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Total Synthesis of (±)-Communesin F via a Cycloaddition with Indol-2-one

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Supporting Information

ABSTRACT: A concise total synthesis of (±)-communesin F has been completed in 15 linear steps from 4-bromotryptophol in an overall yield of 6.7%. A key step features the cycloaddition of indol-2-one with 3-(2-azidoethyl)-4-bromoindole and facilitates the rapid construction of the lower aminal-containing tetracyclic core of the natural product.

The communesins[1] are a group of eight architecturally intriguing natural products and are also biosynthetically and, as a consequence, structurally related to the natural product perophoramidine[2] (Figure 1). In addition, communesin B is uniformly the most active of these natural products in a variety of biological assays and is moderately cytotoxic against P-388 (ED_{50} = 0.88 mM), LoVo (MIC = 3.9 mM) and KB (MIC = 8.8 mM) cells whose mechanism of action may involve the disruption of microfilaments.[1a] Accordingly, the communesins[3] as well as perophoramidine[4] have been the subject of numerous synthetic investigations and total syntheses of communesin A,[5] B,[5] F[6] and perophoramidine[7] have been recorded.

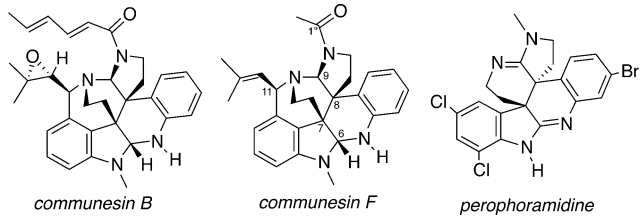
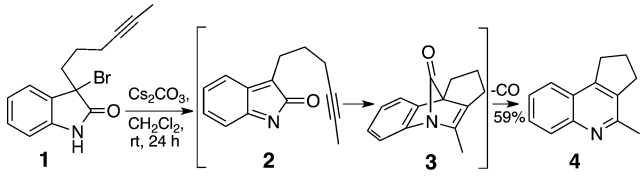


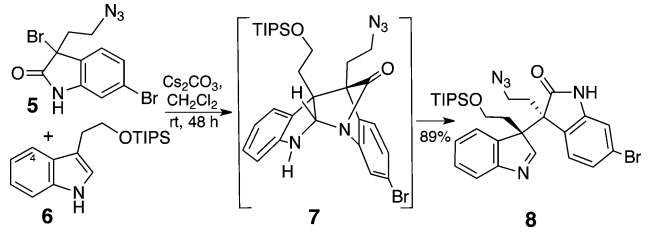
Figure 1. Communesins B, F, and perophoramidine.

Our own perophoramidine total synthesis took advantage of an indol-2-one cycloaddition.[7a] Thus, in our methodological studies,[8] we gathered firm evidence that indol-2-ones such as **2** (Scheme 1) are indeed generated via dehydrohalogenations of 3-alkyl-3-bromooxindoles,[9] for example, **1**, and that these quasi-antiaromatic compounds function as reactive dienes in Diels–Alder cycloadditions, in this case to provide the strained bridged bicyclic lactam **3** which undergoes a retrocheletropic reaction to furnish the quinoline **4**. A related *intermolecular* indol-2-one cycloaddition was employed to quickly and stereoselectively introduce the vicinal quaternary centers of perophoramidine (Scheme 2). Thus, the *endo*-cycloadduct **7** was presumably generated from bromooxindole **5** and protected tryptophol **6** which underwent concomitant ring-opening to the indolenine/lactam **8** as a single stereoisomer.

Scheme 1



Scheme 2



One could conceivably exploit this methodology in a communesin total synthesis if an analogous indol-2-one cycloaddition could be channeled through an *exo*-transition state. This is mandated since the presumed tryptamine derived 2-aminoethyl substituents at C(7) and C(8) bear a *cis* relationship as opposed to the *trans* orientation found in perophoramidine. We hoped that a C(4) substituent on the indole reactant, necessary for eventual construction of the benzazepine substructure, might alter the stereochemical preference. Unfortunately, an initial scouting experiment using the 4-vinyl derivative of indole **6** also proceeded exclusively through the *endo* cycloaddition pathway.

