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A New Synthesis of, α-Unsaturated Aldehydes: Synthesis of Traumatin and Bombykol

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A NEW SYNTHESIS OF α,β-UNSATURATED ALDEHYDES : SYNTHESIS OF TRAUMATIN AND BOMBYKOL

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Abstract: A novel conversion of an alkene to a higher homologue α,β-unsaturated aldehyde was achieved in three steps. The aldehydes were used for the synthesis of traumatin, a wound hormone and bombykol, the pheromone of **bombyx mori.**

α,β-Unsaturated aldehydes serve as synthons for pheromones[1] and biologically active compounds which are conjugated dienes with an E/E or E/Z configuration. The most commonly used route for the synthesis of α,β-enals employ Wittig or Wittig Horner type reaction of suitably functionalised alkyl fragments[2].

Our approach to the synthesis of traumatin and bombykol involves a facile and novel three step conversion of an alkene to a higher homologue α,β-unsaturated aldehyde employing readily available reagents. Copper[3a-c] catalysed bromoform addition to alkenes (**1a-c**) gave 1,1,3-tribromoderivatives (**2a-c**). Treatment of **2** with potassium acetate in dimethyl formamide using 18-Crown-6

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as a phase transfer catalyst resulted in the substitution of secondary bromide with acetoxy group and loss of one molecule of HBr to give 3-acetoxy-1-bromo-1-alkenes (**3a-c**) in 65-70% yield[3b]. γ-Halo allylic acetates are synthons for biologically active compounds like coriolic acid and arachidonic acid metabolites[4]. They also serve as latent β-hydroxy carbonyl compounds[5] and 1,3-diols[6]. Vinyl halides can be converted to carbonyl compounds on reaction with mercuric acetate in trifluoroacetic acid[7]. But treatment of γ-halo allylic acetates (**3a-c**) under the same conditions afforded α,β-unsaturated aldehydes (**4a-c**) in 45-53% yield. Thus, this represents a useful conversion of γ-halo allyic acetates to α,β-unsaturated aldehydes.

The synthesis of Traumatin (5), a wound hormone in plants and Bombykol (7), pheromone of **Bombyx Mori** was achieved from the same intermediate as shown in the Figure.

Methyl 12,12,10-tribromododecanoate (**2a**) on treatment with potassium acetate in DMF gave methyl 10-acetoxy-12-bromo-11-(E)-dodecenoate (**3a**) in 68% yield. Reaction of (**3a**) with trifluoroacetic acid and mercuric acetate furnished methyl 12-oxo-(E)-10-dodecenoate (**4a**) in 53% yield. Traumatin 12-oxo-(E)-10-dodecenoic acid[8] (5) was obtained by hydrolysis of (**4a**), whereas Wittig olefination of (**4a**)[9] with butyl phosphonium bromide in tetrahydrofuran/potassium tertiary butoxide gave (**6a**). Lithium aluminium hydride reduction of (**6a**)[10] affords bombykol (7).

EXPERIMENTAL

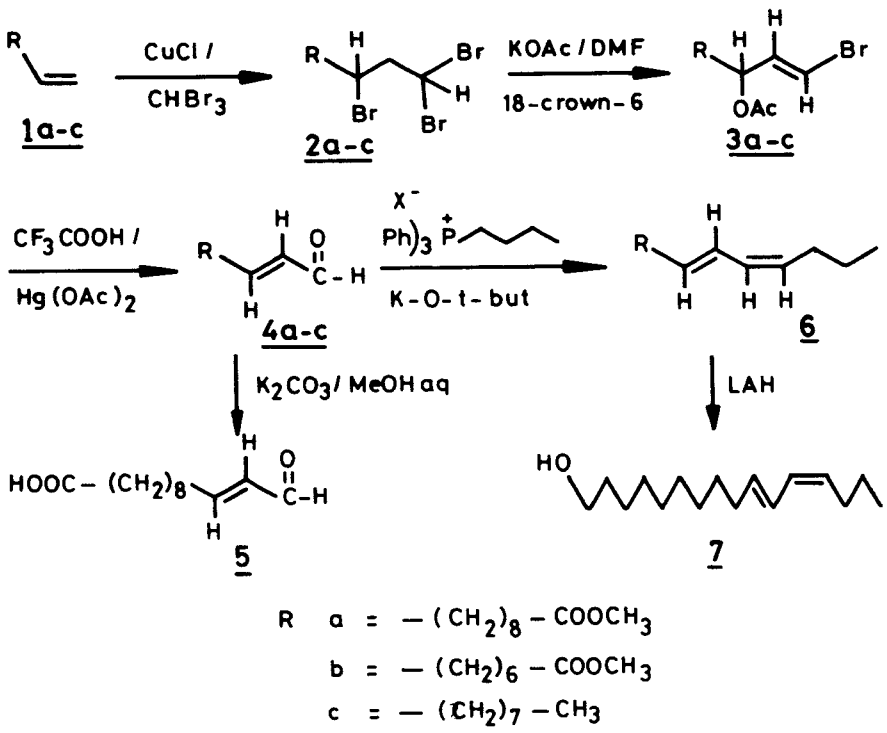
All solvents were of laboratory grade and dried using standard procedures. The ^1H NMR spectra were recorded on Bruker 300 MHz and 80 MHz Varian spectrometers. IR spectra were recorded with a Perkin Elmer 810 spectrometer model. Mass spectra were recorded on VG Micromass-7070H.

