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Total Synthesis of Lycopladine A and Carinatine A via a Base-Mediated Carbocyclization

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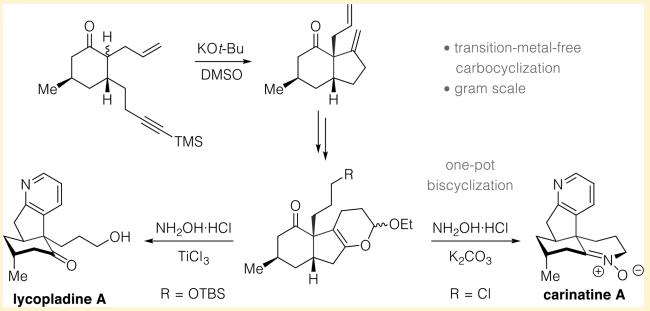
Supporting Information

ABSTRACT: A concise, enantioselective synthesis of lycopladine A and carinatine A is presented. Our synthetic approach hinges on the recently developed mild carbocyclization of ynones to furnish the hydrindane core of the alkaloids. Their pyridine ring was efficiently installed using the Ciufolini method. Both heterocycles of carinatine A, a rare naturally occurring nitrone, were formed in a single operation.



Club mosses, such as *Lycopodium complanatum* and *Lycopodium carinatum*, are a rich source of structurally attractive and bioactive alkaloids, a sample of which is shown in Figure 1.[1−3] Lycoposerramine R (**1**), which features a previously unknown skeleton with a pyridone and piperidine heterocycle, was isolated by Takayama and co-workers in 2009.[4] Its simplified pyridine congener lycopladine A (**2**) was isolated from *L. complanatum* in 2006 and showed modest cytotoxicity against murine lymphoma cells.[5] Carinatine A (**3**) was recently obtained from *L. carinatum*.[6] Lycoposerramine R (**1**), lycopladine A (**2**), and carinatine A (**3**) share a common carbocyclic core that consists of a *cis*-hydrindane with a methyl substituent and a three-carbon side chain. In lycoposerramine R, this side chain is incorporated in the piperidine ring, which is oxidized to a nitrone in the case of carinatine A.

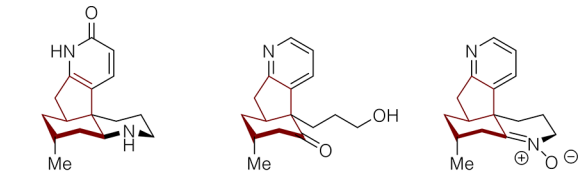


Figure 1. Alkaloids isolated from *Lycopodium serratum*, *L. complanatum*, and *L. carinatum*.

Because of their compact and beautiful structures, combined with some biological activity, these *Lycopodium* alkaloids have received a significant amount of attention from the synthetic community (Figure 2). Toste and co-workers[7] accomplished the first synthesis of (+)-lycopladine A via a gold-catalyzed 5-*endo-dig* cyclization of a silyl enol ether onto an iodoalkyne. In 2010, Martin and co-workers[8] accomplished the shortest synthesis of (±)-lycopladine A via a palladium-catalyzed enolate arylation. In 2011, Hiroya et al.[9] utilized a desymmetrization of a 1,3-cyclohexanedione via diastereoselective ketalization for an enantioselective synthesis. More recently, Yang and co-workers[10] and Meng[11] developed aldol-based approaches to furnish the central quaternary stereocenter of (+)-lycopladine A. Because of the convergent nature of his approach, Meng was able to access the target in eight steps. The first synthesis of (+)-carinatine from a common intermediate was also reported, making use of a complex reaction cascade to furnish the pyridine ring from a dieneone. Very recently, Liu and You[12] published a conceptually different approach to (−)-lycopladine A. An Ir-catalyzed allylic substitution with a 2-methylpyridine nucleophile was utilized to set the first stereocenter. The five-membered ring was furnished with a Heck reaction, and finally, the six-membered ring was closed via aldol condensation.[12]

We now wish to report our own approach toward lycopladine A and carinatine A, which exploits the carbocyclization of ynones (**4**) recently developed in our laboratory (Scheme 1).[13] Our method gives access to ring systems with a quaternary stereocenter next to a carbonyl group (**5**) and proceeds under mild basic conditions (KO*t*-Bu in DMSO at room temperature). It corresponds to the classic Conia−Ene reaction, which requires harsh thermal conditions, and modern transition metal-mediated variants thereof.[14−18] As an initial demonstration of the utility of this cyclization, we completed a short enantioselective synthesis of the *Lycopodium* alkaloid lycoposerramine R (**1**) as well as a formal synthesis of sieboldine A (**6**).[4,19] The *exo*-alkene obtained in the key cyclization could be used to directly mount the pyridone

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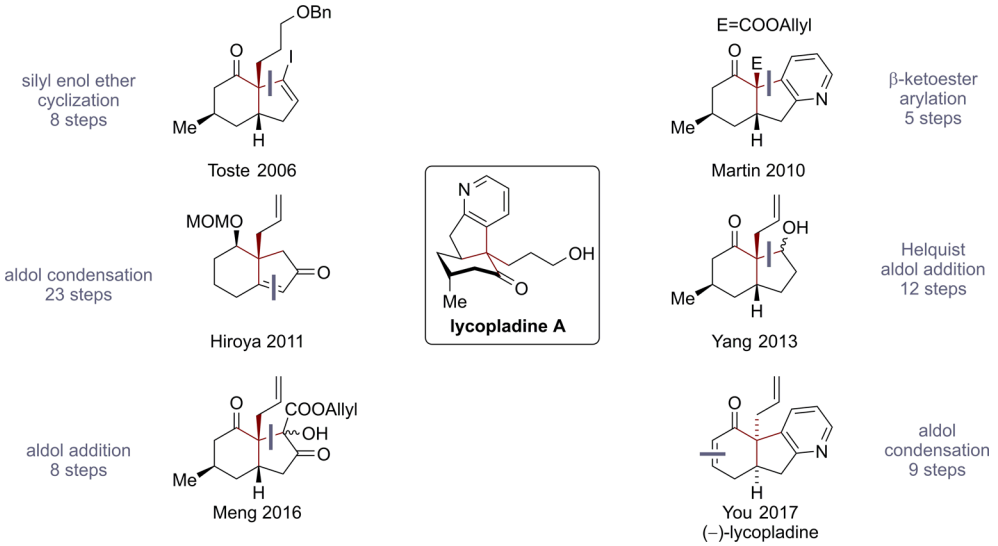
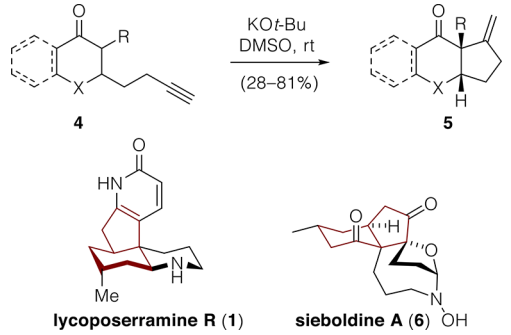


Figure 2. Previous approaches to the hydrindane core of lycopladine A with a total step count from known compounds.

