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Stereoselective Total Synthesis of (±)-Samin and the Dimethoxy Analogue, the General Furofuran Lignan Precursors

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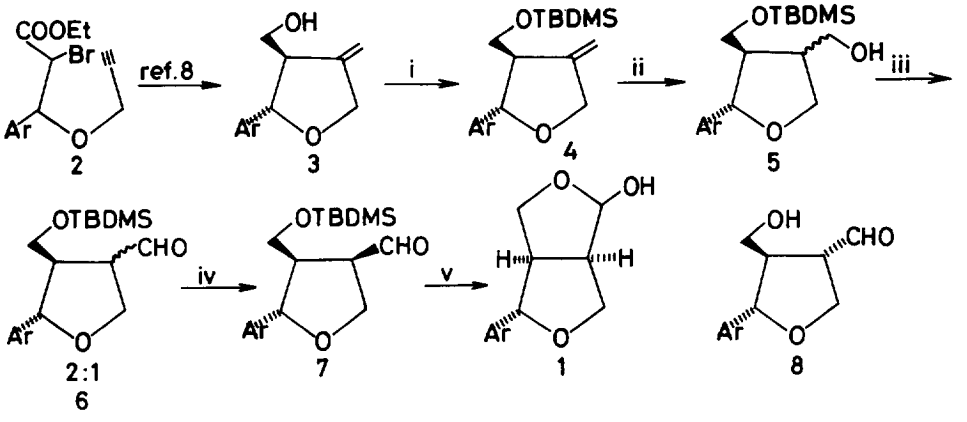
Abstract : A concise stereoselective synthesis of the general furofuran lignan precursors (±)-Samin **1a** and its dimethoxy analogue **1b** has been achieved through a radical annulation reaction in good overall yield.

Due to the widespread occurrence in nature[1] and broad range of biological activities, [2] lignans have attracted much interest over the years. Some lignans are known to exhibit anti-tumour activity while others function as growth inhibitors and antifungal agents. The many varied types of structures that lignans can possess have presented a considerable challenge to organic chemists. The furofuran lignans are one of the largest groups of naturally occurring lignans, whose members show a variety of biological activities .[3] Although interesting syntheses[4] providing these natural products have been achieved, the tin hydride-mediated intramolecular radical cyclisation strategy is still unexplored. We have described here, in detail,[5] a stereoselective synthesis of racemic Samin **1a**[6] and the dimethoxy analogue **1b** through tin-hydride mediated radical annulation route in good overall yield. Samin **1a** has been shown[7] to be a suitable precursor for both symmetrical and unsymmetrical types of the furofuran lignans, such as Acuminatolide, Sesamolin and Sesamin. Compound **1b** could also be a versatile precursor for Eudesmin, Methyl piperitol and many other furofuran lignans.

Results and Discussion

Recently, we have reported[8] the stereoselective syntheses of (±)-Paulownin and (±)-Isogmelinol through the alcohol **3** using the tin-hydride mediated intramolecular radical cyclisation of the bromoester **2** as a key step. The present synthesis consists of only four steps starting from the easily accessible alcohol **3** without employing any difficult procedure. Treatment of the alcohol **3** with TBDMS-Cl and Et_3N in presence of a catalytic amount of 4-DMAP and imidazole afforded the olefin **4** in

excellent yield (Scheme). Hydroboration of the olefin 4 by passing B_2H_6 gas (prepared from $BF_3.Et_2O$ and $NaBH_4$ in diglyme) followed by oxidation with alkaline H_2O_2 (30%) furnished the alcohol 5 in 70-75% yield. In this stage it was not possible to predict (^1H NMR, TLC or GC) whether 5 was a pure isomer or a mixture of stereoisomers. But this was immediately realised when the crude alcohol 5 was subjected to Swern oxidation (oxalyl chloride, DMSO, Et_3N) to give an inseparable isomeric mixture of



a, Ar = 3,4-methylenedioxyphenyl
b, Ar = 3,4-dimethoxyphenyl

Scheme. Reagents and Conditions : 1, TBDMS-Cl, Et_3N, 4-DMAP (cat), imidazole (cat)., CH_2Cl_2, 12h at rt; ii, B_2H_6, 0 °C, 1.5h then 3N NaOH, H_2O_2 (30%), rt; iii, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to rt., 5h; iv, NaOMe, MeOH, 10h, rt; v, excess $Bu_4NF.3H_2O$, THF, 6h, rt.

