Tetrahedron Vol. 41, No. 21, pp. 4765 to 4769, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00

TOTAL SYNTHESIS OF THE SESQUITERPENE (±)-HIRSUTENE USING AN ORGANOSELENIUM-MEDIATED CYCLIZATION REACTION

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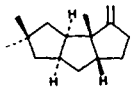
(*Received in USA* 14 *November* 1984)

Abstract—Cyclization of 2-carbomethoxy-3-(4',4'-dimethylcyclopent-2-enylmethyl)cyclopentanone (**4**) with N-phenylselenophthalimide and tin(IV) chloride affords *cis-syn-cis*-1β-carbomethoxy-4,4-dimethyl-3β-phenylselenotricyclo[6.3.0.0^{2,6}]undecan-11-one (**8**) and *cis-anti-cis*-1β-carbomethoxy-4,4-dimethyl-3α-phenylselenotricyclo[6.3.0.0^{2,6}]undecan-11-one (**9**). Both of these selenides can be elaborated to *cis-anti-cis*-4,4-dimethyl-1β-methyltricyclo[6.3.0.0^{2,6}]undecan-11-one (**13**) which upon treatment with CH_2Br_2/$TiCl_4$/Zn affords the sesquiterpene (±)-hirsutene (**1**) in 20% overall yield.

The linearly fused *cis-anti-cis*-tricyclo[6.3.0.0^{2,6}]-undecanoid carbon skeleton occurs in many sesquiterpene natural products as typified by hirsutene (**1**),[1] hirsutic acid (**2**)[2] and coriolin (**3**).[3] Owing to the anti-



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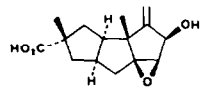

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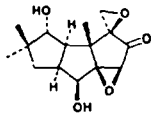

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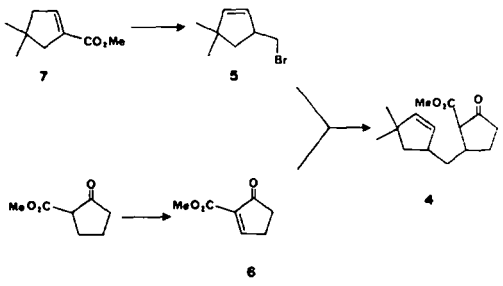
biotic and antitumour properties shown by a number of these molecules intense interest in their synthesis has arisen. Hirsutene (**1**), which was isolated as a mold metabolite from *Coriolus consors*,[1] is the simplest member of the series and is thought to be the biogenetic precursor of **2** and **3**. Several syntheses of hirsutene (**1**) have already appeared in the literature encompassing a wide range of interesting solutions for the construction of the inherent tricyclopentanoid framework.[1,4,5] Here we describe the use of an organoselenium-mediated cyclization reaction[6] as the key step in total synthesis of (±)-hirsutene (**1**).[5]

We have previously shown[7] that alkenyl-substituted β-keto-esters can be selectively cyclized, using various selenating reagents, to afford either carbocyclic or heterocyclic ring systems depending upon the reaction conditions. The preparation of the starting alkenyl-β-keto-ester (**4**) necessary for the present work was readily achieved by Cu(I) catalysed coupling of the Grignard reagent derived from the unsaturated bromide (**5**) with 2-carbomethoxycyclopent-2-enone (**6**) to provide **4** in 58% yield. The bromide (**5**) was obtained by deconjugation of the ester (**7**)[8] using potassium diisopropylamide[9] followed by reductive work-up with $LiAlH_4$ and bromination using the Vilsmeier salt $Me_2N{=}CHBr^+Br^-$.[10] Compound **6** was prepared from 2-carbomethoxycyclopentanone in quantitative yield using a modification of the Liotta method[11] and was used immediately in the next step owing to its instability. Cyclization[7] of **4** was effected by treatment with N-phenylselenophthalimide (NPSP) and tin(IV) chloride at room temperature in methylene chloride for 2.5 hr to give the *cis-syn-cis*-isomer (**8**) and the *cis-anti-cis*-isomer (**9**) both in 45% yield. The structural assignment for **8** and **9** follows from their high field ^{1}H-NMR spectra and by X-ray crystallographic determination.† Reductive removal of the phenylseleno group from **9** using Raney nickel in ethanol at 50° afforded the ketoester (**10**) in 91% yield. Selective reduction of the ester functional group in **10** to produce **11** was achieved by protection of the carbonyl group as its enolate using LDA followed by treatment with $LiAlH_4$ (66% yield).[12] Conversion of **11** to the primary selenide (**12**) using NPSP/^{n}Bu$_3$P[13] followed by Raney nickel deselenation gave the tricyclic ketone (**13**) in 52% overall yield (Scheme 2). Compound **13** was identical in all respects to previously synthesized material,[4] and has been used by several groups as the immediate precursor for hirsutene (**1**) synthesis. In an effort to develop a more expedient route to **13**, the selenide (**9**) was selectively reduced to the hydroxyketo selenide (**14**) in 66% yield using the LDA/$LiAlH_4$ method. Treatment of **14** with NPSP/^{n}Bu$_3$P afforded the bis-selenide (**15**) (63%), and subsequent Raney nickel reduction provided **13** (Scheme 2). Conversion of **13** to hirsutene (**1**) using methylenetriphenylphosphorane has been previously reported to proceed in 70% yield.[7] In our hands this reaction was extremely capricious and consequently we sought a much more reliable alternative. The best of these proved to be the use of CH_2Br_2/$TiCl_4$/Zn[14] which afforded hirsutene (**1**) in essentially quantitative yield. The spectral properties of this material were identical in all respects to those of authentic (±)-hirsutene.‡ On heating a sample of **1** under vacuum a smooth conversion to *endo*-hirsutene[4f] (**16**) could also be achieved.

