ORGANIC LETTERS

2006
Vol. 8, No. 17
3757−3760

Total Synthesis of (±)-Hasubanonine

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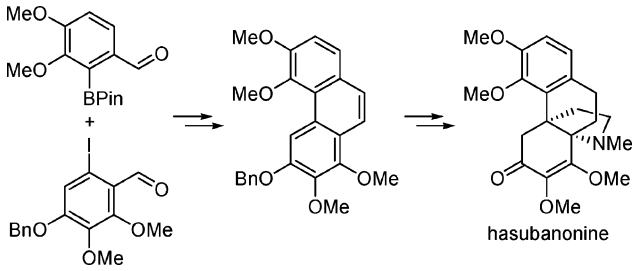
Received June 2, 2006

ABSTRACT



Total synthesis of the alkaloid (±)-hasubanonine is described. A key feature of the route is generation of a phenanthrene intermediate via a Suzuki coupling–Wittig olefination–ring-closing metathesis sequence. Conversion of the phenanthrene into the target molecule required six steps including dearomatization by means of oxidative phenolic coupling, anionic oxy-Cope rearrangement, and a final acid-promoted cyclization. Production of an undesired rearranged product in the last step could be suppressed by moderating the acid strength.

Hasubanonine (**1**, Figure 1), a member of the hasubanan family of alkaloids,[1] was isolated from the vine *Stephania japonica*.[2] Although it bears some structural resemblance to the morphine alkaloids, neither **1** nor any other hasubanan alkaloid examined to date possesses analgesic activity.[1a] Schultz noted that the relative orientation of the aromatic ring and the nitrogen atom is reversed in the two classes of alkaloids and posited that the *unnatural* enantiomers of hasubanan alkaloids may function as painkillers. Accordingly, Schultz performed a synthesis of unnatural (+)-cepharamine,[3] which is the only asymmetric synthesis to date of a hasubanan alkaloid.[4,5] However, to the best of our knowledge, no studies of the analgesic properties of this or any other unnatural hasubanan alkaloid enantiomer have been reported. As a prelude to an asymmetric synthesis, we report a concise total synthesis of (±)-**1** utilizing a strategy that is also well-suited for the construction of other hasubanan alkaloids.

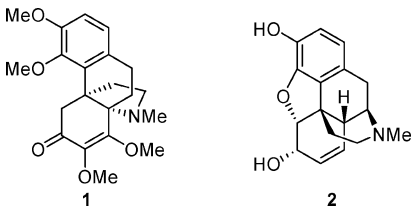


Figure 1. Hasubanonine (**1**) and morphine (**2**).

Our retrosynthetic analysis of **1** is presented in Scheme 1. At the outset of our planning, we recognized that the route we developed to the propellane-type[6] tricyclic core of the alkaloid acutumine[7] would be applicable to the construction of **1**. Thus, we anticipated that dihydrophenanthrene **3** could be transformed into **1** via a five-step sequence that includes an oxidative phenolic coupling, an anionic oxy-Cope rearrangement, and a Michael-type cyclization. The immediate precursor to **3**, phenanthrene **4**, was disconnected into aryl iodide **5** and arylboronic ester **6**. This simplification takes advantage of a phenanthrene synthesis reported by Iuliano

(1) (a) Matsui, M. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1988; Vol. 33, pp 307−347. (b) Inubushi, Y.; Ibuka, T. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1977; Vol. 16, pp 393−430. (c) Bentley, K. W. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1971; Vol. 13, pp 131−143.

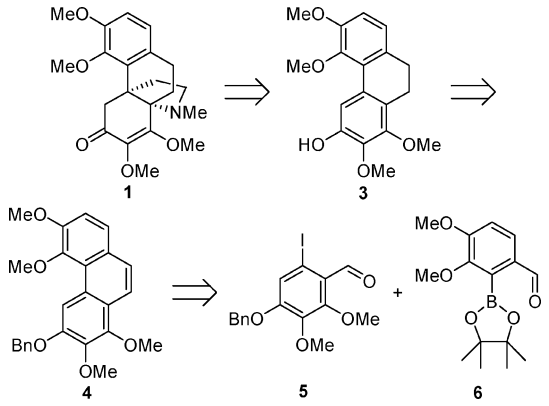
(2) (a) Tomita, M.; Ibuka, T.; Inubushi, Y.; Watanabe, Y.; Matsui, M. *Chem. Pharm. Bull.* **1965**, *13*, 538. (b) Tomita, M.; Ibuka, T.; Inubushi, Y.; Watanabe, Y.; Matsui, M. *Tetrahedron Lett.* **1964**, 2937. (c) Kondo, H.; Satomi, M.; Odera, T. *Annu. Rep. ITSUU Lab.* **1951**, *2*, 35.

