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A STRAIGHTFORWARD SYNTHESIS OF PYRAN[2’,3’:4,5]FURO-[3, 2-*b*]PYRAN FROM FURAN

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Abstract – A convenient synthesis of the title compound **1** and the related lactone **2** has been achieved through a sequence involving a Diels-Alder reaction with vinylene carbonate followed by a ring-opening metathesis (ROM)-ring closing metathesis (RCM) tandem reaction of the corresponding oxabicyclic intermediate.

Polycyclic ethers feature widely in nature being found, for instance, in many marine metabolites,[1] nucleoside antibiotics,[2] excitatory amino acids[3] and some antitumoral styryl-lactones from terrestrial origin.[4] Different synthetic strategies have been employed for the synthesis of such systems,[5] including ring-closing metathesis (RCM) reactions.[6] Among the variety of structural motifs present in these compounds, the system of pyran[2’, 3’:4, 5]furo[3, 2-*b*]pyran **1** and the related lactone **2** (Figure 1) have not been found and, perhaps by this reason, this structures have never been synthesized.

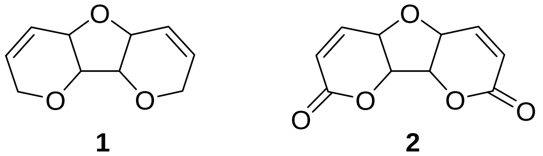
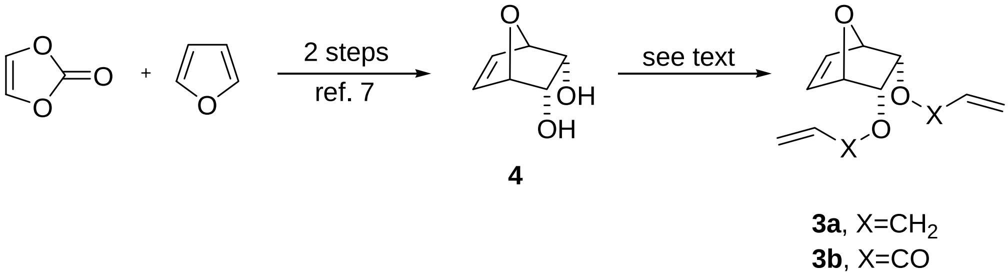


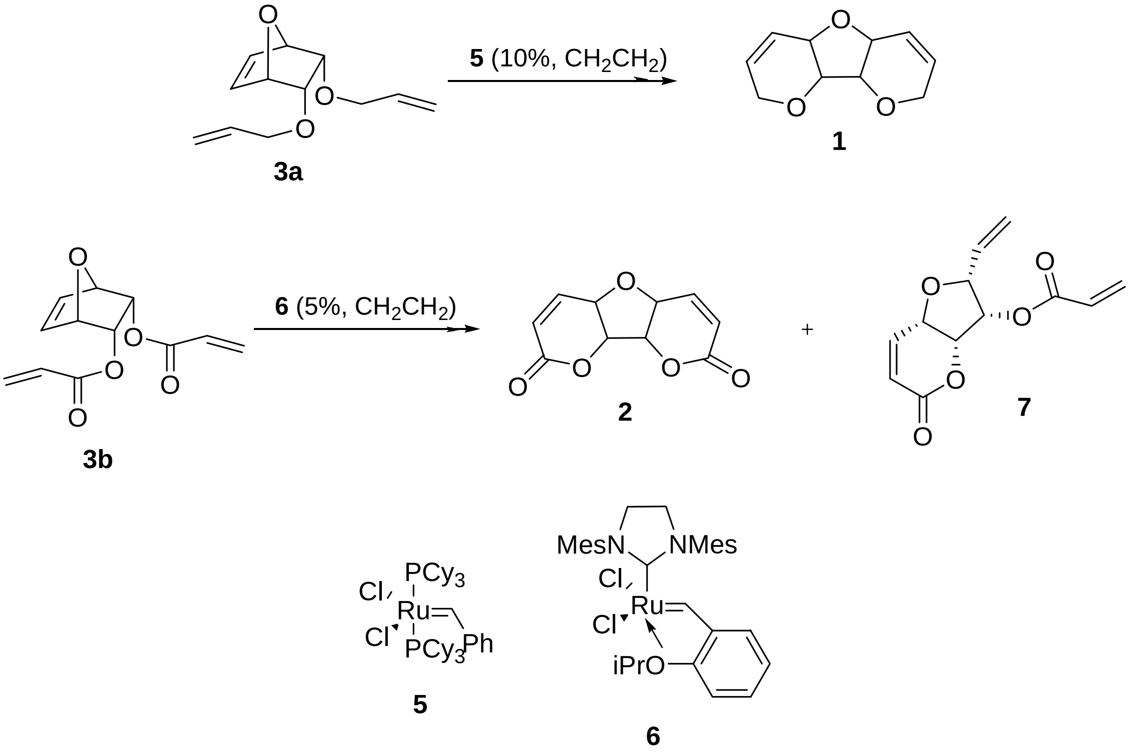
Figure 1. The pyran[2’, 3’:4, 5]furo[3, 2-*b*]pyran ring systems

