Electrophilic Reaction on Plinol C and Syntheses of Functionalized 2-Oxabicyclo[2,2,1]heptane Derivatives

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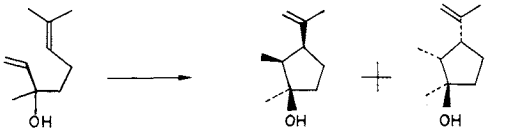
New functionalized 2-oxabicyclo[2,2,1]heptane derivatives were synthesized for their potential biological activities by way of the intramolecular ether bond formation of plinol C that was obtained from linalool by a thermal ene reaction. The mechanism for the ether-forming reactions is discussed.

During the last decade, much attention has been focused on various physiological activities of cyclopentanoids and derivatives of related fused-ring systems, especially those of prostacyclines and thromboxanes. Along these lines, it seemed appropriate to explore some other "oxabicyclo"-cyclopentanoids for their biological interest and we undertook the preparation of a series of compounds containing a 2-oxabicyclo[2,2,1]heptane ring system with suitable functional groups, based on an interest in the stereo- and regio-chemical outcome of the cyclization of plinol C and an expectation of some biological activities.[1)]

Although stereoisomers of 3,3,7-trimethyl-2-oxabicyclo[2,2,1]heptane have been reported as minor products from the oxymercuration-demercuration reaction of linalool,[1)] those products seemed to be insufficient for further conversion. We attempted to construct the desired 2-oxabicyclo[2,2,1]heptane system from plinol C (**2**),[3)] which could be prepared by the pyrolytic ene reaction of linalool (**1**). Racemic plinol C (**2**) was thus prepared according to the literature procedures with a slight modification.[4～6)]

A crucial and intriguing feature for creating a 2-oxabicyclo[2,2,1]heptane ring system from **2** was the stereo- and regio-chemistry of the electrophilic addition reaction.[7)] Various reaction conditions were attempted to see what the stereochemical outcomes were. Before carrying out the reactions, the ground state conformational energies of the conformers **A** and **B** (Fig. 1) were calculated by a molecular mechanics approach (MM2).[8)] Little energy difference (0.86 kcal/mol) and the small rotational barrier (4.2 kcal/mol) between these conformers suggested less selective reactions upon this olefin (**2**) and the probable formation of a mixture of products.

Treatment of **2** with either *N*-iodosuccinimide or *N*-bromosuccinimide in acetonitrile at room temperature gave **4a** or **4b** exclusively,[9)] the numbering system being assigned arbitrarily as shown in Scheme 2. The 2-oxabicyclo[2,2,1]heptane structures of **4a** and **4b** rather than 2-oxabicyclo[3,2,1]octane were first confirmed by the ^{13}C-NMR spectrum, *i.e.* carbons being involved in the ether linkage were observed at 80.7 ppm and 87.6 ppm in **4a**,



SCHEME 1.

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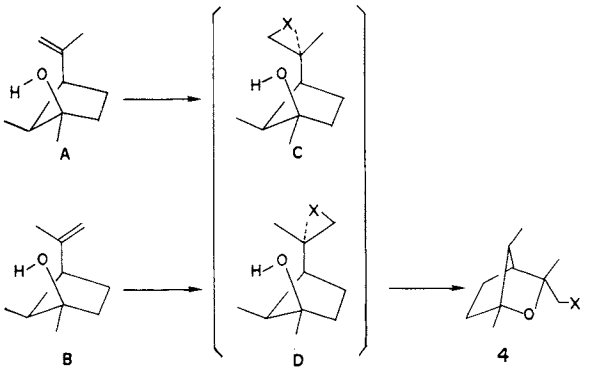
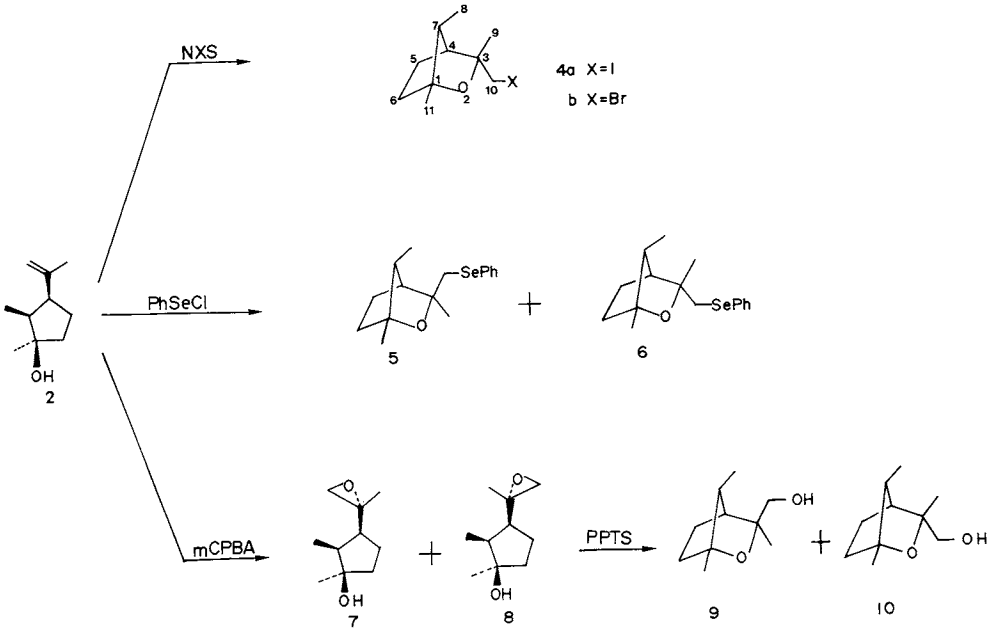


FIG. 1.



SCHEME 2.

and at 81.2 ppm and 87.0 ppm in **4b** as quaternary carbons when judged by INEPT experiments. The stereochemistry of **4a** was deduced from the ^{1}H-NMR analysis. The C-11 methyl signal was assigned to a doublet at 1.48 ppm ($J=1.22$ Hz) because the signal was long-range coupled with a proton at 3.10 ppm ($J=1.22$ and 10 Hz) of the C-10 methylene group. The remaining two methyl signals were observed at 1.14 ppm (d, $J=8$ Hz, 8-CH_3) and at 1.18 ppm (s, 9-CH_3). Next, use was made of the nuclear Overhauser effect (NOE). Upon irradiation to a methyl signal at 1.14 ppm (C-8), a NOE enhancement was observed on the signal at 1.48 ppm (C-11) using a difference spectrum method, the singlet methyl signal at 1.18 ppm (C-9) remaining unchanged. The structure of **4b** was similarly assigned.

