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A TOTAL SYNTHESIS OF (±)-GIBBERELLIN A_{12} VIA METHYL (±)-7,16-DIOXO-17-NORKAURAN-19-OATE†

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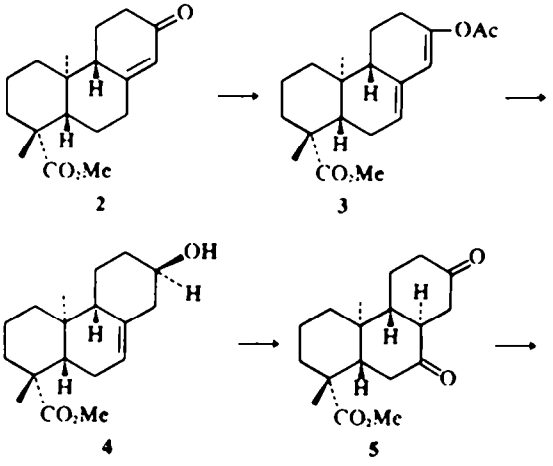
Abstract—A formal total synthesis of (±)-gibberellin A_{12} (1) was achieved by employing methyl (±)-7,16-dioxo-17-norkauran-19-oate (13) as a relay compound.

The gibberellins are biosynthesized from geranylgeranyl pyrophosphate (A) by cyclization to kaurene via a tricyclic intermediate (B) followed by oxidation to C and its ring contraction to give C_{20}-gibberellins such as gibberellin A_{12} (1).[1] The existing total syntheses of both the C_{19}-gibberellins[4] and a C_{20}-gibberellin (gibberellin A_9),[5] however, were not carried out along this biosynthetic pathway. In continuation of our work, we focused our attention on the synthesis of gibberellin A_{12}(1) mimicking the biogenetical pattern. As our starting material we employed a racemic tricyclic enone (2)‡[6] which served as an intermediate in our synthesis of (±)-kaur-16-en-19-oic acid (D)[7] and (±)-steviol (E).[8]

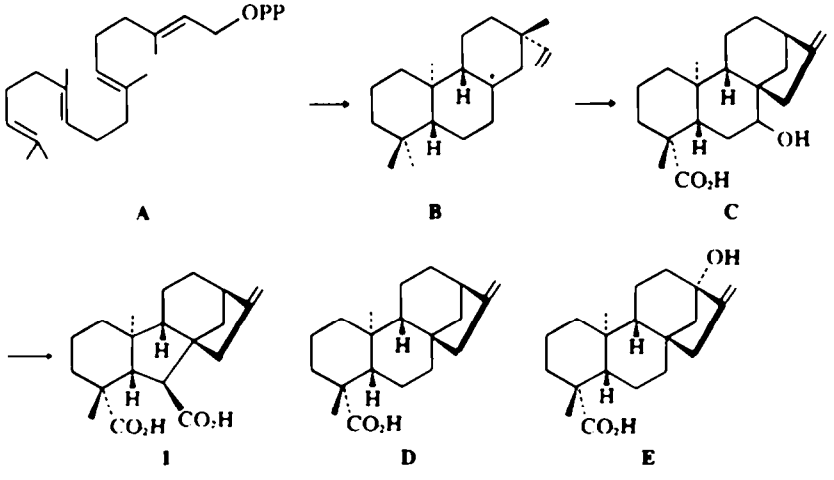
The enone (2) was converted to an enol acetate (3).[9,10] This was reduced to give a hydroxy ester (4).[11] Hydroboration–oxidation followed by CrO_3 oxidation of 4 gave a diketo ester (5) in 27% overall yield from 2. Reaction of 5 with *p*-tolyloxymethylene triphenylphosphorane[12] afforded a mixture of products, 6, 7 and 8, from which the desired mono-condensation product at C-13 (6) was isolated. The structure of this compound was deduced from its later conversion to methyl (±)-7,16-dioxo-17-norkauran-19-oate (13). The enol ether (6) was

