A CONVENIENT METHOD FOR THE SYNTHESIS OF 9-ARYL-4-METHOXYNAPHTHO[2,3-*c*]FURAN-1(3*H*)-ONES

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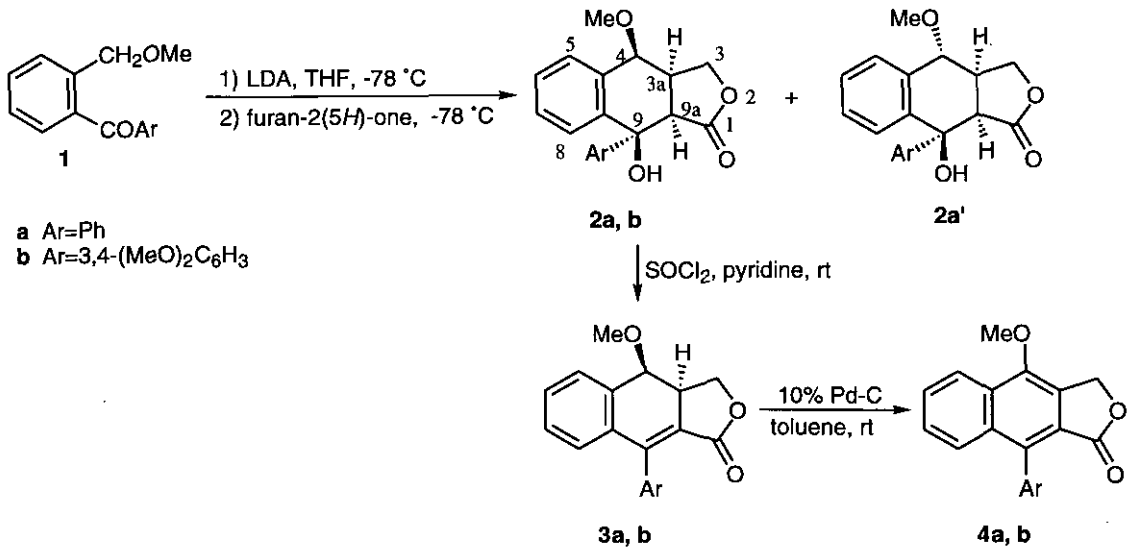
Abstract- A three-step procedure for the synthesis of the title lignan lactone derivatives is described. The route involves a tandem Michael addition/cyclization reaction between *o*-aroyl-α-methoxybenzyllithiums, which are generated *in situ* by the treatment of aryl 2-methoxymethylphenyl ketones with lithium diisopropylamide (LDA) in THF at -78 °C, and furan-2(5*H*)-one to give the corresponding 9-aryl-9-hydroxy-4-methoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-ones in moderate to good yields. These products are readily transformed into the title naphthofuranones by dehydration with thionyl chloride in pyridine, followed by aromatization with palladium on activated carbon.

In our previous paper,[1] we have described a simple method for the synthesis of 9-arylnaphthofuranone lignan derivatives {9-arylnaphtho[2,3-*c*]furan-1(3*H*)-ones}, including a natural product, such as collinusin, and deoxydimethylretrodendrin. The key step in our procedure is a tandem Michael addition/cyclization between *o*-aroylbenzyllithiums, derived from aryl 2-methylphenyl ketones, and furan-2(5*H*)-one followed by the sequential dehydration/aromatization. We report here that this method can be applied to the preparation of 9-aryl-4-methoxynaphtho[2,3-*c*]furan-1(3*H*)-ones by using *o*-aroyl-α-



methoxybenzyllithiums derived from aryl 2-methoxymethylphenyl ketones with furan-2(5*H*)-one.[2]

Our sequence is outlined in the Scheme. Deprotonation of 2-methoxymethylphenyl phenyl ketone (**1a**) with 2 equivalents of lithium diisopropylamide (LDA)[4] in THF at -78 °C generated the corresponding α-lithiated product, *o*-benzoyl-α-methoxybenzyllithium, which was treated with furan-2(5*H*)-one to afford the Michael addition/cyclization products. Two of the possible eight diastereomers (**2a**) and (**2a'**) were isolated from the reaction mixture in 43 and 9% yields, respectively, by purification using preparative TLC on silica gel. The *cis*-configuration of 3a-H and 9a-H was confirmed on the basis of a NOE experiment. Thus, irradiation of the signal at δ 3.55-3.65 due to 3a-H resulted in enhancements of the signals at δ 3.35 due to 9a-H and at 4.87 due to 4-H. This result indicates the *cis*-configuration of 3a-H and 4-H as well. The relative stereochemistry between C-9 and C-9a was determined on the basis of the IR spectrum, which showed an absorption band at 1732 cm^{-1} assignable to the lactone carbonyl group, in a similar manner as described previously.[1] This considerable decrease in wavenumber is probably attributable to the hydrogen bonding between the carbonyl and 9-OH groups, and indicates that they are *cis*-orientated. The stereochemistry of **2a'** was also established on the basis of a NOE experiment and IR spectra. An enhancement was observed between the signals at δ 3.3-3.45 due to 3a-H and δ 3.84 due to 9a-H, but no enhancement was observed between the signals at δ 3.3-3.45 due to 3a-H and δ 3.88 due to 4-H. The IR spectra exhibited a band at 1742 cm^{-1}, which indicates the presence of hydrogen bonding. The reaction of *o*-3,4-dimethoxybenzoyl-α-

