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STEREOSELECTIVE TOTAL SYNTHESIS OF 10-(R)-HYDROXY-8E,12Z-OCTADECADIENOIC ACID : THE FUNGITOXIC COMPOUND IN TIMOTHY PLANT

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Abstract : A convenient synthesis of 10-(R)-hydroxy-8E,12Z-octadecadienoic acid, the fungitoxic compound in the timothy plant (Phleum pratense) against leaf spot disease is described utilising D-xylose as chiral source.

In the recent years considerable attention has been focussed on the identification and characterisation of several C-18 unsaturated hydroxy fatty acids, which are mainly responsible for the self defense mechanism in plants[1] against fungal diseases. The synthesis of these fatty acids[2,3] has gained importance, as it facilitates the study of the mechanism of action and aids further evaluation of their biological properties. In 1986 Koshino et al[4] isolated the fatty acid (**1**) from timothy plant (Phleum pratense) infected by the phytopathogenic fungus Epichloe typhina and this was found to have fungitoxic properties against another timothy leaf spot disease pathogen Cladosporium phlei. It was pointed out that the formation of the title fatty acid

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(1) indicated participation of an enzyme system in timothy plants which differed from that in rice plants.[4]

In continuation of our programme[3] on the synthesis of unsaturated hydroxy fatty acids, we report herein the first stereoselective total synthesis of the fatty acid[5] (1) (Fig. 1).

It was envisaged to introduce the lone hydroxyl group present in (**1**) from the chiral synthon (**2**) which was easily obtained from D-xylose. Further, the aliphatic chain of the acid (**1**) was realised from the elaboration of (**2**) by Wittig olefinations as desired.

Consequently, the treatment of 2-deoxy-4,5-isopropylidene-D-threopentose-diethyldithio acetal[6] (**2**) with benzoyl chloride in pyridine resulted in the benzoate (**3**) $[\alpha]_D$ + 43.18° (c 1.5 in $CHCl_3$) in 80% yield. The ester (**3**) on dethio-ketalisation by red mercury (II) oxide in the presence of borontrifluoride etherate in aq. THF (85%) afforded the corresponding aldehyde.

The resultant aldehyde, without further purification, was subjected to Wittig coupling reaction under cis selective reaction conditions developed by Schlosser.[7] Thus, the aldehyde was reacted with phosphorane obtained from n-hexyltriphenylphosphonium iodide and sodamide in THF-HMPA (7.5:1) at -78°C, after which the reaction mixture was warmed to room temperature. The ^1H NMR of the olefin (**4**) has clearly shown the coupling constant of olefinic protons to be 11.0 Hz, corresponding to its double bond. The trans isomer could not be detected by examination of this spectrum.

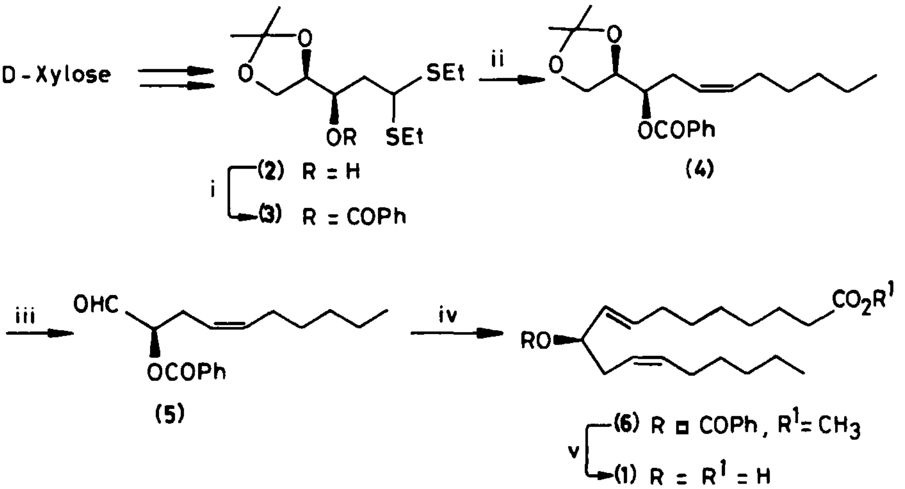

Figure-1

Reagents: (i) PhCOCl, C_5H_5N, rt, 6h; (ii) $^-IPh_3{}^+PCH_2(CH_2)_3CH_3$, $NaNH_2$, THF-HMPA (7.5:1), -78°C rt, 8h; (iii) TFA:H_2O (9:1), 0°C, 0.5h, then $Pb(OAc)_4$, $NaHCO_3$, CH_2Cl_2, 0°C, 0.5h; (iv) $^-IPh_3{}^+PCH_2$-$(CH_2)_6CH_3$, THF-HMPA (2:1), n-BuLi, -78°C, 2h, then MeOH, at -40°C, 4h; CH_2N_2, Ether; (v) K_2CO_3, MeOH-H_2O (4:1), rt, 6h.

