Stereoselective Synthesis of (−)-α-Kainic Acid and (+)-α-Allokainic Acid via Trimethylstannyl-Mediated Radical Carbocyclization and Oxidative Destannylation

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(−)-α-Kainic acid (**1**) and its C4 epimer (+)-α-allokainic acid (**2**) have been prepared from L-serine. The requisite stereochemical array in (−)-α-kainic acid (**1**) was introduced using a trimethylstannyl radical carbocyclization of a diene, which gave the 2,3-*trans*/3,4-*cis* and 2,3-*trans*/3,4-*trans* compounds in a 2.8:1 ratio and in high yield. The destannylation of the trisubstituted pyrrolidine nucleus was achieved via an oxidative cleavage of the C−Sn bond with ceric ammonium nitrate. This provided a dimethyl acetal that was further transformed into the intended α-kainic acid. When the same radical carbocyclization was attempted on a triene, the 2,3-*trans*/3,4-*trans* and the 2,3-*trans*/3,4-*cis* adducts were obtained in a 2.5:1 ratio, respectively. This approach was used to synthesize (+)-α-allokainic acid.

The marine product (−)-α-kainic acid (**1**)[1] has attracted considerable interest since it was first isolated by Takemoto in 1953,[1a] principally because of its potent neurotransmitting activity in the central nervous system[2] (Figure 1). Other naturally occurring kainoids, like acromelic acid[3] and domoic acid,[4] possess powerful biological properties as well, and they seem to exert their action by mimicking glutamic acid.[2a,5] Several total syntheses of such kainoids have been achieved during the last decade.[3b−d,4c,d,6]

Oppolzer's enantioselective synthesis of α-kainic acid[6l] by an intramolecular ene reaction stands as the first and, as yet, the most efficient approach in terms of steps and overall yields (10 steps, 4.8% overall yield starting from ethyl glutamate). This work also led to the unequivocal establishment of absolute configuration of α-kainic acid. A related synthesis of allokainic acid was also reported by Oppolzer and co-workers.[6f] More recently, Baldwin and co-workers have reported the synthesis of several kainoids using a cobalt-mediated free radical intramolecular cyclization reaction.[3d,6h,k] The intramolecular Pauson−Khand reaction[6a,d,f] and a tandem Micheal

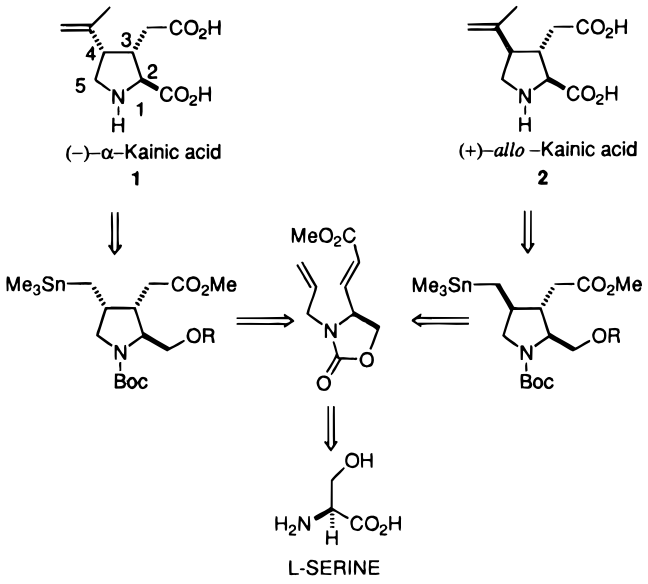

Figure 1.

reaction[7b] were also used for the construction of the C3−C4 bond. An interesting approach that involves the simultaneous formation of C2−C3 and C4−C5 bonds utilizes an intramolecular azomethine ylide cycloaddition that generates three chiral centers in a single step.[6j] A number of other approaches have been reported.[8] The above cited syntheses have involved 10−21 steps in overall yields ranging from 0.7% to 6%. The synthesis

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of allokainic acid **2** has also been the subject of several reports,[6c,g,k,7] mostly in conjunction with methods intended for the synthesis of α-kainic acid itself.

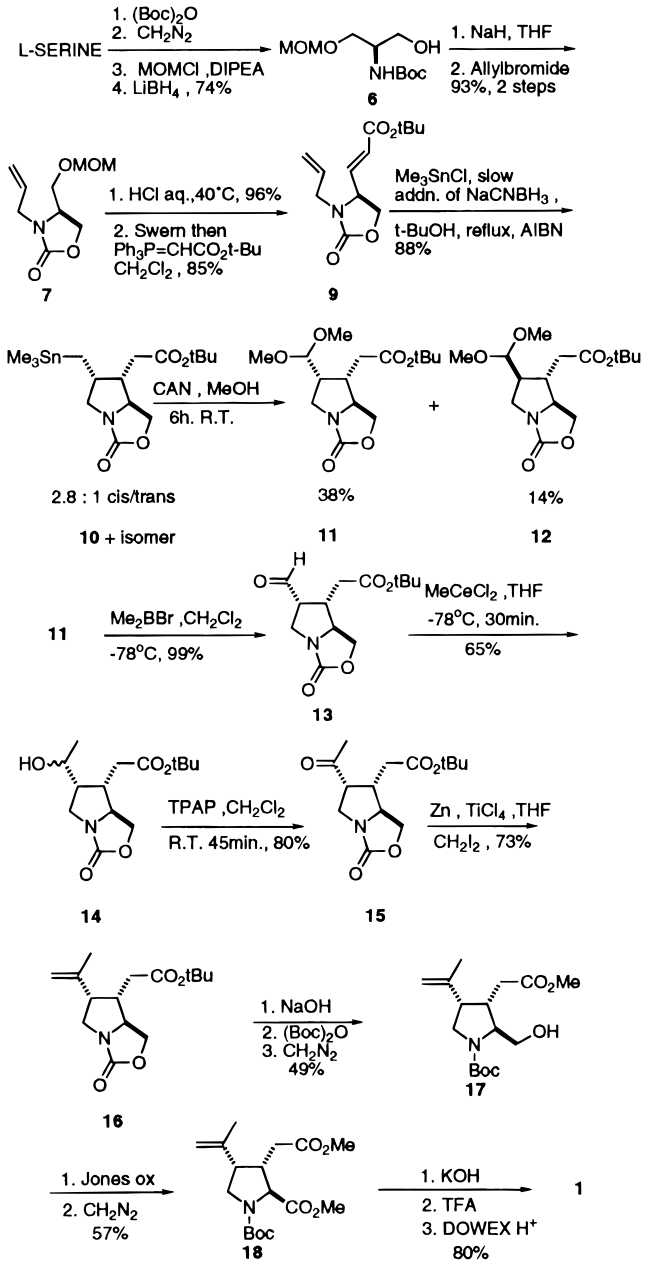
Results and Discussion

Of the above-mentioned total syntheses of α-kainic acid and allokainic acid, three use a free-radical carbocyclization strategy[6c,h,k] to construct the heterocyclic ring system. Our approach to the trisubstituted pyrrolidine ring comprising the kainic acids relied on the trimethylstannyl-mediated carbocyclization of terminal dienes and related systems, followed by a chemoselective oxidative cleavage of the C−Sn bond.[9] A disconnective analysis is shown in Figure 1 for α-kainic acid. Past experience in our group[9,10] has shown that such free-radical carbocyclizations favor the *cis*-stereochemistry at the newly formed bond, which argued well for the α-kainic acid series. The prospects of internal stereochemical control by a resident group on an adjacent stereogenic center during the radical-induced carbocyclization was expected to offer an added element of interest in overall stereoselectivity.

