The Synthesis of Two 6-Acetyl-2,3-dihydro-5-benzofuranols Naturally Obtained from *Baccharis conferta*

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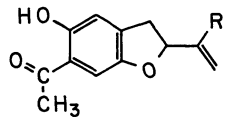
6-Acetyl-2-isopropenyl-5-methoxy-2,3-dihydrobenzofuran was prepared from 2-isopropenyl-5-methoxy-2,3-dihydrobenzofuran via formylation, Grignard methylation, and oxidation. It was then converted to two racemic dihydrobenzofuran derivatives obtained from *Baccharis conferta*.

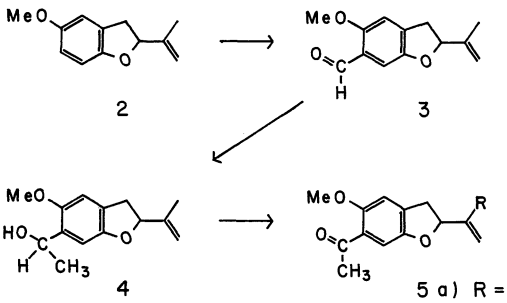
Many naturally occurring 2-isopropenyl-2,3-dihydrobenzofuran derivatives have been reported.[1] Most of them have an acetyl group in their 5-position because of their biosynthesis via polyketide. In 1970, F. Bohlmann and C. Zdero obtained oily materials from *Baccharis conferta* and elucidated their structure by spectroscopic methods to be 6-acetyl-5-benzofuranol structures (**1b** and **1c**) having oxidized isopropenyl and biosynthetically irregular 6-acetyl groups.[2] So far, however, there has been no report on their synthesis. In the course of our synthetic studies of natural 2-isopropenyl-2,3-dihydrobenzofurans,[3a–h] we describe here the synthesis of a 6-acetyl-5-hydroxy derivative (**1a**) and the conversion from 6-acetyl-5-methoxy derivative (**5a**) to two naturally obtained 6-acetyl-2,3-dihydro-5-benzofuranol derivatives (**1b** and **1c**).



1 a) R = CH_3
b) R = CH_2OAc
c) R = CHO

As we have already reported,[3f] a direct cyclization of 2-acetylhydroquinone with 1,4-dibromo-2-methyl-2-butene gave 4-acetyl-5-benzofuranols. We have reported[3d] that the direct introduction of an acetyl group in 2-isopropenyl-5-methoxy-2,3-dihydrobenzofuran (**2**) was unsuccessful. However, 6-acetyl-2-isopropenyl-5-methoxy-2,3-dihydrobenzofuran (**5a**) was obtained from 6-formyl-2-isopropenyl-5-methoxy-2,3-dihydrobenzofuran (**3**), obtained by a Vilsmeier formylation of **2**.[3d] The Grignard methylation of **3** with methylmagnesium iodide gave an alcohol **4** in 98% yield, which was easily oxidized to 6-acetyl-2-isopropenyl-5-methoxy-2,3-dihydrobenzofuran (**5a**) with active manganese dioxide[4] in 87% yield.

Selenium dioxide oxidation of **5a** in refluxing acetic anhydride gave 6-acetyl-2-[1-(acetoxymethyl)vinyl]-5-methoxy-2,3-dihydrobenzofuran (**5b**) in 16% yield. A new carbonyl absorption at 1740 cm^{-1} in its IR



5 a) R = CH_3
b) R = CH_2OAc
c) R = CH_2OH
d) R = CHO

spectrum and a new methyl signal at δ=2.0 in its ^1H NMR spectrum showed the existence of a new acetoxyl group. Furthermore, a methylene signal at δ=4.6 showed that the acetoxyl group was on the methyl carbon of the isopropenyl group. Demethylation of **5b** with magnesium iodide–diethyl ether (1/2)[3e] in refluxing dry benzene gave 2-[1-(acetoxymethyl)vinyl]-6-acetyl-2,3-dihydro-5-benzofuranol (**1b**) in 53% yield. In the IR spectra, carbonyl absorption was shifted from 1660 cm^{-1} (in **5b**) to 1630 cm^{-1} (in **1b**). Further, the ^1H NMR spectrum of **1b** showed a hydroxyl proton signal at δ=12.1. These indicated a new intramolecular hydrogen bonding. The ^1H NMR spectral data of this demethylated compound **1b** were identical with the reported data of the natural oily mixture from *Baccharis conferta*.[2] A similar demethylation of **5a** gave 6-acetyl-2-isopropenyl-2,3-dihydro-5-benzofuranol (**1a**) in 39% yield, which also showed an intramolecular hydrogen bonding in its IR and ^1H NMR spectra.

