

Total Synthesis and Anti-Cancer Activity of All Known Communesin Alkaloids and Related Derivatives

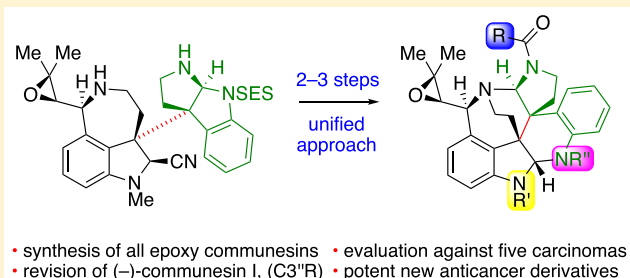
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Supporting Information

ABSTRACT: A unified enantioselective total synthesis and anticancer evaluation of all known epoxide-containing communesin alkaloids and related derivatives is described. Our synthesis is predicated on the convergent and modular diazene-directed assembly of two complex fragments to secure the critical C3a–C3a' linkage followed by a guided biomimetic amination reorganization to deliver the heptacyclic core of these alkaloids. Concise enantioselective syntheses of the fragments were devised, with highlights including the application of a rationally designed sulfonamide chiral auxiliary, an efficient calcium trifluoromethanesulfonate promoted intramolecular amination, and a diastereoselective epoxidation that simultaneously converts the new chiral auxiliary to a versatile amine protective group. The modularity of our convergent approach enabled the rapid synthesis of all epoxide-containing members of the communesin family from a single heterodimeric intermediate, including the first total synthesis of communesins C–E, and G–I, and facilitated our stereochemical revision of (–)-communesin I, the most recently isolated communesin alkaloid. Furthermore, the generality of our biogenetically inspired heterodimer rearrangement was demonstrated in a guided synthesis of a communesin derivative with an unnatural topology. Finally, we report the first comparative analysis of the anticancer activities of all naturally occurring communesin alkaloids A–I and eight complex derivatives against five human cancer cell lines. From these data, we have identified (–)-communesin B as the most potent natural communesin and discovered that derivatives with N8'-sulfonamide substitution exhibit up to a 10-fold increase in potency over the natural alkaloids.



INTRODUCTION

The communesin alkaloids are a family of nine polycyclic natural products, which possess notable biological activities and a range of interesting structural features (Figure 1).¹ (–)-Communesin A (2) and B (4) were first isolated in 1993 by Numata and co-workers from an algal-derived *Penicillium* fungus and were found to exhibit moderate to potent cytotoxicity against cultured murine lymphocytic leukemia cells.^{1a} In the years since, seven more communesin alkaloids C–I (Figure 1) have been isolated and shown to possess insecticidal, antiproliferative, and vasculogenetic activities.¹ The core structures of these alkaloids feature seven contiguous rings, two amination linkages, and up to six stereogenic centers, of which two are vicinal and quaternary (C3a/C3a'). This formidable structural complexity coupled with an array of important biological activity prompted research efforts directed toward their total chemical synthesis, culminating in inventive solutions for the preparation of racemic² and enantiomerically enriched³ samples of communesin F (1). However, access to the more complex C10-epoxide-containing communesins remains challenging. Indeed, other than Zuo and Ma's total synthesis of (–)-communesin A (2) and B (4) in 2011,⁴ there

have been no reports describing the synthesis of epoxy-communesins 2–9. Therefore, we sought to develop a unified and convergent approach to all members of the communesin family and related complex derivatives to enable their detailed study. Herein, we report the first biomimetic enantioselective total synthesis of all eight known epoxide-bearing communesin alkaloids, including the first total synthesis of communesins C–E, and G–I, a set of unnatural analogues, and their side-by-side anticancer profiling against five human cancer cell lines. In addition, we revise the reported structure of (–)-communesin I (9)^{1f} to (–)-(3''R)-communesin I (10, Figure 1).

In 2016, we reported the first biomimetic enantioselective total synthesis of (–)-communesin F (1) inspired by a hypothetical biosynthesis involving the oxidative union of *Penicillium* fungal alkaloid (–)-aurantioclavine (11) and tryptamine (12, Scheme 1).^{3b} We anticipated that the resulting C3a–C3a' linked heterodimer 15 would undergo a dynamic reorganization to afford the key structural elements of the communesin core 16. Fortuitously, Tang, Garg, and Houk

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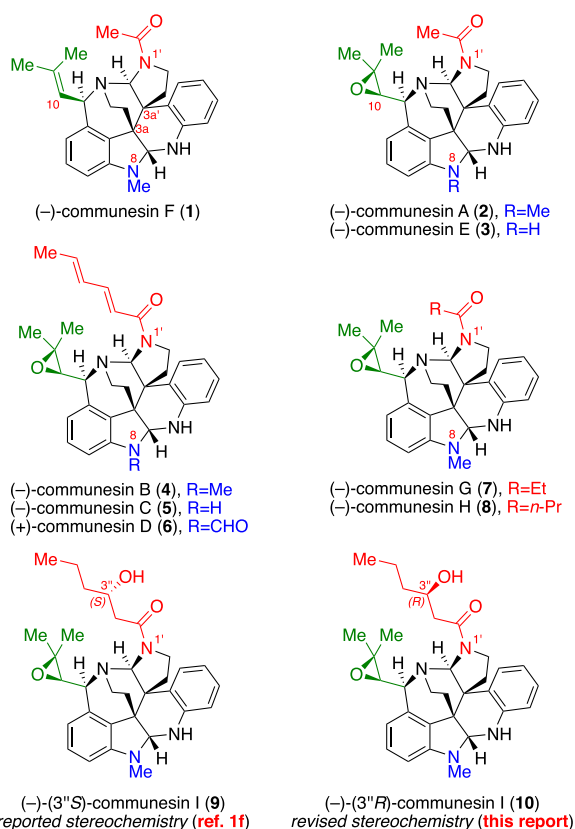
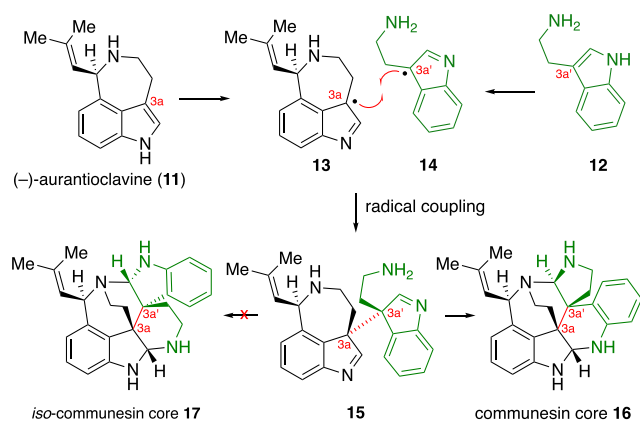


Figure 1. Structures of the Communesin Alkaloids.

Scheme 1. Biogenesis of the Communesin Alkaloids



disclosed landmark biosynthetic and computational studies⁵ which were in full accord with our biosynthetic hypotheses. They demonstrated that alkaloids (-)-11 and 12 were essential biosynthetic precursors and, further, they identified a *Penicillium* P450 monooxygenase enzyme (CnsC) responsible for both their oxidative union and selective conversion to heptacycle 16 in preference to isomeric heptacycle 17.

