Network-analysis-guided synthesis of weisaconitine D and liljestrandinine

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General strategies for the chemical synthesis of organic compounds, especially of architecturally complex natural products, are not easily identified. Here we present a method to establish a strategy for such syntheses, which uses network analysis. This approach has led to the identification of a versatile synthetic intermediate that facilitated syntheses of the diterpenoid alkaloids weisaconitine D and liljestrandinine, and the core of gomandonine. We also developed a web-based graphing program that allows network analysis to be easily performed on molecules with complex frameworks. The diterpenoid alkaloids comprise some of the most architecturally complex and functional-group-dense secondary metabolites isolated. Consequently, they present a substantial challenge for chemical synthesis. The synthesis approach described here is a notable departure from other single-target-focused strategies adopted for the syntheses of related structures. Specifically, it affords not only the targeted natural products, but also intermediates and derivatives in the three families of diterpenoid alkaloids (C-18, C-19 and C-20), and so provides a unified synthetic strategy for these natural products. This work validates the utility of network analysis as a starting point for identifying strategies for the syntheses of architecturally complex secondary metabolites.

Chemical synthesis is fundamental to the preparation of small-molecule active pharmaceutical ingredients1–4. Advances in the field of chemical synthesis continue to be marked by the methods and strategies for the preparation of complex natural products, which, more effectively than any other exercise, expose challenges that still exist in the field5–7. Over the last half century, natural product synthesis has continued to be driven by three general motivations: (1) to achieve the practical synthesis of highly complex structures for which a synthesis plan is not readily apparent; (2) to highlight the power, and identify the scope and limitations, of a newly developed synthesis method; and (3) to facilitate exploration of biological function of the synthetically prepared molecules (and their derivatives). Although the second and third motivations have received considerable attention (especially over the last two decades), the first motivation, which has historically served to advance the field, has waned as the notion that any desired molecule can be prepared given enough resources and time has prevailed7–9. Yet, efficient and versatile syntheses of many complex molecules still have not been realized. This is especially true for molecules that feature polycyclic, highly caged frameworks for which effective strategic solutions are not immediately obvious. For these architecturally complex skeletons (for example, aconitine, Fig. 1a), the biosynthetic transformations that lead to these secondary metabolites in nature are often not fully vetted, are low yielding, or cannot be efficiently reproduced in the laboratory10,11. Therefore, de novo strategic approaches for their chemical syntheses are required12.

Here, we demonstrate that for a subset of topologically complex and functional-group-dense secondary metabolites in the diterpenoid alkaloid family (representative of the aconitine structural type; >700 members), the iterative application of network analysis at the initial stages of synthetic planning yields a unified strategy for their synthesis. This type of analysis has proved to be highly enabling, by identifying a strategy that is a notable departure from previously established synthesis strategies for related alkaloids. The network analysis approach13 involves ‘strategic bond disconnections’ of bridged polycycles. Despite the emergence of other philosophies, guidelines and methods for synthesis, network analysis remains immutable. Total syntheses of weisaconitine D (2; a C-18 alkaloid) and liljestrandinine (3; C-19), and the preparation of the skeleton of natural products in the denudatine-type diterpenoid alkaloids (for example, gomandonine, 4; C-20) reported here illustrate the power of this type of analysis.

The diterpenoid alkaloids (including weisaconitine D and liljestrandinine) have also gained in prominence as small-molecule ligands for voltage-gated Na+ and K+ ion channels14. In some cases, these small molecules may be isoform-specific in their interactions with ion channels (presumably binding at the aconitine binding site) and therefore hold potential as the basis for new therapeutics to address myriad channelopathies15,16; for example, the Na+ channel blocker lappaconitine (allapinin; 5) is already administered as a non-narcotic analgesic drug17. However, to better identify the salient features of these molecules that lead to desirable medicinal properties, versatile de novo syntheses are required, because they facilitate the synthesis of analogues featuring deep-seated skeletal changes that might not be otherwise efficiently accessed (for example, by a biomimetic pathway or semi-synthesis).

