A Total Synthesis of (−)-α-Kainic Acid Involving a Pauson–Khand Reaction as the Key Step

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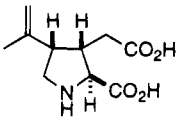
A synthetic route to (−)-α-kainic acid has been developed based on the Pauson–Khand reaction as a key step for the construction of the bicyclic ring system. In this reaction a built-in oxazolidinone ring serves as a rigid template for good diastereofacial selectivity.

(−)-α-Kainic acid (**1**) is a potent neuronal exitant[1] which was isolated from the marine algae *Digenea simplex*[2] and *Centrocerus clavulatum*.[3] Other structurally related compounds also have been isolated, namely acromelic acid A & B from the toxic principles of *Clitocybe acromelalga*[4] and domoic acid and its family from the red algae *Chondria armata*.[5] Neuronal lesions caused by intracranial injections of **1** are widely used in investigations of neuronal networks in the central nervous system and as pharmacological models for human disease state including Huntington's chorea.[6] The above mentioned novel biological activities and the unique structure of **1** had justified the development of several interesting synthetic strategies[7] for this family of natural products.



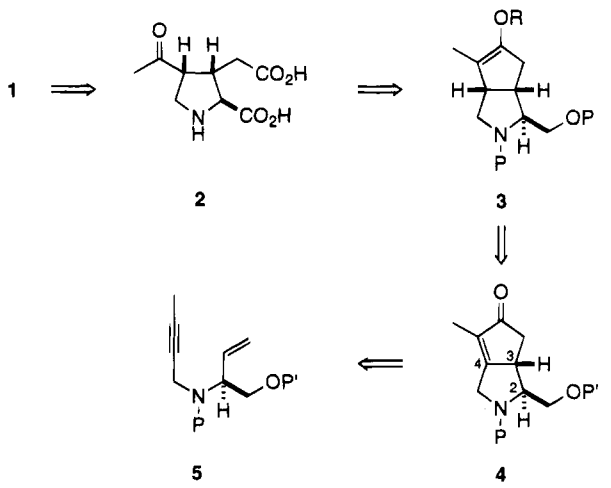
(-)-α-Kainic acid (**1**)

Figure 1.

Results and Discussion

In devising a synthetic scheme for kainic acid, one must deal with the control of stereochemistry at C-3 and C-4, since the *cis* stereochemistry at these positions is crucial for the biological activity of kainic acid. Our retrosynthetic analysis (Scheme 1) suggested that the ketone **2**, which can be readily transformed into **1**, can be derivable by the oxidative cleavage of the enol ether **3**. The enol ether **3** would be obtained by trapping the regiospecific enolate generated by 1,4-reduction of the enone **4**. The most important aspect in the scheme for controlling the steroechemistry at C3 and C4 positions lies in the fact that the reduction would proceed to form the *cis* fused bicyclo system favorably due to the nature of the ring system. Furthermore, the *trans* stereochemistry between C2 and C3 would be realized during the Pauson–Khand reaction.[8,11]

Scheme 1



We expected that the Pauson–Khand reaction of **6** would give **7** preferentially mainly due to the steric hindrance between the MOM group and the methyl group if the reaction proceeds through the transition state "B" (Scheme 2) as proposed by Magnus in a similar case.[12]

However, previous study[9] showed that in our case diastereoselectivity was rather low (**7**:**8** = 1.7:1). A number of attempts to improve the diastereoselectivity by changing either protecting groups[10] or reaction conditions[11] were not successful. One explanation for this low diastereoselectivity can be found in the conformation of the transition state of the reaction. The X-ray single crystallographic study of the hydrogenated product **9** shows that the tosyl group is located under the bicyclic

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(4) Konno, K.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1983**, 939.

(5) (a) Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982**, *104*, 3511. (b) Maeda, M.; Kodama, T.; Yoshimuzu, H.; Takemoto, T.; Nomoto, K.; Fujita, T. *Tetrahedron Lett.* **1987**, , 633.

(6) McGeer, E. G.; Olney, J. W.; McGeer, P. L. *Kainic acid as a Toll in Neurobiology*; Raven Press: New York, 1978.

(7) (a) Oppolzer, W.; Thirring, K. *J. Am. Chem. Soc.* **1982**, *104*, 4978. (b) Copper, J.; Knight, D. W.; Gallagher, P. T. *J. Chem. Soc., Chem. Commun.* **1987**, 1220. (c) Takano, S.; Sugihara, T.; Satoh, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1988**, *110*, 6467.

(8) (a) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E. *J. Chem. Soc. Perkin Trans 1* **1973**, 977. (b) Pauson, P. L. *Tetrahedron* **1985**, *41*, 5855.

(9) Yoo, S.; Lee, S.; Jeong, N.; Cho, I. *Tetrahedron Lett.* **1993**, *34*, 3435.

(10) We have tested the Cbz, tosyl, or benzoyl group as an *N*-protecting group and CH_2SCH_3, $Si(CH_3)_2$(t-Bu), or $SiPh_2$(t-Bu) as a protecting group for the hydroxyl group. In all cases, the diastereoselectivity was in the range of 1.5:1–1.8:1 for **7**:**8**.

(11) Under the alternative conditions (SiO_2,[16] 50 °C, 1 h; Florisil, 50 °C, 4 h; heptane, reflux, 10 h), the diastereoselectivity was not improved and the yield was even lower than the NMO[17] or TMANO[18] condition.

(12) Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*, 4851.

