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Synthesis of (−)-α-Kainic Acid via TMSCl-Promoted Pd-Catalyzed Zinc-ene Cyclization of an Allyl Acetate†

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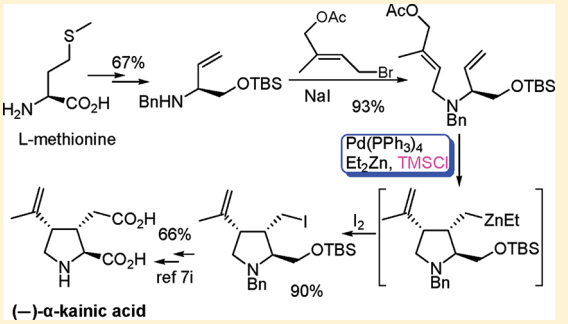
Supporting Information

ABSTRACT: A highly practical synthesis of enantiopure (−)-α-kainic acid is accomplished in 37% overall yield, using 13 linear steps and a minimum of chromatographic separations via an unprecedented TMSCl-promoted palladium-catalyzed zinc-ene cyclization of an allyl acetate.



INTRODUCTION

(−)-α-Kainic acid (**3**) was first isolated from the Japanese marine *Digenea Simplex*[1] in 1953, and it exhibits an exceptional pharmacological profile, acting as a potent agonist for ionotropoic glutamate receptors in the central nervous system and inducing seizures and neurodegeneration *in vivo*.[2] This pronounced neuroexcitatory activity stems from its conformationally rigid structure composed of a *trans*-C2,C3/*cis*-C3,C4 pyrrolidine core analogous to glutamic acid, a neuroexcitatory neurotransmitter in the central nervous system. Recently, (−)-α-kainic acid has been widely used in neuroscience research as a neurodegenerative agent for modeling epilepsy,[3] Parkinson's disease,[4] and Alzheimer's disease.[5] However, the supply of (−)-α-kainic acid from natural sources is very limited. The worldwide shortage and extremely high price of (−)-α-kainic acid have severely hampered research projects in neurodegenerative disorders.[6] In order to address these challenges, including diastereoselective construction of a *trans*-C2,C3/*cis*-C3,C4 pyrrolidine core, numerous syntheses[7] have been disclosed since the first total synthesis[8] was reported by Oppolzer and coworkers in 1982. Despite the advances achieved over the past decades, a practical synthesis of (−)-α-kainic acid is still highly desired in terms of atom economy[9] and green chemistry[10] in organic synthesis.

A short synthesis[7i] of kainic acid was reported in 2007 from this laboratory, using a high-yielding and completely diastereoselective palladium-catalyzed zinc-ene cyclization of allylic chloride **1a** derived from D-serine as the key step to construct the pyrrolidine (Scheme 1). However, the brevity was overshadowed by the partial racemization resulting from the use of a racemization prone α-amino aldehyde precursor of **1a**.

We now report an equally expeditious synthesis, but this time of enantiomerically pure (−)-α-kainic acid (**3**) by a similar palladium-catalyzed zinc-ene cyclization of allylic acetate **1b**. The latter was generated in one step from the key doubly protected (*S*)-2-vinylglycinol **8a** derived from natural L-methionine ($0.43/g from Sigma-Aldrich) by a process that does not proceed through an α-amino aldehyde and thus does not involve any loss in enantiomeric purity. It turns out that the palladium-catalyzed zinc-ene cyclization of allylic acetate **1b** occurs in as remarkably high yield and diastereoselectivity as that of the corresponding allyl chloride **1a** but only in the presence of trimethylsilyl chloride, a surprising discovery that may have wider applicability.

RESULTS AND DISCUSSION

The synthesis of the precursor **8a** of **1b** commenced with $LiAlH_4$ reduction[11] of L-methionine in THF at reflux to provide β-amino alcohol **4** (Scheme 2). Introduction of the benzyl protecting group onto nitrogen by condensation of **4** with benzaldehyde followed by reduction with $NaBH_4$, generated **5a**,[11a] whose silylation with TBSCl[12] after chromatography furnished **6a**, with a combined yield of 75% over 4 steps from methionine. Subsequent oxidation of **6a** with $NaIO_4$ in mixed solvents (H_2O/MeOH/EtOAc 1:1:1)[13] provided quantitatively the crude sulfoxide **7a**, which was subjected to thermal elimination[11b,c] to give the desired allylamine **8a** in 57% yield. However, the disappointing yield was not improved in attempts at optimization, and a scaleup experiment of this pyrolysis led to a

