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Rearrangement Approaches to Cyclic Skeletons. II. Structural Revision and Total Synthesis of (±)-Isosesquicarene, a [3—6] Fused-Ring Sesquiterpene[1)]

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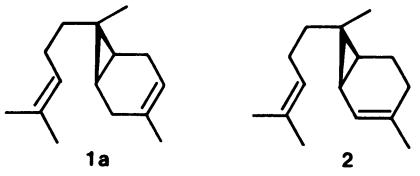
The *exo*-7-(4-methyl-3-pentenyl) derivative of 3-carene (**1a**), the original structure reported for (±)-isosesquicarene, was synthesized starting from tropone, and it was found that **1a** is not identical with natural isosesquicarene. The structure of isosesquicarene was reinterpreted as *endo*-7-(4-methyl-3-pentenyl) derivative of 3-carene (**1b**). The first total synthesis of (±)-isosesquicarene, **1b**, has been accomplished on the basis of the photochemical transformation of 4-methylbicyclo[3.2.2]nona-3,6-dien-2-one into the 7-*exo*-methylbicyclo-[4.1.0]hept-2-ene.

The structure proposed for isosesquicarene, a sesquiterpenic hydrocarbon isolated from *Haplopappus tenuisectus* (Greene) Blake, is the 3-carene derivative (**1a**)[3)] which is very similar to that of sesquicarene (**2**).[4)] In connection with the stereoselective synthesis of **2** from tropone,[2)] we attempted a total synthesis of (±)-isosesquicarene, and found that **1a** is not the correct structure of isosesquicarene. In this paper we detail i) a stereoselective synthesis of **1a**, ii) proposal of the probable structure (**1b**) for isosesquicarene, and iii) the first total synthesis of (±)-isosesquicarene, **1b**.



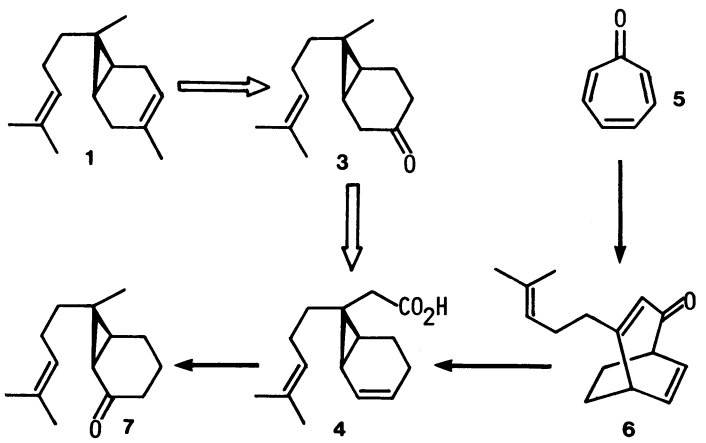
1a **2**

Results and Discussion

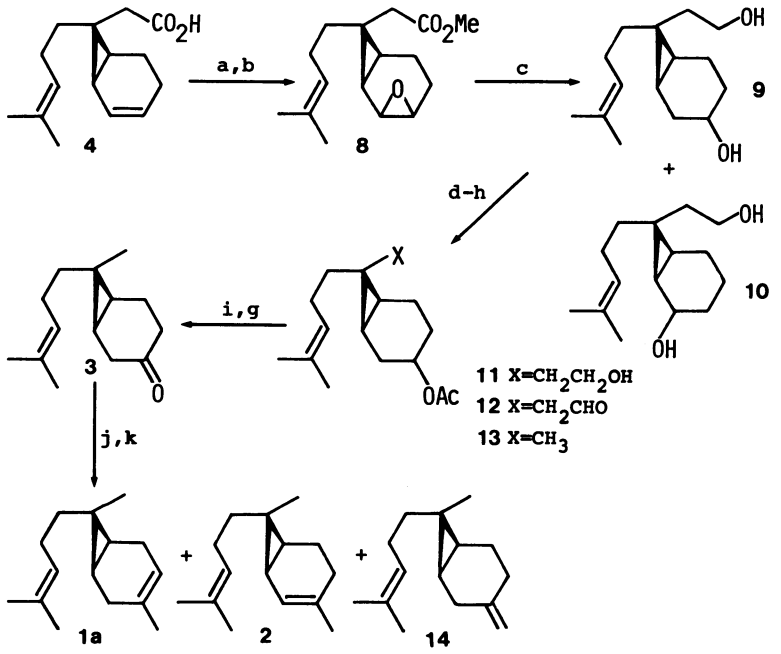
Synthesis of the Original Structure Reported for Isosesquicarene. Scheme 1 shows our synthetic plan along with the background.[2)] The ketone (**3**), a presumable precursor of **1a**, would be derived from the bicyclic acid (**4**) in a manner similar to the conversion of **4** into ketone **7** which is a key synthetic intermediate for sesquicarene (**2**). A practical synthetic route to **4** from tropone (**5**) has already been established *via* photochemical transformation of **6** into the acid.

The iodo lactone, derived from **4**,[2)] was transformed into the epoxide (**8**) in 95% yield from **4** by treating with sodium methoxide in methanol, as shown in Scheme 2. The stereochemistry of the epoxide followed from its ^{1}H-NMR spectra which showed $J_{1,2}$=3.6 Hz.[5)] A regioselective opening of the oxirane ring of **8** was done by heating with $LiAlH_4$ in tetrahydrofuran (THF) to give diols **9** and **10** in 76 and 19% yields, respectively. The minor product was identical with the diol obtained from the iodo lactone by treating with $LiAlH_4$.[2)] A better level of stereocontrol was obtained with diisobutylaluminium hydride (DIBAH) at 0 °C but the yield of **9** was not superior to the $LiAlH_4$ reduction; 67%, **9** and 8%, **10**.

In order to prepare an aldehyde suitable for one-



Scheme 1.