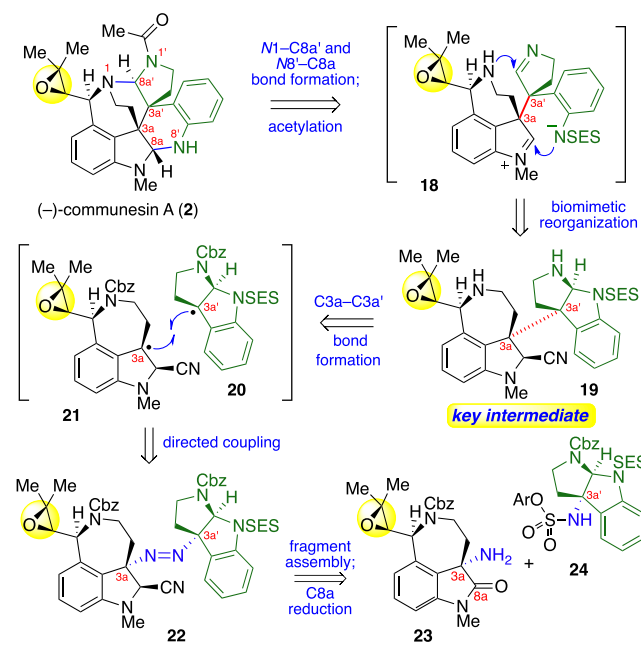
Our biomimetic approach to alkaloid (-)-1 was predicated on the late-stage diazene-directed assembly of two amine fragments to secure the key C3a–C3a' linkage with complete stereochemical control.^{3b} We then deployed the resulting heterodimeric structure as a surrogate for the hypothetical biosynthetic intermediate 15, which enabled the examination of conditions for a guided biomimetic amination reorganization to furnish the core of the communesin alkaloids to the exclusion

of other possible constitutional isomers. From this penultimate intermediate, we were able to access (-)-communesin F (1) in only one additional step. The success of our strategy to alkaloid (-)-1 prompted the development of a unified approach to access the challenging epoxy-communesin alkaloids 2–10 (Figure 1) via a convergent synthesis while accommodating acid sensitive intermediates bearing the C10-epoxide.

RESULTS AND DISCUSSION

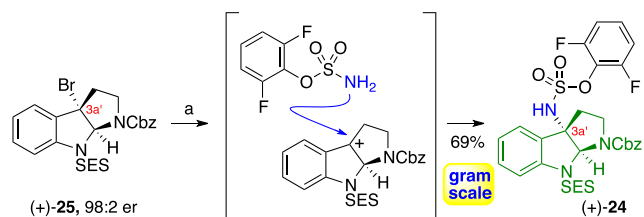
As depicted in our representative retrosynthetic analysis of (-)-communesin A (2, Scheme 2), we envisioned access to all

Scheme 2. Retrosynthetic Analysis of (-)-Communesin A (2)



C10-epoxy-communesins 2–9 via a late-stage biomimetic amination reorganization of the intermediate epoxy-heterodimer 19 followed by N1' acylation. Importantly, we anticipate this late-stage N1'-acylation will enable access to all members of this alkaloid class containing diverse N1' substituents. Next, consistent with our diazene-directed strategy for complex fragment assembly,^{3b,6} we projected that the critical C3a–C3a' linkage in 19 could be assembled via photoextrusion of dinitrogen from unsymmetrical diazene 22 and recombination of the resulting radical fragments 20 and 21. We expected to assemble diazene 22 from epoxide-bearing C3a-amino oxindole 23 and C3a'-sulfamate 24. We envisioned an early stage epoxidation to permit the key biomimetic rearrangement and to fully exploit our versatile and convergent approach. This strategy provides maximally divergent access to all C10-epoxy-communesins 2–9 from a single advanced synthetic intermediate, heterodimer 19.

Our total synthesis of alkaloids 2–10 (Figure 1) began with the preparation of oxindole 23 and sulfamate 24, the key amine fragments required for the synthesis of complex diazene 22. The application of our silver(I)-mediated substitution chemistry enabled rapid and scalable access to sulfamate (+)-24 (Scheme 3). Electrophilic activation of readily available enantioenriched C3a'-bromocyclotryptamine (+)-25^{3b,6d,7}

Scheme 3. Gram-Scale Synthesis of Sulfamate (+)-24^a

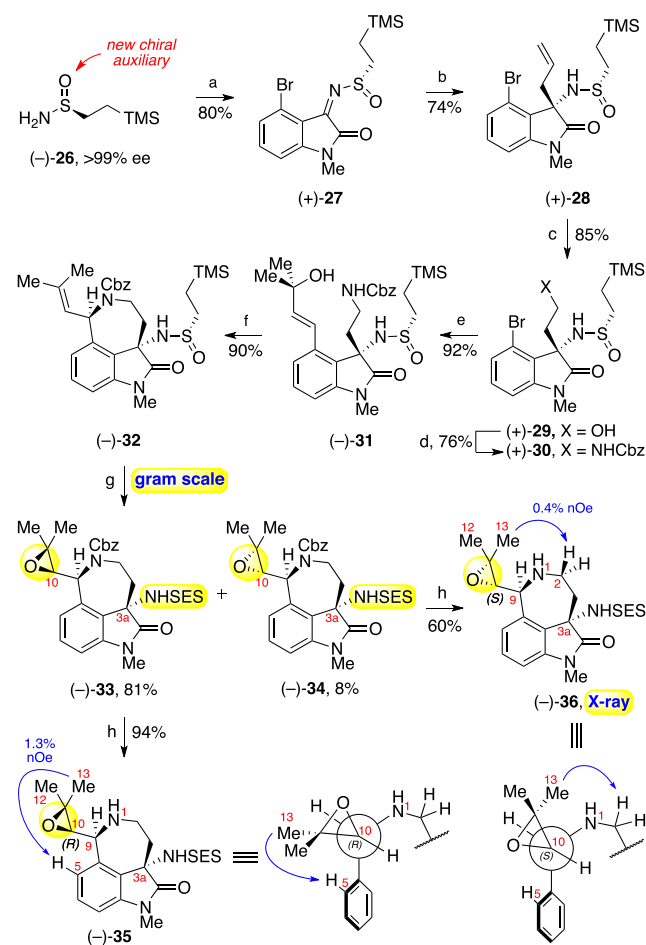
^aReagents and conditions: (a) AgOTf, 2,6-di-*tert*-butyl-4-methylpyridine, 2,6-difluorophenyl sulfamate, CH₂Cl₂, 23 °C.

with silver(I) trifluoromethanesulfonate in the presence of 2,6-difluorophenylsulfamate and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) afforded the corresponding sulfamate ester (+)-24 in 69% yield.

