_{27}NO_6$: C, 59.81; H, 7.93; N, 4.10. Found: C, 59.51; H, 7.82; N, 3.99. **29b**: mp 64−67 °C; $^1H$ NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 7.24−7.05 (m, 5H), 5.28−5.15 (m, 1H), 4.59 and 4.48 (2s, 1H), 4.30−4.16 (m, 2H), 3.30−3.17 (m, 2H), 3.09−2.94 (m, 1H), 2.50−2.36 (m, 1H), 1.73 (s, 1H), 1.32−1.03 (m, 12H), 0.64 (s, 3H); $^{13}C$ NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 213.1, 172.6, 172.2, 155.0, 154.4, 139.8, 138.8, 128.5, 128.2, 127.9, 127.7, 80.8, 80.6, 78.8, 65.6, 65.0, 63.1, 62.8, 61.5, 55.1, 54.2, 41.3, 40.2, 40.1, 28.1, 27.8, 18.2, 14.3, 14.2; IR (KBr) 3422, 2978, 1745, 1695, 1388, 1188 $cm^{-1}$. Anal. Calcd for $C_{22}H_{29}NO_6 \cdot {}^1/_2H_2O$: C, 64.06; H, 7.33; N, 3.40. Found: C, 64.11; H, 7.37; N, 3.36.

**Ethyl (1*SR*,2*SR*,4*RS*,5*SR*)-*N*-(*tert*-Butoxycarbonyl)-3-aza-4-methyl-6-methylidene-7-oxobicyclo[3.3.0]-octane-2-carboxylate (30a) and Ethyl (1*SR*,2*SR*,4*SR*,5*SR*)-*N*-(*tert*-Butoxycarbonyl)-3-aza-4-phenyl-6-methylidene-7-oxobicyclo[3.3.0]octane-2-carboxylate (30b).** To a solution of **29a**,**b** (2 mmol) in toluene (2 mL) was added 620 mg (2.6 mmol) of the Burgess reagent. The reaction mixture was stirred at 60−65 °C for 2 h, and then the solvent was evaporated in vacuo. Flash chromatography (hexane/ethyl acetate 2:1) of the crude gave the enones **30a**,**b** (45% for **30a** and 42% for **30b**). **30a**: colorless oil; $^1H$ NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 6.12 (s, 1H), 5.36 and 5.33 (2s, 1H), 4.40−4.05 (m, 4H), 3.77−3.64 (m, 1H), 2.83−2.64 (m, 2H), 2.36−2.21 (m, 1H), 1.42 and 1.36 (2s, 9H), 1.29−1.20 (m, 3H), 1.07−0.99 (m, 3H); $^{13}C$ NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 204.7, 172.5, 172.2, 155.1, 154.3, 145.1, 144.9, 120.9, 120.5, 80.5, 80.4, 64.6, 61.2, 56.5, 56.0, 47.8, 46.7, 42.7, 41.8, 40.9, 28.2, 19.2, 18.6, 14.2; IR (film) 2978, 1732, 1703, 1368, 1194 $cm^{-1}$; HRMS (*m*/*z*): calcd for $C_{12}H_{16}NO_3$ ($M^+ - CO_2tBu$): 222.1130. Found: 222.1126. **30b**: mp 111−114 °C; $^1H$ NMR ($CDCl_3$, doubling due to rotamers) $\delta$ 7.29−6.95 (m, 5H), 5.77 (s, 1H), 5.44−5.29 (m, 1H), 5.01−4.93 (2s, 1H), 4.63−4.53 (2s, 1H), 4.32−4.20 (m, 2H), 4.00−3.91 (m, 1H), 3.00−2.87 (m, 1H), 2.78−2.36 (m, 2H), 1.61−1.04 (m, 12H); $^{13}C$ NMR ($CDCl_3$, 333 K) $\delta$ 202.9, 172.0, 154.3, 144.3, 139.8, 127.9 (2C), 126.8, 126.7 (2C), 121.3, 80.4, 65.8, 65.6, 61.1, 49.4, 42.4, 41.3, 27.8, 14.0; IR (KBr) 2977, 1734, 1699, 1374, 1186 $cm^{-1}$. Anal. Calcd for $C_{22}H_{27}NO_5 \cdot {}^2/_3H_2O$: C, 66.48; H, 7.18; N, 3.52. Found: C, 66.50; H, 7.28; N, 3.60.