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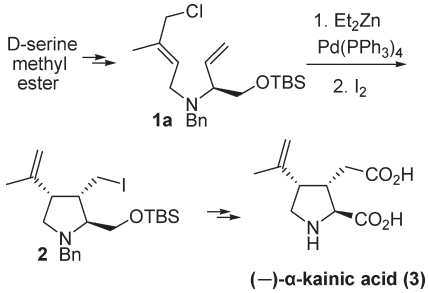
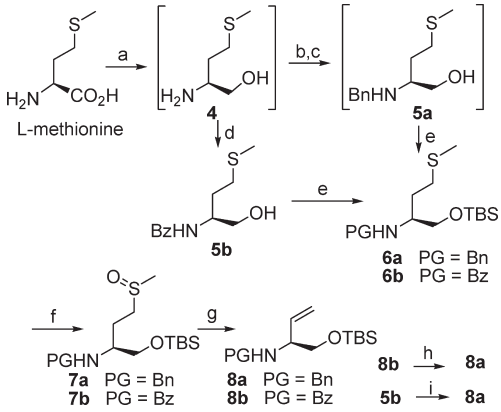
Scheme 1. Earlier Synthesis of (−)-α-Kainic Acid (3)



Scheme 2. Two Syntheses of 8a[a]

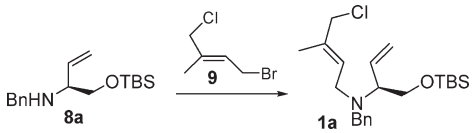


[a] Conditions: (a) $LiAlH_4$, THF, reflux, 24 h; (b) PhCHO, MeOH, 0 °C, 2 h; (c) $NaBH_4$, MeOH, 0 °C, 1 h; (d) 15% NaOH, BzCl, 0 °C to rt, 24 h, 82% for **5b** from methionine; (e) TBSCl, CH_2Cl_2, imidazole, 0 °C to rt, 2 h, 75% for **6a** from methionine and 82% for **6b** from methionine; (f) $NaIO_4$, H_2O/MeOH/EtOAc (1:1:1), rt, 3 h, quant; (g) *o*-dichlorobenzene, $CaCO_3$, reflux, 5 h, 57% for **8a** and 86% for **8b**; (h) procedures a and e, 78%; (i) procedures e, f, g, a and e, 82%. Note: no purifications were carried out for the crude intermediates in procedures h and i.

very low yield (19%). In view of the failure of this sequence, we replaced the benzyl protecting group with the benzoyl group, anticipating that the more stable benzamide could survive the harsh pyrolytic conditions better than the benzylamine (Scheme 2). A one-pot[14] sequential reduction of methionine with $LiAlH_4$, followed by acylation with benzoyl chloride, provided analytically pure **5b** in 82% yield after simple acid−base washes.

In a fashion similar to the above procedure, silylation of **5b** followed by oxidation of the product **6b** gave rise quantitatively to analytically pure **7b**. Gratifyingly, pyrolysis of **7b** furnished the desired compound **8b** in 86% yield. Notably, this robust protocol was smoothly carried out on a 20 g scale with equal efficiency. Conversion of **8b** to **8a** was achieved in 78% yield after chromatography in two steps by treatment of **8b** with $LiAlH_4$ at reflux overnight and resilylation of the resulting desilylated product with TBSCl. In order to streamline this new reaction sequence, crude product **8b** from the pyrolysis was directly subjected to reduction and resilylation, affording after chromatographic purification the desired product **8a** in 82% yield over 5 steps from **5b**. Thus, the key intermediate **8a** ($[\alpha]^{20}_D$ +26.0 (*c* 0.92 $CHCl_3$)),[15] required for the synthesis of (−)-α-kainic acid,

Scheme 3. Intended Synthesis of (−)-Kainic Acid Precursor 1a



could be readily synthesized from methionine in 7 steps and 67% overall yield and only one chromatographic purification for the final product **8a** was necessary.

There have been several reported asymmetric methods for the synthesis of (*S*)-2-vinylglycinol and its protected analogues by either employing a chiral substrate[16] or asymmetric allylic aminations.[15,17] However, none of these provide enantiomerically pure product, and the cost associated with the recovery of the chiral auxiliary or ligands could be prohibitive in the large scale production of this intermediate. In fact, compound **8a** itself has been prepared in a short synthesis by an iridium-catalyzed asymmetric allylic amination in 97% ee.[15] Disadvantages of this procedure, in addition of the necessity of enriching the enantiomerism of the protected (*S*)-2-vinylglycinol to 100%, would be the expense of preparing the chiral ligand, the fact that the expensive iridium catalyst bearing this ligand would not be recoverable because of the homogeneous nature of the reaction, and the fact that the product is formed in the presence of 17% of an isomeric material that would have to be removed by a tedious procedure. In contrast, our longer synthesis is easy to perform and involves a simple base−acid wash workup procedure and one chromatographic separation for the final compound **8a**.

