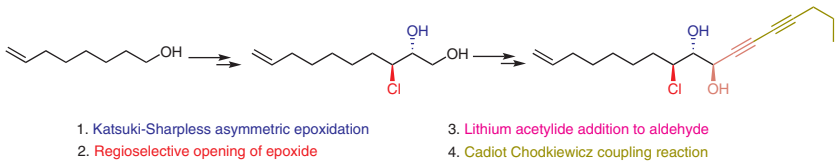
SynOpen A. Sharada et al. THIEME OPEN ACCESS Paper

First Stereoselective Total Synthesis of Ciryneol C

Ambati Sharada[a]
Lakshmi Srinivasa Rao Kundeti[a]
Kallaganti V. S. Ramakrishna[b]
Kommu Nagaiah*[a]

[a] Centre for Natural Products & Traditional Knowledge, CSIR-Indian Institute of Chemical Technology, Hyderabad, 500 007, India
nagaiah@iict.res.in
[b] Centre for NMR and SC, CSIR-Indian Institute of Chemical Technology, Hyderabad, 500 007, India

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

License terms:

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 polyacetylenes, **1**, **2**, and **4** inhibited the mycelial growth of plant pathogenic fungi such as *Magnaporthe oryzae* (rice blast), *Rhizoctonia solani* (rice sheath blight), *Phytophthora infestants* (tomato late blight), *Puccinia recondita* (wheat leaf rust), and *Colletotrichum coccodes* (red pepper anthracnose) at 500 μg mL^{-1} with control values of over 90%.[3] These polyacetylenes were also highly active against wheat leaf rust at concentrations of 125 μg 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 μg 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**.

© 2019. Thieme. All rights reserved.

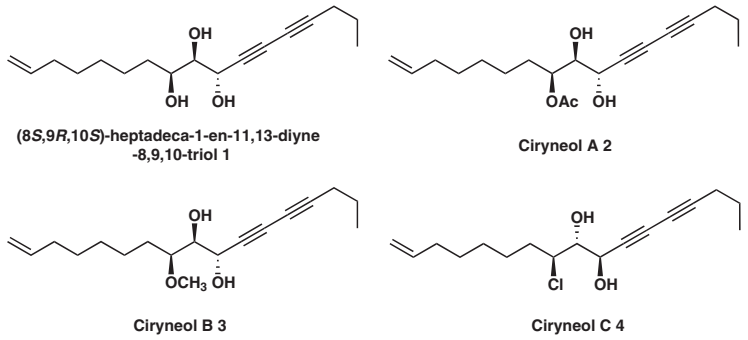
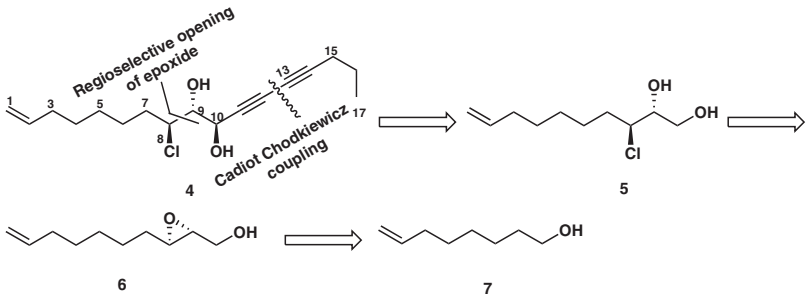


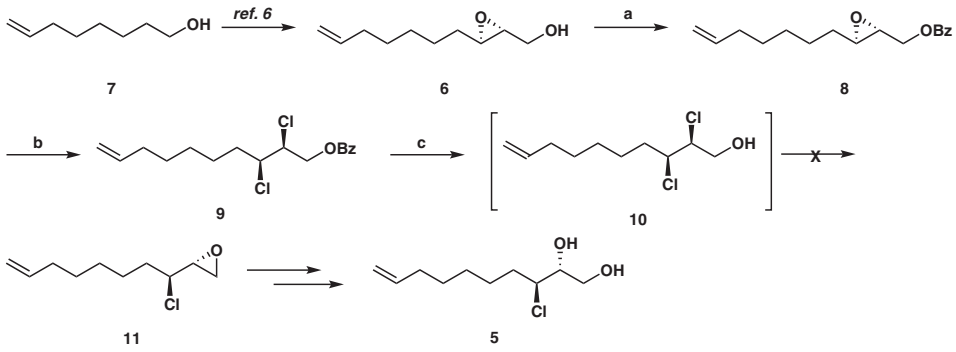
Figure 1 Compounds isolated from *C. Japonicum*



