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New synthetic routes to the kainoids: a synthesis of kainic acid and its analogues

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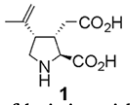
ABSTRACT

New approaches to the synthesis of kainic acid and its analogues are presented. Two distinctly different approaches are described; the former utilised an intermolecular nitrile oxide addition to a homochiral substrate to furnish epikainate models and the second utilised amino acid chemistry to secure kainic acid.

1. Introduction

(−)-Kainic acid **1** and its analogues[1] have attracted a great deal of interest from the chemical and biological communities since the 1950's. Their potent anthelmintic properties have been utilized for hundreds of years[2] and kainic acid has become a very powerful tool in neurobiology[3] through use in experimental models for Huntington's chorea,[4,5] epilepsy[6] and dementia. Although the kainates are unlikely to be used in therapeutic areas, the information gained from biological models could lead to treatments for neuronal diseases.



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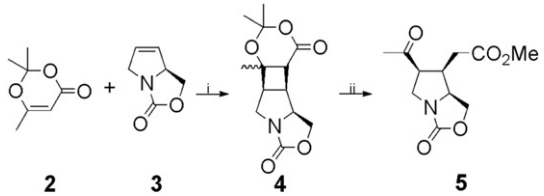
The limited availability of kainic acid[7,8] and its analogues mean that new and efficient routes are still required to fulfil the demands of the neuropharmacologists.

Kainic acid **1** has a highly functionalised pyrrolidine ring containing three contiguous asymmetric centres and has attracted significant synthetic interest, particularly with regard to the crucial *syn*-relationship that exists between the substituents at the C-3 and C-4 positions. Many past syntheses have solved this issue by utilising a stereoselective formation of the C-3/C-4 bond or by using a stereoselective ring closure with the C-2 substituent. There have been more than 30 enantioselective syntheses to date,[9–48] many of which are included in a review by Parsons.[1] Despite this devotion to kainic acid **1**, which is one of the most investigated synthetic targets to date, many of the published syntheses are limited in yield and stereoselectivity.

Our approaches to the kainates reported herein offer alternative routes to analogues of kainic acid **1** and provide hitherto unknown structures, which possess kainate like architecture. These compounds will be useful for the design of novel excitatory amino acids. The nitrile oxide approach to the epikainates demonstrates further the unexpected stereocontrol of addition to the alkene **3**.

We have shown previously that photoaddition of the ketal **2** to the alkene **3** proceeds with regio and stereochemical control (Scheme 1).[49]



2 **3** **4** **5**

Scheme 1. Reagents and conditions: (i) *hν*, EtOAc (38%); (ii) MeONa.

Methoxide induced ring opening of the cyclobutane **4** gave the carboxylate **5**. This initially surprising stereochemical result led us[49] and others[50] to investigate the general chemistry of the alkene **3**.

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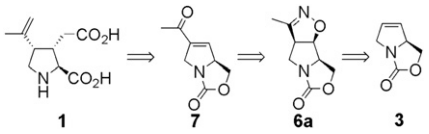
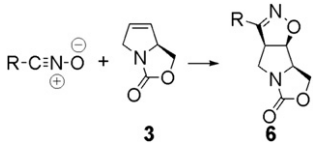
1.1. Cyclisation studies and the new approach to kainate synthesis

In view of the unexpected photoaddition of alkenes to the more hindered face of **3** and the unexpected addition of electrophiles to the more hindered face of the double bond in **3** we initially investigated the intermolecular addition of a range of nitrile oxides to **3**. Our retrosynthetic analysis of the kainoids is shown in Scheme 2



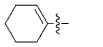
Scheme 2.

The alkene **3** was treated with a series of nitrile oxides (Scheme 3), which were generated by known methods (Table 1).[51,52]



Scheme 3.

Table 1
Nitrile oxides for cycloaddition.

R	Compound	Yield (%)
Me	**6a**	68
Ph	**6b**	68
Et	**6c**	36
	**6d**	95
	**6e**	24

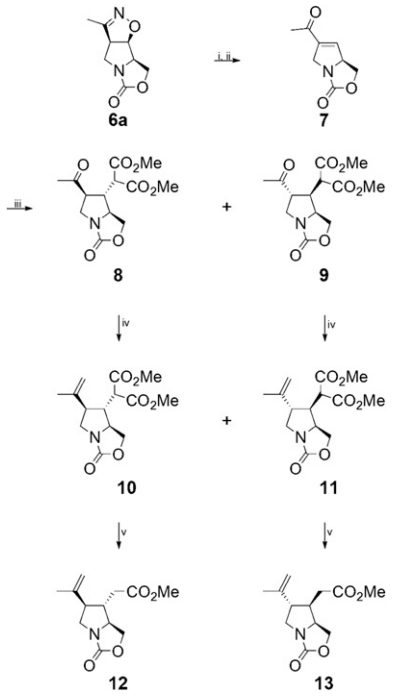
Calculations from our laboratory have shown that the homo of the alkene **3** reveals an unsymmetrical pi bond with a higher electron density on its *endo* face.[49]

Cleavage of the weak N–O bond in **6**a with Raney-Nickel[53] gave the enone **7**. Addition of sodio dimethyl malonate[54] to **7** gave a mixture of adducts **8** and **9** in a 1:1 ratio, which, were easily separated on silica (Scheme 4). Reaction of **8** and **9** with methylidene-triphenylphosphorane[22] gave the alkenes **10** and **11**, which, followed by decarboxylation[55] afforded the esters **12** and **13**.

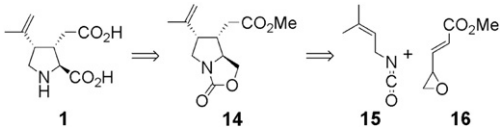
In view of the results obtained, which allow the preparation of the allo-kainate models, we were encouraged to design a specific synthesis of kainic acid **1**, which utilised the cyclic carbamate unit as a template for intramolecular ene reactions.

1.2. Investigation into kainate synthesis

We have devised a 'one-pot' synthesis of kainic acid, which utilises a two component coupling sequence (Scheme 5).

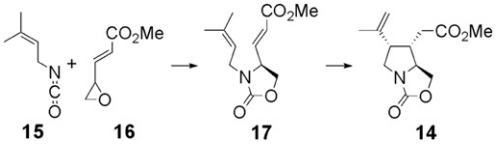


Scheme 4. Reagents and conditions: (i) Raney Ni, H_2, $B(OH)_3$, MeOH+H_2O (5:1) (77%); (ii) *p*TSA, toluene, reflux, (75%); (iii) NaH, DMM, THF, 0 °C to rt (90% 1:1); (iv) $Ph_3P{=}CH_2$, −78 °C, (70%); (v) NaCl, DMSO+H_2O (9:1), 170 °C, 8 h, (72%).



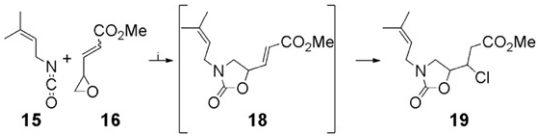
Scheme 5.

Isocyanates are known to react with epoxides and we envisaged that the readily available isocyanate **15** could react with epoxide **16** to form the heterocycle **14** in one synthetic operation (Scheme 6).



