

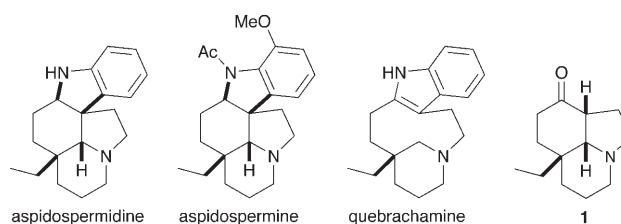
Highly Efficient Synthesis of Tricyclic Amines by a Cyclization/Cycloaddition Cascade: Total Syntheses of Aspidospermine, Aspidospermidine, and Quebrachamine**

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Reactions that occur in a single pot to form more than two chemical bonds or new ring systems provide the means to prepare complex compounds in a highly efficient manner. Multicomponent reactions or multiple-bond formations through cascade processes can be exploited for such chemistry.^[1] For example, a powerful method to access bicyclic compounds involves the formation of a 1,3-dipole followed by intramolecular cycloaddition.^[2] Such processes are generally atom economic and occur with very high levels of regio- and stereocontrol, in addition to saving time and effort in comparison with sequential formation of each ring. Even more efficient, however, are processes that allow the formation of three rings in a single pot. There are few examples of this type of method, yet this approach has the potential to provide a rapid access to tricyclic compounds with significant structural and stereochemical complexity.^[3,4] This strategy has recently received considerable attention for the synthesis of various oxygen-containing products using cyclic carbonyl ylides (often generated by reaction of a carbenoid with a carbonyl group).^[4] Herein, we describe an important development of this method that leads to tricyclic amines in one pot from acyclic precursors. Nitrogen-containing compounds are prevalent in natural products and biologically active compounds. Therefore this procedure has significant potential, illustrated here by the shortest total synthesis to date of the alkaloid (±)-aspidospermine, together with efficient syntheses of the related alkaloids (±)-aspidospermidine and (±)-quebrachamine.

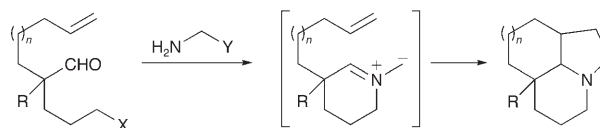
Many *Aspidosperma* alkaloids are known and have attracted considerable attention, not least because of their complex structures and interesting biological activities.^[5] Aspidospermidine is one of the simplest of these alkaloids

and contains a pentacyclic ring system (Scheme 1). The alkaloids aspidospermine and quebrachamine were first synthesized by Stork and Dolfini over 40 years ago.^[6] In their classic synthesis, the ketone **1** was prepared as a key intermediate in approximately 13 steps. Since then many other syntheses or formal syntheses have been reported.^[7]



Scheme 1. *Aspidosperma* alkaloid targets.

Our strategy to tricyclic amine products was based on the reasoning that if an azomethine ylide can be formed from an aldehyde and a secondary amine, then it should be possible to form the ylide from an aldehyde and a primary amine, together with in situ N alkylation. Indeed, such a process has been reported by Pearson et al. using (2-azaallyl)stannanes and silanes, and used in intermolecular cycloadditions to give two new rings.^[8] By preparing the substrate in which the dipolarophile is tethered to the ylide dipole, intramolecular cycloaddition should ensue to give tricyclic products.^[9] This is illustrated by the general reaction depicted in Scheme 2. To



Scheme 2. Planned synthesis of tricyclic amines. X = leaving group; Y = SiMe₃, SnBu₃, or CO₂H.

test this procedure, we required a method to access aldehyde substrates that bear a dipolarophile (for example, an alkene) and a leaving group (X) to allow ylide formation (for example, after loss of Y by desilylation, destannylation, or decarboxylation).

The aldehyde substrates were prepared readily by alkylation of butanenitrile. This preparation allows the formation of quaternary centers in high yield.^[10] Thus, deprotonation of butanenitrile with LDA and alkylation with 4-bromo-1-

