Potentially Mutagenic, Chlorine-Substituted 2(5*H*)-Furanones: Studies of Their Synthesis and NMR Properties

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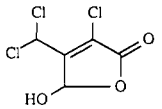
The mutagen 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone (MX), **1**, and seven analogues of it were synthesized from 4-(hydroxymethyl)-2(5*H*)-furanone, **2**. This investigation was undertaken to learn if **2** would serve as a versatile starting point for the preparation of MX analogues required for structure/activity studies of genotoxicity. Compound **2** was treated with thionyl chloride–pyridine to develop the C-4 chloromethyl group. Oxidation of **2** with pyridinium chlorochromate to the aldehyde, followed by treatment of the latter with phosphorus pentachloride, developed the C-4 dichloromethyl group. Thereafter, when attachment of chlorine at C-3 was desired, the aluminum chloride promoted chlorine addition to the C-3–C-4 double bond followed by the triethylamine-promoted elimination of hydrogen chloride resulted in the required 3-chloro-4-(chloromethyl) or 4-(dichloromethyl)-5-desoxy analogues of MX. Hydroxylation at C-5 was achieved in two steps, involving first bromine substitution employing NBS under free radical conditions followed by metal ion assisted hydrolysis of the bromide in aqueous acetone. Special regard was paid to the characterization of MX and its analogues by assessing the values of ^{13}C NMR chemical shift, the consistency of substitution effects, and the occurrence and magnitude of direct and long-range couplings in the spectra of these compounds.

To date, 3-chloro-4-(dichloromethyl)-5-hydroxy-2-(5*H*)-furanone (**1**), often referred to simply as MX, is the most potent member of a class of mutagens originating from chlorination in softwood pulping[1] and disinfection of humic waters.[2] Mutagenicity is reported to range from



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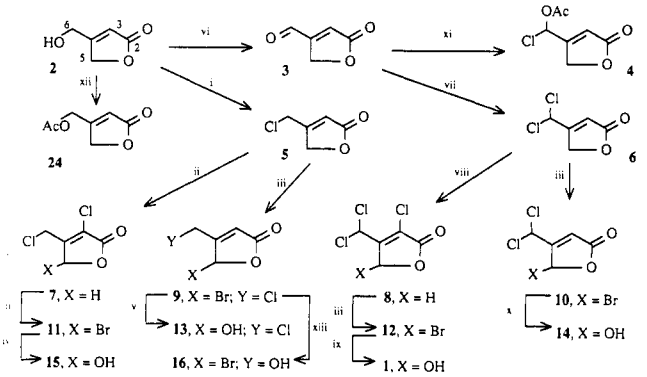
$\sim 10^3$–10^4 revertants/nmol in the Ames test using *Salmonella typhimurium* (TA100) in the absence of rat liver homogenate (S9) fraction.[1b,2c,3] MX is clastogenic in studies with Chinese hamster ovary cells,[2e] and recently evidence has been presented showing that DNA–MX adducts form when both bacterial and mammalian cell lines are treated with MX.[2f] Although MX has been synthesized,[4] the method is not generally applicable to the preparation of a number of MX analogues required for stability and structure/activity investigations.[5] With the need for a more versatile synthetic method in mind, we studied the utility of 4-(hydroxymethyl)-2(5*H*)-furanone, **2** (Scheme I), which in our laboratory is readily obtained in 50% overall yield in three steps from commercially available starting materials employing the method of Thaller and co-workers.[6]

Scheme I[a]



[a] Starting from **2**, overall yields in the preparation of **1**, **5**–**8**, and **13**–**15** and reagents used in each of the indicated steps: (i) $SOCl_2$/pyridine (**5**, 88%); (ii) $Cl_2/AlCl_3$, then Et_3N (**7**, 58%); (iii) NBS; (iv) AgOAc/10% H_2O–acetone (**15**, 23%); (v) AgOAc/3% H_2O–acetone (**13**, 45%); (vi) PCC on NaCl (**3**, 66%); (vii) PCl_5 (**6**, 48%); (viii) $Cl_2/AlCl_3$, then Et_3N (**8**, 41%); (ix) $Hg(OAc)_2$/3% H_2O–acetone (**1**, 15%); (x) AgOAc/1% H_2O–acetone (**14**, 17%); (xi) AcCl/$AlCl_3$; (xii) AcCl; (xiii) LiOH, H_2O.

Since **2** incorporates all the carbon–oxygen skeletal requirements of the desired group of MX analogues, only functional group modifications were called for. The compounds of interest are distinguished by the oxidation state of the carbon atom attached to C-4, as reflected in the presence of chloromethyl or dichloromethyl groups. The compounds are further distinguished by the presence of hydrogen or chlorine at C-3 and of hydrogen or hydroxyl group at C-5. Thus the several MX analogues are simply related by the oxidation states of C-3 and C-5 and the carbon (C-6) affixed to C-4.

Preceding our study of the transformations of **2**, we had investigated the use of MX, and an intermediate utilized in the preparation of MX, as entries into **8** and **14**. The latter compounds are key analogues required for mutagenic testing. We observed[7] that the preparation of **8** by reduction of MX at C-5 was complicated by a high degree of conjugate reduction at C-3 as well. Since considerable effort was entailed in preparing MX by the published

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procedure, the reduction route to 8 from MX was judged inefficient. Moreover, the attempt to prepare 14 from an intermediate used in the previously reported synthesis of MX was unsuccessful (vide infra). These early attempts in our laboratory underscored the peculiarities of MX analogue preparation and the consequent need for the alternative versatile synthesis which is reported here.

Because of multiple chlorine substitution in MX and its derivatives, ^{1}H NMR often was unable to provide comprehensive structural information. Therefore, we paid special attention to ^{13}C NMR properties, including long-range J_{CH} values, which we believed should prove useful in future characterizations of the heavily chlorine substituted MX class of mutagens.

Results and Discussion

Synthesis in both the chloromethyl and dichloromethyl series of 5-hydroxy-2(5*H*)-furanones followed the same sequence of steps. This sequence involved first the incorporation of the requisite chlorine at the exocyclic carbon atom (C-6), bromination of C-5, and the selective replacement of the bromine atom by the hydroxyl group. When chlorine was required at C-3, it was introduced after the incorporation of exocyclic chlorine but prior to the bromination step. Overall yields of both the 5-desoxy and 5-hydroxy MX analogues, which were the compounds selected for future stability and mutagenicity studies, are noted in Scheme I. Similarly, the ^{1}H and ^{13}C NMR parameters for this group of compounds have been compiled and are set aside in tables (Table II and III, respectively) in the interest of future ready access to NMR properties of the MX class of mutagens. However, NMR properties of intermediates leading to the 5-desoxy and 5-hydroxy MX analogues appear as usual within the appropriate subheadings of the Experimental Section.

While the starting point for the synthesis in the chloromethyl series was the primary alcohol 2, the starting point for the synthesis in the dichloromethyl series was the corresponding aldehyde 3. The latter was best prepared by the oxidation of 2 with pyridinium chlorochromate (PCC)[8] supported on powdered sodium chloride. Numerous trials employing several other oxidizing agents, including *N*-iodosuccinimide,[9] 2,2′-bipyridinium chlorochromate,[10] and the Swern oxidation,[11] showed that the use of these oxidizing agents would be of no advantage or avail in the routine preparation of 3.

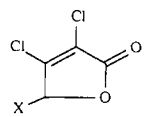
Concentrating solutions of 3 resulted in its polymerization as evidenced by the appearance of resonances in the ^{1}H NMR attributable to the OCHO groups. Therefore 3 was prepared fresh for use or, when required, stored in dilute solution in the cold, but it was not kept longer than a few days since on prolonged storage it oxidized to the corresponding carboxylic acid. In order to facilitate the characterization of 3, the geminal acetoxy chloride 4 was prepared. This transformation was realized with acetyl chloride in the presence of aluminum chloride. Use of these conditions has been recommended[12] for the conversion of α,β-unsaturated aldehydic carbonyls to geminal dichlorides, but, in the present case, the geminal acetoxy chloride resulted.

Attempts to convert the hydroxymethyl group of 2 to the chloromethyl group of 5 by employing triphenylphosphine–carbon tetrachloride[13] resulted in extremely low yields of the desired product, which, in some cases, was mixed with a rearranged byproduct whose spectral data were consistent with 5-chloro-4-methyl-2(5*H*)-furanone. These difficulties were circumvented when thionyl chloride–pyridine[14] in dichloromethane was substituted for the above reagent.

