Isolation, structure, and synthesis of chenopodanol and the absolute configuration of chenopodene and chenopodanol

Motoo Tori, Tomonobu Hamaguchi, Mamiko Aoki, Masakazu Sono, and Yoshinori Asakawa

Abstract: (−)-Chenopodanol (**2**) has been isolated from the liverwort *Marchantia chenopoda* and its structure determined by spectroscopic techniques as well as by total synthesis. Chenopodene (**1**) has also been synthesized in an optically active form, resulting in revision of the originally assigned absolute configuration.

Key words: chenopodanol, chenopodene, liverwort, *Marchantia chenopoda*, sesquiterpene.

Résumé : On a isolé du (−)-chénopodanol (**2**) de l'hépatique trilobée *Marchantia chenopoda*; on en a déterminé la structure par des techniques spectroscopiques ainsi que par une synthèse totale. On a aussi synthétisé le chénopodène (**1**) sous forme optiquement active; il en résulte que l'on doit réviser la configuration absolue qui lui avait été originalement attribuée.

Mots clés : chénopodanol, chénopodène, hépatique trilobée, *Marchantia chenopoda*, sesquiterpène.

[Traduit par la rédaction]

Introduction

The absolute configuration of terpenoids isolated from liverworts is very interesting and important (1). In connection with our synthetic studies on liverwort terpenoids in optically active form, we undertook the synthesis of chenopodene (**1**), whose structure, including the absolute configuration, has already been reported (2). At the same time, we further searched for new compounds in the extract of *Marchantia chenopoda* collected in Venezuela and found (−)-chenopodanol (**2**) as a minor constituent. Because **2** is not chemically related to **1**, we decided to prepare both **1** and **2** in optically active forms. We are currently engaged in synthetic studies using the chiral Michael reaction product (+)-**3** to prepare several liverwort sesquiterpenoids (3). This kind of substance could be prepared through the intermediate **4** by introduction of a cyclopropane ring *cis* to the methyl group as shown in Scheme 1. We now describe the details of structure elucidation and the synthesis of **1** and **2**.

Results and discussion

Isolation and structure of chenopodanol

A slightly more polar fraction than (+)-chenopodene (**1**) was further separated by HPLC to afford (−)-chenopodanol (**2**) (see Experimental). The molecular formula of **2** was determined by HRMS to be $C_{15}H_{26}O$, and its IR spectrum indicated the presence of a hydroxyl group (3400 cm^{-1}), which was supported by the ^{13}C NMR (δ 68.5). The presence of a cyclopropane ring and a trisubstituted double bond was indicated by the ^1H NMR spectrum (δ: 5.12 (1H, t, J = 6.8 Hz), 0.44 (1H, ddd, J = 7.4, 7.4, 4.4 Hz), 0.34 (1H, ddd, J = 4.4, 4.4, 4.4 Hz)). The chenopodane skeleton was deduced by HMBC along with the HSQC spectra as shown in Fig. 1. The stereochemistry was inferred by the NOESY spectrum as shown in Fig. 2. Thus the structure of chenopodanol was determined as depicted in formula **2**. The isolation of a compound having the chenopodane skeleton is the second example from nature (2). However, the absolute configuration could not be verified due to the minute quantity of the compound. Because the absolute configuration of (+)-chenopodene (**1**) was deduced by the CD spectrum as reported (2), **2** was temporarily assigned to have the same configuration.

Synthesis of chenopodanol and chenopodene

Chiral keto ester (+)-**3** was easily prepared by the Michael reaction between the imine, prepared from 2-methylcyclohexanone and (*S*)-(−)-1-phenylethylamine and methyl acrylate (96% ee) (4). The absolute configuration was already determined by the original workers by conversion into the known substance (4) and also by our independent work (3). Ketone (+)-**3** was reduced and the primary alcohol **5** was selectively protected by TBDMS to afford a monoprotected alcohol **6**. The alcohol was dehydrated to give olefin **7**, which was oxidized by PDC and *t*BuOOH to afford enone **4**. Attempted cyclopropanation using trimethylsulfoxonium iodide and dimsyl anion (5) failed due to deprotection of the TBDMS group, followed by etherification to the α,β-unsaturated double bond. Methylation (MeLi) and Simmons–Smith cyclopropanation (6) resulted mainly in dehydration of the tertiary hydroxyl group. Therefore, enone **4** was first reduced and the isomeric

Received October 23, 1996.

This paper is dedicated to Professor William A. Ayer on the occasion of his 65th birthday.

M. Tori,[1] T. Hamaguchi, M. Aoki, M. Sono, and Y. Asakawa. Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro cho, Tokushima 770, Japan.

[1] Author to whom correspondence may be addressed. Telephone: +81-886-22-9611, ext. 5631. Fax: +81-886-55-3051. E-mail: tori@mxs.meshnet.or.jp

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Scheme 1.

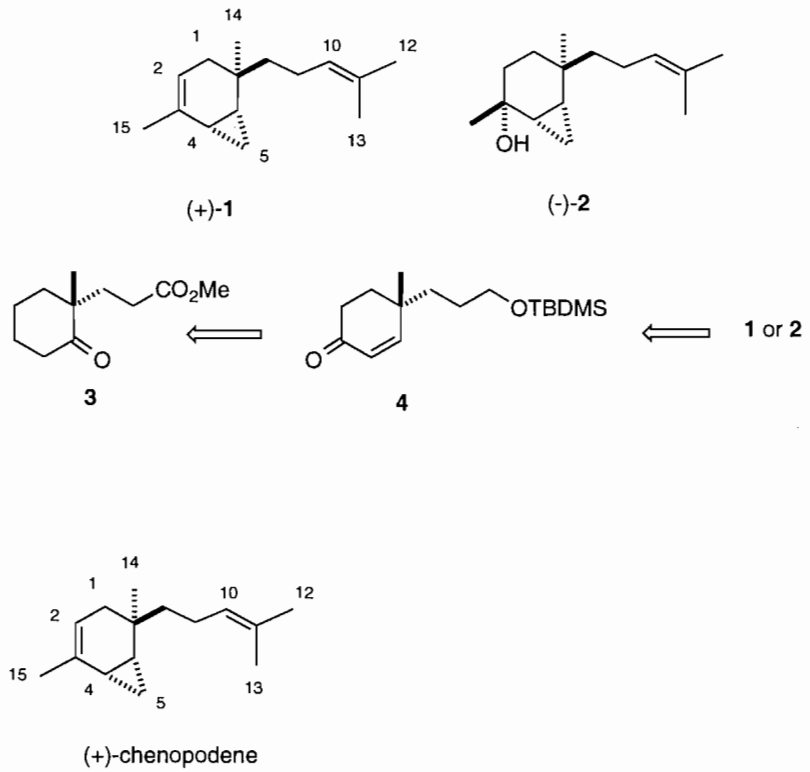


Fig. 1. HMBC correlations for (−)-chenopodanol (**2**).

