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Synthesis of (−)-kainic acid using chiral lithium amides in an asymmetric dearomatizing cyclization

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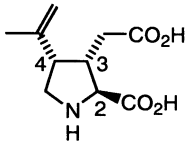
Abstract—Chiral lithium amide bases are able to deprotonate *N*-benzyl-*N*-cumyl anisamides enantioselectively to yield enantiomerically enriched benzylic organolithiums. These spontaneously undergo dearomatising cyclisation to yield, in high enantiomeric excess enantiomerically enriched partially saturated isoindolones, which in some cases may be recrystallised to enantiomeric purity. These isoindolone derivatives are converted in nine steps, among them a surprisingly regioselective Baeyer–Villiger reaction, to (−)-kainic acid. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

(−)-Kainic acid **1** is the parent member of a class of substituted prolines known as the kainoids.[1–3] The kainoids have a common substitution pattern and stereochemistry, and members of the class differ only in the nature of the unsaturated substituent at C4.[4] Kainic acid, like other kainoids, exhibits a wide variety of biological activity, and has been used as an anthelmintic and as an insecticide.[5,6] It is widely used as a tool in neuropharmacology,[7] and binds strongly to the class of neurotransmitter receptors, the kainate receptors, which take its name.[8,9] Kainic acid was, until recently, readily available from its most abundant natural source, the alga *Digenea simplex*.[10] Supplies were interrupted in 1999,[11] leading to a fifty-fold increase in the cost of kainic acid and enhancing the desirability of a synthetic route to this useful natural product.



(–)-kainic acid, 1

Over two dozen syntheses of (−)-kainic acid have been published[12] since Oppolzer's 1982 route from L-glutamic acid,[13] and many more syntheses provide (±)-kainic acid[14] or its analogues.[1,15–18] One of the main challenges in kainoid chemistry is the C3–C4 stereochemistry, which, in biologically active kainoids is always *cis*.[19,20] In our recently published[14] synthesis of (±)-kainic acid the relative stereochemistry was controlled by maintaining the C3 and C4 substituents as part of a six-membered ring until late in the synthesis. The 5,6-fused isoindolinone ring system required for this synthesis was formed from benzamide **5a** by a dearomatizing cyclization of the type we first reported in 1998,[21–24] and which we now interpret as a six-electron electrocyclization.[25] Recently, we found that replacement of the *t*-BuLi/HMPA or LDA used for the racemic cyclisation with a chiral lithium amide base allows control over the absolute stereochemistry of the product.[26] As far as we are aware, this reaction is the first use of a chiral lithium amide base to deprotonate a prochiral methylene group enantioselectively and thus form an enantiomerically enriched organolithium compound. Previous asymmetric functionalisation α to nitrogen has employed the much more basic *s*-BuLi-(−)-sparteine combination.[27–30] We now report in full[31] the application of our chiral lithium amide-protomated asymmetric cyclisation to the synthesis of **10** and the conversion of **10** to (−)-kainic acid in nine steps.[12]

2. Results and discussion

The cyclisation starting materials, **5**, were made in one of two ways. Acylation of cumylamine **2**[32,33] with *p*-methoxybenzoyl chloride gave **3**, whose slow benzylation gave the tertiary amide **5a**. Alternatively, alkylation of cumylamine **2** with *m*-methoxybenzyl chloride gave the secondary amine **4** which was acylated with *p*-methoxybenzoyl chloride to yield **5b**. We have found that *N*-cumyl amides are ideal starting materials for dearomatising cyclisations because they carry a bulky *N*-substituent (a prerequisite for good diastereoselectivity) and the cumyl group may be removed later under acid conditions (Schemes 1 and 2).[23]

Keywords: kainic acid; stereoselective; cyclization; lithium amide; organolithium.

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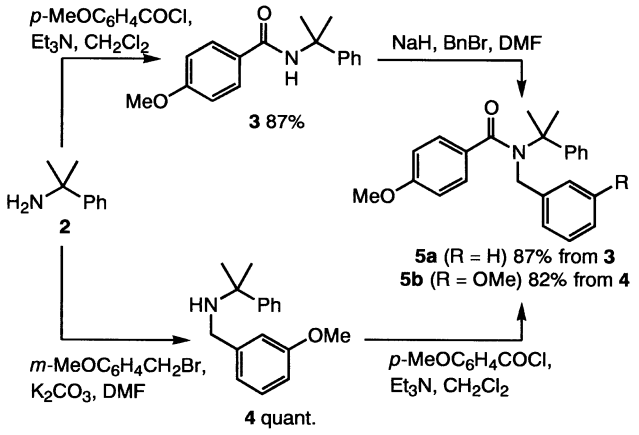
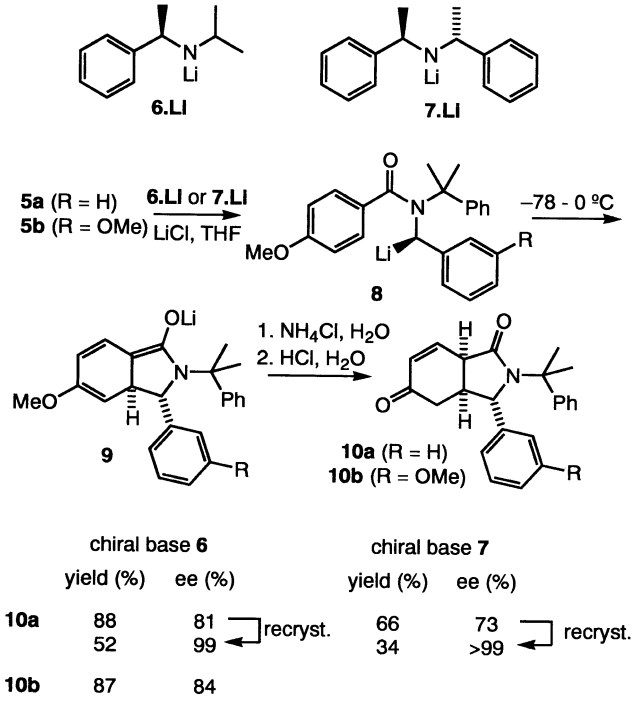


