Note

Total Synthesis of (-)-alpha- Kainic acid via Chirality Transfer through Ireland – Claisen Rearrangement

Naredla Kesava Reddy, and Srivari Chandrasekhar

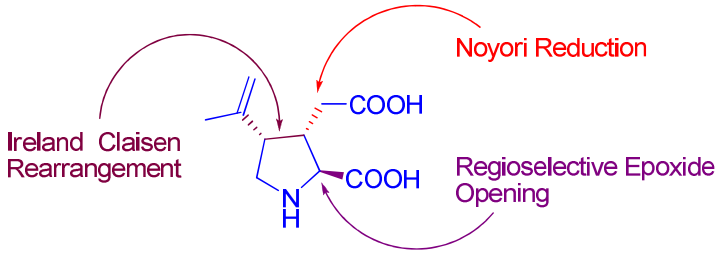
J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/jo400001t • Publication Date (Web): 07 Mar 2013

Total Synthesis of (-)-α- Kainic acid via Chirality Transfer through Ireland – Claisen Rearrangement

Naredla Kesava Reddy and Srivari Chandrasekhar*

Division of Natural Products Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad, India 500 007

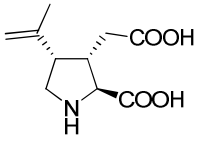
srivaric@iict.res.in



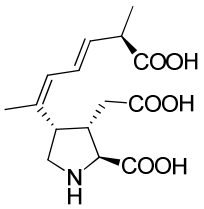
(-)-α- Kainic acid (1)

Abstract: The total synthesis of (-)-α- Kainic acid is accomplished using a linear strategy involving Noyori asymmetric reduction and chirality transfer through Ireland-Claisen rearrangement as key steps.

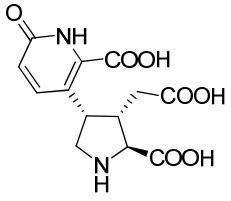
(-)-α-Kainic acid is isolated from Japanese marine alga *Digenia simplex* 1953 later found in related algae as well.[1] (-)-α-kainic acid (**1**)**,** domoic acid (**2**) and acromelic acid B (**3**) are categorized under the kainoid family of non proteinogenic amino acids. These amino acids have the same relative stereochemistry *i.e. trans*-C2/C3, *cis*-C3/C4 which is crucial for its biological activity.



(-)- α- Kainic acid (**1**)

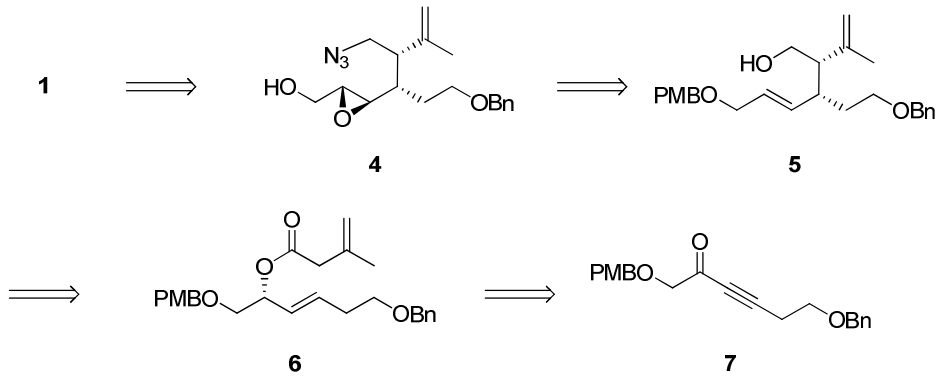


Domoic acid (**2**)



Acromelic acid B (**3**)

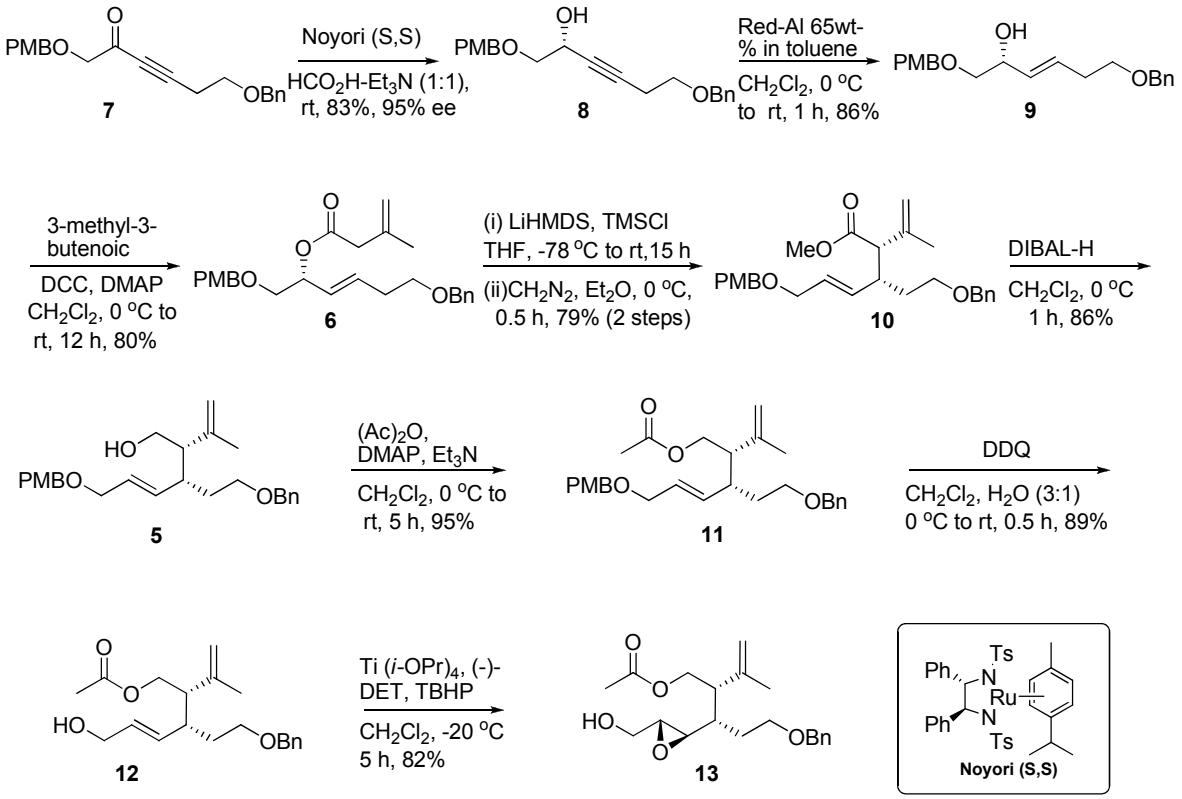
(-)-α-Kainic (**1**) acid is characterized as a five membered pyrrolidine skeleton with an isopropenyl group, methylene carboxyl and carboxyl group appended onto it in a *syn-anti* fashion. Compound **1** has been widely used as an experimental tool, due to its neuroexcitotoxic and epileptogenic properties in screening of CNS disorders such as Alzheimer's disease[2] and epilepsy[3] in animal models. It is also reported that *Digenia simplex* exhibited antihelminthic properties in traditional Japanese folklore. The structure of kainic acid can be envisaged as a conformationally restricted analogue of the neurotransmitter glutamic acid and is also confirmed by its neuroexcitation activity leading to specific neuronal death in brain.[3b] The interesting biological properties and the challenging structural complexity with three contiguous chiral stereo centers has attracted the attention of organic chemists. To date, over 30 total syntheses of (-)-α-kainic acid and its congeners have been reported in literature using diverse synthetic strategies.[4] Very recently Gallos and co-workers have compiled a review on recent approaches.[5] Most of the synthetic strategies revolved around cycloadditions,[4h,4l,4x] ene-reaction,[4q] radical cyclisation,[4u] Pauson-Khand reaction[4r] and Diels-Alder reaction[4o] as key reaction for the construction of C3-C4 *cis* stereochemistry. Furthermore the asymmetric carbon bearing -COOH group (C2) was generally achieved using chiral starting materials. In continuation of our interest in the synthesis of pyrrolidine class of natural products and marine originated bioactive molecules,[6] herein we report the total synthesis of **1** using an altogether different strategy involving Ireland-Claisen rearrangement for C3-C4 *cis* stereocenters[7] and Sharpless asymmetric epoxidation as key reactions in installing the chirality at C2.