In contrast, phenylselenoetherification of **2** initiated by phenylselenenyl chloride in CH_2Cl_2 at 0°C gave in a 71% yield an approximately 5:6 mixture of **5** and **6** as judged by their isolation.[10] The 2-oxabicyclo[2,2,1]heptane structures of the prod-

ucts were again confirmed by ^{13}C-NMR INEPT spectra, *i.e.* two quaternary oxygenated sp^3 carbon signals were observed at 82.3 ppm and 86.3 ppm in **5**, and at 81.4 ppm and 86.4 ppm in **6**. The stereochemistry at the C-3 position of **5** and **6** was deduced in a similar manner to that already discussed. Thus, the one in which irradiation of a doublet methyl signal at 1.07 ppm enhanced the methylene double doublet signal at 2.97 and 3.34 ppm was assigned to **5**, and the other in which irradiation of a doublet methyl signal at 1.14 ppm enhanced a broad methyl singlet at 1.38 ppm was assigned to **6**.

This difference of reactivity between the haloetherification and phenylselenoetherification deserves noting. The haloetherification was almost stereospecific and this seemed to have been due to the stereoelectronic effect. Thus, an inspection of the molecular models implied that the attacking hydroxyl group in the intermediate **D** could align linearly to the elongating carbon-halogen bond on the opposite side so that the displacement reaction was facilitated, whereas this was not the case in the intermediate **C**. The C-8 methyl group might have had a steric effect to some extent, but details are not clear at present. On the contrary, phenylselenoetherification may have proceeded kinetically through immediate attack of the hydroxyl group to the developing highly reactive selenenium center, giving rise to a mixture of isomers in a ratio reflecting the population of conformers **A** and **B**.

Epoxydation was also examined by a standard procedure with *m*-chloroperbenzoic acid in CH_2Cl_2 solvent. The ^{1}H-NMR spectrum of the extracted products revealed that the resulting epoxides were obtained as a 1 : 1 mixture of **7** and **8**. The product mixture was not separated into individual isomers, but was rather treated with 10 mol% of pyridinium *p*-toluenesulfonate to give, along with various by-products, a mixture of the bicyclic alcohols, which were separated by preparative TLC to give **9** and **10** in 11% and 36% yields, respectively.

The strucrures of **9** and **10** were again

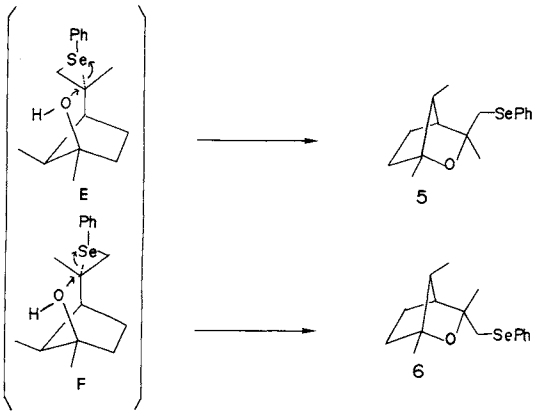


FIG. 2.

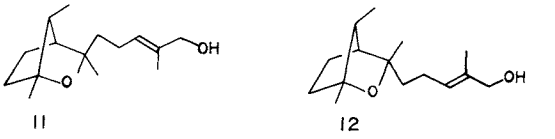
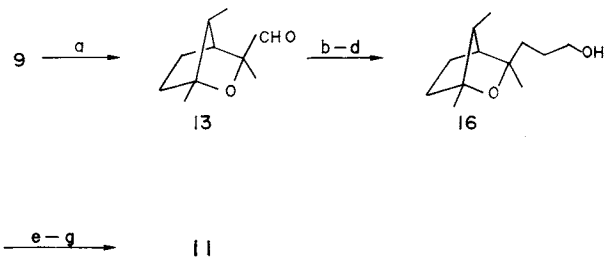


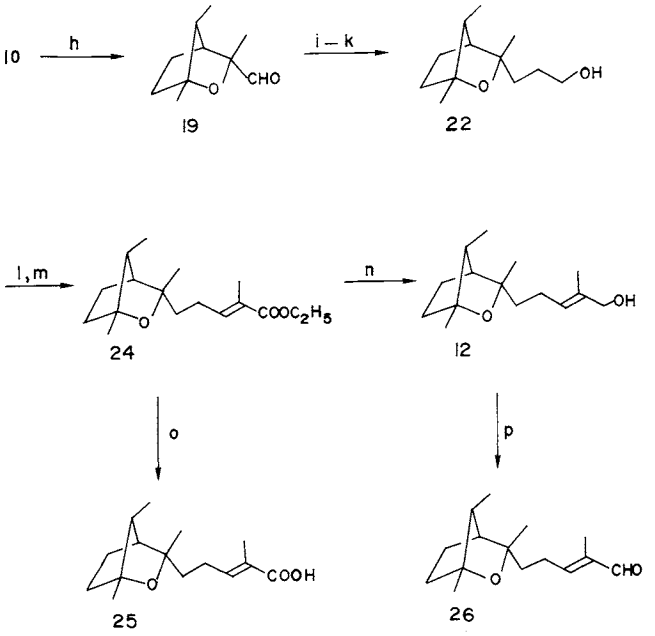
FIG. 3.

determined by making use of ^{13}C-NMR INEPT techniques and ^{1}H-NMR NOE experiments. Thus, the major isomer (more polar) was assigned to be **10**, since, in the ^{13}C-NMR spectrum, the carbons being involved in the ether linkage were observed at 81.3 ppm and 85.6 ppm as quaternary carbons, while a hydroxymethyl carbon resonated at 69.3 ppm. In addition, irradiation to a doublet signal at 1.13 ppm in the ^{1}H-NMR spectrum showed an NOE on the signal of a broad singlet at 1.30 ppm, but not on the methylene protons resonating at 3.45 ppm and 3.54 ppm. The less polar compound, which showed an AB type of double doublet at 3.22 ppm and 3.67 ppm, was assigned to **9**, because irradiation of a doublet methyl signal at 1.07 ppm induced an NOE enhancement of a signal at 3.67 ppm. The expected NOE effect on the signal at 3.22 ppm was little, suggesting a rather restricted rotation of the bond between C-3 and C-11, possibly due to hydrogen bonding. A complementary result of the enhancement of a methyl signal at 1.07 ppm by irradiating the signal at 3.67 ppm further supported this assignment.