For a conversion to a natural aldehyde **1c**, acetate **5b** was hydrolyzed to a corresponding alcohol **5c**, which was oxidized to a corresponding aldehyde, 2-(6-acetyl-5-methoxy-2,3-dihydro-2-benzofuranyl)acrylaldehyde (**5d**) with active manganese dioxide in 28% yield. This aldehyde **5d** was similarly demethylated to 2-(6-acetyl-5-hydroxy-2,3-dihydro-2-benzofuranyl)acrylaldehyde (**1c**) with anhydrous magnesium iodide–diethyl ether (1/2); the ^1H NMR spectral data of this demethylated aldehyde **1c** were also identical with the reported data

of the natural oily mixture from *Baccharis conferta*.[2]

Experimental

The melting points and boiling points were uncorrected (in boiling points; 1 mmHg=133.322 Pa). The IR spectra were measured on a Hitachi EPI-S2 or 260-50 spectrophotometer in liquid films or KBr disks, and the UV spectra were taken on a Hitachi 220A spectrophotometer in ethanolic solutions. The ^{1}H NMR spectra were recorded on a JEOL PMX-60Si or FX-90Q NMR spectrometer, and the Mass spectra were recorded on a JEOL JMS-OISG-2 mass spectrometer.

Preparation of 6-acetyl-2-isopropenyl-5-methoxy-2,3-dihydrobenzofuran (5a): According to a procedure described previously,[3d] 2-isopropenyl-5-methoxy-2,3-dihydrobenzofuran-6-carbaldehyde (**3**) was prepared by cyclization of *p*-methoxyphenol with 1,4-dibromo-2-methyl-2-butene followed by the formylation of 2-isopropenyl-5-methoxy-2,3-dihydrobenzofuran (**2**) with *N*-methylformanilide and phosphoryl chloride. A solution of aldehyde **3** (2.14 g, 9.82 mmol) in dry ether (10 ml) was added to a cold Grignard solution, prepared from magnesium metal (0.55 g, 20.6 mmol), iodomethane (3.31 g, 23.3 mmol), and dry ether (40 ml). After refluxing for 1 h, the mixture was treated with a 1 M ammonium chloride solution (1 M=1 mol dm^{-3}) and extracted with ether. The ether layer was washed with a saturated aqueous sodium hydrogencarbonate solution and dried over anhydrous sodium sulfate. After removal of the ether, pure 1-(2-isopropenyl-5-methoxy-2,3-dihydro-6-benzofuranyl)ethanol (**4**)(2.28 g, 97.5%) was obtained as colorless oil. IR (neat) 3350 cm^{-1}. ^{1}H NMR (CCl_4) δ=1.3 (3H, d, J=6 Hz), 1.7 (3H, s), 2.4 (1H, broad s), 2.9 (1H, dd, J=15 and 8 Hz), 3.2 (1H, dd, J=15 and 9 Hz), 3.7 (3H, s), 4.8 (1H, broad s), 5.0 (1H, broad s), 5.0 (1H, dd, J=9 and 8 Hz), 4.8—5.1 (1H, m), 6.6 (1H, s), 6.7 (1H, s). This alcohol **4** was homogeneous in both TLC and GLC.

To a solution of alcohol **4** (1.07 g, 4.58 mmol) in dry acetone (70 ml) was added active manganese(IV) dioxide (24 g), freshly prepared from potassium permanganate and manganese(II) sulfate.[4] The mixture was then stirred at room temperature for 24 h, and the manganese(IV) dioxide was filtered off. After removing the solvent under reduced pressure, an oily residue was crystallized from hexane–ether to give 6-acetyl-2-isopropenyl-5-methoxy-2,3-dihydrobenzofuran (**5a**)(0.93 g, 87%) as colorless crystals; mp 49—50 °C. IR (KBr) 1660 cm^{-1}. ^{1}H NMR (CCl_4) δ=1.7 (3H, s), 2.5 (3H, s), 3.0 (1H, dd, J=16 and 8 Hz), 3.4 (1H, dd, J=16 and 9 Hz), 3.8 (3H, s), 4.8 (1H, broad s), 5.0 (1H, broad s), 5.1 (1H, dd, J=9 and 8 Hz), 6.7 (1H, s), 7.0 (1H, s). MS m/z 232 (M$^+$), 217. Found: C, 72.09, H, 6.79%. Calcd for $C_{14}H_{16}O_3$: C, 72.39, H, 6.94%. UV (EtOH) 230 (log ε 4.25), 258 (3.81), 344 nm (3.74).