The formyl group of 3 was transformed with a 5-fold excess of phosphorus pentachloride to the dichloromethyl group in 6. However the crude product contained approximately 5% of the rearranged chloromethyl 7. The formation of 7 was not unexpected based on previous examples of the behavior of α,β-unsaturated aldehydes and ketones to the action of phosphorus-, sulfur-, and selenium-based halogenating agents.[15]

The introduction of chlorine at C-3 in both the chloromethyl and dichloromethyl series of compounds was achieved by the aluminum chloride catalyzed addition of chlorine to 5 and 6 followed by triethylamine–promoted elimination of hydrogen chloride in order to obtain 7 and 8 respectively. To facilitate the synthesis of 8, 4-(hydroxymethyl)-2(5*H*)-furanone (2) was transformed in the same dichloromethane solution through all successive steps. Only crude 8 was chromatographed, to obtain the pure compound. Also separated in minor amount was a compound whose spectra agreed with the structure of 4-(chloromethyl)-3,3,4-trichloro-2(5*H*)-furanone, which resulted from byproduct 7 at the chlorine addition step.

Introduction of the C-5 hydroxyl group was achieved through bromination followed by selective hydrolysis at the bromine-bearing carbon. The free-radical bromination employing NBS,[16] proceeded without attack at the exocyclic carbon. Only in the case of the transformation of 8 to 12 were exceptional conditions involving a large excess of NBS, a long reaction period, and a lower temperature required for the complete conversion to bromide. In all but one case the critical hydrolysis step succeeded in satisfactory yields when the C-5 bromo compound in acetone, which contained 3–10% by volume of water, was treated with 1.1 equiv of silver acetate. Under these conditions, the pH of the medium became less than 7 through the buffering action of acetate anion. Typically, 1 g of bromide per 50 mL of aqueous acetone was the concentration employed. Only in the case of the hydrolysis of bromide 12 to MX was silver acetate ineffective in promoting the hydrolysis of the bromide. However, when mercuric acetate replaced silver acetate, MX was realized in 37% yield from 8 via bromide 12.[17] Conditions appropriate for the hydrolyses of the various bromides were established first by various trials with 17.[18] Compound 17 was readily prepared in two steps from commercially available mucochloric acid (18) by reduction[19] of the latter followed by NBS bromination of the resulting 19. Further



17, X = Br
18, X = OH
19, X = H

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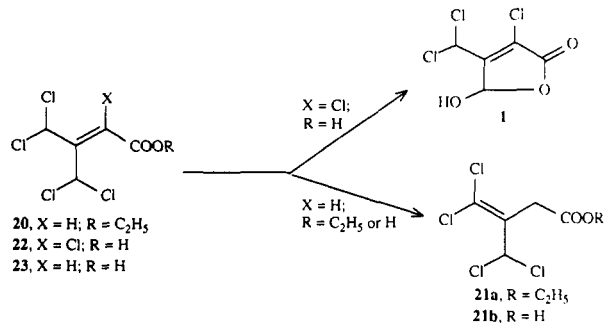
(17) The selective promotion of halide hydrolysis by heavy atom cations is currently under further study in our laboratory.
(18) Mowry, D. T. *J. Am. Chem. Soc.* **1953**, *75*, 1909.
(19) LaLonde, R. T.; Perakyla, H.; Cook, G. P.; Dence, C. W. *Environ. Toxicol. Chem.*, in press.

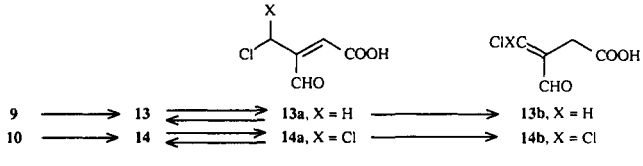
Scheme II



refinements of the hydrolysis procedure with silver and mercuric acetates were pursued using the 4-(chloromethyl) and 4-(dichloromethyl) compounds. For highest conversions and fewest byproducts, the water content of the acetone solvent was confined to the limits indicated above. Analysis of reaction products by ^1H NMR and/or GC revealed that when the acetone contained less than 3% water the formation of a 5-acetoxyfuranone was favored. The latter could not be cleanly hydrolyzed to the 5-hydroxy compound. Greater than 10% water resulted in the formation of several byproducts.

The reason why mercuric and not silver acetate succeeded in promoting the hydrolysis of **12** may lie in the greater Lewis acidity of the mercury(II) cation as opposed to the silver(I) cation as reflected by the former's greater hydrolysis constant.[20] A parallel contrast in cationic promotion of hydrolysis was observed when bromide **17** was treated with weak Lewis acids potassium and cadmium(II) acetates and the stronger Lewis acid, silver(I) acetate. The first two failed to promote hydrolysis while the last-named did so successfully as already indicated.

To illustrate further the sensitivity of the course of hydrolysis to conditions, as exemplified with bromide **9**, the use of THF–water alone resulted in several products, as indicated by TLC. However, THF–water in the presence of 1 equiv of lithium hydroxide resulted in the formation of a product whose spectra were consistent with the structure of 5-bromo-4-(hydroxymethyl)-2(5*H*)-furanone (**16**) as the major product. This result contrasted sharply with that obtained when silver acetate in acetone–water was used, as described above. Also notable was the result from stirring bromide **9** in the presence of 2 equiv of potassium bicarbonate in acetone–water. In this case, the ^1H NMR of the major byproduct was consistent with the structure of **13b** as evidenced by the emergence of three ^1H NMR singlets: an aldehydic proton (9.52 ppm), a vinyl proton (7.65 ppm), and two methylene protons (3.39 ppm). The formation of **13b** can be explained by the base-catalyzed isomerization of the open-ring isomer **13a** as depicted below. Under the same hydrolysis conditions, the $CHCl_2$ analogue of **9**, compound **10**, appeared to yield a similar result in its conversion to byproduct **14a** and major product **14b**. The presence of the latter was indicated by the ^1H NMR (acetone-d_6) spectrum which showed methylene group protons at 3.46 ppm and the aldehydic proton at 10.06 ppm (relative to TMS). Precedent for the double bond migrations was found in the attempted hydrolysis of ester **20** (Scheme II), which was converted to the deconjugated ester **21a**.[4,7,21] In contrast the position of the olefinic double bond does not migrate when an α-chlorine substituent is present. Thus, carboxylic acid **22** is converted to MX upon treatment with aqueous potassium bicarbonate in the previously reported[4] synthesis of **1**. These observations may explain our repeated failure to detect the formation of the MX analogue **14** by treating carboxylic acid **23** with aqueous potassium bicarbonate. Instead the ^1H NMR (acetone-d_6) spectrum of **23** underwent change with the gradual appearance of methylene and new $CHCl_2$ signals at 3.57 (2 H) and 7.20 ppm (1 H), respectively. This observation was consistent with the formation of the deconjugated acid **21b**. Simultaneously, only a relative trace of CHO resonance (10.1 ppm), presumably from hydrolysis of the dichloromethylene group, was observed. These results necessitated our preparation of **14** by the routine involving **3**, **6**, and **10**. Subsequently, in monitoring changes in a D_2O solution of **14** by ^1H NMR spectroscopy, we observed that **14** was stable at pH 5 but as the pH approached 7, **14** rapidly produced a complex mixture which was not investigated further. However the instability of **14** at pH 7 showed that had it been formed from **23**, **14** would not have survived isolation under conditions sufficient for preparing **1**.



The mutagenicity of MX prepared as described here was 3200 net revertants/nmol when assayed with *Salmonella typhimurium* tester strain TA100 in the absence of rat liver homogenate fraction S9. This level of mutagenicity was within the range previously reported for this compound.[2c,3,4,16] The study of the relative mutagenicity of the synthesized analogues of MX is underway. Results will be reported elsewhere in due course.