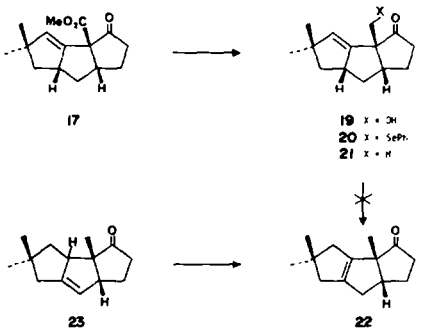
In order to increase the overall yield of hirsutene (**1**) methods for elaborating the *cis-syn-cis*-isomer (**8**) to **1** were investigated. Oxidation of **8** to the corresponding selenoxide followed by *syn*-elimination readily provided the unsaturated keto-ester (**17**) in 95% yield.

† We thank Dr D. J. Williams, Department of Chemistry, Imperial College, for these studies.

‡ We thank Professor P. D. Magnus, Indiana University, U.S.A., for providing authentic spectra of hirsutene for comparison purposes.

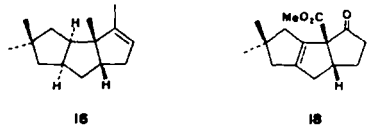


Scheme 1.



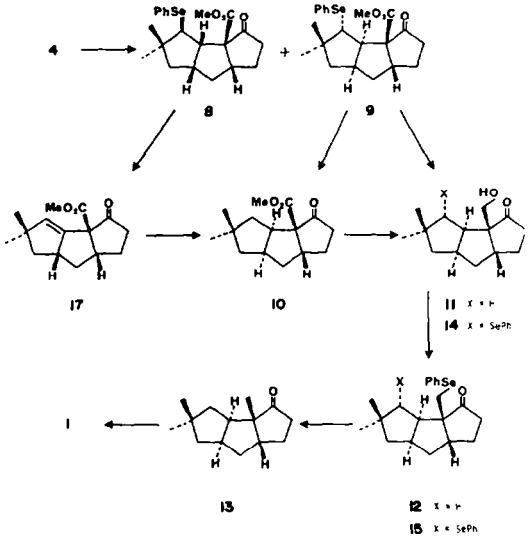
Scheme 3.

Attempts, with a variety of reagents, to isomerize the double bond in **17** to the tetra-substituted endocyclic position (**18**) and hence hydrogenation to the correct *cis-anti-cis* arrangement as in **10**, following the



literature precedence, failed.[4f] Partial success, however, was realized under reductive rearrangement conditions[15] ($Pd/C/H_2/HCl$) when **17** gave **10** directly in 35% yield (Scheme 2). As a consequence both of the cyclization products **8** and **9** function as precursors for the synthesis of hirsutene.

In another approach the unsaturated keto-ester (**17**) was selectively reduced to the hydroxyketone (**19**) using $LDA/LiAlH_4$ (68%). Compound **19** was readily converted into the selenide (**20**) with $NPSP/^nBu_3P$ (60%) which could be deselenated under the usual conditions with Raney nickel to afford **21** (82%). However, once again various attempts to isomerize the double bond to **22** were unsuccessful. This result was disappointing as a related unsaturated compound (**23**) was easily converted to **22**, and hence **13**, by treatment with $RuCl_3$[4f] (Scheme 3).



Scheme 2.

Nevertheless the route to (±)-hirsutene described above not only demonstrates the effectiveness of the organoselenium-mediated cyclization reaction in synthesis but it also highlights several other reactions in which selenium plays a key role in functional group manipulation. The overall yield of hirsutene from **4** using this selenium-based protocol is 20%, which compares very favourably with all previous syntheses.

EXPERIMENTAL

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer 298 spectrometer for solutions in $CHCl_3$ unless otherwise stated. ^{1}H-NMR spectra were recorded at 60 MHz using a Varian EM 360A, or at 250 MHz using a Bruker WH250 spectrometer, for solutions in deuteriochloroform with tetramethylsilane as internal standard. Mass spectra were obtained using a V.G. Micromass 7070 B spectrometer. Solvents were dried using standard methods. Chromatography was performed on MN-Silica gel 60 (230–400 mesh) under pressure.

