An Easy Access to γ-Lactone-Fused Cyclopentanoids

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The tricyclic α-keto hemiacetals **3a,b** and **8a**−**d** obtained from ruthenium-catalyzed oxidation of tetrahalonorbornyl derivatives possessing a pendant hydroxymethyl group were cleaved using $Pb(OAc)_4$ or alkaline H_2O_2 to give γ-lactone-fused cyclopentane derivatives **5a,b** and **9a**−**d**. The α-keto hemiacetal **3b** has also been elaborated to spiroepoxide derivative **25**. The stable hydrate **4** formed from ruthenium-catalyzed oxidation of acrolein adduct **10** furnished an intramolecular hemiacetal **11** upon cleavage with $Pb(OAc)_4$. The α-halo ester moiety in **5a** was transformed smoothly in a highly regio- and stereoselective manner to α-hydroxy esters through a lactone-assisted intermediate to furnish **18**.

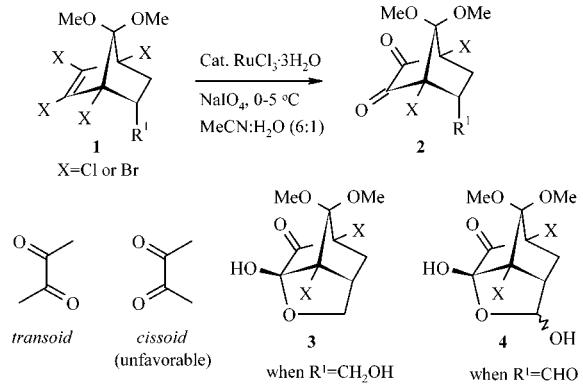
Introduction

γ-Lactone-fused cyclopentanoids are important intermediates in organic synthesis and are among the most abundant substructures found in numerous naturally occurring molecules. A cyclopentane ring *cis*-fused at the α,β-bond of the γ-lactone is the basic structural unit of many complex and challenging biologically active natural products[1] and also functions as the basic building block for the synthesis of a variety of cyclopentanoid natural products.[2] This provided us the impetus to conceive a convenient and general method for their preparation. Various synthetic methods have been adopted in the literature to acquire this important ring system.[3] However, many of these are target-oriented. We describe herein a novel, short, and efficient methodology to realize the cyclopentannulated γ-lactones making use of the persuasive advantages of the structural flexibility and stereochemical control offered by the tetrahalonorbornene derivatives.[4]

Results

As a part of our research program on the selective utilization of two sets of halogens (bridgehead vs vinylic)[5] in tetrahalonorbornene derivatives, we have recently recognized the feasibility of ruthenium-catalyzed oxidation of 1,2-dihaloalkenes to α-diketones on a variety of norbornyl derivatives (**1** → **2**),[5b] which have been serving as highly potent and inextricable templates in organic synthesis. One of the obvious consequences of the geometrical constraints on the α-dione moiety in norbornyl derivatives **2** is the imposition of the unfavorable cissoidal conformation, rendering one of the carbonyl groups of α-dione to acquire high propensity to interact either with a nucleophilic or electrophilic substituent, which is suitably disposed, to avoid unfavorable electrostatic interactions. Thus, when the *endo*-substituent R^1 in **1** is hydroxymethyl, a stable hemiacetal **3** in which one of the carbonyl groups of α-dione is switched to sp^3-hybridized carbon was isolated. On the other hand, an electrophilic *endo*-substituent (R^1 = CHO) promotes the formation of a stable hydrate **4** (Scheme 1).

Scheme 1



The tricyclic α-keto hemiacetals **3** are important not only because of the occurrence of closely related substructure in some of the biologically active natural products[6] but also because they could serve as potential building blocks in organic syntheses. The substrates **3**

(1) For some recent examples, see: (a) Wang, R.; Shimizu, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 413. (b) Huang, J.; Yokoyama, R.; Yang, C.; Fukuyama, Y. *Tetrahedron Lett.* **2000**, *41*, 6111. (c) Morita, H.; Fujiwara, M.; Naotoshi, Y.; Kobayashi, J. *Tetrahedron* **2000**, *56*, 5801. (d) Miyaoka, H.; Tamura, M.; Yamada, Y. *Tetrahedron* **2000**, *56*, 8083.