Having secured an efficient gram-scale synthesis of cyclo-tryptamine (+)-24, we turned our attention to the preparation of amino azepane fragment 23 which contains the key (C10R)-configured epoxide, a critical structural feature found in communesins 2–10. Our initial efforts directed toward the synthesis of this intermediate and related derivatives revealed a *pronounced* acid-sensitivity of the C10-epoxide, which stems from facile intramolecular opening of the protonated epoxide with the N1-carbamate to form stable oxazolidinone products.⁸ This precluded the use of Ellman's *tert*-butanesulfinamide chiral auxiliary,⁹ which we previously employed en route to (–)-communesin F (1).^{3b} Specifically, epoxidation of intermediates containing Ellman's auxiliary (i.e., the *tert*-butanesulfinamide variant of 32) resulted in rapid concomitant oxidation of the sulfinamide to the corresponding *tert*-butanesulfonyl sulfonamide (Bus), which requires strong Brønsted acids, such as trifluoromethanesulfonic acid, to remove.¹⁰ This unforeseen incompatibility prompted our design of 2-(trimethylsilyl)ethane sulfinamide (26), a new sulfinamide auxiliary whose oxidation product, 2-(trimethylsilyl)ethane sulfonamide (SES), can be removed under nonacidic and nonreducing conditions,¹¹ an essential requirement for the preservation of the sensitive C10-epoxide (Scheme 4).

Multigram quantities of enantiopure (*S*)-sulfinamide (–)-26 were prepared using readily available (–)-diacetone-D-glucose¹² as a chiral controller.¹³ Condensation of the new chiral auxiliary (–)-26 with *N*-methyl-4-bromoisatin in the presence of titanium(IV) ethoxide^{3b,9} then afforded the corresponding sulfinyl imine (+)-27 in 80% yield. Subsequent allylation with allylmagnesium bromide afforded the corresponding addition product (+)-28 in 74% yield as a single diastereomer on a multigram scale after flash column chromatography. We were pleased to discover that the inherent diastereoselectivity imparted by this new auxiliary (84:16 dr) was remarkably similar to that observed with Ellman's *tert*-butanesulfinamide (87:13 dr) under identical reaction conditions,^{3b,9} thereby validating the broader utility of sulfinamide (–)-26 in stereoselective synthesis.

Ozonolysis of alkene (+)-28 followed by in situ ozonide reduction with sodium borohydride furnished primary alcohol (+)-29 in 85% yield. Mitsunobu displacement of the alcohol with *N*-carbobenzyloxy-2-nitrobenzenesulfonamide (*o*-NsNHCbz) and in situ desulfonylation then afforded benzyl carbamate (+)-30 in 76% overall yield. A palladium-catalyzed Mizoroki–Heck reaction with 1,1-dimethylallyl alcohol and silver(I) carbonate as the base then proceeded to furnish allylic

Scheme 4. Synthesis of Epoxide (–)-33 and Determination of Relative Stereochemistry at C10^a

^aReagents and conditions: (a) *N*-methyl-4-bromoisatin, Ti(OEt)₄, CH₂Cl₂, 23 °C; (b) allylMgBr, MgBr₂, CH₂Cl₂, –78 °C, >99:1 dr; (c) O₃, MeOH, –78 °C; NaBH₄, –78 °C → 23 °C; (d) *o*-NsNHCbz, DIAD, PPh₃, THF, 50 °C; PhSH, Cs₂CO₃, 50 °C; (e) 1,1-dimethylallyl alcohol, Pd(OAc)₂, Ag₂CO₃, DMF–H₂O, 90 °C; (f) Ca(OTf)₂, MeCN, 80 °C; (g) 1,1,1-trifluoroacetone, 30% aq. H₂O₂, K₂CO₃, EDTA, MeCN–H₂O, 0 °C; (h) H₂, Pd(OH)₂/C, EtOH, 23 °C.

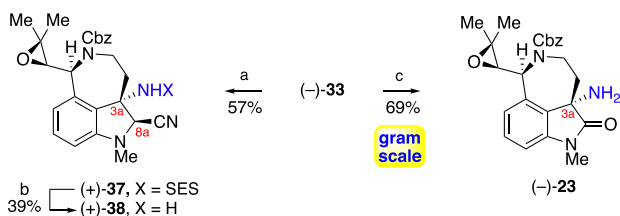
alcohol (–)-31 in 92% yield.¹⁴ Unexpectedly, subjecting (–)-31 to our previously employed palladium-catalyzed allylic amination conditions (PdCl₂MeCN₂, MeCN, 80 °C)^{3b,15} resulted in complex mixtures containing only trace amounts of azepane (–)-32. The major side products were derived from sulfinamide epimerization and desulfonylation. We hypothesize that the transiently generated hydrochloric acid necessary for catalyst turnover¹⁶ resulted in sulfinamide cleavage and release of the free amine and the corresponding sulfinyl chloride, which is expected to be configurationally unstable.¹⁷ Recombination of the amine and the racemized sulfinyl chloride would then afford the observed diastereomeric sulfinamide. After extensive experimentation, we discovered that calcium(II) trifluoromethanesulfonate and related Lewis acids¹⁸ could promote a highly efficient allylic amination without concomitant sulfinamide degradation. Indeed, under optimal conditions, gram scale synthesis of azepane (–)-32 was achieved in 90% yield.

We then focused on the introduction of the critical C10-epoxide. We were pleased to discover that mild, efficient, and stereoselective epoxidation of this key intermediate could be achieved using *in situ* generated methyl(trifluoromethyl)dioxirane (TFDO).^{19,20} Exposure of an acetonitrile solution of (–)-**32** to aqueous potassium carbonate and aqueous hydrogen peroxide in the presence of 1,1,1-trifluoroacetone at 0 °C furnished the desired (C10R)-configured epoxide (–)-**33** in 81% yield in addition to the (C10S)-configured epoxide (–)-**34** in 8% yield, coupled with concomitant and planned oxidation of the alkane sulfonamide to the corresponding 2-(trimethylsilyl)ethane sulfonamide (SES).²¹

The relative configuration at C10 of these epimeric epoxides was determined by nuclear Overhauser effect analysis on free amines (–)-**35** and (–)-**36** after hydrogenolytic removal of the benzyl carbamates (Scheme 4). According to Murata's $J_{\text{H-H}}$ -based method²² as employed by Proksch,^{1b} Christophersen,^{1e} and Chen^{1f} for communesins 4–9, the large coupling constant between C9H and C10H ($J \approx 9.0$ Hz) in both epoxides (–)-**35** and (–)-**36** indicates an approximately 180° dihedral angle between C9H and C10H, affording two possible diastereomeric *anti* configurations. In the case of epoxide (–)-**35**, the NOE enhancement observed at C5H when irradiating the geminal methyl groups is consistent with a *syn* orientation between the epoxide oxygen and N1 as depicted in the Newman projection in Scheme 4 and the (R)-configuration at C10. Conversely, the NOE enhancements observed at C2H in epoxide (–)-**36** when irradiating the geminal methyl groups suggests an *anti* orientation between the epoxide oxygen and N1 and thus the (S)-configuration at C10. Indeed, this assignment of epoxide (–)-**36** was later unambiguously confirmed by single-crystal X-ray diffraction.¹³

