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Stereoselective Total Synthesis of (±)-Paulownin and (±)-Isogmelinol through Radical Annulation Route

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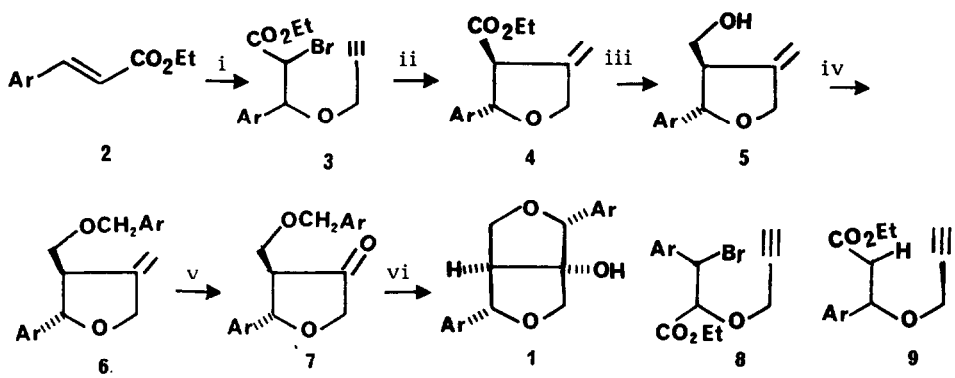
Abstract : A highly stereocontrolled synthesis of furofuran lignans, (±)-Paulownin (1a) and (±)-Isogmelinol (1b) is described involving intramolecular radical cyclisation as a key step.

Lignans have attracted much interest over the years on account of their widespread occurrence in nature[1] and broad range of biological activities[2]. Some lignans are known to exhibit anti-tumour activity while others function as growth inhibitors and antifungal agents. Recent isolation of lignans from animals led to a suggestion that such compounds may be examples of a new type of hormone controlling cell growth[3]. The many varied types of structures that lignan can possess have presented a considerable challenge to organic chemists over the years and indeed many elegant syntheses depending upon a limited number of key reactions to construct the basic 18-carbon skeleton have been reported[4]. Though several syntheses have been reported, the radical cyclisation reactions, which witnessed a renaissance recently[5] leading to the preparation of complex natural products, remained unexplored. We have described here, in detail, the intramolecular radical annulation strategy[6] for the total synthesis of (±)-Paulownin (1a)[7] and (±)-Isogmelinol (1b)[8] in good overall yield.

Results and Discussion :

Treatment of the cinnamic ester 2 with N-Bromosuccinimide and propargyl alcohol in CH_2Cl_2 at -15 °C to room temperature afforded the single bromoester 3 in about 78-80% yield (Scheme). No regioisomer 8 was formed at all. Bromoester 3 was found to be a mixture of threo and erythro isomers in a ratio of 1:1 (^{1}H NMR). While 3a was a viscous oil, 3b was crystalline solid, m.p. 80-81 °C. The methylene protons at δ 3.86 and 4.12 for 3a and at δ 3.92 and 4.16 for 3b adjacent to the acetylenic triple bond appeared as $AB_{quartet}$, further coupled with remote acetylenic proton having the coupling constants 16 and 2.4 Hz. The acetylenic proton at δ 2.43

for 3a and 2.45 for 3b also coupled with that methylene protons and appeared as a triplet (J = 2.4 Hz). The equal intensity of two quartets at δ 4.30 and 4.33 for 3a and at δ 4.34 and 4.37 for 3b with coupling constant 9 Hz for the methylene protons of the ethyl ester indicated the ratio of the threo and the erythro isomers. Intramolecular radical cyclisation of 3 was successfully achieved with n-Bu_3SnH and AIBN (cat.) in refluxing benzene (0.02M) producing exclusively the 5-exo-dig cyclised ester 4 in about 80-82% yield. No reduced product 9 was isolated. 9.9 Hz coupling constant in ^1H NMR for the benzylic methine protons at δ 5.18 for 4a and at δ 5.22 for 4b indicated the trans relationship[4b] between the aryl and the carbethoxy groups. It is very interesting that the mixture of isomers of the bromoester 3 on radical cyclisation gave only the trans product 4, which is expected to form only from the threo isomer. It is well documented in the literature[9] that the threo diastereo selection occured during radical reduction of the β-alkoxy- α-haloesters due to (1) the delocalisation of the radical through the carbethoxy group (2) the strong influence of the electronic effects on the substituent α to the radical and (3) the non-pyramidalised structure of the radical. Reduction of the ester 4 with $LiAlH_4$ in refluxing Et_2O furnished the alcohol 5 as viscous liquid in almost quantitative yield. Alcohol 5a was refluxed with NaH and 3,4-methylenedioxybenzyl chloride in DME for 20h to afford the protected alcohol 6a as a viscous oil in 75% yield. 6b was prepared from 5b under identical reaction