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

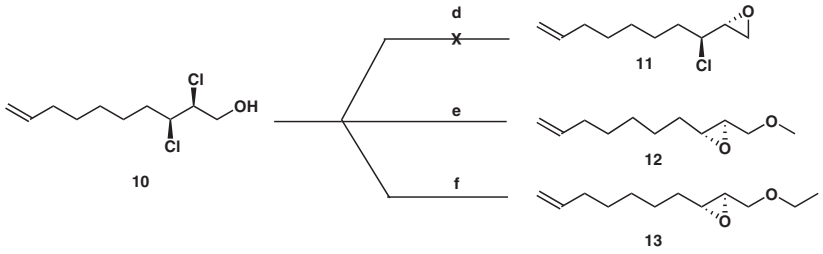
The key fragment, chlorohydrin **5** was synthesized from epoxy alcohol **6**, which was, in turn, accessed from **7** through oxidation, Horner–Wittig olefination followed by reduction and Sharpless asymmetric epoxidation (Scheme 2).[6] The epoxy alcohol **6** was protected as its benzoate ester (BzCl, Et_3N, DMAP and CH_2Cl_2)[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 methanol[7] 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 Cs_2CO_3 in ethanol at room temperature, giving epoxyether **13** in 86% yield (Scheme 3).



Scheme 2 *Reagents and conditions*: (a) Et_3N, DMAP, C_6H_5COCl, CH_2Cl_2, 0 °C to r.t., 2 h, 92% yield. (b) Triphenylphosphine, NCS, toluene, 90 °C, 1 h, 88% yield. (c) K_2CO_3, methanol, 0 °C to r.t., 2 h, 89% yield.

© 2019. Thieme. All rights reserved.

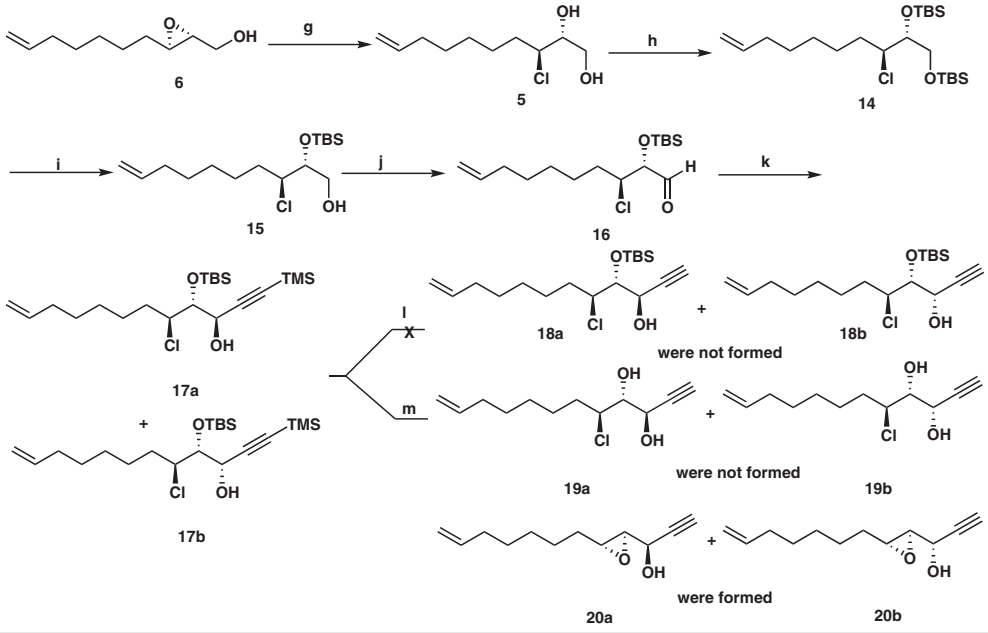


Scheme 3 *Reagents and conditions*: (d) NaH, THF, 66 °C, 1 h. (e) K_2CO_3, CH_3OH, 65 °C, 2 h, 85% yield. (f) Cs_2CO_3, C_2H_5OH, 0 °C, 1 h, 86% yield.

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 $CeCl_3$ 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 (K_2CO_3 in methanol)[13] led to an unidentified 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).

