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# Total Synthesis of Highly Oxygenated Bisabolane Sesquiterpene Isolated from *Ligularia lankongensis*: Relative and Absolute Configurations of the Natural Product

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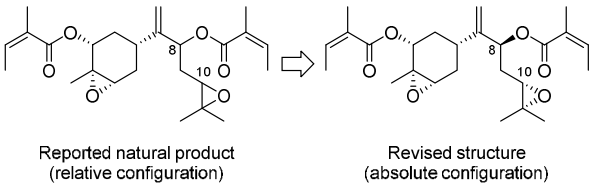
**Table of Contents**




**Abstract**

The relative and absolute configurations of an oxygenated bisabolane natural product, isolated from *L. lankongensis*, were determined by synthesis. All four possible stereoisomers and their tiglate analogues were synthesized from *R*-(–)-carvone, and their $^{1}$H and $^{13}$C NMR spectra were compared to establish the 6*R*,8*S*,10*S* configuration. The stereoselective synthesis of the natural product was also achieved, featuring Brown allylation, vanadium-catalyzed epoxidation, and the Mitsunobu reaction.

## Introduction

Bisabolanes are a major class of sesquiterpenoids,[1] and highly oxidized bisabolanes with a hydroxy or acyloxy group at C(8) and an epoxy group between C(10) and C(11) are found in many *Ligularia* species (Asteraceae).[2] Some of us and co-workers isolated oxidized bisabolane compounds from *L. lankongensis*[3,4] and *L. hodgsonii*[5] during a study into the diversity of *Ligularia* species.[6] However, the relative and absolute configurations at C(8) and C(10) of these compounds were not determined because the configuration of the flexible side-chain from the NMR data could not be established. Related oxygenated bisabolanes, such as hydroxy derivatives at C(10) and

C(11), have also been isolated from *Ligularia* species without determining the configurations at C(8) and C(10).[2] To understand the diversity and evolution of *Ligularia* species, it is essential to determine the configuration of natural bisabolanes, because diversity in chemical composition is often recorded in difference of oxygen functionalities.[6] Previously, our group synthesized all four possible side-chain stereoisomers of model compounds **1**–**4** as acetates **1a**–**4a**, isobutyrates **1b**–**4b**, and tiglates **1c**–**4c** (Figure 1), and their NMR spectra were compared.[7] It was suggested that the four isomers could be distinguished by measuring the NMR spectra in various solvents. The difference between compounds in δ and *J*-values of C(8)-H and C(10)-H can be explained in terms of steric congestion between the side chain and oxygen functionality at C(1). However, the NMR data of the four isomers were so similar that the application was limited to natural compounds with a substituent at the trans position of C(1) to C(6). To determine the relative and absolute configurations of natural products without ambiguity, a typical compound must be synthesized. Here, we report the synthesis of four possible stereoisomers of natural oxygenated bisabolane **5**, isolated from *L. lankongensis*,[4] and the determination of the relative and absolute configurations of the compound.

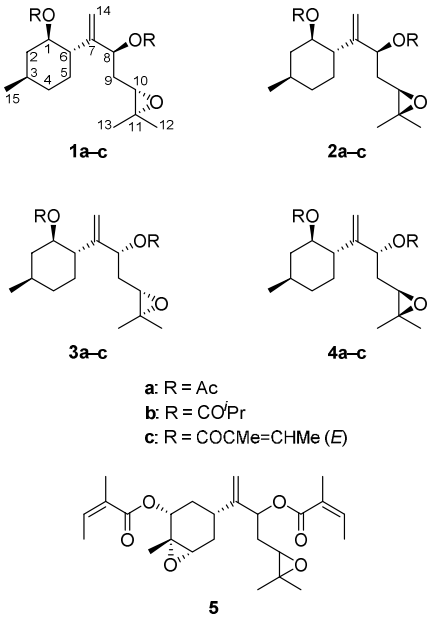
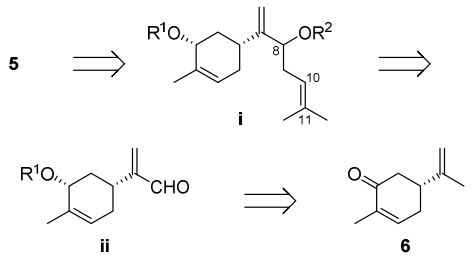



**Figure 1.** Model compounds of 8,10,11-oxygenated bisabolanes **1**–**4** and natural bisabolane **5**.

**Results and Discussion**

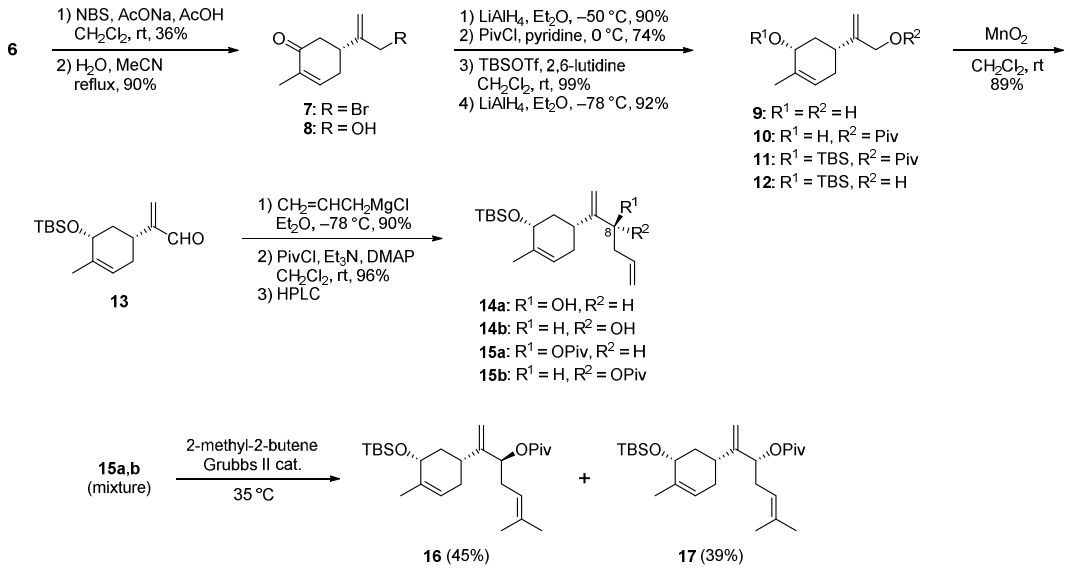
The synthetic strategy is shown in Scheme 1. Both α- and β-epoxides between C(10) and C(11) can be introduced from alkene **i** by a non-stereoselective method. The two isomers at C(8) can be obtained by allylation of **ii**, derived from *R*-(–)-carvone (**6**).

**Scheme 1.** Retrosynthetic analysis of **5**



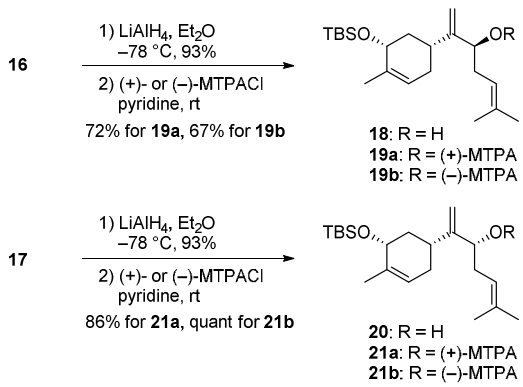

We commenced with the preparation of both isomers at C(8). Thus, compound **8**[8] was prepared from **6** *via* a two-step reaction involving bromination[9] (**7**, 36%) and hydrolysis (90%) (Scheme 2), although direct allylic oxidation with $SeO_2$, as in a previous model study,[7] and $B(OMe)_3$ oxidation[10] were unsuccessful. Compound **8** was stereoselectively reduced to a diol **9** (90%; the configuration was confirmed from the *J*-values) and the primary alcohol was protected with a pivaloyl group to afford **10** in 74% yield. Protection of the secondary alcohol with the *tert*-butyldimethylsilyl (TBS) group (**11**, 99%) followed by cleavage of the pivaloyl group afforded **12** (92%). Oxidation of **12** with $MnO_2$ afforded **13** (corresponding to **ii**, $R^1$ = TBS) in 89% yield. Aldehyde **13** was subjected to a Grignard reaction using allyl magnesium chloride to give a mixture of alcohols **14a** and **14b** in 90% yield.[11] Compounds **14a** and **14b** were inseparable; however, when the hydroxy group was converted to bulky pivaloyl esters **15a** and **15b** (96%), the two isomers could be separated by HPLC. Separation of the 8*R*- and 8*S*-isomers was also performed after a metathesis reaction without HPLC. Specifically, a mixture of **15a** and **15b** was subjected to a metathesis reaction with 2-methyl-2-butene in the presence of Grubbs II catalyst to afford a mixture of prenyl derivatives **16** and **17**, which was separated by repetitions of silica gel column chromatography using pentane/$CH_2Cl_2$ (4:1) solvent system to yield **16** (45%) and **17** (39%).

**Scheme 2.** Synthesis of pivalates **16** and **17**




Since each isomer was obtained in its pure form, the configuration at C(8) (carbon numbering based on the bisabolane skeleton) was determined by a modified Mosher's method. Thus, compound **16** was treated with $LiAlH_4$ to generate alcohol **18,** which was converted to (+)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) ester **19a** and (–)-MTPA ester **19b** (Scheme 3). Similarly, **21a** and **21b** were prepared from **17** via **20**. According to the differences in the chemical shifts between (+)- and (–)-MTPA esters shown in Figure 2, the configuration of C(8) was determined to be *S* for **18** and *R* for **20**.

**Scheme 3.** Synthesis of alcohols **18** and **20**, and MTPA esters **19** and **21**



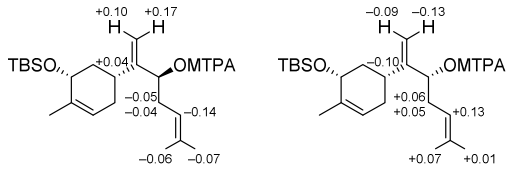
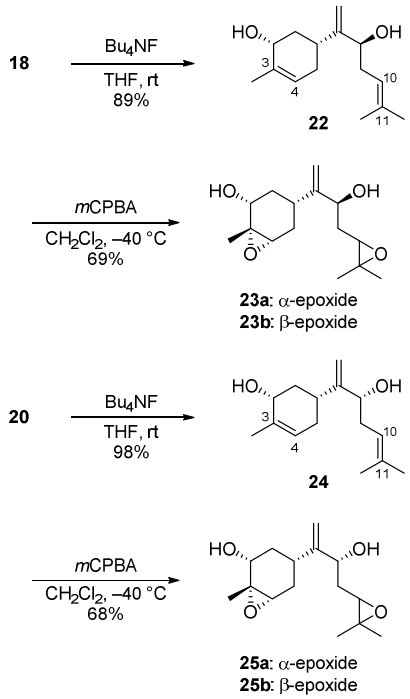



**Figure 2.** $\Delta\delta$ ($\delta_{(-)MTPA} - \delta_{(+)MTPA}$) Value of MTPA esters **19** (left) and **21** (right).

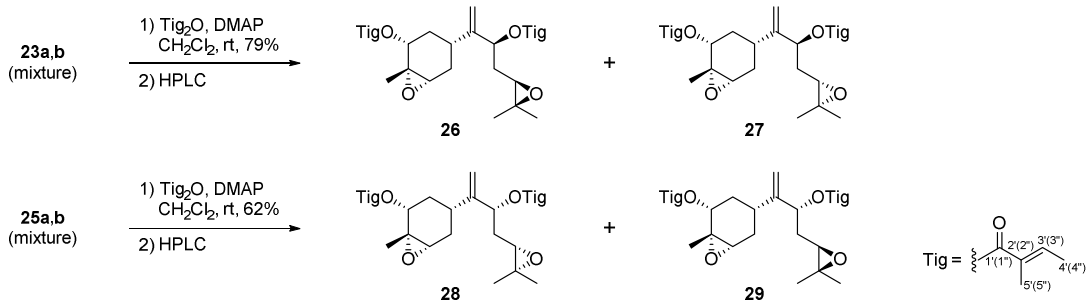
Compounds **18** and **20** were then deprotected to diols **22** (89%) and **24** (98%), respectively (Scheme 4). When **22** was treated with *m*-chloroperbenzoic acid (*m*CPBA), epoxidation occurred at both C(3)-C(4) and C(10)-C(11) bonds to afford a mixture of **23a** and **23b** (69% yield) at a ratio of 5:3 to 4:3.[12] The stereoselective epoxidation at C(3)-C(4) occurred due to the presence of a C(2)-OH group, and its orientation was deduced to be α from the $^1$H NMR signal of C(4)-H (δ 3.15, d, $J$ = 4.8 Hz), which was similar to that of natural product **5** (δ 3.13, d, $J$ = 5.0 Hz).[4] In contrast, epoxidation at C(10)-C(11) was non-selective, as expected, to afford a mixture of isomers. Epoxidation of **24** gave a parallel result affording **25a**,**b** in 68% yield as a mixture of isomers at a 3:1 to 4:3 ratio.[12] By this stage, all four possible stereoisomers of C(8) and C(10) were prepared.

**Scheme 4.** Synthesis of epoxides **23** and **25**



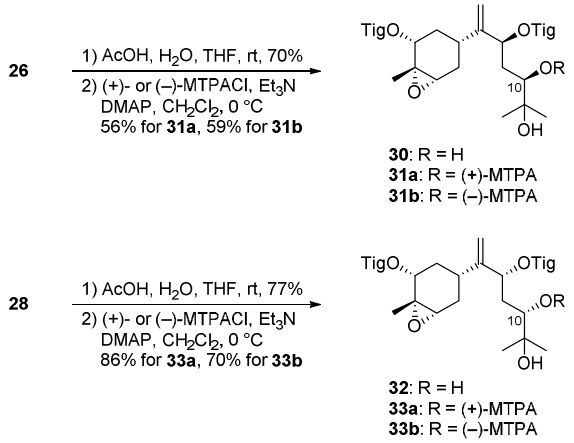
The last synthetic stage is esterification and separation of each isomer. When a mixture of epoxide isomers **23a**,**b** was treated with angelic anhydride ((*Z*)-2-methyl-2-butenoic anhydride) in the presence of 4-dimethylaminopyridine (DMAP), esterification at both C(2)-OH and C(8)-OH proceeded, but isomerization of the angelic acid part resulted in a mixture of angelate ((*Z*)-2-methyl-2-butenoate) and tiglate ((*E*)-2-methyl-2-butenoate). The $^1$H NMR spectrum of the product was too complex to analyze. Thereafter, before the synthesis of angelate, tiglate was prepared as a model study. Both angelates and tiglates are often found in nature in various sesquiterpenoids.[1] When **23a**,**b** was treated with tiglic anhydride, **26** and **27** were afforded (79% yield) and the two isomers were separated by HPLC (Scheme 5).[12] In the same way, **25a**,**b** afforded **28** and **29** (62% yield).[12]

**Scheme 5.** Preparation of tiglates **26**–**29**



The configurations of the epoxides were determined by a modified Mosher's method after cleavage of the epoxide ring, as previously reported.[7] Thus, **26** was treated with AcOH to give diol **30** (70%) and its secondary hydroxy group was converted to both (+)-MTPA ester **31a** and (–)-MTPA ester **31b** (Scheme 6). In this reaction, the epoxide at C(3)-C(4) did not react. Similarly, **28** was treated with AcOH (**32**, 77%) and either (+)- or (–)-MTPACl to yield **33a** and **33b**. The Δδ value between (+)- and (–)-MTPA esters **31** and **33** are shown in Figure 3. From these data, it was concluded that **30** and **32** had 10*R* and 10*S* configurations, respectively. Thus, **26**, **27**, **28**, and **29** were established as 8*S*,10*R*-, 8*S*,10*S*-, 8*R*,10*S*-, and 8*R*,10*R*-isomers, respectively.

