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# Construction of the Fused Pentacycle of Talatisamine via a Combination of Radical and Cationic Cyclizations

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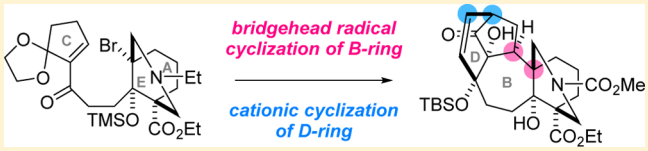
Supporting Information

**ABSTRACT:** The fused 6/7/5/6/6-membered (ABCDE) ring system of talatisamine was synthesized in 22 steps. After preparation of the AE-ring structure from 2-(ethoxycarbonyl)-cyclohexanone, elaboration of the carboskeleton was realized by sequential additions of allyl magnesium bromide and the lithiated C-ring. The C11-bridgehead radical derived from the ACE-ring underwent the 7-endo cyclization with the enone moiety to form the B-ring in C10-stereoselective and C11-stereospecific manners. The 6-endo cyclization of the remaining D-ring was in turn attained by using the silyl enol ether as the nucleophile and the PhSeCl-activated olefin as the electrophile. These radical and cationic cyclizations were demonstrated to be highly chemoselective, and they significantly contributed to streamlining the route to the intricately fused pentacycle of talatisamine.




## INTRODUCTION

Over 600 species of C19-diterpenoid alkaloids have been isolated from the plants of the genera *Aconitum* and *Delphinium*, and many of them possess pharmacologically important biological activities.[1] As exemplified by talatisamine,[2,3] circinasine E,[4] deoxydelsoline,[5] and 9-hydroxysenbushine A[6] in Scheme 1, the C19-diterpenoid alkaloids all share the hexacyclic ABCDEF-ring framework, but they differ in their oxidation states (highlighted in red or blue). The cage-like hexacycle of the alkaloids is composed of a fused 6/7/5/6/5-membered ABCDF-carbocycle and the piperidine E-ring, and it is functionalized by multiple oxygen functional groups. These architectural features mark this class of compounds as exceedingly challenging targets for synthesis.[7] Among the numerous synthetic studies on the C19-diterpenoid alkaloids[8] to date, the total syntheses of talatisamine, chasmanine, and 13-desoxydelphonine from Wiesner's group,[9] neofinaconitine from Gin's group,[10] and weisaconitine D and liljestrandinine from Sarpong's group[11] are landmark accomplishments in the field of organic chemistry.

Wiesner and co-workers reported the single-step conversion of pentacycle **A** to hexacyclic talatisamine, in which $Hg(OAc)_2$ oxidized the tertiary amine to the corresponding C17-iminium, and the C7-olefin participated in the transannular aza-Prins-type reaction (Scheme 1).[9a,12] Inspired by this elegant late-stage F-ring formation, we envisioned the development of a concise and general synthetic route to the pentacyclic ABCDE-ring system for the unified total syntheses of talatisamine and other C19-diterpenoid alkaloids. For the initial phase of the study, we designed pentacycle **1** as a model target compound. Model **1** has the common ABCDE-ring framework of the C19-diterpenoids, and three tetrasubstituted (C4, 8, 11), and two trisubstituted carbons (C10, 13) of its 7 stereocenters directly match those of talatisamine. Here, we report the efficient synthesis of **1** by utilizing bridgehead radical-mediated 7-endo and selenium-induced 6-endo cyclizations as the two key transformations.

## RESULTS AND DISCUSSION

Retrosynthetically, the 6-membered D-ring of pentacycle **1** was opened by disconnecting the C13,16-bond to provide tetracycle **2** (Scheme 1). In the synthetic direction, the $\alpha$-position of the C14-carbonyl group of **2** was expected to stereoselectively react with the C15,16-unsaturated bond via 6-endo cyclization. After the retrosynthetic removal of the $\beta$-oriented two-carbon unit of **2** at C8, the central C10,11-bond of the 7-membered B-ring of **3** was cleaved to generate **4**. To construct the hindered bond between the C10-tertiary and C11-quaternary carbons of **3** stereoselectively, we planned to employ an intramolecular C11-bridgehead radical reaction from **4**, because of its potent reactivity, minimized steric hindrance, and predestined C11-stereochemistry.[13,14] Thus, the C11-bromide and the carbonyl conjugated C9,10-olefin were implemented within the structure of **4** as the bridgehead radical donor and acceptor, respectively. Compound **4** would be simply prepared from the known chiral AE-ring **5** through sequential carbon extensions by addition of allylmagnesium bromide **D** and the lithiated C-ring **C**.

The radical precursor **4** was prepared from 2-(ethoxycarbonyl)cyclohexanone (**6**) in 8 steps (Scheme 2). According to the literature method,[15] **6** was brominated to **7**, which was treated with ethylamine and formaldehyde for the double Mannich reaction to generate the AE-ring **5** with installation of the C4,11-tetrasubstituted carbons. Allylmagnesium bromide **D** chemoselectively added to the C5-carbonyl

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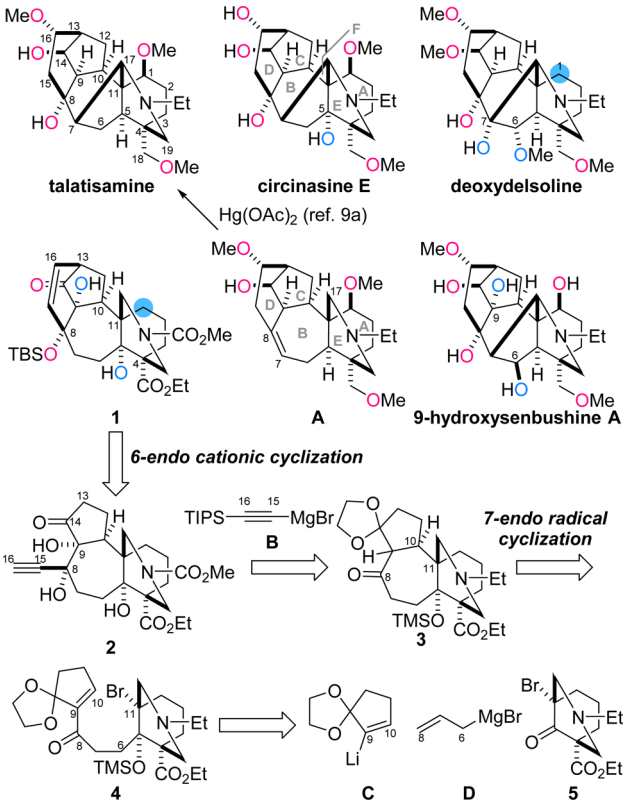
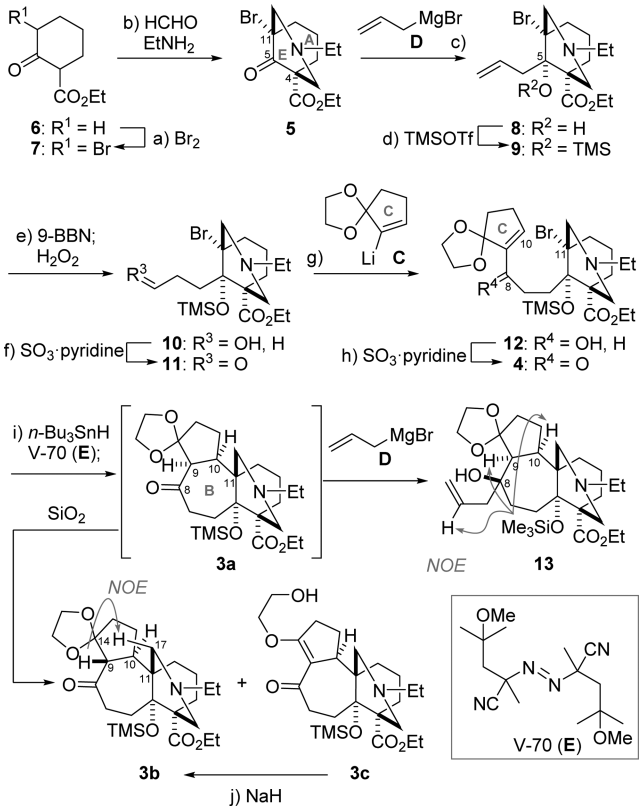
**Scheme 1. Structures of Talatisamine and Other C19-Diterpenoid Alkaloids, and the Synthetic Plan of Model Pentacycle 1**




group of **5** without affecting the ethoxycarbonyl group at C4, affording the diastereomixture of **8** and its C5-epimer (1.7:1). After the silylation of the C5-tertiary alcohol of the mixture with TMSOTf and $Et_3N$, the C5-diastereomers were separated by silica gel column chromatography to provide pure **9**. Hydroboration of terminal olefin **9**, followed by oxidative workup, gave primary alcohol **10**, which was oxidized to aldehyde **11** using the reagent combination of $SO_3$·pyridine and DMSO.[16] The cyclopentenyl lithium derivative **C**[17] then chemoselectively reacted with the aldehyde of **11** in the presence of the ester, attaching the 5-membered C-ring structure to afford **12**. The newly generated allylic alcohol of **12** was converted to the C8-ketone of **4** by the action of $SO_3$·pyridine/DMSO to furnish **4** equipped with the bromide and the $\alpha,\beta$-unsaturated ketone.

Remarkably, the 7-endo radical cyclization of **4** stereoselectively connected the sterically cumbersome bond between the C11-quaternary and C10-tertiary carbons at room temperature (Scheme 2). Thus, treatment of **4** with *n*-$Bu_3SnH$ and V-70 at room temperature produced the stereochemically fixed C11-bridgehead radical,[18,19] which added to the C8-carbonyl conjugated olefin to install the correct C10,11-stereocenters of the central B-ring of **3a**.[20] The 6-exo product or the C10-stereoisomer was not observed, demonstrating the high regio- and stereoselectivity of the cyclization. Upon silica gel purification of **3a**, epimerization at the C9 stereogenic center and $\beta$-elimination of the C14-oxygen functionality occurred to transform the initially formed *cis*-fused **3a** to *trans*-fused **3b** and enone **3c**, respectively. The latter **3c** was converted to the former **3b** by the oxy-Michael addition with NaH, yielding **3b** in 79% combined yield from **4**. While the epimerized C9-

**Scheme 2. Synthesis of Tetracycle 3b by the 7-endo Bridgehead Radical Cyclization**[a]




[a]Reagents and conditions: (a) $Br_2$, $Et_2O$; (b) HCHO aq., $EtNH_2$, MeOH; (c) **D**, $CH_2Cl_2$, −78 °C (dr at C5 = 1.7:1); (d) TMSOTf, $Et_3N$, $CH_2Cl_2$, 28% for **9**, 11% for the C5-diastereomer of **9** (4 steps); (e) 9-BBN, THF; $H_2O_2$, 3 M NaOH; (f) $SO_3$·pyridine, $Et_3N$, DMSO, 90% (2 steps); (g) **C**, THF, −78 °C; (h) $SO_3$·pyridine, $Et_3N$, DMSO, 55% (2 steps); (i) *n*-$Bu_3SnH$, V-70 (**E**), benzene; $SiO_2$ for **3b** and **3c**; *n*-$Bu_3SnH$, V-70 (**E**), benzene; **D** for **13**, 81%; (j) NaH, THF, 0 °C, 79% (2 steps). 9-BBN = 9-borabicyclo[3.3.1]nonane, TMS = trimethylsilyl, V-70 = 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile).

stereochemistry of **3b** was established by the NOE signal between C9−H and C17−H, the C9- and C10-stereochemistries of configurationally labile **3a** were determined by NOE experiments of **13**, which was prepared by in situ allylation of **3a** with **D**.

