Tetrahedron. Vol. 26, pp. 649 to 655. Pergamon Press 1970. Printed in Great Britain

STUDIES IN SESQUITERPENES—XLIII
ISOLONGIFOLENE (PART 4): SYNTHESIS*†

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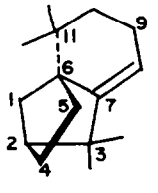
(*Received in the UK* 15 *March* 1969; *accepted for publication* 2 *October* 1969)

Abstract—Starting with camphene-1-carboxylic acid (III), both C_{13}-keto acid (II), the key degradation product of isolongifolene, and (±)-isolongifolene itself, have been synthesized by an unambiguous route.

EVIDENCE based on spectral and degradative studies and leading to the formulation of isolongifolene, the acid-catalysed rearranged product of longifolene, as I, has already been described.[1-3] We now report on synthetic experiments describing the synthesis of the key degradation product of isolongifolene,viz. the C_{13}-keto acid[3] (II), and culminating in the total synthesis of (±)-isolongifolene.‡

The reaction sequence successfully followed for the synthesis of II and I is briefly summarized in Fig. 1.

(±)-Camphene-1-carboxylic acid (III), available by a known procedure,[4] was sought to be converted into the required methyl ketone (IV), first by the malonic ester synthesis.[5] However, the crude condensation product resulting from the interaction of camphene-1-carbonyl chloride with sodio malonic ester yielded, after acid hydrolsis, an over 60% yield of a product which, from its elemental analysis ($C_{12}H_{20}O_2$) and spectral characteristics (IR: C=O 1712 cm^{-1}; PMR: two quaternary Me's, 6H singlet at 64 c/s; two $\underline{CH_3}$—CO groups, 6H singlet at 125·5 c/s; no olefinic protons), is assigned structure IX. Evidently the olefinic methyl ketone (IV) after being formed (or conceivably the acyl malonate itself) underwent hydrolytic cleavage (X) to the diketone. This is supported by the fact that the methyl ketone (IV), accessible by alternate methods [*vide infra*], on treatment with aqueous H_2SO_4–AcOH under identical conditions smoothly furnished IX.



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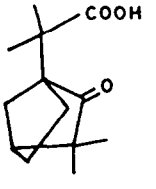
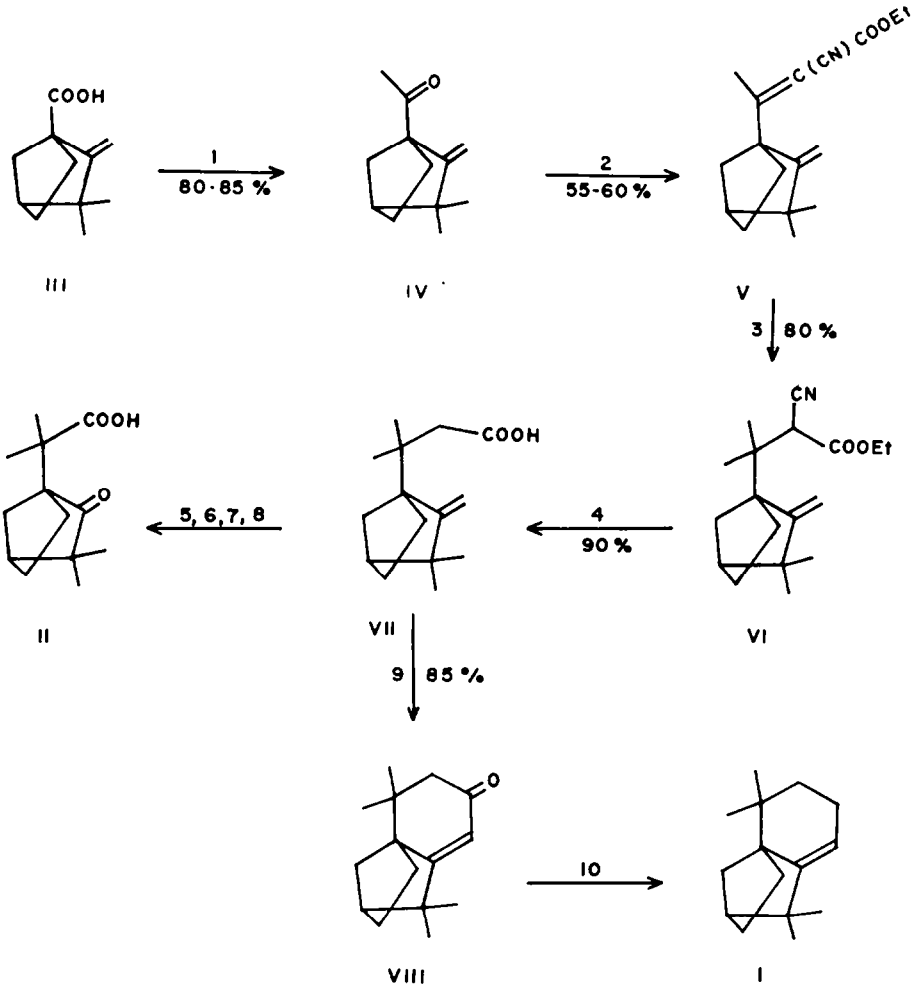


