

Terpenoids Part LXXXIV : Synthesis of β -Elemene and Elemol

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A new synthesis of β -Elemene (I) has been accomplished through the application of Wittig reaction with methylene-triphenylphosphorane on the key intermediate, 1-methyl-1-vinyl-2-isopropenyl-4-acetyl cyclohexane (X), which was obtained through the cyclisation of the dibromide (IX) with nickel carbonyl in DMF. The same intermediate (X) was subjected to Grignard reaction with methyl magnesium iodide to furnish elemol (II).

IN continuation of our studies towards the syntheses of terpenoids¹⁻³ through Wittig reaction on suitably substituted ketones, a successful attempt has been made to synthesise elemene group of sesquiterpenes.

The synthesis of this class of hydrocarbons poses a difficulty in the fixation of the sensitive double bonds in the desired position and in the introduction of the angular methyl group.

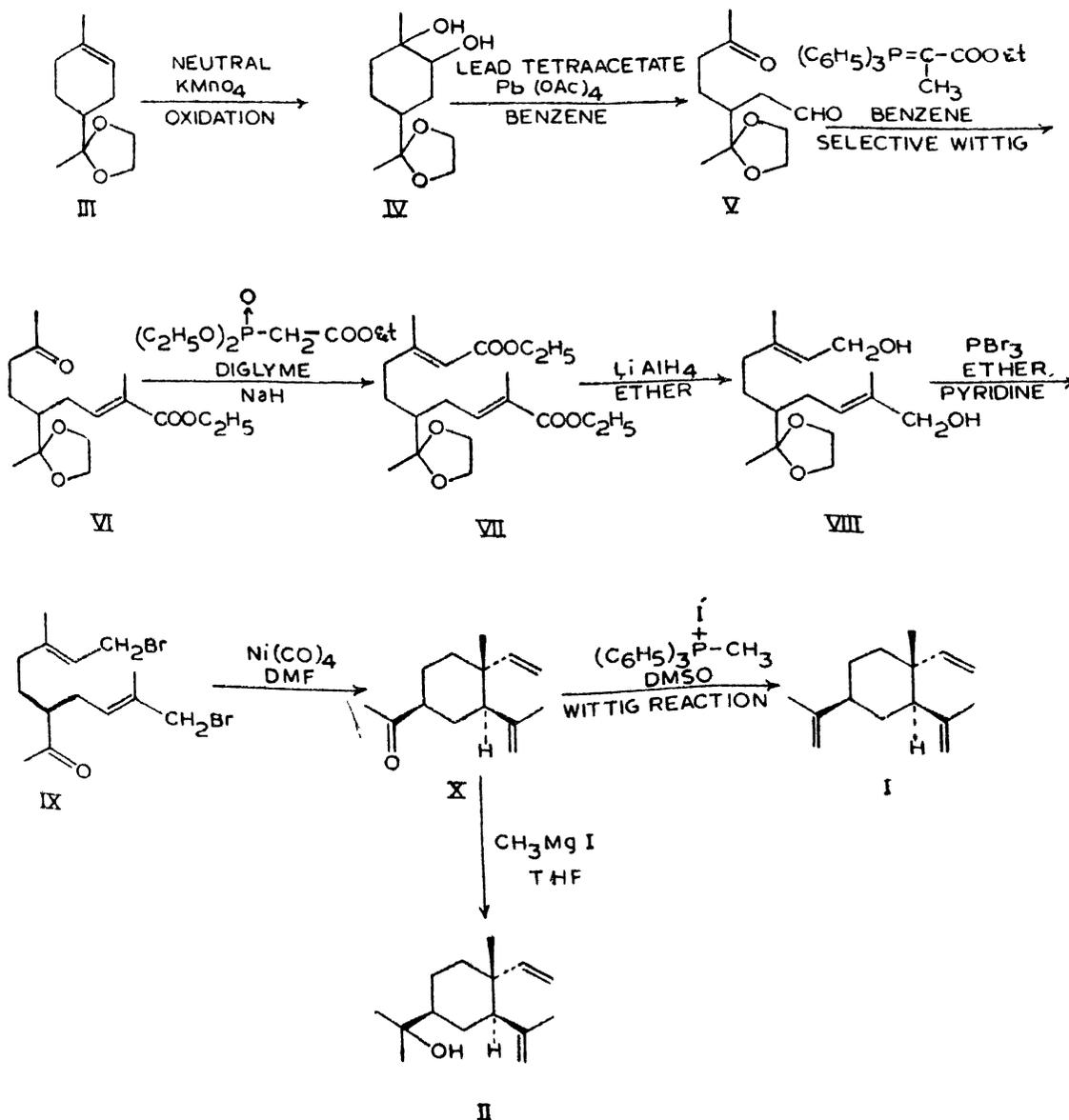


CHART-1

Making use of the recent findings of Corey and coworkers⁴ that the formation of 1:2 *trans* and *cis* divinyl cyclohexane is preferred to 10-membered 1:5 cyclic diene when an acyclic bisallyl bromide is cyclised with nickel carbonyl in a polar aprotic solvent. Vig et al⁵ have recently synthesised β -elemene (I). The present studies, however, report another clean approach to the synthesis of β -elemene (I), a sesquiterpene hydrocarbon, obtained from a number of essential oils e. g. valerian⁶, sweetflag⁷, carrot⁸, juniper⁷, orange⁹ and eucamphane¹⁰. A new synthesis of elemol (II), a constituent of Manila elemi oil¹¹ and java citronella oil¹², is also included in the present communication.

The scheme of reactions leading to the synthesis of the title compounds is outlined in Chart I.

