Efficient Synthesis of (1*S*,5*S*)-4-Alkyl-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-ones from (1*R*,5*S*)-(+)-Nopinone and Preparation of Some Chiral Building Blocks Suitable for the Asymmetric Synthesis

Masataka Watanabe, Bahlul Z. Awen, and Michiharu Kato*

Institute for Chemical Reaction Science, Tohoku University, Katahira, Aoba-Ku, Sendai 980, Japan

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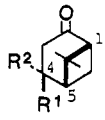
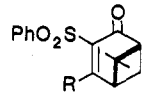
A general and convenient transformation of (1*R*,5*S*)-(+)-nopinone (1) into (1*S*,5*S*)-4-alkyl-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-ones, i.e., (−)-verbenone (**6a**) as the simplest compound and its C(4)-alkyl homologs **6b-f**, via (+)-apoverbenone (**7**) is developed and applied, starting with **6a,e**, to the syntheses of (4*R*,5*R*)-1-acetoxy-4-isopropenyl-5-methyl-5-vinyl-1-cyclohexene (**12a**) and (4*R*,5*S*)- and (4*R*,5*R*)-1-acetoxy-5-(3-butenyl)-4-isopropenyl-5-methyl-1-cyclohexene (**12b** and **12c**), in connection with a search for chiral building blocks suitable for the asymmetric synthesis. Preparation of **12a** indicates the formal synthesis of the elemanoid sesquiterpenes (−)-β-elemenone and (−)-eleman-8β,12-olide.

Introduction

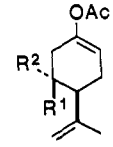
We have been studying the asymmetric synthesis of natural products starting with (1*R*,5*S*)-(+)-nopinone (**1**), readily obtainable in large quantities by ozonolysis of (1*S*,5*S*)-(−)-β-pinene, and recently reported that the conjugated enones **2**, readily accessible from **1**, are suitable



1 $R^1 = R^2 = H$



2 R= Me, Et



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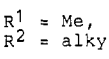
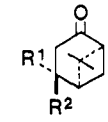


3 R^1 = Me, Et; R^2 = alkyl

precursors for the preparation of (1*R*,5*R*)-4,4-dialkylnopinones **3** by stereoselective conjugate addition reactions of **2** with carbon nucleophiles followed by desulfonylation and that the enol acetates **4** derived from **3** by BF_3·OEt_2-catalyzed cyclobutane opening with little loss of optical integrity[1] act as versatile building blocks suitable for natural product synthesis.[2] By use of **4**, some asymmetric syntheses of elemane and nardosinane sesquiterpenes have been achieved to date.[2,3]

In connection with our search for chiral building blocks for asymmetric synthesis, an efficient and convenient synthetic route for the enantiomers **5** of **3** was much required because the cyclobutane opening reaction of **5** could provide the enantiomers of **4**. In view of the fact



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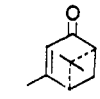

6a

7

that (1*R*,5*R*)-(+)-β-pinene,[4] the precursor of (1*S*,5*R*)-(−)-nopinone,[5] is scarcely found in nature,[6] we envisioned a short step transformation of **1** to **5**, so that (−)-verbenone (**6a**) and its C(4)-alkyl homologs seemed quite feasible as the synthetic key intermediates because their stereoselective conjugate addition reactions with carbon nucleophiles based on the well-known reactivity[2] characteristic of pinane-type compounds, namely, approach of the nucleophile to the reaction site away from the *gem*-dimethyl bridge, would produce the requisite **5**. Although only (−)-**6a** itself is a natural product and available commercially, it has disadvantages, namely that (−)-**6a** with highly optical purity is high in price and that little is known for a practical preparation of (−)-**6a**, although a few transformations of (−)-α-pinene to (−)-**6a** in low yields have been reported.[6] In addition, synthesis of the C(4)-alkyl homologs of **6a**, one of our main objectives, has not been reported. Herein, we wish to describe a general and convenient synthesis of (1*S*,5*S*)-4-alkyl-6,6-dimethylbicyclo-[3.1.1]hept-3-en-2-ones including (−)-verbenone (**6a**) as the simplest compound from (1*R*,5*S*)-(+)-nopinone (**1**) via (+)-apoverbenone (**7**), as well as their cyclobutane-opening reactions. The present synthesis is also of importance from the viewpoint that optically active verbenone and its derivatives such as verbenols and verbanols display unique biological activities and some of them are known as insect pheromones.[7]

(1) Kato, M.; Kamat, V. P.; Tooyama, Y.; Yoshikoshi, A. *J. Org. Chem.* **1989**, *54*, 1536.

(2) (a) Kato, M.; Kido, F.; Masuda, Y.; Watanabe, M. *J. Chem. Soc., Chem. Commun.* **1992**, 697. (b) Kato, M.; Watanabe, M.; Vogler, B.; Awen, B. Z.; Masuda, Y.; Tooyama, Y.; Yoshikoshi, A. *J. Org. Chem.* **1991**, *56*, 7071. (c) Kato, M.; Watanabe, M.; Awen, B. Z.; Vogler, B. *Tetrahedron Lett.* **1991**, *32*, 7434. (d) Kato, M.; Watanabe, M.; Awen, B. Z. *Ibid.* **1991**, *32*, 7443. (e) Kato, M.; Vogler, B.; Tooyama, Y.; Yoshikoshi, A. *Chem. Lett.*, **1990**, 151.

