Concise Total Syntheses of the Sesquiterpenoids (−)-Homalomenol A and (−)-Homalomenol B

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The conjugate additions of the organocopper(I) reagents **22** and **27** to the enantiomerically homogeneous bicyclic enone **4** provided, after epimerization (NaOMe, MeOH) of the resultant product mixtures and appropriate chromatographic separations, the bicyclo[4.3.0]nonan-2-ones **24** and **28**. Compounds **24** and **28** were readily converted, via two synthetic steps in each case, into the sesquiterpenoids (−)-homalomenols B (**2**) and A (**1**), respectively.

Introduction

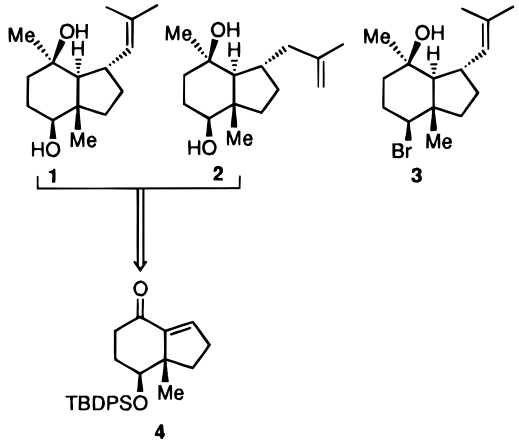
The sesquiterpenoids homalomenols A (**1**) and B (**2**) have been isolated from the chloroform extract of the roots of *Homalomena aromatica* (Roxb.) Schott (Araceae).[1] These roots are used in Vietnamese folk medicine as an anti-inflammatory agent, as a tonic drug, and for the treatment of stomach diseases.[1] On the basis of evidence from circular dichroism measurements,[1] it is likely that the absolute configurations of (+)-homalomenols A and B are enantiomeric with those shown by the structural formulas **1** and **2**, respectively. This initial assignment of absolute configuration is now confirmed by the enantiocontrolled syntheses of (−)-homalomenols A (**1**) and B (**2**). A natural product very similar in structure to the homalomenols, oppositol (**3**), has been isolated from the marine red alga *Laurencia subopposita* Setchell.[2] The absolute stereochemistry of **3** was determined via a single-crystal X-ray diffraction analysis.[2]

Although the total syntheses of homalomenols A and B have not been reported previously, a biomimetic synthesis[3a] of (±)-**3** from germacrene-D, an arduous 28-step synthesis[3b] of (±)-**3**, and a formal total synthesis[3c] of (−)-**3** have been described. We report herein relatively short total syntheses of (−)-homalomenols A (**1**) and B (**2**) via routes in which the key steps involve stereoselective conjugate addition reactions to the intermediate bicyclo[4.3.0]non-9-en-2-one **4** (Scheme 1). The stereochemical outcomes of these additions were predicted to parallel those obtained in the previously reported conjugate addition reactions of the organocopper(I) reagent **6** to the enones **5** (Scheme 2).[4]

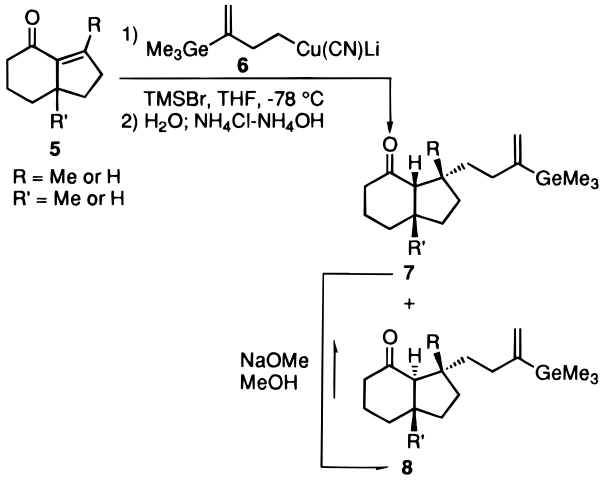
Interestingly, prior to our work,[4] very little was known about the stereochemical outcome of the conjugate addition of organocopper(I) reagents to bicyclo[4.3.0]non-9-en-2-ones.[5] We have found that the conjugate addition of reagent **6** to enones of general structure **5** proceeds completely stereoselectively, with the 3-(trimethylgermyl)-3-butenyl group being introduced trans to the angular R′ group (Scheme 2).[4] In all cases, except when both R and R′ = Me, the major cis-fused isomer **7** initially isolated from the reaction mixture could be equilibrated with NaOMe/MeOH to produce a mixture of epimers in which the trans-fused substance **8**, the thermodynamically more stable of the two epimers, predominates. These equilibration results are consistent with those reported in the literature for structurally related compounds.[6]

The bicyclo[4.3.0]non-9-en-2-one **4** was to be derived from the enone **9** via a five-membered ring annulation

Scheme 1



Scheme 2



[⊗] Abstract published in *Advance ACS Abstracts,* November 15, 1996.

(1) Sung, T. V.; Steffan, B.; Steglich, W.; Klebe, G.; Adam, G. *Phytochemistry* **1992**, *31*, 3515.

(2) Hall, S. S.; Faulkner, D. J.; Fayos, J.; Clardy, J. *J. Am. Chem. Soc.* **1973**, *95*, 7187.

(3) (a) Shizuri, Y.; Yamaguchi, S.; Terada, Y.; Yamamura, S. *Tetrahedron Lett.* **1986**, *27*, 57. (b) Fukuzawa, A.; Sato, H.; Masamune, T. *Tetrahedron Lett.* **1987**, *28*, 4303. (c) Sato, Y.; Mori, M.; Shibasaki, M. *Tetrahedron: Asymmetry* **1995**, *6*, 757.

(4) Piers, E.; Oballa, R. M. *Tetrahedron Lett.* **1995**, *36*, 5857.

(5) Wang, X.; Paquette, L. A. *Tetrahedron Lett.* **1993**, *34*, 4579.

(6) Cicero, B. L.; Weisbuch, F.; Dana, G. *J. Org. Chem.* **1981**, *46*, 914.

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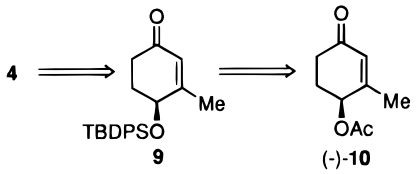
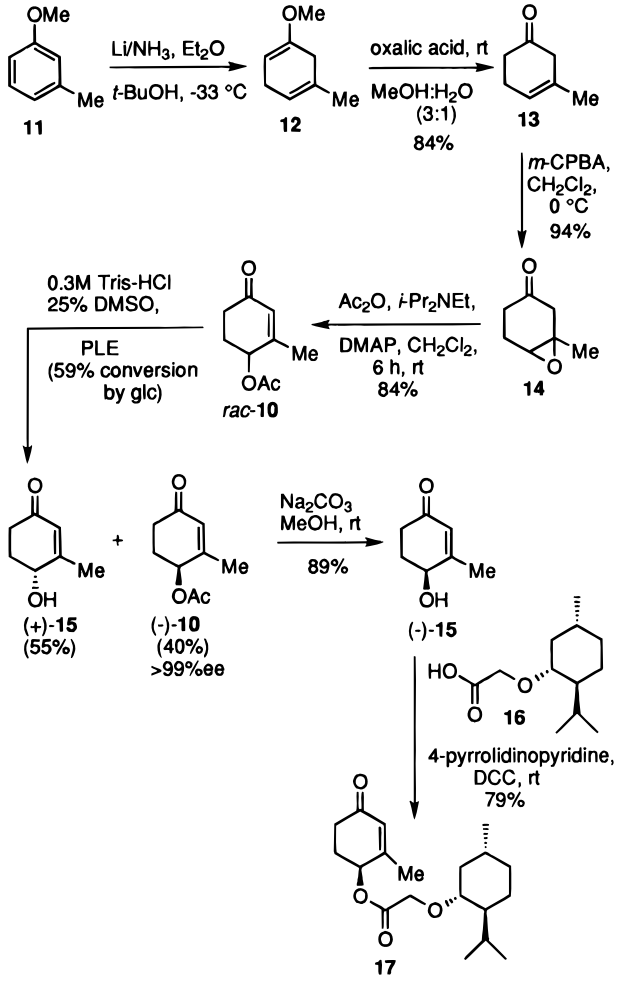
Scheme 3



Scheme 4

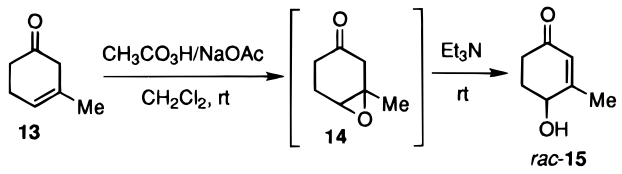


sequence (Scheme 3). Intermediate **9**, in turn, was envisaged to be obtained from a protecting group manipulation sequence involving the known homochiral allylic acetate (−)-**10**.

Results and Discussion

(a) Preparation of (*S*)-(−)-4-Acetoxy-3-methyl-2-cyclohexen-1-one ((−)-10). The synthesis of the enantiomerically pure allylic acetate (−)-**10** was readily accomplished via the route outlined in Scheme 4. Reduction (Li/NH_3, *t*-BuOH)[7] of commercially available 3-methylanisole (**11**) afforded the (crude) enol ether **12**, which was hydrolyzed with aqueous oxalic acid to yield 3-methyl-3-cyclohexen-1-one (**13**) in 84% overall yield. Although Polla and Frejd reported[8] that the enone **13** could be transformed into the epoxide **14** with peroxyacetic acid (Scheme 5), we found that employing *m*-chloroperoxybenzoic acid (*m*-CPBA) as the epoxidation reagent in place of AcO_2H afforded the epoxide **14** in 94% yield (Scheme 4).