With a stereoselective synthesis of epoxide (–)-**33** in hand, we moved to investigate C8a reduction and unveiling of the C3a amine as a prelude to our planned diazene synthesis. We initially targeted the introduction of a C8a-nitrile, which we have shown to be an ideal trigger for late-stage C8a-iminium ion formation while providing adequate stability during the fragment assembly steps (Scheme 5).^{3b} To this end, partial

Scheme 5. Synthesis of Amine Fragments (+)-**38** and (–)-**23**^a



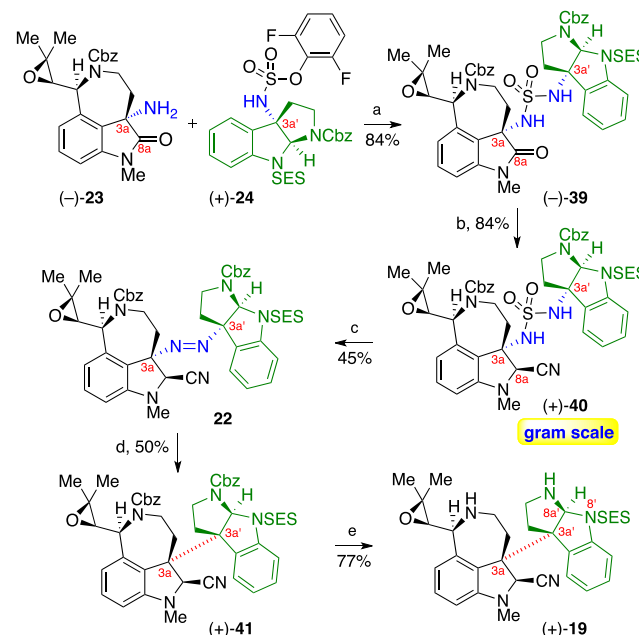
^aReagents and conditions: (a) (i) LiBH_4 , MeOH, THF, 23 °C; (ii) TMSCN , H_2O , HFIP, 0 °C → 23 °C. (b) TASF, DMF, 100 °C. (c) TASF, H_2O , DMF, 100 °C.

reduction of oxindole (–)-**33** with lithium borohydride afforded the corresponding C8a-hemiaminal as a mixture of diastereomers. Treatment of the crude hemiaminal with trimethylsilyl cyanide in wet hexafluoroisopropanol (HFIP) afforded aminonitrile (+)-**37** in 57% yield.^{13,23} Fluoride-mediated C3a-N desulfonylation with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)²⁴ in anhydrous *N,N*-dimethylformamide (DMF) at 100 °C provided benzylic

amine (+)-**38** in 39% yield, with the C8a-epimer and the C8a-cyanoindole elimination product comprising the remainder of the mass balance. Attempts to attenuate the basicity of the reagent by the addition of water or other acidic additives proved unsuccessful in reducing the propensity of the substrate to undergo elimination or epimerization. To circumvent problematic side reactions, we opted to desulfonylate oxindole (–)-**33** directly and investigate C8a reduction after the fragment assembly. Indeed, treatment of sulfonamide (–)-**33** with TASF in wet DMF at 100 °C provided gram-scale access to amino-oxindole (–)-**23** in 69% yield.

With both critical amine fragments in hand, we then moved to explore their union and the introduction of the key C3a–C3a' linkage. Simply stirring a tetrahydrofuran solution of amine (–)-**23** and sulfamate (+)-**24** in the presence of 4-(*N,N*-dimethylamino)pyridine (DMAP) afforded oxindole sulfamide (–)-**39** in 84% yield on a gram scale (Scheme 6). Partial

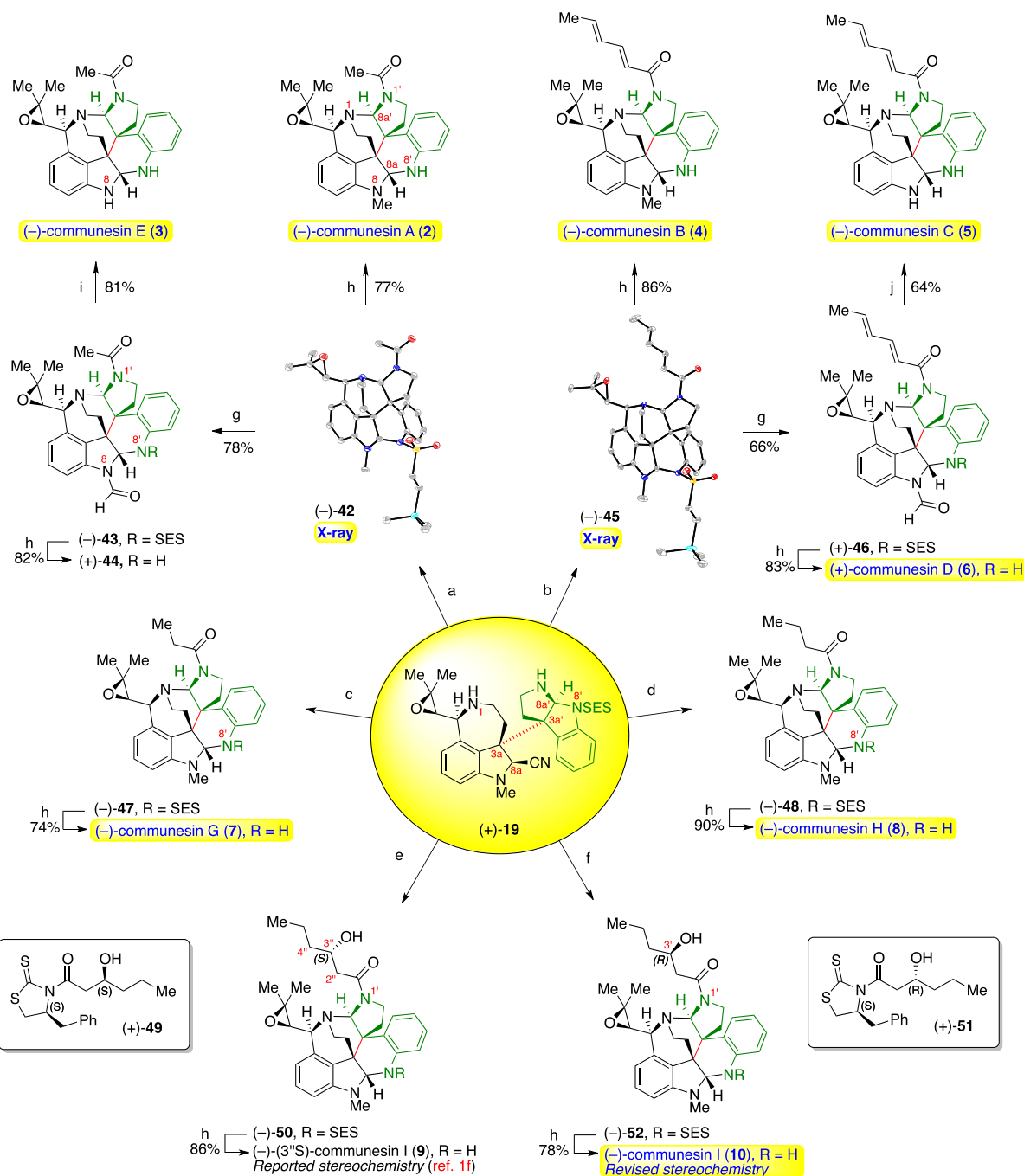
Scheme 6. Directed Synthesis of Heterodimer (+)-**19** via Diazene-Directed Fragment Assembly^a



