An efficient synthesis of \( \text{trans-}\gamma\text{-oxo-}\alpha,\beta\text{-unsaturated carboxylic acids, the intermediates for patulolide A and pyrenophorin} \)

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An efficient synthesis of intermediates for macroclide antifungals patulolide A 14 and pyrenophorin 16 are described with the key steps involving (i) coupling of the alkyl lithium with \( \alpha,\beta\text{-unsaturated aldehyde} \) 8, (ii) the oxidation of the \( \text{cis-trans} \) mixture of \( \gamma\text{-oxo-}\alpha,\beta\text{-unsaturated carboxylic acid} \) 12.

Patulolide A 14 is a 12-membered macroclide isolated\(^1\) from \textit{Penicillium urticae} S11R59. Pyrenophorin 16 is isolated\(^2\) from \textit{Pyrenophora avenae} and \textit{Stemphylium radicum}. Both these macrolides show high degree of antifungal activity and possess characteristic structural feature i.e., \( \gamma\text{-oxo-}\alpha,\beta\text{-unsaturated carboxylic acid ester} \). The \( \gamma\text{-oxo-}\alpha,\beta\text{-unsaturated ester moiety} \) is crucial for the biological activity\(^3\), and is also found as a structural unit in many of the important natural products like A26771B, Vermiculine, etc. There are several chiral and achiral synthetic methods reported for these molecules\(^4\). This paper reports a simple and convenient method for the synthesis of intermediates for patulolide A 14 and pyrenophorin 16.

The synthetic scheme for the preparation of patulolide A 14 involves the monomethylhydroxypyranation of diol 1a (n=5) using stannous chloride dihydrate catalyst\(^5\) in chloroform to yield the alcohol 2a which on oxidation with chromium trioxide and pyridine\(^6\) in chloroform afforded the aldehyde 3a.

The aldehyde 3a was reacted with methyl magnesium iodide\(^7\) in dry ether to provide the secondary alcohol 4a. The secondary alcohol 4a was protected as benzylic ether\(^8\) 5a using sodium hydride and benzyl bromide in the presence of catalytic amount of tetrabutyl ammonium iodide in N,N-di-methylformamide solvent. Deprotection of tetrahydroxynalyl ether in 5a with catalytic amount of stannous chloride\(^7\) in methanol gave the primary alcohol 6a which was converted to the stable iodide\(^10\) 7a by triphenyl phosphine, iodine and imidazole in ether (Scheme I).

Treatment of the iodide 7a with \textit{tert}-butyllithium\(^11\) at \(-78^\circ\text{C}\) in pentane-ether mixture (1:1) yielded the alkyllithium. The alkyllithium in turn was treated with tetrahydroxynalyldehyde\(^12\) 8 resulting in a \( \text{cis-trans} \) mixture of the allyl alcohol derivative 9a. Compound 9a on oxidation with chromium trioxide and pyridine furnished the corresponding \( \alpha,\beta\text{-unsaturated ketone} \) which however, polymerized under acidic conditions. This difficulty was overcome by treating the allyl alcohol derivative 9a with SnCl\(_2\) (ref. 9) in methanol to yield the stable diol 10a. The diol underwent smooth oxidation with iodoxybenzoic acid\(^13\) (IBX) in dimethyl sulfoxide at room temperature to give \( \gamma\text{-oxo-}\alpha,\beta\text{-unsaturated aldehyde} \) 11a as \( \text{cis-trans} \) isomeric mixture. Further oxidation of the aldehyde 11a with sodium chlorite\(^14\) in \( t\)-butanol and water provided the thermodynamically more stable and desired \( \alpha,\beta\text{-unsaturated} \) carboxylic acid 12a selectively in quantitative yield constituting an important step of the synthesis. The key synthon 12a was characterised by IR (960 cm\(^{-1}\)) and \( ^1\text{H} \) NMR data. The olefinic hydrogens were observed as doublets (\( J=16\) Hz) at 6 6.62-6.70 and 7.08-7.16 indicating the \( \text{trans} \)-configuration. Cleavage of the benzyl ether by BF\(_3\),OEt\(_2\) and Me\(_2\)S\(^15\), followed by intramolecular esterification by Yamaguchi lactonization\(^16\) to patulolide A 14 is already known in the literature.