II

* Communication No. 1330. National Chemical Laboratory, Poona.

† In part abstracted from the Ph.D Thesis (Bombay, 1967) of R. R. Sobti.

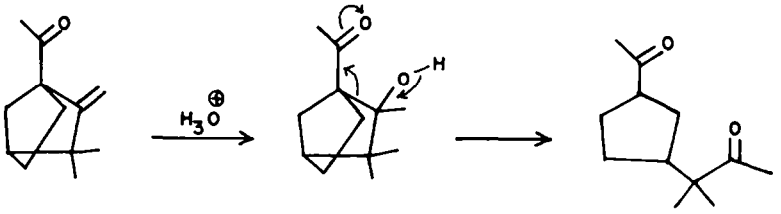
‡ Synthesis of (±)-isolongifolene was reported earlier in a preliminary communication: *Tetrahedron Letters*, 2893 (1967).



Reagents:

1 MeLi	5 CH_2N_2	8 RuO_4-$NaIO_4$
2 $CNCH_2COOEt$, NH_4OAc	6 $\phi MgBr$	9 $(COCl)_2$, $SnCl_4$
3 $Me_2Cu^-(OEt_2)_2\ Li^+$	7 Al_2O_3	10 $(CH_2SH)_2$, $BF_3{\cdot}Et_2O$; Raney Ni
4 KOH, $(CH_2OH)_2$		

FIG. 1. Synthesis of C_{13}-Keto acid (II) and isolongifolene



IV X IX

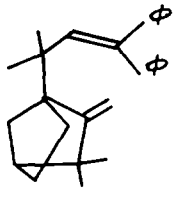
The desired methyl ketone (IV) could finally be prepared from camphene-1-carboxylic acid, either *via* the diazoketone-HI method[6] or more conveniently by the action of MeLi.[7] The ketone displays the expected spectral properties (IR: C=O 1712 cm^{-1}; $C{=}CH_2$ 3080, 1660 and 890 cm^{-1}; PMR: two quaternary Me's, 6H singlet at 69 c/s; CH_3CO, 3H singlet at 127 c/s; $C{=}C\underline{H}_2$, two 1H singlets at 275·5 and 279 c/s).

Condensation of the methyl ketone with ethyl cyanoacetate in the presence of NH_4OAc,[8] furnished the anticipated product V (λ_{max}^{EtOH} 236 mμ, ε, 13,970; IR: $C{\equiv}N$ 2230 cm^{-1}; COOEt 1735, 1245, 1220 cm^{-1}; $C{=}CH_2$ 3080, 1650 and 890 cm^{-1}; PMR: two quaternary Me's, 6H singlet at 69 c/s; vinylic Me, 3H singlet at 136 c/s; $C{=}CH_2$, two 1H singlets at 274·5 and 282 c/s).

Conjugate addition of lithium dimethyl copper[9]* to V gave a 80% yield of a diastereoisomeric mixture of VI which, without separation, was hydrolysed by KOH in ethylene glycol to give a 90% yield of a single acid VII (m.p. 87–88°; PMR: four quaternary Me's, 3H singlets at 60, 65, 71 and 75 c/s; —C—CH_2COOH, 2H broad singlet at 150 c/s; $COOH_9$, 1H broad singlet at 712 c/s; $C{=}C\underline{H}_2$, two 1H singlets at 285 and 297 c/s).

