Enantioselective Synthesis of *trans*-Octahydro-1,6-dioxoinden-4-ylpropionic Acid from (*R*)-2,3-*O*-Isopropylideneglyceraldehyde by Tandem Orthoester Claisen Rearrangement

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The optically active *trans*-octahydrodioxoinden-4-ylpropionic acid (**6**) was synthesized *via* the methylcyclopentanone (**8**) which was constructed through consecutive orthoester Claisen rearrangement of compounds (**9**) and (**12**) derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**1**). Compounds (**31**) and (**32**), possessing *trans*-ring fusion, were prepared by Dieckmann condensation of the corresponding dimethyl esters (**27**) and (**28**) which were derived from the regio- and stereo-selective alkylation of the methylcyclopentanone (**8**), and then orthoester Claisen rearrangement of the allyl alcohol (**26**).

As part of our general investigations of the use of (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**1**)[1] as a chiral starting material in synthesis of natural products, we have recently reported enantioselective total syntheses of indole alkaloids such as (−)-dihydrocorynantheol (**2**),[2] (−)-antirhine (**3**),[3] and its related compound (+)-dihydroantirhine (**4**)[4] (Scheme 1).

Recently there has been a recurrence of interest in the total synthesis of 11-keto steroids[5] and a stereocontrolled synthesis of the *trans*-octahydroindenone system which is a typical synthetic precursor for various steroids and related compounds.[6] In particular, Stork and co-workers recently reported several new approaches to this system, especially an elegant construction of an 11-keto steroid in only five steps from the *trans*-octahydro-oxoindenepropionic acid (**5**).[5b]

However, most previous syntheses of steroid nuclei are racemic approaches, and the enantioselective synthetic approach is a recently introduced requisite for steroid synthesis. For this purpose, we have developed a procedure for the preparation of the optically active *trans*-octahydro-oxoindenepropionic acid (**6**), a promising precursor of 11-keto steroids.

In this paper we report the enantioselective synthesis of *trans* angularly methylated octahydro-oxoindenepropionic acid (**6**) from (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**1**). Our retrosynthetic strategy of the compound (**6**) from (**1**) is shown in Scheme 2.

Our first target compound (**8**), possessing the required chirality at C-3, can be accessed from the readily available chiral starting material (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**1**), through consecutive orthoester Claisen rearrangement[7] of the partially protected pentenetriol (**9**) followed by Dieckmann condensation. Both the requisite ester function for Dieckmann condensation and the vinyl group, in compound (**7**), to lead eventually to a propionic acid side-chain can be introduced simultaneously by orthoester Claisen rearrangement of the allyl alcohol obtained by regio- and stereo-selective introduction of a C$_2$ unit into the methylcyclopentanone (**8**). Introduction of the propionic acid side-chain possessing the required stereochemistry at C-8 (steroid numbering) can be performed by oxidative cleavage of the double bond followed by epimerization into the more stable configuration, and then Wittig reaction of the resulting aldehyde.

First, we examined a synthesis of (2*S*,3*S*)-3-[3-hydroxyprop-1(*E*)-enyl]-2-methylcyclopentanone (**8**).

Grignard reaction of (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**1**)[1] (derived from D-mannitol) with vinylmagnesium

(2)

(3) R = CH=CH$_2$
(4) R = Et

Scheme 1.

(5)
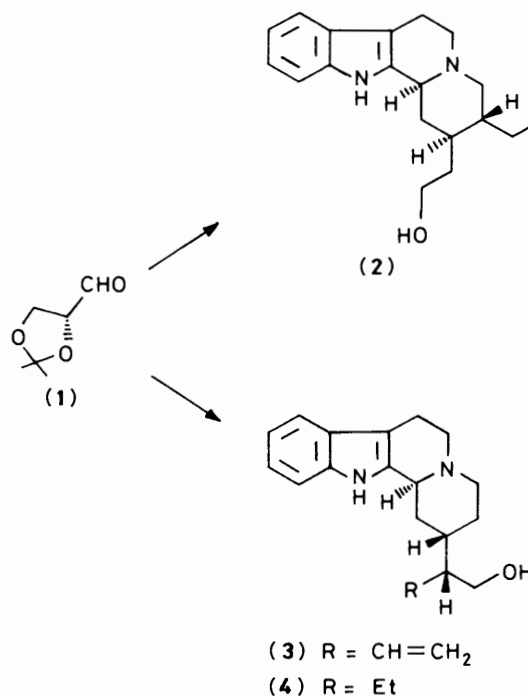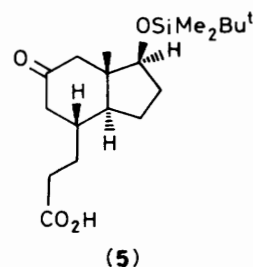
bromide in dichloromethane at 0 °C afforded the allyl alcohol (**9**) as a diastereoisomeric mixture in 45.8% overall yield from D-mannitol. Orthoester Claisen rearrangement[7] of compound (**9**) with trimethyl orthoacetate, in the presence of a catalytic amount of propionic acid, at 140 °C provided the methyl ester
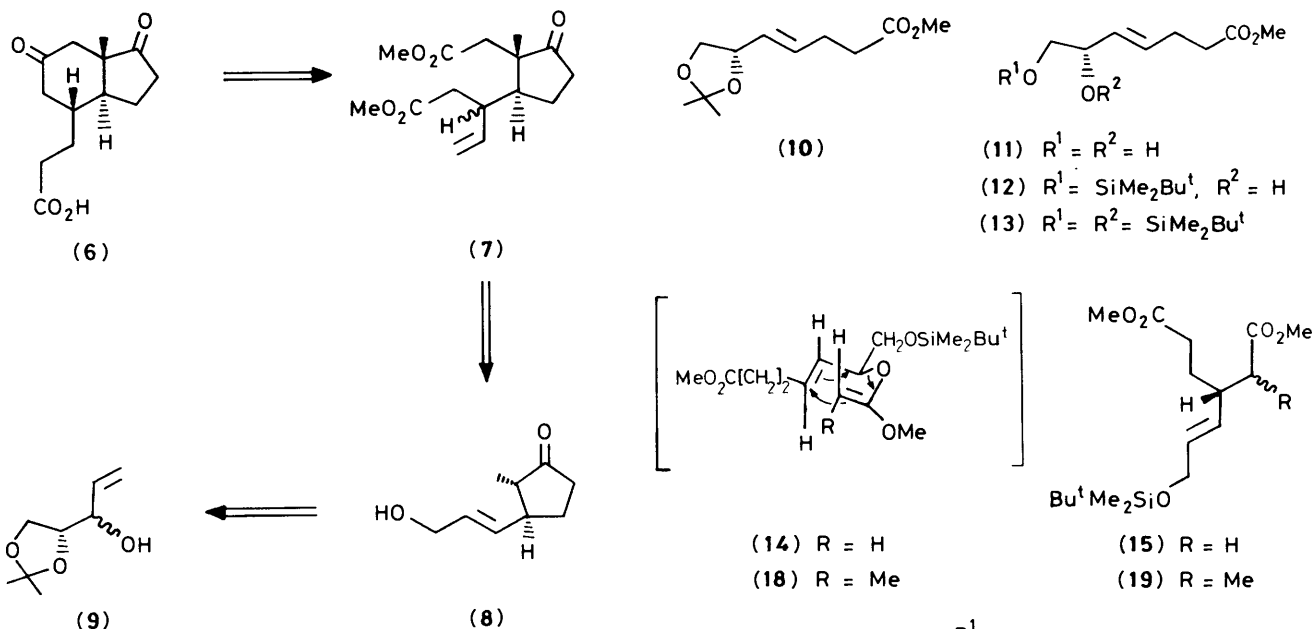
Scheme 2.

