J|A|C|S
COMMUNICATIONS

Published on Web 04/02/2004

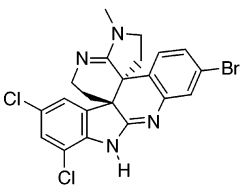
Total Synthesis of (±)-Perophoramidine

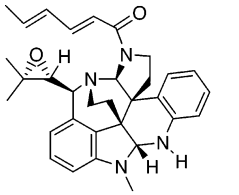
James R. Fuchs and Raymond L. Funk*

Department of Chemistry, Pennsylvania State University, University Park, Pennsylvania 16802

Received January 24, 2004; E-mail: rlf@chem.psu.edu

Perophoramidine[1] and communesin B[2] are two architecturally intriguing natural products related by their presumed biosynthetic origin from two molecules of tryptamine. Their structural differences are substantial, however, since perophoramidine (1) embodies a bis-amidine rather than the bis-aminal functionality present in communesin B, (2) lacks the azepine ring system of communesin B, (3) possesses a *trans*- rather than *cis*-stereochemical relationship of the vicinal quaternary centers, and (4) contains halogenated aromatic rings.

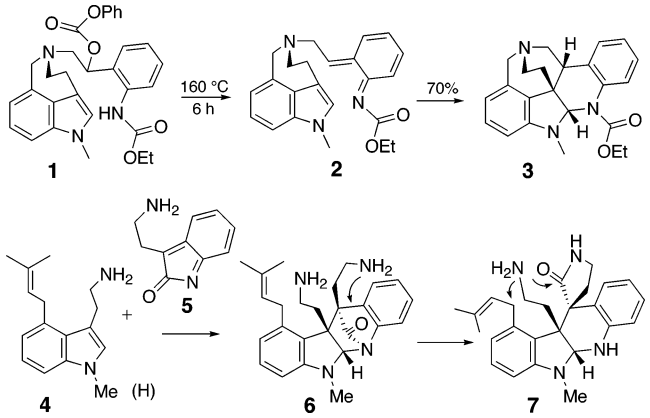




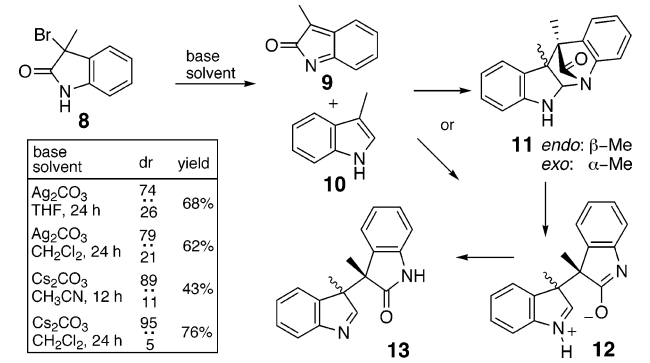
Accordingly, the structural features and biological properties[3] of these natural products have elicited activity directed toward their chemical synthesis.[4] Indeed, we recently reported that the hexacyclic substructure **3** of communesin B could be rapidly assembled by an intramolecular cycloaddition of the indole, *N*-acyl-aza-*o*-xylylene intermediate **2**, in turn, generated from carbonate **1** (Scheme 1).[4c] This result led us to contemplate the union of the two tryptamine moieties in the putative biosynthetic pathway through an analogous hetero Diels−Alder reaction of the prenylated tryptamine **4** with an oxidized tryptamine, 3-(2-aminoethyl)indol-2-one (**5**).[5] The resulting *exo*-cycloadduct **6** would be expected to undergo a rapid transamidation reaction with the strained bridged bicyclic lactam to afford the spirolactam **7**. Reduction of the lactam carbonyl and cyclizations with the primary amine nitrogen would then afford the complete ring system of communesin B.