(3) For related syntheses, see: (a) Kato, M.; Watanabe, M.; Vogler, B.; Tooyama, Y.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1990**, 1706; (b) *Synthesis* **1992**, 1055. (c) Kato, M.; Watanabe, M.; Masuda, Y. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 207.

(4) For preparation of (+)-β-pinene from (+)-α-pinene, see: Brown, H. C.; Joshi, N. N. *J. Org. Chem.* **1988**, *53*, 4059 and references cited therein.

(5) For conversion of (+)-α-pinene to (−)-nopinone in five steps, see: Lavallee, P.; Bouthillier, G. *J. Org. Chem.* **1986**, *51*, 1362 and references cited therein.

(6) Thomas, A. F.; Bessiere, Y. *The Total Synthesis of Natural Products*; Apsimon, J., Ed.; Wiley-Interscience: New York, 1988; Vol. 7, pp 275–454.

(7) Mori, K. *Tetrahedron* **1989**, *45*, 3233.

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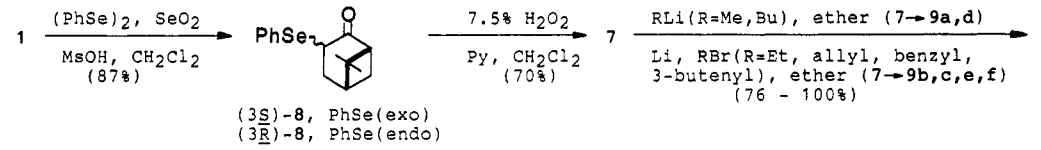
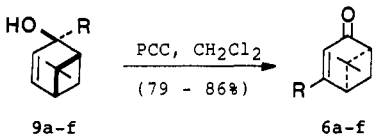
Scheme I





a, R = Me, b, R = Et, c, = $CH_2CH{=}CH_2$

d, Bu, e, = $CH_2CH_2CH{=}CH_2$, f, R = CH_2Ph

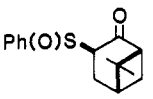
Results and Discussion

Our synthesis is shown in Scheme I, in which transformation of (1*R*,5*S*)-(+)-nopinone (**1**) to (+)-apoverbenone (**7**) followed by 1,2-addition using alkyllithium reagents and oxidative rearrangement using pyridinium chlorochromate (PCC) to give (−)-verbenone (**6a**) and its homologs **6b–f** are included. Phenylselenenylation of **1** in 92% ee was carried out according to the published procedure employing diphenyl diselenide [$(PhSe)_2$] and selenium(IV) oxide (SeO_2)[8] with the modification of using methanesulfonic acid (MsOH) as a catalyst in place of sulfuric acid on account of the fact that **1** is unstable to mineral acids. (1*R*,3*S*,5*R*)-3-(Phenylseleno)nopinone (**8**)[9] was obtained as the sole product in 87% yield (For the stereochemical assignment of **8**, see below). The present preparation can be scaled up to 0.1 mol of **1** with invariably good reproducibility of the yield.

Here it is worthy to note the stability of 3-substituted nopinones with respect to configuration of the substituent. Recently, Razdan and co-workers reported that phenylselenenylation of **1** with phenylselenenyl bromide under the kinetically controlled conditions provided a mixture of (1*R*,3*S*,5*R*)-**8**, the *trans*-isomer,[9] and (1*R*,3*R*,5*R*)-**8**, the *cis*-isomer,[9] in 91% yield and a 7:3 ratio.[10] Configurational assignment of these diastereomers was established by NOE studies.[10] The stereochemistry of (1*R*,3*S*,5*R*)-**8** obtained in the present study was assigned by correlation of the ^1H NMR spectral data with literature values.[10,11] The exclusive formation of (1*R*,3*S*,5*R*)-**8** under our thermodynamically controlled conditions is quite interesting since it is known that methylation,[12] bromination,[13] and phenylsulfenylation[2b] of **1** under kinetically controlled conditions give exclusively the thermodynamically less stable *trans*-substituted products, which then epimerize to the stable *cis*-isomers by base or acid. Then, we prepared the mixture of (1*R*,3*S*,5*R*)- and (1*R*,3*R*,5*R*)-**8** according to the procedures reported by Razdan.[10] Treatment of this mixture[14] with MsOH in CH_2Cl_2 gave an intractable mixture of products, while on treatment under our phenylselenenylation reaction conditions a tendency to convert (1*R*,3*R*,5*R*)-**8** into (1*R*,3*S*,5*R*)-**8** was observed. These facts imply that (1*R*,3*R*,5*R*)-**8**, the *cis*-isomer, must be thermodynamically disfavored. This is probably the result of severe steric repulsion between the comparatively bulkier phenylseleno group and the *gem*-dimethyl bridge. We have, at present, no reasonable explanation for this observation.[15]

Returning to the synthesis, oxidation of (1*R*,3*S*,5*R*)-**8** with 7.5% hydrogen peroxide followed by selenoxide fragmentation provided (+)-apoverbenone (**7**), $[\alpha]^{20}_D$ + 289° ($CHCl_3$) [lit.[13] $[\alpha]^{25}_D$ + 319° ($CHCl_3$)] in 61% overall yield from **1**.[16]

Interestingly, attempted syn-elimination of (1*R*,3*R*,5*R*)-3-(phenylsulfoxy)nopinone (**10**)[2b] was unsuccessful; heating **10** in CCl_4 containing pyridine afforded 3-(phenylthio)-apoverbenone (**11**)[2b] as the major product (49% yield)



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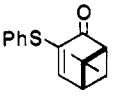


11

along with a mixture of **7** (2% yield) and a few byproducts. Assuming that the *gem*-dimethyl bridge hinders formation of the cyclic transition state necessary for the syn-elimination, this result is accounted for by the consideration that the competing Pummerer reaction proceeds to yield **11**.

