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SYNTHESIS OF MONO- AND SESQUITERPENOIDS—II*

(±)-SESQUICARENE AND A MIXTURE OF (±)-SIRENIN AND ITS C-7 EPIMER

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Abstract—The title compounds were synthesized by the application of the intramolecular α-ketocarbene olefin addition. Some intermediates for the synthesis of (±)-sirenin showed insect juvenile hormone activity.

THE SYNTHESIS of some caran-2-ones (I) by the intramolecular α-ketocarbene—olefin addition[1] has recently been reported by us.[2] This paper describes in detail its application to the synthesis of (±)-sesquicarene (IIa)† and a mixture of (±)-sirenin and its C-7 epimer; this work has been reported in preliminary form.[3,4]

Racemic sesquicarene

Sesquicarene (deoxysirenin, IIa) is a sesquiterpene hydrocarbon isolated from the essential oil of fruits of *Schisandra chinensis* Bail. by Ohta and Hirose.[5] It is the isoprene homologue of Δ^2-carene[5] and postulated to be a precursor of sirenin (IIb) in the possible biogenetic scheme.[6] Since its synthesis seemed more feasible than that of sirenin, we attacked this problem first as described below.

4,8-Dimethylnona-3,7-dienyl bromide (III)[7] was condensed with diethyl methylmalonate to give a disubstituted malonic ester (IVa, 42%). This was hydrolyzed and decarboxylated to give an acid (Va, 80%), which consisted of Δ^5-*trans* Δ^5-*trans*- and *cis*-isomers (3·5 : 1) judging from the GLC analysis of the corresponding Me ester (VIa). The sodium salt of the acid (Va) was treated with oxalyl chloride to give an acyl chloride (VIIa). This was converted into a diazoketone (VIIIa) by treatment with ethereal diazomethane. A cyclohexane solution of the diazoketone (VIIIa) was heated under reflux in the presence of powdered copper and cupric sulfate to give a crude product (IXa + IXa') in 59% yield from the acid (Va). This was chromatographed on silicic acid impregnated with silver nitrate[8] to give an analytically pure product (IXa + IXa') which was revealed by GLC analysis to be a mixture of (±)-sesquicaran-2-one (IXa) and its C-7 epimer (IXa') in the ratio of 2·4 : 1. The 7β-Me isomer (IXa) was assumed to exhibit a longer retention time because of its extending C_6 side-chain. The assignment of the α-configuration to the C-3 Me group is based on our previous observa-

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† Although the formulae depicted represent only the enantiomer, they are taken to mean a racemate in the case of synthetic products.

tion[2] that 1-diazo-3,7-dimethyloct-6-en-2-one yields (±)-*trans*-caran-2-one upon cyclization.

The introduction of the C-2,3-double bond was accomplished by the treatment of the corresponding oily tosylhydrazone (X + X') with n-butyllithium[9,10] to give a crude mixture of hydrocarbons (mainly IIa + IIa') in 22% yield from the ketone (IXa + IXa'). This was purified by preparative GLC to give pure (±)-sesquicarene (IIa) which showed IR and NMR spectra identical with those of the natural product. The identity was also demonstrated by the GLC comparison kindly carried out by Dr. Y. Ohta.

After the completion of our work, four other syntheses of this hydrocarbon have been announced as preliminary communications,[11,12,13,14] all employing the carbene addition as the key step.

Racemic sirenin

Sirenin (IIb) is the sperm attractant produced by the female gametes of the water mold *Allomyces*.[15] Its structure was elucidated by Nutting, Rapoport and Machlis.[6,16] Aside from its own importance as a plant sex hormone, sirenin is structurally very similar to the bisabolene-type sesquiterpenes with insect juvenile hormone activity such as juvabione (XI)[17,18] and dehydrojuvabione (XII).[18,19] Therefore our synthetic scheme was planned to include some intermediates such as XVIIa, XXa and XXIIa which might possess juvenile hormone activity.

The earlier stages of the synthesis leading to a bicyclic ketone (IXb) are entirely parallel to those employed for the preparation of IXa. The bromide (III)[7] was condensed with diethyl malonate to give a monosubstituted malonic ester (IVc, 69%). This was hydrolyzed and decarboxylated to give an acid (Vb, 90%) which was a mixture of Δ^5-*trans*- and *cis*-isomers (2·5 : 1) as shown by the GLC analysis of the corresponding Me ester (VIb). The acid (Vb) in benzene was treated with thionyl chloride to give an unstable acyl chloride (VIIb, 73%) which was converted to a diazoketone (VIIIb) by treatment with ethereal diazomethane. Its cyclohexane solution was heated under reflux in the presence of powdered copper and cupric sulfate to give a crude product (IXb + IXb') in 84% yield from the acyl chloride (VIIb). This was chromatographed on silicic acid impregnated with silver nitrate[8] to give an analytically pure product (IXb + IXb'). The ratio of IXb to IXb' was approximately 2:1 by GLC analysis. In the NMR spectrum of the analytically pure ketone, the signal due to C-7 β-Me protons appeared at 1·13 ppm (>2H), while the C-7 α-Me protons absorbed at 1·16 ppm (<1H). Rapoport *et al.* report 1·11 and 1·13 ppm for the C-7 Me absorptions of pure IXb and IXb' respectively.[20]

Introduction of the one-carbon unit at C-3 was carried out in the following manner. The bicyclic ketone (IXb + IXb') was formylated with ethyl formate and sodium hydride to give a formyl ketone (XIII).* This yielded the n-butylthiomethylene derivative (XIV) by treatment with *p*-toluenesulfonyl chloride and n-butyl mercaptan in pyridine.[21] Its reduction by sodium borohydride in ethanol afforded a crude alcohol (XV), which, without further purification, was treated with mercuric chloride and cadmium carbonate in ethanol to give an impure aldehyde (XVI). This was converted into an ester (XVIIa) by the method of Corey *et al.*[22] followed by chromatographic

* The intermediates XIII–XXII were obtained as stereoisomeric mixtures epimeric at C-7. For simplicity the formulae XIII–XXII were depicted without configurational notation.

purification on silicic acid impregnated with silver nitrate to remove bisabolene-type by-products generated by the cleavage of the cyclopropane ring. However, the recently described alternate preparation of the ethyl ester (XVIIb) was more convenient.[11] Thus the ketone (IXb + IXb') was carbethoxylated with diethyl carbonate and sodium hydride in benzene to give a β-keto ester (XVIII) which was reduced with sodium borohydride to give a hydroxy ester (XIXa). The corresponding benzoate (XIXb) was treated with potassium t-butoxide in t-butanol-benzene to yield the α,β-unsaturated ester (XVIIb). Its alkaline hydrolysis gave an acid (XVIIc). This was methylated to give the methyl ester (XVIIa) identical with the sample prepared *via* the formyl ketone (XIII). The esters XVIIa and XVIIb were shown to be mixtures of C-7 β-Me and C-7 α-Me isomers in the ratio of 2 ~ 2·6:1 by GLC. In the NMR spectra of XIII, XIV, XV and XVI, the signals due to C-7 α-Me protons were indiscernible because of the complex absorptions at 1·0–1·5 ppm, although the sharp C-7 β-Me absorptions (>2H) were clearly discernible. The presence of the corresponding C-7 α-Me isomers in the other intermediates was indicated by the appearance of a sharp signal (<1H) near the main sharp signal (>2H) due to the C-7 β-Me protons at 1·00 ppm (see *Experimental*). Although the relative intensity of the two peaks (area ratio) was difficult to determine, it was in rough accord with the ratio of the two isomers revealed by GLC in the cases of XVIIa and XVIIb. For almost all intermediates (XVIIa, b; XVIII; XXa, b; XXIa, b; and XXIIa, b) the C-7 β-Me protons absorbed at higher field than those of the C-7 α-Me group. In the NMR spectra of the hydroxy ester (XIXa) and the benzoate (XIXb), however, the situation was reversed suggesting that the conformation of the bicyclic ring system in XIXa, b is different from that in the others.

