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Convergent and Biomimetic Enantioselective Total Synthesis of (–)-Communesin F

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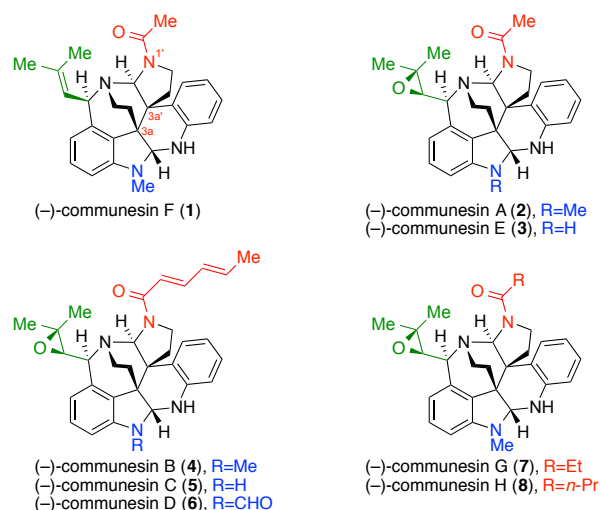# Convergent and Biomimetic Enantioselective Total Synthesis of (–)-Communesin F

Stephen P. Lathrop, Matthew Pompeo, Wen-Tau T. Chang, and Mohammad Movassaghi*

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Supporting Information Placeholder

ABSTRACT: The first biomimetic enantioselective total synthesis of (–)-communesin F based on a late-stage heterodimerization and aminal exchange is described. Our synthesis features the expedient diazene–directed assembly of two advanced fragments to secure the congested C3a–C3a' linkage in three steps, followed by a highly efficient biogenetically inspired aminal reorganization to access the heptacyclic communesin core in only two additional steps. Enantioselective syntheses of the two fragments were developed, with highlights including the catalytic asymmetric halocyclization and diastereoselective oxyamination reactions of tryptamine derivatives, a stereoselective sulfinimine allylation, and an efficient cyclotryptamine–C3a-sulfamate synthesis by either a new silver–promoted nucleophilic amination or a rhodium–catalyzed C–H amination protocol. The versatile synthesis of the fragments, their stereocontrolled assembly, and the efficient aminal–exchange as supported by in situ monitoring experiments, in addition to the final stage N1'-acylation of the communesin core provide a highly convergent synthesis of (–)-communesin F.
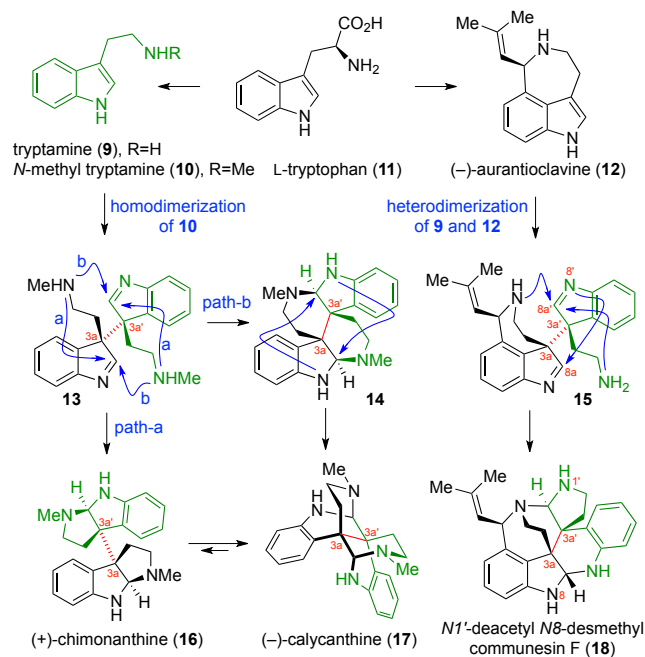
Figure 1. The Structure of Communesin Alkaloids

Introduction. The communesin alkaloids are a family of structurally complex natural products isolated from various marine and terrestrial *Penicillium* fungi, which have been shown to possess insecticidal and antiproliferative activities as well as significant cytotoxicity against lymphocytic leukemia.[1,2] The core structures of these alkaloids share a unique heptacyclic skeleton containing two aminals and at least five stereogenic centers, of which two are vicinal and quaternary (Figure 1). This exquisite structural complexity coupled with an array of interesting biological properties has prompted investigations directed towards the chemical synthesis of these alkaloids,[2] culminating in innovative solutions for the total synthesis of (±)-communesin F (**1**) by Qin,[3] Weinreb,[4] and Funk,[5] in addition to a formal synthesis by Stoltz.[6] To date, Ma's total synthesis of (–)-communesin F (**1**)[7] remains the only enantioselective

