A Novel Synthesis of Cyclobutane Monoterpenes, (±)-Grandisol and (±)-Lineatin

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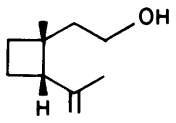
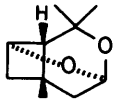
A novel synthesis of cyclobutane monoterpenes (±)-grandisol and (±)-lineatin from a readily available benzocyclobutene derivative is described.

Grandisol (**1**)[1] isolated from *Anthonomus grandis* is known to be a major component of grandlure, the sex attractant of the boll weevil, and lineatin (*2*)[2] has been isolated from the frass of the Douglas fir beetle, *Trypodendron lineatum* as a pheromone.

Owing to the interesting biological activity of these compounds and the structural novelty, these cyclobutane monoterpenes have been the subject of the extensive synthetic efforts which have culminated in several total syntheses in recent years.[3]



(**1**)



(**2**)

In the course of our synthetic studies of natural products utilising benzocyclobutene derivatives (which were mostly diene moieties participating in intra- and inter-molecular [4 + 2]-cycloadditions to construct polycyclic compounds) as useful starting materials, we were interested in the synthesis of cyclobutane monoterpenes, since manipulation of a benzene ring of a benzocyclobutene derivative would be expected to provide an alternative route to the synthesis of such monoterpenes.

We report here a novel synthesis of (±)-grandisol and (±)-lineatin. First we have investigated the synthesis of (±)-grandisol as follows.

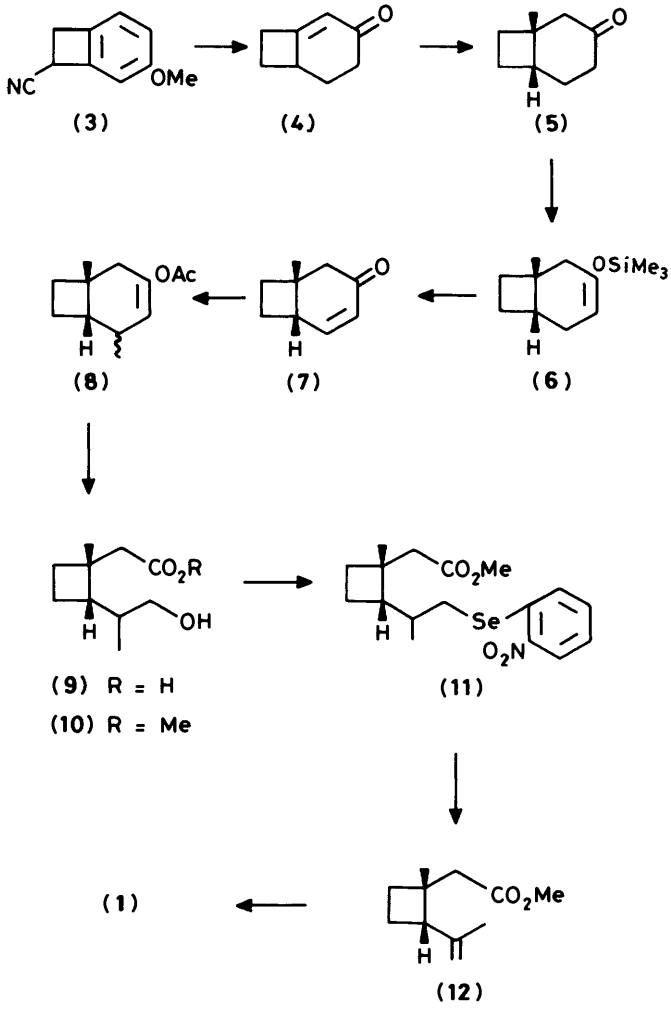
Results and Discussion

The benzocyclobutene (**3**)[4] prepared from *m*-hydroxybenzaldehyde on a large scale, was subjected to the Birch reduction and the product was treated with toluene-*p*-sulphonic acid to afford the enone (**4**) in 78% yield. A methyl group was introduced by treatment of (**3**) with lithium dimethylcuprate in dry ether in 83% yield, and the resulting ketone (**5**) was converted into the enone (**7**) by adopting Saegusa's procedure[5] *via* the corresponding silyl enol ether (**6**), in 65% yield.

A 1,4-conjugate addition to (**7**) using lithium dimethylcuprate in dry ether at −25 °C, followed by treatment with acetic anhydride, provided the enol acetate (**8**), in 81% yield. Its n.m.r. spectrum showed the presence of three methyl groups at δ 1.13 and 1.98, both singlets, and at δ 0.93 as a doublet with *J* 7 Hz. The alkenic proton resonated at δ 5.23 with *J* 5 Hz.

Ozonolysis of the enol acetate (**8**), with a reductive work-up with sodium borohydride in dichloromethane–methanol (1:5, v/v) furnished the acid (**9**), which without purification was converted into the ester (**10**) by treatment with diazomethane in 45% yield based on compound (**8**).