1-Methyl-4(1',1'-ethylenedioxyethyl) cyclohexane-1, 2, diol (IV), the starting material, was prepared by the alkaline potassium permanganate oxidation of 1-methyl-4(1',1'-ethylenedioxyethyl)-1-cyclohexene¹³(III) in 30% yield. The diol (IV), thus obtained, upon oxidation with lead tetraacetate¹⁴ in dry benzene smoothly provided the keto-aldehyde (V), which was subjected to selective Wittig reaction¹⁵ with α -ethoxycarbonylethylidene triphenyl-phosphorane in refluxing benzene to yield 8-carbethoxy-5-(1',1'-ethylenedioxyethyl) non-*trans*-7-ene-2-one (VI) in 70% yield. In view of the fact that the reaction of the phosphonate carbanion with aldehydes yields only *trans* isomer^{15,16}, the compound (VI) is given the *trans* olef in configuration. This is further supported by the presence of a strong band at 970 cm⁻¹ in the IR spectrum of (VI). Subsequently the keto-ester (VI) was submitted to modified Wittig reaction with ethyl diethylphosphonacetate¹⁷ using diglyme as solvent and sodium hydride as a base to furnish the diester (VII) in 68% yield.

Lithium aluminium hydride reduction of this ketal-diester (VII) produced the diol (VIII) as a viscous liquid which was converted to the corresponding dibromide (IX) with phosphorous tribromide in dry ether¹⁸. The compound got deketalised during the formation of dibromide as was shown by the IR absorption peak at 1710 cm⁻¹. As the presence of carbonyl groups in the bisallyl bromide do not interfere with the reaction of organo nickel complexes¹⁹, the keto-dibromide (IX) was subjected as such to the cyclisation reaction according to the conditions of Corey and coworkers⁴. Three spots in t. l. c. analysis (Pet. ether : ether : 4:1) indicated the presence of three components in the cyclised product. The most polar *trans* component²⁰ (X) was separated through column chromatography and was subjected to the well known Wittig reaction with methylenetriphenylphosphorane to furnish β -elemene (I).

