SHORT PAPER

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2-Methoxy-5-(2-bromoethyloxy)-2,5-dihydrofuran: a useful building block for the synthesis of dihydro- and tetrahydro-furan moieties†

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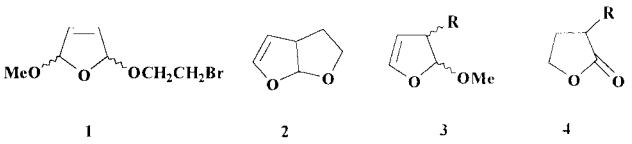
New syntheses of structures of biological interest containing the tetrahydro-, dihydro- and furo-furan rings are reported employing simple experimental procedures and mild reaction conditions.

Keywords: 2-methoxy-5-(2-bromoethyloxy)-2,5-dihydrofuran

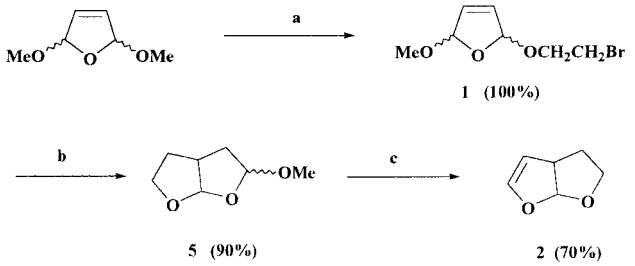
In a previous paper[1] we reported the synthesis of 2-methoxy-5-(2-bromoethyloxy)-2,5-dihydrofuran (**1**). Dihydrofurans are starting materials for cyclic or acyclic functionalized compounds that have a framework of four carbon atoms. In particular, compound **1** represents a useful starting point in the synthesis of furofuran structures, which are present in many biologically active natural substances.[2] We therefore set out to explore alternative economical ways to prepare 2,8-dioxabicyclo[2.2.0]oct-3-ene (**2**). This moiety is presumed to be responsible for at least part of the biological activity of molecules such as the insect-antifeedant clerodanes. Although many synthetic methods for such furofurans have been reported[3] there is still a need for synthetic methods suitable for compound **2**.



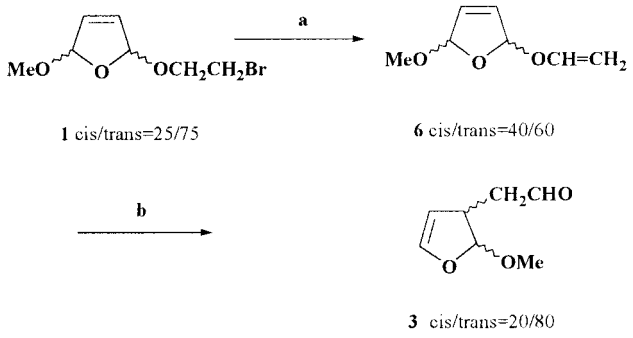
1 **2** **3** **4**

We now describe a mild, efficient procedure for the preparation of compounds like **2**, **3** and **4**. Our strategy is based on the radical cyclization of **1** in the presence of Bu_3SnH (1 mol.eq.), in benzene, with a catalytic amount of AIBN (Scheme 1), followed by the elimination of a molecule of methanol under Miginiac reaction conditions.[4] This simple two step process represents a convenient approach to the large scale preparation of **2** compared with the multistep synthesis of this compound reported in the literature.[3]

The synthesis of structure **6** can easily be achieved starting from compound **1** (Scheme 2) by dehydrobromination in the conditions reported in the literature for similar substrates[5], in a 98% overall yield.



Scheme 1
(a) Ref.1 **(b)** Bu_3SnH, AIBN, 80 ^{0}C, benzene, 8h. **(c)** $AlCl_3$, Et_3N, Et_2O

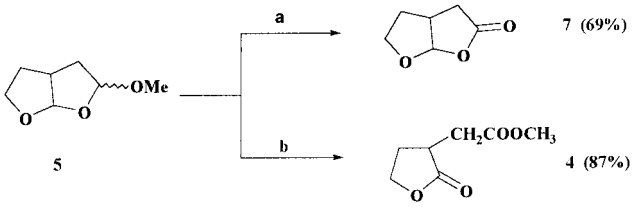


Scheme 2
(a) NaOH (5%), TBAHS, 12h, 50°C; **(b)** 3h, 185°C

Compound **3** (Scheme 2) is obtained in 25% yield from the vinyl ether **6,** by a thermal Claisen rearrangement.[6] Note that compound **3** represents a polyfunctionalized molecule characterized by the presence of three aldehydic functionalities, two of which are protected as acetal and vinyl ether moieties, respectively.

