Total Synthesis

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Total Synthesis of the Polycyclic Fungal Metabolite (±)-Communesin F**

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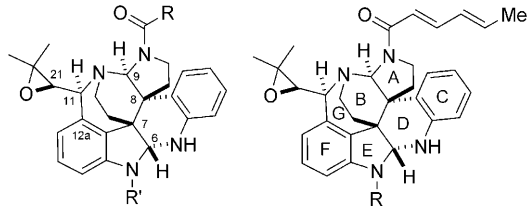
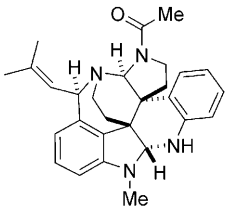
In 1993, Numata et al. isolated two unique natural products from a *Penicillium* mold, which was found growing on the marine alga *Enteromorpha intestinalis*.[1] The structures of these compounds, communesin A (**1**) and communesin B (**5**), were determined by spectroscopic analysis (Scheme 1). Notable features of these complex, highly functionalized polycyclic metabolites are the two contiguous quaternary centers at C7/8, and the presence of the two aminal moieties. The communesins were found to have cytotoxic activity against P-388 lymphoid leukemia cells in vitro. In 2001, Hemscheidt and co-workers described an alkaloid called nomofungin, which was isolated from an unidentified fungus growing on the bark of *Ficus microcarpa* in Hawaii.[2] This material was found to have cytotoxic activity against LoVo and KB cells, which resulted from the ability of the metabolite to cause microfilament disruption. The initial structural assignment of this metabolite, however, was incorrect, and nomofungin was in fact found to be communesin B (**5**). Notably, however, Hemscheidt and co-workers established the configuration at C21 of **5**, together with the absolute configuration of the molecule; these structural features were not originally determined by the Numata group. More recently, several other structurally modified communesin derivatives have been isolated,[3,4] including communesin C (**6**), D (**7**), E (**2**), F (**8**), G (**3**), and H (**4**). Some of these new compounds were found to have significant biological activity. For example, communesins D, E, and F are insecticidal, and communesins C and D are moderately active against various leukemia cell lines.



1:R = R' = Me communesin A
2:R = Me, R' = H communesin E
3:R = Et, R' = Me communesin G
4:R = Pr, R' = Me communesin H
5:R = Me communesin B
6:R = H communesin C
7:R = CHO communesin D



8:communesin F

Scheme 1. The communesin family of natural products.

Several research groups have reported studies on the synthesis of communesins.[5] In 2007, Qin and co-workers reported the first successful construction of a communesin in the form of a total synthesis of racemic communesin F (**8**).[6] Herein, we report a new stereoselective synthesis of this metabolite. Our approach employs a pivotal intramolecular Heck reaction of a tetrasubstituted olefin to construct the B, C, E, and F ring system as well as the C7 quaternary center.

The synthesis commenced with the known compound enol triflate **9**[7] (easily prepared from the corresponding commercially available *N*-benzylpiperidine β-ketoester), which was coupled with 2-nitrobenzeneboronic acid (**10**) in a Suzuki–Miyaura reaction and afforded the arylated product **11** (Scheme 2). Basic hydrolysis of ester **11** gave the acid, which was transformed into the acid chloride and then coupled with readily prepared iodo aniline **12** (see Supporting Information) and yielded amide **13**. At this point, the benzyl group of **13** was replaced by an ethyl carbamate moiety in a one-pot procedure using ethyl chloroformate, and the resulting amide was alkylated to form the *N*-methyl compound **14**. To our delight, tetrasubstituted alkene **14** underwent a clean intramolecular Heck reaction,[8] and subsequent β-hydride elimination afforded tetracyclic enamide **15** (bearing the quaternary center at C7 of the alkaloid) in high yield. It should be pointed out that intra-[9a] or intermolecular[9b] Heck reactions involving tetrasubstituted olefins are uncommon.

