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## Total Synthesis of ( $\pm$ )-Communesin F

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Since the isolation of potent cytotoxic communesins A and B from a marine fungal strain of *Penicillium* sp. in 1993,<sup>1</sup> eight members (A–H) of this structurally intriguing indole alkaloid family were consecutively disclosed over the past 5 years<sup>2</sup> (Figure 1). Although the polycyclic framework and multiple stereocenters of communesins have attracted intensive synthetic efforts toward skeletal construction in recent years,<sup>3</sup> the successful synthesis of members of this indole alkaloid family still remains unresolved.<sup>4</sup> In this communication, we describe the first total synthesis of ( $\pm$ )-communesin F.

In view of construction of the multi-ring system (Figure 1), we envisioned that formation of the F ring could be accomplished by displacement of the imidate ether group with the second amine group on the G ring (5 to 6) at a later stage of the synthesis. An acid-catalyzed cyclization of 4, after introducing an allylic alcohol side chain at C12a of 3 by a Heck reaction, could readily generate the azepine ring. Stereoselective  $\alpha$ -allylation of the ester functional group of 2 would lead nicely to set up the C8 quaternary carbon and would guarantee the subsequent formation of the C, E, F, and G rings with the correct stereochemical centers. The pentacyclic substructure 2 with a C7 quaternary carbon could be efficiently assembled from diazo 1 using a methodology of intramolecular cyclopropanation, ring opening, and ring closing reactions, the methodology of which was developed in our group.<sup>5</sup>

As demonstrated in Scheme 1, the preparation of 3 commenced with indole  $7^6$  and acid 8.5 Condensation of 7 and 8, followed by two steps of functional transformation from ketone to diazo. furnished 1. Treatment of 1 with CuOTf led to the formation of a stable cyclopropane intermediate 9 in an 88% yield as a mixture of two diastereomeric isomers in a 1.6:1 ratio. Reduction of the azide group in 9 with PBu<sub>3</sub> in aqueous THF resulted in a two-step cascade reaction of cyclopropane ring collapse and ring closure with an in situ generated aniline, to give the kinetic product 2 in an 83% yield as a single diastereoisomer. For stereoselective generation of the C8 quaternary center by  $\alpha$ -allylation for further construction of the E ring, the nitrogen in 2 had to be protected first with a methoxycarbonyl group. The N5-protection was easily completed to afford carbamate 10 in excellent yield when 2 was treated with methyl chloroformate and DMAP in CHCl<sub>3</sub>. Interestingly, quantitative conversion of 10 to its epimer 11 was realized by treatment of 10 with DMAP in CH<sub>2</sub>Cl<sub>2</sub> at room temperature.

We originally thought that epimeric carbamates **10** and **11** might provide diastereomeric allylation products, but both isomers yielded the same compound **3** as the sole product with an 84% yield when **10** and **11** were treated with NaH and allyl bromide in dry DMF at 0 °C for 1 h, then at 65 °C for 3 h, respectively. Successful isolation of the ketene acetal intermediate **12** confirmed that  $\alpha$ -allylation of this type of six-membered lactone proceeded through a stereoselective 3,3-rearrangement.<sup>7</sup> In such a rearrangement, one face of the dihydropyran ring was completely shielded by the bromophenyl group to provide **3** with a secured *cis* relationship between the C7



Figure 1. Retrosynthetic analysis of communesin F.

Scheme 1<sup>a</sup>



<sup>*a*</sup> Reagents and conditions: (a) **8**, SOCl<sub>2</sub>, 60 °C, 2 h; (b) **7**, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 5 h (95%); (c) TsNHNH<sub>2</sub>, TsOH, CHCl<sub>3</sub>, reflux, 5 h (85%); (d) DBU, CH<sub>2</sub>Cl<sub>2</sub>, 12 h (85%); (e) CuOTf, CH<sub>2</sub>Cl<sub>2</sub>, rt, 1 h (88%); (f) PBu<sub>3</sub>, aq. THF, 0 °C, 0.5 h (83%); (g) ClCO<sub>2</sub>Me, DMAP, CHCl<sub>3</sub>, rt, 7 h, 93%; (h) DMAP, CH<sub>2</sub>Cl<sub>2</sub>, rt, 6 h, 99%; (i) NaH, allyl bromide, DMF, 0 $\rightarrow$ 65 °C, 4 h (84%).

ethylene group and the C8 allylic side chain, verified by a NOEDs experiment of **3**.

Completion of the total synthesis of communesin F from **3** is depicted in Scheme 2. Oxidative cleavage of the double bond in **3** gave aldehyde **13** in a 95% yield. Conversion of the aldehyde functionality of **13** into an amine, followed by heating the resulting amino product with MeONa in MeOH at reflux, furnished the E ring and left the hydroxyl group of the C7 side chain unprotected (**14**). Dess-Martin oxidation, conversion of the resulting aldehyde



