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\textsubscript{50} = 1.44 ± 0.59 µM), while gymnasterkoreaynes E and G were mildly inhibitory (IC\textsubscript{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-diyne-2,3,8-triol 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\text{S}), (3\text{S}, 8\text{S}) respectively, by comparison of optical rotations and 

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 be syn (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 gymnasterkoreayne B, D, E, and F and 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\text{S},3\text{R},8\text{R})- and (2\text{R},3\text{S},8\text{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

Scheme 1. Restrosynthetic Plan.
assembly of three components, C\textsubscript{10}-cis-enal (8), C\textsubscript{2}-diyne (9), and C\textsubscript{2}-silyloxypropanals (6 or 7), would deliver the target compounds. Two addition reactions of diacetylenic anions to the corresponding aldehydes are the keystothisynthesis. The first addition of the diacetylenic anion from bis-(TMS)-diacetylene 9 to the enal 8 can furnish allyl propargylcarbinol 5, and the second addition of the resulting diacetylenic anion to the α-alkoxyaldehyde can provide the desired diols 3 and 4 with defined stereochernomy.

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)\textsubscript{2}, DMSO, CH\textsubscript{2}Cl\textsubscript{2}; then Et\textsubscript{3}N), and the resulting aldehyde 11 was converted to the gem-dibromide 12 by the Corey-Fuchs reaction (CBr\textsubscript{4}, PPh\textsubscript{3}), with a yield of 79% over two steps. Generation of the alkynylalan from dibromide 12 with 2 equivalents of n-butyllithium and in situ capture with dimethylformamide delivered alkynalan 13, the triple bond of which was reduced by partial hydrogenation (Pd on BaCO\textsubscript{3}, H\textsubscript{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%.

Scheme 2. Reagents and Conditions: a. DMSO (3.0 equiv.), (COCl)\textsubscript{2}; (1.5 equiv.), CH\textsubscript{2}Cl\textsubscript{2}, −78 °C; then Et\textsubscript{3}N (5.0 equiv.), −78 °C to rt b. CBr\textsubscript{4} (1.2 equiv.), PPh\textsubscript{3} (2.4 equiv.), CH\textsubscript{2}Cl\textsubscript{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\textsubscript{3} (5.0 wt %, H\textsubscript{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%.

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\textsubscript{2}O/THF (1:3), rt, 5 hrs, 69% c. TBSCI (2.0 equiv.), imidazole (3.0 equiv.), CH\textsubscript{2}Cl\textsubscript{2}, 0 °C to rt, 1.5 hr, 100%.

Scheme 4. Synthetic of (8R)- and (8S)-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\textsubscript{2}O (3:1) medium, followed by TBS protection (TBSCI, imidazole, CH\textsubscript{2}Cl\textsubscript{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. 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\textsubscript{2}Cl\textsubscript{2} at room temperature, to deliver the corresponding (8R)-Mosher’s ester 17 and (8S)-Mosher’s ester 18 respectively (Scheme 4). The chemical shifts of four protons H\textsubscript{a}, H\textsubscript{b}, H\textsubscript{c}, and H\textsubscript{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\textsubscript{d} exhibited a negative value and those of the other three protons positive ones, which implies that the absolute configuration of the chiral alcohol-stereocenter 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

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<th></th>
<th>H&lt;sub&gt;a&lt;/sub&gt;</th>
<th>H&lt;sub&gt;b&lt;/sub&gt;</th>
<th>H&lt;sub&gt;c&lt;/sub&gt;</th>
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<td>5.460</td>
<td>5.716</td>
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<tr>
<td>Δδ = δ&lt;sub&gt;R&lt;/sub&gt; - δ&lt;sub&gt;S&lt;/sub&gt; (Hz)</td>
<td>-14.4</td>
<td>93.6</td>
<td>36</td>
<td>24.3</td>
</tr>
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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<sub>2</sub> column chromatography. The stereoselectivity can be explained by the Felkin-Ahn model, and the relative stereochemistry was confirmed by NOE study of model compound<sup>10</sup> and a reference article.<sup>11</sup> 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 two triols 3 and 4 gave very similar spectral data, and the coupling constant of H2-H3 of the two synthesized erythro-(2S,3R)-diol 3 and erythro-(2R,3S)-diol 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.<sup>2,12</sup> The authors of the 2002 and 2005 publications assigned the relative configuration of the 2,3-diol in gymnasterkoreayne E as three (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<sub>3</sub>) and −174.4° (c = 0.03, CHCl<sub>3</sub>), respectively, which showed that the optical rotations of 3 corresponds to the opposite value of the optical rotations reported for (+)-gymnasterkoreayne G ([α]<sub>10</sub> = +40.0°, c = 0.3, CHCl<sub>3</sub>).

In summary, we completed the asymmetric total synthesis of (2S,3R,8R)-heptadeca-9(Z), 16-dien-4,6-diyne-2,3,8-triol (3) and (2R,3S,8R)-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 compound 5 using Lipase AK “Amano” and the stereochemistry of C3 was generated by a substrate-controlled, stereoselective addition reaction. Finally, (2S,3R,8R)-heptadeca-9(Z), 16-dien-4,6-diyne-2,3,8-triol (3) was proved to be the (−)-gymnasterkoreayne G.

**Experimental Section**

(Z)-1-(Trimethylsilyl)tetradeca-6,13-dien-1,3-diyne-5-ol (14). McLi-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<sub>4</sub>Cl. Layers were separated and the aqueous layer extracted with EtOAc. Combined organic extracts were washed with water and brine, dried by Na<sub>2</sub>SO<sub>4</sub> and filtered. The filtrate was evaporated under reduced pressure. Silica gel chromatography (50:1 EtOAc/hexanes) gave the desired compound (535 mg, 93%)<sup>3</sup> 1H-NMR (300 MHz, CDCl<sub>3</sub>) δ 5.78 (dtdd, J = 8.7, 10.8, 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);<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) 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<sub>max</sub> 3394, 2930, 2857, 2221, 2106, 1641, 1252, 996, 910, 846, 761, 638 cm<sup>−1</sup>; HRMS (ESI<sup>+</sup>): calcd for [C<sub>33</sub>H<sub>47</sub>O<sub>5</sub>Si]: 275.1831, found: 275.1820.

(R.Z)-1-(Trimethylsilyl)tetradeca-6,13-dien-1,3-diyne-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%)<sup>4</sup> [α]<sub>10</sub> = −0.5 (c = 0.09, CHCl<sub>3</sub>);<sup>3</sup> 1H-NMR (300 MHz, CDCl<sub>3</sub>) 6.10 (d, J = 8.7 Hz, 1H), 5.78 (dtdd, 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);<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) 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<sub>max</sub>
(2S,3R,8R,Z)-2,8-Bis(tert-butylidimethylsilyloxy)heptadeca-9,16-dien-4,6-diyne-3-ol (19). EtMgBr (0.114 mL, 1 M sol’n in THF), diyne (32 mg, 0.17 mmol) was added to the reaction mixture at 0 °C and reaction mixture was gradually warmed to room temperature and stirred for 2 h. 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%).

HRMS (ESI) Caled for [C_{29}H_{52}O_3Si]$: 504.3455, found: 504.3452.

References


10. The structure of a model compound
