Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 1203–1205

TETRAHEDRON LETTERS

# Biomimetic approach to communesin B (a.k.a. nomofungin)

Jeremy A. May, Ryan K. Zeidan and Brian M. Stoltz*

*The Arnold and Mabel Beckman Laboratory for Chemical Synthesis Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125, USA*

Received 26 November 2002; revised 9 December 2002; accepted 9 December 2002

**Abstract**—The development of an approach to the alkaloid communesin B (**2**) is presented. The approach is based on considerations of a possible biosynthetic sequence involving an oxidative coupling of tryptamine with a derivative of the ergot alkaloid aurantioclavine. Structure revision is also suggested for the recently isolated microfilament disrupting alkaloid nomofungin. 

Indole alkaloids and related indoline-containing natural products are among the most intensely studied and interesting classes of molecules available for synthetic chemists. We have recently initiated synthetic studies directed toward the indoline alkaloids communesins A (**1**) and B (**2**).[1] Interestingly, the structure of communesin B is nearly identical to that of nomofungin (**3**), a natural product that was recently reported[2] (Fig. 1). Herein, we report our preliminary studies directed toward the synthesis of the communesins and attempt to clarify the structure of nomofungin based on a biosynthetic hypothesis and $^{1}H$ and $^{13}C$ NMR chemical shift data of synthetic intermediates.

Biogenetically, the communesins can be thought of as arising via an oxidative union of tryptamine (**6**) with the related natural product, aurantioclavine (**7**, Scheme 1).[3] Perhaps more provocative is the notion that an oxidation of tryptamine leads to the quinone methide imine **9**, which undergoes a Diels–Alder reaction with aurantioclavine derivative **8** to form polycyclic intermediate **10**. This intermediate, possessing a highly twisted lactam (analogous to the strained quinuclidone ring system) should be easily cleaved by the residual primary amine to produce the spiro lactam **11**. Biosynthetic reduction of the lactam, aminal closure, epoxidation, and acylation affords communesins A and B. It was based on this hypothesis that we began our investigations. It is also intriguing to note that there is not a reasonable biogenetic equivalent that would lead to the proposed structure for nomofungin.

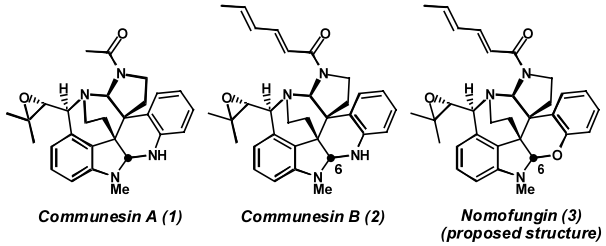
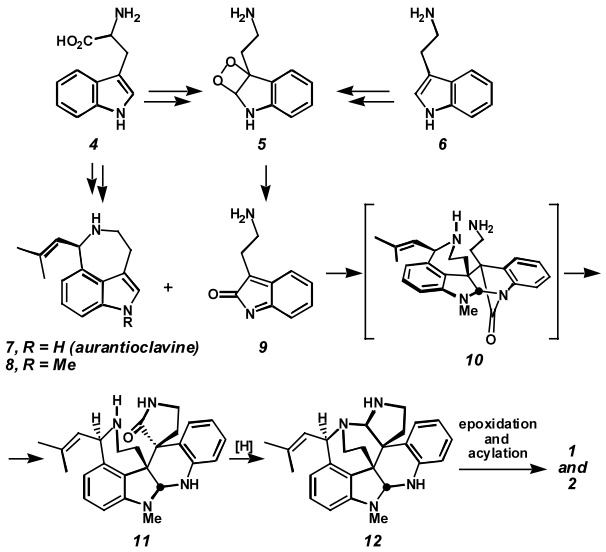



