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TETRAHEDRON

Syntheses and Stereochemical Assignment of Toxic C_{17}-Polyacetylenic Alcohols, Virols A, B, and C, Isolated from Water Hemlock (*Cicuta virosa*)[1]

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Abstract: In the course of our study on neurotoxic C_{17}-polyacetylenic alcohols of the toxic plant, *Cicuta virosa*, virols A (**1**), B (**2**), and C (**3**) were synthesized by stereoselective routes to confirm their stereochemistry and to obtain supply of these compounds for pharmacological study. The syntheses used chiral 3-hydroxy-1-alkyne building blocks, Pd(0)-CuI(I)-catalyzed coupling of acetylene with vinyl chloride, and heterocoupling reaction of acetylene mediated by CuI. As a result, the absolute configuration of the stereogenic center of virols A (**1**), B (**2**), and C (**3**) was confirmed as *S*, *S*, and *S*, respectively. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: *Cicuta virosa*, C_{17}-polyacetylenic alcohol, toxin

INTRODUCTION

Water hemlock, *Cicuta virosa* (Umbelliferae), which is widely distributed in the temperate regions, is well known as a violent toxin to all classes of livestock and human beings. The major toxic component of the plant, cicutoxin (**4**),[2] was isolated and its planar structure was reported in 1953, which was shown to induce tonic and clonic convulsions and breath paralysis by affecting the central nervous system. Although cicutoxin (**4**) is a chemically and pharmacologically interesting polyacetylenic alcohol, its precise mode of pharmacological action has not been studied because of its chemical instability. Our phytochemical investigation isolated cicutoxin analogues, virols A (**1**),[3a] B (**2**), and C (**3**),[3c] from the plant as the minor toxic components, which are chemically more stable than cicutoxin (**4**) (Fig. 1). The absolute configuration of the stereogenic center of virols A (**1**) and C (**3**) was assigned tentatively as *S* and *S*, respectively, by spectroscopic method,[3c] while that of virol B (**2**) remains unsettled. In order to confirm the absolute stereochemistry of virols A (1) and C (3), to

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determine that of virol B (2), and to supply the compounds in substantial quantity for pharmacological studies, we decided to synthesize virols A (**1**), B (**2**), and C (**3**) starting from chiral building blocks developed by Takano *et al.*[3]

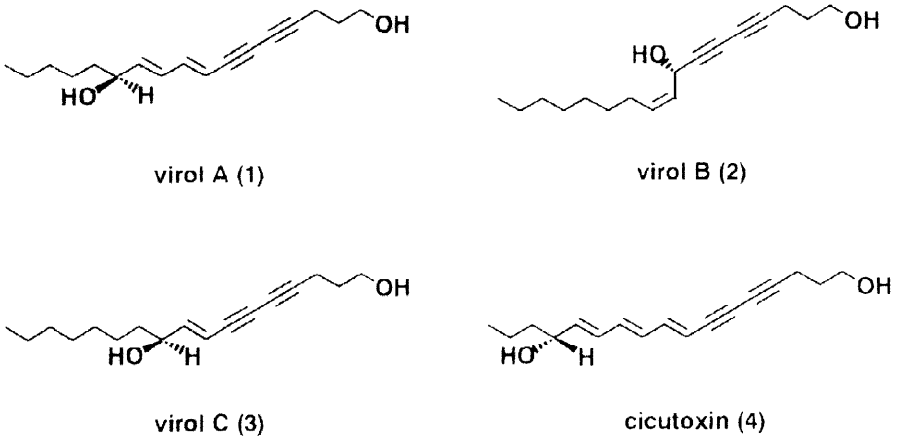


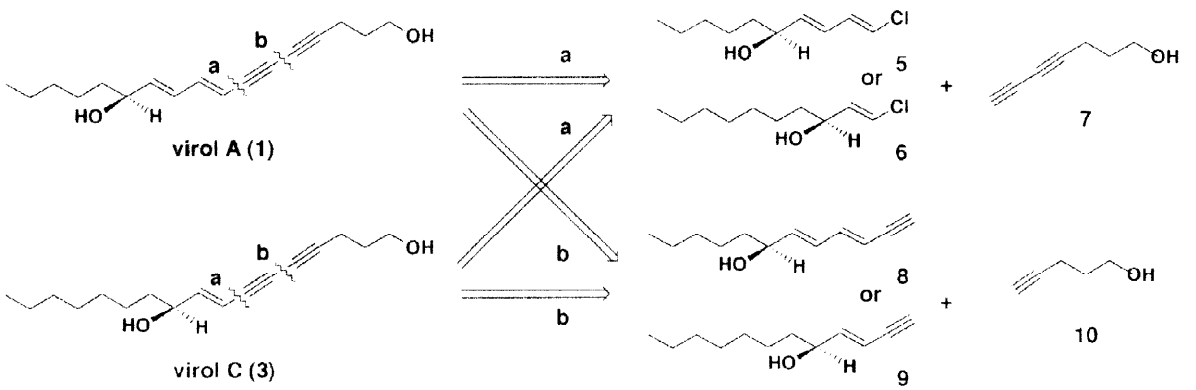
Fig. 1

RESULTS AND DISCUSSION

The syntheses of virols A (**1**), B (**2**), and C (**3**) using chiral building blocks as the starting materials is a promising method to elucidate the absolute configuration at the stereogenic center. Chiral 3-hydroxy-1-alkynes[4] were considered to be the best building blocks for the present syntheses, since the terminal alkynes could be coupled with alkenyl halides under Sonogashira's conditions[5] and with another terminal alkyne under Cadiot-Chodkiewicz's conditions.[6]

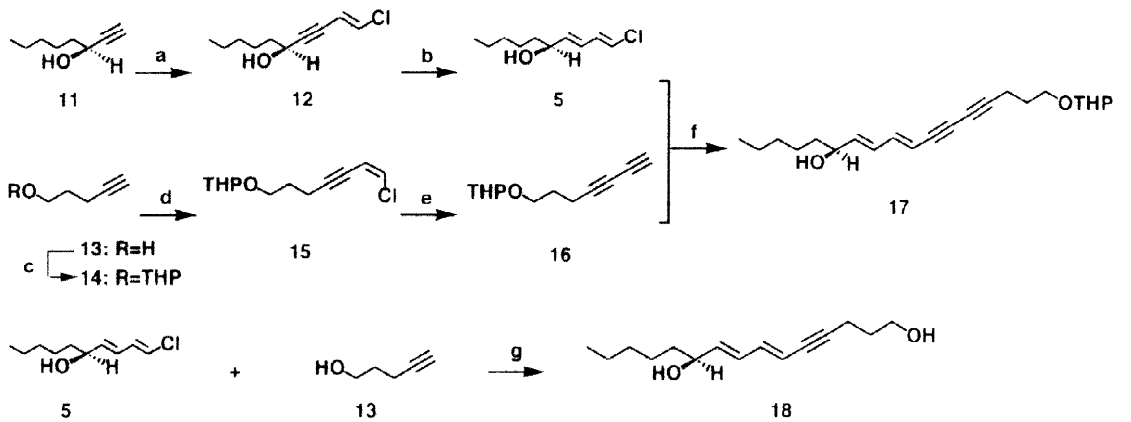
Syntheses of Virols A (1) and C (3)

Our strategy to synthesize virols A (**1**) and C (**3**) is presented as two routes, **a** and **b**, based on cross-coupling reactions (Scheme 1). The route **a** uses a coupling reaction of alkenyl halides **5** or **6** with terminal diyne **7** under Sonogashira's conditions,[5] and the route **b** involves the reaction of another alkyne **8** or **9** with terminal alkyne **10** under Cadiot-Chodkiewicz's conditions.[6] Since the substrates **5**, **8**, **6**, and **9** can be prepared from chiral 3-hydroxy-1-alkynes **11** and **22** in a stereoselective manner, we started our synthesis of virol A (**1**) from (*S*)-1-octyn-3-ol (**11**).[4]