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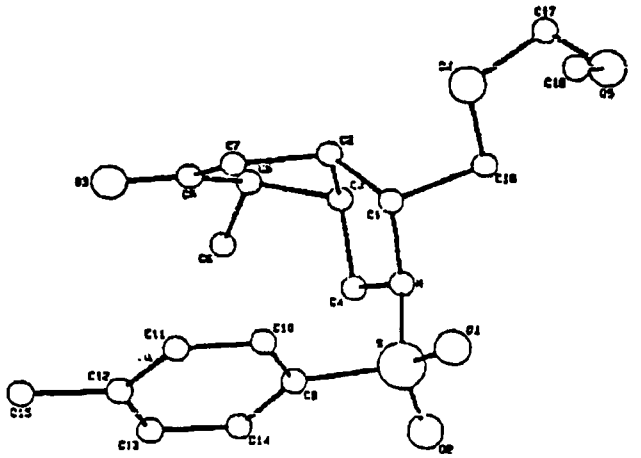
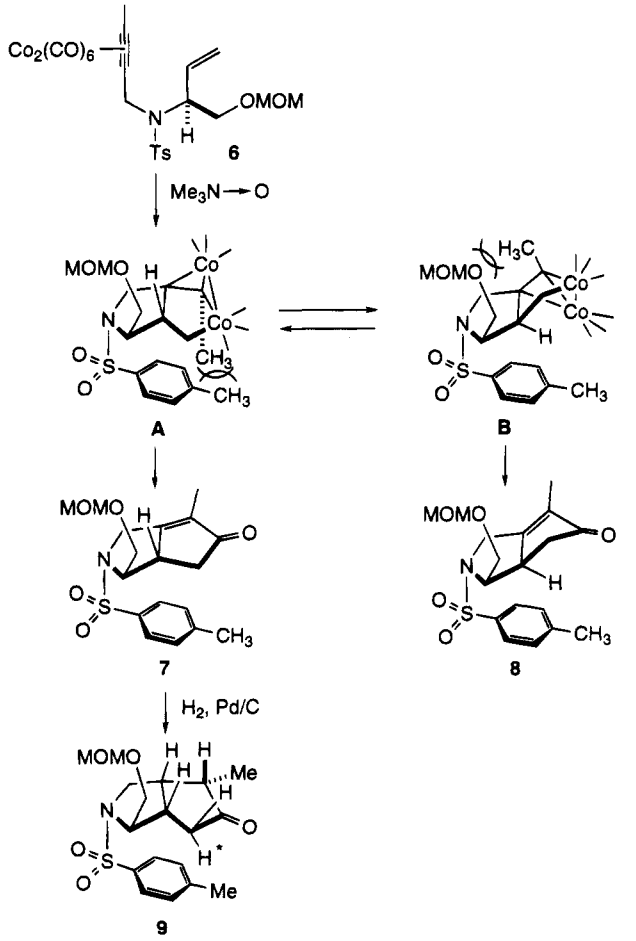


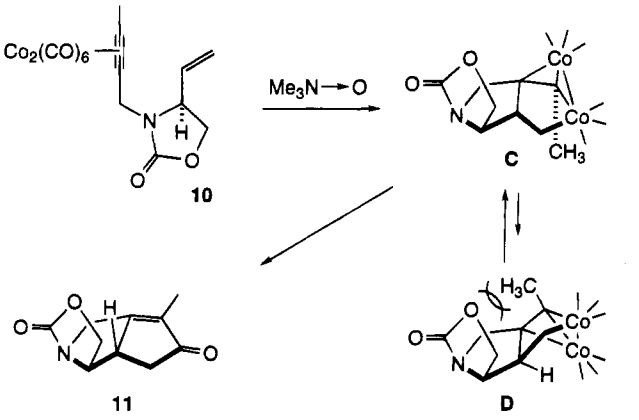
Figure 2. ORTEP diagram of **9**.

Scheme 2

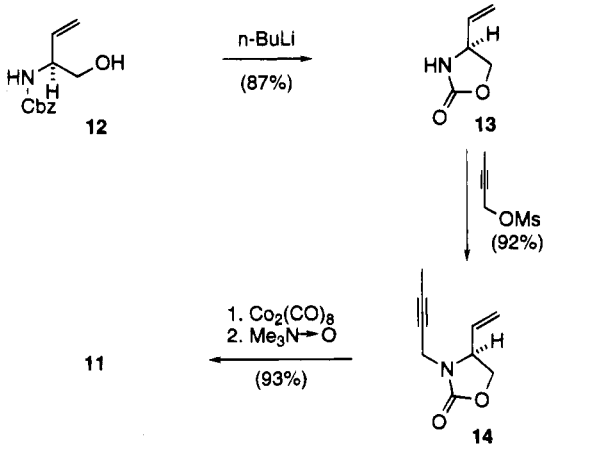


ring (Figure 2). The ^1H NMR spectrum also indicates that the solution conformation of **9** might be similar to that of the solid state conformation. An unusually upfield-shifted peak (0.82 ppm in $CDCl_3$) of H* in **9** seems to be due to the anisotropic effect of the tosyl group and this upfield-shift indicates that H* is in the shielding region of the phenyl group. The steric hindrance between the tosyl group and the methyl group in the transition state "A" seems to lower the diastereoselectivity. In order to improve the diastereoselectivity, a protecting group for nitrogen should be sufficiently small or should be on the same side of the MOM group. Taking all these considerations into account, an oxazolidinone ring system was chosen to test this idea. Furthermore, increased steric

Scheme 3



Scheme 4



hindrance between the rigid oxazolidinone ring and the methyl group in the tricyclic transition state "**D**" will also favor the formation of the desired product **11** (Scheme 3).

