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Studies on the Terpenoids and Related Alicyclic Compounds. XXXV.[1] Studies Directed toward a Total Synthesis of Ingenol Esters: Synthesis of the C/D-Ring Moiety of Ingenol Esters from (+)-3-Carene *via* Tin(IV) Chloride-Promoted Intramolecular Directed Aldol Reaction

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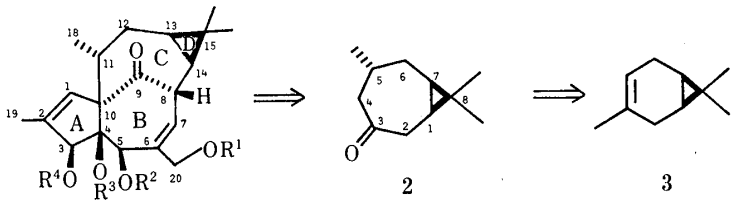
(+)-(1*S*,5*R*,7*R*)-5,8,8-Trimethylbicyclo[5.1.0]octan-3-one (**2**), which comprises the C/D-ring moiety of ingenol esters (**1**) and is an important chiral synthon for a total synthesis of ingenol esters from easily available (+)-3-carene (**3**), was synthesized. Intramolecular alkylation of **5b** with a strong base under kinetic control gave only the undesired five-membered ketone (**6**). The intramolecular directed aldol reaction of a mixture of the silyl enol ethers, (**9**) and (**10**), easily derived from (+)-**3** in good overall yield, was achieved in the presence of tin(IV) chloride to afford **11**, **12**, and **13** in 66, 9, and 6% yields, respectively. β-Elimination of the methoxy group of **11** gave an enone (**14**), which was methylated with lithium dimethylcuprate to afford the title compound (**2**) in good yield. The configuration of the C-5 methyl group of **2** was deduced from the fact that catalytic hydrogenation of the enone (**16**), derived from **14** *via* **15**, gave **2**. Finally the stereochemistry of **2** was unambiguously determined by the chemical correlation of **18a**, derived from **15**, with **24b**, derived from the known compound **19**.

Keywords——diterpenoid; carene; ingenol ester; directed aldol reaction; ozonolysis; chiral synthon

The plants belonging to *Euphorbiaceae* have many kinds of biological activity[2] such as cytotoxic, irritant, cocarcinogenic, antileukemic, and piscicidal activities. Ingenol esters (**1**)[3] are one of the principal mediators of the biological activity of the plants. The basic carbon skeleton of this tetracyclic diterpenoid consists of a cyclopentene A-ring, *cis*-fused to a cycloheptene B-ring, with a *trans*-fused cycloheptanone C-ring and attached cyclopropane D-ring. Oxygen functional groups (hydroxy groups) are located at carbons 3, 4, 5, 20 and in most cases they are esterified with long chain fatty acids. In connection with our interest in the synthesis of biologically active diterpenoids having a dimethylcyclopropane ring[4] we planned to attempt the total synthesis of ingenol esters *via* the key intermediate, (1*S*,5*R*,7*R*)-5,8,8-



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R^1-R^4=H, $COCH_3$, $COCH_2CH_3$, $COCH(CH_3)_2$, long-chain fatty acid, *etc.*

Chart 1

trimethylbicyclo[5.1.0]octan-3-one (**2**), from a very easily available monoterpene, (+)-3-carene (**3**). In this paper, we report a short and efficient route to (+)-**2**, the C/D-ring moiety of ingenol esters, *via* Lewis acid-promoted intramolecular directed aldol reaction[5,6] of the silyl enol ether (**9**), together with an unambiguous determination of the stereochemistry of the C-5 methyl group of **2**.

An Attempt to Synthesize the Bicyclo[5.1.0]octane System *via* Intramolecular Alkylation Reaction

In the synthesis of the C/D-ring system of ingenol esters, intramolecular alkylation of a keto-iodide (**5b**) with a strong base under kinetic control was first examined. (+)-3-Carene (**3**) was ozonolyzed to give a keto-aldehyde (**4**), which was reduced with lithium tri-*tert*-butoxyaluminumhydride to afford a keto-alcohol (**5a**) in good yield as described previously.[4]

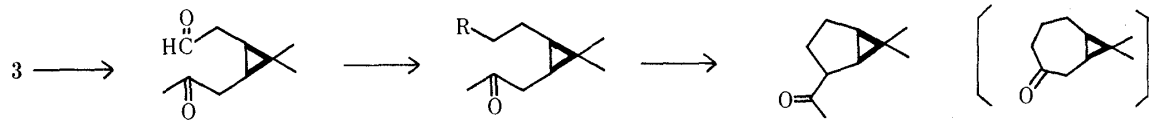

Chart 2

Treatment of **5a** with triphenylphosphite methiodide[7] in dimethylformamide (DMF) gave the desired iodide (**5b**), as an oil, in 95% yield. Intramolecular alkylation of **5b** with a strong base in tetrahydrofuran (THF) containing hexamethylphosphoric triamide (HMPA) at −78 °C gave a main product **6** and trace amounts of many by-products, among which the desired seven-membered ketone (**7**) could not be observed. In this reaction, when lithium diisopropyl amide (LDA), lithium dicyclohexylamide, or lithium hexamethyldisilazide was used, 26, 47, and 65% yields of **6** were obtained, respectively. The main product (**6**) shows acetyl methyl protons at δ 2.18 (s) in its nuclear magnetic resonance (NMR) spectrum. Even though the reaction was carried out under conditions giving kinetic control, so that the carbanion should be mainly generated on the methyl carbon, only a five-membered compound was obtained. Usually the rate of formation of a five-membered ring is much faster than that of a seven-membered ring, and the result obtained is consistent with this generalization. Therefore we tried to utilize an intramolecular directed aldol reaction.