Nonetheless, it was still considered desirable to utilize this methodology for the rapid construction of the lower aminal-containing tetracyclic core of the communesins and then introduce the vicinal quaternary centers at a stage late in the synthesis. Our retrosynthetic plan is outlined in Scheme 3. Thus, it was envisaged that stereoselective alkylation of the enolate of twisted, bridged lactam **9** with 2-iodoethylazide, reduction of the azide to an amino group, reductive amination with the reactive bridged lactam carbonyl[10] and acetylation would afford communesin F. The benzazepine ring of lactam **9** could be constructed by allylic substitution of the carbamate

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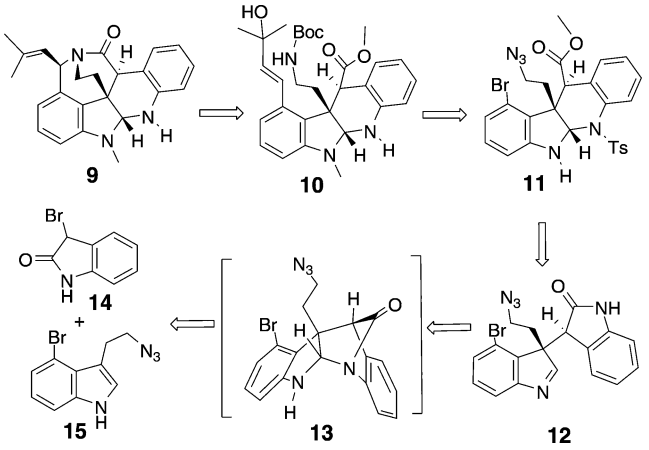
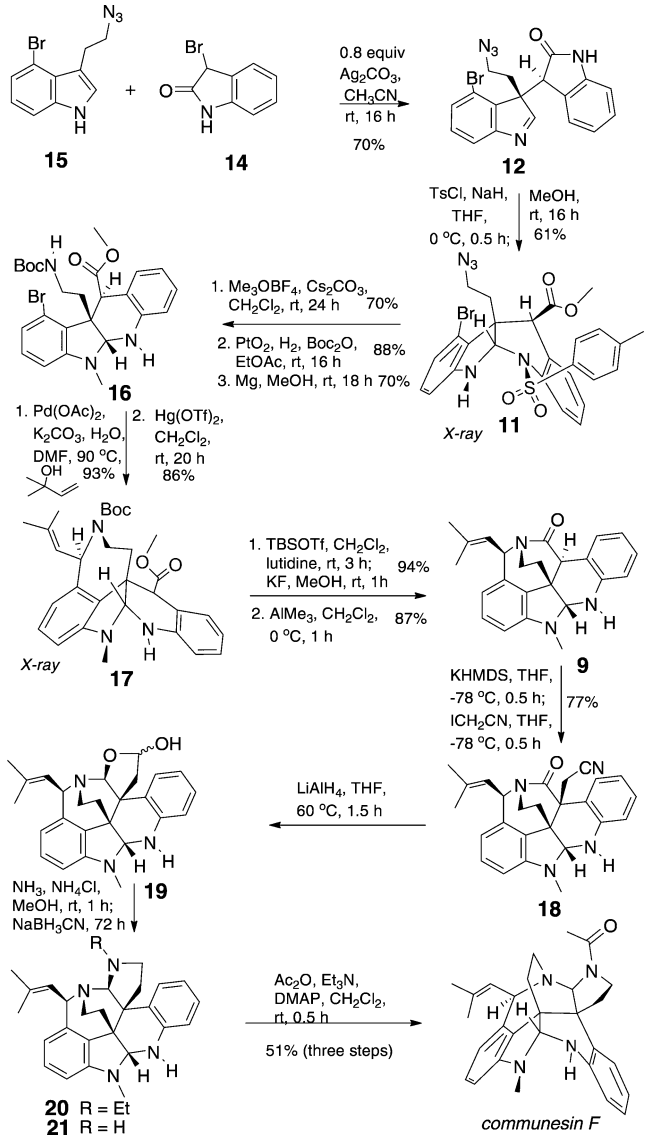
Scheme 3



Scheme 4



functionality as precedented in the Qin pioneering synthesis[6a] followed by deprotection and lactamization to afford twisted lactam **9**. *N*-Methylation, transformation of the azide functionality of **11** to the Boc-protected amine, and deprotection of the tosyl amine were expected to be straightforward. Moreover, Heck reactions analogous to the one that would afford the allylic alcohol **10** had been documented in the Qin[6a] and Ma[6c] studies. The construction of the lower aminal functionality of **11** would draw upon a strategy similar to that employed in our perophoramidine total synthesis. Thus, it seemed likely that the tosyl imide derivative of lactam **12** would undergo methanolysis and concomitant closure of a tosyl amide intermediate upon the indolenine functionality. Finally, cycloaddition of indol-2-one, in turn generated by dehydrohalogenation of 3-bromooxindole (**14**), with indole **15** would afford indolenine **12** by way of *endo* adduct **13**.