Scheme 1. Ynone Carbocyclization under Mild Conditions

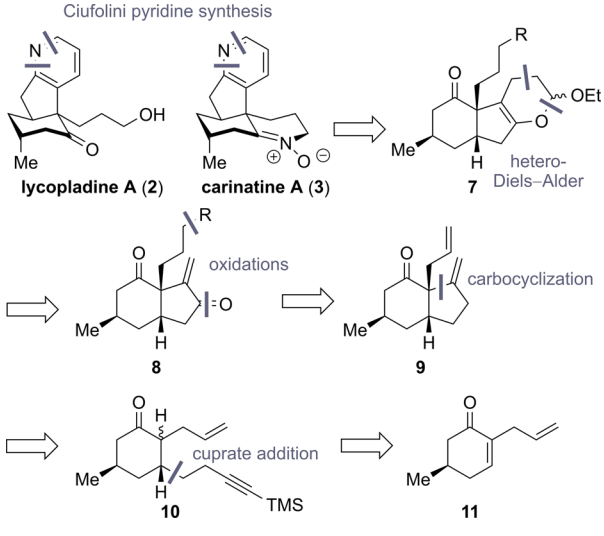


moiety of lycoposerramine R, significantly reducing the total step count relative to those of earlier approaches.[20−22]

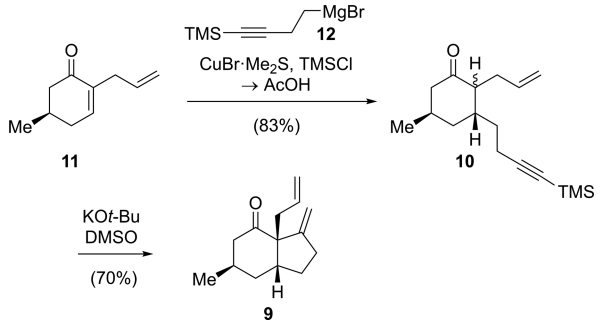
Our retrosynthetic analysis of lycopladine A and carinatine A is shown in Scheme 2. We planned to furnish their characteristic pyridine ring using a Ciufolini pyridine synthesis involving an acetal **7**, which could be obtained through a hetero-Diels−Alder cycloaddition from an enone **8**. The enone moiety would be installed through a selective allylic oxidation of hydrindane **9**, which would be accessible via carbocyclization of **10**.[13] This compound, in turn, could be traced back to the known enone **11**.[23−25]

Hydrindanone **9**, which had been previously described in the context of our formal synthesis of sieboldine A,[13] was prepared on a gram scale using a shortened route (Scheme 3). Conjugate

Scheme 2. Retrosynthetic Analysis of Lycopladine A and Carinatine A



Scheme 3. Two-Step Procedure To Access Hydrindanone 9



addition of **12** followed by treatment with acetic acid gave TMS-protected alkyne **10**. We reasoned that the cyclization conditions would rapidly remove the trimethylsilyl group. Therefore, we directly submitted **10** to the basic reaction conditions. Indeed, substoichiometric amounts of potassium *tert*-butoxide gave the desired product **9** in 70% yield. The hydrindanone core of the alkaloids featuring the central quaternary stereocenter could thus be obtained in two instead of three steps from enone **11**.

To minimize protecting group manipulations, we first investigated whether direct allylic oxidation of this substrate was possible, anticipating the steric hindrance conferred by the quaternary stereocenter would lead to selective oxidation at C-5 over C-11 (Scheme 4). We subjected **9** to a wide range of allylic oxidation conditions but were never able to obtain more than traces of the desired product **15**, which can be rationalized by competing Riley oxidation at C-14 or at the other allylic site (C-11). Since direct oxidation failed, we decided to reinvestigate the previously described hydroboration−oxidation

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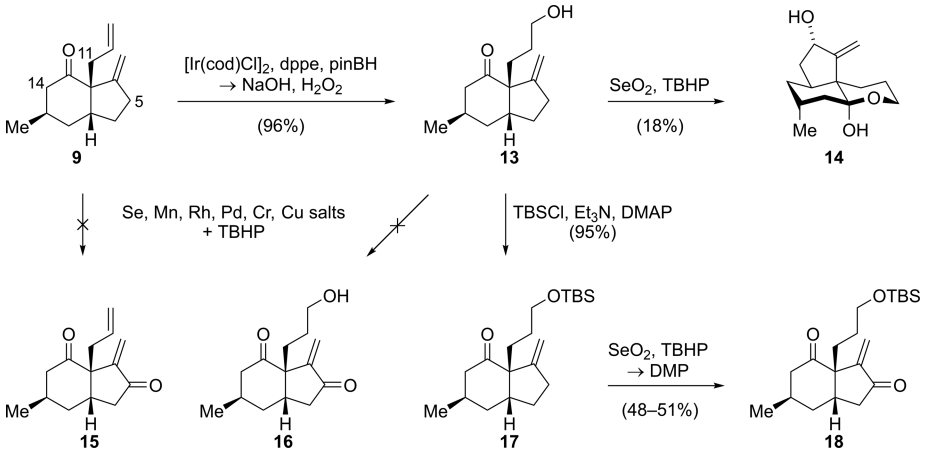
Scheme 4. Attempts To Oxidize the Cyclization Product 9

