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Total Synthesis of Optically Active Lycopladine A by Utilizing Diastereoselective Protection of Carbonyl Group in a 1,3-Cyclohexanedione Derivative

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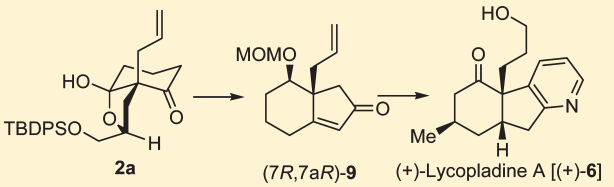
Supporting Information

ABSTRACT: We successfully synthesized two enantiomers of bicyclic enones, (7*R*,7a*R*)- and (7*S*,7a*S*)-**9**, from the hemiacetal **2a**, which we first synthesized from the symmetrical diketone **1a** via diastereoselective carbon−oxygen bond formation between one of the carbonyl groups and the chiral alcohol on the C2 side chain in a 2,2-disubstituted 1,3-cycloalkanedione derivative. We also report the total synthesis of natural (+)-lycopladine A [(+)-**6**] from (7*R*,7a*R*)-**9** and the formal synthesis of unnatural (−)-lycopladine A [(−)-**6**] from (7*S*,7a*S*)-**9**.



INTRODUCTION

Chiral quaternary centers at the angular positions are commonly found in biologically active compounds such as steroidal compounds, terpenes, and alkaloids. Thus, the discovery of general and efficient methods to prepare such structures, particularly in optically pure forms, may be the long-awaited solution for synthesizing complex natural products.

Chiral discrimination of the symmetrical substrates utilizing remote chiral sources is an efficient strategy to construct quaternary carbon centers.[1] We have established an efficient method to construct asymmetric quaternary carbon centers based on discrimination of the carbonyl groups at C1 and C3, which have reflected the chirality on the C2 side chain of 2,2-disubstituted 1,3-cycloalkanedione derivatives (Scheme 1).[2] Hydrolysis of the acetal group of **1a**−**e**, followed by intramolecular hemiacetal formation, and conversion of the primary alcohol to *tert*-butyldiphenylsilyl (TBDPS) ether briefly gave the hemiacetals **2a**−**e** and **3a**−**e** in more than 95:5 diastereomeric ratios. The hydrogen bonds between the hydrogen atom in the hydroxyl group and the oxygen atom in the TBDPS ether in **2a**−**e** play an important role in maintaining their configurations. Alternatively, acetal formation could be directed to the other carbonyl group when using isopropyl alcohol to produce **5a**−**e** with high selectivity (Scheme 1; **2a**−**e** → **5a**−**e**). Although the relationship between compounds **2** and **5** is diastereomeric, their absolute configuration at C3a is opposite to each other.

Researchers have widely investigated desymmetrization reactions of 2,2-disubstituted 1,3-cyclohexanedione or 3,3-disubstituted 1,4-cyclohexadiene derivatives[3] by either catalytic reaction[4] or intramolecular chiral induction.[5] As recent examples, Scheidt et al. reported NHC-catalyzed reactions,[4a] and Riant proposed the Cu(I)-catalyzed, highly stereoselective desymmetrization reactions of 2,2-disubstituted 1,3-cyclohexanedione derivatives[4b] (Scheme 2a,b). On the other hand, Landais et al. developed the intramolecular addition of the lithium amide,[5j] and Elliot et al. reported the addition of alkyllithium to 3,3-disubstituted 1,4-cyclohexadiene derivatives[5b] (Scheme 2c,d). However, the major difference between our method and the examples shown in Scheme 2 is reversibility. Our method is based on an addition of the oxygen atom to the carbonyl group and can be regarded as the diastereoselective protection of the carbonyl group at the symmetrical position. After being modified from the unprotected carbonyl group to the suitable functional group, the diastereoselectively protected carbonyl group can revert to a carbonyl group when necessary, and it can be utilized for the transformation to the other functional group. Moreover, the diastereoselectivities by internal asymmetric induction in most examples were achieved by kinetic control. It is noteworthy that the diastereoselectivities of the hemiacetal syntheses in our method (Scheme 1; **1a**−**e** → **2a**−**e**) were controlled by the thermodynamic stabilities among the possible compounds. Therefore, the diastereoselectivities were almost independent of the substituents on C2 (R for **1a**−**e** in Scheme 1). On the other hand, the preferential formation of **5a**−**e** over **4a**−**e** can be rationalized by kinetic controls.

Kobayashi et al. in 2006 isolated (+)-lycopladine A [(+)-(**6**)] from the club moss *Lycopodium complanatum* and clarified its structure and relative stereochemistry by careful analysis of the NMR spectra.[6] In 2006, Toste et al. reported the first total synthesis of (+)-lycopladine A [(+)-(**6**)] by utilizing a Au(I)-catalyzed cyclization reaction as a key step and also determined the absolute configuration of (+)-**6** (Scheme 3).[7a] Recently, Martin et al. reported the second efficient total synthesis of (±)-**6** via sequential conjugate addition and enolate arylation to construct the tricyclic framework (Scheme 3).[7b]

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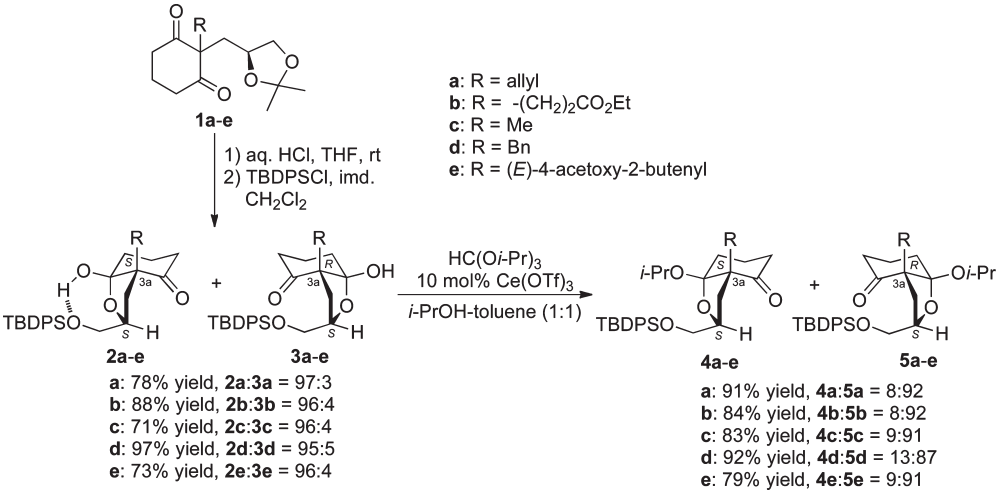
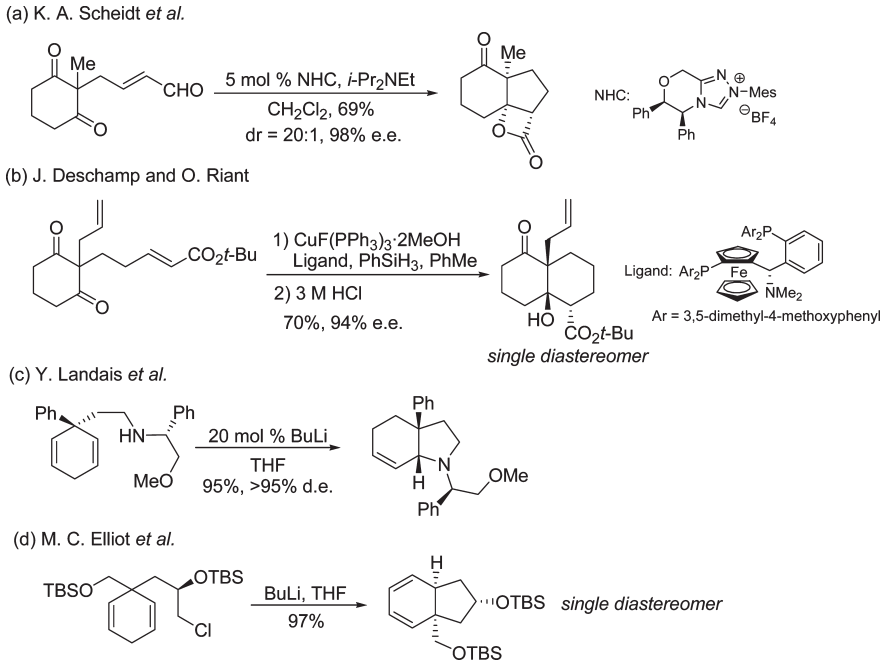
Scheme 1. Desymmetrization Reactions of 2,2-Disubstituted 1,3-Cyclohexanedione Derivatives



Scheme 2. Previous Examples of Desymmetrization Reactions of 2,2-Disubstituted 1,3-Cyclohexanedione or 3,3-Disubstituted 1,4-Cyclohexadiene Derivatives



The key features of the synthesis of lycopladine A [(+)-(**6**)] are the installation of all carbon quaternary centers at the benzylic position (C12), the construction of the *cis*-fused bicyclo[4.3.0] ring system, and the stereoselective introduction of the methyl group at C15. With these difficulties in mind, we planned the synthetic strategy for (+)-lycopladine A [(+)-(**6**)], as shown in Figure 1.

The introduction of the methyl group at C15 was planned on the conjugate addition from the convex face into **7**. Both the primary alcohol and the α,β-unsaturated ketone in **7** were considered being converted from the allyl group and the protected secondary alcohol in **8**, respectively. We considered both the construction of the *cis*-fused ring system by the stereoselective reduction of the enone and generating the pyridine ring from the resulting ketone of (7*R*,7a*R*)-**9**. The bicyclic α,β-unsaturated ketone (7*R*,7a*R*)-**9** was expected to be synthesized from **2a**, whose synthesis from **1a** has been already established.[2]

In this study, we report the synthesis of both enantiomers of **9** using **2a** as a common intermediate and the total synthesis of natural (+)-lycopladine A [(+)-(**6**)] from (7*R*,7a*R*)-**9**.