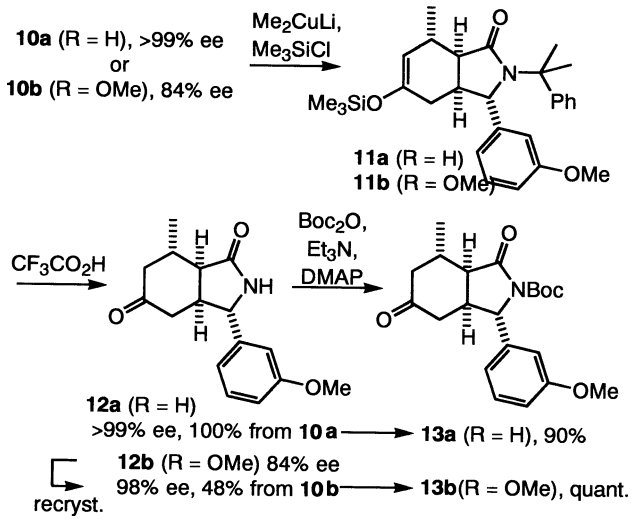
Scheme 1.

Two chiral lithium amide bases, **6**·Li and **7**·Li,[34] were used to promote the asymmetric cyclisation of **5a** and **b** to yield the partially saturated isoindolones **10a** and **b**. The hydrochloride salt **6**·HCl[35–37] or **7**·HCl[38] was dissolved in THF, and 2 equiv. of BuLi were added to form a solution of chiral lithium amide **6**·Li or **7**·Li plus lithium chloride. Once the amide **5a** or **b** had been added the mixture was allowed to warm, promoting asymmetric deprotonation[26] to **8** and cyclisation[23] to the enolate **9**. An aqueous quench and acidic work-up returned the enones **10a** or **b** in good yield and enantiomeric excess.[39] The ee of **10a** (but not **10b**) could be improved to >99% by one recrystallisation from EtOAc.

Conjugate addition of Me_2CuLi to **10a** or **b** in the presence of Me_3SiCl gave single diastereoisomers of the enol ethers **11a** and **b**, which were subjected without purification to trifluoroacetic acid, which both removed the cumyl group and hydrolysed the enol ether to yield deprotected ketones



Scheme 2.



Scheme 3.

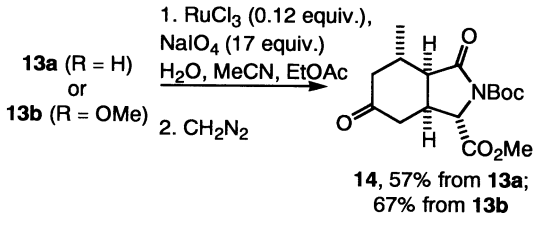
12a and **b**. At this stage, the enantiomeric excess of **12b** was improved by recrystallisation from ethyl acetate, returning material of 98% ee, which was carried through the synthesis (Scheme 3).[40]

Few *N*-protecting groups are compatible with the harshly oxidising conditions required for the formation of the C2-carboxylic acid substituent,[41,42] but Boc withstands the oxidation well. Treatment with Boc_2O in the presence of DMAP and then catalytic $RuCl_3$ in the presence of stoichiometric $NaIO_4$ gave **14** which was isolated as its methyl ester after treatment with diazomethane (Scheme 4).

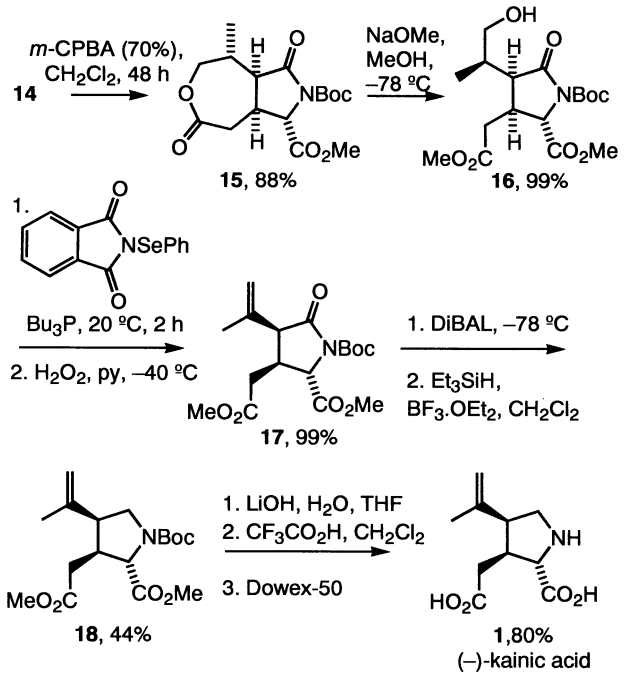
Baeyer–Villiger oxidation of **14** expands the cyclohexanone ring to a seven-membered lactone with a remarkable level of regioselectivity. Although we have not determined precisely the origin of this regioselectivity, it appears to be conformational in origin.[43] The presence of the methyl group β to the ketone is essential: the un-methylated analogue of **14** is oxidised without regioselectivity to give a mixture of lactones.[44]