1,2-Addition reactions of **7** with a variety of alkyllithium reagents in ether proceeded smoothly to give allyl alcohols **9a–f** in high to excellent yields. In these reactions the use of the Grignard reagents was unsuitable because the reaction provided a mixture of 1,2- and 1,4-adducts. Methyllithium and butyllithium are available as commercial products of high purity. One-step synthesis of allyl alcohols was accomplished according to the Barbier reaction;[17] preparation of alkyllithiums from ethyl, allyl, and benzyl bromides and lithium wire in ether and followed by the 1,2-addition reaction with **7** *in situ* afforded **9b,c,f**.

(8) Miyoshi, N.; Yamamoto, T.; Kambe, N.; Murai, S.; Sonoda, N. *Tetrahedron Lett.* **1982**, *23*, 4813.

(9) The terms trans and cis refer to whether the substituent points away from (trans) or toward (cis) the *gem*-dimethyl bridge.

(10) Siegel, C.; Gordon, D. H.; Vliss, D. B.; Handrick, G. R.; Dalzell, H. C.; Razdan, R. K. *J. Org. Chem.* **1991**, *56*, 6865.

(11) Characteristic resonances due to the methyne protones bonded with selenium atom occur at δ 3.83 (dd, J = 10, 2 Hz) for (1*R*,3*S*,5*R*)-**8** and at δ 4.38 (dd, J = 11, 8 Hz) for (1*R*,3*R*,5*R*)-**8** (see ref 10).

(12) Konopelski, J. P.; Djerassi, C. *J. Org. Chem.* **1980**, *45*, 2297. Konopelski, J. P.; Sundararaman, P.; Barth, G.; Djerassi, C. *Ibid.* **1980**, *102*, 2737.

(13) Grimshaw, J.; Grimshaw, J. T.; Juneja, H. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 50. In this report, determination of the structure of 3-bromonopinone by X-ray crystallography and conformational assignment by the ^1H NMR spectra are discussed.

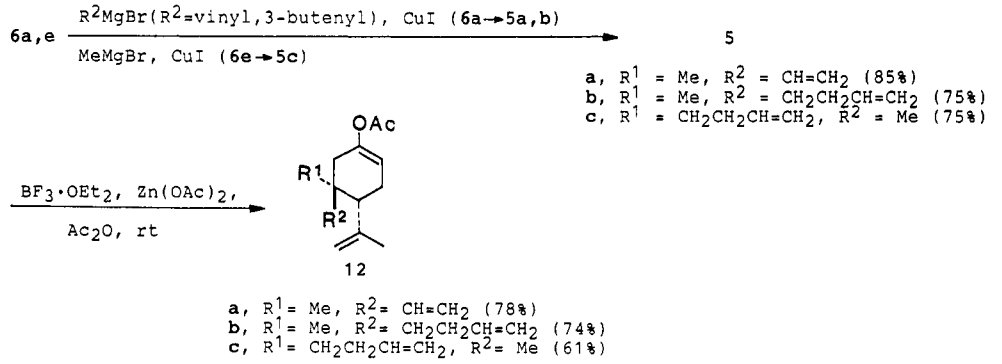
(14) A mixture of diastereomers **8** was used since they are difficult to separate by chromatography on silica gel.

(15) To our knowledge, this represents the first procurement of the *trans*-isomer, i.e., (1*R*,3*S*,5*R*)-**8**, as a thermodynamically stable form in a 3-substituted nopinone series. Further investigations including theoretical aspects are under way.

(16) For the synthesis of **7** by a sequence of bromination–dehydrobromination, see ref 13 and references cited therein.

(17) Blombery, C.; Hartog, F. A. *Synthesis* **1977**, 18.

Scheme II



Similarly, **9e** was prepared using lithium dispersion in a mineral oil in place of lithium wire because use of the latter resulted in recovery of **7**. The configuration of the hydroxy group in **9** was tentatively assigned as cis to the *gem*-dimethyl bridge on the basis of the well-known reactivity of pinane compounds.[2]

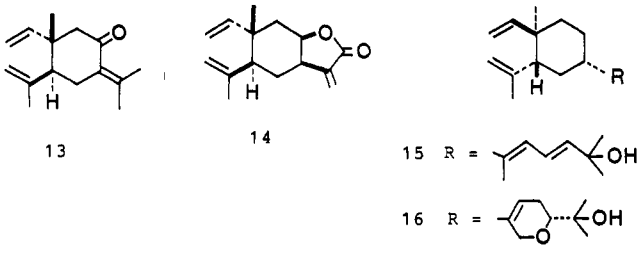
The oxidative rearrangement of **9** with PCC in CH_2Cl_2 proceeded smoothly to give, after chromatographic purification on silica gel, (1*S*,5*S*)-4-alkyl-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-ones, (−)-verbenone (**6a**), and its C(4)-alkyl homologs **6b–f** in high isolated yields. The specific rotation of the synthetic (−)-**6a** shows $[\alpha]^{20}_D$ −251° ($CHCl_3$). Since the specific rotation of (−)-**6a** of 80% optical purity is reported to be $[\alpha]^{20}_D$ −217° ($CHCl_3$),[18] it was proven that the present conversion of **1** into **6** by a four-step sequence can be carried out without any loss of optical purity.