Scheme 5



In the preparation of the racemic acetate **10** described in the literature,[8] the crude epoxide **14** was immediately converted to the allylic alcohol *rac*-**15** with Et_3N (Scheme 5). We discovered that *rac*-**15** is quite unstable to purification and cannot be stored without decomposition for any length of time. Consequently, a modified procedure that allowed direct conversion of the epoxide **14** into the allylic acetate *rac*-**10** was developed (Scheme 4). To that end, treatment of the epoxide **14** with acetic anhydride in the presence of *i*-Pr_2NEt and 4-(dimethylamino)pyridine (DMAP) provided, after flash chromatography of the crude product and distillation of the acquired oil, the stable racemic acetate **10** in 84% yield.

The kinetic resolution of racemic **10** was accomplished according to the procedure of Polla and Frejd.[8] Thus, treatment of *rac*-**10** with the enzyme pig liver esterase (PLE)[9] in the presence of a 0.3 M Tris-HCl buffer (pH 7) and 25% DMSO resulted in the isolation of the (*R*)-allylic alcohol (+)-**15** and the unreacted (*S*)-allylic acetate (−)-**10**. If the reaction was allowed to proceed to ~36% conversion, the enantiomeric excess recorded for the alcohol (+)-**15** was only 88%.[10] However, in line with other findings of Polla and Frejd,[8] we were able to obtain (−)-**10** in higher ee by increasing the degree of conversion.[11] By hydrolyzing *rac*-**10** with PLE to an extent of 59%, the unreacted acetate (−)-**10** was isolated in 40% yield and >99% ee. The enantiomeric excess of (−)-**10** was determined by hydrolyzing this material with Na_2CO_3 in MeOH and esterifying the resultant alcohol (−)-**15** with (−)-menthoxyacetic acid (**16**) (Scheme 4).[12] The ^1H NMR spectrum of the ester **17** in the presence of 0.1−0.2 equiv of $Eu(fod)_3$ revealed the presence of only one diastereomer. Since the (*S*)-allylic acetate (−)-**10** could be obtained in an enantiomeric purity significantly higher than that of the (*R*)-allylic alcohol (+)-**15** (>99 vs 88% ee, respectively), we elected to carry out the syntheses of (−)-homalomenols A and B rather than those of the naturally occurring (+)-homalomenols.

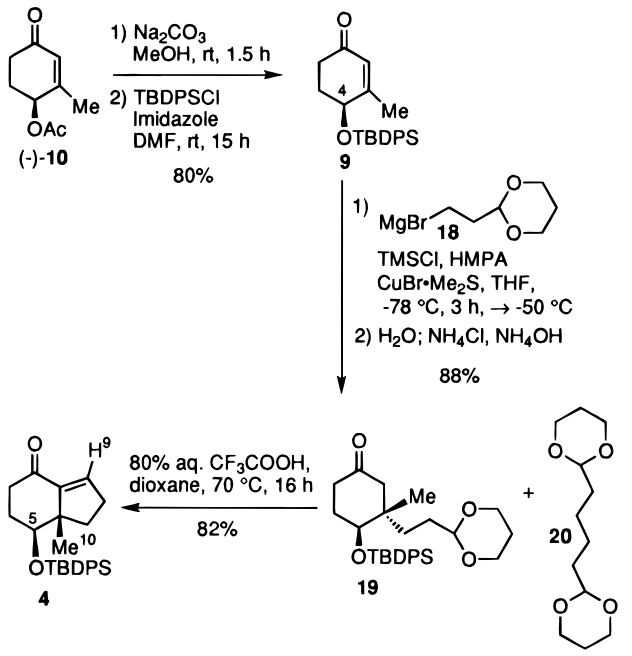
(b) Preparation of the Bicyclic Enone 4. For the synthesis of the intermediate bicyclic enone **4**, the acetyl function of (−)-**10** was replaced by a more chemoresistant group, namely, a *tert*-butyldiphenylsilyl (TBDPS) protecting group (Scheme 6). Thus, base hydrolysis of (−)-**10** was followed immediately by conversion of the resultant, rather unstable (*vide supra*) alcohol (−)-**15** into the TBDPS ether **9** (80% overall yield).

Conversion of the enone **9** into the bicyclic substance **4** was accomplished by employing a modified version of the five-membered-ring annulation sequence reported by

(7) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1977**, *42*, 1051.
(8) Polla, M.; Frejd, T. *Tetrahedron* **1991**, *47*, 5883.

(9) PLE was purchased as a suspension in 3.2 M $(NH_4)_2SO_4$, pH 8, from Sigma.
(10) In Polla and Frejd's work,[8] the alcohol (+)-**15** was obtained in 90% ee following a 45% enzymatic conversion. These workers explored the use of a number of other enzyme systems, but the enantiomeric excess of (+)-**15** could not be improved upon.[8]
(11) For a quantitative treatment of biochemical kinetic resolution, see: Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.
(12) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475.

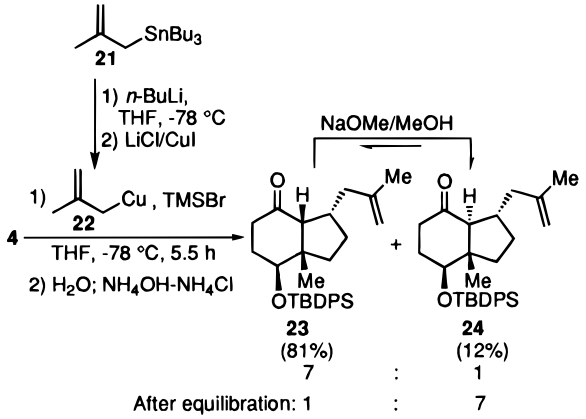
Scheme 6



Helquist and co-workers.[13] Copper(I)-catalyzed conjugate addition of the Grignard reagent **18**[14] to **9** in the presence of HMPA and TMS-Cl[15] provided, after an appropriate workup procedure, the keto acetal **19**, accompanied by a small amount of the diacetal **20** (Scheme 6). Flash chromatography of this mixture and subsequent crystallization of **19** from the mixed fractions afforded the desired acetal **19** in 88% yield. Only one stereoisomer was evident in the ^{1}H NMR spectrum of **19**. Thus, the aforementioned copper-catalyzed Grignard addition had proceeded in the precedented[8,16] stereoselective manner, trans to the oxygen substituent at carbon 4. The configuration of the product **19** was subsequently confirmed (*vide infra*).

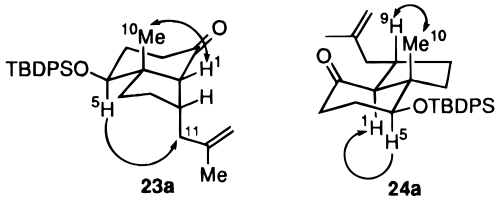
In attempts to effect the conversion of the keto acetal **19** into the enone **4**, the conditions reported by Helquist and co-workers[13] (HCl/H_2O/THF) could not be employed because the TBDPS ether would, in all likelihood, be hydrolyzed.[17] Initial attempts to promote the aldol cyclization resulted in the nearly quantitative recovery of starting material.[18] Hanessian and Lavallee[17] have shown that TBDPS ethers are stable to 50% aqueous CF_3CO_2H in dioxane at room temperature; however, these conditions also failed to effect the cyclization. On the other hand, heating a mixture of the keto acetal **19** in 80% aqueous CF_3CO_2H/dioxane (1:2) for 16 h accomplished the required cyclization reaction and produced the bicyclic enone **4** in 82% yield (Scheme 6). The IR spectrum of enone **4** revealed absorbances at 1687 and 1618 cm^{-1}, characteristic of an α,β-unsaturated ketone. The ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **4** revealed a three-proton signal at δ 1.20 (s, Me-10) and one-proton resonances at δ 3.76−3.80 (dd, J = 11, 4 Hz, H-5) and 6.42−6.66 (dd, J = 2.5, 2.5 Hz, H-9).

Scheme 7



(c) Synthesis of (−)-Homalomenol B (2). For the synthesis of (−)-**2**, the stereoselective conjugate addition of the organocopper(I) reagent **22** to the bicyclic enone **4** was required (Scheme 7). Initial attempts to prepare reagent **22** by reaction of methallyl bromide with either magnesium or *t*-BuLi failed due to the sole formation of the coupled product, 2,5-dimethyl-1,5-hexadiene.[19] However, following the procedure reported by Lipshutz and co-workers,[20] the organocopper(I) reagent **22** was prepared from 2-methyl-3-(tri-*n*-butylstannyl)propene (**21**)[21] by sequential treatment of the latter substance with *n*-BuLi and LiCl/CuI. For this convenient procedure to work well, it was found necessary to use freshly recrystallized CuI.[22]

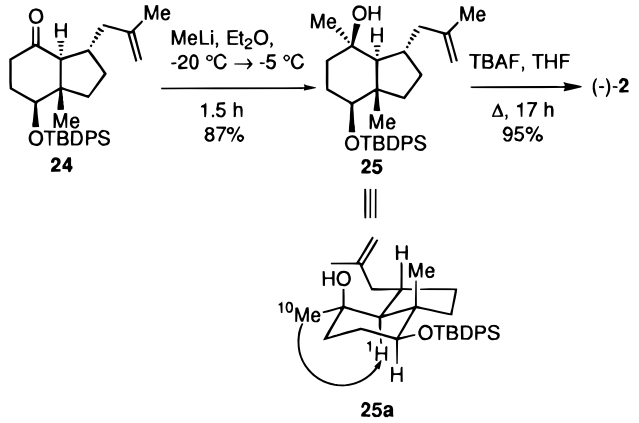
The conjugate addition of reagent **22** to the bicyclic enone **4** in the presence of TMS-Br[23] provided, after hydrolysis of the resultant silyl enol ether, a mixture of epimeric adducts **23** and **24** in a ratio of 7:1 (overall yield



of 93%, see Scheme 7). It was gratifying to find that the conjugate addition had proceeded stereoselectively, as expected (*vide supra*). The cis- and trans-fused epimers **23** and **24** were easily separated by flash chromatography of the mixture on silica gel, and their relative configura-