Synthesis of (+)-(1*S*,5*R*,7*R*)-5,8,8-Trimethylbicyclo[5.1.0]octan-3-one *via* Tin(IV) Chloride-Promoted Intramolecular Directed Aldol Reaction

Lewis acid-promoted directed aldol reaction of ketones or acetals with silyl enol ethers, first reported by Mukaiyama,[5] is now one of the most reliable methods for carbon–carbon bond formation. Despite numerous examples of the intermolecular reaction, however, only four examples[6] of the intramolecular directed aldol reaction have so far been reported. The intramolecular reaction of the silyl enol ether (**9**) to form the seven-membered ketone (**11**) was therefore attempted next.

The selective acetalization of the aldehyde group of **4** was achieved by Luch's method[8] to give **8** in 85% yield. Attempts to get the pure silyl enol ether (**9**) were unsuccessful. Under the usual conditions (LDA/THF at −78 °C, then chlorotrimethylsilane), **8** gave a mixture of **9** and **10** in a ratio of 5 : 1 in 97% yield. The Lewis acid-promoted intramolecular directed aldol reaction of the mixture (**9** and **10**) was investigated using various kinds of Lewis acid ($TiCl_4$, $ZnBr_2$, $ZnCl_2$, BF_3–OEt_2, $SnCl_4$, and TMS–Tf) under various conditions. Only tin(IV) chloride worked, and acetonitrile was found to be the best solvent. In this system at −20 °C, the mixture gave the desired seven-membered ketone **11** (66% yield as a mixture at the methoxy group) and two five-membered ketones **12** (9%) and **13** (6%). The stereochemistry of

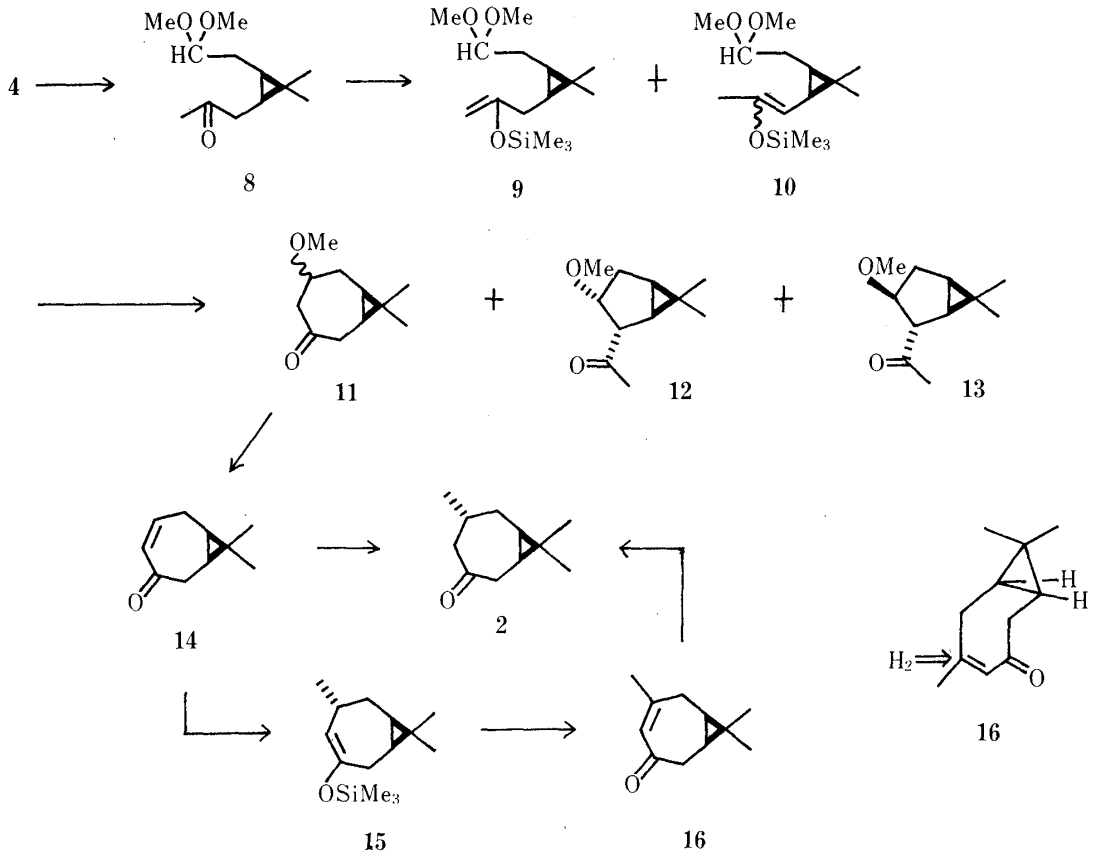

Chart 3

the acetyl and methoxy groups of **12** and **13** was tentatively assigned on the basis of the coupling constants in the NMR spectra [**12**: δ 2.60 (1H, dd, J=7.6, 1.8 Hz, 2-H), 4.23 (1H, ddd, J=9.0, 7.6, 7.6 Hz, 3-H); **13**: δ 2.82 (1H, dd, J=6.6, 2.0 Hz, 2-H), 4.00 (1H, ddd, J=6.6, 5.6, 3.3 Hz, 3-H)]. β-Elimination of the methoxy group of the mixture (**11**) was achieved by refluxing **11** in acetic acid for 2 h to give an enone (**14**), mp 58—58.5 °C, in 48% yield (88%; calculated from consumed **11**) and unchanged **11** (45%). In this reaction, base treatment (LDA, sodium hydride, or potassium *tert*-butoxide) gave a complex mixture. Treatment of the enone (**14**) with lithium dimethylcuprate followed by quenching with acetic acid[9] gave a ketone (**2**) as an oil, in 84% yield. The purity of this product was checked by gas liquid chromatography (GLC) and carbon-13- nuclear magnetic resonance (^{13}C-NMR) and no other isomer could be detected. At this stage the stereochemistry of the introduced methyl group was obscure. In this methylation, quenching with chlorotrimethylsilane[9] afforded a silyl enol ether (**15**) as an oil, in quantitative yield. Oxidation of **15** with palladium(II) acetate[10] gave an enone (**16**) as an oil, in 81% yield. This enone (**16**) was hydrogenated with rhodium on alumina in ethyl acetate to give the ketone (**2**) in quantitative yield, and again no other isomer could be detected.

