Synthesis of 2,3-*trans*-Disubstituted 2,3-Dihydrobenzofurans[1]

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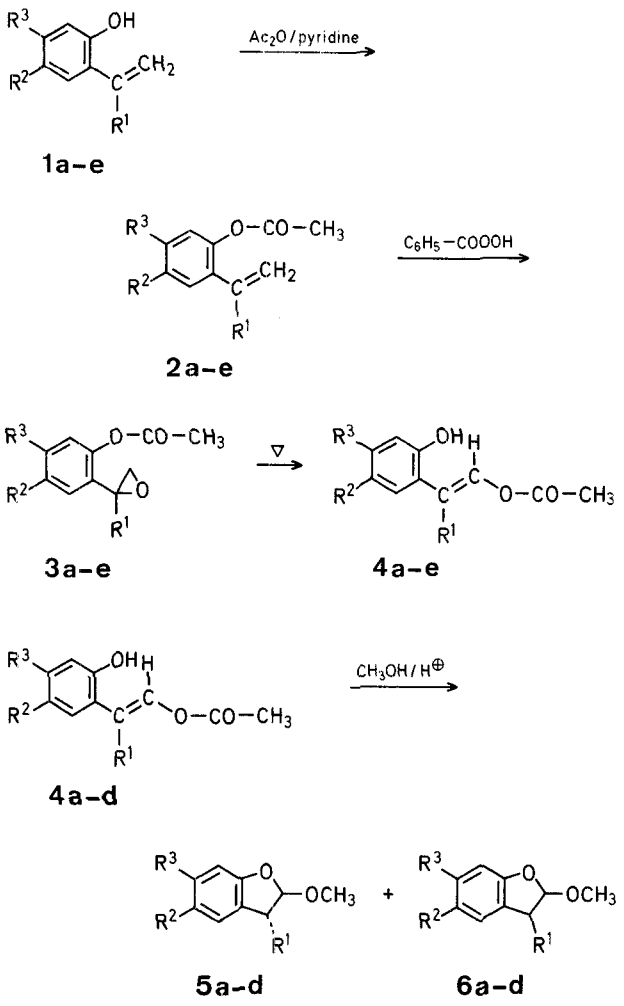
A number of substituted 2,3-dihydrobenzofurans have been isolated from natural sources[2]. The synthesis of these substances as well as their analogues has been extensively studied[3] because of their interesting physiological activities. A novel synthesis of 2-methoxy-3-methyl 2,3-dihydrobenzofurans **5a–d** is presented in this communication.



	R^1	R^2	R^3
a	CH_3	CH_3	H
b	CH_3	H	CH_3
c	CH_3	Br	H
d	CH_3	Cl	H
e	H	H	H

The *o*-isopropenylphenol **1a** was prepared by a route[4] involving the action of alkali on 4,6-dimethylcoumarin. Acetylation of **1a** yielded the acetate **2a**, which furnished the epoxide **3a** on treatment with perbenzoic acid. The epoxide **3a** underwent a thermal rearrangement to give the enol acetate **4a**. The facile conversion of the aldehyde **7** (≡**2**, $R^1 = CHO$, $R^2 = H$, $R^3 = CH_3$) to the methoxy compound **8** (≡**5**, $R^1 = CH_2$, $R^2 = H$, $R^3 = CH_3$) observed by us[5] suggested that the enol acetate **4a**, being a masked aldehyde, can be transformed to the dihydrobenzofuran **5a**. Treatment of **4a** with hot methanol in the presence of *p*-toluenesulphonic acid furnished a 4:1 mixture of **5a** and **6a**. The *trans*-stereochemistry is assigned to the major product on the basis[6] of the observed coupling constant ($J = 2$ Hz) between the protons at C-2 and C-3. Employing the sequence of reactions described above, the isopropenyl phenols **1b–d** were also transformed to the dihydrobenzofurans **5b–d**.

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Table 1. 2-(2-Acetoxyaryl)-alk-1-enes[a] **2a–e** and 2-(2-Acetoxyaryl)-oxiranes **3a–e**

