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Total Synthesis of a Norneolignan from *Ratanhia* Radix

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The total synthesis of a norneolignan isolated from *Ratanhia*, 5-(3-hydroxypropyl)-2-(2'-methoxy-4'-hydroxyphenyl)benzofuran (**8**), is described. The key steps contain the one-pot reaction for a 2-arylbenzofuran **6** from methyl 3-(4-hydroxyphenyl)propionate with 2-chloro-2-methylthio-(2'-methoxy-4'-acetoxy)acetophenone (**5**) in the presence of $ZnCl_2$, and reductive desulfurization of the resulting product **6**.

Key words: Norneolignan, *Ratanhia*, 5-(3-Hydroxypropyl)-2-(2'-methoxy-4'-hydroxyphenyl)benzofuran, 2-Arylbenzofuran, Methyl 3-(4-hydroxyphenyl)propionate, 2-Chloro-2-methylthio-(2'-methoxy-4'-acetoxy)acetophenone, $ZnCl_2$, Desulfurization

INTRODUCTION

5-(3-Hydroxypropyl)-2-(2'-methoxy-4'-hydroxyphenyl)benzofuran (**8**) is a norneolignan isolated in 1988 from *Ratanhia* radix, being effective as an antibacterial agent. The structure of **8** was assigned through examination of its UV, ^1H and ^{13}C NMR, and mass spectral characteristics (Arnone *et al.*, 1988).

As part of our research for the carbon-carbon bond formation by using 1-acyl-1-thiocarbocations, we recently reported that the one-pot reaction of substituted phenols with 1-acyl-1-chlorosulfides in the presence of Lewis acid afforded 2-arylbenzofuran moiety (Choi *et al.*, 1999 and Seo *et al.*, 2000).

Also, our method for the construction of 2-arylbenzofuran ring was applied to the total synthesis of a naturally occurring demethoxy egonol (Choi *et al.*, 2000), isolated from *Styrax obassia* (Takanishi *et al.*, 1974).

In this paper, we present the details of our work on the first total synthesis of a norneolignan **8** isolated from *Ratanhia* radix (Arnone *et al.*, 1988).

MATERIALS AND METHODS

Melting points were determined on a Gallenkamp capillary melting point apparatus and uncorrected. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained on a JEOL JNM-ECP 400 NMR spectrometer, using TMS as an internal standard. IR spectra were recorded on a JASCO FT/IR-300E spectrometer. MS spectra were obtained on a Hewlett Packard 5973 GC/MS system.

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3-(*p*-Toluenesulfonyloxy)anisole (1)

A mixture of 3-methoxyphenol (2.48 g, 20 mmol), *p*-toluenesulfonyl chloride (3.81 g, 20 mmol), and K_2CO_3 (4.15 g, 30 mmol) in acetone (50 mL) was refluxed for 6 h. The inorganic materials were removed by filtration and the solvent was evaporated off. The residual solid was recrystallized from isopropanol to give **1** (4.96 g, 89%) as a white solid. mp 59-60°C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.71 (s, 3H), 6.53-6.56 (m, 2H), 6.76-6.79 (m, 1H), 7.13-7.18 (m, 1H), 7.30 (d, J = 8.16 Hz, 2H), 7.71 (d, J = 8.16 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.612, 55.357, 108.172, 112.949, 114.218, 128.428, 129.657, 129.795, 132.353, 145.287, 150.403, 160.321; IR (KBr) 3085, 2954, 2833, 1590, 1489, 1365, 1264, 1181, 1126, 1085 cm^{-1}; MS m/z 278 (M^+), 214, 199, 186, 171, 155, 139, 128, 91 (base peak), 80, 65, 52.

