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Asymmetric Total Synthesis of (−)-Gymnasterkoreayne G

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Naturally occurring diynes are found as metabolites in a variety of fungi, higher plants, and marine sponges; their pharmacological properties, including cytotoxic, antimicrobial, and enzyme inhibitory activities, attract special attention in the realm of medicinal chemistry.[1]

Since Jung *et al.* reported the first isolation of gymnasterkoreaynes A-F from the roots of *Gymnasterkoraiensis* in 2002, gymnasterkoreayne G, a new compound, was isolated from the leaves of the same plant by the same group in 2005 (Figure 1).[2,3] The gymnasterkoreayne family exhibits significant biological activities including inhibition of the NFAT (nuclear factor of activated T-cells) transcription factor and cytotoxicity. In particular, gymnasterkoreayne B showed the highest potency against the NFAT transcription factor (IC_{50} = 1.44 ± 0.59 μM), while gymnasterkoreaynes E and G were mildly inhibitory (IC_{50} = 7.24 ± 0.42 and 43.9 ± 2.24 μM, respectively).

The structures of gymnasterkoreaynes B-G were elucidated as diyne natural products with linear (*Z*)-heptadeca-9,16-dien-4,6-diyn-8-ol skeletons using spectroscopic methods, while gymnasterkoreayne A is a C10 diyne. The absolute configuration of the C8 stereocenter of gymnasterkoreayne F was determined using the modified Mosher's Ester method, and was further confirmed through the total synthesis of (+)-gymnasterkoreayne F by Carpita *et al.* in 2005.[4] However, the absolute stereochemistries of other gymnasterkoreaynes have not been solidly assigned, though those of gymnasterkoreayne B and gymnasterkoreayne C were assumed as (10*S*) and (3*S*, 8*S*), respectively, by comparison of optical rotations and ^{13}C-NMR data of structurally similar natural products.

Gymnasterkoreaynes G and E are the most structurally and stereochemically complex gymnasterkoreaynes. Both compounds are triols with three stereogenic centers (C2, C3, and C8). According to the previous publication, the relative stereochemical relationship of C2 and C3 in gymnasterkoreayne E was reported to besyn (*threo*), while that of gymnasterkoreayne G is *anti* (*erythro*), which was predicted by comparisons of the coupling constants of H-2 and H-3 with those of other diols.[2,3]

Recently, in the course of the discovery of new cancer chemopreventive agents, we isolated gymnasterkoreaynes with significant chemopreventive activities from the root barks of *Gymnasterkoraiensis*, which include gymnasterkoreaynes B, D, E, and Fand reported preliminary structure-activity relationship study.[5] However, the limited quantity of the isolated compounds prevented further *in vivo* experiments. The interesting biological activity and the scarcity of the natural compounds, in addition to the necessity of stereochemical confirmation, prompted us to develop a general synthetic method for the gymnasterkoreayne natural products.

Herein, we disclose the first concise total synthesis of two enantiomerically pure (2*S*,3*R*,8*R*)- and (2*R*,3*S*,8*R*)-heptadeca-9(*Z*),16-dien-4,6-diyne-2,3,8-triol(C2,C3-*anti* relationship), one of which is expected to be either natural (+)-gymnasterkoreayne G (**1**) or its enantiomer.

The retrosynthetic plan is outlined in Scheme 1. Considering the structural features, we envisioned that the rapid

