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Synthesis of isoquinuclidinones via a tandem amination/imination sequence: application to the synthesis of (−)-mearsine

James D. Cuthbertson [a], Andrew A. Godfrey [b], Richard J. K. Taylor [a,*]

[a] Department of Chemistry, University of York, Heslington, York YO10 5DD, UK
[b] AstraZeneca, Pharmaceutical Development, Silk Road Business Park, Macclesfield, Cheshire, SK10 2 NA, UK

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Dedicated to Prof. Harry Wasserman in recognition of his many seminal achievements in organic chemistry and his friendship over numerous years of Tetrahedron Board Meetings.

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ABSTRACT

The facile synthesis of a range of novel isoquinuclidinones from 6-acyl-cyclohex-2-enones is described, employing aqueous ammonia in a one-pot procedure involving initial conjugate addition of ammonia followed by cyclisation via intramolecular imine formation. The scope and limitations of the methodology are described as is an efficient synthesis of the *Elaeocarpus* alkaloid (−)-mearsine.

The development of new and improved routes to nitrogen-containing heterocycles represents an important and continuing challenge in organic chemistry,[1] due to the prevalence of such systems in natural products and pharmaceuticals/agrochemicals. Recently,[1b] we have become interested in naturally occurring isoquinuclidine alkaloids such as compounds **1–3** isolated from *Daphniphyllum*,[2] *Securinega*[3] and *Tabernaemontana*[4] species, respectively (Fig. 1). In turn, we were attracted to the rare isoquinuclidinone alkaloids mearsine **4**[5] and grandisine B **5**[6] which contain the unusual 2-azabicyclo[2.2.2]oct-2-en-5-one nucleus.

Functionalised 2-azabicyclo[2.2.2]octanes have previously been prepared via Diels–Alder cyclisations,[7] thermal cyclisations of 4-amino-cyclohexane carboxaldehyde derivatives,[8] double conjugate addition of aqueous ammonia into bifunctional Michael acceptors[9] and recently via cyclisation of silyl enol ethers onto iminium ions.[10] However, to our knowledge, there are no established methods for the direct preparation of 2-azabicyclo[2.2.2]oct-2-en-5-ones (i.e., containing both the ketone and imine functionalities). Retrosynthetic analysis as shown in Scheme 1, based on the biosynthetic proposal for mearsine put forward by Bick and co-workers,[5] suggested that the target compounds **6** might be accessed from 6-acyl-cyclohex-2-enones **8** by initial conjugate addition of ammonia to give the intermediate amine **7** which might then be expected to give the bicyclic system by intramolecular imine formation.

In this Letter, we describe the successful implementation of the tandem amination/imination route to isoquinuclidinones **6** as a one-pot process, and its application in natural product synthesis. Similar chemistry was utilised by Tamura and co-workers as part of their recent total synthesis of grandisine B **5**.[11]

Initial studies concentrated on the cyclisation of diketone **8a**, which bears the 5-methyl substituent found in mearsine **4** and grandisine B **5**. This was prepared (Scheme 2) by treatment of 5-methylcyclohexenone **9**[12] with LDA in THF at −78 °C and subsequent trapping with cyclohexane carboxaldehyde, followed by oxidation of the resulting β-hydroxy ketone **10**[13] using Dess–Martin periodinane. The novel 1,3-diketone **8a** exists as a mixture of diasteroisomers/tautomers, with the *trans*-diastereoisomer predominating.

With the desired 1,3-diketone **8a** in hand, we were in a position to investigate the proposed cyclisation sequence (Scheme 3). Upon treatment of diketone **8a** with 35% aqueous ammonia in methanol, rapid consumption of starting material was observed, with the formation of a single product. Isolation and analysis by $^{1}H/^{13}C$ NMR spectroscopy revealed the product to be the desired isoquinuclidinone **6a** [characteristic bridgehead proton signals at 4.5 and 3.2 ppm; ^{13}C NMR signals at 209.0 ppm (bridging ketone) and 179.7 ppm (imine)]. Compound **6a** was obtained in excellent yield

* Corresponding author. Tel.: +44 (0)1904 432606; fax: +44 (0)1904 434523.
E-mail address: rjkt1@york.ac.uk (R.J.K. Taylor).

