

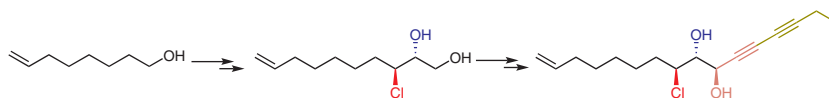
First Stereoselective Total Synthesis of Ciryneol C

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1. Katsuki-Sharpless asymmetric epoxidation

2. Regioselective opening of epoxide

3. Lithium acetylide addition to aldehyde

4. Cadiot-Chodkiewicz coupling reaction

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CSIR-IICT, Communication No. IICT/Pubs./2019/064

Received: 27.03.2019

Accepted after revision: 06.06.2019

Published online: 25.06.2019

DOI: 10.1055/s-0037-1611876; Art ID: so-2019-d0010-op

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Abstract The acetylene derivative Ciryneol C was isolated from the roots of *C. japonicum*. The asymmetric total synthesis of Ciryneol C was achieved in seven steps, with Horner–Wittig olefination, regioselective epoxide opening, and Cadiot–Chodkiewicz coupling reactions being the key steps.

Key words acetylene, Cadiot–Chodkiewicz coupling, natural products, Sharpless asymmetric epoxidation, total synthesis

Living organisms such as phytoplankton, wood-rotting fungi, and plants produce enzymes such as chloroperoxidase that can use chloride ions to chlorinate organic compounds for use in cell adhesion and in defense processes.¹ To date, more than 5000 halogenated natural products have been described. Chlorinated acetylene compounds have been found in the secretory canals of *Asteraceae* species and chlorohydrins in some straight chain acetylenic compounds have been found in *Centaurea ruthenica*, *C. scabiosa* and *Carthamus tinctorius*.²

Plant natural products have been used as an alternative to synthetic fungicides because they are considered to be biodegradable and safe for the environment and delicate ecosystems.³ *Cirsium japonicum* is a wild perennial herb used as a herbal remedy to treat uterine bleeding and inflammation and is a widely used in Korea, China, Australia, and Japan.³ Extracts of *C. japonicum* roots are also highly active antifungal agents. Polyacetylenes 1-heptadecene-11,13-diyne-8,9,10-triol (**1**), ciryneol A (**2**), B (**3**) and C (**4**) were isolated from the methanol extract of *C. japonicum* roots by Takaishi in 1990 (Figure 1).⁴ Among these polyacet-

ylenes, **1**, **2**, and **4** inhibited the mycelial growth of plant pathogenic fungi such as *Magnaporthe oryzae* (rice blast), *Rhizoctonia solani* (rice sheath blight), *Phytophthora infestans* (tomato late blight), *Puccinia recondita* (wheat leaf rust), and *Colletotrichum coccodes* (red pepper anthracnose) at 500 $\mu\text{g mL}^{-1}$ with control values of over 90%.³ These polyacetylenes were also highly active against wheat leaf rust at concentrations of 125 $\mu\text{g mL}^{-1}$.³ Both **2** and **4** inhibited the mycelial growth of *Botrytis cinerea* but **1** had little effect.³ Ciryneol C **4** strongly inhibited the mycelial growth of *Fusarium oxysporum* while the other two compounds expressed weak in vitro antifungal activity.³ Ciryneol C **4** was highly effective in controlling barley powdery mildew, while the other two compounds were moderately active against this plant disease.³

KB (Keratin-forming tumor cell line) cell growth inhibited by ciryneols and its derivatives was measured in vitro, with concentrations required to give 50% growth inhibition (ID_{50}) of 39.5, 10.3, 8.6 $\mu\text{g mL}^{-1}$ for **1**, **3**, and **4**, respectively.⁴ The absolute configuration of ciryneol C **4** was proposed on the basis of CD studies and Mosher's ester analysis.⁵

In a continuation of our synthetic studies on bioactive natural products, we report herein the first total synthesis of ciryneol C **4** from oct-7-en-1-ol (**7**). Molecules containing a chlorine atom at the stereogenic centre along with an adjacent hydroxyl group are not trivial to synthesize under basic conditions. We designed our synthetic strategy as shown in Scheme 1. Ciryneol C **4** could be obtained from an addition of lithium acetylide and Cadiot–Chodkiewicz coupling of chlorohydrin **5**. The synthetic key intermediate chlorohydrin **5** could be derived from regioselective ring opening of *trans*-epoxy alcohol **6**. The latter could, in turn, be obtained from **7**.

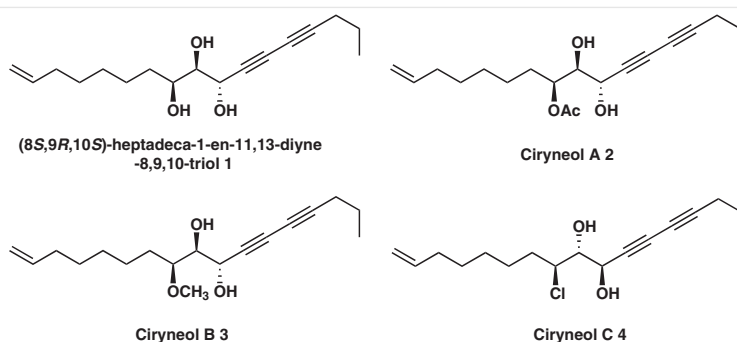
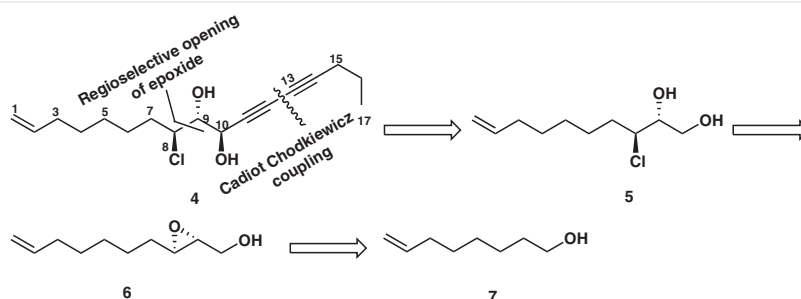


