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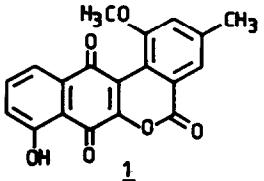
A New Convergent Synthesis Of WS-5995-B, An Anticoccidial Antibiotic From *Streptomyces Auranticolor*

Rama Devi A, Iyengar D S* and Pardhasaradhi M

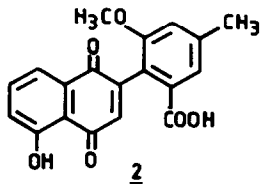
Organic Division II, Indian Institute of Chemical Technology, Hyderabad 500 007, India.

Abstract : A new synthesis of WS-5995-B, an anticoccidial antibiotic isolated from *Streptomyces auranticolor* is reported via the coupling reaction between 3-bromo-5,6,7,8-tetrahydrojuglone, and 3-methoxy-5-methyl anthranilic acid. A simple method for the preparation of the anthranilate 7 starting from p-toluidine by shorter sequence is reported.

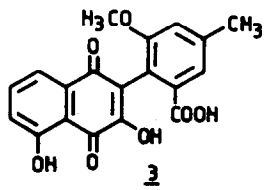
The anticoccidial antibiotics WS-5995- A (1), B (2) and C (3) were isolated[1] from the new strains of Streptomyces designated as *Streptomyces auranticolor.* Among these compounds WS-5995-A and B have shown excellent activity against Eimeria tenella infection. The structures of these antibiotics were elucidated by Tanaka and coworkers[2].



1
WS-5995-A



2
WS-5995-B



3
WS-5995-C

The synthetic methods reported earlier for the preparation of WS-5995-A and B involve a diazocoupling reaction, either on naphthaquinone[3] or benzoquinone[4]. The diazocoupling on naphthaquinone led to poor yields of target molecule, while on benzoquinone, though good yields of aryl benzoquinone were obtained, a regiospecific annulation is required to prepare aryl naphthaquinone. The other methods[5,6] involve tedious and multistep syntheses.

In view of the biological activity associated with these molecules and the inadequacy in the earlier syntheses, a new approach involving a shorter synthetic sequence has been investigated in the present communication. A modified benzoquinone is conceived for the coupling reaction since benzoquinones are expected to give high yields of the coupled products. Thus a suitably substituted tetrahydronaphthalene derivative **6** should behave like a benzoquinone to give high yields of the coupled product and finally suitable to be converted into the corresponding naphthaquinone in high yields. The envisaged strategy should be free from the problems faced by

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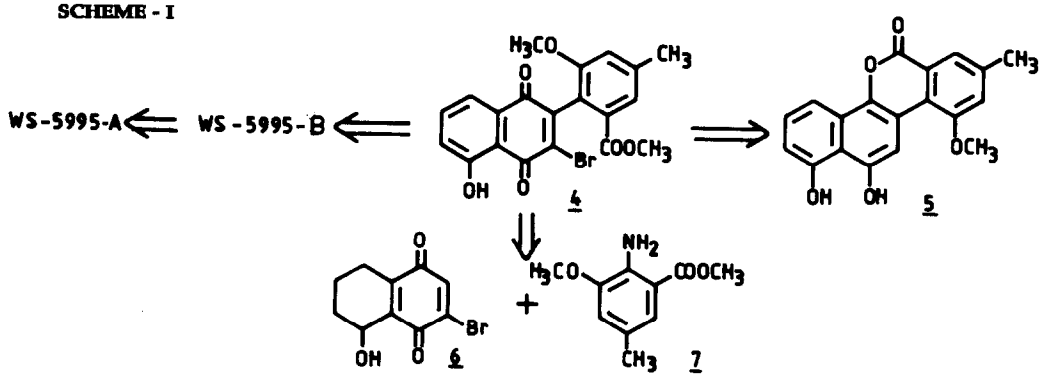
earlier methods. Retrosynthetic sequence of WS-5995-B is outlined in Scheme I involving the two fragments, 3-bromo-5,6,7,8-tetrahydrojuglone **6** and 3-methoxy-5-methyl methylanthranilate **7**.