^aReagents and conditions: (a) DMAP, THF, 23 °C. (b) (i) LiBH_4 , MeOH, THF, 23 °C; (ii) TMSCN , H_2O , HFIP, 0 °C → 23 °C. (c) polystyrene-2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine, *N*-chloro-*N*-methylbenzamide, MeOH, 23 °C. (d) $h\nu$ (350 nm), 25 °C. (e) H_2 , $\text{Pd}(\text{OH})_2/\text{C}$, EtOH, 23 °C.

reduction of the oxindole with excess lithium borohydride and treatment of the resulting hemiaminal with trimethylsilyl cyanide in wet²⁵ hexafluoroisopropanol then afforded aminonitrile sulfamide (+)-**40** as a single diastereomer in 84% overall yield on a gram scale. Fortuitously, formation of the C8a-nitrile after fragment assembly proved to be much more efficient and diastereoselective, likely due to the steric bulk of the cyclotryptamine moiety that more effectively shields the bottom face of the C8a-iminium.

Exposure of (+)-**40** to *N*-chloro-*N*-methylbenzamide in the presence of polystyrene-bound 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) in methanol then afforded sensitive diazene **22** in 45% yield, without competitive oxidation of the electron-rich arene.^{3b}

Scheme 7. Synthesis of All Known Epoxide-Bearing Communesins and Stereochemical Revision of (–)-Communesin I (10)^a

^aReagents and Conditions: (a) *t*-BuOLi, EtOH, 60 °C; PPTS, Ac₂O, 23 °C, 82%. (b) *t*-BuOLi, EtOH, 60 °C; PPTS, sorbic anhydride, 23 °C, 82%. (c) *t*-BuOLi, EtOH, 60 °C; PPTS, propionic anhydride, 23 °C, 86%. (d) *t*-BuOLi, EtOH, 60 °C; PPTS, butyric anhydride, 23 °C, 84%. (e) *t*-BuOLi, EtOH, 60 °C; PPTS, (+)-49, 23 °C, 84%. (f) *t*-BuOLi, EtOH, 60 °C; PPTS, (+)-51, 23 °C, 48%. (g) pyridinium dichromate (PDC), K₂CO₃, 1,2-dichloroethane, 60 °C. (h) TASF, DMF, 23 °C. (i) (i) KOH, H₂O–DMSO, 23 °C; (ii) TASF, DMF, 45 °C. (j) (i) KOH, H₂O–DMSO, 23 °C; (ii) TASF, DMF, 23 °C. In the ORTEP representations of sulfonamide (–)-42 and (–)-45, the thermal ellipsoids are drawn at 30% probability.

Photoexcitation and expulsion of dinitrogen from a thin film of diazene **22** afforded the C3a–C3a' linked heterodimer (+)-41 in 50% yield as a single diastereomer via a completely stereoselective combination of the radical fragments **20** and **21** (Scheme 2).²⁶

Hydrogenolysis of the benzyl carbamates then furnished heterodimeric diamine (+)-19 in 77% yield, setting the stage for our key biomimetic amination rearrangement. Consistent with

the design principles underpinning our synthetic strategy, the position of the electron withdrawing group on the cyclotryptamine moiety enables selective cleavage of either amination linkage, thereby controlling the regiochemical outcome of the rearrangement (*vide infra*). The N8'-sulfonamide of diamine (+)-19 was expected to guide the cleavage of the C8a'–N8' bond under basic conditions, leading to the heptacyclic core of

the communesin alkaloids after formation of the C8a–N8' and C8a'–N1 aminals (Scheme 2).

With the critical intermediate heterodimer (+)-19 in hand, we turned our attention to the preparation of all known epoxide-containing members of the communesin family, beginning with N1'-acetyl communesins (-)-2 and (-)-3, respectively. Importantly, we observed that a clean and complete rearrangement to the epoxide-appended communesin core could be achieved by exposing heterodimer (+)-19 to ethanolic lithium *tert*-butoxide at 60 °C (Scheme 7).²⁷ In situ neutralization of excess alkoxide with pyridinium *p*-toluenesulfonate (PPTS) followed by acetylation of the resulting sensitive heptacycle with acetic anhydride then furnished communesin derivative (-)-42 in 82% yield. Analysis of the advanced intermediate (-)-42 by single-crystal X-ray diffraction unambiguously confirms the stereochemical configuration of the C10-epoxide and provided the first solid-state structure of the full polycyclic topology of the communesin alkaloids.¹³ The structure of intermediate (-)-42 illustrates the compressed pyramidal N1-amine,²⁸ the preferred orientation of the N1'-acetyl group, and the positioning of the N8'-sulfonyl group, a substitution critical to the enhanced anticancer activity observed of new communesin derivatives (vide infra). Treatment of (-)-N8'-SES-communesin A (42) with TASF in degassed²⁹ DMF provided (-)-communesin A (2) in 77% yield. All ¹H and ¹³C NMR data as well as optical rotation (observed $[\alpha]_D^{24} = -165$ ($c = 0.39$, CHCl₃); lit: $[\alpha]_D^{22} = -58$ ($c = 0.14$, CHCl₃),^{1a} $[\alpha]_D^{20} = -174$ ($c = 1.34$, CHCl₃),^{1c} $[\alpha]_D^{30} = -163.5$ ($c = 0.14$, CHCl₃)⁴) for synthetic alkaloid (-)-2 were consistent with literature values.

Oxidation of (-)-N8'-SES-communesin A (42) with pyridinium dichromate (PDC, 10 equiv)^{2d,30} and potassium carbonate (40 equiv) in 1,2-dichloroethane at 60 °C provided the corresponding N8-formyl derivative (-)-43 in 78% yield. Removal of the N8'-sulfonyl group from intermediate (-)-43 resulted in (+)-N8-formyl communesin E (44) in 82% yield. Interestingly, this communesin derivative has not yet been isolated in nature to date, which is notable given that natural samples of (+)-communesin D (6), the closely related N1'-sorbyl derivative, have been repeatedly and independently isolated.^{1b,c} Alternatively, mild hydrolysis of formamide (-)-43 with potassium hydroxide in wet dimethyl sulfoxide (DMSO) followed by desulfonylation afforded the first synthesis of (-)-communesin E (3) in 81% yield. All spectral data and optical rotation (observed $[\alpha]_D^{23} = -191$ ($c = 0.31$, CHCl₃); lit: $[\alpha]_D^{20} = -156$ ($c = 0.11$, CHCl₃)^{1c}) for alkaloid (-)-3 were in agreement with the isolation report.