Figure 1 Compounds isolated from *C. Japonicum*

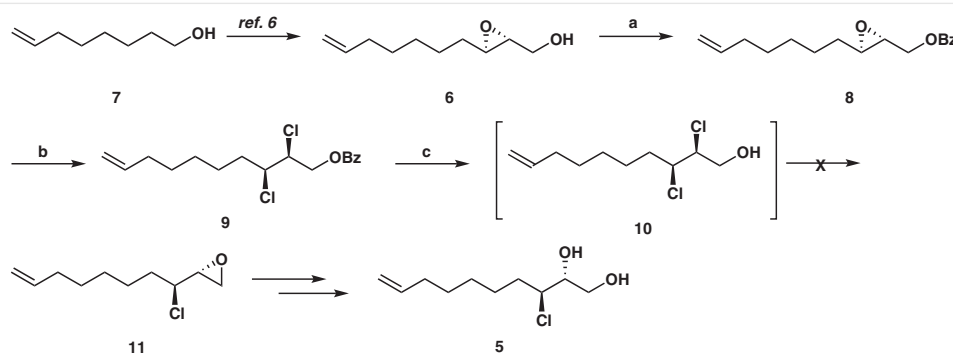


Scheme 1 Retrosynthetic analysis of ciryneol C **4**

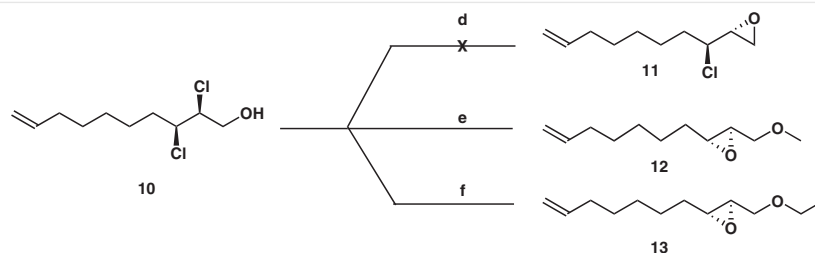
The key fragment, chlorohydrin **5** was synthesized from epoxy alcohol **6**, which was, in turn, accessed from **7** through oxidation, Horner–Wittig olefination followed by reduction and Sharpless asymmetric epoxidation (Scheme 2).⁶ The epoxy alcohol **6** was protected as its benzoate ester (BzCl, Et₃N, DMAP and CH₂Cl₂)⁷ to give epoxy benzoate **8** in 92% yield. Treatment of epoxy benzoate **8** with the chlorophosphonium reagent generated in situ from *N*-chlorosuccinamide and triphenylphosphine in toluene at 90 °C gave

vicinal dichloride **9** in good yield.⁸ The latter was then treated with potassium carbonate in methanol⁷ to give alcohol **10** exclusively, but did not furnish chloroepoxide **11**.

Treating alcohol **10** with NaH in THF at 0 °C led to no reaction, and the starting material decomposed on heating to reflux. When the reaction was repeated with potassium carbonate in methanol at reflux, epoxyether **12** was obtained in 85% yield instead of chloroepoxide **11**; the same outcome was observed with Cs₂CO₃ in ethanol at room temperature, giving epoxyether **13** in 86% yield (Scheme 3).



Scheme 2 Reagents and conditions: (a) Et₃N, DMAP, C₆H₅COCl, CH₂Cl₂, 0 °C to r.t., 2 h, 92% yield. (b) Triphenylphosphine, NCS, toluene, 90 °C, 1 h, 88% yield. (c) K₂CO₃, methanol, 0 °C to r.t., 2 h, 89% yield.



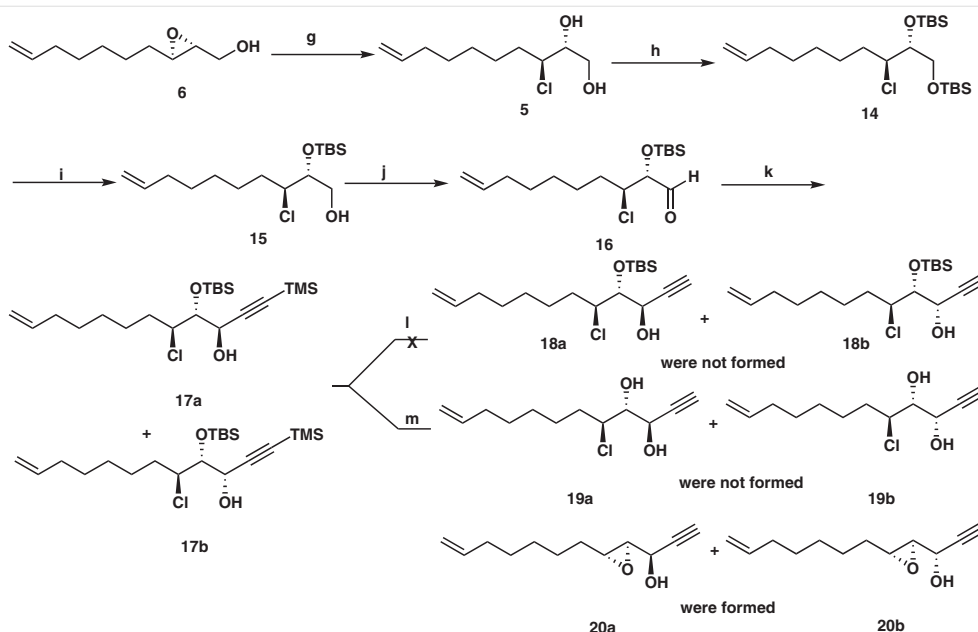
Scheme 3 Reagents and conditions: (d) NaH, THF, 66 °C, 1 h. (e) K₂CO₃, CH₃OH, 65 °C, 2 h, 85% yield. (f) Cs₂CO₃, C₂H₅OH, 0 °C, 1 h, 86% yield.