2-Methylthio-[2'-methoxy-4'-(*p*-tolylsulfonyloxy)] acetophenone (2)

$SnCl_4$ (3.9 g, 15 mmol) was added to a stirred solution of α-(methylthio)acetyl chloride (2.9 g, 16 mmol) and **1** (4.17 g, 15 mmol) in 1,2-dichloroethane (30 mL) at 0°C under Ar atmosphere, and stirring was continued at the same temperature for 1 h. The reaction was quenched by the

addition of water and the organic layer was separated. The aqueous layer was extracted with methylene chloride (20 mL×2), and the combined extracts dried over anhydrous $MgSO_4$. After the removal of solvent *in vacuo*, the residue was chromatographed on silica gel using hexane/ethyl acetate (2/1) to give **2** (3.46 g, 63%) as a high viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 3H), 2.45 (s, 3H), 3.66 (s, 2H), 3.76 (s, 3H), 6.62 (d, *J* = 2.40 Hz, 1H), 6.85 (dd, *J* = 8.24 Hz and *J* = 2.40 Hz, 1H), 7.33 (d, *J* = 8.48 Hz, 2H), 7.77 (d, *J* = 8.36 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.431, 21.613, 42.842, 55.633, 108.402, 112.929, 123.679 128.402, 129.894, 131.608, 132.373, 146.034, 148.448, 163.142, 192.719; IR (neat) 3659, 3336, 2924, 2845, 1675 (CO), 1605, 1498, 1376, 1273, 1187, 1092, 1038 cm^{-1}; MS m/z 366 (M$^+$), 305 (base peak), 291, 256, 225, 198, 183, 155, 139, 107, 91, 79, 61.

2-Methylthio-(2'-methoxy-4'-hydroxy)acetophenone (3)

A solution of **2** (4.76 g, 13 mmol) in 10% KOH (50 ml) and methanol (50 mL) was refluxed for 3 h, then cooled. The solution was washed with methylene chloride (30 mL). The aqueous layer was acidified to pH 3 with *c*-HCl, extracted with methylene chloride (30 mL×2), and dried over anhydrous $MgSO_4$. After the removal of solvent *in vacuo*, the residual solid was recrystallized from diisopropyl ether to give **3** (2.48 g, 90%) as a white solid. mp 56-57°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 3H), 3.70 (s, 2H), 3.84 (s, 3H), 6.43-6.47 (m, 2H), 7.63 (dd, *J* = 6.0 Hz and *J* = 1.68 Hz, 1H), 12.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.082, 38.708, 55.580, 101.086, 107.845, 111.802, 131.943, 166.104, 166.316, 198.859; IR (KBr) 3235 (OH), 3084, 2981, 2948, 1631 (CO), 1450, 1349, 1261, 1210, 1123, 1017 cm^{-1}; MS m/z 212 (M$^+$), 197, 166, 151 (base peak) 137, 108, 95, 79, 61.

2-Methylthio-(2'-methoxy-4'-acetoxy)acetophenone (4)

Acetyl chloride (942 mg, 12 mmol) was added to a stirred solution of **3** (2.55 g, 12 mmol) in pyridine (10 mL) at 0 °C, and stirring was continued at room temperature for 30 min. The reaction was quenched by the addition of 1 M HCl (50 mL), extracted with methylene chloride (20 mL×2), and dried over anhydrous $MgSO_4$. The solvent was evaporated off, and the residual solid was recrystallized from diisopropyl ether to give **4** (2.69 g, 88%) as a white solid. mp 70-71°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.11 (s, 3H), 2.36 (s, 3H), 3.67 (s, 2H), 3.85 (s, 3H), 6.65 (d, *J* = 2.44 Hz, 1H), 6.83 (dd, *J* = 6.24 Hz and *J* = 2.60 Hz, 1H), 7.88 (d, *J* = 8.84 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.631 21.208, 41.529, 55.690, 109.532, 111.652, 120.929, 132.583, 151.860, 163.854, 169.173, 191.899; IR (KBr) 3481, 3331, 2978, 2914, 1753 (CO), 1679, 1612, 1422, 1299, 1210, 1129, 1019 cm^{-1}; MS m/z 254 (M$^+$), 236, 208, 193, 175, 151 (base peak), 137, 129, 108, 95, 79, 61.