(2) (a) Scarborough, R. M., Jr.; Toder, B. H.; Smith, A. B., III. *J. Am. Chem. Soc.* **1980**, *102*, 3904. (b) Smith, A. B., III; Boschelli, D. *J. Org. Chem.* **1983**, *48*, 1217. (c) Hudlicky, T.; Govindan, S. V.; Frazier, J. O. *J. Org. Chem.* **1985**, *50*, 4166.

(3) For a few examples, see: (a) Wolinsky, J.; Wolf, H.; Gibson, T. *J. Org. Chem.* **1963**, 28, 274. (b) Niwa, H.; Wakamatsu, K.; Hida, T.; Niiyama, K.; Kigoshi, H.; Yamada, M.; Nagase, H.; Suzuki, M.; Yamada, K. *J. Am. Chem. Soc.* **1984**, *106*, 4547. (c) Ernst, A. B.; Fristad, W. E. *Tetrahedron Lett.* **1985**, *26*, 3761. (d) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140. (e) Kraus, G. A.; Landgrebe, K. *Tetrahedron* **1985**, *41*, 4039. (f) Lange, J. H. M.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron Lett.* **1989**, *30*, 127. (g) Iwasa, S.; Yamamoto, M.; Kohmoto, S.; Yamada, K. *J. Org. Chem.* **1991**, *56*, 2849. (h) Lee, J.; Barchi, J. J., Jr.; Marquez, V. E. *Chem. Lett.* **1995**, 299. (i) Hibbs, D, E.; Hursthouse, M. B.; Jones, I. G.; Jones, W.; Malik, K. M. A.; North, M. *J. Org. Chem.* **1999**, *64*, 5413. (j) Mandal, S. K.; Amin, S. R.; Crowe, W. E. *J. Am. Chem. Soc.* **2001**, *123*, 6457.

(4) Khan, F. A.; Prabhudas, B.; Dash, J. *J. Prakt. Chem.* **2000**, *342*, 512.

(5) (a) Khan, F. A.; Prabhudas, B. *Tetrahedron Lett.* **1999**, *40*, 9289. (b) Khan, F. A.; Prabhudas, B.; Dash, J.; Sahu, N. *J. Am. Chem. Soc.* **2000**, *122*, 9558.

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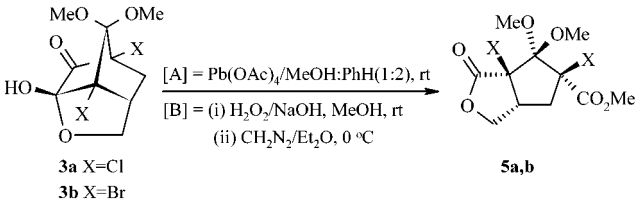
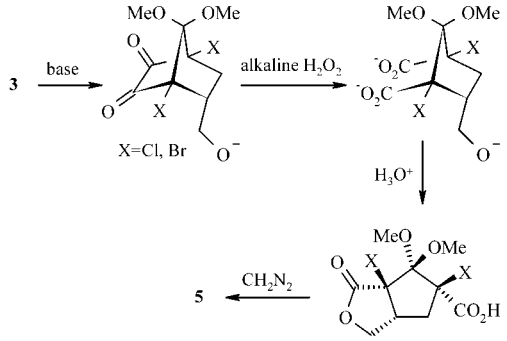
Table 1. Synthesis of γ-Lactone-Fused Cyclopentanoids 5a,b



substrate **3**	method	time, h	yield of **5** (%)	overall yield of **5** from **1**[a] (%)
a (X = Cl)	A	1.5	71	65
	B	2	96	71
b (X = Br)	A	2	64	59
	B	1	83	76

[a] When $R^1 = CH_2OH$.

Scheme 2



possessing an α-hydroxy carbonyl unit on the norbornane framework would reveal the γ-lactone-fused cyclopentane ring system bearing α-halo ester functionality upon cleavage of the bond between the carbonyl group and hydroxyl group. To check the feasibility of this scheme, the hemiacetals **3a**,**b** were subjected to both neutral and basic cleavage reaction conditions using $Pb(OAc)_4$ (method A) and alkaline hydrogen peroxide (method B), respectively. The results are summarized in Table 1. The method A directly furnished lactone **5** possessing methyl ester since MeOH was used as a cosolvent. In method B, which involves basic reaction conditions, the α-keto hemiacetal could exist in equilibrium with α-diketone and the latter underwent cleavage with alkaline hydrogen peroxide to give the diacid first. Upon acidic workup, one of the carboxylic acid groups lactonized with the free primary alcohol and the other carboxylic acid group was converted to methyl ester by treatment with diazomethane (Scheme 2).