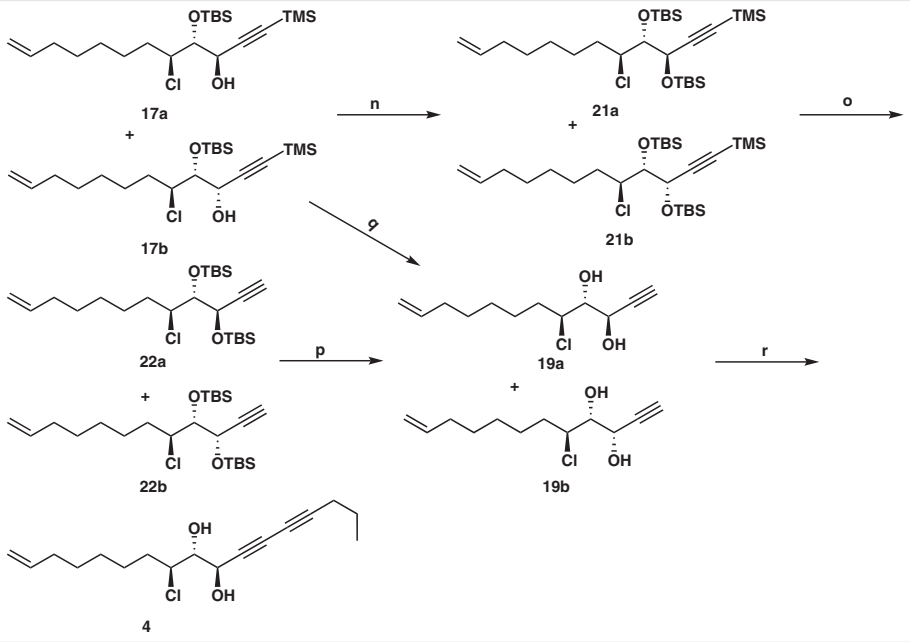
To avoid this issue, the resulting alcohols **17a** and **17b** were protected using TBSCl, imidazole and DMAP in DMF[15] to give fully protected alkyne **21a** and **21b** in 92% yield (Scheme 5); deprotection of the acetylenic function was then successfully achieved (K_2CO_3 in CH_3OH, 91%),[13] followed 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 C **4** was obtained under Cadiot–Chodkiewicz[16] coupling conditions between diol **19a** and 1-iodopent-1-yne.



Scheme 4 *Reagents and conditions*: (g) $CeCl_3$, monoglyme, r.t., 12 h, 84% yield. (h) TBSCl, imidazole, DMAP, DMF, 0 °C to r.t., 24 h, 90% yield. (i) CSA, CH_2Cl_2, methanol (1:1), –10 °C, 2 h, 85% yield. (j) IBX, DMSO, CH_2Cl_2, 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) K_2CO_3, CH_3OH, 0 °C, 2 h. (m) TBAF, THF, 0 °C, 1 h, 81% yield.

© 2019. Thieme. All rights reserved.



Scheme 5 *Reagents and conditions*: (n) TBSCl, imidazole, DMAP, DMF, 0 °C to r.t., 24 h, 92% yield. (o) K_2CO_3, CH_3OH, 0 °C to r.t., 1 h, 91% yield. (p) PTSA, CH_3OH, 0 °C to r.t., 2 h, 89% yield. (q) TBAF, acetic acid, THF, 0 °C, 1 h, 74%. (r) CuCl, NH_2OH·HCl, *n*-$BuNH_2$, 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 N_2 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 $CDCl_3$ with Bruker 300, 400, and 500 MHz spectrometers. Chemical shifts are reported in parts per million (δ) relative to TMS (0.00 ppm) for ^{1}H NMR and $CDCl_3$ (77.00 ppm) for ^{13}C 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 CH_2Cl_2 (10 mL) at 0 °C were sequentially added Et_3N (1.0 mL, 7.05 mmol), DMAP (86 mg, 705 µmol) and benzoyl chloride (751 µL, 6.46 mmol). Stirring was continued for 2 h and a saturated solution of NH_4Cl (3 mL) was added at 0 °C. The reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic phases were dried over Na_2SO_4, 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; $[\alpha]_D^{20}$ +23.6 (*c* 2.0, $CHCl_3$).

IR (neat): 3069, 2928, 1720, 1640, 1451, 1111, 907, 710 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): 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).

^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{17}H_{23}O_3^+$: 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 Ph_3P (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. $Na_2S_2O_3$ (20 mL) and sat. aq. $NaHCO_3$ (30 mL). The reaction mixture was extracted with EtOAc (3 × 20 mL), the combined organic phases were dried over Na_2SO_4, 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; $[\alpha]_D^{20}$ –34.2 (*c* 2.0, $CHCl_3$).

IR (neat): 3073, 2925, 1725, 1641, 1452, 1268, 911, 710 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): 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).

^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{17}H_{23}Cl_2O_2^+$: 329.1070; found: 329.1063.