The optically active alcohol **12** was prepared from /-glutamic acid by the known method.[9,13] Treatment of alcohol **12** with n-BuLi gave **13** and subsequent *N*-alkylation of **13** using 2-butyn-1-yl mesylate gave **14** in high yield. With the substrate for the crucial cyclization reaction ready, we subjected **14** to a typical Pauson–Khand reaction. To our delight, the Pauson–Khand reaction of **14** gave exclusively a single diastereoisomer **11**, in 93% yield. At this point the structure of **11** was conclusively determined by X-ray crystallography.

The rest of the transformation from **11** to **1** is summarized in Schemes 5 and 6. In order to prepare the regiospecific enol ether, we first attempted the 1,4-reduction of **11** followed by trapping the resulting enolate with TMSCl. However, all reactions tried[14] were unsatisfactory. Alternatively, the enone **11** was catalytically hydrogenated in the presence of Pd/C to give a mixture of **15** and **16** (**15**:**16** = 1:3–1:5). After hydrolysis of the mixture of **15** and **16** under the acidic condition, the resulting amines were treated with *p*-toluenesulfonyl chloride to give **17** and **18** (**17**:**18** = 2:1). Under this acidic condition, the methyl group was easily epimerized. In order to prepare thermodynamically stable enol ether **20**, compounds **9** and **19** were separately treated with

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(14) (a) $(Ph_3P)_3RhCl$, Et_3SiH: Ojima, I.; Kogure, T. *Organometallics* **1982**, *1*, 1390. (b) $[(Ph_3P)CuH]_6$, TMSCl: Stryker, J. M.; Mahoney, W. S.; Brestensky, D. M. *J. Am. Chem. Soc.* **1988**, *110*, 291. (c) Bu_3SnH, CuI, LiCl, TMSCl: Lipshutz, B. H.; Ung, C. S.; Sengupta, S. *Synlett* **1989**, 64.

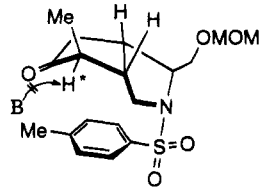

Figure 3.

Fe(O)[15] and TMSCl. As we expected, the ketone **9** gave the desired enol ether **20** exclusively. However, in the case of **19**, the isomeric enol ether **21** was produced exclusively. This result can be explained by the fact that H* is not available for abstraction by the base because it is *endo* on a [3.3.0] ring system and it is also completely blocked by the tosyl group (Figure 3). In order to exclude the formation of β-methyl compounds (**16**, **18**, and **19**), **11** was transformed to **17** via **22**. A catalytic hydrogenation of **22** gave a single diastereoisomer **17**. It is noteworthy that a mixture of **15** and **16** was obtained from **11** under the same condition. In the case of **22**, the bottom side seems to be blocked by the tosyl group during the catalytic hydrogenation.

The ketone **23** was prepared from **20** by ozonolysis followed by esterification with diazomethane. The Wittig reaction of **23** proceeded smoothly to give **24** without epimerization at the C4 position. A MOM group on **24** was deprotected with trifluoroacetic acid and the resulting alcohol was oxidized to the acid **26** with PDC. For the purpose of purification, the acid **26** was esterified to **27** with diazomethane. The diester **27** was then hydrolyzed and the tosyl group was removed by dissolving metal reduction to give **1**. Treatment of the reaction mixture with weakly acidic ion-exchange resin (Amberlite CG50) followed by recrystallization in ethanol afforded the optically pure α-kainic acid [$[\alpha]_D^{20} = -14.7°$ ($c = 1.5$, H_2O)] which is identical to the natural kainic acid as confirmed by ^1H NMR (300 MHz, D_2O).

In conclusion, in this synthetic scheme we successfully controlled the relative stereochemistry of C3:C4 (*cis*) and C2:C3 (*trans*) by employing the oxazolidinone ring not only as a protecting group for amine and alcohol groups but more importantly as a rigid template for controlling diastereofacial selectivity during the Pauson–Khand reaction.

Experimental Section

General. Melting points were determined on a Haake-Bucher capillary melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were obtained at 300 MHz ^1H (75.5 MHz ^{13}C) and were recorded in $CDCl_3$ with TMS as an internal standard. Elemental analyses were performed by Korea Research Institute of Chemical Technology, Microanalytical Service Laboratory, DaeJeon, Korea. IR spectra were recorded on a Bio-Red Digilab Division FTS-80 FT-IR spectrophotometer. Optical rotations were measured with a Perkin-Elmer 241 MC polarimeter. In the standard reaction workup, the organic solution containing the product was dried over Na_2SO_4 and filtered, and the solvent was removed with a rotary evaporator.