NMR Characterization of Chlorinated and Hydroxylated 2(5*H*)-Furanones

All newly synthesized compounds have been characterized by their spectra, which includes ^1H and ^{13}C NMR, IR, and MS. In addition we have scrutinized the NMR of MX (**1**) and mucochloric acid (**18**) by 2D spectra in order to secure their resonance assignments. In the case of MX, proton assignments were made on the basis of the direct bond ^1H–^{13}C 2D spectrum which demonstrated correlation of the 6.42 ppm ^1H resonance with the 96.8 ppm ^{13}C resonance (C-5) and the 6.58 ppm ^1H resonance with the 60.3 ppm ^{13}C resonance (C-6). In the case of **18**, the high and low chemical shift (δ_C) values for the olefinic carbons have been given the opposite carbon assignments by two different groups of workers without explanation.[22] Similarly, high and low δ_C values of the olefinic carbons in MX have been assigned to α- and β-unsaturated carbons, respectively,[4] although the β-carbon of nearly all α,β-unsaturated carbonyl compounds,[23] such as in a butenolide,[24] has a higher δ_C value than the α-carbon. Mucochloric acid, as opposed to MX, was chosen for study to settle the question of olefinic carbon chemical shift in chlorinated 2(5*H*)-furanones because the former compound was more readily available in an amount required for the INADEQUATE 2D spectrum. This spectrum demonstrated that the β-

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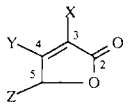
Table I. A Comparison of the Mean Chemical Shifts (δ)[a] and Incremental Shifts ($\Delta\delta_X$, $\Delta\delta_{Y(C\text{-}6)}$, $\Delta\delta_Z$)[a] of the *j*th Carbon Atom (C-*j*) Resulting from the Replacement of the Hydrogen Atoms by Chlorine and/or a Hydroxyl Group in the Substituents X, Y, and Z



C-*j*	data set	substituent X	substituent Y	substituent Z	δ[b]	s[a,c]	n[d]	Δ[e] δ_X	$\Delta\delta_{Y(C\text{-}6)}$	$\Delta\delta_Z$
2	1	H	*f*	H	172.2	1.8	5			
		Cl	*f*	H	166.5	1.0	3	−5.7		
	2	H	*f*	OH	169.4	0.7	2			
		Cl	*f*	OH	165.0	1.3	3	−4.4		
3	3	H	*f*	H	116.9	2.2	5			
		Cl	*f*	H	120.4	0.5	3	+3.5		
	4	H	*f*	OH	120.9	1.4	2			+4.0
		Cl	*f*	OH	124.2	0.9	3	+3.3		+4.2
4	5	H	*f*	H, OH[g]	164.5	3.0	7			
		Cl	*f*	H, OH[g]	151.5	1.8	6	−13.0		
5	6	H, Cl[h]	*f*	H	97.1	0.4	5			
		H, Cl[h]	*f*	OH	70.2	1.2	8			+26.9
6	7	H	CH_2Cl[i]	H, OH[g]	37.7	0	2			
		Cl	CH_2Cl[i]	H, OH[g]	34.9	0.4	2	−2.8		
	8	H	$CHCl_2$[i]	H, OH[g]	62.9	0.6	2		+25.2	
		Cl	$CHCl_2$[i]	H, OH[g]	60.8	0.7	2	−2.1	+25.9	

[a] In ppm, relative to TMS (δ 0.00). [b] The mean δ values for the data sets of the *j*th carbon atom were different at least to the 95% confidence level as determined by *t* test. [c] Standard deviation [d] Number of observations. [e] Calculated by difference between the mean δ values within the same or two different data sets of the *j*th carbon atom; − is upfield; + is downfield. [f] Y = Cl, CH_2OH, CH_2OAc, CHClOAc, CH_2Cl, or $CHCl_2$. [g] Z = H or OH. [h] X = H or Cl. [i] The carbon atom in CH_2Cl and $CHCl_2$ is C-6.

unsaturated carbon occurred at a higher δ_C value than its α counterpart when the highest of all δ_C values was taken as the carbonyl resonance. Thus, δ_C values of chlorinated α- and β-unsaturated carbons of mucochloric acid follow the normal chemical shift pattern of α,β-unsaturated carbonyl compounds. The carbons of MX and all the other 2(5*H*)-furanones were assigned to correspond with the δ_C values of mucochloric acid and to be consistent with the expected one-bond carbon–hydrogen splittings. Moreover, the δ_C values for each of the five carbon atoms have been analyzed for consistency in terms of the influence of substitution at any carbon atom. For example, as indicated by comparison of data sets 1 and 2 in Table I, the influence of chlorine atom introduction at C-3 on $\delta_{C\text{-}2}$ was an upfield shift of between 4.4 and 5.7 ppm regardless of whether a hydroxyl group was present at C-5 or not. Similarly, substitutions at other carbon atoms resulted in no statistically significant value changes of $\delta_{C\text{-}2}$, and therefore the effects of these substitutions were not entered into Table I. However, as a comparison of data sets 3 and 4 shows, $\delta_{C\text{-}3}$ values are shifted to higher values consistently by two substituents, chlorine at C-3 as well as the hydroxyl group at C-5. The downfield α-substituent effects on $\delta_{C\text{-}3}$, $\delta_{C\text{-}5}$, and $\delta_{C\text{-}6}$ and the upfield β- and α-substituent effects on $\delta_{C\text{-}4}$ and $\delta_{C\text{-}6}$, respectively, are all in accord with well-known chemical shift changes.[23,25,26]

One bond carbon–hydrogen couplings observed in all cases for C-5 and C-6, and for C-3 when hydrogen is attached to this carbon, are represented by $^1J_{CH}$ values, Table III, of a magnitude consistent[25] with the carbon hybrid orbital involved in carbon–hydrogen bonding as well as with the number of chlorine and oxygen atoms also bound to the coupled carbon.

Regarding long-range ^{13}C–H couplings, readily distinguishable doublets resulting from two-bond couplings were observed for C-2 in the seven 2(5*H*)-furanones in which hydrogen was attached to C-3. The mean $^2J_{C\text{-}2,C\text{-}3H}$ was 8.8 with a standard deviation (s) = 1.9 Hz. Longer range couplings giving rise to doublets ($^nJ_{C\text{-}2,H} \simeq 3$ Hz) were observed for compounds **1**, **14**, **15**, and **18**.

Four unambiguous cases consisting of compounds **18**, **19**, **13**, and **15** distinguished three-bond coupling of C-3 to protons on C-5 on the one hand from C-6 on the other. Thus, as expected, C-3, C-5H coupling in **18** and **19** appeared as a doublet and a triplet, respectively. For both compounds **13** and **15**, doublets resulted from coupling of C-3 to a proton at C-5 and triplets resulted from similar coupling to protons at C-6. Although the C-6 diastereotopic protons (A_HB_H of system $A_HB_HX_C$), resulting from the C-5 stereogenic center, were clearly differentiated from one another in the ^1H spectra of **13** and **15**, they were undifferentiated in their coupling to C-3 in the two ^{13}C spectra. Likewise compound **4**, which has diastereotopic protons at C-5 as a result of the C-6 stereogenic center, showed no differentiation of these protons in any of their couplings in ^1H or ^{13}C spectra under the usual conditions of observation. The three-bond couplings between C-3 and protons attached to C-5 and C-6 were also clearly observed in compounds in the ^{13}C spectra of **1** (dd), **5** (tt), and **14** (dd).

Long-range, two-bond couplings of C-4, though infrequently observed in our spectral characterizations, were consistent with the structures of the compounds for which they were observed. Three-bond couplings between C-5 and protons at C-6 were unambiguous in the spectra of compounds **1**, **7**, **8**, and **15** in which chlorine was substituted at C-3. The mean $^3J_{CH}$ for the coupling between C-5 and the C-6 proton was 4.5 with s = 1.3 Hz for five observations, which included the two values 6.0 and 2.5 Hz, resulting from coupling to the two diastereotopic protons at C-6 in **15**. This last case is the only one of the several potential cases in which splitting of a ^{13}C signal by diastereotopic protons actually resulted in different $^3J_{CH}$ values. The mean $^3J_{CH}$ value for all four compounds agrees with the 4–4.5 Hz expected for three-bond couplings of

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Table II. ^{1}H Chemical Shifts (δ_{H-i}) in ppm[a,b] and ^{1}H–^{1}H Coupling Constants ($^nJ_{HH}$) (Hz) Obtained from the NMR Data of Selected Chlorinated and Hydroxylated 2(5*H*)-Furanones in $CDCl_3$ Solution

	δ_{H-j}, integration, splitting, and $^nJ_{HH}$							
compd	δ_{H-3}	^4J	δ_{H-5}	^4J	δ_{H-6}	^2J	^4J	other
1			6.45 (br s, 1 H)[c]		6.65 (s, 1 H)[c]			variable (br s, OH, ~1 H)
2	6.03 (p, 1 H)	1.8	4.93 (d, 2 H)	1.8	4.61 (br s, 2 H)			3.28 (br m, OH, ~1 H)
4	6.26 (td, 1 H)	2.0 1.4	4.97 (dd, 2 H)	2.0 0.8	7.24 (m, 1 H)		2.0	2.23 (s, CH_3, 3 H)
5	6.15 (p, 1 H)	1.6	4.90 (m, 2 H)		4.39 (m, 2 H)			
6[d]	6.25 (td, 1 H)	1.93 1.01	5.02 (dd, 2 H)	1.93 0.65	6.60 (m, 1 H)			
7			4.98 (t, 2 H)	0.8	4.46 (t, 2 H)		0.8	
8			5.15 (d, 2 H)	0.7	6.76 (t, 1 H)		0.7	
13[e,g]	6.27 (s, 1 H)				4.53 (d, 1 H_B) 4.58 (d, 1 H_A)	15.25 15.25		6.98 (br s, OH, 1 H)
14	6.37 (dd, 1 H)	1.5 0.8	6.31 (d, 1 H)	0.8	6.50 (d, 1 H)		1.5	~5.2 (br s, OH, ~1 H)
15[d,g]			6.38 (s, 1 H)		4.36 (d, 1 H_B) 4.49 (d, 1 H_A)	12.27 12.27		6.14 (br s, OH, 1 H)
18			6.32 (d, ^3J = 9.0, 1 H)					7.5 (d, ^3J = 9.0 Hz, OH, 1 H)
19[h]			4.90 (s, 2 H)[g]					
24[i,j]	6.03 (p, 1 H)	1.8	4.84 (m, 2 H)		4.97 (m, 2 H)			2.15 (s, CH_3, 3 H)

