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Total Synthesis of (−)-Carinatine A and (+)-Lycopladine A

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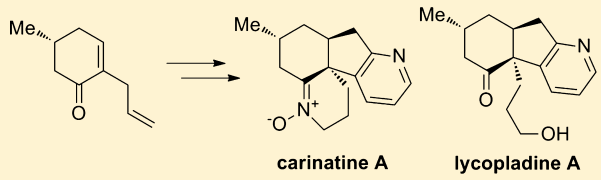
Supporting Information

ABSTRACT: An efficient synthesis of two *Lycopodium* alkaloids, (−)-carinatine A and (+)-lycopladine A, is achieved in eight steps. The synthesis features an intramolecular aldol reaction for assembling the 6,5-fused ring system, a subsequent Tsuji-Trost allylation for generating a quarternary carbon center, and a 6π-electrocyclization to form the pyridine ring.



INTRODUCTION

Carinatine A (**1**) is a tetracyclic alkaloid isolated from *Phlegmariurus carinatus*, a plant that has been used as a traditional Chinese medicine for the treatment of rheumatism, swelling, and pain.[1] This compound, together with the structurally related lycopladine A (**2**)[2] and lycoposerramine R (**3**),[3] belongs to the growing *Lycopodium* alkaloid family (Figure 1). The family contains at least 300 members with a

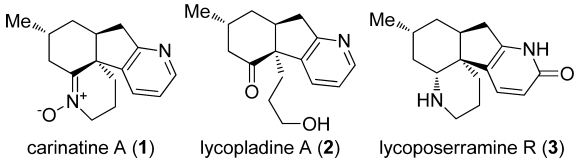


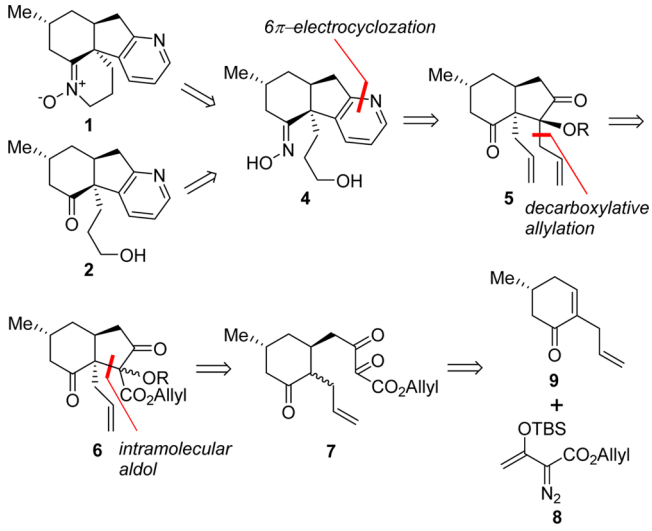
Figure 1. Structures of carinatine A, lycopladine A, and lycoposerramine R.

wide range of biological activities, such as antitumor and acetylcholine esterase (AChE) inhabition.[4] During the past decades, these alkaloids have piqued the interest of a large number of research groups, whose studies have culminated in elegant total syntheses of some *Lycopodium* alkaloids and new synthetic methodologies for assembling their core structures.[5]

To date, four groups have disclosed their results on the total synthesis of lycopladine A. In 2006, Toste group achieved the first total synthesis of (+)-lycopladine A by taking advantage of gold-catalyzed cyclization of silylenol ether with alkyne to install the key quaternary center of hydrindanone intermediate.[6a] Four years later, Martin and co-workers reported their synthesis of (±)-lycopladine A, in which the key tricyclic framework was elaborated via sequential conjugate addition and enolate arylation reactions of 3-chloro-2-methylpyridine and an unsaturated β-ketoester.[6b] In 2011, Hiroya et al. accomplished their total synthesis of (+)-lycopladine A by utilizing diastereoselective protection of carbonyl group in a 1,3-cyclohexanedione derivative as the key step.[6c] Recently, Yang group described another route for total synthesis of (+)-lycopladine A, in which Helquist annulation was employed as the key step.[6d] In this paper, we wish to report the total synthesis of (−)-carinatine A and (+)-lycopladine A by using the same intermediate.

Scheme 1 depicts our retrosynthetic analysis for carinatine A and lycopladine A. We believed that these two alkaloids could

Scheme 1. Retrosynthetic Analysis of Carinatine A and Lycopladine A



be assembled from common intermediate **4** via suitable transformations. The pyridine ring in the oxime **4** is traced back to diallyl compound **5** via transformation and subsequent 6π-electrocyclozation. This *cis*-6,5 fused ring system bearing the key quarternary C12 may generate from the corresponding allyl ester **6** via Tsuji-Trost allylation, **6** could be formed by intramolecular aldol reaction of tricarbonyl compound **7**. **7** is disassembled into known ketone **9** and diazo ester **8**.

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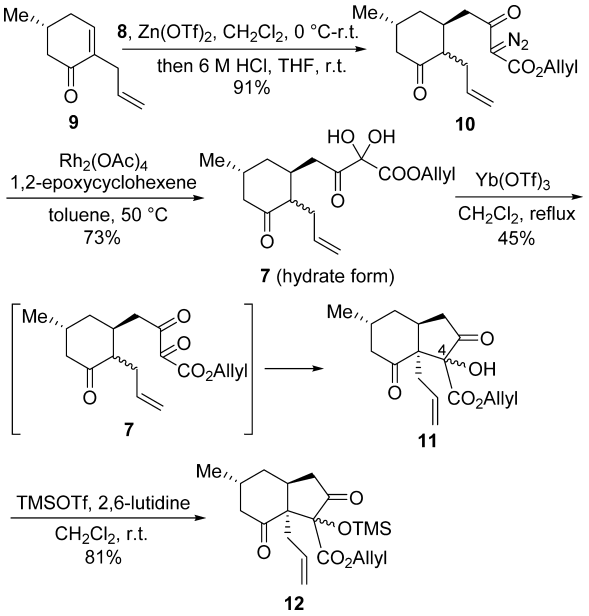
RESULTS AND DISCUSSION

As shown in Scheme 2, our synthesis started from the diastereoselective Michael addition of silylenol ether **8** to

