JOC*Note*

First Enantioselective Synthesis and Absolute Stereochemistry Assignment of New Monocyclic Sesquiterpenes from *Artemisia chamaemelifolia*

Jean-Pierre Uttaro, Gérard Audran, Elie Palombo, and Honoré Monti*

Laboratoire de Réactivité Organique Sélective UMR 6516 Faculté des Sciences de St-Jérôme, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France

honore.monti@univ.u-3mrs.fr

Received April 2, 2003

Abstract: We herein report the first enantioselective synthesis of two new monocyclic sesquiterpenes from *Artemisia chamaemelifolia* starting from an enantiopure building block. The key feature of the present approach is to allow complete control of all the stereogenic centers present in the natural products and to elucidate their absolute stereochemistry, which to date is unknown.

Oxygenated monocyclic terpenoids are not very common metabolites in nature because biosynthetic processes are usually based on polycyclization. However, during the past few years, identification of several natural oxygenated monocyclic sesquiterpenes suggests that they may be more prevalent than it was presumed within the plant kingdom.[1] In 1996, Marco et al.[2] isolated three new monocyclic sesquiterpenes **1**−**3** from the aerial parts of *Artemisia chamaemelifolia* ssp. *Chamaemelifolia* (Figure 1). These authors established both the structure and relative stereochemistry of **1**−**3** by spectroscopy, but since then, only one racemic synthesis of **2** and **3** has been published[3] and the absolute configurations still remain unknown.

Starting from an enantiopure building block for the introduction and determination of the absolute stereochemistry, we have carried out the first enantioselective synthesis of (+)-**1** to confirm the structural assignment and to determine the absolute stereochemistry of the four chiral centers present in the natural product. Our methodology is depicted in Schemes 1 and 2. After achieving the efficient synthesis of derivative (+)-**1**, we then sought to use it as a valuable starting block for the expeditious two-step synthesis of (−)-**2**. We had in mind that the three remaining chiral centers share the same absolute stereochemistry because it was suggested that compound (+)-**1** is formed from (−)-**2** by enzymatic oxidation, most likely via an intermediate hydroperoxide.[2] Our approach is outlined in Scheme 3.

We recently reported the straightforward synthesis of the required enantiopure building blocks, (1*R*,5*S*)-8,8-dimethyl-2-methylene-6-oxabicyclo[3.2.1]octan-7-one, (+)-**4** (karahana lactone), or its enantiomer.[4] Starting from (+)-**4**, allylic hydroxylation with SeO_2/*t*-BuOOH (70 wt % in water) in dichloromethane afforded, after stirring for 3 days under reflux, the alcohol (+)-**5** as a single stereoisomer in 85% isolated yield.[5]

The stereochemistry of the hydroxyl function was inverted at this stage by a two-step procedure. Dess−Martin periodinane[6] oxidation of (+)-**5** and subsequent $NaBH_4$−$CeCl_3$ Luche reduction[7] of the intermediate ketone afforded the single stereomer *epi*-**5** in 83% yield over two steps. Each product was found to be pure enough for the next step, but our attempts to stringently purify them resulted in partial degradation. Thus, only a small sample was purified by silica gel column chromatography for the purpose of characterization. The stereochemistry at the 3-position of *epi*-**5** was unambiguously assigned, based on NOESY analysis (Figure 2). A strong correlation between the signal at $\delta = 1.0$ (Me) and $\delta = 1.71$ (4-H) means that these chemical shifts could be assigned to 10β-Me_{ax} and 4β-H_{ax}. Moreover, a NOE effect for 5β-H_{eq} ($\delta = 4.34$), 4β-H_{ax}, for 4α-H_{eq} ($\delta = 2.50$), 5β-H_{eq}, 3-H ($\delta = 4.37$) and the absence of NOE for 4β-H_{ax}, 3-H established the 3α-H_{ax} position.

The protection of the hydroxyl group of *epi*-**5** was conducted on the crude alcohol, and TBS (*tert*-butyldimethylsilane) derivative (+)-**6** was obtained in 78% yield using the usual method (TBSCl, imidazole, DMF).[8] Reduction of (+)-**6** with diisobutylaluminum hydride (DIBAL) in toluene at −78 °C afforded a mixture of diastereomeric lactols **7** in 89% yield. Application of the mild and efficient barium hydroxide-promoted Horner−Wadsworth−Emmons (HWE) reaction[9] to the mixture **7**, using the barium derivative of diethyl-2-oxopropylphosphonate in THF at room temperature, gave 92% as an easily separable 1:3 mixture of the expected derivative (+)-**8** and diastereomeric bicyclic compounds **9** resulting from the intramolecular domino[10] oxa-conjugate addition of the hydroxyl group to the intermediate enone system generated by the HWE reaction. Acetylation of (+)-**8** using the usual procedure (Ac_2O, pyridine) and irreversible retro-Michael acetylation of **9** by heating under reflux with acetic anhydride and pyridinium *p*-toluenesulfonate (PPTS) furnished crystalline (+)-**10** (mp 40 °C) as a single *E* stereomer ($^3J_{trans} = 15.8$ Hz) in 91% and 89% yield,

