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Synthesis of a potent (±)-4-(2-hydroxyphenyl) analogue of the acromelic acids by dearomatising cyclisation of a lithiated *N*-*p*-methoxybenzyl-4-methoxy-1-naphthamide

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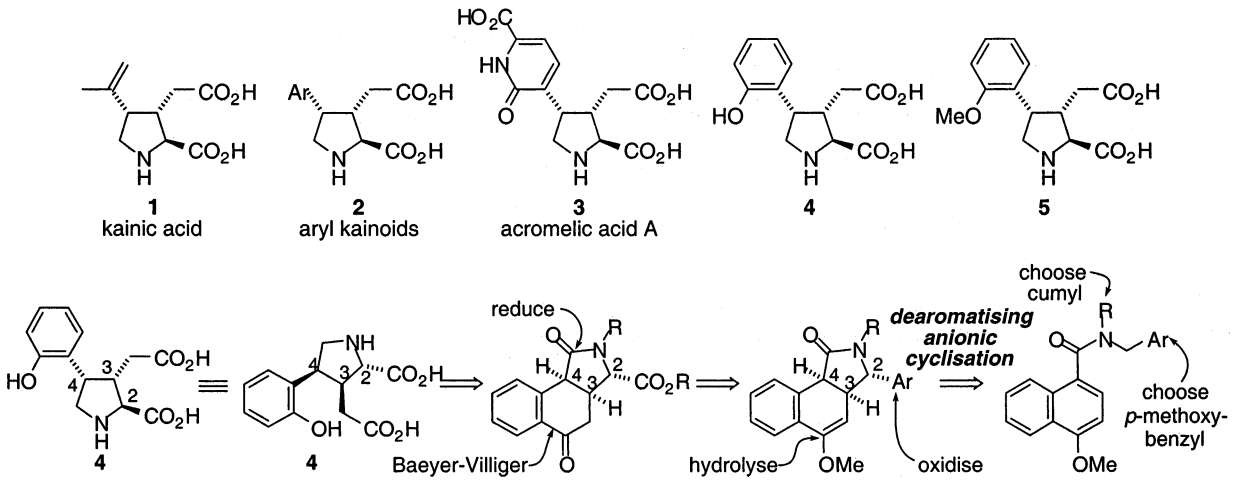
Abstract—Dearomatising anionic cyclisation of *N*-cumyl-*N*-*p*-methoxybenzyl-4-methoxy-1-naphthamide **8** diastereoselectively generates a pyrrolidinone-fused tetralone **12** which may be transformed in seven steps to the racemic form of a known non-natural member of the aryl kainoid family **4** having potent biological activity. Key steps of the synthesis are ruthenium-catalysed oxidation of the C2-*p*-methoxybenzyl ring of **12** to a carboxylic acid and Baeyer–Villiger cleavage of the tetralone to a lactone whose hydrolysis reveals the two-carbon substituent at C3 and the 2-hydroxyphenyl substituent at C4. Selective reduction of the lactam yields the kainoid **4**. Control of epimerisation at the C-4 centre during the lactone hydrolysis leads to either the (active) 3,4-*cis* or the (inactive) 3,4-*trans* epimers of the target.

Many members of the aryl kainoid family[1] of natural and non-natural products, represented by the general structure **2**, are powerful neuroexcitatory agents.[2] The natural acromelic acids such as acromelic acid A **3**[3] and their unnatural analogues[4] including **4** and **5**[5,6] show greater biological activity even than kainic acid **1**. Until recently, kainic acid was widely used as a tool in neuropharmacology[7] for the stimulation of nerve cells and the mimicry of disease states such as Alzheimer's and Huntington's diseases. However, a current shortage of naturally extracted kainic acid[8] has led to an acute need for efficient synthetic routes both to kainic acid[9] and its potent aryl kainoid analogues.[10]

In this Letter, we report a short synthesis of a potent aryl kainoid **4** which uses, as a key step, the dearomatising anionic cyclisation of a 1-naphthamide **8**.[11] We recently published[12] a short synthesis of (±)-kainic acid **1** which employed a similar dearomatising anionic cyclisation of an *N*-benzyl-*p*-anisamide.[13] Our retrosynthetic



Scheme 1. Retrosynthetic analysis of kainoid **4**.

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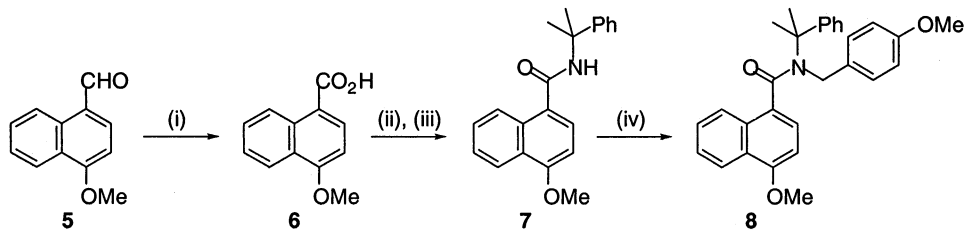
analysis of **4** is shown in Scheme 1. We aimed to form the carboxylate substituent at C2 by oxidation of the aromatic ring required for the cyclisation, and the two *cis*-related substituents at C3 and C4 of the pyrrolidinone ring by a Baeyer–Villiger cleavage of the tetralone generated on cyclisation of the 4-methoxy-1-naphthamide. The 3,4-*cis* stereochemistry of all members of the kainoid class is essential for their biological activity: our strategy uses the six-membered ring as a means of ensuring the groups remain *cis* for the duration of the synthesis—a strategy also employed by Shirahama[5] in the first synthesis of **4**.