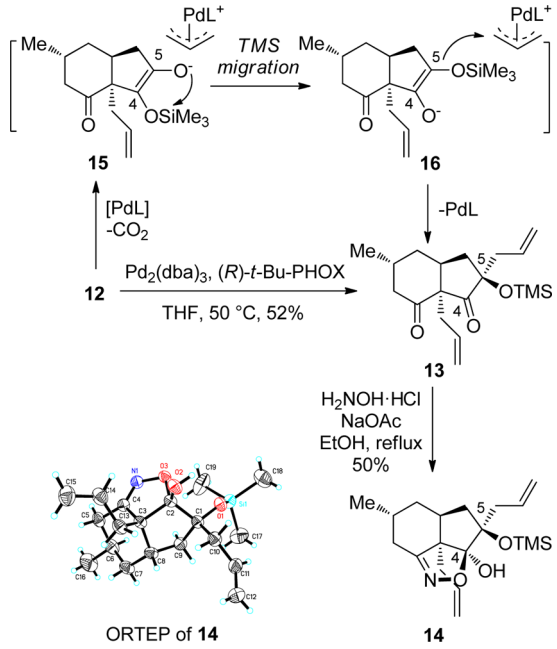
Scheme 2. Construction of *cis*-6,5 Fused Bicyclic Intermediate 12



known unsaturated ketone **9** under the activation of zinc trifluoromethanesulfonate, which generated diazo compound **10** in 91% yield with 2:1 diastereomeric ratio.[7] The transformation of diazo group in **10** to the corresponding carbonyl group proved to be problematic. Initial attempts by using oxidative reagents (e.g., *m*-CPBA, *t*-BuOCl, or DMDO) failed to give the tricarbonyl compound **7** because of easy epoxidation of C−C double bond. This problem forced us to consider applying Ganem's deoxygenation method to accomplish the desired transformation.[8] To our delight, treatment of **10** with substoichiometric amount of rhodium(II) acetate dimer and 2.0 equiv of 1,2-epoxycyclohexene delivered the tricarbonyl compound **7** in 33% yield (isolated as its monohydrate form, see Experiental Section). It was found that major side reaction was the cyclopropanation of resultant rhodium carbene with the olefin moiety, we decided to inhibit this side reaction by introducing more epoxide reagent and increasing concentration of the reaction. Yield could be increased to 73% if 10 equiv of 1,2-epoxycyclohexene was used when the reaction was carried out at 0.5 M. Although tricarbonyl form of **7** was not isolated directly, we attempted the intramolecular aldol reaction of **7**. $Yb(OTf)_3$ was a suitable catalyst,[9] leads to the formation of **11** in moderate yield (53% at 0.5 mmol scale, 45% at 4 mmol scale) with 1.5:1 diastereoselectivity at C4 position.[10] Subsequent protection of tertiary alcohol with TMS group gave allyl carboxylate ester **12**.

With **12** in hand, we tried Tsuji-Trost allylation under the conditions developed by Stoltz and co-workers.[11] It was found that under the catalysis of $Pd_2(dba)_3$ and (*R*)-*t*-Bu-PHOX, decarboxylative allylation of **12** proceeded smoothly to afford product **13** as a single isomer. After oxidation of **13**, unexpected hemiketal compound **14** was isolated, whose structure was established via X-ray structural analysis (Scheme 3). The formation of **14** indicated that the decarboxylative

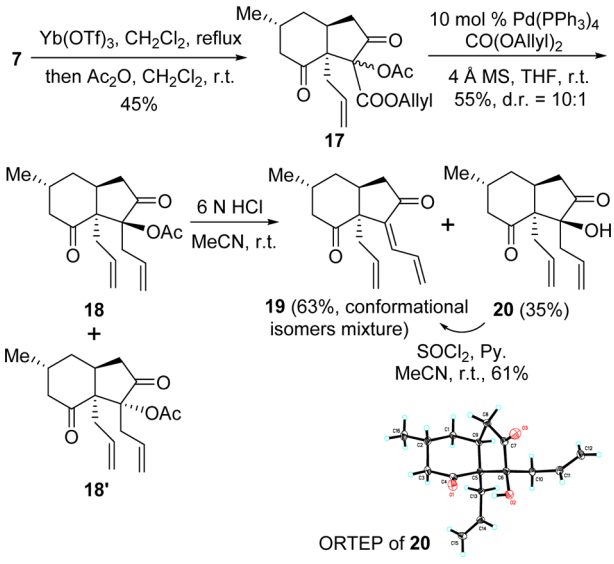
Scheme 3. Decarboxylative Allylation of Silyl Ether 12



allylation took place at C5 position of **13** rather than the desired C4. This result implied that enolate **15** generated in the decarboxylative step might undergo TMS migration to produce the more stable enolate **16**, for its less steric repulsion between the enolate anion (smaller than -OTMS) and the quarternary center.

Since trimethylsilyl protecting group underwent migration, we decided to change the protecting group of tertiary alcohol **11** (Scheme 4). After the intramolecular aldol reaction of **7**,

Scheme 4. Synthesis of Dienone 19



acetyl anhydride was added to quench the reaction to give ester **17**.[12] Surprisingly, the ester **17** was inert under the previous decarboxylative allylation conditions. After some trials, we found that under the catalysis of 10 mol% $Pd(PPh_3)_4$, the decarboxylative allylation occurred at room temperature to provide the desired product **18** and **18′** in 55% yield with 10:1 diastereoselectivity. It is notable that addition of 1.0 equiv of

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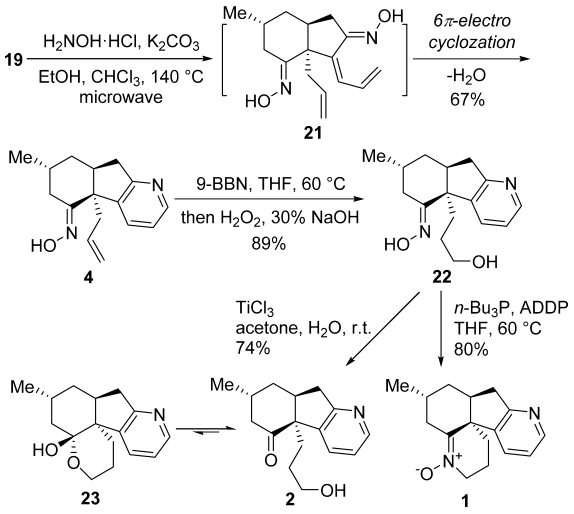
$CO(OAllyl)_2$ and 4 Å molecular sieves were necessary to suppress the protonation side product. After treatment of **18** with 6 N HCl in MeCN, elimination took place to provide dienone **19** in 63% yield as a mixture of *s-trans* and *s-cis* conformational isomers, together with simple hydrolysis product **20** in 35% yield. The structure of alcohol **20** was confirmed by X-ray crystallographic analysis, which was subjected to $SOCl_2$/pyridine mediated elimination to give the dienone **19** in 61% yield.

