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Total Synthesis of a Demethoxy-egonol from *Styrax obassia*

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The total synthesis of a demethoxy-egonol isolated from *Styrax obassia*, 5-(3-hydroxypropyl)-2-(3',4'-methylenedioxyphenyl)benzofuran (**9**), is described. The key steps involve the construction of a 2-arylbenzofuran skeleton **7** from methyl 3-(4-hydroxyphenyl)propionate with 2-chloro-2-methylthio-(3',4'-methylenedioxy)acetophenone (**6**) in the presence of $ZnCl_2$ and successive desulfurization of the resulting product **7**.

Key words: Demethoxy-egonol, *Styrax obassia*, 5-(3-Hydroxypropyl)-2-(3',4'-methylenedioxyphenyl)benzofuran, 2-Arylbenzofuran skeleton, Methyl 3-(4-hydroxyphenyl)propionate, 2-Chloro-2-methylthio-(3',4'-methylenedioxy)acetophenone, $ZnCl_2$, Desulfurization

INTRODUCTION

A number of the constituents isolated from *Krameria ramosissima* (Achenbach *et al.*, 1987), *Myroxylon balsamum* (Oliveria *et al.*, 1978), *Sophora tomentosa* (Komatsu *et al.*, 1978), and *Styrax obassia* (Takanashi *et al.*, 1974), are well-known natural products bearing a 2-arylbenzofuran skeleton.

Of the several methods available for the preparation of the 2-arylbenzofuran ring, the route via the coupling reaction between an *o*-halogenophenol and a copper(I) arylacetylide was used for the key step of the synthesis of a demethoxy-egonol **9** (Schreiber and Stevenson 1976).

We recently reported that one-pot reaction of substituted phenols with the chloride **1** in the presence of Lewis acid afforded 2-methylbenzofurans (Choi *et al.*, 1998 and 1999) and 2-phenylbenzofurans (Choi *et al.*, 1999). As shown in scheme 1, our method for the construction of a benzofuran ring **3** could be proceeded by successive dehydrocyclization of Friedel-Crafts reaction intermediates **2,** prepared from substituted phenols with the chloride **1** in the presence of Lewis acid.

In this paper the method is applied to the total synthesis of the naturally occuring demethoxy-egonol (**9**), isolated from *Styrax obassia* (Takanashi *et al.*, 1974), a congener of which is used in the treatment of asthma and rheumatism (Schneiders and Stevenson, 1979).

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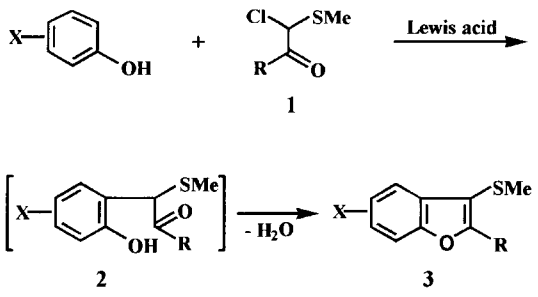
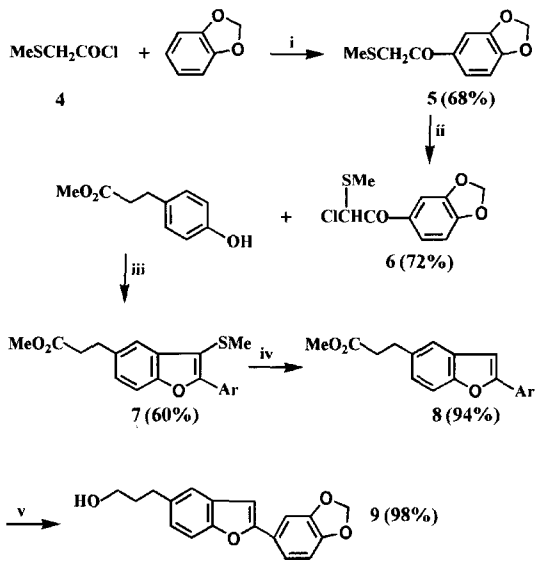
MATERIALS AND METHODS

All reagents and solvents were obtained from commercial suppliers, and used without further purification. Thin layer chromatography was carried out on a Merck silica gel 60 F_{254} and column chromatography was performed using silica gel 60 (70-230 mesh, Merck). Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 60 MHz with a Hitachi R-1500 FT NMR spectrometer using tetramethylsilane as an internal standard. IR spectra were recorded on a JASCO FT IR-300E spectrometer. Mass spectra were measured at 70eV with a Hewlett Packard 5970 GC/MS system by electron impact method. Elemental analyses were performed by an Elementar



X = alkyl; R = methyl or phenyl.