We next focused on the synthesis of N1'-sorbyl alkaloids (-)-communesins B–D (4–6, respectively). Treatment of heterodimeric diamine (+)-19 with the aminal rearrangement conditions described above followed by acylation with sorbic anhydride afforded (-)-N8'-SES-communesin B (45) in 82% yield. Mild N8'-desulfonylation with TASF then afforded (-)-communesin B (4) in 86% yield, whose spectroscopic data as well as optical rotation (observed $[\alpha]_D^{23} = -64$ ($c = 0.46$, CHCl₃); lit: $[\alpha]_D^{22} = +8.7$ ($c = 0.23$, CHCl₃),^{1a} $[\alpha]_D = -58$ ($c = 0.10$, MeOH),^{1b} $[\alpha]_D^{20} = -74.9$ ($c = 1.50$, CHCl₃),^{1c} $[\alpha]_D^{30} = -51.3$ ($c = 0.30$, CHCl₃)⁴) were consistent with previously reported values, with the exception of the anomalous positive value described in the first isolation report.^{1a,31} Oxidation of advanced intermediate (-)-45 with PDC provided the sensitive N8-formamide (+)-46 in 66% yield which was then desulfonylated to provide the first synthesis of (+)-communesin

D (6) in 83% yield. All ¹H and ¹³C data as well as optical rotation (observed $[\alpha]_D^{23} = +151$ ($c = 0.23$, CHCl₃); lit: $[\alpha]_D^{20} = +150$ ($c = 0.14$, CHCl₃)^{1c}) of (+)-6 were fully consistent with literature values. To complete the synthesis of all known N1'-sorbyl communesin derivatives, deformylation of the N8-formamide (+)-46 followed by desulfonylation of the resulting crude amine produced (-)-communesin C (5) in 64% yield. The spectral data and optical rotation of alkaloid (-)-5 (observed $[\alpha]_D^{23} = -108$ ($c = 0.28$, MeOH); lit: $[\alpha]_D = -30$ ($c = 0.038$, MeOH)^{1b}) were in agreement with literature values. Importantly, analysis of the common precursor (-)-45 by single-crystal X-ray diffraction unambiguously confirms the relative and absolute stereochemical configuration of all known N1'-sorbyl communesin alkaloids (-)-4, (-)-5, and (+)-6 for the first time.

We next proceeded with the first total synthesis of (-)-communesin G (7) and H (8). Rearrangement of key intermediate (+)-19 under the standard conditions followed by acylation with propionic anhydride efficiently furnished (-)-N8'-SES-communesin G (47) in 86% yield. Subsequent desulfonylation with TASF then afforded (-)-communesin G (7) in 74% yield, with spectral data and optical rotation (observed $[\alpha]_D^{23} = -163$ ($c = 0.20$, MeOH); lit: $[\alpha]_D^{25} = -157$ ($c = 0.021$, MeOH)^{1c}) fully consistent with those reported in the isolation report. Similarly, rearrangement of heterodimer (+)-19, acylation with butyric anhydride, and desulfonylation of the intermediate heptacycle (-)-48 efficiently furnished (-)-communesin H (8) in 76% overall yield, with all spectral data and optical rotation (observed $[\alpha]_D^{23} = -168$ ($c = 0.38$, MeOH); lit: $[\alpha]_D^{25} = -167$ ($c = 0.024$, MeOH)^{1c}) identical to those available from isolation reports.

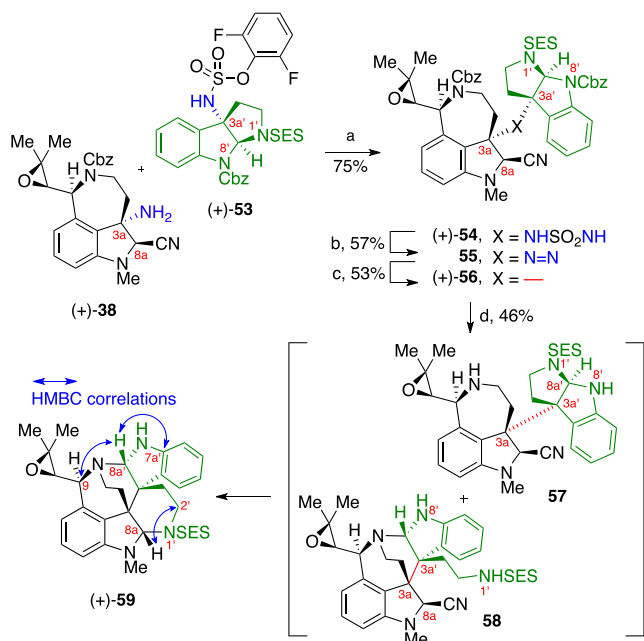
Finally, we turned our attention to the preparation of the reported structure of (-)-communesin I (9), the most recently isolated member of the communesin family. In order to introduce the (3''S)-hydroxy amide at N1', we opted to use aldol addition product (+)-49 as the acyl donor¹³ after the key aminal reorganization. Rearrangement of heterodimer (+)-19 followed by acylation of the resulting communesin core with excess aldol adduct (+)-49 furnished amide (-)-50 in 84% yield. Desulfonylation with TASF then afforded (-)-(3''S)-communesin I (9) in 86% yield, which enabled careful analysis of all spectral data and conclusive comparisons with the isolation data originally reported by Fan and co-workers^{1f} for natural (-)-communesin I. The ¹H and ¹³C NMR signals associated with the core of the alkaloid were in good agreement with the isolation report, however key ¹H and ¹³C signals on the acyl chain deviated notably from the expected values. Specifically, the ¹³C NMR chemical shifts of C2'' (41.1¹³ vs 42.1^{1f} ppm), C3'' (68.1¹³ vs 69.0^{1f} ppm), and C4'' (38.8¹³ vs 39.5^{1f} ppm) were found to be the most divergent.

In light of these data, we hypothesized that the stereochemical configuration at C3'' had been incorrectly assigned in the isolation report. Given the ease with which the diastereomeric aldol addition product (+)-51 could be prepared, we opted to synthesize the corresponding (3''R) derivative (10) to test our hypothesis. Reorganization of key intermediate (+)-19 followed by acylation with aldol addition product (+)-51 furnished (3''R) derivative (-)-52 in 48% yield, which upon N8'-desulfonylation afforded (-)-(3''R)-communesin I (10) in 78% yield. Importantly, all ¹H and ¹³C NMR data of this alkaloid were in excellent agreement with those reported in Fan's isolation report^{1f} of (-)-communesin

I. The optical rotation was also consistent with the reported data, albeit our synthetic sample had a higher value (observed $[\alpha]_D^{23} = -137$ ($c = 0.22$, MeOH); lit: $[\alpha]_D^{20} = -59$ ($c = 0.1$, MeOH)^{1f}). As a result, we herein reassign the stereochemical configuration at C3'' of this new communesin alkaloid from (S) to (R). This important finding validates the importance of our strategic late-stage N1' acylation, which enables the rapid diversification and functional derivatization of the communesin core.