[a] Relative to TMS at δ = 0.00 ppm. [b] Spectra recorded at 60 MHz unless indicated otherwise. [c] Assignments made on the basis of the direct bond 2D spectrum as discussed in the text. [d] Spectrum recorded at 500 MHz. [e] Spectrum recorded at 360 MHz. [f] Assignments for H-3 and H-5 may be interchanged. [g] Solvent acetone-d_6. [h] δ_{H-5} = 5.10 ppm when solvent is acetone-d_6. [i] Spectrum recorded at 100 MHz. [j] Assignments for H-5 and H-6 may be interchanged.

carbon to protons in freely rotating alkyl groups.[25] The three-bond couplings of C-5 in compounds **6** and **14** appeared as double doublets resulting from coupling to both C-3 and C-6 protons.

Long-range coupling of C-6 gave rise to doublets in the spectra of compounds **2**, **4**, **5**, and **6** in which methylene protons are also found at C-5. Thus it would appear that the splitting results only from coupling of C-6 to the C-3 vinyl proton. Since only doublets of similar J_{CH} value are observed as well for compounds **13** and **14**, these doublets were attributed to coupling to the vinyl proton rather than the proton at C-5. However, $^3J_{C\text{-}6,C\text{-}3H}$ values differed depending on the substituent at C-6. Compounds **2**, **4**, and **24**, all having hydroxyl or acetoxyl groups at C-6, gave a mean value of 2.1 Hz (s = 0.1) while **5**, **6**, **13**, and **14**, having only chlorine atoms attached to C-6, gave a mean value of 3.5 Hz (s = 0.2) for $^3J_{C\text{-}6,C\text{-}3H}$.

Conclusion

Our work demonstrates that the starting 4-(hydroxymethyl)-2(5*H*)-furanone (**2**) is useful in the preparation of seven chlorinated hydroxy and desoxy analogues of MX, and MX itself. The most efficient methods for introducing chlorine at C-6 involved the treatment of **2** with thionyl chloride–pyridine when a chloromethyl group was required and the treatment of the corresponding aldehyde **3** with a large excess of phosphorus pentachloride when a dichloromethyl group was called for. Although the aldehyde **3** was unstable, it could be usefully employed in the synthesis of dichloromethyl compounds if precautions were taken in its storage and use. Introduction of a hydroxyl group at C-5 could be achieved in a chlorinated 2(5*H*)-furanone by treating the latter with NBS followed by the carefully controlled hydrolysis of the resulting bromide in a process promoted by the presence of silver or mercuric acetate. Although the preparation of MX by this route was inferior in yield compared to that from the method previously reported,[4] we believe it compensates for this shortcoming in being a more versatile method leading to the preparation of several MX analogues. Moreover, it provides an alternative route to MX that circumvents the use of 1,1,3,3-tetrachloroacetone, which is no longer commercially available at reasonable cost as a starting material. The resolution of earlier, confused ^{13}C NMR assignments for MX (**1**) and mucochloric acid (**19**) was the basis for a comprehensive analysis of ^{13}C NMR spectra of MX and its analogues, which indicates agreement of determined NMR parameters with expected values for the pertinent structures. However, three-bond couplings of carbon to diastereotopic protons were undifferentiated except in one situation, and thus they should be used with caution when obtaining detailed structural information about chlorinated 2(5*H*)-furanones.

Experimental Section

General. Melting points were determined in capillary tubes with a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Desert Analytics, Tucson, Arizona.

Spectra. ^{1}H and ^{13}C NMR spectra, from which the data given in Tables II and III were obtained, were determined in $CDCl_3$ solution in 5-mm tubes, unless indicated otherwise, on Varian EM360, XL100, Bruker WM360, and GE-GN500 spectrometers, the latter two being located at the NIH Resources, Multinuclear NMR and Data Processing Laboratory, Syracuse University. Internal tetramethylsilane (TMS) was used as a standard (δ 0.00). ^{1}H NMR are recorded at 60 MHz unless indicated otherwise. ^{13}C NMR were determined as fully coupled spectra. The INADEQUATE spectrum of mucochloric acid in acetone-d_6 solution (Cr^{3+} ion added to reduce T^1s from 20+ to 2s) was determined at the NMR Research Laboratory, the University of Rhode Island, Kingston, RI, by Dr. Michael McGregor who acquired a total of 256 FID's with 128 scans each at 75.5 MHz with a spectral width of 6 kHz.The final matrix size was 512 complex data points. A 90-deg-shifted sine bell function was applied in both directions. A spin echo period of 0.00385 s was used corresponding to a $J_{C\text{-}C}$ of 65 Hz. The recycle time was 7 s. The 2d ^{13}C–^{1}H direct bond correlated spectra of MX were obtained in $CDCl_3$ solution at the NIH Resources, Multinuclear NMR and Data Processing Laboratory, Syracuse University, from 128 FID's with 8 scans each at 125.8 MHz. The spectral width in *X* and *Y* dimensions was 6849.3 Hz (^{13}C) and 1972.4 Hz (^{1}H), respectively. The matrix size was 1K complex data points. A 90-degree-shifted sine bell function was applied in both directions. The recycle time was 3 s.

IR spectra were recorded by a Perkin-Elmer 1310 spectrometer on samples in CCl_4 solution or as otherwise indicated. Designations s, m, w, and br refer to strong, medium, weak, and broad bands. MS were obtained from a Finnigan 4021 mass spectrometer as EI solid bombardment (designated simply as MS), GCMS (conducted in the EI mode) or CI/GCMS as indicated at 70 eV. GCMS included the use of a 30 m × 0.25 mm SPB-5 capillary column. CIMS used methane as the reagent gas; M + 41 and M

Table III. ^{13}C Chemical Shifts ($\delta_{C,j}$)[a] in ppm and ^{13}C–^{1}H Coupling Constants ($^{n}J_{CH}$)[b] (Hz) for Selected Chlorinated and Hydroxylated 2(5*H*)-Furanones[c]

	$\delta_{C,j}$, splittings,[d] and $^{n}J_{CH}$													
compd	δ_{C-2}	^{2}J	^{n}J	δ_{C-3}	^{1}J	^{3}J	δ_{C-4}	^{2}J	δ_{C-5}	^{1}J	^{3}J	δ_{C-6}	^{1}J	^{3}J	other
1	165.2		d, 3.3	124.8		d, 4.0; d, 2.9	150.7, m		96.8	d, 197.4	d, 5.0	60.3	d, 182.2		
2	174.4	d, 9.1		114.1	d, 178.5	t or p, 3.5	171.0, m		71.6	t, 152.0	d, 8.1	58.6	t, 143.4	d, 2.2	
4	171.3	d, 7.8		118.4	d, 184.2		161.8, m		69.8	t, 153.9	d, 7.3	75.6	d, 177.8	d, 2.0	167.3, m, C=O; 20.5, q, CH_3
5	172.3	d, 12.9	m	118.4	d, 182.0	t, 4.4; t, 3.4	163.5, m		71.4	t, 152.7	m, m	37.7	t, 152.2	d, 3.3	
6	171.0	d, 8.5		118.5	d, 184.3	m	163.4, m		69.7	t, 153.8	d, 7.5; d, 2.5	63.3	d, 182.4	d, 3.5	
7	167.4, m			121.0, m			153.6	p, 5.2	70.1	t, 155.2	t, 4.4	35.2	t, 154.6		
8	166.3, s			120.2		q, 3.8	152.7	t, 5.4; d, 1.7	67.8	t, 156.4	d, 4.7	61.3	d, 182.6		
13[e]	169.9	d, 8.0		119.9	d, 183.1	d, 4.9; d, 1.8	164.3	tm, 5.2	97.8	d, 174.9	dm, 8.6	37.7	t, 153.6	d, 3.7	
14	168.9	d, 7.0	d, 3.5	121.9	d, 186.1	d, 4.0; d, 1.7	163.2, m		96.9	d, 176.6	d, 9.0; d, 1.5	62.5	d, 180.6	d, 3.5	
15	166.3		d, 2.6	124.7		d, 7.3; d, 2.6	152.6	t, 4.6	96.8	d, 178.5	d, 6.0; d, 2.5	33.8	t, 155.3		
18[e]	163.6		d, 2.9	123.2		d, 2.5	150.0, br s		97.4	br d, 180.5					
19	165.5, s			120.0		t, 3.7	149.2	t, 6.8	70.8	t, 157.6					
24	172.1	d, 8.8		115.1	d, 181.7		164.2, m		70.5	t, 152.6	d, 7.8	58.8	t, 150.1	d, 2.1	169.2, m, C=O; 19.6, q, CH_3

[a] The chemical shift of the *j*th carbon is relative to TMS at $\delta_C = 0.0$ ppm. [b] The number of bonds between coupled nuclei is indicated by *n*. [c] In $CDCl_3$ unless indicated otherwise. [d] Abbreviations br, s, d, t, q, and p refer respectively to broad, singlet, doublet, triplet, quartet, and pentuplet. [e] In acetone-d_6.