Finally, dehydration of a primary alcohol (**10**) was successfully achieved *via* the selenide (**11**), which was oxidatively eliminated using Grieco's method,[6] to afford the alkene (**12**), the physicochemical properties of which were identical with those reported,[7] in 66% yield. Since the transformation of the ester (**12**) into (±)-grandisol had already been accomplished by reduction of the ester group, this procedure constitutes a formal synthesis (Scheme 1).

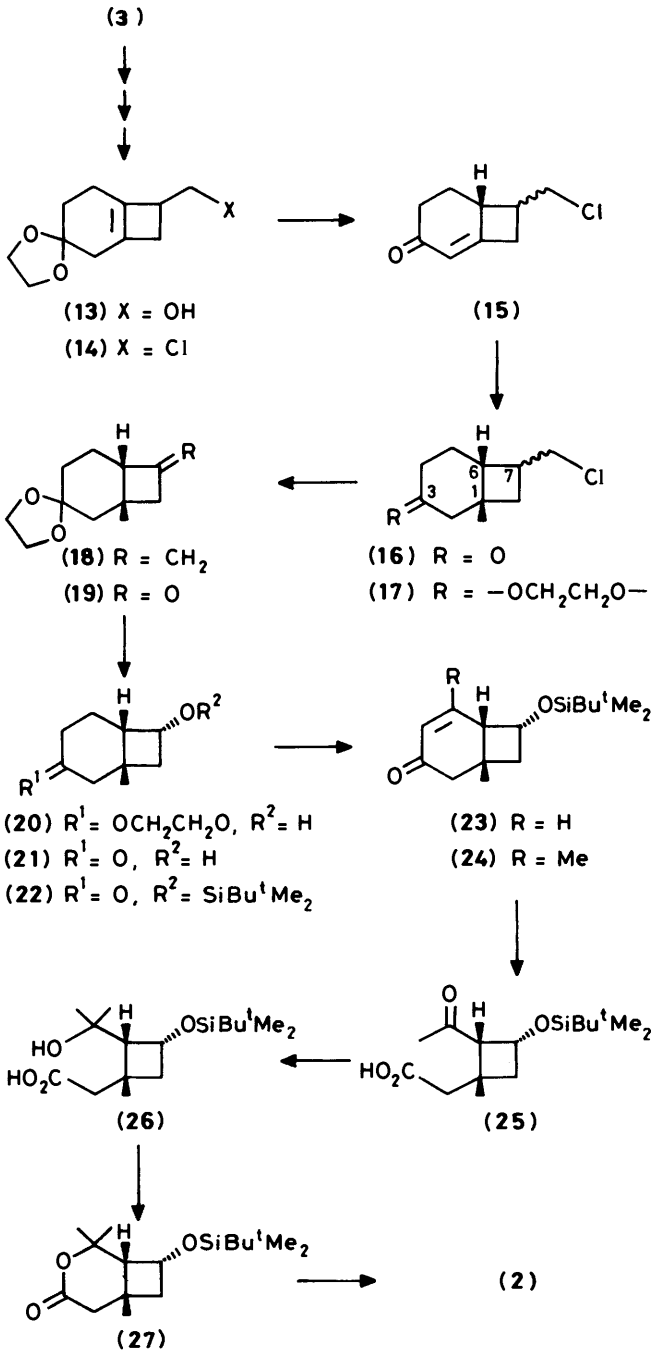


Scheme 1.

Our attention was then focused on the synthesis of an acetal monoterpene, (±)-lineatin (**2**). In order to synthesize (**2**), the introduction of a hydroxy group on the cyclobutane ring was required. Thus, the alcohol (**13**), readily derived from the benzocyclobutene (**3**), was converted into the chloride (**14**) by treatment with triphenylphosphine and carbon tetrachloride[8] at room temperature in 82.7% yield. Deprotection of ethylene

acetal function of the chloride (**14**) with toluene-*p*-sulphonic acid in acetone, followed by isomerisation of the double bond to give the α,β-unsaturated ketone with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in refluxing benzene yielded the enone (**15**) in 66.5% yield. Following the introduction of an angular methyl group by a 1,4-conjugate addition with lithium dimethylcuprate, the resulting ketone (**16**) was transformed to the ethylene acetal derivative (**17**) in 88.9% yield from (**15**). Treatment of the chloride (**17**) with potassium t-butoxide in dimethyl sulphoxide (DMSO) brought about dehydrochlorination to give the alkene (**18**) in 86.4% yield, the oxidation of which with osmium tetraoxide and sodium periodate in t-butyl alcohol–tetrahydrofuran–water (10:8:1, v/v) at ambient temperature furnished the ketone (**19**) in 72.6% yield. In order to increase the stereoselectivity, K-Selectride was employed for the reduction of the ketone to give the alcohol (**20**) as the sole product in 90.9% yield. Following deacetalisation of the alcohol (**20**) in acetone with toluene-*p*-sulphonic acid, and silylation of the resulting keto alcohol (**21**) with dimethyl(t-butyl)silyl chloride in *N*,*N*-dimethylformamide in the presence of imidazole, afforded the silyl derivative (**22**) in 95.2% yield from (**20**). The relative stereochemistry of the alcohol function in (**22**) was easily determined based on its n.m.r. spectrum in which 7-H resonated at δ 4.50 as double doublet with *J* 8 and 15 Hz. With the alcohol (**22**) in hand we next investigated the construction of a lactone moiety. Conversion of the ketone (**22**) into the enone (**23**) was achieved by adopting Saegusa's method [5] *via* the corresponding silyl enol ether in two steps in 71.9% yield. Introduction of a methyl group to the enone (**23**) by 1,4-conjugate addition with lithium dimethylcuprate, followed by treatment of the resulting lithium enolate with dimethyl(t-butyl)silyl chloride afforded the silyl enol ether, the oxidation of which under Saegusa's reaction conditions [5] using palladium(II) acetate furnished the enone (**24**) in 69.2% yield. Bond cleavage of the enone (**24**) by ozonolysis and subsequent oxidation of the ozonide with alkaline hydrogen peroxide [9] gave the keto acid (**25**) in 65.2% yield. The ketone (**25**) when treated with methyllithium was converted into the tertiary alcohol (**26**), which was then cyclised to the lactone (**27**) by treatment with pyridinium toluene-*p*-sulphonate in dichloromethane at ambient temperature in 68.2% yield [from (**25**)]. The spectroscopic data and melting point of synthesized compound (**27**) were identical with those reported.[3m] Since the lactone (**27**) had already been transformed [3m] into lineatin, our procedure constitutes a formal synthesis (Scheme 2).