In the hydrogenation, it is assumed that hydrogen was introduced from the convex face, as shown in Chart 3, to give the C-5 methyl group having *R* absolute configuration. From this result we speculated that in the cuprate reaction, as shown in Fig. 1, the conformation of the initially formed anion radical[11] (A) changed to the more stable (a relaxation of the repulsion between the underlined hydrogen and methyl group as illustrated by A in Fig. 1) conformation (B) and then methyl radical was transferred from the metal to the β-carbon atom from outside the seven-membered ring of B to give 5*R* stereochemistry. At this stage the stereochemistry of the C-5 methyl group was still speculative. The stereochemistry of the C-5 methyl group was determined unambiguously as follows.

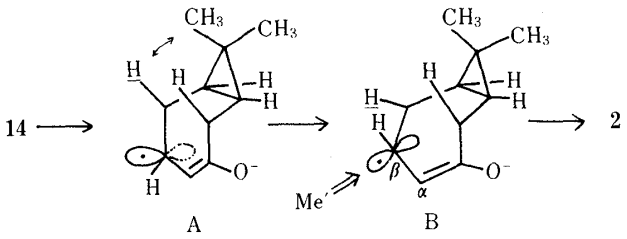

Fig. 1

Determination of the Stereochemistry of the C-5 Methyl Group of the Ketone (2)

Ozonolysis[12] of the silyl enol ether (**15**) at −78 °C in a mixture of methanol and dichloromethane followed by treatment with diazomethane gave **17a**, which was immediately reduced with sodium borohydride to afford an alcohol (**18a**) as an oil, in 33% overall yield. In this reaction, after the ozonolysis, treatment with 10% NaOH followed by diazomethane gave a mixture of **17a** and **17b** (about equal amounts). Reduction of this mixture with sodium borohydride gave a mixture of **18a** and **18b**. On the other hand, (−)-*cis*-caranone (**19**) was transformed to an aldehyde (**21a**) *via* a silyl enol ether (**20**) as described previously.[4] The aldehyde group of **21a** was protected as the dimethylacetal to give **21b** in 90% yield. The methoxycarbonyl group of **21b** was reduced with lithium aluminum hydride to give **22a**, which was treated with benzyl bromide and sodium hydride in the presence of tetrabutylammonium iodide[13] to afford **22b** in 97% overall yield. At this stage the purity of **22b** was checked by ^{13}C-NMR; no isomer could be detected. The dimethylacetal (**22b**) was hydrolyzed in aqueous THF with *p*-toluenesulfonic acid to give **22c** in 96% yield. The aldehyde (**22c**) was treated with methylenetriphenylphosphorane in THF to afford **22d** in 93% yield. Hydroboration–oxidation of **22d** with diborane followed by treatment with hydrogen peroxide cleanly afforded the desired alcohol (**23**) in 92% yield. The hydroxy group of **23** was oxidized with pyridinium dichromate[14] to carboxylic acid and this was esterified with diazomethane to give **24a** in 48% overall yield. Finally the benzyl protecting group was hydrogenolyzed with palladium on carbon to give **24b** as an oil, in 96% yield. The purity of **24b** was checked by GLC and ^{13}C-NMR, which showed that the product **24b** was pure.

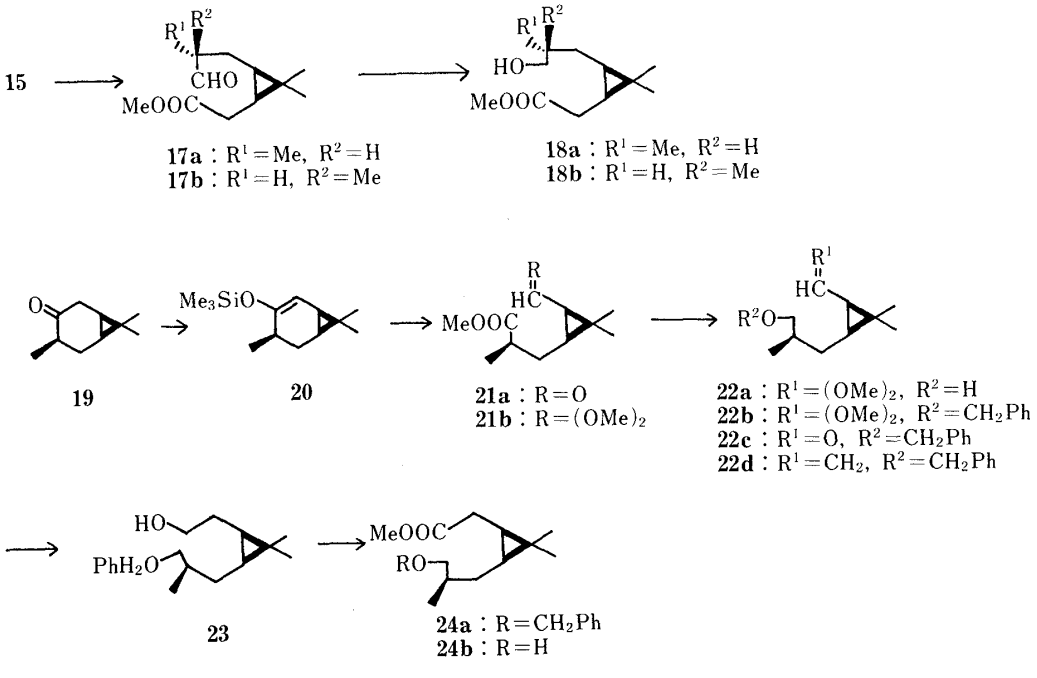

Chart 4

As the absolute configuration of the methyl group at the 2′ position of **24b** is clearly *R*, we could determine the absolute configuration of the methyl group of **18a** or **18b** by comparison of their spectral data with those of **24b**. If the introduced methyl group of **15** has the desired configuration (as shown in Chart 3) the spectral data of **24b** and **18a** should be different and those of **18b** and **24b** must be the same. The results are consistent with expectation, namely the NMR (^{1}H- and ^{13}C-) spectra of **18a** and **24b** are different and the ^{13}C-NMR spectrum of **24b** is superimposable upon that of **18b** (note that **18b** is the enantiomer of **24b**).

