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

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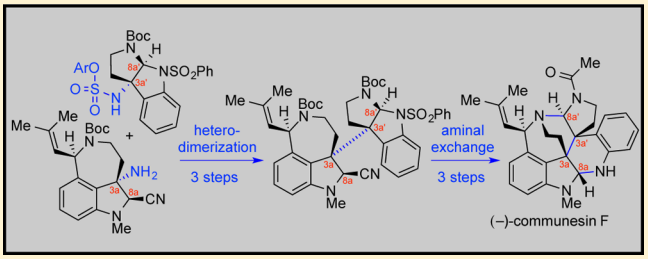
Supporting Information

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 syntheses 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.



INTRODUCTION

The communesin alkaloids are a family of structurally complex natural products isolated from various marine and terrestrial *Penicillium* fungi that 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 toward 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 archetypical 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,[10−13] 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 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 the 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). Woodward and

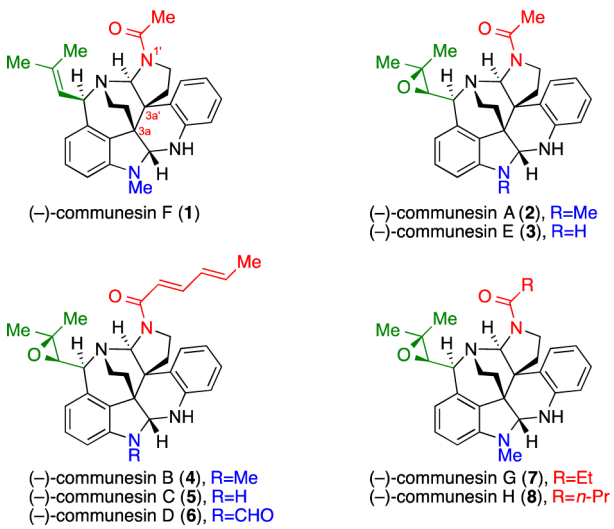


Figure 1. Structures of communesin alkaloids.

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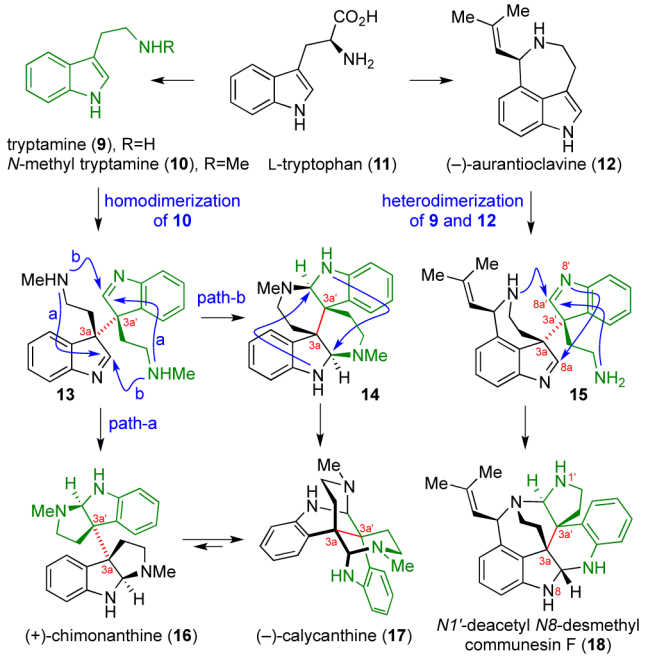
Scheme 1. Comparison of the Bond Formations in the Biogenesis of Structurally Related Dimeric Alkaloids