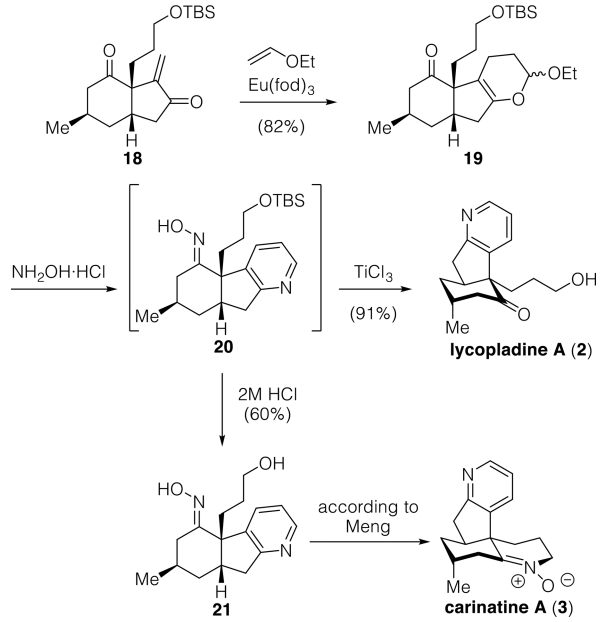


sequence to give **13**.[13] While organoboranes such as Cy_2BH, Sia_2BH, 9-BBN, $BH_3{\cdot}SMe_2$, and $BH_3{\cdot}THF$ delivered the alcohol after oxidation with $NaOH/H_2O_2$ or sodium perborate, they proved to give low or variable yields on larger scale, as did reactions using Wilkinson's catalyst with catecholborane or pinacolborane. Eventually, we found that an iridium-based catalyst {$[Ir(cod)Cl]_2$/dppe} in combination with pinacolborane[26] cleanly and rapidly gave an intermediate boronic ester (not isolated) that could be transformed to the alcohol in almost quantitative yield upon oxidative workup. Allylic oxidation of **13** using SeO_2/*tert*-butyl hydroperoxide (TBHP) gave the tricyclic hemiacetal **14** in low yield. Interestingly, the cyclization occurred exclusively under these reaction conditions, whereas attempts to oxidize **13** to enone **16** with combinations of metal salts and TBHP mainly led to decomposition.

To our disappointment, we were unable to oxidize the allylic alcohol **14** further. Therefore, we decided to protect the hydroxy group in **13** as a silyl ether.[27] This transformation proved to be surprisingly difficult under standard conditions. Eventually, it was found that TBSCl/Et_3N/DMAP in DMF at −15 °C gave product **17** in excellent yield. After extensive screening of the subsequent allylic oxidation, we found that SeO_2/TBHP furnished a mixture of allylic alcohol and ketone **18**, which was fully oxidized *in situ* using Dess−Martin periodinane (DMP). While the yield was moderate, it supplied ample material to finish our synthesis (Scheme 5). A hetero-Diels−Alder reaction with ethyl vinyl ether catalyzed by $Eu(fod)_3$ yielded acetal **19**,[28,29] which was subsequently used to reach both lycopladine A (**2**) and carinatine A (**3**). Treatment with hydroxylamine hydrochloride in refluxing acetonitrile furnished **20** *in situ*,[28] which was directly converted to lycopladine A (**2**) through TBS deprotection and oxime cleavage with $TiCl_3$.[30] Our synthetic material, accessed in seven steps from enone **11**, was identical with the material obtained by isolation from natural sources in all respects.[5]

Having accomplished a total synthesis of lycopladine A, we turned to the synthesis of carinatine A.[6] When $TiCl_3$ was replaced with aqueous HCl, only the TBS group was removed to give **21** in moderate yield. This oxime could be converted to carinatine A (**3**) by Meng's method via a Mitsunobu-type reaction.[11] While this route provided a formal synthesis of the natural product, we wanted to probe a different, potentially more efficient route (Scheme 6). In an alternative end game, both the pyridine and the cyclic nitrone would be closed in the same step. To this end, primary alcohol **13** was converted to chloride **22** using triphosgene and triethylamine,[31] which outperformed classical $SOCl_2$ or Appel conditions. *In situ* oxidation of the allylic alcohol/enone mixture under our previously established conditions occurred in low yields when using DMP. However, pyridinium chlorochromate (PCC) smoothly gave the desired enone **23**.

Scheme 5. End Game of the Lycopladine A Synthesis and Formal Synthesis of Carinatine A



With the enone in hand, we proceeded to the hetero-Diels−Alder reaction. Once more using ethyl vinyl ether and catalytic quantities of $Eu(fod)_3$, the enol acetal **24** was obtained in good yield. This mode intermediate was then treated with hydroxylammonium chloride and refluxed in acetonitrile. After full conversion to the pyridine **25** had occurred, we added solid potassium carbonate and water.[32,33] After 2 h at reflux, clean cyclization was observed and carinatine A (**3**) was isolated in 75% yield. Adding potassium carbonate from the start completely inhibited the pyridine synthesis, and very little oxime to nitrone cyclization was observed in the absence of a base. In this way, we were able to access carinatine A in seven steps overall from enone **11**.

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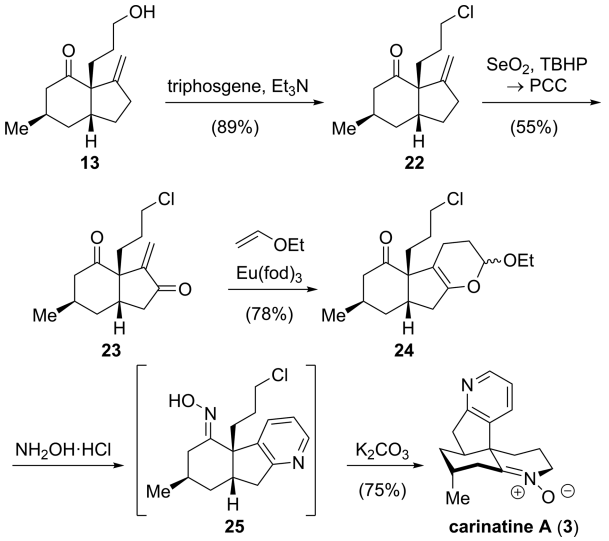
Scheme 6. Completion of the Synthesis of Carinatine A via Double Cyclization



In summary, we have used a recently developed carbocyclization reaction to access the two aromatic fawcettimine-type *Lycopodium* alkaloids, lycopladine A and carinatine A. In both cases, carefully choreographed reaction sequences that minimize protecting group manipulations allowed for the most concise, enantioselective routes to date. The Ciufolini method not only proved to be a powerful way to install the pyridine ring of the alkaloids but also was compatible with concomitant oxime hydrolysis and nitrone formation.