a, Ar=3,4-methylenedioxophenyl

b, 3,4-dimethoxyphenyl

Scheme : Reagents and conditions : i, NBS, propargyl alcohol (excess), CH_2Cl_2, -15 °C to rt, overnight; ii, n-Bu_3SnH, AIBN (cat.), benzene, reflux, 4h; iii, $LiAlH_4$, Et_2O, reflux, 3h; iv, NaH, DME, $ArCH_2Cl$, reflux, 20h; v, O_3, CH_2Cl_2, -78 °C, 15 min for 6a; OsO_4, $NaIO_4$, Et_2O, H_2O, rt, overnight for 6b; vi, hν, benzene, 45 min for 7b.

condition as for **6a** using 3,4-dimethoxybenzyl chloride as the protecting reagent in about 76% yield. Oxidation of the double bond in **6a** was performed by ozonolysis at -78°C in CH_2Cl_2 followed by quenching with Me_2S to the known ketone **7a**[4b] in 79% yield. IR and ^1H NMR spectra are in full agreement with the reported values. Since conversion of **7a** to (±)-Paulownin (**1a**) has already been reported[4b], we described here the formal total synthesis of **1a**. Ozonolysis of **6b** under identical condition as described for **6a** resulted in an intractable mass. **6b** underwent smooth oxidation with OsO_4 (cat.) and $NaIO_4$ in aqueous Et_2O[10] at room temperature for 24h to afford the ketone **7b** in 90% yield. Finally, synthesis of (±)-Isogmelinol (**1b**) from ketone **7b** was completed by type **II** photocyclisation involving 1,6-hydrogen shift as follows. Irradiation of **7b** with 450W Hanovia medium pressure mercury lamp in degassed (argon) benzene for 45 min in a quartz vessel furnished **1b** in 72% yield as a crystalline solid, m.p. 150-151°C (Reported m.p. 152-153°C) (conversion 90%, GC). IR and ^1H NMR spectra of **1b** are in full agreement with the reported values.

In conclusion, the stereoslective radical annulation strategy has been demonstrated by total synthesis of racemic Paulownin and Isogmelinol in only six steps from cinnamic ester.

Experimental :

Melting points were determined in capillary tubes and are uncorrected. IR spectra were determined with a Perkin-Elmer 298 spectrometer. ^1H NMR spectra were recorded on Varian XL 200 or Varian EM 360L instruments in $CDCl_3$ (unless otherwise stated) with TMS as internal reference. Chemical shifts were expressed in ppm, coupling constants in Hz. UV spectra were recorded on a Hitachi model 200-20 spectrophotometer in ethanol solution. Analytical GC was performed on Shimadzu GC-9A model with a flame ionisation detector employing 1.5% OV-17 (6.5 ft x 0.25 inch) and SE-30 (6.5 ft x 0.25 inch) column with N_2 as the carrier gas. Diethyl ether and tetrahydrofuran were distilled from sodium-benzophenone ketyl. Other solvents and reagents were purified by standard procedures as necessary. Column chromatography was performed on silica gel (60-120 mesh) and preparative thin layer chromatography was performed using silica gel HF254. Petroleum ether of boiling range from 60°C to 80°C was used for column chromatography.

