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Dearomatising cyclisation of lithiated 1-naphthamides with a phenylglycinol-derived chiral auxiliary: asymmetric synthesis of an arylkainoid and a kainoid-like pyroglutamate

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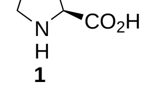
Abstract—1-Naphthamides of *N*-benzylphenylglycinols undergo a diastereoselective dearomatising cyclisation on treatment with *t*-BuLi and DMPU or HMPA. A new pyrrolidinone ring is formed bearing three new stereogenic centers of defined absolute stereochemistry. Removal of the phenylglycinol auxiliary gives enantiomerically pure substituted lactams exhibiting the stereochemistry of the kainoids. These may be converted to kainoid-like pyroglutamates, or alternatively, using the method of the previous paper, to analogues of acromelic acid.

In the preceding paper,[1] we reported the synthesis of an important analogue[2] **1** of acromelic acid (in racemic form) by use of a dearomatising anionic cyclisation of a lithiated naphthamide.[3] In this paper, we describe the development of an asymmetric version of this cyclisation using a phenylglycinol-derived chiral auxiliary. The asymmetric cyclisation allows the synthesis, in high enantiomeric excess, of an intermediate **2** in our route to the acromelic analogue **1**, constituting a formal enantioselective synthesis of **1**. We also describe the use of the asymmetric dearomatising cyclisation in the synthesis of an analogue **3** of (*R*)-pyroglutamate **4** with kainoid-like substituents and relative stereochemistry. Both kainoids and pyroglutamates are important neuroexcitatory amino acids, and there is interest in combining features of the two classes of molecules.[4]

We first noted the dearomatising anionic cyclisation of *N*-benzyl-1-naphthamides[5] when attempted ortholithiation of **5** gave only a small amount of the expected **7**: the major product was **6**, formed as a single diastereoisomer.[6] We later showed that the reaction was stereospecific, with the *meso* diastereoisomer of **5** yielding a different diastereoisomer of the cyclized product, although the origin of the stereospecificity was complex.[7] It was clear at that stage that the stereogenic center of **5** which remains exocyclic in **6** had little effect on the cyclisation. Nonetheless, this position-the non-cyclizing *N*-substituent-seemed the obvious place to attach a chiral auxiliary, and in an attempt to promote an asymmetric cyclisation we lithiated **8** and treated it with DMPU at −50°C.[8] Two products, **11a** and **11b**, were obtained in a 60:40 ratio (Scheme 1), and an X-ray crystal structure (Fig. 1) of the minor product proved their relative stereochemistry. A similar result was obtained with the analogous compound **9**.

Hoping that coordination of lithium by oxygen might improve the selectivity of the reaction, we made **10** from (*R*)-phenylglycine (*R*)-**14** by the route described below (Scheme 2). Exposing doubly lithiated **10** to DMPU at −35°C[8] promoted its cyclisation to **13** as a 10:1 ratio of diastereoisomers. The stereochemistry of **13a** was proved by its reduction to **11a**.



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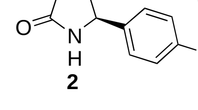

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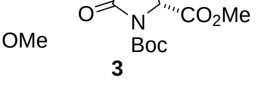

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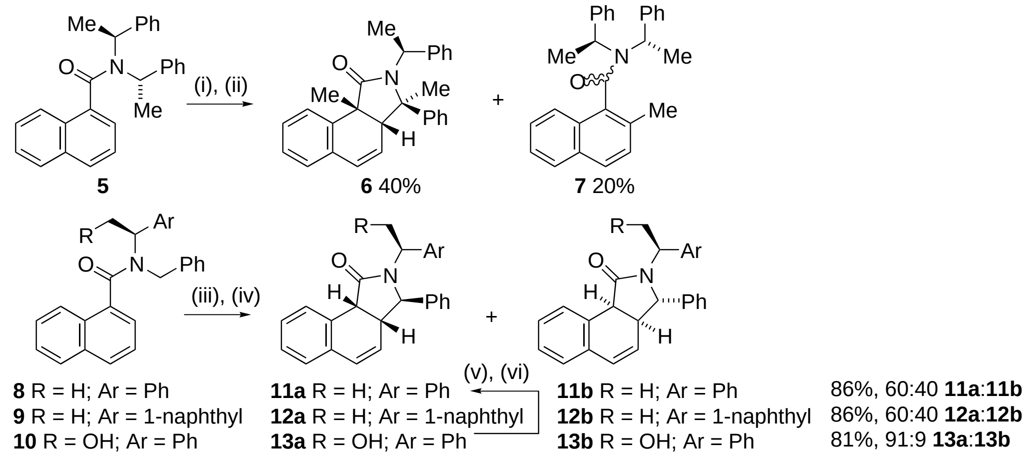