To overcome the above problem, an alternative route was utilized for the synthesis of chlorohydrin **5**, involving regioselective ring opening of epoxy alcohol **6** with CeCl₃ in monoglyme to furnish the required chlorohydrin **5** in 84% yield (Scheme 4).⁹ Both hydroxy groups of chlorohydrin **5** were then protected as TBS ethers by treatment with TBS chloride and imidazole in DMF to afford **14** in 90% yield.¹⁰ The di-TBS ether **14** underwent subsequent regioselective controlled desilylation in the presence of camphorsulfonic acid in methanol at 0 °C to yield the corresponding primary alcohol **15** in 85% yield.¹¹ The primary alcohol **15**, on treatment with 2-iodoxybenzoic acid (IBX), afforded the corresponding aldehyde **16**¹⁰ in 88% yield, and addition of the organolithium reagent derived from trimethylsilylacetylene to aldehyde **16** afforded a mixture of diastereomers **17a** and **17b**¹² (9:2 ratio, confirmed by ¹H NMR analysis). Attempted removal of the trimethylsilyl group in **17a** and **17b** under basic conditions (K₂CO₃ in methanol)¹³ led to an unidenti-

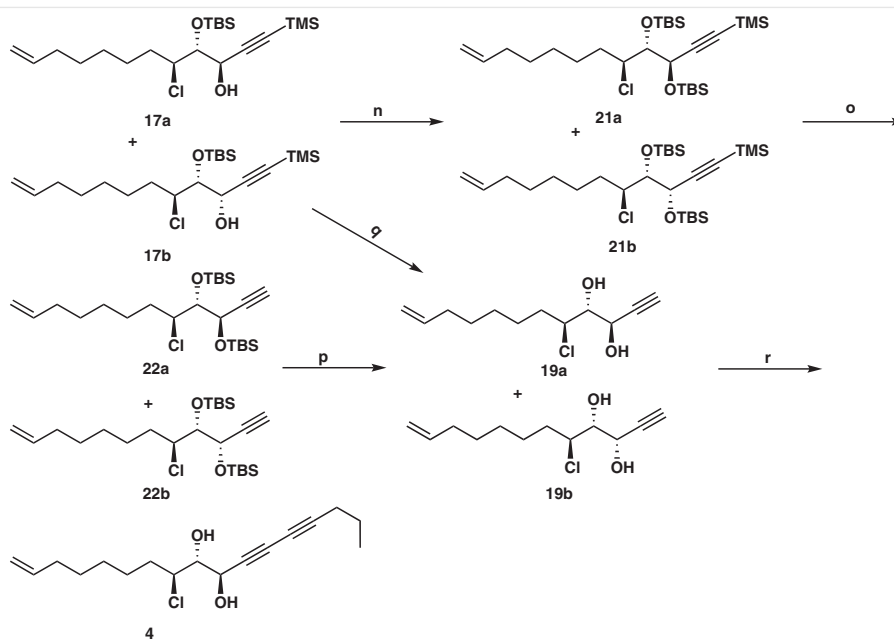
fied product. Subsequently, we tried to remove both silyl groups with tetrabutylammonium fluoride (TBAF) in THF,¹⁴ but this furnished epoxy alcohols **20a** and **20b** instead of diols **19a** and **19b** (Scheme 4).

To avoid this issue, the resulting alcohols **17a** and **17b** were protected using TBSCl, imidazole and DMAP in DMF¹⁵ to give fully protected alkyne **21a** and **21b** in 92% yield (Scheme 5); deprotection of the acetylenic function was then successfully achieved (K₂CO₃ in CH₃OH, 91%),¹³ followed by deprotection of the di-TBS ether using PTSA (20 mol%) in methanol to give diols **19a** and **19b** in 89% yield. The diastereomers were separated by column chromatography. Alternatively, alcohols **17a** and **17b** could be reacted with TBAF (1 M in THF) and acetic acid (1 M in THF) at 0 °C to furnish diols **19a** and **19b** in 74% yield.

The target molecule ciryneol **4** was obtained under Cadiot–Chodkiewicz¹⁶ coupling conditions between diol **19a** and 1-iodopent-1-yne.



Scheme 4 Reagents and conditions: (g) CeCl₃, monoglyme, r.t., 12 h, 84% yield. (h) TBSCl, imidazole, DMAP, DMF, 0 °C to r.t., 24 h, 90% yield. (i) CSA, CH₂Cl₂, methanol (1:1), -10 °C, 2 h, 85% yield. (j) IBX, DMSO, CH₂Cl₂, 0 °C to r.t., 4 h, 88% yield. (k) (i) *n*-BuLi, TMS acetylene, THF, -78 °C (ii) **16**, THF, -78 °C, 1 h, 87% yield. (l) K₂CO₃, CH₃OH, 0 °C, 2 h. (m) TBAF, THF, 0 °C, 1 h, 81% yield.



Scheme 5 Reagents and conditions: (n) TBSCl, imidazole, DMAP, DMF, 0 °C to r.t., 24 h, 92% yield. (o) K₂CO₃, CH₃OH, 0 °C to r.t., 1 h, 91% yield. (p) PTSA, CH₃OH, 0 °C to r.t., 2 h, 89% yield. (q) TBAF, acetic acid, THF, 0 °C, 1 h, 74%. (r) CuCl, NH₂OH·HCl, *n*-BuNH₂, 1-iodopent-1-yne, diethyl ether, 0 °C, 1 h, 81% yield.

All commercially available chemicals and reagents were used without further purification unless otherwise indicated. All reactions are carried out under N₂ atmosphere. Thin-layer chromatography was performed using commercially available silica plates coated with fluorescent indicator and visualization was effected at 254 nm. Column chromatography was carried out using Merck 60–120 mesh silica gel. NMR spectra were recorded in CDCl₃ with Bruker 300, 400, and 500 MHz spectrometers. Chemical shifts are reported in parts per million (δ) relative to TMS (0.00 ppm) for ¹H NMR and CDCl₃ (77.00 ppm) for ¹³C NMR. Specific rotations were measured with a Digipol 781 M6U Automatic Polarimeter. IR spectra were measured with a Jasco FT/IR-410 spectrometer. HRMS were recorded with an Agilent 6545 Q-TOF LCMS, source ESI. Compounds **6** and **7** were prepared according to the reported methods.⁶

((2*R*,3*R*)-3-(Hept-6-enyl)oxiran-2-yl)methylbenzoate (**8**)

To a stirred solution of epoxide **6** (1 g, 5.88 mmol) in CH₂Cl₂ (10 mL) at 0 °C were sequentially added Et₃N (1.0 mL, 7.05 mmol), DMAP (86 mg, 705 μ mol) and benzoyl chloride (751 μ L, 6.46 mmol). Stirring was continued for 2 h and a saturated solution of NH₄Cl (3 mL) was added at 0 °C. The reaction mixture was extracted with CH₂Cl₂ (3 \times 20 mL) and the combined organic phases were dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by silica column chromatography (hexane/EtOAc, 19:1) gave epoxy benzoate **8**.