Thus, we have developed novel methods for the synthesis of the cyclobutane monoterpenes (±)-grandisol and (±)-lineatin from the readily available benzocyclobutene derivative, and these syntheses suggest that the benzocyclobutenes would be useful starting materials for the synthesis of various types of natural products containing a cyclobutane ring.



Scheme 2.

Experimental

I.r. spectra were run on a Hitachi 260-10 spectrophotometer for samples in $CHCl_3$ solution. ^1H N.m.r. spectra were determined with JEOL PMX-60 and JEOL JNM-FX-100 spectrometer for samples in $CDCl_3$ and CCl_4 solution, and chemical shifts are expressed in p.p.m. downfield from internal $SiMe_4$. Mass spectra were obtained with a JEOL JMS-D300 spectrometer.

Bicyclo[4.2.0]*oct*-1-*en*-3-*one* (**4**).—To a stirred solution of compound (**3**) (20 g, 125.64 mmol) in liquid ammonia (2 l), dry tetrahydrofuran (100 ml), and anhydrous methanol (50 ml) was added sodium metal (11.5 g, 502.6 mmol) at −78 °C. The mixture was further stirred at the same temperature for 15 min and methanol was then added to the mixture to decompose the excess of sodium metal. After the solvent had been evaporated, the residue was treated with water and extracted with CH_2Cl_2. The extract was washed with 10% aqueous HCl and water, and dried (Na_2SO_4). Removal of the solvent gave a residue which was taken up in acetone (1.5 l) containing a catalytic amount of toluene-*p*-sulphonic acid (PTSA), and the resulting mixture was refluxed for 7 h. The cooled mixture was basified with saturated aqueous $NaHCO_3$ and the solvent was distilled off to leave the residue, which was extracted with CH_2Cl_2. The organic layer was washed with water and dried ($NaSO_4$). Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (97:3, v/v) afforded the enone (**4**) (12.0 g, 78%) as a colourless oil; $\nu_{max.}(CHCl_3)$ 1 660 cm^{-1}; $\delta(CDCl_3)$ 5.62 (1 H, br s, alkene-H);

m/z 122 (M^+) (Found: M^+, 122.0718. $C_8H_{10}O$ requires *M*, 122.0730.

1-*Methylbicyclo*[4.2.0]*octan*-3-*one* (**5**).—To a stirred solution of lithium dimethylcuprate [prepared from CuI (1.28 g, 6.70 mmol) and a solution of MeLi in ether (1.7M; 11.52 ml, 18.4 mmol)] in ether (23 ml) was added a solution of the enone (**4**) (300 mg, 2.46 mmol) in ether (23 ml) at −25 °C over a period of 10 min under an atmosphere of nitrogen. The resulting solution was further stirred for 70 min at the same temperature, then allowed to warm gradually to ambient temperature. The mixture was poured slowly into vigorously stirred 1.2M hydrochloric acid and extracted with ether. The ethereal layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (97:3, v/v) yielded the ketone (**5**) (281 mg, 82.8%) as a colourless oil; $\nu_{max.}(CHCl_3)$ 1 700 cm^{-1}; $\delta(CCl_4)$ 1.22 (3 H, s, Me); *m/z* 138 (M^+) (Found: M^+, 138.1030. $C_9H_{14}O$ requires *M*, 138.1043).