In this report, we wish account for a convenient synthesis of compound **1** and **2** using as key steps the Diels-Alder reaction of furan and vinylene carbonate[7] (Scheme 1) and the ROM-RCM reaction of the oxabicyclic intermediate[8] **3a** and **3b**.



Scheme 1

Thus reaction of *endo*-diol **4** with allyl bromide (DMF, NaH, rt, 12 h.) or acryloyl chloride (DMPA, CH_2Cl_2, rt, 24 h.) afforded compounds **3a** (77%) and **3b** (76%) respectively. Treatment of **3a** with Grubbs' Ru catalyst **5** (10%, CH_2Cl_2) and of **3b** with Hoveyda-Grubbs' catalyst **6** (10%, CH_2Cl_2) (Scheme 2) afforded compounds **1** (89%) and **2** (90%). In this last case 5% of compound **7**, arising from ROM and RCM reaction on only one side of the starting material **3b** was also isolated.



Scheme 2

In summary, in this report a convenient synthesis of the hitherto not synthesized fused tricyclic furopyran derivatives **1** and **2** starting from furan has been carried out in a convenient fashion and using a tandem sequence ROM-RCM reaction as key step.

EXPERIMENTAL

General Methods

All reactions were carried out under an argon atmosphere employing techniques in handling materials. All solvents were reagents grade. Dichloromethane was freshly distilled from calcium hydride. All other reagents and solvents were used as supplied. Flash chromatography was performed on silica gel columns (Keselgel 60, 230-400 mesh). Yields refer to chromatographically and spectroscopically pure compounds. Melting points were determined on a Gallenkamp apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM- 200 and Bruker AM- 300 at room temperature in $CDCl_3$ as solvent. Coupling constants are given in Hz and chemical shift are expressed in δ values (ppm). IR spectra were recorded on a Perkin- Elmer 781 apparatus in solution of dichloromethane (compounds **1**, **3a**, **3b**, and **7**) or as a thin film on NaCl plates (compound **2**). Elemental analyses were carried out Perkin Elmer 2400 CHN apparatus at the Complutense University, Faculty of Pharmacy, Madrid.

5S*, 6R*-Bis-(allyloxy)-7-oxabicyclo[2.2.1]hept-2-ene (3a).

To a solution of diol **4**[7] (50.0 mg, 0.39 mmol) in DMSO (2.5 mL), at 0 ºC were added NaH (34.4 mg, 0.86 mmol) and allyl bromide (0.075 mL, 086 mmol). Then the reaction was stirred at rt for 24 h. After the reaction was completed, the reaction mixture was treated with 1N HCl (10 mL) and then extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with 5% aqueous $NaHCO_3$ (3 x 5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane: AcOEt, 7: 3) to afford 62.0 mg of **3a** (colourless oil, 77%).

