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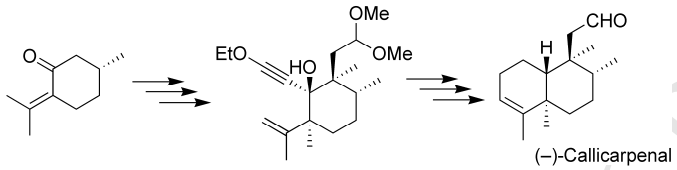

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A novel synthesis of (−)-callicarpenal

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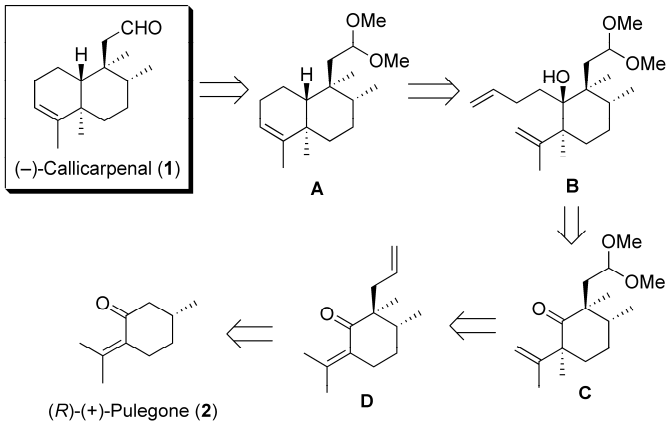
ABSTRACT

Callicarpenal, isolated from the leaves of American beautyberry (*Callicarpa americana*) and Japanese beautyberry (*Callicarpa japonica*), exhibits significant mosquito bite-deterring activity and repellent activity against ticks and fire ants. The mosquito bite-deterring activity level of callicarpenal was reported to be similar to that of *N*,*N*-diethyl-*m*-toluamide. The novel synthesis of (−)-callicarpenal reported herein was accomplished by starting from (+)-pulegone. In our original approach, a novel Prins-type cyclization based on Meyer–Schuster rearrangement was featured as a key step.

1. Introduction

Callicarpenal (**1**) is a tetranorclerodane-type aldehyde isolated in 2005 from the leaves of American beautyberry (*Callicarpa americana*) and Japanese beautyberry (*Callicarpa japonica*).[1] This aldehyde has been reported to exhibit significant mosquito bite-deterring activity against *Aedes aegypti* and *Anopheles stephensi*,[1] and repellent activity against host-seeking nymphos of ticks (*Ixodes scapularis* and *Amblyomma americanum*)[2] and workers of imported fire ants (*Solenopsis invicta* Buren, *Solenopsis richteri* Forel and their hybrid).[3] Since the mosquito bite-deterring activity level of callicarpenal was reported to be similar to that of *N*,*N*-diethyl-*m*-toluamide (DEET), the most commonly used mosquito repellent agent, callicarpenal is expected to be a naturally occurring DEET alternative. Quite interestingly, the absolute configuration of the natural callicarpenal (Scheme 1) was confirmed by an "unintended" synthesis once (−)-**1** has already been reported as an intermediate in the synthesis of a clerodane diterpenoid before the isolation of callicarpenal.[4] Besides the serendipitous first synthesis, Ling *et al.* reported the enantioselective synthesis of (−)-**1**.[5] It is also interesting that (+)-**1** was also unintentionally synthesized before the isolation of callicarpenal.[6] Herein, we report a novel approach for the synthesis of (−)-**1** using the readily available (*R*)-(+)-pulegone (**2**) as a chiral starting material.



Scheme 1. Structure of (−)-**1** and our initial synthetic plan.

2. Results and Discussion

Our initial synthetic plan for (−)-**1** is shown in Scheme 1. The protected target compound **A** could be synthesized from **B** *via* ring-closing metathesis (RCM) and reductive deoxygenation. The key intermediate **B** would be prepared by the homoallylation of **C**. The ketone **C** would be synthesized by appropriate manipulations of the allyl side-chain of **D**, which should be obtainable through two consecutive alkylations of the starting material (*R*)-(+)-pulegone (**2**).