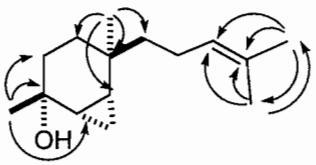
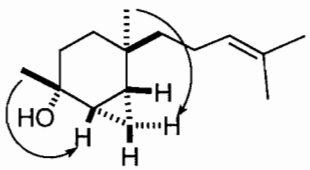
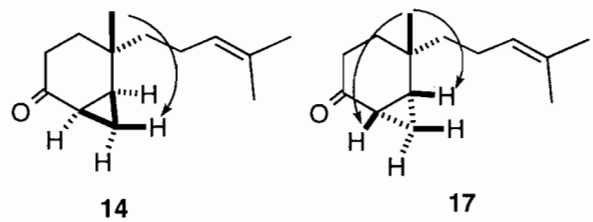


Fig. 2. NOEs detected for (−)-chenopodanol (**2**).



alcohols were separated to give **8** and **9**, although the stereochemistry was not clear at this stage. Simmons–Smith cyclopropanation (6) of alcohols **8** and **9** occurred smoothly to give a sole product, **10** and **11**, respectively, each of which must be a *cis* product, considering the cyclopropane and hydroxyl groups from the mechanistic standpoint (Scheme 2) (7). They were further oxidized by PDC to give the ketones **12** and **15**, respectively. The side chain was formed by a three-step conversion ((*i*) TBAF, (*ii*) PDC, (*iii*) Wittig) to afford **14** and **17**. The stereochemical assignment of the resulting ketones **14** and **17** was determined by the CD spectra as well as NOESY experiments (Fig. 3.). In the case of the α,β-cyclopropyl ketones, the expected Cotton effect is opposite to those for normal ketones as discussed by Djerassi et al. (8). Ketone **14**

Fig. 3. NOEs for ketones **14** and **17**.



14 **17**

showed a positive Cotton effect, while ketone **17** showed a negative effect. Therefore, the stereochemistries were assigned as depicted in Scheme 3.

When ketone **14** was methylated with MeLi, the major product was (+)-**18**, while the desired chenopodanol (**2**) was the minor one. The stereochemistry for the alkylation of the cycloalkanone having a cyclopropane ring in its α,β-position has been discussed by Mash et al. (9). Thus there was poor selectivity for the alkylation of **14** or **17**. The spectral data for product **2** were completely identical with those of the natural product. However, the specific rotation of the synthetic **2** was $[\alpha]_D$ +56.0, while that of the natural product was $[\alpha]_D$ −59.1. Thus the synthetic **2** was the enantiomer and the absolute configuration of the natural chenopodanol ((−)-**2**) must be as depicted in Scheme 1.

Ketone **17** was similarly methylated to afford **19** and **20**, neither of which was identical to chenopodanol. The stereochemistry of these products was determined by the NOESY spectra.

Compound (+)-**18** was dehydrated by $SOCl_2$ to afford chenopodene (−)-(**1**), which showed the specific rotation $[\alpha]_D$

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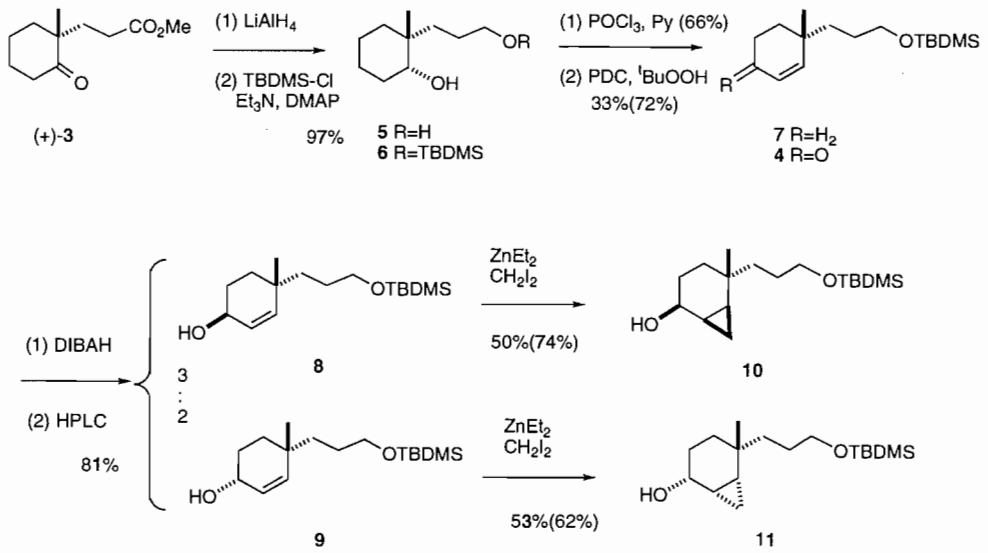
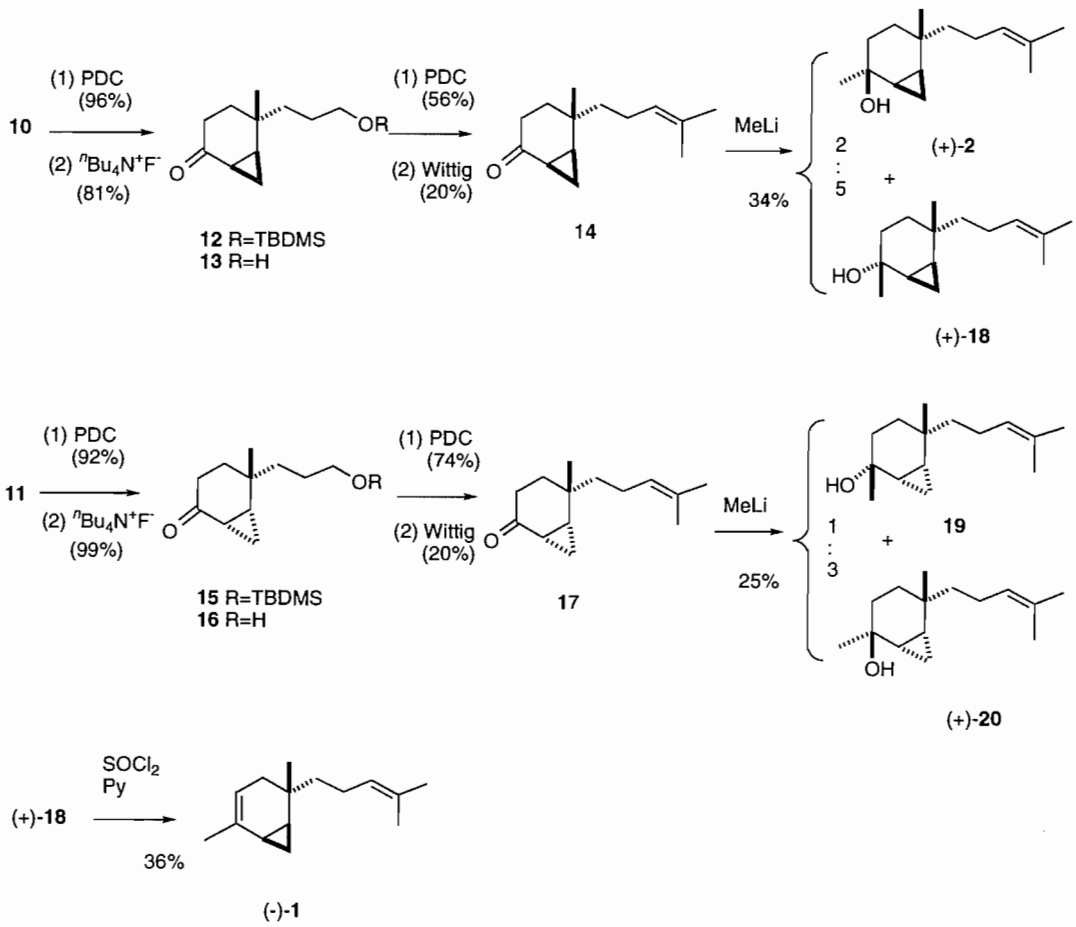
Scheme 2.