EXPERIMENTAL SECTION

All reactions were performed with standard Schlenk techniques under an atmosphere of nitrogen in oven-dried glassware (100 °C oven temperature) that was further dried using a heat gun (set to 650 °C) for all water-sensitive reactions. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled over sodium and benzophenone prior to use. Triethylamine (Et_3N) and dichloromethane (CH_2Cl_2) were distilled from calcium hydride. *N*,*N*-Dimethylformamide (DMF), acetonitrile (MeCN), and methanol (MeOH) were purchased from Acros Organics as "extra dry" reagents under an inert gas atmosphere and over molecular sieves. All other reagents were purchased from commercial sources and used without further purification. Reaction progress was monitored by analytical thin-layer chromatography (TLC), which was performed using precoated glass plates (silica gel 60 F_{254}) from Merck. Visualization was achieved by exposure to ultraviolet light (254 nm) where applicable followed by staining with a potassium permanganate solution. Flash column chromatography was performed using Merck silica gel (40−63 μm particle size). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian 400, Inova 400, or Varian 600 spectrometer. Chemical shifts (δ scale) are expressed in parts per million and calibrated using a residual protic solvent as an internal reference ($CHCl_3$, δ 7.26; CD_2HOD, δ 3.31). Data for ^{1}H NMR spectra are reported as follows: chemical shift (ppm) [multiplicity, coupling constants (hertz), integration]. Couplings are expressed as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; or combinations thereof. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on the same spectrometers at 100 and 150 MHz (±1 MHz variance). Carbon chemical shifts (δ scale) are also expressed in parts per million and are referenced to the central carbon resonances of the solvents ($CDCl_3$, δ 77.16; MeOH-d_4, δ 49.00). To assign the ^{1}H and ^{13}C NMR spectra, a range of two-dimensional NMR experiments (COSY, HMQC, HMBC, and NOESY) was used as appropriate. Infrared (IR) spectra were recorded on a PerkinElmer Spectrum BX II instrument (FTIR System) equipped with an attenuated total reflection (ATR) measuring unit. IR data are reported in frequency of absorption (inverse centimeters). Mass spectroscopy (MS) experiments were performed on a Thermo Finnigan MAT 95 (electron ionization double-focusing magnetic sector instrument, abbreviated as EI in this section) or on a Thermo Finnigan LTQ FT (electrospray ionization ion trap-based Fourier transform ion cyclotron resonance mass spectrometer, abbreviated as ESI in this section) instrument.

(5*R*)-2-Allyl-5-methyl-3-[4-(trimethylsilyl)but-3-yn-1-yl]-cyclohexan-1-one (10). Four drops of 1,2-dibromoethane were added to Mg chips (305 mg, 12.6 mmol, 4.00 equiv) in THF (20 mL), and the mixture was heated to reflux for 5 s. After the mixture had cooled to room temperature, (4-bromobut-1-yn-1-yl)trimethylsilane (1.61 g, 7.85 mmol, 2.5 equiv) was added dropwise. The reaction mixture was stirred at 50 °C for 1 h and then slowly cooled to −78 °C. CuBr·SMe_2 (132 mg, 0.63 mmol, 0.20 equiv) was added in one portion, and after the mixture had been stirred for 15 min, enone **11** (473 mg, 3.14 mmol, 1.00 equiv) in THF (12 mL), TMSCl (0.82 mL, 6.28 mmol, 2.0 equiv), and HMPA (1.10 mL, 6.28 mmol, 2.0 equiv) were added sequentially to the brown suspension. The reaction mixture was stirred for 2.0 h at −78 °C, then acetic acid (5 mL) was added and the cooling bath removed. The reaction mixture was stirred for 3 h before H_2O (20 mL) was added. The mixture was extracted with Et_2O (3 × 60 mL), and the combined organic layers were washed with saturated aqueous NaCl (30 mL), dried over $MgSO_4$, and concentrated. The obtained brown oil was purified by column chromatography (7:1 pentane:Et_2O) to give ketone **10** as a variable mixture of diastereomers (713 mg, 2.58 mmol, 83%): R_f = 0.66 (5:1 hexane:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80−5.63 (m, 1H), 5.12−4.93 (m, 2H), 2.58−2.43 (m, 1H), 2.38 (t, J = 7.0, 2H), 2.34−2.18 (m, 3H), 2.18−1.88 (m, 4H), 1.72−1.58 (m, 2H), 1.53−1.41 (m, 1H), 1−0.99 (2 d, J = 5.9 and 5.7, 3H), 0.14 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.7, 136.4, 135.6, 116.9, 116.4, 106.5, 85.3, 54.4, 53.8, 50.3, 47.4, 37.4, 36.4, 34.5, 33.5, 32.1, 30.0, 29.6, 22.4, 21.7, 17.7, 0.3 (note that due to extensive signal overlap, the carbon count does not add up to two full sets of carbons); IR (ATR) 2956, 2926, 2174, 1710, 1641, 1456, 1334, 1249, 1003, 913, 841, 760 cm^{-1}; HRMS (ESI) m/z [M − H$^-$]$^+$ calcd for $C_{17}H_{27}OSi$ 275.1826, found 275.1826.