IR: ν_{max} (CH_2Cl_2) 3054, 2986, 1727, 1422, 1265. Anal. Calcd for $C_{12}H_{16}O_3$ (208.2): C, 69.21, H, 7.74. Found: C, 69.31, H, 7.83. ^{1}H-NMR: (200 MHz, $CDCl_3$) δ 6.52 (broad s, 2H, H-2 , H-3), 5.92 (ddt , 2H, J= 17.33, 10.30, 6.0 Hz, H-2'), 5.27 (dq, 2H, J = 17.33, 1.44 Hz, H-3'$_{trans}$), 5.20 (dq, 2H, J= 10.30, 1.44 Hz, H-3'$_{cis}$), 4.93 (m, 2H, H-1, H-4), 4.07 (qd, 2H, J= 12.8, 5.65 Hz, H-5, H-6), 3.98 (dd, 4H, J= 2.51, 1.44 Hz, H-1);^{13}C-RMN: (50 MHz, $CDCl_3$) δ 134.97 (C2, C3), 134.73 (C2'), 117.72 (C3'), 79.74 (C5, C6), 75.43 (C1, C4), 72.15 (C1') ppm.

2S*,3R*-Bis-(acryloyl)-7-oxabicyclo[2.2.1]hept-5-ene (3b).

To a solution of diol **4** (120.0 mg, 0.94 mmol) in CH_2Cl_2 (5.0 mL) was added Et_3N (0.4 mL, 2.81 mmol). On this mixture cooled at 0 ºC were added acryloyl chloride (0.16 mL, 2.81 mmol) and 4-dimethyl-aminopyridine (46.0 mg, 0.375 mmol). Then the reaction was stirred at rt for 24 h. After the reaction was completed, the reaction mixture was treated with 1 N HCl (15 mL) and then extracted with CH_2Cl_2 (3 x 10 mL). The combinated organic layers were washed with saturated aqueous $NaHCO_3$ (3 x 10 mL), saturated aqueous of NaCl (3 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane: AcOEt, 7:3) to afford 160.0 mg of **3b** (colourless oil, 76%).

IR: ν_{max} (CH_2Cl_2) 3016, 2921, 2852, 1728, 1409, 1184, 809. Anal. Calcd for $C_{12}H_{12}O_5$ (236.2): C, 61.01, H, 5.12. Found: C, 61.27, H, 5.22. ^{1}H-NMR: (200 MHz, $CDCl_3$) δ (ppm) 6.50 (t, 2H, J= 0.91 Hz, H-5, H-6), 6.32 (dd, 2H, J= 17.10, 1.75 Hz, H-3'$_{trans}$), 6.02 (dd, 2H, J= 17.10, 10.34 Hz, H-2'), 5.82 (dd, 2H, J= 10.34, 1.71 Hz, H-3'$_{2cis}$), 5.26 (dd, 2H, J= 3.0, 1.64 Hz, H-2, H-3), 5.177 (m, 2H, H-1, H-4) ppm; ^{13}C-RMN: (75.5 MHz, $CDCl_3$) δ (ppm) 165,39 (C-1'), 135,14 (C5, C6), 131,89 (C-3'), 127,88 (C-2'), 79,17 (C-1, C-4), 69,16 (C-2, C-3).

Pyran[2',3':4,5]furo[3,2-*b*]pyran (1).

To a solution of **3a** (40.0 mg, 0.2 mmol) in CH_2Cl_2 (4.2 mL) at rt was added a solution of **5** (16.5 mg, 0.022 mmol) in CH_2Cl_2 (1.1 mL). Then the reaction was stirred at rt for 24 h. After the reaction was completed, the solvent was evaporated *in vacuo* and the crude product was purified by column chromatography (hexane: AcOEt, 7:3) to afford 31.0 mg of **1** (colourless oil, 89%).