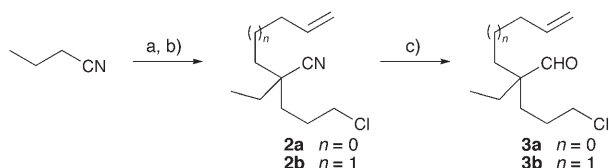
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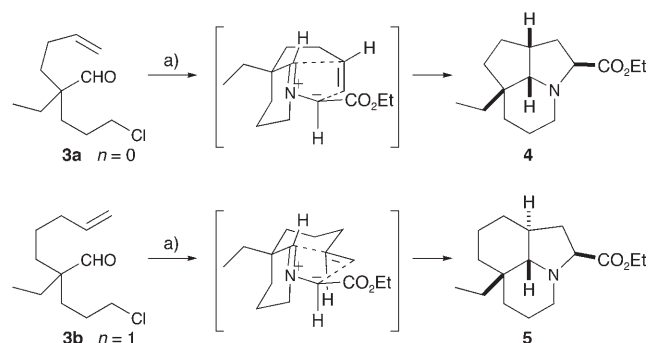
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butene, followed by a second deprotonation then alkylation with 1-bromo-3-chloropropane gave the nitrile **2a** ($n=0$, Scheme 3). Simple reduction of the nitrile using DIBAL-H then gave the aldehyde **3a**. Likewise the product **3b** ($n=1$) was prepared in only three steps via the nitrile **2b**.



Scheme 3. Preparation of the aldehyde substrates. a) LDA (0.5 equiv), THF, -78°C , 1 h; then ($n=0$) 4-bromo-1-butene (0.25 equiv), 80% or ($n=1$) 5-bromo-1-pentene, 99%; b) LDA (2 equiv), THF, -78°C , 1 h; then 1-bromo-3-chloropropane, $n=0$, 95% or $n=1$, 96%; c) DIBAL-H (1.2 equiv), CH_2Cl_2 , -78°C ; then aq HCl, $n=0$, 87% or $n=1$, 89%. DIBAL-H = diisobutylaluminum hydride, LDA = lithium diisopropylamide.

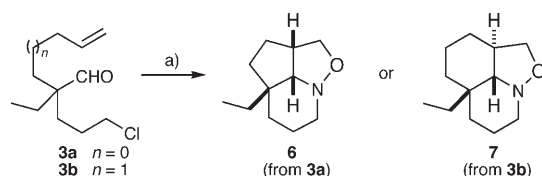
Treatment of the aldehydes **3a** and **3b** with glycine ethyl ester gave the products **4** or **5**, respectively, each as a single stereoisomer (Scheme 4). Yields were very good (72–74%)



Scheme 4. Cyclization/cycloaddition of **3a** and **3b** with glycine ethyl ester that includes possible transition-state conformation. a) $\text{Cl}\cdot\text{H}_3\text{NCH}_2\text{CO}_2\text{Et}$, toluene, $i\text{Pr}_2\text{NEt}$, heat, 2 h; **4** 72% or **5** 74%.

for a process that involved the formation of four new σ bonds, three new rings, and three new stereocenters with complete selectivity. The stereochemistry was confirmed by reduction of the ester, conversion into the *para*-bromobenzoate, and X-ray analysis of the HCl salt (see the Supporting Information). The configuration of the products indicates that cycloadditions occur through the azomethine ylides with S-shaped geometry, and this conforms to other examples of cycloadditions that use ester-stabilized ylides.^[2b] The difference in the stereochemistry at the ring junction must be a reflection of the greater conformational freedom in the longer tethered substrate ($n=1$) which allows preferential formation of the *trans* product **5**, whereas the shorter chain length necessarily leads to the all *cis* product **4**.

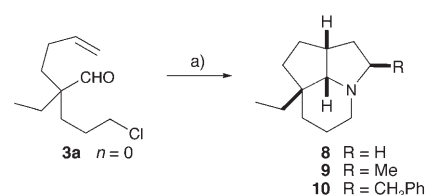
Addition of hydroxylamine to the aldehydes **3a** and **3b** gave the tricyclic products **6** or **7** (Scheme 5). The relative stereochemistry was confirmed by the reduction of the N–O bond (Zn, AcOH), followed by diacylation (*para*-bromoben-



Scheme 5. Cyclization/cycloaddition of **3a** and **3b** with hydroxylamine. a) $\text{Cl}\cdot\text{H}_3\text{NOH}$, toluene, $i\text{Pr}_2\text{NEt}$, heat, 18 h; **6** 67% or **7** 64%.

zoyl chloride) and X-ray analysis. In line with the results using glycine ethyl ester described above, the reactions led to different stereoisomers of the products for $n=0$ and $n=1$.