methoxybenzyllithium, derived from 3,4-dimethoxyphenyl 2-methoxymethylphenyl ketone (**1b**), with furan-2(5*H*)-one was conducted similarly to give the product (**2b**) in 56% purified yield, the stereochemistry of which was assigned by a comparison of its spectral data with those of **2a**, and none of the other diastereomers could be isolated in synthetically significant quantities. Although we have no firm explanation at this point, it can be assumed that the selective formation of these *cis*-fused products is attributable to the thermodynamic stability of their lithium alkoxides over those of the corresponding *trans*-fused products,[1] and that the high selectivity may be ascribed to a repulsive force between the 4-methoxy group and the lactone ring.

The 9-aryl-9-hydroxy-4-methoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-ones (**2a**) and (**2b**) thus obtained were readily converted into the corresponding 9-aryl-4-methoxy-3a,4-dihydronaphtho[2,3-*c*]furan-1(3*H*)-ones (**3a**) and (**3b**) in good yields of 86 and 78%, respectively, by treatment with thionyl chloride in pyridine at room temperature.

Subsequent dehydrogenation of **3** was first carried out at higher temperature. We have found that, when a solution of **3a** in toluene containing a catalytic amount of 10% palladium on activated carbon was heated at reflux temperature for 3 h, undesired elimination of methanol occurred in competition with dehydrogenation to give the desired 4-methoxy-9-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (**4a**) along with 9-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one[1,5] as an inseparable mixture (*ca.* 1:1). Next, the dehydrogenation of **3a** was conducted at room temperature so as to prevent the elimination of methanol. Although rather slow, the reaction was very clean and gave an almost quantitative yield of the desired product (**4a**) after stirring overnight. In contrast, the dihydronaphthofuranone (**3b**) was more susceptible to the elimination of methanol than **3a**; it gave the desired 9-aryl-4-methoxynaphthofuranone (**4b**) in 75% yield along with the demethoxylated product, 9-(3,4-dimethoxyphenyl)naphtho[2,3-*c*]furan-1(3*H*)-one (23%),[1,6] even when the dehydrogenation was carried out at room temperature.

Some products having a 9-aryl-4-oxynaphtho[2,3-*c*]furan-1(3*H*)-one skeleton have been found in nature.[7] The present construction of this system may found some value in synthesis.

EXPERIMENTAL SECTION

All procedures, analytical techniques and instruments employed were as previously described.[1]

2-Methoxymethyl-α-phenylbenzyl Alcohol. To a stirred solution of 1-bromo-2-methoxymethylbenzene (1.5 g, 7.5 mmol; readily prepared according to the procedure reported by Khanapure and Biehl[3]) in dry Et_2O (50 mL) at 0 °C under argon was added *n*-BuLi (1.6 M in hexane, 15 mmol), and the resulting mixture was refluxed for 1 h. After cooling to 0 °C, a solution of PhCHO (0.71 g, 6.7 mmol) in Et_2O (12 mL) was added dropwise to the resulting suspension of 1-lithio-2-methoxymethylbenzene. After stirring overnight at rt, the mixture was poured into 1 N H_2SO_4. The organic layer was separated, washed with brine, and dried over anhydrous $MgSO_4$. The solvent and unreacted PhCHO were removed under reduced pressure to give a residue, which was purified by preparative TLC on silica gel to give the alcohol (1.4 g, 80%) as a colorless liquid; R_f 0.35 (1:3 EtOAc-hexane); IR (neat) 3392 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 3.33 (s, 3H), 3.89 (d, *J*=5.2 Hz, 1H), 4.28 (d, *J*=11 Hz, 1H), 4.38 (d, *J*=11 Hz, 1H), 6.00 (d, *J*=5.2 Hz, 1H), 7.2-7.35 (m, 9H). Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.92; H, 7.07.