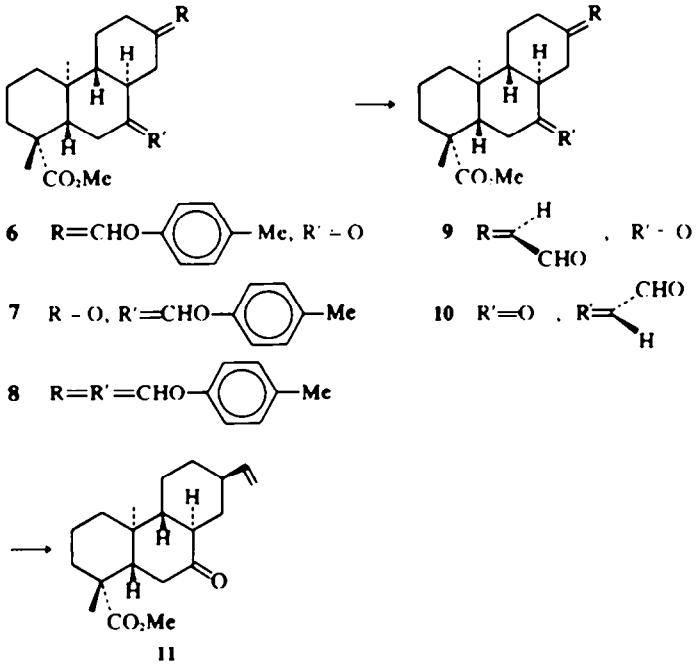


hydrolyzed to give a keto aldehyde (9).[13] Since 9 was recovered unchanged when treated with NaOMe/MeOH, an equatorial configuration was assigned to its formyl group. The position isomer 7 gave an isomeric aldehyde 10 upon acid hydrolysis. This was also recovered unchanged when equilibrated with NaOMe/MeOH. Owing to the difficulty in isolating 6, the overall yield of the keto aldehyde (9) from the diketone (5) was 4.5%, although no effort was made to optimize the reaction condition. The Wittig methylenation of the keto aldehyde (9) proceeded fairly regioselectively and afforded the desired keto olefin (11) in 60% yield. The minor product was a diene (11, CH_2 instead of O at C-7) obtained in 10% yield. The keto olefin

†Synthesis of Substances related to Gibberellins—XXVI. The experimental part of this work was mainly taken from the doctoral dissertation of I.T., March 1976. Part XXV, K. Mori, *Agric. Biol. Chem.* (*Tokyo*) **36**, 2519 (1972).

‡Although the formulas depicted represent only one enantiomer, they are taken to mean a racemate in the case of totally synthetic material.





(**11**) corresponds to the tricyclic intermediate (**B**) in the biosynthetic scheme.

The next stage was the cyclization to a tetracyclic compound (**13**). Our strategy was to effect the intramolecular alkylation at C-8 as the key step.† The keto olefin (**11**) was converted into the corresponding bromohydrin (**12a**) by treatment with N-bromosuccinimide in aqueous dimethoxyethane. The structure **12a** was assigned on the basis of Overton's rosenonolactone work dealing with a similar system.[14] Protection of the OH group as THP ether gave **12b** as a gummy mixture of two stereoisomers at C-15. This was heated with NaH in xylene to effect cyclization. The product was chromatographed over alumina and the fractions exhibiting the IR absorption due to THP group were combined and treated with *p*-TsOH in MeOH to remove the THP protecting group. The resulting tetracyclic alcohol was oxidized with the Jones CrO_3. Purification of the product by preparative TLC afforded crystalline diketo ester (**13**) in 16% yield from the keto olefin (**11**). The recrystallized racemic diketone (**13**) was identical with the optically active authentic sample (**13**)[15] in its spectral (IR, NMR and MS) and chromatographic (GLC and TLC) properties. This diketo ester (**13**) corresponds to the tetracyclic intermediate (C) in the biosynthetic scheme.

The remaining steps to gibberellin A_{12} were previously investigated by the British workers in their efforts to convert *ent*-kaurenolides into gibberellins. They converted the optically active diketone (**13**) into 7,16-diketo lactone (**14**) by bromination followed by treatment with LiCl/DMF.[16] On the other hand *ent*-7-oxokaurenolide (**15**) was transformed into the tosylate of *ent*-7α-hydroxykaurenolide (**16**) which was treated with base to effect the contraction of ring B with the extrusion of a formyl group.[16] The resulting aldehyde was finally converted to gibberellin A_{12} (**1**) by Cross and Norton in the course of their structure determination of **1**.[17] Therefore the only remaining step to complete the formal total synthesis of gibberellin A_{12} (**1**) was the regioselective methylenation of the diketo lactone (**14**) to *ent*-7-oxokaurenolide (**15**). In order to achieve this goal, we prepared **14** from *ent*-7β,18-dihydroxykaurenolide (**17a**) by modification of the published procedures.[18] *ent*-7β,18-Dihydroxykaurenolide (**17a**) was tosylated as described to give **17b**.[18] This was treated with OsO_4–$NaIO_4$ to give a nor-ketone (**18**) in 60% yield.[19] This tosylate (**18**) was heated with NaI in methyl ethyl ketone to give an iodide (**19**) in 81% yield. Reduction of **19** over Raney Ni W-7 gave a crystalline dihydroxy lactone (**20**) in a quantitative yield.[20] The β-configuration was tentatively assigned to the OH group at C-16 assuming that the less hindered side of the molecule was adsorbed on the catalyst surface. Oxidation of **20** with the Jones CrO_3 gave the desired diketo lactone (**14**). The Witting reaction between **14** and methylene triphenylphosphorane was regioselective. The resulting *ent*-7-oxokaurenolide (**15**)[15,21] was identical with an authentic sample on the basis of IR, NMR, MS, GLC, TLC and m.m.p. This completed the formal total synthesis of (±)-gibberellin A_{12} in view of the omission of the optical resolution of the racemic diketone (**13**).[22]