The sole by-product present in the formation of **6** and in its subsequent conversion into compound **3** is the volatile 2-methoxyfuran.

Further: the oxidation of **5** with MCPBA in the presence of stoichiometric amounts of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at room temperature[7] (Scheme 3) gives **4**[8] (R= CH_2COOMe) or 2,8-dioxabicyclo[2.2.0]octan-3-one **7**[3] (Scheme 3).



Scheme 3
(a) **5** / BF_3OEt_2/MCPBA= 1/1/1; **(b)** **5** / BF_3OEt_2/MCPBA= 1/1/2

All the structures herein synthesized are useful intermediates to more functionalized building blocks of biological interest, now easily obtainable starting from the readily accessible **1**, without employing any difficult procedures.

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Experimental

Materials and instruments: Diethyl ether was purified by distillation from $LiAlH_4$; benzene was distilled from sodium before use. Glc analyses were performed on a Perkin Elmer 8600, on a DB1, 12m × 0.22mm capillary column, and using argon as the carrier gas, equipped with a flame ionisation detector. ^1H and ^{13}C NMR (200 and 50 MHz, respectively) spectra were recorded on a Varian Gemini 200 spectrometer; all NMR data were obtained using $CDCl_3$ solutions. Chemical shifts (δ, ppm) use tetramethylsilane (TMS) (^1H NMR) or $CDCl_3$ (^{13}C NMR) as the internal standard. IR spectra were recorded on a Perkin Elmer FT-IR, 1760X spectrophotometer, using liquid films. Mass spectra (*m/z*, I%) were taken on a Perkin Elmer 8500 gas chromatograph equipped with a Q-Mass 910 detector. All isolated compounds gave satisfactory elemental analyses. The synthesis of compound **1** (Scheme 1) is described in ref.1.

3-Methoxy-2,8-dioxabicyclo[2.2.0]octane (**5**): Tri *n*-butyltin hydride (5.37ml, 0.02mol), in anhydrous benzene (50ml), was added dropwise to a solution of **1** (4.46g, 0.02mol) in the same solvent (50ml) containing a catalytic amount of azobisisobutyronitrile, at room temperature. After 15 min at room temperature the mixture was warmed at reflux for 8h. After elimination of the volatile compounds at reduced pressure (0.1 mmHg), chemically pure 3-methoxy-2,8-dioxabicyclo[2.2.0]octane (**5**) was obtained in 90% overall yield having: ν_{max}/cm^{-1} 2970, 2947, 2902, 2835, 1461, 1445, 1366, 1260, 1204, 1160, 1087, 997, 964, 902. δ_H 1.87–1.73 (m, 2H, C^6H_2), 2.35-1.95 (m, 2H, C^4H_2), 2.95-2.70 (m, 1H, C^5H), 3.37 (s, 3H, OCH_3), 4.15-3.75 (m, 2H, C^7H_2), [4.97 (d., *J* = 5.8, exo), 5.12 (dd., *J* = 5.0, 1.1, *endo*), 1H, C^3H], [5.78 (d., *J* = 5.2 *endo*), 5.86 (d., *J* = 5.3 *exo*), 1H, C^1H]. δ_C (*exo*) 32.67, 39.26, 40.75, 56.60, 66.55, 104.86, 110.83; (*endo*) 32.50, 37.42, 40.33, 54.75, 66.28, 105.26, 108.95. *m/z(%)*: 143(M^+-1, 2.6), 113(57.1), 112(37.9), 199(4.3), 98(18.0), 97(18.7), 84(32.7), 83(23.4), 81(4.1), 69(21.0), 68(9.3), 58(41.5), 55(100), 53(17.3).

