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The first total synthesis of naturally occurring (+)-gymnasterkoreayne F and its enantiomer

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Abstract—The first total synthesis of naturally occurring (+)-gymnasterkoreayne F and its enantiomer is reported. The seven-step route to these two polyacetylenes in enantiomerically pure form involves the use of (+)-2,3-*O*-isopropylidene-L-threitol and (−)-2,3-*O*-isopropylidene-D-threitol, respectively, as the starting material and a Cadiot–Chodkiewicz reaction as a key step. The absolute configuration of (+)-gymnasterkoreayne F has been confirmed to be (2*E*,8*S*,*Z*). The natural product and its enantiomer have been found to exhibit modest cytotoxicity against the 60 human tumor cell lines of the National Cancer Institute.

1. Introduction

Polyacetylenes are widely recognized as one of the most frequently encountered groups of metabolites of basidiomycete fungi[1] and higher plants, such as Compositae (Asteraceae),[2] Olacaceae,[3] Santalaceae,[4] Umbelliferae (Apiaceae),[5] Araliaceae,[6] and Loranthaceae.[7] Moreover, in recent years several polyacetylenes have been isolated from marine sponges.[8] The biological properties of these metabolites, which include antifungal,[9] antimicrobial,[10] cytotoxic,[11] and enzyme-inhibitory activities,[12] make them to be of particular interest to pharmacologists and plant pathologists.

In 2002, Jung et al.[13] isolated six new polyacetylenes, gymnasterkoreaynes A–F, (−)-**1**, (+)-**2**, (+)-**3**, (+)-**4**, (+)-**5**, and (+)-**6**, respectively (Fig. 1), from the roots of *Gymnaster koreaiensis* (Nakai) Kitamura (Compositae), an endemic species in Korea, by bioassay-guided fractionation of an 80% EtOH extracts of these roots using L1210 mouse leukemia tumor cell line as a model for cytotoxicity. These authors also elucidated the structure of compounds **1**–**6** by spectroscopic methods and assigned their absolute stereochemistry. However, only in the case of compound (−)-**1** did they specify that the absolute stereochemistry had been determined using the modified Mosher method.[14] In fact, they assigned

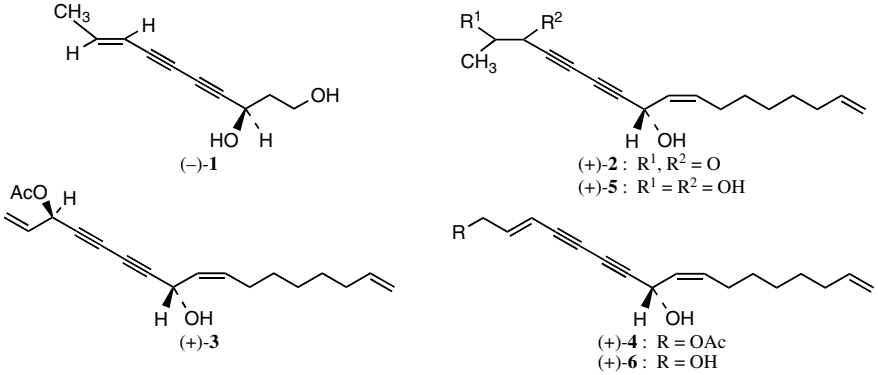

Figure 1. Gymnasterkoreaynes A–F.

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the (10*S*)- and (3*S*,8*S*)-configurations to (+)-**2** and (+)-**3**, respectively, on the basis of their ^{13}C NMR data and specific rotations, which resembled analogous data of well-known natural products,[13] but they did not mention on which basis it had been possible to establish the absolute configurations of (+)-**4**, (+)-**5**, and (+)-**6**.

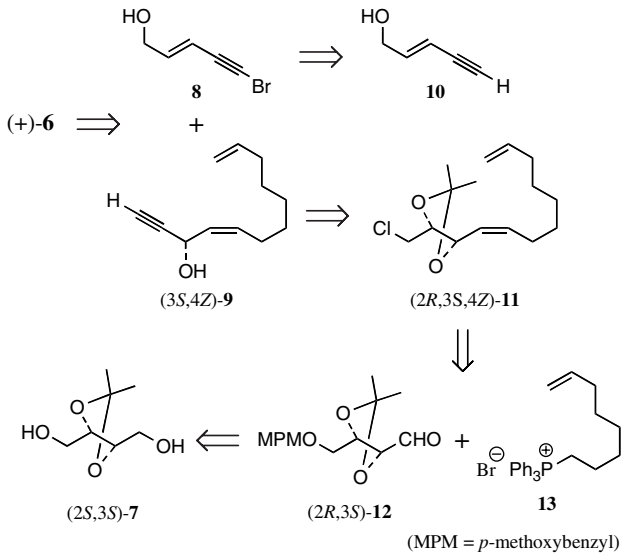
Interestingly, compounds (+)-**2**, (+)-**3**, and (+)-**6** were found to exhibit significant cytotoxicity against the L1210 tumor cell line with ED_{50} values of 3.3, 2.1, and 3.1 μg/mL, respectively.[13]

Motivated by the biological activity of these polyacetylenes, their low availability from natural sources and our interest in the synthesis of naturally occurring compounds and their analogues, which exhibit cytotoxic activity against tumor cell lines,[15] we decided to investigate the total synthesis of compounds (+)-**3** and (+)-**6**. In fact, we wished also to verify their structural and configurational assignment and to evaluate their cytotoxic activity against the entire panel of 60 human tumor cell lines of the National Cancer Institute (NCI). Herein, we report a concise and efficient synthesis of naturally occurring (+)-**6** and (−)-**6** in enantiomerically pure forms starting from (+)-2,3-*O*-isopropylidene-L-threitol, (+)(2*S*,3*S*-)-**7**, and (−)-(2*R*,3*R*)-**7**, respectively.

