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Total synthesis and absolute stereochemistry of (9*R*,10*S*)-epoxyheptadecan-4,6-diyn-3-one, a diacylglycerol acyltransferase inhibitor from *Panax ginseng*

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Abstract—Asymmetric synthesis of four possible stereoisomers of (9,10)-epoxyheptadecan-4,6-diyn-3-one was accomplished, and the absolute configuration of the naturally occurring (9*R*,10*S*)-epoxyheptadecan-4,6-diyn-3-one (**1**) was elucidated.
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Acyl-CoA:diacylglycerol acyltransferase (DGAT, EG 2.3.1.20) is a microsomal enzyme that catalyzes the formation of triacylglycerol from 1,2-diacylglycerol and fatty acyl CoA.[1] Triacylglycerol (TG) plays a crucial role as energy-storage molecules in mammals. However, a high level of TG is known to be a major risk factor for coronary heart disease, obesity, and hypertriglyceridemia.[2] Accordingly, DGAT inhibitors are expected to be an attractive target for the prevention and treatment of obesity and hypertriglyceridemia.

In the course of screening for inhibitors of diacylglycerol acyltransferase (DGAT) from medicinal herbs, we isolated a new polyacetylene compound bearing an epoxy ring from the roots of *Panax ginseng* C. A. Meyer. The polyacetylene compound, (9*R*,10*S*)-epoxyheptadecan-4,6-diyn-3-one (**1**), exhibited DGAT inhibition with IC_{50} of 9 μg/mL and optical rotation of $[\alpha]_{25}^{D}$ −70.0 (*c* 1.0, $CHCl_3$).[3] The connectivity of **1** was established by NMR analysis, however, the relative and absolute configuration of an epoxy moiety in **1** was not elucidated. As we have been interested in further biological studies including in vivo activities, the stereochemistry of **1** should be determined, thereby enabling to provide a synthetic way that would bring a large quantity of **1**. Herein we describe the synthesis of four possible stereoisomers of (9,10)-epoxyheptadecan-4,6-diyn-3-one and the determination of the relative and absolute configuration of naturally occurring (9*R*,10*S*)-epoxyheptadecan-4,6-diyn-3-one (**1**) (Fig. 1).

The synthesis of (9*R*,10*S*)-epoxyheptadecan-4,6-diyn-3-one (**1**) and its stereoisomers was achieved by a general coupling of two components, polyacetylene **5** and epoxy triflate **6**, and subsequent oxidation of the resultant secondary alcohol to furnish **1** as shown in Scheme 1. We envisioned that the relative stereochemistry at epoxy moiety in **1** could be determined by the difference in olefin geometry of allylic alcohol **7**. And, the absolute stereochemistry of epoxy triflate **6** could be determined by Sharpless asymmetric epoxidaion[4] of the corresponding allylic alcohol **7** and followed by triflation, thereby establishing the absolute chemistry of **1**.

The acetylenic C_1–C_7 moiety **5** was prepared from acetylide-carbonyl condensation (Scheme 2). Addition of propionaldehyde to disodiobutadiynlide generated in situ by the reaction of 1,4-dichloro-2-butyn (**8**) and sodium amide in THF afforded hepta-4,6-diyn-3-ol (**5**).[5] The C_8–C_{17} epoxy triflate moiety **6** was obtained starting from 1-nonyne in four steps. Lithiation of 1-nonyne (**9**) using *n*-BuLi and addition of paraformaldehyde provided dec-2-yn-1-ol (**10**).[6] Acetylenic alcohol **10** was selectively hydrogenated with Lindlar catalyst to yield the corresponding *cis*-allylic alcohol **7**. Sharpless

