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An S_N1-type Reaction To Form the 1,2-Dioxepane Ring: Synthesis of 10,12-Peroxycalamenene

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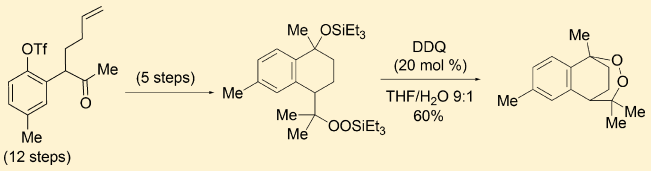
Supporting Information

ABSTRACT: The synthesis of the sesquiterpene endoperoxide natural product 10,12-peroxycalamenene has been achieved. Featured transformations include an intramolecular Heck reaction to build the fused bicyclic core and a cobalt-catalyzed peroxidation to install the peroxide functional group. The final step involved an S_N1-type ring closure catalyzed by DDQ to construct the 1,2-dioxepane ring.



INTRODUCTION

10,12-Peroxycalamenene (**1**, Figure 1) was found to be an active constituent in traditional medicines derived from the

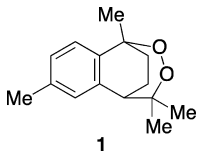


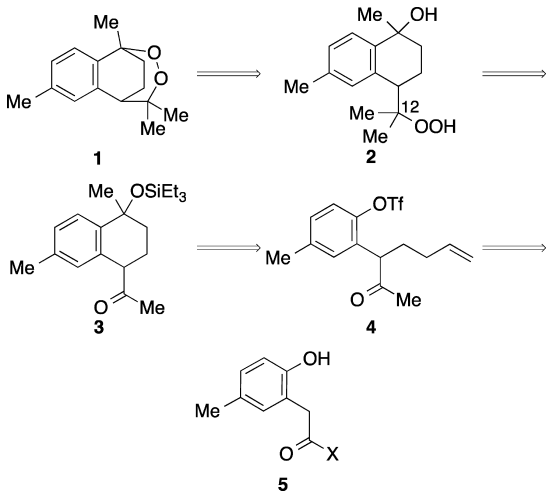
Figure 1. 10,12-Peroxycalamenene (**1**).

roots of nut-grass (*Cyperus rotundus*).[1] Extracts from this plant have been used to treat a number of ailments, including blood disorders and leprosy.[2] From 10 kg of the dried tubers of the common plant, 4.5 mg of the natural product **1** was isolated, which was found to be active against *Plasmodium falciparum* at low-micromolar concentrations (EC_{50} = 2.3 μM).[1] No synthesis of this molecule has appeared, however, likely because the seven-membered ring peroxide motif, which is present in a number of natural products with biological activity, remains a synthetic challenge.[1,3−13]

Considering the general challenges of synthesizing peroxides and in particular seven-membered ring peroxides,[14] we considered that peroxide **1** could serve as a vehicle for the discovery of methods of preparing cyclic peroxides and the isolation of larger quantities of the material. In this paper, we report the synthesis of 10,12-peroxycalamenene (**1**) by an S_N1-type ring closing reaction.

A retrosynthetic analysis of 10,12-peroxycalamenene is shown in Scheme 1. It was anticipated that an S_N1-like ring closure of hydroperoxide **2** would lead to the target **1**. The success of this step was not assured, however. Few methods for cyclizing hydroperoxides by an S_N1 mechanism have been reported, and those reactions often suffer from low yields.[5,15,16] The conditions for the planned cyclization would need to be mild, because decomposition of both cyclic and linear peroxides has been observed in some cases to proceed through an S_N1

Scheme 1. Retrosynthetic Analysis



mechanism.[17,18] In addition, the benzylic peroxide would be prone to Criegee rearrangements under acidic conditions.[19] Contingent upon the development of successful cyclization conditions, synthesis of the precursor hydroperoxide **2** could be achieved by a cobalt-catalyzed peroxidation of the alkene obtained from **3**. The fused bicyclic structure could be formed by an intramolecular Heck reaction of aryl triflate **4**.[20] The ketone **4** could be prepared by alkylation of acid derivative **5** followed by conversion of the carbonyl group to the acetyl group.

RESULTS AND DISCUSSION

The synthesis began with a Claisen rearrangement starting from *p*-cresol **6** (Scheme 2). Allylation of **6** gave allyl ether **7**, which underwent Claisen rearrangement in high yield.[21] Protection followed by oxidative cleavage of the carbon−carbon double

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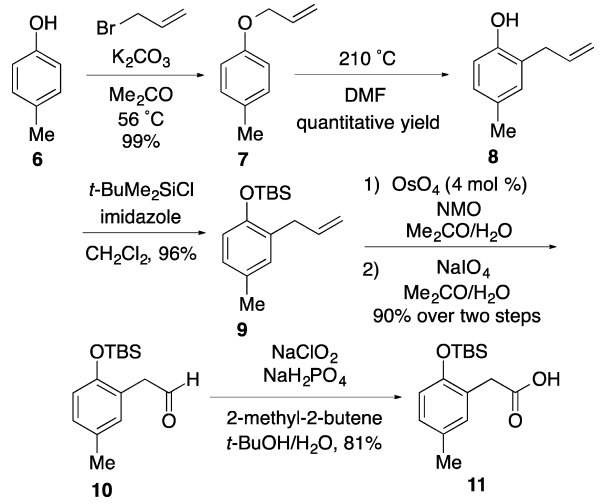
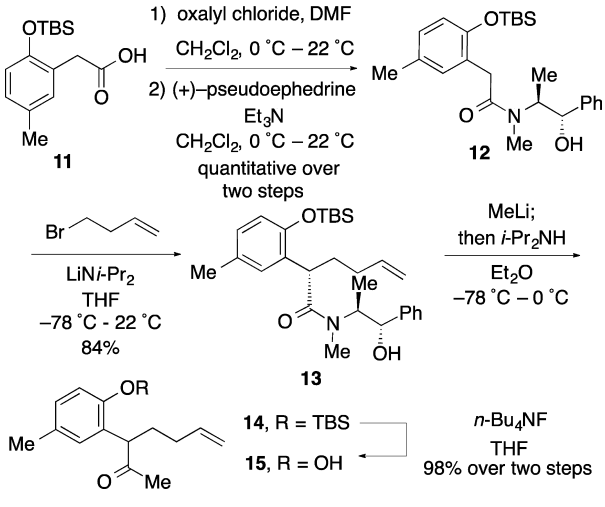
Scheme 2. Synthesis of Acid 11



bond provided the corresponding aldehyde **10**, which was oxidized to form carboxylic acid **11**.[22,23] It was anticipated that converting carboxylic acid **11** to an amide would enable alkylation of the resulting enolate, and if a chiral auxiliary were introduced, the alkylated product could be formed with control of the absolute stereochemistry.

