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Enantioselective Total Synthesis of (−)-Acutumine

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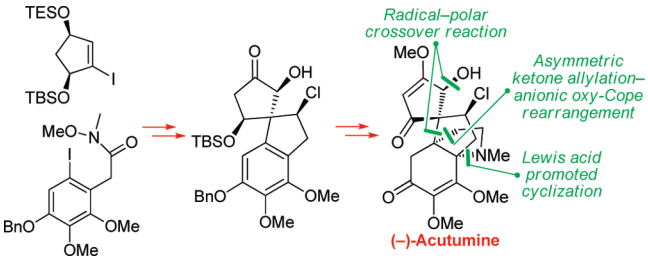

An account of the total synthesis of the tetracyclic alkaloid (−)-acutumine is presented. A first-generation approach to the spirocyclic subunit was unsuccessful as a result of incorrect regioselectivity in a radical cyclization. However, this work spawned a second-generation strategy in which the spirocycle was fashioned via a radical−polar crossover reaction. This process merged an intramolecular radical conjugate addition with an enolate hydroxylation and created two stereocenters with excellent diastereoselectivity. The reaction was promoted by irradiation with a sunlamp, and a ditin reagent was required for aryl radical formation. These facts suggest that the substrate may function as a sensitizer, thereby facilitating homolytic cleavage of the ditin reagent. The propellane motif of the target was then installed via annulation of a pyrrolidine ring onto the spirocycle. The sequence of reactions used included a phenolic oxidation, an asymmetric ketone allylation mediated by Nakamura's chiral allylzinc reagent, an anionic oxy-Cope rearrangement, a one-pot ozonolysis−reductive amination, and a Lewis acid promoted cyclization of an amine onto an α,β-unsaturated dimethyl ketal. Further studies of the asymmetric ketone allylation demonstrated the ability of the Nakamura reagent to function well in a mismatched situation. A $TiCl_4$-catalyzed regioselective methyl enol etherification of a 1,3-diketone completed the synthesis.

Introduction

Acutumine (**1**, Figure 1) is a tetracyclic alkaloid that was originally isolated by Goto and Sudzuki in 1929 from *Sinomenium acutum*.[1] Later, Tomita and co-workers obtained **1** from *Menispermum dauricum* and determined its structure via X-ray crystallography.[2] Other members of the acutumine family include acutumidine[2] (**2**), dechloroacutumine[3] (**3**), and the epimeric alcohols dauricumine[4] (**4**), dauricumidine[4] (**5**), and dechlorodauricumine[5] (**6**). Recently, a diethylamino congener of **4** known as hypserpanine (**7**) was isolated from *Hypserpa nitida*.[6] Since the plants from which the acutumine alkaloids are obtained have been used in traditional Chinese medicine to treat fever and pain,[6,7] it is not surprising that the pure natural products possess interesting bioactivity. For example, acutumine is endowed with both selective T-cell cytotoxicity[7] and antiamnesic properties.[8]

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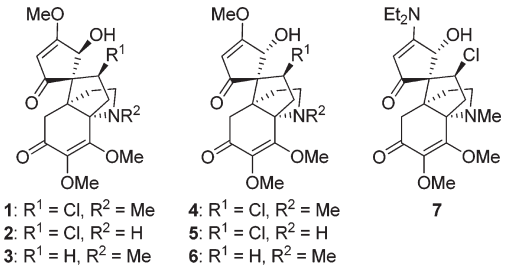


FIGURE 1. Acutumine (**1**) and related alkaloids.

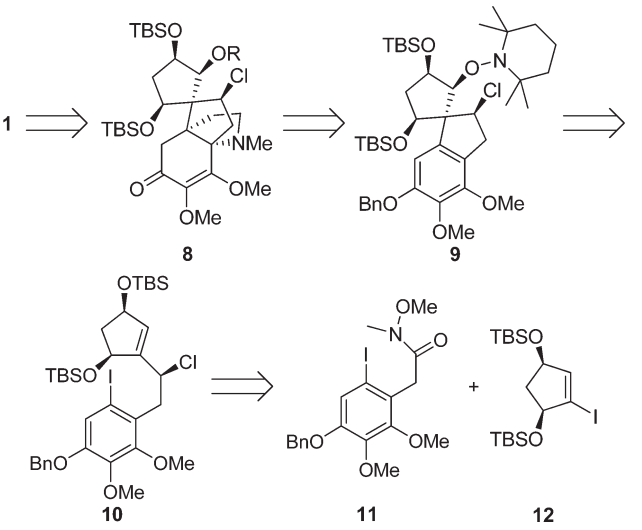
The striking molecular architecture of **1** includes a propellane-type system[9] and a spirocycle. The cyclopentane ring, which is common to both of the aforementioned features, possesses a neopentylic secondary chloride and three contiguous quaternary stereocenters including two all-carbon quaternary centers. Shortly after the structure of acutumine was established, Barton and co-workers postulated that it could be derived biosynthetically from a benzylisoquinoline alkaloid via an oxidative phenolic coupling followed by oxidation and rearrangement steps.[10] Recently, synthetic investigations by Wipf and co-workers have suggested that modifications to the Barton proposal may be in order.[11] Sugimoto and co-workers have determined that **1** is produced in nature from two units of tyrosine[12] and that dechlorodauricumine (**6**) is the biosynthetic precursor to **1**−**5**.[13]

Despite the fact that the structure of acutumine was published in 1967, it did not attract the attention of the synthetic community until recently. In 2005, our laboratory developed a route to the propellane core of acutumine in which the pyrrolidine ring was annulated onto an aromatic precursor.[14] Shortly thereafter, Sorensen and Moreau disclosed a concise sequence featuring a β-elimination−Michael addition cascade for construction of the propellane subunit.[15] Then, we fashioned the spirocycle of **1** via a radical−polar crossover reaction[16] and subsequently elaborated this advanced intermediate into the natural product.[17] Herein, we provide a full account of the development and execution of our synthetic strategy, which culminated in the first total synthesis of acutumine.

Results and Discussion

Our initial retrosynthetic analysis of acutumine is depicted in Scheme 1. Manipulation of the oxygenated functional groups contained in the cyclopentenone ring of **1** leads to tetracyclic intermediate **8**. The most challenging step in the

SCHEME 1. First-Generation Retrosynthetic Analysis



conversion of **8** into **1** was anticipated to be the regioselective methyl enol etherification of a 1,3-diketone. Simplification of **8** according to our previously developed pyrrolidine annulation strategy[14] reveals tricycle **9**. Key reactions in this section of the synthesis would include a phenolic oxidation, an anionic oxy-Cope rearrangement, and an acid-promoted cyclization of an amine onto an α,β-unsaturated ketal. We hoped to fashion the spirocycle of **9** via 5-*exo*-*trig* radical cyclization of aryl iodide **10** with trapping of the cyclic radical intermediate by TEMPO. Cyclization substrate **10** can be dissected into two monocyclic coupling partners: Weinreb amide **11**, and enantiopure vinyl iodide **12**. Amide **11** could be obtained by homologation of a benzaldehyde derivative employed in our isohasubanan alkaloid synthesis.[18] Vinyl iodide **12** is a single step removed from a known alcohol[19] that has been constructed by a route featuring enzymatic hydrolysis of *cis*-3,5-diacetoxycyclopentene.[20]

Although some precedent existed for the radical cyclization with TEMPO trapping,[21] we had three major concerns regarding this proposed transformation. First, we were unsure if the allylic chloride would survive the radical reaction conditions. However, we felt that installation of the chloride would be quite challenging after formation of the neighboring quaternary spirocyclic carbon, so we elected to introduce this substituent at an early stage of the synthesis. Second, we feared that the hindered nature of the trisubstituted alkene radical acceptor in **10** might force the cyclization to proceed via a 6-*endo* rather than the typically favored 5-*exo* pathway. Finally, although examination of molecular models suggested that TEMPO trapping of the radical intermediate on its less-hindered face would deliver the desired adduct **9**, we were hesitant to predict the degree of stereoselectivity that could be achieved in this reaction.

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(13) Sugimoto, Y.; Matsui, M.; Babiker, H. A. A. *Phytochemistry* **2007**, *68*, 493.
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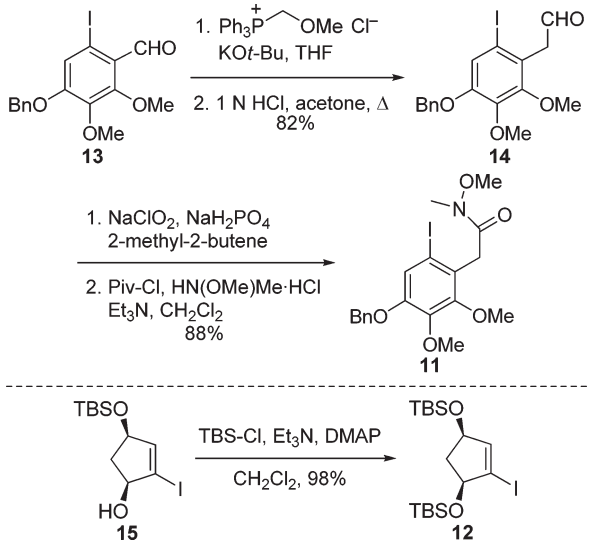
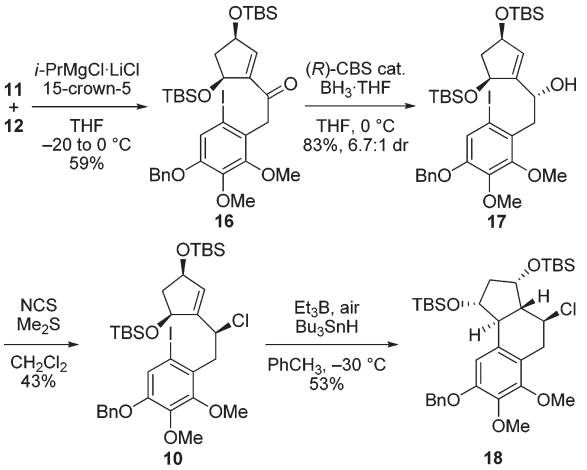
(21) Boger, D. L.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 1271.

SCHEME 2. Synthesis of Weinreb Amide 11 and Vinyl Iodide 12



SCHEME 3. Preparation and 6-*endo* Radical Cyclization of 10



Our attempt at constructing **1** according to the plan described above commenced with the preparation of two coupling partners, Weinreb amide **11** and vinyl iodide **12**, as depicted in Scheme 2. We previously reported the synthesis of pentasubstituted benzaldehyde **13** in three steps from 4-benzyloxy-2,3-dimethoxybenzaldehyde,[18] itself accessible in two steps from commercially available 2,3-dimethoxyphenol.[22] Wittig homologation of **13** provided aldehyde **14**, which underwent oxidation and amidation to afford **11**. Then, silylation of enantiopure alcohol **15**, which was obtained from a straightforward eight-step sequence beginning with *cis*-3,5-diacetoxycyclopentene,[19,20] afforded bis-TBS-protected vinyl iodide **12**.