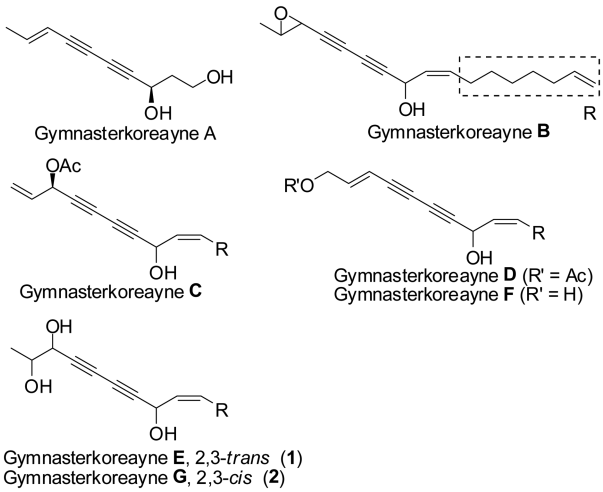
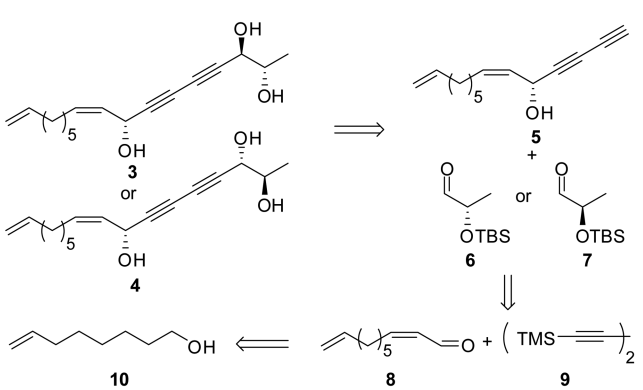
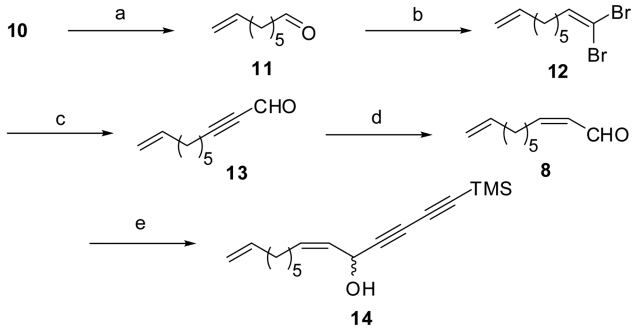


Figure 1. The structures of gymnasterkoreaynes **A-G**.



Scheme 1. Restrosynthetic Plan.

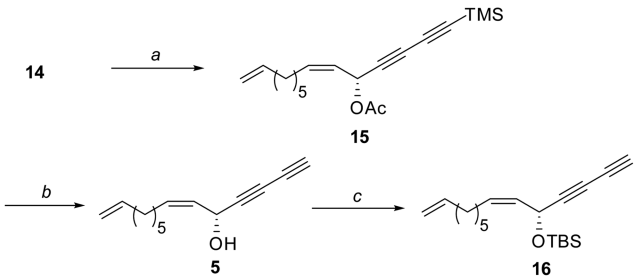


Scheme 2. Reagents and Conditions: a. DMSO (3.0 equiv.), $(COCl)_2$ (1.5 equiv.), CH_2Cl_2, −78 °C; then Et_3N (5.0 equiv.), −78 °C to rt b. CBr_4 (1.2 equiv.), PPh_3 (2.4 equiv.), CH_2Cl_2, 0 °C, 79% for two steps c. *n*-BuLi (2.0 equiv.), THF, −78 °C to −20 °C; then DMF, −78 °C to rt, 87% d. Pd/$CaCO_3$ (5.0 wt %, H_2 (Balloon), cyclohexene/ EtOAc (1:10), rt, 71% e. 1,4-bis(trimethylsilyl)-buta-1,3-diyne (1.2 equiv.), MeLi-LiBr (1.0 equiv. based on diacetylene), THF, 0 °C, 2 hrs; then aldehyde **8**, 10 min, 93%.