The functionalized 2-oxabicyclo[2,2,1]hep-



SCHEME 3. a, PCC/CH_2Cl_2; b, $Ph_3P=CHCO_2C_2H_5$/benzene; c, H_2/5% Pd-C; d, $LiAlH_4$/THF; e, PCC/CH_2Cl_2; f, $Ph_3P=C(CH_3)CO_2C_2H_5$/benzene; g, DIBAH/THF.



SCHEME 4. h, PCC/CH_2Cl_2; i, $Ph_3P=CHCO_2C_2H_5$; j, H_2/10% Pd-C; k, $LiAlH_4$/THF; l, PCC/CH_2Cl_2; m, $Ph_3P=C(CH_3)CO_2C_2H_5$/benzene; n, DIBAH/THF; o, 5% aq. KOH/MeOH; p, MnO_2/acetone.

tane compounds were thus obtained, and our attention was turned to constructing various derivatives containing modified side chains, especially analogues of cyclonerotriol,[11] whose plant growth-promoting activities have been recently suggested.[1]

Although the attempted deprotonation for alkylating either **5** or **6** with lithium diisopropylamide in THF was unsuccessful, transformation of **9** and **10** into **11** and **12**, respectively, involved the rather straightforward chemistry shown in Schemes 3 and 4. Oxidation of **9** with PCC gave an aldehyde (**13**), which in turn was reacted with a stable ylide to give a *trans* α,β-unsaturated ester (**14**; olefinic protons, 5.79 d, 7.09 d, $J=16$ Hz). Hydrogenation of **14** and subsequent reduction with $LiAlH_4$ provided an elongated alcohol (**16**) without any difficulties. Further oxidation of **16** to an aldehyde (**17**) was affected again with PCC, and the resulting **17** was coupled further with a propionate unit by the Wittig reaction. Reduction of the resulting ester (**18**) was conducted with DIBAH in THF to produce **11** in a 32% yield. The stereochemistry of the side chain double bond was assigned to be an *E* configuration by comparing the ^{13}C-NMR spectrum of **11** with cyclonerotriol. Thus, olefinic carbon signals

were observed at 126.4 ppm and 134.6 ppm in **11**, those of cyclonerotriol being at 126.9 ppm and 135.8 ppm.[11] Hydroxymethyl signals were found at 68.8 ppm in both cases.

The stereoisomer **10** was transformed in practically the same way to the series of compounds shown in Scheme 4.

A carboxylic acid (**25**) and an aldehyde (**26**) were also prepared from the intermediary **24** and **12**, respectively.

These compounds so far prepared include a unique 2-oxabicyclo[2,2,1]heptane system with a sesquiterpene-like carbon skeleton and are being currently subjected to biological assays, which will be reported elsewhere.

EXPERIMENTAL

Melting points (mp) were measured on a Yanagimoto BY-1 hot stage apparatus and are uncorrected. Infrared spectra were measured on a JASCO IR-810 spectrophotometer. Proton NMR spectra were recorded on either a JEOL FX-200 (200 MHz) or a JEOL GX-400 (400 MHz) spectrometer, and all the chemical shifts are reported as δ ppm from the TMS internal standard in a $CDCl_3$ solvent. Carbon-13 NMR spectra were recorded at 50 MHz on a JEOL FX-200 spectrometer unless otherwise stated, and the chemical shifts were calculated from the central signal of the $CDCl_3$ solvent as 77.0 ppm. Electron ionization MS were taken on a Shimadzu-LKB 9020DF spectrometer at an ionization potential of 70 eV, and high-resolution MS were obtained on a Hitachi M80-B spectrometer. Silica gel column chromatography was conducted using Kieselgel 60 (Merck, 230~400 mesh).

Plinol C (**2**). In an autoclave, 26.10 g (0.15 mol) of linalool (**1**) was pressurized with nitrogen gas to an initial pressure of 90 atm. The pyrolytic reaction was carried out by heating at 250°C for 12 hr, during which the internal pressure was raised to 150 atm. After cooling, the reaction products were separated by silica gel column chromatography, using *n*-hexane–ether (3 : 1) as the eluent, to give 3.5 g of a less polar mixture of the dehydration products and 25.0 g of a plinol-containing fraction. The plinol-containing fraction (865.4 mg) was further chromatographed on silica gel using the same solvent system to give, along with 63.8 mg of recovered **1** and 228.7 mg of crystalline plinol D (**3**, mp 67°C), 436.2 mg of oily plinol C (**2**) in a 41.6% yield; IR (neat): 3580, 3500~3100, 2960, 2870, 1638, 1445, 1375 and 1090 cm^{-1}; ^{1}H-NMR (200 MHz): 0.81 (3H, d, J=8.0 Hz), 1.35 (3H, s), 1.60~2.04 (5H), 1.75 (3H, s), 2.64 (1H, q), 4.68 (1H, s) and 4.84 ppm (1H, s); ^{13}C-NMR: 9.3, 23.3, 25.3, 29.4, 39.3, 45.2, 48.7, 80.2, 110.5 and 146.5 ppm.

