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Asymmetric Total Syntheses of (+)-Cheimonophyllon E and (+)-Cheimonophyllal

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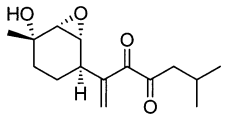
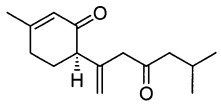
The highly enantiocontrolled total syntheses of natural (+)-cheimonophyllon E **(5)** and (+)-cheimonophyllal (**6**), biologically intriguing oxygenated bisabolane-type sesquiterpenoids, have been completed. The present synthetic strategy featured the use of an asymmetric aldol-type reaction for preparing in the first synthetic step an optically active 6-C-substituted 3-methyl-2-cyclohexenone derivative. Thus, a Mukaiyama aldol reaction of 1-methyl-3-silyloxy-1,3-cyclohexadiene **31** with α,β-unsaturated aldehyde **11** in the presence of a chiral (acyloxy)borane (CAB)-type Yamamoto catalyst **33** proceeded with high levels of both diastereo- and enantioselectivities. The predominant aldol adduct, *syn*-**9**, was transformed into γ,δ-epoxy allylic alcohol **8** by a nine-step sequence, including the substrate-controlled 1,2-reduction of enone, *syn*-**12**, also the epoxidation of allylic alcohol **15**. Epoxy-alcohol **8** underwent 5-*exo*-cyclization in a high regioselective manner under acidic conditions to produce a bicyclic key intermediate (+)-**7**, which was eventually efficiently converted to (+)-cheimonophyllon E (**5**) or (+)-cheimonophyllal (**6**).

Introduction

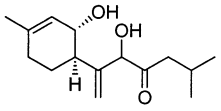
During a screening of the higher fungal metabolites for nematicidal activities, six new bisabolane-type sesquiterpenoids, cheimonophyllons A−E and cheimonophyllal (**1**−**6**), were isolated from the submerged cultures of basidiomycete *Cheimonophyllum candidissimum*.[1] These compounds were found to exhibit not only nematicidal but also antifungal, antibacterial, and cytotoxic activities.[1] Their relative structures have been determined by extensive ^{1}H and ^{13}C NMR spectroscopic analysis.[2] Their absolute stereochemistries have not been established. Among these cheimonophyllons, **5** and **6** possess five or four stereogenic carbons, respectively, in a highly oxygenated 7-oxabicyclo[4.3.0]nonane core skeleton. We have recently reported preliminarily the first total syntheses of (+)- and (−)-cheimonophyllon E (**5**) using an optical resolution strategy; thereby, the previously unknown absolute stereochemistry of **5** has been established.[3] As a result of our continuous interest in synthetic studies on biologically active sesquiterpenoides,[4] we have completed the highly enantioselective syntheses of (+)-cheimonophyllon E (**5**) and (+)-cheimonophyllal (**6**), employing a catalytic asymmetric aldol reaction in the initial stage of their total synthesis. Herein, we describe the complete details of the asymmetric total syntheses of **5** and **6**. The present asymmetric approach relies on the enantioselective construction of the absolute stereochemistry of C-6 (cheimonophyllons numbering), using the chiral Lewis acid catalyzed asymmetric aldol methodology, and the introduction of all remaining stereogenic centers at C-1, -2, -3, and -8 by internal asymmetric inductions.



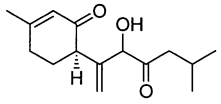
cheimonophyllon A (**1**)



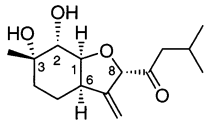
cheimonophyllon B (**2**)



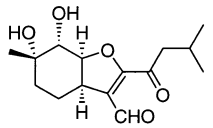
cheimonophyllon C (**3**)



cheimonophyllon D (**4**)



cheimonophyllon E (**5**)



cheimonophyllal (**6**)

Results and Discussion

Synthetic Plan. Our retrosynthesis for cheimonophyllon E (**5**) and cheimonophyllal (**6**) is outlined in

(1) (a) Stadler, M.; Anke, H.; Sterner, O. *J. Antibiot.* **1994**, *47*, 1284−1289. (b) Stadler, M.; Fouron, J.-Y.; Sterner O.; Anke, H. *Z. Naturforsch.* **1995**, *50c*, 473−475.

(2) Stadler, M.; Anke, H.; Sterner, O. *Tetrahedron* **1994**, *50*, 12649−12654.

(3) Preliminary communication on part of the results described here: Takao, K.; Hara, M.; Tsujita, T.; Yoshida, K.; Tadano, K. *Tetrahedron Lett.* **2001**, *42*, 4665−4668.

(4) For our previous results on this subject, see: (a) A formal synthesis of enantiomeric paniculide B. Tadano, K.; Miyake, A.; Ogawa, S. *Tetrahedron* **1991**, *47*, 7259−7270. (b) A total synthesis of (+)-eremantholide A. Takao, K.; Ochiai, H.; Yoshida, K.; Hashizuka, T.; Koshimura H.; Tadano, K.; Ogawa, S. *J. Org. Chem.* **1995**, *60*, 8179−8193. (c) Total synthesis of (−)-verrucarol. Ishihara, J.; Nonaka, R.; Terasawa, Y.; Shiraki, R.; Yabu, K.; Kataoka, H.; Ochiai, Y.; Tadano, *K. J. Org. Chem.* **1998**, *63*, 2679−2688. (d) Total synthesis of (−)-mniopetal E. Suzuki, Y.; Nishimaki, R.; Ishikawa, M.; Murata, T.; Takao, K.; Tadano, K. *J. Org. Chem.* **2000**, *65*, 8595−8607. (e) Total synthesis of (−)-mniopetal F. Suzuki, Y.; Ohara, A.; Sugaya K.; Takao, K.; Tadano, K. *Tetrahedron* **2001**, *57*, 7291−7301.

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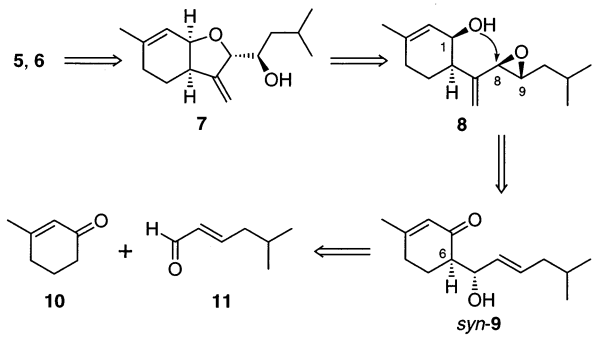
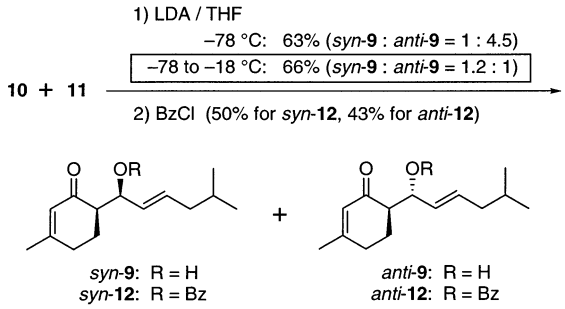
SCHEME 1



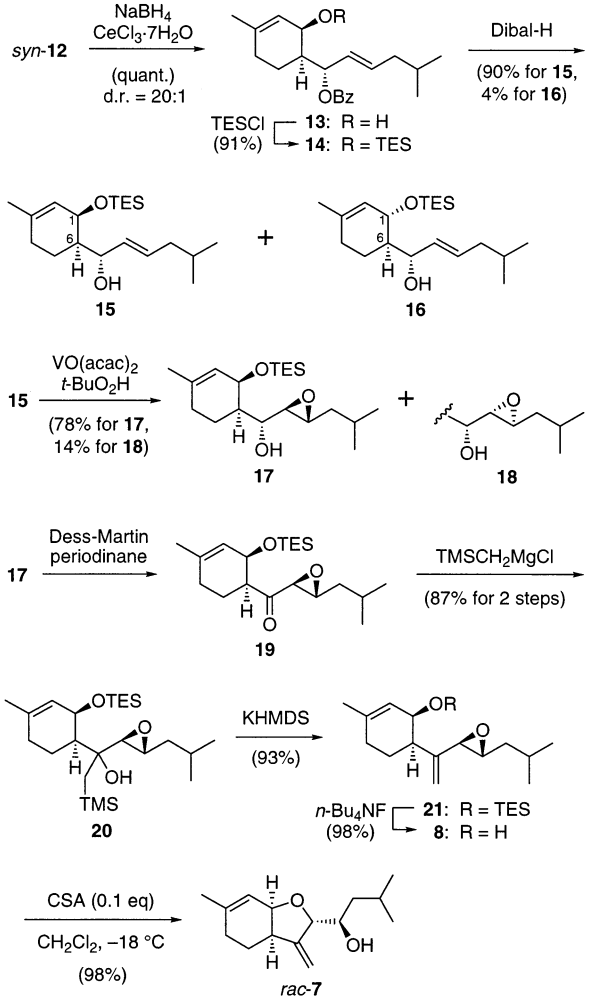
SCHEME 2



Scheme 1. We considered a 7-oxabicyclo[4.3.0]non-4-ene derivative **7**, which possesses the cheimonophyllons skeleton as well as modifiable carbon−carbon double bonds, to be an advanced synthetic intermediate. For the construction of the bicyclic core in **7**, the cyclization of 6-[(α-methylene-*β*,*γ*-epoxy]cyclohexen-1-ol **8** was expected to proceed via 5-*exo-tet* mode,[5] forming a tetrahydrofuran ring exclusively. The three stereogenic centers (C-1, -8, and -9) in **8** could be introduced via stereoselective 1,2-reduction and epoxidation of the cyclohexenone *syn*-**9**, which has a 5-methyl-2-hexen-1-ol as a side chain. The intermediate, *syn*-**9**, in turn could be prepared by the aldol reaction of commercially available 3-methyl-2-cyclohexenone **10** and known (*E*)-5-methyl-2-hexenal **11**.[6] As no information on the absolute stereochemistries of cheimonophyllons was available for us, we first explored the syntheses and establishment of the absolute stereochemistries of both enantiomers (+)- and (−)-**5** through the optical resolution of the key intermediate **7**.

