Notes

A Convenient Synthesis of (1*S*,5*S*)-4-Alkyl-3-carbomethoxy-6,6-dimethylbicyclo[3.1.1]-hept-3-en-2-ones with High Optical Purity

Masataka Watanabe,* Tetsuya Abe, and Nobuyuki Harada

Institute for Chemical Reaction Science, Tohoku University, Katahira, Aoba-ku, Sendai 980-77, Japan

Received July 1, 1996

Compounds with the 6,6-dimethylbicyclo[3.1.1]heptane skeleton (so-called pinane skeleton) have been frequently used as chiral starting materials for the asymmetric synthesis of natural products.[1] Previously, we reported that the methylation of sulfone (+)-**3a** prepared from β-pinene (−)-**1** *via* nopinone (+)-**2** by the treatment with potassium carbonate in acetonitrile at 50 °C afforded the γ-dimethylated product (+)-**3c** as a major product without any formation of the γ-monomethylated product (+)-**3b**.[2] We also reported that (+)-**3b**, derived from (+)-**2** by a different route, gave the stereocontrolled γ-alkylated product (+)-**3d**, having the *S* configuration, as a major product. We reported its utilization in the total synthesis of kanshone **4** (nardosinane sesquiterpene).[3,4]

In connection with our asymmetric synthesis of natural products, convenient syntheses of 6,6-dimethylbicyclo-[3.1.1]hept-3-en-2-one derivatives such as (−)-**3**, (−)-**7a**, and its γ-alkyl homologues (−)-**8** have been required. Although they may be easily derived from (−)-**2**, preparation of (−)-**2** is difficult because of the poor natural abundance of (+)-**1.**[5] Many synthetic routes to prepare (−)-**2** or its precursor (+)-**1** have been reported. Examples include the conversion from α-pinene (+)-**5** to (+)-**1**,[6] transformation from (+)-camphor sulfonyl chloride to (+)-**1**,[7] degradation of myrtenal to **2**,[8] the conversion from (+)-**5** to (−)-**2**,[9a] and transformation from camphor to (−)-**2.**[10]

Instead of utilization of (−)-**2**, we directed our attention to verbenone (−)-**6a** which is available as a chiral source

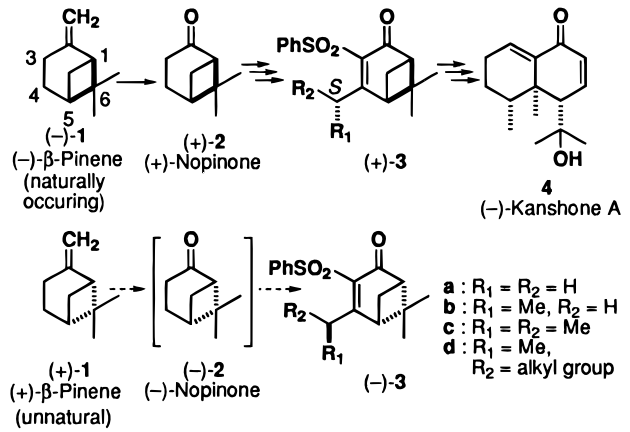


Figure 1.

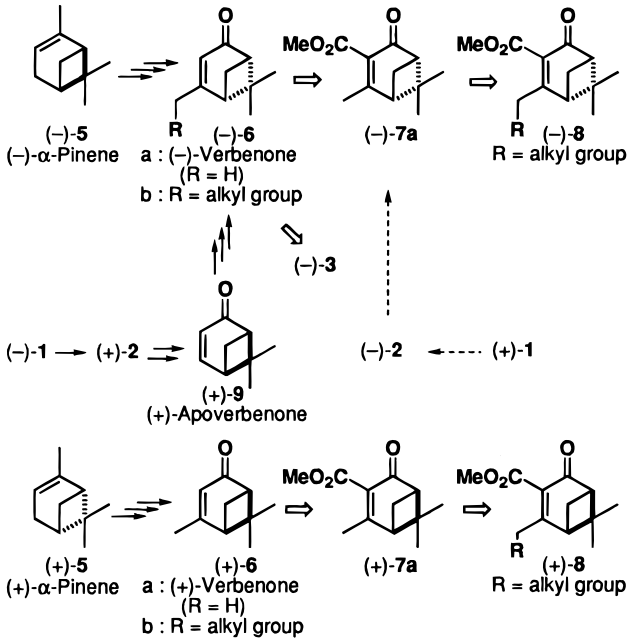


Figure 2.