With enantiomerically pure **8a** in hand, we pursued the preparation of allyl chloride **1a** (Scheme 3) that we had previously shown[7i] to be an efficient precursor of (−)-α-kainic acid after the Zn-ene cyclization. In our previous synthesis, **1a** was prepared in high yield by allylating an amine bearing a carboxylic ester group with **9** and converting the ester group to a vinyl group, but this procedure led to partially racemized **1a**. This racemization cannot occur in the present synthesis. However, it was found that the sequence outlined in Scheme 3 gave poor yields probably due to the fact that the *Z*-isomer of **1a**, arising from allylation of **8a** with the *Z*-isomer contaminating **9**, was probably unstable because of cyclization by nucleophilic displacement of the chloride ion by the amine.[18]

Since allyl acetates are versatile precursors of π-allyl palladium(II) complexes,[19] we replaced the chloride of **9** with an acetoxy group (**1b**, Scheme 4), which would be incapable of this unwanted nucleophilic displacement. The synthesis of allylic bromide allylic acetate **12** began with allylic chloride allylic alcohol **10**, readily available in two steps from isoprene.[20] Reaction with KOAc in the presence of a catalytic amount of NaI gave the allylic acetate allylic alcohol **11** in moderate yield (Scheme 4). Treatment of **11** with PBr_3 at 0 °C for 1 h afforded the desired product **12** in 73% yield.[21] When alkylation[22] of **8a** with **12** was performed in DMF at room temperature in the same manner as with **9**, we were surprised to observe that this reaction was extremely sluggish. With the addition of a catalytic amount of NaI, the reaction proceeded well and provided the zinc-ene cyclization precursor **1b** in 93% yield (Scheme 4).

However, when we performed the palladium-catalyzed zinc-ene cyclization of **1b** following the reported[7i] procedure, we surprisingly observed that this reaction completely stalled after 30−40%

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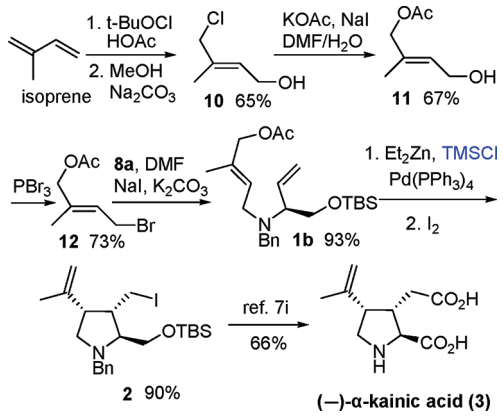
Scheme 4. (−)-Kainic Acid 3 from Allylic Acetate 1b



conversion of **1b** to cyclization product and never proceeded to completion even with a much longer reaction time. In a number of cases, Oppolzer and co-workers had also observed low yields of Pd-catalyzed Zn-ene cyclizations using a similar procedure starting from allyl acetates.[19b,23] In one case,[23] in order to obtain good yields, the catalyst was changed to palladium acetate in the presence of $P(Bu)_3$ and *20 equivalents of diethylzinc was used*. Since such conditions would be very detrimental to any effective industrial process, we developed a novel approach to solve this problem. It is based on the likelihood that the oxidative addition of Pd(0) to the allyl acetate is reversible[24] and that the subsequent steps leading to the cyclization may be as well and/or that a chloride ligand on Pd is far more effective[25] in this process than the acetate ligand, as evidenced by our previous very successful cyclization of **1a**. It appeared that a practical method for addressing either or both possibilities might be to add TMSCl along with the Pd and diethylzinc in order to silylate the acetate ion released during the oxidative addition of the Pd to the allyl acetate. Remarkably, when 1 equiv of TMSCl was present during the palladium-catalyzed zinc-ene cyclization, the reaction was complete in a much shorter period of time, and after quenching with iodine, iodide **2** was obtained in 90% yield (Scheme 4).

To further prove that no racemization occurred in the synthesis of chiral allylamine **8a** by the method described herein, conversion of iodide **2** to (−)-α-kainic acid was carried out following our previously reported procedure.[7i] Cyanation of iodide **2**, followed by debenzylation with methyl chloroformate, Jones oxidation, basic hydrolysis, and purification by ion exchange chromatography (DOWEX 50WX8-200) furnished enantiomerically pure (−)-α-kainic acid (**3**, mp 243−246 °C (dec), $[\alpha]^{20}_{D}$ −15.0 (*c* 0.61 H_2O),[26] whose spectroscopic data were identical with those reported in the literature. Remarkably, this synthesis provides rapid access to enantiopure (−)-α-kainic acid (**3**) in 37% overall yield in 13 linear steps.