Preparation of 4,4-dimethylcyclopent-2-enyl methanol. To a mixture of potassium t-butoxide (22.4 g, 0.2 mol), diisopropylamine (28.0 ml, 1.0 equiv.) and hexamethylphosphoramide (35.8 ml, 1.0 equiv.) in tetrahydrofuran (500 ml), cooled to −78°, was added dropwise n-butyllithium (128 ml, 1.53 M in pentane, 1.0 equiv.) over 10 min. The resulting orange–yellow solution of KDA–HMPA was stirred at −78° for 20 min and the ester (**7**) (23.1 g, 0.15 mol, 0.75 equiv.) was added over 10 min. After 40 min the yellow anion was quenched by the rapid addition of concentrated hydrochloric acid (17.3 ml, 1.0 equiv.) in THF (50 ml), stirred for 2–3 min and poured into a mixture of ether (1.0 l) and saturated ammonium chloride solution (500 ml). The ethereal layer was washed with water (7 × 500 ml), extracted with brine (1 × 100 ml) and concentrated to approx. 300 ml *in vacuo*. After drying, the solution was added dropwise to a suspension of lithium aluminium hydride (5.7 g, 0.15 mol) in ether (50 ml) at 0° and stirred at room temperature for 1 hr. The mixture was recooled to 0° and treated with hydrochloric acid (4 M) until the solids redissolved. The ethereal layer was washed with water (100 ml), saturated sodium bicarbonate solution (100 ml) and then worked up to give the crude alcohol (> 95% pure by ^{1}H-NMR) as a pale yellow oil (16.2 g, 86%). Distillation gave pure *4,4-dimethylcyclopent-2-enyl methanol* as a colourless oil b.p. 53°/3 mmHg; IR (film) 3340 (br), 3019, 2950, 2860, 1460, 1358, 1048, 1024, and 757 cm^{-1}; δ (250 MHz) 5.62 (1H, dd, J = 5.5, 2.5 Hz, C<u>H</u>=CH), 5.50 (1H, dd, J = 5.5, 2.0 Hz, CH=C<u>H</u>), 3.57 (1H, dd, J = 12, 6.5 Hz, —C<u>H</u>H—O), 3.53 (1H, dd, J = 12, 6.5 Hz, —CH<u>H</u>—O), 2.98 (1H, m, CH), 1.85 (1H, dd, J = 12, 8 Hz), 1.39 (1H, dd, J = 12, 6.5 Hz), 1.10 (3H, s), and 1.04 (3H, s); *m/z* 126 (M^+), 111, and 108. (Found: C, 75.78; H, 11.21. $C_{18}H_{14}O$ requires: C, 76.14; H, 11.18%.)

Preparation of 4,4-dimethylcyclopent-2-enylmethyl bromide (**5**). To a rapidly stirred solution of triphenylphosphine (35.2 g,

0.13 mol) and dry DMF (9.8 g, 10.4 ml, 1.0 equiv.) in benzene (250 ml) was added bromine (21.5 g, 6.9 ml, 1.0 equiv.) dropwise over 3–4 min without cooling. The exothermic reaction reached approx. 60° and rapidly became viscous as triphenylphosphine oxide and the Vilsmeier salt $Me_2N{=}CHBr^+Br^-$ were precipitated. The vigorously stirred reaction mixture was allowed to cool to room temperature over 45 min, giving a buff-coloured suspension of Vilsmeier salt. The neat alcohol from the previous step (15.4 g, 0.91 equiv.) was added dropwise to the mixture over 3–4 min.

After 3 hr the reaction mixture was poured into ether (250 ml) and washed with water (3 × 150 ml). Following washing with brine (150 ml) the solution was concentrated to a small volume and the mixture triturated with pet. ether (250 ml). The solid was filtered, washed with pet. ether and the combined solution evaporated to give a crude oil. Distillation of the residue gave the *bromide* (**5**) as a colourless oil (13.6 g, 59%), b.p. 49°/7 mmHg; IR (film) 3020, 2950, 2860, 1460, 1445, 1355, 1265, and 1209 cm^{-1}; δ (250 MHz) 5.66 (1H, dd, J = 5.5, 2 Hz, —CH=CH—), 5.50 (1H, dd, J = 5.5, 2 Hz, —CH=CH—), 3.39 (1H, dd, J = 10, 6 Hz, CHH—Br), 3.32 (1H, dd, J = 10, 4 Hz, CHH—Br), 3.20 (1H, m, CH), 1.97 (1H, dd, J = 13, 8.5 Hz), 1.40 (1H, dd, J = 13, 7 Hz), 1.12 (3H, s), and 1.05 (3H, s); *m/z* 190, 188 (M^+ ^{79}Br), and 109 (M − Br). (Found: C, 51.08; H, 7.06. $C_8H_{13}Br$ requires: C, 50.81; H, 6.93%.)

Preparation of 2-carbomethoxy-2-phenylselenylcyclopentanone. Phenylselenylchloride (21.6 g, 0.11 mol) was dissolved in dichloromethane (500 ml), cooled to 0° and treated with pyridine (9.9 ml, 1.2 equiv.). After 15 min 2-carbomethoxycyclopentanone (14.5 g, 0.9 equiv.) was added, and the reaction stirred at 0° for 90 min and then allowed to warm to room temperature. The reaction was poured into 10% aqueous hydrochloric acid (400 ml) and the organic phase was separated and washed with saturated sodium hydrogen carbonate solution (100 ml). Evaporation of the solvent gave 2-carbomethoxy-2-phenylselenylcyclopentanone as a yellow oil (30.5 g, 100%); IR (film) 3080, 2980, 1750, 1730, 1440, 1225, 1136, and 1000 cm^{-1}; δ (60 MHz) 7.8–7.0 (5H, m), 3.75 (3H, s), and 2.8–1.6 (6H, m); *m/z* 298 (M^+), 266.

