Tetrahedron Vol. 41, No. 23, pp. 5653 to 5660, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00

SYNTHESIS OF ORYZALEXINS A, B AND C, THE DITERPENOIDAL PHYTOALEXINS ISOLATED FROM RICE BLAST LEAVES INFECTED WITH *PYRICULARIA ORYZAE*†

KENJI MORI* and MICHIRU WAKU‡
Department of Agricultural Chemistry, The University of Tokyo, Yayoi 1-1-1, Bunkyo-ku, Tokyo 113, Japan

(*Received in Japan* 19 *December* 1984)

Abstract—Naturally occurring enantiomers of three diterpenes isolated as phytoalexins from rice blast leaves were synthesized: (+)-oryzalexin A [*ent*-3β-hydroxyisopimara-8(14),15-dien-7-one, **1**], (+)-oryzalexin B [*ent*-7α-hydroxyisopimara-8(14),15-dien-3-one, **2**] and (+)-oryzalexin C [*ent*-isopimara-8(14),15-diene-3,7-dione, **3**]. Their antipodes were also synthesized.

In 1983 Akatsuka *et al.* isolated three new tricyclic diterpenes as the phytoalexins produced by rice plants (*Oryza sativa*) infected with the notorious parasitic fungus *Pyricularia oryzae* which causes rice blast disease.[2] They are oryzalexins A(**1**),[2] B(**2**)[3] and C(**3**).[3] The isolated amounts of these diterpenoidal phytoalexins were very small. Indeed only 1.5 mg of oryzalexin A(**1**) was isolated from *ca* 1.5 kg of the lesions obtained from 50 kg of the foliar part of rice plants infected with blast disease in the paddy field. Oryzalexin A significantly inhibits the germ tube elongation of *Pyricularia oryzae* at 40 ppm and completely inhibits its spore germination at 200 ppm.[2] Extensive spectral studies on these phytoalexins led to the structure proposal depicted in Fig. 1.[2,3] Owing to the potential utility of these isopimaradiene-type diterpenoidal phytoalexins in crop protection in Asian countries where rice is the most important crop, we undertook the total synthesis of oryzalexins A–C as well as their antipodes in order to evaluate their biological properties.

Our simple retrosynthetic analysis of the phytoalexins is shown in Fig. 1. (+)-*ent*-3β-Hydroxyisopimara-8(14),15-diene (**4a**) was chosen as the key intermediate, since its allylic oxidation at C-7 would furnish the target molecules.[3] Both the enantiomers of **4a** are known as natural products: (+)-**4a** was isolated from the heartwood of *Cleistanthus schlechteri*,[4] while (−)-**4a** was obtained from the heartwood of *Xylia dolabriformis*.[5] The enantiomers of **4a** would be prepared by the optical resolution of (±)-**4a**. The racemate, (±)-**4a**, would be synthesized without difficulty from the known tricyclic ketone, (±)-**5**,[6] whose preparation is an established process starting from the commercially available naphthalene derivative **6**.[7]

The synthesis of (±)-**4a** from **6** is shown in Fig. 2. According to the procedure of Cornforth and Robinson,[7] **6** was converted to (±)-**7**. For the final C-methylation step to give **7**, we used the enamine alkylation as reported previously.[8] Then (±)-**7** was converted to a tricyclic ketone (±)-**8** according to Ireland and Schiess[9] and Turner *et al.*[6] in 10.3% overall yield from **6** in five steps. Hydrogenation of (±)-**8** over Pd–C[6,9] gave, in 91.6% yield, a 2:1 mixture of the desired A/B *trans*-fused (±)-**9a** and the unwanted A/B *cis*-isomer (±)-**10a**. Recrystallization of the mixture from EtOH gave pure (±)-**9a**, which was demethylated with TMSCl and NaI[10] to give (±)-**9b**.[6] This was reduced with Li/NH_3 to give a C-3 eq. alcohol (±)-**11a**. Subsequently, the OH-3 group of (±)-**11a** was selectively protected as an acetate by transesterification with MeOAc and TsOH[11,12] to give (±)-**11b** in 79.4% overall yield from (±)-**9a**. Hydrogenation of (±)-**11b** over Raney Ni W-2 in EtOH was followed by Jones oxidation to give (±)-**5**. The yield of (±)-**5**, however, was disappointingly low (9%), mainly giving the undesired hydrogenolysis product. With Raney Ni W-7 as the catalyst, the yield of (±)-**5** was remarkably improved to 59.6%. We then explored a short-cut to avoid the separation of (±)-**9a** from the undesired (±)-**10a**, which was laborious and inefficient, yielding (±)-**9a** in an amount equivalent to *ca* one-third of the original mixture. Separation of the desired A/B-*trans* isomer from the A/B-*cis* isomer was assumed to be possible at a later stage. The mixture of (±)-**9a** and (±)-**10a** was processed as before to give a mixture of (±)-**11b** and (±)-**12b**, which was hydrogenated over Raney Ni W-7. Oxidation of the crude product with Jones CrO_3 was followed by chromatographic purification to give the desired (±)-**5**, m.p. 153°, in 49.3% yield based on the amount of the mixture at the start. The fate of the unwanted contaminant, (±)-**12b**, was to furnish an oily hydrogenolysis product (±)-**13** (21.0% yield), whose structure was supported by the spectral data [^{13}C-NMR: δ 81.0 (C—O), 128.9 (C=C), 132.3 (C=C), 170.7 (C=O); ^{1}H-NMR: δ 4.43 (1H, dd, J = 5 and 9 Hz, CHOAc), no olefinic proton was observable]. These two products were so readily separable by SiO_2 chromatography that the preparation of (±)-**5** was very much facilitated compared with Turner's process

† Part 23 in the series 'Diterpenoid Total Synthesis'. For Part 22, see K. Mori and M. Waku, *Tetrahedron* **40**, 305 (1984). This work was presented by K.M. at a seminar held at the University Chemical Laboratory, Cambridge, U.K. (24 September, 1984). The nomenclature used in this paper is that proposed by Rowe.[1]

‡ Research Fellow on leave from T. Hasegawa Co., Ltd. (1982–1985).

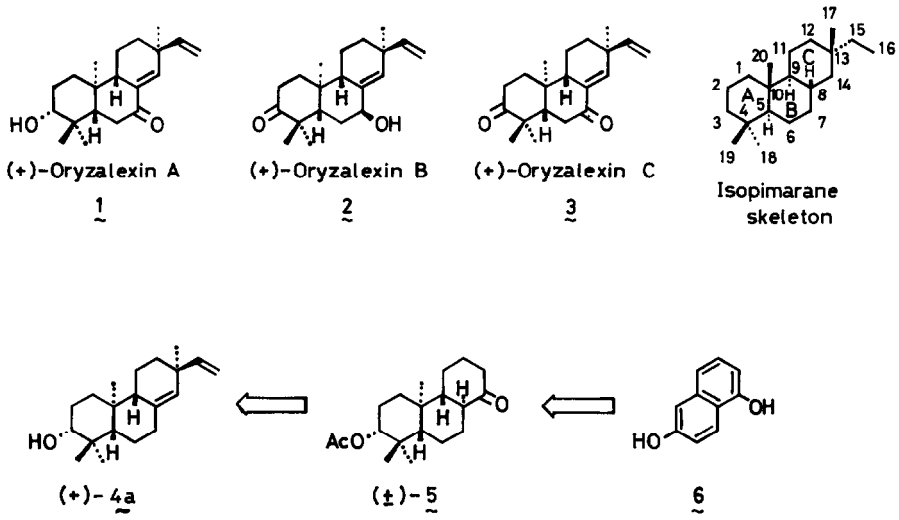

Fig. 1. Structures of oryzalexins A–C and their synthetic plan.

which gave a poor overall yield of (±)-**5** from (±)-**8** by Birch reduction of the aromatic C-ring.[6]

The next stage was the introduction of two substituents at C-13. For that purpose we followed the procedure developed by Ireland *et al.*[9,13] and used by us in the synthesis of (±)-4-episandaracopimaric acid.[14] Thus, (±)-**5** was formylated with HCO_2Et and NaOMe to give a crude formyl ketone. This was heated with *n*-BuSH in the presence of TsOH to give a mixture of (±)-**14a** and (±)-**14b**, the latter being the transesterification product during the formylation and the former the hydrolysis product thereof. Alkaline hydrolysis of (±)-**14b** gave an additional amount of (±)-**14a**, increasing its overall yield from (±)-**5** to 74.4%. Protection of the OH-3 group of (±)-**14a** as *t*-butyldimethylsilyl ether (±)-**14c** was followed by $NaBH_4$ reduction and removal of the *n*-butylthio protective group with $HgCl_2$–$CdCO_3$ to give (±)-**15**, m.p. 142–143°, in 84.7% overall yield from (±)-**14a**. Methylation of (±)-**15** was effected by quenching with MeI the K-enolate of (±)-**15** generated by treatment of (±)-**15** with $KOBu^t$ in *t*-BuOH for 4 min under reflux. Prolonged heating before quenching drastically decreased the yield of the methylation product (±)-**16**. GLC analysis and ^{1}H-NMR measurement of the stereoisomeric mixture (±)-**16** revealed the quasi-eq. CHO isomer (^{1}H-NMR: δ 9.39 = quasi-eq. CHO) to be the major isomer with *ca* 33% of the quasi-ax. CHO isomer (δ 9.49 = quasi-ax CHO). The mixture (±)-**16** was submitted to Wittig methylenation to give a stereoisomeric mixture, (±)-**17**, as a solid (m.p. 82.5–83°) in 71.9% yield from (±)-**15**. Desilylation of (±)-**17** with aq. HF in MeCN gave a stereoisomeric mixture of (±)-**4a** and (±)-**18**. Separation of these two isomers was achieved by chromatography over SiO_2–$AgNO_3$, since we had experience in the separation of an isopimaradiene derivative from the isomeric pimaradiene compound by Al_2O_3–$AgNO_3$ chromatography.[14] After the chromatographic separation (±)-**4a**, m.p. 232.5–234°, was obtained in 56% yield from (±)-**17**. The yield of (±)-**18**, m.p. 110–110.5°, was 33% from (±)-**17**. 400 MHz ^{1}H-NMR spectrum of (±)-**4a** was identical with the authentic spectrum of (−)-**4a** kindly provided by Drs S. Takeuchi and Y. Kono. The overall yield of (±)-**4a** from (±)-**8** was 8.5% in 14 steps or 0.88% from **6** in 19 steps.