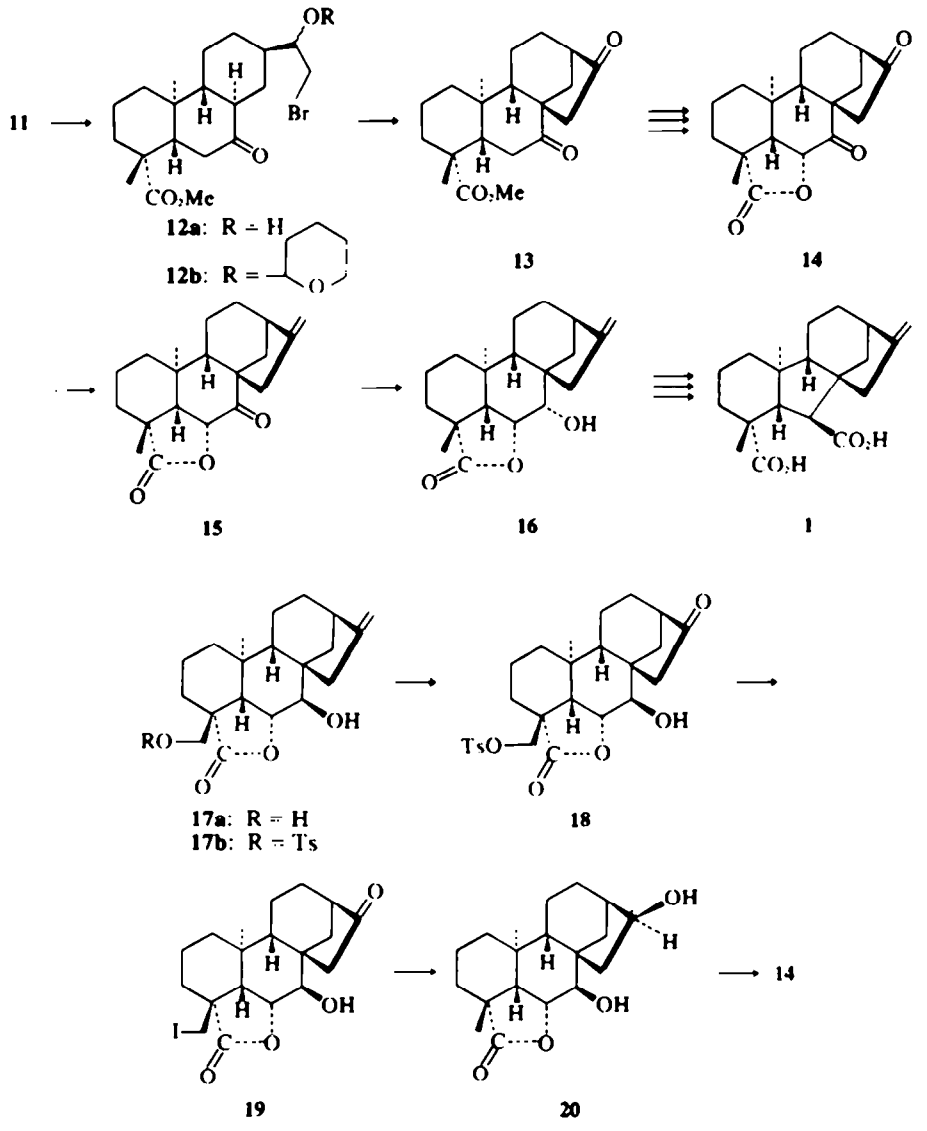
†This cyclization was studied extensively employing model compounds derived from cholesterol as described in the doctoral dissertation of I. Takemoto.

EXPERIMENTAL

All m.ps were uncorrected. IR spectra refer to Nujol mulls for solid samples and films for gums unless otherwise stated. NMR spectra were recorded at 100 MHz in $CDCl_3$ with TMS as an internal standard.

Methyl (±) - 13 - *acetoxy* - 5β,9β,10α - *podocarpa* - 7, 13 - *dien* - 19 - *oate* (**3**)

AcCl (147 ml) and pyridine (16.5 ml) were added to a soln of **2** (20 g) in Ac_2O (367 ml) and the mixture was heated under reflux for 2.5 hr in an atm of N_2. The mixture was filtered, washed with Ac_2O and the filtrate was evaporated to dryness under reduced pressure. Trituration of the residue with MeOH afforded **3** (27 g), which was recrystallized from EtOAc–MeOH, m.p. 119–120°; ν_{max} 1750, 1725, 1675, 1650, 1240, 1220, 1195, 925 cm^{-1}; δ 0.65 (3H, s), 1.19



(3H, s), 2.10 (3H, s), 3.65 (3H, s), 5.55 (1H, m), 5.78 (1H, br. s); λ_{max} 235 nm (ϵ 18,000, EtOH). (Found: C, 71.93; H, 8.30. $C_{20}H_{28}O_4$ requires: C, 72.26; H, 8.49%).

