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Navigating Excess Complexity: Total Synthesis of Daphenylline

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Abstract

Retrosynthetic analysis is a framework for designing synthetic routes to complex molecules that generally prioritizes disconnections which reduce molecular complexity. However, strict adherence to this principle can overlook pathways involving highly complex intermediates that can be easily prepared through powerful bond-forming transformations. Herein, we demonstrate this tactic of generating excess complexity, followed by strategic bond-cleavage, as a highly effective approach for the 11-step total synthesis of the *Daphniphyllum* alkaloid daphenylline. To implement this strategy, we accessed a bicyclo[4.1.0]heptane core through a dearomative Buchner cycloaddition, which enabled construction of the seven-membered ring after C–C bond cleavage. Installation of the synthetically challenging quaternary stereocenter methyl group was achieved through a thia-Paternò–Büchi [2 + 2] photocycloaddition followed by stereospecific thietane reduction, further illustrating how building excess complexity can enable desired synthetic outcomes after strategic bond-breaking events. This strategy leveraging bond cleavage transformations should serve as a complement to traditional bond-forming, complexity-generating synthetic strategies.

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Supporting Information

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Experimental procedures, spectroscopic data, and X-ray crystallographic data (PDF)

Accession Codes

CCDC 2297673–2297678 and 2306174 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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A total synthesis of daphenylline was reported by Yang and coworkers in this journal (https://doi.org/10.1021/jacs.3c12741) during the review of this work.

Retrosynthetic analysis is central to planning the synthesis of complex molecules. Starting from a target compound, possible bond disconnections are triaged according to their reduction in structural complexity, ultimately revealing sufficiently simple and commercially available starting materials. Since its introduction by Corey,[1] this analytical framework has since been adapted to retrosynthesis algorithms,[2,3] which have shown emerging value as tools for computer-aided synthesis planning (CASP) of natural products[4,5] and pharmaceutically relevant targets.[6,7] However, while simple complexity scoring functions in CASP tools have proven sufficient for targets of moderate synthetic difficulty, application of network analysis[8–10] remains especially useful for identifying optimal retrosynthetic disconnections in highly complex settings. Through network analysis, identification of the maximally bridged ring as a locus of complexity within the molecular topology can highlight maximally simplifying disconnections and thus serve as a starting point for the development of efficient routes to complex natural products.[9,11–13]

Our laboratory has been engaged in several total syntheses of *Daphniphyllum* alkaloids (Figure 1A).[14] These natural products bear a rich history in organic chemistry and continue to serve as a crucible for advances in synthetic strategy and methodology.[14–20] In particular, daphenylline (**1**), found in the fruits of *Daphniphyllum longeracemosum,*[21] has been the subject of numerous synthetic approaches from the Li,[17,22] Fukuyama,[23] Zhai,[24] Qiu,[25,26] and Lu[27] groups since its isolation. Structurally, **1** possesses a 2-azabicyclo[3.3.l]nonane core appended to a characteristic 5–7–5 ring system and contains six stereogenic centers, one all-carbon quaternary center, and a fused benzenoid core which is unique among its biosynthetically related calyciphylline A-type congeners.[22]

In our network analysis of the daphenylline (**1**) framework, we identified the benzo-fused A-ring to be maximally bridged according to insights from Corey.[8] Retrosynthetically, we reasoned that disconnection of the C1–C2 bond within the maximally bridged ring would eliminate all bridging motifs, leaving the carbon skeleton composed only of fused rings. This pentacyclic intermediate (**7**) could be converted to daphenylline (**1**) through a cationic arylation.

Pentacycle **7** could be simplified to α,β-unsaturated lactam **8**, potentially enabled by conjugate addition to install the requisite all-carbon quaternary center. Inspired by Huisgen,[28] Mander,[29] and others,[30,31] we envisioned that the characteristic seven-membered ring in **8** could arise from a bicyclo[4.1.0]-heptane motif through a 6π-electrocyclic ring opening in the forward sense from **9**. While this disconnection counter-intuitively *increases* structural complexity in the retrosynthetic sense, crucially, it enables the construction of the norcaradiene substructure through a Buchner cycloaddition from the corresponding diazoacetamide (**10**). Here, *structural* complexity (inherent molecular features and connectivity) and *synthetic* complexity[32,33] (synthetic accessibility based on known methods) diverge: a temporary *increase* in structural complexity in order to access a key retron, as has been demonstrated by Baran,[34] Hoffmann,[35] Wender,[36] and others, dramatically simplifies the synthetic sequence and provides entry into this key scaffold of daphenylline (**1**). Finally, α-arylated piperidone **10** could be prepared by dearomative pyridinium arylation from commercial pyridine **11** and acenaphthene (**12**), a readily abundant byproduct of coal tar production.

Our synthesis began with establishment of the piperidone scaffold (Scheme 1). Addition of acenaphthyl Grignard **13** into an activated pyridinium species[37] formed from **11** and Cbz-Cl afforded dihydropyridone **15** in near-quantitative yield after hydrolytic workup. Mild reduction of the dihydropyridone alkene with zinc and acetic acid according to a protocol reported by Comins[38] gave the corresponding piperidone, which was then deprotected by hydrogenolysis to **16** in the same step. With the goal of installing a carbene precursor suitable for the envisaged Buchner cycloaddition, a one-pot adaptation of Fukuyama's protocol[39,40] involving *N*-acetylation, *bis*-tosylhydrazide addition, and tetramethylguanidine (TMG)-mediated double sulfinate elimination converted **16** to diazoacetamide **10** in excellent yield. This initial sequence to **10** from pyridine **11** could be routinely performed on multigram scales.