Scheme 6.

The isocyanate **15** was prepared by the method reported by Christopherson[56] and the epoxides **16** were prepared by modification of the procedure reported by Font et al.[57] When the isocyanate and epoxide were reacted together following the general procedure reported by Herweh et al.[58] the ester **19** was isolated instead of the desired product **17** (Scheme 7). The unsaturated ester moiety seems to destabilize cation formation and hence the isocyanate reacted at the least hindered face.

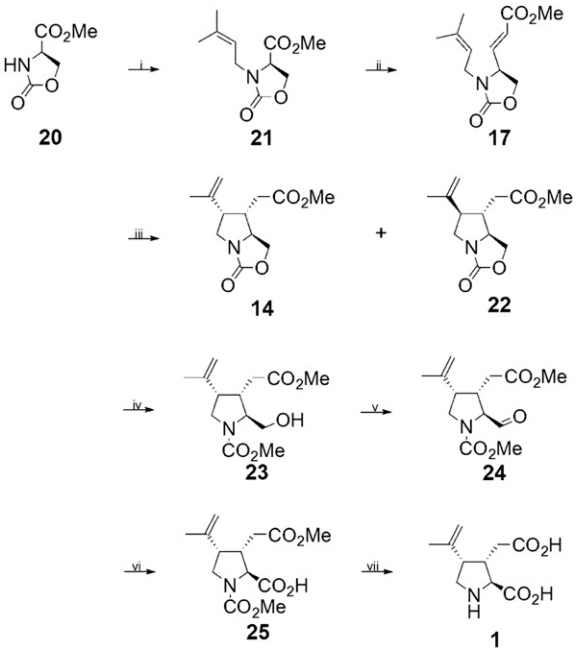


Scheme 7. Reagents and conditions: (i) $CaCl_2$, DMF, Δ (4%).

Calcium chloride was added to the DMF in order to act as a Lewis acid and to remove any traces of dimethylamine. Chloride anion was found to add to the initially formed acrylate **18**.

1.3. Total synthesis of kainic acid

In view of the undesired regiochemistry of addition of epoxide **16** to the isocyanate **15** we elected to carry out the synthesis of kainic acid using D-Serine methyl ester as the starting material. The new route to kainic acid is shown in Scheme 8.



Scheme 8. Reagents and conditions: (i) NaH, THF+DMF (4:1), 1-bromo-3-methyl-2-butene 0 °C-rt, (78%); (ii) DIBAL-H, CH_2Cl_2, −78 °C, followed by NH_4Cl $(C_6H_5)_3P{=}CHCO_2CH_3$, −20 °C, (83%); (iii) MW, DEA, 200 °C, 4 h (80% 7:1 in favour of **14**); (iv) Cs_2CO_3, MeOH, rt, 5 days (80%); (v) SO_3, Et_3N, DMSO, CH_2Cl_2, 0 °C-rt, (89%); (vi) $NaClO_2$, $NaHPO_4$, 2-methyl-2-butene, ^tBuOH, H_2O, rt; (vii) $NaOH_{(aq)}$, MeOH, Δ, 18 h followed by Ion-exchange chromatography and recrystallisation from water (60% from aldehyde).

D-Serine hydrochloride was treated with triphosgene to afford ester **20** quantitatively.[59] N-alkylation of the ester **20** with 1-bromo-3-methyl-2-butene in the presence of sodium hydride gave the *N*-alkylated ester **21** in 78% isolated yield.[60] DIBAL reduction of the aforementioned ester **21** gave an aldehyde,[60] which was converted directly to the unsaturated ester **17** using Wittig methodology. When a solution of the unsaturated ester was heated in diethylaniline to 200 °C in a microwave oven the ene-product **14** and an allo-kainate precursor **22** were isolated in a combined yield of 80% in a diastereomeric ratio of 7:1 in favour of the desired enantiomer. This product was carried through to final steps as a crude mixture containing traces of the allo-kainate compound.

In contrast to the work of Oppolzer and Thirring the intramolecular ene-reaction in our system took only 4 h to complete instead of 40 h.[9] With the crude ene-product **14** in hand we saponified with methanol in the presence of caesium carbonate[61] to afford the desired alcohol **22** in 80% isolated yield. Oxidation of the alcohol **23** using Parikh–Doering conditions afforded the aldehyde **24** in high yield.[62] Oxidation of the aldehyde with sodium chlorite[63] gave the intermediate carboxylic acid **25**, which was not isolated but globally deprotected with aqueous sodium hydroxide in methanol. Ion-exchange chromatography followed by recrystallisation from water removed any traces of the undesirable allo-type compound and afforded (−)-α-kainic acid **1** in 60% isolated yield.[9]

2. Conclusion

The overall yield of kainic acid **1** starting from D-serine is 20% over eight steps and compares favourably with previous synthetic approaches including the most recent route by Fukuyama, which, gives a 10% yield over thirteen operations.[40] We believe that this approach offers a new and simple access to kainic acid and its analogues using chemistry well suited to scale up without the need for use of heavy metal derivatives. The unusual addition of nitrile oxides to the double bond of the carbamate **3** offers additional flexibility for the preparation of a wide range of hitherto unknown amino acids.

3. Experimental

3.1. General

Reactions were conducted at room temperature under an atmosphere of nitrogen unless otherwise stated. They were monitored using analytical thin layer chromatography with visualization by UV light and potassium permanganate ($KMnO_4$) dip. Reaction solvents were purified and dried according to the literature methods. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone as indicator; dichloromethane was distilled from calcium hydride. Petrol refers to distilled petroleum 40–60 °C. All other solvents were used as supplied. Flash chromatography was performed using silica gel 60, 230–400 mesh. ^1H NMR spectra were recorded on a Varian 500 MHz machine operating at ambient probe temperature using an internal deuterium lock. Chemical shifts were reported in parts per million (ppm) using residual solvent as an internal standard. Standard abbreviations were used throughout. (s singlet; br d broad doublet; br s broad singlet; d doublet; dd doublet of doublets; dt doublet of triplets; dq doublet of quartets; t triplet; q quartet; m multiplet). Coupling constants were measured in hertz (Hz). ^{13}C NMR spectra were recorded at 126 Hz operating at ambient probe temperature using an internal deuterium lock. Chemical shifts were reported in parts per million (ppm) using residual solvent as an internal standard. DEPT and correlation experiments were used for assignment of spectra. ESI mass spectra were recorded on a Bruker Daltonics Apex spectrometer with methanol as a solvent. EI mass data were recorded on a Fisons VG Autospec spectrometer. Infra red spectra were recorded on a Perkin–Elmer spectrum One FT-IR spectrometer fitted with an ATR accessory. Crystal structures were obtained from a Bruker/Enraf Nonius Fr590 KappaCCD. Structures were named using the ACD labs ACD/IUPAC name v8.05. The result of the ACD/IUPAC Name was obtained using ACD/I-Lab service.