The crucial next stage was the optical resolution of (±)-**4a** (Fig. 3). Our first attempt was the acylation of (±)-**4a** with 3β-acetoxyetienyl chloride[15] to give a diastereomeric mixture of esters. The mixture, however, could not be separated in our hands. We then employed (1*R*,4*R*,5*S*) - 4 - hydroxy - 6,6 - dimethyl - 3 - oxabicyclo[3.1.0]hexan - 2 - one[16] as the resolving agent, which had been used successfully in our pheromone synthesis.[17] The resulting diastereomers **4b** and **4b'** were separable by chromatography, however, they were so unstable in the presence of a trace amount of acid that their rigorous purification was quite difficult. The purified **4b** and **4b'** were treated separately with HCl–MeOH to remove the resolving agent, giving the enantiomers of **4a**. The best result obtained with this resolving agent was the preparation of 86.4% e.e. (+)-**4a** and 85.6% e.e. (−)-**4a'** as checked by HPLC analysis of the MTPA esters[18] **4c** and **4c'**. Our third and successful choice of resolving agent was (−)-camphanic acid.[19] Acylation of (±)-**4a** with (−)-camphanyl chloride yielded a mixture of **4d** and **4d'**, which was separated by chromatography in 39% and 45% yield, respectively, from (±)-**4a** to give **4d**, m.p. 232–233.5°, and **4d'**, m.p. 196.5–197.5°. Both **4d** and **4d'** were 100% pure as checked by their HPLC analyses. Hydrolysis of **4d** with K_2CO_3 yielded (+)-**4a**, m.p. 126–127°, $[\alpha]_D^{22}$ +13° ($CHCl_3$) [lit.[4] m.p. 126–127°, $[\alpha]_D$ +12.5° ($CHCl_3$)], in 87% yield. Similarly, **4d'** gave (−)-**4a'**, m.p. 127–128°, $[\alpha]_D^{22}$ −14° ($CHCl_3$) [lit.[5] m.p. 126.5–127.5°, $[\alpha]_D$ −19.5° ($CHCl_3$)], in 89% yield.

With pure enantiomers of **4a** available, we proceeded to the final stage of the conversion of **4a** to oryzalexins A–C. Prior to the oxidation, the OH-3 group of **4a** was protected as the corresponding acetate **4e**. Attempts to oxidize **4e** with various chromic acid reagents such as $K_2Cr_2O_7$–HOAc, $CrO_3 \cdot 2C_5H_5N$ or CrO_3·3,5-dimethylpyrazole[20] were uniformly unsuccessful. We then turned our attention to SeO_2 oxidation of (±)-**4e**.

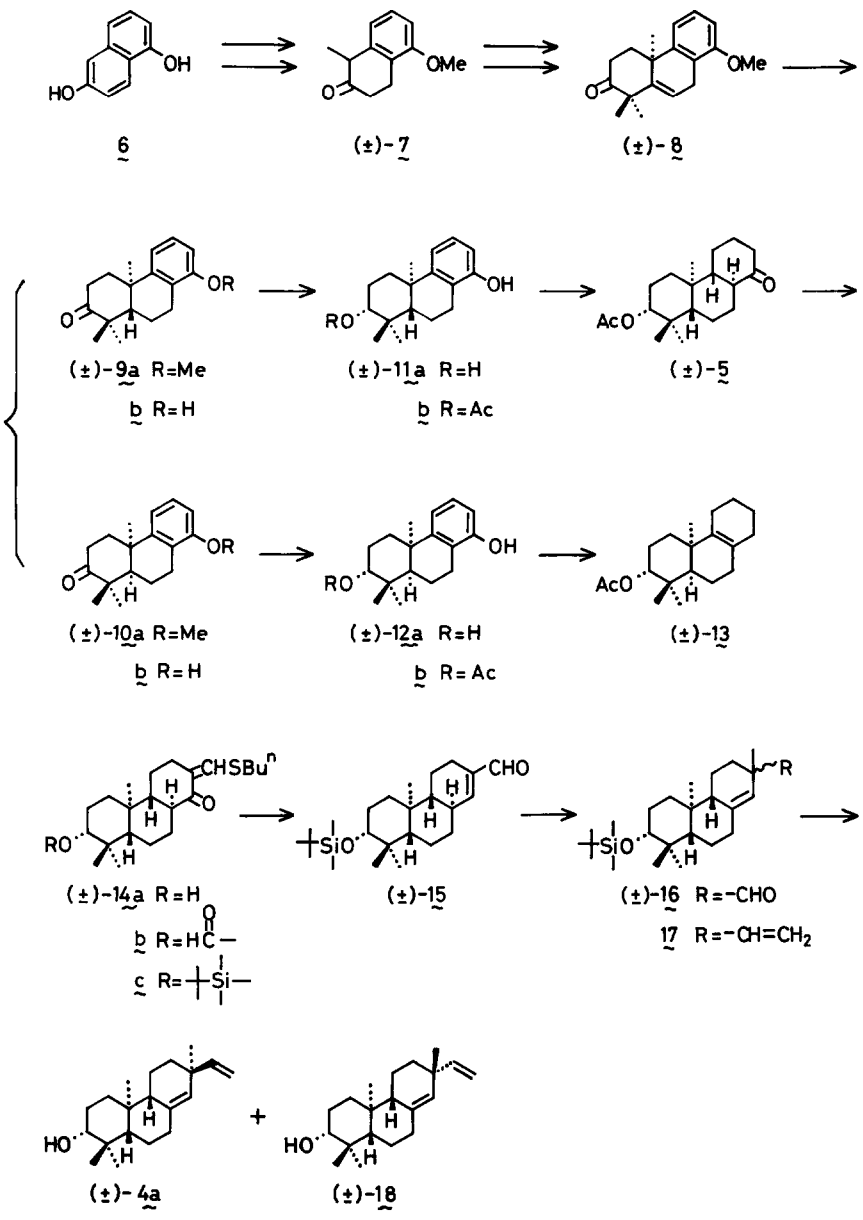

Fig. 2. Synthesis of (±)-3β-hydroxyisopimara-8(14),15-diene.

Under a variety of conditions, such as SeO_2–aq HOAc, SeO_2–*t*-BuOH or SeO_2–EtOH, there was obtained a mixture of many products more polar than (±)-**4e** from which pure (±)-**19a** could not be isolated. Eventually SeO_2 oxidation of (±)-**4e** in C_6H_6–aq HOAc at 65° for only 1.5 min was found to give (±)-**19a** in 49% yield. Alkaline hydrolysis of (±)-**19a** furnished (±)-**19b**, whose ^{1}H-NMR data were identical with those reported by Kono *et al.*[3] Once this was achieved (+)-**4e** was oxidized with SeO_2 to give **19a**. Oxidation of the OH-7 group of **19a** was successfully carried out with DMSO–Ac_2O,[21] and the product was hydrolysed with K_2CO_3–MeOH to give (+)-oryzalexin A(**1**), m.p. 170–171°, $[\alpha]_D^{23}$ +46° (MeOH) [lit.[2] $[\alpha]_D^{27}$ +20° (MeOH) with no reported m.p.], in 23% yield from (+)-**4a**. Similarly, unnatural (−)-oryzalexin A(**1'**), m.p. 170–171°, $[\alpha]_D^{23}$ −47° (MeOH), was also synthesized. The IR and ^{1}H-NMR spectra of our synthetic enantiomers of oryzalexin A(**1**) were identical with those of natural (+)-**1**. The overall yield of (+)-oryzalexin A(**1**) from **6** was 0.07% in 25 steps. For the synthesis of (+)-oryzalexin B(**2**), (+)-**4a** was oxidized with CrO_3 and the product treated with SeO_2. After chromatographic purification, there was obtained a 66% yield of (+)-**2**, m.p. 113–113.5°, $[\alpha]_D^{23}$ +120° (MeOH). (−)-Oryzalexin B(**2'**), m.p. 108.5–109.5°, $[\alpha]_D^{23}$ −110° (MeOH), was similarly obtained. The overall yield of (+)-oryzalexin B(**2**) from **6** was 0.20% in 23 steps. The ^{1}H-NMR spectral data of the synthetic enantiomers of **2** were in accord with published data.[3] Oxidation of (+)-oryzalexin A(**1**) with Jones CrO_3 gave (+)-oryzalexin C(**3**), m.p. 147–148°, $[\alpha]_D^{23}$ +100° (MeOH), in 0.07%

