Total Synthesis

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Concise Syntheses of Strychnine and Englerin A: the Power of Reductive Cyclizations Triggered by Samarium Iodide**

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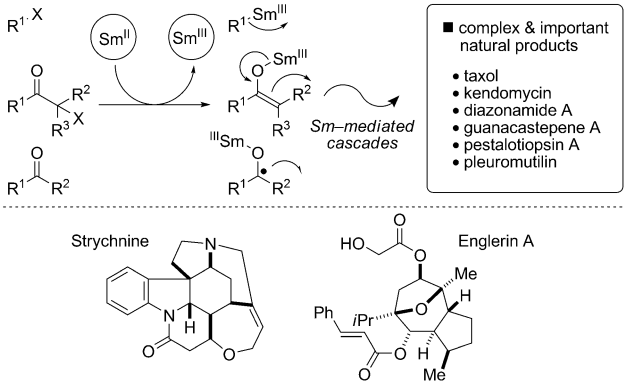
Dedicated to Professor Henri Kagan

englerin A · natural products · samarium iodide · strychnine · total synthesis

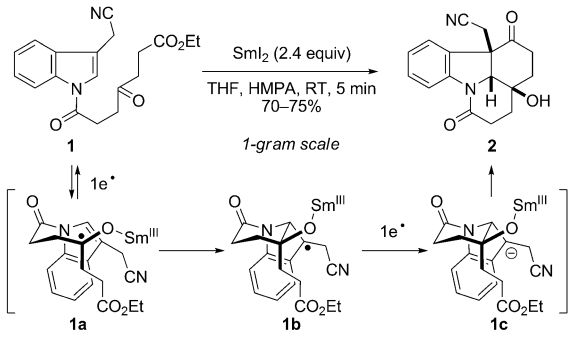
Since its introduction to the synthetic chemistry community in 1977 by Kagan,[1] samarium diiodide (SmI_2) has become one of the most important reductants in synthesis.[2] One of the fascinating features of SmI_2 is its ability to orchestrate powerful cascade processes, often with exquisite control of structure and stereochemistry (Scheme 1). In particular, SmI_2



Scheme 1. SmI_2 in target synthesis: strychnine and englerin A.

has been exploited in numerous total-synthesis endeavors, including such "heavy-weight molecules" as taxol, diazonamide A, kendomycin, and guanacastepene A.[3,4] In all cases, the use of SmI_2 enabled strategic bond constructions for the rapid generation of the challenging target frameworks. The recent syntheses of strychnine[5] and englerin A[6] using SmI_2-mediated cyclizations provide a vivid illustration of the power of the reagent for the total synthesis of complex and important targets.

Strychnine, a high-profile *Strychnos* alkaloid, occupies a prominent place as arguably one of the most famous molecules of all time. Since Woodward's achievement in 1954,[7] strychnine remains a benchmark for the evaluation of synthetic strategies.[8] The Reissig synthesis of strychnine[5] exploits a SmI_2-induced cascade reaction to forge two rings and three stereogenic centers, turning a simple, readily available precursor into a highly complex molecule, in a beautiful example of the power of the reagent en route to the classic alkaloid. Acylation of commercial indolylacetonitrile formed indole derivative **1** and subsequent exposure to SmI_2 initiated a cascade reaction to deliver the highly functionalized tetracyclic strychnine precursor **2** with complete diastereoselectivity (Scheme 2).



Scheme 2. A SmI_2-mediated cascade in a synthesis of strychnine by Reissig. HMPA = hexamethylphosphoric triamide.

This key step is an impressive application of methodology developed in the Reissig group[9] and begins with the well-established reduction of a ketone to form the ketyl radical (Scheme 2). The resulting ketyl samarium **1a** cyclizes to give **2** through a transition state in which the bulky samarium alkoxide occupies an equatorial position. After the second electron transfer, the resulting, unstabilized organosamarium(III) intercepts the pendant ester to complete the remarkable cascade. This highly efficient process was readily performed on a gram scale and has also been employed for the synthesis of complex tetracyclic analogues. Having assembled the skeleton of strychnine, reduction of the nitrile allowed construction of the pyrrolidine ring. Subsequent elimination of the tertiary alcohol and N-allylation allowed straightforward access to the pentacycle **4**, first reported by

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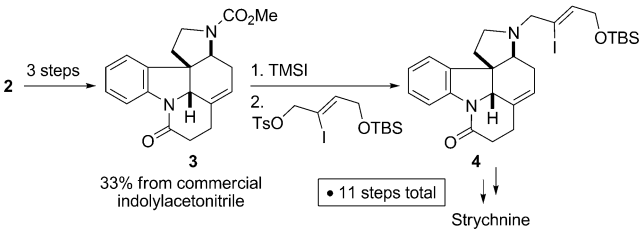
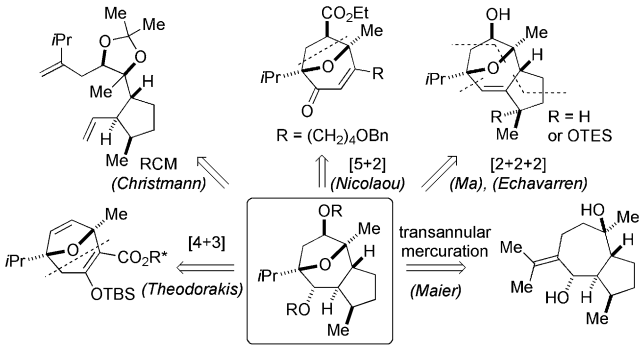


Scheme 3. Final steps in the synthesis of strychnine by Reissig. TMS = trimethylsilyl; TBS = *tert*-butyldimethylsilyl.