Scheme 1

The cross-coupling reaction of **11** with *trans*-1,2-dichloroethylene under modified Sonogashira's conditions[5e] proceeded stereoselectively to produce **12** in good yield (Scheme 2). Hydroalumination of **12** followed by protonolysis gave **5**.[7a,8] The other segment **16** in the synthesis of virol A (**1**) was prepared as follows: cross-coupling reaction of **14**[9] with *cis*-1,2-dichloroethylene followed by dehydrochlorination[10] gave **16**. Although **16** was rather unstable and polymerized instantaneously on concentration, its coupling reaction with **5** in the presence of $(PhCN)_2PdCl_2$ and CuI was carried out. As a result, a major part of **5** was recovered and the expected product **17** was not satisfactorily produced (maximal yield: 23%) probably because of side reactions producing selfpolymerization compounds of **16**. The fact that the coupling reaction of **5** with **13** under the same conditions as in the reaction of **5** and **16** gave the desired **18**, clearly shows that use of a compound bearing a diyne moiety in its molecule dose not give satisfactory results in this type of coupling reaction.[11]



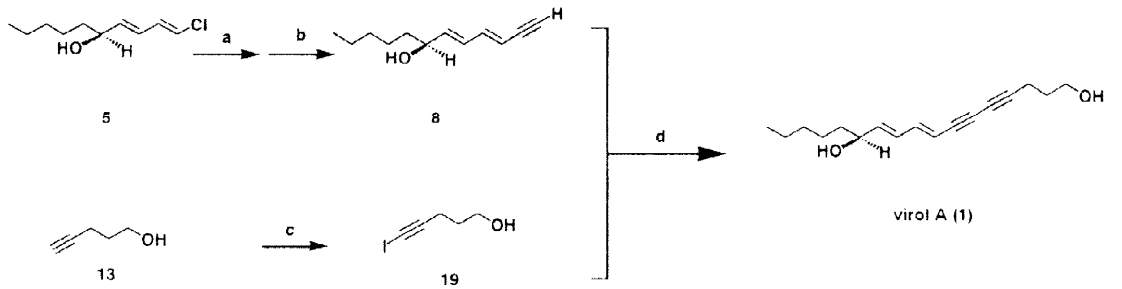
Reagents and conditions :a) *trans*-1,2-dichloroethylene (5 equiv.), $(Ph_3P)_4Pd$ (5 mol%), CuI (10 mol%), piperidine (2 equiv.), benzene, r.t., 3 h (91%); b) $Na[AlH_2(OCH_2CH_2OCH_3)_2]$ (1 equiv.), THF, -10 °C, 2 h; then sat. NH_4Cl aq. -10 °C-r.t. (87%); c) 3,4-dihydro-[2*H*]-pyran (1.5 equiv.), PPTS (0.1 mol%), CH_2Cl_2, r.t., 3 h (98%); d) *cis*-1,2-dichloroethylene (4 equiv.), $(Ph_3P)_4Pd$ (5 mol%), CuI (15 mol%), *n*-$BuNH_2$ (5 equiv.), benzene, r.t., 15 h (92%); e) TBAF (2.5 equiv.), THF, r.t., 21.5 h (91 %); f) $(PhCN)_2PdCl_2$ (10 mol%), CuI (5 mol%), piperidine (110 equiv.), r.t., 3 h (23%); g) $(PhCN)_2PdCl_2$ (5 mol%), CuI (10 mol%), piperidine (110 equiv.), r.t., 3 h (85%).

Scheme 2

We, therefore, changed our strategy to the route **b**, in which the diyne moiety is constructed in the final step of the synthesis of virol A (**1**). The chiral building block **8**[12] was prepared by a cross-coupling reaction of **5** with ethynyltrimethylsilane followed by desilylation. The other segment **19** was prepared from **13** by the literature method.[13] The reaction of **8** with **19** in the presence of CuI and pyrrolidine completed the synthesis of virol A (**1**) in a good yield (Scheme 3). All spectroscopic data were identical with those of natural virol A.[3e] Both the synthetic and natural virol A indicated optical rotations, $[\alpha]_D$ +15.4 ° (*c* 0.67, MeOH) and +15.5° (*c* 1.10, MeOH),[3e] respectively, revealing that the configuration at the stereogenic center (C-12) was determined as *S*.

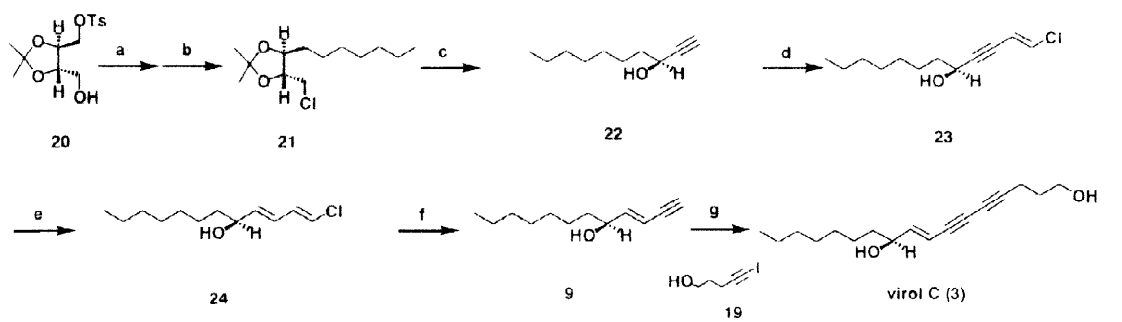
Since the route **b** was found to be appropriate for the synthesis of virol A (**1**), we next started the synthesis of virol C (**3**) by the same route. (*S*)-1-Decyn-3-ol (**22**)[14] was prepared from threitol derivative (**20**)[4b] in three steps according to the modified method reported by Takano *et al.*[4] (Scheme 4). Cross-coupling reaction of **22** with *trans*-1,2-dichloroethylene gave **23** in good yield. Hydroalumination of **23** followed by protonolysis gave **24**, which was subsequently treated with *n*-BuLi to produce the segment **9**. Cross-coupling reaction of **9** with **19** proceeded smoothly to give virol C (**3**) in a good yield. All spectral data of the synthetic

virol C, including its optical rotation, were identical with those of the natural compound.[3e] Thus, the absolute configuration of virol C (**3**) was confirmed as *S*.



Reagents and conditions :a) ethynyltrimethylsilane (2.5 equiv.), $(PhCN)_2PdCl_2$ (17 mol%), CuI (17 mol%), piperidine (170 equiv.), r.t., 3 h (81%); b) TBAF (1.7 equiv.), THF, r.t., 10 min (99 %); c) I_2 (5 equiv.), morphorine (5 equiv.), benzene, 60 °C, 2 h (92%); d) CuI (10 mol%), pyrrolidine (100 equiv.), r.t., 2 h (91%).

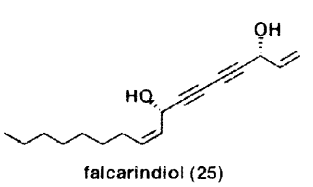
Scheme 3



Reagents and conditions :a) *n*-hexylcopper lithium (3 equiv.), Et_2O, -30 °C, 1 h ; b) PPh_3 (6 equiv.), CCl_4, reflux, 26 h (71 %, 2 setps); c) *n*-BuLi (6 equiv.), HMPA (6 equiv.), THF, -35 °C, 1.5 h (65%); d) *trans*-1,2-dichloroethylene (5 equiv.), $(Ph_3P)_4Pd$ (5 mol%), CuI (10 mol%), piperidine (2 equiv.), benzene, r.t., 4h (85%), e) $Na[AlH_2(OCH_2CH_2OCH_3)_2]$ (1.2 equiv.), THF, -10 °C, 2 h; then sat. NH_4Cl aq -10 °C-r.t. (84%); f) *n*-BuLi (6 equiv.), HMPA (6 equiv.), THF, -35 °C, 1.5 h (77%); g) **19** (1.1 equiv.), CuI (10 mol%), pyrrolidine (91 equiv.), r.t., 2 h (65%).

