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Biomimetic Approach to Perophoramidine and Communesin via an Intramolecular Cyclopropanation Reaction

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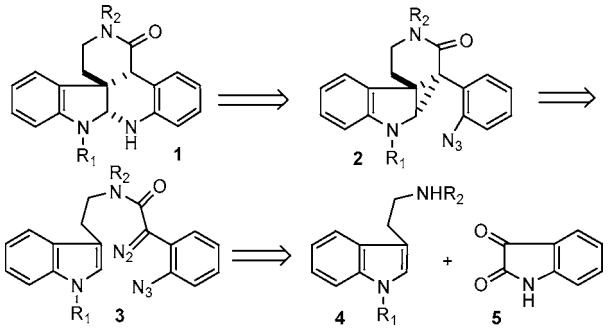
ABSTRACT



Starting from tryptamine 4 and isatin 5, a biomimetic approach to the pentacyclic substructure 1 of perophoramidine and communesin was developed. The key steps were to create a stable three/six bicyclic system 2 on the 2,3-double bond of an indole derivative 3 by an intramolecular cyclopropanation, followed by ring opening of the resulting cyclopropane ring with the in situ generated amine group of an aniline.

Indole alkaloids form an important class of natural products that have been studied extensively by chemists interested in synthesis because of their intriguing structures and exhibited biological activities. Recently, two indole alkaloids, perophoramidine[1] and communesin,[2] with novel molecular skeletons were isolated from ascidian *Perophora namei* and a strain of *Penicillium* sp., respectively. Both indole alkaloids have a similar polycyclic system containing two vicinal quaternary centers with relatively inverted stereochemistry at the 4-position of the part-saturated quinoline moiety.

The structural novelty and complexity of these indole alkaloids, along with their anticancer activities, have attracted intense synthetic interest over the last five years. A few modeling studies for constructing part of the polycyclic ring system were attempted through a halogen-selective tandem Heck carbonylation reaction[3] and a hetero Diels−Alder reaction between an indole moiety and an aza-*o*-xylylene intermediate,[4] which led to the first total synthesis of perophoramidine.[5]

(1) For an isolation and anticancer activity study of perophoramidine, see: Verbitski, S. M.; Mayne, C. L.; Davis, R. A. *J. Org. Chem*. **2002**, *67*, 7124.

(2) For an isolation and anticancer activity study of communesin, see: (a) Dalsgaard, P. W.; Blunt, J. W.; Munro, M. H. G.; Frisvad, J. C.; Christophersen, C. *J. Nat. Prod.* **2005**, *68*, 258. (b) Jadulco, R.; Edrada, R. A.; Ebel, R.; Berg, A.; Schaumann, K.; Wray, V.; Steube, K.; Proksch, P. *J. Nat. Prod.* **2004**, *67*, 78. (c) Ratnayake, A. S.; Yoshida, W. Y.; Mooberry, S. L.; Hemscheidt, T. K. *J. Org. Chem*. **2003**, *68*, 1640. (d) Ratnayake, A. S.; Yoshida, W. Y.; Mooberry, S. L.; Hemscheidt, T. K. *J. Org. Chem*. **2001**, *66*, 8717. (e) D'Amours, D.; Sallmann, F. R.; Dixit, V. M.; Poirier, G. G. *J. Cell Sci.* **2001**, *114*, 3771. (f) Numata, A.; Takahashi, C.; Ito, Y.; Takada, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Imachi, M.; Ito, T.; Hasegawa, T. *Tetrahedron Lett.* **1993**, *34*, 2355.

(3) Artman, G. D.; Weinreb, S. M. *Org. Lett*. **2003**, *5*, 1523.

(4) (a) Crawley, S. L.; Funk, R. L. *Org. Lett*. **2003**, *5*, 3169. (b) May, J. A.; Zeidan, R. K.; Stoltz, B. M. *Tetrahedron Lett.* **2003**, *44*, 1203.

(5) Fuchs, J. R.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 5068.