Methyl (±)-13β-*hydroxy*-5β,9β,10α-*podocarp*-7-*en*-19-*oate* (**4**)

To an ice-cooled soln of **3** (25 g) in EtOH (300 ml) and dioxan (75 ml), $NaBH_4$ (17 g) dissolved in EtOH (250 ml) and water (60 ml) was added dropwise at 1–5°. After stirring for 2 hr at room temp., the mixture was heated for 20 min at 50–53°. The excess $NaBH_4$ was destroyed by dil. HCl, and the product was taken into EtOAc. The EtOAc soln was washed with water, sat $NaHCO_3$ aq and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo* to give 12.6 g (63% from **2**) of **4**, which was recrystallized from EtOAc–light petroleum, m.p. 120–121°, ν_{max} 3300, 1720, 820 cm^{-1}; δ 0.62 (3H, s), 1.20 (3H, s), 1.74 (1H, s), 3.50 (1H, m, $W_{1/2}$ = 22 Hz), 3.69 (3H, s), 5.52 (1H, m); MS: *m/e* 292 (M^+), 291, 274, 259. (Found: C, 73.51; H, 9.67. $C_{18}H_{28}O_3$ requires: C, 73.93; H, 9.65%).

Methyl (±)-7,13-*dioxo*-5β,8α,9β,10α-*podocarpan*-19-*oate* (**5**)

Diborane (120 ml of 1 M soln in THF) was added slowly to an ice-cooled soln of **4** (5.9 g) in THF (40 ml) under N_2. After the addition, the flask was kept for 3.5 hr at 2–8°. The organoborane was oxidized by the addition of a soln of NaOH (5 g) in water (15 ml), followed by the dropwise addition of 30% H_2O_2 (36 ml). The mixture was heated for 1 hr at 60°. The product was taken into ether. The ether soln was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo* to afford diol. Jones CrO_3 (15 ml) was added to an ice-cooled soln of the diol in acetone (100 ml) and the mixture was left to stand at room temp. for 1 hr. MeOH was added to destroy the excess of the oxidant. After the removal of the solvents *in vacuo*, the residue was diluted with water and extracted with EtOAc. The EtOAc soln was washed with water, sat $NaHCO_3$ aq and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo* to give **5** (2.6 g, 42%; 27% overall yield from **2**). Recyrstallization from EtOAc–light petroleum gave rods, m.p. 141–142°, ν_{max} 1725, 1715, 1225, 1165 cm^{-1}; δ 0.93 (3H, s), 1.22 (3H, s), 3.73 (3H, s); MS: *m/e* 306 (M^+), 275, 246; GLC (5% SE-30, 0.75 m × 3 mm i.d., at 244°; Carrier gas He, 2.2 kg/cm^2) Rt 4.3 min. (Found: C, 70.68; H, 8.72. $C_{18}H_{26}O_4$ requires: C, 70.56; H, 8.55%).

Methyl (±)-13-p-*tolyloxymethylene*-7-*oxo*-5β,8α,9β,10α-*podocarpan*-19-*oate* (**6**)

Procedure A. NaH (2.4 g, 50% dispersion in mineral oil) was washed with light petroleum to remove the mineral oil and DMSO (25 ml) was introduced via a syringe. The mixture was heated at 75–80° until the evolution of H_2 ceased. To a soln of *p*-tolyloxymethyltriphenylphosphonium chloride (6.6 g) in DMSO (40 ml) was added the soln of methylsulfinyl carbanion (3.6 ml) in DMSO via a syringe under N_2. The resulting red soln of the ylide was stirred at room temp. for 10 min. A soln of **5** (2 g) in dry THF (30 ml) was added quickly to a stirred phosphorane soln. The

stirring was continued for 3 hr at room temp. The mixture was poured into ice-water and extracted with n-hexane. The extract was washed with 75% MeOH aq, water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue (3.2 g) was chromatographed over neutral alumina (Woelm, activity grade II, 32 g, 25 × 1.6 cm) in n-hexane. Elution with n-hexane gave divinyl ether **8** (342 mg, 10%), ν_{max} 1730, 1680, 1615, 1510, 1250, 1230, 1160, 1020, 810 cm^{-1}; δ 0.74 (3H, s), 1.20 (3H, s), 2.29 (6H, s), 3.62 (3H, s), 6.20 (2H, br. s), 6.75–7.25 (8H, m); MS: *m/e* 514 (M^+). Fractions eluted with EtOAc-n-hexane (3:97) gave a crystalline **6** (165 mg, 6.3%), which was recrystallized from EtOAc-light petroleum, m.p. 198–199°, ν_{max} 1725, 1705, 1620, 1520, 1385, 1245, 1230, 1165, 1105, 820 cm^{-1}; δ 0.88 (3H, s), 1.20 (3H, s), 2.36 (3H, s), 3.76 (3H, s), 6.19 (1H, s), 6.80–7.14 (4H, m). (Found: C, 76.01; H, 8.22. $C_{26}H_{34}O_4$ requires: C, 76.06; H, 8.34%). Subsequent fractions afforded a mixture of **6** and **7** (748 mg, 28%, *ca.* 1:1). Recrystallization of **7** from EtOAc-light petroleum gave prisms, m.p. 130.5–131°, ν_{max} 1730, 1715, 1660, 1605, 1580, 1505, 1380, 1240, 1230, 1160, 1100, 815 cm^{-1}; δ 0.78 (3H, s), 1.24 (3H, s), 2.32 (3H, s), 3.68 (3H, s), 6.01 (1H, s), 6.82–7.16 (4H, m) (Found: C, 76.14; H, 8.28. $C_{26}H_{34}O_4$ requires: C, 76.06; H, 8.34%). The aqueous layer left after n-hexane extraction was re-extracted with ether. The ether soln was washed with water and sat NaCl aq, dried ($MgSO_4$) and evaporated *in vacuo*. The residue (2.1 g) was chromatographed over netural alumina (Woelm, activity grade II, 21 g, 18 × 1.5 cm). Elution with EtOAc-n-hexane (3:97–1:9) yielded starting diketone **5** (332 mg, 17%).