Scheme 4

Structural Analysis and Synthesis of Virol B (2)

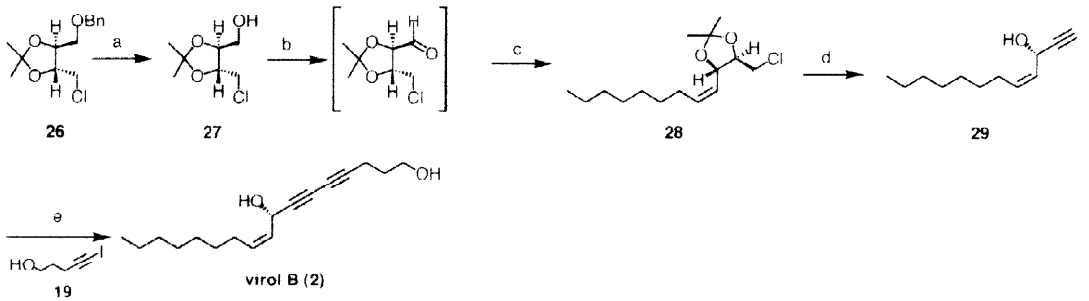


falcarindiol (25)

Virol B (**2**) , $[\alpha]_D$ +221° (*c* 0.21, MeOH), $C_{17}H_{26}O_2$, showed very similar UV absorption maxima (λ 231, 243 and 257 nm) to those of falcarindiol (**25**) (λ 234, 246 and 260 nm).[3d] The ^1H and ^{13}C NMR signals of virol B (**2**) showed, revealed the presence of two acetylenes (δ_C 64.9, 69.8, 75.6, 81.2), an olefin (δ_H/δ_C 5.51/128.1; 5.59/134.3), an oxymethine (δ_H/δ_C 5.18/58.6), an oxymethylene (δ_H/δ_C 3.75/61.3), a methyl (δ_H/δ_C 0.88/14.1) and eight methylenes (δ_H/δ_C 1.25-1.30/22.6, 29.1, 29.3, 31.79; 1.39/29.1; 1.79/30.8; 2.11/27.7; 2.43/15.8). Correlation of these ^1H and ^{13}C NMR signals was unambiguously confirmed by the HMQC spectrum. Moreover, the HMBC spectrum of virol B (**2**) clarified the connectivities of the functional groups, allowing us to propose the structure for virol B (**2**) without stereochemistry.

The construction of the diyne moiety was undertaken as the final step in the synthesis of virol B (**2**). As the segment **29** appeared to be a suitable partner for coupling reaction with **19**, it was prepared from threitol derivative (**26**)[4] *via* four steps: debenzylation of **26** followed by oxidation, the Wittig olefination[15] and formation

of alkyne (Scheme 5). Double elimination reaction of **28** resulted in the formation of the expected acetylene **29**. Finally, cross-coupling reaction of **29** with **19** under modified Cadiot-Chodkiewicz's conditions proceeded smoothly to afford virol B (**2**) in a good yield. The synthesis of virol B (**2**) proposed the *S*-configuration at C-8.



Reagents and conditions :a) H_2,10%-Pd on carbon, MeOH-$CHCl_3$, r.t., 15 min,(95%) ; b) $(COCl)_2$ (3 equiv.), DMSO (6 equiv.), CH_2Cl_2, -78 °C, 1.5 h, then Et_3N (9 equiv.), -78 °C-r.t.; c) *n*-octyltriphenylphosphonium bromide (1.5 equiv.), *n*-BuLi (1.3 equiv.), THF-HMPA (1:1), -78 °C, 1 h, then 0 °C, 19 h (54%, 2 steps); d) *n*-BuLi (6 equiv.), HMPA (6 equiv.), THF, -35 °C, 1.5 h (73%); e) CuI (10 mol%), pyrrolidine (176 equiv.), r.t., 2 h (91%).

Scheme 5

Although Wittstock *et al.*[3d] obtained two polyacetylenic alcohols from *C. virosa* whose planar structures are the same as those of virols B (**2**) and C (**3**), they reported no data leading to determination of their absolute configuration at the stereogenic center. Wittstock *et al.* also suggested that both alcohols are isomerized by allylic rearrangement in the isolation process from the extract. In our experiment, we clearly detected virols B (**2**) and C (**3**) in the methanol extract of the plant by the HPLC method, and could not observe isomerization between virols B (**2**) and C (**3**), indicating both virols (**2** and **3**) to be genuine natural products in the plant.

Bioassay

The acute toxicity (LD_{50}) of virols A (**1**), B (**2**), C (**3**), and cicutoxin (**4**) in mice was determined by the Litchfield-Wilcoxon method.[16] The result demonstrated that virols B (**2**) and C (**3**) show no acute toxicity even at 100 mg/kg of intraperitoneal injections, whereas cicutoxin (**4**) and virol A (**1**) are strongly toxic. The preliminary toxicological data suggested that the length of the conjugation in the molecule has an important role in the toxicity.

Table 1 Acute toxicity of the cicutoxin and the virols

	cicutoxin (**1**)	virol A (**2**)	virol B (**3**)	virol C (**4**)
LD_{50} mg/kg (μmol/kg)	2.8 (10.8)	9.5 (36.7)	>100 (>400)	>100 (>400)

CONCLUSION

In the C_{17}-polyacetylenic cicutoxin homologues from *C. virosa*, virols A (**1**), B (**2**), and C (**3**) were synthesized to supply them for pharmacological study. Moreover, their absolute stereochemistries were completely established by the syntheses of the virols. Investigation on the mode of action of virol A (**1**)-induced tonic and clonic convulsions and a systematic study of the structure-activity relationship of the

compounds will be reported elsewhere in the near future.

EXPERIMENTAL SECTION

All reactions were carried out in oven-dried glassware under argon atmosphere, unless otherwise noted. All solvents were reagent grade. Diethyl ether and tetrahydrofuran (THF) were freshly distilled over sodium/benzophenone ketyls under argon atmosphere prior to use. Dichloromethane and hexamethylphosphoramide (HMPA) were also distilled over calcium hydride. Merck silica gel-60 (230-400 mesh ASTM) was used for column chromatography. Optical rotations were recorded on JASCO DIP-370 and DIP-340 polarimeters. Infrared spectra and Ultraviolet spectrum were also recorded on a JASCO A-100-S-IR spectrometer and a HITACHI U-3000 spectrophotometer, respectively. ^{1}H and ^{13}C NMR spectra were measured at 300 and 75 MHz, respectively, with a Varian Gemini 2000 spectrometer and at 500 and 125 MHz, respectively, with a JEOL JMN-GX500 spectrometer. Chemical shifts are reported as parts per million (ppm) downfield from tetramethylsilane (TMS) in δ units, and coupling constants are given in hertz. TMS was defined as 0 ppm for ^{1}H NMR spectra and the center line of the triplet of $CDCl_3$ was also defined as 77.1 ppm for ^{13}C NMR spectra. Multiplicity is indicated as follows: s (singlet); d (doublet); dd (doublet of doublets); ddd (doublet of double doublets); t (triplet); m (multiplet); br (broad); etc. Mass spectra were recorded on JEOL JMS-DX303, JMS-AX-500 and JEOL HX-105 spectrometers.

(*S*)-(*E*)-1-Chlorodec-1-en-3-yn-5-ol (12)

A mixture of (-)-(*S*)-1-octyn-3-ol[4] (**11**; 294 mg, 2.33 mmol), piperidine (0.46 mL, 4.66 mmol), *trans*-1,2-dichloroethylene (1.12 g, 11.7 mmol), $Pd(PPh_3)_4$ (135 mg, 117 μmol), and CuI (44.4 mg, 233 μmol) in benzene (1.3 mL) was stirred at room temperature for 3 h. Et_2O was added to the reaction mixture and then the resulting solution was washed with saturated solution of aqueous NH_4Cl and brine, successively, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane-AcOEt, 10:1 *v/v*) gave the title compound **12** (395 mg, 91%) as a colorless oil: $[\alpha]_D$ +7.0° (*c* 0.57, $CHCl_3$). IR ν_{max} (neat): 3314, 2214, 1586 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.90 (br.t, *J*=6.9 Hz, 3H), 1.22-1.39 (m, 4H), 1.40-1.50 (m, 2H), 1.60-1.81 (m, 2H), 1.92 (br. s, 1H), 4.45 (dt, *J*=1.4, 6.6 Hz, 1H), 5.96 (dd, *J*=13.7, 1.4 Hz, 1H), 6.53 (d, *J*=13.7 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 13.9, 22.5, 24.8, 31.4, 37.6, 62.9, 79.9, 93.0, 113.4, 130.9. MS *m/z*: 188 (M^++2), 186 (M^+), 168, 151, 117, 95, 81, 51. High-resolution MS calcd for $C_{10}H_{15}O^{35}Cl$ (M^+): 186.0811. Found: 186.0821.