<sup>*a*</sup> Reagents and conditions: (a)  $OsO_4$ , aq. acetone; (b)  $NaIO_4$ , aq. THF (95% from **3**); (c)  $NH_2OH$ ·HCl,  $Na_2CO_3$ , aq. THF; (d) H<sub>2</sub>, Raney-Ni, MeOH, 40 °C, 3 h (87% based on recovered **13**); (e) MeONa, MeOH, 70 °C, 12 h (98%); (f) Dess-Martin reagent,  $CH_2CI_2$ , rt, 5 min; (g)  $NH_2OH$ ·HCl,  $Na_2CO_3$ , aq. THF, 10 min; (h) H<sub>2</sub>, Raney-Ni, MeOH, 50 °C, 1 h; (i) Boc<sub>2</sub>O,  $Na_2CO_3$ ,  $CH_2CI_2$  (50% from **17**); (j) Pd(OAc)<sub>2</sub>, P(*o*-Tol)<sub>3</sub>, Et<sub>3</sub>N, neat 2-methyl-3-butyen-2-ol, microwave, 2 h (68% **4**, 21% of **15** recovered); (k) PPTS, CHCl<sub>3</sub>, rt, 1 h (66% **17**, 26% **16**); (l) BF<sub>4</sub>OEt<sub>3</sub>, 'PrNEt<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 2 h (95%); (m) 5% TFA in CH<sub>2</sub>Cl<sub>2</sub>, rt, 30 min; (n) silica gel, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 1:1, 50 °C, 12 h (81% from **17**); (o) KOH, MeOH/ H<sub>2</sub>O 10:1, 100 °C, 24 h (65%); (p) NaBH<sub>4</sub>, AcOH/Ac<sub>2</sub>O 1:1, 0 °C, 73%; (q) 5% CF<sub>3</sub>CO<sub>2</sub>H in CDCl<sub>3</sub>.

to an amine, and protection of the amine with Boc provided **15** in a 50% overall yield. A standard Heck reaction of **15** with neat 2-methyl-3-butyen-2-ol at 100 °C for 10 h in the presence of 0.5 equiv of Pd(OAc)<sub>2</sub>, 2 equiv of P(o-Tol)<sub>3</sub>, and Et<sub>3</sub>N was unsuccessful, and only trace amounts of the desired alcohol **4** were obtained. Fortunately, when the same reaction was irradiated with a microwave for 2 h, we were able to isolate **4** in a 68% yield and to recover **15** in a 21% yield (86% yield of **4** based on recovered **15**). As we anticipated, although partial dehydration of **4** was unavoidable to give diene **16** in a 26% yield, the stereoselective acidcatalyzed cyclization of **4** was readily accomplished to form the desired azepine ring with an acceptable yield (**17**, 66%) when **4** was treated with PPTS in chloroform at room temperature.

With 17 in hand, our last task for ring system construction was to convert the amide to a more reactive imidate functionality, which might allow us to build the F ring upon removal of the Boc protecting group. In contrast to our anticipation, treatment of 17 with freshly made BF4OEt3 and PrNEt2, followed by removal of the Boc group, was not accompanied by direct attack of the resulting second amine on the imidate group to form the F ring, instead of giving the chromatographically unstable imidate 5. To our delight, without purification, direct treatment of 5 with silica gel at 50 °C furnished 6a in a 77% yield from 17. Removal of the carbamate protecting group in 6a with KOH provided 6b in a 65% yield. A stereoselective reduction of **6b** with a large excess of NaBH<sub>4</sub> in a 1:1 mixture of AcOH and Ac2O at 0 °C resulted in simultaneous acetylation of the resulting bisaminal group to afford  $(\pm)$ -communesin F as an inseparable mixture of two amide rotamers in a 73% yield. The <sup>1</sup>H and <sup>13</sup>C NMR spectra of the synthetic ( $\pm$ )-

communes in F were consistent with that of the natural communes in F provided by Prof. Hayashi.8 The characterization of two rotamers and assignments of the isomer geometry were based on careful NMR studies. The major rotamer with s-cis conformation was found to have NOEDs among the C9 proton with protons of the C1, C11, and C2" in CDCl<sub>3</sub>. The minor rotamer with s-trans conformation was found to have NOEDs between the C17 proton and the C2" proton. Interestingly, the conformational distribution has been shown to be solvent dependent. For example, a 2.6:1 ratio in CDCl<sub>3</sub> and a 5.1:1 ratio in DMSO- $d_6$  were observed, respectively. The thermodynamic equilibrium between two rotamers was studied to show that the s-cis rotamer was favorably formed and became predominant as the temperature increased to over 80 °C in DMSO $d_6$ . Importantly, protonation of (±)-communes in F with 5% of CF<sub>3</sub>- $CO_2H$  in  $CDCl_3$  provided **18** as single isomer, presumably as a result of the fixed amide bond by formation of an intramolecular hydrogen bond.

In summary, we have accomplished the total synthesis of  $(\pm)$ communesin F in 23 reaction steps in about a 3% overall yield. The key steps relied on a highly efficient methodology for assembling the pentacyclic substructure, the stereoselective preparation of the second C8 quaternary carbon by O-allylation and consecutive 3,3-rearrangement, and the stereoselective acidcatalyzed cyclization to form the azepine ring. These highly stereoselective reactions guaranteed the stereochemical results, allowing the construction of the C, E, F, and G ring systems. Further synthesis of other promising indole alkaloids of this family is under investigation and will be disclosed in due course.

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**Supporting Information Available:** Experimental details and NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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- (7) Similar 3,3-rearrangement was also observed in Weinreb's experiments of model study; see ref 3c.
- (8) The original paper for isolation and characterization of the natural communesin F reported the major (*s-cis*) rotamer with NMR data, but the detectable minor rotamer (*s-trans*) was ignored by authors; see ref 2e and personal communication with Prof. H. Hayashi.

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