solution for this archetypal alkaloid. As an outgrowth of our investigations in the area of *calycanthaceous* alkaloids,[8,9] we sought to develop a unified and convergent approach to the communesin alkaloids. We drew inspiration from a speculated biogenesis involving the stereocontrolled oxidative union of two dissimilar tryptamine derivatives followed by reorganization of a C3a–C3a' linked heterodimer,[10,11,12,13] reminiscent of the pathways leading to the related calycanthoids.[12,14,] While our biosynthetic considerations were purely hypothetical at the outset of this synthesis campaign, Houk, Garg, and Tang have recently disclosed[15] incisive biosynthetic and computational studies that echo the key transformations developed in our synthesis. Herein, we present the shortest enantioselective total chemical synthesis of (–)-communesin F (**1**) with late-stage chemistry that fortuitously parallels the latest insights[15b] and hypotheses concerning the biogenesis of these alkaloids.

The expectation that the biosynthesis of *calycanthaceous* family of alkaloids[14] has relevance to the biogenesis of the communesins stems from the structural similarity of these alkaloids and their precursors (Scheme 1).

Scheme 1. Comparison of the Bond Formations in the Biogenesis of Structurally Related Dimeric Alkaloids
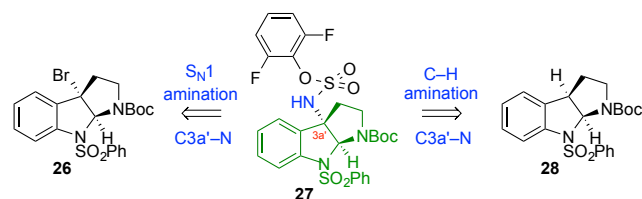

tryptamine (**9**), R=H
N-methyl tryptamine (**10**), R=Me   L-tryptophan (**11**)   (–)-aurantioclavine (**12**)

homodimerization of **10**   heterodimerization of **9** and **12**

13   path-b   **14**   **15**

path-a

(+)-chimonanthine (**16**)   (–)-calycanthine (**17**)   *N1'*-deacetyl *N8*-desmethyl communesin F (**18**)

Scheme 2. Biogenetically Inspired Retrosynthetic Analysis of (–)-Communesin F (**1**)

(–)-communesin F (**1**)

