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A New 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 found growing on the marine alga *Enteromorpha intestinalis*.^[1] The structures of these compounds, communesin A (**1**) and communesin B (**5**), were established by spectroscopic analysis (Figure 1). Notable features of these complex, highly functionalized polycyclic metabolites are the two contiguous quaternary centers at C-7/8, and the presence of two aminated moieties. The communesins were found to have cytotoxic activity against P-388 lymphoid leukemia cells *in vitro*. In 2001, Hemscheidt and coworkers 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 was shown to be due to 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**). It should be noted, however, that the Hemscheidt work did serve to establish both the configuration at C-21 of **5** as well as the absolute configuration of the molecule, which 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.

Several groups have reported studies on synthesis of the communesins.^[5] In 2007, Qin and coworkers 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 which employs a pivotal intramolecular Heck reaction of a tetrasubstituted olefin to construct the B,C,E,F-ring system as well as the C-7 quaternary center.

The synthesis commenced with the known^[7] enol triflate **9** (easily prepared from the corresponding commercially available *N*-benzylpiperidine β -ketoester) which was coupled with 2-nitrobenzeneboronic acid (**10**) in a Suzuki-Miyaura reaction to afford the arylated product **11** (Scheme 1). Basic hydrolysis of ester **11** gave the acid which was transformed to the acid chloride and then coupled with readily prepared iodo aniline **12** (see Supporting Information) to yield 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**. We were pleased to find that

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tetrasubstituted alkene **14** underwent a clean intramolecular Heck reaction,^[8] followed by β -hydride elimination, to afford tetracyclic enamide **15** in high yield bearing the C-7 quaternary center of the alkaloid. It should be pointed out that intra-^[9a] or intermolecular^[9b] Heck reactions involving tetrasubstituted olefins are rare.

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 2). It was then found that lactam **16** can be partially reduced with alane-dimethylethylamine complex, followed by in situ cyclization to produce the lower aminal **17** having the requisite stereochemistry at C-6/7.^[10]

After some exploration, it was decided that the best approach for introduction of the C-8 quaternary center would be to alkylate a Bring lactam. To implement this strategy, enamide **17** was first hydrolyzed to the enamine **18**, which reacts with in situ-generated cyanogen azide to afford *N*-cyanoamidine **20**.^[11] This transformation presumably occurs via an initial [3+2]-dipolar cycloaddition of the enamine to afford adduct **19**, which rearranges spontaneously to **20**. Basic hydrolysis of this amidine gave the corresponding lactam, and acylation subsequently led to *N*-Boc lactam **21** (3:1 mixture of epimers).

The key alkylation step could be effected by treating *N*-Boc lactam **21** with potassium *t*-butoxide and allyl iodide to afford the desired product **23** as a single C-8 stereoisomer in high yield. This alkylation proceeds via attack of the iodide on lactam enolate **22** from the least hindered convex face. In order to prepare for construction of the upper aminal system, after selectively removing the Boc group on the lactam nitrogen of **23** by basic hydrolysis, the allyl group was oxidatively cleaved and the resulting aldehyde was manipulated via a straightforward sequence to form mesylate **24**.

The BOM protecting group of **24** was next removed by catalytic hydrogenolysis, and the resulting benzylic alcohol was oxidized with Dess-Martin periodinane to yield aldehyde **25** (Scheme 3). Following conversion of mesylate **25** to the azide **26** with sodium azide in DMF, we investigated conversion of this aldehyde to the α,β -unsaturated ketone **27**. Surprisingly this transformation could not be effected via Wittig chemistry, but we were gratified to find that the aldehyde underwent a clean mixed aldol reaction with acetone using aqueous sodium hydroxide as catalyst to produce the desired (*E*)-unsaturated ketone **27** in excellent yield. After reinstalling a Boc group on the δ -lactam nitrogen of **27**, azide reduction using trimethylphosphine in aqueous THF caused an in situ rearrangement to form spiro- γ -lactam **28**.

In order to expedite construction of the remaining B- and G-rings of the alkaloid, the unsaturated ketone **28** was first treated with methyllithium to produce allylic alcohol **29** in high yield (Scheme 4). The remaining steps of the synthesis were then patterned on the work of Qin, et al.^[6] Thus, exposure of **29** to PPTS in chloroform at room temperature leads to hexacycle **30** in 62% yield via a stereoselective allylic substitution reaction to form the G-ring with the requisite configuration at C-11. In addition, a small amount of the diene resulting from dehydration of starting alcohol **29** is 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 lactam A-ring.