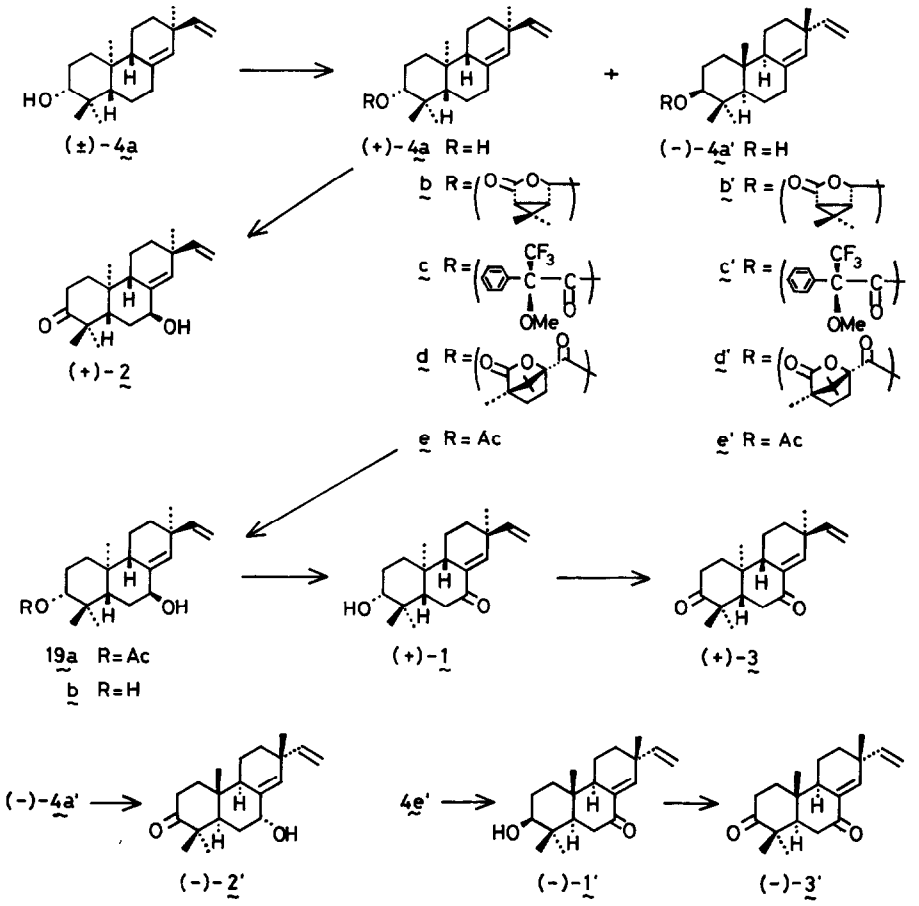

Fig. 3. Synthesis of oryzalexins A–C.

overall yield from **6** in 26 steps. In the same manner, (−)-oryzalexin C(3'), m.p. 146–147.5°, $[\alpha]_D^{23}-120°$ (MeOH), was also synthesized. The 400 MHz ^{1}H-NMR data of the synthetic enantiomers of **3** coincided with those of the natural product.

In summary, the enantiomers of oryzalexins A–C were synthesized, confirming their proposed structures. Biological studies on our synthetic materials are under way by Akatsuka and colleagues.

EXPERIMENTAL

All m.ps were uncorrected. IR spectra were measured as films for oils or as KBr disks for solids on a Jasco IRA-102 spectrometer. NMR spectra were recorded at 60 MHz with TMS as an internal standard on a Hitachi R-24A spectrometer unless otherwise stated. Optical rotations were measured on a Jasco DIP-140 polarimeter.

(±) - 14 - *Methoxy* - 4α,4β,10α - *trimethyl* - 3 - *oxo* - 1,2,3,4,5β,6,7,10 - *octahydrophenanthrene* (**9a**). To a soln of (±)-**8** (80.0 g, 296 mmol) in HOAc (750 ml) was added 10% Pd–C (8 g). The mixture was stirred under H_2 for 24 hr at room temp. An additional amount of 10% Pd–C (4 g) was added to the mixture and the hydrogenation was continued for a further 3 days. The reaction sequence was monitored by GLC analysis. The mixture was then filtered through Celite and concentrated *in vacuo* to give 86.4 g (quantitative) of a mixture of (±)-**9a** and (±)-**10a**. This was repeatedly recrystallized from EtOH to give 13.2 g (16.4%) of (±)-**9a** (98.5% purity as checked by GLC) and 60.8 g (75.3%) of a mixture of (±)-**9a** and (±)-**10a**. The (±)-**9a** showed the following properties: m.p. 99.5–100° (lit.[6] m.p. 90–93°; lit.[9] m.p. 93–96°). IR ν_{max}^{Nujol} cm^{-1}: 1705 (s), 1595 (m), 1260 (s), 775 (s), 715 (s); ^{1}H-NMR ($CDCl_3$): δ 1.13 (6H, s), 1.30 (3H, s), 1.50–3.00 (9H, m), 3.79 (3H, s), 6.50–7.40 (3H, m). GLC analysis of the crude **9a** and **10a** (column: 5% PEG-20M, 2 m × 3 mm at 220°; carrier gas: N_2, 1.5 kg/cm^2): R_t: 28.8 min (**9a**, 63.4%), 19.9 min (**10a**, 36.3%). GLC analysis of (±)-**9a** (column: 1.5% SE-30, 2 m × 3 mm at 200°; carrier gas: N_2, 0.8 kg/cm^2): R_t: 9.7 min (98.5%).

(±) - 14 - *Hydroxy* - 4α,4β,10α - *trimethyl* - 3 - *oxo* - 1,2,3,4,5β,6,7,10 - *octahydrophenanthrene* (**9b**). To a stirred soln of (±)-**9a** (12.57 g, 46.1 mmol) and NaI (17.5 g, 117 mmol) in dry MeCN (120 ml) was added, over 5 min, Me_3SiCl (14.8 ml ≡ 12.7 g, 117 mmol) at room temp under N_2. The mixture was stirred and heated under reflux for 45 hr (inner temp, 69–75°). After cooling, the mixture was poured into Et_2O (400 ml) and H_2O (100 ml) containing a small amount of $NaHSO_3$. The Et_2O layer was separated and washed with sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give (±)-**9b** as a solid. This was triturated with *n*-hexane (200 ml) and the crystals (10.17 g) were collected on a filter. The filtrate was concentrated *in vacuo* and the residue purified by SiO_2 chromatography to give 1.13 g of (±)-**9b**. In sum total, 11.30 g (94.8%) of (±)-**9b** was obtained, m.p. 210.5–213° (lit.[6] m.p. 219–220°). IR ν_{max}^{Nujol} cm^{-1}: 3500 (m), 1690 (s), 1590 (m), 780 (m), 715 (m); ^{1}H-NMR (DMSO-d_6): δ 1.01 (3H, s), 1.06 (3H, s), 1.18 (3H, s), 1.40–3.10 (9H, m), 6.40–7.10 (3H, m), 9.10 (1H, s). GLC (column: 1.5% SE-30, 2 m × 3 mm at 200°; carrier gas: N_2, 0.8 kg/cm^2): R_t: 13.3 min (98.5%), 10.6 min [1.3% due to (±)-**10b**].

(Found: C, 78.93; H, 8.51. Calc for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58%.)

(±) - 3α,14 - *Dihydroxy* - 4α,4β,10α - *trimethyl* - 1,2,3,4,5β,6,7,10 - *octahydrophenanthrene* (**11a**). To a stirred and cooled soln of Li (0.80 g, 115 mmol) in liq NH_3 (50 ml) was added, over 10 min, a soln of (±)-**9b** (2.36 g, 9.13 mmol) in dry THF (50 ml) at −60 to −50° (inner temp). The soln was stirred for 1 hr at this temp. Solid NH_4Cl (7 g, 131 mmol) was then added to the mixture and NH_3 was allowed to evaporate overnight. The residue was acidified with cold 6 M HCl and extracted with Et_2O. The Et_2O soln was washed with water, dried ($MgSO_4$) and concentrated *in vacuo* to give crude (±)-**11a** as a solid. This was recrystallized from EtOH. The mother liquor was concentrated *in vacuo* and the residue purified by SiO_2 chromatography to give a further amount of (±)-**11a**. The total yield of (±)-**11a** was 2.10 g (88.2%), m.p. 199–202° (prisms). IR ν_{max}^{Nujol} cm^{-1}: 3610 (s), 3400 (br s), 1590 (m), 1270 (s), 1020 (s), 1000 (s), 785 (s), 720 (m). ^{1}H-NMR (DMSO-d_6): δ 0.78 (3H, s), 0.97 (3H, s), 1.07 (3H, s), 0.50–3.20 (10H, m), 4.35 (1H, d, J = 5 Hz, —OH), 6.30–7.10 (3H, m), 9.00 (1H, s). GLC (column: 3% SE-30, 2 m × 3 mm at 200°; carrier gas: N_2, 0.8 kg/cm^2): R_t: 13.4 min (100%). (Found: C, 78.80; H, 9.36. Calc for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29%.)