(3) Schultz, A. G.; Wang, A. *J. Am. Chem. Soc.* **1998**, *120*, 8259.

(4) Total synthesis of (±)-hasubanonine: (a) Ibuka, T.; Tanaka, K.; Inubushi, Y. *Chem. Pharm. Bull.* **1974**, *22*, 782. (b) Ibuka, T.; Tanaka, K.; Inubushi, Y. *Tetrahedron Lett.* **1970**, 4811.

10.1021/ol0613564 CCC: $33.50
Published on Web 07/15/2006

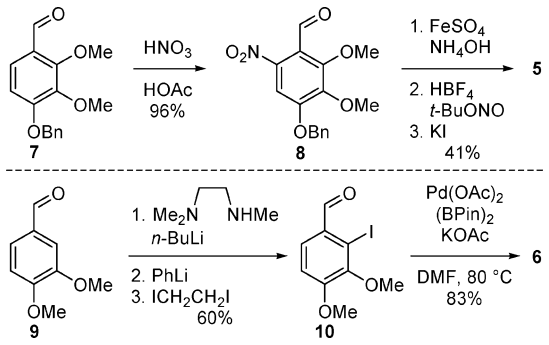
Scheme 1. Retrosynthetic Analysis of **1**



that consists of a Suzuki coupling followed by Wittig olefination and ring-closing metathesis.[8] We reasoned that both **5** and **6** should be available in straightforward fashion from known or commercially available aromatic compounds.

The syntheses of **5** and **6** are shown in Scheme 2. Nitration

Scheme 2. Syntheses of **5** and **6**



of 4-benzyloxy-2,3-dimethoxybenzaldehyde (**7**, available in two steps from commercially available 2,3-dimethoxyphenol)[9] afforded **8**.[10] A sequence of nitro reduction, diazotization, and iodination delivered aryl iodide **5** in 41% yield from the nitro compound. Regioselective iodination of 3,4-dimethoxybenzaldehyde (**9**) according to the directed ortho metalation[11] protocol of Comins[12] produced **10**, which was subjected to a Suzuki coupling with bis(pinacolato)diboron[13] to provide arylboronic ester **6**.

Suzuki coupling[14] of **5** and **6** constructed a hindered trisubstituted biaryl axis, delivering dialdehyde **11** in 79% yield (Scheme 3). Conversion of both aldehydes into terminal alkenes was accomplished via Wittig olefination, and ring-closing metathesis of the resultant diene **12** with the Grubbs second-generation ruthenium catalyst[15] provided phenanthrene **4** in 92% yield from **11**. Cleavage of the benzyl ether and reduction of the phenanthrene were both accomplished by catalytic hydrogenation, affording phenolic dihydrophenanthrene **3** in excellent yield (95%).

At this point, we commenced the transformation of **3** into **1** by means of our previously developed sequence. Accordingly, treatment of **3** with $PhI(OAc)_2$ in the presence of MeOH[16] resulted in a facile oxidative phenolic coupling that produced masked *o*-benzoquinone[17] **13**. 1,2-Addition of allylmagnesium chloride to **13** provided tertiary alcohol **14**, which was transformed into ketone **15** via an anionic oxy-Cope rearrangement.[18] Ozonolysis of **15** was regioselective, delivering the aldehyde derived from oxidative cleavage of the terminal olefin. Reductive amination of the crude aldehyde afforded a secondary amine, which cyclized to form hemiaminal **16** as evidenced by NMR spectroscopy. Notably, this ozonolysis−reductive amination sequence was more facile relative to our earlier work on the acutumine core, in which oxidation of the tetrasubstituted alkene by O_3 was competitive with the desired process. We believe that the less-hindered nature of the terminal olefin of **15** compared to the corresponding olefin in the acutumine substrate is responsible for the improved regioselectivity.[7]

To our surprise, subjection of **16** to our previously developed conditions (TMSOTf, 4 Å MS, CH_2Cl_2, −10 °C) for cyclization of an amine onto an α,β-unsaturated ketal[19] did not afford **1**. Rather, an unstable constitutional isomer of **1** was obtained, as evidenced by HRMS. We have tentatively assigned the structure of this product as hemiaminal **17** on the basis of ^{1}H NMR of a partially purified sample.[20] We presume that this compound arises from a pinacol-like rearrangement of the oxocarbenium ion derived