Following the same sequence of reactions key synthon 7-benzyloxy-4-oxide 12b, for pyrenophorin 16 was achieved utilising diol 1b (n=1). Further chemical transformations of 12b by ketalization, cleavage of the benzyl ether with BF\(_3\),OEt\(_2\) and Me\(_2\)S followed by cycldimerisation by
Mitsunobu procedure\textsuperscript{17} to pyrenophorin 16 is known in the literature.

Thus the synthesis of 12a and 12b, the important precursors for patulolide A and pyrenophorin constitutes a formal total synthesis of these macrolide natural products.

**Experimental Section**

**General.** All the products were characterized by \textsuperscript{1}H NMR, IR and mass spectroscopy. \textsuperscript{1}H NMR spectra were recorded on a FT NMR, Varian 200 MHz spectrometer; Infrared spectra on a FT IR 740 Nicolet spectrophotometer; and mass spectra on either VG Micromass 7070 H or VG Autospec Mass spectrometers. The starting diols were purchased from Lancaster Chemical Company (UK). The solvents and other chemicals used for the reactions were purchased from local chemical companies and purified and/or dried as per the standard literature methods.\textsuperscript{18}
7-(Tetrahydro-2H-pyran-2-yl)oxy heptanol 2a.

1.7-Hepanediol (25g, 190 mmol) and 3,4-dihydro-2H-pyran (17.24 mL, 190 mmol) were stirred in chloroform (420 mL) in the presence of stannous chloride dihydrate (0.43 g, 1.9 mmol). After the completion of the reaction (24 hr) the chloroform layer was decanted and concentrated under reduced pressure. The residual liquid was column chromatographed over silica gel with EtOAc-pet.ether (2:8) to give the pure alcohol as a yellow liquid, yield 7g (93% yield). IR (neat): 3370, 2900, 1110, 1065 and 1025 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta 1.15\) (d, 3H, \(J=6\)Hz), 1.21-1.92 (m, 17H), 3.25-3.53 (m, 2H), 3.54-3.9 (m, 3H) 4.52 (b.s, 1H); Mass: \(m/z\) 230(M\(^+\)).

7-Benzylxoxy-1-(tetrahydro-2H-pyran-2-yl)oxy octane 5a. A solution of 4a (6.5g, 28.26 mmol) in N,N-dimethylformamide (10 mL) was added slowly to a 60% suspension of sodium hydride in mineral oil (1.35g, 33.4 mmol) suspended in DMF (5 mL) and catalytic tetra n-butylammonium chloride (0.5g, 1 mole% in 2mL DMF under nitrogen atmosphere at 0°C. After half an hour of stirring benzyl bromide (3.7 mL, 31.08 mmol) was injected slowly. After the completion of the reaction (TLC, 4 hr), the reaction mixture was cooled to 0°C and quenched by adding ice-cold water (10 mL) slowly. The product was isolated by extraction with solvent ethyl ether (50 mL). The ether layer was washed with water (3×25 mL) and dried over anhydrous sodium sulphate. The crude benzyl ether obtained on concentration of ether layer was purified by column chromatography with EtOAc-pet.ether (5:95) to give the pure compound 5a as a light yellow liquid, yield 7g (93% yield). IR (neat): 2910, 1720, 1175, 1065 and 1025 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta 1.17\) (d, 3H, \(J=6\)Hz), 1.2-1.94 (m, 16H), 3.26-3.55 (m, 3H), 3.62-3.84 (m, 2H) 4.38-4.6 (m, 3H), 7.3 (b.s, 5H); Mass: \(m/z\) 321(M\(^+\)).