To continue the synthesis, the nitro group of **15** was reduced by catalytic hydrogenation, and the resulting aniline was protected as the Boc derivative **16** (Scheme 3). It was then found that lactam **16** can be partially reduced with alane–dimethylethylamine complex, and subsequent in situ cyclization to produce the lower aminal **17** having the requisite configuration at C6 and C7.[10]

After some exploration, it was decided that the best approach for installation of the quaternary center at C8 would be to alkylate the B-ring lactam. To implement this strategy,

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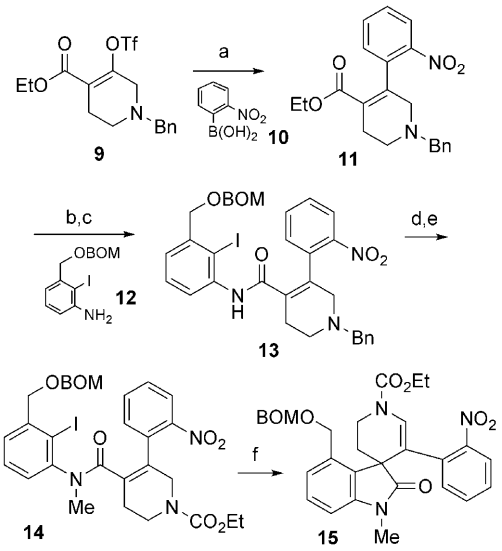
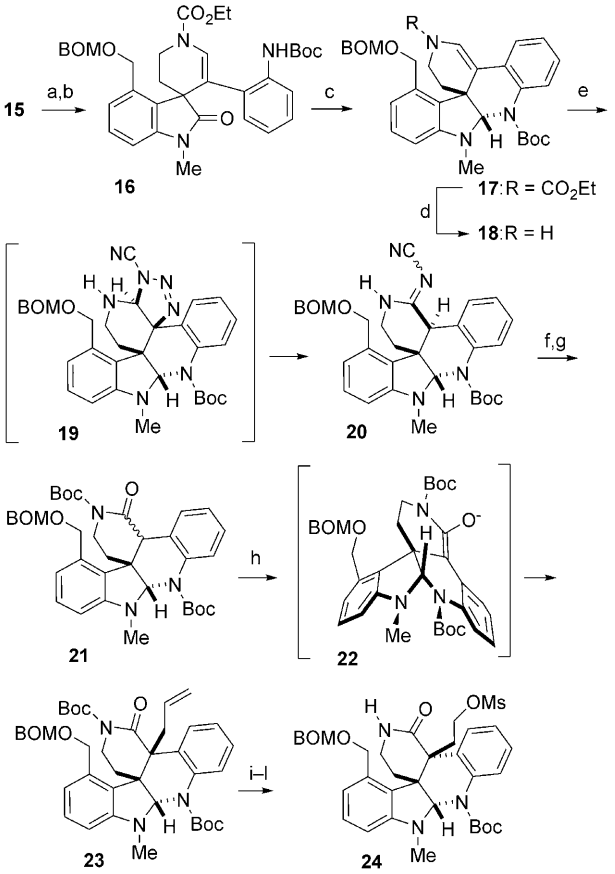


Scheme 2. a) $[Pd(PPh_3)_4]$, DME, H_2O, Na_2CO_3, 80 °C, **10**, 98 %; b) LiOH, H_2O, MeOH, 50 °C, 86 %; c) $SOCl_2$, reflux; then iPr_2NEt, CH_2Cl_2, RT, **12**, 87 %; d) $ClCO_2Et$, CH_2Cl_2, 0 °C→RT, 96 %; e) NaH, THF, MeI, 0 °C→RT, 92 %; f) $Pd(OAc)_2$, PPh_3, DMA, K_2CO_3, nBu_4NBr, 150 °C, 90 %. DME = 1,2-dimethoxyethane, DMA = *N*,*N*-dimethylacetamide, Tf = trifluoromethanesulfonyl, BOM = benzyloxymethyl, THF = tetrahydrofuran.