for asymmetric synthesis of nagilactones,[11] and reported that the new route from (+)-**2** *via* apoverbenone (+)-**9** to (−)-**6a** and its C-4 alkyl homologues (−)-**6b**.[1d] Still, our newly developed method is not practical on a large scale to produce (+)-**9** because of the risk of explosion in the stage of the preparation of (+)-**2** by ozonolysis[9] and because of the toxicity and odor characteristics of diphenyl diselenide. Then, we focused on the enantiomeric purification of **6a**, expecting to obtain (−)-**3**, (−)-**7a**, and (−)-**8** starting from (−)-**5** *via* (−)-**6a** as shown in Figure 2. Their enantiomers, (+)-**7a** and (+)-**8**, starting from (+)-**5** *via* (+)-**6a**, could also be obtained, because both optical impure enantiomers of **6a** are easily accessible

(1) (a) Mori, K. *Tetrahedron* **1989**, *45*, 3233. (b) Huffman, J. W.; Joyner, H. H.; Lee, M. D.; Jordan, R. D.; Pennington, W. T. *J. Org. Chem.* **1991**, *56*, 2081. (c) Ho, T.-L. *Enantioselective Synthesis. Natural Products from Chiral Terpenes*, Wiley: New York, 1992. (d) Watanabe, M.; Awen, B. Z.; Kato, M. *J. Org. Chem.* **1993**, *58*, 3923 and references cited therein.

(2) The terms α and γ relate to the C(3) ketone in **3**, **6**, **8**, and **9**.

(3) Kato, M.; Watanabe, M.; Awen, B. Z.; Vogler, B. *Tetrahedron Lett.* **1991**, *32*, 7439.

(4) (a) Kato, M.; Watanabe, M.; Awen, B. Z. *Tetrahedron Lett.* **1991**, *32*, 7443. (b) Kato, M.; Watanabe, M.; Awen, B. Z. *J. Org. Chem.* **1993**, *58*, 5415.

(5) (a) (1*R*,5*R*)-(+)-β-pinene (+)-**1** is relatively rare in nature, see: Baslas, K. K. *Perfum. Oil Rec.* **1959**, *50*, 823. (b) Recently, (+)-**1** with 92% ee is available from Aldrich Chemical Co., but the price is very expensive, although (−)-**1** with 92% ee is inexpensive. For the determination of the optical purity, see; Kato, M.; Watanabe, M.; Vogler, B.; Awen, B. Z.; Masuda, Y.; Tooyama, Y.; Yoshikoshi, A. *J. Org. Chem.* **1991**, *56*, 7071.

(6) (a) Andrianome, M.; Delmond, B. *J. Chem. Soc., Chem. Commun.* **1985**, 1203. (b) Brown, H. C.: Joshi, N. N. J. *Org. Chem.* **1988**, *53*, 4059 and references cited therein.

(7) Kirmse, W.; Gruber, W. *Chem. Ber.* **1972**, *105*, 2764.

(8) Fisher, R.; Lardelli, G.; Jeger, O. *Helv. Chim. Acta* **1951**, *34*, 1575.

(9) (a) Javallee, P.; Bouthillier, G. *J. Org. Chem.* **1986**, *51*, 1362 and references cited therein. (b) Gordon, P. M. *Chem. Eng. News* **1990**, 68.

(10) Paukstelis, J. V.; Macharia, B. W. *Tetrahedron* **1973**, *29*, 1955.

(11) (a) Watanabe, M.; Awen, B. Z.; Kato, M.; Harada, N. *Abstracts of Papers*; 206th American Chemical Society National Meeting, Division of Organic Chemistry, Chicago, IL, August 1993; American Chemical Society: Washington, DC; p 360. (b) Watanabe, M.; Harada, N. *Abstracts of Papers*; 12th International Conference on the Chemistry of the Organic Solid State, Matsuyama, Japan, July 1995; p 32.

S0022-3263(96)01227-3 CCC: $14.00

from **5**.[12,13] Finally, we have succeeded in the efficient enantiomeric purification of (−)-**6a** by the inclusion complex method using a chiral host obtained from naturally occurring tartaric acid.[14]

There have been some results concerning the reactivity of the anion generated from **6a**. Treatment of (−)-**6a** with sodium hydride in THF and successive quenching with boric acid afforded the β,γ-deconjugated ketone (−)-**11a** in high yield.[15] We have also reported that (+)-**3b** afforded the β,γ-deconjugated ketone (−)-**11b** in 74% yield by treatment with sodium hydride in THF at rt.[4b] P. A. Wender *et al.* also reported the synthesis of taxol homologues in which the alkylation of (+)-**6a** by potassium *tert*-butoxide in DME gave the α-alkylated product in a moderate yield.[16] L. A. Paquette *et al.* have recently reported that oxidative coupling of the lithium anion of (+)-**6a**, which afforded a mixture of α−γ coupling products, α−γ and γ−γ bis-coupling products, and γ−γ coupling products, dependent on the presence of Fe(III) salt or Cu(II) salts.[17] M. Majewski *et al.* reported that **6a** afforded α-aldols under kinetic conditions and bis-aldols at α- and γ-position under thermodynamic conditions.[18] Judging from the results described above, it is clear that the position of alkylation is dependent on the electrophile and the reaction temperature.