The isopropylidene group in the olefin (4) was deprotected in a mixture of TFA-H_2O (9:1) at 0°C for 0.5 h. The diol obtained was cleaved to afford the aldehyde (5) by using lead tetraacetate in dichloromethane in 90% overall yield. Subsequently, the transformation (5) to (6) was effected as follows. The aldehyde (5) was first reacted with the phosphonium salt of 8-iodooctanoic acid[3e] in THF-HMPA (2:1) at -78°C in presence of n-butyllithium for 2 h. Then, a prolonged equilibration[8] of the intermediate betaine was effected by the addition of methanol at -40°C for 4 h. Subsequently, the crude acid obtained was treated with ethereal diazomethane which afforded the benzoate ester (**6**) $[\alpha]_D$ - 12.0° (c 1 in $CHCl_3$) in 45% overall yield. The high resolution ^1H NMR spectrum of ester (**6**) has revealed the coupling constants for cis and trans double bond protons as 11.0 and 14.8 Hz respectively. Further, the corresponding diastereomeric cis, cis isomer could not be detected from its ^1H NMR spectrum.

Finally, the hydrolysis of benzoate ester (**6**) was effected using K_2CO_3 in $MeOH$-H_2O (4:1) at room temperature for 2 h which afforded the title acid (**1**) whose physical and spectral data were in agreement with the reported values.

Experimental

IR spectra were recorded on Perkin Elmer 683 or 1310 spectrometers, PMR spectra were recorded on Varian FT-80A, JeOL PMX-90 or Bruker AM 300 MHz spectrometers using TMS internal standard. Mass spectra were recorded on a Finnigam Mat 1210 spectrometer.

2-Deoxy-4,5-O-isopropylidene-3-O-benzoyl-D-threo-pentose diethyl dithioacetal (3)

The hydroxy compound (**2**) (7.5 g, 26.78 mmol) was dissolved in pyridine (20 ml) and cooled to 0°C. The solution was treated with benzoyl chloride (4.53 g, 32.14 mmol) and stirred additionally for 6 h at room temperature. The reaction mixture was quenched with ice and extracted with ethyl acetate (2 x 100 ml). The combined ethyl acetate extracts were successively washed with cold 5% aqueous HCl, 5% aqueous $NaHCO_3$, brine and dried (Na_2SO_4). Concentration of the solution and the resultant concentrate on purification over a silica gel chromatography afforded the benzoate (**3**) (8.74 g, 85%).

$[\alpha]_D$ + 43.4° (c 1.5 in $CHCl_3$); IR (neat) 1720 cm^{-1} (C=O); ^1H NMR (80 MHz, $CDCl_3$) : δ 8.06 (2H, dd, J = 8.0 Hz, H-2 and H-6 of phenyl group), 7.50 (3H, m, H-3, H-4 and H-5 of phenyl group), 5.56 (1H, m, $-C\underline{H}-OCOPh$), 4.31 (1H, m, $-SC\underline{H}S-$), 3.90 (3H, m, $C-C\underline{H}_2-O-$ and $C-C\underline{H}-O$), 2.59 (4H, m, 2 x $-SC\underline{H}_2-$), 2.18 (2H, m, $-C\underline{H}_2-C$), 1.43 (6H, 2s, $CH(C\underline{H}_3)_2$), 1.37 (6H, t, 2 x $-CH_2-C\underline{H}_3$); m/z 384 (M^+). Analysis calculated for $C_{19}H_{28}O_4S_2$: C, 59.37; H, 7.5; Found : C, 59.27; H, 7.20%.