Additionally, we also report the cytotoxicity data of the natural product and its enantiomer against the NCI's 60 tumor cell lines.

2. Results and discussion

Our synthetic approach to the synthesis of naturally occurring (+)-**6** was envisioned through the retrosynthetic analysis shown in Scheme 1.



Scheme 1.

In particular, (+)-**6** should be accessible through a Cadiot–Chodkiewicz-type reaction[16] between (*E*)-5-bromo-2-penten-4-yn-1-ol **8** and (3*S*,4*Z*)-dodeca-4,11-dien-1-yn-3-ol (3*S*,4*Z*)-**9**. Compound **8** can be prepared from commercially available **10**[15b] while (3*S*,4*Z*)-**9** is available from (2*R*,3*S*,4*Z*)-1-chloro-2,3-(isopropylidenedioxyl)-dodeca-4,11-diene (2*R*,3*S*,4*Z*)-**11**, which in turn can be synthesized by a Wittig reaction between aldehyde (2*R*,3*S*)-**12** and the ylide derived from phosphonium bromide **13**. Conversely, (2*R*,3*S*)-**12** can be prepared from (2*S*,3*S*)-**7**, which is commercially available or can be prepared from L-tartaric acid.[17]

A very similar retrosynthetic analysis involving the use of commercially available (2*R*,3*R*)-**7** as the starting material and (3*R*,4*Z*)-**9** as the key intermediate was envisioned for the synthesis of (−)-**6** (Fig. 2).

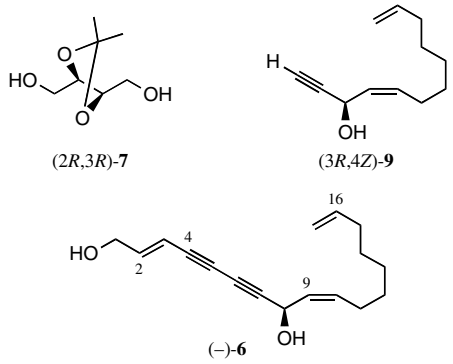
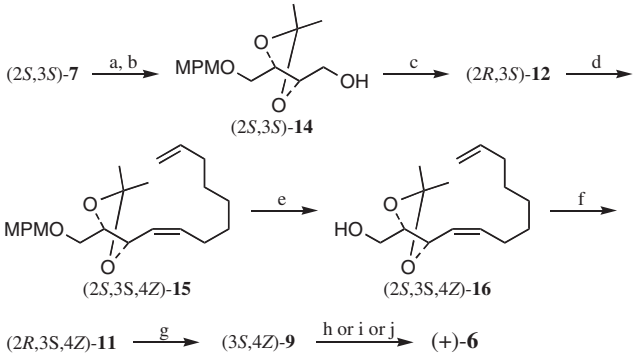


Figure 2.

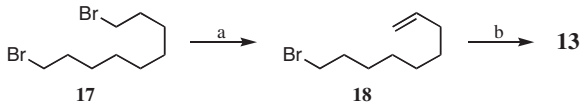
Scheme 2 provides details of the synthetic route followed to prepare (+)-**6**. In particular, compound (2*S*,3*S*)-**14** was prepared in 72% yield by the reaction of (2*S*,3*S*)-**7** with 1.07 equiv of NaH in a 1:1 mixture of THF and



Scheme 2. Reagents and conditions: (a) NaH (1.07 equiv), DMF/THF (1:1), 0 °C, 1.5 h; (b) MPMCl (1.05 equiv), 0–20 °C, 18 h (72%); (c) DMSO (3 equiv), $(COCl)_2$ (1.5 equiv), Et_3N (1.7 equiv), CH_2Cl_2, −78 °C, 10 min; (d) **13** (1.2 equiv), *t*-BuOK (1.2 equiv), THF, −78 °C, 2 h, then 20 °C, 12 h (87% from (2*S*,3*S*)-**14**); (e) DDQ (1.5 equiv) CH_2Cl_2/H_2O (20:1), 20 °C, 2.5 h (85%); (f) PPh_3 (2 equiv), CCl_4, 90 °C, 16 h (91%); (g) LDA (5 equiv), THF, −78 °C, 3 h, 0 °C, 30 min, then aq NH_4Cl (55%); (h) **8** (1.1 equiv), CuCl (6 mol %), $NH_2OH{\cdot}HCl$ (0.3 equiv), $EtNH_2$, H_2O, CH_3OH, 0 °C, 45 min (76%); (i) **8**, (1.0 equiv), CuCl (10 mol %), $NH_2OH{\cdot}HCl$ (0.3 equiv), Et_3N (1 equiv), DMF, 0 °C, 30 min, then 20 °C, 23 h (13%); (j) **8** (1 equiv), CuCl (10 mol %), $NH_2OH{\cdot}HCl$ (0.3 equiv), 2,2,6,6-tetramethylpiperidine (TMP) (2.1 equiv), DMF, 0 °C, 30 min, then 20 °C, 5 h (51%).