+ 29 peaks are omitted from peak listings. Numbers of halogens in molecular ion and fragmentation peaks were ascertained from the isotopic satellite peaks and are designated as Cl_n or Br_n.

Chromatography. TLC was determined on Merck silica gel 60F-254 (no. 5554) sheets in the solvent systems indicated. Spots were visualized by UV irradiation. Flash, vacuum,[27] and medium-pressure chromatography used Merck Kieselgel 60 (230–400 mesh) (E. Merck). GC was carried out on a Varian 3300 gas chromatograph equipped with a 30 m × 0.25 mm SPB-5 capillary column, which under normal operating conditions was at 180 °C. Normally the injector and FID detector were operated at 250 and 310 °C, respectively. The nitrogen flow rate was 1.1 mL/min.

4-(Chloromethyl)-2(5*H*)-furanone (5). (A) From Triphenylphosphine and Carbon Tetrachloride in Concentrated Solution. A mixture of 2.82 g of **2** (25.3 mmol), obtained by the method of Thaller,[6] and 6.65 g of triphenylphoshine (25.4 mmol) suspended in 9.1 mL of CCl_4 (94.3 mmol) was stirred at 25 °C for 72 h, at the end of which time the CCl_4 was removed from the resulting dark brown solution on the rotary evaporator. The residual, dark brown, glasslike material was treated three times with hot EtOAc. The combined EtOAc extract was cooled and filtered. Rotary evaporation of the filtrate followed by TLC-monitored (EtOAc) vacuum chromatography[27] of 1 g of the 2.5 g quantity of resulting residue using hexanes–EtOAc (from 25 to 100% EtOAc) yielded combined fractions 4 and 5 amounting to 100 mg of pure **5** (8% based on the portion of the crude product purified), $bp_{0.4mm}$ 84 °C, whose ^{1}H NMR data was identical with that of **5** prepared by procedure B below. Fraction 8 consisted of 40 mg of pure 5-chloro-4-methyl-2(5*H*)-furanone[28] (2% based on the portion of the crude purified product) whose IR and ^{1}H NMR agreed with those of an authentic sample of this compound prepared by the action of thionyl chloride–aluminum chloride on 5-hydroxy-4-methyl-2(5*H*)-furanone.[29] Observed for 5-chloro-4-methyl-2(5*H*)-furanone were the following: IR 1807 (s), 1660 (w), 1300 (w), 1143 (m), 1062 (s), 996 (w), 880 (m); ^{1}H NMR δ 6.46 (s, C-5 H), 6.01 (br s, C=CH, 1 H), 2.19 (s, CH_3, 3 H); GC/CIMS *m/z* 133 (Cl_1, base peak, MH), 97 (MH – HCl). Anal. Calcd for $C_5H_5ClO_2$: C, 45.31; H, 3.80; Cl, 26.75. Found: C, 45.17; H, 4.10; Cl, 26.82.

4-(Chloromethyl)-2(5*H*)-furanone (5). (B) From Thionyl Chloride–Pyridine. Under anhydrous conditions, a solution at 0 °C of 4.17 g of thionyl chloride (35 mmol) in 30 mL of CH_2Cl_2 was added slowly dropwise over a period of 20 min to a stirred solution at 0 °C of 2.0 g of **2** (17.5 mmol) and 1.7 g of pyridine (17.5 mmol) in 30 mL of CH_2Cl_2 contained in an oven-dried flask. The resulting clear, yellow solution was allowed to stand for 15 min at 20–25 °C, at the end of which time the volatiles and solvent were removed under a stream of dry nitrogen. At 30-mL quantity of CH_2Cl_2 was added to the residue. The solution was washed four times with water, dried over anhydrous sodium sulfate, and filtered. Removal of solvent on a rotatory evaporator gave 2.05 g of a brownish yellow oil, **5** (88%): bp 127–130 °C (5.5 mmHg); IR 2904 (w), 1789 (s), 1760 (s), 1650 (w), 1263 (m), 1170 (m), 1126 (m), 1040 (s), 880 (m), 710 (w) cm^{-1}; MS *m/z* 132 (Cl_1, M), 103 (Cl_1, base peak, M – CHO), 96 (M – HCl), 75 (Cl_1, M – [CO + CHO]), 68 (M – [Cl + CHO]), 67 (M – [HCl + CHO]), 49 (Cl_1, CH_2Cl). See Tables II and III for NMR data. Anal. Calcd for $C_5H_5ClO_2$: C, 45.31; H, 3.80; Cl, 26.75. Found: C, 45.03; H, 3.84; Cl, 26.47.

Mucochloric Acid (18) from 3,4-Dichloro-2(5*H*)-furanone (19). The following procedure is typical of the procedure for brominating C-5 of a 2(5*H*)-furanone. A 200-mg quantity of **19**[19] (13 mmol) and 233 mg of NBS (13 mmol) in 12 mL of CCl_4 in an oven-dried flask, provided with reflux condenser and calcium chloride drying tube, were irradiated for 10 min with a 100-W bulb placed under the reaction flask, which, together with the light bulb, was surrounded by aluminum foil. The mixture was allowed to cool to 20–25 °C. Filtration and removal of solvent on the rotary evaporator left 233 mg of liquid **17** (97%): ^{1}H NMR δ 6.90 (s). To a stirred solution of a 1-g sample of the bromide

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17 (4.3 mmol) in 20 mL of reagent grade acetone was added 2 mL of water. Immediately 0.72 g of silver acetate (4.3 mmol) was added, and the mixture was stirred at ambient temperature for a total of 20 h with aliquots taken at 0.5, 1, 2, 3, 6, and 20 h for GC analysis, which first showed the formation of a mixture of **18** and its corresponding acetoxy derivative at 2 h and complete transformation of starting **17** by 20 h. ^{1}H NMR (acetone-d_6) for **18**: δ 6.24 (s, C-5 H, 1 H), 8 parts; 5-acetoxy-3,4-dichloro-2-(5*H*)-furanone δ 7.05 (s, C-5 H, 1 H), 2.22 (s, CH_3COO, 3 H), 1 part.

5-Bromo-4-(chloromethyl)-2(5*H*)-furanone (9). A 400-mg quantity of **5** (3 mmol) and 540 mg of NBS (3 mmol) in 25 mL of CCl_4 were irradiated for 30 min and then processed as described in the conversion of **19** to **17**. Thereby was obtained 620 mg of yellow oil, **9** (98%): IR 1801 (s), 1652 (w), 1030 (s), 910 (s), 870 (m) cm^{-1}; ^{1}H NMR (500 MHz) δ 6.98 (d, J = 0.59 Hz, C-5 H, 1 H), 6.33 (m, C-3 H, 1 H), 4.59 (dd, ^2J = 14.45, ^4J = 1.18 Hz, H_A of $ClCH_2$, 1 H), 4.47 (ddd, ^2J = 14.45, ^4J = 2.95, ^4J = 1.77 Hz, H_B of $ClCH_2$, 1 H); ^{13}C NMR (125.8 MHz) δ 167.87 (m, C-2), 165.14 (m, C-4), 118.56 (dddd, $^1J_{CH}$ = 185.83, $^3J_{CH}$ = 4.90, $^3J_{CH}$ = 3.81, $^3J_{CH}$ = 2.18 Hz, C-3), 75.94 (dm, $^1J_{CH}$ = 190.53 Hz, C-5), 37.10 (td, $^1J_{CH}$ = 153.68, $^3J_{CH} \simeq$ 2.4 Hz, CH_2Cl); MS m/z 209 (Cl_1, Br_1, M - 1), 181 (Cl_1, Br_1, M - CHO), 175 (Br_1, M - Cl), 131 (Cl_1, base peak, M - Br), 103 (Cl_1, M - [Br + CO]), 95 (M - [Br + HCl]), 87 (Cl_1, M - [Br + CO_2]), 67 (M - [Br + HCl + CO]), 49 (Cl_1, CH_2Cl).