Scheme 1. Retrosynthesis for (-)-α-Kainic Acid (**1**)

As delineated in retrosynthetic planning (**Scheme 1)**, we envisaged a 5-*exo*-tet cyclization of azido epoxy alcohol **4** which in turn was planned to be synthesized through chirality transfer from allyl ester **6** involving Ireland-Claisen rearrangement *via* homoallylic alcohol **5**. Compound **6** could in turn be obtained from ynone **7**. By applying Ireland-Claisen rearrangement it is also possible to synthesize other kainoid family of natural products.

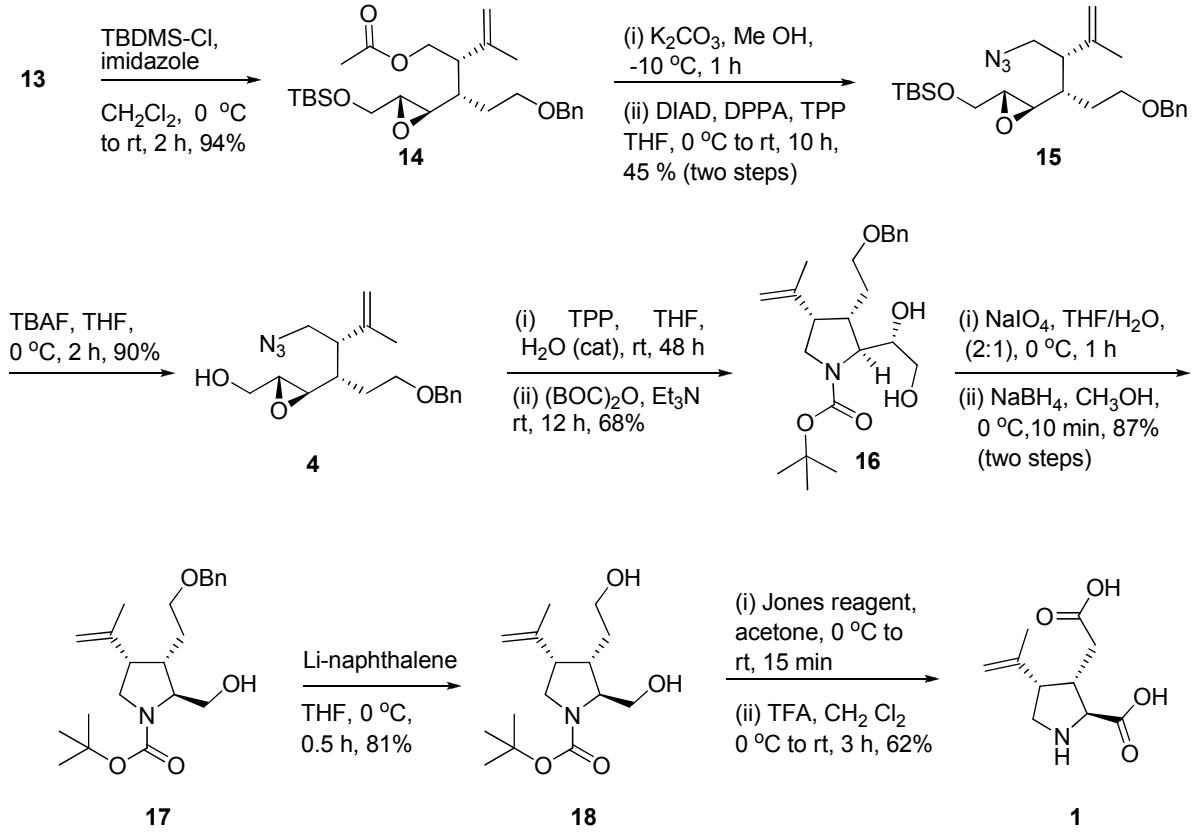
The differentially protected ynone **7**[8] was subjected to Noyori asymmetric reduction conditions to obtain secondary propargyl alcohol **8** in 83% yield and with >95% ee.[9] The classical reduction of triple bond to (*E*)-olefin was achieved using Red-Al to generate allyl alcohol **9** in 86% yield. The next task of introducing the appendage for Ireland-Claisen rearrangement was accomplished by coupling of alcohol **9** with 3-methyl-3-butenoic acid[10] under DCC-DMAP conditions. The obtained ester **6** was subjected to LiHMDS/TMSCl for a smooth sigmatropic reaction with an excellent chirality transfer followed by the treatment with diazomethane provided **10** in 79% yield over two steps.[11] Having installed the desired arms with right chirality, the next challenge was to construct the pyrrolidine ring. This process commenced with a DIBAL-H reduction of **10** to generate the homoallylic alcohol **5** (86% yield) which was protected as acetate **11** in 95% yield.



Scheme 2. Synthetic of epoxy alcohol **13**

The *p*-methoxybenzyl group was knocked down oxidatively using DDQ to produce allyl alcohol **12** (89% yield), a desirable building block for Sharpless asymmetric epoxidation. The asymmetric epoxidation using (-) DET and TBHP produced epoxy alcohol **13** in 82% yield as an exclusive diastereomer (**Scheme 2)**. The silylation of **13** to**14** was uneventful. The deacetylation and azidation were achieved using K_2CO_3/MeOH followed by Mitsunobu reaction to generate epoxy azide **15** albeit in low yields (45% over two steps). The removal of silyl group was mediated by TBAF to furnish azido epoxy alcohol **4**. The pyrrolidine ring was constructed in one stroke by reduction of **4** with TPP in THF, wherein azide was reduced to amine which further

underwent a facile 5-*exo*-tet cyclisation[12] and was in turn trapped as carbamate **16** in 68% yield (**Scheme 3)**.