aldehydes **6** in a ratio of 2:1. In the ^1H NMR spectrum of the crude aldehyde **6a**, the aldehyde proton appeared at δ 9.90 as a doublet (J=2.5 Hz) for the major isomer and at δ 9.78 as a doublet for the minor isomer (J=2.5 Hz). Similarly, that of **6b** appeared at δ 9.91 for the major isomer and at δ 9.80 for the minor isomer (both are doublet, J=2.5 Hz). Since, two isomers could not be separated by usual chromatographic methods, in this stage it was not possible to deduce with complete confidence which isomer had which stereochemistry. However, this was immediately realised when the crude isomeric mixture of aldehydes **6** was isomerised to get quantitatively the thermodynamically more stable cis-aldehyde **7** followed by cyclisation to afford **1** in excellent yield. In the ^1H NMR of **7** the chemical shift value of the aldehyde proton is identical with that of the minor

isomer in the mixture **6**. Thus, treatment of the crude isomeric mixture of aldehyde **6** with methanolic NaOMe at 0 °C for overnight furnished **7** in almost quantitative yield. In ^{1}H NMR, the aldehyde proton of **7a** appeared at δ 9.78 as a doublet (J=2.5 Hz) and that of **7b** at δ 9.80 as a doublet (J=2.5 Hz). Cyclisation was performed in good yield by simply treatment of **7** with excess of n-Bu_4NF.$3H_2O$ in THF at room temperature to give **1**. **1a**, m.p. 108-109 °C (lit.[6b] m.p. 106 °C) was identical in all respect with Samin.[6,7] Compound **1b**, m.p. 119-120 °C has not yet been reported in the literature. Interestingly, when the crude isomeric mixture of aldehydes **6** was treated with excess of n-Bu_4NF.$3H_2O$ in THF under identical reaction condition, exclusively **1** was isolated in even better yield. No trans-aldehyde **8**, which could not be cyclised was detected. Probably, the fluoride ion present in the reaction mixture was responsible for in situ isomerisation finally leading to **1** as the sole product.

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Experimental

Melting points were determined in capillary tubes and are uncorrected. IR spectra were determined with a Perkin-Elmer 298 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian XL-200 or Zeol FX-100 instruments in $CDCl_3$ (unless otherwise stated) with TMS as internal reference. Chemical shifts were expressed in ppm, coupling constants in Hz. 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 using silica gel (60-120 mesh) and preparative thin layer chromatography was performed using silica gel HF 254. Petroleum ether of boiling range from 60 °C to 80 °C was used for column chromatography.

Olefin 4a : To a magnetically stirred solution of the alcohol **3a** (2.3 g, 9.8 mmol), TBDMS-Cl (2.2 g, 14.7 mmol), imidazole (20 mg) and 4-DMAP (20

mg) in CH_2Cl_2 (30 mL) was added dropwise Et_3N (4 mL, 29.5 mmol) at 0°C under N_2. The reaction mixture was then stirred at room temperature for 12 h. It was diluted with CH_2Cl_2 (50 mL), washed with 1N aqueous HCl solution, brine and dried (Na_2SO_4). Volatiles were removed under reduced pressure and the residue was column chromatographed over silica gel (petroleum ether-ethyl acetate, (98:2) to afford **4a** (2.9 g, 85%) as a colorless oil. IR (Neat) ν_{max} 2960, 2940, 2900, 2870, 1610, 1510, 1490, 1450, 1260, 1110, 1050, cm^{-1}; ^1H NMR δ 0.02 (s, 6H), 0.88 (s, 9H), 2.56-2.88 (m, 1H), 3.74 (d, J=6 Hz, 2H), 4.24-4.68 (m, 2H), 4.84 (d, J=8 Hz, 1H), 4.96-5.08 (m, 2H), 5.96 (s, 2H), 6.72-6.92 (m, 3H); Anal. Calcd for $C_{19}H_{28}O_4Si$: C, 65.47; H, 8.09. Found : C, 65.37; H, 7.93.

