was removed at reduced pressure, yielding 1.06 g (97%) of the urea **5**, mp 112-113 °C (lit.[17] mp 110-112 °C). The NMR spectrum of the urea fit the structure nicely.

Preparation of α-n-Butylcyclohexanecarboxylic Acid. A. Using LDA. Diisopropylamine (1.40 mL, 10 mmol) was added to 50 mL of dry THF at -75 °C. To this solution was added 4.33 mL (10 mmol) of 2.3 M *n*-butyllithium, and the mixture stirred at -75 °C for 0.5 h. Cyclohexanecarboxylic acid (0.64 g, 5 mmol) was added as a THF solution, and the mixture was heated to 50 °C for 1 h. The reaction was cooled to -75 °C and *n*-butyl bromide (0.54 mL, 5 mmol) added neat. The mixture was stirred for 2 h at room temperature, and the product was isolated as in general procedure A. An 85% yield of alkylated acid (0.79 g) was isolated.

B. Using Lithium Naphthalenide-TMEDA. Lithium metal (0.69 g, 10 mmol) was added to a solution of naphthalene (1.28 g, 10 mmol) in 50 mL of dry THF. The mixture was stirred at room temperature for 2 h, TMEDA (1.5 mL, 10 mmol) was added at room temperature, and the mixture was stirred for 0.5 h. Cyclohexanecarboxylic acid (0.64 g, 5 mmol) was added at room temperature, and the mixture was heated to 50 °C for 1 h. The reaction was cooled to -75 °C, and *n*-butyl bromide (0.54 mL, 5 mmol) was added. The mixture was stirred at room temperature for 2 h, and the product was isolated as described in general procedure A. An 85% yield of the alkylated acid (0.79 g) was isolated.

Acknowledgment. The financial support of the Humphrey Chemical Co., North Haven, CT, is gratefully acknowledged.

Registry No. **1** ($R_1 = R_2 = CH_3$), 79-31-2; **1** ($R_1 = C_6H_5$, $R_2 = H$), 103-82-2; **1** ($R_1 = R_2 = (CH_2)_5$), 98-89-5; **1** ($R_1 = CH_3$, $R_2 = H$), 79-09-4; **4a**, 72708-59-9; **4b**, 72708-60-2; **4c**, 41951-10-4; **4d**, 72708-61-3; **4e**, 15601-92-0; **4f**, 72708-62-4; **4g**, 2719-28-0; **4h**, 72708-63-5; **4i**, 72708-64-6; **4j**, 72708-65-7; **4k**, 72708-66-8; **4l**, 72708-67-9; **4m**, 72708-68-0; **5**, 1461-81-0; phenyl isocyanate, 103-71-9; propyl isocyanate, 110-78-1; methyl isothiocyanate, 556-61-6; 1-naphthyl isothiocyanate, 551-06-4; diisopropylamine, 108-18-9; α-*n*-butylcyclohexanecarboxylic acid, 62410-48-4.

Conversion of Secondary Furfuryl Alcohols and Isomaltol into Maltol and Related γ-Pyrones

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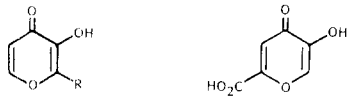
A one-pot synthesis of maltol and ethylmaltol is reported. Treatment of methylfurfuryl alcohol with 2 equiv of halogen affords good yields of 4-halo-6-hydroxy-2-methyl-2*H*-pyran-3(6*H*)-ones (**8**), which need not be isolated and can be converted to maltol by aqueous hydrolysis in the same vessel. A similar sequence employing ethylfurfuryl alcohol yields ethylmaltol. By a related series of reactions, isomaltol (**9**) can be converted to maltol.

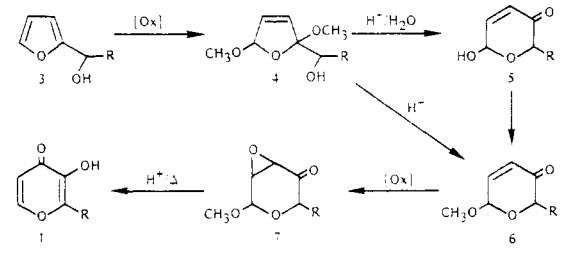
Maltol (**1**, R = CH_3; 2-methyl-3-hydroxy-4*H*-pyran-4-one) is a naturally occurring substance found in the bark of young larch trees, pine needles, and chicory.[1] Maltol and its homologue ethylmaltol (**1**, R = CH_2CH_3) are important commercial flavor and aroma agents used in a variety of food products. Early commercial production of maltol was from the destructive distillation of wood. The



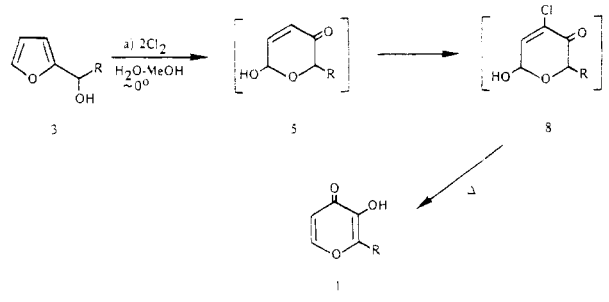
1 **2**

first synthesis of maltol was reported by Spielman and Freifelder[2] and involved the alkylation of pyromeconic acid (**1**, R = H), which had been derived from comenic acid (**2**), a fermentation product. A superior modification of this process was developed by Tate and Miller of these laboratories.[3] Subsequently, several novel syntheses of the γ-pyrone derivatives **1** have appeared in the patent literature;[4] in addition, several carbohydrate routes have been published.[5,6] Recently two similar furfuryl alcohol based syntheses have appeared, one[7] employing the known[8] **4** to **5** rearrangement and the other[9] employing the direct conversion of **4** to **6** as outlined in Scheme I.