Preparation of 2-carbomethoxycyclopent-2-enone (**6**). The selenide from the previous step (5.0 g, 16.8 mmol), dissolved in dichloromethane (350 ml) was added dropwise over 0.5 hr, with vigorous stirring, to hydrogen peroxide (6.5 ml, *ca* 28%, 3 equiv.) at 0°. After stirring for a further 0.5 hr at room temperature the reaction was worked up to give the enone (**6**) as an unstable light-brown oil (2.04 g, 96%); IR (film) 2950, 1750, 1720, 1620, 1437, 1340, 1290, and 1218 cm^{-1}; δ (60 MHz) 8.40 (1H, t, J = 2 Hz, CH=C(CO_2Me)CO), 3.86 (3H, s, CO_2Me), 2.95–2.35 (4H, m, CH_2CH_2CO): (lit.[10] δ 8.38 (1H, t, J = 2.5 Hz), 3.92 (3H, s), and 2.70 (4H, m).

Preparation of 2-carbomethoxy-3-(4',4'-dimethylcyclopent-2-enylmethyl)cyclopentanone (**4**). The bromide (**5**) (9.2 g, 48.6 mmol) was added dropwise to a suspension of magnesium (1.3 g, 1.1 equiv.) in THF (45 ml). When the Grignard reagent had formed the resulting grey solution was added dropwise to copper(I) bromide–dimethylsulphide complex (5.4 g, 0.54 equiv.) suspended in THF (90 ml) at −50°. The Grignard precipitated at −50° but on warming slowly to −30° the solids dissolved over 0.5 hr and the dark brown cuprate was formed. The enone (**6**) (3.5 g, 0.51 equiv.) was added at −30° and after 20 min the mixture was allowed to reach room temperature and stirred for a further 0.5 hr. The resulting black mixture was poured into ether (300 ml) and saturated ammonium chloride solution (200 ml), the ethereal layer extracted once more with ammonium chloride solution (100 ml) and then worked up to give a crude yellow oil. Chromatography (ether gradient to 5% in pet. ether) gave **4** as a colourless oil (3.5 g, 58%); IR (film) 3030, 2945, 2860, 1756, 1724, 1458, 1432, 1275, and 1250 cm^{-1}; δ (250 MHz) 5.52 (1H, dd, J = 5.5, 2.5 Hz, —CH=CH—), 5.47 (1H, dd, J = 5.5, 2 Hz, —CH=CH—), 3.76 (3H, s, CO_2Me), 2.84 (1H, d, J = 11.5 Hz, $COCHCO_2Me$), 2.78 (1H, d, J = 11.5 Hz, >CH—C—CO_2Me), 2.65 (1H, m, >CH—CH=C), 2.52–2.20 (3H, m), 1.89 (1H, ddd, J = 12.5, 8, 4.5 Hz), 1.76–1.32 (3H, m), 1.23 (1H, dd, J = 12.5, 7 Hz), 1.09 (3H, s), and 1.01 (3H, s); *m/z* 250 (M^+). (Found: C, 72.01; H, 9.03. $C_{15}H_{22}O_3$ requires: C, 71.97; H, 8.86%.)

Preparation of cis-anti-cis-1β-carbomethoxy-4,4-dimethyl-3α-phenylselenotricyclo[6.3.0.0^{2,6}]undecan-11-one (**9**) *and cis-syn-cis-1β-carbomethoxy-4,4-dimethyl-3β-phenylselenotricyclo[6.3.0.0^{2,6}]undecan-11-one* (**8**). The β-ketoester (**4**) (3.5 g, 14.0 mmol) was dissolved in dichloromethane (150 ml) containing NPSP (4.6 g, 1.1 equiv.), cooled to 0° and treated with tin tetrachloride (14.0 ml, 1.0 M in dichloromethane, 1.0 equiv.). The mixture was allowed to reach room temperature and stirred for 2.5 hr. The mixture was poured into ether (400 ml) and saturated sodium bicarbonate solution (250 ml), and the ethereal layer was separated and extracted with sodium hydroxide solution (1.0 M, 2 × 100 ml). After drying, removal of the solvent gave a crude yellow oil (6 g, approx. 100%) which after careful chromatography (300 g silica gel H, with 3% ether in pet. ether) gave the *cis-anti-cis-selenide* (**9**) (2.5 g, 45%) as colourless crystals, m.p. 106–108°; IR (film) 3040, 2940, 2855, 1745, 1720, 1575, and 1450 cm^{-1}; δ (250 MHz) 7.62 (2H, m, SePh), 7.22 (3H, m, SePh), 3.61 (3H, s, CO_2Me), 3.27 (1H, m, C—8H), 3.21 (1H, d, J = 10.5 Hz, >CH—SePh), 3.05 (1H, dd, J = 10.5, 10 Hz, C—2H), 2.56 (1H, m, C—6H), 2.31 (2H, m), 2.05 (1H, dddd, J = 14, 10.5, 8, 6 Hz), 1.81 (2H, m), 1.67 (1H, m), 1.20 (2H, m), 0.97 (3H, s, C—CH_3), and 0.74 (3H, s, C—CH_3); *m/z* 406 (M^+), 249 (M − SePh) (found: C, 62.30; H, 6.47; $C_{21}H_{26}O_3Se$ requires: C, 62.22; H, 6.46%), and the *cis-syn-cis-selenide* (**8**) (2.5 g, 45%) as colourless crystals, m.p. 109–112°; IR ($CHCl_3$) 3040, 2940, 2860, 1745, 1725, 1580, and 1460 cm^{-1}; δ (250 MHz) 7.73 (2H, m, SePh), 7.21 (3H, m, SePh), 3.81 (1H, d, J = 11 Hz, CH—SePh), 3.67 (3H, s, CO_2Me), 3.50 (1H, dd, J = 11, 11 Hz, C—2H), 3.08 (1H, dddd, J = 11.5, 7.5, 7.5, 1.5 Hz, C—8H), 2.75 (1H, m, C—6H), 2.51 (2H, m), 2.18 (1H, ddd, J = 14, 7.5, 7.5 Hz), 2.06 (1H, m), 1.81 (2H, m), 1.03 (3H, s, C—CH_3), and 0.82 (3H, s, C—CH_3); *m/z* 406 (M^+), 249 (M^+ − SePh). (Found: C, 62.17; H, 6.44. $C_{21}H_{26}O_3Se$ requires: C, 62.22; H, 6.46%.)

