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Synthesis of the Acutumine Spirocycle via a Radical–Polar Crossover Reaction

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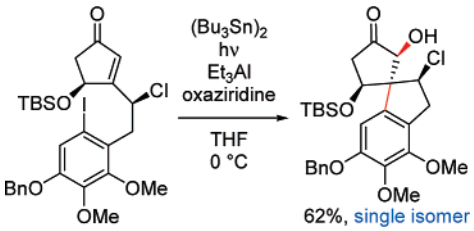
ABSTRACT



A new radical–polar crossover reaction was developed that consists of intramolecular conjugate addition of an aryl radical followed by enolate formation and hydroxylation. A C–C bond, a C–O bond, and two congested stereocenters are created in the process. The product is obtained as a single isomer. The method was used to synthesize the spirocyclic subunit of the alkaloid acutumine.

Acutumine (**1**, Figure 1) is a tetracyclic alkaloid isolated from the Asian vine *Menispermum dauricum*[1] that manifests

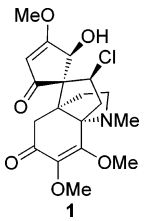


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Figure 1. Acutumine.

selective T-cell cytotoxicity[2] and antiamnesic properties.[3] The structure of **1** includes a propellane-type system, a spirocycle, and a neopentylic secondary chloride. The chloride resides in the cyclopentane ring along with three contiguous quaternary stereocenters, two of which are all-carbon quaternary centers. Previously, we constructed the propellane-type substructure of **1**;[4,5] recently, Sorensen disclosed the preparation of a similar fragment of the natural product.[6] Herein, we report the synthesis of the spirocycle of acutumine via a novel, stereoselective radical−crossover reaction[7,8] that combines an intramolecular radical conjugate addition[9] with a subsequent enolate hydroxylation.[10]

The proposed radical−polar crossover reaction is depicted in Scheme 1. We reasoned that exposure of substrate **2** to a

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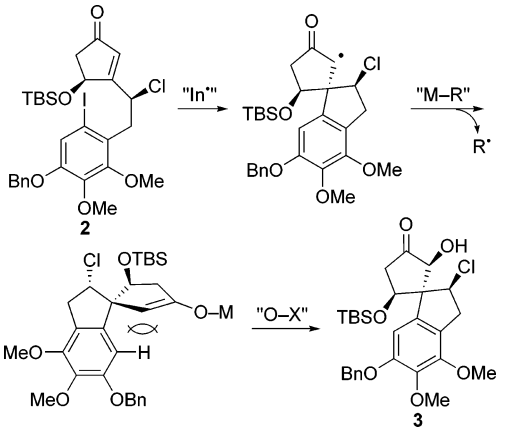
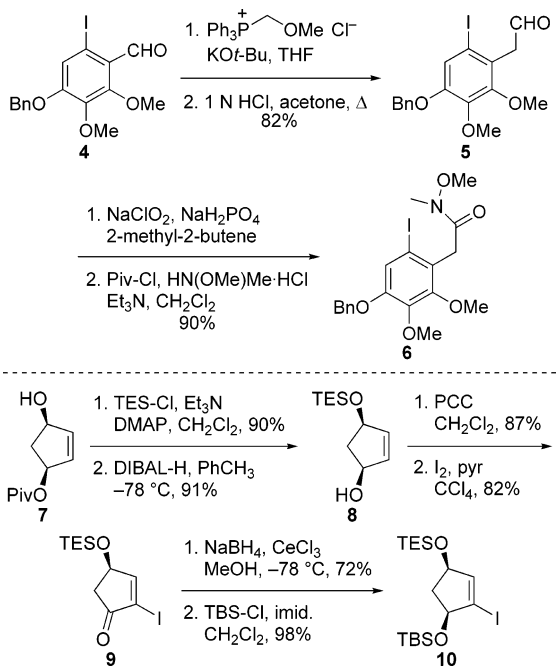
Scheme 1. Proposed Radical−Polar Crossover Reaction