Scheme I



Scheme II



Inasmuch as 3-hydroxy-4*H*-pyran-4-ones **1** are formally only two oxidations and a rearrangement removed from

(1) F. M. Dean, "Naturally Occurring Oxygen Ring Compounds", Butterworths, London, 1963, p 108.
(2) M. A. Spielman and M. Freifelder, *J. Am. Chem. Soc.*, **69**, 2908 (1947).
(3) B. E. Tate and R. L. Miller, U.S. Patent 3 130 204 (1964).
(4) (a) A. A. Schleppnik and M. L. Oftedahl, U.S. Patents 3 621 063 (1971), 3 491 122 (1970), 3 949 959 (1970), 3 455 960 (1969), 3 468 914 (1969), 3 476 778 (1969), 3 474 113 (1969). (b) I. Takasa, M. Higuchi, and H. Hotta, U.S. Patent 3 665 015 (1972).
(5) R. K. Chawla and W. E. McGonigal, *J. Org. Chem.*, **39**, 3281 (1974).
(6) F. W. Lichtenthaler and P. Heidel, *Angew. Chem.*, **81**, 998 (1969).
(7) T. Shono and Y. Matsumura, *Tetrahedron Lett.*, 1363 (1976); S. Torii, H. Tanaka, T. Anoda, and Y. Simizu, *Chem. Lett.*, 495 (1976).
(8) O. Achmatowicz, Jr., P. Bukowski, B. Szechner, Z. Zwierzchowska, and A. Zamojski, *Tetrahedron*, **27**, 1973 (1971).
(9) R. P. Allingham and P. D. Weeks, Belgium Patent 843 953 (1977); P. D. Weeks, D. E. Kuhla, R. P. Allingham, H. A. Watson, and B. Wlodecki, *Carbohydr. Res.*, **56**, 195 (1977).

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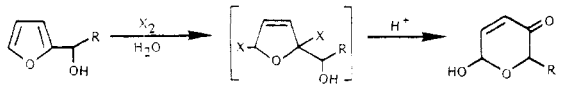
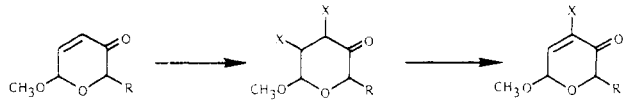
the furfuryl alcohols **3**, we sought to devise a sequence in which the oxidations could be effected sequentially under reaction conditions in which suitably formed intermediates would rearrange in situ to afford the desired γ-pyrone. We now report that the conversion of readily available furfuryl alcohols **3** to the desired γ-pyrones **1** can indeed be carried out in high yield in a one-pot sequence without isolation of intermediates, as depicted in Scheme II.[10] An analysis of the chemical events believed to occur in this unique transformation is discussed below. In addition, we report the conversion of isomaltol (**9**) to maltol (**1**) by a related sequence.

Oxidation of Furfuryl Alcohols to 6-Hydroxy-2-alkyl-2*H*-pyran-3(6*H*)-ones (5). It is known that the halogenation of furfuryl alcohols in buffered methanol leads to the formation of stable, isolable 2,5-dimethoxy-2,5-dihydrofurans (**4**),[8] presumably via intermediacy of the corresponding 2,5-dihalo-2,5-dihydrofurans (**10**, X = Br or Cl). When the halogenation is carried out in *aqueous* tetrahydrofuran or methanol (hypohalous acid being the active oxidant), presumed intermediate **10** (X = OH[11] and/or halogen[12]) undergoes smooth rearrangement to the more stable hemiacetal **5**[13] with overall liberation of 2 equiv of HBr or HCl. Since precursor furfuryl alcohol **3** is prone to polymerization under strongly acidic conditions, it is desirable to carry out these reactions by adding furfuryl alcohol **3** to preformed hypohalous acid. The resulting hydroxy enone **5** is formed in high yield, may be isolated by extraction, and is identical with a sample of **5** prepared by known methods.[8]



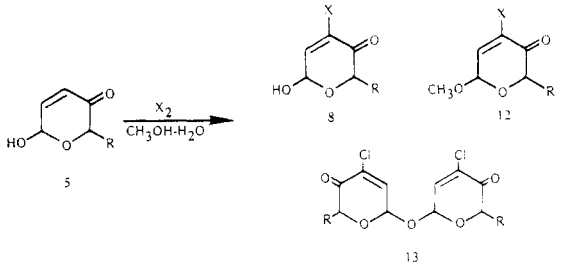
3 10 5

Addition of Halogen to the Enones 5 and 6. While oxidation of 6-methoxy enones **6** with alkaline hydrogen peroxide has been reported to afford epoxide **7** in good yield,[7,9] analogous reactions on the corresponding 6-hydroxy derivatives **5** were unsuccessful, presumably due to the lability of the hemiacetal and ketol moieties. We have also observed that 6-methoxy enones **6** are smoothly converted to the 4-halo-6-alkoxy enones **12**[14] by treatment with 1 equiv of halogen and 1 equiv of organic base. The conversion of **6** to **12** proceeds via the labile 4,5-dihalide **11**, which was not isolated in this sequence. Extrapolating