(3a*S*,6*R*,7a*R*)-3a-Allyl-6-methyl-3-methyleneoctahydro-4*H*-inden-4-one (9). To KO*t*-Bu (406 mg, 3.60 mmol, 0.70 equiv) in DMSO (40 mL) was added **10** (1.43 g, 5.16 mmol, 1.00 equiv) in DMSO (20 mL) over 3 min. After 10 min, the dark-brown reaction mixture was diluted with Et_2O (50 mL) and cooled with an ice bath before pH 5.5 phosphate buffer (40 mL) was added dropwise. The phases were separated, and the aqueous phase was extracted with Et_2O (2 × 60 mL). The combined organic phases were washed with saturated aqueous NaCl (50 mL), dried over $MgSO_4$, and concentrated. The brown oil was purified by column chromatography (11:1 pentane:Et_2O) to give **9** (1.00 g, 3.62 mmol, 70%) as a yellow oil: R_f = 0.74 (5:1 hexane:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (dddd, J = 19.9, 9.4, 8.1, 6.3, 1H), 5.08−5.03 (m, 1H), 5.03 (t, J = 2.1, 2H), 4.80 (t, J = 2.5, 1H), 2.64 (ddt, J = 13.9, 6.3, 1.1, 1H), 2.53 (dddd, J = 22.9, 11.5, 5.2, 2.8, 3H), 2.41 (dddt, J = 16.9, 9.5, 4.9, 2.3, 1H), 2.26−2.17 (m, 1H), 2.17−2.11 (m, 1H), 2.08 (ddd, J = 14.7, 6.4, 1.3, 1H), 1.92−1.78 (m, 1H), 1.69 (ddd, J = 12.6, 8.6, 3.8, 1H), 1.61−1.43 (m, 2H), 0.94 (d, J = 6.9, 3H); HRMS (EI) m/z [M]$^+$ calcd for $C_{14}H_{20}O$ 204.1509, found 204.1507. The analytical data were in good agreement with literature values.[13]

(3a*S*,6*R*,7a*R*)-3a-(3-Hydroxypropyl)-6-methyl-3-methyleneoctahydro-4*H*-inden-4-one (13). To **9** (223 mg, 1.09 mmol, 1.00 equiv) in CH_2Cl_2 (12 mL) was added $[Ir(cod)Cl]_2$ (36 mg, 55 μmol, 0.05 equiv) followed by dppe (43 mg, 109 μmol, 0.10 equiv) to give a green solution. After 10 min, dropwise addition of pinBH (190 μL, 1.31 mmol, 1.20 equiv) gave a yellow solution. After further stirring for 25 min, the reaction mixture was cooled to 0 °C before 2 M NaOH (2.4 mL) and 30% aqueous H_2O_2 (2.4 mL) were added under vigorous stirring, resulting in a dark-gray suspension. After 1 h, the biphasic mixture was diluted with Et_2O (20 mL) and H_2O (10 mL), then saturated aqueous NH_4Cl (5 mL) was added. The aqueous phase was extracted with Et_2O (3 × 10 mL), and the combined organic

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phases were washed with saturated aqueous NaCl (15 mL), dried over $MgSO_4$, and concentrated. The greenish oil was purified by column chromatography (2:1 → 1:1 pentane:Et_2O) to give the desired alcohol **13** (232 mg, 1.05 mmol, 96%) as a viscous colorless oil: R_f = 0.44 (1:1 hexane:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.00 (t, J = 2.1, 1H), 4.74 (t, J = 2.4, 1H), 3.66−3.56 (m, 2H), 2.58−2.34 (m, 4H), 2.25−2.18 (m, 1H), 2.07 (ddd, J = 14.9, 6.4, 1.4, 1H), 1.91−1.81 (m, 2H), 1.70 (ddd, J = 13.8, 8.5, 3.8, 1H), 1.64 (s, 1H), 1.60−1.46 (m, 5H), 0.96 (d, J = 6.9, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 212.9, 153.9, 108.5, 63.2, 63.1, 46.0, 42.6, 34.3, 31.6, 30.3, 29.6, 29.0, 28.6, 20.2; IR (ATR) 3383, 2949, 2872, 1697, 1646, 1457, 1382, 1333, 1217, 1054, 886, 801 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{14}H_{23}O_2$ 223.1693, found 223.1693; $[\alpha]^D_{20}$ − 21 (c 0.7, CH_2Cl_2).

(4a*S*,7a*S*,9*R*,10a*S*)-9-Methyl-5-methyleneoctahydro-2*H*-cyclopenta[*e*]chromene-6,10a(5*H*)-diol (14). To a solution of **13** (16 mg, 70 μmol, 1.0 equiv) in CH_2Cl_2 (0.7 mL) was added SeO_2 (7.8 mg, 70 μmol, 1.0 equiv) followed by TBHP (5.5 M in decane, 63 μL, 0.35 mmol, 5.0 equiv). The reaction mixture was stirred at room temperature for 15 h before H_2O (2 mL) was added. The aqueous phase was extracted with EtOAc (3 × 5 mL), and the combined organic phases were washed with saturated aqueous $Na_2S_2O_3$ (5 mL), dried over $MgSO_4$, and concentrated. Purification of the yellow oil by flash column chromatography (3:1 pentane:Et_2O) yielded **14** as a colorless oil (3.0 mg, 13 μmol, 18%): R_f = 0.60 (1:1 hexane:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 (s, 1H), 4.75 (s, 1H), 4.41 (s, 1H), 3.85 (dd, J = 12.1, 5.2, 1H), 3.60 (td, J = 12.4, 2.7, 1H), 2.03 (qp, J = 7.5, 5.6, 3.8, 2H), 1.94−1.83 (m, 3H), 1.77 (td, J = 11.7, 10.7, 1.8, 1H), 1.70−1.58 (m, 3H), 1.48 (dt, J = 13.9, 3.9, 1H), 1.44−1.36 (m, 1H), 1.11 (td, J = 13.0, 3.3, 1H), 0.96 (d, J = 6.6, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2, 103.8, 99.5, 64.0, 47.4, 38.0, 36.2, 34.7, 32.7, 24.3, 22.5, 21.8, 20.9; IR (ATR) 2982, 2958, 1718, 1646, 1465, 1367, 1294 1257, 1176, 1152, 1095, 1032, 978, 774 cm^{-1}; HRMS (ESI) m/z [M − H_2O + H]$^+$ calcd for $C_{14}H_{21}O_2$ 221.1536, found 221.1537; $[\alpha]^D_{20}$ − 10 (c 0.2, CH_2Cl_2).