Preparation of tribromo derivatives (2a-c)

The tribromo derivatives were prepared according to our earlier procedure[3a-c].

3-Acetoxy-1-bromo-1-alkene (3a-c)

To a stirred solution of dry DMF 100 mL containing potassium acetate (4.3 g; 0.044 mol) and 18-Crown-6 (0.004 mol) under nitrogen was added through a septum **2a** (9 g; 0.02 mol) over a period of 30 min. The temperature was raised to 70°C and the reaction was continued for 8 h. The residue left after distillation of DMF under reduced pressure was diluted with water and extracted with ether. The organic layer after washing with water, drying over sodium sulfate and concentration, gave a dark coloured liquid which on chromatography employing a silica gel column and using 1:1 benzene and hexane as eluent gave methyl 10-acetoxy-12-bromo-11-dodecenoate, **3a** (4.7 g; 68% yield); IR(Neat): 1740, 1735, 1620, 1040, 980 cm^{-1}. ^1H NMR ($CDCl_3$): 0.9 (m, 14H, $7CH_2$); 1.9 (s, 3H, $OCOCH_3$); 2.1 (t, 2H, J = 6.6, CH_2COOCH_3); 3.6 (s, 3H, $COOCH_3$);



4.9 (m, 1H, CH_2 = CH-C<u>H</u>OCOCH$_3$); 5.9-6.1 (m, 2H, C<u>H</u>Br=C<u>H</u>). Mass : CI (methanol) m/e 349/351 $(M+H)^+$. Anal.calc. for $C_{15}H_{25}BrO_4$; C, 51.57; H, 7.16; Found : C, 51.42; H, 7.34. The other acetoxy-1-bromo alkenes were prepared using the same methodology. NMR spectral data of compounds (**3a-c**) were in agreement with the reported γ-halo allylic alcohols[11a].

Methyl 8-acetoxy-10-bromo-9-decenoate (3b)

Compound **3b** (5.3 g; 67% yield) was obtained from **2b** (10.5 g; 0.025 mol). ^{1}H NMR ($CDCl_3$): 1.0-1.75 (m, 10H, 5C<u>H</u>$_2$); 2.0 (s, 3H, COC<u>H</u>$_3$); 2.25 (t, J = 6.6, 2H, C<u>H</u>$_2$COOCH$_3$); 3.62 (s, 3H,

$COOCH_3$); 5.1 (m, 1H, HC-$OCOCH_3$); 5.87-6.37 (m, 2H, $BrCH{=}CH$). Anal.calc. for $C_{13}H_{21}BrO_4$: C, 48.59; H, 6.5; Found: C, 48.32; H, 6.65.

3-Acetoxy-1-bromo-1-undecene (3c)

Compound **3c** (5 g; 70% yield) was obtained from **2c** (10 g; 0.025 mol). ^1H NMR ($CDCl_3$): 0.9 (t, 3H, CH_3); 1.2 (br, 14H, $7CH_2$); 1.97 (s, 3H, $COCH_3$); 4.96 (m, 1H, HC-$OCOCH_3$); 5.7-6.23 (m, 2H, $BrCH{=}CH$). Anal.calc. for $C_{13}H_{23}BrO_2$: C, 53.60; H, 7.90; Found: C, 53.28; H, 7.73.