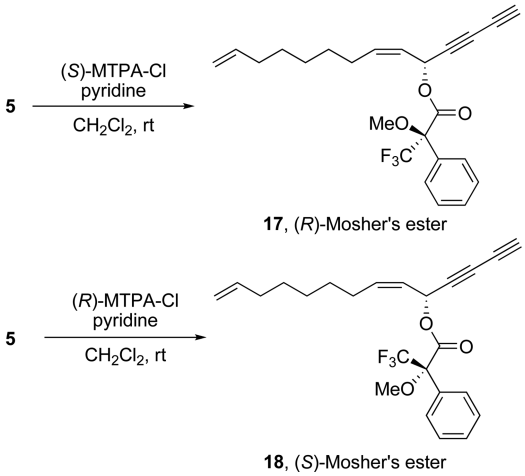
assembly of three components, C_{10}-*cis*-enal (**8**), C_4-diyne (**9**), and C_3-2-silyloxypropanals (**6** or **7**),[6] would deliver the target compounds. Two addition reactions of diacetylenic anions to the corresponding aldehydes are the keystothis synthesis. The first addition of the diacetylenic anion from bis-(TMS)-diacetylene **9** to the enal **8** can furnish allyl propargylic carbinol **5**, and the second addition of the resulting diacetylenic anion to the α-alkoxyaldehyde can provide the desired diols **3** and **4** with defined stereochemistry.

The preparation of racemic alcohol **14** is presented in Scheme 2. Commercially available 7-octen-1-ol (**10**) was oxidized under Swern oxidation conditions ($(COCl)_2$, DMSO, CH_2Cl_2; then Et_3N), and the resulting aldehyde **11** was converted to the *gem*-dibromide **12** by the Corey-Fuchs reaction (CBr_4, PPh_3), with a yield of 79% over two steps. Generation of the alkynylanion from dibromide **12** with 2 equivalents of *n*-butyllithium and *in situ* capture with dimethylformamide delivered alkynal **13**, the triple bond of which was reduced by partial hydrogenation (Pd on $BaCO_3$, H_2) to give *cis*-enal **8** in 71% yield. Care is required in handling *cis*-enal **8**, due to facile isomerization to the more stable *trans*-enal underany acidic or basic conditions. Thus, after rapid flash column chromatographic separation from the small amount of the *trans*-enal contaminant, the *cis* compound was readily reacted with the anion of buta-1,3-diynyltrimethylsilane (obtained by reaction of 1,4-bis(trimethylsilyl)-buta-1,3-diyne **9** with methyllithium-lithium bromide complex), to afford the desired racemic alcohol **14** in 93% yield.[7]

There are several methods for the resolution of racemic secondary alcohols, which include separation by chiralchromatography, chiral auxiliary assisted separation, kinetic resolution by enzyme or chemical reaction, and asymmetric reduction of the ketone derived from the racemic alcohol. After attempts with several different methods, enzymatic kinetic resolution was found to be very effective in our case.[8] The reaction was carried out using Lipase "Amano" in hexanes at room temperature to give the chiral acetate **15** in



Scheme 3. Reagents and Conditions: a. Amano lipase AK (1.5 equiv. by mass of racemic alcohol), vinyl acetate (4.0 equiv.), 4 Å molecular sieves (1.0 equiv. by mass of racemic alcohol), hexane, rt, 16 hrs, 43% b. LiOH (5.0 eq.), H_2O/THF (1:3), rt, 5 hrs, 69% c. TBSCl (2.0 equiv.), imidazole (3.0 equiv.), CH_2Cl_2, 0 °C to rt, 1.5 hr, 100%.



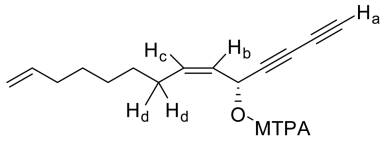
Scheme 4. Synthesis of (8*R*)- and (8*S*)-Mosher's esters.

43% yield (enantiomeric ratio > 98:2), which was confirmed bychiral HPLC analysis (Chiracel OD-H column) by comparing with the racemic acetate (Scheme 3). Both trimethylsilyl and acetyl groups were removed by lithium hydroxide monohydrate in THF/H_2O (3:1) medium, followed by TBS protection (TBSCl, imidazole, CH_2Cl_2) of the resulting alcohol **5** to afford the diyne **16** in a two-step yield of 78%.