The viability of this type[6] of "biomimetic" approach rests on the ability to generate and trap the quasi-antiaromatic indol-2-one. While we are not aware of any reactions in the literature where this intermediate has been explicitly stated or deliberately generated, numerous examples can be found that suggest that it may have been.[7] In view of this precedent, we were gratified to discover that subjection of 3-bromo-3-methylindolin-2-one (**8**)[8] and 3-methylindole (**10**) to the Kitagawa reaction conditions[7b] afforded the indolenine **13** (Scheme 2) as a mixture of stereoisomers (74:26). Moreover, the stereoselectivity could be significantly improved (95:5) by employing cesium carbonate in methylene chloride, a protocol reported by Corey for the generation of acyclic *N*-acyl-aza-*o*-xylylenes.[9] Thermodynamic control does not appear to be operative here since resubjection of the minor isomer to these reaction conditions afforded none of the major isomer. The direct formation of intermediate **12** via a conjugate addition pathway involving the putative indol-2-one intermediate **9** is in accord with the observed solvent and counterion effects. However, it is also possible that Lewis acid catalysis modulates the stereoselectivity en route to cycloadduct **11** which undergoes subsequent ring opening to **12**.[10]

Scheme 1

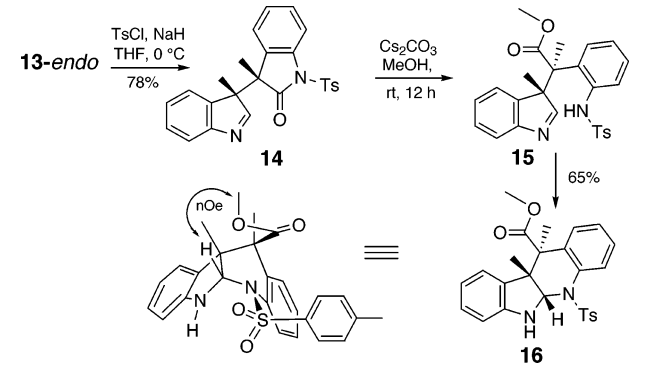


Scheme 2



base solvent	dr	yield
Ag_2CO_3 THF, 24 h	74 : 26	68%
Ag_2CO_3 CH_2Cl_2, 24 h	79 : 21	62%
Cs_2CO_3 CH_3CN, 12 h	89 : 11	43%
Cs_2CO_3 CH_2Cl_2, 24 h	95 : 5	76%

