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Synthesis of the Core Structure of Acutumine

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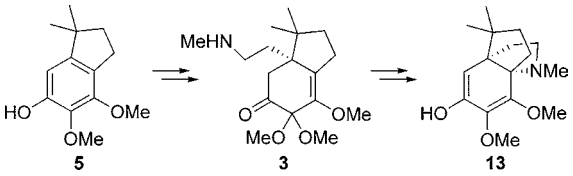
ABSTRACT



The tricyclic core of the bioactive natural product acutumine has been synthesized. Key steps include an oxidative phenolic coupling to form a masked *o*-benzoquinone, an anionic oxy-Cope rearrangement to construct an all-carbon quaternary center, and a Michael-type cyclization to form an amine-bearing quaternary carbon. The target compound exists in solution as an enol, in contrast to related compounds that are ketones. A model explaining these observations is presented.

Acutumine (**1**, Figure 1) is a tetracyclic alkaloid isolated from the Asian vine *Menispermum dauricum*.[1] Recently, **1** has been noted to possess both selective T-cell cytotoxicity[2] and antiamnesic properties.[3] Structurally, **1** is distinguished by the presence of a neopentylic secondary chloride in addition to three contiguous quaternary stereocenters, two of which are all-carbon quaternary stereocenters.[4] Although the combination of interesting biological activity with challenging structural motifs renders **1** a worthy target, to the best of our knowledge no synthetic studies toward **1** or related alkaloids have been reported. Herein, we disclose our initial efforts toward the total synthesis of acutumine, which have resulted in the construction of the tricyclic core structure of this molecule. Additionally, we document the tautomeric properties of our synthesized compounds, which differ from those of the natural product.

To focus on the development of chemistry suitable for the construction of the tricyclic core of **1**, we selected compound **2**, which lacks both the oxygenated spirocyclopentenone ring and the secondary chloride, as our first target structure. Our retrosynthetic analysis of **2** is depicted in Scheme 1. The recognition that the highly oxygenated cyclohexenone ring could be derived from an aromatic precursor guided our planning from the outset. Disconnection of the pyrrolidine

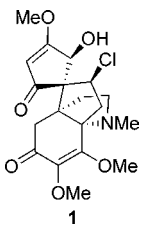


Figure 1. Acutumine.

(1) (a) Tomita, M.; Okamoto, Y.; Kikuchi, T.; Osaki, K.; Nishikawa, M.; Kamiya, K.; Sasaki, Y.; Matoba, K.; Goto, K. *Chem. Pharm. Bull.* **1971**, *19*, 770. (b) Tomita, M.; Okamoto, Y.; Kikuchi, T.; Osaki, K.; Nishikawa, M.; Kamiya, K.; Sasaki, Y.; Matoba, K.; Goto, K. *Tetrahedron Lett.* **1967**, 2421. (c) Tomita, M.; Okamoto, Y.; Kikuchi, T.; Osaki, K.; Nishikawa, M.; Kamiya, K.; Sasaki, Y.; Matoba, K.; Goto, K. *Tetrahedron Lett.* **1967**, 2425. (d) Goto, K.; Sudzuki, H. *Bull. Chem. Soc. Jpn.* **1929**, *4*, 220.

(2) Yu, B.-W.; Chen, J.-Y.; Wang, Y.-P.; Cheng; K.-F.; Li, X.-Y.; Qin, G.-W. *Phytochemistry* **2002**, *61*, 439.

(3) Qin, G.-W.; Tang, X.-C.; Lestage, P.; Caignard, D.-H.; Renard, P. PCT Int. Appl. WO 2004000815, 2003.

(4) (a) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (b) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (c) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688. (d) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (e) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (f) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037.