Yield: 1.48 g (92%); colorless liquid; [α]_D²⁰ +23.6 (c 2.0, CHCl₃).

IR (neat): 3069, 2928, 1720, 1640, 1451, 1111, 907, 710 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 8.07 (dd, *J* = 1.5, 8.4 Hz, 2 H), 7.58 (tt, *J* = 1.3, 8.6 Hz, 1 H), 7.45 (tt, *J* = 1.5, 7.3 Hz, 2 H), 5.88–5.72 (m, 1 H), 5.05–4.89 (m, 2 H), 4.60 (dd, *J* = 3.2, 12.0 Hz, 1 H), 4.20 (dd, *J* = 6.0, 12.0 Hz, 1 H), 3.14–3.06 (m, 1 H), 2.94 (td, *J* = 2.2, 5.4 Hz, 1 H), 2.10–1.98 (m, 2 H), 1.66–1.54 (m, 2 H), 1.54–1.28 (m, 6 H).

¹³C NMR (100 MHz, CDCl₃): δ = 166.2, 138.8, 133.1, 129.7 (3C), 128.3 (2C), 114.3, 65.2, 56.6, 55.3, 33.5, 31.4, 28.7, 28.7, 25.6.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₇H₂₃O₃⁺: 275.1642; found: 275.1639.

(2*S*,3*S*)-2,3-Dichlorodec-9-enyl Benzoate (**9**)

To a stirred solution of epoxy benzoate **8** (1.0 g, 3.64 mmol) in toluene (45 mL) at r.t. were added Ph₃P (2.86 g, 10.9 mmol) and NCS (1.45 g, 10.9 mmol). The mixture was heated at 90 °C for 1 h and the mixture was cooled to 0 °C and treated with sat. aq. Na₂S₂O₃ (20 mL) and sat. aq. NaHCO₃ (30 mL). The reaction mixture was extracted with EtOAc (3 \times 20 mL), the combined organic phases were dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by silica column chromatography (hexane/EtOAc, 98:2) to give dichloride **9**.

Yield: 1.05 g (88%); colorless oil; [α]_D²⁰ –34.2 (c 2.0, CHCl₃).

IR (neat): 3073, 2925, 1725, 1641, 1452, 1268, 911, 710 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 8.05 (dd, *J* = 1.2, 8.2 Hz, 2 H), 7.59 (tt, *J* = 1.3, 8.8 Hz, 1 H), 7.46 (tt, *J* = 1.5, 8.0 Hz, 2 H), 5.84–5.74 (m, 1 H), 5.02–4.97 (m, 1 H), 4.96–4.92 (m, 1 H), 4.64 (d, *J* = 2.7 Hz, 1 H), 4.62 (d, *J* = 2.8 Hz, 1 H), 4.41 (td, *J* = 2.4, 6.7 Hz, 1 H), 4.25–4.21 (m, 1 H), 2.08–2.02 (m, 2 H), 1.96–1.89 (m, 2 H), 1.63–1.53 (m, 1 H), 1.48–1.30 (m, 5 H).

¹³C NMR (100 MHz, CDCl₃): δ = 165.8, 138.6, 133.9, 129.7, 129.3, 128.4, 114.4, 65.5, 61.8, 60.9, 35.0, 33.5, 28.5, 28.3, 26.3.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₇H₂₃Cl₂O₂⁺: 329.1070; found: 329.1063.

(2*S*,3*S*)-2,3-Dichlorodec-9-en-1-ol (**10**)

Potassium carbonate (84 mg, 609 μ mol) was added to a stirred solution of benzoate **9** (100 mg, 304 μ mol) in MeOH (2 mL) at 0 °C and the mixture allowed to stir for 2 h before quenching with NH₄Cl (2 mL).

The reaction mixture was concentrated and extracted with EtOAc (3 × 5 mL), the combined organic phases were dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica column chromatography (hexane/EtOAc, 9:1) to give alcohol **10**.

Yield: 60.7 mg (89%); colorless liquid; $[\alpha]_D^{20}$ -62.2 (c 2.0, CHCl₃).

IR (neat): 3396, 3077, 2924, 1641, 1461, 1051, 901 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 5.88–5.71 (m, 1 H), 5.06–4.90 (m, 2 H), 4.28–4.13 (m, 2 H), 4.01–3.81 (m, 2 H), 2.12–1.82 (m, 5 H), 1.68–1.18 (m, 5 H).

¹³C NMR (125 MHz, CDCl₃): δ = 138.7, 114.4, 65.3, 64.4, 61.9, 35.1, 33.5, 28.6, 28.3, 26.3.

HRMS (ESI): m/z [M + Na]⁺ calcd for C₁₀H₁₈Cl₂O₂Na⁺: 247.0627; found: 247.0636.

(2R,3R)-2-(Hept-6-enyl)-3-(methoxymethyl)oxirane (12)

Potassium carbonate (123 mg, 892 μ mol) was added to a stirred solution of alcohol **10** (100 mg, 446 μ mol) in MeOH (2 mL) at 0 °C, the mixture allowed to stir at 65 °C for 2 h and then quenched with NH₄Cl (20 mL). The reaction mixture was concentrated and extracted with EtOAc (3 × 5 mL) and the combined organic phases were dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica column chromatography (hexane/EtOAc, 97:3) to give epoxyether **12**.

Yield: 69.8 mg (85%); colorless liquid; $[\alpha]_D^{20}$ -1.2 (c 1.0, CHCl₃).

IR (neat): 3070, 2924, 1685, 1453, 1127, 933 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 5.89–5.71 (m, 1 H), 5.06–4.89 (m, 2 H), 3.64 (dd, J = 3.0, 11.2 Hz, 1 H), 3.43–3.34 (m, 1 H), 3.39 (s, 3 H), 2.93–2.87 (m, 1 H), 2.82 (td, J = 2.2, 5.5 Hz, 1 H), 2.11–2.00 (m, 2 H), 1.65–1.28 (m, 8 H).