(13) Bal, S. A.; Marfat, A.; Helquist, P. *J. Org. Chem.* **1982**, *47*, 5045. Marfat, A.; Helquist, P. *Tetrahedron Lett.* **1978**, 4217.
(14) Stowell, J. C. *J. Org. Chem.* **1976**, *41*, 560. Stowell, J. C. *Chem. Rev.* **1984**, *84*, 409.
(15) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025.
(16) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015.
(17) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.
(18) Conditions that failed to promote the cyclization are as follows: PPTS, aqueous acetone, heat, 15 h; 80% aqueous AcOH, THF, rt, 4 h; *p*-toluenesulfonic acid, CH_2Cl_2, heat, 5 h; 50% aqueous CF_3CO_2H, dioxane, rt, 4 h.
(19) Allylic halides are known to be quite reactive and prone to Wurtz coupling. See: Lipshutz, B. H.; Crow, R.; Dimock, S. H.; Ellsworth, E. L.; Smith, R. A. J.; Behling, J. R. *J. Am. Chem. Soc.* **1990**, *112*, 4063. Katzenellenbogen, J. A.; Lenox, R. S. *J. Org. Chem.* **1973**, *38*, 326. Seyferth, D.; Weiner, M. A. *Organolithium Compd.* **1961**, *26*, 4797.
(20) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Smith, R. A. J. *J. Am. Chem. Soc.* **1990**, *112*, 4404.
(21) The allylstannane **21** was prepared from the commercially available 3-chloro-2-methylpropene and tri-*n*-butylstannyl chloride as described by: Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079.
(22) Kauffman, G. B.; Teter, L. A. *Inorg. Synth.* **1963**, *7*, 9.
(23) The use of TMS-Br instead of TMS-Cl was found to increase the overall yield of the conjugate addition reaction by 16%. For the use of TMS-Br as an additive in conjugate addition reactions, see: Cahiez, G.; Venegas, P.; Tucker, C. E.; Majid, T. N.; Knochel, P. *J. Chem. Soc., Chem. Commun.* **1992**, 1406. Bergdahl, M.; Lindstedt, E.-L.; Nilsson, M.; Olsson, T. *Tetrahedron* **1989**, *45*, 535.

Scheme 8



tions were confirmed by the following ^{1}H NMR NOE difference experiments.

For the major cis-fused epimer **23**, irradiation of the signal at δ 1.18 (Me-10) caused an enhancement of the signal at δ 2.49−2.52 (H-1) and vice versa (see **23a**). These experiments confirmed the cis-fused nature of the ring junction. Irradiation of the signal at δ 3.74−3.77 (H-5) caused an enhancement of the signal at δ 1.56−1.70 (H-11), thereby verifying that reagent **22** had introduced the methallyl group trans to the angular methyl group, as predicted. For the minor trans-fused epimer **24**, irradiation of the signal at δ 0.89 (Me-10) caused an enhancement of the signal at δ 2.44−2.51 (H-9) and vice versa (see **24a**). In addition, saturation of the resonance at δ 3.33−3.44 (H-5) increased the intensity of the H-1 signal (δ 1.87−1.90). Collectively, these experiments not only confirmed the stereochemical outcome of the conjugate addition reaction but also verified that the ring junction in **24** is trans-fused.[24]

The epimer required for the synthesis of (−)-**2** was, in fact, the minor product **24**. According to our previous studies[4] and results reported by Dana and co-workers,[6] **24** should be thermodynamically more stable than the corresponding cis-fused epimer **23**. In fact, treatment of **23** with NaOMe in MeOH resulted in a 7:1 mixture of **24** and **23**, respectively (see Scheme 7). These two diastereomers were separated by flash chromatography on silica gel, and the recovered cis-fused epimer **23** was resubjected to the epimerization conditions. The total yield of the desired synthetic intermediate **24** after two such epimerizations and chromatographic separations was 87%, based on the enone **4**.

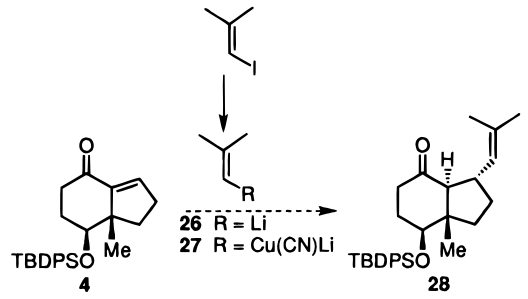
Reaction of **24** with MeLi provided a single tertiary alcohol in 87% yield (Scheme 8). Since axial approach of MeLi to the carbonyl moiety of **24** would involve a 1,3-diaxial interaction between the angular methyl group and the incoming reagent, it was expected that this process would involve equatorial attack to produce the axial alcohol **25**.[25] The fact that the latter substance was the sole product was confirmed by a ^{1}H NMR NOE difference experiment in which irradiation of the signal at δ 1.17 (Me-10) caused enhancement of the H-1 resonance at δ 0.79 (see **25a**).

Treatment of **25** with tetrabutylammonium fluoride (TBAF) in refluxing THF afforded (−)-**2** in 95% yield (Scheme 8). Recrystallization of the product from ethyl

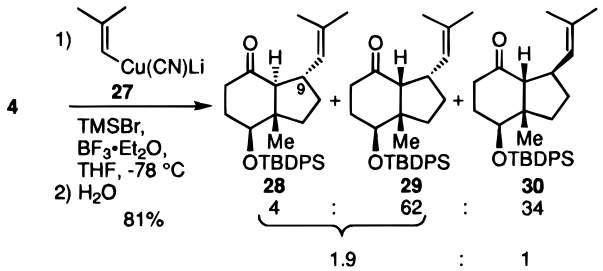
(24) Examination of molecular models indicates that a NOE enhancement between H-9 and Me-10 is possible only when the ring junction is trans-fused.

(25) For an equatorial approach of MeLi to a carbonyl group in a structurally related compound, see: Reference 3.

Scheme 9



Scheme 10



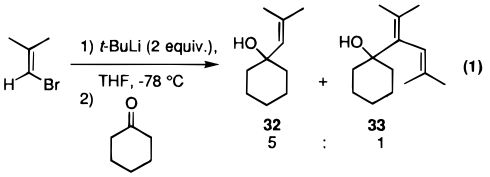
acetate/petroleum ether provided a colorless, crystalline solid, mp 94−95 °C (lit.[1] mp 78−81 °C). The IR, ^{1}H NMR, ^{13}C NMR, and HRMS data derived from the synthetic (−)-**2** are identical with those of natural (+)-homalomenol B.[1] That the absolute configuration of the synthetic material is opposite to that of the natural product was confirmed by the sign of the specific optical rotation (observed $[\alpha]^{20}_D$ −43.0 (*c* 1.71, $CHCl_3$) for the synthetic material; reported[1] $[\alpha]^{20}_D$ +20.4 (*c* 1.745, $CHCl_3$) for the natural product). Thus, the synthesis of (−)-**2** was accomplished in a concise and enantioselective manner. The overall yield of (−)-**2** from the homochiral acetate (−)-**10** was 42%.

(d) Synthesis of (−)-Homalomenol A (1). For the synthesis of (−)-**1**, the conjugate addition of the organocopper(I) reagent **27** to the enone **4** to produce the ketone **28** was required (Scheme 9). The formation of the required vinyllithium species **26** was found to occur much more smoothly from reaction of *t*-BuLi with 1-iodo-2-methylpropene[26] than from an analogous protocol involving the corresponding bromide.[27] Addition of a solubilized solution of CuCN (1 equiv) and LiCl (2 equiv) in THF[28] to the vinyllithium species **26** produced the desired organocopper(I) reagent **27**. Reaction of **27** with the bicyclic enone **4** in the presence of TMS-Br[23] and BF_3•Et_2O afforded, after hydrolysis of the resultant silyl enol ethers, a mixture of three isomeric products **28**, **29**, and **30** in a ratio of 4:62:34, respectively (81% overall yield, see Scheme 10).

By changing the additives used in the conjugate addition reaction or modifying the nature of the organo-

(26) Takagi, K.; Hayama, N.; Inokawa, S. *Chem. Lett.* **1978**, 1435.

(27) Reaction of 1-bromo-2-methylpropene with *t*-BuLi in THF, followed by addition of cyclohexanone, gave a product mixture that consisted of a 5:1 mixture of the expected product **32** and the diene alcohol **33**, respectively (eq 1).

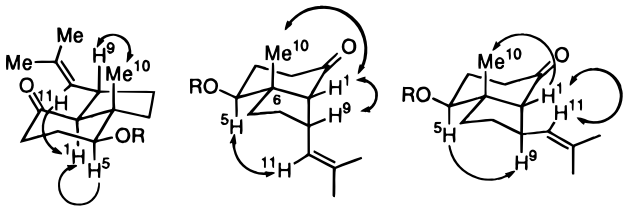


(28) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

copper(I) reagent (e.g., using the higher order cuprate reagent derived from 2 equiv of **26** and 1 equiv of CuCN), the ratio of the desired (**28** and **29**) to undesired (**30**) adducts varied from 1.9:1 (Scheme 10) to 1:2.[29] When the mixture of adducts **28**, **29**, and **30** was treated with NaOMe/MeOH, the trans- and cis-fused isomers **28** and **29**, each possessing the correct (*S*) configuration at C-9, were equilibrated to a mixture with a ratio of 1.3:1, respectively.[30] On the other hand, as expected, the cis-fused compound **30** with the incorrect (*R*) configuration at C-9 did not epimerize under these conditions. It is evident from an examination of molecular models that the trans-fused epimer of **30** would be notably destabilized by a pseudo-1,3-diaxial interaction between the 2-methyl-1-propenyl group and the angular methyl group.