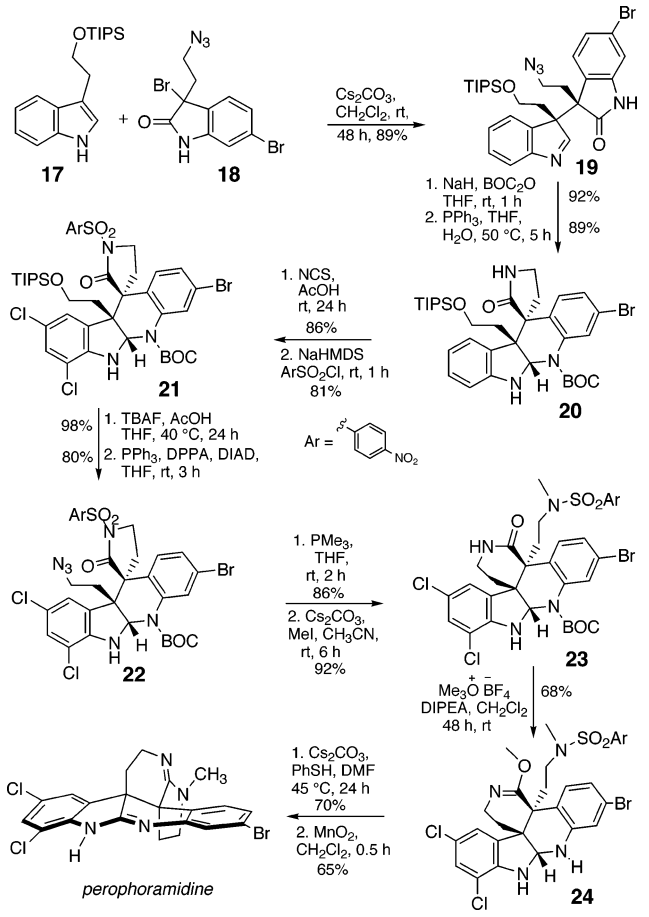
Scheme 3



The elucidation of the stereochemistry of indolenines **13** was a prerequisite for the orientation of our synthetic effort toward the appropriate natural product target, perophoramidine/communesin B. Toward that goal, the readily separable major isomer of indolenine **13** was converted into the conformationally less mobile aminal **16** (Scheme 3). Thus, tosylation of the lactam functionality followed by treatment of the resulting imide **14** with basic methanol effected ring opening and subsequent closure of the tosylamide anion of **15** upon the indolenine functionality to afford aminal **16**.

10.1021/ja049569g CCC: $27.50

Scheme 4



A diagnostic, albeit surprising, nOe was observed between the aminal and methyl ester proton resonances, which thereby establishes the *trans* relationship of the methyl substituents.

On the basis of this result, a "biomimetic" strategy for the total synthesis of perophoramidine was envisaged analogous to the one outlined for communesin B in Scheme 1. To that end, we were gratified to discover that the indole **17**[8] and 3-bromoindolin-2-one **18**[8] could be coupled (Scheme 4) without deleterious consequence due to the replacement of the methyl substituents of the previously discussed model system (Scheme 2) with functionalized side chains and/or the bromine substituent on the aromatic ring of oxindole **18** (89%, dr > 20:1). The lactam **19** was converted into the corresponding BOC-imide derivative that underwent a cascade reaction sequence upon reduction of the azido functionality involving transamidation and closure of the resulting carbamate upon the indolenine to deliver the aminal **20**. The opportunity to introduce the chloro substituents now presented itself since the aromatic rings were differentially activated for electrophilic aromatic substitution. Thus, chlorination of aminal **20** followed by nosylation of the lactam functionality proceeded uneventfully to afford the imide **21**. Next, the silyloxy functionality of **21** was converted into the azido group present in **22** by the straightforward reaction sequence. It should be noted here that the *N*-methyl lactam analogous to **22** was also prepared during the course of this investigation, although all attempts to convert it to the corresponding amidine via an intramolecular Staudinger reaction failed. Consequently, the imide **22** was subjected to the second transamidation reaction in the synthetic sequence, and the newly generated *p*-nosylamide was selectively methylated in preference to the six-membered lactam to afford the pentacyclic compound **23**. Treatment of lactam **23** with Meerwein's reagent effected its conversion into the corresponding imidate **24** as well as the fortuitous removal of the BOC protecting group. As anticipated, deprotection of nosylamide **24** according to the Fukuyama protocol[11] was accompanied by attack of the resulting methylamine from the easily accessible α-face of the imidate to introduce the more basic of the two amidine functionalities. The remaining amidine was then installed upon oxidation (MnO_2 or DDQ) to furnish racemic perophoramidine whose ^1H and ^{13}C spectral characteristics were identical to those previously published.[1]

In conclusion, we have discovered that 3-alkylindoles undergo base-promoted alkylation reactions with 3-bromo-3-alkylindolin-2-ones.[7] This methodology facilitated the first total synthesis of the cytotoxic agent perophoramidine through the early stage, highly stereoselective introduction of the vicinial quaternary centers. Current effort is directed toward delineating the mechanism and stereocontrol elements of this reaction as well as its application in other total synthesis endeavors.

Acknowledgment. We thank Professors Samuel Danishefsky and Ken Feldman for helpful discussions. We appreciate the financial support provided by the National Institutes of Health (GM28553).

Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Isolated from the ascidian *Perophora namei* (cytotoxicity, HCT116, IC_{50} = 60 μM) Verbitski, S. M.; Mayne, C. L.; Davis, R. A.; Concepcion, G. P.; Ireland, C. M. *J. Org. Chem.* **2002**, *67*, 7124.

(2) (a) Isolated from the fungal strain *Penicillium* sp. (P-388, ED_{50} = 0.88 μM): 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. (b) Isolated from an unidentifed fungus but structurally misassigned as nomofungin (LoVo, MIC = 3.9 μM) Ratnayake, A. S.; Yoshida, W. Y.; Mooberry, S. L.; Hemscheidt, T. K. *J. Org. Chem.* **2001**, *66*, 8717. (c) Erratum: Ratnayake, A. S.; Yoshida, W. Y.; Mooberry, S. L.; Hemscheidt, T. K. *J. Org. Chem.* **2003**, *68*, 1640. (d) Recently isolated derivatives: Jadulco, R.; Edrada, R. A.; Ebel, R.; Berg, A.; Schaumann, K.; Wray, V.; Steube, K.; Proksch, P. *J. Nat. Prod.* **2004**, *67*, 78.

(3) Communesin B was observed to disrupt microfilaments in cultured mammalian cells,[2b] and perophoramidine induces apoptosis via PARP-1 cleavage,[1] a signal of irreparable DNA damage, see: D'Amours, D.; Sallmann, F. R.; Dixit, V. M.; Poirier, G. G. *J. Cell Sci.* **2001**, *114*, 3771.

(4) Perophoramidine: (a) Artman, G. D.; Weinreb, S. M. *Org. Lett.* **2003**, *5*, 1523. Communesin B: (b) May, J. A.; Zeidan, R. K.; Stoltz, B. M. *Tetrahedron Lett.* **2003**, *44*, 1203. (c) Crawley, S. L.; Funk, R. L. *Org. Lett.* **2003**, *5*, 3169.

(5) Stoltz and co-workers have proposed a very similar biosynthetic route through the cycloaddition of indol-2-one **5** with *N*-methylaurantioclavine, i.e, the azepine analogue of indole **4**, see ref 4b.

(6) For the seminal examples of proposed alkaloid biosynthesis (calycanthaceous) originating from tryptamine dimers, see: (a) Robinson, R.; Teuber, H. J. *Chem. Ind.* **1954**, 783. (b) Woodward, R. B.; Yang, N. C.; Katz, T. J. *Proc. Chem. Soc.* **1960**, 76. Indeed, the gross structure of perophoramidine was predicted, albeit, bearing aminals instead of amidines (northern aminal dimethylated) and lacking the halogen substituents. It was subsequently synthesized, see: (c) Hendrickson, J. B.; Rees, R.; Göschke, R. *Proc. Chem. Soc.* **1962**, 383.

(7) (a) For example, the substitution reaction of an 3-alkyl-3-chloroindolin-2-one with KCN might proceed by an elimination−addition pathway rather than direct displacement. Labroo, R. B.; Labroo, V. M.; King, M. M.; Cohen, L. A. *J. Org. Chem.* **1991**, *56*, 3637. (b) More pertinent to our specific application is the Kitagawa synthesis of the antibiotic trisindoline by the silver carbonate-promoted replacement of the two bromine substituents of 3,3-dibromoindolin-2-one with two indole moieties. Kobayashi, M.; Aoki, S.; Gato, K.; Matsunami, K.; Kurosu, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1994**, *42*, 2449.

(8) See Supporting Information for the preparation of this compound.

(9) Steinhagen, H.; Corey, E. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 1928.

(10) Alternative pathways for the formation of indolenines **13** other than direct displacement can also be envisaged, for example, one involving transfer alkylation. For an instructive example, see: Melvin, L. S.; Trost, B. M. *J. Am. Chem. Soc.* **1972**, *94*, 1790.

(11) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.

JA049569G