Scheme 3. Completion of Total Synthesis of (-)-α-Kainic Acid

The resultant vicinal diol functionality in **16** was oxidatively cleaved with $NaIO_4$ and the resultant aldehyde was subjected to $NaBH_4$ reduction to produce **17** which has all the necessary substituents stitched on the pyrrolidine ring with requisite stereogenic centers. The Li-naphthalide mediated debenzylation yielded the diol **18** which underwent a smooth oxidation with Jones reagent followed by Boc-deprotection to realize (-)-α-kainic acid **1** in (62% yield over two steps). This compound exhibited all the desired spectral data, fully identical to the reported ones.[4r]

In summary, the natural (-)-α-kainic acid has been synthesized involving chirality transfer through sigmatropic rearrangement and 5-*exo*-tet-cyclisation with complete regio and stereocontrol.

Experimental Section

General

NMR spectra were recorded in $CDCl_3$ or D_2O solvent on 300, 400 or 500 MHz spectrometers. Chemical shifts are reported in parts per million (ppm). ^{1}H NMR spectra were recorded at 300, 400 or 500 MHz and chemical shifts are referenced to TMS (δ = 0.0) as internal standard. ^{13}C NMR spectra were recorded at 75, 100 or 125 MHz and chemical shifts are referenced to $CDCl_3$ (δ = 77.0). FTIR spectra were recorded on KBr thin films. Optical rotations were measured on an digital polarimeter by using a 2-mL cell with a path length of 1 dm. HRMS were recorded on an LC-ESI-QTOF-mass spectrometer. All the reagents and solvents were of reagent grade and used without further purification unless otherwise stated. Technical-grade EtOAc, hexanes, $CHCl_3$ and MeOH used for column chromatography were distilled before use. THF, when used as a solvent for reactions, was freshly distilled from sodium benzophenone ketyl. Column chromatography was carried on silica gel (60–120 mesh) packed in glass columns. All the reactions were performed under N_2 in flame- or oven dried glassware with magnetic stirring.

Experimental procedures

6-(Benzyloxy)-1-(4-methoxybenzyloxy)hex-3-yn-2-one (7)

To a solution of alkyne (5.0 g, 31.2 mmol) in THF (62 ml) was added *n*-BuLi (15 ml, 37.5 mmol, 2.5 molar) at -78^{o}C. After stirring for 2 h a solution of weinreb amide (8.9 g, 37.5 mmol) in THF (38 ml) was added slowly to it. Stirring continued for 20 min at -78^{o}C and for 2 h at 0^{o}C and then

the mixture was quenched with saturated NH_4Cl solution. The mixture was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silicagel chromatography (1:10 EtOAc/hexanes) to afford 7.03 g alkynone **7** (67%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38-7.24 (m, 7H), 6.88 (d, J = 8.3 Hz, 2H), 4.54 (d, J = 4.5 Hz, 4H), 4.16 (s, 2H), 3.79 (s, 3H), 3.61 (t, J = 6.7 Hz, 2H), 2.67 (t, J = 6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 184.5, 159.4, 137.5, 129.6, 128.4, 127.7, 127.6, 113.8, 93.7, 79.1, 75.3, 73.0, 66.8, 65.1, 55.1, 20.5; IR (KBr) ν_{max}: 3031, 2932, 2863, 1728, 1710, 1611, 1249 cm^{-1}; HRMS: Calcd for $C_{21}H_{23}O_4$ $(M+H)^+$: 339.1591, found: 339.1599.

(*S*)-6-(Benzyloxy)-1-(4-methoxybenzyloxy)hex-3-yn-2-ol (8)

To a solution of (*S,S*) Noyori catalyst (376 mg, 0.05 mmol) in 10 ml CH_2Cl_2 was added a solution of alkynone **7** (4 g, 11.8 mmol) in 24 ml of formic acid triethylamine mixture (1:1). The resultant mixture was stirred for 6 h, and then water 10 ml was added to dilute and extracted with CH_2Cl_2. The combined organic layers were washed with $NaHCO_3$, dried over Na_2SO_4, concentrated under reduced pressure to afford crude oil. The crude product was purified by silica gel chromatography eluting with (EtOAc/hexanes 3:10) to give propargyl alcohol **8** (3.3 g, 83%) as a colorless oil. $[\alpha]^{20}_D$ −0.83 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34-7.24 (m, 7H), 6.88 (d, J = 7.9 Hz, 2H), 4.57-4.49 (m, 5H), 3.81 (s, 3H), 3.62-3.46 (m, 4H), 2.53 (td, J = 6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.2, 137.8, 129.6, 129.3, 128.2, 127.5, 113.7, 82.8, 78.8, 73.4, 72.8, 72.7, 68.0, 61.6, 55.1, 20.0; IR (KBr) ν_{max}: 3430, 3063, 2923, 2860, 1612, 1513, 1248 cm^{-1}; HRMS: Calcd for $C_{21}H_{24}O_4Na$ $(M+Na)^+$: 363.1567, found: 363.1559.

(*S, E*)-6-(Benzyloxy)-1-(4-methoxybenzyloxy)hex-3-en-2-ol (9)

Red-Al® (5.4 mL of a 65% w/w solution in toluene, 17.6 mmol) was added drop wise to a stirred solution of alkyneol **8** (3 g, 8.8 mmol) in dry CH_2Cl_2 (25 ml) at 0 ^oC under nitrogen. The reaction mixture was stirred at room temperature for 1 h, and then quenched by drop wise addition of saturated aqueous potassium sodium tartrate. The mixture was vigorously stirred for 0.5 h and then filtered under vacuum. The filter residues were exhaustively washed with CH_2Cl_2, the layers separated and the organic phase dried (Na_2SO_4) and concentrated. The viscous oil obtained was purified by chromatography eluting with EtOAc / hexanes (3:10) to give alcohol **9** (2.59 g, 86%) as a colorless oil. $[\alpha]^{20}{}_D$ – 6.71 (*c* 2.92, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34-7.22 (m, 7H), 6.87 (d, *J* = 7.9 Hz, 2H), 5.78 (m, *J* = 14.9 Hz, 1H), 5.5 (dd, *J* = 15.9 Hz, 1H), 4.49 (m, 4H), 4.27 (br, 1H), 3.79 (s, 3H), 3.5 (t, *J* = 6.9 Hz, 2H), 3.46 (dd, *J* = 8.99 Hz, 1H), 3.32 (t, *J* = 6.9 Hz, 2H), 2.49 (br, 1H), 2.35 (q, *J* = 6.9 Hz, 2H) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.2, 138.2, 130.0, 129.8, 129.7, 129.3, 128.2, 127.5, 127.4, 113.7, 73.8, 72.9, 72.8, 71.1, 69.4, 55.1, 32.7; IR (KBr) ν_{max} : 3433, 3030, 2930, 2858, 1612, 1513, 1247 cm^{-1}; HRMS: Calcd for $C_{21}H_{26}O_4Na$ $(M+Na)^+$: 365.1723, found: 365.1701.