Fortunately, column chromatography (silica gel) effected clean separation of **28** from the equilibrated mixture of **28**, **29**, and **30**. The remaining mixture of cis-fused adducts **29** and **30** was resubjected to the equilibration conditions, and the desired isomer **28** was again separated by chromatography. After three such epimerizations and separations, the overall yield of **28** from the enone **4** was 43%.

The relative configurations of the three adducts **28**, **29**, and **30** were confirmed by the ^{1}H NMR NOE difference experiments depicted on the conformational formulas **28a**, **29a**, and **30a**. With respect to the desired epimer



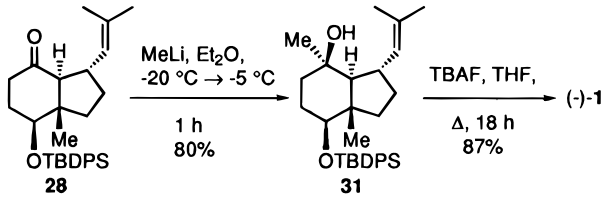
28a R = TBDPS **29a** R = TBDPS **30a** R = TBDPS

28, the mutual enhancements observed upon irradiation of the resonances due to Me-10 (δ 0.91) and H-9 (δ 3.03−3.10), as well as the enhancement of the signal (δ 2.01) derived from H-1 when either the H-5 (δ 3.87−3.91) or H-11 (δ 4.78) signals were irradiated, confirmed both the trans-fused nature of the ring junction and the configurational assignment at C-9.

For the cis-fused adduct **29**, mutual signal enhancements were observed upon irradiation of the following pairs of resonances: δ 1.17 (Me-10) and 2.48−2.51 (H-1), δ 2.48−2.51 (H-1) and 3.12−3.21 (H-9), and δ 3.77−3.81 (H-5) and 4.51 (H-11) (see **29a**). Collectively, these experiments verified the cis-fused nature of this compound and the assigned configuration at C-9.

With respect to the product **30**, which possesses the "incorrect" configuration at C-9, the enhancement of the Me-10 resonance (δ 1.16) upon irradiation of the H-1 signal (δ 2.00), the mutual enhancements caused by saturation of the H-1 (δ 2.00) and H-11 (δ 4.92) resonances, and the increase of intensity of the H-9 multiplet

Scheme 11



(δ 2.79−2.88) upon irradiation of the H-5 signal (δ 3.86−3.91) (see **30a**) clearly confirmed that this substance is cis-fused and that, in the conjugate addition reaction, the 2-methyl-1-propenyl group had been introduced cis to the angular methyl group.

Stereoselective addition of MeLi to the carbonyl moiety of **28** provided the tertiary alcohol **31** in 80% yield (Scheme 11). Treatment of **31** with TBAF in refluxing THF for 18 h provided, in 87% yield, (−)-**1**. Recrystallization of this material from diethyl ether/petroleum ether provided thin, needlelike plates that exhibited mp 99−100 °C (lit.[1] reports (+)-homalomenol A as an oil). The IR, ^{1}H NMR, ^{13}C NMR, and HRMS data for (−)-**1** are identical with those of the naturally occurring (+)-homalomenol A.[1] That the absolute configuration of the synthetic (−)-homalomenol A is opposite to that of the natural product was confirmed by the sign of the specific optical rotation (observed $[\alpha]^{20}_D$ −51.5 (*c* 1.30, $CHCl_3$) for the synthetic material; reported[1] $[\alpha]^{20}_D$ +33.2 (*c* 1.205, $CHCl_3$) for the natural product).

Conclusion

The work described in this paper culminated in the first total syntheses of the two sesquiterpenoids (−)-**1** and (−)-**2**. The key steps of the overall synthetic sequences involved the conjugate addition of the organocopper(I) reagents **27** and **22**, respectively, to the enantiomerically homogeneous bicyclic enone **4**. In the synthesis of (−)-**2**, the conjugate addition of **22** to **4** proceeded stereoselectively, and after equilibration and chromatographic separation of the epimers **23** and **24**, the required adduct **24** was obtained in excellent yield. However, in the synthesis of (−)-**1**, 1,4-addition of **27** to **4** exhibited rather poor stereoselectivity. Nonetheless, the desired intermediate **28** was readily obtained, albeit in moderate yield, from the mixture of adducts (**28**, **29**, **30**) and the synthesis of **1** was easily completed.

Experimental Section

General Experimental Details. Distillation temperatures, which refer to short-path (Kugelrohr) distillations, and melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded using $CDCl_3$ as the solvent, and signal positions (δ values) were measured relative to the signals for $CHCl_3$ (δ 7.26), unless otherwise noted, and $CDCl_3$ (δ 77.0), respectively. GLC was performed on instruments equipped with capillary columns (25 m, HP-5) and flame ionization detectors. TLC was carried out using commercial aluminum-backed silica gel 60 plates. Flash chromatography[31] was carried out with 230−400 mesh silica gel (E. Merck) or 10−50 μm Type H silica (TLC grade silica).

Et_2O and THF were distilled from sodium/benzophenone, while CH_2Cl_2, *i*-Pr_2NEt, DMF, DMSO, HMPA, *t*-BuOH, and Me_3SiCl were distilled from CaH_2. Magnesium was added to MeOH, and after the mixture had been refluxed, the MeOH was distilled from the resulting solution of magnesium methoxide and was stored over 4 Å molecular sieves. Acetic

(29) It is known that the use of TMS-X and/or BF_3·Et_2O can affect the stereoselectivity of conjugate addition reactions. See: Reference 16. Lipshutz, B. H.; Ellsworth, E. L.; Siahaan, T. J. *J. Am. Chem. Soc.* **1988**, *110*, 4834 and citations therein. Lipshutz, B. H.; Ellsworth, E. L.; Siahaan, T. J.; Shirazi, A. *Tetrahedron Lett.* **1988**, *29*, 6677. Zhao, S.-K.; Helquist, P. *Tetrahedron Lett.* **1991**, *32*, 447. Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *J. Org. Chem.* **1986,** *51*, 4323.

(30) This 1.3:1 equilibrium ratio of **28**:**29** is in contrast to the 7:1 ratio observed for the trans- and cis-fused adducts **24** and **23** used in the synthesis of (−)-**2**. Obviously, the nature of the substituent at C-9 has a significant effect on the relative stabilities of 9-substituted bicyclo[4.3.0]nonan-2-ones.

(31) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

anhydride was refluxed over and then distilled from phosphorus pentoxide. Trimethylsilyl bromide was distilled from calcium hydride using a Kugelrohr distillation apparatus and was used immediately. $BF_3{\cdot}Et_2O$ was purified by distillation from calcium hydride under reduced pressure (60 °C (20 Torr)). CuBr−Me_2S complex was prepared by the method described by Wuts[32] and was stored in a desiccator under an atmosphere of dry argon.

A solution of NaOMe in dry MeOH was prepared as follows. To a cold (−78 °C) flask containing dry NaH was added the appropriate amount of dry MeOH. The mixture was stirred at −78 °C for 10 min, warmed to rt, and used immediately. Aqueous NH_4Cl/NH_4OH (pH 8−9) was prepared by the addition of ∼50 mL of aqueous NH_3 (30%) to ∼950 mL of saturated aqueous NH_4Cl.

Unless stated otherwise, all reactions were carried out under an atmosphere of dry argon using glassware that had been thoroughly flame- and/or oven-dried (∼140 °C).

3-Methyl-3-cyclohexen-1-one (13). To cold (−78 °C), stirred liquid NH_3 (200 mL, distilled from sodium) was added a solution of 3-methylanisole (**11**; 8.3 mL, 66 mmol) in dry Et_2O (50 mL). This was followed by the addition of *t*-BuOH (62 mL, 0.66 mol). Li metal (2.3 g, 0.33 mol) was added in small portions over a period of 15 min. The blue solution was refluxed at −33 °C for 3.5 h. The reaction mixture was cooled to −78 °C, and the excess Li was destroyed by portionwise addition of solid NH_4Cl (52 g, 0.97 mol). The cloudy white suspension was opened to the atmosphere via an air-cooled condenser, and the NH_3 was allowed to evaporate. Pentane (150 mL) was added, and the flask was warmed in a water bath to drive off any residual ammonia. H_2O (150 mL) was added, and the layers were separated. The aqueous layer was extracted with pentane (2 × 90 mL), and the combined organic extracts were washed (H_2O, 4 × 100 mL), dried ($MgSO_4$), and concentrated by distillation of the solvent at atmospheric pressure through a jacketed Vigreux column (20 cm) to avoid loss of product.

