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Oxidative rearrangement of 2-alkoxy-3,4-dihydro-2*H*-pyrans: stereocontrolled synthesis of 4,5-cis-disubstituted tetrahydrofuranones

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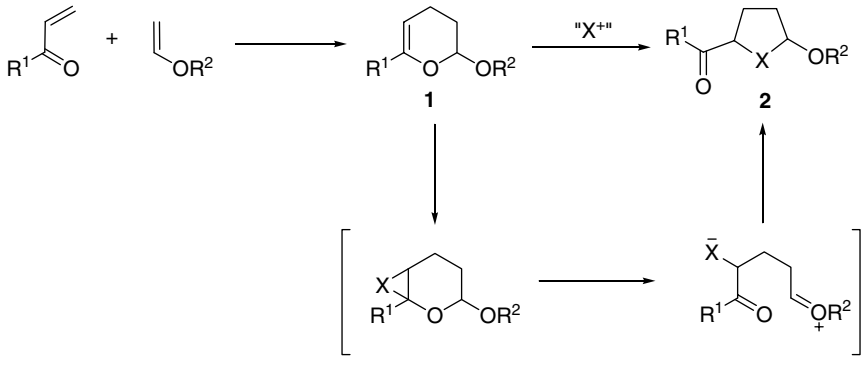
Abstract—Oxidation of 2-alkoxy-3,4-dihydro-2*H*-pyrans with dimethyldioxirane followed by Jones oxidation leads to rearrangement and stereocontrolled formation of 4,5-cis-disubstituted tetrahydrofuranones; the method is applied to the synthesis of the whisky lactone **13** and cognac lactone **14**.

We recently reported the aminative rearrangement of 2-alkoxy-3,4-dihydro-2*H*-pyrans **1**, allowing a concise and stereocontrolled synthesis of substituted pyrrolidines (**2**, X = NTs) (Scheme 1), which harnesses the initial 4+2-cycloaddition reaction between an enone and an enol ether to construct the carbon framework.[1] Products **2** are useful bis-electrophiles for synthesis of azabicycles.[2] The oxygen version of this rearrangement could potentially provide an equally rapid approach to tetrahydrofurans (**2**, X = O), which are present in a wide range of natural products. Indeed, there are several specific examples of the use of this ring contraction process for the synthesis of spiroacetals,[3] and oxidative rearrangement of two very simple substrates using mCPBA was reported by Hall in 1970.[4] We wished to explore the generality of the method and, in line with our work in the pyrrolidine series, we were particularly interested in whether substituents on the pyran substrate **1** could control the relative configuration of the THF products. Here we report our preliminary work towards this goal, leading to a stereocontrolled synthesis of 4,5-cis-disubstituted tetrahydrofuranones, a class which relatively



Scheme 1.

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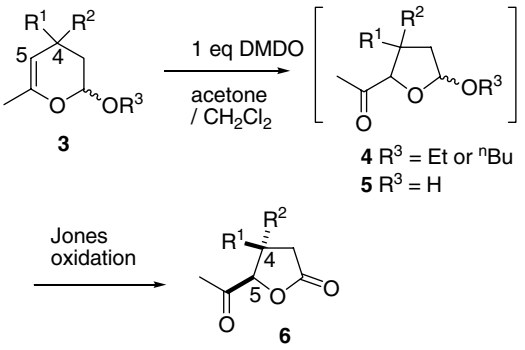
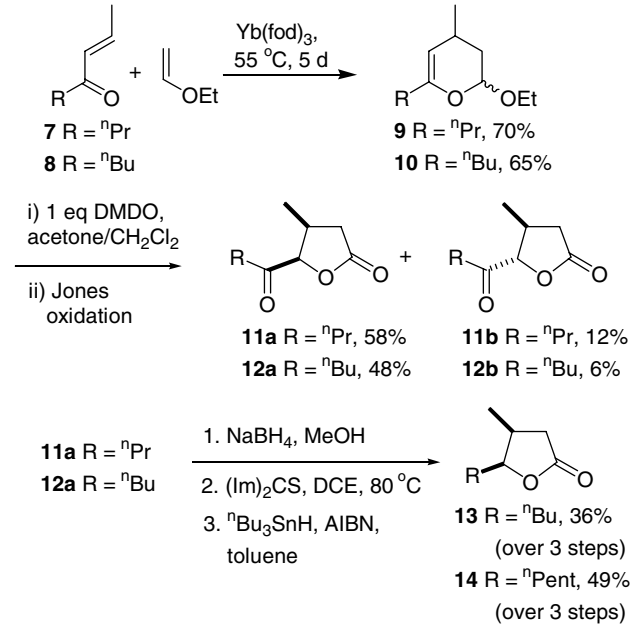