Scheme 1. *Cyclisation of chiral 1-naphthamides.* (i) *s*-BuLi, THF, −78°C; (ii) MeI; (iii) *t*-BuLi (1.3 equiv. for **8** and **9**; 2.3 equiv. for **10**), THF, −78°C, 2 h, then DMPU (6 equiv.), −50°C (for **8** and **9**) or −35°C (for **10**), 16 h; (iv) NH_4Cl, H_2O; (v) MsCl, Et_3N, CH_2Cl_2 (60%); $LiBHEt_3$, THF, Δ (traces).

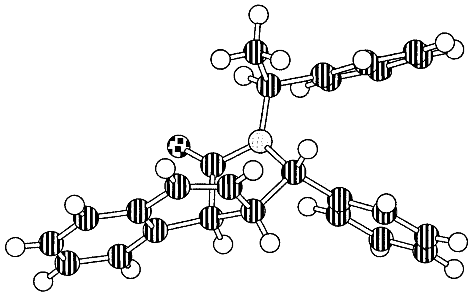


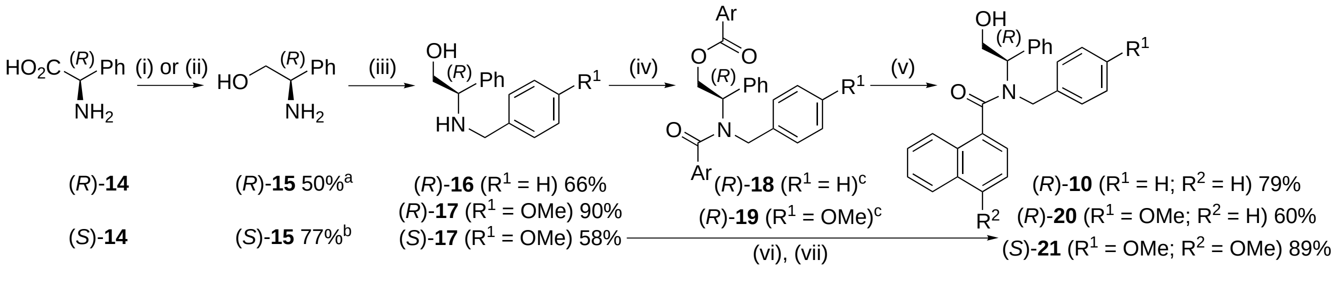
Figure 1. X-Ray crystal structure of **11b**.

In the light of these results, we chose to work with phenylglycinol as our chiral auxiliary,[9] and constructed a further small group of amides, as shown in Scheme 2, for use as starting materials for a series of dearomatising cyclisations. (*R*)- and (*S*)-phenylglycinol **15** were made from (*R*)- and (*S*)-phenylglycine **14** by the methods of Abiko[10] or Hruby.[11] They were alkylated[12] with benzyl bromide or *p*-methoxybenzyl chloride to give (*R*)-**16** and both (*R*)- and (*S*)-**17**. (*R*)-**16** and (*R*)-**17** were doubly acylated with 1-naphthoyl chloride to give (*R*)-**18** and (*R*)-**19**. Ester hydrolysis gave amides (*R*)-**10** and (*R*)-**20**: we were unable to find conditions for direct formation of the hydroxyamide from **16**.[13] For the synthesis of (*S*)-**21** using the more valuable 4-methoxynaphthoyl chloride[1] we chose to ensure monoacylation at N by selective silylation of (*S*)-**17** at O.