Construction of the Common Bicyclic Core Skeleton of 5 and 6. At the outset, the aldol reaction of **10** and **11** was performed in a racemic manner (Scheme 2). The kinetic enolate derived from **10**, using LDA as a base at −78 °C, reacted with **11** at the same temperature to afford an inseparable mixture of *syn*-**9** and *anti*-**9** in a combined yield of 63%. The ratio of the desired *syn*-**9** to the *anti*-**9**[7] was disappointingly determined to be 1:4.5 (^{1}H NMR analysis). It has been reported that diastereoselectivity in the aldol reaction of cyclohexanone lithium enolate with benzaldehyde depends strongly on the reaction temperaure.[8] In fact, when the aldol reaction mixture was allowed to warm to −18 °C, the ratio of *syn*-**9** and *anti*-**9** was improved to 1.2:1 without a loss of the combined yield (66%). This fact indicated that a warming reaction temperature occurs with the equilibration of the two diastereomers resulting in the preferred formation of *syn*-**9**. Benzoylation of the aldol mixture provided *syn*-**12** and *anti*-**12**, which were cleanly separated by chromatography on silica gel.

SCHEME 3



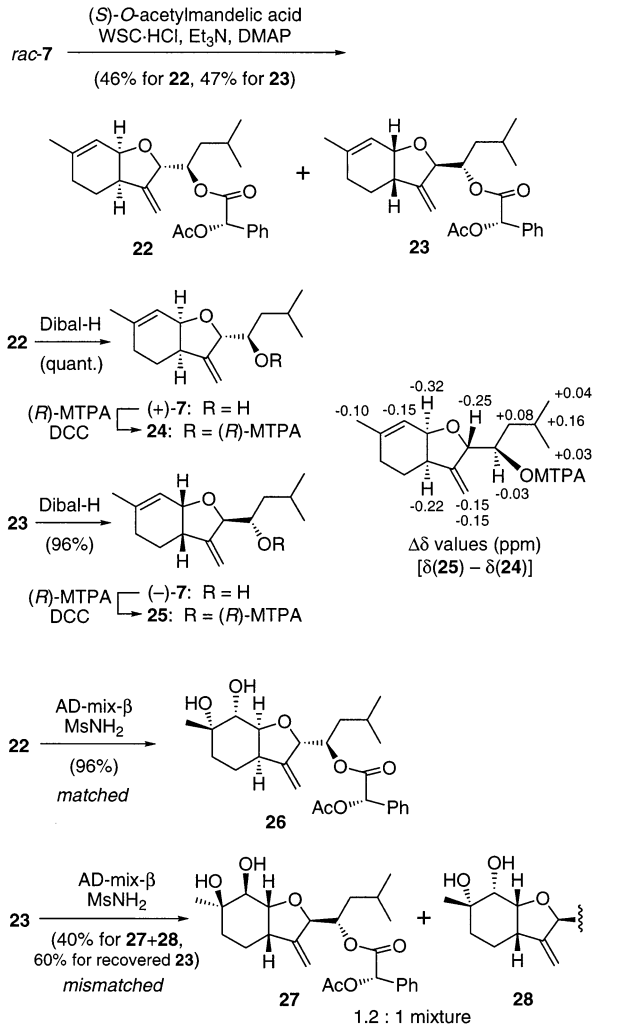
The 1,2-reduction of the enone *syn*-**12** was conducted using Luche's conditions[9] to afford allylic alcohol **13** with a high level of diastereoselectivity (dr = 20:1) (Scheme 3). Protection of **13** as the triethylsilyl (TES) ether followed by reductive cleavage of the benzoyl group in the resulting **14** gave **15** (90%) along with a trace amount (4%) of the diastereomer **16**, which could be removed by chromatography on silica gel. The stereochemistries of C-1 in **15** and **16** were determined by the ^{1}H NMR analysis. A large coupling constant between H-1 and H-6 ($J_{1,6}$ = 8.1 Hz) was observed for **16**, whereas that of **15** was $J_{1,6}$ = 4.0 Hz. This stereochemical outcome of the

(5) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734−736.
(6) Compound **11** was prepared from isovaleraldehyde by a modified literature procedure: (i) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0 °C; (ii) Dibal-H, CH_2Cl_2, −78 °C; (iii) MnO_2, CH_2Cl_2. Vig, O. P.; Bari, S. S.; Puri, S. K.; Dua, D. M. *Indian J. Chem.* **1981**, *20B*, 342−343.
(7) The relative configurations (*syn* or *anti)* in the aldol products were determined by ^{1}H NMR analysis: Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, pp 111−212.
(8) Hirama, M.; Noda, T.; Takeishi, S.; Itô, S. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2645−2646.
(9) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454−5459.

1,2-reduction indicated that the hydride attack occurred preferentially from the less-hindered α-face of the enone face. As expected, the vanadium-catalyzed epoxidation[10] of **15** preferentially provided α,*β* anti-epoxy alcohol **17** (anti-isomer **17**:syn-isomer **18** = 5.6:1). These allylic alcohols **17** and **18** were readily separated by chromatography on silica gel. The introduction of an *exo*-methylene group into **19**, which was prepared by the oxidation of **17** with Dess−Martin periodinane,[11] was achieved efficiently using a Peterson olefination strategy.[12,13] Thus, ketone **19** was reacted with (trimethylsilylmethyl)magnesium chloride to provide **20** as a single diastereomer,[14] which was subjected to *β*-elimination with potassium hexamethyldisilazide (KHMDS) to give *exo*-methylene-epoxide **21**. Desilylation of the TES group in **21** provided *γ*,*δ*-epoxy allylic alcohol **8**. As we anticipated, exposure of **8** to a catalytic amount of camphorsulfonic acid (CSA) in CH_2Cl_2 underwent intramolecular epoxy-ring-opening cyclization in an exclusive 5-*exo*-*tet* mode, resulting in the formation of *rac*-**7** almost quantitatively.[15]

Optical Resolution of Racemic 7. We then investigated the optical resolution of the bicyclic alcohol *rac*-**7**. When *rac*-**7** was acylated with (*S*)-*O*-acetylmandelic acid,[16] diastereomers **22** and **23** were obtained, which were readily separated by chromatography on silica gel (Scheme 4). With the diisobutylaluminum hydride (Dibal-H) reduction of **22** and **23**, optically pure (+)-**7** and (−)-**7**, respectively, were obtained. The assignment of the absolute stereochemistries for both enantiomers was conducted by the following two methods. The esterification of (+)- and (−)-**7** with (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA)[17] afforded the MTPA esters **24** and **25**, respectively. As shown, positive Δ*δ* values [*δ*(**25**) − *δ*(**24**)] were observed for the protons on the right side of the MTPA plane, whereas negative values were observed for those on the left side, indicating that the absolute configuration of **24** was that depicted in Scheme 4.[18,19] In addition, the diastereomer **22** was subjected to the Sharpless asymmetric dihydroxylation conditions using AD-mix-*β*.[20] As a result, α-vicinal diol **26** was obtained as the sole product with excellent

SCHEME 4



stereoselectivity. In contrast, the treatment of another diastereomer **23** under the same dihydroxylation conditions led to an inseparable mixture of *β*- and α-vicinal diols **27** and **28**, respectively, with a complete loss of stereoselectivity (1.2:1) in a low combined yield of 40%.[21] The latter case is considered to be mismatched, resulting from the fact that the substrate and the chiral oxidizing reagent have opposite stereofacial preferences. Consequently, based on the Sharpless mnemonic device,[20,22] the structures of **22** and **23** were established as those depicted. These results also were consistent with the result obtained from the above modified Mosher's ester method.

(10) Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, 4733−4736.

(11) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(12) Anger, D. J. *Org. React.* **1990**, *38*, 1−223.

(13) When ketone **19** was subjected to Wittig methylenation ($Ph_3P{=}CH_2$), the undesired *β*-elimination of TESOH occurred to produce α,*β*:*γ*,*δ*-unsaturated ketone. When the Takai reagent (CH_2Br_2-Zn-$TiCl_4$; Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1698−1702) was employed, the epoxide in **19** was reduced to an olefin.

(14) We did not determined the configuration of the newly introduced stereogenic center in **20**.

(15) The following alternative route to **7** from **17** was investigated. Namely, the benzoate of **17** was desilylated, and the resulting allylic alcohol derivative was subjected to the epoxy ring opening intramolecular cyclization (CSA in CH_2Cl_2). As a result, two cyclization products were obtained with incomplete regioselectivity (5-*exo*:6-*endo* = 6:1). Furthermore, the introduction of an *exo*-methylene group into the 5-*exo*-cyclization product under several conditions did not gave fruitful results.

(16) (a) Whitesell, J. K.; Reynolds, D. *J. Org. Chem.* **1983**, *48*, 3548−3551. (b) Garegg, P. J.; Lindberg, B.; Kvarnström, I.; Svensson, S. C. T. *Carbohydr. Res.* **1985**, *139*, 209−215.

(17) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519.

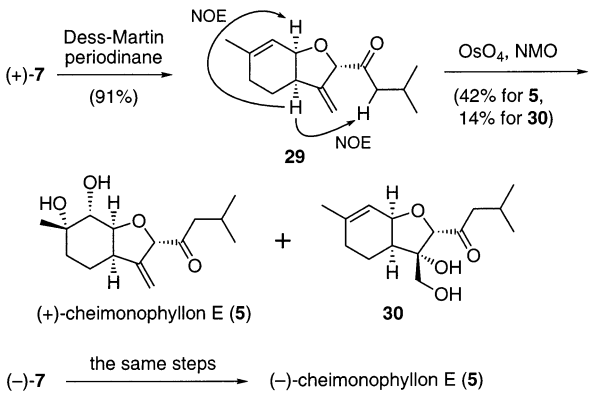
(18) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

(19) (a) Kusumi, T. *J. Synth. Org. Chem. Jpn.* **1993**, *51*, 462−470. (b) Mori, M.; Saitoh, F.; Uesaka, N.; Shibasaki, M. *Chem. Lett.* **1993**, 213−216.

(20) For a leading review on this subject, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

(21) On the other hand, dihydroxylation of **22** and **23** using a standard achiral reagent system (OsO_4−NMO) exclusively provided **26** (84%) and **27** (91%), respectively. Under these conditions as well as the Sharpless asymmetric dihydroxylation conditions, dihydroxylation of the *exo*-methylene group in **22** or **23** was not observed. We concluded that the use of **26** or **27** for the aimed total synthesis was unacceptable as a result of longer reaction steps and more manipulation steps for protection-deprotection.