Network analysis as a starting point in retrosynthesis

The application of network analysis to the diterpenoid alkaloids is illustrated in our retrosynthesis of the C-18 diterpenoid alkaloid weisaconitine D (Fig. 1b). The aim of this analysis is to minimize, in the retrosynthetic direction, the number of bridged rings, which, in addition to the density of stereochemically disposed functional groups, heightens the complexity of these molecules. Targeting the maximally bridged ring (highlighted in red for perspective IV of 2; see box in Fig. 1b) possessing five bridgehead atoms (highlighted in purple), for disconnection leads back to 6, to which a bicyclization/cycloaddition
could be applied in the forward sense to forge the bicyclo[3.2.1] framework. In turn, identification of the piperidine ring in 6 as the maximally bridged ring for this compound triggered a retrosynthetic simplification by disconnection of the C19–N bond (see B in Fig. 1b for atom numbering) leading back to a bicycle that could be derived from 7. Bicycle 7 was anticipated to be available from diene 8 and dienophile 9 using a Diels–Alder cycloaddition. Although alternative Diels–Alder cycloadditions (compare C, D and E in Fig. 1c) have also been used in related total syntheses18–20, the iterative application of network analysis, along with other retrosynthetic considerations such as the availability of starting materials and minimizing functional-group interconversions, led us to an alternative bond construction. Dehydro-hydrindane 7 possesses a variety of strategic synthetic handles that facilitate divergence in the synthetic scheme.

Similar retrosynthetic analyses can be proffered for the C-19 diterpenoid alkaloid liljestrandinine and for the C-20 alkaloid gomandonine (see Supplementary Information for more details). However, in these cases, the C4 bridgehead carbon would need to be quaternized, and 7 is suited for this purpose. From our analysis, 7 may also be used in the syntheses of other diterpenoid alkaloids of the hetidine, hetisine, denudatine and aconitine structural types (for example, gomandonine, denudatine-type diterpenoid alkaloids (for example, gomandonine, 4), bearing a bicyclo[2.2.2] moiety. The structure of this polycycle served as a substrate for a Rh-catalysed conjugate addition with in situ generated lithium boronate 11, to afford 12 in 60% yield. This conjugate addition step, which required careful optimization, provides a modular way to introduce the guaiacol derivative with high diastereoselectivity and enables access to various oxidation patterns on the C/D bicycle of the diterpenoid alkaloids by using other differently substituted arenes. Selective reduction of the ester group of 12 (in the presence of the cyano group) with Red-Al (ref. 25) and reoxidation of the resulting alcohol group to the aldehyde using the Dess–Martin periodinane reagent gives 13. At this stage, Wittig olefination of the aldehyde group and hydration of the nitrite group using the conditions of ref. 26 provides carboxamide 14.

Hofmann rearrangement of the amide group and attendant trapping of the intermediate isocyanate with methanol, followed by fluoride-mediated cleavage of the tert-butyl dimethyl silyl (TBS) group gives 15. Activation of the primary hydroxyl as the mesylate and exposure to KOtBu effects alkylation to forge the C19–N bond and fashion the piperidine ring of 16 to complete the A, E and F rings (see A, Fig. 1b, for ring labelling) of the C-18 diterpenoid alkaloids. In preparation for the installation of the B, C and D rings, the methoxymethyl (MOM) group of 16 was removed and the resulting phenol subjected to oxidative deaeromatization27 to afford 17. Dieneone 17 smoothly undergoes intramolecular Diels–Alder cycloaddition upon heating to 150 °C to provide 18, which is the core framework of the C-20 denudatine-type diterpenoid alkaloids (for example, gomandonine, 4), bearing a bicyclo[2.2.2] moiety. The structure of this polycycle was secured by X-ray crystallographic analysis of benzyolated derivative 24 (Fig. 2b). In preparation for the transformation of the bicyclo[2.2.2] structural motif to the bicyclo[3.2.1] framework that is characteristic of the aconitine-type C-18 and C-19 alkaloids, the carbonyl group of 18 was reduced stereoselectively (presumably steered away from torsional strain with the β-disposed methoxy group of the dimethyloketone), and the ketol was hydrolysed to unveil α-ketol 19. Protection (MOM) of the secondary hydroxyl of 19 and diastereoselective reduction of rings (red) and the corresponding bridgehead atoms (purple), and the labelling of rings and atom numbering for the aconitine-type skeleton (bottom right, boxed). c. Highlighted bonds that are forged in three different Diels–Alder approaches to the A ring of diterpenoid alkaloids.