(3a*S*,6*R*,7a*R*)-3a-{3-[(*tert*-Butyldimethylsilyl)oxy]propyl}-6-methyl-3-methyleneoctahydro-4*H*-inden-4-one (17). To a solution of **13** (60 mg, 0.27 mmol, 1.0 equiv) in DMF (5 mL) at −15 °C was added Et_3N (46 μL, 0.34 mmol, 1.3 equiv) followed by DMAP (3.4 mg, 28 μmol, 0.10 equiv) and TBSCl (44 mg, 0.30 mmol, 1.1 equiv). After 15 min at −15 °C, the reaction mixture was diluted with Et_2O (5 mL) and 1 M HCl (2 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL), and the combined organic phases were washed with 10% aqueous LiCl (2 × 10 mL) and saturated aqueous NaCl (10 mL), dried over $MgSO_4$, and concentrated to give the desired product **17** as a colorless oil (43 mg, 0.25 mmol, 95%). Note that the crude yield takes into account the presence of traces of DMF that did not hamper subsequent reactions. An analytically pure sample was obtained using column chromatography (11:1 pentane:Et_2O): R_f = 0.76 (5:1 hexane:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.03 (t, J = 2.2, 1H), 4.78 (t, J = 2.5, 1H), 3.63−3.52 (m, 2H), 2.55−2.42 (m, 3H), 2.40−2.33 (m, 1H), 2.19 (qt, J = 7.6, 4.5, 1H), 2.09 (ddd, J = 14.6, 7.7, 1.1, 1H), 1.85−1.75 (m, 2H), 1.71 (dddd, J = 13.9, 7.3, 3.9, 1.0, 1H), 1.60−1.44 (m, 5H), 0.97 (d, J = 6.9, 3H), 0.89 (s, 9H), 0.05−0.02 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 212.5, 153.5, 108.6, 63.5, 62.9, 46.4, 43.0, 34.1, 31.8, 30.5, 29.5, 28.7, 28.6, 26.1, 20.7, 18.5, −5.1; IR (ATR) 2952, 2928, 2362, 2340, 1702, 1647, 1472, 1462, 1384, 1254, 1208, 1097, 1006, 989, 938, 889, 834, 813, 775 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{20}H_{37}O_2Si$ 337.2557, found 337.2560; $[\alpha]^D_{20}$ − 2.0 (c 2.5, CH_2Cl_2).

3a-{3-[(*tert*-Butyldimethylsilyl)oxy]propyl}-6-methyl-3-methylenehexahydro-1*H*-indene-2,4-dione (18). SeO_2 (50 mg, 0.45 mmol, 2.5 equiv) and a TBHP solution (5.5 M in decane, 0.16 mL, 0.90 mmol, 5.0 equiv) were added to **17** (44 mg, 0.18 mmol, 1.0 equiv) in CH_2Cl_2 at 0 °C. The mixture was stirred at room temperature for 17 h. At this point, the reaction mixture was cooled to 0 °C before DMP (58 mg, 0.27 mmol, 1.5 equiv) was added to the reaction mixture. Stirring was continued for 1 h at the same temperature. Thereafter, a mixture (1:1, 2 mL) of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ was added, and the reaction mixture was stirred vigorously at room temperature. Afterward, H_2O (5 mL) and CH_2Cl_2 (5 mL) were added and the phases separated. Following extraction of the aqueous phase with CH_2Cl_2 (2 × 5 mL), the combined organic phases were washed with saturated aqueous NaCl (5 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (5:1 pentane:Et_2O) to yield **18** as a colorless oil (33 mg, 92 μmol, 51%): R_f = 0.42 (5:1 hexane:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.23 (s, 1H), 5.30 (s, 1H), 3.66−3.48 (m, 2H), 2.71 (p, J = 6.8, 1H), 2.56−2.42 (m, 2H), 2.26−2.11 (m, 3H), 1.93 (ddd, J = 13.5, 11.9, 4.7, 1H), 1.80−1.65 (m, 3H), 1.50 (m, 2H), 1.04 (d, J = 6.3, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 210.6, 204.4, 146.6, 121.2, 62.9, 60.2, 46.0, 42.2, 36.7, 34.3, 32.1, 28.5, 28.3, 26.1, 21.0, 18.4, −5.2; IR (ATR) 2982, 2958, 1718, 1646, 1465, 1367, 1294 1257, 1176, 1152, 1095, 1032, 978, 774 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{20}H_{35}O_3Si$ 351.2350, found 351.2351; $[\alpha]^D_{20}$ 59 (c 1.1, CH_2Cl_2).

(4b*S*,7*R*,8a*S*)-4b-{3-[(*tert*-Butyldimethylsilyl)oxy]propyl}-2-ethoxy-7-methyl-3,4,4b,6,7,8,8a,9-octahydroindeno[2,1-*b*]-pyran-5(2*H*)-one (19). **18** (18 mg, 52 μmol, 1.0 equiv) was dissolved in 1,2-dichloroethane (0.5 mL) and ethyl vinyl ether (0.5 mL) before $Eu(fod)_3$ (5.0 mg, 5.2 μmol, 0.10 equiv) was added in one portion. The solution was stirred at 50 °C for 20 h, concentrated, and directly loaded on a florisil column (7:1 pentane:Et_2O) to give **19** (18 mg, 43 μmol, 82%) as a colorless oil: R_f = 0.62 (5:1 hexane:EtOAc); ^{1}H NMR (600 MHz, C_6D_6) δ 4.86 (ddd, J = 13.1, 3.8, 2.5, 1H), 3.87−3.74 (m, 1H), 3.66−3.49 (m, 2H), 3.43−3.30 (m, 1H), 2.61−2.43 (m, 1H), 2.41−2.02 (m, 4H), 1.93−1.71 (m, 5H), 1.67−1.43 (m, 2H), 1.35−1.24 (m, 1H), 1.18−1.02 (m, 5H), 1.00 (m, 9H), 0.69−0.62 (m, 3H), 0.09 (m, 6H) (note that due to extensive signal overlap, the integral sum is 41, not 42); ^{13}C NMR (101 MHz, C_6D_6) δ 212.9, 212.3, 150.3, 150.0, 110.7, 110.3, 98.6, 63.9, 61.3, 47.2, 46.9, 39.1, 38.8, 37.3, 37.3, 37.1, 36.7, 31.7, 31.6, 28.3, 28.3, 27.3, 26.2, 25.9, 22.3, 22.2, 18.6, 16.7, 16.6, 15.6, 15.5, −5.0, −5.1 (note that due to extensive signal overlap, two full sets of signals could not be observed); IR (ATR) 2926, 2853, 1689, 1455, 1382, 1340, 1296, 1212, 1115, 1045, 968, 934, 849, 732 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{24}H_{43}O_4Si$ 423.2925, found 423.2927.