SCHEME 5



Total Syntheses of (+)- and (−)-Cheimonophyllon E (5). The remaining tasks for the total synthesis of **5** were the oxidation of the hydroxy group at the side chain in **7** and the stereoselective introduction of the vicinal dihydroxy group to the endocyclic double bond. These were achieved as follows (Scheme 5). Dess−Martin oxidation of the stereochemically defined (+)-**7** gave **29**, of which the structure was again confirmed by ^{1}H NMR analysis, including NOE experiments, as shown in Scheme 5. Finally, **29** was subjected to standard dihydroxylation conditions using the OsO_4−NMO system. The vicinal diol was introduced exclusively from the convex face of the bicyclic system to provide a 42% yield of (+)-cheimonophyllon E (**5**).[23] A small amount of the regioisomeric α-diol **30** was also obtained (14%).[24] Analogously, (−)-**7** was converted into (−)-cheimonophyllon E (**5**). The spectroscopic data (IR, ^{1}H, and ^{13}C NMR; HRMS) of synthetic (+)- and (−)-**5** matched well those reported for natural **5**.[2] In addition, the synthetic sample (+)-**5** derived from (+)-**7** had the same specific rotation (sign and magnitude) as that of the natural product. Therefore, the absolute stereochemistry of the natural product was established as (+)-**5**, depicted in Scheme 5.

Catalytic Asymmetric Mukaiyama Aldol Reaction for Diastereoselective Preparation of Enantioenriched *syn*-9. Having assigned the absolute stereochemistry of (+)- and (−)-**5**, our interest was next focused on the enantioselective synthesis of cheimonophyllons by an asymmetric aldol reaction approach. The asymmetric aldol reaction is one of the most promising methods for the enantioselective construction of carbon−carbon bonds.[25] As one of the representative approaches to this subject, the chiral auxiliary-based aldol reactions have been explored extensively, resulting in numerous successes in the synthesis of complex chiral compounds.[25a] On the other hand, catalytic versions of the asymmetric aldol reaction have become major topics in synthetic organic chemistry.[25b,c,e] A number of chiral catalysts have been devised, and their usefulness has been demonstrated through the asymmetric total syntheses of natural products.[26] We were concerned with the catalytic asymmetric Mukaiyama aldol reaction of the trimethylsilyl enol ether **31**, kinetically derived from **10**,[27] with aldehyde **11** (Scheme 6). In some cases, 2-silyloxy-1,3-dienes, such as **31** are known to serve as dienes for [4 + 2] cycloadditions[28] or as substrates for sequential Michael reactions[29] with α,β-unsaturated carbonyl compounds. To confirm the feasibility of the aldol addition of **31** to α,β-unsaturated aldehyde **11**, the mixture was treated with a variety of achiral Lewis acids. The results are summarized in Table 1. In every case, a mixture of *syn*-**9** and *anti*-**9** was obtained in moderate yields. Neither the cycloaddition product(s) nor the Michael adduct(s) was found in the reaction mixture. The ratio of *syn*/*anti* depended on the Lewis acid used, whereas the *anti*-adduct was preferentially formed in all cases.

SCHEME 6

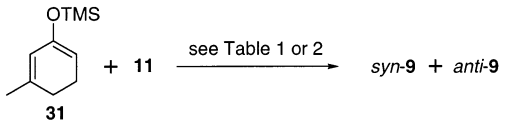


TABLE 1. Mukaiyama Aldol Reaction of 31 with 11

entry	conditions[a]	yield (%)[b]	*syn*:*anti*[c]
1	$TiCl_4$, CH_2Cl_2, −78 °C	53	1:5.8
2	$Cl_2Ti(O\text{-}i\text{-}Pr)_2$, CH_2Cl_2, −18 °C	57	1:4.0
3	$EtAlCl_2$, CH_2Cl_2, −78 °C	76	1:2.3
4	Et_2AlCl, CH_2Cl_2, −78 °C	31	1:2.5
5	$BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C	68	1:3.0
6[d]	TMSOTf, CH_2Cl_2, −78 °C	52	1:1.6

[a] Unless otherwise noted, 1.1 equiv of Lewis acid was used. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] 0.2 equiv of Lewis acid was used.

Since the Mukaiyama aldol reaction of **31** with **11** approved successful, the use of chiral Lewis acid for the enantioselective reaction was next investigated. Yamamoto and co-workers reported the use of a chiral (acyloxy)borane (CAB) complex **32** as the Lewis acid catalyst

(22) A publication on the Sharpless asymmetric dihydroxylation of 2-methylcyclohexene derivatives: Becker, H.; Soler, M. A.; Sharpless, K. B. *Tetrahedron* **1995**, *51*, 1345−1376. In the present case, the methyl group is pointing to the *southwest quadrant* in the mnemonic device.

(23) We noticed that compound **5** decomposed slowly upon storage at an ambient temperature.

(24) We made an effort to improve the yield of **5** in the final dihydroxylation step. AD-mix reagents and the addition of tertiary amine (diisopropylethylamine or 1,4-diazabicyclo[2.2.2]octane; DABCO) to the OsO_4−NMO conditions were both ineffective.

(25) For recent reviews on the asymmetric aldol reaction, see: (a) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1−200. (b) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357−389. (c) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137−1141. (d) Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917−947. (e) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int Ed.* **2000**, *39*, 1352−1374.

(26) For some recent examples for this subject, see: (a) Kobayashi, S.; Furuta, T.; Hayashi, T.; Nishijima, M.; Hanada, K. *J. Am. Chem. Soc.* **1998**, *120*, 908−919. (b) Kim, Y.; Singer, R. A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1261−1263. (c) Kobayashi, S.; Furuta, T. *Tetrahedron* **1998**, *54*, 10275−10294. (d) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H.; Kim, H.-S.; Wataya, Y. *J. Org. Chem.* **1999**, *64*, 6833−6841. (e) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033−10046. (f) Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 10521−10532. (g) Wakabayashi, T.; Mori, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 1372−1375. (h) Kobayashi, S.; Mori, K.; Wakabayashi, T.; Yasuda, S.; Hanada, K. *J. Org. Chem.* **2001**, *66*, 5580−5584.

(27) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1977**, *42*, 1051−1056.

(28) (a) Jung, M. E.; McCombs, C. A. *Tetrahedron Lett.* **1976**, 2935−2938. (b) Rubottom, G. M.; Krueger, D. S. *Tetrahedron Lett.* **1977**, 611−614.

(29) (a) Mukaiyama, T.; Sagawa, Y.; Kobayashi, S. *Chem. Lett.* **1986**, 1821−1824. (b) Asaoka, M.; Ishibashi, K.; Takahashi, W.; Takei, H. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2259−2260. (c) Spitzner, D.; Wagner, P.; Simon, A.; Peters, K. *Tetrahedron Lett.* **1989**, *30*, 547−550. (d) Hagiwara, H.; Okano, A.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2109−2113.

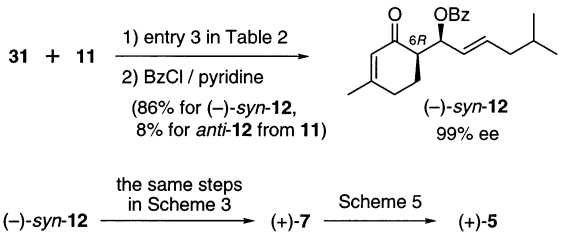
TABLE 2. Asymmetric Mukaiyama Aldol Reaction of 31 with 11

entry	conditions[a]	yield (%)[b]	*syn*:*anti*[c]	ee (%) of *syn*[d] (config)[e]
1	**32** (20 mol %), EtCN, −78 °C	51	1:1.4	24 (*R*)
2	**32** (50 mol %), EtCN,−78 °C	37	1:1.4	18 (*R*)
3	**33** (20 mol %), EtCN, −78 °C	94[f]	10:1	99 (*R*)[g]
4	*ent*-**33** (20 mol %), EtCN, −78 °C	85[f]	10:1	97 (*S*)[g]
5	**34** (10 mol %), Et_2O, −20 °C	15	1:1.2	75 (*S*)

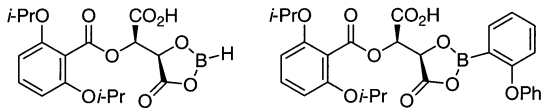
[a] Quenched with diluted hydrochloric acid. [b] Isolated yield. [c] Determined by ^1H NMR analysis. [d] Determined by HPLC analysis using a chiral column. [e] Absolute configuration of C-6 is indicated in parentheses. [f] Combined isolated yields of *syn*- and *anti*-**12** for two steps. [g] ee of *syn*-**12**.

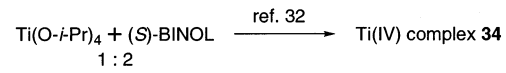
for the highly diastereo- and enantioselective Mukaiyama aldol reaction of silyl enol ethers or ketene silyl acetals with various aldehydes.[30] In addition, a modified CAB complex **33** was also found to increase the enantioselectivity without reducing the chemical yield.[30c] The CAB complexes **32** and **33** were easily prepared from a natural tartaric acid derivative.[31] On the other hand, Keck and co-workers reported that the chiral Ti(IV) complex **34**, derived from Ti(*O*-*i*-Pr)$_4$ and BINOL (1:2), catalyzed the enantioselective addition of Danishefsky's diene to aldehydes with good to excellent asymmetric induction.[32] These chiral Lewis acids **32**−**34** were examined as the catalyst for our aldol reaction of **31** with **11**. The results are shown in Table 2. In the presence of 20 mol % CAB complex **32**, a mixture of the aldol products and the corresponding trimethylsilyl ether was observed. After a workup with diluted hydrochloric acid, the desilylated aldol products *syn*-**9** and *anti*-**9** were obtained (entry 1). Disappointingly, the ratio was 1:1.4 and the enantiomeric excess of the *syn*-adduct was determined to be 24% by chiral HPLC analysis. Despite using 50 mol % **32**, neither the *syn*/*anti* selectivity nor the ee of *syn*-**9** improved (entry 2). Gratifyingly, another CAB complex **33** realized high levels of diastereo- and enantioselectivities for *syn*-**9** (entry 3).[33] It should be emphasized that both excellent enantioselectivity and high *syn* selectivity were observed in this case. The absolute stereochemistry in the predominant enantiomer *syn*-**9** was assigned to be *R* and was

SCHEME 7



confirmed after being transformed into the aforementioned advanced intermediate (+)-**7** (Scheme 7). Interestingly, the minor *anti*-**9** was obtained as an almost racemic form. The observed *syn*-selectivity and *re*-face attack of the nucleophile to the aldehyde carbonyl are well consistent with Yamamoto's explanation in previous reports.[30] The acyclic extended transition state model has been proposed for the high *syn*-selectivity.[30] As for enantioselectivity, it has been pointed out that the benzene ring of the CAB catalyst shields the *si*-face of the coordinating aldehyde, which is fixed by π-stacking and formyl CH-O hydrogen bonds.[31h,34] The use of *ent*-**33**, derived from unnatural D-tartaric acid, as a chiral source afforded the opposite enantiomeric adduct in a similar yield and stereoselectivity (entry 4).[33] On the other hand, the aldol reaction using the Ti(IV) complex **34** gave the adducts in a poor yield along with less satisfactory diastereo- and enantioselectivites (entry 5), precluding further investigation of this catalyst.





