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Total synthesis of (+)-cheimonophyllon E, a bisabolane sesquiterpenoid

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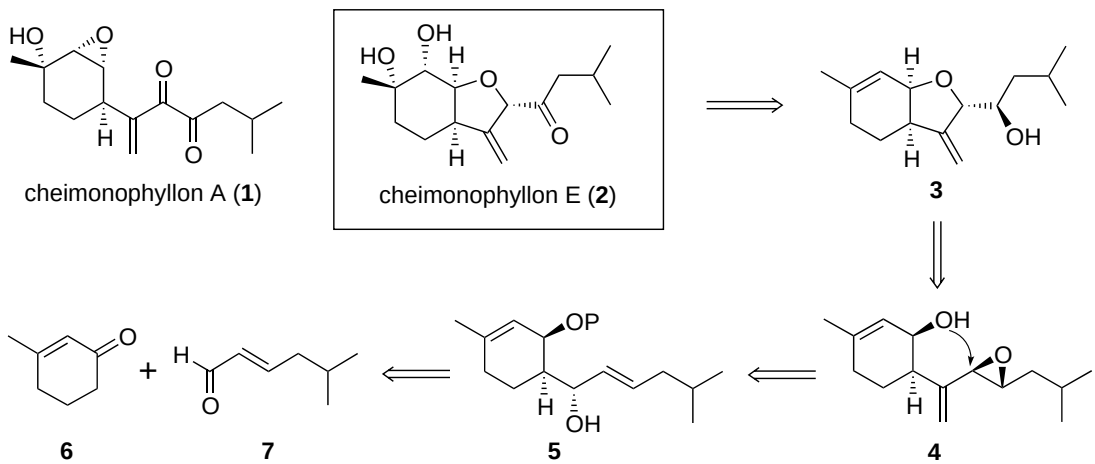
Abstract—Total synthesis of (±)-cheimonophyllon E was accomplished starting from 3-methyl-2-cyclohexen-1-one. Also, synthesis of (+)-cheimonophyllon E, the natural enantiomer, was achieved through optical resolution of a key intermediate in the racemic synthesis.

Six new bisabolane-type sesquiterpenoids, cheimonophyllons A (**1**)–E (**2**) (Scheme 1) and cheimonophyllal, were isolated from the culture fluid of the basidiomycete *Cheimonophyllum candidissimum*.[1] These natural products exhibit nematicidal, antifungal, antibacterial, and cytotoxic activities.[1] Their structures have been determined by spectroscopic analysis; however, the absolute stereochemistry remained unknown.[2] Among them, cheimonophyllon E (**2**) possesses five stereogenic carbons in a highly oxygenated 7-oxabicyclo[4.3.0]nonane core skeleton. Our interest in their intriguing structures and biological activities led us to study the synthesis of the cheimonophyllons. We describe here the first total synthesis of cheimonophyllon E, thereby establishing its previously unknown absolute stereochemistry.

Our retrosynthetic analysis of **2** is shown in Scheme 1. A 7-oxabicyclo[4.3.0]non-4-ene derivative **3** was considered to be an advanced synthetic intermediate for **2**. For the construction of the bicyclic core in **3**, we anticipated that a cyclization of γ,δ-epoxy allylic alcohol **4** would proceed regioselectively for the construction of a tetrahydrofuran ring in **3**. The key intermediate **4** would be obtained from a 2-cyclohexen-1-ol derivative **5**. Then, we expected the allylic alcohol **5** to be prepared by the aldol reaction of commercially



Scheme 1.

