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Total Synthesis of (−)-Acutumine

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The tetracyclic alkaloid acutumine (**1**, Figure 1), originally isolated from the Asian vine *Menispermum dauricum*,[1] possesses selective T-cell cytotoxicity[2] and antiamnesic properties.[3] Structurally, **1** is characterized by a propellane-type system, a spirocycle, and a neopentylic secondary chloride. The congested cyclopentane ring of **1** contains the chloride along with three contiguous quaternary stereocenters, two of which are all-carbon quaternary stereocenters. Other related compounds isolated from the same source include the epimeric alcohol dauricumine,[4] the N-demethylated congeners acutumidine[1] and dauricumidine,[4] dechloroacutumine,[5a] and dechlorodauricumine.[5b] We[6] and Sorensen[7] have constructed simplified versions of the propellane core of **1**, and we recently fashioned the spirocyclic portion of the natural product via a stereoselective radical−polar crossover reaction.[8] Moreover, Wipf[9] has conducted investigations that led to a revision of Barton's biosynthetic proposal for **1**.[10] Despite this progress, a total synthesis of **1** has yet to be achieved. Herein, we report the enantioselective total synthesis of (−)-acutumine.

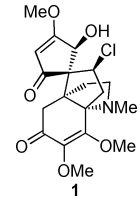

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Figure 1. Acutumine.

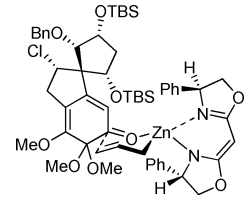
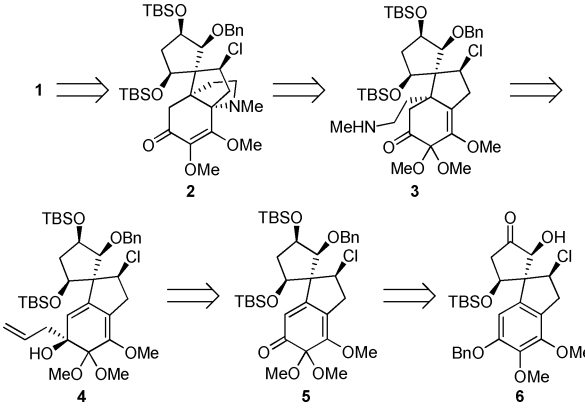


Figure 2. Model of the allylation transition state.

Scheme 1. Retrosynthesis



Our retrosynthetic analysis of **1** is shown in Scheme 1. We anticipated that a sequence of reactions including methyl enol etherification would transform tetracycle **2** into the natural product. The pyrrolidine ring of **2** was to be formed via Lewis or Brønsted acid-promoted cyclization[6] of α,β-unsaturated ketal **3**, itself accessible by means of anionic oxy-Cope rearrangement of homoallylic alcohol **4**. This key intermediate could be constructed by a diastereoselective allylation of ketone **5**, a process that would likely involve a chiral reagent or catalyst. We planned to obtain **5** from **6** through the use of a phenolic oxidation. We previously prepared ketone **6** via our tandem intramolecular radical conjugate addition−enolate hydroxylation reaction.[8]

The total synthesis of (−)-**1** is outlined in Scheme 2. Stereoselective reduction of ketone **6** with L-Selectride afforded diol **7** with 9:1 dr. Although the newly formed stereocenter would be destroyed at a later stage of the synthesis, we found it convenient for characterization purposes to proceed with a single diastereomer of **7**. Silylation of this diol was selective for the less-hindered alcohol, and subsequent hydrogenolysis of the benzyl ether of **8** provided phenol **9**. Phenolic oxidation of **9** in MeOH delivered masked *o*-benzoquinone[11] **10**, which was protected as a benzyl ether to give **5**, setting the stage for the critical ketone allylation.

From inspection of molecular models of ketone **5**, it appeared that the *re* face was slightly less hindered than the *si* face. In fact, addition of allylmagnesium bromide to **5** afforded homoallylic alcohol **4** in modest (70:30) dr. Fortunately, use of Nakamura's chiral allylzinc reagent (*S*,*S*)-**11**,[12] which was effective in our recent synthesis of isohasubanan alkaloids,[13] delivered **4** in good yield (79%) and dr (93:7). The configuration of the newly formed stereocenter was established by conversion of **4** into (−)-**1** and is consistent with Nakamura's proposed six-membered cyclic transition state[12] (Figure 2). The bulky dimethyl ketal of the substrate can occupy an equatorial position, thereby placing the less-hindered alkene carbon in an axial position. The facial selectivity of the allylation is controlled by the ability of the spirocycle to avoid steric interactions with the phenyl group of the bisoxazoline ligand in the orientation shown. In this case, the substrate and the reagent are matched, as the less-hindered *re* face of the ketone is exposed to the allyl group. Alcohol **4** was then transformed into ketone **12** via an extremely facile (0 °C, 1 h, 92%) anionic oxy-Cope rearrangement generating an all-carbon quaternary stereocenter adjacent to a congested spirocyclic carbon. It is likely that conjugation of the methyl enol ether with the homoallylic alcohol accelerated this reaction, as conjugation has been noted to promote anionic oxy-Cope rearrangements.[13,14]

The conversion of **12** into secondary amine **3** required alkene oxidative cleavage followed by reductive amination. While the latter reaction proceeded smoothly, the former was problematic.