(4b*S*,7*R*,8a*S*,*E*)-4b-(3-Hydroxypropyl)-7-methyl-4b,6,7,8,8a,9-hexahydro-5*H*-indeno[2,1-*b*]pyridin-5-one Oxime (21). NH_2OH·HCl (9.4 mg, 0.14 mmol, 8.0 equiv) was added to a solution of **19** (7.0 mg, 17 μmol, 1.0 equiv) in MeCN (0.5 mL). The suspension was heated to 80 °C for 12 h, at which point it had turned into a dark-orange solution. The reaction mixture was cooled to room temperature, and 2 M HCl (0.5 mL) was added, turning the reaction mixture bright yellow. After 2 h, saturated aqueous $NaHCO_3$ (5 mL) was added, followed by EtOAc (10 mL). The aqueous phase was further extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with saturated aqueous NaCl (10 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (30:1:0.3 CH_2Cl_2:MeOH:NH_4OH) to yield **21** as a colorless oil (2.8 mg, 10 μmol, 60%): R_f = 0.48 (9:1 CH_2Cl_2:MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 5.0, 1H), 7.63 (d, J = 7.6, 1H), 7.18 (dd, J = 7.7, 5.1, 1H), 3.54 (td, J = 6.5, 2.4, 2H), 3.04−2.89 (m, 2H), 2.87−2.64 (m, 2H), 2.05−1.98 (m, 1H), 1.96−1.71 (m, 4H), 1.69−1.55 (m, 2H), 1.45−1.32 (m, 1H), 1.03 (d, J = 5.6, 3H); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{23}N_2O_2$ 275.1754, found 275.1758. The analytical data were in good agreement with literature values.[11]

Lycopladine A (2). NH_2OH·HCl (17 mg, 0.24 mmol, 7.0 equiv) was added to a solution of **19** (15 mg, 34 μmol, 1.0 equiv) in MeCN (1.0 mL). The suspension was heated to 80 °C for 14 h, at which point it had turned into a dark-orange solution. The reaction mixture was cooled to room temperature, and $TiCl_3$ (~13% aqueous HCl solution, 0.2 mL) and acetone (0.2 mL) were added. The reaction mixture turned dark violet and then gradually back to light yellow. After 30 min, saturated aqueous $NaHCO_3$ (5 mL) was added, followed by EtOAc (10 mL) and filtration through a Celite pad. The aqueous phase was further extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with saturated aqueous NaCl (10 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (30:1:0.3 CH_2Cl_2:MeOH:NH_4OH) to yield lycopladine A (**2**) as a colorless solid (8.0 mg, 31 μmol, 91%): R_f =

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0.52 (9:1 CH_2Cl_2:MeOH); ^1H NMR (400 MHz, CD_3OD) δ 8.30 (dd, J = 5.1, 1.4, 1H), 7.68 (dd, J = 7.8, 1.5, 1H), 7.25 (dd, J = 7.7, 5.1, 1H), 3.54 (td, J = 6.3, 1.8, 2H), 3.09 (dd, J = 16.1, 8.1, 1H), 3.02−2.92 (m, 1H), 2.83 (dd, J = 16.1, 8.9, 1H), 2.29 (d, J = 8.0, 2H), 2.18−2.00 (m, 2H), 1.94−1.77 (m, 3H), 1.62−1.50 (m, 1H), 1.41−1.30 (m, 1H), 1.09 (d, J = 6.5, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 214.6, 164.3, 148.7, 140.0, 136.2, 123.1, 62.8, 62.7, 47.7, 43.5, 38.5, 34.7, 33.3, 29.6, 29.1, 22.0; IR (ATR) 2982, 2958, 1718, 1646, 1465, 1367, 1294 1257, 1176, 1152, 1095, 1032, 978, 774 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{22}NO_2$ 260.1645, found 260.1644; $[\alpha]^D_{20}$ + 79 (c 1.0, CH_2Cl_2); $[\alpha]^D_{20}$ + 110 (c 0.4, MeOH); mp 160 °C dec. The data were in full agreement with the literature (see also the Supporting Information).[5,11]

3a-(3-Chloropropyl)-6-methyl-3-methyleneoctahydro-4*H*-inden-4-one (22). **13** (44 mg, 0.20 mmol, 1.0 equiv) in CH_2Cl_2 (1.5 mL) was cooled to 0 °C before triethylamine (70 μL, 0.50 mmol, 2.5 equiv) was added. After 5 min, triphosgene (30 mg, 0.10 mmol, 0.5 equiv) was added in one portion. The reaction mixture quickly turned cloudy and was slowly warmed to room temperature. After 3 h, the reaction mixture was poured onto saturated aqueous $NaHCO_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic phases were dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (12:1 pentane:Et_2O) to yield **22** as a colorless oil (43 mg, 0.18 mmol, 89%): R_f = 0.80 (5:1 hexane:EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 5.02 (t, J = 2.2, 1H), 4.74 (t, J = 2.5, 1H), 3.61−3.42 (m, 2H), 2.60−2.49 (m, 2H), 2.49−2.36 (m, 2H), 2.28−2.16 (m, 1H), 2.06 (ddd, J = 14.8, 6.4, 1.3, 1H), 1.95−1.65 (m, 5H), 1.64−1.47 (m, 3H), 0.96 (d, J = 6.9, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.3, 153.6, 108.8, 62.9, 46.0, 45.7, 42.7, 34.2, 32.9, 30.2, 29.6, 28.9, 28.6, 20.2; IR (ATR) 2953, 2924, 1697, 1646, 1458, 1443, 1333, 1310, 1246, 1133, 1048, 1015, 886 cm^{-1}; HRMS (ESI) m/z $[M]^+$ calcd for $C_{14}H_{21}ClO$ 240.1281, found 240.1274; $[\alpha]^D_{20}$ − 43 (c 0.7, CH_2Cl_2).