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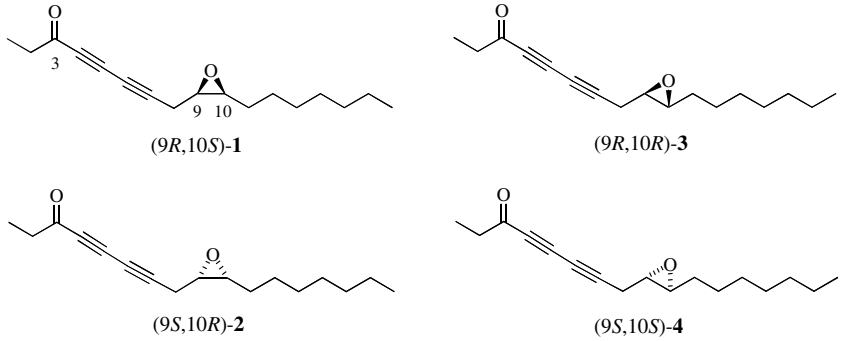
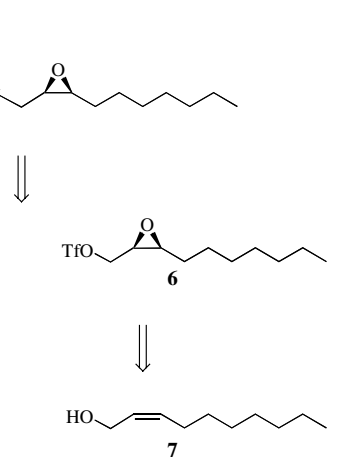
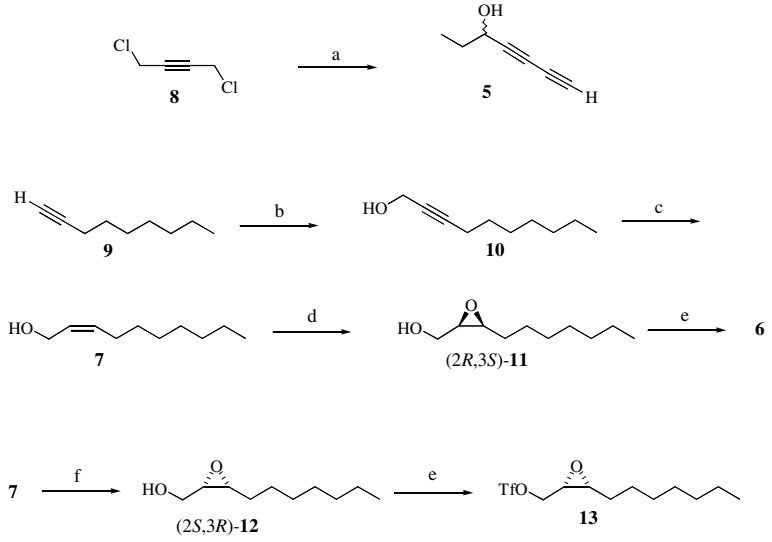


Figure 1. Structure of four stereoisomers of (9,10)-epoxyheptadecan-4,6-diyn-3-one.

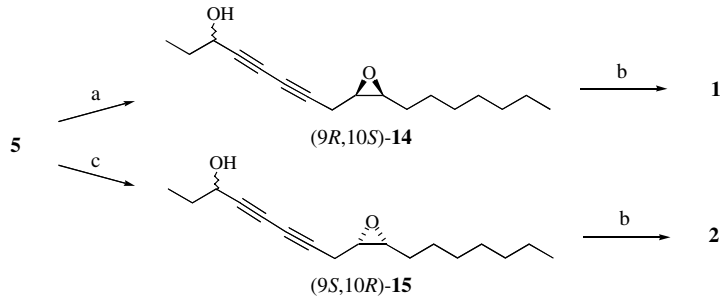
asymmetric epoxidation of *cis*-2-decen-1-ol (**7**) utilizing (−)-diethyl D-tartrate afforded (2*R*,3*S*)-3-heptyloxirane methanol (**11**) in >99% ee after recrystallization from petroleum ether.[4,7] Then, the epoxy alcohol **11** was converted to the corresponding triflate **6** by treatment with trifluoromethane sulfonic anhydride. On the other hand, the enantiomeric epoxy alcohol (2*S*,3*R*)-**12** was obtained from same *cis*-allylic alcohol **7** using (+)-diethyl L-tartrate in >99% ee after recrystallization from petroleum ether.[4,7] With two building blocks, acetylenic C_1–C_7 moiety **5** and epoxy triflate **6** and **13**, in hand, we tried dianionic condensation reaction to furnish (9,10)-epoxyheptadecan-4,6-diyn-3-one (Scheme 3). The epoxy triflate **6** was treated with dilithio complex generated by the reaction of acetylenic alcohol **5** and *n*-BuLi to yield (9*R*,10*S*)-heptadeca-4,6-diyn-9,10-epoxy-3-ol (**14**). Finally, the secondary alcohol group in **14** was oxidized to yield **1**. In addition, enantiomer **2** of compound **1** was prepared by using same procedures.[8] Having clarified the asymmetric approach to **1** and its enantiomer **2** containing a *cis*-epoxy moiety, we prepared the diastereomeric isomer **3** and its enantiomer **4** from *trans*-2-decen-1-ol (**16**) using the same procedures as those described for **1** and **2** in Schemes 2 and 3.[9] Synthesis of stereoisomers **3** and **4** starting from commercially available *trans*-2-decen-1-ol (**16**) is summarized in



