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Note

The facile preparation of 6-alkoxy-2*H*-pyran-3(6*H*)-ones, and their subsequent conversion into maltol and analogous γ-pyrones

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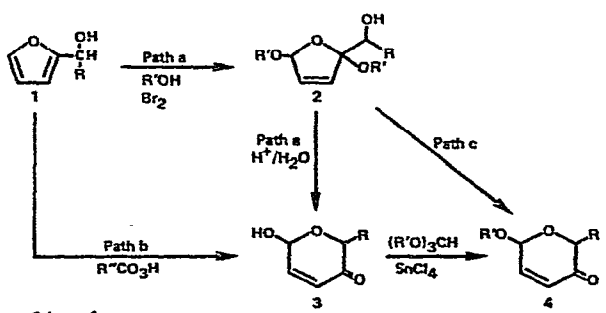
6-Alkoxy-2*H*-pyran-3(6*H*)-ones (**4**) have been shown to be versatile synthetic intermediates in carbohydrate research[1–3]. A high-yield synthesis of these compounds from furfuryl alcohols, and their efficient conversion into useful γ-pyrones, including 3-hydroxy-2-methyl-4*H*-pyran-4-one (maltol), is reported here. Compounds **4** were viewed by us as attractive intermediates to the γ-pyrones maltol (Veltol^R) and 3-hydroxy-4*H*-pyran-4-one (pyromeconic acid). Heretofore, compounds **4** have been best prepared from furfuryl alcohols (**1**) *via* the 6-hydroxy derivatives **3**, as outlined in Scheme 1(path a or b).



Scheme 1

In the widely used procedure of Achmatowicz *et al.*[2] (path a), furfuryl alcohols (**1**) are converted into dialkoxydihydrofurans (**2**) with bromine in methanol; **2** is hydrolyzed to **3**, and this is converted into the desired glycosides **4** in ~40% yield by treatment with orthoformate under Lewis-acid catalysis. Overall yields of **4** of ~30% are obtained. An alternative synthesis of **3**, developed by Lefebre and co-workers[3] (path b), involves the direct conversion of substituted furfuryl alcohols **1** into **3** in

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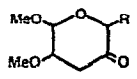
40–80% yield by oxidation with peroxy acids, followed by the low-yield conversion of **3** into **4** as just described. Major drawbacks to the envisaged route (**1** → **3** → **4**) to γ-pyrones are low overall yield, tedious isolation of **3**, and its conversion into **4** by use of expensive reagents.

Therefore, a direct conversion of the readily accessible dialkoxydihydrofurans **2** into the desired 6-alkoxy compounds **4** was sought. Acid-catalyzed rearrangement of **2** in methanolic hydrogen chloride led to a very low yield of product **4** in admixture with polymethoxylated products of types **5** and **6***.



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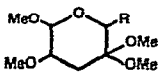

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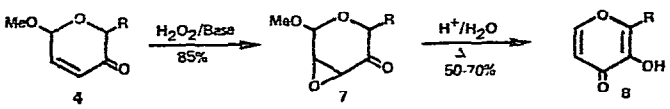
Such organic acids as formic or trifluoroacetic acid were, however, observed to convert **2** into glycoside **4** under mild conditions (path c). Initially, yields of 50–60% of **4** were obtained, together with 20–30% of a high-boiling material, presumably polymeric. However, the addition of a small proportion of a protic solvent such as methanol obviates formation of most of the polymer, and yields of 80% of **4** can be realized. The only identifiable by-product in this reaction is a small proportion (<5%) of the dimethoxy derivative **5**. In this way, **4** can conveniently be obtained in an overall yield of 70% from furfuryl alcohols **1**.

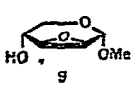
The conversion of **4** into such commercially valuable γ-pyrones as maltol (**8**, R = Me) and pyromeconic acid (**8**, R = H) was achieved *via* a carefully controlled epoxidation with hydrogen peroxide at 5°, to afford **7** in 85% yield, followed by acid-catalyzed hydrolysis–elimination[4], to give **8**, as outlined in Scheme 2.



4 7 8

Scheme 2

To confirm the identity of **7** (R = H), the β-L isomer (**7a**; methyl 2,3-anhydro-β-L-*erythro*-pentopyranosid-4-ulose) of **7** (R = H)** was synthesized from the known methyl 2,3-anhydro-α-D-lyxopyranoside[5] (**9**) by the bi-phasic, oxidation procedure with ruthenium tetraoxide[6–8]. The α-D isomer of **7** (R = H) has been reported by Paulsen *et al.*[9].



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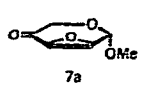

7a

*Similar products have been noted by Achmatowicz *et al.* (see ref. 2a) in the attempted conversion of **3** into **4** by methanolic acid.