DMF followed by treatment of the so-obtained monosodium salt with a molar excess of *p*-methoxybenzyl chloride (MPMCl). Swern oxidation of (2*S*,3*S*)-**14** provided aldehyde (2*R*,3*S*)-**12**, which was subsequently reacted with the ylide derived from treatment of phosphonium bromide **13** with *t*-BuOK in THF to afford 92% stereoisomerically pure (2*S*,3*S*,4*Z*)-**15** in 87% yield from (2*S*,3*S*)-**14** after chromatographic purification. It should be noted that freshly prepared crude (2*R*,3*S*)-**12** was employed in the Wittig reaction. In fact, we observed that this compound easily undergoes epimerization at −23 °C. Moreover, we found that the crude product of the Wittig reaction was contaminated by three stereoisomers of the required (2*S*,3*S*,4*Z*)-**15**, which presumably corresponded to (2*S*,3*R*,4*Z*)-, (2*S*,3*S*,4*E*)-, and (2*S*,3*R*,4*E*)-**15**. We also noticed that the chromatographic purification of this crude reaction product did not allow us to obtain (2*S*,3*S*,4*Z*)-**15** in its stereoisomerically pure form.

Crude compound **13** was prepared in a quantitative yield by reaction of PPh_3 with a CH_3CN solution of 8-bromo-1-octene **18** at 90 °C for 140 h (Scheme 3). On the other hand, this halide was obtained in 39% yield by the reaction of 1,8-dibromooctane **17** with *t*-BuOK in THF at room temperature for 1.5 h (Scheme 3). On the contrary, the procedure reported in the literature for the preparation of **18**, which involves treatment of **17** with *t*-BuOK in THF under reflux,[18] provided the desired monobromide in a very low yield.



Scheme 3. Reagents and conditions: (a) *t*-BuOK (1.15 equiv), THF, 20 °C, 1.5 h, then H_2O; (b) PPh_3 (1.2 equiv), CH_3CN, 90 °C, 140 h.

Deprotection of 92% stereoisomerically pure (2*S*,3*S*,4*Z*)-**15** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[19] in a CH_2Cl_2–H_2O system followed by chromatographic purification of the crude reaction product provided alcohol (2*S*,3*S*,4*Z*)-**16** in 85% yield. This compound was smoothly converted to stereoisomerically pure chloride (2*R*,3*S*,4*Z*)-**11** in 91% yield by reaction with PPh_3 and CCl_4.[20] Treatment of (2*R*,3*S*,4*Z*)-**11** with 5 equiv of LDA in THF at −78 °C[21] gave 1-alkyne (3*S*,4*Z*)-**9** in 55% yield. On the other hand, this alkyne was obtained in a negligible yield, when we used the procedure reported in the literature to prepare 1-alkyne **20** from chloride **19** (Fig. 3),

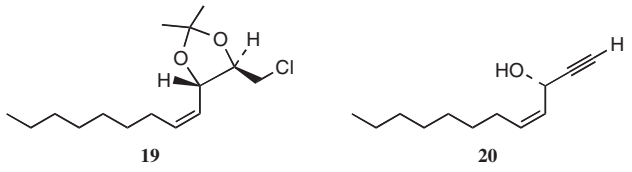


Figure 3.

which involves the use of 6 equiv of BuLi in HMPA at −35 °C.[22]

Finally, a Cadiot–Chodkiewicz reaction between (3*S*,4*Z*)-**9** and (*E*)-1-bromo-3-en-1-yne **8** under standard conditions[20b,23] gave (+)-**6** in 76% yield. This same compound could be prepared in 51% yield employing a modification of the Cadiot–Chodkiewicz reaction, which we developed for the synthesis of a chiral precursor of naturally occurring (−)-nitidon and its enantiomer.[15b] This modification involves the CuCl-catalyzed coupling of **8** with (3*S*,4*Z*)-**9** in DMF in the presence of 0.3 equiv of $NH_2OH{\cdot}HCl$ and 2,2,6,6-tetramethylpiperidine (TMP) as a base. On the other hand, we found that the CuCl-catalyzed reaction of **8** with (3*S*,4*Z*)-**9** in DMF in the presence of Et_3N and 0.3 equiv of $NH_2OH{\cdot}HCl$ furnished chemically pure (+)-**6** only in 13% yield.

Compound (+)-**6**, which was so prepared in seven steps and 20% overall yield from (2*S*,3*S*)-**7** and **8**, was estimated to have 98.5% enantiomeric excess on the basis of HPLC analyses on a Chiracel OD-H column. This compound had physical and spectral properties in satisfactory agreement with those of the natural product,[13] but its specific rotatory power, $[\alpha]_D^{20} = +370$ (*c* 0.525, CH_3OH), was higher than that reported for naturally occurring (+)-**6**, $[\alpha]_D^{20} = +296$ (*c* 0.5, CH_3OH).[13] It should also be noted that this stereospecific synthesis of (+)-**6** from (2*S*,3*S*)-**7** allowed us to confirm that the natural product has a (2*E*,8*S*,9*Z*)-configuration.

Finally, we used a reaction sequence very similar to that reported in Scheme 2 to prepare (−)-**6**, which had (2*E*,8*R*,9*Z*)-configuration and $[\alpha]_D^{20} = -380$ (*c* 0.50, CH_3OH), from (−)-2,3-*O*-isopropylidene-D-threitol (−)-(2*R*,3*R*)-**7** in 16% overall yield. Compound (−)-**6** was estimated to have 97% enantiomeric excess on the basis of HPLC analyses on a Chiracel OD-H column.

Finally, compounds (+)-**6** (NSC 735472) and (−)-**6** (NSC 735473) were evaluated over a 5-log dose range in the NCI's in vitro human disease-oriented tumor cell line screening panel that consisted of 60 human tumor cell lines. The natural product and its enantiomer were found to exhibit modest cytotoxicity. In fact, their MG–MID Log GI_{50} values were −4.44 and −4.27, respectively. Nevertheless, (+)-**6** had Log GI_{50} −5.44 against the HL-60 leukemia cell line, but (−)-**6** had Log GI_{50}−4.95.

