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Total Synthesis of Cortistatins A and J

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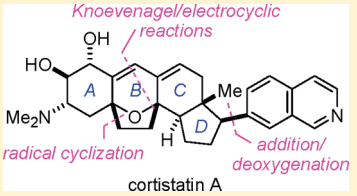
Supporting Information

ABSTRACT: This paper describes the details of our synthetic studies on the marine steroidal alkaloids cortistatins A and J. The key features of our strategy include (i) an efficient Knoevenagel/electrocyclic strategy to couple the diketone and the CD-ring fragment, (ii) a chemoselective radical cyclization to construct the oxabicyclo[3.2.1]octene B-ring system, (iii) a highly stereocontrolled installation of the isoquinoline unit, and (iv) a late-stage functionalization of the A-ring.



INTRODUCTION

Regulation of angiogenesis is one of the most important goals in medicine because the disorder of angiogenesis results in serious diseases such as atherosclerosis, arthritis, diabetic retinopathy, and cancer.[1] In particular, solid tumor growth depends greatly on the formation of new capillary blood vessels, such that inhibitors of angiogenesis are considered to ha ve high potential as antitumor agents.[2] Kobayashi and co-workers isolated the cortistatins (Figure 1), unique *abeo*-9(10,19)-androstane-type steroidal alkaloids that possess an oxabicyclo[3.2.1]octene system, from the marine sponge *Corticium simplex*.[3] Cortistatin A (**1**), the most potent congener, exhibited strong inhibition against the proliferation of human umbilical vein endothelial cells (HUVECs: IC_{50} = 1.8 nM) with extreme selectivity among cell lines. The SAR studies of natural and related synthetic samples revealed that the isoquinoline and dimethylamino groups were essential for their potent and selective antiangiogenic activities.[3,4] Kobayashi and co-workers showed that **1** inhibited phosphorylation of the unidentified 110 kDa protein in HUVECs.[4a] Moreover, kinase binding assays by the Nicolaou−Chen group suggested that cortistatins bind to the ATP-binding site of protein kinases.[5]

Because of their impressive inhibition activities of angiogenesis and unusual steroidal architecture, the cortistatins have been challenging targets for the synthetic community. To date, four research groups have accomplished the synthesis of the cortistatins,[6] and one racemic formal synthesis[7] and a number of synthetic studies have also been reported.[8] In this paper, we describe the development of an efficient strategy for assembling the pentacyclic ring system and isoquinoline moiety of the cortistatins, which culminated in the total syntheses of cortistatins A (**1**) and J (**5**).[9]

RESULTS AND DISCUSSION

Synthesis Plan. We originally envisaged cortistatin A (**1**), as well as other cortistatin congeners, to be accessible from

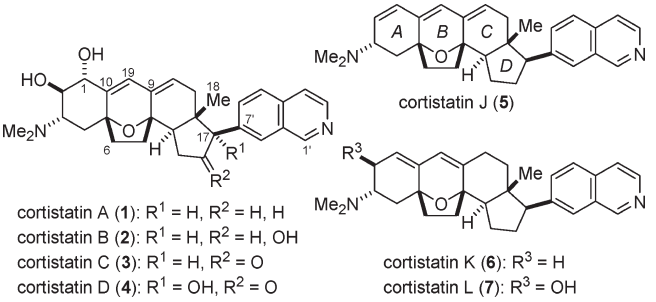


Figure 1. Structures of cortistatins.

pentacyclic framework **8** through installation of an isoquinoline moiety and functionalizations of the A-ring (Scheme 1). Disconnection of the tetrahydrofuran ring at the C5−C6 position of **8** unmasks the internal pyran **9**, which could be generated from chromene **10** by oxidative dearomatization. The intermediate **10** would be assembled from two fragments, aldehyde **11** and phloroglucinol **12**. The requisite CD-ring **11** was to be prepared from 3-methylanisole **14** and optically active iodide **15** via tricyclic intermediate **13**. The construction of the steroidal carbon skeleton from the two simple aromatic rings **12** and **14** would be an attractive aspect of this synthesis.

Attempts To Construct the Cortistatin Ring System via Dearomatization of *2H*-chromene. Synthesis of chiral side chain **15** began with methacrolein **16** (Scheme 2). Aldol condensation of **16** with ethyl acetate afforded β-hydroxy ester **17** in quantitative yield. According to Kobayashi's report,[10] kinetic resolution of racemic **17** by Sharpless epoxidation gave (−)-**17** (95% ee) in 45% yield along with the corresponding epoxide **18**. The secondary alcohol of (−)-**17** was protected as a benzyl ether under acidic conditions to provide **19** (82% yield). The requisite iodide **15** was obtained from **19** via reduction of the ester group

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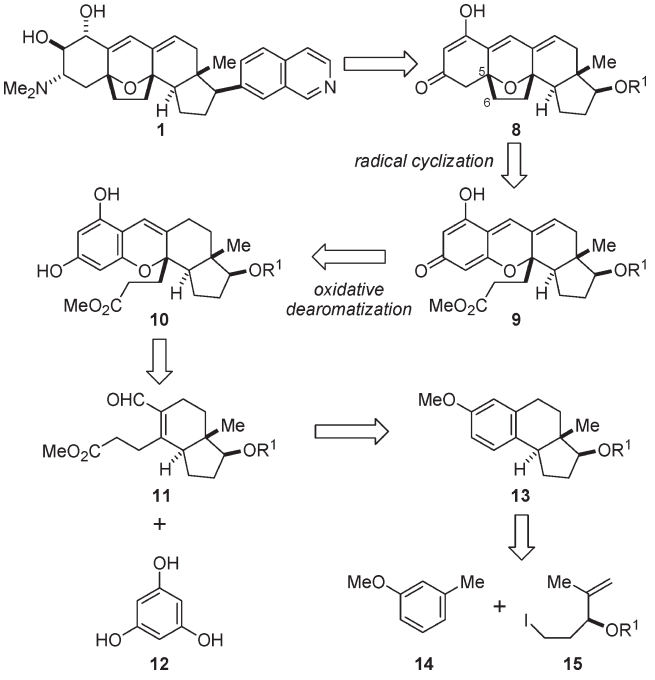
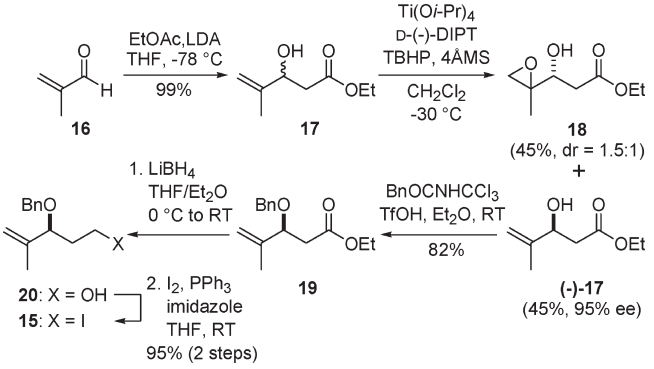
Scheme 1. Initial Synthesis Plan of Cortistatin A (1)



Scheme 2. Synthesis of Iodide 15



and subsequent iodination of the resultant alcohol **20** (95%, two steps).

The coupling partner benzocyclobutene **23** was prepared from commercially available 3-methylanisole **14** (Scheme 3). Bromination of **14** using 2.1 equiv of *N*-bromosuccinimide (NBS) in refluxing CH_2Cl_2 under exposure to a sunlamp afforded bisbromide **21** in 79% yield after recrystallization from *n*-hexane.[11] The two C−Br bonds of **21** were converted to C−C bonds in the following two steps. Nucleophilic substitution of benzyl bromide **21** with lithiated acetonitrile and subsequent treatment of the resulting nitrile **22** with sodium amide in liquid ammonia afforded cyclobutane **23** in 64% overall yield.[12] Coupling of **23** and **15** using LDA led to **24** as a 2:1 inseparable diastereomeric mixture. Careful treatment of **24** with sodium metal in THF/ammonia accomplished the simultaneous removal of the cyano and benzyl groups to give **25** in 87% yield. Intramolecular Diels−Alder reaction of *o*-quinodimethane intermediate **26**, which was generated by the thermal electrocyclic reaction of **25** according to Lett's procedure (*n*-BuLi, toluene, 180 °C),[13] furnished the desired tricyclic compound **27** as the major isomer. Protection of the secondary alcohol **27** as a TBS ether followed by

Scheme 3. Synthesis of Cyclohexadiene 29

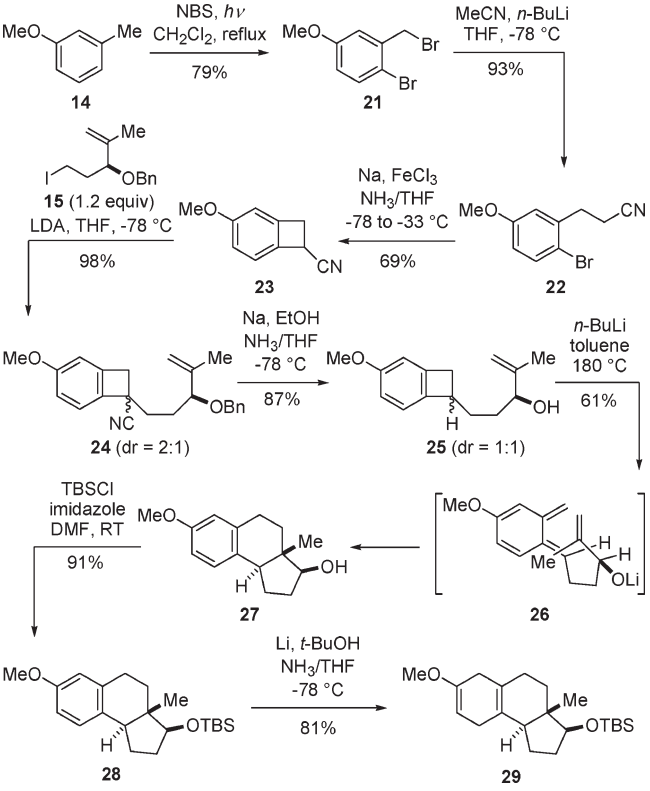


Table 1. Attempted Isomerization to Conjugated Diene

entry	substrate	conditions	results
1	**29**	$NaNH_2$, DME, rt	no reaction
2	**29**	*t*-BuOK, DMSO, rt	**30**:**29** = 2:1[a]
3	**29**	LiHMDS, THF, −78 °C to rt	no reaction
4	**31**	*t*-BuOK, DMSO, rt to 60 °C	**32**:**31** = 1:1[a]

[a] Inseparable mixture.

Birch reduction of the resulting **28** gave cyclohexadiene **29**. To directly introduce the hydroxy group at C19 through Rubbotom-type oxidation, isomerization of the double bond of **29** was attempted as summarized in Table 1. After examining several protocols, we found that treatment of **29** or alcohol **31** with *t*-BuOK in DMSO yielded conjugated dienes **30** or **32** (entries 2 and 4). Under these conditions, however, a significant amount of starting material **29** or **31** was recovered, and problematic separation prevented further transformations of **30** or **32**.

An alternative approach to the CD-ring was explored from ketone **33**, which was formed by acid treatment of **29** (Scheme 4). Installation of the hydroxy group at C19 of **33** was accomplished using Davis reagent and the subsequent Pb(OAc)$_4$-mediated oxidative cleavage of hydroxy ketone **35** afforded aldehyde **36**.

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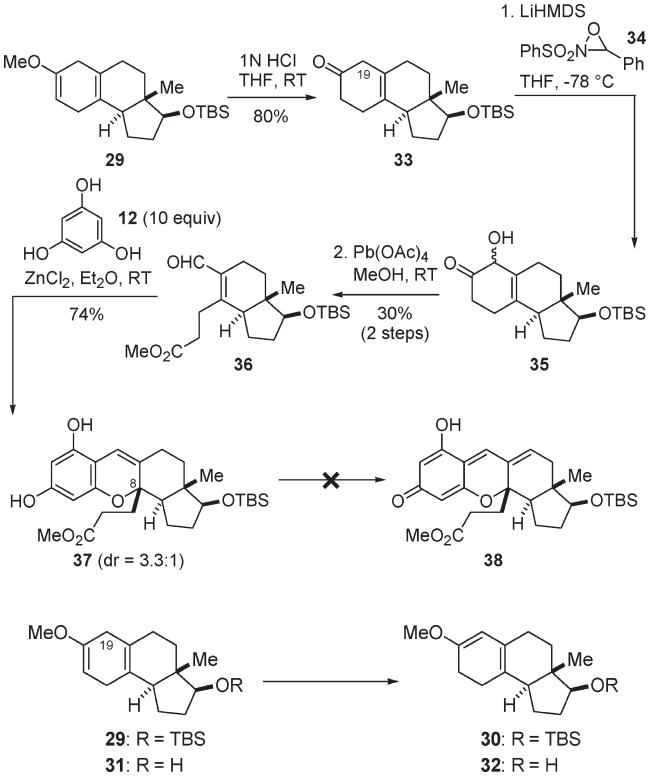
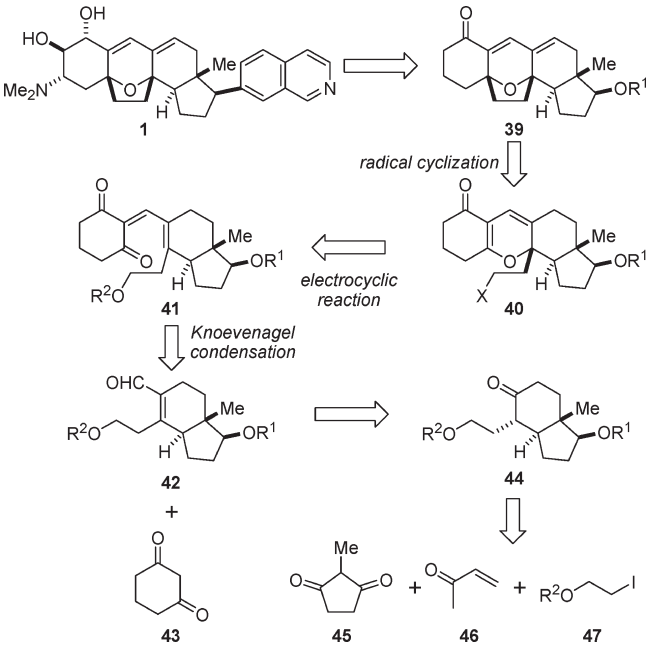
Scheme 4. Attempted Synthesis of Dearomatized 38



Scheme 5. Successful Synthetic Plan of Cortistatin A (1)



Having stereoselectively constructed the CD-ring, we turned our attention to the condensation of aldehyde **36** with phloroglucinol **12**. After a considerable number of attempts, we found that treatment of **36** with **12** in the presence of $ZnCl_2$ furnished 2*H*-chromene **37** as a 3.3:1 inseparable C8-stereoisomeric mixture. Oxidative dearomatization of **37** was examined prior to the radical cyclization. Although a variety of experimental factors

Scheme 6. Synthesis of Enone 51

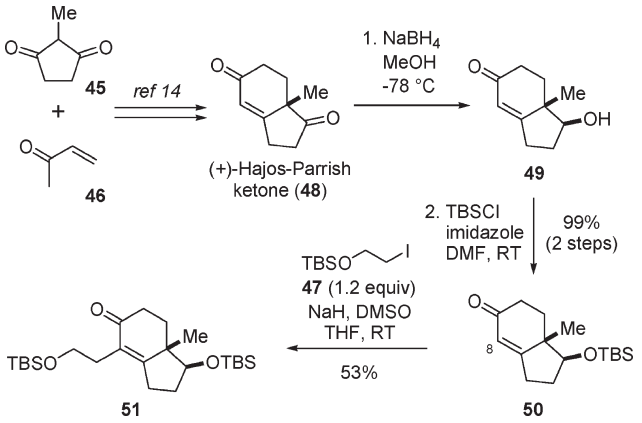
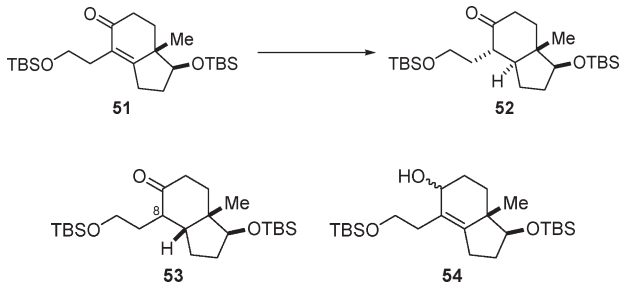


Table 2. Reduction of Enone 51 to *Trans*-Fused Ketone 52



entry	conditions	results[a]
1	H_2, Pd/C, EtOAc, rt	**52**: 25%, **53**[b]: 61%
2	Li, NH_3, Et_2O, −78 to −35 °C	complex mixture
3	CuI, *t*-BuLi, DIBAL, HMPA, THF, −78 to −40 °C	no reaction
4	$NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH, −78 °C	**52**: 60%, **53**: 5%, **54**: 15%

[a] Yields of **52** and **53** were calculated by NMR analysis. [b] Although **53** was obtained as a single isomer, the stereochemistry at C8 was not determined.

were tested, with a particular emphasis on the oxidant, we could not obtain the desired compound **38**. On the basis of these unsuccessful results and the difficulty of large-scale preparation of the CD-ring moiety, we were forced to abandon this strategy.

Successful Strategy and Stereoselective Synthesis of Pentacyclic Framework. The revised synthetic strategy for **1** is described in Scheme 5. The pentacyclic dienone **39** was chosen as the key intermediate, which could be formed by radical cyclization of **40**. We conceived **40** to be accessible from the CD-ring aldehyde **42** and 1,3-cyclohexadione **43** through Knoevenagel and electrocyclic reactions. The aldehyde **42** would be derived from three smaller fragments, 2-methyl-1,3-cyclopentadione **45**, methyl vinyl ketone **46**, and iodide **47**, via intermediate **44**.