(*S*)-(1*E*,3*E*)-1-Chlorodeca-1,3-dien-5-ol (5)

To a solution of **12** (400 mg, 2.15 mmol) in THF (6 mL) was added dropwise Vitride® (70% *w/w* solution in toluene; 620 μL, 2.15 mmol) in THF (3 mL) at -10 °C over 10 min. The reaction mixture was stirred at -10 °C for 2 h and quenched with Et_2O and saturated solution of aqueous NH_4Cl. The resulting mixture was gently warmed up to room temperature. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane-AcOEt, 10:1 *v/v*) gave the title compound **5** (350 mg, 87%) as a colorless oil: $[\alpha]_D$ +20.5° (*c* 0.52, $CHCl_3$). IR ν_{max} (neat): 3353, 1651 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 (br.t, *J*=6.9 Hz, 3H), 1.20-1.44 (m, 7H), 1.45-1.65 (m, 2H), 4.14 (q, *J*=6.3 Hz, 1H), 5.72 (ddd, *J*=14.8, 6.3, 1.4 Hz, 1H), 6.17 (dd, *J*=14.8, 11.3 Hz, 1H), 6.20 (d, *J*=13.6 Hz, 1H), 6.45 (dd, *J*=13.6, 11.3 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.0, 22.6, 25.0, 31.7, 37.2, 72.4, 121.1, 126.2, 133.2, 137.5. MS *m/z*: 190 (M^++2), 188 (M^+), 153, 117, 99, 81 (100%). High-resolution MS calcd for $C_{10}H_{15}O^{37}Cl$ (M^{*+}): 190.0938. Found: 190.0937. Calcd for $C_{10}H_{15}O^{35}Cl$ (M^+): 188.0968. Found: 188.0971.

1-(Tetrahydropyranyloxy)-4-pentyne (14)

A mixture of 4-pentyn-1-ol (**13**; 1.00 g, 11.9 mmol), 3,4-dihydro-[2*H*]-pyran (1.63 mL, 17.8 mmol), and pyridinium *p*-toluenesulfonate (300 mg, 1.19 mmol) in CH_2Cl_2 (60 mL) was stirred at room temperature for 3 h. Et_2O was added to the reaction mixture and then the resulting solution was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane-AcOEt, 10:1 *v/v*) gave the title compound **14** (2.00 g, >98%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.45-1.63 (m, 4H), 1.64-1.87 (m, 4H), 1.95 (t, *J*=2.6 Hz, 1H), 2.32 (dt, J=2.6, 6.8 Hz, 2H), 3.43-3.56 (m, 2H), 3.77-3.93 (m, 2H), 4.60 (t, *J*=3.5 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 15.26, 19.44, 25.42, 28.65, 30.61, 62.19, 65.79, 68.46, 84.01, 98.87. MS *m/z*: 168 (M^+), 167, 149 (100%), 85. High-resolution MS calcd for $C_{10}H_{15}O_2$ (M^+-1): 167.1071. Found: 167.1028.

2-[(*Z*)-7-Chlorohept-6-en-4-ynyl-1-oxy]tetrahydropyran (15)

A mixture of **14**[10] (2.00 g, 11.9 mmol), *n*-butylamine (5.88 mL, 59.5 mmol), *cis*-1,2-dichloroethylene

(4.61 g, 47.6 mmol), $Pd(PPh_3)_4$ (687 mg, 0.595 mmol) and CuI (359 mg, 1.79 mmol) in benzene (25 mL) was stirred at room temperature for 15 h Et_2O was added to the reaction mixture and then the resulting solution was washed with saturated solution of aqueous NH_4Cl and brine, successively, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane-AcOEt, 10:1 *v/v*) gave the title compound **15** (2.50 g, 92%) as a colorless oil. IR ν_{max} (neat): 2216 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.46-1.65 (m, 4H), 1.66-1.82 (m, 2H), 1.87 (dt, *J*=13.2, 7.2 Hz, 2H), 2.52 (dt, *J*=7.2, 2.1 Hz, 2H), 3.47-3.57 (m, 2H), 3.82-3.92 (m, 2H), 4.62 (br.t, *J*=3.6 Hz, 1H), 5.85 (dt, *J*=7.4, 2.1 Hz, 1H), 6.30 (d, *J*=7.4 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 16.5, 19.5, 25.5, 28.7, 30.6, 62.2, 65.9, 75.0, 98.7, 98.9, 112.6, 127.1. MS *m/z*: 230 (M^++2), 228 (M^+), 193, 144, 128, 91, 85, 67, 57, 43. High-resolution MS calcd for $C_{12}H_{16}O_2{}^{37}Cl$ (M^{*+}-H): 229.0809. Found: 229.0799. Calcd for $C_{12}H_{16}O_2{}^{35}Cl$ (M^+): 228.0917. Found: 228.0860. Calcd for $C_{12}H_{16}O_2{}^{35}Cl$ (M^+-H): 227.0838. Found: 227.0828.

2-(Hepta-4,6-diynyl-1-oxy)tetrahydropyran (16)

A mixture of **15** (2.17 g, 9.52 mmol) and TBAF (1.0 M solution in THF; 23.8 mL, 23.8 mmol) in THF (75 mL) was stirred at room temperature for 21.5 h The reaction mixture was washed with saturated solution of aqueous NH_4Cl and brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane-AcOEt 30:1 *v/v*) gave the title compound **16** (1.66 g, 91%) as a slightly brown oil. IR ν_{max} (neat): 2226 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.48-1.64 (m, 4H), 1.65-1.76 (m, 1H), 1.76-1.92 (m, 3H), 1.97 (t, *J*=1.1 Hz, 1H), 2.39 (dt, *J*=1.1, 6.9 Hz, 2H), 3.42-3.58 (m, 2H), 3.77-3.92 (m, 2H), 4.59 (t, *J*=4.1 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 16.0, 19.5, 25.4, 28.2, 30.6, 62.2, 64.6, 65.0, 65.7, 68.5, 77.9, 98.9. MS *m/z*: 193 (M^++1), 192 (M^+), 91, 90, 89, 85, 55, 44, 40. High-resolution MS calcd for $C_{12}H_{15}O_2$ (M^+-H): 191.1072. Found: 191.1066.

(*S*)-(8*E*,10*E*)-1-(Tetrahydropyranyl-2-oxy)heptadeca-8,10-diene-4,6-diyn-12-ol (17)

A mixture of **5** (79.5 mg, 420 μmol), **16** (120 mg, 624 μmol), $PdCl_2(PhCN)_2$ (16.1 mg, 42.2 μmol), and CuI (4.23 mg, 21.0 μmol) in piperidine (4.2 mL) was stirred at the room temperature for 3 h. Et_2O was added to the reaction mixture and then the resulting solution was washed with saturated solution of aqueous NH_4Cl and brine, successively, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane-AcOEt, 6:1 *v/v*) gave the title compound **17** (33.1 mg, 23%) as a colorless oil: $[\alpha]_D$ +10.7° (*c* 1.10, $CHCl_3$). IR ν_{max} (neat): 3400, 2225, 1630 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 (br.t, 3H), 1.19-1.43 (m, 6H), 1.50-1.64 (m, 6H), 1.50-1.64 (m, 1H, exchangable with D_2O), 1.66-1.97 (m, 4H), 2.47 (t, *J*=7.0 Hz, 2H), 3.42-3.59 (m, 2H), 3.79-3.97 (m, 2H), 4.17 (q, *J*=6.2 Hz, 1H), 4.60 (m, 1H), 5.61 (d, *J*=15.7 Hz, 1H), 5.84 (dd, *J*=15.2, 6.5 Hz, 1H), 6.27 (dd, *J*=15.2, 11.0 Hz, 1H), 6.68 (dd, *J*=15.2, 11.0 Hz, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 14.0, 16.7, 19.5, 22.6, 25.0, 25.5, 28.5, 30.7, 31.7, 37.2, 62.2, 65.6, 65.8, 72.3, 74.3, 77.3, 85.0, 98.9, 110.2, 129.0, 140.0, 143.7. MS *m/z*: 344 (M^+), 271, 259, 85 (100%). High-resolution MS calcd for $C_{22}H_{32}O_3$ (M^+): 344.2351. Found: 344.2378.