Coupling of the vinyllithium reagent derived from **12** with Weinreb amide **11** proceeded in low yield (9%). Although not investigated in detail, it is likely that competitive deiodination of **11** was a prominent side reaction. Formation of the corresponding vinylmagnesium reagent by treating **12** with PhMgBr, $PhCH_2MgBr$, or allylMgBr was a very sluggish process. Fortunately, the protocol of Knochel and co-workers, which utilizes the complex *i*-PrMgCl·LiCl in conjunction with 15-crown-5,[23] generated the desired Grignard reagent from **12** in a reasonable time frame (ca. 1 h). Addition of this species to **11** provided enone **16** in moderate yield (Scheme 3). Then, a diastereoselective reduction of **16** was accomplished by enlisting the Corey–Bakshi–Shibata (CBS) catalyst.[24] The configuration of the newly formed stereocenter of alcohol **17** was assigned by Mosher ester analysis.[25] The minor diastereomer was partially separable from **17**, and it could be completely removed after the following step. Next, S_N2 chlorination of the allylic alcohol was conducted under Corey's conditions,[26] affording chloride **10** in 43% yield. Presumably, elimination of the chloride to give the corresponding dienyl benzene species is at least partially responsible for the low yield of this transformation. Although its isolation was not pursued, the elimination product was detected by mass spectrometry. We elected not to optimize the chlorination, as sufficient quantities of **10** were obtained to permit examination of the radical cyclization. When exposed to Et_3B, air, and Bu_3SnH[27] at a low temperature, **10** was transformed into a single tricyclic product. Unfortunately, spectroscopic studies identified the adduct as compound **18**, product of a 6-*endo* radical cyclization instead of the desired 5-*exo* process. Apparently, steric hindrance associated with the 5-*exo* pathway enabled the typically less favored 6-*endo* cyclization to proceed. Since the undesired regioisomer was formed in the cyclization, the feasibility of trapping with TEMPO was not investigated. Nevertheless, we were heartened by the fact that the allylic chloride emerged unscathed from the radical cyclization. This observation gave us confidence regarding the viability of a radical-based approach to the acutumine spirocycle, as long as the required 5-*exo* pathway could be enforced by appropriate changes to the substrate.

We reasoned that use of an α,β-unsaturated ketone instead of a simple alkene as radical acceptor would cause the electron-rich aryl radical to cyclize onto the electron-deficient β-carbon of the enone. This radical conjugate addition[28] could allow us to surmount the steric obstacles associated with the desired 5-*exo* cyclization. A modified retrosynthesis of **1** based on this concept is portrayed in Scheme 4. We did not envision our new strategy requiring changes to the final stages of the synthesis; accordingly, tetracycle **8** was still projected as a key precursor to **1**. However, **8** would now be derived from spirocyclic α-hydroxy ketone **19**. Removal of the hydroxyl moiety from **19** and disconnection of the aryl–alkyl C–C bond from the spirocyclic carbon reveals enone **20**, substrate for the radical

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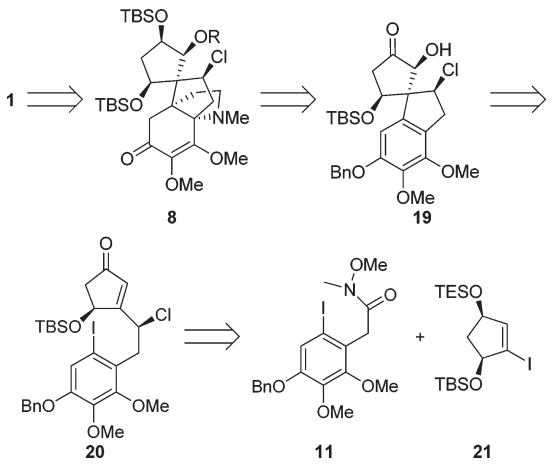
SCHEME 4. Second-Generation Retrosynthetic Analysis



cyclization. Instead of relying on TEMPO trapping to install the hydroxyl group, we planned to take advantage of the α-keto radical intermediate that would form upon 5-*exo*-*trig* cyclization of **20**. These species are known to react with reagents such as Et_3B,[29] Et_2Zn,[30] and Et_3Al[31] to generate enolates, which can then participate as nucleophiles in polar reactions. The three-step sequence of a radical process, conversion of a radical intermediate to a polar intermediate, and a polar process has been termed a radical−polar crossover reaction by Murphy.[32] Thus, the transformation of **20** into **19** would constitute a radical−polar crossover reaction that merges an intramolecular radical conjugate addition with an enolate hydroxylation.[33] A report by Kunz and Rück provided encouraging precedent, but successful reactions in their study were limited to intermolecular conjugate additions of methyl radicals generated by homolysis of Me_2AlCl to α,β-unsaturated *N*-acyl oxazolidinones. Moreover, the diastereoselectivity of the reaction was low.[34] Clearly, a new protocol would be required to enable the stereoselective formation of **19** from **20**.

In the proposed cyclization−hydroxylation of **20**, two new stereocenters would be formed. We hypothesized that the bulky silyloxy group would direct the aryl radical to the opposite face of the enone, thereby setting the spirocyclic carbon in the proper configuration. Then, examination of molecular models suggested that the aryl group would shield the *re* face of the putative enolate intermediate, whereas the neighboring chlorine atom would protrude away from the *si* face (Figure 2). The pseudoequatorial orientation of the silyl ether would minimize its impact on the steric environment of

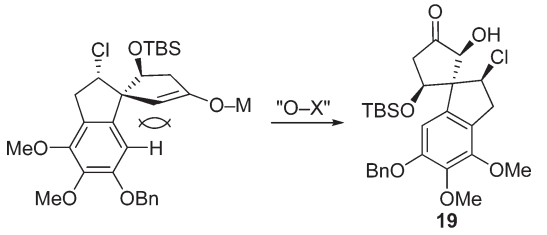
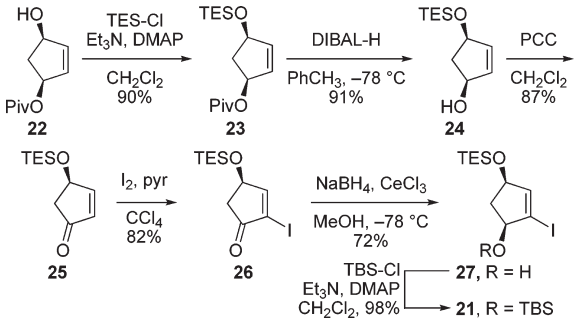


FIGURE 2. Proposed stereocontrol in enolate hydroxylation.

SCHEME 5. Synthesis of Vinyl Iodide 21



the enolate. As a result, the hydroxyl group would likely be delivered to the *si* face. Consequently, it appeared that, out of four possibilities, the desired isomer of **19** would predominate in the planned radical−polar crossover reaction of **20**.

We envisioned preparing substrate **20** via the same Weinreb amide−Grignard reagent coupling employed in the previous route (Scheme 3). In fact, the identical Weinreb amide (**11**) would be used in this case. However, construction of the enone moiety required a vinyl iodide in which the two hydroxyl groups were differentiated. Therefore, vinyl iodide **21** would be employed in place of **12**.

The synthesis of **21**, which largely parallels the known route[19,20] used to prepare **12**, is shown in Scheme 5. Protection of enantiopure alcohol **22** (available in three steps from *cis*-3,5-diacetoxycyclopentene)[20] as a TES ether afforded **23**, which was subjected to pivaloate cleavage with DIBAL-H, providing alcohol **24**. Oxidation followed by iodination[19] delivered α-iodo enone **26**. Then, Luche reduction[35] and masking of the resulting alcohol as a TBS ether gave **21**, in which the two hydroxyl groups are differentiated.

Coupling of the Grignard reagent derived from **21** with Weinreb amide **11** provided enone **28** (Scheme 6). As before, Knochel's procedure[23] was essential to obtaining reproducible yields. The CBS reduction of **28** proceeded under carefully optimized conditions (**28**/CBS cat./BH_3·THF = 1.0:0.2:1.2, −10 °C, ≤4 h) to give allylic alcohol **29** in 89% yield and 9:1 dr. The configuration of the hydroxyl-bearing carbon was determined by Mosher ester analysis and was consistent with the CBS reduction of **16** (Scheme 3).[25] The next transformation, S_N2 chlorination of **29**, afforded low and variable yields when the Corey protocol[26] was employed, presumably as a result of elimination of HCl from the product **30**. Fortunately, consistent results with minimal elimination could be achieved by enlisting MsCl and Et_3N.[36]

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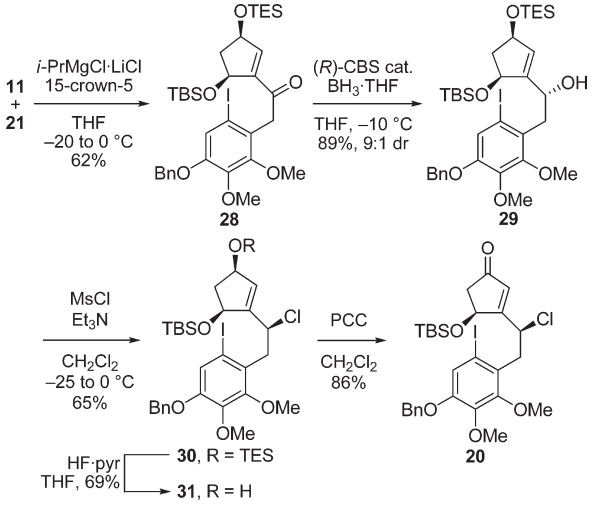
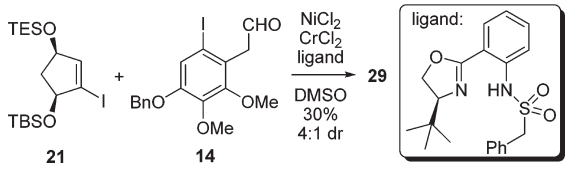
SCHEME 6. Synthesis of Enone 20



SCHEME 7. Asymmetric Nozaki–Hiyama–Kishi Coupling

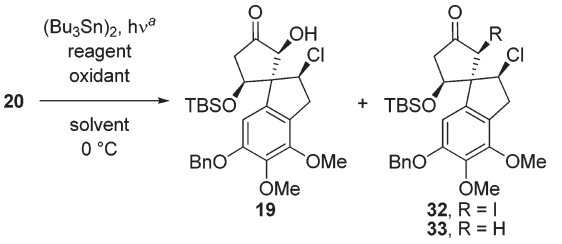


Then, the TES group of **30** was selectively removed with HF·pyridine, and oxidation of the resulting alcohol **31** afforded enone **20**.