2-Methoxymethylphenyl Phenyl Ketone (1a). To a stirred solution of the above alcohol (2.7 g, 12 mmol) in CH_2Cl_2 (300 mL) containing Celite® (5.0 g) at rt was added PCC (7.5 g, 35 mmol) in portions, and the mixture was stirred for 1 h at the same temperature. After removal of Celite® by filtration, the filtrate was washed with 5% aq. HCl three times and then brine once, and dried over anhydrous $MgSO_4$. Evaporation of the solvent and purification of the residue by preparative TLC on silica gel (R_f 0.54, 1:3 EtOAc-hexane) gave crude **1a** (2.5 g), which was distilled by using Kugelrohr to give pure **1a** (2.1 g, 77%) as a yellow liquid; bp 190 °C (bath temp)/0.15 Torr; IR (neat) 1667 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 3.21 (s, 3H), 4.46 (s, 2H), 7.2-7.85 (m, 9H). Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.60; H, 6.24.

3,4-Dimethoxy-α-(2-methoxymethylphenyl)benzyl Alcohol. This compound was obtained from 1-bromo-2-methoxymethylbenzene and 3,4-dimethoxybenzaldehyde by the same procedure described above for the preparation of 2-methoxymethyl-α-phenylbenzyl alcohol in 83% yield as a yellow liquid; R_f 0.10 (1:3 EtOAc-hexane); IR (neat) 3407 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 3.36 (s, 3H), 3.55-3.75 (m

including 2s at 3.63, 3.69, combined 7H), 4.23 (s, 2H), 5.71 (d, *J*=2.8 Hz, 1H), 6.6-6.75 (m, 2H), 7.05-7.3 (m, 5H). Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.84; H, 6.95.

3,4-Dimethoxyphenyl 2-Methoxymethylphenyl Ketone (1b). This compound was obtained from the above alcohol by the same procedure described above for the preparation of **1a** in 68% yield as yellow liquid; R_f 0.20 (1:3 EtOAc-hexane); bp 190 °C (bath temp)/0.1 Torr; IR (neat) 1652 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 3.22 (s, 3H), 3.90 (s, 6H), 4.47 (s, 2H), 6.78 (d, *J*=7.8 Hz, 1H), 7.1-7.55 (m, 6H). Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.09; H, 6.28.

(3a*S,4*R**,9*S**,9a*R**)-9-Hydroxy-4-methoxy-9-phenyl-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one (2a) and (3a*S**,4*S**,9*S**,9a*R**)-9-Hydroxy-4-methoxy-9-phenyl-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one (2a').** To a stirred solution of LDA (13 mmol) in THF (40 mL) at -78 °C under argon, which was generated by the standard method, was added dropwise a solution of **1a** (1.5 g, 6.5 mmol) in THF (30 mL). After 5 min, furan-2(5*H*)-one (1.1 g, 13 mmol) was added to the resulting deep red mixture. The deep red color faded gradually in 30 min. The resulting mixture was quenched by adding aq saturated NH_4Cl and extracted with Et_2O. The extract was washed with brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by preparative TLC on silica gel to afford **2a** (0.82 g, 43%) and **2a'** (0.17 g, 9%) each as a white solid. **2a**; R_f 0.08 (1:3 EtOAc-hexane); mp 175-176 °C (CH_2Cl_2); IR (KBr disk) 3398, 1732 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.35 (d, *J*=10.2 Hz, 1H), 3.44 (s, 3H), 3.55-3.65 (m, 1H), 4.10 (dd, *J*=9.1, 7.6 Hz, 1H), 4.31 (dd, *J*=9.1, 8.7 Hz, 1H), 4.87 (d, *J*=5.8 Hz, 1H), 5.16 (s, 1H), 7.25-7.45 (m, 8H), 7.56 (d, *J*=8.0 Hz, 1H); MS *m/z* (%) 292 [$(M-H_2O)^+$, 0.59], 260 (100). Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.39; H, 5.90.

2a'; R_f 0.16 (1:3 EtOAc-hexane); mp 141-143 °C (hexane-CH_2Cl_2); IR (KBr disk) 3428, 1742 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.3-3.45 (m including s at 3.34, 4H), 3.84 (d, *J*=10.6 Hz, 1H), 3.88 (d, *J*=6.6 Hz, 1H), 4.28 (dd, *J*=9.6, 8.3 Hz, 1H), 4.45 (dd, *J*=9.6, 3.0 Hz, 1H), 5.64 (s, 1H), 7.25-7.5 (m, 8H), 7.75-7.8 (m, 1H); MS *m/z* (%) 310 (M^+, 0.37), 292 (27), 260 (100). Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.55; H, 5.65.