While the regioselectivity of the radical cyclization would originate from the favorable orbital interaction, the stereochemical outcomes of the cyclization and the $\alpha$-epimerization/$\beta$-elimination would be explained by unfavorable steric interactions (Scheme 3). To maximize the SOMO/LUMO interaction, the nucleophilic C11-bridgehead radical of **4** reacted with C10 of the electron deficient enone, thereby participating in the 7-endo cyclization rather than the 6-exo counterpart. On the other hand, the correct C10-isomer **G** would be selectively generated via intermediacy of conformer **F**, because conformer **H**, which leads to the incorrect isomer **I**, would suffer from large steric repulsion between the C14-acetal and C5-TMS ether moieties. The C9-radical of the thus generated **G** is hydrogenated from the convex face to temporarily form the *cis*-fused **3a**, which then undergoes either C9-epimerization to afford the *trans*-fused **3b** or C14−O



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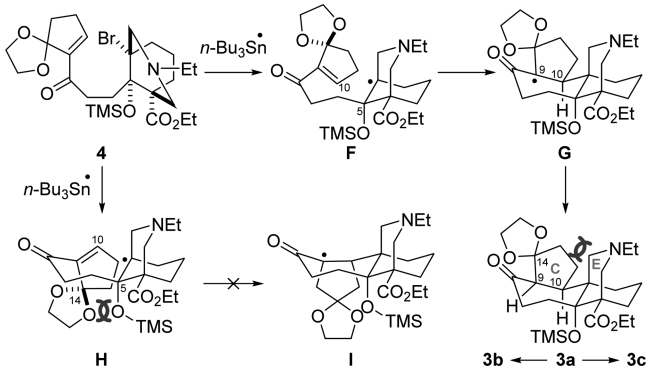
**Scheme 3. Plausible Mechanisms for the Stereoselective Outcome of the Radical Cyclization**

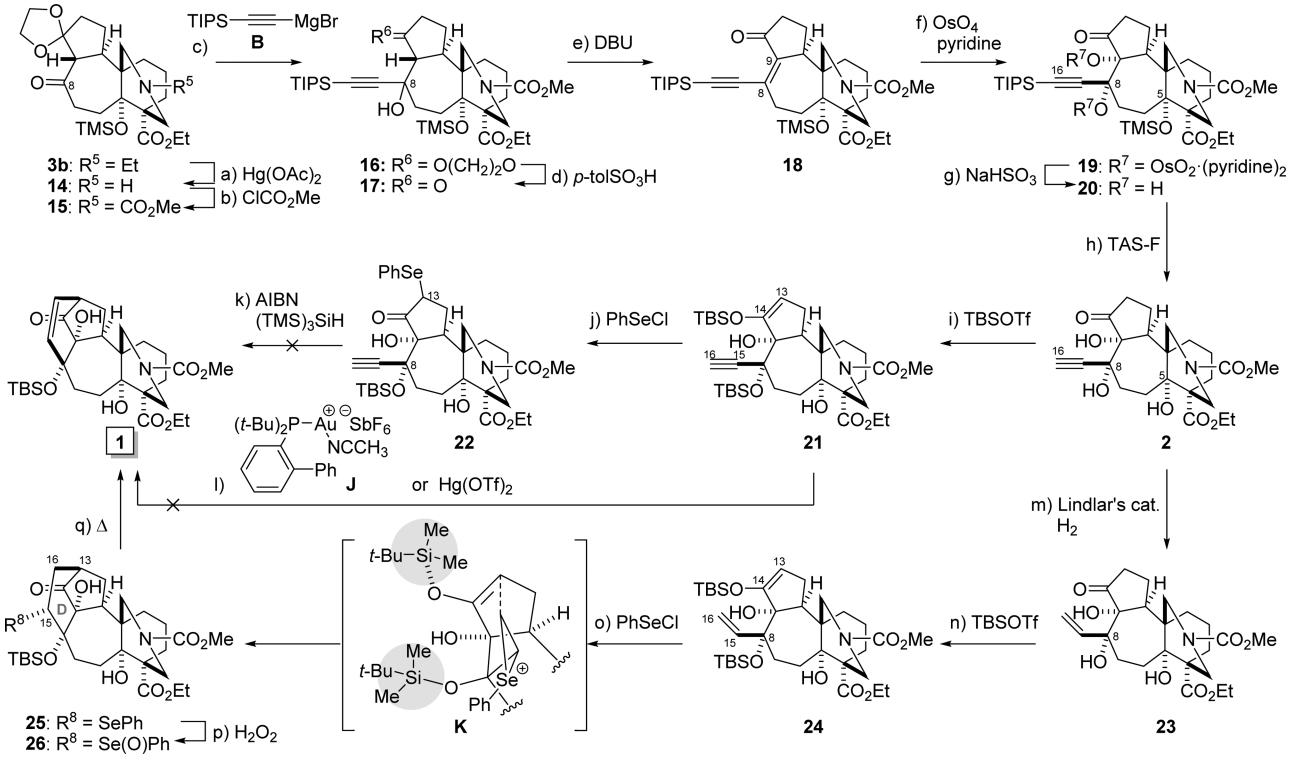


elimination to provide enone **3c**, releasing the steric strain of the closely situated C- and E-rings of **3a**.

Having realized the stereoselective radical cyclization of the 7-membered B-ring, our focus turned to stereoselective construction of the 6-membered D-ring from tetracycle **3b** (Scheme 4). As tertiary amines are generally susceptible to oxidative and electrophilic reagents, the ethyl group of the nitrogen atom of **3b** was exchanged to the carbomethoxy group of **15** prior to the subsequent transformations. Namely, $Hg(OAc)_2$-promoted oxidation of tertiary amine **3b** to the iminium cation[21] and in situ hydrolysis afforded secondary amine **14**, which was converted to methyl carbamate **15** using $ClCO_2Me$. To prepare for the cationic cyclization between the C13 and 16 positions, the unsaturated two-carbon unit was attached to C8, and the *cis*-1,2-diol was introduced at C8,9 to locate the C13- and 16-carbon centers in close proximity. Thus, TIPS-protected ethynyl magnesium bromide **B** was added to the C8-ketone of **15**. Removal of the acetal of **16** under acidic conditions, followed by DBU-promoted dehydration of the tertiary C8-hydroxy group, gave rise to the enyne structure of **18**. When stoichiometric $OsO_4$ was applied to the tetrasubstituted double bond of **18** in a mixture of 1,4-dioxane and pyridine, osmylation proceeded from the opposite side of the sterically shielding E-ring to stereoselectively form the osmate ester-pyridine complex **19**.[22] The potentially oxidizable triple bond was intact under the conditions, presumably due to the kinetic protection by the bulky TIPS group.[23] Osmate ester **19** was in turn reductively hydrolyzed in aqueous $NaHSO_3$ to provide diol **20** with the correct C8,9-stereocenters.[24] TAS-F[25] simultaneously deprotected the C16-TIPS and C5O-TMS groups of **20**, leading to **2**.

To build the remaining 6-membered D-ring of the targeted **1**, we envisioned the use of the C13,14-enol ether as the nucleophile and the C15,16-terminal unsaturated bond as the electrophile precursor (Scheme 4). TBSOTf and $Et_3N$ simultaneously formed the TBS-enol ether at C14 and the TBS-ether at C8 to furnish bis-TBS ether **21**. Next, alkyne **21** was subjected to $Hg(OTf)_2$[26] or Au(I) complex **J**[27] because of

**Scheme 4. Synthesis of Pentacycle 1 via the 6-endo Cationic Cyclization**[a]



[a]Reagents and conditions: (a) $Hg(OAc)_2$, $H_2O$, 1,4-dioxane, 60 °C; (b) $ClCO_2Me$, $Et_3N$, $CH_2Cl_2$, 0 °C, 46% (2 steps); (c) **B**, THF, 98%; (d) *p*-$tolSO_3H$, acetone; (e) DBU, THF, 60 °C, 100% (2 steps); (f) $OsO_4$, pyridine, 1,4-dioxane, $H_2O$; (g) $NaHSO_3$, pH 7 buffer, THF, 55% (2 steps); (h) TAS-F, $H_2O$, DMF, 0 °C, 85%; (i) TBSOTf, $Et_3N$, $CH_2Cl_2$, 0 °C, 68%; (j) PhSeCl, $CH_2Cl_2$, −78 °C, 39%; (k) AIBN, $(TMS)_3SiH$, benzene, reflux; (l) **J** (20 mol %), acetone, or $Hg(OTf)_2$ (100 mol %), $CH_3NO_2$, 0 °C; (m) Pd/$CaCO_3$/Pb (Lindlar's catalyst), $H_2$, EtOAc, MeOH; (n) TBSOTf, $Et_3N$, $CH_2Cl_2$, 0 °C, 64% (2 steps); (o) PhSeCl, $CH_2Cl_2$, −78 °C, 87%; (p) 30% $H_2O_2$ aq. $CH_2Cl_2$; (q) benzene, 100 °C, 85% (2 steps). AIBN = azobis(isobutyronitrile), DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TAS-F = tris(dimethylamino)sulfonium difluorotrimethylsilicate, TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.



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the high affinity of mercury(II) or gold(I) salts toward triple bonds. However, the reaction did not produce the desired product **1**, and only resulted in removal of the TBS group from the enol ether. Alternative application of PhSeCl to **21** did not activate the alkyne,[28] and selectively converted the electron-rich TBS enol ether to the $\alpha$-phenylseleno ketone of **22**. Despite this failure in the selenium-mediated cyclization, we attempted to utilize the introduced phenylselenide as the radical donor. Treatment of **22** with $(TMS)_3SiH$ and AIBN did not create the C13,16-bond, and merely produced the C13-methylene via reduction of the C13-Se bond. These unsuccessful results together emphasized the low reactivity of the alkyne and the spatial distance between the reacting C13 and 16, and they indicated that alkyne **21** was not suitable for the requisite cationic cyclization.

