ORGANIC LETTERS

2008
Vol. 10, No. 2
157−159

Total Synthesis of (±)-Goniomitine via a Formal Nitrile/Donor–Acceptor Cyclopropane [3 + 2] Cyclization

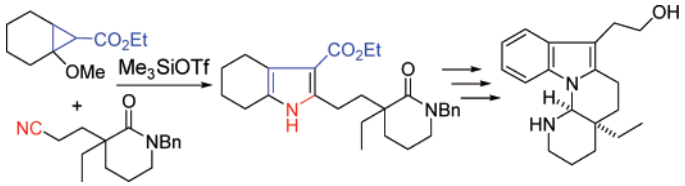
Christian L. Morales and Brian L. Pagenkopf*

Department of Chemistry, The University of Western Ontario, London, Ontario, N6A 5B7 Canada

bpagenko@uwo.ca

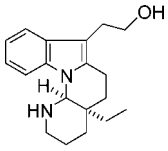
Received September 29, 2007

ABSTRACT



The total synthesis of (±)-goniomitine has been accomplished in 17 linear steps with 5.2% overall yield starting from commercially available *δ*-valerolactam. A synthetic highlight includes the first application of a formal [3 + 2] cycloaddition between a highly functionalized nitrile and a donor–acceptor cyclopropane to prepare an indole nucleus. The use of a microwave reactor is shown to greatly improve the reaction times for two steps.

The indole alkaloid (−)-goniomitine **1** (Figure 1) is a member of the aspidosperma family of natural products, many of which have been targets of total synthesis because of their interesting structures and biological activities.[1] Goniomitine was isolated in 1987 from the root bark of *Gonioma malagasy* by Husson and co-workers,[2] and its unique structure has attracted the attention of several groups, and this has culminated in one total synthesis by Takano and co-workers.[3] Additionally, several goniomitine analogues including bisindoles have been prepared,[4] some of which show weak cytotoxicity (IC_{50} = 7.1 mM) toward L1210 leukemia cells in culture.[4d]



1

Figure 1. (−)-Goniomitine.

In recent years, we have developed dipolar cycloaddition reactions of donor−acceptor (DA) cyclopropanes with nitriles for the synthesis of pyrroles[5] and have expanded such methodology to encompass a wide variety of annelation partners such as pyridines,[6] indoles,[7] and other dipolarophiles.[8,9] The pyrrole synthesis is most easily executed when

(1) Saxton, J. E. *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998: Vol. 51, Chapter 1.

(2) Randriambola, L.; Quirion, J.-C.; Kan-Fan, C.; Husson, H.-P. *Tetrahedron Lett.* **1987**, *28*, 2123−2126.

(3) Takano, S.; Sato, T.; Inomata, K.; Ogasawara, K. *Chem. Commun.* **1991**, 462−464.

(4) (a) Hashimoto, C.; Husson, H.-P. *Tetrahedron Lett.* **1988**, *29*, 4563−4566. (b) Lewin, G.; Schaeffer, C.; Lambert, P. H. *J. Org. Chem.* **1995**, *60*, 3282−3287. (c) Lewin, G.; Schaeffer, C. *Nat. Prod. Lett.* **1995**, *7*, 227−234. (d) Lewin, G.; Schaeffer, C.; Hocquemiller, R.; Jacoby, E.; Leonce, S.; Pierre, A.; Atassi, G. *Heterocycles* **2000**, *53*, 2353−2356.

(5) (a) Yu, M.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 8122−8123. (b) Yu, M.; Pagenkopf, B. L. *Org. Lett.* **2003**, *5*, 5099−5101. (c) Yu, M.; Pantos, G. D.; Sessler, J. L.; Pagenkopf, B. L. *Org. Lett.* **2004**, *6*, 1057−1059.

(6) Morra, N. A.; Morales, C. L.; Bajtos, B.; Wang, X.; Jang, H.; Wang, J.; Yu, M.; Pagenkopf, B. L. *Adv. Synth. Catal.* **2006**, *8*, 4379−4382.