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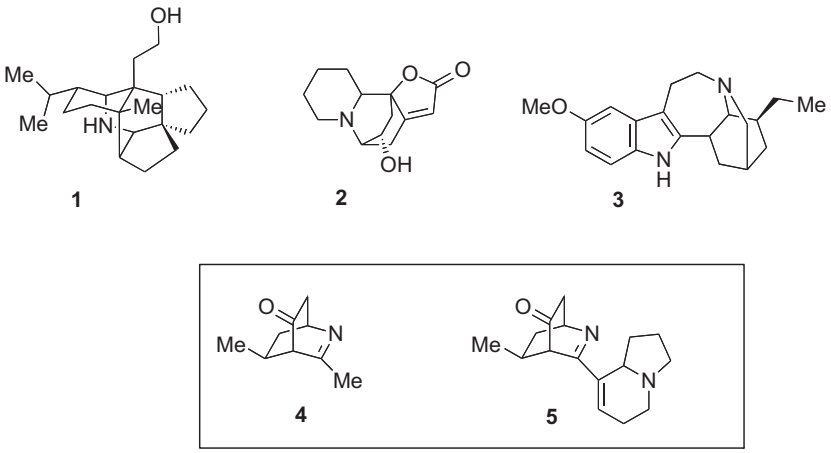
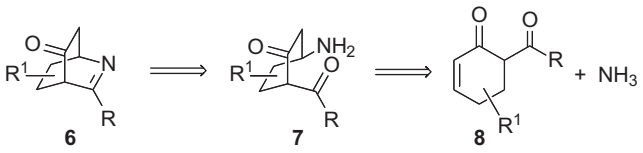


Figure 1. Isoquinuclidine and isoquinuclidinone alkaloids.



Scheme 1. Retrosynthetic analysis of isoquinuclidinone **6**.

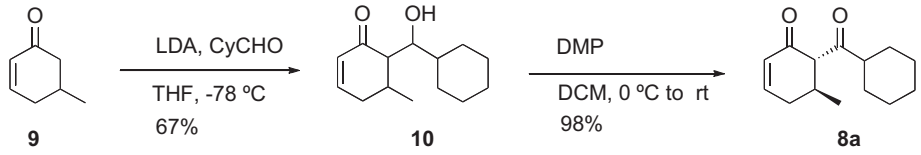
as a single diastereoisomer (8β-Me) and the isomeric compound **11** (8α-Me) was not observed. We assume that initial, reversible 1,4-addition of ammonia occurs followed by imine formation; presumably, some addition of ammonia *syn*-to the methyl group takes place but cyclisation to give **11** is unfavourable for steric reasons.

Having confirmed the viability of the proposed sequence, the scope of the reaction was investigated next utilising a range of substituted diketone substrates **8** (Table 1). The starting 1,3-diketones **8** were prepared from the corresponding cyclohexenones using the procedure outlined in Scheme 2.

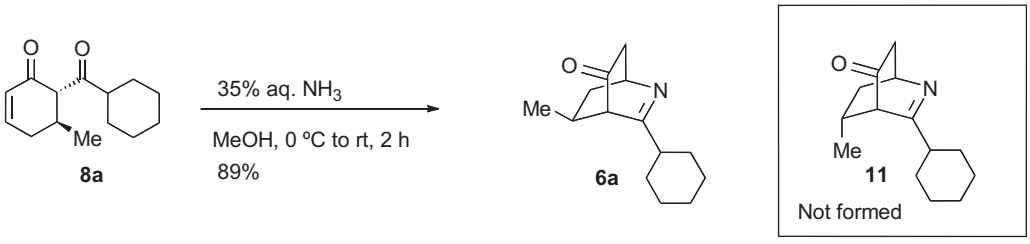
As can be seen, this tandem process was compatible with a range of aliphatic, aromatic and alkenyl substituents on the ketone (entries i–iv). However, on increasing the steric bulk of the substituents on the cyclohexenone ring, longer reaction times were required although the expected isoquinuclidinones **6e–g** were obtained in fair to excellent yield (entries v–vii). In the case of the 5-phenyl-cyclohexenone **8f**, a number of by-products were formed in addition to isoquinuclidinone **6f** (entry vi), and with the trisubstituted carvone-derived cyclohexenone **8g** the expected isoquinuclidinone **6g** was formed but a three-day reaction time was required (entry vii). In all cases, the reactions proceeded stereoselectively to give the 8β-substituted products exclusively.