Treatment of **2** *with N-iodosuccinimide*. To a solution of **2** (109.8 mg, 0.71 mmol) in 4 ml of dry acetonitrile was added 242.6 mg of *N*-iodosuccinimide (1.08 mmol, 1.5 eq.). The mixture was stirred for 10 min at room temperature in a nitrogen atmosphere without exposure to the light. The excess *N*-iodosuccinimide was decomposed by adding a saturated aqueous solution of Na_2SO_3. The product was extracted with ether, and the ethereal extract was successively washed with dilute hydrochloric acid, saturated aqueous Na_2SO_3 solution and brine, and then dried over anhydrous $MgSO_4$. Filtration and stripping of the solvent under reduced pressure gave 197.4 mg (0.67 mmol, 95% yield) of labile **4a** as a yellow oil; IR ($CHCl_3$): 2960, 2925, 1720, 1380, 1155 and 910 cm^{-1}; ^{1}H-NMR (400 MHz): 1.14 (3H, d, J=8.0 Hz), 1.18 (3H, s), 1.48 (3H, d, J=1.22 Hz), 1.55~1.70 (3H, m), 1.78~1.90 (2H), 2.20 (1H, br.), 3.10 (1H, qd, J=1.22 and 10 Hz) and 3.19 (1H, br.d, J=10 Hz); ^{13}C-NMR: 12.7, 17.5, 17.8, 24.5, 25.5, 35.5, 49.0, 50.2, 80.7 and 87.6 ppm; MS: m/z 280 (M^+), 251, 153, 119, 109, 95, 81 and 43.

Treatment of **2** *with N-bromosuccinimide*. To a solution of **2** (130.0 mg, 0.84 mmol) in dry CH_3CN was added 224.0 mg of *N*-bromosuccinimide (1.25 mmol, 1.5 eq.), and the mixture was stirred for 5 min at room temperature in an N_2 atmosphere without exposure to the light. Extraction and working-up as just described afforded 202.3 mg of **4b** quantitatively as a labile oil; ^{1}H-NMR (200 MHz): 1.16 (3H, d, J=8 Hz), 1.20 (3H, s), 1.41 (3H, s), 1.50~1.92 (5H), 2.18 (1H, s) and 3.28 ppm (2H, br.); ^{13}C-NMR: 12.6, 24.5, 24.7, 35.6, 41.2, 48.5, 49.4, 81.2 and 87.0 ppm.

Phenylselenoetherification of **2**. To a solution of **2** (103.3 mg, 0.67 mmol) in 4 ml of dry CH_2Cl_2 was added 170.1 mg (1.3 eq., 0.88 mmol) of phenylselenenyl chloride at 0°C, and the mixture was stirred for 15 min at the same temperature. The reaction mixture was then diluted with water and extracted three times with ether. The combined extract was successively washed with saturated $NaHCO_3$ solution and brine, and then dried over anhydrous $MgSO_4$. Filtration and stripping of the solvent under reduced pressure yielded a crude product, which was separated by medium-pressure chromatography with a Lobar column (Merck Lichroprep Si60, 40~63 μm) using *n*-hexane–ethyl acetate (20 : 1) as the eluent to give 52.8 mg of yellowish **5** (25.1% yield); IR ($CHCl_3$): 3060, 2980, 2960, 1585, 1480, 1210 and 905 cm^{-1}; ^{1}H-NMR (200 MHz): 1.05 (3H, d, J=8.0 Hz), 1.20 (3H, s), 1.37 (3H, s), 1.50~2.06 (5H), 2.17 (1H, br.), 2.97 (1H, d, J=11.4 Hz), 3.34 (1H, d, J=11.4 Hz), 7.22 (3H, m, aromatic) and 7.50 ppm (2H, m, aromatic); ^{13}C-NMR: 12.8, 17.4, 25.2, 26.4, 35.8, 40.3, 48.6, 50.1, 82.3, 86.3, 128.6, 128.8, 129.0, 131.4, 132.2 and 132.8 ppm; EI-MS (70 eV): m/z 309 (M^+), 214, 171, 139, 95 and 43. Continued elution afforded, after removing the solvent, 69.1 mg of a yellow oil of **6** (32.9% yield); IR ($CHCl_3$): 3060, 2980, 2960, 1580, 1480, 1385 and 910 cm^{-1}; ^{1}H-NMR (200 MHz): 1.14 (3H, d, J=8 Hz),

1.20 (3H, s), 1.38 (3H, s), 1.50~2.06 (5H), 2.18 (1H, br.), 3.02 (1H, d, J=11 Hz), 3.12 (1H, d, J=11 Hz), 7.22 (3H, m) and 7.50 ppm (2H, m); ^{13}C-NMR: 12.5, 17.3, 25.0, 26.4, 35.4, 40.4, 48.4, 50.1, 81.4, 86.4, 126.6, 128.8, 129.0, 131.4, 132.2 and 132.8 ppm; EI-MS: m/z 309 (M^+), 214, 171, 139, 95 and 43.

Epoxydation and etherification. To a solution of **2** (4.536 g, 29.4 mmol) in 70 ml of dried CH_2Cl_2 was added 5.8 g of *meta*-chloroperbenzoic acid (mCPBA, 85% purity, 28.6 mmol), and the mixture was stirred at room temperature for 2 hr. An additional 1 g of mCPBA was then added and stirring was continued for a further 1 hr. The reaction mixture was diluted with ethyl acetate and treated with saturated aq. $NaHCO_3$. The aqueous layer was further extracted twice with ethyl acetate, before the organic extracts were combined, washed again with saturated aq. $NaHCO_3$ and brine, and then dried over anhyd. $MgSO_4$. Filtration and stripping of the solvent gave 5.09 g of a stereoisomeric mixture of epoxide products, the ratio of which was estimated by its ^{1}H-NMR spectrum. The intensities of the doublet methyl signals at 0.96 ppm and 1.14 ppm were almost same, and those of epoxide methylene groups (2.49 and 2.64 ppm) and (2.54 and 2.78 ppm) also appeared in equal intensities.

To a solution of the epoxide mixture (5.09 g, 29.9 mmol) in 25 ml of CH_2Cl_2 was added pyridinium *p*-toluenesulfonate (937.5 mg, 12 mol%) and the mixture was stirred at room temperature for 30 min. To the reaction mixture was added a small volume of water, and the whole was extracted with CH_2Cl_2. The organic extract was successively washed with 2 N HCl, aq. sat. $NaHCO_3$ and brine, and then dried over anhyd. $MgSO_4$. Filtration and stripping of the solvent under reduced pressure provided 4.51 g of an oily mixture of products. A portion of this oil (1.52 g) was successively purified by column chromatography on silica gel, using *n*-hexane–ethyl acetate (2:1) as the eluent and by medium-pressure liquid chromatography on a Lobar colum (Merck, Lichroprep Si60, 40~63 μm) using *n*-hexane–ethyl acetate (4:1) to give 191 mg (11.2% yield) of the colorless oil of an alcohol **9**; IR ($CHCl_3$): 3600, 3580~3300, 2970, 1460, 1380, 1240, 1030 and 905 cm^{-1}; ^{1}H-NMR (200 MHz): 1.07 (3H, d, J=7.3 Hz), 1.21 (3H, s), 1.28 (3H, s), 1.42~1.80 (5H), 1.94 (1H, br.), 3.22 (1H, d, J=10.3 Hz) and 3.67 ppm (1H, d, J=10.7 Hz); MS: m/z 170 (M^+), 152, 139, 113, 95, 76, 55 and 43. *Anal.* Found: C, 69.83; H, 10.58. Calcd. for $C_{10}H_{18}O_2$: C, 70.53; H, 10.58%.