The crude enol ether **12** was dissolved in 130 mL of MeOH/H_2O (3:1), oxalic acid dihydrate (412 mg, 3.30 mmol, 5 mol % with respect to **11**) was added, and the resultant mixture was stirred at rt for 1.5 h. H_2O (200 mL) was added and the suspension was extracted with CH_2Cl_2 (6 × 100 mL) until the extracts no longer contained any product, as indicated by GLC analysis. The combined organic extracts were washed with H_2O (1 × 100 mL), dried ($MgSO_4$), and concentrated by distillation of the solvent at atmospheric pressure through a jacketed Vigreux column (20 cm). The oil thus obtained was distilled (88 °C (50 Torr)) to give 6.0 g (84%) of **13**.[33]

1-Methyl-7-oxabicyclo[4.1.0]heptan-3-one (14). To a cold (0 °C), stirred solution of *m*-CPBA (purity 50−60%, 4.30 g, 12.5 mmol) in dry CH_2Cl_2 (90 mL) was added, via a large cannula, a solution of **13** (1.05 g, 9.53 mmol) in dry CH_2Cl_2 (5 mL). After the mixture had been stirred at 0 °C for 2.5 h, excess *m*-CPBA was destroyed by the addition of saturated aqueous $Na_2S_2O_3$ (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (5 × 100 mL), dried ($MgSO_4$), and concentrated by distillation of the solvent at atmospheric pressure through a jacketed Vigreux column (20 cm). The oil thus obtained was distilled (80 °C (32 Torr)) to afford 1.12 g (94%) of the epoxide **14**, a colorless oil: IR (neat) 1713, 1198, 1044 cm^{-1}; ^1H NMR (400 MHz) δ 1.36 (s, 3H, Me), 2.14−2.19 (m, 2H), 2.34−2.40 (m, 2 H), 2.56 (d, 1 H, J = 19 Hz), 2.78 (d, 1H, J = 19 Hz), 3.20 (br d, 1 H, J = 2.5 Hz); ^{13}C NMR (75.3 MHz) δ 22.1, 22.3, 33.8, 43.8, 56.7, 58.1, 207.7; HRMS calcd for $C_7H_{10}O$ 126.0681, found 126.0677. Anal. Calcd: C, 66.64; H, 7.99. Found: C, 66.51; H, 8.03.

4-Acetoxy-3-methyl-2-cyclohexen-1-one (*rac*-10). To a stirred solution of the epoxide **14** (4.19 g, 33.2 mmol) in dry CH_2Cl_2 (110 mL) at rt was added dry Ac_2O (6.3 mL, 66 mmol), DMAP (812 mg, 6.60 mmol), and dry *i*-Pr_2NEt (11.6 mL, 66.5 mmol). The mixture was stirred at rt for 6 h. EtOAc (100 mL) and saturated aqueous $NaHCO_3$ (100 mL) were added, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 75 mL), and the combined organic extracts were washed (saturated aqueous $NaHCO_3$, 2 × 100 mL; H_2O, 100 mL), dried ($MgSO_4$) and concentrated. The crude product was flash chromatographed (300 g of silica gel, 1:1 petroleum ether/CH_2Cl_2), and the oil thus obtained was distilled (90−94 °C (0.2 Torr)) to provide 4.7 g (84%) of the allylic acetate *rac*-**10**,[34] a colorless oil.

(*R*)-(+)-4-Hydroxy-3-methyl-2-cyclohexen-1-one ((+)-15) and (*S*)-(−)-4-Acetoxy-3-methyl-2-cyclohexen-1-one ((−)-10). To a stirred mixture of *rac*-**10** (4.57 g, 27.2 mmol) in Tris-HCl buffer,[35] pH 7 (0.3 M, 600 mL), and DMSO (200 mL) at rt was added PLE (6 mL of enzyme suspension, 100 mg of protein, ∼1.7 × 10^4 units of activity). The above materials were dispensed with glass pipets or with Eppendorf plastic tips. In order to avoid inactivation of the enzyme, metal needles were not used. The pH of the solution was monitored using a pH meter (Fischer Accumet pH meter, Model 140) and was kept at pH 7 by the appropriate addition of 0.1 M aqueous NaOH. A total of 155 mL of 0.1 M aqueous NaOH was used, indicating that the reaction had proceeded to the extent of 57% (i.e., 57% of the racemic acetate had been hydrolyzed to the corresponding alcohol). Analysis (GLC) at this time (26 h) confirmed that ∼59% of the acetate had been hydrolyzed. The solution was extracted with EtOAc (4 × 600 mL), and the combined organic extracts were washed (brine, 1 × 200 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (275 g of silica gel, 3:2 petroleum ether/Et_2O to elute the unreacted allylic acetate, followed by 100% EtOAc to elute the allylic alcohol) provided fractions containing the allylic acetate followed by fractions containing the more polar alcohol. Concentration of the first set of fractions provided 1.81 g (40%) of (−)-4-acetoxy-3-methyl-2-cyclohexen-1-one ((−)-**10**) as a colorless oil ($[\alpha]^{25}_D$ −46.7 (*c* 1.69, $CHCl_3$); lit.,[8] −35.1 (*c* 0.61, $CDCl_3$)). The spectral data are identical with those derived from *rac*-**10**. Concentration of the late fractions afforded 2.0 g (58%) of (+)-4-hydroxy-3-methyl-2-cyclohexen-1-one ((+)-**15**).[36]

The enantiomeric excess of the desired (−)-**10** was ascertained by converting the acetate to the corresponding alcohol (−)-**15** (*vide infra*), transforming (−)-**15** into the ester **17** by reaction with (−)-menthoxyacetic acid (**16**),[12] and recording the ^1H NMR spectrum of this ester in the presence of 0.1−0.2 equiv of Eu(fod)$_3$. Only one diastereomer was observed; hence an ee > 99% was obtained.

(*S*)-(+)-4-(*tert*-Butyldiphenylsiloxy)-3-methyl-2-cyclohexen-1-one (9). To a solution of the allylic acetate (−)-**10** (717 mg, 4.26 mmol) in dry MeOH (43 mL) at rt was added solid Na_2CO_3 (2.26 g, 21.3 mmol). The heterogeneous reaction mixture was stirred at rt for 1.5 h. The resultant pink mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was subjected to flash chromatography (35 g of silica gel, 3:1 EtOAc/petroleum ether) to afford 538 mg (quantitative yield) of the colorless allylic alcohol (−)-**15**, which was used immediately in the next step.

To a solution of (−)-**15** (538 mg, 4.26 mmol) in dry DMF (8.5 mL) at rt was added sequentially imidazole (1.16 g, 17.1 mmol) and TBDPS-Cl (2.2 mL, 8.5 mmol). The reaction mixture was stirred at rt for 15 h, at which time H_2O (10 mL) was added. The aqueous phase was separated and extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed (H_2O, 5 × 30 mL), dried ($MgSO_4$), and concentrated. The crude product was subjected to flash chromatography (50 g of silica gel, 9:1 petroleum ether/EtOAc) and the viscous oil thus obtained, upon heating to 70 °C (0.2 Torr) for 1 h to remove any residual solvent, provided 1.2 g (80%, based on

(32) Wuts, P. G. M. *Synth. Commun.* **1981**, *11*, 139.

(33) The spectral data of **13** are identical with those reported by: Noyce, D. S.; Evett, M. *J. Org. Chem.* **1972**, *37*, 394.

(34) The spectral data of the allylic acetate **10** are identical with those reported in ref 8.

(35) The Tris-HCl buffer was prepared by adding 0.3 M aqueous tris(hydroxymethyl)aminomethane to a stirred aqueous solution of 0.3 M tris(hydroxymethyl)aminomethane hydrochloride until the pH of the solution reached 7.

(36) The spectral data of (+)-**15** are identical with those reported in ref 8.

(−)-**10**) of the TBDPS ether (+)-**9**[37] ($[\alpha]^{25}_D$ +8.7 (*c* 2.05, $CHCl_3$); lit.,[8] +4.7 (*c* 1.03, $CDCl_3$)).

(3*S*,4*S*)-(+)-4-(*tert*-Butyldiphenylsiloxy)-3-[2-(1,3-dioxan-2-yl)ethyl]-3-methylcyclohexanone (19). To a stirred suspension of freshly ground Mg turnings (1.01 g, 41.7 mmol) and I_2 (a few crystals) in dry THF (5 mL) at rt was added dropwise (via a large cannula) a solution of 2-(2-bromoethyl)-1,3-dioxane (4.06 g, 20.8 mmol) in dry THF (5 mL). Formation of the Grignard reagent **18** began immediately, and the bromide solution was added at such a rate that reflux of the reaction mixture was maintained. After the addition was complete, the mixture was heated to reflux for an additional 35 min. The mixture was cooled to rt, diluted with THF (90 mL), and further cooled to −78 °C. Solid CuBr−Me_2S (1.07 g, 5.20 mmol, 25 mol % with respect to **18**) was added, and the resultant cloudy mixture was stirred at −78 °C for 1 h. Addition of dry HMPA (3.7 mL) was followed by the dropwise addition (via a large cannula over 10 min) of a solution of the enone **9** (3.08 g, 8.45 mmol) and TMS-Cl (2.7 mL, 21 mmol) in dry THF (8 mL). The resultant bright yellow solution was stirred at −78 °C for 3 h and was then warmed to −50 °C over a period of 2.5 h, at which point the solution became colorless. H_2O (20 mL) was added, and the mixture was stirred at rt for 2 h, open to the atmosphere, to hydrolyze the silyl enol ether. Aqueous NH_4Cl/NH_4OH (pH 8−9, 50 mL) and Et_2O (50 mL) were added, and the mixture was stirred vigorously until the aqueous phase became bright blue. The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed (H_2O, 5 × 75 mL), dried ($MgSO_4$), and concentrated.[38] The crude oil thus obtained was subjected to chromatography[39] (50 g of TLC grade silica gel, 5.7:1 petroleum ether/EtOAc), which yielded 3.0 g of the solid acetal (+)-**19**, as well as a mixture of **19** and the byproduct **20**. The acetal **19** was separated from this mixture by crystallization from petroleum ether. The combined acetal fractions were then recrystallized from petroleum ether to yield 3.6 g (88%) of (+)-**19** as a colorless crystalline solid: mp 99−101 °C; $[\alpha]^{25}_D$ +15.72 (*c* 1.62, $CHCl_3$); IR (KBr) 1704, 1588, 1145, 1111, 1088, 706 cm^{-1}; ^1H NMR (400 MHz) δ 0.96 (s, 3H), 1.09 (s, 9H), 1.27−1.47 (m, 5H), 1.74−1.79 (br ddd, 2H, J = 7.5, 7.5, 5 Hz), 1.96−2.07 (m, 3H), 2.38−2.43 (br dt, 1H, J = 14, 7.5 Hz), 2.47−2.51 (br d, 1H, J = 14 Hz), 3.65−3.72, 3.66−3.73 (ddd, 1H each, J = 12, 12, 2 Hz for each ddd), 3.81−3.84 (dd, 1H, J = 5, 5 Hz), 4.03−4.07 (br ddd, 2H, J = 12, 5, 1 Hz), 4.34−4.36 (dd, 1H, J = 5, 4.5 Hz), 7.35−7.72 (m, 6H), 7.66−7.72 (m, 4H); ^{13}C NMR (75.3 MHz) δ 19.6, 21.2, 25.7, 27.2, 28.8, 29.0, 33.1, 36.8, 42.7, 49.2, 66.8, 73.9, 102.4, 127.5, 127.6, 129.7, 129.8, 133.4, 134.3, 135.9, 136.0, 211.4; HRMS calcd for $C_{29}H_{40}O_4Si$ 480.2696, found 480.2668. Anal. Calcd: C, 72.46; H, 8.39. Found: C, 72.57; H, 8.52.