Optically pure (+)-Hajos−Parrish ketone **48**, which was synthesized from **45** and **46** in three steps,[14] was converted to TBS ether **50** by chemoselective reduction of **48** followed by

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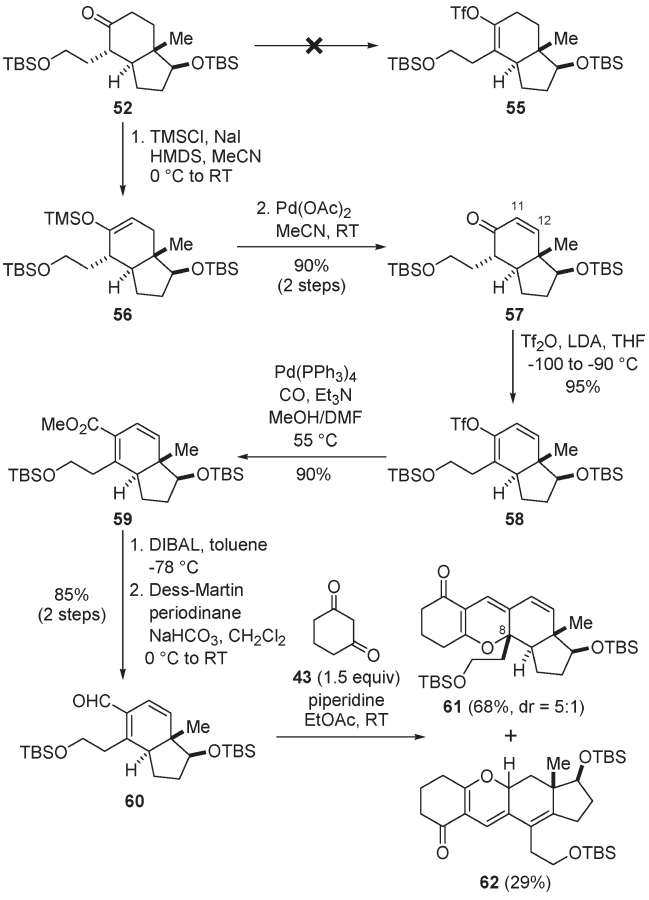
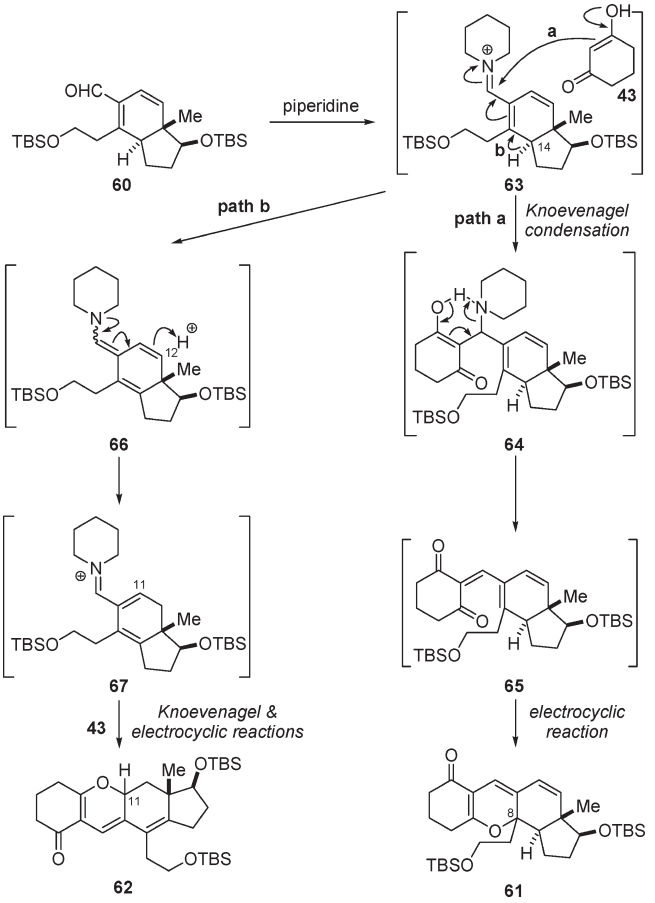
Scheme 7. Coupling Reaction of the A and CD Rings



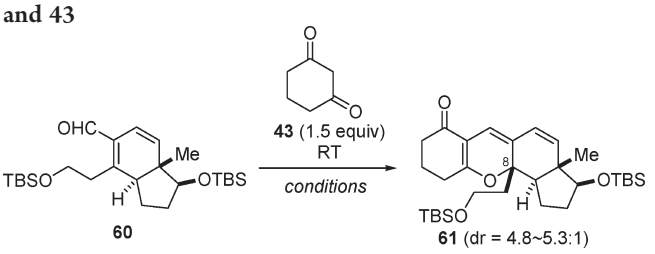
Scheme 8. Plausible Mechanism for the Formation of 61 and 62



TBS protection of the newly formed secondary alcohol **49** (Scheme 6).[15] The two-carbon unit **47** was attached at C8 of **50** according to Molander's protocol[16] to give **51**. Stereoselective reduction of enone **51** is summarized in Table 2. Palladium-catalyzed hydrogenation (entry 1) or Birch reduction (entry 2) mainly afforded the undesired *cis*-isomer **53** rather than the desired ketone **52**, whereas the organocopper reagent did not react with **51** (entry 3). After examining several alternative procedures, we finally found that nickel-boride reduction at low temperature furnished **52** in 60% yield along with the allylic alcohol **54** (15%) and the *cis*-isomer **53** (5%).[17]

We next focused on assembling the cortistatin framework (Scheme 7). Initially, preparation of a coupling precursor was envisioned through enol triflate **55**. The ketone **52**, however, could not be converted to **55** irrespective of direct and indirect approaches. During this study, we found that treatment of **52** with TMSCl and hexamethyldisilazane (HMDS) in the presence of NaI selectively afforded TMS-enol ether **56** in good yield. Thus, we turned to the construction of the CD-ring, which possesses the C11−12 double bond. Saegusa oxidation[18] of **56** furnished enone **57**, and formation of triflate **58** was accomplished using LDA and Tf_2O. Palladium-catalyzed methoxycarbonylation provided methyl ester **59** in 77% overall yield from ketone **52**.[19] The ester **59** was then converted to the CD-ring aldehyde **60** in 85% yield. Knoevenagel condensation was performed between **60** and cyclohexane-1,3-dione **43**.[20] Treatment of **60** with **43** (1.5 equiv) and piperidine (1.2 equiv) in EtOAc afforded tetracyclic compounds **61** (68%, dr =5:1 at C8) along with the unanticipated byproduct **62** (29%).

Table 3. Optimization of Coupling Reaction between 60 and 43



entry	conditions	**61** (%)	**62** (%)
1[a]	piperidine (1.2 equiv), EtOAc (200 mM)	68	29
2	piperidine hydrochloride (1.2 equiv), EtOAc (200 mM)	no reaction	
3	piperidinium acetate (1.2 equiv), EtOAc (200 mM)	71	25
4	piperidine (1.2 equiv), EtOAc (25 mM)	81	10
5	piperidine (1.2 equiv), EtOAc (15 mM)	87	trace

[a] Initial conditions.

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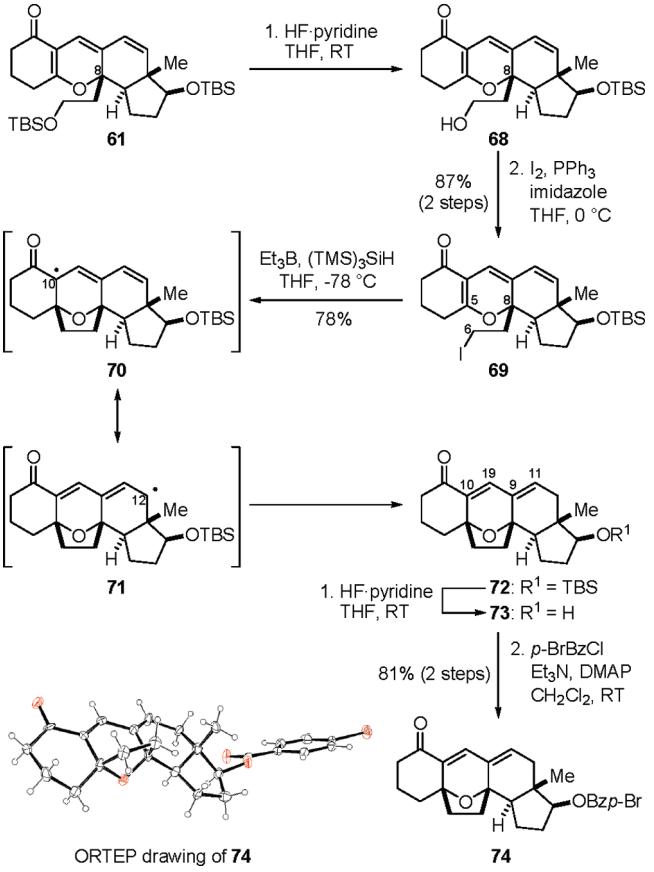
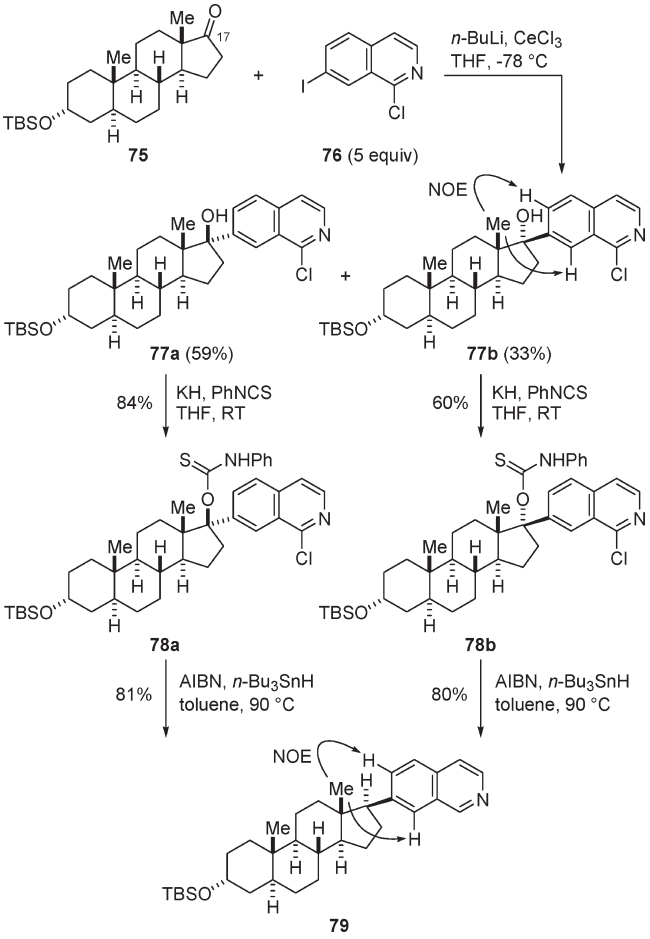
Scheme 9. Radical Cyclization To Construct the B-Ring



Scheme 10. Model Studies for Installing the Isoquinoline Unit



The formation of **62** can be explained by the mechanism proposed in Scheme 8. Reaction of **60** with piperidine would afford the iminium cation **63**. As expected, **63** reacts with **43** to generate **64**, which undergoes elimination of piperidine and subsequent spontaneous 6π-electrocyclization through the intermediate **65** to give **61** (path a). However, if deprotonation of **63** occurs at C14 followed by protonation at C12, the resulting conjugated iminium cation **67** would produce **62** via Knoevenagel condensation with **43** and subsequent undesired electrocyclization at C11. Optimum reaction conditions for selective formation of **61** were explored as described in Table 3. When piperidine hydrochloride was used instead of piperidine, no coupling products were obtained (entry 2). Although treatment with piperidinium acetate afforded **61** in 71% yield, a significant amount of **62** (25%) was also produced (entry 3). Lowering the concentration of the reaction mixture increased the yield of **61** (entry 4). We eventually obtained **61** as a C8-diastereomeric mixture in 87% combined yield under highly dilute conditions (entry 5).[21] Both isomers of **61** were useful for our synthesis (vide infra).

Selective removal of one TBS group of **61** was achieved by brief exposure to hydrogen fluoride−pyridine complex, and the resulting primary alcohol **68** was converted to the iodide **69** (87%, Scheme 9).[22] Interestingly, **69** underwent a spontaneous epimerization at C8, most likely through back-and-forth electrocyclic reactions. This phenomenon was not observed for TBS ether **61**. The desired C8-isomer of **69** became dominant over the undesired isomer (20:1) by maintaining the solid at −30 °C for 12 h. Construction of the oxabicyclo[3.2.1]octene dienone structure **72** was accomplished in a single step, to our delight, by the treatment of **69** with Et_3B and $(TMS)_3SiH$ in THF at low temperature in 78% yield.[23] The structure of **72** was unambiguously determined by X-ray crystallographic analysis of the corresponding *p*-bromobenzoate **74**. The primary radical, which arose from the iodide **69**, attacked the C5-terminal of the conjugated triene, which was closest in proximity, and subsequent hydrogen abstraction occurred at C12 in the resonance-stabilized radical **71**.

Installation of Isoquinoline Moiety. With a stereoselective route to the pentacyclic cortistatin framework in hand, we then examined the installation of the isoquinoline unit using model compound **75** (Scheme 10). Gratifyingly, the treatment of **75** with an organocerium reagent, which was generated from 1-chloro-7-iodoisoquinoline **76**, *n*-BuLi, and $CeCl_3$ in THF, efficiently afforded the coupling products **77a** and **77b** as a mixture in 92% combined yield.[24] Formation of thiocarbamate **78a** from the congested tertiary alcohol **77a** was realized by treatment with KH and phenyl isothiocyanate in THF at room temperature.[25] Simultaneous removal of the thiocarbamate and chlorine groups of **78a** using AIBN and *n*-Bu_3SnH provided **79** stereoselectively in 68% overall yield. Using the same procedure, the C17-epimer **77b** was also successfully converted to **79** as a single isomer.

Application of the present isoquinoline installation method to the cortistatin skeleton is summarized in Scheme 11. The dienone **72** was transformed to ketone **81** in three steps.[6b,c]

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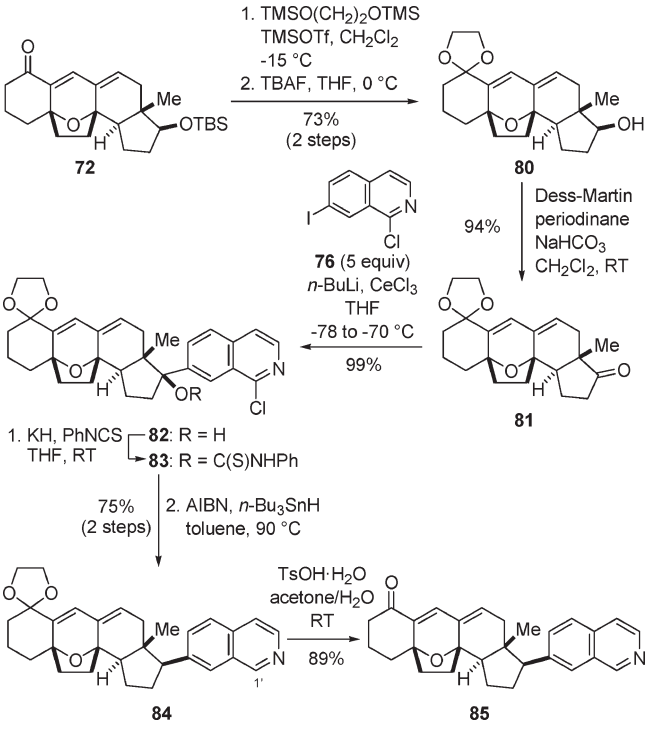
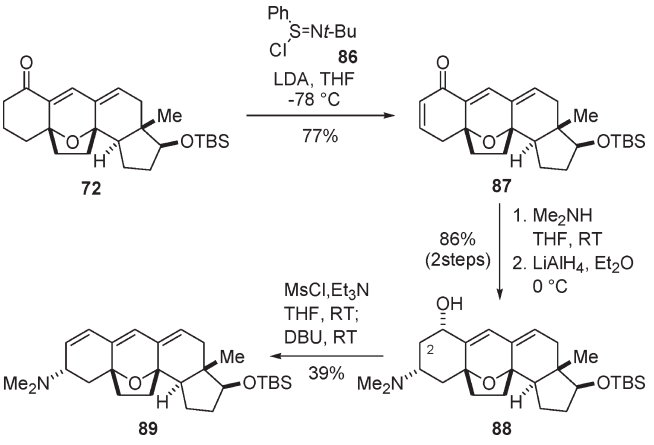
Scheme 11. Synthesis of Ketone 85



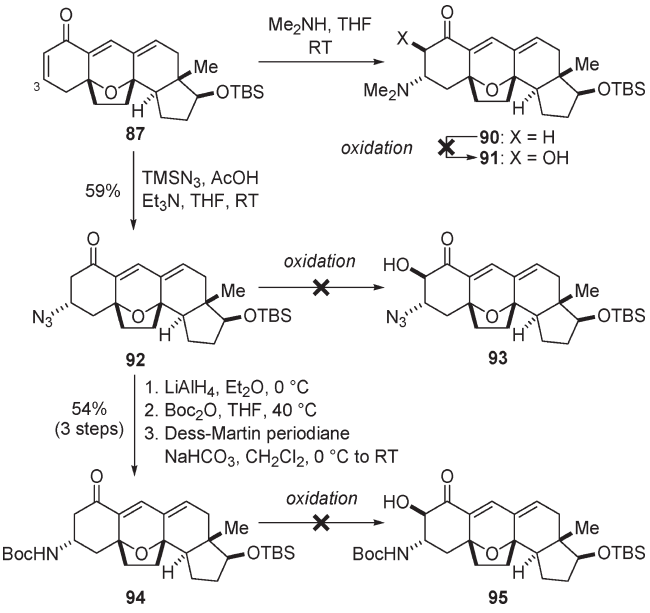
Scheme 12. Model Studies of the A-Ring Functionalization for Constructing Cortistatin J



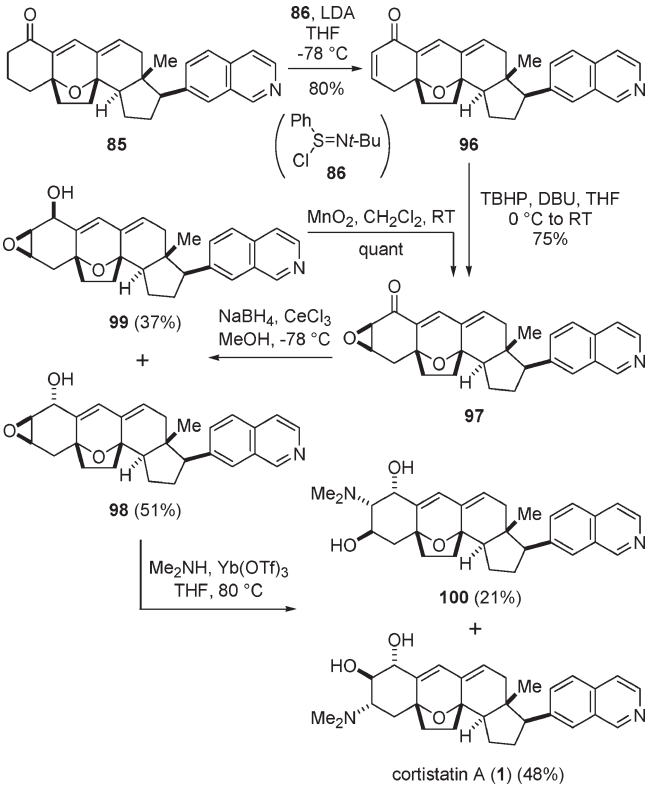
Coupling of **81** and **76** using *n*-BuLi/$CeCl_3$ gave tertiary alcohol **82** in quantitative yield as a single isomer. In this case, addition of the isoquinoline unit occurred only from the α-face. Treatment of **82** with KH and phenyl isothiocyanate afforded the corresponding thiocarbamate **83**, and subsequent reduction also proceeded from the α-side with complete stereocontrol to give **84** as the sole product. Finally, acid hydrolysis of acetal **84** furnished ketone **85** in 67% overall yield from **82**.

Enantioselective Total Syntheses of Cortistatins A and J. We directed our attention to the A-ring functionalization for the total syntheses of cortistatins. Model studies for constructing cortistatin J (**5**) are described in Scheme 12. Direct oxidation of ketone **72** to enone **87** was achieved using Mukaiyama reagent **86** in 77% yield.[26] Chemo- and stereoselective addition of dimethylamine to **87** and subsequent $LiAlH_4$ reduction afforded the 2-deoxy cortistatin A analogue **88** in 86% overall yield. Elimination of the hydroxy group was achieved through the mesylation of **88** followed by treatment with DBU to give the cortistatin J model **89**.

Scheme 13. Model Studies for Constructing the A-Ring of Cortistatin A



Scheme 14. Total Synthesis of Cortistatin A (1)



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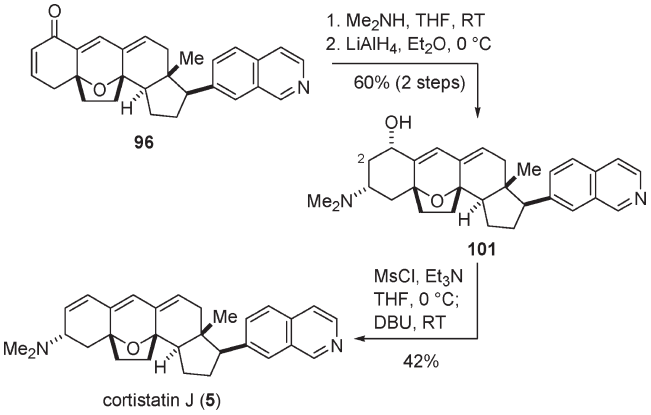
Scheme 15. Total Synthesis of Cortistatin J (5)



A-ring modification toward cortistatin A (**1**) was first attempted as depicted in Scheme 13. We examined the hydroxylation of ketones which possessed C3-dimethylamino (**90**), C3-azido (**92**),[27] and C3-NHBoc (**94**) groups under various conditions. The C2 position, however, was not oxidized successfully and instead the enone **87** was regenerated as a result of β-elimination. Thus, we abandoned this strategy and decided to follow the Nicolaou−Chen protocol for constructing **1**[6b,c] with some modifications.

Mukaiyama oxidation of ketone **85** afforded enone **96** in 80% yield (Scheme 14). Treatment of **96** with TBHP and DBU in THF furnished epoxide **97** stereoselectively, and subsequent Luche reduction[28] of **97** gave the desired α-alcohol **98** (51%) along with the β-isomer **99** (37%). After separation, the undesired alcohol **99** was oxidized quantitatively back to ketone **97** by MnO_2 oxidation and was recycled. We were able to optimize slightly the addition reaction of dimethylamine using $Yb(OTf)_3$, which afforded cortistatin A (**1**) and its regioisomer **100** in 48 and 21% yields, respectively.

The total synthesis of cortistatin J (**5**) is described in Scheme 15. Conjugate addition of dimethylamine to **96**, followed by $LiAlH_4$ reduction, furnished 2-deoxycortistatin A (**101**) in 60% yield from **96**. Treatment of **101** with MsCl and DBU provided **5** in 42% yield. Synthetic samples **1** and **5** exhibited identical spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, MS) with those of the natural cortistatins A and J, respectively.[3]

CONCLUSION

We accomplished the total syntheses of cortistatins A (**1**) and J (**5**). The enantioselective route reported herein features (a) an enantioselective construction of the CD-ring moiety from Hajos−Parrish ketone, (b) Knoevenagel/electrocyclic reactions to couple the A-ring and the CD-ring moieties, (c) a chemoselective radical cyclization to construct the oxabicyclo[3.2.1]octene B-ring system, (d) a stereocontrolled installation of the isoquinoline unit, and (e) a late-stage functionalization of the A-ring. We hope the present methodologies en route to cortistatins A and J will contribute to the development of new antiangiogenesis agents and anticancer research.