Next, we aimed to cyclopropanate the acenaphthyl moiety through an intramolecular Buchner reaction. Treatment of diazoacetamide **10** with a panel of transition metal catalysts ($Cu(acac)_2$,[41] $Rh_2(esp)_2$,[42] $Cu(hfacac)_2$[43]) revealed that $Rh_2(OAc)_4$ (1 mol %) was especially effective at promoting the dearomative cycloaddition, affording norcaradiene **9**, which was unambiguously characterized by X-ray crystallographic analysis. While complete minimization of deleterious homodimerization of the Rh-carbenoid species proved challenging, slow addition of **10** into a dilute solution (0.01 M) of catalyst over several hours partially mitigated this competing reaction.[42] Rigorously dry solvent (obtained by the addition of 4 Å MS) also improved the yield of **9** by preventing unwanted O–H bond insertion products.

The Buchner cycloaddition had generated excess structural complexity—now, complexity reduction through selective C–C cleavage to form the seven-membered ring became our next task. Despite the high degree of strain, vinyl cyclopropane **9** remained surprisingly resistant to all bond-cleaving tactics, including radical, cationic, and transition-metal-mediated approaches. Ultimately, thermolysis of **9** through microwave irradiation (250 °C)[28,30] successfully gave rise to cycloheptadiene **17**, establishing the seven-membered ring in addition to installing the distal C10 stereocenter. Mechanistically, we propose that under the reaction conditions, **9** undergoes disrotatory 6π-electrocyclic ring opening to a dearomatized cycloheptatriene intermediate, which is then poised for rearomatization through suprafacial [1,5]-hydride shift to **17**.[28] Crucially, this transformation not only constructs the key seven-membered ring but also accomplishes transannular stereochemical relay to set the remote stereocenter of the indenyl substructure in **17**. Saturation of the disubstituted alkene through palladium-mediated hydrogenation afforded **18** as a crystalline solid, facilitating the unambiguous confirmation of its structure by X-ray diffraction. Subsequent to the 6π-electrocyclic ring opening, hydrogenation and ketone reduction could be adapted to a one-step protocol to deliver **8**.

Our attention then turned to the installation of the all-carbon quaternary center through conjugate methylation of the α,β-unsaturated lactam moiety. Using ketone **18**, chemoselectivity proved to be challenging, with methyl nucleophiles such as Gilman reagents (Me_2CuLi),[44] $Me_3Al/Ni(acac)_2$,[45] or methyl radical sources ($PhthN\text{-}OAc/Ir^{III}$)[46] resulting in competitive reactivity with the ketone or nonspecific decomposition. Methyl surrogates such as Nagata's reagent (Et_2AlCN),[47] 1,3-dithianes,[48] or Corey–Chaykovsky

cyclopropanation[49] were similarly unproductive toward conjugate addition. Although ketone reduction of **18** to the corresponding secondary alcohol (**8**) mitigated this chemoselectivity problem, the α,β-unsaturated lactam remained stubbornly resistant to all attempts at 1,4-addition, likely due to (1) the crowded steric environment of the tetrasubstituted alkene and (2) deprotonation or tautomerization of the C4 position to give deactivated 2-hydroxypyrroles, as evidenced by observed epimerization at this position.

Given our repeated failed attempts to methylate through nucleophilic addition, we envisioned that generation of a triplet biradical from unsaturated lactam 8 could enable productive C–C bond construction through [2 + 2] cycloaddition. However, formation of a four-membered ring would then require subsequent single-atom excision to yield the formal *syn*-hydromethylation product. Inspired by the work of Padwa[50] and Trauner,[51] we anticipated that this could be achieved by cycloaddition of a sulfur-containing fragment followed by subsequent desulfurization. To this end, we performed a thia-Paternò–Büchi [2 + 2] photocycloaddition of **8** with 1,3-dithiolane-2-thione through blue 400 LED irradiation in the presence of an Ir^{III} triplet photosensitizer (**19**)[52] to afford spirocyclic thietane **20**, which was confirmed by X-ray crystallographic analysis. Importantly, this transformation exclusively gave the head-to-tail product, placing the newly formed C–C bond at the desired β-position. In this way, the goal of engaging C5 in C–C bond formation was achieved through excited state photochemistry, whereas ground state reactivity had failed.

Despite our initial plan, desulfurization of the thietane to afford the methyl group proved elusive. Attempts to remove the vestigial sulfur atoms in thietane **20** with Raney Ni reformed **8** through formal retro-[2 + 2] fragmentation. Single-electron reductants such as SmI_2 and LiDBB[39] behaved similarly, returning lactam **8** after fragmentation. However, ring-opening of thietane **20** with $LiAlH_4$, followed by careful quench with Raney Ni as a slurry in water, remarkably gave the desired β-methylated lactam **21** displaying the desired *syn*-stereochemical outcome in 68% yield. Conducting the reaction at elevated temperatures achieved concomitant reduction of the lactam, yielding pyrrolidine **7** following Raney Ni desulfurization in 64% yield.

With the all-fused pentacyclic scaffold successfully established, we directed our efforts to the formation of the final Cl–C2 bond. Initial attempts to cyclize piperidol **7** through Grewe-type cyclization reactions were unfruitful under a variety of ionizing conditions (PP A,[53] Eaton's reagent,[54] H_2SO_4, HCl, HBr,[53] TfOH), perhaps due to the boat conformation required in the piperidine ring for arylation or the susceptibility of the resulting cation to undergo undesirable reactivity. Oxidation of the secondary hydroxy group to the corresponding ketone, however, opened new possibilities: after surveying a set of conditions similar to those to which piperidol **7** was subjected, treatment of ketone **22** with a strong Bronsted acid (48% HBr) at elevated temperatures produced the targeted azabicylo[3.3.1]nonane (**23**) in 67% combined yield as a 1:1.4 mixture of diastereomers with respect to the C18 methyl-bearing stereocenter. The minor β-disposed C18 diastereomer (isolated in 28% yield) was then carried on toward daphenylline through deoxygenation of the bridgehead tertiary alcohol. This was accomplished in a final two-step procedure involving activation as the methyl oxalyl ester[55] (87% yield) followed by Barton–McCombie reduction with Bu_3SnH/AIBN, which successfully gave (±)-daphenylline (**1**) in 57% yield.