Modification of the side-chain was accomplished in a somewhat involved manner but resulted in the preparation of some new compounds with juvenile hormone activity. Treatment of the esters (XVIIa and b) with *m*-chloroperbenzoic acid in dichloromethane gave epoxy esters XXa (94%) and XXb (94%), respectively. The epoxides were reacted with periodic acid (H_5IO_6) in ether[23] to yield aldehydes XXIa (99%) and XXIb (99%). Both were characterized as their crystalline 2,4-dinitrophenylhydrazones. Although the epoxides and the aldehydes are mixtures of stereoisomers at C-7 (C-7 β-Me isomer: α-isomer = 2–2·5:1) judging from their NMR spectra, the recrystallized and sharply melting 2,4-dinitrophenylhydrazones seem to be the pure C-7 β-Me isomers, for in their NMR spectra only a sharp 3H singlet due to C-7 Me protons was observed (*see Experimental*) with no other sharp signal at 1·00–1·60 ppm. The aldehydes were subjected to the modified Wittig reaction[24] with ethyl α-diethylphosphonopropinate and sodium hydride in 1,2-dimethoxyethane to give diesters XXIIa (36% yield after chromatographic purification on alumina) and XXIIb (39% after the purification). The *trans* geometry of the double bond in the side chain was supported by the NMR spectra of XXIIa and b. The olefinic proton on that double bond absorbed at δ = 6·68–6·70 ppm. The previously observed values for this type of olefinic proton are 6·42–6·86 ppm while the olefinic proton of *cis* isomers absorbs at 5·35–5·91 ppm.[25] The ratio of the stereoisomers at C-7 in XXIIa and b could not be determined by GLC owing to their thermal decomposition (Castor wax column at 190°). The NMR spectrum of XXIIa, however, revealed it to be a mixture of C-7 β-Me and α-Me isomers (approx 2·5:1). Reduction of the diesters (XXIIa and b) with lithium aluminum hydride gave a crude product which was chromatographed on

TABLE 1. NMR DATA FOR NATURAL SIRENIN AND THE SYNTHETIC PRODUCT

Natural Product (at 60 MHz)			Synthetic Product (at 100 MHz)		
δ (ppm)	Splitting	Integration (H's)	δ (ppm)	Splitting	Integration (H's)
			0·84	s	< 1
0·88[a]	s	3	0·87[a]	s	> 2
0·98	br.s	1–2	0·98	br.s	1–2
1·25	m	2–3	1·15	br.s	< 1
1·40	br.s	1–2	1·20	br.s	~ 1
			1·28	br.s	~ 1
			1·40	s	< 1
1·67[a]	br.s	3	1·66[a]	br.s	3
1·83	br.s	1–2	1·78	br.s	1–2
	(with shoulders)		1·86	s	~ 1
2·10	br.s	~ 2	2·00	br s	< 1
2·20	br.s	~ 1	2·10	s	~ 1
2·30	br.s	< 1	2·15	s	< 1
2·91[b]	s	2	2·25[b]	s	2
3·97[a]	s	4	3·96[a]	s	4
5·39[a]	t (J = 7Hz)	1	5·40[a]	t (J = 7Hz)	1
5·80[a]	br.s ($W_{\frac{1}{2}}$ = 8Hz)	1	5·85[a]	br.s ($W_{\frac{1}{2}}$ = 8Hz)	1

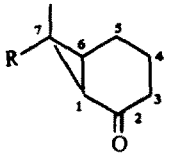
[a] Major characteristic absorptions

[b] Absorption due to two-OH. Variable with concentration of the sample.

alumina[15] to afford (±)-sirenin (IIb) contaminated with some C-7 epimer (IIb') as a viscous oil (62% yield). Its acetylation with acetic anhydride-pyridine gave (±)-sirenin diacetate (IIc) containing some C-7 epimer (IIc'). Attempted GLC analysis of the synthetic sirenin and its acetate failed owing to their thermal decomposition on the column (Castor wax at 190°). The IR and NMR data for the synthetic sirenin are in gross agreement with the spectral data kindly sent to us by Professor H. Rapoport. The NMR data for natural and the synthetic sirenin are shown in Table 1.

Since the high field region of the spectrum of the synthetic product is rather complicated, it is difficult to discern the absorption due to C-7 α-Me protons. If a shoulder-like sharp singlet at 0·84 ppm is to be ascribed to that Me group, the ratio of IIb and IIb' is approx 2·5 : 1. Some minor differences observable in the spectra of the natural and synthetic products are due to the presence of the C-7 α-Me isomer in the synthetic product. The difference in the field strength of the two spectrometers is also partly responsible. The bis-*p*-(*p*-nitrophenylazo) benzoate ester (bis-NABS-(±)-sirenin, IId)[15,26] was obtained as orange-red prisms, m.p. 168–170°, after chromatographic purification on alumina followed by repeated recrystallization. The crude bis-NABS ester, before recrystallization, contained the C-7 α-Me isomer as indicated by the presence of a sharp singlet (< 1H) at 1·15 ppm in its NMR spectrum in addition to a singlet (> 2H) at 0·98 ppm due to the C-7 β-Me protons. The former absorption was absent in the spectrum of the recrystallized product. The pure bis-NABS-(±)-sirenin (IId) was both spectrophotometrically and chromatographically identical with an authentic sample. The comparison was kindly carried out by Professor H. Rapoport.

At about the same time as the submission of our preliminary communication,[4]



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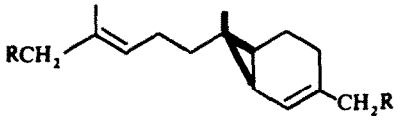
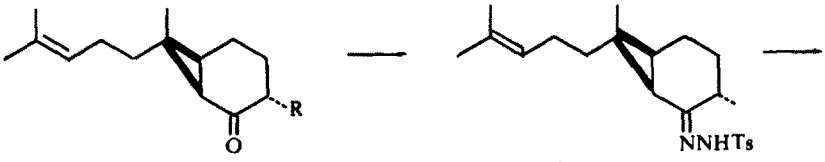


IIa R = H; IIb R = OH

$Me_2C = CH(CH_2)_2CMe = CH(CH_2)_2Br \rightarrow$  $\rightarrow$

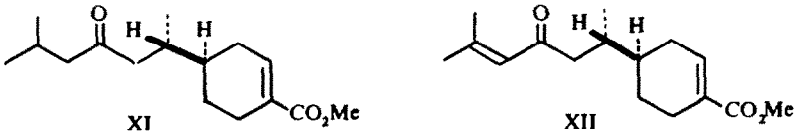
III IVa R′ = Me; IVb R′ = H
R = $Me_2C{=}CH(CH_2)_2CMe{=}CH(CH_2)_2$–

Va R′ = Me R″ = H VIIa R′ = Me VIIIa R′ = Me
b H H b H b H
VIa Me Me R = $Me_2C = CH(CH_2)_2CMe = CH(CH_2)_2$–
b H Me

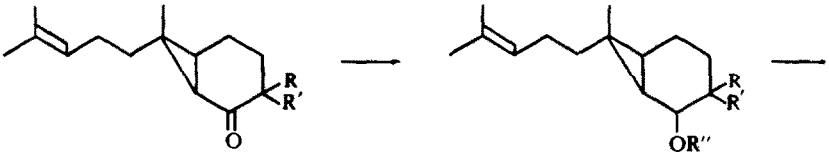


IXa, R = Me C-7 β-Me X C-7 β-Me
IXa′ Me C-7 α-Me X′ C-7 α-Me
IXb H C-7 β-Me
IXb′ H C-7 α-Me

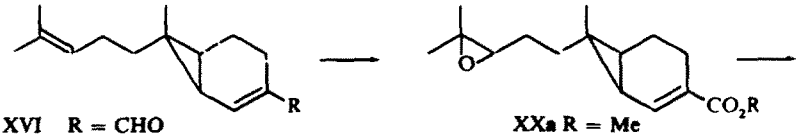
IIa IIa′



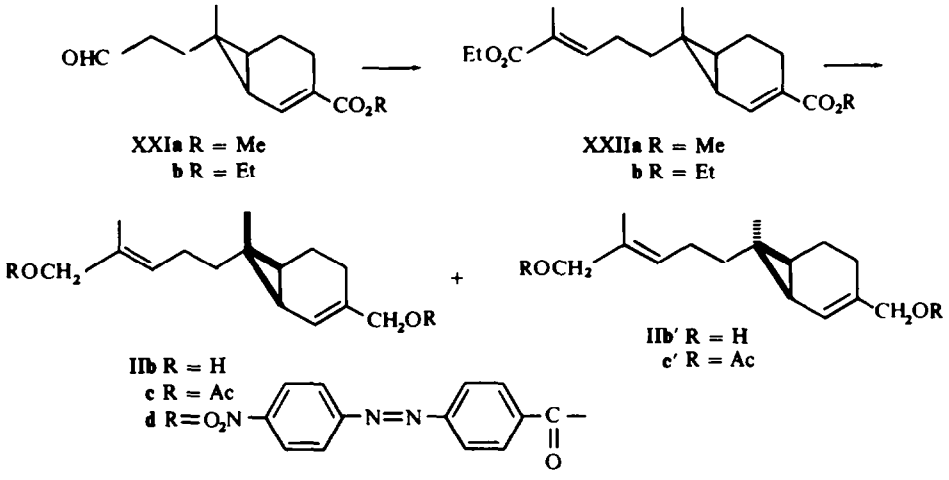
XI XII



XIII R,R′ = CHOH XV R,R′ = CHSBu^a; R″ = H
XIV R,R′ = CHSBu^a XIXa R,R″ = H; R′ = CO_2Et
XVIII R = H; R′ = CO_2Et b R = H; R′ = CO_2Et; R″ = COC_6H_5



