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Synthetic Applications of the Baylis-Hillman Reaction: Simple Synthesis of [2E]-2-Butyloct-2-enal and [2E]-2-Tridecylheptadec-2-enal

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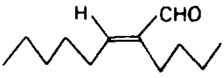
Abstract: A simple synthesis of [2E]-2-butyloct-2-enal, an alarm pheromone component of the African weaver ant, *Oecophylla longinoda*, and [2E]-2-tridecylheptadec-2-enal, an unusual metabolite from the red alga, *Laurencia* species using Baylis-Hillman adducts has been described.

A trisubstituted olefin moiety [1-3] has been a regular feature of many naturally occurring biologically active molecules such as terpenoids, pheromones, macrolide antibiotics *etc*,. Since the physiological activity of these natural products is often highly sensitive to isomeric purity of the olefin, a number of synthetic methodologies have been developed for obtaining trisubstituted olefins with high stereoselectivity[3-7]. As a part of our research program on the synthetic applications of the Baylis-Hillman reaction, we herein report a simple synthesis of [2E]-2-butyloct-2-enal (**1**),[8-11] an alarm pheromone component of the African weaver ant, *Oecophylla longinoda*, and [2E]-2-tridecylheptadec-2-enal[12] (**2**), an unusual metabolite from the red alga *Laurencia* species (*Laurencia undulata* and *Laurencia papillosa*).



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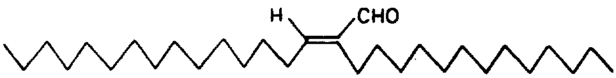

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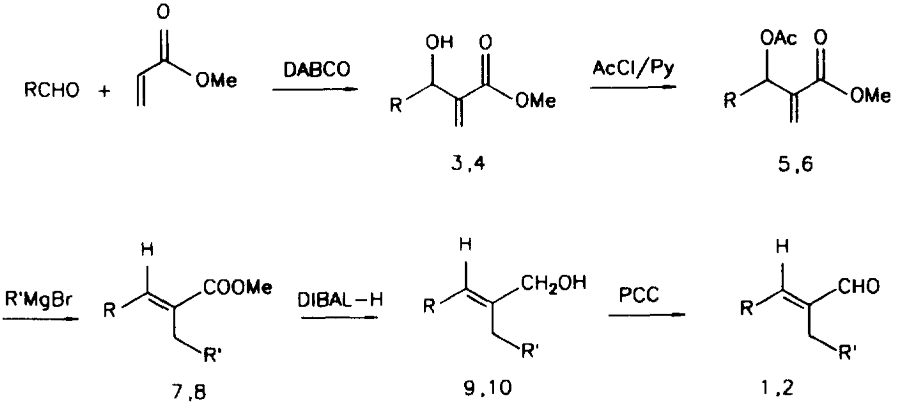
The Baylis-Hillman reaction is a versatile carbon-carbon bond forming reaction providing synthetically useful multifunctional molecules[13-15]. These multifunctional molecules have been successfully utilized in various stereoselective processes and synthetic transformations[7,16-19]. We have recently developed a simple methodology for the synthesis of [2E]-2-substituted alk-2-enoates *via* the reaction of Grignard reagent with 3-acetoxy-2-methylenealkanoates[17]. With a view to prove the efficacy of this methodology we have undertaken the synthesis of biologically active molecules, [2E]-2-butyloct-2-enal (**1**) and [2E]-2-tridecylheptadec-2-enal (**2**) according to Scheme 1.

SCHEME 1



R= $^{n}C_5H_{11}$ R'= $^{n}C_3H_7$ (1,3,5,7,9)

R= $^{n}C_{14}H_{29}$ R'= $^{n}C_{12}H_{25}$ (2,4,6,8,10)

First, we have carried out the synthesis of [2E]-2-butyloct-2-enal. The Baylis-Hillman coupling reaction of hexanal with methyl acrylate produced methyl 3-hydroxy-2-methyleneoctanoate (**3**) in 85% yield. This was converted into the corresponding acetate **5** by treating with acetyl chloride in the presence of pyridine. Subsequent reaction with propylmagnesium bromide provided methyl [2E]-2-butyloct-2-enoate (**7**) in 61% yield. This ester on treatment with diisobutylaluminum hydride (DIBAL-H) gave [2E]-2-butyloct-2-en-1-ol (**9**) which on further treatment with pyridinium chlorochromate (PCC) furnished the desired [2E]-2-butyloct-2-enal (**1**).