In conclusion, we obtained the important key chiral synthon (**2**) for a total synthesis of ingenol esters (**1**) in six steps from easily available (+)-3-carene (**3**) in 30% overall yield. A total synthesis of ingenol esters is in progress.

Experimental

All melting points and boiling points are uncorrected. A Shibata GTO-250 glass tube oven was used for bulb-to-bulb distillation and boiling points are given as the temperature of the heating bath. A JASCO DIP-SL automatic polarimeter was used for specific rotations. Infrared (IR) spectra were measured directly on an NaCl plate or in KBr disks with a Hitachi 215 spectrometer. Ultraviolet (UV) spectra were measured with a Hitachi 200 spectrometer. NMR spectra were measured in $CDCl_3$ solution with a JEOL FX-100 pulse Fourier-transform spectrometer (100 MHz) using Me_4Si as an internal standard. Electron impact mass spectra (MS) were obtained on a Hitachi M-80 double focusing spectrometer at 70 eV by direct insertion. Wako silica gel C-200 (200 mesh) containing 2% fluorescence reagent 254 was used in column chromatography.

2,2-Dimethyl-3-(2′-iodoethyl)-1-(2′-oxopropyl)-*cis*-cyclopropane (5b)——A solution of triphenylphosphite methiodide (2.71 g; 6 mmol) in 3 ml of dry DMF was added to a solution of **5a** (510 mg; 3 mmol) in 9 ml of dry DMF at room temperature with stirring and the mixture was stirred for 2 h. The reaction mixture was diluted with benzene and washed successively with 2% NaOH, sat. brine and water. The organic layer was dried, concentrated and the residue was purified by silica gel column chromatography followed by bulb-to-bulb distillation, bp 105 °C/2 mmHg, to give 798 mg (95%) of **5b** as a colorless oil. High-resolution MS for $C_{10}H_{17}OI$: Mol. Wt. 280.0324. Observed: M^+ 280.0298. IR cm^{-1}: 1720 (CO). NMR δ: 0.91, 1.10 (each 3H, s, CH_3–), 1.78 (2H, m, $ICH_2\underline{CH_2}CH$–), 2.16 (3H, s, CH_3CO–), 2.36 (2H, d, J=7 Hz, $CH_3COC\underline{H_2}$–), 3.13 (2H, t, J=7 Hz, $IC\underline{H_2}CH_2$–). MS *m/z* (% Rel. int.): 280 (M^+, 0.5), 265 (0.8), 223 (88), 153 (16), 95 (42), 43 (100).

2-Acetyl-6,6-dimethylbicyclo[3.1.0]hexane (6)——BuLi (1.5 M in hexane; 392 μl; 0.6 mmol) was added to a solution of 1,1,1,3,3,3-hexamethyldisilazane (127 μl; 0.6 mmol) and HMPA (122 μl; 0.7 mmol) in 2 ml of dry THF at 0 °C with stirring. After 10 min the solution was cooled to −78 °C and a solution of **5b** (148 mg; 0.53 mmol) in 0.5 ml of dry THF was added dropwise through a syringe. The reaction mixture was allowed to warm slowly to 0 °C and the reaction was quenched by adding sat. aq. NH_4Cl. The mixture was extracted with ether and the extract was washed with sat. brine, dried and concentrated. The product was purified by silica gel column chromatography followed by bulb-to-bulb distillation, bp 70 °C/5 mmHg, to afford 53 mg (65%) of **6** as a colorless oil. High-resolution MS for $C_{10}H_{16}O$: Mol. Wt. 152.1200. Observed: M^+ 152.1219. IR cm^{-1}: 1710 (CO). NMR δ: 0.96, 1.00 (each 3H, s, CH_3–), 1.24 (2H, m, $W/2$=6 Hz), 2.18 (3H, s, CH_3CO–), 2.75 (1H, m, $W/2$=15 Hz, $CH_3COC\underline{H}$–). MS *m/z* (% Rel. int.): 152 (M^+, 15), 137 (7), 109 (100).

In this reaction, lithium dicyclohexylamide and lithium diisopropylamide gave **6** in 47 and 26% yields, respectively.

2,2-Dimethyl-3-(2′,2′-dimethoxyethyl)-1-(2′-oxopropyl)-*cis*-cyclopropane (8)——Methyl orthoformate (8.6 ml; 70 mmol) was added to a solution of **4** (1.68 g; 10 mmol) and $CeCl_3 \cdot 7H_2O$ (4.1 g; 11 mmol) in 26 ml of MeOH with stirring at room temperature. After 30 min, the reaction was quenched by adding an excess of sat. aq. $NaHCO_3$ and the MeOH was evaporated off *in vacuo*. The residue was extracted with ether and the organic layer was washed with brine, dried and concentrated. The residue was purified by silica gel column chromatography followed by bulb-to-bulb distillation, bp 147 °C/2 mmHg, to give 1.82 g (85%) of **8** as a colorless oil. High-resolution MS for $C_{12}H_{22}O_3$: Mol. Wt. 214.1567. Observed: M^+ 214.1551. IR cm^{-1}: 1710 (CO). NMR δ: 0.91, 1.09 (each 3H, s, CH_3–), 1.50 (2H, m, $W/2$=12 Hz, $(CH_3O)_2CHC\underline{H_2}$–), 2.16 (3H, s, CH_3CO–), 2.35 (2H, d, J=7 Hz, $CH_3COC\underline{H_2}$–), 3.33, 3.34 (each 3H, s, CH_3O–), 4.31 (1H, t, J=6 Hz, $(CH_3O)_2C\underline{H}CH_2$–). MS *m/z* (% Rel. int.): 214 (M^+, 0.07), 182 (2.4), 156 (6.8), 124 (13), 75 (100).

Silyl Enol Ethers (9) and (10)——BuLi (1.5 M in hexane; 8 ml; 12 mmol) was added to a solution of diisopropylamine (1.68 ml; 12 mmol) in dry THF (16 ml) at 0 °C under N_2 with stirring. After 10 min, this solution was cooled to −78 °C and a solution of **8** (1.7 g; 8 mmol) in 3.5 ml of dry THF was added slowly through a syringe. The reaction mixture was stirred at −78 °C for 30 min and then chlorotrimethylsilane (2.03 ml; 16 mmol) was added.