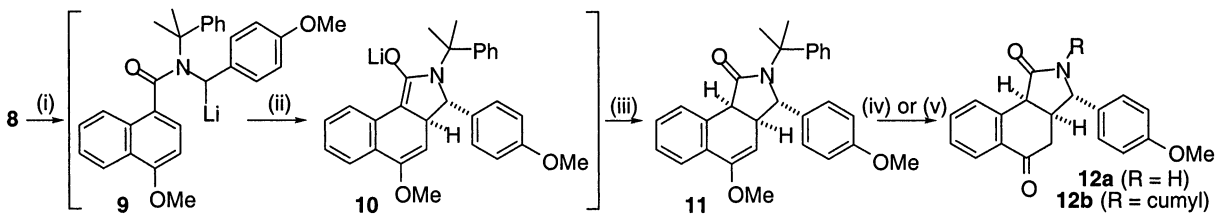
Our choice of R and Ar was influenced by the function of these groups in the cyclisation and in later stages of the synthesis. The most high-yielding cyclisations are those in which the non-cyclising substituent at *N* is branched and bulky,[14] and difficulties removing *t*-Bu from the cyclised products have meant that we now prefer cumyl as a base-stable, strong acid-labile protecting group for nitrogen during the cyclisation.[12,15] Although Ar = Ph has served us well both in the cyclisations and in subsequent oxidation to a carboxylic acid,[12] we hoped to improve the aryl oxidation by choosing the more electron-rich *p*-methoxyphenyl group as Ar.[16]

The starting material for the cyclisation was made from the commercially available aldehyde **5** by oxidation[17] to **6** and coupling with cumylamine. Alkylation of the resulting secondary amide **7** with *p*-methoxybenzyl chloride gave the cyclisation precursor **8** (Scheme 2).

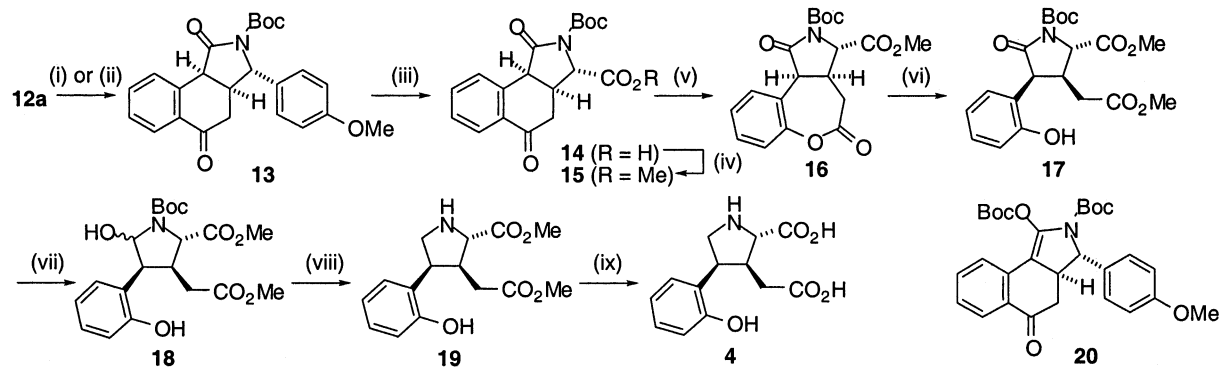
Amide **8** was deprotonated by *t*-BuLi in THF at −78°C to afford a benzylic organolithium **9** which cyclised over a period of 16 h at −78°C on addition of DMPU[18] (Scheme 3). The resulting enolate **10** was protonated to yield the tricyclic lactam **11** as a single diastereoisomer.[19] Refluxing in wet trifluoroacetic acid both deprotected the amide group and the hydrolysed the enol ether to yield the amidoketone **12a**. Hydrolysis without deprotection to give **12b** could be accomplished with 1 M HCl.