The ring opening of the lactone must be carried out carefully to avoid epimerisation of the centre α to the amide carbonyl group.[16] We have found that the most reliable way to avoid unwanted epimerisation to the allokainic acid series is to carry out a methanolysis (sodium methoxide in methanol) of **15** at −78°C. Alcohol **16** may then be isolated as a single diastereoisomer. The use of LiOMe or higher temperatures risks significant epimerisation.

Elimination of water from **16** is best performed by first



Scheme 4.



Scheme 5.

converting the alcohol to a selenide. We found *N*-phenylselenenylphthalimide[45] to be the most consistently reliable selenium source, though we have also had success with *o*-nitrophenylselenocyanate.[14,46] Treatment with the selenium reagent in the presence of Bu_3P at room temperature, followed by oxidation to the selenoxide with hydrogen peroxide at −40°C gave, after spontaneous elimination, the alkene **17**. Reduction of the Boc-protected amide was achieved by the method of Rubio[47] (DIBAL followed by triethylsilane and boron trifluoride etherate). The final deprotections take place on treatment with LiOH and trifluoroacetic acid,[48] and after purification a sample of (−)-kainic acid was obtained with spectroscopic data and optical rotation identical with the natural product (Scheme 5).[48]

3. Conclusion

Chiral lithium amide bases are valuable reagents for promoting a new type of dearomatising asymmetric cyclisation. A product of this cyclisation is a valuable intermediate for the synthesis of (−)-kainic acid, and we are currently seeking to apply similar cyclisations to the synthesis of other members of the kainoid family.

4. Experimental

4.1. General methods

Diethyl ether (referred to as 'ether') and tetrahydrofuran (THF) were distilled under nitrogen from sodium benzophenone ketyl. Dry solvents were transferred to reaction vessels by syringe. 'Petrol' refers to redistilled petroleum ether (bp 40–60°C). Melting points are uncorrected. Column chromatography was performed with Merck silica gel 60H (230–300 mesh) as the stationary phase. Thin layer chromatography was performed using Merck silica 60 F_{254} aluminium-backed plates.

4.1.1. *N*-(1-Methyl-1-phenylethyl)-4-methoxybenzamide 3. *p*-Anisoyl chloride (1.39 g, 8.14 mmol) was added dropwise to a solution of cumylamine **2** (1 g, 7.4 mmol) and triethylamine (1.12 g, 11.1 mmol) in DCM (10 mL). After 12 h, water was added to the reaction mixture which was extracted with DCM, washed with brine, dried with $MgSO_4$, and evaporated under reduced pressure. Purification by recrystallisation (ethyl acetate) afforded the title compound **1** as a white solid (1.73 g, 87%). Mp 60–62°C. Found: M^+, 269.1419; $C_{17}H_{19}NO_2$ requires M, 269.14157; δ_H (300 MHz, $CDCl_3$) 7.78 (2H, d, *J*=9 Hz, H3, H5), 7.5–7.2 (5H, m, ArH), 6.95 (2H, d, *J*=9 Hz, H2, H6), 6.43 (1H, br s, NH), 3.88 (3H, s, MeO), 1.86 (6H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 165.89, 161.96, 146.99, 128.38, 127.65, 126.59, 124.68, 113.60, 56.07, 55.34, 29.21; *m/z* (EI) 269 (M^+, 35%), 135 (100%); ν_{max}(film)/cm^{-1} 3279 (NH), 1632 (C=O), 1607 (Ar).

4.1.2. *N*-(3-Methoxybenzyl)-*N*-(1-methyl-1-phenylethyl)-amine 4. 3-Methoxybenzyl bromide (0.37 g, 1.85 mmol) was added to a solution of cumylamine **2** (0.25 g, 1.85 mmol) and potassium carbonate (2.4 mmol) in DMF (10 mL). The reaction mixture was stirred for 12 h. Water was added, and the mixture was extracted with ether, washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. Purification by flash chromatography (1:1 ethyl acetate–petroleum ether) afforded the title compound **4** as a colourless oil (0.48 g, 100%). Found: M^+, 255.1628; $C_{17}H_{21}NO$ requires M, 255.1623; δ_H (300 MHz, $CDCl_3$) 7.7–7.2 (9H, m, ArH), 3.84 (3H, s, CH_3O), 3.51 (2H, s, CH_2), 1.59 (2H, br s, NH_2), 1.57 (6H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 159.60, 147.71, 142.95, 129.23, 128.14, 126.20, 125.80, 125.35, 113.68, 112.06, 56.04, 55.10, 47.52, 29.68; *m/z* (CI) 256 ($M+H^+$, 100%), 138 (30%); ν_{max}(film)/cm^{-1} 1601 (Ar).