C_{13}–*Keto acid* (II)

For converting VII into the C_{13}-keto acid (II), the methyl ester of VII was first reacted with excess PhMgBr. This reaction led to the formation of two diphenyl carbinols but only one of these (major) exhibited the vinylidene absorption in its IR spectrum. This carbinol was dehydrated by heating with alumina[12] to give a product displaying spectral characteristics expected of XI (IR: $C{=}CH_2$ 3050, 1650 and 890 cm^{-1}; PMR: four quaternary Me's, 55, 61, 61 and 66 c/s; $C{=}C\underline{H}_2$, two 1H singlets at 284 and 303 c/s; $C{=}C\underline{H}$—, 1H singlet at 380 c/s; aromatic protons, two 5H singlets at 422 and 431 c/s). This olefin was directly oxidized with RuO_4–$NaIO_4$[13] to



XI

* Before this method became available conjugate addition of MeMgI, in presence of cupric acetate[10, 11] was investigated. This reaction, which was patterned after the conditions prescribed by Birch,[10] resulted in a rather complex reaction product, containing no more than 40% of the desired 1,4-addition product.

give a ~50% yield of an acid fraction, the major component of which was separated by preparative-layer-chromatography. This product, m.p. 119–120°*, shows an IR spectrum completely superimposable on that of the C_{13}-keto acid obtained[3] from isolongifolene by systematic degradation.

(±)-Isolongifolene

Acid VII was converted into its acid chloride, intramolecular acylation of which proceeded smoothly at −15°, in CS_2 in presence of $SnCl_4$[14], to give an 85% yield of the unsaturated ketone VIII, m.p. 54–55·5°, identical (mixed m.p., IR) with the (±)-ketone of structure VIII, obtained earlier[1] as a $Na_2Cr_2O_7$–AcOH oxidation product of partially racemic isolongifolene. This unsaturated ketone was thio-ketalized (BF_3–Et_2O)[15] to give a product (PMR: C=C<u>H</u>—, 1H singlet at 316·5 c/s) which was refluxed with Raney Ni in EtOH[16]. The product, after separation of a trace impurity by chromatography over $AgNO_3$–SiO_2 gel, was found to be identical in all respects (GLC, TLC[17], IR, PMR) with isolongifolene.

EXPERIMENTAL

For general remarks see Part XL of this series.

Camphene-1-carboxylic acid[4] (III).

(±)-Camphene-1-carboxylic acid amide[4] (10 g) was refluxed with ethanolic KOH (40%, 100 ml) for 30 hr, the reaction mixture cooled, just neutralized with H_3PO_4 aq (50%) and filtered to remove any insoluble material. The filtrate was acidified with H_3PO_4 aq and the ppt (8·3 g, m.p. 104-107·5°), collected. This was crystallized once from EtOH to furnish pure III (7·8 g), m.p. 109–110° (Lit.[4], m.p. 109–110°); IR spectrum: KBr: COOH 3100, 3600, 1700; C=CH_2 1660, 892 cm^{-1}; PMR spectrum: two quaternary Me's, 6H singlet at 67 c/s; C=C<u>H</u>$_2$, two 1H singlets at 281 and 300 c/s; COO<u>H</u>, 1H singlet at 730 c/s.

1-*Acetylcamphene* (IV)

(*i*) *Diazoketone method.* To a dry ethereal soln of CH_2N_2 (from 4 g of nitrosomethyl urea, distilled and dried over KOH) at 0° was added dropwise, with shaking, acid chloride of III (prepared[18] from 1·8 g of III, 2 ml of oxalyl chloride and 20 ml of dry ether containing a drop of pyridine in dry ether (15 ml). After one hr at this temp, solvent was flashed off to give crude diazoketone (yellow viscous liquid, 2·03 g; IR spectrum: HC=N^+=N^- 2110 cm^{-1}; C=O 1725 cm^{-1}; C=CH_2 3080, 1625 and 890 cm^{-1}; PMR spectrum: two quaternary Me's, 6H singlet at 65 c/s; C=CH_2, two 1H singlets at 280 and 288 c/s; —C<u>H</u>N_2, 1H singlet at 322 c/s).

