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SYNTHESIS OF MONO- AND SESQUITERPENOIDS—III*

(±)-THUJOPSENE

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Abstract—Racemic thujopsene (I) was synthesized *via* the tricyclic ketone (VII) prepared by the α-ketocarbene—olefin addition reaction.

THUJOPSENE is a sesquiterpene isolated originally from the Japanese Hiba tree (*Thujopsis dolabrata* Sieb. et Zucc.) by Yano.[1, 2] Later Kawamura purified the hydrocarbon, named it and studied its chemical properties.[3, 4] Its structure[5, 6, 7, 8] and stereochemistry[9] were determined as I. Since then two total syntheses of its racemate have been reported.[10, 11] This paper describes another total synthesis employing the α-ketocarbene—olefin addition[12] as the key reaction.

The starting material was the C_{12}-aldehyde (II) previously prepared by Büchi and White.[11] This was reduced with sodium borohydride to give an alcohol (IIIa). The corresponding tosylate (IIIb) was treated with sodium cyanide in DMSO to afford a nitrile (IV). Its alkaline hydrolysis smoothly yielded an acid (Va) in 56% over-all yield from II. Reaction of its sodium salt with oxalyl chloride gave a crude acyl chloride (Vb), which, without purification, was converted to a diazoketone (VI) by treatment with diazomethane.

An α-ketocarbene was generated from the diazoketone (VI) and cyclized by heating it in cyclohexane in the presence of powdered copper and cupric sulfate. The reaction proceeded in a stereoselective manner to give only one ketonic product in 42·5% yield from Va. The favoured stereochemical result of the reaction should be the *cis*-ketone (VII) due to the steric effect of the Me groups on the cyclohexane ring as discussed previously by Büchi and White.[11*]

The ketone thus obtained was identical, by spectral criteria (IR and NMR), with the racemic ketone (VII) synthesized in an entirely different manner by Dauben and Ashcraft.[10] These spectral comparison were kindly carried out by Professor W. G. Dauben and Dr. E. T. Aoyagi.† Since the racemic ketone (VII) has been converted into (±)-thujopsene (I),[10] this completes the third total synthesis of the tricyclic sesquiterpene.‡

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* Part II, K. Mori and M. Matsui, *Tetrahedron* **26**, 2801 (1970).

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* They observed that the carbene generated from i yielded (±)-thujopsene (I) in a stereoselective manner but only in 4% yield.

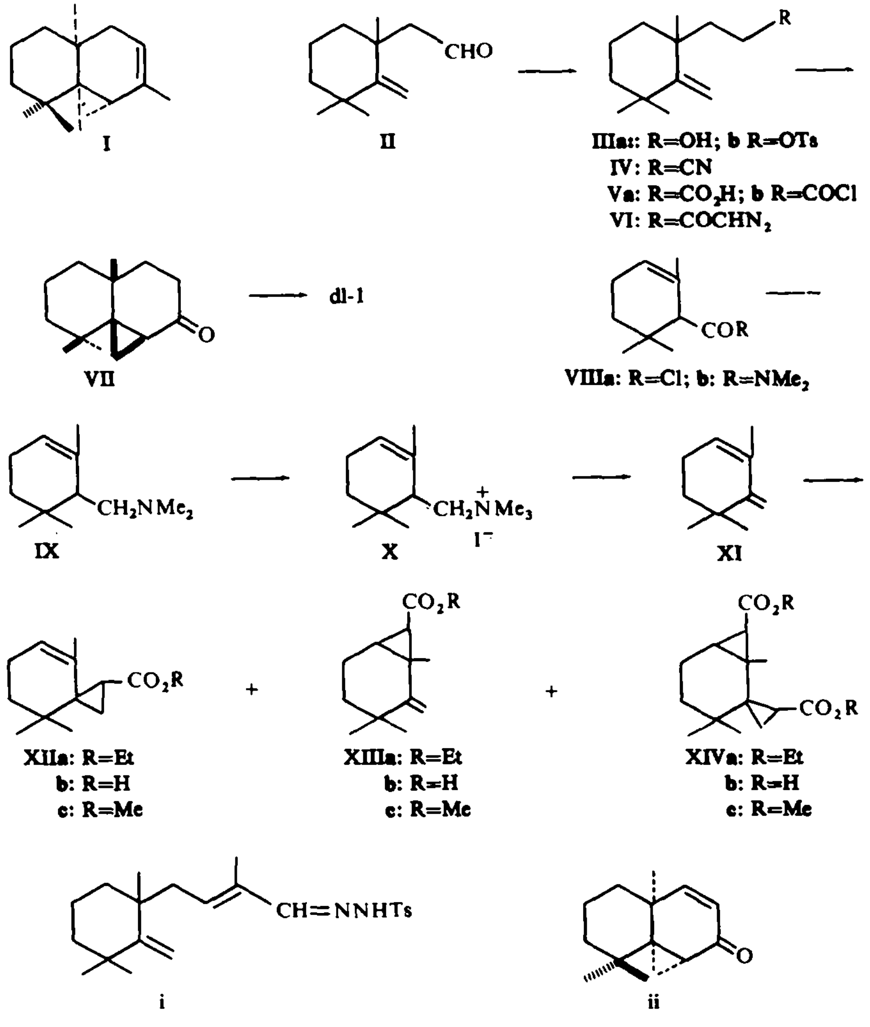
† Recently a C_{14}-ketone ii (mayurone) was isolated from "mayur pankhi"[13] amd from the Hiba tree.[14] The synthetic ketone is therefore (±)-dihydromayurone.