In this work, we chose (−)-**6a** with 99% ee as a chiral starting material[14] to synthesize (−)-**7a** and (−)-**8**. The methoxycarbonylation did not proceed when using bases such as sodium hydride, potassium *tert*-butoxide, and LDA, at low temperature, but we found that the reaction carried out by the treatment with sodium hydride in dimethyl carbonate at *ca.* 50 °C afforded (−)-**7a** as a sole product in 92% yield;[19] the γ-methoxycarbonylated product (−)-**7b** was not isolated at all.

Next, we studied the regioselective γ-alkylation of (−)-**7a**. As the methoxycarbonyl group of (−)-**7a** is less electron withdrawing compared with the phenylsulfonyl group in (+)-**3a**, it was expected that the alkylation of (−)-**7a** would afford γ-monoalkylated products (−)-**8** without formation of γ-bisalkylated products corresponding to (+)-**3c**. On the other hand, it was uncertain whether (−)-**7a**, which has a less bulky methoxycarbonyl group, as compared to a sulfonyl group, would give γ-monoalkylated products (−)-**8** or α-monoalkylated products **10**.[3,4b] In order to optimize the reaction conditions and products, methylation of (−)-**7a** with methyl iodide was carried out. Treatment of (−)-**7a** with a large excess of methyl iodide at 50 °C for 5 h gave (−)-**8a** and **10a** in 83% and 14% yield, respectively. These alkylation reactions are sensitive to the alkyl halides used. The reaction with activated alkyl bromides, such as allyl bromide, 3-bromo-2-methyl-1-propene, and benzyl bromide, proceeded smoothly within 5 h to give the desired products **8c**, **8e**, and **8f**, respectively, in moderate yields. Interestingly, when 3-chloro-2-methyl-1-propene was used as the electrophile, even at *ca.* 80 °C for 12 h, no alkylated products were obtained and **7a** was recovered completely. The reaction with propargyl bromide was so sluggish that it took 10 h to complete the reaction, and the desired product **8d** was obtained in 57% yield. The reaction with a nonactivated alkyl bromide, such as 1-bromo-3-butene, gave no product, and the starting material was completely recovered. On the other hand, the reaction with ethyl iodide gave the desired **8b** in 61% and **10b** in 19% although the reaction was also sluggish and it took 12 h to complete the reaction.

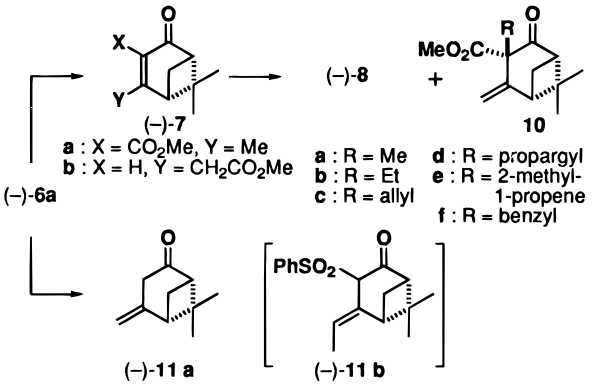


Figure 3.

According to the procedure shown in Figure 2, (+)-**7a** and (+)-**8** could be also easily synthesized from (+)-**6a**. An application of (−)-**7a** and (−)-**8** to the synthesis of natural products is currently in progress.

Experimental Section

General. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded with TMS as an internal standard in $CDCl_3$. All reactions were carried out under N_2 or Ar atmosphere. Anhydrous $MgSO_4$ was used for drying extracts on aqueous workup. Column chromatography was performed on 70−230 mesh silica gel (Merck), and the solvents for elution are

(12) (a) Whitham, G. H. *J. Chem. Soc.* **1961**, 2232. (b) Fallis, A. G. *Can. J. Chem.* **1975**, *53*, 1657. (c) Mori, K.; Mizuguchi, N., Matsui, M. *Agr. Biol. Chem.* **1976**, *48*, 1611. (−)-**6**a is commercially available, but the optical purity is very low (*ca.* 50%); see reference 14.

(13) The optical purity of **5** depends on the natural source; see Banthorpe, D. A.; Whittoker, D. *Chem. Rev.* **1966**, *66*, 643. Recently, both enantiomers, (−)- and (+)-**7** with 97% ee, have become commercially available.

(14) Toda, F. Tanaka, K., Watanabe, M. Abe, T., Harada, N. *Tetrahedron Asym.* **1995**, *6*, 1495. Recently, Paquette, L. A. *et al.* reported the synthesis of (−)-**6a** in high optical purity starting from (−)-**5**; see Poupart, M.-A.; Lassalle, G.; Paquette, L. A. *Org. Synth.* **1990**, *69*, 173, and (+)-**6a** could be also synthesized from (+)-**5**.