6 11 12

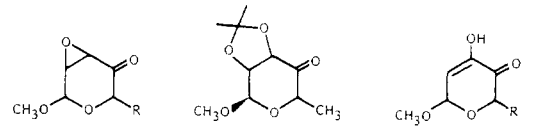
this finding to 6-hydroxy enones **5**, we were pleased to observe that treatment of our aqueous solution of **5**, prepared in situ from furfuryl alcohol **3** by halogen oxidation/rearrangement as described above, with chlorine or bromine at ice-bath temperature gave a clean conversion to the desired 4-halo-6-hydroxy-2-alkyl-2*H*-pyran-3-(6*H*)-ones (**8**). Although the spectra of isolated **8** could be taken, attempts to obtain highly purified samples of **8** resulted in dehydration to form the dimeric material **13** as a stable, crystalline mixture of cis–trans isomers. In fact, TLC analysis of the reaction mixture of the halogenation of **5** in tetrahydrofuran/water indicated that **13** was present in small amounts, even at ice-bath temperature. If methanol is employed as cosolvent, the methoxychloro enone **12** can be detected, along with **13** and the major product **8**. If this reaction mixture is allowed to warm to room temperature and sit overnight, the methoxy enone **12** precipitates as the major reaction product, presumably formed via equilibration of **8** and **13** with solvent methanol.



5 8 12 13

Hydrolysis of 6-Hydroxy- and 6-Methoxy-2-alkyl-4-halo-2*H*-pyran-3(6*H*)-ones to γ-Pyrones. As noted above, the oxidation of the furfuryl alcohol **3** in unbuffered aqueous methanol with 2 equiv of chlorine affords a solution of the 6-hydroxy-4-chloro enone **8** in hydrochloric acid, along with lesser amounts of the 6-methoxy-4-chloro enone **12** and the dimeric halo enone **13**. Upon heating this mixture to reflux for 3 h, we were able to effect the acid-catalyzed hydrolysis of the several α-halo enone species to afford the desired α-pyrone **1**. The yield of **1** based on starting **3** for this one-vessel sequence illustrated in Scheme II is ca. 70%.

Although we were unable to isolate any intermediate in the conversion of the halo enones **8**, **12**, or **13** into **1**, the conditions employed are similar to those published for the conversion of the epoxide **7** and the carbohydrate derivative **14**[5] to γ-pyrones. It is likely that all of these hydrolyses follow a common pathway involving an intermediate related to **15**.[15]



7 14 15

Conversion of Isomaltol to Maltol. Isomaltol (**9**) is available in a simple two-step procedure from lactose[16] and was therefore considered as a potentially attractive starting material for a new maltol synthesis. It is to be noted that this material is already one oxidation state closer to maltol than those furfuryl alcohols **3** discussed above. Although isomaltol itself proved too labile for our reaction sequence, the known *O*-methyl derivative **16**[16] proved suitable. To this end the trimethoxyfurfuryl alcohol **17** was prepared in good yield via a bromination–reduction sequence. As expected, this material could be converted by mild acid treatment to the 4,6-dimethoxy enone **18**. More vigorous

(10) A brief preliminary account of a portion of this material has been published: T. M. Brennan, P. D. Weeks, D. P. Brannegan, D. E. Kuhla, M. L. Elliott, H. A. Watson, and B. Wlodecki, *Tetrahedron Lett.*, 331 (1978).

(11) J. Froborg, G. Magnusson, and S. Thôren, *J. Org. Chem.*, **40**, 122 (1975).

(12) E. Baciocchi, S. Clementi, and G. V. Sebastiani, *J. Chem. Soc., Chem. Commun.*, 875 (1975).

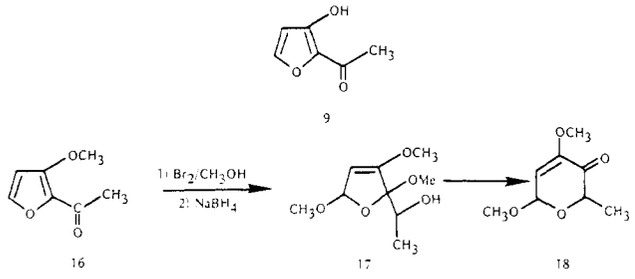
(13) Y. Lefebvre, *Tetrhaedron Lett.*, 133 (1972); R. Laliberté, G. Mêdawar, and Y. Lefebvre, *J. Med. Chem.*, **16**, 1084 (1973). Also see: J. B. Petersen, K. Norris, N. Clauson-Kaas, and K. Svanholt, *Acta Chem. Scand.*, **23**, 1785 (1969); G. Piancatelli, A. Scettri, and M. D'Auria, *Tetrahedron Lett.*, 2199 (1977).

(14) H. Paulsen, K. Eberstein, and W. Koebernick, *Tetrahedron Lett.*, 4377 (1974).

(15) F. W. Lichtenthaler, *Pure Appl. Chem.*, **50**, 1343 (1978).

(16) B. E. Fisher and J. E. Hodge, *J. Org. Chem.*, **29**, 776 (1964); J. E. Hodge and E. C. Nelson, *Cereal Chem.*, **38**, 207 (1961).

hydrolysis conditions gave maltol directly; alternately 18 could be isolated and then rearranged to 1 in good yield.[17]



Experimental Section

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Model 21 727B spectrometer. NMR spectra were obtained with a Varian XL-100 or LM360L spectrometer with Me_4Si as an internal standard. Mass spectra were taken with an AEI-MS-30 mass spectrometer. Microanalyses were performed by the Pfizer Analytical Department. Many reactions were monitored by TLC in which Brinkmann precoated silica gel plates were used together with one of the following systems: TLC system A, 95 parts of CH_2Cl_2, 5 parts of EtOAc; TLC system B, 95 parts of $CHCl_3$, 5 parts of MeOH, one part of HOAc.