After we had completed the total synthesis of **1** in racemic form, we next explored opportunities to render the route enantioselective (Scheme 2). Drawing on work from Hayashi and co-workers,[56] arylzinc reagent **26** was employed in a Rh-mediated 1,4-conjugate addition with dihydropyridone **25**. A short survey of *bis*-phosphine ligands identified (*S,S*)-Ph-BPE as optimal, yielding piperidone **27** in 60% yield and 99% *ee* (see Supporting Information for full optimization). Derivatization of the resulting enantioenriched pyridone to the ferrocene amide[57,28] enabled assignment of the absolute configuration through X-ray crystallography, with the Flack parameter near zero. Alpha-methylation of pyridone **27** was carried out with LiHMDS and methyl triflate affording the corresponding piperidone (**29**, 98% *ee*) without erosion of enantiopurity. Hydrogenolysis of the −CBz protecting group afforded piperidone **16** with a minor loss of enantioenrichment (93% *ee*), which could be advanced further to obtain (−)-**1**.

Given its key role in the completion of the synthesis of **1** and the unusual, yet fortuitous, diastereoselectivity outcome of the reduction sequence of thietane **20**, we studied this reaction in greater detail (Scheme 3). Treatment of **20** with $LiAlH_4$, followed by quenching with HCl, afforded thiol **30**, suggesting that this thiol is formed *in situ* prior to Raney Ni desulfurization. To probe the origin of the *syn*-stereochemical outcome and the role of the hydride source, isotopic labeling studies were carried out using $LiAlD_4$, yielding trideuterated compound **31** after desulfurization. While the C21 methyl contained two deuterium atoms (arising from reduction of the thioketal), the C6 position alpha to the lactam carbonyl was unexpectedly also deuterated. This suggested that hydride-mediated thietane opening, rather than the desulfurization step, is responsible for the introduction of the proton at C6 (and therefore the resulting *syn*-stereochemistry). Taken together, we propose that $LiAlH_4$ attacks the strained sulfur atom on thietane **20** to give enolate **32**, which undergoes kinetic protonation by the pendant thiol in a “reduction-rebound” mechanistic sequence. After exhaustive reduction of the thio-orthoformate to primary thiolate **30**, desulfurization with Raney Ni leads to **21**. This transformation ultimately achieves a formal *syn*-hydromethylation of unsaturated lactam **8** over two steps, uniquely enabled by the stereospecific nature of the thia-Paternò–Büchi [2 + 2] photocycloaddition and $LiAlH_4$-mediated reduction-rebound transformations.

In summary, we have developed a concise, 11-step total synthesis of daphenylline (**1**) from commercially available starting materials. Our synthesis represents the shortest preparation of this *Daphniphyllum* alkaloid to date. Strategic modifications to our initial synthetic plan proved to be essential to the completion of the synthesis. First, in the face of unfruitful attempts to install the C21 methyl group by conjugate addition, we turned to a thia-Paternò–Büchi [2 + 2]/reduction sequence to achieve formal *syn*-hydromethylation across the tetrasubstituted alkene. Second, even though a direct cationic arylation of piperidol **7** to **1** via Grewe-type cyclization would have been an ideal final step, the cyclization of piperidone **22**, followed by deoxygenation, ultimately enabled access to daphenylline (**1**). Although future methodological advances might provide direct, one-step, solutions to these synthetic challenges, lessons from this synthesis suggest that rapid generation of target-relevant molecular complexity often pairs well with powerful bond-cleavage tactics to achieve the desired synthetic outcomes. We expect that the continued development of

novel bond-cleavage transformations will have a broad impact as an essential complement to traditional bond forming complexity-generating synthetic strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

(1). Corey EJ; Cheng X-M The Logic of Chemical Synthesis; John Wiley & Sons, Ltd: 1996.

(2). Sun Y; Sahinidis NV Computer-Aided Retrosynthetic Design: Fundamentals, Tools, and Outlook. Curr. Opin. Chem. Eng 2022, 35, 100721.

(3). Molga K; Szymkuć S; Grzybowski BA Chemist Ex Machina: Advanced Synthesis Planning by Computers. Acc. Chem. Res 2021, 54, 1094–1106. [PubMed: 33423460]

(4). Lin Y; Zhang R; Wang D; Cernak T Computer-Aided Key Step Generation in Alkaloid Total Synthesis. Science 2023, 379, 453–457. [PubMed: 36730413]

(5). Mikulak-Klucznik B; Gołębiowska P; Bayly AA; Popik O; Klucznik T; Szymkuć S; Gajewska EP; Dittwald P; Staszewska-Krajewska O; Beker W; Badowski T; Scheidt KA; Molga K; Mlynarski J; Mrksich M; Grzybowski BA Computational Planning of the Synthesis of Complex Natural Products. Nature 2020, 588, 83–88. [PubMed: 33049755]

(6). Klucznik T; Mikulak-Klucznik B; McCormack MP; Lima H; Szymkuć S; Bhowmick M; Molga K; Zhou Y; Rickershauser L; Gajewska EP; Toutchkine A; Dittwald P; Startek MP; Kirkovits GJ; Roszak R; Adamski A; Sieredzińska B; Mrksich M; Trice SLJ; Grzybowski BA Efficient Syntheses of Diverse, Medicinally Relevant Targets Planned by Computer and Executed in the Laboratory. Chem. 2018, 4, 522–532.

