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Total Synthesis and Absolute Configuration of (−)-Gummiferol

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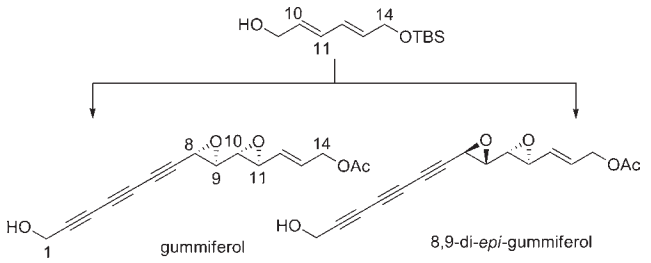
ABSTRACT



Stereoselective synthesis of two possible diastereomers of (−)-gummiferol was accomplished by the stepwise epoxidation and Cadiot−Chodkiewicz reaction as the key transformations. Detailed comparison of their ^{1}H and ^{13}C NMR data and specific rotation with those of the natural product led to the absolute structural elucidation of (−)-gummiferol.

(−)-Gummiferol was isolated from the 50% MeOH/$CHCl_3$ extract of the leaves of *Adenia gummifera* in 1995 by Wall et al.[1] This molecule exhibits a cytotoxicity against various cell lines including strong activity against P-388 (ED_{50}: 0.03 μg/mL) and U-373 (ED_{50}: 0.05 μg/mL). The planar structure of (−)-gummiferol, which has featured the triacetylene and diepoxide moieties, was elucidated on the basis of $^{3}J_{H,H}$ analysis and the ^{1}H−^{1}H COSY, HMQC, and HMBC spectra (Figure 1). However, the stereochemistries of the contiguous epoxide moiety at the C8 to C11 positions were not determined. Herein, we report the stereoselective synthesis of two possible diastereomers of (−)-gummiferol and comparison of their spectroscopic data with those of the natural product, which has resulted in the absolute structural determination of (−)-gummiferol.

Our synthetic stategy toward two possible diastereomers of (−)-gummiferol, diepoxides **5** and **6**, is outlined in Scheme 1. The key synthetic intermediate **1** would be stereoselectively converted to *syn*-diepoxide **2** and *anti*-diepoxide **3** via Sharpless epoxidation, respectively.[2] The triacetylene unit could be constructed by a Cadiot−Chodkiewicz reaction[3] through a combination of the bromoacetylenes **2** and **3** and diacetylene **4** to yield the triacetylenes **5** and **6**, respectively.

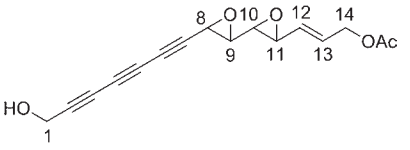


Figure 1. Planar structure of (−)-gummiferol.

First, we examined the stereocontrolled synthesis of the *syn*-diepoxide **5**. Sharpless asymmetric epoxidation[2] of dienol **7**[4] with (+)-diisopropyl tartrate (DIPT) provided epoxy alcohol **8** as a single stereoisomer (Scheme 2).[5] Although Sharpless asymmetric epoxidation

(1) Fullas, F.; Brown, D. M.; Wani, M. C.; Wall, M. E.; Chagwedera, T. E.; Farnsworth, N. R.; Pezzuto, J. M.; Kinghorn, A. D. *J. Nat. Prod.* **1995**, *58*, 1625.

(2) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

(3) (a) Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: Amsterdam, 1988. (b) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632.

(4) Zhang, P.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 12550.

(5) The optical purity of **8** was judged by comparison of the ^{1}H NMR spectrum of its (*R*)-MTPA ester with that of the (*R*)-MTPA ester prepared from the racemic epoxy alcohol, which was available from **7** using *m*-CPBA.