(5*S*,6*S*)-(−)-5-(*tert*-Butyldiphenylsiloxy)-6-methylbicyclo[4.3.0]non-9-en-2-one (4). To a stirred solution of the acetal **19** (2.04 g, 4.24 mmol) in 1,4-dioxane (57 mL) at rt was added 80% aqueous CF_3COOH (28 mL: 5.5 mL H_2O + 22.5 mL of 100% CF_3COOH). The mixture was heated at 80 °C for 16.5 h. The dark brown solution was neutralized by the careful, dropwise addition (via the condenser) of saturated aqueous $NaHCO_3$. The aqueous phase was separated and extracted with Et_2O (3 × 75 mL) and EtOAc (1 × 75 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography (125 g of silica gel, 4:1 petroleum ether/Et_2O) of the brown oil thus obtained afforded 1.33 g (77%) of the enone (−)-**4** as a viscous, yellow oil.

After acquisition of **4** from the chromatography column, the column was flushed with Et_2O (600 mL). The eluate was concentrated, the residue was dissolved in a mixture of dioxane (16 mL) and 100% CF_3COOH (8 mL), and the solution was heated to 75 °C for 16 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$. The aqueous layer was separated and extracted with Et_2O (3 × 25 mL) and EtOAc (1 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residual material was flash chromatographed (25 g of silica gel, 4:1 petroleum ether/Et_2O) to yield a further 81 mg (5%) of (−)-**4**. The total yield of the enone **4** was 2.14 g (82%): $[\alpha]^{25}_D$ −22.2 (*c* 0.92, $CHCl_3$); IR (neat) 1687, 1618, 1428, 1111, 1069, 703 cm^{-1}; ^1H NMR (400 MHz) δ 1.09 (s, 9H), 1.20 (s, 3H), 1.70−1.75 (m, 2H), 1.99−2.08 (m, 3H), 2.26−2.50 (m, 3H), 3.76−3.80 (dd, 1H, J = 11, 4 Hz, H-5), 6.42−6.43 (dd, 1H, J = 2.5, 2.5 Hz, H-9), 7.37−7.47 (m, 6H), 7.68−7.72 (m, 4H); ^{13}C NMR (75.3 MHz) δ 17.6, 19.4, 27.0, 29.2, 30.0, 38.1, 40.6, 52.4, 78.2, 127.5, 127.6, 129.6, 129.8, 133.4, 134.5, 135.8, 135.9, 138.3, 147.7, 198.7; HRMS calcd for $C_{26}H_{32}O_2Si$ 404.2171, found 404.2178. Anal. Calcd: C, 77.18; H, 7.97. Found: C, 76.88; H, 7.91.

(1*R*,5*S*,6*S*,9*S*)-(−)-5-(*tert*-Butyldiphenylsiloxy)-6-methyl-9-(methallyl)bicyclo[4.3.0]nonan-2-one (23) and (1*S*,5*S*,6*S*,9*S*)-(−)-5-(*tert*-Butyldiphenylsiloxy)-6-methyl-9-(methallyl)bicyclo[4.3.0]nonan-2-one (24). A suspension of flame-dried LiCl[40] (267 mg, 6.30 mmol) and freshly recrystallized CuI[22] (1.20 g, 6.30 mmol) in dry THF (35 mL) was stirred at rt for 15 min until a clear yellow solution resulted. The mixture was cooled to −78 °C. To a cold (−78 °C), stirred solution of **21**[21] (2.12 g, 6.14 mmol) in dry THF (10 mL) was added a solution of *n*-BuLi in hexanes (1.61 M, 3.6 mL, 5.8 mmol). The resultant yellow solution was stirred at −78 °C for 25 min and was quickly cannulated (via a large cannula) into the LiCl/CuI/THF solution to produce a clear red solution containing the organocopper(I) reagent **22**. Cannulation of dry TMS-Br (2.20 g, 14.4 mmol) into the red solution was followed by the addition of a solution of the enone **4** (829 mg, 2.05 mmol) in dry THF (5 mL). The reaction mixture was stirred at −78 °C for 5.5 h. H_2O (20 mL) was added, and the mixture was stirred at rt, open to the atmosphere, for 45 min. Aqueous NH_4Cl/NH_4OH (pH 8−9, 50 mL) was added, and the mixture was stirred rapidly until the aqueous layer became bright blue. The phases were separated, and the aqueous layer was extracted with Et_2O (3 × 75 mL). The combined organic extracts were washed (brine, 1 × 100 mL), dried ($MgSO_4$), and concentrated. ^1H NMR spectroscopic analysis of the crude oil thus obtained indicated a 7:1 ratio of the two isomers **23** and **24**, as determined by the integration of their respective vinyl proton signals. The two isomers were easily separated by flash chromatography (125 g of silica gel, 11.5:1 petroleum ether/Et_2O). The first compound to be eluted was the adduct **24** possessing the trans ring junction. Concentration of the appropriate fractions, followed by recrystallization (from Et_2O/petroleum ether) of the solid thus obtained, provided 113 mg (12%) of the trans-fused compound (−)-**24**, a colorless crystalline solid: mp 98−99 °C; $[\alpha]^{25}_D$ −37.1 (*c* 1.27, $CHCl_3$); IR (KBr) 1716, 1649, 1590, 1112, 1094, 704 cm^{-1}; ^1H NMR (400 MHz) δ 0.89 (s, 3H), 1.06 (s, 9H), 1.14−1.34 (m, 2H), 1.65−1.80 (m, 1H), 1.71 (s, 3H), 1.81−1.95 (m, 5H, one of which is H-1 (d, J = 11 Hz)), 2.01−2.19 (m, 2H), 2.14−2.19 (br dd, 1H, J = 14, 4.5 Hz), 2.44−2.51 (m, 1H, H-9), 3.33−3.40 (dd, 1H, J = 10.5, 5 Hz, H-5) 4.59 (br s, 1H), 4.64 (br s, 1H), 7.36−7.52 (m, 6H), 7.66−7.73 (m, 4H); ^{13}C NMR (75.3 MHz) δ 13.3, 19.4, 22.4, 27.0, 27.1, 32.0, 32.6, 38.4, 39.5, 44.5, 52.4, 62.9, 78.8, 110.6, 127.5, 127.6, 129.6, 129.8, 133.6, 134.5, 135.9, 136.0, 145.2, 209.7; HRMS calcd for $C_{30}H_{40}O_2Si$ 460.2798, found 460.2792. Anal. Calcd: C, 78.21; H, 8.75. Found: C, 78.25; H, 8.78.

The second compound to be eluted was the conjugate addition product **23** bearing the cis ring junction. Concentration of the appropriate fractions, followed by removal of traces of solvent (vacuum pump) from the acquired oil, provided 763 mg (81%) of the cis-fused product (−)-**23** as a colorless oil: $[\alpha]^{25}_D$ −73.0 (*c* 1.79, $CHCl_3$); IR (neat) 1702, 1648, 1590, 1112,

(37) The spectral data of the TBDPS ether (+)-**9** are identical with those reported in ref 8.

(38) In the event that the silyl enol ether failed to hydrolyze, the crude oil was dissolved in THF (1 mL/mmol of starting material) and treated with 1 equiv of TBAF in THF. The mixture was stirred at rt for ~10 min. H_2O (10 mL/mmol of starting material) and Et_2O (20 mL/mmol of starting material) were added to the mixture, and the layers were separated. The aqueous layer was extracted thoroughly with Et_2O, and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The keto acetal **19** was purified as described.

(39) Taber, D. F. *J. Org. Chem.* **1982**, *47*, 1351.

(40) LiCl was flame-dried according to the following procedure. A round-bottomed flask containing solid LiCl was placed under reduced pressure (vacuum pump) and flame-dried using a Bunsen burner. The flask was then filled with argon and cooled to rt.