Later, we attempted to streamline the route to **20** by examining the asymmetric Nozaki–Hiyama–Kishi coupling[37] of vinyl iodide **21** with aldehyde **14** (Scheme 7). Allylic alcohol **29** could be obtained directly from this reaction. Unfortunately, the yield and dr remained low despite attempts at optimization. Since this more direct pathway was less efficient, we continued to use the route depicted in Scheme 6 to construct enone **20**.

At this point, we commenced our investigation of the radical–polar crossover reaction, which is summarized in Table 1. Since tin radicals are commonly employed to generate aryl radicals,[27] we included hexabutylditin, which functions as a source of tin radicals under nonreducing conditions, in the reaction mixture. We found that the desired cascade process occurred upon photolysis with a simple sunlamp at 0 °C.[38] Efforts to discover the optimal promoter for the radical–polar crossover step revealed that Et_3Al[31] was more effective than Et_3B[29] or Et_2Zn[30] (cf. entry 6 vs entries 1 and 3 or entry 7 vs entries 2 and 4). As for the hydroxylating agent, 3-phenyl-2-(phenylsulfonyl)oxaziridine[39]

TABLE 1. Radical–Polar Crossover Reaction of 20



entry	reagent (equiv)	oxidant (equiv)	solvent	**19**/**32**/**33** (%)
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 (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 (5)	CH_2Cl_2	42/11/3
12	Et_3Al (3)	oxaziridine (5)	$PhCF_3$	40/9/13
13	Et_3Al (3)	oxaziridine (5)	THF/PhH 1:1	47/10/5
14	Et_3Al (1)	oxaziridine (1)	THF	9/4/–
15	Et_3Al (5)	oxaziridine (10)	THF	45/6/4

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

emerged as superior to O_2,[40] DMDO,[41] *t*-BuOOH,[42] or $(Me_3SiO)_2$.[43] After varying other parameters, we established the optimal conditions listed in entry 8. The α-hydroxy ketone **19** was obtained in 62% yield, along with iodide **32** (7%) and reduced compound **33** (3%). Thus, the yields of the cyclization and hydroxylation steps were 72% and 86%, respectively. Importantly, no diastereomers of **19**, **32**, or **33** were detected in the reaction mixture, and consistent results were obtained when the reaction was conducted on a preparative scale (59% yield of **19** on > 100 mg scale). Ketone **33** is likely produced by reduction of the α-keto radical intermediate or protonation of the enolate intermediate. However, the origin of iodide **32** is less certain. It is possible that $I^{\bullet}$ or I_2, both of which would be present if the aryl iodide is cleaved directly via photolysis (vide infra), could react with the α-keto radical intermediate to create this byproduct. Alternatively, the α-keto radical or the enolate may react with either Bu_3SnI (presumably generated by iodine atom abstraction from **20** by $Bu_3Sn^{\bullet}$) or an electrophilic species formed upon in situ oxidation of Bu_3SnI[44] to form **32**.

The configurations of the two stereocenters formed in the radical–polar crossover reaction were assigned with the aid of NOE experiments conducted on a PMB ether derivative of **19**. The diagnostic correlations are illustrated in Figure 3. These assignments were ultimately confirmed by the conversion of **19** into (–)-**1** and are consistent with the reaction pathway proposed above (see Figure 2).

To improve the overall efficiency of the process, we explored the conversion of iodide **32** into α-hydroxy ketone **19**. In principle, this transformation could be accomplished

(37) (a) Wan, Z.-K.; Choi, H.-w.; Kang, F.-A.; Nakajima, K.; Demeke, D.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4431. (b) Kurosu, M.; Lin, M.-H.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 12248.

(38) Frequent addition of ice to the cooling bath was necessary to maintain this temperature in the presence of a sunlamp.

(39) Davis, F. A.; Vishawakarma, L. C.; Billmers, J. G.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241.

(40) (a) Gardner, J. N.; Carlon, F. E.; Gnoj, O. *J. Org. Chem.* **1968**, *33*, 3294. (b) Wender, P. A.; Mucciaro, T. P. *J. Am. Chem. Soc.* **1992**, *114*, 5878.

(41) (a) Guertin, K. R.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 715. (b) Adam, W.; Prechtl, F. *Chem. Ber.* **1991**, *124*, 2369. (c) Adam, W.; Mueller, M.; Prechtl, F. *J. Org. Chem.* **1994**, *59*, 2358.

(42) Schulz, M.; Kluge, R.; Schüssler, M.; Hoffmann, G. *Tetrahedron* **1995**, *51*, 3175.

(43) (a) Camici, L.; Dembech, P.; Ricci, A.; Seconi, G.; Taddei, M. *Tetrahedron* **1988**, *44*, 4197. (b) Dahnke, K. R.; Paquette, L. A. *J. Org. Chem.* **1994**, *59*, 885.

(44) For related observations with Bu_3SnBr, see: Blaszykowski, C.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2003**, *5*, 1341.

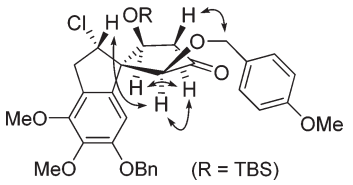
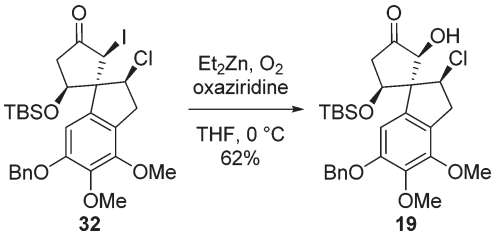


FIGURE 3. Diagnostic NOE enhancements.

SCHEME 8. Conversion of Byproduct 32 into 19



via a radical−polar crossover reaction consisting of α-keto radical formation, enolate generation, and hydroxylation. In practice, the use of Et_2Zn/O_2 in conjunction with the oxaziridine provided **19** in 62% yield (Scheme 8). This raised the overall yield of **19** from **20** to 66%. Interestingly, the use of Et_3Al in place of Et_2Zn afforded lower yields (40%).

We also examined the possibility of using SmI_2/HMPA[45] instead of hexabutylditin to generate the aryl radical in the radical−polar crossover reaction. α-Hydroxy ketone **19** was produced in low yields (ca. 15%) from these reactions, along with **32**, **33**, and several other uncharacterized byproducts. This negative outcome is likely a result of the number of functional groups (aryl iodide, enone, allylic chloride) in **20** that are capable of reacting with SmI_2.

As we pondered the role of the ditin reagent in the radical−polar crossover reaction, we were intrigued by the fact that the process utilized photochemical initiation. Hexabutylditin does not absorb light (λ_{max} = 236 nm); accordingly, photolytic reactions that employ this reagent typically require a sensitizer.[46] However, the conversion of **20** into **19** proceeds in the absence of typical sensitizing agents. Accordingly, we considered two possible roles for the ditin species. First, the enone moiety of **20** could act as a sensitizer and mediate the homolytic cleavage of hexabutylditin into two tributyltin radicals. Then, abstraction of the aryl iodide by $Bu_3Sn^{\bullet}$ would initiate the radical−polar crossover reaction. Alternatively, the aryl iodide might be cleaved directly by photolysis. In this scenario, the ditin reagent would function as an iodine trap, thereby preventing iodine radicals from reacting with subsequent intermediates.[47] If hexabutylditin is involved in trapping iodine but not in aryl radical formation, then omitting it from the reaction mixture should result in atom transfer cyclization[47] due to the presence of untrapped $I^{\bullet}$. In fact, the formation of α-iodo ketone **32** as a byproduct lends some credence to the idea that the aryl radical is formed by direct photolysis of **20**. However, reactions run in the absence of hexabutylditin did not proceed, and starting material was recovered. Although further study is required to more fully elucidate the mechanism of the radical−polar crossover reaction, this observation indicates that the ditin reagent is instrumental in generating the aryl radical intermediate from **20** and is not merely functioning as an iodine trap. Thus, the enone moiety of **20** may be mediating homolytic cleavage of hexabutylditin by functioning as a sensitizer, as posited above. Another possibility is that coordination of the iodine atom in **20** to the ditin reagent weakens the C−I and/or Sn−Sn bonds, thereby facilitating the photolysis.[48]

Before we could fashion the propellane system of acutumine, some routine functional group manipulations of spirocycle **19** were necessary. Although the carbonyl carbon of this intermediate is maintained at the same oxidation state in **1**, the incompatibility of a ketone at this position with an upcoming allylation reaction required us to perform a reduction−protection sequence. Accordingly, treatment of **19** with L-Selectride provided diol **34** in 9:1 dr (Scheme 9). The *cis* relative stereochemistry of the diol moiety was assigned on the basis of the coupling constant (6.6 Hz) measured for the two α-hydroxy hydrogen atoms.[49] This configuration is consistent with attack of the bulky reducing agent on the less hindered *si* face of the ketone or the face opposite the neighboring OTBS, hydroxyl, and chloro substituents. A stereoselective reduction of **19** was not essential, since the alcohol would be oxidized in the final stages of the synthesis. However, the isolation and characterization of intermediates was simplified by working with diastereomerically pure compounds, so the L-Selectride protocol was beneficial. Then, the more accessible secondary alcohol of **34** was selectively silylated. Subsequent cleavage of the benzyl ether of **35** via hydrogenolysis afforded phenol **36**.

Using a sequence of reactions devised with a model compound,[14] phenol **36** was transformed into amine **42** as outlined in Scheme 10. Phenolic oxidation of **36** by $PhI(OAc)_2$ in MeOH delivered masked *o*-benzoquinone **37**. Masked *o*-benzoquinones have great utility in organic synthesis due to the density of functionality that is contained in a single six-membered ring.[50] We planned on utilizing each of the functional groups (enone, dimethyl ketal, methyl enol ether) created in the phenolic oxidation to complete the synthesis of **1**. Thus, this reaction was one of the cornerstones of our strategy. Then, the neopentylic alcohol of **37** was benzylated in preparation for the crucial asymmetric ketone allylation. Examination of molecular models of **38** revealed that the *re* face of the ketone was slightly less congested than the *si* face. However, the difference in steric hindrance between the two diastereotopic faces appeared to be minor. Consequently, we postulated that substrate-directed stereocontrol would be minimal and that catalyst or reagent control would be required to accomplish the allylation. During the course of our synthesis of isohasubanan alkaloids, we discovered that Nakamura's chiral allylzinc reagent (*S*,*S*)-**39**[51] was uniquely

(45) (a) Iwasaki, H.; Eguchi, T.; Tsutsui, N.; Ohno, H.; Tanaka, T. *J. Org. Chem.* **2008**, *73*, 7145. (b) Ohno, H.; Iwasaki, H.; Eguchi, T.; Tanaka, T. *Chem. Commun.* **2004**, 2228.

(46) Harendza, M.; Junggebauer, J.; Lessmann, K.; Neumann, W. P.; Tews, H. *Synlett* **1993**, 286.

(47) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1989**, *111*, 6265.

