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Note

Convenient synthesis of (*E*)-methyl *O*-alkylferulates: Formal synthesis of *O*-geranylconiferyl alcohol, a metabolite of *Fagara rhetza*

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A convenient two step stereoselective synthesis of (*E*)-methyl *O*-alkylferulate **5a-c** is described from vanillin **1**. Reaction of vanillin **1** with allyl-, prenyl- or geranyl- bromide **2a-c** has afforded alkyl ethers **3a-c** which on reaction with phosphorane **4**, under microwave irradiation, gives (*E*)-methyl *O*-alkylferulates **5a-c** in high yield. In an alternative approach vanillin **1** on reaction with phosphorane **4** provides (*E*)-methyl ferulate **6** which on reaction with the corresponding bromides **2a-c** gives (*E*)-methyl *O*-alkylferulates **5a-c**.

Keywords: Methyl ferulates, microwave, Wittig reaction

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A large number of methyl cinnamates have been isolated from natural sources[1]. Thus, methyl ferulate **6** has been isolated[2] from the stem of *Bauhinia manca* Standley, a climber found in the forests of Costa Rica and Panama. The stems of *Bauhinia manca* are reported to possess antirheumatic properties[2]. Methyl cinnamates have been used for the synthesis of *N*-β-phenylethyl-3-(3,4-dialkoxyphenyl) propenamide[3], α- and β-truxillines[4] and quinolizidine alkaloids[5], (-) lasubine I , II and (+) subcosine II. Methyl ferulate **6** has been used for the synthesis of glucosidoferulic acid[6]. Methyl *O*-geranylferulate **5c** has been used[7] for the synthesis of naturally occurring[8] *O*-geranyl-coniferyl alcohol **7**.