**Figure 1.**

This conjecture prompted us to examine the reported $^{1}H$ and $^{13}C$ NMR data for nomofungin more closely. Interestingly, the chemical shifts and coupling constants are essentially identical to those reported for communesin B. In particular, the chemical shift of the C(6) proton is reported to be 4.70 for communesin B and 4.69 for nomofungin. Analogously, the $^{13}C$ NMR chemical shift for C(6) is 82.4 ppm for both compounds. From these data, and the similarity of the full NMR data set, we conclude that communesin B and nomofungin must be the same molecule. Furthermore, comparison to known chemical shift values for diaminal and aminal residues confirms the tendency for the $^{1}H$ NMR chemical shifts of the former to reside upfield relative to the latter (4.5–5.5 ppm versus 5.5–6.4 ppm).[4] Similarly, $^{13}C$ chemical shifts for aminal carbons are typically in the range of 97.0–107.0 ppm, while those for diaminal carbons are between 80.0–85.0 ppm.[5] Given the $^{1}H$ and $^{13}C$ NMR chemical shift data and the biogenetic proposal outlined in Scheme 1, we have undertaken the synthesis of the structure proposed for communesin B (**2**).[6,7]

* Corresponding author. Tel.: +1-626-395-6064; fax: +1-626-564-9297; e-mail: stoltz@caltech.edu

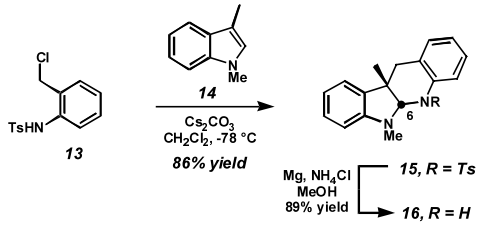
0040-4039/03/$ - see front matter 
PII: S0040-4039(02)02790-9



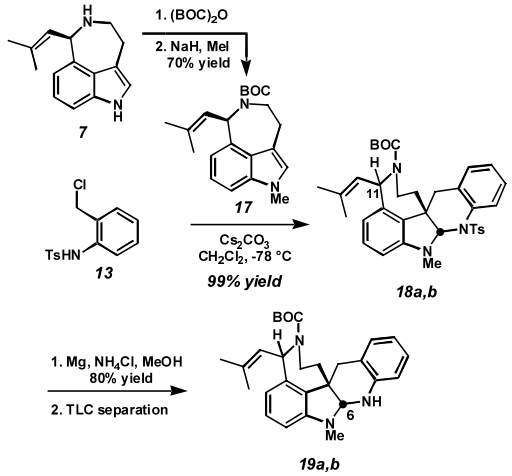

Scheme 1.

As a model system for the proposed Diels–Alder type cycloaddition of **8** and **9**, we investigated the cyclization of 1,3-dimethylindole (**14**) and chloroaniline **13** using conditions previously developed by Corey for the cycloaddition of **13** with electron rich olefins[8] (Scheme 2). To our delight, upon slow addition of chloride **13** to a mixture of indole **14** and $Cs_2CO_3$ in $CH_2Cl_2$ at −78°C, a reaction immediately occurred to provide a single diastereomeric adduct **15** in 86% yield.[9] Cleavage of the sulfonamide group by exposure of tetracycle **15** to Mg, MeOH, and $NH_4Cl$ produced diaminal **16**. Interestingly, the $^1H$ NMR chemical shift of the proton at C(6) is at 4.14 ppm and the $^{13}C$ resonance is at 83.9 ppm.[10] These shifts are in good accord with the values of 4.69–4.70 ppm ($^1H$) and 82.4 ppm ($^{13}C$) reported for both communesin B and nomofungin, strongly suggesting that the communesin structure is the appropriate representation for the natural product.

More recently, we have prepared (±)-aurantioclavine (**7**) by known methods[11] and utilized the *N*-BOC-*N*-methyl derivative **17** in the cycloaddition reaction with **13** (Scheme 3). Smooth cycloaddition proceeded again upon treatment with $Cs_2CO_3$ to produce an adduct that we have assigned as **18a**,**b**. Unfortunately, the putative cycloadduct was produced as a 1:1 mixture of diastereomers with respect to the methylpropenyl side chain at C(11). Following cleavage of the sulfonyl group with Mg and $NH_4Cl$ in MeOH, separation of the




Scheme 2.