To demonstrate the versatility of our highly convergent synthetic approach to all communesin alkaloids and related derivatives, we applied our synthetic strategy to prepare a constitutional isomer of the communesin skeleton, namely the *iso*-communesin^{5b} core **17** (Scheme 1). We anticipated that this unnatural polycyclic topology would be accessible via an analogous aminal reorganization of a C3a–C3a' linked heterodimer containing a cyclotryptamine fragment with an inverted N1'/N8' substitution pattern. Treatment of this hypothetical substrate with the same basic conditions required to reorganize (+)-**19** should result in the selective cleavage of the C8a'–N1' aminal, thereby resulting in the elements of the *iso*-communesin core after formation of the C8a–N1' and C8a'–N1 aminal linkages. As depicted in Scheme 8, fragment

Scheme 8. Guided Rearrangement to an Unnatural Communesin Related Topology^a



^aReagents and conditions: (a) DMAP, THF, 23 °C; (b) polystyrene–BEMP, *N*-chloro-*N*-methylbenzamide, MeOH, 23 °C; (c) $h\nu$ (350 nm), 25 °C; (d) (i) H_2 , Pd(OH)₂/C, EtOH, 23 °C; (ii) *t*-BuOLi, EtOH, 60 °C.

assembly of aminonitrile (+)-**38**³² and the appropriately substituted C3a'–sulfamate (+)-**53**¹³ afforded sulfamide (+)-**54** in 75% yield. Oxidation of (+)-**54** under the same conditions employed for sulfamide (+)-**40** afforded the sensitive diazene **55** in 57% yield. Photochemical irradiation of the diazene as a neat thin film at 350 nm then furnished the C3a–C3a' fused heterodimer (+)-**56** in 53% yield. Hydrogenolysis of heterodimer (+)-**56** resulted in formation of the anticipated heterodimeric diamine **57** along with the partially

rearranged compound **58** (57:58, 3:1). Notably, when a pure sample of diamine **57** was treated with lithium *tert*-butoxide (10 equiv) in methanol-*d*₄ at 23 °C, rapid and complete conversion to **58** was observed by ¹H NMR analysis. Evidently, the lower p*K*_a of indoline N8'H in heterodimer **57** relative to pyrrolidine N1'H in (+)-**19** enables cyclotryptamine-aminal opening even under the hydrogenolysis reaction conditions. Treatment of the crude hydrogenolysis product mixture of **57** and **58** with lithium *tert*-butoxide in ethanol at 60 °C resulted in clean conversion to *iso*-communesin derivative (+)-**59** in 46% overall yield from (+)-**56**. The structural assignment of the unnatural polycyclic topology of alkaloid (+)-**59** is supported by key HMBC data including the observed correlations C8aH–C2' and C8a'H–C9 that conclusively establish the presence of the C8a–N1' and C8a'–N1 aminals, respectively. The successful implementation of our synthetic strategy for the preparation of *iso*-communesin (+)-**59** further highlights the generality of our guided heterodimer rearrangement utilized in our syntheses described above.

With samples of all known communesin alkaloids and a selection of unnatural derivatives in hand, we set out to probe the anticancer activity for this entire class of natural products. While previous isolation reports have evaluated the activity of selected natural communesins, no comprehensive comparison of the entire class of alkaloids across multiple cell lines has been performed.¹ To this end, our synthetic samples of all nine naturally occurring communesins, a selection of seven complex intermediates from our synthetic campaign, and the N8'-sulfonylated *iso*-communesin (+)-**59** were examined for cytotoxicity against human lung carcinoma (A549), prostate carcinoma (DU 145), colorectal carcinoma (HCT 116), cervical adenocarcinoma (HeLa), and breast adenocarcinoma (MCF7) cell lines.¹³ As depicted in Table 1, (–)-communesin B (**4**) exhibited the highest potency of all the natural alkaloids tested across all cell lines, which is consistent with leukemia-focused assays performed in early isolation reports.^{1a,b} The cytotoxicity of the natural products in our assays against adherent cell lines representing solid tumors is slightly less than those performed against the leukemia cell lines. This observation is not surprising given that it has been previously observed in large scale cell line profiling experiments that cell lines grown in suspension, such as leukemia and lymphoma, can be generally more sensitive to cytotoxic compounds relative to adherent cell lines.³³ The next most active natural alkaloid, (–)-communesin C (**5**), exhibited an approximately 2-fold decrease in potency in our assays, whereas alkaloids (–)-**2**, (–)-**3**, (–)-**7**, (–)-**9**, and (+)-**43** were principally inactive across the cell lines examined.

Interestingly, advanced synthetic intermediates that contain an N8'-SES substituent generally exhibited a dramatic increase in potency relative to the N8' unsubstituted natural products (Table 1). For example, N8'-SES-communesin G, (–)-**47**, was found to exhibit an approximately 10-fold increase in potency relative to (–)-communesin G (**7**). This increase in activity was found to hold irrespective of N8 substitution (e.g., (+)-**46** vs (+)-**6**) or N1' substitution (e.g., (–)-**45** vs (–)-**4**). In this preliminary structure–activity relationship study, we also noted that the N8 substituent exerts a small but measurable influence on potency. For example, a two- to three-fold decrease in activity was observed moving from N8-methyl alkaloid (–)-**4** to either N8-H alkaloid (–)-**5** or N8-formyl alkaloid (+)-**6**. Additionally, we observed a general correlation between the size of the N1' substituent and the potency of the

Table 1. Assessment of All Known Communesin Alkaloids and a Selection of Unnatural Derivatives for Cytotoxicity Against Five Human Carcinoma Cell Lines.^a

Compound	Communesin	N1'	N8	N8'	IC ₅₀ (μM)				
					A549	DU 145	HCT 116	HeLa	MCF7
SES Derivatives									
(-)-45	N8'-SES-B	Sorbyl	Me	SES	19	24	>250	>125	5
(-)-47	N8'-SES-G	Propionyl	Me	SES	19	17	18	16	8
(-)-48	(3''S)-N8'-SES-I	(S)-3-pentanol	Me	SES	24	36	32	17	15
(+)-46	N8'-SES-D	Sorbyl	CHO	SES	39	29	27	15	24
(-)-42	N8'-SES-A	Acetyl	Me	SES	34	53	31	35	30
(+)-59	iso-communesin	SES	Me	H	335	>125	>62.5	64	58
N8'-H Natural Products and Derivatives									
(-)-4	B	Sorbyl	Me	H	56	45	60	47	34
(-)-5	C	Sorbyl	H	H	115	82	106	94	65
(-)-1	F	Acetyl	Me	H	117	119	>125	115	84
(-)-10	(3''R)-I (natural)	(R)-3-pentanol	Me	H	120	>125	>125	120	90
(-)-8	H	Butyryl	Me	H	>125	>125	109	82	90
(+)-6	D	Sorbyl	CHO	H	>125	84	111	63	>125
(-)-9	(3''S)-I (unnatural)	(S)-3-pentanol	Me	H	>125	>125	>125	>125	>250
(-)-7	G	Propionyl	Me	H	>125	>125	>125	>125	>250
(-)-2	A	Acetyl	Me	H	>125	>250	>250	>125	>250
(+)-43	N8'-formyl-E	Acetyl	CHO	H	>250	>250	>250	>125	>250
(-)-3	E	Acetyl	H	H	>500	>500	>500	>500	>500
1 < x ≤ 10 μM		10 < x ≤ 25 μM		25 < x ≤ 50 μM		50 < x ≤ 125 μM		> 125 μM	

^aCytotoxicity IC₅₀ values (in μM) after 72 h of compound treatment as determined by Cell Titer-Glo (Promega) which measures ATP levels as a surrogate for cell viability. Error is standard deviation of the mean, $n \geq 2$; IC₅₀ = half maximal inhibitory concentration; Human Carcinoma Cell Lines: Lung (A549), Prostate (DU 145), Colorectal (HCT 116), Cervical (HeLa), and Breast (MCF7).

compound. This is particularly evident in the natural series, where the activity generally follows the trend N1'-sorbyl > pentan-3R-ol > butyryl > propionyl > acetyl. As noted with the N8 substituent, the N8'-SES derivatives also followed the same general trend, but they were less sensitive to variation at this position. Lastly, the *iso*-communesin derivative (+)-59 exhibited inferior activity to all N8'-SES communesin derivatives tested as well as a number of more modestly active N8'-unsubstituted natural products.