(*S*)-(6*E*,8*E*)-Pentadeca-6,8-dien-4-yne-1,10-diol (18)

A mixture of **5** (91.9 mg, 488 μmol), 4-pentyn-1-ol (**13**; 42.1 mg, 500 μmol), $PdCl_2(PhCN)_2$ (9.4 mg, 25 μmol) and CuI (9.8 mg, 49 μmol), in piperidine (5 mL) was stirred at the room temperature for 3 h. Et_2O was added to the reaction mixture and then the resulting solution was washed with saturated solution of aqueous NH_4Cl and brine, successively, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane-AcOEt, 2:1 *v/v*) gave the title compound **18** (98.0 mg, 85%) as a colorless oil: $[\alpha]_D$ +19.4° (*c* 0.13, MeOH). IR ν_{max} ($CHCl_3$): 3609, 3452, 2210 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (br.t, *J*=6.7 Hz, 3H), 1.20-1.44 (m, 6H), 1.46-1.64 (m, 2H), 1.78 (quint, *J*=6.2 Hz, 2H), 2.46 (dt, *J*=1.9, 6.2 Hz, 2H), 3.74 (t, *J*=6.7 Hz, 2H), 4.13 (m, 1H), 5.58 (d, *J*=15.5 Hz, 1H), 5.74 (dd, *J*=15.2, 6.7 Hz, 1H), 6.22 (dd, *J*=15.2, 10.9 Hz, 1H), 6.50 (dd, *J*=15.5, 10.9 Hz, 1H). ^{13}C-NMR (75MHz, $CDCl_3$) δ: 13.9, 16.1, 22.5, 25.0, 31.3, 31.7, 37.1, 61.6, 72.4, 80.2, 92.4, 111.9, 130.0, 138.2, 140.3. MS *m/z*: 236 (M^+), 218 (M^+-18), 137, 71. High-resolution MS calcd for $C_{15}H_{24}O_2$ (M^+): 236.1776. Found: 236.1772.

(*S*)-(7*E*,9*E*)-Dodeca-7,9-dien-11-yn-6-ol (8)

A mixture of **5** (100 mg, 319 μmol), ethynyltrimethylsilane (78.1 mg, 800 μmol), $PdCl_2(PPh_3)_2$ (20.3 mg, 53.0 μmol) and CuI (10.0 mg, 53.0 μmol), in piperidine (5.3 mL) was stirred at room temperature for 3 h. Et_2O was added to the reaction mixture and then the resulting solution was washed with saturated solution of aqueous NH_4Cl and brine, successively, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane-AcOEt, 10:1 *v/v*) gave TMS-acetylene (165 mg, 81.0%) as a colorless oil: $[\alpha]_D$ +10.2° (*c* 0.15, $CHCl_3$). IR ν_{max} (neat): 3605, 3430, 2118 cm^{-1}. ^{1}H-NMR (300 MHz,

$CDCl_3$) δ: 0.20 (s, 9H), 0.90 (br.t, *J*=6.9 Hz, 3H), 1.22-1.45 (m, 6H), 1.47-1.63 (m, 2H), 1.96 (br s, 2H, exchangable with D_2O), 4.16 (q, *J*=6.3 Hz, 1H), 5.62 (d, *J*=15.7 Hz, 1H), 5.81 (dd, *J*=15.1, 6.3 Hz, 1H), 6.25 (dd, *J*=15.1, 10.9 Hz, 1H), 6.63 (dd, *J*=15.7, 10.9 Hz, 1H). ^{13}C-NMR (75MHz, $CDCl_3$) δ: -0.2, 13.9, 22.5, 25.0, 31.7, 37.3, 76.7, 97.3, 104.4, 111.3, 129.3, 139.6, 142.3. MS *m/z*: 250 (M^+), 235, 207, 193, 179, 151, 99, 73 (100%). High-resolution MS calcd for $C_{15}H_{26}OSi$ (M^+): 250.1751. Found: 250.1718.

To the solution of TMS-acetylene (598 mg, 2.38 mmol) in THF (16 mL) was added TBAF (1.0 M solution in THF, 4.07 mL, 4.07 mmol) at 0 °C. The reaction mixture was gently warmed up to room temperature and stirred for 10 min. To the reaction mixture were added Et_2O and saturated solution of aqueous NH_4Cl. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane-AcOEt, 10:1 *v/v*) gave the title compound **8** (421 mg, 99%) as a colorless oil: $[\alpha]_D$ +25.9° (*c* 0.69, $CHCl_3$). IR ν_{max} (neat): 3308, 2254 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 (br.t, *J*=6.9 Hz, 3H), 1.18-1.45 (m, 6H), 1.48-1.66 (m, 2H), 3.03 (d, *J*=2.2 Hz, 1H), 4.17 (q, *J*=6.4 Hz, 1H), 5.58 (ddd, *J*=15.7, 2.2, 1.1 Hz, 1H), 5.83 (dd, *J*=15.2, 6.4 Hz, 1H), 6.26 (ddd, *J*=15.2, 10.7, 1.1 Hz, 1H), 6.66 (dd, *J*=15.7, 10.7 Hz, 1H). ^{13}C-NMR (75MHz, $CDCl_3$) δ: 14.0, 22.5, 25.0, 31.7, 37.2, 72.3, 79.7, 82.8, 110.3, 129.0, 139.8, 143.0. MS *m/z*: 178 (M^+), 161, 135, 122, 107, 99 (100%), 79, 77, 71. High-resolution MS calcd for $C_{12}H_{18}O$ (M^+): 178.1358. Found: 178.1385.

5-Iodopent-4-yn-1-ol (19)

A mixture of 4-pentyn-1-ol (**13**; 100 mg, 1.19 mmol), morphorine (1.55 g, 17.8 mmol), and iodine (1.51 g, 5.95 mmol) in benzene (17 mL) was stirred at 60 °C for 2 h. The reaction mixture was concentrated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane-AcOEt, 2:1 *v/v*) gave the title compound **19** (230 mg, 92%) as a colorless oil: IR ν_{max} (neat): 3299 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.60-1.90 (m, 3H), 2.50 (t, *J*=7.0 Hz, 2H), 3.75 (t, *J*=6.0 Hz, 2H). ^{13}C-NMR (75MHz, $CDCl_3$) δ: -6.5, 17.2, 31.0, 61.2, 93.9. MS *m/z*: 210 (M^+), 127, 83, 65. High-resolution MS calcd for C_5H_7OI (M^+): 209.9543. Found: 209.9541.

(*S*)-(8*E*,10*E*)-Heptadeca-8,10-diene-4,6-diyne-1,12-diol (virol A) (1)

A mixture of **8** (286 mg, 1.60 mmol), **19** (370 mg, 1.77 mmol), and CuI (32.0 mg, 0.160 mmol) in pyrrolidine (16 mL) was stirred at room temperature for 2 h. Et_2O was added to the reaction mixture and then the resulting solution was washed with saturated solution of aqueous NH_4Cl and brine, successively, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane-AcOEt, 2:1 *v/v*) gave the title compound **1** (378 mg, 91%) as a colorless oil: $[\alpha]_D$+15.4° (*c* 0.67, MeOH) (lit.[3e] $[\alpha]_D$ +15.5° (*c* 1.10, MeOH)). IR ν_{max} (neat): 3302, 2361 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 (br.t, *J*=6.7 Hz, 3H), 1.18-1.46 (m, 6H), 1.20-1.62 (m, 2H), 1.71 (br s, 2H, exchangeable with D_2O), 1.80 (m, 2H), 2.48 (t, *J*=7.0 Hz, 2H), 3.75 (t, *J*=6.2 Hz, 2H), 4.17 (quint., *J*=6.5 Hz, 1H), 5.61 (d, *J*=15.4 Hz, 1H), 5.84 (dd, *J*=15.2, 6.5 Hz, 1H), 6.27 (dd, *J*=15.4, 10.9 Hz, 1H), 6.68 (dd, *J*=15.4, 10.9 Hz, 1H). ^{13}C-NMR (75MHz, $CDCl_3$) δ: 14.0, 16.2, 22.5, 25.0, 30.9, 31.7, 37.2, 61.4, 65.8, 72.3, 74.6, 76.9, 84.8, 110.2, 129.1, 140.3, 144.0. MS *m/z*: 260 (M^+), 242 (M^+-18), 155, 105. High-resolution MS calcd for $C_{17}H_{24}O_2$ (M^+-H_2O): 242.1671. Found: 242.1671. All spectral data were agreed with those of natural product.[3e]

(2*S*,3*S*)-1-Chloro-2,3-(*O*-isopropylidene)decan-2,3-diol (21)

To a suspension of CuI (490 mg, 2.58 mmol) in Et_2O (5.5 mL) was added *n*-hexyl lithium (0.88 M solution in *n*-hexane, 5.8 mL, 5.15 mmol) at -30 °C. After 1 h, a solution of **20**[4b] (163 mg, 515 μmol) in Et_2O (3.7 mL) was added dropwise over 5 min. The reaction mixture was stirred for 1 h, quenched with saturated solution of aqueous NH_4Cl, and then gently warmed up to room temperature. Et_2O was added to the reaction mixture and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane-AcOEt, 4:1 *v/v*) gave the crude product (118 mg), which was used for the next reaction without further purification.