¹³C NMR (125 MHz, CDCl₃): δ = 138.9, 114.3, 72.7, 59.1, 56.7, 55.9, 33.6, 31.6, 28.8, 28.7, 25.7.

HRMS (ESI): m/z [M + Na]⁺ calcd for C₁₁H₂₀O₂Na⁺: 207.1356; found: 207.1369.

(2R,3R)-2-(Ethoxymethyl)-3-(hept-6-enyl)oxirane (13)

Cesium carbonate (174 mg, 535 μ mol) was added to a stirred solution of alcohol **10** (100 mg, 446 μ mol) in EtOH (2 mL) at 0 °C and the mixture allowed to stir for 1 h before quenching with NH₄Cl (20 mL). The reaction mixture was concentrated to remove EtOH and extracted with EtOAc (3 × 5 mL). The combined organic phases were dried over Na₂SO₄, filtered, and concentrated. The residue was purified by silica column chromatography (hexane/EtOAc, 97:3) to give epoxyether **13**.

Yield: 76 mg (86%); colorless liquid; $[\alpha]_D^{20}$ -0.9 (c 1.0, CHCl₃).

IR (neat): 3076, 2925, 1640, 1461, 1116, 909 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 5.85–5.76 (m, 1 H), 5.00 (dd, J = 1.5, 17.0 Hz, 1 H), 4.94 (dd, J = 1.5, 10.8 Hz, 1 H), 3.66 (dd, J = 3.3, 11.4 Hz, 1 H), 3.60–3.49 (m, 2 H), 3.42 (dd, J = 5.6, 11.4 Hz, 1 H), 2.92–2.88 (m, 1 H), 2.81 (td, J = 2.1, 5.6 Hz, 1 H), 2.08–2.02 (m, 2 H), 1.65–1.31 (m, 8 H), 1.21 (t, J = 7.0 Hz, 3 H).

¹³C NMR (125 MHz, CDCl₃): δ = 138.9, 114.3, 70.8, 66.7, 56.9, 56.1, 33.6, 31.6, 28.8, 28.7, 25.7, 15.1.

HRMS (ESI): m/z [M + H]⁺ calcd for C₁₂H₂₃O₂: 199.1693; found: 199.1694.

(2R,3S)-3-Chlorodec-9-ene-1,2-diol (5)

To a stirred solution of epoxy alcohol **6** (3 g, 17.6 mmol) in monoglyme (30 mL) at r.t. was added cerium chloride (2.53 g, 8.82 mmol) and stirring was continued for 12 h. The reaction mixture was

quenched with sat. aq. NaHCO₃ at 0 °C and extracted with diethyl ether (3 × 15 mL). The combined organic phases were washed with brine, dried over Na₂SO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by silica column chromatography (hexane/EtOAc, 85:15) to give chlorohydrin **5**.

Yield: 3.0 g (84%); colorless liquid; $[\alpha]_D^{20}$ -26.0 (c 3.0, CHCl₃).

IR (neat): 3358, 3078, 2926, 1640, 1435, 1054, 909, 688 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 5.86–5.75 (m, 1 H), 5.04–4.97 (m, 1 H), 4.97–4.92 (m, 1 H), 3.99–3.92 (m, 1 H), 3.86–3.73 (m, 3 H), 3.04–2.78 (brs, 1 H), 2.57–2.23 (brs, 1 H), 2.10–2.02 (m, 2 H), 1.95–1.85 (m, 1 H), 1.76–1.55 (m, 2 H), 1.48–1.24 (m, 5 H).

¹³C NMR (100 MHz, CDCl₃): δ = 138.8, 114.3, 74.6, 63.8, 63.4, 33.5, 33.5, 28.6, 28.4, 26.1.

HRMS (ESI): m/z [M + Na]⁺ calcd for C₁₀H₁₉ClO₂Na: 229.0966; found: 229.0969.

(R)-5-((S)-1-Chlorooct-7-enyl)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxo-3,8-disiladecane (14)

To a stirred solution of diol **5** (1.30 g, 6.31 mmol) in DMF (10 mL) were added imidazole (1.28 g, 18.9 mmol), TBSCl (2.37 g, 15.7 mmol), and DMAP (178 mg, 0.63 mmol) at 0 °C and the mixture was stirred at r.t. for 24 h. The reaction mixture was quenched by the addition of cold water (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic phases were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by silica column chromatography (hexane, 100%) to afford bis-silyl ether **14**.

Yield: 2.46 g (90%); colorless oil; $[\alpha]_D^{20}$ -15.6 (c 0.9, CHCl₃).

IR (neat): 2952, 2928, 1641, 1465, 1116, 909, 668 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 5.86–5.75 (m, 1 H), 5.03–4.98 (m, 1 H), 4.96–4.91 (m, 1 H), 4.09–4.03 (m, 1 H), 3.89–3.83 (m, 1 H), 3.66–3.56 (m, 2 H), 2.10–2.02 (m, 2 H), 1.85–1.74 (m, 1 H), 1.72–1.54 (m, 2 H), 1.46–1.25 (m, 5 H), 0.90 (s, 18 H), 0.12 (s, 3 H), 0.09 (s, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 138.9, 114.2, 76.8, 64.6, 64.1, 33.7, 31.7, 28.7, 28.6, 26.4, 25.9, 25.8, 18.2, 18.1, -4.3, -4.6, -5.4, -5.4.

HRMS (ESI): m/z [M + H]⁺ calcd for C₂₂H₄₈ClO₂Si₂⁺: 435.2876; found: 435.2885.

(2R,3S)-2-(tert-Butyldimethylsilyloxy)-3-chlorodec-9-en-1-ol (15)

To a stirred solution of the di-TBS ether **14** (1.30 g, 2.99 mmol) in CH₂Cl₂ (5 mL) and MeOH (5 mL) at -10 °C, CSA (70 mg, 300 μ mol) was added and stirring was continued for 2 h at the same temperature. The reaction mixture was quenched with solid NaHCO₃ (52 mg, 620 μ mol), filtered, extracted with CH₂Cl₂ (3 × 20 mL), and the combined extracts were dried over Na₂SO₄. Filtration, concentration under reduced pressure and purification of the residue by silica column chromatography (hexane/EtOAc, 95:5) gave alcohol **15**.

Yield: 814 mg (85%); colorless oil; $[\alpha]_D^{20}$ -18.2 (c 0.7, CHCl₃).

