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A Synthetic Approach to Nomofungin/ Communesin B

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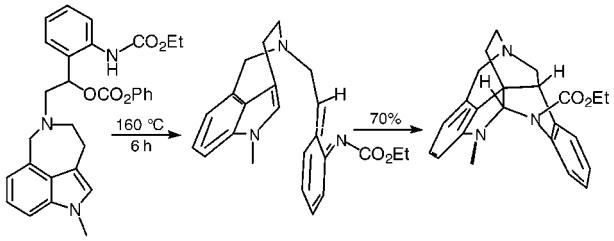
ABSTRACT

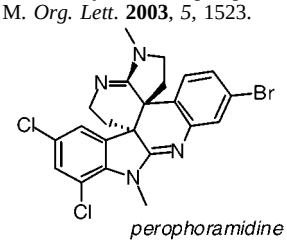


A highly stereoselective intramolecular cycloaddition of an indole tethered to an aza-*ortho*-xylylene intermediate effects the rapid construction of a substantial portion of the ring system of the cytotoxic natural product communesin B. An analogous cycloaddition involving an *ortho*-quinone methide intermediate provides an adduct that clearly revealed that the structural assignment for nomofungin was in error.

Hemscheidt and co-workers recently reported the discovery of a structurally intriguing polycyclic natural product from an endophytic fungus using a bioassay designed to detect antimicrotubule/antimicrofilament agents.[1a] The unidentified fungus was isolated from the bark of *Ficus microcarpa* L. and has subsequently been lost. Accordingly, the natural product was given the name nomofungin (Scheme 1). The structural assignment was based primarily on NMR spectroscopic measurements, and the exiton chirality method was used to determine the absolute stereochemistry.[1a] Curiously, a structurally quite similar natural product, communesin B (Scheme 2), which has an NH instead of the proposed pyran oxygen for nomofungin,[2a] had previously been reported and gone relatively unnoticed by the synthetic community. Moreover, communesin B gives proton and carbon spectra nearly identical to those reported for nomofungin. This discrepancy was recently clarified by Stolz and co-workers who proposed a biosynthetic route to communesin B through the oxidative coupling of tryptamine with the ergot alkaloid aurantioclavine.[3] Preliminary experimental work corroborated this conjecture and prompted the retraction of the nomofungin structure.[1b] We describe herein our independent observations that the natural products nomofungin and communesin B are the same compound and provide unequivocable evidence that the structural assignment for communesin B is correct.

(1) (a) Ratnayake, A. S.; Yoshida, W. Y.; Mooberry, S. L.; Hemscheidt, T. K. *J. Org. Chem.* **2001**, *66*, 8717. As expected, nomofungin was subsequently found to be moderately cytotoxic (LoVo, MIC = 3.9 μM; KB, MIC = 8.8 μM) and shown to disrupt microfilaments in cultured mammalian cells. (b) Erratum: Ratnayake, A. S.; Yoshida, W. Y.; Mooberry, S. L.; Hemscheidt, T. K. *J. Org. Chem.* **2003**, *68*, 1640.

(2) (a) 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. Communesin A has an acetamide instead of the sorbamide functionality found in communesin B. (b) For the isolation of a related alkaloid, perophoramidine, which possesses a bis-amidine rather than the bis-aminal functionality present in communesin B, lacks the azepine ring system of communesin B and has a *trans*-C(7)−C(13) rather than a *cis* stereochemical relationship, see: Verbitski, S. M.; Mayne, C. L.; Davis, R. A.; Concepcion, G. P.; Ireland, C. M. *J. Org. Chem.* **2002**, *67*, 7124. (c) For an approach to the total synthesis of perophoramidine, see: Artman, G. D.; Weinreb, S. M. *Org. Lett.* **2003**, *5*, 1523.



perophoramidine

(3) May, J. A.; Zeidan, R. K.; Stoltz, B. M. *Tetrahedron Lett.* **2003**, *44*, 1203.