1-*Methyl*-cis-*bicyclo*[4.2.0]*oct*-4-*en*-3-*one* (**7**).—To a stirred solution of lithium di-isopropylamide (LDA) [prepared from di-isopropylamine (1.54 ml, 11.00 mmol) and a solution of butyllithium in hexane (15%; 4.27 ml, 7.60 mmol)] in dry tetrahydrofuran (9 ml) was added a solution of the ketone (**5**) (362 mg, 2.62 mmol) in dry tetrahydrofuran (9 ml) at −78 °C. After having been stirred for 30 min at −78 °C, a mixture of trimethylsilyl chloride (1.30 ml, 10.22 mmol) and hexamethylphosphoric triamide (0.344 ml) was added in small portions to the reaction mixture and the resulting solution was further stirred for 3 h at −78 °C, and gradually warmed to room temperature. The reaction was quenched by the addition of water, the solvent was removed, and the aqueous layer was extracted with ether. The ethereal layer was washed with saturated aqueous $NaHCO_3$ and brine, and dried (Na_2SO_4). After the solvent had been evaporated, the crude product was dissolved in acetonitrile (4.7 ml), and the solution was added to a suspension of palladium acetate (529 mg, 2.36 mmol) in acetonitrile (11 ml) with stirring. The resulting mixture was further stirred for 1 h at ambient temperature. Removal of the solvent gave a black residue, which was taken up in CH_2Cl_2. The insoluble material was filtered off through a Celite pad and the filtrate was concentrated. The ensuing residue was then subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (97:3, v/v) afforded the enone (**7**) (231 mg, 64.7%) as a colourless oil; $\nu_{max.}(CHCl_3)$ 1 660 cm^{-1}; $\delta(CCl_4)$ 1.30 (3 H, s, Me), 5.95 (1 H, d, *J* 10 Hz, alkene-H), and 6.75 (1 H, dd, *J* 4 and 10 Hz, alkene-H); *m/z* 136 (M^+) (Found: M^+, 136.0868. $C_9H_{12}O$ requires *M*, 136.0886).

3-*Acetoxy*-1,5-*dimethyl*-cis-*bicyclo*[4.2.0]*oct*-3-*ene* (**8**).—To a stirred solution of lithium dimethylcuprate [prepared from CuI (755 mg, 3.97 mmol) and a solution of MeLi in ether (1.7M; 6.48 ml, 11.02 mmol)] in dry ether (15 ml) was added a solution of the enone (**7**) (200 mg, 1.47 mmol) in dry ether (5 ml) over a period of 10 min at −25 °C under a current of nitrogen. Stirring was continued for 70 min at the same temperature, whereupon 1,2-dimethoxyethane (20 ml) was added to the reaction mixture. To the resulting solution was added acetic anhydride (1.1 ml, 11.75 mmol) and the mixture was gradually warmed to ambient temperature, and poured into a chilled 10% ammonium hydroxide solution. The aqueous layer was extracted with ether and the ethereal layer was washed with water and the combined ethereal layers were dried (Na_2SO_4). Evaporation of the solvent gave a residue, which was chromatographed on silica gel using hexane–ethyl acetate (98:2, v/v) as the eluant to provide the enol acetate (**8**) (230 mg, 80.6%) as a colourless oil; $\nu_{max.}(CHCl_3)$ 1 750 cm^{-1}; $\delta(CCl_4)$ 0.93 (3 H, d, *J* 7 Hz, Me), 1.13 (3 H, s, Me), 1.98 (3 H, s, OAc), and 5.23 (1 H, d, *J* 5 Hz, alkene-H); *m/z* 194 (M^+) (Found: M^+, 194.1308. $C_{12}H_{18}O_2$ requires *M*, 194.1307).

cis-1-[1-(*Hydroxymethyl*)*ethyl*]-2-*methoxycarbonylmethyl*-2-*methylcyclobutane* (**10**).—Ozone gas was bubbled through a stirred solution of the enol acetate (**8**) (150 mg, 0.772 mmol) in CH_2Cl_2 (1 ml) and methanol (5 ml) at −78 °C. To the solution was added sodium borohydride (117 mg, 3.09 mmol) in four equal portions at 15 min intervals at the same temperature. The reaction was allowed to warm to room temperature, whereupon the solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The solution was washed with brine and dried (Na_2SO_4). Removal of the solvent gave the crude carboxylic acid, which without being isolated was taken up in ether (2 ml) and treated with an excess of diazomethane in ether. The solvent and the excess of diazomethane were evaporated off and the residue was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (85:15, v/v) afforded the ester (**10**) (70 mg, 45.3%) as a colourless oil; $\nu_{max.}$ 1 720 cm^{-1}; $\delta(CCl_4)$ 0.78 (3 H, d, *J* 5.5 Hz, Me), 1.15 (3 H, s, Me), 2.46 (2 H, d, *J* 4.7 Hz, CH_2CO), 2.92—3.56 (2 H, m, CH_2OH), and 3.62 (3 H, s, OMe); *m/z* 182 ($M^+ - H_2O$).

