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Synthesis of (±)-kainic acid by dearomatising cyclisation of a lithiated *N*-benzyl *p*-anisamide

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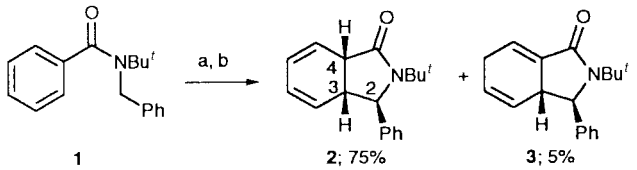
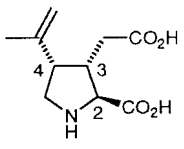
_N_-Benzyl _p_-anisamide 6, on lithiation with Bu^{t}Li in the presence of HMPA, undergoes a stereoselective anionic cyclisation with loss of aromaticity to give a bicyclic enone which may be converted in nine steps to (±)-kainic acid.

We recently described[1] the dearomatising cyclisation reaction of lithiated *N*-benzyl benzamides **1** to give bicyclic cyclohexadienes **2** and **3** (Scheme 1).[2] The reaction is stereoselective, creating three new stereogenic centres, and it is noticeable that the pyrrolidine ring of the major product **2** has the relative stereochemistry of kainic acid **4**. (−)-Kainic acid[3] **4** was first isolated in 1953 from the Japanese marine alga *Digenea simplex*.[4] It has diverse biological activity: as an anthelmintic, *D. simplex* is a traditional remedy in which kainic acid is the active component.[5] Kainic acid is an extremely potent neuroexcitor, binding specifically at the kainate receptor and leading to specific neuronal death.[6,7] Both the anthelmintic and neuroexcitatory properties of kainic acid are dependent on the *cis* C-3–C-4 relative stereochemistry: allokainic acid, the C-4 epimer, is inactive as an anthelmintic[8] and has lower neuroexcitatory activity than kainic acid.[9]

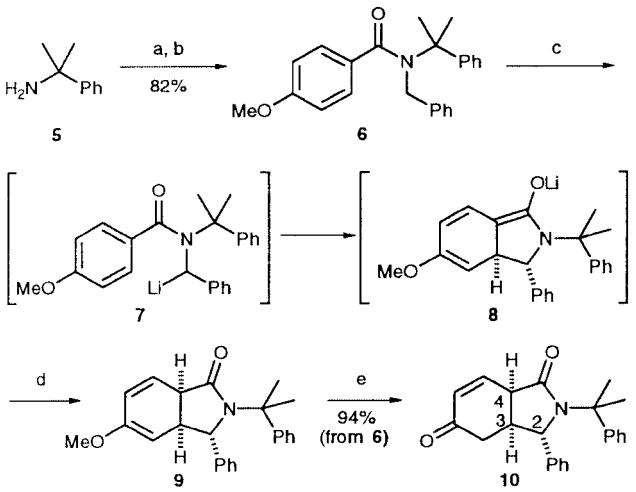


Scheme 1 *Reagents and conditions*: (a) Bu^{t}Li (1.3 equiv.), HMPA (6 equiv.), THF, −78 °C, 16 h; (b) NH_4Cl.

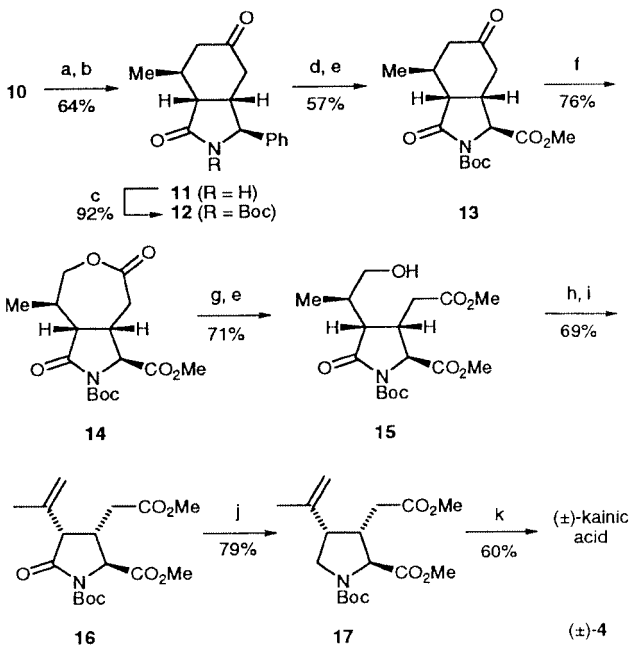


A number of syntheses of (−)-kainic acid[10] and (±)-kainic acid[11] have been reported, several of which[10g–k,p,s,11a] achieve control over the C-3–C-4 stereochemistry by forming these substituents from a cyclic precursor. Our approach to (±)-kainic acid, presented in Schemes 2 and 3, also uses this strategy, exploiting the relative stereochemistry of the dearomatising cyclisation reaction.