(*S, E*)-6-(Benzyloxy)-1-(4-methoxybenzyloxy)hex-3-en-2-yl 3-methylbut-3-enoate (6)

To a solution of alkenol **9** (2 g, 342 mmol) in CH_2Cl_2 (35 mL) were added 3-methyl-3-butenoic acid (760 mg, 7.6 mmol), DMAP (214 mg, 1.75 mmol) and DCC (1.44 g, 7.01 mmol) at 0 $^\circ C$. The reaction was stirred for 12 h at room temperature followed by dilution with hexane. The generated white precipitate was removed by filtration through celite. The filtrate was concentrated and residue was purified by column chromatography on silica gel (EtOAc/hexanes 1:9) to give **6** (1.98 g, 80%) as an oil. $[\alpha]^{20}{}_D$ −15.9 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36-7.22 (m, 7H), 6.87 (d, *J* = 7.7 Hz, 2H), 5.8 (dt, *J* = 14.4 Hz, 1H), 5.53 (m, 2H), 4.9 (s, 1H), 4.87 (s, 1H), 4.5 (m, 4H), 3.79 (s, 3H), 3.58-3.48 (m, 4H), 3.06 (s, 2H), 2.37 (q, *J* = 6.6 Hz, 2H),

1.8 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.3, 159.0, 138.4, 138.2, 131.6, 129.9, 129.0, 128.2, 127.4, 126.7, 114.4, 113.6, 73.0, 72.7, 72.5, 71.0, 69.2, 55.0, 43.5, 32.6, 22.3; IR (KBr) ν_{max} : 3060, 3031, 2918, 2852, 1733 cm^{-1}; HRMS: Calcd for $C_{26}H_{36}NO_5$ $(M+NH_4)^+$: 442.2565, found: 442.2565.

(*2S, 3R, E*)-Methyl 3-(2-(benzyloxy)ethyl)-6-(4-methoxybenzyloxy)-2-(prop-1-en-2-yl)hex-4-enoate (10)

To a stirred solution of ester **6** (1.9 g, 4.48 mmol) in dry THF (45 mL) and TMSCl (1.2 ml, 8.9 mmol) was added. After the mixture was cooled to –78 °C, LiHMDS (6.7 mL, 1M in THF, 6.7 mmol) was slowly added. The reaction was slowly warmed to room temperature and stirred for 15 h. It was acidified to pH 2-3 with 1N HCl aqueous solution and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The crude acid was taken to next step without purification. Acid was dissolved in to dry ether and treated with ethereal solution of diazomethane at 0 °C. After stirring the mixture for 0.5 h, aqueous NH_4Cl solution was added and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel hexanes/EtOAc 8:2 to give **10** (1.55 g, 79%) for two steps. $[\alpha]^{20}_D$ +25.30 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35-7.20 (m, 7H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.61-5.50 (dt, *J* = 15.4 Hz, 1H), 5.3 (dd, *J* = 15.4 Hz, 1H), 4.88 (d, *J* = 6.7 Hz, 2H), 4.46 (q, *J* = 11.8 Hz, 2H), 4.35 (q, *J* = 11.5 Hz, 2H), 3.9 (m, 2H), 3.80 (s, 3H), 3.67 (s, 3H), 3.45 (m, 2H), 3.03 (d, *J* = 10.5 Hz, 1H), 2.76 (qd, *J* = 10.1 Hz, 2.6 Hz, 1H), 1.84-1.73 (m, 1H), 1.71 (s, 3H), 1.54-1.40 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.9, 159.0, 141.3, 138.4, 133.6, 130.3, 129.3, 128.7, 128.2, 127.6, 127.4, 115.5, 113.7, 72.7, 70.8, 69.8, 67.9, 58.4,

55.2, 51.8, 39.8, 32.8, 19.8; IR (KBr) ν_{max} : 2946, 2855, 1734, 1513, 1247cm^{-1}; HRMS: Calcd for $C_{27}H_{38}NO_5$ $(M+NH_4)^+$: 456.2744, found: 456.2733.

(*2S, 3R, E*)-3-(2-(Benzyloxy)ethyl)-6-(4-methoxybenzyloxy)-2-(prop-1-en-2-yl)hex-4-en-1-ol (5)

A solution of methyl ester **10** (1.5 g, 3.42 mmol) in CH_2Cl_2 (35 mL) was cooled in 0 ^oC and treated drop wise with DIBAL-H (3.88 mL, 6.84 mmol, 25% in toluene). The reaction mixture was stirred at 0 $^\circ C$ for 1 h and then quenched with saturated aqueous potassium sodium tartrate. The biphasic mixture was washed with CH_2Cl_2. The combined organic layers washed with H_2O and brine, dried over (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexanes/EtOAc, 7:3) which gives alcohol **5** (1.4 g, 86%) as an oil. $[\alpha]^{20}_D$ −25.30 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.34-7.20 (m, 7H), 6.87 (d, *J* = 8.3 Hz, 2H), 5.55-5.33 (m, 2H), 4.94 (s, 1H), 4.80 (s, 1H), 4.46 (q, *J* = 11.3 Hz, 2H), 4.37 (q, *J* = 12.0 Hz, 2H), 3.91 (m, 2H), 3.70 (dd, *J* = 10.5 Hz, 1H), 3.56 (t, *J* = 10.5 Hz, 1H), 3.51-3.35 (m, 2H) 2.40-2.21 (m, 2H), 1.86 (m, 1H), 1.68 (s, 3H), 1.60 (br, 1H), 1.45 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.0, 144.1, 138.3, 135.0, 130.4, 129.2, 128.3, 127.8, 127.7, 127.5, 114.9, 113.7, 72.9, 70.0, 68.0, 62.0, 55.2, 53.9, 39.2, 32.1, 20.1; IR (KBr) ν_{max} : 3454, 3067, 2935, 2858, 1612, 1513, 1248 cm^{-1}; HRMS: Calcd for $C_{26}H_{38}NO_4$ $(M+NH_4)^+$: 428.2795, found: 428.2779.