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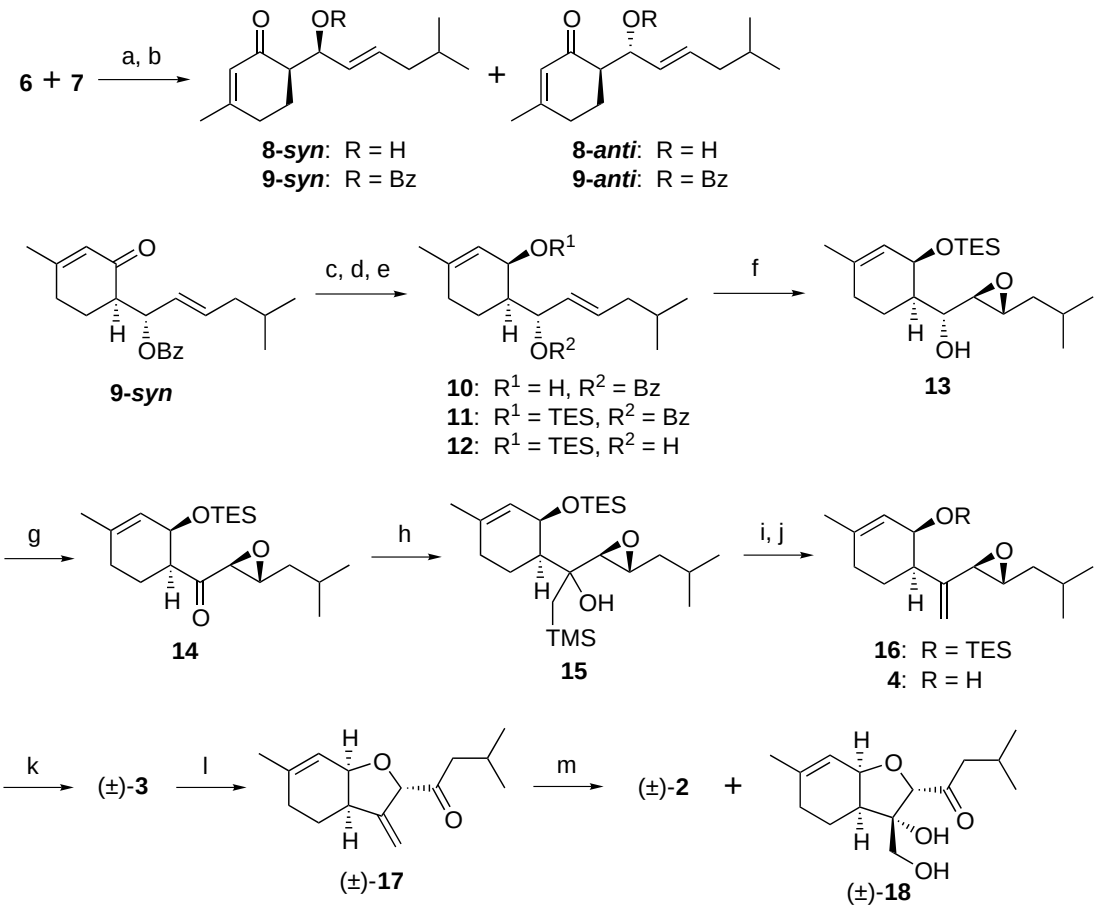
available 3-methyl-2-cyclohexen-1-one (**6**) and (*E*)-5-methyl-2-hexenal (**7**).[3]

First, we explored a racemic synthesis of cheimonophyllon E (**2**). The aldol reaction of enone **6** and aldehyde **7** using LDA as a base at −78°C afforded an inseparable mixture of **8-*syn*** and **8-*anti*** in a combined yield of 63% (Scheme 2).† The relative configurations (*syn* or *anti*) in the aldols were determined by ^{1}H NMR analysis.[4] The ratio of the desired **8-*syn*** to the isomer **8-*anti*** was determined to be 1:4.5. It has been reported that diastereoselectivity in the aldol reaction of cyclohexanone lithium enolate with benzaldehyde depends strongly on the reaction temperature.[5] In fact, when the reaction mixture of **6** and **7** was allowed to warm to −18°C, the *syn*/*anti* stereoselectivity was improved to 1.2:1, and the yield of the diastereomeric mixture was 66%. Benzoylation of the aldol mixture provided **9-*syn*** and **9-*anti***, which were cleanly separated by chromatography on silica gel. The 1,2-reduction of the enone in **9-*syn*** was conducted using the Luche's conditions[6] to afford the desired allylic alcohol **10** with a high level of diastereoselectivity (d.r. = 20:1). By a protection–deprotection sequence, **10** was converted into **12** (corresponding to **5**: P = triethylsilyl = TES). A vanadium-catalyzed oxidation[7] of the allylic alcohol **12** predominantly provided *anti*-α,β-epoxy alcohol **13** (*anti*/*syn* = 5.6:1). Introduction of the *exo*-methylene group in the tetrahydrofuran ring in **2** was carried out by a Peterson olefination strategy.[8] Thus, **13** was oxidized with Dess–Martin periodinane,[9] and the resulting ketone **14** was reacted with $TMSCH_2MgCl$ to provide **15** as a single diastereomer, which was then subjected to β-elimination with KHMDS to give *exo*-methylene-epoxide **16**. Desilylation of the TES group in **16** with *n*-Bu_4NF gave **4**. Exposure of **4** to a catalytic amount of CSA underwent intramolecular cyclization as a result of the stereoselective epoxy ring opening. As expected, the 5-*exo* cyclization product (±)-**3** was obtained exclusively in an almost quantitative yield. Oxidation of **3** gave ketone **17**, which was finally subjected to OsO_4–NMO oxidation. Stereoselective dihydroxylation occurred