(10) in 88.1% yield. Cleavage of the acetonide in compound (10), followed by selective protection of the primary alcohol in the derived diol (11), at −10 °C, as the dimethyl-t-butylsilyl ether gave, in 83.1% overall yield from compound (10), the monoprotected allyl alcohol (12) in addition to a small amount of the fully protected derivative (13) which could be easily recycled in our synthesis. Chirality transfer of the secondary allyl alcohol group in (12) from C–O to C–C was also performed by orthoester Claisen rearrangement[7] to give, in 95.0% yield, the dimethyl ester (15), possessing the required chirality at C-4, *via* a six-membered-ring transition state (14). Dieckmann condensation of compound (15) with potassium t-butoxide in tetrahydrofuran (THF), followed by demethoxycarbonylation and simultaneous deprotection of the dimethyl-t-butylsilyl group, in the intermediate (16a) or (16b), by treatment with magnesium chloride in dimethyl sulphoxide (DMSO)[8] at 110 °C, gave the cyclopentanone (17) in 70.7% overall yield from diester (15).

In order to synthesize the *trans*-octahydroindenone system, it is necessary to introduce regioselectively a methyl group at C-2 at this stage; however, attempts to introduce a methyl group at C-2 in compound (17) under various conditions resulted in failure. This problem was easily overcome by orthoester Claisen rearrangement[7] of the allyl alcohol (12) with trimethyl orthopropionate, prepared in 2 steps from propiononitrile, and a catalytic amount of propionic acid in xylene at 160 °C. This afforded the dimethyl ester (19) in 93.4% yield *via* intermediate (18). Dieckmann condensation of compound (19) with lithium hexamethyldisilazide (LiHMDS) in THF, followed by treatment of the resultant compound (20) with magnesium chloride in DMSO,[8] provided the desired methylcyclopentanone (8) as the sole product in 90.9% overall yield from diester (19). None of the other isomer could be detected. Since no change could be observed on treatment of compound (8) with potassium carbonate, the configuration of the methyl group at C-2 was assigned as α, although no problem existed for further elaboration in the synthesis of the *trans*-octahydroindenone system.
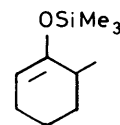
Since compound (8) was at hand, our attention was focused on the regio- and stereo-selective introduction of a C₂ unit to the carbonyl group in (8) and the formation of the c ring containing
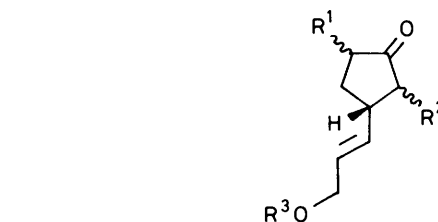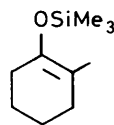
a requisite functional group at C-8 (steroid numbering). Many procedures concerned with this thermodynamic alkylation are known;[9] however, attempts to alkylate compound (23) under various conditions did not afford any satisfactory results, although Muller and McKean[10] had previously shown that 2-methylcyclohexanone is converted into the enol ethers (21) and (22), ratio 9:1, by reaction with trimethylsilyl iodide-hexamethyldisilazane (HMDS).

Application of this procedure to compound (23), derived from the corresponding alcohol (8), in dichloromethane, followed by fast elution on alumina with triethylamine, provided the pure enol ether (24). Treatment of the enolate,[9a,10] generated from compound (24), with an excess of methyl bromoacetate in hexamethylphosphoramide (HMPA) gave the desired methyl ester (25) as the sole product in 76.1% yield from the ketone (23).