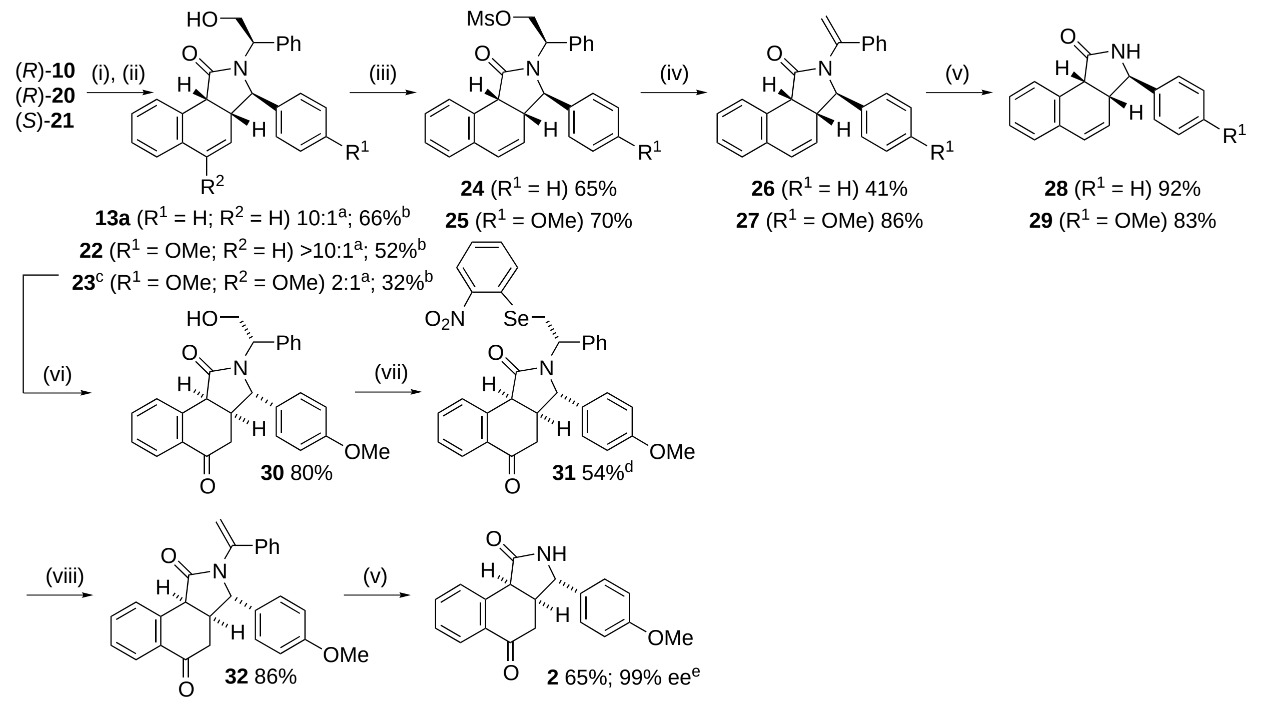
The amides (*R*)-**20** and (*S*)-**21** were cyclized by a modification of the method used for amide **10**: HMPA was used in place of DMPU, which gave low yields with *p*-methoxybenzylamides. The stereoselectivities of the reactions and the yields of single, pure stereoisomers of **13a**, **22** and **23** isolated after flash chromatography are shown in Scheme 3.

Products **13a** and **22** were relieved of their chiral auxiliary by a route developed by Vernon[14] and by Villiéras[15] for the removal of the phenylglycinol protecting group, as shown in Scheme 3.[16] Mesylation of the primary hydroxyl groups of **13a** and **22** gave **24** and **25**; base-promoted elimination gave acyl enamines **26** and **27** which hydrolyzed to the lactams **28** and **29**.[17]

Enol ether **23** was readily hydrolyzed to the ketone **30**, but attempted deprotection of **30** by the mesylation method failed at the elimination step, possibly due to competing enolization. Instead, **30** was converted to the selenide **31**[18] and oxidized to a selenoxide which underwent rapid elimination[19] to the acylenamine **32**. Hydroly-



Scheme 2. *Synthesis of phenylglycinol-derived naphthamides.* [a] From (*R*)-**14** using method (i); [b] From (*S*)-**14** using method (ii); [c] Ar = 1-naphthyl; (i) $NaBH_4$, H_2SO_4, THF; (ii) $LiBH_4$, Me_3SiCl, THF; (iii) BnBr or *p*-$MeOC_6H_4CH_2Cl$, DBU, toluene; (iv) 1-naphthoyl chloride (2 equiv.), Et_3N, CH_2Cl_2; (v) K_2CO_3, MeOH; (vi) Me_3SiCl (2 equiv.), imidazole, CH_2Cl_2; (vii) 4-methoxynaphthoyl chloride (1 equiv.), Et_3N, CH_2Cl_2 then H_2O.



