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 aminal 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 amiation, 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 aminal 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)5 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).6 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
disclosed landmark biosynthetic and computational studies\textsuperscript{5} 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.\textsuperscript{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 aminal 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.

\section*{RESULTS AND DISCUSSION}

As depicted in our representative retrosynthetic analysis of (−)-communesin A (2, Scheme 2), we envisioned access to all C10-epoxy-communesins 2−9 via a late-stage biomimetic aminal 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,\textsuperscript{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′-bromocycloptryptamine (+)-25\textsuperscript{5b,6a,7}
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 cyclotryptamine (+)-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. This precluded the use of Ellman’s tert-butylenesulfonamide chiral auxiliary, which we previously employed en route to (+)-communesins F (1). Specifically, epoxidation of intermediates containing Ellman’s auxiliary (i.e., the tert-butylenesulfonamide variant of 24) resulted in rapid concomitant oxidation of the sulfonamide to the corresponding tert-butylenesulfonamide (Bus), which requires strong Bronsted acids, such as trifluoromethanesulfonic acid, to remove. This unforeseen incompatibility prompted our design of 2-(trimethylsilyl)ethane sulfonamide (26), a new sulfonamide auxiliary whose oxidation product, 2-(trimethylsilyl)ethane sulfonamide (SES), can be removed under nonacidic and nonreducing conditions, an essential requirement for the preservation of the sensitive C10-epoxide (Scheme 4).

Multigram quantities of enantiopure (S)-sulfonamide (−)-26 were prepared using readily available (−)-diacetone-D-glucose as a chiral controller. Condensation of the new chiral auxiliary (−)-26 with N-methyl-4-bromoisoquinoline in the presence of titanium(IV) ethoxide then afforded the corresponding sulfanyl 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-butylenesulfonamide (87:13 dr) under identical reaction conditions, thereby validating the broader utility of sulfonamide (−)-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-NsNHBz) and in situ desulfonylation then afforded benzyl carbamate (+)-30 in 76% overall yield. A palladium-catalyzed Mizoroki–Heck reaction with 1,1-dimethylyl alcohol and silver(I) carbonate as the base then proceeded to furnish allylic alcohol (−)-31 in 92% yield. Unexpectedly, subjecting (−)-31 to our previously employed palladium-catalyzed allylic amination conditions (PdCl2MeCN2, MeCN, 80 °C) resulted in complex mixtures containing only trace amounts of azepane (−)-32. The major side products were derived from sulfonamide epimerization and desulfonylation. We hypothesize that the transiently generated hydrochloric acid necessary for catalyst turnover resulted in sulfonamide cleavage and release of the free amine and the corresponding sulfanyl chloride, which is expected to be configurationally unstable. Recombination of the amine and the racemized sulfanyl chloride would then afford the observed diastereomeric sulfonamide. After extensive experimentation, we discovered that calcium(II) trifluoromethanesulfonate and related Lewis acids could promote a highly efficient allylic amination without concomitant sulfonamide 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). Exposure of an acetonitrile solution of (-)-32 to aqueous potassium carbonate and aqueous hydrogen peroxide in the presence of 1,1,1-trifluoroacetate 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 JH−HF− based method as employed by Proksch, Christophersen, and Chen for communesins for communesins

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 the 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). To this end, partial reduction of the oxindole (-)-33 with lithium borohydride and treatment of the resulting hemiaminal with trimethylsilyl cyanide in wet hexafluoroisopropanol then afforded amino-nitrile 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 cyclopropylamine 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-diisopropylidene-1,3-diaminopropane (BEMP) in methanol then afforded sensitive diazene 22 in 45% yield, without competitive oxidation of the electron-rich arene.26

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

Reduction of oxindole (-)-33 with excess lithium borohydride and treatment of the resulting hemiaminal with trimethylsilyl cyanide in wet hexafluoroisopropanol then afforded amino-nitrile 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 cyclopropylamine moiety that more effectively shields the bottom face of the C8a-iminium.

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**Reagents and conditions: (a) DMAP, THF, 23 °C. (b) (i) LiBH₄, MeOH, THF, 23 °C; (ii) TMS-CN, H₂O, HFIP, 0 °C → 23 °C. (c) polystyrene-2-tert-butylamino-2-diethylamino-1,3-diisopropylidene-1,3-diaminopropane, N-chloro-N-methylbenzamide, MeOH, 23 °C. (d) 1H 350 nm), 25 °C. (e) H₂, Pd(OH)₂/C, EtOH, 23 °C.
Photoexcitation and expulsion of dinitrogen from a thin film of diazene \( \text{II} \) 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).