Orthoester Claisen rearrangement[7] of the allyl alcohol (26), obtained by deprotection of compound (25), with trimethyl orthoacetate and a catalytic amount of propionic acid in xylene at 150 °C proceeded smoothly to give diesters (27) and (28) in

(23)

(24)

(25) R = SiMe$_2$Bu^t

(26) R = H

(27) R^1 = H, R^2 = CH=CH$_2$

(28) R^1 = CH=CH$_2$, R^2 = H
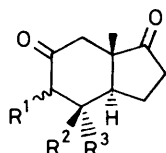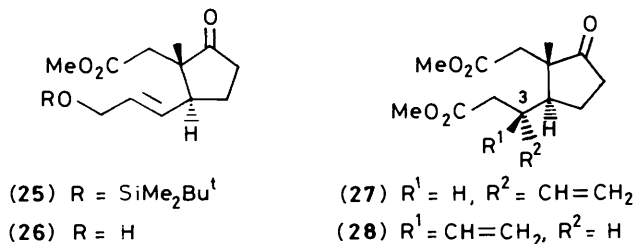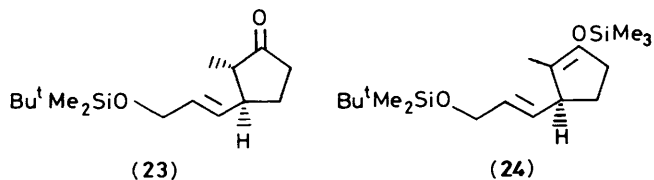
(29) R^1 = CO$_2$Me, R^2 = H, R^3 = CH=CH$_2$

(30) R^1 = CO$_2$Me, R^2 = CH=CH$_2$, R^3 = H

(31) R^1 = R^2 = H, R^3 = CH=CH$_2$

(32) R^1 = R^3 = H, R^2 = CH=CH$_2$

(33) R^1 = R^2 = H, R^3 = CHO

(34) R^1 = R^3 = H, R^2 = CHO

(35) R^1 = R^2 = H, R^3 = CH=CHCO$_2$Me

(36) R^1 = R^2 = H, R^3 = [CH$_2$]$_2$CO$_2$Me

88.8% yield (ratio 1:1) as a separable diastereoisomeric mixture at C-3. Dieckmann condensation of compounds (27) and (28) with LiHMDS in THF, followed by demethoxycarbonylation on treatment with aqueous hydrochloric acid produced, in 62.9 and 62.1% yield, the *trans*-hexahydroindene-1,6-diones (31) and (32) *via* the β-keto esters (29) and (30), respectively.

Oxidative cleavage of the double bond in compounds (31) and (32) with osmium tetraoxide and sodium periodate gave the aldehydes (33) and (34) respectively, in almost quantitative yield. Epimerization of the aldehyde group in the 4S aldehyde (34) proceeded smoothly on brief treatment with potassium carbonate in methanol to give the 4R compound (33) in 57.4% yield. Introduction of a C$_2$ unit into compound (33) was easily accomplished by treatment with methyl (triphenylphosphoranylidene)acetate in benzene to provide the α,β-unsaturated ester (35) in 71.1% yield. Hydrogenation over 10% palladium-carbon in methanol afforded the saturated methyl ester (36) in 87.9% yield. Finally, saponification of compound (36) produced the optically active *trans*-octahydrodioxoinden-4-ylpropionic acid (6) in 85.6% yield after purification by t.l.c.

Experimental

M.p.s were measured on a Yazawa BY-1 micro melting-point apparatus and are uncorrected. Optical rotations were measured with a JASCO-DIP-4 automatic polarimeter. I.r. spectra were recorded on a JASCO IR-810 spectrophotometer.

^{1}H N.m.r. spectra were taken from solutions in deuteriochloroform with tetramethylsilane as internal standard on a JEOL-JNM-PMX-60 instrument. Mass spectra were obtained with a JEOL-JMS-01-SG-2 spectrometer.

(4R)-4,5-*Isopropylidenedioxypent*-1-*en*-3-*ol* (9).—To an ice-cooled solution of vinylmagnesium bromide (1M solution in THF) (192 ml, 192 mmol) in dichloromethane (100 ml) was added dropwise a solution of the practically pure protected glyceraldehyde (1), prepared from D-mannitol (10 g, 54.9 mmol) according to the procedure by Fischer and Baer,[1] in dichloromethane (50 ml) during 30 min at 0 °C under nitrogen. After being stirred for 3 h at 0 °C, the reaction mixture was quenched by addition of acetic acid (11.5 g, 192 mmol) during 10 min at 0 °C, and the mixture was then stirred for an additional 10 min at the same temperature. The mixture was washed successively with saturated aqueous sodium hydrogen carbonate and brine, and then dried (MgSO$_4$). Evaporation of the solvent left a residue, which was purified by distillation to yield the *allyl alcohol* (9)[11] (7.95 g, 45.8% overall yield from D-mannitol) as an oil b.p. 63—64 °C (1 mmHg); [α]$_D$ +5.6° (c 1.113 in CHCl$_3$); ν$_{max.}$(CHCl$_3$) 3 600—3 200 cm^{-1} (OH); δ(CDCl$_3$) 1.37 (3 H, s, CMe), 1.43 (3 H, s, CMe), and 5.03—6.13 (3 H, m, CH=CH$_2$) [Found: m/z, 159.1020 (M^+ + 1). C$_8$H$_{15}$O$_3$ requires m/z, 159.1020 (M^+ + 1)].

Methyl (6S,4E)-6,7-*Isopropylidenedioxyhept*-4-*enoate* (10).—A mixture of the allyl alcohol (9) (7.08 g, 44.8 mmol), trimethyl orthoacetate (53.8 g, 448 mmol), and propionic acid (332 mg, 4.48 mmol) was stirred and heated at 140 °C for 1 h. Methanol was allowed to distil from the mixture as it formed. After evaporation of an excess of trimethyl orthoacetate under reduced pressure, the resultant residue was distilled to give the *methyl ester* (10) (8.45 g, 88.1%) as an oil, b.p. 105—108 °C (1 mmHg); [α]$_D$ +27.2° (c 0.228 in CHCl$_3$); ν$_{max.}$(CHCl$_3$) 1 736 cm^{-1} (C=O); δ(CDCl$_3$) 1.37 (3 H, s, CMe), 1.40 (3 H, s, CMe), 3.63 (3 H, s, CO$_2$Me), 5.40 (1 H, dd, J 16 and 6 Hz, 5-H), and 5.83 (1 H, dt, J 16 and 3 Hz, 4-H) (Found: M^+, 214.1179. C$_{11}$H$_{18}$O$_4$ requires M, 214.1204).

