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Ir-Catalyzed Asymmetric Total Synthesis of (−)-Communesin F

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Supporting Information

ABSTRACT: The first catalytic asymmetric total synthesis of the heptacyclic alkaloid (−)-communesin F is described. A key step features an iridium-catalyzed asymmetric intermolecular cascade cyclization, constructing the lower *N*,*N*-aminal-containing CDEF tetracyclic core in one step. Another notable element is the closure of final ring system (A ring) via a facile reduction of a twisted amide and concomitant cyclization activated by mesylation of *N*,*O*-hemiaminal intermediate.

The communesins (**1**−**8**) are a family of complex polycyclic indole alkaloids isolated from marine and terrestrial *Penicillium* fungi that demonstrate significant cytotoxicity and insecticidal activity (Figure 1).[1] These alkaloids share an identical

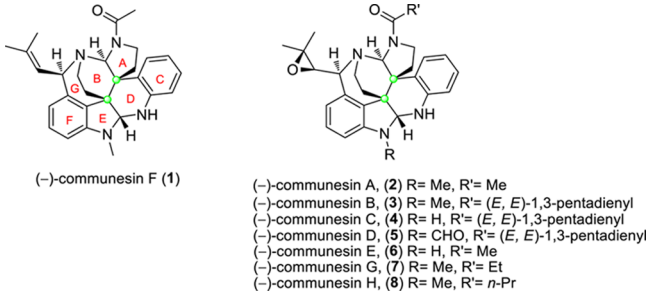


Figure 1. Communesin family of natural products.

synthetically challenging heptacyclic core arrayed with two aminal groups and at least five stereogenic centers, including two vicinal quaternary carbons. This combination of intriguing structural complexity and interesting biological activities renders these alkaloids popular synthetic targets.[2]

In 2007, Qin reported the inaugural synthesis of (±)-communesin F (**1**) employing a strategic cyclopropanation (Figure 2).[3] Later, Weinreb disclosed a second route to (±)-communesin F (**1**) using an intramolecular Heck cyclization of a tetrasubstituted alkene as a key step.[4] In 2010, Ma adopted an intramolecular oxidative coupling strategy to complete the first asymmetric synthesis as well as the assignment of the absolute configuration of (−)-communesin F (**1**).[5] In 2012, Funk reported a shorter route to (±)-communesin F (**1**) by cycloaddition of indol-2-one with a bromoindole.[6] Recently, Movassaghi utilized a diazene-directed fragment assembly strategy and finished the second reported asymmetric synthesis of (−)-communesin F (**1**).[7] The innovative strategies for these five total syntheses of communesin

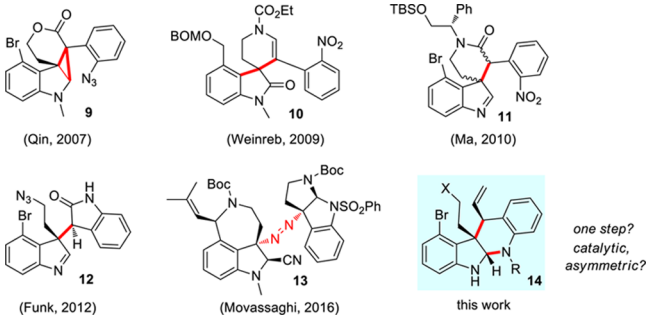
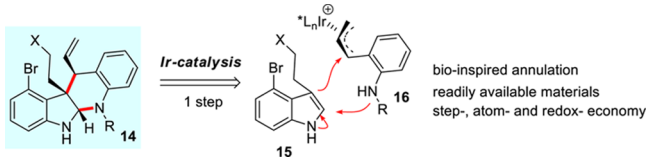


Figure 2. Highlights of the strategies in the synthesis of communesin F.

F, along with one formal synthesis[8a] are all impressive. To the best of our knowledge, however, a one-step biomimetic, direct construction of the lower *N*,*N*-aminal-containing tetracyclic core **14** in a highly convergent and catalytic enantioselective manner, which represents an attractive and efficient strategy, has yet to be reported. Tetracyclic indoline **14** harbors three contiguous chiral centers and a skeleton so similar to that of the communesins that the remaining tasks are apparent, namely (1) generation of the second quaternary carbon and the upper aminal functionality, and (2) introduction of the prenyl group and formation of the benzazepine.