(1) (a) Barrero, A. F.; Alvarez-Manzaneda R., E. J.; Alvarez-Manzaneda R., R. *Tetrahedron Lett.* **1989**, *30*, 3351. (b) Barrero, A. F.; Manzaneda R., E. A.; Manzaneda R., R. A.; Arseniyadis, S.; Guittet, E. *Tetrahedron* **1990**, *46*, 8161. (c) Barrero, A. F.; Haidour, A.; Muñoz-Dorado, M.; Akssira, M.; Sedqui, A.; Mansour, I. *Phytochemistry* **1998**, *48*, 1237. (d) Akihisa, T.; Arai, K.; Kimura, Y.; Koike, K.; Kokke, W. C. M. C.; Nikaido, T. T. *J. Nat. Prod.* **1999**, *62*, 265. (e) Barrero, A. F., Alvarez-Manzaneda, E. J.; Herrador, M. M.; Alvarez-Manzaneda, R.; Quilez, J.; Chahboun, R.; Linarez, P.; Rivas, A. *Tetrahedron Lett.* **1999**, *40*, 8273. (f) Akihisa, T.; Akai, K.; Kimura, Y.; Koike, K.; Kokke, W. C. M. C.; Shibata, T.; Nikaido, T. *Lipids* **1999**, *34*, 1151. (g) Caglioti, L.; Naef, H.; Arigoni, D.; Jeger, O. *Helv. Chim. Acta* **1959**, *42*, 2557. (h) Marco, J. A.; Sanz, J. F.; Yuste, A.; Carda, M.; Jakupovic, J. *Phytochemistry* **1991**, *30*, 3661.

(2) Marco, J. A.; Sanz-Cervera, J. F.; Morante, M. D.; Garcia-Lliso, V.; Valles-Xirau, J.; Jakupovic, J. *Phytochemistry* **1996**, *41*, 837.

(3) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Rivas, A. R.; Palomino, P. L.; *Tetrahedron* **2000**, *56*, 6099.

(4) Galano, J. M.; Audran, G.; Monti, H. *Tetrahedron* **2000**, *56*, 7477.

(5) The data match spectral data for the enantiomer of (+)-**5**: Audran, G.; Uttaro, J.-P.; Monti, H. *Synlett* **2002**, 1261.

(6) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(7) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(8) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(9) Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774.

(10) (a) Ho, T.-L. *Tandem Organic Reactions*; Wiley: New York, 1992. Reviews: Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Bunce, R. A. *Tetrahedron* **1995**, 51, 13103. (c) Rodriguez, J. *Synlett* **1999**, 505.

10.1021/jo034424y CCC: $25.00
Published on Web 05/23/2003

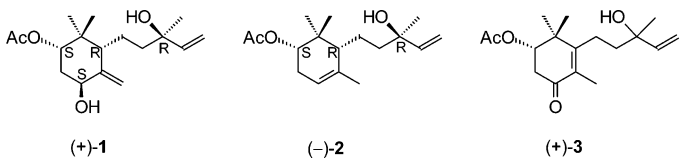
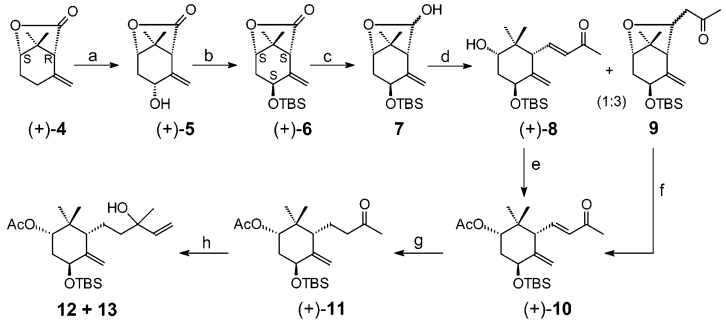


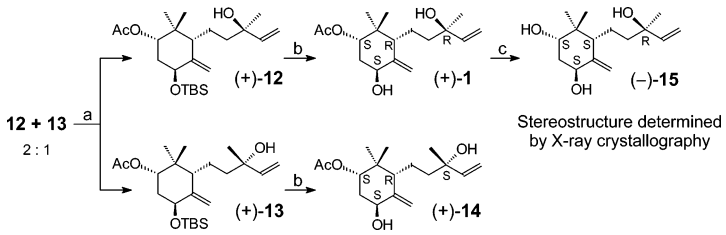
FIGURE 1. Natural monocyclic sesquiterpenes **1**−**3**: (+)-**1** and (−)-**2** are represented with the absolute stereochemistry as determined in this work.