N1–C8a' and N8'–C8a bond formation; acetylation

19

biomimetic reorganization

22   **21**   C3a–C3a' bond formation   **20**

directed coupling

23   diazene synthesis   **24**   +   **25**

Woodward and Robinson independently proposed that the biogenesis of the calycanthoids is predicated on the oxidative homodimerization of *N*-methyl tryptamine (**10**) to form indolenine dimers, such as **13**, which can give rise to five constitutional isomers upon reorganization of the two aminal functional groupings.[10–11] In the illustrative case of indolenine dimer **13** (Scheme 1), amine cyclization via path-a results in (+)-chimonanthine (**16**), whereas an alternative cyclization via path-b, perhaps through the intermediacy of hexacycle **14**, affords the isomeric alkaloid (–)-calycanthine (**17**). Indeed, the equilibration of (+)-chimonanthine (**16**) to (–)-calycanthine (**17**) under acidic aqueous conditions (**16**:**17**=15:85)[8a,16] demonstrates the potential dynamic nature of these polycyclic structures. Anticipating a related biogenesis for the communesins, we expected the heterodimeric intermediate **15** to undergo a similar dynamic reorganization to afford heptacycle **18**. Consistent with this hypothesis, an enzyme capable of the oxidative coupling of tryptamines and *Penicillium* fungal alkaloid (–)-aurantioclavine (**12**)[17,18] has been identified that leads to the formation of the communesin core or an isomeric heptacycle depending on the tryptamine.[15b] We began our studies with the recognition that successful implementation of a biomimetic strategy for the efficient synthesis of these alkaloids requires the directed and stereocontrolled union of two dissimilar fragments followed by selective reorganization of a C3a–C3a' linked heterodimer to a single constitutional isomer consistent with the communesin skeleton **18**.
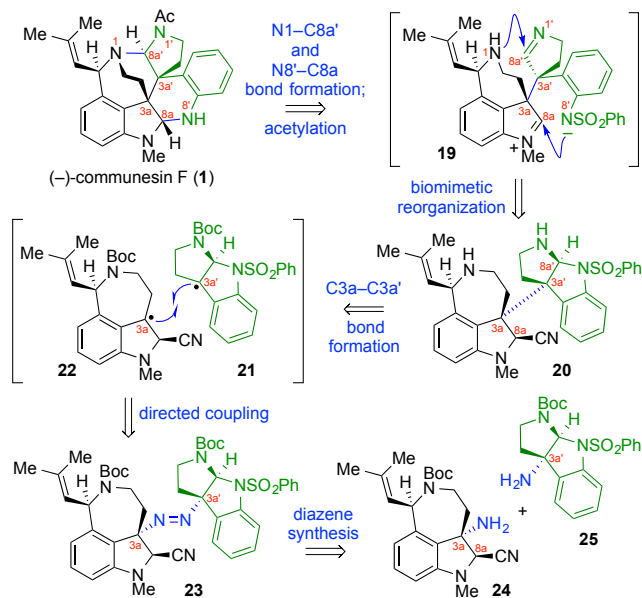
Results and Discussion. As illustrated in our retrosynthetic analysis of (–)-communesin F (**1**, Scheme 2), strict adherence to the central paradigm in the biogenesis of *calycanthaceous* alkaloids focused our design on the efficient assembly and reorganization of a key heterodimeric intermediate **20**. Prompted by our strategy for directed heterodimerization of cyclotryptamines,[19] we envisioned hexacycle **20** (Scheme 2) to serve as a surrogate for the hypothetical biosynthetic intermediate **15** (Scheme 1). We anticipated the N8'-sulfonamide would guide the opening of the C8a'-aminal to present the C8a'-imine for N1-addition. Furthermore, we projected the ionization of the C8a-nitrile would offer the C8a-imininium ion needed for aminal formation via N8'-addition. The challenging C3a–C3a' linkage of heterodimer **20** required a directed and stereocontrolled union of a cyclotryptamine fragment **21** and aurantioclavine derivative **22** to simultaneously secure the two critical quaternary stereocenters. Our diazene-based strategy for directed complex fragment assembly[19] provided the essential framework to explore this exciting and convergent approach to (–)-communesin F (**1**). While we were confident the C8a'-stereochemisry of the cyclotryptamine moiety would guide the desired C3a'-stereochemical outcome in this union, we were intrigued by the potential level of stereochemical control expected at C3a during carbon–carbon bond formation. We envisioned the synthesis of complex heterodimeric diazene **23** from tricyclic amines **24** and **25** as tryptamine–surrogates necessary for securing the C3a–C3a' linkage (Scheme 2).
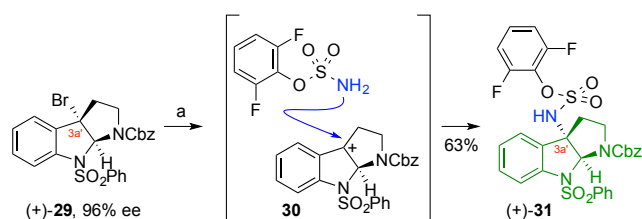
Scheme 3. Strategies for Synthesis of Tricycle **27**

Scheme 4. Concise Synthesis of Sulfamate (+)-**31**[a]

[a]Reagents and conditions: (a) AgSbF$_6$, 2,6-di-*tert*-butyl-4-methylpyridine, 2,6-difluorophenylsulfamate, CH$_2$Cl$_2$, 23 °C, 63%.

Scheme 5. Gram-scale Synthesis of Sulfamate (+)-**27**[a]

[a]Reagents and conditions: (a) (Me$_3$Si)$_3$SiH, Et$_3$B, air, 23 °C, >99:1 dr; (b) (i) KOH (aq.), MeOH, CH$_2$Cl$_2$, 23 °C, (ii) *N,N,N′,N′*-tetramethylchloroformamidinium hexafluorophosphate, thiopyridine *N*-oxide, 4-(*N,N*-dimethylamino)pyridine, Et$_3$N, THF; *t*-BuSH, hv, 23 °C; (c) Rh$_2$(esp)$_2$, H$_2$NSO$_3$Ar, PhI(OAc)$_2$, Ph(CH$_3$)$_2$CCO$_2$H, MgO, 5Å-MS, *i*-PrOAc, 23 °C; Ar=2,6-difluorobenzene.
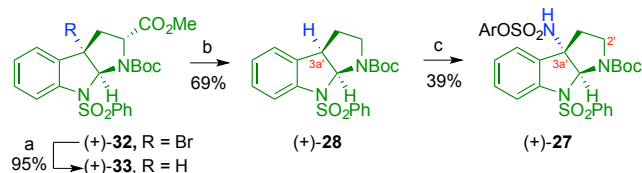
Our synthesis of (−)-communesin F (**1**) commenced with the preparation of the two key tricyclic amines **24** and **25** required for the assembly of critical diazene **23** (Scheme 2). We pursued two approaches to the synthesis of the C3a'-amino cyclotryptamine **25** and the corresponding sulfamate **27** (Scheme 3). In the first approach, motivated by efficient access to enantiomerically enriched C3a'-halocyclotryptamine derivatives,[20a] we envisioned a nucleophilic C3a'-amination (Scheme 4) reminiscent of our Friedel-Crafts strategy for C3a-derivatization developed in the context of our naseseazine alkaloid total synthesis.[21] Our second approach to amine **25** relied on Du Bois amination[22] of cyclotryptamine **28** to secure the sulfamate **27** (Scheme 5).[19c]