(3a*S,4*R**,9*S**,9a*R**)-9-(3,4-Dimethoxyphenyl)-9-hydroxy-4-methoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one (2b)**. This compound was obtained from **1b** by the same procedure described above for the preparation of **2a** and **2a'** in 56% yield as a pale yellow solid; R_f 0.03 (1:2 EtOAc-hexane); mp 156-157 °C (hexane-Et_2O); IR (KBr disk) 3380, 1732 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 3.33 (d, *J*=10.6 Hz, 1H), 3.44 (s, 3H), 3.5-3.6 (m, 1H), 3.81 (s, 3H), 3.88 (s, 3H), 4.09 (dd, *J*=9.2, 7.4 Hz, 1H), 4.30 (dd, *J*=9.2, 8.6 Hz, 1H), 4.85 (d, *J*=5.6 Hz, 1H), 6.83 (d, *J*=8.2 Hz, 1H), 6.94 (dd, *J*=8.2, 2.3 Hz, 1H), 7.3-7.45 (m, 4H), 7.54 (d, *J*=7.9 Hz, 1H); MS *m/z* 370 (M^+, 0.59), 352 (15), 320 (100). Anal. Calcd for $C_{21}H_{22}O_6$: C, 68.10; H, 5.99. Found: C, 68.02; H, 5.96.

(3a*R,4*S**)-4-Methoxy-9-phenyl-3a,4-dihydronaphtho[2,3-*c*]furan-1(3*H*)-one (3a).** To a stirred solution of **2a** (0.25 g, 0.90 mmol) in pyridine (10 mL) at rt was added $SOCl_2$ (0.13 g, 1.0 mmol). After stirring for 1 h, the solvent was removed under reduced pressure. The residual solid was purified by recrystallization to give **3a** (0.23 g, 86%) as a pale yellow solid; mp 146-148 °C (hexane-CH_2Cl_2); IR (KBr disk) 1749 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.22 (s, 3H), 3.63 (ddd, *J*=9.4, 9.1, 4.4 Hz, 1H), 4.13 (d, *J*=4.4 Hz, 1H), 4.59 (dd, *J*=9.4, 8.3 Hz, 1H), 4.65 (dd, *J*=9.1, 8.3 Hz, 1H), 7.06 (d, *J*=7.3 Hz, 1H), 7.25-7.5 (m, 8H); MS *m/z* 292 (M^+, 16), 260 (100). Anal. Calcd for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 77.76; H, 5.67.

(3a*R,4*S**)-9-(3,4-Dimethoxyphenyl)-4-methoxy-3a,4-dihydronaphtho[2,3-*c*]furan-1(3*H*)-one (3b).** This compound was obtained from **2b** by the same procedure described above for the preparation of **3a** in 78% yield as a pale yellow solid; mp 159-160 °C (hexane-Et_2O); IR (KBr disk) 1753 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.24 (s, 3H), 3.62 (ddd, *J*=9.5, 9.0, 4.2 Hz, 1H), 3.86 (s, 3H), 3.93 (s, 3H), 4.11 (d, *J*=4.2 Hz, 1H), 4.58 (dd, *J*=9.5, 8.4 Hz, 1H), 4.66 (dd, *J*=9.0, 8.4 Hz, 1H), 6.85-6.95 (m, 3H), 7.1-7.15 (m, 1H), 7.25-7.4 (m, 3H); MS *m/z* 352 (M^+, 39), 320 (100). Anal. Calcd for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found: C, 71.50; H, 5.64.

4-Methoxy-9-phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (4a).[8] A solution of **3a** (0.10 g, 0.34 mmol) in toluene (10 mL) containing 10% Pd-C (0.18 g) was stirred overnight at rt. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by

preparative TLC to give **4a** (0.10 g, quantitative) as a pale-yellow solid; R_f 0.28 (1:2-EtOAc-hexane); mp 196-197 °C (hexane-$CHCl_3$) (lit.,[8] 194-196 °C); IR (KBr disk) 1759 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.17 (3H, s), 5.60 (2H, s), 7.2-7.3 (7H, m), and 7.5-7.55 (2H, m); MS *m/z* 290 (M^+, 100).

9-(3,4-Dimethoxyphenyl)-4-methoxynaphtho[2,3-*c*]furan-1(3*H*)-one (4b).[9] This compound was obtained from **3b** by the same procedure described for the preparation of **3a** in 75% yield as a pale-yellow solid; R_f 0.28 (1:2-EtOAc-hexane); mp 224-225 °C (hexane-$CHCl_3$) (lit.,[9] 225-226 °C). The spectral data (IR, ^1H NMR, and MS) were consistent with those reported previously.[9]

ACKNOWLEDGEMENTS

We thank Mrs. Miyuki Tanmatsu of this Department for determining the mass spectra.

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Received, 22nd May, 1997