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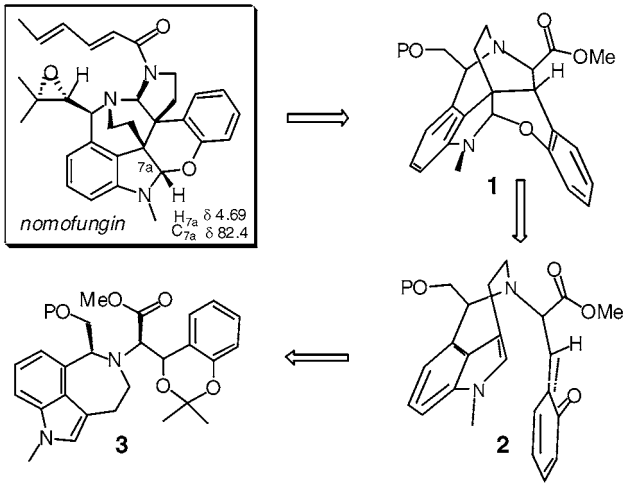
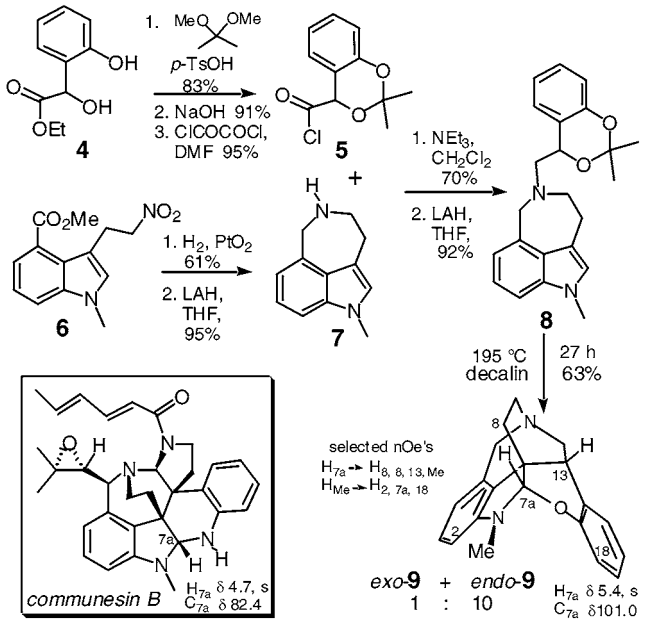
Scheme 1



Scheme 2



We were intrigued by the prospect of rapidly assembling a substantial portion of the core ring system of nomofungin via an intramolecular cycloaddition reaction involving an *ortho*-quinone methide intermediate.[4] An abbreviated retrosynthetic plan that features this key step is outlined in Scheme 1. Thus, the carboxyl functionality of cycloadduct **1** could serve as a suitable handle for the elaboration of the pyrrolidine ring of nomofungin by one of several conceivable synthetic sequences and the transformation of the protected hydroxymethyl group to the epoxide moiety should be relatively straightforward. The *N*,*O*-acetal **1** was expected to arise from the cycloaddition of the *ortho*-quinone methide **2** with the tethered indole heterodienophile[5] through the preferred *endo*-transition state.[6] While there are many ways to thermally produce *ortho*-quinone methides (e.g., from 2-vinylphenols, *ortho*-hydroxybenzyl halides, *ortho*-hydroxybenzyl ethers, 1,2-benzooxazines, etc.),[4] we elected to examine the thermolysis of the benzodioxin **3**. The basis for the selection of this particular thermal precursor was threefold: (1) the benzodioxin functionality is inert, in comparison to the aforementioned precursors, to reagents required for its incorporation into the retrocycloaddition−cycloaddition substrate; (2) to the best of our knowledge, the generation of *ortho*-quinone methides by this protocol has not been previously reported;[7] and (3) we were biased by our successful exploitation of the related retrocycloadditions of substituted 4*H*-1,3-dioxins in a variety of synthetic endeavors.[8]