(15) Ohloff, G.; Giersch, W. *Helv. Chim. Acta* **1977**, *60*, 1496.

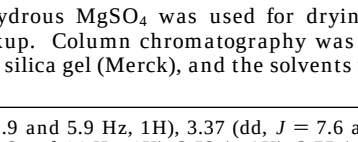
(16) Wender, P. A.; Mucciaro, T. P. *J. Am. Chem. Soc.* **1992**, *114*, 5878.

(17) Paquette, L. A.; Bzowej, E. I.; Branan, B. M.; Stanton, K. J. *J. Org. Chem.* **1995**, *60*, 7277.

(18) Majewski, M; Irvine, N. M.; Zook, S. E.; *Synth. Commun.* **1995**, *25*, 3237.

(19) (a) Inokuch, T.; Asanuma, G.; Torii, S. *J. Org. Chem.* **1982**, *47*, 4622. (b) Boger, D. L.; Mullican, M., D.; Hellberg, M., R.; Patel, M. *J. Org. Chem.* **1985**, *50*, 1904. (c) Liu, H.-J; Chew, S. Y.; Browne, E. N. C. *Tetrahedron Lett.* **1991**, *32*, 2005.

(20) To our surprise, a small amount of unstable α,γ-bisalkylated product **12d**, **12e**, and **12f** contaminated with **10d**, **10e**, and **10f**, respectively, were isolated although **12a**, **12b**, and **12c** were not isolated. ^{1}H (400 MHz) and IR data of **12d**−**f** are as follows. **12d**: 1737 and 1716 cm^{-1}; δ 1.06 (s, 3H), 1.46 (s, 3H), 1.95 (d, J = 11 Hz, 1H), 1.98 (t, J = 2.8 Hz, 1H), 2.13 (t, J = 2.5 Hz, 1H), 2.70 (ddd, J = 5.9, 5.9, and 11 Hz, 1H), 2.81 (dd, J = 5.9 and 5.9 Hz, 1H), 2.97 (ddd, J = 2.5, 6.8, and 16 Hz, 1H), 2.99 (dd, J = 2.5, 6.8, and 16 Hz, 1H), 3.05 (dd, J = 2.5 and 16 HZ, 1H), 3.07 (dd, J = 2.5 and 16 Hz, 1H), 3.20 (dd, J = 5.8 and 5.8 Hz, 1H), 3.79 (s, 3H) and 5.68 (t, J = 6.8, 1H). **12e**: 1730 and 1720 cm^{-1}; δ 0.97 (s, 3H), 1.42 (s, 3H), 1.70 (s, 6H), 2.06 (d, J = 11 Hz, 1H), 2.65 (ddd, J = 5.9, 5.9, and 11 Hz, 1H), 2.71−2.82 (m, 5H), 3.21 (dd, J = 5.8 and 5.8 Hz, 1H), 3.76 (s, 3H), 4.71 (s, 1H), 4.79 (s, 2H), 4.80 (s, 1H), 5.58 (t, J = 7.5 Hz, 1H). **12f**: 1733 and 1717 cm^{-1}; 0.97 (s, 3H), 1.37 (s, 3H), 1.38 (d, J = 11 Hz, 1H), 2.47 (ddd, J = 5.9, 5.9, and 11 Hz, 1H), 2.73 (dd, J = 5.9 and 5.9 Hz, 1H), 3.25 (dd, J = 5.9 and 5.9 Hz, 1H), 3.37 (dd, J = 7.6 and 14 Hz, 1H), 3.43 (dd, J = 7.6 and 14 Hz, 1H), 3.53 (s, 2H), 3.75 (s, 3H), 5.61 (t, J = 7.6 Hz, 1H), 7.05−7.29 (m, 10H).



12

Table 1. Alkylation of (−)-7a with Alkyl Halide

		reaction conditions			
entry	alkyl halide	temp (°C)	time (h)	yield (%)	ratio of **8**:**10**
a	Methyl Iodide	50	5	97	5.6:1
b	Ethyl Iodide	50	12	80	3.3:1
c	Allyl Bromide	50	5	82	2.0:1
d	Propargyl Bromide	50	10	77	4.8:1
e-1	3-Chloro-2-methyl-1-propene	80	12	no reaction	
e-2	3-Bromo-2-methyl-1-propene	50	5	81	3.0:1
f	Benzyl Bromide	50	5	65	3.2:1
g	1-Bromo-3-butene	80	12	no reaction	

shown in parentheses. All analytical samples were purified again by HPLC.