(7). Coley CW; Thomas DA; Lummiss JAM; Jaworski JN; Breen CP; Schultz V; Hart T; Fishman JS; Rogers L; Gao H; Hicklin RW; Plehiers PP; Byington J; Piotti JS; Green WH; Hart AJ; Jamison TF; Jensen KF A Robotic Platform for Flow Synthesis of Organic Compounds Informed by AI Planning. Science 2019, 365, No. eaax1566. [PubMed: 31395756]

(8). Corey EJ; Howe WJ; Orf HW; Pensak DA; Petersson G General Methods of Synthetic Analysis. Strategic Bond Disconnections for Bridged Polycyclic Structures. J. Am. Chem. Soc 1975, 97, 6116–6124.

(9). Marth CJ; Gallego GM; Lee JC; Lebold TP; Kulyk S; Kou KGM; Qjn J; Lilien R; Sarpong R Network-Analysis-Guided Synthesis of Weisaconitine D and Liljestrandinine. Nature 2015, 528, 493–498. [PubMed: 26675722]

(10). Doering NA; Sarpong R; Hoffmann RW A Case for Bond-Network Analysis in the Synthesis of Bridged Polycyclic Complex Molecules: Hetidine and Hetisine Diterpenoid Alkaloids. Angew. Chem., Int. Ed 2020, 59, 10722–10731.

(11). Owens KR; McCowen SV; Blackford KA; Ueno S; Hiraoka Y; Weber M; Sarpong R Total Synthesis of the Diterpenoid Alkaloid Arcutinidine Using a Strategy Inspired by Chemical Network Analysis. J. Am. Chem. Soc 2019, 141, 13713–13717. [PubMed: 31276621]

(12). Haider M; Sennari G; Eggert A; Sarpong R Total Synthesis of the Cephalotaxus Norditerpenoids (±)-Cephanolides A-D. J. Am. Chem. Soc 2021, 143, 2710–2715. [PubMed: 33577317]

(13). Lusi RF; Sennari G; Sarpong R Total Synthesis of Nine Longiborneol Sesquiterpenoids Using a Functionalized Camphor Strategy. Nat. Chem 2022, 14 (4), 450–456. [PubMed: 35165424]

(14). Hugelshofer CL; Palani V; Sarpong R Calyciphylline B-Type Alkaloids: Total Syntheses of (−)-Daphlongamine H and (−)-lsodaphlongamine H. J. Am. Chem. Soc 2019, 141, 8431–8435. [PubMed: 31074980]

(15). Heathcock CH Nature Knows Best: An Amazing Reaction Cascade Is Uncovered by Design and Discovery. Proc. Natl. Acad. Sci. U.S.A 1996, 93, 14323–14327. [PubMed: 8962049]

(16). Chattopadhyay AK; Hanessian S Recent Progress in the Chemistry of *Daphniphyllum* Alkaloids. Chem. Rev 2017, 117, 4104–4146. [PubMed: 28205435]

(17). Lu Z; Li Y; Deng J; Li A Total Synthesis of the Daphniphyllum Alkaloid Daphenylline. Nat. Chem 2013, 5, 679–684. [PubMed: 23881499]

(18). Zhang W; Lu M; Ren L; Zhang X; Liu S; Ba M; Yang P; Li A Total Synthesis of Four Classes of *Daphniphyllum* Alkaloids. J. Am. Chem. Soc 2023, 145, 26569–26579. [PubMed: 38032297]

(19). Heathcock CH; Davidsen SK; Mills SG; Sanner MA *Daphniphyllum* Alkaloids. 10. Classical Total Synthesis of Methyl Homodaphniphyllate. J. Org. Chem 1992, 57, 2531–2544.

(20). Weiss ME; Carreira EM Total Synthesis of (+)-Daphmanidin E. Angew. Chem., Int. Ed 2011, 50, 11501–11505.

(21). Zhang Q; Di Y-T; Li C-S; Fang X; Tan C-J; Zhang Z; Zhang Y; He H-P; Li S-L; Hao X-J Daphenylline, a New Alkaloid with an Unusual Skeleton, from *Daphniphyllum Longeracemosum*. Org. Lett 2009, 11, 2357–2359. [PubMed: 19438261]

(22). Chen Y; Zhang W; Ren L; Li J; Li A Total Syntheses of Daphenylline, Daphnipaxianine A, and Himalenine D. Angew. Chem., Int. Ed 2018, 57, 952–956.

(23). Yamada R; Adachi Y; Yokoshima S; Fukuyama T Total Synthesis of (−)-Daphenylline. Angew. Chem., Int. Ed 2016, 55, 6067–6070.

(24). Chen X; Zhang H-J; Yang X; Lv H; Shao X; Tao C; Wang H; Cheng B; Li Y; Guo J; Zhang J; Zhai H Divergent Total Syntheses of (−)-Daphnilongeranin B and (−)-Daphenylline. Angew. Chem., Int. Ed 2018, 57, 947–951.

(25). Xu B; Wang B; Xun W; Qiu FG Total Synthesis of (−)-Daphenylline. Angew. Chem., Int. Ed 2019, 58 (17), 5754–5757.

(26). Wang B; Xu B; Xun W; Guo Y; Zhang J; Qiu FG A General Strategy for the Construction of Calyciphylline A-Type Alkaloids: Divergent Total Syntheses of (−)-Daphenylline and (−)-Himalensine A. Angew. Chem., Int. Ed 2021, 60, 9439–9443.