Scheme 3.

diastereomers was possible by preparative thin layer silica gel chromatography.[12] Importantly, the $^{13}C$ NMR residues for C(6) of diastereomers **19a** and **19b** were at 84.8 and 83.9 ppm, again in full accord with the data for the communesins and nomofungin.

In conclusion, we propose that the natural products nomofungin and communesin B are, in fact, identical molecules and that the structure of communesin B more correctly represents the actual structure. We initially came to this conclusion based on biosynthetic thoughts that have influenced our synthetic direction. More recently, $^1H$ NMR chemical shift data of synthetic analogs to the communesin structure have bolstered this argument. Finally, a potential intermediate (**18**) in our synthesis of communesin B has been prepared by a [4+2] cycloaddition route (Scheme 3) that is similar to the biosynthetic proposal outlined in Scheme 1.[13] Efforts to complete the total synthesis of communesin B (a.k.a. nomofungin) by such biomimetic routes are ongoing. Progress toward these ends will be reported in due course.

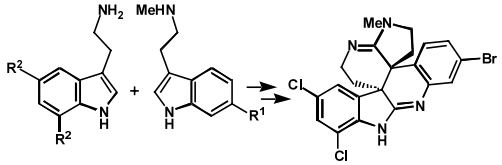
## Acknowledgements

The authors wish to thank the Dreyfus Foundation, Merck Research Laboratories, and Abbott Laboratories for financial support.

## References

1. Numata, A.; Takahashi, C.; Ito, Y.; Takada, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Imachi, M.; Tadayoshi, I.; Hasegawa, T. *Tetrahedron Lett*. **1993**, *34*, 2355.
2. Ratnayake, A. S.; Yoshida, W. Y.; Mooberry, S. L.; Hemsheidt, T. K. *J. Org. Chem*. **2001**, *66*, 8717.
3. (a) Soloveva, T. F.; Kuvichkina, T. N.; Baskunov, B. P.; Kozlovskii, A. G. *Microbiol*. **1995**, *64*, 550; (b) Kozlovskii, A. G.; Soloveva, T. F.; Sakharovskii, V. G.; Adanin, V. M. *Dokl. Akad. Nauk. SSSR* **1981**, *260*, 230.

4. For $^1$H NMR data, see Refs. 1, 2, and; (a) Jackson, A. H.; Smith, A. E. *J. Chem. Soc.* **1964**, 5510; (b) Dachriyanus; Sargent, M. V.; Wahyuni, F. S. *Aust. J. Chem.* **2000**, *53*, 159; (c) Horne, S.; Taylor, N.; Collins, S.; Rodrigo, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3047; (d) Nyerges, M.; Rudas, M.; Bitter, I.; Töke, L. *Tetrahedron* **1997**, *53*, 3269; (e) Spande, T. F.; Wilchek, M.; Witkop, B. *J. Am. Chem. Soc.* **1968**, 3256; (f) Chan, T.-L.; Schellenberg, K. A. *J. Biol. Chem.* **1968**, *243*, 6284; (g) Decodts, G.; Wakselman, M.; Vilkas, M. *Tetrahedron* **1970**, *26*, 3313; (h) Britten, A. Z.; Bardsley, W. G.; Hill, C. M. *Tetrahedron* **1971**, *27*, 5631; (i) Lyle, F. R. US Patent 5 973 257, 1985; *Chem. Abstr.* **1985**, *65*, 2870; (j) Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303; (k) Li, J.; Burgett, A. W. G.; Esser, L.; Amezcua, C.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4770; (l) Li, J.; Jeong, S.; Esser, L.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4765.
5. For $^{13}$C NMR data, see Refs. 1, 2, 4b, and 4d.
6. Recently, the novel polycyclic alkaloid perophoramidine (**i**) was isolated.[7] A similar tryptamine oxidative dimerization would account for its biogenesis as well.




