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SYNTHESIS OF 2,3-SUBSTITUTED TETRAHYDROPYRANS BY REARRANGEMENT OF 5,6-DIHYDRO-4*H*-1,3-DIOXOCINS

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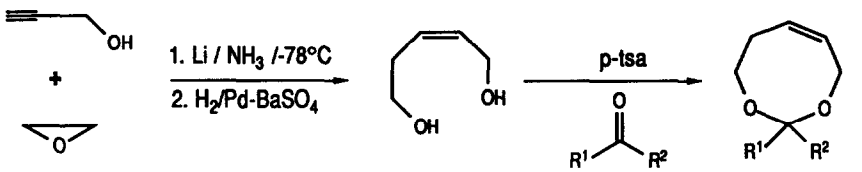
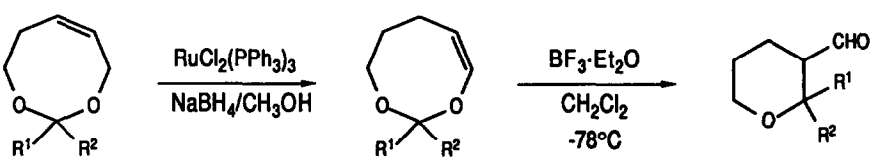
Abstract - The synthesis of 5,8-dihydro-4*H*-1,3-dioxocins **2** and 5,6-dihydro-4*H*-1,3-dioxocins **3** is described. 2-Substituted tetrahydropyran-3-carbaldehydes are obtained by acid-catalyzed rearrangement of **3**.

Tetrahydrofurans and tetrahydropyrans are often found as structural subunits in naturally occurring polyether antibiotics.[1,2] One strategy for the stereoselective synthesis of 2,3- and 2,3,5-substituted tetrahydrofurans is the rearrangement of 4,5-dihydro-1,3-dioxepins.[3,4] This procedure generally involves acetalization, double-bond isomerization and acid-catalyzed rearrangement. Analogeous to this reaction sequence we have now investigated the synthesis of tetrahydropyrans by rearrangement of 5,6-dihydro-4*H*-1,3-dioxocins **3**.



1 **2**

Even though eight-membered cyclic acetals of type **2** and **3** are not well established in the literature, 5,8-dihydro-4*H*-1,3-dioxocins **2** are easily obtained in high yields (R^1 = H, R^2 = CH_3, C_6H_5, n-C_3H_7; R^1 = CH_3, R^2 = CH_3; 68 - 80%) by acetalization of aldehydes or ketones with **1**[5] by usual procedures.



2 **3** **4**

The double-bond isomerization of the allylic precursors **2** is achieved with hydridric transition metal catalysts, whereas the isomerization with KO-*tert*-Bu only gives sluggish results. When

the eight-membered cyclic vinyl acetals[4] are reacted with Lewis acids at -78 °C, tetrahydropyran-3-carbaldehydes **4** with substituents in the 2-position are formed. Surprisingly, this rearrangement proceeds with high stereoselectivity, although no preferential conformations could be detected by first inspections of the NMR spectra of **3**. Probably the trans isomers are formed predominantly. Detailed stereochemical investigations are now in progress.

As a typical example, the synthesis and the transformation of 5,8-dihydro-2-propyl-4*H*-1,3-dioxocin are described in the following experimental details.