Scheme 2.

few synthetic methods for THF synthesis address,[5] and application of the method to the synthesis of γ-lactone-containing natural products.

A range of substrates **3** (Scheme 2) was prepared by Lewis acid-catalysed enol ether/enone cycloaddition.[1,6] We were pleased to find that treatment of **3a** with a solution of dimethyldioxirane (DMDO) in acetone[7] did effect the desired oxidative rearrangement. However, even when the DMDO solution was dried over K_2CO_3 prior to use, we obtained a mixture of lactol **5a** as well as the expected lactol ether product **4a**. In order to converge these to a single product, as well as to remove the lactol stereocentre to allow stereochemical analysis, we treated the product mixture with Jones reagent to provide lactone **6a** cleanly in good yield (Scheme 2; Table 1, entry 1). This process was then applied to substrate **3b** bearing a CH_3-substituent at C4. The corresponding lactone **6b** was obtained as a 3:1 mixture of diastereomers, and NOE studies indicated that the cis-isomer was the major.[8] This outcome is consistent with initial epoxidation of **3b** on the less hindered face, trans to the R^1-substituent. Pleasingly, as would be expected, higher levels of stereocontrol were observed with more sterically demanding and branched R^1 substituents (entries 3–6), with only the 4,5-cis-isomer being observed in some cases (entries 5 and 6). The process tolerates the presence of an oxygen functionality (entry 3), an isolated alkene (entry 6) and a quaternary centre in the substrate (entry 7). However, to date, substrates with a hydrogen in place of the methyl group at C6, which would lead initially to aldehyde-containing products, do not undergo the desired rearrangement with DMDO.



Scheme 3.

With the method established as a stereocontrolled route to 4,5-cis-disubstituted tetrahydrofuranones, we demonstrated its application to natural product targets, lactones **13** and **14** (Scheme 3) partly responsible for aroma and flavour in whisky and cabernet sauvignon wine.[10] The requisite substrates **9** and **10** were again prepared using a hetero Diels–Alder reaction. Oxidative rearrangement with DMDO followed by Jones oxidation proceeded to give a mixture of diastereomers (5:1 for **11a**; 8:1 for **12a** by ^{1}H NMR analysis), from which the desired cis-isomers could be separated (58% for **11a**; 48% for **12a**). The superfluous ketone moiety was removed by reduction ($NaBH_4$) followed by Barton-McCombie deoxygenation, providing the *cis*-lactones **13** and **14**, the spectroscopic data of which matched those reported for the natural products.[11]

In conclusion, we have developed a concise stereocontrolled route to 4,5-cis-disubstituted tetrahydrofuranones via oxidative rearrangement of readily available 2-alkoxy-3,4-dihydro-2*H*-pyrans. Efforts to extend this to enantioselective synthesis via use of catalytic asym-

Table 1. Conversion of pyrans **3** to lactones **6**[a]

Entry	**3**	R^1	R^2	R^3	Yield[b]	d.r.[c]
1	**a**	H	H	^{n}Bu	69	—
2	**b**	Me	H	^{n}Bu	53	3:1[d]
3	**c**	CH_2OBn	H	Et	48	95:5
4	**d**	^{i}Pr	H	^{n}Bu	63	9:1
5	**e**	Ph	H	Et	65	>95:5[e]
6	**f**	$(CH_2)_4CH{=}CHEt$	H	Et	64	>95:5[e]
7	**g**	Me	Me	^{n}Bu	50	—

[a] Typical procedure: see Ref. 9.
[b] Isolated yield of **6** over two steps from **3**.
[c] Estimated by integration of the ^{1}H NMR spectrum of the crude reaction mixture.
[d] Isomers separable by column chromatography: *cis*-lactone 32%, *trans*-lactone 10%.
[e] Only the cis product observed by ^{1}H NMR.

metric Diels–Alder or epoxidation processes are underway in our labs.