Scheme 3.



−31.0 (lit. $[\alpha]_D$(2) +32.0). These results established the absolute configuration for both chenopodanol and chenopodene (Scheme 1). The absolute configuration of chenopodene ((+)-**1**) was originally deduced by the CD spectrum to be the enantiomer (2). This was based on the empirical rule proposed by Itô et al. (10). However, this rule was highly dependent upon the molecular conformation and, as pointed out in the literature (10), there is an exception. This must be one of the ambiguous cases for this rule. In such a case, the synthesis is really necessary.

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Experimental

General

IR spectra were measured on a Jasco FTIR 500 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity 600, a JEOL JNM GX-400, a Varian Unity 200, or a Gemini 200 spectrometer. The solvent used for NMR spectra was $CDCl_3$ unless otherwise stated. Mass spectra were measured on a JEOL JMS HX-100 or a JEOL AX-500 spectrometer. The specific rotation and the CD spectra were taken on a JASCO DIP-140 polarimeter and a JASCO J- 500 spectrometer, respectively. Chemcopak Nucleosil 50-5 (10 × 250 mm), (4.6 × 250 mm), and Develosil 60-10 (20 × 250 mm) columns were used for HPLC (JASCO pump system). Silica gel 60 for column chromatography was purchased from Merck.

Isolation of chenopodanol

The crude ether extract of *M. chenopoda*, collected in Venezuela, was separated by Sephadex LH-20 ($CHCl_3$–MeOH) followed by silica gel column chromatography (hexane–EtOAc) to afford chenopodene (**1**) as described in ref. 2. A slightly more polar fraction (101 mg) than **1** was further purified by silica gel column chromatography (hexane-EtOAc) to give a mixture of several compounds (43 mg). This fraction was then separated by HPLC (Nucleosil 50-5, 10 × 250 mm, hexane–EtOAc 9:1, 3.5 mL/min) to give marchantin P (2) and impure chenopodanol (9.6 mg), which was again purified by HPLC (Nucleosil 50-5, 4.6 × 250 mm, hexane–EtOAc 95/5, 3.5 mL/min) to isolate pure (−)-chenopodanol (**2**) (1.0 mg).

(−)-Chenopodanol (2): oil; $[\alpha]_D^{20}$ −59.1 (*c* 0.1, $CHCl_3$); IR: 3400 cm^{-1}; ^1H NMR (600 MHz) δ: 0.34 (1H, ddd, *J* = 4.4, 4.4, 4.4 Hz, H-5), 0.44 (1H, ddd, *J* = 7.4, 7.4, 4.4 Hz, H-5), 0.92 (1H, m, H-6), 0.94 (3H, s, H-14), 1.05 (1H, ddd, *J* = 11, 8, 2.3 Hz, H-1 or H-2), 1.10 (1H, ddd, *J* = 7.4, 7.4, 4.4 Hz, H-4), 1.20 (1H, m, H-1 or H-2), 1.27 (1H, m, H-1 or H-2), 1.33 (1H, m, H-8b), 1.35 (1H, m, H-1 or H-2), 1.41 (3H, s, H-15), 1.43 (1H, m, H-8a), 1.62 (3H, s, H-12), 1.69 (3H, s, H-13), 1.98 (2H, m, H-9), 5.12 (1H, t, *J* = 6.8 Hz, H-10); ^{13}C NMR (150 MHz) δ: 5.1 (C-5), 17.6 (C-12), 22.7 (C-9), 24.4 (C-4), 25.1 (C-6), 25.7 (C-13), 26.7 (C-14), 30.0 (C-7), 30.1 (C-2 or C-1), 31.6 (C-15), 33.2 (C-1 or C-2), 42.9 (C-8), 68.5 (C-3), 125.0 (C-10), 131.2 (C-11); MS *m/z*: 222 $(M)^+$, 207, 204, 189, 179, 161, 151, 135, 121, 107, 93 (base), 81, 69, 55; HRMS *m/z* calcd. for $C_{15}H_{26}O$ 222.1944; found: 222.1955.

