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Formal Synthesis of Cortistatins

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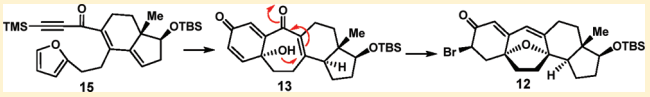
Supporting Information

ABSTRACT: A unified strategy toward the asymmetric facile construction of the [6.7.6.5]oxapentacyclic skeleton of cortistatins is reported, featuring intramolecular Diels−Alder (IMDA), oxidative dearomatization, and an oxy-Michael addition reaction.



INTRODUCTION

Cortistatins, isolated from the marine sponge *Corticium simplex* in 2006 and 2007, are a novel type of steroidal natural products.[1] Among cortistatins, cortistatins **A** and **J** (Figure 1) exhibit exceedingly potent and selective antiproliferative activity against human umbilical vein endothelial cells (HUVECs).[2]

Cortistatins have an unprecedented oxabicyclo[3.2.1]heptane ring system that lies within a complex tetracarbocyclic skeleton. Given its fascinating structure and distinguished biological activity, intensive efforts have been directed toward exploring feasible strategies for the chemical syntheses of natural products, as exemplified by their recent accomplishments of four total syntheses of cortistatin A (**1**),[3,11] and two formal total syntheses of cortistatin A (**1**),[4] as well as a number of studies toward the total synthesis of cortistatins.[5]

In our previous communication,[5i] we reported our developed strategy toward the concise synthesis of the [6.7.6.5]oxapentacyclic core of cortistatins, featuring an intramolecular Diels−Alder (IMDA) reaction to synthesize intermediate **10** from **11** (with a dual-site activated acetylene), and an oxidatively dearomatizative cyclization to construct **8** from **10** (Figure 2).

When we carried out the proposed strategy toward the total synthesis of cortistatin **J**, however, we found out that the removal of the C1 carboxylate group in intermediate **8** became difficult, which led us to explore an alternative approach toward its total synthesis.

To apply retrosynthetic analysis to the second generation of our total synthesis (Figure 2), compound **12**, endowed with suitable functionalities for further elaboration into the scaffold of cortistatins **A** (**1**) and **J** (**5**), could be derived from **13** through an intramolecular oxy-Michael reaction. We reasoned that such cyclization could be a favorable process in consideration of the fact that the ring strain of **13** would be higher than that of the cyclized adduct **28**.[6]

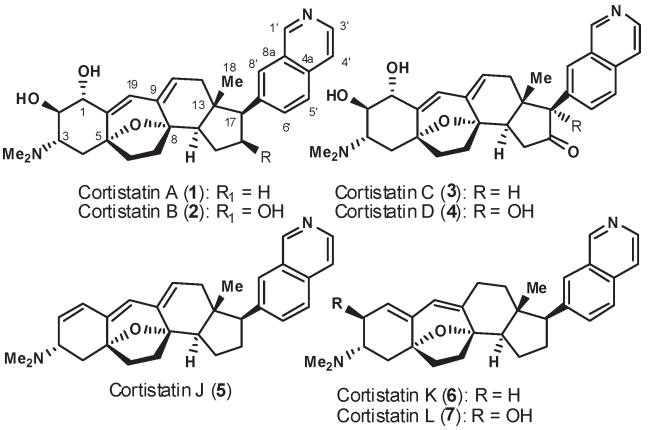


Figure 1. Structures of cortistatins.

The construction of **13** was expected to be derived from **14** via a nucleophilic addition of water at C-5 in the course of a hypervalent iodine[7]-triggered oxidative dearomatization event.[8] We also envisaged that **14** could be constructed via the furan-based IMDA[9] promoted by a preorganized, favorable conformation of substrate **15** (see Scheme 1).[10] Precursor **15** could be conveniently assembled from simpler building blocks **16**, **17**, and **18**.

We believed the proposed chemistry mentioned above would allow for rapid access to the elaborated polycyclic ring system in a highly convergent manner. Herein we report our success in implementing these synthetic designs for the synthesis of **12**, a key intermediate recently employed in the total syntheses of cortistatins **A**, **J**, **K**, and **L** by Myers group.[11]

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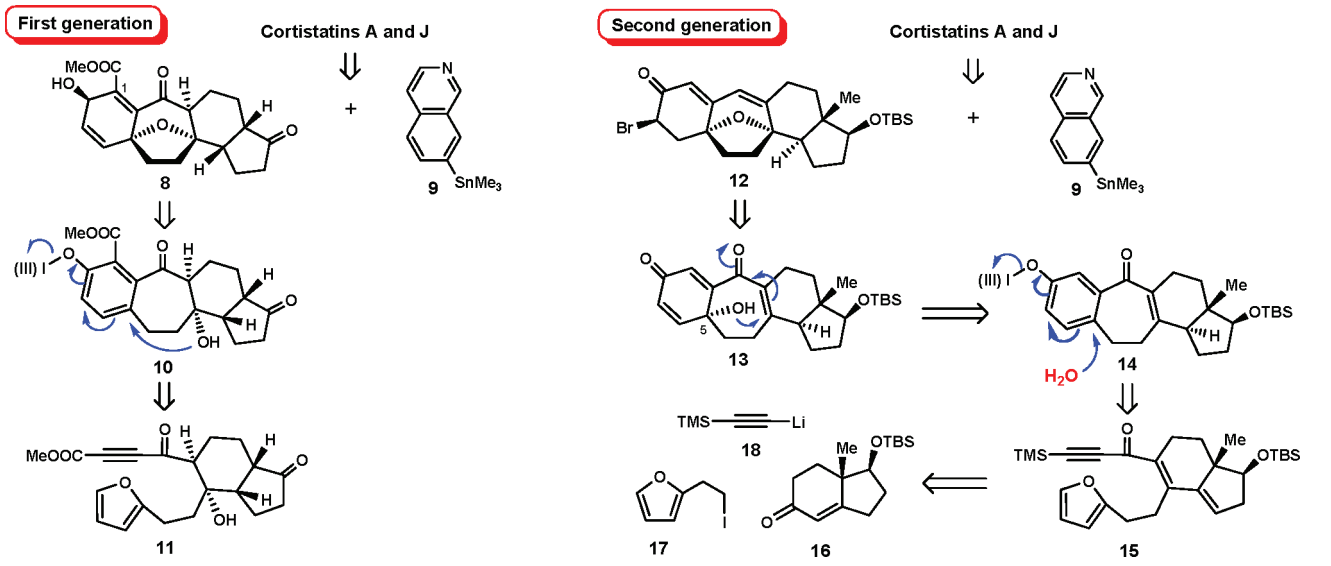
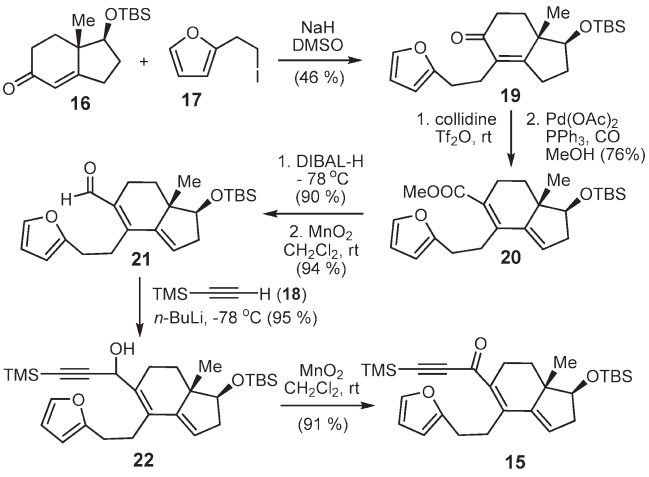
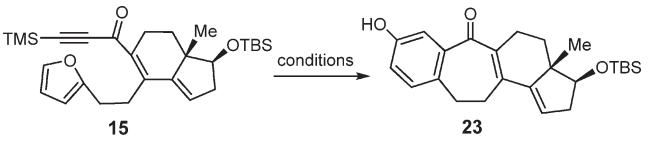


Figure 2. Strategies for synthesis of cortistatins.