Conversion of Furfuryl Alcohol 3 (R = CH_3) to Maltol (1, R = CH_3). One-Pot Procedure. A 500-mL, four-necked vessel equipped with a thermometer, an addition funnel which was modified to add liquid below the liquid level of the reaction, a mechanical stirrer, and a gas inlet/vent assembly was charged with 60 mL of MeOH and 90 mL of H_2O and then cooled to −10 °C. The addition funnel was charged with 56.0 g (0.50 mol) of methylfurfuryl alcohol dissolved in 40 mL of methanol and 10 mL of water. Chlorine gas (74.6 g, 1.05 mol) was added below the liquid level of the well-stirred reaction mixture, and the furfuryl solution was added at a rapid dropwise fashion. The addition of alcohol and chlorine was controlled such that the alcohol addition was complete after ca. two-thirds of the chlorine had been added, the temperature of the reaction being controlled between −10 and −5 °C by external cooling. The remainder of the chlorine was then added at −5 °C. The reaction was then heated to 90 °C, distilling off a portion of the methanol, and heating was continued at 90–95 °C for 3–3.5 h. At this point the reaction was cooled to 25 °C by pulling a vacuum on the system, and the aqueous maltol-rich solution (200 mL) was decanted from the tarlike residue (5.2 g of residue). The aqueous layer was then adjusted to pH 2.2 with 50% NaOH (45 mL), while the temperature was kept below 40 °C. The well-stirred solution was then cooled to 5 °C for 0.5 h to allow maltol granulation. Filtering and air-drying yielded 52.1 g of a first-crop maltol wet cake that assayed 77.4% maltol by UV analysis (40.3 g of assayed maltol, 64% yield). Extraction of the aqueous filtrate with 4 × 25 mL of $CHCl_3$ (or CH_2Cl_2) yielded 5.1 g of second-crop maltol as a semisolid that assayed 50% by UV analysis (2.35 g of assayed maltol, 4% yield). The total yield of assayed maltol, including the 3% maltol found in the reaction residue, was 71%. Analytically pure maltol, mp 159.5–160.5 °C could be obtained from the first- or second-crop material by methanol recrystallization. The UV assays discussed above were done at 274 nm, using a pure reference sample of maltol for calibration. Maltol can also be assayed by GC, using a 3 ft × $^1/_4$ in. glass column packed with Porapak P, 80–100 mesh (column temperature 200 °C, tetradecane internal standard; maltol retention time 6.5 min, tetradecane retention time 13.6 min).

By the process described above, ethylfurfuryl alcohol (3, R = CH_2CH_3) can be converted to ethylmaltol in 67% yield.

Isolation of 6-Hydroxy-2-methyl-2*H*-pyran-3(6*H*)-one (5, R = CH_3). One equivalent (35.7 g) of bromine was added to a solution of 25 g of methylfurfuryl alcohol in 125 mL of tetrahydrofuran and 125 mL of water at 5 °C. The temperature was maintained at 5 °C throughout the addition. The solution was adjusted to pH 2.1 with 10% NaOH and extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated to yield a yellow oil which was purified by chromatography on a silica gel column (3:1 chloroform–ethyl acetate eluant) to give 4.8 g (17%) of pure **5** as a clear oil, which was identical by NMR, IR, and TLC comparisons with a sample of **5** made by known methods.[8]

4-Bromo-6-hydroxy-2-methyl-2*H*-pyran-3(6*H*)-one (8, R = CH_3, X = Br) and 6,6′-Oxybis[4-bromo-2-methyl-2*H*-pyran-3(6*H*)-one] (13, R = CH_3, X = Br). To a solution containing 25 mL of water and 15 mL of tetrahydrofuran at 0 °C was added via two addition funnels at equal rates a solution containing 11.2 g (0.10 mol) of methylfurfuryl alcohol in 15 mL of tetrahydrofuran and 5 mL of water and (in the other funnel) bromine (32.0 g, 0.20 mol). The rates of addition were controlled to maintain an almost colorless reaction mixture, at −10 to 0 °C. After the addition was completed (30 min), the reaction was assayed by TLC (system A) with vanillin spray. This assay showed a clean conversion to the desired 4-bromohydroxy enone **8** (R = CH_3, X = Br) (two isomers, R_f 0.40–0.47, intense red-orange spots), along with a trace of the 6-hydroxy enone **5** (R = CH_3) (R_f 0.25, brown spot) and a trace of the dimeric material **13** (R = CH_3, X = Br) (mixture of isomers, three spots, R_f 0.60–0.70, red-orange spots). After 2 h of stirring at 25 °C, the reaction was adjusted to pH 2.2 with 50% NaOH, and extracted 3 × 50 mL with chloroform. After brine washing and drying ($MgSO_4$), concentration yielded 18.5 g of brown oil, which was chromatographed on a column of 200 g of silica gel (95:5 CH_2Cl_2–EtOAc). In this manner 4.8 g (24%) of the dimeric material **13** (R = CH_3, X = Br) (mixture of isomers) was isolated as a white solid which was recrystallized from absolute EtOH: mp 117 °C (shrinks at 114 °C); IR 1724 cm^{-1}; NMR ($CDCl_3$) δ 7.2–7.4 (2 H, m), 6.6–6.8 (2 H, m), 4.5–4.9 (2 H, m), 1.4–1.6 (6 H, m).

Anal. Calcd for $C_{12}H_{12}O_5Br_2$: C, 36.39; H, 3.05; Br, 40.35. Found: C, 36.40; H, 3.04; Br, 40.64.