4.1.3. *N*-1-Benzyl-*N*-(1-methyl-1-phenylethyl)-4-methoxybenzamide 5a. A solution of amide **1** (2.18 g, 8.1 mmol) in DMF (20 mL) was added dropwise to dry NaH (0.65 g, 16.2 mmol) under N_2. After 12 h, benzyl bromide (12.15 mmol, 2.08 g) was added to the reaction mixture. After 24 h, the reaction was quenched with water at 0°C, extracted with ether, washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. Purification by recrystallisation (ethyl acetate) afforded the title compound **5a** as a white solid (2.38 g, 82%). Mp 118–119°C. Found: M^+ 359.1879; $C_{24}H_{25}NO_2$ requires M, 359.1885; δ_H (300 MHz, $CDCl_3$) 7.39 (12H, m, ArH), 6.85 (2H, d, *J*=9 Hz, H1, H2), 5.82 (2H, s, CH_2), 3.81 (3H, s, CH_3), 1.75 (6H, s, CH_3), δ_C (75 MHz, $CDCl_3$) 172.95, 160.35, 148.72, 139.77, 139.77, 130.70, 128.61, 128.45, 128.17, 127.03, 126.73, 126.06, 124.37, 113.48, 62.29, 55.19, 52.25, 28.50; *m/z* (CI) 360 ($M+H^+$, 90%); ν_{max}(film)/cm^{-}1 1638 (C=O), 1606 (Ar).

4.1.4. *N*-(3-Methoxybenzyl)-*N*-(1-methyl-1-phenylethyl)-4-methoxybenzamide 5b. By the procedure used for **3**, amine **4** (0.93 g, 3.65 mmol) and *p*-anisoyl chloride (0.87, 4.7 mmol) gave, after purification by recrystallisation (ethyl

acetate), the title compound **5b** as a white solid (1.23 g, 87%). Mp 124–126°C. Found: M^+, 390.2068; $C_{25}H_{28}NO_3$ requires M, 390.2069; δ_H (300 MHz, $CDCl_3$) 7.20 (13H, m, ArH), 5.83 (2H, s, CH_2), 3.85 (3H, s, CH_3O), 3.81 (3H, s, CH_3O), 1.81 (6H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 172.91, 160.40, 159.74, 148.78, 141.53, 131.76, 130.69, 129.56, 128.61, 128.47, 128.30, 126.79, 127.04, 126.09, 119.03, 113.55, 112.46, 112.42, 62.36, 55.21, 55.14, 52.22, 28.57; *m/z* (CI) 390 (M^+, 100%), 272 ($M^+-C_6H_5C(CH_3)_2$); ν_{max}(film)/cm^{-1} 1639 (C=O), 1606 (Ar).

4.2. General procedure for cyclisation using a chiral lithium amide

The benzamide **5a** or **b** (1 equiv.) was added to a freshly prepared solution of the chiral lithium amide (HCl salt **6**·HCl or **7**·HCl (1.3 equiv.) and BuLi (2.6 equiv.) in THF (10 mL) at −78°C. The mixture was allowed to warm to room temperature. Saturated ammonium chloride solution was added. The aqueous layer was extracted with ether. The combined organic layers were washed with dilute hydrochloric acid and brine, dried over $MgSO_4$ and evaporated under reduced pressure to afford the crude product.

4.2.1. 2-(1-Methyl-1-phenylethyl)-3-phenyl-2,3,3a,4,5,7a-hexahydro-1*H*-1,5-isoindoledione 10a. By this method, amide **5a** (0.25 g, 0.696 mmol), **7**·HCl (0.24 g, 0.90 mmol) and *n*-BuLi (1.8 mmol) in THF (20 mL) gave, after purification by flash chromatography (7:3 petroleum ether–ethyl acetate), the title compound **10a** as a white solid (0.157 g, 66%). Mp 127–128°C. Analytical HPLC (β-GEM, Regis), eluting with IPA and hexane (30:70), showed it to consist of a 86.5:13.5 mixture of two enantiomers, t_R 8.16 and 8.95 min (ee=73%). Recrystallisation from ethyl acetate gave material (0.081 mg, 34%) of ee >99%, $[\alpha]_D^{20}=-224$ (*c*=0.17, $CHCl_3$). Found: M^+, 345.1732; $C_{23}H_{23}NO_2$ requires M, 345.17287; δ_H (300 MHz, $CDCl_3$) 7.34 (10H, m, ArH), 6.92 (1H, dd, *J*=10, 5 Hz, H7), 6.16 (1H, dd, *J*=10, 2 Hz, H6), 4.47 (1H, d, *J*=2.5 Hz, H3), 3.67 (1H, m, H7a), 2.66 (3H, m, H4+H3a), 1.85 (3H, s, CH_3), 1.52 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 196.52, 171.48, 145.87, 144.33, 141.46, 130.25, 128.99, 128.09, 126.90, 125.80, 125.20, 67.25, 59.91, 42.38, 41.47, 39.04, 28.21, 27.14; *m/z* (CI) 346 ($M+H^+$, 100%), ν_{max} 2978 (CH), 1680 (C=O).

By the same method, amide **5a** (0.25 g, 0.696 mmol), **6**·HCl (0.24 g, 0.90 mmol) and *n*-BuLi (1.8 mmol) in THF (20 mL) afforded the title compound **10a** as a white solid (0.211 g, 88, 81% ee).