Scheme 1. Synthesis of D-A Precursor 15



Scheme 2. Optimization of the Key Diels–Alder Reaction



lewis acid	conditions	yield of **23**
$TiCl_4$	-78 °C	substrate decomposed
$BF_3\,Et_2O$	-78 °C to 0 °C	< 10 %
TMSOTf	-78 °C to 0 °C	12 %
$Zn(OTf)_2$	0 °C to 40 °C	trace product
Al(*n*-propyl)$_3$	0 °C to 40 °C	no reaction
$AlCl_3$	-78 °C to 0 °C	29 %
Et_2AlCl	-78 °C to rt	10 %
$EtAlCl_2$	**-78 °C to 0 °C**	**51 %**

RESULTS AND DISCUSSION

Constrution of the Pentacyclic Core Structure 28. Our synthesis started with the preparation of the precursor **15** (Scheme 1). Synthetically, the easily prepared bicyclic enone **16** and furan-based alkyl iodide **17** were coupled[12] under the conditions listed in Scheme 1, affording **19** in 31% yield as well as 32% of **16** recovered. This low yield presumably was due to the competitive β-elimination of iodide **17** under basic conditions.

To make **20**, **19** was first converted into enol triflate, followed by Pd-catalyzed methoxy carbonylation to give **20** in 76% combined yield.[13] Compound **20** first underwent DIBAL-H reduction, and then was subjected to the oxidation of MnO_2, affording aldehyde **21** in 85% yield in two steps. Next, aldehyde **21** was treated with the in situ generated lithium trimethylsilyl acetylene **18**. The newly formed propargylic alcohol **22** was oxidized to **15** in high yield by MnO_2-mediated oxidation.

With **15** in hand, we then started to investigate the proposed furan-based IMDA reaction. However, when we attempted the IMDA reaction with **15** as the substrate, the expected cyclization product could not be formed or in low yield even at elevated temperature or in the presence of Lewis acids, including $TiCl_4$, $Zn(OTf)_2$, $BF_3\cdot Et_2O$, and TMSOTf (Scheme 2).

We then speculated that aluminum-based Lewis acids might have the capability to promote the IMDA of **15**, in consideration of their highly oxygenophilic tendency,[14] and of their successful applications in the Diels–Alder reactions.[15] To verify the analysis, when **15** was treated with the dilute solutions of $EtAlCl_2$ and Et_2AlCl at low temperature, to our delight, **23** was obtained in 51% yield and 10% yield, respectively. This transformation was actually achieved by way of three reactions, namely Diels–Alder reaction, aromatization, and TMS-deprotection.

To evaluate the TMS-group effect on the outcome of the products of the Diels–Alder reaction, we then tested the reaction with **25** as the substrate. To this end, aldehyde **21** was first treated with ethynylmagnesium chloride, and the formed secondary alcohol **24** was oxidized by MnO_2 in CH_2Cl_2, affording **25** in 77% overall yield. We then started to evaluate the Diels–Alder reaction. In the event, substrate **25** was treated with various Lewis acids under the conditions listed in Scheme 3, and the results are listed in Scheme 3. Among the Lewis acids screened, $BF_3\cdot Et_2O$

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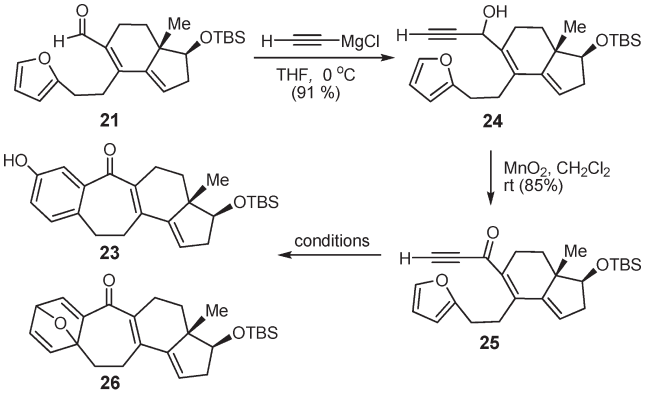
Scheme 3. Alternative Diels−Alder Reaction



Lewis acid	conditions	yield of **26**
$EtAlCl_2$	-78 °C to 0 °C	33 % (+ 10 % **23**)
Et_2AlCl	-78 °C to 0 °C	13 % (+ 27 % **23**)
$AlCl_3$	-78 °C	26 %
$TiCl_4$	-78 °C	17 %
$BF_3•Et_2O$	-78 °C	47 %
TMSOTf	-78 °C	17 %

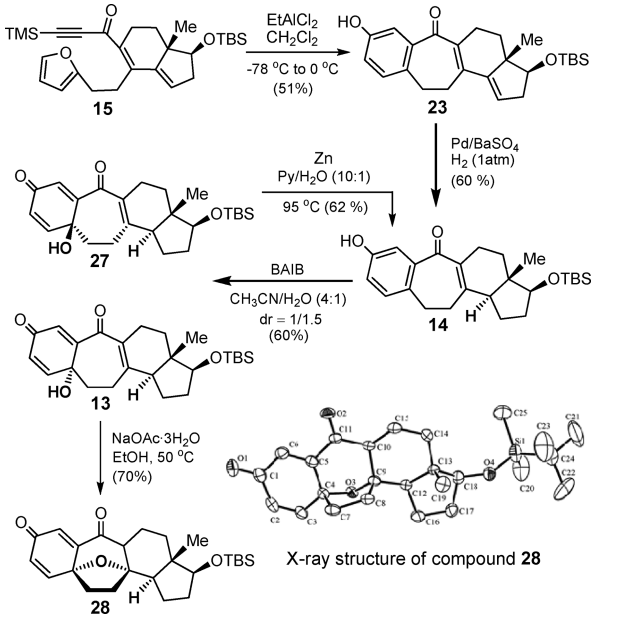
mediated Diels−Alder reaction gave the best result (47%), affording **26** as a pair of inseparable diastereoisomers. When $EtAlCl_2$ and Et_2AlCl were utilized as the activating agents to promote the reactions, **23** and **26** were obtained, and in both cases, the combined yields are less than 50%. It seemed that the TMS group was a beneficial substitute for the aromatization step. We therefore decided to employ **15** as the substrate to do the Diels−Alder reaction.

Having established the method for the construction of the [6.7.6.5]tetracyclic core structure **23**, we then shifted attention to investigating the formation of oxabicyclo[3.2.1]heptane core by directing the intramolecular Michael addition of the C-5 hydroxyl group to the Michael receptor in the presence of protic or Lewis acids. To this end, **23** was first subjected regioselective hydrogenation[3f,16] to give **14** in 60% yield. The selectivity observed in this reaction might be attributed to the steric effect of the α-methyl group and also the high stability of the trans product. After further treatment of **14** with BAIB[17](bisacetoxyiodobenzene) in the presence of water, **13** was obtained in 36% yield, together with its diastereoisomer **27** in 24% yield in a ratio of 1.5:1. **27** could in turn be converted to **14** by Zn-Py/H_2O mediated reductive aromatization.[18]

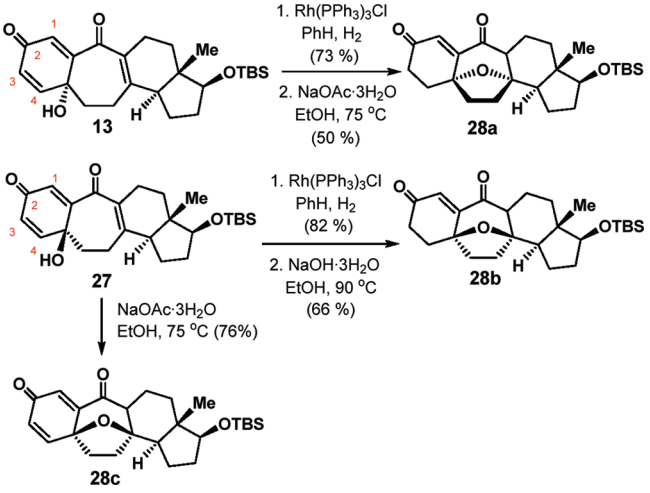
We then began to study the formation of the oxabicyclo[3.2.1]heptane core of **28** from **13** (Scheme 4). Initially, we attempted to use Amberlyst-15, Pd-catalyst,[19a] NaH, and *t*-BuOK to promote the expected annulation; however, no desired product was observed. We then applied NaOAc as the annulating agent in ethanol[19b,c] to perform this annulation reaction, and the expected product **28** was generated in 70% yield. The stereochemistry of **28** was confirmed by the X-ray crystallography analysis.