**Ethyl (1*SR*,2*SR*,4*RS*,5*SR*,6*SR*)-*N*-(*tert*-Butoxycarbonyl)-3-aza-4,6-dimethyl-6-(hydroxymethyl)-7-oxobicyclo-[3.3.0]octane-2-carboxylate (31a) and Ethyl (1*SR*,2*SR*,4*SR*,5*SR*,6*SR*)-*N*-(*tert*-Butoxyarbonyl)-3-aza-4-phenyl-6-(hydroxymethyl)-6-methyl-7-oxobicyclo[3.3.0]octane-2-carboxylate (31b).** To a suspension of CuBr·$Me_2S$ (62 mg, 0.3 mmol) in THF (4 mL) at −40 °C was added a 1.6 M solution of MeLi in ether (188 mL, 0.3 mmol), and the mixture was stirred at −40 °C for 10 min. The mixture was cooled to −50 °C and then was sequentially added a 1 M solution of diisobutylaluminum hydride in hexane (2.2 mL, 2.2 mmol) and HMPA (1 mL). The reaction mixture was stirred for 30 min prior to the addition of a solution of **30a**,**b** (1.0 mmol) in THF (1 mL). After stirring at −50 °C for 2 h, paraformaldehyde (150 mg, 5 mmol) was added and the mixture stirred at −50 °C for 5 min. The reaction mixture was stirred at room temperature overnight and then partitioned between ether (10 mL) and a 1 N HCl solution (10 mL). The layers were separated, and the aqueous phase was extracted with ether (3 × 10 mL). The combined organic phases were dried ($Na_2SO_4$) and concentrated to dryness. Flash column chromatography (hexane/ethyl acetate 1:1) gave compounds **31a**,**b** (80% for **31a** and 81% for **31b**) **31a**: colorless oil; $^1H$ NMR ($CDCl_3$, doubling due to rotamers)

δ 4.38−4.05 (m, 4H), 3.61−3.44 (m, 2H), 3.05−2.83 (m, 2H), 2.77−2.59 (m, 1H), 2.43−2.27 (m, 1H), 1.43 and 1.37 (2s, 9H), 1.33−1.21 (m, 6H), 1.17 (s, 3H); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) δ 219.8, 219.6, 172.7, 172.3, 153.8, 153.0, 80.5, 80.4, 68.2, 65.2, 65.0, 61.2, 56.3, 55.8, 54.2, 54.1, 50.2, 49.1, 42.1, 42.0, 41.3, 40.2, 28.3, 28.2, 18.1, 17.2, 15.8, 15.6, 14.2, 14.1; IR (film) 3450, 1742, 1699, 1393, 1368, 1192 cm$^{-1}$. Anal. Calcd for $C_{18}H_{29}NO_6$: C, 60.83; H, 8.22; N, 3.94. Found: C, 60.53; H, 8.16; N, 3.71. **31b**: colorless oil; $^1$H NMR ($CDCl_3$, doubling due to rotamers) δ 7.24−7.13 (m, 5H), 5.40−5.25 (m, 1H), 4.48−4.19 (m, 3H), 3.46−2.48 (m, 6H), 1.79 (br s, 1H), 1.35−1.07 (m, 12H), 0.53 (s, 3H); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) δ 219.7, 219.4, 172.7, 172.3, 154.5, 153.5, 139.8, 138.3, 128.0, 127.9, 127.7, 127.2, 80.7, 80.5, 68.3, 68.1, 66.8, 66.3, 64.9, 64.8, 61.4, 55.5, 55.1, 50.5, 49.3, 41.6, 41.4, 41.2, 40.5, 28.0, 27.7, 15.8, 15.7; IR (film) 3418, 2976, 2934, 1740, 1695, 1390, 1171 cm$^{-1}$. Anal. Calcd for $C_{23}H_{31}NO_6 \cdot {}^1/_3H_2O$: C, 65.22; H, 7.55; N, 3.31. Found: C, 65.46; H, 7.95; N, 3.47.