Starting from the dienone **19**, we completed the total syntheses of carinatine A and lycopladine A (Scheme 5).

Scheme 5. Completion of the Synthesis of (−)-Carinatine A and (+)-Lycopladine A



Treatment of **19** with 2.5 equiv of $NH_2OH·HCl$ and 2.5 equiv of K_2CO_3 in EtOH/$CHCl_3$ under microwave irradiation gave the cyclization product **4** in 67% yield.[13] This process might go through four cascade steps: oximation, isomerization of the *s-trans*-diene to form the intermediate **21**, 6π-electrocyclization of **21**, and dehydrative aromatization. Finally, hydroboration-oxidation of terminal olefin moiety in **4** produced alcohol **22**, which was subjected to reductive removal of oxime with $TiCl_3$ to furnish (+)-lycopladine A (**2**).[14] We also observed the isomeric lactol form **23** coexisting with **2** as reported previously.[6b,d] In a parallel procedure, intramolecular Mitsunobu reaction of **22** with *n*-Bu_3P and 1,1′-(azodicarbonyl)-dipiperidine (ADDP) afforded (−)-carinatine A (**1**).[15] The analytical data of these two synthetic compounds were identical with those reported.

In summary, we have achieved the first total synthesis of (−)-carinatine A (**1**) and developed another synthetic route to (+)-lycopladine A (**2**). Only 8 steps were required for synthesizing both alkaloids from the known enone **9**. The synthesis features an intramolecular aldol reaction, a Tsuji-Trost allylation, and a 6π-electrocyclization as the key steps. This strategy may be applicable for assembling other related alkaloids.

EXPERIMENTAL SECTION

General Methods. Tetrahydrofuran was freshly redistilled from sodium under argon when using it. Thin layer chromatography was performed on TLC silica gel 60 F254. Flash column chromatography was performed using normal phase silica gel. Preparative thin layer chromatography separations were carried out on 0.50 mm silica gel plates (60 F254). In ^1H NMR spectra, chemical shifts were given in relative to tetramethylsilane (δ 0.00 ppm) in $CDCl_3$ or the undeuterated solvent residual signals. In ^{13}C NMR spectra, chemical shifts were internally referenced to the deuterated solvent signals. Mass spectra and high resolution mass spectra were recorded on an ESI, ESI-FTMS, or EI type spectrometer.

(*R*)-2-Allyl-5-methylcyclohex-2-enone (9). The procedure was modified from Caine's method.[16] To a solution of (*R*)-pulegone (54 mL, 92% pract. from Acros, 0.33 mol) in 260 mL MeOH was added H_2O_2 (61 mL, 30% aq., 0.60 mol). A solution of $LiOH·H_2O$ (1.38 g, 0.033 mol) in 20 mL deionized water was added dropwise. The flask was immerged in water bath to maintain the reaction temperature at rt. After stirring for 6 h, 260 mL saturated NaCl solution was added to quench, and MeOH was removed under reduced pressure. The solution was extracted by EtOAc (250 mL × 3), washed with brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave epoxide product as colorless liquid, which was used without any further purification.

To a suspension of NaH (16.4 g, 60% in oil, 0.41 mol) in 300 mL dry THF at 0 °C was added 4-methylbenzenethiol (51.0 g, 0.41 mol, in 200 mL THF). The solution was slowly warmed to rt and stirred for 30 min. After no gas released, epoxide (from previous step) in 80 mL THF was added slowly. The solution was heated to reflux for 8 h. After slightly cooling the solution, allyl bromide (41 mL, 0.48 mol) in 100 mL THF was added dropwise. The solution was maintained at 50 °C for 6 h and cooled to rt. The suspension was filtered through a pad of Celite, washed with EtOAc, and filtrate was concentrated under reduced pressure. NH_4Cl solution (300 mL) was added to quench, followed by extracting with EtOAc (250 mL × 3), and washing with brine. Removal of the solvent under reduced pressure gave crude sulfide as yellow oil, which was used directly in next step.

To a solution of sulfide (from previous step) in 400 mL EtOAc was added HOAc (95 mL, 1.6 mol), $NaBO_3·4H_2O$ (152 g, 1.0 mol), and H_2O (80 mL). The suspension was heated to 60 °C and stirred on a mechanical stirrer overnight. After cooling, the suspension was filtered through a pad of Celite and concentrated under reduced pressure. Na_2CO_3 solution was slowly added to quench until no gas evolved. The solution was extracted by EtOAc (250 mL × 3), washed with brine, and dried over Na_2SO_4. The solvent was concentrated to give crude product, which was purified by vacuum distillation (88−90 °C, 10 mbar). Unsaturated ketone **9** (20.0 g, 44% for 3 steps) was a light yellow liquid. The spectrum data were identical with those reported.[16]

^1H NMR (400 MHz, $CDCl_3$) δ 6.74−6.64 (m, 1H), 5.85−5.75 (m, 1H), 5.11−4.94 (m, 2H), 2.93 (d, *J* = 6.5 Hz, 2H), 2.55−2.33 (m, 2H), 2.26−1.96 (m, 3H), 1.04 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.3, 145.2, 137.8, 136.0, 116.3, 46.6, 34.5, 33.4, 30.7, 21.3. HRMS (ESI) calcd. for $C_{10}H_{15}O$ $(M+H)^+$ 151.1118, found 151.1117.