Profiling the Scope of the Oxy-Michael Addition Reaction. To demonstrate the significance of the oxy-Michael addition reaction as a useful method for the formation of the oxabicyclo[3.2.1]heptane core, substrates **13** and **27** were subjected to the regioselective hydrogenation to remove the double bond at C3 and C4 with $Rh(PPh_3)_3Cl$ as catalyst. As a result, the desired

Scheme 4. Construction of Pentacyclic Intermediate 28



Scheme 5. Oxy-Michael Addition Reaction



products **13a** and **27a** were obtained in good yields. **13a** and **27a** then underwent the oxy-Michael reactions under the conditions listed in Scheme 2, and the cyclized products **28a** and **28b** were obtained in 50% yield and 66% yield, respectively. In addition, **27** could also be annulated, affording product **28c** in 76% yield at elevated temperature (75 °C) (Scheme 5).

Construction of the Functionalized Pentacyclic Core. To complete the synthesis of key intermediate **12**, we started from exploring the installation of both the alkene group in the central 7-membered ring and the functionalization of the A ring.

We tested various regioselective methods to reduce the ketone at C-19 of **28**, and eventually found out that $LiBHEt_3$ served as an effective agent to fulfill this conversion. In that event, compound **28** was dissolved in THF, and treated with $LiBHEt_3$ (1.0 equiv) at −78 °C to regioselectively generate a secondary alcohol of C-19 in good yield. To form the double bond, the newly formed

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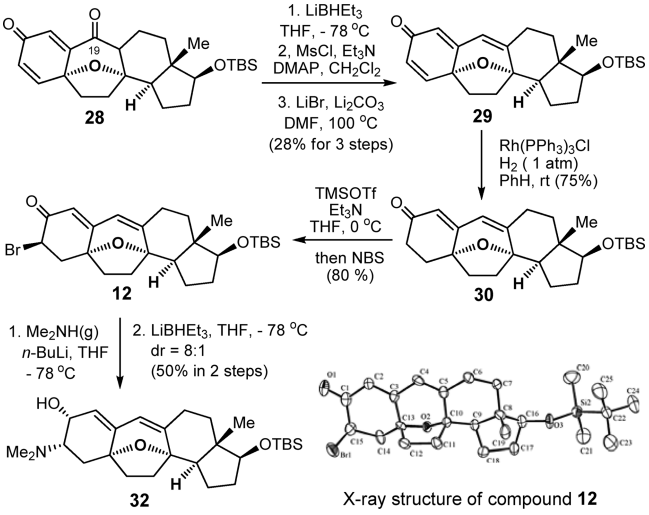
Scheme 6. Synthesis of Key Intermediates 12 and 31



secondary alcohol was first treated with the typical dehydration agents, such as Py/$SOCl_2$, Burgess reagent,[20] *p*-TSA/$CH(OEt)_3$,[21] and Martin's sulfurane.[22] To our surprise, no desired product was obtained. Gratifyingly, when the alcohol was converted into its mesylate, followed by treatment with LiBr and Li_2CO_3 under elevated temperature,[23] the desired elimination product **29** was obtained in moderate yield. To make the target molecule **12**, compound **29** was regioselectively hydrogenated in the presence of Wilkinson's catalyst[24] under balloon pressure of hydrogen to give dienone **30**. Dienone **30** was then converted to its corresponding silyl enol ether, followed by a regio- and stereoselective reaction with NBS[25] to afford the expected product **12** in 80% yield (Scheme 6). The stereochemistry of compound **12** was also confirmed by its X-ray crystallography analysis.

Furthermore, after accomplishing the key intermediate **12**, we also did further manipulations of the A ring. According to the configuration of the bromo in **12**, we envisioned that a direct SN2-type displacement would install the dimethyl amino group in the desired configuration. Fortunately, when substrate **12** was treated with dimethyl amino lithium at −78 °C, which was generated by deprotonation of Me_2NH gas in solution, the desired amino product **31** was generated in good yield. Compound **31** was found to be quite unstable, even in $CDCl_3$ at room temperature for several hours. Finally, reduction of the ketone with $LiBHEt_3$ furnished amino alcohol **32** in good yield, although the configuration of hydroxyl group was found opposite to that of natural product. This may provide an opportunity for total synthesis of C(2)-*epi*-cortistatins.

CONCLUSION

In summary, we have developed an asymmetric synthesis of oxabicyclo[3.2.1]heptane core via a furan-based IMDA reaction and an intramolecular oxy-Michael addition as the key steps. The work described herein demonstrates the usefulness of our strategy for the synthesis of the key intermediate **12**, which can be used for the syntheses of cortistatins, as well as other analogues.

EXPERIMENTAL SECTION

Materials and Methods. All reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. All the chemicals were purchased commercially, and used without further purification. Anhydrous THF and dioxane were distilled from sodium-benzophenone, and dichloromethane was distilled from calcium hydride. Yields refer to chromatographically, unless otherwise stated.

Experimental Procedures. Synthesis of (1*S*,7a*S*)-1-(*tert*-butyldimethylsilyloxy)-4-(2-(furan-2-yl)ethyl)-7a-methyl-2,-3,7,7a-tetrahydro-1*H*-inden-5(6*H*)-one (19): To a solution of DMSO (30 mL) was added NaH (60%, 855 mg, 21.36 mmol), and the mixture was stirred at 65 °C under N_2 for 2 h, and then cooled to 0 °C. To this solution was added bicyclic enone **16** (5 g, 17.8 mmol) in DMSO (50 mL) in a dropwise manner, and the formed mixture was then warmed to room temperature and stirred for an additional 4 h. The mixture was cooled to 0 °C again, and to this solution was slowly added a solution of 2-(2-iodoethyl)furan **17** (4.35 g, 19.6 mmol) in 30 mL of DMSO, and the reaction mixture was then warmed to room temperature and stirred overnight. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (50 mL), and the aqueous layer was extracted by EtOAc (3 × 100 mL). The combined organic layer was dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel (hexane/EtOAc = 100/1) to give the desired alkylation product **19** (2.1 g, 31% yield) as a yellow oil (R_f 0.8 (hexane/EtOAc = 8/1), together with recovered starting material (1.6 g): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.25 (dd, J = 2.8, 2.0 Hz, 1H), 5.89 (d, J = 2.9 Hz, 1H), 3.63 (dd, J = 10.2, 7.4 Hz, 1H), 2.69 (t, J = 7.2 Hz, 2H), 2.58−2.43 (m, 2H), 2.38 (ddd, J = 6.7, 5.7, 2.2 Hz, 2H), 2.24−2.09 (m, 2H), 1.97 (ddd, J = 12.7, 5.4, 1.8 Hz, 1H), 1.85 (ddd, J = 15.8, 9.2, 2.3 Hz, 1H), 1.74−1.64 (m, 2H), 1.02 (s, 3H), 0.90 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 168.7, 155.1, 140.2, 131.1, 109.7, 105.2, 80.4, 45.0, 33.7, 33.0, 29.4, 26.1, 25.3, 24.3, 17.5, 14.9, −4.9, −5.4; HRMS-ESI Calcd for $C_{22}H_{35}O_3Si$ [M + H^+] 375.2350, found 375.2357.

Synthesis of (1*S*,7a*S*)-methyl 1-(*tert*-butyldimethylsilyloxy)-4-(2-(furan-2-yl)-ethyl)-7a-methyl-2,6,7,7a-tetrahydro-1*H*-indene-5-carboxylate (20): To a solution of alkylation compound **19** (749 mg, 2 mmol) in DCM (20 mL) was added 2,4,6-trimethylpyridine (485 mg, 0.53 mL, 4 mmol) in a dropwise manner, and the formed mixture was cooled to 0 °C. To this solution was added trifluoromethanesulfinic anhydride (677 mg, 0.4 mL, 2.4 mmol) slowly, and the reaction mixture was stirred for an additional 1 h. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (20 mL), and the mixture was extracted by CH_2Cl_2 (3 × 30 mL). The combined organic layer was sequentially washed with 1 N HCl (2 × 8 mL), water (8 mL), and brine (8 mL), and finally dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was used directly in the next step without purification. It is worthwhile to mention that the crude product was not stable, even at −20 °C.