Preparation of diol 5

A solution of keto ester **3** (9.0 g, 37.5 mmol) in dry ether (100 mL) was added slowly to a stirred suspension of $LiAlH_4$ (4.1 g, 0.107 mol) in dry ether (300 mL), and the mixture was stirred at room temperature for 3 h. Ethyl acetate (40 mL), H_2O (4 mL), 15% NaOH solution (4 mL), and H_2O (12.0 mL) were added successively, and filtration followed by evaporation afforded diol **5** (7.8 g, quant.); oil; FTIR: 3350 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.77 (s), 0.83 (s), 1.0–1.8 (m), 2.80 (br s), 3.3–3.4 (m), 3.5–3.6 (m); MS (CI) *m/z*: 173 $(M + H)^+$, 155, 137, 129, 109, 95 (base), 81, 69, 55; CI-HRMS *m/z* calcd. for $C_{10}H_{21}O_2$: 173.1542; found: 173.1538.

Preparation of monosilyl ether 6

A mixture of diol **5** (4.54 g, 27.48 mmol), triethylamine (5.9 mL, 42.3 mmol), 4-DMAP (0.43 g), and TBDMSCl (6.3 g, 41.8 mmol) in CH_2Cl_2 (180 mL) was stirred at 0°C for 10 min and was kept at room temperature overnight. Water was added and the mixture was extracted with CH_2Cl_2. The organic phase was washed with water, HCl (1.0 M), saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and evaporated to give a residue. The residue was purified by silica gel column chromatography (hexane–EtOAc, 0-20%) to afford monosilyl ether **6** (7.33 g, two steps, 97%); oil; FTIR: 3460 cm^{-1}; ^1H NMR (200 MHz) δ: 0.09 (6H, s), 0.90 (12H, s), 1.2–1.8 (12H, m), 1.65 (1H, br s), 3.4 (1H, m), 3.5–3.7 (2H, m); MS (CI) *m/z*: 287 $(M + H)^+$, 269, 253, 153, 137 (base), 109, 95, 81; CI-HRMS *m/z* calcd. for $C_{16}H_{35}O_2Si$: 287.2406; found: 287.2408.

Preparation of olefin 7

A solution of mono silyl ether **6** (18.7 g, 65.38 mmol) in pyridine (150 mL) was treated with $POCl_3$ (20.0 mL, 0.22 mol) at 0°C in the presence of 4A molecular sieves (900 mg). The mixture was stirred at room temperature overnight. Saturated $NaHCO_3$ solution was added and the mixture was extracted with ether. The organic phase was washed with water, dried ($MgSO_4$), and evaporated to give a residue, which was purified by silica gel column chromatography (hexane–EtOAc, 0–20%) to afford olefin **7** (11.5 g, 66%); oil; $[\alpha]_D^{21}$ −9.7 (*c* 0.94, $CHCl_3$); FTIR: 1650, 1460, 780 cm^{-1}; ^1H NMR (200 MHz) δ: 0.05 (6H, s), 0.89 (9H, s), 0.92 (3H, s), 1.2–2.0 (10H, m), 3.57 (2H, t, *J* = 6.6 Hz), 5.39 (1H, br dt, *J* = 10.0, 1.8 Hz), 5.58 (1H, dt, *J* = 10.0, 3.6 Hz); ^{13}C NMR (50 MHz) δ: −5.22 (q × 2), 19.3 (t), 25.2 (t), 26.0 (q × 3), 27.3 (q), 27.6 (t), 29.7 (s), 33.9 (s), 34.8 (t), 38.7 (t), 64.1 (t), 125.3 (d), 136.8 (d); MS (CI) *m/z*: 269 $(M + H)^+$, 267, 253, 211 (base), 137, 135, 109, 95, 81; CI-HRMS *m/z* calcd. for $C_{16}H_{33}OSi$: 269.2301; found: 269.2272.

A solution of the olefin **7** (11.4 g, 42.5 mmol) in PhH (800 mL) was treated with PDC (23.2 g, 63.2 mmol), Celite (89.0 g), and 70% *t*BuOOH (27 mL) at 0°C. The mixture was stirred at room temperature overnight. The mixture was filtered under reduced pressure and the solvent was almost evaporated. The residue was extracted with ether, and the ethereal solution was washed with 10% KOH solution. The residue was purified by silica gel column chromatography (hexane–EtOAc, 0–20%) to afford enone **4** (4.0 g, 33%, 72% based on consumed **7**) and the recovered olefin **7** (6.1 g).

4: oil; $[\alpha]_D^{22}$ −22.2 (*c* 0.90, $CHCl_3$); CD (EtOH) [θ]: −290 (311 nm), −3940 (245 nm); FTIR: 1690, 1620 cm^{-1}; ^1H NMR (200 MHz) δ: 0.03 (6H, s), 0.88 (9H, s), 1.13 (3H, s), 1.4–1.6 (4H, m), 1.7–1.8 (1H, m), 1.95 (1H, m), 2.35–2.45 (2H, m), 3.60 (2H, dd, *J* = 5.8, 4.8 Hz), 5.86 (1H, d, *J* = 10.2 Hz), 6.63 (1H, d, *J* = 10.2 Hz); ^{13}C NMR (50 MHz) δ: −5.4 (q × 2), 18.2 (s), 24.8 (q), 25.9 (q × 3), 27.5 (t), 33.4 (t), 34.1 (t), 35.2 (s), 37.0 (t), 63.2 (t), 127.3 (d), 159.2 (d), 199.5 (s); MS (CI) *m/z*: 283 $(M + H)^+$, 267, 225 (base), 165, 151, 133, 123, 105; CI-HRMS *m/z* calcd. for $C_{16}H_{31}O_2Si$: 283.2093; found: 283.2086.