**Scheme 6.** Synthesis of MTPA esters **31** and **33**



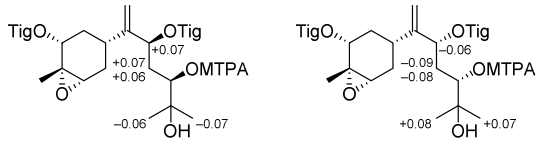




**Figure 3.** Δδ ($\delta_{(-)MTPA} - \delta_{(+)MTPA}$) Values of MTPA esters **31** (left) and **33** (right).

With all four possible stereoisomers in hand, we compared their NMR spectra. The previous model study indicated that it is essential to measure NMR spectra in different solvents.[7] Thus, data in both $CDCl_3$ and $CD_3OD$ were obtained and compared against those of natural angelate **5**[4] (Tables 1 and 2). C(8)-H of **26** and **27** was observed in a doublet of doublet, as in **5**, but the protons of **28** and **29** were in triplet in $CDCl_3$, while no distinct differences between the compounds were observed in $CD_3OD$. In the $CD_3OD$ data , both δ and *J*-values of C(10)-H of **27** and **29** were closer to **5** than those of **26** and **28**. Differences in the chemical shifts were also observed in C(1)-H and C(5)-H; that is, **26** and **27** were close to **5** but **28** and **29** differed. These data suggested that **27** is likely to have a natural-type configuration. Chemical shifts in all $^{13}C$ NMR signals of **27** in both $CD_3OD$ and $CD_3OD$ were within ±0.4 ppm, while some signals of **26**, **28**, and **29** differed (more than ±0.5 ppm).

**Table 1.** $^{1}$H- and $^{13}$C NMR data of compounds **26**–**29** and **5** ($CDCl_3$)[a]

| Carbon no.[b] | **26** | | **27** | | **28** | | **29** | | **5**[4] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $\delta_H$ | $\delta_C$ | $\delta_H$ | $\delta_C$ | $\delta_H$ | $\delta_C$ | $\delta_H$ | $\delta_C$ | $\delta_H$ | $\delta_C$ |
| 1 | 1.58, 1.76 | 30.6 | 1.58, 1.76 | 30.7 | 1.56, 1.81 | 30.9 | 1.57, 1.83 | 30.8 | 1.62, 1.77 | 30.8 |
| 2 | 5.22 (dd, 5.5, 10.7) | 73.7 | 5.21 (dd, 5.3, 10.8) | 73.8 | 5.23 (dd, 5.4, 10.7) | 73.6 | 5.24 (dd, 5.3, 10.8) | 73.6 | 5.25 (dd, 5.5, 10.5) | 73.6 |
| 3 | - | 58.3 | - | 58.2 | - | 58.3 | - | 58.3 | - | 58.1 |
| 4 | 3.10 (d, 5.0) | 60.7 | 3.11 (d, 5.1) | 60.8 | 3.10 (d, 4.8) | 60.7 | 3.09 (d, 4.8) | 60.7 | 3.13 (d, 5.0) | 60.9 |
| 5 | 1.72, 2.24 | 30.9 | 1.72, 2.27 | 30.9 | 1.78, 2.11 | 30.3 | 1.74, 2.09 | 30.4 | 1.77, 2.32 | 31.0 |
| 6 | 2.15 | 35.5 | 2.12 | 35.2 | 2.17 | 35.2 | 2.18 | 35.4 | 2.14 | 35.3 |
| 7 | - | 150.9 | - | 151.0 | - | 150.1 | - | 150.6 | - | 151.0 |
| 8 | 5.34 (dd, 5.7, 6.8) | 73.5 | 5.35 (dd, 4.8, 8.0) | 73.4 | 5.41 (t, 6.2) | 73.3 | 5.42 (t, 6.5) | 73.0 | 5.37 (dd, 4.5, 8.5) | 73.2 |
| 9 | 1.90 (2H)[c] | 33.8 | 1.88 (2H)[c] | 33.8 | 1.92 (2H) | 33.2 | 1.90 (2H) | 33.7 | 1.88, 1.92 | 33.9 |
| 10 | 2.74 (t, 5.8) | 60.8 | 2.78 (t, 5.8) | 61.0 | 2.74 (t, 5.8) | 60.7 | 2.78 (t, 6.0) | 61.1 | 2.80 (t, 6.0) | 61.0 |
| 11 | - | 57.8 | - | 58.4 | - | 57.8 | - | 58.4 | - | 58.4 |
| 12 | 1.26 | 18.9 | 1.27 | 18.9 | 1.27 | 18.9 | 1.25 | 18.9 | 1.28 | 18.9 |
| 13 | 1.29 | 24.6 | 1.28 | 24.7 | 1.29 | 24.6 | 1.27 | 24.6 | 1.29 | 24.7 |
| 14 | 4.95, 5.12 | 110.7 | 4.94, 5.11 | 110.6 | 5.00, 5.16 | 111.8 | 4.99, 5.14 | 111.8 | 4.98, 5.14 | 111.0[d] |
| 15 | 1.32 | 19.1 | 1.32 | 19.1 | 1.32 | 19.1 | 1.32 | 19.1 | 1.34 | 19.2 |
| 1′, 1″ | - | 167.0<br>167.6 | - | 166.9<br>167.6 | - | 167.0<br>167.6 | - | 167.0<br>167.6 | - | 166.7<br>167.6 |
| 2′, 2″ | - | 128.3<br>128.5 | - | 128.3<br>128.5 | - | 128.3<br>128.5 | - | 128.3<br>128.5 | - | 127.5<br>127.5 |
| 3′, 3″ | 6.91, 6.94 | 138.0<br>138.0 | 6.90, 6.95 | 137.9<br>138.0 | 6.91, 6.95 | 137.9<br>138.1 | 6.89, 6.95 | 137.9<br>138.0 | 6.11, 6.11 | 138.3<br>139.0 |
| 4′, 4″ | 1.79, 1.81 | 14.1<br>14.5 | 1.80, 1.82 | 14.4<br>14.5 | 1.80, 1.81 | 14.4<br>14.5 | 1.80, 1.82 | 14.4<br>14.5 | 2.01. 2.01 | 15.8<br>15.9 |
| 5′, 5″ | 1.84, 1.85 | 12.1<br>12.1 | 1.85, 1.86 | 12.1<br>12.1 | 1.85, 1.86 | 12.1<br>12.1 | 1.85, 1.86 | 12.1<br>12.1 | 1.93, 1.93 | 20.6<br>20.6 |

[a] The *J*-values are in Hz. Compounds **26-29** are ditiglates and **5** is a diangelate.

[b] Signals of two tiglates and angelates are not distinguished.

[c] The δ values of the two 9-Hs may be slightly different (within 0.02 ppm), but the exact value of each proton could not be determined.

[d] The δ value in Ref. 4 was an error.

**Table 2.** $^{1}$H- and $^{13}$C NMR data of compounds **26**–**29** and **5** ($CD_3OD$)[a]

| Carbon no.[b] | **26** | | **27** | | **28** | | **29** | | **5**[c] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $\delta_H$ | $\delta_C$ | $\delta_H$ | $\delta_C$ | $\delta_H$ | $\delta_C$ | $\delta_H$ | $\delta_C$ | $\delta_H$ | $\delta_C$ |
| 1 | 1.48, 1.71 | 32.2 | 1.48, 1.69 | 32.3 | 1.46, 1.81 | 32.4 | 1.45, 1.83 | 32.3 | 1.52, 1.73 | 32.3 |
| 2 | 5.22 (dd, 5.3, 10.7) | 75.3 | 5.21 (dd, 5.2, 10.7) | 75.4 | 5.23 (dd, 5.3, 10.7) | 75.4 | 5.23 (dd, 5.3, 10.7) | 75.3 | 5.26 (dd, 5.2, 10.7) | 75.1 |
| 3 | - | 59.7 | - | 59.7 | - | 59.7 | - | 59.7 | - | 59.6 |
| 4 | 3.16 (d, 4.6) | 62.2 | 3.16 (d, 4.8) | 62.2 | 3.14 (d, 5.0) | 62.2 | 3.14 (d, 5.0) | 62.2 | 3.17 (d, 4.7) | 62.3 |
| 5 | 1.65, 2.25 | 31.9 | 1.65, 2.26 | 31.9 | 1.71, 2.12 | 31.4 | 1.70, 2.10 | 31.4 | 1.66, 2.30 | 32.0 |
| 6 | 2.29 | 36.1 | 2.27 | 35.9 | 2.26 | 36.4 | 2.26 | 36.5 | 2.27 | 36.1 |
| 7 | - | 152.5 | - | 152.7 | - | 152.2 | - | 152.7 | - | 152.8 |
| 8 | 5.40 (dd, 5.6, 7.0) | 75.3 | 5.40 (dd, 4.5, 8.5) | 75.0 | 5.40 (dd, 5.3, 7.5) | 75.2 | 5.38 (dd, 4.4, 8.7) | 74.8 | 5.42 (dd, 4.5, 8.5) | 74.7 |
| 9 | 1.90, 1.99 | 34.4 | 1.92 (2H)[d] | 34.6 | 1.90, 2.01 | 34.3 | 1.93 (2H) | 34.8 | 1.94 (2H) | 34.6 |
| 10 | 2.78 (dd, 5.1, 7.8) | 62.5 | 2.82 (t, 6.0) | 62.7 | 2.78 (dd, 5.0, 6.6) | 62.6 | 2.83 (t, 6.2) | 62.7 | 2.84 (t, 6.0) | 62.7 |
| 11 | - | 59.5 | - | 60.2 | - | 59.4 | - | 60.2 | - | 60.2 |
| 12 | 1.27 | 19.1 | 1.26 | 19.1 | 1.27 | 19.1 | 1.25 | 19.1 | 1.28 | 19.1 |
| 13 | 1.27 | 24.8 | 1.25 | 24.9 | 1.26 | 24.8 | 1.24 | 24.9 | 1.26 | 24.9 |
| 14 | 4.99, 5.13 | 111.6 | 4.97, 5.12 | 111.5 | 5.02, 5.15 | 112.0 | 4.99, 5.14 | 111.9 | 5.00, 5.15 | 111.7 |
| 15 | 1.29 | 19.3 | 1.29 | 19.3 | 1.29 | 19.3 | 1.28 | 19.3 | 1.31 | 19.4 |
| 1′, 1″ | - | 168.4<br>168.9 | - | 168.3<br>168.9 | - | 168.5<br>169.0 | - | 168.4<br>169.0 | - | 168.1<br>168.9 |
| 2′, 2″ | - | 129.6<br>129.6 | - | 129.6<br>129.6 | - | 129.6<br>129.7 | - | 129.6<br>129.7 | - | 128.9<br>129.0 |
| 3′, 3″ | 6.92, 6.92 | 139.2<br>139.4 | 6.93, 6.93 | 139.2<br>139.4 | 6.92, 6.93 | 139.2<br>139.3 | 6.93, 6.93 | 139.2<br>139.3 | 6.15, 6.16 | 139.3<br>139.9 |
| 4′, 4″ | 1.80, 1.82 | 14.4<br>14.5 | 1.82, 1.82 | 14.4<br>14.5 | 1.82, 1.82 | 14.4<br>14.5 | 1.82, 1.82 | 14.4<br>14.5 | 1.97, 1.98 | 16.1<br>16.1 |
| 5′, 5″ | 1.84, 1.85 | 12.1<br>12.1 | 1.84, 1.85 | 12.1<br>12.2 | 1.84, 1.85 | 12.1<br>12.2 | 1.84, 1.85 | 12.1<br>12.2 | 1.90, 1.91 | 20.8<br>20.9 |

[a] The *J*-values are in Hz. The signal of methanol was used as a reference (3.30 ppm for $^{1}$H; 49.0 ppm for $^{13}$C). Compounds **26-29** are ditiglates and **5** is a diangelate.

[b] Signals of two tiglates and angelates are not distinguished.

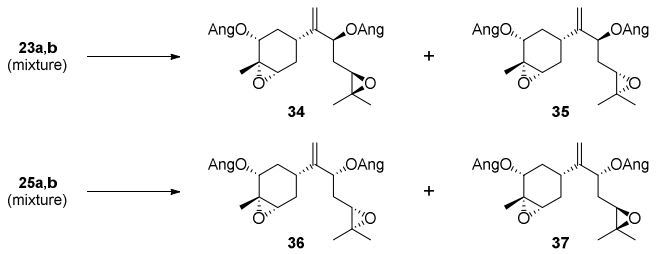
[c] The data are not shown in Ref. 4.

[d] The δ values of the two 9-Hs may differ slightly (within 0.05 ppm), but the exact value of each proton could not be determined.

Although **27** was likely to have a natural configuration, it was essential for the synthesis of a completely identical compound to confirm the structure. To achieve this, we first tried solvolysis of both the tiglate **27** (synthetic) and angelate **5** (natural). Compound **27** was treated with $K_2CO_3$/MeOH to afford the corresponding diol (**23a**); however, a complex mixture was obtained by the same treatment of **5**. We subsequently reattempted to synthesize angelate from diols **23a**,**b** and **25a**,**b**.

In our first attempt at preparing the angelate, DMAP was used as a base; however, the products were a mixture of angelates and tiglates. Thus, we examined the selective synthesis of the angelate with a non-nucleophilic base (Table 3). A reaction of **23a**,**b** (mixture) with angeloyl chloride was initially attempted for the synthesis of diangelates **34** and **35** (entries 1–6). Without a base,[13] two angeloyl groups were introduced with a concomitant epoxide ring-opening (by-product A, 43%; entry 1). Similar results were obtained with the use of $NaHCO_3$ (entry 2), $Na_2CO_3$ (entry 3), *t*-BuOK (entry 4), and NaH (entry 5). The reaction with 2,6-di-*tert*-butylpyridine (DTBP) as a base resulted in an epoxide ring-opening with no installation of the angeloyl group (by-product B, 43%; entry 6). Further investigation into angeloylation was carried out with angelic anhydride as an acylating agent (entries 7–9). Fortunately, the desired diangelates **34** (4.6%) and **35** (3.2%) were obtained, albeit in a low yield, by using $Cs_2CO_3$[14] as a base in $CH_3CN$ (entry 7).[12] Similarly, the reaction of **25a**,**b** gave an inseparable mixture of diangelates **36** and **37** (22% combined yield) (entry 8). The structure of each isomer was not determined; however, it is likely that **36** and **37** are α- and β-epoxides, respectively, as deduced by a comparison of the $^1$H NMR data with tiglates **28** and **29**. LHMDS,[15] surprisingly, afforded only diangelate **34** in 28% yield without the formation of **35** (entry 9).