2(R), 3(R) 1,2-O-Isopropylidene-3-O-benzoyl-5Z-undecene (4)

To a mixture of mercury (II) oxide (5.6 g, 25.85 mmol) and boron trifluoride etherate (3.67 g, 25.85 mmol) in 85% aqueous THF (25 ml), the dithioacetal **3** (5.0 g, 13.02 mmol) was added under nitrogen atmosphere and stirred for 20 min. Ether (125 ml) was added and the reaction was neutralised with anhydrous sodium carbonate (approx. 5 g). The solids were filtered over celite and washed with ether (2 x 50 ml). The combined filtrate was concentrated to dryness to give a residue which was dissolved in toluene. The insoluble mercury salts were further removed by filtration, concentration of the filtrate afforded the aldehyde as a syrup in 90% (3.25 g) yield, which was used immediately in Wittig coupling without further purification.

While n-Hexyl triphenylphosphonium iodide (10.91 g, 23.38 mmol) and sodamide (0.91 g, 23.38 mmol) were suspended in THF (39 ml). HMPA (5.2 ml) was added and the suspension was stirred for 90 min at room temperature. The deep orange solution of the ylide was cooled (-78°C) and the above aldehyde (3.25 g, 11.69 mmol) in THF (5 ml) was added dropwise. The reaction mixture was allowed to come to room temperature and was stirred for 8 h. It was quenched with ice cold water (50 ml) and extracted with ethyl acetate (2 x 150 ml). The ethyl acetate layer was successively washed with water, brine, dried (Na_2SO_4). Concentration of the solution and purification of the crude product by silica gel chromatography afforded the pure product (**4**) (3.15 g, 70%). $[\alpha]_D$ + 14.5° (c 2.25 in CCl_4) (lit.[6c] $[\alpha]_D$ + 15.0° (c 2.25 in CCl_4)); IR (neat) 1710 (C=O), 690 (cis-olefin) cm^{-1}; ^1H NMR (90 MHz; $CDCl_3$) : δ 8.05 (2H, dd, H-2 and H-6 of phenyl group), 7.50 (3H, m, H-3, H-4 and H-5 of phenyl group), 5.45 (m, 2H, J = 11.0 Hz, -C$\underline{H}$-CH$_2$), 5.15 (1H, t, J = 5.5 Hz, C-C$\underline{H}$-OCOPh), 3.60-4.35 (3H, m, -O-C$\underline{H}_2$-C$\underline{H}$-O-), 2.45 (2H, m, -CH-C$\underline{H}_2$-CH=), 1.6-1.85 (2H, m, =CH-C$\underline{H}_2$-CH$_2$), 1.05-1.45 (12H, m, -CH(C$\underline{H}_3$)$_2$ and 3 x C$\underline{H}_2$-), 0.89 (3H, dist. t, -CH$_2$-C$\underline{H}_3$). Analysis calculated for $C_{21}H_{30}O_4$: C, 72.83; H, 8.67; Found : C, 72.75; H, 8.55%.

2(R)-2-O-Benzoyl-4Z-decenal (5)

The acetonide (**4**) (2.38 g, 6.87 mmol) was treated with a mixture trifluoroacetic acid and water (10 ml, 9:1) and stirred at 0°C for 0.5 h. Removal of volatile compounds under reduced pressure afforded the corresponding diol (2.0 g) in 95% crude yield. The crude product was carried forward as such without further purification.

The above diol was treated with lead tetracetate (3.18 g, 7.18 mmol) and sodium bicarbonate (2.19 g, 26.14 mmol) in dichloromethane (20 ml) at 0°C for 0.5 h. Dichloromethane (10 ml) and water (10 ml) were further added and stirred for 15 min. The solids were filtered over a celite bed and the filtrate was washed with water (2 x 10 ml), brine (2 x 10 ml) and dried (Na_2SO_4). Concentration of the filtrate and the purification of the resultant concentrate over a silica gel column afforded the aldehyde (5) (1.69, 90%). $[\alpha]_D$ + 30.31° (c 1.9 in CCl_4) (lit.[6c] $[\alpha]_D$ + 32.0° (c 1.5 in CCl_4); IR 1720 (C=O), 690 (cis-olefin) cm^{-1}; ^1H NMR (90-MHz; $CDCl_3$) : δ 9.56 (1H, s, -C$\underline{H}$O), 8.00 (2H, dd, H-2 and H-6 of phenyl group), 7.43 (3H, m, H-3, H-4 and H-5 of phenyl group), 5.43 (2H, m, J = 10.8 Hz, -C$\underline{H}$=C$\underline{H}$-), 5.15 (1H, t, J = 6.0 Hz, C-C$\underline{H}$-OCOPh), 2.50-2.75 (2H, m, =CH-C$\underline{H_2}$-CH-), 1.81-2.18 (2H, m, -CH_2-C$\underline{H_2}$-CH=), 1.18-1.31 (6H, m, 3 x -C$\underline{H_2}$-), 0.81 (3H, dist.t, -C$\underline{H_3}$). Analysis calculated for $C_{17}H_{22}O_3$: C, 74.45; H, 8.02; Found : C, 74.25; H, 7.95%.