To a stirred soln of the above diazoketone (2 g) in $CHCl_3$ (20 ml) at ~5° was added dropwise HI aq (48% 4 ml). After stirring for another 0·5 hr, the $CHCl_3$ layer was separated, washed with $Na_2S_2O_3$ aq (10%, 5 ml × 4), water, brine and dried (Na_2SO_4). The solvent was removed and the residue (1·71 g) distilled to give desired IV as a colourless liquid (1·31 g), b.p. 77°/2·5 mm, n_D^{30} 1·4780. (Found: C, 81·14; H, 10·20. $C_{12}H_{18}O$ requires: C, 80·85; H, 10·18%).

(*ii*) *Methyl lithium method.* To a stirred soln of camphene-1-carboxylic acid (5·4 g, 0·03 mole) in ether (50 ml) was introduced slowly (15 min) an ether soln of MeLi (5 ml, 1·3 molar; 0·061 mole). Stirring was continued for another 2 hr, after which water (20 ml) was added and the ether layer separated and worked up in the usual manner to give, after distillation, 4·55 g (83%) of IV.

Diketone IX

Camphene-1-carbonyl chloride (from 180 mg of III, 200 mg of oxalyl chloride; in 5 ml ether) was

* The m.p. of the C_{13}-keto acid obtained from isolongifolene,[3] is 115–116·5°, mixed m.p. with the synthetic sample 115–120°. The higher m.p. of the synthetic product must be ascribed to the fact that it cannot be contaminated with the optically active isomers, whereas the sample from isolongifolene is somewhat contaminated ($[\alpha]_D$–3·7°, $CHCl_3$).

added to sodio diethyl malonate (from 36 mg NaH, 240 mg diethyl malonate, 10 ml ether) and the reaction mixture, stirred and refluxed for 5 hr. This was worked up in the usual manner and the crude condensation product (322 mg) refluxed for 5 hr with AcOH (5 ml), water (2 ml) and conc H_2SO_4 (0·6 ml). Usual work up with light petroleum gave as the neutral fraction, an oil (110 mg) which was distilled to give IX, as a colourless liquid (95 mg), b.p. 77–78°/1·5 mm, n_D^{30} 1·471. (Found: C, 73·62; H, 10·34. $C_{12}H_{20}O_2$ requires: C, 73·43; 10·27%).

When IV (100 mg) was refluxed with AcOH (5 ml), water (2 ml) and conc H_2SO_4 (0·6 ml) for 5 hr and then worked up, 82 mg of IX was obtained.

Ethyl β-*(camphenyl-1)-ethylidene cyanoacetate* (V)

Ethyl cyanoacetate (7·91 g, 0·07 mole), IV, (8·9 g, 0·05 mole), gl AcOH (1 ml) and benzene (40 ml) were placed in 100 ml flask attached to a Dean-Stark-type constant water separator[19] carrying a reflux condenser. The reaction mixture was refluxed with addition of NH_4OAc in lots of 0·4 g at 0, 4, 6 and 9 hr intervals. Heating was stopped after 11 hr when further separation of water (separated water, 1·5 ml) had ceased. Reaction mixture was cooled, washed with water, brine and dried (Na_2SO_4). Solvent was flashed off and the residue distilled, first at 2·5 mm to remove unchanged starting materials (b.p. 70–78°/2·5 mm, 6 g) and then at 0·15 mm to collect, after a small forerun (420 mg, b.p. 120–127°/0·15 mm), the required V, b.p. 128–131°/0·15 mm, n_D^{30} 1·5090, yield, 7·73 g. (Found: C, 74·80; H, 8·30; N, 5·75. $C_{17}H_{23}O_2N$ requires: C, 74·69; H, 8·48; N, 5·12%).