The choice of chiral auxiliary for the alkylation was limited by the nature of the substrate. The arylacetic acid **11** would have a particularly acidic CH_2 group,[24] which would facilitate deprotonation, but the resulting alkylation product would be prone to racemization during subsequent transformations. This problem remains a challenge in synthesis. Difficulties have been encountered in forming chiral arylacetic acid derivatives using the Evans[25] oxazolidinone and the Oppolzer[26] camphorsultam in similar substrates. Our own initial studies with the oxazolidinone auxiliary were unsuccessful. Consequently, we chose the Myers pseudoephedrine auxiliary because the amide enolate is particularly nucleophilic.[27] Pseudoephedrine amide **12** was formed by generating the acid chloride of acid **11** and coupling with (+)-(1*S*,2*S*)-pseudoephedrine (Scheme 3).[27] Asymmetric alkylation of amide **12** using lithium diisopropylamide furnished alkylated amide **13** as a mixture of amide rotamers. Variable-temperature NMR spectroscopy revealed

Scheme 3. Completion of the Carbon Skeleton



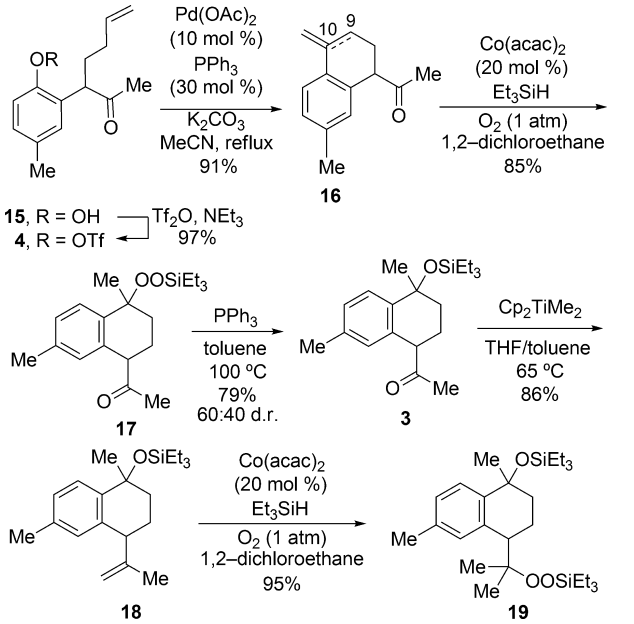
the coalescence of the two isomers, thus confirming that the reaction was diastereoselective. The configuration of amide **13** was assigned on the basis of analogy to previous studies.[27]

The removal of the pseudoephedrine auxiliary proved to be problematic. All attempts to remove the auxiliary by conversion to the corresponding methyl ketone **15** led to racemization of the product. Myers has also observed a loss of stereochemical integrity upon attempted preparation of arylacetic acid derivatives.[27]

Although we had not been able to devise an enantioselective synthesis of ketone **15**, the use of the amide auxiliary did enable us to advance the synthesis. Enolate alkylation proceeded cleanly, and the conversion of the amide **13** to the methyl ketone **15** occurred in high yield upon addition of methyllithium[27] and subsequent deprotection with tetra-*n*-butylammonium fluoride. Effort was made to develop a synthesis of ketone **15** by other routes, but these attempts were unsuccessful. Given the relatively high overall yield of ketone **15** (57% from commercially available compounds), the decision was made to complete the synthesis using the present route.

The closure of the second ring to construct the tetrahydronaphthalene core of the molecule proceeded, as planned (Scheme 1), by an intramolecular Heck reaction.[20] Phenol **15** was first converted to aryl triflate **4** and then cyclized with a palladium catalyst to provide tetrahydronaphthalene **16** (77%) and small amounts of its alkene isomer $\Delta_{9,10}$-**16** (14%, Scheme 4).[20] This isomeric mixture was of no consequence:

Scheme 4. Synthesis of Peroxide 2



both products converged to a single regioisomer of oxidized product **17** as a 60:40 mixture of diastereomers upon cobalt-catalyzed peroxidation.[28,29]

The introduction of the hydroperoxide functional group at C12 (Scheme 1) required some optimization. Initially, olefination of the silyl peroxide **17** was considered because the silylperoxy group would be suitable for the planned ring closure. The peroxide functional group, however, was too sensitive for ketone **17** to be converted to the alkene without decomposition.[30] Because the benzylic carbon did not yet need

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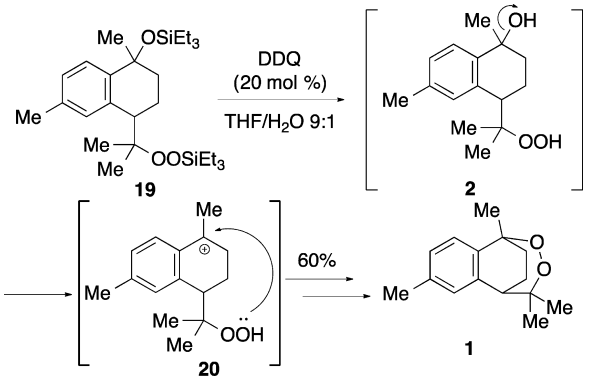
a peroxide substituent, that group was reduced with Ph_3P to provide silyl ether **3**.[31] Ketone **3** was converted to the alkene **18** using dimethyltitanocene,[32] and subsequent cobalt-catalyzed peroxidation furnished silyl peroxide **19**.[28]

The silyl peroxide **19** initially appeared to be an unsuitable synthetic intermediate. It was anticipated that this compound might undergo the desired ring closure under acidic conditions, but exposure to Brønsted acids led only to extensive decomposition. Upon treatment with tetra-*n*-butylammonium fluoride, a compound was formed that originally appeared to be the hydroperoxide **2** (Scheme 5), albeit with much decom-

Scheme 5. Peroxide Ring Closure Mechanism



position. That hydroperoxide was sensitive to standing in an NMR tube as a solution in $CDCl_3$. Acquiring an NMR spectrum of the same sample after standing for 1 day revealed the presence of a small quantity of a compound with spectroscopic characteristics similar to the target molecule, **1**. Presumably, the ring closure had been catalyzed by the small amount of acid present in $CDCl_3$.[33] Even with this success, however, it was not possible to control this cyclization with an added Brønsted acid; only decomposition was observed.