2-Chloro-2-methylthio-(2'-methoxy-4'-acetoxy)acetophenone (5)

N-Chlorosuccinimide (1.34 g, 10.0 mmol) was added to a stirred solution of **4** (2.54 g, 10.0 mmol) in carbon tetrachloride (30 mL) in small portions at 0°C, and stirring was continued at room temperature for 10 h. The precipitated succinimide was filtered off and the solvent was removed *in vacuo*. The residual oil **5** was used without further purification. Yield 75% (2.16 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.21 (s, 3H), 2.37 (s, 3H), 3.88 (s, 3H), 6.24 (s, 1H), 6.64 (d, *J* = 2.45 Hz, 1H), 6.82 (dd, *J* = 6.22 Hz and *J* = 2.53 Hz, 1H), 7.87 (d, *J* = 8.82 Hz, 1H).

Methyl 3-[2-(2'-methoxy-4'-acetoxyphenyl)-3-(methylthio)benzofuran-5-yl]propionate (6)

$ZnCl_2$ (818 mg, 6.0 mmol) was added to a stirred solution of methyl 3-(4-hydroxyphenyl)propionate (900 mg, 5.0 mmol) and **5** (1.73 g, 6.0 mmol) in methylene chloride (30 mL) at 0°C under Ar atmosphere, and stirring was continued at the same temperature for 1 h. The reaction was quenched by the addition of water and the organic layer was separated. The aqueous layer was extracted with methylene chloride (10 mL×2), and the combined extracts were dried over anhydrous $MgSO_4$. and concentrated under reduced pressure. The residue was purified column chromatography (benzene/acetone=9/1) to give **6** (1.28 g, 62%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H), 2.29 (s, 3H), 2.70 (t, *J* = 7.96 Hz, 2H), 3.09 (t, *J* = 7.92 Hz, 2H), 3.68 (s, 3H), 3.85 (s, 3H), 6.76 (d, *J* = 2.44 Hz, 1H), 6.91 (dd, *J* = 6.12 Hz and *J* = 2.56 Hz, 1H), 7.16 (dd, *J* = 6.48 Hz and *J* = 1.84 Hz, 1H), 7.37 (d, *J* = 8.48 Hz, 1H), 7.52 (d, *J* = 1.36 Hz, 1H), 7.81 (d, *J* = 8.96 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.212, 20.924, 30.904, 36.267, 51.564, 55.519, 108.956, 111.013, 111.787, 115.391, 119.194, 125.272, 128.255, 130.173, 132.124, 135.489, 149.563, 152.831, 153.749, 161.249, 169.060, 173.220; IR (neat) 3013, 2942, 2844, 1742 (CO), 1616, 1459, 1362, 1199, 1028 cm^{-1}; MS m/z 414 (M$^+$), 372 (base peak), 357, 325, 283, 265, 237, 209, 165, 139, 115, 102, 69.

Methyl 3-[2-(2'-methoxy-4'-acetoxyphenyl)benzofuran-5-yl]propionate (7)

Compound **6** (1.04 g, 2.50 mmol) was heated under reflux for 2 h in ethanol (100 mL) containing Raney nickel (W-2, ca. 4 g). The Raney nickel was removed by filtration and the solvent was evaporated off. The residual solid was recrystallized from ethanol to give **7** (865 mg, 92%) in white solid. mp 125-126°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.68 (t, *J* = 7.52 Hz, 2H), 3.04 (t, *J* = 7.64 Hz, 2H), 3.67 (s, 3H), 3.85 (s, 3H), 6.73 (d, *J* = 2.52 Hz,