XVI R = CHO XXa R = Me
XVIIa R = CO_2Me b R = Et
b R = CO_2Et
c R = CO_2H



XXIa R = Me
b R = Et

XXIIa R = Me
b R = Et

IIb R = H
c R = Ac
d R = O_2N

IIb′ R = H
c′ R = Ac

TABLE 2. BIOLOGICAL ACTIVITY OF THE SYNTHETIC SIRENIN

Compound	Concentration	Male gametes per unit membrane
Natural sirenin (IIb)	10^{-7}M	59
(±)-Sirenin[a] (IIb + IIb′)	10^{-7}M	15
Natural sirenen (IIb)	10^{-7}M	49
Natural sirenin (IIb)	10^{-8}M	7
(±)-Sirenin[b] (IIb + IIb′)	10^{-6}M	39
(±)-Sirenin[b] (IIb + IIb′)	10^{-7}M	9
(±)-Sirenin[b] (IIb + IIb′)	10^{-8}M	1

[a] Chemically impure material sent by us was assayed immediately after the receipt at Berkeley.

[b] Chemically pure material after chromatographic purification was stored as CH_2Cl_2 soln for approx 20 days at Berkeley prior ro the assay.

TABLE 3. INSECT JUVENILE HORMONE ACTIVITY OF THE SYNTHETIC MATERIALS

Compounds	Dosage		
	0·1 μg	1·0 μg	10 μg
XVIIa	0	0	NAI[a]
XXa	0	0	NAI
XXIIa	0	NAI	SN[b]
(±)-Sirenin (IIb + IIb′)	0	0	0
Juvabione (XI)	0	NAI	SN

[a] Nymphal-adult intermediate—active.

[b] Supernumerary nymph—highly active.

three other groups published their results on the synthesis of racemic sirenin, all of them employing the α-ketocarbene—olefin addition as the key step.[20,27,28]

The biological activity of the synthetic sirenin on the sperm of *Allomyces* was kindly tested by Professor L. Machlis.[29] The results are summarized in Table 2. The activity was qualitatively identical with but quantiatively less (1/4–1/10) than that of the natural material.*

The insect juvenile hormone activity of XVIIa, XXa, XXIIa and the synthetic sirenin was tested on *Dysdercus koenigii* (red cotton stainer) by the courtesy of Dr. W. S. Bowers, USDA Agricultural Research Service. The results are shown in Table 3. All compounds except (±)-sirenin were active but only the diester (XXIIa) was as active as juvabione (XI). Contrary to expectation, the epoxy ester (XXa) was not so active. Why the diester (XXIIa) is more active than the epoxy ester (XXa) is an interesting question.

EXPERIMENTAL

All m.ps. and b.ps. were uncorrected. IR spectra refer to Nujol mulls for solid samples and films for liquids. NMR spectra were recorded at 100 MHz in CCl_4 with TMS as an internal standard unless otherwise stated.

Ethyl 2-carbethoxy-2,6,10-trimethylundeca-5,9-dien-1-oate (IVa). A soln of diethyl methylmalonate (52g) in EtOH (60 ml) was added to a soln of NaOEt (from 7g of Na) in EtOH (140 ml). To this mixture III (50g) in EtOH (20 ml) was added with stirring at 0–5°. After stirring for 30 min at 0–5°, the mixture was heated under reflux for 4 h with stirring, concentrated *in vacuo*, poured into water and extracted with ether. The ethereal soln was washed with sat NaCl aq, dried ($MgSO_4$) and concentrated. The residue was distilled to give 32·5g (48%) of IVa, b.p. 160–174°/5mm. An analytical sample boiled at 161–162°/4mm, n_D^{18} 1·4612; ν_{max} 1725, 1280, 1250, 1180, 1120, 1040, 860 cm^{-1}; δ 1·25 (6H, t, J = 6Hz), 1·35 (3H, s), 1·58 (6H, s), 1·66 (3H, s), 6·10 (4H, q, J = 6Hz), 5·05 (2H, broad) ppm. (Found: C, 70·24; H, 9·91. $C_{19}H_{32}O_4$ requires: C, 70·33; H, 9·94%).

Ethyl 2-carbethoxy-6,10-dimethylundeca-5,9-dien-1-oate (IVb). This was prepared in the same manner as described above from III (60 g), diethyl malonate (48g) and Na (7g) in EtOH (200 ml) in 69% yield (55g), b.p. 145–160°/3mm. An analytical sample boiled at 135–138°/3mm, n_D^{14} 1·4630; ν_{max} 1730, 1300, 1250, 1220, 1145, 1090, 1050, 1030, 860 cm^{-1}; δ 1·25 (6H, t, J = 6Hz), 1·56 (6H, s), 1·63 (3H, s), 4·06 (4H, q, J = 6Hz), 5·00 (2H, broad) ppm. (Found: C, 69·66; H, 9·25. $C_{18}H_{30}O_4$ requires: C, 69·64; H, 9·74%).

2,6,10-Trimethylundeca-5,9-dien-1-oic acid (Va). A soln of IVa (31 g) in 95% EtOH (50 ml) was mixed with KOH aq (31g in 80 ml). The mixture was stirred and heated under reflux for 3 h and concentrated *in vacuo* to remove EtOH. After acidification with AcOH (100 ml) the mixture was heated under reflux for 2 days, cooled, diluted with water and extracted with ether. The ethereal soln was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 19·2 g (80%)

* The reason for this low activity may be as follows: (i) The sample contains the C-7 epimer (IIb') although its amount is at most 1/3 of the total material (in XVIIb, C-7 β-Me isomer: α-isomer = 2·6 : 1; see also the NMR data for the synthetic sirenin and its bis-NABS ester). (ii) The sample is racemic. Assuming that only IIb with proper absolute stereochemistry is biologically active, the activity of our material should be (2/3) × (1/2) = 1/3 that of the natural material. (iii) Our sample is not so impure to cause such a drop in activity because of the reasonable IR, NMR and analytical data. Moreover, quite pure bis-NABS-(±)-sirenin could be obtained from our material. (iv) It is possible that our sample partly decomposed during its storage as a methylene chloride solution prior to the bioassay (about 20 days). This cannot be evaluated at present, since nothing is known about the stability of such a solution. Grieco mentioned such a possibility.[28] (v) Our material may possibly contain some inhibitory compounds, for it is not known what kind of substances are inhibitory.

of Va, b.p. 150–160°/0·5 mm. An analytical sample boiled at 131–132°/0·15 mm, n_D^{17} 1·4714; ν_{max} ~3200 – ~2600, 1700, 1300, 1250, 1180, 1120, 950, 900, 840 cm^{-1}; δ 1·18 (3H, d, J = 6Hz), 1·58 (6H, s), 1·66 (3H, s), 5·05 (2H, broad) ppm. (Found: C, 75·00; H, 10·69. $C_{14}H_{24}O_2$ requires: C, 74·95; H, 10·78%). GLC (as Me ester VIa): Castor wax, 45m × 0·5 mm i.d., Column temp 190°, Carrier gas, N_2, 0·5kg/cm^2, Rt 9·8 min (Δ^5-*cis*), 10·8 min Δ^5-*trans*)(*cis*:*trans* = 1:3·5).