Methyl (6S,4E)-6,7-*Dihydroxyhept*-4-*enoate* (11).—A mixture of the methyl ester (10) (8.12 g, 37.9 mmol) and 10% sulphuric acid (5.4 ml) in methanol (36 ml) was stirred for 3 h at room temperature, and neutralized with solid sodium hydrogen carbonate, and diluted with ethyl acetate. The organic layer was separated, washed with brine, and then dried (MgSO$_4$). The solvent was concentrated to leave a residue, which was chromatographed on silica gel. Elution with chloroform-methanol (97:3, v/v) as eluant provided the diol (11) (6.61 g, quantitative yield) as a syrup, [α]$_D$ +11.3° (c 0.458 in CHCl$_3$); ν$_{max.}$(CHCl$_3$) 3 600—3 200 (OH) and 1 725 cm^{-1} (C=O); δ(CDCl$_3$) 3.52 (2 H, br s, 2 × OH, exchanged with D$_2$O), 3.63 (3 H, s, CO$_2$Me), 5.35 (1 H, dd, J 16 and 5 Hz, 5-H), and 5.77 (1 H, dt, J 16 and 3 Hz, 4-H).

Methyl (6S,4E)-7-(*Dimethyl-t-butylsiloxy*)-6-*hydroxyhept*-4-*enoate* (12) *and Methyl* (6S,4E)-6,7-*Bis*(*dimethyl-t-butylsiloxy*)-*hept*-4-*enoate* (13).—To a stirred solution of the diol (11) (6.61 g, 38.0 mmol) and imidazole (3.88 g, 57.0 mmol) in dimethylformamide (DMF) (35 ml) at −10 °C under nitrogen was added dropwise a solution of dimethyl-t-butylsilyl chloride (5.73 g, 38.0 mmol) in DMF (15 ml) during 20 min. The solution was stirred for 2 h at −10 °C and the reaction was quenched by addition of water. The solvent was removed under reduced pressure and the residue was extracted with diethyl ether. The extract was washed with brine, dried (MgSO$_4$), and then evaporated to leave a residue, which was chromatographed on silica gel. The first elution with hexane–ethyl acetate (8:2, v/v)

gave the diprotected compound (13) (1.05 g, 6.5%) as a syrup, $[\alpha]_D$ $-4.0°$ (c 0.555 in CHCl$_3$); $\nu_{max.}$(CHCl$_3$) 1 734 cm^1 (C=O); δ(CDCl$_3$) 0.03 (12 H, s, 2 × SiMe$_2$), 0.87 (18 H, s, 2 × Bu^t), 3.63 (3 H, s, CO$_2$Me), and 5.20—5.97 (2 H, m, CH=CH); m/z 345 ($M^+ - 57$), and the second elution with the same solvent afforded the monoprotected *allyl alcohol* (12) (9.09 g, 83.1%) as a syrup (Found: C, 57.85; H, 9.9. C$_{14}$H$_{28}$O$_4$Si requires C, 58.3; H, 9.8%); $[\alpha]_D$ $+7.3°$ (c 0.412 in CHCl$_3$); $\nu_{max.}$(CHCl$_3$) 3 600—3 200 (OH) and 1 730 cm^1 (C=O); δ(CDCl$_3$) 0.03 (6 H, s, SiMe$_2$), 0.87 (9 H, s, Bu^t) 3.58 (3 H, s, CO$_2$Me), 5.32 (1 H, dd, J 16 and 5 Hz, 5-H), and 5.75 (1 H, dt, J 16 and 3 Hz, 4-H); m/z 231 ($M^+ - 57$).

Conversion of the Diprotected Compound (13) *into the Diol* (11).—A solution of compound (13) (794 mg, 1.98 mmol) and 10% aqueous sulphuric acid (0.1 ml) in methanol (0.5 ml) was stirred for 18 h at room temperature. The mixture was neutralized with conc. ammonia solution and the precipitate was filtered off. The filtrate was evaporated to leave a residue, which was extracted with ethyl acetate. The extract was washed with cooled brine, and dried (MgSO$_4$). Evaporation of the solvent left a residue, which was chromatographed on silica gel with chloroform–methanol (97:3, v/v) as eluant to provide the diol (11) (252 mg, 73.3%). Both i.r. and n.m.r. spectra and t.l.c. behaviour were identical with those of an authentic sample.

Dimethyl (3R)-3-[(3-*Dimethyl-t-butylsiloxy*)prop-1(E)-enyl]-adipate (15).—The allyl alcohol (12) (5.29 g, 1.84 mmol), trimethyl orthoacetate (22.0 g, 184 mmol), and propionic acid (136 mg, 1.84 mmol) were stirred and heated at 145 °C for 30 min with removal of methanol by distillation. This procedure was repeated three times. After evaporation of an excess of trimethyl orthoacetate under reduced pressure, distillation of the residue yielded the *dimethyl ester* (15) (6.01 g, 95.0%) as a syrup, b.p. 132—133 °C (1 mmHg) (Found: C, 59.0; H, 9.6. C$_{17}$H$_{32}$O$_5$Si requires C, 59.3; H, 9.4%); $[\alpha]_D$ $+6.9°$ (c 0.232 in CHCl$_3$); $\nu_{max.}$(CHCl$_3$) 1 720 cm^{-1} (C=O); δ(CDCl$_3$) 0.05 (6 H, s, SiMe$_2$), 1.13 (9 H, s, Bu^t), 3.63 (6 H, s, 2 × CO$_2$Me), 3.97—4.32 (2 H, m, CH$_2$OSi), and 5.08—5.83 (2 H, m, CH=CH); m/z 287 ($M^+ - 57$).

(3R)-[3-*Hydroxyprop*-1(E)-enyl]cyclopentanone (17).—A solution of the dimethyl ester (15) (2.00 g, 5.81 mmol) in THF (40 ml) was added to a stirred solution of potassium t-butoxide (6.52 g, 5.81 mmol) in THF (95 ml) during 30 min under nitrogen, and the mixture was stirred for 2 h at room temperature. Acetic acid (3.49 g, 5.80 mmol) was then added and the mixture was stirred for 5 min and then extracted with diethyl ether. The extract was washed with brine, and dried (MgSO$_4$). The solvent was removed to give the practically pure β-keto ester (16a) or (16b), $\nu_{max.}$(CHCl$_3$) 1 755, 1 728, and 1 665 cm^1 (β-keto ester); δ(CDCl$_3$) 0.07 (6 H, s, SiMe$_2$), 0.91 (9 H, s, Bu^t), 3.58 (3 H, s, CO$_2$Me), 3.90—4.38 (2 H, m, CH$_2$OSi), and 5.30—5.98 (2 H, m, CH=CH).