4-(Chloromethyl)-5-hydroxy-2(5*H*)-furanone (13). A 776-mg quantity of silver acetate (4.6 mmol) was added portionwise over 5 min to a stirred solution of 890 mg of **9** (4.3 mmol) in 44.5 mL of acetone containing 3% water. The resulting mixture, contained in a stoppered flask, was stirred rapidly at 25 °C for 100 h, at the end of which time the mixture was filtered, the residue was rinsed with 5 mL of acetone (0.1% water), and the combined filtrate and rinse solution was concentrated on the rotary evaporator. To the concentrate was added 20 mL of ether, and the resulting mixture was mixed thoroughly. The ether solution was decanted, and the residue was washed with 15 mL of ether. The combined ether wash and decantate was dried over anhydrous sodium sulfate. Removal of the ether on the rotary evaporator at room temperature, further rotary evaporation from a warm water bath at 40–50 °C for 30 min, and gradient medium-pressure chromatography employing CH_2Cl_2–ether (100%/0% to 75%/25%) yielded 20 fractions whose compositions were monitored by GC conducted at normal operating conditions. In this manner 330 mg of **13** (52%) was obtained: IR (neat) 3350 (br), 1745 (s), 1650 (m), 1120 (s), 950 (s) cm^{-1}; CI/GCMS m/z 149 (Cl_1, MH), 113 (Cl_1, base peak, MH - HCl), 97 (MH - [H_2O + Cl]), 57. See Tables II and III for NMR data. Anal. Calcd for $C_5H_5ClO_3$: C, 40.43; H, 3.39; Cl, 23.87. Found: C, 40.15; H, 3.45; Cl, 23.33.

3-Chloro-4-(chloromethyl)-2(5*H*)-furanone (7). Into a 250-mL CH_2Cl_2 solution of 2.05 g of **5** (19.5 mmol) was added 20 mg of aluminum chloride. Dry chlorine was bubbled through the resulting mixture for 16 h at 20–25 °C. Thereafter the reaction flask was swept through with dry nitrogen to displace chlorine and the resulting yellow solution was filtered. To the stirred filtrate at 0 °C was added slowly dropwise over 20 min 1.57 g (15.5 mmol) of triethylamine in 50 mL of CH_2Cl_2. The resulting mixture was stirred at 0 °C for 12 h. An additional 1-g quantity of triethylethylamine in 10 mL of CH_2Cl_2 at 0 °C was added slowly over 15 min, and the clear purple solution was allowed to stand for 12 h after which time the solution was washed repeatedly with 50-mL quantities of water, dried over anhydrous sodium sulfate, and concentrated on the rotary evaporator first at 20–25 °C and then for 1 h at a bath temperature of 50 °C to yield 2.9 g of clear brown residue, of which 200 mg was chromatographed at medium pressure employing CH_2Cl_2–hexanes (6:1) to obtain 117 mg of **7** (66% based on the portion of the crude product purified): mp 35.5–37.0 °C; IR 1780 (s), 1760 (s), 1645 (m), 1030 (s), 1010 (s) cm^{-1}; GCMS m/z 166 (Cl_2, M), 137 (Cl_2, base peak, M - CHO), 131 (Cl_1, M - Cl), 117 (Cl_1, M - CH_2Cl), 109 (Cl_2, M - [CHO + CO]), 73 (Cl_1, M - [CHO + CO + Cl]), 49 (Cl_1, CH_2Cl). See Tables II and III for NMR data. Anal. Calcd for $C_5H_4Cl_2O_2$: C, 35.96; H, 2.41; Cl, 42.46. Found: C, 35.89; H, 2.17; Cl, 42.26.

3-Chloro-4-(chloromethyl)-5-hydroxy-2(5*H*)-furanone (15). Bromination of **7** was achieved using the same procedure as that employed to convert **19** to **17**. Thus a solution of 300 mg of crude **7** and 320 mg of NBS in 50 mL of CCl_4 was irradiated for 35 min. The mixture was cooled and filtered, and the filtrate was rotary evaporated to 450 mg of a yellow oil, **11**: IR 1745 (s), 1720 (m), 1645 (w), 1040 (m), 930 (s); ^{1}H NMR (360 MHz) δ 7.03 (s, CHBrO, 1 H), 4.58 (d, ^2J = 13.02 Hz, H_A of CH_2Cl, 1 H), 4.45 (d, ^2J = 13.02 Hz, H_B of CH_2Cl, 1 H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 163.49 (dm, $^3J_{CH}$ = 3.59 Hz, C-2), 154.40 (m, C-4), 123.50 (m, C-3), 74.98 (ddd, $^1J_{CH}$ = 198.08, $^3J_{CH}$ = 7.63, 2.69 Hz, C-5), 34.56 (t, $^1J_{CH}$ = 155.28 Hz, CH_2Cl); GC/CIMS m/z 245 (Cl_2, Br_1, MH), 167 (Cl_2, base peak, MH - 78), 133 (Cl_1), 99.

A 1.30-g sample of bromide **11** (5.28 mmol), prepared as described above, was dissolved in 65 mL of acetone containing 10% water. To the resulting solution was added 970 mg of silver acetate (5.81 mmol), and the resulting mixture was stirred for 4 days, at the end of which time the acetone was removed on the rotary evaporator. The gray residue was triturated three times with 50-mL portions of CH_2Cl_2, and the combined dichloromethane extract was dried over anhydrous sodium sulfate and filtered. Rotary evaporation of the filtrate yielded 890 mg of a yellow oil, which was chromatographed at medium pressure with a CH_2Cl_2–MeOH gradient of 100% CH_2Cl_2 to 75% CH_2Cl_2 - 25% MeOH. The chromatography was monitored by TLC (CH_2Cl_2–MeOH, 9:1) and by GC. Four fractions eluting with CH_2Cl_2–MeOH (15% to 20%) afforded 2.65 g of **15** (73%) whose ^{1}H NMR and GCMS were essentially identical with those reported[5] for this compound prepared by another method. Also observed for **15**: IR ($CDCl_3$) 3568 (w), 3400 (br), 1790 (s), 1675 (w), 1025 (m) cm^{-1}; ^{1}H NMR (60 MHz, acetone-d_6) δ 7.33 (d, $^3J_{HOH}$ = 9 Hz, OH, 1 H), 6.40 (d, ^3J = 9 Hz, C-5 H, 1 H), 4.66 (d, ^2J = 13.00 Hz, H_A of CH_2Cl, 1 H), 4.43 (d, ^2J = 13.00 Hz, H_B of CH_2Cl, 1 H); GC/CIMS m/z 183 (Cl_2, base peak, MH), 165 (Cl_2, MH - H_2O), 149 (Cl_1), 131 (Cl_1). See Tables II and III for NMR data.

4-Formyl-2(5*H*)-furanone (3). A 3-g quantity of PCC was dispersed on 15 g of powdered sodium chloride by grinding the two together with a mortar and pestle then suspending the resulting solid in 90 mL of CH_2Cl_2. A solution of 1 g of **2** (8.76 mmol) in 10 mL of CH_2Cl_2 was stirred into the dispersed PCC. After the mixture was stirred for 1.7 h at ambient temperature the liquid was decanted onto the top of a narrow column packed with a CH_2Cl_2-wetted mixture of 5 g of powdered sodium sulfate on top and 10 g of Kieselgel on the bottom. A moderate air pressure was applied to the top of the column to effect the rapid passage of liquids through the column. The solid residue from decantation was stirred briefly with 50 mL of CH_2Cl_2, and the liquid was likewise passed through the column. Finally 100 mL of CH_2Cl_2 was forced through the column. It was necessary to perform this workup procedure rapidly without interruption to minimize loss of **3** through its decomposition on the Kieselgel.

The first 60 mL of liquid eluting contained only CH_2Cl_2 as determined by TLC. The next 120 mL contained the bulk of the desired product. Collection of column-absorbed materials was continued until yellow-colored material began to emerge. Concentration of a small aliquot of the 185 mL of selected eluent indicated a total of 648 mg of pure aldehyde **3** (66%): IR (CH_2Cl_2) 1760 (vs), 1735 (s), 1680 (s), 1350 (w), 1315 (w), 1150 (w), 1115 (m), 1020 (m), 860 (m) cm^{-1}; ^{1}H NMR δ 10.17 (s, CHO), 6.38 (t, ^4J = 2.2 Hz, C-3 H, 1 H), 5.03 (d, ^4J = 2.2 Hz, C-5 H, 2 H); ^{13}C NMR δ 186.1 (d, CHO), 171.6 (s, C-2), 159.0 (s, C-4), 129.1 (d, C-3), 69.5 (t, C-5); GCMS m/z 112 (base peak, M), 84 (M - CO), 83 (M - CHO), 56, 55 (M - [CO + CHO]), 53.