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7. Solutions of DMDO in acetone (ca. 0.05 M; titrated against iodine before use) prepared according to the procedures in: (a) Burke, S. D.; Danheiser, R. L. Oxidizing and Reducing Agents. In Handbook of Reagents for Organic Synthesis; Wiley: New York, 1999; Vol. 2, pp 149–152; (b) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377–2378.
8. Expected key NOE interactions between the substituents at C4 and C5 were observed in the major isomers.
9. Typical procedure for oxidative rearrangement: synthesis of lactone **6d**. To *n*-butyl vinyl ether (6.0 mL, 47 mmol) were added methyl vinyl ketone (3.1 mL, 24 mmol) and $Yb(fod)_3$ (1.0 g, 0.94 mmol). After heating in a pressure tube at 55 °C for 3 days, the solution was purified by column chromatography (5:95 ether/petrol) to give dihydropyran **3d** (3.8 g, 75%) as a 6:1 inseparable mixture of diastereoisomers and as a pale yellow oil, ν_{max}/cm^{-1} 2958, 2873, 1721, 1678; δ_H (250 MHz, $CDCl_3$) peaks for major isomer: 4.84 (1H, dd, *J* 9.4, 2.1 Hz, OC*H*O), 4.36 (1H, d, *J* 0.7 Hz, CC*H*), 3.90 (1H, dt, *J* 9.5, 6.6 Hz, OCH_2), 3.47 (1H, dt, *J* 9.5, 6.7 Hz, OCH_2), 2.08 (1H, dqq, *J* 12.3, 4.1, 2.1 Hz, CC*H*), 1.86 (1H, ddt, *J* 12.6, 6.2, 1.7 Hz, C*H*), 1.71 (1H, s, CH_3), 1.64–1.25 (6H, m, $3\times$CH_2), 0.94–0.82 (9H, m, $3\times$CH_3); *m*/*z* (CI) 213 (MH^+, 100%); Found: MH^+, 213.1860. $C_{13}H_{24}O_2$ requires: MH^+, 213.1854. The minor isomer, which became more significant on standing due to epimerisation, showed distinct ^{1}H NMR resonances at 5.01 (1H, t, *J* 2.7 Hz, OC*H*O) and 4.49 (1H, d, *J* 0.7 Hz, CC*H*).