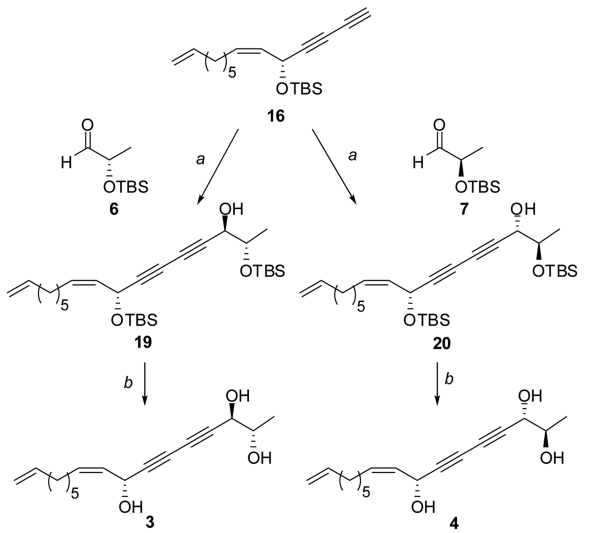
To confirm the absolute stereochemistry, the Mosher's Ester method was applied.[9] The chiral secondary alcohol **5** was treated with (*S*)-1,1-methoxy trifluoromethyl phenylacetyl chloride ((*S*)-MTPA-Cl) and (*R*)-1,1-methoxy trifluoromethyl phenylacetyl chloride ((*R*)-MTPA-Cl) in the presence of pyridine in CH_2Cl_2 at room temperature, to deliver the corresponding (8*R*)-Mosher's ester **17** and (8*S*)-Mosher's ester **18** respectively (Scheme 4). The chemical shifts of four protons H_a, H_b, H_c, and H_d of the (*R*)-and (*S*)-Mosher's esters and their chemical shift differences are summarized in Table 1. Applying the subtraction protocol, the Δδ of the acetylenic proton H_a exhibited a negative value and those of the other three protons positive ones, which implies that the absolute configuration ofthe chiral alcohol-stereo center is (*S*) according to the standard Mosher rule.

The completion of synthesis is shown in Scheme 5. The TBS-protected diyne **16** was deprotonated by EtMgBr, followed by treatment with (*S*)-2-(*tert*-butyldimethylsiloxy)-propanal (**6**) or (*R*)-2-(*tert*-butyldimethylsiloxy)propanal (**7**)

Table 1. Calculation of chemical shift differences



	H_a	H_b	H_c	H_d
δ_S	2.241	5.564	5.756	2.184
δ_R	2.257	5.460	5.716	2.157
$\Delta\delta = \delta_S - \delta_R$ (Hz)	-14.4	93.6	36	24.3



Scheme 5. Reagents and Conditions: a. EtMgBr (1.0 equiv.), THF, 0, 30 min; then aldehyde **6** or **7**, 68% and 73%, respectively b. TBAF (3.0 equiv.), THF, rt, 10 min, 91%, and 99%, respectively.

at −78 °C, respectively, to give *anti*-alcohols **19** and **20** predominantly (*anti*/*syn* ratio > 90:10). *Anti*/*syn*-diastereomers were easily separated by SiO_2 column chromatography. The stereoselectivity can be explained by the Felkin-Ahn model, and the relative stereochemistry was confirmed by NOE study of model compound[10] and a reference article.[11] Finally, deprotection of the two TBS groups in compounds **19** and **20** with TBAF in THF provided the desired 2,3-*anti*-diols **3** and **4** in quantitative yields, respectively.