Enantioselective Total Syntheses of (+)-Cheimonophyllon E (5) and (+)-Cheimonophyllal (6). As shown in Table 2 (entry 3), practical *syn*-selectivity and exceptionally high enantioselectivity were realized with the CAB catalyst **33**. The conversion of the highly enantioenriched aldol adduct into (+)-cheimonophyllon E **(5)** was then pursued. After benzoylation of the aldol mixture, (−)-*syn*-**12** was isolated in an 86% yield in two steps along with an 8% yield of *anti*-**12** (Scheme 7). The ee of (−)-*syn*-**12** was determined to be 99%, indicating that no racemization occurred during the benzoylation and purification. From (−)-*syn*-**12**, the aforementioned reaction sequence used for the conversion of *syn*-**12** into (+)-**5** via *rac*- and (+)-**7** was repeated to complete the asymmetric total synthesis of (+)-cheimonophyllon E (**5**). The optical rotation of the synthetic sample was confirmed to be well matched again with the natural one.

We also achieved the total synthesis of (+)-cheimonophyllal (**6**). The synthesis of (+)-**6** began with the bicyclic intermediate (+)-**7** (Scheme 8). The vanadium-catalyzed epoxidation of (+)-**7** and the Dess−Martin oxidation of the resulting **35** gave keto-epoxide **36** as a single isomer.

(30) (a) Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041−1042. (b) Furuta, K.; Maruyama, T.; Yamamoto, H. *Synlett* **1991**, 439−440. (c) Ishihara, K.; Maruyama, T.; Mouri, M.; Gao, Q.; Furuta, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3483−3491.

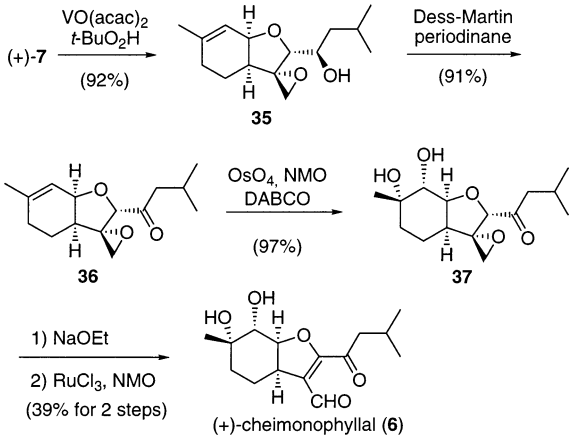
(31) The CAB-type complexes have been widely used as Lewis acids in the asymmetric Diels−Alder, hetero-Diels−Alder, allylation, and Baylis−Hillman reactions; see: (a) Furuta, K.; Miwa, Y.; Iwanaga, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 6254−6255. (b) Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1481−1483. (c) Furuta, K.; Kanematsu, A.; Yamamoto, H.; Takaoka, S. *Tetrahedron Lett.* **1989**, *30*, 7231−7232. (d) Furuta, K.; Mouri, M.; Yamamoto, H. *Synlett* **1991**, 561−562. (e) Gao, Q.; Maruyama, T.; Mouri, M.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 1951−1952. (f) Marshall, J. A.; Tang, Y. *Synlett* **1992**, 653−654. (g) Ishihara, K.; Gao, Q.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 6917−6919. (h) Ishihara, K.; Gao, Q.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10412−10413. (i) Gao, Q.; Ishihara, K.; Maruyama, T.; Mouri, M.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 979−988. (j) Barrett, A. G. M.; Kamimura A. *J. Chem. Soc., Chem. Commun.* **1995**, 1755−1756.

(32) Keck, G. E.; Li, X.-Y.; Krishnamurthy, D. *J. Org. Chem.* **1995**, *60*, 5998−5999. The exact structure of the catalyst **34** has not yet been clarified in detail.

(33) In this case, the desired adduct **9** was inseparable from **33**-derived *o*-phenoxyphenyl-boronic acid. The yield and ee of the product were determined after the conversion of **9** into the benzoates *syn*-**12** and *anti*-**12**, which were isolated in their pure forms.

(34) Corey, E. J.; Rohde, J. J. *Tetrahedron Lett.* **1997**, *38*, 37−40.

SCHEME 8



Under the analogous conditions (OsO_4−NMO) used for the synthesis of **5**, vicinal dihydroxylation of **36** afforded an inseparable mixture of diol **37** and its diastereomer at a ratio of 10:1. The addition of 1,4-diazabicyclo[2.2.2]-octane (DABCO)[35] to these oxidation conditions improved the diastereoselectivity (more than 20:1), and the desired **37** was obtained as an almost single isomer. Finally, compound **37** was subjected to the β-elimination accompanying the epoxy ring opening mediated by sodium ethoxide, followed by the chemoselective oxidation of the resulting allylic alcohol with $RuCl_3$−NMO reagents,[36] eventually providing (+)-cheimonophyllal (**6**).[37] Our synthetic (+)-**6** was identical in all respects to a natural sample ($[\alpha]_D$, IR, ^{1}H and ^{13}C NMR, HRMS).[2]

Conclusions

The highly enantiocontrolled total syntheses of (+)-cheimonophyllon E (**5**) and (+)-cheimonophyllal (**6**) have been accomplished. Highlights of these synthetic ventures include the CAB (**33**)-catalyzed asymmetric Mukaiyama aldol reaction of the 2-silyloxy-1,3-cyclohexadiene derivative **31** and the α,β-unsaturated aldehyde **11** for the enantioselective preparation of the enantioenriched cyclohexenone building block *syn*-**9**; the substrate-induced diastereoselective 1,2-reduction of the enone *syn*-**12** and epoxidation of the allylic alcohol **15**; and the assembly of the bicyclic core skeleton by the highly selective 5-*exo*-*tet* cyclization of the γ,δ-epoxy allylic alcohol **8**. Our asymmetric synthesis of (+)-cheimonophyllon E (**5**) was accomplished in 13 steps with a 16% overall yield from the known achiral α,β-unsaturated aldehyde **11** and the synthesis of (+)-cheimonophyllal (**6**) in 16 steps with a 14% overall yield.

Experimental Section[38]

Melting points are uncorrected. Specific rotations were measured in a 10-mm cell. ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ solution with tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ solution. Thin-layer chromatography (TLC) was performed on Kieselgel 60 F_{254} plates (Merck). The crude reaction mixtures and extractive materials were purified by chromatography on Daisogel IR-60 (Daiso) or Wakogel C-300 (Wako). Unless otherwise described, reactions were carried out at ambient temperature. Combined organic extracts were dried over anhydrous Na_2SO_4. Solvents were removed from the reaction mixture or combined organic extracts by concentration under reduced pressure using an evaporator with a water bath at 35−45 °C.

Mixture of *rel*-(6*R*)-6-[(1*S* and *R*,2*E*)-1-Hydroxy-5-methyl-2-hexenyl]-3- methyl-2-cyclohexen-1-one (*syn*-9 and *anti*-9). The following reaction was carried out under Ar. To a cooled (0 °C) stirred solution of *i*-Pr_2NH (2.8 mL, 20 mmol) in THF (20 mL) was added *n*-BuLi (1.54 M solution in hexane, 11.5 mL, 18.4 mmol). After being stirred at 0 °C for 30 min, the mixture was cooled to −78 °C, and **10** (2.10 mL, 18.1 mmol) was added. The mixture was stirred at −78 °C for 30 min and then warmed to −18 °C, and a solution of **11** (2.03 g, 18.1 mmol) in THF (20 mL) was added. After being stirred at −18 °C for 15 min, the mixture was quenched with saturated aqueous NH_4Cl (3 mL), diluted with EtOAc (200 mL), and washed with saturated aqueous NH_4Cl (200 mL × 3). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:8) to provide 2.64 g (66%) of an inseparable mixture (1.2:1) of *syn*-**9** and *anti*-**9** as a colorless oil: TLC R_f 0.35 (EtOAc/hexane, 1:3); IR 3450, 1670, 1650 cm^{-1}; ^{1}H NMR δ 0.86 (d, 3 H, J = 6.6 Hz), 0.88 (d, 3 H, J = 6.6 Hz), 1.62 (m, 1 H), 1.81−2.51 (m, 7 H), 1.96 (s, 3 H), 4.24 (t, 1 H × 5/11, J = 8.3 Hz, H-1 of the side chain at C-6 in *anti*-**9**), 4.43 (dd, 1 H × 6/11, J = 3.5, 7.0 Hz, H-1 of the side chain at C-6 in *syn*-**9**), 5.41 (m, 1 H × 5/11), 5.49 (m, 1 H × 6/11), 5.67 (m, 1 H), 5.89 (s, 1 H); ^{13}C NMR signals attributable to *syn*-**9** δ 22.2, 22.3, 23.7, 24.2, 28.1, 30.9, 41.6, 50.2, 72.8, 126.9, 130.3, 132.1,163.5, 201.7; signals attributable to *anti*-**9** δ 22.2, 22.4, 24.1, 25.3, 28.1, 30.8, 41.6, 50.2, 74.2, 126.7, 130.5, 133.4, 163.9, 203.3; HRMS calcd for $C_{14}H_{22}O_2$ (M^+) m/z 222.1620, found 222.1619.