A mixture of the above β-keto ester (16a) or (16b) and magnesium chloride hexahydrate (1.18 g, 5.81 mmol) in DMSO (5 ml) was stirred and heated at 110 °C under nitrogen. After 1 h, the reaction mixture was treated with water and then extracted with diethyl ether. The extract was washed with brine, dried (MgSO$_4$), and concentrated to leave a residue, which was chromatographed on silica gel. Elution with hexane–ethyl acetate (1:1, v/v) afforded the *cyclopentanone* (17) [0.575 g, 70.7% overall yield from (15)] as a syrup (Found: C, 68.9; H, 8.3. C$_8$H$_{12}$O$_2$ requires C, 68.55; H, 8.6%); $[\alpha]_D$ $+94.4°$ (c 0.22 in CHCl$_3$); $\nu_{max.}$(CHCl$_3$) 3 650—3 200 (OH) and 1 730 cm^{-1} (C=O); δ(CDCl$_3$) 3.27 (1 H, br s, OH, exchanged with D$_2$O), 3.73—4.48 (2 H, m, CH_2OH), and 5.37—6.00 (2 H, m, CH=CH) (Found: M^+, 140.0831. C$_8$H$_{12}$O$_2$ requires M, 140.0836).

Trimethyl Orthopropionate.—Anhydrous HCl gas (dried by passing through conc. sulphuric acid) was bubbled through dry diethyl ether (400 ml, freshly distilled from lithium aluminium hydride) at -78 °C until 60 g of gas had been dissolved. To this stirred solution at -78 °C was added dropwise a solution of propiononitrile (69.5 g, 1.26 mol) and dry methanol (44.5 g, 1.36 mol) in dry diethyl ether (250 ml) during 30 min. The reaction mixture was stored at -20 °C and briefly shaken periodically. After 15 days, it had separated into two layers. The ethereal layer was removed by decantation and the residue was washed with dry pentane to give a solid (75.5 g), which was collected by washing with dry pentane and then dried.

To an ice-cooled suspension of the above imidate hydrochloride in dry pentane (500 ml) was added dropwise dry methanol (59.0 g, 1.84 mol), and the mixture was stirred at room temperature under nitrogen. After 20 min, sodium carbonate (8g) was added and the mixture was stirred for 4 h at room temperature. The mixture was washed successively with saturated aqueous sodium hydrogen carbonate and brine, dried (MgSO$_4$), and then evaporated to leave a syrupy residue, which was distilled to give trimethyl orthopropionate (64.6 g, 38.2%) as a syrup, b.p. 85 °C (23 mmHg); δ(CDCl$_3$) 0.83 (3 H, t, J 7 Hz, Me), 1.70 (2 H, q, J 7 Hz, CH$_2$), and 3.12 (9 H, s, 3 × OMe).

Dimethyl (3S)-3-[(*Dimethyl-t-butylsiloxy*)prop-1(E)-enyl]-2-methyladipate (19).—A mixture of the allyl alcohol (12) (3.72 g, 12.9 mmol), trimethyl orthopropionate (3.46 g, 25.8 mmol), and propionic acid (47.8 mg, 0.645 mmol) in xylene (30 ml) was stirred and heated at 150 °C for 2 h with removal of methanol by distillation. Xylene and excess of trimethyl orthopropionate were removed, and the resultant residue was purified by distillation to give the *dimethyl ester* (19) (4.32 g, 93.4%) as a syrup, b.p. 139—142 °C (1 mmHg) (Found: C, 60.3; H, 9.9. C$_{18}$H$_{34}$O$_5$Si requires C, 60.3; H, 9.6%); $[\alpha]_D$ $+0.7°$ (c 1.95 in CHCl$_3$); $\nu_{max.}$(CHCl$_3$) 1 732 cm^{-1} (C=O); δ(CDCl$_3$) 0.05 (6 H, s, SiMe$_2$), 0.87 (9 H, s, Bu^t), 1.08 and 1.13 (each 1.5 H, each d, J 6 Hz, Me), 3.57 and 3.58 (each 3 H, each s, 2 × CO$_3$Me), 3.92—4.23 (2 H, m, CH$_2$OSi), and 4.93—5.72 (2 H, m, CH=CH) [Found: m/z, 343.1934 ($M^+ - 15$). C$_{17}$H$_{31}$O$_5$Si requires m/z, 343.1939 ($M^+ - 15$)].

(2S,3S)-3-[3-*Hydroxyprop*-1(E)-enyl]-2-methylcyclopentan-one (8).—To a stirred solution of the dimethyl ester (19) (14.5 g, 40.5 mmol) in THF (200 ml) at -78 °C under nitrogen was added dropwise a solution of LiHMDS (1M in hexane) (97.2 ml, 97.2 mmol) during 30 min, and the mixture was then stirred for 2 h at -78 °C. The reaction was quenched with saturated aqueous ammonium chloride. The mixture was acidified with 6M-HCl, and then extracted with diethyl ether. The extract was washed with brine, dried (MgSO$_4$), and then evaporated to leave the practically pure β-keto ester (20) as a pale yellow syrup, $\nu_{max.}$(CHCl$_3$) 1 755, 1 729, and 1 655 cm^{-1} (β-keto ester); δ(CDCl$_3$) 0.07 (6 H, s, SiMe$_2$), 0.83 (9 H, s, Bu^t), 1.02 and 1.07 (each 1.5 H, each d, J 6 Hz, Me), 3.63 (3 H, s, CO$_2$Me), 3.90—4.23 (2 H, m, CH$_2$OSi), and 4.68—5.90 (2 H, m, CH=CH).