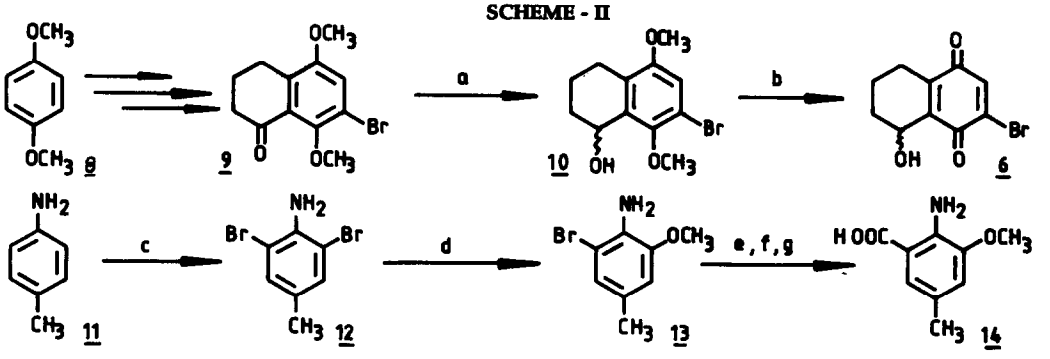
The starting material bromotetralone **9**, was prepared by modification of the reported method with a 40% increase in yield[7]. Reduction of tetralone using $NaBH_4$ followed by CAN oxidation gave quantitative yields of 3-bromo-5,6,7,8-tetrahydrojuglone **6**.

SCHEME - I



The key intermediate 3-methoxy-5-methyl methylanthranilate which also constitutes ring D in the structures of potent antitumour antibiotics such as Gilvocarcin-M 5[8], Virenomycin-M[9] and Albacarcin-M[10], was prepared in better yields (Scheme-II) when compared to the reported methods.[3,11]

SCHEME - II



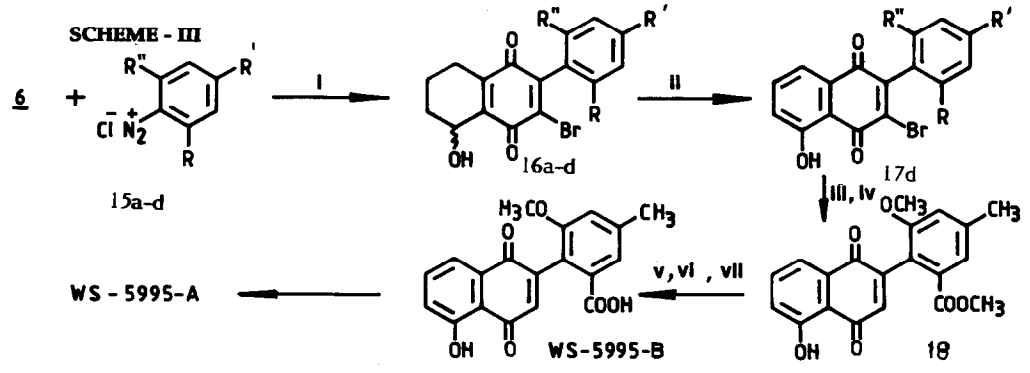
(a) $NaBH_4$/MeOH/2 hr; (b) CAN/CH_3CN/H_2O/-10-15°C; (c) Br_2-dioxane complex/dioxane/5-10°C/1 hr; (d) NaOMe/CuI/MeOH/DMF/100°C/1 hr; (e) Ac_2O/RT; (f) Pd(O) complex/CO (10 atm)/tributylamine/110°C/18 hrs; (g) NaOH (10%)/100°C/1 hr.

2,6-Dibromo p-toluidine **12** prepared by bromination of p-toluidine **11** was selectively mono-methoxylated in the presence of CuI at 105°C. 2-Bromo-6-methoxy-4-methyl aniline **13** thus obtained, was converted into the corresponding acetanilide and subjected to carbonylation using

CO in the presence of $PdCl_2$ $(TPP)_2$ catalyst to give N-acetyl-3-methoxy-5-methyl anthranilic acid. Alkaline hydrolysis followed by esterification using methanolic HCl gave the required ester[11] **7** in 50% overall yield. The crucial step in constructing the desired arylnaphthaquinone is the regioselective coupling between 3-bromo-5,6,7,8-tetrahydrojuglone and 3-methoxy-5-methyl methyl anthranilate **7**.