Allyl-4-((1*S*,5*R*)-2-allyl-5-methyl-3-oxocyclohexyl)-2-diazo-3-oxobutanoate (10). To a solution of zinc trifluoromethanesulfonate (129 mg, 0.36 mmol) in 15 mL dry CH_2Cl_2 under argon atmosphere was added **9** (1.07 g, 7.1 mmol, in 5.0 mL CH_2Cl_2). The solution was cooled to 0 °C and **8** (10.6 mmol, crude, in 8.0 mL CH_2Cl_2)[7] was added. The reaction was warmed to rt and stirred overnight. After concentration and redissolving in 25 mL THF, HCl (25 mL, 6.0 N) was added and then the solution was stirred for 6 h. The solution was extracted by EtOAc (50 mL × 3), washed with $NaHCO_3$, brine, and dried over Na_2SO_4. Purification by column chromatography (SiO_2, 230−400 mesh, eluting with hexane/EtOAc, 15:1 to 10:1) gave epimer mixture **10** (2.06 g, 91%, ca. 2.0:1 d.r.) as yellow liquid. Futher purification by preparative thin layer chromatography gave individual isomers for NMR analysis.

Major Isomer. ^1H NMR (400 MHz, $CDCl_3$) δ 5.97−5.90 (m, 1H), 5.82−5.67 (m, 1H), 5.40−5.25 (m, 2H), 5.06−4.92 (m, 2H), 4.71 (dt, *J* = 5.8, 1.3 Hz, 2H), 2.95−2.86 (m, 1H), 2.79 (dd, *J* = 16.4, 4.4 Hz, 1H), 2.64−2.56 (m, 2H), 2.47 (ddd, *J* = 14.1, 7.6, 6.3 Hz, 1H), 2.39 (ddd, *J* = 12.6, 4.2, 1.8 Hz, 1H), 2.18−2.07 (m, 1H), 2.05−1.91 (m, 2H), 1.85−1.76 (m, 1H), 1.61−1.50 (m, 1H), 0.99 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.3, 191.4, 160.8, 136.3, 131.4, 119.4, 116.3, 76.4, 66.0, 53.4, 50.1, 38.2, 38.0, 36.3, 30.6, 30.4, 22.3.

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HRMS (ESI) calcd. for $C_{17}H_{22}N_2NaO_4$ $(M+Na)^+$ 341.1476, found 341.1472.

Minor Isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97−5.89 (m, 1H), 5.76−5.66 (m, 1H), 5.39−5.24 (m, 2H), 5.08−4.96 (m, 2H), 4.74−4.66 (m, 2H), 2.96 (dd, J = 17.0, 7.1 Hz, 1H), 2.82 (dd, J = 17.0, 6.9 Hz, 1H), 2.65−2.55 (m, 1H), 2.43−2.23 (m, 4H), 2.19−2.05 (m, 2H), 1.76−1.68 (m, 1H), 1.64−1.54 (m, 1H), 0.99 (d, J = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.1, 191.1, 160.9, 135.4, 131.4, 119.3, 116.8, 76.3, 65.9, 54.2, 47.2, 43.9, 34.8, 34.7, 34.5, 29.8, 21.5. HRMS (ESI) calcd. for $C_{17}H_{22}N_2NaO_4$ $(M+Na)^+$ 341.1476, found 341.1472.

Allyl-4-((1*S*,5*R*)-2-allyl-5-methyl-3-oxocyclohexyl)-2,2-dihydroxy-3-oxobutanoate (7, Hydrate Form). To a solution of **10** (6.36 g, 20 mmol) in 20 mL dry toluene was added 1,2-epoxycyclohexene (20 mL, 200 mmol) and rhodium(II) acetate dimer (44 mg, 0.10 mmol). The reaction was heated to 50 °C and stirred for 1 h until no gas evolved. The solution was concentrated and purified by column chromatography (SiO_2, 230−400 mesh, eluting with hexane/acetone, 6:1 to 4:1), which produced mixture **7** (4.64 g, 73%) as dark yellow liquid.

Tricarbonyl compound **7** reacted with residual water in silica column and deuterated solvents so NMR spectra were recorded as hydrate form. Further efforts for purification, such as heating, caused complex mixture.[9]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02−5.84 (m, 1H), 5.74−5.65 (m, 1H), 5.46−5.21 (m, 2H), 5.12−4.88 (m, 2H), 4.83−4.60 (m, 2H), 2.94−2.69 (m, 1H), 2.47−2.00 (m, 7H), 1.91−1.55 (m, 3H), 0.99 (d, J = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.9, 211.5, 202.3, 202.1, 168.5, 168.5, 135.7, 135.1, 130.5, 130.3, 120.5, 120.3, 117.1, 116.7, 92.8, 92.7, 67.7, 67.7, 54.0, 52.7, 50.2, 47.1, 39.8, 37.6, 35.6, 34.5, 34.1, 34.04, 33.9, 30.5, 30.5, 29.8, 22.3, 21.4. IR (neat, cm^{-1}) ν 3439, 2955, 1745, 1733, 1705, 1455, 1275. HRMS (ESI) calcd. for $C_{17}H_{23}O_5$ $(M+H-H_2O)^+$ 307.1540, found 307.1538.

(3a*S*,5*R*,7a*S*)-Allyl-7a-allyl-1-hydroxy-5-methyl-2,7-dioxooctahydro-1*H*-indene-1-carboxylate (11). To a solution of **7** (918 mg, 3.0 mmol) in 30 mL dry CH_2Cl_2 was added ytterbium(III) trifluoromethanesulfonate (186 mg, 0.30 mmol). The solution was heated to 60 °C (bath temp) for 24 h. After cooling to rt, $NaHCO_3$ solution was added to quench the reaction. The mixture was filtered through Celite and extracted by CH_2Cl_2 (30 mL × 3), washed with brine, and dried over Na_2SO_4. Purification by column chromatography (SiO_2, 230−400 mesh, eluting with hexane/acetone, 10:1 to 6:1) gave **11** (413 mg, 45%, ca. 1.5:1 d.r.) as yellow liquid. Futher purification by preparative thin layer chromatography gave individual isomers for NMR analysis.

