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A Powerful New Construction of Complex Chiral Polycycles by an Indium(III)-Catalyzed Cationic Cascade

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Supporting Information

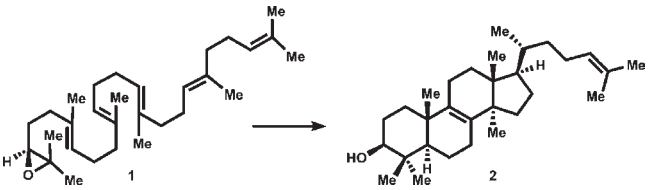
ABSTRACT: InI_3 and $InBr_3$ have been found to be effective catalysts for the π activation of C≡C bonds to initiate the conversion of chiral propargylic alcohols or silyl ethers to polycyclic products in excellent yields and with high stereoselectivity. The method has been applied to the synthesis of chiral fused hexacyclic ring systems with the creation of multiple new stereocenters. The power and scope of the method are illustrated by a variety of examples.

The enzymic cyclization of (*S*)-2,3-oxidosqualene (**1**)[1] to sterols and polycyclic triterpenoids is one of the most powerful, versatile, and impressive biosynthetic constructions known,[2] as exemplified by the one-step biosynthesis of lanosterol (**2**) (Scheme 1). This remarkable process involves a succession of highly reactive carbocationic intermediates that are exquisitely controlled by an enzyme that can channel the complex sequence of carbocyclizations and rearrangements to a single major product.[3] The chemical emulation of the biosynthesis of sterols and polycyclic triterpenoids represents a major challenge to, and a frontier of, synthetic chemistry. Although the efficiency of biosynthesis has never been matched under nonenzymic conditions, it has been possible to utilize suitable chiral epoxides in cationic polycyclization to achieve fairly short and effective stereocontrolled syntheses of lanosterol,[4] dammarenediol,[5] β-amyrin,[6,7] germanicol,[8] lupeol,[9] onocerin,[10] serratenediol,[11] and scalarenedial.[12,13]

The most effective procedure for the key epoxide-initiated polycyclization step in these synthetic examples entails the use of low temperature (−78 °C or lower), a non-nucleophilic cation-stabilizing solvent (CH_2Cl_2), and methylaluminum dichloride (ca. 3 equiv) as a Lewis acid catalyst. One consequence of the need for such strongly Lewis acidic conditions is that the presence of coordinating heteroatoms in the cyclization substrate is highly deleterious,[14] which limits greatly the scope of the epoxide-initiated cation−olefin polycyclization process. We were for this reason motivated to find alternative ways to initiate such polycyclizations that would be useful for enantioselective synthesis and also more tolerant of functionality. This approach led us to find the novel polycyclization method described herein.

We speculated that a soluble indium(III) salt might serve to activate the acetylenic subunit of a propargylic alcohol or ether by virtue of its vacant 5s and 5p orbitals, which might coordinate with the C≡C bond by bidentate complexation with the π_x and π_y orbitals (taking the C≡C linkage as the *z* axis reference) while also coordinating to the propargylic oxygen. Such a mode of π interaction for indium clearly would be favored by the larger radius of the In 5s and 5p orbitals, which would allow better orbital overlap. We suspect that this effect is also operative with

Scheme 1. Synthesis of Lanosterol (2) from (*S*)-2,3-Oxidosqualene (1)