**Table 3.** Attempts at angeloyl ester formation




| Entry | Substrate | Acylating agent | Base | Solvent | Result[a] |
|---|---|---|---|---|---|
| 1 | **23a**,**b** | AngCl | – | $CH_2Cl_2$ | by-product A (43%) |
| 2 | **23a**,**b** | AngCl | $NaHCO_3$ | $CH_2Cl_2$ | by-product A (31%) |
| 3 | **23a**,**b** | AngCl | $Na_2CO_3$ | $CH_2Cl_2$ | by-product A (31%) |
| 4 | **23a**,**b** | AngCl | *t*-BuOK | $CH_2Cl_2$ | by-product A (10%) |
| 5 | **23a**,**b** | AngCl | NaH | $CH_2Cl_2$ | by-product A (32%) |
| 6 | **23a**,**b** | AngCl | DTBP | $CH_2Cl_2$ | by-product B (43%) |
| 7 | **23a**,**b** | $Ang_2O$ | $Cs_2CO_3$ | $CH_3CN$ | **34** (4.6%), **35** (3.2%) |
| 8 | **25a**,**b** | $Ang_2O$ | $Cs_2CO_3$ | $CH_3CN$ | **36** + **37** (22%)[b] |
| 9 | **23a**,**b** | $Ang_2O$ | LHMDS | THF | **34** (28%) |

[a] Two by-products (A and B) seem to be chlorohydrins with and without angeloyloxy groups, respectively, judging from their mass (*m/z*: 469 $[M + H]^+$ and 305 $[M + H]^+$, for A and B, respectively) and $^1H$ NMR spectra.

[b] Ratio 5:1. The structure of each isomer was not determined.

The $^{1}$H NMR spectra of synthetic four compounds (**34**, **35**, and a mixture of **36** and **37**) were compared with the natural product **5** (Table 4). The data for **35** was identical to that of **5**, while the data for **34**, **36**, and **37** were clearly different. The $^{13}$C NMR spectrum of **35** was also identical to that of **5**. The optical rotation of **35** ($[\alpha]^{20}_{D}$ –27.3 (*c* 0.073, $CHCl_3$)) has the same sign as natural product **5** ($[\alpha]^{27}_{D}$ –108.4 (*c* 0.042, $CHCl_3$)).[4,16] From these data, as well as the data of tiglates **26**–**29**, it was suggested that **35** have 8*S*,10*S* configuration. However, we could not determine the configuration at C(10) of angelate **35** by the same method used with tiglates **26** and **28**, because the MTPA ester did not form.

**Table 4.** $^{1}$H- and $^{13}$C NMR data of compounds **34**–**37** ($CDCl_3$)[a]

| Carbon no.[b] | **34** | | **35** | | **36** and **37** | |
|---|---|---|---|---|---|---|
| | $\delta_H$ | $\delta_C$ | $\delta_H$ | $\delta_C$ | $\delta_H$ | $\delta_C$[c] |
| 1 | 1.63, 1.80 | 30.7 | 1.62, 1.77 | 30.8 | 1.60, 1.84[c,d] | 30.9 |
| 2 | 5.26 (dd, 5.5, 10.5) | 73.5 | 5.25 (dd, 5.5, 10.5) | 73.6 | 5.27 (dd, 5.5, 10.5) | 73.4 |
| 3 | - | 58.1 | - | 58.1 | - | 57.8 |
| 4 | 3.12 (d, 5.5) | 60.8 | 3.12 (d, 5.0) | 60.9 | 3.11 (d, 5.5)[c] and 3.10 (d, 5.0)[e] | 60.7 |
| 5 | 1.75 (dd, 11.5, 15.0), 2.27 | 31.0 | 1.75, 2.32 | 31.0 | 1.79, 2.13[c,d] | 31.1 |
| 6 | 2.17 | 35.6 | 2.13 | 35.3 | 2.19[c,d] | 35.4 |
| 7 | - | 150.8 | - | 151.0 | - | 150.0 |
| 8 | 5.39 (dd, 4.5, 8.0) | 73.2 | 5.38 (dd, 4.5, 8.0) | 73.2 | 5.45 (br t, 6.5)[c] and 5.43 (dd, 4.6, 8.3)[e] | 73.1 |
| 9 | 1.91, 1.94 | 33.9 | 1.88, 1.92 | 33.9 | 1.95 (2H)[c,f] and 1.91 (2H)[e,f] | 33.2 |
| 10 | 2.76 (t, 6.0) | 60.8 | 2.80 (t, 6.0) | 61.0 | 2.75 (t, 6.0)[c] and 2.80 (t, 6.0)[e] | 60.8 |
| 11 | - | 57.8 | - | 58.4 | - | 58.2 |
| 12 | 1.28 | 18.9 | 1.28 | 18.9 | 1.29[c,d] | 18.9 |
| 13 | 1.30 | 24.6 | 1.29 | 24.7 | 1.30[c,d] | 24.6 |
| 14 | 5.00, 5.16 | 111.1 | 4.98, 5.14 | 111.0 | 5.04[c] and 5.02,[e] 5.19 (d, 1.2)[c] and 5.17 (d, 1.5)[e] | 112.1 |
| 15 | 1.34 | 19.2 | 1.35 | 19.2 | 1.34[c,d] | 19.2 |
| 1′, 1″ | - | 166.9 167.6 | - | 166.7 167.6 | - | 166.8 167.6 |
| 2′, 2″ | - | 127.6 127.8 | - | 127.6 127.8 | - | 127.6 127.7 |
| 3′, 3″ | 6.09, 6.12 | 138.2 138.8 | 6.11, 6.11 | 138.3 138.9 | 6.11, 6.11 | 138.5 138.8 |
| 4′, 4″ | 2.01, 2.01 | 15.8, 15.9 | 2.01, 2.01 | 15.8 15.9 | 2.00, 2.02 | 15.8 15.9 |
| 5′, 5″ | 1.93, 1.93 | 20.6 20.6 | 1.92, 1.93 | 20.6 20.6 | 1.92, 1.93 | 20.6 20.7 |

[a] The *J*-values are in Hz.

[b] Signals of two angelates are not distinguished.

[c] Assigned for the major isomer.

[d] The δ value of the minor isomer could not be determined because of overlapping.

[e] Assigned for the minor isomer.

[f] The δ values of the two 9-Hs may be slightly different (within 0.05 ppm), but the exact value of each proton could not be determined.

To reveal the exact stereostructure of **35**, we attempted to synthesize compound **35** stereoselectively. Thus, the enal **13** was initially allylated under Brown's conditions using (+)-$Ipc_2B$-allyl[17] to produce alcohol **14b** in 89% yield as a single diastereomer, in which the configuration at C(8) opposed that of the natural product so as to utilize the C(8)-OH directed diastereoselective epoxidation at the C(10)-C(11) olefin at a later step (Scheme 7).[18,19] A subsequent olefin metathesis reaction with 2-methyl-2-butene in the presence of Grubbs II catalyst produced **20** in 48% yield. The crucial regio- and stereoselective epoxidation of **20** was examined next (Table 5). We first tried Yamamoto's method using $VO(O^iPr)_3$ and *tert*-butyl hydroperoxide (TBHP; entries 1–4).[18] An excess of TBHP (decane solution) gave the undesired bis-epoxide **39** in 67% yield, even though the C(3)-C(4) olefin was not affected (entry 1). Reduction of TBHP to 1.5 equiv resulted in a scramble of the products, including unreacted **20** (6%), desired mono-epoxide **38** (8%), bis-epoxide **39** (56%), and undesired C(7)-C(14) epoxide **40** (19%; entry 2). Further reduction of TBHP (1.0 equiv) enhanced the product ratio of **38**, but the yield was still fairly low (19%; entry 3). Switching the solvent of TBHP solution to water slightly improved the yield of **38** (24%; entry 4). Catalytic $Mo(CO)_6$ in combination with TBHP[19] was next evaluated (entries 5 and 6) to reveal that the 1.0 equiv of TBHP (decane solution) gave the highest yield of desired **38** (29%), but the stereoselectivity was moderate (10*S*:10*R* = 5:1; entry 5). The reaction using $Al(O^tBu)_3$ and TBHP recovered the starting material **20** (entry 7).

**Scheme 7.** Stereoselective synthesis of **20**

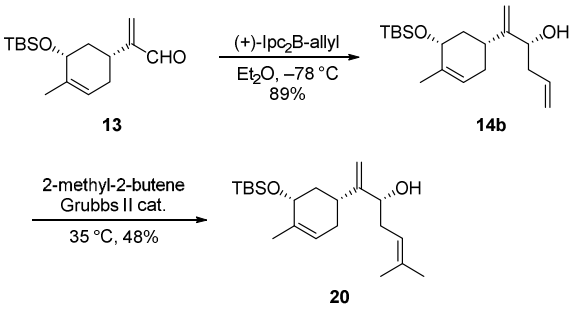
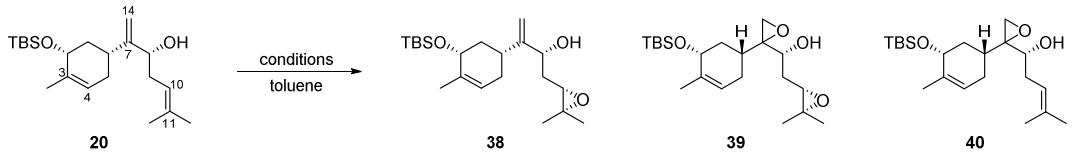


**Table 5.** Diastereoselective epoxidation of **20**




**20** **38** **39** **40**

| Entry | Catalyst | TBHP (eq) | Temp. | Result |
|---|---|---|---|---|
| 1 | $VO(O^iPr)_3$ | 10[a] | 0°C | **39** (67%) |
| 2 | $VO(O^iPr)_3$ | 1.5[a] | 0°C | **20** (6%), **38** (8%), **39** (56%),[c] **40** (19%)[c] |
| 3 | $VO(O^iPr)_3$ | 1.0[a] | 0°C | **20** (14%), **38** (19%), **39** (10%),[c] **40** (16%)[c] |
| 4 | $VO(O^iPr)_3$ | 1.0[b] | 0°C | **20** (19%), **38** (24%), **39** (13%),[c] **40** (31%)[c] |
| 5 | $Mo(CO)_6$ | 1.0[a] | 35°C | **20** (9%), **38** (29%),[d] **39** (18%),[c] **40** (13%)[c] |
| 6 | $Mo(CO)_6$ | 1.0[b] | rt | **20** (29%), **38** (24%),[d] **40** (8%)[c] |
| 7 | $Al(O^tBu)_3$ | 4.0[b] | rt | NR |

[a] 5.5 M solution in decane.

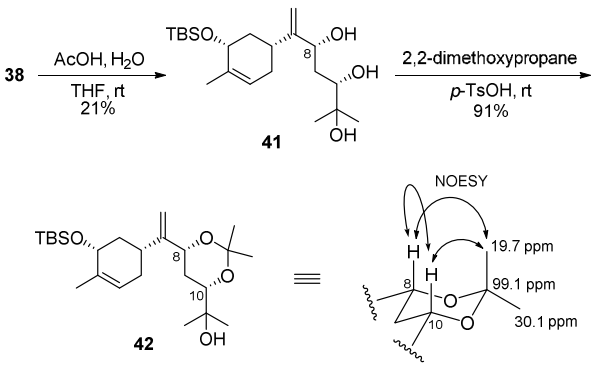
[b] 70% solution in water.

[c] The stereochemistry at C(7) was not determined.

[d] 10*S*:10*R* = 5:1.

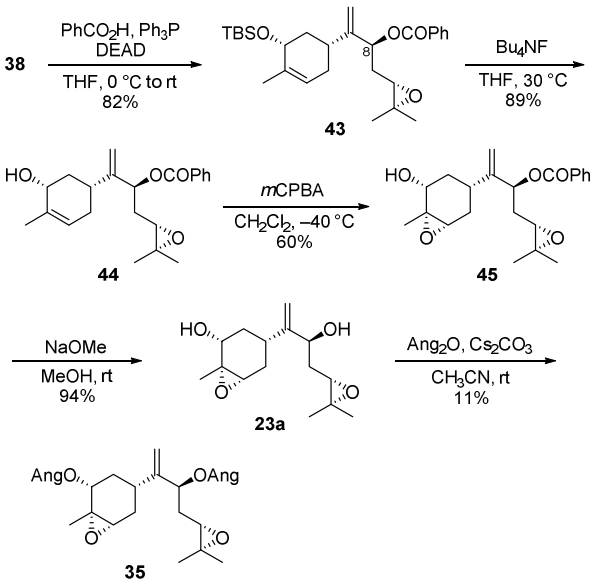
The configuration at C(10) in **38** was determined as follows (Scheme 8): Epoxide **38** was hydrolyzed under acidic conditions in AcOH/$H_2O$/THF to give triol **41**, which was converted into acetonide **42**. The $^{13}C$ NMR spectrum of **42** showed two different methyl signals at δ 19.7 and 30.1 ppm and a quaternary carbon signal at δ 99.1 ppm.[20] NOESY correlations among methine protons at C(8)-H and C(10)-H and axial methyl protons of the acetonide were also observed. Furthermore, the *J*-values of C(8)-H (dd, *J* = 2.6, 10.9 Hz) and C(10)-H (dd, *J* = 2.6, 11.7 Hz) clearly revealed 1,3-diaxial relationships between these methine protons. These results clearly indicated that compound **42** is a *syn*-1,3-diol acetonide. Thus, the absolute configuration at C(10) of **38** was finally deduced to be *S*.

**Scheme 8.** Stereochemical assignment of acetonide **42**




Since the anticipated α-epoxide at C(10)-C(11) was formed by stereoselection through C(8)-OH-directed epoxidation, the final task was stereoinversion at C(8) and subsequent conversion of the functional groups (Scheme 9). To achieve this, the secondary alcohol **38** was transformed into benzoate **43** (82%) with stereoinversion at C(8) by the Mitsunobu reaction. Cleavage of TBS group in **43** with $Bu_4NF$ (**44**, 89%) was followed by complete diastereoselective epoxidation using *m*CPBA to provide bis-epoxide **45** in 60% yield. Base-catalyzed solvolysis of **45** gave diol **23a** in 94% yield, which was finally acylated with $Ang_2O$ and $Cs_2CO_3$ in $CH_3CN$ (see Table 3, entry 7) to provide **35** in 11% yield. The spectral data of **35** fully matched that of natural product **5**.

**Scheme 9.** Completion of stereoselective total synthesis of **35**




We previously demonstrated that bisabolane sesquiterpene **46**, isolated from *L. lankongensis* collected at Yongsheng, Yunnan Province, China, has either a 6*S*,8*S*,10*R* or 6*R*,8*R*,10*S* configuration.[4] The present results clarified that another component (**5**) from the same plant sample had a 6*R*,8*S*,10*S* configuration (Figure 4). By supposing that the carbon skeleton of all bisabolane compounds in the same plant are generated via the same biosynthetic pathway, **46** could have a 6*S*,8*S*,10*R* configuration. Thus, the stereochemical difference between **5** and

**46** is recorded in the configuration of epoxide at C(10)-C(11). The two compounds, **5** and **46**, showed different *J*-values for C(10)-H (t, *J* = 6.0 Hz for **5**; dd, *J* = 9.0, 5.0 Hz for **46**),[4] which supports the different stereochemistry of epoxide at C(10)-C(11).

