SYNTHESIS OF (*Z*)-1,8- AND (*E*)-1,8-PENTADECADIENE: TUMOR INHIBITORS

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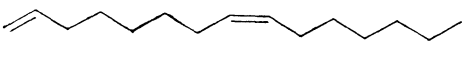
Syntheses of (*Z*)-1,8- and (*E*)-1,8-pentadecadienes have been achieved through Wittig, Claisen ortho ester rearrangement and Li_2CuCl_4 catalysed coupling reactions.

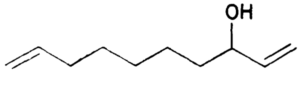
Echinacea angustifolia DC. at one time had a reputation for antiseptic and analgetic properties[1] to various Indian tribes of Nebraska. Voaden and Jacobson[2] have isolated a constituent of the root oil of *Echinacea angustifolia* DC. and *E. pallida* (NUTT.) and identified it as (Z)-1,8-pentadecadiene and its *trans*-isomer. Literature[2,3] records a few syntheses of *I* and *VII*. We wish to report herein a simple and straight forward syntheses of *I* and *VII*.

Octenaldehyde *II* on stereoselective Wittig reaction with the ylide generated from heptyltriphenylphosphonium bromide and sodium amide in THF–HMPA[4] afforded the *cis* olefinic compound *I* (98% pure) in 61% yield.

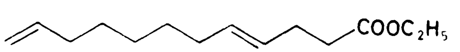


I

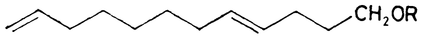
II



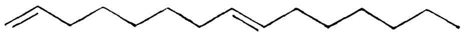
III



IV



V, R = H
VI, R = CH_3SO_2



VII

The key intermediate *IV* for synthesis of *VII* was prepared by Claisen ortho ester rearrangement[5] of *III*. Reduction of *IV* with $LiAlH_4$ furnished the alcohol *V* in 70% yield. The alcohol *V* was converted into its mesylate *VI* which was reacted further as such with propylmagnesium bromide in the presence[6] of Li_2CuCl_4 as a catalyst to afford the required compound *VII* in 38% yield.

EXPERIMENTAL

All the glassware used for the experiment was thoroughly dried in an oven and cooled under the stream of nitrogen. Purity of the samples was checked by TLC using silica gel impregnated with 13% calcium sulfate. Silica gel (Acme, 60—80 mesh) was used for column chromatography. IR spectra were recorded on Perkin–Elmer 377 spectrophotometer (wavenumbers in cm^{-1}) and ^1H NMR spectra (CCl_4) on a Varian EM-390 instrument using tetramethylsilane as an internal standard. Chemical shifts are given in ppm (δ-scale), coupling constant (J) in Hz. Unless otherwise stated, all the organic extracts were dried over anhydrous sodium sulfate.

(*Z*)-1,8-Pentadecadiene (*I*)

Heptyltriphenylphosphonium bromide (7·05 g, 16·0 mmol) and sodium amide (0·62 g, 16·0 mmol) were suspended in THF (20 ml). HMPA (3 ml) was added and the suspension was stirred for 90 min at room temperature. The deep orange solution of the ylide was then cooled to −75°C and the aldehyde *II* (1·0 g, 8·0 mmol) in THF (10 ml) was added dropwise during 10 min. The reaction mixture was allowed to warm to room temperature and stirred for 6 h. The reaction mixture was quenched with ice and extracted with benzene. The benzene solution was washed with brine and dried. Purification of the crude compound by column chromatography afforded *I* 1·0 g (61%). IR spectrum (neat): 3 050, 3 000, 2 860, 1 650, 1 460, 990, 900, 720. ^1H NMR spectrum: 4·85—6·05 bm, 5 H ($CH{=}CH$, $CH{=}CH_2$); 2·1 m, 6 H (allylic methylenes); 1·2 to 1·6 bs, 14 H (saturated methylenes); 0·95 t, 3 H (CH_3, $J = 3$). For $C_{15}H_{28}$ (208·4) calculated 86·46% C, 13·54% H; found: 86·13% C, 13·86% H.

3-Hydroxy-1,9-decadiene (*III*)

Grignard was prepared from magnesium turnings (0·8 g, 33·3 mmol) and 6-heptenyl bromide (5·8 g, 33·3 mmol) in THF (100 ml), cooled to 0°C and added to the acrolein (1·7 g, 30·4 mmol) in THF (20 ml) dropwise with constant stirring during 30 min. The mixture was left overnight at room temperature and then refluxed for 3 h. The cooled reaction mixture was decomposed with saturated solution of ammonium chloride and the organic layer separated. The aqueous phase was extracted with ether and the combined organic extracts dried. Solvent removal and distillation of the residue afforded *III*; 3 g (60%). IR spectrum (neat): 3 450—3 300, 3 010, 2 920, 1 650, 965, 910. ^1H NMR spectrum: 5·8—6·1 m, 2 H ($2 \times HC{=}CH_2$); 5·0—5·6 m, 4 H ($2 \times HC{=}CH_2$); 3·6 m, 2 H ($CH(OH){-}C{=}$); 2·2 m, 2 H (allylic methylenes); 1·4—1·6 bs, 8 H (saturated methylenes). For $C_{10}H_{18}O$ (154·3) calculated: 77·9% C, 11·8% H; found: 77·8% C, 11·8% H.