cis-1-*Isopropenyl*-2-*methoxycarbonylmethyl*-2-*methylcyclobutane* (**12**).—To a stirred solution of the alcohol (**10**) (40.0 mg, 0.20 mmol) and *o*-nitrophenyl selenocyanate (68.0 mg, 0.30 mmol) in dry tetrahydrofuran (2 ml) was added tributylphosphine (0.075 ml, 0.30 mmol) at ambient temperature under an atmosphere of nitrogen. After the stirring had been continued for 1 h, the solvent was removed under reduced pressure to leave a residue, which was chromatographed on silica gel using hexane–ethyl acetate (99:1, v/v) as the eluant to give the selenide as a yellowish oil. To a solution of the selenide in tetrahydrofuran (2 ml) was added dropwise, at 0 °C, aqueous hydrogen peroxide (30%; 0.40 mmol) and the resulting mixture was warmed to room temperature and allowed to stir for 3.5 h. The solvent was evaporated and the residue was extracted with ethyl acetate. The organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave the residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (99:1, v/v) afforded the alkene (**12**) (24.0 mg, 65.9%) as a yellowish oil; $\nu_{max.}(CHCl_3)$ 1 720 cm^{-1}; $\delta(CCl_4)$ 1.28 (3 H, s, Me), 1.66 (3 H, br s, Me), 3.58 (3 H, s, OMe), and 4.62 and 4.80 (2 H, each br s, 2 × alkene-H); *m/z* 182 (M^+) (Found: M^+, 182.1309. $C_{11}H_{18}O_2$ requires *M*, 182.1308).

7-*Chloromethyl*-3,3-*ethylenedioxybicyclo*[4.2.0]*oct*-1(6)-*ene* (**14**).—To a stirred solution of compound (**13**) (20 g, 102 mmol) in CH_2Cl_2 (400 ml) were added triphenylphosphine (40 g, 153 mmol) and carbon tetrachloride (14.8 ml, 153 mmol) at ambient temperature. After 24 h of stirring the mixture was poured into water, and extracted with CH_2Cl_2. The organic layer was washed with water, and dried (Na_2SO_4). Evaporation of the solvent gave the residue which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (97:3, v/v) afforded the chloride (**14**) (18.1 g, 82.7%) as a colourless oil; $\delta(CCl_4)$ 3.56 (2 H, d, *J* 8 Hz, CH_2Cl) and 3.83 (4 H, s, OCH_2CH_2O); *m/z* 214 (M^+) (Found: M^+, 214.0768. $C_{11}H_{15}ClO_2$ requires *M*, 214.0761).

7-*Chloromethylbicyclo*[4.2.0]*oct*-1-*en*-3-*one* (**15**).—A solution of the acetal (**14**) (18 g, 83.84 mmol) and toluene-*p*-sulphonic acid (300 mg) in acetone (500 ml) and water (50 ml) was refluxed for 18 h. The solvents from the cooled reaction

were removed and the residue was treated with water and extracted with CH_2Cl_2. The organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave a residue which was dissolved in benzene (500 ml) containing DBU (12.8 g). The resulting mixture was refluxed for 2 h. The cooled reaction was washed with water and dried (Na_2SO_4). Removal of the solvent gave a residue, which was purified by column chromatography on silica gel using hexane–ethyl acetate (97:3, v/v) as the eluant to afford the enone (**15**) (9.52 g, 66.5%) as a pale yellow oil; $\nu_{max.}(CHCl_3)$ 1 660 cm^{-1}; $\delta(CCl_4)$ 3.71 (2 H, d, *J* 6 Hz, CH_2Cl) and 6.70 (1 H, br s, alkene-H); *m/z* 170 (M^+) (Found: M^+, 170.0489. $C_9H_{11}ClO$ requires *M*, 170.0497).

7-*Chloromethyl*-1-*methyl*-cis-*bicyclo*[4.2.0]*octan*-3-*one* (**16**)—To a stirred solution of lithium dimethylcuprate [prepared from CuI (12.7 g, 66.91 mmol) and a solution of MeLi in ether (1.7M; 104 ml, 111.52 mmol)] in ether (300 ml) was added a solution of the enone (**15**) (9.52 g, 55.76 mmol) in ether (100 ml) at −25 °C over a period of 20 min under an atmosphere of nitrogen. The resulting solution was further stirred for 1 h at the same temperature, then allowed to warm to room temperature gradually. Following the addition of saturated ammonium chloride solution, the mixture was extracted with ethyl acetate and the organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave the residue which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (97:3, v/v) afforded the ketone (**16**) (9.60 g, 92.2%) as a colourless oil; $\nu_{max.}(CHCl_3)$ 1 705 cm^{-1}; $\delta(CCl_4)$ 1.18 (3 H, s, Me) and 3.60 (2 H, d, *J* 6 Hz, CH_2Cl); *m/z* 186 (M^+) (Found: M^+, 186.0809. $C_{10}H_{15}ClO$ requires *M*, 186.0810).

7-*Chloromethyl*-3,3-*ethylenedioxy*-1-*methyl*-cis-*bicyclo*[4.2.0]*octane* (**17**).—A solution of the ketone (**16**) (9.4 g, 50.35 mmol), ethylene glycol (4.69 g), and toluene-*p*-sulphonic acid (300 mg) in benzene (200 ml) was refluxed for 3 h. The cooled solution was washed with saturated aqueous $NaHCO_3$ and water, and dried (Na_2SO_4). Evaporation of the solvent gave the residue which was purified by column chromatography on silica gel using hexane–ethyl acetate (97:3, v/v) as the eluant to afford (**16**) (11.16 g, 96.4%) as a colourless oil; $\delta(CCl_4)$ 1.13 (3 H, s, Me), 3.50 (2 H, br d, *J* 6 Hz, CH_2Cl), and 3.85 (4 H, s, OCH_2CH_2O); *m/z* 230 (M^+) (Found: M^+, 230.1073. $C_{12}H_{19}ClO_2$ requires *M*, 230.1073).