This mixture was gradually allowed to warm to room temperature over a period of 3 h, then it was diluted with hexane. The hexane extract was washed with cold aq. $NaHCO_3$, dried and concentrated. The residue was distilled (bulb-to-bulb distillation), bp 106—110 °C/2.5 mmHg, to give 2.23 g (97%) of a mixture of **9** and **10** as a colorless oil. From GLC the ratio of **9** to **10** was 5 to 1. IR cm^{-1}: 840 (C–Si). NMR δ: 0.21 ($(CH_3)_3Si$), 0.93, 1.07 (CH_3–), 3.33 (CH_3O–), 4.11 (d, J=6.5 Hz, $\overset{H}{H}\!>\!=$), 4.36 (t, J=6 Hz, $(CH_3O)_2C\underline{H}CH_2$–).

Treatment of the Silyl Enol Ethers (9) and (10) with Tin(IV) Chloride——A solution of the mixture of **9** and **10** (858 mg; 3 mmol) in 7.5 ml of dry acetonitrile was added dropwise to a solution of tin(IV) chloride (351 μl; 3 mmol) in 22.5 ml of dry acetonitrile at −20 °C under N_2 with stirring. After 5 min, the reaction mixture was diluted with ether and sat. aq. $NaHCO_3$ was added. The whole was extracted with ether and the organic layer was washed with sat. brine, dried and concentrated. The products were separated by silica gel column chromatography and then repurified by bulb-to-bulb distillation.

11: A mixture of diastereomers due to the methoxy group; colorless oil, bp 105 °C/1 mmHg, 603 mg (66%). IR cm^{-1}: 1710 (CO). NMR δ: 3.33, 3.35 (s, CH_3O–), 3.64 (m, $W/2$=16 Hz, $CH_3OC\underline{H}$–).

12: (1*R*,2*S*,3*R*,5*R*)-2-Acetyl-3-methoxy-6,6-dimethylbicyclo[3.1.0]hexane; colorless oil, bp 100 °C/2 mmHg, 79 mg (9%). High-resolution MS for $C_{11}H_{18}O_2$: Mol. Wt. 182.1306. Observed: M^+ 182.1317. IR cm^{-1}: 1710 (CO). NMR δ: 1.02, 1.09 (each 3H, s, CH_3–), 2.24 (3H, s, CH_3O–), 2.60 (1H, dd, J=7.6, 1.8 Hz, $CH_3COC\underline{H}$–), 3.22 (3H, s, CH_3O–), 4.23 (1H, ddd, J=9.0, 7.6, 7.6 Hz, $CH_3OC\underline{H}$–). MS m/z (% Rel. int.): 182 (M^+, 1.6), 150 (9.2), 139 (26), 107 (100).

13: (1*R*,2*S*,3*S*,5*R*)-2-Acetyl-3-methoxy-6,6-dimethylbicyclo[3.1.0]hexane; colorless oil, bp 110 °C/2 mmHg, 52 mg (6%). IR cm^{-1}: 1710 (CO). NMR δ: 0.88, 1.01 (each 3H, s, CH_3–), 2.16 (3H, s, CH_3CO–), 2.82 (1H, dd, J=6.6, 2.0 Hz, $CH_3COC\underline{H}$–), 3.21 (3H, s, CH_3O–), 4.00 (1H, ddd, J=6.6, 5.6, 3.3 Hz, $CH_3OC\underline{H}$–). MS m/z (% Rel. int.): 182 (M^+, 1.1), 150 (11), 139 (6), 93 (100).

(+)-8,8-Dimethylbicyclo[5.1.0]oct-4-en-3-one (14)——A solution of the mixture of the seven-membered ring ketone (**11**) (858 mg; 4.7 mmol) in 30 ml of acetic acid was refluxed for 2.5 h. The acetic acid was evaporated off and the residue was dissolved with ether. This solution was washed with sat. aq. Na_2CO_3, dried and concentrated. The residue was purified by silica gel column chromatography to give 340 mg (48%) of the desired enone (**14**) and 390 mg (45.5%) of unchanged **11**. **14**: mp 58—58.5 °C (sublimation). *Anal.* Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.73; H, 9.41. IR cm^{-1}: 1660 (enone). UV λ_{max}^{EtOH} 220.5 nm (ε 9600). $[\alpha]_D$ +308° (c=3.73, $CHCl_3$). NMR δ: 0.59—0.85 (2H, m, cyclopropane-H), 1.08, 1.19 (each 3H, s, CH_3–), 5.95 (1H, ddd, J=8.5, 1.9, 1.8 Hz, 4-H), 6.77 (1H, ddd, J=8.5, 6.5, 3.0 Hz, 5-H). MS m/z (% Rel. int.): 150 (M^+, 41), 135 (18), 108 (26), 82 (100).

(+)-(1*S*,5*R*,7*R*)-5,8,8-Trimethylbicyclo[5.1.0]octan-3-one (2)——MeLi (1.47 M in ether; 544 μl; 0.8 mmol) was added dropwise to a suspension of purified CuI (76.2 mg; 0.4 mmol) in 2.5 ml of dry ether with stirring under N_2 at −55 °C. The mixture was stirred and cooled at −65 °C for 10 min and then a solution of **14** (30 mg; 0.2 mmol) in 0.6 ml of dry ether was added dropwise at that temperature. After 5 min, the reaction was quenched by adding 250 μl of acetic acid and the mixture was allowed to warm to room temperature. The mixture was neutralized with sat. aq. Na_2CO_3 and the whole was extracted with ether. The extract was washed with sat. brine, dried and concentrated. The residue was purified by silica gel column chromatography followed by bulb-to-bulb distillation, bp 117 °C/2 mmHg, to give 28 mg (84%) of **2** as a colorless oil. IR cm^{-1}: 1710 (CO). $[\alpha]_D$ +215° (c=2.92, $CHCl_3$). NMR δ: 0.76 (2H, m, cyclopropane-H), 1.00, 1.09 (each 3H, s, 8-CH_3), 1.05 (3H, d, J=7 Hz, 5-CH_3). ^{13}C-NMR δ: 15.03, 19.90, 20.08, 20.31, 22.43, 28.47, 28.77, 30.35, 39.28, 50.49, 211.83. MS m/z (% Rel. int.): 166 (M^+, 18), 151 (13), 124 (68), 109 (44), 81 (100).

