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Synthesis of α-methyl kainic acid by stereospecific lithiation–dearomatizing cyclization of a chiral benzamide

Jonathan Clayden,* Faye E. Knowles and Christel J. Menet

Department of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, UK

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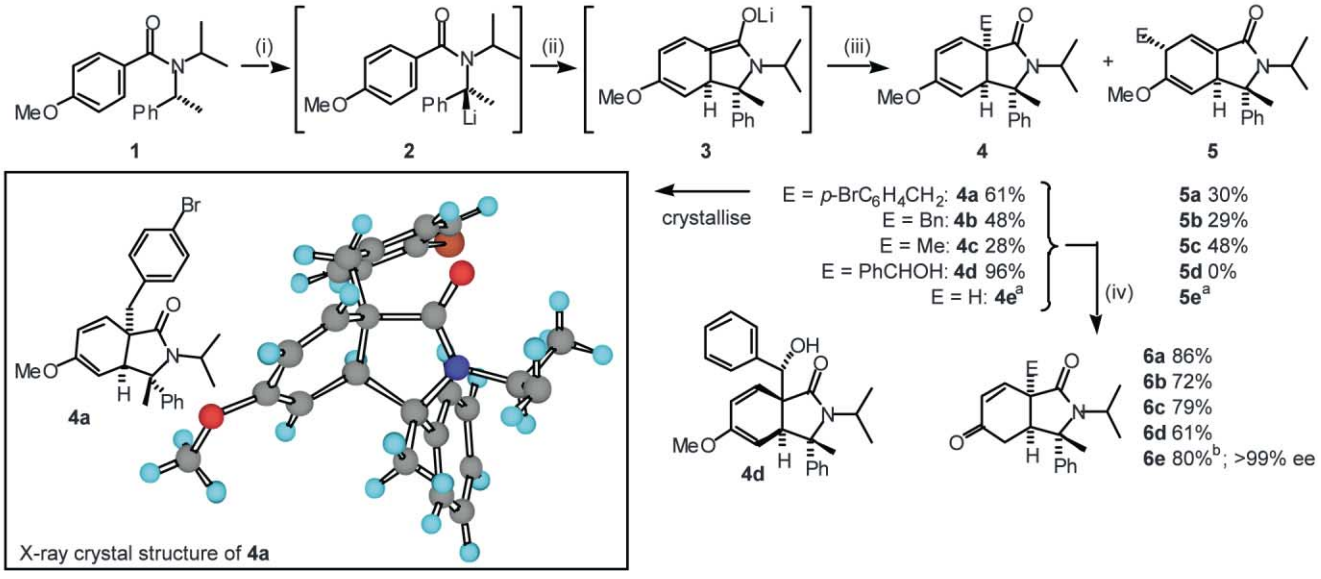
Abstract—Stereospecific lithiation of *N*-α-methylbenzyl benzamides gives configurationally stable tertiary benzyllithiums which undergo a stereospecific dearomatizing cyclization with >99% retention of stereochemistry. The products are partially saturated isoindolinones which carry a new fully-substituted stereogenic centre. A ten-step sequence converts one of these products to the α-methyl analogue of kainic acid. © 2003 Elsevier Science Ltd. All rights reserved.

While stereospecific[1] nucleophilic substitution at an electrophilic stereogenic centre is commonplace, reliable stereospecific electrophilic substitution at a nucleophilic stereogenic centre is more elusive.[2] Some chiral organolithium nucleophiles—most notably those with α-heteroatom substituents—can translate stereochemistry at the C–Li bond directly into stereochemistry at a C–C bond. Often, however, stereochemical fidelity is compromised either by lack of stereospecificity in the electrophilic substitution step or by lack of configurational stability at the C–Li bond.[3] Even when stereospecific electrophilic substitution is possible, it can be of synthetic value only when the organolithium can be made in a stereocontrolled manner.

In this paper we describe a stereospecific reaction sequence which starts with a deprotonation yielding stereospecifically a configurationally stable tertiary



Scheme 1. Dearomatizing cyclization of an *N*-α-methylbenzyl benzamide. *Reagents and conditions*: (i) *t*-BuLi, THF, −78°C; (ii) warm to 0°C; (iii) *p*-$BrC_6H_4CH_2Br$ or BnBr or MeI or PhCHO; (iv) HCl, H_2O. [a]Yield not determined; [b]From **1**.