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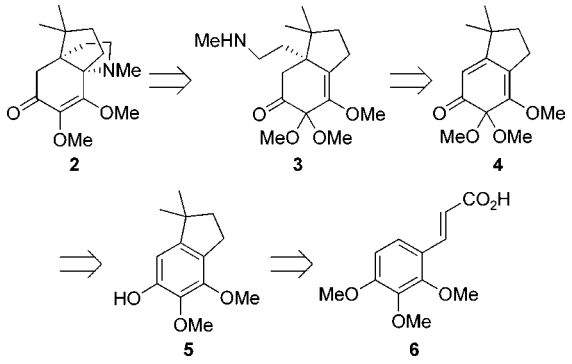
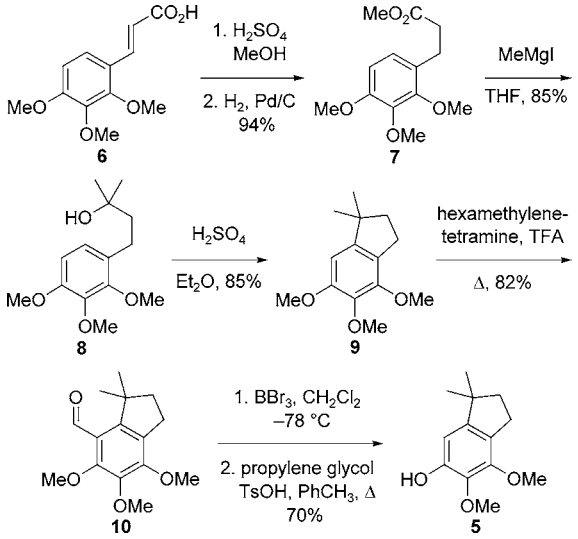
Scheme 1. Retrosynthesis of **2**



ring of **2** affords α,*β*-unsaturated ketal **3**, which could be expected to undergo a Michael-type cyclization under the influence of a suitable Lewis acid.[5] Removal of the ethylamino side chain of **3** reveals masked *o*-benzoquinone[6] **4** as an intermediate in our route. In the synthetic direction, conversion of **4** into **3** would enlist the anionic oxy-Cope rearrangement[7] to install the congested all-carbon quaternary stereocenter that is adjacent to another quaternary carbon.[8] Ketal **4** can be derived from indan **5** via a hypervalent-iodine-mediated oxidative phenolic coupling reaction.[9] Finally, we anticipated that **5** could be synthesized from commercially available *trans*-2,3,4-trimethoxycinnamic acid (**6**) by means of a relatively straightforward sequence.

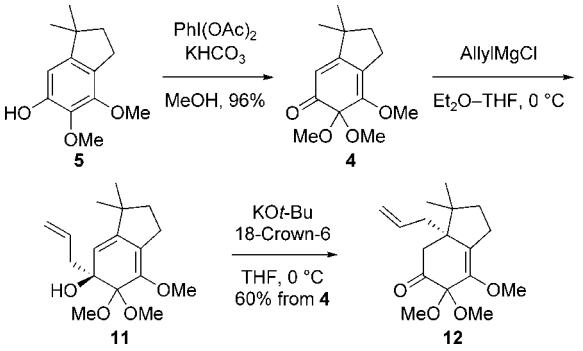
Our synthesis commenced as outlined in Scheme 2. Fischer esterification of **6** and hydrogenation of the resultant methyl ester afforded **7**. Treatment of **7** with excess (4 equiv) methylmagnesium iodide provided tertiary alcohol **8**, which cyclized upon exposure to acid,[10] giving trimethoxyindan **9** in 85% yield. Conversion of **9** into the oxidative phenolic coupling precursor **5** required the regioselective scission of one of the three methyl ethers. To accomplish this task, we used a strategy published by Tanaka and Wakamatsu.[11] Thus, **9** was formylated, and the derived aldehyde **10** underwent selective cleavage of the *o*-formyl methyl ether promoted by BBr_3. Deformylation of the intermediate phenol was accomplished by propylene glycol and TsOH, delivering phenol **5** in 70% yield from **10**. An X-ray crystal structure of **5** unambiguously established the demethylation regioselectivity.[12]

Scheme 2. Synthesis of Oxidative Coupling Precursor **5**



With phenol **5** in hand, we were ready to examine its oxidative dearomatization and subsequent installation of the vicinal quaternary stereocenters. The oxidative phenolic coupling proceeded smoothly with $PhI(OAc)_2$ under conditions reported by Liao,[13] affording masked *o*-benzoquinone **4** in 96% yield (Scheme 3). Although nucleophiles in these