Procedure B. To a suspension of *p*-tolyloxymethyltriphenylphosphonium chloride (1 g) in dry THF (10 ml), cooled at −40°, was added to a soln of n-BuLi in n-hexane (1.07 N, 1.0 ml) via a syringe under N_2. The resulting mixture was warmed to 0° and stirred for 15 min. To the red ylide soln, cooled again to −40°, was added quickly a soln of **5** (306 mg) in dry THF (10 ml). The mixture was stirred at −43 ~ −37° for 30 min, poured into ice-water, and extracted with n-hexane. The extract was washed with 75% MeOH aq, water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue (416 mg) was chromatographed over neutral alumina (Woelm, activity grade II, 5 g, 7 × 1.1 cm). Elution with EtOAc-n-hexane (5:95) gave crystalline **6** (53 mg). Subsequent fractions were the mixture of **6** and **7** (61 mg, 15%, *ca.* 1:1). Further elution gave crystalline **7** (23 mg, 6%). Both **6** and **7** were proved to be identical with those samples obtained in procedure A. Elution with EtOAc-n-hexane (5:95–10:0) gave **5** (12 mg). The aqueous layer left after n-hexane extraction was re-extracted with ether. The ether soln was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue (551 mg) was chromatographed over neutral alumina (Woelm, activity grade II, 6 g, 8.5 × 1.1 cm). Elution with EtOAc-n-hexane (1:9) gave crystalline unreacted **5** (60 mg, total 72 mg, 24%).

Methyl (±)-13β-*formyl*-7-*oxo*-5β,8α,9β,10α-*podocarpan*-19-*oate* (**9**)

To a soln of **6** (311 mg) in ether (100 ml) was added 70% $HClO_4$ (10 ml) and the mixture was heated under reflux for 1.5 hr under N_2. The mixture was poured into ice-water. After cautious neutralization with Na_2CO_3 under ice cooling, the products were extracted with ether. The ether soln was washed with 2 N-NaOH aq, water and sat NaCl aq, dried ($MgSO_4$). The ether was evaporated under reduced pressure to give the crystalline **9** (152 mg, 64%). Recrystallization from EtOAc-light petroleum gave plates, m.p. 125–126°, ν_{max} 2720, 1735, 1720, 1710, 1160 cm^{-1}; δ 0.90 (3H, s), 1.20 (3H, s), 3.76 (3H, s), 9.69 (1H, s). (Found: C, 71.46; H, 8.71. $C_{26}H_{36}O_4$ requires: C, 71.22; H, 8.81%).

Treatment of **9** *with* NaOMe. A soln of **9** (32 mg) in MeOH (3 ml) was treated with NaOMe (3 mg) at room temp. for 1 hr. The mixture was poured into ice-water and extracted with ether. The extract was washed with water and sat NaCl aq and dried ($MgSO_4$). Evaporation of ether gave the crystalline aldehyde **9** (25 mg). This sample showed an IR spectrum, NMR spectrum and a TLC (silica gel G, EtOAc-n-hexane (1:1): R_f 0.51) completely identical with those of the the starting material.

Methyl (±)-7α-*formyl*-13-*oxo*-5β,8α,9β,10α-*podocarpan*-19-*oate* (**10**)

In a similar manner, **7** (23 mg) afforded **10** (12 mg, 70%), which was recrystallized from EtOAc-light petroleum, m.p. 111–113°, ν_{max} 2750, 1735, 1725, 1715, 1250, 1180, 1165 cm^{-1}; δ 0.70 (3H, s), 1.20 (3H, s), 3.68 (3H, s), 9.59 (1H, d, J = 2 Hz). (Found: C, 71.17; H, 8.84. $C_{26}H_{36}O_4$ requires: C, 71.22; H, 8.81%). Similarly treatment of **10** with NaOMe gave the starting material.