SCHEME 1[a]



[a] Reagents and conditions: (a) cat. SeO_2, cat. salicylic acid, *t*-BuOOH 70% in water, CH_2Cl_2, reflux, 85%; (b) (i) Dess−Martin reagent, CH_2Cl_2, (ii) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −18 °C, 83% (two steps), (iii) TBSCl, imidazole, DMF, rt, 78%; (c) DIBAL, toluene, −78 °C, 89%; (d) $(EtO)_2P(O)CH_2COMe$, $Ba(OH)_2$, THF, rt, 92%; (e) Ac_2O, cat. DMAP, Pyr, rt, 91%; (f) Ac_2O, PPTS, toluene, reflux, 89%; (g) $HSnBu_3$, cat. $Pd(PPh_3)_4$, $ZnCl_2$, THF, rt,83%; (h) CH_2═$CHMgBr$, THF, −20 °C, 90%.

SCHEME 2[a]



[a] Reagents and conditions: (a) separated by flash chromatography; (b) TBAF, THF, rt, 95%; (c) $LiAlH_4$, ether, rt, 99%.

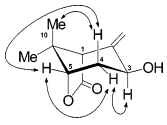
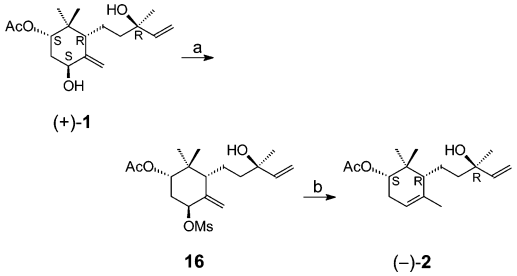


FIGURE 2. Selected NOESY interactions for *epi*-**5**.

respectively.[11] The chemoselective 1,4-conjugate reduction of the α,*β*-enone system of (+)-**10** using Bu_3SnH/cat. $Pd(PPh_3)_4$ in the presence of anhydrous $ZnCl_2$ as the reducing system[12] yielded 83% of (+)-**11**. Subsequent exposure of (+)-**11** to vinylmagnesium bromide furnished the two desired diastereomeric alcohols **12** and **13** in a 2:1 ratio and 90% combined yield.

Gratifyingly, (+)-**12** and (+)-**13** differ significantly in polarity and therefore proved to be chromatographically separable at this stage (Scheme 2). Removal of the TBS protecting group of (+)-**12**, the first eluted derivative, and (+)-**13** furnished the corresponding dihydroxy acetate (+)-**1** and (+)-**14**, respectively. The spectroscopic data (IR, ^1H and ^{13}C NMR) of synthetic (+)-**1** matched that reported for natural **1** and the specific rotation was comparable in magnitude and the same in sign, indicating the synthesis of the natural enantiomer.[2] The remaining task for the complete identification was the determination of the absolute stereochemistry of the quaternary stereogenic center at the side chain of (+)-**1**. This stereochemistry was unequivocally determined to be the *R* configuration via reduction of (+)-**1** to the corresponding crystalline triol (−)-**15** and subsequent X-ray crystallographic analysis. Therefore, the absolute stereochemistry of the natural product was established as (+)-**1**, depicted in Scheme 2 and Figure 1.

SCHEME 3[a]



[a] Reagents and conditions: (a) MsCl, CH_2Cl_2−Pyr (1:1), rt, (b) 5 equiv of $LiAlH(O\text{-}t\text{-}Bu)_3$, Et_2O, rt, 70% (two steps).

With (+)-**1** in hand, our attention was then focused on the synthesis of the target molecule (−)-**2** from (+)-**1**

(11) Harrison, I. T.; Grayshan, R.; Williams, T.; Semenovski, A.; Fried, J. H. *Tetrahedron Lett.* **1972**, *13*, 5151.
(12) (a) Four, P.; Guibe, F. *Tetrahedron Lett.* **1982**, *23*, 1825. (b) Xian, Y. T.; Four, P.; Guibe, F.; Balavoine, G. *Nouv. J. Chim.* **1984**, *8*, 611.

using, as the key step, the reductive transposition of an allylic derivative (Scheme 3).

Of the several methods available to reach our goal,[13] the two-step procedure involving transformation of (+)-**1** into **16** and hydrogenolysis of the crude allylic mesylate with $LiAlH(O\text{-}t\text{-}Bu)_3$ was found to be the most effective, giving the desired target (−)-**2** and its exocyclic double bond regioisomer in a 92:8 ratio and 70% yield (two steps). This byproduct posed minimal problem as it was easily removed by careful flash chromatography to afford pure (−)-**2** whose optical rotation and spectroscopic properties are identical to those reported for the natural product.[2] This is in agreement with our working assumption and therefore, the absolute stereochemistry of the natural product was established as (−)-**2**, depicted in Scheme 3 and Figure 1.

In summary, an asymmetric synthesis of two new monocyclic sesquiterpenes isolated from *A. chamaemelifolia* has been achieved for the first time, and the absolute configurations have been fully determined. The merits of this approach are high-yielding reaction steps, secured absolute stereochemistry, and applicability of this methodology to the synthesis of the enantiomers, starting from (−)-**4**. We trust that this work will be useful for the characterization of these molecules, in the event of their isolation in other natural sources, and to deduce the absolute configurations, simply by the measurement of the specific rotation. This will enrich the natural products databases.