Scheme 2. Synthesis of 3,*endo*-7-Dimethyl-*exo*-7-(4-methyl-3-pentenyl)bicyclo[4.1.0]hept-3-ene (**1a**).[a)]

a) (a): I_2, $NaHCO_3$, ether, H_2O, (b): MeONa, MeOH, (c): $LiAlH_4$, THF, (d): TBDMS–Cl, DMAP, $N(CH_2CH_3)_3$, (e): Ac_2O, Py, (f): AcOH, THF, H_2O, (g): CrO_3–2Py, (h): $RhCl(PPh_3)_3$, PhCN, (i): $LiAlH_4$, ether, (j): MeLi, (k): $POCl_3$, DMAP, Py.

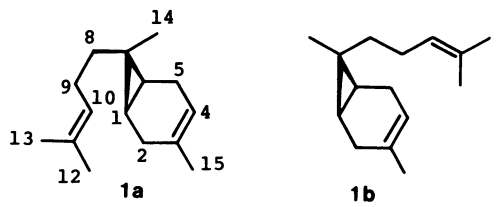
carbon removal from the *endo*-side chain as carbon monoxide using Wilkinson's complex,[6)] the major diol (**9**) was converted into monoacetate **11** in 78% yield. Oxidation of **11** by Collins reagent gave aldehyde **12** in 82% yield. Decarbonylation of **12** by heating with just one equivalent of Wilkinson's complex in benzonitrile at 145 °C for 8 min afforded the acetate (**13**) in 84% yield. Reduction of **13** with $LiAlH_4$ followed by oxidation with Collins reagent produced the desired ketone, **3**, in 91% yield.

Treatment of **3** with an excess of methyllitium at −78 °C gave a mixture of the tertiary alcohols in 73% yield and 22% of unchanged **3**. Dehydration of the alcohols with phosphoryl chloride, pyridine and 4-dimethylaminopyridine (DMAP) produced a 81% yield of three hydrocarbons in a ratio of 63:31:6. The second major product was identical with (±)-sesquicarene (**2**). The specimen of the minor product (**14**) was prepared from **3** by treatment with methylenetriphenylphosphorane in dimethyl sulfoxide (DMSO).

The spectral characteristics of the major product support that its structure is **1a**. However, the NMR spectral data of hydrocarbon **1a** are significantly different from those reported for natural isosesquicarene.

A Structural Revision of Isosesquicarene. It is interesting that both the ^{1}H-NMR data of **1a** and natural isosesquicarene can be arranged in the same tabular form, as shown in Table 1. The assignments of the spectrum of **1a** were performed easily starting from the largest coupling of the H_4 to one of the vicinal methylene protons. Table 1 suggests that both the compounds are the 3-carene derivatives possessing a homoprenyl side chain. A large difference between the chemical shifts of their cyclopropyl methyl protons, H_{14}, indicates that the lower-field resonance of isosesquicarene is not affected largely by the anisotropy effect of the C_3–C_4 double bond.

Thus we propose the C_7-stereoisomer of the original structure, **1b**, as the revised stereostructure of isosesquicarene. The following studies are in order to confirm our proposal.



Total Synthesis of (±)-Isosesquicarene (1b). The synthesis was initiated with ketone **15** as shown in Scheme 3. The ketone has already been prepared form bicyclo[3.2.2]nona-3,6-dien-2-one.[2)] The photochemical conversion of **15** into **16** in a good yield was performed by irradiation of a methanolic solution using a high-pressure mercury lamp through a Pyrex

filter. The fact that ^{1}H-NMR of **16** shows the resonance due to the cyclopropyl methyl protons at δ=1.13 prompted us to forward the scheme.

In order to elongate the endo-side chain, **16** was reduced by $LiAlH_4$ to the alcohol, which was tosylated. Treating of the tosylate with sodium cyanide in DMSO gave nitrile **17** in 84% yield (from **16**). The silyl ether (**19**) was derived from **17** in 70% yield *via* the aldehyde (**18**) by sequential treatment with (i) DIBAH, (ii) aqueous ammonium chloride solution, (iii) $LiAlH_4$, and (iv) *t*-butyldimethylchlorosilane, triethylamine, and DMAP.

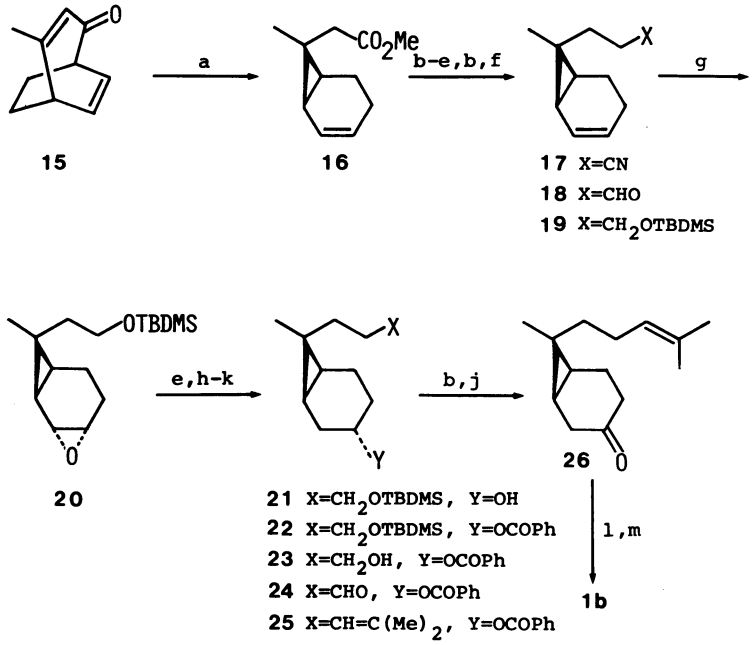
Table 1. Proton NMR data of compound **1a** and isosesquicarene (in $CDCl_3$)