Methyl (±)-7-*oxo*-13β-*vinyl*-5β,8α,9β,10α-*podocarpan*-19-*oate* (**11**)

A mixture of NaH (2.4 g, 50% dispersion in mineral oil) and dry DMSO (25 ml) was heated at 75–80° until the evolution of H_2 ceased. To a soln of triphenylmethylphosphonium bromide (0.5 g) in dry DMSO (10 ml) was added the soln of methylsulfinyl carbanion (0.5 ml) in DMSO via a syringe under N_2. The resulting ylide soln was stirred at room temp. for 10 min. A soln of **9** (261 mg) in dry THF (10 ml) was added to the phosphorane soln. The mixture was stirred at room temp. for 4 hr and poured into ice-water. The products were taken into n-hexane. The extract was washed with 75% MeOH aq, water and sat NaCl aq, dried ($MgSO_4$) and condentrated *in vacuo*. The residue (272 mg) was chromatographed over silica gel (Mallinckrodt, 3 g, 9 × 1.1 cm). Elution with light petroleum gave diene **11** (CH_2 instead of O at C-7) (25 mg, 10%) which was recrystallized from EtOAc-MeOH, m.p. 90.5–91°, ν_{max} 3080, 1730, 1645, 1240, 1160, 1000, 990, 910, 890, 880 cm^{-1}; δ 0.76 (3H, s), 1.23 (3H, s), 3.74 (3H, s), 4.64 (1H, m), 4.78 (1H, m), 4.9–5.3 (2H, m), 5.7–6.2 (1H, m). (Found: C, 79.92; H, 10.04. $C_{21}H_{32}O_2$ requires: C, 79.70; H, 10.19%). Elution with EtOAc-n-hexane (3:97) gave **11** (155 mg, 60%), which was recrystallized from MeOH, m.p. 79–79.5°, ν_{max} 3080, 1730, 1710, 1640, 1220, 1160, 990, 900 cm^{-1}; δ 0.90 (3H, s), 1.18 (3H, s), 3.76 (3H, s), 4.9–5.2 (2H, m), 5.6–6.1 (1H, m). (Found: C, 75.46; H, 9.48. $C_{26}H_{38}O_3$ requires: C, 75.43; H, 9.50%). The aqueous layer left after n-hexane extraction was re-extracted with ether. The extract was washed with water and sat NaCl aq and dried ($MgSO_4$). Evaporation of ether gave the mixture of unreacted aldehyde **9** and triphenylphosphine oxide, which was chromatographed over silica gel to afford pure **9** (27 mg, 10%).

Methyl (±)-7,16-*dioxo*-17-*norkauran*-19-*oate* (**13**)

Keto olefin **11** (62 mg) was stirred with N-bromosuccinimide (77 mg) in DME-water (8:1; 4 ml) at room temp. for 6 hr. The mixture was poured into ice-water and extracted with ether. The ether soln was washed with sat $NaHCO_3$ aq, water, and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo* to give **12a** (85 mg), as a mixture of almost inseparable C-15 epimers, ν_{max} (film) 3400, 1735, 1715, 1165 cm^{-1}. A soln of **12a** (85 mg) in dry ether (10 ml) was mixed with dihydropyran (1 ml) and *p*-toluenesulfonic acid (63 mg) and stirred overnight at room temp. Then the soln was washed with K_2CO_3 aq, dried (K_2CO_3) and concentrated *in vacuo* to give oily **12b**, ν_{max} 1735, 1715, 1160, 1130, 1080, 1035, 970 cm^{-1}. The THP ether **12b**, as a mixture of C-15 epimers, was dissolved in *p*-xylene (20 ml), and added to NaH (95 mg, 50% dispersion in mineral oil) under N_2. The mixture was stirred at 31° for 1 hr, heated gradually to the reflux temperature and then refluxed for 1.5 hr. MeOH was added to destroy the excess of NaH. The products were taken into ether. The ether soln was washed with K_2CO_3 aq, dried (K_2CO_3) and evaporated *in vacuo*. The residue (372 mg) was chromatographed over neutral alumina (Woelm, activity grade II, 4 g, 5 × 1.1 cm) to give the following fractions. No. 1–7 (EtOAc-n-hexane: 0:10 ~ 5:95): hydrocarbon (249 mg). No. 8–14 (EtOAc-n-hexane 5:95 ~ 1:4): THP ether (74 mg), ν_{max} 1735, 1715, 1165, 1130, 1080, 1040 cm^{-1}. No. 15–18 (EtOAc-n-hexane 1:4 ~ 10:0): gum. The THP ether obtained from No. 8–14 was treated with *p*-toleunesulfonic acid (60 mg) in MeOH (5 ml) at room temp. for 2 hr. The mixture was diluted with water and extracted with ether. The ether soln was washed with sat $NaHCO_3$ aq, water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo* to afford an alcohol (60 mg), ν_{max} 3400, 1730, 1715, 1150, 1120, 1070 cm^{-1}. The resulting alcohol was dissolved in acetone (5 ml) and oxidized by Jones CrO_3 reagent (8 N, 0.2 ml). MeOH was added to destroy the excess of the