The synthesis commenced with L-serine, which was transformed into compound **6** in a four-step procedure without the need for purification (Scheme 1). Formation of the oxazolidinone ring as well as *in situ* N-allylation was efficently carried out leading to **7**. It is noteworthy that when a *tert*-butyldiphenylsilyl ether was used instead of the MOM protecting group, racemization occurred during the formation of the oxazolidinone ring. This is most probably due to a 1,3-silyl shift in a precursor related to **6** prior to ring formation. Deprotection of **7** and Swern oxidation of the resulting alcohol, followed by a Wittig olefination,[11] gave the chiron **9**, which was subjected to carbocyclization.

When diene **9** was treated with trimethyltin hydride generated under Stork's conditions,[12] the resulting mixture of stannylated compounds was obtained in only 50% yield, favoring the *cis* stereochemistry at the C3−C4 centers in a ratio of 2.8:1. However, a slow addition of sodium cyanoborohydride over a period of 1 h to a refluxing solution containing the substrate **9** and trimethyltin chloride afforded the cyclized products **10** and its C4 isomer as an inseparable mixture in 88% yield without compromising the *cis*/*trans* ratio. We have previously shown[9,10] that the carbon−tin bond in alkyltrimethylstannanes can be selectively cleaved in the presence of ceric ammonium nitrate (CAN) to give an aldehyde or its dialkyl acetal from the carbon atom bearing the longer alkyl chain. In the present case, treatment of the mixture containing **10** and its C4 isomer

Scheme 1



with excess CAN in methanol gave the dimethyl acetals **11** and **12** in 38% and 14% yields, respectively, after chromatographic separation. It is of practical importance to point out that the *cis*/*trans* ratio was maintained in the products **11** and **12** during the oxidative cleavage. The *in situ* transformation of the initially formed aldehyde into the corresponding dimethyl acetals is a form of temporary protection from the risk of epimerization.

Nevertheless, the problem of epimerization emerged during the deprotection of the acetal and its further elaboration into the intended 2-propenyl side chain. Our initial attempts to obtain the desired aldehyde **13** using TsOH or $SnCl_2 \cdot H_2O$[13] led in fact to epimerization at the C4 center. However, treatment of **11** with bromodimethylborane[14] at −78 °C for 30 min led to the aldehyde **13** in quantitative yield based on the crude product without any detectable epimerization. Treatment of **13**

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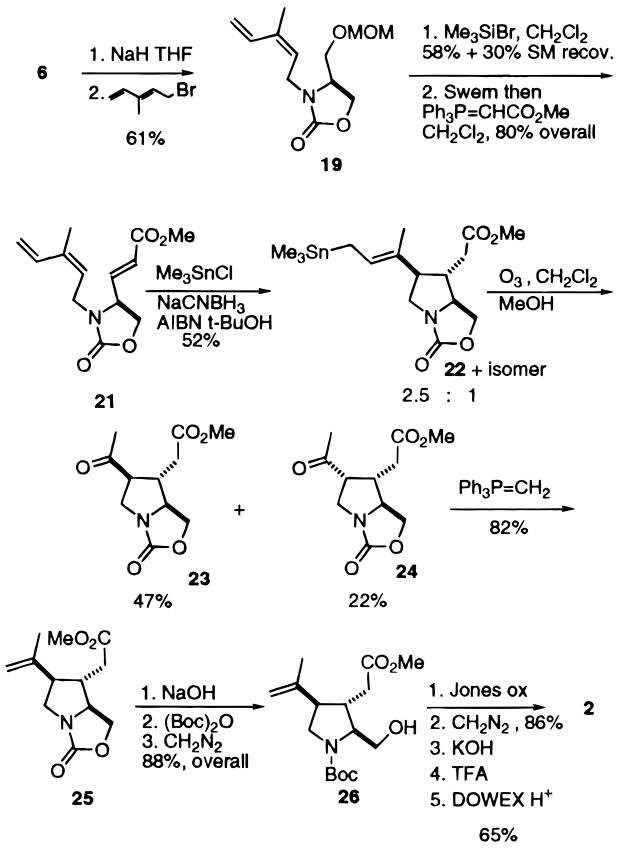
under the mildest possible conditions with methylmagnesium chloride or methyllithium led to addition accompanied by epimerization at C4. We were successful in obtaining the intended methyl carbinol **14** in 65% yield using the less basic and more oxophilic methyl cerium chloride.[15] Oxidation of alcohol **14** with tetra-*n*-propylammonium perruthenate[16] afforded ketone **15**, which could be purified by chromatography without any detectable epimerization at C-4. There remained to effect a methylenation reaction on **15** in order to complete the elaboration of the side chain. Wittig reactions are known to produce significant epimerization on analogous ketones.[6b] In a thiazolium ylide approach to racemic α-kainic acid, Monn and Valli[6b] were able to avoid epimerization by using the nonbasic Nozaki reagent,[17] $CH_2I_2-Zn-TiCl_4$. Thus, when ketone **15** was treated with this reagent combination in THF at 0 °C, compound **16** was formed in excellent yield without evidence of formation of the trans C3/C4 allokainate diastereoisomer. Although **16** has already been synthesized by Baldwin and co-workers,[6h] no spectral data were reported since the mentioned compound was isolated as a mixture of its C4 isomers and purified at a later stage. We were able to obtain **16** as a crystalline solid and to characterize it by NOE as well as by X-ray crystallography. Cleavage of the oxazolidinone ring in **16** was effected with aqueous base with simultaneous removal of the *tert*-butyl ester essentially as described by Baldwin.[6h] At this juncture in the synthesis, it was necessary to protect the nitrogen atom as the *tert*-butyloxycarbonyl derivative before oxidation of the primary hydroxyl group.

The oxidation of **17** has been previously carried out using PDC at 60 °C.[6h] In our case, we opted for a Jones oxidation at 0 °C, which after esterification with diazomethane afforded **18** in 57% overall yield. Hydrolysis of the *N*-Boc group and the ester function afforded crystalline (−)-α-kainic acid (**1**).

An alternative route to the kainoid skeleton was sought on the basis of the trimethyltin carbocyclization of a terminal diene, which would directly lead to a methyl ketone by oxidative cleavage of an intermediate olefin. Thus, triene **21** was synthesized essentially by the same reaction sequence used for the preparation of **9** from L-serine as shown in Scheme 2. N-Alkylation with 5-bromo-3-methylpenta-1,3-diene gave the diene **19**, which was deprotected in the presence of bromotrimethylsilane.[18] Oxidation of the resulting alcohol **20** and chain extension then gave the triene intermediate **21**.

When triene **21** was subjected to the trimethyltin radical addition−carbocyclization conditions, compound **22** and its C4 isomer were isolated in 52% yield as a 2.5:1 ratio, favoring the *all-trans* stereochemistry. The stereochemistry of the double bond was ascertained by NMR studies. Ozonolyzis afforded the ketones **23** and **24** in 47% and 22% yield, respectively, after separation by column chromatography. Ketone **24** could then be epimerized to the *all-trans* isomer **23** in high yield by treatment

Scheme 2



with DBU. Methylenation of **23** gave the olefin **25** in excellent yield. The remainder of the sequence was similar to that of **1** and proceeded uneventfully to give intermediate **26**, which was further transformed to (+)-allokainic acid.