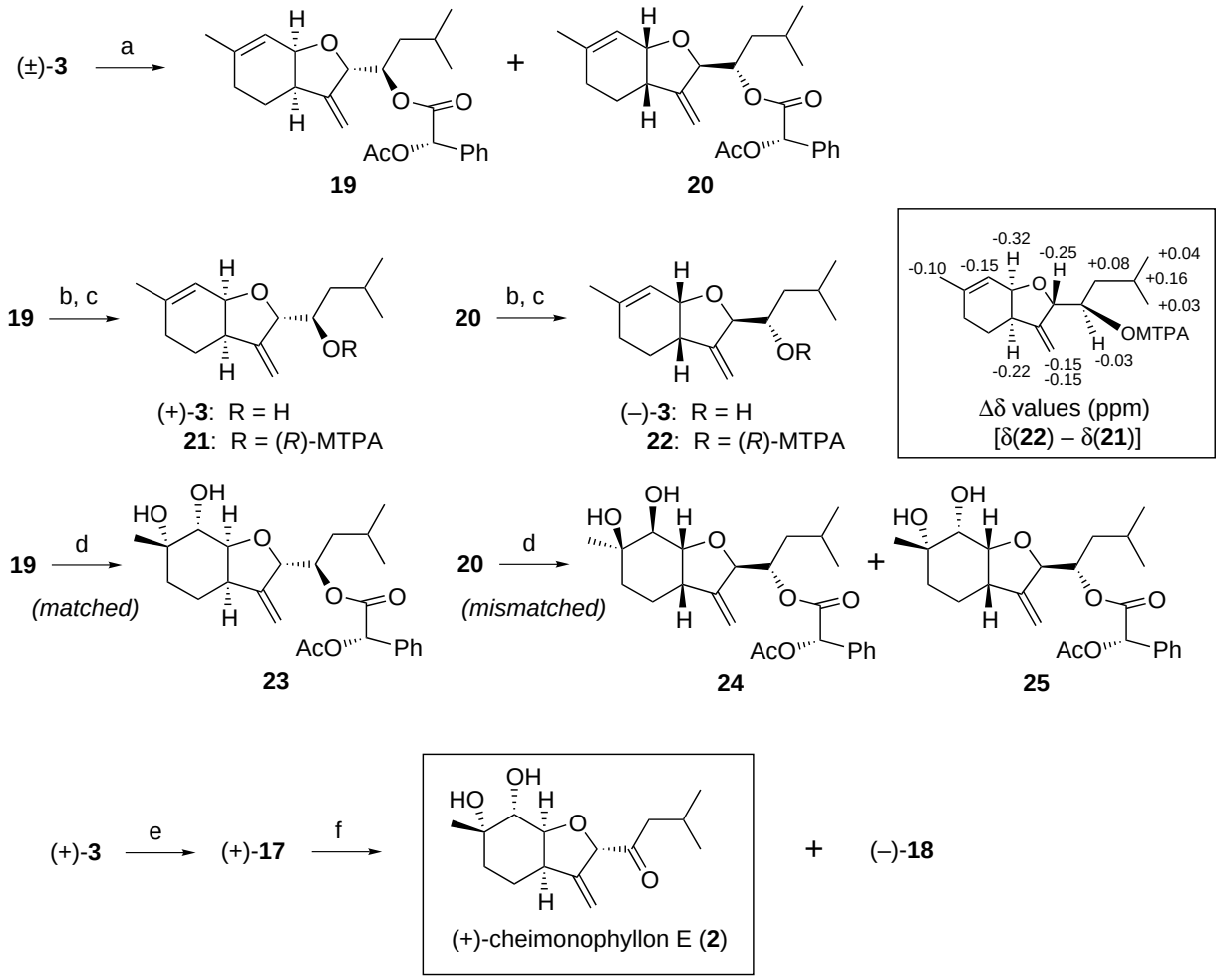


Scheme 2. *Reagents and conditions*: (a) LDA, THF, −18°C, 66% (1.2:1 mixture); (b) BzCl, pyridine, 50% for **9-*syn*** and 43% for **9-*anti***; (c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0°C, quant. (d.r. = 20:1); (d) imidazole, TESCl, DMF, 0°C, 91% (d.r. = 20:1); (e) Dibal-H, CH_2Cl_2, −78°C, 90% for **12** and 4% for its diastereomer; (f) $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2, 0°C, 78% for **13** and 14% for *syn*-epoxide; (g) Dess–Martin periodinane, CH_2Cl_2; (h) $TMSCH_2MgCl$, THF, 0°C, 87% for two steps; (i) KHMDS, THF, 0°C, 93%; (j) *n*-Bu_4NF, THF, 0°C, 98%; (k) CSA, CH_2Cl_2, −18°C, 98%; (l) Dess–Martin periodinane, CH_2Cl_2, 0°C, 98%; (m) OsO_4, NMO, acetone–*t*-BuOH–H_2O, 0°C, 48% for **2** and 19% for **18**.