7-Benzylxoyoctanol 6a. Stannous chloride (0.83g, 4.38 mmol) was added to a stirred solution of benzyl ether 5a (7g, 21.9 mmol) in methanol (1: mL) at room temperature. After completion of the reaction as monitored by TLC, methanol was removed under reduced pressure and the product was extracted with solvent ether (25 mL). The ether layer was washed with water (2×20 mL) and dried over anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure resulted in the crude alcohol which was purified by column chromatography with EtOAc-pet.ether (2:8) to yield the deprotected alcohol 6a as a colourless liquid, yield 4.6g (89% yield). IR (neat): 3350, 2900, 1175 and 1050 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta 1.2\) (d, 3H, \(J=6\)Hz), 1.22-1.75 (m, 11H), 3.4-3.54 (m, 1H), 3.61 (t, 2H, \(J=6\)Hz), 4.39-4.62 (m, 2H), 7.31 (b.s, 5H); Mass: \(m/z\) 236(M\(^+\)).
7-Benzylxoy-1-iodooctane 7a. To a mixture of alcohol 6a (1 g, 4.24 mmoles), triphenylphosphine (2.22 g, 8.48 mmoles) and imidazole (1.16 g, 16.96 mmoles) in dry ether at 0°C, iodine (3.23 g, 12.72 mmoles) was added slowly. At the end of the reaction as evidenced by TLC, the reaction mixture was diluted with ether (20 mL) and the ethereal layer was separated. It was washed with saturated sodium thiosulfate solution (2 x 50 mL) followed by water (2 x 25 mL). The ethereal layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure as evidenced by TLC, the reaction mixture was washed with water (2 x 5 mL) and the ethereal layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure and the mixture extracted with EtOAc-pet.ether (3:97) yielded a nhydrous sodium sulfate and concentrated under reduced pressure. Purification by column chromatography with EtOAc-pet.ether (3:97) yielded 1.3 g (89%) of the iodide 7a as a colourless liquid. IR (neat): 2925, 1150, 1080 and 1030 cm⁻¹; ¹H NMR (CDCl₃): δ 1.16 (d, 3H, J=6 Hz), 1.21-1.68 (m, 8H), 1.72-1.91 (m, 2H), 3.15 (t, 2H, J=7.5 Hz), 3.37-3.54 (m, 1H), 4.35-4.60 (m, 2H), 7.26 (b.s, 5H); MS (LSIMS): m/z 347 [M+H]⁺, 345 [M-H]⁻, 239 [(M+H)-PhCH₂OH]⁺, 181 [C₃H₇]⁻, 155 [CH₂CH₆H]⁻, 135 [PhCH₂CHCH₃]⁻, 107 [PhCH₂OH]⁻ and 105 [PhC=O]⁻.

11-Benzylxoy-(tetrahydro-2H-pyran-2-yl)oxy-2-dodecene-4-ol 9a. To a stirred solution of 7a (1.0 g, 2.89 mmoles) in ether-pentane (1:1, 15 mL each) at −78°C under nitrogen atmosphere, t-butyllithium (2.75 mL, 6.36 mmoles, 15% solution in pentane) was added slowly. At the end of the reaction (10 min), 20 mL ether was added and the mixture was extracted. The ethereal layer was washed with water (2 x 10 mL) followed by water (2 x 10 mL) and the ethereal layer was washed with water (2 x 5 mL) and concentrated under reduced pressure to yield the crude product. Purification by column chromatography with EtOAc-pet.ether (4:6) afforded 0.35 g (88%) of diol 10a as colourless syrupy liquid. IR (neat): 3320, 3250, 1450, 1120, 740 cm⁻¹; ¹H NMR (CDCl₃): 8 1.19 (d, 3H, J=6 Hz), 1.21-1.73 (m, 12H), 1.95-2.35 (br, 2H), 3.4-3.55 (m, 1H), 4.4-4.61 (m, 2H), 5.61-5.9 (m, 2H), 7.3 (b.s, 5H); MS: m/z 306 (M⁺).