EXPERIMENTAL SECTION

General Experimental Procedures. All reactions sensitive to air or moisture were carried out under argon or nitrogen atmosphere in dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Chemical shifts of NMR spectra are reported in δ (ppm) downfield from tetramethylsilane with reference to solvent signals [^{1}H NMR:$CHCl_3$ (7.26), C_6D_5H (7.16); ^{13}C NMR $CDCl_3$ (77.0), C_6D_6 (128.0)]. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. NMR peak assignments were performed by COSY, HSQC, HMBC, and NOESY experiments.

Alcohol (−)-17. To a solution of LDA [79.9 mmol, prepared from diisopropylamine (12.8 mL, 91.3 mmol) and *n*-BuLi (1.56 M in hexane, 51.2 mL, 79.9 mmol)] in THF (65 mL) was added EtOAc (7.85 mL, 79.9 mmol) at −78 °C. After the solution was stirred for 20 min at the same temperature, methacrolein **16** (5.0 g, 71.3 mmol) was added and the mixture stirred for an additional 1 h. The mixture was quenched with aqueous saturated NH_4Cl and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and flash column chromatography (hexane/EtOAc 20:1−5:1) gave **17** (11.2 g, 70.1 mmol) in 99% yield.

To a mixture of $Ti(O\text{-}i\text{-}Pr)_4$ (3.88 mL, 13.1 mmol) and 4 Å molecular sieves (984 mg) in CH_2Cl_2 (32 mL) at −40 °C were successively added D-(−)-DIPT (11.0 mL, 32.7 mmol), alcohol **17** (5.18 g, 32.7 mmol) in CH_2Cl_2 (7 mL), and TBHP (3 M in CH_2Cl_2, 11.0 mL, 33 mmol). After the reaction mixture was stirred for 24 h at −30 °C, 5% aqueous citric acid was added and the resulting mixture stirred for an additional 2 h. The mixture was extracted with EtOAc, and the organic layer was washed with brine and dried over Na_2SO_4. Concentration and flash column chromatography (hexane/EtOAc 15:1−10:1) gave (−)-**17** (2.33 g, 14.7 mmol, 95% ee) in 45% yield along with epoxide **18** (2.4 g, 14.5 mmol). (−)-**17**: colorless oil; R_f = 0.50 (hexane/EtOAc 5:1); $[\alpha]_D^{31}$ −27.0 (*c* 0.25, $CHCl_3$); IR (film) ν 3443, 2982, 1731, 1651, 1372, 1276, 1165, 1024, 902 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, t, *J* = 7.2 Hz, Et), 1.75 (3H, s, Me18), 2.56 (2H, m, H16 × 2), 2.95 (1H, brs, OH), 4.17 (2H, q, *J* = 7.2 Hz, Et), 4.46 (1H, m, H17), 4.88 (1H, dd, *J* = 1.6, 0.8 Hz, H12), 5.03 (1H, dd, *J* = 1.6, 1.2 Hz, H12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (Et), 18.2 (C18), 40.1 (C16), 60.8 (Et), 71.5 (C17), 111.4 (C12), 145.5 (C13), 172.5 (C15); HRMS (ESI) *m*/*z* calcd for $C_8H_{14}NaO_3$ 181.0835 $[M + Na]^+$, found 181.0834.

Benzyl Ether 19. To a solution of (−)-**17** (2.5 g, 15.8 mmol) and benzyl 2,2,2-trichloroacetimidate (4.4 mL, 23.7 mmol) in Et_2O (63 mL) at 0 °C was added TfOH (700 μL, 7.9 mmol). The reaction mixture was warmed to room temperature and stirred for 12 h. The mixture was treated with aqueous saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and flash column chromatography (hexane/EtOAc 50:1) gave benzyl ether **19** (3.23 g, 13.0 mmol) in 82% yield: colorless oil; $[\alpha]_D^{20}$ −26.5 (*c* 0.29, $CHCl_3$); IR (film) ν 2797, 1738, 1452, 1274, 1173, 1069, 908 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (3H, t, *J* = 7.2 Hz, Et), 1.73 (3H, s, Me18), 2.48 (1H, dd, *J* = 14.8, 4.8 Hz, H16), 2.69 (1H, dd, *J* = 14.8, 9.2 Hz, H16), 4.14 (2H, q, *J* = 7.2 Hz, Et), 4.28 (1H, dd, *J* = 9.2, 4.8 Hz, H17), 4.30 (1H, d, *J* = 11.6 Hz, Bn), 4.49 (1H, d, *J* = 11.6 Hz, Bn), 5.01 (1H, m, H12), 5.04 (1H, d, *J* = 5.5 Hz, H12), 7.28−7.37 (5H, m, Bn); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (Et), 16.7 (C18), 39.9 (C16), 60.5 (Et), 70.3 (Bn), 79.9 (C17), 114.5 (C12), 127.5 (Bn), 127.7 (Bn × 2), 128.2 (Bn × 2), 138.2 (Bn), 143.2 (C13), 171.0 (C15); HRMS (ESI) *m*/*z* calcd for $C_{15}H_{20}NaO_3$ 271.1305 $[M + Na]^+$, found 271.1305.

Alcohol 20. To a solution of **19** (425 mg, 1.71 mmol) in THF/Et_2O = 1 (23 mL) at 0 °C was added $LiBH_4$ (91 mg, 4.19 mmol). After being stirred for 12 h at room temperature, the mixture was quenched with aqueous saturated NH_4Cl at 0 °C and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and flash column chromatography (hexane/EtOAc 10:1−5:1) gave alcohol **20** (340 mg, 1.65 mmol) in 98% yield: colorless oil; $[\alpha]_D^{21}$ −46.9 (*c* 1.00, $CHCl_3$); IR (film) ν 3365, 2945, 1452, 1170, 1066, 906 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68−1.76 (4H, m, H16,

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Me18), 1.96 (1H, m, H16), 3.74 (2H, dd, J = 5.2, 5.2 Hz, H15), 4.00 (1H, dd, J = 8.8, 4.0 Hz, H17), 4.29 (1H, d, J = 12.0 Hz, Bn), 4.55 (1H, d, J = 12.0 Hz, Bn), 5.02 (2H, m, H12), 7.27−7.38 (5H, m, Bn); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8 (C18), 36.1 (C16), 60.8 (C15), 69.9 (Bn), 82.3 (C17), 113.6 (C12), 127.6 (Bn), 127.7 (Bn × 2), 128.3 (Bn × 2), 138.1 (Bn), 144.0 (C13); HRMS (ESI) m/z calcd for $C_{13}H_{18}O_2Na$ 229.1199 $[M + Na]^+$, found 229.1197.

Iodide 15. To a mixture of **20** (340 mg, 1.65 mmol), imidazole (169 mg, 2.48 mmol), and PPh_3 (564 mg, 2.15 mmol) in THF (17 mL) at 0 °C was added iodine (503 mg, 1.98 mmol). After being stirred for 2 h at room temperature, the mixture was quenched with aqueous saturated $NaHCO_3$ and aqueous $Na_2S_2O_3$. After the extraction with EtOAc, the organic layer was washed with brine and dried over Na_2SO_4. Concentration and flash column chromatography (hexane/EtOAc 50:1) afforded iodide **15** (511 mg, 1.62 mmol) in 95% yield from **19**: colorless oil; $[\alpha]_D^{21}$ −47.5 (c 1.00, $CHCl_3$); IR (film) ν 2862, 1651, 1453, 1235, 1093, 907 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75 (3H, s, Me18), 2.00 (1H, dddd, J = 14.4, 7.2, 6.8, 4.8 Hz, H16), 2.19 (1H, dddd, J = 14.4, 8.4, 7.2, 6.8 Hz, H16), 3.26 (2H, ddd, J = 14.4, 6.8, 6.8 Hz, H15), 3.91 (1H, dd, J = 8.4, 4.8 Hz, H17), 4.32 (1H, d, J = 11.6 Hz, Bn), 4.55 (1H, d, J = 11.6 Hz, Bn), 5.06−5.07 (2H, m, H12), 7.30−7.40 (5H, m, Bn); ^{13}C NMR (100 MHz, $CDCl_3$) δ 2.8 (C15), 16.8 (C18), 37.6 (C16), 70.2 (Bn), 82.6 (C17), 114.3 (C12), 127.5 (Bn), 127.8 (Bn × 2), 128.3 (Bn × 2), 138.2 (Bn), 143.3 (C13); HRMS (ESI) m/z calcd for $C_{13}H_{17}INaO$ 339.0216 $[M + Na]^+$, found 339.0212.

Dibromide 21. To a solution of **14** (6.3 mL, 50 mmol) in CH_2Cl_2 was added NBS (18.7 g, 105 mmol). The mixture was irradiated by 450 W sunlamp for 4 h at 40 °C. The reaction was quenched with H_2O at room temperature and extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration gave a crude solid, which was recrystallized from hexane to afford bis-bromide **21** (11.1 g, 39.8 mmol) in 79% yield: needles; mp 92−93 °C; IR (film) ν 2938, 2246, 1573, 1471, 1238, 1160, 802 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (3H, s, MeO), 4.56 (2H, s, H11), 6.74 (1H, dd, J = 9.0, 3.0 Hz, H6), 6.99 (1H, d, J = 3,0 Hz, H19), 7.45 (1H, d, J = 9.0 Hz, H7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.4 (C11), 55.6 (MeO), 114.7 (C8), 116.1 (C6), 116.5 (C19), 133.9 (C7), 137.8 (C9), 159.1 (C6″); HRMS (ESI) m/z calcd for $C_8H_8Br_2NaO$ 302.8819 $[M + Na]^+$, found 302.8822.

Nitrile 22. To a solution of MeCN (866 μL, 16.6 mmol) in THF (100 mL) at −78 °C was added n-BuLi (1.56 M in hexane, 10.7 mL, 16.6 mmol). After the soltion was stirred for 15 min at the same temperature, **21** (3.58 g, 12.8 mmol) in THF (70 mL) was added and the resulting mixture stirred for an additional 30 min. The reaction mixture was treated with aqueous saturated NH_4Cl and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and flash column chromatography (hexane/EtOAc 20:1−5:1) gave nitrile **22** (2.86 g, 11.9 mmol) in 93% yield: colorless oil; IR (film) ν 2939, 1708, 1475, 1284, 1250, 813 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.67 (2H, t, J = 7.0 Hz, H14), 3.04 (2H, t, J = 7.0 Hz, H11), 3.80 (3H, s, MeO), 6.72 (1H, dd, J = 8.5, 3.0 Hz, H6), 6.85 (1H, d, J = 3.0 Hz, H19), 7.44 (1H, d, J = 8.5 Hz, H7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5 (C14), 32.3 (C11), 55.5 (MeO), 114.2 (C8), 114.6 (C6), 116.4 (C19), 118.8 (CN), 133.6 (C7), 138.0 (C9), 159.2 (C6″); HRMS (ESI) m/z calcd for $C_{10}H_{10}BrNNaO$ 261.9843 $[M + Na]^+$, found 261.9843.

Cyclobutane 23. To a solution of $NaNH_2$ [16.6 mmol, prepared from Na (381 mg, 16.6 mmol), $FeCl_3$ (10 mg, 62 μmol), and NH_3 (~10 mL)] in THF (10 mL) was added **22** (1.0 g, 4.16 mmol) in THF (3 mL) at −78 °C. After being stirred for 1.5 h at −33 °C, the solution was quenched with solid NH_4Cl and excess NH_3 removed at room temperature. The mixture was filtrated through a pad of Celite and washed with Et_2O and H_2O. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and flash column chromatography (hexane/EtOAc 10:1−2:1) gave **23** (457 mg, 2.87 mmol) in 69% yield: yellow oil; IR (film) ν 2939, 2835, 2236, 1589, 1473, 1272, 1166, 817 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.49 (1H, dd, J = 14.5, 1.5 Hz, H11), 3.62 (1H, dd, J = 14.5, 5.5 Hz, H11), 3.78 (3H, s, OMe), 4.17 (1H, dd, J = 5.5, 1.5 Hz, H14), 6.72 (1H, d, J = 1.5 Hz, H19), 6.84 (1H, dd, J = 8.5, 1.5 Hz, H6), 7.12 (1H, d, J = 8.5 Hz, H7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0 (C14), 35.6 (C11), 55.5 (MeO), 108.8 (C19), 115.2 (C6), 119.9 (CN), 123.8 (C7), 130.4 (C8), 143.7 (C9), 161.1 (C6″); HRMS (ESI) m/z calcd for $C_{10}H_9NNaO$ 182.0576 $[M + Na]^+$, found 182.0576.

Coupling Adduct 24. To a solution of LDA [1.82 mmol, prepared from diisopropylamine (255 μL, 1.82 mmol) and n-BuLi (1.56 M in hexane, 1.2 mL, 1.82 mmol)] in THF (5 mL) at −78 °C was added **23** (192 mg, 1.21 mmol). After the solution was stirred for 30 min at the same temperature, a solution of **15** (458 mg, 1.45 mmol) in THF (2 mL) was added at −78 °C and the resulting solution stirred for an additional 30 min. The mixture was treated with aqueous saturated NH_4Cl and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and flash column chromatography (hexane/EtOAc 20:1−10:1) gave **24** (409 mg, 1.18 mmol) as a 2:1 diastereomer mixture in 98% yield: colorless oil; IR (film) ν 2937, 2232, 1647, 1590, 1475, 1328, 1278, 1069, 910, 817 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70 (H, s, Me18), 1.73 (2H, s, Me18), 1.74−2.12 (4H, m, H15 × 2, H16 × 2), 3.20 (2/3H, d, J = 14.4 Hz, H11), 3.22 (1/3H, d, J = 14.4 Hz, H11), 3.63 (1H, d, J = 14.4 Hz, H11), 3.74−3.82 (4H, m, H17, MeO), 4.26 (1H, d, J = 11.6 Hz, Bn), 4.52 (1H, d, J = 11.6 Hz, Bn), 4.97 (1H, m, H12), 5.02 (1H, m, H12), 6.72 (1H, s, H19), 6.82 (1H, d, J = 8.0 Hz, H6), 7.10 (2/3H, d, J = 8.0 Hz, H7), 7.12 (1/3H, d, J = 8.0 Hz, H7), 7.27−7.36 (5H, m, Bn); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6 (C18), 30.1 (C16 × 2/3), 3.03 (C16 × 1/3), 33.7 (C15 × 2/3), 33.9 (C15 × 1/3), 41.8 (C14), 42.1 (C11), 55.5 (MeO), 69.9 (Bn × 2/3), 70.0 (Bn × 1/3), 82.4 (C17 × 2/3), 82.6 (C17 × 1/3), 109.2 (C19), 114.4 (C12), 114.8 (C6), 121.9 (CN), 122.9 (C7), 127.4 (Bn), 127.7 (Bn × 2), 128.3 (Bn × 2), 135.1 (C9), 138.4 (Bn), 141.9 (C8), 143.7 (C13), 161.0 (C6″); HRMS (ESI) m/z calcd for $C_{23}H_{25}NNaO$ 370.1777 $[M + Na]^+$, found 370.1778.

Alcohol 25. To a mixture of **24** (200 mg, 576 μmol), NH_3 (10 mL), and EtOH (140 μL) in THF (2.5 mL) was slowly added Na (33.0 mg, 1.44 mmol). After being stirred for 1.5 h at −78 °C, the mixture was quenched with solid NH_4Cl and excess NH_3 removed at room temperature. The mixture was washed with brine and dried over Na_2SO_4. Concentration and flash column chromatography (hexane/EtOAc 10:1) gave **25** (116 mg, 499 μmol) as a 1:1 diastereomer mixture in 87% yield: colorless oil; IR (film) ν 3414, 2918, 1647, 1602, 1469, 1271, 1021, 898 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.61−1.78 (7H, m, H15 × 2, H16 × 2, Me18), 2.68 (1H, d, J = 14.0 Hz, H11), 3.25 (1/2H, d, J = 14.0 Hz, H11), 3.28 (1/2H, d, J = 14.0 Hz, H11), 3.40 (1H, m, H14), 3.77 (3H, s, MeO), 4.11 (1H, m, H17), 4.85 (1H, m, H12), 4.95 (1H, m, H12), 6.98 (1H, s, H19), 6.73 (1H, d, J = 9.0 Hz, H17), 6.97 (1/2H, d, J = 9.0 Hz, H6), 6.99 (1/2H, d, J = 9.0 Hz, H6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.46 (C18 × 1/2), 17.49 (C18 × 1/2), 30.5 (C15 × 1/2), 30.6 (C15 × 1/2), 33.2 (C16 × 1/2), 33.3 (C16 × 1/2), 35.4 (C11), 42.25 (C14 × 1/2), 42.31 (C14 × 1/2), 55.4 (MeO), 75.9 (C17 × 1/2), 76.0 (C17 × 1/2), 109.1 (C19), 111.19 (C12 × 1/2), 111.24 (C12 × 1/2), 113.1 (C6), 122.8 (C7), 141.16 (C8 × 1/2), 141.19 (C8 × 1/2), 144.5 (C9), 147.38 (C13 × 1/2), 147.43 (C13 × 1/2), 159.6 (C6″); HRMS (ESI) m/z calcd for $C_{15}H_{20}NaO_2$ 255.1355 $[M + Na]^+$, found 255.1356.

Tricyclic Compound 27. To a solution of **25** (420 mg, 1.81 mmol) in toluene (36 mL) at 0 °C was added n-BuLi (1.56 M, 1.5 mL, 2.35 mmol). The reaction mixture was stirred for 30 min at room temperature and then heated to 180 °C in a shield tube. After being stirred for 24 h at 180 °C, the mixture was cooled to 0 °C and quenched with aqueous saturated NH_4Cl. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and flash column chromatography (hexane/EtOAc 20:1−10:1) gave **27** (266 mg, 1.14 mmol) in 61%

yield: colorless oil; $[\alpha]_D^{30}$ +10.9 (*c* 0.83, $CHCl_3$); IR (film) ν 3389, 2953, 1722, 1613, 1504, 1264, 1067, 1037, 817 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.64 (3H, s, Me18), 1.43 (1H, m, H12), 1.54−1.73 (3H, m, H15, H16, OH), 1.98 (1H, ddd, *J* = 10.0, 4.5, 4.5 Hz, H12), 2.06 (1H, m, H15), 2.30 (1H, m, H16), 2.58 (1H, dd, *J* = 11.5, 7.5 Hz, H14), 2.90−2.94 (2H, m, H11 × 2), 3.77 (3H, s, MeO), 3.88 (1H, dd, *J* = 14.5, 7.0 Hz, H17), 6.68−6.72 (2H, m, H7, H19), 6.90 (1H, d, *J* = 9.0 Hz, H6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5 (C18), 23.1 (C15), 27.0 (C11), 31.2 (C16), 33.7 (C12), 43.2 (C13), 45.6 (C14), 55.2 (MeO), 81.0 (C17), 111.0 (C11), 113.7 (C7), 126.4 (C6), 131.7 (C8), 137.3 (C9), 157.6 (C6″); HRMS (ESI) *m*/*z* calcd for $C_{15}H_{20}NaO_2$ 255.1355 $[M + Na]^+$, found 255.1357.

TBS Ether 28. To a solution of **27** (112 mg, 482 μmol) in DMF at 0 °C were added imidazole (134 mg, 1.93 mmol) and TBSCl (146 mg, 966 μmol). After being stirred for 15 h at room temperature, the mixture was treated with H_2O and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and flash column chromatography (hexane/EtOAc 20:1) gave **28** (152 mg, 439 μmol) in 91% yield: colorless oil; $[\alpha]_D^{28}$ +6.7 (*c* 1.17, $CHCl_3$); IR (film) ν 2954, 2928, 2856, 1608, 1503, 1248, 1098, 836 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.05 (3H, s, TBS), 0.06 (3H, s, TBS), 0.60 (3H, s, Me18), 0.90 (9H, s, TBS), 1.46−1.68 (3H, m, H12, H15, H16), 1.91 (1H, ddd, *J* = 12.5, 6.0, 3.5 Hz, H12), 2.01 (1H, m, H15), 2.11 (1H, dddd, *J* = 12.5, 12.5, 12.5, 2.5 Hz, H16), 2.52 (1H, dd, *J* = 11.0, 7.5 Hz, H14), 2.89 (2H, m, H11 × 2), 3.78 (4H, m, H17, MeO), 6.66−6.68 (2H, m, H7, H19), 6.90 (1H, d, *J* = 9.5 Hz, H6); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8 (TBS), −4.6 (TBS), 10.8 (C18), 18.1 (TBS), 23.3 (C15), 25.9 (TBS), 27.1 (C11), 31.6 (C16), 34.2 (C12), 43.6 (C13), 45.1 (C14), 55.1 (MeO), 80.9 (C17), 110.9 (C19), 113.6 (C7), 126.4 (C6), 132.2 (C8), 137.6 (C9), 157.5 (C6″); HRMS (ESI) *m*/*z* calcd for $C_{21}H_{34}NaO_2Si$ 369.2220 $[M + Na]^+$, found 369.2223.