In order to establish the diazo coupling reaction of 3-bromo-5,6,7,8-tetrahydrojuglone **6**, as visualized in the present work, the diazonium compounds prepared from p-toluidine, methyl anthranilate and 4-methyl methylanthranilate were reacted with **6** under nitrogen atmosphere. The coupled products 2-aryl-3-bromo-5,6,7,8-tetrahydrojuglones (**16a-c**) were obtained in 50% yields (Scheme III). Active MnO_2 oxidation of **16a-c** yielded the corresponding 2-aryl-3-bromo-juglones in quantitative yields. Thus, the diazonium compound prepared from 3-methoxy-5-methyl methylanthranilate was reacted with **6** and 3-bromo-2-(2-methoxycarbonyl-6-methoxy-4-methyl) phenyl-5,6,7,8-tetrahydrojuglone (**16d**) was obtained in 50% yield. It was quantitatively converted into 3-bromo 2-(2-methoxycarbonyl-6-methoxy-4-methyl)-phenyljuglone (**17d**) by MnO_2 oxidation. $PdCl_2(TPP)_2$ catalyzed debromination of **17d** using $NaBH_4$ followed by reoxidation

SCHEME - III



a. R=H, R'=CH_3, R"=H
b. R=$COOCH_3$, R'=H, R"=H
c. R=$COOCH_3$, R'=CH_3, R"=H
d. R=$COOCH_3$, R'=CH_3, R"=OCH_3

i) dioxane/H_2O/80°C/N_2; ii) MnO_2/DCM/1/2 hr; iii) $NaBH_4$/$PdCl_2$(TPP) /-10°C/15 min; iv) MnO_2/DCM/1/2 hr; v) $Ti(i\text{-}opr)_4$/BzOH/16 hr; vi) Pd/C/H_2 (150 psi)/15 hr; vii) MnO_2/DCM/1/2 hr.

using active MnO_2 gave the required 2-(2-methoxycarbonyl-6-methoxy-4-methyl) phenyljuglone **18** in high yields. In order to convert **18** into the biologically active target molecules WS-5995-B and A by ester hydrolysis and lactonization respectively, it was attempted to hydrolyze **18** under acidic conditions but **18** resisted hydrolysis. This difficulty was circumvented by initial transesterification of **18** using benzyl alcohol in the presence of titanium isopropoxide followed by hydrogenolysis over Pd/C. The leuco intermediate thus obtained, was oxidized with MnO_2 to give the target molecule WS-5995-B. The conversion of WS-5995-B into the second target molecule namely WS-5995-A was accomplished by Ikushima *et al.*[3]

EXPERIMENTAL

Melting points were determined in open capillaries with mettler FP-51 melting point apparatus and are uncorrected. IR spectra were recorded in KBr pellets on Perkin-Elmer model 293B spectrophotometer. PMR spectra were obtained on 300 MHz and Varian FT-80 AM instruments in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on VG micromass 7070H.

2,6-Dibromo-p-toluidine 12 : The bromine-dioxane complex was prepared by mixing equimolar amounts of the components and quenching the hot product in ice water. The complex (25 g) was added over 15 min. to p-toluidine (10.7 g, 0.1 M), in dioxane (40 ml) at 5-10°C under stirring. The resulting precipitate was filtered off, washed first with little water and later with dil. NaOH (20 ml) and again with water. It was crystallised from ethanol, m.p. 78°C (21.2 g, 80%) (lit.[12] 78°C).