Scheme 1. Synthesis of 2-substituted benzofurans



Scheme 2. Synthesis of 5-(3-hydroxypropyl)-2-(3',4'-methylenedioxyphenyl)benzofuran (**9**)

Vario EL apparatus.

2-Methylthio-(3',4'-methylenedioxy)acetophenone (5)

$SnCl_4$ (9.64 g, 0.037 mol) was added to a stirred solution of α-(methylthio)acetyl chloride (**4**) (4.6 g, 0.037 mol) and 1,2-(methylenedioxy)benzene (4.5 g, 0.037 mol) in 1,2-dichloroethane (30 ml) at 0°C under N_2 atmosphere, and stirring was continued at the same temperature for 1 h. The reaction mixture was quenched by the addition of water and the organic phase separated. The aqueous phase was extracted with methylene chloride (10 ml × 2), and the combined extracts dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate=4/1) to give **5** (5.3 g, 68%) as a white solid. mp 47-48°C; ^{1}H NMR ($CDCl_3$) δ 2,14 (3H, s, SCH_3), 3.69 (2H, s, CH_2CO), 6.05 (2H, s, OCH_2O), 6.86 (1H, d, J=8.2Hz, Ar-H), 7.46-7.68 (2H, m, Ar-H); IR (KBr) 2979, 2906, 1666 (CO), 1598, 1482, 1443, 1398, 1304, 1242, 1107, 1034 cm^{-1}; MS m/z 210 (M^+), 167, 149 (base peak), 121, 77, 65, 51; Anal. Calcd for $C_{10}H_{10}O_3S$: C, 57.13; H, 4.79. Found C, 57.32; H, 4.97.

2-Chloro-2-methylthio-(3',4'methylenedioxy)acetophenone (6)

N-Chlorosuccinimide (2.54 g, 0.019 mol) was added to a stirred solution of **5** (4 g, 0.019 mol) in carbon tetrachloride (20 ml) in small portions at 0°C, and stirring continued at room temperature for 12 h. The precipitated succinimide was filtered off and the solvent removed *in vacuo*, and the residual oil used without further purification. Yield 72% (3.34 g); ^{1}H NMR ($CDCl_3$) δ 2,25 (3H, s, SCH_3), 6.06 (2H, s, OCH_2O), 6.24 (1H, s, CHCO), 6.87 (1H, d, J=8.2Hz, Ar-H), 7.48-7.74 (2H, m, Ar-H); IR (KBr) 3032, 2904, 1682 (CO), 1608, 1489, 1442, 1354, 1261, 1200, 1103, 1041 cm^{-1}; MS m/z 246 (M+2), 244 (M^+), 209, 149 (base peak), 121, 91, 65.

Methyl 3-[2-(3',4'-methylenedioxyphenyl)-3-methylthiobenzofuran-5-yl] propionate (7)

$ZnCl_2$ (546 mg, 4.0 mmol) was added to a stirred solution of methyl 3-(4-hydroxyphenyl)propionate (685 mg, 3.8 mmol) and **6** (930 mg, 3.8 mmol) in methylene chloride (20 ml) at -5°C under N_2 atmosphere, and stirring continued at the same temperature for 1 h. The reaction mixture was quenched by the addition of water and the organic phase separated. The aqueous phase was extracted with methylene chloride (10 ml), and the combined extracts dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography(hexane/ethyl acetate=4/1) to give **7** (844 mg, 60%) as a white solid. mp 86-87°C; ^{1}H NMR ($CDCl_3$) δ 2,35 (3H, s, SCH_3), 2.47-3.34 (4H, m, -CH_2CH_2-), 3.68 (3H, s, CO_2CH_3), 6.03 (2H, s, OCH_2O), 6.80-8.02 (6H, m, Ar-H); IR (KBr) 2943, 2899, 1735, 1498, 1469, 1232, 1170, 1043 cm^{-1}; MS m/z 370 (M^+), 312, 297, 221, 207, 194, 129, 117 (base peak), 103; Anal. Calcd for $C_{20}H_{18}O_5S$: C, 64.85; H, 4.90. Found C, 64.78; H, 4.92.