*3.1.1. (Z)-6-(1-(Methoxyimino)ethyl)tetrahydropyrrolo[1,2-c]oxazol-3(1H)-one (**6a**).* Triethylamine (162 mg, 1.6 mmol) was added to a stirred solution of 1,7a-dihydropyrrolo[1,2-*c*]oxazol-3(5*H*)-one **3** (100 mg, 0.8 mmol), nitroethane (72 mg, 0.96 mmol) and *p*-toluene sulphonyl chloride (305 mg, 1.6 mmol) in benzene (20 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. Solvent removed under reduced pressure and residue purified by flash chromatography (1:1 hexane/ethyl acetate—100% ethyl acetate) yielded **6a** (98 mg, 68%) as a white crystalline solid, mp 123–127 °C. Spectra consistent with those previously reported. $[\alpha]_D^{25}$ −1.7 (*c* 1.00, CH_2Cl_2). IR (neat) ν (cm^{-1}) 2922, 1737 (C=O), 1463, 1192 (C–O), 993 (N–O), 777; δ_H (500 MHz $CDCl_3$): 5.06 (m, 1H, OCH), 4.69 (dd, 1H, *J*=2.59, 8.98 Hz, OCH_2), 4.48 (t, 1H, *J*=8.39, 17.16 Hz, OCH_2), 4.05 (d, 1H, *J*=5.41 Hz NCH_2), 4.08 (m, 1H, NCH), 3.84 (t,1H, *J*=8.12 Hz, NCH_2CH), 3.27 (ddd, 1H, *J*=7.69, 12.84, 20.52 Hz, NCH_2), 2.03 (s, 2H, CH_3). δ_C (126 MHz, $CDCl_3$): 175.3 (C=O), 155.1 (N=C), 83.6 (OCH), 64.3 (OCH_2), 62.7 (NCH), 58.1 (N=

CCH), 48.0 (NCH_2), 11.2 (CH_3). HRMS (ESI^+) calcd for $C_8H_{10}N_2O_3$, *m*/*z* 205.0583, found 205.0584.

*3.1.2. (3aS,8aR,8bR)-3-Phenyl-3a,8,8a,8b-tetrahydro-4H[1,3]oxazolo[3′,4′:1,5]pyrrolo[3,4-d]isoxazol-6-one (**6b**).* *N*-Hydroxybenzenecarboximidoyl chloride (2.0 g, 10.0 mmol) and 1,7a-dihydropyrrolo[1,2-*c*]oxazol-3(5*H*)-one **3** (1.26 g, 10.0 mmol) were dissolved in benzene (25 mL). To this stirring solution, triethylamine (1.21 g, 12.0 mmol) was added dropwise. Following 18 h the white solid was filtered, washed with cold ether (30 mL) and recrystallised from dichloromethane to yield **6b** as colourless crystals (1.63 g, 68%), mp 225–226 °C, $[\alpha]_D^{25}$ −197 (*c* 0.60, MeOH); IR (neat) ν (cm^{-1}) 2974, 1745 (C=O carbamate), δ_H (500 MHz CD_3OD): 7.75–7.78 (tt, 2H, *J*=1.9, 5.2 Hz, H*meta*) 7.69 (d, 2H, *J*=1.8 Hz, H*ortho*), 7.56 (d,1H, *J*=1.9 Hz, H*para*) 5.54 (dd, 1H, *J*=4.3, 8.6 Hz, OCH_2), 4.94 (dd, 1H, *J*=2.5, 8.9 Hz, OCH_2), 4.73 (t, 1H, *J*=8.6 Hz, NCH), 4.55 (td, 1H, *J*=2.1, 8.4 Hz, NOCH), 4.41 (m, 1H, NCH_2CH), 4.25 (dd, 1H, *J*=1.8, 12.7 Hz, NCH_2), 3.66 (dd, 1H, *J*=8.2, 12.7 Hz, NCH_2). δ_C (126 MHz, CD_3OD): 157.3 (C=O) 147.6 (N=C), 131.2 (C*para*), 131.0 (N=C*C*), 129.4 (C*meta*), 127.5 (C*ortho*), 85.9 (OCH), 64.9 (OCH_2), 63.1 (NCH), 55.0 (NCH_2CH), 49.9 (NCH_2). HRMS (ESI^+) calcd for $C_{13}H_{12}N_2O_3$, *m*/*z* 267.0745, found 267.0735.

*3.1.3. (3aS,8aR,8bR)-3-(4-Ethylphenyl)-3a,8,8a,8b-tetrahydro-4H-[1,3]oxazolo[3′,4′:1,5]pyrrolo[3,4-d]isoxazol-6-one (**6c**).* To a stirred solution of 1,7a-dihydropyrrolo[1,2-*c*]oxazol-3(5*H*)-one **3** (164 mg, 1.31 mmol), ethyl benzaldehyde oxime (234 mg, 1.57 mmol), triethylamine (0.22 mL, 1.573 mmol) in dichloromethane (10 mL), 8% aqueous sodium hypochlorite (10 mL) was added dropwise over 15 min at 0 °C. The reaction mixture was allowed to stir for 12 h, the aqueous layer was separated before extraction with dichloromethane (3×50 mL), and the organic phases were combined and washed with water (2×50 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. The solid residue was filtered and washed with diethyl ether (30 mL), and then recrystallised from methanol to give **6c** as a white solid (128 mg, 36%), mp 260–263.5 °C, $[\alpha]_D^{29}$ −318 (*c* 0.35, $CHCl_3$); IR (neat) ν (cm^{-1}) 1736, C=O, 2968; δ_H (500 MHz $CDCl_3$): 7.53 (d, 2H, *J*=7.9 Hz, H*ortho*), 7.25 (t, 2H, *J*=8.4 Hz, H*meta*), 5.22 (m, 1H, NOCH), 4.74 (d, 1H, *J*=8.9 Hz, OCH_2), 4.52 (t, 1H, *J*=8.6 Hz, OCH_2), 4.33 (t, 1H, *J*=8.3 Hz, NCH_2CH), 4.19 (m, 1H, NCH), 4.05 (d, 1H, 12.6 Hz, NCH_2, 12.6 Hz, NCH_2), 3.45 (ddd, 1H, *J*=1.5, 8.2 Hz), 2.68 (q, 2H, *J*=7.5 Hz, CH_2), 1.25 (t, 3H, *J*=7.5 Hz, CH_3). δ_C (126 MHz, $CDCl_3$): 157.5 (C=O), 147.0 (N=C), 128.3 (CH*meta*), 126.9 (CH*ortho*), 124.7 (CH_3CH_2C), 109.8 (*C*C=N), 85.1 (NOCH), 64.3 (OCH_2), 62.5 (NCH), 54.5 (NCH_2CH), 49.3 (NCH_2), 28.6 (CH_2),15.1 (CH_3) HRMS (ESI^+) calcd for $C_{15}H_{16}N_2O_3Na$, *m*/*z* 295.1059, found 295.1043.