2-Bromo-6-methoxy-p-toluidine 13 : Sodium (0.115 g, 0.005 g.atm.) was dissolved in methanol (10 ml) in a reaction vessel. To the sodium methoxide solution, 2,6-dibromo-p-toluidine (2.65 g, 0.01 M) and DMF (25 ml) were added and heated to 100°C, while methanol was allowed to distill out. Anhydrous cuprous iodide (1.9 g, 0.01 M) was added to the reaction mixture and heating continued for 1 hr. The cooled reaction mixture was poured into ice water and the resulting precipitate filtered, washed with water and with chloroform. The chloroform layer of the filtrate was separated. The aqueous layer was again extracted into chloroform. The combined chloroform extracts were dried ($MgSO_4$) and the solvent evaporated. The residue thus obtained, was purified by column chromatography over neutral alumina using hexane and benzene (1:1) as eluent, to give a low melting solid (1.72 g, 80%). IR ($CHCl_3$) : 3350, 3260, 1150 and 1040 cm^{-1}. PMR ($CDCl_3$) : (δ ppm); 2.31 (s, 3H); 3.87 (s, 3H); 4.25 (br, 2H, D_2O exchanged); 6.5(br, s, 1H, J=2 Hz); 6.87 (br, s, 1H, J=2 Hz). MS : m/z (%) 215, 217 (97, M^+).

N-Acetyl-2-bromo-6-methoxy-p-toluidine : To 2-bromo-6-methoxy-p-toluidine (2.15 g, 0.01 M) acetic anhydride (1.53 g, 0.015 M) and catalytic amount of sulfuric acid were added while stirring. After 5 min. the reaction mixture was treated with cold water. The resulting precipitate was filtered, washed with water, dried and crystallised from benzene/hexane (3:1) (2.55 g, 95%), m.p. 174°C. IR (KBr) : 3220, 1660 and 1140 cm^{-1}. PMR ($CDCl_3$) (δ ppm) : 2.06 (s, 3H); 2.31 (s, 3H); 3.81 (s, 3H); 6.68 (br, s, 1H, J=2 Hz); 7.0 (br, s, 1H); 7.18 (br, 1H, D_2O exchanged). MS : m/z (%) : 257, 259, (20, M^+).

N-Acetyl-3-methoxy-5-methyl anthranilic acid : Into an autoclave N-acetyl-2-bromo-6-methoxy p-toluidine (2.57 g, 0.01 M), $PdCl_2(PPh_3)_2$ (8 mg, 1.4 x 10^{-5}M), triphenyl phosphine (40 mg), n-tributyl amine (4.4 ml) and deoxygenated water (2 ml) were charged and pressurised with CO (10 atm). It was heated to 110°C and stirred for 18 hrs to complete the reaction. The reaction mixture was cooled and diluted with water (10 ml) and filtered. The filtrate was acidified with 6N HCl. The resulting precipitate was filtered and washed with water. The solid thus obtained, was dissolved in satd. $NaHCO_3$ solution to remove neutral impurities and reprecipitated with 6N HCl. It was crystallised from ethanol (1.91 g, 86%). IR (KBr) : 3200,

3000-2400 and 1670 cm^{-1}. PMR (DMSO-D_6) : 2.18 (s, 3H); 2.43 (s, 3H); 3.93 (s, 3H); 7.0 (br, s, 1H, J=2 Hz); 7.25 (br, s, 1H, J=2 Hz). MS : m/z (%) 223 (30, M^+).

3-Methoxy-5-methyl anthranilic acid 14 : N-acetyl-3-methoxy-5-methyl anthranilic acid (0.72 g, 0.001 M) was dissolved in NaOH (10%, 5 ml) and refluxed for 1 hr. The reaction mixture was cooled and neutralised carefully with 5% HCl using pH meter. The resulting solid was filtered and washed thrice with water, dried and crystallised from ethanol, m.p. 170°C (lit.[3] 170°C) (0.15 g, 95%).

Methyl-3-methoxy-5-methyl anthranilate 7 : 3-methoxy-5-methyl anthranilic acid **14** (3.62 g, 0.02 M) was heated in methanol (20 ml), while passing dry HCl gas for 4 hrs. Methanol was removed and the free base regenerated by addition of NH_4OH. It was Kugel rohred at 96°C/ 0.05 mm (lit.[11] 96°C/0.05 mm) to give **7** (3.12 g, 80%).