(27). Cao M-Y; Ma B-J; Gu Q-X; Fu B; Lu H-H Concise Enantioselective Total Synthesis of Daphenylline Enabled by an Intramolecular Oxidative Dearomatization. J. Am. Chem. Soc 2022, 144, 5750–5755. [PubMed: 35289615]

(28). Huisgen R; Juppe G Benzo-Norcaradien-Carbonsäure Und Benzo-Cycloheptatrien-Carbonsäure. Chem. Ber 1961, 94, 2332–2349.

(29). Frey B; Wells AP; Rogers DH; Mander LN Synthesis of the Unusual Diterpenoid Tropones Hainanolidol and Harringtonolide. J. Am. Chem. Soc 1998, 120, 1914–1915.

(30). Jones DW Thermal Rearrangements of Benzobicyclononatrienes (1,4-Propeno-1,4-Dihydronaphthalenes) to Benzobarbaralanes; Intramolecular Diels-Alder Rather than Intramolecular Ene Reactions. J. Chem. Soc., Chem. Commun 1989, 19, 1481–1483.

(31). Reisman S; Nani R; Levin S Buchner and Beyond: Arene Cyclopropanation as Applied to Natural Product Total Synthesis. Synlett 2011, 2011, 2437–2442.

(32). Li J; Eastgate MD Current Complexity: A Tool for Assessing the Complexity of Organic Molecules. Org. Biomol. Chem 2015, 13, 7164–7176. [PubMed: 25962620]

(33). Coley CW; Rogers L; Green WH; Jensen KF SCScore: Synthetic Complexity Learned from a Reaction Corpus. J. Chem. Inf Model 2018, 58, 252–261. [PubMed: 29309147]

(34). Cherney EC; Green JC; Baran PS Synthesis of Ent-Kaurane and Beyerane Diterpenoids by Controlled Fragmentations of Overbred Intermediates. Angew. Chem., Int. Ed 2013, 52, 9019–9022.

(35). Hoffmann RW Elements of Synthesis Planning; Springer: Heidelberg, 2009.

(36). Wender PA; Howbert JJ Synthetic Studies on Arene-Olefin Cycloadditions: Total Synthesis of (.+−.)-.Alpha.-Cedrene. J. Am. Chem. Soc 1981, 103, 688–690.

(37). Connns DL; Brown JD Addition of Grignard Reagents to 1-Acyl-4-Methoxypyridinum Salts. An Approach to the Synthesis of Quinolizidinones. Tetrahedron Lett. 1986, 27, 4549–4552.

(38). Comins DL; Brooks CA; Ingalls CL Reduction of N-Acyl-2,3-Dihydro-4-Pyridones to N-Acyl-4-Piperidones Using Zinc/Acetic Acid. J. Org. Chem 2001, 66, 2181–2182. [PubMed: 11300923]

(39). Toma T; Shimokawa J; Fukuyama TN,N'-Ditosylhydrazine: A Convenient Reagent for Facile Synthesis of Diazoacetates. Org. Lett 2007, 9, 3195–3197. [PubMed: 17629296]

(40). Kaupang A; Bonge-Hansen T α-Bromodiazoacetamides-a New Class of Diazo Compounds for Catalyst-Free, Ambient Temperature Intramolecular C-H Insertion Reactions. Beilstein J. Org. Chem 2013, 9, 1407–1413. [PubMed: 23946835]

(41). Mo S; Xu J Chemospecific Intramolecular Buchner Reaction Catalyzed by Copper (II) Acetylacetonate. ChemCatChem. 2014, 6, 1679–1683.

(42). Zeng Q; Dong K; Pei C; Dong S; Hu W; Qiu L; Xu X Divergent Construction of Macrocyclic Alkynes via Catalytic Metal Carbene C(Sp2)-H Insertion and the Buchner Reaction. ACS Catal. 2019, 9, 10773–10779.

(43). Levin S; Nani RR; Reisman SE Enantioselective Total Synthesis of (+)-Salvileucalin B. J. Am. Chem. Soc 2011, 133, 774–776. [PubMed: 21174417]

(44). Wright SW; Choi C; Chung S; Boscoe BP; Drozda SE; Mousseau JJ; Trzupek JD Reversal of Diastereoselection in the Conjugate Addition of Cuprates to Unsaturated Lactams. Org. Lett 2015, 17, 5204–5207. [PubMed: 26485576]

(45). Flemming S; Kabbara J; Nickisch K; Neh H; Westermann J Nickel-Catalysed Conjugate Addition of Trimethylaluminum to Sterically Hindered α,β-Unsaturated Ketones. Synthesis 1995, 1995, 317–320.

(46). Leibler IN-M; Tekle-Smith MA; Doyle AG A General Strategy for C(Sp3)-H Functionalization with Nucleophiles Using Methyl Radical as a Hydrogen Atom Abstractor. Nat. Commun 2021, 12, 6950. [PubMed: 34845207]

(47). Nagata W; Yoshioka M; Hirai S Eine Neue Hydro-cyanierungs-Methode. Tetrahedron Lett. 1962, 3, 461–466.

(48). Brown CA; Yamaichi A Induced Conjugate Addition of Simple 2-Lithio-1,3-Dithians to Cyclic α,β-Unsaturated Ketones. J. Chem. Soc., Chem. Commun 1979, 3, 100–101.

(49). Corey EJ; Chaykovsky M Dimethyloxosulfonium Methylide ((CH3)-2SOCH2) and Dimethylsulfonium Methylide ((CH3)-2SCH2). Formation and Application to Organic Synthesis. J. Am. Chem. Soc 1965, 87, 1353–1364.