*3.1.4. (3aS,8aR,8bR)-3-Cyclohex-1-en-1-yl-3a,8,8a,8b-tetrahydro-4H-[1,3]oxazolo[3′,4′:1,5]pyrrolo[3,4-d]isoxazol-6-one (**6d**).* Triethylamine (221 mg, 2.192 mmol) was added to a stirred solution of 1,7a-dihydropyrrolo[1,2-*c*]oxazol-3(5*H*)-one **3** (137 mg, 1.096 mmol), 1-(nitromethyl) cyclohexene (170 mg, 1.21 mmol) and *p*-toluenesulfonyl chloride (418 mg, 2.19 mmol) in chloroform (25 mL) at 0 °C, the reaction mixture was allowed to warm room temperature for 15 h before being washed with water (3×50 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with 7:1 diethyl ether/petrol to yield **6d** as colourless crystals (284 mg, 95%), mp 228–232 °C. $[\alpha]_D^{28}$ −288.4 (*c* 0.95, MeOH); IR (neat) ν (cm^{-1}) 1742 (C=O), 2924; δ_H (500 MHz $CDCl_3$): 1.59 (m, 2H,=CCH*CHCH*), 2.20 (m, 4H, *H*CHCHC=), 3.31 (dd, 1H, *J*=8.3, 12.4 Hz, NCH_2), 3.93 (dd, 1H, *J*=2.0, 12.6 Hz, NCH_2) 4.00 (td, 1H, *J*=2.1, 8.4 Hz, NCH_2CH), 4.09 (m, 1H, NCH), 4.42 (t, 1H, *J*=8.5 Hz, NOCH), 4.61 (dd, 1H, *J*=2.5, 8.9 Hz, OCH_2), 5.01 (dd, 1H, *J*=4.1, 8.3 Hz, OCH_2), 5.94 (t, 1H, *J*=3.9 Hz, C=CH). δ_C (126 MHz, $CDCl_3$): 22.1, 22.3, 25.3, 26.4, 50.5, 54.1, 63.2, 64.9, 85.5, 133.9. HRMS (ESI^+) calcd for $C_{13}H_{16}N_2O_3$, *m*/*z* 271.1058, found 271.1045.

*3.1.5. (3aS,8aR,8bR)-3-tert-Butyl-3a,8,8a,8b-tetrahydro-4H-[1,3]oxazolo[3′,4′:1,5]pyrrolo[3,4-d]isoxazol-6-one (**6e**).* To a stirred solution of 1,7a-dihydropyrrolo[1,2-*c*]oxazol-3(5*H*)-one **3** (100 mg, 0.80 mmol), 3,3-dimethylbutanal oxime (129 mg, 1.12 mmol), triethylamine (0.13 mL, 0.96 mmol) in dichloromethane (10 mL), 8% aqueous sodium hypochlorite (10 mL) was added dropwise over 15 min at 0 °C. The reaction mixture was allowed to stir for 12 h, the aqueous phase was separated before extraction with dichloromethane (3×50 mL), and the organic layer were combined and washed with water (2×50 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. The solid residue was filtered and rinsed with diethyl ether (30 mL), and then recrystallised from methanol give **6e** as a white solid (45 mg, 24%), mp 200–205 °C, $[\alpha]_D^{27}$ −162 (*c* 0.4, $CHCl_3$); IR (neat) ν (cm^{-1}) 1730 (C=O) 2955; δ_H (500 MHz $CDCl_3$): 1.03 (s, 9H, $C(CH_3)_3$), 1.54 (s, 2H CCH_2), 2.17 (d, 1H, *J*=12.8 Hz), 2.45 (d, 1H, *J*=14.8 Hz), 3.26 (dd, 1H, *J*=7.7, 12.8 Hz), 3.91 (t, 1H, *J*=7.9 Hz), 4.05 (m, 2H), 4.48 (t, 1H, *J*=8.5 Hz), 4.69 (dd, 1H, *J*=2.4, 8.9 Hz), 5.02 (dd, 1H, *J*=4.8, 8.5 Hz). δ_C (126 MHz, $CDCl_3$): 29.8 (CH_3), 31.4 ($C(CH_3)_3$), 39.1 (NCH_2), 48.3 (NCH_2CH), 58.6 (CCH_2), 62.7 (NCH), 64.5 (OCH_2), 83.0 (OCH), 125.2 (N=C), 157.0 (C=O). HRMS (ESI^+) calcd for $C_{12}H_{18}N_2O_3Na$, *m*/*z* 261.1215, found 261.1202.

*3.1.6. 6-Acetyl-1,7a-dihydropyrrolo[1,2-c]oxazol-3(5H)-one (**7**).* Raney-Nickel (20 mg) was added to **6a** (680 mg, 3.73 mmol) and boric acid (485 mg, 7.84 mmol), in 5:1 mixture of methanol and water (30 mL). The reaction mixture was allowed to stir for 8 h under hydrogen atmosphere. Raney-Nickel was removed by filtration through Celite and solvent removed under reduced pressure. The crude residue was dissolved in stirring toluene and a catalytic amount of *p*TSA·H_2O was added and the mixture heated to refluxed using Dean–Stark apparatus. After 2 h the solvent was removed and the residue purified using flash chromatography (9:1 ethyl acetate and hexane) to give **7** (560 mg, 89%) as a brown oil. $[\alpha]_D^{25}$ −0.9 (*c* 1.0, $CHCl_3$); IR (neat) ν (cm^{-1}) 2922 (=C enone), 1733 (C=O carbamate), 1671 (C=O enone), 1185 (C–O), 1006 (H_3C–N), 775; δ_H (500 MHz $CDCl_3$): 6.65 (s, 1H, =CH), 4.93 (m, 1H, NCH), 4.64 (t, 1H, *J*=8.9 Hz, OCH_2), 4.61 (d, 1H, *J*=15.7 Hz, NCH_2), 4.39 (m, 1H, OCH_2), 4.01 (d, 1H, *J*=15.8 Hz, NCH_2), 2.38 (s, 3H, CH_3). δ_C (126 MHz, $CDCl_3$): 193.8 (C=O enone) 162.5 (C=O carbamate), 145.0 (*C*=CH), 138.0 (=CH), 67.3 (OCH_2), 65.3 (NCH), 53.6 (NCH_2), 27.1 (CH_3). HRMS (ESI^+) calcd for $C_8H_9NO_3$, *m*/*z* 190.0475, found 190.0478.

*3.1.7. Dimethyl [(6S,7R,7aS)-6-acetyl-3-oxotetrahydro-1H-pyrrolo[1,2-c][1,3]oxazol-7-yl]malonate (**8**) and dimethyl [(6R,7S,7aS)-6-acetyl-3-oxotetrahydro-1H-pyrrolo[1,2-c][1,3]oxazol-7-yl]malonate (**9**).* To a suspension of sodium hydride (60% dispersion in oil, 0.51 g, 8.5 mmol) in THF (40 mL) was added a solution of dimethyl malonate (1.12 g, 8.5 mmol) in THF (15 mL). After being stirred at room temperature for 2 h, a solution of **7** (1.42 g, 8.5 mmol) in THF (15 mL) was added dropwise at 0 °C. The mixture was stirred overnight at room temperature. The reaction was quenched with a saturated ammonium chloride solution (20 mL) and extracted with diethyl ether (5×30 mL). The combined organic phase was washed with brine (20 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified using flash column chromatography (hexanes/ethyl acetate: 7/3) to yield a separable mixture of two isomers **8** and **9** in 1:1 ratio, (2.33 g, 90%) as a pale yellow solid. Compound **8** $[\alpha]_D^{25}$ −2.5 (*c* 1.0, $CHCl_3$); IR (neat) ν (cm^{-1}): 2929 (CH_3), 1732(C=O lactone),1728 (C=O of ester) 1680 (C=O ketone), 1436 (CH_2), 1248 (C–N), 1154, 767. δ_H (500 MHz

