Organic LETTERS

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pubs.acs.org/OrgLett

A Diastereodivergent Synthetic Strategy for the Syntheses of Communesin F and Perophoramidine

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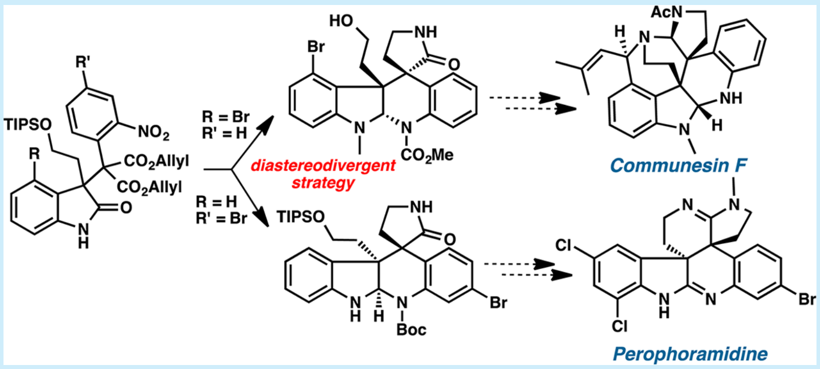
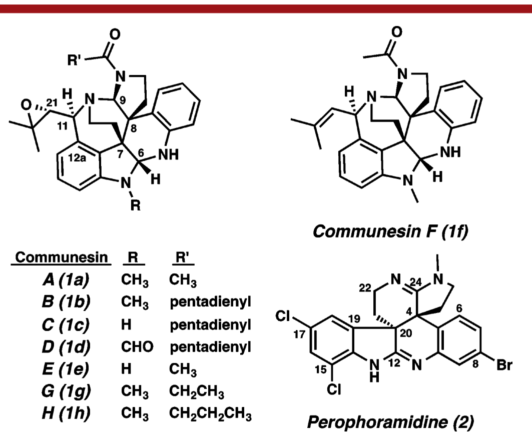
Supporting Information



ABSTRACT: An efficient, unified, and stereodivergent approach toward communesin F and perophoramidine was examined. The C(3) all-carbon quaternary center of an oxindole was smoothly constructed by base-promoted indolone-malonate alkylation chemistry. The complementary relative stereochemistry of the crucial vicinal quaternary centers found in communesin F and perophoramidine was selectively installed by substrate-controlled decarboxylative allylic alkylations.

Communesins A (**1a**) and B (**1b**) were isolated in 1993 from a strain of *Penicillium* sp. found on a marine alga (Figure 1).[1] Communesin B (**1b**) exhibits antiproliferative activity against P-388 lymphocytic leukemia cells (ED_{50} = 0.9 μM), LoVo (MIC = 3.9 μM), and KB cells (MIC = 8.8 μM).[1,2] In the following years, communesins B–H (**1b–1h**) were isolated from related strains of *Penicillium* sp.[3] Communesins A–F (**1a–1f**) show interesting biological activities such as insecticidal and antiproliferative activities against a variety of cancer cells.[1−3] These complex, polycyclic, bioactive alkaloids possess several intriguing architectural features including vicinal quaternary carbon centers and bis-aminal functional groups.



Communesin	R	R'
A (1a)	CH_3	CH_3
B (1b)	CH_3	pentadienyl
C (1c)	H	pentadienyl
D (1d)	CHO	pentadienyl
E (1e)	H	CH_3
G (1g)	CH_3	CH_2CH_3
H (1h)	CH_3	$CH_2CH_2CH_3$

Figure 1. Communesins (**1**) and perophoramidine (**2**).

In 2002, structurally and biosynthetically related perophoramidine (**2**) was isolated from the ascidian *Perophora namei* by the Ireland group.[4] Perophoramidine contains the equally unusual bis-amidine instead of bis-aminal functionality, possesses the alternate diastereomeric relationship between the vicinal quaternary centers, and lacks the azepine ring compared to communesins. Perophoramidine (**2**) exhibits cytotoxicity toward the HCT 116 human colon carcinoma cell line (IC_{50} = 60 μM) and induces apoptosis via PARP cleavage.[5]