A caveat of this overall plan was the identification of conditions that would allow cycloaddition/conjugate addition with the parent indol-2-one, a limitation in our initial methodological study.[8] Indeed, subjection of indole **15** and bromooxindole **14** (Scheme 4) to our standard conditions (2.2 equiv Cs_2CO_3, CH_2Cl_2, rt) gave none of the desired product, indolenine **12**. However, after screening several bases and solvents, it was found that treatment of indole **15** (1 equiv) and freshly recrystallized 3-bromoindol-2-one (**14**, 1.6 equiv) with silver carbonate (0.8 equiv) in acetonitrile did deliver indolenine **12** in good yield as a single diastereomer. Our tentative stereochemical assignment for indolenine **12** was quickly confirmed by tosylation and in situ methanolysis to afford the tetracyclic tosylamide **11** whose structure was confirmed by X-ray crystallographic analysis. Methylation of the nitrogen atom of indoline **11** proved to be problematic. After an exhaustive screening of traditional methylating reagents and protocols (NaH, MeI; KO*t*Bu, MeI; Cs_2CO_3, MeI; HCHO, $NaBH_3CN$; HCHO, $Ti(OiPr)_4$, $NaBH_3CN$; MeOTf), we discovered that we could effect the desired transformation with Meerwein's reagent and cesium carbonate. Subsequent reduction of the azide functionality with in situ protection of the resulting amine as a Boc-carbamate and detosylation provided aminal **16**. It was found that the Heck reaction of bromide **16** with 2-methyl-3-buten-2-ol could be best accomplished by employing the conditions reported by Jew and Park in their clavicipitic acid total synthesis[11] to produce the allylic alcohol **10** (Scheme 3) in excellent yield.

Attempted cyclization of alcohol **10** under conditions (H^+; MsCl, NEt_3) utilized in the previous syntheses of communesin F by Qin, Weinreb and Ma afforded none of the desired benzazepine **17** and instead led exclusively to a diene product resulting from dehydration. Analogous dienes were also obtained as substantial byproducts (24−26%) in the Qin and Weinreb syntheses. Fortunately, the mild protocol recently reported by the Nishizawa group[12] for the mercuric triflate-catalyzed five-membered cyclizations of sulfonylated anilines bearing 2-(2-butene-4-ol) substituents was applicable to our problem. In the case at hand, a smooth seven-membered cyclization of carbamate **10** took place in excellent yield to furnish only the desired benzazepine **17**, whose structure was secured by X-ray crystallographic analysis. Finally, removal of the carbamate functionality of **17** could be accomplished using the Ohfune procedure[13] to provide an amino ester that resisted cyclization upon thermolysis (140 °C, DMSO, 16 h), but did provide the twisted, bridged lactam **9** upon treatment with trimethylaluminum. To the best of our knowledge, this represents the first example of the construction of a twisted,

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bridged lactam[14] using this valuable protocol for the preparation of amides.[15]

The stage was now set for the introduction of the remaining quaternary carbon, aminal moiety and completion of the total synthesis. Attempts to alkylate the bridged lactam **9** with 2-iodoethylazide using conditions we had previously employed using structurally related fused lactams that lacked the N(10), C(11) bond proved unsuccessful. Fortuitously, while this investigation was underway, Ma reported the total syntheses of communesins A and B from a bridged lactam very similar to lactam **9** that has a protected vicinal diol in place of the carbon−carbon double bond. Thus, we elected to adopt their endgame and the first two steps were uneventful, namely, stereoselective alkylation of the enolate derivative of lactam **9** from the convex face to afford nitrile **18** which was then reduced with lithium aluminum hydride to afford lactol **19**. However, we were quite surprised to discover that reductive amination of lactol **19** with sodium triacetoxyborohydride (MeOH, NH_4OAc, rt, 48 h) gave none of the desired aminal **21**, but instead the *N*-ethylaminal **20** (1″-deoxocommunesin F) in good yield (70% from nitrile **18**). Indeed, it has been previously observed that slow reductive aminations (>24 h) employing sodium triacetoxyborohydride produce up to 5% *N*-ethyl derivatives from acetaldehyde generated by self-reduction of the reagent.[16] In this case, the initial reductive amination of the lactol is sufficiently suppressed to allow competitive reductive amination of the resulting primary amine. Fortunately, we eventually were able to discover conditions that avoided the use of sodium triacetoxyborohydride to provide the crude aminal **21** which was directly acetylated to give (±)-communesin F whose spectroscopic properties were identical to those previously reported.

In summary, we have completed a concise total synthesis of (±)-communesin F in 15 linear steps from 4-bromotryptophol in an overall yield of 6.7%. Highlights of this synthesis include: (1) a stereoselective cycloaddition with the *parent* indol-2-one; (2) an underutilized intramolecular mercuric triflate catalyzed cyclization of a carbamate with an allylic alcohol; and (3) the preparation of a twisted, bridged lactam from an amino ester using trimethylaluminum. This total synthesis further documents the value of indol-2-one cycloadditions for the rapid construction of complex natural products that embody indolines bearing C(3) quaternary carbons. Additional applications of this methodology are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, product characterization and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ NOTE ADDED AFTER ASAP PUBLICATION

The TOC graphic was incorrect in the version published ASAP September 28, 2012. The correct version reposted October 3, 2012.