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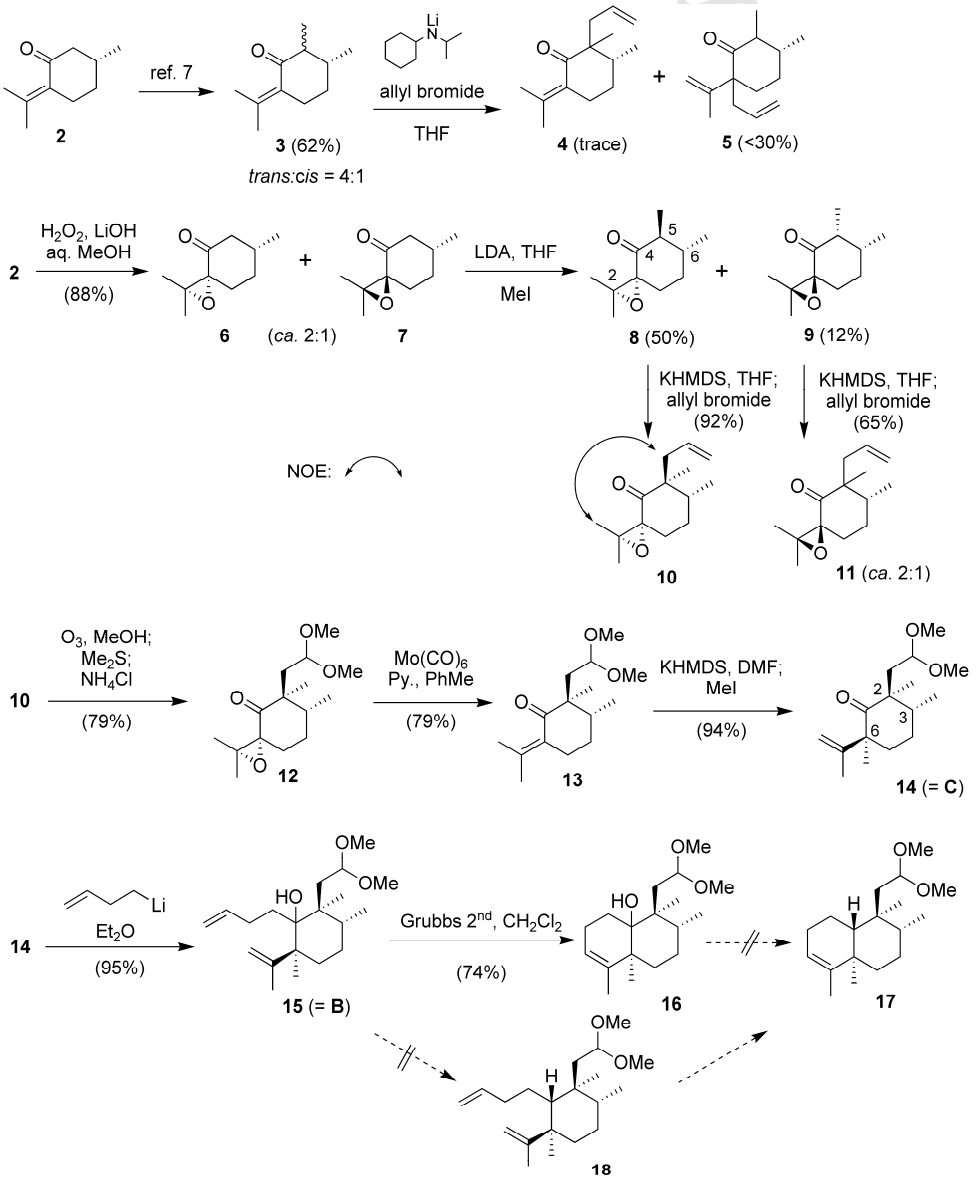
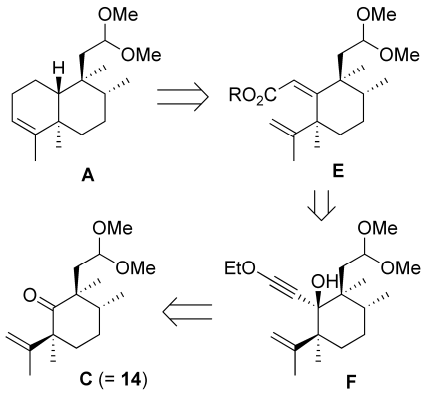
We first attempted to synthesize the intermediate **D** in a straightforward manner, as shown in Scheme 2. According to a previously reported procedure, (*R*)-(+)-pulegone (**2**) was converted to a diastereomeric mixture of **3** (*trans*:*cis* = 4:1) in moderate yield.[7] However, further allylation of **3** was not successful, and only a trace amount of **4** was obtained, whereas the undesired regioisomer **5** was the major product. The undesired regioselectivity could be explained by steric hindrance to proton abstraction. Therefore, we decided to use pulegone oxides (**6**/**7**) as substrates instead of **2**, because base-mediated alkylations of **6**/**7** would avoid the problematic γ-proton abstraction under conventional conditions. Pulegone oxide (**6**/**7**), prepared *via* a known procedure,[8] was methylated by treatment with LDA and MeI to give a separable mixture of **8** (50%) and **9** (12%), respectively. The relative stereochemistries of **8** and **9** with regard to 5-Me were tentatively assigned based on ^{1}H NMR analysis. The major isomer **8** was then treated with KHMDS and allyl bromide to afford **10** in 92% yield with perfect stereoselectivity, while the allylation of **9** afforded **11** in a relatively lower yield with poor selectivity, even under the same conditions. The relative stereochemistry of **10** was confirmed by the observation of NOE depicted in Scheme 2, but that of **11** was not estimated. The oxidative cleavage of a double bond by ozonolysis and subsequent acetalization could convert **10** into **12** in 79% yield. According to a previously reported procedure, the reductive cleavage of an epoxide group was successfully achieved by treatment with $Mo(CO)_6$ to afford **13** in 79% yield.[9] The deconjugative α-methylation of **13** was then investigated. Although none of the desired adduct **14** (= **C**) was obtained using LDA as a base in THF, a small amount of **14** was observed by changing the base from LDA to KHMDS. Thus, we eventually found that the yield of **14** was dramatically improved using DMF as a solvent,[10] and that **14** was obtained as a single diastereomer in excellent yield. The relative stereochemistry was confirmed by the observation of NOE between 2- and 6-Me groups. For synthesizing the RCM precursor, **14** was treated with homoallyllithium to furnish **15** (= **B**) as a single diastereomer in 95% yield. Although the orientation of a hydroxy group could not be determined unambiguously, it should be β based on the judgment from the knowledge acquired at later stages. The RCM reaction of **15** was successfully mediated by Grubbs 2nd catalyst[11] to afford **16** in 74% yield. However, disappointingly, all our attempts to convert **16** into **17** (= **A**) were unsuccessful in spite of



Scheme 2. Synthetic studies based on the initial plan.

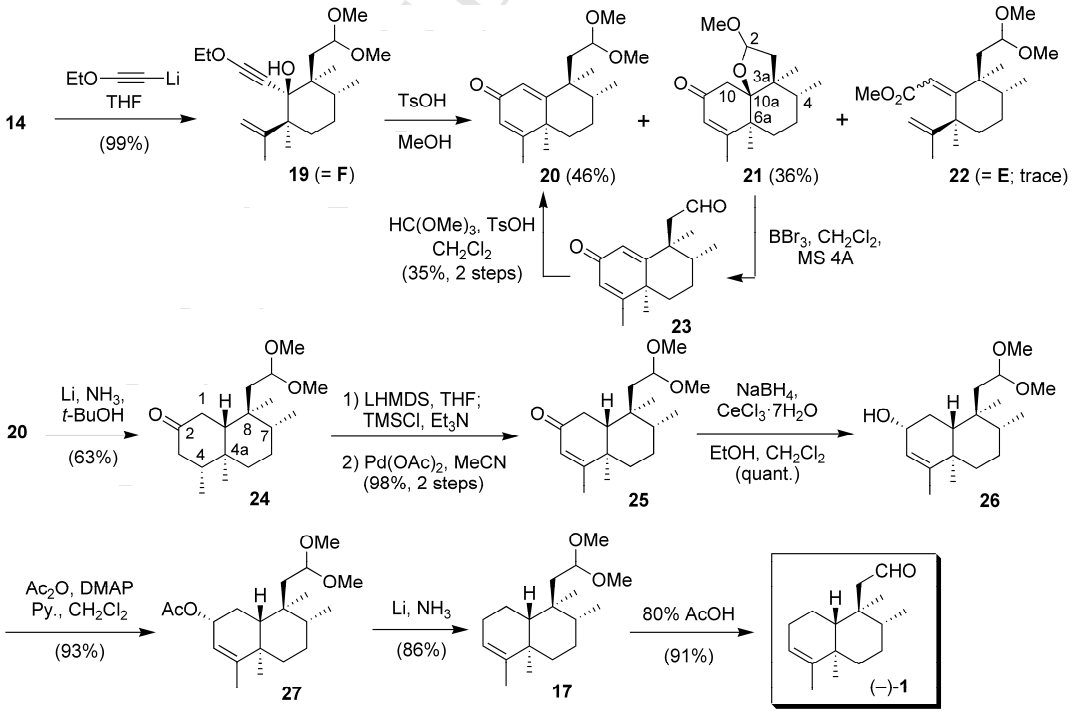
our efforts. The conversion of **15** into **18** also failed completely. In all events, a tertiary hydroxy group was adamantly resistant to derivatization, such as acetylation, phosphorylation and xanthation. These failures might be due to the massive steric hindrance around the hydroxy group, which revealed to be quite difficult to overcome. Thus, we adjusted our initial plan accordingly to address the aforementioned issues.