These intriguing polycyclic alkaloids have attracted much attention from the synthetic community over the past decade.[6] Herein, we report a unified, diastereodivergent approach toward the syntheses of communesin F (**1f**) and perophoramidine (**2**). As a first generation approach to communesin F (**1f**) and perophoramidine (**2**) we chose to pursue formal syntheses by intercepting key intermediates of previous routes. Our overarching plan for synthesis of these diastereodivergent series was to employ stereoselective enolate alkylations of substrates

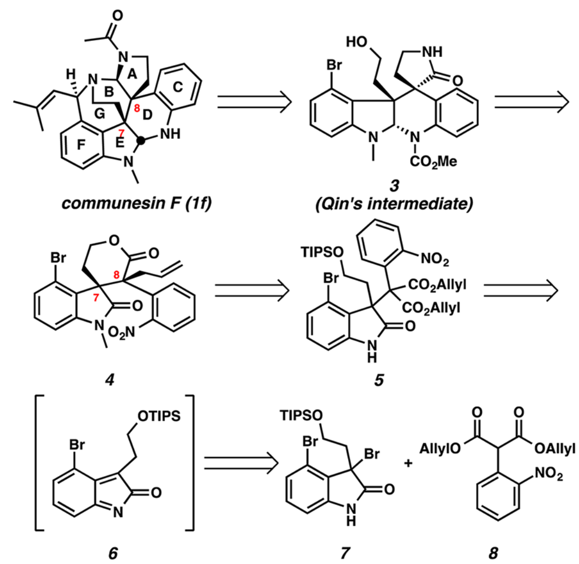
Received: May 8, 2014
Published: June 9, 2014

   dx.doi.org/10.1021/ol5013263 | *Org. Lett.* 2014, 16, 3316–3319

constructed using an oxindole coupling reaction developed in our laboratory for this purpose.[7] Simultaneous to our work, Funk developed a similar oxindole based strategy, and more recently Lu has utilized this for the asymmetric synthesis spirocyclic oxindoles.[8]

Our initial strategic disconnections of pentacycle **3**, an intermediate in Qin's synthesis,[6g] involve late stage introduction of the cyclic aminal functionality by reductive cyclization and installation of γ-lactam by translactamization of lactone **4** (Scheme 1). The relative stereochemical relationship between

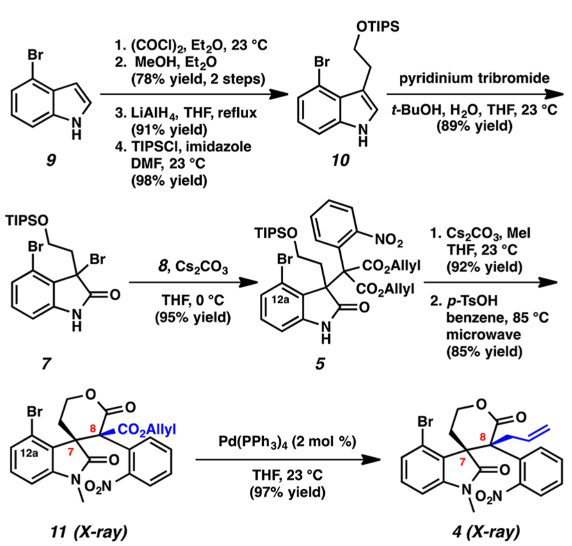
Scheme 1. Retrosynthesis of Communesin F (1f)



C(7) and C(8) of lactone **4** was envisioned to be established by decarboxylative allylic alkylation. We anticipated that the congested vicinal quaternary centers on oxindole **5** could be constructed by the base-promoted alkylation of 3-bromooxindole **7** with aryl diallyl malonate **8** via in situ formation of *o*-azaxylylene intermediate **6**.[7,8]

The diastereoselective synthesis of the key vicinal quaternary centers of lactone **4** is depicted in Scheme 2. 4-Bromoindole **9** was treated with oxalyl chloride and methanol to furnish the