Inspired by our interest in transition-metal-catalyzed allylations of indoles[9] and the communesin biosynthetic pathway,[10] we proposed tetracyclic aminal **14** could be forged most efficiently through an iridium-catalyzed direct coupling of 3-substituted 4-bromoindole **15** with aniline-based allylic electrophile **16** (Scheme 1).[11] Construction of a similar tetracyclic intermediate[12] via a Mo-catalyzed asymmetric allylic allylation (AAA) reaction[14] between an oxindole and an allylic phosphate was reported in Trost's elegant synthesis of (−)-perophoramidine.[13] That reported process, however, required a multistep reaction sequence. Moreover, the differences with our proposed strategy

Scheme 1. Design of Ir-Catalyzed Asymmetric Cyclization Approach to Tetracyclic Aminal



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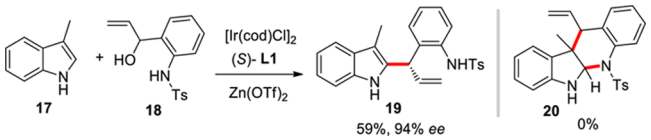
(Mo vs Ir, the oxindole vs indole, and the extra influence of the essential 4-bromine substituent on the electronic nature of indole ring system) rendered the possibility of a one-step construction of animal **14** uncertain and challenging. Nevertheless, we were encouraged to pursue this new design given the two starting materials are readily available[15] and the proposed cyclization would be step-, redox- and atom-economical.[16] Herein, we report the realization of this new indole cyclization and its implementation in the first catalytic asymmetric total synthesis of (−)-communesin F (**1**).[17]

We began our methodological studies with 3-methylindole **17** and secondary allylic alcohol **18** as substrates. To our surprise, using our previously reported conditions for iridium-catalyzed intramolecular cyclization[11a] afforded C-2 alkylated **19** as the major product, albeit in moderate yield with high ee;[18] none of desired tetracycle **20** observed (Scheme 2).[19] Instead of

Scheme 2. Attempted Cyclization of 3-Methylindole

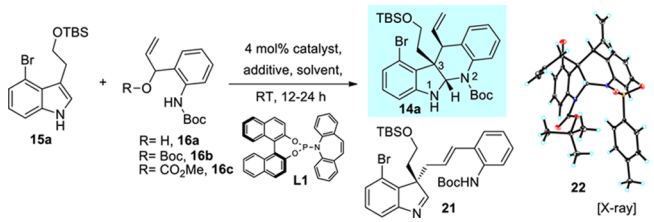


continuing with model substrate **17**, we elected to explore different reaction conditions so as to provide the desired chemoselectivity with 4-bromo-3-substituted indole **15a**, which is better suited for elaboration into our target **1**.[20]

As illustrated in Table 1, entries 1 and 2, we initially evaluated the effectiveness of palladium catalysis for the tandem allylation/cyclization between indole **15a** and secondary allylic alcohol **16a** only to observe formation of the undesired linear indolenine **21**. Encouraged by work from Carreira and co-workers on the Ir-catalyzed reverse prenylation of 3-substitued indoles,[21] we resumed investigation using an iridium catalyst. It is important to note that studies demonstrated activation of indole substrates with KO-*t*-Bu and Et_3B as additives along with chiral ligands enabled the Ir-catalyzed C-3 reverse prenylation to proceed with excellent diastereoselectivities on various substrates, but enantioselectivities were found to be low (<20% ee).[21,22] Despite this uncertainty, we observed that, after changing the secondary allylic alcohol **16a** to *t*-butyl carbonate **16b** as allylic electrophile, the use of [Ir(cod)Cl]2 together with ligand **L1**,[23] KO-*t*-Bu and Et_3B (entry 3) provided the desired tetracycle **14a** in good yield as a single diastereomer (>20:1 d.r.) with excellent enantioselectivity (92% ee). Changing the nature of the carbonate (−CO_2Me, **16c**, entry 4), resulted in somewhat increased amounts of undesired linear indolenine **21**. Further evaluation of the solvent (entries 5−7) revealed toluene lead to satisfactory results comparable to those of 1,4-dioxane. To procure sufficient amounts of tetracycle **14a**, a feasibility study was conducted on the gram-scale. Unfortunately, running on a 0.5 mmol scale, the reaction showed reduced enantioselectivity (83% ee), albeit with unchanged yield (entry 8). In an unsuccessful attempt to improve the enantioselectivity, a bulkier triphenylborane first was used (entry 9). After experimentation, it was found the use of 9-BBN-*n*-C_6H_{13} as an additive not only allows for cyclization to proceed well on 0.1 mmol scale, giving the highest observed ee (entry 10), but also can be employed at the 5 mmol scale, furnishing the desired tetracycle **14a** in respectful yield with only slightly reduced enantioselectivity (entry 11). The absolute configuration of tetracyle **14a** was established through single-crystal X-ray analysis of analog **22** (N1-Boc, N2-Ts, C3-allyl; see SI).