RESULTS AND DISCUSSION

Synthesis of Bicyclic Intermediates (7*R*,7a*R*)- and (7*S*,7a*S*)-9. According to the synthetic plan shown in Figure 1, we proceeded

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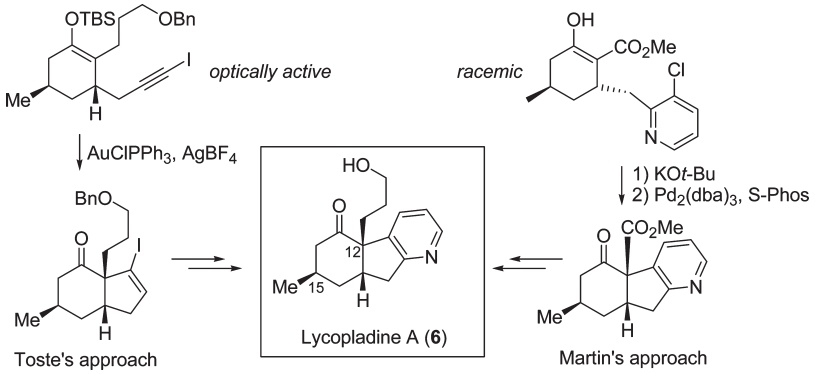
Scheme 3. Previous Synthesis of Lycopladine A



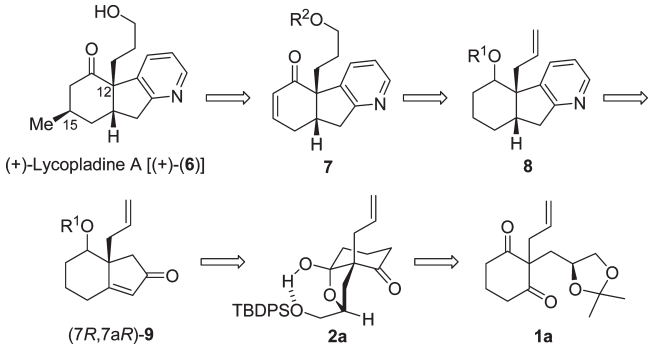


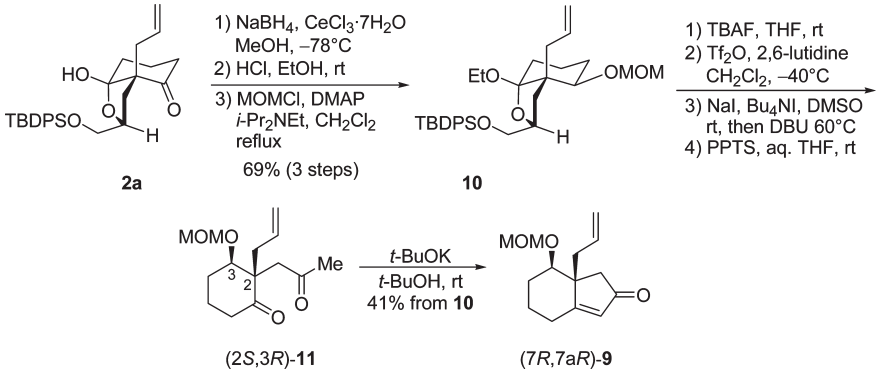
Figure 1. Retrosynthetic analysis of (+)-lycopladine A [(+)-(**6**)].

to establish the synthetic method of the chiral intermediate (7*R*,7a*R*)-**9** for the synthesis of natural (+)-lycopladine A [(+)-(**6**)]. First, the carbonyl group of hemiacetal **2a** was stereo- and chemoselectively reduced by sodium borohydride in the presence of cerium trichloride heptahydrate at −78 °C (Scheme 4). After converting the hemiacetal group to the corresponding ethyl acetal, the secondary hydroxyl group was protected by a MOM ether under standard reaction conditions.[8] We encountered some problems in the conversion of **10** to (2*S*,3*R*)-**11**, for example, the application of Mitsunobu conditions[9] or Burgess reagent[10] to the primary alcohol, which was obtained from **10** via its treatment with TBAF, for the dehydration reaction or the conversion of **10** to 2-nitrophenylselenyl derivatives[11] all failed, and the compounds that we observed were recovered portions or the decomposition of the starting material. Finally, we solved this problem by utilizing the triflate as a transient intermediate. First, the primary alcohol, which was obtained from **10**, was converted to the triflate group by triflic anhydride and 2,6-lutidine. Next, it was immediately treated with sodium iodide and tetrabutylammonium iodide to derive the corresponding iodide, followed by adding DBU to the reaction mixture to promote an E2 reaction of hydrogen iodide yielding the enol ether.[12] Finally, the enol ether was hydrolyzed under weak acidic conditions to give the diketone (2*S*,3*R*)-**11**, which could be converted to the desired bicyclic compound (7*R*,7a*R*)-**9** via an intramolecular aldol reaction in the presence of potassium *tert*-butoxide in 41% overall yield from **10** (Scheme 4).[13]

We also synthesized (7*S*,7a*S*)-**9**, which is the enantiomer of (7*R*,7a*R*)-**9**, from **5a**, as shown in Scheme 5. The stereoselective reduction of the carbonyl group in **5a** was accomplished with DIBALH at −78 °C to afford **12** in an 80% yield. The protection of the resulting hydroxyl group with the MOM group and the removal of the TBDPS group were performed under standard reaction conditions to give **13** in a good overall yield. **13** was successfully converted to (7*S*,7a*S*)-**9** by reactions identical to those required for converting **10** to (7*R*,7a*R*)-**9**, as shown in Scheme 4. All of the spectral data of (7*S*,7a*S*)-**9** were correlated to those of (7*R*,7a*R*)-**9** except for the sign of the specific rotation [(7*R*,7a*R*)-**9**: $[\alpha]^{24}_{D}$ −76.8 (*c* 1.00, $CHCl_3$). (7*S*,7a*S*)-**9**: $[\alpha]^{24}_{D}$ +79.9 (*c* 1.20, $CHCl_3$)].

Enantioselective Synthesis of Natural (+)-Lycopladine A (6) from (7*R*,7a*R*)-9. The introduction of the three-carbon unit

Scheme 4. Synthesis of (7*R*,7a*R*)-9 from 2a



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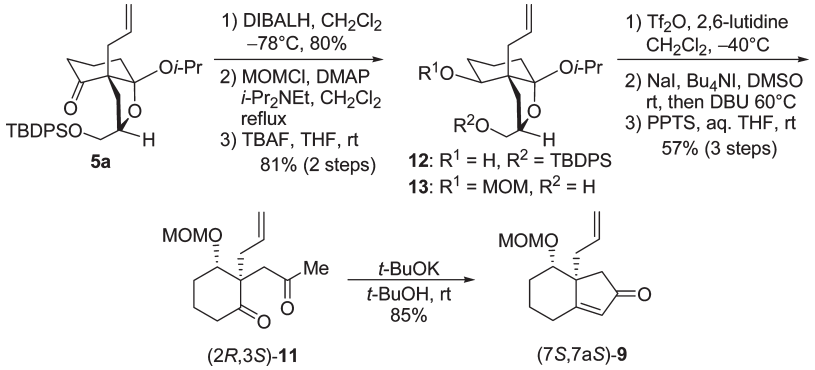
Scheme 5. Synthesis of (7*S*,7a*S*)-9 from 5a



Scheme 6. Deuterium Experiment of (7*R*,7a*R*)-9

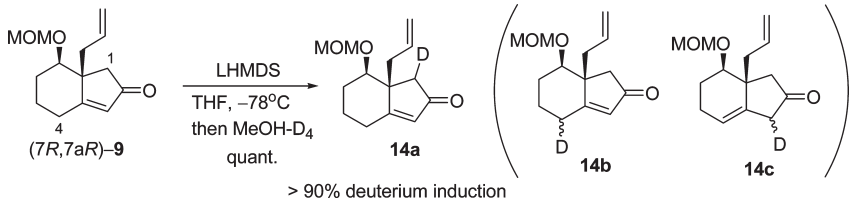
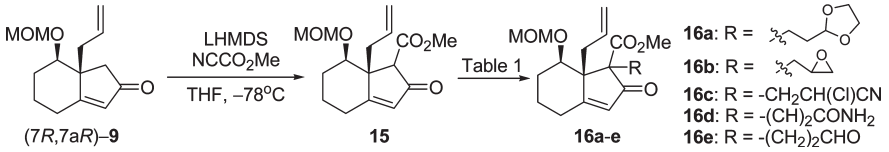


Table 1. Introduction of the Three-Carbon Unit at C1 of 15



entry	base	electrophile	solvent	temperature	product (yield %)
1	NaH	2-(2-bromoethyl)-1,3-dioxolane	DMF	0 to 60 °C	no reaction
2	DBU	epichlorohydrin		rt	**16b** (25)
3	DBU	chloroacetonitrile	MeCN	rt	no reaction
4	$CsCO_3$	propiolamide	DMSO	0 to 100 °C	no reaction
5	DBU	acrolein	MeCN	rt	**16e** (50)

into the C1 position was the main objective of our strategy. Because the C1 position is the neopentyl position (neighboring the quaternary center), we wondered about the possibility of the regioselective deprotonation followed by the substitution reaction at C1 over the C4 position. Therefore, we attempted to identify the reactivity of (7*R*,7a*R*)-**9** with a base by utilizing the deuterium experiment. When (7*R*,7a*R*)-**9** was treated with LHMDS at −78 °C for 1 h followed by treating with methanol-d_4, **14a** was afforded in a quantitative yield, and the ^{1}H NMR spectrum confirmed more than 90% deuterium induction at C1. In this case, both **14b** and **14c** were not detected by ^{1}H NMR spectrum (Scheme 6).

