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Stereospecific formation of tetrasubstituted centres from trisubstituted centres during dearomatising anionic cyclisations

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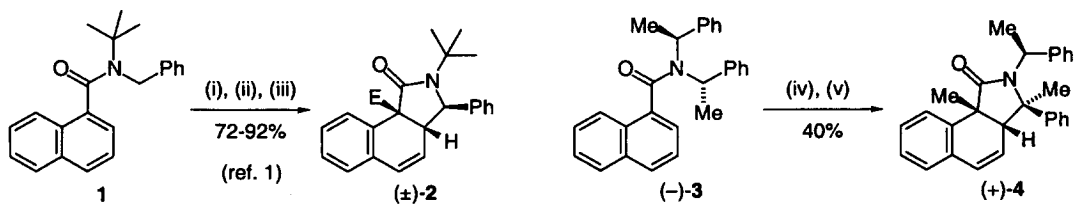
Abstract

Dearomatising anionic cyclisation of tertiary naphthamides bearing chiral *N*-substituents (such as α-methylbenzyl) proceeds with overall retention of configuration at the newly formed tetrasubstituted chiral centre. The cyclisation is stereospecific overall, with the configuration of the starting trisubstituted stereogenic centre controlling the stereochemistry of the product. Highly substituted pyrrolidinone rings may be formed as single enantiomers from enantiomerically pure starting materials.

The *N*-benzyl naphthamide **1**, on lithiation, undergoes a dearomatising anionic cyclisation to give the tricyclic styrene **2** (Scheme 1).[1] We have investigated the mechanism of this reaction[2] and we recently found that even simple benzamides undergo the same type of reaction to give synthetically versatile cyclohexadienes.[3] Although our published results describe the reactions of **1**, in fact we first discovered this cyclisation when we were trying to ortholithiate the *N,N*-bis(α-methylbenzyl)naphthamide **3**. Treatment with *s*-BuLi and MeI gave not the expected 2-methyl compound but instead the tricyclic **4** as a single diastereoisomer in moderate yield. Initially we had decided to work with simpler versions of **3**, such as **1**, to avoid the complications of the additional stereogenic centres, but we have now studied in more detail the stereoselective cyclisation of **3** and some related *N*-(α-alkylbenzyl)naphthamides, and in this Letter we describe our results. In the following Letter, we go on to show how the conformation of these chiral naphthamides plays a key role in determining the stereochemistry of the cyclised products.



1 (±)-2 (–)-3 (+)-4

Scheme 1. Dearomatising anionic cyclisations. (i) *t*-BuLi, THF, –78°C, 2 h; (ii) DMPU (6 equiv.), –78°C, 16 h; (iii) E^+; (iv) *s*-BuLi, THF, –78°C, 30 min; (v) MeI

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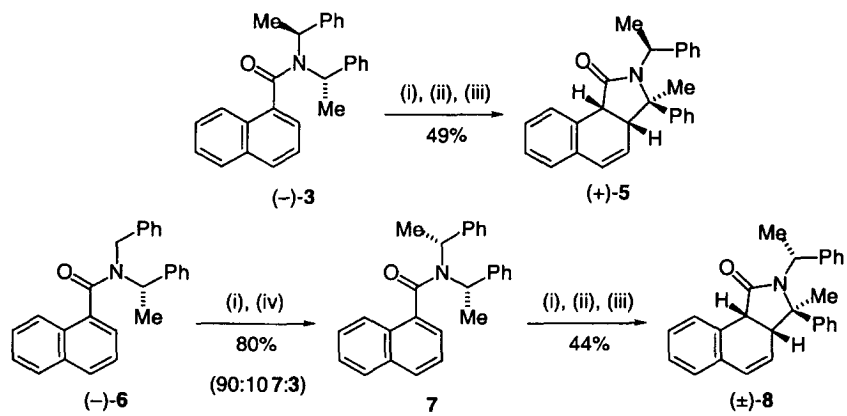
The cyclisation of **3** to a single diastereoisomer of **4** is remarkable in that it creates two new tetrasubstituted centres in one step, and it also poses a number of important stereochemical questions. For example, is the reaction stereospecific, with the product stereochemistry deriving entirely from the stereochemistry of the cyclising centre, or stereoselective, with the exocyclic stereogenic centre controlling the formation of the three new centres of **4**?