3a-(3-Chloropropyl)-6-methyl-3-methylenehexahydro-1*H*-indene-2,4-dione (23). SeO_2 (50 mg, 0.45 mmol, 2.5 equiv) and a TBHP solution (5.5 M in decane, 0.16 mL, 0.90 mmol, 5.0 equiv) were added to **22** (44 mg, 0.18 mmol, 1.0 equiv) in CH_2Cl_2 at 0 °C. The mixture was stirred at room temperature for 17 h. At this point, the reaction mixture was cooled to 0 °C before PCC (58 mg, 0.27 mmol, 1.5 equiv) was added to the reaction mixture, turning it from bright orange to dark brown. Stirring was continued for 1 h at the same temperature. Thereafter, saturated aqueous $NaHCO_3$ (5 mL) was added, followed by dilution with H_2O (5 mL). After extraction with CH_2Cl_2 (3 × 8 mL), the combined organic phases were washed with saturated aqueous NaCl (5 mL), dried over $MgSO_4$, and concentrated. The brown residue was purified by flash column chromatography (5:1 pentane:Et_2O) to yield **23** as a colorless oil (35 mg, 99 μmol, 55%): R_f = 0.23 (5:1 hexane:EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 6.22 (s, 1H), 5.27 (s, 1H), 3.63−3.42 (m, 2H), 2.70 (ddd, J = 13.0, 7.5, 5.5, 1H), 2.64−2.43 (m, 2H), 2.27−2.14 (m, 3H), 2.04−1.91 (m, 1H), 1.87−1.61 (m, 5H), 1.02 (d, J = 6.2, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.2, 204.1, 146.5, 121.2, 59.8, 45.7, 45.1, 42.4, 36.3, 34.9, 33.2, 28.4, 28.2, 20.5; IR (ATR) 2953, 2925, 1727, 1705, 1638, 1457, 1384, 1289, 1257, 1129, 1095, 991, 951, 798 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{19}ClO_2$ 254.1074, found 254.1071; $[\alpha]^D_{20}$ 12 (c 0.3, CH_2Cl_2).

(4b*S*,7*R*,8a*S*)-4b-(3-Chloropropyl)-2-ethoxy-7-methyl-3,4,4b,6,7,8,8a,9-octahydroindeno[2,1-*b*]pyran-5(2H)-one (24). **23** (24 mg, 94 μmol, 1.0 equiv) was dissolved in 1,2-dichloroethane (0.7 mL) and ethyl vinyl ether (0.7 mL) before Eu(fod)$_3$ (10 mg, 9.4 μmol, 0.10 equiv) was added in one portion. The yellow solution was stirred at 60 °C for 15 h, concentrated, and directly loaded on a florisil column (12:1 → 5:1 pentane:Et_2O) to give **24** (24 mg, 73 μmol, 78%) as a colorless oil and mixture of diastereomers: R_f = 0.43 (5:1 hexane:EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 5.04 (t, J = 2.8, 1H), 3.91−3.74 (m, 1H), 3.65−3.44 (m, 3H), 2.75−2.56 (m, 1H), 2.56−2.40 (m, 2H), 2.24−2.06 (m, 2H), 2.01−1.54 (m, 8H), 1.46−1.29 (m, 1H), 1.27−1.15 (m, 4H), 0.97 (d, J = 6.7, 1H), 0.96 (d, J = 6.7, 2H) (note that due to extensive signal overlap, the integral sum is 26, not 27); ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.8, 214.4, 150.9, 150.6, 109.5, 109.3, 98.4, 98.4, 63.9, 63.9, 61.4, 61.3, 47.0, 46.7, 45.6, 45.6, 38.6, 38.5, 37.7, 37.5, 37.4, 37.3, 32.2, 32.0, 27.9, 27.7, 26.9, 26.9, 25.7, 25.6, 22.5, 22.4, 16.2, 16.1, 15.4, 15.3; IR (ATR) 2926, 2853, 1689, 1455, 1382, 1340, 1296, 1212, 1115, 1045, 968, 934, 849, 732 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{28}ClO_3$ 327.1721, found 327.1722.

Carinatine A (3). NH_2OH·HCl (25 mg, 0.37 mmol, 5.0 equiv) was added to a solution of **24** (24 mg, 73 μmol, 1.0 equiv) in MeCN (1.5 mL). The suspension was heated to 70 °C for 15 h, at which point it turned into a dark-orange solution. The reaction mixture was cooled to room temperature; K_2CO_3 (6.9 mg, 50 μmol, 0.7 equiv) and H_2O (0.5 mL) were added, and the mixture was heated to 80 °C. After 2 h, saturated aqueous $NaHCO_3$ (5 mL) was added, followed by $CHCl_3$ (10 mL). The aqueous phase was further extracted with $CHCl_3$ (4 × 8 mL). The combined organic phases were washed with saturated aqueous NaCl (10 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (19:1 → 9:1 CH_2Cl_2:MeOH) to yield carinatine A (**3**) as a slightly yellow oil (14 mg, 54 μmol, 75%): R_f = 0.40 (9:1 CH_2Cl_2:MeOH); ^1H NMR (400 MHz, CD_3OD) δ 8.40 (d, J = 5.0, 1H), 7.53 (d, J = 7.6, 1H), 7.28 (dd, J = 7.6, 5.1, 1H), 4.00 (m, 2H), 3.58 (dd, J = 17.3, 7.5, 1H), 3.04 (dd, J = 17.4, 6.8, 1H), 2.76 (q, J = 7.0, 1H), 2.70 (d, J = 17.5, 1H), 2.16−2.06 (m, 1H), 2.05−1.82 (m, 4H), 1.74−1.65 (m, 1H), 1.60 (dt, J = 14.1, 7.0, 1H), 1.45 (ddd, J = 13.8, 7.0, 3.2, 1H), 0.94 (d, J = 6.8, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 165.0, 156.2, 149.5, 141.8, 134.2, 123.3, 59.1, 52.5, 45.3, 40.7, 38.5, 33.9, 32.9, 27.9, 20.1, 19.5; IR (ATR) 3374, 2919, 2484, 2074, 1655, 1592, 1427, 1180, 1117, 973, 937 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{21}N_2O$ 257.1648, found 257.1647; $[\alpha]^D_{20}$ − 60 (c 1.6, CH_2Cl_2); $[\alpha]^D_{20}$ − 110 (c 0.4, MeOH). The data were in full agreement with the literature (see the Supporting Information).[6,11]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00908.

Comparison of NMR data of isolated and synthetic lycopladine A and carinatine A and ^1H and ^{13}C spectra for all new compounds (PDF)

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Notes

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