‡ Another total synthesis has been recorded by Anderson as his Ph.D. dissertation,[15] although details of his work have not yet been published.

Prior to the achievement of the above successful synthesis, another route was explored which was proved to be fruitless but involved an interesting spiro [2,5] octane carboxylic acid (**XIIb**) as a possible intermediate. Synthesis of this compound is briefly described below.

Cyclogeranic acid chloride (VIII**a**)[16] was treated with dimethylamine to give an amide (VIII**b**). Its reduction with lithium aluminum hydride yielded an amine (IX) which was converted to a quaternary ammonium salt (X). The corresponding quaternary ammonium hydroxide was decomposed at 80–120° to give a hydrocarbon (XI) in 36% over-all yield from cyclogeranic acid.

Treatment of the diene (XI) with 2/3 molar equivalent of ethyl diazoacetate in the presence of powdered copper gave a mixture of the spiro[2·5]octane (XII**a**) and a bicyclo[4.1.0]heptane (XIII**a**) from which a crystalline spiro acid (XII**b**) was obtained after alkaline hydrolysis in 29% yield from the hydrocarbon (XI). The yield of the isomeric acid (XIII**b**) as a crude oil was 42% from the diene (XI). When an



excess of diazoacetate was used, a crystalline dibasic acid (XIVb) was obtained after hydrolysis. In view of the successful synthesis of the tricyclic ketone (VII) by the carbene addition, this route was abandoned at this stage.

EXPERIMENTAL

All mps, 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.

β-(1.3.3-*Trimethyl-2-methylenecyclohexyl)ethyl alcohol* (IIIa). A soln of II (7·26 g) in iso-PrOH (20 ml) was added dropwise during 30 min to an ice-cooled and stirred suspension of $NaBH_4$ (2·38 g) in EtOH-*iso*-PrOH (1 : 1, 30 ml). After the addition the mixture was stirred for 1·5 h at room temp. Then it was poured into water (500 ml). The mixture was saturated with NaCl and extracted with ether. The extract was washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was distilled to give 5·90 g (79%) of IIIa, b.p. 108–110°/6 mm, n_D^{26} 1·4861; ν_{max} 3300, 2970, 1625, 1470, 1390, 1070, 1050, 1030, 920 cm^{-1}; δ 1·15 (6H, s), 1·17 (3H, s), 1·90 (1H, s, —OH), 3·50–3·70 (2 H, m), 4·87 (1H, s), 5·03 (1H, s) ppm. (Found: C, 79·02; H, 11·96. $C_{12}H_{22}O$ requires: C, 79·06; H, 12·16%). GLC: Column, SE-30, 2·0m × 3mm i.d. at 140°; Carrier gas, He, 1·0 kg/cm²; R_t 5·75 min. *The tosylate* (IIIb). A soln of *p*-TsCl (24·7 g) in pyridine (130 ml) was added during 1·5 hr to an ice-cooled and stirred soln of IIIa (9·5 g) in pyridine (70 ml). The mixture was set aside at 0–5° for 2 days, poured into 10% HCl and ice and extracted with ether. The ethereal soln was washed with 10% HCl, $NaHCO_3$ aq and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo* to give 15·53 g (89%) of crude IIIb, ν_{max} 1640, 1625, 1490, 1395, 1215, 1140, 1000, 860 cm^{-1}. This was employed for the next step without further purification.