Reduction of ketone 4

A solution of ketone **4** (1.5 g, 5.32 mmol) in THF (120 mL) was treated with DIBAH (1.0 M in toluene, 16.5 mL, 16.5 mmol) at room temperature for 4 h. Water was added and THF

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was evaporated. The residue was extracted with ether and the ethereal solution was washed with water, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography (hexane–EtOAc, 0–50%) and HPLC (hexane–EtOAc 85:15, Nucleosil 50-5, 10 × 250 mm) to afford alcohols **8** (723 mg, 48%) and **9** (494 mg, 33%).

8: oil; $[\alpha]_D^{21}$ −42.3 (*c*, 1.0, $CHCl_3$); FTIR: 3350 cm^{-1}; ^1H NMR (200 MHz) δ: 0.04 (6H, s), 0.88 (9H, s), 0.99 (3H, s), 1.2–2.0 (8H, m), 3.56 (2H, t, *J* = 6.5 Hz), 4.15 (1H, m), 5.48 (1H, d, *J* = 10.6 Hz), 5.61 (1H, dd, *J* = 10.6, 2.1 Hz); ^{13}C NMR (50 MHz) δ: −5.2 (q × 2), 18.4 (s), 26.0 (q × 3), 26.7 (q), 27.5 (t), 29.3 (t), 31.5 (t), 34.4 (s), 38.2 (t), 63.8 (t), 66.6 (d), 128.6 (d), 139.2 (d); MS (CI) *m/z*: 285 $(M + H)^+$, 283, 267, 251, 227, 211, 171, 151, 135 (base); CI-HRMS *m/z* calcd. for $C_{16}H_{33}O_2Si$: 285.2250; found: 285.2245.

9: oil; $[\alpha]_D^{21}$ +18.9 (*c* 1.0, $CHCl_3$); FTIR: 3350 cm^{-1}; ^1H NMR (200 MHz) δ: 0.04 (6H, s), 0.89 (9H, s), 0.93 (3H, s), 1.2–2.0 (8H, m), 3.57 (2H, t, *J* = 6.1 Hz), 4.15 (1H, m), 5.53 (1H, d, *J* = 10.0 Hz), 5.66 (1H, dd, *J* = 10.0, 3.4 Hz); ^{13}C NMR (50 MHz) δ: −5.2 (q × 2), 18.4 (s), 26.0 (q × 3), 26.2 (q), 27.7 (t), 28.7 (t), 30.6 (t), 34.3 (s), 38.0 (t), 63.9 (t), 65.3 (d), 127.5 (d), 140.0 (d); MS (CI) *m/z*: 285 $(M+H)^+$, 283, 267, 251, 227, 209, 171, 151, 135 (base); CI-HRMS *m/z* calcd. for $C_{16}H_{33}O_2Si$ $(M + H)^+$: 285.2250; found: 285.2223; *m/z* calcd. for $C_{16}H_{31}O_2Si$ $(M - H)^+$: 283.2094; found: 283.2101.

Cyclopropanation of alcohol 8

Diethylzinc (1.0 M in hexane, 6.5 mL, 6.5 mmol) was added to a solution of the alcohol **8** (723 mg, 2.55 mmol) in CH_2Cl_2 (68 mL) at 0°C under Ar atmosphere. Diiodomethane (0.4 mL, 4.97 mmol) was slowly added, and the mixture was stirred for 30 min at this temperature and at room temperature for 5 h. Water was added and the mixture was extracted with CH_2Cl_2. The organic phase was washed with water, 10% H_2SO_4, and brine, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography (hexane–EtOAc, 0–30%) to afford **10** (382 mg, 50%, 74% based on consumed **8**) and the recovered **8** (230 mg).

10: oil; $[\alpha]_D^{21}$ −1.30 (*c* 1.3, $CHCl_3$); FTIR: 3400 cm^{-1}; ^1H NMR (200 MHz) δ: 0.05 (6H, s), 0.3–0.5 (2H, m), 0.90 (12H, s), 0.8–1.7 (10H, m), 3.58 (2H, t, *J* = 6.5 Hz), 4.15 (1H, m); ^{13}C NMR (50 MHz) δ: −5.3 (q × 2), 3.5 (t), 18.4 (s), 18.6 (d), 24.5 (d), 26.0 (q × 3), 26.1 (q), 26.4 (t), 27.6 (t), 29.5 (s), 32.1 (t), 39.8 (t), 63.9 (t), 66.8 (d); MS (CI) *m/z*: 299 $(M + H)^+$, 297, 281, 265, 241, 223, 167, 149 (base); CI-HRMS *m/z* calcd. for $C_{17}H_{35}O_2Si$ $(M + H)^+$: 299.2407; found: 299.2374; *m/z* calcd. for $C_{17}H_{33}O_2Si$ $(M - H)^+$: 297.2250; found: 297.2268.

Cyclopropanation of alcohol 9

Alcohol **9** (889 mg, 3.13 mmol) was similarly treated with Et_2Zn (8 mL, 8 mmol) and CH_2I_2 (0.55 mL, 1.09 mmol) in CH_2Cl_2 (85 mL). Work-up and chromatography (hexane–EtOAc, 0–30%) afforded **11** (495 mg, 53%, 62% based on consumed **9**) and the recovered **9** (131 mg).

11: oil; $[\alpha]_D^{21}$ +26.1 (*c* 0.88, $CHCl_3$); FTIR: 3400 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.05 (6H, s), 0.3–0.6 (2H, m), 0.89 (9H, s), 0.8–1.7 (8H, m), 1.02 (3H, s), 3.60 (2H, t, *J* = 6.6 Hz), 4.23 (1H, ddd, *J* = 6.0, 5.5, 5.8 Hz); ^{13}C NMR (50 MHz) δ: −5.2 (q × 2), 3.5 (t), 18.4 (s), 18.5 (d), 23.8 (d), 26.0 (q × 3), 26.7 (t), 27.6 (t), 27.8 (q), 29.6 (s), 32.4 (t), 38.0 (t), 64.1 (t), 66.2 (d); MS (CI) *m/z*: 299 $(M + H)^+$, 297, 281, 265, 241, 223, 167, 149 (base); CI-HRMS *m/z* calcd. for $C_{17}H_{35}O_2Si$ $(M + H)^+$: 299.2407; found: 299.2377; *m/z* calcd. for $C_{17}H_{33}O_2Si$ $(M - H)^+$: 297.2250; found: 297.2254.