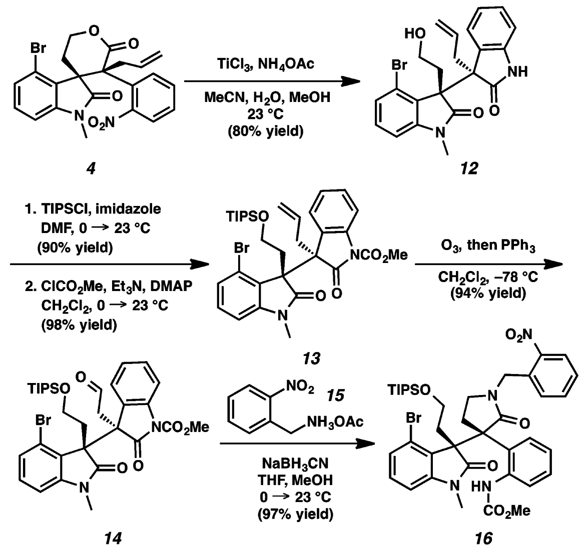
Scheme 2. Construction of the Vicinal Quaternary Centers



corresponding oxoacetate (78% yield, 2 steps), which was subjected to $LiAlH_4$ reduction (91% yield)[6g] and subsequent silylation of the resultant alcohol with TIPSCl to afford silyl ether **10** (98% yield). Indole **10** was oxidized to dibromooxindole **7** with pyridinium tribromide in 89% yield.[9] To our delight, alkylation of dibromooxindole **7** with diallyl malonate **8** smoothly installed the congested quaternary stereocenter on oxindole **5** in 95% yield despite the extra steric hindrance at C(12a) of the oxindole (communesin numbering) and the use of an unprecedented aryl substituted malonate derivative leading to vicinal quaternary centers. Methylation of the oxindole (92% yield) followed by microwave assisted lactonization afforded allyl ester **11** as a single diastereomer in 85% yield. Gratifyingly, decarboxylative allylic alkylation of **11** with catalytic $Pd(PPh_3)_4$ furnished lactone **4** as a single diastereomer. This remarkable reaction not only provides the vicinal quaternary centers needed for the communesin and perophoramidine effort at rt but also proceeds with complete diastereoselectivity. The relative stereochemistry of the vicinal quaternary centers of **11** and **4** was confirmed by single crystal X-ray analysis. Importantly, the diastereomer produced is in line with that needed for the communesins.

Reduction of nitroarene **4** to the aniline by $TiCl_3$ was followed by simultaneous lactone ring opening to furnish bis-oxindole **12** in 80% yield (Scheme 3). Silylation of primary alcohol **12** with

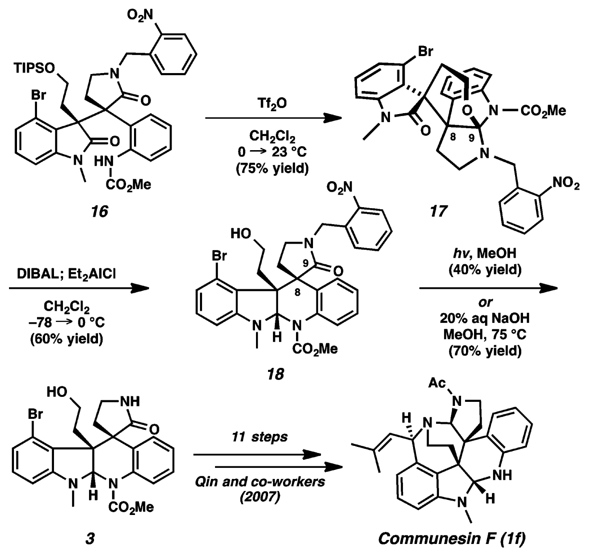
Scheme 3. Synthesis of γ-Lactam 16



TIPSCl (90% yield) and subsequent treatment with methyl chloroformate provided carbamate **13** in 98% yield. Ozonolysis of olefin **13** afforded aldehyde **14** in 94% yield. Next, reductive amination of aldehyde **14** and translactamization provided γ-lactam **16** in 97% yield.

We anticipated that the piperidine D ring of communesin F (**1f**) would be delivered under reductive cyclization conditions (Scheme 4). We attempted to activate oxindole **16** via an imidate by treatment with Tf_2O. Surprisingly, these conditions delivered *o*-nitrobenzyl protected hexacyclic oxindole **17** in 75% yield. At this point, we envisaged that reductive cyclization of hexacycle **17** would produce the desired piperidine ring since the oxidation state at C(9) of **17** is identical to that of desired aminal **18**. Gratifyingly, after extensive experimentation, we could successfully reduce the oxindole of **17** by treatment with a combination of DIBAL and Et_2AlCl, and upon workup the propellane