γ-(1,3,3-*Trimethyl-2-methylenecyclohexyl)propionitrile* (IV). A soln of crude IIIb (15·5 g) and NaCN (2·5 g) in DMSO (100 ml) was stirred and heated at 60–65° for 16 h. The mixture was poured into ice–water and extracted with ether. The ethereal extract was washed with water (x 3) and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 7·8 g (88·6%) of IV, b.p. 85–87°/0·5 mm, n_D^{28} 1·4791; ν_{max} 3050, 2350, 1625, 1480, 1400, 1030, 940 cm^{-1}; δ1·10 (6H, s) 1·15 (3H, s), 1·30–1·83 (8H, m), 2·05–2·20 (2H, m), 4·81 (1H, s), 5·12 (1H, s)ppm. (Found: C, 81·36; H, 10·90; N, 6·99. $C_{13}H_{21}N$ requires: C, 81·61; H, 11·06; N, 7·32%).

γ-(1,3,3-*Trimethyl-2-methylenecyclohexyl)propionic acid* (Va). A soln of IV (7 g) in 95% EtOH (100 ml) was mixed with NaOH aq (30 g in 40 ml) and the mixture was heated under reflux for 3 days. The mixture was concentrated *in vacua*, diluted with water (300 ml) and extracted with ether (200 ml) to remove neutral impurities. The aqueous layer was acidified with conc HCl and extracted with ether (250 ml × 2). The extract was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated. The residue was distilled to give 6·93 g (90%) of Va, b.p. 118–120°/0·38 mm, n_D^{25} 1·4823; ν_{max} ~3400–~2700, 1700, 1620, 1470, 1420, 1305, 1230, 1110, 920 cm^{-1}; δ 1·08 (3H, s), 1·14 (6H, s), 1·30–1·85 (8H, m), 2·05–2·45 (2H, m), 4·83 (1H, s), 5·10 (1H, s) 11·10 (1H, s) ppm. (Found: C, 74·38; H, 10·52. $C_{13}H_{22}O_2$ requires: C, 74·28; H, 10·54%). *The acyl chloride* (Vb). A soln of Va (770 mg) in MeOH (20 ml) was neutralized by the addition of NaOMe (200 mg) with stirring. 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. The dry Na salt was suspended in dry benzene (30 ml). Oxalyl chloride (2·8 g) was added to the suspension with stirring at 0–5°. The mixture was stirred for 40 min at 0–5°, filtered though Celite and concentrated *in vacuo* to give an oily Vb, ν_{max} 1785, 1605 cm^{-1}. This was employed for the next step without further purification. *The diazoketone* (VI). A soln of the above Vb (from 770 mg of Va) in benzene (15 ml) was added to an ethereal soln of CH_2N_2 (approx 560 mg) with stirring at 0–5° during 30 min. The soln was stirred at 0–5° for 1 h and concentrated *in vacuo* to give crude VI, ν_{max} 3050, 2200, 1645, 1470, 1380, 910 cm^{-1}. This was employed for the next reaction without purification.