Similarly, the metabolite [2E]-2-tridecylheptadec-2-enal (**2**) was synthesized starting from the Baylis-Hillman adduct methyl 3-hydroxy-2-methyleneheptadecanoate (**4**), obtained from pentadecanal and methyl acrylate (Scheme 1).

In conclusion, our methodology provides a simple synthesis of [2E]-2-butyloct-2-enal and [2E]-2-tridecylheptadec-2-enal. Further work on the applications of Baylis-Hillman adducts, in organic synthesis is underway in our laboratory.

EXPERIMENTAL

The boiling points and melting points were uncorrected. IR spectra were recorded on JASCO FT/IR-5300 or on Perkin-Elmer model 1310 spectrophotometer. ^{1}H NMR spectra (200 MHz) and ^{13}C NMR spectra (50 MHz) were recorded on BRUKER-AC-200 spectrometer in chloroform-d with TMS as an internal standard. Elemental analyses were performed on a Perkin- Elmer 240C-CHN analyzer. Mass spectrum was recorded on Finnegan MAT instrument.

Methyl 3-hydroxy-2-methyleneoctanoate (3): A mixture of hexanal (30 mM, 3.6 mL), methyl acrylate (45 mM, 4.05 mL) and DABCO (6 mM, 0.672 g) was allowed to react at room temperature for 6 days. The reaction mixture was diluted with ether (20 mL) and washed successively with 2N hydrochloric acid, water and aqueous sodium bicarbonate solution. The ether layer was dried over anhydrous sodium sulphate and concentrated. The residue was distilled under reduced pressure, to afford methyl 3-hydroxy-2-methyleneoctanoate as a colorless liquid. Yield: 4.73 g (85%); bp: 102-104 $^{\circ}$C/4 mm; IR (neat) ν_{max}: 3449, 1720, 1630 cm^{-1}; ^{1}H NMR: δ 0.90 (dist. t, 3H), 1.16-1.75 (m, 8H), 2.43 (b, 1H), 3.77 (s, 3H) 4.45 (t, 1H, J=7 Hz), 5.78 (s, 1H), 6.21 (s, 1H); ^{13}C NMR: δ 13.80, 22.40, 25.26, 31.47, 36.19, 51.58, 70.86, 124.43, 142.91, 166.92.

Methyl 3-acetoxy-2-methyleneoctanoate (5): To a stirred solution of methyl 3-hydroxy-2-methyleneoctanoate (**3**) (20 mM, 3.72 g), and pyridine (30 mM, 2.4 mL) in dry benzene (15 mL) at 0 $^{\circ}$C, acetyl chloride (30 mM, 2.13 mL) was added drop wise. After stirring for 3 h at room temperature the reaction mixture was diluted with ether and washed successively with ice cold 2N HCl, water and aqueous $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude material was column chromatographed (silica gel, 5% ethyl acetate in hexane) to afford the required pure acetate **5** as a colourless liquid. Yield: 3.92 g (86%); bp: 100-101 $^{\circ}$C/4 mm; IR (neat) ν_{max}: 1745, 1633 cm^{-1}; ^{1}H NMR : δ 0.88 (dist. t 3H), 1.18-1.82 (m, 8H), 2.08 (s, 3H); 3.78 (s, 3H), 5.63 (t, 1H, J=7 Hz) 5.76 (s, 1H), 6.27 (s, 1H); ^{13}C NMR: δ 13.78, 20.79, 22.32, 24.83, 31.26, 34.11, 51.67, 71.62, 124.64, 140.26, 165.53, 169.61.