Preparation of cis-anti-cis-1β-carbomethoxy-4,4-dimethyltricyclo[6.3.0.0^{2,6}]undecan-11-one (**10**). The *cis-anti-cis*-selenide (**9**) (2.37 g, 5.8 mmol) was dissolved in absolute ethanol (100 ml). Raney nickel (10.7 g wet weight approx. 4.5 weight equiv.) was added and the rapidly stirred suspension was brought to 50°. After 2 hr the reaction mixture was cooled and allowed to settle. The supernatant was carefully decanted, the nickel extracted with hot ethanol (2 × 50 ml) and the combined ethanolic solution evaporated to give a red oil. Chromatography of the residue (silica gel, 2% ether pet. ether) gave **10** (1.33 g, 91%) as colourless crystals, m.p. 67.5–69; IR ($CHCl_3$) 2940, 2860, 1747, 1720, 1460, and 1240 cm^{-1}; δ (250 MHz), 3.69 (3H, s, CO_2Me), 3.20 (2H, m, C—8H and C—2H), 2.59 (1H, m, C—6H), 2.35 (2H, m), 2.19 (1H, m), 1.82–1.54 (4H, m), 1.35 (1H, ddd, J = 14, 11, 9.5 Hz), 1.06 (2H, m), 1.01 (3H, s), and 0.89 (3H, s); *m/z* 250 (M^+). (Found: C, 72.21; H, 8.97. $C_{15}H_{22}O_3$ requires: C, 71.97; H, 8.86%.)

Preparation of cis-anti-cis-4,4-dimethyl-1β-hydroxymethyltricyclo[6.3.0.0^{2,6}]undecan-11-one (**11**). To a solution of diisopropylamine (240 mg, 335 μl, 2.37 mmol) in THF (5 ml) at room temperature was added n-butyllithium (1.6 ml, 1.5 M in pentane, 1.0 equiv.) dropwise and the mixture stirred for 10 min. The resulting LDA solution was cooled to −78° and the ketone (**10**) (300 mg, 0.5 equiv.) in THF (10 ml) was added dropwise over 3–4 min. After 40 min at this temperature, lithium aluminium hydride (68.5 mg, 1.5 mol equiv.) was added to the solution via a solid addition tube and the reaction stirred at −25° to −20° for 1.5 hr. The suspension was then syringed into rapidly stirred hydrochloric acid (1.0 M, 50 ml) at room temperature and the mixture was extracted with ether (3 × 50 ml). The combined ethereal layers were washed with saturated sodium bicarbonate solution (25 ml), dried and the solvent removed to give crude oil which upon chromatography (ether gradient to 6% in pet. ether) gave **11**

(143 mg, 66%) as a pale yellow oil, b.p. 85°/0.04 mmHg; IR (film), 3430 (br), 2940, 2870, 1730, and 1465 cm^{-1}; δ (250 MHz), 3.75 (1H, dd, J = 11.5, 7 Hz, CHH—O), 3.60 (1H, d, J = 11.5 Hz, CHH—O), 2.76 (1H, m, C—2H), 2.60 (2H, m, C—6H and C—8H), 2.37 (2H, m), 2.01 (2H, m), 1.77–1.50 (5H, m), 1.29 (1H, dd, J = 11.5, 11.5 Hz), 1.08 (1H, m), 1.06 (3H, s) and 0.91 (3H, s); *m/z* 222 (M^+). (Found: C, 75.54; H, 9.91. $C_{14}H_{22}O_2$ requires: C, 75.63; H, 9.97%.)