On the basis of the results shown in Scheme 6, we then attempted the direct introduction of the three-carbon unit at C1. However, in spite of our efforts to introduce the side chain directly by alkylation or by an aldol-type reaction at C1, all attempts failed. Therefore, we converted (7*R*,7a*R*)-**9** into **15**, which has an alkoxycarbonyl group as an activator, and attempted to introduce the three-carbon unit at C1. Table 1 summarizes the results.

The desired compounds could not be obtained in good yields by the alkylation reaction of **15** with the alkyl bromide or epichlorohydrin (Table 1, entries 1 and 2). The Michael addition reactions between **15** and 2-chloroacrylonitrile and propiolamide[14] did not proceed at all (Table 1, entries 3 and 4). However, we successfully obtained **16e** via the reaction of **15** with acrolein in the presence of DBU, although the yield was moderate [50% from (7*R*,7a*R*)-**9**] (Table 1, entry 5).

To construct the pyridine ring of lycopladine A, we then attempted to remove the alkoxycarbonyl group of **16e**. Unfortunately, **16e** was unstable in the presence of the nucleophile (lithium iodide in DMF) or under basic (lithium hydroxide in

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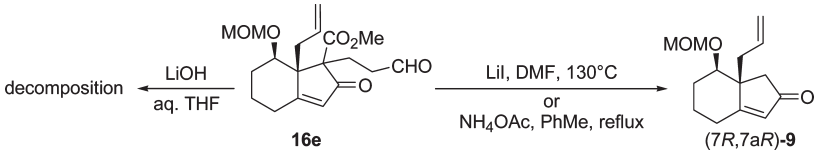
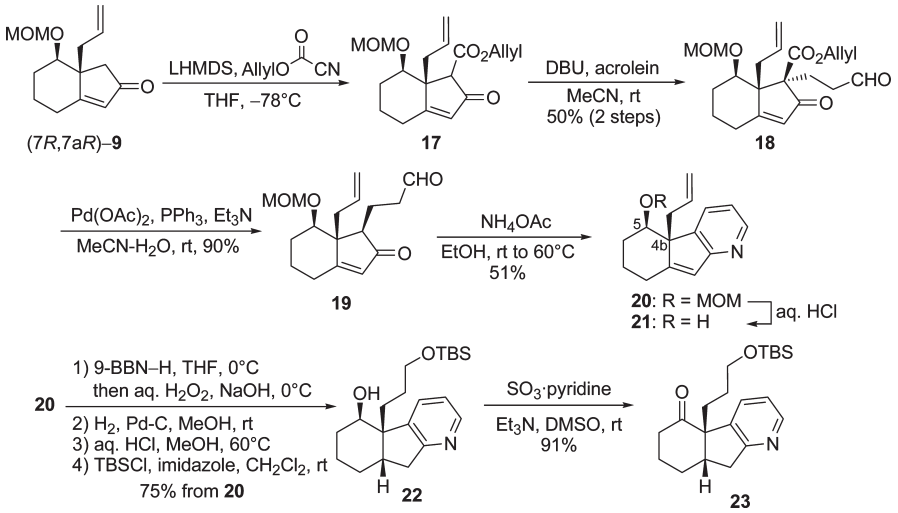
Scheme 7. Removal of the Methoxycarbonyl Group of 16e



Scheme 8. Synthesis of 23 from (7*R*,7a*R*)-9



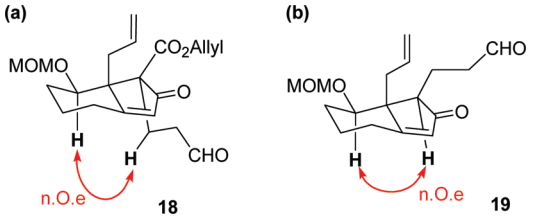


Figure 2. Observed NOE in **18** (a) and **19** (b).

aqueous THF) or nearly neutral conditions (ammonium acetate in toluene). We only observed the decomposition of **16e** or the recovery of (7*R*,7a*R*)-**9** via sequential retro reactions (Scheme 7).

Owing to these disappointing results, we focused on the utilization of another activator. It is well-known that the dealkoxycarbonylation reaction of α-allyloxycarbonyl ketone derivatives can be carried out under neutral conditions utilizing a Pd catalyst.[15] We treated the lithium enolate of (7*R*,7a*R*)-**9** with allyl cyanoformate, which was prepared according to the literature,[16] to afford **17** (Scheme 8). The reaction of **17** with acrolein in the presence of DBU gave **18** as a single isomer in a 50% yield from (7*R*,7a*R*)-**9**. The stereoselectivity may arise from the blocking of the enolate's *β*-face by the angular substituent and acrolein's selective approach from the α-face. The deallyloxycarbonylation reaction was carried out according to the method reported by Kim et al.[17] to afford the desired **19** as a single diastereomer in a 90% yield. We determined the configuration of **18** and **19** at C1 via NOESY spectroscopy as shown in Figure 2a,b, respectively. Fortunately, the oxidation of the dihydropyridine moiety proceeded during the reaction between **19** and ammonium acetate in ethanol, and pyridine **20** was afforded in a 51% yield (Scheme 8).

Because we performed the synthesis of lycopladine A skeleton **20**, the resulting task was assigned as follows: (A) stereoselective introduction of a methyl group, (B) conversion of the vinyl group to its primary alcohol, and (C) stereoselective reduction of the double bond. Although several possible orders of the above conversions (A−C) can be considered, we chose A as the first reaction. However, the alcohol **21**, which was obtained by removing the MOM group under acidic conditions, resisted oxidation (sulfur trioxide pyridine complex and triethylamine in DMSO).[18,19] Accordingly, we altered our approach and selected B as the first reaction.

The hydroboration−oxidation reaction of **20** with 9-BBN-H and an aqueous hydrogen peroxide−sodium hydroxide solution, hydrogenation of the double bond with hydrogen gas and palladium on carbon, removal of the MOM group under acidic conditions, and selective protection of the primary alcohol as the TBS-ether gave **22** in a 75% overall yield from **20**. The oxidation of the secondary hydroxyl group smoothly proceeded by treatment with a sulfur trioxide pyridine complex and triethylamine in DMSO[18] to obtain the tricyclic ketone **23** in a 91% yield. The stereochemistry between the cyclohexanone and cyclopentene moiety in **23** was confirmed as *cis* via NOESY spectroscopy, as shown in Figure 3.

Oxidation from cyclohexanone **23** to cyclohexenone **26** proved to be another difficult reaction (Table 2). The reaction via α-phenylselenyl ketone **24** did not give **26** in satisfactory yields (Table 2, entries 1−3). Direct oxidation of **23** by 2-iodoxybenzoic acid (IBX)[20] or the Saegusa reactions[21] via silyl enol ether **25** by palladium acetate afforded trace amount of **26** (Table 2, entries 4−6). Fortunately, we obtained **26** from **25** in

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good yields by using IBX and 4-methoxypyridine *N*-oxide (MPO) in DMSO, which was developed by Nicolaou et al. (Table 2, entry 7).[22]

The installation of the methyl group at the β-position of the carbonyl group by treating with Me_2CuLi in THF at −40 °C did not give satisfactory results in terms of both yield (38%) and stereoselectivity (**27a**/**27b** = 10:1, inseparable mixture). This problem was solved by utilizing a higher order cuprate [$Me_2Cu(CN)Li_2$, THF, −40 °C].[23] The yield of the product **27a**[24] was improved up to 78% and realized perfect stereoselectivity (Scheme 9). Finally, the TBS group was removed by TBAF to accomplish the total synthesis of (+)-lycopladine A [(+)-(**6**)] (Scheme 9). All of the spectral data of the synthesized (+)-**6** were correlated to those reported.[6,7] Because we have established the synthesis of (7*S*,7a*S*)-**9**, which is the enantiomer of the staring material of the proposed (+)-lycopladine A synthesis, the formal synthesis of unnatural (−)-lycopladine A [(−)-(**6**)] has also been provided.

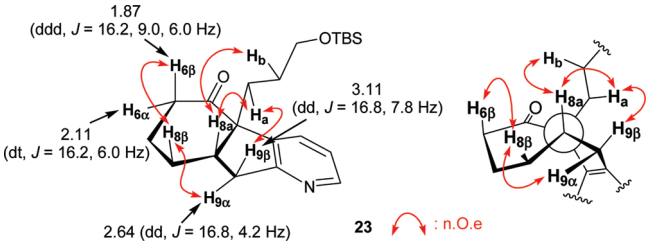


Figure 3. Selected data of the ^{1}H NMR spectrum and observed NOE in **23**.

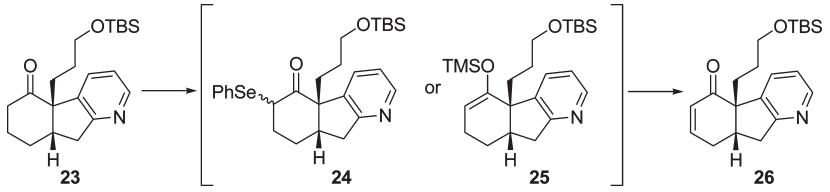
In conclusion, we successfully synthesized both the enantiomers of bicyclic enones (7*R*,7a*R*)- and (7*S*,7a*S*)-**9** from the hemiacetal **2a**, which could be synthesized from the symmetrical diketone **1a** via the diastereoselective protection of one carbonyl group. Furthermore, we provided the total synthesis of natural lycopladine A [(+)-(**6**)] from (7*R*,7a*R*)-**9**.