Although the preponderance of the *cis*-isomer in the carbocyclization of **9** can be rationalized on the basis of a favored early transition state[19] (Figure 2A), the reversal in stereochemistry in the case of diene **21**, which affords the *trans* isomer **22** as the major product, is less evident. It is likely that the cisoid and transoid disposition of the allylic trimethyltin branch affect the relative reactivity of the ensuing radicals in the corresponding transition states. The thermodynamically more stable *all-trans* product could thus predominate in the mixture of isomers contained in **22** as depicted in Figure 2B.

We have described the synthesis of (−)-α-kainic acid (**1**) and (+)-allokainic acid (**2**) in 2% and 3% overall yields, respectively, from L-serine based on a novel free-radical carbocyclization route comprising less then 20 steps in each case. Related studies involving the synthesis of unnatural, conformationnally constrained bicyclic kainoids will be reported in due course.

Experimental Section[20]

General Procedure. All reactions were carried out under a positive atmosphere of dry argon unless otherwise indicated. Solvents were distilled prior to use: THF and Et_2O were

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(20) ^1H and ^{13}C NMR spectra were determined at 300 and 400 MHz. For typical experimental protocols, see: Hanessian,S.; Benalil, A.; Laferrière, C. *J. Org. Chem.* **1995**, *60*, 4786.

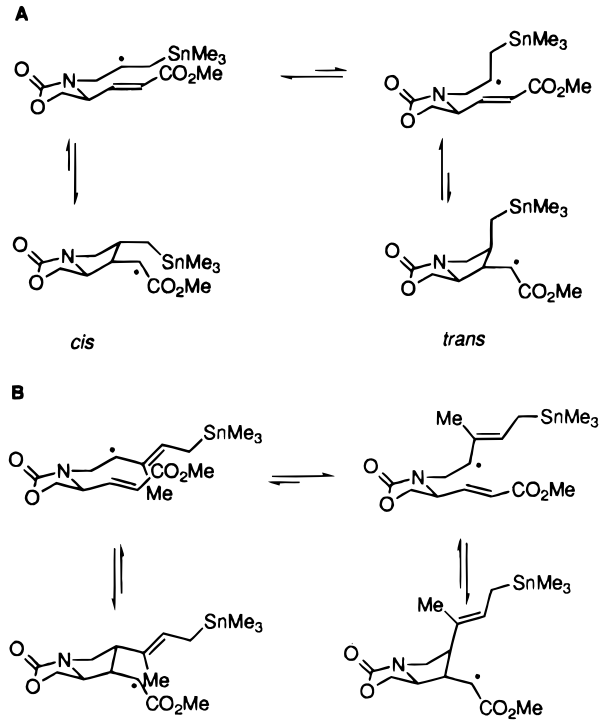

Figure 2.

distilled from sodium benzophenenone; CH_2Cl_2 was distilled from CaH_2. All new compounds are homogeneous on TLC, and their purities were further verified by ^{1}H NMR at 300 and 400 MHz and by ^{13}C NMR spectroscopy at 75 MHz. Optical rotations were recorded at 22 °C.

(2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-(methoxymethoxy)propionic Acid Methyl Ester (5). To a solution of *N*-(*tert*-butoxycarbonyl)-L-serine methyl ester (**4**) (40 g) in dichloromethane (300 mL) at 0 °C were slowly added diisopropylethylamine (65 mL, 2 equiv) and a solution of methoxymethyl chloride (27.7 mL, 2 equiv) in dichloromethane (50 mL, over 20 min). The reaction mixture was stirred at room temperature for 18 h and then diluted with water (100 mL). The mixture was then poured into a separatory funnel containing ethyl acetate (800 mL), and the organic phase was washed with 5% HCl (100 mL), saturated $NaHCO_3$ (100 mL), and brine (100 mL), dried over $MgSO_4$, and concentrated to afford crude **5** (45 g). Flash chromatography (30% ethyl acetate in hexane) gave **5** as an oil: $[\alpha]_D$ +5.9° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.43 (d, 1H, J = 8.3 Hz), 4.46 (s, 2H), 4.34−4.31 (m, 1H), 3.86 (dd, 1H, J = 10.2 and 3.3 Hz), 3.64−3.59 (m, 4H), 3.19 (s, 3H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 170.7, 155.1, 96.3, 79.5, 67.7, 54.9, 53.7, 52.0, 28.0 ; IR (neat) υ_{max} 3300, 2900, 1700, 1575, 1350, 1140, 1090, 1010, 900 cm^{-1}; HRMS calcd for $C_{11}H_{22}O_6N$ + H 264.1447, found 264.1432; MS (CI, isobutane) *m*/*e* 208.1 ($M^+ - (CH_3)_2C{=}CH_2$), 164.1 ($M^+ - (CH_3)_2C{=}CH_2 - CO_2$), 132.1 ($M^+ - (CH_3)_2C{=}CH_2 - CO_2 -$ MeOH).

(2*R*)-2-[(*tert*-Butoxycarbonyl)amino]-3-(methoxymethoxy)propan-1-ol (6). To a solution of crude ester **5** (45 g) in THF (260 mL, 0.7 M) was added at 0 °C a solution of lithium borohydride (2.0 M in THF, 91 mL, 1 equiv). The reaction mixture was stirred for 12 h at room temperature and then treated at 0 °C with saturated NH_4Cl. Extraction with ethyl acetate (600 mL) and usual workup gave a syrup that was chromatographed (60% ethyl acetate in hexane) to give **6** (34 g, 75% yield from serine) as a white solid: $[\alpha]_D$ −3.2° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.25−5.15 (broad s, 1H), 4.50 (s, 2H), 3.71−3.31 (m, 6H), 3.24 (s, 3H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 155.8, 96.4 79.2, 66.9, 62.1, 55.0, 51.6, 28.1; IR υ_{max} 3330, 2910, 1685, 1510, 1365, 1245, 1165, 1110, 1040 cm^{-1}; MS (FAB$^+$) *m*/*e* 236 (M^+ + H), 180 ($M^+ - (CH_3)_2C{=}CH_2$), 148 ($M^+ - (CH_3)_2C{=}CH_2 - CO_2$).

(4*S*)-3-Allyl-4-[(methoxymethoxy)methyl]oxazolidin-2-one (7). To a suspension of sodium hydride (2.4 equiv, 4.90 g, 122 mmol) in THF (0.3 M, 300 mL) at 0 °C was added over 10 min a solution of **6** (12 g, 51 mmol in 50 mL of THF). The reaction mixture was stirred at room temperature for 15 h, after which time freshly distilled allyl bromide (3 equiv, 13 mL) was added and the solution was stirred for another 15 h at room temperature. Quenching with NH_4Cl (saturated) (50 mL) and usual workup as described above gave a syrup that was chromatographed (50% ethyl acetate in hexane) to afford 9.54 g (93%) of **7**: $[\alpha]_D$ −30.2° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.82−5.68 (m, 1H), 5.25−5.17 (m, 2H), 4.58 (s, 2H), 4.34 (dd, 1H, J = 8.8 and 8.7 Hz), 4.15−4.08, 3.95−3.87 and 3.67−3.52 (m, 6H), 3.32 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 157.9, 132.1, 118.3, 96.5, 66.4, 64.8, 45.0, 55.5, 54.1; IR υ_{max} 2890, 1720, 1390, 1200, 1100−1000, 890, 740 cm^{-1}; HRMS for $C_9H_{15}O_4N$ calcd 201.1003, found 201.1001.