Continued elution of the column with *n*-hexane–ethyl acetate (2:1) afforded 623 mg (36.3% yield) of the colorless oil of an alcohol (**10**); IR ($CHCl_3$): 3620, 3580~3300, 2970, 1460, 1380, 1310, 1240, 1080, 1040 and 905 cm^{-1}; ^{1}H-NMR (200 MHz): 1.13 (3H, d, J=7.4 Hz), 1.22 (3H, s), 1.30 (3H, s), 1.40~1.80 (5H), 2.05 (1H, br.), 3.45 (1H, d, J=10.3 Hz) and 3.54 ppm (1H, d, J=10.3 Hz); ^{13}C-NMR: 12.4, 17.1, 23.8, 24.2, 35.6, 48.1, 49.0, 69.3, 81.3 and 85.6 ppm; MS: m/z 170 (M^+), 152, 139, 113, 95, 76, 55 and 43. *Anal.* Found: C, 70.30; H, 10.25. Calcd. for $C_{10}H_{18}O_2$: C, 70.53; H, 10.58%.

(3S,7S*)-3-Formyl-1,3,7-trimethyl-2-oxabicyclo-[2,2,1]heptane* (**13**). To a solution of **9** (410 mg, 2.41 mmol) in 15 ml of CH_2Cl_2 was added 1.3 g of pyridinium chlorochromate (5.28 mmol) and the mixture was vigorously stirred for 40 min in an N_2 atmosphere at 0°C. The mixture was diluted with 100 ml of ether and the organic layer was passed through a column of Florisil (60~100 mesh) using ether as the eluent. The eluate was evaporated to dryness under reduced pressure to give 350 mg (2.08 mmol, 86.4% yield) of an oily aldehyde (**13**); ^{1}H-NMR (200 MHz): 0.74 (3H, d, J=6.9 Hz), 1.18 (3H, s), 1.25 (3H, s), 1.55~1.82 (5H), 2.47 (1H, br.) and 9.61 ppm (1H, s): MS: m/z 168 (M^+), 139, 128, 113, 99, 85 and 43.

(3S,7S*)-3-[2-Ethoxycarbonylethenyl]-1,3,7-trimethyl-2-oxabicyclo[2,2,1]heptane* (**14**). To a solution of **13** (350 mg, 2.08 mmol) in 4 ml of benzene was added ethoxycarbonylmethylene triphenylphosphorane (1.1 g, 3.1 mmol) and the mixture was heated under reflux for 3 hr in an N_2 atmosphere. Water was added to the mixture, which was then extracted with ethyl acetate. The extract was successively washed with 2 N HCl, aq. sat. $NaHCO_3$ solution and brine, and dried over anhyd. $MgSO_4$. Filtration and stripping of the solvent afforded a pale yellowish oil, which was purified by column chromatography on silica gel, using *n*-hexane–ethyl acetate (7:1) as the eluent, to give, after evaporating the solvent and drying, 349 mg (1.47 mmol, 70.7% yield) of **14**; IR ($CHCl_3$): 2960, 2920, 1705, 1645, 1450, 1380, 1365, 1300, 1275, 1180, 1040 and 905 cm^{-1}; ^{1}H-NMR (200 MHz): 0.88 (3H, d, J=7.5 Hz), 1.23 (3H, s), 1.27 (3H, s), 1.31 (3H, t, J=7.1 Hz), 1.48~1.95 (5H), 2.12 (1H, br.), 4.19 (2H, q, J=7.1 Hz), 5.79 (1H, d, J=16 Hz), and 7.09 ppm (1H, d, J=16 Hz); MS: m/z: 238 (M^+), 209, 180, 168, 139, 121, 107, 95, 81, 69 and 43.

(3S,7S*)-3-[2-Ethoxycarbonylethyl]-1,3,7-trimethyl-2-oxabicyclo[2,2,1]heptane* (**15**). To a solution of **14** (330 mg, 1.38 mmol) in 10 ml of ethyl acetate was added 900 mg of 5% Pd–C (Kawaken Fine Chemicals Co.) and the mixture was stirred in an H_2 atmosphere for 2 hr at room temperature. The mixture was filtered through a bed of Celite 545 to remove the catalyst, which was washed thoroughly with ethyl acetate. The combined filtrate and washings were evaporated and dried *in vacuo* to give 292 mg of **15** (1.21 mmol, 87.7% yield); IR ($CHCl_3$): 2960, 1725, 1450, 1380, 1090 and 910 cm^{-1}; ^{1}H-NMR (200 MHz): 1.09 (3H, d, J=6.8 Hz), 1.17 (3H, s), 1.18 (3H, s), 1.25 (3H, t, J=6.8 Hz), 1.40~1.92 (7H), 1.98 (1H, br.), 2.32 and 2.50 (2H, m), and 4.12 ppm (2H, q, J=6.8 Hz); MS: m/z 240 (M^+) and 211. *Anal.* Found: C, 70.17; H, 10.01. Calcd. for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07%.