	Compound **1a**			Isosesquicarene[a]	
H	δ	mult	J, Hz (coupled to)[b]	δ	mult[c]
1	0.72	dd	9.3(6), 7.2(2α)	0.66	dd
2α	2.18	bdd	18.2(2β), 7.2(1)	2.34	bdd
2β	1.81	m		2.03	m
4	5.27	bs		5.25	bs
5α	2.36	m	16.5(5β), 7.2(6), 3.5(4)	2.16	bdd
5β	1.94	m		1.86	bd
6	0.63	dd	9.3(1), 7.2(5α)	0.78	dd
8	1.19	m		(1.14	m)[d]
9	2.07	m	7.0(10)	2.03	
10	5.15	bt	9.0(9)	5.12	bt
12	1.64	bs		1.59	bs
13	1.69	d	1(10)	1.67	bs
14	0.75	s		1.02	
15	1.64	bs		1.59	bs

a) Ref. 3. b) Distinguished coupling are listed. c) $J_{5\alpha,5\beta}$=19 Hz, $J_{4,5\alpha}$=3 Hz, $J_{5\alpha,6}$=8 Hz, $J_{1,2\alpha}$=8 Hz, $J_{1,6}$=8 Hz, and $J_{9,10}$=7 Hz. d) This work.

Epoxidation of **19** with *m*-chloroperoxybenzoic acid yielded only **20**. The stereostructure of **20** was estimated on the basis of its ^{1}H-NMR spectra ($J_{1,2}$<1 Hz).[5] Treatment of **20** with DIBAH gave only the regioselective C–O cleavage product (**21**), which was converted into the benzoate (**22**) in 71% yield from **19**. This regioselective ring opening is with the assistance of the bonding between the reagent and the epoxide oxygen and due to participation of the cyclopropane to tolerate positive charge at the C_2 in the transition state. ^{1}H-NMR spectra of **22** showed the signals due to the C_3–H at δ=4.91 (b, $W_{1/2}$= 13 Hz). This half-hight width is clearly different from those of **12** and **13**: C_3–H of **12**, $W_{1/2}$=19.5 Hz; C_3–H of **13**, $W_{1/2}$=21 Hz. Thus, the 3-proton of **22** should be a pseudoequatrial one and the benzoyloxyl group should be α-configuration as illustrated. Now it is clear that the epoxidation of **19** proceeded at its less-hindered side.

After removal of the silyl group of **22**, the alcohol (**23**) was transformed into the unstable aldehyde (**24**). Immediately after isolation, **24** was treated with isopropylidenetriphenylphosphorane in ether at −30 °C to give **25** in 68% yield from **23**.



Scheme 3. Synthesis of (±)-isosesquicarene.[a]

a) (a): *hv*, MeOH, (b): $LiAlH_4$, (c): TsCl, Py, (d): NaCN, DMSO, (e): DIBAH, $PhCH_3$, (f): TBDMS–Cl, DMAP, $N(CH_2CH_3)_3$, (g): MCPBA, $NaHCO_3$, (h): $(PhCO)_2O$, DMAP, $N(CH_2CH_3)_3$, (i): AcOH, THF, H_2O, (j): CrO_3–2Py, (k): Ph_3P=CMe_2, (l): MeLi, (m): $POCl_3$, DMAP, Py.

We have examined several routes to shorten the synthetic steps but have not yet found more effective ones because of instability of the aldehydes like **24**.

Reduction of **25** with $LiAlH_4$ followed by Collins oxidation gave ketone **26** in 76% yield. Treatment of **26** with methyllithium at −95 °C yielded a mixture of tertiary alcohols in 74% yield. Dehydration of the alcohols gave a mixture of three hydrocarbons in 74% yield. The major product (**1b**) was purified by repeated preparative VPC. Thus obtained was identical spectroscopically with natural isosesquicarene.

*The stereostructure of isosesquicarene is 3,*exo*-7-dimethyl-*endo*-7-(4-methyl-3-pentenyl)bicyclo[4.1.0]hept-3-ene.*

Experimental

General. Melting and boiling points are uncorrected. IR spectra (in CCl_4, unless otherwise mentioned) were recorded on a Hitachi Model 215 spectrometer. NMR spectra (in CCl_4, unless otherwise noted) were obtained on JEOL JNM-PMX60, Varian EM-390 90 MHz, and Varian XL-200 NMR spectrometers, using tetramethylsilane as an internal standard. The mass spectral studies were conducted using a Hitachi M-52 spectrometer and a JEOL DX-300 mass spectrometer. Photochemical reactions were carried out in an immersion well through a Pyrex filter using a Ushio 300 W high pressure mercury lamp, under an inert atmosphere. THF and ether were distilled from benzophenone ketyl under argon, immediately prior to use. Dichloromethane was distilled from P_2O_5 and stored on 4A molecular sieves. Pyridine (from BaO), triethylamine, methanol (from $Mg(OCH_3)_2$), and DMSO (from BaO) were purified by distillation. Collins reagent,[7] and Wilkinson's complex[8] were prepared by using literature procedures. All reactions were monitored by analytical TLC using E. Merck precoated silica gel $60F_{254}$ plates. Column chromatography was carried out with E. Merck silica gel 60 (70—230 mesh ASTM, twenty to fifty times (w/w)). A Warters silica cartridge "Sep-Pack" was used for small scale rapid chromatography. Analytical VPC was performed on a Hitachi 663-50 gas chromatograph, outfitted with a 3 m×3 mm stainless-steel column packed with 10% FFAP on 60/80 Uniport B, and preparative VPC on a Varian Aerograph model 920 gas chromatograph with TC detector, outfitted a with 10 ft×3/8 in. aluminium column containg 10% FFAP on 60/80 Uniport B.