The i.r. and n.m.r. spectra of this β-L isomer **7a and of the racemic material described were identical, suggesting that the epoxidation of **4** occurs in a stereospecific way, *trans* to the 6-methoxyl group.

The foregoing sequence of reactions from furfuryl alcohols (**1**) to 6-alkoxy-2*H*-pyran-3(6*H*)-ones (**4**), and thence to γ-pyrones **8**, represents a new, total synthesis of useful γ-pyrones. After completion of this work[10], two different groups published[11,12] similar routes to maltol and other γ-pyrones, in which 6-hydroxy-2*H*-pyran-3(6*H*)-ones (**3**) are converted into **4** by the method of Achmatowicz *et al.*[2]; compound **4** then gives the desired γ-pyrone **8** by the method already described.

EXPERIMENTAL

General methods. — Melting points (uncorrected) were determined with a Thomas–Hoover capillary apparatus. N.m.r. spectra were recorded with a Varian T-60 spectrometer, with tetramethylsilane as the internal standard. I.r. spectra were recorded with Perkin–Elmer Model 21 and Model 727 B spectrophotometers. Gas–liquid chromatographic studies were conducted with a Varian 90P apparatus having a column (152.4 × 0.635 cm) of SE-30 at 120°. All evaporations were conducted *in vacuo* with a water aspirator. Optical rotations were determined with a Perkin–Elmer Model 141 polarimeter. All solutions were dried with anhydrous magnesium sulfate.

*6-Methoxy-2-methyl-2*H*-pyran-3(6*H*)-one* (**4**, *R* = *R′* = *Me*). — A solution of 2,5-dihydro-2-(1-hydroxyethyl)-2,5-dimethoxyfuran[2(a)] (**2**, R = R′ = Me; 104.4 g, 0.60 mole) in methanol (40 ml) was added during 15 min at 25° to a well stirred solution of methanol (20 ml) in formic acid (400 ml). The mixture was then poured into water (1 liter) and extracted with three 500-ml portions of chloroform. The extracts were combined, washed successively with saturated sodium hydrogencarbonate solution and brine, dried, and evaporated to a light-brown oil (76.0 g). Distillation at 50–52°/2 torr (lit.[2(a)] b.p. 82–85°/30 torr) afforded 68.3 g (80%) of a clear, sharp-smelling oil whose spectral properties were identical with those of an authentic sample of **4** (R = R′ = Me) synthesized by the method of Achmatowicz *et al.*[2(a)]. G.l.c. showed this material to contain a small proportion (<5%) of the dimethoxy derivative **5** (R = Me) [retention times: **4** (R = R′ = Me) 11.0 min; **5** (R = Me) 21.5 min]. The n.m.r. spectrum of **4** showed it to be a mixture of 3 parts of *trans*- and 1 part of *cis*-**4**, based on the assignments of Achmatowicz *et al.*[2(a)].

*6-Methoxy-2*H*-pyran-3(6*H*)-one* (**4**, *R* = *H*, *R′* = *Me*). — The method described was used to convert 2,5-dihydro-2,5-dimethoxy-2-furanmethanol (**2**, R = H, R′ = Me) into the desired enone **4** (R = H, R′ = Me). This material was identical to a sample of **4** (R = H, R′ = Me) synthesized by the method of Achmatowicz *et al.*[2(a)]. G.l.c. analysis showed this material to contain a trace (<5%) of the dimethoxy compound **5** (R = H) [retention times: **4** (R = H, R′ = Me) 10.0 min; **5** (R = Me) 19.0 min].

*Tetrahydro-5,6-dimethoxy-2*H*-pyran-3(4*H*)-one* (**5**, *R* = *H*). — For identification of the minor amount of **5** described, the following synthesis was employed. A mixture of **4** (R = H, R′ = Me) (1.28 g, 10 mmoles), sodium hydrogencarbonate (1.0 g) and methanol (20 ml) was stirred for 12 h at 40°, extracted with chloroform, and the extracts combined, dried, and evaporated, to yield 1.5 g (94%) of **5** (R = H) as a light-yellow oil. Purification by g.l.c. was used to obtain a sample for spectral

analysis: i.r. $\lambda_{max}^{CHCl_3}$ 5.80 μm (C=O); n.m.r. ($CDCl_3$): δ 4.78 (1 H, d, $J_{5,6}$ 6 Hz, H-6), 4.0 (2 H, AB system, $J_{2,2'}$ 18 Hz, H-2,2'), 3.6 (1 H, m, H-4), 3.45 (3 H, s, OCH_3), 3.35 (3 H, s, OCH_3), and 2.64 (2 H, m, H-4,4').

Anal. Calc. for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.20; H, 7.54.

