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Total Syntheses of (−)-α-Kainic Acid and (+)-α-Allokainic Acid via Stereoselective C−H Insertion and Efficient 3,4-Stereocontrol

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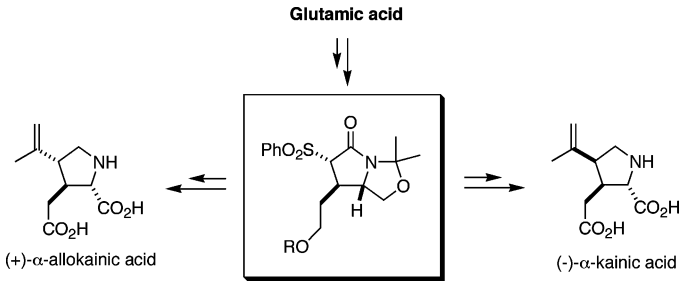

Reported herein is a novel approach to the total syntheses of (−)-α-kainic acid and (+)-α-allokainic acid, where the stereochemistries on C(2), C(3), and C(4) of the pyrrolidine core were introduced efficiently and selectively. A regio- and stereoselective C−H insertion reaction was utilized to prepare the γ-lactam as an intermediate. A Michael-type cyclization of phenylsulfone with a conjugated acetylenic ketone was developed to prepare the tricyclic ketone as a key intermediate for (−)-α-kainic acid. Subsequently, a stereoselective dephenylsulfonylation was carried out successfully to secure the cis relationship at C(3) and C(4) centers. An unprecedented acetylation on the phenylsulfone, followed by a stereoselective dephenylsulfonylation, secured the trans relationship at C(3) and C(4) centers in (+)-α-allokainic acid.

Introduction

Kainoids (**1**), which are nonproteinogenic amino acids consisting of *trans*-2,3-dicarboxylic acids on a pyrrolidine core structure, are an important class of neuroexcitatory amino acid receptors. In particular, the natural product (−)-α-kainic acid (**2**), isolated from the Japanese marine *Digenea simplex*[1] in 1953, shows potent inhibition of neurotransmitting activities of the central nervous system (CNS) along with its C-4 epimer, (+)-α-allokainic acid (**3**) (Figure 1). Owing to its pronounced biological activities, such as the anthelmintic effect,[2] as well as neuroexcitatory properties,[3] (−)-α-kainic acid has been widely used by the neuropharmacological community in the study of epilepsy, Alzheimer's disease,[4] and Huntington's chorea.[5] Recently, a worldwide shortage[6] of natural kainic acid triggered the development of the practical synthesis of kainic acid. In addition, the kainoids received considerable attention from synthetic chemists because of their structural uniqueness, including a highly functionalized trisubstituted pyrrolidine ring with three contiguous stereogenic centers. One of the main

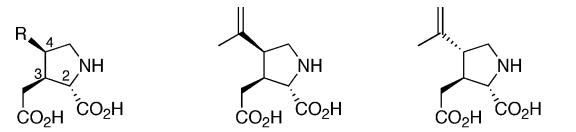

FIGURE 1.

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

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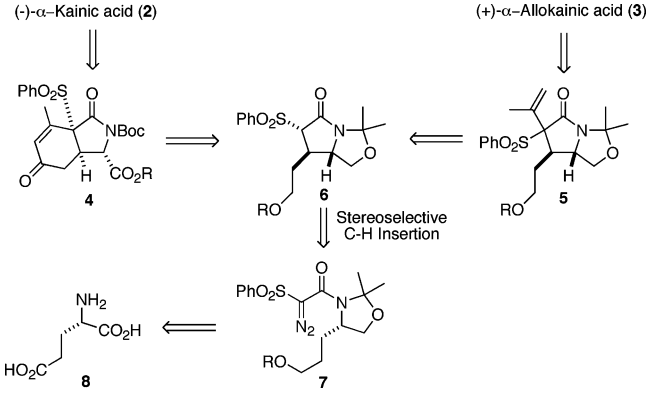
challenges of the synthesis is the installation of *cis*-3,4 stereochemistry in kainic acid, which is a crucial factor for biological activity.[7] Thus, a number of syntheses of (−)-α-kainic acid (**2**)[8] and (+)-α-allokainic acid (**3**)[9] have been reported over the past two decades since Oppolzer's first enantioselective total synthesis of kainic acid.[10] In this account, we would like to discuss an efficient synthetic route to establish the *cis*-3,4 stereochemistry embedded in (−)-α-kainic acid (**2**) along with a facile approach to (+)-α-allokainic acid (**3**).

Over the recent years, the Rh(II)-catalyzed intramolecular C−H insertion reaction has emerged as a prevailing strategy for the construction of numerous cyclic compounds[11] including *β*-, *γ*-lactams.[12] We also reported an efficient methodology to synthesize chiral *γ*-lactams from α-amino acids via stereoselective C−H insertion.[13] Utilizing this protocol, the *γ*-lactam **6** could be prepared from (L)-glutamic acid (**8**), securing the pyrrolidine core of kainoids. This encouraged us to undertake the syntheses of **2** and **3**. As outlined in the synthetic strategy in Scheme 1, it was beneficial for us to employ our C−H insertion protocol as a key method to prepare *γ*-lactam **6**, which can easily be converted to the pyrrolidine core. Therefore, this synthetic endeavor would take advantage of stereogenic induction originating from an amino acid without using any chiral auxiliaries. For the challenging *cis*-C3, C4 conformation in the main target molecule, (−)-α-kainic acid, the bicyclic phenylsulfone **4** was envisioned as a key intermediate after understanding that syn-fashioned dephenylsulfonylation of isopropenylated compound **5** was extremely difficult. Therefore, the desired stereochemistry for (−)-α-kainic acid (**2**) would be introduced efficiently from intermediate **4** via a stereoselective dephenylsulfonylation. As Clayden demonstrated with a similar cyclohexanone substrate to ultimately furnish the isopropenyl moiety,[8f] we envisioned a regioselective Baeyer−Villiger oxidation of dephenylsulfonylated cyclohexenone.[14] An intramolecular Michael-type cyclization[15] reaction of the ynone would facilitate ring formation to secure **4**. Comparatively, (+)-α-allokainic acid (**3**) could be available from the isopropenylated lactam **5**, which could be prepared from bicyclic lactam **6** using the unprecedented acetylation reaction on the α-position of the lactam ring.

SCHEME 1. Synthetic Strategy for (−)-α-Kainic Acid (2) and (+)-α-Allokainic Acid (3)



Results and Discussion

We have developed a Rh(II) catalyzed intramolecular C−H insertion of α-diazo-α-(phenylsulfonyl)-acetamides to afford *γ*-lactams with high regio- and stereoselectivity. This methodology was governed by the α-phenylsulfonyl moiety, which presumably stabilized the electrophilic carbenoid carbon during cyclization, resulting in selective formation of the *γ*-lactam via a relatively late transition state.[16] Encouraged by these results, various stereoselective chiral *γ*-lactams (pyrrolidinones) were obtained using α-amino acids as versatile chiral starting materials because they possess a variety of fuctional groups and are commercially available, usually in both enantiomeric forms. As shown in Table 1, cyclization precursors **9** and **11** were prepared from (L)-α-amino acids and (D)-α-amino acids, respectively, and then subjected to Rh(II)-catalyzed C−H insertion cyclization. Remarkably, the diazo compounds **9** and **11** were smoothly converted to the desired *γ*-lactams **10** and **12** as single stereoisomers in high yields without any byproducts such as *β*-lactams.