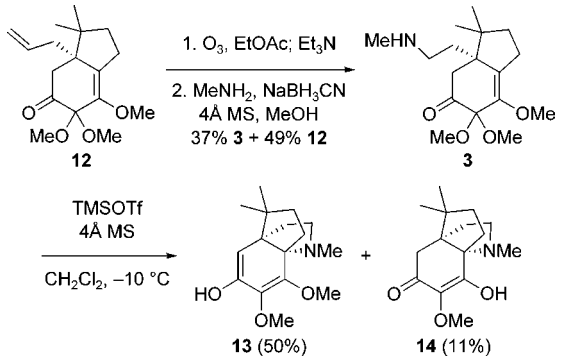
Scheme 3. Dearomatization of **5** and Conversion into **12**



hypervalent-iodine-mediated processes normally attack the carbon *para* to the phenol moiety,[6] the presence of the *o*-methoxy group directs the reaction to this site instead.[14] Subsequent 1,2-addition to the ketone of **4** was accomplished by means of allylmagnesium chloride, smoothly delivering tertiary alcohol **11**. Interestingly, attempts to carry out this reaction with allylmagnesium bromide resulted in rearomatization of **4** to form **5**, demonstrating a delicate balance between the two competing reaction pathways.[15] Fortunately, exposure of **11** to potassium *tert*-butoxide and 18-crown-6 at 0 °C provided ketone **12** in good yield. Notably, the anionic oxy-Cope rearrangement successfully installed an all-

(5) Yasui, Y.; Koga, Y.; Suzuki, K.; Matsumoto, T. *Synlett* **2004**, 615.
(6) Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383.
(7) (a) Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971. (b) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765.
(8) The generation of vicinal quaternary stereocenters via [3,3]-sigmatropic rearrangements was pioneered by Meyers: Lemieux, R. M.; Meyers, A. I. *J. Am. Chem. Soc.* **1998**, *120*, 5453. For a review on the construction of contiguous all-carbon quaternary stereocenters in natural products synthesis, see: Peterson, E. A.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11943.
(9) Kita, Y.; Tohma, H.; Kikuchi, K.; Inagaki, M.; Yakura, T. *J. Org. Chem.* **1991**, *56*, 435.
(10) Blum, R.; Giovannini, E.; Hengartner, U.; Vallat, G. *Helv. Chim. Acta* **2002**, *85*, 1827.
(11) Tanaka, M.; Ohshima, T.; Mitsuhashi, H.; Maruno, M.; Wakamatsu, T. *Tetrahedron* **1995**, *51*, 11693.
(12) Details are provided in Supporting Information.
(13) Yen, C.-F.; Peddinti, R. K.; Liao, C.-C. *Org. Lett.* **2000**, *2*, 2909.
(14) For examples, see ref 6 and the work of Liao: Hou, H.-F.; Peddinti, R. K.; Liao, C.-C. *Org. Lett.* **2002**, *4*, 2477.

Scheme 4. Completion of the Synthesis of **2**



carbon quaternary stereocenter vicinal to another congested quaternary carbon.[16]

To complete the tricyclic core of **1**, it remained for us to construct the pyrrolidine ring via C−N bond formation. Thus, the terminal olefin of **12** was converted into a secondary amine by a two-step sequence of ozonolysis followed by reductive amination with $MeNH_2$ (Scheme 4). While the reductive amination proceeded without complication, the ozonolysis was challenging as a result of competitive oxidation of the tetrasubstituted alkene. The most efficient protocol entailed conducting the ozonolysis in EtOAc and halting the reaction prior to completion.[17] The resulting mixture of **12** and the derived aldehyde (ca. 1:1) was free of overoxidized compounds and could be subjected to reductive amination without purification. Subsequent chromatography afforded pure **3** (37% over 2 steps; 73% based on recovered **12**) and **12** (49%), which could be resubjected to ozonolysis. The alternative method of dihydroxylation−oxidative cleavage was plagued by the sluggishness of the oxidative cleavage step. The diol obtained from dihydroxylation of the terminal alkene of **12** was unaffected by exposure to $NaIO_4$ and reacted too slowly with $Pb(OAc)_4$ for this route to be of value.

We planned to convert **3** into our target structure **2** via Lewis acid promoted cyclization of the secondary amine onto the α,β-unsaturated ketal. Matsumoto has recently disclosed a similar transformation;[5] however, the substrate in this study was devoid of the sensitive enol ether present in **3**. Predictably, the enol ether was difficult to retain, as we obtained varying amounts of demethylated pyrrolidine **14** in all of our cyclizations. After considerable experimentation, we discovered that TMSOTf (2 equiv) in CH_2Cl_2 (−10 °C, 15 min) facilitated cyclization and minimized enol ether hydrolysis, delivering **13** in 50% yield along with a minor amount of **14** (11%). The necessity for an excess of TMSOTf is presumably due to the abundance of Lewis basic functional groups in **3**.