Given the versatility of cyclotryptamine–sulfamates as precursors to the corresponding mixed sulfamides,[19c] we developed an efficient synthesis to access sulfamate (+)-**31** and related derivatives starting with C3a'-bromocyclotryptamine (+)-**29** (Scheme 4). Enantioselective bromocyclization[20a] of *Nβ*-Cbz-*N1*-benzenesulfonyl-tryptamine catalyzed by (*S*)-3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (TRIP)[20b] afforded C3a'-bromocyclotryptamine (+)-**29** in 93% yield and 96% enantiomeric excess.[23] Significantly, electrophilic activation[21] of the tricyclic bromide (+)-**29** in the presence of 2,6-difluorophenylsulfamate[22] provided the desired sulfamate (+)-**31** in 63% yield (Scheme 4). The use of 2,6-difluorophenylsulfamate as a nucleophile to trap an intermediate C3a'-electrophile **30** provides a new and expedient route for the directed synthesis of complex diazenes.[19c] While this new single-step synthesis of C3a'-sulfamates from the corresponding C3a'-bromides offers a concise solution to the desired precursors, its utility in conversion of the more acid sensitive *tert*-butyl carbamate substrate **26** to sulfamate **27** gave capricious and inferior outcomes (~50% yield).

Our alternate approach for the synthesis of *tert*-butylcarbamate derivative **27** relied on the C–H amination chemistry illustrated in Scheme 5. Mild reduction of bromocyclotryptophan (+)-**32** provided the desired C3a'–H cyclotryptophan (+)-**33** in 95% yield.[23] Subsequent decarboxylation furnished cyclotryptamine (+)-**28**

in 69% yield. Under optimal conditions, a Rh-catalyzed C–H amination[22] of cyclotryptamine (+)-**28** afforded the desired sulfamate (+)-**27** in 39% yield after recrystallization.[24] This three-step sequence efficiently generated gram quantities of (+)-**27** from the readily available bromocyclotryptophan (+)-**32** as an activated form of C3a'-aminocyclotryptamine **25** (Scheme 2) that is ready for coupling with tricyclic amine **24** for diazene synthesis.

Scheme 6. Strategies for Synthesis of Tricycle **24**
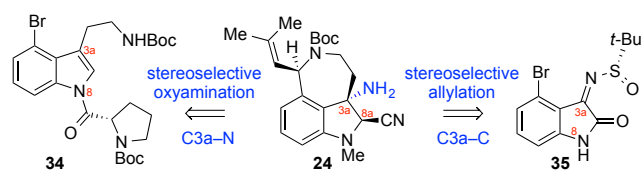
With an expedient synthesis of sulfamate (+)-**27** available, we turned our attention to the synthesis of the tricyclic amine **24** (Scheme 6). While syntheses of aurantioclavine (**12**) have been reported,[18] the synthesis of a derivative needed to mimic fragment **22**, necessary for our biomimetic approach to (−)-communesin F (**1**), has not been described. As a result, we sought to develop an

Scheme 7. Oxyamination Approach to Tricycle (+)-**24**[a]

Scheme 8. Sulfinimine Allylation Approach to Tricycle (+)-**24**[a]
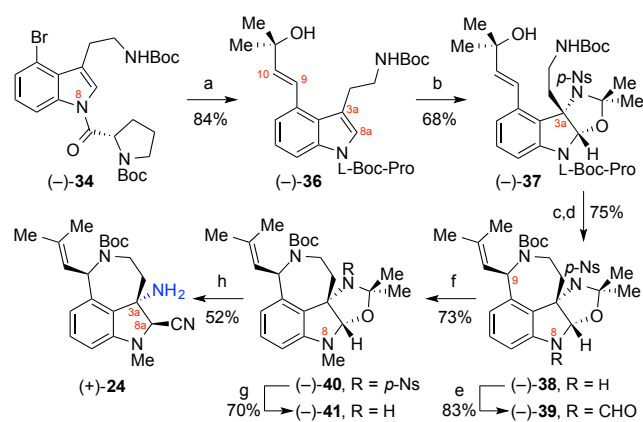
[a]Reagents and conditions: (a) 1,1-dimethylallyl alcohol, Pd(OAc)$_2$, P(o-tol)$_3$, Et$_3$N, MeCN, 95 °C; (b) 3,3-dimethyl-2-(p-nitrobenzenesulfonyl)-1,2-oxaziridine, CuCl$_2$, n-Bu$_4$NCl, CHCl$_3$, 21 °C, 89:11 dr; (c) PdCl$_2$(MeCN)$_2$, MeCN, 82 °C; (d) (i) i-Bu$_2$AlH, THF, 0 °C, (ii) 1,8-diazabicyclo[5.4.0]undec-7-ene, MeOH, 21 °C; (e) Ac$_2$O, HCO$_2$H, pyridine, CH$_2$Cl$_2$, 21 °C; (f) NaBH$_4$, TFA, THF, 0 °C; (g) PhSH, K$_2$CO$_3$, DMF, 50 °C; (h) Me$_3$SiCN, (F$_3$C)$_2$CHOH, H$_2$O, 21 °C; p-Ns = para-nitrobenzenesulfonyl.