The key cyclization by an S_N1-like reaction was ultimately successful, but under conditions that were unanticipated. Upon treatment of silyl peroxide **19** with a catalytic quantity of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the presence of water, the silyl groups were removed, forming the hydroperoxide **2** (Scheme 5).[34] These conditions also initiated the intramolecular S_N1-type ring closure, forming 10,12-peroxycalamenene in 60% yield from **19**. Although we do not know the mechanistic details of this reaction, it is likely that, in an aqueous environment, DDQ acts as both a single-electron acceptor and as a weak acid.[35] These conditions likely led to the formation of a benzylic cation, which can be trapped by the hydroperoxyl group to form the seven-membered ring peroxide (Scheme 5).

CONCLUSIONS

In summary, the first synthesis of the natural product 10,12-peroxycalamenene **1** was accomplished with an overall yield of 17%. The synthesis uses an intramolecular Heck reaction to form the core structure, cobalt-catalyzed peroxidation reactions to introduce the peroxide functionalities, and a DDQ-catalyzed ring-closing reaction to complete the bicyclic seven-membered ring peroxide.

EXPERIMENTAL SECTION

General Information. ^1H NMR spectra were recorded at 400, 500, and 600 MHz on NMR spectrometers. ^{13}C NMR spectra were recorded at 100, 125, and 150 MHz using NMR spectrometers. ^1H and ^{13}C NMR data are reported as follows: chemical shifts reported in ppm on the δ scale, referenced to residual solvent (^1H NMR, $CDCl_3$, δ 7.26; ^{13}C NMR, $CDCl_3$, δ 77.23); multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad); coupling constants in Hz; and integration. Due to difficulties with purification for certain products, only distinctive peaks are listed in tabulated ^1H NMR and ^{13}C NMR spectral data, as indicated. Structures were assigned using a combination of HSQC, DEPT, and COSY experiments. ^{13}C NMR spectra were collected with broadband decoupling on the proton channel. Infrared (IR) spectra were obtained using a FT-IR spectrometer. High-resolution mass spectra (HRMS) were acquired on a time-of-flight spectrometer using either atmospheric pressure chemical ionization source (APCI) or electrospray ionization source (ES) and were obtained by peak matching. Optical rotations were obtained using a digital polarimeter. Liquid chromatography was performed using forced flow (flash chromatography) with the indicated solvent system on silica gel (SiO_2) 60 (230−400 mesh). Analytical thin-layer chromatography was performed on silica gel 60 Å F_{254} plates. Solvents used in reactions were dried and degassed using a solvent purification system before use. Aqueous solutions were prepared from nanopure water with a resistivity over 18 MΩ cm. All reactions were run under an atmosphere of nitrogen in glassware that was flame-dried under vacuum, unless otherwise stated.

Silyl Ether 9. To a solution of phenol[21] **8** (9.56 g, 64.5 mmol) and imidazole (6.59 g, 96.8 mmol) in CH_2Cl_2 (100 mL) was added a solution of *tert*-butyldimethylsilyl chloride (12.7 g, 83.9 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred for 24 h at 25 °C. Saturated aqueous $NaHCO_3$ (130 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The resulting oil was purified by flash chromatography (hexanes:EtOAc = 85:15) to afford silyl ether **9** (16.2 g, 96%) as a clear colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 6.93 (d, J = 2.1, 1H), 6.87 (dd, J = 8.1, 2.0, 1H), 6.68 (d, J = 7.8, 1H), 5.96 (ddt, J = 17.2, 10.7, 6.6, 1H), 5.02−5.06 (m, 2H), 3.33 (d, J = 6.6, 2H), 2.25 (s, 3H), 1.00 (s, 9H), 0.21 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2 (C), 137.4 (C), 130.8 (CH), 130.5 (C), 130.4 (CH), 127.6 (CH), 118.4 (CH), 115.5 (CH_2), 34.6 (CH_2), 26.0 (CH_3), 20.7 (CH_3), 18.4 (C), −4.0 (CH_3); IR (ATR) 3078, 3005, 1639, 1255 cm^{-1}; HRMS (TOF MS APCI+) m/z calcd for $C_{16}H_{27}OSi$ $(M + H)^+$ 263.1826, found 263.1827. Anal. Calcd for $C_{16}H_{26}OSi$: C, 73.22; H, 9.98. Found: C, 73.19; H, 10.16.

Aldehyde 10. To a 0 °C solution of olefin **9** (1.52 g, 5.77 mmol) in acetone (32 mL) was added NMO (50% w/w in H_2O, 4.4 mL, 19 mmol), followed by OsO_4 (4% w/w in H_2O, 2 mL, 0.3 mmol). The solution was warmed to 25 °C and stirred for 12 h. Saturated aqueous $Na_2S_2O_3$ (40 mL) was added, and the mixture was stirred for 1 h. The mixture was extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with brine (1 × 40 mL), dried over Na_2SO_4, and concentrated. The resulting crude oil was taken on without further purification: ^1H NMR (only diagnostic peaks reported, 600 MHz, $CDCl_3$) δ 6.96 (d, J = 2.0, 1H), 6.91 (dd, J = 8.2, 2.3, 1H), 6.71 (d, J = 8.2, 1H), 3.92−3.93 (m, 1H), 3.63 (dd, J = 11.3, 3.3, 1H), 3.48 (dd, J = 11.3, 6.4, 1H), 2.76 (dq, J = 13.5, 5.4, 2H), 2.26 (s, 3H), 1.01 (s, 9H), 0.23 (s, 6H); ^{13}C NMR (only diagnostic peaks reported, 150 MHz, $CDCl_3$) δ 151.6 (C), 132.2 (CH), 130.9 (C), 128.3 (C), 128.1 (CH), 118.7 (CH), 72.6 (CH), 66.4 (CH_2), 34.8 (CH_2), 26.0 (CH_3), 20.6 (CH_3), 18.4 (C), −4.0 (CH_3).