Bromoester 3a : To a stirred solution of N-bromosuccinimide (6 g, 34 mmol) and propargyl alcohol (6.6 mL, 113.5 mmol) in dry CH_2Cl_2 (20 mL) at -15°C (ice-salt bath) was added dropwise a solution of cinnamic ester **2a** (5 g, 22.7 mmol) in dry CH_2Cl_2 (15 mL) under N_2 for 30 min. The reaction mixture was further stirred for 2h at that temperature and left overnight. The mixture was diluted with CH_2Cl_2 (50 mL), washed with 1N aqueous NaOH solution, brine and dried (Na_2SO_4). Solvent was

removed under reduced pressure and the yellow residue was purified b chromatography over silica gel (petroleum ether-ethyl acetate 4:1) to give 3 78%) as a colorless oil, IR (Neat) ν_{max} 3290, 2980, 2900, 1740, 1610, 15 1440, 1370, 1250 cm^{-1}; ^1H NMR δ 1.34 (t, J = 9 Hz, 3H), 2.43 (t, J = 1H), 3.86 and 4.12 (ABX type., J = 16 and 2.4 Hz, 2H), 4.22 (d, J = 10 4.30 and 4.33 (double quartet, J = 9 Hz, 2H), 4.85 (d, J = 10 Hz, 1H), 2H), 6.81-6.97 (m, 3H).

Bromoester 3b : 3b was prepared as described for 3a in 80% yield as crystals, m.p. 80-81°C IR(KBr) ν_{max} 3290, 2980, 2920, 1735, 1605, 1595, 15 1440, 1420, 1370, 1340, 1300, 1260 cm^{-1}; ^1H NMR δ 1.36 (t, J = 8 Hz, 3H), 2 = 2.4 Hz, 1H), 3.90 (s, 6H), 3.92 and 4.16 (ABX type, J = 16 and 2.4 Hz, (d, J = 10 Hz, 1H), 4.34 and 4.37 (double quartet, J = 9 Hz, 2H), 4.93 (d Hz, 1H), 6.96-7.04 (m, 3H); Anal. calcd. for $C_{16}H_{19}O_5Br$: C, 51.75; H, 5. : C, 51.90; H, 5.29.

Compound 4a : A mixture of bromoester 3a (2.5 g, 7.03 mmol), n-Bu_3SnH 8.44 mmol) and AIBN (15 mg) in dry benzene (422 mL, 0.02 M) was reflu preheated oil bath under N_2 for 4h. Volatiles were removed under reduced and the residue was chromatographed over silica gel (5% and 20% ethyla petroleum ether) to furnish 4a (1.5 g, 80%) as a colorless oil. IR(Neat) ν_n 2900, 1730, 1610, 1500, 1490, 1250, 1170, 1160, 1040 cm^{-1}; ^1H NMR δ 1.27 (Hz, 3H) 3.46 (dd, J = 8 and 3 Hz, 1H), 4.05-4.33 (m, 2H), 4.48 and 4.64 (14 Hz, two peaks further coupled, J = 2.5 Hz, 2H), 5.18 (d, J = 9.9 Hz, 1 5.24 (m, 2H), 5.94 (s, 2H), 6.77-6.96 (m, 3H); Anal. calcd. for $C_{15}H_{1}$ 65.21; H, 5.84. Found : C, 65.40; H, 6.09.

Compound 4b : 4b was prepared as described for 4a in 82% yield as a colo IR(Neat) ν_{max} 2940, 2840, 1740, 1610, 1590, 1515, 1460, 1420, 1370, 1340, 1 cm^{-1}; ^1H NMR δ 1.28 (t, J = 8 Hz, 3H), 3.50 (brd J = 8 Hz,, 1H), 3.86 3.88 (s, 3H), 4.12-4.36 (m, 2H), 4.52 and 4.66 (AB_q, J = 16 Hz two peak coupled J = 2.4 Hz, 2H), 5.22 (d, J = 9.9 Hz, 1H), 5.10-5.28 (m, 2H), (m, 3H); Anal. calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found : C, 66.09; H