Accordingly, we decided to employ alkene **23**, because the C15,16-olefin was expected to be more reactive toward electrophilic reagents and to provide a closer proximity for the C13,16-positions. Thus, the C8-ethynyl group of **2** was partially hydrogenated in the presence of the Lindlar's catalyst[29] to the C8-ethenyl group of **23**, which was bis-silylated with TBSOTf and $Et_3N$, leading to the TBS enol ether **24**. When **24** was submitted to PhSeCl in $CH_2Cl_2$ at −78 °C, the TBS-enol ether attacked the selenium-activated C15,16-alkene in the 6-endo manner, giving rise to pentacycle **25** with stereoselective construction of the C13,15-centers.[30] The entire stereostructure of **25** was unambiguously determined by X-ray crystallographic analysis (Figure 1). Finally, oxidation of the

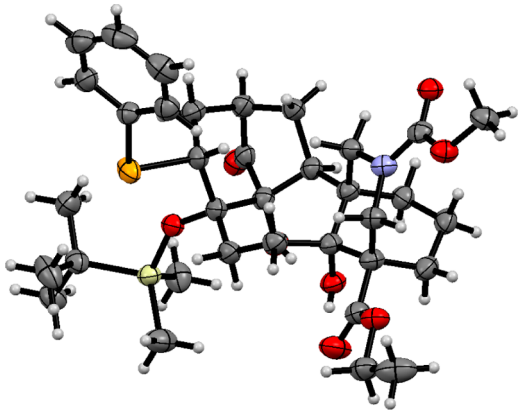

**Figure 1.** X-ray structure of **25** (CCDC1468828) with thermal ellipsoids at the 50% probability level.

PhSe group of **25** with aqueous $H_2O_2$ and subsequent thermal *syn*-elimination of the selenoxide of **26** introduced the C15,16-double bond to deliver the target compound **1**.

The contrasting outcomes of the PhSe-mediated reactions of **21** and **24** would originate from not only the higher $\pi$-donative ability and the more preorganized conformation of the C8-ethenyl group of **24** than those of the C8-ethynyl group of **21**, but also the more sterically shielding effect of the olefin than that of the alkyne. The TBS-enol ether of **24** is kinetically protected by the two bulky TBS groups on the $\alpha$-face and the C8-ethenyl group on the $\beta$-face. Consequently, PhSeCl preferentially reacts with the olefin over the intrinsically more $\pi$-donative enol ether to lead to the cationic intermediate **K**. The nucleophilic attack of the proximal TBS-enol ether of **K** occurs via the energetically favored chairlike transition state, producing 6-endo adduct **25** in the C13,15-stereoselective fashion. Nonformation of the corresponding 5-exo product is attributable to a higher activation barrier for assembling the more strained 7/5/5-membered ring system. It is noteworthy that the present substrate design enabled the 6-endo D-ring cyclization of the intricately fused and multiply oxygenated substrate under neutral conditions at low temperature.

## CONCLUSION

In summary, we developed an effective strategy for construction of the pentacyclic 6/7/5/6/6-membered (ABCDE-ring) **1** of the C19-diterpenoid alkaloid talatisamine [22 steps from 2-(ethoxycarbonyl)cyclohexanone (**6**)]. After cyclization of the AE-ring **5** by the double Mannich reaction, carbon elongation from **5** to **4** was realized by sequential nucleophilic addition of allylmagnesium bromide **D** and the lithiated C-ring structure **C**. Next, the C11-bridgehead radical reaction of the ACE-ring **4** underwent the 7-endo cyclization to form the B-ring of **3b** while establishing the stereochemistries of the C11-quaternary and C10-tertiary carbons in a single step. Finally, the 6-endo cationic cyclization between the TBS-enol ether and the olefin was accomplished by the action of PhSeCl, transforming the ABCE-ring **24** to the targeted ABCDE-ring **1**. The radical and cationic cyclizations were powerful, yet mild and neutral, and thus served as particularly useful reactions in assembly of the highly substituted fused pentacycle **1**. Application of these effective key protocols for total syntheses of talatisamine and other diverse C19-diterpenoid alkaloids is currently underway in our laboratory.

## EXPERIMENTAL SECTION

**General Methods.** All reactions sensitive to air or moisture were carried out in dry solvents under argon atmosphere, unless otherwise noted. THF, $CH_2Cl_2$, toluene, DMF and $Et_2O$ were purified by Glass Contour solvent dispensing system. All other reagents were used as supplied. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm plate. Flash chromatography was performed using 40−100 $\mu$m silica gel. Melting points were measured on micro melting point apparatus, and are uncorrected. Infrared (IR) spectra were recorded as a thin film on a NaCl. $^1H$ and $^{13}C$ NMR spectra were measured at room temperature. Chemical shifts were reported in ppm on the $\delta$ scale relative to $CHCl_3$ ($\delta$ = 7.26 for $^1H$ NMR), $CDCl_3$ ($\delta$ = 77.0 for $^{13}C$ NMR), $C_6D_6$ ($\delta$ = 7.16 for $^1H$ NMR) and $C_6D_6$ ($\delta$ = 128.06 for $^{13}C$ NMR) as internal references. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broaden peak.

*Azabicyclo[3.3.1]nonane* ***9***. $Br_2$ (15.0 g, 93.9 mmol) was added to a solution of ketone **6** (15.2 g, 89.3 mmol) in $Et_2O$ (60 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 18 h. After the mixture was cooled to 0 °C, saturated aqueous $NaHCO_3$ (200 mL) was added. The resultant solution was extracted with $Et_2O$ (30 mL ×3), and the combined organic layers were washed with brine (50 mL), dried over $Na_2SO_4$, filtered and concentrated to afford the crude bromide **7**, which was used in the next reaction without further purification.

HCHO (37% in $H_2O$, 87 mL, 1.1 mol) and $EtNH_2$ (70% in $H_2O$, 17.3 g, 269 mmol) were successively added to a solution of the above crude bromide **7** in MeOH (450 mL) at 0 °C. The reaction mixture was stirred for 2 h, and warmed to room temperature. The mixture was stirred for 47 h, and was poured into $H_2O$ (2.0 L). The resultant mixture was extracted with EtOAc (100 mL ×3), and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (300 g, hexane/EtOAc 20/1 to 5/1) to afford the crude **5**, which was used in the next reaction without further purification.

Allylmagnesium bromide (**D**, 1.0 M in $Et_2O$, 76 mL, 76 mmol) was added to a solution of the above crude **5** in $CH_2Cl_2$ (170 mL) at −78



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°C. The reaction mixture was stirred at −78 °C for 40 min, and then saturated aqueous $NH_4Cl$ (80 mL) was added. After the mixture was warmed to room temperature, saturated aqueous $NaHCO_3$ (80 mL) and $H_2O$ (500 mL) were successively added. The resultant solution was extracted with EtOAc (150 mL ×3), and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated to afford the crude allyl alcohol **8** as a 1.7:1 C5-diastereomixture, which was used in the next reaction without further purification.

$Et_3N$ (28 mL, 0.20 mol) and TMSOTf (18 mL, 0.10 mol) were successively added to a solution of the above allyl alcohol **8** in $CH_2Cl_2$ (170 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 20 h. After the mixture was cooled to 0 °C, $H_2O$ (200 mL) was added. The resultant solution was extracted with EtOAc (100 mL ×3). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (500 g, hexane/$CH_2Cl_2$ 10/1 to 3/1) to afford **9** (10.7 g, 24.7 mmol) and the C5-diastereomer of **9** (4.32 g, 9.99 mmol) in 28% and 11% yields over 4 steps, respectively. **9**: colorless oil; IR (film) $\nu$ 2970, 2932, 2819, 1717, 1455, 1249, 1045, 915, 840 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.29 (9H, s), 1.05 (3H, t, $J$ = 7.3 Hz), 1.22 (3H, dd, $J$ = 7.3, 7.3 Hz), 1.42−1.51 (2H, m), 2.12−2.20 (1H, m), 2.36 (2H, q, $J$ = 7.3 Hz), 2.61 (1H, dddd, $J$ = 13.3, 13.3, 6.9, 2.8 Hz), 2.75−3.02 (7H, m), 3.30 (1H, d, $J$ = 11.4 Hz), 3.94 (1H, dq, $J$ = 11.0, 7.3 Hz), 4.10 (1H, dq, $J$ = 11.0, 7.3 Hz), 5.00 (1H, br d, $J$ = 10.0 Hz), 5.04 (1H, br d, $J$ = 17.4 Hz), 5.78 (1H, dddd, $J$ = 17.4, 10.0, 8.7, 5.0 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 3.1 (3C), 12.5, 14.0, 23.5, 32.0, 39.4, 40.3, 51.3, 52.6, 57.1, 60.1, 64.5, 79.2, 80.6, 117.2, 133.5, 173.4; HRMS (ESI-TOF), calcd for $C_{19}H_{35}BrNO_3Si$ 432.1564 and 434.1544 $[M + H]^+$, found 432.1537 and 434.1532. C5-diastereomer of **9**: yellow solid; mp 43.0−45.0 °C; IR (film) $\nu$ 2972, 2953, 1724, 1465, 1248, 1155, 1057, 841 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.25 (9H, s), 1.03 (3H, t, $J$ = 7.3 Hz), 1.24 (3H, dd, $J$ = 7.3, 7.3 Hz), 1.51 (1H, ddd, $J$ = 12.8, 6.8, 6.8 Hz), 1.85 (1H, dd, $J$ = 14.6, 6.8 Hz), 2.30 (2H, q, $J$ = 7.3 Hz), 2.34−2.43 (1H, m), 2.40 (1H, dd, $J$ = 13.7, 6.8 Hz), 2.56 (1H, d, $J$ = 11.0 Hz), 2.59 (1H, dddd, $J$ = 13.7, 13.7, 7.8, 2.7 Hz), 2.87 (1H, ddddd, $J$ = 13.7, 13.7, 12.8, 6.8, 6.8 Hz), 2.97 (2H, d, $J$ = 6.9 Hz), 3.03 (1H, d, $J$ = 10.6 Hz), 3.14 (1H, dd, $J$ = 11.0, 2.7 Hz), 3.18 (1H, dd, $J$ = 10.6, 2.7 Hz), 4.02 (1H, dq, $J$ = 11.0, 7.3 Hz), 4.08 (1H, dq, $J$ = 11.0, 7.3 Hz), 5.04 (1H, dd, $J$ = 10.5, 1.4 Hz), 5.12 (1H, dd, $J$ = 17.4, 1.4 Hz), 5.89 (1H, ddt, $J$ = 17.4, 10.5, 6.9 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 3.1 (3C), 12.4, 14.0, 23.0, 31.1, 39.4, 41.0, 51.4, 53.7, 57.6, 60.4, 63.6, 78.9, 80.8, 117.1, 134.2, 172.9; HRMS (ESI-TOF) calcd for $C_{19}H_{35}BrNO_3Si$ 432.1564 and 434.1544 $[M + H]^+$, found 432.1566 and 434.1546.

*Aldehyde* ***11***. 9-BBN dimer (9.13 g, 37.4 mmol) was added to a solution of **9** (10.6 g, 24.5 mmol) in THF (49 mL) at room temperature. The reaction mixture was stirred for 1 h at room temperature. After the mixture was cooled to 0 °C, aqueous NaOH (3.0 M, 82 mL, 250 mmol) and $H_2O_2$ (30% in $H_2O$, 82 mL, 0.72 mol) were successively added. The reaction mixture was warmed to room temperature and stirred for 15 h. The solution was extracted with EtOAc (20 mL ×4), and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (270 g, hexane/EtOAc 5/1 to 3/1) to afford the crude alcohol **10**, which was used in the next reaction without further purification.