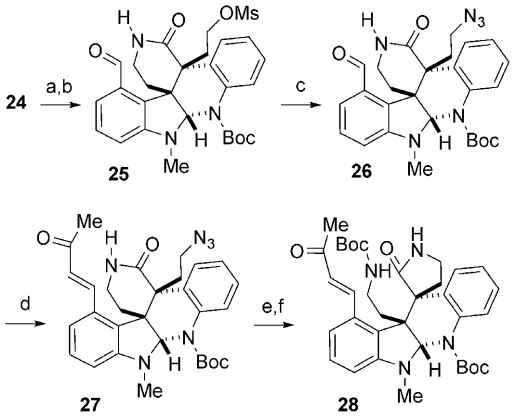
enamide **17** was first hydrolyzed to the enamine **18**, which reacted with cyanogen azide generated in situ and afforded *N*-cyanoamidine **20**.[11] This transformation presumably occurs through an initial [3+2] dipolar cycloaddition of the enamine to afford adduct **19**, which rearranges spontaneously to afford **20**. Basic hydrolysis of this amidine gave the corresponding lactam, and subsequent acylation led to *N*-Boc lactam **21** (3:1 mixture of epimers).

The key alkylation step involved treating *N*-Boc lactam **21** with potassium *tert*-butoxide and allyl iodide to afford the desired product **23** in high yield and as a single stereoisomer at C8. This alkylation proceeds via attack of the iodide on lactam enolate **22** from the less hindered convex face. To prepare for construction of the upper aminal system, after selective removal of the Boc group on the lactam nitrogen atom of **23** by basic hydrolysis, the allyl group was oxidatively cleaved and the resulting aldehyde was manipulated by a straightforward sequence to form mesylate **24**.

The BOM protecting group of **24** was then removed by catalytic hydrogenolysis, and the resulting benzylic alcohol was oxidized with Dess–Martin periodinane and afforded aldehyde **25** (Scheme 4). After conversion of mesylate **25** into the azide **26** with sodium azide in DMF, we investigated the conversion of **26** into the α,β-unsaturated ketone **27**. Surprisingly, this transformation was not feasible using the Wittig reaction, but gratifyingly the aldehyde underwent a clean cross-aldol reaction with acetone using aqueous sodium hydroxide and produced the desired *E*-unsaturated ketone **27** in excellent yield. After reinstalling a Boc group on the δ-lactam nitrogen atom of **27**, azide reduction using trimethylphosphine in aqueous THF caused an in situ rearrangement and formed spiro-γ-lactam **28**.