* Corresponding author.

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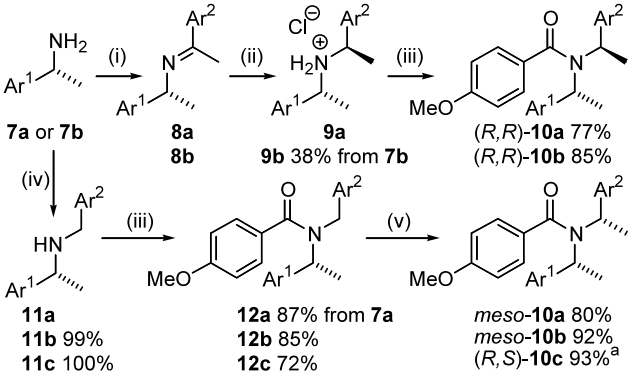
organolithium.[4] This organolithium then undergoes a stereospecific dearomatizing cyclization.[5] Overall, the sequence constructs a fully substituted stereogenic centre from a tertiary centre by stereospecific replacement of the C–H bond with a C–C bond. A further ten synthetic steps allow the newly formed stereogenic centre to be incorporated into the α-position of a new methylated analogue of kainic acid.

Chiral and enantiomerically pure amide (+)-**1** was made by acylation of *N*-isopropyl-α-methylbenzylamine[6] and was lithiated at −78°C with *t*-BuLi in THF to give a red intermediate presumed to be **2** (Scheme 1). Warming to 0°C promoted a dearomatizing cyclization to the extended enolate **3** which reacted with electrophiles to yield either **4** or a mixture of **4** and **5**. Enol ethers **4** were conveniently isolated as the enones **6** after hydrolysis with aqueous acid.[7] Comparison of the HPLC trace[8] of **6e** with that of a racemic sample made from (±)-**1** showed that **6** had retained >99% ee and that the lithiation (**1**→**2**) and cyclization (**2**→**3**) steps therefore proceeded with complete stereospecificity.[9] The X-ray crystal structure of **4a** confirmed that the lithiation–cyclization sequence (**1**→**3**) went with retention of stereochemistry, presumably indicating retention in both steps.[10]

We had previously observed a related stereospecific cyclization of *N*-α-methylbenzyl naphthamides,[11] but in that case we showed that the stereospecificity originated in a chiral memory effect at the stereogenic Ar–CO bond.[12] In **1** and **2** the Ar–CO bond cannot be stereogenic, so stereospecificity at least in these cyclizations must be due to stereospecific formation and reaction of a configurationally stable organolithium intermediate.

The sequence of events running from **1** to **6** makes use of the single stereogenic centre of **1** to construct the three or four stereogenic centres of **6**, up to two of them

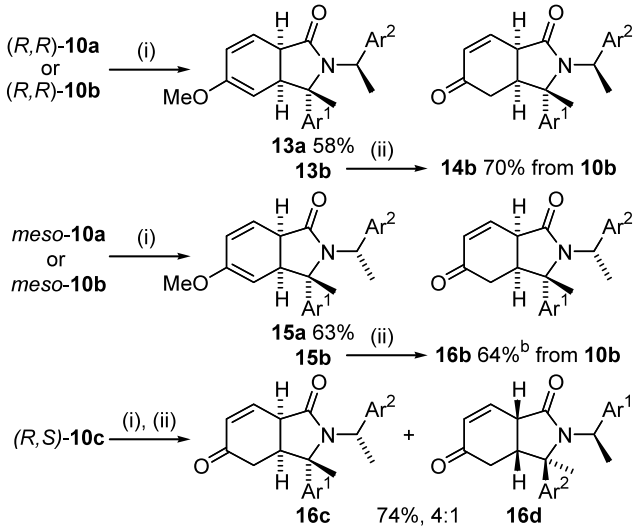


Scheme 2. Diastereoselective amide synthesis[a]. *Reagents and conditions*: (i) Ar^2COMe, toluene, reflux; (ii) 1. $NaBH_4$; 2. crystallise (see Ref. 15); (iii) *p*-$MeOC_6H_4COCl$, Et_3N, CH_2Cl_2; (iv) 1. Ar^2CHO, MeOH, 4 Å sieves, 20°C, 4 h; 2. $NaBH_4$; (v) 1. *t*-BuLi, THF, −78°C; 2. MeI (see Ref. 16). [a]**7a**–**12a** $Ar^1=Ar^2=Ph$; **7b**–**12b** $Ar^1=Ar^2=p$-$MeOC_6H_4$; **10c**–**12c** $Ar^1=p$-$MeOC_6H_4Ph$; $Ar^2=Ph$.