To a solution of $Pd(OAc)_2$ (45 mg, 0.2 mmol) and PPh_3 (105 mg, 0.4 mmol) in MeOH (6 mL) under N_2 was added the fresh made triflate (dissolved in 4 mL of MeOH) and Hunig's base (0.5 mL, 3.0 mmol). The reaction mixture was saturated with CO for 30 min, then heated to 50 °C for 48 h. The reaction was quenched by filtration of the mixture through a plug of Celite and washed with diethyl ether (3 × 20 mL). The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel (hexane/EtOAc = 100/1) to give the desired methyl ester **20** (625 mg) in 76% yield as colorless oil in 2 steps: R_f 0.8 (hexane/EtOAc = 10/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J = 1.1 Hz, 1H), 6.25 (dd, J = 2.9, 2.0 Hz, 1H), 5.98 (d, J = 2.9 Hz, 1H), 5.81 (s, 1H), 3.95 (dd, J = 8.6, 7.8 Hz, 1H), 3.74 (s, 3H), 3.00−2.88 (m, 1H), 2.84−2.76 (m, 3H), 2.58−2.34 (m, 4H), 1.88−1.80 (m, 1H), 1.29 (td, J = 12.0, 6.2 Hz, 1H), 0.92 (s, 9H), 0.89 (s, 3H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 156.7, 147.0, 141.7, 141.6, 127.0, 124.9, 110.9, 105.9, 83.0, 52.2, 46.4, 39.6, 34.5, 29.3, 29.2, 26.7, 25.9,

18.9, 16.0, −3.6, −3.9; HRMS-ESI calcd for $C_{24}H_{37}O_4Si$ [M + H^+] 417.2456, found 417.2463.

Synthesis of (1*S*,7a*S*)-1-(*tert*-butyldimethylsilyloxy)-4-(2-(furan-2-yl)ethyl)-7a-methyl-2,6,7,7a-tetrahydro-1*H*-indene-5-carbaldehyde (21): To a solution of methyl ester **20** (680 mg, 1.63 mmol) in DCM (15 mL) was added DIBAL (1.0 M in toluene, 3.4 mL, 3.4 mmol) at −78 °C slowly over 5 min, and the formed mixture was stirred at the same temperature for 15 min. The reaction was quenched by addition of a saturated solution of sodium potassium tartrate (30 mL), and the mixture was stirred until a clear solution was obtained. The mixture was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layer was dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel (hexane/EtOAc = 6/1) to give a primary alcohol (571 mg) in 90% yield as a colorless oil: R_f 0.4 (hexane/EtOAc = 5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 − 7.27 (m, 1H), 6.26 (dd, J = 3.0, 1.9 Hz, 1H), 5.94 (d, J = 3.0 Hz, 1H), 5.46 (s, 1H), 4.05 (d, J = 12.1 Hz, 1H), 3.94 (dd, J = 14.5, 7.1 Hz, 2H), 2.78−2.67 (m, 2H), 2.61 (dd, J = 14.9, 7.6 Hz, 2H), 2.42 (dd, J = 10.1, 5.6 Hz, 2H), 2.31 (d, J = 6.0 Hz, 2H), 2.04 (s, 1H), 1.89−1.77 (m, 1H), 1.29 (s, 1H), 0.94 (s, 9H), 0.90 (s, 3H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 146.0, 140.9, 134.9, 128.8, 117.6, 110.0, 105.3, 82.1, 62.1, 45.6, 38.4, 33.9, 27.9, 26.0, 25.8, 25.6, 18.0, 15.0, −4.6, −4.9; HRMS-ESI calcd for $C_{23}H_{36}O_3NaSi$ [M + Na^+] 411.2326, found 411.2326.

To a solution of the primary alcohol made above (350 mg, 0.9 mmol) in CH_2Cl_2 (10 mL) was added activated MnO_2 (88%, 886 mg, 9 mmol) at room temperature, and the formed mixture was stirred at the same temperature overnight. The reaction was quenched by filtration of the mixture through a plug of Celite and washed with CH_2Cl_2 (2 × 10 mL). The filtrate was concentrated under vacuum, and the residue was purified by flash chromatography on silica gel (hexane/EtOAc = 15/1) to give the desired aldehyde **21** (327 mg) in 94% yield as a light yellow oil: R_f 0.7 (hexane/EtOAc = 5/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.30 (d, J = 1.1 Hz, 1H), 6.25 (dd, J = 2.9, 1.9 Hz, 1H), 6.06 (s, 1H), 5.95 (d, J = 2.9 Hz, 1H), 3.98 (dd, J = 8.8, 7.7 Hz, 1H), 3.09 (dd, J = 14.0, 7.1 Hz, 1H), 2.98−2.89 (m, 1H), 2.86−2.78 (m, 2H), 2.60−2.48 (m, 2H), 2.45 (d, J = 9.0 Hz, 1H), 2.25−2.14 (m, 1H), 1.87 (dd, J = 12.5, 5.4 Hz, 1H), 1.21 (dd, J = 12.6, 7.0 Hz, 1H), 0.92 (s, 9H), 0.88 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.0, 153.7, 147.0, 146.6, 141.1, 133.5, 126.6, 110.0, 106.1, 81.6, 45.5, 38.8, 32.6, 29.1, 25.6, 24.8, 20.3, 17.8, 15.1, −4.7, −5.0; HRMS-ESI calcd for $C_{23}H_{35}O_3Si$ [M + H^+] 387.2350, found 387.2343.

Synthesis of 1-((1*S*,7a*S*)-1-(*tert*-butyldimethylsilyloxy)-4-(2-(furan-2-yl)ethyl)-7a-methyl-2,6,7,7a-tetrahydro-1*H*-inden-5-yl)-3-(trimethylsilyl)prop-2-yn-1-ol (22): To a solution of trimethylsilyl acetylene **18** (245 mg, 0.36 mL, 2.49 mmol) in THF (10 mL) was added *n*-BuLi (2.5 M in hexane, 1 mL, 2.49 mmol) at −78 °C in a dropwise manner, and the mixture was stirred at the same temperature for 30 min. To this solution was added a solution of aldehyde **21** (320 mg, 0.83 mmol) in THF (10 mL), and the formed mixture was stirred at the same temperature for 40 min. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (20 mL). The mixture was extracted by EtOAc (3 × 30 mL), and the combined organic layer was dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel (hexane/EtOAc = 15/1) to give the desired propagylic alcohol **22** (381 mg) in 95% yield as a pair of diastereoisomers: R_f 0.4 (hexane/EtOAc = 10/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (ddd, J = 6.3, 1.7, 0.7 Hz, 1H), 6.27 (ddd, J = 4.9, 3.1, 1.9 Hz, 1H), 5.97 (d, J = 2.9 Hz, 1H), 5.52 (d, J = 2.6 Hz, 1H), 5.24 (dd, J = 12.1, 3.7 Hz, 1H), 4.00−3.87 (m, 1H), 2.84−2.69 (m, 2H), 2.69−2.55 (m, 2H), 2.54−2.32 (m, 4H), 1.87 (dd, J = 12.0, 3.7 Hz, 1H), 1.32 (dd, J = 13.1, 7.1 Hz, 1H), 0.92 (s, 9H), 0.88 (s, 3H), 0.17 (d, J = 4.2 Hz, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 155.4, 146.2, 141.1, 141.0, 134.5, 134.1, 129.79, 128.8, 118.9, 118.6, 110.1, 105.4, 105.3, 105.1, 89.7, 82.2, 82.1, 62.2, 61.4, 45.8, 45.6, 38.6, 38.6, 33.9, 28.0, 27.7, 26.3, 26.2, 25.9, 22.1, 22.0, 18.1, 15.2, 15.0, −0.15, −0.16, −4.48, −4.79; HRMS-ESI calcd for $C_{28}H_{44}O_3NaSi_2$ [M + Na^+] 507.2721, found 507.2712.