5,8-Dihydro-2-propyl-4*H*-1,3-dioxocin (**2**, R^1 = H, R^2 = n-C_3H_7): Obtained from n-butyraldehyde and **1** by aceotropic removal of water in the presence of p-tsa (71%); bp. 81 °C/12 Torr; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.81 (dtt, *J* = 11, 7.7, 1.2 Hz, 1 H, C*H*-CH_2-CH_2-O), 5.63 (dt, *J* = 11, 5 Hz, 1 H, C*H*-CH_2-O), 4.63 (t, *J* = 5.7 Hz, 1 H, O-CH-O), 4.32 (dd, *J* = 15.2, 5.5 Hz, 1 H, CH-C*H*$_2$-O), 4.06 (dd, *J* = 15.2, 4.2 Hz, 1 H, CH-C*H*$_2$-O), 3.88 (ddd, *J* = 11.8, 6.4, 4.7 Hz, 1 H, CH_2-C*H*$_2$-O), 3.46 (ddd, *J* = 11.8, 8.2, 4.0 Hz, 1 H, CH_2-C*H*$_2$-O), 2.59-2.33 (m, 2 H, O-CH_2-C*H*$_2$-CH), 1.62 (td, *J* = 7.8, 5.7 Hz, 2 H, C*H*$_2$-CH_2-CH_3), 1.38 (sext, *J* = 7.6 Hz, 2 H, C*H*$_2$-CH_3), 0.93 (t, *J* = 7.4 Hz, 3 H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$): δ = 129.79, 127.46 (O-CH_2-*C*H, OCH_2-CH_2-*C*H), 103.24 (O-CH-O), 66.27, 63.40 (O-*C*H_2-CH, O-*C*H_2-CH_2), 36.13 (*C*H_2-CH_2-CH_3), 28.49 (*C*H_2-CH_2O), 18.13 (*C*H_2-CH_3), 13.98 (CH_3).

5,6-Dihydro-2-propyl-4*H*-1,3-dioxocin (**3**, R^1=H, R^2=n-C_3H_7): Obtained by isomerization of **2** with $RuCl_2(PPh_3)_3$ (0.1 mol%) and $NaBH_4$ (0.2 mol%) in CH_3OH (83%); 48 °C/3.5 Torr; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.16 (d, *J* = 5.7 Hz, 1 H, O-C*H*=CH), 5.27 (td, *J* = 7, 5.7 Hz, 1 H, O-CH=C*H*), 4.68 (t, *J* = 5.9 Hz, O-CH-O), 4.02 (dt, *J* = 12.1, 4.7 Hz, 1 H, CH_2-O), 3.64 (ddd, *J* = 12.1, 8.7, 3.8 Hz, 1 H, CH_2-O), 2.29 (dddd, *J* = 14, 10, 8, 3.5 Hz, 1 H, CH=CH-C*H*$_2$), 2.11 (m, 1 H, CH=CH-C*H*$_2$), 1.9-1.5 (m, 4 H, C*H*$_2$-CH_2-CH_3, O-CH_2-C*H*$_2$-CH_2-CH), 1.42 (sext, *J* = 7.1 Hz, 2 H, C*H*$_2$-CH_3), 0.93 (t, *J* = 7 Hz, 3 H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$): δ = 141.37 (CH=*C*HO), 120.25 (*C*H=CHO), 105.16 (OCHO), 69.46 (CH_2O), 35.90 (*C*H_2-CH_2-CH_3), 29.86 (*C*H_2-CH=CH), 22.82 (O-CH_2-*C*H_2-CH_2), 18.22 (*C*H_2CH_3), 13.84 (CH_3).

2-Propyl-tetrahydrofuran-3-carbaldehyde (**4**, R^1=H, R^2=n-C_3H_7): Obtained by rearrangement of **3** with BF_3·Et_2O in CH_2Cl_2 at -78 °C and aqueous workup (74%); 43-45 °C/1 Torr; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.63 (d, *J* = 2.9 Hz, 1 H, CHO), 3.98 (dq, *J* = 11, 2.5 Hz, 1 H, O-CH_2), 3.49 (m, O-C*H*-CH) 3.38 (m, 1 H, O-CH_2), 2.33 (m 1 H, C*H*-CHO), 1.96 (m, 1 H, O-CH_2-CH_2-C*H*$_2$), 1.66-1.59 (m, 3 H, O-CH_2-CH_2-C*H*$_2$, O-CH_2-C*H*$_2$), 1.55-1.47 (m, 4 H, C*H*$_2$-CH_2-CH_3, C*H*$_2$-CH_3), 0.91 (t, *J* = 7 Hz, 3 H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$): δ = 202.74 (CHO), 76.35 (O-CH), 67.53 (O-CH_2), 54.00 (O-CHR-*C*HR), 36.71 (*C*H_2-CH_2-CH_3), 24.67 (O-CH_2-*C*H_2), 23.97 (O-CH_2-CH_2-*C*H_2), 18.56 *C*H_2-CH_3), 14.02 (CH_3).

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