The synthetic hydrocarbon was purified by chromatography over neutral alumina eluting with pet-ether (40°-60°), followed by distillation under reduced pressure. The purity of the synthetic hydrocarbon was checked through t.l.c. which showed a single spot ($R_f=0.65$ pet-ether 40°-60°). The identity of the hydrocarbon (I) was established through comparison of its ir and nmr spectra.

The intermediate, *trans*-ketone (X) was subjected to Grignard reaction with methylmagnesium iodide to afford the *tert*-carbinol, elemol (II). The identity of the synthetic *tert*-alcohol (II) has been confirmed through its ir and nmr spectra.

Experimental

Procedure : Melting and boiling points are uncorrected. ir spectra were recorded on the Perkin-Elmer Infracord using thin liquid film. 60MH_z nmr spectra were taken in CCl₄ using tetramethyl-silane as internal standard.

1-Methyl-4(1',1'-ethylenedioxyethyl) cyclohexane-1,2-diol (IV) : To the colled mixture of 1-Methyl-4(1',1'-ethylenedioxy-ethyl) cyclohex-1-ene, (III ; 40 g) in water (2000 ml) was added slowly with continuous stirring, potassium permanganate (8% ; 380 ml) solution. The stirring was continued for one hour, the mixture was heated on water bath (100°), where the reaction mixture set to a gel prior to the precipitation of manganese dioxide. The mixture was filtered, filtrate concentrated (180 ml) under reduced pressure (50 mm) and the concentrate extracted with ether (5 x 100 ml) after saturating with potassium carbonate (70 g). The extract was dried over (anhydrous potassium carbonate), evaporated and the residue left was recrystallized from solvent ether (m.p. 93°) ; yield 14.5 g (30%) ; (Found : C, 60.75 ; H, 9.15. Calc. for C₁₁H₂₀O₄ : C, 61.09 ; H, 9.39%).

ir Spectrum showed characteristic bands at 3450, 1010(-OH), and 1060 cm⁻¹ (ketal).

3-(1',1'-Ethylenedioxyethyl-hept-6-one-1-al (V) : To a stirred solution of 1-methyl-4-(1',1'-ethylenedioxyethyl) cyclohexane-1,2-diol (IV ; 45 g) in dry benzene (500 ml), was added lead tetraacetate (80 g) slowly at 16°-20°. The mixture was stirred at room temperature for about 2 hr and filtered. Finely powdered potassium carbonate (63 g) was added to the filtrate, which was shaken well and then filtered. The filtrate after drying over anhydrous potassium carbonate was concentrated under reduced pressure. The residue was carefully extracted with ether. The extract was dried, (anhydrous Na₂SO₄) and ether removed to yield the keto-aldehyde (V ; 21.5 g) ; η_D^{25} 1.4720 (Found : C, 61.35 ; H, 8.15. Calc. for C₁₁H₁₈O₄ : C, 61.66 ; H, 8.47%).

Its ir showed characteristic absorption at 2740 (aldehydic C-H), 1720 (>C=O, H>C=O) and 1050 cm⁻¹ (ketal).

8-Carbethoxy-5-(1',1'-ethylenedioxyethyl)-non-7-ene-2-one (VI) : 3-(1',1'-Ethylenedioxyethyl)-heptan-6-one-1-al (V ; 20 g) and α -ethoxycarbonylethylidene triphenyl-phosphorane (30 g) were dissolved in dry benzene (600 ml) and refluxed overnight under nitrogen atmosphere. The solvent was evaporated and residue extracted with light pet-ether (40°-60°). The combined extracts were evaporated and the residue distilled to yield the keto-ester (VI ; 16.5 g) ; b.p. 180°-85°/5 mm ; η_D^{25} 1.4792. (Found : C, 64.10 ; H, 8.52. Calc. for C₁₆H₂₆O₅ : C, 64.40 ; H, 8.78%).

Its ir spectrum showed the absence of absorption in the 2740 cm^{-1} region but showed characteristic peaks at $1725\text{-}1720$ (keto-ester) and 1050 cm^{-1} (ketal).