**Syntheses of weisaconitine D and liljestrandinine**

The total synthesis of weisaconitine D was achieved in 30 steps from diene 8 and dienophile 9, as outlined in the following. Our synthesis of weisaconitine D (Fig. 2a) commenced with the cycloaddition of known diene 8 (ref. 22) and cyclopentenone derivative 9 (ref. 23), yielding a cycloadduct that upon hydrogenation gives bicyclic ketone 10 (70%; 2 steps). Vinyl triflate formation and Pd(0)-catalysed cross-coupling with cyanide24 yields α,β-unsaturated nitrile 7 (70%; 2 steps), which
Figure 2 | Synthesis of weisaconitine D. a, Reaction sequence for the total synthesis of weisaconitine D. Reagents and conditions for each step are as follows: (1) 110 °C, toluene, 110 °C, 64 h; (2) Pd/C (10 wt%), H2 gas (1 atm), EtOAc, room temperature (r.t.), 3 h, 70% yield over steps (1) and (2); (3) LiHMDS (lithium hexamethyldisilazide; 1.3 equiv.), PhNCl (1.4 equiv.), THF, −78 °C to r.t., 12 h; (4) NaCN (2.2 equiv.), Pd(PPh3)4 (0.06 equiv.), CuI (0.12 equiv.), MeCN, reflux, 1.3 equiv.), PhNTf2 (1.4 equiv.), THF, 20 °C, 16 h, 92% yield; (5) lithium boronate (1.3 equiv.), PhNTf2 (1.4 equiv.), THF, 20 °C, 16 h, 92% yield; (6) Red-Al (1.0 equiv.), CH2Cl2, 0 °C to r.t., 3.5 h, 99% yield; (7) Dess–Martin periodinane (2.0 equiv.), NaHCO3 (5.0 equiv.), CH2Cl2, 0 °C, 1.5 h, 91% yield; (8) PPh3MeBr (3.0 equiv.), LiHMDS, THF, 0 °C to r.t., 1 h, 94% yield; (9) RhCl(PPh3)3 (0.3 equiv.), CH3CHNOH/PhMe, reflux, 15 h, 81% yield; (10) KOH (3.4 equiv.), phenyldiazonium diacetate (1.3 equiv.), MeOH, 0 °C to r.t., 3 h; (11) TBAF (tetrabutylammonium fluoride; 3.0 equiv.), THF, r.t., 5 h, 96% yield over steps (10) and (11); (12) MsCl (1.5 equiv.), CH2Cl2/Et3N, 0 °C, 3 h; (13) KOtBu (3.0 equiv.), THF, 0 °C to r.t., 2 h, 73% yield over steps (12) and (13); (14) 2N HCl/iPrOH, 0 °C to r.t., 3.5 h, 99% yield; (15) phenyldiazonium diacetate (1.5 equiv.), NaHCO3 (5.0 equiv.), MeOH, 0 °C, 1 h, 99% yield; (16) p-xylene, 150 °C, 17.5 h, 77% yield; (17) NaBH4 (3.0 equiv.), MeOH, 0 °C to r.t., 3 h; (18) CHCl3/TFA/water, 4 °C, 2 h, 87% yield over steps (17) and (18); (19) MOMCl (4.9 equiv.), DIPEA (N,N-diisopropylethylamine 10 equiv.), 4 °C to r.t., 16 h, 92% yield; (20) NaBH4 (3.3 equiv.), MeOH, 4 °C, 2 h, 95% yield; (21) Ti(OH)4 (10 equiv.), pyridine, CH2Cl2, −78 °C to r.t., 16 h; (22) DBU (3.3 equiv.), DMSO, 120 °C, 1 h, 55% yield over steps (21) and (22); (23) m-CPBA (5.2 equiv.), CH2Cl2, 0 °C to r.t., 16 h; (24) NaH (15 equiv.), EtI (15 equiv.), THF, 40 °C, 16 h, 76% yield over steps (23) and (24); (25) Cp2TiCl2 (2.2 equiv.), Mn (7.6 equiv.), H2O (38 equiv.), THF, r.t., 16 h; (26) NaH (12 equiv.), Me2SO4 (7 equiv.), THF, 60 °C, 2 h, 66% yield over steps (25) and (26); (27) 4 M KOH, ethylene glycol, 100 °C, 120 h; (28) HCl (9.4 equiv.), pyridine (28 equiv.), CH2Cl2, 0 °C to r.t., 16 h; and (29) LiAlH4 (10 equiv.), EtO, 40 °C, 2 h; (30) 2N HCl, THF, 16 h, 54% yield over steps (27)–(30). Cat., catalyst. b, Images of intermediates 24 and 25, and of derivatized weisaconitine D (26), created using CYLview30. Most hydrogens (except stereocentres) have been removed for clarity. Hydrogen, white; carbon, grey; nitrogen, blue; oxygen, red.
The use of methanol in the presence of various protic and bridgehead double bond. Several tactics were explored to achieve a (M06-L/6-311G was first oxidized, using Swern conditions, to the corresponding (92% enantiomeric excess (e.e.); (4) KOtBu (5 equiv.), THF, 50°C, 4 h; (5) 0.5 M NaOMe in MeOH, 120°C, and 32. Ultimately, the requisite methoxy group was installed at C16 cleavage)\(^3\) and variants of the hydration method presented in refs \(3\) and \(3\). Displacement of the remaining mesylate group with methanol, including the use of methanol in the presence of various protons and \(\pi\)-acids to activate the double bond\(^2\), hydroboration (both inter- and intramolecular, directed by the secondary hydroxyl at C14 of 21 following MOM functionalization)\(^3\) and variants of the hydration method described in refs 31 and 32. Ultimately, the requisite methoxy group was installed at C16 of 21 using an epoxide intermediate. Thus, hydroxyl-directed epoxidation of