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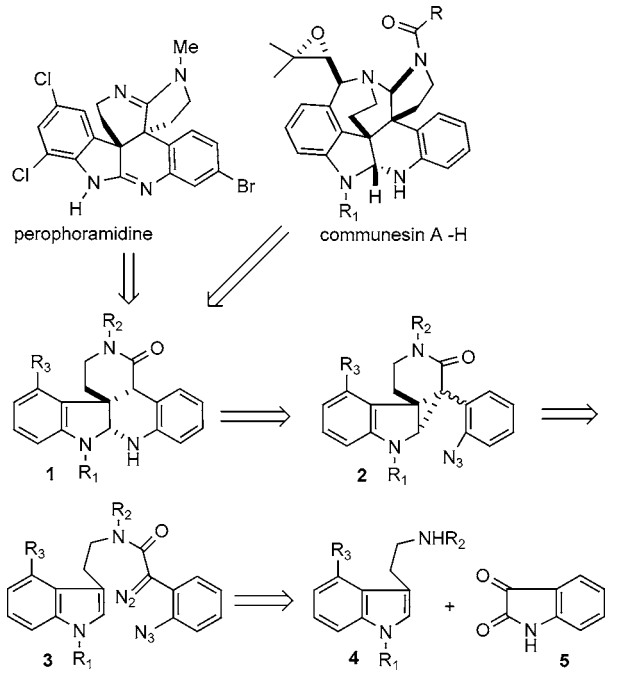
In exploration of a new synthetic approach to perophoramidine and communesin, we report here a biomimetic approach to the pentacyclic substructure **1**, shared by both alkaloids, via intramolecular cyclopropanation, followed by nucleophilic ring opening of the resulting activated cyclopropane ring with an in situ generated amine group of aniline (Scheme 1) as key steps.[6] The synthetic strategy is based on

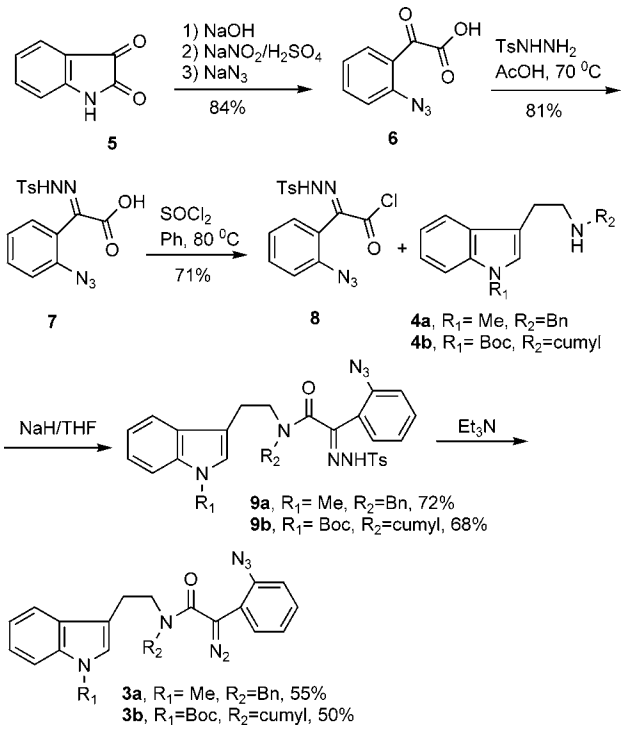
Scheme 1



the hypothesis that these alkaloids have a biosynthetic origin from tryptamine and isatin.

By examining the retrosynthetic plan as outlined in Scheme 1, the feasibility of this type of biomimetic approach will most likely rely on the key step of creating a cyclopropane ring from the 2,3-double bond of indole **3**. Although numerous papers reported the metal-catalyzed diazoalkane decomposition to prepare a cyclopropane ring from a variety of substrates,[7] a literature search found only a few examples describing the cyclopropanation reactions on indoles.[8] Intermolecular cyclopropanation of indole with a carbene could generate a stable cyclopropane ring on the 2,3-double bond of indole, but intramolecular cyclopropanation of 3-substituted indole, with a γ-diazoketone or δ-diazoketo ester functional group at the side chain, provided mainly the C−H substitution product at the 2-position of indole rather than yielding a cyclopropane ring. The C-2 substitution products were formed as a result of ring collapse to relieve ring strain of a spiro fused three/four or three/five bicyclic system. It is reasonable to expect that the ring strain of a three/six bicyclic system in **2** should be lower than that of the three/four and three/five bicyclic systems and in turn allow the three/six bicyclic system's survival from the reaction.[9] To realize the unprecedented reaction of installing a stable cyclopropane ring on the 2,3-double bond of 3-substituted indole, the availability of diazo **3** became the key point needed to be addressed first.

Scheme 2



As described in Scheme 2, starting with isatin **5**, azido acid **6** was prepared in 84% yield through a three-step, one-pot procedure by modifying the literature procedures.[10] Treatment of **6** with *p*-toluenesulfonyl-hydrazine in hot acetic acid provided hydrazone **7** in 81% yield. The stable acyl chloride **8** was easily obtained in 71% yield by reaction of **7** with thionyl chloride at 80 °C for 1 h in benzene, followed by recrystallization from benzene after removing excess thionyl chloride. Treatment of N,N′-disubstituted tryptamines **4a** and **4b** with 2 equiv of NaH in THF, respectively, followed by dropwise addition of **8** (2 equiv) in THF at 0

(6) Intramolecular opening of activated cyclopropane by amine was first reported by Danishefsky. See: Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66.

(7) Doyle, M. P.; Mckervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998.

