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Toward the Synthesis of Sparteine: Intramolecular Schmidt Reactions on a Norbornanone Platform

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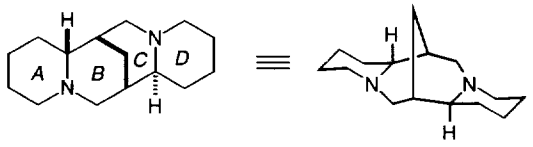
Abstract: The intramolecular Schmidt reaction was applied to the norbornane skeleton to examine an approach to sparteine. In so doing, the stereospecificity of intramolecular Schmidt reactions of ε-azido ketones was demonstrated. The intramolecular Schmidt reaction was found to fail in a ketone containing a lactam moiety.

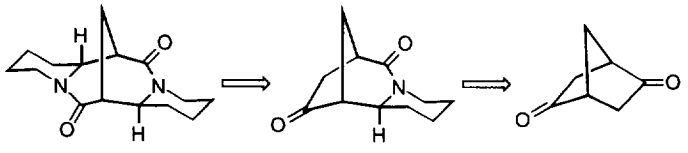
The lupidine alkaloid (–)-sparteine (**1**) has received significant recent attention due to its use as a chiral additive for asymmetric alkylations.[1] Although sparteine is found in nature in both antipodes, it is most commonly found and commercially available only as its (–)-enantiomer. Although four total syntheses of sparteine have been published to date,[2] we are unaware of any asymmetric attempts. The ongoing importance of sparteine as a chiral synthetic reagent has prompted us to attempt a total synthesis of sparteine that could deliver either antipode in enantiomerically pure form. Our plan utilizes the newly developed intramolecular Schmidt reaction of alkyl azides with ketones (Scheme 1).[3]



(–)-sparteine (**1**)

In this scenario, sparteine would arise from reduction of bislactam **2**, retrosynthetically available from chiral C_2-symmetric dione **4** and lactam **3** via sequential side-chain attachment/intramolecular Schmidt reaction iterations.

Scheme 1



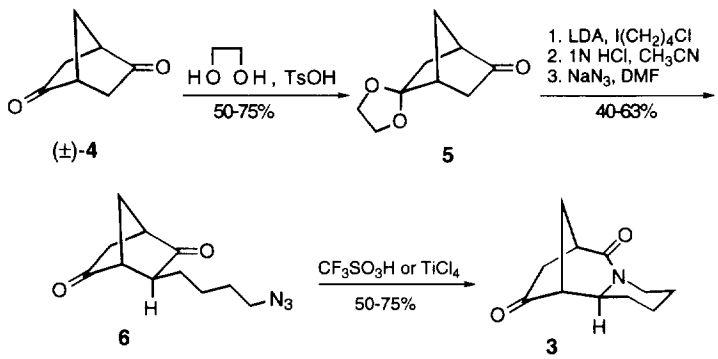
2 **3** **4**

This plan entails some rigorous tests of the Schmidt methodology. Although the bicyclic norbornane core was expected to provide a diastereofacial bias useful in stereoselectively installing the side chains, skeletal rearrangements during the acid-promoted Schmidt reactions were possible. In addition, forming the A and D rings

of sparteine by this strategy requires a seven-membered cyclization of an ε-azido ketone, one carbon greater than the preferred tether length. Although such cyclizations have been reported, the stereochemical integrity of the migrating carbon might be compromised by starting material equilibration under the strongly acidic conditions required.[4] Herein, we address these issues and additionally disclose an important limitation of the intramolecular Schmidt methodology.

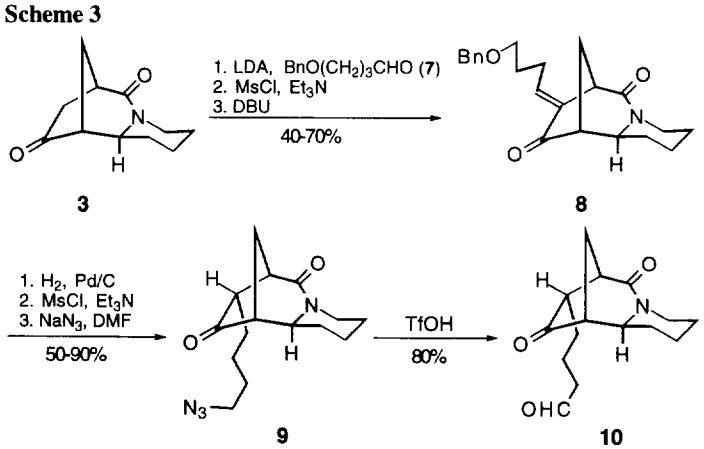
Initial attempts to alkylate (±)-**4**[5] with LDA and 1-chloro-4-iodobutane in THF resulted in destruction of the diketone (Scheme 2). We circumvented this problem by protecting **4** as its monoketal **5**. Alkylation then proceeded smoothly from the *exo* face and the resulting compound was deketalized to afford *exo*-1-(4'-chlorobutyl)bicyclo[2.2.1]hepta-2,5-dione. Displacement of the chloride with NaN_3 in DMF afforded the desired azide **6**. Treatment of **6** with either $TiCl_4$ or TfOH in CH_2Cl_2 triggered the intramolecular Schmidt reaction, resulting in N_2 evolution and production of keto lactam **3** as a single fused product.