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

Potassium carbonate (84 mg, 609 µmol) was added to a stirred solution of benzoate **9** (100 mg, 304 µmol) in MeOH (2 mL) at 0 °C and the mixture allowed to stir for 2 h before quenching with NH_4Cl (2 mL).

© 2019. Thieme. All rights reserved.

The reaction mixture was concentrated and extracted with EtOAc (3 × 5 mL), the combined organic phases were dried over Na_2SO_4, 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, $CHCl_3$).

IR (neat): 3396, 3077, 2924, 1641, 1461, 1051, 901 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): 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).

^{13}C NMR (125 MHz, $CDCl_3$): 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 $C_{10}H_{18}Cl_2ONa^+$: 247.0627; found: 247.0636.

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

Potassium carbonate (123 mg, 892 µmol) was added to a stirred solution of alcohol **10** (100 mg, 446 µmol) in MeOH (2 mL) at 0 °C, the mixture allowed to stir at 65 °C for 2 h and then quenched with NH_4Cl (20 mL). The reaction mixture was concentrated and extracted with EtOAc (3 × 5 mL) and the combined organic phases were dried over Na_2SO_4, 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, $CHCl_3$).

IR (neat): 3070, 2924, 1685, 1453, 1127, 933 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): 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).

^{13}C NMR (125 MHz, $CDCl_3$): 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 $C_{11}H_{20}O_2Na^+$: 207.1356; found: 207.1369.

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

Cesium carbonate (174 mg, 535 µmol) was added to a stirred solution of alcohol **10** (100 mg, 446 µmol) in EtOH (2 mL) at 0 °C and the mixture allowed to stir for 1 h before quenching with NH_4Cl (20 mL). The reaction mixture was concentrated to remove EtOH and extracted with EtOAc (3 × 5 mL). The combined organic phases were dried over Na_2SO_4, 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, $CHCl_3$).

IR (neat): 3076, 2925, 1640, 1461, 1116, 909 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): 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).

^{13}C NMR (125 MHz, $CDCl_3$): 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 $C_{12}H_{23}O_2$: 199.1693; found: 199.1694.

(2*R*,3*S*)-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. $NaHCO_3$ at 0 °C and extracted with diethyl ether (3 × 15 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, 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, $CHCl_3$).

IR (neat): 3358, 3078, 2926, 1640, 1435, 1054, 909, 688 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): 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).

^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{10}H_{19}ClO_2Na$: 229.0966; found: 229.0969.

(*R*)-5-((*S*)-1-Chlorooct-7-enyl)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-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 Na_2SO_4, 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, $CHCl_3$).

IR (neat): 2952, 2928, 1641, 1465, 1116, 909, 668 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): 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).

^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{22}H_{48}ClO_2Si_2^+$: 435.2876; found: 435.2885.

(2*R*,3*S*)-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 CH_2Cl_2 (5 mL) and MeOH (5 mL) at –10 °C, CSA (70 mg, 300 µmol) was added and stirring was continued for 2 h at the same temperature. The reaction mixture was quenched with solid $NaHCO_3$ (52 mg, 620 µmol), filtered, extracted with CH_2Cl_2 (3 × 20 mL), and the combined extracts were dried over Na_2SO_4. 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, $CHCl_3$).

IR (neat): 3422, 3077, 2928, 1641, 1464, 1110, 909, 682 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): 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).

^{13}C NMR (100 MHz, $CDCl_3$): 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.

© 2019. Thieme. All rights reserved.

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

(3*R*,4*R*,5*S*)-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 μmol) in DMSO (0.5 mL) was added alcohol **15** (100 mg, 312 μmol) 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 μmol, 1.6 M in hexane) was added to a solution of trimethylsilyl acetylene (0.2 mL, 1.44 μmol) in THF (2.0 mL) at –78 °C. After 20 min a solution of crude aldehyde **16** (87.4 mg, 275 μmol) 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 × 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}.

^{1}H 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)

^{1}H 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-((2*R*,3*R*)-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 μmol) in THF at 0 °C, TBAF (96 μL, 96.0 μmol) 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}.

^{1}H 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)

^{1}H 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.

(5*R*,6*R*)-5-((*S*)-1-Chlorooct-7-enyl)-2,2,3,3,8,8,9,9-octamethyl-6-((trimethylsilyl)ethynyl)-4,7-dioxa-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}.

^{1}H 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)

^{1}H 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.

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

To a solution of silyl ethers **21a** and **21b** (100 mg, 188 μmol) in MeOH (2 mL), was added K_2CO_3 (52 mg, 376 μmol) 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 × 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}.