11-Benzylxoy-2-dodecene-1,4-diol 10a. The tetrahydropropyl ether 9a (0.5 g, 1.3 mmoles) dissolved in methanol (4 mL) was treated with anhydrous stannous chloride (0.05 g, 0.26 mmoles) at room temperature. After 6 hr, methanol was removed under reduced pressure and the mixture extracted with ethyl acetate (8 mL). The ethyl acetate layer was washed with water (2 x 5 mL) and concentrated under reduced pressure to yield the crude diol, which on column chromatographic separation with EtOAc-pet.ether (4:6) afforded 0.35 g (88%) of diol 10a as colourless syrupy liquid. IR (neat): 3320, 3250, 1450, 1120, 740 cm⁻¹; ¹H NMR (CDCl₃): δ 1.18 (d, 3H, J=6 Hz), 1.22-1.73 (m, 12H), 1.95-2.35 (br, 2H), 3.41-3.56 (m, 1H), 4.01-4.2 (m, 3H), 4.4-4.61 (m, 2H), 5.61-5.9 (m, 2H), 7.3 (b.s, 5H); MS: m/z 306 (M⁺).

11-Benzylxoy-4-oxo-2-dodecenal 11a. To the diol 10a (0.3 g, 0.9803 mmoles) dissolved in DMSO (5 mL) iodoxybenzoic acid (0.66 g, 2.352 mmoles) was added at room temperature with stirring. After 6 hr, 10 mL ether was added and the stirring continued for 10 min and filtered. The residue was washed with ether (2 x 5 mL). The filtrate containing the product was washed with water (2 x 5 mL) and saturated sodium bicarbonate solution (2 x 5 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield the crude product. Purification by column chromatography with EtOAc-pet.ether (1:9) gave 0.23 g (78%) of the aldehyde 11a as a light yellow liquid. IR: 3020, 2940, 1700, 1630, 1550, 1480, 1110, 1060, 970 and 750 cm⁻¹; ¹H NMR (CDCl₃): δ 1.15 (d, 3H, J=6 Hz), 1.21-1.73 (m, 10H), 2.69 (t, J=2H, J=7.5 Hz), 3.4-3.55 (m, 1H), 4.4-4.61 (m, 2H), 6.7-6.91 (m, 2H), 7.3 (b.s, 5H) and 9.79 (d, 1H, J=7 Hz); MS: m/z 301 [M-H]⁻.

11-Benzylxoy-4-oxo-2-(E)-dodecenoic acid 12a. To the aldehyde 11a (0.2 g, 0.6622 mmoles) and catalytic amount of sulfamic acid (0.01 g, 15 mole%) in t-butanol (3 mL), an aqueous solution of sodium chloride (0.18 g, 1.99 mmoles) was added at 0°C while stirring. The reaction mixture was slowly allowed to attain room temperature. At the end of the reaction (45 min) the volatile matter was removed under reduced pressure leaving the sodium salt of the acid, which was neutralized with sodium bisulfate solution (3 mL) and extracted with chloroform (5 mL). The organic layer was washed with water (5 mL), dried over anhydrous sodium sulfate and
concentrated under reduced pressure to afford the crude acid. Further purification was carried out by its conversion to sodium salt by treating with saturated sodium bicarbonate solution (3 × 5 mL) followed by neutralization with saturated sodium bisulphate solution (7 mL) and extraction with chloroform (5 mL). The chloroform layer was dried over anhydrous sodium sulfate and evaporation of the solvent resulted in 0.21 g (99%) of acid 12a as a low melting solid. IR (neat): 3400-2950, 1700, 1450, 1100, 970 cm⁻¹; ¹H NMR (CDCl₃): δ 1.17-1.21 (d, 3H, J = 6 Hz), 1.4-1.98 (m, 8H: 1H, 1.7-1.92 (m, 2H), 2.2-2.70 (br, 1H), 3.4-3.86 (m, 3H), 4.38-4.69 (m, 4H, 1.1), 7.31 (b.s, 5H); MS: m/z 284 [M⁺]⁺.

3-(Tetrahydro-2H-pyran-2-yl)oxy propanol 2b
Colourless liquid, yield 76%; IR (neat): 3400, 2950, 1140, 1120, 1060, 1040 cm⁻¹; ¹H NMR (CDCl₃): δ 1.42-1.93 (m, 8H), 2.1-2.45 (br, 1H), 3.42-3.65 (m, 2H), 3.7-4.0 (m, 4H), 4.6 (b.s, 1H); MS: m/z 16f [M⁺].