***rel*-(6*R*)-6-[(1*S*,2*E*)- (*syn*-12) and *rel*-(6*R*)-6-[(1*R*,2*E*)-1-Benzoyloxy-5-methyl- 2-hexenyl]-3-methyl-2-cyclohexen-1-one (*anti*-12).** To a cooled (0 °C) stirred solution of the 1.2:1 mixture of *syn*-**9** and *anti*-**9** (2.64 g, 11.9 mmol) in pyridine (50 mL) was added benzoyl chloride (2.8 mL, 24 mmol). The mixture was stirred for 2.5 h and diluted with EtOAc (200 mL). The resulting mixture was washed with 1 M aqueous HCl (200 mL), saturated aqueous $NaHCO_3$ (200 mL), and saturated brine (200 mL), successively. The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:16) to provide 1.93 g (50%) of *syn*-**12** and 1.67 g (43%) of *anti*-**12**. Compound *syn*-**12** was obtained as a colorless oil: TLC R_f 0.55 (EtOAc/hexane, 1:3); IR 1720, 1670 cm^{-1}; ^{1}H NMR δ 0.86 (d, 6 H, J = 6.6 Hz), 1.62 (m, 1 H), 1.91−1.96 (m, 2 H), 1.96 (s, 3 H), 2.10−2.26 (m, 2 H), 2.37−2.44 (m, 2 H), 2.54 (dt, 1 H, J = 10.7, 4.5 Hz), 5.56 (ddt, 1 H, J = 15.4, 6.1, 1.0 Hz), 5.74 (ddt, 1 H, J = 15.4, 0.7, 7.1 Hz), 5.89 (d, 1 H, J = 1.2 Hz), 6.07 (br dd, 1 H, J = 6.1, 4.5 Hz), 7.38−7.55 (m, 3 H), 7.98−8.02 (m, 2 H); ^{13}C NMR δ 22.21, 22.24, 22.9, 24.2, 28.1, 30.2, 41.5, 49.7, 72.4, 126.7, 127.1, 128.2 × 2, 129.5 × 2, 130.5, 132.7, 133.6, 162.0, 165.3, 197.2; HRMS calcd for $C_{21}H_{26}O_3$ (M^+) m/z 326.1882, found 326.1883. Compound *anti*-**12** was obtained as a colorless oil: TLC R_f 0.61 (EtOAc/hexane, 1:3); IR 1720, 1670 cm^{-1}; ^{1}H NMR δ 0.85 (d, 3 H, J = 6.6 Hz), 0.86 (d, 3 H, J = 6.6 Hz), 1.63 (m, 1 H), 1.91−1.97 (m, 3 H), 1.95 (s, 3 H), 2.19 (m, 1 H), 2.32−2.36 (m, 2 H), 2.76 (dt, 1 H, J = 11.2, 5.1 Hz), 5.53 (ddt, 1 H, J = 15.4, 6.4,1.2 Hz), 5.82 (ddt, 1 H, J = 15.4,1.0, 7.3 Hz), 5.87 (brd, 1 H, J = 1.5 Hz), 6.06 (brdd, 1 H, J = 6.4, 5.1 Hz), 7.41−7.58 (m, 3 H), 8.03−8.07 (m, 2 H); ^{13}C NMR δ 22.21, 22.24, 23.5, 24.2, 28.1, 30.0, 41.6, 49.2, 73.9, 126.1, 126.6, 128.3 × 2, 129.5 × 2, 130.5, 132.8, 134.2, 161.7, 165.3, 197.6; HRMS calcd for $C_{21}H_{26}O_3$ (M^+) m/z 326.1882, found 326.1874.

(35) Erdik, E.; Kâhya, D.; Daskapan, T. *Synth. Commun.* **1998**, *28*, 1−7.

(36) Sharpless, K. B.; Akashi, K.; Oshima, K. *Tetrahedron Lett.* **1976**, 2503−2506.

(37) As compared to **5**, compound **6** was much more unstable and decomposed slowly upon storage even in a freezer.

(38) The numbering adopted for the nomenclatures of the compounds described in the Experimental Section is in accord with the IUPAC rules and is not in accord with that used in the text.

Mixture of *rel*-(1*R* and *S*,6*S*)-6-[(1*S*,2*E*)-1-Benzoyloxy-5-methyl-2-hexenyl]- 3-methyl-2-cyclohexen-1-ol (13). To a cooled (−78 °C) stirred solution of *syn*-**12** (1.93 g, 5.91 mmol) in MeOH (40 mL) was added $CeCl_3 \cdot 7H_2O$ (6.71 g, 18.0 mmol). After the mixture stirred at −78 °C for 15 min, $NaBH_4$ (340 mg, 8.99 mmol) was added to the solution. The mixture was stirred at −18 °C for 1 h, diluted with EtOAc (200 mL), and washed with H_2O (200 mL × 3). The organic layer was dried and concentrated in vacuo to provide crude **13** (1.94 g) as an inseparable diastereomeric mixture (20:1), which was used directly in the next step. In a small scale experiment, crude **13** was purified by column chromatography on silica gel (EtOAc/hexane, 1:10) and obtained as a colorless oil: TLC R_f 0.56 (EtOAc/hexane, 1:3); IR 3500, 1720 cm^{-1}; ^1H NMR for the major isomer δ 0.86 (d, 3 H, J = 6.6 Hz), 0.88 (d, 3 H, J = 6.6 Hz), 1.55−1.86 (m, 4 H), 1.69 (s, 3 H), 1.88−2.03 (m, 4 H), 4.15 (m, 1 H), 5.57−5.65 (m, 3 H), 5.92 (m, 1 H), 7.41−7.56 (m, 3 H), 8.05−8.08 (m, 2 H); ^{13}C NMR for the major isomer δ 19.4, 22.3 × 2, 23.4, 28.1, 30.6, 41.7, 43.8, 64.4, 77.0, 123.0, 128.2, 128.3 × 2, 129.5 × 2, 130.8, 132.7, 134.8, 140.0, 165.9; HRMS calcd for $C_{21}H_{28}O_3$ (M^+) m/z 328.2039, found 328.2036.

Mixture of *rel*-(3*R* and *S*,4*R*)-4-[(1*S*,2*E*)-1-Benzoyloxy-5-methyl-2-hexenyl]- 1-methyl-3-triethylsilyloxy-1-cyclohexene (14). To a cooled (0 °C) stirred solution of crude **13** obtained above (20:1 mixture, 1.94 g) in DMF (40 mL) were added imidazole (2.42 g, 35.5 mmol) and TESCl (3.0 mL, 18 mmol). The mixture was stirred at 0 °C for 2 h, diluted with EtOAc (200 mL), and washed with saturated aqueous NH_4Cl (200 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:45) to provide 2.37 g (91% from *syn*-**12**) of an inseparable mixture (20:1) of **14** as a colorless oil: TLC R_f 0.78 (EtOAc/hexane, 1:6); IR 1720 cm^{-1}; ^1H NMR for the major isomer δ 0.59 (q, 6 H, J = 8.1 Hz), 0.86 (d, 3 H, J = 6.4 Hz), 0.88 (d, 3 H, J = 6.4 Hz), 0.96 (t, 9 H, J = 8.1 Hz), 1.58−1.78 (m, 4 H), 1.68 (s, 3 H), 1.90−2.04 (m, 4 H), 4.19 (m, 1 H), 5.48−5.73 (m, 3 H), 5.82 (dt, 1 H, J = 14.0, 7.0 Hz), 7.40−7.56 (m, 3 H), 8.02−8.07 (m, 2 H); ^{13}C NMR for the major isomer δ 5.9 × 3, 7.0 × 3, 19.3, 22.3, 22.4, 23.3, 28.1, 30.7, 41.9, 44.7, 65.0, 77.1, 123.7, 128.2 × 2, 128.6, 129.5 × 2, 131.1, 132.6, 134.1, 138.7, 165.9; HRMS calcd for $C_{27}H_{42}O_3Si$ (M^+) m/z 442.2903, found 442.2894.

***rel*-(3*R*,4*R*)-(15) and *rel*-(3*S*,4*R*)-4-[(1*S*,2*E*)-1-Hydroxy-5-methyl-2-hexenyl]-1-methyl-3-triethylsilyloxy-1-cyclohexene (16).** The following reaction was carried out under Ar. To a cooled (−78 °C) stirred solution of **14** (20:1 mixture, 2.20 g, 4.97 mmol) in CH_2Cl_2 (40 mL) was added Dibal-H (1.0 M solution in toluene, 11 mL, 11 mmol). The mixture was stirred at −78 °C for 1.5 h and quenched with H_2O (2 mL). The precipitated solids were removed by filtration through a Celite pad and washed well with CH_2Cl_2. The combined filtrate and washings were concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:40) to provide 1.51 g (90%) of **15** and 63.7 mg (4%) of **16**. Compound **15** was obtained as a colorless oil: TLC R_f 0.59 (EtOAc/hexane, 1:8); IR 3500 cm^{-1}; ^1H NMR δ 0.63 (q, 6 H, J = 7.9 Hz), 0.89 (d, 6 H, J = 6.6 Hz), 0.96 (t, 9 H, J = 7.9 Hz), 1.44 (m, 1 H), 1.59−1.66 (m, 3 H), 1.68 (s, 3 H), 1.72−2.09 (m, 4 H), 3.87 (br s, 1 H, OH), 4.30 (t, 1 H, J = 4.0 Hz), 4.45 (brd, 1 H, J = 4.8 Hz), 5.44 (ddt, 1 H, J = 15.4,4.8, 1.2 Hz), 5.49 (brd, 1 H, J = 4.0 Hz), 5.69 (ddt, 1 H, J = 15.4,1.0, 7.1 Hz); ^{13}C NMR δ 5.5 × 3, 6.8 × 3, 15.8, 22.3 × 2, 23.4, 28.3, 30.9, 41.9, 44.4, 70.4, 74.4, 123.0, 129.6, 132.2, 139.8; HRMS calcd for $C_{20}H_{38}O_2Si$ (M^+) m/z 338.2641, found 338.2657. Compound **16** was obtained as a colorless oil: TLC R_f 0.54 (EtOAc/hexane, 1:8); IR 3450 cm^{-1}; ^1H NMR δ 0.66 (q, 6 H, J = 8.1 Hz), 0.90 (d, 6 H, J = 6.6 Hz), 0.99 (t, 9 H, J = 8.1 Hz), 1.40 (m, 1 H), 1.55−1.75 (m, 3 H), 1.67 (s, 3 H), 1.80−2.10 (m, 4 H), 2.48 (br s, 1 H, OH), 4.25 (m, 1 H), 4.33 (br d, 1 H, J = 8.1 Hz), 5.31 (br s, 1 H), 5.51 (dd, 1 H, J = 15.4, 5.9 Hz), 5.66 (ddt, 1 H, J = 15.4, 1.1, 7.0 Hz); ^{13}C NMR δ 5.3 × 3, 6.9 × 3, 21.4, 22.3, 22.4, 23.2, 28.3, 29.8, 41.8, 46.8, 69.6, 72.9, 125.4, 130.7, 132.0, 136.7; HRMS calcd for $C_{20}H_{38}O_2Si$ (M^+) m/z 338.2641, found 338.2640.