species capable of generating an aryl radical ("In•") would cause a 5-*exo*-*trig* radical cyclization to occur. The regiochemistry of this process would be governed by the polarity of the enone acceptor, and the bulky silyloxy group would presumably direct the aryl radical to the opposite face of the alkene. Then, reaction of the resultant α-keto radical with an organometallic reagent capable of undergoing homolytic cleavage ("M−R") should create an enolate. If a suitable oxidant ("O−X") were present in the mixture, this enolate would be hydroxylated, providing spirocyclic α-hydroxy ketone **3**. We hypothesized that the aryl hydrogen would shield the *re* face of the enolate, delivering the desired isomer of **3**. Thus, we envisioned installing a ring, an alcohol, and two stereocenters including a quaternary carbon in a single step. An isolated report from Kunz of a tandem radical conjugate addition−enolate hydroxylation[11] served as encouraging precedent. However, successful reactions in this prior study were limited to additions of methyl radicals generated from Me_2AlCl. We required a process that would permit use of an aryl radical in the addition step. Moreover, we were concerned about the potential lability of the allylic chloride of **2** in the presence of radicals.

Cyclization substrate **2** was constructed via a convergent route featuring the union of aryl and cyclopentene subunits. The requisite coupling partners were synthesized as outlined in Scheme 2. Wittig homologation of known aldehyde **4**[4b] afforded aldehyde **5**. Oxidation and subsequent amidation provided Weinreb amide **6**. Silylation of enantiopure alcohol **7**[12] followed by pivaloate cleavage delivered alcohol **8**, which was transformed into enone **9** by oxidation and iodination.[13] Then, Luche reduction[14] and silylation afforded vinyl iodide **10**, in which the two alcohol moieties are differentially protected.

Scheme 2. Synthesis of Weinreb Amide **6** and Vinyl Iodide **10**



The vinyl Grignard reagent derived from **10** (prepared according to Knochel's procedure)[15] was added to Weinreb amide **6**, affording enone **11** (Scheme 3). Notably, the aryl iodide was unaffected by this reaction. We were pleased to find that **11** could be reduced in diastereoselective fashion by the Corey−Bakshi−Shibata catalyst (CBS cat.).[16] Identification of the optimal reaction temperature (10 °C), time (≤4 h), and ratio of reactants (**11**/CBS cat./BH_3·THF = 1:0.2:1.2) proved critical to obtaining reproducibly high yields and diastereomeric ratios. The stereochemistry at the hydroxyl-bearing carbon was established by Mosher ester analysis.[17] Then, S_N2 chlorination of the allylic alcohol of **12** was accomplished with methanesulfonyl chloride and triethylamine.[18] The TES group of **13** could be selectively cleaved in the presence of the TBS moiety, and oxidation of the resultant alcohol provided enone **2**.

The results of our investigation of the radical−polar crossover reaction of **2** are summarized in Table 1. Hexabutylditin was employed to generate an aryl radical from **2** under nonreducing conditions. We discovered that Et_3Al[19] was more effective at mediating the radical−polar crossover step than Et_2Zn[20] or Et_3B[21] (cf. entry 6 vs entries 1 and 3 or entry 7 vs entries 2 and 4). Both O_2[22] and dimethyldioxirane

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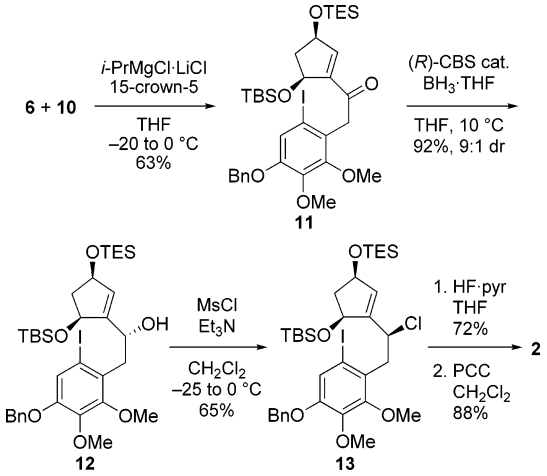
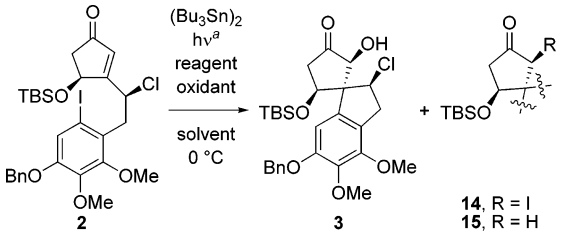
Scheme 3. Synthesis of Enone **2**