704 cm^{-1}; ^1H NMR (400 MHz) δ 1.02−1.21 (m, 1H), 1.07 (s, 9H), 1.18 (s, 3H), 1.30−1.38 (m, 1H), 1.41−1.47 (br dd, 1H, J = 13, 10.5 Hz, H-9), 1.59 (s, 3H), 1.56−1.70 (m, 1H), 1.79−1.95 (m, 5H), 2.29−2.38 (m, 1H), 2.40−2.48 (m, 1H), 2.49−2.52 (dd, 1H, J = 10.5, 2 Hz, H-1), 3.74−3.77 (dd, 1H, J = 8.5, 3.5 Hz, H-5), 4.48 (br s, 1H), 4.65 (br s, 1H), 7.28−7.50 (m, 6H), 7.66−7.73 (m, 4H); ^{13}C NMR (75.3 MHz) δ 19.4, 21.9, 23.5, 27.1, 27.9, 30.2, 37.9, 39.3, 40.4, 40.7, 49.5, 62.8, 74.1, 111.4, 127.5, 127.7, 129.7, 129.8, 133.3, 134.4, 135.9, 136.0, 143.9, 213.5; HRMS calcd for $C_{30}H_{40}O_2Si$ 460.2797, found 460.2804. Anal. Calcd: C, 78.21; H, 8.75. Found: C, 77.88; H, 8.68.

Epimerization of 23. To a cold (−78 °C), stirred solution of the cis-fused compound **23** (264 mg, 0.573 mmol) in dry MeOH (11.5 mL) was added a solution of NaOMe in MeOH (0.40 M, 1.1 mL, 0.44 mmol). The pale yellow solution was warmed to rt and stirred for 19 h. The MeOH was removed under reduced pressure and H_2O (10 mL) and Et_2O (20 mL) were added to the residue. The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. ^1H NMR spectroscopic analysis of the oil thus obtained indicated a 7:1 ratio of compounds **24** and **23**, respectively. Flash chromatography of the crude oil (25 g of silica gel, 19:1 petroleum ether/Et_2O) yielded 223 mg (84%) of the trans-fused compound **24** and 35 mg (13%) of the cis-fused compound **23**.

The recovered **23** (35 mg, 0.076 mmol) was subjected to the above epimerization conditions (2.0 mL MeOH, 0.15 mL of a 0.4 M NaOMe/MeOH solution). Flash chromatography (8 g of silica gel, 19:1 petroleum ether/Et_2O) of the crude product provided a further 24 mg of **24**. After one additional epimerization/chromatography sequence, a total of 247 mg (94%) of the crystalline trans-fused **24** was obtained.

(1*S*,2*R*,5*S*,6*S*,9*S*)-(−)-5-(*tert*-Butyldiphenylsiloxy)-2,6-dimethyl-9-(methallyl)bicyclo[4.3.0]nonan-2-ol (25). To a cold (−20 °C), stirred solution of the trans-fused **24** (61 mg, 0.13 mmol) in dry Et_2O (2.6 mL) was added a solution of MeLi in Et_2O (1.4 M, 140 μL, 0.20 mmol). The solution was warmed to −5 °C over the course of 1.5 h. A few drops of H_2O were added, and the solution was dried ($MgSO_4$), filtered, and concentrated. The crude product was flash chromatographed (8 g of silica gel, 9:1 petroleum ether/Et_2O), and after removal of trace amounts of solvent (vacuum pump) from the resultant liquid, 55 mg (87%) of the tertiary alcohol (−)-**25**, a colorless oil, was obtained: $[\alpha]^{25}_D$ −75.2 (*c* 0.04, $CHCl_3$); IR (neat) 3583, 3481, 3071, 1650, 1590, 1111, 1052, 703 cm^{-1}; ^1H NMR (400 MHz) δ 0.79 (br d, 1H, J = 11 Hz, H-1), 1.05 (s, 9H), 1.00−1.10 (m, 1H), 1.11−1.20 (m, 2H), 1.17 (s, 3H), 1.20 (d, 3H, J = 0.6 Hz), 1.23−1.36 (m, 2H), 1.42−1.47 (m, 1H), 1.61−1.73 (m, 2H), 1.71 (s, 3H), 1.80−1.93 (m, 2H), 2.24−2.32 (m, 1H), 2.52 (br d, 1H, J = 14 Hz), 3.37−3.41 (dd, 1H, J = 11.5, 4.5 Hz), 4.66 (br s, 1H), 4.71 (br s, 1H), 7.34−7.45 (m, 6H), 7.65−7.71 (m, 4H); ^{13}C NMR (75.3 MHz) δ 15.2, 19.5, 22.6, 27.0, 27.9, 28.2, 31.6, 33.4, 39.1, 40.9, 45.8, 48.4, 58.8, 71.8, 81.0, 110.7, 127.3, 127.4, 129.3, 129.5, 134.1, 135.2, 135.9, 136.0, 145.5; HRMS calcd for $C_{27}H_{35}O_2Si$ (M^+ − CMe_3) 419.2406, found 419.2409. Anal. Calcd for $C_{31}H_{44}O_2Si$: C, 78.10; H, 9.30. Found: C, 78.12; H, 9.41.

(−)-Homalomenol B (2). To a stirred solution of the tertiary alcohol **25** (52 mg, 0.11 mmol) in dry THF (2.2 mL) at rt was added a solution of TBAF in THF (1.0 M, 550 μL, 0.55 mmol). The mixture was refluxed for 17 h. The solution was cooled to rt and H_2O (5 mL) and Et_2O (10 mL) were added. The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 10 mL) and EtOAc (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residual oil was flash chromatographed (8 g of silica gel, 3:2 petroleum ether/EtOAc). Recrystallization (EtOAc/petroleum ether) of the acquired solid yielded 25 mg (95%) of (−)-**2**, a colorless crystalline solid: mp 94−95 °C; $[\alpha]^{20}_D$ −43.0 (*c* 1.71, $CHCl_3$); lit.[1] $[\alpha]^{20}_D$ of (+)-homalomenol B +20.4 (*c* 1.745, $CHCl_3$); IR (KBr) 3632, 3371, 3070, 1649, 1194, 1024, 894 cm^{-1}; ^1H NMR (400 MHz, referenced at δ 7.24) δ 0.92 (d, 1H, J = 11 Hz), 1.02 (br d, 3H, J = 0.9 Hz), 1.09 (br s, 1H, tertiary OH, exchanges with D_2O), 1.15−1.27 (m, 2H), 1.25 (s, 3H), 1.30−1.37 (m, 2H, one of which is the secondary OH, which exchanges with D_2O), 1.41−1.66 (m, 3H), 1.70 (s, 3H), 1.72−1.83 (m, 2H), 1.84−1.94 (m, 1H), 2.24−2.34 (m, 1H), 2.56 (br d, 1H, J = 14 Hz), 3.34−3.38 (ddd, 1H, J = 11.5, 4.5, 4.5 Hz, collapses to a dd (J = 11.5, 4.5 Hz) upon addition of D_2O), 4.66 (br s, 1H), 4.71 (br s, 1H); ^{13}C NMR (75.3 MHz) δ 14.5, 22.6, 27.7, 28.0, 31.7, 33.3, 38.3, 41.0, 45.8, 47.7, 59.1, 71.8, 79.7, 110.8, 145.4; HRMS calcd for $C_{15}H_{26}O_2$ 238.1933, found 238.1927. Anal. Calcd: C, 75.58; H, 10.99. Found: C, 75.80; H, 11.14.

(1*S*,5*S*,6*S*,9*S*)-(−)-5-(*tert*-Butyldiphenylsiloxy)-6-methyl-9-(2-methyl-1-propenyl)bicyclo[4.3.0]nonan-2-one (28), (1*R*,5*S*,6*S*,9*S*)-(−)-5-(*tert*-Butyldiphenylsiloxy)-6-methyl-9-(2-methyl-1-propenyl)bicyclo-[4.3.0]nonan-2-one (29), and (1*R*,5*S*,6*S*,9*R*)-(−)-5-(*tert*-Butyldiphenylsiloxy)-6-methyl-9-(2-methyl-1-propenyl)bicyclo[4.3.0]nonan-2-one (30). To a cold (−78 °C), stirred solution of *t*-BuLi (1.62 M in pentane, 4.8 mL, 7.8 mmol) in dry THF (40 mL) was added slowly (over ∼1 h via a small cannula) a solution of 1-iodo-2-methylpropene[26] (701 mg, 3.85 mmol) in dry THF (8 mL). The clear yellow solution became a cloudy, colorless mixture. To the cold (−78 °C), stirred mixture was added (via a large cannula) a clear yellow solution of LiCl (326 mg, 7.69 mmol) and CuCN (345 mg, 3.85 mmol) in dry THF (13 mL).[28] $BF_3 \cdot Et_2O$ (450 μL, 3.6 mmol) was added to the resultant orange-red solution containing the organocopper(I) reagent **27**. Cannulation of dry TMS-Br (558 mg, 3.64 mmol) into the red solution was followed by the addition of a solution of the enone **4** (245 mg, 0.605 mmol) in dry THF (5 mL). The mixture was stirred at −78 °C for 6.5 h. The solution was treated at −78 °C with H_2O (15 mL), and the mixture was stirred, open to the atmosphere, for 1 h. Aqueous NH_4Cl/NH_4OH (pH 8−9, 50 mL) and Et_2O (50 mL) were added, and the mixture was stirred vigorously until the aqueous layer became bright blue. The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed (brine, 1 × 75 mL), dried ($MgSO_4$), and concentrated. The ^1H NMR spectrum of the crude oil thus obtained indicated that the starting material had been consumed and that the ratio of isomers **28**:**29**:**30** was ∼4:62:34.