Scheme 3 illustrates the revised synthetic plan for **1**. The protected target compound **A** might be synthesized from **E** by some means, e.g., by Friedel-Crafts–type reaction. The synthesis of **E** should be possible by Meyer–Schuster rearrangement of **F**. In this approach, the steric hindrance would not matter at all, because the tertiary hydroxy group would be removed through β-elimination. The intermediate **F** would be then prepared from **C** (= **14**) by addition of an alkynyl group.

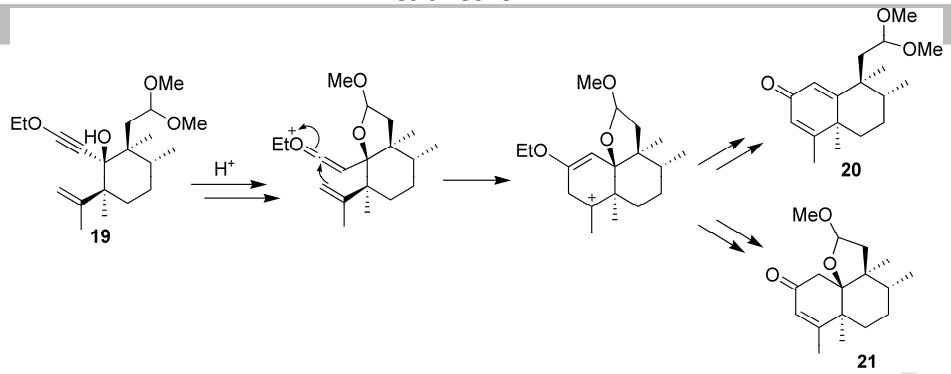


Scheme 3. The revised synthetic plan for **1**.

By treatment with (ethoxyethynyl)lithium, **14** was converted to **19** (= **F**) in excellent yield with perfect stereoselectivity (Scheme 4). Although the relative stereochemistry of **19** was not confirmed at this stage, the β-orientation of the hydroxy group was supported by the formation of **21** in the next step. Then, we examined the acid-mediated Meyer–Schuster rearrangement. Although the desired rearranged product was not obtained under aqueous conditions (aq. H_2SO_4 or aq. AcOH), non-aqueous conditions yielded unexpected and surprising results. Treatment with *p*-TsOH in dry MeOH afforded **20** (46%) and **21** (36%) as major products, while the formation of the expected product **22** (= **E**) was detected but not estimated quantitatively. As reported by Zhang and Kozmin,[12] this unexpected cyclization might proceed by Prins-type reaction *via* a transient ketenium cation (Scheme 5). However, the timing of transacetalization and β-elimination is not certain, because these steps should proceed at any time under the reaction conditions. It was noted that **21** was obtained as a predominant diastereomer according to its NMR spectra. The *cis*-fused 5,6-system of **21** was confirmed by the observation of NOEs between 10-Hα and 3a-Me and between 10-Hα and 6a-Me, but the orientation of 2-OMe could not be determined *via* NOE experiments. However, we presume it to be α-oriented based on thermodynamic stability considerations. The minor product **21** could then be converted to **20** by BBr_3 treatment and subsequent acetalization in moderate yield and not by a simple acid treatment. We were serendipitously successful in the construction of the full carbon skeleton of the target compound **1**.



Scheme 4. Synthesis of (−)-**1**.



Scheme 5. Suggested reaction mechanism for the formation of **20**/**21**.

The dienone **20** was reduced under Birch conditions in the presence of *t*-BuOH as a proton donor to give **24** in 63% yield, and its relative stereochemistry was determined by the observation of NOEs between 4-Me and 4a-Me and between 4a-Me and 8-Me. The conversion of **24** into **25** was successfully executed by Saegusa oxidation[13] in 98% yield, while selenoxide elimination was less effective for this conversion. The DIBAL reduction of **25** afforded **26** in quantitative yield but with poor diastereoselectivity (α:β = 76:24). However, the diastereoselectivity was improved by Luche reduction[14] to afford **26** as a single isomer in quantitative yield. The α-orientation of a hydroxy group was estimated by ^{1}H NMR analysis ($J_{H2–H3}$ = < 1 Hz). Acetylation of **26** (93%) was followed by reductive deoxygenation under Birch conditions to furnish **17** (= **A**) in 86% yield. Finally, deprotection of **17** was performed by treatment with aq. AcOH to afford (−)-**1** (91%), $[\alpha]_D^{20}$ −58.5 (*c* 0.91, $CHCl_3$), {lit.,[4] $[\alpha]_D^{20}$ −30 (*c* 0.39, $CHCl_3$)}. The spectral data of our synthesized (−)-**1** are in good accordance with those previously reported.[1,4,5] Nevertheless, in these previous papers, (−)-**1** was reported as an oil in contrast to what we obtained, i.e., (−)-**1** as colorless prisms. Notably, to our knowledge, there is only one paper reporting that the naturally occurring (−)-**1** was obtained as crystals after extensive purification.[15] These facts might serve as an evidence for the excellent purity of our synthetic (−)-**1**.

3. Conclusion

We achieved a novel synthesis of (−)-callicarpenal (**1**) from (*R*)-(+)-pulegone (**2**) in 15 steps with an overall yield of 5%. Two sequential diastereoselective alkylations of pulegone oxide (**6**/**7**) and the unexpected Prins-type cyclization based on Meyer–Schuster rearrangement were featured as the key steps.