A mixture of the crude alcohol (118 mg) and PPh_3 (806 mg, 3.07 mmol) in CCl_4 (13 mL) was refluxed for 26 h. The reaction mixture was filtered through a Celite pad. The resulting filtrate was washed with brine, successively, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane-Et_2O, 100:1 *v/v*) gave the title compound **21** (90.7 mg, 71% (2 steps)) as a colorless oil: $[\alpha]_D$ -1.4° (*c* 1.20, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 (br.t, *J*=6.7 Hz, 3H), 1.22-1.52 (m, 10H), 1.41 (s, 3H), 1.43 (s, 3H), 1.55-1.66 (m, 2H), 3.61 (d, *J*=4.9 Hz, 2H), 3.82-3.93 (m, 2H). ^{13}C-NMR (75MHz, $CDCl_3$) δ: 14.0, 22.6, 25.9, 27.0, 27.5, 29.1, 29.6, 31.8, 33.5, 44.4, 79.4, 80.3, 109.3. MS *m/z*: 235 (M^++2), 233 (M^+, 100%), 199. High-resolution MS calcd for $C_{13}H_{25}O_2{}^{37}Cl$ ($M^{+\bullet}$): 235.1279. Found: 235.1272. Calcd for $C_{13}H_{25}O_2{}^{35}Cl$ (M^+): 233.1308. Found: 233.1311.

(*S*)-1-Decyn-3-ol (22)

To a solution of HMPA (0.50 mL, 2.90 mmol) in THF (6 mL) was added *n*-BuLi (1.6 M solution in *n*-hexane, 1.81 mL, 2.90 mmol) at -35 °C. After 30 min, a solution of **21** (120 mg, 0.485 mmol) in THF (6 mL) was added dropwise over 5 min. The reaction mixture was stirred for 90 min and quenched with saturated solution of aqueous NH_4Cl. The resulting mixture was gently warmed up to room temperature. Et_2O was added to the reaction mixture and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane-AcOEt, 10:1 *v/v*) gave the title compound **22** (48.6 mg, 65%) as a colorless oil: $[\alpha]_D$ -4.5° (*c* 0.71, $CHCl_3$) (lit.[14c] $[\alpha]_D$ -3.4° ($CHCl_3$, 95% *e.e.*)). IR ν_{max} (neat): 3342, 3312, 2116 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.86 (br.t, *J*=6.9 Hz, 3H), 1.16-1.57 (m, 10H), 1.62-1.82 (m, 2H), 2.41 (br.s, 1H), 2.46 (d, *J*=1.9 Hz, 1H), 4.37 (dt, *J*=1.9, 6.6 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 13.9, 22.5, 24.9, 29.0, 29.1, 31.6, 37.5, 62.2, 72.7, 85.1. MS *m/z*: 153 (M^+), 139, 121, 97, 83, 70, 41 (100%). All spectral data were identical with those of the reported data.[14, 17]

(*S*)-(*E*)-1-Chlorododec-1-en-3-yn-5-ol (23)

A mixture of 1-decyn-3-ol **22** (33.5 mg, 0.217 mmol), piperidine (43.0 μl, 0.43 mmol), *trans*-1,2-dichloroethylene (86.0 μl, 1.08 mmol), $Pd(PPh_3)_4$ (12.5 mg, 10.9 μmol), and CuI (4.1 mg, 21.7 μmol) in benzene (0.12 mL) was stirred at room temperature for 4 h. Et_2O was added to the reaction mixture and then the resulting solution was washed with saturated solution of aqueous NH_4Cl and brine, successively, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane-AcOEt, 10:1 *v/v*) gave the title compound **23** (42.1 mg, 85%) as a colorless oil: $[\alpha]_D$ +7.2° (*c* 0.39, $CHCl_3$). IR ν_{max} (neat): 3333, 2361 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.89 (br.t, *J*=6.7 Hz, 3H), 1.17-1.37 (m, 8H), 1.38-1.52 (m, 2H), 1.65-1.78 (m, 2H), 1.85 (br. s, 1H), 4.48 (dq, *J*=1.9, 6.6 Hz, 1H), 5.96 (dd, *J*=13.7, 1.9 Hz, 1H), 6.54 (d, *J*=13.7 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.0, 22.5, 25.0, 29.1, 29.6, 31.7, 37.6, 62.9, 79.8, 92.9, 113.3, 130.8. MS *m/z*: 215 (M^++1), 213 (M^+-1), 179, 115 (100%). High-resolution MS calcd for $C_{12}H_{19}O^{37}Cl$ ($M^{+\cdot}$): 215.1017. Found: 215.1017. Calcd for $C_{12}H_{18}O^{35}Cl$ (M^+-1): 213.1046. Found: 213.1060.

(*S*)-(1*E*,3*E*)-1-Chlorododeca-1,3-dien-5-ol (24)

To a solution of **23** (29.7 mg, 0.14 mmol) in THF (1 mL) was added dropwise Vitride® (70% *w/w* solution in toluene; 49 μL, 0.17 mmol) in THF (0.2 mL) at -10 °C for 10 min. The reaction mixture was stirred at -10 °C for 2 h and quenched with Et_2O and saturated solution of aqueous NH_4Cl. The resulting mixture was gently warmed up to room temperature. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane-AcOEt, 10:1 *v/v*) gave the title compound **24** (25.0 mg, 84%) as a colorless oil: $[\alpha]_D$ +15.8° (*c* 0.80, $CHCl_3$). IR ν_{max} (neat): 3342, 1651, 1585 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (br.t, *J*=6.9 Hz, 3H), 1.14-1.44 (m, 10H), 1.45-1.64 (m, 2H), 4.14 (q, *J*=6.6 Hz, 1H), 5.72 (dd, *J*=14.8, 6.6 Hz, 1H), 6.17 (dd, *J*=14.8, 11.0 Hz, 1H), 6.20 (d, *J*=13.7 Hz, 1H), 6.45 (dd, *J*=13.7, 11.0 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.1, 22.6, 25.3, 29.2, 29.5, 31.8, 37.3, 72.4, 121.1, 126.2, 133.2, 137.4. MS *m/z*: 218 (M^++2), 216 (M^+), 181, 163, 97 (100%). High-resolution MS calcd for $C_{12}H_{21}O^{37}Cl$ ($M^{+\cdot}$): 218.1251. Found: 218.1225. Calcd for $C_{12}H_{21}O^{35}Cl$ (M^+): 216.1280. Found: 216.1264.

(*S*)-(*E*)-Dodeca-3-en-1-yn-5-ol (9)

To a solution of HMPA (46.9 μl, 0.27 mmol) in THF (0.3 mL) was added *n*-BuLi (1.6 M solution in *n*-hexane; 0.16 mL, 0.27 mmol) at -35 °C. After 1 h, a solution of **24** (9.7 mg, 44.9 μmol) in THF (0.3 mL) was added dropwise at -35 °C over 5 min and stirred at -35 °C for 2 h. The reaction mixture was quenched with saturated solution of aqueous NH_4Cl and gently warmed up to room temperature. Et_2O was added and organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane-AcOEt, 10:1 *v/v*) gave the title compound **9** (6.2 mg, 77%) as a colorless oil: $[\alpha]_D$ +13.5° (*c* 0.62, $CHCl_3$). IR ν_{max} (neat): 3389, 3314, 2104, 1635 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (br.t, J=6.7 Hz, 3H), 1.12-1.48 (m, 10H), 1.48-1.60 (m, 2H), 2.89 (d, *J*=2.2 Hz, 1H), 4.17 (q, *J*=7.1 Hz, 1H), 5.70 (ddd, *J*=15.9, 2.2, 1.3 Hz, 1H), 6.26 (ddd, *J*=15.9, 7.1, 0.5 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 13.9, 22.5, 25.1, 29.1, 29.3, 31.7, 36.8, 72.1, 77.8, 81.8, 106.7, 147.8. MS *m/z*: 180 (M^+), 151, 95, 81 (100%). High-resolution MS calcd for $C_{12}H_{20}O$ (M^+): 180.1514. Found: 180.1520.