***rel*-(3*R*,4*R*)-4-[(1*R*,2*R*,3*R*)- (17) and *rel*-(3*R*,4*R*)-4-[(1*R*,2*S*,3*S*)-2,3-Epoxy-1- hydroxy-5-methylhexanyl]-1-methyl-3-triethylsilyloxy-1-cyclohexene (18).** The following reaction was carried out under Ar. To a cooled (0 °C) stirred solution of **15** (1.51 g, 4.46 mmol) in CH_2Cl_2 (30 mL) were added $VO(acac)_2$ (60.1 mg, 0.23 mmol) and *t*-BuOOH (5.13 M solution in toluene, 2.65 mL, 13.6 mmol). The mixture was stirred at 0 °C for 2.5 h, quenched with saturated aqueous $NaHSO_3$ (2 mL), and diluted with EtOAc (150 mL). The resulting mixture was washed with saturated aqueous $NaHSO_3$ (150 mL), saturated aqueous $NaHCO_3$ (150 mL), and saturated brine (150 mL), successively. The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:40) to provide 1.24 g (78%) of **17** and 217 mg (14%) of **18**. Compound **17** was obtained as a colorless oil: TLC R_f 0.47 (EtOAc/hexane, 1:10); IR 3500 cm^{-1}; ^1H NMR δ 0.62 (q, 6 H, J = 7.8 Hz), 0.95 (t, 9 H, J = 7.8 Hz), 0.99 (d, 6 H, J = 6.8 Hz), 1.39 (m, 1 H), 1.49−1.58 (m, 2 H), 1.65−2.11 (m, 5 H), 1.69 (s, 3 H), 2.81 (dd, 1 H, J = 6.1, 2.2 Hz), 3.02 (ddd, 1 H, J = 7.1, 4.7, 2.2 Hz), 3.70 (dd, 1 H, J = 6.1, 1.8 Hz), 3.80 (s, 1 H, OH), 4.28 (t, 1 H, J = 3.7 Hz), 5.48 (br d, 1 H, J = 3.7 Hz); ^{13}C NMR δ 5.4 × 3, 6.8 × 3, 16.5, 22.5, 22.9, 23.5, 26.5, 30.6, 41.0, 41.2, 56.9, 58.7, 70.4, 74.1, 122.7, 139.8; HRMS calcd for $C_{20}H_{38}O_3Si$ (M^+) m/z 354.2590, found 354.2590. Compound **18** was obtained as a colorless oil: TLC R_f 0.32 (EtOAc/hexane, 1:10); IR 3450 cm^{-1}; ^1H NMR δ 0.61 (q, 6 H, J = 7.9 Hz), 0.95 (t, 9 H, J = 7.9 Hz), 0.97 (d, 3 H, J = 6.7 Hz), 0.98 (d, 3 H, J = 6.7 Hz), 1.41−1.46 (m, 2 H), 1.61 (m, 1 H), 1.69 (s, 3 H), 1.78−2.05 (m, 5 H), 2.85 (dd, 1 H, J = 3.9, 2.2 Hz), 2.98 (dt, 1 H, J = 2.2, 5.9 Hz), 3.38 (br, 1 H, OH), 3.82 (m, 1 H), 4.30 (t, 1 H, J = 3.9 Hz), 5.50 (br d, 1 H, J = 3.9 Hz); ^{13}C NMR δ 5.4 × 3, 6.7 × 3, 17.5, 22.4, 22.9, 23.7, 26.4, 30.6, 40.9, 43.0, 53.9, 60.7, 69.2, 72.7, 122.7, 139.7; HRMS calcd for $C_{20}H_{38}O_3Si$ (M^+) m/z 354.2590, found 354.2586.

***rel*-(3*R*,4*S*)-4-[(2*S*,3*R*)-2,3-Epoxy-5-methylhexanoyl]-1-methyl-3-triethylsilyloxy-1-cyclohexene (19).** To a cooled (0 °C) stirred solution of **17** (1.24 g, 3.50 mmol) in CH_2Cl_2 (14 mL) was added Dess−Martin periodinane (1.65 g, 3.89 mmol). The mixture was stirred for 1 h and diluted with EtOAc (100 mL). The resulting mixture was washed with saturated aqueous $Na_2S_2O_3$ (100 mL), saturated aqueous $NaHCO_3$ (100 mL), and saturated brine (100 mL), successively. The organic layer was dried and concentrated in vacuo to provide crude **19** (1.17 g), which was used directly in the next step. In a small scale experiment, crude **19** was purified by column chromatography on silica gel (EtOAc/hexane, 1:40) and obtained as a colorless oil: TLC R_f O.27 (EtOAc/hexane, 1:20); IR 1720 cm^{-1}; 1 H NMR δ 0.56 (q, 6 H, J = 7.9 Hz), 0.92 (t, 9 H, J = 7.9 Hz), 0.98 (d, 3 H, J = 6.6 Hz), 0.99 (d, 3 H, J = 6.6 Hz), 1.42−1.56 (m, 3 H), 1.71 (s, 3 H), 1.78−2.08 (m, 4 H), 2.63 (ddd, 1 H, J = 11.1, 4.6, 2.8 Hz), 3.07 (ddd, 1 H, J = 6.7, 4.9, 2.2 Hz), 3.48 (d, 1 H, J = 2.2 Hz), 4.64 (t, 1 H, J = 4.6 Hz), 5.53 (dt, 1 H, J = 4.6,1.5 Hz); ^{13}C NMR δ 5.5 × 3, 7.0 × 3, 18.7, 22.5, 23.0, 23.5, 26.5, 29.5, 41.2, 51.1, 58.1,58.6, 66.0, 123.0, 138.9, 206.2; HRMS calcd for $C_{20}H_{36}O_3Si$ (M^+) m/z 352.2434, found 352.2427.

***rel*-(3*R*,4*S*)-4-[(2*S*,3*R*)-2,3-Epoxy-1-hydroxy-5-methyl-1-(trimethylsilylmethyl)hexanyl]-1-methyl-3-triethylsilyloxy-1-cyclohexene (20).** The following reaction was carried out under Ar. To a cooled (0 °C) stirred solution of crude **19** obtained above (1.17 g) in THF (25 mL) was added $TMSCH_2MgCl$ (1.0 M solution in Et_2O, 7.0 mL, 7.0 mmol). The mixture was stirred at 0 °C for 1 h, quenched with H_2O (2 mL), and diluted with EtOAc (100 mL). The resulting mixture was washed with saturated aqueous NH_4Cl (100 mL × 3). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:50) to provide 1.34 g (87% from **17)** of **20** as a colorless oil: TLC R_f 0.47 (EtOAc/hexane, 1:20); IR 3500 cm^{-1}; ^1H NMR δ 0.08 (s, 9 H), 0.62 (q, 6 H, J = 7.8 Hz), 0.95 (t, 9 H, J = 7.8 Hz), 0.98 (d, 6 H, J = 6.1 Hz), 1.17−1.65 (m, 5 H),

1.19 (d, 1 H, J = 14.6 Hz), 1.36 (d, 1 H, J = 14.6 Hz), 1.70 (s, 3 H), 1.80−2.10 (m, 3 H), 2.52 (d, J = 2.4 Hz, 1 H), 3.21 (ddd, 1 H, J = 7.6, 2.8, 2.4 Hz), 4.08 (s, 1 H, OH), 4.52 (m, 1 H), 5.54 (br d, 1 H, J = 4.4 Hz); ^{13}C NMR δ 0.02 × 3, 5.2 × 3, 6.3 × 3, 17.7, 22.1, 22.5, 22.8, 25.0, 27.4, 30.7, 40.8, 44.3, 54.9, 63.7, 66.9, 73.7, 122.1, 139.5; HRMS calcd for $C_{24}H_{48}O_3Si_2$ (M^+) m/z 440.3142, found 440.3126.

***rel*-(3*R*,4*R*)-4-[(2*R*,3*R*)-2,3-Epoxy-5-methyl-1-methylenehexanyl]-1-methyl-3-triethylsilyloxy-1-cyclohexene (21).** The following reaction was carried out under Ar. To a cooled (0 °C) stirred solution of **20** (1.34 g, 3.04 mmol) in THF (25 mL) was added KHMDS (0.5 M solution in toluene, 16 mL, 8.0 mmol). The mixture was stirred at 0 °C for 1.5 h, quenched with saturated aqueous NH_4Cl (2 mL), and diluted with EtOAc (150 mL). The resulting mixture was washed with saturated aqueous NH_4Cl (100 mL × 3). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:50) to provide 0.988 g (93%) of **21** as a colorless oil: TLC R_f 0.58 (EtOAc/hexane, 1:20); ^{1}H NMR δ 0.55 (q, 6 H, J = 7.9 Hz), 0.92 (t, 9 H, J = 7.9 Hz), 0.97 (d, 3 H, J = 6.6 Hz), 0.99 (d, 3 H, J = 6.6 Hz), 1.43−1.51 (m, 3 H), 1.68 (s, 3 H), 1.83 (m, 1 H), 1.94−2.08 (m, 4 H), 2.79 (dt, 1 H, J = 2.1, 5.8 Hz), 3.09 (d, 1 H, J = 2.1 Hz), 4.06 (m, 1 H), 5.00 (s, 1 H), 5.21 (s, 1 H), 5.52 (br d, J = 3.9 Hz, 1 H); ^{13}C NMR δ 5.2 × 3, 6.9 × 3, 22.1, 22.5, 23.0, 23.4, 26.4, 31.0, 41.4, 41.5, 58.9, 60.0, 66.1, 113.9, 124.3, 137.6, 145.9; HRMS calcd for $C_{21}H_{38}O_2Si$ (M^+) m/z 350.2641, found 350.2637.

