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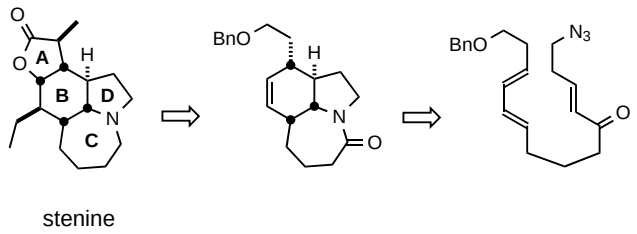
A Combined Intramolecular Diels–Alder/ Intramolecular Schmidt Reaction: Formal Synthesis of (±)-Stenine**

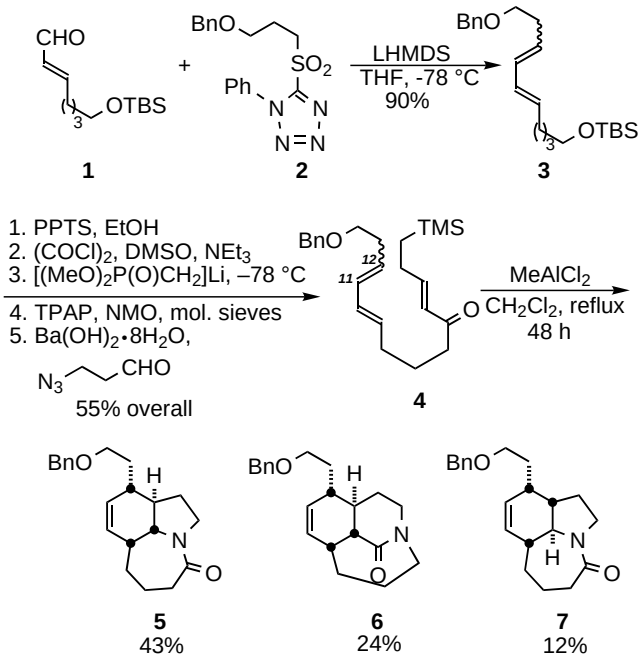
Jennifer E. Golden and Jeffrey Aubé*

One hallmark of an attractive synthetic strategy is the efficient assembly of advanced intermediates. One way of achieving this goal has been the development of cascade reactions.[1] An objective of this laboratory has been to advance the utility of the intramolecular Schmidt reaction of azides and ketones in total synthesis.[2] Herein, we describe the combination of an intramolecular Schmidt reaction with an intramolecular Diels–Alder process—two efficient reactions that benefit from Lewis-acid promotion. The specific context of this work is the formal total synthesis of stenine, shown retrosynthetically in Scheme 1.

Stenine and related alkaloids[3–11] have drawn considerable attention from synthetic chemists, partly because of the historical use of root extracts of stemonaceous plants in Japanese and Chinese folk medicine.[6] Efforts in this area have already culminated in four total syntheses of stenine by teams led by Hart,[7] Wipf,[8] Morimoto,[9] and, most recently, Padwa.[10] The first three of these syntheses feature the stepwise construction of the ABD ring substructure followed by final formation of the C ring. Additionally, routes developed by Hart and Morimoto utilize a Diels–Alder reaction as the key step, and both subsequently implement a Curtius rearrangement to install a nitrogen atom adjacent to the carbonyl group. While the present work was in progress, Jung and co-workers[11] published a partial synthesis, in which a Diels–Alder reaction similar to that shown in Scheme 1 was used, followed by a four-step Beckmann rearrangement/N-alkylation sequence to form the BCD ring skeleton. We now report an approach in which all three rings of a key intermediate and four of the stereocenters were formed in a single chemical step beginning with the acyclic precursor **4** (Scheme 2).



Scheme 1. Retrosynthesis of (±)-stenine.



Scheme 2. Construction of the ABD-ring framework of stenine. TBS = *tert*-butyldimethylsilyl, LHMDS = lithium bis(trimethylsilyl)amide, PPTS = pyridinium 4-toluenesulfonate, TPAP = tetrapropylammonium perruthenate, NMO = 4-methylmorpholine *N*-oxide.