IR: ν_{max} (CH_2Cl_2) 3039, 2927, 2854, 2804, 1736, 1082, 1065, 1016. Anal. Calcd for $C_{10}H_{12}O_3$ (180.2): C, 66.65 , H, 6.71. Found: C, 66.45, H, 6.67. ^{1}H-NMR: (300 MHz, $CDCl_3$) δ (ppm) 6.15 (ddt, 2H, J= 10.33, 4.08, 1.52 Hz, H3, H7), 6.06 (ddt, 2H, J= 10.33, 2.15, 1.33 Hz, H4, H6), 4.37 (ddm, 2H, J= 16.32, 4.08 Hz, H2, H8), 4.30 (dd, 2H, J= 2.86, 1.33 Hz, H9a, H9b), 4.06 (dq, 2H, J= 16.33, 2.15 Hz, H2', H8'), 3.8671 (m, 2H, H4a, H5a); ^{13}C-RMN: (75.5 MHz, $CDCl_3$) δ (ppm) 132.04 (C3, C7), 122.34 (C4, C6), 76.37 (C9a, C9b), 72.28 (C4a, C5a), 69.87 (C2, C8) ppm.

Pyran[2',3':4,5]furo[3,2-*b*]pyran-8,9-dione (2).

To a solution of **3b** (60.0 mg, 0.25 mmol) in CH_2Cl_2 (5.6 mL) at rt was added a solution of **6** (16.0 mg, 0.025 mmol) in CH_2Cl_2 (1.4 mL). Then the reaction was stirred at rt for 24 h. After the reaction was completed, the solvent was evaporated *in vacuo* and the crude product was purified by column chromatography (hexane: AcOEt, 7:3) to afford 46.0 mg of **2** (white solid, mp 200.1- 200.4 ºC, CH_2Cl_2: hexane, 90%), and 5.0 mg of **7** (colourless oil, 5%).

Compound 2.

IR: ν_{max} (film) 2922, 2852, 1732, 1640, 1388, 1125, 1046. Anal. Calcd for $C_{10}H_{12}O_3$ (210.0): C, 57.70, H, 3.87. Found: C, 57.84, H, 3.69. ^{1}H-NMR: (300 MHz, $CDCl_3$) δ (ppm) 6.72 (dd, 2H, J= 10.03, 4.00 Hz, H4, H6), 6.16 (dd, 2H, J= 10.03, 0.71 Hz, H3, H7), 5.21 (dd, 2H, J= 4.75, 1.60 Hz, H9a, H9b), 4.72 (tm, 2H, J= 4.75 Hz, H4a, H5a); ^{13}C-RMN: (75.5 MHz, $CDCl_3$) δ (ppm) 159.49 (C2, C8), 140.21 (C4, C6), 123.31 (C3, C7), 78.18 (C9a, C9b), 67.00 (C4a, C5a).

Compound 7.

IR: ν_{max} (film) 2922, 2853, 1732, 1640, 1388, 1125, 1046. Anal. Calcd for $C_{12}H_{12}O_5$ (236.22): C, 61.01, H, 5.12. Found: C, 62.03, H, 5.93. ^{1}H-NMR: (300 MHz, $CDCl_3$) δ (ppm) 6.79 (dd, 1H, J= 10.15, 3.42 Hz, H7), 6.38 (dd, 1H, J= 17.27, 1.37 Hz, $H3'_{trans}$), 6.11 (d, 1H, J= 10.15 Hz, H6), 6.03 (dd, 1H, J= 17.27, 10.43 Hz, H2'), 5.89 (dd, 1H, J= 10.43, 1.37 Hz, $H3'_{cis}$), 5.77 (ddd, 1H, J= 17.25, 10.43, 6.25 Hz, H4'), 5.64 (dd, 1H, J= 5.20, 4.70 Hz, H3), 5.39 (dt, 1H, J= 17.36, 1.30 Hz, $H5'_{trans}$), 5.32 (dd, 1H, J= 7.88, 5.20 Hz, H3a), 5.28 (dt, 1H, J= 10.43, 1.30 Hz, $H5'_{cis}$), 4.76 (ddd, 1H, J= 7.88, 3.42, 1 Hz, H7a), 4.60 (ddt, 1H, J= 6.25, 4.70, 1 Hz, H2); ^{13}C-RMN: (75.5 MHz, $CDCl_3$) δ (ppm) 164.81 (C1'), 160.68 (C5), 142.23 (C7), 132.66 (C3'), 131.66 (C4'), 127.54 (C2'), 121.51 (C6), 120.09 (C5'), 79.28 (C2), 78.04 (C3a), 73.53 (C3), 67,38 (C7a).

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