6,10-*Dimethylundeca*-5,9-*dien*-1-*oic acid* (Vb). This was prepared in the same manner as described for Va starting from IVb (118g) in 90% yield (72g), b.p. 146–155°/1·2 mm. An analytical sample boiled at 146–148°/0·6 mm, n_D^{17} 1·4732; ν_{max} 3200–2600, 1700, 940 cm^{-1}; δ 1·58 (6H, s), 1·66 (3H, s), 5·01 (2H, broad), 13·71 (1H, s) ppm. (Found: C, 74·17; H, 10·50. $C_{13}H_{22}O_2$ requires: C, 74·24; H, 10·54%). *Methyl ester* (VIb). b.p. 113–115°/4 mm. n_D^{18} 1·4630; ν_{max} 1742, 1255, 1200, 1175, 880, 825 cm^{-1}. (Found: C, 75·02; H, 10·90 $C_{14}H_{24}O_2$ requires: C, 74·95; H, 10·78%). GLC: Castor wax, 45m × 0·5mm i.d., Column temp 190°, Carrier gas, N_2, 0·5kg/cm^2, R, 9·5 min (Δ^5-*cis*), 10·3 min (Δ^5-*trans*)(*cis*:*trans* = 1:2·5).

2,6,10-*Trimethylundeca*-5,9-*dien*-1-*oyl chloride* (VIIa). A soln of Va (18·2 g) in MeOH (50 ml) was neutralized with NaOMe (4·5g) in MeOH (100 ml). The soln was concentrated *in vacuo*. The Na salt of Va was suspended in dry benzene and the benzene was removed *in vacuo*. This was repeated several times to remove MeOH and the dry Na salt was suspended in dry benzene (150 ml) containing pyridine (1·2 ml). Oxalyl chloride (35g) was added to the suspension with shaking at 0–5°. The mixture was stirred for 1 h at 0–5°, filtered through Celite and concentrated *in vacuo* to give an oily VIIa. This was employed for the next step without further purification.

6,10-*Dimethylundeca*-5,9-*dien*-1-*oyl chloride* (VIIb). A soln of Vb (34g) in dry benzene (200 ml) was mixed with thionyl chloride (22·5 g) and the mixture was heated under reflux for 1 h. After removal of the solvent, the residue was distilled to give 27·1g (73%) of VIIb, b.p. 105–115°/0·2 mm; ν_{max} 1790 cm^{-1}. This was unstable and slowly darkened and thus was employed for the next step without delay.

1-*Diazo*-3,7,11-*trimethyldodeca*-6,10-*dien*-2-*one* (VIIIa). A soln of the above described VIIa (from 18·2 g of Va) in dry benzene (50 ml) was added to a soln of CH_2N_2 (from 30 g of N-nitroso-N-methylurea) in ether (approx 500 ml) under ice-cooling. The mixture was left to stand overnight at 5–10°, filtered and concentrated *in vacuo* to give crude VIIIa as a yellow oil, ν_{max} 2120, 1820 (weak, impurity), 1740 (weak, impurity), 1645 (C = O, s), 1380, 1330, 1145, 1100, 1020 cm^{-1}. This was employed for the next step without further purification.

1-*Diazo*-7,11-*dimethyldodeca*-6,10-*dien*-2-*one* (VIIIb). A soln of VIIb (27·1g) in dry benzene (50 ml) was added to a soln of CH_2N_2 (from 60g of N-nitroso-N-methylurea). Subsequent treatments as described for VIIIa gave crude VIIIb as a yellow oil, ν_{max} 2120 (s), 1730 (w, impurity), 1645 (s)cm^{-1}. This was employed for the next step without further purification.

3,7-*Dimethyl*-7-(4′-*methylpent*-3′-*enyl*)*bicyclo*[4.1.0]*heptan*-2-*one* (*a mixture of* (±)-*sesquicaranone and its* C-7 *epimer*) (IXa + IX′a). A soln of the above VIIIa (from 18·2 g of Va) in cyclohexane (200 ml) was added dropwise to a stirred and refluxing suspension of powdered Cu (1·2 g) and $CuSO_4$ (0·2 g) in cyclohexane (400 ml) during 1 h. After the addition the mixture was stirred and heated under reflux for 8 h, then cooled, filtered and concentrated *in vacuo*. The residue was distilled to give the following fractions: (a) b.p. 100–132°/5mm, 1·3 g, (b) b.p. 133–135°/5mm, 5·7 g, (c) b.p. 136–145° (mainly 140°)/5mm, 3·5g, (d) b.p. 146–156°/5mm, 2·8g. Fractions a, b and c exhibited almost identical IR spectra [ν_{max} 1725 (w), 1675 (s), 886 (s)cm^{-1}] and were shown to be an impure mixture of IXa and IX′a. Fraction b had the following properties: n_D^{19} 1·4868; ν_{max} 1725 (w), 1675 (s), 1460, 1380 (s), 1356, 1330, 1240, 1225, 1180, 1115, 1060, 1035, 886 (s) cm^{-1}; δ 0·98 (3H, d, J = 6Hz), 1·16 (3H, s), 1·60 (3H, s), 1·66 (3H, s), 5·03 (1H, t) ppm. (Found: C, 80·83; H, 10·91. $C_{15}H_{24}O$ requires: C, 81·76; H, 10·98%). This was purified by chromatography on SiO_2-$AgNO_3$. A column (27 × 2·5 cm) in light petroleum was prepared from SiO_2 (50g) and $AgNO_3$ aq (4g in 20 ml). A part of the fraction b (2·00g) in a small amount of light petroleum was placed on the top of the column. The eluant was saturated with $Ag^{\oplus}$ by shaking with $AgNO_3$ aq in a separating funnel prior to use. All fractions were 250 ml. Eluants were as follows: fractions 1–9 light petroleum; 10–13, light petroleum benzene = 4:1; 14, benzene. Fractions 2 and 3 gave 827 mg of oily impurity. Fraction 4 was impure IXa + IX′a (130 mg). Fractions 5–8 gave 400 mg of pure bicyclic ketone (IXa + IX′a). Fractions 9–14 gave 710 mg of almost pure IXa + IX′a. Fractions 5–8 gave an analytical sample boiling at 130–131°/5mm, n_D^{20} 1·4898; ν_{max} 2950, 1676, 1450, 1380, 1350, 1330, 1240, 1220, 1185, 1110, 1050, 1030, 886 cm^{-1}; δ 0·98 (3H, d, J = 6Hz), 1·16 (3H, s, C-7 Me), 1·58 (3H, s), 1·65 (3H, s), 5·03 (1H, t) ppm. (Found: C, 81·50; H, 10·92. $C_{15}H_{24}O$ requires: C, 81·76; H, 10·98%). GLC: Castor wax, 45m × 0·5mm i.d.; Column temp 190°; Carrier gas, N_2, 0·5 kg/cm^2; R, 18·7 min (IX′a), 22·8 min (IXa). IX′a: IXa (area ratio) = 1:2·4.

7-*Methyl*-7-(4′-*methylpent*-3′-*enyl*)*bicyclo*[4.1.0]*heptan*-2-*one* (*a mixture of* (±)-3-*demethylsesquicaranone*

and its C-7 *epimer*)(IXb + IXb'). A soln of the above VIIIb (from 27·1g of VIIb) in cyclohexane (250 ml) was added dropwise to a stirred and refluxing suspension of powdered Cu (3g) and $CuSO_4$ (0·2g) in cyclohexane (650 ml) during 1 h. After the addition the mixture was stirred and heated under reflux for 2 h, then cooled, filtered and concentrated *in vacuo*. The residue was distilled to give 20·5g (62% from Vb, 84% from VIIb) of crude bicyclic ketone, b.p. 100–115°/0·3mm, ν_{max} 1730 (w, impurity), 1700 (sh), 1685 (s), 1626 (w, impurity), 1260, 1190, 895 cm^{-1}; δ 1·11 (< 3H, s), 1·56 (3H, s), 1·64 (3H, s), 4·98 (1H, broad) ppm.