4. Experimental section

4.1. General

All air-sensitive and/or water-sensitive reactions were carried out under Ar atmosphere in dry solvents. (*R*)-(+)-Pulegone (**2**) was purchased from Nippon Terpene Chemicals, Inc., and purified by column chromatography and distillation before using. The enantiomeric excess of **2** was determined by gas chromatograph using a chiral separation column, CHIRAMIX® (60 m, ID 0.25 mm).[16] THF and Et_2O were freshly distilled from sodium/benzophenone under Ar. CH_2Cl_2 was freshly distilled from P_2O_5 under Ar. Toluene and MeOH were dried over MS 4Å and 3Å, respectively. Analytical thin-layer chromatography (TLC) was carried out on 0.25 mm Merck silica gel 60 F_{254} pre-coated glass plates. Preparative thin layer chromatography (PTLC) was carried out on 0.5 mm Merck silica gel 60 F_{254} pre-coated glass plates. Column chromatography was performed on Kanto Chemical silica gel 60N (neutral). All melting points (mps) were uncorrected. Melting points were recorded on a Yanaco Micro Melting Point Apparatus. Infrared spectra (IR) were measured on a Jasco FT/IR-470 plus spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a JEOL JNM-ECX 400 spectrometer. ^{1}H NMR (300 MHz) was recorded on a JEOL JNM-AL 300 spectrometer. Chemical shifts (δ) are reported in ppm relative to internal chloroform (C*H*Cl_3 at δ 7.26; *C*DCl_3 at δ 77.0). Optical rotations were measured on a Jasco P-1030 polarimeter. HRMS were recorded with a JEOL JMS-T100LC. GC analyses were carried out with a Shimadzu GC-14B gas chromatograph (TC-1701 capillary column 30 m, ID 0.53 mm, film 1.0 μm) equipped with a flame ionization detector.

*4.2. (3R,6R)- and (3S,6R)-2,2,6-Trimethyl-1-oxaspiro[2.5]octan-4-one (pulegone oxide) (**6** and **7**)*

According to the reported procedure,[8a] (*R*)-(+)-pulegone (**2**, 99.1% *ee*) was converted to pulegone oxides (**6** and **7**) in 88% yield. The ratio of **6**:**7** was determined by GC analysis to be *ca.* 2:1. The assignments (3*R*,6*R*)-**6** and (3*S*,6*R*)-**7** were confirmed by comparing to the reported data.[8b] Compound **6** and **7**; IR (KBr): 2953, 2873, 1715, 1456, 1424, 1376, 1278, 1235, 1119, 879 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05* and 1.07 (total 3H, each d, *J* = 7.2 and 6.0 Hz), 1.20 and 1.22* (total 3H, each s), 1.39 (3H, s), 1.65–2.06 (4H, m), 2.19* (2/3H, dt, *J* = 4.3, 13.2 Hz), 2.41 (2H, m), 2.60 (1/3H, dt, *J* = 13.2, 3.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.93*, 19.37, 19.60*, 19.72, 19.95*, 22.03, 26.28*, 29.93, 30.19*, 30.70*, 33.02, 33.95, 49.49*, 51.37, 63.20, 63.42*, 70.13*, 70.24, 206.47, 207.53* (The peaks with * are due to **6**.); HRMS (ESI) calcd for $C_{10}H_{16}NaO_2$ $[M+Na]^+$: 191.1048, found 191.1039.

*4.3. (3R,5S,6R)-2,2,5,6-Tetramethyl-1-oxaspiro[2.5]octan-4-one (**8**)*

To a solution of $(i\text{-Pr})_2NH$ (1.1 mL, 7.9 mmol) in THF (16 mL), *n*-BuLi (1.60 M in hexane; 4.5 mL, 7.2 mmol) was added dropwise over 10 min at 0 °C. After stirring for 0.5 h, the reaction mixture was cooled to −78 °C. To this solution was added dropwise a solution of pulegone oxides (**6** and **7**, 1.0 g, 6.0 mmol) in THF (6 mL) over 10 min. After stirring for 1 h at −78 °C, MeI (1.1 mL, 18 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature with stirring over 2 h, quenched with sat. aq. NH_4Cl and extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue (1.1 g) was chromatographed on silica gel (45 g). Elution with hexane/EtOAc (30/1–2/1) gave

8 (548 mg, 50%) as a pale yellow oil, and a mixture of (**9**, 12%, determined by GC analysis) and starting material (**6**/**7** = 2:3, 24%, determined by GC analysis). Compound **8**; $[\alpha]_D^{20}$ +70.9 (*c* 1.48, $CHCl_3$); IR (film): 2965, 2930, 1717, 1456, 1378, 1122, 953, 927, 883, 651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (3H, d, *J* = 7.0 Hz), 1.10 (3H, d, *J* = 7.0 Hz), 1.22 (3H, s), 1.40 (3H, s), 1.62 (1H, m), 1.81–1.91 (2H, m), 2.00–2.12 (2H, m), 2.46 (1H, dq, *J* = 6.6, 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.74, 19.67, 19.88, 21.02, 27.17, 27.46, 37.86, 52.08, 64.58, 68.81, 210.62; HRMS (ESI) calcd for $C_{11}H_{18}NaO_2$ $[M+Na]^+$: 205.1205, found 205.1194. Compound **9**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (3H, d, *J* = 7.2 Hz), 0.98 (3H, d, *J* = 6.9 Hz), 1.18 (3H, s), 1.41 (3H, s), 1.65–2.03 (4H, m), 2.10–2.20 (1H, m), 2.65 (1H, dq, *J* = 4.8, 7.2 Hz).

*4.4. (3R,5S,6R)-5-Allyl-2,2,5,6-tetramethyl-1-oxaspiro[2.5]octan-4-one (**10**)*

To a solution of **8** (9.34 g, 51.2 mmol) in THF (93 mL), KHMDS (0.5 M in toluene; 113 mL, 56.3 mmol) was added dropwise over 10 min at −78 °C. After stirring for 1 h at 0 °C, allyl bromide (10.5 mL, 121 mmol) was added dropwise at −78 °C. The reaction mixture was allowed to warm to room temperature with stirring overnight. The reaction mixture was poured into sat. aq. NH_4Cl and extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue (13.6 g) was chromatographed on silica gel (250 g). Elution with hexane/EtOAc (50/1–10/1) gave **10** (11.0 g, 97%) as a pale yellow oil, which was then crystallization from hexane to give colorless prisms. $[\alpha]_D^{20}$ +26.6 (*c* 1.44, $CHCl_3$); mp 62.0–63.0 °C; IR (KBr): 2967, 1710, 1458, 1377, 1138, 1092, 989, 977, 921, 887 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, d, *J* = 7.2 Hz), 1.05 (3H, s), 1.17 (3H, s), 1.45 (3H, s), 1.56 (1H, m), 1.85 (1H, m), 1.97 (1H, dd, *J* = 13.7, 6.5 Hz), 2.13 (1H, m), 2.18–2.27 (2H, m), 2.53 (1H, dd, *J* = 13.7, 8.4 Hz), 5.07–5.14 (2H, m), 5.70 (1H, dddd, *J* = 16.2, 10.6, 8.4, 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.42, 18.73, 19.64, 20.41, 25.83, 26.09, 36.51, 40.38, 53.38, 64.74, 68.45, 118.74, 132.50, 210.65; HRMS (ESI) calcd for $C_{14}H_{22}NaO_2$ $[M+Na]^+$: 245.1518, found 245.1495.