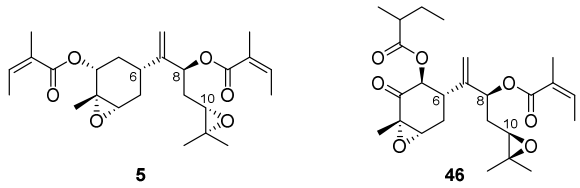



**Figure 4.** Absolute configuration of natural bisabolanes isolated from *Ligularia lankongensis*.

**Conclusion**

In conclusion, the relative and absolute configurations of bisabolane natural product **5** were disclosed through total synthesis. All four possible stereoisomers of tiglate derivatives **26–29** were first synthesized from *R*-(–)-carvone via two non-stereoselective steps, the introduction of an ally group by a Grignard reaction, and *m*CPBA epoxidation. By comparing the NMR spectra, it was suggested that the natural product had 8*S*,10*S* configuration. Total synthesis of **5** was then performed via a stereoselective pathway, featuring Brown allylation, vanadium catalyzed epoxidation, and Mitsunobu reaction to establish both the relative and absolute configurations of the natural product. The present synthetic methods would be useful for the preparation of other highly oxygenated bisabolane natural products.

**Experimental Section**

**General Experimental Methods.** $^{1}$H NMR spectra were measured on a JEOL JNM-AL300 (300 MHz), JEOL JNM-AL500 (500 MHz), or JEOL ECX-400 (400 MHz) spectrometer in $CDCl_3$ as the solvent. The chemical shifts are expressed in ppm downfield from either tetramethylsilane ($\delta$ = 0.00), added as an internal standard, or $CHCl_3$ ($\delta$ = 7.26). Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. $^{13}$C NMR spectra were measured at 125 MHz or 100 MHz. The chemical shifts are reported in ppm, relative to tetramethylsilane ($\delta$ = 0.0) or the central line of a triplet at 77.0 ppm for $CDCl_3$. Infrared spectra (IR) were measured on a JASCO VALOR-III or a JASCO FT/IR-230 spectrometer and are reported as wavenumbers ($cm^{-1}$). Both low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained using a JEOL T100GCV (hybrid of quadrupole and TOF, FI mode), Agilent/Varian QFT-7 (hybrid of quadrupole and ICR/FT, ESI mode), or a JEOL JMS 700 (DFMS, EI or FAB mode) instrument with a direct inlet system. Optical rotations were measured on a JASCO P-2200 or a JASCO DIP-370 polarimeter using a 100 mm pathlength cell. Column chromatography was carried out on silica gel (40−100 mesh). Analytical TLC was performed using 0.25 mm silica gel 60-F plates. HPLC was conducted by either a Shimadzu LC-20AT pump with a SPD-20A Prominence UV/VIS detector or a GL Sciences GL-7410 pump with a GL-7450 UV detector, and a Hitachi D-2500 Chromato-Integrator with a Kanto Mightysil Si60 (10 × 250 mm) column. Melting points were measured on a Yanaco Micro Melting Point apparatus and are uncorrected.

**2-((1*R*,5*R*)-5-Hydroxy-4-methylcyclohex-3-en-1-yl)prop-2-en-1-ol (9)**

A stirred suspension of $LiAlH_4$ (746 mg, 19.7 mmol) in dry $Et_2O$ (90 mL) equipped with $CaCl_2$ drying tube was cooled to –50 °C, and a solution of **8** (1626.1 mg, 9.67 mmol) in $Et_2O$ (10 mL) was added dropwise while stirring. After stirring for an additional 30 min, $Et_2O$/$H_2O$ was added, and the aqueous layer was neutralized by the addition of aqueous HCl. The mixture was extracted with $Et_2O$, dried with $Na_2SO_4$, and the solvent was evaporated off. The resultant crude product was purified by silica gel (50 g) column chromatography (hexane-EtOAc 1:1) to afford **9** (1457.3 mg, 90%) as a white solid. m.p. 77.6-78.9 °C; $[\alpha]_D^{26}$ –45.1 (*c* 0.246, MeOH); IR (neat/NaCl) 3312 (OH), 1647 (C=C), 1451, 1033 $cm^{-1}$; $^{1}$H NMR $\delta$ 1.50-2.25 (m, 6H), 2.39 (br t, *J* = *ca.* 11.5 Hz, 1H), 1.77 (s, 3H), 4.15 (s, 2H), 4.16-4.24 (m, $W_{1/2}$ = *ca.* 20 Hz, 1H), 4.95 (s, 1H), 5.09 (s, 1H), 5.51 (br s, 1H); $^{13}$C NMR $\delta$ 19.0, 31.5, 36.2, 38.1, 65.0, 70.8, 108.9, 123.7, 136.2, 152.4; MS (FI) *m*/*z*: 151 [$MH^+$ - $H_2O$, 30%], 133 (100); HRMS (FI-hybrid of quadrupole and TOF) *m*/*z*: $[M]^+$ Calcd for $C_{10}H_{16}O_2$ 168.1150; Found 168.1142.

**2-((1*R*,5*R*)-5-Hydroxy-4-methylcyclohex-3-en-1-yl)prop-2-en-1-yl pivalate (10)**

Pivaloyl chloride (1.75 mL, 14.2 mmol) was added to a stirred solution of **9** (1567.2 mg, 9.32 mmol) in dry pyridine (150 mL) at 0 °C under Ar. After being stirred at room temperature for 2 days, a saturated $NH_4Cl$ aq was added, and the mixture was extracted with $Et_2O$ and dried. Evaporation of the solvent followed by silica gel (75 g) column chromatography (hexane-EtOAc 9:1) afforded **10** (1744.1 mg, 74%) as a colorless oil. $[\alpha]_D^{27}$ –35.8 (*c* 0.302, MeOH); IR (neat/NaCl) 3406 (OH), 1730 (C=O), 1649 (C=C), 1284, 1153, 1036 $cm^{-1}$; $^{1}$H NMR $\delta$ 1.22 (s, 9H), 1.48-2.26 (m, 5H), 2.35 (br t, *J* = *ca.* 11.5 Hz, 1H), 1.77 (s, 3H), 4.17-4.24 (m, 1H), 4.57 (s, 2H), 5.00 (s, 1H), 5.08 (s, 1H), 5.51 (br s, 1H); $^{13}$C NMR $\delta$ 18.9, 27.2 (3C), 31.4, 36.6, 38.0, 38.8, 65.8, 70.8, 111.2, 123.6, 136.3,

147.4, 178.2; MS (FI) *m*/*z*: 235 [$MH^+$ - $H_2O$, 100%], 133 (58); HRMS (FI-hybrid of quadrupole and TOF) *m*/*z*: $[M]^+$ Calcd for $C_{15}H_{24}O_3$ 252.1725; Found 252.1698.

**2-((1*R*,5*R*)-5-*t*-Butyldimethylsilyloxy-4-methylcyclohex-3-en-1-yl)prop-2-en-1-yl pivalate (11)**

TBSOTf (0.58 mL, 2.54 mmol) was added to a stirred solution of **10** (529.1 mg, 2.10 mmol) in dry $CH_2Cl_2$ (100 mL) and 2,6-lutidine (0.37 mL, 3.18 mmol) under Ar, and the mixture was stirred at room temperature for 1 day. After saturated $NH_4Cl$ aq was added, the mixture was extracted with $CH_2Cl_2$ and dried. Evaporation of the solvent followed by silica gel column chromatography (hexane-EtOAc 95:5) afforded **11** (763.5 mg, 99%) as a colorless oil. $[\alpha]_D^{27}$ –33.3 (*c* 0.300, MeOH); IR (neat/NaCl) 3425 (OH), 1732 (C=O), 1649 (C=C), 1149 $cm^{-1}$; $^1H$ NMR δ 0.09 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 1.22 (s, 9H), 1.50-1.60 (m, 1H), 1.69 (br s, 3H), 1.91-2.14 (m, 3H), 2.31 (br t, *J* = *ca.* 11.5 Hz, 1H), 4.19-4.27 (m, 1H), 4.56 (s, 2H), 4.98 (s, 1H), 5.06 (s, 1H), 5.45 (br s, 1H); $^{13}C$ NMR δ –4.9, –4.2, 18.1, 19.7, 25.9 (3C), 27.2 (3C), 31.5, 37.1, 38.5, 38.8, 65.8, 71.4, 111.1, 122.9, 137.2, 147.6, 178.2; MS (EI) *m*/*z*: 366 $[M]^+$; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{21}H_{38}O_3Si$ 366.2590; Found 366.2591.

**2-((1*R*,5*R*)-5-*t*-Butyldimethylsilyloxy-4-methylcyclohex-3-en-1-yl)prop-2-en-1-ol (12)**

A solution of **11** (727.5 mg, 1.98 mmol) in dry $Et_2O$ (3 mL) was added to a stirred suspension of $LiAlH_4$ (121.4 mg, 3.20 mmol) in $Et_2O$ (17 mL) as described for **9** to afford **12** (525.1 mg, 92%) as a colorless oil. $[\alpha]_D^{28}$ –48.3 (*c* 0.286, MeOH); IR (neat/NaCl) 3334 (OH), 1649 (C=C), 1460, 1254, 1095, 837 $cm^{-1}$; $^1H$ NMR δ 0.09 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 1.51-1.61 (m, 2H), 1.69 (br s, 3H), 1.90-2.14 (m, 3H), 2.34 (br t, *J* = 11.5 Hz, 1H), 4.14 (s, 2H), 4.21-4.28 (m, 1H), 4.93 (s, 1H), 5.07 (s, 1H), 5.43-5.47 (m, 1H); $^{13}C$ NMR δ –4.8, –4.2, 18.1, 19.7, 25.9 (3C), 31.7, 36.7, 38.6, 64.9, 71.5, 108.5, 123.0, 137.2, 152.6; MS (FI) *m*/*z*: 283 [$MH^+$, 3%], 265 (2), 151 (31), 133 (100); HRMS (FI-hybrid of quadrupole and TOF) *m*/*z*: $[M]^+$ Calcd for $C_{16}H_{30}O_2Si$ 282.2015; Found 282.1982.

**2-((1*R*,5*R*)-5-*t*-Butyldimethylsilyloxy-4-methylcyclohex-3-en-1-yl)prop-2-enal (13)**

$MnO_2$ (13.5 g, 159 mmol) was added in one portion to a stirred solution of **12** (1436.9 mg, 5.09 mmol) in dry $CH_2Cl_2$. A $CaCl_2$ drying tube was attached, and the mixture was stirred at room temperature for 15 h. The solid material was filtered off, and the resulting solution was evaporated followed by silica gel (30 g) column chromatography (hexane-EtOAc 98:2) to afford **13** (1263.6 mg, 89%) as a colorless oil. $[\alpha]_D^{29}$ –26.4 (*c* 0.227, MeOH); IR (neat/NaCl) 1695 (C=O), 1254, 1093, 835 $cm^{-1}$; $^1H$ NMR δ 0.07 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.51-2.16 (m, 4H), 1.70 (br s, 3H), 2.83 (br t, *J* = 11.5 Hz, 1H), 4.25-4.32 (m, 1H), 5.43-5.47 (m, 1H), 6.01 (s, 1H), 6.27 (s, 1H), 9.53 (s, 1H); $^{13}C$ NMR δ –4.9, –4.2, 18.1, 19.7, 25.9 (3C), 31.2, 31.4, 38.2, 71.1, 122.7, 133.2, 137.2, 153.8, 194.4; MS (EI) *m*/*z*: 280 $[M]^+$; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{16}H_{28}O_2Si$ 280.1859; Found 280.1858.

**(3*S*)-2-((1*R*,5*R*)-5-*t*-Butyldimethylsilyloxy-4-methylcyclohex-3-en-1-yl)hexa-1,5-dien-3-ol (14a) and (3*R*)-2-((1*R*,5*R*)-5-*t*-butyldimethylsilyloxy-4-methylcyclohex-3-en-1-yl)hexa-1,5-dien-3-ol (14b)**

A solution of **13** (414.0 mg, 1.48 mmol) in dry $Et_2O$ (15 mL) was prepared at –78 °C under $N_2$. A solution of ally magnesium chloride in THF (2 M, 1.5 mL, 3.0 mmol) was added, and the mixture was stirred for 1 h. A saturated

$NH_4Cl$ aq was added, and the mixture was extracted with $Et_2O$. The organic layer was washed with saturated NaCl aq and dried. Evaporation of the solvent followed by silica gel column chromatography (hexane-EtOAc 95:5) afforded a mixture of **14a** and **14b** (435.7 mg, 90%) as a colorless oil. The mixture was used in the next step; however, the following data were collected after separation as a pivalate (see text).

**14a**: $[\alpha]_D^{28}$ –42.3 (*c* 0.149, MeOH); IR (neat/NaCl) 3410 (OH), 1641 (C=C), 1254, 1041 $cm^{-1}$; $^1H$ NMR δ 0.09 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 1.56-2.45 (m, 8H), 1.69 (br s, 3H), 4.13-4.18 (m, 1H), 4.21-4.28 (m, 1H), 4.96 (s, 1H), 5.13 (s, 1H), 5.12-5.19 (m, 2H), 5.43-5.47 (m, 1H), 5.75-5.86 (m, 1H); $^{13}C$ NMR δ –4.9, –4.2, 18.1, 19.7, 25.9 (3C), 33.2, 35.8, 39.5, 40.9, 71.6, 73.1, 108.7, 118.3, 123.2, 134.6, 137.2, 155.4; MS (FI) *m*/*z*: 305 [$MH^+$ - $H_2O$, 25%], 191 (40), 173 (100), 133 (55); HRMS (FI-hybrid of quadrupole and TOF) *m*/*z*: $[M]^+$ Calcd for $C_{19}H_{34}O_2Si$ 322.2328; Found 322.2317.

**14b**: $[\alpha]_D^{28}$ –26.6 (*c* 0.203, MeOH); IR (neat/NaCl) 3404 (OH), 1643 (C=C), 1254, 1092, 837 $cm^{-1}$; $^1H$ NMR δ 0.08 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 1.51-2.46 (m, 8H), 1.69 (br s, 3H), 4.12-4.17 (m, 1H), 4.20-4.27 (m, 1H), 4.98 (s, 1H), 5.13 (s, 1H), 5.12-5.19 (m, 2H), 5.44-5.48 (m, 1H), 5.75-5.87 (m, 1H); $^{13}C$ NMR δ –4.9, –4.2, 18.1, 19.7, 25.9 (3C), 32.7, 36.1, 40.0, 40.8, 71.6, 73.2, 109.1, 118.3, 123.4, 134.6, 137.0, 155.2; MS (FI) *m*/*z*: 305 [$MH^+$ - $H_2O$, 31%], 191 (33), 173 (100), 133 (31); HRMS (FI-hybrid of quadrupole and TOF) *m*/*z*: $[M]^+$ Calcd for $C_{19}H_{34}O_2Si$ 322.2328; Found 322.2317.