(8) (a) Gnad, F.; Poleschak, M.; Reiser, O. *Tetrahedron Lett.* **2004**, *45*, 4277. (b) Jung, M. E.; Slowinski, F. *Tetrahedron Lett.* **2001**, *42*, 6835. (c) Salim, M.; Capretta, A. *Tetrahedron* **2000**, *56*, 8063. (d) Dhanak, D.; Kuroda, R.; Reese, C. B. *Tetrahedron Lett.* **1987**, *28*, 1827. (e) Wenkert, E.; Alonso, M. E.; Gottlieb, H. E.; Sanchez, E. L. *J. Org. Chem.* **1977**, *42*, 3945. (f) Ashmore, J. W.; Radlick, P. C.; Helmkamp, G. K. *Synth. Commun.* **1976**, *6*, 399. (g) Welstead, W. J.; Stauffer, H. F.; Sancilio, L. F. *J. Med. Chem.* **1974**, *17*, 544.

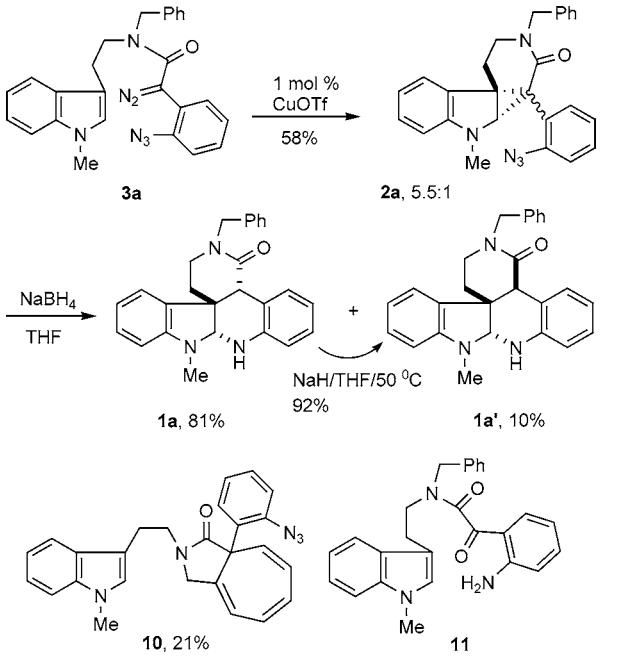
(9) A stable spiro fused three/seven bicycle system was found in indole alkaloid lundurines. See: (a) Kam, T. S.; Lim, K. H.; Yoganathan, K.; Hayashi, M.; Komiyama, K. *Tetrahedron* **2004**, *60*, 10739. (b) Kam, T. S.; Yoganathan, K.; Chuah, Ch. H. *Tetrahedron Lett.* **1995**, *36*, 759.

(10) (a) Hall, J. H.; Patterson, E. *J. Am. Chem. Soc.* **1967**, *89*, 5856. (b) Snyder, H. R.; Thompson, C. B.; Hinman, R. L. *J. Am. Chem. Soc.* **1952**, *74*, 2009.

°C gave amides **9a** and **9b** in 72% and 68% yields. For achieving a successful condensation of **4** with **8**, the second amine functional group in **4** had to be deprotonated first because decomposition of **8** occurred when **8** was directly added into a solution of NaH. Condensation of **4** with **8** in the presence of an organic base such as Et_3N, DMAP, or DBU was unsuccessful. The diazos **3a** and **3b** were prepared in 55% and 50% yields by treatment of the purified **9a** and **9b** with Et_3N for 24 h in CH_2Cl_2, respectively. Attempts to combine the above two steps of amidation and diazo formation into a one-pot procedure (from **8** to **3**) were not feasible under a variety of reaction conditions. Because diazos **3a** and **3b** were not stable enough on heating and under strong base conditions, long time storage of both **3a** and **3b** is not recommended.

With diazo **3a** in hand, our attention then turned to installing a cyclopropane ring on the 2,3-double bond of the indole core by copper-catalyzed intramolecular cyclopropanation (Scheme 3). As anticipated, diazo decomposition of