quaternary, and simultaneously generates useful reactivity from the benzamide's aromatic ring. To widen the scope of the cyclization, we required amides bearing nitrogen substituents which could be manipulated in the cyclised products. We chose the diastereoisomeric pairs of amides *meso*- (or [*R*,*S*]-) and (*R*,*R*)-**10** because of their straightforward synthesis from amines **7a** and **7b** by the usefully complementary amine/amide syntheses shown in Scheme 2. Adapting the known synthesis of (*R*,*R*)-**10a**[13] gave (*R*,*R*)-**10b** selectively by diastereoselective reduction of the imine **8b**, while *meso*-**10a**, *meso*-**10b** and (*R*,*S*)-**10c** were made from **12a**–**c** by our '*meso*-selective' amide α-lithiation–alkylation.[14]

All five *N*-α-methylbenzyl benzamides **10** were deprotonated with *t*-BuLi to give red organolithiums which cyclized on warming to room temperature. Aqueous quench and neutral or acidic aqueous work-up gave good yields of the bicyclic dienes or enones (Scheme 3). Dienes **13a**,**b** and **15a**,**b** contained no trace of each other: the cyclizations are still fully stereospecific. Hydrolysis to the enones **14** and **16** with 0.5 M HCl gave a single stereo- and regioisomer of **14b**.

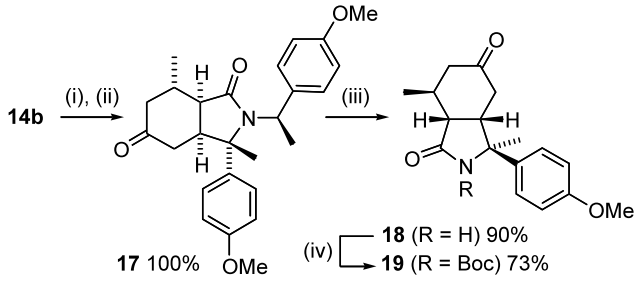
The '*meso*-selective' alkylation–cyclization sequence is devalued by the fact that enantiomerically pure amines **7** necessarily lead to racemic products **15** and **16**. We aimed to overcome this with (*R*,*S*)-**10c**, in which *meso* symmetry is broken by the presence of a methoxy group. Unfortunately, however, the cyclization was not sufficiently selective with respect to the two possible cyclizing groups to be synthetically useful, giving a 4:1 mixture of cyclized enones **16c** and **16d**.[15] The major product **16c** arises by cyclization of the methoxy-substituted α-methylbenzyl group—presumably the *p*-methoxy group destabilizes the benzyllithium (and therefore promotes faster cyclization) more than it disfavours deprotonation.



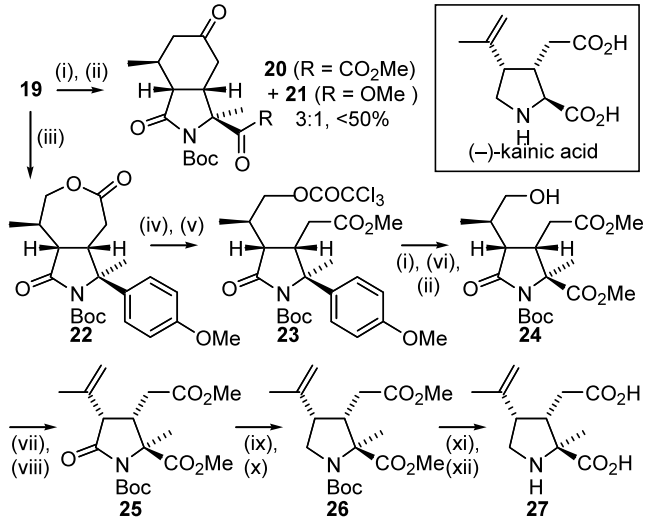
Scheme 3. Diastereospecificity in the cyclization[a]. *Reagents and conditions*: (i) 1. *t*-BuLi, THF, −78 to +20°C; 2. NH_4Cl, (ii) 0.5 M HCl. [a]**13a**, **15a** $Ar^1=Ar^2=Ph$; **13b**–**16b** $Ar^1=Ar^2=p$-$MeOC_6H_4$; **16c**, **16d** $Ar^1=p$-$MeOC_6H_4$; $Ar^2=Ph$. [b]Plus 21% of the β,γ-enone regioisomer.