Hydroxy compound 5a : To a stirred slurry of $LiAlH_4$ (824 mg, 21.6 mmol Et_2O (30 mL) at 0°C was added dropwise a solution of the ester 4a (3 g, 1 in Et_2O (30 mL). The reaction mixture was refluxed for 3h, cooled to quenched carefully with saturated aqueous Na_2SO_4 solution (5 mL). The org was separated and dried (Na_2SO_4). After evaporation of Et_2O, the res chromatographed over silica gel (50% ethyl acetate in petroleum ether) to alcohol 5a (2.5 g, 98%) as a viscous oil. IR(Neat) ν_{max} 3420 (br), 2880, 16 1490, 1440, 1250, 1040 cm^{-1}; ^1H NMR δ (60 MHz) 2.33 (brs, 1H), 2.53-2.98 (b 3.57-3.90 (m, 2H), 4.43-4.63 (m, 2H), 4.83 (d, J = 8 Hz, 1H), 5.01-5.20

6.0 (s, 2H), 6.73-7.02 (m, 3H); Anal. calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02. Found : C, 66.58; H, 6.34.

Hydroxy compound 5b : 5b was prepared as described for 5a in 97% yield as a viscous liquid. IR(Neat) ν_{max} 3410, 2935, 2835, 1610, 1590, 1465, 1430, 1260, 1235 cm^{-1}. ^1H NMR δ 2.14 (brs, 1H), 2.81 (brs, 1H), 3.74 and 3.92 (ABX, J_{AB} = 16, J_{AX} = 8, J_{BX} = 4 Hz, 2H), 3.87 (s, 3H), 3.88 (s, 3H), 4.44 and 4.64 (AB_q, J = 16 Hz, 2H), 4.82 (d, J = 8 Hz, 1H), 5.12 (dd, J = 7 and 2 Hz, 2H), 6.83-7.02 (m, 3H); Anal. calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found : C, 66.95; H, 7.35.

Olefinic compound 6a : To a stirred suspension of NaH (previsously washed with petroleum ether) (123 mg, 5.12 mmol) in DME (4 mL) was added dropwise a mixture of the alcohol 5a (1 g, 4.26 mmol) and 3,4-methylenedioxybenzyl chloride (873 mg, 5.12 mmol) in DME (6 mL) under N_2 at room temperature. The resulting reaction mixture was refluxed for 20h, cooled to 0 °C, decomposed with cold water (5 mL) and extracted with Et_2O (3x30 mL). The organic layer was washed with brine and dried (Na_2SO_4). After evaporation of the solvent, the residue obtained was subjected to column chromatography over silica gel (20% ethylacetate in petroleum ether) to afford 6a (1.18 g, 75%) as an oil. IR(Neat) ν_{max} 2900, 1610, 1500, 1490, 1445, 1370, 1250 cm^{-1}; ^1H NMR δ (60 MHz) (CCl_4) 2.50-2.96 (m, 1H0, 3.50 (d, J = 8 Hz, 2H), 4.23-4.50 (m, 4H, 4.65 (d, J = 8 Hz, 1H), 4.86-5.06 (m, 2H), 5.90 (s, 2H), 5.93 (s, 2H0, 6.66-6.90 (m, 6H); Anal. calcd. for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found : C, 68.17; H, 5.56.

Olefinic compound 6b : 6b was prepared as described for 6a in 76% yield as an oil. IR(Neat) ν_{max} 2940, 2840, 1590, 1505, 1460, 1260, 1235, 1200 cm^{-1}; ^1H NMR δ (60 MHz) (CCl_4) 2.60-2.93 (m, 1H), 3.48 (d, J = 8 Hz, 2H), 3.75 (s, 6H), 3.80 (s, 6H), 4.16-4.43 (m, 4H), 4.80 (d, J = 8 Hz, 1H), 4.83-5.01 (m, 2H), 6.65-6.88 (m, 6H); Anal. calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found : C, 69.09; H, 7.07.