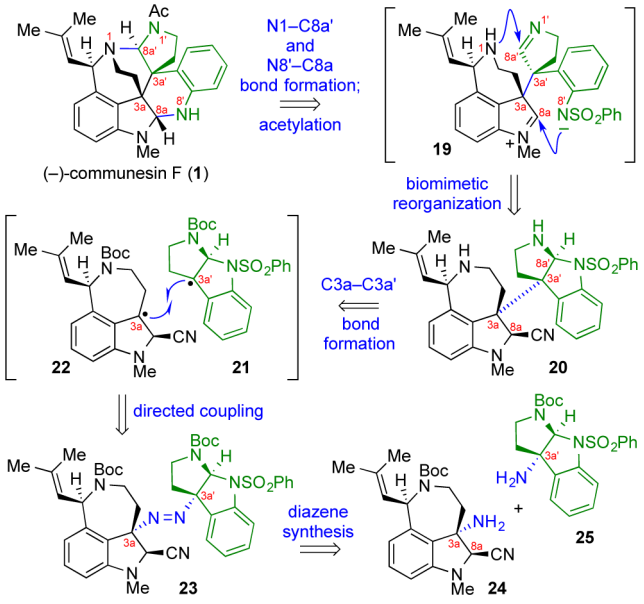


Robinson independently proposed that the biogenesis of the calycanthoids is predicated on the oxidative homodimerization of *N*-methyltryptamine (**10**) to form indolenine dimers, such as **13**, which can give rise to five constitutional isomers upon reorganization of the two aminal functional groups.[10,11] 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 **16** and **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 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 the *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 the 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 that the N8′-sulfonamide would guide the opening

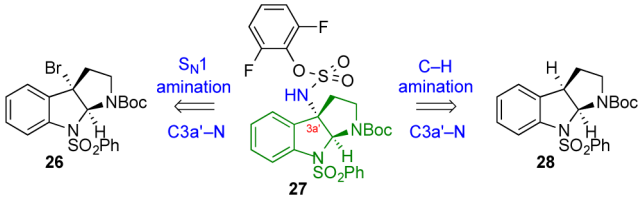
Scheme 2. Biogenetically Inspired Retrosynthetic Analysis of (−)-Communesin F (1)



of the C8a′-aminal to present the C8a′-imine for N1 addition. Furthermore, we projected that 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 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 that the C8a′ configuration 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 to be necessary for securing the C3a−C3a′ linkage (Scheme 2).

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 C3a′-aminocyclotryptamine **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**

Scheme 3. Strategies for the Synthesis of Tricycle 27



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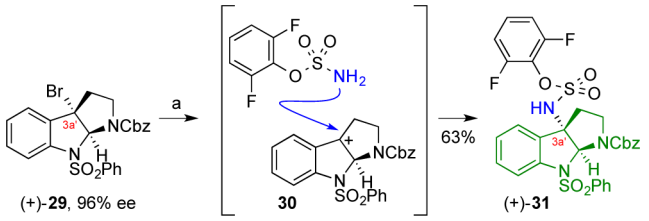
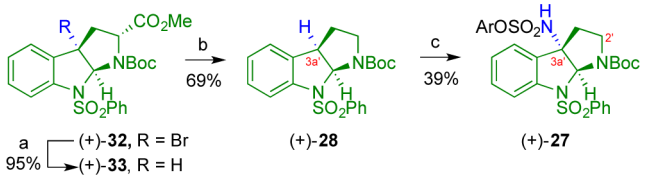
Scheme 4. Concise Synthesis of Sulfamate (+)-31[a]



[a]Reagents and conditions: (a) $AgSbF_6$, 2,6-di-*tert*-butyl-4-methylpyridine, 2,6-difluorophenyl sulfamate, CH_2Cl_2, 23 °C, 63%.

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



[a]Reagents and conditions: (a) $(Me_3Si)_3SiH$, Et_3B, air, 23 °C, >99:1 dr; (b) (i) KOH(aq), MeOH, CH_2Cl_2, 23 °C, (ii) *N*,*N*,*N*′,*N*′-tetramethylchloroformamidinium hexafluorophosphate, thiopyridine *N*-oxide, 4-(*N*,*N*-dimethylamino)pyridine, Et_3N, THF; *t*-BuSH, *hν*, 23 °C; (c) $Rh_2(esp)_2$, H_2NSO_3Ar, $PhI(OAc)_2$, $Ph(CH_3)_2CCO_2H$, MgO, 5 Å MS, *i*-PrOAc, 23 °C. Ar = 2,6-difluorophenyl.