With tetracycle **14a** in hand, we turned to the total synthesis of (−)-**1**. As shown in Scheme 3, *N*-methylation of indole **14a** with KO-*t*-Bu and MeI, followed by removal of the TBS group with CSA, provided the desired tetracyclic primary alcohol **23** (85% yield). To introduce the nitrogen atom, we employed a Mitsunobu reaction using phthalimide as nitrogen source. Accordingly, alcohol **23** was converted to phthalimide **24** in 80% yield following standard protocol. To generate the second quaternary center with the requisite configuration, a strategy harnessing the unique U-shape conformation of the pentacyclic

Table 1. Optimization of Catalyst and Additives Used for Annulation of *N,N*-Aminal-Containing Tetracycle[a]



entry	catalyst	additives	solvent	**14**/**21**[b]	ee (%)[c]	yield (%)[d]
1[e]	$Pd(PPh_3)_4$	Et_3B	THF	1: >20		81
2[e]	$Pd(PPh_3)_4$	Et_3B, DBU	DCM	1: >20		75
3	$[Ir(cod)Cl]_2$ (S)-**L1**	Et_3B, KO-*t*-Bu	1,4-dioxane	>10:1	92	68
4[f]	$[Ir(cod)Cl]_2$ (S)-**L1**	Et_3B, KO-*t*-Bu	1,4-dioxane	3:1	80	35
5	$[Ir(cod)Cl]_2$ (S)-**L1**	Et_3B, KO-*t*-Bu	DCM	9:1	91	60
6	$[Ir(cod)Cl]_2$ (S)-**L1**	Et_3B, KO-*t*-Bu	THF	6:1	91	52
7	$[Ir(cod)Cl]_2$ (S)-**L1**	Et_3B, KO-*t*-Bu	toluene	>10:1	92	65
8[g]	$[Ir(cod)Cl]_2$ (S)-**L1**	Et_3B, KO-*t*-Bu	toluene	>10:1	83	65
9	$[Ir(cod)Cl]_2$ (S)-**L1**	Ph_3B, KO-*t*-Bu	toluene			trace
10	$[Ir(cod)Cl]_2$ (S)-**L1**	9-BBN-*n*-C_6H_{13}, KO-*t*-Bu	toluene	>10:1	99	55
11[h]	$[Ir(cod)Cl]_2$ (S)-**L1**	9-BBN-*n*-C_6H_{13}, KO-*t*-Bu	toluene	>10:1	93	56

[a]The reactions were performed, unless indicated otherwise, on a 0.1 mmol scale using 1 equiv of **15a**, 1.5 equiv of **16b**, 1.1 equiv of additives, 4 mol % of catalyst, 16 mol % of **L1** and 0.5 mL of solvent at ambient temperature. [b]Determined by ^{1}H NMR of crude reaction mixture. [c]Determined by chiral HPLC analysis. [d]Isolated yields. [e]Using **16a**. [f]Using **16c**. [g]Run on 0.5 mmol scale. [h]Run on 5.0 mmol scale.