4.2.2. 3-(3-Methoxyphenyl)-2-(1-methyl-1-phenylethyl)-2,3,3a,4,5,7a-hexahydro-1*H*-1,5-isoindoledione 10b. By the same method, amide **5b** (0.17 g, 0.44 mmol), **6**·HCl (0.12 g, 0.60 mmol) and *n*-BuLi (0.60 mmol) in THF (15 mL) gave, after purification by flash chromatography (7:3 petroleum ether–ethyl acetate) the title compound **10b** as a yellow oil (0.14 g, 87%). Analytical HPLC (β-GEM, Regis), eluting with isopropanol and hexane (30:70), showed it to consist of a 7.9:92.1 mixture of two enantiomers, t_R 8.45 and 8.93 min (ee=84%). $[\alpha]_D^{20}=-159$ (*c*=1.4, $CHCl_3$). Found: M^+, 375.1838; $C_{24}H_{25}NO_3$ requires 375.1834. δ_H (300 MHz, $CDCl_3$) 7.30 (6H, m, ArH), 6.89 (3H, m, ArH, H7), 6.15 (1H, dd, *J*=10, 1.5 Hz, H6), 4.44 (1H, d, *J*=2 Hz, H3), 3.84 (3H, s, CH_3O), 3.68 (1H, m, H7a), 2.64 (3H, m, H4, H3a), 1.86 (3H, s, CH_3), 1.54 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 196.52, 171.51, 160.08, 145.90, 144.34, 143.15, 130.25, 130.12, 128.09, 126.90, 125.22, 117.99, 113.22, 111.56, 67.21, 59.91, 55.22, 42.41, 41.42, 39.10, 28.25, 27.80; ν_{max} 2942 (CH), 1679 (C=O), 1600 (Ar), 1586 (Ar); *m/z* (CI) 376 ($M+H^+$, 90%), 258 (70%), 119 (100%).

4.2.3. (3*R*,3a*R*,7*R*,7a*S*)-3-(3-Methoxyphenyl)-7-methylperhydro-isoindole-1,5-dione 12b. Methyl lithium (7.04 mmol, 1.6 M solution in hexane) was added to a suspension of copper bromide (0.5 g, 3.52 mmol) in THF (5 mL) at −78°C. The solution was stirred for 30 min and allowed to warm to 0°C. Isoindole **10b** (0.66 g, 1.76 mmol) in THF (10 mL) and trimethylsilylchloride (0.45 mL, 3.52 mmol) were added dropwise at −78°C. The resulting mixture was stirred for 3 h at −78°C. Saturated ammonium chloride solution was added, and the mixture allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic fractions were washed with saturated ammonium chloride, dried over $MgSO_4$ and evaporated under reduced pressure to give a crude sample of silyl enol ether **11b**. $[\alpha]_D^{20}=+17$ (*c*=1.17, $CHCl_3$); Found: M^+, 463.2546; $C_{28}H_{37}NO_3Si$ requires M, 463.25426; δ_H (300 MHz, $CDCl_3$) 7.3–6.5 (9H, m, ArH), 4.61 (1H, d, *J*=2.5 Hz, H6), 4.21 (1H, s, H3), 3.62 (3H, s, MeO), 2.6–2.0 (4H, m, H4, H3a, H7a), 1.85–1.7 (1H, m, H7), 1.62 (3H, s, CH_3-cumyl), 1.37 (3H, s, CH_3-cumyl), 0.80 (3H, d, *J*=7.0 Hz, CH_3), 0.0 (9H, s, TMS); δ_C (75 MHz, $CDCl_3$) 175.88, 159.87, 146.78, 146.15, 143.83, 129.74, 127.89, 126.56, 125.54, 118.22, 118.22, 112.67, 111.71, 108.83, 68.60, 58.96, 55.17, 44.60, 39.52, 32.39, 27.86, 27.42, 27.30, 23.28, 0.25; ν_{max} 2953 (CH_3), 1688 (C=O).

Without further purification, trifluoroacetic acid (5 mL) was added to isoindole **11b** (1.76 mmol). The mixture was heated to reflux for 4 h and concentrated under reduced pressure. Purification by flash chromatography (1:2 petroleum ether–ethyl acetate) afforded the title compound **12b** as a white solid (0.32 g, 67% for the two steps). $[\alpha]_D^{19}=+37$ (*c*=1.08, $CHCl_3$). Recrystallisation from ethyl acetate gave a white solid (0.23 g, 48%), $[\alpha]_D^{20}=+48$ (*c*=9.1 mg/mL in $CHCl_3$). Analytical GC, showed this material to consist of a 1.03:98.97 mixture of two enantiomers, t_R 34.57 and 35.58 min (ee=98%). Mp 175–177°C, Found: M^+ 273.1371; $C_{16}H_{19}NO_3$ requires M, 273.1365; δ_H (300 MHz, $CDCl_3$) 7.4–6.8 (4H, m, ArH), 6.2 (1H, br s, NH), 4.34 (1H, d, *J*=4.4 Hz, H3), 4.34 (3H, s, MeO), 3.0–2.0 (7H, m, H3a, H4, H6, H7, H7a), 1.22 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 209.75, 160.04, 141.91, 129.99, 117.98, 113.27, 111.44, 61.92, 55.21, 46.48, 44.94, 41.06, 30.36, 20.51; ν_{max} 3250 (NH), 2900 (CH_3), 1695 (C=O).