To expand the scope of the process to obtain γ-lactone derivatives having substituents in both the lactone part and cyclopentane-ring, tertiary alcohols **7a**−**d** were identified as the suitable precursors. The alcohols **7** could, in principle, be prepared via the Diels−Alder reaction of dimethoxytetrahalocyclopentadiene with either suitably substituted allyl alcohols or substituted methyl acrylate followed by the conversion of ester group to tertiary alcohol. The latter option was preferred because although substituted allyl alcohols are poor dienophiles, substituted methyl acrylate, on the other hand, provides higher

Scheme 3

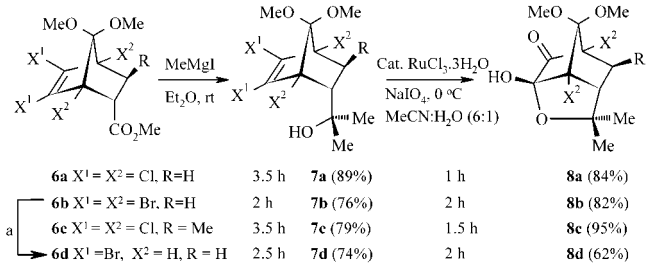
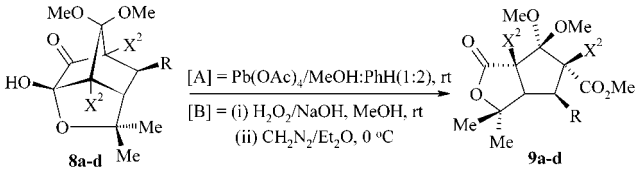
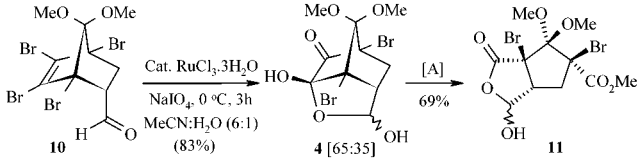


Table 2. Synthesis of γ-Lactone-Fused Cyclopentanoids 9a−d



entry	substrate **8**	method	time, h	yield **9** (%)	overall yield, **6** → **9** (%)
1	**a** (X^2 = Cl, R = H)	A	2	**a**, 81	61
2		B	1	**a**, 86	64
3	**b** (X^2 = Br, R = H)	A	4	**b**, 79	49
4		B	1	**b**, 81	51
5	**c** (X^2 = Cl, R = Me)	A	3	**c**, 62	47
6		B	1.5	**c**, 83	62
7	**d** (X^2 = H, R = H)	A	2	**d**, 69	32

Scheme 4



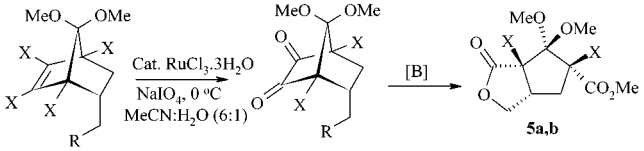
reactivity, *endo*-selectivity, and flexibility of incorporating any desired pair of substituents on the tertiary carbon. Thus, the Diels−Alder adducts of methyl acrylate **6a**,**b** and methyl crotonate **6c** obtained from corresponding dimethoxytetrahalocyclopentadiene were smoothly transformed into the tertiary alcohols **7a**−**c** using Grignard reaction (Scheme 3). Similarly, **6d**, obtained from **6b** via selective bridgehead hydrodebromination[5a] employing Bu_3SnH/AIBN was also converted in good yield to the corresponding alcohol **7d**. Oxidation of these substrates with catalytic $RuCl_3$ and $NaIO_4$ afforded the α-keto hemiacetals **8a**−**d** in good to high yields.

The α-keto hemiacetals **8a**−**d** were subjected to both $Pb(OAc)_4$ and alkaline H_2O_2 mediated cleavage reaction to give highly substituted γ-lactone-fused cyclopentanoids **9a**−**d** in good overall yield from the Diels−Alder precursor **6** (Table 2).