$SO_3$·pyridine complex (11.3 g, 71.0 mmol) was added to a mixture of the above crude alcohol **10** and $Et_3N$ (16 mL, 0.12 mol) in DMSO (240 mL) at room temperature. The reaction mixture was stirred for 2 h at room temperature. After the mixture was cooled to 0 °C, $H_2O$ (600 mL) was added. The resultant solution was extracted with EtOAc (100 mL ×4), and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (360 g, $CH_2Cl_2$) to afford aldehyde **11** (9.86 g, 22.0 mmol) in 90% yield over 2 steps: white solid; mp 43.5−45.0 °C; IR (film) $\nu$ 2968, 2920, 2818, 1727, 1712, 1251, 1220, 1197, 1136, 839 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.26 (9H, s), 1.04 (3H, t, $J$ = 7.5 Hz), 1.27 (3H, dd, $J$ = 7.5, 7.5 Hz), 1.44−1.53 (2H, m), 2.17−2.23 (1H, m), 2.33−2.45 (2H, m), 2.36 (2H, q, $J$ = 7.5 Hz), 2.50−2.63 (3H, m), 2.76−2.88 (2H, m), 2.86 (1H, dd, $J$ = 12.6, 2.9 Hz), 2.97 (1H, d, $J$ = 12.6 Hz), 3.02 (1H, dd, $J$ = 10.9, 2.3 Hz), 3.31 (1H, d, $J$ = 10.9 Hz), 4.02 (1H, dq, $J$ = 11.5, 7.5 Hz), 4.24 (1H, dq, $J$ = 11.5, 7.5 Hz), 9.73 (1H, s); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 3.1 (3C), 12.5, 14.1, 23.3, 26.4, 31.4, 38.9, 40.3, 51.2, 52.9, 57.2, 60.8, 64.4, 78.6, 80.8, 174.2, 201.2; HRMS (ESI-TOF) calcd for $C_{20}H_{39}BrNO_5Si$ 480.1775 and 482.1755 $[M+MeOH+H]^+$, found 480.1726 and 482.1756.

*Enone* ***4***. *n*-BuLi (1.6 M in hexane, 36 mL, 58 mmol) was added to a solution of 6-bromo-1,4-dioxaspiro[4.4]non-6-ene (12.5 g, 61.0 mmol) in THF (80 mL) at −78 °C. The mixture was stirred at −78 °C for 45 min, and then a solution of aldehyde **11** (9.86 g, 22.0 mmol) in THF (140 mL) was added. The reaction mixture was stirred at −78 °C for 1 h, and then saturated aqueous $NH_4Cl$ (100 mL) was added. After the mixture was warmed to room temperature, THF (ca. 150 mL) was removed under reduced pressure. The resultant solution was extracted with EtOAc (30 mL ×4), and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (270 g, hexane/EtOAc 5/1 to 3/1) to afford allyl alcohol **12** as a 2:1 C8-diastereomixture, which was used in the next reaction without further purification.

$SO_3$·pyridine complex (7.0 g, 44 mmol) was added to a solution of the above allyl alcohol **12** and $Et_3N$ (10 mL, 72 mmol) in DMSO (146 mL) at room temperature. The reaction mixture was stirred at room temperature for 23 h, and then $Et_3N$ (10 mL, 72 mmol) and $SO_3$·pyridine complex (7.0 g, 44 mmol) were added. After 7.5 h, $Et_3N$ (10 mL, 72 mmol) and $SO_3$·pyridine complex (7.0 g, 44 mmol) were added. The reaction mixture was stirred for 18 h, and then $H_2O$ (800 mL) and saturated aqueous $NaHCO_3$ (50 mL) were added. The resultant mixture was extracted with EtOAc (100 mL ×4), and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (270 g, hexane/EtOAc 10/1 to 3/1) to afford enone **4** (7.00 g, 12.2 mmol) in 55% yield over 2 steps: yellow solid; mp 77.0−79.0 °C; IR (film) $\nu$ 2969, 2901, 1711, 1683, 1443, 1251, 1209, 1137, 1048, 1016, 840 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.25 (9H, s), 1.03 (3H, t, $J$ = 7.3 Hz), 1.26 (3H, dd, $J$ = 7.3, 7.3 Hz), 1.42−1.52 (2H, m), 2.14 (2H, dd, $J$ = 6.9, 6.4 Hz), 2.15−2.20 (1H, m), 2.30−2.38 (1H, m), 2.35 (2H, q, $J$ = 7.3 Hz), 2.46−2.84 (8H, m), 2.85 (1H, dd, $J$ = 12.8, 2.8 Hz), 2.98 (1H, d, $J$ = 12.8 Hz), 3.01 (1H, dd, $J$ = 11.4, 1.8 Hz), 3.30 (1H, d, $J$ = 11.4 Hz), 3.92−3.98 (2H, m), 4.01 (1H, dq, $J$ = 11.0, 7.3 Hz), 4.20−4.27 (2H, m), 4.22 (1H, dq, $J$ = 11.0, 7.3 Hz), 6.95 (1H, dd, $J$ = 2.8, 2.8 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 3.1 (3C), 12.5, 14.2, 23.4, 28.1, 28.4, 31.6, 34.8, 36.9, 40.4, 51.2, 53.1, 57.2, 60.6, 64.3, 65.8 (2C), 78.6, 81.0, 118.3, 143.4, 148.7, 174.3, 196.3; HRMS (ESI-TOF) calcd for $C_{26}H_{42}BrNO_6SiNa$ 594.1857 and 596.1837 $[M + Na]^+$, found 594.1849 and 596.1832.

*Tetracyclic compound* ***3b***. A solution of enone **4** (7.00 g, 12.2 mmol) and V-70 (**E**, 3.76 g, 12.2 mmol) in benzene (610 mL) was degassed by freeze−thaw procedure (×3). *n*-$Bu_3SnH$ (6.5 mL, 24 mmol) was added, and then the reaction mixture was stirred at room temperature for 4.5 h. After concentration of the mixture, the resultant residue was purified by flash column chromatography three times [a column consecutively packed with silica gel 200 g and 10% (w/w) KF contained silica gel 50 g, hexane to hexane/EtOAc 3/1 to $CHCl_3$/MeOH 10/1 for the first purification; a column packed with silica gel 100 g and 10% (w/w) KF contained silica gel 25 g, hexane/EtOAc 5/1 to 1/1 to $CHCl_3$/MeOH 10/1 for the second; a column packed with silica gel 50 g and 10% (w/w) KF contained silica gel 15 g, hexane to hexane/EtOAc 10/1 to 3/1 for the third] to afford alcohol **3b** (337 mg, 0.682 mmol) in 6% yield and the crude enone **3c**. The crude **3c** was used in the next reaction without further purification. For a characterization of **3c**, a small amount of the crude **3c** was purified by flash column chromatography. Enone **3c**: white amorphous; IR (film) $\nu$ 3393, 2952, 1721, 1661, 1577, 1248, 1234, 1150, 1094, 1016, 840 $cm^{-1}$; $^1H$ NMR (400 MHz, $C_6D_6$) $\delta$ 0.36 (9H, s), 0.92 (6H, dd, $J$ = 7.3, 7.3 Hz), 1.30−1.42 (2H, m), 1.48 (1H, dd, $J$ = 12.8, 6.4 Hz), 1.52−1.67 (3H, m), 1.75−1.90 (3H, m), 1.92−2.00 (1H, m), 2.02−2.11 (2H, m), 2.17 (1H, dd, $J$ = 11.9, 1.4 Hz), 2.28 (1H, dd, $J$ = 12.4, 6.9 Hz), 2.45 (1H, dd, $J$ = 15.1, 13.7 Hz), 2.58 (1H, d, $J$ = 11.4 Hz),


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2.73−2.96 (2H, m), 2.75 (1H, d, $J$ = 12.4 Hz), 2.84 (1H, dd, $J$ = 13.7, 12.4 Hz), 3.00 (1H, d, $J$ = 12.4 Hz), 3.41 (1H, dd, $J$ = 8.7, 8.2 Hz), 3.51−3.61 (4H, m), 3.79 (1H, dq, $J$ = 11.0, 7.3 Hz), 3.96 (1H, dq, $J$ = 11.0, 7.3 Hz); $^{13}$C NMR (100 MHz, $C_6D_6$) $\delta$ 2.9 (3C), 12.9, 14.2, 20.9, 21.9, 28.7, 29.5, 31.3, 32.4, 40.3, 45.2, 45.4, 52.5, 52.9, 56.2, 58.5, 60.3, 61.0, 72.0, 81.4, 118.9, 166.8, 174.5, 198.1; HRMS (ESI-TOF) calcd for $C_{26}H_{44}NO_6Si$ $[M + H]^+$ 494.2932, found 494.2922.

NaH (60% in mineral oil, 910 mg, 22.8 mmol) was added to a solution of the above crude **3c** in THF (110 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min, and then saturated aqueous $NH_4Cl$ (100 mL) and saturated aqueous $NaHCO_3$ (100 mL) were successively added. The resultant mixture was extracted with EtOAc (30 mL ×4), and the combined organic layers were dried over $Na_2SO_4$ and concentrated. The residue was purified by flash column chromatography [a column consecutively packed with silica gel 180 g and 10% (w/w) KF contained silica gel 90 g, hexane/EtOAc 10/1 to 5/1] to afford **3b** (4.40 g, 8.91 mmol) in 73% yield. The overall yield of **3b** from **4** was calculated to be 79% over 2 steps. **3b**: white solid; mp 97.5−99.5 °C; IR (film) $\nu$ 2972, 2943, 2900, 1716, 1708, 1250, 1231, 1153, 1128, 1092, 1043, 1023 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.23 (9H, s), 0.99 (3H, t, $J$ = 7.4 Hz), 1.23−1.34 (1H, m), 1.25 (3H, dd, $J$ = 7.3, 7.3 Hz), 1.37−1.52 (3H, m), 1.65 (1H, dd, $J$ = 16.0, 7.8 Hz), 1.70−1.95 (5H, m), 2.13 (1H, dd, $J$ = 11.9, 7.8 Hz), 2.15−2.25 (3H, m), 2.40 (1H, d, $J$ = 14.2 Hz), 2.52−2.69 (3H, m), 2.60 (1H, dd, $J$ = 12.4, 2.8 Hz), 2.75 (1H, ddd, $J$ = 14.2, 13.7, 1.9 Hz), 2.90 (1H, dd, $J$ = 12.4, 2.2 Hz), 3.04 (1H, dd, $J$ = 13.3, 11.9 Hz), 3.68−3.75 (1H, m), 3.79−3.84 (2H, m), 3.92−3.98 (1H, m), 4.01 (1H, dq, $J$ = 11.0, 7.3 Hz), 4.21 (1H, dq, $J$ = 11.0, 7.3 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 2.4 (3C), 12.6, 14.2, 20.0, 23.5, 29.1, 31.3, 31.9, 36.8, 39.5, 42.1, 42.5, 52.0, 52.2, 56.1, 58.3, 60.3, 60.7, 64.7, 65.0, 80.0, 118.2, 174.4, 212.7; HRMS (ESI-TOF) calcd for $C_{26}H_{44}NO_6Si$ $[M + H]^+$ 494.2932, found 494.2909.