3,3-*Ethylenedioxy*-1-*methyl*-7-*methylene*-cis-*bicyclo*[4.2.0]-*octane* (**18**).—A solution of compound (**17**) (11.0 g, 47.67 mmol) in dry dimethyl sulphoxide (50 ml) was added dropwise to a stirred suspension of potassium t-butoxide (8.7 g, 71.51 mmol) in dry dimethyl sulphoxide (50 ml). After having been stirred for 2 h at ambient temperature, the mixture was poured into water, and extracted with ether. The ethereal layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave a residue which was purified by column chromatography on silica gel using hexane–ethyl acetate (99:1, v/v) as the eluant to afford the alkene (**18**) (8.0 g, 86.4%) as a colourless oil; $\nu_{max.}(CHCl_3)$ 1 675 cm^{-1}; $\delta(CDCl_3)$ 1.24 (3 H, s, Me), 2.32 (2 H, m, 8-H_2), 2.60 (1 H, br s, 6-H), 3.95 (4 H, s, OCH_2CH_2O), and 4.75—4.80 (2 H, m, C=CH_2); *m/z* 194 (M^+) (Found: M^+, 194.1311. $C_{12}H_{18}O_2$ requires *M*, 194.1306).

3,3-*Ethylenedioxy*-1-*methyl*-cis-*bicyclo*[4.2.0]*octan*-7-*one* (**19**).—To a stirred solution of the alkene (**18**) (7.8 g, 40.15 mmol) in t-butyl alcohol (100 ml), tetrahydrofuran (80 ml), and water (10 ml) containing osmium tetraoxide (508 mg, 2 mmol) was added sodium periodate (42.94 g, 200.75 mmol) at ambient temperature and the resulting mixture was further stirred for 1 h. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave the residue which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (95:5, v/v) afforded the ketone (**19**) (5.72 g, 72.6%) as a colourless oil; $\nu_{max.}(CHCl_3)$ 1 765 cm^{-1}; $\delta(CCl_4)$ 1.46 (3 H, s, Me) 2.71 (2 H, s, 8-H_2), and 3.86 (4 H, s, OCH_2CH_2O); *m/z* 196 (M^+) (Found: M^+, 196.1107. $C_{11}H_{16}O_3$ requires *M* 196.1100).

3,3-*Ethylenedioxy*-7-endo-*hydroxy*-1-*methyl*-cis-*bicyclo*-[4.2.0]*octane* (**20**).—A solution of the ketone (**19**) (2.6 g, 13.25 mmol) in dry tetrahydrofuran (20 ml) was added to a stirred solution of K-Selectride (1.2 equiv.) in dry tetrahydrofuran (32 ml) at −78 °C under a current of nitrogen. The mixture was further stirred for 15 min at the same temperature, then warmed gradually to room temperature and stirred for 1 h at room temperature. The mixture was again cooled to 0 °C and treated with aqueous sodium acetate (1M; 2.6 ml). To this mixture was added dropwise at 20—30 °C hydrogen peroxide (35%; 8.6 ml). After the solvent had been removed, the residue was extracted with ethyl acetate and the organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave the residue which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (9:1, v/v) afforded the alcohol (**20**) (2.39 g, 90.9%) as a colourless oil; $\nu_{max.}(CHCl_3)$ 3 440 cm^{-1}; $\delta(CCl_4)$ 1.15 (3 H, s, Me), 3.88 (4 H, s, OCH_2CH_2O), and 4.16—4.50 (1 H, m, 7-H); *m/z* 198 (M^+) (Found: M^+, 198.1246. $C_{11}H_{18}O_3$ requires *M*, 198.1254).

7-endo-*Hydroxy*-1-*methyl*-cis-*bicyclo*[4.2.0]*octan*-3-*one* (**21**).—A solution of compound (**20**) (5.01 g, 25.27 mmol) and toluene-*p*-sulphonic acid (200 mg) in acetone (180 ml) and water (18 ml) was refluxed for 12 h. After the solvent had been removed, the residue was extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$ and water, and dried (Na_2SO_4). Evaporation of the solvent gave a residue which was purified by column chromatography on silica gel using hexane–ethyl acetate (9:1, v/v) as the eluant to yield the ketone (**21**) (3.86 g, 99.1%) as a colourless oil; $\nu_{max.}(CHCl_3)$ 3 400 and 1 680 cm^{-1}; $\delta(CCl_4)$ 1.20 (3 H, s, Me) and 4.46 (1 H, q, *J* 11 Hz, 7-H); *m/z* 154 (M^+) (Found: M^+, 154.0985. $C_9H_{14}O_2$ requires *M*, 154.0992).

