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Rapid Construction of the Aza-Propellane Core of Acutumine via a Photochemical [2 + 2] Cycloaddition Reaction

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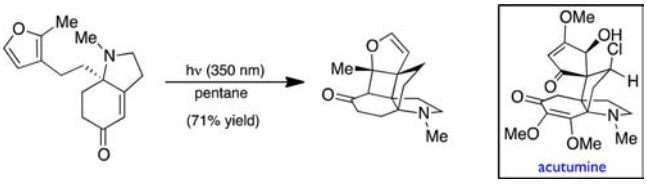
ABSTRACT



Synthetic efforts toward the chlorinated aza-propellane alkaloid acutumine (1) are described. The key vicinal quaternary centers were constructed by a photochemical [2 + 2] cycloaddition reaction of a furanyl-tetrahydroindolone. Dihydroxylation of the [2 + 2] product enabled a tandem retro-aldol/intramolecular ketalization reaction, which revealed the aza-propellane core of 1 while generating an unusual, caged, pentacyclic hemiketal product.

Acutumine (**1**, Scheme 1) is a chlorinated aza-propellane alkaloid first isolated in 1929 by Goto and Sudzuki from the medicinal herb *Sinomenium acutum*.[1,2] This densely functionalized small molecule exhibits promising biological properties, including selective T-cell cytotoxicity[3] and antiamnesic activity.[4] The aza-propellane skeleton is adorned with a spirocyclic cyclopentenone moiety and contains a neopentyl chloride and two all-carbon quaternary centers embedded within five contiguous stereogenic carbons. Although its structural and biological features have attracted attention from the synthetic community,[5] only a single enantioselective synthesis of the alkaloid has been reported to date.[6]

As a part of our program aimed at developing a unified synthetic strategy toward several structurally distinct aza-propellane alkaloids, we recently reported the preparation of *N-tert*-butanesulfinimine **9** (see Scheme 2), a compound that undergoes highly diastereoselective 1,2-addition reactions with a variety of organometallic reagents.[7−9] Based on these findings, we were able to complete concise total syntheses of the hasubanan alkaloid 8-demethoxyrunanine, as well as the structurally related compounds cepharatines A, C, and D.[7] Herein, we report that addition of furanyl-based nucleophiles to *N-tert*-butanesulfinimine **9** enables the rapid construction of the aza-propellane core of acutumine by a photochemical [2 + 2] cycloaddition/retro-aldol sequence.

(1) Original isolation paper: Goto, K.; Sudzuki, H. *Bull. Chem. Soc. Jpn.* **1929**, *4*, 220.

(2) Structural assignment: (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.

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

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

(5) For synthetic studies toward acutumine, see: (a) Nguyen, T. X., Ph.D. Thesis, University of California, San Diego, 2009. (b) Moreau, R. J.; Sorensen, E. J. *Tetrahedron* **2007**, *63*, 6446.

(6) (a) Li, F.; Tartakoff, S. S.; Castle, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 6674. (b) Li, F.; Tartakoff, S. S.; Castle, S. L. *J. Org. Chem.* **2009**, *74*, 9082.

(7) Chuang, K. V.; Navarro, R.; Reisman, S. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 9447.

(8) Chuang, K. V.; Navarro, R.; Reisman, S. E. *Chem. Sci.* **2011**, *2*, 1086.

(9) For a seminal report regarding *N-tert*-butanesulfinimines: Ellman, J. A.; Cogan, D. A. *J. Am. Chem. Soc.* **1999**, *121*, 268.