Scheme 2



Once having demonstrated the first example of a stereoselective five carbon spacer intramolecular Schmidt reaction, our interest was next focused on the installation of an endocyclic azido tether (Scheme 3). Our choice to introduce the endocyclic tether on **3** was via an *exo*-selective hydrogenation of the α,β-unsaturated ketone **8**. A mixed aldol reaction was accomplished by the treatment of **3** with LDA, and addition of aldehyde **7**,[6] which afforded the initial aldol adduct as a mixture of diastereomers.[7] Mesylation of the alcohol and elimination with DBU produced the desired exocyclic alkene **8** as a single double bond isomer.

Scheme 3

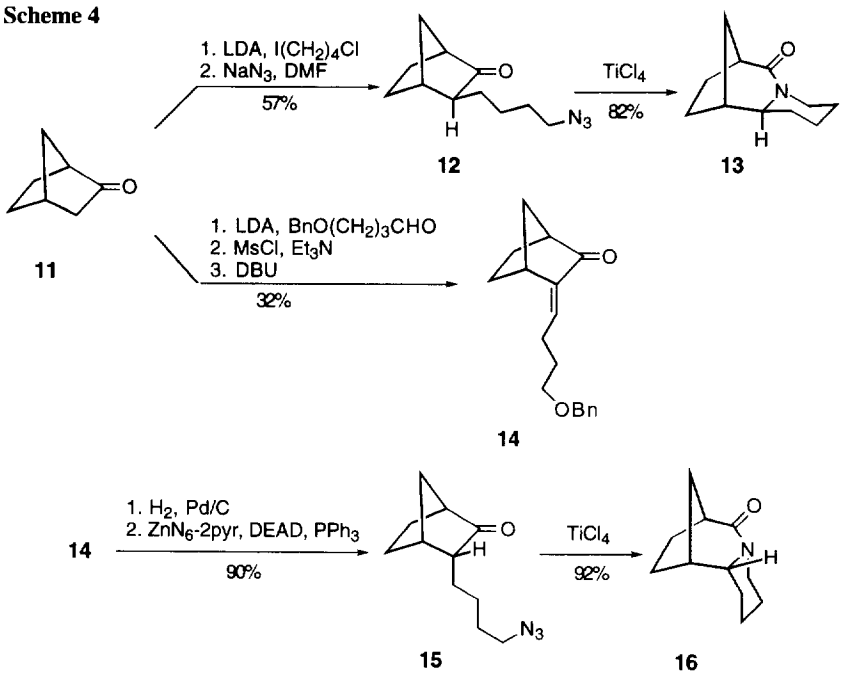


Hydrogenation at 50 psi for 24 h simultaneously placed the alkyl substituent in the *endo* position and removed the benzyl protecting group from the primary alcohol. Mesylation and displacement with NaN_3 afforded the Schmidt reaction substrate **9**. However, treatment of azide **9** with TfOH in CH_2Cl_2 gave only aldehyde **10** in 80% yield, and no sign of the desired product (**2**, Scheme 1). The decomposition of azides to yield aldehydes has been previously reported.[8,3b] Repeating the reaction with $TiCl_4$ was similarly unsuccessful.

It appears that the ketone carbonyl in **9** is reluctant to undergo Lewis acid activation in the presence of the more basic lactam moiety. Ketone **9** is similarly unresponsive to other acid-catalyzed processes, such as ketal or imine formation. However, several model systems were examined to rule out the possibility that the desired conversion of **9** to **3** was thwarted by the requirement for addition of an *endo*-disposed azide to the carbonyl group.

The route to construct the *exo* keto azide tether mirrored that of compound **6** (Scheme 4). Norcamphor (**11**) was alkylated with 1-chloro-4-iodobutane in THF to form 2-(4'-chlorobutyl)-bicyclo[2.2.1]hepta-1-one as exclusively the *exo* product. Conversion of the chloride to the azide was accomplished by displacement with NaN_3; treatment of **12** with $TiCl_4$ in CH_2Cl_2 at room temperature resulted in N_2 evolution and formation of exclusively the *exo* ring juncture lactam **13** in 82% yield.

Scheme 4



The synthesis of the *endo* keto azide was also easily achievable from norcamphor using aldol chemistry. In this case, hydrogenation of **14** was followed by a Mitsunobu reaction with ZnN_6·2pyr complex[9] to afford the *endo* azide **15** in 90% yield. Upon treatment with $TiCl_4$ in CH_2Cl_2 at room temperature, **15** was converted into lactam **16** in 92% yield.

We have therefore demonstrated that both endocyclic and exocyclic intramolecular Schmidt reactions on norbornane derived ketones proceed with complete stereoselectivity with stronger acids ($TiCl_4$ or TfOH) and with a longer tether length. However, we have also shown that the intramolecular Schmidt reactions on ketones

containing other basic sites may not succeed. The utilization of this route toward sparteine continues in this lab. In addition, compounds similar to **3** represent interesting precursors to novel, totally synthetic sparteine derivatives that could prove useful in asymmetric complexation and deprotonation chemistry.

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4. Intramolecular Schmidt reactions containing a four-carbon tether were previously found to be occur with retention of configuration at the migrating carbon.[3b] However, prior to the present work, it was not at all clear whether the more vigorous conditions necessary to effect cyclization of a keto azide containing a five-carbon tether would cause epimerization prior to Schmidt rearrangement.

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