(4*S*)-3-Allyl-4-(hydroxymethyl)oxazolidin-2-one (8). To a solution of oxazolidinone **7** (2.79 g, 13.9 mmol) in THF (1.3 mL) and water (12 mL) was slowly added a solution of 6 N HCl (28 mL). The mixture was stirred at 40 °C for 5 h and then poured into an equal volume of brine. Extraction with dichloromethane (10 × 40 mL) and ethyl acetate (5 times, 40 mL), drying over $MgSO_4$, and chromatography (ethyl acetate) gave alcohol **8** (2.1 g, 96%): $[\alpha]_D$ −44.1° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.79−5.71 (m, 1H), 5.29−5.20 (m, 2H), 4.34 (dd, 1H, J = 8.9, 8.8 Hz), 4.23 (dd, 1H, J = 8.7, 5.8 Hz), 4.12−4.05, 3.87−3.66 (m, 4H), 3.60 (dd, 1H, J = 11.9, 3.2 Hz), 3.30−3.10 (broad s, 1H); ^{13}C NMR ($CDCl_3$) δ 158.2, 131.6, 118.0, 64.3 and 59.7, 55.4, 44.3; IR υ_{max} 3380, 2880, 1420, 1230, 1060, 1015, 945, 905, 740 cm^{-1}; HRMS for $C_7H_{11}O_3N$ + H calcd 158.0817, found 158.0812; MS (FAB$^+$) *m*/*z* 158 (M^+ + H). Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.49; H, 7.26; N, 8.87.

(4*S*)-3′-(3-Allyl-2-oxooxazolidin-4-yl)acrylic Acid *tert*-Butyl Ester (9). To a solution of oxalyl chloride (0.67 mL, 1.15 equiv) in dichloromethane (20 mL) at −65 °C was added freshly distilled DMSO (1.13 mL, 2.4 equiv in 5 mL of CH_2Cl_2) over 2 min, and the reaction mixture was stirred for 5 more min at the same temperature. The alcohol **8** (1.04 g. in 5 mL of CH_2Cl_2) was then added into the reaction mixture over 5 min, and the stirring was continued for another 20 min after which triethylamine (3.7 mL, 4 equiv) was added and the solution brought to −15 °C over 1.5 h. [(*tert*-Butoxycarbonyl)-methylene]triphenylphosphorane (3.5 g, 1.4 equiv in 5 mL of CH_2Cl_2) was added to the mixture, and the temperature was allowed to reach 25 °C over 1.5 h. The reaction mixture was poured into brine (30 mL), and the solution was extracted with CH_2Cl_2 (3 × 50 mL), dried over $MgSO_4$, and chromatographed using 40% ethyl acetate in hexane to afford diene **9** (1.43g, 85%): $[\alpha]_D$ +2.3° (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.52 (dd, 1H, J = 15.6, 8.2 Hz), 5.84 (d, 1H, J = 15.6 Hz), 5.70−5.57 (m, 1H), 5.15−5.07 (m, 2H), 4.40−4.25, 4.06−3.99, 3.92, 3.41 (m, m, dd and dd 5H, first dd: J = 8.2, 5.7 Hz, second dd: J = 15.6, 7.5 Hz), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 163.9, 157.9, 141.0, 131.2, 127.7, 118.8, 81.0, 66.1, 55.8, 44.7, 27.7; IR υ_{max} 2990, 2930, 1760, 1715, 1410, 1370, 1305, 1255, 1225, 1155, 1060, 980, 930, 850, 765 cm^{-1}; MS (FAB$^+$) *m*/*z* 254 (M^+ + H), 198 (M^+ + H − C=C$(CH_3)_2$).

(7*S*,8*S*)-3-Oxo-6-[(trimethylstannyl)methyl]tetrahydropyrrolo[1,2-*c*]oxazol-7-yl]acetic Acid *tert*-Butyl Ester (10). To a refluxing solution of diene **9** (1.24 g) and trimethyltin chloride (1.28 g, 1.3 equiv) in 2-methyl-2-propanol (85 mL) were added a solution of sodium cyanoborohydride (1.28 g, 4.1 equiv) with a syringe pump and AIBN (90 mg, 10%) in methanol (15 mL) over a period of 2 h. After completion of the addition, the reaction mixture was heated under reflux for 30 min and then cooled to room temperature. Ammonium hydroxide (10% solution) was added until the solution became clear. The reaction mixture was then poured into a separatory funnel containing 200 mL of ether. The organic phase was washed two times with brine (30 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (30% ethyl acetate in hexane) gave 1.81 g (88%) of compound **10** and its C-4 isomer as a 2.8:1 *cis*/*trans* mixture: ^{1}H NMR ($CDCl_3$) δ 4.44 (dd, 1H, J = 9.1, 8.3 Hz, *cis*), 4.25 (dd, 1H, J = 9.3, 4.9 Hz, *trans*), 4.13 (dd, 1H, J = 9.1, 4.3 Hz, *cis*), 3.76−3.63 (m, 2H, *cis*), 3.33 (dd, 1H, J = 10.6, 8.5 Hz, *trans*), 2.96 (dd, 1H, J = 10.5, 9.2 Hz,

trans), 2.65−1.95, 1.78−1.55 (m, 5H, *cis*/*trans*), 1.36 (s, 9H), 1.19−0.58 (m, 2H, *cis*/*trans*), 0.03 (s, 9H, *cis*/*trans*); ^{13}C NMR ($CDCl_3$) δ *cis* 171.3, 161.1, 80.8, 68.0, 62.5, 44.8, 40.2, 53.6, 33.8, 27.8, 10.7, −9.9; *trans* 171.1, 160.7, 80.9, 68.2, 64.6, 50.0, 45.8, 52.4, 36.3, 13.4, −9.8; MS (NBA) *m*/*z* 364 ($M^+ + H - C{=}C(CH_3)_2$), 348 ($M^+ + H - C{=}C(CH_3)_2 - Me$). Anal. Calcd for $C_{16}H_{29}NO_4Sn$: C, 45.96; H, 6.99; N, 3.35. Found: C, 46.31; H, 7.08; N, 3.38.