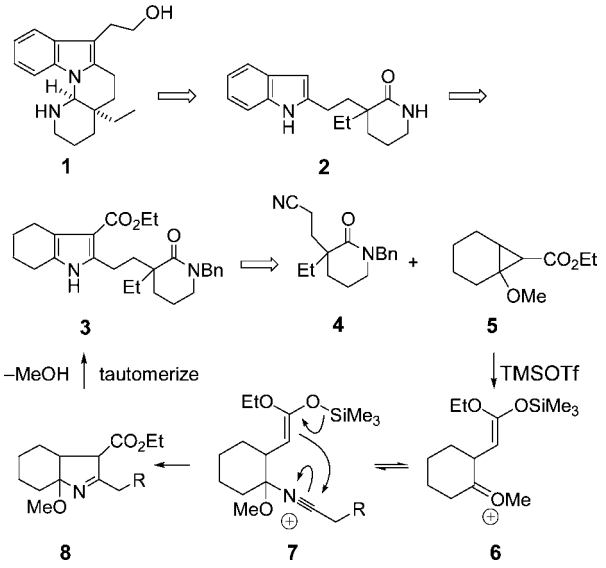
(7) Bajtos, B.; Yu, M.; Zhao, H; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2007**, *129*, 9631−9634.

10.1021/ol702376j CCC: $40.75
Published on Web 12/18/2007

the nitrile can be used as solvent, but this can present obvious disadvantages with expensive or less accessible nitriles. In this regard, we illustrate here through the total synthesis of (±)-goniomitine that a high-value synthetic nitrile can be an effective reaction partner even when used as the limiting reagent in the annelation reaction. Additionally, this work clearly shows for the first time the utility of the DA cyclopropane/nitrile annelation reaction for the synthesis of a functionalized indole.[10]

Retrosynthetic analysis suggested that reaching indole **2**, an intermediate in the Takano synthesis, would be an ideal target for a formal synthesis of goniomitine (Scheme 1). The

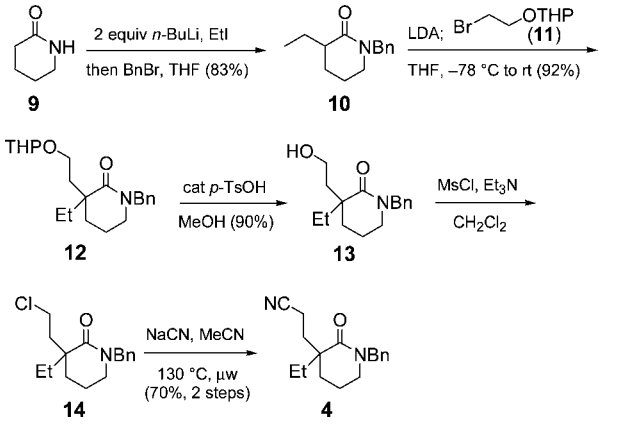
Scheme 1. Retrosynthetic Analysis



indole **2** can be derived from tetrahydroindole **3** by an oxidation state adjustment of the aromatic ring and installation of a keying ester group insertion at C3. The tetrahydroindole intermediate **3** will in turn be accessed in a convergent fashion by the formal [3 + 2] cycloaddition reaction between nitrile **4** and known DA cyclopropane **5**.[5b] A plausible mechanistic pathway for this key step likely involves the nitrilium ion intermediate **7** formed in a Ritter-like process by attack on the oxocarbenium ion **6**. The reversible nature of the nitrile addition is supported by the divergent stereochemical outcomes of allylation reactions[11] and nitrile annelations[5a] of carbohydrate-derived cyclopropyl lactones.

The synthesis of nitrile **4** began with the one-pot alkylation and *N*-benzylation of commercially available *δ*-valerolactam **9** to produce the known lactam **10**[12] (Scheme 2). Creation of the quaternary center of lactam **12** was achieved in 92%