7-Bromo-5,8-dimethoxy-1,2,3,4-tetrahydro-1-naphthol 10 : To a solution of bromotetralone **9**[7] (2.84 g, 0.014 M) in methanol (30 ml) was added in small portions, $NaBH_4$ (0.64 g, 0.02 M) and refluxed for 3 hrs with stirring. The reaction mixture was concentrated, treated with water (20 ml) and extracted into DCM. The organic layer was washed with water, dried over anhydrous $MgSO_4$. The solvent was evaporated and the residue purified by column chromatography over neutral alumina using benzene as eluent (2.5 g, 90%) m.p. 41°C. IR ($CHCl_3$) : 3520-3230 (br), 3000, 2910, 1570, 1450, 1300-1050 (br) cm^{-1}. PMR ($CDCl_3$) : 1.68 (m, 4H); 2.13 (m, 2H); 2.81 (br, 1H, D_2O exchanged); 3.62 (s, 3H); 3.75 (s, 3H); 4.87 (br, 1H); 6.75 (s, 1H). MS : m/z (%), 288 (100, M^+).

3-Bromo-5,6,7,8-tetrahydrojuglone 6 : Ceric ammonium nitrate (2.86 g, 0.006 M) in water (10 ml) was added dropwise to **10** (0.5 g, 0.001 M) in acetonitrile (10 ml) at -20°C while stirring. Stirring was continued for 3-4 hrs. The reaction mixture was diluted with water (20 ml) and extracted into chloroform. The organic layer was dried over anhydrous $MgSO_4$, the solvent evaporated and the residue purified by column chromatography over silica gel using benzene and ethyl acetate (9:1) as eluent (0.25 g, 78%), m.p. 75°C. IR ($CHCl_3$) : 3500-3200 (br), 2910, 1670, 1650 cm^{-1}. PMR ($CDCl_3$) : 1.87 (m, 4H); 2.57 (m, 2H); 2.98 (br, 1H, D_2O exchanged); 4.84 (br, 1H); 7.27 (s, 1H). MS : m/z (%) 256, 258 (14, M^+).

General procedure for diazocoupling reaction : The aryl amines (0.001 M) were dissolved in HCl (6N, 2 ml) and cooled to -10°C. Finely powdered sodium nitrite (0.001 M, 69 mg) was slowly added maintaining the temperature at -10°C while stirring. The diazonium salt solution was deoxygenated by flushing with nitrogen. The diazonium chloride solution was added dropwise while stirring to bromojuglone **6** (0.001 M), dissolved in dioxane and water (1:1) 10 ml at 80°C under nitrogen atmosphere. Stirring was continued for 10 min. and the reaction mixture cooled to room temperature diluted with water (25 ml) and extracted into chloroform. The organic layer was dried over anhydrous $MgSo_4$, the solvent evaporated and the residue purified by column chromatography to obtain pure 2-aryl-3-bromo-5,6,7,8-tetrahydrojuglones.

3-Bromo-2-(4-methyl)phenyl-5,6,7,8-tetrahydrojuglone 16a : According to general procedure, p-toluidine (0.107 g, 0.001 M) gave a low melting solid. (0.19 g, 55%). IR ($CHCl_3$) : 3210 (br), 2910, 1710, 1650, 1430 cm^{-1}. PMR ($CDCl_3$) : 1.81 (m, 4H); 2.1 (m, 6H); 5.06 (br, 1H); 7.18 (m, 4H). MS : m/z (%) 267 (100, M^+-Br).

3-Bromo-2-(2-methoxycarbonyl)phenyl-5,6,7,8-tetrahydrojuglone 16b : According to general procedure, methylanthranilate (0.15 g, 0.01 M) gave a low melting solid **16b** (0.20 g, 50%). IR ($CHCl_3$) : 3210 (br), 2900, 1710, 1650, 1580, 1210 cm^{-1}. PMR ($CDCl_3$) : 1.8 (m, 4H); 2.5 (m, 2H); 2.87 (br, 1H, D_2O exchanged); 3.85 (s, 3H); 4.85 (br, 1H); 7.28 (d, 1H, J=2 Hz); 7.4 - 7.6 (m, 2H); 8.18 (d, 1H). MS : m/z (%) 311 (100, M^+-Br).