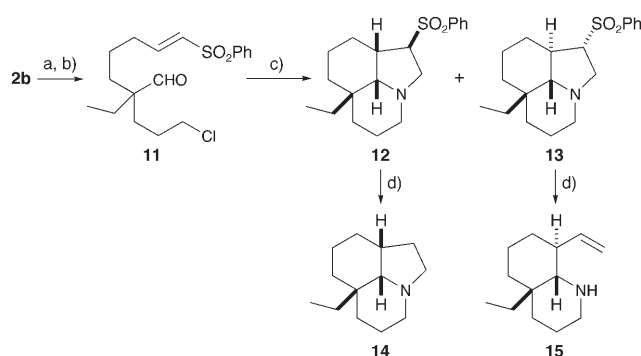
Of particular relevance is the cycloaddition of aldehydes **3a** and **3b** using glycine as the primary amine. With aldehyde **3b** ($n=1$) and glycine, an inseparable mixture of products was obtained (NMR spectroscopy showed the presence of the alkene in the mixture). The aldehyde **3a** ($n=0$) did however



Scheme 6. Cyclization/cycloaddition of **3a** with amino acids. a) $\text{H}_2\text{NCH(R)CO}_2\text{H}$, toluene, heat, 18–36 h; **8** 82%, **9** 78%, **10** 60%.

give the product **8** (Scheme 6). Using alanine and phenylalanine, the cycloadducts **9** and **10** were obtained. A single stereoisomer of the tricyclic amines **8–10** was formed in each case and these were assigned the all *cis* configuration based on NMR spectroscopy.

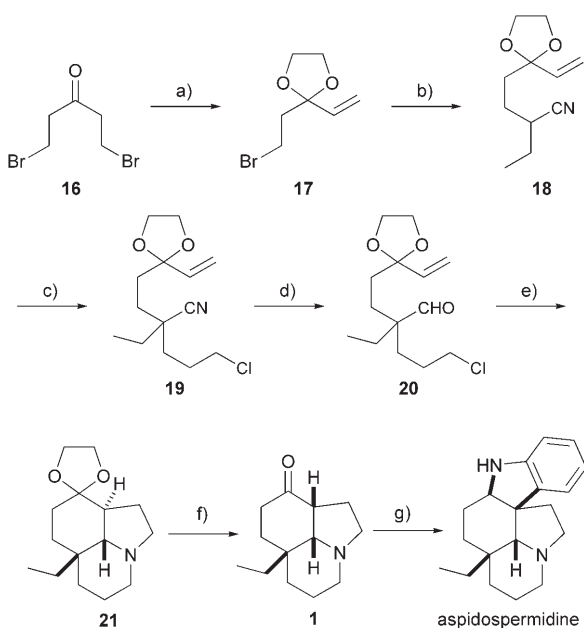
A comparison of the reactions of **3b** with glycine ethyl ester (to give **5**) and with glycine (no cycloaddition) suggests that the electronics of the cycloaddition are important. To test this, a further substrate **11** was prepared by cross-metathesis and reduction (Scheme 7). A cyclization/cycloaddition cascade was now successful using glycine and gave a mixture of



Scheme 7. Cyclization/cycloaddition of **11** with glycine. a) phenyl vinyl sulfone, Grubbs II cat. (5 mol%), CH_2Cl_2 , heat, 24 h, 88%; b) DIBAL-H, CH_2Cl_2 , -78°C ; then aq HCl, 86%; c) $\text{H}_2\text{NCH}_2\text{CO}_2\text{H}$, toluene, heat, 24 h; **12** 36% and **13** 38%; d) Na/Hg, Na_2HPO_4 , MeOH, 0°C ; **14** 57% or **15** 73%.

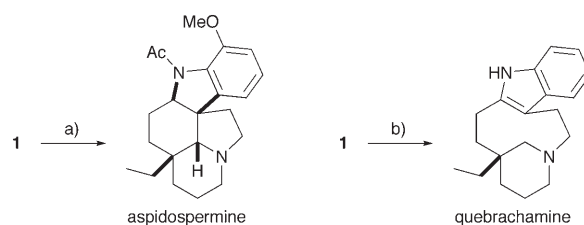
the tricyclic products **12** and **13**. The structures and relative stereochemistry of products **12** and **13** were verified by X-ray analysis. Removal of the sulfone group was achieved using sodium/mercury amalgam; from amine **12**, the tricyclic product **14** was obtained, although desulfonation of **13** gave the bicyclic product **15**, formed by β elimination.

To access the ketone **1**, we needed to use a functionalized version of substrate **3b** or **11**. We reasoned that using an enone or masked enone in place of the alkene dipolarophile could provide the necessary functionality and activation. The bromide **17**, which contains a protected enone, was prepared from the known dibromoketone **16**, itself readily prepared from ethyl 3-bromopropionate (Scheme 8).^[11]



Scheme 8. Synthesis of (±)-aspidospermidine. a) HOCH₂CH₂OH, benzene, TsOH, heat, 18 h; then *t*BuOK, THF/toluene (1:1), 0 °C, 2 h, 82%; b) EtCH₂CN, LDA, THF, −78 °C; then **17**, 88%; c) LDA, THF, −78 °C, 1 h; then 1-bromo-3-chloropropane, 96%; d) DIBAL-H (1.2 equiv), CH₂Cl₂, −78 °C; then oxalic acid (0.5 M), 82%; e) H₂NCH₂CO₂H, toluene, camphor sulfonic acid (10 mol%), heat, 18 h, 79%; f) 5% aq HCl/THF (1:1), 80 °C, 1 h, 89%; g) 1. PhNHNH₂, benzene, heat, 2.5 h; 2. AcOH, 95 °C, 2.5 h; 3. LiAlH₄, THF, heat, 13 h, 42% over 3 steps (the product from Fischer indole synthesis of the regioisomeric enamine was isolated in 8% yield). Ts = toluene-*p*-sulfonyl.