To quickly validate this general plan, we decided to prepare the simplified benzodioxin **8** (Scheme 2), which lacks the carbomethoxy and alkoxymethyl substituents present in benzodioxin **3**. To that end, the Lewis acid-catalyzed condensation product of phenol with ethyl glyoxylate, glycol **4**,[9] was converted to the corresponding acetonide. The ester functionality was then saponified, and the resulting carboxylic acid was transformed to the acid chloride **5**. The construction of the indole sector of the benzodioxin **8** was inititated with the preparation of indole **6** by straightforward adaptation of the previously described synthesis of the analogous *N*-*des*-methyl indole.[10] Hydrogenation of the nitro group of indole **6** led to concomitant cyclization of the intermediate amine to the corresponding lactam, which was then reduced with lithium aluminum hydride to afford the benzazepine **7**. The final reaction sequence further documented the stability of the benzodioxin functionality, namely, acylation of the acid chloride **5** with benzazepine **7** followed by reduction of the intermediate amide to afford the key retrocycloaddition−cycloaddition substrate **8**. We were pleased to observe that thermolysis of benzodioxin **8** in decalin (195 °C, 27 h) resulted in a clean transformation to a mixture (10:1) of *N*,*O*-acetal cycloadducts. The relative stereochemistry for the expected major isomer, *endo*-**9**, was

(4) For a review, see: Pettus, T. R. R.; Van De Walter, R. W. *Tetrahedron* **2002**, *58*, 5367.

(5) (a) For recent examples of cycloaddition reactions of indoles, see: Lynch, S. M.; Bur, S. K.; Padwa, A. *Org. Lett.* **2002**, *4*, 4643 and ref 9 therein. (b) For a review, see: Lee, L.; Snyder, J. K. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI: Stamford, CT, 1999; Vol. 6, p 119.

(6) Both the ester and silyloxymethyl substituents will prefer to emerge on the convex face. The analogous *exo* transition state has a serious peri interaction between the ester substituent and the proximate aryl ring [calculated ΔE = 2.9 kcal/mol, PC Model, transition state bond order C(7a)--O = 0.4, transition state bond order C(7)--C(13) = 0.2].

(7) A benzodioxin has been converted to the corresponding diacetate and then nucleophilically triggered (NaOH) to generate an *ortho*-quinone methide; see: Lhomme, J.; Fixler, N.; Salez, H.; Demeunynck, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1649.

(8) (a) Greshock, T. J.; Funk, R. L. *J. Am. Chem. Soc.* **2002**, *124*, 754. (b) Maeng, J.-H.; Funk, R. L. *Org. Lett.* **2002**, *4*, 331. (c) Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3923. (d) Aungst, R. A., Jr.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3553. (e) Greshock, T. J.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3511. (f) Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3349. (g) Aungst, R. A., Jr.; Funk, R. L. *J. Am. Chem. Soc.* **2001**, *123*, 9455. (h) Maeng, J.-H.; Funk, R. L. *Org. Lett.* **2001**, *3*, 1125. (i) Funk, R. L.; Fearnley, S. P.; Gregg, R. J. *Tetrahedron* **2000**, *56*, 10275.

(9) We followed the procedure used for chiral glyoxylates; see: Bigi, F.; Bocelli, G.; Maggi, R.; Sartori, G. *J. Org. Chem.* **1999**, *64*, 5004.

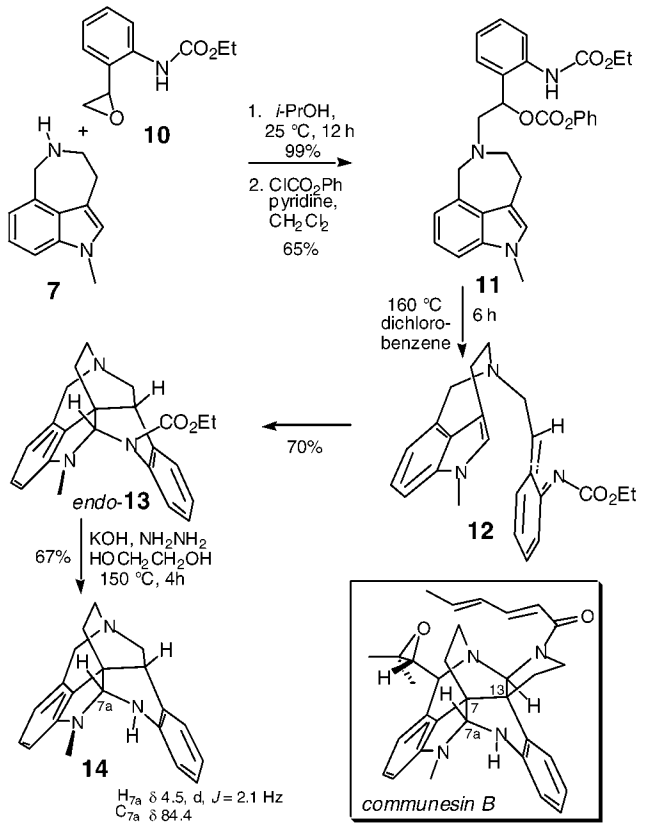
(10) Clark, R. D.; Weinhardt, K. K.; Berger, J.; Fisher, L. E.; Brown, C. M.; MacKinnon, A. C.; Kilpatrick, A. T.; Spedding, M. *J. Med. Chem.* **1990**, *33*, 633.