***rel*-(1*R*,6*R*)-6-[(2*R*,3*R*)-2,3-Epoxy-5-methyl-1-methylenehexanyl]-3-methyl-2-cyclohexen-1 -ol (8).** To a cooled (0 °C) stirred solution of **21** (0.988 g, 2.82 mmol) in THF (15 mL) was added n-Bu_4NF (1.0 M solution in THF, 4.5 mL, 4.5 mmol). The mixture was stirred at 0 °C for 3 h, quenched with saturated aqueous $NaHCO_3$ (2 mL), and diluted with Et_2O (150 mL). The resulting mixture was washed with saturated aqueous $NaHCO_3$ (100 mL) and saturated brine (100 mL × 2), successively. The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:8) to provide 0.652 g (98%) of **8** as a colorless oil: TLC R_f 0.21 (EtOAc/hexane, 1:10); IR 3450 cm^{-1}; ^{1}H NMR δ 0.97 (d, 3 H, J = 6.7 Hz), 0.99 (d, 3 H, J = 6.7 Hz), 1.33 (m, 1 H), 1.40−1.60 (m, 2 H), 1.73 (s, 3 H), 1.77−1.93 (m, 3 H), 2.04−2.08 (m, 2 H), 2.22 (br, 1 H, OH), 2.89 (dt, 1 H, J = 2.0, 6.1 Hz), 3.10 (d, 1 H, J = 2.0 Hz), 4.13 (m, 1 H), 5.05 (s, 1 H), 5.30 (s, 1 H), 5.66 (m, 1 H); ^{13}C NMR δ 21.2, 22.5, 22.9, 23.4, 26.3, 30.9, 41.2, 42.3, 59.0, 59.6, 64.5, 113.7, 122.2, 139.7, 146.4; HRMS calcd for $C_{15}H_{24}O_2$ (M^+) m/z 236.1776, found 236.1783.

***rel*-(1*R*,6*R*,8*S*)-8-[(1*R*)-1-Hydroxy-3-methylbutyl]-3-methyl-7-methylene-9-oxabicyclo[4.3.0]non-2-ene (*rac*-7).** To a cooled (−18 °C) stirred solution of **8** (0.538 g, 2.28 mmol) in CH_2Cl_2 (10 mL) was added CSA (52.9 mg, 0.23 mmol). The mixture was stirred at −18 °C for 1 h, quenched with saturated aqueous $NaHCO_3$ (1 mL), and diluted with EtOAc (50 mL). The resulting mixture was washed with saturated aqueous $NaHCO_3$ (50 mL × 2) and saturated brine (50 mL), successively. The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:10) to provide 0.529 g (98%) of *rac*-**7** as a colorless oil: TLC R_f 0.42 (EtOAc/hexane, 1:3); IR 3450, 1670 cm^{-1}; ^{1}H NMR δ 0.90 (d, 3 H, J = 6.6 Hz), 0.95 (d, 3 H, J = 6.6 Hz), 1.28 (ddd, 1 H, J = 13.9, 9.5, 3.1 Hz), 1.49 (ddd, 1 H, J = 13.9, 10.2, 4.4 Hz), 1.67 (s, 3 H), 1.72−1.85 (m, 4 H), 2.03 (m, 1 H), 2.20 (m, 1 H), 2.78 (m, 1 H), 3.72 (dt, 1 H, J = 10.2, 3.1 Hz), 4.38 (m, 1 H), 4.57 (m, 1 H), 5.01 (t, 1 H, J = 2.2 Hz), 5.04 (t, 1 H, J = 2.2 Hz), 5.42 (br, 1 H); ^{13}C NMR δ 21.6, 22.9, 23.7, 23.8, 24.5, 25.9. 40.7, 41.1, 72.0, 75.9, 82.9, 105.5, 121.5, 139.0, 150.4; HRMS calcd for $C_{15}H_{24}O_2$ (M^+) m/z 236.1776, found 236.1777.

Asymmetric Mukaiyama Aldol Reaction of 31 with 11. The following reaction was carried out under Ar. A solution of (2*R*,3*R*)-2-*O*-(2,6-diisopropoxybenzoyl)tartaric acid (666 mg, 1.80 mmol) and *o*-phenoxyphenylboronic acid (382 mg, 1.79 mmol) in propionitrile (24 mL) was stirred for 30 min to prepare **33**. The solution was cooled to −78 °C, and **11** (1.00 g, 8.92 mmol) and **31** (2.46 g, 13.4 mmol) were added. After being stirred at −78 °C for 2.5 h, the mixture was quenched with 0.2 M aqueous HCl (10 mL), warmed to room temperature, and stirred for an additional 1 h. The resulting mixture was diluted with EtOAc (100 mL) and washed with H_2O (50 mL × 3). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) to provide 2.61 g of crude mixture (10:1) of *syn*-**9** and *anti*-**9** as a pale yellow oil, which was contaminated with *o*-phenoxyphenylboronic acid but used to the next step without further purification: HPLC analysis (column, Daicel Chiralcel OD+OD-H, EtOH/hexane = 1:60, flow rate = 0.7 mL/min); t_R (min) = 22.5 for (6*R*)-*syn*-**9**, 23.2 for (6*S*)-*syn*-**9**, 24.2 and 25.8 for *anti*-**9**.

As described for the preparation of (±)-**12**, the crude mixture of *syn*-**9** and *anti*-**9** obtained above (2.61 g) was treated with benzoyl chloride (2.6 mL, 22 mmol) in pyridine (40 mL) to provide 2.50 g (86% from **11**) of (−)-*syn*-**12** and 247 mg (8% from **11**) of *anti*-**12**: HPLC analysis (column, Daicel Chiralcel OD+OD-H, EtOH/hexane = 1:30, flow rate = 0.7 mL/min); t_R (min) = 21.3 for (−)-*syn*-**12**, 25.3 for (+)-*syn*-**12**. Compound (−)-*syn*-**12** was determined to be 99% ee: $[\alpha]^{25}_D$ −139 (*c* 1.94, $CHCl_3$).

Preparation of (+)-7 from (−)-*syn*-12. Compound (−)-*syn*-**12** was converted into (+)-**7** by the same reaction sequence used for the preparation of *rac*-**7**: (−)-**13** $[\alpha]^{25}_D$ −81.8 (*c* 2.04, $CHCl_3$), (−)-**14** $[\alpha]^{24}_D$ −89.1 (*c* 3.34, $CHCl_3$), (−)-**15** $[\alpha]^{24}_D$ −138 (*c* 2.11, $CHCl_3$), (+)-**16** $[\alpha]^{24}_D$ +6.6 (*c* 1.60, $CHCl_3$), (−)-**17** $[\alpha]^{24}_D$ −107 (*c* 2.93, $CHCl_3$), (−)-**18** $[\alpha]^{24}_D$ −139 (*c* 2.04, $CHCl_3$), (−)-**19** $[\alpha]^{26}_D$ −131 (*c* 1.53, $CHCl_3$), (−)-**20** $[\alpha]^{24}_D$ −84.1 (*c* 3.12, $CHCl_3$), (−)-**21** $[\alpha]^{25}_D$ −120 (*c* 2.30, $CHCl_3$), (−)-**8** $[\alpha]^{24}_D$ −153 (*c* 1.54, $CHCl_3$), (+)-**7** $[\alpha]^{24}_D$ +147 (*c* 4.64, $CHCl_3$).

(1*R*,6*R*,8*S*)-3-Methyl-8-(3-methylbutanoyl)-7-methylene-9-oxabicyclo-[4.3.0]non-2-ene (29). To a cooled (0 °C) stirred solution of (+)-**7** (26.9 mg, 0.114 mmol) in CH_2Cl_2 (2 mL) was added Dess−Martin periodinane (97.7 mg, 0.230 mmol). The mixture was stirred at 0 °C for 15 h and diluted with EtOAc (20 mL). The resulting mixture was washed with saturated aqueous $Na_2S_2O_3$ (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and saturated brine (10 mL), successively. The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:35) to provide 24.2 mg (91%) of **29** as a colorless oil: TLC R_f 0.81 (EtOAc/hexane, 1:3); $[\alpha]^{23}_D$ +67.4 (*c* 3.27, $CHCl_3$); IR 1720, 1670 cm^{-1}; ^{1}H NMR δ 0.89 (d, 3 H, J = 6.7 Hz), 0.93 (d, 3 H, J = 6.7 Hz), 1.71 (s, 3 H), 1.75−1.86 (m, 3 H), 2.02 (m, 1 H), 2.15 (m, 1 H), 2.35 (dd, 1 H, J = 17.3, 7.1 Hz), 2.55 (dd, 1 H, J = 17.3, 6.3 Hz), 2.75 (m, 1 H), 4.66 (m, 1 H), 4.70 (m, 1 H), 5.08 (t, 1 H, J = 2.3 Hz), 5.15 (t, 1 H, J = 2.3 Hz), 5.50 (m, 1 H); ^{13}C NMR δ 22.5, 22.6, 23.4, 23.7, 24.0, 26.8, 40.7, 46.6, 76.5, 84.5, 107.0, 120.2, 140.4, 148.6, 209.6; HRMS calcd for $C_{15}H_{22}O_2$ (M^+) m/z 234.1620, found 234.1618.

(1*S*,2*R*,3*S*,6*R*,8*S*)-2,3-Dihydroxy-3-methyl-8-(3-methylbutanoyl)-7-methylene-9-oxabicyclo[4.3.0]nonane ((+)-cheimonophyllon E) ((+)-5) and (1*R*,6*S*,7*S*,8*S*)-7-Hydroxymethyl-3-methyl-8-(3-methylbutanoyl)-9-oxabicyclo-[4.3.0]non-2-en-7-ol (30). To a cooled (0 °C) stirred solution of **29** (96.3 mg, 0.411 mmol) in acetone and H_2O (2:1, v/v, 2 mL) were added OsO_4 (0.05 M solution in *t*-BuOH, 0.82 mL, 0.041 mmol) and NMO (96.1 mg, 0.823 mmol). The mixture was stirred at 0 °C for 2.5 h, quenched with 10 wt % aqueous $NaHSO_3$ (1 mL), and diluted with EtOAc (20 mL). The resulting mixture was washed with 10 wt % aqueous $NaHSO_3$ (10 mL × 2) and saturated brine (10 mL), successively. The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) to provide 45.7 mg (42%) of (+)-**5** and 15.4 mg (14%) of **30**. Compound (+)-**5** was obtained as a colorless oil: TLC R_f 0.08 (EtOAc/hexane, 1:3); $[\alpha]^{22}_D$ +129 (*c* 1.46, $CHCl_3$);