(±) - 3α - *Acetoxy* - 14 - *hydroxy* - 4α,4β,10α - *trimethyl* - 1,2,3,4,5β,6,7,10 - *octahydrophenanthrene* [(±)-**11b**]. A soln of (±)-**11a** (1.891 g, 7.26 mmol) and *p*-TsOH · H_2O (5.7 g) in MeOAc (400 ml) was stirred and heated under reflux for 1 day. After cooling, the soln was washed with $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2. Elution with *n*-hexane–THF (8:1) gave 1.549 g [95.0% based on the amount of (±)-**11a** consumed] of (±)-**11b** together with 0.488 g of the recovered (±)-**11a**. The pure (±)-**11b** sublimed at 193–195°. IR ν_{max}^{Nujol} cm^{-1}: 3470 (s), 1715 (s), 1595 (m), 1270 (s), 1035 (m), 795 (m), 730 (m). ^{1}H-NMR (DMSO-d_6): δ 0.90 (6H, s), 1.12 (3H, s), 1.00–3.10 (9H, m), 2.00 (3H, s), 4.42 (1H, dd, J = 8 and 8 Hz), 6.40–7.10 (3H, m), 9.04 (1H, s). GLC (column: 3% SE-30, 2 m × 3 mm at 210°; carrier gas: N_2, 0.9 kg/cm^2): R_t: 11.9 min (99.8%). (Found: C, 75.42; H, 8.56. Calc for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67%.)

(±) - 3α - Acetoxy - 14 - oxo - 4α,4β,10α - trimethyl - 1,2,3,4,5β,6,7,8α,9β,10,11,12,13,14 - perhydrophenanthrene [(±)-**5**]. (a) *Hydrogenation of pure* (±)-**11b** *followed by oxidation.* Raney Ni W-7 (Nikko Rika Co., R-100,® 0.8 g) was added to a soln of (±)-**11b** (1.55 g, 5.13 mmol) in 99% EtOH (30 ml) in an autoclave. Hydrogenation was carried out at *ca* 180° for 1.5 hr at an initial H_2 pressure of 88 kg/cm^2. After cooling, the mixture was filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in Me_2CO (40 ml). To the stirred and ice-cooled soln was added Jones CrO_3 (4 ml, 10.7 mmol) over 5 min at 5–10°. After stirring for 30 min at this temp the excess CrO_3 was destroyed by the addition of MeOH and the mixture was concentrated *in vacuo*. The residue was dissolved in H_2O and extracted with EtOAc. The EtOAc soln was washed with sat $NaHCO_3$ aq, dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallization of the residue from EtOAc gave 0.94 g (59.6%) of (±)-**5** as rhombic crystals, m.p. 153° (lit.[6] m.p. 150–152°). IR ν_{max}^{Nujol} cm^{-1}: 1740 (s), 1720 (s), 1245 (s), 1025 (s). ^{1}H-NMR ($CDCl_3$): δ 0.86 (6H, s), 0.96 (3H, s), 0.80–3.00 (17H, m), 2.02 (3H, s), 4.50 (1H, dd, J = 5, 9 Hz). ^{13}C-NMR (25 MHz, $CDCl_3$): δ 13.9, 16.7, 20.1, 21.2, 23.9, 24.4, 26.0, 26.3, 28.1, 37.1 (2C), 37.7, 41.3, 49.3, 53.8, 56.8, 80.6, 170.7, 212.7. GLC (column: 1.5% SE-30, 2 m × 3 mm at 200°; carrier gas: N_2, 0.8 kg/cm^2): R_t: 17.9 min (99.6%). (Found: C, 74.71; H, 9.74. Calc for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87%.)

(b) *Hydrogenation of a mixture of* (±)-**11b** *and* (±)-**12b** *followed by oxidation.* Raney Ni W-7 (4.0 g) was added to a soln of a mixture of (±)-**11b** and (±)-**12b** (**11b**–**12b** = 7:3, 8.3 g, 27.4 mmol) in 99% EtOH (60 ml). Hydrogenation was carried out at *ca* 170° under an initial H_2 pressure of 92 kg/cm^2. At the end of a H_2 uptake of *ca* 2 eq., the hydrogenation bomb was cooled. The catalyst was removed by filtration and the filtrate concentrated *in vacuo*. The residue was dissolved in Me_2CO (200 ml). To the stirred and ice-cooled soln Jones CrO_3 (17 ml, 45 mmol) was added drop-wise over 10 min at 5–10° and the stirring was continued for 20 min at this temp. The excess CrO_3 was then destroyed by the addition of MeOH (50 ml) and the mixture concentrated *in vacuo*. The residue was partitioned between H_2O (300 ml) and EtOAc (300 ml). The aq layer was extracted with EtOAc. The combined EtOAc soln was washed with sat $NaHCO_3$ aq, dried ($MgSO_4$) and concentrated *in vacuo* to give 9.12 g of a crude oil. This was chromatographed over SiO_2 (300 g). Elution with hexane gave 1.67 g (21.0%) of (±)-**13** as an oil, b.p. 143°/0.25 mm. IR ν_{max} cm^{-1}: 1745 (s), 1245 (s). ^{1}H-NMR ($CDCl_3$): δ 0.90 (6H, s), 0.96 (3H, s), 1.99 (3H, s), 0.80–2.20 (17H, m), 4.43 (1H, dd, J = 5, 9 Hz). ^{13}C-NMR (25 MHz, $CDCl_3$): δ 15.9, 18.1, 21.2, 22.9, 24.1, 24.4, 25.6, 27.8, 29.1, 31.0, 31.5, 34.4, 36.7, 39.1, 49.7, 81.0, 128.9, 132.3, 170.7. GLC (column: 1.5% SE-30, 2 m × 3 mm at 200°; carrier gas: N_2, 0.8 kg/cm^2): R_t: 6.7 min (89.9%), 8.4 min (8.3%, presumably due to dihydro-**13**). Further elution with C_6H_6 gave (±)-**5** (4.13 g, 49.3%), m.p. 153°.

(±) - 13 - *Butylthiomethylene* - 3α - *hydroxy* - 4α,4β,10α - *trimethyl* - 14 - *oxo* - 5β,8α,9β - *perhydrophenanthrene* [(±)-**14a**]. Solid NaOMe was prepared by concentrating a soln of NaOMe in MeOH (28%, 15 ml, 77.7 mmol) *in vacuo*. To this were added dry C_6H_6 (55 ml) and a soln of (±)-**5** (3.92 g, 12.8 mmol) in dry THF (90 ml) under N_2. Freshly distilled HCO_2Et (9 ml ≡ 8.25 g, 111 mmol) was added over 10 min to the stirred and ice-cooled mixture at 3–10°. The mixture was left to stand overnight at room temp. It was then poured into iced-H_2O (50 ml) and the aq layer was separated. The organic layer was extracted with 5% NaOH (50 ml × 3). The combined aq soln was acidified with dil HCl and extracted with EtOAc. The EtOAc soln was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 3.90 g of the crude β-keto aldehyde. This was dissolved in dry C_6H_6 (150 ml). To the soln were added *p*-TsOH · H_2O (45 mg) and *n*-BuSH (2.8 ml ≡ 2.36 g, 26.2 mmol) and the mixture was stirred and heated under reflux for 5 hr. It was then poured into H_2O (200 ml) and extracted with C_6H_6 (200 ml). The organic soln was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo* to give a crude oil (4.73 g). This was chromatographed over SiO_2 (150 g). Elution with *n*-hexane–EtOAc (9:1) gave (±)-**14b** (1.35 g, 26.9%) and (±)-**14a** (2.22 g, 50.4%). Conventional alkaline hydrolysis of (±)-**14b** with KOH in aq MeOH gave a further amount of (±)-**14a** (1.25 g). The total amount of (±)-**14a** was 3.47 g (74.4%). This was recrystallized from Et_2O–*n*-hexane to give needles of pure (±)-**14a**, m.p. 68.5–70°. IR ν_{max}^{Nujol} cm^{-1}: 1660 (s), 1540 (s). ^{1}H-NMR ($CDCl_3$): δ 0.79 (3H, s), 0.84 (3H, s), 0.90 (3H, t, J = 6 Hz), 0.96 (3H, s), 0.80–3.40 (21H, m), 2.79 (2H, t, J = 7 Hz), 3.15 (1H, m), 7.45 (1H, s). GLC (column: 3% SE-30, 2 m × 3 mm at 220°; carrier gas: N_2, 1.5 kg/cm^2): R_t: 47.0 min (98.4%). (Found: C, 71.91; H, 9.88. Calc for $C_{22}H_{36}O_2S$: C, 72.48; H, 9.95%.) Pure (±)-**14b** showed the following properties: m.p. 110–111°. IR ν_{max}^{Nujol} cm^{-1}: 1710 (s), 1660 (m), 1540 (s), 1185 (s). ^{1}H-NMR ($CDCl_3$): δ 0.88 (9H, s), 0.60–2.60 (22H, m), 2.80 (2H, t, J = 7 Hz), 4.58 (1H, m), 7.46 (1H, s), 8.07 (1H, s). GLC (column: 3% SE-30, 2 m × 3 mm at 220°; carrier gas: N_2, 1.5 kg/cm^2): R_t: 47.9 min (100%). (Found: C, 70.24; H, 9.31. Calc for $C_{23}H_{36}O_3S$: C, 70.37; H, 9.24%.)