(5) Other synthetic work in the hasubanan alkaloid area: (a) Trauner, D.; Porth, S.; Opatz, T.; Bats, J. W.; Giester, G.; Mulzer, J. *Synthesis* **1998**, 653. (b) Schwartz, M. A.; Wallace, R. A. *Tetrahedron Lett.* **1979**, 3257. (c) Shiotani, S.; Kometani, T. *Tetrahedron Lett.* **1976**, 767. (d) Monković, I.; Wong, H. *Can. J. Chem.* **1976**, *54*, 883. (e) Monković, I.; Wong, H.; Belleau, B.; Pachter, I. J.; Perron, Y. G. *Can. J. Chem.* **1975**, *53*, 2515. (f) Kametani, T.; Kobari, T.; Shishido, K.; Fukumoto, K. *Tetrahedron* **1974**, *30*, 1059. (g) Kametani, T.; Nemoto, H.; Kobari, T.; Shishido, K.; Fukumoto, K. *Chem. Ind.* (London) **1972**, 538. (h) Ibuka, T.; Tanaka, K.; Inubushi, Y. *Chem. Pharm. Bull.* **1974**, *22*, 907. (i) Inubushi, Y.; Kitano, M.; Ibuka, T. *Chem. Pharm. Bull.* **1971**, *19*, 1820. (j) Evans, D. A.; Bryan, C. A.; Sims, C. L. *J. Am. Chem. Soc.* **1972**, *94*, 2891. (k) Evans, D. A.; Bryan, C. A.; Wahl, G. M. *J. Org. Chem.* **1970**, *35*, 4122. (l) Keely, S. L., Jr.; Martinez, A. J.; Tahk, F. C. *Tetrahedron* **1970**, *26*, 4729.

(6) For a review on the synthesis of propellane-containing natural products, see: Pihko, A. J.; Koskinen, A. M. P. *Tetrahedron* **2005**, *61*, 8769.

(7) Reeder, M. D.; Srikanth, G. S. C.; Jones, S. B.; Castle, S. L. *Org. Lett.* **2005**, *7*, 1089.

(8) Iuliano, A.; Piccioli, P.; Fabbri, D. *Org. Lett.* **2004**, *6*, 3711.

(9) Kurosawa, K.; Ollis, W. D.; Sutherland, I. O.; Gottlieb, O. R.; De Oliveira, A. B. *Phytochemistry* **1978**, *17*, 1389.

(10) The unusual regioselectivity of this nitration is precedented, as nitration of 2,3,4-trimethoxybenzaldehyde affords 2,3,4-trimethoxy-6-nitrobenzaldehyde exclusively; see: (a) Lin, A. J.; Pardini, R. S.; Lillis, B. J.; Sartorelli, A. C. *J. Med. Chem.* **1974**, *17*, 668. (b) Cherkaoui, M. Z.; Scherowsky, G. *New. J. Chem.* **1997**, *21*, 1203.

(11) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(12) Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1989**, *54*, 3730.

(13) Zhu, L.; Duquette, J.; Zhang, M. *J. Org. Chem.* **2003**, *68*, 3729.

(14) Lin, S.; Yang, Z.-Q.; Kwok, B. H. B.; Koldobskiy, M.; Crews, C. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 6347.