**(3*S*)-2-((1*R*,5*R*)-5-*t*-Butyldimethylsilyloxy-4-methylcyclohex-3-en-1-yl)hexa-1,5-dien-3-yl pivalate (15a) and (3*R*)-2-((1*R*,5*R*)-5-*t*-butyldimethylsilyloxy-4-methylcyclohex-3-en-1-yl)hexa-1,5-dien-3-yl pivalate (15b)**

$Et_3N$ (0.94 mL, 6.78 mmol) and DMAP (401.6 mg, 3.29 mmol) were added to a stirred solution of **14a**,**b** (1089.0 mg, 3.38 mmol) in $CH_2Cl_2$ (115 mL). PivCl (0.63 mL, 5.12 mmol) was added to the solution, and the mixture was stirred at room temperature for 1 day. An aqueous solution of $NH_4Cl$ was added, extracted with $CH_2Cl_2$, and dried. After evaporation of the solvent, the residue was chromatographed on silica gel (hexane-EtOAc 98:2) to afford **15a**,**b** (1316.2 mg, 96%) as a colorless oil. The mixture was used in the next step; however, the following data were collected after separation.

**15a**: $[\alpha]_D^{29}$ –46.1 (*c* 0.256, MeOH); IR (neat/NaCl) 1732 (C=O), 1645 (C=C), 1155, 837 $cm^{-1}$; $^1H$ NMR δ 0.08 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.20 (s, 9H), 1.52-1.63 (m, 1H), 1.69 (br s, 3H), 1.86-2.04 (m, 2H), 2.15-2.30 (m, 2H), 2.38-2.44 (m, 2H), 4.20-4.27 (m, 1H), 4.96 (s, 1H), 5.03-5.10 (m, 2H), 5.08 (s, 1H), 5.22 (t, *J* = 6.3 Hz, 1H), 5.45 (br d, *J* = 3.8 Hz, 1H), 5.66-5.77 (m, 1H); $^{13}C$ NMR δ –4.8, –4.2, 18.1, 19.7, 25.9 (3C), 27.2 (3C), 33.1, 35.9, 38.5, 38.8, 39.3, 71.6, 74.7, 110.1, 117.6, 123.3, 133.7, 137.1, 151.8, 177.4; MS (FI) *m*/*z*: 407 [$MH^+$, 3%], 305 (14), 275 (26), 173 (100); HRMS (FI-hybrid of quadrupole and TOF) *m*/*z*: $[M]^+$ Calcd for $C_{24}H_{42}O_3Si$ 406.2903; Found 406.2870.

**15b**: $[\alpha]_D^{28}$ –8.9 (*c* 0.246, MeOH); IR (neat/NaCl) 1732 (C=O), 1645 (C=C), 1155, 837 $cm^{-1}$; $^1H$ NMR δ 0.09 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 1.19 (s, 9H), 1.49-1.59 (m, 1H), 1.69 (br s, 3H), 1.91-2.10 (m, 3H), 2.23-2.45 (m, 3H), 4.20-4.26 (m, 1H), 4.98 (s, 1H), 5.03-5.11 (m, 2H), 5.10 (s, 1H), 5.25 (dd, *J* = 5.5, 7.1 Hz, 1H), 5.42-5.47 (m, 1H), 5.66-5.78 (m, 1H); $^{13}C$ NMR δ –4.9, –4.1, 18.1, 19.7, 25.9 (3C), 27.2 (3C), 32.6, 36.2, 38.4, 38.8, 39.6, 71.5, 74.7, 110.9, 117.6, 123.2, 133.7, 137.1, 151.5, 177.4; MS (FI) *m*/*z*: 407 [$MH^+$, 3%], 305 (17), 275 (25), 173 (100); HRMS (FI-hybrid of quadrupole and TOF) *m*/*z*: $[M]^+$ Calcd for $C_{24}H_{42}O_3Si$ 406.2903; Found 406.2884.

**(3*S*)-2-((1*R*,5*R*)-5-*t*-Butyldimethylsilyloxy-4-methylcyclohex-3-en-1-yl)-6-methylhepta-1,5-dien-3-yl pivalate (16) and (3*R*)-2-((1*R*,5*R*)-5-*t*-butyldimethylsilyloxy-4-methylcyclohex-3-en-1-yl)-6-methylhepta-1,5-dien-3-yl pivalate (17)**

A solution of **15a**,**b** (2420.0 mg, 5.95 mmol) in 2-methyl-2-butene (240 mL) was added to a flask containing Grubbs II catalyst (76.0 mg, 0.090 mmol). The mixture was stirred at 35 °C for 23 h, and the solvent was evaporated. The resultant residue was chromatographed on silica gel (hexane-EtOAc 97:3) to afford a mixture of **16** and **17** (2361.7 mg; 91%), which was separated by column chromatography on silica gel (pentane-$CH_2Cl_2$ 4:1) to give **16** (1066.2 mg, 45%) as a colorless oil and **17** (930.7 mg, 39%) as a colorless oil.

**16**: $[\alpha]_D^{29}$ –26.8 (*c* 0.254, MeOH); IR (neat/NaCl) 1732 (C=O), 1647 (C=C), 1154, 837 $cm^{-1}$; $^1H$ NMR δ 0.08 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.19 (s, 9H), 1.52-2.42 (m, 7H), 1.62 (s, 3H), 1.67 (s, 3H), 1.69 (br s, 3H), 4.20-4.26 (m, 1H), 4.94 (s, 1H), 5.04 (br t, *J* = 6.8 Hz, 1H), 5.06 (s, 1H), 5.14 (dd, *J* = 5.6, 7.5 Hz, 1H), 5.43-5.47 (m, 1H); $^{13}C$ NMR δ –4.8, –4.2, 18.0, 18.1, 19.7, 25.7, 25.9 (3C), 27.1 (3C), 32.8, 33.2, 36.0, 38.8, 39.4, 71.7, 75.5, 109.8, 119.4, 123.4, 134.0, 137.0, 152.3, 177.5; MS (FI) *m*/*z*: 333 [$MH^+$ - PivOH, 26%], 201 (100), 133 (17); HRMS (FI-hybrid of quadrupole and TOF) *m*/*z*: $[M]^+$ Calcd for $C_{26}H_{46}O_3Si$ 434.3216; Found 434.3202.

**17**: $[\alpha]_D^{29}$ –6.2 (*c* 0.259, MeOH); IR (neat/NaCl) 1731 (C=O), 1646 (C=C), 1154, 837 $cm^{-1}$; $^1H$ NMR δ 0.09 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 1.18 (s, 9H), 1.49-2.42 (m, 7H), 1.62 (s, 3H), 1.68 (s, 3H), 1.69 (br s, 3H), 4.20-4.26 (m, 1H), 4.97 (s, 1H), 5.05 (br t, *J* = 6.7 Hz, 1H), 5.09 (s, 1H), 5.18 (dd, *J* = 5.8, 7.4 Hz, 1H), 5.43-5.47 (m, 1H); $^{13}C$ NMR δ –4.9, –4.1, 18.0, 18.1, 19.7, 25.7, 25.9 (3C), 27.1 (3C), 32.6, 32.7, 36.3, 38.8, 39.7, 71.6, 75.5, 110.7, 119.5, 123.3, 133.9, 137.0, 151.9, 177.5; MS (FI) *m*/*z*: 333 [$MH^+$ - PivOH, 29%], 201 (100), 133 (24); HRMS (FI-hybrid of quadrupole and TOF) *m*/*z*: $[M]^+$ Calcd for $C_{26}H_{46}O_3Si$ 434.3216; Found 434.3189.

**(3*S*)-2-((1*R*,5*R*)-5-*t*-Butyldimethylsilyloxy-4-methylcyclohex-3-en-1-yl)-6-methylhepta-1,5-dien-3-ol (18) and (3*R*)-2-((1*R*,5*R*)-5-*t*-butyldimethylsilyloxy-4-methylcyclohex-3-en-1-yl)-6-methylhepta-1,5-dien-3-ol (20)**

A solution of **16** (500.0 mg, 1.15 mmol) in $Et_2O$ (6 mL) was treated with $LiAlH_4$ (110.0 mg, 2.90 mmol) in $Et_2O$ (8 mL) as described for **9** to afford **18** (373.2 mg, 93%) as a colorless oil after purification by silica gel column chromatography (hexane-EtOAc 11:1). Similarly, **17** (501.2 mg, 1.15 mmol) afforded **20** (374.9 mg, 93%) as a colorless oil.

**18**: $[\alpha]_D^{27}$ –18.9 (*c* 0.227, MeOH); IR (neat/NaCl) 3410 (OH), 1645 (C=C), 1092, 837 $cm^{-1}$; $^1H$ NMR δ 0.09 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 1.55-2.36 (m, 8H), 1.65 (s, 3H), 1.70 (br s, 3H), 1.74 (s, 3H), 4.07-4.12 (m, 1H), 4.21-4.28 (m, 1H), 4.95 (s, 1H), 5.11-5.17 (m, 1H), 5.13 (s, 1H), 5.43-5.47 (m, 1H); $^{13}C$ NMR δ –4.9, –4.1, 18.1, 18.1, 19.7, 25.9 (3C), 25.9, 33.2, 35.3, 35.9, 39.6, 71.6, 73.8, 108.4, 119.9, 123.3, 135.4, 137.2, 155.8; MS (FI) *m*/*z*: 333 [$MH^+$ - $H_2O$, 49%], 219 (97), 201 (100), 133 (23); HRMS (FI-hybrid of quadrupole and TOF) *m*/*z*: $[M]^+$ Calcd for $C_{21}H_{38}O_2Si$ 350.2641; Found 350.2622.

**20**: $[\alpha]_D^{28}$ –13.0 (*c* 0.262, MeOH); IR (neat/NaCl) 3366 (OH), 1644 (C=C), 1092, 837 $cm^{-1}$; $^1H$ NMR δ 0.08 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.51-2.36 (m, 8H), 1.66 (s, 3H), 1.69 (br s, 3H), 1.74 (s, 3H), 4.07-4.12 (m, 1H), 4.20-4.27 (m, 1H); 4.96 (s, 1H), 5.12-5.17 (m, 1H), 5.13 (s, 1H), 5.44-5.48 (m, 1H); $^{13}C$ NMR δ –4.9, –4.2, 18.1, 18.1, 19.7, 25.9 (3C), 25.9, 32.7, 35.1, 36.1, 40.0, 71.6, 73.8, 108.9, 119.9, 123.5, 135.4, 137.0, 155.5; MS (FI) *m*/*z*:

333 [$MH^+$ - $H_2O$, 51%], 219 (98), 201 (100), 133 (23); HRMS (FI-hybrid of quadrupole and TOF) *m*/*z*: $[M]^+$ Calcd for $C_{21}H_{38}O_2Si$ 350.2641; Found 350.2622.

**Mosher's esters (19a, 19b, 21a, and 21b)**

(+)-MTPACl (5 drops) was added to a stirred solution of **18** (1.2 mg, 0.034 mmol) in dry pyridine (1 mL) at room temperature, and stirring was continued for 14 h. Saturated $NaHCO_3$ aq was added, and the mixture was extracted with $Et_2O$ and dried. Evaporation of the solvent followed by silica gel column chromatography (hexane-EtOAc 19:1) afforded **19a** (1.4 mg, 72%) as a colorless oil. Similarly, **18** (1.3 mg, 0.0037 mmol) was treated with (–)-MTPACl to afford **19b** (1.4 mg, 67%) as a colorless oil; **20** (1.8 mg, 0.0051 mmol) afforded **21a** (2.5 mg, 86%) as a colorless oil; **20** (1.8 mg, 0.0051 mmol) afforded **21b** (3.0 mg, quant) as a colorless oil.

**19a**: $^1$H NMR δ 0.07 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.51-1.59 (m, 1H), 1.61 (s, 3H), 1.69 (s, 3H), 1.70 (s, 3H), 1.84-2.05 (m, 2H), 2.15-2.30 (m, 2H), 2.32-2.42 (m, 1H), 2.48 (dt, *J* = 15.0, 8.5 Hz, 1H), 3.54 (s, 3H), 4.16-4.27 (m, 1H), 4.95 (s, 1H), 4.99 (s, 1H), 5.05-5.14 (m, 1H), 5.35 (dd, *J* = 5.0, 9.0 Hz, 1H), 5.40-5.48 (m, 1H), 7.34-7.43 (m, 3H), 7.47-7.55 (m, 2H).

**19b**: $^1$H NMR δ 0.04 (s, 3H), 0.07 (s, 3H), 0.90 (s, 9H), 1.53 (s, 3H), 1.55-1.62 (m, 2H), 1.63 (s, 3H), 1.67-1.71 (m, 3H), 1.92 (t sext, *J* = 14.0, 2.5 Hz, 1H), 1.99 (ddt, *J* = 6.0, 12.5, 2.5 Hz, 1H), 2.13-2.22 (m, 1H), 2.24-2.37 (m, 1H), 2.43 (dt, *J* = 15.0, 7.5 Hz, 1H), 3.52 (s, 3H), 4.16-4.24 (m, 1H), 4.92-4.98 (m, 1H), 5.05 (s, 1H), 5.16 (s, 1H), 5.41 (dd, *J* = 5.5, 8.0 Hz, 1H), 5.42-5.47 (m, 1H), 7.34-7.42 (m, 3H), 7.47-7.52 (m, 2H).

**21a**: $^1$H NMR δ 0.07 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.51-1.57 (m, 1H), 1.53 (s, 3H), 1.63 (s, 3H), 1.67-1.70 (m, 3H), 1.84-2.12 (m, 3H), 2.24-2.39 (m, 2H), 2.42 (dt, *J* = 15.0, 8.0 Hz, 1H), 3.51 (s, 3H), 4.16-4.25 (m, 1H), 4.92-5.00 (m, 1H), 5.06 (s, 1H), 5.18 (s, 1H), 5.38-5.44 (m, 1H), 5.42 (dd, *J* = 5.5, 8.5 Hz, 1H), 7.33-7.42 (m, 3H), 7.47-7.54 (m, 2H).

**21b**: $^1$H NMR δ 0.07 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.42-1.55 (m, 1H), 1.61 (s, 3H), 1.66-1.69 (m, 3H), 1.70 (s, 3H), 1.77-1.95 (m, 2H), 2.03 (ddt, *J* = 6.0, 12.0, 2.0 Hz, 1H), 2.14-2.24 (m, 1H), 2.35-2.43 (m, 1H), 2.48 (dt, *J* = 15.0, 8.0 Hz, 1H), 3.55 (s, 3H), 4.10-4.19 (m, 1H), 4.97 (s, 1H), 5.04 (s, 1H), 5.06-5.11 (m, 1H), 5.34-5.39 (m, 1H), 5.39 (dd, *J* = 5.0, 8.5 Hz, 1H), 7.33-7.41 (m, 3H), 7.48-7.53 (m, 2H).

**(3*S*)-2-((1*R*,5*R*)-5-Hydroxy-4-methylcyclohex-3-en-1-yl)-6-methylhepta-1,5-dien-3-ol (22) and (3*R*)-2-((1*R*,5*R*)-5-hydroxy-4-methylcyclohex-3-en-1-yl)-6-methylhepta-1,5-dien-3-ol (24)**

A solution of TBAF (1 M in THF, 0.84 mL, 0.84 mmol) was added to a stirred solution of **18** (97.3 mg, 0.28 mmol) in THF (9 mL) and stirring was maintained at room temperature for 1 day. A saturated $NH_4Cl$ aq was added, and the mixture was extracted with EtOAc and dried. Evaporation of the solvent followed by silica gel column chromatography (hexane-EtOAc 8:2) afforded **22** (59.2 mg, 89%) as a colorless oil. By the same procedure, **20** (162.3 mg, 0.46 mmol) afforded **24** (106.7 mg, 98%) as a colorless oil.