(6*R*,7*S*,8*S*)-[6-(Dimethoxymethyl)-3-oxotetrahydropyrrolo[1,2-c]oxazol-7-yl]acetic Acid *tert*-Butyl Ester (11) and (6*S*,7*S*,8*S*)-[6-(Dimethoxymethyl)-3-oxotetrahydropyrrolo[1,2-*c*]oxazol-7-yl]acetic Acid *tert*-Butyl Ester (12). To a solution of **10** and its C-4 isomer (2.6 g) in methanol (125 mL) at 0 °C was added ceric ammonium nitrate (34 g, 10 equiv), portionwise over 30 min. The reaction mixture was stirred at room temperature for 15 h, poured into a separatory funnel containing 350 mL of ethyl acetate, and extracted with water (6 × 50 mL) and brine (2 × 50 mL). The organic phase was dried ($MgSO_4$) and concentrated. Flash chromatography (40% ethyl acetate in hexane, slow elution) gave the *cis*-dimethyl acetal **11** (733 mg, 38%) and *trans*-isomer **12** (335 mg, 17%). For **12**: $[\alpha]_D$ +5.2° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.46 (dd, 1H, J = 9.2, 8.0 Hz), 4.32 (dd, 1H, J = 9.2, 4.2 Hz), 4.20 (d, 1H, J = 5.9 Hz), 3.73 (ddd, 1H, J = 11.9, 7.8, 4.1 Hz), 3.56 (dd, 1H, J = 12.3, 5.1 Hz), 3.36, 3,34 (2 × s, 6H), 3.21 (dd, 1H, J = 12.2, 8.7 Hz), 2.68 (dd, 1H, J = 15.5, 3.1 Hz), 2.29−2.05 (m, 3H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.2, 160.8, 107.0, 81.0, 68.5, 64.7, 55.5, 54.8, 48.6, 46.5, 42.2, 38.2, 27.9; MS (FAB^+) 316 ($M^+ + H$) 284 ($M^+ + H$ − MeOH), 228 ($M^+ + H$ − MeOH − $CH_2{=}C(CH_3)_2$). For **11**: $[\alpha]_D$ +35.0° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.38 (dd, 1H, J = 9.1, 7.8 Hz), 4.18 (d, 1H, J = 4.5 Hz), 4.13 (dd, 1H, J = 9.1, 3.4 Hz), 3.75−3.63 (m, 2H), 3.31, 3.30 (2 × s, 6H), 3.20 (dd, 1H, J = 12.1, 4.7 Hz), 2.73−2.64, 2.49, 2.30−2.16 (m, dd, m, 4H, J = 15.8, 7.6 Hz), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.2, 161.3, 105.2, 80.9, 67.2, 63.1, 55.5, 54.3, 43.0, 41.6, 46.2, 33.2, 27.9; IR υ_{max} 2960, 2810, 1745, 1370, 1355, 1200, 1145, 1080, 1050 cm^{-1}; HRMS for $C_{15}H_{25}NO_6$ + H calcd 316.1760, found 316.1741; MS (FAB^+) *m*/*z* 316 ($M^+ + H$), 260 ($M^+ + H - CH_2{=}C(CH_3)_2$), 228 ($M^+ + H - CH_2{=}C(CH_3)_2$ − MeOH). Anal. calcd for $C_7H_{11}NO_3$: C, 57.13; H, 7.99; N, 4.44. Found: C, 57.00; H, 8.19; N, 4.45.

(6*R*,7*S*,8*S*)-(6-Formyl-3-oxotetrahydropyrrolo[1,2-*c*]oxazol-7-yl)acetic Acid *tert*-Butyl Ester (13). To a solution of **11** (676 mg) in dichloromethane (25 mL, 0.08 M) was slowly added bromodimethylborane (0.42 mL, 2 equiv) at −78 °C. The reaction mixture was stirred at the same temperature for 45 min and then transferred via canula into a solution of saturated sodium bicarbonate−THF (10 and 20 mL, respectively) with vigorous stirring. The solution was poured into a separatory funnel containig ethyl acetate (100 mL), and the organic phase was washed with saturated ammonium chloride (20 mL), and brine (25 mL), dried over $MgSO_4$, and concentrated to afford the crude aldehyde **13** (575 mg, quantitative), which was used as such in the next step: ^{1}H NMR ($CDCl_3$) δ 9.85, (d, 1H, J = 1.7 Hz), 4.50 (dd, 1H, J = 9.4, 7.7 Hz), 4.28 (dd, 1H, J = 9.4, 3.0 Hz), 3.75−3.63 (m, 2H), 3.61 (dd, 1H, J = 12.1, 4.1 Hz), 2.73−2.64, 2.49, 2.30−2.16 (m, dd, m, 4H, J = 15.8, 7.6 Hz), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$) δ: 198.4, 170.2, 160.3, 81.4, 67.3, 64.1, 57.5, 40.9, 44.8, 36.6, 27.7.

(6*R*,7*S*,8*S*)-[6-(1′-Hydroxyethyl)-3-oxotetrahydropyrrolo-[1,2-*c*]oxazol-7-yl]acetic Acid *tert*-Butyl Ester (14). Cerium trichloride (400 mg, 3.0 equiv, obtained by drying cerium chloride heptahydride at 160 °C and 1 mmHg for 6 h) was mixed with THF (10 mL), and the mixture was stirred at room temperature for 1 h. The suspension was cooled to −78 °C, a solution of MeLi (1.2M in ether, 1.31 mL, 2.9 equiv) was slowly added, and the resulting yellowish mixture was stirred for another 45 min. A solution of aldehyde **13** (143 mg) in THF (4 mL) was then added to the reaction mixture over 1 min. After the mixture was stirred at −78 °C for 25 min, saturated ammonium chloride (3 mL) was added and the mixture was extracted with ethyl acetate (30 mL). The organic phase was washed with saturated ammonium chloride (4 mL), saturated sodium bicarbonate (4 mL), and brine (5 mL), dried over $MgSO_4$, and concentrated. Flash chromatography (10−15% methanol in dichloromethane) afforded alcohol **14** (32mg, 65%): ^{1}H NMR ($CDCl_3$) δ 4.40 (dd, 1H, J = 9.2, 7.8 Hz), 4.17 (dd, 1H, J = 9.2, 3.5 Hz), 4.01 (ddd, 1H, J = 8.4, 6.3, 2.1 Hz), 3.85 (ddd, 1H, J = 9.8, 7.8, 3.5 Hz), 3.70 (dd, 1H, J = 11.7, 8.8 Hz), 3.35 (dd, 1H, J = 11.8, 4.2 Hz), 2.58 (dd, 1H, J = 16.0, 7.6 Hz), 2.47−2.31, 2.28−2.14 (m, 3H), 1.42 (s, 9H), 1.16 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 171.6, 161.5, 81.1, 67.5, 65.5, 63.1, 46.8, 43.1, 44.5 33.3 , 27.9, 22.6; HRMS for $C_{14}H_{23}NO_5$ + H calcd 286.1654, found 286.1664; MS (FAB^+) 286 ($M^+ + H$), 230 ($M^+ + H - CH_2{=}C(CH_3)_2$).

(6*R*,7*S*,8*S*)-(6-Acetyl-3-oxotetrahydropyrrolo[1,2-*c*]oxazol-7-yl)acetic Acid *tert*-Butyl Ester (15). To a solution of **14** (74 mg) in dichloromethane (3 mL, 0.1 M) and molecular sieves (3 Å) was added at room temperature *N*-methylmorpholine *N*-oxide (76 mg, 2.5 equiv) and tetrapropylammonium perruthenate (cat.). The reaction mixture was stirred for 30 min, filtered over Celite−silica gel, and concentrated. Flash chromatography (ethyl acetate) afforded ketone **15** (58 mg, 80%): $[\alpha]_D$ +57.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.45 (dd, 1H, J = 9.3, 7.7 Hz), 4.20 (dd, 1H, J = 9.2, 3.2 Hz), 3.87−3.80, 3.62−3.55 (m, 3H), 3.24 (dd, 1H, J = 12.0, 4.8 Hz), 2.43−2.23 (m, 3H), 2.19 (s, 3H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 209.5, 170.8, 161.1, 81.5, 66.8, 63.0, 52.3, 42.9, 32.1, 48.6, 33.2, 27.9; HRMS for $C_{14}H_{21}NO_5$ + H calcd 284.1498, found 284.1499; MS (FAB^+) *m*/*z* 284 ($M^+ + H$), 228 ($M^+ + H - CH_2{=}C(CH_3)_2$).