Cyclohexadiene 29. To a solution of **28** (72 mg, 208 μmol), NH_3 (10 mL), and *t*-BuOH (600 μL) in Et_2O (4 mL) at −78 °C was added Li (∼20 mg). After being stirred for 4 h at −78 °C, the reaction mixture was quenched with solid NH_4Cl and excess NH_3 removed at room temperature. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and flash column chromatography (hexane/EtOAc 15:1−10:1) gave **29** (59 mg, 169 mmol) in 81% yield: colorless oil; $[\alpha]_D^{20}$ +63.4 (*c* 0.16, $CHCl_3$); IR (film) ν 2930, 1669, 1392, 1252, 1221, 1159, 1073, 897, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.01 (3H, s, TBS), 0.02 (3H, s, TBS), 0.71 (3H, s, Me18), 0.87 (9H, s, TBS), 1.24−1.34 (2H, m, H12, H15), 1.43−1.66 (2H, m, H12, H16), 1.77 (1H, dd, *J* = 12.0, 7.0 Hz, H14), 1.93−2.07 (4H, m, H11 × 2, H15, H16), 2.54−2.63 (2H, m, H19 × 2), 2.68−2.74 (2H, m, H7 × 2), 3.55 (3H, s, MeO), 3.68 (1H, dd, *J* = 8.0, 8.0 Hz, H17), 4.63 (1H, br, H6); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8 (TBS), −4.5 (TBS), 16.4 (C18), 18.1 (TBS), 25.8 (TBS), 26.9 (C15), 28.8 (C11), 28.9 (C12), 30.9 (C7), 33.1 (C16), 33.6 (C19), 45.5 (C13), 47.0 (C14), 53.7 (MeO), 80.7 (C17), 90.7 (C6), 122.2 (C9), 128.8 (C8), 153.0 (C6″); HRMS (ESI) *m*/*z* calcd for $C_{21}H_{36}NaO_2Si$ 371.2377 $[M + Na]^+$, found 371.2378.

Ketone 33. To a solution of **29** (123 mg, 353 μmol) in THF (1 mL) was added 1 N aqueous HCl (0.1 mL) at room temperature. After being stirred for 30 min, the mixture was treated with aqueous saturated $NaHCO_3$ and extracted with EtOAc. The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration and flash column chromatography (hexane/EtOAc 15:1) afforded **33** (94 mg, 281 μmol) in 80% yield: colorless oil; $[\alpha]_D^{21}$ +65.5 (*c* 1.00, $CHCl_3$); IR (film) ν 2953, 1720, 1466, 1252, 1069, 900, 837, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (6H, s, TBS), 0.71 (3H, s, Me18), 0.89 (9H, s, TBS), 1.22−1.59 (4H, m, H12 × 2, H15, H16), 1.78 (1H, dd, *J* = 12.8, 6.0 Hz, H14), 1.94−2.12 (4H, m, H11 × 2, H15, H16), 2.35−2.49 (4H, m, H6 × 2, H7 × 2), 2.72−2.76 (2H, m, H19), 3.69 (1H, m, H17); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9 (TBS), −4.5 (TBS), 16.2 (C18), 18.0 (TBS), 25.8 (TBS), 27.0 (C7), 28.5 (C15), 29.4 (C16), 29.7 (C12), 32.8 (C11), 39.1 (C6), 43.7 (C13), 44.3 (C19), 47.4 (C14), 80.2 (C17), 123.3 (C9), 131.8 (C8), 211.3 (C6″); HRMS (ESI) *m*/*z* calcd for $C_{20}H_{34}NaO_2Si$ 357.2220 $[M + Na]^+$, found 357.2226.

Aldehyde 36. To a solution of **33** (5.0 mg, 15 μmol) in THF (500 μL) at −78 °C was added LiHMDS (1.0 M, 75 μL, 75 μmol). After the solution was stirred for 30 min, Davis reagent **34** (19 mg, 75 μmol) in THF (300 μL) was added and the resulting solution stirred for an additional 30 min at −78 °C. The reaction mixture was quenched with aqueous saturated NH_4Cl and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and flash column chromatography (hexane/EtOAc 20:1−10:1) gave **35**, which was used in the next reaction without further purification.

To a solution of **35** (∼8.6 μmol) in MeOH/benzene = 4 (500 μL) at room temperature was added $Pb(OAc)_4$ (9.0 mg, 21 μmol). After being stirred for 2 h at room temperature, the mixture was quenched with H_2O and extracted with EtOAc. The combined organic layer was washed with brine and dried over Na_2SO_4. Concentration and flash column chromatography (hexane/EtOAc 20:1−10:1) gave **36** (1.0 mg, 2.6 μmol) in 30% yield from **33**: colorless oil; $[\alpha]_D^{22}$ +74.4 (*c* 0.52, $CHCl_3$); IR (film) ν 1741, 1669, 1629, 1467, 1364, 1254, 1175, 1062, 837, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (6H, s, TBS), 0.86 (3H, s, Me18), 0.90 (9H, s, TBS), 1.22−1.39 (3H, m, H12 × 2, H15), 1.59 (1H, m, H16), 2.03−2.57 (8H, m, H6 × 2, H7, H11 × 2, H14, H15, H16), 3.25 (1H, m, H7), 3.68 (3H, s, OMe), 3.72 (1H, dd, *J* = 5.6, 4.0 Hz, H17), 10.12 (1H, s, H19); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8 (TBS), −4.5 (TBS), 18.1 (TBS), 19.1 (C18), 19.5 (C15), 25.8 (TBS), 26.0 (C7), 28.2 (C16), 29.6 (C12), 32.8 (C14), 34.1 (C11), 44.0 (C13), 48.5 (C6), 51.7 (MeO), 80.5 (C17), 132.2 (C9), 160.1 (C8), 172.5 (C6″), 190.8 (C19); HRMS (ESI) *m*/*z* calcd for $C_{21}H_{36}NaO_4Si$ 403.2275 $[M + Na]^+$, found 403.2278.

Diol 37. To a solution of **36** (2 mg, 5.25 μmol) and **12** (7 mg, 52.5 μmol) in Et_2O (500 μL) was added $ZnCl_2$ (1 mg, 5.25 μmol) at room temperature. After being stirred for 8 h, the mixture was quenched with H_2O and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration and flash column chromatography (hexane/EtOAc 5:1−3:1) gave **37** (1.9 mg, 3.89 μmol) in 74% yield as a 3.3:1 diastereomer mixture. Major isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (6H, s, TBS), 0.88 (9H, s, TBS), 1.11 (3H, s, Me18), 1.20−1.39 (2H, m, H12 × 2), 1.43 (1H, m, H16), 1.80 (1H, m, H15), 1.89−2.10 (3H, m, H7, H15, H16), 2.24 (1H, m, H11), 2.30−2.56 (5H, m, H6 × 2, H7, H11, H14), 3.60 (1H, m, H17), 3.62 (3H, s, MeO), 5.27 (2H, brs, OH × 2), 5.75 (1H, d, *J* = 1.2 Hz, H4), 5.77 (1H, d, *J* = 1.2 Hz, H2), 6.40 (1H, s, H19); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9 (TBS), −4.5 (TBS), 18.1 (TBS), 21.5 (C18), 25.8 (TBS), 26.5 (C15), 28.7 (C6, C11), 31.5 (C16), 31.8 (C12), 34.7 (C7), 47.0 (C13), 51.7 (MeO), 52.0 (C14), 83.7 (C17), 84.0 (C8), 95.1 (C2 or C4), 95.2 (C2 or C4), 102.1 (C10), 113.7 (C19), 131.0 (C9), 151.5 (C5), 155.2 (C1), 156.0 (C3), 174.6 (C6″); HRMS (ESI) *m*/*z* calcd for $C_{27}H_{40}NaO_8Si$ 511.2486 $[M + Na]^+$, found 511.2486

TBS Ether 50. To a solution of **48** (5.0 g, 30.5 mmol) in MeOH (200 mL) at −78 °C was added $NaBH_4$ (575 mg, 15.2 mmol). The resulting mixture was stirred for 20 min. The reaction was then quenched with acetone (20 mL) and the mixture allowed to warm to room temperature. The mixture was directly passed through a pad of silica gel with EtOAc and concentrated to afford the corresponding alcohol **49**, which was used in the next reaction without further purification.

To a solution of the obtained alcohol and imidazole (8.3 g, 122 mmol) in DMF (76 mL) at 0 °C was added TBSCl (6.0 g, 40 mmol). The resulting mixture was stirred for 12 h at room temperature. The reaction was quenched with aqueous NH_4Cl and extracted twice with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (hexane/EtOAc 100:1−15:1) of the residue gave TBS ether **50** (8.5 g, 30.3 mmol) in

quantitative yield from **48** as colorless oil. The ^{1}H NMR spectrum of this compound was consistent with reported data.[29]

Iodide 47. To a suspension of NaH (60% in mineral oil, 1.2 g, 30.0 mmol; washed with hexane) in THF (65 mL) at 0 °C was added ethylene glycol (1.67 mL, 30.0 mmol) and the mixture stirred for 2 h at room temperature. Then TBSCl (4.5 g, 30.0 mmol) was added at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl and extracted twice with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford monoalcohol, which was used in the next reaction without further purification.

To a solution of the obtained alcohol, imidazole (3.06 g, 45.0 mmol), and triphenylphosphine (10.2 g, 39.0 mmol) in THF (150 mL) at 0 °C was added iodine (9.1 g, 36.0 mmol) over 20 min. The resulting mixture was stirred for 40 min at room temperature. The reaction was quenched with aqueous $Na_2S_2O_3$ and aqueous NH_4Cl, extracted twice with EtOAc, and concentrated. Produced triphenylphosphine oxide was precipitated out using diethyl ether followed by hexane. Concentration and flash column chromatography (hexane) gave iodide **47** (7.7 g, 26.9 mmol) in 90% from ethylene glycol as a colorless oil. The ^{1}H NMR spectrum of this compound was consistent with the reported data.[30]

Bis TBS Ether 51. A suspension of NaH (60% in mineral oil, 472 mg, 11.8 mmol; washed with hexane) in DMSO (14 mL) was stirred for 2 h at 55 °C. To the resulting mixture were successively added THF (32 mL) and **50** (3.0 g, 10.7 mmol) in DMSO (18 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 2 h. A solution of iodide **47** (3.37 g, 11.8 mmol) in THF (10 mL) was added and the mixture stirred for 1 h at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted twice with EtOAc, and the organic layer was washed with brine and dried over Na_2SO_4. Concentration and flash column chromatography (hexane/EtOAc 50:1) gave enone **51** (2.51 g, 5.72 mmol) in 53% yield: colorless oil; R_f = 0.50 (hexane/EtOAc 5:1); $[\alpha]_D^{24}$ +18.4 (*c* 1.02, $CHCl_3$); IR (film) ν 2955, 2929, 2857, 1665, 1471, 1255, 1122, 1095, 837 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.01 (3H, s, TBS), 0.00 (3H, s, TBS), 0.04 (3H, s, TBS), 0.05 (3H, s, TBS), 0.86 (9H, s, TBS), 0.90 (9H, s, TBS), 1.07 (3H, s, Me18), 1.68 (1H, ddd, *J* = 13.5, 13.5, 5.3 Hz, H12), 1.78 (1H, m, H16), 1.93 (1H, m, H16), 1.97 (1H, dddd, *J* = 13.5, 13.5, 5.3, 1.7 Hz, H12), 2.33−2.40 (3H, m, H7, H7, H11), 2.48−2.68 (3H, m, H11, H15, H15), 3.58 (1H, ddd, *J* = 9.8, 6.4, 6.4 Hz, H6), 3.60 (1H, ddd, *J* = 9.8, 6.4, 6.4 Hz, H6), 3.72 (1H, dd, *J* = 10.3, 7.4 Hz, H17); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.46 (TBS), −5.41 (TBS), −4.92 (TBS), −4.48 (TBS), 15.5 (C18), 18.0 (TBS), 18.2 (TBS), 25.70 (C15), 25.74 (TBS), 25.9 (TBS), 29.3 (C7), 29.8 (C16), 33.5 (C11), 34.2 (C12), 45.6 (C13), 61.8 (C6), 81.0 (C17), 130.0 (C14), 170.5 (C8), 198.5 (C9); HRMS (ESI) *m*/*z* calcd for $C_{24}H_{46}NaO_3Si_2$ 461.2878 $[M + Na]^+$, found 461.2876. Anal. Calcd for $C_{24}H_{46}O_3Si_2$: C, 65.69; H, 10.57. Found: C, 65.56; H, 10.32.

Ketone 52. To a solution of **51** (1.0 g, 2.28 mmol) and $NiCl_2 \cdot 6H_2O$ (2.3 g, 11.4 mmol) in MeOH (45 mL) at −90 °C was added $NaBH_4$ (1.3 g, 34.2 mmol). The resulting mixture was stirred for 20 min at the same temperature and allowed to warm to −70 °C over 40 min. The reaction was quenched with saturated aqueous NH_4Cl and extracted twice with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (hexane/EtOAc 30:1−20:1) gave ketone **52** (615 mg, 1.40 mmol) in 60% yield, **53** (30 mg, 0.07 mmol) in 3% yield, and **54** (150 mg, 0.34 mmol) in 15% yield: colorless oil; R_f = 0.5 (hexane/EtOAc 5:1); $[\alpha]_D^{26}$ +19.3 (*c* 1.01, $CHCl_3$); IR (neat) ν 2954, 2857, 1711, 1471, 1253, 1100, 900, 837, 775 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.01 (6H, s, TBS), 0.02 (3H, s, TBS), 0.03 (3H, s, TBS), 0.880 (9H, s, TBS), 0.884 (9H, s, TBS), 1.03 (3H, s, Me18), 1.39 (1H, ddd, *J* = 12.7, 12.7, 5.4 Hz, H12), 1.42−1.53 (3H, m, H7, H14, H15), 1.56−1.69 (2H, m, H16, H15), 1.82 (1H, dddd, *J* = 13.7, 8.8, 6.3, 4.9 Hz, H7), 1.91 (1H, ddd, *J* = 12.7, 6.9, 2.0 Hz, H12), 1.98 (1H, m, H16), 2.31 (1H, ddd, *J* = 15.2, 5.4, 2.0 Hz, H11), 2.47 (1H, ddd, *J* = 15.2, 12.7, 6.9 Hz, H11), 2.50 (1H, ddd, *J* = 13.7, 8.8, 3.0 Hz, H8), 3.57 (1H, ddd, *J* = 9.8, 7.8, 6.3 Hz, H6), 3.62 (1H, dd, *J* = 8.3, 8.3 Hz, H17), 3.71 (1H, ddd, *J* = 9.8, 7.3, 4.9 Hz, H6); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.36 (TBS), −5.28 (TBS), −4.9 (TBS), −4.5 (TBS), 10.8 (C18), 18.0 (TBS), 18.2 (TBS), 24.3 (C15), 25.8 (TBS), 25.9 (TBS), 29.7 (C7), 31.5 (C16), 35.9 (C12), 38.0 (C11), 43.7 (C13), 47.0 (C8), 49.7 (C14), 61.4 (C6), 80.4 (C17), 212.9 (C9); HRMS (ESI) *m*/*z* calcd for $C_{24}H_{48}NaO_3Si_2$ 463.3034 $[M + Na]^+$, found 463.3032. Anal. Calcd for $C_{24}H_{48}O_3Si_2$: C, 65.39; H, 10.98. Found: C, 65.25; H, 10.85.

Enone 57. To a mixture of **52** (634 mg, 1.44 mmol), $HN(SiMe_3)_2$ (3.06 mL, 14.4 mmol), and NaI (1.08 g, 7.2 mmol) in MeCN (29 mL) at 0 °C was added TMSCl (0.91 mL, 7.2 mmol). After the mixture was stirred for 6.5 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted twice with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Purification through a pad of silica gel (EtOAc) gave the corresponding silyl enol ether, which was used in the next reaction without further purification.

To a solution of silyl enol ether **56** in MeCN (29 mL) at room temperature was added $Pd(OAc)_2$ (646 mg, 2.88 mmol). The resulting mixture was stirred for 12 h at room temperature. After filtration through a pad of silica gel (EtOAc), the filtrate was washed with aqueous $NaHCO_3$, NH_4Cl, and brine and dried over Na_2SO_4. Concentration and flash column chromatography (hexane/EtOAc 100:1−50:1) gave enone **57** (567 mg, 1.29 mmol) in 90% yield from **52**: colorless oil; R_f = 0.3 (hexane/EtOAc 10:1); $[\alpha]_D^{24}$ −3.44 (*c* 1.05, $CHCl_3$); IR (neat) ν 2954, 2929, 2882, 2857, 1676, 1471, 1361, 1252, 1144, 1089, 836, 775 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ −0.023 (3H, s, TBS), −0.017 (3H, s, TBS), 0.10 (3H, s, TBS), 0.11 (3H, s, TBS), 0.84 (3H, s, Me18), 0.94 (9H, s, TBS), 0.99 (9H, s, TBS), 1.22−1.36 (2H, m, H15, H16), 1.45 (1H, m, H15), 1.61 (1H, ddd, *J* = 13.7, 12.2, 6.8 Hz, H14), 1.69 (1H, m, H16), 1.87 (1H, dddd, *J* = 13.7, 7.3, 7.3, 3.9 Hz, H7), 1.98 (1H, ddd, *J* = 13.7, 6.4, 6.4 Hz, H7), 2.41 (1H, ddd, *J* = 13.7, 6.4, 3.9 Hz, H8), 3.55 (1H, dd, *J* = 8.3, 6.9 Hz, H17), 3.82−3.92 (2H, m, H6), 5.90 (1H, d, *J* = 9.8 Hz, H11), 6.78 (1H, d, *J* = 9.8 Hz, H12); ^{13}C NMR (125 MHz, C_6D_6) δ −4.6 (TBS), −4.5 (TBS), −4.3 (TBS), −3.7 (TBS), 13.3 (C18), 18.8 (TBS), 19.1 (TBS), 24.7 (C15), 26.6 (TBS), 26.8 (TBS), 31.0 (C16), 31.9 (C7), 45.3 (C8), 46.4 (C14), 47.1 (C13), 62.4 (C6), 77.6 (C17), 129.8 (C11), 154.9 (C12), 201.5 (C9); HRMS (ESI) *m*/*z* calcd for $C_{24}H_{46}NaO_3Si_2$ 461.2878 $[M + Na]^+$, found 461.2875. Anal. Calcd for $C_{24}H_{46}O_3Si_2$: C, 65.69; H, 10.57. Found: C, 65.72; H, 10.36.

Triflate 58. To a solution of **57** (587 mg, 1.34 mmol) in THF (44 mL) at −100 °C was added LDA [0.4 M, 33 mL, 13.4 mmol, fleshly prepared from *i*-Pr_2NH (6.0 mL, 42.8 mmol), *n*-BuLi (1.56 M, 19.2 mL, 30 mmol), and THF (50 mL)]. After the mixture was stirred for 20 min, Tf_2O (0.67 mL, 3.99 mmol) was added at −100 °C. The reaction mixture was allowed to warm to −90 °C over 20 min and quenched with aqueous saturated NH_4Cl. The mixture was extracted twice with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (hexane) afforded triflate **58** (727 mg, 1.27 mmol) in 95% yield: colorless oil; R_f = 0.5 (hexane/EtOAc = 10:1); $[\alpha]_D^{27}$ −24.3 (*c* 1.00, $CHCl_3$); IR (film) ν 2956, 2931, 2885, 2859, 1472, 1419, 1250, 1212, 1144, 1124, 1097, 872 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (3H, s, TBS), 0.05 (6H, s, TBS), 0.06 (3H, s, TBS), 0.82 (3H, s, Me18), 0.88 (9H, s, TBS), 0.89 (9H, s, TBS), 1.61 (1H, m, H16), 1.72−1.81 (2H, m, H15), 2.10 (1H, m, H16), 2.33 (1H, ddd, *J* = 13.4, 6.9, 6.9 Hz, H7), 2.56−2.64 (2H, m, H7, H14), 3.66 (2H, dd, *J* = 6.9, 6.9 Hz, H6), 3.97 (1H, dd, *J* = 8.8, 7.6 Hz, H17), 5.76 (1H, d, *J* = 9.8 Hz, H11), 6.13 (1H, d, *J* = 9.8 Hz, H12); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.48 (TBS), −5.47 (TBS), −4.86 (TBS), −4.42 (TBS), 9.4 (C18), 18.0 (TBS), 18.2 (TBS), 21.2 (C15), 25.7 (TBS), 25.8 (TBS), 31.2 (C7), 31.4 (C16), 45.6 (C14), 46.0 (C13), 61.2 (C6), 75.4 (C17), 120.7 (C11), 129.7 (C8), 138.8 (C12), 141.8 (C9) (one

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CF_3 carbon could not identified due to its C−F coupling); HRMS (ESI) m/z calcd for $C_{25}H_{45}F_3NaO_5SSi_2$ 593.2371 $[M + Na]^+$, found 593.2368. Anal. Calcd for $C_{25}H_{45}F_3O_5SSi_2$: C, 52.60; H, 7.95. Found: C, 52.70; H, 7.92.