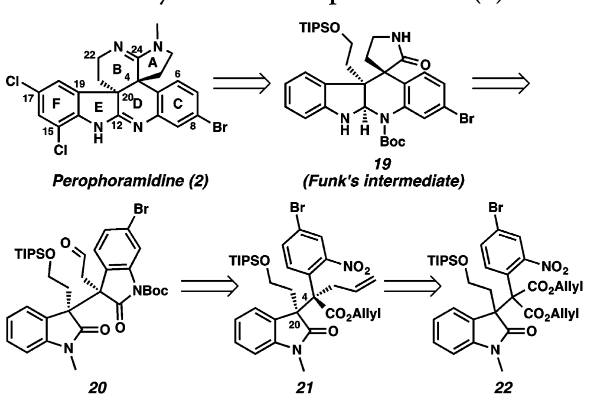
Scheme 4. Formal Synthesis of Communesin F (1f)



structure unravels to produce pentacyclic aminal **18**. We were pleased to find that the *o*-nitrobenzyl group was cleaved by photolysis at 350 nm in 40% yield.[10] Unexpectedly, we discovered that cleavage of the *o*-nitrobenzyl group was also achieved using 20% aq NaOH in methanol at 75 °C in 70% yield. To the best of our knowledge, this constitutes the first use of aqueous hydroxide for removal of an *o*-nitrobenzyl group.[11] Aminal **3** proved identical to an intermediate previously advanced by the Qin group to communesin F,[6g] thus completing a formal synthesis of the natural product.

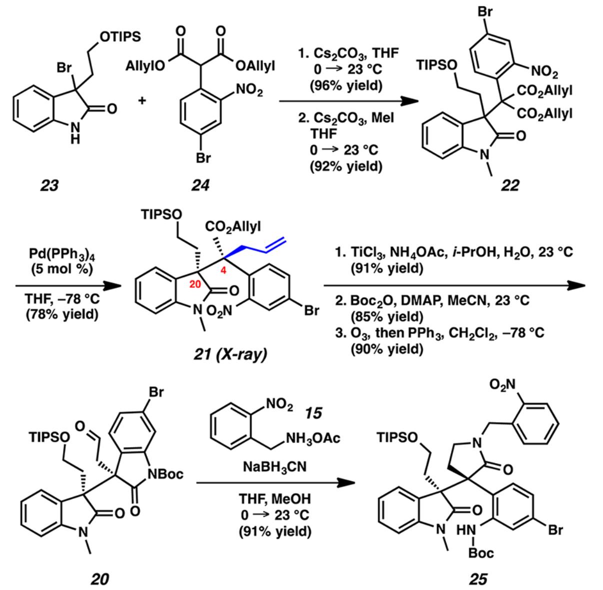
Having successfully completed a formal synthesis of communesin F (**1f**), our attention turned to perophoramidine (**2**) (Scheme 5). We envisaged that aminal **19** could be disconnected to afford aldehyde **20** (diastereomeric at the vicinal quaternary carbons compared to analogue **14**) based on the expedient strategy that was used in our progress toward communesin F. Boc-protected oxindole **20** was excised to afford allyl ester **21**. The vicinal quaternary centers of **21** was anticipated to be installed by decarboxylative allylic alkylation, although the relative stereochemistry was indeed an open question.

Scheme 5. Retrosynthesis of Perophoramidine (2)



In analogy to our communesin F synthesis, the quaternary centers of sterically congested diester **22** were constructed by alkylation of 3-bromooxindole **23** with aryl substituted malonate ester **24** (96% yield), followed by *N*-methylation of the resulting oxindole in 92% yield (Scheme 6). To our delight, direct decarboxylative allylic alkylation of diester **22** with catalytic