Synthesis of 1-((1*S*,7a*S*)-1-(*tert*-butyldimethylsilyloxy)-4-(2-(furan-2-yl)ethyl)-7a-methyl-2,6,7,7a-tetrahydro-1*H*-inden-5-yl)-3-(trimethylsilyl)prop-2-yn-1-one (15): To a solution of propagylic alcohol **22** (350 mg, 0.72 mmol) in CH_2Cl_2 (10 mL) was added activated MnO_2 (88%, 711 mg, 7.2 mmol) at room temperature, and the mixture was stirred at the same temperature overnight. The reaction was quenched by filtration of the mixture through a plug of Celite, and washed with CH_2Cl_2 (3 × 30 mL). The filtrate was concentrated under vacuum to give the crude alkynyl ketone product **15** (317 mg) in 91% yield as a yellow oil: R_f 0.8 (hexane/EtOAc = 10/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J = 1.0 Hz, 1H), 6.26 (dd, J = 3.0, 1.9 Hz, 1H), 6.00 (d, J = 3.0 Hz, 1H), 5.96 (s, 1H), 3.95 (dd, J = 8.8, 7.7 Hz, 1H), 3.15−3.03 (m, 1H), 2.98−2.87 (m, 1H), 2.79 (dd, J = 14.8, 6.7 Hz, 3H), 2.61−2.46 (m, 2H), 2.40 (dd, J = 16.9, 9.0 Hz, 1H), 1.91 (dd, J = 12.5, 4.6 Hz, 1H), 1.34−1.28 (m, 1H), 0.92 (s, 9H), 0.89 (s, 3H), 0.23 (s, 9H), 0.06 (d, J = 2.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1, 154.8, 146.0, 142.8, 140.0, 131.6, 126.5, 109.4, 104.4, 102.6, 98.1, 81.1, 44.7, 38.2, 32.7, 27.8, 27.1, 25.1, 24.5, 17.3, 14.5, −1.5, −5.2, −5.5; HRMS-ESI calcd for $C_{28}H_{43}O_3Si_2$ [M + H^+] 483.2745, found 483.2752.

Synthesis of dienone-phenol 23: To a solution of the crude alkynyl ketone **15** (410 mg, 0.85 mmol) made above in CH_2Cl_2 (140 mL) was slowly added $EtAlCl_2$ (0.9 M in heptane, 1.4 mL, 1.3 mmol) at −78 °C, and the mixture was stirred at the same temperature for 10 min. After worming to °C, the mixture was stirred for an additional 1 h. The reaction was quenched by addition of a saturated solution of sodium potassium tartrate (50 mL), and the formed water layer was extracted with CH_2Cl_2 (3 × 60 mL), then the combined organic layer was dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel (hexane/EtOAc = 10/1) to give the desired dienone-phenol product **23** (177 mg) in 51% yield as a light yellow solid: R_f 0.2 (hexane/EtOAc = 5/1). This procedure was applied to the other Lewis acid-catalyzed reactions described in the text. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 2.7 Hz, 1H), 7.05 (d, J = 8.2 Hz, 1H), 6.92 (dd, J = 8.1, 2.7 Hz, 1H), 6.23 (s, 1H), 6.00 (s, 1H), 4.04−3.95 (m, 1H), 3.05−2.80 (m, 4H), 2.64−2.37 (m, 4H), 1.92 (dd, J = 12.5, 5.0 Hz, 1H), 1.30 (d, J = 5.7 Hz, 1H), 0.92 (s, 9H), 0.89 (s, 3H), 0.06 (d, J = 3.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 155.1, 147.8, 145.1, 140.5, 135.0, 132. 8, 129.4, 126.4, 119.3, 116.6, 81.9, 45.7, 39.0, 33.5, 32.4, 30.2, 25.87, 25.1, 18.0, 15.0, −4.6, −4.8; HRMS-ESI calcd for $C_{25}H_{35}O_3Si$ [M + H^+] 411.2350, found 411.2351.

Synthesis of 1-((1*S*,7a*S*)-1-(*tert*-butyldimethylsilyloxy)-4-(2-(furan-2-yl)ethyl)-7a-methyl-2,6,7,7a-tetrahydro-1*H*-inden-5-yl)prop-2-yn-1-ol (24): To a solution of aldehyde **21** (1160 mg, 3.0 mmol) in THF (30 mL) was added ethynyl magnesium chloride (0.6 M in THF/toluene, 10 mL, 6.0 mmol) at 0 °C in a dropwise manner, and the mixture was stirred at the same temperature for 30 min. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (20 mL), and the formed mixture was extracted by EtOAc (3 × 40 mL). The combined organic layer was dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel (hexane/EtOAc = 15/1) to give propagylic alcohol **24** (1126 mg) in 91% yield as a pair of diastereoisomers: R_f 0.5 (hexane/EtOAc = 5/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.30 (m, 1H), 6.28 (ddd, J = 4.9, 3.1, 1.9 Hz, 1H), 5.97 (d, J = 3.0 Hz, 1H), 5.62−5.46 (m, 1H), 5.33−5.16 (m, 1H), 3.95 (t, J = 7.8 Hz, 1H), 2.74 (td, J = 8.2, 3.1 Hz, 2H), 2.63 (dd, J = 7.4, 4.4 Hz, 2H), 2.52−2.31 (m, 5H), 1.93−1.81 (m, 1H), 1.37−1.26 (m, 1H), 0.96−0.87 (m, 12H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 155.2, 146.0, 145.9, 141.2,

141.1, 134.0, 133.5, 129.9, 128.8, 119.2, 119.0, 110.1, 105.5, 105.4, 83.3, 83.0, 82.1, 82.0, 73.2, 73.1, 61.6, 60.8, 45.6, 45.5, 38.5, 38.4, 33.7, 28.0, 27.6, 26.2, 26.0, 25.8, 21.9, 21.8, 18.0, 15.1, 15.0, −4.5, −4.8; HRMS-ESI calcd for $C_{25}H_{36}O_3NaSi$ [M + Na^+] 435.2326, found 435.2332.

Synthesis of 1-((1*S*,7a*S*)-1-(*tert*-butyldimethylsilyloxy)-4-(2-(furan-2-yl)ethyl)-7a -methyl-2,6,7,7a-tetrahydro-1*H*-inden-5-yl)prop-2-yn-1-one (25): To a solution of propagylic alcohol **24** (95 mg, 0.23 mmol) in CH_2Cl_2 (6 mL) was added activated MnO_2 (88%, 227 mg, 2.3 mmol) at room temperature, and the mixture was stirred overnight. The reaction mixture was filtered off through a silica gel pad and washed through with CH_2Cl_2 (3 × 20 mL). The filtrate was removed under vacuum, and the residue was purified by flash chromatography on silica gel (hexane/EtOAc = 20/1) to give alkynyl ketone **25** (80 mg) in 85% yield: R_f 0.5 (hexane/EtOAc = 10/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (dd, J = 1.7, 0.7 Hz, 1H), 6.26 (dd, J = 3.0, 1.9 Hz, 1H), 6.00 (dd, J = 4.9, 1.8 Hz, 2H), 3.96 (dd, J = 8.9, 7.6 Hz, 1H), 3.31 (s, 1H), 3.11−3.01 (m, 1H), 2.91 (dt, J = 12.3, 8.0 Hz, 1H), 2.86−2.75 (m, 3H), 2.65−2.55 (m, 1H), 2.50 (ddd, J = 17.0, 7.5, 3.6 Hz, 1H), 2.40 (dd, J = 17.0, 9.0 Hz, 1H), 1.91 (dd, J = 12.6, 4.4 Hz, 1H), 1.31 (td, J = 12.5, 5.7 Hz, 1H), 0.92 (s, 9H), 0.89 (s, 3H), 0.06 (d, J = 1.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.2, 155.3, 146.5, 144.4, 140.7, 131.7, 128.0, 110.1, 105.2, 82.5, 81.7, 79.8, 45.3, 38.9, 33.3, 28.4, 27.9, 25.7, 25.2, 18.0, 15.2, −4.6, −4.9; HRMS-ESI calcd for $C_{25}H_{35}O_3Si$ [M + H^+] 411.2350, found 411.2357.