(3S,7S*)-3-[3-Hydroxypropyl]-1,3,7-trimethyl-2-oxabicyclo[2,2,1]heptane* (**16**). To a solution of **15** (286

mg, 1.19 mmol) in 6 ml of THF was added 72 mg of $LiAlH_4$, and the mixture was stirred for 10 min in an N_2 atmosphere at room temperature. The reaction was quenched by adding water, and the mixture was extracted twice with 50 ml portions of ethyl acetate. The organic layer was washed with 2 N HCl, aq. sat. $NaHCO_3$ and brine, and then dried over anhyd. $MgSO_4$. Filtration and evaporation of the solvent afforded 214 mg of **16** (1.08 mmol, 90.0% yield); IR ($CHCl_3$): 3620, 3580~3200, 2960, 1730, 1460, 1375, 1230, 1085 and 905 cm^{-1}; ^{1}H-NMR (200 MHz): 1.11 (3H, d, J=7.2 Hz), 1.20 (3H, s), 1.21 (3H, s), 1.40~1.92 (9H), 1.97 (1H, br.), 2.80 (1H, br., OH) and 3.60 ppm (2H, m); MS: *m/z* 198 (M^+), 180 and 169. *Anal.* Found: C, 72.44; H, 10.95. Calcd. for $C_{12}H_{22}O_2$: C, 72.73; H, 11.11%.

(3S,7S*)-3-[3-Formylethyl]-1,3,7-trimethyl-2-oxabicyclo[2,2,1]heptane* (**17**). To a solution of **16** (214 mg, 1.08 mmol) in 10 ml of CH_2Cl_2 was added 500 mg of pyridinium chlorochromate (PCC, 2.03 mmol) and the mixture was stirred for 30 min at room temperature in an Ar atmosphere. The mixture was diluted with dry ether (50 ml) and passed through a column of Florisil (60~100 mesh), the column being washed with ether. The eluate and washings were combined and purged of solvent under reduced pressure to give 209 mg of **17** (1.06 mmol, 98.1%); IR ($CHCl_3$): 2960, 2840, 2730, 1725, 1450, 1380, 1235, 1090 and 910 cm^{-1}; ^{1}H-NMR (200 MHz): 1.07 (3H, d), J=7.8 Hz), 1.17 (3H, s), 1.18 (3H, s), 1.40~1.92 (7H), 2.00 (1H, br.), 2.50~2.64 (2H, m) and 9.83 ppm (1H, s); MS: *m/z* 196 (M^+), 153, 139, 123, 95, 81, 55 and 43.

(3S,7S*)-3-[4-Ethoxycarbonylpent-3-enyl]-1,3,7-trimethyl-2-oxabicyclo[2,2,1]heptane* (**18**). To a solution of **17** (63 mg, 0.31 mmol) in 8 ml of benzene was added 1-ethoxycarbonylethylidene triphenylphosphorane (156 mg, 0.43 mmol) and the mixture was stirred overnight at room temperature. The mixture was evaporated to dryness and the residue was chromatographed over silica gel using *n*-hexane–ethyl acetate (7:1) as the eluent. Appropriate fractions, as judged by TLC, were combined and evaporated to dryness to give 61 mg of **18** (0.22 mmol, 68.5%); UV (MeOH): 220.4 nm (ε 10,360); IR ($CHCl_3$): 2980, 1700, 1645, 1445, 1380, 1370, 1275, 1245, 1155, 1095 and 910 cm^{-1}; ^{1}H-NMR (200 MHz): 1.07 (3H, d, J=7.0 Hz), 1.20 (3H, s), 1.21 (3H, s), 1.31 (3H, t, J=7.3 Hz), 1.40~1.96 (9H), 1.98 (1H, br.), 4.18 (2H, q, J=7.3 Hz) and 6.74 ppm (1H, t, J=7.9 Hz); ^{13}C-NMR: 12.2, 12.6, 14.3, 17.4, 23.0, 24.7, 25.3, 35.6, 39.0, 48.4, 50.5, 60.3, 80.6, 85.5, 127.5, 142.3 and 168.1 ppm; MS: *m/z* 251, 235, 208, 139, 95, 81, 55 and 43.

(3S,7S*)-3-[5-Hydroxy-4-methylpent-3-enyl]-1,3,7-trimethyl-2-oxabicyclo[2,2,1]heptane* (**11**). To a solution of **16** (227 mg) in 2 ml of THF was added 1.35 ml of diisobutylaluminum hydride (25 w/v% in hexane) and the mixture was stirred for 1 hr at −78°C. The mixture was then warmed up to room temperature and water was added. The whole was extracted with ether and the organic extract was washed with 2 N HCl, sat. aq. $NaHCO_3$ and brine, and then dried over anhyd. $MgSO_4$. Filtration and evaporation of the solvent afforded an oily residue, which was chromatographed through silica gel using *n*-hexane–ethyl acetate (2:1) to yield, after removing the solvent, 63 mg of **11** (32.4% yield); ^{1}H-NMR (200 MHz): 1.08 (3H, d, J=7.4 Hz), 1.20 (3H, s), 1.21 (3H, s), 1.40~2.20 (10H), 3.99 (2H, br.) and 5.39 ppm (1H, t, J=7.0 Hz); ^{13}C-NMR (100 MHz): 12.6, 13.5, 17.3, 22.1, 24.7, 25.4, 35.6, 40.3, 48.5, 50.2, 68.8, 81.1, 85.4, 126.4 and 134.6 ppm; HRMS: Found, *m/z* 238.1938 (M^+); Calcd. for $C_{15}H_{26}O_2$, 238.1934.

(3R,7S*)-3-Formyl-1,3,7-trimethyl-2-oxabicyclo[2,2,1]-heptane* (**19**). To a solution of **10** (1.36 g, 8.0 mmol) in 40 ml of CH_2Cl_2 was added 3.6 g of PCC (13.6 mmol, 1.7 eq.) and the mixture was stirred for 20 min. After a further addition of PCC (1.5 eq.), stirring was continued for 1 hr. The mixture was diluted with ether and the whole was passed through a column of Florisil. The eluate and washings were combined and stripped of solvent to give 1.25 g of **19** (7.41 mmol, 92.6%); ^{1}H-NMR (200 MHz): 1.14 (3H, d, J=6.8 Hz), 1.31 (3H, s), 1.33 (3H, s), 1.40~1.82 (5H), 2.26 (1H, br.) and 9.71 ppm (1H, s); MS: *m/z* 168 (M^+), 139, 113, 99, 85 and 43.