   To a solution of 2-alkoxydihydropyran **3d** (191 mg, 0.9 mmol) in CH_2Cl_2 (10 mL) under nitrogen was added DMDO/acetone solution (20 mL of 0.045 M, 0.9 mmol). The mixture was stirred for 30 min at 0 °C followed by 3 h at room temperature, then washed with saturated aqueous $NaHCO_3$ solution and evaporated to give a mixture of lactol **5d** and lactol ether **4d**. This mixture was dissolved in acetone (10 mL) at 0 °C and Jones reagent (0.9 mL of 3.0 M, 2.7 mmol) was added dropwise. After stirring for 3 h, the excess of oxidant was quenched by the dropwise addition of 2-propanol until the brown colour of the mixture turned green. The reaction mixture was diluted with diethyl ether and the precipitated chromium salts were dissolved by the addition of saturated aqueous NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organics were dried ($MgSO_4$) and evaporated. Column chromatography (1:1 EtOAc/petrol) afforded lactone **6d** (96 mg, 63% over two steps from **3d**) as a colourless oil and as an inseparable 9:1 mixture of diastereoisomers by ^{1}H NMR, ν_{max}/cm^{-1} 2965, 2933, 2879, 1787, 1720, 1644; δ_H (250 MHz, $CDCl_3$) 4.88 ($1H_{major}$, d, *J* 7.1 Hz, OC*H*), 4.56 ($1H_{minor}$, d, *J* 4.9 Hz, OC*H*) 2.64–2.34 (3H, m, $COCH_2$, CH), 2.29 ($3H_{major}$, s, CH_3), 2.26 ($3H_{minor}$, s, CH_3), 1.90 ($1H_{minor}$, m, C*H*CH_3), 1.68 ($1H_{major}$, m, C*H*CH_3), 0.99 ($3H_{major}$, d, *J* 6.6 Hz, CHCH_3), 0.96 ($3H_{minor}$, d, *J* 2.1 Hz, CHCH_3), 0.94 ($3H_{minor}$, d, *J* 2.1 Hz, CHCH_3), 0.87 ($3H_{major}$, d, *J* 6.7 Hz, CHCH_3); δ_C (125 MHz, $CDCl_3$) resonances for major isomer: 205.7 (CH_3*C*O), 175.4 (O*C*O), 84.3 (CH), 46.4 (CH_2), 31.3 (CH), 29.1 (CH), 27.6 (CH_3), 21.4, 20.0 (CH_3); *m*/*z* (CI) 188 (MNH_4^+, 100%); Found: MNH_4^+, 188.1289. $C_9H_{14}O_3$ requires: MNH_4^+, 188.1287.
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11. Data for **13**: ^{1}H NMR (250 MHz, $CDCl_3$) 4.44 (1H, dd, *J* 5.8, 4.5 Hz, OC*H*), 2.66 (1H, dd, *J* 17.0, 8.0 Hz, OC(O)CH_2), 2.60–2.50 (1H, m, C*H*CH_3), 2.16 (1H, dd, *J* 17.0, 4.0 Hz, OC(O)CH_2), 1.80–1.27 (6H, m, $3\times$CH_2), 0.98 (3H, d, *J* 7.0 Hz, CH_3CH), 0.91 (3H, t, *J* 7.1 Hz, CH_2CH_3); δ_C (125 MHz, $CDCl_3$) 176.9 (O*C*O), 83.7 (CH*C*O), 37.6 (CH), 33.0 (CH_2), 29.6 (CH_2), 28.0 (CH_2), 22.5 (CH_2), 13.9 (CH_3), 13.8 (CH_3). These data are in accord with the literature: (a) Reissig, H.; Angert, H.; Kunz, T.; Janowitz, A.; Handke, G.; Bruce-Adjei, E. *J. Org. Chem.* **1993**, *58*, 6280–6285; (b) Moret, E.; Schlosser, M. *Tetrahedron Lett.* **1984**, *25*, 4491–4494.
    Data for **14**: ^{1}H NMR (250 MHz, $CDCl_3$) 4.40 (1H, dd, *J* 5.8, 4.5 Hz, OC*H*), 2.66 (1H, dd, *J* 16.9, 7.8 Hz, OCOCH_2), 2.60–2.50 (1H, m, C*H*CH_3), 2.16 (1H, dd, *J* 16.9, 3.9 Hz, OCOCH_2), 1.69–1.26 (8H, m, 3CH_2), 0.98 (3H, d, *J* 7.0 Hz, CH_3CH), 0.87 (3H, t, *J* 7.0 Hz, CH_2CH_3), δ_C (125 MHz, $CDCl_3$) 176.8 (O*C*O), 83.6 (CH*C*O), 37.6, 31.6, 29.8, 25.6, 22.5 ($5\times$CH_2), 33.0 (*C*H), 25.1, 13.9 (*C*H_3, *C*H_3). These data are in accord with the literature: (a) Jefford, C. W.; Sledeski, A. W.; Boukouvalas, J. *Helv. Chim. Acta* **1989**, *72*, 1362–1370; (b) Rojo, J.; Garcia, M.; Carretero, J. C. *Tetrahedron* **1993**, *49*, 9787–9800.