Preparation of Methyl endo*-2,3-Epoxy-*exo*-7-(4-methyl-3-pentenyl)bicyclo[4.1.0]heptane-*endo*-7-acetate (8).* To a solution of 262.4 mg (1.12 mmol) of **4** in 7 ml of saturated aqueous $NaHCO_3$ was added a solution of 285 mg (1.12 mmol) of iodine in 10 ml of ether over a period of 20 min at room temperature in the dark. After 1 h of stirring, the mixture was diluted with water, and extracted with several portions of ether. The extracts were combined, washed with 5% aqueous $Na_2S_2O_3$ and saturated brine, and then dried over $MgSO_4$. Evaporation of the solvent without heating from outside gave 443.3 mg of a pale yellow oil, which was supplied directly to the following reaction. To a solution of the oil in 5 ml of methanol was added a solution of sodium methoxide in methanol, prepared from 60 mg of sodium and 1.2 ml of methanol, at 0 °C. After 2 h standing at 0 °C, the mixture was diluted with water, and extracted with two portions of ether. The extracts were combined, washed with two portions of water and with saturated brine, and then dried over $MgSO_4$. Removal of the solvent gave 297.5 mg of yellow oil, which was purified by column chromatography (5:1 hexane, ethyl acetate) to yield 280.7 mg (95%) of **8**: bp 100—105 °C/2 Torr; IR 1740 (s), 1190 (m), and 1165 (m) cm^{-1}; NMR δ=5.00 (1H, tm, J=7.2 Hz), 3.62 (3H, s), 3.25 (1H, dd, J=3.6 and 3.6 Hz), 2.83 (1H, dd, J=3.6 and 2.7 Hz), 2.68 (2H, s), 1.66 (3H, bs), 1.60 (3H, bs), and 0.79 (1H, dd, J= 9.0 and 3.6 Hz); MS, m/z (rel intensity) 264 (M^+, 13) and 167 (100). Found: C, 72.67; H, 9.38%. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15%.

Reduction of Epoxide 8. Preparation of endo*-7-(2-Hydroxyethyl)-*exo*-7-(4-methyl-3-pentenyl)bicyclo[4.1.0]heptan-3-ol (9).* To a mixture of 146 mg (3.85 mmol) of $LiAlH_4$ and 5 ml of dry THF was added a solution of 398.5 mg of **8** in 30 ml of dry THF at 0 °C. The reaction mixture was heated under reflux for 1.5 h. After cooling to 0 °C, the resulting suspension was treated by successive dropwise addition of a few ml of ethyl acetate, 0.15 ml of water, 0.15 ml of 15% aqueous NaOH, and 0.45 ml of water, and then allowed to warm to room temperature with stirring. The THF solution was filtered, and the filtrate was concentrated *in vacuo* to afford 389.1 mg of a colorless oil. Separation of the products by column chromatography (1:1 hexane, ethyl acetate) gave 287.7 mg (76%) of **9** and 72 mg (19%) of **10**.[2] **9**: IR 3340 (m) and 1055 (s) cm^{-1}; NMR δ=5.00 (1H, tm, J=6.9 Hz), 4.05 (2H, bs), 1.67 (3H, s), and 1.61 (3H, s). The diacetate of **9**: C, 71.07; H, 9.51%. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38%.

Transformation of Diol 9 into endo*-7-(2-Hydroxyethyl)-*exo*-7-(4-methyl-3-pentenyl)bicyclo[4.1.0]hept-3-yl Acetate (11).* In order to protect the primary hydroxyl group selectively, a solution of 220 mg (1.2 equiv) of *t*-butyldimethylchlorosilane in 10 ml of CH_2Cl_2 was added to a solution of 287.7 mg (1.21 mmol) of **9**, 137.8 mg (0.19 ml, 1.1 equiv) of triethylamine, and a small amount of DMAP in 9 ml of CH_2Cl_2. After standing for 21 h at room temperature, the solution was washed with saturated aqueous NH_4Cl, dried over $MgSO_4$, and concentrated *in vacuo*. Chromatography (15:1 hexane, ethyl acetate) of the residue gave 341.8 mg (80%) of the monosilyl ether of **9**: IR 3620 (w), 3350 (w), 1090 (s), and 1050 (m) cm^{-1}; NMR δ=4.97 (1H, tm, J= 6.9 Hz), 3.67 (2H, m), 3.47 (1H, m), 1.64 (3H, bs), 1.58 (3H, bs), 0.90 (6H, s), and 0.05 (9H, s).

To protect the secondary hydroxyl group, 2 ml of acetic anhydride was added to a solution of 603.2 mg (1.71 mmol) of the monosilyl ether in 3 ml of dry pyridine. After standing overnight at room temperature, evaporation of the solvent *in vacuo* gave 670.5 mg of the residue, which was chromatographed (10:1 hexane, ethyl acetate) to afford 665.6 mg (98%) of the acetate: IR 1730 (s) and 1030 (m) cm^{-1}. Found: C, 70.01; H, 10.62%. Calcd for $C_{23}H_{42}O_3Si$: C, 70.00; H, 10.73%.

In order to remove the silyl group,[9] 665.6 mg (1.68 mmol) of the acetate was treated with a mixture of 3.4 ml of THF, 3.4 ml of water, and 10.2 ml of acetic acid for 7 h at room temperature. The solution was diluted with ether, washed successively with water (four times), saturated $NaHCO_3$ and brine solutions, dried over $MgSO_4$, and concentrated *in vacuo*. Chromatography (3:1 hexane, ethyl acetate) of the

residue gave 467 mg (99%) of **11**: IR 1730 (s) and 1030 (s) cm^{-1}; NMR δ=4.97 (1H, tm, J=6.9 Hz), 4.56 (1H, m, $W_{1/2}$=21.3 Hz), 3.67 (2H, m), 1.93 (3H, s), 1.65 (3H, bs), and 1.59 (3H, bs).