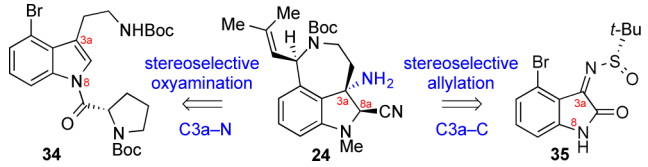
relied on Du Bois amination[22] of cyclotryptamine **28** to secure sulfamate **27** (Scheme 5).[19c]

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*-benzenesulfonyltryptamine catalyzed by (*S*)-3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (TRIP)[20b] afforded C3a′-bromocyclotryptamine (+)-**29** in 93% yield with 96% enantiomeric excess.[23] Significantly, electrophilic activation[21] of tricyclic bromide (+)-**29** in the presence of 2,6-difluorophenyl sulfamate[22] provided the desired sulfamate (+)-**31** in 63% yield (Scheme 4). The use of 2,6-difluorophenyl sulfamate as a nucleophile to trap 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*-butyl carbamate 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.

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

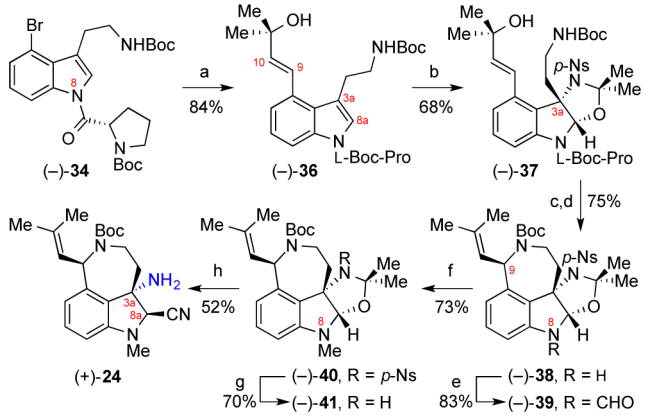
Scheme 6. Strategies for the Synthesis of Tricycle 24



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 enantioselective synthesis of a tricycle reminiscent of alkaloid **12** that would enable the implementation of our synthetic strategy (Scheme 2). Tricyclic aminonitrile **24** offered the necessary C3a-amine for diazene synthesis and the C8a-nitrile to enable 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

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



[a]Reagents and conditions: (a) 1,1-dimethylallyl alcohol, $Pd(OAc)_2$, $P(o\text{-tol})_3$, Et_3N, MeCN, 95 °C; (b) 3,3-dimethyl-2-(*p*-nitrobenzenesulfonyl)-1,2-oxaziridine, $CuCl_2$, *n*-Bu_4NCl, $CHCl_3$, 21 °C, 89:11 dr; (c) $PdCl_2(MeCN)_2$, MeCN, 82 °C; (d) (i) *i*-Bu_2AlH, THF, 0 °C, (ii) 1,8-diazabicyclo[5.4.0]undec-7-ene, MeOH, 21 °C; (e) Ac_2O, HCO_2H, pyridine, CH_2Cl_2, 21 °C; (f) $NaBH_4$, TFA, THF, 0 °C; (g) PhSH, K_2CO_3, DMF, 50 °C; (h) Me_3SiCN, $(F_3C)_2CHOH$, H_2O, 21 °C. *p*-Ns = *p*-nitrobenzenesulfonyl.

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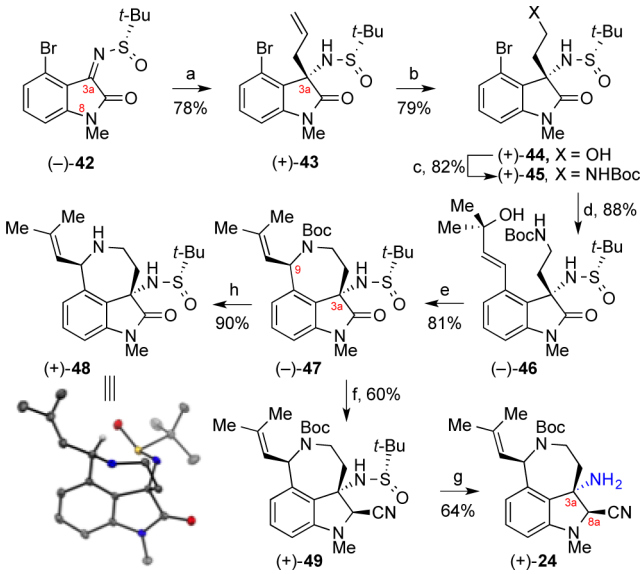
form the desired azepane (85% yield)[23] followed by removal of the chiral auxiliary (88% yield) provided the desired indoline (−)-**38**. Formylation of indoline (−)-**38** to give formamide (−)-**39** (83% yield) followed by mild reduction with sodium borohydride in the presence of trifluoroacetic acid gave the desired *N*-methylindoline (−)-**40** (73% yield).[29] Exposure of sulfonamide (−)-**40** to thiophenol and potassium carbonate led to removal of the *p*-nitrobenzenesulfonyl group and isolation of the stable oxazolidine (−)-**41** in 70% yield. Given the propensity of oxazolidine (−)-**41** and aminonitrile (+)-**24** to undergo elimination of the C3a-amino group under strongly acidic or basic conditions, we developed mild hydrolysis conditions to allow 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%