Nevertheless, the cyclization of (*R*,*R*)-**10b** incorporating *two* methoxy-substituted α-methylbenzyl groups offers several advantages. Schemes 4 and 5 illustrate this in a practical synthetic application of the enantiomerically pure cyclized product **14b**. Firstly, the exocyclic α-methyl-*p*-methoxybenzyl group is susceptible to oxidative cleavage with ceric ammonium nitrate.[16] Conjugate addition of Me_2CuLi to **14b** gave the ketone **17** quantitatively, and treatment with ceric ammonium nitrate followed by Boc_2O gave the carbamate **19**.

The carbamate **19** exhibits the same absolute and relative stereochemistry as the kainoid series of amino acids,[17] and we have used related cyclization products in syntheses of (–)-kainic acid itself[18] and of other members of the kainoid family.[19] Conversion of **19** to a kainoid analogue is assisted by a second property of the



Scheme 4. Oxidative deprotection. *Reagents and conditions*: (i) $Me_2CuLi{\cdot}LiBr$, Me_3SiCl, THF, −78°C; (ii) 2 M HCl; (iii) $Ce(NH_4)_2(NO_3)_6$, H_2O, MeCN; (iv) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 12 h.



Scheme 5. Synthesis of α-methyl kainic acid. *Reagents and conditions*: (i) $RuCl_3$, $NaIO_4$, H_2O, MeCN, EtOAc, 4 h; (ii) Me_3SiCHN_2; (iii) *m*-CPBA, CH_2Cl_2, 48 h (80%); (iv) NaOMe, MeOH, −78°C, 2 h (82%); (v) Cl_3CCOCl, Et_3N, CH_2Cl_2, 0°C (85%); (vi) H_2O_2, Na_2CO_3, dioxane (35% **24** from **23**); (vii) *N*-PhSe-phthalimide, *n*-Bu_3P, THF, 20°C, 2 h; (viii) H_2O_2, py, THF, 20°C, 12 h (64% from **24**); (ix) DIBAL, THF, −78°C, 2 h; (x) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78°C (41% from **25**); (xi) LiOH, MeOH, 12 h, 20°C; (xii) CF_3CO_2H, reflux, 2 h (45% from **26**).

p-methoxyphenyl group: its enhanced susceptibility to oxidation with Ru(VIII) to provide carboxyl substituents.[20] However, oxidative removal of the methoxyphenyl ring of **19** with Ru(VIII) was only partially successful—steric hindrance from the methyl group largely derailed the degradation of the ring one stop before the target carboxylic acid derivative, giving (after methylation) mainly **20** and little **21**. We returned to the carbamate **19** and subjected it to Baeyer–Villiger oxidation with *m*-CPBA, regioselectively rupturing the cyclohexanone ring to give lactone **22**.[21] Careful methanolysis (NaOMe, −78°C) of the lactone avoided epimerization α to the amide carbonyl group, giving an alcohol which was protected as its trichloroacetate **23**. Oxidative degradation of the methoxyphenyl ring at this stage in the synthesis still stopped short of completion, but basic hydrogen peroxide was sufficient to further oxidise any α-ketoacid to the carboxylic acid. Hydrolysis of the trichloroacetate ester took place concurrently, and the product was isolated after methylation with trimethylsilyldiazomethane as the ester **24**. The kainoid isopropenyl group of **25** was revealed by elimination of water from **24** via a selenoxide; reduction of the lactam carbonyl group with DIBAL and Et_3SiH gave **26** and deprotection yielded **27**, an α-methylated analogue of kainic acid. Alkyl substituted kainoids have been made before and their properties investigated, but this is the first synthesis of **27**.[22]

Supplementary material

X-Ray crystallographic data for **4a** and experimental details for the synthesis of **27**.

Acknowledgements

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