The observed stereochemical outcomes are rationalized in Scheme 2. The cyclizations were highly regio- and stereoselective affording functionalized chiral *γ*-lactam motifs in high yields. The gem-dimethyl moiety forces the diazo-intermediate to adopt an *s*-cis conformation, which is the only conformation suitable for C−H insertion. In the absence of the gem-dimethyl

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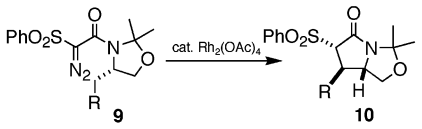
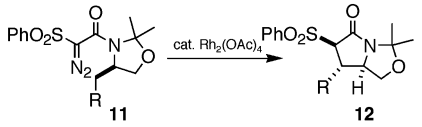
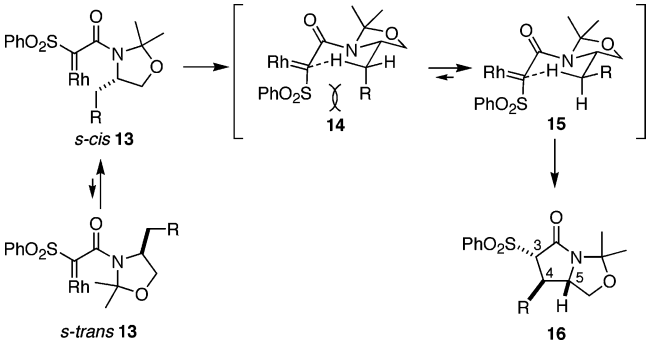
TABLE 1. C−H Insertion of α-Diazo Compounds Derived from Various α-Amino Acids

entry	R	reactant	yield (%)	product
				
1	Et	**9a**	92	**10a**
2	Ph	**9b**	91	**10b**
3	O^{t}Bu	**9c**	86	**10c**
				
4	Et	**11a**	95	**12a**
5	OTBS	**11b**	97	**12b**

SCHEME 2

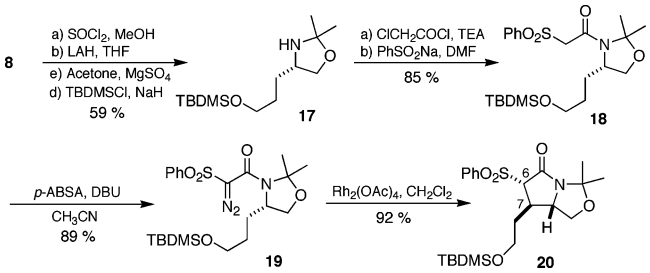


moiety, the unfavorable *s*-trans conformer **13** is predominant and C−H insertion does not occur.[17] On the basis of these results, conformational factors rather than α-substituents play a key role in the insertion of the rigid cyclic system.

There are two possible transition states, **14** and **15**, where the "R" group can be located in either the pseudoaxial or the pseudoequatorial positions, respectively.[18] The former case experiences a severe 1,3-diaxial nonbonded interaction, making this transition state less favorable. In the latter case, the large group occupies an equatorial position, which leads to relative stereochemistries at C-3, C-4, and C-5 of compound **16**, as shown in Scheme 2. The newly generated stereochemical senses at C-3 and C-4 were induced by the chirality of the α-amino acid during the insertion reaction.

In an application toward kainoids, preparation of the chiral γ-lactam **20** began with the regioselective formation of five-membered N,O-acetonide **17** from the amino diol, prepared from (L)-glutamic acid in two steps by a known procedure (Scheme 3).[19] The remaining alcohol group in the acetonide was protected with TBDMS using McDougal conditions,[20] resulting in the

SCHEME 3. Synthesis of γ-Lactam 20 *via* C−H Insertion



formation of **17**. The amine compound **17** was subjected to a chloroacetylation reaction, followed by displacement of chloride with the phenylsulfonyl group to produce the phenylsulfone **18**. The subsequent diazo transfer using *p*-ABSA produced C−H insertion precursor **19**. Intramolecular C−H insertion of diazo compound **19** then gave the desired trans-γ-lactam **20** as a single isomer in 92% yield with excellent regio- and stereoselectivities. The configuration of the two newly generated stereocenters, C-6 and C-7 of γ-lactam **20** was unambiguously elucidated and discussed briefly in our previous reports.[13]

Upon obtaining the bicyclic γ-lactam **20**, the next challenging goal was the introduction of the isopropenyl group onto C-6 of the γ-lactam **20**. Moreover, the stereochemistry at C-6, which would bear the isopropenyl group, was one of the key issues for this synthesis because the critical step, dephenylsufonylation, would produce (−)-α-kainic acid (**2**) or (+)-α-allokainic acid (**3**) depending on the stereochemical outcome. First, the acetylation of the phenylsulfone was carried out efficiently, giving **21** as a white solid under the optimized conditions utilizing Ac_2O and NaH in THF solution (Scheme 4). The reaction was regio- and stereoselective, offering only one diastereomer while the new stereochemistry was assigned on the basis of the previous similar examples.[13d] Next, attention was paid to the vinylation of the carbonyl group in acetyl compound **21**. However, typical olefination protocols including Wittig,[21] Tebbe,[22] Lombardo, and Takai[23] were not effective mainly because of rapid deacetylation. As an alternative, triflate **22** was prepared by treating compound **21** with Tf_2O and KHMDS.[24] Methylation of triflate **22** was effected by a Negishi type Pd(0)-catalyzed alkylation protocol,[25] where dimethyl zinc was successfully employed as a coupling partner to produce the isopropenyl compound **23**.[26] From the isopropenylated compound **23**, a stereoselective dephenylsulfonylation became the focus of the next part of the synthesis. We anticipated syn-fashioned dephenylsulfonylation to generate the cis compound **24** owing to the probable kinetic protonation of the incipient carbanionic species. However, a myriad of different conditions resulted in consistent formation of the trans intermediate **25**, presumably via a thermodynamically driven pathway. The stereochemical assignment of compound **25** was made on the basis of ^{1}H NMR coupling constant analysis, and it was proved that the product **25** had the appropriate stereochemistry for (+)-α-allokainic acid (**3**) by later completing the total synthesis (vide infra). The coupling constant (*J*) of the C6

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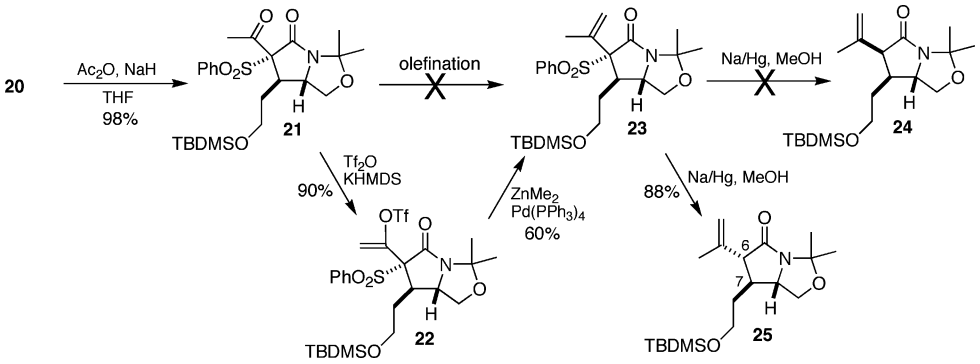
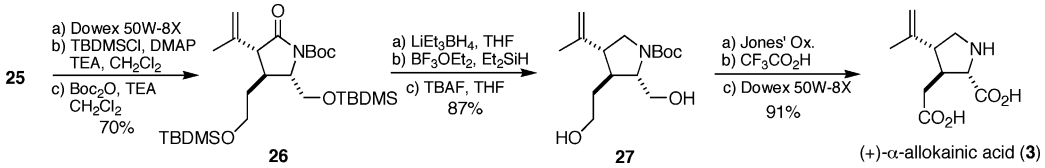
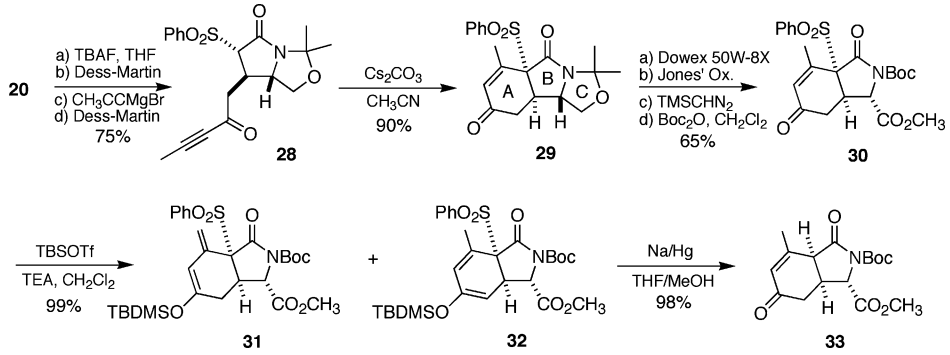
SCHEME 4. Isopropenylation and Dephenylsulfonylation