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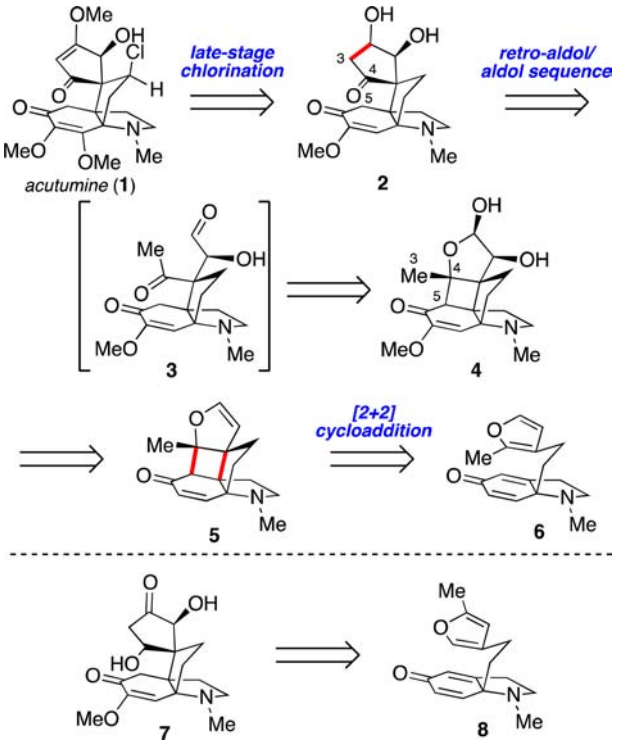
Scheme 1. Retrosynthetic Analysis of Acutumine (**1**)

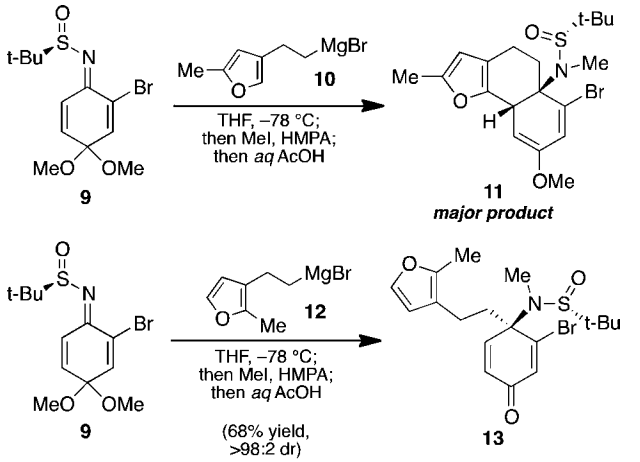


Retrosynthetically, acutumine (**1**) was simplified to diol **2**, an intermediate envisioned to arise from lactol **4** by a retro-aldol/aldol sequence (Scheme 1). In this key reaction, the strained nature of the cyclobutane embedded within **4** was expected to facilitate cleavage of the C4−C5 bond to give keto-aldehyde **3**, which is poised to undergo intramolecular aldol ring closure. We hypothesized that lactol **4** could be prepared by dihydroxylation of the corresponding dihydrofuran (**5**), which itself was expected to arise from an intramolecular photochemical [2 + 2] cycloaddition of furanyl-dihydroindolone **6**.

Alternatively, we recognized that isomeric dihydroindolone **8** could also be a viable intermediate en route to acutumine. Indeed, its advancement through the same reaction sequence was anticipated to produce cyclopentanone **7**, an isomeric intermediate also amenable to elaboration to **1**. We expected both dihydroindolones **6** and **8** to be accessible from **9** by short reaction sequences involving Grignard addition, *N*-methylation, and pyrrolidine formation.[7,8]

To rapidly assess the feasibility of our [2 + 2] cycloaddition/retro-aldol/aldol strategy, we began our studies by targeting compounds **6** and **8**. To this end, we examined the use of furan-containing Grignard reagents **10** and **12** as nucleophiles for our sulfinimine methodology. Exposure of bromo-sulfinimine **9** to Grignard reagent **10** at −78 °C resulted in the expected 1,2-addition reaction; however, upon purification by flash chromatography, the major product was enol ether **11** (Scheme 2).[10] Presumably, the mildly acidic silica gel mediates an intramolecular Friedel−Crafts type conjugate addition. Although it might have been possible to identify purification conditions that allowed for isolation of the 1,2-addition product, the acid sensitivity of this substrate suggested it would not be amenable to pyrrolidine formation using our previously established conditions.[7] We hypothesized that, in the analogous 2,3-disubstituted furanyl substrate (**12**), the C2 methyl group should mitigate this type of reactivity and allow for the isolation of the corresponding 1,2-addition product. This hypothesis was validated when, upon treatment of sulfinimine **9** with Grignard reagent **12** followed by in situ methylation, sulfinamide **13** was isolated in 68% yield as a single diastereomer.