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(16) Smit, W. A.; Simonyan, S. O.; Tarasov, V. A.; Mikaelian, G. S.; Gybin, A. S.; Ibragimov, I. I.; Caple, R.; Froen, D.; Kreager, A. *Synthesis* **1989**, 472.
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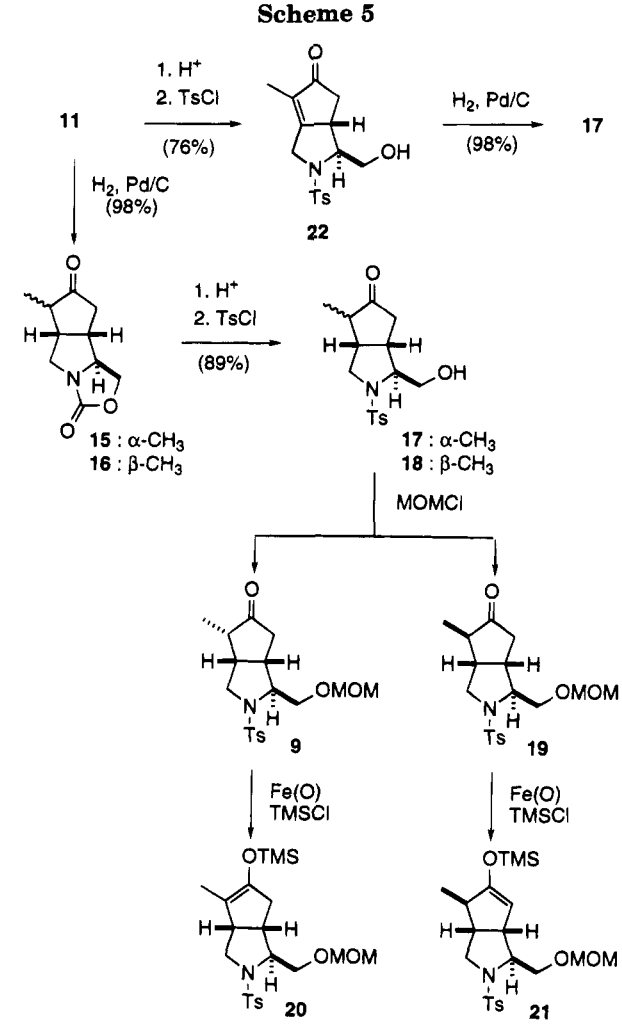
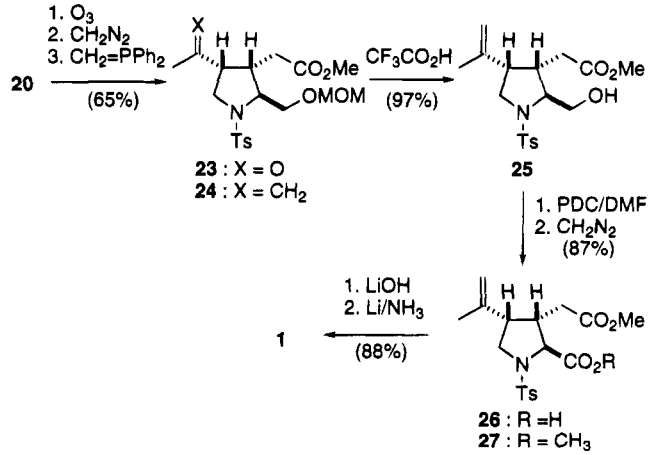
Scheme 5



Scheme 6



(4*S*)-4-Vinyloxazolidin-2-one (13). To a solution of **12** (5.0 g, 22.6 mmol) in 30 mL of THF at 0 °C was added a hexane solution of *n*-BuLi (1.4 ml, 1.6 M, 2.3 mmol). The solution was stirred for 2 h at rt and then quenched with solid NH_4Cl. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was chromatographed over silica gel (eluting with hexane–EtOAc (2:1)), to afford 2.2 g (87%) of **13** as pale yellow oil: $[\alpha]_D^{20} = -17.6$ ($c = 1.0$, $CHCl_3$); IR (neat) 1751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.07 (dd, 1H, J = 8.3, 6.5 Hz), 4.40 (m, 1H), 4.55 (t, 1H, J = 8.5 Hz), 5.29 (m, 2H), 5.83 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.2, 69.9, 118.5, 135.7, 159.9; EIMS *m/e* 113 (M^+, 65), 83 (60), 68 (100), 55 (87); HRMS calcd for $C_5H_7NO_2$ 113.0477, found 113.0468.

(4*S*)-3-But-2-ynyl-4-vinyloxazolidin-2-one (14). To **13**

(4 g, 35.4 mmol) in 30 mL of DMF at 0 °C was added NaH (60%, 1.7 g, 42.5 mmol) portionwise. The resulting solution was stirred for 1 h at rt. After standard workup, the residue was purified by column chromatography (SiO_2, hexane:EtOAc = 3:1) to give **14** as pale yellow oil (5.4 g, 92%): $[\alpha]_D^{20} = +11.5$ (c = 1.0, $CHCl_3$); IR (neat) 1759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.69 (m, 3H), 3.48 (dq, 1H, J = 17.4, 2.3 Hz), 3.85 (dd, 1H, J = 7.1, 7.1 Hz), 4.13 (dq, 1H, J = 17.4, 2.4 Hz), 4.24–5.65 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 3.1, 31.9, 57.9, 66.7, 71.9, 80.4, 121.5, 133.6, 157.3; HRMS calcd for $C_9H_{11}NO_2$ 165.0790, found 165.0808.

(3a*S*,3b*S*)-6-Methyl-3a,3b,4,7-tetrahydro-3*H*-2-oxa-7a-azacyclopenta[*a*]pentalene-1,5-dione (11). To dicobaltoctacarbonyl (6.5 g, 19.0 mmol) under nitrogen atmosphere was added a solution of enyne **14** (3 g, 18.2 mmol) in 300 mL of dry dichloromethane at room temperature. The solution was stirred for 1 h at room temperature, at which time TLC analysis indicated conversion to a less polar, purple cobalt–alkyne complex. To the reaction mixture at room temperature was added trimethylamine *N*-oxide (9.8 g, 0.13 mol) portionwise over 1 h. After additional stirring for 2 h, the resulting reaction mixture was passed through silica gel with ethyl acetate elution, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (elution with hexane:ethyl acetate = 1:2) to give the tricyclic enone **11** as white solid (3.3 g, 93%). For the purpose of X-ray study, single crystals were obtained by recrystallizing from hexane–ethyl acetate: $[\alpha]_D^{20} = -75.4$ (c = 1.0, $CHCl_3$); IR (KBr) 1751, 1708, 1674 cm^{-1}; mp 181–182 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.81 (s, 3H), 2.15 (dd, 1H, J = 17.8, 2.5 Hz), 2.72 (dd, 1H, J = 17.8, 6.3 Hz), 2.93 (m, 1H), 3.64 (m, 1H), 4.06 (d, 1H, J = 17.0 Hz), 4.40 (dd, 1H, J = 9.3, 2.9 Hz), 4.48 (d, 1H, J = 17.0 Hz), 4.62 (dd, 1H, J = 9.3, 7.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 8.7, 38.2, 46.1, 46.8, 63.5, 66.5, 135.6, 160.7, 173.0, 207.3; EIMS *m/e* 193 (M^+, 80), 149 (15), 121 (10), 108 (100), 79 (58), 66 (12); HRMS calcd for $C_{10}H_{11}NO_3$ 193.0739, found 193.0750. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.53; H, 5.74; N, 7.24.