Preparation of endo-*7-(2-Oxoethyl)*-exo-*7-(4-methyl-3-pentenyl)bicyclo[4.1.0]hept-3-yl Acetate (12).* To a solution of 3.20 g (12.4 mmol) of Collins reagent in 40 ml of dry CH_2Cl_2 was added a solution of 578.2 mg (2.06 mmol) of the hydroxy acetate in 24 ml of CH_2Cl_2. After 6 min stirring at room temperature, the solution was decanted, and the black residue was washed with several portions of ether. The organic layers were combined, washed successively with 5% aqueous NaOH, 5% HCl, saturated $NaHCO_3$ and brine solution, dried over $MgSO_4$, and evaporated. Column chromatography (3:1 hexane, ethyl acetate) of the residue (553.1 mg) gave 529.7 mg (92%) of the unstable aldehyde, **12**: IR 2710 (w), 1730 (s), and 1245 (s) cm^{-1}; NMR δ=9.70 (1H, t, J=2.3 Hz), 4.97 (1H, tm, J=6.9 Hz), 4.58 (1H, m, $W_{1/2}$=19.5 Hz), 2.29 (2H, d, J=2.3 Hz), 1.91 (3H, s), 1.63 (3H, bs), and 1.56 (3H, s); MS, m/z (rel intensity) 218 (M^+−60, 98), 200 (74), 131 (74), and 82 (100).

Decarbonylation of 12. Preparation of endo-*7-Methyl-exo-7-(4-methyl-3-pentenyl)bicyclo[4.1.0]hept-3-yl Acetate (13).* A flask containing of a mixture of 155.3 mg (0.56 mmol) of **12**, 514.3 mg (0.56 mmol) of Wilkinson's complex and 2 ml of benzonitrile, prepared under argon, was immersed in a preheated oil bath at 145 °C for 8 min with stirring. The bulk of benzonitrile was removed by Kugelrohr distillation (100 °C/3 Torr), and the residue was rinsed with ethanol, filtered, and washed with ethanol. After evaporation of the solvent, chromatography (10:1 hexane, ethyl acetate) of the residue (343.3 mg) gave 117.3 mg (84%) of **13**: bp 55—60 °C/0.5 Torr (1 Torr=133.322 Pa); IR 1730 (s) and 1250 (s) cm^{-1}; NMR δ=4.98 (1H, tm, J=6.9 Hz), 4.52 (1H, m, $W_{1/2}$=21 Hz), 1.93 (3H, s), 1.65 (3H, s), 1.58 (3H, s), and 1.00 (3H, s); MS, m/z (rel intensity) 190 (M^+−60, 100), 108 (66), and 105 (51). Found: C, 76.95; H, 10.46%. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47%.

Preparation of endo-*7-Methyl*-exo-*7-(4-methyl-3-pentenyl)bicyclo[4.1.0]heptan-3-one (3).* To a suspension of 50 mg (1.32 mmol) of $LiAlH_4$ in 2 ml of dry ether was added a solution of 208.6 mg (0.83 mmol) of **13** in 10 ml of ether at 0 °C. After 20 min stirring, to the reaction mixture were added successively 0.05 ml of water, 0.05 ml of 15% aqueous NaOH, and 0.15 ml of water. After stirring until a granular precipitate was formed, $MgSO_4$ was added to the mixture and filtered. Concentration of the filtrate gave 176.3 mg of an oil. Chromatography (5:1 hexane, ethyl acetate) of the oil gave 164.7 mg (95%) of the alcohol: IR 3620 (w), 3330 (m), and 1055 (s) cm^{-1}; NMR δ=4.98 (1H, tm, J=6.9 Hz), 3.43 (1H, m, $W_{1/2}$=22.8 Hz), 1.65 (3H, bs), 1.59 (3H, bs), 1.53 (1H, s), and 0.98 (3H, s).

The alcohol (164.7 mg, 0.79 mmol) was treated with 1.14 g (4.75 mmol) of Collins reagents in 10 ml of dry CH_2Cl_2 at room temperature for 5 min. A workup similar to that employed for the synthesis of **12** gave 165.4 mg of the crude product. Chromatography on silica gel (10:1 hexane, ethyl acetate) gave 143.2 mg (96%) of pure **3**: IR 1710 (s) cm^{-1}; NMR δ=4.95 (1H, tm, J=6.9 Hz), 1.62 (3H, bs), 1.56 (3H, bs), and 0.88 (3H, s); MS, m/z (rel intensity) 206 (M^+, 11) and 82 (100). Found: C, 81.55; H, 10.89%. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75%.

*Preparation of 3,*endo-*7-Dimethyl*-exo-*7-(4-methyl-3-pentenyl)bicyclo[4.1.0]hept-3-ene (1a).* To a solution of 144.7 mg (0.70 mmol) of **3** in 1.5 ml of ether was added dropwise a methyllithium solution, prepared from 500 mg of methyl iodide (3.53 mmol) and 70 mg (10.1 mmol) of lithium in 3 ml of ether at 0 °C by 10 min of sonication,[10] at −78 °C. After 1 h stirring followed by addition of methanol, the mixture was diluted with ether and washed with saturated brine. The etherial solution was dried over $MgSO_4$, and concentrated. Chromatography (15:1 hexane, ethyl acetate) of the residue gave 113.2 mg (73%) of a mixture of the alcohols and 32.5 mg (22%) of **3**.

Three drops of $POCl_3$ were added to a solution of 31.0 mg (0.14 mmol) of the mixture of the alcohols and a small amount of DMAP in 2 ml of pyridine at 0 °C. After 1.5 h stirring at 0 °C, the mixture was diluted with pentane, washed successively with 5% HCl, saturated $NaHCO_3$ and NaCl solutions, and then dried over Na_2SO_4. Concentration of the solution followed by purification using a silica cartridge (pentane) gave 23.1 mg of a colorless oil. The product was shown by analytical VPC and NMR to consist of 63% **1a**, 31% **2**, and 6% **14**. Preparative VPC (10% FFAP, 150 °C) afforded **1a**: IR 2980 (s), 2920 (s), 2830 (s), 1450 (m), and 1380 (m) cm^{-1}; MS, m/z (rel intensity) 204 (M^+, 14), 161 (16), 119 (70), and 93 (100). Found: m/z 204.18590. Calcd for $C_{15}H_{24}$: M, 204.18776.