Taken together, these preliminary data allow for the first side-by-side comparative analysis of a collection of communesin derivatives, including all nine naturally occurring communesins A–I (Figure 1), suggest primarily that (a) substitution at N8' can have a dramatic effect on potency; (b) N8-methyl derivatives exhibit improved activity relative to their N8-formyl or N8-unsubstituted counterparts; and (c) activity is nominally proportional to the size of the N1' substituent.

CONCLUSIONS

In summary, we have developed a *unified enantioselective total synthesis of all known epoxide-containing communesin alkaloids* (Figure 1), including the first total synthesis of communesins C–E, and G–I, in addition to related derivatives from a single advanced synthetic intermediate (+)-19. Our synthesis is predicated on the convergent and modular diazene-directed assembly of two complex fragments to secure the critical C3a–C3a' linkage followed by a guided biomimetic amination reorganization to deliver the heptacyclic core of these alkaloids. Concise gram-scale enantioselective syntheses of the fragments were devised, with highlights including the application of a new, specifically designed sulfinamide chiral auxiliary, an

efficient calcium trifluoromethanesulfonate promoted intramolecular amination, a diastereoselective epoxidation that simultaneously converts the new chiral auxiliary to a sulfonyl-based amine protective group, and the application of a silver-mediated cyclotryptamine-C3a'-sulfamate synthesis from a readily available enantioenriched C3a'-bromocyclotryptamine. The modularity of our convergent approach enabled the *stereochemical revision of (-)-communesin I* (Figure 1), the most recently isolated communesin analogue. Furthermore, the generality of our biomimetic heterodimer reorganization was demonstrated in the synthesis of an unnatural constitutional isomer of the communesin skeleton, the *iso*-communesin^{5b} derivative (+)-59. We also disclose the first side-by-side anticancer profiling of all nine naturally occurring communesin alkaloids and a selection of eight complex derivatives for cytotoxicity against five human cancer cell lines. From these data, we have identified (-)-communesin B as the most potent natural isolate and discovered that derivatives containing an N8'-SES substituent exhibit up to a 10-fold increase in potency over the natural products, with (-)-N8'-SES-communesins B (45) and G (47) being the most potent communesin derivatives found to date. These findings form the basis of our ongoing efforts aimed at detailed chemical and biological study of these fascinating alkaloids.

ASSOCIATED CONTENT

Supporting Information

(PDF) The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b07397.

Experimental procedures, spectroscopic data, and copies of NMR spectra (PDF)

Crystallographic data (CIF)
Crystallographic data (CIF)
Crystallographic data (CIF)

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(23) The stereochemical configuration at C8a was determined by nuclear Overhauser effect analysis of a derivative.

(24) Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. Tris(dimethylamino)sulfonium Difluorotrimethylsilicate, a Mild Reagent for the Removal of Silicon Protecting Groups. *J. Org. Chem.* **1998**, *63*, 6436–6437.

(25) The addition of water was necessary to suppress intramolecular trapping of the C8a-iminium with the sulfamide.

(26) (a) Two disproportionation products account for the majority of the mass balance: the oxidized tetracyclic C3a-cyanoindole and the corresponding reduced C3a'-H cyclotryptamine. (b) In a related system, calculations suggest that the C8a-CN provides 3.8 kcal/mol in favor of the observed C3a-stereochemical outcome. See the Supporting Information in ref 3b.

(27) For in situ monitoring of the rearrangement by ^1H NMR in CD_3OD , see the SI.

(28) The average C-N1-C bond angle of 113.8° and 114.1° observed in the solid state structure of (–)-42 and (–)-45, respectively, demonstrates steric compression of the pyramidal tertiary amine.

(29) Deoxygenation suppresses the formation of minor side products derived from oxidation at the N8-methyl. For example, when (–)-45 was treated with TASF in nondegassed *N,N*-dimethylformamide, 5% (+)-6 and 1% (–)-5 were isolated in addition to 86% of (–)-4.

(30) For examples of chromium mediated oxidation of *N*-methyl amines to the corresponding formamides, see: (a) Cavé, A.; Kan-Fan, C.; Potier, P.; Le Men, J.; Janot, M.-M. Oxidation de quelques amines tertiaires par l'anhydride chromique dans la pyridine. *Tetrahedron* **1967**, *23*, 4691–4696. (b) Corey, E. J.; Balanson, R. D. A Total Synthesis of (\pm)-Porantherine. *J. Am. Chem. Soc.* **1974**, *96*, 6516–6517. (c) He, B.; Song, H.; Du, Y.; Qin, Y. Total Synthesis of (–)-Ardeemin. *J. Org. Chem.* **2009**, *74*, 298–304. (d) Wu, H.; Xue, F.; Xiao, X.; Qin, Y. Total Synthesis of (+)-Perophoramidine and Determination of the Absolute Configuration. *J. Am. Chem. Soc.* **2010**, *132*, 14052–14054.

(31) The specific rotation data described in Numata's 1993 isolation report (ref 1a) for (–)-communesin A (2) and (–)-communesin B (4) are 116° and 84° more positive, respectively, than the data reported for the same compounds in Hayashi's 2004 isolation report (ref 1c). Our data for both compounds is fully consistent with the Hayashi isolation report and with Ma's total synthesis report.

(32) In this illustrative example, we elected to use aminonitrile (+)-38 instead of oxindole (–)-23 to facilitate access to the desired sulfamide (+)-54.

(33) Basu, A.; Bodycombe, N. E.; Cheah, J. H.; Price, E. V.; Liu, K.; Schaefer, G. I.; Ebright, R. Y.; Stewart, M. L.; Ito, D.; Wang, S.; Bracha, A. L.; Liefeld, T.; Wawer, M.; Gilbert, J. C.; Wilson, A. J.; Stransky, N.; Kryukov, G. V.; Dancik, V.; Barretina, J.; Garraway, L. A.; Hon, C. S.-Y.; Munoz, B.; Bittker, J. A.; Stockwell, B. R.; Khabele, D.; Stern, A. M.; Clemons, P. A.; Shamji, A. F.; Schreiber, S. L. An Interactive Resource to Identify Cancer Genetic and Lineage Dependencies Targeted by Small Molecules. *Cell* **2013**, *154*, 1151–1161.