(±) - 3α - t - *Butyldimethylsilyloxy* - 13 - *butylthiomethylene* - 4α,4β,10α - *trimethyl* - 14 *oxo* - 5β,8α,9β - *perhydrophenanthrene* [(±)-**14c**]. A soln of (±)-**14a** (2.75 g, 7.54 mmol) in DMF (15 ml) was added to a stirred soln of *t*-$BuMe_2SiCl$ (1.70 g, 11.3 mmol) and imidazole (1.55 g, 22.6 mmol) in DMF (30 ml) at 25–30°. The mixture was stirred for 20 hr and then poured into iced-H_2O (150 ml) and extracted with Et_2O. The Et_2O soln was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue (4.75 g) was chromatographed over SiO_2 to give (±)-**14c** [2.85 g, 92.3% yield based on the amount of (±)-**14a** consumed] and the recovered (±)-**14a** (0.264 g). Oily (±)-**14c**. IR ν_{max} cm^{-1}: 1670 (s), 1545 (s), 1465 (s), 1250 (s), 1090 (s), 1070 (s), 830 (s), 770 (s). ^{1}H-NMR ($CDCl_3$): δ 0.03 (6H, s), 0.74 (3H, s), 0.87 (15H, s), 0.80–2.60 (22H, m), 2.27 (2H, t, J = 7 Hz), 3.17 (1H, m), 7.42 (1H, s), was used in the next step without further purification.

(±) - 3α - t - *Butyldimethylsilyloxy* - 13 - *formyl* - 4α,4β,10α -

trimethyl - 1,2,3,4,5β,6,7,8α,9β,10,11,12 - *dodecahydrophenanthrene* [(±)-**15**]. A soln of $NaBH_4$ (370 mg, 9.78 mmol) in 95% EtOH (20 ml) was added drop-wise over 30 min to a stirred and ice-cooled soln of (±)-**14c** (1.868 g, 3.90 mmol) in THF (15 ml) at 3–6°. The soln was stirred for 2 hr at 10° and the solvent then removed *in vacuo*. The residue was dissolved in H_2O and extracted with Et_2O. The Et_2O soln was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give an oil (1.87 g). This was dissolved in 95% EtOH (25 ml). To this were added $CdCO_3$ (668 mg, 3.90 mmol) and a soln of $HgCl_2$ (1.065 g, 3.90 mmol) in 95% EtOH (10 ml). The mixture was stirred and heated under reflux for 5 min. After cooling, the mixture was diluted with C_6H_6 and H_2O, and filtered through Celite. The organic layer was separated and the aq layer was extracted with C_6H_6. The combined organic soln was washed with H_2O and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 1.6 g of crude (±)-**15**. This was recrystallized from *n*-hexane. The mother liquor was concentrated *in vacuo* and the residue was purified by SiO_2 chromatography. The total yield of (±)-**15** was 1.349 g (84.7%). (±)-**15** crystallized as needles, m.p. 142–143°. IR ν_{max}^{Nujol} cm^{-1}: 2750 (w), 1675 (s), 1650 (m), 1250 (s), 1090 (s), 1070 (s), 830 (s), 770 (s). ^{1}H-NMR ($CDCl_3$): δ 0.04 (6H, s), 0.77 (3H, s), 0.88 (15H, s), 0.80–2.50 (15H, m), 3.17 (1H, m), 6.45 (1H, s), 9.40 (1H, s). GLC (column: 3% SE-30, 2 m × 3 mm at 210°; carrier gas: N_2, 0.9 kg/cm^2): R_t: 27.9 min (100%). (Found: C, 73.67; H, 10.91. Calc for $C_{24}H_{42}O_2Si$: C, 73.29; H, 10.84%.)

(±)-3α-t-*Butyldimethylsilyloxy* - 13 - *formyl* - 4α,4β,10α,13-*tetramethyl* - 1,2,3,4,5β,6,7,9β,10,11,12,13 - *dodecahydrophenanthrene* [(±)-**16**]. A soln of (±)-**15** (240 mg, 0.61 mmol) in dry C_6H_6 (2 ml) was added to a stirred and heated soln of *t*-BuOK [prepared from 2.4 g (61 mg atom) of K] in dry *t*-BuOH (30 ml) under N_2. The mixture was heated under reflux for 4 min and then cooled immediately with an ice bath. When the inner temp was 20°, MeI (93% purity, 6 ml, 96 mmol) was added to the mixture. Stirring was continued for 1 hr under ice cooling. The mixture was then poured into H_2O and extracted with Et_2O. The Et_2O soln was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo* to give 270 mg (quantitative) of crude (±)-**16**. IR ν_{max} cm^{-1}: 2700 (w), 1720 (s), 1680 (w), 1245 (s), 1095 (s), 1060 (s), 830 (s), 770 (s). ^{1}H-NMR ($CDCl_3$): δ 0.03 (6H, s), 0.87 (9H, s), 1.18 (6H, s), 0.80–2.50 (13H, m), 3.00–3.50 (2H, m), 5.29 and 5.37 [total 1H (1:2), both s], 9.39 and 9.49 [total 1H (2:1), both s]. GLC (column: 3% SE-30, 2 m × 3 mm at 200°; carrier gas: N_2, 1.0 kg/cm^2): R_t: 31.7 min (73%), 34.1 min (27%). This was employed in the next step without further purification.

A mixture of (±) - 3β - t - *Butyldimethylsilyloxyisopimara* - 8(14),15 - *diene and* (±) - 3β - t - *butyldimethylsilyloxypimara* - 8(14),15 - *diene* [(±)-**17**]. A Wittig reagent was prepared by the addition of *n*-BuLi (1.84 M in hexane, 2.3 ml, 4.23 mmol) over 10 min to a stirred and ice cooled suspension of Ph_3PMeBr (1.500 g, 4.20 mmol) in dry THF (4 ml) at 2–12° under N_2. The stirring was continued for 10 min at 0–5°. Subsequently a soln of (±)-**16** (270 mg as a crude gum, 0.61 mmol) in dry THF (2 ml) was added over 2 min. The mixture was stirred overnight at room temp. It was then poured into H_2O and extracted with Et_2O. The Et_2O soln was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by SiO_2 chromatography to give 176 mg (71.9%) of (±)-**17**. This was recrystallized from 99% EtOH to give plates, m.p. 82.5–83°. IR ν_{max} cm^{-1}: 3080 (w), 1630 (w), 1100 (s), 835 (s). ^{1}H-NMR ($CDCl_3$): δ 0.04 (6H, s), 0.78 (3H, s), 0.88 (9H, s), 0.92 and 1.03 (total 3H, both s), 1.25 (3H, s), 0.80–2.30 (17H, m), 3.00–3.40 (1H, m), 4.70–5.80 (4H, m). GLC (column: 3% SE-30, 2 m × 3 mm at 200°; carrier gas: N_2, 1.0 kg/cm^2): R_t: 22.6 min (96.1%, no separation of the two isomers). (Found: C, 77.53; H, 11.33. Calc for $C_{26}H_{46}OSi$: C, 77.54; H, 11.51%.)