Methyl Ester 59. To a solution of $Pd(PPh_3)_4$ (199 mg, 172 μmol) in DMF (50 mL) was added a solution of triflate **58** (0.98 g, 1.72 mmol) and Et_3N (5 mL) in MeOH (30 mL). The resulting mixture was stirred for 17 h at 55 °C under CO atmosphere (balloon filled with CO gas). The reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted twice with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (hexane/EtOAc 1:0−20:1) gave ester **59** (745 mg, 1.55 mmol) in 90% yield: colorless oil; R_f = 0.5 (hexane/EtOAc 10:1); $[\alpha]_D^{25}$ −60.5 (c 0.91, $CHCl_3$); IR (film) ν 2955, 2929, 2884, 2857, 1716, 1472, 1250, 1124, 1095, 836, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.35 (3H, s, TBS), 0.41 (3H, s, TBS), 0.41 (3H, s, TBS), 0.67 (3H, s, TBS), 0.70 (3H, s, Me18), 0.88 (9H, s, TBS), 0.89 (9H, s, TBS), 1.59 (1H, m, H16), 1.77−1.84 (2H, m, H15), 2.08 (1H, m, H16), 2.50 (1H, brdd, J = 9.8, 9.8 Hz, H14), 2.69 (1H, ddd, J = 11.5, 7.3, 7.3 Hz, H7), 3.01 (1H, dddd, J = 11.5, 6.4, 6.4, 1.3 Hz, H7), 3.68−3.74 (2H, m, H6), 3.74 (3H, s, OMe), 3.96 (1H, dd, J = 8.6, 7.7 Hz, H17), 6.03 (1H, d, J = 9.4 Hz, H12), 6.24 (1H, d, J = 9.4 Hz, H11); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.4 (TBS × 2), −4.8 (TBS), −4.4 (TBS), 9.5 (C18), 18.0 (TBS), 18.3 (TBS), 21.2 (C15), 25.8 (TBS), 25.9 (TBS), 31.4 (C16), 34.8 (C7), 44.8 (C13), 48.9 (C14), 51.3 (MeO), 62.5 (C6), 76.3 (C17), 123.7 (C11), 124.5 (C9), 136.0 (C12), 152.5 (C8), 166.8 (C19); HRMS (ESI) m/z calcd for $C_{26}H_{48}NaO_4Si_2$ 503.2983 $[M + Na]^+$, found 503.2980. Anal. Calcd for $C_{26}H_{48}O_4Si_2$: C, 64.95; H, 10.06. Found: C, 64.75; H, 9.80.

Aldehyde 60. To a solution of ester **59** (745 mg, 1.55 mmol) in toluene (52 mL) at −78 °C was added DIBAL (0.99 M in toluene, 4.7 mL, 4.6 mmol). After being stirred for 40 min at −78 °C, the reaction mixture was quenched with aqueous Rochelle's salt and stirred for an additional 2 h at room temperature. The mixture was extracted twice with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (hexane/EtOAc 20:1) gave the corresponding alcohol (624 mg, 1.38 mmol) in 89% yield: colorless crystals; mp 85.0−85.4 °C; R_f = 0.4 (hexane/EtOAc 5:1); $[\alpha]_D^{25}$ −73.3 (c 0.97, $CHCl_3$); IR (film) ν 3391(br), 2955, 2929, 2883, 2857, 1471, 1360, 1255, 1119, 1098, 835, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.04 (3H, s, TBS), 0.065 (6H, s, TBS), 0.070 (3H, s, TBS), 0.71 (3H, s, Me18), 0.889 (9H, s, TBS), 0.892 (9H, s, TBS), 1.58 (1H, m, H16), 1.62−1.69 (2H, m, H15, H15), 2.09 (1H, m, H16), 2.39 (1H, ddd, J = 13.7, 4.7, 3.9 Hz, H7), 2.45 (1H, dd, J = 9.8, 9.8 Hz, H14), 2.56 (1H, ddd, J = 13.7, 8.6, 5.2 Hz, H7), 2.79 (1H, dd, J = 7.3, 4.3 Hz, OH), 3.61 (1H, ddd, J = 9.6, 8.6, 3.9 Hz, H6), 3.72 (1H, ddd, J = 9.6, 5.2, 4.7 Hz, H6), 3.94−4.00 (2H, m, H17, H19), 4.18 (1H, dd, J = 11.5, 4.3 Hz, H19), 5.90 (1H, d, J = 9.4 Hz, H11), 6.00 (1H, d, J = 9.4 Hz, H12); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.6 (TBS), −5.5 (TBS), −4.8 (TBS), −4.4 (TBS), 9.5 (C18), 18.0 (TBS), 18.6 (TBS), 21.2 (C15), 25.8 (TBS), 26.0 (TBS), 31.8 (C16), 32.5 (C7), 45.6 (C13), 46.2 (C14), 60.9 (C19), 61.4 (C6), 76.2 (C17), 127.7 (C11), 133.2 (C9), 135.4 (C8), 136.0 (C12); HRMS (ESI) m/z calcd for $C_{25}H_{48}NaO_3Si_2$ 475.3034 $[M + Na]^+$, found 475.3032. Anal. Calcd for $C_{25}H_{48}O_3Si_2$: C, 66.31; H, 10.68. Found: C, 66.02; H, 10.40.

To a mixture of the obtained alcohol (932 mg, 2.06 mmol) and $NaHCO_3$ (865 mg, 10.3 mmol) in CH_2Cl_2 (41 mL) at 0 °C was added Dess−Martin periodinane (1.31 g, 3.09 mmol). The resulting mixture was stirred for 40 min at room temperature and then the reaction quenched with aqueous $Na_2S_2O_3$ and aqueous NH_4Cl. The mixture was extracted twice with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (hexane/EtOAc 40:1) gave aldehyde **60** (888 mg, 1.97 mmol) in 96% yield: colorless crystal; mp 73.0−73.4 °C; R_f = 0.4 (hexane/EtOAc 10:1); $[\alpha]_D^{25}$ −77.82 (c 1.07, $CHCl_3$); IR (film) ν 2950, 2938, 2856, 2882, 1660, 1469, 1250, 1123, 1096, 1082 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.01 (3H, s, TBS), 0.01 (3H, s, TBS), 0.05 (3H, s, TBS), 0.08 (3H, s, TBS), 0.71 (3H, s, Me18), 0.85 (9H, s, TBS), 0.89 (9H, s, TBS), 1.63 (1H, m, H16), 1.74−1.81 (2H, m, H15), 2.13 (1H, m, H16), 2.64 (1H, dd, J = 9.8, 9.8 Hz, H14), 2.75 (1H, ddd, J = 12.8, 6.4, 6.4 Hz, H7), 2.97 (1H, ddd, J = 12.8, 6.4, 6.4 Hz, H7), 3.71 (1H, ddd, J = 9.8, 6.4, 6.4 Hz, H6), 3.74 (1H, ddd, J = 9.8, 6.4, 6.4 Hz, H6), 4.00 (1H, dd, J = 9.0, 7.7 Hz, H17), 6.11 (1H, d, J = 9.4 Hz, H12), 6.40 (1H, d, J = 9.4 Hz, H11), 9.98 (1H, s, H19); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.49 (TBS), −5.46 (TBS), −4.8 (TBS), −4.4 (TBS), 9.9 (C18), 18.0 (TBS), 18.2 (TBS), 20.6 (C15), 25.77 (TBS), 25.82 (TBS), 31.4 (C16), 31.7 (C7), 45.6 (C13), 48.5 (C14), 61.6 (C6), 76.1 (C17), 120.0, (C11), 133.6 (C9), 137.0 (C12), 157.4 (C8), 188.8 (C19); HRMS (ESI) m/z calcd for $C_{25}H_{46}NaO_3Si_2$ 473.2878 $[M + Na]^+$, found 473.2875. Anal. Calcd for $C_{25}H_{46}O_3Si_2$: C, 66.61; H, 10.29. Found: C, 66.32; H, 10.15.

Tetracyclic Compound 61. To a mixture of **60** (520 mg, 1.15 mmol) and 2,3-cyclohexanedione **43** (194 mg, 1.73 mmol) in EtOAc (77 mL) at room temperature was added piperidine (126 μL, 1.27 mmol). After being stirred for 6 h at room temperature, the reaction mixture was directly passed through a pad of flash silica gel and concentrated. Flash column chromatography (hexane/EtOAc = 15:1−10:1) gave a mixture of tetracyclic triene **61** and its C8-epimer (544 mg, 1.00 mmol, dr =5:1) in 87% combined yield. **61** (major isomer): R_f = 0.3 (hexane/EtOAc 5:1); ^1H NMR (600 MHz, $CDCl_3$) δ 0.01 (3H, s, TBS), 0.02 (3H, s, TBS), 0.02 (3H, s, TBS), 0.03 (3H, s, TBS), 0.86 (9H, s, TBS), 0.89 (9H, s, TBS), 1.02 (3H, s, Me18), 1.50 (1H, m, H16), 1.73 (1H, m, H15), 1.81 (1H, dddd, J = 10.4, 10.4, 6.7, 3.4 Hz, H15), 1.87−2.04 (2H, m, H3), 1.99 (1H, m, H16), 2.08 (1H, m, H7), 2.14 (1H, m, H7), 2.23 (1H, dd, J = 13.6, 6.7 Hz, H14), 2.23−2.41 (2H, m, H2), 2.40−2.48 (2H, m, H4), 3.71 (1H, dd, J = 8.4, 8.2 Hz, H17), 3.73−3.78 (2H, m, H6), 5.77 (1H, d, J = 9.8 Hz, H12), 5.93 (1H, d, J = 9.8 Hz, H11), 6.28 (1H, s, H19); ^{13}C NMR (150 MHz, $CDCl_3$) δ −5.20 (TBS), −5.19 (TBS), −4.9 (TBS), −4.5 (TBS), 14.1 (C18), 18.0 (TBS), 18.3 (TBS), 20.3 (C15), 20.7 (C3), 25.8 (TBS), 25.9 (TBS), 28.2 (C4), 30.6 (C16), 36.5 (C2), 39.3 (C7), 47.2 (C13), 50.9 (C14), 58.9 (C6), 77.9 (C17), 83.1 (C8), 113.3 (C19), 113.5 (C10), 125.1 (C11), 129.3 (C9), 134.9 (C12), 171.6 (C5); 190.5 (C1); HRMS (ESI) m/z calcd for $C_{31}H_{52}NaO_4Si_2$ 567.3296 $[M + H]^+$, found 567.3296.

Iodide 69. To a solution of triene **61** and its C8-epimer (1.17 g, 2.15 mmol) in THF (100 mL) at room temperature was added HF·pyridine (70:30, 7.0 mL). The resulting mixture was stirred for 20 min at room temperature, and then the reaction was quenched with aqueous $NaHCO_3$. The mixture was extracted twice with EtOAc, and the organic layer was washed with NH_4Cl and brine, dried over Na_2SO_4, and concentrated to afforded alcohol **68**, which was used in the next reaction without further purification.

To a solution of **68** in THF (37 mL) at room temperature was added a solution of I_2 (1.2 g, 4.6 mmol), PPh_3 (2.4 g, 9.2 mmol), and imidazole (1.3 g, 18.4 mmol) in THF (25 mL). After the mixture was stirred for 30 min, the reaction was quenched with aqueous $Na_2S_2O_3$, and the mixture was extracted twice with EtOAc. The organic layer was washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (hexane/EtOAc 15:1−10:1) gave a mixture of iodide **69** and its C8-epimer (1.01 mg, 1.87 mmol, dr =8:1) in 87% combined yield. **69**: R_f = 0.2 (hexane/Et_2O 2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (3H, s, TBS), 0.03 (3H, s, TBS), 0.89 (9H, s, TBS), 1.00 (3H, s, Me18), 1.49 (1H, dddd, J = 18.8, 11.2, 7.6, 3.6 Hz, H16), 1.70−1.90 (2H, m, H15, H15), 1.90−2.08 (3H, m, H3, H3, H16), 2.25 (1H, dd, J = 13.2, 6.8 Hz, H14), 2.36−2.60 (6H, m, H2, H2, H4, H4, H7, H7), 3.16 (1H, ddd, J = 12.0, 9.2, 5.6 Hz, H6), 3.27 (1H, ddd, J = 12.0, 9.2, 4.4 Hz, H6), 3.70 (1H, dd, J = 8.4, 7.6 Hz, H17), 5.79 (1H, d, J = 9.6 Hz, H12), 5.93 (1H, d, J = 9.6 Hz, H11), 6.32 (1H, s, H19); ^{13}C NMR

(100 MHz, $CDCl_3$) δ −4.9 (TBS), −4.5 (TBS), −1.6 (C6), 14.0 (C18), 18.0 (TBS), 20.1 (C15), 20.7 (C3), 25.8 (TBS), 28.1 (C4), 30.5 (C16), 36.5 (C2), 41.7 (C7), 47.1 (C13), 50.5 (C14), 77.7 (C17), 84.7 (C8), 113.6 (C10), 113.7 (C19), 124.9 (C11), 128.3 (C9), 135.1 (C12), 171.5 (C5), 194.9 (C1); HRMS (ESI) m/z calcd for $C_{25}H_{37}INaO_3Si$ 563.1449 $[M + H]^+$, found 563.1448.

The structure of **62** was confirmed by the corresponding iodide, which was obtained by the same procedure as above: pale yellow oil; R_f = 0.17 (hexane/EtOAc 10:1); $[\alpha]_D^{22}$ +53.1 (c 1.23, $CHCl_3$); IR (film) ν 2952, 2855, 2248, 1658, 1614, 1400, 1239, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (3H, s, TBS), 0.06 (3H, s, TBS), 0.90 (9H, s, TBS), 0.93 (3H, s, Me18), 1.53 (1H, dd, J = 11.8, 11.8 Hz, H12), 1.75 (1H, m, H16), 1.86−2.08 (3H, m, H3, H3, H16), 2.27−2.39 (2H, m, H12, H15), 2.39−2.61 (5H, m, H2, H2, H4, H4, H15), 2.77 (2H, dd, J = 8.0, 8.0 Hz, H7, H7), 3.12−3.26 (2H, m, H6, H16), 3.70 (1H, dd, J = 10.3, 7.3 Hz, H17), 4.95 (1H, ddd, J = 12.2, 5.4, 2.2 Hz, H11), 6.30 (1H, s, H19); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9 (TBS), −4.4 (TBS), 3.6 (C6), 18.0 (TBS), 18.1 (C18), 20.7 (C3), 24.8 (C15), 25.7 (TBS), 27.9 (C2), 29.6 (C16), 31.6 (C7), 36.6 (C4), 39.5 (C12), 45.3 (C13), 74.9 (C11), 81.1 (C17), 108.7 (C19), 114.9 (C10), 124.2 (C9), 126.8 (C8), 147.5 (C14), 172.7 (C1), 195.3 (C5); HRMS (ESI) m/z calcd for $C_{25}H_{38}IO_3Si$ 541.1629 $[M + H]^+$, found 541.1632.

Dienone 72. A solution of the mixture of **69** and its C8-epimer (100 mg, 185 μmol) and $(TMS)_3SiH$ (285 μL, 925 μmol) in THF (18.5 mL) was degassed under reduced pressure, and filled with Ar. To the solution at −78 °C was added BEt_3 (1.0 M in THF, 37 μL, 37 μmol) and 2 mL of air. After the mixture was stirred for 30 min, additional reagents [BEt_3 (1.0 M in THF, 80 μL, 80 μmol) and 1 mL of air] were added and the resulting mixture stirred for an additional 1 h at −78 °C. The reaction was quenched with aqueous $NaHCO_3$. The organic layer was washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4 and concentrated. Flash column chromatography (hexane/EtOAc 10:1−15:1) gave dienone **74** (59.9 mg, 144 μmol) in 78% yield; colorless amorphous; Rf = 0.15 (toluene/Et_2O 10:1); $[\alpha]_D^{23}$ +116.8 (c 0.56, $CHCl_3$); IR (film) ν 2948, 2860, 1735, 1674, 1622, 1577, 1466, 1250, 1106, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.027 (3H, s, TBS), 0.030 (3H, s, TBS), 0.75 (3H, s, Me18), 0.88 (9H, s, TBS), 1.54 (1H, m, H16), 1.63−1.80 (5H, m, H3, H6, H7, H15, H15), 1.91−2.08 (5H, m, H3, H4, H4, H12, H16), 2.13 (1H, dd, J = 11.6, 8.0 Hz, H14), 2.17−2.27 (3H, m, H6, H7, H12), 2.33 (1H, ddd, J = 18.0, 12.8, 6.8 Hz, H2), 2.56 (1H, dddd, J = 18.0, 4.8, 2.0, 2.0 Hz, H2), 3.77 (1H, dd, J = 8.4, 8.4 Hz, H17), 5.87 (1H, dd, J = 5.2, 2.8 Hz, H11), 6.92 (1H, s, H19); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9 (TBS), −4.4 (TBS), 13.6 (C18), 18.0 (TBS), 19.0 (C3), 19.5 (C15), 25.8 (TBS), 30.4 (C7), 30.7 (C16), 33.4 (C4), 39.4 (C2), 40.1 (C12), 40.4 (C6), 43.3 (C13), 46.2 (C14), 81.0 (C5), 81.5 (C17), 82.5 (C8), 132.0 (C19), 132.3 (C11), 139.8 (C10), 140.8 (C9); 198.6 (C1); HRMS (ESI) m/z calcd for $C_{25}H_{38}NaO_3Si$ 437.2482 $[M + Na]^+$, found 437.2482.

Alcohol 73. To a solution of **72** (37 mg, 92 μmol) in THF (3.7 mL) at room temperature was added HF·pyridine (70:30, 0.37 mL). After the mixture was stirred for 4 h at room temperature, the reaction was quenched with aqueous $NaHCO_3$ and extracted twice with EtOAc. The organic layer was washed with NH_4Cl and brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (hexane/EtOAc 1:1−2:3) gave alcohol **73** (26 mg, 86.6 μmol) in 94% yield: colorless crystal; mp 177.5−178.0 °C; R_f = 0.4 (hexane/EtOAc 1:2); $[\alpha]^{26}$ +107.63 (c 1.00, $CHCl_3$); IR (film) ν 3433, 2951, 2872, 1672, 1621, 1573, 1195, 994, 908, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (3H, s, Me18), 1.52 (1H, m, H16), 1.66−1.88 (5H, m, H3, H6, H7, H15 × 2), 1.92−2.08 (3H, m, H3, H4 × 2), 2.08−2.40 (7H, m, H2, H6, H7, H12 × 2, H14, H16), 2.57 (1H, ddd, J = 18.0, 2.4, 2.4 Hz, H2), 3.86 (1H, dd, J = 8.8, 8.8 Hz, H17), 5.88 (1H, dd, J = 4.9, 2.8 Hz, H11), 6.93 (1H, s, H19); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3 (C18), 19.0 (C3), 19.3 (C15), 30.3 (C7), 30.4 (C6), 33.3 (C4), 39.4 (C2), 39.6 (C12), 40.3 (C6), 42.9 (C13), 46.6 (C14), 81.1 (C5), 81.5 (C17), 82.2 (C8), 131.8 (C11, C19), 139.8 (C10), 140.7 (C9), 198.6 (C1); HRMS (ESI) m/z calcd for $C_{19}H_{24}NaO_3$ 323.1618 $[M + Na]^+$, found 323.1617.

Benzoate 74. To a solution of the obtained alcohol **73** (17 mg, 56.6 μmol), 4-(dimethylamino)pyridine (DMAP) (6.9 mg, 56.6 μmol), and Et_3N (39 μL, 283 μmol) in CH_2Cl_2 (0.6 mL) at room temperature was added p-bromobenzoyl chloride (25 mg, 113 μmol). After the mixture was stirred for 10 min at room temperature, the reaction was quenched with saturated aqueous NH_4Cl and extracted twice with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (hexane/EtOAc 5:1−4:1) gave p-bromobenzoate **74** (23.4 mg, 48.4 μmol) in 86%. Recrystallization was performed from EtOAc and pentane; colorless prism crystal; mp 209.5−210.0 °C; R_f = 0.6 (hexane/EtOAc 1:2); $[\alpha]_D^{25}$ +56.1 (c 1.22, $CHCl_3$); IR (film) ν 2949, 2873, 1717, 1675, 1623, 1578, 1282, 1117, 989, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, s, Me18), 1.58−1.94 (6H, m, H3, H6, H7, H15 × 2, H16), 1.94−2.10 (3H, m, H3, H4 × 2), 2.20−2.45 (7H, m, H2, H6, H7, H12 × 2, H14, H16), 2.57 (1H, ddd, J = 18.0, 2.4, 2.4 Hz, H2), 5.06 (1H, dd, J = 8.0, 8.0 Hz, H17), 5.86 (1H, dd, J = 4.8, 3.2 Hz, H11), 6.92 (1H, s, H19), 7.55−7.62 (2H, m, Ar), 7.85−7.92 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7 (C18), 19.0 (C3), 19.6 (C15), 27.3 (C16), 30.5 (C7), 33.3 (C4), 39.4 (C2), 39.9 (C12), 40.3 (C6), 43.0 (C13), 46.7 (C14), 81.1 (C5), 82.0 (C8), 82.9 (C17), 128.1 (CH, Ar), 129.2 (CH, Ar), 131.0 (Ar, CH × 2), 131.4 (C11), 131.6 (C19), 131.7 (Ar, CH × 2), 139.9 (C10), 140.4 (C9), 165.5 (ester), 198.5 (C1); HRMS (ESI) m/z calcd for $C_{26}H_{27}BrNaO_4$ 505.0985 $[M + Na]^+$, found 505.0984.