This crude ketone was purified by chromatography on SiO_2-$AgNO_3$. A column (51 × 6 cm) in n-hexane was prepared from SiO_2 (500g) and $AgNO_3$ aq (40g/170 ml). The crude ketone (IXb + IXb', 32·6g) in a small amount of n-hexane was placed on the top of the column. The eluant was saturated with $Ag^{\oplus}$ by shaking with $AgNO_3$ aq in a separating funnel prior to use. All fractions were 500 ml. Eluants were as follows: fractions 1–12, n-hexane; 13–17, n-hexane: benzene = 1:1; 18–21, benzene. Fractions 1 and 2 gave 11·6g of oily impurity. Fraction 3 was 4·0g of impure ketone. Fractions 3–17 gave 15·9g of pure ketone. Fractions 18–21 gave 0·5g of impure ketone. Fractions 3–17 gave an analytical sample boiling at 117–118°/5mm, n_D^{19} 1·4948; ν_{max} 2980, 1680, 1455, 1420, 1390, 1350, 1335, 1250, 1220, 1190, 1120, 1070, 1050, 990, 930, 890, 830 cm^{-1}; δ 1·13 (> 2H, s, C-7 β-Me), 1·16 (< 1H, C-7 α-Me), 1·59 (3H, s), 1·65 (3H, s), 4·99 (1H, broad t) ppm. (Found: C, 81·65; H, 10·65. $C_{14}H_{22}O$ requires: C, 81·50; H, 10·75%). GLC: Castor wax, 45m × 0·5mm i.d.; Column temp, 190°; Carrier gas N_2, 0·5kg/cm^2; R_t 17·6 min (IXb'), 20·6 min (IXb). IXb': IXb (area ratio) = 1:2.

A mixture of tosylhydrazones of (±)-*sesquicaranone and its* C-7 *epimer* (X and X'). A soln of the crude ketone (IXa + IXa', 5·90g) in MeOH (20 ml) was mixed with a soln of tosylhydrazide (5·10g) in THF (45 ml). The mixture was left to stand at 5–10° for 15 h and concentrated *in vacuo*. Dry benzene was added to the residue and the benzene was removed *in vacuo*. This was repeated several times to remove water and MeOH. The oily crude tosylhydrazone (X + X'), ν_{max} 3200, 2950, 1615, 1600, 1455, 1390, 1340, 1175, 1110, 1030, 890, 820 cm^{-1}, was employed for the next step without further purification.

A mixture of (±)-*sesquicarene* (IIa) *and its* C-7 *epimer* (IIa'). A soln of the above X + X' (from 5·90g of IXa + IXa') in benzene (70 ml) was added dropwise during 30 min to a soln of n-BuLi (from 43g of n-BuBr and 4·0g of Li) in ether (150 ml) at 0–5° with stirring. After the addition, the mixture was stirred at room temp for 2 h. Subsequently water was added to the mixture under ice-cooling. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic soln was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated. The residue was fractionally distilled to give 1·2g (22%) of a hydrocarbon fraction, b.p. 95–105°/6mm. n_D^{17} 1·4850: ν_{max} 3360, 2950 (s), 1460 (s), 1390, 1130, 1040 (s), 830, 800 cm^{-1}; δ 0·84 (3H, s, C-7 Me), 1·58 (3H, s), 1·65 (6H, s), 5·03 (1H, broad, t) 5·46 (1H, broad, s) ppm. GLC: Castor wax, 45 m × 0·5 mm i.d.; Column temp, 170°; Carrier gas N_2, 0·5 kg/cm^2; 21 peaks were detected. Retention times of main peaks were: (a) 6·3; (b) 7·0; (c) 9·4; (d) 11·2 min. a:b:c:d (area ratio) = 1:1·9:1·8:4·1. All the four peaks showed M^+ at m/e 204 and similar MS patterns with that of the authentic MS of IIa. The peak d was thought to be racemic IIa.

(±)-*Sesquicarene* (IIa). The above described crude hydrocarbon mixture (1·15g) was purified by preparative GLC to give 0·15g of pure IIa. GLC: Column, Silicon oil DC 200 (20%) on Celite 545, 3m × 3mm i.d.; column temp, 200°, Carrier gas, He, 100 ml/min. The analytical GLC showed that this material corresponds to pure "peak d" of the crude mixture. An analytical sample boiled at 102–103°/6 mm, n_D^{17} 1·4920; ν_{max} 2960, 2920, 2850, 2730, 1660 (w), 1442 (s), 1375 (m), 1290 (w), 1200 (w), 1115 (w), 1090 (w), 1065, 990–945 (w), 880 (w), 850 (w), 820 (m) cm^{-1}; δ 0·83 (3H, s), 1·10, 1·16, 1·24, 1·30, 1·58 (3H, s), 1·64 (6H, s), 1·75, 1·82, 1·90, 1·96, 2·05, 2·13, 5·02 (1H, broad t), 5·45 (1H, broad, s) ppm. (Found: C, 88·24; H, 11·91. $C_{15}H_{24}$ requires: C, 88·16; H, 11·84%). M^+ 204. GLC (by Dr. Y. Ohta, Institute of Food Chemistry, Osaka): Gorey Column, HB 2000 at 150°; Carrier gas, N_2 (1·5 kg/cm^2); R_t 11·5 min (identical with that of authentic IIa).

3-*Formyl-7-methyl-7-(4'-methylpent-3'-enyl)bicyclo*[4.1.0]*heptan-2-one* (XIII, a stereoisomeric mixture). A mixture of the ketone (IXb + IXb', 6·5 g), HCO_2Et (8 ml) and NaOMe (4·0 g) in dry ether (40 ml) was stirred at 0–5° for 3 h. The gelatinous mixture was left to stand at 5–10° for 15 h, poured into ice-water and the aqueous layer was separated. The organic layer was extracted with ice-cooled 5% NaOH aq. The combined aqueous soln was acidified with dil HCl at 0–5° and rapidly extracted with ether. The extract was washed with sat NaCl aq, dried ($MgSO_4$) and concentrated. The residue was distilled to give 6·8 g (92%) of XIII, b.p. 117–119°/0·2 mm, n_D^{26} 1·5250; ν_{max} ~1640–~1580, 1460, 1390, 1330, 1220, 1170, 1065, 910, 880 cm^{-1}; δ 1·08 (>2H, s), 1·62 (3H, s), 1·68 (3H, s), 5·05 (1H, broad t), 6·25 (1H, s), 14·54 (1H, broad) ppm. (Found: C, 76·43; H, 9·30. $C_{15}H_{22}O_2$ requires: C, 76·88; H, 9·46%).

3-n-*Butylthiomethylene-7-methyl-7-(4'-methylpent-3'-enyl)bicyclo*[4.1.0]*heptan-2-one* (XIV, a stereoiso-

and the mixture was stirred for 45 min at 0–5°. n-BuSH (3·0 g) was added to the mixture and it was left to stand at 0–5° for 20 h. The mixture was poured into ice-cooled 1% NaOH aq (300 ml) and extracted with ether. The ethereal soln was washed with water, 10% NaOH aq, water and sat NaCl aq, dried (K_2CO_3) and evaporated. The residue was distilled to give 4·7 g (56%) of XIV, b.p. 190–200°/0·1 mm. An analytical sample boiled at 195–198°/0·1 mm, n_D^{24} 1·5426; ν_{max} 1655, 1560, 1460, 1390, 1320, 1230, 1200, 1120, 1070, 890 cm^{-1}; δ 0·99 (3H, t, J = 6 Hz), 1·06 (>2H, s), 1·63 (3H, s), 1·68 (3H, s), 5·05 (1H, broad, t), 7·25 (1H, s) ppm. (Found: C, 74·44; H, 9·72. $C_{19}H_{30}OS$ requires: C, 74·47; H, 9·87%).

3-n-*Butylthiomethylene-7-methyl-7-(4'-methylpent-3'-enyl)bicyclo*[4.1.0]*heptan-2-ol* (XV, a stereoisomeric mixture). To a soln of XIV (4·6 g) in 95% EtOH (100 ml), $NaBH_4$ (2·0 g) was added at 0–5°. The mixture was left to stand in a refrigerator for 16 h, concentrated *in vacuo*, diluted with water and extracted with ether. The ethereal soln was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo* to give 4·5 g (98%) of crude XV, ν_{max} ~3400, 1630, 1460, 1390, 1115, 1060 cm^{-1}; δ 0·94 (3H, t, J = 6 Hz), 1·09 (>2H, s), 1·61 (3H, s), 1·67 (3H, s), 2·98 (1H, s), 4·75 (1H), 5·05 (1H), 5·56 (1H) ppm. This was employed for the next step without further purification.