7-endo-*Dimethyl*(*t-butyl*)*silyloxy*-1-*methyl*-cis-*bicyclo*[4.2.0]-*octan*-3-*one* (**22**).—A solution of the alcohol (**21**) (3.86 g, 25.06 mmol), dimethyl(t-butyl)silyl chloride (4.53 g, 30.07 mmol), and imidazole (2.05 g, 30.07 mmol) in dimethylformamide (40 ml) was stirred at ambient temperature for 3 h. The mixture was treated with water and extracted with benzene. The benzene layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave a residue which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (97:3, v/v) afforded the silyl ether (**22**) (6.51 g, 96.7%) as a colourless oil; $\nu_{max.}(CHCl_3)$ 1 700 cm^{-1}; $\delta(CCl_4)$ 0.06 (6 H, s, $SiMe_2$), 0.96 (9 H, s, $SiBu^t$), 1.25 (3 H, s, Me), and 4.56 (1 H, q, *J* 11 Hz, 7-H); *m/z* 211 ($M^+ - 57$) (Found: $M^+ - 57$, 211.1151. $C_{11}H_{19}O_2Si$ requires $M - 57$, 211.1153).

7-endo-*Dimethyl*(*t-butyl*)*silyloxy*-1-*methyl*-cis-*bicyclo*-[4.2.0]*oct*-4-*en*-3-*one* (**23**).—To a stirred solution of lithium di-isopropylamide [prepared from di-isopropylamine (2.27 ml, 16.23 mmol) and a solution of butyl-lithium in hexane (15%; 8.27 ml)] in dry tetrahydrofuran (30 ml) was added a solution of the ketone (**22**) (2.9 g, 10.82 mmol) in tetrahydrofuran (20 ml) at −78 °C. The reaction was stirred at the same temperature for 0.5 h, whereupon trimethylsilyl chloride (2.06 ml, 16.23 mmol) was added dropwise and stirring was further continued for 3 h.

The mixture was warmed to 0 °C over 1 h, then treated with water. The mixture was extracted with ether and the ethereal layer washed with saturated aqueous $NaHCO_3$ and cold water, and dried (Na_2SO_4). After the solvent had been removed, the residue was dissolved in acetonitrile (20 ml), and the resulting solution was added to a stirred solution of palladium(II) acetate (2.43 g, 10.82 mmol) in acetonitrile (45 ml) at ambient temperature. The mixture was further stirred for 10 h. Removal of the solvent gave a black residue which was taken up in CH_2Cl_2 (50 ml). Insoluble material was filtered off through a Celite pad and the filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (97:3, v/v) furnished the enone (**23**) (2.07 g, 71.9%) as a colourless oil; $\nu_{max.}(CHCl_3)$ 1 660 cm^{-1}; $\delta(CCl_4)$ 0.03 (6 H, s, $SiMe_2$), 0.85 (9 H, s, $SiBu^t$), 1.23 (3 H, s, Me), 2.03 (2 H, d, *J* 8 Hz, 8-H_2), 2.13 (2 H, s, 2-H_2), 2.97 (1 H, m, 6-H), 4.68 (1 H, q, *J* 11 Hz, 7-H), 6.13 (1 H, d, *J* 10 Hz, 4-H), and 6.77 (1 H, dd, *J* 4 and 10 Hz, 5-H); *m/z* 209 ($M^+ - 57$) (Found: $M^+ - 57$, 209.1000. $C_{11}H_{17}O_2Si$ requires $M - 57$, 209.0998).

7-endo-*Dimethyl*(*t-butyl*)*silyloxy*-1,5-*dimethyl*-cis-*bicyclo*[4.2.0]*oct*-4-*en*-3-*one* (**24**).—To a stirred solution of lithium dimethylcuprate [prepared from CuI (1.33 g, 7.00 mmol) and an ethereal solution of methyl-lithium (0.99M; 12.5 ml, 12.36 mmol)] in dry ether (50 ml) was added a solution of the enone (**23**) (1.10 g, 4.12 mmol) in dry tetrahydrofuran (50 ml) over 15 min at −45 °C under a current of nitrogen. The reaction was stirred at 0 °C for 45 min, whereupon trimethylsilyl chloride (0.81 ml, 6.18 mmol) and triethylamine (0.86 ml, 6.18 mmol) were added and the resulting mixture was stirred at ambient temperature for 2 h. The organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave the residue which was dissolved in acetonitrile (25 ml). This solution was added to a stirred suspension of palladium(II) acetate (925 mg, 4.12 mmol) in acetonitrile (30 ml) and the mixture was further stirred at room temperature for 10 h. Removal of the solvent gave a black residue which was taken up with CH_2Cl_2 (80 ml) and passed through Celite. The filtrate was concentrated to leave a residue which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (98:2, v/v) afforded the enone (**24**) (800 mg, 69.2%) as needles, m.p. 44 °C (from isopropyl alcohol–water) (Found: C, 68.55; H, 10.35. $C_{16}H_{28}O_2Si$ requires C, 68.50; H, 10.05%); $\nu_{max.}(CHCl_3)$ 1 650 cm^{-1}; $\delta(CCl_4)$ 0.03 (6 H, s, $SiMe_2$), 0.83 (9 H, s, $SiBu^t$), 1.22 (3 H, s, Me), 1.88 (3 H, s, Me), 1.66—2.33 (4 H, m, 2-H_2 and 8-H_2), 2.73 (1 H, br d, *J* 8 Hz, 6-H), 4.40 (1 H, q, *J* 11 Hz, 7-H), and 5.78 (1 H, br s, 4-H); *m/z* 223 ($M^+ - 57$).