Product	Yield [%]	b.p./torr	Molecular formula[b]	^{1}H-N.M.R. (CCl_4/TMS) δ [ppm]
2a	85	130 °C/2	$C_{12}H_{14}O_2$ (190.2)	2.0 (m, 3H, H_3C—C≡C); 2.13 (s, 3H, H_3C—CO—O); 2.32 (s, 3H, Ar—CH_3); 4.90 (m, 1H_{vinyl}); 5.07 (m, 1H_{vinyl})
2b	80	90 °C/0.5	$C_{12}H_{14}O_2$ (190.2)	2.02 (m, 3H, H_3C—C≡C); 2.13 (s, 3H, H_3C—CO—O); 2.32 (s, 3H, Ar—CH_3); 4.90 (m, 1H_{vinyl}); 5.07 (m, 1H_{vinyl})
2c	80	140 °C/5	$C_{11}H_{11}BrO_2$ (255.1)	2.03 (m, 3H, H_3C—C≡C); 2.18 (s, 3H, H_3C—CO—O); 5.00 (m, 1H_{vinyl}); 5.15 (m, 1H_{vinyl})
2d	85	130 °C/2	$C_{11}H_{11}ClO_2$ (210.7)	2.02 (m, 3H, H_3C—C≡C); 2.15 (s, 3H, H_3C—CO—O); 5.00 (m, 1H_{vinyl}); 5.15 (m, 1H_{vinyl})
2e	75	85 °C/1	$C_{10}H_{10}O_2$ (162.2)	2.15 (s, 3H, H_3C—CO—O); 5.17 (q, 1H_{vinyl}, J=2, 10 Hz); 5.57 (q, 1H_{vinyl}, J=2, 18 Hz)
3a	95	—	$C_{12}H_{14}O_3$ (206.2)	1.50 (s, 3H, H_3C-oxirane); 2.18 (s, 3H, H_3C—CO—O); 2.28 (s, 3H, Ar—CH_3); 2.62 (m, 2$H_{oxirane}$)
3b	97	—	$C_{12}H_{14}O_3$ (206.2)	1.52 (s, 3H, H_3C-oxirane); 2.22 (s, 3H, H_3C—CO—O); 2.30 (s, 3H, Ar—CH_3); 2.63 (m, 2$H_{oxirane}$)
3c	96	—	$C_{11}H_{11}BrO_3$ (271.1)	1.55 (s, 3H, H_3C-oxirane); 2.27 (s, 3H, H_3C—CO—O); 2.70 (m, 2$H_{oxirane}$)
3d	95	—	$C_{11}H_{11}ClO_3$ (226.7)	1.55 (s, 3H, H_3C-oxirane); 2.27 (s, 3H, H_3C—CO—O); 2.70 (m, 2$H_{oxirane}$)
3e	95	—	$C_{10}H_{10}O_3$ (178.2)	2.20 (s, 3H, H_3C—CO—O); 2.55 (m, 1$H_{oxirane}$); 2.95 (m, 1$H_{oxirane}$); 3.80 (m, 1$H_{oxirane}$)

[a] The phenols **1a–e** were prepared by known methods[4,7,8].
[b] The microanalyses were in satisfactory agreement with the calculated values (C ±0.28, H ±0.22).

Table 2. Enol Acetates **4a–e**

Product	Yield [%]	m.p.	Molecular formula[a]	I.R. (nujol) ν [cm^{-1}]	^{1}H-N.M.R. (CCl_4/TMS, 60 MHz) δ [ppm]
4a	35	77 °C	$C_{12}H_{14}O_3$ (206.2)	3330, 1735, 1645, 1610, 1260	1.98 (d, 3H, H_3C—C≡C, J=2 Hz); 2.18 (s, 3H, H_3C—CO—O); 7.08 [m, 1H, HC(OAc)=C]
4b	40	92 °C	$C_{12}H_{14}O_3$ (206.2)	3310, 1730, 1660, 1620, 1265	2.02 (d, 3H, H_3C—C≡C, J=2 Hz); 2.20 (s, 3H, H_3C—CO—O); 7.17 [m, 1H, HC(OAc)=C]
4c	25	101 °C	$C_{11}H_{11}BrO_3$ (271.1)	3250, 1720, 1640, 1600, 1250	1.98 (d, 3H, H_3C—C≡C, J=2 Hz); 2.18 (s, 3H, H_3C—CO—O); 7.12 [m, 1H, HC(OAc)=C]
4d	25	60 °C	$C_{11}H_{11}ClO_3$ (226.7)	3400, 1730, 1640, 1600, 1260	2.00 (d, 3H, H_3C—C≡C, J=2 Hz); 2.20 (s, 3H, H_3C—CO—O); 7.23 [m, 1H, HC(OAc)=C]
4e[b]	20	140 °C	$C_{10}H_{10}O_3$ (178.2)	3200, 1715, 1645, 1600, 1250	2.07 (s, 3H, H_3C—CO—O); 6.87 (d, 1H_{vinyl}, J=13 Hz); 8.42 (d, 1H_{vinyl}, J=13 Hz)[c]

[a] The microanalyses were in satisfactory agreement with the calculated values (C ±0.23, H ±0.10).
[b] The coupling constant of 13 Hz between the vinyl protons is indicative for the (*E*)-isomer[9].
[c] Pyridine-d_5 solution.