Methyl 3-[2-(3',4'-methylenedioxyphenyl)benzofuran-5-yl] propionate (8)

Raney nickel (W-2, ca. 5 g) was added to a solution of **7** (500 mg, 1.4 mmol) in ethanol (30 ml), and the mixture was heated at 60-70°C for 1 h. The Raney nickel was then filtered off and the solvent evaporated. The residual solid was recrystallized from methanol to give **8** (410 mg, 94%) as a white solid. mp 127-129°C (lit.125-128, Schreiber and Stevenson, 1976); ^{1}H NMR ($CDCl_3$) δ 2.32-3.30 (4H, m, -CH_2CH_2-), 3.66 (3H, s, CO_2CH_3), 6.00 (2H, s, OCH_2O), 6.50-7.64 (7H, m, Ar-H); IR (KBr) 2943, 2899, 1732, 1499, 1466, 1243, 1199 cm^{-1}; MS m/z 324 (M^+), 294, 251 (base peak), 238, 165, 125.

5-(3-Hydroxypropyl)-2-(3',4'-methylenedioxyphenyl) benzofuran (9)

A solution of **8** (200 mg, 0.62 mmol) in tetrahydrofuran (10 ml) was added to a stirred suspension of $LiAlH_4$ (235 mg, 6 mmol) in tetrahydrofuran (10 ml) at 0°C under N_2 atmosphere. The reaction mixture was allowed to come to room temperature and stirred for 4h. The mixture was quenched by the addition of water (20 ml) and 10% H_2SO_4

(20 ml), and extracted with diethyl ether (30 ml × 2). The extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residual solid was recrystallized from aqueous methanol to give **9** (180 mg, 98%) as a solid. mp 124-125°C (lit. 124-125, Schreiber and Stevenson, 1976); ^{1}H NMR ($CDCl_3$) δ 1.48 (1H, s, OH), 1.65-2.16 (2H, m, $HOCH_2\underline{CH_2}CH_2$), 2.80 (2H, t, J=8.2 Hz, $HOCH_2CH_2\underline{CH_2}$), 3.68 (2H, t, J=6.4Hz, $HO\underline{CH_2}CH_2CH_2$), 5.99 (2H, s, OCH_2O), 6.72-7.53 (7H, m, Ar-H); IR (KBr) 3289, 3199, 2899, 1499, 1466, 1243, 1044 cm^{-1}; MS m/z 296 (M^+), 252 (base peak), 238, 165, 125.

RESULTS AND DISCUSSION

We began the synthesis of 2-chloro-2-methylthio-(3',4'-methylenedioxy)acetophenone (**6**) starting from-(methylthio)acetyl chloride (**4**) (Mooradian *et al.*, 1949). Freidel-Crafts acylation of 1,2-(methylenedioxy)benzene with **4** in the presence of $SnCl_4$ afforded 2-methylthio-(3',4'-methylenedioxy)acetophenone (**5**) in 68% yield. The chloride **6** was prepared from the sulfide **5** by chlorination with *N*-chlorosuccinimide according to the procedure described by Bohme and Krack in 1977.

The treatment of methyl 3-(4-hydroxyphenyl) propionate and the chloride **6** in the presence of $ZnCl_2$ gave methyl 3-[2-(3',4'-methylenedioxyphenyl)-3-methylthiobenzofuran-5-yl]propionate (**7**) in 60% yield. The structure of **7** was assigned on the basis of spectroscopic evidence. Elemental analysis and the mass spectrum (MS) (M^+ m/z 370) showed the molecular formula to be $C_{20}H_{18}O_5S$. The ^{1}H NMR spectrum was readily compared with that of the methyl ester **8** reported in the literature (Schreiber and Stevenson, 1976), and exhibited methylthio protons as a singlet at δ 2,35 ppm in place of the C_3-position.

The desulfurization of **7** with Raney nickel in ethanol furnished methyl 3-[2-(3',4'-methylenedioxyphenyl)benzofuran-5-yl]propionate (**8**) in 94% yield, the mp, IR and ^{1}H NMR data were in good agreement with those reported by Schreiber and Stevenson in 1976. Finally the desired demethoxy-egonol, 5-(3-hydroxypropyl)-2-(3',4'-methylenedioxyphenyl)benzofuran (**9**), was obtained by the reduction of the methyl ester **8** with excess $LiAlH_4$ in a high yield.

Of the several methods available for the preparation of the 2-arylbenzofuran ring, the route involving the reaction of an *o*-halogenophenol with a copper(I) arylacetylide was chosen to synthesize demethoxy-egonol (**9**) (Schreiber and Stevenson, 1976) as the key step. The present sequence of reactions can be conducted under mild conditions in high yields.

In conclusion, demethoxy-egonol (**9**) from *Styrax obassia* was synthesized using a new synthetic route by one-pot reaction of methyl 3-(4-hydroxyphenyl) propionate with the chloride **6** under Freidel-Crafts reaction conditions and successive desulfurization of the resultant product **7**, as the key steps. Now synthetic applications of this route for other natural products with the 2-arylbenzofuran skeleton are in progress.

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