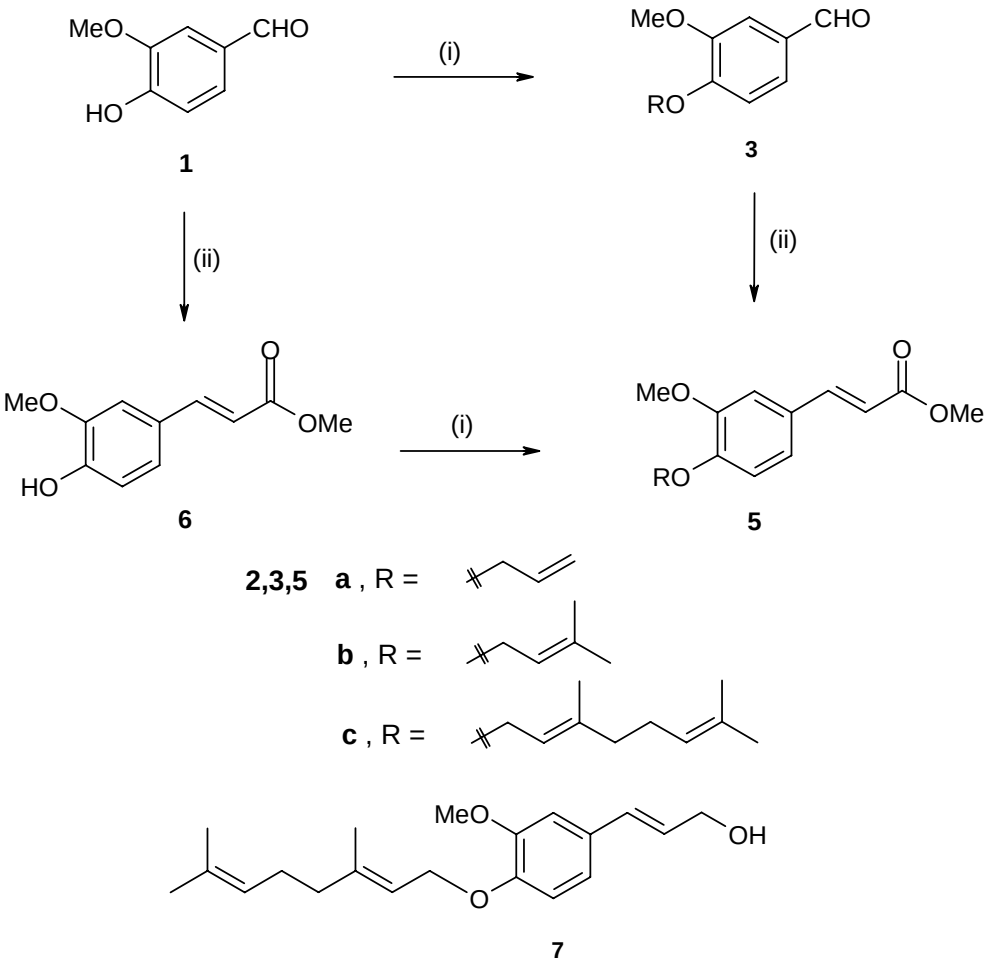
The classical method frequently used for the synthesis of methyl ferulate involves Knoevenagel condensation, to obtain ferulic acid followed by esterification[6,7]. We describe herein a convenient method for the synthesis of methyl *O*-alkylferulates **5a-c** starting from vanillin **1**. Thus, vanillin **1** on reaction with appropriate allyl-, prenyl- or geranyl-bromide **2a-c** in DMF solution in presence of K_2CO_3 at room temp provided the alkyl ethers **3a-c** in 62-75% yield. The ethers **3a-c** on reaction with phosphorane **4** (ref. 9) under microwave irradiation for 2-3 min gave stereoselectively the desired (*E*)-methyl *O*-alkylferulates **5a-c** in 70-72% yield. The stereochemistry of the esters **5a-c** was established on the basis of the coupling constants of the olefinic protons. The olefinic α– and β– protons in the esters **5a-c** appeared as doublets (*J* ~16 Hz) at ~ δ 6.20 and ~ 7.60, respectively. The coupling constant value thus indicated *E* geometry. In an alternative approach vanillin **1** was reacted with phosphorane **4** under microwave irradiation to obtain stereoselectively (*E*)-methyl ferulate **6** in 83% yield. The stereochemistry of **6** was also established on the basis of the coupling constants of the olefinic protons. The olefinic α– and β–protons in the ester **6** appeared as doublet (*J* 16 Hz) at ~ δ 6.29 and 7.62, respectively. (*E*)-Methyl ferulate **6** on reaction with allyl-, prenyl- and geranyl-bromide **2a-c** in DMF solution in presence of K_2CO_3, at room temp provided (*E*)-methyl *O*-alkylferulates **5a-c** in 73-93% yield. The geranyl ether **5c** on reduction with LAH in THF provided *O*-geranylconiferyl alcohol **7** in high yield[7].

A stereoselective two step method for the synthesis of (*E*)-methyl *O*-alkylferulates **5a-c** from vanillin **1** using Wittig reaction under microwave irradiation condition has been described. (*E*)-Methyl *O*-geranylferulate **5c** has been converted[7] into *O*-geranylconiferyl alcohol **7**, hence it completes its formal synthesis (**Scheme I**).

Experimental Section

All melting points are uncorrected. IR spectra were recorded on a Shimadzu FTIR-8400S spectrometer using KBr pellets. ^{1}H NMR spectra were recorded on a 300 MHz Varian mercury spectrometer, in $CDCl_3$ using TMS as an internal standard. The FAB mass spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer/data system using argon/xenon (6kV, 10 mA) as the FAB gas. Kenstar-OM 9918C, 2450 MHz (900 W) microwave oven was used for microwave irradiation. Silica gel 60-120 mesh supplied by SD Fine-chem Ltd. was activated before use.

General procedure for the preparation of aryl ethers 3a-c. Potassium carbonate (1.78 g,



Reagents: (i) R-Br (**2**), K_2CO_3, DMF, r.t.; (ii) SiO_2, Ph_3P=CHCOOMe (**4**), MW

Scheme I

13.02 mmoles) was added to a solution of vanillin **1** (0.33 g, 2.17 mmoles) in dry DMF (5 mL) under nitrogen atmosphere and the reaction mixture was stirred at room temp for 10 min. Appropriate bromide **2a-c** (4.34 mmoles) was added to it and the reaction mixture was stirred at room temp for 2 hr. Water (5 mL) was added to it and extracted with ethyl acetate (3×5 mL). The ethyl acetate layer was washed with water and dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure gave an oily product. It was chromatographed over silica gel using hexane : ethyl acetate (9:1) as an eluent to give ethers **3a-c**.