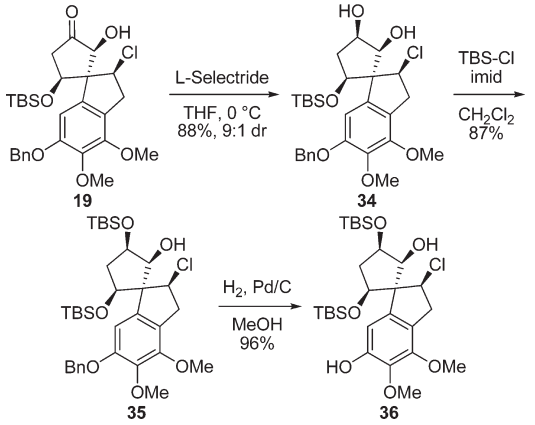
(48) We thank a reviewer for this suggestion.

(49) (a) Hartung, R. E.; Paquette, L. A. *Synthesis* **2005**, 3209. (b) Christol, H.; Vanel, R. *Bull. Soc. Chim. Fr.* **1968**, 1393.

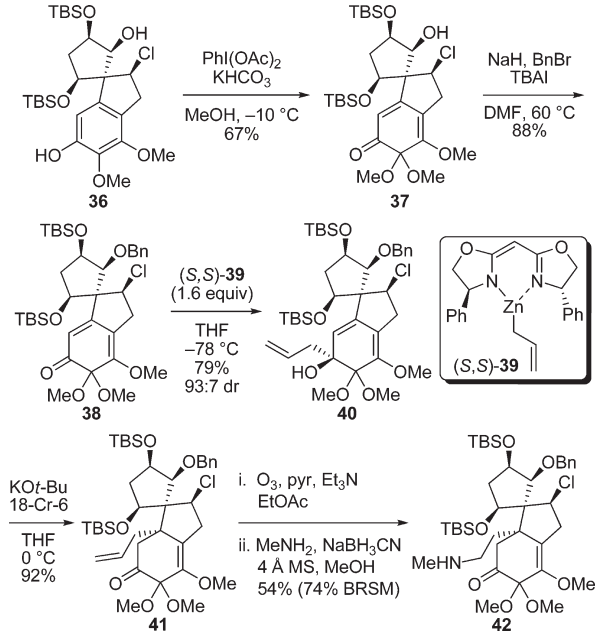
(50) For a review, see: Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383.

(51) Nakamura, M.; Hirai, A.; Sogi, M.; Nakamura, E. *J. Am. Chem. Soc.* **1998**, *120*, 5846.

SCHEME 9. Synthesis of Phenol 36



SCHEME 10. Preparation of Amine 42



effective in enantioselective allylations of achiral ketones related to **38**.[18a] We were pleased to discover that allylation of **38** with (*S*,*S*)-**39** proceeded in good yield (79%) and dr (93:7) to afford homoallylic alcohol **40**. Although an excess of **39** (1.6 equiv) was required to ensure a reasonable reaction rate with the bulky ketone, the pure bisoxazoline ligand could be reisolated from the reaction mixture.[52] The configuration of the newly formed stereocenter in alcohol **40** was tentatively assigned by considering the six-membered cyclic transition state for the asymmetric ketone allylation proposed by Nakamura and co-workers[51] (Figure 4). The dimethyl ketal of **38** likely occupies an equatorial position on the ring, which causes the sp^2 alkene carbon to reside in an axial position. The ability of the phenyl groups on the bisoxazoline ligand to avoid steric interactions with the substrate in the orientation shown leads to excellent facial selectivity. The stereochemical

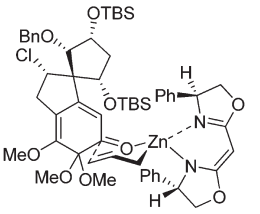
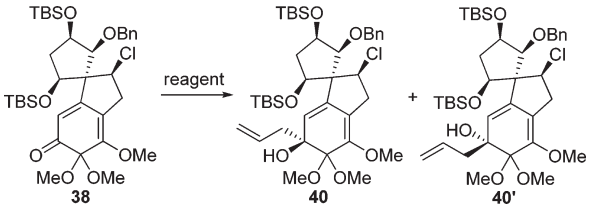


FIGURE 4. Proposed transition state for allylation of **38**.

TABLE 2. Allylations of Ketone 38



entry	reagent	yield (%)	**40**:**40′**
1	(*S*,*S*)-**39**	79	93:7
2	allylMgBr	88	70:30
3	(*R*,*R*)-**39**	70	13:87

assignment based on this reasoning was eventually confirmed by conversion of **40** into (−)-**1**.

To ascertain the degree of substrate-directed stereocontrol and determine the prospects for reagent control with **39** in a mismatched case, we performed two additional allylations of **38**. These experiments are described in Table 2 along with the allylation discussed above. The use of allylmagnesium bromide in place of (*S*,*S*)-**39** afforded a 70:30 mixture of **40** and its diastereomer **40′** (entry 2), thereby confirming our hypothesis regarding moderate levels of stereocontrol by the substrate. Interestingly, allylation with (*R*,*R*)-**39**, the enantiomeric Nakamura reagent, delivered **40′** as the major product in good yield and dr (entry 3). Thus, (*R*,*R*)-**39** is able to overcome the mismatched stereochemistry of **38**, albeit with slighty reduced yield and dr. The performance of the Nakamura reagent in this work and in our isohasubanan alkaloid synthesis[18a] demonstrates that its scope is not limited to the alkynyl ketones for which it was designed.[51] Studies to determine the types of ketones amenable to asymmetric allylation by **39** are in progress and will be the subject of a future report.

Exposure of **40** to KO*t*-Bu and 18-crown-6 triggered an anionic oxy-Cope rearrangement that produced ketone **41** in excellent yield (92%, Scheme 10). Notably, this reaction was capable of forming an extremely congested C−C bond at 0 °C. The facile nature of this process is likely a consequence of conjugation of the trisubstituted double bond with the methyl enol ether. Such conjugation has previously been noted to accelerate anionic oxy-Cope rearrangements.[53] The allylation−anionic oxy-Cope sequence accomplishes a formal conjugate addition of an allyl group to enone **38**. The direct 1,4-addition was not attempted due to discouraging results with model compounds.[54]

(52) The bisoxazoline ligand is obtained as a Zn complex after chromatography and can be decomplexed according to the procedure of Nakamura and co-workers: Nakamura, M.; Arai, M.; Nakamura, E. *J. Am. Chem. Soc.* **1995**, *117*, 1179.

(53) Gentric, L.; Hanna, I.; Huboux, A.; Zaghdoudi, R. *Org. Lett.* **2003**, *5*, 3631.

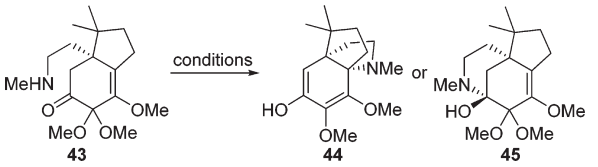
(54) Reeder, M. D. M.S. Thesis, Brigham Young University, **2004**.

We approached the next step, oxidative cleavage of **41** followed by reductive amination of the crude aldehyde, with some trepidation due to problems encountered in the model studies. Specifically, ozonolysis of a compound analogous to **41** was plagued by competitive oxidation of the methyl enol ether. Dihydroxylation was possible, but oxidative cleavage of the resulting diol was unsuccessful.[14] These challenges persisted, as treatment of **41** with $OsO_4/NaIO_4$ returned negligible quantities (ca. 10%) of the aldehyde. Similarly poor results were obtained from ozonolysis reactions conducted by bubbling O_3 through the reaction mixture. Numerous byproducts were generated, and it became apparent that a method of controlling the stoichiometry of O_3 was required. We were intrigued by a report from Wender and co-workers describing the use of standard solutions of O_3.[55] In the model system, we found EtOAc to be the most effective solvent for the ozonolysis.[14] Accordingly, we determined the concentration of a saturated solution of O_3 in EtOAc to be 0.007 M by titration with styrene.[55] Addition of 1.5 equiv of O_3 from this solution to a solution of **41** in EtOAc provided ca. 30% of the aldehyde, along with 30% of recovered **41**. Greater quantities of O_3 gave lower yields due to increased byproduct formation. Fortunately, a significant improvement was achieved by including pyridine in the reaction mixture. This additive has been shown to modulate the reactivity of O_3.[56] The best results (54% yield of amine **42**, 27% recovery of **41**) were obtained by adding 1.5 equiv of O_3 via standard solution to a solution of **41**, pyridine, and Et_3N in EtOAc, and then conducting the reductive amination in the same pot. Amine **42** and recovered alkene **41** were readily separable on SiO_2.

The cyclization of amine **42** to give the tetracyclic framework of acutumine was projected to occur via acid-promoted ionization of the dimethyl ketal and subsequent attack of the amine at the β-carbon of the resulting α,β-unsaturated oxonium ion intermediate.[57] In our synthesis of a model system representing the propellane core of **1**, we discovered that TMSOTf could mediate this reaction, affording moderate yields (50%) of the desired product.[14] Unfortunately, application of these conditions to the highly functionalized substrate **42** induced decomposition, and the desired tetracycle was only produced in trace amounts ($< 10\%$). Since we possessed limited quantities of **42**, we returned to the more readily available model compound **43** in order to develop alternative conditions for the cyclization (Table 3). In our prior investigation, we found that enol **44**, not the corresponding ketone, was produced by cyclization of **43**. We believe that the combination of a stabilizing intramolecular hydrogen bond in the enol and destabilizing steric interactions in the ketone are responsible for this phenomenon.[14]

Our study of the cyclization of **43** is summarized in Table 3. A brief survey of Brønsted acids (entries 1−4) showed that reasonable yields of **44** could be obtained with TFA at 0 °C (entry 2). Similar conditions led to an undesired rearrangement in our attempted synthesis of hasubanan alkaloids, producing unnatural compounds that we refer to as isohasubanan alkaloids.[18] These contrasting results reflect subtle differences in the structures of the acutumine and hasubanan alkaloids. Surpisingly, the use of HCl afforded low yields of hemiaminal **45** (entry 3). It is unclear why **45** was only detected under these conditions and not in any other reactions. Switching to the Lewis acid BCl_3 yielded promising results, and detailed optimization established the superiority of the conditions listed in entry 11. Interestingly, use of the solvent hexafluoroisopropanol (HFIP) without any added Lewis or Brønsted acid[58] resulted in modest yields of **44** (entries 13 and 14). However, substitution of HFIP for CH_2Cl_2 as solvent in the optimized BCl_3 conditions did not improve the yield further (cf. entries 11 and 15). In all cases, 4 Å MS were employed to suppress cleavage of the acid-sensitive methyl enol ether of **43**.