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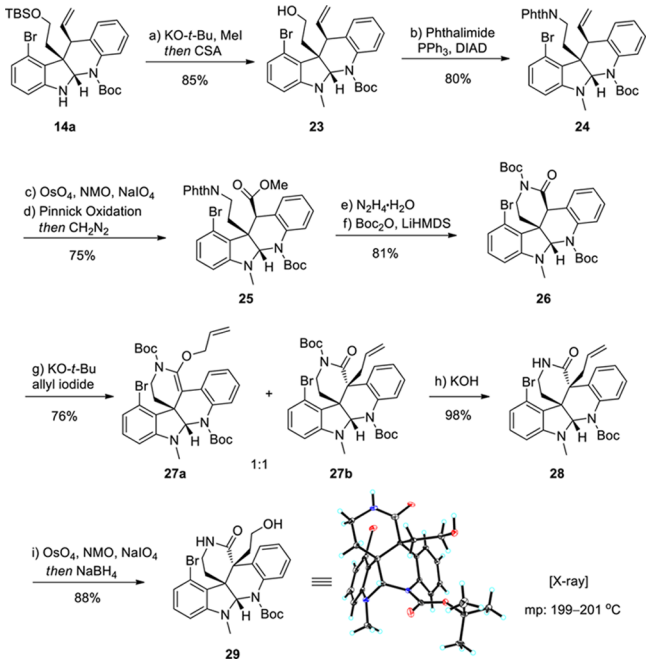
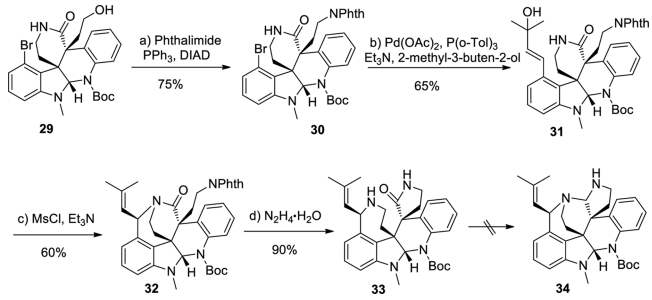
Scheme 3. Synthesis of the Pentacyclic Intermediates



lactam **26** to introduce an allyl group stereospecifically was adopted. Toward this end, we first performed the oxidative cleavage of **24** employing a Lemieux–Johnson oxidation, affording the desired aldehyde product. Subsequent Pinnick oxidation of the aldehyde intermediate and methylation of the resulting carboxylic acid with fresh CH_2N_2 delivered methyl ester **25**. It is noteworthy that the above continuous process was carried out with no chromatographic purification of the intermediates and high overall yield (75%). Deprotection of the phthalimide group led to formation of a primary amine intermediate that underwent spontaneous lactamization, providing a pentacyclic lactam intermediate that could be used without purification for subsequent *N*-acylation to afford *N*-Boc lactam **26** (81% yield). Alkylation of corresponding enolate of **26**, generated with KO-*t*-Bu, with allyl iodide delivered an inseparable ca. 1:1 mixture of *C*- and *O*-allylation adducts in 76% yield. The ratio was inconsequential because both adducts could be converted into the desired pentacycle **28** in nearly quantitative yield when the Boc group on the lactam nitrogen atom was removed by basic hydrolysis at 80 °C;[4a] in the case of *O*-allylated **27a**, a concomitant stereoselective 3,3-rearrangement also took place. Oxidative cleavage of the alkene moiety in **28** using a Lemieux–Johnson oxidation, followed by reduction of the resultant aldehyde with $NaBH_4$ furnished a crystalline alcohol **29**, whose structure was secured by single crystal X-ray analysis and comparison of NMR data with previous reports.[5a]

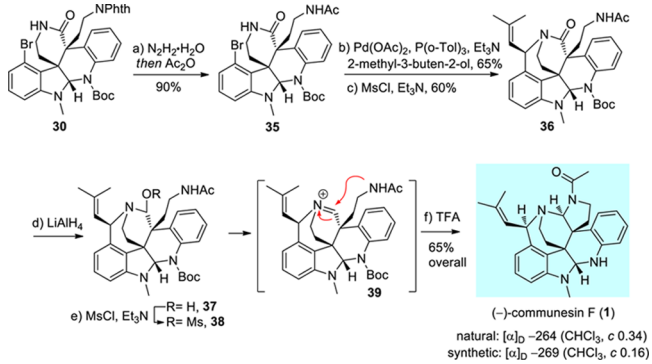
To install the fourth nitrogen atom of the natural product, we employed another Mitsunobu reaction. As shown in Scheme 4, alcohol **29** was converted to phthalimide **30** via standard procedures in good yield. The Heck reaction of bromide **30** with 2-methyl-3-buten-2-ol could be accomplished by heating the reaction mixtures in a sealed tube at 135 °C for 24 h, producing allylic alcohol **31** in 65% yield. The desired benzazepine **32** was cyclized following Ma's conditions (MsCl, NEt_3)[5a] to give the best yield (60%); other conditions (PPTS or $Hg(OTf)_2$) previously utilized by Qin, Weinreb, and Funk afforded inferior results. To complete the synthesis, removal of the phthalimide group so as to close the A ring was required. At this point, a