Ethyl (*E*)-4,11-Dodecadien-1-oate (*IV*)

A mixture of *III* (6·75 g, 43·8 mmol), propionic acid (2·27 g, 30·7 mmol) and triethyl orthoacetate (49·7 g, 0·27 mol) was heated at 140°C for 2 h with distillative removal of ethanol. The solution was poured into ether (100 ml), the ethereal layer washed with sodium bicarbonate solution, brine and dried. The excess triethyl orthoacetate was removed under reduced pressure and the crude product was purified by column chromatography to afford *IV*; 4·95 g (50%) as a colourless liquid. IR spectrum (neat): 3 010, 2 930, 1 730, 1 470, 965, 910. ^{1}H NMR spectrum: 5·7–6·0 bm, 1 H ($CH=CH_2$); 5·4–5·6 m, 4 H ($CH=CH_2$, $CH=CH$); 4·0 q, 2 H ($COOCH_2.CH_3$, J = 7·5); 1·9–2·1 m, 8 H (allylic methylenes, CH_2COO); 1·6–1·8 m, 6 H (saturated methylenes); 1·25 t, 3 H ($COOCH_2CH_3$). For $C_{14}H_{24}O_2$ (224·3) calculated: 75·0% C, 10·8% H; found: 74·8% C, 10·8% H.

(*E*)-4,11-Dodecadien-1-ol (*V*)

To a stirred solution of $LiAlH_4$ (0·30 g, 7·9 mmol) in ether (10 ml) was added an ethereal solution of *IV* (3·4 g, 15·1 mmol) under nitrogen in such a way that the mixture refluxed gently. The flask contents were stirred and monitored by TLC with 1 : 1 hexane-ether as the solvent. After 5 h, when no more ester was seen, the complex was decomposed with saturated aqueous sodium potassium tartrate. The compound was extracted with ether (2 × 40 ml) and the ether extract dried. Distillation of the solvent under reduced pressure afforded crude liquid which upon chromatography over silica gel gave TLC pure *V*, 1·78 g (65%). IR spectrum (neat): 3 450–3 300, 3 010, 2 920, 1 470, 990, 970, 910. ^{1}H NMR spectrum: 5·6–6·0 bm, 1 H ($CH=CH_2$); 5·1 to 5·6 m, 4 H ($CH=CH_2$, $CH=CH$); 3·6–3·8 m, 3 H (CH_2OH); 2·0–2·1 m, 6 H (allylic methylenes); 1·4–1·6 bs, 8 H (saturated methylenes). For $C_{12}H_{22}O$ (182·3) calculated: 79·1% C, 12·2% H; found: 79·0% C, 12·1% H.

(*E*)-1-Methanesulphonyloxy-4,11-dodecadiene (*VI*)

To a solution of *V* (2·0 g, 11 mmol) and triethylamine (1·5 ml) in methylene chloride (20 ml) maintained at 0°C was added mesyl chloride (0·85 ml, 11 mmol) in methylene chloride (5 ml) dropwise and stirred for 30 min, washed with water and dried. Solvent removal gave crude *VI*; 2·71 g (95%), which was used as such for the next operation.

(*E*)-1,8-Pentadecadiene (*VII*)

To a stirred and cooled solution of Grignard reagent, prepared from propyl bromide (1·23 g 10 mmol) and activated magnesium turnings (0·24 g, 10 mmol) in THF (10 ml) under nitrogen atmosphere, was added *VI* (2·60 g, 10 mmol) in THF (15 ml) over a period of 20 min, stirred for 45 min at −10°C, thereafter, a 0·1M solution of Li_2CuCl_4 in THF (2 ml) was added, stirred for 4 h at −10°C nad left overnight. The reaction mixture was quenched by the addition of saturated solution of NH_4Cl. The resulting solution was extracted with ether, washed with brine and dried. Solvent was removed and the residue was purified by column chromatography over silica gel using light petroleum-ether (9 : 1) yielded pure *VII*; 0·79 g (38%). IR spectrum (neat): 3 060, 2 900, 2 840, 1 650, 1 460, 1 380, 1 260, 990, 960, 910, 725. ^{1}H NMR spectrum: 4·8–5·9 m, 5 H ($CH=CH_2$, $CH=CH$); 2·0–2·3 m, 6 H (allylic methylenes); 1·1–1·6 bs, 14 H (saturated methylenes); 0·9 t, 3 H (CH_3, J = 3). For $C_{15}H_{28}$ (208·4) calculated: 86·46% C, 13·54% H; found: 86·15% C, 13·84% H.

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