Preparation of (1*S*,5*S*)-(−)-Verbenone (6a). The enone (−)-**6a** used in this work was prepared according to the published procedure.[14] This enantiomeric purification was scaled up four times. The optical resolution started from 78% ee (−)-**6a** (30 g, 200 mmol) to afford 99% ee (−)-**6a** (11.5 g); $[\alpha]^{22}_D$ −273.5° (*c* 1.0, $CHCl_3$). Enantiomeric excess of (−)-**6a** was determined by HPLC using the Chiralpak AS column (available from Daicel Chemical Industries Ltd, Japan) and hexane: EtOH (95:5).

Preparation of (1*S*,5*S*)-3-Carbomethoxy-4-methyl-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (7a) from (−)-Verbenone (6). A mixture of (−)-**6** (3.0 g, 20 mmol) and sodium hydride (60% mineral oil dispersion) (1.2 g, 30 mmol) in dimethyl carbonate (20 mL) was stirred at rt for 2 h. Monitoring on TLC showed that no reaction proceeded. The reaction temperature was elevated to 50−60 °C, and the reaction mixture was stirred 3 h. An additional portion of dimethyl carbonate (10 mL) was added after 3 h, and then the reaction mixture was stirred at 50−60 °C until the starting material was not detected by TLC monitoring. The reaction mixture was diluted with aqueous NH_4Cl, and extracted with ether. The ethereal layer was washed with water and brine, dried, and evaporated, affording a crude product, which was purified by column chromatography (ether−hexane, 1:1) to give (−)-**7a** (3.84 g, 92%) as an oil: $[\alpha]_D$ −216.1° (*c* 1.37, $CHCl_3$); IR (neat) 1737, 1683 cm^{-1}, ^1H NMR δ 1.05 (s, 3H), 1.50 (s, 3H), 2.14 (d, *J* = 9.2 Hz, 1H), 2.17 (s, 3H), 2.53 (dd, *J* = 6.1 and 6.1 Hz, 1H), 2.75 (dd, *J* = 6.1 and 6.1 Hz, 1H), 2.81 (ddd, *J* = 6.1, 6.1, and 9.2 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR δ 21.57, 21.99, 26.30, 38.91, 50.53, 51.74, 53.24, 57.12, 126.06, 165.61, 171.69, 198.16. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.19; H, 7.75. Found: C, 68.98; H, 7.79.

Reaction of (−)-7a with Methyl Iodide. A mixture of (−)-**7a** (208 mg, 1.0 mmol), K_2CO_3 (1.38 g, 10.0 mmol), and methyl iodide (0.5 mL, 8.0 mmol) in acetone (10 mL) was stirred at 50 °C for 5 h. The reaction mixture was passed through a short SiO_2 pad eluted by a mixture of ether and hexane (1:1). The obtained eluant was evaporated to afford a crude mixture, which was purified by column chromatography (ether−hexane, 1:1) to give (1*S*,3*S*,5*S*)-3-carbomethoxy-3-methyl-4-methylene-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (**10a**) (32 mg, 14%) as a minor product; IR (neat) 1733 and 1716 cm^{-1}; ^1H NMR δ 1.07 (s, 3H), 1.41 (s, 3H), 1.79 (s, 3H), 1.91 (d, *J* = 10.7 Hz, 1H), 2.71 (ddd, *J* = 5.7, 5.7, and 10.7 Hz, 1H), 2.79 (dd, *J* = 5.7 and 5.7 Hz, 1H), 2.88 (dd, *J* = 5.7 and 5.7 Hz, 1H), 3.76 (s, 3H), 5.08 (s, 1H), and 5.11 (s, 1H);[4b] ^{13}C NMR δ 22.57, 26.72, 27.77, 30.63, 43.13, 52.51, 52.55, 58.66, 59.04, 112.10, 148.52, 171.70, 210.23. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.23; H, 8.17. Found: C, 70.39; H, 8.24. Continued column chromatography afforded (1*S*,5*S*)-3-carbomethoxy-4-ethyl-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (**8a**) (184 mg, 83%) as a major product: $[\alpha]_D$ −176.9° (*c* 1.63, $CHCl_3$); IR (neat) 1737, 1687 cm^{-1}; ^1H NMR[4b] δ 1.05 (s, 3H), 1.10 (t, *J* = 7.6 Hz, 3H), 1.51 (s, 3H), 2.13 (d, *J* = 9.2 Hz, 1H), 2.38 (dq, *J* = 7.6 and 11.4 Hz, 1H), 2.50 (dq, *J* = 7.6 and 11.4 Hz, 1H), 2.62 (dd, *J* = 5.9 and 5.9 Hz, 1H), 2.75 (dd, *J* = 5.9 and 5.9 Hz, 1H), 2.83 (ddd, *J* = 5.9, 5.9, and 9.2 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR δ 11.10, 22.26, 26.46, 28.40, 39.51, 48.46, 51.95, 53.45, 57.32, 125.59, 165.85, 175.27, 198.79. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.23; H, 8.17. Found: C, 70.36; H, 8.31.