Scheme 8. Sulfinimine Allylation Approach to Tricycle (+)-24[a]

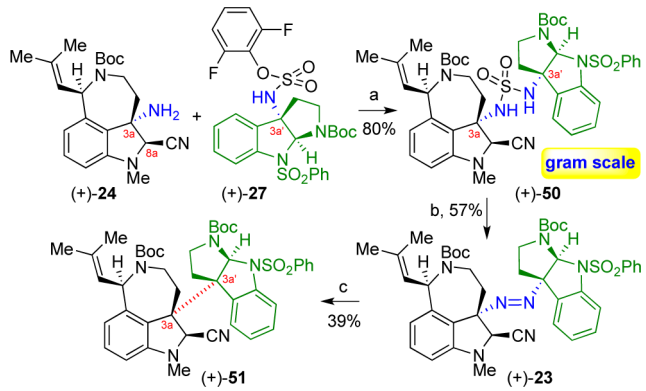


[a]Reagents and conditions: (a) allylMgBr, $MgBr_2$, CH_2Cl_2, −78 °C, >98:2 dr; (b) O_3, MeOH, −78 °C; $NaBH_4$, −78 → 23 °C; (c) *o*-NsNHBoc, diisopropyl azodicarboxylate, polystyrene−PPh_3, THF, 50 °C; PhSH, Cs_2CO_3, 50 °C; (d) $Me_2C(OH)CH{=}CHSn(n\text{-}Bu)_3$, $PdCl_2(PPh_3)_2$, PhMe, THF, 110 °C; (e) $PdCl_2(MeCN)_2$, MeCN, 80 °C; (f) (i) $LiBH_4$, MeOH, THF, 0 → 23 °C, (ii) Me_3SiCN, $(F_3C)_2CHOH$, 0 °C; (g) HCl, dioxane, MeOH, 23 °C; (h) $Sc(OTf)_3$, F_3CCH_2OH, 23 °C. *o*-Ns = *o*-nitrobenzenesulfonyl. In the ORTEP representation of amine (+)-**48**, the thermal ellipsoids are drawn at 50% probability.[23]

yield 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 workup afforded primary alcohol (+)-**44** in 79% yield. 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 the 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 the 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 *tert*-butyl sulfinamide (+)-**49** provided the desired aminoazepane (+)-**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 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 a gram scale (Scheme 9).[23]

Scheme 9. Directed Synthesis of Heterodimer (+)-51[a]



[a]Reagents and conditions: (a) 4-(*N*,*N*-dimethylamino)pyridine, THF, 23 °C; (b) polystyrene−2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine, *N*-chloro-*N*-methylbenzamide, MeOH, 23 °C; (c) *hν* (350 nm), 25 °C.