TABLE 3. Development of Cyclization Conditions in Model System



entry	conditions[a]	product[b]
1	TFA (5 equiv), CH_2Cl_2	**44** (31);
2	TFA (5 equiv), CH_2Cl_2, 0 °C	**44** (41);
3	HCl (2 equiv), MeOH	**45** (10);
4	HOAc (3 equiv), MeOH	**44** (12);
5	BCl_3 (1 equiv), CH_2Cl_2	**44** (19)[c]
6	BCl_3 (2 equiv), CH_2Cl_2	**44** (27);
7	BCl_3 (3 equiv), CH_2Cl_2	**44** (39);
8	BCl_3 (4 equiv), CH_2Cl_2	**44** (38);
9	BCl_3 (3 equiv), CH_2Cl_2, 0 °C	**44** (35);
10	BCl_3 (3 equiv), CH_2Cl_2, −15 °C	**44** (39);
11	BCl_3 (3 equiv), CH_2Cl_2, −40 °C	**44** (41);
12	BCl_3 (3 equiv), CH_2Cl_2, −78 °C	**44** (37);
13	HFIP,[d] 0 °C	**44** (27);
14	HFIP, −40 °C	**44** (31);
15	BCl_3 (3 equiv), HFIP, −40 °C	**44** (40);

[a]Reactions were conducted at room temperature in the presence of 4 Å MS unless otherwise indicated. [b]Percent yield is given in parentheses. [c]27% of **43** was recovered. [d]1,1,1,3,3,3-Hexafluoro-2-propanol.

TFA and BCl_3 emerged from this study as the reagents of choice for the key cyclization reaction. Accordingly, both were evaluated in the cyclization of amine **42**. We recognized that **42** was likely to be more acid-sensitive than the simpler compound **43**; consequently, we employed slightly milder conditions than were optimal in the model study. When **42** was exposed to TFA at −10 °C, the desired tetracycle **46** was detected by ^1H NMR and MS. Unfortunately, it was produced in low yield ($< 40\%$) and alongside an inseparable byproduct that was not identified. Fortunately, BCl_3 (1.5 equiv) at −40 °C afforded better results, as pure **46** could be isolated in 45% yield (Scheme 11). The modest outcome of this cyclization is likely a consequence of the congested nature of the C−N bond which is formed combined with the acid sensitivity of substrate **42**.

The elaboration of **46** into **1** commenced with TBAF-mediated cleavage of the two TBS ethers. The resulting diol was surprisingly unstable, so it was immediately converted into the isolable 1,3-diketone **47** by treatment with TPAP and NMO. Then, hydrogenolysis of the benzyl ether proceeded in

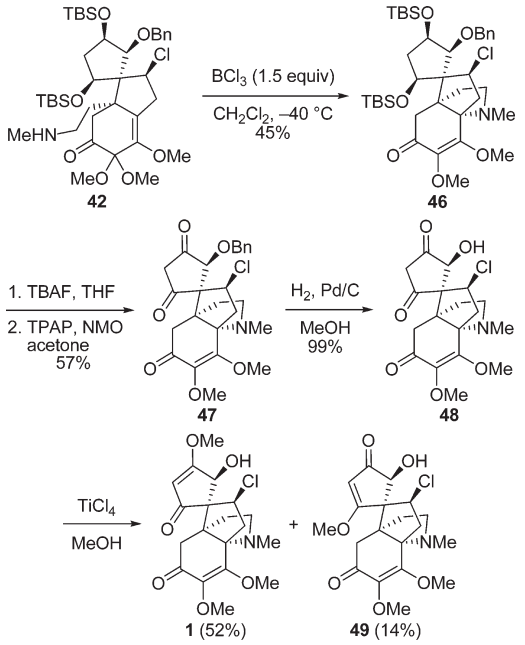
(55) Wender, P. A.; DeChristopher, B. A.; Schrier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 6658.

(56) (a) Donohoe, T. J.; Ironmonger, A.; Kershaw, N. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7314. (b) Slomp, G., Jr.; Johnson, J. L. *J. Am. Chem. Soc.* **1958**, *80*, 915.

(57) Yasui, Y.; Koga, Y.; Suzuki, K.; Matsumoto, T. *Synlett* **2004**, 615.

(58) Ratnikov, M. O.; Tumanov, V. V.; Smit, W. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9739.

SCHEME 11. Completion of Total Synthesis of 1



virtually quantitative yield without competitive reduction of the tetrasubstituted alkene or the alkyl chloride. This facile reaction delivered alcohol **48**, the immediate precursor to acutumine.

A multitude of protocols exist for the conversion of 1,3-diketones into β-keto enol ethers, encompassing basic,[59] Lewis acidic,[60] and neutral (CH_2N_2)[61] conditions. Nonetheless, we were unsure of the prospects for a regioselective transformation of **48** into **1**. The outcomes of O-methylations of asymmetric 1,3-diketones are difficult to predict, and equimolar mixtures of the two regioisomeric products are often produced.[61a] After considering the various procedures available, we were attracted to the method of Porta and co-workers, which employs catalytic quantities of $TiCl_4$ in MeOH. This protocol was modestly selective (ca. 3:1 ratio of products) for generation of the less hindered enol ether from an asymmetric cyclic 1,3-diketone.[60a] We were also mindful of the report by Danishefsky and co-workers of a regioselective methyl enol etherification with CH_2N_2,[61b] although the complete lack of selectivity observed by Pettus and Wang with this reagent[61a] provides a sobering contrast. Unfortunately, our experience resembled that of Pettus and Wang, as exposure of **48** to CH_2N_2 provided 40% of **1** along with 35% of its enol ether regioisomer **49**. However, switching to $TiCl_4$/MeOH yielded a more favorable 3.7:1 ratio in favor of **1**. The overall yield of this reaction (66%) was lower, but the isolated yield of **1** (52%) was greater. Accordingly, we employed the Porta methodology in our efforts. The synthetic sample of **1** produced by this route was identical to an authentic natural sample of acutumine as evidenced by spectroscopic and chromatographic techniques.

Conclusions

We have achieved the enantioselective total synthesis of (−)-acutumine (**1**). A first-generation approach to the spirocyclic subunit based on a 5-*exo* aryl radical cyclization with TEMPO trapping was unsuccessful, as the 6-*endo* pathway prevailed. However, this result paved the way for a successful second-generation strategy featuring a novel radical−polar crossover reaction for construction of the spirocycle. This cascade process comprised a 5-*exo* intramolecular conjugate addition of an aryl radical onto an enone acceptor, conversion of the resulting α-keto radical into an enolate, and hydroxylation of the enolate. Both the radical cyclization and enolate hydroxylation steps were highly stereoselective, and a single product was generated that possessed the requisite stereochemistry for conversion into **1**. The reaction was conducted under irradiation by a sunlamp, yet the ditin reagent that was required for aryl radical formation does not possess a chromophore. Thus, it is possible that the enone moiety of the substrate may function as a sensitizing agent. Alternatively, complexation of the aryl iodide with the ditin reagent may facilitate photolysis.

The tetracyclic framework of the natural product was then fashioned by annulation of a pyrrolidine ring onto the spirocycle. The annulation sequence consisted of a phenolic oxidation, a diastereoselective ketone allylation utilizing Nakamura's chiral allylzinc reagent, an anionic oxy-Cope rearrangement, a one-pot ozonolysis−reductive amination, and a Lewis acid promoted cyclization of an amine onto an α,β-unsaturated dimethyl ketal. Further studies of the asymmetric ketone allylation revealed the ability of the Nakamura reagent to control the stereochemistry of the reaction in a mismatched case. The successful cyclization conditions (BCl_3, CH_2Cl_2, −40 °C) were discovered by extensive optimization of a model reaction. Finally, elaboration of the tetracycle into **1** required four steps, including the $TiCl_4$-mediated regioselective methyl enol etherification of a 1,3-diketone. We are hopeful that the methods that were developed and refined in the course of this venture will find application in the synthesis of other complex molecules.

Experimental Section

α-Hydroxy Ketone 19. A solution of **20** (107 mg, 0.166 mmol) in anhydrous THF (1.5 mL) at 0 °C was treated with hexabutylditin (89 μL, 102 mg, 0.168 mmol) and triethylaluminum (1.0 M solution in THF, 490 μL, 0.49 mmol). The resultant mixture was irradiated at 0 °C with a 660 W sunlamp for 6 h (frequent addition of ice to the cooling bath was necessary to maintain this temperature). Then, 3-phenyl-2-(phenylsulfonyl)-oxaziridine[39] (ca. 0.5 M solution in THF, 1.53 mL, 0.765 mmol) was added to the mixture, and it was stirred at 0 °C (without irradiation) for 5 h, then at rt for 2 h. The resultant mixture was extracted with EtOAc (3 × 5 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 14 cm, 10−15% EtOAc in hexanes gradient elution) afforded **19** (52.7 mg, 0.0989 mmol, 59%) as a colorless oil: $[\alpha]^{25}_D$ +26 (*c* 0.23, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.53−7.32 (m, 6H), 5.06 (s, 2H), 4.82 (t, J = 7.2 Hz, 1H), 4.45 (t, J = 6.6 Hz, 1H), 4.25 (s, 1H), 3.90 (s, 3H), 3.84 (s, 3H), 2.99 (d, J = 6.9 Hz,

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1H), 2.91 (d, J = 6.6 Hz, 1H), 2.62 (d, J = 6.9 Hz, 1H), 2.02 (d, J = 7.2 Hz, 1H), 1.51 (br s, 1H), 0.93 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.5, 149.7, 149.6, 146.4, 142.5, 134.8, 127.8 (2C), 127.3, 126.4 (2C), 121.8, 103.4, 92.2, 72.1, 66.2, 64.2, 63.8, 63.1, 49.7, 42.7, 38.8, 22.2 (3C), 16.1, −4.9, −5.0; DEPT NMR ($CDCl_3$, 75 MHz) **C** 207.5, 149.7, 149.6, 146.4, 142.5, 134.8, 121.8, 64.2, 16.1; **CH** 127.8, 127.3, 126.4, 103.4, 92.2, 66.2, 49.7; **CH_2** 72.1, 42.7, 38.8; **CH_3** 63.8, 63.1, 22.2, −4.9, −5.0; 2D ^{1}H−^{1}H COSY NMR ($CDCl_3$, 500 MHz) 4.82/2.62 (s), 4.82/2.11 (s), 4.45/2.99 (s), 4.45/2.91 (s); 2D ^{1}H−^{13}C HMQC NMR ($CDCl_3$, 500 MHz) 7.53−7.32/127.8, 7.53−7.32/127.3, 7.53−7.32/126.4, 7.53−7.32/103.4, 5.06/72.1, 4.82/66.2, 4.45/49.7, 4.25/92.2, 3.90 and 3.84/63.8 and 63.1, 2.99/38.8, 2.91/38.8, 2.62/42.7, 2.11/42.7, 0.88/22.2, 0.13 and 0.11/−4.9 and −5.0; IR (film) ν_{max} 3012, 2955, 2878, 2857, 1728, 1471, 1356, 1251, 1134, 1087 cm^{-1}; HRMS (ESI) m/z 533.21177 (MH^+, $C_{28}H_{37}O_6ClSiH^+$ requires 533.21207).