Ketone 7a : Dry ozone was passed through a solution of the olefin 6a (150 mg, 0.40 mmol) in dry CH_2Cl_2 at -78 °C for 20 min until light blue color appeared (Approx, 15 min). Any excess ozone in the solution was removed by passing oxygen for 5 min. The mixture was treated with Me_2S (2 mL) at -78 °C for 1h, 0 °C for 2h and left overnight. Diluted with CH_2Cl_2 and the organic part was washed with water (3x30 mL) and dried (Na_2SO_4). Removal of solvent gave a yellow residue which was purified by column chromatography over silica gel (20% ethyl acetate in petroleum ether) to furnish the known ketone 7a (120 mg, 79%) as a viscous oil. IR(Neat) ν_{max} 2880, 1755, 1610, 1500, 1485, 1440, 1245, 1100, 1035, 930 cm^{-1}; ^1H NMR δ 2.38-2.43 (m, 1H), 3.48 (dd, J = 9.7 and 3.3 Hz, 1H), 3.83 (dd, J = 9.7 and 3.3 Hz, 1H), 3.95 (d, J = 17 Hz, 1H), 4.29 (d, J = 17 Hz, 1H), 4.31 (d, J=12 Hz, 1H), 4.41 (d, J=12 Hz, 1H), 5.08 (d, J=9.9 Hz, 1H), 5.94 (s, 4H), 6.68-6.84 (m, 6H).

Ketone 7b : A mixture of 6b (500 mg, 1.24 mmol), $NaIO_4$ (934 mg, 4.37 mmol) and OsO_4 (10 mg) in Et_2O-H_2O (10 mL) (5:1) was stirred at room temperature for 24h (monitored by TLC). The reaction mixture was diluted with Et_2O (40 mL). Ether layer was washed with brine and dried (Na_2SO_4). Removal of ether left a residue which was chromatographed over silica gel (20% and 40% ethylacetate in petroleum ether) to give 7b (452 mg, 90%) as a white crystalline solid, M.p. 120-121°C. UV (EtOH) λ_{max} 232 (14, 017), 280 (5, 388) nm; IR (KBr) ν_{max} 2940, 2840, 1760, 1610, 1590, 1520, 1460, 1420, 1265, 1240 cm^{-1}; ^1H NMR δ 2.43-2.49 (m, 1H), 3.49 (dd, J = 9.7 and 3.3 Hz, 1H), 3.83 (s, 3H), 3.85 (s, 6H), 3.86 (s, 3H), 3.84 (dd, J = 9.7 and 4 Hz, 1H), 3.97 (d, J = 17 Hz, 1H), 4.31 (d, J = 17 Hz, 1H), 4.36 (d, J = 12 Hz, 1H), 4.45 (d, J = 12 Hz, 1H), 5.13 (d, J = 9.9 Hz, 1H), 6.79-6.98 (m, 6H); Anal. calcd for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51. Found : C, 65.74; H, 6.68.

Isogmelinol 1b : A solution of the ketone 7b (150 mg, 0.37 mmol) in dry degassed (argon) benzene (200 mL) was irradiated in a quartz vessel with 450W Hanovia medium pressure mercury lamp for 45 min. The progress of the reaction was monitored by GC and irradiation was stopped at the stage of 90% conversion. Otherwise, undesired reaction product started forming. Benzene was removed under reduced pressure and the brown residue was subjected to preparative TLC (ethylacetate-petroleum ether 4:1) to yield 1b (108 mg, 72%), M.p. 150-151°C (reported m.p. 152-153°C). IR(KBr) ν_{max} 3370, 2960, 2940, 2870, 2840, 1605, 1590, 1510, 1415, 1265, 1240, 1155, 1140, 1060, 1030 cm^{-1}; ^1H NMR δ 1.56 (s, 1H), 3.07-3.17 (m, 1H), 3.80-3.92 (m, 14H with three singlets at δ 3.86, 3.88 and 3.90), 4.05 (d, J = 9.3 Hz, 1H), 4.54 (t, J = 8.4 Hz, 1H), 4.85 (s, 1H), 4.87 (d, J = 4.8 Hz, 1H), 6.82-7.0 (m, 6H); Anal. calcd for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51. Found : C, 65.45; H, 6.64.

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