Diethyl 2,8-dimethyl-5(1',1'-ethylenedioxyethyl)-deca-2,8-diene-1,10-dioate (VII): A slurry of sodium hydride (3 g; 50%) was placed in diethylene glycol-dimethyl ether and ethyl diethylphosphontacetate (12 gms) was added dropwise at room temperature. After the addition, the solution was stirred until the evolution of gas had ceased. To the resulting yellow solution was then added the keto-ester (VI; 15g) slowly below 10° . After the addition, the solution was further stirred for next 3 hr and then heated on water bath (60°) for 30 min. The product was extracted with ether and dried (Na_2SO_4). The solvent was removed and distillation of the residue under reduced pressure afforded diethyl 2,8-dimethyl-5(1',1'-ethylenedioxyethyl)-deca-2,8-diene-1,10-dioate; (VII, 11g) in 75% yield; b.p. $200\text{-}10^\circ/5\text{-}7\text{ mm}$; η_D^{25} 1.4820. (Found: C, 64.85; H, 8.45. Calc. for $\text{C}_{20}\text{H}_{32}\text{O}_6$: C, 65.19; H, 8.75%).

Its ir spectrum showed prominent peaks at 1720, 1650, 1040 and 950 cm^{-1} .

2,8-Dimethyl 5-(1',1'-ethylenedioxyethyl)-deca-2,8-diene-1,10-diol (VIII): To a fine suspension of lithium aluminium hydride (2.10 g) in anhydrous ether (200 ml) was added dropwise slowly with stirring, the diester (10 g) in (50 ml) ether at such a rate as to maintain the ether at gentle reflux. After the mixture had been stirred for next four hours at room temperature, the contents were decomposed with saturated solution of sodium-potassium tartrate. The organic layer was taken up in ether and dried (Na_2SO_4). Evaporation of solvent followed by vacuum distillation afforded the diol (VIII, 6 g) in 65% yield; b.p. $160^\circ\text{-}70^\circ/5\text{-}7\text{ mm}$; η_D^{25} 1.4980 (Found: C, 67.24; H, 9.60. Cal. for $\text{C}_{16}\text{H}_{28}\text{O}_4$: C, 67.57, H, 9.93).

Its ir spectrum showed characteristic peaks at 3350 (-OH), 1040 (a broad band, ketal and -OH) and absence of absorption in the region of 1700 cm^{-1} .

2,8-Dimethyl-5-acetyl-deca-2,8-diene-1,10-dibromide (IX): The diol (5.5 g) in dry ether (200 ml) was mixed with PBr_3 (3.54 g) during 0.5 hr in the dark. The solution was refluxed for 2.5 hr cooled, poured in ice water, shaken and extracted with ether. The combined extracts were washed with aqueous sodium hydrogen carbonate and water (twice). The solvent was removed after drying the ether extract (anhyd. Na_2SO_4). The residue was used as such for next reaction.

Its ir spectrum showed absence of absorption in the alcoholic region but a peak at 1710 cm^{-1} showing that the compound got deketalised.

1-Methyl-1-vinyl-2-isopropenyl-4-acetylcyclohexane (X): The allylic dibromide (IX; 5.0 g) dissolved in dry dimethyl formamide (12 ml) was slowly (10 hr) introduced via syringe to a solution of nickel carbonyl (9.0 g) in DMF (350 ml) under nitrogen at 50° . The reaction mixture was further heated at the same

temperature for 12 hr. During the addition a red colour appeared and at the end it faded. It gave a characteristic colour of nickel bromide (green) in DMF. The solvent was removed under reduced pressure. The reaction mixture was diluted with water and extracted with ether. The solvent was then evaporated and the residue was distilled under reduced pressure, b.p. $110\text{-}11^\circ/5\text{-}7\text{ mm}$. t.l.c. analysis using silica gel with (pet-ether: 14:15) as eluent showed the presence of three ether ($R_f=0.53, 0.28$ & 0.03) indicating the presence of three components. The most polar *trans* component¹⁸ ($R_f=0.03$) was collected through column chromatography eluting with (Benzene: ether: 1:2) η_D^{25} 1.5090 (Found C, 81.25; H, 10.55. Calc. for $\text{C}_{14}\text{H}_{22}\text{O}$: C, 81.50; H, 10.75%).