EXPERIMENTAL SECTION

General Experimental Methods. For ^{1}H NMR spectra, chemical shifts (δ) are given from TMS (0.00 ppm) in $CDCl_3$ and from residual nondeuterated solvent peak in the other solvents (benzene-d_6, 7.15 ppm; pyridine-d_5, 7.55 ppm; and MeOH-d_4, 3.30) as internal standards. For ^{13}C NMR spectra, chemical shifts (δ) are given from $CDCl_3$ (77.0 ppm), pyridine-d_5 (149.0 ppm), benzene-d_6 (128.0 ppm), and MeOH-d_4 (49.0 ppm) as internal standards. The synthesis of the starting material **2a** was reported in our previous communication,[2] and the Supporting Information is available. The commercially available anhydrous solvents were used without further distillation.

((2*S*,3a*S*,4*R*,7a*R*)-3a-Allyl-7a-ethoxy-4-methoxymethoxyoctahydrobenzofuran-2-ylmethoxy)-*tert*-butyldiphenylsilane (10). A suspension of cerium trichloride heptahydrate (0.847 g, 2.27 mmol) in methanol (20 mL) was added to a solution of **2a** (2.113 g, 4.55 mmol) in methanol (25 mL) at −78 °C and stirred for 30 min at the same temperature. Sodium borohydride (0.138 g, 3.64 mmol) was added in a portion, and the mixture was stirred for 1.75 h at the same temperature. Acetone was added to quench the excess sodium borohydride, and water was added to the mixture. The aqueous phase was extracted with ethyl acetate, and the combined organic solution was washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated. The residue was

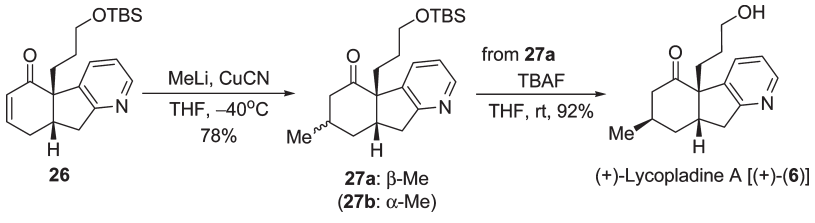
Table 2. Conversion of 23 to 26



entry	compounds	conditions		yield (%)[a]
1	**23** → **24** → **26**	(1) LHMDS, PhSeCl, THF −78 to −40 °C	(2) aq H_2O_2, pyridine, CH_2Cl_2, 0 °C	30−50
2			(2) aq H_2O_2, pyridine, CH_2Cl_2, −30 °C	42
3			(2) $NaIO_4$, aq MeOH, rt	44
4	**23** → **26**	IBX, MPO, DMSO, rt		trace
5		IBX, DMSO, 70 °C		trace
6	**23** → **25** → **26**	(1) LHMDS, TMSCl HMPA, THF, −40 °C	(2) $Pd(OAc)_2$, MeCN	trace
7			(2) IBX, MPO, DMSO, rt	80

[a] Overall yield from **23**.

Scheme 9. Synthesis of (+)-Lycopladine A [(+)-(6)]



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passed through a silica gel pad to afford the alcohol (1.81 g) as a colorless oil, which was used in the next reaction without further purification.

Acetyl chloride (0.011 g, 0.14 mmol) was added to a solution of the alcohol (1.81 g) in anhydrous ethanol (45 mL) at room temperature. After stirring for 25 min, one drop of *N*,*N*-diisopropylethylamine was added to the mixture to neutralize the reaction mixture. The solvent and the excess reagent were evaporated to give the residue that was passed through a silica gel pad to afford the crude acetal (1.64 g) as a colorless oil, which was used in the next reaction without further purification.

N,*N*-Diisopropylethylamine (2.538 g, 19.64 mmol), chloromethyl methyl ether (1.318 g, 16.37 mmol), and DMAP (0.040 g, 0.33 mmol) were successively added to a solution of the crude acetal (1.64 g) in anhydrous dichloromethane (13 mL) at 0 °C, and the mixture was refluxed for 11 h. Saturated aqueous ammonium chloride solution was added to the mixture, and the aqueous phase was extracted with chloroform. The combined organic solution was washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography [ethyl acetate−hexane (1:15)] to afford **10** (1.68 g, 69% from **2a**) as a colorless oil: $[\alpha]^{25}_{D}$ −33.2 (*c* 1.00, $CHCl_3$); IR ν (neat, cm^{-1}) 1146, 1113, 1078, 1042, 702; ^{1}H NMR (600 MHz, C_5D_5N) δ 0.94 (3H, t, *J* = 7.2 Hz), 1.14 (9H, s), 1.27−1.41 (2H, m), 1.44−1.56 (2H, m), 1.82 (1H, m), 1.88 (1H, dd, *J* = 12.0, 8.4 Hz), 2.08 (1H, br d, *J* = 12.0 Hz), 2.30 (1H, dd, *J* = 12.0, 7.2 Hz), 2.61 (2H, d, *J* = 7.8 Hz), 3.33 (1H, dq, *J* = 9.0, 7.2 Hz), 3.38 (3H, s), 3.51 (1H, dq, *J* = 9.0, 7.2 Hz), 3.57 (1H, dd, *J* = 12.0, 4.2 Hz), 3.81 (1H, dd, *J* = 10.2, 5.4 Hz), 3.96 (1H, dd, *J* = 10.2, 7.2 Hz), 4.55−4.62 (1H, m), 4.70 (1H, d, *J* = 7.2 Hz), 4.81 (1H, d, *J* = 7.2 Hz), 5.02−5.06 (1H, m), 5.10−5.16 (1H, m), 6.29 (1H, ddt, *J* = 18.0, 10.2, 7.8 Hz), 7.14−7.50 (6H, m), 7.82−7.91 (4H, m); ^{13}C NMR (150 MHz, C_5D_5N) δ 15.7, 19.5, 20.2, 27.1, 27.4, 28.3, 33.3, 36.1, 53.9, 55.2, 55.5, 69.5, 78.1, 80.4, 96.3, 108.8, 115.5, 123.1, 128.2, 128.3, 130.2, 135.1, 136.1, 139.4; MS *m*/*z* 538 (M^+, 9.4%), 481 (M^+ − *t*-Bu, 100.0%), 435 (60.6%), 373 (47.4%); HRMS calcd for $C_{32}H_{46}O_5Si^+$ (M^+) 538.3114, found 538.3091.

(7*R*,7a*R*)-7a-Allyl-7-methoxymethoxy-1,4,5,6,7,7a-hexahydroinden-2-one [(7*R*,7a*R*)-9]. TBAF (1.0 M solution in THF, 2.54 mL, 2.54 mmol) was added to a solution of **10** (0.94 g, 1.56 mmol) in THF (8.5 mL) at room temperature. After stirring for 3 h, phosphate buffer solution (pH 6.86) was added to the mixture. The aqueous phase was extracted with ethyl acetate, and the combined extract was washed with saturated aqueous NaCl solution, dried over anhydrous magnesium sulfate, and concentrated. The residue was passed through a silica gel pad to afford the crude alcohol (0.423 g) as a colorless oil, which was used in the next reaction without further purification.

2,6-Lutidine (0.362 g, 3.38 mmol) and trifluoromethanesulfonic anhydride (0.477 g, 1.69 mmol) were successively added to a solution of the crude alcohol (0.423 g) in anhydrous dichloromethane (14 mL) at −40 °C, and the mixture was stirred for 20 min at the same temperature. Diethyl ether was added to the mixture, and the precipitate was filtered through a pad of Celite eluting with diethyl ether. The filtrate was concentrated to afford the crude triflate as a yellow oil, which was immediately subjected to the next reaction.

Tetrabutylammonium iodide (0.111 g, 0.282 mmol) and sodium iodide (0.634 g, 4.224 mmol) were successively added to a solution of the crude triflate in anhydrous DMSO (14 mL) at room temperature. After stirring for 10 min, DBU (2.144 g, 14.08 mmol) was added and the mixture was stirred at 60 °C for 8 h. Saturated aqueous ammonium chloride solution was added to the mixture, and the aqueous phase was extracted with ethyl acetate. The combined organic solution was successively washed with saturated aqueous ammonium chloride solution (3 times) and saturated aqueous sodium chloride solution. The organic solution was dried over anhydrous magnesium sulfate and concentrated to give the crude enol ether as a yellow oil, which was immediately used in the next reaction.

A solution of the crude enol ether and PPTS (0.171 g, 0.282 mmol) in a mixture of THF and water (1:1, 14 mL) was stirred for 12 h at room temperature. Saturated aqueous sodium hydrogen carbonate solution was added to the mixture, and the aqueous phase was extracted with ethyl acetate. The combined organic solution was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography [ethyl acetate−hexane (1:6)] to afford (2*S*,3*R*)-**11** (0.220 g) as a yellow oil with inseparable impurities. It was used in the next reaction without further purification.

Potassium *tert*-butoxide (0.097 g, 0.865 mmol) was added to a solution of (2*S*,3*R*)-**11** (0.220 g) in anhydrous *tert*-butyl alcohol (8.6 mL) at room temperature. After stirring for 5 h at the same temperature, saturated aqueous ammonium chloride solution was added to the mixture and the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated to afford the solid, which was recrystallized from hexane to provide (7*R*,7a*R*)-**9** (0.150 g, 41% from **10**) as colorless needles: mp 104−105 °C; $[\alpha]^{24}_{D}$ −76.8 (*c* 1.00, $CHCl_3$); IR ν (neat, cm^{-1}) 1703, 1624, 1097, 1028, 910; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (1H, qt, *J* = 13.6, 4.0 Hz), 1.65−1.83 (1H, m), 1.92−2.11 (2H, m), 2.23 (1H, td, *J* = 13.6, 6.8 Hz), 2.35 (1H, d, *J* = 19.2 Hz), 2.44 (1H, d, *J* = 19.2 Hz), 2.50 (2H, d, *J* = 7.6 Hz), 2.61 (1H, m), 3.37 (3H, s), 3.38−3.45 (1H, m), 4.58 (1H, d, *J* = 7.2 Hz), 4.73 (1H, d, *J* = 7.2 Hz), 5.04 (1H, dd, *J* = 9.6, 1.6 Hz), 5.08 (1H, dd, *J* = 17.2, 1.6 Hz), 5.47 (1H, ddt, *J* = 17.2, 9.6, 7.2 Hz), 5.88 (1H, d, *J* = 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 26.9, 27.1, 34.1, 46.6, 51.7, 55.6, 83.7, 95.3, 118.8, 129.4, 132.1, 182.6, 207.5; MS *m*/*z* 236 (M^+, 66.1%), 204 (M^+ − MeOH, 19.3%), 174 (42.3%); HRMS calcd for $C_{14}H_{20}O_3^+$ (M^+) 236.1412, found 236.1400.