(3*S*,3a*S*)-3-(Hydroxymethyl)-6-methyl-2-(toluene-4-sulfonyl)-2,3,3a,4-tetrahydro-1*H*-cyclopenta[*c*]pyrrol-5-one (22). Oxazolidinone **11** (1.5 g, 7.77 mmol) in 100 mL of 4 N HCl was refluxed for 6 h. The reaction mixture was neutralized with 4 N NaOH. To the resulting solution was added *p*-toluenesulfonyl chloride (1.63 g, 8.55 mmol). After stirring overnight at rt, the standard workup followed by column chromatography (SiO_2, hexane:ethyl acetate = 1:1 → 1:2) provided the alcohol **22** (1.9 g, 76%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.59 (t, 3H, J = 1.5 Hz), 1.98 (dd, 1H, J = 18.0, 3.2 Hz), 2.18 (s, 2H), 2.44 (s, 3H), 2.62 (dd, 1H, J = 18.0, 6.4 Hz), 2.90 (dt, 2H, J = 9.3, 3.7 Hz), 3.20 (m, 1H), 3.82–3.90 (m, 1H), 4.10–4.17 (m, 1H), 4.25 (dd, 1H, J = 35.5, 16.0 Hz), 7.34 (m, 2H), 7.69 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 8.5, 21.6, 30.9, 39.3, 44.2, 49.2, 63.3, 67.6, 127.5, 130.1, 132.7, 133.6, 168.1, 207.2.

(1*S*,3a*S*,4*S*,6a*S*)-1-(Hydroxymethyl)-4-methyl-2-(toluene-4-sulfonyl)-hexahydrocyclopenta[*c*]pyrrol-5-one (17). The enone **22** was catalytically hydrogenated in the presence of Pd/C as described in the preparation of **15** to give **17**. IR (KBr) 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.76 (dd, 1H, J = 19.5, 9.5 Hz), 0.83 (m, 1H), 0.95 (d, 3H, J = 7.1 Hz), 2.24–2.38 (m, 2H), 2.42 (s, 3H), 2.54–2.65 (m, 2H), 3.12 (m, 1H), 3.50 (m, 1H), 3.63 (dd, 1H, J = 9.7, 8.3 Hz), 3.77 (s, 2H), 7.32 (d, 2H, J = 7.9 Hz), 7.68 (d, 2H, J = 7.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 10.5, 21.6, 39.8, 40.4, 46.6, 49.9, 65.8, 67.0, 127.4, 130.0, 132.6, 144.5, 217.0; EIMS *m/e* 292 ($M^+ - CH_2OH$, 100), 155 (60), 91 (55); HRMS calcd for $C_{16}H_{21}NO_4S - CH_2OH$ 292.1007, found 292.1030. Anal. Calcd for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.55; N, 4.34. Found: C, 59.50; H, 6.89; N, 4.11.

(3a*S*,3b*S*,6*S*,6a*S*)-6-Methylhexahydro-2-oxa-7a-aza-cyclopenta[*a*]pentalene-1,5-dione (15) and (3a*S*,3b*S*,6*R*,-6a*S*)-6-Methylhexahydro-2-oxa-7a-azacyclopenta[*a*]pentalene-1,5-dione (16). The enone **11** (3 g, 15.38 mmol) was dissolved in 50 mL of ethyl acetate and 0.3 g of Pd/C (10%) was added. The resulting solution was stirred for 1 h under hydrogen (1 atm). After removal of Pd/C by filtration through Celite, the resulting filtrate was concentrated and chromatographed (SiO_2, hexane:ethyl acetate = 1:1) to give **15** and **16**.

15: IR (KBr) 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (d, 3H, J = 7.2 Hz), 2.10 (dd, 1H, J = 24.0, 10.6 Hz), 2.57 (m, 1H), 2.70–2.81 (m, 2H), 3.02 (m, 1H), 3.82 (m, 1H), 3.92 (dd, 1H, J = 12.3, 7.6 Hz), 4.19 (dd, 1H, J = 9.1, 4.7 Hz), 4.64 (dd, 1H, J = 9.1, 8.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 10.2, 41.0, 43.0, 44.3, 45.1, 47.9, 65.6, 68.9, 161.1, 216.9; EIMS *m/e* 195 (M^+, 60), 167 (5), 137 (15), 108 (10), 99 (100), 82 (15), 67 (15), 55 (43); HRMS calcd for $C_{10}H_{13}NO_3$ 195.0895, found 195.0898. Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.57; H, 6.72; N, 7.18. Found: C, 61.67; H, 6.68; N, 7.15.