The monohydrate **4** derived from the acrolein adduct **10** under $Pb(OAc)_4$/MeOH conditions gave the half-acetal **11** (Scheme 4). It is interesting to note that the α-diketones **12a**,**b** with *endo*-CH_2OAc group also furnished, upon cleavage with alkaline H_2O_2, γ-lactone derivatives **5a**,**b** in moderate to good yields (Scheme 5). The diketones bearing halomethyl groups **16** and **17**, derived from adducts **13** and **14**, also serve as potential precursors for the synthesis of the lactones **5a**,**b**, thus providing a choice from a range of allylic dienophile precursors that

(6) (a) Shizuri, Y.; Okuno, Y.; Shigemori, H.; Yamamura, S. *Tetrahedron* **1987**, *28*, 6661. (b) Rodríguez, A. D.; Ramírez, C.; Rodríguez, I. I.; Barnes, C. L. *J. Org. Chem.* **2000**, *65*, 1390.

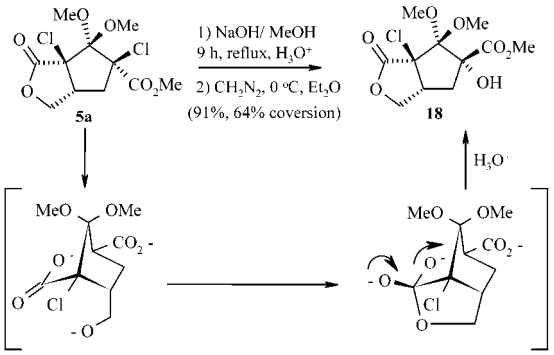
Scheme 5



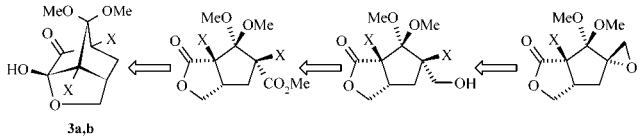
12a X=Cl, R= OAc	30 min	**15a**, 99%	2h	**5a**, 79%
12b X=Br, R= OAc	30 min	**15b**, 90%	2h	**5b**, 52%
13a X = Cl, R= Br	15 min	**16a**, 89%	3h	**5a**, 98%
13b X = Br, R= Br	25 min	**16b**, 80%	30 min	**5b**, 95%
14 X=Cl, R= Cl	10min	**17**, 90%	3h	**5a**, 73%

[B] = (i) H_2O_2/NaOH, MeOH, rt, (ii) CH_2N_2/Et_2O, 0 °C

Scheme 6



Scheme 7



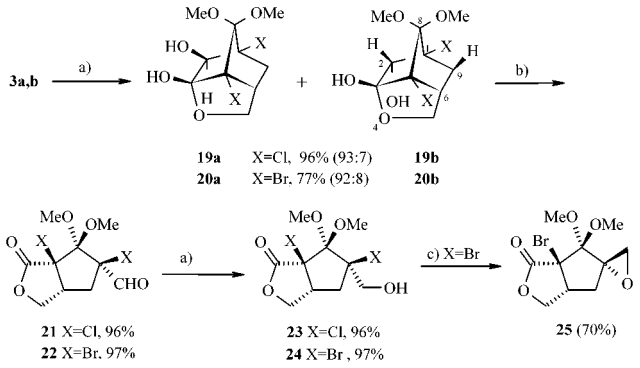
contribute three carbons to the γ-lactone-fused cyclopentanoid skeleton.

α-Hydroxy esters are important in organic syntheses; an α-halo ester could serve as a precursor for the former through nucleophilic displacement of halide by hydroxide anion. However, the halogens in the γ-lactone derivative are tertiary in nature, and a S_N2 reaction at this center would be rather difficult. We thought of preparing α-hydroxy esters through a lactone-assisted, highly regio- and stereoselective strategy as shown in Scheme 6. Treatment of **5a** with NaOH followed by diazomethane treatment furnished α-hydoxy ester bearing γ-lactone-fused cyclopentane derivative **18**, probably via a bridged-lactone intermediate as depicted in Scheme 6.