Scheme 6. Construction of the Contiguous Vicinal Quaternary Centers

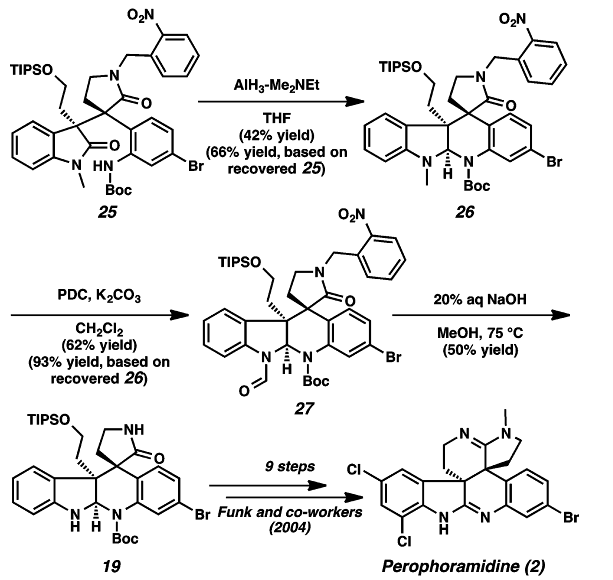


$Pd(PPh_3)_4$ furnished allyl ester **21** in 78% yield as a single diastereomer. Interestingly, through X-ray analysis we discovered that the relative stereochemistry of the vicinal quaternary centers in this acyclic example was complementary to that of lactone **4** (Scheme 2) and, thus, suitable for elaboration to perophoramidine (**2**).[12] Bis-oxindole **20** was obtained from allyl ester **21** by nitroarene reduction and simultaneous lactamization (91% yield),[13] followed by Boc protection (85% yield) and subsequent ozonolysis (90% yield). Reductive amination of aldehyde **20** with *o*-nitroammonium acetate **15** provided lactam **25**.

In contrast to the communesin system, we discovered that the desired aminal **26** was obtained directly by reduction with AlH_3-Me_2NEt in 42% yield (66% yield based on recovered starting material) (Scheme 7).[14] The indoline methyl group was oxidized to a formyl functionality using PDC to produce **27** in 62% yield (93% yield based on recovered starting material).[15] To our delight, the cleavage of both formyl and *o*-nitrobenzyl groups was achieved using 20% aq NaOH at 75 °C to deliver aminal **19** in 50% yield.[16] Aminal **19** was advanced by Funk in his synthesis of perophoramidine,[6o] thus completing our formal synthesis of the natural product.

In summary, we have completed stereocontrolled formal syntheses of communesin F (**1f**) and perophoramidine (**2**) using a stereodivergent alkylation approach. The highly congested all-carbon quaternary center of the oxindoles (**5** and **22**) was constructed by stabilized enolate alkylation of 3-bromooxindoles, a remarkably facile method discovered by our laboratory. The complementary relative stereochemistry of the contiguous vicinal quaternary centers found in communesin F and perophoramidine was introduced by substrate controlled diastereoselective decarboxylative allylic alkylation, again under exceedingly mild conditions. Several novel and intriguing intermediates such as the propellane hexacyclic oxindole were encountered toward the formal synthesis of communesin F. Finally, a previously unknown *o*-nitrobenzyl group cleavage protocol was discovered serendipitously and proved critical to

Scheme 7. Formal Synthesis of Perophoramidine (2)



the formal syntheses of both communesin F and perophoramidine.

■ ASSOCIATED CONTENT

Supporting Information

The authors declare no competing financial interest. 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.

■ ACKNOWLEDGMENTS

The authors wish to thank NIH-NIGMS (R01GM080269), Amgen, the Gordon and Betty Moore Foundation, and Caltech for financial support. S.-J.H. thanks Fulbright (Foreign Student Program, No. 15111120) and the Ilju Foundation of Education & Culture (Predoctoral Research Fellowship) for financial support. F.V. thanks the German Academic Exchange Service (DAAD) (postdoctoral fellowship). S.K. thanks California TRDRP for financial support (postdoctoral fellowship 14FT-0002). J.A.M. is grateful for a fellowship by Bristol-Myers Squibb and Amgen. M.G. is grateful to the Swiss National Science Foundation for financial support (postdoctoral fellowship). Dr. David VanderVelde (Caltech) is gratefully acknowledged for assistance with the characterization of compounds by NMR spectroscopy. Lawrence Henling (Caltech) is acknowledged for X-ray crystallographic structural determination.

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(11) Explorations in our laboratory regarding the generality of this deprotection method are ongoing.

(12) Despite the high levels of diastereocontrol observed in the allylic alkylations described in this manuscript (i.e., **11** → **4** and **22** → **21**), a reasonable explanation for these selectivities has not been as forthcoming. Investigations into these fascinating reactions and the underlying principles guiding the observed stereoselectivities are ongoing.

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