Major Isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89−5.80 (m, 1H), 5.77−5.68 (m, 1H), 5.36−5.24 (m, 2H), 5.14−5.05 (m, 2H), 4.69−4.60 (m, 1H), 4.56 (dd, J = 12.7, 6.3 Hz, 1H), 3.83 (s, br, 1H), 2.85 (dd, J = 16.5, 12.4 Hz, 1H), 2.76−2.66 (m, 1H), 2.56 (dd, J = 13.7, 7.5 Hz, 1H), 2.52−2.43 (m, 2H), 2.38 (dd, J = 13.7, 7.3 Hz, 1H), 2.31−2.20 (m, 1H), 2.00 (dd, J = 16.9, 11.2 Hz, 1H), 1.95−1.86 (m, 1H), 1.68 (ddd, J = 14.1, 10.7, 5.9 Hz, 2H), 1.06 (d, J = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.2, 209.4, 170.6, 133.6, 130.8, 120.3, 119.5, 84.4, 67.5, 61.1, 48.8, 42.5, 41.6, 37.4, 34.4, 25.9, 21.8. HRMS (ESI) calcd. for $C_{17}H_{23}O_5$ $(M+H)^+$ 307.1540, found 307.1539.

Minor Isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12−6.03 (m, 1H), 5.96−5.87 (m, 1H), 5.55 (s, 1H), 5.40−5.26 (m, 2H), 5.12−5.03 (m, 2H), 4.74−4.66 (m, 2H), 3.06 (ddd, J = 13.2, 8.9, 3.8 Hz, 1H), 2.88 (dd, J = 14.9, 9.9 Hz, 1H), 2.64 (dd, J = 19.7, 9.1 Hz, 1H), 2.49−2.37 (m, 2H), 2.30−2.22 (m, 1H), 2.20−2.04 (m, 2H), 1.85−1.76 (m, 2H), 1.10 (d, J = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 217.3, 210.0, 167.7, 131.9, 130.9, 120.2, 118.4, 88.5, 66.8, 60.2, 47.7, 38.9, 37.9, 37.8, 31.7, 31.7, 22.1. HRMS (ESI) calcd. for $C_{17}H_{23}O_5$ $(M+H)^+$ 307.1540, found 307.1539.

(3a*S*,5*R*,7a*S*)-Allyl-7a-allyl-5-methyl-2,7-dioxo-1-((trimethylsilyl)oxy)octahydro-1*H*-indene-1-carboxylate (12). To a solution of **11** (675 mg, 2.2 mmol) in 22 mL dry CH_2Cl_2 was added 2,6-lutidine (0.41 mL, 3.5 mmol) and trimethylsilyl trifluoromethanesulfonate (0.60 mL, 3.3 mmol). The reaction was stirred at rt for 30 min, quenched by $NaHCO_3$ solution, extracted by CH_2Cl_2 (30 mL × 3), washed with brine, and dried over Na_2SO_4. Purification by column chromatography (SiO_2, 230−400 mesh, eluting with hexane/EtOAc, 20:1) gave a mixture of **12** (675 mg, 81%, ca. 1.5:1 d.r.) as colorless liquid. Futher purification by preparative thin layer chromatography gave individual isomers for NMR analysis.

Major Isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95−5.90 (m, 1H), 5.72−5.68 (m, 1H), 5.33 (ddd, J = 13.8, 11.5, 1.2 Hz, 2H), 5.12−4.99 (m, 2H), 4.75−4.70 (m, 1H), 4.61−4.49 (m, 1H), 2.85−2.70 (m, 2H), 2.65 (dd, J = 13.8, 4.8 Hz, 1H), 2.51 (dd, J = 15.1, 5.8 Hz, 1H), 2.38−2.21 (m, 3H), 2.13 (dd, J = 13.8, 9.7 Hz, 1H), 1.98−1.92 (m, 1H), 1.72−1.64 (m, 1H), 0.99 (d, J = 7.0 Hz, 3H), 0.13 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.0, 209.0, 168.7, 133.8, 131.1, 119.6, 119.1, 86.6, 66.3, 60.6, 48.7, 41.2, 37.3, 34.9, 34.0, 29.4, 20.7, 1.4. HRMS (ESI) calcd. for $C_{20}H_{31}O_5Si$ $(M+H)^+$ 379.1935, found 379.1933.

Minor Isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97−5.74 (m, 2H), 5.37−5.21 (m, 2H), 5.08−4.97 (m, 2H), 4.70−4.65 (m, 1H), 4.55−4.50 (m, 1H), 2.76−2.64 (m, 2H), 2.64−2.53 (m, 1H), 2.43−2.26 (m, 3H), 2.25−2.13 (m, 1H), 2.03 (dd, J = 15.7, 11.3 Hz, 1H), 1.87−1.81 (m, 1H), 1.76−1.69 (m, 1H), 1.02 (d, J = 6.5 Hz, 1H), 0.16 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.4, 209.3, 170.7, 134.3, 131.5, 119.3, 118.1, 85.4, 66.4, 63.5, 48.6, 41.6, 40.3, 38.1, 33.3, 26.9, 21.7, 1.7. HRMS (ESI) calcd. for $C_{20}H_{31}O_5Si$ $(M+H)^+$ 379.1935, found 379.1933.

(2*R*,3a*S*,5*R*,7a*R*)-2,7a-Diallyl-5-methyl-2-((trimethylsilyl)oxy)-hexahydro-1*H*-indene-1,7(7a*H*)-dione (13). To a hot air gun dried Schlenk bottle, charged with bis(dibenzylideneacetone)palladium(0) (85 mg, 93 μmol) and (*R*)-4-*tert*-butyl-2-[2-(diphenylphosphino)-phenyl]-2-oxazoline (89 mg, 0.23 mmol) under Ar atmosphere was added **12** (700 mg, 1.9 mmol, in 19 mL THF) via syringe. The solution was bubbled under argon for 5 min and heated to 50 °C. After 2 h, the solvent was removed under reduced pressure, which was chromatographed (SiO_2, 230−400 mesh, eluting with hexane/EtOAc, 15:1), single isomer product **13** (322 mg, 52%) was obtained as light yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84−5.75 (m, 1H), 5.64−5.56 (m, 1H), 5.20−4.99 (m, 4H), 2.56 (dd, J = 13.6, 6.6 Hz, 1H), 2.47−1.98 (m, 8H), 1.85−1.61 (m, 3H), 1.05 (d, J = 6.2 Hz, 3H), 0.13 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.3, 205.9, 132.6, 132.6, 119.6, 118.9, 80.6, 65.0, 47.4, 40.5, 38.5, 37.9, 35.8, 32.5, 28.9, 22.2, 2.1. HRMS (ESI) calcd. for $C_{19}H_{31}O_3Si$ $(M+H)^+$ 335.2039, found 335.2037.