10(R)-Methyl-10-O-benzoyl-8E,12Z-octadecadienoate (6)

To the well stirred phosphonium salt (0.582 g, 1.09 mmol) in THF-HMPA (5 ml, 2:1) was slowly added a solution of n-butyllithium (0.105 g, 1.64 mmol, 0.9 ml, 1.8N n-BuLi in pet.ether) under argon atmosphere at -78°C. After the mixture was stirred for 0.5 h the aldehyde 5 (0.20 g, 0.72 mmol) in THF (5 ml) was added. After 2 h at -78°C the mixture was cooled to -40°C and methanol (2 ml) was slowly added. The reaction mixture was again stirred at -40°C for 4 h. The reaction was quenched with ice and carefully acidified with dil. HCl (5% V/V) and extracted with ether (2 x 50 ml). The ethereal layer was washed with water (2 x 10 ml), brine (2 x 10 ml) and dried (Na_2SO_4). Concentration of the ethereal layer afforded crude acid. The crude acid was treated with ethereal diazomethane followed by silica gel chromatography to afford the compound (6)

(0.135 g, 45%. $[\alpha]_D$ - 12.0° (c 1 in $CHCl_3$); IR ($CHCl_3$) 1720 cm^{-1} (C=0); ^1H NMR (300 MHz; $CDCl_3$) : δ 8.06 (2H, dd, H-2 and H-6 of phenyl ring), 7.48 (3H, m, H-3, H-4 and H-5 of phenyl ring), 5.78 (1H, q, J = 14.6 Hz, -CH=C$\underline{H}$-CH_2-, trans), 5.5 (1H, m, O-CH-C$\underline{H}$=CH-, trans), 5.58 (1H, m, cis olefinic), 5.42 (1H, m, cis olefinic), 4.32 (1H, t, J = 7.08 Hz, CH_2-C$\underline{H}$-O), 3.68 (3H, s, -OC$\underline{H_3}$), 2.29 (2H, t, J = 6.66 Hz, -C$\underline{H_2}$-$COOCH_3$), 2.03-2.10 (2H, m, -C$\underline{H_2}$-CH=CH-), 1.54-1.68 (4H, m, 2x-C$\underline{H_2}$-CH=CH-), 1.26-1.42 (14H, m, 7 x -C$\underline{H_2}$-), 0.89 (3H, dist.t, -CH_2-C$\underline{H_3}$); m/z 415 (M^+). Analysis calculated for $C_{26}H_{38}O_4$: C, 75.36; H, 9.2; Found : C, 75.30; H, 9.2%.

10(R)-Hydroxy-8E,12Z-octadecadienoic acid (1)

The benzoate ester (**6**) (0.10 g, 0.24 mmol) in aqueous methanol (5 ml, 1:4) was treated with potassium carbonate (0.66 g, 4.8 mmol) for 2 h at room temperature. Ethyl acetate (10 ml) was added and the reaction mixture was carefully neutralised with cold dil. HCl (5% V/V) to pH=2. The organic layer was washed with water, dried (Na_2SO_4) and concentrated. Purification of the crude product on silica gel column afforded the title acid (**1**) (0.053 g, 75%); $[\alpha]_D$ - 2.35° (c 0.25, ethanol) (lit.[4] $[\alpha]_D$ - 2.41° (c 0.25 in ethanol); IR ($CHCl_3$) 3370 (-OH) 1700 cm^{-1} (C=O); ^1H NMR (80 MHz; $CDCl_3$) : δ 5.55-5.65 (2H, m, trans olefinic), 5.36-5.48 (2H, m, cis-olefinic), 4.12 (1H, m, -C$\underline{H}$OH), 2.05-2.45 (8H, m, 3 x -C$\underline{H_2}$-CH=CH- and -C$\underline{H_2}$-CO_2H), 1.23-1.73 (14H, m, 7 x -C$\underline{H_2}$-), 0.89 (3H, dist.t, 3H, -C$\underline{H_3}$); m/z 278 (M^+ -18).

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