Experimental Section

(1*R*,3*R*,5*S*)-3-Hydroxy-8,8-dimethyl-2-methylene-6-oxabicyclo[3.2.1]octan-7-one (+)-5. To a stirred solution of (+)-**4** (1.20 g, 7.22 mmol) in dry CH_2Cl_2 (80 mL) were added selenium dioxide (321 mg, 2.89 mmol), *tert*-butyl hydroperoxide (70 wt % in water, 2.60 g, 28.88 mmol), and a catalytic amount of salicylic acid under an argon atmosphere. The reaction mixture was heated to reflux for 3 days and cooled to rt, and Na_2SO_3 (7.50 g, 60 mmol) and 1 mL of water were added. The mixture was stirred for a further 30 min, filtered through a pad of $MgSO_4$, and concentrated to give a residue solid. After purification by crystallization from Et_2O−hexane, 1.13 g of pure alcohol (+)-**5** was obtained as white crystals (86%). Mp = 157 °C. $[\alpha]^{25}_D$ = +145.0 (*c* 1.0, $CHCl_3$). IR (KBr): ν 3440, 3091, 1759, 905 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.18 (s, 1H), 5.07 (s, 1H), 4.42 (d, J = 6.1 Hz, 1H), 4.35 (br d, J = 3.7 Hz, 1H), 2.76 (s, 1H), 2.23 (dd, J = 15.7, 3.8 Hz, 1H), 2.08 (ddd, J = 15.7, 6.1, 1.5 Hz, 1H), 1.21 (s, 3H), 0.94 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 176.6 (C), 143.9 (C), 117.0 (CH_2), 84.4 (CH), 67.9 (CH), 56.6 (CH), 42.8 (C), 32.6 (CH_2), 25.3 (CH_3), 20.1 (CH_3). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.72; H, 7.71.

(1*S*,3*S*,5*S*)-3-(*tert*-Butyldimethylsilyloxy)-8,8-dimethyl-2-methylene-6-oxabicyclo[3.2.1]octan-7-one (+)-6. To a stirred solution of alcohol (+)-**5** (1.00 g, 5.49 mmol) in dry CH_2Cl_2 (40 mL) at 0 °C was added Dess−Martin periodinane (3.48 g, 8.24 mmol) under an argon atmosphere. After being stirred for 1 h at rt, the mixture was poured into a solution of Na_2SO_3 (4.84 g, 38.43 mmol) and extracted with CH_2Cl_2. The organic layers were combined, washed with a saturated solution of $NaHCO_3$ and brine, dried, filtered, and concentered to afford 970 mg (98% crude) of ketone. A small sample of the oily residue was chromatographed on silica gel and recrystallized (Et_2O−hexane) for characterization. Mp = 127 °C. $[\alpha]^{25}_D$ = +94.7 (*c* 1.0, $CHCl_3$). IR (KBr): ν 3082, 1763, 1674, 1629, 891 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 6.28 (s, 1H), 5.53 (s, 1H), 4.51 (s, 1H), 3.15 (s, 1H), 2.83 and 2.66 (AB, J = 19.7, 2.4, 1.8 Hz, 2H), 1.30 (s, 3H), 1.10 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 193.6 (C), 174.8 (C), 138.5 (C), 126.1 (CH_2), 83.3 (CH), 56.3 (CH), 41.6 (C), 41.2 (CH_2), 24.8 (CH_3), 19.3 (CH_3). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.87; H, 6.68.

To a stirred solution of the above ketone (950 mg, 5.27 mmol) in MeOH (80 mL) was added $CeCl_3{\cdot}7H_2O$ (2.55 g, 6.85 mmol) under an argon atmosphere. After being stirred for 1 h at rt, the solution was cooled to −18 °C and $NaBH_4$ (220 mg, 5.80 mmol) was added. The solution was stirred for 15 min and concentrated under reduced pressure. Water (200 mL) and CH_2Cl_2 (100 mL) were added to the residue. After extraction with CH_2Cl_2, the combined extracts were dried with $MgSO_4$ and concentrated in vacuo to afford 813 mg of crude alcohol (85% yield; 83% for the two steps). A part of the residue was chromatographed on silica gel, recrystallized (Et_2O−hexane), and characterized. Mp = 78 °C. $[\alpha]^{25}_D$ = +162.0 (*c* 1.0, $CHCl_3$). IR (KBr): ν 3451, 3083, 1762, 894 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.28 (d, J = 2.2 Hz, 1H), 5.00 (d, J = 2.2 Hz, 1H), 4.37 (br t, J = 8.0 Hz, 1H), 4.34 (d, J = 4.3 Hz, 1H), 2.85 (s, 1H), 2.50 (ddd, J = 13.4, 7.8, 4.3 Hz, 1H), 1.71 (dd, J = 13.9, 9.7 Hz, 1H), 1.16 (s, 3H), 1.01 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.4 (C), 142.8 (C), 111.1 (CH_2), 85.6 (CH), 65.9 (CH), 58.5 (CH), 42.9 (C), 34.8 (CH_2), 24.8 (CH_3), 20.2 (CH_3). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.64; H, 7.72.