Methyl 12-oxo-(E)-10-dodecenoate (4a)

Vinyl bromide (**3a**, 0.90 g; 0.0027 mol) was added under nitrogen through a septum to a stirred solution of trifluoroacetic acid (20 mL) containing mercuric acetate (1.21 g; 0.0038 mol). Stirring was continued for 4 h. The mixture was filtered and excess of acid distilled off under vacuum. The residue was cautiously treated with dilute sodium bicarbonate, brine and then extracted with ether. The combined organic layers were dried and the excess solvent removed under reduced pressure. Column chromatographic purification of the residue over alumina using hexane/benzene (1:1) as eluent gave **4a** (0.32 g; 53% yield). IR(Neat): 1740, 1690, 1640, 1040 and 980 cm^{-1}. ^1H NMR ($CDCl_3$): 1.37 (br, 12H, $6CH_2$); 2.31 (t, 4H, $C{=}C$-CH_2 and CH_2COOCH_3); 3.6 (s, 3H, $COOCH_3$); 6.15 (dd, 1H, J = 15, 8); 6.89 (dd, 1H, J = 15, 7, CHO-$CH{=}CH$); 9.5 (d, 1H, CHO, J = 8). Mass: m/e 226 (M^+). The other , -unsatu-

rated aldehydes were prepared employing the same methodology. The spectral data were in accordance with the reported ones for compounds **4a-c**[11b].

Methyl 10-oxo-(E)-8-decenoate (4b)

IR(Neat): 1730, 1690, 1640, 970 cm^{-1}. ^1H NMR ($CDCl_3$): 1.4 (b, 8H, $4CH_2$); 2.31 (t, J = 7, 4H, $C{\equiv}C\text{-}CH_2$ + CH_2COOCH_3); 3.62 (s, 3H, OCH_3); 6.18 (m, J = 15, 8, 1H); 6.72 (m, J = 15, 7, 1H, CHO-CH=CH); 9.45 (d, J = 8, 1H, CHO).

2(E)-Undecenal (4c)

IR(Neat): 1690, 970 cm^{-1}. ^1H NMR ($CDCl_3$): 0.81 (t, 3H, CH_3); 1.25 (br, 12H, $6CH_2$); 2.19 (t, J = 7, 2H, CH_2-C=C); 6.0 (m, J = 15, 8, 1H); 6.75 (m, J = 15, 7, 1H, CHO-CH=CH); 9.45 (d, J = 7, 1H, CHO).

12-Oxo-(E-10-dodecenoic acid (5)

To a stirred solution of **4a** (0.2 g; 0.0008 mol) in 1:1 aqueous methanol (20 mL), was added, potassium carbonate (0.152 g; 0.001106 mol). The reaction was stirred at room temperature for 24 h. Neutralisation and extraction with dichloromethane gave 0.13 g (80%) of traumatin. The compound was crystallised from cyclohexane and ether, mp 65.4°C (lit. mp 65.3)[8]. The spectral data were in agreement with those reported in the literature[8].

Methyl 9(E)-11(Z)-hexadecadienoate (6)

Potassium tertiary butoxide (0.198 g; 0.0016 mol) and butyl phosphonium bromide (0.7 g; 0.0016 mol) were stirred in 20 mL of dry THF at room temperature under nitrogen. After 5 min.

4a was added (0.2 g; 0.008 mol) through a septum and the reaction was left overnight. Water (10 mL) was added and after 1 h stirring the organic layer was separated and dried and solvent removed under vacuum. Column chromatographic purification using benzene as solvent over alumina gave **5a**(0.134 g; 63% yield). IR(Neat): 1740, 1620, 1200, 1050, 980 cm^{-1}. ^1H NMR ($CDCl_3$): 0.687-1.68 (m, 17H, $7C\underline{H}_2$, $C\underline{H}_3$); 1.8-2.3 (m, 6H, $3C\underline{H}_2$); 3.6 (s, 3H, $COOC\underline{H}_3$); 5.0-6.37(m, 4H, $\underline{C}=\underline{C}(H)-\underline{C}=\underline{C}$); Mass: m/e 266 ($M^+$). The spectral data were in agreement with the reported ones[11b].

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