3-Bromo-2-(2-methoxycarbonyl-4-methyl)phenyl-5,6,7,8-tetrahydrojuglone 16c : According to general procedure 5-methyl-methyl anthranilate (0.165 g, 0.001 M) gave **16c** (0.194 g, 48%). IR ($CHCl_3$) : 3200 (br), 2910, 1710, 1650, 1590, 1200 cm^{-1}. PMR ($CDCl_3$) : 1.87 (m, 4H); 2.45 (m, 5H); 2.81 (br, 1H, D_2O exchanged); 3.81 (s, 3H); 4.87 (br, 1H); 7.12 (d, 1H, J=7 Hz); 7.43 (d, 1H, J=7 Hz); 7.93 (s, 1H). MS : m/z (%) 325 (100, M^+-Br).

3-Bromo-2-(2-methoxycarbonyl-6-methoxy-4-methyl)phenyl-5,6,7,8-tetrahydrojuglone 16d: According to general procedure, 3-methoxy-5-methyl methyl anthranilate 7 (0.195 g, 0.001 M) gave **16d** (0.215 g, 52%). IR ($CHCl_3$) : 3200 (br), 2910, 1710, 1650 and 1070 cm^{-1}. PMR ($CDCl_3$) : 1.87 (m, 4H); 2.43 (m, 5H); 3.12 (br, 1H, D_2O exchanged); 3.75 (s, 6H); 4.87 (br, 1H); 6.93 (d, 1H, J=2 Hz); 7.5 (d, 1H, J=2 Hz). MS : m/z (%) 355 (100, M^+-Br).

General procedure for oxidation of 5,6,7,8-tetrahydrojuglones to juglone derivatives : The 5,6,7,8-tetrahydrojuglones were dissolved in DCM (20 ml) and stirred at room temperature with active MnO_2 (100 mg) for 2 to 3 hrs. The deep yellow coloured solution was filtered from MnO_2 and the solvent evaporated to a residue. It was purified by column chromatography to obtain pure 2-aryl-3-bromojuglones.

3-Bromo-2-(4-methyl)phenyljuglone 17a : According to general procedure **16a** (0.34 g, 0.001 M) gave **17a** m.p. 204°C (0.27 g, 80%). IR (KBr) : 3400 (br), 3000, 1720, 1680, 1350, 1035 cm^{-1}. PMR ($CDCl_3$) : 2.4 (s, 3H); 7.1 (m, 1H); 7.3 (m, 4H); 7.4 - 7.2 (m, 2H). MS : m/z (%) 263 (100, M^+-Br). (CI) m/z : 344, 342. Anal. Calcd. for $C_{17}H_{11}BrO_3$: C, 59.64; H, 3.216. Found : C, 59.62; H, 3.18.

3-Bromo-2-(2-methoxycarbonyl)phenyljuglone 17b : According to general procedure **16b** (0.39 g, 0.001 M) gave **17b**. m.p. 212°C (0.33 g, 85%). IR ($CHCl_3$) : 3200 (br), 2910, 1710, 1650, 1590, 1430 cm^{-1}. PMR ($CDCl_3$) : 3.8 (s, 3H); 7.26 (m, 2H); 7.55 - 7.85 (m, 4H); 8.1 (d, 1H); 12.0 (s, 1H, D_2O exchanged). MS : m/z (%) 307 (100, M^+-Br). (CI) m/z 388, 386. Anal. Calcd. for $C_{18}H_{11}BrO_5$: C, 55.96; H, 2.84. Found : C, 56.02; H, 2.84.

3-Bromo-2-(2-methoxycarbonyl-4-methyl)phenyljuglone 17c : According to general procedure, **16c** (0.4 g, 0.001 M) afforded **17c**. m.p. 220°C (0.32 g, 80%). IR (KBr) : 3400 (br), 3000, 1720, 1680, 1350, 1035 cm^{-1}. PMR ($CDCl_3$) : 2.5 (s, 3H); 3.79 (s, 3H); 7.2 (d, 1H, J=7 Hz); 7.3 (m, 1H), 7.5 (d, 1H); 7.7 (m, 2H); 8.0 (s, 1H); 12.0 (s, 1H, D_2O exchanged). MS : m/z (%) 321 (100, M^+-Br). (CI) m/z 402, 400. Anal. Calcd. for $C_{19}H_{13}BrO_5$:C, 57.0; H, 3.25. Found : C, 56.96; H, 3.28.