The iodide **32** (6.9 mg, 0.011 mmol, 6.4%) and reduced compound **33** (3.0 mg, 0.0058 mmol, 3.5%) were also obtained. For **32**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.49−7.34 (m, 6H), 5.13 (s, 2H), 4.98−4.92 (m, 1H), 4.72−4.63 (m, 1H), 4.59 (s, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.00 (d, J = 6.6 Hz, 1H), 2.93 (d, J = 6.6 Hz, 1H), 2.65 (d, J = 6.6 Hz, 1H), 2.02 (d, J = 6.9 Hz, 1H), 0.89 (s, 9H), 0.14 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.1, 146.3, 146.2, 144.4, 139.1, 139.0, 120.8 (2C), 120.1 (2C), 119.5, 113.6, 91.4, 71.2, 67.1, 63.9, 63.5, 63.0, 53.2, 47.4, 41.1, 37.3, 22.0 (3C), 14.4, −4.4, −4.5; HRMS (ESI) m/z 643.11245 (MH^+, $C_{28}H_{36}O_5ClISiH^+$ requires 643.11380). For **33**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46−7.31 (m, 6H), 5.10 (s, 2H), 4.93−4.88 (m, 1H), 4.65 (t, J = 6.3 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 2.92 (d, J = 6.6 Hz, 1H), 2.85 (d, J = 6.6 Hz, 1H), 2.65 (d, J = 6.9 Hz, 1H), 2.49 (s, 1H), 2.05 (s, 1H), 2.00 (d, J = 6.9 Hz, 1H), 0.92 (s, 9H), 0.11 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 208.2, 145.4, 144.1, 143.8, 142.6, 139.8, 120.1 (2C), 118.8, 118.3 (2C), 114.4, 96.5, 73.0, 69.6, 65.5, 63.9, 62.7, 51.2, 40.6, 40.0, 39.2, 25.8 (3C), 17.6, −4.3, −4.4; HRMS (ESI) m/z 534.23974 ($M(NH_4)^+$, $C_{28}H_{37}O_5ClSi(NH_4)^+$ requires 534.24370).

(+)-(1*R*,2*S*,2′*S*,3*R*,5*S*)-6′-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-2′-chloro-4′,5′-dimethoxy-2′,3′-dihydrospiro[cyclopentane-1,1′-indene]-2,3-diol (34). A solution of **19** (150 mg, 0.281 mmol) in anhydrous THF (2 mL) at 0 °C under Ar was treated with L-Selectride (1.0 M solution in THF, 280 μL, 0.28 mmol). The resultant mixture was stirred at 0 °C for 1.5 h, then treated with satd aq NH_4Cl (1 mL), and warmed to rt. The mixture was extracted with EtOAc (3 × 3 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 2.5 cm × 11 cm, 20% EtOAc−hexanes elution) afforded **34** (132 mg, 0.247 mmol, 88%) as a pale yellow solid in 9:1 dr. A diastereomerically pure sample could be obtained after further purification: $[\alpha]^{25}_D$ +22.7 (c 1.39, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42−7.12 (m, 5H), 6.75 (s, 1H), 5.07 (s, 2H), 4.87 (dd, J = 11.1, 5.7 Hz, 1H), 4.27 (d, J = 6.6 Hz, 1H), 4.08 (br s, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.64 (br s, 1H), 3.56−3.38 (m, 2H), 3.06 (t, J = 12.0 Hz, 1H), 2.89 (dd, J = 12.6, 7.2 Hz, 1H), 2.03−1.98 (m, 1H), 1.70−1.61 (m, 1H), 0.88 (s, 9H), 0.21 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.6, 146.4, 146.3, 144.3, 139.1, 139.0, 120.8 (2C), 120.1, 119.5 (2C), 113.6, 73.5, 71.2, 67.2, 64.0, 63.5, 63.0, 53.2, 47.4, 41.1, 37.3, 23.9, 22.0 (3C), −4.4, −4.5; IR (film) ν_{max} 3548, 2911, 1626, 1450, 1219, 1091, 933 cm^{-1}; HRMS (ESI) m/z 557.20989 (MNa^+, $C_{28}H_{39}ClO_6SiNa^+$ requires 557.20966).

The *cis* relative stereochemistry of **34** was assigned based on the 6.6 Hz coupling constant of the two α-hydroxy hydrogens. This value is similar to coupling constants reported by Hartung and Paquette[49a] for related *cis* compounds (4.2−5.8 Hz) and differs markedly from the value reported by Christol and Vanel[49b] for a related *trans* compound (10 Hz). Additionally, molecular models of **20** demonstrate that approach of the reducing agent to the top (*re*) face of the carbonyl, which would afford the *trans* isomer, is hindered by the neighboring chloride substituent.

(+)-(1*R*,2*S*,2′*S*,3*R*,5*S*)-6′-(Benzyloxy)-3,5-bis(*tert*-butyldimethylsilyloxy)-2′-chloro-4′,5′-dimethoxy-2′,3′-dihydrospiro[cyclopentane-1,1′-inden]-2-ol (35). A solution of **34** (140 mg, 0.262 mmol) in anhydrous CH_2Cl_2 (5.0 mL) under Ar was treated with Et_3N (450 μL), then cooled to 0 °C. TBS-Cl (59 mg, 0.39 mmol, 1.5 equiv) was added portionwise to the mixture, and it was stirred at 0 °C for 2 h, then at rt for 1 h. The resultant mixture was diluted with EtOAc (5 mL), treated with satd aq NH_4Cl (3 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 2.5 cm × 10 cm, 7.5% EtOAc−hexanes elution) afforded **35** (148 mg, 0.228 mmol, 87%) as a light yellow oil: $[\alpha]^{25}_D$ +17 (c 1.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.49−7.27 (m, 5H), 6.54 (s, 1H), 5.07 (s, 2H), 4.67 (dd, J = 12.6, 7.2 Hz, 1H), 4.16 (d, J = 6.9 Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.71 (br s, 1H), 3.62−3.44 (m, 2H), 3.05 (t, J = 12.0 Hz, 1H), 2.70 (dd, J = 12.6, 7.5 Hz, 1H), 2.01−1.94 (m, 1H), 1.67−1.63 (m, 1H), 1.17 (s, 9H), 0.99 (s, 9H), 0.20 (s, 6H), 0.14 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.2, 160.4, 155.1, 151.8, 145.9, 145.6, 137.6 (2C), 136.9, 136.0 (2C), 133.7, 79.9, 79.5, 75.2, 72.6, 72.2, 70.3, 53.7, 51.8, 38.1, 34.1 (3C), 34.0 (3C), 33.2, 26.3, 17.1,−4.4 (2C), −4.5 (2C); IR (film) ν_{max} 3577, 2897, 1610, 1442, 989 cm^{-1}; HRMS (ESI) m/z 649.31418 (MH^+, $C_{34}H_{53}ClO_6Si_2H^+$ requires 649.31420).

(+)-(1*R*,2*S*,2′*S*,3*R*,5*S*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-2′-chloro-4′,5′-dimethoxy-2′,3′-dihydrospiro[cyclopentane-1,1′-indene]-2,6′-diol (36). A solution of **35** (148 mg, 0.228 mmol) in anhydrous MeOH (5.0 mL) was treated with 10% Pd/C (40 mg, 0.27 wt equiv). The resultant mixture was stirred at rt under H_2 (1 atm) for 4 h, then filtered through a plug of Celite (washed with CH_2Cl_2), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 8 cm, 10% EtOAc−hexanes elution) afforded **36** (123 mg, 0.220 mmol, 96%) as a pale yellow oil: $[\alpha]^{25}_D$ +27 (c 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.82 (s, 1H), 4.43 (dd, J = 12.6, 7.2 Hz, 1H), 4.21 (d, J = 6.9 Hz, 1H), 3.91 (s, 3H), 3.88−3.84 (br s, 1H), 3.84 (s, 3H), 3.63 (br s, 1H), 3.54−3.31 (m, 2H), 2.87 (t, J = 12.0 Hz, 1H), 2.66 (dd, J = 12.6, 7.2 Hz, 1H), 2.00−1.90 (m, 1H), 1.74−1.62 (m, 1H), 1.16 (s, 9H), 1.10 (s, 9H), 0.19 (s, 6H), 0.16 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.1, 142.8, 139.1, 133.2, 128.6, 128.1, 82.7, 75.8, 75.3, 69.5, 69.0, 66.5, 61.1, 40.8, 36.7, 25.8, 22.1 (6C), 13.8, −4.4 (2C), −4.5 (2C); IR (film) ν_{max} 3212, 1258, 1122, 1077 cm^{-1}; HRMS (ESI) m/z 559.26731 (MH^+, $C_{27}H_{47}ClO_6Si_2H^+$ requires 559.26725).

(−)-(1*R*,2*S*,2′*S*,3*R*,5*S*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-2′-chloro-2-hydroxy-4′,5′,5′-trimethoxy-2′,3′-dihydrospiro[cyclopentane-1,1′-inden]-6′(5′*H*)-one (37). A solution of **36** (98.0 mg, 0.175 mmol) in anhydrous CH_3OH (3.0 mL) was added to a mixture of $KHCO_3$ (30 mg, 0.35 mmol, 2.0 equiv), $PhI(OAc)_2$ (62 mg, 0.19 mmol, 1.1 equiv), and anhydrous CH_3OH (3.0 mL) at −10 °C under Ar. The resulting yellow−orange mixture was stirred for 10 min, diluted with CH_2Cl_2 (5 mL), and washed with brine (10 mL). The layers were separated, and the organic layer was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, 2.5 cm × 10 cm, 10% EtOAc−hexanes elution) afforded **37** (69.0 mg, 0.117 mmol, 67%) as a yellow oil: $[\alpha]^{25}_D$ −15 (c 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.25 (s, 1H), 4.55 (dd, J = 12.6, 7.5 Hz, 1H), 4.13 (d, J = 6.9 Hz, 1H), 3.98 (s, 3H), 3.61 (br s, 1H), 3.49−3.24 (m, 2H), 3.37 (s, 3H), 3.32 (s, 3H), 2.79 (t, J = 11.8 Hz, 1H), 2.58 (dd, J = 12.6, 7.5 Hz, 1H), 1.93−1.81 (m, 1H), 1.58−1.49 (m, 1H), 0.91 (s, 9H), 0.86 (s, 9H), 0.10 (s, 6H) 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.1, 142.8, 139.1, 133.2, 121.4, 117.7, 82.8, 69.9, 69.5, 69.0, 66.5, 61.1, 56.5, 56.4, 40.9, 37.7, 23.8, 22.1 (6C), 13.8, −4.4 (2C), −4.6 (2C); IR (film) ν_{max} 3337, 2450, 1755, 1233, 956 cm^{-1}; HRMS (ESI) m/z 606.30440 ($M(NH_4)^+$, $C_{28}H_{49}ClO_7Si_2(NH_4)^+$ requires 606.30436).