To distinguish between these two mechanistic possibilities we needed to cyclise both **3** and its diastereoisomer, the *meso* compound **7**. We decided to get **7** from the mixture of diastereoisomers we expected on α-lithiation and methylation of **6**. Remarkably, in the event, this method (*t*-BuLi, –78°C, THF, then MeI) gave the *meso* diastereoisomer **7** with high stereoselectivity (90:10 of **7**:**3** by HPLC) (Scheme 2).[4]



Scheme 2. Stereospecific cyclisation of diastereoisomeric bis(α-methylbenzyl) amides. (i) *t*-BuLi, THF, –78°C, 2 h; (ii) DMPU (6 equiv.), –78°C, 16 h; (iii) MeOH; (iv) MeI

Both amides **3** and **7** were treated with *t*-BuLi and then DMPU under our optimised conditions,[1,2] and each gave a single diastereoisomer of the cyclised product. The two products **5** and **8** were clearly different compounds by ^{1}H NMR.[5] The cyclisation must therefore be stereospecific: the relative stereochemistry of the starting material controls the relative stereochemistry of the product.

The relative stereochemistry of (+)-**5** was assigned from its X-ray crystal structure, shown in Fig. 1.

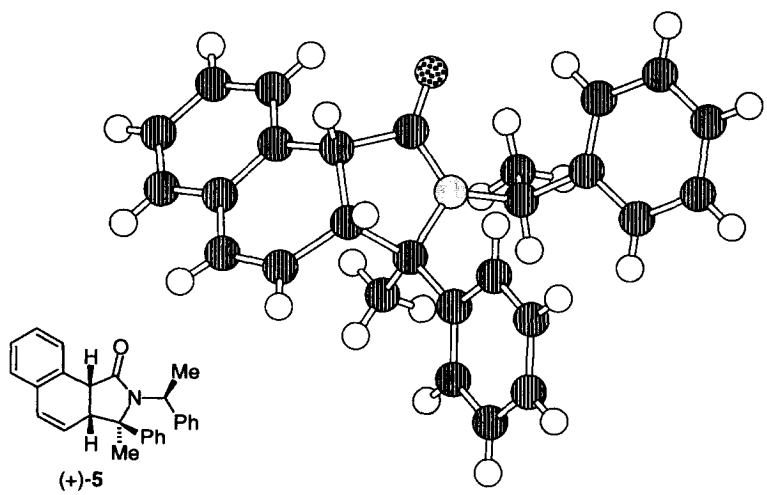
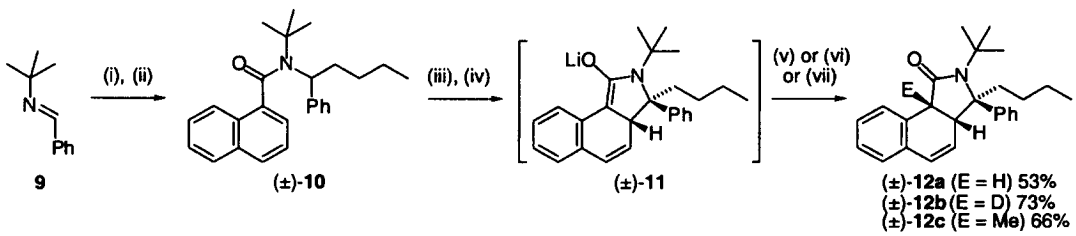


Figure 1. X-Ray crystal structure of (+)-**5**

This confirms that the reaction is not only stereospecific, but that it proceeds with retention at the cyclising centre.

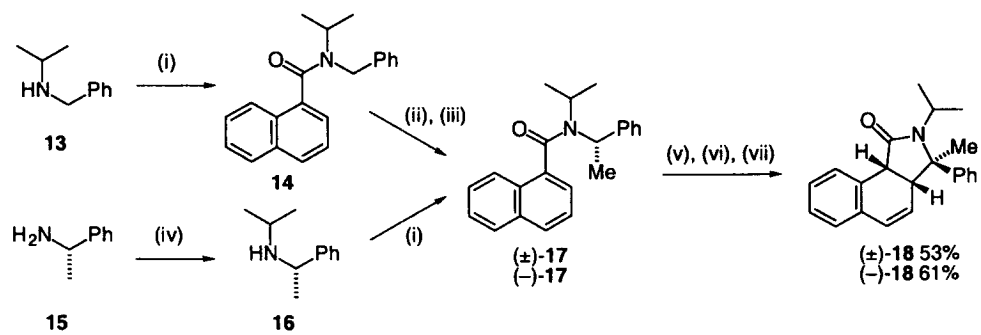
The cyclisation of *N*-α-alkylbenzyl naphthamides to make highly substituted fused five-membered nitrogen heterocycles turns out to be a general reaction.[6] Racemic *N*-(α-butylbenzyl)naphthamide **10** was made by acylation of the addition product of *N*-*t*-butylbenzaldimine **9** and BuLi (Scheme 3).[7] Compound **10** was lithiated in the usual way with *t*-BuLi at −78°C to give a red organolithium which, on treatment with 6 equiv. of DMPU, cyclised to the enolate **11**. Reaction of **11** with electrophiles MeOH, CD_3OD or MeI gave **12a–c** as single diastereoisomers in 53–73% yield,[6] confirming that the cyclisation still works even when hindered quaternary centres are being formed (**12c** has an almost completely substituted pyrrolidinone ring).[8]