Conjugate addition reactions of **6a,e** with a few Grignard reagents were examined next (Scheme II). In an earlier paper,[2b] we described that introduction of an electron-withdrawing group such as the phenylsulfonyl function at the C(3) position of the parent apoverbenone enhances its potential as the acceptor in conjugate additions. Recently, it was found that apoverbenones themselves operate sufficiently as the acceptor to provide the 1,4-adducts in synthetically satisfactory yields.[2a] In fact, the conjugate addition reactions of **6a** with vinyl- and 3-butenylmagnesium bromides in the presence of copper(I) iodide (CuI) proceeded in a stereoselective fashion to give good yields of the 1,4-adducts, (1*S*,4*R*,5*S*)-**5a** and (1*S*,4*S*,5*S*)-**5b**, antipodal to (1*R*,4*S*,5*R*)-**3** (R^1 = Me, R^2 = vinyl) and (1*R*,4*R*,5*R*)-**3** (R^1 = 3-butenyl, R^2 = Me), respectively, which have been synthesized from (1*R*,5*S*)-(+)-nopinone (**1**).[2b] Similarly, the reaction of **6e** with methylmagnesium bromide provided (1*S*,4*R*,5*S*)-**5c**, a diastereomer of both **5b** and (1*R*,4*S*,5*R*)-**3** (R^1 = Me, R^2 = 3-butenyl).[2b] No formation of stereoisomers at the C(4) position was detected in these conjugate addition reactions.

The cyclobutane-opening reactions of **5a** and **5b** under our reaction conditions, BF_3·OEt_2 and $Zn(OAc)_2$ in acetic anhydride,[1] followed by aqueous workup provided, as the sole ring-opened product, (4*R*,5*R*)-1-acetoxy-4-isopropenyl-5-methyl-5-vinyl- and (4*R*,5*S*)-1-acetoxy-5-(3-butenyl)-4-isopropenyl-5-methyl-1-cyclohexene (**12a** and **12b**), antipodal to (4*S*,5*S*)-**4** (R^1 = Me, R^2 = vinyl) and (4*S*,5*R*)-**4** (R^1 = Me, R^2 = 3-butenyl), respectively, which have been synthesized from (+)-**1**.[2b] Similarly, the cyclobutane opening of **5c** afforded (4*R*,5*R*)-enol acetate **12c**, a diastereomer of **12b**.

(18) Ohloff, G.; Giersh, W. *Helv. Chim. Acta* **1977**, *60*, 1496.

Since the enol acetate function is synthetically equivalent to an enolate anion and plays an important role in regioselective introduction of a substituent, the enol acetates **12a–c** could serve as versatile building blocks for the asymmetric synthesis. For example, since the enol acetate **4** (R^1 = Me, R^2 = vinyl) has been used as the common key intermediate for the synthesis of (5*S*,10*S*)-elemanoid sesquiterpenes such as (+)-β-elemenone (**13**)[2b,e] and (+)-eleman-8 β,12-olide (**14**),[2b] the present synthesis



of enol acetate **12a** is a formal synthesis of their enantiomers; (−)-**13** and (−)-**14**.[19,20] Furthermore, **12a** is a promising key intermediate for the synthesis of marine, loban-type diterpenes, fuscol (**15**)[21] and lobatriene (**16**),[22] which commonly possess a (5*R*,10*R*)-elemane moiety. In addition, the compounds **12b,c** could serve as chiral building blocks for the asymmetric synthesis of bicyclic natural products via manipulation of the 3-butenyl side chain followed by cyclization, as discussed and demonstrated in earlier papers.[2b,d,3c]

In conclusion, we have developed a general transformation of (1*R*,5*S*)-(+)-nopinone (**1**) into (1*S*,5*S*)-4-alkyl-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-ones, i.e., (−)-verbenone (**6a**) as well as its C(4)-alkyl homologs **6b-f** which have now been successfully synthesized for the first time. The present methodology is useful for the laboratory-scale

(19) The sesquiterpenes **13** and **14** themselves are not known to occur in nature in optically active form.

(20) Hydrolysis of **12a** provided **i**, $[\alpha]^{20}_D$ +30.2° (*c* 1.18, $CHCl_3$), in high yield. Racemic **i** has been synthesized by Bohlmann and transformed into racemic elemasteriactinolide and its C(15)-oxygenated homolog, **ii** and **iii**, respectively (Friedrich, D.; Bohlmann, F. *Tetrahedron* **1988**, *44*, 1369); the synthesis of **12a** is also a formal synthesis of these compounds.

(21) Gopichand, Y.; Schnitz, F. J. *Tetrahedron Lett.* **1978**, 3641.