Scheme 2. Diastereoselective 1,2-Addition of Furanyl Grignard Nucleophiles



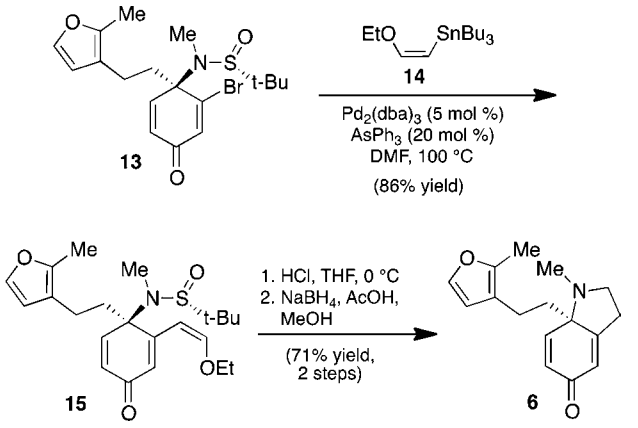
Sulfinamide **13** was elaborated to dihydroindolone **6** following our optimized three-step protocol for pyrrolidine formation. Thus, Pd-catalyzed cross-coupling of sulfinamide **13** with vinyl stannane **14** proceeded smoothly to give enol ether **15** (Scheme 3). Acid-mediated cyclization furnished an enamine intermediate, which was then selectively reduced to afford photocycloaddition substrate **6** in 61% yield over three steps.

With dihydroindolone **6** in hand, we conducted a screen of photochemical reaction conditions, varying both the solvent and the irradiation wavelength.[11] Irradiation of **6** at 350 nm in benzene did afford trace amounts of the desired [2 + 2] product (as determined by ^{1}H NMR analysis). However, following characterization by NMR and IR spectroscopy and HRMS, the major product of this reaction was assigned as diketone **18** (Scheme 4). Diketone **18** is hypothesized to form by a photolytic oxa-di-π-methane rearrangement,[12] which, following C−C bond

(10) Enol ether **11** was isolated in 54% yield as a difficult to separate 9:1 mixture with an unidentified side product. Analytically pure material was obtained by multiple purifications. See Supporting Information.

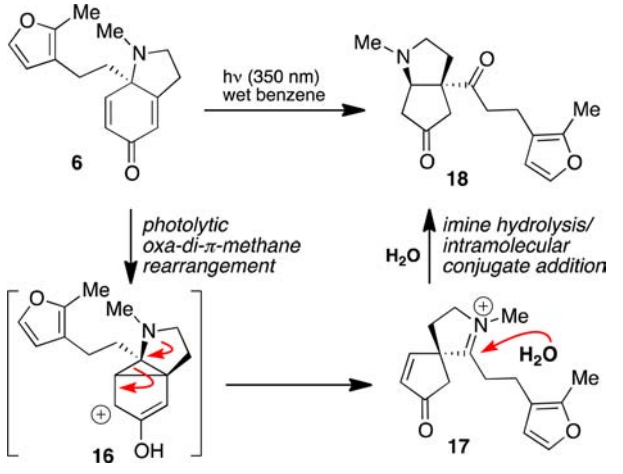
(11) For examples of intramolecular [2 + 2] photocycloadditions between furan and enone systems, see: (a) Fontana, G.; Savona, G.; Vivona, N.; Rodriguez, B. *Eur. J. Org. Chem.* **1999**, 2011. (b) Crimmins, M. T.; Pace, J. M.; Nantermet, P. G.; Kim-Meade, A. S.; Thomas, J. B.; Watterson, S. H.; Wagman, A. S. *J. Am. Chem. Soc.* **1999**, *121*, 10249.