4.2.4. (3*R*,3a*R*,7*R*,7a*S*)-7-Methyl-3-phenylperhydro-isoindole-1,5-dione 12a. By the same method, enone **10a** (0.56, 1.72 mmol) gave title compound **12a** (0.42 g, 100%) as a white solid. Mp 170–171°C. $[\alpha]_D=+51$ (*c*=0.63 in $CHCl_3$). Found: M^+, 243.1263; $C_{15}H_{17}NO_2$ requires M, 243.1259; δ_H (300 MHz, $CDCl_3$) 7.45–7.10 (5H, m, ArH), 4.32 (1H, d, *J*=4.5 Hz, H3), 2.81–2.22

(7H, m, H3a, H4, H6, H7, H7a), 2.06 (1H, dd, J=11, 4.8 Hz, H4), 1.11 (3H, d, J=6.2 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 209.9, 178.1, 140.0, 128.9, 126.1, 125.7, 61.9, 46.4, 45.8, 44.9, 40.9, 30.4, 20.5; *m/z* (CI) 244 ($M+H^+$ 100%); ν_{max}(film)/cm^{-1} 3300 (NH), 1710 (C═O), 1670 (C═O).

4.2.5. (1*R*,3a*S*,4*R*,7a*R*)-1-(3-Methoxyphenyl)-4-methyl-3,6-dioxo-octahydro-isoindole-2-carboxylic acid *tert*-butyl ester 13b. Triethylamine (0.14 mL, 0.99 mmol), Boc-anhydride (0.44 g, 1.96 mmol) and DMAP (0.12 g, 0.99 mmol) were added to a solution of isoindole **12b** (0.27 g, 0.99 mmol) in CH_2Cl_2 (15 mL). The mixture was stirred for 12 h and concentrated under reduced pressure. The residue was purified by flash chromatography (2:1 petroleum ether–ethyl acetate) to afford the title compound **13b** as a colourless oil (0.37 g, quant.). $[\alpha]_D^{19}$=+30 (c=1.19, $CHCl_3$). Found: M^+ 373.1894, $C_{21}H_{27}NO_4$ requires M, 373.18891; δ_H (300 MHz, $CDCl_3$) 7.4–6.6 (4H, m, ArH), 4.77 (1H, s, H3), 3.83 (3H, s, MeO), 2.8–2.4 (6H, m, H7a, H3a, H7, H6, H4), 2.10 (1H, dd, J=15.0, 7.5 Hz, H4), 1.38 (9H, s, *t*-Bu), 1.17 (3H, d, J=6.5 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 208.92, 173.97, 160.10, 149.58, 141.43, 130.01, 117.06, 113.08, 110.76, 83.39, 65.25, 55.24, 46.63, 45.46, 42.12, 40.61, 29.93, 27.65, 20.31; *m/z* (CI) 374 ($M+H^+$, 5%), 291 ($M+NH_4$–Boc, 25%, 274 (M+H–Boc 100%); ν_{max} 2975 (CH_3), 1782 and 1718 (2×C═O).

4.2.6. (1*R*,3a*S*,4*R*,7a*R*)-4-Methyl-3,6-dioxo-1-phenyl-octahydro-isoindole-2-carboxylic acid *tert*-butyl ester 13a. By the same method, amide **12a** (0.42 g, 1.72 mmol) gave **13a** (0.53 g, 90%) as a white solid. Mp 133–135°C. Found: M^+, 343.1778; δ_H (300 MHz, $CDCl_3$) 7.41–7.16 (5H, m, ArH), 4.79 (1H, s, H3), 2.74–2.34 (6H, m, H3a, H4, H6, H7, H7a), 2.09 (1H, dd, J=14.8, 8.8 Hz, H4), 1.3 (9H, *t*-Bu), 1.13 (3H, d, J=6.7 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 208.9, 174.1, 149.5, 139.7, 128.9, 127.9, 124.9, 83.3, 65.3, 46.6, 45.5, 41.9, 40.7, 29.9, 27.6, 20.3; *m/z* (CI) 344 ($M+H^+$, 20%), 244 ($M+H^+$−Boc, 100%); ν_{max}(film)/cm^{-1} 1786 (C═O), 1745 (C═O), 1713 (C═O).