Olefin 4b : **4b** was prepared by the procedure as described for **4a** in 80% yield as a colorless oil. IR (Neat) ν_{max} 2960, 2940, 2860, 1610, 1600, 1520, 1470, 1420, 1390, 1260, 1240, 1150, 1100, 1070, 1040 cm^{-1}; ^1H NMR δ0.04 (s, 6H), 0.88 (s, 9H), 2.60-2.92 (m, 1H), 3.76 (d, J=6 Hz, 2H), 3.88 (s, 6H), 4.28-4.72 (m, 2H), 4.88 (d, J=7 Hz, 1H), 5.0-5.08 (m, 2H), 6.80-7.0 (m, 3H); Anal. Calcd. for $C_{20}H_{32}O_4Si$: C, 65.89; H, 8.85. Found : C, 66.20; H, 8.97.

Alcohol 5a : Diborane gas (prepared from $BF_3.Et_2O$ and $NaBH_4$ in diglyme) was passed through a solution of the olefin **4a** (3g, 8.6 mmol) in THF (30 mL) during 30 min at 0°C. The reaction mixture was further stirred for 1h at that temperature and then oxidised with 30% H_2O_2 (9 mL) and 3N aqueous NaOH solution. Solvent was removed under reduced pressure and the residue was extracted with Et_2O (3x40 mL), washed with brine and dried (Na_2SO_4). After evaporation of the solvent under reduced pressure, the residue obtained was subjected to column chromatography over silica gel (30% ethyl acetate in petroleum ether) to furnish the alcohol **5a** (2.2 g, 70%) as an oil. IR (Neat) ν_{max} 3460(br), 2960, 2940, 2900, 2860, 1610, 1510, 1490, 1450, 1390, 1360, 1250, 1100, 1050 cm^{-1}; ^1H NMR δ 0.06 (s, 6H), 0.90 (s, 9H), 2.18-2.46 (m, 1H), 2.50-2.86 (m, 1H), 3.28 (br s, 1H), 3.52-4.0 (m, 5H), 4.20 (dd, J=9 and 8 Hz, 1H), 4.56 (d, J=8 Hz, 1H), 5.96 (s, 2H), 6.68-6.92 (m, 3H); Anal. Calcd. for $C_{19}H_{30}O_5Si$: C, 62.26; H, 8.25. Found : C, 62.09; H, 8.48.

Alcohol 5b : **5b** was prepared by the procedure as described for **5a** in 75% yield as an oil. IR (Neat) ν_{max} 3460(br), 2960, 2940, 2870, 1610, 1600, 1520, 1470, 1260, 1240, 1140, 1100, 1030 cm^{-1}; ^1H NMR δ 0.08 (s, 6H), 0.92 (s, 9H), 2.24-2.52 (m, 1H), 2.52-2.84 (m, 1H), 3.60-4.0 (m, 5H), 3.88 (s, 3H), 3.90 (s, 3H), 4.24 (dd, J=9 and 8 Hz, 1H), 4.60 (d, J=8

Hz, 1H), 6.84-6.92 (m, 3H); Anal. Calcd. for $C_{20}H_{34}O_5Si$: C, 62.79; H, 8.96. Found : C, 62.81; H, 8.95.