(3R,7S*)-3-[2-Ethoxycarbonylethenyl]-1,3,7-trimethyl-2-oxabicyclo[2,2,1]heptane* (**20**). To a solution of **19** (683 mg, 40.7 mmol) in 10 ml of benzene was added 2.0 g of ethoxycarbonylmethylene triphenylphosphorane (5.73 mmol, 1.4 eq.) and the mixture was heated under reflux for 1 hr. The mixture was evaporated to dryness, and the residue was purified through a column of silica gel using *n*-hexane–ethyl acetate (10:1~7:1). Appropriate fractions were judged by TLC, combined and evaporated to dryness to give 757 mg of **20** (3.18 mmol, 78.2%); IR ($CHCl_3$): 2950, 1700, 1645, 1360, 1295, 1275, 1170, 1025 and 895 cm^{-1}; ^{1}H-NMR (200 MHz): 1.14 (3H, d, J=6.8 Hz), 1.27 (3H, s), 1.29 (3H, s), 1.29 (3H, t, J=7.1 Hz), 1.40~1.80 (5H), 2.15 (1H, br.), 4.19 (2H, q, J=7.1 Hz), 6.17 (1H, d, J=15.7 Hz) and 7.01 ppm (1H, d, J=15.7 Hz); MS: *m/z* 238 (M^+), 223, 209, 139, 121, 95, 81 and 43. *Anal.* Found: C, 70.42; H, 9.34. Calcd. for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31%.

(3R,7S*)-3-[2-Ethoxycarbonylethyl]-1,3,7-trimethyl-2-oxabicyclo[2,2,1]heptane* (**21**). A mixture of 720 mg (3.0 mmol) of **20**, 10 ml of ethyl acetate and 739 mg of 10% Pd–C (Kawaken Fine Chemicals Co.) was stirred in an H_2 atmosphere for 2 hr at room temperature. The catalyst was removed by passing the reaction mixture through a column of silica gel. The combined filtrate and washings were purged of solvent under reduced pressure to afford a residue, which was purified by a column of silica gel using *n*-hexane–ethyl acetate (7:1) as the eluent. Fractions were collected and examined by TLC. Appropriate fractions

were combined and evaporated to dryness to afford 420 mg of **21** (1.75 mmol, 57.8%); IR ($CHCl_3$): 2980, 1725, 1380, 1300, 1180, 1090 and 915 cm^{-1}; ^{1}H-NMR (200 MHz): 1.11 (3H, d, J=7.4 Hz), 1.19 (3H, s), 1.21 (3H, s), 1.26 (3H, t, J=7.3 Hz), 1.40~1.90 (7H), 1.97 (1H, br.), 2.30 (2H, m) and 4.13 ppm (2H, q, J=7.3 Hz); MS: *m/z* 240 (M^+), 222, 211, 195, 169, 139, 123, 99, 81, 55 and 43.

(3R,7S*)-3-[3-Hydroxypropyl]-1,3,7-trimethyl-2-oxabicyclo[2,2,1]heptane* (**22**). To a solution of **21** (626 mg, 2.63 mmol) in 10 ml of dry THF was added 82 mg of $LiAlH_4$, and the mixture was stirred for 20 min in an N_2 atmosphere at room temperature. The excess $LiAlH_4$ was decomposed by adding water, and the whole was extracted twice with 50 ml portions of ethyl acetate. The combined organic extract was successively washed with 2 N HCl, aq. sat. $NaHCO_3$ and brine, and then dried over anhyd. $MgSO_4$. Filtration and stripping of the solvent afforded 514 mg of **22** (2.6 mmol, 98.7%); IR ($CHCl_3$): 3830, 3400, 2960, 1450, 1380, 1240, 1065, 1015 and 915 cm^{-1}; ^{1}H-NMR (200 MHz): 1.12 (3H, d, J=7.3 Hz), 1.20 (3H, s), 1.24 (3H, s), 1.40~1.80 (7H), 1.98 (1H, br.), 2.63 (1H, br., OH), 3.65 (2H, br., $-CH_2OH$); MS: *m/z* 198 (M^+), 169, 151, 139, 109, 96, 85, 81 and 43. *Anal.* Found: C, 72.90; H, 11.28. Calcd. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18%.

(3R,7S*)-3-[2-Formylethyl]-1,3,7-trimethyl-2-oxabicyclo[2,2,1]heptane* (**23**). To a solution of **22** (344 mg, 1.73 mmol) in 6 ml of CH_2Cl_2 was added 1.2 g of PCC (4.87 mmol, 2.8 eq.) and the mixture was stirred for 30 min in an Ar atmosphere at room temperature. The mixture was diluted with ether and the whole was passed through a column of Florisil. The column was eluted with ether and the eluate was evaporated to give a residue, which was further purified by a column of silica gel using *n*-hexane–ethyl acetate (7:1~5:1). Appropriate fractions were combined and purged of solvent to give 241 mg of an oily **23** (1.23 mmol, 71.1%); IR ($CHCl_3$): 2960, 2740, 2730, 1725, 1445, 1380, 1240, 1160, 1090 and 920 cm^{-1}; ^{1}H-NMR (200 MHz): 1.12 (3H, d, J=8.0 Hz), 1.20 (3H, s), 1.21 (3H, s), 1.40~2.00 (8H), 2.48 (2H, m) and 9.80 ppm (1H, s); MS: *m/z* 196 (M^+), 167, 139, 123, 96, 81, 55 and 43. *Anal.* Found: C, 73.20; H, 10.00. Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27%.

(3R,7S*)-3-[4-Ethoxycarbonylpent-3-enyl]-1,3,7-trimethyl-2-oxabicyclo[2,2,1]heptane* (**24**). To a solution of **23** (223 mg, 1.14 mmol) in 15 ml of benzene was added 485 mg of 1-ethoxycarbonylethylidene triphenylphosphorane (1.33 mmol, 1.2 eq) and the mixture was stirred overnight at room temperature. The mixture was evaporated and the residue was passed through a column of silica gel, using *n*-hexane–ethyl acetate (7:1) as the eluent to give, after removing the solvent, 212 mg of **24** (0.76 mmol, 66.9% yield); UV (MeOH): 221.8 nm (ε 15,120); IR ($CHCl_3$): 2980, 1700, 1645, 1445, 1380, 1275, 1250, 1235, 1155, 1085 and 910 cm^{-1}; ^{1}H-NMR (200 MHz): 1.12 (3H, d, J=6.8 Hz), 1.20 (3H, s), 1.26 (3H, s), 1.30 (3H, t, J=7.3 Hz), 1.40~1.90 (7H), 1.98 (1H, br.), 2.15 (2H, m), 4.19 (2H, q, J=7.3 Hz) and 6.77 ppm (1H, t, J=7.3 Hz); ^{13}C-NMR: 12.3, 12.8, 14.2, 17.3, 24.6, 25.0, 25.6, 35.5, 40.1, 48.2, 50.0, 60.3, 81.0, 85.2, 127.5, 141.8 and 168.0 ppm. *Anal.* Found: C, 72.59; H, 9.78. Calcd. for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06%.