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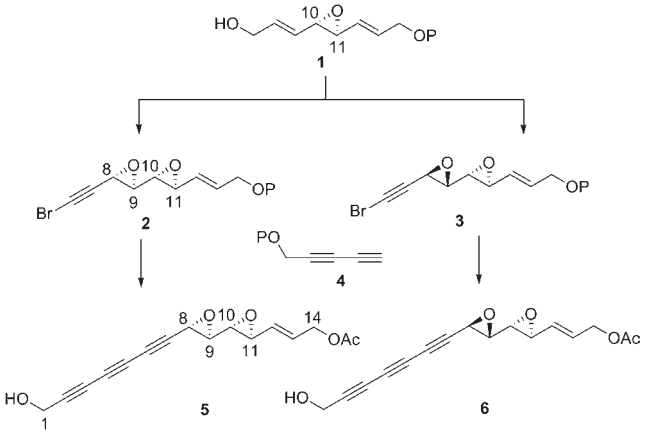
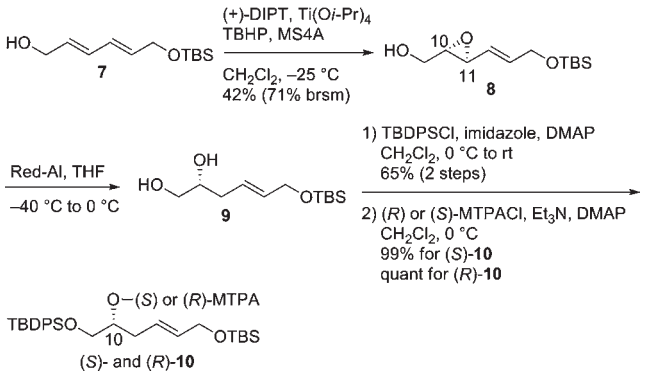
is a well-established method, the unambiguous stereochemical elucidation of **8** was performed by the derivatization and the modified Mosher method.[6] When the epoxy alcohol **8** was treated with Red-Al,[7] epoxide ring opening occurred regioselectively at the C11 position due to the C−O bond activation by the adjacent π-orbital to afford 1,2-diol **9**. The primary hydroxy group of **9** was selectively protected to give the corresponding TBDPS ether. The resulting secondary alcohol was converted to MTPA esters (*S*)- and (*R*)-**10** by the standard conditions (MTPACl/Et_3N/DMAP). Figure 2 describes the $\Delta\delta_{S-R}$ values of the (*S*)- and (*R*)-**10**.[6] The signs at the left side of the C10 positon were negative, and those at the right side were positive. Therefore, the absolute configuration of **10** was assigned to be 10*R*, which resulted in the structural elucidation of **8**.

Scheme 1. Synthetic Plan of **5** and **6**



Scheme 2. Synthesis and Derivatization of **8**



As shown in Scheme 3, the epoxy alcohol **8** was converted to allylic alcohol **11** by the following three step sequence: (1) Parikh−Doering oxidation,[8] (2) Horner−Wadsworth−Emmons reaction,[9] and (3) DIBAL-H reduction.[10] Second Sharpless asymmetric epoxidation[2] with (+)-DIPT proceeded smoothly to provide *syn*-diepoxide **12** as a sole product in 80% yield. The diepoxide **12** was derivatized for the structural determination of the resulting 8,9-epoxide moiety. Thus, diimide reduction of the olefin unit and subsequent regioselective reduction of the 8,9-epoxide moiety with Red-Al[7] gave 1,3-diol **13**. Protection of the primary alcohol of **13** as the TBDPS ether followed by reaction with MTPACl afforded esters (*S*)- and (*R*)-**14**. In the observed $\Delta\delta_{S-R}$ values of the (*S*)- and (*R*)-**14**, the signs at the left side of the C9 positon were positive, and those at the right side were negative (Figure 3). Therefore, the absolute stereochemistry of **14** was elucidated to be 9*R*, leading to the structural determination of the 8,9-epoxide moiety of **12**.

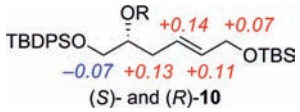
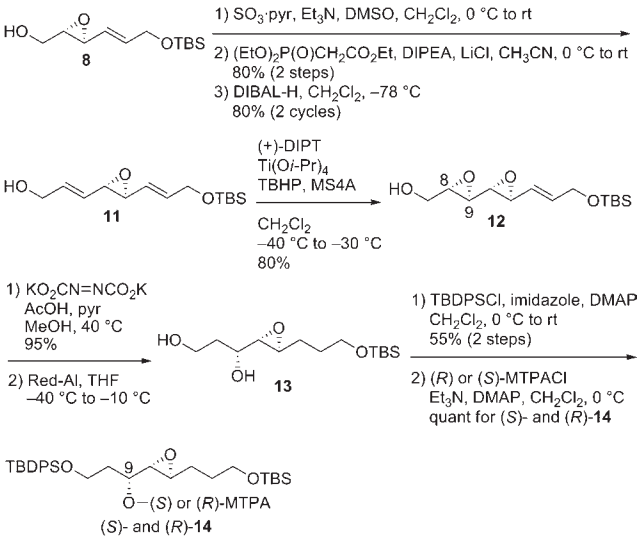


Figure 2. Chemical shift differences ($\Delta\delta_{S-R}$) of (*S*)- and (*R*)-**10**. R = MTPA. MTPA = α-methoxy-α-(trifluoromethyl)phenylacetyl.