Attempts were also made to prepare the 'unsubstituted' isoquinuclidinones **6h** and **6i** (Scheme 4). However, treatment of precursors **8h** and **8i** using the optimised reaction conditions did not produce the expected isoquinuclidinones **6h** and **6i** but instead gave clean conversion to the monocyclic methyl esters **12a** and **12b**. It seems likely that isoquinuclidinones **6h** and **6i** were formed but then underwent methoxide-induced ring-opening as illustrated in Scheme 4 to give compounds **13**.[15] We assume that the additional substitution around the isoquinuclidinone ring in compounds **6a–g** slows down this ring-opening process. The structural resemblance between esters **12** and the *Elaeocarpus* alkaloid grandisine G **13**, recently isolated by Carroll and co-workers,[16] should also be noted; it was proposed that grandisine G **13** results from the corresponding methanol-induced ring-opening of grandisine B **5**.[16]

In order to demonstrate the utility of this tandem amination/imination sequence, we utilised the procedure in a short total synthesis of (−)-mearsine **4** (Scheme 5). Mearsine was isolated in 1984 by Bick and co-workers from the Australian rainforest species *Peripentadenia mearsii*,[5] and subsequently the (+)-enantiomer of mearsine was synthesised from (+)-pulegone by Crouse and Pinder.[17] The first requirement was to prepare the requisite cyclohexenone **8j** and this was achieved prepared from 2,4-pentanedione and crotonaldehyde via an enantioselective, organocatalytic Michael addi-

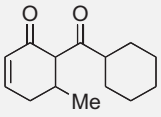
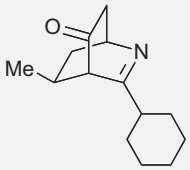
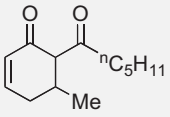
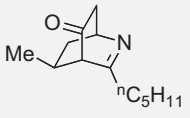
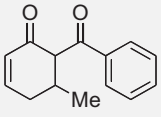
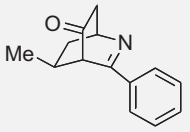
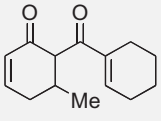
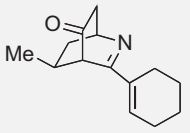
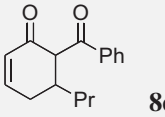
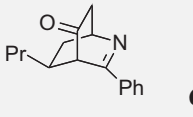
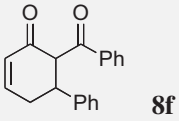
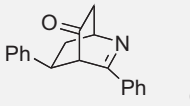
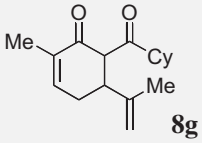
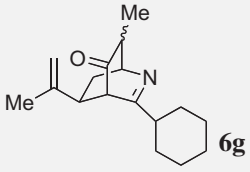


Scheme 2. Synthesis of cyclisation precursor 1,3-diketone **8a**.

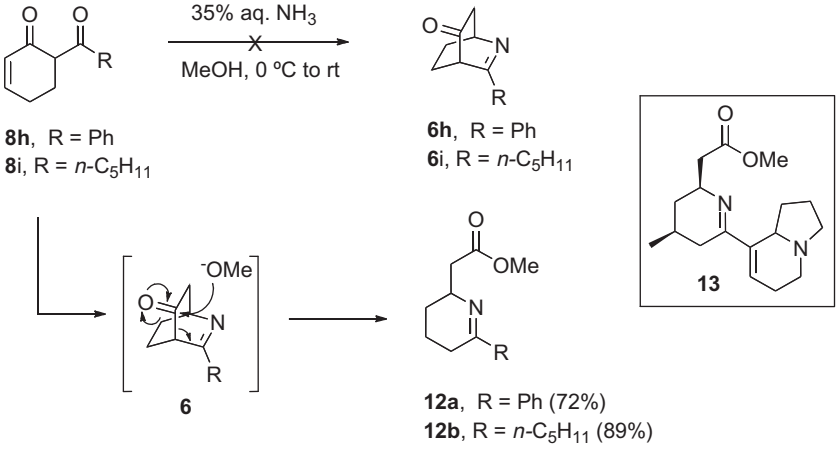


Scheme 3. Synthesis of isoquinuclidinone **6a** via amination/imination sequence.