Methyl [2E]-2-butyloct-2-enoate (7): A solution of the acetate **5** (10 mM, 2.28 g) in 10 mL of dry THF was added to the freshly prepared propylmagnesium bromide (15 mM) in THF (10 mL) at 0°C. After addition was complete the reaction mixture was refluxed for 6 h. The reaction mixture was cooled to 0°C and saturated aqueous NH_4Cl solution was carefully added and extracted with ether (3 x 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue obtained was purified by column chromatography (silica gel, hexane) to provide methyl [2E]-2-butyloct-2-enoate. Yield: 1.29 g (61%); bp: 105-106°C/1 mm; IR (neat) ν_{max}: 1716, 1645 cm^{-1}; ^1H NMR: δ 0.90 (m, 6H), 1.17-1.51 (m, 10H), 2.06-2.36 (m, 4H), 3.72 (s, 3H), 6.73 (t, 1H, J=8 Hz); ^{13}C NMR: δ 13.92, 22.50, 22.67, 26.53, 28.50, 28.56, 31.59, 51.48, 132.38, 142.75, 168.57; Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39; Found: C, 73.54; H, 11.42.

[2E]-2-Butyloct-2-en-1-ol (9): To a solution of **7** (5 mM, 1.06 g) in dry ether, was added DIBAL-H solution in hexanes (2.2 M, 5.4 mL, 12 mM) at -78°C. After stirring 3h at -78°C, aqueous sodium tartarate and ether were successively added. The reaction mixture was allowed to warm to room temperature. The organic layer was washed successively with dil HCl and water and dried over anhydrous Na_2SO_4. Solvent was removed and the crude compound was column chromatographed (silica gel, 5% ethyl acetate in hexane) to afford the alcohol **9** in pure form. Yield: 0.65 g (71%) ; IR (neat) ν_{max}: 3344 cm^{-1} ; ^1H NMR: δ 0.89 (m, 6H), 1.16-1.49 (m, 11H), 1.91-2.11 (m, 4H), 4.03 (d, 2H, J= 0.8 Hz), 5.40 (t, 1H, J=7 Hz); ^{13}C NMR: δ 14.06, 22.64, 22.93, 27.48, 27.83, 29.54, 30.92, 31.67, 67.28, 127.09, 139.16.

[2E]-2-Butyloct-2-enal (1): To a stirred suspension of pyridinium chlorochromate (PCC) (4.5 mM, 0.97 g) and sodium acetate (1.8 mM, 0.14 g) in dry dichloromethane (5 mL) was added, the alcohol **9** (3 mM, 0.552 g) in dichloromethane at room temperature. After 3h, dry ether (10 mL) was added and the supernatant liquid was decanted from the black gum. The insoluble residue was washed thoroughly thrice with 5 mL portions of dry ether. The combined organic solution was passed through a short column containing silica gel. Removal of the solvent gave a colorless liquid which on column chromatography (silica gel 1% ethyl acetate in hexane) afforded the aldehyde **1** in pure form. Yield: 0.354 g (65%); IR (neat) ν_{max}: 1689, 1639 cm^{-1}; ^1H NMR: δ 0.89 (m, 6H), 1.12-1.72 (m, 10H), 2.16-2.50 (m, 4H), 6.43 (t, 1H, J=7.4 Hz), 9.36 (s, 1H); ^{13}C NMR: δ 13.87, 22.44, 22.74, 23.77, 28.38, 28.86, 30.95, 31.55, 143.72, 155.09, 195.13. This aldehyde was converted into the corresponding 2,4-dinitrophenylhydrazone (by treatment with a solution of 2,4-dinitrophenylhydrazine in ethanol containing sulphuric acid), mp: 131-132°C {lit: 129-130°C}[11].