(22) Kusumi, T.; Hamada, T.; Ishitsuka, M. O.; Ohtani, I.; Kakisawa, H. *J. Org. Chem.* **1992**, *57*, 1033.

preparation of **6** in view of simplicity of operations, good overall yields, and applicability. In addition, since compounds **6** are easily convertible, by a two-step sequence, into the chiral building blocks 1-acetoxy-4-isopropenyl-5,5-dialkyl-1-cyclohexenes **12**, it is demonstrated that (1*R*,5*S*)-(+)-nopinone (**1**) and consequently its precursor (1*S*,5*S*)-(−)-β-pinene as well serve as the common chiral source for the asymmetric synthesis in terms of absolute configuration of the target molecule.

Syntheses of natural products starting with **12** are in progress.

Experimental Section

^{1}H NMR spectra were recorded at 90 MHz. All organic solvents were purified and dried by using standard procedures. All reactions were carried out under N_2 or Ar atmosphere. Na_2SO_4 was used as the drying agent for the extracts on aqueous workup. Column chromatography was performed on 70–230-mesh silica gel (Merck). Solvents for elution are shown in parentheses.

(1*R*,5*R*)-6,6-Dimethylbicyclo[3.1.1]hept-3-en-2-one (Apoverbenone) (7). A mixture of (+)-nopinone (**1**) in 92% ee (13.8 g, 0.10 mol), SeO_2 (6.65 g, 60 mmol), $(PhSe)_2$ (18.73 g, 60 mmol), and MsOH (0.8 mL, 12.3 mmol) in CH_2Cl_2 (100 mL) was stirred at rt for 24 h. The organic layer was separated by decantation, and the precipitate was washed several times with a small amount of CH_2Cl_2. The combined CH_2Cl_2 solutions were concentrated to ca. 100 mL under reduced pressure. To this was added additional SeO_2 (2.0 g, 18 mmol), and the resulting mixture was stirred at rt for 15 h. This procedure was repeated twice, while compound **1** was almost consumed. After the reaction was complete, the precipitate was filtered off and the filtrate was washed successively with aqueous $NaHCO_3$ and water and dried. Evaporation of the solvent left a residue which was filtered through a silica gel column with benzene followed by ether to remove the unreacted $(PhSe)_2$. Concentration of the filtrate followed by chromatography of the oily residue on silica gel (hexane–ether (5:1)) to give **(1*R*,3*S*,5*R*)-6,6-dimethyl-3-(phenylseleno)bicyclo[3.1.1]heptan-2-one** (**8**) (25.5 g, 87%) as an oil: ^{1}H NMR ($CDCl_3$) δ 0.84 (s, 3 H), 1.34 (s, 3 H), 1.84 (d, 1 H, J = 11 Hz), 2.0–2.8 (m, 4 H), 3.83 (dd, 1 H, J = 10, 2 Hz), 7.15–7.38 (m, 3 H) and 7.5–7.72 (m, 2 H).

A solution of **8** (25.5 g, 87.1 mmol) and pyridine (15 mL) in CH_2Cl_2 (200 mL) was stirred at 0 °C as 7.5% H_2O_2 (60 mL) was added dropwise, and stirring was continued at 0 °C for 5 h and then at rt for 2 h. The reaction mixture was washed successively with water, aqueous $NaHSO_3$, aqueous $CuSO_4$, and water and dried. Removal of the solvent left an oil which was distilled by use of a Kugelrohr distillation apparatus to give **7** (8.18 g, 70%) as an oil: bp 48 °C (2 Torr); $[\alpha]^{20}_D$ +289° (*c* 1.34, $CHCl_3$) [lit.[10] $[\alpha]^{25}_D$ + 319° (*c* 2.4, $CHCl_3$)]; HRMS calcd for $C_9H_{12}O$ *m/z* 136.0878, found *m/z* 136.0888; IR (film) 1687 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.03 (s, 3 H), 1.52 (s, 3 H), 2.14 (d, 1 H, J = 8 Hz), 2.45–3.0 (m, 3 H), 5.94 (d, 1 H, J = 9 Hz), 7.50 (dd, 1 H, J = 9, 2 Hz).

(1*R*,2*R*,5*R*)-2,6,6-Trimethylbicyclo[3.1.1]hept-3-en-2-ol (9a) and (1*S*,5*S*)-4,6,6-Trimethylbicyclo[3.1.1]hept-3-en-2-one (Verbenone) (6a). To a stirred solution of **7** (1.13 g, 8.3 mmol) in ether (50 mL) was added dropwise at rt a 1.02 M solution of methyllithium in ether (10 mL, 10.2 mmol), and stirring was continued for an additional 30 min. The reaction was quenched by addition of aqueous NH_4Cl, and the product was extracted with ether. The combined extracts were washed with brine and dried. The solvent was removed at atmospheric pressure with care to avoid sublimation of the product, giving **9a** (1.38 g, quantitative) as a semisolid: HRMS calcd for $C_9H_{16}O$ *m/z* 152.1200, found *m/z* 152.1192; IR (film) 3388, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 3 H), 1.30 (s, 3 H), 1.38 (s, 3 H), 1.55–1.75 (br s, 1 H), 1.90 (br s, 1 H), 2.06–2.23 (m, 2 H), 2.40–2.65 (m, 1 H), 5.56 (d with fine splittings, 1 H, J = 9 Hz), 6.26 (dd, 1 H, J = 9, 3 Hz).