The cascade reaction substrate **4** was prepared by using standard methodology (Scheme 2). Diene **3** was generated in 90% yield from a modified Julia coupling[12] between aldehyde **1** and sulfone **2** to afford an inseparable 85:15-mixture of isomers at the new double bond.[13] Removal of the silyl group of **3**, followed by Swern oxidation, gave an aldehyde that was treated with the lithium anion of dimethyl methylphosphonate. This provided a β-hydroxyphosphonate that was subsequently oxidized with TPAP/NMO. The resulting β-oxophosphonate was subjected to a Horner–Wadsworth–Emmons reaction[14] with 3-azidopropanal[15] to afford triene **4** in 55% yield from **3**.

Treatment of **4** with $MeAlCl_2$ in refluxing dichloromethane afforded tricyclic lactams **5**, **6**, and **7** in 79% overall yield and

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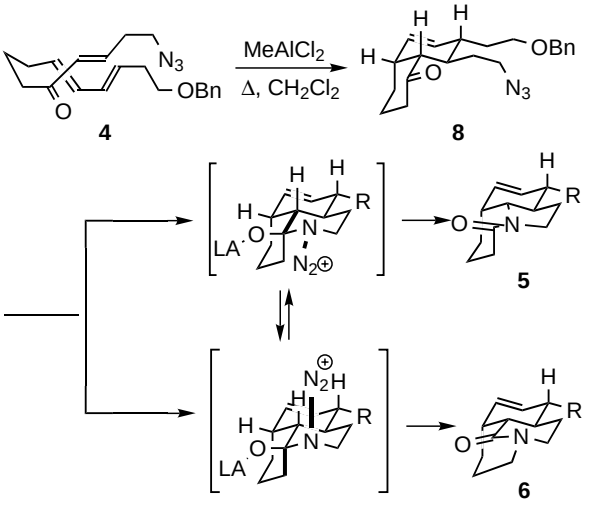
a ratio of 3.6:2:1, respectively. As expected (see below), the major diastereomer, **5**, has the stereochemistry required for the stenine synthesis. The structures of lactams **5** and **7** were confirmed by X-ray crystallographic analysis of the corresponding debenzylated derivatives. We assign the unusual bridged lactam structure to compound **6** based on ^{13}C NMR chemical shifts (the signal of the carbonyl group of **6** appears at $\delta = 188$ ppm vs. $\delta = 171$–175 ppm for compounds **5** and **7**) and a $\tilde{\nu}_{C=O}$ value of 1690 cm^{-1} (cf. $\tilde{\nu} = 1625$–1600 cm^{-1} for **5** and **7**). These data are consistent with considerable loss of conjugation between the nitrogen lone pair and the carbonyl group in the twisted amide linkage and are in agreement with data of similar bridged lactams.[16] Additionally, this structure is consistent with the 2D NMR spectrum of **6**.

Both **5** and **6** are proposed to result from a single Diels–Alder adduct **8** via an *endo* transition state (Scheme 3).[17] The azide can then add to the Lewis acid coordinated ketone.

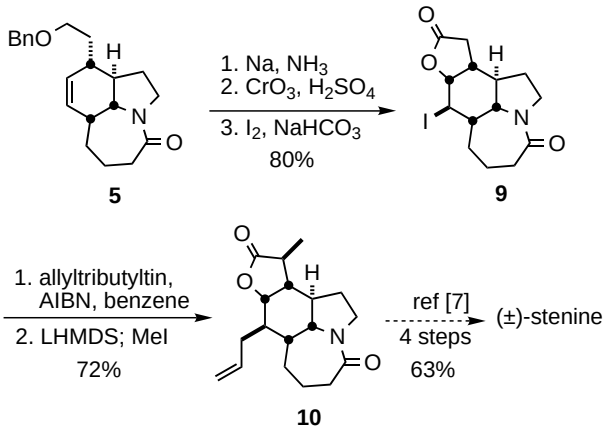


Scheme 3. Domino reaction of **4** consisting of a Diels–Alder reaction and an intramolecular Schmidt reaction to give **6**. LA = Lewis acid.