Scheme 2. Synthesis of Nitrile **4**



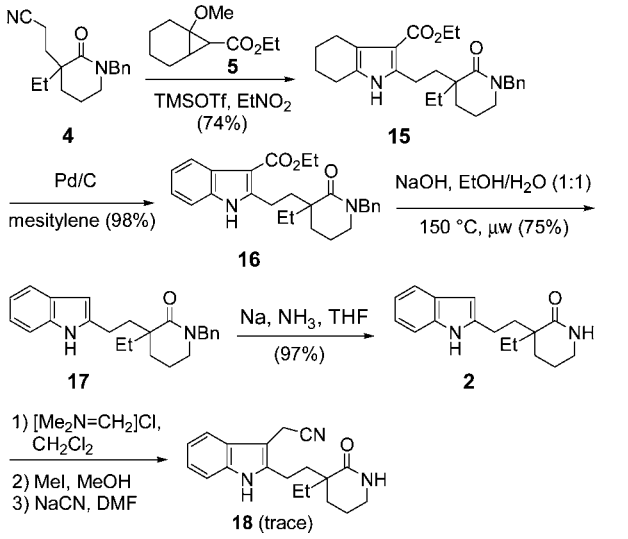
yield by enolization of **10** with LDA in THF followed by alkylation with THP ether **11**. The cyano substituent was introduced through a three-step sequence involving THP hydrolysis (cat. TsOH, MeOH, 90%), formation of chloride **14** with methanesulfonyl chloride (MsCl, Et_3N, CH_2Cl_2), and displacement of the intermediate halide with sodium cyanide in DMSO (70% over two steps). The reaction was more conveniently performed without loss in yield by heating the reaction to 130 °C in a microwave reactor with MeCN as solvent. Attempts to secure nitrile **4** directly by alkylation of lactam **10** with acrylonitrile or 3-halopropionitrile (chloro, bromo, and iodo) gave low yields and complex mixtures, even after pretreatment of the lithium enolate with $MgBr_2$ or $ZnCl_2$. However, reaction of **10** with a mixture of $ZnCl_2$, TMSOTf, and Et_3N (30 min, 0 °C) followed by addition of acrylonitrile gave **4** in 38% yield. Curiously, isolation of the silyl ether and subsequent reaction with acrylonitrile in the presence of various Lewis acids was less effective. For large scale work, the three-step sequence was preferred.

With nitrile **4** at hand, the stage was set for the critical cycloaddition between it and DA cyclopropane **5** (Scheme 3). Gratifyingly, after some straightforward optimization, the tetrahydroindole adduct **15** was secured in 74% yield on 10 g scale (by reaction of nitrile **4** (1.0 equiv), cyclopropane **5** (2.9 equiv), and Me_3SiOTf (1.05 equiv) in $EtNO_2$ (2.7 M) at −30 °C). Catalytic oxidation of tetrahydroindole **15** with palladium on carbon in refluxing mesitylene gave indole **16** in an excellent 98% yield. Catalysis of the oxidation with palladium hydroxide gave similar results, but the use of manganese oxide or DDQ as the oxidant resulted in lower yields. Together, these steps illustrate the power of the formal [3 + 2] nitrile/DA cyclopropane annelation methodology to prepare functionalized indoles in a straightforward and efficient manner.

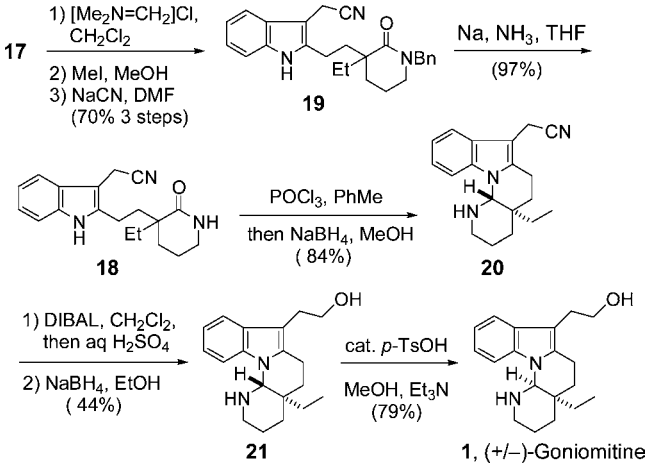
The C3 ester side chain, an artifact of the cycloaddition methodology, can in principle serve as an intermediate for constructing the hydroxyethyl side chain in the natural product. In practice, it was found more convenient to remove the ester through decarboxylation and subsequently build the hydroxyethyl group. The decarboxylation was achieved by heating **16** to reflux in a mixture of NaOH, EtOH, and water