(*S*)-(8*E*)-Heptadeca-8-ene-4,6-diyne-1,10-diol (virol C) (3)

A mixture of **9** (5.9 mg, 32.8 μmol), **19** (7.5 mg, 36.1 μmol), and CuI (1 mg, 5.3 μmol) in pyrrolidine (0.3 mL) was stirred at room temperature for 1.5 h. Et_2O was added to the reaction mixture and then the

resulting solution was washed with saturated solution of aqueous NH_4Cl and brine, successively, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane-AcOEt, 3:1 *v/v*) gave the title compound **3** (5.6 mg, 65%) as a colorless oil: $[\alpha]_D$ +6.8° (*c* 0.44, MeOH) (lit.[3c] $[\alpha]_D$ +6.4° (*c* 0.82, MeOH)). IR ν_{max} (neat): 3605, 3435, 2233, 1602 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (br.t, J=6.7 Hz, 3H), 1.18-1.44 (m, 10H), 1.47-1.70 (m, 2H), 1.80 (quint, *J*=6.3 Hz, 2H), 2.47 (t, *J*=6.3 Hz, 2H), 3.76 (t, *J*=6.3 Hz, 2H), 4.17 (dq, *J*=1.1, 6.0 Hz, 1H), 5.73 (dd, *J*=15.9, 1.1 Hz, 1H), 6.28 (dd, *J*=15.9, 6.0 Hz, 1H). ^{13}C-NMR (75MHz, $CDCl_3$) δ: 13.9, 16.0, 22.5, 25.1, 29.1, 29.3, 30.8, 31.7, 36.9, 61.4, 65.5, 72.1, 73.3, 74.7, 83.5, 108.6, 149.0. MS *m/z*: 262 (M^+), 261, 231, 217, 191, 177, 163, 149, 135, 127, 57 (100%). High-resolution MS calcd for $C_{17}H_{26}O_2$ (M^+): 262.1933. Found: 262.1938. All spectral data were identical with those of natural product.[3c]

Isolation and structure elucidation of virol B (2)

Cicuta virosa was collected in Sendai in May, 1992. Flesh plant material (1.8 kg) of rhizoma of *C. virosa* was extracted with MeOH at room temperature for 3 days after mincing in the solvent. The MeOH extract was filterted and the filtrate was concentrated *in vacuo* (residue; 200 g), and distributed between Et_2O and H_2O. The concentrated Et_2O layer (20.0 g) was separated roughly by column chromatography on silica gel (200 g) (*n*-hexane and *n*-hexane-acetone (9/1, 4/1, 7/3, 3/2, 1/1 *v/v*, stepwise)) and yielded 18 fractions (fraction A-R). The fraction K (0.65 g), which was eluted with *n*-hexane-acetone (4:1 *v/v*) was subjected to column chromatography on silica gel (65 g) to afford the fraction K-1 (149 mg) with *n*-hexane-AcOEt (7:2 *v/v*) eluent. The fraction K-1 was further purified by column chromatography on silica gel (14 g) with $CHCl_3$-MeOH (199:1 *v/v*) to give virol B (**2**; 40.6 mg) as a colorless oil: $[\alpha]_D$ +221° (*c* 0.21, MeOH). IR ($CHCl_3$) ν_{max}: 3596, 3420, 2255 cm^{-1}. UV (Et_2O) λ_{max} (ε): 230.8 (1174), 243.2 (1148), 256.6 (708) nm. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.88 (t, *J*=7.0 Hz, 3H, H-17), 1.25-1.30 (m, 8H), 1.39 (m, 2H), 1.79 (quint, *J*=7.0 Hz, 2H, H-2), 2.11 (q, *J*=7.5 Hz, 2H, H-11), 2.43 (t, *J*=7.0 Hz, 2H, H-3), 3.75 (t, *J*=7.0 Hz, 2H, H-1), 5.18 (d, *J*=8.0 Hz, 1H, H-8), 5.51 (dd, *J*=10.5, 8.0 Hz, 1H, H-9), 5.59 (dt, *J*=10.5, 7.5 Hz, 1H, H-10). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 14.1 (q, C-17), 15.8 (t, C-3), 22.6 (t, C-15), 27.7 (t, C-11), 29.1 (t, C-12), 29.1 (t, C-13), 29.3 (t, C-14), 30.8 (t, C-2), 31.8 (t, C-16), 58.6 (d, C-8), 61.3 (t, C-1), 64.9 (s, C-5), 69.8 (s, C-6), 75.6 (s, C-7), 81.2 (s, C-4), 128.1 (d, C-9), 134.3 (d, C-10). EI-MS *m/z*: 262 (M^+), 261 (M^+-1), 244, 231, 202, 191, 177, 163, 57 (100%). High-resolution EI-MS calcd for $C_{17}H_{26}O_2$ (M^+): 262.1933. Found: 262.1911.

(2*S*,3*S*)-4-Chloro-2,3-(*O*-isopropylidene)butane-1,2,3-triol (27)

A mixture of **26**[4a] (258 mg, 957 μmol), 10%-Pd/C (26 mg) and $CHCl_3$ (1 drop) in MeOH (5 mL) was stirred at room temperature for 15 min under H_2 atmosphere. The reaction mixture was filtered through a Celite pad and concentrated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane-AcOEt, 4:1 *v/v*) gave the title compound **27** (164 mg, 95%) as a colorless oil: $[\alpha]_D$ +2.9° (*c* 1.44, $CHCl_3$). IR ν_{max} (neat): 3445 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.45 (s, 6H), 1.86-1.99 (m, 1H, exchangable with D_2O), 3.60-3.76 (m, 2H), 3.66 (dd, *J*=11.8, 6.0 Hz, 1H), 3.89 (ddd, *J*=11.8, 5.1, 3.8 Hz, 1H), 4.04 (dt, *J*=7.7, 4.1 Hz, 1H), 4.17 (ddd, *J*=7.7, 6.0, 5.1 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 27.0, 27.2, 44.2, 62.3, 76.3, 79.7, 110.1. MS *m/z*: 167 (M^+-13), 165 (M^+-15), 105, 43. High-resolution MS calcd for $C_6H_{10}O_3{}^{37}Cl$ (M^{*+}-Me): 167.0289. Found: 167.0280. Calcd for $C_6H_{10}O_3{}^{35}Cl$ (M^+-Me): 165.0318. Found: 165.0309.

(2*S*, 3*S*)-(*Z*)-1-Chloro-2,3-(*O*-isopropyridene)dodec-4-ene-2,3-diol (28)

To a stirred solution of oxalyl chloride (210 μL, 2.41 mmol) in CH_2Cl_2 (7 mL) was added DMSO (341 μl, 4.81 mmol) at -78 °C. After 20 min, a solution of alcohol **27** (144 mg, 801 μmol) in CH_2Cl_2 (12 mL) was added dropwise for 10 min. The reaction mixture was stirred at -78 °C for 1.5 h and Et_3N (1.05 mL, 7.21 mmol) was added dropwise over 10 min and stirred for 15 min. The reaction mixture was gently warmed up to room temperature and diluted with Et_2O. The resulting mixture was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was used without further purification.