Ethyl α-*cyano*-β-*methyl*-β-*(camphenyl-1) butyrate* (VI)

In a 3-necked flask (100 ml) fitted with a reflux condenser, dropping funnel and a stirrer were placed CuI (1·143 g, 0·006 mole) and anhyd ether (35 ml), which were then cooled in an ice–salt bath (~ −14°). MeLi (10 ml, 0·012 molar ether soln; 0·012 mole) was, next, introduced (N_2) dropwise with stirring during 10 min. Stirring was continued at the same temp for another 15 min and then the unsaturated V (0·546 g, 0·002 mole) in ether (10 ml) added (5 min). After stirring at the same temp for another 2 hr, the reaction mixture was allowed to attain room temp (25–28°) and left as such for 12 hr. The reaction mixture was worked up by pouring into NH_4Cl aq (15%, 30 ml) and extracting with ether. The combined ether extracts were washed with water, brine and dried. Solvent was removed and the pale yellow liquid residue distilled to give VI, b.p. 140–145° (bath)/0·02 mm, yield 463 mg; IR spectrum: CN 2250 cm^{-1}; COOEt 1742 cm^{-1}; $C{=}CH_2$ 3050, 1650 and 890 cm^{-1} (broad). (Found: C, 74·78; H, 9·38; N, 5·11. $C_{18}H_{27}O_2N$ requires: C, 74·70; H, 9·40; N, 484%).

β-*(Camphenyl-1)*-β-*methyl-butyric acid* (VII)

The above product (356 mg) was hydrolysed by refluxing (9 hr) with KOH (560 mg) in ethylene glycol (2·5 ml) and worked up in the usual fashion to give a sticky solid, which was taken up in ether. The ether soln was washed with water, brine and dried. Removal of solvent yielded a gum (263 mg) which slowly solidified (m.p. 85–87°) and was twice recrystallized from pentane to furnish colourless needles (193 mg), m.p. 87–88°; IR spectrum (KBr): COOH 2600, 2700, 1690 cm^{-1}; $C{=}CH_2$ 1650, 890 cm^{-1}. (Found: C, 76·20; H, 10·38. $C_{13}H_{24}O_2$ requires: C, 76·22; H, 10·24%).

Methyl ester was obtained by interaction with CH_2N_2 in ether: b.p. 135–140°/1·5 mm; IR spectrum: COOMe 1748; $C{=}CH_2$ 3050, 1650, 890 cm^{-1}; PMR spectrum: four quaternary Me's, 3H singlets at 59·5, 64·5, 66 and 71 c/s; $COOC\underline{H}_3$, 3H singlet at 217 c/s; $C{=}C\underline{H}_2$, 1H singlets at 285, 297 c/s. (Found: C, 76·70; H, 10·57. $C_{16}H_{26}O_2$ requires: C, 76·75; H, 10·47%).

C_{13}-*Keto acid* (II)

To the Me ester of VII (125 mg) in ether (10 ml) was added with stirring (N_2) an ether soln of PhMgBr (3 ml, 0·33 molar). The reaction mixture was stirred at room temp for 1 hr, refluxed for 2·5 hr and then left aside as such overnight (13 hr). This was worked up in the usual manner with NH_4Cl to furnish a brown gum (187 mg). This was chromatographed over SiO_2-gel (0·3 cm × 8 cm) which was eluted with light petroleum (5 ml × 2), 50% C_6H_6 in light petroleum (5 ml × 3) and C_6H_6 (5 ml × 3); the material (92 mg, gum) eluted with C_6H_6 was the required diphenyl carbinol (IR spectrum: OH 3490, 1030 cm^{-1}; $C{=}CH_2$ 3030, 1650, 890 cm^{-1}; C_6H_5 1590, 1495, 770, 750, 700 cm^{-1}).

The above product (90 mg) was dehydrated by heating for 2 hr at 230–235° with alumina[12b] (2 g). Working up with light petroleum in the usual manner gave a gum (75 mg), which was filtered through a short column of Al_2O_3 (2 g; light petroleum) and distilled to give XI (66 mg), b.p. 140–150° (bath)/2 mm.