4.2.7. (1*R*,3a*S*,4*R*,7a*R*)-4-Methyl-3,6-dioxooctahydro-isoindole-1,2-dicarboxylic acid 2-*tert*-butyl ester 1-methyl ester 14. A solution of isoindole **13b** (0.37 g, 0.99 mmol) in ethyl acetate (15 mL) was added dropwise to a solution of sodium periodate (3.64 g, 17 mmol) and ruthenium trichloride hydrate (0.025 g, 0.12 mmol) in water (30 mL) and acetonitrile (15 mL). The mixture was stirred for 4 h, after which time a white precipitate had formed. The mixture was filtered and the filtrate was extracted with ethyl acetate, dried over $MgSO_4$, filtered through Celite®, and evaporated under reduced pressure and dissolved in ether. Freshly prepared diazomethane was added, followed by a sodium bicarbonate solution, and the ether was evaporated under reduced pressure. Purification by flash chromatography (2:1 petroleum ether–ethyl acetate) afforded the ester **14** (0.21 g, 67%). $[\alpha]_D^{21}$=+67 (c=0.62, $CHCl_3$). Found: $M+H^+$, 325.1522; $C_{16}H_{23}NO_6$ requires 325.1525; δ_H (300 MHz, $CDCl_3$) 4.2 (1H, d, J=1.3 Hz, H3), 3.72 (3H, s, CO_2Me), 2.82–2.72 (1H, m, H7), 2.62 (1H, dd, J=7.5, 5 Hz, H7a), 2.53 (1H, dd, J=10, 6 Hz, H6), 2.50 (1H, m, H3a), 2.38 (dd, J=9.5, 4.5 Hz, H4), 2.24 (1H, dd, J=10, 7.5 Hz, H6), 2.0 (1H, dd, J=9.6, 7.5 Hz, H4), 1.42 (9H, s, *t*-Bu); δ_C (75 MHz, $CDCl_3$) 207.95, 172.75, 170.34, 149.41, 84.08, 62.65, 52.73, 47.09, 44.97, 42.05, 34.54, 29.34, 27.78, 20.30; *m/z* (CI) 343 ($M+NH_4^+$, 100%), 326 ($M+H^+$, 25%), 226 ($M+H^+$−Boc, 60%), 243 ($M+NH_4^+$−Boc, 70%); ν_{max}(film)/cm^{-1} 1789, 1746, 1729, 1713 (4×C═O).

Isoindole **13a** (1.03 g, 3 mmol) was treated in the same way to give, after purification by flash chromatography, the ester **14** (0.56 g, 57%). $[\alpha]_D^{21}$=+67 (c=0.62, $CHCl_3$).

4.2.8. (1*R*,3a*R*,4*S*,8a*R*)-4-Methyl-3,7-dioxoperhydrooxepino[4,5-*c*]pyrrole-1,2-dicarboxylic acid 2-*tert*-butyl ester 1-methyl ester 15. *m*CPBA (70%) (0.76 g, 3.1 mmol) was added in one portion to a stirred solution of ketone **14** (0.53 g, 1.55 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 48 h. Sodium sulfite (5 mL of saturated aqueous solution) was added and the mixture was extracted with ethyl acetate. The combined extracts were washed with sodium hydrogen carbonate (10 mL of saturated aqueous solution), water (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to afford the crude product. Purification by flash chromatography, eluting with 2:1 Pet–EtOAc, gave the lactone **15** (0.46 g, 88%) as a colourless oil. $[\alpha]_D^{19}$=+5 (c=0.57, $CHCl_3$). Found: M^+, 341.1480; $C_{16}H_{23}NO_7$ requires M, 341.1474; δ_H (300 MHz, $CDCl_3$) 4.29 (1H, s, H1), 4.26 (1H, dd, J=14.2, 4.4 Hz, H5), 4.10 (1H, dd, J=14.2, 7.0 Hz, H5), 3.83 (3H, s, CO_2Me), 3.0–2.7 (5H, m, H3a, H4, H8, H8a), 1.51 (9H, s, $(CH_3)_3$), 1.3 (3H, d, J=7.5 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 171.5, 171.3, 169.7, 149.2, 84.4, 68.9, 63.0, 52.9, 48.7, 36.5, 32.5, 29.8, 27.8, 15.5; *m/z* (CI) 342 ($M+H^+$, 5%), 242 ($M+H^+$−Boc, 60%); ν_{max}(film)/cm^{-1} 1780 (C═O), 1755 (C═O), 1748 (C═O), 1723 (C═O).

4.2.9. 1-(*tert*-Butyl) 2-methyl (2*R*,3*R*,4*R*)-4-[(1*S*)-2-hydroxy-1-methylethyl]-3-(2-methoxy-2-oxoethyl)-5-oxo-tetrahydro-1*H*-1,2-pyrroledicarboxylate 16. Sodium methoxide (5.44 mmol, 1 M in methanol) was added dropwise over 0.5 h to a solution of the lactone **15** (0.46 g, 1.36 mmol) in methanol (10 mL) at −78°C. The reaction mixture was stirred for 1 h. Saturated ammonium chloride solution was added and the mixture was extracted with ethyl acetate, washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure to afford the crude product. Purification by flash chromatography, eluting with 1:1 pet. ether–EtOAc, gave the alcohol **16** (0.50 g, 99%) as a colourless oil. $[\alpha]_D^{22}$=−8 (c=4.71, $CHCl_3$). Found: $M+H^+$, 374.1816; $C_{17}H_{28}NO_8$ requires M, 374.1814; δ_H (300 MHz, $CDCl_3$) 4.24 (1H, d, J=5 Hz, H3), 3.74 (3H, s, CO_2Me), 3.65 (3H, s, CO_2Me), 3.62 (2H, m, CH_2OH), 2.90 (2H, m, H4, H5), 2.59 (1H, dd, J=17, 6 Hz, CH_aH_bCOMe), 2.45 (1H, dd, J=17, 8 Hz, $CH_aH_bCO_2Me$), 1.87 (1H, q, J=5 Hz, $CHCH_3$), 1.42 (9H, s, $(CH_3)_3$), 1.02 (3H, d, J=7 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 173.6, 171.5, 170.6, 149.1, 83.9, 66.3, 62.6, 52.6, 52.1, 46.3, 35.1, 33.3, 32.9, 27.8, 13.6; *m/z* (CI) 374 ($M+H^+$, 15%), 274 ($M+H^+$−Boc, 100%); ν_{max}(film)/cm^{-1} 3527 (OH), 1786, 1742 (C═O).