A mixture of the above β-keto ester (20) and magnesium chloride hexahydrate (8.23 g, 40.5 mmol) in DMSO (60 ml) was stirred and heated at 160 °C for 12 h. The reaction mixture was diluted with water and extracted with diethyl ether. The extract was washed with brine, dried (MgSO$_4$), and then evaporated to leave a residue, which was chromatographed on silica gel with hexane–ethyl acetate (8:2, v/v) as eluant to provide the *methylcyclopentanone* (8) [5.67 g, 90.9% overall yield from (19)] as a syrup, $[\alpha]_D$ $+80.8°$ (c 1.54 in CHCl$_3$); $\nu_{max.}$(CHCl$_3$) 3 608, 3 570—3 200 (OH), and 1 730 cm^{-1} (C=O); δ(CDCl$_3$) 1.02 (3 H, d, J 6 Hz, Me), 3.00 (1 H, br s, OH, exchanged with D$_2$O), 3.83—4.43 (2 H, m, CH_2OH), and 5.30—5.97 (2 H, m, CH=CH) (Found: M^+, 154.0987. C$_9$H$_{14}$O$_2$ requires M, 154.0992).

(2S,3S)-3-[3'-(Dimethyl-t-butylsiloxy)prop-1'(E)-enyl]-2-methylcyclopentanone (23).—A mixture of the methylcyclopentanone (8) (5.58 g, 36.2 mmol), dimethyl-t-butylsilyl chloride (6.54 g, 43.4 mmol), and 4-dimethylaminopyridine (6.62 g, 54.3 mmol) in dichloromethane (100 ml) was stirred for 2 h at room temperature. The reaction was quenched by addition of water and the mixture was extracted with diethyl ether. The extract was washed with brine, dried (MgSO₄), and then evaporated off. The resultant residue was chromatographed on silica gel. Elution with hexane–ethyl acetate (98:2, v/v) afforded the dimethyl-t-butylsilyl ether (23) (9.72 g, quantitative yield) as a syrup, $[\alpha]_D$ + 59.8° (c 1.97 in CHCl₃); $\nu_{max.}$(CHCl₃) 1 730 cm⁻¹ (C=O); δ(CDCl₃) 0.08 (6 H, s, SiMe₂), 0.90 (9 H, s, Buᵗ), 1.07 (3 H, d, J 6 Hz, Me), 4.08—4.27 (2 H, m, CH₂OSi), and 5.57—5.83 (2 H, m, CH=CH); m/z 211 (M^+ − 57).

Methyl (1S,2S)-{2-[3'-(Dimethyl-t-butylsiloxy)prop-1'(E)-enyl]-1-methyl-5-oxocyclopentyl}acetate (25).—To a stirred solution of compound (23) (116 mg, 0.433 mmol) in dichloromethane (2 ml) at − 20 °C under nitrogen, containing one piece of 4 Å molecular sieve, were added HMDS (252 mg, 1.56 mmol) and trimethylsilyl iodide (260 mg, 1.30 mmol). The mixture was stirred under nitrogen for 15 min at − 20 °C, and for 1 h at room temperature. After the reaction had gone to completion, the mixture was extracted with dry diethyl ether. The extract was washed with ice-cold saturated aqueous sodium hydrogen carbonate, dried (MgSO₄), and then concentrated. The residue was passed rapidly through a short alumina column with 4 drops of triethylamine in dry diethyl ether as eluant to give the pure silyl enol ether (24).

A solution of methyl-lithium (1.6M in Et₂O) (0.406 ml, 0.650 mmol) was added dropwise to a stirred solution of the above silyl enol ether (24) (134 mg, 0.433 mmol) in dry diethyl ether (2 ml) at − 15 °C, and the mixture was stirred for 1 h at room temperature under nitrogen. This lithium enolate was added all at once to a stirred solution of methyl bromoacetate (332 mg, 2.17 mmol) and HMPA (389 mg, 2.17 mmol) in THF (1 ml) at − 40 °C, and the mixture was stirred for 1 h at room temperature. The reaction was then quenched by addition of saturated aqueous ammonium chloride, and the mixture was extracted with diethyl ether. The extract was washed with brine, dried (MgSO₄), and then evaporated to leave a residue, which was chromatographed on silica gel with hexane–ethyl acetate (9:1, v/v) as eluant to provide the methyl ester (25) (112 mg, 76.1%) as a syrup, $[\alpha]_D$ + 16.0° (c 2.24 in CHCl₃); $\nu_{max.}$(CHCl₃) 1 737 cm⁻¹ (C=O); δ(CDCl₃) 0.07 (6 H, s, SiMe₂), 0.85 (3 H, s, Me), 0.90 (9 H, s, Buᵗ), 3.57 (3 H, s, CO₂Me), 4.03—4.20 (2 H, m, CH₂OSi), and 5.43—5.65 (2 H, m, CH=CH) [Found: m/z, 283.1336 (M^+ − 57). C₁₄H₂₃O₄Si requires m/z, 283.1364 (M^+ − 57)].

Methyl (1R,2S)-{2-[3'-Hydroxyprop-1'(E)-enyl]-1-methyl-5-oxocyclopentyl}acetate (26).—A mixture of the silyl ether (25) (277 mg, 0.815 mmol) and toluene-p-sulphonic acid (20 mg) in methanol (2 ml) was stirred for 2 h at room temperature. The solvent was evaporated off to leave a residue, which was diluted with chloroform. The organic layer was washed with brine and dried (MgSO₄). Removal of the solvent, and chromatography of the residue on silica gel with hexane–ethyl acetate (6:4, v/v) as eluant, afforded the allyl alcohol (26) (157 mg, 85.3%) as a syrup, $[\alpha]_D$ + 39.1° (c 0.557 in CHCl₃); $\nu_{max.}$(CHCl₃) 3 650—3 300 (OH) and 1 732 cm⁻¹ (C=O); δ(CDCl₃) 0.85 (3 H, s, Me), 1.82 (1 H, br s, OH, exchanged with D₂O), 3.53 (3 H, s, CO₂Me), 3.90—4.23 (2 H, m, CH₂OH), and 5.48—5.78 (2 H, m, CH=CH) (Found: M^+, 226.1210. C₁₂H₁₈O₄ requires M, 226.1205).