*4.5. (3R,5S,6R)-5-(2,2-Dimethoxyethyl)-2,2,5,6-tetramethyl-1-oxaspiro[2.5]octan-4-one (**12**)*

Ozone, generated from ON-3-2 ozonator (Nippon Ozone Co., Ltd.), was bubbled into a solution of **10** (1.11 g, 4.99 mmol) in MeOH (100 mL) at −78 °C until saturation. After removal of excess ozone by a stream of Ar, the reaction mixture was quenched with Me_2S (2.2 mL, 15 mmol) at −78 °C. After stirring overnight with warming to room temperature, NH_4Cl (0.10 g, 1.9 mmol) was added to the reaction mixture, which was then heated under reflux for 0.5 h. After cooling, $NaHCO_3$ (300 mg, 3.6 mmol) was added, and the mixture was concentrated *in vacuo*. The residue was poured into sat. aq. Na_2CO_3 and extracted with toluene. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue (1.40 g) was chromatographed on silica gel (50 g). Elution with hexane/EtOAc (10/1–5/1) gave **12** (1.06 g, 79%) as a colorless oil. $[\alpha]_D^{20}$ −0.3 (*c* 0.95, $CHCl_3$); IR (film): 2936, 1716, 1456, 1378, 1192, 1120, 1057, 994, 920, 887 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, d, *J* = 6.8 Hz), 1.10 (3H, s), 1.17 (3H, s), 1.43 (3H, s), 1.51 (1H, dd, *J* = 14.4, 3.6 Hz), 1.57 (1H, m), 1.84 (1H, m), 2.07 (1H, dd, *J* = 14.4, 6.0 Hz), 2.13–2.30 (3H, m), 3.27 (3H, s), 3.34 (3H, s), 4.40 (1H, dd, *J* = 6.0, 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.68, 18.80, 19.78, 20.40, 26.00, 26.32, 37.54, 38.66, 52.05, 52.51, 53.50, 64.92, 68.46, 102.24, 210.06; HRMS (ESI) calcd for $C_{15}H_{26}NaO_4$ $[M+Na]^+$: 293.1729, found 293.1713.

*4.6. (2S,3R)-2-(2,2-Dimethoxyethyl)-2,3-dimethyl-6-(1-methylethylidene)cyclohexanone (**13**)*

A mixture of **12** (54 mg, 0.20 mmol), $Mo(CO)_6$ (58 mg, 0.22 mmol), pyridine (64 μL, 0.80 mmol) and toluene (2 mL) was heated under reflux for 1 h. After cooling, the mixture was diluted with Et_2O (2 mL), stirred for 15 min and filtered through Celite® pad. The filtrate was concentrated *in vacuo*. The residue (92 mg) was chromatographed on silica gel (3 g). Elution with hexane/EtOAc (50/1–20/1) to give a mixture of **13** and polar impurity (not identified), which was further chromatographed on silica gel (3 g) and eluted with $CHCl_3$/EtOAc (30/1) to give **13** (43 mg, 85%) as a colorless oil. $[\alpha]_D^{20}$ +70.8 (*c* 0.83, $CHCl_3$); IR (film): 2932, 1681, 1443, 1372, 1284, 1190, 1121, 1074, 1056, 985 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, d, *J* = 7.2 Hz), 0.97 (3H, s), 1.49 (1H, ddt, *J* = 14.0, 5.6, 10.0 Hz), 1.75 (1H, m), 1.75 (3H, s), 1.75 (1H, dd, *J* = 14.4, 5.7 Hz), 1.87 (3H, s), 2.00 (1H, m), 2.02 (1H, dd, *J* = 14.4, 4.6 Hz), 2.36 (1H, m), 2.54 (1H, m), 3.28 (3H, s), 3.30 (3H, s), 4.39 (1H, dd, *J* = 5.7, 4.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.77, 18.27, 21.61, 22.61, 28.10, 28.24, 37.35, 39.60, 50.58, 53.12, 53.22, 103.09, 131.85, 140.32, 209.30; HRMS (ESI) calcd for $C_{15}H_{26}NaO_3$ $[M+Na]^+$: 277.1780, found 277.1795.

*4.7. (2S,3R,6S)-2-(2,2-Dimethoxyethyl)-6-isopropenyl-2,3,6-trimethylcyclohexanone (**14**)*

To a mixture of KHMDS (0.5 M in toluene; 55 mL, 27.5 mmol) in DMF (41 mL), a solution of **13** (3.50 g, 13.7 mmol) in DMF (41 mL) was added dropwise over 0.5 h at −78 °C. After stirring for 0.5 h at −78 °C, MeI (2.6 mL, 41 mmol) was added dropwise, and the stirring was continued for 2 h. The reaction mixture was then poured into sat. aq. NH_4Cl and extracted with Et_2O. The extract was successively washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue (3.4 g) was chromatographed on silica gel (160 g). Elution with hexane/EtOAc (100/1–20/1) gave **14** (3.45 g, 94%) as a colorless oil. $[\alpha]_D^{20}$ −47.5 (*c* 1.18, $CHCl_3$); IR (film): 2934, 2829, 1697, 1457, 1372, 1124, 1075, 1050, 1017, 991 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, d, *J* = 6.8 Hz), 1.00 (3H, s), 1.20 (3H, s), 1.52 (1H, dd, *J* = 14.4, 5.2 Hz), 1.50–1.67 (2H, m), 1.70 (3H, s), 1.83 (1H, m), 2.09–2.20 (2H, m), 2.33 (1H, dd, *J* = 14.4, 5.2 Hz), 3.25(3H, s), 3.26 (3H, s), 4.33 (1H, t, *J* = 5.2 Hz), 4.91 (1H, br s), 4.92 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.04, 20.32, 21.48, 25.83, 25.93, 32.76, 34.56, 39.38, 50.43, 52.78, 52.82, 53.52, 102.89, 111.33, 147.98, 217.37; HRMS (ESI) calcd for $C_{16}H_{28}NaO_3$ $[M+Na]^+$: 291.1936, found 291.1961.