Scheme 2. Synthesis of Chiral Pentacycle 4

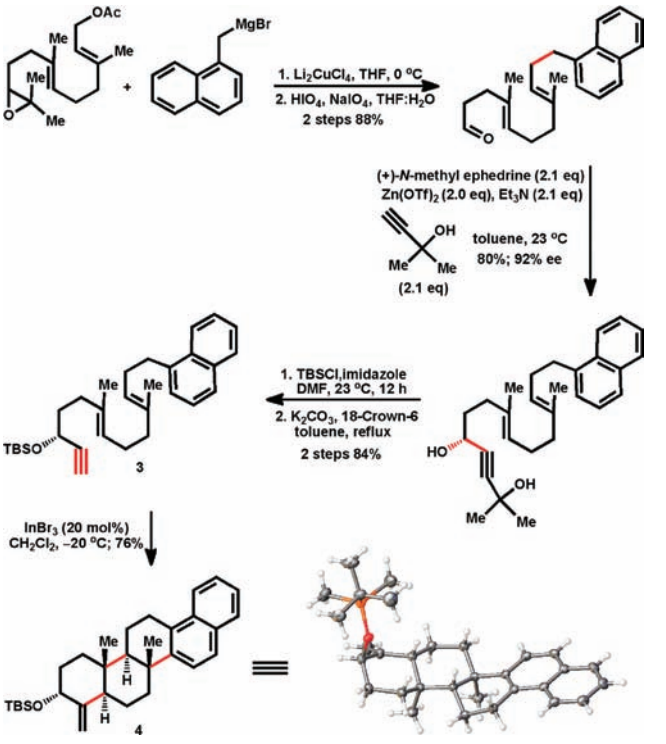


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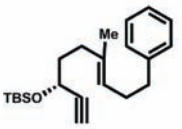
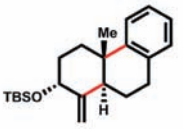
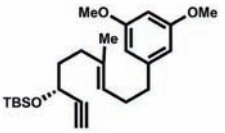
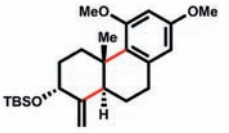
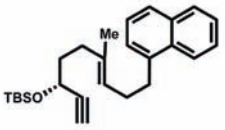
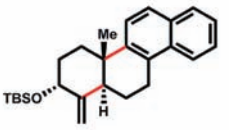
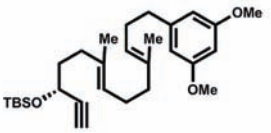
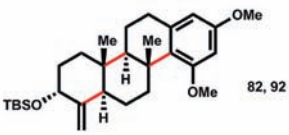
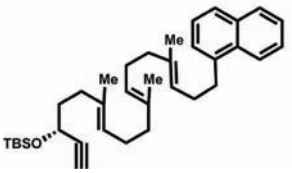
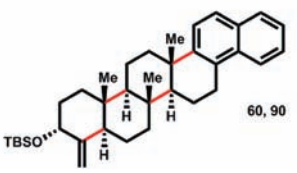
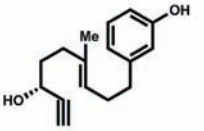
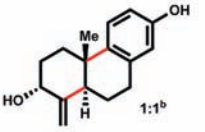
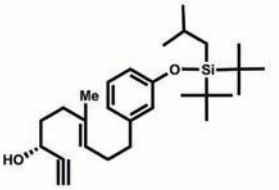
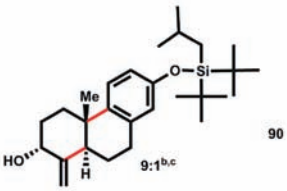
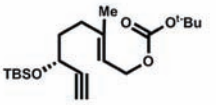
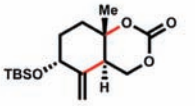
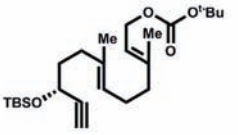
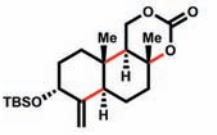
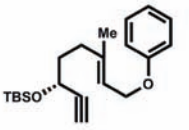
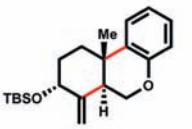
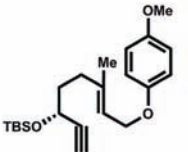
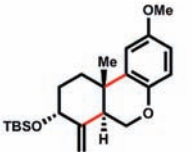
Table 1. $InBr_3$-Catalyzed Polycyclization in CH_2Cl_2 at −20°C

Entry	Substrate	Product	Yield,[a] ee,%[b]
1			78, 92
2			90, 94
3			88, 95
4			82, 92
5			60, 90

[a] Isolated yields of products fully characterized by NMR, IR, and MS. [b] ee determined by HPLC analysis using a Chiralcel OD-H column.

Table 2. InI_3-Catalyzed Polycyclization in CH_2Cl_2 at −20 °C

Entry	Substrate	Product	Yield (%)[a]
1			95
2			90
3			82
4			78
5			75
6			84

[a] Isolated yields of products fully chartacterized by NMR, IR, and MS. [b] Cyclization occurred both ortho and para to the phenolic hydroxyl group. [c] Reaction was carried out at −50 °C.

the other heavy metals that show high π affinity [e.g., Hg(II) and Tl(III)]. In the case of In(III), overlap with the orthogonal π orbitals of C≡C may be further enhanced by some mixing of a 5p orbital with the 5s orbital, as the energy difference between these orbitals is less than that for metals of lower atomic number. We were pleased that the experimental test of this surmise led to a useful discovery, which extends the promise of indium reagents to new and powerful applications.[15] The new In(III)-based process for polycyclization of propargylic alcohol/polyene derivatives is exemplified by the conversion of chiral acetylenic diene **3** to pentacyclic allylic *tert*-butyldimethylsilyl ether **4** in a single step in 76% yield (ca. 90% yield per ring formed) (Scheme 2). The cyclization reaction produced the crystalline chiral pentacycle **4** (mp 152−154 °C), in which the silyloxy group is attached axially in ring A, and was completely stereoselective. The structure and absolute configuration of **4** were proven by single-crystal X-ray diffraction analysis.[16]

Either InI_3 or $InBr_3$ may be utilized as the cyclization catalyst. InI_3, which is dimeric in the solid state, is more soluble than $InBr_3$ (which is polymeric in the crystalline form) and thus offers some advantages. The cyclization **3** → **4** was conducted using 20 mol % In(III) catalyst in CH_2Cl_2 at −20 °C for several hours, and approximately the same conditions were applied in the other cationic polyannulations that are reported herein.