Alcohol 77. A fine powder of anhydrous $CeCl_3$ (310 mg, 1.24 mmol, purchased from a commercial supplier), which was crashed with mortar and pestle in glovebox, was dried at 90 °C under high vacuum for 2 h. After being filled with Ar, the reaction flask was cooled to 0 °C. Freshly distilled THF (3.0 mL) was added at 0 °C and the mixture stirred for 2 h at 0 °C and then 16 h at room temperature within a tightly sealed flask under a positive pressure of Ar. Iodoisoquinoline **76** (182 mg, 640 μmol) was transferred with THF (1.0 mL). The mixture was cooled to −78 °C, and n-BuLi (397 μL, 620 μmol, 1.56 M in hexane) was added. After the mixture was stirred for 30 min, **75** (50 mg, 124 μmol) was transferred with THF (1.0 mL). The resulting mixture was stirred for 30 min at −78 °C. Celite was added to the reaction mixture, which was quenched with aqueous NH_4Cl. The precipitate was filtered through a pad of Celite and washed with EtOAc. The organic layer was washed with saturated aqueous NH_4Cl, and the mixture was extracted twice with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (hexane/EtOAc 50:1 to 10:1) of the residue gave the alcohol **77a** (42.0 mg, 73.9 μmol) in 59% yield and **77b** (23.0 mg, 40.5 μmol) in 33% yield. **77a**: colorless solid; R_f = 0.38 (hexane/EtOAc 4:1); mp 236−238 °C; $[\alpha]_D^{23}$ +18.9 (c 0.42, $CHCl_3$); IR (film) ν 2929, 2356, 1589, 1549, 1467, 1379, 1300, 1253, 1169, 1046 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.06 (3H, s, TBS), −0.04 (3H, s, TBS), 0.29 (1H, ddd, J = 14.8, 14.8, 4.4 Hz, H16), 0.37 (1H, ddd, J = 12.4, 12.4, 4.0 Hz, H14), 0.74 (3H, s, Me18), 0.80 (9H, s, TBS), 0.89 (1H, m, H7), 1.10 (3H, s, Me19), 1.13−1.56 (14H, m, H1 × 2, H2 × 2, H4 × 2, H5, H6 × 2, H8, H9, H15 × 2, H16), 1.62 (1H, ddd, J = 12.4, 12.4, 4.8 Hz, H11), 1.73 (1H, m, H7), 1.95 (1H, ddd, J = 17.6, 12.4, 4.8 Hz, H11), 2.15−2.24 (2H, m, H12, OH), 2.53 (1H, ddd, J = 17.6, 9.6, 4.8 Hz, H12), 3.89 (1H, m, H3), 7.58 (1H, d, J = 5.6 Hz, H3′), 7.78 (1H, d, J = 8.8 Hz, H5′), 7.88 (1H, d, J = 8.8 Hz, H6′), 8.22 (1H, s, H8′), 8.25 (1H, d, J = 5.6 Hz, H2′); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.8, 11.3, 14.8, 18.0, 20.2, 24.4, 25.8, 28.5, 29.6, 31.7, 32.1, 33.5, 35.9, 36.3, 36.6, 38.9, 39.0, 47.1, 49.1, 53.4, 66.7, 86.2, 120.3, 124.0, 125.5, 126.1, 131.5, 136.6, 141.3, 146.9, 151.7; HRMS (ESI) calcd for $C_{34}H_{50}ClNO_2SiNa$ 590.3192 $[M + Na^+]$, found 590.3191. **77b**: colorless solid; mp 227−228 °C; $[\alpha]_D^{25}$ +18.9 (c 0.42,

$CHCl_3$); R_f = 0.57 (hexane/EtOAc 4:1); IR (film) ν 2928, 2186, 1589, 1254, 1048, 835, 776, 686, 592 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.03 (6H, s, TBS), 0.45 (3H, s, Me18), 0.75 (3H, s, Me19), 0.90 (9H, s, TBS), 0.89 (1H, m, H12), 1.07−1.26 (5H, m, H5, H6 × 2, H7, H12), 1.37−1.55 (9H, m, H1 × 2, H2 × 2, H4 × 2, H8, H14, H16), 1.66−1.68 (2H, m, H11 × 2), 1.77 (1H, m, H7), 1.82−2.06 (4H, m, H9, H15 × 2, OH), 2.98 (1H, m, H16), 3.97, (1H, m, H3), 7.58 (1H, d, J = 5.5 Hz, H3′), 7.80 (1H, d, J = 8.5 Hz, H5′), 7.98 (1H, d, J = 8.5 Hz, H6′), 8.25 (1H, d, J = 5.5 Hz, H2′), 8.38 (1H, s, H8′); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.86, −4.83, 11.4, 16.1, 18.0, 20.2, 23.4, 25.8, 28.5, 29.7, 29.8, 32.2, 32.4, 36.0, 36.2, 36.4, 36.7, 39.0 48.5, 50.9, 54.1, 66.8, 85.6, 120.3, 123.4, 126.1, 126.3, 131.0, 136.6, 141.2, 144.8, 151.7; HRMS (ESI) calcd for $C_{34}H_{50}ClNO_2SiNa$ 590.3192 $[M + Na^+]$, found 590.3192.

Thiocarbamate 78a. To a suspension of KH (30% in mineral oil, excess amount) in THF (0.2 mL) at room temperature was added a solution of **77a** (8.0 mg, 14.1 μmol) and PhNCS (67 μL, 5.48 mmol) in THF (0.3 mL). The resulting mixture was stirred for 30 min at room temperature. The reaction was quenched with MeOH and aqueous NH_4Cl, and then the mixture was extracted twice with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (hexane/EtOAc 20:1−10:1) gave the thiocarbamate **78a** (6.9 mg, 9.9 μmol) in 70% yield as rotamer mixture: yellow oil; R_f = 0.4 (hexane/EtOAc 4:1); HRMS (ESI) m/z calcd for $C_{41}H_{55}ClN_2O_2SSiNa$ 725.3334 $[M + Na]^+$, found 725.3331. **78b** was synthesized in the same procedure with **78a**. **78b**: R_f = 0.4 (hexane/EtOAc 4:1).

Isoquinoline 79. A solution of **78a** (5.0 mg, 7.1 μmol), AIBN (1.2 mg, 7.1 μmol) and n-Bu_3SnH (58.0 mL, 213 mmol) in toluene (1.0 mL) was degassed by the freeze−pump−thaw method. The mixture was warmed to 90 °C and stirred for 3.5 h. Concentration and flash column chromatography (hexane/EtOAc 20:1−10:1) of the residue gave **79** (3.0 mg, 5.8 μmol) in 81% yield. From **78b**, **79** was obtained in 80% yield by the same procedure. **79**: colorless solid; R_f = 0.28 (hexane/EtOAc 4:1); $[\alpha]_D^{22}$ +41.7 (c 0.083, $CHCl_3$); IR (film) ν 3749, 2928, 2360, 1458, 1253, 1050, 840, 775, 681 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (6H, s, TBS), 0.48 (3H, s, Me18), 0.75 (3H, s, Me19), 0.91 (9H, s, TBS), 1.04 (1H, m, H12), 1.16−1.26 (5H, m, H2, H8, H9, H11 × 2), 1.31−1.43 (7H, m, H1 × 2, H2, H6 × 2, H14, H15), 2.04 (1H, m, H16), 2.23 (1H, m, H16), 2.88 (1H, dd, J = 9.6, 9.6 Hz, H17), 3.97 (1H, m, H3), 7.58 (1H, d, J = 8.4 Hz, H5′), 7.61 (1H, d, J = 5.6 Hz, H3′), 7.73 (1H, d, J = 8.4 Hz, H6′), 7.77 (1H, s, H8′), 8.47 (1H, d, J = 5.6 Hz, H2′), 9.21 (1H, s, H1′); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.83, −4.81, 11.4, 12.9, 18.1, 20.4, 24.5, 25.9, 26.1, 26.6, 29.7, 32.2, 32.4, 35.0, 36.7, 37.9, 39.1, 44.8, 54.5, 56.4, 57.2, 66.8, 120.1, 125.4, 125.9, 128.6, 132.5, 132.5, 140.9, 142.2, 152.3; HRMS (ESI) calcd for $C_{34}H_{51}NOSiNa$ 540.3632 $[M + Na^+]$, found 540.3621.

Alcohol 80. To a solution of dienone **72** (400 mg, 960 μmol) in CH_2Cl_2 (40 mL) at −15 °C were added ethylenedioxybis(trimethylsilane) (2.36 mL, 9.6 mmol) and TMSOTf (343 μL, 1.9 mmol). The resulting mixture was stirred at −15 °C for 20.5 h. The reaction was quenched with TBAF (5.0 mL, 1.0 M solution in THF) and then saturated aqueous NH_4Cl. The mixture was extracted twice with EtOAc, and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Without further purification, this crude was used in the next step.

To a solution of the resulting crude in THF (10 mL) at 0 °C was added TBAF (1.0 mL, 1 M solution in THF). The resulting mixture was stirred for 30 min at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl, and the mixture was extracted twice with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (hexane/EtOAc 3:1−2:1) of the residue gave alcohol **80** (241 mg, 0.7 mmol) in 73% yield in two steps from **72**: colorless powder; R_f = 0.18 (hexane/EtOAc 1:1); $[\alpha]_D^{25}$ +165.8 (c 0.99, $CHCl_3$); IR (film) ν 3269, 2949, 2868, 1468, 1355, 1271, 1179, 1014, 924 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.79 (3H, s, Me18), 1.38−1.58 (3H, m, H6, H16, OH), 1.62−1.87 (8H, m, H2, H3, H3, H4, H4, H7, H15, H15), 1.89 (1H, m, H2), 2.03−2.24 (5H, m, H7, H12, H12, H14, H16), 2.45 (1H, ddd, J = 9.2, 9.2, 1.6 Hz, H6), 3.77 (1H, ddd, J = 7.6, 7.6, 6.4 Hz, acetal), 3.86 (1H, brdd, J = 8.4, 8.4 Hz, H17), 3.91 (1H, ddd, J = 7.6, 6.4, 6.4 Hz, acetal), 3.98 (1H, ddd, J = 7.6, 6.4, 3.2 Hz, acetal), 4.06 (1H, ddd, J = 6.4, 6.4, 3.2 Hz, acetal), 5.44 (1H, dd, J = 5.2, 2.8 Hz, H11), 6.10 (1H, s, H19); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9 (C18), 19.3 (C3), 19.6 (C15), 30.4 (C16), 30.8 (C7), 34.4 (C4), 36.3 (C2), 38.9 (C12), 39.1 (C6), 43.0 (C13), 46.8 (C14), 62.9 (acetal), 65.8 (acetal), 81.2 (C8), 81.4 (C5), 81.8 (C17), 107.6 (C1), 120.0 (C19), 122.4 (C11), 140.1 (C9), 140.8 (C10); HRMS (ESI) m/z calcd for $C_{21}H_{29}O_4$ 345.2060 $[M + H]^+$, found 345.2062.

Ketone 81. To a solution of alcohol **80** (87.0 mg, 253 mmol) in CH_2Cl_2 (5.1 mL) at 0 °C were added $NaHCO_3$ (107 mg, 1.27 mmol) and Dess−Martin periodinane (129 mg, 303 μmol). The resulting mixture was stirred for 45 min at room temperature. The reaction was quenched with aqueous $Na_2S_2O_3$ and aqueous NH_4Cl, and the mixture was extracted twice with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (hexane/EtOAc 10:1−3:1) of the residue gave ketone **81** (81.8 mg, 239 μmol) in 94% yield: pale yellow amorphous; R_f = 0.40 (hexane/EtOAc 1:1); $[\alpha]_D^{27}$ +291.2 (c 0.82, $CHCl_3$); IR (film) ν 2966, 2939, 2889, 1739, 1471, 1274, 1179, 1152, 1028, 925 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, s, Me18), 1.60 (1H, m, H6), 1.66−1.96 (8H, m, H2, H2, H3, H3, H4, H4, H7, H15), 2.10−2.29 (5H, m, H7, H12, H12, H15, H16), 2.38 (1H, dd, J = 12.8, 5.6 Hz, H14), 2.45−2.56 (2H, m, H6, H16), 3.77 (1H, ddd, J = 7.6, 0.7.6, 6.4 Hz, acetal), 3.92 (1H, ddd, J = 7.6, 6.4, 6.4 Hz, acetal), 3.99 (1H, ddd, J = 7.6, 6.4, 3.2 Hz, acetal), 4.06 (1H, ddd, J = 6.4, 6.4, 3.2 Hz, acetal), 5.45 (1H, dd, J = 4.8, 2.8 Hz, H11), 6.11 (1H, s, H19); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9 (C18), 18.9 (C15), 19.6 (C3), 31.5 (C7), 34.0 (C12), 34.3 (C4), 35.9 (C16), 36.3 (C2), 39.1 (C6), 47.2 (C13), 47.9 (C14), 63.0 (acetal), 65.8 (acetal), 81.0 (C8), 81.7 (C5), 107.5 (C1), 119.7 (C19), 121.4 (C11), 140.3 (C9), 141.3 (C10), 220.6 (C17); HRMS (ESI) m/z calcd for $C_{21}H_{27}O_4$ 343.1904 $[M + H]^+$, found 343.1905.

Alcohol 82. A fine powder of anhydrous $CeCl_3$ (648 mg, 2.63 mmol, purchased from a commercial supplier), which was crashed with mortar and pestle in glovebox, was dried at 90 °C under high vacuum for 2 h. After being filled with Ar, the reaction flask was cooled to 0 °C. Freshly distilled THF (8.0 mL) was added at 0 °C, and the mixture was stirred for 2 h at 0 °C and then 16 h at room temperature within a tightly sealed flask under a positive pressure of Ar. Iodoisoquinoline **76** (457 mg, 1.58 mmol) was transferred with THF (4.0 mL). The mixture was cooled to −78 °C, and n-BuLi (846 μL, 1.32 mmol, 1.56 M in hexane) was added. After the mixture was stirred for 30 min, **81** (90 mg, 263 μmol) was transferred with THF (4.5 mL). The resulting mixture was stirred for 30 min at −70 °C. Celite was added to the reaction mixture, which was quenched with aqueous NH_4Cl. The precipitate was filtered through a pad of Celite and washed with EtOAc. The organic layer was washed with saturated aqueous NH_4Cl, and the mixture was extracted twice with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (hexane/EtOAc 3:1) of the residue gave alcohol **82** (132 mg, 261 μmol) in 99% yield: colorless oil; R_f = 0.24 (hexane/EtOAc 1:1); $[\alpha]_D^{27}$ +358.3 (c 1.01, $CHCl_3$); IR (film) ν 3428 (br), 2948, 2886, 1587, 1547, 1378, 1302, 1266, 1178, 1021 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (3H, s, Me18), 1.48−1.98 (10H, m, H2, H2, H3, H3, H4, H4, H6, H7, H12, H12), 2.04−2.23 (3H, m, H15, H15, OH), 2.26−2.52 (4H, m, H6, H7, H14, H16), 2.64 (1H, ddd, J = 14.6, 9.2, 4.4 Hz, H16), 3.78 (1H, m, acetal), 3.87 (1H, m, acetal), 3.93−4.04 (2H, m, acetal), 5.24 (1H, dd, J = 5.2, 2.4 Hz, H11), 5.99 (1H, s, H19), 7.56 (1H, dd, J = 5.6, 0.4 Hz, H4′), 7.77 (1H, d, J = 8.4 Hz, H5′), 7.85 (1H, brd, J = 8.4 Hz, H6′), 8.25 (1H, d, J = 5.6 Hz, H3′), 8.36 (1H, brs, H8′); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 17.3 (Me18), 19.6 (C3), 20.7 C15), 31.1 (C7), 34.4 (C4), 35.6 (C12), 36.2 (C2), 38.9 (C6), 39.0 (C16), 45.9 (C14), 47.6 (C13), 62.9 (acetal), 65.8 (acetal), 81.4 (C5), 81.7 (C8), 85.6 (C17), 107.5 (C1), 119.8 (C19), 120.2 (C4′), 122.7 (C11), 124.0 (C8′), 126.2 (C5′), 126.3 (C1′), 131.0 (C6′), 136.7 (C4a′), 138.9 (C9), 140.7 (C10), 141.5 (C3′), 146.8 (C7′), 151.8 (C8a′); HRMS (ESI) m/z calcd for $C_{30}H_{33}ClNO_4$ 506.2093 $[M + H]^+$, found 506.2092.

Thiocarbamate 83. To a suspension of KH (30% in mineral oil, 488 mg, 3.65 mmol; washed with hexane) in THF (6.0 mL) at room temperature was added a solution of **82** (185 mg, 365 μmol) and PhNCS (650 μL, 5.48 mmol) in THF (6.0 mL). The resulting mixture was stirred for 4 h at room temperature. The reaction was quenched with aqueous NH_4Cl, and the mixture was extracted twice with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (hexane/EtOAc 10:1−1:1) gave the thiocarbamate **83** (196 mg, 306 μmol, 4:1 mixture): pale yellow oil; R_f = 0.50 (hexane/EtOAc 1:2); HRMS (ESI) m/z calcd for $C_{37}H_{38}ClN_2O_4S$ 641.2235 $[M + H]^+$, found 641.2229.

Isoquinoline 84. A solution of **83** (196 mg, 306 μmol), AIBN (17.1 mg, 104 μmol), and *n*-BuSnH (1.09 mL, 4.16 mmol) in toluene (31 mL) was degassed by the freeze−pump−thaw method. The mixture was warmed to 90 °C and stirred for 3.5 h. The reaction mixture was directly passed through a pad of silica gel with EtOAc. Concentration and flash column chromatography (hexane/EtOAc 1:0−2:1) of the residue gave **84** (113 mg, 275 μmol) in 75% (two steps from **82**) yield: pale yellow oil; R_f = 0.15 (hexane/EtOAc 1:2); $[\alpha]_D^{27}$ +13.55 (*c* 0.848, $CHCl_3$); IR (film) ν 3256 (br), 2947, 2876, 1592, 1272, 1179, 1140, 1046 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.55 (3H, s, Me18), 1.56 (1H, m, H6), 1.62−1.94 (8H, m, H2, H2, H3, H3, H4, H4, H7, H15), 1.96 (1H, dd, *J* = 17.6, 5.2 Hz, H12), 2.04 (1H, m, H15), 2.12−2.42 (4H, m, H7, H12, H16, H16), 2.43−2.55 (2H, m, H6, H14), 3.14 (1H, dd, *J* = 10.8, 8.8 Hz, H17), 3.76 (1H, ddd, *J* = 7.6, 7.6, 6.4 Hz, acetal), 3.91 (1H, ddd, *J* = 7.6, 6.4, 6.4 Hz, acetal), 3.98 (1H, ddd, *J* = 7.6, 6.4, 3.2 Hz, acetal), 4.04 (1H, ddd, *J* = 6.4, 6.4, 3.2 Hz, acetal), 5.44 (1H, dd, *J* = 5.2, 2.4 Hz, H11), 6.12 (1H, s, H19), 7.58 (1H, dd, *J* = 8.4, 1.6 Hz, H6′), 7.62 (1H, d, *J* = 5.6 Hz, H4′), 7.75 (1H, d, *J* = 8.4 Hz, H5′), 7.79 (1H, brs, H8′), 8.48 (1H, d, *J* = 5.6 Hz, H3′), 9.22 (1H, brs, H1′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2 (C18), 19.6 (C3), 20.5 (C15), 26.4 (C16), 30.6 (C7), 34.4 (C4), 36.3 (C2), 38.9 (C6), 40.1 (C12), 44.7 (C13), 51.6 (C14), 56.9 (C17), 62.9 (acetal), 65.7 (acetal), 81.3 (C5), 81.4 (C8), 107.5 (C1), 119.9 (C19), 112.0 (C4′), 122.1 (C11), 125.7 (C5′), 126.2 (C8′), 128.5 (C8a′), 131.9 (C6′), 134.6 (C4a′), 140.0 (C7′), 140.2 (C9), 140.9 (C10), 142.5 (C3′), 152.3(C1′); HRMS (ESI) m/z calcd for $C_{30}H_{34}NO_3$ 456.2533 $[M + H]^+$, found 456.2534.