Aldehyde 7a : To a stirred solution of oxalyl chloride (140 µL, 1.6 mmol) in CH_2Cl_2 (5 mL) at -60 °C was added to solution of dry DMSO (230 µL), 3.29 mmol) in CH_2Cl_2 (50 mL) under Argon. After 10 min a solution of the alcohol **5a** (500 mg, 1.37 mmol) in CH_2Cl_2 (10 mL) was added dropwise and the reaction mixture was further stirred for 1 h at -60 °C. Then Et_3N (0.95 mL, 6.85 mmol) was added dropwise to the solution and stirred for another 1 h at room temperature. The reaction mixture was decomposed with water (5 mL) and diluted with CH_2Cl_2 (50 mL). the organic part was washed with 1N aqueous HCl solution (10 mL), brine and dried (Na_2SO_4). Removal of solvent afforded a deep yellow residue which was purified by passing through a short column of silica gel (25% ethyl acetate in petroleum ether) to give an unseparable isomeric mixture of aldehydes **6a** (440 mg, 88%) as a light yellow oil in a ratio of 2:1 (in ^1H NMR spectrum, the aldehyde proton for the major isomer appeared at δ 9.90 as a doublet, J=2.5 Hz and for the minor isomer at δ 9.78 as a doublet, J=2.5 Hz). The crude isomeric mixture of aldehydes was stirred with methanolic NaOMe for 2h at 0 °C under N_2 and left overnight in the freezer. Methanol was removed under reduced pressure and the residue was decomposed with water (5 mL) and extracted with Et_2O (3x10 mL). The organic layer was washed with brine and dried (Na_2SO_4). Removal of solvent under reduced pressure and column chromatography of the residue on silica gel afforded the aldehyde **7a** as a light yellow oil in quantitative yield. IR (Neat) ν_{max} 2960, 2940, 2900, 1730, 1610, 1510, 1490, 1400, 1360, 1250 cm^{-1}; ^1H NMR δ0.04 (s, 6H), 0.88 (s, 9H), 2.32-2.64 (m, 1H), 3.0-3.40 (m, 1H), 3.70 (dd, J=6 and 3 Hz, 2H), 4.0 (dd, J=9 and 8 Hz, 1H), 4.40 (dd, J=9 and 6 Hz, 1H), 4.60 (d, J=9 Hz, 1H), 5.96 (s, 2H), 6.72-6.92 (m, 3H), 9.78 (d, J=2.5 Hz, 1H); ^{13}C NMR δ 5.8, 17.9, 25.6, 51.1, 55.0, 61.4, 66,8, 82.7, 100.7, 106.4, 107.7, 119.6, 134.2, 147.0, 147.7, 200.1; Anal. Calcd. for $C_{19}H_{28}O_5Si$: C, 62.60; H, 7.74. Found : C, 62.83; H, 8.18.

Aldehyde 7b : **7b** was prepared by the procedure as described for **7a**. Initially the isomeric mixture of aldehydes **6b** was obtained in 91% yield in a ratio of 2:1 (in ^1H NMR spectrum, the aldehyde proton of the major isomer appeared at δ 9.91 as a doublet, J=3 Hz and for the minor isomer at δ 9.80 as a doublet, J=2.5 Hz) which on treatment with methanolic NaOMe afforded **7b** in quantitative yield. IR (Neat) ν_{max} 2980, 2960, 2880, 1730, 1620, 1600, 1530, 1480, 1430, 1400, 1270, 1250, 1170, cm^{-1}; ^1H NMR δ 0.06 (s, 6H), 0.90 (s, 9H), 2.40 - 2.68 (m, 1H), 3.0 - 3.48 (m

1H), 3.72 (dd, J=6 and 3 Hz, 2H), 3.88 (s, 3H), 3.90 (s, 3H), 4.02 (dd, J=9 and 8 Hz, 1H), 4.42 (dd, J=9 and 6 Hz, 1H), 4.64 (d, J=9 Hz, 1H), 6.76-6.98 (m, 3H), 9.80 (d, J=2.5 Hz, 1H); ^{13}C NMR δ -5.7, 18.0, 25.6, 51.1, 55.1, 55.7, 61.5, 66.9, 82.8, 109.3, 110.9, 118.7, 132.7, 148.7, 149.1, 200.4; Anal. Calcd. for $C_{20}H_{32}O_5Si$: C, 63.12; H, 8.48. Found : C, 62.79; H, 8.05.