enantioselective synthesis of a tricycle reminiscent of alkaloid **12** that would allow for implementation of our synthetic strategy (Scheme 2). The tricyclic aminonitrile **24** offered the necessary C3a-amine for diazene synthesis and the C8a-aminonitrile to allow for mild generation of the corresponding C8a-iminium ion needed for aminal synthesis. We developed two strategies to access the key intermediate **24** as illustrated in Scheme 6. The first strategy involved tryptamine **34** as the substrate for the application of Yoon's oxyamination chemistry,[25] while the second strategy utilized *tert*-butyl sulfinimine **35** and Ellman's asymmetric allylation[26] of such substrates.[27]

The oxyamination[25] route to aminonitrile **24** commenced with a Mizoroki-Heck reaction of bromoindole (−)-**34**[23] with 1,1-dimethylallyl alcohol to provide allylic alcohol (−)-**36**. Despite early reservations regarding possible competing C9-C10-oxyamination[25b-f] of vinyl indole (−)-**36** in place of the desired C3a-C8a-oxyamination, we observed higher levels of diastereoselection[28] for the oxyamination of the more advanced substrate (−)-**36** (Scheme 7). The use of stoichiometric copper(II) chloride facilitated the reaction and gave oxazoline (−)-**37** in 68% yield (89:11 dr). Treatment of alcohol (−)-**37** with bis(acetonitrile)dichloropalladium(II) in acetonitrile to form the desired azepane (85% yield)[23] followed
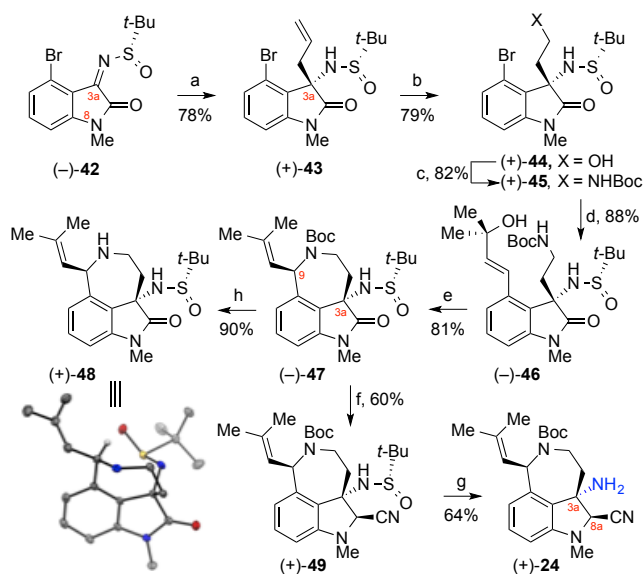
[a]Reagents and conditions: (a) allylMgBr, MgBr$_2$, CH$_2$Cl$_2$, −78 °C, >98:2 dr; (b) O$_3$, MeOH, −78 °C; NaBH$_4$, −78 → 23 °C; (c) o-NsNHBoc, diisopropyl azodicarboxylate, polystyrene–PPh$_3$, THF, 50 °C; PhSH, Cs$_2$CO$_3$, 50 °C; (d) Me$_2$C(OH)CH=CHSn(n-Bu)$_3$, PdCl$_2$(PPh$_3$)$_2$, PhMe, THF, 110 °C; (e) PdCl$_2$(MeCN)$_2$, MeCN, 80 °C; (f) (i) LiBH$_4$, MeOH, THF, 0 → 23 °C; (ii) Me$_3$SiCN, (F$_3$C)$_2$CHOH, 0 °C; (g) HCl, dioxane, MeOH, 23 °C; (h) Sc(OTf)$_3$, F$_3$CCH$_2$OH, 23 °C; o-Ns = ortho-nitrobenzenesulfonyl. ORTEP representation of amine (+)-**48**: thermal ellipsoids drawn at 50% probability.[23]