To a solution of crude diol **21** (1.71 g, 5.77 mmol) in acetone/H_2O (1:1, 40 mL) was added sodium periodate (1.48 g, 6.93 mmol). The reaction mixture was stirred at 25 °C for 15 h. Saturated aqueous $NaHCO_3$ (40 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The resulting oil was purified by flash chromatography (hexanes:EtOAc = 93:7) to afford aldehyde **10** (1.37 g, 90% over two steps) as a yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ

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9.68 (t, J = 2.2, 1H), 6.98 (dd, J = 7.8, 1.7, 1H), 6.94 (d, J = 2.2, 1H), 6.76 (d, J = 8.2, 1H), 3.59 (d, J = 2.2, 2H), 2.27 (s, 3H), 0.98 (s, 9H), 0.23 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4 (CH), 151.9 (C), 132.2 (CH), 130.8 (C), 129.3 (CH), 123.1 (C), 118.3 (CH), 45.8 (CH_2), 25.9 (CH_3), 20.6 (CH_3), 18.4 (C), −4.0 (CH_3); IR (ATR) 2819, 2717, 1727, 1269 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{15}H_{25}O_2Si$ $(M + H)^+$ 265.1618, found 265.1628.

Carboxylic Acid 11. To a 0 °C solution of aldehyde **10** (8.56 g, 32.4 mmol) in t-BuOH (81 mL) was added 2-methyl-2-butene (13.7 mL, 130 mmol). A solution of sodium chlorite (8.79 g, 97.2 mmol) and $NaH_2PO_4{\cdot}H_2O$ (13.4 g, 97.2 mmol) in H_2O (81 mL) was added to the reaction mixture. The reaction mixture was allowed to warm to 25 °C and stir for 16 h. The mixture was quenched with aqueous 1 M HCl (160 mL) and extracted with EtOAc (3 × 160 mL). The combined organic layers were washed with brine (1 × 160 mL), dried over Na_2SO_4, and concentrated. The crude mixture was purified by flash chromatography (hexanes:EtOAc with 0.5% AcOH additive = 95:5) to afford acid **11** (7.36 g, 81%) as a white solid: mp 59−60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.24 (br s, 1H), 7.26 (d, J = 2.0, 1H), 6.96 (dd, J = 8.2, 2.0, 1H), 6.71 (d, J = 8.2, 1H), 3.60 (s, 2H), 2.26 (s, 3H), 0.99 (s, 9H), 0.23 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7 (C), 151.6 (C), 132.0 (CH), 130.7 (C), 129.3 (CH), 124.3 (C), 118.3 (CH), 36.3 (CH_2), 25.9 (CH_3), 20.7 (CH_3), 18.42 (C), −4.01 (CH_3); IR (thin film) 3417, 2927, 1716, 1504, 1271, 1244 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{15}H_{24}NaO_3Si$ $(M + Na)^+$ 303.1392, found 303.1389. Anal. Calcd for $C_{15}H_{24}O_3Si$: C, 64.24; H, 8.63. Found: C, 64.33; H, 8.42.

Amide 12. To a 0 °C solution of acid **11** (1.88 g, 6.56 mmol) in CH_2Cl_2 (66 mL) was added oxalyl chloride (0.733 mL, 8.53 mmol). One drop of DMF was added. The reaction mixture was stirred for 15 min, warmed to 25 °C, and stirred for an additional 60 min. The resulting mixture was concentrated to afford crude acid chloride **22**, which was taken on immediately: ^{1}H NMR (only diagnostic peaks reported, 600 MHz, $CDCl_3$) δ 7.01 (dd, J = 8.2, 2.3, 1H), 6.96 (d, J = 2.3, 1H), 6.74 (d, J = 8.2, 1H), 4.08 (s, 2H), 2.27 (s, 3H), 1.00 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (only diagnostic peaks reported, 150 MHz, $CDCl_3$) δ 172.0, 151.9, 131.9, 130.6, 130.1, 122.7, 118.1, 48.6, 25.9, 20.6, 18.4, −4.1; IR (ATR) 1802, 1272 cm^{-1}.