A mixture of **9a** (1.57 g, 10.3 mmol), Celite 545 (3.0 g), and PCC (3.20 g, 14.8 mmol) in CH_2Cl_2 (100 mL) was stirred at rt overnight. The reaction mixture was washed with aqueous $NaHSO_3$ and filtered through a small bed of Celite 545. The filtrate was washed successively with water, aqueous $CuSO_4$, and water and dried. Removal of the solvent followed by chromatography of the oily residue on silica gel (hexane-ether (4:1)) gave **6a** (1.22 g, 79%) as an oil: $[\alpha]^{20}_D$ −251° (*c* 1.28, $CHCl_3$) [lit.[12] $[\alpha]^{20}_D$ −217° (*c* 10, $CHCl_3$)]; HRMS calcd for $C_9H_{14}O$ *m/e* 150.1044, found *m/e* 150.1051; IR (film) 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (s, 3 H), 1.48 (s, 3 H), 2.00 (d, 3 H, J = 1.5 Hz), 2.25–2.95 (m, 4 H), 5.75 (q, 1 H, J = 1.5 Hz).

The following compounds were prepared in a similar manner. Starting material, reagents, yields, elemental analyses, and physical data of the products are as follows.

(1*R*,2*R*,5*R*)-2-Butyl-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-ol (9d) and (1*S*,5*S*)-4-Butyl-6,6-dimethylbicyclo[3.1.1]hept-3-en2-one (6d). **7** (136 mg, 1.0 mmol), a 1.54 M solution of butyllithium in ether (0.8 mL, 1.23 mmol) and ether (10 mL) gave **9d** (194 mg, quant): oil; HRMS calcd for $C_{13}H_{22}O$ *m/z* 194.1670, found *m/z* 194.1698; IR (film) 3432, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (br t, 3 H, J = 5 Hz), 1.0–2.8 (m 7 H), 1.12 (s, 3 H), 1.37 (s, 3 H), 2.05–2.22 (m, 2 H), 2.30–2.40 (m, 1 H), 5.60 (d with fine splittings, 1 H, J = 9 Hz), 6.24 (m, 1 H, J = 9 Hz).

9d (194 mg, 1.0 mmol), PCC (32 mg, 1.50 mmol), Celite 545 (1.0 g), and CH_2Cl_2 (15 mL) gave **6d** (160 mg, 83%): oil; $[\alpha]^{20}_D$ −165° (*c* 1.28, $CHCl_3$); HRMS calcd for $C_{13}H_{20}O$ *m/z* 192.1513, found *m/z* 192.151; IR (film) 1683 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (br s, 3H), 1.00 (s, 3 H), 1.25–1.58 (m, 3 H), 1.50 (s, 3 H), 2.06 (d, 1 H, J = 9 Hz), 2.15–2.97 (m, 6 H), 5.72 (t, 1 H, J = 1 Hz).

(1*R*,2*R*,5*R*)-2-Ethyl-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-ol (9b) and (1*S*,5*S*)-4-Ethyl-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (6b). A suspension of **7** (680 mg, 5.0 mmol) and lithium wire (350 mg, 0.05 g-atom) cut into small pieces in ether (25 mL) was stirred at rt as ethyl iodide (2.0 mL, 25 mmol) was added dropwise by use of a syringe pump over a period of 1 h. Additional ethyl iodide (0.8 mL, 10.0 mmol) was added to the reaction mixture, and stirring was continued for an additional 1 h. After the reaction was complete, excess lithium was filtered off, and the filtrate was washed with brine and dried. Concentration followed by chromatography of the oily residue on silica gel (hexane–ether (4:1)) gave **9b** (632 mg, 76%) as an oil: HRMS calcd for $C_{11}H_{18}O$ *m/z* 166.1375, found *m/z* 166.1364; IR (film) 3422, 724 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3 H, J = 7 Hz), 1.13 (s, 3 H), 1.25 (br s, 1 H), 1.36 (s, 3 H), 1.45–1.67 (m, 3 H), 2.0–2.2 (m, 2 H), 2.3–2.6 (m, 1 H), 5.60 (d with fine splittings, 1 H, J = 9 Hz), 6.24 (m, 1 H).

According to the procedure for oxidation of **9a** to **6a**, a mixture of **9b** (498 mg, 3.0 mmol), Celite 545 (1.0 g), and PCC (973 mg, 4.5 mmol) in CH_2Cl_2 (30 mL) was stirred at rt overnight. Workup followed by chromatography of an oily residue on silica gel (hexane–ether (3:1)) gave **6b** (387 mg, 79%) as an oil: $[\alpha]^{20}_D$ −224° (*c* 1.22, $CHCl_3$); HRMS calcd for $C_{11}H_{16}O$ *m/z* 164.1200, found *m/z* 164.1180; IR (film) 1683 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.98 (s, 3 H), 1.08 (t, 3 H, J = 7 Hz), 1.50 (s, 3 H), 2.0–2.95 (m, 6 H), 5.72 (s with fine splittings, 1 H).

The following compounds were prepared in a similar manner. Starting material, reagents, yields, elemental analyses, and physical data of the products are as follows.

(1*R*,2*R*,5*R*)-2-Allyl-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-ol (9c) and (1*S*,5*S*)-4-Allyl-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (6c). **7** (680 mg, 5.0 mmol), lithium wire (120 mg, 0.02 g-atom), allyl bromide (1.3 mL, 15.0 mmol), and ether (25 mL) gave **9c** (815 mg, 91%) as an oil: HRMS calcd for $C_{12}H_{18}O$ *m/z* 178.1357, found *m/z* 178.1350; IR (film) 3445, 737 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 3 H), 1.36 (s, 3 H), 1.56 (m, 1 H), 1.92 (s, 1 H), 1.20–1.61 (m, 5 H), 4.97–5.25 (m, 2 H), 5.56 (d with fine splittings, 1 H, J = 9 Hz), 5.75–6.1 (m, 1 H), 6.30 (m, 1 H).

