Diversity-oriented synthesis of bicyclic and tricyclic alkaloids†

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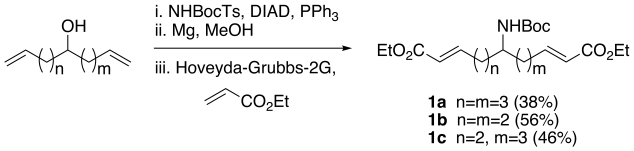
A diversity-oriented synthesis involving a cascade sequence, taking linear aminoalkenes to polycyclic scaffolds reminiscent of natural alkaloids, is presented.

Diversity-oriented synthesis (DOS) aims to efficiently prepare structurally diverse compounds, particularly involving variation of molecular scaffolds and stereochemistry.[1] An effective strategy for DOS is to fold linear starting materials into complex polycyclic frameworks,[2] and this has been elaborated elegantly in the preparation of natural products[3] and compounds for screening.[4] We envisaged combining the folding pathway approach (to give different polycyclic scaffolds) with reagent diversity (to vary the stereochemistry of products).[5] Inspiration came from naturally occurring bicyclic and tricyclic alkaloids.[6] For example, the tricyclic diastereoisomeric family of *Coccinellidae* defensive alkaloids (Fig. 1), which are secreted by ladybirds as a repellent for predators.[7] Three diastereoisomers have been isolated and synthesized,[8] namely precoccinelline, hippodamine[9] and myrrhine.[10] The *N*-oxides of precoccinelline and hippodamine are natural products; however, the *N*-oxide of myrrhine has not been isolated from nature to date. Herein, we report a diversity-oriented synthesis of bicyclic and tricyclic scaffolds reminiscent of natural alkaloids. The new methodology developed was applied to the total synthesis of previously unknown myrrhine *N*-oxide.

In order to discover novel biological functions of small molecules the diversity-oriented synthesis was designed to include populating new areas of chemical space. Nature illuminates the constitution and three dimensional shapes required for evolved biological activity. Therefore, we designed a diversity-oriented synthesis around bicyclic and tricyclic *alkaloid* scaffolds. Inspired by the elegant two-directional approach towards such scaffolds pioneered by Stockman *et al.*, our synthetic strategy was based around the folding of suitably designed linear substrates.[11] Towards this end linear aminoalkenes (**1**) were prepared *via* Mitsunobu substitution,[12] tosyl deprotection,[13] and cross-metathesis with ethyl acrylate[14] (Scheme 1).



Scheme 1 Synthesis of *N*-Boc-aminodialkenes (**1**).

We envisaged that the *N*-Boc group could be deprotected by various Lewis acids, which could also catalyze a double conjugate addition[15] and Dieckmann condensation cascade, thereby converting **1** into cyclic frameworks. Heating **1a** with aluminium chloride or scandium triflate led to the synthesis of bicyclic ***trans*-2a** (Scheme 2).[16] Whereas, heating **1a** with tin(II) triflate (0.5 equiv.) resulted in the synthesis of tricyclic **3a** (along with ***cis*-2a** [9%] and ***trans*-2a** [2%]).

Interestingly, use of higher amounts of tin(II) triflate led to the formation of ***trans*-2a**, with no trace of ***cis*-2a** or **3a**.[17] Since the stereochemistry of **3a** is expected from a Dieckmann condensation on ***cis*-2a**, this suggested that a different mechanism is in operation depending on the amount of $Sn(OTf)_2$ present. To test this, the following experiments and observations were made: (1) when ***trans*-2a** was treated with catalytic or excess $Sn(OTf)_2$[18] starting material was recovered; (2) treatment of the *cis*-2,6-disubstituted monocyclic intermediate with catalytic $Sn(OTf)_2$ led to a mixture of ***trans*-2a** and **3a**; (3) treatment of **3a** with catalytic $Sn(OTf)_2$ gave ***cis*-2a**. These data could indicate that when $Sn(OTf)_2$ is used in catalytic amounts the enolate formed after the first conjugate addition undergoes a Dieckmann condensation before the second conjugate addition. Therefore, ***cis*-2a** would originate from **3a** by a retro-Dieckmann reaction.[19]

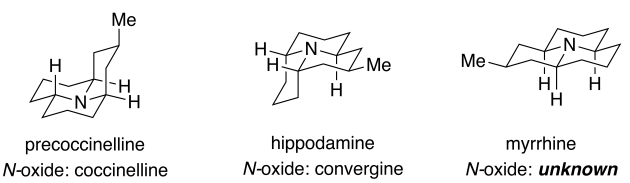
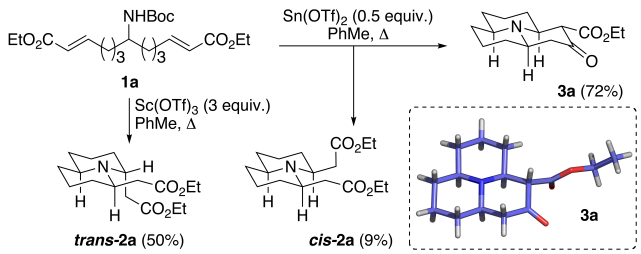


Fig. 1 Ladybird alkaloids.