To a solution of (+)-(1S, 2S)-pseudoephedrine (1.41 g, 8.53 mmol) in CH_2Cl_2 (21 mL) was added triethylamine (1.30 mL, 9.85 mmol). The mixture was cooled to 0 °C, and a solution of acid chloride **22** (1.96 g, 6.56 mmol) in CH_2Cl_2 (8.0 mL) was added. The reaction mixture was warmed to 25 °C and stirred for 16 h. H_2O (30 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude mixture was purified by flash chromatography (hexanes: EtOAc = 60:40) to afford amide **12** (2.81 g, quantitative over two steps) as a white solid: mp 113−114 °C; $[\alpha]_D^{20}$ +62.6 (MeOH, c 8.18); ^{1}H NMR (7:3 rotamer ratio, 600 MHz, $CDCl_3$) δ 7.19−7.35 (m, 5H), 7.05 (d, J = 1.6, 0.3H), 7.00 (d, J = 1.9, 0.7H), 6.93 (dd, J = 8.2, 2.4, 1H), 6.76 (d, J = 8.2, 0.3H), 6.70 (d, J = 8.2, 0.7H), 4.58 (t, J = 7.6, 0.7H), 4.47−4.52 (m, 0.7H), 4.42 (dd, J = 9.1, 3.1, 0.3H), 4.19 (br s, 1H), 3.90 (dd, J = 9.1, 6.8, 0.3H), 3.86 (d, J = 15.4, 0.3H), 3.73 (d, J = 15.4, 0.3H), 3.64 (dd, J = 19.6, 15.6, 1.4H), 2.94 (s, 0.9H), 2.76 (s, 2.1H), 2.25 (s, 2.1H), 2.23 (s, 0.9H), 1.08 (d, J = 7.0, 2.1H), 0.99 (s, 9H), 0.79 (d, J = 6.7, 0.9H), 0.22 (s, 1.8H), 0.21 (s, 4.2H); ^{13}C NMR (7:3 rotamer ratio, asterisk denotes minor rotamer peaks, 150 MHz, $CDCl_3$) δ 174.3 (C), 173.0* (C), 150.9 (C), 150.4* (C), 142.5 (C), 141.2* (C), 131.2* (C), 130.8 (C), 130.5 (CH), 130.1* (CH), 128.71 (CH), 128.65* (CH), 128.53* (CH), 128.51 (CH), 128.4* (CH), 127.8 (CH), 127.1* (CH), 126.6 (CH), 126.0* (C), 125.2 (C), 119.1* (CH), 118.4 (CH), 76.8 (CH), 75.6* (CH), 58.50* (CH), 58.47 (CH), 36.3 (CH_2), 35.9* (CH_2), 32.8 (CH_3), 26.78* (CH_3), 26.77* (C), 25.9 (C), 20.8 (CH_3), 20.7* (CH_3), 18.4 (C), 15.4* (C), 15.1* (CH_3), 14.5 (CH_3), −4.0* (CH_3), −4.1 (CH_3); IR (ATR) 3269, 2928, 1607, 1501, 1252, 904, 698, 646 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{25}H_{37}NNaO_3Si$ $(M + Na)^+$ 450.2435, found 450.2425. Anal. Calcd for $C_{25}H_{37}NO_3Si$: C, 70.21; H, 8.72. Found: C, 70.35; H, 8.62.

Alkylated Amide 13. To a −78 °C solution of diisopropylamine (1.63 mL, 11.6 mmol) in THF (6.4 mL) was added n-BuLi (2.4 M in hexanes, 4.5 mL, 11 mmol). The mixture was stirred for 30 min. A 0 °C solution of amide **12** (2.20 g, 5.14 mmol) in THF (17 mL) was added dropwise. The mixture was stirred for 30 min. The mixture was warmed to 0 °C, and 4-bromo-1-butene (1.04 mL, 10.3 mmol) was added dropwise over 5 min. The reaction mixture was warmed to 25 °C and stirred for 16 h. Saturated aqueous NH_4Cl (24 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 24 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude mixture was purified by flash chromatography (hexanes:EtOAc = 65:35) to afford alkylated amide **13** (2.09 g, 84%) as a yellow oil: $[\alpha]^{20}_D$ +73.4 (MeOH, c 0.995); ^{1}H NMR (9:1 rotamer ratio, 600 MHz, $CDCl_3$) δ 7.21−7.37 (m, 5H), 7.10 (d, J = 1.8, 0.9H), 6.93 (s, 0.1H), 6.89 (dd, J = 8.2, 2.2, 0.9H), 6.82 (d, J = 8.3, 0.1H), 6.70 (d, J = 8.2, 0.9H), 6.68−6.69 (m, 0.1H), 5.76−5.87 (m, 1H), 4.91−5.01 (m, 2H), 4.54 (br s, 0.9H), 4.41 (br s, 0.9H), 4.30−4.34 (m, 0.1H), 4.17 (dd, J = 9.1, 4.7, 0.1H), 4.08 (dd, J = 9.3, 4.6, 0.9H), 3.93−3.97 (m, 0.1H), 2.92 (s, 0.3H), 2.62 (s, 2.7H), 2.22 (s, 3H), 2.13−2.22 (m, 2H), 1.90−1.98 (m, 1H), 1.52−1.60 (m, 1H), 1.07 (s, 2.7H), 1.01 (s, 0.9H), 1.01 (s, 8.1H), 0.93 (s, 0.3H), 0.25 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.9 (C), 149.9 (C), 142.4 (C), 138.6 (CH), 131.1 (C), 129.9 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.7 (CH), 126.6 (CH), 117.6 (CH), 114.8 (CH_2), 76.4 (CH), 57.5 (CH), 41.6 (CH), 33.7 (CH_2), 32.6 (CH_2), 26.0 (CH_3), 20.7 (CH_3), 18.4 (C), 14.1 (CH_3), −3.8 (CH_3); IR (ATR) 3405, 2930, 1623, 1499, 1256 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{29}H_{43}NNaO_3Si$ $(M + Na)^+$ 504.2904, found 504.2906. Anal. Calcd for $C_{29}H_{43}NO_3Si$: C, 72.30; H, 9.00. Found: C, 72.48; H, 9.03.

Phenol 15. To a −78 °C solution of amide **13** (2.18 g, 4.53 mmol) in diethyl ether (90 mL) was added methyllithium (1.5 M in Et_2O, 7.6 mL, 11 mmol). The mixture was warmed to 0 °C and stirred for 4 h, whereupon diisopropylamine (0.640 mL, 4.50 mmol) was added. The mixture was stirred for an additional 15 min. A solution of acetic acid in Et_2O (10% v/v, 90 mL) was added, and the mixture was warmed to 25 °C. Saturated aqueous $NaHCO_3$ (200 mL) was added, and the mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The resulting crude oil was taken on without further purification: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.91 (dd, J = 8.2, 2.2, 1H), 6.85 (d, J = 2.2, 1H), 6.74 (d, J = 8.2, 1H), 5.77 (ddt, J = 17.0, 10.2, 6.7, 1H), 4.97 (dq, J = 17.1, 1.6, 1H), 4.93 (ddt, J = 10.2, 2.3, 1.2, 1H), 4.12 (t, J = 7.3, 1H), 2.23 (s, 3H), 2.16 (dddd, J = 13.5, 9.2, 7.5, 6.0, 1H), 2.01 (s, 3H), 1.98−2.05 (m, 1H), 1.90−1.96 (m, 1H), 1.64 (dddd, J = 13.3, 9.4, 7.1, 6.1, 1H), 1.03 (s, 9H), 0.28 (s, 3H), 0.26 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.7 (C), 151.2 (C), 138.6 (CH), 130.8 (C), 129.3 (C), 129.2 (CH), 128.6 (CH), 118.2 (CH), 114.9 (C), 51.0 (CH), 31.9 (CH_2), 30.3 (CH_2), 29.4 (CH_3), 26.0 (CH_3), 20.7 (CH_3), 18.5 (C), −3.9 (CH_3), −4.0 (CH_3); IR (ATR) 2930, 1716, 1500, 1268 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{20}H_{33}O_2Si$ $(M + H)^+$ 333.2244, found 333.2249. Anal. Calcd for $C_{20}H_{32}O_2Si$: C, 72.23; H, 9.70. Found: C, 72.31; H, 9.69.