The twotriols **3** and **4** gavevery similar spectral data, andthe coupling constant of H2-H3 of the two synthesized *erythro*-(2*S*,3*R*)-diol **3** and *erythro*-(2*R*,3*S*)-diols **4** were 3.3 and 3.4 Hz, respectively, which are same with recently reported data of (+)-Gymnasterkoreayne G in which the coupling constant of the *erythro* diol was also 3.3 Hz.[3,12] The authors of the 2002 and 2005 publications assigned the relative configuration of the 2,3-diol in gymnasterkoreayne E as *threo* (*syn*) and gymnasterkoreayne G as *erythro* (*anti*), based on the literature or empirical results, and our data confirmed that the relative stereochemistry of 2,3-diols in gymnasterkoreayne G is *erythro* (*anti*). Finally, Absolute configuration was determined by optical rotation, of which **3** and **4** were −45.2° (c = 0.03, $CHCl_3$) and −174.4° (c = 0.03, $CHCl_3$), respectively, which showed that the optical rotations of **3** corresponds to the opposite value of the optical rotations reported for (+)-gymnasterkoreaynes G [$[\alpha]_D^{20}$ = +40.0°, c = 0.3, $CHCl_3$].

In summary, we completed the asymmetric total synthesis of (2*S*,3*R*,8*R*)-heptadeca-9(*Z*), 16-dien-4,6-diyne-2,3,8-triol (**3**) and (2*R*,3*S*,8*R*)-heptadeca-9(*Z*), 16-dien-4,6-diyne-2,3,8-triol (**4**) as a structural proof of gymnasterkoreayne G or its enantiomer. The syntheses were accomplished in 10 steps with 11% overall yields, starting from 7-octen-1-ol (**10**). Racemic alcohol **14** was resolved by enzymatic kinetic resolution to enantiomerically enriched **5** using Lipase AK "Amano" and the stereochemistry of C3 was generated by a substrate-controlled, stereoselective addition reaction. Finally, (2*S*,3*R*,8*R*)-heptadeca-9(*Z*), 16-dien-4,6-diyne-2,3,8-triol (**3**) wasproved to bethe (−)-gymnasterkoreayne G.

Experimental Section

(*Z*)-1-(Trimethylsilyl)tetradeca-6,13-dien-1,3-diyn-5-ol (14). MeLi-LiBr (1.85 mL, 2.78 mmol) was added to a solution of 1,4-bis(trimethylsilyl)-buta-1,3-diyne (491 mg, 2.53 mmol) in THF (10 mL) at 0 °C. The reaction mixture was gradually warmed to room temperature and stirred for 2 h. After 2 h, the mixture was re-cooling to 0 °C and aldehyde (316 mg, 2.10 mmol) was added to the reaction mixture with stirring for 10 min. The reaction was quenched by addition of saturated aq. NH_4Cl. Layers were separated and the aqueous layer extracted with EtOAc. Combined organic extracts were washed with water and brine, dried by Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure. Silica gel chromatography (50:1 EtOAc/hexanes) gave the desired compound (535 mg, 93%) ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 6.6, 10.2, 16.8 Hz, 1H), 5.61-5.44 (m, 2H), 5.15 (d, *J* = 7.8 Hz, 1H), 5.00-4.89 (m, 2H), 2.11-1.98 (m, 4H), 1.41-1.23 (m, 6H), 0.17 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 139.2, 134.6, 128.1, 114.6, 88.4, 87.5, 70.0, 58.8, 34.0, 29.4, 29.0, 28.9, 27.9, 16.9, −0.2; FT-IR (neat) ν_{max} 3394, 2930, 2857, 2221, 2106, 1641, 1252, 996, 910, 846, 761, 638 cm^{-1}; HRMS (ESI^+): calcd for $[C_{17}H_{27}OSi]^+$: 275.1831, found: 275.1820.