A later fraction from the column yielded 4.0 g of the 6-hydroxy-4-bromo enone **8** (R = CH_3, X = Br) as a tacky tan solid: IR 3500, 1710 cm^{-1}; NMR ($CDCl_3$) δ 7.3 (1 H, d, 4 Hz), 5.62 (1 H, d, 4 Hz), 4.85 (1 H, q, 7 Hz), 3.2 (1 H, br s, OH), 1.39 (3 H, t, 7 Hz). Attempts to obtain analytically pure samples of this material resulted in dehydration to give the dimer **12** (R = CH_3, X = Br).

4-Bromo-6-methoxy-2-methyl-2*H*-pyran-3(6*H*)-one (12, R = CH_3, X = Br) from Methylfurfuryl Alcohol. To a solution containing 25 mL of water and 15 mL of methanol at −10 °C was added 11.2 g (0.10 mL) of methylfurfuryl alcohol in 5 mL of water and 15 mL of methanol, while neat bromine (32.0 g, 0.20 mol) was added. A temperature of −10 °C was maintained throughout the addition. Following this addition (30 min) TLC analysis (see above) showed a clean conversion of **3** (R = CH_3) to the 6-hydroxy-4-bromo enone **8** (R = CH_3, X = Br). After the mixture was warmed to 25 °C and stirred for 2 h, most of the hydroxy enone **8** had been converted to two new, less polar compounds which developed as red spots on the TLC system, R_f 0.80 (major) and R_f 0.75 (minor). The reaction was adjusted to pH 2.0 with 50% NaOH and cooled to 5 °C. A solid precipitated from the solution during the cooling. This material was filtered and air-dried to yield 2.7 g. This solid by TLC was mainly a mixture of the two less polar compounds with a minor amount of the 6-hydroxy compound **8** and the dimer **13**. Column chromatography on 100 g of silica gel (90% hexane–10% acetone eluant) yielded 0.7 g of the pure R_f 0.80 material and 0.9 g of a mixture of this material together with the R_f 0.75 compound. NMR analysis clearly showed that the R_f 0.80 material was *trans*-4-bromo-6-methoxy-2-methyl-2*H*-pyran-3(6*H*)-one,[18] which was recrystallized from EtOAc to yield white needles: mp 77–78 °C; IR 1710 cm^{-1}; NMR ($CDCl_3$) δ 7.2 (1 H, d, 4 Hz), 5.05 (1 H, d, 4 Hz), 4.70 (1 H, q, 6.5 Hz), 3.55 (3 H, s), 1.5 (3 H, d, 6.5 Hz).

Anal. Calcd for $C_7H_9O_3Br$: C, 38.03; H, 4.10; Br, 36.14. Found: C, 38.19; H, 4.07; Br, 36.39.

NMR analysis of the crude solid isolated from the above reaction showed that the trans–cis ratio of **12** was about 4/1. The cis isomer was never isolated in pure form, but the second fraction from the above column (mp 57–64 °C) was enriched in this minor

(17) Compound **17**, derived from a carbohydrate source and having $[\alpha]_D$ −64°, has recently been isolated by workers at Syntex: A. Craz, I. Garcia, J. Iriarte, J. M. Muchowsky, and I. Regla, *J. Org. Chem.*, **42**, 3580 (1977).

isomer: NMR ($CDCl_3$) δ 7.3 (1 H, m), 5.15 (1 H, m), 4.50–4.70 (1 H, q, 7 Hz), 3.60 (3 H, s), 1.55 (3 H, d, 7 Hz).

4-Bromo-6-methoxy-2-methyl-2*H*-pyran-3(6*H*)-one (12, R = CH_3, X = Br) from 6-Methoxy-2-methyl-2*H*-pyran-3(6*H*)-one by Bromination. To a solution of 14.2 g (0.10 mol) of the methoxy enone **6** (R = CH_3) in 40 mL of CH_2Cl_2 at 0 °C was added 16.0 g (0.10 mol) of bromine in 10 mL of CH_2Cl_2. Then 14 mL of Et_3N was added dropwise at 0 °C and the reaction was allowed to come to 25 °C and stir for 2 h. The reaction was then diluted with 200 mL of benzene and filtered to enone Et_3N·HBr. The organic solution was then washed with 5% $NaHCO_3$ and brine, treated with activated carbon and $MgSO_4$, filtered, and concentrated to yield 20.5 g of the solid bromo enone **12** (93%), having a trans–cis ratio of 4/1 by NMR (see above).

4-Chloro-6-hydroxy-2-methyl-2*H*-pyran-3(6*H*)-one (8, R = CH_3, X = Cl) and 6,6′-Oxybis[4-chloro-2-methyl-2*H*-pyran-3(6*H*)-one] (13, R = CH_3, X = Cl). To a solution containing 25 mL of water and 15 mL of tetrahydrofuran at −10 °C was added 11.2 g (0.10 mol) of methylfurfuryl alcohol in 5 mL of water and 15 mL of tetrahydrofuran, while gaseous chloride (7.46 g, 0.11 mol) was added simultaneously below the liquid level of the reaction (temperature maintained at −10 °C). After the addition was completed (30 min), the reaction was assayed by TLC (system A) with vanillin spray. This system showed very clean conversion to the desired 4-chlorohydroxy enone **8** (R = CH_3, X = Cl) (two isomers, R_f 0.40–0.45, intense orange spots), along with a trace of the hydroxy enone **5** (R = CH_3) and a trace of the dimeric product **13** (R = CH_3, X = Cl) (mixture of isomers, R_f 0.60–0.70, bright orange spots). After 2 h of stirring at 25 °C, the reaction was adjusted to pH 2.2 with 50% NaOH solution and extracted three times with 50 mL of chloroform. After brine washing and drying ($MgSO_4$), concentration yielded a light yellow oil which was chromatographed on a column of 200 g of silica gel (95:5 CH_2Cl_2–EtOAc eluant). An early fraction contained 5.0 g of 6,6′-oxybis[4-chloro-2-methyl-2*H*-pyran-3(6*H*)-one] (**13**, R = CH_3, X = Cl) as a white solid which was recrystallized from isopropyl alcohol: mp 176–179 °C; IR 1724 cm^{-1}; NMR ($CDCl_3$) δ 7.2–7.43 (2 H, m), 5.05–5.9 (2 H, m), 4.46–4.95 (2 H, m), 1.3–1.58 (6 H, m).