The above crude alcohol (725 mg, 3.98 mmol) was dissolved in DMF (20 mL), imidazole (813 mg, 11.94 mmol) and *tert*-butyldimethylsilyl chloride (1.20 g, 7.96 mmol) were added, and the mixture was stirred for 12 h at rt. The solution was concentrated in vacuo, and the residue was purified by column chromatography to give 920 mg (78%) of compound (+)-**6** as a solid. Recrystallization from Et_2O−hexane afforded pure (+)-**6** as white crystals. Mp = 72 °C. $[\alpha]^{25}_D$ = +127.8 (*c* 1.0, $CHCl_3$). IR (KBr): ν 3086, 1761, 1642, 892 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.24 (dd, J = 2.1, 1.5 Hz, 1H), 4.94 (br s, 1H), 4.36−4.30 (m, 2H), 2.84 (s, 1H), 2.38 (ddd, J = 13.7, 7.8, 4.4 Hz, 1H), 1.71 (dd, J = 13.8, 9.2 Hz, 1H), 1.16 (s, 3H), 1.01 (s, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.4 (C), 142.7 (C), 111.4 (CH_2), 85.6 (CH), 66.7 (CH), 58.3 (CH), 42.9 (C), 35.7 (CH_2), 25.7 (CH_3), 24.8 (CH_3), 20.3 (CH_3), 18.1 (C), −4.9 (CH_3), −5.1 (CH_3). Anal. Calcd for $C_{16}H_{28}O_3Si$: C, 64.82; H, 9.52. Found: C, 65.09; H, 9.48.

(1′*S*,3′*S*,5′*S*)-(3*E*)-4-(5′-*tert*-Butyldimethylsilyloxy-3′-hydroxy-2′,2′-dimethyl-6′-methylenecyclohex-1′-yl)but-3-en-2-one (+)-8 and (1*S*,3*S*,5*S*)-(3-*tert*-Butyldimethylsilyloxy-8,8-dimethyl-2-methylene-6-oxabicyclo[3.2.1]oct-7-yl Acetone 9. A mixture of diethyl 2-oxopropylphosphonate (1.0 g, 5.18 mmol) and $Ba(OH)_2{\cdot}8H_2O$ (653 mg, 2.07 mmol, heated at 140 °C for 2 h under a flux of argon before use) in THF (6 mL) was stirred at rt for 30 min under an argon atmosphere. A solution of **7** (772 mg, 2.59 mmol) in wet THF (6 mL, 40:1 THF/H_2O) was then added at this temperature. After being stirred for 24 h, the reaction mixture was diluted with CH_2Cl_2 and washed with aqueous $NaHCO_3$ and brine. The organic extract was dried ($MgSO_4$), filtered, and concentrated. Purification by column chromatography gave (+)-**8** as a solid (204 mg) and a partially separable mixture of diastereomers **9** (598 mg). (+)-**8**. Mp = 87 °C. $[\alpha]^{25}_D$ = +58.4 (*c* 1.0, $CHCl_3$). IR (KBr): ν 3423, 3083, 3021, 1735, 1663, 910 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.90 (dd, J = 15.8, 10.2 Hz, 1H), 6.05 (d, J = 15.9 Hz, 1H), 4.94 (s, 1H), 4.59 (s, 1H), 4.33 (br s, 1H), 3.81 (br dd, J = 10.0, 3.6 Hz, 1H), 2.98 (d, J = 10.0 Hz, 1H), 2.25 (s, 3H), 1.90 (dt, J = 13.1, 4.4 Hz, 1H), 1.66 (ddd, J = 13.0,10.2, 3.1 Hz, 1H), 0.94 (s, 3H), 0.85 (s, 9H), 0.80 (s, 3H), −0.02 (s, 3H), −0.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.3 (C), 149.1 (C), 145.7 (CH), 133.4 (CH), 110.8 (CH_2), 73.2 (CH), 72.6 (CH), 51.2 (CH), 40.2 (C), 39.5 (CH_2), 27.2 (CH_3), 26.3 (CH_3), 25.7 (CH_3), 18.1 (C), 14.7 (CH_3), −4.8 (CH_3), −5.2 (CH_3). Anal. Calcd for $C_{19}H_{34}O_3Si$: C, 67.40; H, 10.12. Found: C, 67.74; H, 10.09. Major **9**. $[\alpha]^{25}_D$ = +44.6 (*c* 1.0, $CHCl_3$). IR (film): ν 3068, 1722, 1654, 925 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.16 (br t, J = 2.0 Hz, 1H), 4.75

(13) (a) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons Ltd.: Chichester, 1999; pp 366−379. (b) Hegedus, L. S. In *Organometallics in Synthesis. A Manual*; Schlosser, M., Ed.; John Wiley & Sons Ltd.: Chichester, 2002; pp 1191−1195. (c) Larock, R. C.; John Wiley & Sons: New York, 1999; pp 229−231.