To a solution of crude silyl ether **14** (1.51 g, 4.53 mmol) in THF (45 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 11 mL, 11 mmol). The mixture was stirred at 25 °C for 3 h and then concentrated. The resulting oil was purified by flash chromatography (hexanes:EtOAc = 75:25 → 50:50) to afford phenol **15** (0.97 g, 98% over two steps) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.95 (dd, J = 8.1, 2.8, 1H), 6.84 (d, J = 2.8, 1H), 6.77 (d, J = 8.1, 1H), 5.77 (ddt, J = 16.9, 10.2, 6.5, 1H), 4.98−5.02 (m, 2H), 3.87 (t, J = 7.5, 1H), 2.25 (s, 3H), 2.20 (s, 3H), 2.11−2.16 (m, 1H), 1.95−2.02 (m, 2H), 1.87−1.93 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 212.8 (C), 152.6 (C), 137.9 (CH), 130.6 (CH), 130.2 (C), 129.5 (CH), 123.6 (C), 117.4 (CH), 115.6 (CH_2), 54.9 (CH), 31.8 (CH_2), 30.0 (CH_3), 29.3 (CH_2), 20.6 (CH_3); IR (ATR) 3362, 2926, 1694, 1509, 1355, 911 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{14}H_{18}NaO_2$ $(M + Na)^+$ 241.1199, found 241.1206. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.86; H, 8.07.

Triflate 4. To a 0 °C solution of phenol **15** (0.045 g, 0.20 mmol) in CH_2Cl_2 (1.0 mL) was added triethylamine (0.045 mL, 0.27 mmol).

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Trifluoromethanesulfonic anhydride (0.037 mL, 0.27 mmol) was added dropwise over 10 min, and the resulting mixture was stirred for 3 h. Water (2 mL) was added, and the mixture was warmed to 25 °C. The mixture was extracted with CH_2Cl_2 (3 × 1 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The resulting oil was purified by flash chromatography (hexanes:EtOAc = 96:4) to afford triflate **4** (0.069 g, 97%) as a yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.19 (d, J = 8.4, 1H), 7.14 (dd, J = 8.4, 2.2, 1H), 7.07 (d, J = 2.2, 1H), 5.76 (ddt, J = 17.0, 10.2, 6.7, 1H), 4.97−5.02 (m, 2H), 4.05 (t, J = 7.2, 1H), 2.34 (s, 3H), 2.19 (dddd, J = 13.6, 8.9, 7.6, 6.0, 1H), 2.12 (s, 3H), 2.00−2.07 (m, 1H), 1.92−1.99 (m, 1H), 1.65−1.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.8 (C), 145.6 (C), 139.3 (C), 137.5 (CH), 131.7 (C), 129.87 (CH), 129.84 (CH), 121.5 (CH), 118.7 (q, J = 312, CF_3), 115.6 (CH_2), 50.6 (CH), 31.6 (CH_2), 31.4 (CH_3), 30.0 (CH_2), 21.1 (CH_3); ^{19}F NMR (377 MHz, $CDCl_3$) δ −73.8 (s); IR (ATR) 2931, 1720, 1421, 1358, 1216, 1168, 1141 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{15}H_{17}F_3NaO_4S$ $(M + Na)^+$ 373.0692, found 373.0680. Anal. Calcd for $C_{15}H_{17}F_3O_4S$: C, 51.42; H, 4.89. Found: C, 51.44; H, 4.90.

Enones 16 and $\Delta_{9,10}$-16. To a sealed bomb were added K_2CO_3 (0.705 g, 5.10 mmol), triphenylphosphine (0.134 g, 0.510 mmol), and palladium(II) acetate (0.038 mg, 0.17 mmol), followed by a solution of triflate **4** (0.596 g, 1.70 mmol) in acetonitrile (22 mL). The sealed bomb was heated at 80 °C for 20 h and then cooled to 25 °C. The mixture was filtered through a plug of silica, eluted with CH_2Cl_2 (75 mL), and concentrated. The resulting oil was purified by flash chromatography (hexanes:EtOAc = 85:15) to afford an inseparable mixture of isomers **16** and **$\Delta_{9,10}$-16** (20:3, 0.312 g, 91%) as a clear colorless oil (note that isomeric ratios vary greatly in repeated experiments). **16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.1, 1H), 7.16 (d, J = 8.1, 1H), 6.82 (s, 1H), 5.47 (m, 1H), 4.96 (m, 1H), 3.82 (t, J = 6.5, 1H), 2.56−2.63 (m, 1H), 2.43−2.50 (m, 1H), 2.31 (s, 3H), 2.11 (s, 3H), 2.10 (q, J = 6.3, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.5 (C), 142.2 (C), 138.0 (C), 133.7 (C), 132.5 (C), 129.8 (CH), 128.4 (CH), 124.9 (C), 123.6 (CH), 122.7 (C), 108.3 (CH_2), 54.5 (CH), 30.4 (CH_2), 28.1 (CH_3), 21.3 (CH_3), 19.2 (CH_2). **$\Delta_{9,10}$-16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 7.8, 1H), 7.09 (d, J = 7.8, 1H), 7.00 (s, 1H), 5.72−5.73 (m, 1H), 3.53 (dd, J = 7.5, 3.7, 1H), 2.70−2.77 (m, 1H), 2.47−2.54 (m, 1H), 2.34 (s, 3H), 2.04 (s, 3H), 2.00−2.01 (m, 3H); ^{13}C NMR (only diagnostic peaks reported, 100 MHz, $CDCl_3$) δ 129.7 (CH), 123.6 (C), 122.7 (CH), 52.2 (CH), 28.4 (CH_2), 26.6 (CH_2). Mixture: IR (ATR) 2932, 1704, 1353, 1152, 881, 821 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{14}H_{16}NaO$ $(M + Na)^+$ 223.1099, found 223.1093. Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.85; H, 7.90.