4-(Acetoxychloromethyl)-2(5*H*)-furanone (4). Under anhydrous conditions a 120-mg quantity of anhydrous aluminum chloride was added to 120 mg of freshly prepared 4-formyl-2-(5*H*)-furanone (1.07 mmol) dissolved in 2 mL of acetyl chloride, and the resulting mixture was stirred at ambient temperature for 48 h. Thereafter the liquid was separated by decantation, and the solid was extracted with two 1-mL quantities of CH_2Cl_2. The combined extract was concentrated on the rotary evaporator, and the residue was redissolved in CH_2Cl_2. The resulting solution was washed with water, dried over anhydrous magnesium sulfate, and concentrated on the rotary evaporator. The resulting white crystalline residue amounted to 90 mg of crude **4** (44%): mp 70–75 °C. Flash chromatography using hexanes–EtOAc (2:1) produced pure **4**: mp 77–78 °C; IR 1730 (br), 1190, 1120, 1050, 1015, 870 cm^{-1} all strong, 1340, 760, 740, 710, 690 cm^{-1} all medium, and 2980, 1440, 950 and 630 cm^{-1} all weak intensity; GCMS m/z 161 (M

– CHO), 155 (base peak, M – Cl), 148 (M – C_2H_2O), 130 (M – $CH_3COOH)_3$, 113 (M – [Cl + C_2H_2O]), 101 (M – [CHO + CH_3COOH]), 95 (M – [CH_3COOH + Cl]), 73 (M – [CHO + CH_3COOH + CO]); CI/GCMS m/z 231 (C_1, M + 41), 219 (C_1, M + 29), 191 (C_1, M + 1), 131 (Cl, M + 1 – [CH_3COOH]), 113 (M + 1 – [$C_2H_2O_2$ + HCl]). See Tables II and III for NMR data. Anal. Calcd for $C_7H_7ClO_4$: C, 44.12; H, 3.70; Cl, 18.70. Found: C, 43.98; H, 3.53; Cl, 18.30.

4-(Dichloromethyl)-2(5*H*)-furanone (6). To a freshly prepared 133-mL CH_2Cl_2 solution containing 5.78 mmol of **3** was added at ambient temperature 3 g of PCl_5 (24 mmol). The resulting mixture was stirred until the PCl_5 dissolved. Not earlier than 16 min from the time the PCl_5 was added, 12 g of sodium bicarbonate and then 150 mL of water were added to the CH_2Cl_2 reaction solution. The resulting mixture was gently stirred for several hours until CO_2 evolution ceased. The CH_2Cl_2 solution was washed with water and dried over anhydrous magnesium sulfate. Such a solution of crude **6** could be used to prepare **8**. Instead removal of the CH_2Cl_2 on the rotary evaporator would give 0.82 g of crude **6** (85%) whose ^1H NMR showed, in addition to the major signals expected of **6**, minor intensity (5%) signals corresponding to **7** (δ 4.98, 4.45) and whose GC revealed a peak corresponding to that of authentic **7**, which emerged after the peak representing **6**. GC monitored flash chromatography of a 1.55-g sample of **6** on 82 g of Kieselgel eluted by CH_2Cl_2 yielded 623 mg of pure and 110 mg of 93% pure **6**, together amounting to 76% yield. Properties of **6**: IR 1780 and 1750 cm^{-1}, both strong, 1175, 1125, 1030, 880 cm^{-1}, all medium, and 3100, 3010, 2970, 2910, 2850, 1640, 1440, 1350, 1320, 1225 cm^{-1}, all weak; GCMS m/z 166 (Cl_2, M), 137 (Cl_2, M – CHO), 131 (Cl_1, M – Cl), 109 (Cl_2, M – [CHO + CO]), 101 (Cl_1, M – [CHO + HCl]), 95 (M – [Cl + HCl]), 83 (base peak, M – $CHCl_2$), 73 (Cl_1, M – [HCl + CHO + CO]), 55 (M – [$CHCl_2$ + CO]). See Tables II and III for NMR data. Anal. Calcd for $C_5H_4Cl_2O_2$: C, 35.96; H, 2.41. Found: C, 36.36; H, 2.41.

4-(Dichloromethyl)-5-hydroxy-2(5*H*)-furanone (14). A 1.512-g quantity of pure **6** (9.06 mmol) was treated with 9.94 mmol of NBS in 75 mL of CCl_4 for 35 min as described in the conversion of **19** to **17**. The solution of the resulting bromide was filtered through 2.5 g of Kieselgel, which thereafter was eluted with 10 mL of 1:1 CH_2Cl_2–CCl_4 to obtain 1.8 g of **10** (81%): IR (CCl_4) 1800 (s), 1180 (w), 1130 (m), 1630 cm^{-1} (s); ^1H NMR δ 6.97 (d, ^4J = 0.8 Hz, C-5 H, 1 H), 6.63 (d, ^4J = 1.5 Hz, $CHCl_2$, 1 H), 6.52 (dd, ^4J = 1.5, 0.8 Hz, C-3 H, 1 H); ^{13}C NMR (25.2 MHz) δ 166.45 (m, C-2), 165.21 (d, $^2J_{CH}$ = 4.3 Hz, C-4), 120.26 (dm, $^1J_{CH}$ = 186.6, $^3J_{CH}$ < 10 Hz, C-3), 74.89 (dd, $^1J_{CH}$ = 191.7, $^3J_{CH}$ = 9.4 Hz, C-5), 63.03 (dd, $^1J_{CH}$ = 180.0, $^3J_{CH}$ = 3.0 Hz, $CHCl_2$); CI/GCMS m/z 245 (Cl_2Br_1, base peak, MH), 209 (Cl_1, Br_1, MH – HCl), 167 (Cl_2, MH – [Br + H]), 165 (Cl_2, MH – HBr), 131 (Cl_1, MH – [Br + Cl]), 81 (Br_1, H_2Br).

A 130-mg sample (0.529 mmol) of **10** was dissolved in 4 mL of reagent grade acetone, containing 1% water, and then treated with 100 mg of silver acetate (0.599 mmol) followed by 0.2 mL of water. The reaction was allowed to proceed for 13 h and then processed as previously described for the conversion of **9** to **13** in order to obtain 94 mg of crude product, which was flash chromatographed on 4.7 g of Kieselgel using a stepwise gradient of CH_2Cl_2–ether, ranging from zero to 20% ether increased in 5% increments. The chromatography was monitored by TLC. Thus afforded was 41.4 mg of crystalline **14** (43%): mp (from benzene) 59.5–61.0 °C; IR ($CDCl_3$) 3560 (m), 3350 (m, br), 1750 (s), 1130 (s), 970 (m); CI/GCMS m/z 183 (Cl_2, MH), 165 (Cl_2, base peak, MH – H_2O), 147 (MH – HCl), 131 (Cl_1, MH – [OH + Cl]), 113 (MH – Cl_2). See Tables II and III for NMR data. Anal. Calcd for $C_5H_4Cl_2O_3$: C, 32.82; H, 2.20; Cl, 38.75. Found: C, 32.86; H, 2.23; Cl, 38.54.

3-Chloro-4-(dichloromethyl)-2(5*H*)-furanone (8) from 4-(Hydroxymethyl)-2(5*H*)-furanone (2). A 1.0-g quantity of **2** was treated with PCC and PCl_5 as described in producing the solution of crude **6**. To the resulting dichloromethane solution of crude **6** was added 500 mg of aluminum chloride. Dry chlorine gas was bubbled through the resulting mixture on two successive days for 2.5 h each day. Thereafter the mixture was allowed to stand overnight, washed with water, dried with anhydrous magnesium sulfate, filtered, and concentrated. GC indicated the presence of two major components confirmed by ^1H NMR: a major component (1 part) δ 6.28 (s, $CHCl_2$, 1 H), 4.60 (d, J = 0.9 Hz, CH_2O, 2 H), 4.49 (s, CHCl, 1 H); a second major component (0.22 parts) δ 6.02 (s, $CHCl_2$, 1 H), 5.16 (s, CHCl, 1 H), 4.47 (d, J = 1.0 Hz, CH_2O, 2 H); CI/GCMS m/z 237 (Cl_4, base peak, MH), 201 (Cl_3, MH – HCl), 167 (Cl_2, MH – Cl_2), 157 (Cl_3, MH – [HCl + CO_2]), 133 (MH – 3[Cl] + H).