*4.8. (2S,3R,6S)-2-(2,2-Dimethoxyethyl)-1-(ethoxyethynyl)-6-isopropenyl-2,3,6-trimethylcyclohexanol (**19**)*

To a solution of ethoxyacetylene (50 wt% in hexane; 0.88 mL, 4.5 mmol) in THF (4 mL), *n*-BuLi (1.65 M in hexane; 2.28 mL, 3.76 mmol) was added dropwise at −78 °C. After stirring for 0.5 h, a solution of **14** (67 mg, 0.25 mmol) in THF (3 mL) was added dropwise. After stirring at −78 °C for 15 min and at 0 °C overnight, the reaction mixture was quenched with sat. aq. NH_4Cl and extracted with Et_2O. The extract was successively washed with sat. aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue (155 mg) was chromatographed on silica gel (8 g). Elution with hexane/EtOAc (10/1) gave **19** (84 mg, 99%) as a pale yellow oil. $[\alpha]_D^{20}$ −54.4 (*c* 1.32, $CHCl_3$); IR (film): 3402, 2936, 2259, 1385, 1119, 1084, 1042, 1026, 913, 883 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (3H, d, *J* = 6.8 Hz), 1.05 (3H, s), 1.15 (3H, s), 1.34 (3H, t, *J* = 7.0 Hz), 1.35–1.70 (4H, m), 1.56 (1H, dd, *J* = 15.0, 2.4 Hz), 1.99 (3H, s), 2.00 (1H, m), 2.35 (1H, dd, *J* = 15.0, 7.6 Hz), 3.31 (3H, s), 3.34 (3H, s), 4.02 (2H, q, *J* = 7.0 Hz), 4.35 (1H, s), 4.71 (1H, dd, *J* = 7.6,

2.4 Hz), 4.75 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.57, 14.72, 16.63, 20.28, 23.50, 27.30, 34.02, 38.26, 41.77, 43.02, 46.45, 47.72, 51.84, 52.50, 73.95, 77.83, 95.06, 102.85, 109.69, 155.81; HRMS (ESI) calcd for $C_{20}H_{34}NaO_4$ $[M+Na]^+$: 361.2355, found 361.2330.

*4.9. (4aS,7R,8S)-8-(2,2-Dimethoxyethyl)-4,4a,7,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2(4aH)-one (**20**) and (3aS,4R,6aS,10aS)-2-methoxy-3a,4,6a,7-tetramethyl-3,3a,4,5,6,6a-hexahydro-2H-naphtho[8a,1-b]furan-9(10H)-one (**21**)*

To a solution of **19** (10 mg, 0.030 mmol) in MeOH (1 mL), *p*-TsOH·H_2O (0.16 M in MeOH; 10 μL, 1.6 μmol) was added at room temperature. After stirring at room temperature overnight, the reaction mixture was neutralized by addition of $NaHCO_3$ and evaporated. The residue was extracted with Et_2O, and the extract was successively washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue (8 mg) was purified by PTLC to give **20** (4.0 mg, 46%; more polar) and **21** (3.0 mg, 36%; less polar) both as a colorless oil. Compound **20**; $[\alpha]_D^{20}$ +8.2 (*c* 2.58, $CHCl_3$); IR (film): 2951, 1660, 1625, 1452, 1385, 1192, 1117, 1048, 1006, 898 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (3H, d, *J* = 7.2 Hz), 1.09 (3H, s), 1.36 (3H, s), 1.41 (1H, m), 1.55–1.75 (3H, m), 1.90–2.10 (3H, m), 1.99 (3H, s), 3.24 (3H, s), 3.27 (3H, s), 4.28 (1H, dd, *J* = 5.6, 1.2 Hz), 6.07 (1H, s), 6.31 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.18, 19.40, 24.27, 26.30, 27.57, 33.95, 36.40, 41.95, 43.65, 43.92, 52.41, 102.50, 125.71, 126.01, 167.77, 171.98, 186.78; HRMS (ESI) calcd for $C_{18}H_{28}NaO_3$ $(M+Na)^+$: 315.1936, found 315.1917. Compound **21**; $[\alpha]_D^{20}$ +120.4 (*c* 1.05, $CHCl_3$); IR (film): 2957, 1667, 1460, 1379, 1327, 1274, 1107, 1028, 1000, 971 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, d, *J* = 6.8 Hz), 0.96 (3H, s), 1.27 (3H, s), 1.36–1.51 (3H, m), 1.55 (1H, dt, *J* = 11.6, 3.2 Hz), 1.71 (1H, dd, *J* = 13.6, 5.0 Hz), 1.85 (1H, m), 1.90 (3H, s), 2.24 (1H, dd, *J* = 13.6, 6.6 Hz), 2.72 (1H, d, *J* = 16.8 Hz), 2.88 (1H, d, *J* = 16.8 Hz), 3.20 (3H, s), 4.86 (1H, dd, *J* = 6.6, 5.0 Hz), 5.81 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.17, 16.62, 19.46, 22.48, 26.31, 29.77, 35.86, 42.34, 42.73, 45.58, 46.81, 55.68, 89.43, 102.58, 125.43, 168.23, 198.57; HRMS (ESI) calcd for $C_{17}H_{26}NaO_3$ $[M+Na]^+$: 301.1780, found 301.1770.

*4.10. (4aS,7R,8S)-4,4a,7,8-Tetramethyl-8-(2-oxoethyl)-5,6,7,8-tetrahydronaphthalen-2(4aH)-one (**23**)*

To a suspension of **21** (30 mg, 0.10 mmol) and MS4A (30 mg) in CH_2Cl_2 (1 mL), BBr_3 (1.0 M in CH_2Cl_2; 110 μL, 0.11 mmol) was added dropwise over at −78 °C. After stirring for 2 h at −78 °C, the reaction mixture was allowed to warm to room temperature with stirring over 2.5 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted with Et_2O. The extract was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue (28 mg) was chromatographed on silica gel (2 g). Elution with hexane/EtOAc (20/1–1/1) gave **23** (13 mg, 52%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (3H, d, *J* = 6.3 Hz), 1.23 (3H, s), 1.39 (3H, s), 1.43–1.97 (5H, m), 2.00 (3H, s), 2.55 (1H, dd, *J* = 2.7, 17.5 Hz), 2.94 (1H, dd, *J* = 1.7, 17.5 Hz), 6.07 (1H, s), 6.23 (1H, s), 9.67 (1H, dd, *J* = 2.7, 1.7 Hz). This was employed for the next step immediately.