Table 3. 2-Methoxy-3-methyl-2,3-dihydrobenzofurans **5a–d**

Product	Yield[a] [%]	b.p./torr	Molecular formula[b]	^{1}H-N.M.R. (CCl_4/TMS) δ [ppm]
5a	64	120 °C/2	$C_{11}H_{14}O_2$ (178.2)	1.20 (d, 3H, H_3C—CH, J=6 Hz); 2.25 (s, 3H, Ar—CH_3); 3.20 (m, 1H, H—C-3); 3.42 (s, 3H, OCH_3); 5.02 (d, 1H, H—C-2, J=2 Hz)
5b	60	125 °C/2	$C_{11}H_{14}O_2$ (178.2)	1.20 (d, 3H, H_3C—CH, J=6 Hz); 2.27 (s, 3H, Ar—CH_3); 3.17 (m, 1H, H—C-3); 3.42 (s, 3H, OCH_3); 5.03 (d, 1H, H—C-2, J=2 Hz)
5c	60	130 °C/3	$C_{10}H_{11}BrO_2$ (243.1)	1.25 (d, 3H, H_3C—CH, J=6 Hz); 3.23 (m, 1H, H—C-3); 3.45 (s, 3H, OCH_3); 5.08 (d, 1H, H—C-2, J=2 Hz)
5d	50	115 °C/1	$C_{10}H_{11}ClO_2$ (198.7)	1.25 (d, 3H, H_3C—CH, J=6 Hz); 3.33 (m, 1H, H—C-3); 3.47 (s, 3H, OCH_3); 5.12 (d, 1H, H—C-2, J=2 Hz)

[a] In addition to **5a–d**, the corresponding *cis*-isomers **6a–d** were also formed; in all cases the *trans*:*cis* ratio was 4:1.
[b] The microanalyses were in satisfactory agreement with the calculated values (C ±0.27, H ±0.04).

2-(2-Acetoxy-5-methylphenyl)-prop-1-ene (2a):
A mixture of 2-(2-hydroxy-5-methylphenyl)-prop-1-ene[4] **(1a;** 7.41 g, 50 mmol), pyridine (70 ml), and acetic anhydride (12.25 g, 120 mmol) is kept at room temperature for 24 h and then poured into ice/water (250 ml). After 2 h, the reaction product is extracted with ether (3 × 50 ml). The combined extracts are washed with water, 5% hydrochloric acid, and again with water. The ether layer is dried with sodium sulphate, the solvent distilled off, and the residue vacuum distilled to furnish the acetate **2a**; yield: 8.01 g (84%); b.p. 130 °C/2 torr (see Table 1).

I.R. (neat): $\nu = 1770, 1635, 1605, 1580, 1210, 1180, 900\ cm^{-1}$.

2-(2-Acetoxy-5-methylphenyl)-2-methyloxirane (3a):
To a solution of the acetate **2a** (7.6 g, 40 mmol) in chloroform (30 ml) is added at 0 °C a 0.85 molar solution of perbenzoic acid in chloroform (100 ml, 85 mmol). The reaction mixture is kept at 0–5 °C for 48 h, then washed with aqueous potassium carbonate solution, water, and dried with sodium sulphate. The solvent is removed in vacuum below 60 °C to furnish the oxirane **3a;** yield: 8.10 g (98%) (see Table 1).

I.R. (neat): $\nu = 1770, 1210, 1055, 750\ cm^{-1}$.

2-(2-Hydroxy-5-methylphenyl)-prop-1-enyl Acetate (4a):
Oxirane **3a** (1.03 g, 5 mmol) is heated under nitrogen at 160 °C for 20 min and the products are distilled at 140–180 °C/2 torr. Recrystallisation of the distillate from petroleum ether (b.p. 60–80 °C) furnishes the enol ester **4a;** yield: 0.36 g (35%) m.p. 77 °C (see Table 2).

(±)-*trans*-3,5-Dimethyl-2-methoxy-2,3-dihydrobenzofuran (5a):
A mixture of enol ester **4a** (0.41 g, 2 mmol), methanol (25 ml), and *p*-toluenesulphonic acid (0.04 g) is heated under reflux for 1 h, cooled, diluted with ice/water, and extracted with ether. The ether extract is washed with water and dried with sodium sulphate. After distilling off the solvent the residue is vacuum distilled to furnish a 4:1 mixture (±)-**5a** and (±)-**6a;** yield: 0.29 g (80%); b.p. 120 °C/2 torr (see Table 3).

I.R. (neat): $\nu = 1620, 1090, 930, 905, 805\ cm^{-1}$.

^{1}H-N.M.R. (CCl_4): $\delta = 1.20$ (d, 3H, $\underline{H}_3C-CH-$, $J = 6$ Hz); 2.25 (s, 3H, Ar–$C\underline{H}_3$); 3.20 (m, 1H, H–C-3); 3.42 (s, 3H, $\underline{H}_3C-O-$); 5.02 (d, 0.8H, H–C-2, $J = 2$ Hz); 5.28 (d, 0.2H, H–C-2, $J = 6$ Hz); 6.50–6.75 ppm (m, $3H_{arom}$).

The *cis* **(6a)** and *trans* **(5a)** isomers are separated by G.L.C. using an acetylated carbowax column at 160 °C; the *trans*-isomer has the shorter retention time.

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