(2a^1*R*,4*R*,5a*S*,7*R*,7a*S*)-2a^1,7-Diallyl-4-methyl-7-((trimethylsilyl)oxy)-2a^1,3,4,5,5a,6,7,7a-octahydroindeno[7,1-*cd*]isoxazol-7a-ol (14). To a solution of **13** (67 mg, 0.20 mmol) in 2.0 mL ethanol was added $NH_2OH{\cdot}HCl$ (15 mg, 0.22 mmol) and NaOAc (25 mg, 0.30 mmol). The solution was heated to reflux for 2 h and cooled, diluted by water (10 mL), extracted by EtOAc (5 mL × 3), washed with brine, and dried over Na_2SO_4. Purification by column chromatography (SiO_2, 230−400 mesh, eluting with hexane/EtOAc, 8:1) gave **14** (36 mg, 50%) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88−5.76 (m, 2H), 5.18−5.08 (m, 4H), 2.93 (s, br, 1H), 2.57−2.47 (m, 3H), 2.38 (dd, J = 14.7, 8.4 Hz, 1H), 2.07−1.99 (m, 2H), 1.78−1.65 (m, 3H), 1.65−1.54 (m, 2H), 1.46−1.37 (m, 1H), 1.01 (d, J = 6.0 Hz, 3H), 0.17 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.3, 134.5, 134.1, 119.0, 117.9, 115.2, 85.4, 59.7, 40.8, 40.4, 35.6, 34.2, 32.8, 32.6, 31.7, 22.1, 2.7. HRMS (ESI) calcd. for $C_{19}H_{32}NO_3Si$ $(M+H)^+$ 350.2148, found 350.2146. mp 94−96 °C (recrystallized from ethanol).

(3a*S*,5*R*,7a*S*)-Allyl-1-acetoxy-7a-allyl-5-methyl-2,7-dioxooctahydro-1*H*-indene-1-carboxylate (17). To a solution of **7** (1.22g, 4.0 mmol) in 40 mL dry CH_2Cl_2 was added ytterbium(III) trifluoromethanesulfonate (248 mg, 0.40 mmol). The solution was stirred at 60 °C (bath temp) for 24 h (TLC monitored). After cooling to rt, Ac_2O (1.2 mL, 12 mmol) was added and the mixture was stirred for 3 h. Then 30 mL saturated $NaHCO_3$ solution was added to quench and stirred for 30 min. The mixture was filtered and filtrate was extracted by CH_2Cl_2 (40 mL × 3), washed with brine, and dried over Na_2SO_4. Purification by column chromatography (SiO_2, 230−400 mesh, eluting with hexane/EtOAc, 10:1 to 6:1) gave mixture **17** (630 mg, 45%, ca. 1.5:1 d.r.) as yellow liquid. Futher purification by

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preparative thin layer chromatography gave individual isomers for NMR analysis.

Major Isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94−5.86 (m, 1H), 5.84−5.73 (m, 1H), 5.39−5.25 (m, 2H), 5.15−5.05 (m, 2H), 4.75−4.62 (m, 2H), 2.85−2.54 (m, 4H), 2.43−2.35 (m, 1H), 2.34−2.16 (m, 3H), 2.15 (s, 3H), 1.83−1.67 (m, 2H), 1.05 (d, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.1, 203.1, 169.5, 165.9, 132.5, 131.0, 119.9, 118.9, 88.9, 66.8, 59.3, 48.2, 39.2, 38.7, 37.7, 33.2, 29.8, 21.8, 21.0. HRMS (ESI) calcd. for $C_{19}H_{25}O_6$ $(M+H)^+$ 349.1648, found 349.1646.

The minor isomer decomposed smoothly (acetyl removed) in column chromatography, preparative thin layer chromatography, or HPLC so no clear NMR data were recorded.

18 and 18′. To a hot air gun dried Schlenk bottle charged with 4 Å molecular sieves (200 mg) and $Pd(PPh_3)_4$ (116 mg, 0.10 mmol) under Ar atmosphere was added 6.0 mL dry THF. **17** (348 mg, 1.0 mmol, in 4.0 mL THF) and diallyl carbonate (0.14 mL, 1.0 mmol) was added via syringe. The solution was bubbled under argon for 5 min and stirred at rt for 12 h. After completion of the reaction, the mixture was filtered by Celite and filtrate was concentrated. Purification by column chromatography (SiO_2, 230−400 mesh, eluting with hexane/EtOAc, 12:1 to 8:1) gave **18** (151 mg, 50%) as yellow semisolid and its epimer **18′** (15 mg, 5%) as yellow oil.

(1*S*,3a*S*,5*R*,7a*S*)-1,7a-Diallyl-5-methyl-2,7-dioxooctahydro-1*H*-inden-1-yl acetate (18). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96−5.83 (m, 1H), 5.64−5.49 (m, 1H), 5.15−4.98 (m, 4H), 2.81 (dd, J = 13.2, 5.4 Hz, 1H), 2.71−2.58 (m, 3H), 2.56−2.48 (m, 2H), 2.43 (dd, J = 14.4, 8.4 Hz, 1H), 2.34−2.25 (m, 1H), 2.20−2.12 (m, 1H), 2.00 (s, 3H), 1.88−1.81 (m, 1H), 1.79−1.71 (m, 1H), 1.68−1.59 (m, 1H), 0.98 (d, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.6, 207.7, 169.3, 133.0, 132.0, 120.0, 119.4, 88.4, 56.3, 49.5, 40.0, 39.1, 37.2, 34.8, 33.0, 27.1, 21.4, 20.6. HRMS (ESI) calcd. for $C_{18}H_{24}NaO_4$ $(M+Na)^+$ 327.1565, found 327.1567.