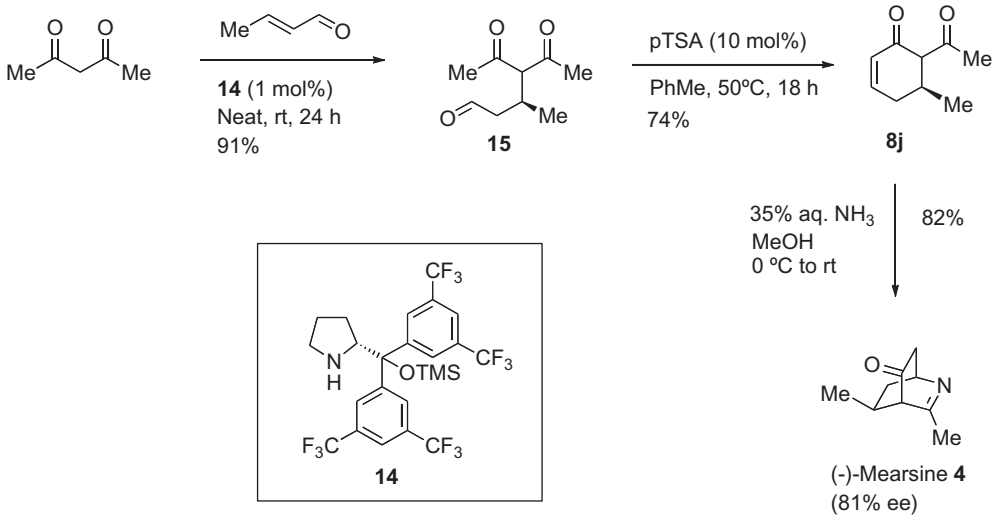
Table 1
Scope of amination/cyclisation sequence[a]

Entry	Substrate **8**	Product **6**	Time (h)	Yield[b] (%)
i	 **8a**	 **6a**	2	89
ii	 **8b**	 **6b**	2	65
iii	 **8c**	 **6c**	2	91
iv	 **8d**	 **6d**	2	80[c]
v	 **8e**	 **6e**	4	80
vi	 **8f**	 **6f**	8	~50%[d]
vii	 **8g**	 **6g**	72	75[e]

[a] All reactions were performed on 0.25 mmol scale using MeOH (1 mL), 35% aq NH_3 (0.5 mL) at 0 °C to rt.
[b] Isolated yields.
[c] Representative experimental procedure.[14]
[d] An inseparable mixture of **6f** (confirmed by ^{1}H NMR/HRMS) and by-products obtained; yield estimated using NMR spectroscopy.
[e] Dr = 3.4:1.



Scheme 4. Methoxide promoted ring-opening of isoquinuclidinone **6**.



Scheme 5. Synthesis of (−)-mearsine **4**.

tion[18] and subsequent aldol condensation. Thus, addition of 2,4-pentanedione to crotonaldehyde mediated by Jorgensen's catalyst **14** (1 mol %)[19] gave aldehyde **15** in 91% unpurified yield. Immediate treatment of the aldehyde **15** with pTSA (10 mol %) furnished the desired cyclohexenone **8j**, which was isolated as a complex mixture of diastereoisomers/tautomers. Treatment of diketone **8j** with 35% aqueous ammonia in methanol initiated the required tandem amination/imination sequence to produce (−)-mearsine **4** in 82% yield;[20] the melting point (mp 38–40 °C; lit.[5] 43–44 °C) and spectral data for the isolated product corresponded closely to those reported,[5,17] although there was a discrepancy in the optical rotation data {lit. $[\alpha]_D$ −34.5 (*c* 0.495, CH_2Cl_2);[5] synthetic **4**, $[\alpha]_D$ −252.6 (*c* 0.51, CH_2Cl_2)}. For this reason, chiral HPLC analysis (Phenomenex Lux Cellulose-2 column, 95:5 *iso*-hexane/EtOH, flow rate 1.0 mL/min) was performed which confirmed that the enantiomeric ratio was 90.5:9.5, and conclusive evidence for the structure and relative stereochemistry of synthetic **4** was provided by single crystal X-ray analysis of the picrate salt (mp 208–210 °C dec; lit.[5] mp 212–213 °C).