by removal of the chiral auxiliary (88% yield) provided the desired indoline (−)-**38**. The formylation of indoline (−)-**38** to give formamide (−)-**39** (83% yield) followed by mild reduction with sodium borohydride in the presence of trifluoroacetic acid gave the desired N-methylindoline (−)-**40** (73% yield).[29] Exposure of sulfonamide (−)-**40** to thiophenol and potassium carbonate led to removal of the *para*-nitrobenzenesulfonyl group and the isolation of the stable oxazolidine (−)-**41** in 70% yield. Given the propensity of oxazolidine (−)-**41** and aminonitrile (+)-**24** toward elimination of the C3a-amino group under strongly acidic or basic conditions, we developed mild hydrolysis conditions to allow for cyanation of a transient C8a-hemiaminal leading to aminonitrile (+)-**24** in 52% yield in addition to the C8a-epimer (26%). While this approach provides flexibility for the late-stage introduction of various N8-substituents and establishes the C3a-configuration, the challenge in unraveling the oxazolidine substructure prompted our investigation of an

alternate route to aminonitrile (+)-**24** (Scheme 6) involving C3a–C bond formation.

Our alternative synthesis of aminonitrile (+)-**24** began with the diastereoselective allylation[26] of N8-methyl sulfinimine (−)-**42** (Scheme 8) to provide allyl oxindole (+)-**43** in 78% yield and with excellent diastereopurity after trituration of the crude addition product with hexane (>98:2 dr).[23] In contrast to our first approach to aminonitrile (+)-**24**, the placement of the chiral auxiliary on the C3a-substituent enabled our use of the N8-methyl variant of sulfinimine **35** (Scheme 6).[23] Ozonolysis of alkene (+)-**43** followed by a reductive work-up afforded the primary alcohol (+)-**44** in 79% yield. The alcohol (+)-**44** was then converted to *tert*-butyl carbamate (+)-**45** in 82% yield via a Mitsunobu displacement and subsequent in situ desulfonylation. The allylic alcohol needed for synthesis of the azepane substructure was introduced via a Stille vinylation to furnish allylic alcohol (−)-**46** in 88% yield.[30] A palladium-catalyzed allylic amination provided azepane (−)-**47** in 81% yield as a single diastereomer. The stereochemistry at C3a and C9 of azepane (−)-**47** was confirmed unambiguously through analysis of the crystal structure of the corresponding amine (+)-**48** (Scheme 8). We then focused on development of conditions for mild and efficient conversion of oxindole (−)-**47** to the desired aminonitrile (+)-**24**. Partial reduction of oxindole (−)-**47** with lithium borohydride afforded a mixture of C8a-hemiaminal diastereomers that were too labile for isolation. Direct treatment of the crude hemiaminal with trimethylsilyl cyanide in hexafluoroisopropanol[31] furnished the desired aminonitrile (+)-**49** in 60% yield[32] and the easily separable minor C8a-epimer (30%).[23] Methanolysis of the *tert*-butyl sulfinamide (+)-**49** provided the desired amino-azepane (+)-**24** in 64% yield.[33] The C8a-aminonitrile proved to be an ideal trigger for late stage hemiaminal formation[34] while providing adequate stability for the implementation of an efficient fragment assembly. We anticipate future adaptation of this robust synthetic route to other N8-variants of azepane (+)-**24** via judicious N8-substitution of sulfinimine **35**.

After developing versatile syntheses of both essential fragments, we next examined the union of azepane (+)-**24** and cyclotryptamine (+)-**27** to introduce the critical C3a–C3a' bond. Dissolution of the two fragments in tetrahydrofuran in the presence of 4-(N,N-dimethylamino)pyridine afforded sulfamide (+)-**50** in 80% yield on gram-scale (Scheme 9).[23] Consistent with our prior observation, the oxidation of sterically shielded sulfamides containing electron-rich arenes, such as the N-methyl aniline substructure of sulfamide (+)-**50**,

**Scheme 9.** Directed Synthesis of Heterodimer (+)-**51**[a]
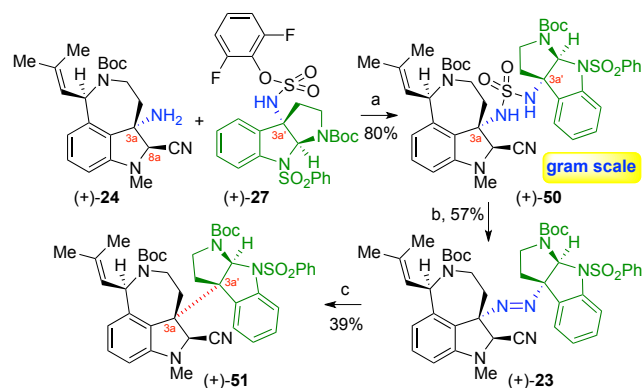
[a]Reagents and conditions: (a) 4-(N,N-dimethylamino)pyridine, THF, 23 °C; (b) polystyrene–2-*t*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphos-phorine, N-chloro-N-methylbenzamide, MeOH, 23 °C; (c) hv (350 nm), 25 °C.