Preparation of endo-*7-Methyl-3-methylene*-exo-*7-(4-methyl-3-pentenyl)bicyclo[4.1.0]heptane (14).* Methylenetriphenylphosphorane was generated by a typical method[11] from 760 mg (2.13 mmol) of methyltriphenylphosphonium bromide in DMSO. The ylide solution was added to a solution of 76 mg (0.37 mmol) of **3** in 2 ml of DMSO at 35 °C. After 3 h standing at room temperature, the mixture was chilled by ice-water, diluted with water, and extracted with three potions of pentane. The extracts were combined washed with two portions of water and with saturated brine, and then dried over Na_2SO_4. Concentration of the solution followed by purification using a silica cartridge (pentane) gave 68.3 mg (90%) of colorless oil. **14**: IR 3085 (m), 1654 (m), and 888 (s) cm^{-1}; NMR ($CDCl_3$) δ=5.05 (1H, tm, J=6.9 Hz), 4.59 (2H, b, $W_{1/2}$=3.5 Hz), 1.68 (3H, bs), 1.62 (3H, bs), and 0.92 (3H, s); MS, m/z (rel intensity) 204 (M^+, 28), 189 (35), 161 (100), and 122 (86). Found: m/z 204.18822. Calcd for $C_{15}H_{24}$: M, 204.18776.

Photochemical Transformation of 15 into Methyl exo-*7-Methylbicyclo[4.1.0]hept-2-ene*-endo-*7-acetate (16).* A solution of 1.14 g (7.69 mmol) of **15** in 750 ml of methanol was irradiated by a 300 W Hg-lamp for 1.5 h. Evaporation of the solvent gave 1.24 g of a yellow oil. Column chromatography of the crude oil (10:1 hexane, ethyl acetate) gave 1.11 g (80%) of pure **16**: IR 1735 (s) cm^{-1}; NMR δ=5.80 (1H, dm, J=10.2 Hz), 5.60 (1H, dm, J=10.2 Hz), 3.60 (3H, s), 2.20 (2H, s), 2.2—1.4 (4H, m), 1.13 (3H, s), and 1.04 (2H, m); MS, m/z (rel intensity) 180 (M^+, 13), 106 (100), and 91 (94). Found: C, 73.40; H, 8.97%. Calcd for $C_{11}H_{16}O_2$: C, 73.30; 8.95%.

Preparation of exo-*7-Methylbicyclo[4.1.0]hept-2-ene*-endo-*7-propanenitrile (17).* Ester **16** (1.641 g, 9.88 mmol) was reduced by lithium aluminium hydride (570 mg, 15.0 mmol) in ether (120 ml) at 0 °C. A similar workup to that employed for the reduction of **13** gave the corresponding alcohol (1.677 g). To a solution of the crude alcohol in pyridine (10 ml) was added a solution of tosyl chloride (2.75 g,

14.4 mmol) in pyridine (3 ml) at 0 °C. After 2 h stirring at 0 °C, the mixture was diluted with water (50 ml), and extracted with three portions of ether. The combined extracts were washed successively with 5% HCl, saturated $NaHCO_3$ and NaCl solutions, dried over $MgSO_4$, and then concentrated. To a solution of the tosylate (2.784 g) in DMSO (20 ml) was added sodium cyanide (730 mg, 14.9 mmol), and the mixture was heated at 90 °C for 2 h under a nitrogen atmosphere. After dilution with water, the solution was extracted with three portions of CH_2Cl_2. The extracts were combined, washed with three portions of water, dried over $MgSO_4$, and concentrated *in vacuo*. Chromatography (20:1 hexane, ethyl acetate) of the residue gave pure **17** (1.327 g, 84%). **17**: bp 75 °C/15 Torr; IR 2260 (w) and 1455 (s) cm^{-1}; NMR δ=5.82 (1H, dm, J=10.5 Hz), 5.65 (1H, dm, J=10.5 Hz), 2.27 (2H, m), 1.64 (2H, m), 1.11 (3H, s), and 1.06 (3H, s); MS, m/z (rel intensity) 161 (M^+, 13), 119 (100), 107 (37), and 79 (30). Found: C, 82.24; H, 9.60; N, 8.84%. Calcd for $C_{11}H_{15}N$: C, 81.94; H, 9.38; N, 8.69%.

Preparation of exo-*7-Methylbicyclo[4.1.0]hept-2-ene*-endo-*7-propanal (18).* To a solution of 914.6 mg (5.67 mmol) of **17** in 57 ml of toluene was added 3.9 ml of a solution of DIBAH in hexane (1.76 M, 6.86 mmol (1 M=1 mol dm^{-3})) at 0 °C under an argon atmosphere. After 2 h stirring at room temperature, the mixture was cooled by ice-water. Careful addition of 50 ml of saturated aqueous NH_4Cl followed by stirring at room temperature for 30 min gave a suspension, which was filtered through a sintered-glass disk and washed with several portions of ether. The filtrates were combined, washed successively with water, saturated $NaHCO_3$ and NaCl solutions, dried over Na_2SO_4, and concentrated *in vacuo*. Column chromatography (15:1 hexane, ethyl acetate) of the residue (937.0 mg) gave 790.6 mg (85%) of **18**: IR 2815 (m) and 1725 (s) cm^{-1}; NMR δ=9.62 (1H, t, J=1.5 Hz), 5.73 (1H, dm, J=10.1 Hz), 5.62 (1H, dm, J=10.2 Hz), 2.37 (2H, m), 1.57 (2H, m), and 1.05 (3H, s). The 2,4-DNP derivative of **18**: mp 119.5—121.0 °C. Found: C, 59.44; H, 5.92; N, 16.03%. Calcd for $C_{17}H_{20}N_4O_4$: C, 59.29; H, 5.85; N, 16.27%.