$CDCl_3$): 4.41 (m, 2H), 4.06 (m, 2H), 3.77–3.72 (s and s, 6H), 3.46 (d, 2H), 3.34 (m, 2H), 3.03 (dd, 1H, J=19.0, 8.1 Hz), 2.22 (s, 3H); δ_C (126 MHz, $CDCl_3$): 205.5 (C=O ketone), 168.4 (C=O ester), 168.1 (C=O ester), 160.3 (C=O lactone), 64.1 (C–O lactone), 59.9 (CH lactone), 55.1 (CH attached to esters), 53.0 (OCH_3), 53.1 (OCH_3), 51.2 (CH), 48.3 (CH_2), 42.2 (CH), 29.8 (CH_3); HRMS (ESI): calcd. For $C_{13}H_{17}NO_7$ $[M+Na]^+$ 322.0897 found 322.0893. Compound **9** $[\alpha]_D^{23}$ −0.9 (*c* 1.0, $CHCl_3$); IR (neat) ν (cm^{-1}): 2959 (CH_3), 1737 (C=O lactone),1730 (C=O ester) 1701 (C=O ketone), 1432 (CH_2), 1273 (C–N), 1020, 769. δ_H (500 MHz $CDCl_3$): 4.52 (m, 1H), 4.44 (m, 1H), 4.33(m, 1H), 4.01(m, 1H), 3.87 (m, 1H), 3.74 (s and s, 6H), 3.51(s, 1H), 3.27(s, 1H), 3.04(s, 1H), 2.22(d, 3H); δ_C (126 MHz, $CDCl_3$): 205.5 (C=O ketone), 168.3 (C=O ester), 168.2 (C=O ester), 160.4 (C=O lactone), 68.6 (C–O lactone), 62.5(CH lactone), 58.4(CH attached to esters), 55.9(OCH_3), 52.9(OCH_3), 52.5(CH), 47.5(CH_2), 44.8(CH), 29.8(CH_3). HRMS (ESI^+): calcd for $C_{13}H_{17}NO_7$ $[M+Na]^+$ 322.0897 found 322.0906.

*3.1.8. Dimethyl [(6R,7R,7aS)-6-isopropenyl-3-oxotetrahydro-1H-pyrrolo[1,2-c][1,3]oxazol-7-yl]malonate (**10**).* ^{n}BuLi in hexane (2.5 M, 2.84 mL) was added to a suspension of Ph_3PMeBr (12.03 g) in THF (30 mL) at −78 °C. The mixture was stirred at room temperature for 20 min and then brought to −60 °C prior to the addition of a solution of **8** (0.85 g) in THF (20 mL). The reaction mixture was kept at −60 °C for 1 h and warmed to 25 °C over a period of 0.5 h, after which time it was filtered over Celite-silica gel. The solvent was removed under reduced pressure and the residue subject to column chromatography (60% ethyl acetate in hexane) to afford **10** as a white solid (0.61 g, 72%): $[\alpha]_D^{25}$ −1.28 (*c* 1.0, $CHCl_3$); IR (neat) ν (cm^{-1}): 2956 (CH_3), 2929 (=CH_2), 2163 (C=C), 1728 (C=O lactone), 1645 (C=O ester), 1435 (CH_2), 1225 (C–N), 1157, 1005, 902. δ_H (500 MHz $CDCl_3$): 4.83–4.81(s and s, 2H); 4.51(dd, 1H, J=9.5, 8.0 Hz); 4.42 (dd, 1H, J=9.5, 4.3 Hz); 4.05 (m, 1H, J=8.5,4.3 Hz); 3.76–3.68 (m, 6H); 3.54–3.45 (m, 1H); 3.37 (dd, 1H, J=11.6–9.4 Hz); 3.0–2.92 (m, 1H); 2.43 (m, 1H); 1.69 (s, 3H); δ_C (126 MHz, $CDCl_3$): 168.1 (C=O ester), 167.5 (C=O ester), 160.3 (C=O lactone), 141.7 (C=O ketone), 114.7 (=CH_2), 68.2 (C–O lactone), 62.2(CH lactone), 53.1 (CH attached to esters), 52.7 (OCH_3), 52.5 (OCH_3), 52.3 (CH), 48.5 (CH_2), 45.7 (CH), 17.6 (CH_3); HRMS (ESI^+): calcd for $C_{14}H_{19}NO_6$ $[M+Na]^+$ 320.1105 found 320.1101.

*3.1.9. Dimethyl [(6S,7S,7aS)-6-isopropenyl-3-oxotetrahydro-1H-pyrrolo[1,2-c][1,3]oxazol-7-yl]malonate (**11**).* Compound **11** was prepared by same method as previous to yield **11** (0.69 g, 81%) as a white solid $[\alpha]_D^{24}$ −2.1 (*c* 1.0, $CHCl_3$); IR (neat) ν (cm^{-1}): 2962(CH_3), 2929 (=CH_2), 2030 (C=C), 1728 (C=O lactone), 1690 (C=O ester), 1440 (CH_2), 1243 (C–N), 1150, 1008, 923. δ_H (500 MHz $CDCl_3$): 4.88–4.82 (s and s, 2H), 4.54 (m, 1H, J=8.8, 5.2 Hz); 4.4 (dd, 1H, J=9.9, 8.9 Hz); 3.9 (dd, 1H, J=10.2, 5 Hz); 3.90–3.83 (m, 1H); 3.76–3.65 (s, 6H), 3.43 (dd, 1H, J=19.4, 10.9 Hz); 3.08–2.90 (m, 2H); 2.59 (td, 1H, J=9.8, 7.6 Hz); 1.72 (s, 3H); δ_C (126 MHz, $CDCl_3$): 168.8 (C=O ester), 167.8 (C=O ester), 160.9 (C=O lactone), 141.0 (C=O ketone), 114.5 (=CH_2), 68.4 (C–O lactone), 59.9 (CH lactone), 53.1(CH attached to esters), 52.2 (OCH_3), 52.2 (OCH_3), 51.4 (CH), 50.8 (CH_2), 42.6 (CH), 18.8 (CH_3). HRMS (ESI^+): calcd for $C_{14}H_{19}NO_6$ $[M+Na]^+$ 320.1105 found 320.1102.