*Allyl alcohol* ***13***. A solution of enone **4** (97 mg, 0.17 mmol) and V-70 (**E**, 52 mg, 0.17 mmol) in benzene (8.5 mL) was degassed by freeze−thaw procedure (×3). $n$-$Bu_3SnH$ (90 $\mu$L, 0.33 mmol) was added, and then the reaction mixture was stirred at room temperature for 5 h. After concentration of the mixture, the resultant residue was dissolved in THF (1.7 mL). The solution was cooled to −78 °C, and allylmagnesium bromide (**D**, 1.0 M in $Et_2O$, 0.85 mL, 0.85 mmol) was added. The reaction mixture was stirred at −78 °C for 10 min, and then saturated aqueous $NH_4Cl$ (2 mL) and saturated aqueous KF (1 mL) were successively added. The mixture was warmed to room temperature, stirred for 17 h and extracted with EtOAc (3 mL ×4). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (10 g, hexane/EtOAc 10/1 to 3/1) to afford allyl alcohol **13** (73.0 mg, 0.136 mmol) in 81% yield: yellow solid; mp 99.0−103.0 °C; IR (film) $\nu$ 3497, 2952, 2857, 1720, 1248, 1151, 1118, 1080, 1022, 866, 838 cm$^{-1}$; $^1$H NMR (400 MHz, $C_6D_6$) $\delta$ 0.47 (9H, s), 0.97 (3H, dd, $J$ = 6.9, 6.9 Hz), 1.08 (3H, t, $J$ = 7.3 Hz), 1.32 (1H, ddd, $J$ = 12.8, 10.5, 8.2 Hz), 1.45 (1H, ddd, $J$ = 12.8, 8.2, 4.6 Hz), 1.57−1.83 (8H, m), 1.99 (1H, dd, $J$ = 14.2, 13.2 Hz), 2.37−2.47 (2H, m), 2.60 (1H, d, $J$ = 11.4 Hz), 2.66 (1H, dd, $J$ = 13.3, 6.9 Hz), 2.75 (1H, ddd, $J$ = 11.4, 8.2, 8.2 Hz), 2.86−2.95 (2H, m), 2.90 (1H, d, $J$ = 11.4 Hz), 2.97−3.07 (1H, m), 3.11−3.23 (4H, m), 3.28−3.37 (3H, m), 3.46 (1H, dd, $J$ = 11.4, 2.3 Hz), 3.86 (1H, dq, $J$ = 11.0, 6.9 Hz), 4.08 (1H, dq, $J$ = 11.0, 6.9 Hz), 4.76 (1H, s), 5.17 (1H, dd, $J$ = 10.1, 2.3 Hz), 5.24 (1H, dd, $J$ = 17.4, 2.3 Hz), 6.10−6.20 (1H, m); $^{13}$C NMR (100 MHz, $C_6D_6$) $\delta$ 3.0 (3C), 13.1, 14.3, 21.9, 24.3, 28.2, 32.6, 34.7, 35.8, 36.4, 43.6, 47.1, 50.0, 51.5, 52.9, 53.4, 55.8, 59.0, 60.1, 63.0, 63.5, 74.1, 82.3, 117.9, 119.8, 136.4, 175.2; HRMS (ESI-TOF) calcd for $C_{29}H_{50}NO_6Si$ $[M + H]^+$ 536.3402, found 536.3390.

*Carbamate* ***15***. $Hg(OAc)_2$ (3.55 g, 11.1 mmol) was added to a solution of **3b** (2.75 g, 5.57 mmol) in a mixture of 1,4-dioxane (56 mL) and $H_2O$ (22 mL) at room temperature. The reaction mixture was warmed to 60 °C and stirred for 13 h. After the mixture was cooled to room temperature, saturated aqueous $Na_2S_2O_3$ (30 mL) and Celite (2 g) were added. The suspension was stirred for 3 h, and filtered through a pad of Celite with $CHCl_3$. Saturated aqueous $NaHCO_3$ (50 mL) was added, and the resultant solution was extracted with a 2:1 mixture of $CHCl_3$ and EtOH (50 mL ×3). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (80 g, hexane/EtOAc 5/1 to EtOAc to $CHCl_3$/MeOH 10/1) to afford the crude amine **14** and the unreacted **3b** (1.25 g, 1.18 mmol). The recovered **3b** was subjected to the above procedure to convert into amine **14** by using $Hg(OAc)_2$ (1.61 g, 5.05 mmol) in 1,4-dioxane (25 mL) and $H_2O$ (10 mL). The crude **14** was combined and used in the next reaction without further purification.

$ClCO_2Me$ (0.71 mL, 9.2 mmol) was added to the above crude amine **14** and $Et_3N$ (2.6 mL, 19 mmol) in $CH_2Cl_2$ (46 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, and then $H_2O$ (50 mL) was added. The resultant solution was extracted with EtOAc (20 mL ×3), and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (40 g, hexane/EtOAc 10/1 to 1/1) to afford carbamate **15** (1.34 g, 2.56 mmol) in 46% yield over 2 steps. Carbamate **15** exists as a 1:1 mixture of the rotamers in $C_6D_6$: colorless amorphous; IR (film) $\nu$ 2953, 2875, 1703, 1456, 1279, 1128, 1108, 862, 840 cm$^{-1}$; $^1$H NMR (400 MHz, $C_6D_6$) $\delta$ 0.32 (9H, s), 0.86 (3H, m), 0.94−1.03 (1H, m), 1.20−1.50 (3H, m), 1.51−1.88 (6H, m), 1.96 (1H, dd, $J$ = 14.6, 14.2 Hz), 2.25 (1H, dd, $J$ = 12.4, 6.9 Hz), 2.47−2.63 (2H, m), 2.48 (1H, d, $J$ = 13.8 Hz), 2.82 (1H, ddd, $J$ = 13.7, 13.7, 6.0 Hz), 3.15 (1H, dd, $J$ = 12.4, 12.4 Hz), 3.17 (1H x1/2, d, $J$ = 14.6 Hz), 3.21 (1H x1/2, d, $J$ = 14.6 Hz), 3.31−3.37 (1H, m), 3.40−3.47 (2H, m), 3.52 (3H x1/2, s), 3.53 (3H x1/2, s), 3.72 (1H, dq, $J$ = 11.0, 7.3 Hz), 3.73 (1H x1/2, d, $J$ = 13.8 Hz), 3.80−3.92 (2H, m), 4.11 (1H x1/2, d, $J$ = 14.6 Hz), 4.20 (1H x1/2, d, $J$ = 13.8 Hz), 4.52 (1H x1/2, d, $J$ = 14.6 Hz); $^{13}$C NMR (100 MHz, $C_6D_6$) $\delta$ 2.6 (3C), 14.1 (1C), 19.4 (1C), 23.5 (1C), 23.7 (1C), 28.9 (1C), 31.3 (1C), 31.4 (1C), 37.2 (1C x1/2), 37.4 (1C x1/2), 40.0 (1C), 42.2 (1C), 46.6 (1C), 48.3 (1C), 51.1 (1C), 52.5 (1C), 60.6 (1C), 61.2 (1C), 65.0 (1C), 65.5 (1C), 80.2 (1C), 118.8 (1C x1/2), 118.9 (1C x1/2), 155.2 (1C), 173.4 (1C), 210.1 (1C); HRMS (ESI-TOF) calcd for $C_{26}H_{41}NO_8SiNa$ $[M + Na]^+$ 546.2494, found 546.2497.

*Alkyne* ***16***. EtMgBr (3.0 M in $Et_2O$, 2.4 mL, 7.2 mmol) was added to a solution of TIPS-acetylene (1.7 mL, 7.6 mmol) in THF (7 mL). The mixture was warmed to 60 °C and stirred for 30 min. After being cooled to room temperature, the mixture was added to a solution of carbamate **15** (1.34 g, 2.56 mmol) in THF (19 mL) at room temperature. The reaction mixture was stirred at room temperature for 15 min. After the mixture was cooled to 0 °C, saturated aqueous $NH_4Cl$ (40 mL) was added. The resultant solution was extracted with EtOAc (10 mL ×3), and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (20 g, hexane/EtOAc 20/1 to 5/1) to afford alkyne **16** (1.78 g, 2.52 mmol) in 98% yield. Alkyne **16** exists as a 1:1 mixture of the rotamers in $C_6D_6$: yellow amorphous; IR (film) $\nu$ 3525, 2943, 2865, 2158, 1730, 1708, 1473, 1456, 1250, 1191, 1175, 1141, 1043, 864, 842 cm$^{-1}$; $^1$H NMR (400 MHz, $C_6D_6$) $\delta$ 0.35 (9H, s), 0.87 (3H, m), 0.97−1.05 (3H, m), 1.08 (18H, d, $J$ = 6.8 Hz), 1.24−1.95 (10H, m), 2.23 (1H, dd, $J$ = 15.6, 11.4 Hz), 2.42−2.47 (2H, m), 2.52−2.60 (2H, m), 2.76 (1H, m), 3.20 (1H x1/2, d, $J$ = 13.7 Hz), 3.24 (1H x1/2, d, $J$ = 13.7 Hz), 3.36 (1H, d, $J$ = 13.3 Hz), 3.41−3.49 (5H, m), 3.64−3.69 (1H, m), 3.77−3.83 (1H, m), 3.89−3.98 (2H, m), 4.08 (1H x1/2, br d, $J$ = 13.7 Hz), 4.18 (1H x1/2, br d, $J$ = 13.3 Hz), 4.33 (1H, br s), 4.43 (1H x1/2, br d, $J$ = 13.7 Hz), 4.62 (1H x1/2, br d, $J$ = 13.3 Hz); $^{13}$C NMR (100 MHz, $C_6D_6$) $\delta$ 2.9 (3C), 11.7 (3C), 14.1 (1C), 18.9 (6C), 19.1 (1C), 23.8 (1C), 26.4 (1C), 30.8 (1C), 31.5 (1C), 37.6 (1C), 38.8 (1C), 41.6 (1C), 42.4 (1C), 46.7 (1C), 48.8 (1C), 52.1 (1C), 52.4 (1C), 55.7 (1C), 60.5 (1C), 63.5 (1C), 65.4 (1C), 70.7 (1C), 81.3 (1C), 81.7 (1C), 116.5 (1C), 118.3 (1C), 155.2 (1C), 173.4 (1C); HRMS (ESI-TOF) calcd for $C_{37}H_{63}NO_8Si_2Na$ $[M + Na]^+$ 728.3984, found 728.3967.

*Enyne* ***18***. $p$-$tolSO_3H{\cdot}H_2O$ (370 mg, 1.95 mmol) was added to a solution of alkyne **16** (1.39 g. 1.97 mmol) in acetone (20 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 h, and then saturated aqueous $NaHCO_3$ (30 mL) was added. The resultant solution was extracted with EtOAc (10 mL ×3), and the combined organic layers were dried over $Na_2SO_4$, filtered and


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concentrated to afford the crude ketone **17**, which was used in the next reaction without further purification.