*4.11. (4aS,7R,8S)-8-(2,2-Dimethoxyethyl)-4,4a,7,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2(4aH)-one (**20**)*

To a solution of **23** (13 mg, 0.053 mmol) and $HC(OMe)_3$ (55 μL, 0.05 mmol) in CH_2Cl_2 (1.3 mL), *p*-TsOH·H_2O (1.0 mg, 5.3 μmol) was added at room temperature. After stirring overnight, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue (17 mg) was purified by PTLC to give **20** (10 mg, 68%) as a colorless oil.

*4.12. (4R,4aS,7R,8S,8aS)-8-(2,2-Dimethoxyethyl)-4,4a,7,8-tetramethyloctahydronaphthalen-2(1H)-one (**24**)*

To a solution of Li (173 mg, 24.9 mmol) in liq. NH_3 (230 mL), a solution of *t*-BuOH (475 μL, 5.04 mmol) in THF (10 mL) and a solution of **20** (368 mg, 1.25 mmol) in THF (10 mL) were added dropwise at −78 °C. After stirring for 1 h at the same temperature, the reaction mixture was quenched by cautious addition of NH_4Cl. After removal of NH_3 at room temperature, the residue was diluted with a mixture of Et_2O and sat. aq. $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layer was successively washed with sat. aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue (369 mg) was chromatographed on silica gel (15 g). Elution with hexane/EtOAc (50/1–2/1) gave **24** (232 mg, 63%) as a colorless oil. $[\alpha]_D^{20}$ +41.9 (*c* 1.32, $CHCl_3$); IR (film): 2954, 2829, 1715, 1443, 1387, 1192, 1120, 1054, 984, 961 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (3H, s), 0.84 (3H, d, *J* = 6.4 Hz), 0.86 (3H, d, *J* = 6.4 Hz), 0.94 (3H, s), 1.03 (1H, dt, *J* = 13.0, 8.7 Hz), 1.40–1.46 (2H, m), 1.49–1.63 (5H, m), 1.75 (1H, dt, *J* = 12.8, 3.3 Hz), 2.10–2.17 (2H, m), 2.24 (1H, t, *J* = 14.2 Hz), 2.46 (1H, br d, *J* = 12.8 Hz), 3.26 (3H, s), 3.27 (3H, s), 4.38 (1H, t, *J* = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.53, 14.85, 16.24, 17.10, 27.11, 36.54, 37.57, 38.44, 38.80, 39.19, 40.03, 45.64, 46.32, 49.64, 51.89, 53.42, 101.79, 211.72; HRMS (ESI) calcd for $C_{18}H_{32}NaO_3$ $[M+Na]^+$: 319.2249, found 319.2241.

*4.13. (4aR,7R,8S,8aR)-8-(2,2-Dimethoxyethyl)-4,4a,7,8-tetramethyl-4a,5,6,7,8,8a-hexahydronaphthalen-2(1H)-one (**25**)*

To a solution of **24** (198 mg, 0.668 mmol) in THF (20 mL), LHMDS (1.0 M in THF; 1.3 mL, 1.3 mmol) was added dropwise over 10 min at −78 °C. After stirring for 15 min at –78 °C and for 2 h at −40 °C, a solution of TMSCl (255 μL, 2.01 mmol) and Et_3N (28 μL) in THF (1.4 mL) was added dropwise at −78 °C. After stirring for 0.5 h at the same temperature, the reaction mixture was poured into sat. aq. $NaHCO_3$ and extracted with Et_2O. The extract was washed with brine, dried (Na_2CO_3) and concentrated *in vacuo* to give the crude product (280 mg). This was employed for the next step without further purification.

To a solution of the crude product (280 mg) in CH_3CN (28 mL), $Pd(OAc)_2$ (195 mg, 0.869 mmol) was added, and the reaction mixture was stirred at room temperature for 2 days. After filtration through Celite® pad, the filtrate was concentrated *in vacuo*. The residue (307 mg) was chromatographed on silica gel (15 g). Elution with hexane/EtOAc (5/1–2/1) gave **25** (193 mg, 98%, two steps) as a pale yellow oil. $[\alpha]_D^{20}$ −5.8 (*c* 1.10, $CHCl_3$); IR (film): 2930, 1670, 1617, 1437, 1380, 1325, 1279, 1191, 1118, 1048 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (3H, s), 0.85 (3H, d, *J* = 6.8 Hz), 1.09 (3H, s), 1.34 (1H, ddd, *J* = 12.5, 9.7, 7.5 Hz), 1.45–1.54 (2H, m), 1.60 (1H, m), 1.57 (1H, dd, *J* = 15.3, 4.4 Hz), 1.66 (1H, dd, *J* = 15.3, 5.6 Hz), 1.80 (1H, dt, *J* = 12.5, 3.2 Hz), 1.86 (3H, d, *J* = 1.6 Hz), 1.94 (1H, dd, *J* = 13.6, 3.2), 2.31 (1H, dd, *J* = 17.6, 13.6 Hz), 2.53 (1H, dd, *J* = 17.6, 3.2 Hz), 3.22 (3H, s), 3.24 (3H, s), 4.37 (1H, dd, *J* = 5.6, 4.4 Hz), 5.69 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.04, 17.44, 18.26, 18.90, 26.90, 35.40, 35.47, 36.87, 38.43, 39.97, 39.99, 46.56, 51.79, 53.27, 101.57, 125.51, 172.15, 200.37; HRMS (ESI) calcd for $C_{18}H_{30}NaO_3$ $[M+Na]^+$: 317.2093, found 317.2077.

*4.14. (2R,4aR,7R,8S,8aR)-8-(2,2-Dimethoxyethyl)-4,4a,7,8-tetramethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-2-ol (**26**)*