(6*S*,7*S*,8*S*)-(6-Isopropenyl-3-oxotetrahydropyrrolo[1,2-*c*]oxazol-7-yl)acetic Acid *tert*-Butyl Ester (16). To a suspension of zinc dust (110 mg, 12 equiv) in THF (1 mL) was added diiodomethane (75 μL, 6.5 equiv). After the mixture was stirred for 30 min, a solution $TiCl_4$ in dichloromethane (1.0 M, 240 μL, 2 equiv) was added, and the resulting dark brown solution was stirred for another 30 min at room temperature. Ether (5 mL) was added to the mixture, and the organic phase was washed with 10% HCl (1 mL) and brine (1 mL), dried over $MgSO_4$, and concentrated. Flash chromatography (60% ethyl acetate in hexane) afforded **16** (23 mg, 63%) as a white solid. Recrystallization from petroleum ether afforded crystals suitable for X-ray analysis: mp 87 °C; $[\alpha]_D$ −8.8° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.95, 4.76 (2 × s, 2H), 4.56 (dd, 1H, J = 9.1, 8.3 Hz), 4.24 (dd, 1H, J = 9.2, 4.8 Hz), 3.86−3.79 (m, 2H), 3.18 (dd, 1H), 3.02, 2.43−2.10 (dd, m, 4H, J = 14.0, 7.7 Hz), 1.74 (s, 3H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.4, 161.4, 142.3, 114.4, 81.2, 68.8, 63.5, 49.2, 43.2, 49.7, 34.4, 28.0, 22.5; X-ray crystal structure data have been deposited with the Cambridge Crystallographic Data Centre.[22]

(2*S*,3*R*,4*S*)-2-(Hydroxymethyl)-4-isopropenyl-3-[(methoxycarbonyl)methyl]pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (17). Compound **16** (34 mg) was dissolved in dioxane (0.75 mL) and an aqueous solution of NaOH (3N, 0.3 mL). The reaction mixture was brought to 70 °C and kept at that temperature for 16 h. After the mixture was cooled to 0 °C, a solution of Boc_2O (70 mg, 2.4 equiv) in dioxane (0.75 mL) was added and the reaction mixture stirred at room temperature for 2 h. After water (2.5 mL) was added, citric acid (10% solution) was used to adjust the pH to around 3−4 and the product was extracted with ethyl acetate (15 mL). The organic phase was dried ($MgSO_4$) and concentrated. The crude acid was then redissolved in ether (10 mL), and diazomethane was added at 0 °C. After the reaction was completed, the excess diazomethane was removed, the solvent was evaporated under reduced pressure, and the residue was chromatographed (60% ethyl acetate in hexane) to afford compound **17** (16 mg, 43%): $[\alpha]_D$ −41.7° (*c* 0.69, $CHCl_3$) [lit.[6h] $[\alpha]_D$ −38.0° (*c* 0.2, $CHCl_3$)]; $_1$H NMR ($CDCl_3$) δ 4.91, 4.67 (m, 2H), 3.80−3.50, 3.46 (m, d, 8H, J = 7.7 Hz), 2.96−2.88, 2.56−2.42 (m, 2H), 2.33−2.16, (m, 2H), 1.70 (s, 3H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.8, 156.8, 142.0, 113.0, 80.6, 66.9, 65.1, 51.8, 48.9, 45.6, 39.3, 33.1, 28.4, 22.2; HRMS for $C_{16}H_{27}NO_5$ + H calcd 314.1968, found 314.1954; MS (FAB^+) *m*/*z* 314.2 ($M^+ + H$), 282.2 ($M^+ + H$ − MeOH), 258.3 ($M^+ + H - CH_2{=}C(CH_3)_2$), 226.1 ($M^+ + H$ − MeOH − $CH_2{=}C(CH_3)_2$), 214.1 ($M^+ + H - CH_2{=}C(CH_3)_2 - CO_2$).

1-(*tert*-Butyloxycarbonyl)-α-kainic Acid Dimethyl Ester (18). Compound **17** (15 mg, 0.05 mmol) was dissolved in acetone (0.05 M, 1 mL) and the solution cooled to 0 °C prior to the addition of freshly prepared Jones reagent (8 equiv). After the solution was stirred for 1 h, 2-propanol (few drops) was added and the mixture stirred for 15 min. The product was

extracted with ethyl acetate (5 mL). The organic phase was dried ($MgSO_4$) and concentrated. The crude acid was redissolved in ether (10 mL), and diazomethane was added at 0 °C. After the reaction was completed, the excess diazomethane removed, and the solvent was evaporated under reduced pressure. Flash chromatography (40% ethyl acetate in hexane) afforded compound **18** (9 mg, 56%): $[\alpha]_D$ 18.9° (*c* 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.93, 4.70 (2 × s, 2H), 4.17, 4.07 (2 × d, 1H, J = 3.4, 3.6 Hz), 3.77−3.62 (m, 7H), 3.51−3.40 (m, 1H), 3.08−2.97 and 2.91−2.81 (2 × m, 2H), 2.42−2.25 (m, 2H), 1.70 (s, 3H), 1.48 and 1.41 (2 x s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.6, 172.4, 172.3, 172.2, 154.2, 153.6, 141.3, 141.2, 113.4, 113.1, 80.2, 63.9, 63.6. 52.3, 52.1, 51.7, 47.8, 47.5, 45.9, 45.2, 41.8, 40.8, 32.9, 28.3, 28.1, 27.9, 22.3, 22.1; MS (EI) m/z 342.3 (M^+ + H), 286.3 (M^+ + H − $(CH_3)_2$=CH_2), 242 (M^+ + H − $(CH_3)_2$=CH_2 − CO_2); HRMS calcd for $C_{17}H_{27}O_6N$ + H 342.1916, found 342.1902.

(−)-α-Kainic Acid (1). Compound **18** (9 mg) was dissolved in a mixture of THF (0.25 mL) and a 2.5% solution of KOH (1 mL). The reaction mixture was stirred for 12 h at room temperature, and a solution of citric acid (10%) was added untill pH ∼3. The diacid was extracted with ethyl acetate and the solvent dried (Na_2SO_4) and removed under reduced pressure. Dichloromethane (1 mL) and TFA (12 equiv) were added, and the reaction mixture was stirred for 12 h. After removal of the solvent, the crude product was added, to a column containing Dowex-50 H^+ (WX8-200, 8% cross-linking, 100−200 wet mesh). Elution with NH_4OH (1 N), evaporation, and treatment with Amberlite CG-50 (100−200 dry mesh)[6e] afforded after recrystallization α-kainic acid (**1**) (4.5 mg, 80%): mp 242−244 °C (lit.[6i] mp 243−244); $[\alpha]_D$ −13.9° (*c* 0.18, H_2O) [lit.[6i] $[\alpha]_D$ −14.2° (*c* 0.18, H_2O)]; ^{1}H NMR (D_2O) δ 5.02, 4.73 (2 × s, 2H), 4.06 (d, 1H, J = 3.1 Hz) 3.61 (dd, 1H, J = 11.6, 7.3 Hz), 3.43 (dd, 1H, J = 11.7, 10.7 Hz), 3.08−2.94 (m, 2H), 2.31 (dd, 1H, J = 15.7, 6.4 Hz), 2.19 (dd, 1H, J = 15.7, 8.1 Hz), 1.76 (s, 3H); ^{13}C NMR (D_2O) δ 179.6, 174.3, 141.0, 113.9, 66.7, 47.2, 46.6, 42.4, 36.1, 23.0; MS (EI) m/z 214 (M^+ + H).