3-*Formyl-7-methyl-7-(4'-methylpent-3'-enyl)bicyclo*[4.1.0]*hept-2-ene* (XVI, a stereoisomeric mixture). A soln of XV (4·5 g) in 99% EtOH (80 ml) was mixed with $CdCO_3$ (2·6 g) and $HgCl_2$ (3·0 g) in 99% EtOH (50 ml). The mixture was stirred and heated under reflux for 1 h, concentrated *in vacuo*, diluted with ether and water and filtered. The ethereal soln was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was fractionally distilled to give the following fractions: (a) b.p. 98–118°/0·2 mm, 301 mg. (b) b.p. 118–126°/0·2 mm, 471 mg. (c) b.p. 126–140°/0·2 mm, 1·621 g. (d) b.p. 140–170°/0·2 mm, 813 mg. Inspection of the NMR spectra showed that all fractions were contaminated with products of cyclopropane ring cleavage with diminished high field Me signal at δ 0·95. The fraction b was the purest one containing at least 85% XVI judging from its NMR spectrum, ν_{max} 2720, 1680, 1645, 1400, 1180 cm^{-1}: δ 0·95 (<3H, s) 1·63 (>3H, s), 1·70 (3H), 5·05 (1H), 6·66 (1H), 9·41 (1H) ppm. Each fraction was separately employed for the next step.

3-*Carbomethoxy-7-methyl-7-(4'-methylpent-3'-enyl)bicyclo*[4.1.0]*hept-2-ene* (XVIIa, a stereoisomeric mixture). The crude XVI (fraction b, 450 mg) was dissolved in MeOH (30 ml) and mixed with AcOH (0·18 ml), MnO_2 (3·5 g) and NaCN (0·5 g). The mixture was stirred at room temp for 15 h, concentrated *in vacuo*, diluted with ether and water and filtered. The ethereal layer was separated and the aqueous layer was extracted with ether. The combined ethereal soln was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 250 mg of crude XVIIa, b.p. 140–145°/5 mm, n_D^{27} 1·5000; δ 0·92 (<3H, s), 1·61 (>3H, s), 1·67 (3H, s), 3·66 (3H, s), 5·06 (1H, t), 7·17 (1H, d, J = 5 Hz) ppm. The other fractions (a, c and d) were also processed as above to give 1·0 g of distilled crude XVIIa. This was chromatographed on SiO_2 (50 g) impregnated with $AgNO_3$ (10 g in 20 ml of water). The ester dissolved in a small amount of n-hexane was placed on the top of the column in n-hexane and the column was eluted with n-hexane. All fractions were 100 ml. Fractions 1 and 2 were foreruns. Fractions 3–5 gave 366 mg of almost pure XVIIa. Fractions 6–11 gave 457 mg of bisabolene-type esters without the cyclopropane ring. Fractions 3–5 (366 mg) were rechromatographed on SiO_2 (20 g) impregnated with $AgNO_3$ (4 g in 8 ml of water) in n-hexane. Elution with n-hexane gave 240 mg of pure XVIIa in the early fractions. An analytical sample boiled at 125–128°/1 mm, n_D^{30} 1·4958; ν_{max} 1700, 1630, 1440, 1390, 1280, 1250, 1110, 1070, 755 cm^{-1}; δ 0·92 (>2H, s, C-7 β-Me), 1·15 (<1H, s, C-7 α-Me), 1·61 (3H, s), 1·67 (3H, s), 3·66 (3H, s), 5·05 (1H, t), 7·16 (1H, d, J = 5 Hz) ppm. (Found: C, 77·69; H, 10·14. $C_{16}H_{24}O_2$ requires: C, 77·37; H, 9·74%).

3-*Carbethoxy-7-methyl-7-(4'-methylpent-3'-enyl)bicyclo*[4.1.0]*heptan-2-one* (XVIII, a stereoisomeric mixture). A soln of the chromatographically pure ketone (IXb + IXb', 8·5 g) in dry benzene (40 ml) was added to a suspension of 50% NaH (5 g) in ethyl carbonate (50 ml) under N_2. The mixture was gently heated with stirring for 1 h and then heated under reflux for 3 h. After cooling, it was poured into ice-water containing AcOH (8 ml) and extracted with ether. The extract was washed with water, $NaHCO_3$ aq and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 10·5 g (91%) of XVIII, b.p. 150–160°/1·2 mm. An analytical sample boiled at 142–143°/0·8 mm, n_D^{29} 1·4978; ν_{max} 1735 (w), 1640, 1610, 1310, 1260, 1230, 1120, 1070, 820 cm^{-1}; δ 1·06 (>2H, s, C-7 β-Me), 1·18 (<1H, s, C-7 α-Me), 1·31 (3H, t, J = 6 Hz), 1·63 (3H, s), 1·68 (3H, s), 4·17 (2H, q, J = 6 Hz), 5·10 (1H, t), 12·27 (1H, s) ppm. (Found: C, 73·71; H, 9·50. $C_{17}H_{26}O_3$ requires: C, 73·34; H, 9·41%).

3-*Carbethoxy-7-methyl-7-(4'-methylpent-3'-enyl)bicyclo*[4.1.0]*heptan-2-ol* (XIXa, a stereoisomeric mixture). To a soln of XVIII (10·2 g) in 95% EtOH (50 ml), $NaBH_4$ (2·8 g) in 95% EtOH (50 ml) was added with stirring at 5–10°. The mixture was stirred for 3 h at 5–10°, concentrated *in vacuo*, diluted with ice-water containing AcOH and extracted with ether. The ethreal soln was washed with $NaHCO_3$ aq and sat NaCl aq,

dried ($MgSO_4$) and concentrated *in vacuo* to give 10·0 g (98%) of XIXa. An analytical sample boiled at 150–152°/1 mm, n_D^{28} 1·4868; ν_{max} ~3400, 1715, 1200, 1050 cm^{-1}; δ ~0·90–~0·96 (2H, m), 1·05 (<1H, s, C-7 α-Me), 1·15 (>2H, s, C-7, β-Me), 1·26 (3H, t, J = 6 Hz), 4·12 (2H, q, J = 6 Hz), 4·35 (1H, broad), 5·06 (1H, t) ppm. (Found: C, 72·61; H, 10·31. $C_{17}H_{28}O_3$ requires: C, 72·82; H, 10·06%).

3-*Carbethoxy-7-methyl-7-(4'-methylpent-3'-enyl)bicyclo*[4.1.0]*heptan-2-ol benzoate* (XIXb, a stereoisomeric mixture). Benzoyl chloride (6 g) was added dropwise to a soln of XIXa (10·0 g) in dry benzene (60 ml) and dry pyridine (40 ml) at 0–5° with stirring. The mixture was left to stand in a refrigerator for 2 days, diluted with ice-water and extracted with ether. The extract was washed with water, $NaHCO_3$ aq and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo* to give crude oily XIXb (13·8 g, quantiative), ν_{max} 1705 (broad), 1600, 1585, 1280, 1120, 710 cm^{-1}; δ 1·00 (<1H, s, C-7 α-Me), 1·18 (>2H, s, C-7 β-Me), 1·21 (3H, t, J = 6 Hz), 1·45 (3H, s), 1·55 (3H, s), 4·03 (2H, q, J = 6 Hz), 4·95 (1H), 5·76 (1H, q), 7·30–8·20 (5H) ppm. This was employed for the next step without further purification.

3-*Carbethoxy-7-methyl-7-(4'-methylpent-3'-enyl)bicyclo*[4·1.0]*hept-2-ene* (XVIIb, a stereoisomeric mixture). A soln of XIXb (13·8 g) in dry benzene (60 ml) was added to a soln of t-BuOK (from 4·2 g of K) in t-BuOH (180 ml) at 0–5° with stirring. The stirring was continued for 1·5 h at 0–5°. Then the mixture was neutralized with AcOH aq and concentrated *in vacuo*. The residue was diluted with water and extracted with ether. The ethereal soln was washed with water, $NaHCO_3$ aq and sat NaCl aq, dried ($MgSO_4$) and concentrated. The residue was distilled to give 6·2 g (66%) of XVIIb, b.p. 140–155°/0·8 mm. An analytical sample boiled at 145–148°/2·0 mm, n_D^{31} 1·4962; ν_{max} 1708, 1635, 1280, 1240, 1095, 1055, 750 cm^{-1}; δ 0·93 (2·5H, s, C-7 β-Me), 1·16 (0·5H, s, C-7 α-Me), 1·29 (3H, t, J = 6 Hz), 1·60 (3H, s), 1·67 (3H, s), 4·12 (2H, q, J = 6 Hz), 5·05 (1H, t), 7·16 (1H, d, J = 5 Hz) ppm. (Found: C, 77·74; H, 9·96. $C_{17}H_{26}O_2$ requires: C, 77·82; H, 9·99%). GLC: Column, Castor wax, 45 m × 0·5 mm i.d.; Column temp, 190; Carrier gas, N_2, 1·2 kg/cm^2; R_t 12·7 (C-7 α-Me), 17·8 (C-7 β-Me) min. α-Me: β-Me (area ratio) = 1:2·6.