Demethylation of 5a: A solution of **5a** (2.20 g, 9.48 mmol) in dry benzene was added to a benzene solution of magnesium iodide - diethyl ether (1/2), prepared from magnesium metal (1.08 g, 43 matom), iodine (5.49, 21.6 mmol), dry ether (6 ml), and dry benzene (6 ml) by a similar procedure described before;[3e] the mixture was refluxed for 3 h. After cooling, the mixture was treated with 10% hydrochloric acid. The organic layer was collected and washed with a saturated sodium hydrogencarbonate solution and dried over anhydrous sodium sulfate. After removing the solvent, the residual oil was purified by silica-gel column chromatography. Fractions eluted with benzene were crystallized from cyclohexane to give 6-acetyl-2-isopropenyl-2,3-dihydro-5-benzofuranol (**1a**) (0.80 g, 39%) as colorless crystals; mp 84—85 °C. IR (KBr disk) 1620 cm^{-1}. ^{1}H NMR (CCl_4) δ=1.8 (3H, s), 2.5 (3H, s), 3.0 (1H, dd, J=16 and 8 Hz), 3.4 (1H, dd, J=16 and 9 Hz), 4.9 (1H, broad s), 5.0 (1H, broad s), 5.1 (1H, broad s), 5.1 (1H, dd, J=9 and 8 Hz), 6.7 (1H, s), 7.0 (1H, s), 12.1 (1H, s). MS m/z 218 (M$^+$), 203. Found: C, 71.29, H, 6.40%. Calcd for $C_{13}H_{14}O_3$: C, 71.54, H, 6.47%. UV (EtOH) 235 (log ε 4.26), 264 (3.84), 365 nm (3.73).

Selenium Dioxide-Oxidation of 5a: To a solution of **5a** (1.70 g, 7.31 mmol) in acetic anhydride (100 ml) was added powdered selenium dioxide (0.87 g, 7.84 mmol); the mixture was refluxed for 3 h. After cooling, the mixture was diluted with ether and filtered off the selenium compounds. From the filtrate, the ether and the excess acetic anhydride was removed under reduced pressure, and the residue was redissolved in benzene. The benzene solution was washed with sat. sodium hydrogencarbonate solution and sat. sodium chloride solution, and then dried over anhydrous sodium sulfate. After removing the benzene, the residual oil was purified on a silica-gel column. Fractions eluted with benzene–chloroform (1:1) gave 2-[1-(acetoxymethyl)vinyl]-6-acetyl-5-methoxy-2,3-dihydrobenzofuran (**5b**)(0.33 g, 16%) as pale yellow oil; bp 190—220 °C (6 mmHg)(bath temp). IR (neat) 1740, 1660 cm^{-1}. ^{1}H NMR (CCl_4) δ=2.0 (3H, s), 2.5 (3H, s), 3.1 (1H, dd, J=16 and 8 Hz), 3.4 (1H, dd, J=16 and 9 Hz), 3.8 (3H, s), 4.6 (2H, broad s), 5.2 (1H, dd, J=9 and 8 Hz), 5.2 (1H, broad s), 5.3 (1H, broad s), 6.7 (1H, s), 7.1 (1H, s). MS m/z 290 (M$^+$), 230. Found: C, 66.07, H, 6.16%. Calcd for $C_{16}H_{18}O_5$: C, 66.19, H, 6.25%.

Demethylation of 5b to 1b: By a similar procedure to that described above, **5b** (0.19 g, 0.655 mmol) was demethylated with a refluxing solution of magnesium(IV) iodide etherate, prepared from magnesium metal (40 mg, 0.833 mmol), dry ether (1.5 ml), dry benzene (3 ml), and iodine (0.19 g, 0.665 mmol). Fractions eluted by benzene gave **1b** (96 mg, 53%) as pale yellow oil; bp 205—210 °C (5 mmHg)(bath temp). IR (neat) 1730, 1630 cm^{-1}. ^{1}H NMR (CCl_4) δ=2.0 (3H, s), 2.5 (3H, s), 3.1 (1H, dd, J=16 and 8 Hz), 3.3 (1H, dd, J=16 and 10 Hz), 4.6 (2H, broad s), 5.2 (1H, dd, J=10 and 8 Hz), 5.2 (1H, broad s), 5.3 (1H, broad s), 6.7 (1H, s), 6.9 (1H, s), and 12.0 (1H, s). MS m/z 276 (M$^+$). Found: C, 65.15, H, 5.97%. Calcd for $C_{15}H_{16}O_5$: C, 65.21, H, 5.84%.