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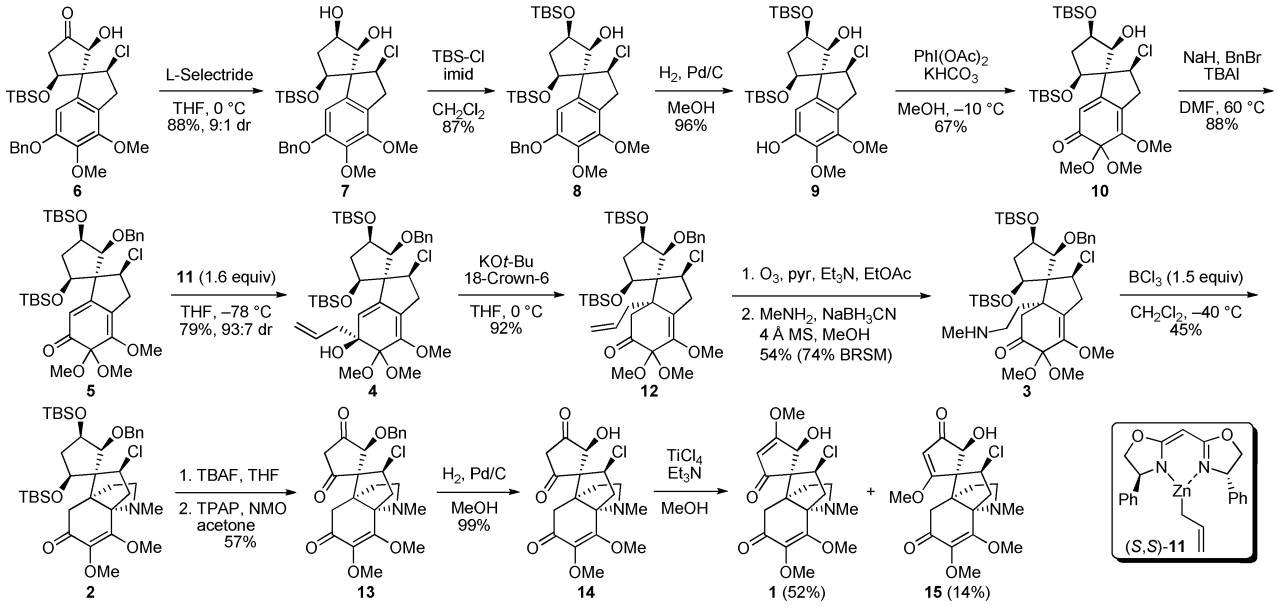
Scheme 2. Total Synthesis of Acutumine



Exposure of **12** to OsO_4/$NaIO_4$ provided small quantities (~10% yield) of the aldehyde. Attempts at ozonolysis were characterized by the production of byproducts presumably derived from competitive oxidation of the electron-rich methyl enol ether. Consistent results (~30% yield of aldehyde, 30% recovery of **12**) could be obtained by employing a standard solution of O_3 in EtOAc.[15] However, the best outcome (54% yield of amine **3**, 27% recovery of **12**, separable on SiO_2) was obtained through the use of pyridine to modulate the reactivity of O_3,[16] which was dispensed via a standard solution in EtOAc.

After surveying a variety of Lewis and Brønsted acids, we determined that BCl_3 was the most effective reagent for promoting cyclization of **3** to provide pyrrolidine **2**, which contains the entire tetracyclic framework of acutumine. Notably, the cyclization proceeds at low temperature (−40 °C) and is free of the undesired rearrangements that thwarted our attempts to construct hasubanan alkaloids via a similar reaction.[13] Subsequent silyl ether cleavage and oxidation of the crude diol afforded 1,3-diketone **13**. Next, hydrogenolysis of the benzyl ether of **13** could be accomplished without reduction of the tetrasubstituted alkene or the alkyl chloride. Finally, treatment of **14** with $TiCl_4$ and Et_3N in MeOH[17] delivered (−)-**1** as the major component of a separable 3.7:1 mixture with enol ether regioisomer **15** in good yield (66%; 52% isolated yield of **1**). The use of CH_2N_2 resulted in a better overall yield (75%) but minimal selectivity for **1** (40% yield of **1**, 35% yield of **15**). Synthetic **1** was determined to be identical to an authentic sample of acutumine using spectroscopic and chromatographic techniques.

In conclusion, we have accomplished the enantioselective total synthesis of (−)-acutumine. Spirocyclic ketone **6**, the product of a stereoselective radical−polar crossover reaction, was the starting point for the sequence reported herein. Noteworthy reactions include a reagent-controlled diastereoselective ketone allylation, an anionic oxy-Cope rearrangement to form a congested quaternary stereocenter, a pyridine-mediated selective ozonolysis, and a Lewis acid-promoted cyclization of an amine onto an α,β-unsaturated ketal. We believe that these processes will have further applications in the synthesis of complex molecules.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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