In summary, a tandem amination/imination route has been developed to convert 6-acyl-cyclohex-2-enones **8** into isoquinuclidinones **6** in a one-pot process.

The scope and limitations of the methodology have been investigated, and the utility of the sequence has been demonstrated with an efficient synthesis of the alkaloid (−)-mearsine (the first synthesis of the (−)-enantiomer). Applications of this new tandem methodology in the preparation of more complex natural product targets are currently underway.

Acknowledgements

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13. All novel compounds were fully characterised by $^1H/^{13}C$ NMR spectroscopy, IR spectroscopy and HRMS.
14. *Representative experimental procedure*: To a stirred solution of diketone **8d** (55 mg, 0.25 mmol) in MeOH (1 mL) at 0 °C was added dropwise 35% aqueous NH_3 (0.5 mL). The resulting yellow solution was held at 0 °C for 30 min, then warmed to rt with stirring until consumption of starting material was observed by TLC analysis (DCM/MeOH, 95:5). The reaction mixture was then diluted with water (5 mL) and extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and then concentrated in vacuo to afford a colourless oil which was purified by column chromatography (SiO_2, DCM/MeOH, 98:2) to give isoquinuclidinone **6d** (44 mg, 80%) as a colourless oil R_f 0.49 (DCM/MeOH, 95:5); ν_{max}/cm^{-1} (neat) 2930, 2868, 1731, 1576, 1340; δ_H (400 MHz, $CDCl_3$) 6.41 (1H, m), 4.60 (1H, dddd, *J* = 3.6, 3.6, 1.8, 1.8), 3.62 (1H, d, *J* = 3.1), 2.30–2.25 (2H, m), 2.21–2.15 (2H, m), 2.12 (1H, dm, *J* = 19.0), 2.02 (1H, dd, *J* = 19.0, 1.8), 2.01–1.93 (1H, m), 1.91–1.81 (1H, m), 1.67–1.54 (4H, m), 1.24 (1H, ddd, *J* = 12.8, 4.4, 1.8), 1.03 (3H, d, *J* = 7.0); δ_C (100 MHz, $CDCl_3$) 209.2 (CO), 172.2 (CN), 135.3 (C), 133.0 (CH), 55.8 (CH), 55.6 (CH), 39.8 (CH_2), 32.7 (CH_2), 29.2 (CH), 26.0 (CH_2), 24.0 (CH_2), 22.1 (CH_2), 21.8 (CH_2), 21.3 (CH_3); *m/z* (ESI) 218 $[MH]^+$; [HRMS (ESI): calcd for $C_{14}H_{20}NO$, 218.1539; found: MH^+, 218.1540 (0.4 ppm error)].
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20. *(−)-Mearsine* **4**: R_f 0.45 (DCM/MeOH, 9:1); ν_{max}/cm^{-1} (neat) 2957, 1729, 1633, 1379; δ_H (400 MHz, $CDCl_3$) 4.50 (1H, dddd, *J* = 3.5, 3.5, 1.9, 1.9), 3.13 (1H, d, *J* = 2.9), 2.17–2.08 (1H, m), 2.12 (3H, s), 2.01 (1H, dd, *J* = 19.0, 1.8), 1.97 (2H, m), 1.22 (1H, m), 1.04 (3H, d, *J* = 6.9); δ_C (100 MHz, $CDCl_3$) 208.4 (CO), 173.7 (CN), 61.4 (CH), 55.5 (CH), 39.5 (CH_2), 32.4 (CH_2), 28.8 (CH), 24.5 (CH_3), 21.0 (CH_3); *m/z* (ESI) 152 $[MH]^+$; [HRMS (ESI): calcd for $C_9H_{14}NO$, 152.1070; found: MH^+, 152.1070 (0.1 ppm error)]; HPLC Analysis [Phenomenex Lux Cellulose-2 column, 95:5 *iso*-hexane/EtOH, flow rate 1.0 mL/min; R_T = 9.51 (minor, 9.5%) and 10.62 (major, 90.5%)]. Picrate salt mp 208–210 °C dec (lit.[5] mp 212–213 °C).