DBU (0.75 mL, 5.0 mmol) was added to a solution of the above crude ketone **17** in THF (28 mL) at room temperature. The reaction mixture was heated to 60 °C and stirred for 16 h. After the mixture was cooled to room temperature, saturated aqueous $NH_4Cl$ (30 mL) was added. The resultant solution was extracted with EtOAc (10 mL ×3), and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (40 g, hexane/EtOAc 10/1 to 5/1) to afford enyne **18** (1.27 g, 1.97 mmol) in 100% yield over 2 steps. Enyne **18** exists as a 1:1 mixture of the rotamers in $C_6D_6$: green amorphous; IR (film) $\nu$ 2946, 2865, 2135, 1709, 1602, 1455, 1254, 1184, 1121, 1024 $cm^{-1}$; $^1H$ NMR (400 MHz, $C_6D_6$) $\delta$ 0.25 (9H x1/2, s), 0.26 (9H x1/2, s), 0.82 (3H x1/2, dd, $J$ = 7.3, 7.3 Hz), 0.84 (3H x1/2, dd, $J$ = 7.3, 7.3 Hz), 1.21−1.87 (12H, m), 1.32 (18H, m), 1.90−1.99 (1H, m), 2.06−2.15 (1H, m), 2.50 (1H, dd, $J$ = 15.1, 6.0 Hz), 2.53−2.65 (2H, m), 2.90 (1H, dd, $J$ = 15.1, 13.7 Hz), 3.10 (1H x1/2, d, $J$ = 15.1 Hz), 3.16 (1H x1/2, d, $J$ = 14.6 Hz), 3.18−3.25 (1H, m), 3.50 (3H, s), 3.59 (1H x1/2, d, $J$ = 13.7 Hz), 3.73 (1H, dq, $J$ = 11.0, 7.3 Hz), 3.79−3.90 (1H, m), 4.04 (1H x1/2, d, $J$ = 13.3 Hz), 4.05 (1H x1/2, d, $J$ = 15.1 Hz), 4.47 (1H x1/2, d, $J$ = 14.6 Hz); $^{13}C$ NMR (100 MHz, $C_6D_6$) $\delta$ 3.0 (3C), 11.9 (3C), 14.1 (1C), 19.01 (3C), 19.04 (3C), 19.6 (1C), 20.3 (1C x1/2), 20.4 (1C x1/2), 28.27 (1C x1/2), 28.35 (1C x1/2), 30.0 (1C x1/2), 30.1 (1C x1/2), 31.4 (1C x1/2), 31.5 (1C x1/2), 32.7 (1C), 37.6 (1C), 43.6 (1C x1/2), 43.7 (1C x1/2), 43.8 (1C x1/2), 43.9 (1C x1/2), 46.1 (1C x1/2), 46.2 (1C x1/2), 48.19, (1C x1/2), 48.25 (1C x1/2), 51.76 (1C x1/2). 51.83 (1C x1/2), 52.5 (1C), 60.6 (1C), 81.7 (1C x1/2), 81.8 (1C x1/2), 102.3 (1C x1/2), 102.5 (1C x1/2), 107.9 (1C x1/2), 108.0 (1C x1/2), 128.6 (1C x1/2), 129.0 (1C x1/2), 146.7 (1C x1/2), 147.0 (1C x1/2), 155.2 (1C), 173.3 (1C), 200.8 (1C x1/2), 200.9 (1C x1/2); HRMS (ESI-TOF) calcd for $C_{35}H_{57}NO_6Si_2Na$ $[M + Na]^+$ 666.3617, found 666.3613.

*Diol* ***20***. $OsO_4$ (0.16 M in $H_2O$, 27 mL, 4.3 mmol) was added to a solution of enyne **18** (939 mg, 1.46 mmol) in 1,4-dioxane (15 mL) and pyridine (7.3 mL) at room temperature. The reaction mixture was stirred at room temperature for 20 min. After the mixture was cooled to 0 °C, saturated aqueous $NaHSO_3$ (50 mL) was added. The mixture was warmed to room temperature and stirred for 2 h, and then solid NaCl was added. The resultant solution was extracted with EtOAc (20 mL ×8), and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (40 g, hexane/EtOAc 5/1 to 1/10) to afford the crude **19**, which was used in the next reaction without further purification. Compound **19** exists as a 3:2 mixture of the rotamers in $CDCl_3$: brown amorphous; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.25 (9H, s), 0.95−1.10 (21H, m), 1.24 (3H x 3/5, dd, $J$ = 7.3, 7.3 Hz), 1.26 (3H x2/5, dd, $J$ = 7.3, 7.3 Hz), 1.47−1.87 (7H, m), 2.03−2.17 (2H, m), 2.19−2.34 (1H, m), 2.37−2.48 (1H, m), 2.53−2.64 (1H, m), 2.88 (1H, dd, $J$ = 13.7, 13.2 Hz), 3.00−3.04 (1H, m), 3.06 (1H, dd, $J$ = 14.6, 13.7 Hz), 3.65 (3H x3/5, s), 3.66 (3H x2/5, s), 3.75 (1H x3/5, dd, $J$ = 14.6, 2.3 Hz), 3.80 (1H x2/5, dd, $J$ = 14.6, 2.3 Hz), 3.87 (1H x3/5, d, $J$ = 13.3 Hz), 3.97−4.04 (1H, m), 4.04 (1H x2/5, br d, $J$ = 14.6 Hz), 4.09 (1H x2/5, d, $J$ = 14.2 Hz), 4.12 (1H x2/5, d, $J$ = 14.2 Hz), 4.23 (1H x3/5, br d, $J$ = 14.6 Hz), 4.25 (1H x3/5, br d, $J$ = 13.3 Hz), 4.25−4.33 (1H, m), 7.41 (4H, dd, $J$ = 6.9, 6.4 Hz), 7.89 (2H, br s), 8.73 (4H, br s); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 2.3 (3C), 11.4 (3C), 14.11 (1C x3/5), 14.13 (1C x2/5), 18.52 (3C x2/5), 18.57 (3C x2/5), 18.60 (6C x3/5), 19.7 (1C), 19.8 (1C x3/5), 19.9 (1C x2/5), 30.2 (1C x3/5), 30.3 (1C x2/5), 30.6 (1C x3/5), 30.7 (1C x2/5), 32.8 (1C x2/5), 32.9 (1C x3/5), 33.19 (1C x2/5), 33.25 (1C x3/5), 34.8 (1C), 46.5 (1C x3/5), 46.6 (1C x2/5), 47.2 (1C x2/5), 47.3 (1C x3/5), 48.0 (1C), 50.4 (1C x3/5), 50.7 (1C x2/5), 51.8 (1C x3/5), 51.9 (1C x2/5), 52.6 (1C), 60.49 (1C x3/5), 60.52 (1C x2/5), 80.5 (1C x3/5), 80.6 (1C x2/5), 88.5 (1C x3/5), 88.7 (1C x2/5), 90.6 (1C), 100.3 (1C x3/5), 100.4 (1C x2/5), 107.69 (1C x2/5), 107.74 (1C x3/5), 125.1 (2C), 140.3 (1C x3/5), 141.0 (1C x2/5), 149.1 (2C), 155.2 (1C x2/5), 155.4 (1C x3/5), 173.8 (1C x3/5), 174.0 (1C x2/5), 207.3 (1C x2/5), 207.4 (1C x3/5).

A solution of $NaHSO_3$ (1.01 g 9.71 mmol) in pH 7 phosphate buffer (9.7 mL) was added to a solution of the above crude **19** in THF (9.7 mL) at room temperature. The reaction mixture was stirred at room temperature for 26 h, and then $H_2O$ (50 mL) was added. The resultant solution was extracted with EtOAc (20 mL ×3), and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (40 g, hexane/EtOAc 10/1 to 3/1) to afford diol **20** (542 mg, 0.799 mmol) in 55% yield over 2 steps. Diol **20** exists as a 3:2 mixture of the rotamers in $C_6D_6$: white amorphous; IR (film) $\nu$ 3447, 2945, 2866, 2280, 2162, 1731, 1705, 1456, 1257, 1177, 868, 840 $cm^{-1}$; $^1H$ NMR (400 MHz, $C_6D_6$) $\delta$ 0.37 (9H x3/5, s), 0.38 (9H x2/5, s), 0.85 (3H x2/5, dd, $J$ = 7.3, 7.3 Hz), 0.88 (3H x3/5, dd, $J$ = 7.3, 7.3 Hz), 0.93−1.12 (21H, m), 1.40−1.49 (1H, m), 1.53−1.62 (1H, m), 1.64−1.94 (7H, m), 1.98−2.24 (2H, m), 2.55−2.69 (3H, m), 2.83−2.92 (1H, m), 3.51 (3H x3/5, s), 3.57 (3H x2/5, s), 3.69−3.80 (1H, m), 3.84−3.96 (2H, m), 3.84−3.96 (1H x2/5, m), 4.19 (1H x3/5, s), 4.20 (1H x2/5, s), 4.26 (1H x3/5, d, $J$ = 13.7 Hz), 4.35 (2H x3/5, d, $J$ = 13.7 Hz), 4.40 (1H x2/5, dd, $J$ = 13.7, 2.3 Hz), 4.44 (1H x2/5, s), 4.47 (1H x3/5, s), 4.69 (1H x2/5, d, $J$ = 14.7 Hz); $^{13}C$ NMR (100 MHz, $C_6D_6$) $\delta$ 3.1 (3C x3/5), 3.2 (3C x2/5), 11.5 (3C), 14.0 (1C x2/5), 14.1 (1C x3/5), 18.67 (3C x2/5), 18.72 (3C x2/5), 18.8 (3C), 20.3 (1C), 21.1 (1C x2/5), 21.2 (1C x3/5), 30.4 (1C x2/5), 30.5 (1C x3/5), 31.57 (1C x3/5), 31.60 (1C x2/5), 31.7 (1C x2/5), 31.8 (1C x3/5), 34.8 (1C x3/5), 35.0 (1C x2/5), 36.7 (1C x2/5), 36.9 (1C x3/5), 47.1 (1C x2/5), 47.2 (1C x3/5), 47.8 (1C), 48.8 (1C x3/5), 48.9 (1C x2/5), 51.75 (1C x2/5), 51.83 (1C x3/5), 52.2 (1C x2/5), 52.3 (1C x3/5), 52.6 (1C), 60.7 (1C), 73.6 (1C x2/5), 73.7 (1C x3/5), 80.9 (1C x2/5), 81.0 (1C x3/5), 82.1 (1C x2/5), 82.2 (1C x3/5), 92.7 (1C x2/5), 92.8 (1C x3/5), 109.7 (1C x3/5), 109.8 (1C x2/5), 155.5 (1C x2/5), 155.6 (1C x3/5), 173.6 (1C x2/5), 173.7 (1C x3/5), 218.2 (1C x2/5), 218.7 (1C x3/5); HRMS (ESI-TOF) calcd for $C_{35}H_{59}NO_8Si_2Na$ $[M + Na]^+$ 700.3671, found 700.3654.