3-*Carboxy-7-methyl-7-(4'-methylpent-3'-enyl)bicyclo*[4.1.0]*hept-2-ene* (XVIIc, a stereoisomeric mixture). A soln of XVIIb (1·0 g) in MeOH (20 ml) was mixed with KOH aq (1·0 g in 2 ml). The mixture was left to stand at room temp for 2 days, concentrated *in vacuo*, acidified with dil AcOH and extracted with ether. The extract was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo* to give an oily XVIIc (approx 0·9 g), ν_{max} ~3400–~2600, 1690 (broad), 1625, 1310 cm^{-1}. This was converted to XVIIa without further purification.

3-*Carbomethoxy-7-methyl-7-(4'-methylpent-3'-enyl)bicyclo*[4.1.0]*hept-2-ene* (XVIIa, a stereoisomeric mixture). The above XVIIc was esterified to give XVIIa identical in every respect with an authentic sample prepared by another route. GLC: Column, Castor wax 45 m × 0·5 mm i.d.; Column temp 190°; Carrier gas, N_2, 1·2 kg/cm^2; R, 10·6 (C-7 α-Me), 14·5 (C-7 β-Me) min. α-Me: β-Me (area ratio) = 1:2 ~ 2·6.

3-*Carbomethoxy-7-methyl-7-(3',4'-oxido-4'-methylpentyl)bicyclo*[4.1.0]*hept-2-ene* (XXa, a stereoisomeric mixture). A soln of *m*-chloroperbenzoic acid (85% purity, 1·44 g) in CH_2Cl_2 (30 ml) was added to a stirred soln of XVIIa (1·5 g) in CH_2Cl_2 (10 ml) at 0–5°. The mixture was left to stand at 0–5° for 15 h. During that time *m*-chlorobenzoic acid precipitated from the solution. The mixture was diluted with CH_2Cl_2, washed with Na_2CO_3 aq, dried ($MgSO_4$) and concentrated *in vacuo* to give 1·5 g (94%) of XXa. An analytical sample boiled at 134–136°/0·8 mm, n_D^{30} 1·4890; ν_{max} 1700, 1630, 1290, 1250, 1100, 1060, 750 cm^{-1}; δ 0·95 (~2·5H, s, C-7 β-Me), 1·18 (~0·5H, s, C-7 α-Me), 1·26 (3H, s), 1·29 (3H, s), 3·70 (3H, s), 7·18 (1H) ppm. (Found: C, 72·37; H, 9·42. $C_{16}H_{24}O_3$ requires: C, 72·69; H, 9·15%).

3-*Carbethoxy-7-methyl-7-(3',4'-oxido-4'-methylpentyl)bicyclo*[4.1.0]*hept-2-ene* (XXb, a stereoisomeric mixture). In the same manner as described above, XVIIb (3·0 g) and *m*-chloroperbenzoic acid (2·65 g) gave XXb (3·0 g, 94%). An analytical sample boiled at 147–148°/1·2 mm, n_D^{31} 1·4864; ν_{max} 1695, 1630, 1280, 1240, 1100, 1060, 750 cm^{-1}; δ 0·94 (>2H, s, C-7 β-Me), 1·18 (<1H, s, C-7 α-Me), 1·25 (3H, s), 1·27 (3H, t, J = 6 Hz), 1·29 (3H, s), 4·12 (2H, q, J = 6 Hz), 7·15 (1H, d, J = 5 Hz) ppm. (Found: C, 73·34; H, 9·52. $C_{17}H_{26}O_3$ requires: C, 73·34; H, 9·41%).

3-*Carbomethoxy-7-methyl-7-(2'-formylethyl)bicyclo*[4.1.0]*hept-2-ene* (XXIa, a stereoisomeric mixture). A soln of XXa (1·4 g) in dry ether (50 ml) was added to a stirred soln of H_5IO_6 (1·2 g) in dry ether (250 ml) under N_2 at room temp. HIO_3 completely precipitated from the soln after 1 h. The ethereal soln was washed with $NaHCO_3$ aq and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo* to give 1·2 g (99%) of XXIa. An analytical sample boiled at 123–125°/1·0 mm, n_D^{29} 1·5014; ν_{max} 2720, 1710, 1690, 1630, 1280, 1240, 1100, 1050, 750 cm^{-1}; δ 0·90 (>2H, s, C-7 β-Me), 1·13 (<1H, s, C-7 α-Me), 3·66 (3H, s), 7·14 (1H, d, J = 5 Hz), 9·03 (1H, s) ppm. (Found: C, 70·01; H, 8·60. $C_{13}H_{18}O_3$ requires: C, 70·24; H, 8·16%). *2,4-dinitrophenylhydrazone*: Orange-yellow prisms from EtOAc-EtOH, m.p. 186–187·5°, ν_{max} 3350, 3100, 1685, 1615, 1590, 1340, 1260, 1135, 1080, 910, 840, 740, 725 cm^{-1}; δ ($CDCl_3$) 0·99 (3H, s), 3·72 (3H, s), 7·23 (1H), 7·57

(1H), 7·97 (1H, d), 8·38 (1H, d) ppm. (Found: C, 56·69; H, 5·58; N, 14·13. $C_{19}H_{22}O_6N_4$ requires: C, 56·71; H, 5·51; N, 13·92%).

3-Carbethoxy-7-methyl-7-(2'-formylethyl)bicyclo[4.1.0]*hept-2-ene* (XXIb, a stereoisomeric mixture). In the same manner as described above, XXb (3·0 g) in THF (50 ml) and H_5IO_6 (2·6 g) in ether (500 ml) gave XXIb (2·4 g, 99%). An analytical sample boiled at 131–133°/1·0 mm, n_D^{30} 1·4960; ν_{max} 2720, 1710, 1690, 1630, 1280, 1240, 1100, 1050, 750 cm^{-1}; δ 0·95 (>2H, s, C-7 β-Me), 1·16 (<1H, s, C-7 α-Me), 1·32 (3H, t, J = 6 Hz), 4·13 (2H, q, J = 6 Hz), 7·16 (1H, d, J = 5 Hz), 9·03 (1H, s) ppm. (Found: C, 71·28; H, 8·91. $C_{14}H_{20}O_3$ requires: C, 71·16; H, 8·53%). *2,4-dinitrophenylhydrazone*: orange-yellow prisms from EtOAc-EtOH, m.p. 164–165°, ν_{max} 3350, 3100, 1625, 1615, 1590, 1340, 1265, 1135, 1080, 740 cm^{-1}; δ ($CDCl_3$) 1·00 (3H, s), 1·32 (3H, t, J = 6 Hz), 4·22 (2H, q, J = 6 Hz), 7·26 (1H), 7·65 (1H), 7·98 (1H, d), 8·38 (1H, d) ppm. (Found: C, 57·59; H, 5·85; N, 13·67. $C_{20}H_{24}O_6N_4$ requires: C, 57·68; H, 5·81; N, 13·46%).