oxidant. After the removal of the solvents *in vacuo*, the residue was diluted with water and extracted with ether. The extract was washed with sat $NaHCO_3$ aq, water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by preparative TLC (silica gel, ether–n-hexane 1:1) to afford crystalline diketone **13** (10 mg, 16% from **11**), which was recrystallized from acetone to give prisms, m.p. 132–133°C, ν_{max} (CHCl₃ soln) 1740 (vs), 1722 (s), 1705 (vs), 1316 (w), 1156 (m), 1138 (w), 1120 (w), 1100 (w), 982 (w) cm^{-1}; ν_{max} (KBr) 1751 (s), 1715 (vs), 1701 (vs), 1465 (w), 1455 (w), 1430 (w), 1315 (w), 1263 (w), 1224 (m), 1186 (w), 1165 (w), 1152 (m), 1135 (w), 1120 (w), 1095 (w), 1040 (w), 980 (w), 950 (w) cm^{-1}. (*cf.* The optically active **13**; ν_{max} (KBr) 1740 (vs), 1715 (s), 1698 (vs), 1475 (w), 1455 (w), 1430 (w), 1317 (w), 1288 (w), 1266 (w), 1245 (w), 1224 (m), 1188 (w), 1170 (w), 1153 (m), 1137 (w), 1119 (w), 1100 (w), 1090 (w), 1041 (w), 980 (w), 960 (w) cm^{-1}). δ 0.8–1.3 (2H), 1.08 (3H, s), 1.18 (3H, s), 1.3–2.1 (11H), 2.1–2.6 (3H), 2.6–2.9 (1H, 2.62, 2.66, 2.77, 2.79), 2.9–3.3 (2H, 2.97, 3.02, 3.12, 3.20, 3.26), 3.68 (3H, s); MS: *m/e* 332 (M^+, 62%), 272 (42%) 165 (25%), 149 (35%), 136 (26%), 109 (100%), 95 (31%), 79 (28%), 57 (27%), 55 (34%), 43 (34%), 41 (41%); GLC: (3% Silicone Gum SE-30, 0.75 m × 3 mm i.d., at 230°; Carrier gas N_2, 0.7 kg/cm^2) Rt 4.4 min. This sample showed an IR spectrum (in $CHCl_3$ soln), NMR spectrum, mass spectrum, gas chromatogram and TLC (silica gel, ether-n-hexane (4:1) R_f 0.46, benzene-EtOAc (1:4) R_f 0.62) completely identical with those of the optically active **13**.

ent-7β-*Hydroxy*-18-p-*tosyloxy*-*kaurenolide* (**17b**)

(−)-7,18-Dihydroxykaurenolide (**17a**, 1 g) was treated with *p*-toluenesulfonyl chloride (1.31 g) in pyridine (50 ml) at room temp. for 90 hr. The mixture was poured into ice-dil H_2SO_4 (250 ml) and the product was recovered in EtOAc. The extract was washed with ice-water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo* to afford **17b** (1.3 g, quantitative), which was recrystallized from benzene–light petroleum, m.p. 183–184° (lit.[18] 185–186°), ν_{max} 3540, 1760, 1660, 1595, 1200, 1185, 980, 970, 890, 815 cm^{-1}; δ 0.88 (3H, s), 1.90 (1H, s, –OH), 2.44 (3H, s), 4.00 (2H, s), 4.32 (1H, d, J = 7 Hz), 4.54 (1H, t, J = 7 Hz), 4.90 (1H, m), 5.04 (1H, m), 7.36 (2H, d, J = 8 Hz), 7.77 (2H, d, J = 8 Hz).

ent-6α,7β-*Dihydroxy*-18-p-*tosyloxy*-17-*norkauran*-19-*oic acid* 19→6α-lactone (**18**)

To a soln of **17b** (1.125 g) in THF (100 ml)–water (35 ml), OsO_4 (100 mg) was added. After stirring for 10 min, finely powdered $NaIO_4$ (3.6 g) was added portionwise. The mixture was stirred at room temp. for 16 hr and filtered. The filtrate was concentrated *in vacuo* to afford crystalline **18**, which was collected on a filter and washed with ether (550 mg). The mother liquor was extracted with EtOAc. The extract was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue (980 mg) was purified by filtration chromatography over alumina (Woelm, activity grade II, 10 g, 8 × 1.5 cm) to give crude **18** (392 mg). Crude **18** was chromatographed over silica gel (Mallinckrodt, 4 g, 7 × 1.5 cm). Elution with EtOAc–n-hexane (3:7–10:0) gave pure **18** (130 mg, total yield 680 mg, 60%), m.p. 256–258° (lit.[18] 255–257°), ν_{max} 3400, 1775, 1730, 1600, 1200, 1190, 820 cm^{-1}; δ (CDCl₃–DMSO-d_6) 0.90 (3H, s), 2.47 (3H, s), 4.00 (2H, s), 4.14 (1H, d, J = 7 Hz), 4.44 (1H, t, J = 7 Hz), 7.44 (2H, d, J = 8 Hz), 7.80 (2H, d, J = 8 Hz).