(15) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

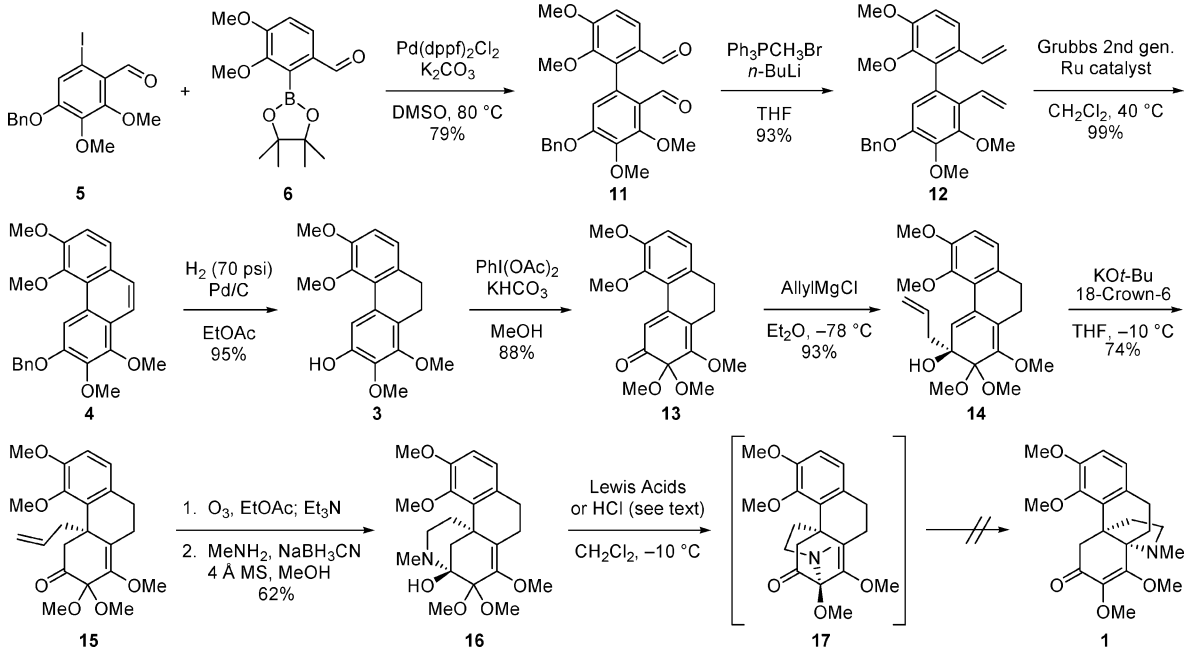
(16) Yen, C.-F.; Peddinti, R. K.; Liao, C.-C. *Org. Lett.* **2000**, *2*, 2909.

(17) For a review on the chemistry of masked *o*-benzoquinones, see: Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383.

(18) (a) Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971. (b) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765.

(19) These conditions (reported in ref 7) are based on the work of Matsumoto: Yasui, Y.; Koga, Y.; Suzuki, K.; Matsumoto, T. *Synlett* **2004**, 615.

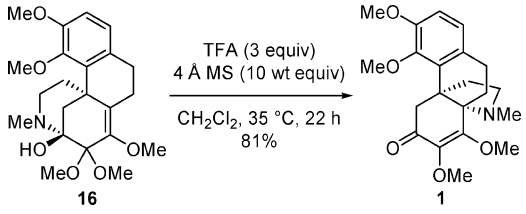
Scheme 3. Coupling of **5** and **6** and Attempted Conversion into **1**



from interaction of **16** with TMSOTf or TfOH.[21] The formation of **17** was quite rapid (≤10 min) and could also be accomplished by treatment of **16** with BCl_3 or HCl. Unfortunately, attempts to convert **17** into **1** were fruitless.

After considerable experimentation, we discovered that trifluoroacetic acid facilitated the clean transformation of **16** into **1**.[22] Optimized conditions entailed warming a solution of **16** in CH_2Cl_2 at 35 °C in the presence of 3 equiv of TFA and 10 wt equiv of 4 Å MS for 22 h (Scheme 4). Reactions

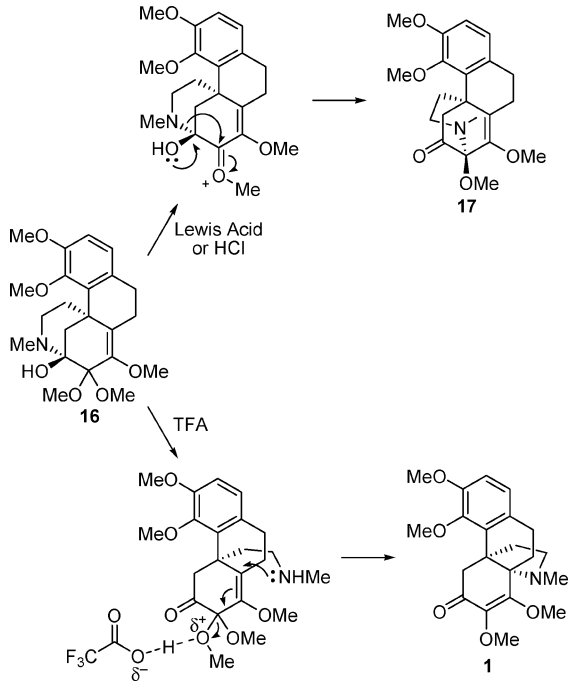
Scheme 4. Successful Conversion of **16** into **1**



conducted at room temperature were sluggish, proceeding to <50% completion after 24 h. We attribute the modest rate of reaction to the fact that the amino ketone tautomer of **16** required for cyclization is present in very low concentration.[23] In contrast, the substrate analogous to **16** in our synthesis of the acutumine core did not form a hemiaminal; thus, it cyclized rapidly without interference from the rearrangement.[7]