Silyl Enol Ether (15)——MeLi (1.6 M in ether; 1.75 ml; 2.8 mmol) was added dropwise to a suspension of copper(I) bromide–dimethyl sulfide complex ($CuBr \cdot SMe_2$) (288 mg; 1.4 mmol) in 8 ml of dry ether with stirring under N_2 at −55 °C. The mixture was stirred and cooled at −65 °C for 10 min and then a solution of **14** (105 mg; 0.7 mmol) in 1.5 ml of dry ether was added dropwise through a syringe at that temperature. After 5 min, chlorotrimethylsilane (533 μl; 4.2 mmol) followed by triethylamine (644 μl; 4.62 mmol) were added to the reaction mixture. The cooling bath was removed and after 40 min the reaction was quenched by adding sat. aq. NH_4Cl. The whole was extracted with hexane. The extract was washed with sat. brine, dried and concentrated. The residue was distilled, bp 140 °C/3 mmHg, to give 165 mg (99%) of **15** as a colorless oil. IR cm^{-1}: 1660 (C=C), 835 (C–Si). NMR δ: 0.17 (9H, s, $(CH_3)_3Si$–), 1.01, 1.05 (each 3H, s, CH_3–), 1.10 (3H, d, J=7 Hz, $C\underline{H}_3CH$–), 4.67 (1H, br d, J=5 Hz, vinyl-H).

(1*S*,7*R*)-5,8,8-Trimethylbicyclo[5.1.0]oct-4-en-3-one (16)——A solution of **15** (127 mg; 0.53 mmol) in 1.2 ml of dry acetonitrile was added dropwise to a solution of palladium(II) acetate (144 mg; 0.64 mmol) in 3 ml of dry acetonitrile under N_2 with stirring at room temperature. After 30 min the precipitated metallic palladium was filtered off and the filtrate was diluted with ether then washed with sat. aq. $NaHCO_3$, dried and concentrated. The residue was purified by silica gel column chromatography followed by bulb-to-bulb distillation, bp 105 °C/0.8 mmHg, to give 71 mg (81%) of **16** as a colorless oil. High-resolution MS for $C_{11}H_{16}O$: Mol. Wt. 164.1200. Observed: M^+ 164.1194. IR cm^{-1}: 1660, 1650 (enone). UV λ_{max}^{EtOH} 231.5 nm. NMR δ: 0.60—0.88 (2H, m, cyclopropane-H), 1.08, 1.18 (each 3H, s, CH_3–), 2.02 (3H, d, J=0.5 Hz, 5-CH_3), 5.84 (1H, m, $W/2$=5 Hz, vinyl-H). ^{13}C-NMR δ: 15.50, 23.07, 23.95, 28.06, 28.36, 30.12, 31.53, 41.04, 129.75, 160.33, 200.72. MS m/z (% Rel. int.): 164 (M^+, 17), 149 (7), 135 (4), 82 (100).

Catalytic Hydrogenation of the Enone (16)——A suspension of **16** (16.4 mg; 0.1 mmol) and 3 mg of rhodium on alumina (5%) in 1.5 ml of ethyl acetate was stirred under an H_2 atmosphere at room temperature for 30 min. The catalyst was filtered off and the filtrate was evaporated. The product was purified by silica gel column chromatography to give 17 mg (100%) of **2** as a colorless oil. The IR, ^{1}H-NMR and ^{13}C-NMR spectral data of this product are superimposable upon those of (+)-**2** described above.

(+)-(1*S*,3*R*,2′*R*)-Methyl-2,2-dimethyl-3-(2′-methyl-3′-hydroxypropyl)-cyclopropane-*cis*-acetate (18a)——A solution of **15** (71 mg; 0.3 mmol) in a mixture of dry MeOH (3 ml) and dry CH_2Cl_2 (1 ml) was treated with ozone at −78 °C until **15** could no longer be detected by thin-layer chromatography (TLC). Dimethyl sulfide (110 μl; 1.5 mmol) was added and the mixture was allowed to warm to room temperature then stirred for another 1 h. The solvent was evaporated off and the residue was dissolved in 3 ml of ether. This solution was treated with an excess of diazomethane at room temperature. The solvent was evaporated off, the residue was dissolved in MeOH (4 ml) and 11.3 mg (0.3 mmol) of $NaBH_4$ was added. After 5 min, the excess $NaBH_4$ was destroyed by adding NH_4Cl. The solvent was evaporated off and the residue was extracted with ether. The extract was washed with water, dried and concentrated. The crude product was purified by silica gel column chromatography followed by bulb-to-bulb distillation, bp 130 °C/3 mmHg, to give 21 mg (33%) of **18a** as a colorless oil. High-resolution MS for $C_{12}H_{22}O_3$: Mol. Wt. 214.1568. Observed: M^+ 214.1575. IR cm^{-1}: 3400 (OH), 1745 (CO). $[\alpha]_D$ +2.3° (c=2.6, $CHCl_3$). NMR δ: 0.90, 1.07 (each 3H, s, CH_3–), 0.94 (3H, d, J=7 Hz, $HOCH_2(C\underline{H}_3)CH$–), 2.26 (2H, d, J=7 Hz, $CH_3OCOC\underline{H}_2$–), 3.45, 3.48 (each 1H, dd, J=16, 6 Hz, $HOC\underline{H}_2$–), 3.67 (3H, s, $C\underline{H}_3OCO$–). ^{13}C-NMR δ: 14.91, 16.67, 17.08, 22.02, 24.13, 27.71, 28.83, 29.94, 36.46, 51.55, 67.93, 174.31. MS m/z (% Rel. int.): 214 (M^+, 0.8), 196 (0.5), 184 (4), 141 (100).