assigned on the basis of the observed NOEs, the most diagnostic of which are provided in Scheme 2. While at first glance these conditions may appear to be harsh, they are actually ideal in the sense that a reactive intermediate, prone to side reactions,[4] is generated slowly and trapped immediately by a conformationally restricted and reactive heterodienophile to afford a quite stable product.

Unfortunately, our gratification was short-lived. Comparison of the diagnostic H_{7a} and C_{7a} NMR resonances of *N*,*O*-acetal *endo*-**9** with those reported for nomofungin[1a] suggested a serious discrepancy. The chemical shift of the resonance for the *N*,*O*-acetal proton in *endo*-**9** (δ 5.4, $CDCl_3$) is significantly downfield from the analogous resonance reported for nomofungin (δ 4.7, $CDCl_3$). The carbon resonance is also in disagreement (δ 101.0 vs 82.4). Moreover, it seemed highly unlikely that conformational effects were responsible for the chemical shift differences since *N*,*O*-acetal *endo*-**9** and nomofungin are locked into nearly identical conformers. Hence, on the basis of our experimental work, we were forced to conclude that communesin B represented the correct structure.[11]

Fortunately, we could readily adapt the general synthetic plan outlined in Scheme 1, which now required the generation of an aza-*ortho*-xylylene intermediate.[12] Hopefully, this reactive intermediate would also undergo the intramolecular cycloaddition with the indole heterodienophile and thereby introduce the "southern" aminal substructure of communesin B (Scheme 3). Pursuant to that goal, ring opening of the known epoxide **10**[13] with the benzazepine **7** gave a regioisomeric mixture (9:1) of amino alcohols that could be readily separated upon conversion to the corresponding phenyl carbonates. Upon thermolysis in dichlorobenzene, the major carbonate **11**[14] was found to be an efficient precursor to *N*-acyl-aza-*ortho*-xylylene **12** that gave rise to a single cycloadduct, aminal *endo*-**13**. The stereochemical assignment was secured upon hydrolysis of the carbamate moiety of *endo*-**13** to the aminal **14**, which exhibited the analogous NOEs previously observed for the "nomofungin" structure

Scheme 3



endo-**9**. More importantly, the chemical shift of the resonances for the aminal proton and aminal carbon of aminal **14** (δ 4.5 and 84.4, respectively) are quite similar to those reported for communesin B (δ 4.7 and 82.4).

In conclusion, we have shown that a hexacyclic substructure of the core heptacyclic ring system of communesin B can be rapidly constructed by a novel indole, aza-*ortho*-xylylene intramolecular hetero Diels−Alder reaction. Synthetic effort directed toward introduction of the remaining pyrrolidine ring and completion of the natural product synthesis is currently underway.

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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.

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(11) We also recognized that biosynthetic considerations favor communesin B and proposed a pathway involving tryptamine dimerization similar to the one advanced by Stolz.[3] The validation of our hypothesis will be the subject of a future communication. For 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.

(12) For a recent review, see: Wojciechoski, K. *Eur. J. Org. Chem.* **2001**, 3587.

(13) Ruano, J. L. G.; Pedrega, C.; Rodriguez, J. H. *Tetrahedron* **1989**, *45*, 203.

(14) This relatively mild protocol for generating an aza-*ortho*-xylylene intermediate is underutilized. For the first and only examples, see: Kubo, H.; Nishiyama, K.; Sato, T.; Higashiyama, K.; Ohmiya, S. *Heterocycles* **1998**, *48*, 1103.