Reaction of (−)-7a with Ethyl Iodide. A mixture of (−)-**7a** (208 mg, 1.0 mmol), K_2CO_3 (1.38 g, 10.0 mmol), and ethyl iodide (0.5 mL, 6.2 mmol) in acetone (10 mL) was stirred at 50 °C for 12 h. The workup was carried out as described above and purification by column chromatography (ether−hexane, 1:1) gave (1*S*,3*S*,5*S*)-3-carbomethoxy-3-ethyl-4-methylene-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one **10b** (44 mg, 19%) as a minor product: IR (neat) 1733, 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (t, *J* = 7.3 Hz, 3H), 1.03 (s, 3H), 1.40 (s, 3H), 1.93 (d, *J* = 11 Hz, 1H), 2.13 (dq, *J* = 7.3 and 14.6 Hz, 1H), 2.25 (dq, *J* = 7.3 and 14.6 Hz, 1H), 2.63 (ddd, *J* = 5.7, 5.7, and 11 Hz, 1H), 2.74 (dd, *J* = 5.7 and 5.7 Hz, 1H), 2.85 (dd, *J* = 5.7 and 5.7 Hz, 1H), 3.76 (s, 3H), 5.05 (s, 1H), 5.12 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 10.55, 22.37, 26.66, 26.71, 35.58, 43.71, 52.34, 52.62, 58.55, 63.77, 112.97, 146.49, 170.94, 208.13. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.14; H, 8.54. Found: C, 71.27; H, 8.65. Continued column chromatography afforded (1*S*,5*S*)-3-carbomethoxy-4-propyl-6,6-dimethylbicyclo-[3.1.1]hept-3-en-2-one (**8b**) (144 mg, 61%) as a major product; $[\alpha]_D$ −177.3° (*c* 1.31, $CHCl_3$); IR(neat) 1736, 1687 cm^{-1}; ^1H NMR δ 0.97 (t, *J* = 7.4 Hz, 3H), 1.05 (s, 3H), 1.51 (s, 3H), 1.51 (sext, *J* = 7.4 Hz, 2H), 2.12 (d, *J* = 9.4 Hz, 1H), 2.35−2.45 (m, 2H), 2.61 (dd, *J* = 5.9 and 5.9 Hz, 1H), 2.75 (dd, *J* = 5.9 and 5.9 Hz, 1H), 2.83 (ddd, *J* = 5.9, 5.9, and 9.4 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR δ 14.14, 20.14, 22.09, 26.38, 37.10, 39.42, 48.64, 51.79, 53.32, 57.21, 126.13, 165.78, 173.92, 198.67. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.14; H, 8.54. Found: C, 71.17; H, 8.59.

Reaction of (−)-7a with Allyl Bromide. A mixture of (−)-**7a** (208 mg, 1.0 mmol), K_2CO_3 (1.38 g, 10.0 mmol), and allyl bromide (605 mg, 5 mmol) in acetone (10 mL) was stirred at 50 °C for 5 h. The workup was carried out as described above, and purification by column chromatography (ether−hexane, 1:1) gave (1*S*,3*S*,5*S*)-3-allyl-3-carbomethoxy-4-methylene-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (**10c**) (67 mg, 27%) as a minor product: IR (neat) 1736, 1717 cm^{-1}; ^1H NMR δ 1.02 (s, 3H), 1.40 (s, 3H), 1.97 (d, *J* = 11 Hz, 1H), 2.63 (ddd, *J* = 5.7, 5.7, and 11 Hz, 1H), 2.75 (dd, *J* = 5.7 and 5.7 Hz, 1H), 2.82 (dd, *J* = 6.6 and 13.9 Hz, 1H), 2.86 (dd, *J* = 5.7 and 5.7 Hz, 1H), 2.99 (dd, J = 6.6 and 13.9, 1H), 3.76 (s, 3H), 4.98−5.08 (m, 2H), 5.07 (s, 1H), 5.15, (s, 1H), 5.75−5.85 (m, 1H); ^{13}C NMR δ 22.46, 26.29, 26.65, 43.47, 46.54, 52.55, 52.58, 58.61, 63.41, 113.73, 118.24, 133.76, 145.66, 170.78, 207.28. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.54; H, 8.12. Found: C, 72.44; H, 8.21. Further elution gave (1*S*,5*S*)-3-carbomethoxy-4-(3-butenyl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (**8c**) (258 mg, 55%) as a major product: $[\alpha]_D$ −188.5° (*c* 1.37, $CHCl_3$); IR (neat) 1736, 1685 cm^{-1}; ^1H NMR δ 1.05 (s, 3H), 1.51 (s, 3H), 2.12 (d, *J* = 9.1 Hz, 1H), 2.18−2.31 (m, 2H), 2.47−2.59 (m, 2H), 2.67 (dd, *J* = 5.9 and 5.9 Hz, 1H), 2.75 (dd, *J* = 5.9 and 5.9 Hz, 1H), 2.82 (ddd, *J* = 5.9, 5.9, and 9.1 Hz, 1H), 3.84 (s, 3H) 5.01−5.08 (m, 2H), 5.75−5.85 (m, 1H); ^{13}C NMR δ 21.94, 26.17, 30.58, 34.36, 39.11, 48.40, 51.56, 53.11, 57.00, 115.51, 126.18, 136.42, 165.38, 172.87, 198.20. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.54; H, 8.12. Found: C, 72.81; H, 8.15.