9c (534 mg, 3.0 mmol), PCC (973 mg, 4.5 mmol), Celite 545 (1.0 g), and CH_2Cl_2 (30 mL) gave **6c** (427 mg, 81%): oil; $[\alpha]^{20}_D$ −218° (*c* 1.26, $CHCl_3$); HRMS calcd for $C_{12}H_{16}O$ *m/z* 176.1200, found *m/z* 176.1207; IR (film) 1679 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.99 (s, 3 H), 1.48 (s, 3 H), 2.07 (d, 1 H, J = 7 Hz), 2.4–3.1 (m, 5 H), 5.04–5.28 (m, 2 H), 5.56–6.02 (m, 1 H), 5.74 (s with fine splittings, 1 H).

(1*R*,2*R*,5*R*)-2-Benzyl-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-ol (9f) and (1*S*,5*S*)-4-Benzyl-6,6-dimethylbicyclo[3.1.1]-hept-3-en-2-one (6f). **7** (680 mg, 5.0 mmol), lithium wire (105 mg, 0.02 g-atom), benzyl bromide (1.81 g, 10.5 mmol), and ether (25 mL) gave **9f** (982 mg, 86%): oil; HRMS calcd for $C_{16}H_{20}O$

m/z 228.1531, found m/z 228.1536; IR (film) 3463 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (s, 3 H), 1.33 (s, 3 H), 2.88 (s, 2 H), 5.32 (dd, 1 H, J = 9, 2 Hz), 6.32 (dd, 1 H, J = 9, 6 Hz), 7.1–7.48 (br s with fine splittings, 5 H).

9f (960 mg, 4.2 mmol), PCC (1.36 g, 6.3 mmol), Celite 545 (2.0 g), and CH_2Cl_2 (50 mL) gave **6f** (785 mg, 83%): oil; $[\alpha]^{20}_D$ −174° (c 1.22, $CHCl_3$); HRMS calcd for $C_{16}H_{18}O$ m/z 226.1357, found m/z 226.1361; IR (film) 1679, 703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (s, 3 H), 1.42 (s, 3 H), 2.04 (d, 1 H, J = 7 Hz), 2.38–2.90 (m, 3 H), 3.57 (br s, 2 H), 5.67 (m, 1 H), 7.1–7.45 (m, 5 H).

(1*R*,2*R*,5*R*)-2-(3-Butenyl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-ol (9e) and (1*S*,5*S*)-4-(3-Butenyl)-6,6-dimethylbicyclo-[3.1.1]hept-3-en-2-one (6e). A suspension of **7** (408 mg, 3.0 mmol) and lithium dispersion (25 wt %) in mineral oil (130 mg, 4.5 mmol) in ether (15 mL) was stirred at rt as 4-bromo-1-butene (607 mg, 4.5 mmol) was added dropwise. After the solution was stirred for 30 min, additional lithium dispersion (80 mg) and 4-bromo-1-butene (375 mg) were added successively to the reaction mixture, and stirring was continued for an additional 30 min. The reaction mixture was cooled in an ice–water bath, and the reaction was carefully quenched by addition of aqueous NH_4Cl. The product was extracted with ether, and the combined extracts were washed successively with water and brine and dried. Concentration followed by chromatography of the oily residue on silica gel (hexane–ether (4:1)) gave **9e** (499 mg, 87%) as an oil: HRMS calcd for $C_{18}H_{20}O$ m/z 192.1513, found m/z 192.1533; IR (film) 3441 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (s, 3 H), 1.37 (s, 3 H), 1.4–2.60 (m, 9 H), 4.84–5.16 (m, 2 H), 5.60 (d with fine splittings, 1 H, J = 9 Hz), 5.7–6.04 (m, 1 H), 6.28 (m, 1 H).

According to the procedure described for oxidation of **9a** to **6a**, oxidation of **9e** (575 mg, 3.0 mmol) with PCC (970 mg, 4.5 mmol) and Celite 545 (1.0 g) in CH_2Cl_2 (30 mL) gave **6e** (488 mg, 86%): oil; $[\alpha]^{20}_D$ −207° (c 1.22, $CHCl_3$); HRMS calcd for $C_{13}H_{18}O$ m/z 190.1357, found m/z 190.1362; IR (film) 1683 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (s, 3 H), 1.50 (s, 3 H), 2.08 (d, 1 H, J = 9 Hz), 2.15–2.95 (m, 7 H), 4.95–5.2 (m, 2 H), 5.64–6.08 (m, 1 H), 5.76 (m, 1 H).