Methyl 3-hydroxy-2-methyleneheptadecanoate (4): This was obtained as a white solid by the reaction of pentadecanal with methyl acrylate in the presence of DABCO (30 mole %) following similar procedure described for the molecule **3**. Reaction time: 9 days. Yield: 72%; mp: 63-64°C; IR (CHCl$_3$) ν_{max}: 3450, 1710, 1630 cm^{-1}; ^{1}H NMR: δ 0.87 (dist. t, 3H), 1.20-1.75 (m, 26H), 2.65 (b, 1H), 3.77 (s, 3H), 4.37(m, 1H), 5.79 (s, 1H), 6.21 (s, 1H); ^{13}C NMR: δ 14.05, 22.67, 25.81, 29.36, 29.46, 29.67, 31.93, 36.35, 51.72, 71.49, 124.60, 142.88, 167.02.

Methyl 3-acetoxy-2-methyleneheptadecanoate (6): This was obtained as a white solid by the action of acetyl chloride on methyl 3-hydroxy-2-methyleneheptadecanoate (**4**) in presence of pyridine following similar procedure described for the molecule **5**. Yield: 82% ; mp: 48-49°C IR (CHCl$_3$) ν_{max}: 1730, 1630 cm^{-1}; ^{1}H NMR: δ 0.86 (dist. t, 3H), 1.16-1.82 (m, 26H), 2.09 (s, 3H), 3.78 (s, 3H), 5.60 (m, 1H), 5.75 (s, 1H), 6.31 (s, 1H); ^{13}C NMR: δ 14.12, 21.08, 22.71, 25.34, 29.28, 29.38, 29.49, 29.69, 31.95, 34.32, 51.94, 71.89, 124.99, 140.32, 165.78, 169.96.

Methyl [2E]-2-tridecylheptadec-2-enoate (8): This was obtained as a white solid by the reaction of the acetate **6** with dodecylmagnesium bromide following similar procedure described for the compound **7**. Yield: 60%; mp: 54-56°C ; IR (CHCl$_3$) ν_{max}: 1710, 1640 cm^{-1}; ^{1}H NMR: δ 0.87 (m, 6H), 1.00-1.41 (m, 46H), 1.90-2.22 (m, 4H), 3.71 (s, 3H), 6.72 (t, 1H, J= 8 Hz); ^{13}C NMR: δ 14.19, 22.80, 26.88, 28.65, 28.99, 29.49, 29.59, 29.80, 32.05, 51.56, 132.45, 142.84, 168.57; Anal. Calcd. for $C_{31}H_{60}O_2$: C, 80.10; H, 13.01; Found: C, 80.52; H, 13.06.

[2E]-2-Tridecylheptadec-2-en-1-ol (10): This was obtained as a white solid by the reduction of methyl [2E]-2-tridecylheptadec-2-enoate (**8**) with DIBAL-H following similar procedure described for compound **9**. Yield 77%; mp: 56-58°C; IR (CHCl$_3$) ν_{max}: 3330 cm^{-1}; ^{1}H NMR: δ 0.87 (m, 6H), 1.16-1.62 (m, 47H), 1.90-2.19 (m, 4H), 4.03 (s, 2H), 5.40 (t, 1H, J= 8 Hz); ^{13}C NMR: δ 14.20, 22.80, 27.58, 28.13, 28.75, 29.50, 29.81, 32.05, 67.34, 127.15, 139.23.

[2E]-2-Tridecylheptadec-2-enal (2): This was obtained as a colorless viscous liquid by the oxidation of the alcohol **10** with PCC following similar procedure described for compound **1**. Yield: 64%; IR (neat) ν_{max}:1690, 1640 cm^{-1}; ^{1}H NMR: δ 0.88 (m, 6H); 1.18-1.65 (m, 46H), 2.18-2.40 (m, 4H), 6.44 (t, 1H, J= 7.8 Hz), 9.36 (s, 1H); ^{13}C NMR: δ 14.08, 22.69, 24.06, 28.77, 28.94, 29.37, 29.42, 29.68, 31.93, 143.99, 155.13, 195.21 ; MS, m/z (relative intensity): **434** (**M^+**, **44**), 265 (7), 237 (26), **121** (**15**), **119** (**13**), 97 (33), 83 (41), 71 (42) 57 (72), 55 (62), **43** (100).

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