CONCLUSIONS

In summary, a practical synthesis of enantiopure (−)-α-kainic acid (**3**) is accomplished in 37% overall yield in 13 linear steps from inexpensive L-methionine, featuring an unprecedented TMSCl-promoted palladium-catalyzed intramolecular zinc-ene cyclization of allyl acetate **1b**. The low cost of the reagents used, the absence of any cryogenic steps, the small number of required chromatographic separations, and the ease of handling and scale-up permit an especially industrially adaptable access to enantiomerically pure (−)-α-kainic acid to satisfy the needs of the neuroscience research community.

EXPERIMENTAL SECTION

General Remarks. Reactions were performed in oven-dried glassware fitted with rubber septa under an argon atmosphere. Unless otherwise noted, all starting materials and reagents were purchased from commercial sources and used without further purification. THF and Et_2O were distilled over sodium/benzophenone. CH_2Cl_2, Et_3N, pyridine, and toluene were distilled over CaH_2. Glass-backed silica gel TLC plates (0.25 mm) were used for thin layer chromatography (TLC) analysis. Visualization of TLC plates was accomplished with aqueous $KMnO_4$ or ninhydrine stain. All products were purified by flash chromatography on silica gel (32−63 μm) when necessary. NMR spectra were recorded using $CDCl_3$ as solvent, and chemical shifts are reported in ppm (δ value) with solvent signals [^{1}H NMR (300 MHz): $CDCl_3$ (7.27); ^{13}C NMR (75 MHz): $CDCl_3$ (77.0)]. Signal splitting patterns are indicated as br, broad peak; s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet.

(*S*)-*N*-[1-Hydroxy-4-(methylthio)butan-2-yl]benzamide (5b). To a 100 mL flask charged with $LiAlH_4$ (1.1 g, 29.0 mmol) and anhydrous THF (40 mL) was added portionwise (*S*)-methionine (2.0 g, 13.4 mmol) under an argon atmosphere. After being stirred for 10 min, the mixture was heated at reflux overnight. The mixture was then allowed to cool to room temperature and was slowly treated with water (1.1 mL), 15% aqueous NaOH (1.1 mL), and water (3.3 mL), successively. After addition of 15% aqueous NaOH (15.6 mL), benzoyl chloride (1.44 mL, 12.4 mmol) was added dropwise at 0 °C, and the resulting mixture was then stirred for 2 h. The reaction mixture was diluted with water (200 mL) and then acidified to pH 1.5 with 6 N aqueous HCl and extracted with CH_2Cl_2 (100 mL × 3). The extracts were combined, washed with water, saturated aqueous $NaHCO_3$, and brine, successively, and dried over anhydrous Na_2SO_4. After filtration, concentration of the filtrate afforded 2.63 g (82%) of analytically pure **5b** as a white semisolid. IR (neat): 3284, 1636 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.00 (qd, *J* = 6.0, 3.0 Hz, 2H), 2.15 (s, 3H), 2.64 (t, *J* = 6.0 Hz, 2H), 2.69 (t, *J* = 6.0 Hz, 1H), 3.74−3.88 (m, 2H), 4.23−4.35 (m, 1H), 6.66 (d, *J* = 6.0 Hz, 1H), 7.41−7.57 (m, 3H), 7.76−7.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.6, 30.4, 30.8, 51.7, 64.9, 127.0, 128.6, 131.7, 134.1, 168.1; HRMS−ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{17}NO_2$-NaS 262.0878, found 262.0877.

(*S*)-*N*-[1-(*tert*-Butyldimethylsilyloxy)-4-(methylthio)butan-2- yl]benzamide (6b). To a 250 mL flask were added compound **5b** (2.4 g, 10.0 mmol), CH_2Cl_2 (70 mL) and imidazole (1.04 g, 15.1 mmol) under an argon atmosphere. The resulting solution was allowed to cool to 0 °C, and *tert*-butylchlorodimethylsilane (1.7 g, 10.9 mmol) was then added portionwise. After 30 min, the reaction mixture was stirred at room temperature overnight. The reaction was quenched with water and extracted with CH_2Cl_2 (30 mL × 2). The combined organic layer was washed with 1 N HCl (20 mL × 2), water and brine, successively, dried over anhydrous Na_2SO_4, filtered, and concentrated to give 3.56 g (100%) of analytically pure **6b** as a clear oil. IR (neat): 3306, 3063, 1638, 1538, 838 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.09 (s, 3H), 0.92 (s, 9H), 1.96 (q, *J* = 6.0 Hz, 2H), 2.13 (s, 3H), 2.52−2.70 (m, 2H), 3.75 (d, *J* = 3.0 Hz, 2H), 4.26−4.38 (m, 1H), 6.53 (d, *J* = 9.0 Hz, 1H), 7.41−7.56 (m, 3H), 7.74−7.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.5, 15.5, 18.2, 25.8, 30.8, 31.2, 50.2, 64.3, 126.8, 128.6, 131.5, 134.6, 166.8; HRMS−ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{31}NO_2NaSiS$ 376.1742, found 376.1746.