Scheme 3. Synthesis and Derivatization of **12**



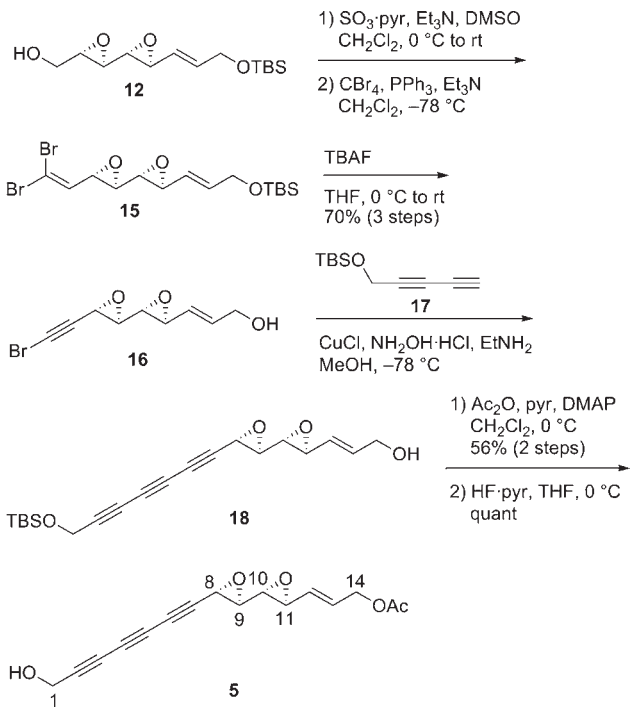
Further transformation of **12** to the *syn*-diepoxide **5** is described in Scheme 4. Parikh−Doering oxidation[8] of **12**

(6) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
(7) Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719.
(8) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
(9) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
(10) When we tried DIBAL-H reduction (2.2 equiv), we observed the epoxide opening as a side reaction. Therefore, we chose the stepwise DIBAL-H reduction. The first reaction (1.1 equiv) gave the corresponding aldehyde, and the second reduction (1.1 equiv) provided **11**.

Figure 3. Chemical shift differences ($\Delta\delta_{S-R}$) of (*S*)- and (*R*)-**14**. R = MTPA. MTPA = α-methoxy-α-(trifluoromethyl)phenylacetyl.

and subsequent one-carbon homologation with CBr_4/PPh_3/Et_3N[11,12] gave dibromoolefin **15**. Treatment of **15** with TBAF (4.0 equiv) induced desilylation and dehydrobromination simultaneously to afford bromoacetylenic alcohol **16**.[12b] After the detailed investigation on the introduction of the triacetylenic moiety, it was found that Cadiot−Chodkiewicz reaction[3] between **16** (1.0 equiv) and diacetylene **17** (1.1 equiv)[13] with CuCl/NH_2OH•HCl/$EtNH_2$ at −78 °C proceeded smoothly to provide triacetylene **18**.[14] Finally, acetylation of the alcohol **18** and subsequent deprotection of the TBS group with HF·pyr afforded the *syn*-diepoxide **5**.

Scheme 4. Synthesis of **5**



(11) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

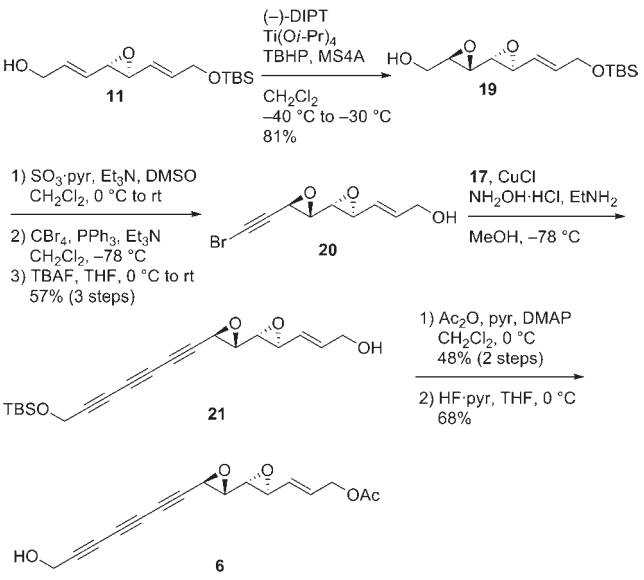
(12) In the absence of Et_3N, only a trace amount of **15** was obtained because the epoxide opening occurred as a side reaction. For the related examples, see: (a) Grandjean, D.; Pale, P.; Chuche, J. *Tetrahedron Lett.* **1994**, *35*, 3529. (b) González, I. C.; Forsyth, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 9099. (c) Díaz, D.; Martín, T.; Martín, V. S. *J. Org. Chem.* **2001**, *66*, 7231.