SCHEME 5. Synthesis of (+)-α-allokainic Acid (3)



SCHEME 6. Cyclization and Stereoselective Dephenylsulfonylation



proton was 12.8 Hz, similar to natural products, implying a high possibility of a trans relationship with the C7 proton.

With the successful isolation of *trans*-C6, C7 conformational product **25**, we then embarked on the synthesis of (+)-α-allokainic acid (**3**) as depicted in Scheme 5. The acetonide in compound **25** was unmasked by using Dowex 50W-8X in boiling MeOH, which resulted in simultaneous loss of TBDMS groups. After both hydroxyl groups were masked again with TBDMS groups, subsequent BOC protection furnished amide **26**.

Next, the Rubio method[27] was employed to reduce the carbonyl selectively without harming the alkene. The BOC protected amide **26** was treated with superhydride at −78 °C, resulting in a high yield of the hemiaminal compound. Consecutive reaction with $BF_3{\cdot}OEt_2$ in the presence of Et_3SiH provided the reduced pyrrolidine compound, which was subjected to TBDMS removal to provide diol **27**. Jones' oxidation and subsequent deprotection of the BOC group using TFA gave the crude (+)-α-allokainic acid (**3**). After purification with ion-exchange resin, the pure (+)-α-allokainic acid (**3**) was obtained successfully. Spectroscopic data were identical to the reported data,[10] and the physical data such as specific rotation and the high-resolution mass spectrum were also satisfactory.[10]

Since we were unable to synthesize (−)-α-kainic acid (**2**) via syn-fashioned dephenylsulfonylation of compound **23**, we directed our attention toward a new strategy for the stereoselective installation of the *cis*-C3,C4 relationship to achieve the synthesis of (−)-α-kainic acid (**2**). For this purpose, we envisioned bicyclic compound **4** as an intermediate for stereoselective dephenylsulfonylation. Thus, compound **20** was converted to phenylsulfone **28**, containing a conjugated acetylenic ketone (Scheme 6). First, the TBDMS group was removed using TBAF, and the resulting alcohol was oxidized by Dess−Martin periodinane.[28] Addition of 1-propynylmagnesium bromide delivered the secondary alcohol, which was then oxidized to ynone **28** using Dess−Martin periodinane. Subsequently, we carried out the Michael-type cyclization[28] of compound **28** using Cs_2CO_3 as a base. This reaction proceeded readily to provide the desired tricyclic lactam **29** successfully with high regio- and stereoselectivities to yield one diastereomer. It was believed that the stereochemistry would be A/B cis junction and A/C trans placement on the basis of Deslongchamps's results.[29] Low concentration (0.025 M) of the reaction solution was a key factor for the high yield; however, prolonged reaction time and high concentration gave low yields.

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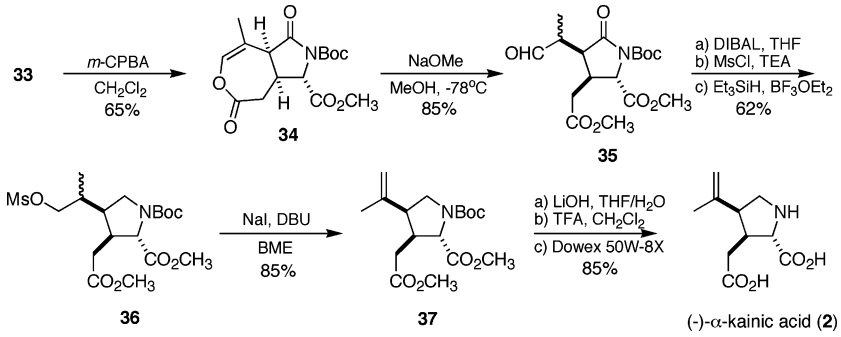
SCHEME 7. Synthesis of (−)-α-Kainic Acid (2)



After learning that reductive dephenylsulfonylation of this tricyclic system resulted in poor selectivity (the first dephenylsulfonylation approach),[30] we synthesized another bicyclic substrate by unmasking the acetonide in **29** and functionalizing the resulting alcohol to the ester compound **30**. Treatment of tricyclic compound **29** with Dowex 50W-8X in MeOH led to the quantitative formation of the primary alcohol. After Jones' oxidation and ensuing esterification using $TMSCHN_2$,[31] the BOC protection of the resulting amide group furnished bicyclic enone **30**. Initially, we considered using this enone as the next precursor for the challenging desulfonylation step (the second dephenylsulfonylation approach); however, we observed decomposition of the substrate owing to its instability under reductive conditions. In the end, we were able to demonstrate efficient and selective reduction by the use of the corresponding silyl enol ether derived from the cyclohexenone (the third dephenylsulfonylation approach).[32] Silylation of cyclohexenone **30** using TBSOTf in the presence of TEA occurred readily to give a mixture of two isomers **31** and **32** in a ratio of 2:1. The mixture of both isomers was subjected to reduction conditions using Na/Hg at −20 °C, providing only one diastereomer in 98% yield. Advantageously, concomitant deprotection of the TBDMS group took place during dephenylsulfonylation to yield the cyclohexenone **33**. A mixture of THF/MeOH (9/1) was used as the solvent for the dephenylsulfonylation step to furnish the desired product in a high yield.

It was presumed that the diene system on the six-membered ring would make the ring planar during reduction, preventing epimerization at C(4), as described in the proposed transition state model in Figure 2. Presumably, the sp^2 character on ring A would keep the ring system flat, while the enolate picks up a proton from the convex α-face in the protic environment. Similar arguments can account for the poor selectivity derived from tricyclic **29**, which would block the convex α-face of the AB rings due to the presence of the C ring in the same face. The stereochemical assignment of compound **33** was made on the basis of NOE experiments and coupling constant analysis.

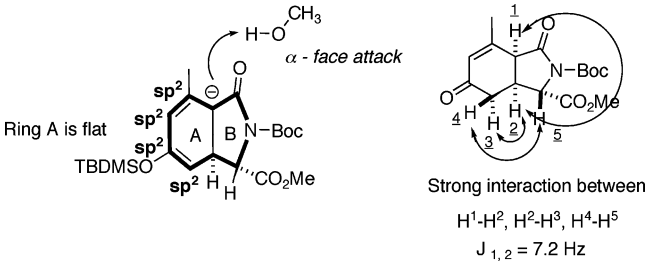
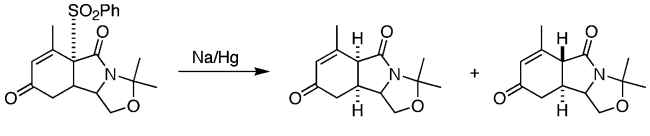


FIGURE 2. Stereoselective dephenylsulfonylation and NOE study.