(*R*,*Z*)-1-(Trimethylsilyl)tetradeca-6,13-dien-1,3-diyn-5-yl acetate (15). The racemic alcohol **14** (595 mg, 2.17 mmol) was mixed with Amano lipase AK (893 mg, 1.5 equiv. by mass of racemic alcohol), vinyl acetate (0.80 mL, 8.67 mmol) and molecular sieves (595 mg, 1.0 equiv. by mass of racemic alcohol) in anhydrous hexane (12 mL). The reaction mixture was stirred under nitrogen atmosphere for 16 hours at room temperature. After 16 hours, the mixture was filtered by paper and the residue was evaporated under reduced pressure. Silica gel chromatography (60:1 EtOAc/hexane) gave the desired acetate. (294 mg, 43%) $[\alpha]_D^{20}$ = −0.5 (c = 0.09, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) 6.10 (d, *J* = 8.7 Hz, 1H), 5.78 (ddt, *J* = 6.6, 10.2, 17.1 Hz, 1H), 5.62 (dt, *J* = 7.5, 10.8, 1H), 5.44 (dd, *J* = 9.0, 10.5 Hz, 1H), 5.01-4.89 (m, 2H), 2.15-1.98 (m, 4H), 2.04 (s, 3H), 1.40-1.29 (m, 6H), 0.17 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.4, 139.0, 136.2, 124.3, 114.6, 88.4, 87.4, 74.2, 70.5, 60.2, 33.9, 29.2, 28.9, 28.8, 28.0, 21.0, 0.1; FT-IR (neat) ν_{max}

3435, 2934, 2860, 2281, 2202, 1671, 1138, 995, 912 cm^{-1} ; Calcd for $[C_{19}H_{28}OSi]^+$: 316.1859, found: 316.1863.

(2*S*,3*R*,8*R*,*Z*)-2,8-Bis(tert-butyldimethylsilyloxy)heptadeca-9,16-dien-4,6-diyne-3-ol (19). EtMgBr (0.114 mL, 1 M sol'n in THF), was added to a solution of diyne (36 mg, 0.114 mmmol) in anhydrous THF (2 mL) at 0 °C and stirred for 30 min. After 30 min, the reaction mixture was gradually warmed to room temperature and stirred for 2 h. Then (*S*)-2-(*tert*-butyldimethylsilyloxy)propanal (32 mg, 0.17 mmol) was added to the reaction mixture at 0 °C and reaction mixture was gradually warmed to room temperature. The mixture was stirred for 2 hr. The reaction was quenched by addition saturated aq. NH_4Cl. Layers were separated and the aqueous layer extracted with EtOAc. Combined organic extracts were washed with water and brine, dried by Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure. Silica gel chromatography (EtOAc/hexanes = 1:80) gave the desired alcohol as a colorless oil. (39 mg, 68%) $[\alpha]_D^{20} = -82.1$ (c = 0.01, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.78 (ddt, *J* = 16.8, 9.9, 7.2 Hz, 1H), 5.50-5.40 (m, 2H), 5.15 (d, *J* = 6.9 Hz, 1H), 5.01-4.90 (m, 2H), 4.27 (dd, *J* = 3.9, 6.3 Hz, 1H), 3.89 (dq, *J* = 3.3, 6.3 Hz, 1H), 2.34 (d, *J* = 6.3 Hz, 1H), 2.05-1.99 (m, 4H), 1.41-1.28 (m, 6H), 1.20 (d, *J* = 6.3 Hz, 3H), 0.87 (s, 18H), 0.11 (s, 3H), 0.09 (s, 1H), 0.07 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 139.3, 132.2, 129.6, 114.6, 79.9, 77.3, 71.2, 7068.6, 68.1, 59.7, 34.0, 30.0, 29.4, 29.03, 29.01, 28.0, 26.0, 18.8, 18.5, 18.3, 0.27, –4.15, –4.24, –4.47, –4.57; IR (neat) ν_{max} 3437, 2931, 2859, 1641, 1464, 1256, 1137, 1077, 939, 838, 778, 669 cm^{-1}; HRMS (ESI^+) Calcd for $[C_{29}H_{52}O_3Si_2]^+$: 504.3455, found: 504.3450.