the C15–C16 double bond, including the use of methanol in the presence of various protons and \(\pi\)-acids to activate the double bond\(^2\), hydroboration (both inter- and intramolecular, directed by the secondary hydroxyl at C14 of 21 following MOM functionalization)\(^3\) and variants of the hydration method described in refs 31 and 32. Ultimately, the requisite methoxy group was installed at C16 of 21 using an epoxide intermediate. Thus, hydroxyl-directed epoxidation of the C15–C16 olefin group of 21 from the \(\beta\)-face using \(\text{meta}\)-chloroperbenzoic acid (\(\text{m}-\text{CPBA}\)) (see coloured model of 25, Fig. 2b) and ethylation of the tertiary hydroxyl yielded 22 (76% over 2 steps). Regioselective reductive opening of the epoxide using the conditions given in ref. 33 gave a \(\beta\)-disposed secondary alcohol group that was methyalted to furnish 23 (66% over 2 steps). With the oxygenation of the D-ring of weisacinate D secured, all that remained was to install the ethyl group on the piperidine nitrogen and to remove the MOM group to complete the synthesis. These tasks were accomplished in four steps: removal of the methoxycarbonyl (MOC) group of 23 (using KOH); acylation of the resultant secondary amine group (using \(\text{Ac}_2\text{O}\)); reduction of the amide (using LiAlH\(_4\)); and treatment with acid to remove the MOM group. One key challenge that was not overcome in this current syntheses of C-18, C-19 and C-20 diterpenoid alkaloids is how to achieve modular functionalization of the C4 position of the shared carbon framework. Here, we demonstrate that alcohol 15, a derivative of dehydro-hydrindane 7, can be used in the synthesis of the C-19 diterpenoid alkaid liljestrandinine, which possesses a methoxymethylene group at C4 (Fig. 3a). Overall, the synthesis of liljestrandinine proceeds in 29 steps from diene 8 and diones 9, as summarized in the following. The primary hydroxyl of 15 was first oxidized, using Swern conditions, to the corresponding aldehyde (not shown). Various attempts to alkylate the aldehyde enolate (as well as the enolates of related 6,5-bicycles) proved unfruitful and resulted in either non-specific decomposition or the addition of the electrophile from the undesired \(\alpha\)-face (presumably due to developing syn-pentane interactions of the electrophile with the angular vinyl group). Ultimately, we found that an aldol-Cannizzaro sequence on the intermediate aldehyde, effected using KOH and formaldehyde, furnishes a geminal bis-methylene diol that was functionalized as the bis-mesylate (see 27 in Fig. 3a), where the C4 stereocentre is ablated. At this stage, alkylation of the carbamate nitrogen was accomplished (following ref. 34) with KOtBu to forge the piperidine ring and reconstitute the C4 stereocentre (see 27 in Fig. 3a). Displacement of the remaining mesylate group with methanol, reinstallation of the nitrogen protecting MOC group (which is partially cleared during the methoxide displacement) and removal of the MOM group provides 28. Phenol 28 was advanced to an intermediate that is analogous to 21 (8 steps), and then to liljestrandidine using a sequence analogous to that described for 23 \(\rightarrow\) 24 (4 steps; see Supplementary Information for details). An enantioselective Diels–Alder cycloaddition The chemical syntheses of weisacinate D and liljestrandidine described here rely on subsequent diastereoselective installation of all stereocentres from the four contiguous stereocentres that are introduced in the Diels–Alder reaction between diene 8 and diones 9. As such, a catalytic, enantioselective, Diels–Alder cycloaddition would enable enantioselective access to the natural products. In this regard, initial attempts to render the cycloaddition between 8 and 9 enantioselective with the aid of chiral, non-racemic, Lewis acid catalysts (for example, using the method of refs 35 and 36) resulted in low enantioselectivity and non-specific decomposition (primarily of diene 8 under the acidic conditions). Ultimately, 29 (ref. 37; for which see CYLview in Fig. 3b) was obtained using the conditions described.
A web–based network analysis program