It was also proven that product **33** had the desired stereochemistry for (−)-α-kainic acid by later synthesizing the targeted (−)-α-kainic acid (**2**) and comparing with the known data. As summarized in Figure 2, strong interactions between H^1 and H^2, H^2 and H^3, and H^4 and H^5 were observed. The coupling constant (*J*) between H^1 and H^2 was 7.2 Hz, which correlated with a typical value of syn coupling in similar systems.[8f]

After successful introduction of 3,4-stereochemistry, ring opening of the cyclohexenone by C−C bond cleavage became the focus of the final part of the synthesis. Schultz previously reported a Baeyer−Villiger oxidation[14] of primary alkyl-substituted α,β-unsaturated ketone to prepare a seven-membered enol lactone. According to the procedure reported by Schultz, cyclohexenone compound **33** underwent a regioselective Baeyer−Villiger oxidation with pertrifluoroacetic acid prepared in situ, whereby trifluoroacetic anhydride was reacted with urea-hydrogen peroxide in dichloromethane in the presence of sodium hydrogen phosphate (Scheme 7). Under these reaction conditions, the resulting enol lactone **34** was unstable and prolonged reaction time resulted in a low yield of the product. Fortunately, *m*-CPBA was also effective as an excellent oxidation reagent to give **34** with a high regioselectivity, along with a trace amount of the corresponding epoxide compound. The vinyl group of a primary alkyl-substituted α,β-unsaturated ketone showed preferential migration aptitude in the Baeyer−Villiger oxidation.[33] Subsequently, the ring opening reaction of the enol lactone **34** utilizing NaOMe at −78 °C was examined. Despite the possibility of epimerization at the α-position to the lactam carbonyl, the aldehyde ester compound **35** was prepared efficiently.[34] Then, one-pot reduction of both aldehyde and amide carbonyl groups employing DIBAL at −78 °C occurred readily to afford the corresponding hemiaminal alcohol in high yields.[35] After

(30) Dephenylsulphonylation of tricyclic system.



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selective mesylation on the primary alcohol, the mixture of diastereomers was further subjected to reduction using a Et_3SiH and $BF_3{\cdot}OEt_2$ protocol to generate the pyrrolidine core for the kainoid synthesis.[27] In an attempt to implement the isopropenyl group, the mesylated pyrrolidine intermediate **36** underwent elimination smoothly, where NaI/DBU in boiling DME[28] was employed successfully for this purpose. The final deprotections of the key intermediate **37** were effected by treatment with LiOH and trifluoroacetic acid.[36] After purification with ion-exchange resin, the final product, (−)-α-kainic acid (**2**), was obtained successfully. The spectroscopic data were identical to those reported[8] while physical data such as melting point (242−244 °C, lit. 243−244 °C) and specific rotation ($[\alpha]^{25}_D = -13.9$ (*c* 0.33, H_2O), lit. $[\alpha]^{25}_D = -14.2$ (*c* 0.18, H_2O)) agreed with the literature values of the natural product within an error range.[8]

In conclusion, we have successfully synthesized (−)-α-kainic acid (**2**) and (+)-α-allokainic acid (**3**) stereoselectively utilizing three key reactions: C−H insertion, intramolecular Michael-type cyclization, and stereoselective dephenylsulfonylation. The trans relationship between C(2) and C(3) was installed by the C−H insertion reaction and the cis relationship of (−)-α-kainic acid (**2**) between C(3) and C(4) was installed using stereoselective dephenylsulfonylation of the silyl enol ether. All stereochemistries were introduced from (L)-glutamic acid without using any chiral auxiliaries. Synthesis of (+)-α-allokainic acid (**3**) was also achieved successfully.

Experimental Section

All experiments were carried out under a nitrogen atmosphere using oven-dried glassware (or flame dried when necessary). All chemicals were purchased from major manufacturers and used without further purification unless otherwise noted. CH_2Cl_2 was distilled over calcium hydride. THF and diethyl ether were distilled over sodium metal. . All chemical shifts (δ) are recorded in ppm with the solvent resonance as the internal standard and coupling constants (*J*) recorded in Hz. Infrared spectra are reported in reciprocal centimeters (cm^{-1}). Thin layer chromatography (TLC) was preformed on EMD precoated silica plates with silica gel 60 Å, 250 μm thickness. Visualization of TLC was accomplished using a UV lamp (254 nm), iodine or charring solutions (ninhydrin and PMA).

(6*S*,7*R*,7α*S*)-3,3-Dimethyl-7-(2-oxopent-3-ynyl)-6-(phenylsulfonyl)-dihydropyrrolo-[1,2-c]oxazol-5(1*H*,3*H*,6*H*)-one (28). To a solution of γ-lactam **20** (5 g, 11.4 mmol) in dried THF (57 mL), was slowly added TBAF (17 mL, 1 M in THF). The reaction mixture was stirred for 2 h at room temperature, concentrated in vacuo and diluted with 100 mL of EtOAc. The organic layer was washed with brine solution, dried over Na_2SO_4, and concentrated in vacuo. The products were separated by flash column chromatography (EtOAc) to afford the alcohol (3.7 g, 96%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, 2H, $J = 7.2$ Hz), 7.62 (m, 1H), 7.53 (m, 2H), 4.16 (d, 1H, $J = 9.2$ Hz), 4.10 (*A*BX, 1H, $J_{AB}= 8.6$ Hz, $J_{AX}= 5.6$ Hz), 3.88∼3.82 (m, 1H), 3.77∼3.65 (m, 2H), 3.46 (A*B*X, 1H, $J_{AB}= 8.6$ Hz, $J_{AX}= 8.8$ Hz), 2.92∼2.83 (m, 1H), 2.22 (broad s, 1H), 2.23∼2.15 (m, 1H), 1.89∼1.79 (m, 1H), 1.46 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.8, 137.7, 134.5, 130.1, 129.1, 92.5, 75.2, 69.7, 64.4, 60.5, 36.4, 36.2, 26.7, 23.6. IR (thin film, cm^{-1}): 3507, 2987, 1701, 1263, 1147, 774. HRMS (ESI^+) for $[M + H^+]$ $C_{16}H_{22}NO_5S$: calcd, 340.1213; found, 340.1216; $[\alpha]^{25}_D = +46.8$ (*c* 3.53, $CHCl_3$).

To a solution of 4 g (11.8 mmol) of alcohol in CH_2Cl_2 (118 mL), was added $NaHCO_3$ (3 g, 3 equiv) and Dess−Martin periodinane solution (35 mL, 1.4 equiv, 15 wt % in CH_2Cl_2) at room temperature. The reaction mixture was stirred for 20 min and quenched by addition of the 1:1 mixture of $NaHCO_3$ and $Na_2S_2O_3$ aqueous solution (118 mL). The resulting solution was stirred for 1 h and the aqueous layer was extracted with EtOAc (50 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated. The product was separated by flash column chromatography (Hex/EtOAc = 1/2, v/v) to afford the aldehyde compound (3.8 g, 95%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (s, 1H), 7.97 (d, 2H, $J = 7.2$ Hz), 7.66 (m, 1H), 7.54 (m, 2H), 4.17 (*A*BX, 1H, $J_{AB}= 8.9$ Hz, $J_{AX}= 5.5$ Hz), 3.71∼3.64 (m, 1H), 3.58 (A*B*X, 1H, $J_{AB}= 8.9$ Hz, $J_{AX}= 9.3$ Hz), 3.43 (*A*BX, 1H, $J_{AB}= 19.3$ Hz, $J_{AX}= 2.7$ Hz), 3.10∼3.00 (m, 1H), 2.85 (A*B*X, 1H, $J_{AB}= 19.3$ Hz, $J_{AX}= 10.5$ Hz) 1.42 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.6, 161.1, 137.3, 134.6, 130.2, 129.1, 92.4, 73.9, 70.3, 64.2, 47.3, 33.7, 26.6, 23.6. IR (thin film, cm^{-1}): 2985, 1735, 1706, 1240, 1044. HRMS (ESI^+) for $[M + H^+]$ $C_{16}H_{20}NO_5S$: calcd, 338.1057; found, 338.1058; $[\alpha]^{25}_D = -0.4$ (*c* 0.54, $CHCl_3$).