**Ethyl (1*SR*,2*SR*,4*RS*,5*SR*,6*SR*)-*N*-(*tert*-Butoxycarbonyl)-3-aza-4,6-dimethyl-6-(*p*-toluenesulfonyloxymethyl)-7-oxobicyclo[3.3.0]octane-2-carboxylate (32a) and Ethyl (1*SR*,2*SR*,4*SR*,5*SR*,6*SR*)-*N*-(*tert*-Butoxycarbonyl)-3-aza-4-phenyl-6-methyl-6-(*p*-toluenesulfonyloxymethyl)-7-oxobicyclo[3.3.0]octane-2-carboxylate (32b).** To a solution of **31a**,**b** (1 mmol) in pyridine (5 mL) was added 286 mg (1.5 mmol) of tosyl chloride, and the reaction mixture was stirred at 0 °C for 2 h and at room temperature overnight. The mixture was partitioned between ether (20 mL) and a 1 N HCl solution (10 mL). The layers were separated, and the organic phase was washed with 1 N HCl solution till pH ∼ 1, dried ($MgSO_4$), and evaporated to dryness. Flash column chromatography (hexane/ethyl acetate 3:1) afforded **32a**,**b** (72% for **32a** and 63% for **32b**). **32a**: colorless oil; $^1$H NMR ($CDCl_3$, doubling due to rotamers) δ 7.74−7.68 (m, 2H), 7.36−7.32 (m, 2H), 4.33−3.98 (m, 4H), 3.91−3.76 (m, 2H), 3.09−2.96 (m, 1H), 2.90−2.74 (m, 1H), 2.67−2.30 (m, 2H), 2.43 (s, 3H), 1.43 and 1.36 (2s, 9H), 1.32−1.22 (m, 6H), 1.09 and 1.08 (2s, 3H); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) δ 216.0, 215.8, 172.2, 171.7, 153.6, 152.8, 145.2, 131.9, 129.8, 127.7, 80.4, 80.2, 72.6, 65.5, 65.3, 61.1, 56.3, 55.7, 51.7, 51.5, 49.2, 48.1, 41.0, 40.9, 40.6, 39.6, 28.1, 28.0, 21.4, 17.4, 16.3, 16.1, 16.0, 14.0; IR (film) 1747, 1705, 1699, 1393, 1368, 1179 cm$^{-1}$; HRMS (*m*/*z*): calcd for $C_{20}H_{26}NO_6S$ ($M^+ - CO_2tBu$): 408.1481, found: 408.1482. **32b**: mp 151−155 °C; $^1$H NMR ($CDCl_3$, doubling due to rotamers) δ 7.66 (d, 2H, $J$ = 8.3 Hz), 7.32 (d, 2H, $J$ = 8.3 Hz),7.24−7.09 (m, 5H), 5.44−5.28 (m, 1H), 4.36−4.20 (m, 3H), 3.63 (d, 1H, $J$ = 9.3 Hz), 3.53−3.45 (m, 1H), 3.25−3.02 (m, 2H), 2.68−2.44 (m, 2H), 2.43 (s, 3H), 1.36−1.10 (m, 12H), 0.49 (s, 3H); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) δ 216.1, 215.9, 172.3, 171.7, 154.4, 153.5, 145.2, 138.6, 137.0, 132.0, 129.9, 127.9, 127.7, 127.4, 127.2, 80.9, 80.8, 72.8, 67.2, 66.8, 64.7, 64.5, 61.5, 52.6, 52.2, 49.2, 48.2, 41.6, 40.6, 40.2, 28.0, 27.8, 21.6, 16.6, 14.1; IR (KBr) 2978, 2930, 1744, 1697, 1368, 1180 cm$^{-1}$. Anal. Calcd for $C_{30}H_{37}NO_8S \cdot 2H_2O$: C, 59.29; H, 6.80; N, 2.31. Found: C, 59.38; H, 6.46; N, 2.18.