Our iterative application of network analysis\(^\text{13}\) to initiate a strategy for the syntheses of weisacconitine D and liljestrandinine led us to develop general ways to conduct such analyses. Previous implementations of network analysis in retrosynthesis, especially in the identification of the maximally bridged ring, have been carried out in a probabilistic manner, which invariably heightens the risk of errors\(^\text{39,40}\). To overcome this shortcoming, we developed a web-based deterministic graphing program that permits the identification of the maximally bridged ring (or rings) for any molecule using the Chemistry Development Kit (CDK) software library\(^\text{41,42}\) (see Fig. 4a for the output of a test set; see Supplementary Information for more details). The algorithm we developed for this purpose is guaranteed to identify the maximally bridging ring. The program output is the ’.pdb’ image in grey. The maximally bridging ring or that span bridging atoms in the maximally bridging ring. ChemDraw renditions of the graphing program output are provided for four bridgehead atoms. By focusing on these rings for disconnection, maximum retrosynthetic simplification (that is, removal of bridging chains and fused rings) is achieved in the least number of steps with our approach (see F in Fig. 4b). A retrosynthetic analysis of the aconite framework, informed by network analysis (Fig. 4c) suggests that disconnections represented by I would provide maximum simplification. These latter strategic disconnections, which guided our approach to the syntheses of weisacconitine D and liljestrandinine, also indicate that a direct bicyclization to construct the bicyclo[3.2.1] moiety would provide the maximum benefit. Efforts to achieve this type of bicyclization are the subject of our ongoing studies. The creation of this web-based program should further facilitate the use of network analysis in developing retrosyntheses of other architecturally complex molecules and enable the identification of an efficient path to their syntheses.