Its ir spectrum showed characteristic peaks at 1710 ($\text{C}=\text{O}$), 890 ($-\text{C}=\text{C}-$) 910 ($-\text{CH}=\text{CH}_2$) and other peaks were at 3060, 2900 and 1640 cm^{-1} .

1-Methyl-1-vinyl-2,4-diisopropenylcyclohexane (I). (*β -elemene*): The phosphorane was prepared from methylene triphenylphonium iodide (0.88 g) in DMSO (2 ml) and sodium hydride (0.11 g, 50%) in DMSO (1 ml) under nitrogen atmosphere. To this was added the ketone (X, 0.300 g) in THF (1 ml). The contents were stirred and warmed for 30 min at 40° and left overnight at room temperature. The contents were poured on crushed ice and extracted with pet-ether ($40^\circ\text{-}60^\circ$). The pet-ether extract was dried (anhyd. Na_2SO_4), evaporated and residue chromatographed over silica gel, when elution with pet-ether ($40^\circ\text{-}60^\circ$) gave the hydrocarbon (I). This was further purified by distillation under reduced pressure: b. p. $90^\circ\text{-}100^\circ/5\text{-}7\text{ mm}$; η_D^{25} 1.4930 (lit. η_D^{25} 1.4935). The purity of the hydrocarbon was checked through t. l. c. which showed a single spot (Pet-ether $40^\circ\text{-}60^\circ$) ($R_f=0.65$) (Found: C, 88.35; H, 11.55. $\text{C}_{16}\text{H}_{24}$ requires C, 88.16; H, 11.84%).

The synthetic product (I) was characterised through its ir spectrum ν_{max} 3070, 2960, 2850, 1760, 1645, 1450, 1360, 1250, 1145, 1110, 1075, 1060, 1010, 915, 890, 800, 750 and 715 cm^{-1} comparable to those given in literature.²¹

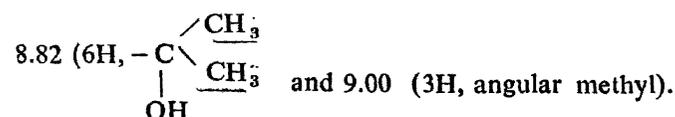
The structure of the hydrocarbon was further confirmed by its nmr spectrum: τ_{ppm} 3.98 4.14, 4.30 (1H, $-\text{CH}=\text{CH}_2$), 5.0-5.30 (6H, $-\text{CH}=\text{CH}_2, -\text{C}=\text{CH}_2$), 8.32 (6H, $\text{C}=\text{C}-\text{CH}_3$) and 9.01 (3H, angular methyl). The values were found in exact correspondence with those reported in the literature⁵.

1-Methyl-1-vinyl-2-isopropenyl-4-(α, α -dimethyl-methanol)-cyclohexane (II): Grignard reagent was prepared to the exclusion of moisture from dry magnesium turnings (0.11 g), methyl iodide (0.700 g) in anhydrous THF (50 ml). This was cooled in ice cold water and key intermediate (X, 300 mg) in THF (40 ml) was added dropwise with constant shaking during a period of 30 min. After the addition was complete the contents were left overnight at room temperature and thereafter, the reaction mixture was heated under reflux for about half an hour to complete the reaction. The

cooled contents were decomposed with saturated solution of ammonium chloride. The organic layer was separated and aqueous phase extracted with ether (3×50 ml). The combined THF-ether extract was dried (anhyd., Na₂SO₄) and solvent removed. The residue was distilled under reduced pressure to furnish elemol (II); b. p. 125-30°/5-7 mm; η_D^{18} 1.4970; (lit η_D 1.4980). The purity of the product was checked through t. l. c. which showed a single spot ($R_f=0.46$) (50 : 50 :: Benzene; ether). (Found C, 80.98; H, 11.77; C₁₅H₂₆O requires C, 81.02; H, 11.79%).