Preparation of cis - anti - cis - 4,4 - dimethyl - 1β - phenylselenomethyltricyclo[6.3.0.0^{2,6}]*undecan - 11 - one* (**12**). The β-hydroxyketone (**11**) (143 mg, 0.64 mmol) was dissolved in THF (5 ml) containing NPSP (36 mg, 1.2 equiv.) and tri-n-butylphosphine (240 mg, 300 μl, 1.2 equiv.) was added. The reaction was stirred at room temperature for 2 hr and then syringed slowly into vigorously stirred pet. ether (70 ml). The supernatant was decanted carefully from the white precipitate and the solid washed with pet. ether (2 × 10 ml). The combined petroleum solution was washed successively with 1 M hydrochloric acid in methanol (5 ml), sodium hydroxide solution (2.0 M aq. solution 5 ml) (5 ml) dried and solvent removed to give a yellow oil. Chromatography (1% ether in pet. ether) afforded **12** (145 mg, 62%) as colourless crystals, m.p. 50–52°; IR (film) 3060, 2940, 2840, 2870, 1735, 1580, 1480, 1465 and 1440 cm^{-1}; δ (250 MHz) 7.47 (2H, m, SePh), 7.22 (3H, m, SePh), 3.08 (1H, d, J = 12 Hz, CH—SePh), 3.05 (1H, d, J = 12 Hz, CH—SePh), 2.82 (1H, m, C—2H), 2.55 (1H, m, C—8H), 2.56 (1H, m, C—6H), 2.35 (2H, m), 2.06 (1H, m), 1.74–1.48 (6H, m), 1.29 (1H, dd, J = 11, 11 Hz), 1.08 (1H, m), 1.07 (3H, s), and 0.91 (3H, s); *m/z* 362 (M^+), 205 (M − SePh). (Found: C, 66.45; H, 7.24. $C_{20}H_{26}OSe$ requires: C, 66.47; H, 7.25%.)

Preparation of cis - anti - cis - 4,4 - dimethyl - 1β - methyltricyclo[6.3.0.0^{2,6}]*undec - 11 - one* (**13**). The selenide (**12**) (125 mg, 0.35 mmol) was dissolved in absolute ethanol (10 ml) and stirred with Raney nickel (625 mg wet weight, 5 weight equiv.) at 45° for 20 min. The solution was decanted from the nickel and the metal extracted with hot ethanol (10 ml). Evaporation of the combined ethanolic solution and chromatography (1% ether in pet. ether) of the residue provided **13** (59.5 mg, 83%) as colourless crystals, m.p. 39–41° (lit.[4a] m.p. 44–45°); δ (250 MHz) 2.80 (1H, m, C—2H), 2.51 (1H, dddd, J = 17, 8.8, 8.5, 3.5 Hz, C—8H), 2.42–2.18 (3H, m), 2.00 (1H, dddd, J = 12.5, 9.5, 8.6 Hz), 1.78–1.53 (3H, m), 1.50–1.32 (2H, m), 1.18 (1H, dd, J = 11, 11 Hz), 1.03 (3H, s), 1.01 (1H, m), 0.94 (3H, s), and 0.90 (3H, s) (lit.[4a] δ 3.1–0.73 (13H, m), 1.07 (3H, s), 0.95 (3H, s), and 0.92 (3H, s)); *m/z* 206 (M^+). (Found: M^+ 206.1518. $C_{14}H_{22}O$ requires: M^+ 206.1514.)

Preparation of cis - anti - cis - 4,4 - dimethyl - 1β - hydroxymethyl - 3α - phenylselenotricyclo[6.3.0.0^{2,6}]*undecan - 11 - one* (**14**). To a solution of diisopropylamine (0.018 ml, 0.128 mmol) in THF (1 ml) at 0° was added n-butyllithium (0.086 ml of a 1.48 N solution in hexane, 0.128 mmol). After stirring at this temperature for 15 min the mixture was cooled to −78° and a solution of the keto-ester (**9**) (43.4 mg, 0.107 mmol) in THF (0.5 ml) was added dropwise. After a further 30 min at −78° lithium aluminium hydride (6.1 mg, 0.160 mmol) was added in one portion. The mixture was stirred at −30° for 2 hr, re-cooled to −50°, and a saturated aqueous solution of ammonium chloride (2 ml) was added in one portion with vigorous stirring. The mixture was extracted with ether (3 × 20 ml) and the combined extracts were washed with saturated sodium bicarbonate solution (2 × 20 ml), water (20 ml) and worked up to give an oil. Chromatography (silica gel using 10% ether acetate–pet. ether) afforded the *hydroxyketone* (**14**) (26.6 mg, 66%) as a solid, m.p. 132–135° (sublimed at 120°/0.030 mmHg); IR ($CHCl_3$) 3420 (br), 1735, and 1580 cm^{-1}; δ (250 MHz) ($CDCl_3$) 7.65 (2H, m, ArH), 7.28 (3H, m, ArH), 3.88 (1H, dd, J = 12, 3 Hz, CHHOH), 3.62 (1H, dd, J = 12, 11 Hz, CHHOH), 3.26 (1H, dd, J = 11, 3 Hz, OH), 3.00 (1H, m, CHSePh), 2.64–2.23 (4H, m), 2.02 (1H, m), 1.90–1.52 (4H, m), 1.31 (1H, m), 1.08 (1H, m, CH—5α), 1.02 (S, 3H, C—4βMe), and 0.95 (S, 3H, C—4αMe): *m/z* 378 (M^+). (Found: M^+ 378.1100. $C_{20}H_{26}O_2Se$ requires: M^+ 378.1097.)