Conclusion

The preparation of the denudatine core and total syntheses of weisacconitine D and liljestrandinine presented here reaffirm the utility of complex molecule synthesis as a driver for the implementation of chemical synthesis strategies that advance the field. Our approach offers a plan for the synthesis of a subset of C-18 and C-19 diterpenoid alkaloids and could enable access to related secondary metabolites including those in the C-20 family. The web-based deterministic graphing program we developed to analyse these topologically complex molecules, which builds on the work of ref. 13, should be useful in other contexts and might be valuable in the analysis and synthesis of other architecturally challenging molecules.

Figure 4 | Selected illustrations for network analysis graphing program. a. Selected molecules of a test set analysed using the newly developed graphing program to detect the maximally bridging ring. The program output is the ’.pdb’ image in grey. The maximally bridging ring is indicated by a combination of grey and purple spheres. The purple spheres represent bridgehead atoms in the maximally bridging ring and the grey spheres represent other atoms in the maximally bridging ring. ChemDraw renditions of the graphing program output are provided for in Fig. 3b. Furthermore, 31 is easily converted to 32, which provides the enantio-enriched intermediate used in the racemic syntheses described in Figs 2a and 3a.

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21. Author Contributions R.S. wrote the manuscript and all authors contributed to the reading and editing of the manuscript. C.J.M., G.M.G., J.C.L., T.P.L., S.K. and K.G.M.K. conducted the chemical reactions. S.K., G.M.G. and C.J.M. conducted the Supplementary Information. T.P.L. and G.M.G. made revisions and contributions to the Supplementary Information. J.Q., R.L. and R.S. conceptualized the graphing program, which was executed by J.Q. and R.L. J.Q., R.L. and R.S. prepared the portion of the Supplementary Information describing the graphing program. C.J.M. completed the synthesis and characterization of weisacintone D, including the conversion of the 12,22 to the 3,2,2 bicyclic aldehyde (135, 135), the formal hydromethoxylation sequence (21 → 23) and the identification of robust conditions for the aryl conjugate addition (7 → 12) with K.G.M.K. and Hofmann rearrangement (13 → 14). G.M.G. developed steps 3–17 in the synthesis of [2,2,2] bicyclic 19, including establishing a large-scale synthesis of 10, synthesis of piperidine 16, Diels-Alder cyclicaddition of 17 and stereoselective reduction of ketone 18. J.C.L. completed the synthesis of lilijestrandine, including synthetic optimization of the nitro as a nitrogen atom surrogate, developing conditions for the conjugate addition of the functionalized arene (7 → 12) and establishing the sequence described for the conversion of 23 → 2 and 15 → 28. T.P.L. contributed to the conceptualization of the synthetic route with substantial synthetic contributions made to the early portion of the synthesis including the establishment of a large-scale synthesis of 10. S.K. developed the antiepileptic Diels-Alder reaction (synthesis of 32, 32) and completed the optimization, scale-up and characterization of lilijestrandine. K.G.M.K. completed the optimization, scale-up and characterization of weisacintone D, and optimized the conjugate addition (7 → 12) with C.J.M.) and the construction of piperidine 16.

22. Author Information Crystallographic data can be obtained free of charge from the Cambridge Crystallographic Data Centre (CCDC; https://s Hands-on: Crystalstructure-MAP, figure reference numbers 1402704, 1402820 and 1403763). The web-based Graphing program we developed is available at http://www.cadlerl.com/maxbridge. Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of this paper. Correspondence and requests for materials should be addressed to R.S. (rsarp@berkeley.edu).