3-Bromo-2-(2-methoxycarbonyl-6-methoxy-4-methyl)phenyljuglone 17d : According to general procedure **16d** (0.43 g, 0.001 M) afforded **17d**. m.p. 165°C (0.365 g, 85%). IR (KBr) : 3400 (br), 3000, 1715, 1680, 1350, 1035, 800 cm^{-1}. PMR ($CDCl_3$) : 2.5 (s, 3H); 3.8 (s, 3H); 3.81 (s, 3H); 7.16 (d, 1H, J=2 Hz); 7.33 - 7.70 (m, 4H). MS : m/z (%) 351 (100, M^+-Br). (CI) m/z 432, 430. Anal. Calcd. for $C_{20}H_{15}BrO_6$: C, 55.81; H, 3.48. Found : C, 55.79; H, 3.51.

2-(2-methoxycarbonyl-6-methoxy-4-methyl)phenyljuglone 18 : Bromojuglone **17d** (88 mg, 0.0002 M) and $PdCl_2(PPh_3)_2$ (8 mg. 1.4×10^{-5} M) in absolute methanol (10 ml) were cooled to -20°C. To this suspension powedered $NaBH_4$ (6 mg, 0.0004 M) was added while stirring. Stirring was continued for 15 min. and the leuco reaction mixture filtered, the solvent evaporated and the residue washed with cold water and extracted into DCM. The DCM layer was dried and the solvent evaporated. The residue was dissolved in DCM and oxidised using active MnO_2 (15 mg) for 30 min. The yellow coloured solution was filtered and the solvent evaporated. The residue was purified over column chromatography over silica gel using hexane and ethyl acetate (2%). m.p. 145°C. (0.042 g, 60%). IR (KBr) : 3200 (br), 2910, 1710, 1680, 1590, 1350 cm^{-1}. PMR ($CDCl_3$) : 2.5 (s, 3H); 3.75 (s, 3H); 3.79 (s, 3H); 6.87 (s, 1H); 7.02 (d, 1H, J=2 Hz); 7.33 - 7.71 (m, 4H). MS : m/z (%) 352 (50, M^+). Anal. Calcd. for $C_{20}H_{16}O_6$: C, 68.18; H, 4.54. Found : C, 68.21; H, 4.54.

WS-5995-B : To the phenyljuglone **18** (100 mg, 0.0028 M) dissolved in benzyl alcohol (10 ml) titanium isopropoxide (0.1 ml, 0.002 M) was added and heated to 120-130°C for 15 hr. The reaction mixture was cooled and benzyl alcohol removed under vacuum. The residue was dissolved in ethyl acetate (50 ml) and washed with 3N HCl (10 ml), brine (10 ml) and dried over anhydrous $MgSO_4$. Filtration and evaporation of solvent gave a crude brown solid (125 mg). It was dissolved in ethyl acetate and subjected to hydrogenation over 20% Pd/C (50 mg) for 15 hr at 150 psi H_2 pressure. The reaction mixture was filtered through celite and the solvent evaporated. The residue was oxidised with active MnO_2 (100 mg) in DCM (50 ml) for 30 min. The solution was filtered and solvent evaporated to give a crude product. It was recrystallised from ethyl acetate and hexane to give WS-5995-B, a yellow solid. (0.065 g, 75%). m.p. 300°C (sublimation) (lit.[1] 300°C). IR ($CHCl_3$) : 3040, 2940, 1710, 1680, 1650 and 1170 cm^{-1}. PMR ($CDCl_3$) : 2.42 (s, 3H); 3.75 (s, 3H); 6.78 (s, 1H); 7.0 (s, 1H); 7.25 - 7.62 (m, 4H). MS : m/z (%) 338 (60, M^+). Anal. Calcd. for $C_{19}H_{14}O_6$:C, 67.45; H, 4.17. Found : C, 67.32; H, 4.34.

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