3-Carbomethoxy-7-methyl-7-(4'-carbethoxypent-3'-enyl)bicyclo[4.1.0]*hept-2-ene* (XXIIa, a stereoisomeric mixture). Ethyl α-diethylphosphonopropionate (1·6 g) was added to a suspension of 50% NaH (350 mg) in dry 1,2-dimethoxyethane (30 ml) under N_2 and the mixture was stirred for 1 h at room temp. To this soln, a soln of XXIa (1·1 g) in 1,2-dimethoxyethane (15 ml) was added and the soln was stirred at room temp for 1 h, then heated under reflux for 30 min and left to stand overnight at room temp. The reaction mixture was poured into ice-water and extracted with ether. The ethereal extract was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residual oil was chromatographed on alumina (Merck, activity grade II–III, 50 g, 15 × 2·5 cm in n-hexane). All fractions were 200 ml each. Fractions 1 and 2 (n-hexane) contained some mineral oil. Fractions 3–5 (n-hexane:benzene = 1:1) gave the diester (XXIIa contaminated with XXIIb resulting from ester-exchange, 536 mg, 36%). An analytical sample boiled at 180–190° (bath temp)/0·5 mm, n_D^{31} 1·5006; ν_{max} 1695, 1635, 1260, 1225, 1090, 1050, 745 cm^{-1}; δ 0·95 (>2H, s, C-7 β-Me), ~1·16 (<1H, s, C-7 α-Me), 1·30 (~5H, J = 6 Hz), 1·83 (3H, s), 3·66 (~1H, s), 4·12 (~3H, q, J = 6 Hz), 6·70 (1H, d) ppm. (Found: C, 71·12; H, 8·78. $C_{18}H_{26}O_4$ requires: C, 70·56; H, 8·55%).

3-Carbethoxy-7-methyl-7-(4'-carbethoxypent-3'-enyl)bicyclo[4.1.0]*hept-2-ene* (XXIIb, a stereoisomeric mixture). Ethyl α-diethylphosphonopropionate (3·0 g) was added to a suspension of 50% NaH (690 mg) in 1,2-dimethoxyethane (60 ml) under N_2 and the mixture was stirred for 1 h at room temp. To this soln, a soln of XXIb (2·3 g) in 1,2-dimethoxyethane (30 ml) was added and the soln was stirred for 1 h at 0–5° and left to stand overnight at room temp. Subsequent treatments afforded an oil which was chromatographed on alumina (Merck, activity grade II–III, 50 g, 15 × 2·5 cm in n-hexane). All fractions were 200 ml. Fraction 1 (n-hexane) contained some mineral oil. Fractions 2 and 3 (n-hexane), 4–6 (n-hexane:benzene = 1:1) and 7 gave 1·20 g (39%) of the desired diester XXIIb. An analytical sample boiled at 190° (bath temp)/0·5 mm, n_D^{31} 1·4978; ν_{max} 1690, 1630, 1260, 1225, 1090, 1050, 745 cm^{-1}; δ 0·95 (>2H, s, C-7 β-Me), ~1·16 (<1H, s, C-7 α-Me; overlapped on $C\underline{H}_3CH_2$-), 1·30 (6H, t, J = 6 Hz), 1·82 (3H, s), 4·12 (4H, q, J = 6 Hz), 6·68 (1H, t), 7·14 (1H, d) ppm. (Found: C, 71·33; H, 8·97. $C_{19}H_{28}O_4$ requires: C, 71·22; H, 8·81%).

(±)-Sirenin (*3-hydroxymethyl-7-methyl-7(4'-hydroxymethylpent-3'-enyl)bicyclo*[4.1.0]*hept-2-ene*, (IIb) *containing C-7 epimer* (IIb'). (a) A soln of XXIIa (429 mg) in dry ether (20 ml) was added to a stirred soln of LAH (300 mg) in dry ether at 0–5° under N_2 and the mixture was stirred for 2 h at room temp. Then the excess of LAH was destroyed by the addition of wet ether. The ethereal soln was washed with sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo* to give crude racemic sirenin (IIb, 330 mg, 99%). This was employed for the preparation of bis-NABS-*dl*-sirenin (IId) without further purification. (b) Reduction of XXIIb (1·1 g) with LAH (0·6 g) in ether (60 ml) gave 0·85 g (quantitative yield) of crude (±)-sirenin as a viscous oil. A part of it (617 mg) was chromatographed on alumina (Merck, activity grade II–III, 60 g, 16·5 × 2·5 cm in benzene). The column was washed with benzene (200 ml) and CH_2Cl_2 (200 ml). Subsequent elution with $CHCl_3$ (200 ml) and $CHCl_3$-MeOH (50:1, 200 ml) as described by Machlis *et al.*[15] gave the purified diol (IIb, contaminated with some IIb', 504 mg, 62% yield) as a viscous colourless oil. ν_{max} ($CHCl_3$) 3680, ~3400, 2995, 2925, 2860, 1660, 1445, 1378, ~1220, 1160, 1113, 1057, 1030, ~980, 906, 864, 823 cm^{-1}; δ ($CDCl_3$) 0·87 (>2H, s), 1·66 (3H, s), 1·69 (2H, s, 2-O$\underline{H}$, disappeared on D_2O addition), 3·96 (4H, s), 5·40 (1H, t), 5·85 (1H, broad s) ppm. The spectral data are in accord with the data kindly supplied by Professor H. Rapoport. (Found: C, 75·76; H, 10·11. $C_{15}H_{24}O_2$ requires: C, 76·22; H, 10·24%).

(±)-Sirenin diacetate (IIc) *containing C-7 epimer* (IIc'). To a soln of crude racemic sirenin (IIb + some IIb', 272 mg) in dry pyridine (7 ml), Ac_2O (7 ml) was added. The soln was left to stand overnight at room temp, concentrated *in vacuo* and diluted with ether and water. The ethereal soln was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on alumina (Merck, activity grade II–III, 25 g, 11 × 1·8 cm in light petroleum). Elution with light petroleum (100 ml) and n-hexane (50 ml) gave a small amount of forerun. Subsequent elution with benzene (200 ml) gave pure (±)-

sirenin diacetate (IIc, probably containing some IIc', 258 mg, 68% yield) as a colourless oil. An analytical sample boiled at 190° (bath temp)/ 0·3 mm, n_D^{29} 1·4870; ν_{max} 1725, 1450, 1380, 1235, 1020, 950, ~850 cm^{-1}; δ 0·89 (>2H, s), 1·65 (3H, s), 2·00 (6H, s), 4·39 (4H, s), 5·44 (1H, t), 5·96 (1H, broad s) ppm. A signal due to C-7 α-Me was indiscernible. (Found: C, 70·79; H, 8·86. $C_{19}H_{28}O_4$ requires: C, 71·22; H, 8·81%).

bis-*NABS-(±)-sirenin* (IId). To a stirred and ice-cooled soln of crude (±)-sirenin (IIb + IIb', 403 mg) in dry benzene (50 ml) and dry pyridine (4 ml) under N_2, a soln of *p*-(*p*-nitrophenylazo)benzoyl chloride (2·0 g) in dry benzene (50 ml) was added. After stirring for 30 min at 0–5°, the flask was wrapped with Al foil and left to stand overnight at room temp. The mixture was filtered to remove precipitates which were washed with benzene. The combined filtrate and washings was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residual orange-red solid was chromatographed over alumina (Merck, activity grade II–III, 100 g, 12 × 4 cm in benzene). Benzene (1·5 *l*) eluted the desired bis-NABS-(±)-sirenin (IId, 677 mg, 56% yield) as an orange-red crystalline mass. Elution with benzene-ether (10:1, 1:1) gave mono-NABS-ester (323 mg). The crude bis-NABS-ester was recrystallized from benzene-$CHCl_3$ to give 286 mg of orange-red prisms, m.p. 163–164°. An analytical sample crystallized from $CHCl_3$-light petroleum (three recrystallizations) as orange-red prisms, m.p. 168–170°; ν_{max} (nujol) 1712, 1605, 1515, 1450, 1400, 1370 (w), 1340, 1315 (w), 1270, 1210 (w), 1165 (w), 1140 (w), 1110, 1000, 930, 855, 768, 746 (w), 690 cm^{-1}; ν_{max} ($CHCl_3$) 1730 (sh), 1715 (vs), 1605, 1590, 1580 (w), 1520 (s), 1460, 1410, 1348 (vs, max), 1270 (vs), 1105 (s), 1092 (sh), 1010 (s), 935 (w), 863, 855, 695 cm^{-1}; δ ($CDCl_3$) 0·98 (3H, s), 1·82 (3H, s), 4·80 (4H, s), 5·65 (1H, t), 6·10 (1H, broad s), 8·02–8·51 (16H, m) ppm. These spectral data are in good accord with Professor Rapoport's data. TLC: Kieselgel G nach Stahl, benzene-EtOAc (30:1), R_f 0·62(single spot). Identification with an authentic sample was kindly carried out by Professor Rapoport by spectral and chromatographic comparisons. (Found: C, 66·55; H, 5·26; N, 11·26. $C_{41}H_{38}O_6N_8$ requires: C, 66·3; H, 5·2; N, 11·3%).

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