To a solution of aldehyde (3.5 g, 10.3 mmol) in dried THF (50 mL) under a N_2 atmosphere at −78 °C, was added 1-propynylmagnesium bromide (45.4 mL, 22.7 mmol, 0.5 M solution in THF) dropwise, and the reaction was allowed to warm to 0 °C. After stirring for 1 h, the reaction was quenched with saturated aqueous NH_4Cl solution (25 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 15 min. The aqueous layer was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The product was separated using flash column chromatography (Hex/EtOAc = 1/2) to produce the propargyl alcohol (3.6 g, 92%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (m, 2H), 7.65 (m, 1H), 7.55 (m, 2H), 4.55∼4.40 (m, 1H), 4.20∼4.05 (m, 2H), 3.97∼3.83 (m, 1H), 3.47 (m, 1H), 3.10∼2.82 (m, 1H), 2.50∼2.40 (m, 1H), 2.09∼1.90 (m, 1H), 1.89∼1.80 (m, 3H), 1.50∼1.39 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.5, 137.7, 137.6, 134.5, 134.4, 130.3, 130.1, 129.0, 128.9, 92.5, 92.4, 82.9, 82.4, 75.2, 74.9, 70.1, 70.0, 64.7, 64.3, 61.2, 61.0, 41.8, 40.4, 36.3, 35.9, 26.7, 23.7, 3.8. IR (thin film, cm^{-1}): 3448, 2983, 1734, 1703, 1146. HRMS (ESI^+) for $[M + H^+]$ $C_{19}H_{24}NO_5S$: calcd, 378.1370; found, 378.1367; $[\alpha]^{25}_D = +15.4$ (*c* 1.4, $CHCl_3$).

To a solution of alcohol (3.5 g, 9.3 mmol) in CH_2Cl_2 (93 mL), were added $NaHCO_3$ (2.3 g, 2.9 equiv.) and Dess−Martin periodinane solution (28 mL, 1.4 equiv, 15 wt % in CH_2Cl_2) at room temperature. The reaction mixture was stirred for 1 h and quenched by addition of 1:1 mixture of $NaHCO_3$ and $Na_2S_2O_3$ aqueous solution (93 mL). The resulting solution was stirred for 1 h, and then the aqueous layer was extracted with EtOAc (40 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated. The product was separated by flash column chromatography (Hex/EtOAc = 1/2, v/v) to afford the ketone **28** (3.3 g, 93%) as a colorless oil. For compound **28**, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, 2H, $J = 7.2$ Hz), 7.66 (m, 1H), 7.55 (m, 2H), 4.16 (*A*BX, 1H, $J_{AB}= 8.9$ Hz, $J_{AX}= 5.5$ Hz), 4.10 (d, 1H, $J = 10.4$ Hz), 3.72∼3.65 (m, 1H), 3.55 (A*B*X, 1H, $J_{AB}= 8.9$ Hz, $J_{AX}= 9.3$ Hz), 3.50 (*A*BX, 1H, $J_{AB}= 19.3$ Hz, $J_{AX}= 2.7$ Hz), 3.10 ∼ 3.00 (m, 1H), 2.88 (A*B*X, 1H, $J_{AB}= 19.3$ Hz, $J_{AX}= 10.5$ Hz), 2.03 (s, 3H), 1.42 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.0, 161.0, 137.3, 134.6, 130.2, 129.1, 92.5, 92.3, 79.9, 73.7, 70.4, 64.2, 48.6, 34.7, 26.6, 23.6, 4.4. IR (thin film, cm^{-1}): 2985, 2222, 1734, 1706, 1671, 1242, 1147. HRMS (ESI^+) for $[M + H^+]$ $C_{19}H_{22}NO_5S$: calcd, 376.1213; found, 376.1219; $[\alpha]^{25}_D = -19.4$ (*c* 1.2, $CHCl_3$).

(5a*R*,9α*R*,9*β*S*)-3,3,6-Trimethyl-5a-(phenylsulfonyl)-1,9,9a,9b-tetrahydrooxazolo[4,3-*a*]isoindole-5,8(3*H*,5*aH*)-dione (29). To a solution of ketone **28** (3.2 g, 8.5 mmol) in CH_3CN (1700 mL, 0.005 M) was added Cs_2CO_3 (3.3 g, 10.2 mmol) at room temperature. The reaction mixture was stirred for 2 h and quenched with saturated aqueous NH_4Cl solution (50 mL) at room temperature. The reaction solution was concentrated in vacuo and diluted with 200 mL of EtOAc. The organic layer was washed with brine, dried over Na_2-

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SO_4, and concentrated in vacuo. The product was separated by flash column chromatography (Hex/EtOAc = 1/1, v/v) to produce the tricyclic enone **29** (3.0 g, 93%) as a colorless oil. For compound **29**, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, 2H, J = 8.8 Hz), 7.69 (m, 1H), 7.56 (m, 2H), 6.27 (s, 1H), 4.11 (*A*BX, 1H, J_{AB}= 8.6 Hz, J_{AX}= 5.8 Hz), 3.74∼3.66 (m, 1H), 3.40 (A*B*X, 1H, J_{AB}= 8.6 Hz, J_{AX}= 8.6 Hz), 3.19∼3.15 (m, 1H), 2.91 (*A*BX, 1H, J_{AB}= 18.2 Hz, J_{AX}= 6.4 Hz), 2.26 (A*B*X, 1H, J_{AB}= 18.2 Hz, J_{AX}= 0.0 Hz), 1.96 (s, 3H), 1.44 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.9, 162.4, 146.5, 136.2, 135.2, 133.6, 131.4, 129.2,93.4, 80.0, 68.7, 61.3, 41.7, 35.0, 26.2, 23.5, 21.7. IR (thin film, cm^{-1}): 2985, 2928, 1705, 1673, 1146. HRMS (ESI$^+$) for [M + H$^+$] $C_{19}H_{22}NO_5S$: calcd, 376.1213; found, 376.1211; $[\alpha]^{25}_D$ = +7.7 (*c* 0.73, $CHCl_3$).