(±) - 3β - *Hydroxyisopimara* - 8(14),15 - *diene* [(±)-**4a**] *and* (±) - 3β - *hydroxypimara* - 8(14),15 - *diene* [(±)-**18**]. A suspension of (±)-**17** (81 mg, 0.20 mmol) in MeCN (2 ml) containing a drop of 46% HF was stirred for 1.5 hr at room temp. The mixture became homogeneous at the end of the reaction. It was then neutralized with solid $NaHCO_3$ and poured onto a short SiO_2 column. Elution with Et_2O gave a mixture of (±)-**4a** and (±)-**18** (56 mg, 99.5%). This was chromatographed over SiO_2–$AgNO_3$ [prepared from SiO_2 (25 g), $AgNO_3$ (2.5 g) and H_2O (10 ml)]. Elution with *n*-hexane–EtOAc (20:1) yielded (±)-**4a** (56%), a mixture of (±)-**4a** and (±)-**18** (11%) and (±)-**18** (33%). Recrystallization of (±)-**4a** from EtOH–H_2O (2:1) gave needles, m.p. 232.5–234°. IR ν_{max} cm^{-1}: 3330 (br s), 3080 (w), 1635 (m), 1090 (s), 1030 (s), 995 (s), 910 (s). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.80 (3H, s), 0.82 (3H, s), 1.01 (3H, s), 1.04 (3H, s), 1.13–1.78 (13H, m), 2.03 (1H, m), 2.28 (1H, ddd, J = 1.6, 4.8 and 14.4 Hz), 3.26 (1H, dd, J = 2.0 and 11.2 Hz), 4.88 (1H, dd, J = 1.6 and 10.4 Hz), 4.91 (1H, dd, J = 1.6 and 17.2 Hz), 5.23 (1H, br s), 5.77 (1H, dd, J = 10.4 and 17.2 Hz). ^{13}C-NMR (25 MHz, $CDCl_3$): δ 15.0, 15.7, 18.8, 22.3, 26.0, 27.7, 28.5, 34.6, 35.9, 37.3, 37.5, 38.2, 39.0, 50.4, 54.2, 79.1, 110.1, 128.9, 136.6, 148.9. GLC (column: 3% SE-30, 2 m × 3 mm at 180°; carrier gas: N_2, 1.0 kg/cm^2): R_t: 16.3 min (99.6%). MS: *m/z* 288.2467 $[M]^+$. Calc for $C_{20}H_{32}O$: 288.2452. Recrystallization of (±)-**18** from EtOH–H_2O (2:1) gave needles, m.p. 110–110.5°. IR ν_{max} cm^{-1}: 3330 (br s), 3080 (w), 1630 (m), 1025 (s), 990 (s), 910 (s). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.74 (3H, s), 0.82 (3H, s), 0.99 (3H, s), 1.01 (3H, s), 0.80–1.70 (13H, m), 2.05 (1H, m), 2.34 (1H, ddd, J = 1.6, 4.8 and 13.6 Hz), 3.26 (1H, dd, J = 4.0 and 11.2 Hz), 4.91 (1H, dd, J = 1.6 and 17.2 Hz), 4.95 (1H, dd, J = 1.6 and 10.4 Hz), 5.15 (1H, d, J = 1.6 Hz), 5.72 (1H, dd, J = 10.4 and 17.2 Hz). ^{13}C-NMR (25 MHz, $CDCl_3$): δ 14.8, 15.7, 19.2, 22.2, 27.7, 28.5, 29.4, 35.7 (2C), 37.2, 38.2, 38.6, 39.0, 51.2, 54.2, 79.2, 112.8, 128.2, 137.9, 147.3. GLC (column: 3% SE-30, 2 m × 3 mm at 180°; carrier gas: N_2, 1.0 kg/cm^2): R_t: 15.5 min (100%). MS: *m/z* 288.2473 $[M]^+$. Calc for $C_{20}H_{32}O$: 288.2452.

Resolution of (±)-**4a** *employing* (1R,4R,5S) - 4 - *hydroxy* - 6,6 - *dimethyl* - 3 - *oxabicyclo*[3.1.0]*hexan* - 2 - *one as the resolving agent*. A soln of (±)-**4a** (154 mg, 0.534 mmol), (1*R*,4*R*,5*S*) - 4 - hydroxy - 6,6 - dimethyl - 3 - oxabicyclo[3.1.0]hexan - 2 - one (159 mg, 1.12 mmol) and *p*-TsOH · H_2O (5 mg) in C_6H_6 (40 ml) was stirred and heated under reflux for 1 hr to remove H_2O with a Dean–Stark H_2O separator. After cooling, a small amount of K_2CO_3 was added and the mixture was stirred for a further 5 min before being filtered through a small amount of SiO_2. The filtrate was concentrated *in vacuo* to give 220 mg of an oil. This was chromatographed over SiO_2 (10 g). Elution with CH_2Cl_2–*n*-hexane (1:1, previously treated with K_2CO_3 to remove traces of acid) gave less polar **4b** (50 mg, 42%) and more polar **4b'** (40 mg, 33%) together with recovered **4a** (70 mg). The recovered **4a** was resolved again as described above. Compound **4b** showed the following properties. M.p. 127.5–129.0°. $[\alpha]_D^{21}$ −94° (*c* = 0.55, $CHCl_3$). IR ν_{max} cm^{-1}: 1770 (s), 1630 (w), 1110 (s), 930 (s). ^{1}H-NMR ($CDCl_3$): δ 0.82 (6H, s), 0.99 (3H, s), 1.04 (3H, s), 1.16 (3H, s), 1.20 (3H, s), 1.00–2.40 (16H, m), 3.37 (1H, dd, J = 4 and 11 Hz), 4.88 (1H, dd, J = 2 and 10 Hz), 4.91 (1H, dd, J = 2 and 18 Hz), 5.23 (1H, s), 5.29 (1H, s), 5.78 (1H, dd, J = 10 and 18 Hz). (Found: C, 78.52; H, 9.60. Calc for $C_{27}H_{40}O_3$: C, 78.60; H, 9.77%.) Compound **4b'** showed the following properties. M.p. 134.5–135.5°. $[\alpha]_D^{21}$ −89° (*c* = 0.39, $CHCl_3$). IR ν_{max} cm^{-1}: 1775 (s), 1115 (s), 940 (s). ^{1}H-NMR ($CDCl_3$): δ 0.80 (3H, s), 0.85 (3H, s), 1.00 (3H, s), 1.03 (3H, s), 1.17 (3H, s), 1.19 (3H, s), 1.00–2.40 (16H, m), 3.24 (1H, dd, J = 4 and 11 Hz), 4.88 (1H, dd, J = 2 and 10 Hz), 4.91 (1H, dd, J = 2 and 18 Hz), 5.21 (1H, s), 5.23 (1H, s), 5.79 (1H, dd, J = 10 and 18 Hz). (Found: C, 78.87; H, 9.46. Calc for $C_{27}H_{40}O_3$: C, 78.60; H, 9.77%.)

Resolution of (±)-**4a** *employing* (−)-*camphanic acid as the resolving agent*. (−)-Camphanic acid (1.00 g, 5.04 mmol) was added to stirred and ice cooled $SOCl_2$ (3.7 ml ≡ 6 g, 50 mmol). The mixture was stirred and heated under reflux for 2 hr. Excess $SOCl_2$ was removed *in vacuo*. The residue was purified by sublimation *in vacuo* to give 1.038 g (95.0%) of the acyl chloride, m.p. 68.5–69.0°. The acyl chloride (252 mg, 1.28 mmol) was added to a stirred and ice cooled soln of (±)-**4a** (185 mg, 0.64 mmol) in C_5H_5N (3 ml). After stirring for 1 hr at 0–5°, the mixture was poured into H_2O and extracted with Et_2O. The Et_2O soln was washed with $CuSO_4$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude solid was

chromatographed over SiO_2 (70 g). Elution with C_6H_6–EtOAc (100 : 3) yielded more polar **4d** (31 mg), less polar **4d'** (41 mg) and a mixture of both. The mixture was further chromatographed over a Merck Lobar column. The total yield of **4d** was 117 mg (39%), while that of **4d'** was 135 mg (45%). In addition, a mixture of **4d** and **4d'** (16 mg, 5%) was obtained. Compound **4d** showed the following properties. M.p. 232–233.5° (needles from $CHCl_3$–*n*-hexane). $[\alpha]_D^{22}$ −2.67° (*c* = 1.32, $CHCl_3$). IR ν_{max} cm^{-1}: 1780 (s), 1735 (s), 1255 (s), 1055 (s). ^{1}H-NMR ($CDCl_3$): δ 0.83 (3H, s), 0.91 (6H, s), 0.96 (3H, s), 1.03 (3H, s), 1.06 (3H, s), 1.10 (3H, s), 1.00–2.50 (18H, m), 4.70 (1H, t, J = 2 Hz), 4.82 (1H, dd, J = 2 and 17 Hz), 4.83 (1H, dd, J = 2 and 10 Hz), 5.19 (1H, br s), 5.73 (1H, dd, J = 10 and 17 Hz). HPLC (column: Nucleosil® 50-5, 25 cm × 4.1 mm; solvent: dichloroethane; flow rate: 1 ml/min; detector: UV, 217 nm): R_t: 22.0 min (100%). (Found: C, 76.82; H, 9.43. Calc for $C_{30}H_{44}O_4$: C, 76.88; H, 9.46%.) Compound **4d'** showed the following properties. M.p. 196.5–197.5° (recrystallized from *n*-hexane). $[\alpha]_D^{22}$ −4.41° (*c* = 1.02, $CHCl_3$). IR ν_{max} cm^{-1}: 1780 (s), 1735 (s), 1630 (w), 1265 (s), 1100 (m), 1055 (m). ^{1}H-NMR ($CDCl_3$): δ 0.83 (3H, s), 0.93 (6H, s), 0.97 (3H, s), 1.04 (3H, s), 1.07 (3H, s), 1.10 (3H, s), 1.00–2.50 (18H, m), 4.71 (1H, t, J = 2 Hz), 4.83 (1H, dd, J = 2 and 17 Hz), 4.84 (1H, dd, J = 2 and 10 Hz), 5.20 (1H, br s), 5.75 (1H, dd, J = 10 and 17 Hz). HPLC (under the same condition as described for **4d**): R_t: 16.7 min (100%). (Found: C, 76.56; H, 9.32. Calc for $C_{30}H_{44}O_4$: C, 76.88; H, 9.46%.)