(8) Yu, M.; Pagenkopf, B. L. *Org. Lett.* **2003**, *5*, 5099−5101.
(9) (a) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, 61, 321−347. (b) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603−1624. (c) Reissig, H. Y.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151−1196.
(10) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045−1075.
(11) Yu, M.; Pagenkopf, B. L. *Org. Lett.* **2003**, *5*, 4639−4640.
(12) Suh, Y.-G.; Kim, S.-A.; Jung, J.-K.; Shin, D.-Y.; Min, K.-H.; Koo, B.-A.; Kim, H.-S. *Angew. Chem., Int. Ed.* **1999**, *38*, 3545−3547.

Scheme 3. Formal Synthesis



Scheme 4. Completion of the Synthesis



(75% yield).[13] Under these conditions, the decarboxylation reaction required 3 days for completion, but when heated under microwave conditions at 150 °C, the reaction was completed in 3 h in the same yield. Debenzylation of **17** revealed the secondary lactam **2**, a synthetic intermediate common to the Takano synthesis, and constitutes a formal synthesis of goniomitine. To complete the total synthesis, the plan was to proceed along the pathway described by Takano, the next steps of which involve a sequential Mannich/amine methylation reaction followed by displacement with sodium cyanide to give **18**. However, we obtained only trace amounts of **18** using this sequence.

The same series of reactions for installing the C3 hydroxyethyl side chain was found to be more successful when applied to the benzyl-protected lactam **17** (Scheme 4), and the cyanomethyl group was introduced without difficulty to give **19** in 70% over three steps. After the homologation, the *N*-benzyl group was cleanly removed in 97% yield with sodium in ammonia/THF to give **18**, whereas several high-pressure hydrogenation reactions failed.[14] The reaction time for this debenzylation proved to be critical in order to avoid elimination of the nitrile to give the C3 methyl indole.[15] The successful deprotection of **19** to give **18** again merged the sequence back into the synthetic stream pioneered by Takano.

The final four steps of the total synthesis were duplicated without incident. Specifically, construction of the tetracyclic core was achieved by dehydration of lactam **18** with $POCl_3$ followed by reduction of the intermediate imine with $NaBH_4$. The cyanomethyl group was transformed into the C3 hydroxyethyl side chain by sequential reduction of the nitrile **20** with DIBAL and then $NaBH_4$ (44%, two steps). Finally, the natural product (±)-goniomitine (**1**) was obtained by epimerization of the *trans* ring fusion in **21** to the *cis* with catalytic *p*-TsOH in MeOH and Et_3N. The ^1H NMR spectra of synthetic **1** obtained from acid-catalyzed isomerization matched that of the natural product, and a ^{13}C NMR spectrum was identical to one from the work of Takano and coworkers.

In summary, the total synthesis of (±)-goniomitine was achieved in 17 steps from commercially available δ-valerolactam with an overall yield of 5.2%. This constitutes the shortest total synthesis of (±)-goniomitine reported to date. The highlights of the synthesis include the first application of a formal [3 + 2] cycloaddition between nitriles and DA cyclopropanes in total synthesis and the use of microwave-assisted reactions in order to shorten reaction times.

Acknowledgment. We thank NSERC, the donors of the American Chemical Society Petroleum Research fund, and the University of Western Ontario for financial assistance. We thank Prof. Kohei Inomata of Tohoku Pharmaceutical University and Prof. Yoshiharu Iwabuchi of Tohoku University for providing copies of the NMR spectra for both synthetic and natural goniomitine. We thank Mr. Jian Wang and Ms. Barbora Bajtos for helpful discussions.

Supporting Information Available: General experimental procedures and characterization of all new compounds, copies of NMR spectra, and copies of NMR from the isolation and Takano synthesis of goniomitine. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702376J

(13) Mohan, B.; Nagarathnam, D.; Vedachalam, M.; Srinivasan, P. C. *Synthesis* **1985**, 188−190.
(14) Heureux, N.; Wouters, J.; Marko, I. E. *Org. Lett.* **2005**, *7*, 5245−5248.
(15) Mander, L. N.; McLachlan, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 2400−2401.