(−)-(1*R*,2*S*,2′*S*,3*R*,5*S*)-2-(Benzyloxy)-3,5-bis(*tert*-butyldimethylsilyloxy)-2′-chloro-4′,5′,5′-trimethoxy-2′,3′-dihydrospiro[cyclopentane-1,1′-inden]-6′(5′*H*)-one (38). A solution of **37** (110 mg, 0.187 mmol) in anhydrous DMF (1.5 mL) at rt under Ar was treated with NaH (60% dispersion in mineral oil, 7.6 mg, 4.6 mg NaH, 0.19 mmol), tetrabutylammonium iodide (70 mg, 0.19 mmol), and benzyl bromide (23 μL, 32.9 mg, 0.192 mmol). The resultant brown solution was stirred at 60 °C for 5 h, cooled to rt, diluted with CH_2Cl_2 (2 mL), and washed with brine (2 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (5 × 3 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 cm × 12 cm, 1% Et_3N in 5% EtOAc−hexanes elution) afforded **38** (111 mg, 0.163 mmol, 88%) as a brown oil: $[\alpha]^{25}_D$ −21 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.42−7.18 (m, 5H), 6.39 (s, 1H), 5.20 (s, 2H), 4.99 (dd, *J* = 12.6, 7.5 Hz, 1H), 4.76−4.72 (m, 1H), 3.92 (s, 3H), 3.63−3.46 (m, 2H), 3.56 (s, 3H), 3.51 (s, 3H), 3.14 (t, *J* = 11.8 Hz, 1H), 2.77 (dd, *J* = 12.6, 7.5 Hz, 1H), 1.83−1.71 (m, 1H), 1.49−1.38 (m, 1H), 0.98 (s, 9H), 0.97 (s, 9H); 0.089 (s, 6H), 0.086 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 192.7, 150.3, 145.1, 141.3, 135.4, 126.6 (2C), 126.0, 125.4 (2C), 123.1, 107.4, 72.1, 71.5, 71.0, 69.5, 66.0, 59.2, 59.0, 55.1, 43.4, 39.6, 27.8, 24.1 (3C), 24.0 (3C), 16.3 (2C), −4.4 (2C), −4.5 (2C); IR (film) ν_{max} 3284, 2566, 1727 cm^{-1}; HRMS (ESI) *m*/*z* 679.32488 (MH^+, $C_{35}H_{55}ClO_7Si_2H^+$ requires 679.32476).

(−)-(1*R*,2*S*,2′*S*,3*R*,5*S*,6′*S*)-6′-allyl-2-(benzyloxy)-3,5-bis(*tert*-butyldimethylsilyloxy)-2′-chloro-4′,5′,5′-trimethoxy-2′,3′,5′,6′-tetrahydrospiro[cyclopentane-1,1′-inden]-6′-ol (40). A solution of bis((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)methane[62] (76 mg, 0.24 mmol) and 2,2′-dipyridyl (2 crystals) in anhydrous THF (200 μL) at 0 °C under Ar was treated dropwise with *n*-BuLi (1.6 M in hexanes, 250 μL, 0.40 mmol) until the mixture turned a reddish-brown color. The solution was warmed to rt and stirred for 1 h, then treated dropwise with allylzinc bromide (1.0 M in THF, 240 μL, 0.24 mmol), and cooled to −78 °C. A solution of ketone **38** (95 mg, 0.14 mmol) in anhydrous THF (220 μL) was added dropwise, and the resultant mixture was stirred at −78 °C under Ar for 1 h. The reaction was quenched by the addition of MeOH−H_2O (1:1, 1 mL), and the mixture was extracted with Et_2O (3 × 1 mL). The combined organic layers were washed with NaOH (0.5 M, 1 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 2:23:75 Et_3N−EtOAc−hexanes elution) afforded **40** (79 mg, 0.11 mmol, 93:7 dr, 79%) as a colorless oil: $[\alpha]^{25}_D$ −36 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.47−7.31 (m, 5H), 6.37−6.27 (m, 1H), 6.21 (s, 1H), 5.24 (dd, *J* = 12.3, 7.2 Hz, 1H), 5.09 (s, 2H), 4.93−4.79 (m, 2H), 4.65 (d, *J* = 6.9 Hz, 1H), 3.82 (s, 3H), 3.47−3.27 (m, 3H), 3.41 (s, 3H), 3.37 (s, 3H), 3.09 (t, *J* = 12.0 Hz, 1H), 2.74 (dd, *J* = 12.3, 7.2 Hz, 1H), 1.85−1.77 (m, 1H), 1.73−1.65 (m, 1H), 1.57−1.53 (m, 1H), 1.50−1.37 (m, 1H), 0.91 (s, 9H), 0.85 (s, 9H), 0.11 (s, 6H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.3, 145.1, 141.3, 140.9, 135.4, 126.7 (2C), 126.1, 125.5 (2C), 123.3, 123.2, 107.4, 73.8, 72.1, 71.5, 71.0, 69.1, 65.4, 59.1, 59.0, 55.5, 48.0, 43.1, 39.6, 27.9, 24.1 (3C), 24.0 (3C), 16.4 (2C), −4.4 (2C), −4.5 (2C); IR (film) ν_{max} 3087, 2991, 2836, 1629, 1467, 933 cm^{-1}; HRMS (ESI) *m*/*z* 721.37162 (MH^+, $C_{38}H_{61}ClO_7Si_2H^+$ requires 721.37171).

(−)-(1*R*,2*S*,2′*S*,3*R*,5*S*,7a′*R*)-7a′-Allyl-2-(benzyloxy)-3,5-bis(*tert*-butyldimethylsilyloxy)-2′-chloro-4′,5′,5′-trimethoxy-2′,3′,7′,7a′-tetrahydrospiro[cyclopentane-1,1′-inden]-6′(5′*H*)-one (41). A mixture of 18-crown-6 (34 mg, 0.13 mmol), KO*t*-Bu (14 mg, 0.13 mmol), and anhydrous THF (700 μL) at 0 °C under Ar was stirred for 15 min, then treated with a solution of **40** (30.0 mg, 0.0416 mmol) in anhydrous THF (150 μL, added dropwise over 3 min). The resulting mixture was stirred at 0 °C under Ar for 1 h. The reaction was quenched by the addition of H_2O (1 mL), and the mixture was diluted with Et_2O (2 mL). The layers were separated, and the organic layer was dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, 1% Et_3N in 10% EtOAc−hexanes elution) afforded **41** (27.5 mg, 0.0381 mmol, 92%) as a colorless oil: $[\alpha]^{25}_D$ −22 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.52−7.34 (m, 5H), 5.88−5.76 (m, 1H), 5.27 (dd, *J* = 12.2, 7.0 Hz, 1H), 5.20 (s, 2H), 5.00−4.88 (m, 2H), 4.60 (d, *J* = 6.9 Hz, 1H), 3.91 (s, 3H), 3.58−3.42 (m, 2H), 3.50 (s, 3H), 3.45 (s, 3H), 3.10 (t, *J* = 11.8 Hz, 1H), 2.98 (d, *J* = 14.7 Hz, 1H), 2.72 (dd, *J* = 12.2, 7.0 Hz, 1H), 2.56 (d, *J* = 15.0 Hz, 1H), 1.89−1.81 (m, 1H), 1.78−1.69 (m, 1H), 1.67−1.62 (m, 1H), 1.58−1.51 (m, 1H). 0.97 (s, 9H), 0.94 (s, 9H), 0.10 (s, 6H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 192.5, 147.7, 142.5, 138.8, 132.8, 124.2 (2C), 123.5, 122.9 (2C), 120.7, 104.8, 71.1, 69.6, 68.9, 68.4, 66.6, 56.6, 56.4, 52.9, 49.8, 41.2, 40.5, 37.0, 36.3, 25.3, 21.5 (3C), 21.4 (3C), 13.9 (2C), −5.0 (2C), −5.1 (2C); IR (film) ν_{max} 3055, 2978, 2844, 1782, 1631, 1423, 1012, 941 cm^{-1}; HRMS (ESI) *m*/*z* 721.37180 (MH^+, $C_{38}H_{61}ClO_7Si_2H^+$ requires 721.37171).

(−)-(1*R*,2*S*,2′*S*,3*R*,5*S*,7a′*R*)-2-(Benzyloxy)-3,5-bis(*tert*-butyldimethylsilyloxy)-2′-chloro-4′,5′,5′-trimethoxy-7a′-(2-(methylamino)-ethyl)-2′,3′,7′,7a′-tetrahydrospiro [cyclopentane-1,1′-inden]-6′(5′*H*)-one (42). A saturated solution of O_3 in EtOAc was prepared by bubbling ozone through EtOAc at −78 °C for 10 min. The concentration was determined to be 0.007 M as measured by titration with styrene.[55] Then, a solution of **41** (27 mg, 0.037 mmol), pyridine (10 μL), and Et_3N (16.0 μL, 11.6 mg, 0.115 mmol, 3.1 equiv) in EtOAc (0.5 mL) was cooled to −40 °C. A portion of the previously prepared solution of O_3 in EtOAc (0.007 M, 8 mL, 0.056 mmol, 1.5 equiv), which was precooled to −78 °C, was then added to this solution. The resultant mixture was stirred at −78 °C for 5 min, then diluted with anhydrous MeOH (1.0 mL) and treated with powdered 4 Å molecular sieves (30 mg) and CH_3NH_2 (2.0 M in MeOH, 76 μL, 0.15 mmol, 4.1 equiv). This mixture was stirred at rt under Ar for 30 min, then treated with $NaBH_3CN$ (4.8 mg, 0.076 mmol) and stirred for 16 h. It was then diluted with EtOAc (2 mL) and washed with aq KOH (10 M, 1 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 2 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (SiO_2, 1% Et_3N in 15−20% EtOAc−hexanes gradient elution) afforded recovered **41** (7.3 mg, 27% recovery) and **42** (15 mg, 0.020 mmol, 54%, 74% based on recovered **41**) as a yellow oil: $[\alpha]^{25}_D$ −25 (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.52−7.32 (m, 5H), 5.05 (s, 2H), 4.83 (dd, *J* = 12.0, 6.9 Hz, 1H), 4.61 (d, *J* = 6.9 Hz, 1H), 4.02 (s, 3H), 3.87−3.73 (m, 2H), 3.62 (s, 3H), 3.57 (s, 3H), 3.06 (t, *J* = 11.8 Hz, 1H), 2.97 (s, 3H), 2.71−2.62 (m, 2H), 2.38 (dd, *J* = 12.2, 7.0 Hz, 1H), 2.28 (d, *J* = 15.0 Hz, 1H), 2.23 (br s, 1H), 2.18−2.13 (m, 1H), 2.00 (d, *J* = 15.0 Hz, 1H), 1.69−1.61 (m, 1H), 1.44−1.38 (m, 1H), 1.35−1.28 (m, 1H), 0.87 (s, 9H), 0.81 (s, 9H), 0.10 (s, 6H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.1, 152.4, 147.1, 137.4, 128.8 (2C), 128.1, 127.5 (2C), 109.4, 75.1, 74.1, 73.6, 73.0, 71.2, 61.2, 61.0, 54.1, 50.0, 47.0, 45.9, 45.1, 41.7, 40.9, 39.2, 29.9, 26.1 (3C), 26.0 (3C), 18.2 (2C), −4.5 (2C), −5.0 (2C); IR (film) ν_{max} 3125, 2923, 2810, 1741, 1633, 1420, 1208, 1138, 982 cm^{-1}; HRMS (ESI) *m*/*z* 760.38014 (MNa^+, $C_{38}H_{64}ClNO_7Si_2Na^+$ requires 760.38021).