**(2*SR*,3*SR*,4*SR*,5*RS*)-*N*-(*tert*-Butoxycarbonyl)-2-(ethoxycarbonyl)-4-isopropenyl-5-methylpyrrolidine-3-acetaldehyde (33a) and (2*SR*,3*SR*,4*SR*,5*SR*)-*N*-(*tert*-Butoxycarbonyl)-2-(ethoxycarbonyl)-4-isopropenyl-5-phenylpyrrolidine-3-acetaldehyde (33b).** To a solution of **32a**,**b** (1 mmol) in THF (7 mL) at −78 °C and under argon was added a 1 M solution of $LiBEt_3H$ in THF (1.1 mL, 1.1 mmol), and the mixture was stirred at −78 °C for 30 min. Then the reaction was quenched with a saturated $NaHCO_3$ solution (1 mL), and the mixture was allowed to reach 0 °C. $H_2O_2$ (33%) (10 drops) was added, and the mixture stirred at 0 °C for 20 min. The solvent was eliminated in vacuo, and the residue was extracted with ether (3 × 10 mL). The combined organic phases were dried ($Na_2SO_4$) and evaporated to dryness. To a solution of the crude alcohols in *tert*-butyl alcohol (20 mL) was added potassium *tert*-butoxide (135 mg). The mixture was stirred at 25−30 °C for 2 h and then partitioned between a mixture of ether (40 mL) and a saturated $NH_4Cl$ solution (10 mL). The organic phase was washed with $H_2O$ (3 × 10 mL), dried ($Na_2SO_4$), and evaporated to dryness. Flash chromatography (hexane/ethyl acetate 3:1) gave **33a**,**b** (37% for **33a** and 25% for **33b**). **33a**: colorless oil; $^1$H NMR ($CDCl_3$, doubling due to rotamers) δ 9.72 (s, 1H), 4.94 (s, 1H), 4.65 (s, 1H), 4.24−3.92 (m, 4H), 2.96−2.68 (m, 4H), 1.69 (s, 3H), 1.46−1.19 (m, 15H); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) δ 199.9, 199.8, 172.8, 172.3, 154.6, 152.4, 141.0, 117.7, 80.4, 80.1, 65.7, 61.2, 61.1, 57.3, 56.7, 53.7, 52.9,43.2, 38.8, 38.1, 28.3, 28.2, 22.6, 22.5, 16.8, 15.7, 14.1; IR (film) 1748, 1715, 1393, 1368, 1184 cm$^{-1}$. Anal. Calcd for $C_{18}H_{29}NO_5$: C, 63.70; H, 8.62; N, 4.13. Found: C, 63.54; H, 8.90; N, 4.05. **33b**: $^1$H NMR ($CDCl_3$, doubling due to rotamers) δ 9.69 (s, 1H), 7.24−7.10 (m, 5H), 5.25−5.13 (m, 1H), 4.82 and 4.78 (2s, 1H), 4.46 and 4.38 (2s, 1H), 4.31−4.13 (m, 3H), 3.27−3.20 (m, 1H), 3.12−2.95 (m, 1H) 2.93−2.66 (m, 2H), 1.36−1.05 (m, 15H); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) δ 199.7, 172.7, 172.2, 154.6, 153.4, 140.5, 139.3, 137.9, 127.4, 127.1, 126.8, 126.6, 126.4, 117.2, 117.1, 80.6, 80.3, 66.5, 66.2, 66.1, 61.4, 53.8, 53.1, 43.3, 43.0, 40.1, 39.5, 28.1, 27.6, 24.8, 24.5, 14.2; IR (film) 2976, 2931, 1743, 1725, 1696, 1392, 1369, 1174 cm$^{-1}$. Anal. Calcd for $C_{23}H_{31}NO_5$: C, 68.81; H, 7.78; N, 3.49. Found: C, 68.50; H, 7.91; N, 4.42.