IR (neat): 3422, 3077, 2928, 1641, 1464, 1110, 909, 682 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 5.87–5.75 (m, 1 H), 5.03–4.97 (m, 1 H), 4.96–4.93 (m, 1 H), 4.00–3.94 (m, 1 H), 3.85 (dd, J = 3.5, 11.3 Hz, 1 H), 3.80–3.74 (m, 1 H), 3.66 (dd, J = 3.6, 11.3 Hz, 1 H), 2.11–2.00 (m, 2 H), 1.97–1.86 (m, 1 H), 1.86–1.72 (brs, 1 H), 1.68–1.51 (m, 2 H), 1.46–1.23 (m, 5 H), 0.92 (s, 9 H), 0.13 (s, 3 H), 0.12 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 138.8, 114.2, 76.0, 63.7, 62.7, 33.6, 33.5, 28.6, 28.4, 26.2, 25.7, 18.0, -4.4, -4.6.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{16}H_{33}ClO_2Si$ Na^+ : 343.1831; found: 343.1838.

(3R,4R,5S)-4-(tert-Butyldimethylsilyloxy)-5-chloro-1-(trimethylsilyl)dodec-11-en-1-yn-3-ol (17a)

To a stirred solution of IBX (131.2 mg, 468 μ mol) in DMSO (0.5 mL) was added alcohol **15** (100 mg, 312 μ mol) in CH_2Cl_2 (2 mL) at 0 °C and stirring was continued at r.t. for 4 h. The reaction mixture was directly purified by silica column chromatography (hexane/EtOAc, 98:2) to give aldehyde **16** (87.4 mg, 88%). A solution of *n*-BuLi (0.2 mL, 330 μ mol, 1.6 M in hexane) was added to a solution of trimethylsilyl acetylene (0.2 mL, 1.44 μ mol) in THF (2.0 mL) at -78 °C. After 20 min a solution of crude aldehyde **16** (87.4 mg, 275 μ mol) in THF (2.0 mL) was added at -78 °C, stirring was continued for 1 h and the reaction was allowed to warm to 0 °C over 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl (1 mL) and extracted with diethyl ether (3 \times 25 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated in vacuo. The crude product was purified by silica column chromatography (hexane/EtOAc, 98:2) to give a mixture of alcohols **17a** and **17b** (99.4 mg, 87%) as a colorless liquid.

Major Isomer (17a)

IR (neat): 3364, 3077, 2929, 2175, 1641, 1463, 909, 698 cm^{-1} .

1H NMR (500 MHz, $CDCl_3$): δ = 5.85–5.76 (m, 1 H), 5.03–4.97 (m, 1 H), 4.96–4.92 (m, 1 H), 4.60–4.55 (m, 1 H), 4.14–4.09 (m, 1 H), 3.91 (dd, J = 4.4, 5.0 Hz, 1 H), 2.14–2.03 (m, 2 H), 2.03–1.95 (m, 1 H), 1.68–1.54 (m, 2 H), 1.46–1.24 (m, 5 H), 0.93 (s, 9 H), 0.17 (s, 9 H), 0.16 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.9, 114.2, 103.0, 92.1, 78.4, 65.4, 63.5, 33.6, 32.7, 28.7, 28.4, 26.2, 25.9, 18.3, -0.2, -4.1, -4.2.

Minor Isomer (17b)

1H NMR (500 MHz, $CDCl_3$): δ = 5.85–5.76 (m, 1 H), 5.03–4.97 (m, 1 H), 4.96–4.92 (m, 1 H), 4.60–4.55 (m, 1 H), 4.07–4.01 (m, 1 H), 3.89 (dd, J = 3.3, 5.7 Hz, 1 H), 2.14–2.03 (m, 2 H), 1.94–1.86 (m, 1 H), 1.68–1.54 (m, 2 H), 1.46–1.24 (m, 5 H), 0.94 (s, 9 H), 0.17 (s, 9 H), 0.16 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8, 114.3, 104.7, 90.9, 79.0, 63.7, 63.4, 33.6, 33.0, 28.7, 28.4, 26.1, 25.7, 18.3, -0.2, -4.3, -4.4.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{21}H_{42}ClO_2Si_2$: 417.2406; found: 417.2412.

(R)-1-((2R,3R)-3-(Hept-6-enyl)oxiran-2-yl)prop-2-yn-1-ol (20a)

To a stirred solution of alcohol **17a** and **17b** (20.0 mg, 48.0 μ mol) in THF at 0 °C, TBAF (96 μ L, 96.0 μ mol) was added. After 1 h, the reaction mixture was concentrated and purified by silica column chromatography (hexane/EtOAc, 9:1) to give epoxyalcohols **20a** and **20b** (9.3 mg, 81%) as a colorless liquid.

Major Isomer (20a)

IR (neat): 3442, 3309, 2922, 2309, 1642, 1462, 1118, 910 cm^{-1} .

1H NMR (400 MHz, $CDCl_3$): δ = 5.86–5.75 (m, 1 H), 5.03–4.97 (m, 1 H), 4.96–4.92 (m, 1 H), 4.62–4.58 (m, 1 H), 3.13 (td, J = 2.2, 5.6 Hz, 1 H), 3.03 (dd, J = 2.2, 3.1 Hz, 1 H), 2.52 (d, J = 2.3 Hz, 1 H), 2.39–2.22 (brs, 1 H), 2.10–1.99 (m, 2 H), 1.64–1.56 (m, 2 H), 1.54–1.31 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8, 114.3, 80.2, 74.6, 60.7, 59.3, 56.0, 33.5, 31.1, 28.7 (2C), 25.6.

Minor Isomer (20b)

1H NMR (400 MHz, $CDCl_3$): δ = 5.86–5.75 (m, 1 H), 5.03–4.97 (m, 1 H), 4.96–4.92 (m, 1 H), 4.35–4.30 (m, 1 H), 3.02–2.99 (m, 2 H), 2.53 (s, 1 H), 2.39–2.22 (brs, 1 H), 2.10–1.99 (m, 2 H), 1.64–1.56 (m, 2 H), 1.54–1.31 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8, 114.3, 81.0, 74.1, 61.9, 60.2, 56.3, 33.5, 31.1, 28.7 (2C), 25.6.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{12}H_{18}O_2Na$: 217.1199; found: 217.1204.