**22**: $[\alpha]_D^{28}$ –24.5 (*c* 0.139, MeOH); IR (neat/NaCl) 3348 (OH), 1645 (C=C), 1450, 1036, 756 $cm^{-1}$; $^1$H NMR δ 1.54-1.82 (m, 3H), 1.65 (s, 3H), 1.74 (s, 3H), 1.77 (br s, 3H), 1.88-1.99 (m, 1H), 2.11-2.38 (m, 5H), 4.09-4.14 (m, 1H), 4.19-4.25 (m, 1H), 4.96 (s, 1H), 5.10-5.16 (m, 1H), 5.14 (s, 1H), 5.48-5.52 (m, 1H); $^{13}$C NMR δ 18.1, 18.9, 25.9, 33.0, 35.2, 35.6, 39.2, 71.0, 73.7, 108.7, 119.8, 123.9, 135.5, 136.2, 155.4; MS (FI) *m*/*z*: 218 [$M^+$ - $H_2O$,

100%], 200 (23), 149 (12); HRMS (FI-hybrid of quadrupole and TOF) *m*/*z*: [$M^+$ - $H_2O$] Calcd for $C_{15}H_{22}O$ 218.1671; Found 218.1710.

**24**: $[\alpha]_D^{28}$ +2.7 (*c* 0.474, MeOH); IR (neat/NaCl) 3357 (OH), 1645 (C=C), 1450, 1038 $cm^{-1}$; $^1H$ NMR δ 1.52-1.82 (m, 3H), 1.65 (s, 3H), 1.74 (s, 3H), 1.76 (br s, 3H), 1.97-2.39 (m, 6H), 4.09-4.14 (m, 1H), 4.14-4.22 (m, 1H), 4.97 (s, 1H), 5.11-5.17 (m, 1H), 5.15 (s, 1H), 5.49-5.53 (m, 1H); $^{13}C$ NMR δ 18.1, 19.0, 25.9, 32.4, 35.2, 35.8, 39.3, 70.9, 73.7, 109.1, 119.8, 124.1, 135.5, 136.0, 155.3; MS (FAB+) *m*/*z*: 259 $[M + Na]^+$; HRMS (FAB-DFMS) *m*/*z*: $[M + Na]^+$ Calcd for $C_{15}H_{24}O_2Na$ 259.1674; Found 259.1681.

**(3*S*)-2-((1*S*,3*S*,4*R*,5*R*)-3,4-Epoxy-5-hydroxy-4-methylcyclohex-1-yl)-5,6-epoxy-6-methylhept-1-en-3-ol (23a,b) and (3*R*)-2-((1*S*,3*S*,4*R*,5*R*)-3,4-epoxy-5-hydroxy-4-methylcyclohex-1-yl)-5,6-epoxy-6-methylhept-1-en-3-ol (25a,b)**

*m*CPBA (containing 30% water, 102.8 mg, 0.42 mmol) was added to a stirred solution of **22** (49.4 mg, 0.21 mmol) in $CH_2Cl_2$ (9 mL) at –40 °C. After stirring for 2 h, a saturated $NaHCO_3$ aq was added, and the mixture was extracted with $CH_2Cl_2$ and dried. Evaporation of the solvent followed by silica gel (5.5 g) column chromatography (hexane-EtOAc 1:1) afforded **23a**,**b** (38.7 mg, 69%) as a colorless oil. By the same procedure, **24** (21.5 mg, 0.09 mmol) afforded **25a**,**b** (16.5 mg, 68%) as a colorless oil.

**23a**,**b**: IR (neat/NaCl) 3433 (OH), 1645 (C=C), 1446, 1379, 1050 $cm^{-1}$; $^1H$ NMR δ 1.29 (s, 3H × 3/7), 1.30 (s, 3H × 4/7), 1.33 (s, 3H × 3/7), 1.33 (s, 3H × 4/7), 1.46 (s, 3H), 1.57-2.15 (m, 9H), 2.90 (dd, *J* = 4.1, 8.2 Hz, 1H × 4/7), 2.95 (dd, *J* = 4.0, 7.8 Hz, 1H × 3/7), 3.15 (d, *J* = 4.8 Hz, 1H), 3.83-3.90 (m, 1H), 4.29 (dd, *J* = 3.7, 8.3 Hz, 1H × 3/7), 4.35 (dd, *J* = 3.9, 8.6 Hz, 1H × 4/7), 4.95 (s, 1H), 5.16 (s, 1H × 4/7), 5.17 (s, 1H × 3/7); $^{13}C$ NMR δ 19.0, 19.0, 19.1 (both isomers), 24.6, 24.7, 31.3 (both isomers), 34.9, 35.0, 35.0, 35.1, 35.2, 35.3, 57.9, 58.6, 60.3 (both isomers), 61.4, 62.2, 62.2, 62.4, 72.1 (both isomers), 72.2, 73.1, 109.6, 109.9, 154.2, 154.9; MS (EI) *m*/*z*: 268 $[M]^+$; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{15}H_{24}O_4$ 268.1675; Found 268.1672.

**25a**,**b**: IR (neat/NaCl) 3419 (OH), 1647 (C=C), 1446, 1381, 1049 $cm^{-1}$; $^1H$ NMR δ 1.29 (s, 3H × 3/7), 1.31 (s, 3H × 4/7), 1.33 (s, 3H), 1.46 (s, 3H), 1.57-2.18 (m, 9H), 2.90 (dd, *J* = 3.9, 8.5 Hz, 1H × 4/7), 2.94 (dd, *J* = 4.2, 7.8 Hz, 1H × 3/7), 3.15 (d, *J* = 4.8 Hz, 1H × 3/7), 3.16 (d, *J* = 5.0 Hz, 1H × 4/7), 3.82-3.89 (m, 1H), 4.29 (dd, *J* = 3.7, 8.5 Hz, 1H × 3/7), 4.37 (dd, *J* = 3.8, 8.5 Hz, 1H × 4/7), 4.96 (s, 1H), 5.14 (s, 1H × 4/7), 5.15 (s, 1H × 3/7); $^{13}C$ NMR δ 19.0, 19.0, 19.1 (both isomers), 24.6, 24.8, 31.1 (both isomers), 34.8, 34.8, 35.0, 35.0, 35.6 (both isomers), 57.9, 58.5, 60.3 (both isomers), 61.4, 62.3, 62.3, 62.4, 72.1, 72.2, 72.4, 73.3, 110.1, 110.3, 153.9, 154.7; MS (EI) *m*/*z*: 268 $[M]^+$; HRMS (EI-DFMS) *m*/*z*: $[M]^+$ Calcd for $C_{15}H_{24}O_4$ 268.1675; Found 268.1672.

**Synthesis of tiglates**

**(3*S*,5*R*)-2-((1*R*,3*S*,4*S*,5*R*)-3,4-Epoxy-4-methyl-5-tigloyloxycyclohex-1-yl)-5,6-epoxy-6-methylhept-1-en-3-yl tiglate (26), (3*S*,5*S*)-2-((1*R*,3*S*,4*S*,5*R*)-3,4-epoxy-4-methyl-5-tigloyloxycyclohex-1-yl)-5,6-epoxy-6-methylhept-1-en-3-yl tiglate (27), (3*R*,5*S*)-2-((1*R*,3*S*,4*S*,5*R*)-3,4-epoxy-4-methyl-5-tigloyloxycyclohex-1-yl)-5,6-epoxy-6-methylhept-1-en-3-yl**

**tiglate (28), and (3*R*,5*R*)-2-((1*R*,3*S*,4*S*,5*R*)-3,4-epoxy-4-methyl-5-tigloyloxycyclohex-1-yl)-5,6-epoxy-6-methylhept-1-en-3-yl tiglate (29)**

DMAP (328.3 mg, 2.69 mmol) and tiglic anhydride (0.16 mL, 0.90 mmol) were added successively at room temperature to a stirred solution of **23a**,**b** (60.1 mg, 0.22 mmol) in dry $CH_2Cl_2$ (13 mL), and stirring was maintained for 3 days. Saturated $NH_4Cl$ aq was added, and the mixture was extracted with $CH_2Cl_2$ and dried. After removal of the solvent, the resultant residue was chromatographed on silica gel (5 g) (hexane-EtOAc 92:8) to afford a mixture of **26** and **27** (74.9 mg, 79%), which was separated by HPLC (Mightysil, hexane-EtOAc 85:15). By the same procedure, **25a**,**b** (56.3 mg, 0.21 mmol) was treated with tiglic anhydride (0.15 mL, 0.85 mmol) to afford a mixture of **28** and **29** (55.8 mg, 62%), which was separated by HPLC (Mightysil, hexane-EtOAc 85:15).

**26**: Oil; $[\alpha]_D^{24}$ –7.7 (*c* 0.298, MeOH); IR (neat/NaCl) 1713 (C=O), 1651 (C=C), 1258, 1137, 735 $cm^{-1}$; $^1H$ NMR See Tables 1 and 2; $^{13}C$ NMR See Tables 1 and 2; MS (ESI) *m*/*z*: 455 $[M + Na]^+$; HRMS (ESI-hybrid of quadrupole and ICR/FT) *m*/*z*: $[M + Na]^+$ Calcd for $C_{25}H_{36}O_6Na$ 455.2411; Found 455.2404.

**27**: Oil; $[\alpha]_D^{22}$ –20.1 (*c* 0.114, MeOH); IR (neat/NaCl) 1713 (C=O), 1651 (C=C), 1258, 1136, 735 $cm^{-1}$; $^1H$ NMR See Tables 1 and 2; $^{13}C$ NMR See Tables 1 and 2; MS (ESI) *m*/*z*: 455 $[M + Na]^+$; HRMS (ESI-hybrid of quadrupole and ICR/FT) *m*/*z*: $[M + Na]^+$ Calcd for $C_{25}H_{36}O_6Na$ 455.2411; Found 455.2404.

**28**: Oil; $[\alpha]_D^{23}$ –21.6 (*c* 0.324, MeOH); IR (neat/NaCl) 1711 (C=O), 1651 (C=C), 1258, 1137, 735 $cm^{-1}$; $^1H$ NMR See Tables 1 and 2; $^{13}C$ NMR See Tables 1 and 2; MS (ESI) *m*/*z*: 455 $[M + Na]^+$; HRMS (ESI-hybrid of quadrupole and ICR/FT) *m*/*z*: $[M + Na]^+$ Calcd for $C_{25}H_{36}O_6Na$ 455.2411; Found 455.2404.

**29**: Oil; $[\alpha]_D^{24}$ –9.4 (*c* 0.460, MeOH); IR (neat/NaCl) 1711 (C=O), 1651 (C=C), 1258, 1137, 735 $cm^{-1}$; $^1H$ NMR See Tables 1 and 2; $^{13}C$ NMR See Tables 1 and 2; MS (ESI) *m*/*z*: 455 $[M + Na]^+$; HRMS (ESI-hybrid of quadrupole and ICR/FT) *m*/*z*: $[M + Na]^+$ Calcd for $C_{25}H_{36}O_6Na$ 455.2411; Found 455.2403.

**(3*S*,5*R*)-2-((1*R*,3*S*,4*S*,5*R*)-3,4-Epoxy-4-methyl-5-tigloyloxycyclohex-1-yl)-5,6-dihydroxy-6-methylhept-1-en-3-yl tiglate (30) and (3*R*,5*S*)-2-((1*R*,3*S*,4*S*,5*R*)-3,4-epoxy-4-methyl-5-tigloyloxycyclohex-1-yl)-5,6-dihydroxy-6-methylhept-1-en-3-yl tiglate (32)**

A solution of **26** (25.6 mg, 0.059 mmol) in THF (2 mL), AcOH (1 mL), and $H_2O$ (1 mL) was stirred at room temperature for 1 day. Saturated $Na_2SO_3$ aq was added, and the mixture was extracted with $Et_2O$ and dried. Evaporation of the solvent followed by silica gel (4 g) column chromatography (hexane-EtOAc 8:2) afforded **30** (18.5 mg, 70%) as a colorless oil. By the same procedure, **28** (22.5 mg, 0.052 mmol) afforded **32** (18.0 mg, 77%) as a colorless oil.

**30**: $[\alpha]_D^{20}$ –9.7 (*c* 0.185, MeOH); IR (neat/NaCl) 3471 (OH), 1707 (C=O), 1649 (C=C), 1265, 1140 $cm^{-1}$; $^1H$ NMR δ 1.17 (s, 3H), 1.20 (s, 3H), 1.33 (s, 3H), 1.52-2.28 (m, 20H), 2.63-2.67 (m, 1H), 3.12 (d, *J* = 4.8 Hz, 1H), 3.39-3.44 (m, 1H), 4.99 (s, 1H), 5.16 (s, 1H), 5.22 (dd, *J* = 5.3, 10.6 Hz, 1H), 5.39 (t, *J* = 6.5 Hz, 1H), 6.85-6.99 (m, 2H); $^{13}C$ NMR δ 12.1 (2C), 14.4, 14.5, 19.1, 23.9, 25.9, 31.0, 31.0, 35.0, 36.1, 58.3, 60.8, 72.6, 73.8, 75.4, 75.9, 111.7, 128.3, 128.5, 138.0, 138.2, 150.9, 167.0, 167.6; MS (ESI) *m*/*z*: 473 $[M + Na]^+$; HRMS (ESI-hybrid of quadrupole and ICR/FT) *m*/*z*: $[M + Na]^+$ Calcd for $C_{25}H_{38}O_7Na$ 473.2516; Found 473.2508.

**32**: $[\alpha]_D^{21}$ –33.9 (*c* 0.271, MeOH); IR (neat/NaCl) 3470 (OH), 1708 (C=O), 1649 (C=C), 1263, 1140 $cm^{-1}$; $^1H$ NMR δ 1.18 (s, 3H), 1.20 (s, 3H), 1.33 (s, 3H), 1.53-2.26 (m, 20H), 2.48-2.57 (m, 1H), 3.10 (d, *J* = 4.9 Hz, 1H), 3.40 (br d, *J* = 10.0 Hz, 1H), 5.04 (s, 1H), 5.19 (s, 1H), 5.22 (dd, *J* = 5.2, 10.8 Hz, 1H), 5.44 (t, *J* = 6.5 Hz, 1H), 6.87 (qq, *J* = 1.3, 7.0 Hz, 1H), 6.95 (qq, *J* = 1.3, 7.0 Hz, 1H); $^{13}C$ NMR δ 12.1, 12.2, 14.4, 14.5, 19.1, 24.0, 25.7, 30.9, 31.2, 34.7, 35.4, 58.3, 60.8, 72.7, 73.7, 75.5, 75.9, 112.9, 128.3, 128.6, 137.9, 138.1, 150.2, 167.1, 167.7; MS (ESI) *m*/*z*: 473 $[M + Na]^+$; HRMS (ESI-hybrid of quadrupole and ICR/FT) *m*/*z*: $[M + Na]^+$ Calcd for $C_{25}H_{38}O_7Na$ 473.2516; Found 473.2510.