(2*S*,3a*R*,4*S*,7a*S*)-3a-Allyl-2-(*tert*-butyldiphenylsilanyloxymethyl)-7a-isopropoxyoctahydrobenzofuran-4-ol (12). DIBALH (0.99 M solution in toluene, 1.6 mL, 1.584 mmol) was added to a solution of **5a** (0.540 g, 1.067 mmol) in anhydrous dichloromethane (20 mL) at −78 °C. After stirring for 1.5 h at the same temperature, diethyl ether and phosphate buffer solution (pH 6.86) were successively added to the mixture. The precipitate was filtered through a pad of Celite eluting with ethyl acetate, and the filtrate was extracted with ethyl acetate. The combined organic solution was washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography [ethyl acetate−hexane (1:12)] to afford **12** (0.435 g, 80%) as a colorless oil: $[\alpha]^{25}_{D}$ +9.3 (*c* 1.40, $CHCl_3$); IR ν (neat, cm^{-1}) 3425, 1113, 702; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (9H, s), 1.09 (3H, d, *J* = 6.4 Hz), 1.10 (3H, d, *J* = 6.4 Hz), 1.32−1.70 (5H, m), 1.95−2.08 (2H, m), 2.12 (1H, d, *J* = 12.0 Hz), 2.41 (1H, dd, *J* = 14.8, 8.8 Hz), 2.53 (1H, m), 3.61 (1H, m), 3.76 (2H, d, *J* = 4.8 Hz), 4.06 (1H, quint, *J* = 2.4 Hz), 4.20 (1H, m), 4.97 (1H, br d, *J* = 10.0 Hz), 5.09 (1H, dd, *J* = 17.2, 1.2 Hz), 6.00−6.14 (1H, m), 7.31−7.47 (6H, m), 7.62−7.79 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 19.8, 24.4, 24.7, 26.8, 29.2, 30.6, 33.4, 34.7, 53.6, 62.7, 66.6, 75.4, 76.9, 108.8, 115.6, 127.60, 127.63, 129.6, 133.66, 133.71, 135.68, 135.70, 139.4; MS *m*/*z* 451 (M^+ − *t*-Bu, 21.0%), 391 (M^+ − *t*-Bu − *i*-PrOH, 100.0%), 373 (32.4%), 335 (29.9%); HRMS calcd for $C_{27}H_{35}O_4Si^+$ (M^+ − *t*-Bu) 451.2305, found 451.2289.

((2*S*,3a*R*,4*S*,7a*S*)-3a-Allyl-7a-isopropoxy-4-methoxymethoxyoctahydrobenzofuran-2-yl)methanol (13). *N*,*N*-Diisopropylethylamine (0.126 g, 0.971 mmol), chloromethyl methyl ether (1.318 g, 16.37 mmol), and DMAP (0.004 g, 0.028 mmol) were successively added to a solution of **12** (0.141 g, 0.278 mmol) in anhydrous dichloromethane (2.8 mL) at 0 °C, and the mixture was refluxed for 15 h. Saturated aqueous ammonium chloride solution was added to the mixture, and the aqueous phase was extracted with diethyl ether. The combined

organic solution was successively washed with saturated aqueous ammonium chloride solution (2 times), saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated. The residue (0.160 g) was used in the next reaction without further purification.

TBAF (1.0 M solution in THF, 0.416 mL, 0.416 mmol) was added to a solution of the crude product (0.160 g) in THF (2.8 mL) at room temperature. After stirring for 2 h, water was added to the mixture and the aqueous phase was extracted with diethyl ether. The combined extract was washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography [ethyl acetate−hexane (1:4−1:2)] to afford **13** (0.071 g, 81% from **12**) as a colorless oil: $[\alpha]^{23}_{D}$ +80.6 (*c* 1.05, $CHCl_3$); IR ν (neat, cm^{-1}) 3450, 1070, 1036; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (3H, d, *J* = 6.8 Hz), 1.13 (3H, d, *J* = 6.8 Hz), 1.32−1.55 (3H, m), 1.61 (1H, m), 1.66 (1H, dd, *J* = 8.4, 4.4 Hz), 1.75 (1H, m), 2.05 (1H, dd, *J* = 8.8, 6.0 Hz), 2.10−2.26 (2H, m), 2.35−2.44 (2H, m), 3.38 (3H, s), 3.49 (1H, dd, *J* = 12.0, 4.0 Hz), 3.65−3.72 (2H, m), 4.08 (1H, septet, *J* = 6.8 Hz), 4.15−4.24 (1H, m), 4.56 (1H, d, *J* = 6.8 Hz), 4.70 (1H, d, *J* = 6.8 Hz), 4.92 (1H, m), 5.00 (1H, m), 6.08 (1H, ddt, *J* = 13.2, 10.0, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 24.5, 24.7, 27.1, 29.1, 33.1, 34.6, 53.1, 55.6, 62.7, 65.8, 81.4, 95.7, 109.2, 115.2, 138.9; MS *m*/*z* 314 (M^+, 3.5%), 283 (M^+ − MeO, 84.1%), 255 (76.9%), 197 (100.0%), 179 (86.6%); HRMS calcd for $C_{17}H_{30}O_5^+$ (M^+) 314.2094, found 314.2086.

(2*R*,3*S*)-2-Allyl-3-methoxymethoxy-2-(2-oxopropyl)cyclohexanone [(2*R*,3*S*)-11]. 2,6-Lutidine (0.030 g, 0.278 mmol) and trifluoromethanesulfonic anhydride (0.041 g, 0.145 mmol) were successively added to a solution of **13** (0.035 g, 0.111 mmol) in anhydrous dichloromethane (1.1 mL) at −40 °C, and the mixture was stirred for 30 min at the same temperature. Diethyl ether was added to the mixture, and the precipitate was filtered through a pad of Celite eluting with diethyl ether. The filtrate was concentrated to afford the crude triflate as a yellow oil, which was immediately subjected to the next reaction.

Tetrabutylammonium iodide (0.009 g, 0.022 mmol) and sodium iodide (0.050 g, 0.334 mmol) were successively added to a solution of the crude triflate in anhydrous DMSO (1.1 mL) at room temperature. After stirring for 5 min, DBU (0.169 g, 1.113 mmol) was added and the mixture was stirred at 60 °C for 7.5 h. Saturated aqueous ammonium chloride solution was added to the mixture, and the aqueous phase was extracted with ethyl acetate. The combined organic solution was successively washed with saturated aqueous ammonium chloride solution (3 times) and saturated aqueous sodium chloride solution. The organic solution was dried over anhydrous magnesium sulfate and concentrated to give the crude enol ether as a yellow oil, which was immediately used in the next reaction.

A solution of the crude enol ether and PPTS (0.006 g, 0.022 mmol) in a mixture of THF and water (1:1, 2.2 mL) was stirred for 20 h at room temperature. Saturated aqueous sodium hydrogen carbonate solution was added to the mixture, and the aqueous phase was extracted with ethyl acetate. The combined organic solution was washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography [ethyl acetate−hexane (1:4)] to afford (2*R*,3*S*)-**11** (0.016 g, 57% from **13**) as a yellow oil: $[\alpha]^{21}_{D}$ +115.7 (*c* 1.02, $CHCl_3$); IR ν (neat, cm^{-1}) 1715, 1705, 1030; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64−1.77 (1H, m), 1.80−1.96 (2H, m), 2.09 (1H, m), 2.14 (3H, s), 2.27 (1H, ddd, *J* = 16.0, 12.8, 6.0 Hz), 2.32−2.43 (2H, m), 2.46 (1H, dd, *J* = 14.4, 6.8 Hz), 2.57 (1H, d, *J* = 17.6 Hz), 3.06 (1H, d, *J* = 17.6 Hz), 3.35 (3H, s), 4.24 (1H, dd, *J* = 11.2, 5.2 Hz), 4.58 (1H, d, *J* = 6.4 Hz), 4.65 (1H, d, *J* = 6.4 Hz), 5.01−5.08 (2H, m), 5.50−5.62 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 26.9, 30.7, 35.7, 38.3, 44.3, 55.6, 56.5, 79.3, 96.4, 118.4, 133.0, 207.0, 210.0; MS *m*/*z* 254 (M^+, 30.2%), 211 (60.5%), 209 (M^+ − $MeOCH_2$, 100.0%); HRMS calcd for $C_{14}H_{22}O_4^+$ (M^+) 254.1518, found 254.1517.

(7*S*,7a*S*)-7a-Allyl-7-methoxymethoxy-1,4,5,6,7,7a-hexahydroinden-2-one [(7*S*,7a*S*)-9]. Potassium *tert*-butoxide (0.026 g, 0.232 mmol) was added to a solution of (2*R*,3*S*)-**11** (0.059 g, 0.232 mmol) in anhydrous *tert*-butyl alcohol (1.5 mL) at room temperature. After stirring for 4 h at the same temperature, saturated aqueous ammonium chloride solution was added to the mixture and the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography [ethyl acetate−hexane (1:4)] to afford (7*S*,7a*S*)-**9** (0.047 g, 85%) as a colorless solid: mp 103−105 °C (hexane); $[\alpha]^{24}_{D}$ +79.9 (*c* 1.20, $CHCl_3$); IR, ^{1}H NMR, ^{13}C NMR, and MS spectra were identical to those of (7*R*,7a*R*)-**9**.