3. Conclusions

We have developed a route for the preparation of naturally occurring (+)-gymnasterkoreayne F and its enantiomer, which involves the use of an inexpensive derivative of L- and D-tartaric acid, respectively, as the starting material. The natural product was found to exhibit cytotoxic activity against the HL-60 leukemia cell line higher than that of the corresponding enantiomer. It should also be noted that (3*S*,4*Z*)-dodeca-4,11-dien-1-yn-3-ol, which we used as a key intermediate for the synthesis of (+)-gymnasterkoreayne F, can

represent a useful intermediate for the preparation of other cytotoxic gymnasterkoreaynes, such as those of B and C. Studies on the synthesis of (+)-gymnasterkoreayne C are in progress.

4. Experimental

4.1. General

Pre-coated Merk 60 F254 aluminum silica gel sheets were used for TLC analyses. GLC analyses were performed on a Dani GC 1000 instrument with a PTV injector, which was equipped with a Dani DDS 1000 data station. Two types of capillary columns were used: an Alltech AT-35 bonded FSOT column (30 m× 0.25 mm i.d.) and an Alltech AT-1 bonded Fsot column (30 m× 0.25 mm i.d.). Purifications by MPLC on silica gel (Merk 60 silica gel, particle size 0.015–0.040 mm) were performed on a Büchi B-680 system with a Knauer K-2400 differential refractometer as detector. GLC/EI-MS analyses were performed with an Agilent Technologies 5973 Network mass selective detector interfaced with an Agilent Technologies 6890N Network GC system. The MS spectrum of compound (+)-**6** was recorded with a Perkin–Elmer SCIEX API III triple quadrupole mass spectrometer by the atmospheric pressure photoionization (APPI) technique by a tandem mass spectrometry approach. HPLC analyses were performed on a Waters system with a 1525 LC pump and a 2996 photodiode array detector. IR spectra were recorded with a Perkin–Elmer 1725 FT-IR spectrophotometer. NMR spectra were recorded with a Varian Gemini 200 MHz and Varian Gemini 300 MHz spectrometers with TMS as the internal standard. Measurements of optical activity were performed with a Perkin–Elmer 142 spectropolarimeter in 1 dm tubes. All reactions involving air- and water-sensitive materials were performed in flame-dried glassware under argon by standard syringe, cannula, and septa techniques. (+)-2,3-*O*-Isopropylidene-L-threitol (2*S*,3*S*)-**7** and (−)-2,3-*O*-isopropylidene-D-threitol (2*R*,3*R*)-**7** were commercially available. The following compounds were prepared according to the literature: $PdCl_2(PhCN)$,[24] (*E*)-5-bromo-2-penten-4-yn-1-ol **8**.[15b]

4.2. (2*S*,3*S*)- and (2*R*,3*R*)-4-(*p*-Methoxybenzyloxy)-2,3-(isopropylidendioxy)-butan-1-ol, (2*S*,3*S*)-14 and (2*R*,3*R*)-14, respectively

To a solution of (2*S*,3*S*)-**7** (8.75 g, 53.9 mmol) in a 1:1 mixture of THF and DMF (70 mL) was added portionwise, in 20 min, a 60% dispersion of NaH in mineral oil (2.32 g, 58.0 mmol) at 0 °C. After 1.5 h stirring, *p*-methoxybenzyl chloride (7.68 mL, 56.7 mmol) was added dropwise to the solution at 0 °C and the mixture stirred overnight at room temperature. It was then treated with water (20 mL), poured into a saturated aqueous NaCl solution (150 mL) and extracted with AcOEt (6 × 50 mL). The combined organic solution was washed with brine (3 × 50 mL), dried, and concentrated under reduced pressure. The residue was purified by MPLC on silica gel, with a mixture of hexane and AcOEt (60:40) as eluent, to give (2*S*,3*S*)-**14** (10.9 g, 72%) as a light yellow liquid. EI-MS, *m/z* (%): 282 (0.5) [M^+], 163 (7), 162 (13), 137 (19), 135 (5), 131 (8), 122 (12), 121 (100), 77 (6). IR (film): *ν* 3463, 1612, 1514, 1371, 1249, 1171, 1082, 1036, 846 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): *δ* 1.41 (6H, s, CMe_2), 2.60 (1H, s, OH), 3.48–3.80 (4H, m, H-1 and H-4), 3.79 (3H, s, OMe), 3.91 (1H, dt, *J* = 8.4 and 4.5 Hz, H-2), 4.02 (1H, ddd, *J* = 8.4, 5.6, and 4.5 Hz, H-3), 4.51 (2H, s, $ArCH_2O$), 6.87 (2H, d, *J* = 9.0 Hz, H_{arom}), 7.25 (2H, d, *J* = 9.0 Hz, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 26.82, 26.84, 55.1, 62.3, 69.9, 73.2, 76.6, 79.6, 109.2, 113.7 (2C), 129.3 (2C), 129.5, 159.2 ppm. The spectral properties of this compound were in good agreement with those previously reported.[25] Compound (2*R*,3*R*)-**14** was synthesized in 74% yield from (2*R*,3*R*)-**7**, according to the procedure used to prepare (2*S*,3*S*)-**14**. The spectral properties of (2*R*,3*R*)-**14** were in good agreement with those of the corresponding enantiomer.