(4′*S*,2*E*)-4′-[(Methoxymethoxy)methyl]-3′-(3-methylpenta-2,4-dienyl)-2′-oxooxazolidin-2-one (19). To a suspension of sodium hydride (3 equiv, 1.65 g, 41.2 mmol) in THF (0.1 M, 140 mL) at 0 °C was added over 10 min a solution of **6** (3.26 g, 13.9 mmol) in 10 mL of THF. The reaction mixture was stirred at room temperature for 15 h, after which time freshly prepared 5-bromo-3-methylpenta-1,3-diene (3 equiv, 13 mL)[21,22] was added and the solution was stirred for another 15 h at room temperature. Quenching with NH_4Cl (saturated) (10 mL) and usual workup (ethyl acetate, brine) followed by chromatography (40% ethyl acetate in hexane) gave **19** (2.06 g, 62%): $[\alpha]_D$ −17.2° (*c* 1.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.31 (dd, 1H, J = 17.4, 10.7 Hz), 5.42 (dd, 1H, J = 7.3, 7.3 Hz), 5.17, 5.02 (2 × d, 2H, J = 17.4, 10.7 Hz), 4.57 (s, 2H), 4.30 (dd, 1H, J = 8.8, 8.7 Hz), 4.20−4.06, 3.90−3.82 and 3.56−3.53 (m, 6H), 3.31 (s, 3H), 1.78 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 158.1, 140.2, 125.5, 137.8, 113.3, 96.6, 66.8, 64.8, 40.3, 55.5, 54.3, 11.8; IR υ_{max} 2900, 1740, 1420, 1410, 1240, 1210, 1140, 1100−1030, 903, 750 cm^{-1}.

(4′*S*,2*E*)-4′-(Hydroxymethyl)-3′-(3-methylpenta-2,4-dienyl)-2′-oxooxazolidin-2-one (20). Bromotrimethylsilane (6 mL, 6 equiv, 45 mmol) was added at −35 °C into a solution of **19** (1.87 g, 7.8 mmol) in dichloromethane (80 mL, 0.1 M), and the reaction mixture was stirred for 1.5 h at the same temperature. It was left for another 0.5 h at 0 °C and then added into a saturated solution of $NaHCO_3$ with a cannula with vigorous stirring. Extraction with ethyl acetate (200 mL) and usual processing of the organic phase, evaporation, and chromatography (60% ethyl acetate in hexane to 100% ethyl acetate) afforded **20** (904 mg, 59%) and starting material **19** (493 mg, 26%): $[\alpha]_D$ −30.0° (*c* 1.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.29 (dd, 1H, J = 17.4, 10.7 Hz), 5.40 (dd, 1H, J = 7.0, 6.9 Hz), 5.16 and 5.00 (2 × d, 2H, J = 17.4, 10.7 Hz), 4.30−4.02 and 3.90−3.53 (m, 8H), 1.76 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 158.7, 140.0, 125.1, 137.8, 113.2, 64.7, 60.4, 55.9, 39.9, 11.6.

(4′*S*,2*E*)-3″-[3′-(3-Methylpenta-2,4-dienyl)-2′-oxooxazolidin-4′-yl]acrylic Acid Methyl Ester (21). To a solution of oxalyl chloride (0.47 mL, 1.15 equiv) in dichloromethane (15 mL) at −65 °C was added freshly distilled DMSO (0.70 mL, 2.2 equiv in 3 mL of CH_2Cl_2) over 2 min, and the reaction mixture was then stirred for 5 min more at the same temperature. The alcohol **20** (920 mg, 4.7 mmol) in CH_2Cl_2 (5 mL) was then added to the reaction mixture over 5 min, and stirring was continued for another 20 min, after which time triethylamine (2.35 mL, 3.7 equiv) was added and the solution cooled to −15 °C over 1.5 h. Methyl (triphenylphosphoranylidene)acetate (2.34 g, 1.5 equiv) was added to the mixture and the temperature brought to 25 °C over 1.5 h. The reaction mixture was poured into brine (30 mL), extracted with CH_2Cl_2 (3 × 50 mL), and dried over $MgSO_4$, and the residue was chromatographed with 60% ethyl acetate in hexane to afford **21** (940 mg, 80%): ^{1}H NMR ($CDCl_3$) δ 6.74 (dd, 1H, J = 15.6, 8.3 Hz), 6.33 (dd, 1H, J = 17.4, 10.7 Hz), 6.00 (d, 1H, J = 15.6 Hz), 5.38 (dd, 1H, J = 7.1, 7.1 Hz), 5.20, 5.06 (2 × d, 2H, J = 17.4, 10.7 Hz), 4.46−4.31, 4.29−4.12, 4.01−3.96, 3.76−3.68 (m, dd, dd and m, 8H, first dd: J = 15.6 and 6.2 Hz, second dd: J = 8.2, 6.4 Hz), 1.73 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 165.3, 157.5, 142.9, 140.1, 125.5, 124.3, 138.6, 113.8, 66.2, 56.3, 51.9, 40.2, 11.9.

(8′*S*,1*E*)-[6′-[1-Methyl-3-(trimethylstannyl)propenyl]-3′-oxotetrahydropyrrolo[1′,2′-*c*]oxazol-7′-yl]acetic Acid Methyl Ester (22). To a refluxing solution of triene **21** (268 mg, 1.07 mmol) and trimethyltin chloride (280 mg, 1.3 equiv) in 2-methyl-2-propanol (30 mL) was added a solution of sodium cyanoborohydride (280 mg, 4.1 equiv) and AIBN (20 mg, 10%) in methanol (5 mL) over a period of 1 h with a syringe pump. After completion of the addition, the reaction mixture was kept under reflux for 2 h then cooled to room temperature. Ammonium hydroxide (10% solution) was added until the solution became clear. The reaction mixture was poured into a separatory funnel containing 100 mL of ether. The organic phase was washed twice with brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (40% ethyl acetate in hexane) gave **22** and its C-4 epimer (257 mg, 52%) as an unseparable 2.8:1 mixture of *trans* and *cis* isomers: ^{1}H NMR ($CDCl_3$) δ 5.49−5.32 (m, 1H, cis/trans), 4.48−4.10 (m, 2H, cis/trans), 3.75−3.52, 3.32−1.92 (m, 10H), 1.68−1.37 (m, 5H), +0.18 to −0.10 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 172.6 (cis), 172.3 (trans), 161.1 (cis), 160.6 (trans), 128.3 (trans), 127.9 (cis), 125.9 (cis), 124.3 (trans), 68.6 (cis), 67.6 (trans), 64.3, 63.5, 56.8, 51.6, 51.2 43.6, 42.9 (cis and trans), 49.4 (cis), 48.2 (trans), 34.5 (trans), 33.0 (cis), 15.3 (cis), 12.8 (trans), 12.7 (cis), 11.4 (trans), −9.8 (cis), −9.9 (trans); HRMS for $C_{16}H_{27}O_4NSn$ +H calcd 416.0884, found 416.0904.