Scheme 3. *Cyclisation and transformation of the cyclized products.* [a] Crude ratio of diastereoisomers (exocyclic center relative to ring); [b] isolated yield of one single, pure diastereoisomer; [c] shown as its enantiomer; [d] absolute and relative stereochemistry confirmed by X-ray crystal structure; [e] determined by HPLC on chiral stationary phase [(*R*,*R*)-β-GEM, Regis]; (i) *t*-BuLi, THF, −78°C, 2 h then DMPU, −35°C (or HMPA, −30°C for **20**, **21**), 16 h; (ii) NH_4Cl, H_2O; (iii) MsCl, Et_3N, CH_2Cl_2; (iv) *t*-BuOK, *t*-BuOH, THF; (v) 3 M HCl (aq.), EtOH, Δ; (vi) 1 M HCl (aq.), THF; (vii) *o*-$NO_2C_6H_4SeCN$, Bu_3P, THF; (viii) H_2O_2, THF, −40 to 25°C.

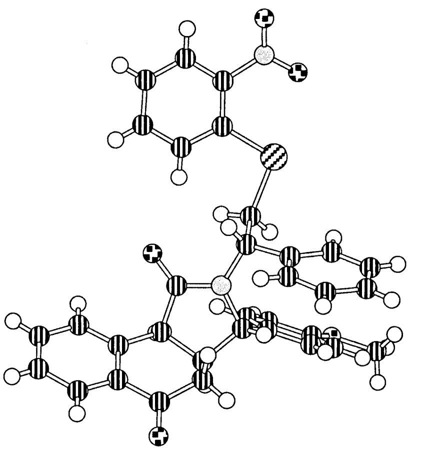
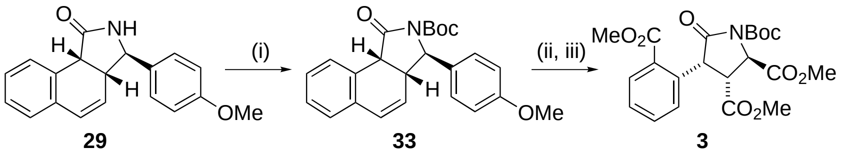


Figure 2. X-Ray crystal structure of **31**.

sis of **32** gave the lactam **2**. An X-ray crystal structure (Fig. 2) of selenide **31** confirmed our assignment of absolute and relative stereochemistry.

The tricyclic lactams **28**, **29** and **2** contain a pyroglutamate ring bearing substituents with relative stereochemistry identical to that of the kainoid series[20] of natural and unnatural products. Lactam **2** is itself an intermediate in our synthesis of the acromelic acid analogue **4**.[1] The enantiomeric purity (99% ee) of **2** was confirmed by HPLC on a chiral stationary phase, and the synthesis of **2** therefore constitutes a formal asymmetric synthesis of the acromelic acid analogue **1**.[21]

A simple transformation leading to ring cleavage of the central six membered ring of the lactam **29** allowed us to make an enantiomerically pure pyroglutamate analogue **3** bearing features of the kainoid series (Scheme 4).[4] We protected **29** as its *N*-*t*-butoxycarbonyl derivative **33**.[22] Ruthenium-catalysed oxidation of **33** using Shioiri's modification[23] of Sharpless's conditions[24] gave, after a trimethylsilyldiazomethane quench, the triester **3** in 60% yield. Pyrrolidinone **3** has the same relative stereochemistry as the kainoids, but opposite absolute stereochemistry, and its synthesis demonstrates that



Scheme 4. *Synthesis of a pyroglutamate bearing kainoid features.* (i) Boc_2O, Et_3N, DMAP, CH_2Cl_2; (ii) cat. $RuCl_3$, $NaIO_4$ (100 equiv.), MeCN, EtOAc, H_2O (1:1:34); (iii) Me_3SiCHN_2, MeOH, benzene.

dearomatising anionic cyclisation onto naphthamides is a versatile means of producing new kainoid-like structures.

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