Preparation of exo-*7-Methyl*-endo-*7-[3-(t-butyldimethylsiloxy)propyl]bicyclo[4.1.0]hept-2-ene (19).* To a suspension of 240 mg (6.32 mmol) of $LiAlH_4$ in 30 ml of ether was added a solution of 1.03 g (6.25 mmol) of **18** in 20 ml of ether at 0 °C. After stirring for 30 min, a similar workup to that employed for the reduction of **13** gave the corresponding alcohol. To a solution of the alcohol, 0.96 ml (6.88 mmol) of triethylamine, and a small amount of DMAP in 30 ml of dry CH_2Cl_2 was added a solution of 1.13 g (7.50 mmol) of *t*-butyldimethylchlorosilane in 30 ml of dry CH_2Cl_2 under argon. After standing for 17 h at room temperature, the solution was washed with saturated NH_4Cl solution, dried over $MgSO_4$, and evaporated. Chromatography (15:1 hexane, ethyl acetate) of the residue (1.78 g) gave 1.44 g (82%) of **19**: IR 1100 (s) and 840 (m) cm^{-1}; NMR δ=5.81 (1H, dm, J=10.5 Hz), 5.62 (1H, dm, J=10.5 Hz), 3.57 (2H, t, J=6.0 Hz), 1.10 (3H, s), 0.93 (9H, s), and 0.05 (6H, s); MS, m/z (rel intensity) 263 (16), 223 (100), and 147 (69). Found: C, 72.53; H, 11.31%. Calcd for $C_{17}H_{32}OSi$: C, 72.79; H, 11.50%.

Preparation of 2,3-Epoxy-exo-*7-methyl*-endo-*7-[3-(t-butyldimethylsiloxy)propyl]bicyclo[4.1.0]heptane (20).* To a mixture of a solution of 564.8 mg (2.01 mmol) of **19** in 9 ml of CH_2Cl_2 and 339.8 mg (4.04 mmol) of $NaHCO_3$ was added a solution of 415.9 mg (2.40 mmol) of *m*-chloroperoxybenzoic acid in 9 ml of CH_2Cl_2 at 0 °C under an argon atmosphere. After 2 h stirring at 0 °C, the mixture was diluted with water, and extracted with ether. The etherial solution was washed successively with two portions of saturated aqueous $NaHCO_3$, water, and saturated brine, dried over $MgSO_4$, and then concentrated to give 667.3 mg of an oil. An analytical sample of the epoxide (**20**) was purified by column chromatography (10:1 hexane, ethyl acetate). **20**: IR 1265 (m) and 1100 (s) cm^{-1}; NMR δ=3.80—3.61 (2H, m), 3.36—3.13 (2H, m), 1.07 (3H, s), 0.93 (9H, s), and 0.08 (6H, s); MS, m/z (rel intensity) 296 (M^+, 3), 130 (87), and 104 (100).

Preparation of exo-*7-Methyl*-endo-*7-[3-(t-butyldimethylsiloxy)propyl]bicyclo[4.1.0]hept-3-yl Benzoate (22).* A 1.76 M solution of DIBAH in hexane (2.46 ml) was added to a solution of 667.3 mg of the crude epoxide (**20**) in 20 ml of toluene at 0 °C under an argon atmosphere. After 1.5 h stirring at room temperature, the mixture was cooled by ice-water. After addition of 20 ml of saturated aqueous NH_4Cl, the mixture was stirred for 30 min at room temperature. A similar workup to that employed for the synthesis of **18** afforded 661.5 mg of a colorless oil. An analytical sample of the alcohol (**21**) was purified by column chromatography (15:1 hexane, ethyl acetate). **21**: IR 3620 (w), 3450 (w), 1110 (s), and 1095 (s) cm^{-1}; NMR δ=3.68 (1H, m), 3.63 (2H, t, J=6.0 Hz), 1.01 (3H, s), 0.94 (9H, s), 0.72 (2H, m), and 0.08 (6H, s).

Benzoic anhydride (1.20 g, 5.30 mmol) was added to a solution of 661.5 mg of the crude alcohol and a small amount of DMAP in 5 ml of triethylamine under argon. After standing for 24 h at room temperature, the solution was diluted with ether. Aqueous workup followed by chromatography (25:1 hexane, ethyl acetate) gave 573.4 mg (71%) of **22**: IR 1720 (s) and 1115 (s) cm^{-1}; NMR δ=8.5—7.83 (2H, m), 7.55—7.16 (2H, m), 4.91 (1H, m, $W_{1/2}$=13 Hz), 3.61 (2H, t, J=6.0 Hz), 1.00 (3H, s), 0.89 (9H, s), and 0.04 (6H, s). Found: C, 71.83; H, 9.51%. Calcd for $C_{24}H_{38}O_3Si$: C, 71.59; H, 9.51%.

Preparation of exo-*7-Methyl*-endo-*7-(4-methyl-3-pentenyl)bicyclo[4.1.0]heptan-3-yl Benzoate (25).* In order to remove the silyl group, 176.3 mg (0.438 mmol) of **22** was treated with a mixture of 0.88 ml of THF, 0.88 ml of water, and 2.64 ml of acetic acid[9] for 17.5 h at room temperature. A similar workup to that employed for the synthesis of **11** gave 185.4 mg of an oil. Purification by chromatography (3:1 hexane, ethyl acetate) gave 113.8 mg (90%) of the hydroxy benzoate (**23**): IR 3630 (w), 3540 (w), 1715 (s), and 1280 (s) cm^{-1}; NMR δ=8.05—7.83 (2H, m), 7.54—7.18 (3H, m), 4.93 (1H, m, $W_{1/2}$=12 Hz), 3.62 (2H, t, J=6.0 Hz), and 1.00 (3H, bs).

To a solution of 1.75 g (6.8 mmol) of Collins reagent in 20 ml of dry CH_2Cl_2 was added a solution of 324.6 mg (1.13 mmol) of **23** in 15 ml of CH_2Cl_2. The resulting mixture was stirred for 6 min at room temperature. A similar workup to that employed for the synthesis of **12** gave 272.8 mg of an oil. An analytical sample of the aldehyde (**24**) was purified by column chromatography (5:1 hexane, ethyl acetate). **24**: IR 2720 (w), 1720 (s), and 1280 (s) cm^{-1}; NMR δ=9.73 (1H, t, J=1.5 Hz), 8.02—7.82 (2H, m), 7.55—7.18 (3H, m), 4.92 (1H, m, $W_{1/2}$=13.8 Hz), 2.51 (2H, m), and 1.00 (3H, s); MS, m/z (rel intensity) 286 (M^+, 3) and 146 (100).