Scheme 3. Preparation of Dihydroindolone **6**



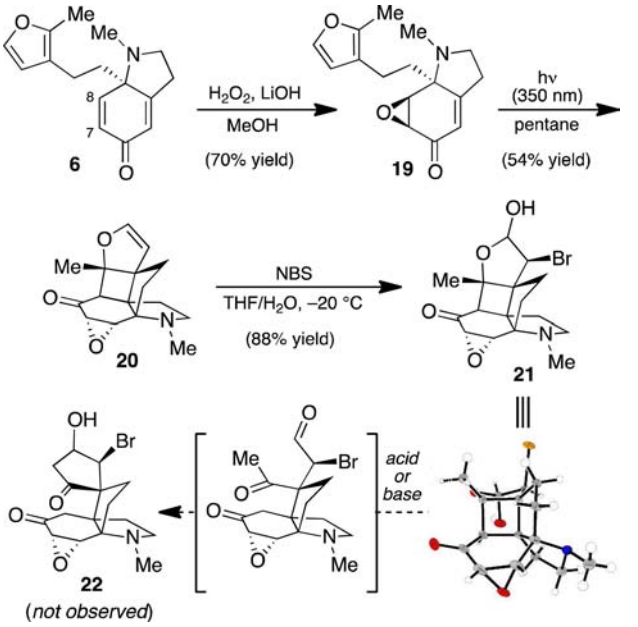
fragmentation, generates the unstable iminium ion **17**. Nucleophilic addition of adventitious water results in iminium hydrolysis and intramolecular conjugate addition to produce **18**. To circumvent this type of undesired reactivity, the C7−C8 enone functionality of **6** was masked as its epoxide under nucleophilic epoxidation conditions (Scheme 5). We were pleased to find that photochemical [2 + 2] cycloaddition of enone **19** proved more fruitful: irradiation of **19** at 350 nm in pentane delivered dihydrofuran **20** in 54% yield. Notably, this reaction exhibits a high degree of regioselectivity (for the linear vs crossed product) and installs the vicinal all-carbon quaternary centers of acutumine in a single step.

Scheme 4. [2 + 2] Photocycloaddition of Dihydroindolone **6**



Having successfully prepared the propellane core of acutumine (**1**), we examined the conversion of the dihydrofuran to a viable retro-aldol/aldol substrate. Whereas subjection of **20** to a number of electrophilic epoxidation conditions led primarily to *N*-oxidation, exposure to *N*-bromosuccinimide in aqueous THF[13] afforded bromohydrin **21** in excellent yield (~3:1 mixture of diastereomers at the lactol carbon). The structural assignment of **21** was confirmed by single-crystal X-ray diffraction. To our dismay, attempts to effect a retro-aldol fragmentation of **21** under mildly acidic or basic conditions led to significant decomposition and failed to produce detectable quantities of **22** or similar fragmentation products.

Scheme 5. [2 + 2] Photocycloaddition of Epoxy Enone **19**



In light of these results, we suspected that the epoxide moiety of **21** might be a source of undesired reactivity under our retro-aldol conditions. We turned our attention to the construction of dihydrofuran **24**, an intermediate in which the C7−C8 alkene has been reduced (Scheme 6). To this end, Cu-catalyzed conjugate reduction of **6** furnished enone **23**, a substrate that performed well under our optimized photochemical [2 + 2] reaction conditions to give dihydrofuran **24** in 71% yield. Oxidation of dihydrofuran **24** was achieved under Upjohn dihydroxylation conditions,[14] providing diol **25** in good yield.