16: IR (KBr) 1732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.23 (d, 3H, J = 6.9 Hz), 2.04 (m, 1H), 2.29 (m, 1H), 2.42–2.62 (m, 3H), 3.14 (dd, 1H, J = 12.0, 2.5 Hz), 3.70 (m, 1H), 4.06 (dd, 1H, J = 12.0, 7.6 Hz), 4.23 (dd, 1H, J = 9.0, 2.5 Hz), 4.54 (dd, 1H, J = 7.9, 7.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.3, 38.4, 42.6, 48.7, 49.1, 51.7, 64.3, 66.9, 76.6, 77.0, 77.4, 160.9, 217.0; EIMS *m/e* 195 (M^+, 50), 199 (100); HRMS calcd for $C_{10}H_{13}NO_3$ 195.0895, found 195.0905. Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.57; H, 6.72; N, 7.18. Found: C, 61.05; H, 6.59; N, 7.03.

(1*S*,3a*S*,4*S*,6a*S*)-1-(Methoxymethoxymethyl)-4-methyl-2-(toluene-4-sulfonyl)hexahydrocyclopenta[*c*]pyrrol-5-one (9). A solution of alcohol **17** (3.5 g, 10.84 mmol), chloromethyl methyl ether (2.46 mL, 32.5 mmol), and diisopropylethylamine (7.54 mL, 43.3 mmol) in 100 mL of dichloromethane was stirred for 3 h at RT. After the standard work up, the residue was purified by column chromatography (SiO_2, hexane:ethyl acetate = 2:1) to give **9** as white solid: mp 104–105 °C; $[\alpha]_D^{15} = +48.2$ (c = 1.0, $CHCl_3$); IR (KBr) 1774 cm^{-1}; ^1H NMR (300 MHz, benzene-d_6) δ 0.56 (dd, 1H, J = 19.3, 9.5 Hz), 0.75 (d, 3H, J = 7.1 Hz), 1.74 (m, 1H), 1.84 (s, 3H), 1.86 (dd, 1H, J = 19.3, 9.8 Hz), 2.25–2.33 (m, 1H), 2.50–2.59 (m, 1H), 3.20 (s, 3H), 3.42–3.51 (m, 1H), 3.56–3.63 (m, 1H), 3.84–3.91 (m, 1H), 4.52 (dd, 2H, J = 8.5, 6.5 Hz), 6.77 (d, 2H, J = 8.3 Hz), 7.66 (d, 2H, J = 8.3 Hz); ^{13}C NMR (75.5 MHz, benzene-d_6) δ 10.5, 21.0, 39.6, 40.4, 43.2, 46.5, 39.6, 55.1, 65.0, 70.9, 97.1, 127.6, 129.8, 133.9, 143.8, 215.1; EIMS *m/e* 336 ($M^+ - OCH_3$, 15), 292 (125), 212 (20), 155 (100), 91 (95); CIMS *m/e* 368 ($M^+ + H$), 382 ($M^+ + CH_3$); HRMS calcd for $C_{18}H_{25}NO_5S$ 336.1270, found 336.1273. Anal. Calcd for $C_{18}H_{25}NO_5S$: C, 58.90; H, 6.87; N, 3.82. Found: C, 58.66; H, 6.97; N, 3.81.

(1*S*,3a*S*,4*R*,6a*S*)-1-(Methoxymethoxymethyl)-4-methyl-2-(toluene-4-sulfonyl)hexahydrocyclopenta[*c*]pyrrol-5-one (19). Following the same reaction with **18** as described above, the compound **19** was obtained as white solid: ^1H NMR (300 MHz, benzene-d_6) δ 0.64 (d, 3H, J = 7.2 Hz), 106 (m, 1H), 1.54 (dd, 1H, J = 19.1, 5.1 Hz), 1.77–1.83 (m, 1H), 1.85 (s, 3H), 1.90 (dd, 1H, J = 19.1, 8.7 Hz), 2.46–2.51 (m, 1H), 3.08 (dd, 1H, J = 11.0, 4.5 Hz), 3.5 (s, 3H), 3.42–3.48 (m, 2H), 3.71 (dd, 1H, J = 9.8, 7.0 Hz), 3.88 (dd, 1H, J = 9.8, 3.4 Hz), 4.45 (dd, 2H), 6.77 (m, 2H), 7.67 (m, 2H).

(3*S*,3a*S*,6a*S*)-5-[(Trimethylsilyl)oxy]-3-(methoxymethoxymethyl)-6-methyl-2-(toluene-4-sulfonyl)-1,2,3,-3a,4,6a-hexahydrocyclopenta[*c*]pyrrole (20). To anhydrous ferric chloride (3.31 g, 20.4 mmol) in 50 mL of dry ethyl ether at 0 °C was added dropwise MeMgBr (3 M in ethyl ether, 20.4 mL, 61.2 mmol). After stirring for 1 h at rt, a solution of the ketone **9** (5 g, 13.62 mmol) in 10 mL of dry THF was added. After stirring for additional 10 min, trimethylsilyl chloride (5.9 mL, 54.48 mmol), triethylamine (8.8 mL, 61.29 mmol), and HMPA (2.6 mL, 15 mmol) were added. The reaction mixture was stirred for 2 h a rt, washed with aqueous $NaHCO_3$, dried with Na_2SO_4, and concentrated. The resulting residue was purified by column chromatography (SiO_2, hexane:ethyl acetate = 1:1) to give **20** as colorless oil (5.7 g, 95%): ^1H NMR (300 MHz, benzene-d_6) δ 0.02 (m, 9H), 1.26 (d, 3H, J = 1.0 Hz), 1.94 (s, 3H), 2.23–2.41 (m, 1H), 2.56–2.63 (m, 1H), 2.70 (m, 1H), 3.16 (s, 3H), 3.41 (d, 2H, J = 5.3 Hz), 3.67 (dd, 1H, J = 9.0, 6.4 Hz), 3.76 (m, 1H), 3.83 (dd, 1H, J = 9.0, 3.5 Hz), 4.45 (dd, 2H, J = 78.5, 6.4 Hz), 6.79 (d, 2H, J = 8.1 Hz), 7.75 (dm, 2H); ^{13}C NMR (75.5 MHz, benzene-d_6) δ 0.6, 10.5, 21.1, 40.0, 42.4, 49.7, 52.0, 55.0, 67.3, 70.9, 96.9, 113.1, 129.1, 137.5, 142.4, 146.1.