(1*S*,3α*R*,7α*R*)-2-*tert*-Butyl-1-methyl 4-methyl-3,6-dioxo-3a-(phenylsulfonyl)-3,3a,7,7a-tetrahydro-1*H*-isoindole-1,2(6*H*)-dicarboxylate (30). To a solution of tricyclic acetonide **29** (3 g, 8 mmol) in MeOH (40 mL, 0.2 M) was added Dowex-50W-8X (9 g) in one portion. The resulting solution was heated under reflux condition for 10 h. The mixture was filtered and concentrated to provide the alcohol (2.6 g, 95%) as pale yellowish oil. The product was used for the next step without further purification. ^{1}H NMR (400 MHz, CD_3OD): δ 7.98 (d, 2H, J = 8.0 Hz), 7.76 (m, 1H), 7.62 (m, 2H), 6.28 (s, 1H), 3.80∼3.20 (m, 4H), 2.35 (d, 2H, J = 2.8), 2.16 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 195.3, 167.7, 147.9,136.1, 135.0, 133.3, 130.7, 129.3, 74.9, 60.4, 57.2, 38.6, 33.0, 21.1. IR (thin film, cm^{-1}): 3340, 2945, 2834, 2071, 1716, 1671, 1448. HRMS (ESI$^+$) for [M + H$^+$] $C_{16}H_{18}NO_5S$: calcd, 336.0900; found, 336.0900; $[\alpha]^{25}_D$ = +4.3 (*c* 1.59, MeOH).

Jones' reagent (1.0 M, 103 mL, 103 mmol) was added to a solution of the alcohol (2.5 g, 7.5 mmol) in acetone (75 mL, 0.1 M) at room temperature, and the resulting mixture was stirred for 2 h at that temperature. The reaction was quenched with *i*-PrOH and concentrated in vacuo. The mixture was dissolved in 50 mL of CH_2Cl_2, and 2 mL of brine solution was added. After phase separation, the aqueous layer was extracted three times with CH_2Cl_2, and the organic layers were combined, dried over Na_2SO_4, and concentrated to give the carboxylic acid compound (2.6 g, 99%) as a white solid, which was used for the next step without further purification: mp 216∼218 °C. ^{1}H NMR (400 MHz, CD_3OD): δ 8.00 (d, 2H, J = 7.6 Hz), 7.78 (m, 1H), 7.64 (m, 2H), 6.32 (s, 1H), 3.83 (d, 1H, J = 9.6 Hz), 3.31 (m, 1H), 2.68 (*A*BX, 1H, J_{AB}= 18.6 Hz, J_{AX}= 0.1 Hz), 2.46 (A*B*X, 1H, J_{AB}= 18.6 Hz, J_{AX}= 7.3 Hz), 2.12 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 194.67, 170.89, 167.2, 147.2, 135.9, 135.2, 133.6, 130.7, 129.3, 74.3, 56.5, 41.2, 33.5, 20.9. IR (thin film, cm^{-1}): 3352, 2985, 2071, 1718, 1673, 1025. HRMS (ESI$^-$) for [M − H$^+$] $C_{16}H_{14}NO_6S$: calcd, 348.0543; found, 348.0543; $[\alpha]^{25}_D$ = −3.4 (*c* 0.29, MeOH).

To a solution of acid (2.6 g, 7.4 mmol) in a mixture of methanol (74 mL) and toluene (185 mL), was added $TMSCHN_2$ (5.5 mL, 11.1 mmol, 2 M solution in ether) dropwise at room temperature. After stirring for 5 min, the reaction was quenched with acetic acid (2 drops) and the solvent was removed under reduced pressure. The resulting mixture was diluted with EtOAc (100 mL), washed with brine, then dried over Na_2SO_4, and concentrated in vacuo to give the crude product. The residue was purified by flash chromatography (EtOAc), affording the ester amide product as a colorless oil (2.3 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, 2H, J = 8.0 Hz), 7.68 (m, 1H), 7.54 (m, 2H), 6.25 (s, 1H), 3.80 (d, 1H, J = 9.6 Hz), 3.73 (s, 3H), 3.42 (m, 1H), 2.69 (*A*BX, 1H, J_{AB}= 18.4 Hz, J_{AX}= 0.4 Hz), 2.60 (A*B*X, 1H, J_{AB}= 18.4 Hz, J_{AX}= 6.8 Hz), 1.98 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.6, 169.5, 167.1, 146.3, 136.0, 135.4, 134.1, 131.0, 129.5, 74.4, 56.5, 53.4, 41.1, 34.2, 21.8. IR (thin film, cm^{-1}): 2985, 1724, 1675, 1149. HRMS (ESI$^+$) for [M + H$^+$] $C_{17}H_{18}NO_6S$: calcd, 364.0849; found, 364.0844; $[\alpha]^{25}_D$ = +27.1 (*c* 1.33, $CHCl_3$).

Et_3N (0.77 g, 1.1 mL, 7.6 mmol), Boc-anhydride (2.7 g, 12.6 mmol) and DMAP (0.77 g, 6.3 mmol) were added to a solution of the γ-lactam (2.3 g, 6.3 mmol) in CH_2Cl_2 (63 mL). The mixture was stirred for 2 h and concentrated under reduced pressure. The residue was purified by flash chromatography (Hex/EtOAc = 1:1, V/V) to afford the title compound **30** as colorless oil (2.8 g, 95%). For compound **30**, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, 2H, J = 8.0 Hz), 7.73 (m, 1H), 7.60 (m, 2H), 6.31 (s, 1H), 4.00 (d, 1H, J = 10.0 Hz), 3.76 (s, 3H), 3.38 (m, 1H), 2.90 (*A*BX, 1H, J_{AB}= 18.2 Hz, J_{AX}= 6.8 Hz), 2.55 (A*B*X, 1H, J_{AB}= 18.2 Hz, J_{AX}= 0.0 Hz), 1.87 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.8, 169.2, 163.8, 147.9, 145.3, 135.8, 135.5, 134.5, 131.4, 129.5, 85.8, 75.0, 60.5, 53.2, 37.5, 33.5, 27.9, 21.7. IR (thin film, cm^{-1}): 2985, 1795, 1754, 1678, 1144. HRMS (ESI$^+$) for [M + Na]$^+$ $C_{22}H_{25}NO_8SNa$: calcd, 486.1193; found, 486.1188; $[\alpha]^{25}_D$ = −28.8 (*c* 0.32, $CHCl_3$).

(1*S*,3α*R*,7α*R*)-2-*tert*-Butyl-1-methyl 6-(tert-butyldimethylsilyloxy)-4-methylene-3-oxo-3a-(phenylsulfonyl)-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,2(3*H*)-dicarboxylate (31 + 32). To a solution of ester **30** (2.8 g, 6.0 mmol) in CH_2Cl_2 (240 mL, 0.025 M), was added freshly distilled (over KOH) Et_3N (3.0 g, 4.2 mL, 30 mmol) and TBSOTf (4.8 g, 4.1 mL, 18 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After stirring for 1 h at 20 °C, the mixture was poured into aqueous saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and evaporated to give a residue (3.5 g, 100%), which was purified by chromatography through a silica gel column with elution by Hex/EtOAc/Et_3N (5:1:1, v/v/v) to give mixture of **31** and **32** (3.5 g, 100%). For compound **31**,**32**, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94∼7.40 (m, 5H), 5.54 (s, 1H), 4.87 (s, 1H), 4.53 (s, 1H), 4.03 (d, 1H, J = 10.4 Hz), 3.77 and 3.70 (s, 3H), 3.50∼3.40 (m, 1H), 2.80 (*A*BX, 1H, J_{AB}= 18.0 Hz, J_{AX}= 5.8 Hz), 2.23 (A*B*X, 1H, J_{AB}= 18.0 Hz, J_{AX}= 0.2 Hz), 1.42 and 1.39 (s, 9H), 0.90 and 0.84 (s, 9H), 0.25 and 0.18 and 0.00 (s, 6H). ^{13}C NMR (100 MHz, CD_3OD): δ 172.2, 171.4, 171.2, 167.8, 166.7, 152.6, 149.7, 149.6, 137.6, 136.1, 136.0, 135.9, 135.2, 133.0, 132.3, 132.2, 131.7, 130.0, 129.9, 129.5, 127.8, 118.4, 109.2, 107.5, 97.3, 86.3, 86.2, 84.8, 75.9, 73.3, 68.1, 64.9, 63.9, 63.3, 61.8, 58.9, 56.3, 53.6, 53.4, 53.2, 41.2, 37.7, 37.5, 31.9, 30.2, 28.5, 28.1, 28.0, 27.9, 26.7, 26.4, 26.2, 26.0, 25.9, 22.7, 20.0, 18.9, 18.7, −4.1, −4.2, −4.7. IR (thin film, cm^{-1}): 2960, 2214, 2070, 1742, 1242, 1122. HRMS (ESI$^+$) for [M + H$^+$] $C_{28}H_{40}NO_8SSi$: calcd, 578.2238; found, 578.2233; $[\alpha]^{25}_D$ = +24.1 (*c* 0.78, $CHCl_3$).