*Tetrahydro-5,6-dimethoxy-2-methyl-2*H*-pyran-3(4*H*)-one* (**5**, *R* = *Me*). — The method described was employed to produce **5** (R = Me); i.r. $\lambda_{max}^{CHCl_3}$ 5.80 μm (C=O); n.m.r. ($CDCl_3$): δ 4.7–4.8 [1 H, two d in 5:1 ratio, corresponding to two different stereoisomers, $J_{5,6}$ 3 (major) and 7 (minor) Hz, H-6], 4.2 (1 H, m, H-2), 3.7 (1 H, m, H-5), 3.52 (3 H, s, OCH_3), 2.85 (2 H, m, H-4), and 1.2 (3 H, two d, in 3:1 ratio, *J* 7 Hz, CH_3).

Anal. Calc. for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 54.96; H, 8.14.

2-Methoxy-4-methyl-3,7-dioxabicyclo[4.1.0]heptan-5-one (**7**, *R* = *Me*). — A solution of **4**, R = Me (2.84 g, 20 mmoles) in isopropyl alcohol (10 ml) and water (10 ml) was cooled to 0°, and the pH was adjusted to 9.0 with M sodium hydroxide. To this well stirred, cooled solution was added hydrogen peroxide (30%; 2.1 ml, 24 mmoles) dropwise at 5°, with addition of sodium hydroxide as necessary to maintain the pH between 8.0 and 9.0. The mixture was stirred for 1 h at 5°, poured into water (75 ml), and extracted with three 50-ml portions of chloroform. The extracts were combined, dried, and evaporated, to yield 2.99 g of a clear oil. Distillation at 56–58°/1 torr yielded 2.7 g (85%) of **7** (R = Me) as a clear oil. G.l.c. showed this to be a mixture of two stereoisomers in 3:1 ratio, only partly resolved in the system used (17.2 and 18.6 min); i.r. $\lambda_{max}^{CHCl_3}$ 5.75 μm (C=O); n.m.r. ($CDCl_3$): δ 5.3 (1 H, br. s, H-6), 4.1 (1 H, q, *J* 7 Hz, H-2), 3.3–3.5 (5 H, m including 3 H, s, OCH_3 and 2 H, m, H-4,5), and 1.3 (3 H, d, *J* 7 Hz).

Anal. Calc. for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 52.90; H, 6.27.

2-Methoxy-3,7-dioxabicyclo[4.1.0]heptan-5-one (**7**, *R* = *H*). — The method described for **7** (R = Me) was used to produce **7** (R = H), using **4** (R = H) as the starting enone; i.r. $\lambda_{max}^{CHCl_3}$ 5.76 μm (C=O); n.m.r. ($CDCl_3$): δ 5.2 (1 H, s, H-6), 4.1 (2 H, s, H-2,2'), and 3.3–3.6 (5 H, m including 3 H, s, OCH_3).

Anal. Calc. for $C_6H_8O_4$: C, 50.00; H, 5.59. Found: C, 50.09; H, 5.81.

*Methyl 2,3-anhydro-β-*L*-erythro-pentopyranosid-4-ulose* (**7a**). — A solution of methyl 2,3-anhydro-α-D-lyxopyranoside[7] (**9**) (0.64 g, 14.3 mmoles) in chloroform (20 ml) was mixed with water (20 ml) containing potassium metaperiodate (1.6 g) and potassium carbonate (0.14 g). To the well stirred, two-phase mixture was added ruthenium dioxide (10 mg). After being stirred for 3 h, isopropyl alcohol (2 ml) was added, and stirring was continued for 0.5 h. The phases were separated, and the aqueous layer was extracted with chloroform. The extracts were combined, washed with brine, dried, and evaporated, to yield 0.41 g (73%) of a low-melting solid having spectral properties identical to those described for **7** (R = H). Recrystallization from ether–hexane afforded white needles, m.p. 43.5–44.5°, $[\alpha]_D^{23}$ +187° (chloroform); lit.[10] m.p. for the α-D isomer of this compound, 42–45°.

Conversion of the epoxide **7** (*R* = *Me*) *into maltol* (**8**). — A solution of **7**, R = Me (14.90 g, 80 mmoles) in 2M sulfuric acid (250 ml) was boiled for 2 h under reflux, and

cooled. The pH was adjusted to 2 with 50% sodium hydroxide solution, and the mixture was extracted with three portions of chloroform. The extracts were evaporated, yielding 7.48 g of an orange solid which was recrystallized from methanol to yield analytically pure maltol (7.06 g, 70%), m.p. 159.5–160.5°.

Similarly, the epoxide 7 (R = H) was converted in 50% yield into pyromeconic acid, m.p. 113–115°, which was identical to a sample prepared by the decarboxylation of 5-hydroxy-4-oxo-4*H*-pyran-2-carboxylic acid (comenic acid[13]).

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