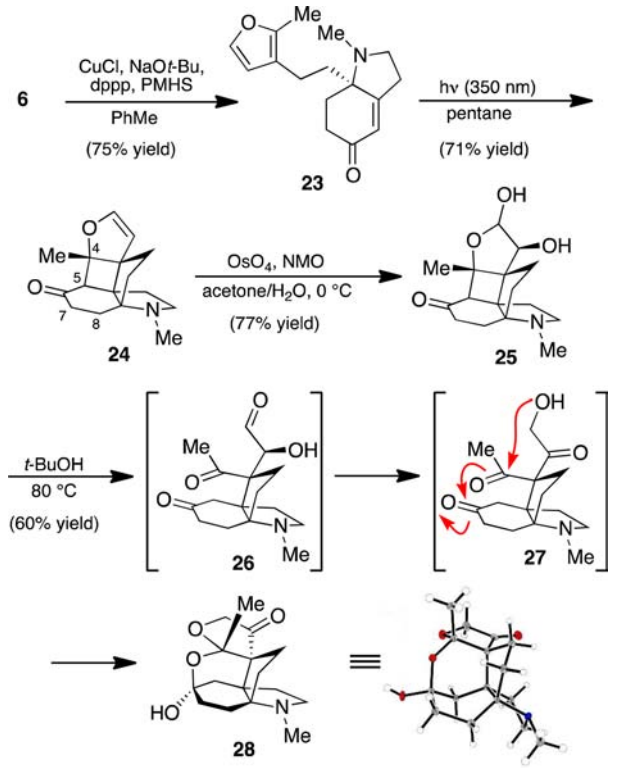
With access to lactol **25**, a number of conditions were evaluated for their ability to cleave the C4−C5 bond by a retro-aldol reaction. Unfortunately, as observed with bromohydrin **21**, a variety of acidic or basic conditions failed to deliver the desired product. However, we noticed that a benzene stock solution of diol **25** used for TLC analysis slowly developed a single, new spot over the course of several

(12) For examples of oxa-di-π-methane rearrangements of cyclohexadienones, see: (a) Pirrung, M. C.; Nunn, D. S. *Tetrahedron* **1996**, *52*, 5707. (b) Schuster, D. I.; Brisimitzakis, A. C. *J. Org. Chem.* **1987**, *52*, 3644. (c) Zimmerman, H. E.; Swenton, J. S. *J. Am. Chem. Soc.* **1967**, *89*, 906. (d) Zimmerman, H. E.; Schuster, D. I. *J. Am. Chem. Soc.* **1961**, *83*, 4486. (e) Barton, D. H. R.; de Mayo, P.; Shafiq, M. *J. Chem. Soc.* **1958**, 3314.

(13) de Cienfuegos, L. A.; Mota, A. J.; Robles, R. *Org. Lett.* **2005**, *7*, 2161.

(14) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973.

Scheme 6. Isolation of Ketal Rearrangement Product **28**



days. To our surprise, isolation and single-crystal X-ray diffraction of this compound identified it as hemiketal **28**.

It is proposed that aldehyde **26**, the product directly formed by retro-aldol fragmentation of **25**, readily tautomerizes to keto-alcohol **27**. Formation of this primary alcohol triggers an intramolecular cyclization cascade, leading to hemiketal **28**. A brief solvent screen identified *t*-BuOH as the optimal solvent for this rearrangement, which could be achieved in 60% yield when the reaction mixture was heated to 80 °C. Ketal **28** has thus far proven recalcitrant to our efforts toward further elaboration to **1**.

In conclusion, we have enantioselectively prepared hemiketal **28**, a compound that contains the aza-propellane core of acutumine, in only eight steps from *N-tert*-butanesulfinimine **9**. The key vicinal quaternary centers were constructed by a photochemical [2 + 2] cycloaddition reaction of furanyl-tetrahydroindolone **23** to give **24**, which was elaborated by dihydroxylation and retro-aldol fragmentation to ketal **28**. Although it is unlikely that **28** will serve as an intermediate en route to acutumine, these studies confirm the viability of a [2 + 2] cycloaddition/retro-aldol sequence to prepare the aza-propellane core. Studies aimed at advancing **25** and more appropriately oxidized intermediates to the natural product are ongoing in our laboratory.

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Supporting Information Available. Experimental procedures and spectral data (^{1}H and ^{13}C NMR, IR, and HRMS) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.