Of the other heavy-metal catalysts that were examined for the acetylene-initiated polycyclization, only Ag(I) (as the soluble nonaflate) seemed operative, but its use resulted in decidedly lower yields than obtained with InI_3 or $InBr_3$. Obviously, In(III) catalysis is far superior to the use of heavy metals such as Ag(I), Hg(I), or Au(I)[17] in terms of cost, lack of toxicity, and intrinsic effectiveness.

The enantioselective synthetic route to cyclization substrate **3** is outlined in Scheme 2. The Carreira method for the enantioselective ethynylation of aldehydes was both convenient and effective and led to **3** with ca. 24:1 enantioselectivity.[18] The same general approach was employed for the synthesis of the five cyclization substrates shown in Table 1.

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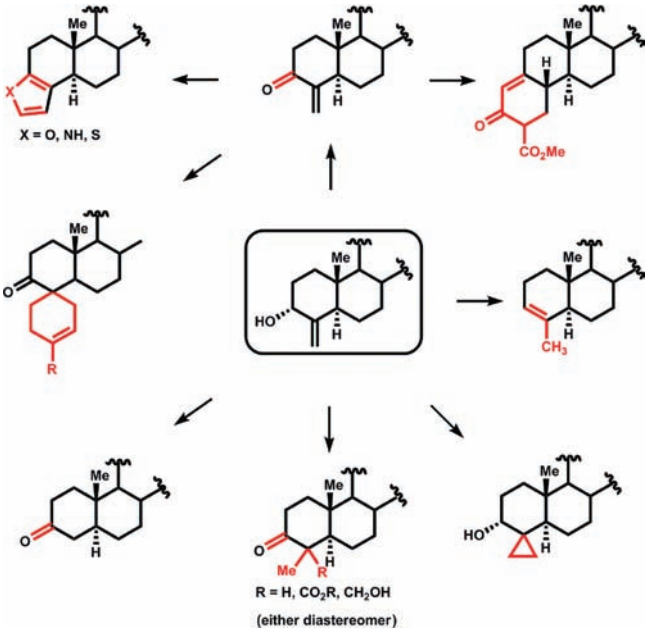
Scheme 3. Synthetic Transformations



The syntheses of the substrates in entries 1−3 of Table 1 started with geraniol and those in entries 4 and 5 with farnesol and geranylgeraniol, respectively. For each case in Table 1, $InBr_3$-catalyzed cyclization occurred cleanly and stereoselectively to give the product shown. The cyclization reactions were easily monitored by TLC analysis. The reaction times were in the range 4−8 h with 20 mol % $InBr_3$ and 2−4 h with 20 mol % InI_3 (the yields were comparable). The cyclization shown in entry 1 of Table 1 occurred somewhat more rapidly with the corresponding free alcohol, but the yield of tricyclic product was slightly lower than with the TBS ether.

The In(III)-promoted cyclization of unsaturated propargylic alcohols (or TBS ethers) is tolerant of oxygen-containing subunits, as shown by the six examples listed in Table 2, all of which employed InI_3 as the catalyst and used racemic substrates. It is evident that a phenolic hydroxyl substituent (entry 1), an ester function (entries 3 and 4), and skeletal ether oxygens (entries 5 and 6) did not interfere with the polycyclization process.

The effectiveness and facility of the In(III)-catalyzed cyclization at −20 °C appears to be due to the highly electrophilic reactivity of the indium complex with the ethynyl subunit rather than the degree of In(III)/C≡C complexation (which is clearly low, but higher than with any C═C linkages in the substrate). The ease of the cyclizations reported herein contrasts sharply with the forcing conditions (100 °C) for the known addition of enolizable 1,3-dicarbonyl compounds to acetylenes.[19] Further research is needed to ascertain the full scope and utility of the powerful new In(III)-mediated construction outlined herein.

The cyclization products obtained in this research are especially interesting because they can be transformed into a wide range of other structures using well-known synthetic methods. The A-ring subunit, for example, can serve to provide such compounds as are shown in Scheme 3.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data for all reactions and products, including copies of ^1H NMR and ^{13}C NMR spectra and single-crystal X-ray diffraction analysis (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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