(1*S*,3α*S*,7α*S*)-2-*tert*-Butyl-1-methyl 4-methyl-3,6-dioxo-3,3a,7,7a-tetrahydro-1*H*-isoindole-1,2(6*H*)-dicarboxylate (33). A 10% portion of sodium amalgam (6.9 g, 30 mmol) was added to a solution of the silyl enol ether compound **31** + **32** (3.5 g, 6.0 mmol) and anhydrous disodium hydrogen phosphate (2.6 g, 18 mmol) in a mixture of dry MeOH (12 mL) and THF (108 mL) at −78 °C. The reaction mixture was warmed to −20 °C and stirred for 3 h. The reaction solution was quenched with aqueous NH_4Cl and warmed to room temperature. After filtration, the resulting solution was concentrated in vacuo and diluted with EtOAc (100 mL). The organic solution was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by chromatography through a silica gel column with elution by Hex/EtOAc (1/1, v/v) to give the product **33** (1.85 g, 95%) as a colorless oil. For compound **33**, ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.94 (s, 1H), 4.25 (s, 1H), 3.77 (s, 3H), 3.39 (d, 1H, J = 7.2 Hz), 2.99∼2.92 (m, 1H), 2.61 (*A*BX, 1H, J_{AB}= 16.1 Hz, J_{AX}= 5.6 Hz), 2.38 (A*B*X, 1H, J_{AB}= 16.1 Hz, J_{AX}= 12.0 Hz), 2.18 (s, 3H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.1, 170.5, 168.9, 154.5, 149.5, 128.0, 84.7, 62.4, 53.1, 47.1, 38.5, 35.5, 28.1, 23.7. IR (thin film, cm^{-1}): 2980, 1790, 1750, 1670, 1304, 1148. HRMS (ESI$^+$) for [M + Na]$^+$ $C_{16}H_{21}NO_6Na$: calcd, 346.1261; found, 346.1257; $[\alpha]^{25}_D$ = −41.6 (*c* 1.53, $CHCl_3$).

(1*S*,3α*S*,8α*S*,*Z*)-2-*tert*-Butyl-1-methyl 4-methyl-3,7-dioxo-3,3a,8,8a-tetrahydro-1*H*-oxepino[4,5-*c*]pyrrole-1,2(7*H*)-dicarboxylate (34). To a solution of the enone compound **33** (1.8 g, 5.5 mmol) in CH_2Cl_2 (55 mL, 0.1M), was added m-CPBA (1.9 g, 11 mmol)

in one portion at room temperature. After stirring at room temperature for 48 h, the reaction was quenched with saturated sodium sulfite. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried and evaporated. Flash chromatography (Hex/EtOAc = 1/2, v/v) gave **34** as a colorless oil (1.1 g, 60%). For compound **34**, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.37 (d, 1H, J = 1.2), 4.58 (s, 1H), 3.76 (s, 3H), 3.25 (d, 1H, J = 8.8 Hz), 3.08∼3.02 (m, 2H), 2.60∼2.53 (m, 1H), 1.85 (d, 3H, J = 1.6 Hz), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 170.3, 168.4, 148.9, 137.3, 122.4, 84.6, 62.5, 53.1, 47.6, 39.4, 36.8, 28.0, 20.1. IR (thin film, cm^{-1}): 2980, 2200, 1793, 1756, 1265, 907. HRMS (ESI$^+$) for [M + Na]$^+$ $C_{16}H_{21}NO_7Na$: calcd, 362.1210; found, 362.1208; $[\alpha]^{25}_D$ = +15.7 (*c* 1.11, $CHCl_3$).

(2*S*,3*S*,4*S*)-1-*tert*-Butyl-2-methyl 3-(2-methoxy-2-oxoethyl)-5-oxo-4-(1-oxopropan-2-yl)pyrrolidine-1,2-dicarboxylate (35). Sodium methoxide solution (4.77 mmol, 1 M in MeOH) was added dropwise over 30 min to a solution of the enol lactone **34** (1.1 g, 3.2 mmol) in methanol (64 mL, 0.05 M) at −78 °C. The reaction mixture was stirred for 20 min and quenched with saturated NH_4Cl solution and warmed to room temperature. The reaction mixture was concentrated in vacuo and diluted with 50 mL of EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to afford the crude product. Purification by flash chromatography (Hex/EtOAc = 1:1, v/v) gave the ester aldehyde compound **35** (1.0 g, 87%, mixture of two diastereomers) as a colorless oil. For compound **35**, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79 and 9.58 (s, 1H), 4.45 and 4.39 (s, 1H), 3.79 and 3.71 and 3.67 (s, 6H), 3.2∼2.2 (m, 6H), 1.46 (s, 9H), 1.37 and 1.10 (d, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.9, 201.7, 172.2, 171.4, 171.3, 170.8, 170.6, 149.6, 84.5, 84.3, 62.5, 61.9, 60.6, 53.1, 53.0, 52.5, 52.4, 47.2, 45.5, 44.0, 43.0, 34.9, 34.6, 34.0, 33.3, 28.1, 12.2. IR (thin film, cm^{-1}): 2980, 1790, 1735, 1309, 1150. HRMS (ESI$^+$) for [M + Na]$^+$ $C_{17}H_{25}NO_8Na$: calcd, 394.1472; found, 394.1469; $[\alpha]^{25}_D$ = −1.4 (*c* 0.59, $CHCl_3$).

(2*S*,3*S*,4*S*)-1-*tert*-Butyl-2-methyl 3-(2-methoxy-2-oxoethyl)-4-(1-(methylsulfonyloxy)-propan-2-yl)pyrrolidine-1,2-dicarboxylate (36). A solution of DIBAL (21.6 mL, 8 equiv, 1.0 M in THF) was added dropwise to a solution of the aldehyde **35** (1.0 g, 2.7 mmol) in THF (27 mL) at −78 °C under a N_2 atmosphere. After stirring for 1 h, the reaction was quenched with methanol and the mixture was warmed to room temperature. To the resulting solution were added saturated potassium tartrate solution and EtOAc. The mixture was stirred for 15 min. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to afford the diol compound (1.0 g, 97%). The crude product was used for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.52∼5.35 (m, 1H), 4.24 and 4.17 (s, 1H), 3.87 (d, 1H, J = 2.8 Hz), 3.69 (s, 3H), 3.67 (s, 3H), 3.60∼3.50 (m, 1H), 3.42∼3.35 (m, 2H), 2.73∼2.60 (m, 2H), 2.12∼1.82 (m, 2H), 1.36 (s, 9H), 1.04 (d, 3H, J = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 172.7, 154.6, 82.2, 81.4, 66.4, 64.6, 52.5, 52.0, 46.8, 40.7, 34.7, 31.4, 28.4, 15.9. IR (thin film, cm^{-1}): 3440, 2977, 1739, 1685, 1368. HRMS (ESI$^+$) for [M + Na]$^+$ $C_{17}H_{29}NO_8Na$: calcd, 398.1785; found, 398.1785; $[\alpha]^{25}_D$ = −22.6 (*c* 1.11, $CHCl_3$).