Preparation of cis - anti - cis - 4,4 - dimethyl - 1β - phenylselenomethyl - 3α - phenylselenotricyclo - [6.3.0.0^{2,6}]undecan - 11 - one (**15**). A mixture of n-phenylselenophthalimide (34 mg, 0.110 mmol) and tri-n-butylphosphine (0.028 ml, 0.110 mmol) in THF (2 ml) was stirred at room temperature for 10 min. To the resulting solution was added a solution of the alcohol (**14**) (21.1 mg, 0.056 mmol) in THF (1 ml) and stirring was continued for 2 hr. Work-up as above gave an oil which was chromatographed (silica gel using pet. ether) to give the *bis-selenide* (**15**) (18.1 mg, 63%) as an oil; IR ($CHCl_3$) 3040, 3020, 1735, and 1577 cm^{-1}; δ (250 MHz) ($CDCl_3$) 7.62 (4H, m, ArH), 7.19 (6H, m, ArH), 3.22 (1H, d, J = 12 Hz, CHHSePh), 3.15 (1H, d, J = 10 Hz, CHHSePh), 3.03 (1H, d, J = 12 Hz, CHHSePh), 2.90–2.58 (3H, m, H-8, 10), 2.50–1.78 (2H, m, H-2, 6), 1.72–1.46 (4H, m), 1.14 (1H, m), and 1.00 (6H, s, C—4 Me_2), 0.96 (1H, m); *m/z* 518 (M^+). (Found: M^+ 518.1457. $C_{26}H_{30}OSe_2$ requires: M^+ 518.1461.)

Deselenation of the bis-selenide (**15**). A mixture of the bis-selenide (**15**) (15 mg, 0.029 mmol) and Raney nickel (*ca* 50 mg) in ether (4 ml) was stirred at room temperature under an atmosphere of hydrogen for 2 hr. The metal was filtered off and the filtrate was concentrated to an oil. Chromatography on silica using 10% ether–pet. ether gave the norketone (**13**) (4.9 mg, 82%) as an oily solid (identical to material prepared earlier).

Preparation of (±)*-hirsutene.* A solution of titanium tetrachloride (1.15 ml, 0.010 mol) in dichloromethane (2 ml) was added dropwise at −40° to a vigorously stirred suspension of zinc dust (2.87 g, 0.044 mol) in dibromomethane (1.01 g, 0.014 mol) and THF (25 ml). The mixture was allowed to warm to 0° and was stirred at this temperature for 18 hr. A portion (0.5 ml) of the resulting slurry was added dropwise at 0° to a stirred solution of the norketone (**13**) (10 mg, 0.048 mmol) in dichloromethane (1 ml). After 1.5 hr at 0° the mixture was poured into saturated aqueous sodium bicarbonate (20 ml) and extracted with ether (3 × 30 ml). The combined ether portions were washed with water (2 × 10 ml), dried and concentrated to an oil. Chromatography on silica using pet. ether afforded (±)-hirsutene (**1**) (9.6 mg, 98%) as an oil; IR (film) 2940, 2860, 1645, 1460, and 1360 cm^{-1}; δ (250 MHz) 4.83 (1H, brs), 4.78 (1H, brs), 2.68–2.43 (3H, m), 2.22–2.1 (1H, m), 1.82–1.61 (2H, m), 1.55–1.4 (6H, m), 1.25–1.08 (1H, m), 1.05 (3H, s), 0.97 (3H, s), and 0.93 (3H, s); *m/z* 204 (M^+); identical to previously synthesised material.

Preparation of cis - syn - cis - 1β - carbomethoxy - 4,4 - dimethyltricyclo[6.3.0.0^{2,6}]*undec - 2 - en - 11 - one* (**17**). A solution of the *cis-syn-cis*-selenide (**8**) (0.72 g, 1.8 mmol) in dichloromethane (50 ml) was stirred vigorously with hydrogen peroxide (10 ml, approx. 28% soln, 45 equiv.) at room temperature for 2 hr. The organic layer was worked up by the standard procedure and the residue chromatographed (ether–pet. ether) to provide **17** (0.39 g, 88%) as a colourless oil; IR (film) 2970, 2880, 1750, 1730, and 1460 cm^{-1}; δ (250 MHz) 5.55 (1H, d, J = 2.5 Hz, C=CH), 3.71 (3H, s, CO_2Me), 3.38 (1H, m, C—8H), 3.21 (1H, m, C—6H), 2.46 (2H, m), 2.2 (2H, m), 1.90 (1H, dd, J = 12, 7 Hz), 1.79 (1H, dddd, J = 12.5, 8, 2.5, 2.5 Hz), 1.30 (1H, dd, J = 12, 8.5 Hz), 1.11 (3H, s, C—CH_3), 1.09 (3H, s, C—CH_3), and 0.98 (1H, ddd, J = 12, 10.5, 10.5 Hz); *m/z* 249 (M^+). (Found: C, 72.40; H, 8.16. $C_{15}H_{20}O_3$ requires: C, 72.55; H, 8.12%.)

Reductive isomerization of the olefin (**17**). A solution of the unsaturated keto-ester (**17**) (40 mg, 0.161 mmol) in absolute ethanol (75 ml) containing 10% palladium on carbon (40 mg) and 3 N hydrochloric acid (0.10 ml) was stirred under an atmosphere of hydrogen for 4 hr. The catalyst was filtered off and the filtrate was concentrated to give an oil. Capillary GLC analysis indicated the presence of three products in a ratio of 40:30:30, the major component of which was the keto-ester (**10**). Separation was achieved by reversed-phase HPLC on a Zorbax ODS column using 20% water–methanol to give pure **10** (14 mg, 35%) (identical to material prepared earlier).