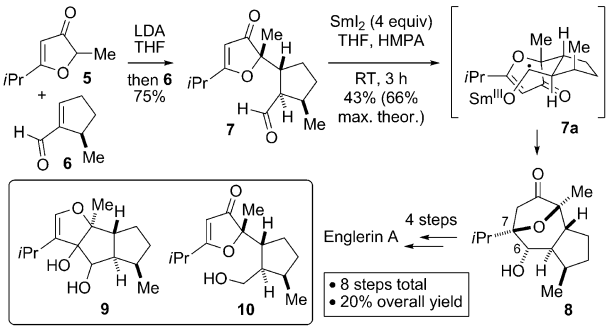
Rawal in 1994 (Scheme 3). Overall, this elegant approach required only 11 steps and demonstrates how SmI_2 can control challenging C–C bond-forming events in a concise synthesis of a *Strychnos* alkaloid.[10]

In contrast to strychnine, a classic target known for almost 200 years, englerin A, a guaiane sesquiterpene, was only isolated in 2009.[11] Englerin A features a highly functionalized 5–6–5 oxatricyclic framework and displays a host of biological activities, including selective growth inhibition against renal cancer cell lines (10 times more potent than taxol). Not surprisingly, englerin A has attracted significant interest from the synthetic community: six innovative total and formal syntheses and a number of synthetic approaches have appeared since its isolation (Scheme 4).[12]



Scheme 4. Advanced intermediates and key steps in the syntheses of englerin A. RCM = ring-closing metathesis; TES = triethylsilyl.

The impressive synthesis of englerin A, recently disclosed by Chain and co-workers,[6] relies on an imaginative sequence climaxing in a SmI_2-mediated cyclization to form the tricyclic core and establishing five stereocenters (Scheme 5). The enantioselective total synthesis of englerin A was completed in only 8 steps and 20% overall yield. This remarkable synthesis paves the way for the preparation of diverse analogues and affinity probes for the identification of the biological target of englerin A and clearly sets a new standard for the assembly of the newly discovered guaiane sesquiterpene. The Chain synthesis rapidly establishes the core of the englerins using a simple two-stage process. Firstly, the Michael reaction between **5** and **6** exploits a single stereocontrol element in electrophile **6** to guide the formation of three new stereocenters. Out of eight possible diastereoisomers, the desired isomer is formed preferentially (2:1, desired:Σothers). Secondly, the application of SmI_2 allowed for completion of the sequence, readily transforming the adduct **7** into the ketoalcohol **8** (Scheme 5). Thus, the densely functionalized skeleton of englerin A was generated in just two steps, while the correct oxidation level and alcohol configuration at C6 allowed the Chain group to minimize subsequent functional-group manipulations that have typically been required in previous approaches to englerin A. Notably, the reductive cyclization was only possible using SmI_2. Other single-electron reducing agents were ineffective and attempts to forge the C6–C7 bond using a Stetter reaction were unsuccessful.



Scheme 5. A SmI_2-mediated cyclization in a synthesis of englerin A by Chain. LDA = lithium diisopropylamide.

Mechanistically, it seems likely that the cyclization proceeds by a traditional mechanism ("carbonyl first"), as opposed to an alternative pathway ("alkene first"),[2] and involves six-membered transition structure **7a** (Scheme 5). α,β-Unsaturated alkenes bearing β-heteroatoms are not widely used as components in SmI_2-mediated reductive couplings[2] and this type of reductive cyclization shows considerable potential for the assembly of other natural products featuring bridging oxygen atoms.

Interestingly, both Reissig and Chain exploited the ability to tune the properties of SmI_2 through the choice of appropriate co-solvents and additives.[13] For example, the Chain group observed that the addition of LiCl (to form $SmCl_2$, a stronger reducing agent than SmI_2; $E°[SmI_2^+/SmI_2] = -1.33$ V; $E°[SmCl_2^+/SmCl_2] = -2.11$ V; vs. $Ag/AgNO_3$ in THF) resulted in a reductive pinacol-type coupling to give tricycle **9**, while the use of protic additives facilitated protonation of the intermediate ketyl radical en route to alcohol **10** (Scheme 5). The use of HMPA, a common co-solvent in SmI_2-mediated chemistry that is used to increase the reduction potential of the reagent ($E°[SmI_2(HMPA)_n^+/SmI_2(HMPA)_n] = -2.05$ V vs. $Ag/AgNO_3$ in THF), ultimately proved to be the key to the success of both cyclizations.

Recently, significant advances have been made in the mechanistic understanding of ligand effects in SmI_2-mediated reactions.[14] However, the challenge remains to identify activating additives to replace carcinogenic HMPA. Furthermore, additives based on chiral scaffolds could be used to mediate asymmetric cyclizations. Finally, although, reagent systems that are catalytic in SmI_2 have been reported, a general solution to this problem remains elusive.[2]

In summary, recent syntheses by Reissig and by Chain showcase exciting new applications of SmI_2 in the synthesis of two very different natural products: strychnine, an indole alkaloid, and englerin A, an oxygenated terpene. As synthetic chemists strive for efficient routes to ever more intricate bioactive structures, further spectacular applications of Kagan's reagent are sure to be disclosed.

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