A solution of hemiaminal compound (200 mg, 0.44 mmol) and Et_3SiH (52 mg, 0.072 mL, 0.44 mmol) in CH_2Cl_2 (4.4 mL) was cooled at −78 °C, and $BF_3{\cdot}OEt_2$ (67 mg, 0.061 mL, 0.48 mmol) was then added dropwise under a N_2 atmosphere. After stirring for 30 min, Et_3SiH (52 mg, 0.072 mL, 0.44 mmol) and $BF_3{\cdot}OEt_2$ (67 mg, 0.061 mL, 0.48 mmol) were added. The resulting mixture was stirred for 2 h at −78 °C. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, and dried over Na_2SO_4. Evaporation of the solvent and purification by flash column chromatography (Hex/EtOAc = 1/1, v/v) gave the alcohol product (138 mg, 72%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.21−3.90 (m, 2H), 3.80∼3.60 (m, 6H), 3.40 (m, 1H), 3.10∼2.90 (m, 4H), 2.80∼2.60 (m, 2H), 2.30∼2.10 (m, 2H), 1.90 (m, 1H), 1.50∼1.35 (m, 9H), 1.10∼0.93 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 172.4, 172.3, 154.1, 82.0, 80.6, 72.4, 64.9, 64.6, 52.7, 52.3, 52.2, 48.5, 48.3, 46.4, 42.5, 41.7, 41.3, 40.5, 40.3, 37.7, 32.8, 32.4, 29.4, 28.6, 28.4, 15.9. IR (thin film, cm^{-1}): 2989, 2974, 1738, 1697, 1355, 1172. HRMS (ESI$^+$) for [M + Na]$^+$ $C_{18}H_{31}NO_9SNa$: calcd, 460.1612; found, 460.1608; $[\alpha]^{25}_D$ = −10.0 (*c* 0.28, $CHCl_3$).

p-Methanesulfonyl chloride (189.0 mg, 1.7 mmol) was added to a solution of diol compound (400 mg 1.1 mmol) and TEA (278 mg, 0.38 mL, 2.75 mmol) in CH_2Cl_2 (11 mL) at 0 °C. After stirring for 15 min at 0 °C, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution, diluted with EtOAc (30 mL), and washed with brine solution. The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford the crude product. The residue was purified by flash chromatography (Hex/EtOAc = 1:1, v/v) to give the mesylated compound (300 mg, 65%) as a colorless oil. For the compound **36**, ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.50∼5.38 (m, 1H), 4.25 and 4.18 (s, 1H), 4.10∼3.92 (m, 2H), 3.81 (d, 1H, J = 2.8 Hz), 3.69 (s, 3H), 3.68 (s, 3H), 2.96 (s, 3H), 2.78∼2.57 (m, 3H), 2.20∼2.02 (m, 2H), 1.35 (s, 9H), 1.10 (d, 3H, J = 6.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 172.4, 154.4, 81.9, 81.5, 72.5, 64.6, 52.6, 52.1, 46.4, 40.5, 37.6, 34.5, 29.4, 28.4, 15.8. IR (thin film, cm^{-1}): 3436, 2977, 1736, 1697, 1355, 1173. HRMS (ESI$^+$) for [M + Na]$^+$ $C_{18}H_{31}NO_{10}SNa$: calcd, 476.1561; found, 476.1555; $[\alpha]^{25}_D$ = −18.2 (*c* 1.01, $CHCl_3$).

(2*S*,3*S*,4*S*)-1-*tert*-Butyl-2-methyl 3-(2-methoxy-2-oxoethyl)-4-(prop-1-en-2-yl)-pyrrolidine-1,2-dicarboxylate (37). To a solution of the mesylate **36** (100 mg, 0.22 mmol) in DME (2.2 mL), was added NaI (66 mg, 0.44 mmol) in one portion. After the reaction mixture was stirred for 5 h at 60 °C, DBU (100 mg, 0.66 mmol) was added, and the reaction mixture was refluxed for 3 h. After the reaction mixture had cooled to room temperature, EtOAc (30 mL) and H_2O (20 mL) were added, and the layers were separated. The combined organic layers were washed with saturated $NaHCO_3$ solution and brine and then dried over Na_2SO_4. Evaporation of the solvent and purification by flash column chromatography (Hex/EtOAc = 2/1, v/v) gave the product **37** (60 mg, 79%) as a colorless oil. For compound **37** (two rotamers), ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.89 (s, 1H), 4.67 (s, 1H), 4.13 and 4.04 (d, 1H, J = 3.2 Hz, 4.0 Hz), 3.74 and 3.73 (s, 3H), 3.68 and 3.66 (s, 3H), 3.70∼3.58 (m, 1H), 3.48∼3.36 (m, 1H), 3.02∼2.95 (m, 1H), 2.85∼2.78 (m, 1H), 2.36∼2.20 (m, 2H), 1.67 (s, 3H), 1.44 and 1.38 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 172.4, 172.3, 172.2, 154.3, 153.7, 141.4, 141.2, 113.4, 113.1, 80.2, 80.1, 64.0, 63.6, 52.3, 52.2, 51.8, 47.8, 47.6, 46.0, 45.2, 41.9, 40.9, 32.9, 28.4, 28.2, 22.3, 22.2. IR (thin film, cm^{-1}): 2989, 2975, 1740, 1701, 1397, 1170. HRMS (ESI$^+$) for [M + Na]$^+$ $C_{17}H_{27}NO_6Na$: calcd, 364.1731; found, 364.1729; $[\alpha]^{25}_D$ = −18.9 (*c* 1.03, CHCl3), [lit: $[\alpha]^{25}_D$ = - 19.1 (*c* 0.62, $CHCl_3$)].

α-(−)-Kainic Acid (2). The diester compound **37** (30 mg, 0.088 mmol) was dissolved in a mixture of THF (1 mL) and a 2.5% solution of LiOH (1 mL). The reaction mixture was stirred for 12 h at room temperature, and a solution of HCl (2 M) was added until pH 3. The mixture was extracted with EtOAc, and the organic layers were combined and dried over Na_2SO_4 and then concentrated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 (2 mL) and TFA (12 equiv) and refluxed for 2 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) and evaporation afforded (−)-kainic acid **2** (15 mg, 80%): mp 242∼244 °C [lit. mp 243−244 °C]. HRMS (ESI$^-$) for [M − H$^+$] $C_{10}H_{14}NO_4$: calcd, 212.0928; found, 212.0932; $[\alpha]^{25}_D$ = −13.9° (*c* 0.33, H_2O). [lit. $[\alpha]^{25}_D$ = −14.2° (*c* 0.18, H_2O)];. ^{1}H NMR (D_2O): δ 5.03 (s, 1H), 4.74 (s, 1H), 4.06

(d, 1H, $J = 3.1$ Hz), 3.62 (dd, 1H, $J = 11.6$, 7.3 Hz), 3.44 (dd, 1H, $J = 11.7$, 10.7 Hz), 3.08∼2.95 (m, 2H), 2.29 (dd, 1H, $J = 15.7$, 6.4 Hz), 2.16 (dd, 1H, $J = 15.7$, 8.1 Hz), 1.78 (s, 3H). ^{13}C NMR (100 MHz, D_2O): δ 178.6, 174.3, 140.9, 114.1, 66.6, 47.2, 46.6, 42.1, 35.4, 23.0.

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Supporting Information Available: Experimental procedures for the steps shown in Scheme 3 along with all of the ^{1}H and ^{13}C NMR spectra for the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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