Reaction of (−)-7a with Propargyl Bromide. A mixture of (−)-**7a** (208 mg, 1.0 mmol), K_2CO_3 (1.38 g, 10.0 mmol), and propargyl bromide (675 mg, 5 mmol) in acetone (10 mL) was stirred at 50 °C for 10 h. The workup was carried out as described above, and purification by column chromatography (ether−hexane, 1:1) gave (1*S*,3*S*,5*S*)-3-carbomethoxy-3-propargyl-4-methylene-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (**10d**) (29 mg, 12%) as a minor product:[19] IR (neat) 1736, 1717 cm^{-1}; ^1H NMR δ 1.04 (s, 3H), 1.42 (s, 3H), 1.97 (d, *J* = 11 Hz, 1H), 2.13 (t, *J* = 2.3, 1H), 2.70 (ddd, *J* = 5.7, 5.7, and 11 Hz, 1H), 2.81 (dd, *J* = 5.7 and 5.7 Hz, 1H), 2.88 (dd, *J* = 5.7 and 5.7 Hz, 1H), 3.05 (dd, *J* = 2.3 and 14 Hz, 1H), 3.11 (dd, *J* = 2.3 and 14 Hz, 1H), 3.80 (s, 3H), 5.22 (s, 1H) and 5.24 (s, 1H); ^{13}C NMR δ 22.49, 26.58, 27.09, 31.76, 43.53, 52.33, 52.82, 58.48, 61.68, 71.94, 79.60, 114.92, 144.47, 169.88, 206.20. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.13; H, 7.37. Found: C, 73.14; H, 7.36. Further elution gave (1*S*,5*S*)-3-carbomethoxy-4-(3-butynyl)-6,6-dimethylbicyclo-[3.1.1]hept-3-en-2-one (**8d**) (140 mg, 57%) as a major product product: $[\alpha]_D$ −161.6° (*c* 1.41, $CHCl_3$); IR (neat) 1737, 1684 cm^{-1}; ^1H NMR δ 1.09 (s, 3H), 1.52 (s, 3H), 2.01 (t, *J* = 2.7 Hz, 1H), 2.17 (d, *J* = 9.5 Hz, 1H), 2.35−2.48 (m, 2H), 2.66−2.73 (m, 3H), 2.77 (dd, *J* = 5.9 Hz, 1H), 2.85 (ddd, *J* = 5.9, 5.9 and 9.5 Hz, 1H), 3.85 (s, 3H); 100-MHz ^{13}C NMR δ 16.53, 22.21, 26.44, 33.73, 39.56, 48.93, 52.00, 53.5, 57.40, 69.97, 82.17, 127.08, 165.47, 171.72, 198.43. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.13; H, 7.37. Found: C, 73.12; H, 7.34.

Reaction of (−)-7a with 3-Chloro-2-methyl-1-propene. A mixture of (−)-**7a** (208 mg, 1.0 mmol), K_2CO_3 (1.38 g, 10.0 mmol), and 3-chloro-2-methylpropene (590 mg, 5 mmol) in acetone (10

mL) was stirred at 50 °C for 12 h. The starting material (−)-**7a** was recovered after the workup was carried out as described above.