(*2S, 3R, E*)-3-(2-(Benzyloxy)ethyl)-6-(4-methoxybenzyloxy)-2-(prop-1-en-2-yl)hex-4-enyl acetate (11)

To a solution of alcohol **5** (1.2 g, 2.9 mmol) in anhydrous dichloromethane (20 mL) cooled at 0 ^oC were added dry TEA (2.0 mL, 14.6 mmol) followed by DMAP (5 mol %). Acetic anhydride

(0.85 mL, 8.7 mmol) was added dropwise and the reaction was stirred at the room temperature for 5 h. The mixture was diluted with dichloromethane (20 mL) and washed with water (2 x 10 mL), brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure yielded the crude product which was purified by flash column chromatography on silica gel using EtOAc/hexanes as eluent to afford acetate **11** as a oil (1.19 g) 95% yield. $[\alpha]^{20}_D$ −18.10 (*c* 1.16, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37-7.19 (m, 7H), 6.88 (d, J = 8.3 Hz, 2H), 5.58-5.36 (m, 2H), 4.85 (s, 1H), 4.71 (s, 1H), 4.52- 4.34 (m, 4H), 4.23-4.03 (m, 2H), 3.95-3.90 (m, 2H), 3.80 (s, 3H), 3.52-3.35 (m, 2H), 2.42 (m, 2H), 2.02 (s, 3H), 1.94-1.80 (m, 1H), 1.68 (s, 3H), 1.57-1.42 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.9, 159.0, 143.4, 138.4, 134.3, 130.4, 129.2, 128.3, 128.2, 127.5, 127.4, 114.0, 113.7, 72.8, 71.0, 70.0, 68.1, 64.6, 55.1, 49.7, 39.6, 32.2, 20.99, 20.90; IR (KBr) ν_{max} : 2922, 2852, 1736, 1511, 1239 cm^{-1}; HRMS: Calcd for $C_{28}H_{36}O_5Na$ $(M+Na)^+$: 475.2455, found: 475.2485.

(*2S, 3R, E*)-3-(2-(Benzyloxy)ethyl)-6-hydroxy-2-(prop-1-en-2-yl)hex-4-enyl acetate (12)

To a solution of acetylated compound **11** (1.1 g, 2.43 mmol) in a mixture of CH_2Cl_2 (9 mL) and water (3 mL), DDQ (1.1 g, 4.89 mmol) was added at 0 °C. After 30 min, the reaction mixture was warmed to room temperature and stirred for an additional 30 min before it was diluted with CH_2Cl_2 (10 mL) and quenched with water (10 mL). The resulting heterogeneous mixture was filtered, and the organic phase was separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (20 mL), dried with Na_2SO_4, and filtered. The organic solvent was removed under reduced pressure, and the residue was purified by flash column chromatography, eluting with (EtOAc/hexanes 3:7) to afford the pure allylic alcohol **12** (719 mg) as a colorless oil in 89% yield. $[\alpha]^{20}_D$ −22.70 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38-7.22 (m, 5H), 5.60-5.49 (dt, J = 15.1 Hz, 1H), 5.39 (dd, J = 15.8 Hz, 1H), 4.85 (s, 1H), 4.69 (s, 1H), 4.46 (q, J = 12.0 Hz,

2H), 4.21-4.05 (m, 2H), 4.02 (d, J = 6.7 Hz, 2H), 3.52-3.35 (m, 2H), 2.4 (m, 2H), 2.02 (s, 3H), 1.86 (m, 2H), 1.66 (s, 3H), 1.56-1.42 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.0, 143.1, 138.3, 132.6, 130.9, 128.2, 127.6, 127.4, 114.0, 72.7, 67.9, 64.5, 63.1, 49.5, 39.2, 32.0, 21.1, 20.8; IR (KBr) ν_{max} : 3442, 3069, 3030, 2920, 2861, 1737, 1242 cm^{-1}; HRMS: Calcd for $C_{20}H_{28}O_4Na$ $(M+Na)^+$:355.1880, found: 355.1888.

(*2S,3S*)-5-(Benzyloxy)-3-((*2R,3R*)-3-(hydroxymethyl)oxiran-2-yl)-2-(prop-1-en-2-yl)pentyl acetate (13)

To a stirred suspension of activated 4 A^o molecular sieves (2 g) in CH_2Cl_2 (12 mL) was added D-(-)-DET (0.72 mL, 4.2 mmol) and Ti(O-*i*-Pr)$_4$ (1.28 mL, 4.2 mmol) and the resulting mixture was stirred for 30 min at -20 °C. The allyl alcohol **12** (700 mg, 2.1 mmol) in dry CH_2Cl_2 (4 mL) was added dropwise and the resulting mixture was stirred for another 30 min at -20 °C. TBHP (1.6 mL, 4M in toluene, 6.3 mmol) was added and the resulting mixture stirred at the same temperature for 5 h. It was then warmed to 0 °C, quenched with TPP and stirred for 1 h at room temperature. The resulting mixture was filtered through Celite and the filter cake was washed well with CH_2Cl_2. Combined organic layers were washed with brine and dried over Na_2SO_4. Removal of solvent under reduced pressure and purification by silica gel column chromatography using ethyl acetate and hexanes (3:7) afforded **13** (600 mg, 82%) as a colorless viscous liquid. $[\alpha]^{20}_D$ +10.4 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36 -7.23 (m, 5H), 4.91 (s, 1H), 4.75 (s, 1H), 4.51 (s, 2H), 4.25 (dd, J = 10.9 Hz, 1H), 4.11 (dd, 1H), 3.80 (dd, J = 11.9 Hz, 3H), 3.72-3.66 (m, 1H), 3.62-3.54 (m, 2H), 2.87 (br, 1H), 2.82 (dd, J = 8.9 Hz, 1H), 2.53 (q, J = 7.9 Hz, 1H), 2.01(s, 3H), 1.96-1.89 (m, 1H), 1.79 (m, 1H), 1.71 (s, 3H), 1.56-1.49 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.9, 143.2, 138.3, 128.2, 127.5, 127.4, 113.9, 72.9,

68.0, 64.0, 61.5, 58.6, 58.3, 47.3, 38.2, 30.5, 20.8; IR (KBr) ν_{max} : 3447, 3070, 3027, 2917, 2862, 1734, 1238 cm^{-1}; HRMS: Calcd for $C_{20}H_{29}O_5$ $(M+H)^+$: 349.2010, found: 349.1991.