Silyl Peroxide 17. A flask containing 1,2-dichloroethane (12 mL) was sparged with oxygen for 30 min. To a separate flask were added isomers **16** and **$\Delta_{9,10}$-16** (0.963 g, 4.81 mmol) and $Co(acac)_2$ (0.247 mg, 0.962 mmol). The reaction flask was flushed with oxygen, and the oxygenated solvent was added. Triethylsilane (1.92 mL, 12.0 mmol) was added, and the mixture was stirred for 24 h under a balloon of oxygen. The mixture was concentrated, and the resulting residue was taken up in CH_2Cl_2 and filtered through a plug of silica eluted with CH_2Cl_2 (125 mL). The filtrate was concentrated to afford silyl peroxide **17** (1.42 g, 85%) as a clear colorless oil. Characterization was performed using a 60:40 mixture of diastereomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (d, J = 8.0, 0.4H), 7.43 (d, J = 8.0, 0.6H), 7.08−7.09 (m, 1H), 6.80 (s, 0.4H), 6.78 (s, 0.6H), 3.80 (t, J = 5.8, 0.6H), 3.65 (dd, J = 7.7, 7.3, 0.4H), 2.52 (ddd, J = 13.9, 7.7, 3.3, 0.4H), 2.38 (ddd, J = 13.9, 7.6, 3.2, 0.6H), 2.30 (s, 1.2H), 2.29 (s, 1.8H), 2.16−2.24 (m, 1H), 2.17 (s, 1.8H), 2.02 (s, 1.2H), 1.90−2.00 (m, 1H), 1.73 (ddd, J = 12.9, 10.8, 3.1, 0.6H), 1.60 (ddd, J = 13.7, 10.3, 3.2, 0.4H), 1.55 (s, 3H), 0.93−0.96 (m, 9H), 0.61−0.67 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.4 (C), 210.4 (C), 138.0 (C), 137.6 (C), 136.1 (C), 135.7 (C), 134.7 (C), 134.5 (C), 129.6 (CH), 129.2 (CH), 128.3 (CH), 128.24 (CH), 128.22 (CH), 128.1 (CH), 80.99 (C), 80.96 (C), 54.7 (CH), 53.8 (CH), 31.2 (CH_2), 30.5 (CH_2), 28.5 (CH_3), 27.3 (CH_3), 26.4 (CH_3), 25.8 (CH_3), 22.84 (CH_2), 22.80 (CH_2), 21.21 (CH_3), 21.19 (CH_3), 6.90 (CH_3), 6.89 (CH_3), 3.99 (CH_2), 3.97 (CH_2); IR (ATR) 2955, 2877, 1709, 1164, 522 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{20}H_{32}NaO_3Si$ $(M + Na)^+$ 371.2013, found 371.2013.

Silyl Ether 3. To a solution of silyl peroxide **17** (0.056 g, 0.16 mmol) in toluene (0.40 mL) was added triphenylphosphine (0.059 g, 0.22 mmol). The mixture was heated to 100 °C and stirred for 24 h. Upon cooling to 25 °C, H_2O (2 mL) was added, and the mixture was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The resulting oil was purified by flash chromatography (hexanes/Et_2O = 80:20) to afford silyl ether **3** (0.042 g, 79%) as a clear colorless oil. Characterization was performed on an inseparable 60:40 mixture of diastereomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 (d, J = 8.3, 0.6H), 7.49 (d, J = 8.4, 0.4H), 7.06−7.08 (m, 1H), 6.78 (s, 0.4H), 6.69 (s, 0.6H), 3.81−3.82 (m, 0.6H), 3.68 (t, J = 6.5, 0.4H), 2.29 (s, 1.2H), 2.27 (s, 1.8H), 2.18−2.29 (m, 1H), 2.12 (s, 1.2H), 2.11 (s, 1.8H), 1.88−2.06 (m, 2.6H), 1.77−1.81 (m, 0.4H), 1.56 (s, 1.8H), 1.53 (s, 1.2H), 0.88−0.91 (m, 9H), 0.46−0.58 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.9 (C), 210.7 (C), 141.8 (C), 141.3 (C), 136.8 (C), 136.7 (C), 132.2 (C), 131.9 (C), 129.5 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 127.1 (CH), 127.0 (CH), 72.8 (C), 72.4 (C), 54.3 (CH), 53.7 (CH), 37.7 (CH_2), 37.3 (CH_2), 32.5 (CH_3), 31.9 (CH_3), 27.8 (CH_3), 27.5 (CH_3), 23.9 (CH_2), 23.1 (CH_2), 21.14 (CH_3), 21.13 (CH_3), 7.24 (CH_3), 7.26 (CH_3), 6.84 (CH_2), 6.79 (CH_2); IR (ATR) 2952, 2875, 1707, 1159, 904, 733 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{20}H_{32}NaO_2Si$ $(M + Na)^+$ 355.2064, found 355.2070.