Oxidation of alcohol 10

A solution of alcohol **10** (382 mg, 1.28 mmol) in CH_2Cl_2 (40 mL) was treated with PDC (975.0 mg, 2.66 mmol) and 4A molecular sieves (318.0 mg) for 12 h at room temperature. The mixture was filtered through Celite and passed through a short column of silica gel (elution with ether). Evaporation of the solvents afforded a ketone **12** (363 mg, 96%); oil; $[\alpha]_D^{21}$ −1.85 (*c* 1.0, $CHCl_3$); CD ($CHCl_3$) [θ]: +2020 (298 nm); FTIR: 1700 cm^{-1}; ^1H NMR (200 MHz) δ: 0.04 (6H, s), 0.7–1.6 (9H, m), 0.90 (9H, s), 1.06 (3H, s), 1.85 (1H, m), 2.1–2.2 (2H, m), 3.59 (2H, t, *J* = 5.9 Hz); ^{13}C NMR (50 MHz) δ: −5.2 (q × 2), 10.0 (t), 18.3 (s), 26.0 (q × 3), 26.5 (q), 26.6 (d), 27.3 (t), 28.1 (t), 29.8 (d), 31.0 (s), 32.7 (t), 35.3 (t), 63.6 (t), 209.4 (s); MS (CI) *m/z*: 297 $(M + H)^+$, 281, 239 (base), 193, 165, 147; CI-HRMS *m/z* calcd. for $C_{17}H_{33}O_2Si$: 297.2250; found: 297.2245.

Oxidation of alcohol 11

Alcohol **11** (195 mg, 0.65 mmol) was treated with PDC (517.0 mg, 1.41 mmol) and molecular sieves (168 mg) in CH_2Cl_2 (20 mL) for 12 h at room temperature. Work-up as above afforded a ketone **15** (178 mg, 92%); oil; $[\alpha]_D^{21}$ −18.0 (*c* 1.3, $CHCl_3$); CD ($CHCl_3$) [θ]: −2340 (297 nm); FTIR: 1700 cm^{-1}; ^1H NMR (200 MHz) δ: 0.04 (6H, s), 0.88 (9H, s), 1.06 (3H, s), 1.0–1.8 (10H, m), 2.19 (2H, q, *J* = 5.1 Hz), 3.60 (2H, t, *J* = 6.3 Hz); ^{13}C NMR (50 MHz) δ: −5.3 (q × 2), 10.5 (t), 18.3 (s), 24.6 (q), 25.9 (q × 3), 26.1 (d), 27.3 (t), 28.7 (t), 29.0 (d), 30.9 (s), 32.9 (t), 39.1 (t), 63.7 (t), 209.6 (s); MS (CI) *m/z*: 297 $(M + H)^+$, 281, 239 (base), 193, 165, 147; CI-HRMS *m/z* calcd. for $C_{17}H_{33}O_2Si$: 297.2250; found: 297.2242.

Deprotection of silyl ether 12

A solution of silyl ether **12** (363 mg, 0.99 mmol) in THF (5 mL) was treated with TBAF (1.0 mol/L, 1.5 mL, 1.5 mmol) at 0°C for 4 h. Water was added and the mixture was extracted with ether. The organic phase was washed with water and brine, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography (hexane–EtOAc, 0–100%) to afford alcohol **13** (181 mg, 81%); oil; $[\alpha]_D^{21}$ +9.4 (*c* 1.2, $CHCl_3$); CD ($CHCl_3$) [θ]: +1820 (297 nm); FTIR: 3440, 1690 cm^{-1}; ^1H NMR (200 MHz) δ: 1.06 (3H, s), 1.2–2.2 (12H, m), 3.63 (2H, t, *J* = 6.0 Hz); ^{13}C NMR (50 MHz) δ: 10.1 (t), 26.5 (q), 26.6 (d), 27.1 (t), 28.1 (t), 29.8 (d), 31.0 (s), 32.7 (t), 35.4 (t), 63.3 (t), 209.6 (s); MS (CI) *m/z*: 183 $((M + H)^+$ (base), 165, 147, 137, 123, 111, 95; CI-HRMS *m/z* calcd. for $C_{11}H_{19}O_2$: 183.1385; found: 183.1373.

Deprotection of silyl ether 15

Silyl ether **15** (178 mg, 0.60 mmol) in THF (2 mL) was similarly treated with TBAF (1.0 M, 0.71 mL, 0.71 mmol) and work-up afforded alcohol **16** (108 mg, 99%); oil; $[\alpha]_D^{21}$ −23.9 (*c* 1.0, $CHCl_3$); CD ($CHCl_3$) [θ]: −2040 (296 nm); FTIR: 3450, 1690 cm^{-1}; ^1H NMR (200 MHz) δ: 1.10 (3H, s), 1.0–1.8 (10H, m), 2.22 (2H, m), 3.65 (2H, t, *J* = 6.4 Hz); ^{13}C NMR

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(50 MHz) δ: 10.5 (t), 24.5 (q), 26.0 (d), 27.0 (t), 28.4 (t), 29.0 (d), 30.8 (s), 32.7 (t), 39.0 (t), 63.0 (t), 210.0 (s); MS (CI) *m/z*: 183 ((M + H)$^+$ (base), 165, 147, 123, 111, 95, 81; CI-HRMS *m/z* calcd. for $C_{11}H_{19}O_2$: 183.1385; found: 183.1385.

Preparation of ketone 14

A solution of alcohol **13** (181 mg, 0.99 mmol) in CH_2Cl_2 (20 mL) was treated with PDC (703.0 mg, 1.91 mmol) and 4A molecular sieves (120 mg) at room temperature for 2 h. The mixture was filtered through Celite and passed through a short column of silica gel (elution with ether) to afford the aldehyde (101 mg, 56%); oil; $[\alpha]_D^{21}$ +7.0 (*c* 1.0, $CHCl_3$); CD ($CHCl_3$) [θ]: +1870 (297 nm); FTIR: 1720, 1690 cm^{-1}; ^{1}H NMR (200 MHz) δ: 1.08 (3H, s), 1.1 (1H, m), 1.29 (1H, td, *J* = 5.5, 4.6 Hz), 1.4–1.6 (3H, m), 1.7–1.9 (3H, m), 2.1–2.2 (2H, m), 2.45–2.60 (2H, m), 9.81 (1H, t, *J* = 1.6 Hz); ^{13}C NMR (50 MHz) δ: 9.7 (t), 26.1 (q), 26.4 (d), 28.0 (t), 29.0 (d), 30.6 (s), 30.7 (t), 32.3 (t), 38.6 (t), 201.7 (d), 208.5 (s); MS (EI) *m/z*: 180 (M$^+$), 165, 137, 123 (base), 107, 95, 81; CI-HRMS *m/z* calcd. for $C_{11}H_{16}O_2$: 180.1150; found: 180.1148.