*Triol* ***2***. A solution of TAS-F (337 mg, 1.22 mmol) and $H_2O$ (44 $\mu$L, 2.4 mmol) in DMF (4.8 mL) was added to a solution of diol **20** (328 mg, 0.484 mmol) in DMF (4.8 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min, and then saturated aqueous $NH_4Cl$ (30 mL) and EtOAc were successively added. The mixture was warmed to room temperature and stirred for 1 h, and then solid NaCl was added. The resultant solution was extracted with EtOAc (6 mL ×5), and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (30 g, hexane/EtOAc 1/1 to 1/5) to afford triol **2** (184 mg, 0.409 mmol) in 85% yield. Triol **2** exists as a 1:1 mixture of the rotamers in $CDCl_3$: white solid; mp 177.5−179.0 °C; IR (film) $\nu$ 3371, 3301, 2958, 2935, 2250, 2102, 1736, 1693, 1452, 1273, 1185, 1041, 915, 731 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.27 (3H x1/2, dd, $J$ = 7.8, 7.8 Hz), 1.29 (3H x1/2, dd, $J$ = 7.8, 7.8 Hz), 1.42−1.48 (1H, m), 1.49−1.56 (1H, m), 1.70−1.83 (4H, m), 1.94−2.03 (1H, m), 2.09−2.57 (8H, m), 2.60 (1H x1/2, s), 2.61 (1H x1/2, s), 3.39 (1H x1/2, d, $J$ = 15.1 Hz), 3.43 (1H x1/2, d, $J$ = 14.2 Hz), 3.72 (3H x1/2, s), 3.73 (3H x1/2, s), 3.77 (1H x1/2, d, $J$ = 13.8 Hz), 3.80 (1H x1/2, d, $J$ = 14.2 Hz), 3.84 (1H x1/2, d, $J$ = 14.2 Hz), 3.94 (1H x1/2, d, $J$ = 13.8 Hz), 4.11 (1H x1/2, d, $J$ = 14.2 Hz), 4.19−4.28 (2H, m), 4.26 (1H x1/2, d, $J$ = 15.1 Hz), 4.42 (1H, br s), 5.41 (1H x1/2, s), 5.51 (1H x1/2, s), 5.78 (1H x1/2, s), 5.84 (1H x1/2, s); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 13.96 (1C x1/2), 14.00 (1C x1/2), 20.0 (1C), 20.6 (1C), 29.7 (1C), 32.16 (1C x1/2), 32.23 (1C x1/2), 32.5 (1C), 36.0 (1C x1/2), 36.1 (1C x1/2), 38.2 (1C x1/2), 38.3 (1C x1/2), 42.0 (1C), 46.4 (1C x1/2), 46.6 (1C x1/2), 49.6 (1C x1/2), 49.9 (1C x1/2), 50.1 (1C x1/2), 50.3 (1C x1/2), 52.96 (1C x1/2), 53.01 (1C x1/2), 58.5 (1C x1/2), 58.6 (1C x1/2), 62.0 (1C), 71.8 (1C), 75.4 (1C), 75.9 (1C x1/2), 76.1 (1C x1/2), 80.4 (1C), 84.4 (1C x1/2), 84.5 (1C x1/2), 155.9 (1C), 177.1 (1C x1/2), 177.4 (1C x1/2), 217.4 (1C x1/2), 217.7 (1C x1/2); HRMS (ESI-TOF) calcd for $C_{23}H_{31}NO_8Na$ $[M + Na]^+$ 472.1942, found 472.1941.

*TBS enol ether* ***21***. TBSOTf (74 $\mu$L, 0.32 mmol) was added to a solution of **2** (14.5 mg, 0.0323 mmol) and $Et_3N$ (90 $\mu$L, 0.64 mmol) in $CH_2Cl_2$ (0.6 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, and then pH 7 phosphate buffer was added. The resultant


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mixture was extracted with EtOAc, and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel to afford TBS enol ether **21** (15.0 mg, 0.0221 mmol) in 68% yield. TBS enol ether **21** exists as a 3:2 mixture of the rotamers in $CDCl_3$: white amorphous; IR (film) $\delta$ 3401, 3301, 2932, 2858, 1700, 1657, 1455, 1385, 1245, 1182, 1091, 1065, 1016 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.09 (3H, s), 0.10 (3H, s), 0.17 (3H, s), 0.20 (3H, s), 0.85 (9H, s), 0.92 (9H, s), 1.26 (3H x2/5, dd, $J$ = 6.9, 6.9 Hz), 1.27 (3H x3/5, dd, $J$ = 6.8, 6.8 Hz), 1.47−1.53 (2H, m), 1.57−1.75 (5H, m), 1.99−2.15 (2H, m), 2.32 (1H, dd, $J$ = 10.3, 8.6 Hz), 2.40−2.55 (5H, m), 3.52 (1H x2/5, d, $J$ = 14.3 Hz), 3.60 (1H x3/5, d, $J$ = 14.3 Hz), 3.70 (3H, s), 3.85−3.98 (2H, m), 4.08 (1H x3/5, s), 4.14−4.20 (2H, m), 4.31 (1H x2/5, s), 4.87 (1H x3/5, s), 4.92−4.94 (1H, m), 4.96 (1H x2/5, s); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ −4.7 (1C x2/5), −4.6 (1C x3/5), −3.3 (1C), −2.9 (1C x3/5), −2.8 (1C x2/5), −2.5 (1C), 14.10 (1C x2/5), 14.14 (1C x3/5), 18.2 (1C), 18.8 (1C), 20.2 (1C), 26.27 (3C), 26.29 (3C), 26.67 (1C x3/5), 26.71 (1C x2/5), 29.1 (1C x3/5), 29.3 (1C x2/5), 31.4 (1C x3/5), 31.5 (1C x2/5), 34.6 (1C x2/5), 34.7 (1C x3/5), 38.7 (1C x3/5), 38.8 (1C x2/5), 42.2 (1C x2/5), 42.3 (1C x3/5), 47.3 (1C), 50.5 (1C x2/5), 50.6 (1C), 50.9 (1C x3/5), 52.7 (1C x3/5), 52.8 (1C x2/5), 58.9 (1C x3/5), 59.2 (1C x2/5), 61.1 (1C x3/5), 61.2 (1C x2/5), 73.9 (1C x3/5), 74.1 (1C x2/5), 75.9 (1C x3/5), 76.0 (1C x2/5), 76.1 (1C x2/5), 76.4 (1C x3/5), 85.4 (1C x2/5), 85.6 (1C x3/5), 85.7 (1C x3/5), 85.8 (1C x2/5), 104.9 (1C x2/5), 105.2 (1C x3/5), 156.0 (1C), 156.1 (1C x3/5), 156.6 (1C x2/5), 175.2 (1C); HRMS (ESI-TOF) calcd for $C_{35}H_{59}NO_8Si_2Na$ 700.3671 $[M + Na]^+$, found 700.3672.

*Selenide* ***22***. A solution of PhSeCl (1.5 mg, 7.8 $\mu$mol) in $CH_2Cl_2$ (0.13 mL) was added to a solution of TBS enol ether **21** (4.5 mg, 6.6 $\mu$mol) in $CH_2Cl_2$ (0.2 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 20 min, and then a solution of PhSeCl (1.5 mg, 7.8 $\mu$mol) in $CH_2Cl_2$ (0.20 mL) was added. The reaction mixture was stirred at −78 °C for 30 min, and then isoprene (9.4 $\mu$L, 0.094 mmol) was added. After the mixture was stirred at −78 °C for 20 min, pH 7 phosphate buffer was added. The resultant solution was extracted with EtOAc, and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel to afford selenide **22** (1.9 mg, 2.6 $\mu$mol) in 39% yield. Selenide **22** exists as a 3:2 mixture of the rotamers in $CDCl_3$: white solid; mp 197−199 °C; IR (film) $\delta$ 3377, 3297, 2930, 2856, 1748, 1698, 1454, 1387, 1268, 1187, 1093, 1027, 957 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.16 (6H, s), 0.92 (9H, s), 1.25−1.31 (3H, m), 1.48−1.76 (7H, m), 2.11−2.20 (2H, m), 2.41−2.58 (5H, m), 2.78 (1H x2/5, s), 2.80 (1H x3/5, s), 3.50 (1H x2/5, d, $J$ = 13.8 Hz), 3.59 (1H x3/5, d, $J$ = 14.6 Hz), 3.68−3.80 (5H, m), 3.98 (1H x2/5, d, $J$ = 13.8 Hz), 4.05 (1H, d x3/5, $J$ = 14.6 Hz), 4.18−4.25 (2H, m), 4.74 (1H x3/5, s), 4.90 (1H x3/5, s), 4.99 (1H x2/5, s), 5.07 (1H x2/5, s), 7.28 (3H, br d, $J$ = 2.7 Hz), 7.69 (2H, br s); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ −3.0 (1C), −2.7 (1C), 14.09 (1C x2/5), 14.13 (1C x3/5), 18.2 (1C), 20.1 (1C), 25.7 (3C), 28.8 (1C x3/5), 29.0 (1C x2/5), 29.57 (1C x3/5), 29.64 (1C x2/5), 31.29 (1C x3/5), 31.34 (1C x2/5), 34.4 (1C x2/5), 34.5 (1C x3/5), 38.2 (1C x3/5), 38.3 (1C x2/5), 42.9 (1C x2/5), 43.0 (1C x3/5), 43.1 (1C x2/5), 43.3 (1C x3/5), 47.1 (1C), 49.7 (1C x2/5), 50.0 (1C x3/5), 50.5 (1C x2/5), 50.6 (1C x3/5), 52.9 (1C x3/5), 53.0 (1C x2/5), 55.3 (1C x3/5), 55.5 (1C x2/5), 61.4 (1C x3/5), 61.5 (1C x2/5), 72.9 (1C x3/5), 73.0 (1C x2/5), 74.4 (1C x3/5), 74.6 (1C x2/5), 79.0 (1C x2/5), 79.5 (1C x3/5), 83.2 (1C x2/5), 83.4 (1C x3/5), 84.6 (1C x3/5), 85.1 (1C x2/5), 127.67, 127.72, 129.1, 130.2, 130.5, 131.4, 133.7, 134.1, 155.9 (1C x2/5), 156.0 (1C x3/5), 175.2 (1C x3/5), 175.7 (1C x2/5), 210.2 (1C x2/5), 210.5 (1C x3/5); HRMS (ESI-TOF) calcd for $C_{35}H_{49}NO_8SeSiNa$ 742.2285 $[M + Na]^+$, found 742.2297.

*TBS enol ether* ***24***. 5% Pd on $CaCO_3$ treated with Pb (Lindlar's catalyst, 445 mg) was added to a solution of **2** (89.1 mg, 0.198 mmol) in a mixture of EtOAc (8.8 mL) and MeOH (0.87 mL) at room temperature. The reaction mixture was stirred at room temperature under $H_2$ atmosphere (1 atm) for 70 min, and then filtered through a pad of Celite with EtOAc. The filtrate was concentrated to afford the crude **23**, which was used in the next reaction without further purification.