(3R,7S*)-3-[5-hydroxy-4-methylpent-3-enyl]-1,3,7-trimethyl-2-oxabicyclo[2,2,1]heptane* (**12**). To a solution **24** (236 mg, 0.85 mmol) in 5 ml of THF was added 1.7 ml of diisobutylaluminium hydride (25 w/v% in hexane) at −20°C in an Ar atmosphere with stirring, which was continued for 30 min at the same temperature. The reaction was quenched by adding water, and the whole was extracted with ethyl acetate. The organic extract was washed with dilute HCl solution, sat. aq. $NaHCO_3$ and brine, and then dried over anhyd. $MgSO_4$. Filtration and stripping of the solvent gave a residue, which was purified through a column of silica gel, using *n*-hexane–ethyl acetate (2:1) as the eluant to afford, after removing the solvent, 180 mg of **12** (0.75 mmol, 89.8% yield); IR ($CHCl_3$): 3620, 3450, 2960, 1700, 1445, 1380, 1240, 1155, 990 and 910 cm^{-1}; ^{1}H-NMR (200 MHz): 1.12 (3H, d, J=8.0 Hz), 1.20 (3H, s), 1.25 (3H, s), 1.40~2.20 (11H), 4.01 (2H, br.) and 5.41 ppm (1H, t, J=7.3 Hz); ^{13}C-NMR: 12.7, 13.5, 17.2, 23.8, 24.5, 25.5, 35.5, 41.1, 48.0, 49.6, 68.1, 81.4, 85.2, 125.4 and 134.4 ppm; MS: *m/z* 238 (M^+), 220, 209, 191, 166, 139, 107, 95, 81 and 43.

(3R,7S*)-3-[4-Formylpent-3-enyl]-1,3,7-trimethyl-2-oxabicyclo[2,2,1]heptane* (**26**). To a solution of **12** (58 mg) in 4 ml of acetone was added 160 mg of activated MnO_2, and the mixture was stirred for 2 hr at room temperature. The whole mixture was passed through a short column of silica gel to remove the MnO_2, and the eluate was evaporated to dryness to afford 57 mg of **26**; IR ($CHCl_3$): 2960, 2830, 2720, 1680, 1645, 1445, 1385, 1240, 1085 and 915 cm^{-1}; UV (MeOH): 230.5 nm (ε 5,760); ^{1}H-NMR (200 MHz): 1.13 (3H, d, J=6.8 Hz), 1.21 (3H, s), 1.28 (3H, s), 1.40~1.80 (7H), 2.00 (1H, br.), 2.36 (2H, m), 6.51 (1H, t, J=6.8 Hz) and 9.40 ppm (1H, s); ^{13}C-NMR: 9.2, 12.9, 17.4, 24.6, 25.4, 25.7, 35.6, 39.9, 48.3, 50.1, 81.1, 85.6, 139.0, 154.5 and 195.1 ppm; MS: *m/z* 236 (M^+), 235, 208, 179, 153, 139, 111, 95, 81, 55 and 43.

(3R,7S*)-3-[4-Carboxypent-3-enyl]-1,3,7-trimethyl-2-oxabicyclo[2,2,1]heptane* (**25**). A mixture of **24** (100 mg, 0.36 mmol), 6 ml of 5% KOH–H_2O and 4 ml of MeOH was heated under reflux for 1 hr. The reaction mixture was neutralized by adding 2 N HCl and extracted with ethyl acetate. The organic extract was washed with brine and then dried over anhyd. $MgSO_4$. Filtration and removal of the solvent under reduced pressure afforded 90 mg of **25**; IR ($CHCl_3$): 3200, 2960, 1685, 1445, 1380, 1290, 1160, 1085 and 915 cm^{-1}; UV (MeOH): 211.4 nm (ε 12,630); ^{1}H-NMR (200 MHz): 1.12 (3H, d, J=6.9 Hz), 1.21 (3H, s),

1.26 (3H, s), 1.40 ~ 1.80 (7H), 1.99 (1H, br.), 2.18 (2H, m) and 6.91 ppm (1H, t, $J=7.8$ Hz); ^{13}C-NMR: 12.01, 12.8, 17.3, 24.6, 25.2, 25.6, 35.6, 39.9, 48.3, 50.0, 81.3, 85.6, 126.9, 144.5 and 173.0 ppm. *Anal.* Found: C, 71.29; H, 9.69. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59%.

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REFERENCES AND NOTES

1) T. Ishiyama, personal communication to KK.
2) Y. Matsuki, M. Kodama and S. Ito, *Tetrahedron Lett.*, **1979**, 2901.
3) T. Ikeda and K. Wakatsuki, *J. Chem. Soc. Jpn.*, **57**, 425 (1936).
4) H. Stricker, G. Ohloff and E. sz. Kovats, *Tetrahedron Lett.*, **1964**, 649.
5) H. Stricker, G. Ohloff and E. sz. Kovats, *Helv. Chim. Acta*, **50**, 759 (1967).
6) W. Oppolzer and V. Sniekus, *Angew. Chem. Int. Ed. Engl.* **17**, 476 (1978).
7) P. A. Bartlett, in "Asymmetric Synthesis," Vol. 3, Part B, ed. by J. D. Morrison, Academic Press, New York, 1984, pp. 411 ~ 454.
8) E. Osawa and Y. Mochizuki, *Kagaku* (*Chemistry*), **40**, 703 (1985).
9) K. Kondo and M. Matsumoto, *Tetrahedron Lett.*, **1976**, 4363.
10) K. C. Nicolaou, R. L. Magolda, W. J. Sipio, W. E. Barnette, Z. Lysenko and M. M. Joullie, *J. Am. Chem. Soc.*, **102**, 3784 (1980).
11) J. R. Hanson, P. B. Hitchcock and R. Nyfeler, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1586.