In this reaction, after the ozonolysis, treatment of the product with aqueous NaOH (10%) gave a diastereomeric mixture of **17a** and **17b** (in about equal amounts). This mixture was methylated, then reduced with $NaBH_4$ to give a mixture of **18a** and **18b**.

Acetalization of 21a——A solution of $CeCl_3 \cdot 7H_2O$ (1.14 g; 3 mmol) in 7 ml of MeOH was added to a solution of **21a** (480 mg; 2.42 mmol) in 3 ml of MeOH. To the mixture was added 1.86 ml (17 mmol) of methyl orthoformate and the reaction mixture was stirred at room temperature for 30 min. The reaction was quenched by adding sat. aq. $NaHCO_3$ and the MeOH was evaporated off. The aqueous solution was extracted twice with ether. The extract was washed with sat. brine, dried and concentrated. The residue was purified by silica gel column chromatography followed by bulb-to-bulb distillation, bp 180 °C/4 mmHg, to give 531 mg (90%) of **21b** as a colorless oil. IR cm^{-1}: 1740 (CO). NMR δ: 1.03, 1.07 (each 3H, s, CH_3–), 1.16 (3H, d, J=7 Hz, $CH_3OCOCH(C\underline{H}_3)$–), 3.33 (6H, s, CH_3O–), 3.67 (3H, s, CH_3OCO–), 4.14 (1H, d, J=8 Hz, $(CH_3O)_2C\underline{H}$–). MS m/z (% Rel. int.): 213 [$(M-CH_3O]^+$, 4), 181 (3), 149 (5), 121 (13), 75 (100).

(−)-(1*R*,3*S*,2′*R*)-2,2-Dimethyl-3-(3′-benzyloxy-2′-methylpropyl)-*cis*-cyclopropane-carbaldehyde Dimethyl Acetal (22b)——$LiAlH_4$ (156 mg; 4.11 mmol) was added to a solution of **21b** (1 g; 4.11 mmol) and the reaction mixture was stirred at room temperature for 20 min. The mixture was diluted with ether and sat. aq. NH_4Cl was added. The whole was extracted with ether, washed with sat. aq. NH_4Cl, dried and concentrated to give crude **22a**. This was dissolved with 15 ml of dry THF and NaH (50% in mineral oil; 395 mg; 8.22 mmol) was added and then stirred at room temperature under N_2 for 1 h. To the mixture was added tetrabutylammonium iodide (15.2 mg; 0.04 mmol) and benzyl bromide (0.98 ml; 8.22 mmol) and the reaction mixture was stirred at room temperature under N_2 for overnight. Sat. aq. NH_4Cl was added to the mixture and the whole was extracted with ether, washed with sat. brine, dried and concentrated. The crude product was purified by silica gel column chromatography followed by bulb-to-bulb distillation, bp 95 °C/1 mmHg, to give 1.22 g (97% overall) of **22b** as a colorless oil. IR cm^{-1}: 1105, 1055 (COC). $[\alpha]_D$ −6.26° (c=7.35, $CHCl_3$). NMR δ: 0.96 (3H, d, J=7 Hz, $PhCH_2OCH_2CH(C\underline{H}_3)$–), 1.01, 1.07 (each 3H, s, CH_3–), 3.30 (6H, s, CH_3O–), 4.12 (1H, d, J=8 Hz, $(CH_3O)_2C\underline{H}$–), 4.47 (2H, s, $PhC\underline{H}_2O$–), 7.27 (5H, br s, aromatic-H). ^{13}C-NMR δ: 15.84, 17.01, 18.27, 25.49, 27.34, 28.60, 28.85, 34.26, 51.41, 52.43, 72.90, 75.87, 102.14, 127.48, 128.26, 138.83. MS m/z (% Rel. int.): 275 ([$M-CH_3O]^+$, 2), 183 (3), 91 (55), 75 (100).

(1*R*,3*S*,2′*R*)-2,2-Dimethyl-3-(3′-benzyloxy-2′-methylpropyl)-*cis*-cyclopropane-carbaldehyde (22c)——A solution of **22b** (1.1 g; 3.6 mmol) and *p*-toluenesulfonic acid (6.9 mg; 0.036 mmol) in a mixture of THF (25 ml) and water (12 ml) was stirred at room temperature for 2 h. Excess sat. aq. $NaHCO_3$ was added to the reaction mixture and the THF was evaporated off. The residue was extracted with ether, and the extract was washed with sat. brine, dried and concentrated. The residue was purified by silica gel column chromatography followed by bulb-to-bulb distillation, bp 140 °C/1.5 mmHg, to give 897 mg (96%) of **22c** as a colorless oil. IR cm^{-1}: 1695 (CO). NMR δ: 0.98 (3H, d, J=7 Hz, $PhCH_2OCH_2CH(C\underline{H}_3)$–), 1.18, 1.32 (each 3H, s, CH_3–), 3.32 (2H, d, J=6 Hz, $PhCH_2OC\underline{H}_2CH(CH_3)$–), 4.46 (2H, s, $PhC\underline{H}_2O$–), 7.28 (5H, br s, aromatic-H), 9.36 (1H, d, J=6.5 Hz, aldehyde-H). MS m/z (% Rel. int.): 260 (M^+, 1), 169 (4), 91 (100), 85 (93).