(50). Padwa A; Jacquez MN; Schmidt A An Approach toward Azacycles Using Photochemical and Radical Cyclizations of *N*-Alkenyl Substituted 5-Thioxopyrrolidin-2-ones. J. Org. Chem 2004, 69, 33–45. [PubMed: 14703376]

(51). Winter N; Trauner D Thiocarbonyl Ylide Chemistry Enables a Concise Synthesis of (±)-Hippolachnin A. J. Am. Chem. Soc 2017, 139, 11706–11709. [PubMed: 28753024]

(52). He J; Bai Z-Q; Yuan P-F; Wu L-Z; Liu Q Highly Efficient Iridium-Based Photosensitizers for Thia-Paternò-Büchi Reaction and Aza-Photocyclization. ACS Catal. 2021, 11, 446–455.

(53). Comins DL; Zhang Y; Joseph SP Enantiopure N-Acyldihydropyridones as Synthetic Intermediates: Asymmetric Synthesis of Benzomorphans. Org. Lett 1999, 1, 657–660. [PubMed: 10823197]

(54). Eaton PE; Carlson GR; Lee JT Phosphorus Pentoxide-Methanesulfonic Acid. Convenient Alternative to Polyphosphoric Acid. J. Org. Chem 1973, 38, 4071–4073.

(55). Dolan SC; MacMillan J A New Method for the Deoxygenation of Tertiary and Secondary Alcohols. J. Chem. Soc., Chem. Commun 1985, 22, 1588–1589.

(56). Shintani R; Tokunaga N; Doi H; Hayashi T A New Entry of Nucleophiles in Rhodium-Catalyzed Asymmetric 1,4-Addition Reactions: Addition of Organozinc Reagents for the Synthesis of 2-Aryl-4-Piperidones. J. Am. Chem. Soc 2004, 126, 6240–6241. [PubMed: 15149215]

(57). Holstein PM; Holstein JJ; Escudero-Adán EC; Baudoin O; Echavarren AM Ferrocene Derivatives of Liquid Chiral Molecules Allow Assignment of Absolute Configuration by X-Ray Crystallography. Tetrahedron: Asymmetry 2017, 28, 1321–1329.

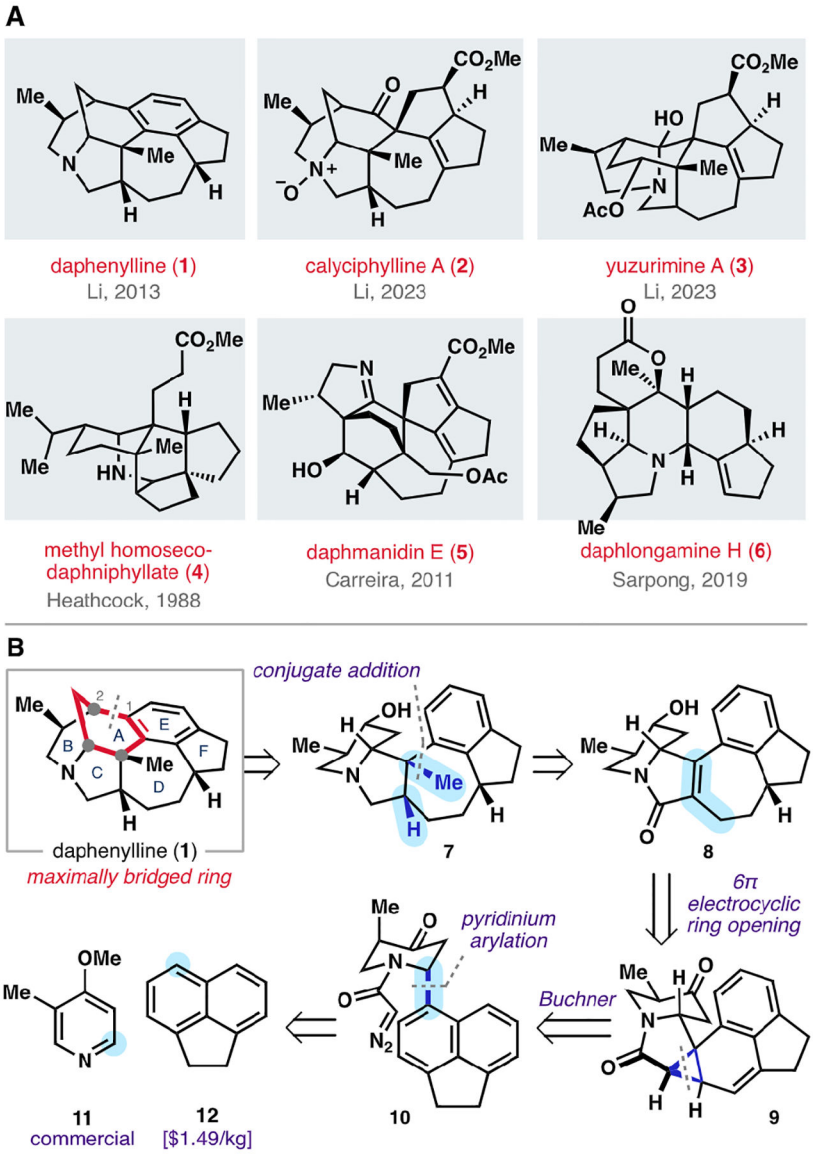
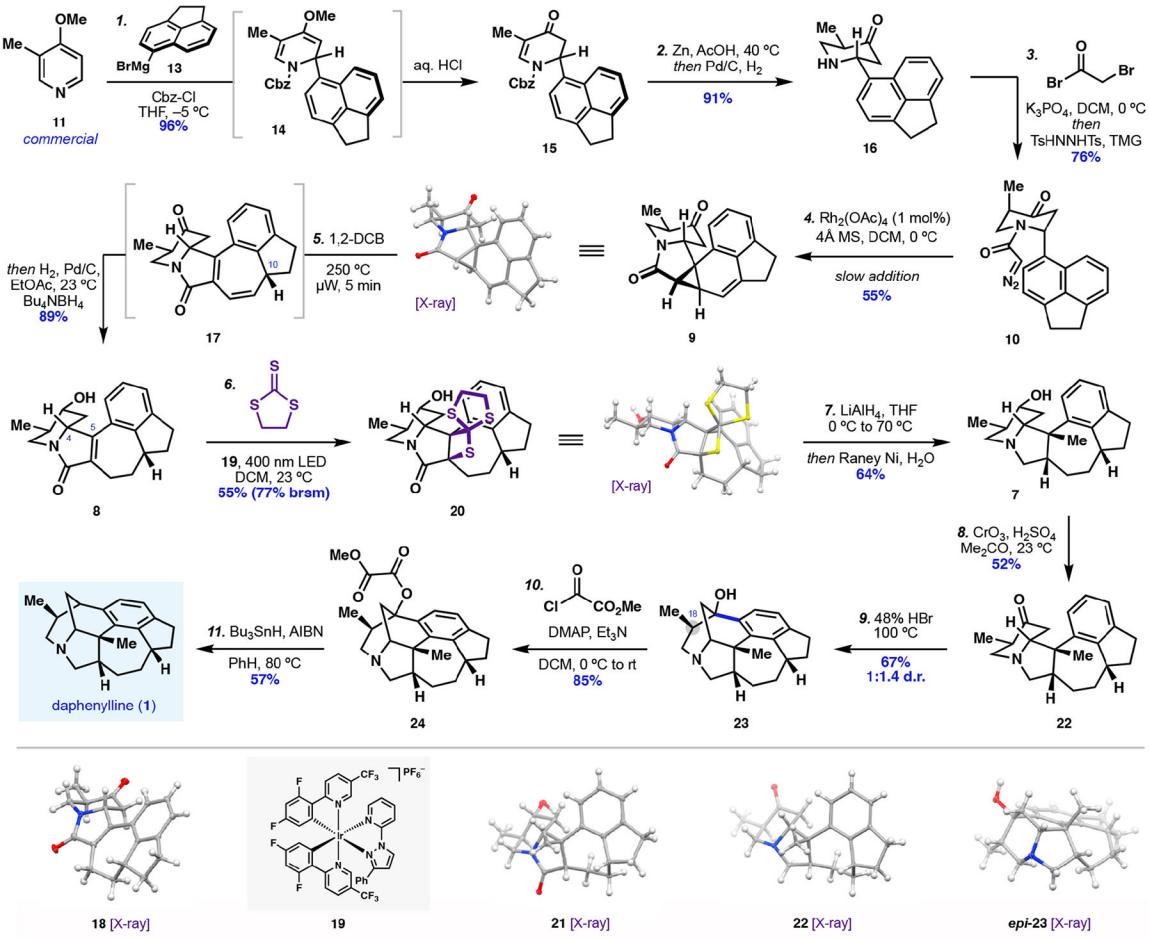