*3.1.10. Methyl [(6R,7S,7aS)-6-isopropenyl-3-oxotetrahydro-1H-pyrrolo[1,2-c][1,3]oxazol-7-yl]acetate (**12**).* NaCl (29 mg) was added to 150 mg of **10** in 12 mL of hydrated DMSO and heated to 170 °C for 8 h. After cooling down to room temperature, extraction with ethyl acetate and removing the solvent under reduced pressure gave (80 mg, 83%) of **12** as orange oil, $[\alpha]_D^{25}$ +5.2 (*c* 1.0, $CHCl_3$); IR (neat) ν (cm^{-1}): 2953 (CH_3), 2918 (=CH_2), 1730 (C=O lactone), 1644 (C=O ester), 1437 (CH_2), 1394 (CH_2), 1206 (C–N), 1166, 1002, 897. δ_H (500 MHz $CDCl_3$): 4.89–4.85 (s and s, 2H), 4.50 (dd, 1H, J=9.4, 7.8 Hz), 4.38 (dd, 1H, J=9.3, 4.2 Hz), 3.84–3.72 (m, 1H), 3.67 (s, 3H,), 3.48–3.34 (m, 2H), 2.72, 2.56, 2.23–2.04 (dd, dd, m, 4H, first dd: J=19.4, 7.7 Hz, second dd: J=15.7, 3.7 Hz), 1.69 (s, 3H); δ_C (126 MHz, $CDCl_3$): 172.2 (C=O ester), 160.8 (C=O lactone), 141.2 (C=C), 114.1 (=CH_2), 67.7 (C–O lactone), 64.7 (CH of lactone), 52.9 (CH attached to esters), 51.8 (OCH_3), 48.7 (CH), 43.4 (CH_2), 34.9 (CH), 18.2 (CH_3); HRMS (ESI): calcd. For $C_{12}H_{17}NO_4$ $[M+Na]^+$ 240.1050 found 240.1228.

*3.1.11. Methyl [(6S,7R,7aS)-6-isopropenyl-3-oxotetrahydro-1H-pyrrolo[1,2-c][1,3]oxazol-7-yl]acetate (**13**).* Prepared by same method as previous to yield (72 mg, 75%) of **13** as an orange oil $[\alpha]_D^{24}$ +3.2 (*c* 1.0, $CHCl_3$); IR (neat) ν (cm^{-1}): 2945 (CH_3), 2920 (=CH_2), 1730 (C=O lactone), 1645 (C=O ester), 1437 (CH_2), 1378 (CH_2), 1207 (C–N), 1169, 1013, 895. δ_H (500 MHz $CDCl_3$): 4.92–4.83 (s and s, 2H), 4.45 (dd, 1H, J=9.5, 8.7 Hz), 4.37 (dd, 1H, J=8.4, 4.2 Hz), 4.12 (1H, dt, J=11.5, 5.8 Hz), 3.85 (1H, dd, J=11.9, 7.2 Hz), 3.70 (3H, s), 3.05–2.97 (1H, m), 2.65–2.55 (1H, m), 2.47 (1H, dt, J=13.0, 6.5 Hz), 2.40–2.30 (2H, m), 1.76 (3H, s). δ_C (126 MHz, $CDCl_3$): 172.4 (C=O ester), 161.5 (C=O lactone), 141.9 (C=C), 113.3 (=CH_2), 64.7 (C–O lactone), 59.6 (CH lactone), 52.7 (CH attached to esters), 51.9 (OCH_3), 50.2 (CH), 40.5 (CH_2), 33.3 (CH), 20.2 (CH_3). HRMS (ESI^+): calcd for $C_{12}H_{17}NO_4$ $[M+Na]^+$ 240.1050 found 240.1233.

*3.1.12. Methyl 3-chloro-3-[3-(3-methylbut-2-en-1-yl)-2-oxo-1,3-oxazolidin-5-yl] propanoate **19**.* To a stirring solution of epoxide **16** (551 mg, 4.3 mmol) in DMF (10 mL) was added $CaCl_2$ (150 mg, 1.4 mmol) in 1 portion, at room temperature. The resulting solution was heated to 160 °C and once all solid had dissolved 3,3-dimethylallyl isocyanate **15** was added dropwise. The resulting solution was held at reflux for 6 h, after this time the reaction was cooled and water (50 mL) was added. The organic components were extracted using diethyl ether (3×30 mL) washed with saturated brine (1×25 mL) then dried, ($MgSO_4$) concentrated under reduced pressure and purified via flash chromatography (1:1 hexanes/diethyl ether) to afford the title compound **19** (45 mg, 4%) as a brown liquid. IR (neat) ν (cm^{-1}) 2966 (C–H), 1731 (C=O), 1436 (C–H), 1241 (C–O), 1200 (C–O_{ester}), 1165 (C–N), 755 (C–Cl); δ_H (500 MHz $CDCl_3$): δ_C (500 MHz, $CDCl_3$): 5.14 (t, J=7.0 Hz, 1H, CH alkene), 4.5 (dt, J=4.1, 8.4 Hz, 1H, CH), 4.06 (dd, J=6.2, 15.5 Hz, 1H, CH_2), 3.96 (ddd, J=3.9, 8.2 Hz, 1H, CH), 3.75 (d, J=4.2 Hz, 2H, CH_2), 3.71 (s, 3H, Me), 3.67 (dd, J=7.9, 15.4 Hz, 1H, CH_2), 2.82–2.76 (dd, J=3.7, 16.4 Hz, 1H, CH_2), 2.56 (dd, J=9.1, 16.4 Hz, 1H, CH_2), 1.74 (s, 3H, Me), 1.70 (s, 3H, Me): δ_C (125.7 MHz, $CDCl_3$): 170.3 (CO), 156.3 (CO), 137.9 (alkene), 117.7 (CH alkene), 76.9 (CH), 54.2 (CH), 52.0 (OMe), 45.4 (N–C), 40.1 (CH_2) 37.0 (CH_2), 25.6 (Me), 17.96 (Me). HRMS (ESI^+) calcd for $C_{12}H_{18}ClNO_4Na$, *m/z* 298.0810, found 298.0816.

*3.1.13. (4S)-3-(3-Methylbut-2-en-1-yl)-2-oxo-1,3-oxazolidine-4-carboxylate **21**.* Oxazolidinone **20** (360 mg, 2.48 mmol) was added dropwise to a stirring suspension of NaH (65 mg 2.73 mmol) in 4:1 THF/DMF (5 mL). Upon complete dissolution of solids, 3,3-dimethylallyl bromide (506 mg, 3.23 mmol) was added dropwise. Following 16 h, water (5 mL) was added and organics extracted with diethyl ether (3×30 mL), combined, dried (Na_2SO_4) and solvent removed under reduced pressure. The residue was subject to flash chromatography (3:1 hexanes/ethyl acetate) to afford the title compound **21** (410 mg, 78%) as a colourless liquid. $[\alpha]_D^{24}$ +21.1 (*c* 1.00, CH_2Cl_2). IR (neat) ν (cm^{-1}) 2919 (C–H), 1739 (C=O), 1207 (C–O), 1173; δ_H (500 MHz $CDCl_3$): 5.13 (t, J=7.4 Hz, 1H, CH alkene), 4.50–4.36 (m, 1H, O–CH_2), 4.35–4.25 (m, 2H, O–CH_2), 4.13 (ddd, J=14.9, 6.2, 0.7 Hz, 1H, CH_2), 3.3 (dd, J=8.8, 14.8 Hz, 1H, CH_2), 3.78 (s, 3H, Me), 1.76 (s, 3H, Me), 1.65 (s, 3H, Me). δ_C (126 MHz, $CDCl_3$): 170.3 (CO), 157.4 (CO), 139.0 (alkene), 117.3 (CH alkene), 64.3 (CH_2), 56.2 (N–C)

52.8 (OMe), 40.9 (NCH_2), 25.7 (Me), 17.7 (Me) HRMS (ESI^+) calcd for $C_{10}H_{15}NO_4Na$, *m*/*z* 236.0893, found 236.0893.