Synthesis of dienone 26: To a solution of alkynyl ketone **25** (30 mg, 0.073 mmol) in CH_2Cl_2 (12 mL, 0.006 M) at −78 °C was slowly added $BF_3 \cdot Et_2O$ (48% BF_3, 29 μL, 0.11 mmol), and the mixture was stirred at the same temperature for 1 h. The reaction was quenched by addition of a saturated solution of $NaHCO_3$ (10 mL), and the formed mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel (hexane/EtOAc = 15/1) to give dienone product **26** (14 mg) in 47% yield: R_f 0.3 (hexane/EtOAc = 10/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (dd, J = 10.7, 6.1 Hz, 1H), 6.21 (dd, J = 12.6, 3.1 Hz, 1H), 6.12 (d, J = 10.7 Hz, 1H), 5.97 (dd, J = 21.6, 1.8 Hz, 1H), 5.58 (d, J = 15.1 Hz, 1H), 3.87−3.72 (m, 1H), 3.52−3.39 (m, 1H), 2.95 (ddd, J = 38.6, 14.9, 5.1 Hz, 1H), 2.87−2.75 (m, 1H), 2.58 (d, J = 13.5 Hz, 1H), 2.50 (dd, J = 13.4, 5.0 Hz, 1H), 2.41 (ddd, J = 16.2, 7.4, 3.4 Hz, 1H), 2.27 (ddd, J = 30.6, 22.4, 11.3 Hz, 1H), 2.00 (dd, J = 18.4, 5.2 Hz, 1H), 1.67 (dd, J = 12.6, 4.4 Hz, 1H), 1.21 (td, J = 12.4, 5.5 Hz, 1H), 0.88 (d, J = 2.8 Hz, 9H), 0.80 (s, 3H), 0.01 (dd, J = 6.7, 2.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.7, 202.4, 155.3, 155.2, 150.3, 150.1, 146.4, 145.1, 142.0, 140.7, 132.5, 132.4, 131.2, 130.5, 123.6, 123.5, 120.7, 120.2, 109.6, 109.4, 109.2, 108.9, 81.9, 81.7, 45.6, 45.3, 38.4, 33.5, 33.0, 28.5, 27.3, 26.2, 26.0, 25.8, 25.4, 24.3, 18.0, 15.3, 14.8, −4.6, −4.5, −4.8, −4.9; HRMS-ESI calcd for $C_{25}H_{35}O_3Si$ [M + H^+] 411.2350, found 411.2346.

The procedure for other Lewis acids-catalyzed reactions was similar to the one mentioned above.

Synthesis of enone-phenol 14: To a solution of Pd/$BaSO_4$ (5% wt/wt, 52 mg, 0.049 mmol) in dried EtOAc (120 mL) was added dienone-phenol **23** (200 mg, 0.49 mmol), and the mixture was stirred under balloon pressure of H_2 atmosphere at room temperature for 3 h. The reaction was quenched by filtration through Celite, and washed with EtOAc (3 × 30 mL). The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel (hexane/EtOAc = 10/1) to give the desired enone-phenol **14** (120 mg) in 60% yield as a light yellow solid: R_f 0.5 (hexane/EtOAc = 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 2.6 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 6.92 (dd, J = 8.1, 2.6 Hz, 1H), 3.73−3.61 (m, 1H), 3.03−2.91 (m, 1H), 2.83−2.69 (m, 2H), 2.51 (dd, J = 19.2, 10.9 Hz, 3H), 2.32 (d, J = 11.2 Hz, 1H), 2.05 (dt, J = 8.8, 6.6 Hz, 1H), 1.88 (dd, J = 12.4, 7.4 Hz, 1H), 1.82−1.73 (m, 1H), 1.64−1.51 (m, 2H), 1.30 (td, J = 12.0, 8.0 Hz, 1H), 0.90 (s, 9H), 0.70 (s, 3H), 0.04 (d, J = 6.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.0, 157.0, 155.1, 141.9, 133.6, 131.5, 129.0, 118.8, 116.1, 80.2, 49.8, 42.8, 33.6, 33.5, 32.4, 31.4, 26.0, 25.8, 22.5, 18.0, 11.1, −4.5, −4.8; HRMS-ESI calcd for $C_{25}H_{37}O_3Si$ [M + H^+] 413.2506, found 413.2502.

Synthesis of tertiary alcohol 13: To a solution of enone-phenol **14** (100 mg, 0.24 mmol) in CH_3CN (20 mL) and H_2O (5 mL) was slowly added iodobenzene diacetate (116 mg, 0.36 mmol) at 0 °C, and the mixture was stirred at the same temperature for 40 min. The reaction was quenched by addition of a saturated solution of $NaHCO_3$ (20 mL), the mixture was extracted with EtOAc (3 × 30 mL), and the combined organic layer was then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel (hexane/EtOAc = 6/1) to give the desired tertiary alcohol **13** (37 mg) in 36% yield (R_f 0.2 (hexane/EtOAc = 3/1), together with its diastereoisomer **27** (25 mg) in 24% yield (R_f 0.3 (hexane/EtOAc = 3/1)). For tertiary alcohol **13**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (d, J = 10.0 Hz, 1H), 6.15 (d, J = 1.8 Hz, 1H), 6.07 (dd, J = 10.0, 1.9 Hz, 1H), 3.75 (s, 1H), 3.68 (t, J = 8.1 Hz, 1H), 2.48−2.26 (m, 5H), 2.17 (ddd, J = 13.9, 5.2, 3.1 Hz, 1H), 2.12−1.99 (m, 2H), 1.88−1.79 (m, 1H), 1.75 (dd, J = 11.6, 6.9 Hz, 1H), 1.62−1.46 (m, 2H), 1.28 (dd, J = 21.2, 9.8 Hz, 1H), 0.87 (s, 9H), 0.64 (s, 3H), 0.01 (d, J = 5.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.8, 185.9, 161.2, 159.3, 151.3, 134.4, 125.9, 125.6, 80.1, 70.1, 48.9, 43.1, 38.5, 32.8, 31.1, 27.5, 25.8, 24.0, 22.5, 18.0, 11.1, −4.5, −4.8; HRMS-ESI calcd for $C_{25}H_{37}O_4Si$ [M + H^+] 429.2456, found 429.2453. For tertiary alcohol **27**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (d, J = 10.0 Hz, 1H), 6.50 (d, J = 1.7 Hz, 1H), 6.11 (dd, J = 10.0, 1.7 Hz, 1H), 3.77−3.67 (m, 1H), 2.69 (d, J = 10.5 Hz, 1H), 2.52−2.44 (m, 1H), 2.33 (d, J = 11.7 Hz, 3H), 2.13 (ddd, J = 29.9, 14.9, 7.5 Hz, 3H), 2.04 (d, J = 12.1 Hz, 1H), 1.87 (dd, J = 12.7, 7.6 Hz, 1H), 1.83−1.75 (m, 1H), 1.63 (s, 2H), 0.90 (s, 9H), 0.80 (s, 3H), 0.04 (d, J = 4.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.0, 187.0, 160.8, 156.5, 152.2, 136.0, 128.2, 126.1, 81.0, 71.3, 49.8, 43.9, 39.1, 33.9, 32.1, 28.3, 26.8, 24.7, 22.8, 19.0, 12.1, −3.6, −3.9; HRMS-ESI calcd for $C_{25}H_{37}O_4Si$ [M + H^+] 429.2456, found 429.2465.

Synthesis of diketone 28: To a solution of tertiary alcohol **13** (100 mg, 0.233 mmol) in EtOH (50 mL) was added $NaOAc \cdot 3H_2O$ (317 mg, 2.33 mmol) at room temperature, and the mixture was stirred at 50 °C for 36 h. After cooling to room temperature, the reaction was quenched by the addition of water (30 mL) and EtOH (30 mL), the mixture was extracted with EtOAc (3 × 30 mL), and the combined organic layer was dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography on Al_2O_3 (hexane/EtOAc = 10/1) to give the desired diketone **28** (70 mg) in 70% yield as a light yellow solid: R_f 0.8 (hexane/EtOAc = 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (d, J =10.1 Hz, 1H), 6.49 (d, J =1.75 Hz, 1H), 6.32 (dd, J = 10.1, 1.8 Hz, 1H), 3.67 (t, J =7.9 Hz, 1H), 2.50 (dd, J =13.2, 3.6 Hz, 1H), 2.18−2.10 (m, 3H), 2.04−1.92 (m, 3H), 1.79−1.72 (m, 3H), 1.59−1.54 (m, 3H), 1.09−1.03 (m, 1H), 0.89 (s, 9H), 0.74 (s, 3H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.2, 186.8, 153.9, 148.5, 130.9, 124.5, 88.3, 82.2, 78.8, 64.3, 51.1, 45.9, 39.6, 36.7, 31.4, 27.7, 26.7, 21.0, 20.3, 19.0, 12.8, −3.5, −3.9; HRMS-ESI calcd for $C_{25}H_{37}O_4Si$ [M + H^+] 429.2456, found 429.2468.

Synthesis of diketone 28a: To a solution of Wilkinson's catalyst (9 mg, 0.01 mmol) in dried benzene (4 mL) was added a solution of the tertiary alcohol **13** (45 mg, 0.1 mmol) in benzene (3 mL), and the reaction mixture was stirred at room temperature under balloon pressure of H_2 overnight. The mixture was then filtered off through a silica gel pad and washed with EtOAc (3 × 10 mL). The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel (hexane/EtOAc = 4/1) to give a tertiary alcohol (33 mg) in 73% yield.