Hydrogenolysis of the benzyl carbamates then furnished heterodimeric diamine \((+)-19\) in 77% yield, setting the stage for our key biomimetic aminal reorganization. Consistent with the design principles underpinning our synthetic strategy, the position of the electron withdrawing group on the cycloptryptamine moiety enables selective cleavage of either aminal 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 epoxy-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). In situ neutralization of excess alkoxide with pyridinium p-toluene sulphonate (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. The structure of intermediate (−)-42 illustrates the compressed pyramidal N1-amine, 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 degassed DMF provided (−)-communesin A (2) in 77% yield. All 1H and 13C NMR data as well as optical rotation (observed \([\alpha]_D^{24} = -165 (c = 0.39, CHCl_3); \text{lit:} [\alpha]_D^{20} = -58 (c = 0.14, CHCl_3); [\alpha]_D^{10} = -174 (c = 1.34, CHCl_3); \text{lit:} [\alpha]_D^{10} = -165.3 (c = 0.14, CHCl_3)\) for synthetic alkald (−)-2 were consistent with literature values.

Oxidation of (−)-N8′-SES-communesin A (42) with pyridinium dichromate (PDC, 10 equiv) and potassium carbonato (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-SF-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.16,23 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 \([\alpha]_D^{23} = -191 (c = 0.31, CHCl_3); \text{lit:} [\alpha]_D^{20} = -156 (c = 0.11, CHCl_3)\)) for alkald (−)-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 \([\alpha]_D^{23} = -64 (c = 0.46, CHCl_3); \text{lit:} [\alpha]_D^{20} = +8.7 (c = 0.23, CHCl_3); \text{lit:} [\alpha]_D^{10} = -58 (c = 0.10, MeOH); [\alpha]_D^{10} = -74.9 (c = 1.50, CHCl_3); [\alpha]_D^{0} = -51.3 (c = 0.30, CHCl_3))\) were consistent with previously reported values, with the exception of the anomalous positive value described in the first isolation report.4,6,31 Oxidation of advanced intermediate (−)-45 with PDC provided the sensitive N8-formamide (+)144 of 46% 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 \([\alpha]_D^{23} = +151 (c = 0.23, CHCl_3); \text{lit:} [\alpha]_D^{20} = +150 (c = 0.14, CHCl_3)\)) of (+)6 were fully consistent with literature values. To complete the synthesis of all known N1′-sorbyl communesin derivatives, dearylylation of the N8-formamide (+)46 followed by desulfonylation of the resulting crude amine provided (−)-communesin C (5) in 64% yield. The spectral data and optical rotation of alkaloid (−)-5 (observed \([\alpha]_D^{23} = -108 (c = 0.28, MeOH); \text{lit:} [\alpha]_D^{20} = -30 (c = 0.038, MeOH)\)) 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 \([\alpha]_D^{23} = -163 (c = 0.20, MeOH); \text{lit:} [\alpha]_D^{25} = -157 (c = 0.021, MeOH)\) 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 \([\alpha]_D^{23} = -168 (c = 0.38, MeOH); \text{lit:} [\alpha]_D^{25} = -167 (c = 0.024, MeOH)\) 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 donor after the key aminal reorganization. Rearrangement of heterodimer (+)-19 followed by acylation of the resulting communesin core with excess aldon aldact (+)-49 furnished amide (−)-50 in 84% yield. Desulfonylation with TASF then afforded (−)-3′-SES-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 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 42.11f ppm), C3′ (68.113 vs 69.01f ppm), and C4′ (38.813 vs 39.51f 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 of (−)-communesin.
assembly of aminonitrile (+)-3832 and the appropriately substituted C3a’-sulfamate (+)-5332 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-d4 at 23 °C, rapid and complete conversion to 58 was observed by 1H NMR analysis. Evidently, the lower pKb of indole N8H in heterodimer 57 relative to pyrrolidine N1’H in (+)-19 enables cycloptryptamine-amin 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 C8aH–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.13 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...
compound. This is particularly evident in the natural series, where the activity generally follows the trend $N_1'$-sorbyl > pentan-3-$R$-ol > butyryl > propionyl > acetyl. As noted with the $N_8$ substituent, the $N_8'$-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 $N_8'$-SES communesin derivatives tested as well as a number of more modestly active $N_8'$-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 $N_8'$ can have a dramatic effect on potency; (b) $N_8$-methyl derivatives exhibit improved activity relative to their $N_8$-formyl or $N_8$-unsubstituted counterparts; and (c) activity is nominally proportional to the size of the $N_1'$ 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 $C_3a-C_3a'$ linkage followed by a guided biomimetic aminal 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-$C_3a'$-sulfamate synthesis from a readily available enantioenriched $C_3a'$-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 $N_8'$-SES substituent exhibit up to a 10-fold increase in potency over the natural products, with ($-$)-$N_8'$-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)
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The authors declare no competing financial interest.

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(26) (a) Two disproportionation products account for the majority of the mass balance: the oxidized tetracyclic C3a-cyanoindole and the corresponding reduced C3a-cyanoindole. (b) In a related system, calculations suggest that the C3a-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$_3$OD, 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-diethylformamide, 5% (+)-6 and 1% (−)-5 were isolated in addition to 86% of (−)-4.

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