Figure 1.

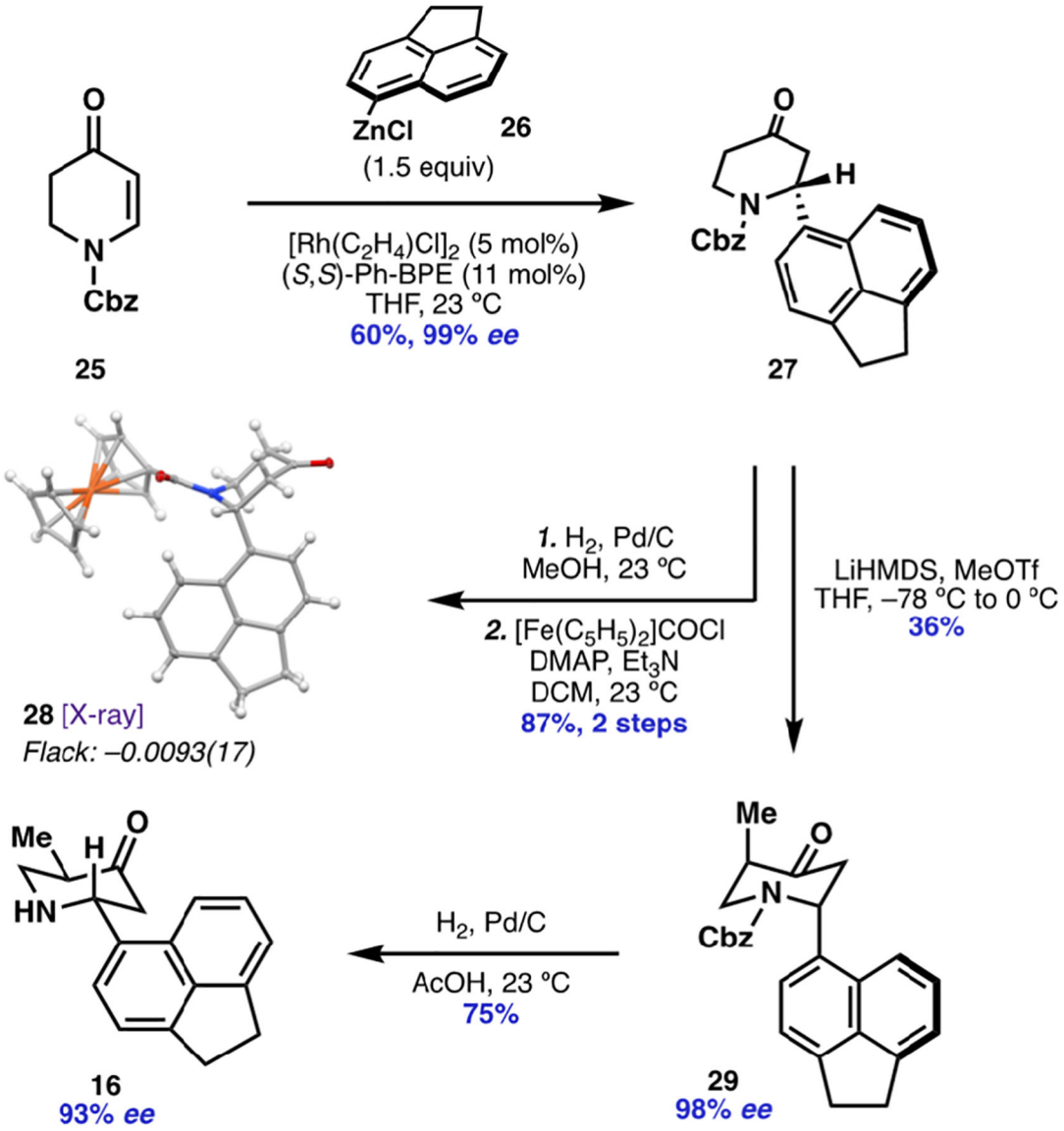
(A) Selected examples of *Daphniphyllum* alkaloids. (B) Retrosynthesis of daphenylline (**1**).