Treatment of 22c with Methylenetriphenylphosphorane——BuLi (1.5 M in hexane; 1.42 ml; 2.13 mmol) was added dropwise to a stirred suspension of methyltriphenylphosphonium iodide (930 mg; 2.3 mmol) in 15 ml of dry THF at 0 °C under N_2. After 30 min, a solution of **22c** (221 mg; 0.85 mmol) in 2 ml of dry THF was added the above yellow Wittig reagent at 0 °C and the mixture was stirred for 15 min. The reaction mixture was diluted with ether, sat. aq. NH_4Cl was added and the whole was extracted with ether. The organic layer was washed with sat. brine, dried and concentrated. The residue was purified by silica gel column chromatography followed by bulb-to-bulb distillation, bp

110 °C/1 mmHg, to give 203 mg (93%) of **22d** as a colorless oil. IR cm^{-1}: 1640 (C=C). NMR δ: 0.95 (3H, d, J= 7 Hz, $PhCH_2OCH_2CH(C\underline{H}_3)$–), 0.99, 1.07 (each 3H, s, CH_3–), 3.27, 3.31 (each 1H, dd, J=15, 6 Hz, $PhCH_2OC\underline{H}_2CH(CH_3)$–), 4.46 (2H, s, $PhC\underline{H}_2O$–), 4.92 (1H, dd, J=9, 3 Hz, vinyl-H), 5.07 (1H, dd, J=16, 3 Hz, vinyl-H), 5.44 (1H, ddd, J=16, 9, 9 Hz, vinyl-H), 7.27 (5H, br s, aromatic-H). MS m/z (% Rel. int.): 167 ($[M-PhCH_2]^+$, 6), 109 (23), 95 (29), 91 (100).

(1*R*,3*S*,2′*R*)-2,2-Dimethyl-3-(2′-methyl-3′-benzyloxypropyl)-1-(2′-hydroxyethyl)-*cis*-cyclopropane (23)——Diborane (1 M in THF, 4.94 ml; 4.94 mmol) was added dropwise to a solution of **22d** (200 mg; 0.78 mmol) in 4 ml of dry THF with stirring under N_2 at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, then water (1 ml), 3 N NaOH (1 ml) and 35% H_2O_2 (1 ml) was added successively and the mixture was warmed at 40 °C with stirring for 1 h. This reaction mixture was diluted with ether and the organic layer was separated. The water layer was extracted three times with ether and the combined organic layer was washed with sat. brine, dried and concentrated. The residue was purified by silica gel column chromatography followed by bulb-to-bulb distillation, bp 160 °C/0.5 mmHg, to give 197 mg (92%) of **23** as a colorless oil. High-resolution MS for $C_{18}H_{28}O_2$: Mol. Wt. 276.2087. Observed: M^+ 276.2104. IR cm^{-1}: 3350 (OH). NMR δ: 0.90, 1.03 (each 3H, s, CH_3–), 0.95 (3H, d, J=7 Hz, $PhCH_2OCH_2CH(C\underline{H}_3)$–), 3.30, 3.33 (each 1H, dd, J=12, 6 Hz, $PhCH_2OC\underline{H}_2CH(CH_3)$–), 3.63 (2H, t, J=7 Hz, $HOC\underline{H}_2CH_2$–), 4.48 (2H, s, $PhC\underline{H}_2O$–), 7.28 (5H, br s, aromatic-H). MS m/z (% Rel. int.): 276 (M^+, 1.4), 185 (4), 168 (3), 91 (100).

(1*R*,3*S*,2′*R*)-Methyl-2,2-dimethyl-3-(2′-methyl-3′-benzyloxypropyl)-cyclopropane-*cis*-acetate (24a)——Pyridinium dichromate (PDC) (3.16 g; 8.41 mmol) was added to a solution of **23** (581 mg; 2.1 mmol) in 12 ml of DMF and the mixture was stirred under N_2 at room temperature for 8 h. The reaction mixture was diluted with ether and washed with sat. brine. The ether layer was extracted three times with 5 ml each of 3 N NaOH. The alkaline layer was acidified with 10% HCl and extracted with ether. The extract was dried and concentrated. The residue was dissolved with ether and the solution was treated with excess CH_2N_2. The ether was evaporated off and the residue was purified by silica gel column chromatography followed by bulb-to-bulb distillation, bp 110 °C/1.5 mmHg, to give 307 mg (48%) of **24a** as a colorless oil. High-resolution MS for $C_{19}H_{28}O_3$: Mol. Wt. 304.2036. Observed: M^+ 304.2009. IR cm^{-1}: 1745 (CO). NMR δ: 0.89, 1.06 (each 3H, s, CH_3–), 0.95 (3H, d, J=7 Hz, $PhCH_2OCH_2CH(C\underline{H}_3)$–), 2.24 (2H, d, J=7 Hz, $CH_3OCOC\underline{H}_2$–), 3.28, 3.31 (each 1H, dd, J=12, 6 Hz, $PhCH_2OC\underline{H}_2CH(CH_3)$–), 3.65 (3H, s, CH_3OCO–), 4.48 (2H, s, $PhC\underline{H}_2O$–), 7.28 (5H, br s, aromatic-H). MS m/z (% Rel. int.): 304 (M^+, 0.8), 213 (8), 196 (4), 181 (6), 91 (100).

(+)-(1*R*,3*S*,2′*R*)-Methyl-2,2-dimethyl-3-(2′-methyl-3′-hydroxypropyl)-cyclopropane-*cis*-acetate (24b)——A suspension of **24a** (281 mg; 0.923 mmol) and 10% Pd–C (60 mg) in 7 ml of EtOH was stirred under an H_2 atmosphere for 4 h. The catalyst was filtered off and the filtrate was evaporated. The crude product was purified by bulb-to-bulb distillation, bp 140 °C/3 mmHg, to give 190 mg (96%) of **24b** as a colorless oil. High-resolution MS for $C_{12}H_{22}O_3$: Mol. Wt. 214.1567. Observed: M^+ 214.1542. IR cm^{-1}: 3400 (OH), 1745 (CO). $[\alpha]_D$ +13.8° (c=5.4, $CHCl_3$). NMR δ: 0.90, 1.07 (each 3H, s, CH_3–), 0.94 (3H, d, J=7 Hz, $HOCH_2CH(C\underline{H}_3)$–), 2.26 (2H, d, J=6 Hz, $CH_3OCOC\underline{H}_2$–), 3.47 (2H, d, J=7 Hz, $HOC\underline{H}_2CH(CH_3)$–), 3.68 (3H, s, CH_3OCO–). ^{13}C-NMR δ: 15.15, 16.67, 17.25, 21.93, 24.56, 27.68, 28.80, 29.87, 36.69, 51.65, 68.07, 174.50. MS m/z (% Rel. int.): 214 (M^+, 0.5), 196 (0.3), 184 (3.3), 141 (76), 95 (62), 81 (94), 41 (100).

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