Reaction of (−)-7a with 3-Bromo-2-methyl-1-propene. A mixture of (−)-**7a** (208 mg, 1.0 mmol), K_2CO_3 (1.38 g, 10.0 mmol), and 3-bromo-2-methyl-1-propene (590 mg, 5 mmol) in acetone (10 mL) was stirred at 50 °C for 5 h. The workup was carried out as described above, and purification by column chromatography (ether−hexane, 1:1) gave (1*S*,3*S*,5*S*)-3-carbomethoxy-3-(2-methyl-2-propenyl)-4-methylene-6,6-dimethylbicyclo[3.1.1]-hept-3-en-2-one (**10e**) (53 mg, 20%) as a minor product (53 mg, 20%):[19] IR (neat) 1736, 1720 cm^{-1}; ^1H NMR δ 0.99 (s, 3H), 1.40 (s, 3H), 1.70 (s, 3H), 2.04 (d, J = 11 Hz, 1H), 2.63 (ddd, J = 5.9 and 5.9 Hz, 1H), 2.75 (dd, J = 5.7 and 5.7 Hz, 1H), 2.79 (d, J = 14, 1H), 2.86 (dd, J = 5.7 and 5.7 Hz, 1H), 3.22 (d, J = 14 Hz, 1H), 3.77 (s, 3H), 4.70 (s, 1H), 4.80 (s, 1H), 5.10 (s, 1H), 5.13 (s, 1H); ^{13}C NMR δ 22.36, 23.14, 25.70, 26.54, 43.34, 50.25, 52.51, 52.63, 58.72, 63.16, 113.05, 115.96, 141.90, 146.10, 171.05, 206.45. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.24; H, 8.46. Found: C, 73.08; H, 8.26. Further elution gave (1*S*,5*S*)-3-carbomethoxy-4-(3-methyl-3-butenyl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (**8e**) (161 mg, 61%) as a major product: $[\alpha]_D$ −177.6° (*c* 1.74 $CHCl_3$); IR (neat) 1736, 1686 cm^{-1}; ^1H NMR δ 1.05 (s, 3H), 1.51 (s, 3H), 1.75 (s, 3H), 2.13 (d, J = 9.5 Hz, 1H), 2.15−2.19 (m, 2H), 2.51−2.69 (m, 2H), 2.62 (dd, J = 5.9 and 5.9 Hz, 1H), 2.75 (dd, J = 5.9 and 5.9 Hz, 1H), 2.83 (ddd, J = 5.9, 5.9, and 9.5 Hz, 1H), 3.84 (s, 3H), 4.72 (s, 1H), 4.77 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.15, 22.22, 26.47, 33.78, 34.66, 39.45, 48.78, 51.94, 53.46, 57.30, 111.00, 126.24, 143.98, 165.71, 173.68, 198.61. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.24; H, 8.46. Found: C, 72.91; H, 8.40.

Reaction of (−)-7a with Benzyl Bromide. A mixture of (−)-**7a** (208 mg, 1.0 mmol), K_2CO_3 (1.38 g, 10.0 mmol), and benzyl bromide (590 mg, 5 mmol) in acetone (10 mL) was stirred at 50 °C for 5 h. The workup was carried out as described above, and purification by column chromatography (ether−hexane, 1:1) gave (1*S*,3*S*,5*S*)-3-benzyl-3-carbomethoxy-4-methylene-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (**10f**) as a minor product (46 mg, 15%): $[\alpha]_D$ −177.6° (*c* 1.74 $CHCl_3$); IR (neat) 1736, 1617 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (s, 3H), 1.12(d, J = 11 Hz, 1H), 1.33 (s, 3H), 2.36 (ddd, J = 5.9, 5.9, and 11 Hz, 1H), 2.68 (dd, J = 5.9 and 5.9 Hz, 1H), 2.72 (dd, J = 5.9, and 5.9, 1H), 3.47 (d, J = 13 Hz, 1H), 3.61 (d, J = 13 Hz, 1H), 3.77 (s, 3H), 5.14 (s, 1H), 5.23 (s, 1H), 7.13−7.17 (m, 2H), 7.19−7.27 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 22.5, 25.0, 26.4, 42.3, 46.4, 52.64, 52.66, 58.8, 64.3, 115.6, 127.0, 127.9, 131.0, 136.3, 143.9, 171.1, 206.4. Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.47; H, 7.44. Found: C, 76.62; H, 7.47. Further elution gave (1*S*,5*S*)-3-carbomethoxy-4-(2-phenylethyl)-3-carbomethoxy-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-one (**8f**) (148 mg, 50%) as a major product: IR (neat) 1732, 1683 cm^{-1}; ^1H NMR δ 1.04 (s, 3H), 1.50 (s, 3H), 2.08 (d, J = 9.2 Hz, 1H), 2.65 (dd, J = 5.9 and 5.9 Hz, 1H), 2.69−2.93 (m, 5H), 2.82 (dd, J = 5.9, 5.9, and 9.5 Hz, 1H), 3.81 (s, 3H), 7.18−7.23 (m, 3H), 7.26−7.32 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.54, 24.97, .26.41, 42.32, 46.40, 52.65, 52.66, 58.83, 64.32, 115.63, 127.03, 127.88, 131.00, 136.27, 143.92, 171.14, 206.44. Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.47; H, 7.44. Found: C, 76.48; H, 7.43.

Reaction of (−)-7a with 1-Bromo-3-butene. A mixture of (−)-**7a** (208 mg, 1.0 mmol), K_2CO_3 (1.38 g, 10.0 mmol), and 1-bromo-3-butene (590 mg, 0.5 mmol) in acetone (10 mL) was stirred at 50 °C for 5 h. The starting material (−)-**7a** was completely recovered after the workup was carried out as described above.

Acknowledgment. This work is supported by grants from the Ministry of Education, Science, and Culture, Japan (Priority Areas No. 082211201).

JO9612279