By using the same method as before, the anion of butanenitrile was treated with the bromide **17** to give the nitrile **18**. A second alkylation with 1-bromo-3-chloropropane gave the nitrile **19** and reduction gave the desired substrate **20**. Successful cyclization/cycloaddition was achieved with this substrate using glycine in the presence of 10 mol% camphor sulfonic acid to give the amine **21**. The relative stereochemistry was confirmed by X-ray analysis and showed the *cis/trans* arrangement. On heating with aqueous acid, the acetal was hydrolyzed with concomitant isomerization of the adjacent stereocenter to provide the *cis/cis* ketone **1**. The



Scheme 9. Synthesis of (±)-aspidospermine and (±)-quebrachamine.

a) 1. 2-MeOC₆H₄NHNH₂, EtOH, RT, 3 h; 2. AcOH, 95 °C, 1 h; 3. LiAlH₄, THF, 50 °C; 4. Ac₂O, pyridine, 22% over 4 steps; b) 1. PhNHNH₂, benzene, heat, 2.5 h; 2. AcOH, 95 °C, 3 h; 3. KBH₄, KOH, MeOH, 39% over 3 steps.

spectroscopic data of this product corresponded with those reported^[7f,j] and it was converted into (±)-aspidospermidine (Scheme 8) in three steps as previously reported.^[7f,j,k] Similarly, (±)-aspidospermine and (±)-quebrachamine were prepared from the ketone **1** (Scheme 9).^[6]

The method described here provides a rapid access to complex tricyclic amines from acyclic precursors with regio- and stereocontrol. Tertiary amines are formed from simple, readily available primary amines. As far as we are aware, the methodology provides the shortest known synthesis of aspidospermine and consists of only six steps (40% yield) from dibromide **16** to the ketone **1**. This efficient methodology is likely to find application in the synthesis of various nitrogen-containing heterocyclic compounds.

Experimental Section

Procedure for the cyclization/cycloaddition cascade with aldehyde **20:** The aldehyde **20** (0.27 g, 0.98 mmol), camphor sulfonic acid (25 mg, 0.1 mmol), and glycine (0.22 g, 2.9 mmol) were heated under reflux in toluene (7.5 mL). After 18 h, the mixture was cooled to room temperature and evaporated. Purification by column chromatography on silica, eluting with CH₂Cl₂/MeOH/NH₃ (95:5:0.1), gave the amine **21** (194 mg, 79%) which was recrystallized from light petroleum as plates; m.p. 94–96 °C; *R*_f 0.27 (CH₂Cl₂/MeOH/NH₃ (95:5:0.1)); ν_{max} = 2920, 2870 cm^{−1}; ¹H NMR (500 MHz, CDCl₃) δ = 3.96–3.84 (m, 4H, 2 × CH₂), 2.94 (ddd, *J* 12.5, 11.0, 5.5, 1H, CH), 2.61–2.56 (m, 1H, CH), 2.53 (ddd, *J* 12.5, 9.0, 5.0, 1H, CH), 2.45–2.37 (m, 1H, CH), 2.33 (d, *J* 12.5, 1H, CH), 2.28–2.22 (m, 1H, CH), 1.98–1.90 (m, 1H, CH), 1.86–1.78 (m, 1H, CH), 1.80–1.79 (m, 1H, CH), 1.87–1.26 (m, 8H, 8 × CH), 1.22–1.13 (m, 1H, CH), 0.78 ppm (t, *J* 7.5, 3H, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ = 111.0, 68.9, 65.5, 64.2, 52.7, 48.7, 40.1, 34.9, 32.8, 31.9, 31.1, 23.2, 21.7, 21.7, 7.4 ppm; HRMS (ES) found: [*M* + *H*]⁺ (ES), 252.1970. C₁₅H₂₆NO₂ requires [*M* + *H*]⁺, 252.1964; LRMS *m/z* (ES) 252 (100%, [*M* + *H*]⁺); C₁₅H₂₅NO₂ (251.19): calcd. C 71.67, H 10.02, N 5.57; found C 71.74, H 10.34, N 5.74.

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