To a solution of the tertiary alcohol (20 mg, 0.046 mmol) made above in EtOH (10 mL) at room temperature was added $NaOAc \cdot 3H_2O$ (63 mg, 0.46 mmol), then the mixture was stirred at 75 °C for 12 h. The

reaction was quenched by addition of water (10 mL) and EtOH, and the mixture was concentrated under vacuum to remove the ethanol. The remaining water layer was extracted with EtOAc (3 × 10 mL), and the combined organic layer was then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography on Al_2O_3 (hexane/EtOAc = 8/1) to give diketone **28a** (10 mg) in 50% yield: R_f 0.7 (hexane/EtOAc = 3/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (d, J = 1.1 Hz, 1H), 3.74−3.59 (m, 1H), 2.72−2.55 (m, 1H), 2.55−2.38 (m, 2H), 2.34−2.07 (m, 4H), 2.07−1.82 (m, 3H), 1.72 (dd, J = 16.7, 7.5 Hz, 3H), 1.52 (d, J = 10.1 Hz, 4H), 1.14−1.00 (m, 1H), 0.90 (d, J = 3.7 Hz, 9H), 0.73 (s, 3H), 0.03 (d, J = 1.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 198.6, 154.2, 124.8, 84.9, 81.4, 80.2, 63.3, 50.4, 45.0, 37.7, 36.2, 36.1, 33.4, 30.5, 26.6, 25.8, 20.1, 19.4, 18.1, 11.9, −4.56, −4.8; HRMS-ESI calcd for $C_{25}H_{39}O_4Si$ [M + H$^+$] 431.2612, found 431.2606.

Synthesis of tertiary alcohol 28b: To a solution of Wilkinson's catalyst (8 mg, 0.009 mmol) in dried benzene (3 mL) was added a solution of tertiary alcohol **27** (38 mg, 0.09 mmol) in benzene (3 mL), and the mixture was stirred at room temperature under balloon pressure of H_2 overnight. The reaction was worked up by filtration of the reaction mixture through a silica gel pad and washed with EtOAc (3 × 10 mL). The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel (hexane/EtOAc = 4/1) to give a dienone (31 mg) in 82% yield.

To a solution of tertiary alcohol **27a** (38 mg, 0.088 mmol) in EtOH (20 mL) was added NaOAc·3H_2O (120 mg, 0.88 mmol) at room temperature, and the mixture was stirred at 90 °C for 36 h. The reaction was quenched by addition of water (15 mL) and EtOH, and the formed mixture was concentrated under vacuum. The remaining water layer was extracted with EtOAc (3 × 20 mL), and the combined organic extract was dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography on Al_2O_3 (hexane/EtOAc = 10/1) to give diketone **28b** (25 mg) in 66% yield: R_f 0.8 (hexane/EtOAc = 3/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.44 (d, J = 1.1 Hz, 1H), 3.57 (t, J = 8.3 Hz, 1H), 2.74−2.56 (m, 1H), 2.50 (ddd, J = 14.0, 7.3, 3.3 Hz, 2H), 2.36−2.09 (m, 4H), 2.09−1.95 (m, 1H), 1.95−1.75 (m, 3H), 1.75−1.63 (m, 3H), 1.57−1.43 (m, 1H), 1.35 (dd, J = 12.5, 7.0 Hz, 2H), 1.12 (td, J = 13.5, 7.2 Hz, 1H), 0.93 (s, 3H), 0.93−0.79 (m, 9H), 0.03 (d, J = 4.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.4, 198.7, 152.6, 125.5, 82.2, 81.6, 81.3, 59.3, 48.0, 43.3, 36.8, 36.2, 35.5, 34.1, 33.9, 29.9, 25.8, 24.7, 18.8, 18.1, 12.1, −4.5, −4.8; HRMS-ESI calcd for $C_{25}H_{39}O_4Si$ [M + H$^+$] 431.2612, found 431.2613.

Synthesis of diketone 28c: To a stirred solution of tertiary alcohol **27** (50 mg, 0.117 mmol) in EtOH (25 mL) was added NaOAc·3H_2O (159 mg, 1.17 mmol) at room temperature, and the mixture was stirred at 75 °C for 20 h. The reaction was quenched by addition of water (15 mL) and EtOH, and the formed mixture was concentrated and removed under vacuum. The remaining water layer was extracted with EtOAc (3 × 15 mL), and the combined extract was dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography on Al_2O_3 (hexane/EtOAc = 10/1) to give diketone **28c** (38 mg) as a light yellow solid in 76% yield: R_f 0.9 (hexane/EtOAc = 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (d, J = 10.0 Hz, 1H), 6.59 (s, 1H), 6.31 (d, J = 10.0 Hz, 1H), 3.58 (t, J = 8.3 Hz, 1H), 2.32 (dd, J = 12.7, 5.1 Hz, 1H), 2.27−2.18 (m, 1H), 2.08 (td, J = 12.7, 6.3 Hz, 1H), 1.91 (ddd, J = 16.8, 10.8, 3.8 Hz, 2H), 1.85−1.75 (m, 3H), 1.66 (d, J = 9.7 Hz, 2H), 1.54 (s, 1H), 1.40 (dd, J = 12.6, 7.0 Hz, 1H), 1.13 (dd, J = 14.3, 11.5 Hz, 1H), 0.92 (s, 3H), 0.89 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.8, 186.1, 151.2, 148.3, 129.3, 124.5, 84.6, 81.4, 78.8, 60.2, 47.5, 43.3, 36.7, 36.0, 34.0, 29.8, 25.8, 24.5, 18.8, 18.1, 12.2, −4.5, −4.8; HRMS-ESI calcd for $C_{25}H_{37}O_4Si$ [M + H$^+$] 429.2456, found 429.2458.

Synthesis of cyclohexatrienone 29: To a solution of diketone **28** (70 mg, 0.16 mmol) in THF (10 mL) was added lithium triethylborohydride (1 M in THF, 0.16 mL, 0.16 mmol) at −78 °C in a dropwise manner, and then the mixture was stirred at the same temperature for 20 min. The reaction was quenched by addition of a saturated solution of sodium chloride (15 mL), then the mixture was first extracted with EtOAc (3 × 20 mL) and the combined organic layer was then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was used directly in the next step without further purification.

To a solution of the crude alcohol made above, Et_3N (486 mg, 0.67 mL, 4.8 mmol), and DMAP (20 mg, 0.16 mmol) in CH_2Cl_2 (15 mL) was slowly added a solution of MsCl (183 mg, 0.12 mL, 1.6 mmol) in CH_2Cl_2 (5 mL) at 0 °C, and the mixture was stirred at the same temperature for 1 h. The reaction was quenched with a saturated solution of $NaHCO_3$ (15 mL). The mixture was first extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layer was then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by fast flash chromatography (<20 min) on silica gel (hexane/EtOAc = 3/1) to give a crude mesylate: R_f 0.5 (hexane/EtOAc = 2/1); HRMS-ESI calcd for $C_{26}H_{41}O_6SiS$ [M + H$^+$] 509.2388, found 509.2394.

To a solution of the crude mesylate made above in dried DMF (5 mL) was added LiBr (139 mg, 1.6 mmol) and Li_2CO_3 (118 mg, 1.6 mmol) at room temperature, then the mixture was stirred at 100 °C for 20 h. The reaction was quenched by addition of a saturated solution of sodium chloride (30 mL). The mixture was extracted with EtOAc (3 × 15 mL), and the combined organic layer was washed with brine (2 × 8 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel (hexane/EtOAc = 5/1) to give the cyclohexatrienone **29** (19 mg) in 28% yield for 3 steps: R_f 0.65 (hexane/EtOAc = 3/1); ^{1}H NMR (300 MHz, C_6D_6) δ 6.45 (d, J = 10.2 Hz, 1H), 6.20 (dd, J = 10.0, 1.9 Hz, 1H), 5.94 (s, 1H), 5.50 (d, J = 2.0 Hz, 1H), 3.45−3.30 (m, 1H), 2.07 (dd, J = 21.2, 9.2 Hz, 1H), 1.99−1.90 (m, 1H), 1.86 (dd, J = 11.7, 7.2 Hz, 1H), 1.81−1.71 (m, 1H), 1.63 (ddd, J = 10.6, 7.7, 5.2 Hz, 3H), 1.58−1.51 (m, 1H), 1.45 (dd, J = 10.0, 5.8 Hz, 3H), 1.18 (s, 1H), 0.99 (s, 9H), 0.90 (s, 1H), 0.71 (s, 3H), 0.02 (d, J = 1.0 Hz, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 185. 8, 157.6, 154.5, 146.7, 129.9, 119.8, 119.1, 86.3, 81.8, 75.3, 47.8, 43.9, 37.3, 36.2, 30.8, 29.1, 28.9, 26.1, 19.7, 18.3, 11.1, −4.3, −4.7; HRMS-ESI calcd for $C_{25}H_{36}O_3NaSi$ [M + Na$^+$] 435.2326, found 435.2330.