© 2019. Thieme. All rights reserved.

^{1}H NMR (400 MHz, $CDCl_3$): 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).

^{13}C NMR (100 MHz, $CDCl_3$): 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)

^{1}H NMR (400 MHz, $CDCl_3$): 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).

^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{24}H_{48}ClO_2Si_2^+$: 459.2876; found: 459.2874.

(3*R*,4*R*,5*S*)-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 $NaHCO_3$ 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)

$[\alpha]_D^{20}$ –18.8 (*c* 1.1, $CHCl_3$).

IR (neat): 3378, 3296, 3076, 2925, 2117, 1640, 1436, 1041, 910, 642 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): 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).

^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{12}H_{20}ClO_2$: 231.1146; found: 231.1152.

Minor Compound (19b)

$[\alpha]_D^{20}$ –11.0 (*c* 0.5, $CHCl_3$).

IR (neat): 3396, 3297, 3076, 2923, 2118, 1640, 1436, 1037, 910, 670 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 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).

^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{12}H_{20}ClO_2$: 231.1146; found: 231.1155.

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

CuCl (1 mg, 10 μmol) was added to a 30% *n*-$BuNH_2$ 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 Na_2SO_4, 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%); $[\alpha]_D^{20}$ +1.3 (*c* 0.9, $CHCl_3$) {lit.[4] ciryneol C, $[\alpha]_D^{23}$ +20.7 (*c* 1.0, $CHCl_3$)}.

IR (neat): 3308, 3289, 3031, 2925, 2254, 1641, 1460, 1053, 910, 649 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): 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, H9-OH), 2.73 (m, 1 H, H10-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).

^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{17}H_{25}ClO_2Na^+$: 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 $C_8H/C_{10}H$, C_8H/α-OH, C_9H/C_7H, $C_{10}H/\beta$-OH, C_8H/C_6H, 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.

© 2019. Thieme. All rights reserved.

References

(1) Myneni, S. C. B. *Science* **2002**, *295*, 1039.
(2) Engvild, K. C. *Phytochemistry* **1986**, *25*, 781.
(3) Yoon, M.-Y.; Choi, G. J.; Choi, Y. H.; Jang, K. S.; Cha, B.; Kim, J. C. *Industrial Crops and Products* **2011**, *34*, 882; and references therein.
(4) Takaishi, Y.; Okuyama, T.; Masuda, A.; Nakano, K.; Murakami, K.; Tomimastu, T. *Phytochemistry* **1990**, *29*, 3849.
(5) Lai, W.-C.; Wu, Y.-C.; Danko, B.; Cheng, Y.-B.; Hsieh, T.-J.; Hsieh, C.-T.; Tsai, Y.-C.; El-Shazly, M.; Martins, A.; Hohmann, J.; Hunyadi, A.; Chang, F.-R. *J. Nat. Prod.* **2014**, *77*, 1624.
(6) Castejon, P.; Moyano, A.; Pericas, M. A.; Riera, A. *Synth. Commun.* **1994**, *24*, 1231.
(7) Watanbe, H.; Watanable, H.; Kitahra, T. *Tetrahedron Lett.* **1998**, *39*, 8313.
(8) Yoshimitsu, T.; Fukumoto, N.; Nakatani, R.; Kojima, N.; Tanaka, T. *J. Org. Chem.* **2010**, *75*, 5425.
(9) Wang, C.; Yamamoto, H. *Org. Lett.* **2014**, *16*, 5937.
(10) Sharada, A.; Rao, S. L. K.; Yadav, S. J.; Rao, P. T.; Nagaiah, K. *Synthesis* **2017**, *47*, 2483.
(11) Ramulu, U.; Ramesh, D.; Reddy, S. P.; Rajaram, S.; Babu, K. S. *Tetrahedron: Asymmetry* **2014**, *25*, 1409.
(12) Mori, K. *Tetrahedron* **2012**, *68*, 1936.
(13) (a) Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc.* **2002**, *124*, 8188. (b) Rao, K. N.; Kanakaraju, M.; Kunwar, C. A.; Ghosh, S. *Org. Lett.* **2016**, *18*, 4092.
(14) Wu, C.-J.; Madhushaw, R. J.; Liu, R.-S. *J. Org. Chem.* **2003**, *68*, 7889.
(15) Vedrenne, E.; Royer, F.; Oble, J.; El Kaïm, L.; Grimaud, L. *Synlett* **2005**, 2379.
(16) Cadiot, P.; Chodkiewicz, W. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, **1969**, 597–647.

© 2019. Thieme. All rights reserved.