suffers from competitive arene-halogenation. After extensive experimentation, we discovered the unique ability of tertiary N-chloroamides to effect chemoselective oxidation of sulfamide (+)-**50** to the corresponding diazene (Scheme 9) without competitive arene-halogenation. Exposure of sulfamide (+)-**50** to N-chloro-N-methylbenzamide (6 equiv) in conjunction with polystyrene-bound 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (BEMP) in methanol provided the desired diazene (+)-**23** in 57% yield.[35] Photoexcitation and expulsion of dinitrogen from a thin film of diazene (+)-**23**, followed by radical combination of the resulting cyclotryptamine **21** and azepane **22** (Scheme 2), afforded the desired heterodimer (+)-**51** in 39% yield as a single diastereomer.[36] While the stereochemical outcome at C3a' of heterodimer (+)-**51** is anticipated,[19] the remarkable diastereoselection at C3a is notable and likely due to the confluence of a rapid radical combination step and the additional stereoinduction imposed by the C8a-nitrile.[23,37] Importantly, our diazene-based strategy for directed complex fragment assembly allowed for the stereoselective construction of the critical C3a–C3a' linkage, securing the corresponding vicinal quaternary stereocenters.

With the successful union of the tricyclic–azepane and the cyclotryptamine fragments at hand, we turned our attention to the development of a biogenetically inspired aminal reorganization of heterodimer (+)-**51** to access the heptacyclic communesin core. Informed by experience in rearrangement of the *calycanthaceous*

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Scheme 10. Synthesis of (–)-Communesin F (**1**) via a Biogenetically Inspired Final Stage Reorganization[a]
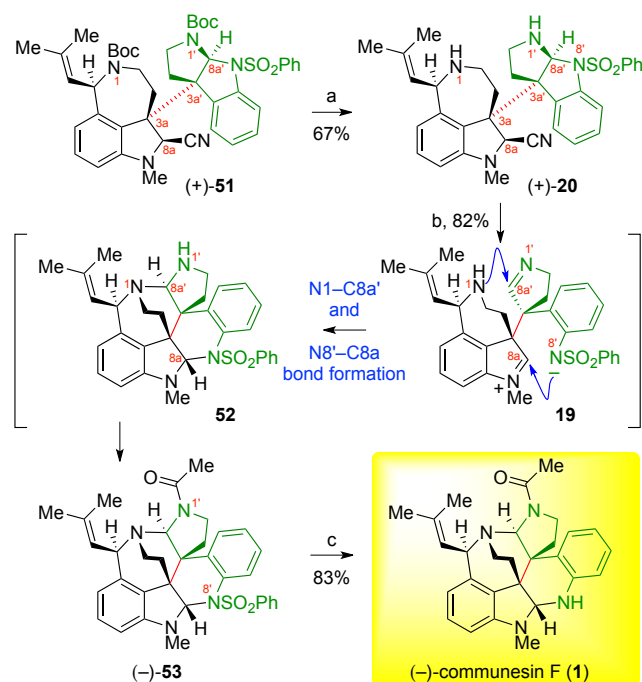
[a]Reagents and conditions: (a) Sc(OTf)$_3$, F$_3$CCH$_2$OH, 23 °C; (b) t-BuOLi, MeOH, 50 °C; dry PPTS, Ac$_2$O, 23 °C; (c) Na(Hg), NaH$_2$PO$_4$, THF, MeOH, 23 °C.