3-(Tetrahydro-2H-pyran-2-yl)oxy propanol 3b
Light yellow liquid, yield 61%; IR (neat): 2930, 1730, 1125, 1060, 1025 cm⁻¹; ¹H NMR (CDCl₃): δ 1.35-1.91 (m, 6H), 2.47-2.71 (m, 2H), 3.35-4.2 (m, 4H), 4.5 (b.s, 1H), 9.75 (b.s, 1H); MS: m/z 157 [M⁺].

3-(Tetrahydro-2H-pyran-2-yl)oxy-2-butenol 8
Colourless liquid, yield 89%; IR (neat): 2925, 1750, 1650, 1510, 1460, 1170, 1130, 1100, 1060, 1040 cm⁻¹; ¹H NMR (CDCl₃): δ 1.12 (d, 3H, J = 6 Hz), 2.65 (t, 2H, J = 7 Hz), 3.0-3.55 (m, 1H), 3.75-4.35 (br, 1H), 4.4-4.65 (m, 2H), 6.62-6.70 (d, 1H, J = 16 Hz) and 7.08-7.16 (d, 1H, J = 16 Hz), 7.3 (b.s, 5H). MS (CI/MS): m/z 319 [M+H⁺], 301 [M+H⁺-CH₃], 212 [M+H-PHOCH₂]⁺, 167 [212 - COOH]⁺.

4-(Tetrahydro-2H-pyran-2-yl) oxy-2-butenal 8
Pyridine (14 mL, 174 mmole) was added slowly to a suspension of chromium trioxide (8.7 g, 87 mmole) in chloroform (60 mL) under stirring and maintaining the mass temperature around 0°C. After 20 minutes of stirring, a solution of 4-(tetrahydro-2H-pyran-2-yl)oxy-2-butenol 11 (5 g, 29 mmole) in chloroform (10 mL) was injected slowly and the reaction mixture stirred for 4 hr. After the completion of the reaction as evidenced by TLC (4 hr), the reaction mixture was diluted with ether (40 mL). The heterogeneous suspension was filtered through a Buchner funnel and the residue was thoroughly washed with ether (2×25 mL). The filtrate was concentrated under reduced pressure and the residual liquid was column chromatographed using EtOAc-pet.ether (1:9) to afford 37.5 g (75%) of the α,β-unsaturated aldehyde 8 as a light yellow oil. IR (neat): 3425, 2950, 2860, 1100, 1040 cm⁻¹; ¹H NMR (CDCl₃): δ 1.12-1.17 (d, 3H, J = 6 Hz), 1.4-1.93 (m, 8H: 1H, 1.7-1.92 (m, 2H), 2.2-2.70 (br, 1H), 3.4-3.86 (m, 3H), 4.38-4.69 (m, 4H, 1b), 7.31 (b.s, 5H); MS: m/z 264 [M⁺].

3-Benzoyloxy-(tetrahydro-2H-pyran-2-yl)oxy butan 5b
Light yellow liquid, yield 87%; IR (neat): 2925, 1125, 1075, 1060, 1025 cm⁻¹; ¹H NMR (CDCl₃): δ 1.21 (d, 3H, J = 6 Hz), 1.4-1.98 (m, 8H: 1H, 3.39-3.62 (m, 2H), 3.63-3.96 (m, 2H), 4.39-4.65 (m, 3H, 7.3, 3H, 5H). MS: m/z 264 [M⁺].

3-Benzoyloxybutanol 6b
Light yellow liquid, yield 85%; IR (neat): 3420, 2920, 2860, 1100, 1040 cm⁻¹; ¹H NMR (CDCl₃): δ 1.21 (d, 3H, J = 6 Hz), 1.4-1.98 (m, 8H: 1H, 3.39-3.62 (m, 2H), 3.63-3.96 (m, 2H), 4.39-4.65 (m, 3H, 7.3, 3H, 5H). MS: m/z 180 [M⁺].