ent-6α,7β-*Dihydroxy*-18-*iodo*-16-*oxo*-17-*norkauran*-19-*oic acid* 19→6α-*lactone* (**19**)

The norketone **18** (589 mg), dry NaI (2 g) and dry methyl ethyl ketone (60 ml) were heated in a sealed tube at 140° for 31 hr. The mixture was filtered, the filtrate evaporated to dryness and the residue washed with water, MeOH, and ether, leaving crystals of **19** (456 mg, 81%), m.p. 268–271° (lit.[18] 269–272°), ν_{max} 3420, 1775, 1725 cm^{-1}; δ (CDCl₃–acetone-d_6) 0.88 (3H, s), 3.30 (2H, AB_q, J_{AB} = 10 Hz), 4.36 (1H, d, J = 7 Hz), 4.56 (1H, t, J = 7 Hz).

ent-6α,7β,16β-*Trihydroxy*-17-*norkauran*-19-*oic acid* 19→6α-*lactone* (**20**)

The iodide **19** (341 mg) dissolved in EtOH (160 ml) was stirred with Raney Ni W-7 (3.5 g) and $CaCO_3$ (0.35 g) at room temp. for 2.5 hr. The mixture was filtered. The filtrate was concentrated *in vacuo* to give crystalline diol **20** (248 mg, quantitative), m.p. 244–246°, ν_{max} 3300, 1765, 1095 cm^{-1}. δ (CDCl₃–acetone d_6) 0.80 (3H, s), 1.24 (3H, s), 2.8 (2H, br, –OH), 4.04 (1H, m, $W_{1/2}$ = 16 Hz), 4.30 (1H, d, J = 7 Hz), 4.56 (1H, t, J = 7 Hz). MS: *m/e* 320 (M^+, 17%), 302 (26%), 129 (80%), 109 (77%), 71 (58%), 57 (75%), 55 (78%), 43 (100%).

ent-6α-*Hydroxy*-7,16-*dioxo*-17-*norkauran*-19-*oic acid* 19→6α-*lactone* (**14**)

Jones CrO_3 reagent (8 N 1.6 ml) was added to an ice-cooled soln of **20** (320 mg) in acetone (100 ml) and the mixture was left to stand at room temp. for 1.5 hr. MeOH was added to destroy the excess of the oxidant. After the removal of the solvents *in vacuo*, the residue was diluted with water and extracted with EtOAc. The EtOAc soln was washed with sat $NaHCO_3$ aq, water and sat NaCl, dried ($MgSO_4$) and concentrated *in vacuo* to afford crystalline **14** (269 mg, 85%). Recrystallization from $CHCl_3$ gave prisms, m.p. 299–301° (lit.[14] 290–295°), ν_{max} 1775, 1740, 1710, 1210, 1105 cm^{-1}; δ 0.75 (3H, s), 1.32 (3H, s), 4.86 (1H, d, J = 7 Hz).

ent-7-*Oxokaurenolide* (**15**)

A suspension of triphenylmethylphosphonium bromide (814 mg) in dry THF (15 ml) was stirred in an atm of N_2 and treated with n-BuLi (1.3 N, 0.9 ml). The resultant phosphorane soln was stirred for 30 min, then the diketone **14** (72 mg) in dry THF (15 ml) was added dropwise. Stirring was continued for another hour. The mixture was poured into ice-water and extracted with EtOAc. The extract was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue (193 mg) was chromatographed over silica gel (Mallinckrodt, 2 g, 3.5 × 1.6 cm). Elution with EtOAc–n-hexane (0:10–1:2) gave crude crystalline **15** (40 mg), contaminated with a small amount of triphenylphosphine oxide. Crude **15** was collected on a filter and washed with ether to afford pure **15** (12 mg). Elution with EtOAc–n-hexane (1:2–10:0) gave unreacted diketone **14** (23 mg). Recrystallization of **15** from acetone–light petroleum gave needles, m.p. 265–266°. (lit.[11] 264–265°), ν_{max} 1780 (vs), 1705 (s), 1660 (w), 1222 (w), 1192 (w), 1150 (w), 1110 (m), 1082 (w), 1059 (w), 1018 (w), 940 (w), 930 (w), 885 (w) cm^{-1}; δ 0.70 (3H, s), 1.30 (3H, s), 4.86 (1H, d, J = 7 Hz), 4.88 (1H, m), 5.06 (1H, m); MS: *m/e* 314 (M^+, 84%), 278 (42%), 277 (58%), 147 (26%), 139 (28%), 137 (100%), 109 (47%), 105 (26%), 91 (40%), 77 (42%), 67 (35%), 55 (44%), 44 (79%), 41 (58%); GLC: SE-30, 0.75 m × 3 mm i.d., at 220°; Carrier gas N_2, 0.8 kg/cm^2) Rt 5.5 min. This sample showed IR, NMR, MS, GLC, TLC (silica gel EtOAc–n-hexane 1:1, R_f 0.46) and m.m.p. (265–266°) completely identical with those of the authentic sample of **15**.

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