Scheme 3. Cyclisation/alkylation of an α-alkylbenzyl amide. (i) *n*-BuLi; (ii) 1-naphthoyl chloride, NaH, toluene, Δ; (iii) *t*-BuLi, THF, −78°C, 2 h; (iv) DMPU (6 equiv.), −78°C, 16 h; (v) MeOH; (vi) CD_3OD; (vi) MeI

These results led us to the conclusion that it should be possible, using a dearomatising anionic cyclisation, to convert an enantiomerically pure starting material containing a single chiral centre to an enantiomerically pure product, creating a tetrasubstituted stereogenic centre directly and stereospecifically from a trisubstituted stereogenic centre. There are few reactions of this type: the most common is perhaps the stereospecific insertion of a carbene into a C–H bond.[9]

To test this idea we made the racemic amide (±)-**17** by α-lithiation and methylation of **14**, and enantiomerically pure (−)-**17** via acylation of the amine **16**, itself available by reductive amination of α-methyl benzylamine.[10] Both samples were cyclised to give the tricyclic amide (±)-**18** or (−)-**18** (Scheme 4).[5]



Scheme 4. Cyclisation of racemic and enantiomerically pure samples of **17**. (i) 1-Naphthoyl chloride, Et_3N, CH_2Cl_2; (ii) *t*-BuLi, THF, −78°C, 2 h; (iii) MeI; (iv) acetone, $NaCNBH_3$, 5 M HCl, MeOH; (v) *t*-BuLi, THF, −78°C, 2 h; (vi) DMPU (6 equiv.), −50°C, 16 h; (vii) MeOH

Comparison of the HPLC trace of (−)-**18** on a chiral stationary phase [(*R,R*)-Whelk-O 1 from Regis] with that of (±)-**18** showed that (−)-**18** still had 99% ee: the cyclisation proceeds with essentially complete stereochemical integrity (Fig. 2).

The dearomatising cyclisation of 1-naphthamides bearing chiral *N*-substituents is fully stereospecific, with the new C–C bond taking the place of the old C–H bond with >99% overall retention of configura-

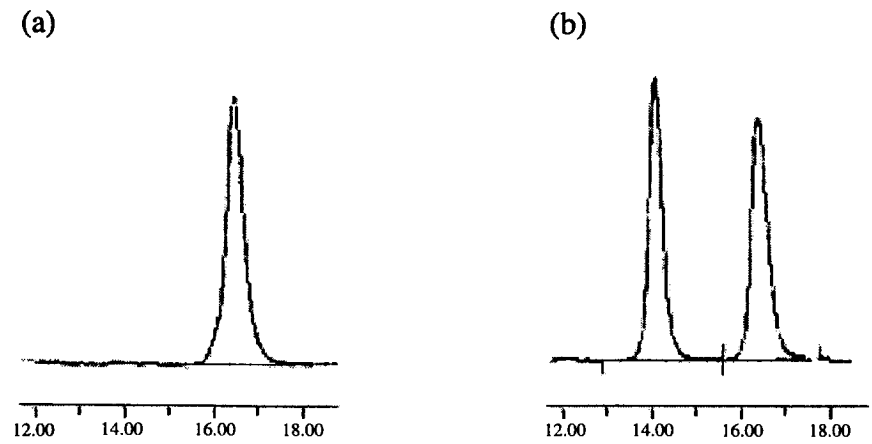


Figure 2. HPLC trace of (a) (−)-**18**; and (b) (±)-**18** on chiral stationary phase

tion. In the accompanying Letter we explore the mechanism of the reaction and draw the conclusion that an unusual diastereoselective ortholithiation step, and not a configurationally stable organolithium, is the source of the reaction's stereospecificity.

Acknowledgements

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5. Unreacted starting material accounted for most of the remaining mass.
6. For syntheses of pyrrolidines by anionic cyclisation, see: Broka, C. A.; Shen, T. *J. Am. Chem. Soc.* **1989**, *111*, 2981; Coldham, I.; Hufton, R.; Snowden, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 5322; Coldham, I.; Hufton, R. *Tetrahedron* **1996**, *52*, 12541; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1996**, *61*, 2594; Bailey, W. F.; Carson, M. W. *Tetrahedron Lett.* **1997**, *38*, 1329.
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