4.2.10. (2*R*,3*R*,4*S*)-4-Isopropenyl-3-methoxycarbonylmethyl-5-oxopyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester 17. Tri-*n*-butylphosphine (0.57 g, 2.8 mmol) was added dropwise to a stirred solution

of pyrrolidinone **16** (0.50, 1.34 mmol) and phenylselenophthalimide (0.6 g, 2.0 mmol) in THF at room temperature. After 2 h, the solution was cooled to −40°C. Pyridine (50 μL) was added followed by dropwise addition of an aqueous solution of hydrogen peroxide (0.5 mL). The mixture was allowed to warm to room temperature and stirred for further 12 h. A saturated solution of sodium bisulfite (5 mL) was added and the reaction mixture was extracted with ethyl acetate. The combined extracts were washed with water, dried over $MgSO_4$, and evaporated under reduced pressure to afford the crude product. Purification by flash chromatography, eluting with 5:1 petroleum ether–EtOAc, gave the title compound **17** (0.31 g, 65%) as a colourless oil. $[\alpha]_D^{22}=-11$ (c=0.95, $CHCl_3$). Found: M+H, 356.1701; $C_{17}H_{25}NO_7$ requires M, 355.16309; δ_H (300 MHz, $CDCl_3$) 5.19 (1H, s, C=CH_aH_b), 5.05 (1H, s, C=CH_aH_b), 4.36 (1H, d, J=4 Hz, H2), 3.85 (3H, s, CO_2CH_3), 3.73 (3H, s, CO_2CH_3), 3.51 (1H, d, J=8.5 Hz, H4), 2.97 (1H, m, H3), 2.50 (1H, dd, J=17, 6 Hz, CH_aH_bCO$_2$Me), 2.40 (1H, dd, J=17, 8.5 Hz, CH$_a$$H_bCO_2$Me), 1.75 (3H, s, CH_3), 1.52 (9H, s, $(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 171.5, 171.2, 170.7, 149.3, 136.6, 117.9, 83.9, 62.0, 52.7, 51.9, 51.7, 34.9, 33.8, 27.8, 22.7; m/z (CI) 356 ($M+H^+$, 20%), 273 ($M+NH_4^+-$Boc, 50%), 256 ($M+H^+-$Boc, 100%); ν_{max}(film)/cm^{-1} 1792 (C=O), 1740 (C=O).

4.2.11. (2*R*,3*R*,4*S*)-4-Isopropenyl-3-methoxycarbonylmethyl-pyrrolidine-1,2-dicarboxylic 1-*tert*-butyl ester 2-methyl ester 18. The reduction was carried out by the method of Rubio.[47] A solution of DIBALH (1.7 mmol, 1 M in toluene) was added dropwise to a stirred solution of **17** (0.075 g, 0.2 mmol) in THF (10 mL) at −78°C under nitrogen. After 1 h, methanol was added and the mixture was warmed to room temperature. Saturated potassium tartrate solution and ethyl acetate were added. The mixture was stirred for 15 min. The layers were separated and aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was used without further purification. Dry CH_2Cl_2 was added and the mixture was cooled to −78°C. Triethylsilane (35 μL, 0.22 mmol) and boron trifluoride etherate (25 μL, 0.2 mmol) were added dropwise under N_2. After 30 min, further triethylsilane (35 μL, 0.22 mmol) and boron trifluoride etherate (25 μL, 0.2 mmol) were added. After 2 h at −78°C, the reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, and dried over $MgSO_4$. Evaporation of the solvent and purification by flash chromatography gave the title compound **18** (0.03 g, 44%) as colourless oil. $[\alpha]_D^{21}=-19.1$ (c=0.62, $CHCl_3$). δ_H (300 MHz, $CDCl_3$) 4.95 (1H, s, C=CH_aH_b), 4.75 (1H, s, C=CH$_a$$H_b$), 4.20 (1H, d, J=3.5 Hz, H2), 3.75 (7H, m, 2×OCH$_3$, H5), 3.5 (1H, m, H5), 3.05 (1H, m, H4), 2.88 (1H, m, H3), 2.35 (1H, m, CH_2CO_2), 1.70 (3H, s, CH_3), 1.48 (9H, s, Boc).

4.2.12. (−)-α-Kainic acid 1. Deprotection of kainic acid was carried out by the method of Hanessian.[48] Compound **18** (0.030 g, 0.09 mmol) was dissolved in a mixture of THF (1 mL) and 2 M aqueous LiOH (1 mL). The reaction mixture was stirred at room temperature for 12 h, and a solution of HCl (2 M) was added to pH 2. The mixture was extracted with ethyl acetate, dried over $MgSO_4$ and evaporated under reduced pressure. CH_2Cl_2 and trifluoroacetic acid were added and the reaction mixture was heated to reflux for 2 h. After removal of the solvent, the crude product was added to a column containing Dowex-50 H^+ (WX8-200, 8% cross-linking, 100–200 wet mesh). Elution with NH_4OH (1N), evaporation, and treatment with Amberlite CG-50 afforded (−)-kainic acid **1** (0.015 g, 80%) as a white solid. $[\alpha]_D^{19}=-13.8$ (c=0.39, $CHCl_3$) [lit.,[48] −13.9], with spectroscopic data as reported in the literature.[48]

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