alkaloids,[8,14] we recognized the significance in the judicious choice of reaction conditions for the planned transformation due to the sensitive nature of the C3a–C3a' linkage. Furthermore, we anticipated that an appropriate sequence of amine unveiling would maximize efficiency for the desired aminal exchange. We projected that unveiling the N1- and N1'-amines of heterodimer (+)-**51** would allow opening of the C8a' aminal with the benzenesulfonamide as the leaving group, thus allowing rapid trapping of the C8a'-imine of intermediate **19** en route to heptacycle **52**. Treatment of heterodimer (+)-**51** with scandium trifluoromethanesulfonate in trifluoroethanol provided the desired heterodimer (+)-**20** by selective removal of the tert-butyl carbamates while preserving the sensitive C8a-aminonitrile (Scheme 10). The electron-withdrawing N8'-sulfonamide enabled our examination of basic conditions to selectively open the cyclotryptamine substructure. In the event, treatment of heterodimer (+)-**20** with lithium tert-butoxide in methanol provided clean and complete conversion to the desired heptacyclic structure **52** within 1 h at 50° C as observed by in situ ¹H-NMR spectroscopy.[23] Significantly, only the desired heptacycle **52** was formed in preference to other constitutional isomers.[15b] Methanol was found to be an excellent solvent[38] for this transformation, likely due to its ability to stabilize reactive intermediates as the corresponding O-alkyl-hemiaminals. Although intermediate **52** could be observed by in situ ¹H NMR spectroscopy,[23] this compound did not show sufficient stability for isolation. We suspect this may be due to the sensitive nature of the C8a'-aminal of heptacycle **52**, which upon reversible opening to the C8a'-imine increases the lability of the C3a–C3a' bond. As a testimony to the sensitivity of the C3a–C3a' linkage of heterodimer (+)-**20**, simple heating of a derivative (C8a-OMe instead of C8a-CN) in acetonitrile-d_3 at 80 °C predominantly led to fragmentation.[39] Indeed, treatment of the basic solution of heptacycle **52** with pyridinium p-toluenesulfonate to quench the alkoxides, followed by addition of acetic anhydride afforded the N1'-acetyl derivative (–)-**53** in 82% overall yield.[23] A final-step unveiling of the N8'-amine was accomplished by treatment of (–)-**53** with sodium amalgam to provide (–)-communesin F (**1**) in 83% yield. All ¹H and ¹³C NMR data as well as optical rotation (observed $[\alpha]_D^{24}$ = –249, c = 0.13, CHCl$_3$; literature $[\alpha]_D^{20}$ = –264, c = 0.34, CHCl$_3$),[1c,23] for our synthetic (–)-communesin F (**1**) were in agreement with literature data.

Conclusion. A highly convergent enantioselective total synthesis of (–)-communesin F (**1**) with late-stage chemistry that parallels the latest insights[15] and hypotheses concerning the biogenesis of these alkaloids is described. Our expedient synthesis involves the union of fragments (+)-**24** and (+)-**27** to provide complex sulfamide (+)-**50** on gram-scale. This advanced intermediate is converted to alkaloid (–)-**1** in only five additional steps (Schemes 9 and 10) which include the application of our diazene–directed fragment assembly strategy to secure the congested C3a–C3a' linkage, and a guided biomimetic rearrangement to selectively provide the heptacyclic core of these alkaloids. Highlights of our synthesis include an efficient cyclotryptamine–C3a-sulfamate synthesis by either a new silver–promoted nucleophilic amination or rhodium–catalyzed C–H amination protocol, application of catalytic asymmetric halocyclization and diastereoselective oxyamination reactions in complex settings, a stereoselective sulfinimine allylation, and efficient assembly and utility of a richly functional diazene for complex fragment coupling. The successful implementation of this synthetic strategy and the versatile synthesis of the fragments, along with a final stage acylation of the communesin core provide a foundation for a unified synthetic route to access structurally related complex alkaloids and derivatives.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, spectroscopic data, crystal structure of (+)-**48** (CIF), and copies of NMR spectra (PDF).

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Notes

The authors declare no competing financial interests.

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(28) For comparison, the oxyamination of the corresponding L-(3,5-di-*tert*-butylphenylcarbamoyl)-Pro derivatives of substrates (–)-**34** and (–)-**36** gave the desired product in 27% (53:47 dr) and 79% (73:27 dr) yield, respectively.

(29) Methylation of indoline (–)-**38** with Meerwein's reagent or its reductive amination with formalin and NaBH$_3$CN resulted in the desired *N*-methylindoline (–)-**40** in 15% and 21% yield, respectively.

(30) Likely due to the greater steric constraints imposed by the fully substituted tetrahedral C3a in bromide (+)-**45**, related Heck protocols described in prior syntheses of alkaloid **1** were unsuccessful.

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(32) The C8a-configuration of the major diastereomer was determined by nOe analysis of a derivative.

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(35) Use of *N*-chlorosuccinimide (6 equiv) as the oxidant in conjunction with *N,N*-dimethylaniline (1 equiv) as electrophilic chlorine scavenger gave only 37% yield of diazene (+)-**23**, in addition to recovered (+)-**50** (17%), and a tricyclic cyanoindole side product (25%) arising from E2-elimination of C3a-sulfamide.

(36) The formation of the tricyclic cyanoindole (~47%) and a C3a'-H cyclotryptamine **28** (~51%) as disproportionation products is reflective of the significant steric barrier for C3a–C3a' bond formation and competitive C8a-H abstraction.

(37) Calculations suggest the C8a-CN provides 3.8 kcal/mol preference for the desired C3a stereochemical outcome.

(38) Use of tetrahydrofuran-d_8 as solvent led to a less efficient aminal reorganization and afforded product (–)-**53** in 52% yield.

(39) Experiment conducted over 13 h in the absence of acid or base promoter. We reason that reversible C8a-iminium ion formation in the absence of the desired N8'-nucleophile increases the lability of C3a–C3a' bond.

8

(9 cm x 3-1/2 cm)