Scheme 2 Preparation of 6–6-fused bicycles and 6–6–6-fused tricycles from **1a**. Inset: X-ray crystal structure of tricycle **3a**.[29]

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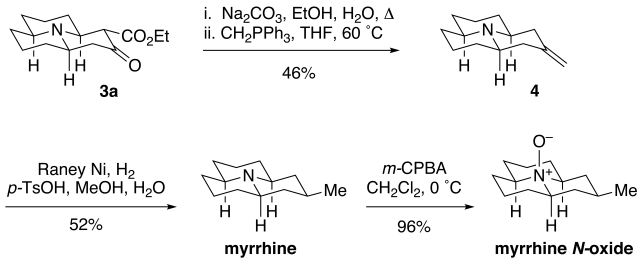
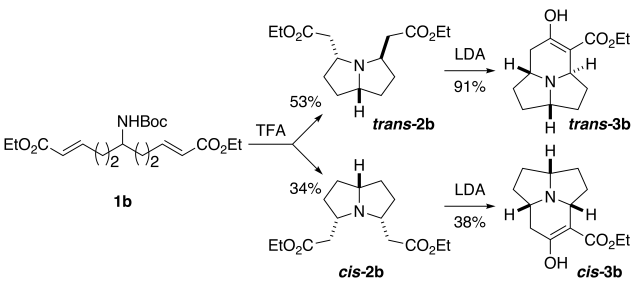


Scheme 3 Total synthesis of myrrhine *N*-oxide.

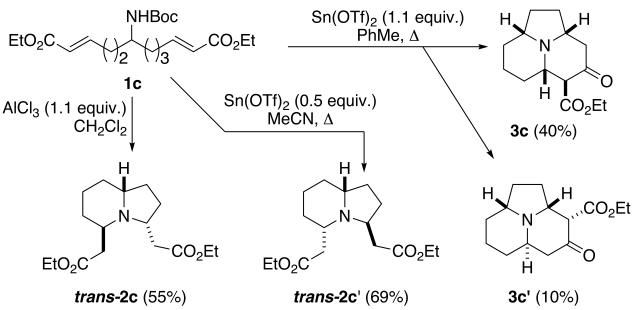
Tricycle **3a** was used as a precursor for the total synthesis of the unknown or unnatural alkaloids *epi*-myrrhine and myrrhine *N*-oxide for inclusion in the DOS. Ester hydrolysis, decarboxylation and Wittig olefination gave the exocyclic alkene **4** (Scheme 3). Diastereoselective reduction of the exocyclic double bond was achieved by protonating the nitrogen lone pair and thereby forcing the hydrogenation to occur on the desired face with the bridge-head hydrogen atoms. Using *p*-toluenesulfonic acid[20] and RANEY® nickel under hydrogen gas we obtained a 10 : 1 ratio of myrrhine: *epi*-myrrhine. As a reference, myrrhine was made in 8 steps with an overall yield of 7% (unoptimized), which compares favourably to former syntheses.[10] The total synthesis of myrrhine *N*-oxide was completed by treatment of myrrhine with *m*-CPBA (dried, titrated, 1 equiv.), which gave the *N*-oxide with complete stereoselectivity.[21]

The DOS included different sized fused tricycles as well as quinolizidine, indolizidine and pyrrolizidine rings, present in and reminiscent of several natural products. These bicyclic and tricyclic products were prepared by the same folding sequences starting from different length aminoalkenes **1b** ($n = m = 2$) (Scheme 4) and **1c** ($n = 2$, $m = 3$) (Scheme 5).

Modified conditions were required for the cascade reactions, depending on the length of the chain. The conversion of **1b** into pyrrolizidine bicycles occurred at room temperature with



Scheme 4 Synthesis of pyrrolizidine bicycles and 5–5–6 tricycles.