4.3. 8-Bromo-1-octene, 18

To a solution of 1,8-dibromooctane **17** (27.2 g, 100 mmol) in THF (53 mL) maintained at room temperature, was added during 0.5 h a solution of *t*-BuOK (13.0 g, 115 mmol) in THF (100 mL) and the resulting mixture stirred at room temperature for 1.5 h. It was then poured into water (200 mL) and extracted with ether (5 × 50 mL). The combined organic phase was washed with brine (3 × 50 mL), dried, and concentrated. The residue was fractionally distilled to give **18** (7.4 g, 39%) as a colorless liquid: bp 86–87 °C/20 mbar (lit.[18] bp 92 °C/24 mmHg).

4.4. 7-Octenyl triphenylphosphonium bromide, 13

A mixture of **18** (11.1 g, 58.2 mmol) and triphenylphosphine (18.3 g, 69.9 mmol) in CH_3CN (150 mL) was refluxed for 140 h and then cooled at room temperature. Most of the solvent was removed under reduced pressure and the residue thoroughly washed with anhydrous ether (2 × 70 mL) and then with hexane (2 × 70 mL). It was then dried under reduced pressure to give **13** (26.3 g, 100%) as a pale brown gummy mass, which was used in the next step without any further purification and characterization.

4.5. (2*R*,3*S*)- and (2*S*,3*R*)-2,3-(Isopropylidenedioxy)-4-(*p*-methoxybenzyloxy)-butanale, (2*R*,3*S*)- and (2*S*,3*R*)-12, respectively

Dimethyl sulfoxide (8.42 mL, 0.118 mmol) was added dropwise to a solution of oxalyl chloride (5.17 mL, 59.2 mmol) in CH_2Cl_2 (88 mL) at −78 °C. After stirring for 15 min, a solution of (2*S*,3*S*)-**14** (11.2 g, 39.5 mmol) in CH_2Cl_2 (21 mL) was added dropwise and the mixture stirred for 40 min at −78 °C. Triethylamine (27.5 g, 197 mmol) in CH_2Cl_2 was then added over 15 min, and the resulting mixture stirred for another 10 min at −78 °C and then allowed to warm to room temperature. It was then poured into a saturated aqueous NaCl solution (500 mL) and extracted with CH_2Cl_2 (5 × 200 mL).

The collected organic phase was washed with 1% HCl (200 mL), brine (2 × 200 mL), and water (200 mL), dried, and concentrated under reduced pressure to give crude (2*R*,3*S*)-**12** (14.0 g) as a pale yellow liquid. EI-MS, *m*/*z* (%): 280 (4) [M^+], 179 (8) 178 (14), 137 (6), 136 (5), 122 (9), 121 (100), 78 (5), 77 (6). GLC analyses showed that crude (2*R*,3*S*)-**12** was contaminated by ca. 4% of a compound, which had an EI-MS spectrum very similar to that of the major component. This crude compound was directly used in the next reaction without any further purification and characterization since this aldehyde undergoes significant epimerization also at room temperature. In fact, GLC analysis of a sample of crude (2*R*,3*S*)-**12** maintained at −23 °C for 48 h showed that the amount of the stereoisomer contaminating the desired compound now figured to more than 10%.

This same procedure was used to prepare crude (2*S*,3*R*)-**12** (14.1 g) starting from (2*R*,3*R*)-**14** (12.2 g, 43.2 mmol). This crude product was also used directly in the next step without any further purification.

4.6. (2*S*,3*S*,4*Z*)- and (2*R*,3*R*,4*Z*)-2,3-(Isopropylidenedioxy)-1-(*p*-methoxybenzyloxy)-dodeca-4,11-diene, (2*S*,3*S*,4*Z*)-15 and (2*R*,3*R*,4*Z*)-15, respectively

To a solution of **13** (21.4 g, 47.4 mmol) in THF (263 mL) was added a 1*M* THF solution of *t*-BuOK (47.4 mL, 47.4 mmol) and the mixture was stirred at room temperature for 1 h and then cooled to −78 °C. To this mixture was added a solution of crude (2*R*,3*S*)-**12** (14.0 g) in THF (110 mL) and the resulting mixture stirred for another 2 h at −78 °C and then for 12 h at room temperature. The reaction was quenched with a saturated aqueous NH_4Cl solution (500 mL) and the resulting mixture extracted with ether (5 × 200 mL). The collected organic phase was washed with brine (3 × 100 mL), dried, concentrated under reduced pressure and the residue was purified by MPLC on silica gel, with a mixture of petroleum ether and AcOEt (94:6) as eluent, to give (2*S*,3*S*,4*Z*)-**15** (12.9 g, 87%) as a yellow oil. EI-MS, *m*/*z* (%): 374 (0.3) [M^+], 137 (37), 136 (4), 135 (5), 122 (10), 121 (100), 97 (10), 81 (6), 77 (7). IR (film): *v* 2929, 1613, 1514, 1369, 1248, 1171, 1081, 1036, 861, 821 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.21–1.42 (6H, m, H-7, H-8, H-9), 1.44 (6H, s, CMe_2), 1.92–2.17 (4H, m, H-6 and H-10), 3.47–3.59 (2H, m, H-1), 3.80 (3H, s, Ome), 3.80–3.88 (1H, m, H-2), 4.52 (2H, s, $ArCH_2O$), 4.61 (1H, *pseudo*-t, *J* = 8.7 Hz, H-3), 4.93 (1H, d, *J* = 10.2 Hz, H-12$_Z$), 5.00 (1H, d, *J* = 16.8 Hz, H-12$_E$), 5.38 (1H, dd, *J* = 11.1 and 8.7 Hz, H-4), 5.65 (1H, dt, *J* = 11.1 and 7.4 Hz, H-5), 5.79 (1H, ddt, *J* = 16.8, 10.2, and 6.7 Hz, H-11), 6.86 (2H, d, *J* = 8.2 Hz, H_{arom}), 7.25 (2H, d, *J* = 8.2 Hz, H_{arom}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.9, 27.1, 27.6, 28.60, 28.64, 29.3, 33.6, 55.1, 68.8, 73.1, 73.4, 80.4, 109.1, 113.6 (2C), 114.2, 126.2, 128.2 (2C), 130.0, 136.1, 138.8, 159.1 ppm. $[\alpha]_D^{28} = +7.0$ (*c* 3.17, $CHCl_3$). Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H 9.15. Found: C, 73.47; H, 9.33. GLC and GLC–MS analyses showed that (2*S*,3*S*,4*Z*)-**15** had stereoisomeric purity higher than 92% and was contaminated by three stereoisomers, which presumably correspond to (2*S*,3*R*,4*Z*)-, (2*S*,3*S*,4*E*)-, and (2*S*,3*R*,4*E*)-**15**.