Anal. Calcd for $C_{12}H_{12}O_5Cl_2$: C, 46.95; H, 3.94; Cl, 23.09. Found: C, 46.71; H, 3.88; Cl, 23.22.

Another fraction from the above column yielded 4.4 g of the monomer **8** (R = CH_3, X = Cl) as a brown oil: IR 3400, 1719 cm^{-1}; NMR ($CDCl_3$) δ 7.1 (1 H, d, 4 Hz), 5.7 (1 H, d, 4 Hz), 4.6 (1 H, m), 1.2–1.4 (3 H, m). Attempts to obtain highly purified samples of **8** resulted in the isolation of the dimer **13**.

6,6′-Oxybis[4-chloro-2-ethyl-2*H*-pyran-3(6*H*)-one] (13, R = CH_2CH_3, X = Cl). By the method described above the ethyl analogue **13** (R = CH_2CH_3, X = Cl) could be prepared from ethylfurfuryl alcohol: mp 132–135 °C (from isopropyl alcohol); IR 1715 cm^{-1}; NMR ($CDCl_3$) δ 7.1 (1 H, d, 4 Hz), 5.8 (1 H, d, 4 Hz), 4.55 (1 H, dd; 4, 7 Hz), 1.68–2.20 (2 H, m), 1.05 (3 H, t, 7 Hz).

Anal. Calcd for $C_{14}H_{16}O_5Cl_2$: C, 50.17; H, 4.81; Cl, 21.17. Found: C, 50.25; H, 4.80; Cl, 20.99.

4-Chloro-6-methoxy-2-methyl-2*H*-pyran-3(6*H*)-one (12, R = CH_3, X = Cl) from Methylfurfuryl Alcohol. To a solution containing 60 mL of methanol and 90 mL of water at −10 °C were simultaneously added 56.0 g (0.50 mol) of methylfurfuryl alcohol in 10 mL of water and 40 mL of methanol and white gaseous chlorine (74.6 g, 1.05 mol). The rate of alcohol solution and chlorine addition was controlled to maintain a clear color; the rapid addition of alcohol would cause the reaction to darken. A temperature of −10 to 0 °C was maintained throughout the addition. After the addition was completed, TLC analysis as above showed a good conversion to the 6-hydroxy-4-chloro enone **8** (R = CH_3, X = Cl). The reaction was then allowed to come to 25 °C and stir for 16 h under N_2. TLC analysis at this time showed the conversion of **8** to a new orange spot, R_f 0.75. The entire reaction mixture was then extracted with 2 × 100 mL of CH_2Cl_2. The organic layers were combined, washed with 10% $NaHCO_3$ and brine, and dried ($MgSO_4$) to yield, upon concentration, 11.3 g of crude 4-chloro-6-methoxy-2-methyl-2*H*-pyran-3(6*H*)-one (**12**, R = CH_3, X = Cl), mp 62–64 °C. This material was recrystallized from methanol to yield white needles: mp 70–70.5 °C; IR 1717 cm^{-1}; NMR ($CDCl_3$) δ 7.0 (1 H, d, 4 Hz), 5.15 (1 H, d, 4 Hz), 4.65 (1 H, q, 7 Hz), 3.5 (3 H, s), 1.45 (3 H, d, 7 Hz).

Anal.: exact mass calcd for $C_7H_9O_3Cl$, 176.0240; found, 176.0243.

The NMR coupling indicates that this material is the trans isomer.[18]

4-Chloro-6-methoxy-2-ethyl-2*H*-pyran-3(6*H*)-one (12, R = CH_2CH_3, X = Cl). By the method described in the previous example the ethyl analogue could be prepared as a thick oil: IR 1715 cm^{-1}; NMR ($CDCl_3$) δ 7.0 (1 H, d, 4 Hz), 5.2 (1 H, d, 4 Hz), 4.4 (1 H, dd), 3.5 (3 H, s), 1.6–2.2 (2 H, m), 1.0 (3 H, t, 7 Hz).

Anal. Calcd for $C_8H_{11}O_3Cl$: C, 50.41; H, 5.82; Cl, 18.60. Found: C, 50.30; H, 5.62; Cl, 18.54.

4-Chloro-6-methoxy-2-methyl-2*H*-pyran-3(6*H*)-one (12, R = CH_3, X = Cl) from 6-Methoxy-2-methyl-2*H*-pyran-3(6*H*)-one (6, R = CH_3). To a solution of 7.1 g (0.05 mol) of the enone **6** (R = CH_3) in 70 mL of CH_2Cl_2 at −10 °C was added chlorine (2.6 mL condensed in a dry ice trap). The reaction warmed to +10 °C during the addition, which required 30 min. The reaction was then cooled to −10 °C and 5.0 g (0.05 mol) of triethylamine was added dropwise. After the addition was complete the reaction was warmed to +10 °C and stirred 25 min. The reaction was then filtered and concentrated, and the resulting oil was taken up in 100 mL of benzene. After filtration, concentration yielded 8.7 g (98%) of **12** (R = CH_3, X = Cl) as a light brown oil which solidified upon standing. NMR analysis of this solid showed the trans–cis ratio of **12** in this reaction to be 3/2.[18] Crystallization from methanol gave the trans isomer, which was identical with the material obtained in the above example. The cis isomer was never isolated in pure form but showed the following: NMR ($CDCl_3$) δ 7.0 (1 H, br s), 5.25 (1 H, br s), 4.55 (1 H, q, 7 Hz), 3.55 (3 H, s), 1.55 (3 H, d, 7 Hz).