Scheme 5 Synthesis of indolizidine bicycles and 5–6–6 tricycles.

excess TFA to give mainly ***trans*-2b** with some ***cis*-2b** (Scheme 4).[22] ^{1}H-NMR and ^{13}C-NMR data for ***cis*-2b** are consistent with the expected values for *cis*-fused pyrrolizidines[23] (unshielded H-7 at 3.5–4.0 ppm, and shielded C-7 at 60–67 ppm) with NOESY interactions between H-7, H-4 and H-10 suggesting a *cis* disposition of all the CH protons in the ring system. Transformation of **1b** into 5–5–6 tricycles in one step was not possible despite exploration of a wide range of reaction conditions (temperature, solvent, equivalents of Lewis acid). Nevertheless, the tricyclic products could be obtained over two steps involving a base-catalyzed Dieckmann condensation on **2b** isomers.

Indolizidine scaffolds ***trans*-2c** and ***trans*-2c′** could be obtained selectively dependent on the amount and identity of the Lewis acid utilized (Scheme 5). Intense bands in the IR spectra (2850 cm^{-1}) and ^{1}H-NMR chemical shifts (H-7 at 2.4 ppm) suggested the *trans*-fused ring junctions.[24] Transformation of **1c** into 5–6–6 tricycles in one step could be achieved with stoichiometric $Sn(OTf)_2$ yielding an inseparable mixture of the isomers **3c** and **3c′** (along with ***cis*-2c** in 13% isolated yield). In contrast to the formation of 6–6–6 tricycles, use of catalytic Lewis acid gave only 4% of **3c** and **3c′**.

We have visually assessed the skeletal diversity of the DOS through the use of ''*Scaffold Hunter*'', a computer-based tool developed by Waldmann *et al.*,[25] which extracts the molecular scaffolds present in a compound collection and correlates the relationship between them in a hierarchical tree-like arrangement.[26] According to this analysis, out of the 14 final compounds synthesized, 7 distinct molecular scaffolds were prepared,[27] in a total of 23 synthetic steps, and contained natural and unnatural products. Although the number of compounds for a library is relatively small compared to typical combinatorial chemistry libraries, we believe that the '*steps per scaffold efficiency*' is highly attractive ($23 \div 7 = 3.3$ steps per scaffold), along with the complexity of the final products.

In summary, we have reported a DOS involving the first diastereoselective one-pot reaction cascade for the total folding of linear aminoalkenes to tricyclic systems, including naturally occurring all-*trans*-perhydro-9*b*-azaphenalene. The reaction sequence includes *N*-Boc deprotection, two conjugate additions and a Dieckmann condensation. The reaction was used for the diversity-oriented synthesis of unknown or unnatural alkaloids *epi*-myrrhine and myrrhine *N*-oxide, along with myrrhine that has been isolated from nature before. Moreover, the new methodology was exploited to make 5–6–6- and 5–5–6-fused tricycles, as well as quinolizidine, indolizidine and pyrrolizidine scaffolds, present in natural alkaloids.[28] In total 7 different scaffolds were generated (3.3 steps per scaffold) that populated new and biologically active areas of chemical space. The synthetic strategy outlined in this report should offer substantial scope for the introduction of additional diversity in the library; for example, variation in ring sizes and substituents could be achieved through alterations in the structure of the linear aminoalkenes and it may prove possible to generate heteroatom-containing scaffolds. Furthermore, we anticipate that this new methodology will prove valuable in a wider synthetic context, with potentially broad applications in the synthesis of a variety of natural product-like alkaloid frameworks.

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20 In the absence of *p*-TsOH, the yield of myrrhine decreased and the reaction became less clean.

21 The total synthesis of myrrhine *N*-oxide has been reported before by Ayer *et al.* (ref. 10) in 8 steps, 2.8% overall yield.

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27 See ESI†. It should be noted that acyclic scaffolds are not 'counted' by *Scaffold Hunter*.

28 The biological activities of the compounds are being characterized and will be reported in due course.

29 Crystal data for **3a**: $M = 265.34$, triclinic, $a = 8.6717(2)$ Å, $b = 8.8865(2)$ Å, $c = 9.6551(2)$ Å, $\alpha = 86.555(1)^\circ$, $\beta = 72.478(1)^\circ$, $\gamma = 80.643(1)^\circ$, $V = 700.02(3)$ Å^3, $T = 180(2)$ K, space group $P\bar{1}$, $Z = 2$, 12 361 reflections measured, 4060 independent reflections ($R_{int} = 0.0271$). The final R_1 values were 0.0412 ($I > 2\sigma(I)$). The final w$R(F^2)$ values were 0.1107 ($I > 2\sigma(I)$). The final R_1 values were 0.0514 (all data). The final w$R(F^2)$ values were 0.1185 (all data). CCDC number 746888.