Methyl (3S,1'S,2'S)-3-[2'-(Methoxycarbonylmethyl-2'-methyl-3'-oxocyclopentyl]pent-4-enoate (27) and Methyl (3R,1'S,2'S)-3-[2'-(Methoxycarbonylmethyl)-2'-methyl-3'-oxocyclopentyl]pent-4-enoate (28).—A mixture of the allyl alcohol (26) (157 mg, 0.695 mmol), trimethyl orthoacetate (418 mg, 3.48 mmol), and propionic acid (3 mg, 0.0348 mmol) in xylene (8 ml) was stirred and heated at 150 °C for 2 h with removal of methanol by distillation. Excess of trimethyl orthoacetate and xylene were removed under reduced pressure to leave the residue, which was extracted with diethyl ether. The extract was washed successively with saturated aqueous sodium hydrogen carbonate and brine, dried (MgSO₄), and then evaporated to leave a residue, which was chromatographed on silica gel with hexane–ethyl acetate (7:3, v/v) as eluant to give the dimethyl ester (27) (85.4 mg, 43.6%) as a syrup, $[\alpha]_D$ + 38.6° (c 0.171 in CHCl₃); $\nu_{max.}$(CHCl₃) 1 732 cm⁻¹ (C=O); δ(CDCl₃) 0.93 (3 H, s, Me), 3.57 (6 H, s, 2 × CO₂Me), 4.98 (1 H, dd, J 18 and 2 Hz, CH=CHH), 4.98 (1 H, dd, J 8 and 2 Hz, CH=CHH), and 5.65 (1 H, ddd, J 18, 8, and 6 Hz, CH=CH₂) (Found: M^+, 282.1436. C₁₅H₂₂O₅ requires M, 282.1466) and the dimethyl ester (28) (88.6 mg, 45.2%) as a syrup, $[\alpha]_D$ + 55.4° (c 0.242 in CHCl₃); $\nu_{max.}$(CHCl₃) 1 733 cm⁻¹ (C=O); δ(CDCl₃) 0.90 (3 H, s, Me), 3.55 (6 H, s, 2 × CO₂Me), 4.97 (1 H, dd, J 18 and 2 Hz, CH=CHH), 4.97 (1 H, dd, J 8 and 2 Hz, CH=CHH), and 5.53 (1 H, ddd, J 18, 8, and 6 Hz, CH=CH₂) (Found: M^+, 282.1451).

(3aS,4S,7aS)-7a-Methyl-4-vinyl-3,3a,4,5,7,7a-hexahydroindene-1,6-dione (31).—A solution of LiHMDS (1M solution in hexane) (0.378 ml, 0.378 mmol) was added dropwise to a stirred solution of compound (27) (42.5 mg, 0.151 mmol) in THF (1 ml) at − 70 °C under nitrogen. The temperature gradually rose to − 10 °C during 1.5 h. The reaction was then quenched by addition of saturated aqueous ammonium chloride, and the mixture was acidified with 6M-HCl. The mixture was extracted with diethyl ether and the extract was washed with brine, dried (MgSO₄), and then evaporated to yield the β-keto ester (29) (44 mg), $\nu_{max.}$(CHCl₃) 1 745, 1 715, and 1 645 cm⁻¹ (C=O and β-keto ester).

The above β-keto ester (29) (44 mg) was dissolved in acetic acid containing 6M-HCl (AcOH–6M-HCl 4:1 v/v, 1 ml). The mixture was heated at 125 °C for 12 h, cooled to room temperature, and then extracted with diethyl ether. The extract was washed successively with saturated aqueous sodium hydrogen carbonate and brine, dried (MgSO₄), and then concentrated to leave a residue, which was chromatographed on silica gel. Elution with hexane–ethyl acetate (8:2, v/v) afforded the (4S)-trans-hexahydroindenedione (31) [18 mg, 62.9% overall yield from (27)] as a solid which, on recrystallization from hexane, gave needles, m.p. 53—55 °C; $[\alpha]_D$ + 103.5° (c 0.170 in CHCl₃); $\nu_{max.}$(CHCl₃) 1 740 and 1 711 cm⁻¹ (C=O); δ(CDCl₃) 0.88 (3 H, s, Me), 4.97 (1 H, dd, J 18 and 2 Hz, CH=CHH), 4.97 (1 H, dd, J 8 and 2 Hz, CH=CHH), and 5.57 (1 H, ddd, J 18, 8, and 6 Hz, CH=CH₂) (Found: M^+, 192.1122. C₁₂H₁₆O₂ requires M, 192.1148).

(3aS,4R,7aS)-7a-Methyl-4-vinyl-3,3a,4,5,7,7a-hexahydroindene-1,6-dione (32).—Compound (28) (45.4 mg, 0.161 mmol) was converted into the (4R)-trans-isomer (32) [19.2 mg, overall yield 62.1% from (28)] as a syrup using the same procedure as that described above via the β-keto ester (30), $\nu_{max.}$(CHCl₃) 1 739, 1 718, and 1 645 cm⁻¹ (C=O and β-keto ester). Compound (32) had $[\alpha]_D$ + 150.8° (c 0.065 in CHCl₃); $\nu_{max.}$(CHCl₃) 1 740 and 1 711 cm⁻¹ (C=O); δ(CDCl₃) 0.92 (3 H, s, Me), 5.03 (1 H, dd, J 18 and 2 Hz, CH=CHH), 5.03 (1 H, dd, J 8 and 2 Hz, CH=CHH), and 5.85 (1 H, ddd, J 18, 8, and 6 Hz, CH=CH₂) (Found: M^+, 192.1084).