TBSOTf (180 $\mu$L, 0.79 mmol) was added to a solution of the above crude **23** and $Et_3N$ (220 $\mu$L, 1.60 mmol) in $CH_2Cl_2$ (2.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2.5 h, and then pH 7 phosphate buffer (2 mL) was added. The resultant mixture was extracted with EtOAc (2 mL ×4), and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (10 g, hexane/EtOAc 20/1 to 5/1) to afford TBS enol ether **24** (85.5 mg, 0.126 mmol) in 64% yield over 2 steps. TBS enol ether **24** exists as a 3:2 mixture of the rotamers in $CDCl_3$: colorless oil; IR (film) $\nu$ 3533, 3416, 2954, 2929, 2857, 1703, 1652, 1462, 1450, 1258, 1242, 838 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ −0.01 (6H x2/5, s), 0.05 (6H x2/5, s), 0.11 (6H x3/5, s), 0.18 (6H x3/5, s), 0.84 (9H, s), 0.92 (9H, s), 1.26 (3H x2/5, dd, $J$ = 6.8, 6.8 Hz), 1.27 (3H x3/5, dd, $J$ = 6.8, 6.8 Hz), 1.44−1.71 (5H, m), 1.91−1.98 (3H, m), 2.04−2.12 (1H, m), 2.19−2.39 (3H, m), 2.59−2.72 (1H, m), 3.33 (1H x3/5, d, $J$ = 13.8 Hz), 3.35 (1H x2/5, d, $J$ = 13.2 Hz), 3.58 (1H x2/5, d, $J$ = 13.2 Hz), 3.62 (1H x2/5, d, $J$ = 14.2 Hz), 3.66 (1H x3/5, d, $J$ = 14.6 Hz), 3.69 (3H, s), 3.75 (1H x3/5, d, $J$ = 13.8 Hz), 3.86 (1H x3/5, s), 3.88 (1H x3/5, d, $J$ = 14.6 Hz), 3.94 (1H x2/5, s), 4.02 (1H x2/5, d, $J$ = 14.2 Hz), 4.12−4.26 (2H, m), 4.90 (1H, br s), 5.17 (1H, s), 5.36 (1H, d, $J$ = 11.4 Hz), 5.48 (1H, d, $J$ = 17.8 Hz), 6.09 (1H, dd, $J$ = 17.8, 11.4 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ −4.5 (2C x2/5), −3.1 (2C x3/5), −1.7 (2C), 14.2 (1C), 18.4 (1C), 18.9 (1C), 20.3 (1C), 25.3 (1C), 26.3 (3C), 26.4 (3C), 29.5 (1C), 30.1 (1C x2/5), 30.2 (1C x3/5), 31.0 (1C), 38.8 (1C x3/5), 38.9 (1C x2/5), 42.66 (1C x2/5), 42.71 (1C x3/5), 47.9 (1C x3/5), 48.0 (1C x2/5), 50.5 (1C x2/5), 50.6 (1C x3/5), 50.7 (1C x2/5), 51.0 (1C x3/5), 52.7 (1C x3/5), 52.8 (1C x2/5), 58.1 (1C), 60.9 (1C), 73.3 (1C x3/5), 73.4 (1C x2/5), 80.3 (1C), 86.8 (1C x2/5), 86.9 (1C x3/5), 104.4 (1C x2/5), 104.8 (1C x3/5), 118.5 (1C x2/5), 118.7 (1C x3/5), 137.3 (1C x3/5), 137.6 (1C x2/5), 155.9 (1C x2/5), 156.0 (1C x3/5), 156.2 (1C x3/5), 156.6 (1C x2/5), 174.20 (1C x2/5), 174.25 (1C x3/5); HRMS (ESI-TOF) calcd for $C_{35}H_{61}NO_8Si_2Na$ $[M + Na]^+$ 702.3828, found 702.3814.

*Pentacyclic compound* ***25***. A solution of PhSeCl (29.5 mg, 0.151 mmol) in $CH_2Cl_2$ (0.50 mL) was added to a solution of TBS enol ether **24** (85.5 mg, 0.126 mmol) in $CH_2Cl_2$ (3.7 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 20 min, and then a solution of PhSeCl (8.8 mg, 0.046 mmol) in $CH_2Cl_2$ (0.30 mL) was added. The reaction mixture was stirred at −78 °C for 10 min, and then isoprene (0.13 mL, 1.3 mmol) was added. After the mixture was stirred at −78 °C for 30 min, pH 7 phosphate buffer (5 mL) was added. The resultant solution was extracted with EtOAc (2 mL ×4), and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (10 g, hexane/EtOAc 10/1 to 1/2) to afford pentacyclic compound **25** (79.0 mg, 0.110 mmol) in 87% yield. Pentacyclic compound **25** exists as a 1:1 mixture of the rotamers in $CDCl_3$: yellow solid; mp 219.5−221.5 °C; IR (film) $\nu$ 3346, 2954, 2927, 2900, 2854, 2246, 1770, 1697, 1470, 1451, 1275, 1106, 1090, 836 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.22 (3H, s), 0.23 (3H, s), 0.85 (9H, s), 1.09 (1H x1/2, br d, $J$ = 16.9 Hz), 1.15 (1H x1/2, br d, $J$ = 16.9 Hz), 1.28 (3H, br t, $J$ = 7.3 Hz), 1.37−1.72 (6H, m), 1.99−2.54 (9H, m), 2.81 (1H, d, $J$ = 14.2 Hz), 3.07 (1H x1/2, d, $J$ = 13.3 Hz), 3.11 (1H x1/2, d, $J$ = 12.8 Hz), 3.39−3.46 (1H, m), 3.71 (1H x1/2, d, $J$ = 12.8 Hz), 3.75 (3H, s), 3.91 (1H x1/2, d, $J$ = 13.3 Hz), 3.98 (1H x1/2, d, $J$ = 14.2 Hz), 4.16 (1H x1/2, d, $J$ = 14.2 Hz), 4.20 (2H, m), 5.51 (1H x1/2, s), 5.63 (1H x1/2, s), 6.08 (1H x1/2, s), 6.25 (1H x1/2, s), 7.20−7.28 (3H, m), 7.61 (2H, d, $J$ = 7.3 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ −1.9 (1C), −1.1 (1C), 14.0 (1C), 18.8 (1C), 20.0 (1C), 22.5 (1C), 26.2 (3C), 28.9 (1C x1/2), 29.0 (1C x1/2), 30.9 (1C), 31.5 (1C), 39.2 (1C x1/2), 39.4 (1C x1/2), 39.8 (1C), 42.1 (1C), 42.3 (1C), 46.0 (1C x1/2), 46.1 (1C x1/2), 49.3 (1C x1/2), 49.6 (1C x1/2), 49.6 (1C), 50.4 (1C x1/2), 50.6 (1C x1/2), 51.1 (1C x1/2), 51.2 (1C x1/2), 53.0 (1C), 61.8 (1C), 75.3 (1C x1/2), 75.4 (1C x1/2), 83.9 (1C), 88.4 (1C), 127.7 (1C x1/2), 128.0 (1C x1/2), 129.2 (1C), 131.0 (1C), 134.8 (1C x1/2), 135.0 (1C x1/2), 155.5 (1C), 176.7 (1C x1/2), 177.1 (1C x1/2), 208.7 (1C x1/2), 208.8 (1C


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x1/2); HRMS (ESI-TOF) calcd for $C_{35}H_{51}NO_8SeSiNa$ $[M + Na]^+$ 744.2441, found 744.2420.

*Compound* **1**. $H_2O_2$ (30% in $H_2O$, 58 μL, 0.51 mmol) was added to a solution of pentacyclic compound **25** (36.6 mg, 0.0508 mmol) in $CH_2Cl_2$ (1.0 mL) at room temperature. The reaction mixture was stirred at room temperature for 30 min, and then saturated aqueous $Na_2S_2O_3$ (10 mL) was added. The resultant solution was extracted with a 2:1 mixture of $CHCl_3$ and EtOH (4 mL ×3), and the combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by flash column chromatography on silica gel (5 g, hexane/EtOAc 1/1 to EtOAc to $CHCl_3$/MeOH 10/1) to afford the crude selenoxide **26**, which was used in the next reaction without further purification.

A solution of the above crude selenoxide **26** in benzene (5.1 mL) was heated in a sealed tube to 100 °C, and stirred for 2 h. After being cooled to room temperature, the reaction mixture was concentrated. The residue was purified by flash column chromatography on silica gel (5 g, hexane/EtOAc 5/1 to 1/1) to afford **1** (24.3 mg, 0.0431 mmol) in 85% yield over 2 steps. Compound **1** exists as a 2:1 mixture of the rotamers in $C_6D_6$: white solid; mp 157.5−159.0 °C; IR (film) $\nu$ 3394, 2953, 2928, 2855, 1772, 1698, 1450, 1272, 1256, 1070, 1051, 1012, 840 $cm^{-1}$; $^1H$ NMR (400 MHz, $C_6D_6$) $\delta$ −0.02 (3H x2/3, s), −0.01 (3H x2/3, s), 0.03 (3H x1/3, s), 0.05 (1H x1/3, s), 0.90 (9H x2/3, s), 0.94 (9H x1/3, s), 0.96 (3H, t, $J$ = 7.3 Hz), 1.10−1.44 (5H, m), 1.51−1.54 (1H, m), 1.63−1.85 (3H, m), 1.96−2.01 (1H, m), 2.23−2.32 (2H, m), 2.37−2.47 (1H, m), 2.58−2.66 (1H x1/3, m), 2.77−2.84 (1H x2/3, m), 3.12 (1H x1/3, d, $J$ = 13.7 Hz), 3.16 (1H x2/3, d, $J$ = 13.7 Hz), 3.54 (1H x1/3, d, $J$ = 13.7 Hz), 3.55 (3H x2/3, s), 3.58 (3H x1/3, s), 3.76 (1H x1/3, d, $J$ = 13.7 Hz), 3.89 (1H x2/3, d, $J$ = 14.2 Hz), 3.91 (1H x2/3, d, $J$ = 13.7 Hz), 3.99 (2H, q, $J$ = 7.3 Hz), 4.11 (1H x2/3, d, $J$ = 14.2 Hz), 4.33 (1H x2/3, s), 4.49 (1H x1/3, d, $J$ = 13.7 Hz), 4.61 (1H x1/3, s), 4.97 (1H x2/3, s), 5.10 (1H x1/3, s), 5.13 (1H x2/3, d, $J$ = 9.2 Hz), 5.20 (1H x1/3, d, $J$ = 9.2 Hz), 5.45 (1H, dd, $J$ = 9.2, 6.4 Hz); $^{13}C$ NMR (100 MHz, $C_6D_6$) $\delta$ −2.3 (1C x2/3), −2.1 (1C x1/3), −2.0 (1C), 14.0 (1C x1/3), 14.1 (1C x2/3), 18.4 (1C x2/3), 18.5 (1C x1/3), 20.6 (1C), 25.87 (3C x1/3), 25.93 (3C x2/3), 28.3 (1C x2/3), 28.6 (1C x1/3), 31.6 (1C), 33.3 (1C), 39.9 (1C), 43.7 (1C x1/3), 44.0 (1C x2/3), 45.2 (1C), 47.3 (1C x2/3), 47.8 (1C x1/3), 48.6 (1C x1/3), 48.7 (1C x2/3), 51.1 (1C x1/3), 51.4 (1C x2/3), 52.1 (1C x1/3), 52.6 (1C x2/3), 52.7 (1C), 61.2 (1C), 74.9 (1C x2/3), 75.1 (1C x1/3), 85.2 (1C), 86.0 (1C), 131.2 (1C x2/3), 131.8 (1C x1/3), 135.4 (1C x1/3), 135.9 (1C x2/3), 155.9 (1C x1/3), 156.1 (1C x2/3), 174.9 (1C x2/3), 175.4 (1C x1/3), 205.3 (1C x1/3), 205.7 (1C x2/3), one $^{13}C$ peak was not observed; HRMS (ESI-TOF) calcd for $C_{29}H_{45}NO_8SiNa$ $[M + Na]^+$ 586.2807, found 586.2822.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01011.

NMR spectra for all new compounds, and X-ray structure and crystal data and structure refinement for compound **25** (PDF)

Crystallographic data of compound **25** (CIF)

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### Notes

The authors declare no competing financial interest.

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