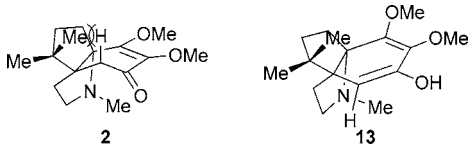


Figure 2. Steric hindrance in **2** relative to **13**.

Surprisingly, all spectral data (^1H NMR, ^{13}C NMR, COSY, HMQC) for **13** are consistent with the enol tautomer shown rather than the expected keto form illustrated for **2** (Scheme 1). Molecular modeling (MacSpartan Pro, semiempirical PM3) suggests that enol **13** is more stable than ketone **2** by 2.9 kcal/mol. In contrast, **14** and acutumine both exist as the keto tautomers in solution.[18] We believe that two structural features are responsible for the stability of **13** relative to **2**. First, the enol moiety in **13** is stabilized by an intramolecular hydrogen bond to the neighboring methoxy group. Second, the steric hindrance between a ketone α-hydrogen in **2** and one of the geminal methyl groups destabilizes this structure with respect to **13** (Figure 2).

Compound **14** possesses the same steric hindrance as **2**; however, it already contains an enol that presumably forms an intramolecular hydrogen bond to the methoxy group. Thus, the bis-enol tautomer of **14** cannot derive any additional benefit from intramolecular hydrogen bonding, and the molecule exists in solution as shown in Scheme 4. In fact, PM3 calculations indicate that **14** is 6.5 kcal/mol more stable than the aforementioned bis-enol. The enol of **1** could be stabilized by intramolecular hydrogen bonding. Nevertheless, the presence of the spirocyclic cyclopentenone instead of the geminal dimethyl groups of **13** affects the geometry at the spirocyclic carbon, presumably attenuating the strain of the keto tautomer and causing it to be more stable than the enol. Again, molecular modeling supports this analysis, as the PM3-minimized structure of **1** is 2.0 kcal/mol lower in energy than its enol tautomer.

In conclusion, we have synthesized tricyclic compound **13**, representative of the core of the bioactive natural product acutumine. In the context of this synthesis, we developed a strategy for the construction of an all-carbon quaternary center and an adjacent amine-bearing quaternary carbon that relies on an anionic oxy-Cope rearrangement followed by a Lewis acid mediated Michael-type cyclization. Additionally,

(15) Allylmagnesium chloride was purchased from Aldrich, whereas allylmagnesium bromide was synthesized in our laboratory. Thus, we believe that unreacted Mg present in the homemade Grignard reagent solution may reduce **4** to the corresponding radical anion. Loss of methoxide and hydrogen atom abstraction by the incipient aryloxy radical from THF or another adventitious hydrogen atom source would provide **5**.

(16) For an oxy-Cope/Claisen/ene reaction cascade that results in the formation of vicinal quaternary stereocenters, see: (a) Sauer, E. L. O.; Barriault, L. *Org. Lett.* **2004**, *6*, 3329. (b) Sauer, E. L. O.; Barriault, L. *J. Am. Chem. Soc.* **2004**, *126*, 8569.

(17) If the reaction was allowed to proceed to more than 50% conversion, overoxidized byproducts began to emerge. Ozonolyses conducted in CH_2Cl_2, MeOH, or mixtures of these solvents were characterized by the predominance of such byproducts. We plan to further optimize this transformation on intermediates relevant to the total synthesis rather than in this model system.

(18) (a) Sugimoto, Y.; Babiker, H. A. A.; Saisho, T.; Furumoto, T.; Inanaga, S.; Kato, M. *J. Org. Chem.* **2001**, *66*, 3299. (b) Sugimoto, Y.; Inanaga, S.; Kato, M.; Shimizu, T.; Hakoshima, T.; Isogai, A. *Phytochemistry* **1998**, *49*, 1293. The NMR spectra of **1** were acquired in pyridine-d_5. Our data were obtained in benzene-d_6; however, a ^1H NMR spectrum of **13** acquired in pyridine-d_5 showed only the enol form.

we discovered that **13** exists in the enol form, and we have formulated a hypothesis that explains its tautomeric properties with respect to those of related compounds. Application of the chemistry described herein to the total synthesis of **1** and other targets accessible by this methodology is in progress.

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Supporting Information Available: Experimental procedures, characterization data, NMR spectra for all new compounds, and X-ray crystallographic data in CIF format for **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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