4–Propenyloxy-3-methoxybenzaldehyde 3a. Oily product (0.31 g); yield 76 %; IR (neat): 1678, 1585 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.96 (3H, s, OMe), 4.72 (2H, d, *J*=6.0 Hz, OC*H*$_2$-CH=), 5.34-5.52 (2H, m, CH=C*H*$_2$), 6.0-6.2 (1H, m, C*H*=CH$_2$), 7.01 (1H, d, *J*=7.8 Hz, C_5H), 7.43-7.48 (2H, m, C_2H and C_6H), 9.87 (1H, s, CHO); MS (m/z): 192 (M^+)**,** 165, 151, 136, 123, 105.

4–Prenyloxy-3-methoxybenzaldehyde 3b. Thick liquid (0.29 g, Lit.[10] semi-solid); yield 62 %; IR (neat): 1678, 1585 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.78 and 1.81 (6H, 2s, 3H each, 2×Me), 3.95 (3H, s, OMe), 4.70 (2H, d, *J*=6.6 Hz, -O-C*H*$_2$-CH=), 5.54 (1H, brt, *J*=6.6 Hz, C*H*=C), 6.99 (1H, d, *J*=7.8 Hz, C_5H), 7.42-7.48 (2H, m, C_2H and C_6H), 9.87 (1H, s, CHO).

4-Geranyloxy–3–methoxybenzaldehyde 3c. Oily product (0.45 g, Lit.[11]oily product); 73%; IR (neat): 1682, 1585 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.55, 1.65 and 1.74 (9H, 3s, 3H each 3×Me), 1.98-2.10 (4H, m, -CH_2-CH_2-), 3.92(3H, s, OMe), 4.70 (2H, d, *J*=6.0 Hz, -O-C*H*$_2$ CH=), 5.15 (1H, m, -C*H*=CMe_2), 5.50 (1H, t, *J*=6.0 Hz, O-CH_2-C*H*=), 6.96 (1H, d, *J*=6.5 Hz, C_6H), 7.40-7.45 (2H, m, C_2H and C_5H), 9.80 (1H, s, CHO).

General procedure for the synthesis of (*E*)-methyl *O*-alkylferulates 5a-c from aryl ethers 3a-c. Silica gel (3.0 g) was added to a solution of appropriate aryl ether **3a–c** (1mmole) and phosphorane **4** (0.43 g, 1.3 mmole) in dichloromethane (5 mL), and the reaction mixture was stirred at room temp for 2 min. The solvent was removed and the residual powder was dried. It was spread in a petri dish, irradiated in a microwave oven for 3 min and chromatographed over silica gel using hexane : ethyl acetate (9:1) as an eluent to afford (*E*)-methyl *O*-alkylferulates **5a-c**.

(*E*)-Methyl *O*-allylferulate 5a. White solid (0.17 g); m.p. 84-85ºC; yield 71 %; IR (KBr,): 1704, 1631, 1510, 1260, 1145 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$,): δ 3.80 and 3.90 (6H, 2s, 3H each, 2×OMe), 4.68 (2H, d, *J*=6.0 Hz, -OC*H*$_2$-CH=), 5.30-5.5 (2H, m, -CH=C*H*$_2$), 6.05-6.15 (1H, m, -C*H*=CH$_2$), 6.31 (1H, d, *J*=16 Hz, CH=C*H*CO), 6.85 (1H, d, *J*=8 Hz, C_5H), 7.05-7.10 (2H, m, C_2H and C_6H), 7.62 (1H, d, *J*=16 Hz, C*H*=CHCO); MS (m/z): 248 (M^+), 217, 207.