3.1.14. Ethyl (2E)-3-[(4R)-3-(3-methylbut-2-en-1-yl)-2-oxo-1,3-oxazolidin-4-yl]acrylate ***17***. To a stirring solution of methyl ester (**21**) (321 mg, 1.51 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added dropwise DIBAL-H (1 M in diethyl ether) (2.4 mL, 2.4 mmol). Following 1 h the solution was warmed to −10 °C and saturated ammonium chloride solution (3.0 mL) was added followed by cannular addition of ethyl (triphenylphosphoranylidene)acetate (1.57 g 4.52 mmol) in CH_2Cl_2 (5 mL) Following 16 h at room temperature, the liquid was decanted and after solvent removal in vacuo, the residue was purified by flash chromatography (4:1 hexanes/ethyl acetate) to afford the title compound **17** (318 mg, 83%) as a colourless liquid. $[\alpha]_D^{24}$ +36.7 (*c* 1.10, CH_2Cl_2).IR (neat) ν (cm^{-1}) 2979 (C–H), 2911 (C–H), 1748 (C=O), 1717 (C=O), 1263, 1175 (C–O), 1055; δ_H (500 MHz $CDCl_3$): 6.76 (dd, *J*=8.5, 15.7 Hz, 1H, CH alkene), 6.00 (d, *J*=15.6 Hz, 1H, CH alkene), 5.13 (t, *J*=7.3 Hz, 1H, CH alkene), 4.43 (app. t, *J*=8.7 Hz, 1H, OCH_2), 4.34 (app. dd, *J*=15.3, 8.5 Hz, 1H, NCH), 4.23 (q, *J*=7.1 Hz, 2H, CH_2CH_3), 4.03 (dd, *J*=6.24, 15.0 Hz, 1H, NCH_2), 3.99 (dd, *J*=6.7, 8.6 Hz, 1H, OCH_2), 3.60 (dd, *J*=15.1, 8.4 Hz, 1H, NCH_2), 1.73 (s, 3H, Me), 1.63 (s, 3H, Me), 1.31 (t, *J*=7.2 Hz, 3H, CH_2CH_3). δ_C (126 MHz, $CDCl_3$): 165.0 (COEt), 157.6 (CO carbamate), 143.0 (alkene), 138.1 ($(CH_3)_2C$), 125.7 (alkene), 117.7 (CH alkene), 66.2 (OCH_2), 61.0 (CH_2 ethyl), 56.3 (NCH), 40.3 (NCH_2), 25.7 (Me), 18.0 (Me), 14.1 (Me ethyl). HRMS (ESI^+) calcd for $C_{13}H_{19}NO_4Na$, *m*/*z* 276.1206, found 276.1215.

3.1.15. Ethyl [(6S,7S)-6-isopropenyl-3-oxotetrahydro-1H-pyrrolo[1,2-c][1,3]oxazol-7-yl]acetate ***14*** *and ethyl [(6R,7S)-6-isopropenyl-3-oxotetrahydro-1H-pyrrolo[1,2-c][1,3]oxazol-7-yl]acetate* ***24***. Ene precursor **17** (1 g 3.95 mmol) was dissolved in *N*,*N*-diethylaniline (20 mL) in a thick walled microwave vial (35 mL). The vial was placed in the microwave at 200 °C for 4 h. The solution was subject to flash chromatography (5:1 hexanes/ethyl acetate) to afford a 7:1 mixture of title compounds **14** and **22** (800 mg, 80%) as a brown liquid. Compound **14** $[\alpha]_D^{23}$ −14.4 (*c* 1.01, CH_2Cl_2). IR (neat) ν (cm^{-1}) 2980 (C–H), 2913 (C–H), 1748 (C=O), 1726 (C=O), 1263, 1175 (C–O); δ_H (500 MHz $CDCl_3$): 4.94 (s, 1H, alkene), 4.75 (s, 1H, alkene), 4.54 (dd, *J*=9.1, 8.3 Hz, 1H, NCH_2), 4.25–4.19 (dd, *J*=4.81, 9.26 Hz, 1H, NCH_2), 4.17–4.06 (m, 2H, CH_2 ethyl), 3.86–3.77 (m, 2H, OCH_2 and NCH), 3.16 (dd, *J*=6.5, 11.8 Hz, 1H, OCH_2 carbamate), 2.99 (app. dd, *J*=14.4, 7.7 Hz, 1H, =CCH), 2.48–2.34 (m, 2H,), 2.26–2.16 (m, 1H), 1.73 (s, 3H, Me), 1.29–1.20 (t, *J*=7.15 Hz, 3H, OMe).δ_C (126 MHz, $CDCl_3$): 172.2 (COEt), 161.3 (CO carbamate), 142.3 (alkene), 114.6 (CH_2 alkene), 68.8 (NCH_2), 63.6 (NCH), 60.8 (CH_2 ethyl), 49.7 (OCH_2 carbamate), 49.3 (NCH_2CH), 43.1 (CH), 33.3 ($COCH_2$), 22.5 (Me), 14.1 (CH_3 ethyl). HRMS (ESI^+) calcd for $C_{13}H_{19}NO_4Na$, *m*/*z* 276.1206, found 276.1217. Compound **22** IR (neat) ν (cm^{-1}) 2974 (C–H), 2904 (C–H), 1750 (C=O), 17,129 (C=O), 1206, 1175 (C–O); δ_H (500 MHz $CDCl_3$): 4.89 (s, 1H, alkene), 4.86 (s, 1H, alkene), 4.52 (app. t, *J*=8.6 Hz, 1H, OCH_2 carbamate), 4.42 (dd, *J*=9.4, 4.2 Hz, 1H, OCH_2 carbamate), 4.13 (t, *J*=6.9 Hz, 2H, CH_2 ethyl), 3.82–3.73 (m, 1H, NCH), 3.47 (app. t, *J*=10.7 Hz, 1H, NCH_2), 3.40 (app. t, *J*=10.2 Hz, 1H, NCH_2), 2.78–2.67 (m, 1H), 2.62–2.51 (dd, *J*=3.6, 15.7 Hz, 1H, $COCH_2$), 2.19 (dd, *J*=9.7, 15.3 Hz, 1H, $COCH_2$), 2.15–2.07 (m, 1H), 1.71 (s, 3H, Me), 1.27 (t, *J*=7.1 Hz, 3H, CH_3 ethyl).δ_C (126 MHz, $CDCl_3$): 172.0 (COEt), 161.4 (CO carbamate), 141.3 (alkene), 114.7 (alkene), 67.8 (OCH_2 carbamate), 64.7 (NCH), 60.9 (CH_2 ethyl), 55.0 (NCH_2CH), 48.67 (NCH_2), 43.3 (CH), 35.3 ($COCH_2$), 18.1 (Me), 14.1 (CH_3 ethyl). HRMS (ESI^+) calcd for $C_{13}H_{19}NO_4Na$, *m*/*z* 276.1206, found 276.1218.