**(2*SR*,3*SR*,4*SR*,5*RS*)-*N*-(*tert*-Butoxycarbonyl)-2-(ethoxycarbonyl)-4-isopropenyl-5-methylpyrrolidin-3-acetic Acid (34a) and (2*SR*,3*SR*,4*SR*,5*SR*)-*N*-(*tert*-Butoxycarbonyl)-2-(ethoxycarbonyl)-5-phenyl-4-isopropenylpyrrolidine-3-acetic Acid (34b).** Compounds **34a**,**b** were obtained from **33a**,**b** following the same procedure as for **18a**,**b** and were used in next reaction without further purification. **34a**: $^1$H NMR ($CDCl_3$, doubling due to rotamers) δ 4.99 (s, 1H), 4.71 (s, 1H), 4.24−3.94 (m, 4H), 2.98−2.89 (m, 1H), 2.77−2.56 (m, 3H), 1.71 (s, 3H), 1.44−1.20 (m, 15H); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) δ 177.1, 172.8, 172.3, 154.6, 153.4, 141.7, 117.5, 80.4, 80.2, 65.5, 61.1, 57.2, 56.6, 53.5, 52.8, 40.7, 39.9, 33.1, 28.3, 28.2, 22.6, 16.8, 15.7; IR (film) 1744, 1713, 1395, 1370, 1186 cm$^{-1}$, HRMS (*m*/*z*): calcd for $C_{13}H_{20}NO_4$ ($M^+ - CO_2tBu$): 254.1392, found: 254.1387. **34b**: $^1$H NMR ($CDCl_3$, doubling due to rotamers) δ 7.24−7.06 (m, 5H), 5.24−5.11 (m, 1H), 4.85 and 4.81 (2s, 1H), 4.48 and 4.42 (2s, 1H), 4.33−4.15 (m, 3H), 3.25−3.18 (m, 1H), 3.01−2.86 (m, 1H) 2.78−2.55 (m, 2H), 1.36−1.04 (m, 15H); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) δ 176.8, 172.7, 172.2, 154.6, 153.4, 140.1, 139.3, 137.8, 127.3, 127.1, 126.8, 126.5, 117.1, 80.6, 80.3, 66.4, 66.0, 66.0, 65.9, 61.4, 53.7, 53.2, 42.0, 41.4, 33.1, 32.8, 28.1, 27.6, 25.0, 24.7, 14.1. IR (film) 3255, 2973, 2925, 1740, 1697, 1393, 1258 cm$^{-1}$.

**(2*SR*,3*SR*,4*SR*,5*RS*)-*N*-(*tert*-Butoxycarbonyl)-2-carboxy-4-isopropenyl-5-methylpyrrolidine-3-acetic Acid (35a) and (2*SR*,3*SR*,4*SR*,5*SR*)-*N*-(*tert*-Butoxycarbonyl)-2-carboxy-5-phenyl-4-isopropenylpyrrolidine-3-acetic Acid (35b).** Compounds **35a**,**b** were obtained from **34a**,**b** folowing the same procedure as for **19a**,**b** and were used in next reaction without further purification. **35a**: colorless oil; $^1$H NMR ($CDCl_3$, doubling due to rotamers) δ 10.06 (br s, 2H), 4.99 (s, 1H), 4.72 (s, 1H), 4.14−3.95 (m, 2H), 2.97−2.72 (m, 2H), 2.60−2.54 (m, 2H), 1.71 (s, 3H), 1.43−1.21 (m, 12H); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) δ 179.2, 178.1, 177.7, 154.9, 153.4, 140.6, 140.5, 117.9, 117.8, 81.1, 80.8, 65.4, 65.3, 57.3, 56.8, 53.9, 53.3, 40.8, 40.0, 33.1, 28.3, 28.2, 22.6, 16.7, 15.5; IR (film) 2980, 2934, 1719, 1408, 1150 cm$^{-1}$. **35b**: $^1$H NMR ($CDCl_3$, doubling due to rotamers) δ 8.07 (br s, 2H), 7.24−7.10 (m, 5H), 5.27−5.13 (m, 1H), 4.85 and 4.79 (2s, 1H), 4.51 (s, 1H), 4.42−4.24 (m, 1H), 3.24−3.06 (m, 2H) 2.75−2.60 (m, 2H), 1.37 (s, 3H), 1.33 and 1.04 (2s, 9H); $^{13}$C NMR ($CDCl_3$, doubling due to rotamers) δ 178.6, 177.5, 177.3, 154.8, 153.4, 140.3, 140.1, 139.0, 137.6, 127.4, 127.2, 127.1, 126.7, 126.6, 117.4, 81.3, 80.9, 66.4, 66.1, 65.9, 65.7, 54.4, 54.1, 42.2, 41.7, 33.4, 28.1, 27.6, 24.9, 24.3; IR (film) 2976, 2931, 1726, 1713, 1695, 1403, 1156 cm$^{-1}$.