To a solution of **25** (157 mg, 0.533 mmol) and $CeCl_3 \cdot 7H_2O$ (260 mg, 0.698 mmol) in EtOH (99%; 5 mL) and CH_2Cl_2 (5 mL), a solution of $NaBH_4$ (30 mg, 0.80 mmol) in EtOH (99%; 2 mL) was added dropwise at −78 °C. After stirring for 10 min, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated *in vacuo*. The residue (181 mg) was chromatographed on silica gel (10 g). Elution with hexane/EtOAc (10/1–3/1) gave **26** (157 mg, quant.) as colorless crystals. $[\alpha]_D^{20}$ +8.7 (*c* 1.36, $CHCl_3$); mp 84.0–85.0 °C; IR (KBr): 3203, 2961, 2940, 2911, 2874, 1452, 1118, 1041, 981, 906 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.72 (3H, s), 0.83 (3H, d, *J* = 7.2 Hz), 1.04 (3H, s), 1.15 (1H, ddd, *J* = 12.6, 9.9, 7.3 Hz), 1.25–1.65 (6H, m), 1.61 (3H, s), 1.70 (1H, dt, *J* = 12.6, 3.2 Hz), 1.73 (1H, dd, *J* = 15.2, 6.0 Hz), 2.06 (1H, dd, *J* = 10.8, 6.0 Hz), 3.27 (3H, s), 3.29 (3H, s), 4.21 (1H, m), 4.40 (1H, dd, *J* = 5.6, 4.0 Hz), 5.21 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.18, 17.80, 17.93, 20.01, 27.25, 29.67, 36.28, 36.90, 38.20, 38.73, 40.48, 45.91, 51.83, 53.26, 69.32, 101.96, 124.51, 147.58; HRMS (ESI) calcd for $C_{18}H_{32}NaO_3$ $[M+Na]^+$: 319.2249, found 319.2270.

*4.15. (2R,4aR,7R,8S,8aR)-8-(2,2-Dimethoxyethyl)-4,4a,7,8-tetramethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-2-yl acetate (**27**)*

To a solution of **26** (132 mg, 0.445 mmol) and 4-DMAP (1.1 g, 8.9 mmol) in CH_2Cl_2 (10 mL), Ac_2O (205 μL, 2.22 mmol) was added dropwise at 0 °C. After stirring for 15 min, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4) and concentrated *in vacuo*. The residue (1.2 g) was chromatographed on silica gel (50 g). Elution with hexane/EtOAc (10/1) gave **27** (146 mg, 97%) as a colorless oil. $[\alpha]_D^{20}$ +60.5 (*c* 1.19, $CHCl_3$); IR (film): 2955, 1732, 1448, 1372, 1242, 1120, 1049, 1019, 986, 966 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.72 (3H, s), 0.84 (3H, d, *J* = 6.8 Hz), 1.06 (3H, s), 1.18 (1H, ddd, *J* = 12.6, 8.7, 6.2 Hz), 1.38–1.64 (6H, m), 1.62 (3H, s), 1.70 (1H, dd, *J* = 15.1, 5.5 Hz), 1.71 (1H, dt, *J* = 12.6, 3.2 Hz), 2.05 (1H, m), 2.05 (3H, s), 3.28 (3H, s), 3.34 (3H, s), 4.41 (1H, dd, *J* = 5.7, 4.3 Hz), 5.16 (1H, br s), 5.31 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.20, 17.88, 19.79, 21.48, 25.30, 27.20, 36.12, 36.88, 38.26, 38.73, 40.48, 45.79, 51.97, 53.54, 72.23, 102.04, 120.28, 149.55, 170.92; HRMS (ESI) calcd for $C_{20}H_{34}NaO_4$ $[M+Na]^+$: 361.2355, found 361.2361.

*4.16. (3R,4S,4aR,8aR)-4-(2,2-Dimethoxyethyl)-3,4,8,8a-tetramethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalene (**17**)*

To a solution of Li (3 mg, 0.4 mmol) in liq. NH_3 (10 mL), a solution of **27** (17 mg, 0.059 mmol) in THF (15 mL) was added dropwise at −78 °C. After stirring for 1.5 h, the reaction mixture was quenched by cautious addition of NH_4Cl. After removal of NH_3 at room temperature, the residue was diluted with a mixture of Et_2O and sat. aq. $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layer was successively washed with sat. aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue (14 mg) was chromatographed on silica gel (0.5 g). Elution with hexane/EtOAc (40/1) gave **17** (12 mg, 86%) as a colorless oil. $[\alpha]_D^{20}$ −41.2 (*c* 1.18, $CHCl_3$); IR (film): 2954, 2830, 1448, 1381, 1191, 1119, 1076, 1050, 989, 961 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.70 (3H, s), 0.83 (3H, d, *J* = 6.8 Hz), 0.99 (3H, s), 1.19 (1H, m), 1.35–1.48 (4H, m), 1.58 (3H, br d, *J* = 2.0), 1.57–1.73 (5H, m), 2.00 (2H, m), 3.29 (3H, s), 3.30 (3H, s), 4.42 (1H, t, *J* = 4.8 Hz), 5.18 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.23, 17.86, 18.03, 18.90, 20.01, 26.73, 27.55, 36.69, 37.19, 38.35, 38.55, 40.68, 47.27, 52.27, 53.05, 102.36, 120.61, 144.29; HRMS (ESI) calcd for $C_{18}H_{32}NaO_2$ $[M+Na]^+$: 303.2300, found 303.2322.

*4.17. (1S,2R,4aR,8aR)-(1,2,4a,5-Tetramethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-yl)acetaldehyde (callicarpenal, **1**)*

A solution of **17** (12 mg, 0.042 mmol) in aq. AcOH (80%; 1 mL) was stirred for 1 h at room temperature. The reaction mixture was concentrated *in vacuo*, and the residue was diluted with sat. aq. $NaHCO_3$ and extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue (10 mg) was chromatographed on silica gel (0.8 g). Elution with hexane/EtOAc (40/1) gave **1** (9 mg, 91%) as a colorless oil. Recrystallization from acetonitrile gave colorless prisms. $[\alpha]_D^{20}$ −58.5 (*c* 0.91, $CHCl_3$); mp 49.0-50.0 °C; IR (KBr): 3010, 2995, 2959, 2868, 2833, 1713, 1456, 1389, 1075, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.81 (3H, s), 0.95 (3H, d, *J* = 6.8 Hz), 1.00 (3H, s), 1.20 (1H, m), 1.42–1.77 (7H, m), 1.57 (3H, s), 1.96–2.05 (2H, m), 2.16 (1H, dd, *J* = 14.6, 3.2 Hz), 2.46 (1H, dd, *J* = 14.6, 3.6 Hz), 5.18 (1H, br s), 9.83 (1H, dd, *J* = 3.6, 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.27, 17.21, 17.92, 18.94, 19.87, 26.56, 27.30, 36.42, 38.42, 39.03, 41.67, 49.36, 51.74, 120.55, 143.61, 203.88; HRMS (APCI) calcd for $C_{16}H_{25}O$ $[M-H]^-$: 233.1905, found 233.1910.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at ~.

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Highlights：

A novel synthesis of (−)-callicarpenal was achieved.

Callicarpenal is a tetranorditerpene aldehyde with a potent mosquito repellent activity.

Prins-type cyclization based on Meyer-Schuster rearrangement was featured as a key step.