Isopropylidenetriphenylphosphorane[12] was generated from 1.46 g (3.38 mmol) of isopropyltriphenylphosphonium iodide and 2.1 ml of a 1.5 M solution of *n*-BuLi (hexane) in 35 ml of ether at 0 °C for 1 h under argon. To the ylide solution was added a solution of 272.8 mg of freshly pre-

pared **24** in 2 ml of ether at −30 °C, and the mixture was stirred for 15 min. The solution was diluted with wet ether, and well stirred at room temperature. After removal of the precipitate by filtration, the filtrates were combined, washed with water and saturated NaCl solution, and then dried over $MgSO_4$. Concentration of the solution followed by chromatography gave 239.2 mg (68%) of **25**: IR 1720 (s) and 715 (s) cm^{-1}; NMR δ=8.10—7.82 (2H, m), 7.55—7.12 (3H, m), 5.25—4.77 (2H, m), 1.70 (3H, bs), 1.65 (3H, bs), and 1.03 (3H, s). Found: C, 80.52; H, 9.07%. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03%.

Preparation of exo-*7-Methyl*-endo-*7-(4-methyl-3-pentenyl)bicyclo[4.1.0]heptan-3-one (**26**).* To a suspension of 20.0 mg (0.527 mmol) of $LiAlH_4$ in 2 ml of dry ether was added a solution of 80.0 mg (0.256 mmol) of 25 in 2.5 ml of ether at 0 °C. After 20 min stirring, a similar workup to that employed for the reduction of **13** gave 76.6 mg of an oil. Chromatography (5:1 hexane, ethyl acetate) of the oil gave 50.8 mg (95%) of the alcohol: IR 3625 (w), 3400 (w), and 1050 (m) cm^{-1}; NMR δ=5.05 (1H, tm, J=6.9 Hz), 3.53 (1H, m, $W_{1/2}$=13.5 Hz), 1.68 (3H, bs), 1.62 (3H, bs), and 0.98 (3H, s).

The alcohol (50.8 mg, 0.243 mmol) was treated with 380 mg (1.46 mmol) of Collins reagents in 3.6 ml of dry CH_2Cl_2 at room temperature for 5 min. A similar workup to that employed for the synthesis of **12** gave 42.3 mg of the crude product. Chromatography on silica gel (20:1 hexane, ethyl acetate) gave 37.4 mg (71%) of pure **26**: IR 1710 (s) cm^{-1}; NMR δ=5.05 (1H, tm, J=6.9 Hz), 1.67 (3H, bs), 1.61 (3H, bs), and 1.04 (3H, s); MS, m/z (rel intensity) 206 (M^+, 100) and 82 (84). Found: C, 81.20; H, 10.45%. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75%.

*Preparation of (±)-Isosesquicarene,3,*exo-*7-Dimethyl*-endo-*7-(4-methyl-3-pentenyl)bicyclo[4.1.0]hept-3-ene (**1b**).* To a solution of 140.0 mg (0.68 mmol) of **26** in 5 ml of ether was added dropwise a methyllithium solution (2.5 equiv) at −95 °C, and the mixture was allowed to warm to room temperature slowly. After addition of methanol–water at 0 °C, the mixture was diluted with ether, washed with saturated brine, dried over $MgSO_4$, and concentrated. Chromatography (20:1 hexane, ethyl acetate) of the residue gave 111.2 mg (74%) of a mixture of the alcohols.

Phosphoryl chloride (0.07 ml) was added to a solution of 130 mg (0.58 mmol) of a mixture of the alcohols and a small amount of DMAP in 5.8 ml of pyridine at 0 °C. After stirring 1 h at 0 °C and 30 min at room temperature, the mixture was diluted with pentane, washed successively with 5% HCl, saturated $NaHCO_3$ and NaCl solutions, dried over $MgSO_4$, and concentrated. Purification using a silica cartridge (pentane) gave 85.7 mg (74%) of a colorless oil. The product was shown by analytical VPC and NMR to consist of 63% **1b** and 28 and 9% of the isomers. Preparative VPC (10% FFAP, 150 °C) afforded pure **1b**: MS, m/z (rel intensity) 204 (M^+, 12), 133 (14), 119 (78), and 93 (100). Found: m/z 204.18840. Calcd for $C_{15}H_{24}$: M, 204.18776.

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References

1) A portion of this work has been published as a preliminary communication: T. Uyehara, J. Yamada, T. Kato, and F. Bohlmann, *Tetrahedron Lett.*, **24**, 4445 (1983). Part I in this series is Ref. 2.

2) T. Uyehara, J. Yamada, K. Ogata, and T. Kato, *Bull. Chem. Soc. Jpn.*, **58**, 211 (1985).

3) F. Bohlmann, U. Fritz, H. Robinson, and R. M. King, *Phytochemistry*, **18**, 1749 (1979).

4) Y. Ohta and Y. Hirose, *Tetrahedron Lett.*, **1968**, 1251.

5) See, for example, H. Prinzbach, H.-P. Bohm, S. Kagabu, V. Wessely, and H. V. Rivera, *Tetrahedron Lett.*, **1978**, 1243.

6) K. Ohno and J. Tsuji, *J. Am. Chem. Soc.*, **90**, 99 (1968).

7) J. C. Collins and W. W. Hess, *Org. Synth.*, **52**, 5 (1972).

8) J. A. Osborn and G. Wilkinson, *Inorg. Synth.*, **10**, 67 (1967).

9) E. J. Corey and A. V. Venkateswarlu, *J. Am. Chem. Soc.*, **84**, 6190 (1972).

10) J. L. Luche and J. C. Damiano, *J. Am. Chem. Soc.*, **102**, 7926 (1980).

11) R. S. Monson, "Advanced Organic Synthesis, METHODS and TECHNIQUES," Academic Press, New York (1971), p. 106.

12) G. Wittig and D. Wittenberg, *Justus Liebigs Ann. Chem.*, **606**, 1 (1957).