**(2*SR*,3*SR*,4*SR*,5*RS*)-2-Carboxy-4-isopropenyl-5-methylpyrrolidine-3-acetic Acid Hydrochloride (4a) and (2*SR*,3*SR*,4*SR*,5*SR*)-2-Carboxy-5-phenyl-4-isopropenylpyrrolidine-3-acetic Acid Hydrochloride (4b).** A solution of **35a**,**b** (1 mmol) in a 1 N HCl solution in ethyl acetate (5 mL) was stirred at room temperature for 8 h. The solvent was eliminated in vacuo, and the resulting solid was washed with ether

and dried to give **4a**,**b** (94% for both **4a** and **4b**, overall yields from **35a**,**b**. **4a**: mp > 200 °C; $^1$H NMR ($CD_3OD$) $\delta$ 5.23 (s, 1H), 4.78 (s, 1H), 4.32 (d, 1H, $J$ = 11.3 Hz), 4.06−3.92 (m, 1H), 3.32−3.24 (m, 1H), 3.13−2.55 (m, 3H), 1.81 (s, 3H), 1.38 (d, 3H, $J$ = 6.8 Hz); $^{13}$C NMR ($CD_3OD$) $\delta$ 174.6, 171.0, 140.3, 119.2, 63.0, 60.8, 53.0, 44.1, 33.5, 24.7, 13.6; IR (KBr) 3424, 2926, 1725, 1410, 1258, 1208 cm$^{-1}$. Anal. Calcd for $C_{11}H_{18}NO_4$-Cl: C, 50.10; H, 6.89; N, 5.31. Found: C, 50.18; H, 6.87; N, 5.23. **4b**: mp > 200 °C; $^1$H NMR ($CD_3OD$) $\delta$ 7.52−7.23 (m, 5H), 5.19 (d, 1H, $J$ = 6.1 Hz), 5.12 (s, 1H), 4.80 (s, 1H), 4.45 (d, 1H), 3.72−3.65 (m, 1H), 3.36−3.20 (m, 1H), 3.05−2.64 (m, 2H), 1.32 (s, 3H); $^{13}$C NMR ($CD_3OD$) $\delta$ 174.5, 170.9, 140.3, 133.6, 129.8, 129.7, 127.7, 118.9, 67.4, 63.4, 53.8, 44.0, 33.9, 24.9; IR (KBr) 3427, 3056, 2972, 2928, 1723, 1405, 1260, 1226 cm$^{-1}$. Anal. Calcd for $C_{16}H_{20}NO_4Cl$: C, 58.99; H, 6.19; N, 4.30. Found: C, 58.87; H, 6.25; N, 4.18.

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**Supporting Information Available:** Copies of $^1$H and $^{13}$C NMR spectra of all compounds lacking elemental analysis (**10**, **11a**,**b**, **13a**,**b**, **14a**, **17a**,**b**, **18a**, **19a**,**b**, **8a**, **21a**,**b**, **23a**, **25a**, **26a**, **27a**, **30a**, **32a**, **34a**,**b**, **35a**,**b**) and NOE experiments (**11a**,**b**, **21a**,**b**, **3a**,**b**, **4a**,**b**). This material is available free of charge via the Internet at http://pubs.acs.org.

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