***Perophoramidine (i)***

7. Verbitski, S. M.; Mayne, C. L.; Davis, R. A.; Concepcion, G. P.; Ireland, C. M. *J. Org. Chem.* **2002**, *67*, 7124.
8. Steinhagen, H.; Corey, E. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 1928.
9. To a cooled solution of 1,3-dimethyl indole (**14**, 23 mg, 0.16 mmol) and $Cs_2CO_3$ (168 mg, 0.360 mmol) in 0.2 mL anhydrous $CH_2Cl_2$ at −78°C was added chloroaniline **13** (53 mg, 0.179 mmol) in 0.8 ml anhydrous $CH_2Cl_2$ via syringe pump over 4 h. The solution was then warmed to 23°C for 30 min, immediately filtered over a Celite plug rinsing with $CH_2Cl_2$ (3×10 mL), concentrated under reduced pressure, and subjected to flash chromatography (6:1 hexane/ethyl acetate eluent) to provide the Diels–Alder adduct **15** (54.7 mg, 86% yield) as a white solid. **15**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.55 (dd, $J$=7.9, 1.2 Hz, 1H), 7.48 (d, $J$=8.5 Hz, 2H), 7.22 (d, $J$=8.2 Hz, 2H), 7.11 (t, $J$=7.6 Hz, 1H), 6.98 (td, $J$=7.6, 4.4 Hz, 1H), 6.88 (dd, $J$=7.6, 7.6 Hz, 1H), 6.76 (dd, $J$=7.6, 7.6 Hz, 2H), 6.45 (dd, $J$=7.3, 7.3 Hz, 1H), 6.14 (d, $J$=7.9 Hz, 1H), 5.66 (s, 1H), 2.99 (s, 3H), 2.52 (d, $J$=14.1 Hz, 1H), 2.42 (s, 3H), 1.62 (s, $J$=14.1 Hz, 1H), 1.34 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 150.0, 143.8, 137.9, 135.3, 135.1, 132.8, 129.8, 128.4, 128.2, 128.0, 127.3, 127.2, 126.8, 121.6, 117.0, 104.5, 86.5, 51.0, 38.1, 29.9, 29.2, 21.8; IR (neat) 3052, 3028, 2951, 2920, 1608, 1494 cm$^{-1}$; MS $m/z$ calcd for $[C_{24}H_{24}N_2O_2S+H]^+$: 405.1637, found 405.1634.
10. **16**: $R_F$ 0.44 (3:1 hexane:ethyl acetate eluent); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.17–7.12 (comp. m, 2H), 7.06 (dd, $J$=7.3, 7.9 Hz, 1H), 7.00 (d, $J$=7.3 Hz, 1H), 6.79 (dd, $J$=7.0, 7.6 Hz, 1H), 6.69 (dd, $J$=7.3, 7.3 Hz, 1H), 6.64 (d, $J$=7.9 Hz, 1H), 6.54 (d, $J$=7.6 Hz, 1H), 4.65 (br. s, 1H), 4.14 (s, 1H), 2.81 (d, $J$=15.2 Hz, 1H), 2.78 (s, 3H), 2.51 (d, $J$=15.2 Hz, 1H), 1.24 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 149.2, 141.1, 137.2, 129.2, 127.9, 127.1, 121.5, 121.4, 118.8, 118.0, 113.5, 108.1, 83.9, 39.1, 37.7, 32.5, 21.7; IR (neat) 3404, 2956, 2851, 1609 cm$^{-1}$; MS $m/z$ calcd for $[C_{17}H_{18}N_2+H]^+$: 250.1470, found 250.1461.