The procedure employed to prepare (2*S*,3*S*,4*Z*)-**15** was also used for the synthesis of 94% stereoisomerically pure (2*R*,3*R*,4*Z*)-**15** in 78% yield starting from **13** and (2*S*,3*R*)-**12**. Compound (2*R*,3*R*,4*Z*)-**15** had $[\alpha]_D^{28} = -8.1$ (*c* 3.09, $CHCl_3$). The spectral properties of this compound were in good agreement with those of the corresponding enantiomer.

4.7. (2*S*,3*S*,4*Z*)- and (2*R*,3*R*,4*Z*)-2,3-(Isopropylidenedioxy)-dodeca-4,11-dien-1-ol, (2*S*,3*S*,4*Z*)-16 and (2*R*,3*R*,4*Z*)-16, respectively

To a stirred solution of 92% stereoisomerically pure (2*S*,3*S*,4*Z*)-**15** (11.9 g, 31.8 mmol) in CH_2Cl_2 (154 mL) and water (8 mL) was added DDQ (10.8 g, 47.7 mmol). After the initially dark solution was stirred for 2 h at room temperature, a saturated aqueous $NaHCO_3$ solution (150 mL) was added and the brown mixture filtered over Celite and extracted with CH_2Cl_2 (5 × 70 mL). The organic extract was washed with a saturated aqueous $NaHCO_3$ solution (3 × 50 mL) and brine (2 × 70 mL), dried, and concentrated under reduced pressure. The residue was purified by MPLC on silica gel, with a mixture of toluene and AcOEt (90:10) as eluent, to give (2*S*,3*S*,4*Z*)-**16** (6.84 g, 85%) as a pale yellow liquid. EI-MS, *m*/*z* (%): 254 (1) [M^+], 239 (11), 179 (8), 123 (8), 97 (47), 95 (25), 81 (32), 67 (29), 59 (100). IR (film): *v* 3482, 2929, 2856, 1640, 1380, 1242, 1165, 1054, 907, 856 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.23–1.40 (6H, m, H-7, H-8, and H-9), 1.41 (6H, s, CMe_2), 1.92–2.20 (4H, m, H-6 and H-10), 3.45–3.83 (3H, m, H-1 and H-2), 4.67 (1H, *pseudo*-t, *J* = 8.8 Hz, H-3), 4.89 (1H, dm, *J* = 10.2 Hz, H-12$_Z$), 4.95 (1H, dm, *J* = 16.8 Hz, H-12$_E$), 5.35 (1H, dd, *J* = 10.8 and 8.8 Hz, H-4), 5.66 (1H, dt, *J* = 10.8 and 7.2 Hz, H-5), 5.76 (1H, ddt, *J* = 16.8, 10.2, and 6.8 Hz, H-11) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.0, 27.2, 27.7, 28.6 (2C), 29.4, 33.7, 60.5, 72.5, 81.3, 108.9, 114.2, 125.8, 136.6, 138.9 ppm. Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.65; H, 10.10. $[\alpha]_D^{28} = -11.3$ (*c* 3.14, $CHCl_3$). GLC and EI-GLC–MS analyses showed that compound (2*S*,3*S*,4*Z*)-**16** was 97% stereoisomerically pure.

The procedure employed to prepare (2*S*,3*S*,4*Z*)-**16** was also used for the synthesis of 99% stereoisomerically pure (2*R*,3*R*,4*Z*)-**16** in 88% yield from (2*R*,3*R*,4*Z*)-**15**. Compound (2*R*,3*R*,4*Z*)-**16** had $[\alpha]_D^{28} = +11.0$ (*c* 3.09, $CHCl_3$). Its spectral properties were in good agreement with those of the corresponding enantiomer.

4.8. (2*R*,3*S*,4*Z*)- and (2*S*,3*R*,4*Z*)-1-Chloro-2,3-(isopropylidenedioxy)-dodeca-4,11-diene, (2*R*,3*S*,4*Z*)-11 and (2*S*,3*R*,4*Z*)-11, respectively