Scheme 1.

Total Synthesis of Daphenylline[a]

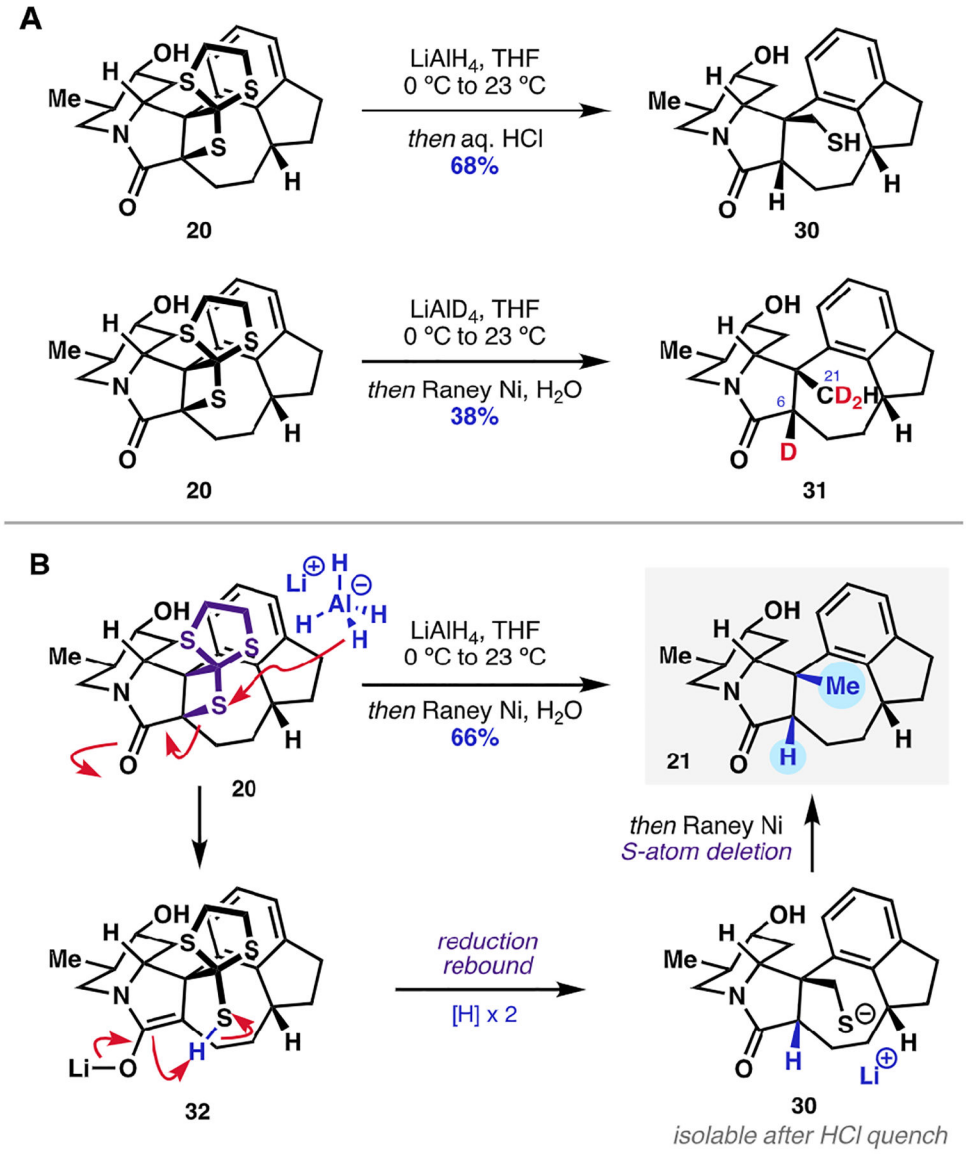
[a]***See*** the Supporting Information for detailed procedures and characterization data.



Scheme 2.

Development of an Enantioselective Rh-Catalyzed 1,4-Conjugate Addition[a]

[a]See the Supporting Information for detailed procedures and characterization data.



Scheme 3.

Thietane Reduction Mechanistic Experiments [a]

[a]See the Supporting Information for detailed procedures and characterization data.