First Stereoselective Total Synthesis of Ciryneol C

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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.

Keywords 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 defense processes. 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.

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. * 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. * 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). * 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 infestans (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%.

These polyacetylenes were also highly active against wheat leaf rust at concentrations of 125 µg mL⁻¹. * Both 2 and 4 inhibited the mycelial growth of Botrytis cinerea but 1 had little effect. * Ciryneol C strongly inhibited the mycelial growth of Fusarium oxysporum while the other two compounds expressed weak in vitro antifungal activity. * Ciryneol C was highly effective in controlling barley powdery mildew, while the other two compounds were moderately active against this plant disease.

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 (IC₅₀) of 39.5, 10.3, 8.6 µg mL⁻¹ for 1, 3, and 4, respectively. * The absolute configuration of ciryneol C was proposed on the basis of CD studies and Mosher’s ester analysis.

In a continuation of our synthetic studies on bioactive natural products, we report herein the first total synthesis of ciryneol C 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 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.
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**Scheme 1** Retrosynthetic analysis of ciryneol C

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). The epoxy alcohol 6 was protected as its benzoate ester (BzCl, Et₃N, DMAP and CH₂Cl₂) 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. The latter was then treated with potassium carbonate in methanol 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).
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). 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. 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. The primary alcohol 15, on treatment with 2-iodoxybenzoic acid (IBX), afforded the corresponding aldehyde 16 in 88% yield, followed by deprotection of the acetylenic function to give diols 19a and 19b (Scheme 5). 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 coupling conditions between diol 19a and 1-iodopent-1-yne.

**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.

**Scheme 4** Reagents and conditions: (g) CeCl₃, monoglyme, r.t., 12 h, 84% yield. (h) TBSCI, 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.
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. Specific rotations were measured with a Digipol 781 M6U Automatic Polarimeter. IR spectra were measured with a Jasco FTIR-610 spectrometer. HRMS were recorded with an Agilent 6545 Q-TOF LCMS, source ESI. Compounds [M + H]+: 275.1642; found: 275.1639.

(S,3S)-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 × 20 mL), the combined organic phases were dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by silica column chromatography (hexane/EtOAc, 80:2) to give dichloride 9.

Yield: 1.05 g (88%); colorless oil; [α]₂⁰ –34.2 (c 2.0, CHCl₃).

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

HRMS (ESI): m/z [M + H]+ calcd for C₁₇H₂₃Cl₂O₂: 275.1642; found: 275.1639.
The reaction mixture was concentrated and extracted with EtOAc (3 × 5 mL), the combined organic phases were dried over Na2SO4 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; [α]D20 = −62.2 (c 2.0, CHCl3).

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

1H NMR (500 MHz, CDC13): δ = 5.85–5.71 (m, 1 H), 5.06–4.90 (m, 2 H), 4.28–4.13 (m, 2 H), 2.12–1.82 (m, 5 H), 1.68–1.18 (m, 5 H).

13C NMR (125 MHz, CDC13): δ = 138.7, 114.4, 65.3, 64.4, 61.9, 35.1, 33.5, 28.6, 28.3, 26.3.


(2R,3R)-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 NH4Cl (20 mL). The reaction mixture was concentrated and extracted with EtOAc (3 × 5 mL) and the combined organic phases were dried over Na2SO4 and filtered. The residue was purified by silica column chromatography (hexane/EtOAc, 97:3) to give epoxyether 12.

Yield: 69.8 mg (85%); colorless liquid; [α]D20 = −12.0 (c 1.0, CHCl3).

IR (neat): 3070, 2924, 1641, 1453, 1127, 933 cm−1.

1H NMR (300 MHz, CDC13): 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, CDC13): δ = 138.9, 114.3, 72.7, 59.1, 56.7, 55.9, 33.6, 31.6, 28.8, 28.7, 25.7.


(2R,3R)-2-(Ethenyloxymethyl)-3-(hex-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 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 and filtered. The residue was purified by silica column chromatography (hexane/EtOAc, 100%) to afford bis-silyl ether 13.

Yield: 76 mg (86%); colorless liquid; [α]D20 = −0.9 (c 1.0, CHCl3).

IR (neat): 3076, 2926, 1640, 1461, 1116, 909 cm−1.

1H NMR (500 MHz, CDC13): 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, CDC13): 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 C14H22O2Si2: 345.2876; found: 345.2885.

(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 chlorohydin 5.

Yield: 3.0 g (84%); colorless liquid; [α]D20 = −26.0 (c 3.0, CHCl3).

IR (neat): 3358, 3078, 2926, 1640, 1455, 1054, 909, 688 cm−1.

1H NMR (400 MHz, CDC13): 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, CDC13): δ = 138.8, 114.3, 74.6, 63.8, 63.4, 33.5, 33.5, 28.6, 28.4, 26.1.

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 CH₂Cl₂ (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 mmol, 1.6 M in hexane) was added to a solution of trimethylsilyl acetylene (0.2 mL, 1.44 mmol) 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. NH₄Cl (1 mL) and extracted with diethyl ether (3 × 25 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by 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): 3634, 3077, 2929, 2175, 1641, 1463, 909, 698 cm⁻¹.

³¹H NMR (500 MHz, CDCl₃): 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).

¹³C NMR (100 MHz, CDCl₃): 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)

¹³C NMR (100 MHz, CDCl₃): 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.


To a stirred solution of alcohol 17a and 17b (200 mg, 480 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 column chromatography (hexane/EtOAc, 9:1) to give epoxyalcohols 20a and 20b (93.9 mg, 81%) as a colorless liquid.

Major Isomer (20a)

IR (neat): 3442, 3309, 2922, 2309, 1642, 1462, 1118, 910 cm⁻¹.

¹¹B NMR (400 MHz, CDCl₃): 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).

¹³C NMR (100 MHz, CDCl₃): 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)

¹¹B NMR (400 MHz, CDCl₃): 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).

¹³C NMR (100 MHz, CDCl₃): δ = 138.8, 114.3, 81.0, 74.1, 61.9, 60.2, 56.3, 33.5, 31.1, 28.7 (2C), 25.6.


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**Minor Compound (19b)**

**IR (neat):** 3378, 3296, 3076, 2925, 2117, 1640, 1461, 1053, 910, 649 cm⁻¹.

**13C NMR (100 MHz, CDCl₃):** δ = 139.8, 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, 18.1, –4.1, –4.2, –4.5, –5.0.

**HRMS (ESI):** m/z [M + H⁺] calculated for C₁₇H₂₅ClO₂Si₂: 459.2874; found: 459.2874.

**(3R,4R,5S)-5-Chlorodec-11-en-1-yn-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 diol 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 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)**

[a]ᵣ₀° –18.8 (c 1.1, CHCl₃).

IR (neat): 3378, 3296, 3076, 2925, 2117, 1640, 1436, 1041, 910, 642 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 = 2.3, 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 = 138.8, 114.3, 82.1, 76.6, 72.4, 71.6, 64.8, 64.2, 62.0, 33.6, 32.5, 28.6, 25.8, 25.5.


The assignment of protons was based on 2D NMR (gDQFCOSY, and NOESY) experiments. The presence of characteristic NOE correlations between C₄H/C₉H, C₉H/a-OH, C₆H/C₇, C₈H/b-OH, C₅H/C₈H, confirmed the assigned structure (see the Supporting Information).

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**Supporting Information**

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