(3a*S*,4*R*,6a*S*)-5-[(Trimethylsilyl)oxy]-1-(methoxymethoxymethyl)-4-methyl-2-(toluene-4-sulfonyl)-1,2,3,-

3a,4,6a-hexahydrocyclopenta[c]pyrrole (21). Following the same reaction sequence as described above, the compound **21** was obtained as colorless oil from the compound **19**: ^{1}H NMR (300 MHz, benzene-d_6) δ 0.07 (s, 9H), 0.90 (d, 3H, J = 7.0 Hz), 1.88 (m, 1H), 1.94 (s, 3H), 2.20 (q, 1H, J = 7.7 Hz), 2.96 (dd, 1H, J = 9.5, 7.6 Hz), 3.18 (s, 3H), 3.41 (m, 1H), 3.64–3.75 (m, 3H), 3.97 (dd, 1H, J = 8.9, 2.8 Hz), 4.03 (s, 1H), 4.50 (s, 2H), 6.80 (m, 2H), 7.75 (m, 2H); ^{13}C NMR (75.5 MHz, benzene-d_6) δ 18.9, 21.4, 45.8, 46.0, 49.3, 55.0, 55.2, 65.1, 71.6, 97.2, 102.2, 128.3, 129.8, 135.8, 142.9, 158.8.

(2S,3R,4R)-4-Acetyl-3-[(methoxycarbonyl)methyl]-2-(methoxymethoxymethyl)-1-(toluene-4-sulfonyl)pyrrolidine (23). Ozone was passed through the solution of enol ether **20** (4.5 g, 10.25 mmol) in dry dichloromethane at −78 °C until the reaction mixture turned blue. The excess ozone was removed by bubbling oxygen and the resulting ozonide was treated with dimethyl sulfide. The reaction mixture was treated with diazomethane and the excess diazomethane was quenched with acetic acid. After washing with aqueous $NaHCO_3$, the organic layer was dried with Na_2SO_4, concentrated and purified by column chromatography (SiO_2, hexane:ethyl acetate = 2:1) to give keto ester **23** (3.8 g, 90%) as thick oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (dd, 1H, J = 17.0, 9.8 Hz), 1.75 (dd, 1H, J = 17.0, 5.2 Hz), 1.83–1.88 (m, 1H), 2.14 (s, 3H), 2.45 (s, 3H), 2.91 (m, 1H), 3.35 (m, 1H), 3.40 (s, 3H), 3.51–3.65 (m, 1H), 3.59 (s, 2H), 3.70–3.81 (m, 3H), 4.67 (dd, 2H), 7.35 (dd, 2H, J = 8.5, 0.6 Hz), 7.74 (m, 2H).

(2S,3S,4S)-4-Isopropenyl-3-[(methoxycarbonyl)methyl]-2-methoxymethoxymethyl)-1-(toluene-4-sulfonyl)pyrrolidine (24). To methyltriphenylphosphonium iodide (3.36 g, 8.32 mmol) in 30 mL of dry THF at −78 °C was added n-BuLi (1.6 M in hexane, 5.2 mL, 8.32 mmol) dropwise. After stirring for 30 min at −78 °C, the ketone **23** (2 g, 4.84 mmol) in 5 mL of THF was added. The reaction mixture was warmed up slowly to rt and quenched with saturated aqueous NH_4Cl. A standard workup followed by purification using chromatography (SiO_2, hexane:ethyl acetate = 3:1) gave 1.4 g (72%) of **24** as white solid: mp 124–126 °C; $[\alpha]_D^{15}$ −31.1 (c = 1.0, $CHCl_3$); IR (KBr) 1736 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (dd, 1H, J = 16.5, 11.5 Hz), 1.67 (s, 3H), 1.79 (dd, 1H, J = 16.5, 3.5 Hz), 2.45 (s, 3H), 2.66 (m, 1H), 2.99–3.11 (m, 2H), 3.39 (s, 3H), 3.52 (dd, 1H, J = 10.4, 5.6 Hz), 3.59 (s, 3H), 3.67 (m, 1H), 3.79 (dd, 1H, J = 9.3, 2.8 Hz), 4.52 (s, 1H), 4.66 (dd, 2H, J = 10.1, 6.4 Hz), 7.33 (d, 2H), 7.76 (d, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.5, 22.7, 31.9, 39.1, 45.1, 48.8, 51.5, 55.3, 64.3, 70.1, 96.5, 112.2, 127.5, 129.6, 133.2, 140.5, 143.7, 172.3; EIMS m/e 380 (M^+ − OCH_3, 30), 336 (100), 276 (37), 234 (55), 181 (23), 155 (36), 91 (70); CIMS m/e 412 (M^+ + H), 426 (M^+ + CH_3). Anal. Calcd for $C_{20}H_{29}NO_6S$: C, 58.42; H, 7.11; N, 3.41. Found: C, 58.00; H, 7.07; N, 3.40.