3-Benzoyloxy-1-iodobutane 7b
Colourless liquid, yield 85; IR (neat): 2920, 2820, 1160, 1090 cm⁻¹; ¹H NMR (CDCl₃): δ 1.25 (d, 3H, J = 6 Hz), 1.8-2.15 (m, 2H), 3.2-3.4 (m, 2H), 3.6-3.74 (m, 1H), 4.4-4.67 (m, 2H), 7.3 (b.s, 5H). MS (Cl/MS): m/z 291 [M⁺+H⁺], 213 [M+H⁺-C₆H₅], 181 [C₆H₅], 149 [M⁺-CH₃]⁺, 135 [M⁺-C₂H₆]⁺, 91 [PhCH₂]⁺, 65 [1H-C₆H₅].

7-Benzoyloxy-1-(tetrahydro-2H-pyran-2-yl)oxy-2- octene-4-ol 9b
Light yellow liquid, yield 50%; IR (neat): 3400, 2930, 1440, 1120, 1075, 1030, 970, 720 cm⁻¹; ¹H NMR (CDCl₃): δ 1.25 (d, 3H, J = 6 Hz), 1.25 (m, 11H), 3.4-3.62 (m, 2H), 3.75-4.0 (m, 2H), 4.02-4.27 (m, 2H), 4.4-4.8 (m, 3H), 6.56-5.8 (m, 2H), 7.28 (b.s, 5H). MS (LSIMS): m/z 335 [M⁺], 317 [M⁺+H⁺-O₂], 233 [M⁺+H⁺-THP-OH]⁺, 213 [M⁺+H⁺-H₂O], 141 [M⁺+H⁺-CH=CHCH₂OPTH]⁺, 113 [M⁺+H⁺-CH₂]-, 107 [PhCH₂OH]⁺, 107 [PhCH₂O⁻].

7-Benzoyloxy-2-octene-1,4-diol 10b
Dens colourless liquid, yield 89%; IR (neat): 3350, 2920, 2970, 1450, 1190, 1175, 1130, 950, 720 cm⁻¹;
NMR (CDCl₃): δ 1.2 (d, 3H, J = 6 Hz), 1.6 (b.s, 2H), 2.9-3.73 (m, 3H, 2 protons D₂O exchangeable), 4.01 (b.s, 3H), 4.36-4.64 (m, 2H), 5.55-5.83 (m, 2H), 7.3 (b.s, 5H); MS: m/z 250 [M⁺].

7-Benzylxoy-4-oxo-2-octenal 11b. Light yellow liquid, yield 77.9%; IR (neat): 2920, 1695, 1455, 1110, 1090, 970, 730 cm⁻¹; ¹H NMR (CDCl₃): δ 1.2 (d, 3H, J = 6 Hz), 1.6-2.2 (m, 2H), 2.6-2.89 (m, 2H), 3.5-3.64 (m, 1H), 4.28-4.60 (m, 2H), 6.61-6.9 (m, 2H), 7.3 (b.s, 5H); MS: m/z 246 [M⁺].

7-Benzylxoy-4-oxo-2-octenoic acid 12b. Colourless low melting solid, yield 99%; IR (neat): 3550-2400, 1700, 1415, 1100, 1080, 980 cm⁻¹; ¹H NMR (CDCl₃): δ 1.2 (d, 3H, J = 6 Hz), 1.75-1.97 (m, 2H), 2.7 (d, 3H, J = 6 Hz), 3.48-3.63 (m, 1H), 4.31-4.65 (m, 2H), 6.55-6.63 (d, 1H, J = 16 Hz), 7.0-7.08 (d, 1H, J = 16 Hz), 7.3 (b.s, 5H). MS (ClMS): m/z 263 [M+H]⁺, 245 [M+H₂O]⁺, 155 [M+H-PhCH₂OH]⁺, 111 [155-CO₂]⁺, 107 [PhCH₂O]⁻, 105 [PhC=O]⁻, 99 [C₆H₅O₂]⁻, 91 [PhCH₂]⁻.

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References