Assuming *anti*-periplanar C→N bond migration,[18] an intermediate containing an equatorial N_2^+ group en route to lactam would afford lactam **5**, whereas an axially oriented leaving group would give the bridged compound **6**. Formation of bridged lactams has not been observed previously in an intramolecular Schmidt reaction, although an analogous case was recently observed in a ketal-mediated reaction.[2d] Lactam **7** results from an *exo* transition state in the Diels–Alder cyclization, followed by the D-ring-forming/C-ring-expansion process.

We could affect modest changes in product distribution by modifying the Lewis acid and the reaction conditions, but the overall yield of 43% for **5** is reproducible and the most favorable result to date. In the context of the inseparable 85:15 mixture of 11,12-double bond stereoisomers of **4**, this yield corresponds to an overall conversion of the reactive *trans-trans* triene isomer to **5** of 51%.

The formal synthesis was finished as shown in Scheme 4. Removal of the benzyl ether from **5**, oxidation of the resulting hydroxy group, and iodolactonization gave butyrolactone **9** in



Scheme 4. Elaboration of **5** to give compound **10**, an intermediate in the synthesis of (±)-stenine by Hart and Chen.[7] AIBN = 2,2′-azobisisobutyronitrile.

80% yield from **5**. Keck allylation[19] followed by methylation[20] of the lactone proceeded stereoselectively to provide Hart intermediate **10** in 72% yield over two steps. All spectroscopic and physical data of compound **10** were in agreement with the published data.[7]

In summary, we have completed a formal synthesis of (±)-stenine by using a domino Diels–Alder/Schmidt reaction strategy. Our route affords advanced intermediate **10** in 12 steps and in 12% overall yield from **1**. We are currently streamlining this overall approach and applying it to the synthesis of other *stemona* alkaloids.[21]

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Octametallic and Hexadecametallic Ferric Wheels**

Leigh F. Jones, Andrei Batsanov, Euan K. Brechin,* David Collison,* Madeleine Helliwell, Talal Mallah, Eric J. L. McInnes, and Stergios Piligkos

The synthesis of paramagnetic molecular clusters has become an area of intense research since the discovery that such molecules can act as nanoscale magnets below a critical temperature.[1,2] Such single-molecule magnets (SMMs) are promising new materials for data storage and quantum computing, which exhibit not only magnetization hysteresis but also display quantum tunneling of magnetization and quantum phase interference.[3,4] In order to function as a SMM a molecule must possess the combination of a large spin and large, easy-axis-type anisotropy. The first SMM was $[Mn_{12}O_{12}(O_2CMe)_{16}(H_2O)_4]$ ("Mn12"), and since its preparation a number of molecules have been reported as new members of this family.[5–9] An intriguing class of cluster in this respect is the "molecular wheel". Most even-membered wheels are antiferromagnetic and characterized by $S=0$ ground states, however, this is not the case for the reported "Ni12" and "Cr10" wheels.[10,11] Indeed "Ni12" was recently reported as the first example of a Ni SMM.[10] Although compounds with $S=0$ ground states cannot function as SMMs, they represent ideal model systems for the study of 1D magnetic materials, quantum effects, and magnetic anisotropy. To this end, molecular wheels and metallocycles with 6, 8, 10, 12, 18, and 24 metal ions have been reported.[12] We have chosen to investigate the use of the pro-ligand 1,1,1-tris(hydroxymethyl)ethane (H_3thme) in the synthesis of novel transition metal clusters, and herein report the synthesis and initial magnetic properties of two new Fe^{III} clusters, the first unsupported octametallic and hexadecametallic ferric wheels (unsupported in the sense that there are no central metal ions present). The H_3thme ligand has been successfully used in vanadium chemistry[13] but has been sparingly employed for other transition metal complexes.[14]

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