(7*R*,7a*R*)-7a-Allyl-1-deuterio-7-methoxymethoxy-1,4,5,6,7,7a-hexahydroinden-2-one (14a). LHMDS (1.0 M solution in THF, 0.279 mL, 0.279 mmol) was added to a solution of (7*R*,7a*R*)-**9** (0.044 g, 0.186 mmol) in THF (1.9 mL) at −78 °C. After stirring for 1 h at the same temperature, methanol-d_4 (0.5 mL) was added and the mixture was stirred for 5 min. Phosphate buffer solution (pH 6.86) was added to the mixture, and the aqueous phase was extracted with diethyl ether. The combined organic solution was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography [ethyl acetate−hexane (1:4)] to afford **14a** (0.043 g, 99%) as a colorless solid: IR ν (neat, cm^{-1}) 1701, 1624, 1097, 1028, 911; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (1H, qt, *J* = 13.2, 4.4 Hz), 1.65−1.82 (1H, m), 1.94−2.08 (2H, m), 2.23 (1H, tdd, *J* = 13.6, 6.0, 2.0 Hz), 2.30−2.46 (1H, m), 2.50 (2H, d, *J* = 7.6 Hz), 2.57−2.65 (1H, m), 3.38 (3H, s), 3.42 (1H, dd, *J* = 11.6, 4.4 Hz), 4.59 (1H, d, *J* = 6.8 Hz), 4.73 (1H, d, *J* = 6.8 Hz), 5.04 (1H, br d, *J* = 9.6 Hz), 5.09 (1H, dd, *J* = 17.2, 1.6 Hz), 5.47 (1H, ddt, *J* = 17.2, 9.6, 7.2 Hz), 5.88 (1H, d, *J* = 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 26.9, 27.0, 34.1, 46.2 (t), 51.7, 55.6, 83.8, 95.4, 118.9, 129.5, 132.3, 182.8, 207.8; MS *m*/*z* 237 (M^+, 72.6%), 181 (41.4%), 175 (48.1%), 45 (100.0%); HRMS calcd for $C_{14}H_{19}DO_3^+$ (M^+) 237.1475, found 237.1473.

(1*R*,7*R*,7a*S*)-7a-Allyl-7-methoxymethoxy-2-oxo-1-(3-oxopropyl)-2,4,5,6,7,7a-hexahydro-1*H*-indene-1-carboxylic Acid Methyl Ester (16e) (Table 1, Entry 5). LHMDS (1.0 M solution in THF, 3.8 mL, 3.81 mmol) was added to a solution of (7*R*,7a*R*)-**9** (0.60 g, 2.54 mmol) in THF (26 mL) at −78 °C. After stirring for 1 h at the same temperature, methyl cyanoformate (0.864 g, 10.2 mmol) was added and the mixture was stirred for 30 min. Saturated aqueous ammonium chloride solution was added to the mixture, and the aqueous phase was extracted with ethyl acetate. The combined organic solution was washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated. The residue was passed through a silica gel pad to afford the crude **15** (1.01 g) as a yellow oil, which was used in the next reaction without further purification.

DBU (0.464 g, 3.05 mmol) was added to a solution of the crude **15** (1.01 g) in anhydrous acetonitrile (20 mL) at room temperature. After stirring for 5 min, a solution of acrolein monomer (90%, 0.158 g, 2.54 mmol) in anhydrous acetonitrile (5 mL) was dropped over 30 min and the mixture was stirred at the same temperature for 30 min. Saturated aqueous ammonium chloride solution was added to the mixture, and the aqueous phase was extracted with ethyl acetate. The combined organic solution was washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography [ethyl acetate−hexane (1:4−1:1)] to afford **16e** [0.445 g, 50% from (7*R*,7a*R*)-**9**] as a pale yellow oil: $[\alpha]^{26}_{D}$ −144.4 (*c* 1.05, $CHCl_3$); IR ν (neat, cm^{-1}) 1741, 1726, 1701, 1633, 1039; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (1H, qt, *J* = 13.7, 3.9 Hz), 1.70−1.90 (2H, m), 1.96 (1H, m), 2.08 (1H, tdd, *J* = 14.2, 5.6, 1.6 Hz), 2.25 (1H, m), 2.45−2.72 (5H, m), 2.92 (1H, ddd, *J* = 18.6, 10.0, 4.6 Hz), 3.44 (3H, s), 3.71 (3H, s), 3.98 (1H, dd, *J* = 11.2, 5.2 Hz), 4.72 (1H, d, *J* = 6.8 Hz), 4.79 (1H, d, *J* = 6.8 Hz), 4.93 (1H, br d, *J* = 10.8 Hz),

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4.99 (1H, dd, J = 16.8, 1.2 Hz), 5.60 (1H, m), 5.80 (1H, d, J = 1.6 Hz), 9.74 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 25.7, 27.3, 28.4, 34.3, 39.5, 51.7, 56.1, 58.2, 64.3, 77.4, 95.5, 117.1, 126.3, 133.2, 170.8, 179.1, 200.8, 203.7; MS m/z 350 (M^+, 5.6%), 294 (34.1%), 262 (69.7%), 232 (84.9%), 200 (100.0%); HRMS calcd for $C_{19}H_{26}O_6^+$ (M^+) 350.1729, found 350.1719.

(1*R*,7*R*,7a*S*)-7a-Allyl-7-methoxymethoxy-2-oxo-1-(3-oxopropyl)-2,4,5,6,7,7a-hexahydro-1*H*-indene-1-carboxylic Acid Allyl Ester (18). LHMDS (1.0 M solution in THF, 19.8 mL, 19.8 mmol) was added to a solution of (7*R*,7a*R*)-**9** (3.12 g, 13.2 mmol) in THF (132 mL) at −78 °C. After stirring for 1 h at the same temperature, allyl cyanoformate (7.33 g, 66.0 mmol) was added and the mixture was stirred for 30 min. Saturated aqueous ammonium chloride solution was added to the mixture, and the aqueous phase was extracted with ethyl acetate. The combined organic solution was washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated. The residue was passed through a silica gel pad to afford the crude **17** (4.20 g) as a yellow oil, which was used in the next reaction without further purification.

DBU (2.54 mL, 17.0 mmol) was added to a solution of the crude **17** (4.20 g) in anhydrous acetonitrile (130 mL) at room temperature. After stirring for 5 min, a solution of acrolein monomer (90%, 0.953 g, 17.0 mmol) in anhydrous acetonitrile (40 mL) was dropped over 30 min and the mixture was stirred at the same temperature for 30 min. Saturated aqueous ammonium chloride solution was added to the mixture, and the aqueous phase was extracted with ethyl acetate. The combined organic solution was washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography [ethyl acetate−hexane (1:4−1:1)] to afford **18** [2.48 g, 50% from (7*R*,7a*R*)-**9**] as a yellow oil: $[\alpha]^{25}_D$ −123.5 (c 0.98, $CHCl_3$); IR ν (neat, cm^{-1}) 1739, 1724, 1703, 1040; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.35 (1H, qt, J = 13.8, 3.6 Hz), 1.75−1.88 (2H, m), 1.95 (1H, m), 2.07 (1H, tdd, J = 14.1, 5.6, 1.8 Hz), 2.25 (1H, m), 2.54 (1H, ddd, J = 19.0, 10.5, 4.8 Hz), 2.59 (2H, d, J = 7.2 Hz), 2.60 (1H, m), 2.65 (1H, ddd, J = 13.7, 10.1, 5.0 Hz), 2.93 (1H, ddd, J = 19.0, 10.1, 4.7 Hz), 3.43 (3H, s), 3.99 (1H, dd, J = 11.4, 4.8 Hz), 4.53 (1H, ddt, J = 13.2, 5.4, 1.2 Hz), 4.67−4.76 (2H, m), 4.77 (1H, d, J = 6.6 Hz), 4.91 (1H, dd, J = 10.2, 1.8 Hz), 4.97 (1H, dd, J = 16.8, 1.8 Hz), 5.25 (1H, dd, J = 10.2, 1.2 Hz), 5.39 (1H, dd, J = 16.8, 1.2 Hz), 5.62 (1H, ddt, J = 16.8, 10.2, 7.2 Hz), 5.79 (1H, d, J = 1.8 Hz), 5.91 (1H, ddt, J = 16.8, 10.8, 6.0 Hz), 9.74 (1H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.2, 25.7, 27.4, 28.4, 34.4, 39.6, 56.1, 58.3, 64.3, 65.5, 77.4, 95.6, 117.0, 118.8, 126.3, 131.5, 133.5, 169.9, 179.0, 200.9, 203.5; MS m/z 376 (M^+, 3.5%), 320 (33.3%), 288 (36.7%), 262 (41.5%), 258 (73.4%), 230 (51.6%), 217 (39.8%), 200 (100.0%); HRMS calcd for $C_{21}H_{28}O_6^+$ (M^+) 376.1886, found 376.1869.