To a solution of octyltriphenylphosphonium salt (547 mg, 1.20 mmol) in THF (2 mL)-HMPA (2 mL), which was prepared from 1-bromooctane and PPh_3 was added dropwise *n*-BuLi (1.6 M solution in *n*-hexane, 651 μL, 1.04 mmol) at -5 °C over 10 min. A solution of the crude aldehyde in THF (2 mL) was added to the reaction mixture at -78 °C over 5 minutes. After 1h, the reaction mixture was warmed up to 0 °C and stirred for 19 h. Et_2O was added to the reaction mixture and then the resulting solution was washed with H_2O and brine, successively, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane-AcOEt, 50:1 *v/v*) gave the title compound **28*Z*** (118 mg, 54% (2 steps)) as a colorless oil and its *E*-isomer **28*E*** (8.9 mg, 4% (2 steps)) as a colorless oil: **28*E***: $[\alpha]_D$ -13.3° (*c* 0.12, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, *J*=6.6 Hz, 3H), 1.16-1.41 (m, 10H), 1.44 (s, 3H), 1.54 (s, 3H), 2.06 (dt, *J*=7.7, 7.4

Hz, 2H), 3.57 (dd, *J*=11.8, 4.9 Hz, 1H), 3.67 (dd, *J*=11.8, 4.1 Hz, 1H), 3.90 (ddd, *J*=8.1, 4.9, 4.1 Hz, 1H), 4.25 (t, *J*=8.1 Hz, 1H), 5.44 (dd, *J*=15.1, 8.1 Hz, 1H), 5.85 (dt, *J*=15.1, 7.7 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.1, 22.6, 27.0, 27.2, 28.8, 29.1, 29.7, 32.3, 43.5, 47.9, 74.5, 80.4, 102.2, 126.2, 137.9. MS *m/z*: 274 (M^+), 261, 259, 239, 85 (100%). High-resolution MS calcd for $C_{15}H_{27}O_2{}^{35}Cl$ (M^+): 274.1699. Found: 274.1738. Calcd for $C_{14}H_{24}O_2{}^{37}Cl$ ($M^{+\cdot}$-Me): 261.1436. Found: 261.1424. Calcd for $C_{14}H_{24}O_2{}^{35}Cl$ (M^+-Me): 259.1465. Found: 259.1428. **28Z**: $[\alpha]_D$ +7.5° (*c* 0.48, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (br.t, *J*=6.6 Hz, 3H), 1.13-1.52 (m, 10H), 1.46 (s, 3H), 1.46 (s, 3H), 1.98-2.25 (m, 2H), 3.56 (dd, *J*=12.0, 4.8 Hz, 1H), 3.70 (dd, *J*=11.9, 3.9 Hz, 1H), 3.88 (ddd, *J*=8.4, 4.8, 3.9 Hz, 1H), 4.70 (dt, *J*=0.7, 8.4 Hz, 1H), 5.38 (ddt, *J*=10.8, 8.4, 1.1 Hz 1H), 5.73 (ddt, *J*=10.8, 0.7, 7.3 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.1, 22.6, 26.9, 27.3, 27.9, 29.1, 29.2, 29.6, 31.8, 43.2, 74.4, 80.2, 109.7, 125.6, 137.5. MS *m/z*: 276 (M^++2), 274 (M^+), 261, 239, 85 (100%). High-resolution MS calcd for $C_{15}H_{27}O_2{}^{37}Cl$ ($M^{+\cdot}$): 276.1670. Found: 276.1694. Calcd for $C_{15}H_{27}O_2{}^{35}Cl$ (M^+): 274.1699. Found: 274.1718.

(*S*)-(*Z*)-Dodec-4-en-1-yn-3-ol (29)

To a solution of HMPA (1 mL, 6.0 mmol) in THF (3 mL) was added *n*-BuLi (1.6 M solution in *n*-hexane, 3.8 mL, 6.0 mmol) at -35 °C. After 30 min, a solution of **28** (276.3 mg, 1.0 mmol) in THF (5 mL) was added dropwise at -35 °C over 5 min and stirred for 90 min. The reaction mixture was quenched with saturated solution of aqueous NH_4Cl and gently warmed up to room temperature. Et_2O was added to the resulting mixture and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by colmn chromatography on silica gel (*n*-hexane-AcOEt, 6:1 *v/v*) gave the title compound **29** (131.4 mg, 73%) as a colorless oil: $[\alpha]_D$ +103° (*c* 0.22, $CHCl_3$). IR ν_{max} (neat): 3381, 3312, 2364 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, *J*=6.9 Hz, 3H), 1.13-1.46 (m, 10H), 1.84 (br.s, exchangable with D_2O, 1H), 2.13 (dt, *J*=7.1, 6.6 Hz, 2H), 2.50 (d, *J*=2.2 Hz, 1H), 5.11-5.27 (m, 1H), 5.52-5.66 (m, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.1, 22.6, 27.6, 29.1, 29.2, 29.3, 31.8, 58.1, 73.0, 84.2, 128.8, 134.4. MS *m/z*: 180 (M^+), 179, 81 (100%). High-resolution MS calcd for $C_{12}H_{19}O$ (M^+-1): 179.1436. Found: 179.1469.

(*S*)-(*Z*)-Heptadec-9-ene-4,6-diyne-1,8-diol (virol B) (2)

A mixture of **29** (120 mg, 0.67 mmol), **19** (140.7 mg, 0.67 mmol), and CuI (127.6 mg, 0.67 mmol) in pyrrolidine (6.7 ml) was stirred at room temperature for 40 min. Saturated solution of aqueous NH_4Cl was added to the reaction mixture and then the quenched mixture was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography on silica gel (*n*-hexane-AcOEt, 3:1 *v/v*) gave the title compound **2** (159.7 mg, 91%) as a colorless oil: $[\alpha]_D$ +232° (*c* 0.33, MeOH). IR ν_{max} (neat): 3595, 3418, 2254 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, *J*=6.9 Hz, 3H), 1.18-1.47 (m, 10H), 1.62 (br. s, 1H, exchangable with D_2O), 1.79 (quint, *J*=13.2, 6.9 Hz, 2H), 1.94 (br. s, 1H, exchangable with D_2O), 2.05-2.16 (m, 2H), 2.43 (t, *J*=6.9 Hz, 2H), 3.75 (t, *J*=6.9 Hz, 2H), 5.18 (d, *J*=8.0 Hz, 1H), 5.45-5.65 (m, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.1, 15.8, 22.6, 27.6, 29.1, 29.2, 29.3, 30.8, 31.8, 58.6, 61.4, 65.0, 69.8, 75.7, 81.3, 128.3, 134.5. MS *m/z*: 262 (M^+), 261, 217, 91(100%). High-resolution MS calcd for $C_{17}H_{25}O_2$ (M^+-1): 261.1853. Found: 261.1846. All spectral data were identical with those of the natural product.

Acute toxicity test

Male mice of ddY strain (21-25 g) were purchased from Nihon SLC Co. (Hamamatsu, Japan). The mice were housed in group of 10 per cage (30x30x16 cm), on keeping in air-conditioned room (22±2 °C of the ambient temperature and 55±5% of the humidity) with 12 h light cycle, and allowed to take food (F-2 obtained from Funabashi farm Co., Funabashi, Japan) and water *ad lib*. Samples were suspended in physiological saline containing 2% alabia gum, and administered in geometrical progression between 0-100% of lethal dose by intraperitoneally (10 mL/kg body weight) to the mice. 10 mice were used per a group in the same dose. The LD_{50} values were estimated according to the Litchfield-Wilcoxon's method.[16]

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17. Since compound **22** showed low intensity at M$^+$ peak in electron inpact mass spectrum, *p*-bromobenzoate (yield: 69 %) was synthesized by the conventional method and identified it by high resolution mass spectrum. **22**: $[\alpha]_D$-15.5° (*c* 0.44, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88 (br.t, *J*=6.7 Hz, 3H), 1.18-1.42 (m, 8H), 1.48-1.60 (m, 2H), 1.85-1.96 (m, 2H), 2.49 (d, *J*=2.2 Hz, 1H), 5.58 (dt, *J*=2.2, 6.6 Hz, 1H), 7.60 (d, *J*=8.5 Hz, 2H), 7.93 (d, *J*=8.5 Hz, 2H). MS *m/z*: 338 (M*$^+$), 336 (M$^+$), 295, 293, 267, 265, 254, 252, 185, 183 (100%), 157, 155, 153. High-resolution MS calcd for $C_{17}H_{21}O_2{}^{81}Br$: 338.0706. Found: 338.0744 (M*$^+$). Calcd for $C_{17}H_{21}O_2{}^{79}Br$: 336.0725. Found: 336.0702 (M$^+$). Calcd for $C_{10}H_{17}O$: 153.1279. Found: 153.1257 (M$^+$-*p*-Br-Bz).