(5R,6R)-5-((S)-1-Chlorooct-7-enyl)-2,2,3,3,8,8,9,9-octamethyl-6-((trimethylsilyl)ethynyl)-4,7-dioxo-3,8-disiladecane (21a)

To a stirred solution of alcohols **17a** and **17b** (500 mg, 1.20 mmol), imidazole (163 mg, 2.40 mmol) and DMAP (15 mg, 0.12 mmol) in DMF (15 mL) was added *tert*-butyldimethylsilyl chloride (271 mg, 1.8 mmol) at 0 °C and the mixture was allowed to stir at r.t. for 24 h. The reaction mixture was then diluted with water, extracted with EtOAc, dried over Na_2SO_4 , filtered, concentrated and purified by silica column chromatography (hexane, 100%) to give fully protected silyl ethers **21a** and **21b** (586, 92% yield) as a colorless liquid.

Major Isomer (21a)

IR (neat): 2954, 2929, 2174, 1642, 1466, 1093, 910, 699 cm^{-1} .

1H NMR (400 MHz, $CDCl_3$): δ = 5.86–5.75 (m, 1 H), 5.03–4.96 (m, 1 H), 4.95–4.90 (m, 1 H), 4.44 (d, J = 5.5 Hz, 1 H), 4.15–4.09 (m, 1 H), 3.91–3.87 (m, 1 H), 2.09–2.01 (m, 2 H), 1.90–1.78 (m, 1 H), 1.75–1.53 (m, 2 H), 1.48–1.17 (m, 5 H), 0.92 (s, 9 H), 0.90 (s, 9 H), 0.17 (s, 3 H), 0.15 (s, 9 H), 0.13 (s, 3 H), 0.12 (s, 3 H), 0.11 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.9, 114.2, 105.5, 91.0, 79.9, 66.3, 64.1, 33.6, 31.9, 28.7, 28.7, 26.3, 26.1, 25.8, 18.4, 18.2, -0.3, -3.8, -4.3 (2C), -4.9.

Minor Isomer (21b)

1H NMR (400 MHz, $CDCl_3$): δ = 5.86–5.75 (m, 1 H), 5.03–4.96 (m, 1 H), 4.95–4.90 (m, 1 H), 4.53 (d, J = 4.7 Hz, 1 H), 4.25–4.20 (m, 1 H), 3.91–3.87 (m, 1 H), 2.18–2.09 (m, 2 H), 1.90–1.78 (m, 1 H), 1.75–1.53 (m, 2 H), 1.48–1.17 (m, 5 H), 0.92 (s, 9 H), 0.91 (s, 9 H), 0.17 (s, 3 H), 0.14 (s, 9 H), 0.13 (s, 3 H), 0.12 (s, 3 H), 0.11 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.0, 114.2, 105.4, 91.3, 79.0, 65.2, 63.8, 33.7, 32.5, 28.8, 28.5, 26.5, 26.1, 25.9, 18.4, 18.3, -0.4, -4.1, -4.1, -4.4, -4.8.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{27}H_{56}ClO_2Si_3$: 531.3271; found: 531.3277.

(5R,6R)-5-((S)-1-Chlorooct-7-enyl)-6-ethynyl-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxo-3,8-disiladecane (22a)

To a solution of silyl ethers **21a** and **21b** (100 mg, 188 μ mol) in MeOH (2 mL), was added K_2CO_3 (52 mg, 376 μ mol) at 0 °C. The reaction mixture was allowed to stir at r.t. for 1 h, then diluted with water and extracted with EtOAc (3 \times 10 mL). The combine organic extracts were dried over Na_2SO_4 , filtered and concentrated. The residue was purified by silica column chromatography (hexane, 100%) to give **22a** and **22b** (78.6 mg, 91%) as a colorless liquid.

Major Isomer (22a)

IR (neat): 3310, 3077, 2926, 2173, 1641, 1465, 1039, 909, 661 cm^{-1} .

¹H NMR (400 MHz, CDCl₃): δ = 5.86–5.75 (m, 1 H), 5.03–4.96 (m, 1 H), 4.96–4.91 (m, 1 H), 4.58 (dd, *J* = 2.0, 4.4 Hz, 1 H), 4.11–4.05 (m, 1 H), 3.86 (dd, *J* = 4.6, 5.1 Hz, 1 H), 2.39 (d, *J* = 2.2 Hz, 1 H), 2.09–2.01 (m, 2 H), 1.97–1.85 (m, 1 H), 1.74–1.55 (m, 2 H), 1.45–1.16 (m, 5 H), 0.92 (s, 9 H), 0.91 (s, 9 H), 0.16 (s, 3 H), 0.16 (s, 3 H), 0.14 (s, 6 H).

¹³C NMR (100 MHz, CDCl₃): δ = 138.9, 114.2, 82.9, 80.0, 74.3, 65.8, 63.7, 33.6, 32.5, 28.7, 28.6, 26.2, 26.0, 25.8, 18.4, 18.2, –3.8, –4.3, –4.4, –5.0.

Minor Isomer (22b)

¹H NMR (400 MHz, CDCl₃): δ = 5.86–5.75 (m, 1 H), 5.03–4.96 (m, 1 H), 4.96–4.91 (m, 1 H), 4.54 (dd, *J* = 2.3, 4.7 Hz, 1 H), 4.26–4.21 (m, 1 H), 3.91 (dd, *J* = 3.9, 4.6 Hz, 1 H), 2.39 (d, *J* = 2.2 Hz, 1 H), 2.09–2.01 (m, 2 H), 1.97–1.85 (m, 1 H), 1.74–1.55 (m, 2 H), 1.45–1.16 (m, 5 H), 0.92 (s, 9 H), 0.91 (s, 9 H), 0.16 (s, 3 H), 0.16 (s, 3 H), 0.14 (s, 6 H).

¹³C NMR (100 MHz, CDCl₃): δ = 139.0, 114.1, 83.3, 79.0, 74.5, 64.7, 63.4, 33.6, 32.5, 28.7, 28.4, 26.4, 25.9, 25.7, 18.3, 18.1, –4.1, –4.2, –4.5, –5.0.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₄H₄₈ClO₂Si₂⁺: 459.2876; found: 459.2874.