(2*R*,3*S*,8*R*,*Z*)-2,8-Bis(tert-butyldimethylsilyloxy)heptadeca-9,16-dien-4,6-diyne-3-ol (20). The experimental procedure was same as above, and EtMgBr (0.139 mL, 0.139 mmol, 1 M sol'n in THF), diyne (44 mg, 0.139 mmol), and (*R*)-2-(*tert*-butyldimethylsilyloxy)propanal (42 mg, 0.222 mmol) were used for this reaction. Yield: 73%, $[\alpha]_D^{20} = -21.7$ (c = 0.02 , $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.85-5.70 (m, 1H), 5.50-5.43 (m, 2H), 5.15 (d, *J* = 6.0 Hz, 1H), 4.97, 4.92 (dd, 18.6, 12.6 Hz, 2H), 2.77 (dd, *J* = 3.9, 5.1, 1H), 3.90 (dq, *J* = 3.9, 6.3 Hz, 1H), 2.33 (d, *J* = 5.1 Hz, 1H), 2.06-2.02 (m, 4H), 1.39-1.22 (m, 6H), 1.20 (d, *J* = 6.3 Hz, 3H), 0.87 (s, 18H), 0.11 (s, 3H), 0.09 (s, 3H), 0.07 (s, 6H); FT-IR (neat) ν_{max} 3435, 2934, 2860, 2281, 2202, 1671, 1138, 995, 912 cm^{-1}; HRMS (ESI^+) Calcd for $[C_{29}H_{52}O_3Si_2]^+$: 504.3455, found: 504.3452.

(2*S*,3*R*,8*R*,*Z*)-Heptadeca-9,16-dien-4,6-diyne-2,3,8-triol (3). TBAF (37 mg, 0.14 mmol) was added to a solution of alcohol **19** (24 mg, 0.048 mmol) in THF (0.2 mL) at room temperature and stirred for 10 min. Then reaction mixture layers were separated and the aqueous layer extracted with EtOAc. Combined organic extracts were washed with water and brine, dried by Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure. Silica gel chromatography (EtOAc/hexanes = 1:2) gave the desired triol. (12 mg, 91%): $[\alpha]_D^{20} = -45.2$ (c = 0.03, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.86 (m, 1H), 5.69 (m, 1H), 5.60 (m, 1H), 5.24 (d, *J* = 7.8, 1H), 5.03, 4.98 (m, 2H), 4.40 (d, *J* = 3.3, 1H), 3.95 (dq, *J* = 3.3, 6.3 Hz, 1H), 2.19-2.06 (m, 4H), 1.44-1.30 (m, 6H), 1.32 (d, *J* = 6.2 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 139.2, 134.8, 128.0, 114.6, 79.7, 77.4, 70.9, 70.5, 69.0, 67.8, 58.9, 33.9, 29.4, 29.0, 28.9, 27.9, 18.6; FT-IR (neat) ν_{max} 3400, 1620, 1210 cm^{-1}; HRMS (ESI^+) Calcd for $[C_{17}H_{24}O_3]^+$: 276.1725, found: 276.1722.

(2*R*,3*S*,8*R*,*Z*)-Heptadeca-9,16-dien-4,6-diyne-2,3,8-triol (4). The experimental procedure was same as above and TBAF (50 mg, 0.19 mmol), alcohol **20** (32 mg, 0.063 mmol) were used for this reaction. Yield: 99%, $[\alpha]_D^{20} = -174.4$ (c = 0.03, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.78 (m, 1H), 5.63-5.46 (m, 2H), 5.17 (d, *J* = 8.1 Hz), 4.96, 4.92 (m, 2H), 4.34 (d, *J* = 3.3 Hz, 1H), 3.89 (dq, *J* = 3.3, 6.3 Hz, 1H), 2.12-1.99 (m, 4H), 1.37-1.23 (m, 6H), 1.24 (d, *J* = 6.2 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 139.4, 134.9, 128.1, 114.7, 79.8, 77.5, 71.0, 70.6, 69.1, 67.8, 59.0, 34.1, 29.4, 28.9, 28.9, 28.0, 18.7; FT-IR (neat) ν_{max} 3390, 1205 cm^{-1}; HRMS (ESI^+) Calcd for $[C_{17}H_{24}O_3]^+$: 276.1725, found: 276.1727.

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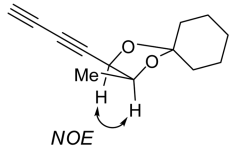
10. The structure of a model compound



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