(1*S*,4*R*,5*S*)-4,6,6-Trimethyl-4-vinylbicyclo[3.1.1]heptan-2-one (5a) and (4*R*,5*R*)-1-Acetoxy-4-isopropenyl-5-methyl-5-vinyl-1-cyclohexene (12a). To a stirred mixture of CuI (640 mg, 3.36 mmol) in THF (15 mL) was added dropwise at −50 °C a 0.98 M solution of vinylmagnesium bromide in THF (17.2 mL, 16.8 mmol). After the mixture was stirred for 30 min, a solution of **6a** (1.26g, 8.4 mmol) in THF (10 mL) was added dropwise and the reaction mixture was gradually warmed to rt within 2 h. After being cooled to −45 °C, the reaction mixture was quenched by addition of aqueous NH_4Cl and extracted with ether. The combined extracts were washed with brine and dried. Concentration followed by chromatography of the oily residue on silica gel (hexane–AcOEt (15:1)) gave **5a** (1.28g, 85%) whose IR and ^1H NMR spectra are identical with those of (1*R*,4*S*,5*R*)-**3** (R^1 = Me, R^2 = vinyl): $[\alpha]^{21}_D$ +87.9°.[2b]

5a: oil; $[\alpha]^{20}_D$ −86.9° (c 2.2, $CHCl_3$). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.95; H, 10.27.

A mixture of **5a** (206 mg, 1.16 mmol), freshly distilled BF_3·OEt_2 (44.2 μL, 0.35 mmol), $Zn(OAc)_2$ (212 mg, 1.16 mmol), and acetic anhydride (3 mL) was stirred at rt for 3 d. To this was added water (20 mL), and the resulting mixture was stirred for 30 min and then extracted with ether. The combined extracts were washed successively with aqueous $NaHCO_3$, water, and brine and dried. Evaporation of the solvent followed by chromatography of the oily residue on silica gel (hexane–AcOEt (20:1)) gave unreacted **5a** (24 mg) and **12a** (175 mg, 69%; 78% based on consumed **5a**) whose IR and ^1H NMR spectra are identical with those of (1*S*,5*S*)-**4** (R^1 = Me, R^2 = vinyl): $[\alpha]^{19}_D$ −7.6° ($CHCl_3$).[2b]

12a: oil; $[\alpha]^{25}_D$ + 6.6° (c 0.33, $CHCl_3$). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 75.99; H, 9.13.

The following compounds were prepared in a similar manner. Starting material, reagents, yields, elemental analyses, and physical data of the products are as follows.

(1*S*,4*S*,5*S*)-4-(3-Butenyl)-4,6,6-trimethylbicyclo[3.1.1]-heptan-2-one (5b) and (4*R*,5*S*)-1-Acetoxy-5-(3-butenyl)-4-isopropenyl-5-methyl-1-cyclohexene (12b). **6a** (600 mg, 4.0 mmol) and a 0.5 M solution of 3-butenylmagnesium bromide in THF (14 mL) gave **5b** (608 mg, 75%) whose IR and ^1H NMR spectra are identical with those of (1*R*,4*R*,5*R*)-**3** (R^1 = Me, R^2 = 3-butenyl): $[\alpha]^{20}_D$ +34.6° ($CHCl_3$).[2b]

5b: oil; $[\alpha]^{20}_D$ −34.5° (c 1.20, $CHCl_3$). Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.68; H, 10.98.

5b (280 mg, 1.36 mmol), BF_3·OEt_2 (51.9 μL, 0.41 mmol), $Zn(OAc)_2$ (249 mg, 1.36 mmol) and acetic anhydride (3 mL) gave unreacted **5b** (38 mg) and **12b** (215 mg, 64%; 74% based on consumed **5b**) whose IR and ^1H NMR spectra are identical with those of (4*S*,5*R*)-**4** (R^1 = Me, R^2 = 3-butenyl); $[\alpha]^{20}_D$ −12.7° ($CHCl_3$).[2b]

12b: oil; $[\alpha]^{20}_D$ +12.0° (c 0.31, $CHCl_3$). Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.52; H, 9.68.

(1*S*,4*R*,5*S*)-4-(3-Butenyl)-4,6,6-trimethylbicyclo[3.1.1]-heptan-2-one (5c) and (4*R*,5*R*)-1-Acetoxy-5-(3-butenyl)-4-isopropenyl-5-methyl-1-cyclohexene (12c). **6e** (213 mg, 1.12 mmol), a 1.02 M solution of methylmagnesium bromide in THF (2.2 mL, 2.24 mmol), CuI (43 mg, 0.22 mmol), and THF (5 mL) gave **5c** (171 mg, 75%) as an oil: $[\alpha]^{20}_D$ −33.6° (c 0.65, $CHCl_3$); IR (film) 1713 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (s, 3 H), 1.08 (s, 3 H), 1.36 (s, 3 H), 1.48–1.84 (m, 4 H), 1.84–2.80 (m, 6 H), 4.80–5.20 (m, 2 H), 5.56–6.04 (m, 1 H). Anal. Calcd for $C_{14}H_{22}O$: C, 81.49; H, 10.75. Found: C, 81.65; H, 10.76.

5c (114 mg, 0.55 mmol), BF_3·OEt_2 (21.1 μL, 0.16 mmol), $Zn(OAc)_2$ (101 mg, 0.55 mmol), and acetic anhydride (3 mL) gave **12c** (84 mg, 61%) as an oil: $[\alpha]^{20}_D$ +45.9° (c 0.30, $CHCl_3$); IR (film) 1756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (s, 3 H), 1.20–2.4 (m, 9 H), 1.80 (s, 3 H), 2.10 (s, 3 H), 4.76–5.2 (m, 4 H), 5.4 (br s, 1 H), 5.60–6.06 (m, 1 H). Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.49; H, 9.74.

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Supplementary Material Available: NMR spectra of obtained compounds (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.