The identity of the synthetic compound was established through its ir absorption spectrum ν_{max} 3400, 3060, 2000, 1820, 1640, 1450, 1370, 1250, 1220, 1145, 1140, 1110, 1050, 1020, 935, 915, 890, 835, 750 and 715 cm⁻¹.

The structure was further confirmed by the nmr which showed singals at τ 3.95, 4.15, 4.30, (1H, -CH=CH₂); 5.0-5.28 (4H, -C=CH₂); 8.35, (3H, C=C-CH₃),



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References

- O. P. VIG, A. K. SHARMA, J. CHANDER and B. RAM., *J. Indian Chem. Soc.*, 1972, **49**, 159.
- O. P. VIG, J. P. SALOTE and B. VIG., *J. Indian Chem.*, 1966, **4**, 323.
- O. P. VIG, S. CHANDER, J. PURI and S. D. SHARMA., *Indian J. Chem.*, 1968, **6**, 63.
- E. J. COREY, E. K. W. WAT., *J. Amer. Chem. Soc.*, 1967, **89**, 2757.
- O. P. VIG, K. L. MATTA, J. C. KAPUR and B. VIG., *J. Indian Chem. Soc.*, 1968, **45**, 973.
- S. WITEK and J. KREPINSKY., *Coll. Czech. Chem. Commun.*, 1966, **31**, 1113.
- V. SYKORA, V. HEROUT and F. SORM., *Coll. Chem. Commun.*, 1956, **21**, 267.
- G. V. PIGULEVSKII and V. I. KOVALEVA., *Rast. Resur.*, 1966, **2**, 527.
- G. L. K. HUNTER and J. L. PARKS., *J. Food. Chem.*, 1964, **29**, 25.
- C. C. ASSELINEAU and J. ASSELINEAU., *Bull. Soc., Chim. de France*, 1957, 1359.
- A. M. CLOVER., *Phillipdine. J. Sci.*, 1907, **2**, A; Ref. in *Ber. Schimmel and Co.*, 1907, II, 21.
- K. KAFUKU, T. IKEDA and Y. FUJITA., *J. Chem. Soc., Japan*, 1932, **53**, 636.
- O. P. VIG, K. L. MATTA., G. SINGH and I. RAJ., *J. Indian Chem. Soc.*, 1966, **43**, 27.
- L. A. YONOVSKAYA, R. N. STEPINOVA., G. A. KOGAN and V. F. KUCHEROV., *Bull. Acad. Sci., U. S. S. R.*, 1963, 774.
- A. J. BIRCH, J. E. T. CORRIE and G. S. R. SUBBA RAO., *Austral. J. Chem.*, 1970, **23**, 1811.
- L. D. BERGELSON and M. M. SHEMYABIN., *Tetrahedron.*, 1963, **19**, 149.
- W. S. WADSWORTH and W. S. EMMONS., *J. Amer. Chem. Soc.*, 1961, **83**, 1733.
- J. M. OSBOND., *J. Chem. Soc.*, 1961, 5270.
- W. CARRUTHERS., "Some modern methods of organic synthesis", 1971, p. 46.
- E. J. COREY and E. A. BROGER., *Tetrahedron Letters* 1969, 1779.
- P. SORM, M. HOLUB, SYKORA, J. MIEZIVA, M. STROISI, J. PLIVIA, B. SCHNEIDER and V. HEROUT., *Collec. Czech. Chem. Commun.*, 1953, **18**, 512.