3-((1*R*,7*R*,7a*R*)-7a-Allyl-7-methoxymethoxy-2-oxo-2,4,5,6,7,7a-hexahydro-1*H*-inden-1-yl)propionaldehyde (19). Palladium acetate (0.0224 g, 0.0999 mmol), triphenylphosphine (0.052 g, 0.199 mmol), and triethylamine (0.121 g, 1.20 mmol) were successively added to a solution of **18** (0.376 g, 0.999 mmol) in a mixture of acetonitrile and water (9:1, 22 mL) at room temperature. After stirring for 1 h at the same temperature, saturated aqueous ammonium chloride solution was added to the mixture and the aqueous phase was extracted with ethyl acetate. The combined organic solution was washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography [ethyl acetate−hexane (1:2−1:1)] to afford **19** (0.263 g, 90%) as a yellow oil: $[\alpha]^{25}_D$ +8.5 (c 1.28, $CHCl_3$); IR ν (neat, cm^{-1}) 1720, 1701, 1626, 1036; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.40 (1H, qt, J = 13.8, 4.2 Hz), 1.75 (1H, tdd, J = 13.5, 11.8, 4.2 Hz), 1.94−2.15 (5H, m), 2.17 (1H, t, J = 7.5 Hz), 2.48 (1H, dd, J = 15.6, 7.8 Hz), 2.60 (1H, m), 2.64 (1H, dd, J = 15.6, 6.6 Hz), 2.75 (1H, dtd, J = 18.0, 7.2, 1.2 Hz), 3.06 (1H, dtd, J = 18.0, 7.2, 1.2 Hz), 3.37 (3H, s), 3.43 (1H, dd, J = 11.8, 4.2 Hz), 4.67 (1H, d, J = 6.0 Hz), 4.75 (1H, d, J = 6.0 Hz), 4.97 (1H, dd, J = 9.6, 1.8 Hz), 5.07 (1H, dd, J = 16.8, 1.8 Hz), 5.29 (1H, ddt, J = 16.8, 9.6, 7.2 Hz), 5.89 (1H, d, J = 1.2 Hz), 9.81 (1H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.0, 23.3, 27.3, 27.4, 31.1, 43.0, 54.5, 55.6, 57.5, 86.2, 95.9, 118.0, 128.1, 133.2, 179.7, 202.4, 209.0; MS m/z 292 (M^+, 5.8%), 260 (13.0%), 230 (15.2%), 149 (21.4%), 45 (100.0%); HRMS calcd for $C_{17}H_{24}O_4^+$ (M^+) 292.1674, found 292.1670.

(4b*S*,5*R*)-4b-Allyl-5-methoxymethoxy-5,6,7,8-tetrahydro-4b*H*-indeno[2,1-*b*]pyridine (20). Ammonium acetate (4.40 g, 57.5 mmol) was added to a solution of **19** (2.80 g, 9.58 mmol) in anhydrous ethanol (479 mL) at room temperature, and the mixture was stirred for 12 h at 60 °C. Saturated aqueous sodium hydrogen carbonate solution was added to the mixture, and the aqueous phase was extracted with ethyl acetate. The combined organic solution was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography [ethyl acetate−hexane (1:4−1:1)] to afford **20** (1.33 g, 51%) as a yellow oil: $[\alpha]^{24}_D$ +51.9 (c 1.20, $CHCl_3$); IR ν (neat, cm^{-1}) 1408, 1146, 1137, 1103, 1037, 916; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (1H, qt, J = 13.5, 4.4 Hz), 1.79 (1H, tdd, J = 13.5, 11.6, 4.4 Hz), 1.94−2.08 (2H, m), 2.19 (1H, tdd, J = 13.5, 5.4, 1.8 Hz), 2.60−2.73 (2H, m), 2.90−3.00 (2H, m), 3.33 (3H, s), 4.55 (1H, d, J = 6.8 Hz), 4.69 (1H, dd, J = 9.6, 2.8 Hz), 4.75 (1H, d, J = 6.8 Hz), 4.80−5.00 (2H, m), 6.62 (1H, d, J = 1.6 Hz), 7.01 (1H, dd, J = 7.5, 5.2 Hz), 7.77 (1H, ddd, J = 7.5, 1.4, 0.6 Hz), 8.39 (1H, dd, J = 5.2, 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 26.1, 27.6, 32.2, 55.6, 57.2, 83.1, 96.3, 117.0, 118.5, 125.3, 130.6, 132.2, 143.4, 147.1, 158.5, 163.2; MS m/z 271 (M^+, 81.3%), 243 (100.0%), 215 (73.8%), 210 (62.7%), 209 (79.7%), 200 (51.3%), 170 (69.6%); HRMS calcd for $C_{17}H_{21}O_2N^+$ (M^+) 271.1572, found 271.1577.

(4b*S*,5*R*,8a*S*)-4b-[3-(*tert*-Butyldimethylsilanyloxy)propyl]-5,6,7,8,8a,9-hexahydro-4b*H*-indeno[2,1-*b*]pyridin-5-ol (22). 9-BBN-H (0.5 M solution in THF, 1.65 mL, 0.825 mmol) was added to a solution of **20** (0.0320 g, 0.118 mmol) in anhydrous THF (3.0 mL) at 0 °C. After stirring for 1 h at the same temperature, a mixture of 6.0 M sodium hydroxide solution (1.0 mL) and 30% hydrogen peroxide solution (1.0 mL) was added and the solution was stirred for 10 min. Water was added to the mixture, and the aqueous phase was extracted with dichloromethane. The combined organic solution was washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, and concentrated. The residue was passed through a silica gel pad to afford the crude alcohol as a yellow oil, which was used in the next reaction without further purification.

A solution of the crude alcohol in methanol (5.0 mL) was hydrogenated in the presence of 10% palladium on carbon (0.0630 g, 0.0590 mmol) under atmospheric pressure of hydrogen gas. After stirring for 12 h, the mixture was filtered through a pad of Celite eluting with ethyl acetate and the filtrate was concentrated to give the crude alcohol as a yellow oil, which was used in the next reaction without further purification.

A solution of the crude alcohol in a mixture of methanol (2.6 mL) and 3.0 M hydrogen chloride solution (1.3 mL) was stirred at 60 °C for 1 h. Saturated aqueous sodium hydrogen carbonate solution was added to the mixture, and the aqueous phase was extracted with dichloromethane. The combined organic solution was dried over anhydrous sodium sulfate and concentrated to afford the crude diol as a yellow oil, which was used in the next reaction without further purification.

To a solution of the crude diol in anhydrous dichloromethane (4.0 mL) were successively added imidazole (0.024 g, 0.354 mmol) and *tert*-butyldimethylsilyl chloride (0.027 g, 0.177 mmol) at room temperature. After stirring for 5 h at the same temperature, phosphate buffer solution (pH 6.86) was added to the mixture and the aqueous phase was extracted with dichloromethane. The combined organic solution was dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography

[ethyl acetate−hexane (1:1)] to afford **22** (0.032 g, 75% from **20**) as a colorless solid: mp 93−95 °C; $[\alpha]^{22}_{D}$ +1.7 (*c* 0.80, $CHCl_3$); IR ν (neat, cm^{-1}) 3375, 1256, 1099, 835, 775; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (6H, s), 0.89 (9H, s), 1.18−1.41 (2H, m), 1.47−1.78 (7H, m), 1.80 (1H, br s), 2.08 (1H, ddd, *J* = 14.2, 11.8, 4.4 Hz), 2.49−2.62 (1H, m), 2.86 (1H, dd, *J* = 16.8, 10.2 Hz), 2.93 (1H, dd, *J* = 16.8, 8.6 Hz), 3.54−3.67 (3H, m), 7.05 (1H, dd, *J* = 7.6, 4.8 Hz), 7.43 (1H, dd, *J* = 7.6, 1.6 Hz), 8.33 (1H, dd, *J* = 4.8, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3, 18.3, 20.1, 22.8, 24.5, 25.9, 27.4, 29.6, 36.6, 40.8, 52.2, 63.5, 72.5, 120.9, 131.5, 142.4, 147.5, 164.3; MS *m*/*z* 361 (M^+, 2.8%), 346 (4.2%), 304 (M^+ − *t*-Bu, 100.0%), 212 (39.9%), 170 (25.5%); HRMS calcd for $C_{21}H_{35}O_2NSi^+$ (M^+) 361.2437, found 361.2432.

(4b*S*,8a*S*)-4b-[3-(*tert*-Butyldimethylsilanyloxy)propyl]-4b,6,7,8,8a,9-hexahydroindeno[2,1-*b*]-pyridin-5-one (23). Sulfur trioxide pyridine complex (0.180 g, 1.13 mmol) and triethylamine (0.229 g, 2.27 mmol) were successively added to a solution of **22** (0.164 g, 0.454 mmol) in anhydrous DMSO (10 mL) at room temperature, and the mixture was stirred at the same temperature for 12 h. Water was added to the mixture, and the aqueous phase was extracted with ethyl acetate. The combined organic solution was dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography [ethyl acetate−hexane (1:3)] to afford **23** (0.148 g, 91%) as a colorless oil: $[\alpha]^{25}_{D}$ +28.8 (*c* 1.24, MeOH); IR ν (neat, cm^{-1}) 1703, 1421, 1256, 1097, 835; ^{1}H NMR (600 MHz, C_6D_6) δ 0.02 (3H, s), 0.03 (3H, s), 0.95 (9H, s), 0.97−1.07 (1H, m), 1.15−1.31 (2H, m), 1.32−1.51 (3H, m), 1.57 (1H, td, *J* = 12.6, 4.2 Hz), 1.87 (1H, ddd, *J* = 16.2, 9.3, 6.3 Hz), 1.95 (1H, td, *J* = 12.6, 4.6 Hz), 2.11 (1H, dt, *J* = 16.2, 6.0 Hz), 2.33 (1H, ddd, *J* = 13.1, 8.2, 4.9 Hz), 2.64 (1H, dd, *J* = 16.8, 4.2 Hz), 3.11 (1H, dd, *J* = 16.8, 7.8 Hz), 3.40 (1H, dt, *J* = 10.2, 6.6 Hz), 3.46 (1H, dt, *J* = 10.2, 6.1 Hz), 6.65 (1H, ddd, *J* = 7.6, 4.8, 0.9 Hz), 7.41 (1H, d, *J* = 7.6 Hz), 8.40 (1H, d, *J* = 4.8 Hz); ^{13}C NMR (150 MHz, C_6D_6) δ −5.24, −5.22, 18.4, 21.5, 26.1, 28.4, 29.3, 34.5, 39.1, 39.5, 42.6, 62.3, 63.3, 121.6, 132.5, 138.2, 149.3, 164.1, 210.4; MS *m*/*z* 344 (M^+ − Me, 8.6%), 302 (M^+ − *t*-Bu, 100.0%), 210 (46.6%), 171 (30.0%); HRMS calcd for $C_{17}H_{24}NO_2Si^+$ (M^+ − *t*-Bu) 302.1576, found 302.1565.