(br t, J = 2.1 Hz, 1H), 4.58 (td, J = 6.7, 3.8 Hz, 1H), 4.38 (tt, J = 8.6, 2.5 Hz, 1H), 3.75 (d, J = 4.1 Hz, 1H), 2.70 and 2.48 (ABX, J = 16.7, 6.9, 6.6 Hz, 2H), 2.39 (d, J = 3.7 Hz, 1H), 2.15 (m partially overlapped, 1H), 2.14 (s, 3H), 1.52 (dd, J = 13.4, 9.1 Hz,1H), 1.14 (s, 3H), 0.95 (s, 3H), 0.91 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 206.7 (C), 148.1 (C), 111.6 (CH_2), 83.0 (CH), 74.7 (CH), 68.1 (CH), 57.4 (CH), 45.1 (CH_2), 42.7 (C), 38.7 (CH_2), 30.8 (CH_3), 25.9 (CH_3), 25.2 (CH_3), 22.2 (CH_3), 18.2 (C), −4.6 (CH_3), −4.9 (CH_3). Anal. Calcd for $C_{19}H_{34}O_3Si$: C, 67.40; H, 10.12. Found: C, 67.13; H, 10.08.

(1*S*,3*S*,5*S*)-5-*tert*-Butyldimethylsilyloxy-2,2-dimethyl-4-methylene-3-[(1′*E*)-3′-oxobut-1′-enyl]cyclohexyl Acetate (+)-10. The alcohol (+)-**8** (175 mg, 0.52 mmol) was dissolved in pyridine−dichloromethane (1:1, 6 mL), Ac_2O (212 mg, 2.08 mmol) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) were added under an argon atmosphere, and the mixture was stirred for 3 h at rt. The solution was poured into water and extracted with ether. The combined organic extracts were washed with water, dried, filtered, and concentrated. Column chromatography gave 179 mg (91%) of (+)-**10** as corlorless crystals. A solution of **9** (550 mg, 1.62 mmol) and Ac_2O (497 mg, 4.87 mmol) in toluene (10 mL) was treated with PPTS (123 mg, 0.49 mmol) and heated at 110 °C for 7 h. After being cooled to 25 °C, the reaction mixture was diluted with Et_2O, washed with aqueous $NaHCO_3$ and brine, and dried ($MgSO_4$). After concentration, column chromatography gave (+)-**10** (550 mg, 89% yield) as colorless crystals. Mp = 40 °C. $[\alpha]^{25}_D$ = +61.9 (c 1.0, $CHCl_3$). IR (KBr): ν 3080, 3015, 1739, 1660, 911 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.90 (dd, J = 15.8, 10.1 Hz, 1H), 6.09 (d, J = 15.7 Hz, 1H), 5.07 (dd, J = 9.6, 4.0 Hz, 1H), 5.00 (s, 1H), 4.65 (s, 1H), 4.33 (br q, J = 2.9 Hz, 1H), 3.06 (d, J = 9.8 Hz, 1H), 2.26 (s, 3H), 2.03 (s, 3H), 1.96−1.89 (m, 1H), 1.76−1.67 (m, 1H), 0.87 (br s, 15H), 0.04 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.9 (C), 170.1 (C), 148.5 (C), 145.0 (CH), 133.2 (CH), 111.0 (CH_2), 75.6 (CH), 71.6 (CH), 52.0 (CH), 39.1 (C), 36.4 (CH_2), 27.4 (CH_3), 26.3 (CH_3), 25.6 (CH_3), 21.1 (CH_3), 18.1 (C), 16.8 (CH_3), −4.9 (CH_3), −5.2 (CH_3). Anal. Calcd for $C_{21}H_{36}O_4Si$: C, 66.27; H, 9.53. Found: C, 65.99; H, 9.49.