Ketone 85. To a solution of **84** (200 mg, 439 μmol) in acetone (40 mL) and water (4.0 mL) at 0 °C was added $TsOH \cdot H_2O$ (41.7 mg, 219 μmol). The resulting mixture was stirred for 25 min at 0 °C, and then another 0.1 equiv of TsOH (10 mg, 53 μmol) was added. After the mixture was stirred for 2 h at room temperature, the reaction was quenched with aqueous $NaHCO_3$, and the resulting mixture was extracted twice with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (hexane/EtOAc 5:1−0:1) of the residue gave ketone **85** (162 mg, 394 μmol) in 89% yield: pale yellow amorphous solid; R_f = 0.1 (hexane/EtOAc 1:2); $[\alpha]_D^{27}$ −8.11 (*c* 0.72, $CHCl_3$); IR (film) ν 3547 (br), 2951, 2878, 2240, 1672, 1575, 1284, 1191 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.57 (3H, s, Me18), 1.74−1.81 (3H, m, H3, H6, H7), 1.91 (1H, ddd, *J* = 24.4, 11.4, 5.2 Hz, H15), 1.97−2.14 (5H, m, H3, H4, H4, H12, H15), 2.16−2.48 (6H, m, H2, H6, H7, H12, H16, H16), 2.53 (1H, dd, *J* = 11.4, 8.4 Hz, H14), 2.58 (1H, dddd, *J* = 18.4, 4.8, 2.4, 2.4 Hz, H2), 3.16 (1H, dd, *J* = 10.4, 8.8 Hz, H17), 5.87 (1H, dd, *J* = 5.2, 2.4 Hz, H11), 6.94 (1H, s, H19), 7.58 (1H, dd, *J* = 8.4, 2.0 Hz, H6′), 7.63 (1H, d, *J* = 5.6 Hz, H4′), 7.77 (1H, d, *J* = 8.4 Hz, H5′), 7.79 (1H, brs, H8′), 8.49 (1H, brd, *J* = 5.6 Hz, H3′), 9.23 (1H, brs, H1′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.6 (C18), 19.0 (C3), 20.6 (C15), 26.4 (C16), 30.2 (C7), 33.3 (C4), 39.4 (C2), 40.2 (C6), 40.8 (C12), 44.5 (C13), 51.5 (C14), 56.8 (C17), 81.1 (C5), 82.4 (C8), 120.0 (C4′), 125.9 (C5′), 126.3 (C8′), 128.6 (C8a′), 131.4 (C11), 131.7 (C19′), 131.8 (C6′), 134.7 (C4a′), 139.6 (C7′), 139.9 (C10), 140.9 (C9), 142.6 (C3′), 152.3 (C1′), 198.5 (C1); HRMS (ESI) m/z calcd for $C_{28}H_{30}NO_2$ 412.2271 $[M + H]^+$, found 412.2270.

Enone 87. To a solution of **72** (50 mg, 121 μmol) in THF (5.0 mL) at −78 °C was added LDA [0.5 M, 0.29 mL, 145 μmol, fleshly prepared from *i*-Pr_2NH (0.55 mL, 3.92 mmol), *n*-BuLi (1.56 M, 2.24 mL, 3.5 mmol) and THF (4.2 mL)]. After the mixture was stirred for 40 min, a solution of **86** (31.3 mg, 145 μmol) in THF (1.0 mL) was added at −55 °C. The resulting mixture was stirred for an additional 1 h and then the reaction quenched with aqueous NH_4Cl. The mixture was extracted twice with EtOAc, and the combined organic layer was washed with brine and dried over Na_2SO_4. Concentration and flash column chromatography (hexane/EtOAc 15:1−10:1) of the residue gave enone **87** (38.5 mg, 93 μmol) in 77%: pale yellow solid; R_f = 0.5 (hexane/EtOAc 2:1); $[\alpha]_D^{20}$ 116.2 (*c* 1.05, $CHCl_3$); IR (film) ν 2953, 2930, 2857, 1660, 1585, 1252, 1109 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s, TBS), 0.035 (3H, s, TBS) 0.76 (3H, s, Me18), 0.88 (9H, s, TBS), 1.75 (1H, m, H16), 1.62−1.81 (4H, m, H6, H7, H15, H15), 1.94−2.10 (2H, m, H12, H16), 2.15 (1H, dd, *J* = 11.3, 8.3 Hz, H14), 2.21 (1H, dd, *J* = 18.7, 5.3 Hz, H12), 2.22−2.40 (2H, m, H6, H7), 2.56 (1H, dd, *J* = 18.5, 6.5 Hz, H4), 2.91 (1H, ddd, *J* = 18.2, 2.6, 2.6 Hz, H4), 5.88 (1H, dd, *J* = 5.3, 2.7 Hz, H11), 6.18 (1H, dd, *J* = 10.2, 2.6 Hz, H2), 6.92 (1H, ddd, *J* = 10.2, 8.8, 2.6 Hz, H3), 7.07 (1H, s, H19); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9 (TBS), −4.4 (TBS), 13.5 (C18), 18.0 (TBS), 19.4 (C15), 25.8 (TBS), 30.5 (C7), 30.6 (C16), 34.5 (C4), 40.0 (C12), 40.8 (C6), 43.4 (C13), 46.2 (C14), 80.2 (C5), 81.4 (C17), 82.2 (C8), 130.1 (C2), 131.6 (C11), 131.7 (C19), 137.4 (C10), 140.4 (C9), 145.7 (C3), 185.9 (C1); HRMS (ESI) m/z calcd for $C_{25}H_{36}NaO_3Si$ 435.2326 $[M + Na]^+$, found 435.2324.

Alcohol 88. Enone **87** (38.0 mg, 72 μmol) was dissolved in Me_2NH solution (3.6 mL, 2.0 M in THF). The mixture was stirred for 45 h at room temperature and then concentrated. The resulting crude was used in the next step without further purification.

To a solution of the resulting crude in Et_2O (14.4 mL) was added $LiAlH_4$ (5.5 mg, 144 μmol) at 0 °C. The resulting mixture was stirred for 20 min at 0 °C. After the mixture was stirred for 20 min at 0 °C, the reaction was quenched with 5.5 μL of H_2O, 11.0 μL of 1 M NaOH, and 16.5 μL of H_2O. After filtration through a pad of Celite, the filtrate was concentrated. Flash column chromatography of the residue (NH silica gel, hexane/EtOAc 10:1 to 1:1) gave amino alcohol **88** (28.4 mg, 61.8 μmol) in 86% yield: colorless powder; R_f = 0.4 (NH-TLC plate, EtOAc/MeOH 20:1); $[\alpha]_D^{22}$ +161.9 (*c* 1.30, $CHCl_3$); IR (film) ν 3438, 2954, 2859, 1462, 1251, 1149, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.017 (3H, s, TBS), 0.020 (3H, s, TBS) 0.74 (3H, s, Me18), 0.87 (9H, s, TBS), 1.36 (1H, dd, *J* = 23.3, 11.7 Hz, H2), 1.45−1.77 (5H, m, H6, H7, H15, H15, H16), 1.83 (1H, dd, *J* = 12.6, 12.5 Hz, H6), 1.89−2.02 (3H, m, H4, H12, H16), 2.02−2.15 (3H, m, H6, H12, H14), 2.16−2.28 (2H, m, H2, H7), 2.27 (6H, s, NMe_2), 2.46 (1H, brs, OH), 2.51 (1H, dddd, *J* = 12.6, 12.6, 2.8, 2.8 Hz, H3), 3.75 (1H, dd, *J* = 8.4, 8.4 Hz, H17), 4.19 (1H, m, H1), 5.39 (1H, dd, *J* = 4.9, 2.1 Hz, H11), 6.10 (1H, d, *J* = 1.6 Hz, H19); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9 (TBS), −4.4 (TBS), 13.2 (C18), 18.0 (TBS), 19.4 (C15), 25.8 (TBS), 30.6 (C7), 30.6 (C16), 36.6 (C4), 37.7 (C2), 39.3 (C12), 39.8 (C6), 40.8 (NMe_2), 43.4 (C13),46.3 (C14), 57.4 (C3), 68.6 (C1), 80.0 (C5), 81.6 (C17), 81.9 (C8), 117.5 (C19), 121.6 (C11), 139.7 (C10), 143.5 (C9); HRMS (ESI) m/z calcd for $C_{27}H_{46}NO_3Si$ 460.3241 $[M + H]^+$, found 460.3242.

Olefin 89. To a solution of amino alcohol **88** (26.0 mg, 56.6 μmol) in THF (11.3 mL) were successively added *i*-Pr_2NEt (1.1 mL) and MsCl (43.8 μL, 566 μmol) at 0 °C. After the mixture was stirred for 2 min at 0 °C, DBU (127 μL, 849 μmol) was added and the mxiture stirred for an additional 15 min. The reaction mixture was directly passed through a

pad of NH silica gel with EtOAc. Concentration and flash column chromatography (NH silica gel, hexane/EtOAc 40:1 to 20:1) of the residue gave triene (9.7 mg, 22.0 μmol) in 39% yield: pale yellow amorphous; R_f = 0.45 (NH-TLC plate, hexane/EtOAc 1:1); $[\alpha]_D^{22}$ +102.2 (*c* 1.08, $CHCl_3$); IR (film) ν 2955, 2857, 1471, 1250, 1105 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.029 (3H, s, TBS), 0.032 (3H, s, TBS) 0.77 (3H, s, Me18), 0.89 (9H, s, TBS), 1.53 (1H, m, H16), 1.58−1.80 (4H, m, H6, H7, H15, H15), 1.86 (1H, dd, *J* = 11.3, 4.4 Hz, H4), 1.92−2.06 (4H, m, H4, H6, H12, H16), 2.12 (1H, dd, *J* = 13.0, 5.1 Hz, H12), 2.16 (1H, dd, *J* = 11.2, 8.5 Hz, H12), 2.24 (1H, ddd, *J* = 12.6, 10.9, 1.7 Hz, H7), 2.29 (6H, s, NMe_2), 3.41 (1H, m, H3), 3.77 (1H, dd, *J* = 8.5, 8.5 Hz, H17),5.41 (1H, dd, *J* = 5.3, 2.91 Hz, H11), 5.78 (1H, d, *J* = 9.9 Hz, H2), 5.82 (1H, s, H19), 6.07 (1H, dd, *J* = 9.8, 2.6 Hz, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8 (TBS), −4.4 (TBS), 13.4 (C18), 18.0 (TBS), 19.4 (C15), 25.8 (TBS), 30.6 (C7), 30.7 (C16), 31.0 (C4), 38.1 (C6), 39.6 (C12), 40.5 (NMe_2), 43.5 (C13), 46.4 (C14), 60.4 (C3), 78.9 (C5), 81.7 (C17), 82.3 (C8), 121.3 (C19), 122.5 (C11), 127.4 (C1), 131.9 (C2), 139.6 (C10), 141.0 (C9); HRMS (ESI) *m*/*z* calcd for $C_{27}H_{44}NO_2Si$ 442.3136 $[M + H]^+$, found 442.3138.

Azido 92. To a solution of enone **87** (50 mg, 121 μmol) in CH_2Cl_2 (6.0 mL) were added AcOH (172 μL, 3.0 mmol), NEt_3 (17 μL, 121 μmol), and $TMSN_3$ (398 μmol, 3.0 mmol) at room temperature. After the mixture was stirred for 43 h, the reaction was quenched with aqueous NH_4Cl. The mixture was extracted twice with EtOAc, and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (hexane/EtOAc 20:1 to 10:1) of the residue gave azide **90** (32.2 mg, 71 μmol) in 59% yield along with enone **87** (19.5 mg, 47.3 μmol) in 39%: colorless solid; R_f = 0.60 (hexane/EtOAc 1:2); $[\alpha]_D^{25}$ +106.9 (*c* 0.64, $CHCl_3$); IR (film) ν 2965, 2930, 2858, 2097, 1676, 1580, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (6H, s, TBS), 0.76 (3H, s, Me18), 0.89 (9H, s, TBS), 1.55 (1H, m, H16), 1.62−1.85 (4H, m, H6, H7, H15, H15), 1.94−2.10 (2H, m, H12, H16), 2.10−2.24 (3H, m, H4, H6, H14), 2.24−2.33 (3H, m, H4, H7, H12), 2.37 (1H, dd, *J* = 17.6, 11.7 Hz, H2), 2.90 (1H, ddd, *J* = 17.6, 5.1, 2.3 Hz, H2), 3.77 (1H, dd, *J* = 8.5, 8.5 Hz, H17), 3.80 (1H, m, H3), 5.95 (1H, dd, *J* = 5.4, 2.6 Hz, H11), 6.98 (1H, s, H19); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9 (TBS), −4.4 (TBS), 13.7 (C18), 18.0 (TBS), 19.4 (C3), 19.4 (C15), 25.8 (TBS), 30.58 (C7), 30.61 (C16), 39.0 (C4), 40.2 (C12), 41.0 (C6), 43.3 (C13), 45.0 (C2), 46.1 (C14), 53.6 (C3), 78.5 (C5), 81.4 (C17), 82.7 (C8), 133.3 (C19), 134.1 (C11), 137.5 (C10), 140.4 (C9); 194.4 (C1); HRMS (ESI) *m*/*z* calcd for $C_{25}H_{38}N_3O_3Si$ 456.2677 $[M + H]^+$, found 456.2679.

Boc Carbamate 94. To a solution of azide **92** (30 mg, 66 μmol) in Et_2O (4.0 mL) was added $LiAlH_4$ (2.5 mg, 66 μmol) at 0 °C. After the mixture was stirred for 30 min, the reaction was quenched by addition of H_2O (2.5 μL), 1.0 M NaOH (5.0 μL), and H_2O (7.5 μL). After filtration through a pad of Celite the filtrate was concentrated. This crude was used in the next reaction without further purification.

To a solution of the resulting amino alcohol in THF (5.0 mL) was added Boc_2O (93 mg, 330 μmol). The reaction mixture was stirred for 12 h at 40 °C. Then concentration and flash column chromatography using NH-silica gel (hexane/EtOAc 10:1 to 2:1) afforded carbamate (22.9 mg, 43.1 μmol) in 65% yield (2 steps from enone): colorless amorphous; R_f = 0.4 (NH-TLC plate, hexane/EtOAc 1:1); $[\alpha]_D^{26}$ +155.2 (*c* 0.97, $CHCl_3$); IR (film) ν 3452, 3352, 2953, 2858, 1692, 1517, 1169, 1152, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.019 (3H, s, TBS), 0.022 (3H, s, TBS), 0.73 (3H, s, Me18), 0.88 (9H, s, TBS), 1.28 (1H, dd, *J* = 23.3, 11.6 Hz, H2), 1.52 (1H, m, H16), 1.58−1.78 (5H, m, H4, H5, H7, H15, H15), 1.86 (1H, brs, OH), 1.90−2.03 (4H, m, H4, H6, H12, H14), 2.22 (1H, m, H7), 2.38 (1H, m, H12), 3.64 (1H, brd, *J* = 7.8 Hz, H3), 3.75 (1H, dd, *J* = 8.5, 8.5 Hz, H17), 4.26 (1H, brd, *J* = 9.4 Hz, H1), 4.52 (1H, brd, *J* = 7.3 Hz, NH), 5.40 (1H, dd, *J* = 4.9, 2.4 Hz, H11), 6.11 (1H, d, *J* = 2.1 Hz, H19); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8 (TBS), −4.4 (TBS), 13.3 (C18), 18.0 (TBS), 19.4 (C15), 25.8 (TBS), 28.4 (Boc), 30.7 (C7), 30.7 (C16), 39.3 (C12), 39.7 (C6), 41.4 (C4) 42.4 (C2), 43.4 (C13), 44.5 (C3), 46.3 (C14), 67.7 (C1), 79.3 (C5), 79.6 (Boc), 81.7 (C17), 82.0 (C8), 117.9 (C19), 121.9 (C11), 139.6 (C10), 142.7 (C9); 155.0 (Boc); HRMS (ESI) *m*/*z* calcd for $C_{30}H_{49}NNaO_5Si$ 554.3272 $[M + Na]^+$, found 554.3273.

To a solution of the resulting carbamate (19.3 mg, 36.0 μmol) in CH_2Cl_2 (3.6 mL) were added $NaHCO_3$ (15.1 mg, 180 μmol) and Dess−Martin periodinane (18.3 mg, 43.2 μmol) at 0 °C. The ice bath was removed, and the reaction was stirred for 30 min. The reaction was quenched with aqueous $Na_2S_2O_3$ and aqueous NH_4Cl, and the mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (hexane/EtOAc 20:1 to 10:1) of the residue gave enone **94** (15.8 mg, 29.8 μmol) in 83% yield: colorless solid; R_f = 0.6 (hexane/EtOAc 1:1); $[\alpha]_D^{25}$ +115.5 (*c* 0.79, $CHCl_3$); IR (film) ν 3346, 2956, 2858, 1680, 1574, 1250, 1171 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (6H, s, TBS), 0.75 (3H, s, Me18), 0.88 (9H, s, TBS), 1.28 (1H, m, H16), 1.58−1.78 (3H, m, H7, H15, H15), 1.83 (1H, m, H6), 1.85−2.38 (9H, m, H2, H4, H4, H6, H7, H12, H12, H14, H16), 2.90 (1H, brd, *J* = 14.4 Hz, H2), 3.76 (1H, dd, *J* = 8.6, 8.6 Hz, H17), 3.96 (1H, brs, H3), 4.53 (1H, brs, NH), 5.92 (1H, brdd, *J* = 4.8, 2.6 Hz, H11), 6.95 (1H, brs, H19); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9 (TBS), −4.4 (TBS), 13.6 (C18), 18.0 (TBS), 19.4 (C15), 25.8 (TBS), 28.3 (Boc), 30.5 (C7), 30.6 (C16), 40.2 (C12), 40.3 (C4), 40.7 (C6), 43.2 (C13), 43.8 (C3, br), 46.1 (C14), 46.1 (C2, br), 78.9 (C5), 79.9 (Boc, br), 81.4 (C17), 82.7 (C8), 132.9 (C19), 133.5 (C11), 138.1 (C10), 140.6 (C9); 154.8 (Boc), 195.6 (C1); HRMS (ESI) *m*/*z* calcd for $C_{30}H_{49}NNaO_5Si$ 552.3116 $[M + Na]^+$, found 552.3113.

Enone 96. To a solution of **85** (48.0 mg, 117 μmol) in THF (3.5 mL) was added LDA (280 μL, 140 μmol, 0.5 M in THF prepared from *i*-Pr_2NH (0.5 mL), *n*-BuLi (1.56 M in hexane), and THF (4.2 mL)) at −78 °C. After the solution was stirred for 30 min, a solution of sulfinimidoyl chloride **86** (32.8 mg, 152 μmol) in THF (1.4 mL) was added. The resulting mixture was stirred for an additional 30 min. The reaction was quenched with aqueous NH_4Cl, and the mixture was extracted twice with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (hexane/EtOAc 3:2−1:1) of the residue gave a mixture of **96** and **85**. Further purification with HPLC (DAICEL CHIRALPAK IC, hexane/EtOAc = 3:2) afforded **96** (t_R = 27 min, 37.0 mg, 90.0 μmol) in 77% yield and **85** (t_R = 20 min, 9.5 mg, 23.1 μmol) in 20% yield. **96**: pale yellow amorphous; R_f = 0.1 (hexane/EtOAc 1:2); $[\alpha]_D^{30}$ −48.38 (*c* 0.646, $CHCl_3$); IR (film) ν 3380 (br), 2962, 2880, 1657, 1626, 1582, 1387, 1286, 1056 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.57 (3H, s, Me18), 1.67−1.83 (2H, m, H6, H7), 1.89 (1H, ddd, *J* = 24.6, 11.9, 5.3 Hz, H15), 2.02−2.14 (2H, m, H12, H15), 2.16−2.49 (5H, m, H6, H7, H12, H16, H16), 2.55 (1H, dd, *J* = 11.4, 8.2 Hz, H14), 2.60 (1H, dd, *J* = 18.9, 6.2 Hz, H4), 2.97 (1H, ddd, *J* = 18.9, 2.7, 2.7 Hz, H4), 3.17 (1H, dd, *J* = 10.7, 9.2 Hz, H17), 5.87 (1H, dd, *J* = 5.4, 2.6 Hz, H11), 6.20 (1H, dd, *J* = 10.4, 2.8 Hz, H2), 6.94, ddd, *J* = 10.4, 6.5, 2.4 Hz, H3), 7.08 (1H, s, H19), 7.58 (1H, dd, *J* = 8.5, 1.6 Hz, H6′), 7.63 (1H, d, *J* = 5.6 Hz, H4′), 7.77 (1H, d, *J* = 8.4 Hz, H5′), 7.79 (1H, brs, H8′), 8.50 (1H, d, *J* = 5.6 Hz, H3′), 9.23 (1H, brs, H1′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5 (C18), 20.6 (C15), 26.4 C16), 30.5 (C7), 34.5 (C4), 40.7 (C6, C12), 44.7 (C13), 51.5 (C14), 56.8 (C7), 80.3 (C5), 82.1 (C8), 120.1 (C4′), 126.0 (C5′), 126.4 (C8′), 128.6 (C8a′), 130.2 (C2), 130.7 (C11), 131.4 (C19), 131.9 (C6′), 134.8 (4a′), 137.7 (C10), 139.6 (C7′), 140.5 (C9), 142.6 (C3′), 145.7 (C3), 152.3 (C1′), 185.8 (C1); HRMS (ESI) *m*/*z* calcd for $C_{28}H_{28}NO_2$ 410.2115 $[M + H]^+$, found 410.2116.