(1*R*,3a*S*,5*R*,7a*S*)-1,7a-Diallyl-5-methyl-2,7-dioxooctahydro-1*H*-inden-1-yl acetate (18′). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00−5.86 (m, 1H), 5.78−5.67 (m, 1H), 5.20−4.99 (m, 4H), 3.20 (ddt, J = 14.6, 6.1, 1.4 Hz, 1H), 2.86−2.76 (m, 2H), 2.72−2.58 (m, 3H), 2.34−2.19 (m, 2H), 2.13−1.98 (m, 2H), 2.04 (s, 3H), 1.78−1.61 (m, 2H), 1.02 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.0, 207.6, 169.7, 133.5, 132.9, 119.1, 119.0, 88.3, 61.5, 48.9, 39.4, 38.9, 37.0, 36.9, 32.8, 29.3, 22.0, 20.7. HRMS (ESI) calcd. for $C_{18}H_{24}NaO_4$ $(M+Na)^+$ 327.1565, found 327.1567.

19 and 20. To a solution of **18** (548 mg, 1.8 mmol) in 18 mL MeCN was added HCl (18 mL, 6.0 N). The reaction was allowed to stir at rt for 24 h and MeCN was removed under vacuum. The solution was extracted by EtOAc (30 mL × 3), washed with $NaHCO_3$ and brine, and dried over Na_2SO_4. Purification by column chromatography (SiO_2, 230−400 mesh, eluting with hexane/EtOAc, 15:1 to 6:1) gave dienone **19** (277 mg, 63%, conformational isomers mixture, which converts into its *s-trans* isomer smoothly) as light yellow oil and alcohol **20** (163 mg, 35%) as light yellow solid.

(3a*S*,6*R*,7a*S*)-3a-Allyl-3-allylidene-6-methylhexahydro-1*H*-indene-2,4-dione (19, *s-trans* Isomer). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 12.0 Hz, 1H), 6.45 (ddd, J = 16.7, 12.0, 10.1 Hz, 1H), 5.81−5.66 (m, 2H), 5.62 (d, J = 10.1 Hz, 1H), 5.13−5.01 (m, 2H), 2.77−2.59 (m, 3H), 2.54 (dd, J = 14.3, 5.0 Hz, 1H), 2.37 (dd, J = 14.0, 7.7 Hz, 1H), 2.19−2.08 (m, 4H), 1.61 (t, J = 5.7 Hz, 2H), 0.95 (d, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.8, 205.6, 137.2, 136.2, 133.8, 130.6, 130.2, 119.1, 59.8, 46.3, 43.2, 39.9, 36.9, 36.6, 28.6, 20.2. HRMS (ESI) calcd. for $C_{16}H_{21}O_2$ $(M+H)^+$ 245.1536, found 245.1537.

(3*S*,3a*S*,6*R*,7a*S*)-3,3a-Diallyl-3-hydroxy-6-methylhexahydro-1*H*-indene-2,4-dione (20). $[\alpha]_D^{23}$ + 143 (*c* 1.0, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05−5.84 (m, 2H), 5.14−5.01 (m, 4H), 4.99 (d, J = 2.2 Hz, 1H), 2.82−2.65 (m, 3H), 2.55 (dd, J = 14.2, 6.2 Hz, 1H), 2.43−2.20 (m, 4H), 2.14−1.97 (m, 2H), 1.86−1.73 (m, 2H), 1.08 (d, J = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 218.3, 214.2, 132.4, 131.9, 118.6, 118.0, 85.2, 59.5, 47.7, 38.3, 36.9, 36.5, 35.8, 32.4, 31.3, 22.1. HRMS (ESI) calcd. for $C_{16}H_{23}O_3$ $(M+H)^+$ 263.1643, found 263.1642. mp 122−124 °C (recrystallized from hexane/EtOAc).

Conversion of 20 to 19. To a solution of **20** (156 mg, 0.59 mmol) in 5.9 mL dry MeCN under Ar atmosphere was added pyridine (0.19 mL, 2.4 mmol) and distilled $SOCl_2$ (68 μL, 0.94 mmol). The reaction was stirred at rt for 16 h and quenched by $NaHCO_3$ solution, extracted by EtOAc (30 mL × 3), washed with brine, and dried over Na_2SO_4. Purification by column chromatography (SiO_2, 230−400 mesh, eluting with hexane/EtOAc, 15:1) gave **19** (87 mg, 61%) as light yellow oil. The spectra data were identical with previous.

(4b*S*,7*R*,8a*S*,*E*)-4b-Allyl-7-methyl-7,8,8a,9-tetrahydro-4b*H*-indeno[2,1-*b*]pyridin-5(6*H*)-one Oxime (4). To a solution of **19** (57 mg, 0.23 mmol) in 1.5 mL $CHCl_3$ and 3.1 mL ethanol in a microwave vial was added $NH_2OH{\cdot}HCl$ (40 mg, 0.58 mmol) and K_2CO_3 (80 mg, 0.58 mmol). The sealed vial was heated to 140 °C in a microwave reactor (Biotage Initiator+, High abs., 15 bar) and stirred for 2 h. After cooling, the solution was diluted with 20 mL water and 5 mL saturated K_2CO_3 solution, extracted by CH_2Cl_2 (10 mL × 3), washed with brine, and dried over Na_2SO_4. Purification by column chromatography (SiO_2, 230−400 mesh, eluting with CH_2Cl_2/MeOH/Et_3N, 30:1:0.3) gave **4** (39 mg, 67%) as white solid.

$[\alpha]_D^{23}$ + 28.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, CD_3OD) δ 8.24 (dd, J = 5.1, 1.5 Hz, 1H), 7.65 (dd, J = 7.7, 1.5 Hz, 1H), 7.18 (dd, J = 7.7, 5.1 Hz, 1H), 5.79−5.67 (m, 1H), 5.14−4.99 (m, 2H), 3.05−2.95 (m, 1H), 2.86 (ddd, J = 15.1, 4.3, 1.7 Hz, 1H), 2.82−2.70 (m, 3H), 2.62 (dd, J = 14.2, 6.6 Hz, 1H), 1.88 (dt, J = 18.2, 9.1 Hz, 1H), 1.81−1.67 (m, 2H), 1.62−1.55 (m,1H), 1.32 (s, br, 1H), 1.02 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 164.1, 161.1, 148.0, 142.5, 135.9, 135.8, 122.5, 118.6, 54.1, 43.2, 42.2, 38.4, 35.3, 30.3, 27.8, 22.0. HRMS (ESI) calcd. for $C_{16}H_{21}N_2O$ $(M+H)^+$ 257.1648, found 257.1648.