(1*S*,3*S*,5*S*)-5-*tert*-Butyldimethylsilyloxy-2,2-dimethyl-3-(3′-hydroxy-3′-methylpent-4′-enyl)-4-methylenecyclohexyl Acetates 12 and 13. To a solution of (+)-**11** (500 mg, 1.30 mmol) in THF (15 mL) at −20 °C under an argon atmosphere was added dropwise vinylmagnesium bromide (1 M in THF, 2.0 mL, 2.0 mmol). The mixture was stirred at −20 °C for 15 min, allowed to warm to 0 °C, and quenched with aqueous NH_4Cl. After being warmed to 25 °C, the reaction mixture was extracted with Et_2O. The organic layer was dried ($MgSO_4$) and concentrated to afford 483 mg (90%) of diastereomers **12** and **13**. Purification by flash chromatography gave 267 mg of pure (+)-**12** (first eluted) and 138 mg of pure (+)-**13**. (+)-**12**. $[\alpha]^{25}_D$ = +14.0 (c 1.0, $CHCl_3$). IR (film): ν 3474, 3069, 1723, 1649, 888 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.90 (dd, J = 17.4, 10.8 Hz, 1H), 5.19 (d, J = 17.4 Hz, 1H), 5.06 (s, 1H), 5.04 (d, J = 10.5 Hz, 1H), 4.98 (dd, J = 8.2, 4.0 Hz, 1H), 4.68 (s, 1H), 4.30 (dd, 1H, J = 6.2, 4.1 Hz), 2.12 (br d, J = 11.9 Hz, 1H), 2.03 (s, 3H), 1.88 (ddd, J = 13.2, 6.5, 4.1 Hz, 1H), 1.74−1.49 (m, 4H), 1.35−1.29 (m, 1H), 1.27 (s, 3H), 0.96 (s, 3H), 0.89 (s, 9H), 0.78 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3 (C), 148.8 (C), 145.2 (CH), 111.5 (CH_2), 109.2 (CH_2), 76.9 (CH), 73.2 (C), 70.7 (CH), 49.2 (CH), 40.9 (CH_2), 39.2 (C), 37.2 (CH_2), 27.5 (CH_3), 26.2 (CH_3), 25.7 (CH_3), 21.2 (CH_3), 19.9 (CH_2), 18.2 (C), 17.6 (CH_3), −4.8 (CH_3), −5.2 (CH_3). Anal. Calcd for $C_{23}H_{42}O_4Si$: C, 67.27; H, 10.31. Found: C, 67.61; H, 10.33. (+)-**13**. $[\alpha]^{25}_D$ = +28.5 (c 1.0, $CHCl_3$). IR (film): ν 3482, 3059, 1727, 1641, 879 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.87 (dd, J = 17.4, 10.7 Hz, 1H), 5.18 (d, J = 17.4 Hz, 1H), 5.05 (d, J = 10.7 Hz, 1H), 5.04 (s, 1H), 4.96 (dd, J = 7.6, 3.8 Hz, 1H), 4.66 (s, 1H), 4.29 (dd, J = 6.6, 4.0 Hz, 1H), 2.11 (br d, J = 10.7 Hz, 1H), 2.03 (s, 3H), 1.87 (ddd, J = 13.2, 6.9, 3.9 Hz, 1H), 1.70 (ddd, J = 12.1, 7.6, 3.9 Hz, 1H), 1.61−1.50 (m, 3H), 1.32−1.26 (m, 1H), 1.27 (s, 3H), 0.96 (s, 3H), 0.88 (s, 9H), 0.78 (s, 3H), 0.04 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.2 (C), 148.9 (C), 145.0 (CH), 111.5 (CH_2), 109.0 (CH_2), 77.1 (CH), 73.3 (C), 70.4 (CH), 49.5 (CH), 40.9 (CH_2), 39.1 (C), 37.3 (CH_2), 28.2 (CH_3), 26.4 (CH_3), 25.7 (CH_3), 21.1 (CH_3), 20.0 (CH_2), 18.2 (C and CH3), −4.8 (CH_3), −5.2 (CH_3). Anal. Calcd for $C_{23}H_{42}O_4Si$: C, 67.27; H, 10.31. Found: C, 67.49; H, 10.29.