To complete the synthesis, γ -lactam **30** was treated with trimethyloxonium tetrafluoroborate in the presence of Hunig's base to generate imidate **31**. The upper Boc protecting group was then selectively removed with 5% trifluoroacetic acid 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 to yield the *N*-acetyl aminal **33**. Finally, removal of the Boc protecting group on the lower aminal with 40% TFA in methylene chloride afforded racemic communesin F (**8**) which had spectral data identical to that reported by the Qin group for the natural product.^[6]

In summary, we have achieved a stereoselective total synthesis of the heptacyclic alkaloid communesin F (**8**) in racemic form in approximately 30 operations from known enol triflate **9**. 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, a stereoselective lactam *C*-allylation to introduce the second quaternary carbon center, and an azide reduction-*N*-Boc- δ -lactam opening cascade leading to the upper aminal functionality. We are currently investigating methodology for effecting the pivotal Heck reaction of **14** enantioselectively to produce natural (–)-communesin F.

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Figure 1.
The communesin family of natural products.

Scheme 1.

a) $\text{Pd}(\text{PPh}_3)_4$, DME, H_2O , Na_2CO_3 , 80°C , **10**, 98%; b) LiOH , H_2O , MeOH , 50°C , 86%; c) SOCl_2 , reflux; $i\text{-Pr}_2\text{NEt}$, CH_2Cl_2 , rt, **12**, 87%; d) ClCOOEt , CH_2Cl_2 , 0°C -rt, 96%; e) NaH , THF, MeI, 0°C -rt, 92%; f) $\text{Pd}(\text{OAc})_2$, PPh_3 , DMA, K_2CO_3 , $n\text{-Bu}_4\text{NBr}$, 150°C , 90%. DME = 1,2-dimethoxyethane; DMA = *N,N*-dimethylacetamide

Scheme 2.

a) 5% Pt/C, H₂ (40 atm) PhMe, rt; b) Boc₂O, K₂CO₃, THF, H₂O, 60°C, 87% (2 steps); c) AlH₃·Me₂NEt, THF, 0°C-rt, 74%; d) 1 N KOH, EtOH, 94°C; e) NCN₃, MeCN, rt, 93% (2 steps); f) 1 N KOH, EtOH, 94°C, 60%; g) Boc₂O, LiHMDS, THF, rt, 95%; h) KO^tBu, THF, allyl iodide, -78°C-rt, 87%; i) 1 N KOH, EtOH, 80°C, 94%; j) OsO₄, NMO, THF, H₂O; NaIO₄, rt; k) NaBH₄, EtOH, 0°C; l) MsCl, NEt₃, CH₂Cl₂, 0°C, 83% (3 steps). Boc = *tert*-butoxycarbonyl; LiHMDS = lithium hexamethyldisilazide; NMO = *N*-methylmorpholine *N*-oxide; MsCl = methanesulfonyl chloride.

Scheme 3.

a) Pearlman's catalyst, H₂, THF, rt; b) Dess-Martin reagent, CH₂Cl₂, rt, 75% (2 steps); c) NaN₃, DMF, 90°C, 61%; d) Me₂CO, 10% NaOH/H₂O, 60°C, 93%; e) Boc₂O, LiHMDS, THF, rt, 81%; f) PMe₃, THF, H₂O, 70°C, 88%. Dess-Martin reagent = 1,1,1-triacetoxy-1,1-dihydro-1,2-benzodioxol-3(1*H*)-one.

Scheme 4.

a) MeLi, THF, -78°C , 73%; b) PPTS, CHCl_3 , rt, 62%; c) Me_3OBF_4 , $i\text{-Pr}_2\text{NEt}$, CH_2Cl_2 , rt, 86%; d) 5% TFA/ CH_2Cl_2 , rt, 88%; e) NaBH_4 , Ac_2O , HOAc; f) 40% TFA/ CH_2Cl_2 , rt, 66% (2 steps). PPTS = pyridinium *p*-toluenesulfonate; TFA = trifluoroacetic acid.