Butyllithium (1.69 M, 1.0 mL, 1.69 mmol) was added to a suspension of isopropyltriphenylphosphonium iodide (730 mg, 1.69 mmol) in ether (25 mL) at room temperature, and the mixture was stirred for 1 h. A solution of the aldehyde (101 mg, 0.56 mmol) in ether (3 mL) was added, and the mixture was stirred for 50 min. Water was added and the mixture was extracted with ether. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography (hexane–EtOAc, 0-100%) to afford olefin **14** (23.2 mg, 20.1%) and the recovered aldehyde (39.7 mg).

14: oil; $[\alpha]_D^{22}$ −5.0 (*c* 1.0, $CHCl_3$); CD ($CHCl_3$) [θ]: +1550 (304 nm); FTIR: 1700 cm^{-1}; ^{1}H NMR (200 MHz) δ: 1.09 (3H, s), 1.09 (1H, m), 1.28 (1H, m), 1.4–1.6 (5H, m), 1.61 (3H, s), 1.68 (3H, s), 1.80 (1H, m), 1.96–2.05 (2H, m), 2.14–2.19 (2H, m), 5.11 (1H, tsept., *J* = 7.0, 1.4 Hz); ^{13}C NMR (50 MHz) δ: 10.0 (t), 17.6 (q), 22.4 (t), 25.7 (q), 26.4 (q), 26.6 (d), 28.1 (t), 29.8 (d), 31.2 (s), 32.7 (t), 39.4 (t), 124.3 (d), 131.6 (s), 209.6 (s); MS (EI) *m/z*: 206 (M$^+$), 191, 163, 149, 137, 123 (base), 109, 95, 81; EI-HRMS *m/z* calcd. for $C_{14}H_{22}O$: 206.1671; found: 206.1653.

Preparation of ketone 17

Alcohol **16** (108 mg, 0.59 mmol) was similarly treated with PDC (426 mg, 1.16 mmol) and 4A molecular sieves (86 mg) in CH_2Cl_2. Work-up as above afforded aldehyde (78.8 mg, 74%); oil; $[\alpha]_D^{21}$ −32.0 (*c* 0.72, $CHCl_3$); CD ($CHCl_3$) [θ]: −3020 (296 nm); FTIR: 1720, 1690 cm^{-1}; ^{1}H NMR (200 MHz) δ: 1.04 (3H, s), 1.0−1.8 (8H, m), 2.1−2.2 (2H, m), 2.4−2.6 (2H, m), 9.77 (1H, t, *J* = 1.6 Hz); ^{13}C NMR (50 MHz) δ: 10.3 (t), 24.5 (q), 25.9 (d), 28.3 (d), 28.4 (t), 30.7 (s), 32.6 (t), 34.4 (t), 38.9 (t), 202.1 (d), 208.7 (s); MS (CI) *m/z*: 181 (M + H)$^+$ (base), 163, 145, 135, 121, 107, 93, 81. CI-HRMS *m/z* calcd. for $C_{11}H_{17}O_2$: 181.1229; found: 181.1209.

The aldehyde (78.8 mg, 0.44 mmol) was similarly treated with Wittig reagent and work-up afforded olefin **17** (18.0 mg, 20%) and the recovered aldehyde (4.1 mg).

17: oil; $[\alpha]_D^{22}$ −22.1 (*c* 0.8, $CHCl_3$); CD ($CHCl_3$) [θ]: −2240 (304 nm); FTIR: 1700 cm^{-1}; ^{1}H NMR (200 MHz) δ: 1.10 (3H, s), 1.08–1.23 (2H, m), 1.34–1.56 (5H, m), 1.62 (3H, s), 1.70 (3H, s), 1.79 (1H, m), 2.03–2.07 (2H, m), 2.20–2.22 (2H, m), 5.13 (1H, tsept., *J* = 7.0, 1.4 Hz); ^{13}C NMR (50 MHz) δ: 10.5 (t), 17.6 (q), 22.5 (t), 24.5 (q), 25.7 (q), 26.1 (d), 28.6 (t), 29.0 (d), 31.2 (s), 32.9 (t), 43.2 (t), 124.6 (d), 131.5 (s), 209.6 (s); MS (EI) *m/z*: 206 (M$^+$), 191, 173, 163, 149, 135, 123 (base), 110, 95, 81; EI-HRMS *m/z* calcd. for $C_{14}H_{22}O$: 206.1671; found: 206.1677.

Methylation of ketone 14

MeLi (1.10 M, 0.6 mL, 0.66 mmol) was added to a solution of the ketone **14** (20.4 mg, 0.1 mmol) in ether (3 mL) at 0°C, and the mixture was stirred for 2 h. Water was added and the mixture was extracted with ether. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by HPLC (hexane–EtOAc 95:5, Nucleosil 50-5, 4.5 × 250 mm) to afford alcohol **2** (2.2 mg, 10.0%), **18** (5.3 mg, 24.1%), and the recovered **14** (3.1 mg).

2: oil; $[\alpha]_D^{20}$ +56.0 (*c* 0.3, $CHCl_3$); FTIR: 3400 cm^{-1}; ^{1}H NMR (400 MHz) δ: 0.34 (1H, q, *J* = 4.4 Hz), 0.44 (1H, td, *J* = 8.0, 4.4 Hz), 0.92 (1H, m), 0.94 (3H, s), 1.00–1.15 (2H, m), 1.20–1.45 (5H, m), 1.41 (3H, s), 1.62 (3H, s), 1.70 (3H, s), 1.96–1.98 (2H, m), 5.12 (1H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz) δ: 5.1 (t), 17.6 (q), 22.8 (t), 24.4 (d), 25.1 (d), 25.7 (q), 26.8 (q), 30.0 (s), 30.1 (t), 31.6 (q), 33.3 (t), 42.9 (t), 68.6 (s), 125.0 (d), 131.2 (s); MS (EI) *m/z*: 222 (M$^+$), 204, 189, 175, 161, 147, 135, 133, 122, 107, 105, 93 (base); EI-HRMS *m/z* calcd. for $C_{15}H_{26}O$: 222.1984; found: 222.2013.

