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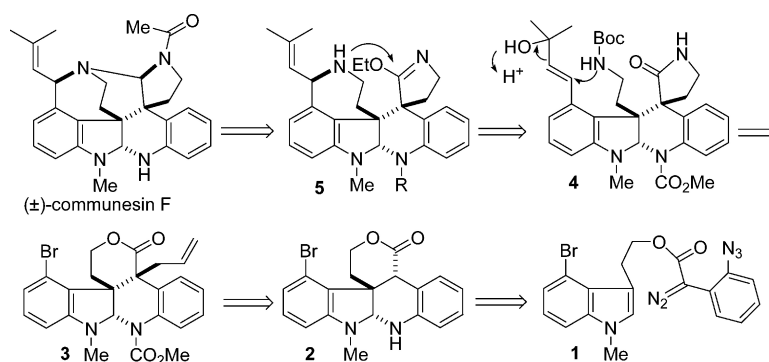
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Total Synthesis of (±)-Communesin F

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Since the isolation of potent cytotoxic communesins A and B from a marine fungal strain of *Penicillium* sp. in 1993,¹ eight members (A–H) of this structurally intriguing indole alkaloid family were consecutively disclosed over the past 5 years² (Figure 1). Although the polycyclic framework and multiple stereocenters of communesins have attracted intensive synthetic efforts toward skeletal construction in recent years,³ the successful synthesis of members of this indole alkaloid family still remains unresolved.⁴ In this communication, we describe the first total synthesis of (±)-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 α -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.⁵

As demonstrated in Scheme 1, the preparation of 3 commenced with indole 7⁶ 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 PBu₃ 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 α -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 CHCl₃. Interestingly, quantitative conversion of 10 to its epimer 11 was realized by treatment of 10 with DMAP in CH₂Cl₂ 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 α -allylation of this type of six-membered lactone proceeded through a stereoselective 3,3-rearrangement.⁷ 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

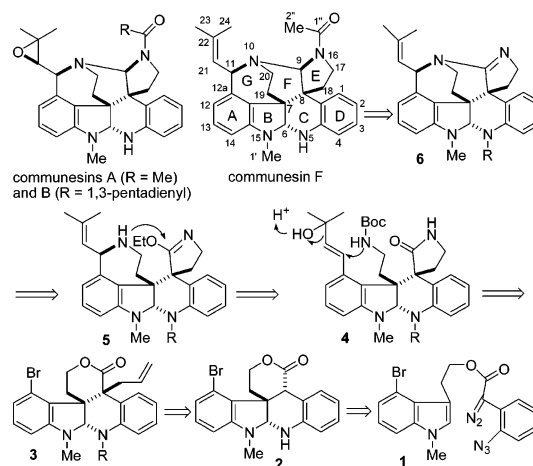
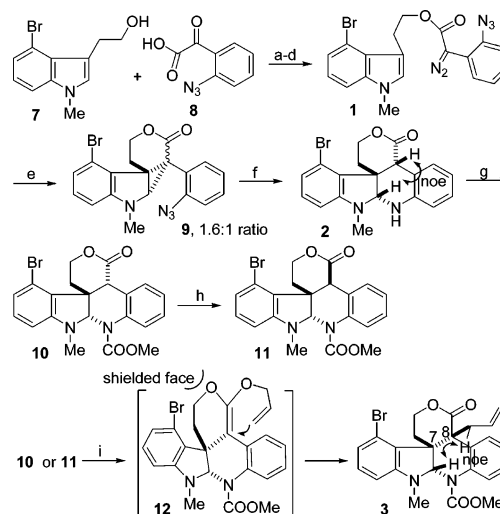


Figure 1. Retrosynthetic analysis of communesin F.