Flash chromatography (25 g of silica gel, 19:1 petroleum ether/Et_2O) of the crude oil provided 9.4 mg (3.4%) of **28** and 220 mg (78%) of a mixture of **29** and **30**. The mixture of **29** and **30** (218 mg, 0.47 mmol) was dissolved in MeOH (9 mL), and the solution was cooled to −78 °C. A solution of NaOMe in MeOH (0.40 M, 1.2 mL, 0.48 mmol) was added, and the solution was warmed to rt and stirred for 17.5 h. The mixture was worked up (see previous procedure for the epimerization **23**), and analysis of the crude product mixture by ^1H NMR spectroscopy indicated that the ratio of isomers **28**:**29**:**30** was 36:28:36. Flash chromatography (15 g of silica gel, 19:1 petroleum ether/Et_2O) of this material provided 64 mg (23% with respect to the enone **4**) of **28** and 140 mg of a mixture of **29** and **30**. The remaining mixture (140 mg of **29** and **30**) was resubjected to the epimerization conditions and the desired isomer **28** was again isolated by flash chromatography. This process was repeated once more (i.e., three epimerization/chromatography sequences in total). The overall yield of the desired isomer (−)-**28**, based on the enone substrate **4**, was 120 mg (43%); $[\alpha]^{25}_D$ −8.0 (*c* 1.05, $CHCl_3$); IR (neat) 1723, 1590, 1112, 1064, 703 cm^{-1}; ^1H NMR (400 MHz) δ 0.91 (s, 3H), 1.06 (s, 9H), 0.97−1.48 (m, 4H), 1.60 (br s, 3H), 1.70 (br s, 3H), 1.73−2.07 (m, 5H, one of which is H-1 (d, J = 10.5 Hz)), 3.03−3.10 (dddd, 1H, J = 10.5, 10.5, 10.5, 6.5 Hz, H-9), 3.87−3.91 (dd, 1H, J = 10.5, 5 Hz, H-5), 4.78 (br d, 1H, J = 10.5 Hz), 7.36−7.48 (m, 6H), 7.66−7.72 (m, 4H); ^{13}C NMR (75.3 MHz) δ 13.4, 18.2, 19.4, 25.8, 27.0, 28.9, 32.1, 33.8, 38.7, 39.6, 52.5, 63.5, 78.8, 127.5, 127.6, 128.7, 129.6, 129.8, 131.5, 133.6, 134.5, 135.9, 136.0, 209.4; HRMS calcd for $C_{30}H_{40}O_2Si$ 460.2797, found 460.2793. Anal. Calcd: C, 78.21; H, 8.75. Found: C, 78.15; H, 8.81.

Subjection of the initially obtained mixture of **29** and **30** to flash chromatography as described above gave, in the first few fractions eluted from the column, pure ketone **30**, a solid. This material was recrystallized from petroleum ether/Et_2O to provide **30** as a colorless crystalline solid: mp 72−74 °C; $[\alpha]^{25}_D$ −30.0 (*c* 1.94, $CHCl_3$); IR (KBr) 1709, 1589, 1109, 1093, 704 cm^{-1}; ^1H NMR (400 MHz) δ 1.02−1.16 (m, 1H), 1.07 (s, 9H),

1.16 (s, 3H), 1.23−1.40 (m, 1H), 1.42 (d, 3H, J = 1 Hz), 1.61 (d, 3H, J = 1 Hz), 1.57−1.70 (m, 1H), 1.82−1.96 (m, 3H), 2.00 (d, 1H, J = 11.5 Hz, H-1), 2.12−2.28 (m, 2H), 2.79−2.88 (m, 1H, H-9), 3.86−3.91 (dd, 1H, J =10.5, 4 Hz, H-5), 4.92 (br d, 1H, J = 9 Hz), 7.36−7.48 (m, 6H), 7.66−7.73 (m, 4H); ^{13}C NMR (75.3 MHz) δ 18.0, 19.5, 21.2, 25.6, 27.0, 29.7, 31.6, 35.9, 37.6, 42.9, 51.7, 67.8, 73.1, 127.5, 127.7, 129.6, 129.8, 132.1, 133.4, 134.4, 135.9, 136.0, 212.2; HRMS calcd for $C_{30}H_{40}O_2Si$ 460.2797, found 460.2799. Anal. Calcd: C, 78.21; H, 8.75. Found: C, 78.28; H, 8.64.

Compound **29** was obtained in a pure form from the late fractions of the above-mentioned flash chromatography. The oil obtained, upon heating at 80−100 °C (0.2 Torr) for 1 h to remove residual solvent, provided pure **29**: $[\alpha]^{25}_D$ −33.5 (*c* 0.84, $CHCl_3$); IR (neat) 1704, 1590, 1112, 1089, 704 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.08 (s, 9H), 1.08−1.17 (m, 1H), 1.17 (s, 3H), 1.31−1.39 (m, 1H), 1.43 (d, 3H, J = 0.8 Hz), 1.50 (br s, 3H), 1.74−2.00 (m, 5H), 2.15−2.19 (m, 1H), 2.48−2.51 (br dd, 1H, J = 10, 2 Hz, H-1), 3.12−3.21 (m, 1H, H-9), 3.77−3.81 (br dd, 1H, J = 10.5, 4 Hz, H-5), 4.51 (br d, 1H, J = 10 Hz), 7.37−7.49 (m, 6H), 7.66−7.75 (m, 4H); ^{13}C NMR (75.3 MHz) δ 18.0, 19.4, 21.6, 25.7, 27.0, 29.0, 31.8, 38.5, 39.6, 41.4, 49.5, 64.8, 73.6, 126.6, 127.4, 127.7, 129.6, 129.8, 133.4, 133.5, 134.5, 135.9, 136.0, 212.7; HRMS calcd for $C_{30}H_{40}O_2Si$ 460.2797, found 460.2797.

(1*S*,2*R*,5*S*,6*S*,9*S*)-(−)-5-(*tert*-Butyldiphenylsiloxy)-2,6-dimethyl-9-(2-methyl-1-propenyl)bicyclo[4.3.0]nonan-2-ol (31). To a cold (−20 °C), stirred solution of the trans-fused compound **28** (170 mg, 0.369 mmol) in dry Et_2O (7 mL) was added a solution of MeLi in Et_2O (1.4 M, 530 μL, 0.74 mmol). The solution was warmed to −5 °C over the course of 1 h. H_2O (10 mL) was added, and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 15 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated. The crude oil was flash chromatographed (8 g of silica gel, 9:1 petroleum ether/Et_2O) to afford, after recrystallization of the acquired solid from Et_2O/petroleum ether, 141 mg (80%) of the (−)-tertiary alcohol **31** as a colorless crystalline solid: mp 98−100 °C; $[\alpha]^{25}_D$ −43.0 (*c* 1.71, $CHCl_3$); IR (KBr) 3602, 3072, 1590, 1111, 703 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.86 (d, 1H, J = 11.5 Hz), 0.97 (s, 1H, OH, exchanges with D_2O), 1.01 (s, 3H), 1.04 (s, 9H), 1.01−1.20 (m, 3H), 1.21 (s, 3H), 1.26−1.35 (m, 1H), 1.41−1.45 (ddd, 1H, J = 14.5, 4.5, 2.5 Hz), 1.62−1.65 (m, 1H), 1.62, 1.63 (d, d, 3H each, J = 1 Hz for each d), 1.79−1.90 (ddd, 1H, J = 18, 14, 4.5 Hz), 1.98−2.08 (m, 1H), 2.86−2.95 (m, 1H), 3.35−3.39 (dd, 1H, J = 11.5, 4 Hz), 5.00 (br d, 1H, J = 9.5 Hz), 7.34−7.42 (m, 6H), 7.68−7.70 (m, 4H); ^{13}C NMR (75.3 MHz) δ 14.9, 18.1, 19.5, 25.7, 27.0, 28.4, 29.5, 30.5, 35.0, 39.4, 40.4, 47.8, 58.8, 71.7, 81.3, 127.3, 127.4, 128.4, 129.3, 129.5, 132.4, 134.1, 135.3, 135.9, 136.0; HRMS calcd for $C_{31}H_{44}O_2Si$ 476.3110, found 476.3103. Anal. Calcd: C, 78.10; H, 9.30. Found: C, 78.12; H, 9.34.

(−)-Homalomenol A (1). To a stirred solution of **31** (141 mg, 0.296 mmol) in dry THF (6 mL) at rt was added a solution of TBAF in THF (1.0 M, 2.4 mL, 2.4 mmol). The mixture was refluxed for 18 h. The solution was cooled to rt; H_2O (25 mL) and Et_2O (25 mL) were added, and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 20 mL) and EtOAc (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude oil was flash chromatographed (8 g of silica gel, 3:2 petroleum ether/EtOAc) to yield 61 mg (87%) of (−)-**1**, a white solid. Recrystallization of this material from Et_2O/petroleum ether provided (−)-**1** as thin, needlelike plates: mp 99−100 °C; $[\alpha]^{20}_D$ −51.5 (*c* 1.30, $CHCl_3$); lit.[1] for (+)-homalomenol A oil, $[\alpha]^{20}_D$ +33.2 (*c* 1.205, $CHCl_3$); IR (KBr) 3617, 3434, 1581, 1023 cm^{-1}; ^{1}H NMR (400 MHz, referenced at δ 7.24) δ 0.93 (s, 1H, OH, exchanges with D_2O), 0.99 (d, 1H, J = 11.5 Hz), 1.04 (d, 3H, J = 0.7 Hz), 1.10 (s, 3H), 1.19−1.39 (m, 3H), 1.41−1.46 (dd, 1H, J = 14, 5 Hz), 1.52−1.64 (m, 3H), 1.63, 1.64 (d, d, 3H each, J = 1.5 Hz for each d), 1.73−1.84 (m, 1H), 2.00−2.11 (m, 1H), 2.88−2.98 (m, 1H), 3.35−3.38 (dd, 1H, J = 11.4, 4.1 Hz), 5.05 (br d, 1H, J = 9.5 Hz); ^{13}C NMR (75.3 MHz) δ 14.1, 18.1, 25.7, 27.9, 29.6, 30.7, 34.9, 38.6, 40.6, 47.1, 59.0, 71.7, 80.0, 128.7, 132.1; HRMS calcd for $C_{15}H_{26}O_2$ 238.1933, found 238.1930. Anal. Calcd: C, 75.58; H, 10.99. Found: C, 75.29; H, 11.12.

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