c-2-*Acetyl*-c-3-*dimethyl*(*t-butyl*)*silyloxy*-1-*methylcyclobutan*-r-1-*ylacetic Acid* (**25**).—Ozone was bubbled into the solution of the enone (**24**) (200 mg, 0.71 mmol) in CH_2Cl_2 (8 ml) at −78 °C until no starting material was detected on t.l.c. (10—20 min). The mixture was gradually warmed to 0 °C. To this solution were added sodium hydroxide pellets (511 mg, 12.8 mmol), hydrogen peroxide (35%; 1.38 ml, 14.2 mmol), and Aliquat (100 mg), and the resulting mixture was stirred at 0 °C for 1 h. The mixture was diluted with water and acidified with 10% aqueous hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave a residue which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (7:3, v/v) afforded the acid (**25**) (139 mg, 65.2%) as needles, m.p. 72—74 °C (from hexane) (Found: C, 59.95; H, 9.65. $C_{15}H_{28}O_4Si$ requires C, 59.95; H, 9.40%); $\nu_{max.}(CHCl_3)$ 1 700 cm^{-1}; $\delta(CDCl_3)$ 0.03 (6 H, s, $SiMe_2$), 0.83 (9 H, s, $SiBu^t$), 1.18 (3 H, s, Me), 2.05 (3 H, s, Me), 2.45 (1 H, d, *J* 16 Hz, C*H*HCO_2), 3.22 (1 H, d, *J* 16 Hz, C*H*HCO_2), 3.28—3.55 (1 H, m, 2-H), 4.53 (1 H, q, *J* 11 Hz, 3-H), and 9.40 (1 H, s, CO_2H); *m/z* 243 ($M^+ - 57$).

c-3-*Dimethyl*(*t-butyl*)*silyloxy*-c-2-(1-*hydroxy*-1-*methylethyl*)-1-*methylcyclobutan*-r-1-*ylacetic Acid* (**26**).—To a stirred solution of the acid (**25**) (100 mg, 0.33 mmol) in dry tetrahydrofuran (5 ml) was slowly added an ethereal solution of methyl-lithium (0.99M; 0.66 ml, 0.66 mmol) at −45 °C. The reaction was stirred for 2 h at 0 °C, whereupon it was quenched by the additon of water and most of the solvent was evaporated. The residue was acidified with 10% aqueous hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave a residue which was chromatographed on silica gel using hexane–ethyl acetate (9:1, v/v) as the eluant to afford the acid (**26**) (100 mg, 91.7%) as a colourless oil; $\nu_{max.}(CHCl_3)$ 1 700 cm^{-1}; $\delta(CDCl_3)$ 0.03 (6 H, s, $SiMe_2$), 0.83 (9 H, s, $SiBu^t$), 1.11 (3 H, s, Me), 1.16 (3 H, s, Me), 1.20 (3 H, s, Me), 2.76 (1 H, d, *J* 14 Hz, C*H*HCO_2), 3.30 (1 H, d, *J* 14 Hz, C*H*HCO_2), and 4.43—4.76 (1 H, m, 3-H).

8-endo-*Dimethyl*(*t-butyl*)*silyloxy*-2,2,6-*trimethyl*-cis-3-*oxabicyclo*[4.2.0]*octan*-4-*one* (**27**).—A solution of the acid (**26**) (60 mg, 0.18 mmol) and a catalytic amount of pyridinium toluene-*p*-sulphonate in dry CH_2Cl_2 (5 ml) was refluxed for 1 h. The mixture was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave a residue which was chromatographed on silica gel using hexane–ethyl acetate (9:1, v/v) as the eluant to provide the lactone (40 mg, 74.4%) as colourless needles, m.p. 60—61 °C (from light petroleum) (lit., m.p. 60.5—61 °C); $\nu_{max.}(CHCl_3)$ 1 710 cm^{-1}; $\delta(CDCl_3)$ 0.03 (6 H, s, $SiMe_2$), 0.92 (9 H, s, $SiBu^t$), 1.30 (3 H, s, Me), 1.36 (3 H, s, Me), 1.56 (3 H, s, Me), 1.66—2.40 (3 H, m), 2.40 (1 H, d, *J* 16 Hz, C*H*HCO_2), 2.60 (1 H, d, *J* 16 Hz, C*H*HCO_2), and 4.56 (1 H, ddd, *J* 4, 8, and 12 Hz, 7-H); *m/z* 241 ($M^+ - 57$). The structure of compound (**27**) was determined by direct comparison of its i.r. and n.m.r. spectra with those of an authentic specimen.

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