(+)-ent-3β-*Hydroxyisopimara*-8(14),15-*diene* [(+)-**4a**] *and its antipode* (−)-**4a'**. (a) *From* **4b** *and* **4b'**. A drop of conc HCl was added to a soln of **4b** (30 mg, 0.073 mmol) in MeOH (3 ml). The soln was stirred for 15 min at room temp, neutralized with K_2CO_3 and concentrated *in vacuo*. The residue was chromatographed over SiO_2. Elution with CH_2Cl_2 gave 20 mg (95%) of (+)-**4a**. This was recrystallized from *n*-hexane to give needles, m.p. 123.5–126.0° (lit.[4] m.p. 126.0–127.0°). $[\alpha]_D^{21.5}$ +11° (*c* = 0.24, $CHCl_3$) [lit.[4] $[\alpha]_D$ +12.5° (*c* = 1, $CHCl_3$)]. GLC (column: 10% PEG 20M, 2 m × 3 mm at 220°; carrier gas: N_2, 1.6 kg/cm^2): R_t: 10.1 min (93.4%). MS: *m/z* 288.2411. Calc for $C_{20}H_{32}O$: 288.2452. The IR and NMR spectra of (+)-**4a** were identical with those of (±)-**4a**. In the same manner, **4b'** (36 mg) yielded 24 mg (95%) of (−)-**4a'**, m.p. 122.0–123.0° (lit.[5] m.p. 126.5–127.5°). $[\alpha]_D^{21}$ −13° (*c* = 0.07, $CHCl_3$) [lit.[5] $[\alpha]_D$ −19.5° (*c* = 5, $CHCl_3$)]. GLC (under the same condition as described for (+)-**4a**): R_t: 10.2 min (89.0%). MS: *m/z* 288.2408 $[M]^+$. Calc for $C_{20}H_{32}O$: 288.2452. The IR and NMR spectra of (−)-**4a** were identical with those of (±)-**4a**. The optical purity of the resolved materials was estimated as follows. (*S*)-MTPA was converted to the corresponding acyl chloride. The acyl chloride (10 μl) was added to a soln of (+)-**4a** (2 mg) in dry C_5H_5N (100 μl). The mixture was stirred overnight and worked-up to give **4c**. This was analysed by HPLC [column: Nucleosil® 50-5, 25 cm × 4.6 mm; solvent: hexane–THF (100 : 1); flow rate: 0.8 ml/min]: R_t: 10.1 min (93.2%), 11.0 min (6.8%). The optical purity of (+)-**4a** was 86.4% e.e. Similarly, (−)-**4a'** was acylated with (*S*)-MTPA to give **4d'** and analysed by HPLC under the same condition as described for **4d**: R_t: 10.2 min (7.2%), 11.1 min (92.8%). The optical purity of (−)-**4a'** was 85.6% e.e.

(b) *From* **4d** *and* **4d'**. K_2CO_3 (58 mg) was added to a soln of **4d** (58 mg, 0.12 mmol) in MeOH (3 ml). The mixture was stirred for 2 days at room temp and filtered through a small SiO_2 column. The filtrate was concentrated *in vacuo* to give 31 mg (87%) of (+)-**4a**, m.p. 126–127°, $[\alpha]_D^{22}$ +13° (*c* = 0.57, $CHCl_3$). As we used pure **4d**, the present sample of (+)-**4a** was thought to be optically pure. In the same manner **4d'** (77 mg) gave (−)-**4a'** (42 mg, 89%), m.p. 127–128°, $[\alpha]_D^{22}$ −14° (*c* = 0.57, $CHCl_3$). Since we employed pure **4d'**, the present sample of (−)-**4a** was thought to be optically pure.

Both the enantiomers of oryzalexin A (+)-**1** *and* (−)-**1'**. A soln of Ac_2O (0.2 ml) and (+)-**4a** (31 mg, 0.11 mmol) in C_5H_5N (0.5 ml) was stirred overnight at room temp. Subsequent work-up including SiO_2 chromatography gave **4e** (34 mg). A soln of **4e** (34 mg) in C_6H_6 (2 ml) was added to a stirred and heated mixture of SeO_2 (340 mg), HOAc (34 ml), C_6H_6 (34 ml) and H_2O (1.3 ml) at the inner temp of 64°. The mixture was stirred for 1.5 min at 61–64° and rapidly filtered through SiO_2. The filtrate was concentrated *in vacuo*. The residue was dissolved in C_6H_6 and filtered through SiO_2. The filtrate was concentrated *in vacuo*. The residue was chromatographed over SiO_2. Elution with C_6H_6 gave **19a** (22 mg) which showed a single spot on SiO_2 TLC [developed with *n*-hexane–EtOAc (2 : 1); R_f 0.41]. Compound **19a** (22 mg) was dissolved in DMSO (0.5 ml) and Ac_2O (0.5 ml) and the soln was stirred overnight at room temp. The mixture was poured onto a column of SiO_2 and chromatographed to give an acetoxy enone (9 mg). Its conventional hydrolysis with K_2CO_3–MeOH gave (+)-**1** [7.5 mg, 23% from (+)-**4a**]. This was recrystallized from *n*-hexane to give needles, m.p. 170–171°, $[\alpha]_D^{23}$ +46° (*c* = 0.13, MeOH) [lit.[2] $[\alpha]_D^{27}$ +20° (*c* = 0.13, MeOH)]. IR ν_{max} cm^{-1}: 3440 (br s), 3100 (w), 2980 (m), 2950 (s), 2860 (m), 1685 (s), 1640 (w), 1620 (s), 1465 (w), 1415 (w), 1390 (w), 1370 (w), 1265 (m), 1220 (m), 1200 (w), 1095 (m), 1035 (w), 1015 (w), 1000 (w), 915 (m), 880 (m). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.84 (3H, s), 0.88 (3H, s), 0.98 (3H, s), 1.11 (3H, s), 1.28 (1H, ddd, J = 4, 14 and 14 Hz), 1.40–1.90 (8H, m), 1.83 (1H, ddd, J = 4, 4 and 13 Hz), 2.03 (1H, ddd, J = 3, 6 and 12 Hz), 2.37 (1H, dd, J = 13 and 19 Hz), 2.56 (1H, dd, J = 5 and 19 Hz), 3.31 (1H, ddd, J = 4, 14 and 12 Hz), 4.98 (1H, dd, J = 2 and 10 Hz), 5.00 (1H, dd, J = 2 and 18 Hz), 5.81 (1H, dd, J = 10 and 18 Hz), 6.74 (1H, dd, J = 2 and 2 Hz). GLC (column: 3% SE-30, 2 m × 3 mm at 200°; carrier gas: N_2, 1.4 kg/cm^2): R_t: 8.2 min (100%). MS: *m/z* 302.2297 $[M]^+$. Calc for $C_{20}H_{30}O_2$: 302.2244. In the same manner as described above, (−)-**4a'** (40 mg) yielded (−)-**1'** (5 mg, 12%), m.p. 170–171°, $[\alpha]_D^{23}$ −47° (*c* = 0.06, MeOH). GLC (column: 3% SE-30, 2 m × 3 mm at 220°; carrier gas: N_2, 1.4 kg/cm^2): R_t: 7.8 min (100%). MS: *m/z* 302.2238 $[M]^+$. Calc for $C_{20}H_{30}O_2$: 302.2244. The (−)-**1'** showed IR and NMR spectra identical with those of (+)-**1**. The synthetic enantiomers of **1** showed IR and NMR spectral data identical with those of natural **1**.[2]