(*E*)-Methyl *O*-prenylferulate 5b. White solid (0.19 g); m.p. 55-56ºC; yield 70 %; IR (KBr): 1704, 1633, 1514, 1255, 1140 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.74 and 1.77 (6H, 2s, 3H each, 2×Me), 3.80 and 3.89 (6H, 2s, OMe), 4.61 (2H, d, *J*=6.7 Hz, -OC*H*$_2$-CH=), 5.50 (1H, brt, *J*=6.8 Hz, C*H*=C), 6.31 (1H, d, *J*=16 Hz, CH=C*H*CO), 6.85 (1H, d, *J*=7.5 Hz, C_5H), 7.03-7.10 (2H, m, C_2H and C_6H) 7.63 (1H, d, *J*=16 Hz, C*H*=CHCO); MS (m/z): 276 (M^+), 245, 208, 177.

(*E*)-Methyl *O*-geranylferulate 5c. White solid (0.24 g); m.p. 53-54ºC; yield 72 % (lit[7]. low melting solid); IR (KBr): 1697, 1596, 1515, 1267, 1246, 1140 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.60, 1.66 and 1.74 (9H, 3s, 3H each, 3×Me), 2.10 (4H, m, -CH$_2$-CH$_2$-), 3.80 and 3.90 (6H, 2s, 3H each 2×OMe), 4.66 (2H, d, *J*=6.5 Hz, -O-C*H*$_2$-), 5.10 (1H, m, C_6H, $(CH_3)_2$C=C*H*-), 5.50 (1H, m, -O-CH$_2$-C*H*=), 6.33 (1H, d, *J*=15.8 Hz, HC=C*H*CO), 6.86 (1H, d, *J*=8.2 Hz, C_5H), 7.10 (2H, m, C_2H and C_6H), 7.64 (1H, d, *J*=15.8 Hz, -*H*C=CH).

(*E*)-Methyl ferulate 6. Silica gel (6.0 g) was added to a solution of vanillin **1** (0.30 g, 2 mmoles) and phosphorane **3** (0.86 g, 2.6 mmoles) in dichloromethane (10 mL), and the reaction mixture was stirred at room temp for 2 min. The solvent was removed and the residual powder was dried. It was spread in a petri dish, irradiated in a microwave oven for 3 min and chromatographed over silica gel using hexane : ethyl acetate (9:1) as an eluent to afford (*E*)-methyl ferulate **6** (0.34 g, 83 %) as colourless oil (Lit.[7] colourless oil); IR (KBr): 3398, 1700, 1635, 1593, 1508 and 1269 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.80 and 3.92 (6H, 2s, 3H each, 2×OMe), 5.86 (1H, s, exchangeable with D_2O, OH), 6.30 (1H, d, *J*=15.8 Hz, -CH=C*H*CO), 6.92 (1H, d, *J*=8 Hz, C_5H), 7.02 (1H, d, *J*=1.75, C_2H), 7.07 (1H, dd, *J*=8 and 1.75 Hz, C_6H), 7.62 (1H, d, *J*=15.8 Hz, C*H*=CHCO).

General procedure for the preparation of (*E*)-methyl *O*-alkylferulates 5a-c from (*E*)-methyl ferulate 6. Potassium carbonate (0.98 g, 7.2 mmoles) was added to a solution of (*E*)-methyl ferulate **6** (0.25 g, 1.20 mmole) in dry DMF (5 mL) under nitrogen atmosphere and the reaction mixture was stirred at room temp for 10 min. Appropriate bromide **2a-c** (2.4 mmoles) was added to it and the reaction mixture was stirred at room temp for 2.5 –3.5 hr. Water (5 mL) was added to it and extracted with ethyl acetate (3×5 mL). The ethyl acetate layer was washed with water and dried over anhydrous sodium sulfate. Removal of solvent under reduced pressure gave crude product. It was chromatographed over silica gel using hexane:ethyl acetate (9:1) as an eluent to afford (*E*)-methyl *O*-alkylferulates **5a-c**. These compounds were identical (superimposable IR, ^1H NMR) with authentic samples prepared above from **3a-c**.

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