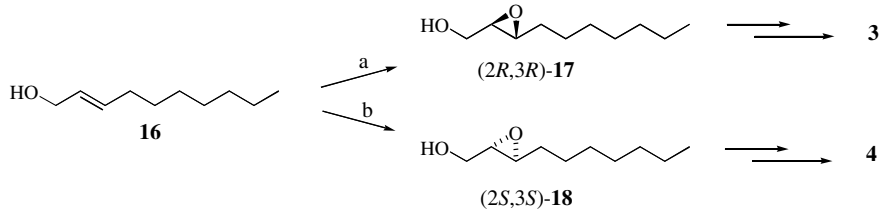
Scheme 1. Retrosynthetic analysis of (9*R*,10*S*)-epoxyheptadecan-4,6-diyn-3-one (**1**).



Scheme 2. Reagents and reaction conditions: (a) $NaNH_2$, THF, −33 to 0 °C; then CH_3CH_2CHO (25%); (b) *n*-BuLi, THF, −78 °C; then paraformaldehyde, −78 °C to rt (95%); (c) Lindlar catalyst, H_2, quinoline, hexane (94%); (d) Ti(O-*i*-Pr)$_4$, (−)-DET, *t*-BuOOH, 4 Å molecular sieves, CH_2Cl_2, −20 °C [98% (>99% ee after recrystallization)]; (e) $(CF_3SO_2)_2O$, Et_3N, −78 °C, CH_2Cl_2 (98%); (f) Ti(O-*i*-Pr)$_4$, (+)-DET, *t*-BuOOH, 4 Å molecular sieves, CH_2Cl_2, −20 °C [92% (>99% ee after recrystallization)].



Scheme 3. Reagents and reaction conditions: (a) 2*n*-BuLi, HMPA–THF, −78 °C; then **6** (76%); (b) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, −20 °C (86%); (c) 2*n*-BuLi, HMPA–THF, −78 °C; then **13** (74%).



Scheme 4. Reagents and reaction conditions: (a) Ti(O-*i*-Pr)$_4$, (−)-DET, *t*-BuOOH, 4 Å molecular sieves, CH_2Cl_2, −20 °C [95% (>99% ee after recrystallization)]; (b) Ti(O-*i*-Pr)$_4$, (+)-DET, *t*-BuOOH, 4 Å molecular sieves, CH_2Cl_2, −20 °C [93% (>99% ee after recrystallization)].

Scheme 4. There were distinct differences in ^1H and ^{13}C NMR between *cis*-epoxy compound **1** (or **2**) and *trans*-epoxy compound **3** (or **4**). Compound **1** was in good accord with a natural authentic sample {lit. $[\alpha]_{25}^{D}$ −70.0 (*c* 1.0, $CHCl_3$)}[3] in all aspects including ^1H NMR, ^{13}C NMR, optical rotation, and TLC in three different solvent systems. On the basis of these data, the absolute configuration of (9*R*,10*S*)-epoxyheptadecan-4,6-diyn-3-one (**1**) was determined.

In conclusion, we have completed the first asymmetric synthesis of (9*R*,10*S*)-epoxyheptadecan-4,6-diyn-3-one (**1**) and determined its absolute stereochemistry to be 9*R* and 10*S*.

Acknowledgements

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7. Enantioselectivity was determined by ^1H NMR analysis of the derived α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA, Mosher) ester, and >99% indicates that the other enantiomer was not detectable by NMR.
8. Optical rotation values of $[\alpha]_{25}^{D}$ −69.0 (*c* 1.0, $CHCl_3$) for (9*R*,10*S*)-**1** and $[\alpha]_{25}^{D}$ +68.0 (*c* 1.0, $CHCl_3$) for (9*S*,10*R*)-**2**.
9. Optical rotation values of $[\alpha]_{25}^{D}$ +10.0 (*c* 1.0, $CHCl_3$) for (9*R*,10*R*)-**3** and $[\alpha]_{25}^{D}$ −10.0 (*c* 1.0, $CHCl_3$) for (9*S*,10*S*)-**4**.