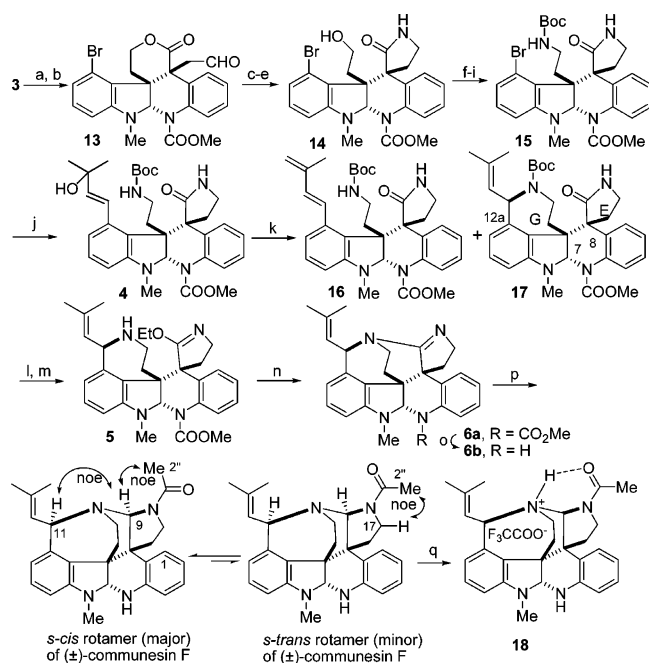
Scheme 1^a

^a Reagents and conditions: (a) 8, SOCl₂, 60 °C, 2 h; (b) 7, Et₃N, CH₂Cl₂, 0 °C, 5 h (95%); (c) TsNHNH₂, TsOH, CHCl₃, reflux, 5 h (85%); (d) DBU, CH₂Cl₂, 12 h (85%); (e) CuOTf, CH₂Cl₂, rt, 1 h (88%); (f) PBu₃, aq. THF, 0 °C, 0.5 h (83%); (g) ClCO₂Me, DMAP, CHCl₃, rt, 7 h, 93%; (h) DMAP, CH₂Cl₂, rt, 6 h, 99%; (i) NaH, allyl bromide, DMF, 0–65 °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

Scheme 2^a



^a Reagents and conditions: (a) OsO₄, aq. acetone; (b) NaIO₄, aq. THF (95% from **3**); (c) NH₂OH·HCl, Na₂CO₃, aq. THF; (d) H₂, Raney-Ni, MeOH, 40 °C, 3 h (87% based on recovered **13**); (e) MeONa, MeOH, 70 °C, 12 h (98%); (f) Dess–Martin reagent, CH₂Cl₂, rt, 5 min; (g) NH₂OH·HCl, Na₂CO₃, aq. THF, 10 min; (h) H₂, Raney-Ni, MeOH, 50 °C, 1 h; (i) Boc₂O, Na₂CO₃, CH₂Cl₂ (50% from **17**); (j) Pd(OAc)₂, P(*o*-Tolyl)₃, Et₃N, neat 2-methyl-3-buten-2-ol, microwave, 2 h (68% **4**, 21% of **15** recovered); (k) PPTS, CHCl₃, rt, 1 h (66% **17**, 26% **16**); (l) BF₃OEt₂, ⁱPrNEt₂, CH₂Cl₂, rt, 2 h (95%); (m) 5% TFA in CH₂Cl₂, rt, 30 min; (n) silica gel, CH₂Cl₂/MeOH 1:1, 50 °C, 12 h (81% from **17**); (o) KOH, MeOH/H₂O 10:1, 100 °C, 24 h (65%); (p) NaBH₄, AcOH/Ac₂O 1:1, 0 °C, 73%; (q) 5% CF₃CO₂H in CDCl₃.

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-buten-2-ol at 100 °C for 10 h in the presence of 0.5 equiv of Pd(OAc)₂, 2 equiv of P(*o*-Tol)₃, and Et₃N 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 acid-catalyzed 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 imide 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 BF_3OEt_2 and $i\text{PrNEt}_2$, followed by removal of the Boc group, was not accompanied by direct attack of the resulting second amine on the imideate group to form the F ring, instead of giving the chromatographically unstable imideate **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_4 in a 1:1 mixture of AcOH and Ac_2O 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 ^1H and ^{13}C NMR spectra of the synthetic (\pm)-

communesin F were consistent with that of the natural communesin 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 CDCl₃. 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 CDCl₃ 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 (±)-communesin F with 5% of CF₃-CO₂H in CDCl₃ 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 (±)-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 acid-catalyzed 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 communines 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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