Both the enantiomers of oryzalexin B (+)-**2** *and* (−)-**2'**. A few drops of Jones reagent (8 N CrO_3) were added to a stirred and ice cooled soln of (+)-**4a** (18 mg, 0.062 mmol) in Me_2CO (5 ml). The mixture was stirred for 3 min at 0–5°. Excess CrO_3 was destroyed by the addition of a small amount of MeOH. The mixture was concentrated *in vacuo*. The residue was triturated with Et_2O and filtered through SiO_2. The filtrate was concentrated *in vacuo*. The residue was dissolved in C_6H_6 (2 ml) and added to a stirred and heated mixture of SeO_2 (190 mg), C_6H_6 (19 ml), HOAc (19 ml) and H_2O (0.7 ml) at the inner temp of 62°. The mixture was stirred for 1.5 min at 62–63° and quickly filtered through SiO_2. The filtrate was concentrated *in vacuo*. The residue was dissolved in Et_2O and again filtered through SiO_2. The filtrate was concentrated *in vacuo* and the residue was chromatographed over SiO_2 to give 12.5 mg [66% from (+)-**4a**] of (+)-**2** as plates from *n*-hexane, m.p. 113–113.5°, $[\alpha]_D^{23}$ +120° (*c* = 0.22, MeOH). IR ν_{max} cm^{-1}: 3550 (s), 3100 (w), 2970 (s), 2880 (s), 1685 (s), 1640 (m), 1475 (m), 1460 (w), 1435 (w), 1410 (m), 1385 (m), 1365 (w), 1295 (w), 1265 (w), 1210 (w), 1195 (m), 1140 (m), 1120 (m), 1080 (m), 1045 (s), 1025 (w), 1015 (w), 1005 (m), 960 (w), 930 (w), 920 (m), 880 (w), 865 (m), 830 (w), 760 (m), 685 (w). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.98 (3H, s), 1.07 (3H, s), 1.08 (3H, s), 1.11 (3H, s), 1.30 (1H, br s), 1.38–1.77 (7H, m), 2.02 (1H, ddd, J = 3, 6 and 14 Hz), 2.07 (1H, dd, J = 5 and 11 Hz), 2.19 (1H, ddd, J = 2, 8 and 8 Hz), 2.34 (1H, ddd, J = 3, 6 and 14 Hz), 2.65 (1H, ddd, J = 6, 14 and 14 Hz), 4.26 (1H, dd, J = 3 and 3 Hz), 4.95 (1H, dd, J = 2 and 10 Hz), 4.96 (1H, dd, J = 2 and 18 Hz), 5.59 (1H, br s), 5.79 (1H, dd, J = 10 and 18 Hz). GLC (column: 3% SE-30, 2 m × 3 mm at 200°; carrier gas: N_2, 1.4 kg/cm^2): R_t: 12.8 min (100%). MS: *m/z* 302.2246 $[M]^+$. Calc for $C_{20}H_{30}O_2$: 302.2244. In the same manner as described above, (−)-**4a'** (19 mg) yielded (−)-**2'** (12 mg, 60%), m.p. 108.5–109.5°, $[\alpha]_D^{23}$ −110° (*c* = 0.14, MeOH). GLC [under the same conditions as described for (+)-**2**]: R_t: 12.7 min (100%). MS: *m/z* 302.2303 $[M]^+$. Calc for $C_{20}H_{30}O_2$: 302.2244. The IR and NMR spectra of (−)-**2'** were identical with those of (+)-**2**. The synthetic enantiomers of **2** showed the IR and NMR spectral data identical with those of natural **2**.[3]

Both the enantiomers of oryzalexin C (+)-3 and (−)-3'. Two drops of Jones reagent (8 N CrO_3) were added to a stirred and ice cooled soln of (+)-**1** (2 mg) in Me_2CO (1 ml). The mixture was stirred for 5 min at 0–5°. The excess of CrO_3 was destroyed by the addition of a small amount of MeOH. The mixture was concentrated *in vacuo*, and the residue was purified by prep. TLC to give (+)-**3** (2 mg) as rhombs from *n*-hexane, m.p. 147–148°, $[\alpha]_D^{23}$ +100° (*c* = 0.015, MeOH). IR ν_{max} cm^{-1}: 3100 (w), 2980 (m), 2950 (s), 1710 (s), 1685 (s), 1635 (w), 1605 (s), 1460 (w), 1430 (w), 1405 (w), 1390 (m), 1375 (m), 1340 (w), 1320 (w), 1310 (w), 1270 (m), 1240 (m), 1220 (w), 1190 (m), 1150 (w), 1130 (w), 1110 (w), 1080 (w), 1065 (w), 1005 (m), 970 (w), 930 (m), 905 (w), 890 (w), 880 (m), 735 (w), 675 (w). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.06 (3H, s), 1.10 (3H, s), 1.13 (3H, s), 1.13 (3H, s), 1.20–1.80 (4H, m), 1.92 (1H, dd, J = 7 and 12 Hz), 2.07–2.17 (3H, m), 2.34 (1H, ddd, J = 3, 4 and 15 Hz), 2.49 (1H, d, J = 7 Hz), 2.50 (1H, d, J = 12 Hz), 2.78 (1H, ddd, J = 5, 15 and 15 Hz), 5.00 (1H, dd, J = 1 and 11 Hz), 5.02 (1H, dd, J = 1 and 18 Hz), 5.83 (1H, dd, J = 11 and 18 Hz), 6.80 (1H, dd, J = 2 and 3 Hz). GLC (column: 3% SE-30, 2 m × 3 mm at 220°; carrier gas: N_2, 1.4 kg/cm^2): R_t: 9.6 min (94.6%). MS: *m/z* 300.2096 $[M]^+$. Calc for $C_{20}H_{28}O_2$: 300.2088. In the same manner as described above, (−)-**1'** (1.5 mg) yielded (−)-**3'** (1.5 mg) as rhombs from *n*-hexane, m.p. 146–147.5°, $[\alpha]_D^{23}$ −120° (*c* = 0.01, MeOH). GLC [under the same conditions as described for (+)-**3**]: R_t: 9.6 min (93.6%). MS: *m/z* 300.2034 $[M]^+$. Calc for $C_{20}H_{28}O_2$: 300.2089. The IR and NMR spectra of (−)-**3'** were identical with those of (+)-**3**. The synthetic enantiomers of **3** showed IR and NMR spectral data identical with those of natural **3**.

(±) - 3β,7α - *Dihydroxyisopimara* - 8(14),15 - *diene* [(±)-**19b**]. As described for the synthesis of (+)-**1**, (±)-**4a** (27 mg) was acetylated and oxidized with SeO_2 to give (±)-**19a** (16 mg, 49%). This was hydrolysed with KOH–MeOH to give (±)-**19b**, m.p. 147–149°. IR ν_{max} cm^{-1}: 3310 (br s), 1625 (w), 1015 (s). ^{1}H-NMR (100 MHz, $CDCl_3$): δ 0.78 (3H, s), 0.83 (3H, s), 1.03 (3H, s), 1.05 (3H, s), 1.00–2.30 (12H, m), 3.29 (1H, dd, J = 4 and 4 Hz), 4.22 (1H, dd, J = 3 and 3 Hz), 4.93 (1H, dd, J = 2 and 10 Hz), 4.94 (1H, dd, J = 2 and 18 Hz), 5.54 (1H, d, J = 2 Hz), 5.80 (1H, dd, J = 10 and 18 Hz). MS: *m/z* 304.2409 $[M]^+$. Calc for $C_{20}H_{32}O_2$: 304.2404. The NMR spectrum of (±)-**19b** was identical with that reported by Kono *et al.*[3]

Acknowledgements—We thank Professor T. Akatsuka of Ibaraki University for his kind supply of authentic samples of oryzalexin A, B and related compounds. We are indebted to Drs S. Takeuchi and Y. Kono of the Institute of Physical and Chemical Research for copies of IR and NMR spectra of oryzalexin A and also for a copy of the NMR spectrum of (−)-**4a**. Our thanks are due to Dr H. Seto and Mr K. Furihata of the Institute of Applied Microbiology, University of Tokyo, for 400 MHz NMR measurements. Financial support of this work by T. Hasegawa Co. is gratefully acknowledged.

REFERENCES

[1] J. W. Rowe, *The Common and Systematic Nomenclature of Cyclic Diterpenes*. Forest Products Laboratories, U.S.D.A. (1968).
[2] T. Akatsuka, O. Kodama, H. Kato, Y. Kono and S. Takeuchi, *Agric. Biol. Chem.* **47**, 445 (1983).
[3] Y. Kono, S. Takeuchi, O. Kodama and T. Akatsuka, *Ibid.* **48**, 253 (1984).
[4] H. A. Candy, J. M. Pakshong and K. H. Pegel, *J. Chem. Soc.* (*C*) 2536 (1970).
[5] R. A. Laidlaw and J. W. W. Morgan, *J. Chem. Soc.* 644 (1963).
[6] R. B. Turner, K. H. Gänshirt, P. E. Shaw and J. D. Tauber, *J. Am. Chem. Soc.* **88**, 1776 (1966).
[7] J. W. Cornforth and R. Robinson, *J. Chem. Soc.* 1855 (1949).
[8] K. Mori and M. Matsui, *Tetrahedron* **24**, 3095 (1968).
[9] R. E. Ireland and P. W. Schiess, *J. Org. Chem.* **28**, 6 (1963).
[10] G. A. Olah, S. C. Narang, R. G. B. Gupta and R. Malhotra, *J. Org. Chem.* **44**, 1247 (1979).
[11] K. Mori, T. Ogawa, N. Itaya, M. Matsui and Y. Sumiki, *Tetrahedron* **25**, 1281 (1969).
[12] M. Shiozaki, K. Mori and M. Matsui, *Agric. Biol. Chem.* **36**, 2539 (1972).
[13] R. F. Church and R. E. Ireland, *J. Org. Chem.* **28**, 17 (1963).
[14] K. Mori and M. Matsui, *Agric. Biol. Chem.* **34**, 1198 (1970).
[15] R. B. Woodward and T. J. Katz, *Tetrahedron* **5**, 70 (1959).
[16] J. J. Martel, J. P. Demoute, A. P. Téche and J. R. Tessier, *Pestic. Sci.* **11**, 188 (1980).
[17] K. Mori, T. Uematsu, M. Minobe and K. Yanagi, *Tetrahedron* **39**, 1735 (1983).
[18] J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.* **95**, 512 (1973).
[19] H. Gerlach, *Helv. Chim. Acta* **51**, 1587 (1968).
[20] E. J. Corey and G. W. J. Fleet, *Tetrahedron Lett.* 4499 (1973).
[21] J. D. Albright and L. Goldman, *J. Am. Chem. Soc.* **87**, 4214 (1965).