Synthesis of dienone 30: To a solution of Wilkinson's catalyst (9 mg, 0.01 mmol) in dried benzene (4 mL) was added a solution of cyclohexatrienone **29** (40 mg, 0.1 mmol) in benzene (3 mL) at room temperature, then the mixture was stirred under balloon pressure of H_2 atmosphere overnight. The reaction was quenched by filtration through a Celite pad and washed with EtOAc (3 × 10 mL). The filtrate was removed under vacuum, and the residue was purified by flash chromatography on silica gel (hexane/EtOAc = 5/1) to give the desired dienone **30** (30 mg) in 75% yield: R_f 0.6 (hexane/EtOAc = 3/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 (d, J = 2.2 Hz, 1H), 5.54 (s, 1H), 3.66 (t, J = 8.3 Hz, 1H), 2.53 (ddd, J = 18.7, 14.9, 8.6 Hz, 2H), 2.48−2.38 (m, 2H), 2.07 (ddd, J = 14.5, 12.7, 6.6 Hz, 5H), 1.93 (dd, J = 11.8, 7.6 Hz, 1H), 1.84−1.77 (m, 2H), 1.66 (dd, J = 11.1, 6.0 Hz, 2H), 1.31−1.20 (m, 3H), 0.90 (s, 9H), 0.83 (s, 3H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.6, 160.4, 157.8, 119.7, 118.6, 84.1, 81.6, 78.1, 47.9, 43.9, 36.2, 35.7, 35.5, 33.6, 30.6, 30.5, 29.1, 25.8, 19.6, 18.1, 10.9, −4.4, −4.9; HRMS-ESI calcd for $C_{25}H_{39}O_3Si$ [M + H$^+$] 415.2663, found 415.2661.

Synthesis of bromo ketone 12: To a solution of dienone **30** (40 mg, 0.1 mmol) in THF (8 mL) at 0 °C was added Et_3N (304 mg, 0.42 mL, 3 mmol) and TMSOTf (333 mg, 0.27 mL, 1.5 mmol) in a dropwise manner, then the reaction mixture was stirred at 0 °C for 30 min. To this solution was added a solution of *N*-bromosuccinimide (36 mg, 0.2 mmol) in THF (5 mL) slowly, and the formed mixture was stirred for 1 h. The reaction was quenched by addition of a saturated solution of sodium chloride (15 mL). The mixture was first extracted with EtOAc (3 × 15 mL), and the combined organic layer was then dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel

(hexane/EtOAc = 6/1) to give the desired bromo ketone **12** (38 mg) in 80% yield: R_f 0.5 (hexane/EtOAc = 5/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 (d, J = 2.0 Hz, 1H), 5.61 (s, 1H), 4.59 (dd, J = 2.4, 1.2 Hz, 1H), 3.65 (t, J = 8.3 Hz, 1H), 2.93 (dd, J = 15.0, 4.6 Hz, 1H), 2.59−2.36 (m, 4H), 2.37−2.27 (m, 1H), 2.09 (td, J = 11.4, 5.9 Hz, 1H), 2.03−1.94 (m, 1H), 1.94−1.86 (m, 1H), 1.84−1.76 (m, 2H), 1.67−1.52 (m, 3H), 1.24 (d, J = 4.9 Hz, 1H), 0.90 (s, 9H), 0.85 (s, 3H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.0, 160.2, 158.8, 119.4, 116.5, 83.4, 81.5, 76.0, 47.7, 44.7, 43.9, 41.2, 37.3, 36.2, 30.6, 30.0, 29.2, 25.8, 19.4, 18.0, 10.9, −4.5, −4.9; HRMS-ESI calcd for $C_{25}H_{38}O_3SiBr$ [M + H$^+$] 493.1768, found 493.1757.

Synthesis of amino alcohol 32: To a saturated solution of Me_2NH gas in THF [prepared by addition of a aqueous solution of $Me_2NH\cdot HCl$ (10 g, 122.7 mmol) in H_2O (20 mL) to sodium hydroxide solid (10 g, 250 mmol) in a dropwise manner, and the generated gas was passed through a drying tube containing sodium hydroxide into THF (5 mL)] was added *n*-BuLi (2.5 M in hexane, 0.65 mL, 1.62 mmol) at −78 °C in a dropwise manner, and the mixture was stirred at the same temperature for 1 h. To this solution was added a solution of bromo ketone **12** (40 mg, 0.081 mmol) in THF (3 mL) in a dropwise manner, and the formed mixture was stirred for an additional 20 min. The reaction was quenched by addition of a saturated solution of NH_4Cl (2 mL) and added water (10 mL). The mixture was extracted with EtOAc (3 × 15 mL), then the combined organic layer was dried over Na_2SO_4. The solvent was removed under vacuum, and the residue (amino ketone) was used directly in the next step. It is worthwhile to mention that the formed amino ketone was unstable at room temperature for ^{13}C NMR analysis: R_f 0.4 (CH_2Cl_2/MeOH = 5/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (d, J = 2.1 Hz, 1H), 5.52 (s, 1H), 3.66 (t, J = 8.3 Hz, 1H), 3.48 (dd, J = 13.8, 4.2 Hz, 1H), 2.52 (s, 1H), 2.46−2.36 (m, 5H), 2.18 (dd, J = 11.8, 4.0 Hz, 1H), 2.15−1.99 (m, 4H), 1.92 (dd, J = 11.7, 7.7 Hz, 1H), 1.71−1.61 (m, 4H), 1.56 (s, 1H), 0.90 (s, 9H), 0.84 (s, 3H), 0.02 (d, J = 12.9 Hz, 6H); HRMS-ESI calcd for $C_{27}H_{44}NO_3Si$ [M + H$^+$] 458.3085, found 458.3101.

To a solution of the crude amino ketone in THF (5 mL) at −78 °C was added $LiBHEt_3$ (1 M in THF, 0.08 mL, 0.08 mmol) in a dropwise manner, then the mixture was stirred at the same temperature for 20 min. The reaction was quenched by addition of a saturated solution of sodium chloride (10 mL). The formed mixture was extracted with EtOAc (3 × 25 mL), and the combined organic layer was dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel (CH_2Cl_2 initially, grading to CH_2Cl_2/MeOH = 3/1) to give amino alcohol **32** (19 mg) in 50% overall yield as a white solid: R_f 0.2 (CH_2Cl_2/MeOH = 5/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71 (d, J = 1.7 Hz, 1H), 5.31 (d, J = 5.3 Hz, 1H), 4.68 (s, 1H), 3.62 (t, J = 8.2 Hz, 1H), 3.09 (d, J = 10.8 Hz, 1H), 2.82 (s, 6H), 2.44 (d, J = 13.4 Hz, 1H), 2.40−2.22 (m, 2H), 2.04 (dd, J = 17.5, 11.1 Hz, 2H), 2.01−1.89 (m, 3H), 1.82 (dt, J = 19.5, 8.5 Hz, 2H), 1.74 (dd, J = 12.5, 3.9 Hz, 1H), 1.65−1.56 (m, 2H), 1.52 (s, 1H), 1.15 (td, J = 13.0, 4.8 Hz, 1H), 0.88 (s, 9H), 0.79 (s, 3H), 0.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.1, 144.0, 118.5, 115.8, 83.9, 81.6, 78.1, 63.1, 62.9, 47.9, 43.9, 41.3, 37. 5, 36.4, 31.6, 30.8, 30.6, 28.6, 25.8, 19.6, 18.0, 10.9, −4.5, −4.9; HRMS-ESI calcd for $C_{27}H_{46}NO_3Si$ [M + H$^+$] 460.3241, found 460.3235.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedure, ^{1}H NMR and ^{13}C NMR spectra, and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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