***N*-(*S*)-[1-(*tert*-Butyldimethylsilyloxy)-4-(methylsulfinyl)butan-2-yl]benzamide (7b).** A 250 mL flask was charged with compound **6b** (3.53 g, 10.0 mmol), methanol (36 mL), and ethyl acetate (36 mL).

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After compound **6b** was dissolved, an aqueous solution of $NaIO_4$ (2.37 g, dissolved in 36 mL of distilled H_2O) was added dropwise over a period of 30 min. After being stirred for 3 h at room temperature, the reaction mixture was diluted with water (150 mL), additional ethyl acetate (50 mL) was added, and then the organic layer was separated. The aqueous layer was extracted with ethyl acetate (50 mL × 2). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated to provide 3.78 g (100%) of analytically pure **7b** as a clear oil. IR (neat): 3304, 3062, 1642, 1539, 1030, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, two diastereomers): δ 0.08 (s, 3H), 0.09 (s, 3H), 0.92 (s, 9H), 2.11−2.30 (m, 2H), 2.58 (2 × s, 3H), 2.72−2.96 (m, 2H), 3.70−3.85 (m, 2H), 4.24−4.42 (m, 1H), 6.85 and 6.94 (2 × d, J = 9.0 Hz, 1H), 7.40−7.57 (m, 3H), 7.76−7.86 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, two diastereomers): δ −5.6, −5.5, 18.1, 24.7, 25.5, 25.8, 38.4, 38.5, 49.7, 50.2, 50.7, 51.2, 64.5, 64.7, 126.9, 126.9, 128.5, 128.5, 131.5, 131.5, 134.0, 134.1, 167.1, 167.1; HRMS−ESI: m/z $[M + H]^+$ calcd for $C_{18}H_{32}NO_3SiS$ 370.1872, found 370.1867.

(*S*)-*N*-[1-(*tert*-Butyldimethylsilyloxy)but-3-en-2-yl]benzamide (8b). To a 100 mL flask equipped with a condenser were added **7b** (3.69 g, 10 mmol), *o*-dichlorobenzene (50 mL), and powdered $CaCO_3$ (2.6 g), and the resulting mixture was heated to reflux. After 5 h, the reaction mixture was cooled to room temperature and filtered over a pad of Celite. The solvent was removed under reduced pressure to give a residual oil, which was purified by column chromatography (10% EtOAc/hexanes) to afford 2.62 g (86%) of analytically pure **8b** as a clear oil. $[\alpha]^{20}_D$ −61.0 (c 1.15, $CHCl_3$); IR (neat): 3310, 3065, 1639, 1538, 839 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.08 (2 × s, 6H), 0.91 (s, 9H), 3.74−3.87 (m, 2H), 4.68−4.78 (m, 1H), 5.18−5.35 (m, 2H), 5.94 (ddd, J = 18.0, 12.0, 6.0 Hz, 1H), 6.60 (d, J = 6.0 Hz, 1H), 7.40−7.56 (m, 3H), 7.76−7.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.3, 18.2, 25.8, 53.0, 65.0, 116.2, 126.8, 128.6, 131.4, 134.6, 136.0, 166.6; HRMS−ESI: m/z $[M + Na]^+$ calcd for $C_{17}H_{27}NO_2NaSi$ 328.1709, found 328.1705.

(*S*)-*N*-Benzyl-1-(*tert*-butyldimethylsilyloxy)but-3-en-2-amine (8a). To a 250 mL flask charged with $LiAlH_4$ (0.87 g, 23 mmol) and anhydrous THF (80 mL) was slowly added a 0.2 M THF solution of **8b** (3.05 g, 10 mmol) via a syringe under an argon atmosphere. After being stirred for 10 min, the mixture was heated at reflux overnight. The mixture was then allowed to cool to room temperature and slowly treated with water (0.87 mL), 15% aqueous NaOH (0.87 mL), and water (2.61 mL) successively. After 1 h, the precipitate was filtered off and washed twice with THF, and the solvent was then removed under reduced pressure to give 1.66 g of the crude product. The crude product was dissolved in CH_2Cl_2 (65 mL) under an argon atmosphere followed by addition of imidazole (0.97 g, 14.1 mmol) and TBSCl (1.74 g, 11.2 mmol). After 2 h, the reaction was quenched with water. The organic layer was separated and washed with water and then brine, and dried over anhydrous Na_2SO_4. The crude obtained after filtration and removal of the solvent was purified by chromatography to afford 2.27 g (78%) of analytically pure **8a** as a clear oil. $[\alpha]^{20}_D$ +26.0 (c 0.92, $CHCl_3$); IR (neat): 3330, 3064, 1461, 1255, 1088, 838, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 2.10 (br s, 1H), 3.14−3.26 (m, 1H), 3.51 (dd, J = 9.0 Hz, 1H), 3.61 (dd, J = 9.0, 6.0 Hz, 1H), 3.65 (d, J = 12.0 Hz, 1H), 3.87 (d, J = 12.0 Hz, 1H), 5.13−5.28 (m, 2H), 5.57−5.72 (m, 1H), 7.17−7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.4, −5.3, 18.2, 25.9, 51.0, 62.4, 66.2, 117.7, 126.7, 128.0, 128.3, 137.9, 140.7; HRMS−ESI: m/z $[M + H]^+$ calcd for $C_{17}H_{30}NOSi$ 292.2097, found 292.2098.