3.1.16. Methyl (2S,3S,4S)-2-(hydroxymethyl)-4-isopropenyl-3-(2-methoxy-2-oxoethyl)pyrrolidine-1-carboxylate ***23***. To a stirring solution of ene-product **14** contaminated with allo-kainate product **22** (500 mg, 1.97 mmol) in MeOH (4 mL) at room temperature was added in one portion Cs_2CO_3 (32 mg, 0.1 mmol). After 5 days the reaction was quenched with H_2O (5 mL) and extracted with AcOEt (3×15 mL). The organic extracts were combined, dried (Na_2SO_4) and solvent removed under reduced pressure. The residue was subject to column chromatography eluting with hexanes/ethyl acetate (3:2) to afford the title compound (**23**) (426 mg, 80%) as a brown oil. $[\alpha]_D^{24}$ −42.3 (*c* 1.00, CH_3Cl). IR (neat) ν (cm^{-1}) 3454 (O–H), 2920 (C–H), 2850 (C–H), 1735 (C=O), 1678 (C=O), 1450, 1376; δ_H (500 MHz $CDCl_3$): 4.89 (s, 1H, alkene), 4.64 (s, 1H, alkene), 3.76 (m, 1H, NCH), 3.70 (app. s, 5H, NCH_2), 3.65 (s, 3H, OMe), 3.47 (m, 2H, CH_2OH), 2.96 (m, 1H, NCH_2CH), 2.56 (m, 1H, CH), 2.22 (m, 2H, $COCH_2$), 1.69 (s, 3H, Me) δ_C (126 MHz, $CDCl_3$): 172.7 (COMe), 157.3 (NCOMe), 141.6 (alkene), 112.9 (CH_2 alkene), 65.8 (NCH_2), 65.4 (NCH), 52.8 (OMe carbamate), 51.7 (OMe ester), 48.3 (CH_2OH), 45.6 (NCH_2CH), 39.0 (CH), 33.0 ($COCH_2$), 22.3 (Me). HRMS (ESI^+) calcd for $C_{13}H_{22}NO_5$, *m*/*z* 272.11492, found 272.1499.

3.1.17. Methyl (2S,3S,4S)-2-formyl-4-isopropenyl-3-(2-methoxy-2-oxoethyl)pyrrolidine-1-carboxylate ***24***. $Py\cdot SO_3$ (1.36 g, 8.55 mmol) was dissolved in DMSO (3 mL) and CH_2Cl_2 (4 mL) and cooled to 0 °C. Triethylamine (1.49 mL, 10.7 mmol) was added dropwise. After 10 mins alcohol **23** in CH_2Cl_2 (4 mL) was added dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature. After 16 h saturated ammonium chloride (4 mL) was added and extracted with CH_2Cl_2 (3×15 mL). The organic layers were collected combined, dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by column chromatography eluting with petrol/ethyl acetate (3:1) to afford the title compound **24** (471 mg, 82%) as a yellow oil $[\alpha]_D^{23}$ −58.1(*c* 1.05, CH_2Cl_2). IR (neat) ν (cm^{-1}) 2958 (C–H), 1693 (C=O), 1689 (C=O), 1449, 1380, 1131 (C–O); δ_H (500 MHz $CDCl_3$): 9.58 (d, *J*=28.1 Hz, 1H, aldehyde), 4.90 (d, *J*=14.8 Hz, 1H, alkene), 4.67 (d, *J*=13.6 Hz, 1H, alkene), 4.14 (d, *J*=54.3 Hz, 1H, NCH), 3.72 (app. s, 1H, NCH_2), 3.70–3.60 (m, 6H, OMe), 3.59–3.41 (m, 1H, NCH_2), 2.87 (m, 1H, CH), 2.84–2.72 (m, 1H, NCH_2CH), 2.36–2.27 (m, 1H, $COCH_2$), 2.27–2.12 (m, 1H, $COCH_2$), 1.68 (s, 3H, Me). δ_C (126 MHz, $CDCl_3$): 198.5 (aldehyde), 172.3 (ester), 155.7 (carbamate), 140.9 (alkene), 113.8 (CH_2 alkene), 69.8 (NCH), 51.9 (OMe carbamate), 48.4 (OMe ester), 47.9 (NCH_2), 45.9 (NCH_2CH), 38.5 (CH), 32.1 ($COCH_2$), 22.3 (Me). HRMS (ESI^+) calcd for $C_{13}H_{19}NO_5Na$, *m*/*z* 292.1155, found 292.1156.

3.1.18. (−)-α-Kainic acid ***1***. To a stirring solution of aldehyde **24** (1.42 g, 5.28 mmol) in ^tBuOH (15 mL) and 2-methyl 2-butene (25 mL) at room temperature was added dropwise a solution of sodium chlorite (4.30 g, 47.5 mmol) and sodium dihydrogenphosphate (5.76 g, 36.9 mmol) in water (150 mL) over a period of 10 m. After 16 h the volatiles were removed under reduced pressure and the residue was dissolved in water (25 mL) and extracted with hexanes (3×25 mL). The aqueous phase was acidified to pH 3 with concentrated $HCl_{(aq)}$ and extracted with diethyl ether (3×50 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated under reduced pressure. The crude acid **25** was dissolved in stirring MeOH (70 mL) and aqueous NaOH (38%) (70 mL) was added. The mixture was heated to reflux. Following 18 h the solvent was removed under reduced pressure and the crude product was added to a column containing Dowex-50H$^+$ (WX8-200 cross-linking, 100–200 wet mesh). Elution with NH_4OH (1 M), evaporation and treatment with Amberlite CG-50 (100–200 dry mesh) afforded after recrystallisation from water, which, removed the undesired allo-kainic acid, the title compound (−)-α-kainic acid **1** (720 mg, 60%) as white needle crystals, mp 245 °C. Spectra consistent with those previously reported. $[\alpha]_D^{23}$ −14.6 (*c* 0.65, H_2O). IR (neat) ν (cm^{-1}) 3534, 2976 (C–H), 2528 (C–H), 1689 (C=O), 1615 (C=O), 1383, 1276, 891. δ_H (500 MHz, D_2O): 4.98 (1H, s, alkene), 4.69 (1H, s, alkene), 4.03 (s 1H, NCH), 3.64 (1H, dd, *J*=11.5, 6.7 Hz, NCH_2), 3.35 (app dd, *J*=27.9, 16.9 Hz, 1H, NCH_2), 2.96 (app s,

1H, NCH_2CH), 2.40 (dd, J=15.5, 4.1 Hz, 1H, $COCH_2$), 2.31 (dd, J=16.2, 8.2 Hz, 1H, $COCH_2$), 1.70 (3H, s, Me). δ_C (126 MHz, D_2O): 176.2 ($COCH_2$), 173.7(NCO), 139.9 (alkene), 113.4 (CH_2 alkene), 65.6 (NCH), 46.4 (NCH_2), 45.7 (CH), 40.7 (NCH_2CH), 33.3 ($COCH_2$), 22.1 (Me). HRMS (ESI^+) calcd for $C_{10}H_{16}NO_4Na$, m/z 214.1074, found 214.1077.

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