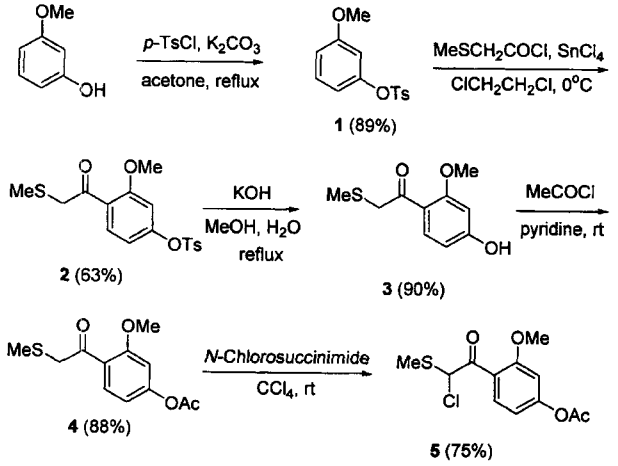
1H), 6.85 (s, 1H), 6.89 (dd, J = 6.28 Hz and J = 2.64 Hz, 1H), 7.10 (dd, J = 6.76 Hz and J = 1.64 Hz, 1H), 7.38-7.40 (m, 2H), 7.88 (d, J = 8.76 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.357, 30.901, 36.317, 51.608, 55.576, 103.345, 109.086, 110.746, 112.399, 116.241, 120.157, 124.654, 128.781, 129.376, 135.149, 148.284, 152.292, 152.993, 160.380, 168.925, 173.389; IR (KBr) 3132, 3075, 2996, 2946, 1734 (CO), 1611, 1435, 1376, 1281, 1211, 1119, 1037 cm^{-1}; MS m/z 368 (M^+), 337, 326 (base peak), 311, 295, 253, 209, 181, 165, 139, 115, 89, 77, 63.

5-(3-Hydroxypropyl)-2-(2'-methoxy-4'-hydroxyphenyl) benzofuran (8)

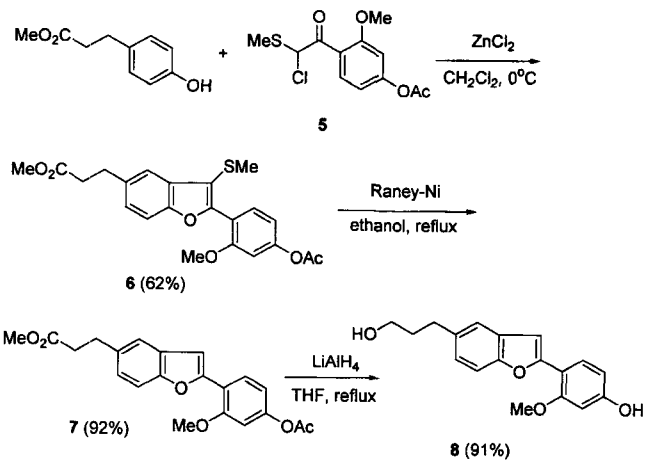
A solution of **7** (442 mg, 1.20 mmol) in tetrahydrofuran (20 mL) was added to a stirred solution of $LiAlH_4$ (114 mg, 3 mmol) in tetrahydrofuran (20 mL) at room temperature under Ar atmosphere. The reaction mixture was refluxed for 5 h. The mixture was quenched by the addition of water (30 mL) and 10% H_2SO_4 (30 mL), extracted with ethyl acetate (30 mL × 2). The extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residual soild was recrystallized from chloroform to give **8** (325 mg, 91%) as white solid. mp 139-141°C (lit. 143-145 °C, Arnone *et al.*, 1988); ^{1}H NMR (400 MHz, acetone-d_6) δ 1.80-1.85 (m, 2H), 2.73 (t, J = 7.56 Hz, 2H), 3.55 (t, J = 6.53 Hz, 2H), 3.76 (s, 3H), 3.81 (s, 1H), 6.55-6.58 (m, 2H), 7.06 (dd, J = 6.52 Hz and J = 1.84 Hz, 1H), 7.20 (s, 1H), 7.34 (br s, 1H), 7.36-7.38 (m, 1H), 7.81 (dd, J = 6.64 Hz and J = 1.20 Hz, 1H), 9.22 (s, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 33.207, 36.566, 56.064, 62.257, 103.241, 104.941, 106.994, 111.336, 112.212, 121.354, 125.581, 128.817, 131.479, 138.161, 153.594, 154.515, 157.049, 162.280; IR (KBr) 3370 (OH), 3192, 2933, 2845, 1609, 1507, 1451, 1287, 1128, 1042 cm^{-1}; MS m/z 298 (M^+, base peak), 283, 269, 254, 239, 225, 209, 181, 165, 139, 127, 115, 97, 77, 63.