(6*S*,7*R*,8*S*)-(6-Acetyl-3-oxotetrahydropyrrolo[1,2-*c*]oxazol-7-yl)acetic Acid Methyl Ester (23) and (6*R*,7*R*,8*S*)-(6-Acetyl-3-oxotetrahydropyrrolo[1,2-*c*]oxazol-7-yl)acetic Acid Methyl ester (24). Ozone was bubbled through a solution containing **22** and its C-4 isomer (210 mg, 0.5 mmol) in methanol/dichloromethane (1:1, 5 mL total) at −78 °C for 20 min. After removal of excess O_3, by bubbling argon through the reaction mixture for 5 min, methyl sulfide (1 mL) was added, and the solution was stirred at 0 °C for 1 h. The solvent was removed under reduced pressure and the residue chromatographed (60% ethyl acetate in hexane) to give 57 mg (47%) of the *trans*-ketone **23** and 27 mg (22%) of the *cis*-ketone **24**. For **23**: $[\alpha]_D$ −17.9° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.51 (dd, 1H, J = 9.3, 7.8 Hz), 4.39 (dd, 1H, J = 9.3, 3.8 Hz), 3.82−3.65 (m, 5H), 3.52 (dd, 1H, J = 11.8, 9.8 Hz), 3.10−3.04 (m, 1H), 2.61−2.53 (m, 2H), 2.37 (dd, 1H, J = 17.3, 9.8 Hz), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 205.5, 171.7, 160.5, 67.8, 64.2, 57.8, 51.9, 41.8, 29.0, 47.2 , 35.5; IR υ_{max} 2940, 2905, 1740, 1385, 1350, 1200, 1165, 1075, 995 cm^{-1}; HRMS for $C_{11}H_{15}NO_5$ M + H calcd 242.1028, found 242.1041; MS (EI) m/e 242 (M^+ + H).

(6*S*,7*R*,8*S*)-(6-Isopropenyl-3-oxotetrahydropyrrolo[1,2-*c*]oxazol-7-yl)acetic Acid Methyl Ester (25). BuLi in hexane (2.5 M, 0.165 mL) was added at −78 °C to a suspension of Ph_3PMeBr (154 mg) in THF (2.5 mL). The mixture was

(21) Oroshnik, W. *J. Am. Chem. Soc.* **1956**, *78*, 2651.

(22) The author has deposited atomic coordinates for **16** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

stirred at room temperature for 20 min and then brought to −60 °C prior the addition of a solution of ketone **23** (52 mg) in THF (2.5 mL). The reaction mixture was kept at −60 °C for 1 h and warmed to 25 °C over a period of 0.5 h, after which time it was filtered over Celite−silica gel. The solvent was removed under reduced pressure and the crude product chromatographed (60% ethyl acetate in hexane) to afford a white solid (43 mg, 83%): $[\alpha]_D$ +4.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.87−4.85, 4.83 (broad s and s, 2H), 4.50 (dd, 1H, *J* = 9.4, 7.9 Hz), 4.38 (dd, 1H, *J* = 9.4, 4.2 Hz), 3.82−3.73 (m, 1H), 3.65 (s, 3H,), 3.47−3.33 (m, 2H), 2.71, 2.55, 2.24−2.04 (dd, dd, m, 4H, first dd: *J* = 19.4, 7.7 Hz, second dd: *J* = 15.6, 3.6 Hz), 1.68 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.2, 160.7, 141.1, 114.7, 67.7, 64.6, 54.9, 51.8, 43.1, 48.5, 34.8, 18.0; HRMS for $C_{12}H_{17}NO_4$ + H calcd 240.1236, found 240.1240; MS (EI) *m*/*e* 240 (M^+ + H).

(2*S*,3*R*,4*S*)-2-(Hydroxymethyl)-4-isopropenyl-3-[(methoxycarbonyl)methyl]pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (26). Compound **25** (39 mg) was dissolved in a mixture of dioxane (0.5 mL) and aqueous NaOH (3 N, 0.4 mL). The reaction mixture was kept at 60 °C for 16 h. After the mixture was cooled to 0 °C, a solution of Boc_2O (85 mg, 2.4 equiv) in dioxane (0.7 mL) was added, and the reaction mixture was stirred at room temperature for 2 h. After the addition of water (2.5 mL), citric acid (10% solution) was used to bring the pH to around 3−4, and the product was extracted with ethyl acetate (10 mL). The organic phase was dried ($MgSO_4$) and concentrated. The crude acid was then redissolved in ether (10 mL), and diazomethane was added at 0 °C. After the reaction was completed, excess diazomethane was removed and the solvent was evaporated under reduced pressure. Flash chromatography (40% ethyl acetate in hexane) afforded compound **26** (45 mg, 88%): $[\alpha]_D$ −27.8° (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.86−4.84 (m, 2H), 3.81−3.60 and 3.12 (m, dd, 8H, *J* = 11.0, 10.9 Hz), 2.54-2.41, 2.23−2.19 (m, 4H), 1.69 (s, 3H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.2, 156.3, 141.5, 114.2, 80.4, 66.1, 65.7, 51.5, 50.8, 40.3, 50.4, 35.9, 18.5; MS (EI) *m*/*z* 314.5 (M^+ + H), 282.5 (M^+ + H − MeOH), 258.3 (M^+ + H − CH_2=$C(CH_3)_2$), 226.1 (M^+ + H − MeOH − CH_2=$C(CH_3)_2$), 214.1 (M^+ + H − CH_2=$C(CH_3)_2$ − CO_2).

1-(*tert*-Butyloxycarbonyl)allokainic Acid Dimethyl Ester (27). Compound **26** was oxidized and esterified following the same procedure described above for kainic acid. Flash chromatography (30% ethyl acetate in hexane) afforded **27** (36 mg, 84%): $[\alpha]_D$ −37.6° (*c* 0.37, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.89−4.82 (m, 2H), 3.96 and 3.91 (2 × d, 1H, *J* = 8.2, 8.8 Hz, 2 rotamers), 3.74−3.61 (m, 7H), 3.31 (dd, 1H, *J* = 10.9, 10.7 Hz), 2.66−2.39 (m, 4H), 1.71 (s, 3H), 1.44 and 1.39 (2 × s, 9H); ^{13}C (400 MHz, $CDCl_3$) δ 172.3, 172.0, 171.1, 152.8, 140.5, 140.4, 114.1, 79.8, 79.7, 64.0, 63.6, 51.7, 51.5, 51.2, 51.1, 50.4, 50.3, 49.8, 49.3, 42.7, 42.0, 35.2, 35.0, 29.2, 28.0, 27.8, 27.7, 27.5, 18.3, 18.2; HRMS for $C_{17}H_{27}NO_6$ + H calcd 342.1916, found 342.1906.

Allokainic Acid (2). Allokainic acid (**2**) was obtained following the same procedure as for kainic acid (**1**). Thus, 33 mg of compound **27** was subjected to the same reactions described for **18**. The crude product was passed through a column containing Dowex-50(H^+). Elution with NH_4OH (1 N), evaporation, and treatment with Amberlite CG-50[6e] gave **2** (13 mg, 65%): mp 239−240 °C (lit.[7f] mp 238−242 °C); $[\alpha]_D$ 7.0° (*c* 0.2, H_2O) [lit.[7f] $[\alpha]_D$ 7.4° (*c* 0.7, H_2O)]; ^{1}H NMR (D_2O) δ 5.01 (s, 2H), 3.96 (d, 1H, *J* = 8.7 Hz) 3.56 (dd, 1H, *J* = 10.9, 8.1 Hz), 3.36 (dd, 1H, *J* = 11.4, 11.0 Hz), 2.95−2.57 (m, 4H), 1.77 (s, 3H); ^{13}C NMR (400 MHz, D_2O) δ 177.4, 174.0, 141.0, 116.0, 65.4, 52.1, 48.7, 42.6, 37.5, 18.2; MS (EI) *m*/*z* 214 (M^+ + H); HRMS for $C_{10}H_{16}O_4N$ calcd 214.1079, found 214.1069.

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra of **8**−**13**, **15**, **16**, **1**, **20**, **21**, **23**, **25**, and **2** (29 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.

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