2,8-Dioxabicyclo[2.2.0]oct-3-ene (**2**): An ethereal solution (50ml) of **5** (0.72g, 0.05mol) was slowly added to a mixture of anhydrous $AlCl_3$ (1.33g, 10mmol) and triethylamine (2.8ml, 20mmol), in the same solvent (100ml). The solution was stirred at room temperature for 20h, filtered, and the filtrate, after elimination of volatile compounds, gave chemically pure **2** in 70% overall yield, having: δ_H 2.30 (m., 2H, C^6H_2), 3.58 (m., 1H, C^5H), 3.75 (m., 2H, C^7H_2), 4.81 (dd., *J* = 3.0, 3.0, 1H, C^4H), 6.10 (d., *J* = 6.0, 1H, C^1H), 6.46 (d., *J* = 3.0, 1H, C^3H). δ_C 32.72, 39.33, 66.68, 101.62, 104.88, 146.24. *m/z(%)*: 112(M^+, 59.8), 97(9.3), 83(100), 81(15.7), 69(5.4), 66(5.3), 65(4.4), 55(98.8).

2-methoxy-5-vinyloxy-2,5-dihydrofuran (**6**): A mixture of benzene (60ml), of NaOH (13g) H_2O (13 ml), **1** (4.46g, 20mmol), and tetrabutylammonium sulfate (11.62g, 20mmol) was stirred at 50°C for 12h. The organic layer was then washed with water, dried over anhydrous K_2CO_3, and then filtered. After elimination of the solvent at reduced pressure (20 mmHg) a *cis: trans* (40:60) mixture of **6** was obtained in 98% overall yield having: ν_{max}/cm^{-1} 3071, 3036, 2956, 2932, 2872, 2798, 1641, 1624, 1467, 1374, 1136, 1280, 1184, 1170, 1154, 1129, 1079, 1026, 979, 941, 837, 805, 720, 679. δ_H (*cis*) 3.43(s., 3H, CH_3), 4.21(dd., *J* = 6.4, 1.7, 1H), 4.57(dd., *J* = 14.0, 1.7, 1H), 6.25–5.60(m., 4H, ring), 6.46(dd., *J* = 14.0, 6.4, 1H); (*trans*) 3.40(s., 3H, CH_3), 4.20(dd., *J* = 6.5, 1.7, 1H), 4.56(dd., *J* = 14.1, 1.7, 1H), 6.25-5.60(m., 4H, ring), 6.51(dd., *J* = 14.1, 6.5, 1H). δ_C (*cis*) 53.95, 91.75, 106.50, 109.50, 131.93, 132.45, 148.43; (*trans*) 53.91, 91.56, 104.72, 107.74, 128.34, 130.70, 148.21. *m/z(%)*: 142 (M^+, 0.1), 141(0.4), 124(0.5), 118(0.5), 111811.6), 99(100), 85(14.2), 83(12.7), 71(37.3), 68(9.2), 55(6.8).

2-Methoxy –2,3-dihydrofuran-3-acetaldehyde (**3**): The *cis/trans* mixture of **6,** obtained as above, was warmed at 185°C for 3h in a Carius tube, under nitrogen. The mixture was extracted with pentane to give, after elimination of the solvent, a *cis/trans* mixture (20:80) of chemically pure **3** in 25% overall yield, (GC and NMR analyses) having: ν_{max}/cm^{-1} 2934, 2835, 2725, 1723, 1686, 1641, 1619, 1467, 1448, 1405, 1373, 1281, 1242, 1193, 1135, 1090, 1066, 1049, 1026, 993, 977, 925, 837, 804. δ_H (*cis*) 2.88–2.39(m, 3H, CH-CH_2), 3.44(s, 3H, OCH_3), 5.01(dd, *J* = 2.0, 2.0, 1H, C<u>H</u>=CH-O), 5.86(d, *J* = 2.0, 1H, OC<u>H</u>O), 6.32(dd, *J* = 2.5, 2.0, 1H, CH=C<u>H</u>-O), 9.68(br s, 1H, CHO); (*trans*) 2.88–2.39(m., 3H, CH-CH_2), 3.40(s, 3H, CH_3), 4.85 (dd, *J* = 2.2, 2.2, 1H, C<u>H</u>=CH-O), 5.38 (d, *J* = 7.2, 1H, OCHO), 6.32(dd, *J* = 2.5, 2.2, 1H, CH=C<u>H</u>-O), 9.72(br s, 1H, CHO). δ_C (*cis*) 39.80, 42.30, 55.80, 102.99, 105.77, 144.12, 200.00; (*trans*) 42.10, 46.12, 56.22, 102.99, 105.77, 143.68, 200.94. *m/z* (%): 113(M^+-CHO, 21.7), 111(15.3), 110(10.5), 85(36.1), 82(95.8), 81(59.6), 71(36.1), 69(18.0), 55(21.7), 53(23.5).