(*2S,3S*)-5-(Benzyloxy)-3-((*2R,3R*)-3-((*tert*-butyldimethylsilyloxy)methyl)oxiran-2-yl)-2-(prop-1-en-2-yl)pentyl acetate (14)

To a stirred solution of epoxy alcohol **13** (600 mg, 5.9 mmol) and imidazole (155 mg, 2.5 mmol) in CH_2Cl_2 (10 mL) was added TBDMS-Cl (336 mg, 2.2 mmol) at 0 ^oC portion wise over a period of 10 min. The reaction mixture was stirred at room temperature for 2 h. The mixture was then diluted with CH_2Cl_2 and washed with water and brine. The separated organic layer was dried over anhydrous Na_2SO_4, and concentrated. The crude was purified by flash silica gel column chromatography using ethyl acetate and hexanes (1:9) to afford TBS protected alcohol **14** (748 mg, 94%) as a colorless oil. $[\alpha]^{20}_D$ +9.4 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.55-7.36 (m, 5H), 5.05 (s, 1H), 4.90 (s, 1H), 4.66 (s, 2H), 4.43-4.24 (m, 2H), 3.96-3.68 (m, 4H), 2.97 (m, 1H), 2.86 (dd, *J* = 8.87 Hz 1H), 2.68 (q, *J* = 7.55 Hz 1H), 2.16 (s, 3H), 2.11-1.90 (m, 2H), 1.65(m, 1H), 1.04 (s, 9H), 0.21 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.6, 143.1, 138.5, 128.2, 127.5, 127.3, 114.0, 72.9, 68.2, 64.2, 63.3, 58.6, 58.4, 47.4, 38.4, 30.8, 25.7, 21.1, 20.8, 18.2, -5.41, -5.49; IR (KBr) ν_{max} : 2954, 2930, 2857, 1742, 1459, 1251, 1231 cm^{-1}; HRMS: Calcd for $C_{26}H_{43}O_5Si$: $(M+H)^+$: 463.2874, found:463.2912.

(((*2R,3R*)-3-((*3S,4S*)-4-(Azidomethyl)-1-(benzyloxy)-5-methylhex-5-en-3-yl)oxiran-2-yl) methoxy)(*tert*-butyl)dimethylsilane (15)

To carry out the deacetylation K_2CO_3 (209 mg, 1.5 mmol) was added to acetate **14** (700 mg, 1.5 mmol) in MeOH (15 mL), and the solution was stirred for 1 h at -10 ^oC. It was then poured in saturated NaCl solution (5 mL), and extracted with EtOAc. Drying with (Na_2SO_4) and concentration of combined organic layers *in vacuo* was carried out. The crude alcohol was taken

to next step without further purification. A solution of alcohol (700 mg, 1.6 mmol) in anhydrous THF (7 mL) was cooled to 0 ^{o}C, and triphenylphosphine (434 mg, 0.75 mmol) was added at once. After 5 min of stirring DIAD (330 mg, 0.33 mL, 1.6 mmol) and subsequently DPPA (440 mg, 0.36 mL, 1.6 mmol) were added. The ice bath was removed, and resulting mixture was stirred from 0 ^{o}C, to rt for 10 h. Volatiles were evaporated under reduced pressure, and the residue was subjected to silica gel column chromatography using ethyl acetate and hexanes (2:8) which afforded **15** (286 mg, 45% for two steps) as a colorless viscous liquid. $[\alpha]^{20}_{D}$ −0.30 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38 -7.23 (m, 5H), 4.98 (s, 1H), 4.83 (s, 1H), 4.52 (s, 2H), 3.78-3.63 (m, 2H), 3.63-3.48 (m, 3H), 3.33 (dd, *J* = 9.8 Hz, 1H), 2.82 (m, 1H), 2.68 (dd, *J* = 9.06 Hz, 1H), 2.45 (m, 1H), 1.91-1.76 (m, 2H), 1.73 (s, 3H), 1.45 (m, 1H), 0.9 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.1, 138.3, 128.3, 127.7, 127.5, 114.8, 73.0, 63.4, 58.7, 58.3, 51.8, 48.2, 39.0, 30.9, 25.8, 20.8, -5.3, -5.4; IR (KBr) ν_{max} : 3030, 2931, 2858, 2101, 1099 cm^{-1}; HRMS: Calcd for $C_{24}H_{39}N_3O_3SiNa$ $(M+Na)^+$: 468.2653, found: 468.2664.

((*2R,3R*)-3-((*3S,4S*)-4-(Azidomethyl)-1-(benzyloxy)-5-methylhex-5-en-3-yl)oxiran-2-yl)methanol (4)

To a solution of **15** (280 mg, 0.62 mmol) in THF (6 mL) was added TBAF (0.7 mL, 1.0 M in THF, 0.69 mmol). The resulting solution was stirred at 0 ^{o}C for 2 h and poured into saturated NH_4Cl. The mixture was extracted with EtOAc followed by drying with Na_2SO_4 and concentration of combined organic layers under reduced pressure. Residue was purified by silica gel column chromatography (hexanes/EtOAc, 7:3) to obtain **4** (187 mg, 90%) as a clear oil. $[\alpha]^{20}_{D}$ −0.62 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39 -7.25 (m, 5H), 4.98 (s, 1H), 4.83 (s, 1H), 4.52 (s, 2H), 3.83 (br, 1H), 3.75-3.48 (m, 4H), 3.30 (dd, *J* = 9.0 Hz, 1H), 2.87 (m, 1H), 2.80 (dd, *J* = 9.0 Hz, 1H), 2.50-2.40 (m, 1H), 1.95-1.82 (m, 1H), 1.82-1.75 (m, 1H), 1.72

(s, 3H), 1.66 (br, 1H), 1.53-1.41 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 143.5, 138.3, 128.3, 127.6, 127.5, 114.7, 73.0, 67.9, 61.5, 58.45, 58.40, 51.6, 48.2, 38.7, 30.6, 20.3; IR (KBr) ν_{max} : 3381, 3030, 2927, 2107 cm^{-1}; HRMS: Calcd for $C_{18}H_{25}N_3O_3Na$ $(M+Na)^+$: 354.1788, found: 354.1804.

(*2S, 3S, 4S*)-*tert*-Butyl 3-(2-(benzyloxy)ethyl)-2-((*S*)-1,2-dihydroxyethyl)-4-(prop-1-en-2-yl)pyrrolidine-1-carboxylate (16)

To a solution of epoxy azido alcohol **4** (100 mg, 0.30 mmol) in THF (1.5 mL) and H_2O (0.2 mL) was added triphenylphosphine (118 mg, 0.45 mmol). The reaction was stirred at room temperature for 48 h after which *tert*-butyl dicarbonate (98 mg, 0.1 mL, 0.45 mmol) and Et_3N were added and the stirring was continued for additional 12 h. The reaction was diluted with EtOAc and washed with water, brine. The organic layer was dried over anhydrous Na_2SO_4, and concentrated. The crude was purified by flash silica gel column chromatography using ethyl acetate and hexanes (5:5) to afford BOC protected diol **16** (83 mg, 68%) as a clear oil. $[\alpha]^{20}_D$ −34.17 (*c* 2.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39 -7.23 (m, 5H), 4.90 (s, 1H), 4.62 (s, 2H), 4.51 (s, 2H), 4.29 (dd, *J* = 4.53 Hz, 1H), 3.71-3.46 (m, 5H), 3.40-3.28 (m, 3H), 2.85 (br, 2H), 2.48 (m, 1H), 1.74 (s, 3H), 1.59 (m, 1H), 1.47 (s, 9H) 1.27 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.2, 141.9, 138.2, 128.3, 127.6, 127.5, 111.7, 80.7, 73.1, 72.6, 68.7, 63.8, 62.4, 47.8, 45.5, 38.9, 28.3, 27.4, 22.7; IR (KBr) ν_{max} : 3047, 3069, 2967, 2926, 2862, 1665, 1415, 1169 cm^{-1}; HRMS: Calcd for $C_{23}H_{35}NO_5$ $(M+H)^+$: 406.2588, found: 406.2590.