A mechanistic explanation for the production of **17** and **1** from **16** is depicted in Scheme 5. Treatment of **16** with a

Scheme 5. Rationale for the Formation of **17** and **1** from **16**



strong Lewis or Brønsted acid presumably results in the formation of an oxocarbenium ion which rapidly undergoes a pinacol-like rearrangement, affording hemiaminal **17**. However, it is likely that the oxocarbenium ion is not generated when **16** is exposed to the slightly weaker acid

(20) Compound **17** is completely unstable to SiO_2, neutral alumina, basic alumina, and Florisil. It can be partially purified by rapid chromatography on SiO_2 that has been pretreated with Et_3N or NaOH, but attempts to obtain a pure sample were thwarted by decomposition.

(21) We believe that reactions employing TMSOTf are actually mediated by TfOH, as they do not proceed in the presence of Et_3N.

TFA. Rather, cyclization of the amino ketone tautomer of **16** to provide **1** may proceed via an S_N2'-type pathway in which a ketal methoxy group is activated by hydrogen bonding to the carboxylic acid. We do not believe that **17** lies on the pathway to **1**, as treatment of **17** with TFA did not provide **1**, and **17** was not detected in the formation of **1** under the conditions shown in Scheme 4.[24] Finally, it is noteworthy that the acid-sensitive methyl enol ether moiety of **16** was stable under most of the conditions examined provided that a sufficient quantity of 4 Å MS was present.

In conclusion, we have synthesized (±)-hasubanonine via an efficient route that features convergent construction of a phenanthrene intermediate followed by a sequence that includes oxidative dearomatization, anionic oxy-Cope rearrangement, and acid-promoted cyclization. The final transformation was plagued by an undesired rearrangement which was ultimately avoided by attenuating the acid strength. The net result of the aforementioned reactions is to annulate a pyrrolidine onto a phenolic aromatic ring, and the method is robust enough to create hindered propellane-type systems. This synthesis could be used to prepare other hasubanan alkaloids by simply modifying the structure of the aryl iodide or the arylboronic ester used in the Suzuki coupling. Additionally, development of an enantioselective total synthesis of unnatural (+)-**1** merely requires the performance of an asymmetric allylation[25] on ketone **13**. Studies along these lines are currently in progress and will be reported in due course.

Acknowledgment. We thank Brigham Young University (Annual Fund Student Mentorships and Undergraduate Research Awards to S.B.J., startup funding to S.L.C.) and the National Institutes of Health (GM70483) for support of this work. We also thank Daniel K. Nielsen for assistance in the preparation of starting materials.

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

OL0613564

(22) The only published NMR spectroscopic data for **1** that we are aware of consist of partially assigned ^{1}H spectra acquired on 60 MHz instruments (see ref 2 and Singh, R. S.; Kumar, P.; Bhakuni, D. S. *J. Nat. Prod.* **1981**, *44*, 664). Accordingly, we obtained high-field ^{1}H, ^{13}C, COSY, and HETCOR spectra of our product, all of which are consistent with structure **1**.

(23) This tautomer was not observed in ^{1}H or ^{13}C NMR spectra of **16**.

(24) Interestingly, pure **1** is completely consumed when treated with 10 equiv of TFA to afford a complex mixture from which **17** can be identified on the basis of TLC and HRMS. This may occur via protonation of the tertiary amine followed by methoxy-assisted ring opening to afford an oxocarbenium ion (i.e., the amino ketone tautomer of the species portrayed in Scheme 5). The preference of the oxocarbenium ion to give **17** instead of **1** upon cyclization is a kinetic rather than a thermodynamic phenomenon, as **1** is 2.71 kcal/mol more stable than **17** according to semiempirical PM3 calculations. Moreover, **1** is significantly more stable to standard purification techniques as documented above. We believe that the facile decomposition of **17** (possibly triggered by enol ether hydrolysis) is responsible for our inability to convert it into the more stable **1**. Further experiments are necessary to clarify the intriguing relationship between these two compounds.

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