Methyl 2-oxotetrahydrofuran-3-acetate (**4**): *m*-Chloroperbenzoic acid (80% w/w, 1.69g, 7.9mmol) was portionwise added, with stirring, to a solution containing **5** (0.72g, 5.0mmol) and $BF_3{\cdot}Et_2O$ (0.61ml, 5.0mmol), in CH_2Cl_2 (ethanol free, 100ml). After standing for 3h at room temperature, the mixture was vigorously stirred with anhydrous K_2CO_3 (2g) for 10min. The organic layers were extracted with water and dried on anhydrous K_2CO_3. The solvent was eliminated at reduced pressure (0.01 mmHg) at room temperature giving chemically pure **4** in 87% overall yield: ν_{max}/cm^{-1} 2983, 2956, 1740, 1732, 1439, 1371, 1332, 1268, 1160, 1100, 1095, 1023, 975, 961, 893, 813. δ_H 2.30–1.95(m, 1H, CH), 2.70-2.45(m, 2H, C<u>H</u>$_2$-CH_2-O), 3.80-2.80(m, 2H, CH_2-C=O), 3.70(s, 3H, CH_3), 4.50-4.15(m, 2H, CH_2-C<u>H</u>$_2$-O). δ_C 28.39, 34.24, 35.80, 51.86, 66.47, 171.54, 193.50. *m/z* (%): 157(M^+-1, 0.5), 127(32.1), 114(5.7), 99(10.6), 97(3.8), 85(6.0), 82(16.0), 72(10.4), 59(48.5), 55(100).

2,8-Dioxabicyclo[2.2.0]octan-3-one (**7**): *m*-Chloroperbenzoic acid (1.07g, 80% w/w, 5.0mmol) was portionwise added, with stirring, to a solution containing **5** (0.72g, 5.0mmol) and $BF_3{\cdot}Et_2O$ (0.61ml, 5.0mmol), in CH_2Cl_2 (ethanol free, 100ml). After stirring (3h) the mixture was vigorously stirred with anhydrous K_2CO_3 (2g, for 10min). The solution, filtered off was extracted with anhydrous pentane. The organic layer was filtered on a short silica gel column to eliminate traces of the *m*-chloroperbenzoic acid. After elimination of the solvent at reduced pressure (20mmHg) chemically pure **7** was obtained in good yield (69%) having: ν_{max}/cm^{-1} 2980, 2950, 1740, 1440, 1332, 1270, 1160, 1100, 1020, 970, 950, 810. δ_H 1.94–1.66(m., 1H, C^6H<u>H</u>), 2.34–2.04(m., 1H, C^6<u>H</u>H), 2.45(dd., *J* = 18.6, 3.6, 1H, C^4H<u>H</u>), 2.90(dd., *J* = 18.6, 10.2, 1H, C^4<u>H</u>H), 3.26-3.08(m, 1H, C^5H), 3.96(dt, *J* = 9.2, 6.0, 1H, C^7H<u>H</u>), 4.11(dt., *J* = 9.2, 2.6, 1H, C^7<u>H</u>H), 6.10(d., *J* = 4.8, 1H, C^1H). δ_C 32.31, 35.02, 38.44, 67.29, 108.43, 170.00. *m/z*(%): 84(M^+-44, 75.9), 83(25.2), 70(7.4), 69(25.0), 57(7.7), 56(48.1), 55(100), 54(71.9), 53(16.6), 51(9.0).

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