Conversion of 4-Chloro-6-methoxy-2-methyl-2*H*-pyran-3(6*H*)-one (12, R = CH_3, X = Cl) to Maltol. A solution of 1.80 g (0.01 mol) of the chloro enone **12** (R = CH_3, X = Cl) in 20 mL of acetic acid was heated to reflux for 1.5 h. The reaction was then cooled to 25 °C and diluted with 20 mL of water, and the pH was adjusted to 6.8 with 50% NaOH. Isolation by chloroform, as in example 1, yielded 0.83 g of pure maltol (66% yield). Other acidic hydrolysis conditions, such as 2 M H_2SO_4 and 10% HCl, could be employed with similar results.

Conversion of 6-Methoxy-2-methyl-2*H*-pyran-3(6*H*)-one (6, R = CH_3) to Maltol. The enone **6** (R = CH_3) (1.42 g, 0.01 mol) was dissolved in 20 mL of acetic acid, and to this rapidly stirred solution at 10 °C was distilled over 30 min 1.0 mL of condensed chlorine. Assay by TLC (see above) showed the clean formation of **12** (R = CH_3, X = Cl). The reaction mixture was then heated to reflux for 1.5 h and cooled to 25 °C. Isolation as above afforded a 56% yield of maltol.

2-Acetyl-2,3,5-trimethoxy-2,5-dihydrofuran. To a solution of isomaltol *O*-methyl ether (10.0 g, 0.072 mol) in 70 mL of methanol was added 17.0 g (0.16 mol) of $NaHCO_3$, and the mixture was cooled to −30 °C. To this well-stirred solution was added a solution of 12.8 g (0.08 mol) of bromine in 10 mL of methanol. The temperature of the reaction was maintained between −30 and 0 °C with cooling. After the addition period the reaction was allowed to warm to room temperature and stir for 2 h. The reaction was then filtered and concentrated to yield 13.4 g of a yellow oil, which was distilled at 79–83 °C (0.75 torr) to yield 10.09 g (75%) of 2-acetyl-2,3,5-trimethoxy-2,5-dihydrofuran: IR 1730, 1666 cm^{-1}; NMR ($CDCl_3$) δ 5.6 (1 H, d, 2 Hz), 5.1 (1 H, d, 2 Hz), 3.7 (3 H, s), 3.5 (3 H, s), 3.37 (3 H, s), 2.3 (3 H, s). This material was not purified further but was used directly in the next step of this sequence.

2-(1-Hydroxyethyl)-2,3,5-trimethoxy-2,5-dihydrofuran (17). The crude ketone produced above (9.22 g, 0.049 mol) was dissolved in 100 mL of methanol and cooled to 0 °C. Solid $NaBH_4$ (4.0 g, 0.105 mol) was added portionwise over 1 h, while a temperature below 15 °C was maintained. The reaction was then allowed to warm to room temperature, and 20 mL of saturated aqueous NH_4Cl was added. Extraction of the crude product with chloroform and concentration yielded 9.3 g of crude 2-(1-hydroxyethyl)-2,3,5-trimethoxy-2,5-dihydrofuran (**17**) (100%) as a clear oil: IR 3450, 1665 cm^{-1}; NMR ($CDCl_3$ + D_2O) δ 5.5 (1 H, m), 5.03 (1 H, m), 3.8 (4 H, m), 3.58 (3 H, s), 3.3 (3 H, s), 1.10 (3 H, t).

(18) The NMR spectra of *cis*- and *trans*-2*H*-pyran-3(6*H*)-ones is well studied; see ref 8 as an example.

Attempts to distill this material resulted in product decomposition, and therefore this material was converted to the ketone **18** without further purification.

4,6-Dimethoxy-2-methyl-2*H*-pyran-3(6*H*)-one (18).[17] To a solution of 6 mL of anhydrous formic acid and 2.3 mL of methanol at 20 °C was added dropwise the crude dihydrofurfuryl alcohol **17** (2.0 g, 0.010 mol) in 1.0 mL of methanol over 15 min. After an additional 10 min of stirring, the reaction was quenched into 20 mL of water and extracted with CH_2Cl_2 (5 × 20 mL). The combined organic layers were washed with saturated $NaHCO_3$ (2 × 20 mL) and brine, dried ($MgSO_4$), and concentrated to yield crude 4,6-dimethoxy-2-methyl-2*H*-pyran-3(6*H*)-one (**18**) as a tan solid: mp 56–64 °C; 1.3 g (77%). Sublimation at 31 °C (0.08 mm) yielded white needles: mp 73–74.5 °C; IR 1710 cm^{-1}; NMR ($CDCl_3$) δ 5.75 (1 H, d, 4 Hz), 5.3 (1 H, d, 4 Hz), 4.62 (1 H, q, 7 Hz), 3.68 (3 H, s), 3.52 (3 H, s), 1.3 (3 H, t, 7 Hz).

Anal. Calcd for $C_8H_{12}O_4$: C, 55.80; H, 7.02. Found: C, 55.55; H, 6.61. Exact mass calcd for $C_8H_{12}O_4$, 172.0735; found, 172.0731. Mass spectrum, *m/e* (relative intensity) 172 (1.9), 141 (43.8), 131 (35.1), 117 (45.2), 85 (100), 71 (24.5), 59 (23.6), 50 (64.9).