Consistent with our prior observation, the oxidation of sterically shielded sulfamides containing electron-rich arenes, such as the *N*-methylaniline substructure of sulfamide (+)-**50**, 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-dime-

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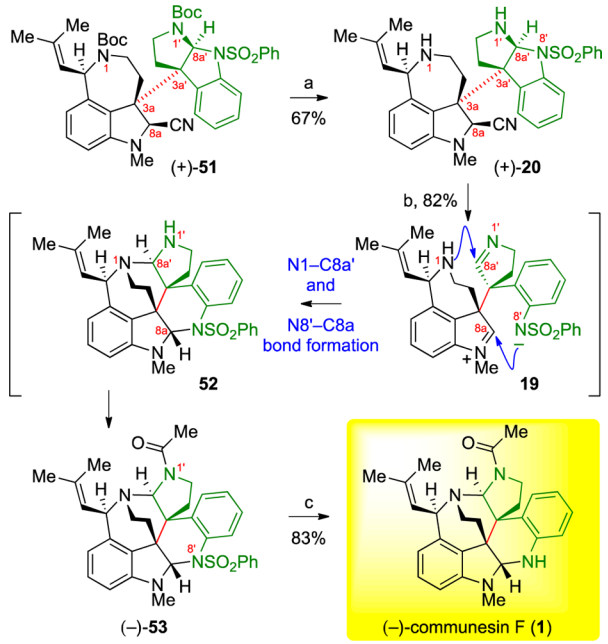
thylperhydro-1,3,2-diazaphosphorine (BEMP) in methanol provided the desired diazene (+)-**23** in 57% yield.[35] Photoexcitation and expulsion of dinitrogen from a thin film of diazene (+)-**23** followed by radical combination of the resulting cyclotryptamine **21** and azepane **22** (Scheme 2) afforded 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 enabled the stereoselective construction of the critical C3a−C3a′ linkage, securing the corresponding vicinal quaternary stereocenters.

With the successful union of the tricyclic azepane fragment and the cyclotryptamine 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 alkaloids,[8,14] we recognized the significance of a 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 the efficiency of 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 ^{1}H 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 because of its ability to stabilize reactive intermediates as the corresponding *O*-alkyl hemiaminals. Although intermediate **52** could be observed by in situ ^{1}H NMR spectroscopy,[23] this compound did not show sufficient stability for isolation. We suspect that this may be due to the sensitive nature of the C8a′-aminal of heptacycle **52**, as 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 to unveil the N8′-amine was accomplished by treatment of (−)-**53** with sodium amalgam to provide (−)-communesin F (**1**) in 83% yield. All of the ^{1}H and ^{13}C NMR data as well as optical rotation data (observed $[\alpha]_D^{24}$ = −249, *c* = 0.13, $CHCl_3$; lit. $[\alpha]_D^{20}$ = −264, *c* = 0.34, $CHCl_3$),[1c,23] for our synthetic (−)-communesin F (**1**) were in agreement with literature data.

Scheme 10. Synthesis of (−)-Communesin F (1) via a Biogenetically Inspired Final-Stage Reorganization[a]



[a]Reagents and conditions: (a) $Sc(OTf)_3$, F_3CCH_2OH, 23 °C; (b) *t*-BuOLi, MeOH, 50 °C; dry PPTS, Ac_2O, 23 °C; (c) Na(Hg), NaH_2PO_4, THF, MeOH, 23 °C.

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 a 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 at DOI: 10.1021/jacs.6b04072.

Experimental procedures, spectroscopic data, crystal structure of (+)-**48**, and copies of NMR spectra (PDF)
Crystallographic data for (+)-**48** (CIF)

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Notes

The authors declare no competing financial interest.

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

(29) Methylation of indoline (−)-**38** with Meerwein's reagent and its reductive amination with formalin and $NaBH_3CN$ resulted in the desired *N*-methylindoline (−)-**40** in 15% and 21% yield, respectively.

(30) Likely as a result of 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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(35) The use of *N*-chlorosuccinimide (6 equiv) as the oxidant in conjunction with *N*,*N*-dimethylaniline (1 equiv) as an electrophilic chlorine scavenger gave only a 37% yield of diazene (+)-**23** in addition to recovered (+)-**50** (17%) and a tricyclic cyanoindole side product (25%) arising from E2 elimination of the C3a-sulfamide.
(36) The formation of the tricyclic cyanoindole (∼47%) and 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 that the C8a-CN provides a 3.8 kcal/mol preference for the desired C3a stereochemical outcome.
(38) The use of tetrahydrofuran-d_8 as the solvent led to a less efficient aminal reorganization, affording product (−)-**53** in 52% yield.
(39) The experiment was 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 the C3a−C3a′ bond.

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