Streamlined Procedure for the Synthesis of (*S*)-*N*-Benzyl-1-(*tert*-butyldimethylsilyloxy)but-3-en-2-amine (8a). The procedures for the syntheses of **6b**, **7b**, **8b**, and **8a**, as described above, were followed except that only final compound **8a** was purified by flash chromatography. The crude **5b** (2.4 g, 10 mmol) was submitted to silylation, oxidation, thermal elimination, reduction, and resilylation, affording after chromatographic purification 2.38 g (82%) of analytically pure compound **8a** as a clear oil. All data for **8a** are consistent with those reported above.

(*S*)-*N*-Benzyl-1-(*tert*-butyldimethylsilyloxy)-4-(methylthio)-butan-2-amine (6a). To a 100 mL flask charged with $LiAlH_4$ (1.1 g, 29 mmol) and anhydrous THF (40 mL) was added portionwise (*S*)-methionine (2.0 g, 13.4 mmol) under an argon atmosphere. After being stirred for 10 min, the mixture was heated at reflux overnight. The mixture was then allowed to cool to room temperature and was slowly treated with water (1.1 mL), 15% aqueous NaOH (1.1 mL), and water (3.3 mL), successively. The precipitate was filtered off, and the solvent was removed under reduced pressure. The residual oil **4** thus obtained was dissolved in anhydrous methanol (55 mL) under an argon atmosphere followed by addition of benzaldehyde (1.37 mL, 13.4 mmol), and the resulting solution was stirred at 0 °C. After 2 h, $NaBH_4$ (0.8 g, 21.1 mmol) was added portionwise. The reaction mixture was stirred for 1 h and quenched with 1 N NaOH. The product was extracted with CH_2Cl_2. The extracts were combined, washed with water and brine, and dried over Na_2SO_4. Filtration and removal of the solvent gave **5a** as a nearly colorless oil. The crude **5a** was dissolved in CH_2Cl_2 (90 mL) under an argon atmosphere followed by addition of imidazole (1.36 g, 19.7 mmol) and TBSCl (2.44 g, 15.7 mmol). After 2 h, the reaction was quenched with water. The organic layer was separated, washed with water and brine, and dried over anhydrous Na_2SO_4. The crude obtained after filtration and removal of the solvent was purified by chromatography to afford 3.4 g (75%) of analytically pure **6a** as a clear oil. IR (neat): 3027, 1468, 1254, 1107, 838, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.92 (s, 9H), 1.68−1.86 (m, 3H), 2.11 (s, 3H), 2.60 (t, J = 9.0 Hz, 2H), 2.78 (quin, J = 6.0 Hz, 1H), 3.54 (dd, J = 12.0, 6.0 Hz, H), 3.70 (dd, J = 12.0, 6.0 Hz, 1H), 3.82 (s, 2H), 7.21−7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.3, −5.2, 15.4, 18.2, 25.8, 30.9, 31.2, 51.1, 57.5, 64.2, 126.8, 128.0, 128.3, 140.7; HRMS−ESI: m/z $[M + H]^+$ calcd for $C_{18}H_{34}NOSiS$ 340.2130, found 340.2120.