RESULTS AND DISCUSSION

As shown in Scheme 1, we designed the preparation of 1,2,4-trisubstituted benzene **4** starting from 3-methoxyphenol. The tosylate **1** was obtained from the reaction of 3-methoxyphenol and *p*-toluenesulfonyl chloride with K_2CO_3 in 89% yield. Friedel-Crafts acylation of **1** with α-(methylthio)acetyl chloride (Mooradian *et al.*, 1949) in the presence of $SnCl_4$ afforded 2-methylthio-[2'-methoxy-4'-(*p*-toluenesulfonyloxy)]acetophenone (**2**) in 63% yield. The phenol **3** was obtained from alkaline hydrolysis of **2** in 90% yield. The O-acylation of **3** with acetyl chloride gave the ester **4** in 88% yield. The chloride **5** was prepared from **4** by the chlorination with N-chlorosuccinimide according to the procedure described by Bohme and Krack in 1977, and **5** was used without further purification in the next step.



Scheme 1. Synthetic route of 2-chloro-2-methylthio-(2'-methoxy-4'-acetoxy) acetopenone (**5**)



Scheme 2. Synthetic route of 5-(3-hydroxypropyl)-2-(2'-methoxy-4'-hydroxyphenyl)benzofuran (**8**)

The one-pot reaction of methyl 3-(4-hydroxyphenyl)propionate and the chloride **5** in the presence of $ZnCl_2$ gave methyl 3-[2-(2'-methoxy-4'-acetoxyphenyl)-3-(methylthio)benzofuran-5-yl]propionate (**6**) in 62% yield. The structure of **6** was assigned on the basis of spectroscopic evidence.The IR spectrum of **6** revealed absorption band for ketone (1742 cm^{-1}). The ^{1}H NMR spectral data for **6** showed the presence of 22 protons, and the ^{13}C NMR spectrum displayed signals due to 16 sp^2- and 6 sp^3-hybridized carbon atoms.

The reductive desulfurization of **6** with Raney nickel in ethanol gave methyl 3-[2-(2'-methoxy-4'-acetoxyphenyl)benzofuran-5-yl]propionate (**7**) in 92% yield. Finally the desired norneolignan, 5-(3-hydroxypropyl)-2-(2'-methoxy-4'-hydroxyphenyl)benzofuran (**8**), was obtained by the reduction of the diester **7** with excess $LiAlH_4$ in a high yield. The mp, ^{1}H and ^{13}C NMR data for **8** were in good agreement

with those reported by Arnone *et al.*, 1988.

Many procedures have been reported for the preparation of 2-arylbenzofuran ring. Among them, the route through the coupling of an *o*-halogenophenol with a copper (I) arylacetylide seems to be the useful method (Lutjens and Scammells, 1998; Schreiber and Stevenson, 1976). However, the above method utilizing stoichiometric amounts of copper proved difficult to scale up.

In summary, the total synthesis of a norneolignan **8** isolated from *Ratanhia* radix was accomplished by one-pot reaction of methyl 3-(4-hydroxyphenyl)propionate and chloride **5** under Friedel-Crafts reaction condition and reductive desulfurization of the resultant product **6**, as the key steps. Now our investigation for synthetic application of other natural products possessing 2-arylbenzofuran moiety is in progress.

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