Triphenylphosphine (12.0 g, 45.8 mmol) was added to a solution of (2*S*,3*S*,4*Z*)-**16** (5.83 g, 22.9 mmol) in CCl_4 (110 mL) and the mixture stirred under reflux for 16 h. It was then cooled to room temperature, poured into petroleum ether (550 mL) and left at 0 °C for 6 h. The

mixture was filtered and the filtrate concentrated under reduced pressure. The residue was purified by MPLC on silica gel, with a mixture of petroleum ether and AcOEt (97:3) as eluent, to give (2*R*,3*S*,4*Z*)-**11** (5.70 g, 91%) as a pale yellow liquid. EI-MS, *m*/*z* (%): 272 (0.3) [M^+], 257 (5), 179 (8), 120 (15), 97 (34), 95 (15), 94 (4), 85 (100), 79 (17), 67 (18). IR (film): *v* 2930, 1640, 1371, 1241, 1163, 1112, 1061, 900, 747 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.32–1.45 (6H, m, H-7, H-8, H-9), 1.46 (6H, s, CMe_2), 1.98–2.24 (4H, m, H-6 and H-10), 3.56 (1H, dd, $J = 12.2$ and 4.5 Hz, H-1), 3.70 (1H, dd, $J = 12.2$ and 4.5 Hz, H-1), 3.84–3.94 (1H, m, H-2), 4.70 (1H, *pseudo*-t, $J = 9.2$ Hz, H-3), 4.93 (1H, dm, $J = 10.2$ Hz, H-12_Z), 5.00 (1H, dm, $J = 17.0$ Hz, H-12_E), 5.39 (1H, dd, $J = 10.8$ and 9.2 Hz, H-4), 5.73 (1H, dt, $J = 10.8$ and 7.8 Hz, H-5), 5.81 (1H, ddt, $J = 17.0$, 10.2, and 6.8 Hz, H-11) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 26.9, 27.3, 27.8, 28.7 (2C), 29.4, 33.7, 43.1, 74.3, 80.0, 109.5, 114.3, 125.4, 137.1, 138.9 ppm. $[\alpha]_D^{28} = -7.65$ (*c* 3.11, $CHCl_3$). Anal. Calcd for $C_{15}H_{25}ClO_2$: C, 66.04; H, 9.24. Found: C, 65.94; H, 9.12. GLC and EI-MS analyses showed that compound (2*R*,3*S*,4*Z*)-**11** was stereoisomerically pure.

The procedure employed to prepare (2*R*,3*S*,4*Z*)-**11** was also used in the synthesis of (2*S*,3*R*,4*Z*)-**11** in 80% yield from (2*R*,3*R*,4*Z*)-**16**. Compound (2*S*,3*R*,4*Z*)-**11**, which was stereoisomerically pure, had $[\alpha]_D^{28} = +8.1$ (*c* 3.12, $CHCl_3$). Its spectral properties were in good agreement with those of the corresponding enantiomer.

4.9. (3*S*,4*Z*)- and (3*R*,4*Z*)-Dodeca-4,11-dien-1-yn-3-ol, (3*S*,4*Z*)-9 and (3*R*,4*Z*)-9, respectively

A 1.72 M solution of *n*-butyllithium (36.3 mL, 62.5 mmol) was added to a solution of diisopropylamine (6.32 g, 62.5 mmol) in THF (105 mL) at 0 °C. After being stirred for 70 min, the mixture was cooled to −78 °C. To this mixture was added a solution of (2*R*,3*S*,4*Z*)-**11** (3.41 g, 12.5 mmol) in THF (10 mL). Stirring was continued for 3 h, then the mixture was warmed to 0 °C, stirred for 30 min, quenched with a saturated aqueous NH_4Cl solution (100 mL) and extracted with ether (5 × 60 mL). The organic extract was washed with brine (3 × 40 mL), dried, and concentrated under reduced pressure. The residue was purified by MPLC on silica gel, with a mixture of hexane and ether (80:20) as eluent, to give (3*S*,4*Z*)-**9** (1.23 g, 55%) as a pale yellow liquid. EI-MS, *m*/*z* (%): 177 (0.5) [M^+-1], 117 (20), 107 (23), 95 (40), 93 (24), 91 (41), 81 (100), 79 (45), 67 (54). IR (film): *v* 3306, 2928, 2856, 2116, 1639, 1438, 1018, 910, 652 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.15–1.50 (6H, m, H-7, H-8, and H-9), 1.85 (1H, br s, OH), 1.92–2.20 (4H, m, H-6 and H-10), 2.51 (1H, d, $J = 2.2$ Hz, H-1), 4.93 (1H, dm, $J = 10.2$ Hz, H-12_Z), 5.00 (1H, dm, $J = 16.8$ Hz, H-12_E), 5.15 (1H, dd, $J = 7.6$ and 2.2 Hz, H-3), 5.50–5.62 (2H, m, H-4 and H-5), 5.81 (1H, ddt, $J = 16.8$, 10.2, and 6.6 Hz, H-11) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.5, 28.7 (2C), 29.1, 33.7, 58.0, 72.9, 84.0, 114.3, 128.6, 133.9, 138.9 ppm. $[\alpha]_D^{28} = +132.4$ (*c* 1.14, $CHCl_3$). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 81.05; H, 10.13.

The procedure used for the preparation of (3*S*,4*Z*)-**9** was also used for the synthesis of (3*R*,4*Z*)-**9** in 53% yield from (2*S*,3*R*,4*Z*)-**11**. Compound (3*R*,4*Z*)-**9** had $[\alpha]_D^{28} = -127.5$ (*c* 1.22, $CHCl_3$). Its spectral properties were in good agreement with those of the corresponding enantiomer.

4.10. (+)-Gymnasterkoreayne F [(*S*,2*E*,9*Z*)-heptadeca-2,9,16-trien-4,6-diyne-1,8-diol], (+)-6

This compound was prepared by three different procedures (Methods A, B, and C).