11. (a) Yamada, F.; Makita, Y.; Suzuki, T.; Somei, M. *Chem. Pharm. Bull.* **1985**, *33*, 2162; (b) Somei, M.; Yamada, F. Jpn. Patent JP 85-47044 19850308, 1986; (c) Iwao, M.; Motoi, O. *Tetrahedron Lett.* **1995**, *36*, 5929.
12. **19a**: $R_F$ 0.33 (3:1 hexane:ethyl acetate eluent); $^1$H NMR (300 MHz, $CDCl_3$, 50°C) $\delta$ 7.10–7.05 (comp. m, 3H), 6.79 (dd, $J$=7.1, 7.7 Hz, 1H), 6.63 (d, $J$=8.2 Hz, 1H), 6.54 (br. s, 1H), 6.42 (d, $J$=7.7 Hz, 1H), 6.15 (br. d, $J$=66.5 Hz, 1H), 5.34 (br. s, 1H), 4.59 (br. s, 1H), 4.01 (br. s, 2H), 3.20–3.12 (m, 1H), 2.77 (app. s, 2H), 2.73 (s, 3H), 1.82 (s, 3H), 1.77 (s, 3H), 1.69–1.62 (comp. m, 3H), 1.53 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$, 50°C) $\delta$ 155.1, 141.2, 139.6, 132.6, 129.8, 129.4, 128.0, 127.2, 124.4, 121.0, 118.0, 113.2, 106.7, 84.8, 80.0, 57.6, 56.4, 40.0, 33.2, 32.1, 29.0, 25.9, 18.7; IR (neat) 3371, 2975, 2245, 1672, 1600 cm$^{-1}$; MS $m/z$ calcd for $[C_{28}H_{35}N_3O_2$-H$]^+$: 444.2651, found 444.2640. **19b**: $R_F$ 0.32 (3:1 hexane:ethyl acetate eluent); $^1$H NMR (300 MHz, $CDCl_3$, 50°C) $\delta$ 7.25 (d, $J$=4.0 Hz, 1H), 7.09-7.01 (comp. m, 2H), 6.69 (dd, $J$=6.0, 7.7 Hz, 1H), 6.63 (d, $J$=7.1 Hz, 1H), 6.52 (br. s, 1H), 6.45 (d, $J$=7.7 Hz, 1H), 6.0 (d, $J$=57.7 Hz, 1H), 5.43 (br. s, 1H), 4.58 (br. s, 1H), 3.96 (s, 1H), 3.91–3.70 (m, 1H), 3.50–3.35 (m, 1H), 3.09–2.80 (comp. m, 2H), 2.74 (s, 3H), 1.84 (s, 3H), 1.77 (s, 3H), 1.57–1.29 (comp. m, 2H), 1.42 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$, 23°C) $\delta$ 154.9, 150.3, 141.4, 141.2, 140.6, 138.5, 138.3, 132.6, 132.2, 129.8, 128.1, 127.8, 127.5, 124.3, 120.1, 119.9, 118.8, 117.9, 113.6, 113.5, 107.5, 83.9, 79.9, 79.5, 59.0, 57.7, 41.7, 41.5, 38.7, 38.1, 33.2, 33.1, 32.5, 32.4, 31.2, 28.7, 26.1, 18.6, 18.5; IR (neat) 3363, 2973, 2242, 1672, 1594 cm$^{-1}$; MS $m/z$ calcd for $[C_{28}H_{35}N_2O_2]^+$: 445.2729, found 445.2731.
13. The biosynthetic proposal depicted in Scheme 1 is only one of a number of potential scenarios. Another possibility might involve a combination of the clavicipitic acid/aurantioclavine and chimonanthine biosyntheses. Nonetheless, these routes would also involve two molecules of tryptamine or tryptophan undergoing an oxidative coupling, see; (a) Kirby, G. W.; Shah, S. W.; Herbert, E. J. *J. Chem. Soc. C* **1969**, 1916; (b) Robbers, J. E.; Otsuka, H.; Floss, H. G.; Arnold, E. V.; Clardy, J. *J. Org. Chem.* **1980**, *45*, 1117.