18: oil; $[\alpha]_D^{21}$ +20.6 (*c* 0.2, $CHCl_3$); FTIR: 3400 cm^{-1}; ^{1}H NMR (600 MHz) δ: −0.07 (1H, q, *J* = 5.4 Hz), 0.49 (1H, td, *J* = 9.3, 5.4 Hz), 0.84 (1H, td, *J* = 9.3, 5.4 Hz), 0.88 (3H, s), 0.93 (1H, ddd, *J* = 13.9, 5.1, 2.9 Hz), 1.01 (1H, m), 1.21 (1H, ddd, *J* = 14.2, 13.2, 2.9 Hz), 1.15 (1H, m), 1.29 (3H, s), 1.30 (1H, m), 1.38–1.50 (3H, m), 1.62 (3H, s), 1.69 (3H, s), 2.05 (2H, m), 5.12 (1H, tsept., *J* = 7.2, 1.3 Hz); ^{13}C NMR (100 MHz) δ: 6.8 (t), 17.6 (q), 22.4 (d), 24.8 (t), 24.1 (d), 25.7 (q), 26.3 (q), 29.2 (s), 29.9 (q), 30.6 (t), 31.6 (t), 45.7 (t), 69.2 (s), 125.1 (d), 131.1 (s); MS (EI) *m/z*: 222 (M)$^+$, 204, 189, 176, 161, 147, 135, 133, 122, 107, 105, 93 (base); CI-HRMS *m/z* calcd. for $C_{15}H_{25}$: 205.1956; found: 205.1941 (M − H_2O + H)$^+$.

Methylation of ketone 17

Ketone **17** (15.0 mg, 0.07 mmol) was similarly methylated with MeLi (1.10 M, 0.4 mL, 0.44 mmol) to afford a mixture of alcohol **19** (1.0 mg, 9.6%, a small amount of the recovered **17** was included) and the alcohol **20** (3.0 mg, 21.9%).

19: oil; ^{1}H NMR (200 MHz) δ: 0.34 (1H, q, *J* = 5.4 Hz), 0.47 (1H, td, *J* = 8.3, 4.8 Hz), 0.8–1.8 (8H, m), 1.04 (3H, s), 1.42 (3H, s), 1.61 (3H, s), 1.69 (3H, s), 1.9–2.1 (2H, m), 5.12 (1H, m); MS (CI) *m/z*: 205 (M − H_2O + H)$^+$ (base), 189, 161, 147, 135, 123, 121, 107, 95, 81; CI-HRMS *m/z* calcd. for $C_{15}H_{25}$: 205.1956; found 205.1961 (M − H_2O + H)$^+$.

20: oil; $[\alpha]_D^{21}$ +51.5 (*c* 0.3, $CHCl_3$); FTIR: 3400 cm^{-1}; ^{1}H NMR (600 MHz) δ: −0.07 (1H, q, *J* = 5.4 Hz), 0.54 (1H, td, *J* = 9.3, 5.4 Hz), 0.76 (1H, td, *J* = 9.3, 5.4 Hz), 1.0–1.1 (3H, m), 1.13 (3H, s), 1.2–1.4 (4H, m), 1.28 (3H, s), 1.62 (3H, s), 1.69

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(3H, s), 2.00 (1H, m), 2.10 (1H, m), 5.13 (1H, tsept., J = 7.1, 1.5 Hz); ^{13}C NMR (50 MHz) δ: 6.8 (t), 17.6 (q), 21.9 (d), 22.7 (t), 24.3 (d), 25.8 (q), 29.3 (s), 29.4 (q), 29.9 (q), 32.1 (t), 32.3 (t), 41.7 (t), 69.5 (s), 125.3 (d), 130.9 (s); MS (EI) *m/z*: 222 (M^+), 204, 189, 175, 161 (base), 147, 135, 133, 123, 107, 105, 93; EI-HRMS *m/z* $C_{15}H_{26}O$: calcd. for 222.1983; found: 222.1976.

Preparation of chenopodene (1)

A solution of alcohol **18** (4.2 mg, 0.02 mmol) in pyridine (0.5 mL) was treated with $SOCl_2$ (0.02 mL, 0.27 mmol) at 0°C for 30 min under stirring. Water was added and the mixture was extracted with ether. The organic phase was washed with water and brine, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography (hexane–EtOAc, 0–100%) to afford chenopodene (**1**) (1.4 mg, 36.3%); oil; $[\alpha]_D^{21}$ −31.0 (*c* 0.1, $CHCl_3$); CD (MeOH) [θ]: −580 (227 nm); ^{1}H NMR (400 MHz) δ: 0.51 (1H, dt, J = 6.0, 4.2 Hz), 0.72 (1H, td, J = 8.4, 4.2 Hz), 0.8–1.8 (6H, m), 1.03 (3H, s), 1.60 (3H, s), 1.67 (3H, s), 1.80 (3H, br s), 1.85–2.00 (2H, m), 4.98 (1H, dq, J = 7.0, 1.4 Hz), 5.12 (1H, tsept., J = 7.0, 1.4 Hz); ^{13}C NMR (100 MHz) δ: 9.6 (t), 15.6 (d), 17.6 (q), 23.0 (t), 23.5 (q), 25.5 (q), 25.7 (d), 27.4 (q), 29.5 (s), 33.2 (t), 40.8 (t), 114.3 (d), 125.5 (d), 130.8 (s), 136.1 (s); MS (EI) *m/z*: 204 (M^+), 189, 161, 133, 107, 93, 55.

Acknowledgements

We thank Drs. R. Gradstein, Göttingen University, Germany, for identification of the liverwort, and T. Nakano, IVIC, Caracas, Venezuela, for help in the collection of the liverwort. The 600 MHz NMR and MS spectra were measured in this University by Ms. Y. Kan and Y. Okamoto, to whom many thanks are due. This work is partly supported by a Grant-in-Aid from the Ministry of Health and Welfare, Japan (to Y.A.).

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