Samin 1a : To a magnetically stirred solution of the pure aldehyde **7a** (250 mg, 0.69 mmol) in THF (5 mL) at 0 °C was added dropwise a solution of n-$Bu_4NF.3H_2O$ (538 mg, 2.06 mmol) in THF (5 mL) under N_2 during 5 min. The reaction mixture was further stirred for 6h at room temperature. THF was removed under reduced pressure, water (20 mL) was added to the residue and extracted with EtOAc (3x15 mL). Organic layer was washed with 10% aqueous NaOH solution (5 mL), brine and dried (Na_2SO_4). After evaporation of the solvent under reduced pressure, the residue obtained was column chromatographed over silica gel (40% ethyl acetate in petroleum ether) to furnish Samin **1a** (130 mg, 76%) as a crystalline solid, m.p. 108-109 °C (reported m.p. 106 °C). IR(KBr) ν_{max} 3420(br), 2940, 2900, 1610, 1510, 1500, 1450, 1350, 1270, 1250, 1220, 1100, 1070, 1030 cm^{-1}; ^{1}H NMR δ 2.81-2.95 (m, 1H), 3.0-3.12 (m, 1H), 3.25 (br s, 1H), 3.55 (dd, J=9 and 7.7 Hz, 1H), 3.91 (dd, J=9 and 1 Hz, 1H), 4.15 (dd, J=9 and 6.2 Hz, 1H), 4.35-4.45 (m, 2H), 5.38 (s, 1H), 5.95 (s, 2H), 6.75-6.95 (m, 3H); ^{13}C NMR δ 52.7, 53.6, 69.4, 71.1, 86.8, 100.9, 102.2, 106.5, 108.1., 119.5, 134.7, 147.2, 148.0.

Dimethoxy compound 1b : **1b** was prepared by the procedure as described for **1a** in 78% yield as a crystalline solid, m.p. 119-120 °C. IR(KBr) ν_{max} 3500(br), 3000, 2960, 2900, 1620, 1610, 1530, 1470, 1430, 1280, 1250, 1170, 1150, 1090, 1050, 1030, 990 cm^{-1}; ^{1}H NMR δ 2.80-3.24 (m, 3H, including -OH), 3.60 (dd, J=9 and 8 Hz, 1H), 3.88 (s, 3H), 3.90 (s, 3H), 3.91-4.0 (m, 1H), 4.20 (dd, J=9 and 6.5 Hz, 1H), 4.32-4.48 (m, 2H), 5.40 (s, 1H), 6.64-6.96 (m, 3H); ^{13}C NMR δ 52.3, 53.4, 55.7, 69.0, 71.0, 86.6, 101.9, 109.2, 111.0, 118.3, 132.9, 148.6, 149.0; Anal. Calcd. for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found : C, 63.13; H, 6.89.

Samin 1a from the isomeric mixture of aldehydes 6a : To a magnetically stirred solution of the mixture **6a** (230 mg, 0.63 mmol) in THF (5 mL) at 0 °C was added dropwise a solution of n-$Bu_4NF.3H_2O$ (495 mg, 1.89 mmol) in THF (5 mL) under N_2 during 5 min. The reaction mixture was further stirred for 6 h at room temperature. THF was removed under reduced pressure, water (20 mL) was added to the residue and extracted with EtOAc

(3x15 mL). The organic layer was washed with 10% aqueous NaOH solution (5 mL), brine and finally dried (Na_2SO_4). Solvent was removed under reduced pressure and the residue was purified by column chromatography over silica gel (40% ethyl acetate in petroleum ether) to afford **1a** (125 mg, 80%).

Compound 1b from the isomeric mixture of aldehydes 6b : 1b was prepared from **6b** by the procedure as described for **1a** from **6a** in 81% yield.

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