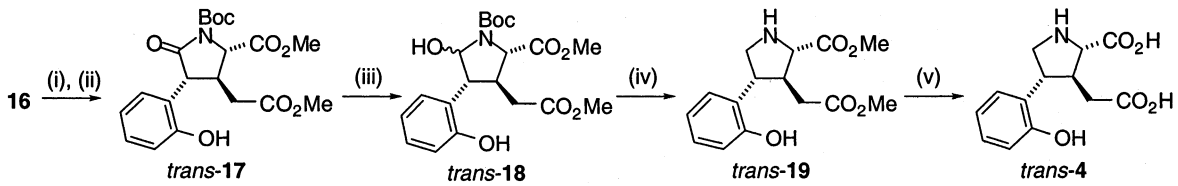
Scheme 2. Synthesis of the cyclisation precursor **8**. (i) $NaClO_2$, NaH_2PO_4, H_2O, *t*-BuOH, 2-methyl-2-butene, 20 h, 96%; (ii) $(COCl)_2$, DMF, $CHCl_3$, 20 h, 100%; (iii) cumylamine, CH_2Cl_2, NaOH, H_2O, 16 h, 92%; (iv) NaH, DMF, 4-methoxybenzyl chloride, 2 days, 74%.



Scheme 3. Cyclisation of **8**. (i) *t*-BuLi (1.3 equiv.), THF, −78°C, 2 h; (ii) DMPU (6 equiv.), −78°C, 16 h, 88%; (iii) NH_4Cl, H_2O; (iv) CF_3CO_2H, H_2O, Δ, 3 h, 87% **12a**; (v) 1 M HCl, THF, 2 h, 85% **12b**.



Scheme 4. Synthesis of **4**. (i) Boc_2O, Et_3N, DMAP, 44% (44% **12**, 12% **20**); (ii) Boc_2O, DMAP (cat.), MeCN, 80% (15% **12**); (iii) $RuCl_3$, $NaIO_4$, H_2O, EtOAc, MeCN, 4 h (iv) CH_2N_2, 52% from **13**; (v) mCPBA, 16 h, 52%; (vi) NaOMe, MeOH, 0°C, 85%; (vii) $NaBH(OMe)_3$, THF; (viii) $BF_3{\cdot}OEt$, Et_3SiH, CH_2Cl_2, 25% (two steps); (ix) 6 M HCl, 1 h, Δ, quant.



Scheme 5. Synthesis of *trans*-**4**. (i) LiOH, H_2O, THF, 20°C, 86%; (ii) CH_2N_2, Et_2O, 55% (5:1 *cis*:*trans*); (iii) $NaBH(OMe)_3$, THF, 52% (single diastereoisomer); (iv) $BF_3{\cdot}OEt$, Et_3SiH, CH_2Cl_2, −78 to 20°C, 70%; (ix) 6 M HCl, 1 h, Δ, 99%.

Oxidation of the *p*-methoxyphenyl group has to be the next step, because the subsequent Baeyer–Villiger reaction increases the electron density in the second aromatic ring and would otherwise lead to a chemoselectivity problem (Scheme 4). Few nitrogen protecting groups are compatible with the ruthenium-catalysed oxidation,[16,20,21] and we chose *N*-*t*-butyloxycarbonyl as the one most likely to yield good results. Boc-protection of the unusually enolisable amide **12a** was initially problematic, and under standard conditions[22] (Boc_2O, Et_3N, DMAP or Boc_2O, NaOH, CH_2Cl_2) a significant quantity of the O-Boc enol carbonate **20** was formed. However, by using only a catalytic quantity of DMAP in MeCN,[23] we were able to isolate a respectable 80% yield of **13** from this step. The protected amide **13** was oxidised to the acid **14** using catalytic $RuCl_3$ with $NaIO_4$ as the stoichiometric reoxidant,[16] and a diazomethane work-up allowed us to isolate the ester **15**.[24]

Baeyer–Villiger oxidation of **15** gave a 52% yield of the lactone **16**, which was opened to the phenol **17** using NaOMe.[25] Selective reduction of the lactam carbonyl group using $NaBH(OMe)_3$[12] gave **18** which was further reduced and deprotected with Et_3SiH,[26] yielding the pyrrolidine **19**. Ester hydrolysis with 6 M HCl yielded the desired diastereoisomer of the target kainoid **4**, which had a ^1H NMR spectrum indicative of a C-3,4-*cis*-substituted kainoid.[27]

Furthermore, we were able to obtain the inactive *trans* stereoisomer of **4**[6] by carrying out the hydrolysis of the lactone **16** under conditions which promoted epimerisation at C-4. Hydrolysis of **16** with LiOH, H_2O, THF at 20°C gave a 5:1 mixture of *trans*-**17** and **17** in 86% yield which was converted to *trans*-**4** by the same sequence of reactions as that used to make **4** (Scheme 5).[28]

The synthesis of **4** and *trans*-**4** demonstrates further the potential of the dearomatising anionic cyclisation of amides for use in the synthesis of kainoids. In the accompanying paper we present the first example of an *asymmetric* dearomatising anionic cyclisation, and we show how it can be used to make a kainoid-like pyroglutamate, as well as the key intermediate **12a** in the synthesis of **4** in enantiomerically enriched form, constituting a formal asymmetric synthesis of **4**.

Acknowledgements

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28. The stereochemistry of *trans*-**19** was confirmed by NOE studies. δ_H H-4 of *trans*-**4** (D_2O, pH 2–3, 400 MHz) 3.5–3.6 (lit. [Ref. 6], pH 4–5: 3.6–3.8).