(*2S,3S,4S*)-*tert*-Butyl3-(2-(benzyloxy)ethyl)-2-(hydroxymethyl)-4-(prop-1-en-2-yl)pyrrolidine-1-carboxylate (17)

To a solution of compound **16** (83 mg, 0.2 mmol) in THF/H_2O (2:1, 3 mL) were added $NaIO_4$ (87 mg, 2 equiv, 0.4 mmol). The solution was stirred at 0 ^oC until completion (1 h), then quenched by addition of H_2O (5 mL) followed by the addition of CH_2Cl_2 (5 mL). The aqueous layer was extracted with CH_2Cl_2 twice and combined organic layer were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude aldehyde was taken to next step without purification. To a solution of the above aldehyde in MeOH (4 mL) at 0 ^oC were added $NaBH_4$ (8 mg, 0.2 mmol). After the mixture was stirred for 10 min to complete the reaction, it was quenched with saturated NH_4Cl solution and aqueous layer was extracted with EtOAc twice. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ethyl acetate and hexanes (4:6) to get alcohol **17 (**66 mg, 87% two steps) as a clear oil. $[\alpha]^{20}_D$ −31.40 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.39 -7.24 (m, 5H), 4.86 (s, 1H), 4.62 (s, 2H), 4.49 (s, 2H), 4.36 (t, J = 4.7 Hz, 1H), 3.82 (br, 1H), 3.65 (t, J = 4.7 Hz, 2H), 3.5 (br, 2H), 3.43 (d, J = 7.3 Hz, 2H), 2.78 (m, 1H), 2.1 (m, 1H), 1.69 (s, 3H), 1.60 (m, 1H), 1.47 (s, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.0, 142.6, 138.2, 128.3, 127.5, 112.5, 80.4, 72.9, 68.1, 67.3, 64.7, 48.9, 46.2, 39.5, 28.4, 28.0, 22.0; IR (KBr) ν_{max} : 3422, 3071, 2973, 2926, 2857, 1691, 1670, 1411 cm^{-1}; HRMS: Calcd for $C_{22}H_{33}O_4NNa$: $(M+Na)^+$: 398.2302, found: 398.2296.

(*2S,3S,4S*)-*tert*-Butyl 3-(2-hydroxyethyl)-2-(hydroxymethyl)-4-(prop-1-en-2-yl)pyrrolidine-1-carboxylate (18)

To a solution of alcohol **17** (60 mg, 0.16 mmol) in THF (2.0 mL) at 0 ^oC was added a solution of Li/naphthalene in THF (prepared by dissolving 204 mg of naphthalene in 2.0 mL of THF and adding 8 mg of Li, stirring vigorously until a dark green solution is obtained) until the persistence of a green color to the solution for more than 1 h. The reaction was monitored by

TLC and complete consumption of starting material. H_2O and EtOAc were added to the solution and the phases were separated. The aqueous layer was extracted with EtOAc (3x3) and the combined organic layers were dried on Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (EtOAc/Hexanes 6:4) to afford 36 mg of **18** as colorless oil (81%). $[\alpha]^{20}_D$ −36.20 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.90 (s, 1H), 4.66 (s, 1H), 4.33 (br, 1H), 3.85-3.54 (br, 5H), 3.43 (d, J = 7.55 Hz, 2H), 2.85 (br, 1H), 2.17 (br, 1H), 1.72 (s, 3H), 1.64-1.45 (br, m, 10H), 1.36 (br, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.7, 142.6, 112.5, 80.4, 66.5, 64.6, 60.7, 48.9, 46.2, 39.2, 30.6, 28.4, 22.1; IR (KBr) ν_{max} : 3380, 2625, 2855, 1669, 1413, 772 cm^{-1}; HRMS: Calcd for $C_{15}H_{27}NO_4Na$ $(M+Na)^+$: 308.1832, found: 308.1854.

(*2S,3S,4S*)-3-(Carboxymethyl)-4-(prop-1-en-2-yl)pyrrolidine-2-carboxylic acid (1)

Jones' reagent (2.3 M, 100 μL) was added drop wise over 2 min to a stirred ice cooled solution of **18** (22 mg, 0.07 mmol) in acetone (2 mL), and stirring was continued for 30 min at 0 °C. The overload of Jones' reagent was quenched by addition of *i*-propanol (200 μL). The green suspension was stirred for 5 min at 0°C and 10 min at room temperature. The clear greenish supernatant was filtered, and the remaining green residue was extracted with EtOAc. The combined organic layers were washed with brine dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (400 μL). The solution was treated with TFA (50 μL). After stirring at room temperature for 3 h solvents were removed under reduced pressure. The residue was dissolved in water (1 mL) and added to a column DOWEX 50 WX8 (H^+) (50-100 mesh). Elution with 1M NH_4OH and evaporation of the collected fractions under reduced pressure yielded an orange oil (-)-α-kainic acid **1** (10 mg, 62 %). $[\alpha]^{20}_D$ −14.3 (*c* 0.6, H_2O); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.04 (s, 1H), 4.75 (s, 1H), 4.08 (s, 1H), 3.63 (dd, J = 12.1Hz, 7.6 Hz, 1H), 3.43 (t, J = 11.4 Hz, 1H), 3.09-2.97 (br, 2H), 2.36 (dd, J = 15.9 Hz, 6.0 Hz,

1H), 2.26 (m, J = 15.9 Hz, 1H), 1.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.3, 173.6, 140.1, 113.2, 66.0, 46.4, 45.9, 41.4, 38.0, 22.3; IR (KBr) ν_{max} : 3364, 3199, 2924, 2846, 1663, 1391, 1219 cm^{-1}; HRMS: Calcd for $C_{10}H_{14}O_4N$: 212.0917, found: 212.0927.

Acknowledgement

N.K.R. thanks UGC-New Delhi, for the award of research fellowship and SCS thank CSIR New Delhi for financial assistance.

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http:// pubs.acs.org.