7-*Keto*-4,4,10β-*trimethyl*-5,6β-*methylenedecalin* (VII). The above VI (from 770 mg of Va) dissolved in cyclohexane (10 ml) was added dropwise to a stirred and refluxing suspension of powdered Cu (1·0 g) and $CuSO_4$ (0·3 g) in cyclohexane (100 ml) during 30 min. After the addition the mixture was stirred and heated under reflux for 1h, then cooled, filtered and concentrated *in vacuo*. The residual oil was chromatographed on silica gel (4 g, 8 cm × 1·2 cm) in n-hexane. Fractions 1–19 were 50 ml and 20–27 were 100 ml. Eluants were as follows: fractions 1–7, n-hexane; 8–21, n-hexane : benzene, 9 : 1; 22–24, n-hexane :

benzene 1 : 1; 25–27, n-hexane : benzene 3 : 7. Fractions 10–25 gave 320 mg of crystalline VII (42·5% from Va). The sublimed ketone was further purified by preparative GLC: Column, SE-30, 3 m × 5 mm i.d. at 230°; Carrier gas N_2, 42·0k g/cm^2; R_t 8·9 min. The pure ketone melted at 99·5–99·7° (lit[10] 100·5–101·5°), ν_{max} 3100, 3020, 1680, 1460, 1440, 1390, 1375, 1267, 1150, 1097, 908 860 cm^{-1}; δ 0·65 (3H, s), 0·9–1·13 (2H, m), 1·17 (3H, s), 1·25 (3H, s), 1·27–2·37 (11H, m)ppm. The spectral data are in good accord with those of an authentic sample.[10] (Found: C, 81·35; H, 10·68. $C_{14}H_{22}O$ requires: C, 81·50; H, 10·75%).

N,N-Dimethylamide of α-cyclogeranic acid (VIIIb). The acyl chloride VIIIa (205 g) was added dropwise to stirred and ice-cooled 40% Me_2NH aq (350 g) at 0° during 1·5 h. After the addition the mixture was stirred at room temp for 1 h. The separated oil was extracted with ether. The extract was washed with 10% NaOH aq, dil HCl and water, dried ($MgSO_4$) and concentrated *in vauo*. The residue was distilled to give 181 g (85%) of VIIIb, b.p. 120–125°/10 mm, ν_{max} 1640 cm^{-1}.

N,N-Dimethyl-2,6,6-trimethylcyclohex-2-enylmethyl amine (IX). To a suspension of LAH (30 g) in ether (500 ml), VIIIb (190 g) was added dropwise with vigorous stirring. The rate of addition was controlled to continue the gentle refluxing of ether. After the exothermic reaction had subsided the mixture was stirred and heated under reflux for 5–6 h and then poured into ice-HCl mixture. The ether layer was separated and the acidic aqueous soln was made alkaline with NaOH. The separated amine was extracted with ether. The combined ethereal soln was washed with water, dried (K_2CO_3) and concentrated *in vacuo*. The residue was distilled to give 126 g (85%) of IX, b.p. 102–107°/20 mm. This was characterized as a crystalline quaternary ammonium salt (X) described below.

Trimethyl-2,6,6-trimethylcyclohex-2-enylmethylammonium iodide (X). The amine IX (126 g) was mixed with MeI (150 g) with shaking and ice-cooling. Refluxing of MeI began spontaneously and continued for 1 h. After standing overnight at room temp the crystalline mass was crushed, washed with ether and collected on a Buchner funnel. The dried salt weighed 213 g (94%), m.p. 216° (dec), ν_{max} 900 cm^{-1}; (Found: C, 48·30; H, 8·16; N, 4·10. $C_{13}H_{26}NI$ requires: C, 48·30; H, 8·04; N, 4·33%).