**Mosher's esters (31a, 31b, 33a, and 33b)**

$Et_3N$ (0.025 mL, 0.18 mmol) and DMAP (54.1 mg, 0.44 mmol) were added successively to a stirred solution of **30** (15.9 mg, 0.035 mmol) in dry $CH_2Cl_2$ (2 mL) under Ar at 0 °C. (+)-MTPACl (0.020 mL, 0.11 mmol) was added, and stirring was maintained for 1 h. $H_2O$ was added, and the mixture was extracted with $Et_2O$ and dried. Evaporation of the solvent followed by silica gel (5 g) column chromatography (hexane-EtOAc 88:12) afforded **31a** (13.1 mg, 56%). Similarly, **30** (9.4 mg, 0.021 mmol) was treated with (–)-MTPACl to afford **31b** (8.2 mg, 59%); **32** (18.9 mg, 0.042 mmol) afforded **33a** (24.2 mg, 86%); and **32** (21.8 mg, 0.048 mmol) afforded **33b** (22.5 mg, 70%).

**31a**: Oil; $^1H$ NMR δ 1.18 (s, 3H), 1.20 (s, 3H), 1.33 (s, 3H), 1.47-2.22 (m, 20H; δ values of C(9)-$H_2$ were determined to be 1.90 and 2.08 by COSY spectrum), 3.09 (d, *J* = 4.6 Hz, 1H), 3.53 (br s, 3H), 4.94 (dd, *J* = 3.7, 7.4 Hz, 1H), 5.02 (s, 1H), 5.14 (s, 1H), 5.21 (dd, *J* = 5.2, 10.8 Hz, 1H), 5.27 (t, *J* = 7.0 Hz, 1H), 6.84-6.98 (m, 2H), 7.39-7.63 (m, 5H).

**31b**: Oil; $^1H$ NMR δ 1.11 (s, 3H), 1.14 (s, 3H), 1.33 (s, 3H), 1.48-2.24 (m, 20H; δ values of C(9)-$H_2$ were determined to be 1.96 and 2.15 by COSY spectrum), 3.08 (d, *J* = 4.9 Hz, 1H), 3.62 (br s, 3H), 4.92 (dd, *J* = 3.3, 7.6 Hz, 1H), 5.05 (s, 1H), 5.16 (s, 1H), 5.21 (dd, *J* = 5.2, 10.7 Hz, 1H), 5.34 (dd, *J* = 6.6, 7.7 Hz, 1H), 6.86 (qq, *J* = 1.3, 7.0 Hz, 1H), 6.94 (qq, *J* = 1.3, 7.0 Hz, 1H), 7.39-7.66 (m, 5H).

**33a**: Oil; $^1H$ NMR δ 1.12 (s, 6H), 1.34 (s, 3H), 1.53-2.39 (m, 20H; δ values of C(9)-$H_2$ were determined to be 1.99 and 2.35 by COSY spectrum), 3.07 (d, *J* = 4.9 Hz, 1H), 3.62 (br s, 3H), 4.84 (dd, *J* = 1.5, 8.4 Hz, 1H), 5.06 (dd, *J* = 5.0, 10.6 Hz, 1H), 5.14 (s, 1H), 5.18 (s, 1H), 5.38 (dd, *J* = 5.6, 9.8 Hz, 1H), 6.84 (br q, *J* = 7.0 Hz, 1H), 6.95 (br q, *J* = 7.0 Hz, 1H), 7.39-7.66 (m, 5H).

**33b**: Oil; $^1H$ NMR δ 1.19 (s, 3H), 1.20 (s, 3H), 1.34 (s, 3H), 1.53-2.37 (m, 20H; δ values of C(9)-$H_2$ were determined to be 1.90 and 2.27 by COSY spectrum), 3.07 (d, *J* = 5.0 Hz, 1H), 3.53 (br s, 3H), 4.84 (dd, *J* = 2.0, 8.4 Hz, 1H), 5.08 (dd, *J* = 5.1, 10.6 Hz, 1H), 5.12 (s, 1H), 5.21 (s, 1H), 5.32 (dd, *J* = 5.6, 9.4 Hz, 1H), 6.84 ( br q, *J* = 7.0 Hz, 1H), 6.96 (br q, *J* = 7.0 Hz, 1H), 7.39-7.62 (m, 5H).

**Non-stereoselective synthesis of angelates**

**(3*S*,5*R*)-2-((1*R*,3*S*,4*S*,5*R*)-5-Angeloyloxy-3,4-epoxy-4-methylcyclohex-1-yl)-5,6-epoxy-6-methylhept-1-en-3-yl angelate (34) and**

**(3*S*,5*S*)-2-((1*R*,3*S*,4*S*,5*R*)-5-angeloyloxy-3,4-epoxy-4-methylcyclohex-1-yl)-5,6-epoxy-6-methylhept-1-en-3-yl angelate (35)**

$Cs_2CO_3$ (195.5 mg, 0.600 mmol) and $Ang_2O$ (0.07 mL, 0.4 mmol) were added to a stirred solution of **23a**,**b** (25.9 mg, 0.0965 mmol) in $CH_3CN$ (10 mL) at room temperature. The resulting mixture was stirred at the same temperature for 3 days. $Et_2O$ and $H_2O$ were added to the reaction mixture, and the whole mixture was extracted with $Et_2O$ and EtOAc. The combined organic layers were dried over $Na_2SO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane-EtOAc 88:12→0:100), and the fraction containing **34** and **35** was concentrated *in vacuo*. The residual oil was purified by column chromatography on silica gel (cyclohexane-$CHCl_3$ 30:70), and the fractions containing **34** and **35** were concentrated *in vacuo*. The residual oil was purified by preparative thin-layer chromatography ($CHCl_3$) to afford **34** (2.0 mg, 4.6%) as a colorless oil and **35** (1.4 mg, 3.2%) as a colorless oil.

**34**: $[\alpha]_D^{25}$ –17.5 (*c* 0.133, $CHCl_3$); IR (neat/NaCl) 1710 (C=O), 1647 (C=C), 1262, 1159, 784 $cm^{-1}$; $^1H$ NMR See Table 4; $^{13}C$ NMR See Table 4; MS (FAB+) *m*/*z*: 433 $[M + H]^+$; HRMS (FAB-DFMS) *m*/*z*: $[M + H]^+$ Calcd for $C_{25}H_{37}O_6$ 433.2590; Found 433.2582.

**35**: $[\alpha]_D^{24}$ –27.3 (*c* 0.073, $CHCl_3$); IR (neat/NaCl) 1715 (C=O), 1647 (C=C), 1262, 1158, 784 $cm^{-1}$; $^1H$ NMR See Table 4; $^{13}C$ NMR See Table 4; MS (FAB+) *m*/*z*: 433 $[M + H]^+$; HRMS (FAB-DFMS) *m*/*z*: $[M + H]^+$ Calcd for $C_{25}H_{37}O_6$ 433.2590; Found 433.2584.

**(3*R*,5*S*)-2-((1*R*,3*S*,4*S*,5*R*)-5-Angeloyloxy-3,4-epoxy-4-methylcyclohex-1-yl)-5,6-epoxy-6-methylhept-1-en-3-yl angelate (36) and (3*R*,5*R*)-2-((1*R*,3*S*,4*S*,5*R*)-5-angeloyloxy-3,4-epoxy-4-methylcyclohex-1-yl)-5,6-epoxy-6-methylhept-1-en-3-yl angelate (37)**

$Cs_2CO_3$ (39.1 mg, 0.12 mmol) and $Ang_2O$ (0.014 mL, 0.080 mmol) were added to a stirred solution of **25a**,**b** (5.0 mg, 0.019 mmol) in $CH_3CN$ (1.0 mL) at room temperature. The resulting mixture was stirred at the same temperature for 20 h. After the addition of $Cs_2CO_3$ (39.1 mg, 0.12 mmol) and $Ang_2O$ (0.014 mL, 0.080 mmol), stirring was continued for 18 h. $Et_2O$ and $H_2O$ were added to the reaction mixture, and the whole mixture was extracted with $Et_2O$ and EtOAc. The combined organic layers were dried over $Na_2SO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane-EtOAc 80:20) to afford a mixture of **36** and **37** (1.9 mg, 22%) as a colorless oil.

IR (neat/NaCl) 1717 (C=O), 1648 (C=C), 1258, 1156, 849 $cm^{-1}$; $^1H$ NMR See Table 4; $^{13}C$ NMR See Table 4; MS (FAB+) *m*/*z*: 433 $[M + H]^+$; HRMS (FAB-DFMS) *m*/*z*: $[M + H]^+$ Calcd for $C_{25}H_{37}O_6$ 433.2590; Found 433.2596.

**Stereoselective synthesis of natural product**

**(3*R*)-2-((1*R*,5*R*)-5-*t*-Butyldimethylsilyloxy-4-methylcyclohex-3-en-1-yl)hexa-1,5-dien-3-ol (14b)**

(+)-Ipc$_2$B-allyl (1 M solution in pentane, 0.036 mL, 0.036 mmol) was added to a stirred solution of **13** (10 mg, 0.036 mmol) in $Et_2O$ (0.5 mL) at –78°C. After stirring at the same temperature for 1 h, 3 M NaOH aq and 30% $H_2O_2$ were added, and the mixture was extracted with $Et_2O$. The combined organic layers were washed with $H_2O$ and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane-EtOAc 90:10) to afford **14b** (10.4 mg, 89%) as a colorless oil.

**(3*R*)-2-((1*R*,5*R*)-5-*t*-Butyldimethylsilyloxy-4-methylcyclohex-3-en-1-yl)-6-methylhepta-1,5-dien-3-ol (20)**

A solution of **14b** (10.4 mg, 0.032 mmol) and Grubbs II catalyst (2.0 mg, 0.48 μmol) in 2-methyl-2-butene (1.0 mL) was stirred at 35 °C for 15 h. Once concentrated, the crude product was purified by column chromatography on silica gel (hexane-EtOAc 10:1) to afford **20** (5.4 mg, 48%) as a colorless oil.

**(3*R*,5*S*)-2-((1*R*,5*R*)-5-*t*-Butyldimethylsilyloxy-4-methylcyclohex-3-en-1-yl)-5,6-epoxy-6-methylhept-1-en-3-ol (38)**

VO($O^i$Pr) (2 μL, 7 μmol) and TBHP (70% solution in $H_2O$, 8 μL, 0.06 mmol) were added to a stirred solution of **20** (20.5 mg, 0.06 mmol) in toluene (0.6 mL) at 0 °C. After stirring for 7 h, the reaction was quenched by adding saturated $Na_2SO_3$ aq, and the mixture was extracted with $Et_2O$. The combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane-EtOAc 10:1→5:1) to afford **20** (3.9 mg, 19%), **38** (5.3 mg, 24%), **39** (4.0 mg, 13%), and **40** (6.9 mg, 31%) as colorless oils.

**38**: $[\alpha]_D^{20}$ –18.5 (*c* 0.35, $CHCl_3$); IR (neat/NaCl) 3672 (OH), 1645 (C=C), 1455, 1058, 744 cm$^{-1}$; $^1$H NMR δ 0.08 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.30 (s, 3H), 1.33 (s, 3H), 1.50-1.72 (m, 2H), 1.69 (br s, 3H), 1.87-2.18 (m, 4H), 2.23-2.38 (m, 2H), 2.92 (dd, *J* = 4.2, 7.8 Hz, 1H), 4.16-4.29 (m, 1H), 4.32-4.43 (m, 1H), 4.99 (s, 1H), 5.18 (s, 1H), 5.42-5.50 (m, 1H); $^{13}$C NMR δ –4.8, –4.2, 18.2, 19.0, 19.7, 24.7, 25.9 (3C), 32.6, 35.2, 36.1, 40.1, 57.8, 62.4, 71.6, 73.2, 109.2, 123.3, 137.1, 155.3; MS (FAB+) *m*/*z*: 367 $[M + H]^+$; HRMS (FAB-DFMS) *m*/*z*: $[M + H]^+$ Calcd for $C_{21}H_{39}O_3Si$ 367.2668; Found 367.2667.

**39**: $^1$H NMR δ 0.08 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.20-1.41 (m, 2H), 1.29 (s, 3H), 1.33 (s, 3H), 1.61-1.74 (m, 1H), 1.67 (s, 3H), 1.77-2.13 (m, 4H), 2.38 (d, *J* = 0.9 Hz, 1H), 2.77 (d, *J* = 4.5 Hz, 1H), 2.87 (d, *J* = 4.5 Hz, 1H), 2.97 (dd, *J* = 4.8, 7.2 Hz, 1H), 4.02-4.11 (m, 1H), 4.14-4.26 (m, 1H), 5.35-5.44 (m, 1H).

**40**: $^1$H NMR δ 0.09 (s, 6H), 0.90 (s, 9H), 1.21-1.42 (m, 2H), 1.63 (s, 3H), 1.67 (s, 3H), 1.73 (s, 3H), 1.81-2.38 (m, 6H), 2.73 (d, *J* = 4.5 Hz, 1H), 2.83 (d, *J* = 4.5 Hz, 1H), 3.80-3.91 (m, 1H), 4.14-4.26 (m, 1H), 5.17-5.28 (m, 1H), 5.36-5.44 (m, 1H).

**(3*R*,5*S*)-2-((1*R*,5*R*)-5-*t*-Butyldimethylsilyloxy-4-methylcyclohex-3-en-1-yl)-6-methylhept-1-en-3,5,6-triol (41)**

A solution of **38** (1.8 mg, 0.0049 mmol) in THF/AcOH/$H_2O$ (2:1:1, 0.5 mL) was stirred at room temperature for 20 h. Saturated $NaHCO_3$ aq was added, and the mixture was extracted with $Et_2O$ and dried. Evaporation of the solvent

followed by silica gel column chromatography (hexane-EtOAc 3:2→1:1 then $CHCl_3$-MeOH 17:3) afforded **41** (0.3 mg, 21%) as a colorless oil. $[\alpha]_D^{29}$ –61.7 (*c* 0.15, $CHCl_3$); IR (neat/NaCl) 3384 (OH), 1646 (C=C), 1454, 1065, 758 $cm^{-1}$; $^1H$ NMR δ 0.08 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 1.18 (s, 3H), 1.22 (s, 3H), 1.53-1.65 (m, 3H), 1.68-1.71 (m, 3H), 1.71-1.77 (m, 1H), 1.94-2.13 (m, 3H), 2.25-2.36 (m, 1H), 2.82 (br s, 1H), 3.60-3.70 (m, 2H), 4.19-4.28 (m, 1H), 4.35 (dd, *J* = 1.5, 10.0 Hz, 1H), 4.97 (s, 1H), 5.17 (s, 1H), 5.43-5.48 (m, 1H); $^{13}C$ NMR δ –4.8, –4.2, 18.1, 19.7, 23.8, 25.9 (3C), 26.3, 32.6, 36.1, 37.0, 40.1, 71.5, 72.6, 75.4, 78.9, 109.4, 123.3, 137.0, 155.9; MS (FAB+) *m*/*z*: 385 $[M + H]^+$; HRMS (FAB-DFMS) *m*/*z*: $[M + H]^+$ Calcd for $C_{21}H_{41}O_4Si$ 385.2774; Found 385.2776.