† All new compounds were fully characterized by spectroscopic means [^{1}H (270 or 300 MHz in $CDCl_3$) and ^{13}C (75 MHz in $CDCl_3$) NMR, IR] and gave satisfactory HRMS. Yields refer to homo-geneous samples purified by chromatography on silica gel.

preferentially at the endocyclic double bond to provide (±)-cheimonophyllon E (**2**) along with a small amount of the regioisomeric diol (±)-**18**. The spectroscopic data (IR, ^{1}H and ^{13}C NMR, LR and HRMS) of synthetic (±)-**2** were well matched with those reported for natural **2**.[2]

Having established an efficient route to racemic **2**, we next focused our attention on the synthesis of an optically active **2**. When racemic (±)-**3** was acylated with (*S*)-*O*-acetylmandelic acid,[10] readily separable diastereomers **19** and **20** were isolated (Scheme 3). Dibal-H reduction of **19** and **20** produced optically pure (+)- and (−)-**3**, respectively. Assignment of the absolute stereochemistries for both enantiomers was carried out by the following two methods. Condensation of (+)- or (−)-**3** with (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA)[11] afforded MTPA esters **21** or **22**, respectively. As shown, the difference in the chemical shift (ppm) [$\Delta\delta = \delta$(**22**)–δ(**21**)] in the ^{1}H NMR spectra of **22** and **21** indicated that the absolute configuration of **21** was that depicted in Scheme 3.[12,13] In addition, **19** was subjected to a Sharpless asymmetric dihydroxylation[14] with AD-mix-β to produce **23** with excellent stereoselectivity in a high yield of 96%.‡ By contrast, treatment of **20** under the same conditions led to an inseparable mixture (1.2:1) of **24** and **25** in low yield.‡ This is a mismatched case resulting from the fact that the substrate and the chiral reagent have opposite stereofacial preferences. Consequently, on the basis of the Sharpless' mnemonic device,[14,15] the structures of **19** and **20** were determined to be those shown. These results are consistent with the result obtained from the modified Mosher's method. Enantiomerically pure (+)-**3** was eventually converted into (+)-cheimonophyllon E (**2**) using the same reaction sequence used for the racemic synthesis.§ Synthetic optically active **2** had an identical specific rotation with that



Scheme 3. *Reagents and conditions*: (a) (*S*)-*O*-acetylmandelic acid, WSC·HCl, Et_3N, 4-DMAP, CH_2Cl_2, 46% for **19** and 47% for **20**; (b) Dibal-H, CH_2Cl_2, −78°C, quant. for (+)-**3**, or 96% for (−)-**3**; (c) (*R*)-MTPA, DCC, 4-DMAP, CH_2Cl_2, 16% for **21** and 52% for recovered (+)-**3**, or 17% for **22** and 48% for recovered (−)-**3**; (d) AD-mix-β, $MsNH_2$, *t*-BuOH–H_2O, 0°C, 22 h, 96% for **23**, or 40% for the mixture (1.2:1) of **24** and **25** and 60% for recovered **20**; (e), (f) same as (l); (m) in Scheme 2.

‡ Treatment of **19** or **20** with standard achiral reagents (OsO_4–NMO) gave exclusively **23** (84%) or **24** (91%), respectively. Under these conditions as well as the Sharpless asymmetric conditions, no dihydroxylation of the *exo*-methylene group in **19** or **20** occurred.

§ Analogously, (−)-**3** was converted into (−)-cheimonophyllon E {$[\alpha]_D^{23}$ −126 (*c* 2.47, $CHCl_3$)}, the unnatural enantiomer.

of natural **2** {$[\alpha]_D^{22}$ +123 (*c* 2.29, $CHCl_3$) for synthetic, lit.[2] $[\alpha]_D$ +125 (*c* 2.2, $CHCl_3$) for natural}. Thus, the absolute stereochemistry of natural **2** was established as depicted.

In conclusion, we have achieved the total synthesis of (±)-cheimonophyllon E in 13 steps starting with commercially available enone **6**. Furthermore, optical resolution of the key intermediate (±)-**3** led to the syntheses of natural (+)- and unnatural (−)-cheimonophyllon E.

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