(DMDO)[23] were able to hydroxylate the intermediate enolate and provide the desired α-hydroxy ketone **3**. However, significantly better yields were obtained with 3-phenyl-2-(phenylsulfonyl)oxaziridine[24] as the hydroxylating agent (entry 8). Screening other oxidants and solvents as well as varying the equivalents of each reagent established the conditions of entry 8 as optimal. Conducting the experiments at temperatures above or below 0 °C led to greatly reduced yields. Importantly, the allylic chloride moiety of **2** remained intact for the duration of the reaction. However, in most cases

Table 1. Radical−Polar Crossover Reaction of **2**



entry	reagent (equiv)	oxidant (equiv)	solvent	**3/14/15** (%)
1	Et_3B (1)	O_2	THF	21/20/19
2	Et_3B (1)	DMDO (10)	THF	16/18/24
3	Et_2Zn (4)	O_2	THF	28/23/5
4	Et_2Zn (4)	DMDO (10)	THF	20/18/3
5	Et_2Zn (4)	oxaziridine[b] (4)	THF	29/27/17
6	Et_3Al (1)	O_2	THF	33/22/19
7	Et_3Al (1)	DMDO (10)	THF	25/11/9
8	**Et_3Al (3)**	**oxaziridine[b] (5)**	**THF**	**62/7/3**
9	Et_3Al (3)	*t*-BuOOH (5)	THF	34/3/27
10	Et_3Al (3)	$(Me_3SiO)_2$	THF	12/−/−
11	Et_3Al (3)	oxaziridine[b] (5)	CH_2Cl_2	42/11/3
12	Et_3Al (3)	oxaziridine[b] (5)	$PhCF_3$	40/9/13
13	Et_3Al (3)	oxaziridine[b] (5)	THF/PhH 1:1	47/10/5
14	Et_3Al (1)	oxaziridine[b] (1)	THF	9/4/−
15	Et_3Al (5)	oxaziridine[b] (10)	THF	45/6/4

[a] A sunlamp was used. [b] 3-Phenyl-2-(phenylsulfonyl)oxaziridine.

varying amounts of iodide **14** and reduced compound **15** were isolated. While **15** is presumably derived from reduction of either the α-keto radical or enolate intermediates, the origin of **14** is unclear. It may be produced via reaction of the α-keto radical or enolate with Bu_3SnI or an electrophilic iodine species generated via in situ oxidation of Bu_3SnI.[25]

Spirocycles **3**, **14**, and **15** were each obtained as single diastereomers. The stereochemistry of **3** was established via NOE experiments performed on a *p*-methoxybenzyl ether derivative; the relevant correlations are depicted in Figure 2. The structures of **14** and **15** are assigned via analogy to

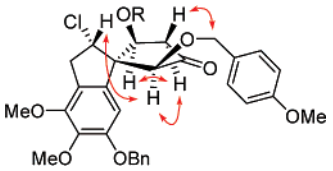
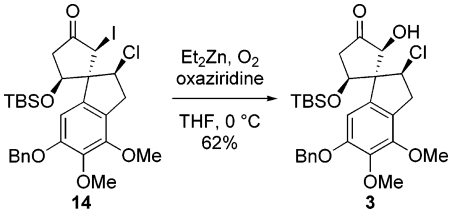


Figure 2. NOE enhancements used to assign the structure of **3**.

3. The configurations of the two stereocenters formed in the radical−polar crossover reaction are consistent with the proposed reaction pathway shown in Scheme 1.

The product distribution (see Table 1, entry 8) indicates that the cyclization is proceeding with 72% yield and the hydroxylation is occurring with 86% yield. Additionally, we have converted **14** into **3** with 62% yield by exposing the iodide to Et_2Zn and air in the presence of the oxaziridine (Scheme 4). Thus, the overall yield of **3** from **2** is 66%.

Scheme 4. Conversion of **14** into **3**



Interestingly, Et_2Zn was superior to Et_3Al (40% yield) in this reaction.

In conclusion, we have constructed the enantiomerically pure acutumine spirocycle by means of a novel radical−polar crossover reaction consisting of an intramolecular aryl

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radical conjugate addition followed by enolate formation and hydroxylation. A spirocyclic quaternary carbon and an adjacent secondary alcohol are each created with complete stereochemical fidelity. Furthermore, an allylic chloride survives the transformation unscathed. The ability to form a congested and functionalized structure with excellent selectivity and good yield suggests that this process may have broad utility. Accordingly, explorations of its scope as well as continuation of the total synthesis of acutumine are currently in progress.

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

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