References

(1) (a) Murakami, S.; Takemoto, T.; Shimizu, Z. *J. Pharm. Soc. Jpn.* **1953**, *73*, 1026. (-)-α-kainic acid has also been isolated from *Centrocerus clavulatum* (b) Impellizzeri, G.; Mangiafico, G.; Oriente, G.; Piattelli, M.; Sciuto, S.; Fattorusso, E.; Magno, S.; Santacroce, C.; Sica, D. *Phytochemistry* **1975**, *14*, 1549. and from *Alsidum helmithocorton* (c) Balansard, G.; Pellegrini, M.; Cavalli, C.; Timon-David, P. *Ann. Pharm. Fr.* **1983**, *41*, 77.

(2) Coyle, J. T.; Schwarcz, R. *Nature* (London) **1976**, *263*, 244.

(3) (a) Sperk, G. Prog. *Neurobiol*. (Oxford) **1994**, *42*, 1. (b) Xiang-Yu, Z.; Hong-Liang Z.; Qi L.; Jie, Z. *Journal of Biomedicine and Biotechnology* **2011**, Article ID 457079

(4) For total syntheses of (+)- and (-)-α-kainic acid, see: (a) Deshong, P.; Kell, D. A. *Tetrahedron Lett*. **1986**, *27*, 3979. (b) Cooper, J.; Knight, D. W.; Gallagher, P. T. *J. Chem. Soc. Chem. Commun.* **1987,** *16*, 1220. (c) Cooper, J.; Knight, D. W; Gallagher, P. T. *J. Chem. Soc, Perkin Trans. 1* **1992**, 553. (d) Yoo, S. E.; Lee, S. H. *J. Org. Chem.* **1994,** *59***,** 6968. (e) Xia, Q.;

Ganem, B. *Org. Lett*. **2001**, *3*, 485. (f) Anderson, J. C.; Whiting, M. *J. Org. Chem.* **2003***, 68,* 6160. (g) Trost, B. M.; Rudd, M. T. *Org. Lett*. **2003**, *5,* 1467. (h) Greenwood, E. S.; Hitchcock, P. B.; Parsons, P. J. *Tetrahedron* **2003***, 59*, 3307. (i) Martinez, M. M.; Hoppe, D. *Org. Lett*. **2004**, *6*, 3743. (j) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc*. **2005**, *127*, 4763. (k) Morita, Y; Tokuyama, H; Fukuyama, T. *Org. Lett*. **2005**, *7*, 4337. (l) Martinez, M. M; Hoppe, D. *Eur. J. Org. Chem.* **2005**, *7*, 1427. (m) Hodgson, D. M.; Hachisu, S.; Andrews, M. D. *Org. Lett*. **2005**, *7*, 815. (n) Scott, M. E.; Lautens, M. *Org. Lett*. **2005**, *7*, 3045. (o) Pandey, S. K.; Orellana, A.; Greene, A. E.; Poisson, J. -F. *Org. Lett*. **2006**, *8*, 5665. (p) Jung, Y. C.; Yoon, C. H.; Turos, E.; Yoo, S. K.; Jung, K. W. *J. Org. Chem.* **2007**, *72*, 10114. (q) Majik, M. S.; Parameswaran, P. S.; Tilve, S. G. *J. Org. Chem.* **2009**, *74*, 3591. (r) Farwick, A.; Helm hen, G. *Org. Lett.* **2010**, *12*, 1108. (s) Kitamoto, K.; Sampei, M.; Nakayama, Y.; Sato, T.; Chida, N. *Org. Lett.* **2010**, *12*, 5756. (t) Takita, S.; Yokoshima, S.; Fukuyama, T. *Org. Lett*. **2011**, *13*, 2068. (u) Kamon, T.; Irifune, Y.; Tanaka, T.; Yoshimitsu, T. *Org. Lett*. **2011**, *13*, 2674. (v) Wei, G.; Chalker, J. M.; Cohen, T. *J. Org. Chem.* **2011**, *76*, 7912. (w) Evans, P. A.; Inglesby, P. A. *J. Am. Chem. Soc.* **2012**, *134*, 3635. (x) Luo, Z.; Zhou, B.; Li, Y. *Org. Lett*. **2012**, *14*, 2540. (y) Orellana, A.; Pandey, S. K.; Carret, S.; Greene, A. E.; Poisson, J. F. *J. Org. Chem*. **2012**, *77*, 5286. (z) Kitamoto, K.; Nakayama, Y.; Sampei, M.; Ichiki, M.; Furuya, N.; Takaaki, S.; Noritaka, C. *Eur. J. Org. Chem.* **2012**, *22*, 4217.

(5) For reviews on the kainoids, see: (a) Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149. (b) Moloney, M. G. *Nat. Prod. Rep.* **2002**, *19*, 597. (c) Stathakis, C. I.; Yioti, E. G.; Gallos, J. K. *Eur. J. Org. Chem.* **2012**, *25,* 4661.

(6) (a) Chandrasekhar, S.; Ramchander, T.; Reddy, M. V. *Synthesis* **2002**, *13*, 1867; (b) Chandrasekhar, S.; Jagadeshwar, V.; Prakash, S. J. *Tetrahedron Lett*. **2005**, *46*, 3127; (c)

Chandrasekhar, S.; Yaragorla, S. R.; Sreelakshmi, L. *Tetrahedron Lett.* **2007**, *48*, 7339. (d) Chandrasekhar, S.; Vijaykumar, B. V. D.; Pratap, T. V. *Tetrahedron:Asymmetry* **2008**, *19*, 746; (e) Chandrasekhar, S.; Rambabu, C.; Syamprasad Reddy, A. R. *Org. Lett.* **2008,** *10,* 4355. (f) Chandrasekhar, S.; Sudhakar, A. *Org. Lett.* **2010**, *12*, 236. (g) Mallesham, P.; Vijaykumar, B. V. D.; Shin D. S.; Chandrasekhar, S. *Tetrahedron Lett*. **2011**, *52*, 6145.

(7) Cooper, J.; Knight, D. W.; Gallager, P. T. *J. Chem. Soc. Chem. Commun.* **1987**, 1220.

(8) Shangguan, N.; Kiren, S.; Williams, L. J. *Org. Lett.* **2007**, *9*, 1093.

(9) Xing, Y.; O'Doherty, G.A. *Org. Lett.* **2009,** *11*, 1107.

(10) Smith, III, A. B.; Toder, B. H.; Branca, S. J.; Dieter R. K. *J. Am. Chem. soc*. **1981,** *103,* 1996.

(11) (a) Williams, D. R.; Cullen Klein, J.; Nicholas S. C. Chow. *Tetrahedron Lett*. **2011**, *52*, 2120; (b) Hwang, S.; Kim, D.; Kim, S. *Chem. Eur. J.* **2012**, *18*, 9977.

(12) Takebayashi, M.; Hiranuma, S.; Kanie, Y.; Kajimoto, T.; Kanie, O. Wong, C. H. *J. Org. Chem.* **1999,** *64,* 5280.