(2S,3S,4S)-2-(Hydroxymethyl)-4-isopropenyl-3-(methoxycarbonylmethyl)-1-(toluene-4-sulfonyl)pyrrolidine (25). A mixture of **24** (1.2 g, 3.27 mmol) and trifluoroacetic acid (1 mL) in 10 mL of dichloromethane was stirred for 1 h at rt. The reaction mixture was washed with aqueous $NaHCO_3$, dried with Na_2SO_4, and concentrated. The resulting white solid was used for the next step (PDC oxidation) without further purification. For the purpose of identification, a fraction of the residue was recrystallized from ethyl ether: mp 112–113 °C; $[\alpha]_D^{15}$ = 13.7 (c = 1.0, $CHCl_3$), IR (KBr) 1732, 1713 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (dd, 1H, J = 17.0, 12 Hz), 1.66 (s, 3H), 1.80 (dd, 1H, J = 17.0, 32 Hz), 2.46 (s, 3H), 2.55 (m, 1H), 2.97–3.10 (m, 2H), 3.54 (dd, 1H, J = 11.1, 5.6 Hz), 3.59 (s, 3H), 3.73–3.84 (m, 2H), 4.52 (s, 1H), 4.86 (d, 1H, J = 1.0 Hz), 7.36 (d, 2H, J = 8.0 Hz), 7.76z (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.5, 22.7, 31.6, 39.0, 45.2, 49.5, 51.6, 65.8, 66.6, 112.3, 127.6, 129.7, 132.5, 140.3, 144.1, 172.5; EIMS m/e 350 (M^+ − OH, 3), 336 (M^+ − CH_2OH, 100); CIMS m/e 368 (M^+ + H), 382 (M^+ + CH_3); HRMS calcd for $C_{18}H_{25}NO_5S-CH_2OH$ 336.1270, found 336.1256. Anal. Calcd for $C_{19}H_{28}NO_6S$: C, 58.89; H, 6.86; N, 3.81. Found: C, 58.63; H, 6.84; N, 3.80.

(2S,3S,4S)-4-Isopropenyl-2-(methoxycarbonyl)-3-[(methoxycarbonyl)methyl]-1-(toluene-4-sulfonyl)pyrrolidine (27). To a solution of alcohol **25** (1.0 g, 2.72 mmol) in 5 mL of DMF at rt was added PDC (3.1 g, 8.17 mmol) and molecular sieves (4 Å, 2 g). The reaction mixture was stirred for 20 h at rt and then treated with diazomethane. Standard workup and purification by column chromatography gave 0.87 g (78%) of **27** as white solid: mp 139–140 °C; $[\alpha]^{15}_D$ = −48.1 (c = 1.0, $CHCl_3$); IR (KBr) 1751, 1740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56 (dd, 1H, J = 16.8, 10.8 Hz), 1.65 (s, 3H), 2.06 (dd, 1H, J = 16.8, 3.9 Hz), 2.44 (s, 3H), 2.81 (m, 1H), 3.09 (m, 1H), 3.25 (dd, 1H, J = 10.4, 9.1 Hz), 3.56 (dd, 1H, J = 8.8, 7.0 Hz), 3.06 (s, 3H), 3.77 (s, 3H), 4.30 (d, 1H, J = 1.7 Hz), 4.59 (s, 1H), 4.89 (d, 1H, J = 1.2 Hz), 7.33 (m, 1H), 7.78 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.5, 22.6, 31.7, 41.4, 46.1, 48.2, 51.8, 65.0, 113.2, 127.4, 129.6, 134.8, 140.0, 143.8, 172.0; EIMS m/e 364 (M^+ − OCH_3, 6), 336 (100), 304 (8), 276 (22), 240 (73); CIMS m/e 396 (M^+ + H), 410 (M^+ + CH_3); HRMS calcd for $C_{18}H_{22}NO_5S$ − OCH_3 364.1219, found 364.1193. Anal. Calcd for $C_{19}H_{25}NO_6S$: C, 57.75; H, 6.38; N, 3.54. Found: C, 57.51; H, 6.34; N, 3.54.

(−)-(α)-Kainic Acid (1). The ester **27** (2.4 g, 6.06 mmol) in 20 mL of 3 N LiOH and 20 mL of methanol was refluxed for 1 h. The reaction mixture was acidified to pH 2, extracted with ethyl acetate, and the ethyl acetate extract was concentrated. The resulting white solid (2.15 g, 5.82 mmol) in 10 mL of dry THF was added to 50 mL of dry liquid ammonia (dried by Li), and then Li (242 mg, 34.92 mmol) was added at −78 °C. After additional stirring for 30 min at −78 °C, the reaction mixture was quenched with isoprene. Ammonia was removed by bubbling argon and THF was evaporated in vacuo. The residue was dissolved in 5 mL of water and neutralized to pH ~7 with cold 2 N HCl. The resulting aqueous solution was loaded on resin (Amberlite CG 50) in a column (3 cm × 30 cm), washed with distilled water, and then eluted with 3% NH_4OH. After concentration, the residue was recrystallized from EtOH to give 0.98 g (75% yield for two steps from **25**) of **1** as white solid: $[\alpha]_D^{20}$ = −14.7 (c = 1.5, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 1.60 (s, 3H), 2.23 (dd, 1H, J = 16.7, 8.2 Hz), 2.33 (dd, 1H, J = 16.7, 6.2 Hz), 2.85–2.96 (m, 2H), 3.13 (dd, 1H, J = 11.6, 11.1 Hz), 3.48 (dd, 1H, J = 11.8, 7.1 Hz), 3.96 (d, 1H, J = 3.2 Hz), 4.64 (s, 1H), 4.89 (s, 3H); ^{13}C NMR (75.5 MHz, D_2O) δ 22.5, 33.5, 41.0, 46.1, 46.8, 66.0, 113.9, 140.2, 173.5, 176.4.

Supplementary Material Available: Copies of NMR spectra of new compounds that lack combustion analysis, to indicate purity (7 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.