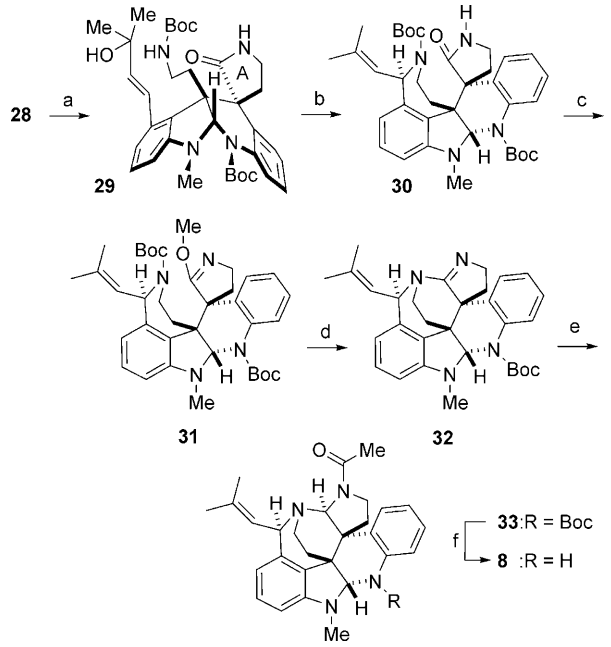


Scheme 3. a) 5 % Pt/C, H_2 (40 atm) toluene, RT; b) Boc_2O, K_2CO_3, THF, H_2O, 60 °C, 87 % (2 steps); c) $AlH_3{\cdot}Me_2NEt$, THF, 0 °C→RT, 74 %; d) 1 M KOH, EtOH, 94 °C; e) NCN_3, MeCN, RT, 93 % (2 steps); f) 1 M KOH, EtOH, 94 °C, 60 %; g) Boc_2O, LiHMDS, THF, RT, 95 %; h) KO*t*Bu, THF, allyl iodide, −78 °C→RT, 87 %; i) 1 M KOH, EtOH, 80 °C, 94 %; j) OsO_4, NMO, THF, H_2O; then $NaIO_4$, RT; k) $NaBH_4$, EtOH, 0 °C; l) MsCl, NEt_3, CH_2Cl_2, 0 °C, 83 % (3 steps). Boc = *tert*-butoxycarbonyl, HMDS = hexamethyldisilazide, NMO = *N*-methylmorpholine *N*-oxide, Ms = methanesulfonyl.



Scheme 4. a) Pearlman's catalyst, H_2, THF, RT; b) DMP, CH_2Cl_2, RT, 75 % (2 steps); c) NaN_3, DMF, 90 °C, 61 %; d) Me_2CO, 10 % NaOH/H_2O, 60 °C, 93 %; e) Boc_2O, LiHMDS, THF, RT, 81 %; f) PMe_3, THF, H_2O, 70 °C, 88 %. DMP = Dess—Martin periodinane, DMF = N,N-dimethylformamide.

To expedite the construction of the remaining B and G rings of the alkaloid, the unsaturated ketone **28** was first treated with methyllithium and produced allylic alcohol **29** in high yield (Scheme 5). The remaining steps of the synthesis were then carried out based on the work of Qin and coworkers.[6] Thus, exposure of **29** to PPTS in chloroform at



Scheme 5. a) MeLi, THF, −78 °C, 73 %; b) PPTS, $CHCl_3$, RT, 62 %; c) Me_3OBF_4, iPr_2NEt, CH_2Cl_2, RT, 86 %; d) 5 % TFA in CH_2Cl_2, RT, 88 %; e) $NaBH_4$, Ac_2O, HOAc; f) 40 % TFA in CH_2Cl_2, RT, 66 % (2 steps). PPTS = pyridinium *p*-toluenesulfonate, TFA = trifluoroacetic acid.

room temperature led to hexacycle **30** in 62 % yield through a stereoselective allylic substitution reaction to form the G ring with the requisite configuration at C11. In addition, a small amount of the diene resulting from dehydration of starting alcohol **29** was produced. The stereochemical outcome of this cyclization is undoubtedly due to attack of the NHBoc group on the isopentenol side chain through the preferred conformation shown in **29**. This conformation is enforced by minimization of steric interactions with the A-ring lactam.

To complete the synthesis, γ-lactam **30** was treated with trimethyloxonium tetrafluoroborate in the presence of Hünig's base to generate imidate **31**. The upper Boc protecting group was then selectively removed with TFA (5 %) in methylene chloride, and upon neutralization of the resulting amine salt, cyclization occurred to form the heptacyclic amidine **32**. Reduction of this amidine with sodium borohydride in acetic acid containing acetic anhydride occurred stereoselectively from the least congested face, and yielded the *N*-acetyl aminal **33**. Finally, removal of the Boc protecting group on the lower aminal functionality with TFA (40 %) in methylene chloride afforded racemic communesin F (**8**).The spectroscopic data for the synthetic product **8** correlated closely with that reported by the Qin group.[6]

In summary, we have achieved a racemic stereoselective total synthesis of the heptacyclic alkaloid communesin F (**8**) in approximately 30 steps from the known compound enol triflate **9**. The key reactions include a novel intramolecular Heck cyclization of a tetrasubstituted alkene to generate a tetracycle with a quaternary carbon center, a reductive cyclization of an *N*-Boc aniline onto an oxindole moiety to form the pentacyclic framework containing the lower aminal group, a stereoselective C allylation of a lactam to introduce the second quaternary carbon center, and an azide reduction *N*-Boc-δ-lactam ring opening cascade leading to the upper aminal functionality. We are currently investigating enantioselective methodologies for improving the pivotal Heck reaction of **14** to produce natural (−)-communesin F.

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