Epoxide 97. To a solution of enone **96** (73.0 mg, 178 μmol) in CH_2Cl_2 (10 mL) were added TBHP (195 μL, 1.07 mmol, 5.5 M in decane) and DBU (150 μL, 534 μmol) at 0 °C. The resulting mixture was stirred for 6 h at room temperature. The reaction was quenched with aqueous NH_4Cl and aqueous $Na_2S_2O_3$ at 0 °C, and the mixture was

extracted twice with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (hexane/EtOAc 1:2) of the residue gave epoxide **97** (59.6 mg, 133 μmol) in 75% yield: colorless thin needle; R_f = 0.4 (EtOAc); $[\alpha]_D^{26}$ −23.8 (*c* 0.67, $CHCl_3$); IR (film) ν 3552 (br), 3350, 2962, 2878, 2243, 1674, 1621, 1574, 1349, 1289, 1252 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.56 (3H, s, Me18), 1.73 (1H, ddd, *J* = 12.9, 9.2, 7.6 Hz, H7), 1.82−1.94 (2H, m, H6, H15), 2.00−2.13 (2H, m, H12, H15), 2.21 (1H, m, H16), 2.26−2.60 (7H, m, H4, H4, H6, H7, H12, H14, H16), 3.15 (1H, dd, *J* = 10.9, 9.4 Hz, H17), 3.46 (1H, d, *J* = 4.0 Hz, H2), 3.68 (1H, dd, *J* = 3.5, 3.5 Hz, H3), 5.93 (1H, dd, *J* = 5.3, 2.7 Hz, H11), 7.14 (1H, s, H19), 7.58 (1H, dd, *J* = 8.7, 1.6 Hz, H6′), 7.63 (1H, d, *J* = 5.7 Hz, H4′), 7.77 (1H, d, *J* = 8.6 Hz, H5′), 7.79 (1H, s, H8′), 8.50 (1H, d, *J* = 5.7 Hz, H3′), 9.23 (1H, s, H1′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.6 (C18), 20.5 (C15), 26.4 (C16), 30.9 (C7), 32.3 (C4), 40.9 (C12), 43.3 (C6), 44.5 (C13), 51.4 (C14), 53.7 (C3), 54.6 (C2), 56.8 (C17), 77.6 (C5), 81.6 (C8), 120.1 (C4′), 126.0 (C5′), 126.4 (C8′), 128.6 (C8a′), 131.8 (C6), 132.7 (C11), 133.9 (C19), 134.7 (C4a′), 136.3 (C9), 139.5 (C7′), 140.8 (C10), 142.7 (C3′), 152.3 (C1′), 192.1 (C1); HRMS (ESI) *m*/*z* calcd for $C_{28}H_{28}NO_3$ 426.2064 $[M + H]^+$, found 426.2066.

Alcohol 98. To a solution of epoxide **97** (56.9 mg, 133 μmol) and $CeCl_3 \cdot 7H_2O$ (496 mg, 1.33 mmol) in MeOH (26 mL) was added $NaBH_4$ (2.5 mg, 66.5 μmol) at −78 °C. The resulting mixture was stirred for 15 min at the same temperature. The reaction was quenched with aqueous NH_4Cl, and the mixture was extracted with EtOAc (three times). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (EtOAc) of the residue gave a mixture of epoxy alcohol **98** and **99**. Further purification with HPLC (DAICEL CHIRALPAK IC, hexane/EtOAc/CH_2Cl_2 35:40:25, flow rate: 5.0 mL/min) gave **98** (28.8 mg, 67.4 μmol) in 51% and **99** (21.0 mg, 49.1 μmol) in 37%. **98**: colorless powder; R_f = 0.1 (EtOAc); $[\alpha]_D^{25}$ 45.3 (*c* 0.58, $CHCl_3$); IR (film) ν 3361, 3194, 2963, 2877, 1632, 1595, 1504, 1377 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.58 (3H, s, Me18), 1.64−1.78 (2H, m, H6, H7), 1.86 (1H, ddd, *J* = 24.5, 11.9, 5.3 Hz, H15), 1.94−2.08 (2H, m, H12, H15), 2.12−2.45 (7H, m, H4, H4, H6, H7, H12, H16, H16), 2.51 (1H, dd, *J* = 11.6, 8.4 Hz, H14), 3.14 (1H, dd, *J* = 10.8, 9.2 Hz, H17), 3.30 (1H, dd, *J* = 3.9, 2.0 Hz, H2), 3.40 (1H, brdd, *J* = 3.5, 3.5 Hz, H3), 4.70 (1H, s, H1), 5.44 (1H, dd, *J* = 5.1, 2.5 Hz, H11), 6.27 (1H, s, H19), 7.60 (1H, dd, *J* = 8.6, 1.4 Hz, H6′), 7.63 (1H, d, *J* = 5.8 Hz, H4′), 7.76 (1H, d, *J* = 8.4 Hz, H5′), 7.77 (1H, s, H8′), 8.46 (1H, d, *J* = 5.9 Hz, H3′), 9.20 (1H, s, H1′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3 (C18), 20.6 (C15), 26.5 (C16), 30.7 (C7), 32.4 (C4), 40.1 (C12), 43.1 (C6), 44.6 (C13), 51.86 (C13), 51.94 (C3), 53.9 (C2), 57.4 (C17), 66.3 (C1), 77.4 (C5), 81.9 (C8), 120.2 (C4′), 121.8 (C11), 125.6 (C19), 125.8 (C5′), 127.0 (C8′), 128.6 (C8a′), 131.6 (C6′), 134.7 (C4a′), 139.9 (C7′), 140.7 (C9), 141.5 (C10), 142.1 (C3′), 152.5 (C1′); HRMS (ESI) *m*/*z* calcd for $C_{28}H_{30}NO_3$ 428.2220 $[M + H]^+$, found 428.2223. **99**: colorless crystal; R_f = 0.1 (EtOAc); $[\alpha]_D^{24}$ −99.2 (*c* 0.40, $CHCl_3$); IR (film) ν 3396 (br), 3241, 2926, 1731, 1593, 1505, 1434, 1377, 1341 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.53 (3H, s, Me18), 1.65−1.80 (2H, m, H6, H7), 1.85 (1H, ddd, *J* = 24.4, 12.0, 5.4 Hz, H15), 1.97 (1H, dd, *J* = 17.5, 5.2 Hz, H12), 2.02 (1H, m, H15), 2.12−2.27 (2H, m, H7, H16), 2.28−2.45 (5H, m, H4, H4, H6, H12, H16), 2.48 (1H, dd, *J* = 11.5, 8.4 Hz, H14), 3.14 (1H, dd, *J* = 10.7, 9.2 Hz, H17), 3.44 (1H, dd, *J* = 4.1, 3.0 Hz, H2), 3.51 (1H, m, H3), 4.69 (1H, brs, H1), 5.43 (1H, dd, *J* = 5.2, 2.5 Hz, H11), 6.24 (1H, s, H19), 7.59 (1H, dd, *J* = 8.6, 1.6 Hz, H6′), 7.63 (1H, d, *J* = 5.6 Hz, H4′), 7.75 (1H, d, *J* = 8.4 Hz, H5′), 7.78 (1H, s, H8′), 8.49 (1H, d, *J* = 5.4 Hz, H3′), 9.22 (1H, s, H1′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3 (C18), 20.5 (C15), 26.4 (C16), 30.5 (C7), 32.2 (C4), 40.0 (C12), 43.4 (C6), 44.6 (C13), 51.6 (C14), 53.1 (C3), 54.2 (C2), 56.9 (C17), 68.2 (C1), 78.4 (C5), 81.7 (C8), 120.1 (C4′), 122.3 (C11), 125.8 (C5′), 126.3 (C8′), 126.4 (C19), 128.6 (C8a′), 131.9 (C6′), 134.7 (C4a′), 139.9 (C7′), 140.6 (C9), 141.6 (C10), 142.4 (C3′), 152.2 (C1′); HRMS (ESI) *m*/*z* calcd for $C_{28}H_{30}NO_3$ 428.2220 $[M + H]^+$, found 428.2221.

Undesired alcohol **99** was reoxidized to the ketone **96** by the following procedure: To a solution of **99** (18.0 mg, 42 μmol) in CH_2Cl_2 (10 mL) was added MnO_2 (109 mg, 1.26 mmol). After the mixture was stirred for 1 h at room temperature, the reaction was directly passed through a pad of silica gel with EtOAc to give **96** (17.5 mg, 41 μmol) in 99%.

Cortistatin A (1). To a solution of **98** (25.1 mg, 58.7 μmol) in Me_2NH (9.8 mL, 2.0 M solution in THF) was added $Yb(OTf)_3$ (36.4 mg, 58.7 μmol). The resulting mixture was stirred for 11 h at 80 °C. The reaction was quenched with aqueous $NaHCO_3$ at 0 °C. Concentration and filtration through a pad of NH silica gel gave a mixture of cortistatin A (**1**) and **100**. HPLC purification (YMC-Pack NH_2, $CH_3CN/CHCl_3/H_2O$ 88:10:2, flow rate: 5.0 mL/min) of the mixture afforded cortistatin A (**1**) (13.3 mg, 28.1 μmol) in 48% and **100** (5.8 mg, 12.3 μmol) in 21%. Cortistatin A (**1**): colorless crystal; R_f = 0.3 (NH-TLC plate, EtOAc/MeOH 10:1); $[\alpha]_D^{25}$ +29.2 (*c* 0.60, MeOH); IR (film) ν 3389 (br), 3234 (br), 2958, 2874, 1593, 1454, 1377, 1266, 1109, 1075, 1044 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.54 (3H, s, Me18), 1.65 (1H, ddd, *J* = 10.8, 10.8, 8.5 Hz, H6), 1.78 (1H, ddd, *J* = 12.3, 8.5, 8.5 Hz, H7), 1.84 (1H, m, H15), 1.89 (1H, dd, *J* = 13.0, 13.0 Hz, H4), 1.92 (1H, dd, *J* = 13.0, 3.5 Hz, H4), 1.97 (1H, dd, *J* = 17.6, 5.2 Hz, H12), 2.04 (1H, m, H15), 2.19 (1H, m, H6), 2.19 (1H, m, H16), 2.28 (1H, m, H7), 2.29 (6H, s, NMe_2), 2.35 (1H, m, H16), 2.38 (1H, d, *J* = 17.6 Hz, H12), 2.41 (1H, ddd, *J* = 13.0, 9.6, 3.5 Hz, H3), 2.51 (1H, dd, *J* = 11.6, 8.5 Hz, H14), 3.14 (1H, dd, *J* = 10.7, 9.4 Hz, H17), 3.33 (1H, dd, *J* = 9.6, 9.6 Hz, H2), 4.09 (1H, brd, *J* = 9.6 Hz, H1), 5.43 (1H, dd, *J* = 5.2, 2.3 Hz, H11), 6.25 (1H, d, *J* = 2.3 Hz, H19), 7.58 (1H, dd, *J* = 8.4, 1.5 Hz, H6′), 7.62 (1H, d, *J* = 5.6 Hz, H4′), 7.75 (1H, d, *J* = 8.4 Hz, H5′), 7.78 (1H, brs), 8.49 (1H, d, *J* = 5.6 Hz, H3′), 9.22 (1H, s, H1′); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.2 (C18), 20.5 (C15), 26.4 (C16), 29.0 (C4), 30.5 (C7), 39.7 (C6), 40.0 (C12), 40.1 (NMe_2), 44.8 (C13), 51.6 (C14), 56.9 (C17), 62.2 (C3), 73.7 (C1), 74.2(C2), 79.5 (C5), 81.9 (C8), 119.5 (C19), 120.1 (C4′), 121.4 (C11), 125.8 (C5′), 126.3 (C8′), 128.6 (C8a′), 132.0 (C6′), 134.7 (C4a′), 139.6 (C9), 140.0 (C7′, C10), 142.5 (C3′), 152.3 (C1′); HRMS (ESI) *m*/*z* calcd for $C_{30}H_{37}N_2O_3$ 473.2799 $[M + H]^+$, found 473.2798.

100: colorless crystal; R_f = 0.5 (NH-TLC plate, EtOAc/MeOH 10:1); $[\alpha]_D^{25}$ −36.1 (*c* 0.28, MeOH); IR (film) ν 3382 (br), 3218 (br), 2959, 2877, 1594, 1456, 1376, 1146, 1042 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.55 (3H, s, Me18), 1.66−1.80 (2H, m, H6, H7), 1.86 (1H, ddd, *J* = 24.5, 11.9, 5.5 Hz, H15), 1.92- 2.11 (5H, m, H4, H4, H6, H12, H15), 2.12−2.24 (2H, m, H7, H16), 2.28−2.40 (2H, m. H12, H16), 2.47 (6H, s, NMe_2), 2.50 (1H, dd, *J* = 11.7, 8.4 Hz, H14), 3.00 (1H, dd, *J* = 8.3, 8.3 Hz, H2), 3.13 (1H, dd, *J* = 10.6, 9.2 Hz, H17), 4.25−4.33 (2H, m, H1, H3), 5.31 (1H, dd, *J* = 5.2, 2.3 Hz, H11), 6.06 (1H, d, *J* = 1.8 Hz, H19), 7.58 (1H, d, *J* = 8.5, 1.6 Hz, H6′), 7.62 (1H, d, *J* = 5.8 Hz, H4′), 7.75 (1H, d, *J* = 8.6 Hz, H5′), 7.78 (1H, s, H8′), 8.48 (1H, d, *J* = 5.8 Hz, H3′), 9.22 (1H, s, H1′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4 (C18), 20.6 (C15), 26.4 (C16), 30.0 (C7), 38.9 (C4), 39.0 (C6), 40.0 (C12), 43.5 (NMe_2), 44.6 (C13), 51.7 (C14), 57.1 (C17), 63.7 (C1), 66.0 (C3), 69.4 (C2), 78.4 (C5), 83.6 (C8), 117.1 (C19), 119.7 (C11), 120.1 (C4′), 125.8 (C5′), 126.3 (C8′), 128.6 (C8a′), 132.0 (C6′), 134.7 (C4a′), 140.1 (C7′), 140.4 (C9), 142.4 (C3′), 144.4 (C10), 152.3 (C1′); HRMS (ESI) *m*/*z* calcd for $C_{30}H_{37}N_2O_3$ 473.2799 $[M + H]^+$, found 473.2796.

Amine 101. Enone **96** (9.3 mg, 22.7 μmol) was dissolved in a solution of Me_2NH (9.3 mL, 2.0 M in THF). The resulting mixture was stirred for 27 h at room temperature and then directly concentrated. The crude was used in the next step without further purification. To a solution of the resulting crude in Et_2O (9.0 mL) was added $LiAlH_4$ (3.0 mg, 79 μmol) at 0 °C. After the mixture was stirred for 15 min at 0 °C, the reaction was quenched by addition of H_2O (3.0 μL), aqueous NaOH (6.0 μL, 1.0 M), and H_2O (9.0 μL). The suspension was filtered

through a pad of Celite and concentrated. Flash column chromatography of the residue using NH-silica gel (hexane/EtOAc 1:1 − 0:1) gave **101** (6.4 mg, 14.0 μmol) in 60% (two steps): colorless amorphous; R_f = 0.4 (NH-TLC plate, EtOAc/MeOH 10:1); $[\alpha]_D^{31}$ +52.3 (*c* 0.39, $CHCl_3$); IR (film) ν 3361 (br), 3223 (br), 2958, 2779, 1730, 1593, 1454, 1378, 1263, 1081, 1003 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.54 (3H, s, Me18), 1.40 (1H, dd, *J* = 23.2, 16.1 Hz, H2), 1.62−1.72 (1H, m, H6), 1.76 (1H, ddd, *J* = 12.5, 8.7, 8.7 Hz, H7), 1.82−2.44 (17H, m, H2, H4, H4, H6, H7, H12, H12, H15, H15, H16, H16, NMe_2), 2.45−2.62 (2H, m, H3, H14), 3.15 (1H, dd, *J* = 10.6, 9.2 Hz, H17), 4.22 (1H, brdd, *J* = 11.4, 4.9 Hz, H1), 5.41 (1H, dd, *J* = 5.2, 2.5 Hz, H11), 6.14 (1H, d, *J* = 2.0 Hz, H19), 7.59 (1H, dd, *J* = 8.6, 1.6 Hz, H6′), 7.62 (1H, d, *J* = 5.8 Hz, H4′), 7.75 (1H, d, *J* = 8.7 Hz, H5′), 7.78 (1H, brs, H8′), 8.48 (1H, d, *J* = 5.7 Hz, H3′), 9.21 (1H, brs, H1′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2 (C18), 20.6 (C15), 26.5 (C16), 30.7 (C7), 36.7 (C4), 37.7 (C2), 39.8 (C6), 40.1 (C12), 40.8 (NMe_2), 44.8 (C13), 51.7 (C14), 56.9 (C7), 57.4 (C3), 68.7 (C1), 80.1 (C5), 81.8 (C8), 117.4 (C19), 120.1 (C4′), 121.1 (C11), 125.8 (C5′), 126.3 (C8′), 128.6 (C8a′), 132.0 (C6′), 134.7 (4a′), 139.9 (C9), 140.1 (C7′), 142.5 (C3′), 143.9 (C10), 152.3 (C1′); HRMS (ESI) *m*/*z* calcd for $C_{30}H_{37}N_2O_2$ 457.2850 $[M + H]^+$, found 457.2850.

Cortistatin J (5). To a solution of **101** (4.0 mg, 8.8 μmol) in THF (4.0 mL) was successively added *i*Pr_2NEt (0.4 mL), MsCl (8.0 μL, 103 μmol) and then DBU (12.0 mL, 80 μmol) at 0 °C. The ice bath was removed and the mixture was stirred for 10 min. The reaction mixture was directly passed through a pad of NH silica gel with EtOAc and concentrated. Purification with HPLC (YMC-Pack NH_2, CH_3CN/$CHCl_3$/H_2O 88:10:2, flow rate: 1.0 mL/min) gave **5** (t_R = 10.1 min, 1.7 mg, 3.9 μmol) in 42% yield: colorless amorphous solid; R_f = 0.4 (NH-TLC plate, EtOAc); $[\alpha]_D^{20}$ −57.2 (*c* 0.22, $CHCl_3$); IR (film) ν 3266 (br), 2961, 2928, 2865, 1592, 1454, 1376, 1262, 1022 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.58 (3H, s, Me18), 1.63−1.82 (2H, m, H6, H7), 1.83−2.13 (6H, m, H4, H4, H6, H12, H15, H15), 2.20 (1H, m, H16), 2.26−2.46 (9H, m, H7, H12, H16, NMe_2), 2.56 (1H, dd, *J* = 11.5, 8.4 Hz, H14), 3.16 (1H, dd, *J* = 10.5, 9.0 Hz, H17), 3.49 (1H, m, H3), 5.42 (1H, dd, *J* = 5.4, 2.8 Hz, H11), 5.82 (1H, d, *J* = 10.2 Hz, H2), 5.84 (1H, s, H19), 6.10 (1H, dd, *J* = 9.7, 2.4 Hz, H1), 7.59 (1H, dd, *J* = 8.5, 1.7 Hz, H6′), 7.63 (1H, d, *J* = 5.8 Hz, H4′), 7.76 (1H, d, *J* = 8.5 Hz, H5′), 7.79 (1H, brs, H8′), 8.49 (1H, d, *J* = 5.7 Hz, H3′), 9.23 (1H, s, H1′); ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.4 (C18), 20.6 (C15), 26.4 (C16), 30.5 (C7), 31.0 (C4), 38.0 (C6), 40.3 (NMe_2), 40.6 (C12), 44.8 (C13), 51.7 (C14), 57.0 (C17), 60.5 (C3), 79.0 (C5), 82.3 (C8), 120.1 (C4′), 121.1 (C19), 121.8 (C11), 125.8 (C5′), 126.3 (C8′), 127.4 (C1), 128.7 (C8a′), 132.0 (C6′), 132.3 (C2), 134.7 (C4a′), 139.9 (C10), 140.1 (C7′), 141.3 (C9), 142.6 (C3′), 152.4 (C1′); HRMS (ESI) *m*/*z* calcd for $C_{30}H_{35}N_2O$ 439.2744 $[M + H]^+$, found 439.2743.

■ ASSOCIATED CONTENT

Supporting Information. NMR spectra for new compounds and X-ray crystallographic data of compound **72**. This material is available free of charge via the Internet at http://pubs.acs.org.

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