1-Methylene-2,6,6-trimethylcyclohex-2-ene (XI). To a soln of X (213 g) in water (1000 ml), wet Ag_2O (prepared from 120 g of $AgNO_3$) was added portionwise during 40 min. After the addition the mixture was stirred and heated under reflux for 1h. The precipitated AgI was separated by filtration and washed with hot water. The combined aqueous soln was condensed below 60° under reduced pressure. Subsequently it was heated on an oil-bath at 80–120° under reduced pressure (30 mm). The generated hydrocarbon was collected in a trap chilled in a dry ice–acetone bath. The condensate in the trap was extracted with ether. The extract was washed with dil HCl, $NaHCO_3$ aq and water, dried ($MgSO_4$) and concentrated. The residue was distilled to give 79 g (83% from IX of XI, b.p. 100–103°/100 mm, ν_{max} 3120, 1640, 1600, 880, 815 cm^{-1}; δ 1·06 (6H, s), 1·45 (2H, t, $J = 5$), 1·80 (3H, q, $J = 1·5$), 2·12 (2H, m), 4·94 (2H, d) 5·62 (1H, broad s) ppm. (Found: C, 87·95; H, 11·97. $C_{10}H_{16}$ requires: C, 88·16; H, 11·84%).

Reaction of the diene XI *with ethyl diazoacetate, 4,8,8-Trimethylspiro*[2·5]*oct-4-ene-1-carboxylic acid* (XIIb) *and other products*. Two-thirds a molar equivalent of ethyl-diazoacetate (30 g) was added dropwise to a mixture of the diene XI (52 g) and powdered Cu (0·2 g) at 160° during 1 h. After the addition the heating was continued for 10 min. From the reaction mixture the unreacted starting material XI was recovered by distillation, b.p. 95–105°/80 mm. The recovered material (22 g) was treated with 15 g of ethyl diazoacetate in the same manner as above. The diene XI (5 g) recovered from the second reaction was reacted with 3 g of ethyl diazoacetate. The combined crude product was distilled to collect the fraction boiling at 120–130°/8 mm which was a mixture of XIIa and XIIIa (62 g). This was heated under reflux with ethanolic KOH (30 g in 250 ml). The alkaline soln was concentrated, diluted with water, adidified with dil HCl and extracted with ether. The ethereal soln was washed with water and sat NaCl aq, dried ($MgSO_4$) and concentrated *in vacuo* to give a viscous oil. This partly solidified on standing in a refrigerator. The crystalline product (18·5 g) was collected and washed with n-hexane. The mother-liquor was dissolved in MeOH-H_2O (1 : 1) and left to stand in a refrigerator to give 3·2 g of the second crop. From the NMR spectrum of the corresponding Me ester, structure XIIb was assigned for this crystalline acid. Total yield: 21·7 g (29% from XI), m.p. 117°; ν_{max} 1685 cm^{-1}. (Found: C, 73·89; H, 9·47. $C_{12}H_{18}O_2$ requires: C, 74·19; H, 9·34%). *Me ester* (XIIc) was prepared by treatment of XIIb with CH_2N_2, b.p. 120–125°/15 mm; m.p. 54°; ν_{max} 1735, 825 cm^{-1}; δ (60 MHz)0·68 (3H, s), 0·91 (3H, s), 0·9–1·1 (2H, m, cyclopropane protons), 1·63 (3H, d, $J = 1·5$ Hz), 3·58 (3H, s), 5·4–5·6 (1H, m, olefinic H) ppm. (Found: C, 75·43; H, 9·25. $C_{13}H_{20}O_2$ requires: C, 74·96; H, 9·68%). After the separation of the crystalline XIIb the residual oil was distilled to give crude XIIIb (30·4 g, 42% from XI), b.p. 124–126°/0·05 mm; ν_{max} 1685 cm^{-1}. Esterification with CH_2N_2 gave XIIIc, b.p. 102–107°/4 mm, ν_{max} 3140, 1732, 895 cm^{-1}.

When excess of ethyl diazoacetate was reacted with XI followed by alkaline hydrolysis in the same manner as for the preparation of XIIb, a *dibasic acid* (XIVb), m.p. 242°, was obtained. (Found: C, 66·67; H, 8·11. $C_{14}H_{20}O_4$ requires: C, 66·64; H, 7·99%). XIVa boiled at 130–140°/0·2 mm. *Me ester* (XIVc) was prepared from XIVb by CH_2N_2 treatment, m.p. 94–97°; ν_{max} 1730 cm^{-1}. (Found: C, 68·05; H, 8·91. $C_{16}H_{24}O_4$ requires: C, 68·54; H, 8·63%).

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