Conversion of 4,6-Dimethoxy-2-methyl-2*H*-pyran-3-(6*H*)-one (18) to Maltol. The ketone **18** (0.65 g, 0.004 mol) in 10 mL of 2 M H_2SO_4 was stirred at 25 °C for 20 min. TLC (system B, with UV visualization) showed that the ketone **18** (R_f 0.66) was cleanly converted to the γ-pyrone **1** (R = CH_3) (R_f 0.50). Isolation by adjustment to pH 2.2 and chloroform extraction yielded a light tan solid, which assayed 88% maltol by the UV assay discussed above (74% adjusted yield).

Conversion of 2-(1-Hydroxyethyl)-2,3,5-trimethoxy-2,5-dihydrofuran (17) to Maltol. The dihydrofurfuryl alcohol **17** (2.30 g, 0.012 mol) was stirred for 4 h in 50 mL of H_2SO_4 at 25 °C. TLC (system A) as above showed a high conversion of **17** to maltol. Isolation as above yielded 1.33 g of crude maltol of 78% purity (67% adjusted yield).

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Registry No. **1** (R = CH_3), 118-71-8; **1** (R = CH_2CH_3), 4940-11-8; **3** (R = CH_3), 4208-64-4; **3** (R = CH_2CH_3), 4208-61-1; **5** (R = CH_3), 41728-14-7; **6** (R = CH_3), 41728-10-3; **8** (R = CH_3, X = Br), 66187-06-2; **8** (R = CH_3, X = Cl), 66187-15-3; **9**, 3420-59-5; *cis*-**12** (R = CH_3, X = Br), 72690-03-0; *trans*-**12** (R = CH_3, X = Br), 72690-04-1; *cis*-**12** (R = CH_3, X = Cl), 72690-05-2; *trans*-**12** (R = CH_3, X = Cl), 72690-06-3; **12** (R = CH_2CH_3, X = Cl), 72622-91-4; **13** (R = CH_3, X = Br), 66187-09-5; **13** (R = CH_3, X = Cl), 66187-10-8; **13** (R = CH_2CH_3, X = Cl), 66187-11-9; **17**, 67171-01-1; **18**, 63493-69-6; 2-acetyl-2,3,5-trimethoxy-2,5-dihydrofuran, 67171-02-2.

trans,trans-Germacra-1(10),4-dien-*cis*-6,12-olides from *Montanoa hibiscifolia*[1]

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The isolation of three germacradienolides from *Montanoa hibiscifolia* (Benth.) Sch.-Bip. is described. The deduction that these lactones, one of which has been reported previously from *M. pteropoda*, are actually members of the new class of *trans,trans*-germacra-1(10),4-dien-*cis*-6,12-olides was verified by X-ray analyses of **2a** and **4a**. Evidence is presented for the absolute configurations.

Sesquiterpene lactones have been isolated from several *Montanoa* species.[2-4] One of these is *Montanoa tomentosa* Cerv. (zoapatle) which enjoys a medicinal reputation in Mexico and also elaborates various diterpenoids, including the friedokauranolide zoapatlin[6] and the contragestationally active oxepane diterpenoids zoapatanol and montanol.[7]

Our attention was attracted to a germacradienolide recently isolated from *M. pteropoda* Blake[3] whose NMR spectrum seemed at variance with either of the proposed structures **1a** or **1b**. In particular, the small value of $J_{7,13}$ (1 Hz) suggested that the molecule might actually be **2a** or **3b** with an unprecedented (among germacradienolides) cis-lactone ring closed to C-6,[8a,b] since a heliangolide formula also capable of giving rise to such small values of $J_{7,13}$[9] was contraindicated by other data. It was also surmised that two congeners from *M. pteropoda*[3] and possibly the germacradienolide tomentosin from *M. tomentosa*[2] might possess analogous structures. We now report verification of this hypothesis for the compounds from *M. pteropoda* by isolation and structure elucidation of **2a**, **3a**, and **4a** from *M. hibiscifolia* (Benth.) Sch.-Bip.[10]

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(2) Geissman, T. A.; Griffin, T. S. *Rev. Latinoam. Quim.* **1971**, *2*, 81.

(3) Bohlmann, F.; LeVan, N. *Phytochemistry* **1978**, *17*, 1957.

(4) Quijano, L.; Calderon, J. S.; Gomez, F.; Rios, C. T. *Phytochemistry* **1979**, *18*, 843.

(5) Martinez, M. "Las Plantas Medicinales de Mexico", 3rd ed.; Ediciones Botas: Mexico, D.F., 1944.

(6) Caballero, Y.; Walls, F. *Bol. Inst. Quim. Univ. Nac. Auton. Mex.* **1970**, *22*, 79.

(7) Levine, S. D.; Adams, R. E.; Chen, R.; Cotter, M. L.; Hirsch, A. F.; Kane, V. K.; Kanojia, R. M.; Shaw, C.; Wachter, M. P.; Chin, E.; Huettemann, R.; Ostrowski, P.; Mateos, J. L.; Noriega, L.; Guzman, A.; Mijarez, A.; Tovar, L. *J. Am. Chem. Soc.* **1979**, *101*, 3404.

(8) (a) Samek, Z. *Tetrahedron Lett.* **1970**, 671. (b) Samek, Z. *Collect. Czech. Chem. Commun.* **1978**, *43*, 3210. (c) Samek, Z.; Harmatha, J. *Ibid.* **1978**, *43*, 2779.

(9) Herz, W.; Wahlberg, I. *J. Org. Chem.* **1973**, *38*, 2485.

0022-3263/80/1945-1113$01.00/0