(4b*S*,7*R*,8a*S*,*E*)-4b-(3-Hydroxypropyl)-7-methyl-7,8,8a,9-tetrahydro-4b*H*-indeno[2,1-*b*]pyridin-5(6*H*)-one Oxime (22). To a solution of **4** (20 mg, 0.078 mmol) in 1.1 mL dry THF under Ar atmosphere was added 9-BBN (0.47 mL, 0.5 M in THF, 0.23 mmol). The solution was heated at 60 °C overnight and then cooled to 0 °C. NaOH solution (2.0 mL, 10% aq.) was added to the solution and then H_2O_2 (1.0 mL, 30% aq.) was added dropwise. The mixture was stirred at rt for 2 h, extracted by EtOAc (8 mL × 3), washed with brine, and dried over Na_2SO_4. Purification by column chromatography (SiO_2, 230−400 mesh, eluting with CH_2Cl_2/MeOH/Et_3N, 25:1:0.25) gave **22** (19 mg, 89%) as white solid.

$[\alpha]_D^{23}$ + 47.8 (*c* 1.0, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 8.23 (dd, J = 5.1, 1.5 Hz, 1H), 7.63 (dd, J = 7.7, 1.5 Hz, 1H), 7.18 (dd, J = 7.7, 5.1 Hz, 1H), 3.59−3.47 (m, 2H), 3.04−2.89 (m, 2H), 2.85−2.67 (m, 2H), 2.08−1.97 (m, 1H), 1.95−1.86 (m, 1H), 1.85−1.71 (m, 3H), 1.68−1.56 (m, 2H), 1.43−1.32 (m, 1H), 1.03 (d, J = 5.9 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 164.1, 161.7, 147.8, 142.9, 135.9, 122.5, 63.1, 54.4, 43.8, 38.3, 35.3, 33.7, 30.3, 29.3, 27.8, 22.1. HRMS (ESI) calcd. for $C_{16}H_{23}N_2O_2$ $(M+H)^+$ 275.1758, found 275.1754.

Lycopladine A (2). To a solution of **22** (26 mg, 0.095 mmol) in 2.0 mL acetone was added $TiCl_3$ (0.20 mL, 20% in HCl aq.) under Ar atmosphere. The reaction was stirred at rt for 1 h and quenched by 10 mL Na_2CO_3 solution. The mixture was filtered by Celite, filtrate was extracted with EtOAc (8 mL × 3), washed with brine, and dried over Na_2SO_4. Purification by column chromatography (SiO_2, 230−400 mesh, eluting with CH_2Cl_2/MeOH/Et_3N, 30:1:0.3) gave **2** (18 mg, 74%) as white solid. The spectrum data were identified with those reported.[2]

$[\alpha]_D^{23}$ + 137 (*c* 0.50, MeOH) lit.[2] $[\alpha]_D^{23}$ + 102 (*c* 1.0, MeOH). ^{1}H NMR (500 MHz, CD_3OD) δ 8.31 (dd, J = 5.1, 1.4 Hz, 1H), 7.67 (dd, J = 7.7, 1.4 Hz, 1H), 7.25 (dd, J = 7.7, 5.1 Hz, 1H), 3.57−3.51 (m, 2H), 3.09 (dd, J = 16.4, 8.2 Hz, 1H), 2.99−2.94 (m, 1H), 2.83 (dd, J = 16.4, 9.0 Hz, 1H), 2.29 (dd, J = 5.3, 4.1 Hz, 2H), 2.16−2.03 (m, 2H), 1.92−1.79 (m, 3H), 1.61−1.52 (m, 1H), 1.39−1.32 (m, 1H), 1.09 (d, J = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 214.6, 164.3, 148.7, 140.0, 136.2, 123.1, 62.8, 62.7, 47.8, 43.5, 38.6, 34.8, 33.4, 29.6, 29.1, 22.0. HRMS (ESI) calcd. for $C_{16}H_{22}NO_2$ $(M+H)^+$ 260.1646, found 260.1645.

Carinatine A (1). To a solution of **22** (13 mg, 0.048 mmol) in 2.5 mL dry THF was added *n*-Bu_3P (26 μL, 0.092 mmol) and 1,1′-(azodicarbonyl)dipiperidine (23 mg, 0.090 mmol). The reaction was

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heated to 60 °C and stirred for 3 h. The mixture was concentrated and purificated by thin layer chromatography, which gave **1** (10 mg, 80%) as colorless oil. The spectra were identified with isolated product.[1]

$[\alpha]_D^{25}$ −127 (*c* 0.50, MeOH) lit.[1] $[\alpha]_D^{26.6}$ −94.4 (*c* 1.2, MeOH). ^{1}H NMR (500 MHz, CD_3OD) δ 8.40 (dd, *J* = 5.1, 1.4 Hz, 1H), 7.53 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.28 (dd, *J* = 7.7, 5.1 Hz, 1H), 4.00 (m, 2H), 3.58 (dd, *J* = 17.2, 7.5 Hz, 1H), 3.04 (dd, *J* = 16.8, 6.7 Hz, 1H), 2.77−2.73 (1H, m), 2.70 (d, *J* = 17.2 Hz, 1H), 2.16−2.07 (m, 1H), 2.04−1.83 (m, 4H), 1.73−1.67 (m, 1H), 1.63−1.56 (m, 1H), 1.48−1.42 (m, 1H), 0.94 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 165.0, 156.3, 149.6, 141.8, 134.2, 123.3, 59.1, 52.6, 45.3, 40.7, 38.5, 33.9, 32.9, 27.9, 20.1, 19.5. HRMS (EI) calcd. for $C_{16}H_{20}N_2O$ $(M)^+$ 256.1576, found 256.1577.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01435.

Copies of NMR data of new compounds, (−)-**1** and (+)-**2** and comparison spectrum of natural product and synthetic (−)-**1** and (+)-**2** (PDF)

X-ray crystallography data for **14** (CIF)

X-ray crystallography data for **20** (CIF)

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Notes

The author declares no competing financial interest.

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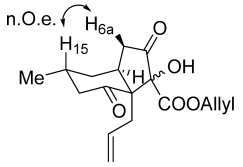

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