(4b*S*,8a*S*)-4b-[3-(*tert*-Butyldimethylsilanyloxy)propyl]-4b,8,8a,9-tetrahydroindeno[2,1-*b*]-pyridin-5-one (26) (Table 2, Entry 7). LHMDS (1.0 M solution in THF, 1.0 mL, 1.0 mmol) was added to a solution of **23** (0.073 g, 0.2030 mmol) in THF (2.8 mL) at −78 °C. After stirring for 1 h at −40 °C, HMPA (0.3 mL) was added and the mixture was stirred for 30 min. Chlorotrimethylsilane (0.22 g, 2.03 mmol) was added at −40 °C, and the stirring was continued for a further 1 h at the same temperature. Triethylamine (0.5 mL) and phosphate buffer solution (pH 6.86) were added to the mixture, and the aqueous phase was extracted with hexane. The combined mixture was dried over potassium carbonate and concentrated to afford the crude silyl enol ether **25** as a yellow oil, which was used in the next reaction without further purification.

To a solution of 2-iodoxybenzoic acid (0.227 g, 0.812 mmol) and 4-methoxypyridine *N*-oxide hydrate (MPO) (0.102 g, 0.812 mmol) in anhydrous DMSO (0.7 mL) was successively added a solution of the crude **25** in anhydrous DMSO (0.30 mL) at room temperature, and the mixture was stirred for 2 days at the same temperature. Water was added to the mixture, and the aqueous phase was extracted with diethyl ether. The combined organic solution was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated. The residue was chromatographed on silica gel [ethyl acetate−hexane (1:3)] to provide **26** (0.058 g, 80% from **23**) as a yellow oil: $[\alpha]^{28}_{D}$ +149.7 (*c* 1.46, MeOH); IR ν (neat, cm^{-1}) 1666, 1097; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (6H, s), 0.88 (9H, s), 1.43−1.59 (2H, m), 1.86 (1H, ddd, *J* = 13.8, 11.2, 5.1 Hz), 2.11 (1H, ddd, *J* = 13.8, 11.2, 5.7 Hz), 2.41−2.54 (1H, m), 2.74 (1H, dquint, *J* = 18.0, 2.8 Hz), 2.87−3.07 (2H, m), 3.19 (1H, dd, *J* = 14.6, 6.6 Hz), 3.51−3.67 (2H, m), 6.17 (1H, dt, *J* = 10.4, 1.9 Hz), 6.95 (1H, m), 7.14 (1H, dd, *J* = 7.6, 5.0 Hz), 7.69 (1H, dd, *J* = 7.6, 1.6 Hz), 8.38 (1H, dd, *J* = 5.0, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, 18.3, 25.9, 27.2, 28.1, 33.4, 38.9, 39.7, 58.5, 63.0, 122.0, 130.8, 133.4, 138.3, 148.2, 148.4, 162.7, 198.6; MS *m*/*z* 342 (M^+ − Me, 3.7%), 300 (M^+ − *t*-Bu, 100.0%), 232 (14.1%), 208 (28.0%) 182 (14.0%), 180 (8.8%); HRMS calcd for $C_{17}H_{22}O_2NSi^+$ (M^+ − *t*-Bu) 300.1420, found 300.1403.

(4b*S*,7*R*,8a*S*)-4b-[3-(*tert*-Butyldimethylsilanyloxy)propyl]-7-methyl-4b,6,7,8,8a,9-hexahydroindeno[2,1-*b*]pyridin-5-one (27a)[7b]. A solution of methyllithium (1.0 M in diethyl ether, 0.738 mL, 0.738 mmol) was added to a suspension of cuprous cyanide (0.033 g, 0.369 mmol) in anhydrous THF (2.0 mL) at 0 °C, and the mixture was stirred for 30 min. A solution of **26** (0.033 g, 0.0923 mmol) in anhydrous THF (1.0 mL) was added at −40 °C, and the resulting mixture was stirred for 1 h at the same temperature. Phosphate buffer solution (pH 6.86) was added to the mixture, and the aqueous phase was extracted with ethyl acetate. The combined organic solution was dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography [ethyl acetate−hexane (1:4)] to afford **27a** (0.027 g, 78%) as a yellow oil: $[\alpha]^{28}_{D}$ +111.8 (*c* 0.70, MeOH); IR ν (neat, cm^{-1}) 1704, 1424, 1255, 1098, 836, 776; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (6H, s), 0.88 (9H, s), 1.06 (3H, d, *J* = 6.0 Hz), 1.30−1.41 (1H, m), 1.47−1.58 (1H, m), 1.72 (1H, ddd, *J* = 14.4, 10.0, 5.0 Hz), 1.78−1.90 (2H, m), 1.98 (1H, ddd, *J* = 14.4, 12.2, 5.0 Hz), 2.05−2.20 (2H, m), 2.30−2.41 (1H, m), 2.83 (1H, dd, *J* = 15.6, 8.8 Hz), 2.85−2.94 (1H, m), 3.12 (1H, dd, *J* = 15.6, 7.2 Hz), 3.53−3.62 (2H, m), 7.11 (1H, dd, *J* = 7.6, 4.8 Hz), 7.53 (1H, dd, *J* = 7.6, 1.6 Hz), 8.38 (1H, dd, *J* = 4.8, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, 18.3, 21.7, 25.9, 28.0, 28.3, 32.7, 34.4, 38.4, 41.8, 46.9, 61.3, 62.8, 121.5, 133.6, 137.8, 148.6, 163.3, 212.8; ^{1}H NMR (400 MHz, C_6D_6) δ 0.026 (3H, s), 0.029 (3H, s), 0.60 (3H, d, *J* = 6.4 Hz), 0.95 (9H, s), 1.19 (1H, ddd, *J* = 14.1, 10.1, 5.5 Hz), 1.24−1.38 (2H, m), 1.38−1.56 (2H, m), 1.71 (1H, ddd, *J* = 13.5, 12.5, 4.1 Hz), 1.81 (1H, dd, *J* = 15.4, 10.2 Hz), 1.91 (1H, ddd, *J* = 13.4, 12.4, 4.8 Hz), 2.09 (1H, ddd, *J* = 15.4, 4.5, 0.9 Hz), 2.42−2.51 (1H, m), 2.66 (1H, dd, *J* = 16.8, 7.8 Hz), 3.04 (1H, dd, *J* = 16.8, 8.4 Hz), 3.36−3.48 (2H, m), 6.70 (1H, dd, *J* = 7.8, 4.8 Hz), 7.44 (1H, dd, *J* = 7.8, 1.4 Hz), 8.43 (1H, dd, *J* = 4.8, 1.4 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ −5.2, 18.4, 21.3, 26.1, 27.5, 28.8, 33.6, 34.7, 39.1, 41.3, 46.8, 61.2, 63.2, 121.5, 133.2, 138.1, 149.3, 164.1, 210.8; MS *m*/*z* 358 (M^+ − Me, 4.2%), 316 (M^+ − *t*-Bu, 100.0%), 224 (16.8%), 185 (12.5%); HRMS calcd for $C_{18}H_{26}O_2NSi^+$ (M^+ − *t*-Bu) 316.1732, found 316.1715.

(+)-Lycopladine A [(+)-(6)][6,7]. TBAF (1.0 M solution in THF, 0.217 mL, 0.217 mmol) was added to a solution **27a** (0.054 g, 0.145 mmol) in THF (2.0 mL) at room temperature. After stirring for 5.5 h at the same temperature, phosphate buffer solution (pH 6.86) was added to the mixture. The aqueous phase was extracted with ethyl acetate and the combined extract was washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by silica gel column chromatography [ethyl acetate−hexane (1:1) → chloroform−methanol (95:5)] to afford (+)-lycopladine A [(+)-(**6**)] (0.034 g, 92%) as a colorless solid: mp 153−155 °C [lit.[7b] 119−121 °C for (±)-(**6**)]; $[\alpha]^{27}_{D}$ +155.5 (*c* 1.10, MeOH) [lit. $[\alpha]^{23}_{D}$ +102 (*c* 1.0, MeOH),[6] $[\alpha]^{23}_{D}$ +144 (*c* 0.7, MeOH)[7a]]; IR ν (neat, cm^{-1}) 3363, 1700, 1424; ^{1}H NMR (400 MHz, CD_3OD) δ 1.07 (3H, d, *J* = 6.4 Hz), 1.27−1.39 (1H, m), 1.49−1.61 (1H, m), 1.76−1.91 (3H, m), 2.05 (1H, ddd, *J* = 13.7, 12.5, 4.7 Hz), 2.09−2.15 (1H, m), 2.25−2.30 (2H, m), 2.82 (1H, dd, *J* = 16.3, 9.0 Hz), 2.88−2.99 (1H, m), 3.08 (1H, dd, *J* = 16.3, 8.0 Hz), 3.47−3.56 (2H, m), 7.23 (1H, dd, *J* = 8.0, 4.8 Hz), 7.66 (1H, dd, *J* = 8.0, 1.6 Hz), 8.29 (1H, dd, *J* = 4.8, 1.6 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 22.0, 29.1, 29.5, 33.4, 34.8, 38.6, 43.4, 47.7, 62.6, 62.8, 123.0, 136.1, 140.0, 148.7, 164.3, 214.5; MS *m*/*z* 259 (M^+, 45.4%), 241 (40.1%), 215 (100.0%), 172 (53.9%), 144 (43.3%), 131 (36.6%), 130 (29.7%); HRMS calcd for $C_{16}H_{21}O_2N^+$ (M^+) 259.1572, found 259.1584.

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■ ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H and ^{13}C NMR spectra of all new compounds, **27a**, and **6**. Copies of NOESY spectra of **10**, **18**, **19**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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