Preparation of cis - syn - cis - 4,4 - dimethyl - 1β - hydroxymethyltricyclo[6.3.0.0^{2,6}]*undec - 2 - en - 11 - one* (**19**). To a solution of diisopropylamine (0.49 ml, 3.07 mmol) in THF (5 ml) at 0° was added n-butyllithium (2.32 ml of a 1.32 M soln

in hexane, 3.07 mmol). After stirring at this temperature for 15 min the mixture was cooled to −78° and a solution of the keto-ester (**17**) (0.431 g, 1.74 mmol) in THF (2 ml) was added dropwise. After a further 30 min at −78° lithium aluminium hydride (0.13 g, 3.42 mmol) was added in one portion. The mixture was stirred at −30° for 2 hr, cooled to −50°, and a saturated aqueous solution of ammonium chloride (5 ml) was added in one portion with vigorous stirring. The mixture was extracted with ether (3 × 40 ml) and the combined extracts were washed with saturated sodium bicarbonate solution (2 × 30 ml), water (40 ml) and worked up to give an oil. Chromatography (silica gel using 20% ethyl acetate–pet. ether) gave the *keto-alcohol* (**19**) as an oil (0.262 g, 68%), distilled at 65°/0.06 mmHg; IR ($CHCl_3$) 3600, 3040, 1725, and 1605 cm^{-1}; δ (250 MHz) ($CDCl_3$) 5.35 (1H, d, J = 5 Hz, H-3), 3.81 (1H, d, J = 11 Hz, CHHOH), 3.58 (1H, d, J = 11 Hz, CHHOH), 3.14 (1H, m), 2.96 (1H, m), 2.53 (1H, m), 2.22 (3H, m), 1.88 (2H, m), 1.65 (1H, brs, OH), 1.28 (1H, m), 1.07 (3H, s, C—4Me), 1.06 (1H, m), and 1.04 (3H, s, C—4Me); *m/z* 220 (M^+). (Found: M^+ 220.1451. $C_{14}H_{20}O_2$ requires: M^+ 220.1463.) (Found: C, 76.08; H, 9.32. $C_{14}H_{20}O_2$ requires: C, 76.32; H, 9.15%.)

Preparation of cis - syn - cis - 4,4 - dimethyl - 1β - phenylselenomethyl - 3α - phenylselenotricyclo - [6.3.0.0^{2,6}]undec - 2 - en - 11 - one (**20**). A mixture of n-phenylselenophthalimide (92 mg, 0.30 mmol) and tri-n-butylphosphine (76 mg, 0.30 mmol) in THF (10 ml) was stirred at room temperature for 10 min. To the resulting solution was added the alcohol (**19**) (34 mg, 0.15 mmol) in THF (1 ml) and stirring was continued for 2 hr. The THF was removed *in vacuo* and the residue was triturated with pet. ether. Chromatography of the triturate (silica gel using 10% ether–pet. ether) gave the *phenylselenide* (**20**) (32.8 mg, 60%) as an oil; IR ($CHCl_3$) 3060, 3040, 1732, and 1578 cm^{-1}; δ (250 MHz) ($CDCl_3$) 7.50 (2H, m, ArH), 7.24 (3H, m, ArH), 5.32 (1H, d, J = 5 Hz, H-3), 3.26 (1H, d, J = 12 Hz, CHHSePh), 3.20 (1H, d, J = 12 Hz, CHHSePh), 3.20 (1H, m, H-6), 2.98 (1H, m), 2.49 (1H, m), 2.20 (2H, m), 2.05 (1H, m), 1.86 (1H, dd, J = 13, 7 Hz), 1.69 (1H, ddt), 1.25 (1H, dd, J = 13, 9 Hz), 1.04 (3H, s, C—4Me), 1.00 (3H, s, C—4Me), and 1.00 (1H, m); *m/z* 360 (M^+). (Found: M^+ 360.0980. $C_{20}H_{24}OSe$ requires: M^+ 360.0993.)

Preparation of cis - syn - cis - 4,4 - dimethyl - 1β - methyltricyclo[6.3.0.0^{2,6}]*undec - 2 - en - 11 - one* (**21**). A mixture of the phenylselenide (**20**) (33 mg, 0.092 mmol) and Raney nickel (*ca* 0.20 g) in absolute ethanol (10 ml) was stirred at room temperature for 45 min. The metal was filtered off and the filtrate was concentrated to give an oil. Chromatography (silica gel using 10% ether–pet. ether) gave the *ketone* (**21**) (15.4 mg, 82%) as an oil; IR ($CHCl_3$) 1728 cm^{-1}; δ (250 MHz) ($CDCl_3$) 5.23 (1H, d, J = 5 Hz, H-3), 3.19 (1H, m), 2.64 (1H, m), 2.48 (1H, m), 2.18 (2H, m), 1.99 (1H, m), 1.87 (1H, m), 1.68 (1H, m), 1.25 (2H, m), 1.18 (3H, s, C—1Me), 1.06 (3H, s, C—4Me), and 1.04 (3H, s, C—4Me); *m/z* 204 (M^+). (Found: M^+ 204.1518. $C_{14}H_{20}O$ requires: M^+ 204.1514.)

Acknowledgement—We acknowledge the S.E.R.C. and Pfizer Ltd., Central Research, Sandwich, Kent, for financial support of this work.

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