To a stirred soln of the above olefin (60 mg) in acetone (5 ml) was added a freshly prepared CCl_4 soln of RuO_4 (prepared[20] from 40 mg RuO_2[21], 5 ml CCl_4 and 320 mg $NaIO_4$ in 5 ml water at 0°) at room temp (25°). After 5 min black ppt of RuO_2 appeared, which was redissolved by addition of $NaIO_4$ aq (50 mg in 1 ml water). Stirring was continued for 6 hr, after which excess of RuO_4 was destroyed by adding a few drops of isopropanol. The reaction mixture was filtered to remove RuO_2 and, the filtrate freed of solvent. The residue was taken up in ether (10 ml) and extracted with Na_2CO_3 aq (10%, 3 ml × 3). The aqueous alkaline extract was acidified with H_3PO_4 aq (50%) and the product taken up in ether (5 ml × 3), which was washed with water, brine and dried. Removal of solvent yielded a gum (22 mg), showing one major spot (R_f~0·4) and a few faint ones on TLC (solvent: 5% AcOH in C_6H_6). The major component (11 mg, m.p. 103–108°) was isolated by PLC and crystallized twice from pentane to yield white needles (3 mg), m.p. 119–121°.

(±)-*Isolongifolene* (I)

9-*Oxoisolongifolan-7-ene* (VIII). To a soln of acid VII (100 mg) in dry C_6H_6 (1·5 ml), was added one drop of pyridine soln (2 drops of pyridine diluted to 1 ml with C_6H_6). This was cooled to 0° and a benzene soln of oxalyl chloride (0·2 ml in 2 ml of C_6H_6) added. After 0·5 hr at 0°, the reaction mixture was allowed to stand at room temp (30°) for 3 hr. It was next gently warmed on a steam-bath for 5 min and the solvent removed under reduced press (30 mm). The crude acid chloride, thus obtained, was taken up in CS_2 (2 ml; dried over P_2O_5 and distilled) and added to a soln of $SnCl_4$ in CS_2 (0·12 ml of freshly distilled $SnCl_4$ diluted with 10 ml of dry CS_2; 1 ml of this soln + 2 ml CS_2 used for the reaction) at −15°. The reaction mixture was allowed to attain room temp (25°) during 15 hr, after which water (5 ml) was added and the organic phase taken up in ether, washed with Na_2CO_3 aq. (10%), brine and dried. Solvent was flashed off to give a product (83·6 mg) which solidified on cooling m.p. 43–47°. This was purified by PLC (SiO_2 gel; solvent: 5% EtOAc in C_6H_6) followed by recrystallization from EtOH to give white needles of VIII[1], m.p. 54–55·5°, yield 55 mg.

Thioketal. The above ketone (109 mg), ethane dithiol (235 mg), MeOH (1 ml) were mixed, BF_3–Et_2O (0·2 ml) added and the mixture allowed to stand at room temp (25–30°) for 18 hr. The reaction mixture was poured into ice-cold NaOHaq (10%, 10 ml) and the product taken up in ether–pentane (1:1; 5 ml × 3), which was washed with water, brine and dried. Solvent was removed to give a viscous liquid (145 mg), which was distilled, b.p. 150–155° (bath)/0·05 mm; PMR spectrum: quaternary Me's, 57, 60·5, 60·5 and 65·5 c/s; —S–C<u>H</u>$_2$—C<u>H</u>$_2$—S—, 4H signal, essentially a singlet at 195 c/s; —C=C<u>H</u>—, 1H singlet at 316 c/s. (Found: C, 69·58; H, 9·35. $C_{17}H_{26}S_2$ requires: C, 69·36; H, 8·90%).

Isolongifolene. The above thioketal (130 mg) was refluxed with Raney Ni (400 mg) in EtOH (6 ml) for 18 hr. The reaction mixture was filtered and the filtrate stripped off the solvent to give a liquid, which was filtered through Al_2O_3 (grade I, 0·6 cm) and eluted with pentane. The product (61 mg) on $AgNO_3$–SiO_2 gel TLC[17] (solvent: 10% C_6H_6 in hexane) showed a minor impurity, which was removed by chromatography over $AgNO_3$–SiO_2 gel (0·6 cm × 5 cm) using light petroleum as the eluent. First two 2 ml eluates gave after solvent removal a product (56 mg, TLC pure) which was distilled to furnish a liquid, identical with (±)-isolongifolene in all respects.

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