Olefin 18. To ketone **3** (0.011 g, 0.034 mmol) was added a solution of Cp_2TiMe_2 (5% w/v in THF/toluene, 0.4 mL, 0.1 mmol). The mixture was heated at 65 °C and stirred for 24 h. Upon cooling to 25 °C, the mixture was filtered through a plug of silica eluted with CH_2Cl_2 (8 mL). The filtrate was concentrated to afford olefin **18** (9.6 mg, 86%) as a clear colorless oil. Characterization was performed using on an inseparable 60:40 mixture of diastereomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (dd, J = 8.0, 1.0, 0.6H), 7.44 (dd, J = 8.0, 0.9, 0.4H), 6.99−7.00 (m, 1H), 6.85−6.86 (m, 1H), 4.91−4.92 (m, 1H), 4.81(m, 0.6H), 4.57 (m, 0.4H), 3.52 (dd, J = 10.2, 6.0, 0.6H), 3.40 (t, J = 6.4, 0.4H), 2.27 (s, 1.2H), 2.26 (s, 1.8H), 1.90−2.07 (m, 2.6H), 1.78−1.85 (m, 1H), 1.72−1.76 (m, 0.4H), 1.70 (s, 1.2H), 1.58 (s, 1.8H), 1.52 (d, J = 1.4, 1.2H), 1.50 (d, J = 1.1, 1.8H), 0.87−0.92 (m, 9H), 0.46−0.57 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.3 (C), 148.5 (C), 142.4 (C), 141.3 (C), 136.7 (C), 136.2 (C), 136.1 (C), 136.0 (C), 129.5 (CH), 128.4 (CH), 127.21 (CH), 127.19 (CH), 126.6 (CH), 126.5 (CH), 113.9 (CH_2), 113.8 (CH_2), 73.6 (C), 72.8 (C), 48.3 (CH), 47.3 (CH), 38.6 (CH_2), 37.3 (CH_2), 33.3 (CH_3), 32.2 (CH_3), 26.8 (CH_2), 25.0 (CH_2), 21.3 (CH_3), 21.2 (CH_3), 20.5 (CH_3), 18.8 (CH_3), 7.29 (CH_3), 7.27 (CH_3), 6.90 (CH_2), 6.88 (CH_2); IR (ATR) 2950, 2875, 1111, 1070, 1038, 1006, 743, 724 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{21}H_{34}NaOSi$ $(M + Na)^+$ 353.2271, found 353.2269.

Silyl Peroxide 19. A flask containing 1,2-dichloroethane (0.20 mL) was sparged with oxygen for 30 min. A separate flask containing olefin **18** (0.013 g, 0.040 mmol) and $Co(acac)_2$ (2 mg, 8 μmol) was flushed with oxygen. The oxygenated solvent was added to the reaction mixture. Triethylsilane (0.016 mL, 0.10 mmol) was added, and the mixture was stirred for 15 h under a balloon of oxygen. The mixture was concentrated, and the resulting residue was taken up in CH_2Cl_2 and filtered through a plug of silica eluted with CH_2Cl_2 (25 mL). The filtrate was concentrated to afford silyl peroxide **19** (0.018 g, 95%) as a clear colorless oil. Characterization was performed on an inseparable 60:40 mixture of diastereomers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57−7.58 (m, 0.6H), 7.50 (m, 0.4H), 7.46 (d, J = 8.0, 0.6H), 7.40 (d, J = 8.0, 0.4H), 6.97−7.00 (m, 1H), 3.41 (dd, J = 10.1, 7.0, 0.6H), 3.34 (t, J = 7.1, 0.4H), 2.30 (s, 1.2H), 2.29 (s, 1.8H), 1.79−2.04 (m, 3.4H), 1.69 (ddd, J = 13.3, 10.1, 3.8, 0.6H), 1.53 (s, 1.2H), 1.48 (s, 1.8H), 1.37 (s, 1.2H), 1.35 (s, 1.8H), 1.02−1.05 (m, 9H), 0.88−0.91 (m, 12H), 0.73−0.78 (m, 6H), 0.46−0.58 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.4 (C), 141.3 (C), 136.4 (C), 135.5 (C), 135.4 (C), 135.2 (C), 131.7 (CH), 130.9 (CH), 126.8 (CH), 126.7 (CH), 125.9 (CH), 125.8 (CH), 87.0 (C), 86.9 (C), 73.3 (C), 72.4 (C), 42.1 (CH), 42.0 (CH), 38.6 (CH_2), 38.4 (CH_2), 32.3 (CH_3), 31.9 (CH_3), 25.0 (CH_3), 24.8 (CH_3), 24.1 (CH_2), 22.4 (CH_2),

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21.8 (CH_3), 21.3 (CH_3), 21.2 (CH_3), 20.5 (CH_3), 7.30 (CH_3), 7.29 (CH_3), 7.01 (CH_3), 7.00 (CH_3), 6.89 (CH_2), 6.88 (CH_2), 4.14 (CH_2), 4.13 (CH_2); IR (ATR) 2954, 2876, 1014, 794, 727 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{27}H_{50}NaO_3Si_2$ $(M + Na)^+$ 501.3191, found 501.3186.

10,12-Peroxycalamenene 1.[1] To a solution of silyl peroxide **19** (0.050 g, 0.10 mmol) in THF/H_2O (9:1 v/v, 0.73 mL) was added a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (9.5 mg, 0.042 mmol) in THF/H_2O (9:1 v/v, 0.73 mL). The mixture was stirred for 16 h and then concentrated. The crude mixture was purified by flash chromatography (hexanes:EtOAc = 95:5) to afford 10,12-peroxycalamenene **1** (0.015 g, 60%) as a light brown solid: mp 64−66 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.15 (d, J = 7.6, 1H), 7.03 (d, J = 7.6, 1H), 6.92 (s, 1H), 2.77−2.78 (m, 1H), 2.59 (br s, 1H), 2.35−2.37 (m, 1H), 2.35 (s, 3H), 1.64−1.75 (m, 2H), 1.60 (s, 3H), 1.26 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.8 (C), 138.6 (C), 137.7 (C), 128.8 (CH), 127.5 (CH), 123.0 (CH), 83.7 (C), 83.5 (C), 51.1 (CH), 33.4 (CH_2), 25.9 (CH_3), 24.8 (CH_3), 23.3 (CH_3), 23.1 (CH_3), 21.9 (CH_2); IR (ATR) 2976, 2934, 1077, 809 cm^{-1}; HRMS (TOF MS APCI+) m/z calcd for $C_{15}H_{21}O_2$ $(M + H)^+$ 233.1536, found 233.1526. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.56; H, 8.87. These results matched with those previously published.[1]

■ ASSOCIATED CONTENT

Supporting Information

Spectral data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01326.

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Notes

The authors declare no competing financial interest.

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