Acylation of cumylamine **5**[12] with *p*-anisoyl chloride, followed by alkylation of the secondary amide with benzyl bromide, gave the cyclisation substrate **6**. Tertiary *N*-substituents are necessary for good yields in the cyclisation step, and our early studies had all used *N*-Bu^t amides. However, we had considerable difficulty removing the *tert*-butyl group from the cyclised products: we turned to the cumyl group for ease of removal under acid conditions.[13] The *N*-cumyl-*N*-benzyl amide **6** was lithiated with Bu^{t}Li in the presence of HMPA, but the more bulky group slowed the reaction considerably and the cyclisation of **6** *via* **7** required 60 h at −40 °C to reach



Scheme 2 *Reagents and conditions*: (a) *p*-anisoyl chloride, Et_3N, CH_2Cl_2; (b) NaH, DMF, BnBr, 18 h; (c) Bu^{t}Li (2 equiv.), HMPA (12 equiv.), THF, −40 °C, 60 h; (d) NH_4Cl; (e) THF, 1 M HCl (aq).



Scheme 3 *Reagents and conditions*: (a) Me_2CuLi, Me_3SiCl, THF, −78 °C, 1 h; (b) CF_3CO_2H, reflux, 6 h; (c) Boc_2O, Et_3N, DMAP, CH_2Cl_2, (d) $NaIO_4$, cat. $RuCl_2$, 1:1 acetone–H_2O; (e) Me_3SiCHN_2, PhH, MeOH; (f) MCPBA, CH_2Cl_2; (g) NaOH (2.2 equiv.), MeOH, reflux, 2 h; (h) *o*-$NO_2C_6H_4SeCN$, Bu_3P, THF, rt; (i) H_2O_2, Py, THF, −40 °C; (j) $NaBH(OMe)_3$ (2 equiv.), THF, reflux; (k) 10:1 CF_3CO_2H–H_2O, reflux, 4 h.

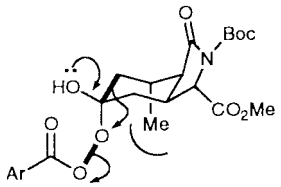
completion. The initial product of the cyclisation was the enolate **8**, which was protonated to give the dienyl ether **9** as a single regioisomer. This was hydrolysed *in situ* to the bicyclic

enone **10**, whose pyrrolidinone ring has the relative stereochemistry of kainic acid.

Lithium dimethyl cuprate, in the presence of trimethylsilyl chloride, attacked solely the *exo* face of the enone **10**: TFA catalysed both hydrolysis of the product silyl enol ether and removal of the cumyl group, and the lactam **11** was reprotected as its Boc derivative **12**.

The phenyl ring of **12** was oxidised with catalytic RuO_4, and we found that replacing the usual MeCN–CCl_4–H_2O system[14] with 1 : 1 acetone–water considerably improved the rate of the reaction. The carboxylic acid product was esterified with trimethylsilyldiazomethane[15] to give **13**.

We used Baeyer–Villiger oxidation to cleave the cyclohexanone ring of **13** into the two portions required in the target: remarkably, despite the fact that the ketone is almost identically substituted on both sides, the oxidation was fully regioselective and gave **14** with no trace of the other regioisomer. We tentatively propose that the regioselectivity is a consequence of the conformational preference of the intermediate peracid adduct in the Baeyer–Villiger reaction. Attack of the peracid on the *exo*-face of **13** gives **18**, whose pseudo-axial methyl group



18

may favour a conformation with the breaking O–O bond antiperiplanar to the C–C bond shown in bold, rather than the C–C bond to the other side of the former ketone.

Seven-membered lactone **14** was converted to diester **15** by hydrolysis with methanolic NaOH (slow addition of base avoided cleavage of the Boc protecting group) and esterification with trimethylsilyldiazomethane.[15] The elimination of water to give the isopropenyl group of **16** was achieved in one step by direct formation of a selenide[16] which was oxidised and eliminated under mild conditions.

Sodium trimethoxyborohydride selectively reduced the lactam carbonyl group of **16** in the presence of the two esters,[17] and wet trifluoroacetic acid both deprotected the amino group and hydrolysed the esters of the product **17**. The racemic product (±)-**4** was recrystallised from methanol and had spectroscopic properties (^{1}H and ^{13}C NMR) identical with those of natural kainic acid.

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