(1*S*,3*R*,5*S*,3′*R*)-3-(3′-Hydroxy-3′-methylpent-4′-enyl)-5-hydroxy-2,2-dimethyl-4-methylenecyclohexyl Acetate (+)-1 and (1*S*,3*R*,5*S*,3′*S*)-3-(3′-Hydroxy-3′-methylpent-4′-enyl)-5-hydroxy-2,2-dimethyl-4-methylenecyclohexyl Acetate (+)-14. To a solution of (+)-**12** (250 mg, 0.61 mmol) in THF (12 mL) was added dropwise tetra-*n*-butylammonium fluoride (1.0 M in THF, 1.8 mL, 1.83 mmol). The reaction mixture was stirred at rt for 12 h and then concentrated. The residual oil was chromatographed on silica gel to afford 172 mg (95%) of (+)-**1**. The same conditions starting from (+)-**13** yielded (+)-**14**. (+)-**1**. $[\alpha]^{25}_D$ = +19.8 (c 1.0, $CHCl_3$) [lit.[2] $[\alpha]^{25}_D$ = +14.0 (c 0.84, $CHCl_3$)]. IR (film): ν 3440, 3061, 1722, 1653, 916 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.90 (dd, J = 17.4, 10.7 Hz, 1H), 5.18 (dd, J = 17.3, 1.2 Hz, 1H), 5.10 (s, 1H), 5.05 (dd, J = 10.7, 1.2 Hz, 1H), 4.96 (dd, J = 7.5, 4.5 Hz, 1H), 4.77 (s, 1H), 4.37 (br t, J = 5.4 Hz, 1H), 2.13 (br d, J = 10.2 Hz, 1H), 2.04 (s, 3H), 1.91 (ddd, J = 13.5, 7.8, 4.4 Hz, 1H), 1.82 (ddd, J = 13.5, 7.6, 4.4 Hz, 1H), 1.70−1.50 (m, 3H), 1.31−1.26 (m, 1H), 1.27 (s, 3H), 0.97 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6 (C), 148.6 (C), 145.1 (CH), 111.6 (CH_2), 109.9 (CH_2), 76.7 (CH), 73.3 (C), 69.8 (CH), 49.4 (CH), 40.9 (CH_2), 39.2 (C), 36.1 (CH_2), 27.6 (CH_3), 26.2 (CH_3), 21.2 (CH_3), 20.0 (CH_2), 17.7 (CH_3). Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.57; H, 9.47. (+)-**14**. $[\alpha]^{25}_D$ = +33.8 (c 1.0, $CHCl_3$). IR (film): ν 3451, 3059, 1719, 1658, 910 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.88 (dd, J = 17.4, 10.8 Hz, 1H), 5.19 (dd, J = 17.4, 1.3 Hz, 1H), 5.10 (s, 1H), 5.05 (dd, J = 10.8, 1.3 Hz, 1H), 4.95 (dd, J = 7.4, 4.4 Hz, 1H), 4.75 (s, 1H), 4.35 (br t, J = 5.6 Hz, 1H), 2.13 (br d, J = 12.9 Hz, 1H), 2.03 (s, 3H), 1.90 (ddd, J = 13.6, 6.8, 4.4 Hz, 1H), 1.82 (ddd, J = 13.6, 7.5, 4.5 Hz, 1H), 1.70−1.40 (m, 3H), 1.37−1.22 (m, 1H), 1.27 (s, 3H), 0.97 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6 (C), 148.6 (C), 144.9 (CH), 111.6 (CH_2), 109.8 (CH_2), 76.7 (CH), 73.4 (C), 69.8 (CH), 49.4 (CH), 40.7 (CH_2), 39.2 (C), 36.2 (CH_2), 28.2 (CH_3), 26.3 (CH_3), 21.2 (CH_3), 20.0 (CH_2), 17.8 (CH_3). Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 67.18; H, 9.49.

(1*S*,3*R*,3′*R*)-3-(3′-Hydroxy-3′-methylpent-4′-enyl)-2,2,4-trimethylcyclohex-4-enyl Acetate (−)-2. To a solution of crude **16** (135 mg) in dry ether (5 mL) was slowly added a freshly prepared solution of $LiAlH(O\text{-}t\text{-}Bu)_3$ (1.8 mmol, 1.35 mL, 1.33 M in ether) at 0 °C. The solution was allowed to warm to rt. After 24 h, celite (2 g) and $Na_2SO_4{\cdot}10H_2O$ (2 g) were added, and the solution was stirred for a further 60 min. The mixture was filtered through a pad of celite and concentrated to afford a 92:8 ratio of (−)-**2** and the exocyclic double-bond regioisomer in 70% yield. Careful silica gel column chromatography gave pure (−)-**2**. $[\alpha]^{25}_D$ = −24 (c 1.0, $CHCl_3$) [lit.[2] $[\alpha]^{25}_D$ = −27 (c 4.0, $CHCl_3$)]. IR (film): ν 3474, 1724, 917 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.91 (dd, J = 17.4, 10.7 Hz, 1H), 5.21 (dd, J = 17.4, 1.0 Hz, 1H), 5.20 (m, 1H), 5.06 (dd, J = 10.8, 1.0 Hz, 1H), 4.68 (t, J = 6.4 Hz, 1H), 2.26 (br d, J = 15.6 Hz, 1H), 2.04−1.94 (m partially overlapped, 1H), 2.02 (s, 3H), 1.70 (s, 3H), 1.28 (s, 3H), 1.78−1.53 (m, 3H), 1.52−1.24 (m, 2H), 0.90 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8 (C), 145.0 (CH), 136.7 (C), 117.5 (CH), 111.8 (CH_2), 76.4 (CH), 73.5 (C), 49.4 (CH), 44.2 (CH_2), 36.9 (C), 28.7 (CH_2), 27.7 (CH_3), 25.8 (CH_3), 22.9 (CH_2), 22.7 (CH_3), 21.3 (CH_3),18.6 (CH_3). Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 73.14; H, 10.09.

Supporting Information Available: Experimental procedures and complete ^{1}H and ^{13}C NMR spectral data for **7**, (+)-**11**, (−)-**15**, and **16**. Spectra (^{1}H NMR, ^{13}C NMR) for compounds (+)-**1**, (−)-**2**, (+)-**5**, (+)-*epi*-**5**, (+)-**6**, (+)-**8**, (+)-**10**, (+)-**12**, (+)-**13**, (+)-**14** and (−)-**15**. X-ray crystallographic data and ORTEP view for (+)-**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034424Y