Scheme 4. Attempted Cyclization to Heptacyclic Core



spontaneous five-membered cyclization of the resulting amine from the deprotection of **32** took place in excellent yield to furnish only the lactam **33**. Although lactam **33** could be converted to the final natural product using the same end-game strategies adopted by Qin and Weinreb, herein a new alternative method to complete the B ring was explored. Unfortunately, direct formation of the *N*,*N*-aminal by reduction of the lactam or formation of an amidine proved problematic. The lactam is inert to various reagents ($LiAlH_4$, $LiBEt_3H$, $POCl_3$), but slowly decomposed under harsher conditions. To avoid formation of unmanageable lactam **33**, we installed the acetamide at an earlier stage. As shown in Scheme 5, pentacyclic phthalimide **30** was

Scheme 5. Completion of the Total Synthesis of (−)-Communesin F



deprotected with hydrazine, and the corresponding amine was acylated to provide **35** in excellent yield (90%). Pentacyclic acetamide **35** was converted to compound **36** through two steps involving Heck reaction and benzazepine cyclization. Drawing inspiration from Ma's work on the twisted amide,[5a] we envisioned the bridged amide of **36** would be much more reactive than amide **33**. Indeed, reduction of **36** with $LiAlH_4$ at 0 °C cleanly delivered the *N*,*O*-hemiaminal intermediate **37**, which was subsequently mesylated accompanied by cyclization, presumably through the highly reactive iminium **39**, to give the heptacyclic skeleton of the communesins. Finally, removal of the Boc protecting group with TFA in CH_2Cl_2 afforded (−)-communesin F (**1**) in 65% overall yield. All ^1H and ^{13}C NMR data for our synthetic sample are in agreement with literature data. The synthetic (−)-**1** exhibits an optical rotation of −269 (*c* 0.16, $CHCl_3$), essentially identical to that of the natural substance (−264, *c* 0.34, $CHCl_3$).[1c]

In summary, we have developed the first catalytic asymmetric total synthesis of the heptacyclic alkaloid (−)-communesin F (**1**). Highlights of this synthesis include: (1) an enantio-, diastereo-, and regioselective iridium-catalyzed annulation between a 3-substituted indole and a protected 2-aminophenyl allylic

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electrophile, constructing the lower *N*,*N*-aminal-containing CDEF tetracyclic core within one step; and (2) the facile closure of the heptacyclic system bearing an *N*-acetyl aminal via reduction of a twisted amide. To the best of our knowledge, this work represents the newest application of iridium-catalyzed asymmetric synthesis of the structurally complex alkaloid, which we postulate may inspire more promising results in future studies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b00854.

Full characterization, analysis of enantioselectivity, spectral data, experimental procedures (PDF)
X-ray crystallographic data for **22** (CIF)
X-ray crystallographic data for **29** (CIF)

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Notes

The authors declare no competing financial interest.

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(15) Our starting materials could be prepared in ≤2 steps from known or commercial compounds; see the SI.

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(17) The previous two asymmetric syntheses of (−)-**1** required the use of chiral auxiliaries to affect stereoselectivity.

(18) The absolute configuration of **19** was assigned by analogy with a crystalline analog that was confirmed by X-ray analysis.

(19) The failure of intermolecular cyclization could be related to the lack of N1 activation and/or the unfavorable entropy.

(20) The analog of **15a** (-NPhth instead of -OTBS) was used at first, but then was no longer considered because this substrate was not very stable, leading to poor repeatability of the key annulation.

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