Hydrolysis of 5b to 5c: To a solution of acetate **5b** (0.10 g, 3.45 mmol) in ethanol (10 ml), was added ca. 10% aqueous potassium hydroxide solution (5 ml); the mixture was refluxed for 1 h. After cooling, the mixture was acidified with 10% hydrochloric acid, and then extracted with ether. The ether layer was washed with sat. sodium hydrogencarbonate solution and sat. sodium chloride solution, and dried over anhydrous sodium sulfate. After removing the ether, pure 6-acetyl-2-[1-(hydroxymethyl)vinyl]-5-methoxy-2,3-dihydrobenzofuran (**5c**)(0.08 g, 96%) was obtained as a pale yellow oil; bp 190—210 °C (4 mmHg)(bath temp). IR (neat) 3400, 1660 cm^{-1}. ^{1}H NMR (CCl_4) δ=2.5 (3H, s), 3.2 (1H, dd, J=16 and 10 Hz), 3.4 (1H, dd, J=16 and 9 Hz), 3.9 (3H, s), 4.2 (2H, broad s), 5.2 (2H, broad s), 5.3 (1H, dd, J=10 and 9 Hz), 6.8 (1H, s), 7.2 (1H, s). MS m/z 231 (M$^+$), 217 (M$^+$–CH_2OH). Found: C, 67.52, H, 6.61%. Calcd for $C_{14}H_{16}O_4$: C, 67.73, H, 6.50%.

Oxidation of Alcohol 5c to Aldehyde 5d: To a solution of **5c** (80 mg, 0.32 mmol) in dry acetone (20 ml) was added manganese(IV) dioxide (840 mg, 9.65 mmol); the mixture was stirred at room temperature for 23 h. After a similar treatment to that described above regarding oxidation of **4** to **5a**, the fractions eluted with benzene–ether (5:1) were recrystallized from chloroform–hexane to give 2-(6-acetyl-5-methoxy-2,3-dihydro-2-benzofuranyl)acrylaldehyde (**5d**)(22,2 mg, 28%) as pale yellow cubes; mp 115.5—116.5 °C. IR (KBr disk) 1680, 1660 cm^{-1}. ^1H NMR ($CDCl_3$) δ=2.5 (3H, s), 2.9 (1H, dd, J=16 and 8 Hz), 3.6 (1H, dd, J=16 and 10 Hz), 3.8 (3H, s), 5.5 (1H, dd, J=10 and 8 Hz), 6.1 (1H, s), 6.5 (1H, s), 6.8 (1H, s), 7.2 (1H, s), 9.6 (1H, s). MS m/z 246 (M^+), 217 (M^+–CHO). Found: C, 68.04, H, 5.63%. Calcd for $C_{14}H_{14}O_4$: C, 68.28, H, 5.73%.

Demethylation of 5d to 1c: To a magnesium etherate solution, prepared from magnesium (5 mg, 0.21 matom), dry ether (5 ml), dry benzene (10 ml), and iodine (25 mg, 0.10 mmol), was added a solution of **5d** (22.2 mg, 0.09 mmol) in dry benzene (15 ml); the mixture was refluxed for 2 h. After a similar treatment to that described above regarding the demethylation of **5a** to **1a**, the fractions eluted with benzene–ether (20:1) gave 2-(6-acetyl-5-hydroxy-2,3-dihydro-2-benzofuranyl)acrylaldehyde (**1c**)(0.90 mg, 4.1%) as colorless oil. IR (neat) 1690, 1645 cm^{-1}. ^1H NMR ($CDCl_3$) δ=2.6 (3H, s), 3.0 (1H, dd, J=16 and 7 Hz), 3.6 (1H, dd, J=16 and 9 Hz), 5.5 (1H, dd, J=9 and 7 Hz), 6.2 (1H, s), 6.6 (1H, s), 6.8 (1H, s), 7.1 (1H, s), 9.6 (1H, s), 12.2 (1H, s). MS m/z 232 (M^+), 203 (M^+–CHO). Found: m/z 232.0736. Calcd for $C_{13}H_{12}O_4$: M 232.074. The ^1H NMR spectra were well corresponded with the data of natural mixture reported by F. Bohlmann and C. Zdero.[2]

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