Tetracycle (−)-46. A mixture of **42** (15 mg, 0.020 mmol), 4 Å MS (80 mg), and anhydrous CH_2Cl_2 (2.0 mL) was stirred at rt under Ar for 10 min, then cooled to −40 °C. Next, BCl_3 (1.0 M in CH_2Cl_2, 30 μL, 0.030 mmol, 1.5 equiv) was added dropwise, and the resultant mixture was stirred at −40 °C under Ar for 18 h, then concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 2:30:68 Et_3N−EtOAc−hexanes elution), affording **46** (6.4 mg, 0.0091 mmol, 45%) as a colorless oil: $[\alpha]^{25}_D$ −79 (*c* 1.2, $CHCl_3$); ^1H NMR (pyridine-d_5, 500 MHz) δ 7.44−7.41 (m, 3H), 7.36−7.33 (m, 2H), 5.25 (dd, *J* = 12.2, 6.8 Hz, 1H), 5.12 (s, 2H), 4.80 (d, *J* = 7.0 Hz, 1H), 4.14 (s, 3H), 3.84 (s, 3H), 3.50−3.44 (m, 1H), 3.41−3.36 (m, 1H), 3.20 (t, *J* = 12.0 Hz, 1H), 3.11 (d,

(62) Hall, J.; Lehn, J.-M.; DeCian, A.; Fischer, J. *Helv. Chim. Acta* **1991**, *74*, 1.

J = 15.5 Hz, 1H), 2.75−2.69 (m, 3H), 2.61 (d, J = 15.5 Hz, 1H), 2.52−2.47 (m, 1H), 2.46 (s, 3H), 1.71−1.68 (m, 1H), 1.55−1.50 (m, 1H), 1.46−1.40 (m, 1H), 0.96 (s, 9H), 0.92 (s, 9H), 0.26 (s, 3H), 0.22 (s, 3H), 0.13 (s, 6H); ^{13}C NMR (pyridine-d_5, 125 MHz) δ 192.0, 158.8, 142.3, 138.1, 129.9 (2C), 129.2, 128.4 (2C), 76.2, 75.8, 75.3, 74.2, 72.0, 67.4, 59.5, 59.2, 56.9, 52.3, 50.8, 46.3, 44.0, 40.5, 37.6, 35.4, 30.0 (3C), 29.8 (3C), 20.0 (2C), −4.1 (2C), −4.2 (2C); IR (film) ν_{max} 3209, 2974, 2795, 1763, 1651, 1402, 1265, 912 cm^{-1}; HRMS (ESI) m/z 706.37199 (MH^+, $C_{37}H_{60}ClNO_6Si_2H^+$ requires 706.37205).

1,3-Diketone (−)-47. A solution of **46** (8.7 mg, 0.012 mmol) in anhydrous THF (100 μL) at 0 °C under Ar was treated with TBAF (1.0 M in THF, 27 μL, 0.027 mmol, 2.2 equiv) in one portion. The resulting mixture was stirred at 0 °C for 20 min. The reaction was quenched by the addition of ice water (0.5 mL), and the mixture was extracted with cold CH_2Cl_2 (cooled in ice bath, 3 × 0.5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo in an ice bath. The unstable crude diol was dissolved in acetone (0.5 mL) at 0 °C, and then 4 Å MS (50 mg), NMO (4.2 mg, 0.036 mmol), and TPAP (0.4 mg, 0.001 mmol) were added in order to the solution. The resulting mixture was stirred at 0 °C under Ar for 30 min, then slowly warmed to rt over 1 h and stirred at rt for 1 additional h. It was then filtered through a plug of SiO_2 (rinsed with 5 mL EtOAc), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 1% Et_3N in 2% MeOH−CH_2Cl_2 elution) afforded **47** (3.3 mg, 0.0070 mmol, 57%) as a white solid: $[\alpha]^{25}_D$ −122 (c 0.7, CH_2Cl_2); ^{1}H NMR (pyridine-d_5, 500 MHz) δ 7.46−7.42 (m, 3H), 7.39−7.37 (m, 2H), 5.20 (dd, J = 12.0, 6.5 Hz, 1H), 5.02 (s, 2H), 4.87 (s, 1H), 4.10 (s, 3H), 3.92 (d, J = 14.0 Hz, 1H), 3.80 (s, 3H), 3.74 (d, J = 14.0 Hz, 1H), 3.16 (t, J = 12.5 Hz, 1H), 3.07 (d, J = 16.0 Hz, 1H), 2.70−2.63 (m, 3H), 2.55 (d, J = 15.5 Hz, 1H), 2.45−2.41 (m, 1H), 2.40 (s, 3H), 1.65−1.62 (m, 1H); ^{13}C NMR (pyridine-d_5, 125 MHz) δ 202.8, 201.4, 193.3, 160.2, 143.6, 139.4, 131.6 (2C), 130.9, 130.3 (2C), 73.4, 71.9, 71.2, 69.1, 60.9, 60.6, 59.3, 58.3, 52.1, 47.7, 46.9, 41.9, 39.0, 36.8; IR (film) ν_{max} 3024, 2931, 2795, 1825, 1633, 1429, 1176, 955 cm^{-1}; HRMS (ESI) m/z 474.16785 (MH^+, $C_{25}H_{28}ClNO_6H^+$ requires 474.16779).

Alcohol (−)-48. To a solution of **47** (3.0 mg, 0.0063 mmol) in anhydrous MeOH (1.0 mL) under Ar was added 10% Pd/C (10 mg, 3.3 wt equiv). The resulting mixture was stirred at rt under H_2 (1 atm) for 2 h, then filtered through a plug of Celite (washed with CH_2Cl_2), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 8 cm, 5% MeOH−CH_2Cl_2 elution) afforded **48** (2.4 mg, 0.0063 mmol, 99%) as a pale yellow oil: $[\alpha]^{25}_D$ −135 (c 0.6, CH_2Cl_2); ^{1}H NMR (pyridine-d_5, 500 MHz) δ 8.66 (br s, 1H), 5.30 (dd, J = 12.0, 6.5 Hz, 1H), 5.13 (s, 1H), 4.14 (s, 3H), 4.03 (d, J = 14.0 Hz, 1H), 3.83 (s, 3H), 3.76 (d, J = 14.0 Hz, 1H), 3.26 (t, J = 12.2 Hz, 1H), 3.17 (d, J = 15.5 Hz, 1H), 2.82−2.74 (m, 3H), 2.65 (d, J = 15.5 Hz, 1H), 2.55−2.52 (m, 1H), 2.50 (s, 3H), 1.76−1.73 (m, 1H); ^{13}C NMR (pyridine-d_5, 125 MHz) δ 203.1. 201.7, 194.1, 160.9, 140.2, 72.9, 71.7, 69.3, 60.2, 59.9, 56.8, 55.5, 53.2, 48.9, 46.1, 42.0, 38.4, 36.4; IR (film) ν_{max} 3054, 2832, 1836, 1477, 1201, 934 cm^{-1}; HRMS (ESI) m/z 406.10270 (MNa^+, $C_{18}H_{22}ClNO_6Na^+$ requires 406.10279).

(−)-Acutumine (1). $TiCl_4$ (0.04 M solution in CH_2Cl_2, 20 μL, 0.0008 mmol) was added to a solution of **48** (2.0 mg, 0.0052 mmol) in anhydrous MeOH (100 μL). The solution was stirred at rt for 15 min, then treated with Et_3N (4 μL, 2.9 mg, 0.029 mmol) and stirred at rt for 45 min. The mixture was concentrated in vacuo, and the residue was purified by flash chromatography (SiO_2, 1.5 × 6 cm, 1% Et_3N in 5−15% MeOH−CH_2Cl_2 gradient elution), affording **1** (1.1 mg, 0.0027 mmol, 52%) and enol ether regioisomer **49** (0.3 mg, 0.00075 mmol, 14%). For **1**: white film, $[\alpha]^{25}_D$ −171 (c 0.81, pyridine), lit.[2b] $[\alpha]^{25}_D$ −206 (c 0.69, pyridine); ^{1}H NMR (pyridine-d_5, 500 MHz) δ 8.47 (br, s, 1H), 5.61 (s, 1H), 5.20 (dd, J = 11.8, 6.8 Hz, 1H), 5.03 (s, 1H), 4.04 (s, 3H), 3.80 (s, 3H), 3.73 (s, 3H), 3.16 (t, J = 12.0 Hz, 1H), 3.07 (d, J = 15.5 Hz, 1H), 2.69−2.63 (m, 3H), 2.54 (d, J = 15.5 Hz, 1H), 2.45−2.42 (m, 1H), 2.39 (s, 3H), 1.65−1.62 (m, 1H); ^{13}C NMR (pyridine-d_5, 125 MHz) δ 201.3, 192.8, 188.9, 159.7, 138.9, 105.5, 72.9, 70.7, 68.3, 60.4, 60.1, 58.8, 57.8, 53.2, 51.6, 47.2, 41.4, 38.5, 36.3; IR (film) ν_{max} 3410, 2899, 2817, 1655, 1641, 1364, 1205, 1079, 935 cm^{-1}; HRMS (ESI) m/z 398.13655 (MH^+, $C_{19}H_{24}ClNO_6H^+$ requires 398.13649).

For **49**: white film, $[\alpha]^{25}_D$ −112 (c 0.3, pyridine); ^{1}H NMR (pyridine-d_5, 500 MHz) δ 8.40 (br, s, 1H), 5.32 (s, 1H), 5.16 (dd, J = 12.0, 7.0 Hz, 1H), 4.94 (s, 1H), 4.07 (s, 3H), 3.74 (s, 3H), 3.57 (s, 3H), 3.13 (t, J = 12.5 Hz, 1H), 3.02 (d, J = 16.5 Hz, 1H), 2.67−2.60 (m, 3H), 2.48 (d, J = 15.5 Hz, 1H), 2.43−2.38 (m, 1H), 2.36 (s, 3H), 1.62−1.60 (m, 1H); HRMS (ESI) m/z 398.13664 (MH^+, $C_{19}H_{24}ClNO_6H^+$ requires 398.13649).

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Supporting Information Available: Experimental procedures and characterization data for new compounds not described in the Experimental Section, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.