IR 3460, 3380,1720, 1670 cm^{-1}; ^1H NMR δ 0.88 (d, 3 H, J = 6.7 Hz), 0.91 (d, 3 H, J = 6.7 Hz), 1.25 (s, 3 H), 1.45 (m, 1 H), 1.56−1.80 (m 2 H), 2.12 (m, 2 H), 2.35 (dd, 1 H, J = 17.3, 7.0 Hz), 2.52 (dd, 1 H, J = 17.3, 6.6 Hz), 2.93 (m, 1 H), 3.16 (d, 1 H, J = 8.0 Hz), 4.36 (t, 1 H, J = 8.0 Hz), 4.71 (q, 1 H, J = 2.2 Hz), 5.04 (dd, 1 H, J = 2.8, 2.2 Hz), 5.24 (dd, 1 H, J = 2.8, 2.2 Hz); ^{13}C NMR δ 18.6, 22.4, 22.6, 23.4, 26.7, 31.8, 41.4, 46.6, 72.3, 74.8, 83.8, 85.2, 106.9, 145.9, 208.4; HRMS calcd for $C_{15}H_{24}O_4$ (M^+) m/z 268.1675, found 268.1675. Compound **30** was obtained as white crystals, mp 153−155 °C; TLC R_f 0.17 (EtOAc/hexane, 1:3); $[\alpha]^{19}_D$ −119 (c 0.515, $CHCl_3$); IR ($CHCl_3$) 3450, 1700 cm^{-1}; ^1H NMR δ 0.93 (d, 6 H, J = 6.6 Hz), 1.27 (m, 1 H), 1.67 (m, 1 H), 1.77 (s, 3 H), 1.96−2.10 (m, 3 H), 2.17 (m, 1 H), 2.55 (dd, 1 H, J = 18.1, 6.8 Hz), 2.71 (dd, 1 H, J = 18.1, 6.6 Hz), 3.73 (d, 1 H, J = 11.6 Hz), 3.94 (d, 1 H, J = 11.6 Hz), 4.24 (s, 1 H),4.76 (m, 1 H), 5.72 (m, 1 H); ^{13}C NMR δ 19.7, 22.6, 22.7, 23.2, 23.7, 29.2, 47.2, 49.2, 64.5, 75.4, 83.8, 88.2, 118.7, 141.2, 216.4; HRMS calcd for $C_{14}H_{21}O_3$ ($M^+ - CH_2OH$) m/z 237.1491, found 237.1489.

(1*R*,6*S*,7*S*,8*R*)-8-[(1*R*)-1-Hydroxy-3-methylbutyl]-3-methyl-9-oxaspiro[bicyclo[4.3.0]non-2-ene-7,3′-oxirane] (35). As described for the preparation of **17** and **18** from **15**, (+)-**7** (35.9 mg, 0.152 mmol) was treated with $VO(acac)_2$ (2.0 mg, 7.5,mol) and *t*-BuOOH (6.63 M solution in isooctane, 46 μL, 0.31 mmol) in CH_2Cl_2 (2 mL) to provide 35.2 mg (92%) of **35** as a colorless oil: TLC R_f 0.62 (EtOAc/hexane, 1:2); $[\alpha]^{22}_D$ +33.2 (c 1.11, $CHCl_3$); IR 3480 cm^{-1}; ^1H NMR δ 0.92 (d, 3 H, J = 5.9 Hz), 0.94 (d, 3 H, J = 5.9 Hz), 1.74 (s, 3 H), 1.25−1.38 (m, 2 H), 1.42−1.72 (m, 3 H), 1.82−1.99 (m, 2 H), 2.05 (m, 1 H), 2.95 (d, 1 H, J = 4.4 Hz), 3.01 (d, 1 H, J = 4.4 Hz), 3.82−3.89 (m, 2 H), 4.51 (t, 1 H, J = 4.3 Hz), 5.57 (m, 1 H); ^{13}C NMR δ 21.3, 21.5, 23.7, 23.8, 24.2, 28.4, 41.7, 42.8, 48.8, 69.3, 70.0, 73.3, 77.6, 119.5, 140.7; HRMS calcd for $C_{15}H_{24}O_3$ (M^+) m/z 252.1726, found 252.1724.

(1*R*,6*S*,7*S*,8*S*)-3-Methyl-8-[3-methylbutanoyl]-9-oxaspiro-[bicyclo[4.3.0]non-2-ene-7,3′-oxirane] (36). As described for the preparation of **29**, **35** (53.7 mg, 0.213 mmol) was treated with Dess−Martin periodinane (182 mg, 0.429 mmol) in CH_2Cl_2 (4 mL) to provide 48.3 mg (91%) of **36** as a colorless oil: TLC R_f 0.68 (EtOAc/hexane, 1:3); $[\alpha]^{23}_D$ −66.4 (c 2.42, $CHCl_3$); IR 1720 cm^{-1}; ^1H NMR δ 0.921 (d, 3 H, J = 6.7 Hz), 0.924 (d, 3 H, J = 6.7 Hz), 1.78 (s, 3 H), 1.47−1.75 (m, 2 H), 1.93−2.01 (m, 3 H), 2.14 (m, 1 H), 2.37 (dd, 1 H, J = 17.8, 6.7 Hz), 2.62 (dd,1 H, J = 17.8, 6.5 Hz), 2.86 (d,1 *H*, J = 4.1 Hz), 2.99 (d, 1 H, J = 4.1 Hz), 4.45 (s, 1 H), 4.77 (t, 1 H, J = 4.7 Hz), 5.67 (m, 1 H); ^{13}C NMR δ 21.5, 22.5, 22.7, 23.2, 23.7, 28.5, 41.4, 46.2, 47.6, 66.9, 75.4, 81.2, 118.8, 141.3, 208.5; HRMS calcd for $C_{15}H_{22}O_3$ (M^+) m/z 250.1569, found 250.1572.

(1*S*,2*R*,3*S*,6*S*,7*S*,8*S*)-2,3-Dihydroxy-3-methyl-8-[3-methylbutanoyl]-9- oxaspiro[bicyclo[4.3.0]nonane-7,3′-oxirane] (37). To a cooled (0 °C) stirred solution of **36** (30.6 mg, 0.122 mmol) in acetone and H_2O (2:1, v/v, 2 mL) were added OsO_4 (0.05 M solution in *t*-BuOH, 0.13 mL, 6.5 μmol), NMO (42.9 mg, 0.366 mmol), and DABCO (42.0 mg, 0.374 mmol). The mixture was stirred for 4 h, quenched with 10 wt % aqueous $NaHSO_3$ (1 mL), and diluted with EtOAc (20 mL). The resulting mixture was washed with 10 wt % aqueous $NaHSO_3$ (10 mL × 2) and saturated brine (10 mL), successively. The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (acetone/hexane, 1:2) to provide 33.9 mg (97%) of **37** as a colorless oil: TLC R_f 0.08 (EtOAc/hexane, 1:1); $[\alpha]^{21}_D$ +10.0 (c 1.78, $CHCl_3$); IR 3450, 1720 cm^{-1}; ^1H NMR δ 0.92 (d, 3 H, J = 6.6 Hz), 0.93 (d, 3 H, J = 6.6 Hz), 1.32 (s, 3 H), 1.26−1.43 (m, 2 H), 1.69−1.90 (m, 2 H), 2.15 (m, 1 H), 2.23 (br, 1 H, OH), 2.33 (dd, 1 H, J = 18.0, 7.3 Hz), 2.42 (m, 1 H), 2.57 (dd, 1 H, J = 18.0, 6.6 Hz), 2.86 (d, 1 H, J = 4.2 Hz), 2.90 (br, 1 H, OH), 2.95 (d, 1 H, J = 4.2 Hz), 3.56 (d, 1 H, J = 5.9 Hz), 4.37 (s, 1 H), 4.55 (t, 1 H, J = 5.9 Hz); ^{13}C NMR δ 19.5, 22.5, 22.6, 23.2, 25.7, 32.5, 39.5, 47.6, 48.1, 65.2, 71.4, 73.4, 80.8, 82.7, 207.2; HRMS calcd for $C_{15}H_{24}O_5$ (M^+) m/z 284.1624, found 284.1627.

(1*S*,2*R*,3*S*,6*R*)-2,3-Dihydroxy-7-formyl-3-methyl-8-[3-methylbutanoyl]-9-oxabicyclo[4.3.0]non-7-ene ((+)-Cheimonophyllal) ((+)-6). To a cooled (0 °C) stirred solution of **37** (33.9 mg, 0.119 mmol) in EtOH (2 mL) was added NaOEt (1.0 M solution in EtOH, 0.18 mL, 0.18 mmol). The mixture was stirred for 15 min, diluted with saturated aqueous $NaHCO_3$ (15 mL), and extracted with CH_2Cl_2 (15 mL × 3). The combined extracts were dried and concentrated in vacuo to provide crude allylic alcohol (33.9 mg), which was used immediately to the next step. To a cooled (0 °C) stirred solution of crude allylic alcohol obtained above (33.9 mg) in DMF (2 mL) were added NMO (27.9 mg, 0.238 mmol) and $RuCl_3 \cdot nH_2O$ (4.9 mg). The mixture was stirred at 0 °C for 4 h, diluted with EtOAc (20 mL), and washed with saturated brine (10 mL × 3). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 2:3) to provide 13.2 mg (39%) of (+)-**6** as a yellow oil: TLC R_f 0.68 (acetone/hexane, 1:1); $[\alpha]^{21}_D$ +106 (c 0.565, $CHCl_3$); IR 3420, 1700, 1650 cm^{-1}; ^1H NMR δ 0.98 (d, 6 H, J = 6.6 Hz), 1.32 (s, 3 H), 1.55 (ddd, 1 H, J = 13.7, 8.6, 4.9 Hz), 1.74 (ddd, 1 H, J = 13.7, 8.5, 4.5 Hz), 1.85 (m, 1 H), 2.10 (m, 1 H), 2.22 (m, 1 H), 2.62 (dd, 1 H, J = 17.0, 6.7 Hz), 2.68 (dd, 1 H, J = 17.0, 7.0 Hz), 3.53 (dt, 1 H, J = 9.6, 6.7 Hz), 3.58 (d, 1 H, J = 6.8 Hz), 4.76 (dd, 1 H, J = 9.6, 6.8 Hz), 10.22 (s, 1 H); ^{13}C NMR δ 20.8, 22.5 × 2, 24.1, 26.8, 33.7, 40.1, 49.3, 70.9, 74.8, 88.0, 125.4, 161.8, 189.0, 195.2; HRMS calcd for $C_{15}H_{22}O_5$ (M^+) m/z 282.1467, found 282.1464.

Supporting Information Available: Experimental procedures for the preparation of **22**, **23**, (+)-**7**, (−)-**7**, **24**−**28**; ^1H and ^{13}C NMR spectra of *syn*-**9** + *anti*-**9**, *syn*-**12**, *anti*-**12**, **13**−**23**, **8**, **7**, **29**, **30**, synthetic **5**, **35**−**37**, synthetic **6**; ^1H NMR spectra of **24**−**28** including COSY ($^1H-^1H$) of **24** and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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