(2*S*)-*N*-Benzyl-1-(*tert*-butyldimethylsilyloxy)-4-(methylsulfinyl)butan-2-amine (7a). A 250 mL flask was charged with compound **6a** (3.39 g, 10.0 mmol), methanol (36 mL), and ethyl acetate (36 mL). After compound **6a** was dissolved, an aqueous solution of $NaIO_4$ (2.37 g dissolved in 36 mL of distilled H_2O) was added dropwise over a period of 30 min. After being stirred for 3 h at room temperature, the reaction mixture was diluted with water (150 mL), additional ethyl acetate (50 mL) was added, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (50 mL × 2). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated to provide 3.62 g (100%) of analytically pure **7a** as a clear oil. IR (neat): 3027, 1468, 1255, 1106, 838, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, two diastereomers): δ 0.06 (s, 6H), 0.90 (s, 9H), 1.78−2.01 (m, 3H), 2.53 and 2.55 (2 × s, 3H), 2.70−2.94 (m, 3H), 3.54 and 3.57 (2 × dd, J = 6.0, 3.0 Hz, 1H), 3.66−3.89 (m, 3H), 7.19−7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, two diastereomers): δ −5.4, 18.2, 24.6, 24.8, 25.9, 38.5, 38.5, 50.9, 51.0, 51.3, 51.4, 56.8, 57.5, 63.7, 63.8, 127.0, 128.1, 128.2, 128.4; HRMS−ESI: m/z $[M + Na]^+$ calcd for $C_{18}H_{33}NO_2NaSiS$ 378.1899, found 378.1898.

(*S*)-*N*-Benzyl-1-(*tert*-butyldimethylsilyloxy)but-3-en-2-amine (8a). To a 100 mL flask equipped with a condenser were added **7a** (3.55 g, 10 mmol), *o*-dichlorobenzene (50 mL) and powdered $CaCO_3$ (2.6 g), and the resulting mixture was heated to reflux. After 5 h, the reaction mixture was cooled to room temperature and filtered over a pad of Celite. The solvent was removed under reduced pressure to give a residual oil, which was purified by column chromatography (15% EtOAc/hexanes) to afford 1.66 g (57%) of analytically pure **8a** as a clear oil. $[\alpha]^{20}_D$ +26.0 (c 0.92, $CHCl_3$); IR (neat): 3330, 3064, 1461, 1255, 1088, 838, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 2.10 (br s, 1H), 3.14−3.26 (m, 1H), 3.51 (dd, J = 9.0 Hz, 1H), 3.61 (dd, J = 9.0, 6.0 Hz, 1H), 3.65 (d, J = 12.0 Hz, 1H), 3.87

(d, J = 12.0 Hz, 1H), 5.13−5.28 (m, 2H), 5.57−5.72 (m, 1H), 7.17−7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.4, −5.3, 18.2, 25.9, 51.0, 62.4, 66.2, 117.7, 126.7, 128.0, 128.3, 137.9, 140.7; HRMS−ESI: m/z $[M + H]^+$ calcd for $C_{17}H_{30}NOSi$ 292.2097, found 292.2098.

(*E*)-4-Hydroxy-2-methylbut-2-enyl Acetate (11). To a 0.25 M DMF solution of **10**[20] (2.41 g, 20.0 mmol) were added KOAc (4.12 g, 42.0 mmol), NaI (0.16 g, 1.06 mmol), and H_2O (5.0 mL). The reaction mixture was stirred overnight and then diluted with water and extracted with EtOAc. The extracts were washed with brine and dried (Na_2SO_4). After filtration and removal of the solvent under reduced pressure, the crude oil was purified by column chromatography (25% EtOAc/hexanes) to afford 1.94 g (67%) of analytically pure **11** as a clear oil. IR (neat): 3460, 1739, 1235 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (br s, 1H), 1.72 (s, 3H), 2.10 (s, 3H), 4.23 (dd, J = 6.0 Hz, 2H), 4.49 (s, 2H), 5.69 (tq, J = 6.0, 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 20.8, 58.8, 68.9, 127.0, 133.0, 170.8.

(*E*)-4-Bromo-2-methylbut-2-enyl Acetate (12). To a 0.25 M Et_2O solution of **11** (1.44 g, 10.0 mmol) was added PBr_3 (0.41 mL, 4.3 mmol) at 0 °C. After 1 h, the reaction mixture was diluted with water and extracted with Et_2O. The combined organic layers were washed with water and dried (Na_2SO_4). After filtration and removal of the solvent, the crude oil was purified by column chromatography (10% Et_2O/pentane) to afford 1.51 g (73%) of analytically pure **12** as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.77 (s, 3H), 2.10 (s, 3H), 4.15 (d, J = 9 Hz, 2H), 4.52 (s, 2H), 5.81 (tq, J = 9.0, 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6, 20.8, 27.4, 68.3, 123.2, 136.7, 170.6.