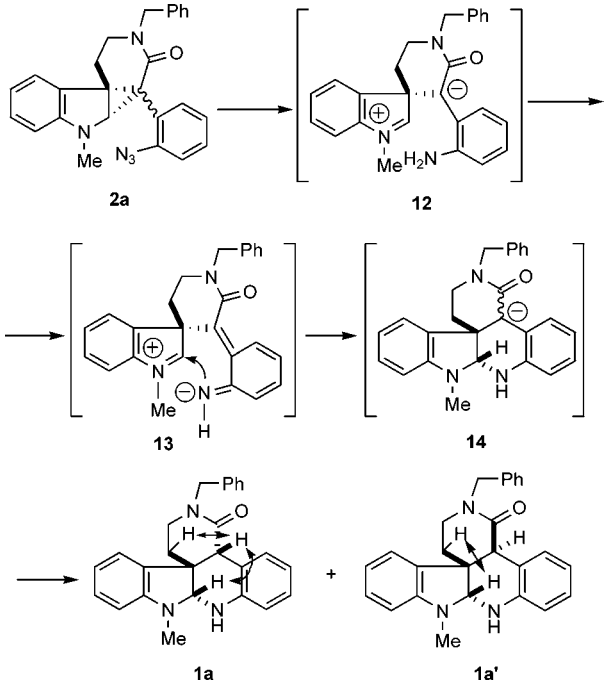
Scheme 3



3a in the presence of 1 mol % of CuOTf in CH_2Cl_2 yielded the stable cyclopropane intermediate **2a** in 58% yield as an inseparable mixture of diastereoisomers in a 5.5:1 ratio and the C−C insertion compound **10** as a byproduct in 21% yield. Reduction of the azide group with $NaBH_4$ in THF, followed by ring opening of the cyclopropane ring by the in situ generated amine, provided the pentacyclic substructure **1a** as the major isomer in 81% yield and the minor isomer **1a′** in 10% yield. The kinetic product **1a** was then isomerized completely to its thermodynamically stable isomer **1a′** under a strong base condition and upon heating. Thus, treatment of **1a** with 2 equiv of NaH in THF at 50 °C gave **1a′** in 92% yield and **11** in 3% yield. Compound **11** was probably formed by oxidation of the sodium enolate of **1a** or **1a′** followed by a retroaldol reaction.

It is interesting to note that ring opening of the cyclopropane ring by the in situ generated aniline provided **1a** and **1a′** with retention of stereochemistry at C-2 of the indole. A rationale for the observed stereochemistry is that an indolenium intermediate **12** is first formed by collapse of the cyclopropane ring (Scheme 4). Aromatic isomerization of

Scheme 4

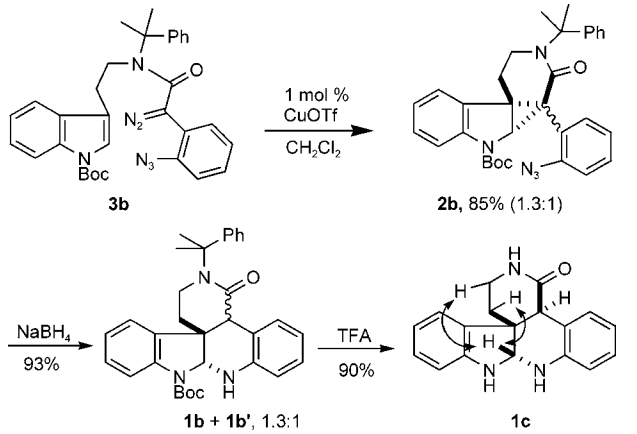


12 leading to intermediate **13**, followed by stereoselective nucleophilic attack of the negative nitrogen in **13** at C-2 from the bottom of the indolenium plane, affords intermediate **14**. Nonstereospecific protonation of **14** provides two isomers **1a** and **1a′**. The stereochemistry in **1a** and **1a′** was secured by proton NOEDs experiments. In the NOEDs experiments, the correlation between the amido α-proton and the bisaminal proton in **1a** and the correlation between the bisaminal proton and the methylene proton in **1a′** were observed.

Similarly, when diazo **3b** was treated with 1 mol % of CuOTf in CH_2Cl_2, an inseparable mixture of **2b** in a 1.3:1 ratio was isolated in 85% yield (Scheme 5). With a cumyl protecting group on the amido nitrogen in **3b** rather than a benzyl protecting group, a C−C insertion reaction of carbene on the phenyl ring was totally avoided.

Reduction of **2b** with $NaBH_4$ gave the pentacyclic products **1b** and **1b′** in 93% yield. Interestingly, upon removing both Boc and cumyl groups in **1b** and **1b′** using 40% of TFA in CH_2Cl_2 at room temperature, the thermodynamically stable isomer **1c** was isolated as the sole product in 90% yield. The stereochemistry of **1c** with a trans relationship between the bisaminal proton and the amido α-proton was confirmed by an NOEDs experiment. In the NOEDs experiment, the

Scheme 5



correlation between the bisaminal proton and the methylene proton was observed.

In summary, starting from tryptamine and isatin, we have developed a biomimetic approach to the pentacyclic substructures **1a′** and **1b′** of perophoramidine and communesin via an intramolecular cyclopropanation as a key step. Synthetic effort directed toward the total syntheses of these indole alkaloids is currently underway.

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Supporting Information Available: Experimental details, ^{1}H and ^{13}C NMR spectra of **1**−**4** and **6**−**9**, DEPT, COSY, HMBC, HMQC, and NOEDs NMR spectra of **1a′**, **1c**, and **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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