4.10.1. Method A. To a suspension of CuCl (10.9 mg, 0.11 mmol), $NH_2OH{\cdot}HCl$ (38.8 mg, 0.568 mmol), and 65% $EtNH_2$ (82.10 mL) in methanol (2.7 mL) at 0 °C were added successively a solution of (*E*)-5-bromo-2-penten-4-yn-1-ol **8** (365 mg, 2.05 mmol) in methanol (1.4 mL) and a solution of (3*S*,4*Z*)-**9** (300 mg, 1.86 mmol) in methanol (1.4 mL). After being stirred for 45 min at 0 °C, the mixture was treated with water (20 mL) and extracted with CH_2Cl_2 (6 × 15 mL). The organic extract was washed with brine (2 × 10 mL), dried, and concentrated under reduced pressure. The residue was purified by MPLC on silica gel, with a mixture of hexane and THF (65:35) as eluent, to give (+)-**6** (365 mg, 76%) as a pale yellow liquid, which proved to be homogeneous to TLC and MPLC analyses. MPLC purification on silica gel of this liquid, with a mixture of hexane and THF (70:30) as eluent, provided an analytically pure sample of (+)-**6**. MS (Tandem Mass Spectrometry on the 281 [M^++Na] ion), *m*/*z* (%): 281 (100), 242 (2), 241 (9), 197 (2), 171 (4), 159 (2), 143 (2), 135 (2), 129 (2). IR (film): *v* 3350, 2927, 2855, 2230, 1640, 1435, 1384, 1092, 909 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.22–1.45 (6H, m, H-12, H-13, H-14), 1.97–2.17 (4H, m, H-11 and H-15), 4.21 (2H, dd, $J = 4.6$ and 1.8 Hz, H-1), 4.93 (1H, dm, $J = 10.2$ Hz, H-17_Z), 4.99 (1H, dm, 16.8 Hz, H-17_E), 5.20 (1H, d, $J = 7.8$ Hz, H-8), 5.49 (1H, dd, $J = 10.8$ and 7.8 Hz, H-9), 5.58 (1H, dt, $J = 10.8$ and 7.0 Hz, H-10) 5.80 (1H, ddt, $J = 16.8$, 10.2, and 6.7 Hz, H-16), 5.81 (1H, d, J =15.8 Hz, H-3), 6.40 (1H, dt, $J = 15.8$ and 4.6 Hz, H-2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.5, 28.6 (2C), 29.0, 33.6, 58.4, 62.2, 69.4, 73.7, 77.3, 81.8, 108.3, 114.2, 127.8, 133.8, 138.8, 145.8 ppm. $[\alpha]_D^{28} = +370.0$ (*c* 0.525, CH_3OH) lit.[13] $[\alpha]_D^{28} = +296$ (*c* 0.5, CH_3OH). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58; Found: C, 78.97; H, 8.40.

The enantiomeric excess of (+)-**6** was estimated as 98.5% by HPLC analysis [column: Chiracel OD-H; solvent: methanol/H_2O (70:30); flow rate: 1 mL/min]; $t_r = 8.33$ min; $R_S = 2.5$. The ^1H and ^{13}C NMR spectra of (+)-**6** were in good agreement with those of the natural product.[13]

4.10.2. Method B. A solution of (3*S*,4*Z*)-**9** (270 mg, 1.68 mmol) in DMF (2.5 mL) and Et_3N (234 μL, 1.68 mmol), were sequentially added to a suspension of CuCl (16.8 mg, 0.168 mmol), $NH_2OH{\cdot}HCl$ (35.0 mg, 0.504 mmol), and **8** (300 mg, 1.68 mmol) in DMF (3 mL) at 0 °C and the resulting mixture stirred at

0 °C for 30 min. It was then warmed to room temperature, stirred at this temperature for 23 h and subsequently poured into 5% HCl (25 mL). The mixture was extracted with CH_2Cl_2 (8 × 10 mL) and the organic extract washed with brine until neutrality (4 × 6 mL) and dried. It was then concentrated under reduced pressure, and the residue purified by MPLC on silica gel, with a mixture of hexane and THF (65:35) as eluent, to give (+)-**6** (55 mg, 13%) as a pale yellow liquid. The spectral properties of this compound were in agreement with those of (+)-**6** prepared with Method A.

4.10.3. Method C. A solution of (3*S*,4*Z*)-**9** (270 mg, 1.68 mmol) in DMF (2.5 mL) and 2,2,6,6-tetramethylpiperidine (TMP) (600 μL, 3.53 mmol) were sequentially added to a mixture of CuCl (16.8 mg, 0.168 mmol), $NH_2OH{\cdot}HCl$ (35.0 mg, 0.504 mmol), **8** (300 mg, 1.68 mmol), and DMF (3 mL), which was stirred at 0 °C. After stirring for 30 min at 0 °C, the mixture was warmed to room temperature for 5 h and then worked up as described for the preparation of (+)-**6** by Method B. The crude product obtained was purified by MPLC on silica gel, with a mixture of hexane and THF (65:35) as eluent, to give (+)-**6** (221 mg, 51%) as a pale yellow liquid. The spectral properties of this chemically pure compound were in agreement with those of (+)-**6** prepared by Methods A and B.

4.11. (−)-Gymnasterkoreayne F [(*R*,2*E*,9*Z*)-heptadeca-2,9,16-trien-4,6-diyne-1,8-diol], (−)-6

This compound was synthesized by reaction of (3*R*,4*Z*)-**9** (400 mg, 224 mmol) with **8** (328 mg, 2.04 mmol) by a procedure very similar to that described for the preparation of its enantiomer according to Method A. The compound (−)-**6** obtained (408 mg, 77%) had $[\alpha]_D^{28} = -380.0$ (*c* 0.500, CH_3OH). Its spectral properties were in very good agreement with those of (+)-**6** synthesized from (2*S*,4*Z*)-**9**. The enantiomeric excess of (+)-**6** was estimated to be 97% by HPLC analysis [column: Chiracel OD-H; solvent: methanol/H_2O (70:30); flow rate: 1 mL/min]; $t_r = 7.18$ min; $R_S = 2.5$.

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