(*S*,*E*)-4-[Benzyl(1-*tert*-butyldimethylsilyloxy)but-3-en-2-yl)-amino]-2-methylbut-2-enyl Acetate (1b). To a 0.1 M DMF solution of **8a** (1.46 g, 5.0 mmol) were added NaI (0.04 g, 0.27 mmol), K_2CO_3 (0.69 g, 5.0 mmol), and **12** (1.04 g, 5.0 mmol). The reaction mixture was stirred at room temperature. After 24 h, the reaction mixture was diluted with water and extracted with EtOAc. The extracts were combined, washed with water and brine, and dried (Na_2SO_4). The crude, obtained after filtration and removal of the solvent under reduced pressure, was purified by column chromatography (10% EtOAc/hexanes) to afford 1.94 g (93%) of analytically pure **1b** as a light yellow oil. IR (neat): 1742, 1231, 1101, 838 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.89 (s, 9H), 1.63 (s, 3H), 2.07 (s, 3H), 3.06−3.31 (m, 3H), 3.54 (d, J = 15.0 Hz, 1H), 3.66−3.85 (m, 3H), 4.44 (s, 2H), 5.12−5.31 (m, 2H), 5.49−5.60 (m, 1H), 5.75−5.91 (m, 1H), 7.17−7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.5, −5.4, 14.2, 18.3, 21.0, 25.9, 47.8, 54.9, 63.4, 64.6, 69.9, 118.1, 126.6, 128.1, 128.4, 128.5, 131.8, 135.4, 140.6, 170.9; HRMS−ESI: m/z $[M + H]^+$ calcd for $C_{24}H_{40}NO_3Si$ 418.2777, found 418.2783.

(2*S*,3*S*,4*S*)-1-Benzyl-2-[(*tert*-butyldimethylsilyloxy)methyl]-3-(iodomethyl)-4-(prop-1-en-2-yl)pyrrolidine (2). To a solution of **1b** (417 mg, 1 mmol) in anhydrous Et_2O (6 mL) were added $Pd(PPh_3)_4$ (58 mg, 0.05 mmol), Et_2Zn (1.0 M in hexanes, 6.0 mL, 6.0 mmol), and TMSCl (0.13 mL, 1.0 mmol). The mixture was stirred at room temperature. After 6 h, the reaction was quenched with a solution of I_2 (3.1 g) in THF (8 mL). After 0.5 h, the reaction mixture was treated with saturated $Na_2S_2O_3$, and the resulting mixture was extracted with EtOAc. The extracts were combined, washed with saturated $Na_2S_2O_3$ and brine, and then dried (Na_2SO_4). The crude obtained after filtration and concentration was purified by column chromatography (5% EtOAc/hexanes) to afford 438 mg (90%) of analytically pure **2** as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.08 (2 × s, 6H), 0.92 (s, 9H), 1.74 (s, 3H), 2.43−2.61 (m, 2H), 2.67−2.85 (m, 3H), 2.90 (dd, J = 9.0, 6.0 Hz, 1H), 3.17 (dd, J = 9.0, 3.0 Hz, 1H), 3.55(d, J = 6.0 Hz, 2H), 3.63 (d, J = 15.0 Hz, 1H), 4.10 (d, J = 12.0 Hz, 1H), 4.61 (s, 1H), 4.86 (s, 1H), 7.19−7.41 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.2, −5.2, 10.5, 18.4, 23.2, 26.0, 45.0, 48.4, 54.2, 60.4, 66.4, 71.2, 111.8, 126.9, 128.2, 128.8, 139.6, 141.8; HRMS−ESI: m/z $[M + H]^+$ calcd for $C_{22}H_{37}NOSiI$ 486.1689, found 486.1675.

(−)-α-Kainic Acid (3). Following our previously reported procedure,[7i] cyanation of iodide **2** followed by debenzylation with methyl chloroformate, Jones oxidation, basic hydrolysis, and purification by ion exchange chromatography (DOWEX 50WX8-200) furnished enantiomerically pure (−)-α-kainic acid **3** [mp 243−246 °C (dec), $[\alpha]^{20}_D$ −15.0 (c 0.61 H_2O)].[8] ^{1}H NMR (300 MHz, D_2O): δ 1.72 (s, 3H), 2.20 (dd, J = 15.0, 6.0 Hz, 1H), 2.32 (dd, J = 18.0, 6.0 Hz, 1H), 2.88−3.09 (m, 2H), 3.38 (dd, J = 12.0 Hz, 1H), 3.58 (dd, J = 12.0, 9.0 Hz, 1H), 4.03 (d, J = 3.0 Hz, 1H), 4.70 (s, 1H), 4.98 (s, 1H); ^{13}C NMR (75 MHz, D_2O): δ 22.1, 34.6, 41.2, 45.7, 46.3, 65.7, 113.1, 140.0, 173.4, 177.9.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra of the compounds **5b**−**8b**, **6a**−**8a**, **11**, **12**, **1b**, **2**, and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ DEDICATION

†This work is dedicated with admiration and affection to Professor William Bailey on his 65th birthday.

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