To a CH_2Cl_2 solution of the chlorination product was added dropwise a 10% solution of triethylamine in CH_2Cl_2 at 20–25 °C until the solution turned a dark purple color at which point 0.45 g of triethylamine had been added and GC indicated both components of the previous chlorination step were absent. After standing for 20 min, the solution was washed with water, dried, and concentrated. The 995 mg of crude product was flash chromatographed on 50 g of Kieselgel by stepwise elution with hexanes–CH_2Cl_2 mixtures in the volume and percentage composition of CH_2Cl_2 as follows: 250 mL, 30%; 100 mL, 40%; 250 mL, 50%. Fractions eluted near the end of the hexanes–CH_2Cl_2 (40%) contained in total 720 mg (41% from **2**) of pure **8** as determined by capillary GC. Properties of **8**: mp 42.5–44.5 °C; IR (film) 1775, 1150, 1045, 1015, 960, 935 cm^{-1} all strong, 3000, 1650, 1450, 1350, 1260 cm^{-1} all of medium intensity; GCMS m/z 200 (Cl_3, M), 171 (Cl_3, M – CHO), 165 (Cl_2, M – Cl), 143 (Cl_3, M – [CHO + CO]), 135 (Cl_2, M – [HCl + CHO]), 117 (base peak, Cl_1, M – $CHCl_2$); 129 (Cl_2, M – [Cl + HCl]); 107 (Cl_2, M – [HCl + CHO + CO]). See Tables II and III for NMR data. Anal. Calcd for $C_5H_3Cl_3O_2$: C, 29.81; H, 1.50; Cl, 52.80. Found: C, 29.96; H, 1.44; Cl, 52.96.

Early fractions from the hexanes–CH_2Cl_2 (40%) eluent afforded 4-(chloromethyl)-2,2,3-trichloromethyl-2(5*H*)-furanone: ^1H NMR δ 4.13 (J_{AB} = 12 Hz, $\nu_A - \nu_B$ = 10.9 Hz CH_2Cl, 2 H), 4.65 (J_{AB} = 10.5 Hz, $\nu_A - \nu_B$ = 4.7 Hz, CH_2O, 2 H); GCMS m/z 157 (Cl_3, M – [Cl + CO_2]), 156 (Cl_3, M – [HCl + CO_2]), 143 (Cl_3, base peak, M – [CH_2Cl + CO_2]), 121 (Cl_2, M – [Cl + HCl + CO_2]), 109, 85, 83, 73.

3-Chloro-4-(dichloromethyl)-5-hydroxy-2(5*H*)-furanone (1, MX) from 8. The bromination of 69.5 mg of 3-chloro-4-(dichloromethyl)-2(5*H*)-furanone (**8**) (0.345 mmol) was carried out in the same manner as described above except NBS was used in large excess (3.5 equiv), CH_2Cl_2 replaced CCl_4, and the reaction was carried out for nearly 4 h, which was the time required according to periodic monitoring of reaction progress by GC. Thereby was obtained 60.4 mg of liquid **12**: ^1H NMR δ 7.1 (s, CHBr, 1 H), 6.66 (s, $CHCl_2$, 1 H); CI/GCMS m/z 279 (Cl_3Br_1, base peak, MH), 243 (Cl_2Br_1, MH – HCl), 201 (MH – [Br] + H), 199 (MH – HBr), 165 (Cl_2, MH – BrCl), 137 (Cl_2, MH – [BrCl + CO]), 81 (Br_1,H_2Br).

Similarly a 125 mg (0.62 mmol) quantity of **8** was treated with NBS, and the resulting crude **12** was dissolved in 4 mL of acetone containing 3% water and 200 mg (0.64 mmol) of mercuric acetate. After stirring the resulting mixture for 40 h at ambient temperature in a stoppered flask, the contents were filtered, concentrated on the rotary evaporator, extracted with CH_2Cl_2, filtered, and concentrated again to obtain a residue which was flash chromatographed on 13 g of Kieselgel (wetted with CH_2Cl_2), which was eluted with 2.5% by volume of MeOH in CH_2Cl_2. From the fractions contained in the first 60–130-mL volume emerging from the column was 50 mg of **1** (37%) whose ^1H NMR (samples in $CDCl_3$ and acetone-d_6) and GCMS were identical with those of a reference sample prepared by another method.[4] See Tables II and III for a listing of NMR parameters. The newly synthesized sample of **1** cochromatographed with the reference sample on a capillary GC column operated at normal conditions.

4-(Acetoxymethyl)-2(5*H*)-furanone (24). A 200-mg quantity of 4-(hydroxymethyl)-2(5*H*)-furanone, **2**, in 1 mL of acetyl chloride solution was warmed for 10 min. The unconverted acetyl chloride was removed on the rotary evaporator to obtain a white solid, which was taken up in dichloromethane. The resulting solution was washed with 2 mL of aqueous sodium bicarbonate solution, dried over anhydrous sodium sulfate, and filtered, and the filtrate was put on the rotary evaporator to remove solvent. Obtained was 245 mg of **26** (90%): mp 40.5–42.5 °C (reported[6] mp 42.5 °C). See Tables II and III for a listing of NMR parameters.

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Supplementary Material Available: Reconstructed CI/GCMS chromatogram of MX (RIC), CI/GCMS of MX, GCMS of MX, 2D ^{13}C-^{1}H correlated spectrum of MX, INADEQUATE spectrum of 18 (5 pages). Ordering information is given on any current masthead page.

(+)- and (−)-[2-(1,3-Dithianyl)]myrtanylborane. Solid and Stable Monoalkylboranes for Asymmetric Hydroboration[1]

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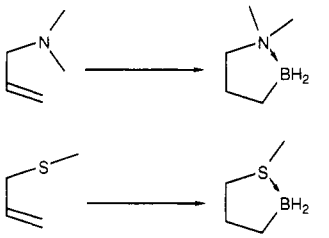
Both (+)- and (−)-myrtenyldithiane derivatives were independently prepared from commercially available chiral precursors and were easily, and in one step, converted by means of borane complexes into solid and stable chiral monoalkylboranes: (+)- and (−)-[2-(1,3-dithianyl)]myrtanylborane ($MDBH_2$). These new chiral reagents, when tested on representative classes of olefins, present a reactivity profile similar to $IpcBH_2$: they achieve the asymmetric hydroboration of trisubstituted double bonds with high asymmetric induction. Reduction of asymmetric prochiral ketones with $MDBH_2$ achieves high diastereoselectivity but low enantioselectivity. The likely intramolecular stabilization of $MDBH_2$ not only accounts for the easy access to monoalkylboranes but also for its remarkable physical properties, whereas its efficiency in asymmetric hydroboration is at the same level as that of similar reagents.

Introduction

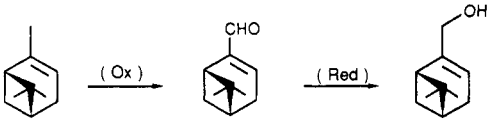
Since the discovery of asymmetric hydroboration by Brown and Zweifel, in 1961,[4] numerous nonenzymatic asymmetric syntheses by means of organoborane reagents have been reported.[5a] Today there exists a large choice of useful chiral organoboranes for asymmetric synthesis from olefins such as, for example, Ipc_2BH, $IpcBH_2$, Lgf_2BH, LimBH,[3] and, more recently, dicaranylboranes.[6-11] However, stable and uncomplexed monosubstituted chiral borane derivatives are rather uncommon: (+)- and (−)-monoisopinocampheylboranes ((+)-$IpcBH_2$, and (−)-$IpcBH_2$, **1** and **2**), were, for a long time, the only synthetically available representatives of chiral monoalkylboranes[7,12,13a,b] in a complexed form (Figure 1). Recently, (−)-mono(2-ethylapoisopinocampheyl)borane ($EapBH_2$) has been described[13c] in a complexed form. The scarcity of chiral monoalkylboranes is largely due to the fact that hydroboration of olefins rapidly passes through the monoalkylborane step to the dialkyl- or trialkylborane one. Consequently, synthesis of a reagent like $IpcBH_2$ cannot result from a one-step addition of "BH_3" to the chiral olefinic precursor.[12]

In some instances intramolecular stabilization is known to stop the reaction at the monohydroboration stage: for example, hydroboration of allylic amines and sulfides proceeds only to the monoalkylborane compounds (Scheme I).[15,16] Therefore, in an attempt to favor such intramolecular stabilization when reacting a borane complex with a chiral olefin, we have considered chiral heterocyclic structures (Figure 2) easily accessible from commercially available compounds.[14] Interestingly, all these olefins when reacted with BH_3–L (L = Lewis base) gave monoalkyl-

Scheme I



Scheme II. (+)-Myrtenol (4) from (+)-α-Pinene (3)



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(2) Thanks are due to Société Expansia, Aramon, France, for a doctoral grant to R. Kiesgen de Richter, analytical support, and technical assistance.
(3) Ipc_2BH, diisopinocampheylborane; $IpcBH_2$, monoisopinocampheylborane; Lgf_2BH, dilongifolylborane; LimBH, limonylborane.
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