(3aS,4R,7aS)-7a-Methyl-1,6-dioxo-octahydroindene-4-carbaldehyde (33).—Osmium tetraoxide (4.47 mg, 0.0176 mmol) was added to a solution of the vinyl diketone (31) (33.5 mg, 0.176 mmol) in 1,4-dioxane (1 ml). The mixture was stirred in

the dark for 2.5 h in order to form the osmate ester, and was then diluted with water. To this mixture was added dropwise a solution of sodium periodate (94 mg, 0.440 mmol) in water (0.94 ml). After the mixture had been stirred for 1.5 h, the resultant precipitate was filtered off and washed with chloroform. The filtrate was condensed to leave a residue, which was extracted with chloroform. The extract was washed with brine and dried ($MgSO_4$). The solvent was evaporated off to give the practically pure aldehyde (33) (35 mg), $\nu_{max.}(CHCl_3)$ 1 742 and 1 723 cm^{-1} (C=O); $\delta(CDCl_3)$ 0.85 (3 H, s, Me) and 9.73 (1 H, s, CHO). This product was used in the next reaction without further purification.

(3aS,4S,7aS)-7a-*Methyl*-1,6-*dioxo-octahydroindene*-4-*carbaldehyde* (34).—The aldehyde (34) (10.1 mg) [$\nu_{max.}(CHCl_3)$ 1 742 and 1 727 cm^{-1} (C=O); $\delta(CDCl_3)$ 0.82 (3 H, s, Me), 9.92 (1 H, s, CHO)] was obtained from vinyl diketone (32) (10 mg, 0.0521 mmol) by the same procedure as described above.

Epimerization of the 4S-*Compound* (34) *to* 4R-*Compound* (33).—A solution of compound (34) (10.1 mg, 0.0521 mmol) in methanol (1 ml) was treated with potassium carbonate (3 mg) for 15 min at room temperature. The solvent was evaporated off to leave a residue, which was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$), and then evaporated to leave a residue, which was purified by preparative t.l.c. on silica gel developed with hexane–ethyl acetate (1 : 1, v/v) to give the pure aldehyde (33) [5.8 mg, 57.4% overall yield from (34)]. I.r. and n.m.r. spectra and t.l.c. behaviour were identical with those of an authentic sample.

Methyl (3′aS,4′S,7′aS)-(E)-3-(7′a-*Methyl*-1′,6′-*dioxo-octahydroinden*-4′-*yl*)*acrylate* (35).—A mixture of the aldehyde (33) (35 mg) and methyl (triphenylphosphoranylidene)acetate (70.5 mg, 0.211 mmol) in dry benzene (3 ml) was stirred for 1.5 h at room temperature under nitrogen. The reaction was quenched by addition of saturated aqueous ammonium chloride, and the mixture was then extracted with diethyl ether. The extract was washed with brine, dried ($MgSO_4$), and then evaporated to leave a residue, which was chromatographed on silica gel. Elution with hexane–ethyl acetate (7 : 3, v/v) afforded the α,β-*unsaturated ester* (35) [31 mg, 71.1% overall yield from (33)] as a syrup, [α]$_D$ +111° (c 0.228 in CHCl$_3$); $\nu_{max.}(CHCl_3)$ 1 743, 1 716, and 1 662 cm^{-1} (C=O and α,β-unsaturated ester); $\delta(CDCl_3)$ 0.85 (3 H, s, Me), 3.70 (3 H, s, CO$_2$Me), 5.87 (1 H, d, J 16 Hz, CH=CHCO$_2$Me), and 6.82 (1 H, dd, J 16 and 7 Hz, CH=CHCO$_2$Me) (Found: M$^+$, 250.1195. C$_{14}$H$_{18}$O$_4$ requires M, 250.1203).

Methyl (3′aS,4′R,7′aS)-3-(7′a-*Methyl*-1′,6′-*dioxo-octahydroinden*-4′-*yl*)*propionate* (36).—A solution of the α,β-unsaturated ester (35) (36 mg, 0.144 mmol) in methanol (3 ml) was hydrogenated over 10% palladium–carbon (18 mg) for 3 h at room temperature. Catalyst was removed by filtration, and the filtrate was condensed to leave a residue, which was chromatographed on silica gel. Elution with hexane–ethyl acetate (7 : 3, v/v) provided the *saturated methyl ester* (36) (31.9 mg, 87.0%) as a syrup, [α]$_D$ +87.0° (c 0.246 in CHCl$_3$) $\nu_{max.}(CHCl_3)$ 1 737 and 1 710 cm^{-1} (C=O); $\delta(CDCl_3)$ 0.85 (3 H, s, Me) and 3.67 (3 H, s, CO$_2$Me) (Found: M$^+$, 252.1357. C$_{14}$H$_{20}$O$_4$ requires M, 252.1360).

(3′aS,4′R,7′aS)-3-(7′a-*Methyl*-1′,6′-*dioxo-octahydroinden*-4′-*yl*)*propionic Acid* (6).—A solution of 2M-potassium hydroxide

(0.1 ml) was added to a solution of the methyl ester (36) (28.2 mg, 0.112 mmol) in methanol (0.2 ml). The mixture was stirred for 15 h at room temperature. After the reaction had gone to completion, the solvent was evaporated off to leave a residue, which was acidified with 6M-HCl and then extracted with diethyl ether. The extract was washed with brine, dried ($MgSO_4$), and then evaporated. The residue was purified by preparative t.l.c. on silica gel developed with chloroform–methanol (85 : 15, v/v) to provide the carboxylic acid (6) (22.8 mg, 85.6%) as a solid, which was recrystallized from chloroform–hexane as prisms, m.p. 123—124 °C; [α]$_D$ +68.4° (c 0.225 in CHCl$_3$); $\nu_{max.}(CHCl_3)$ 3 300—2 500 (CO$_2$H), and 1 741 and 1 711 cm^{-1} (C=O); $\delta(CDCl_3)$ 0.85 (3 H, s, Me), 1.33—1.76 (6 H, m, CH$_2$CHCHCH$_2$CH$_2$CO$_2$H), 1.76—2.73 (8 H, m, 4 × CH$_2$-CO), and 8.53—8.95 (1 H, br s, CO$_2$H, exchanged with D$_2$O) (Found: M$^+$, 238.1218. C$_{13}$H$_{18}$O$_4$ requires M, 238.1206).

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