(13) Reber, S.; Knöpfel, T. F.; Carreira, E. M. *Tetrahedron* **2003**, *59*, 6813.

Next, we investigated the stereoselective synthesis of the *anti*-diepoxide **6** (Scheme 5). The transformation from the key synthetic intermediate **11** to **6** is similar to that toward **5**. The allylic alcohol **11** was subjected to Sharpless asymmetric epoxidation[2] using (−)-DIPT, giving *anti*-diepoxide **19** as a single stereoisomer in 81% yield.[15] Parikh−Doering oxidation[8] of **19** followed by dibromoolefination[11] and desilylation/dehydrobromination[12b] provided bromoacetylene **20** in 57% yield in three steps. The bromoacetylene **20** (1.0 equiv) was coupled with the diacetylene **17** (1.1 equiv) by Cadiot−Chodkiewicz reaction[3] under the optimized conditions affording triacetylene **21**.[14] The final transformation, acetylation and desilylation, was performed to provide the *anti*-diepoxide **6**.

The synthetic diepoxides **5** and **6** were submitted to extensive NMR analysis. The selected $\Delta\delta$ values in ppm between natural (−)-gummiferol and the synthetic products in the ^1H and ^{13}C NMR spectra are depicted in Table 1. The ^1H and ^{13}C NMR data of the synthetic *syn*-diepoxide **5** were in good agreement with those of natural (−)-gummiferol.[1,16] On the other hand, the ^1H and ^{13}C NMR data of the synthetic *anti*-diepoxide **6** were different from those of the natural product.[1,16] It was observed that the chemical shift differences between the natural product and synthetic **6** at the C9 and C10 positions were significant: +0.08 (H-9), +0.12 (H-10), −1.23 (C-9), and −0.88 (C-10). The measured specific rotation of the synthetic **5**, $[\alpha]^{28}_D$ −62.5 (*c* 0.07, CH_3OH), was consistent with that of the natural product.[17,18] Therefore, we concluded that the absolute configuration of (−)-gummiferol was that described in **5**.

Scheme 5. Synthesis of **6**



(14) The homocoupling byproduct was not observed at all.

(15) The diastereomeric purity of **19** was determined by the ^1H and ^{13}C NMR spectra, which were clearly different from those of **12**.

(16) See Supporting Information for details.

Table 1. Selected Chemical Shift Differences in ppm between Natural (−)-Gummiferol and the Synthetic Diepoxides **5** and **6** in the ^{1}H and ^{13}C NMR ($CDCl_3$)[a]

	^{1}H NMR ($\Delta\delta_{N-S}$)		^{13}C NMR ($\Delta\delta_{N-S}$)	
position	**5**	**6**	**5**	**6**
8	+0.02	+0.03	−0.01	−0.42
9	+0.01	+0.08	−0.03	−1.23
10	+0.02	+0.12	−0.02	−0.88
11	+0.01	+0.04	+0.04	−0.71
12	0	+0.01	+0.06	+0.32
13	+0.01	+0.01	+0.09	+0.03
14	−0.01	0	+0.05	+0.10

[a] NMR spectra of the natural product and the synthetic products were recorded at 500 MHz (125 MHz) and 400 MHz (100 MHz), respectively. Chemical shifts are reported in ppm with reference to tetramethylsilane. δ_N and δ_S are chemical shifts of the natural product and the synthetic product, respectively.

In conclusion, we have accomplished the stereocontrolled synthesis of two possible diastereomers of (−)-gummiferol, wherein the stepwise stereoselective epoxidation and Cadiot−Chodkiewicz reaction were utilized for the efficient introduction of the contiguous epoxide unit and the triacetylenic moiety, respectively. The ^{1}H and ^{13}C NMR data of the synthetic *syn*-diepoxide **5** matched with those of natural (−)-gummiferol. On the other hand, the ^{1}H and ^{13}C NMR data of the synthetic *anti*-diepoxide **6** were significantly different, wherein the chemical shift deviations were clearly distinguishable at the C9 and C10 positions. Finally, comparison of the specific rotation between the synthetic **5** and the natural product established the absolute stereochemistry of (−)-gummiferol as shown in **5**.

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Supporting Information Available. Experimental procedures, spectroscopic data, and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) The natural product: $[\alpha]^{25}_{D}$ −170 (*c* 0.2, CH_3OH). Our synthetic *ent*-**5**: $[\alpha]^{25}_{D}$ +76.0 (*c* 0.03, CH_3OH). Our synthetic **6**: $[\alpha]^{23}_{D}$ +32.0 (*c* 0.12, CH_3OH).

(18) The optical purity of the synthetic product **5** was confirmed at the stage of **8** as described in ref 5. Furthermore, the purity of **5** was verified by NMR spectroscopy.