(3R,4R,5S)-5-Chlorododec-11-en-1-yne-3,4-diol (19a)

PTSA (38 mg, 21.8 μmol) was added to a stirred solution of di-TBS ethers **22a** and **22b** (50 mg, 109 μmol) in MeOH at 0 °C and stirring was continued for 2 h. Solid NaHCO₃ was added at 0 °C to quench the reaction and the mixture was filtered and concentrated. The crude residue containing diols **19a** and **19b** was subjected to silica column chromatography (hexane/EtOAc, 7:3) to give diol **19a** (18.2 mg, 72.8%) and **19b** (4.0 mg, 16.1%) [total yield: 22.3 mg (89%)] as colorless liquids.

Alternatively, a mixture of TBAF (293 μmol, 1 M in THF) and acetic acid (293 μmol, 1 M in THF) was added to a solution of alcohols **17a** and **17b** (61 mg, 146.6 μmol) in THF (1 mL) at 0 °C and the mixture allowed to stir for 1 h at the same temperature. Removal of the THF and acetic acid in vacuo and purification by silica column chromatography (hexane/EtOAc, 7:3) gave diol **19a** (20.4 mg, 60.5%) and diol **19b** (4.5 mg, 13.4%) as colorless liquids (total yield: 24.9 mg, 74%).

Major Compound (19a)

[α]_D²⁰ –18.8 (c 1.1, CHCl₃).

IR (neat): 3378, 3296, 3076, 2925, 2117, 1640, 1436, 1041, 910, 642 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 5.86–5.76 (m, 1 H), 5.05–4.90 (m, 2 H), 4.89–4.84 (m, 1 H), 3.93 (td, *J* = 2.4, 9.1 Hz, 1 H), 3.82–3.76 (m, 1 H), 3.42–2.82 (brs, 2 H), 2.56 (d, *J* = 2.1 Hz, 1 H), 2.14–2.04 (m, 3 H), 1.75–1.58 (m, 2 H), 1.49–1.27 (m, 5 H).

¹³C NMR (100 MHz, CDCl₃): δ = 138.8, 114.3, 80.2, 76.3, 75.6, 64.0, 61.9, 33.5 (2C), 28.6, 28.5, 25.5.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₂H₂₀ClO₂: 231.1146; found: 231.1152.

Minor Compound (19b)

[α]_D²⁰ –11.0 (c 0.5, CHCl₃).

IR (neat): 3396, 3297, 3076, 2923, 2118, 1640, 1436, 1037, 910, 670 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 5.85–5.76 (m, 1 H), 5.03–4.97 (m, 1 H), 4.97–4.91 (m, 1 H), 4.75–4.70 (m, 1 H), 4.12–4.07 (m, 1 H), 3.82–3.74 (m, 1 H), 3.03–2.88 (brs, 2 H), 2.55 (d, *J* = 2.2 Hz, 1 H), 2.09–2.02 (m, 2 H), 1.99–1.91 (m, 1 H), 1.80–1.69 (m, 1 H), 1.67–1.57 (m, 1 H), 1.49–1.27 (m, 5 H).

¹³C NMR (100 MHz, CDCl₃): δ = 138.8, 114.3, 81.9, 77.3, 74.8, 62.5, 61.9, 33.5, 32.8, 28.6, 28.4, 25.8.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₂H₂₀ClO₂: 231.1146; found: 231.1155.

(8R,9R,10S)-10-Chloroheptadeca-16-en-4,6-diyne-8,9-diol (4)

CuCl (1 mg, 10 μmol) was added to a 30% *n*-BuNH₂ solution at r.t., leading to a blue solution. To discharge the blue color a few crystals of hydroxylamine hydrochloride were added. Alkyne **19a** (10 mg, 43.4 μmol) in diethyl ether (1 mL) was then added, the mixture was cooled to 0 °C and 1-iodopent-1-yne (10 mg, 52 μmol) in diethyl ether (0.5 mL) was added. The reaction mixture was allowed to warm to r.t. and stirring was continued for 30 min. It was necessary to add hydroxylamine hydrochloride crystals at appropriate intervals during the reaction to prevent the solution from turning blue or green. The reaction mixture was extracted with diethyl ether (3 × 10 mL), the combined extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by silica column chromatography (hexane/EtOAc, 9:1) to give ciryneol C **4**.

Yield: 10.4 mg (81%); [α]_D²⁰ +1.3 (c 0.9, CHCl₃) [lit.⁴ ciryneol C, [α]_D²³ +20.7 (c 1.0, CHCl₃)].

IR (neat): 3308, 3289, 3031, 2925, 2254, 1641, 1460, 1053, 910, 649 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 5.81 (m, 1 H, H-2), 5.00 (m, 1 H, H-1), 4.95 (m, 1 H, H-1'), 4.88 (m, 1 H, H-10), 3.92 (m, 1 H, H-8), 3.77 (m, 1 H, H-9), 2.93 (m, 1 H, H-9-OH), 2.73 (m, 1 H, H-10-OH), 2.26 (m, 2 H, H-15, H-15'), 2.06 (m, 3 H, H-3, H-3', H-6), 1.71 (m, 2 H, H-7, H-7'), 1.62 (m, 3 H, H-5, H-5', H-6'), 1.57 (m, 2 H, H-16, H-16'), 1.41 (m, 2 H, H-4, H-4'), 0.99 (t, 3 H, *J* = 7.4 Hz, H-17).

¹³C NMR (100 MHz, CDCl₃): δ = 138.9, 114.3, 82.1, 76.6, 72.4, 71.6, 64.8, 64.2, 62.0, 33.6, 33.5, 28.6, 28.5, 25.5, 21.5, 21.1, 13.4.

HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₁₇H₂₅ClO₂Na⁺: 319.1435; found: 319.1421.

The assignment of protons was based on 2D NMR (gDQFCOSY, and NOESY) experiments. The presence of characteristic NOE correlations between C₈H/C₁₀H, C₈H/α-OH, C₉H/C₇H, C₁₀H/β-OH, C₈H/C₆H, confirmed the assigned structure (see the Supporting Information).

Funding Information

A.S. thanks UGC, New Delhi, India for the award of a Fellowship. The authors thank CSIR, New Delhi, India for financial support and GAP 0623 Ministry of AYUSH.

Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0037-1611876>.

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