**2-{(4*R*,6*S*)-4-[1-((1*R*,5*R*)-5-*t*-Butyldimethylsilyloxy-4-methylcyclohex-3-en-1-yl)ethen-1-yl]-2,2-dimethyl-1,3-dioxacyclohex-6-yl}propan-2-ol (42)**

*p*-TsOH (0.1 mg, 0.00074 mmol) was added to a stirred solution of **41** (0.4 mg, 0.001 mmol) in 2,2-dimethoxypropane (0.2 mL) at room temperature and stirring was maintained for 23 h. The reaction mixture was diluted with AcOEt, and washed with $H_2O$ and saturated NaCl aq, dried over $Na_2SO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane-EtOAc 19:1→9:1) to afford **42** (0.4 mg, 91%) as a colorless oil. $[\alpha]_D^{29}$ –78.4 (*c* 0.13, $CHCl_3$); IR (neat/NaCl) 2928 (C=C), 1457, 1065, 774 $cm^{-1}$; $^1H$ NMR δ 0.09 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 1.15 (s, 3H), 1.19 (s, 3H), 1.44 (s, 3H), 1.47 (s, 3H), 1.49-1.66 (m, 2H), 1.68-1.72 (m, 3H), 1.87-1.98 (m, 1H), 2.02-2.15 (m, 2H), 2.33-2.43 (m, 2H), 3.49 (s, 1H), 3.67 (dd, *J* = 2.5, 11.5 Hz, 1H), 4.22-4.28 (m, 1H), 4.29-4.35 (m, 1H), 4.98 (s, 1H), 5.11 (s, 1H), 5.42-5.48 (m, 1H); $^{13}C$ NMR δ –4.8, –4.2, 14.1, 18.2, 19.7, 23.7, 25.9 (3C), 29.7 (2C), 30.1, 30.4, 32.5, 36.0, 39.3, 70.4, 71.4, 71.6, 75.5, 99.1, 123.3, 137.1, 153.3; MS (FAB+) *m*/*z*: 447 $[M + Na]^+$; HRMS (FAB-DFMS) *m*/*z*: $[M + Na]^+$ Calcd for $C_{24}H_{44}O_4SiNa$ 447.2907; Found 447.2914.

**(3*S*,5*S*)-2-((1*R*,5*R*)-5-*t*-Butyldimethylsilyloxy-4-methylcyclohex-3-en-1-yl)-5,6-epoxy-6-methylhept-1-en-3-yl benzoate (43)**

Benzoic acid (44.0 mg, 0.36 mmol), $Ph_3P$ (94.4 mg, 0.36 mmol), and DEAD (40% solution in toluene, 0.16 mL, 0.36 mmol) were added successively to a stirred solution of **38** (32.4 mg, 0.088 mmol) in THF (0.7 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 14 h. $Et_2O$ was added, and the mixture was washed with saturated $NaHCO_3$ aq. The organic layer was dried over $Na_2SO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane-EtOAc 10:1) to afford **43** (34.1 mg, 82%) as a colorless oil. $[\alpha]_D^{21}$ –20.3 (*c* 0.18, $CHCl_3$); IR (neat/NaCl) 1717 (C=O), 1647 (C=C), 1112, 837 $cm^{-1}$; $^1H$ NMR δ 0.00 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 1.25 (s, 3H), 1.26 (s, 3H), 1.60 (dt, *J* = 10.0, 13.0 Hz, 1H), 1.67-1.71 (m, 3H), 1.95-2.10 (m, 4H), 2.21-2.30 (m, 1H), 2.32-2.42 (m, 1H), 2.87 (t, *J* = 6.0 Hz, 1H), 4.18-4.29 (m, 1H), 5.05 (s, 1H), 5.23 (s, 1H), 5.42-5.49 (m, 1H), 5.66 (dd, *J* = 5.5, 7.5 Hz, 1H), 7.42-7.49 (m, 2H), 7.58 (tt, *J* = 1.0, 7.5 Hz, 1H), 8.03-8.09 (m, 2H); $^{13}C$ NMR δ –4.9, –4.2, 18.1, 19.0, 19.7, 24.7, 25.9 (3C), 32.9, 33.9, 36.1, 39.6, 58.4, 61.1, 71.6, 74.3, 110.8, 123.2, 128.5 (2C), 129.6 (2C), 130.3, 133.1, 137.2, 151.6, 165.5; MS (FAB+) *m*/*z*: 471 $[M + H]^+$; HRMS (FAB-DFMS) *m*/*z*: $[M + H]^+$ Calcd for $C_{28}H_{43}O_4Si$ 471.2931; Found 471.2928.

**(3*S*,5*S*)-2-((1*R*,5*R*)-5-Hydroxy-4-methylcyclohex-3-en-1-yl)-5,6-epoxy-6-methylhept-1-en-3-yl benzoate (44)**

$Bu_4NF$ (1 M solution in THF, 0.036 mL, 0.036 mmol) was added to a stirred solution of **43** (5.8 mg, 0.012 mmol) in THF (0.4 mL) The mixture was stirred for 13 h at 30 °C, and saturated $NH_4Cl$ aq was added. The mixture was extracted with EtOAc, and the combined organic layers were dried over $Na_2SO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane-EtOAc 65:35) to afford **44** (3.9 mg, 89%) as a colorless oil. $[\alpha]_D^{21}$ –24.0 (*c* 0.26, $CHCl_3$); IR (neat/NaCl) 3596 (OH), 1717 (C=O), 1647 (C=C), 1224, 1098, 813 $cm^{-1}$; $^1H$ NMR δ 1.25 (s, 3H), 1.26 (s, 3H), 1.57 (br s, 1H), 1.58 (dt, *J* = 10.0, 12.5 Hz, 1H), 1.74-1.79 (m, 3H), 1.94-2.09 (m, 3H), 2.20 (ddt, *J* = 6.0, 12.0, 2.0 Hz, 1H), 2.28-2.44 (m, 2H), 2.88 (t, *J* = 6.0 Hz, 1H), 4.18-4.28 (m, 1H), 5.05 (s, 1H), 5.24 (s, 1H), 5.48-5.54 (m, 1H), 5.65 (t, *J* = 6.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 2H), 7.58 (t, *J* = 7.0 Hz, 1H), 8.02-8.10 (m, 2H); $^{13}C$ NMR δ 18.8, 19.0, 24.6, 32.8, 34.1, 36.3, 39.0, 58.4, 61.1, 71.0, 73.8, 110.4, 123.8, 128.5 (2C), 129.6 (2C), 130.2, 133.1, 136.2, 151.6, 165.5; MS (FAB+) *m*/*z*: 357 $[M + H]^+$; HRMS (FAB-DFMS) *m*/*z*: $[M + H]^+$ Calcd for $C_{22}H_{29}O_4$ 357.2066; Found 357.2065.

**(3*S*,5*S*)-2-((1*S*,3*S*,4*R*,5*R*)-3,4-Epoxy-5-hydroxy-4-methylcyclohex-1-yl)-5,6-epoxy-6-methylhep-1-en-3-yl benzoate (45)**

*m*CPBA (30% water, 16.5 mg, 0.067 mmol) was added to a stirred solution of **44** (23.9 mg, 0.067 mmol) in $CH_2Cl_2$ (3.4 mL) at –40 °C, and the mixture was stirred for 7 h [additional *m*CPBA (17.0 mg, 32.7 mg, and 31.9 mg) was added after 4, 5, and 6 h]. The reaction was quenched on the addition of saturated $NaHCO_3$ aq and extracted with $CH_2Cl_2$. The combined organic layers were dried over $Na_2SO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane-EtOAc 6:5) to afford **45** (15.0 mg, 60%) as a colorless oil. $[\alpha]_D^{21}$ –27.4 (*c* 0.133, $CHCl_3$); IR (neat/NaCl) 3588 (OH), 1717 (C=O), 1653 (C=C), 1224, 1098, 805 $cm^{-1}$; $^1H$ NMR δ 1.25 (s, 3H), 1.26 (s, 3H), 1.37-1.48 (m, 1H), 1.46 (s, 3H), 1.55 (br s, 1H), 1.72 (dd, *J* = 12.0, 15.0 Hz, 1H), 1.82 (ddt, *J* = 5.5, 12.5, 2.5 Hz, 1H), 1.96 (ddd, *J* = 4.5, 6.0, 14.5 Hz, 1H), 2.03 (ddd, *J* = 6.0, 9.0, 14.5 Hz, 1H), 2.09 (ddt, *J* = 1.5, 5.5, 12.5 Hz, 1H), 2.27 (ddt, *J* = 2.0, 5.5, 15.0 Hz, 1H), 2.86 (t, *J* = 6.0 Hz, 1H), 3.17 (d, *J* = 5.5 Hz, 1H), 3.80-3.94 (m, 1H), 5.02 (s, 1H), 5.23 (s, 1H), 5.57 (dd, *J* = 4.0, 8.5 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.59 (tt, *J* = 1.0, 7.5 Hz, 1H), 8.01-8.08 (m, 2H); $^{13}C$ NMR δ 19.0, 19.1, 24.6, 31.0, 34.1, 35.0, 35.9, 58.5, 60.2, 61.0, 62.2, 72.2, 73.9, 111.1, 128.6 (2C), 129.6 (2C), 130.1, 133.2, 150.9, 165.5; MS (FAB+) *m*/*z*: 373 $[M + H]^+$; HRMS (FAB-DFMS) *m*/*z*: $[M + H]^+$ Calcd for $C_{22}H_{29}O_5$ 373.2015; Found 373.2023.

**(3*S*,5*S*)-2-((1*S*,3*S*,4*R*,5*R*)-3,4-Epoxy-5-hydroxy-4-methylcyclohex-1-yl)-5,6-epoxy-6-methylhep-1-en-3-ol (23a)**

NaOMe (1 piece) was added to a stirred solution of **45** (2.4 mg, 0.0064 mmol) in MeOH (0.25 mL) at room temperature, and the mixture was stirred for 21 h [additional NaOMe (1 piece at a time) was added after 1.5, 2.5, and 6 h]. The reaction was quenched by the addition of saturated $NH_4Cl$ aq and extracted with $CH_2Cl_2$. The combined organic layers were dried over $Na_2SO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane-EtOAc 1:3) to afford **23a** (1.6 mg, 94%) as a colorless oil. $[\alpha]_D^{19}$ –30.6 (*c* 0.173, MeOH); IR (neat/NaCl) 3419 (OH), 1647 (C=C), 1446, 1381, 1049 $cm^{-1}$; $^1H$ NMR δ 1.29 (s, 3H), 1.33 (s, 3H), 1.46 (s, 3H), 1.55-1.74 (m, 4H), 1.75-1.94 (m, 2H), 1.94-2.17 (m, 3H), 2.94 (dd, *J* = 4.2, 7.8 Hz, 1H), 3.15 (d, *J* = 5.1 Hz, 1H), 3.77-3.93 (m, 1H), 4.29 (dd, *J* = 3.9, 8.7 Hz, 1H), 4.96 (s, 1H), 5.17 (s, 1H); $^{13}C$ NMR δ 19.0, 19.1, 24.8, 31.3, 34.9, 35.0, 35.3, 58.5, 60.2, 61.4, 62.2, 72.1, 72.3, 109.7, 154.8; MS (FAB+) *m*/*z*: 269 [M +

H]$^+$; HRMS (FAB-DFMS) *m*/*z*: [M + H]$^+$ Calcd for $C_{15}H_{25}O_4$ 269.1753; Found 269.1756.

**(3*S*,5*S*)-2-((1*R*,3*S*,4*S*,5*R*)-5-Angeloyloxy-3,4-epoxy-4-methylcyclohex-1-yl)-5,6-epoxy-6-methylhept-1-en-3-yl angelate (35 = 5)**

$Cs_2CO_3$ (143.4 mg, 0.44 mmol) and $Ang_2O$ (0.050 mL, 0.29 mmol) were added to a stirred solution of **23a** (7.7 mg, 0.029 mmol) in $CH_3CN$ (2.9 mL) at room temperature. The resulting mixture was stirred at the same temperature for 3 days. After the addition of $Cs_2CO_3$ (71.7 mg, 0.22 mmol) and $Ang_2O$ (0.025 mL, 0.15 mmol), stirring was continued for 2 days. $Et_2O$ and $H_2O$ were added to the reaction mixture, and the whole mixture was extracted with $Et_2O$. The combined organic layers were dried over $Na_2SO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane-EtOAc 87:13) to afford **35** (1.4 mg, 11%) as a colorless oil.

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**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Copies of $^1$H and $^{13}$C NMR spectra of all new compounds (PDF).

**References and Notes**

1. (a) Davon, T. K.; Scott, A. I. Handbook of Naturally Occurring Compounds, Academic Press, New York and London, 1972. (b) Breitmaier, E. Terpenes, Wiley-VCH, Weinheim, 2006.

2. Fraga, B. M. *Nat. Prod. Rep.* **2013**, *30*, 1226-1264; **2012**, *29*, 1334-1366; **2011**, *28*, 1580-1610; **2009**, *26*, 1125-1155; **2008**, *25*, 1180-1209; **2007**, *24*, 1350-1381.

3. Onuki, H.; Yamazaki, M.; Nakamura, A.; Hanai, R.; Kuroda, C.; Gong, X.; Shen, Y.; Hirota, H. *J. Nat. Prod.* **2008**, *71*, 520-524.

4. Hirota, H.; Horiguchi, Y.; Kawaii, S.; Kuroda, C.; Hanai, R.; Gong, X. *Nat. Prod. Commun*. **2012**, *7*, 451-454.

5. Kuroda, C.; Inagaki, K.; Chao, X.; Inoue, K.; Okamoto, Y.; Tori, M.; Gong, X.; Hanai, R. *Nat. Prod. Commun.* **2015**, *10*, 823-826.

6. (a) Kuroda, C.; Hanai, R.; Nagano, H.; Tori, M.; Gong, X. *Nat. Prod. Commun.* **2012**, *7*, 539-548. (b) Kuroda, C.; Hanai, R.; Tori, M.; Okamoto, Y.; Saito, Y.; Nagano, H.; Ohsaki, A.; Hirota, H.; Kawahara, T.; Gong, X. *J. Synth. Org. Chem., Japan* **2014**, *72*, 717-725.

7. Hirai, M.; Miyazaki, R.; Mitsui, K.; Kiuchi, K.; Onuki, H.; Hirota, H.; Kuroda, C. *Helv. Chim. Acta* **2015**, *98*, 1035-1060.

8. Weinges, K.; Schwarz, G. *Liebigs Ann. Chem.* **1993**, 811-814.

9. Srikrishna, A.; Hemamalini, P. *J. Org. Chem.* **1990**, *55*, 4883-4887.

10. Sera, S.; Fuganti, C.; Gatti, F. G. *Eur. J. Org. Chem.* **2008**, 1031-1037.

11. The configuration at C(8) of each isomer was determined at a later stage.

12. The configuration at C(10) of each isomer was determined at a later stage.

13. Nakai, K.; Kubo, K.; Yokoya, M.; Saito, N. *Tetrahedron* **2014**, *70*, 6529-6545.

14. Liang, X.; Grue-Sørensen, G.; Månsson, K.; Vedsø, P.; Soor, A.; Stahlhut, M.; Bertelsen, M.; Engell, K. M.; Högberg, T. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5624-5629.

15. Liang, X.; Grue-Sørensen, G.; Peterson, A. K.; Högberg, T. *Synlett* **2012**, *23*, 2647-2652.

16. The optical rotation of synthetic **35** is much smaller than the reported data for natural product **5**. We assume the concentration in the data for **5** (*c* 0.042) in reference 4 was not accurate. For reference, tiglate **27** with same absolute configurations as natural product has similar optical rotation to that of angelate **35** (see experimental section).

17. Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401-404.

18. Zhang, W.; Basak, A.; Kosugi, Y.; Hoshino, Y.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 4389-4391.

19. Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136- 6137.

20. (a) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099-7100. (b) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945-948. (c) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511-3515.