A spiroepoxide-bearing cyclopentane ring with oxygen-bearing substituents in the α-position is a structural feature found in many natural products such as coriolin, coriamyrtin, tutin, calonectrin, varrucarin A, etc.[7] We thought that the α-halo ester functionality in **5** could be elaborated to spiroepoxide via the halohydrin as depicted in the retrosynthetic Scheme 7. Achievement of selective reduction of the ester group in the presence of lactone moiety poses a potential problem to execute the proposed strategy. This difficulty was circumvented by sequencing the reduction step prior to the release of lactone moiety taking advantage of internal protection in the form of a hemiacetal. Reduction of the carbonyl group in **3** followed by cleavage would give the α-halo aldehyde instead of an ester and paves the way for selective reduction.

(7) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley: New York, 1989. (b) Kraus, G. A.; Roth, B.; Frazier, K.; Shimagaki, M. *J. Am. Chem. Soc.* **1982**, *104*, 1114.

Scheme 8



a) $NaBH_4$, MeOH, 0 °C, 1 h, b) $Pb(OAc)_4$, MeOH, rt, 30 min; c) NaH/THF, reflux, 8 h (for X=Cl, no reaction after 12 h).

The execution of this strategy is shown in Scheme 8. Sodium borohydride reduction of α-keto hemiacetals **3a**,**b** was highly diastereoselective, giving the *exo*-alcohols **19a** and **20a** as the major products in high yield. The hydride attack was predominantly from the *endo*-face. The stereochemistry of the minor isomer **19b** and **20b** was elucidated on the basis of the unique W-coupling ($J = \sim 2$ Hz) shown by the carbinol H on C_2 and *exo*-H on C_9.

The mixture of diastereomers was exposed to $Pb(OAc)_4$ in MeOH to give high yield of the α-halo aldehydes **21** and **22**, which upon sodium borohydride reduction gave halohydrins **23** and **24**. The bromohydrin **24** under NaH conditions underwent smooth cyclization to form the spiro epoxide **25** in 70% yield. The chlorohydrin **23** upon refluxing with NaH in THF for 12 h did not undergo any reaction, and the starting material was recovered back.

In conclusion, the γ-lactone-fused cyclopentane ring system was accessed in just two steps from Diels−Alder adducts. The methodology provides flexibility to use Grignard reagent to achieve numerous structurally varied systems. Lactone-assisted selective transformation of an α-halo ester to an α-hydroxy ester functionality at a sterically congested tertiary center was achieved. Further, an efficient method for the elaboration of α-keto hemiacetals to spiroepoxide was demonstrated.

Experimental Section

General. Melting points are uncorrected. IR spectra were recorded as KBr pellets (solids) or thin films (liquids). ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ and reported in the δ scale. Tetramethylsilane was used as the internal standard. Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; integration; coupling constant(s) in Hz. Column chromatography was performed using silica gel (100−200 mesh), and 15−25% ethyl acetate−hexane was used as eluent. Acetonitrile and CCl_4 were distilled over P_2O_5. Ether was distilled immediately prior to use from sodium/benzophenone ketyl under argon. Distilled water was used for the reactions. The tetrahalonorbornene derivatives were prepared according to literature procedures.[4]

General Procedure for the Grignard Reaction of Tetrahaloesters 6a−d. Preparation of 7a−d. An ether solution of methylmagnesium iodide was prepared from Mg turnings (412 mg, 17.16 mmol), a crystal of I_2, and MeI (1.6 mL, 25.74 mmol) in 15 mL of dry ether as per standard procedures. After the metal completely dissolved, the *endo*-ester derivative **6a** (1.0gm, 2.86 mmol) in 5 mL of ether was added slowly over 10 min under an argon atmosphere. The reaction mixture was stirred for 3.5 h at room temperature (completion of starting material as per TLC), cooled, and

quenched with saturated NH_4Cl solution (2 mL). The reaction mixture was extracted thrice with ethyl acetate. The combined organic layer was washed once with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated, and the crude reaction mixture was purified by chromatography using silica gel to yield the tertiary alcohol derivative **7a**. Similar reaction conditions were followed for other substrates **7b**−**d**.

2-(1,4,5,6-Tetrachloro-7,7-dimethoxy-bicyclo[2.2.1]hept-5-en-2-yl)-propan-2-ol (7a): yield 89%, colorless solid, mp 70−71 °C; ^{1}H NMR δ 3.54 (s, 3H), 3.48 (s, 3H), 2.58 (dd, 1H, J = 9.2, 4.9 Hz), 2.35 (dd, 1H, J = 11.6, 9.5 Hz), 2.01 (dd, 1H, J = 11.6, 4.9 Hz), 1.38 (s, 3H), 1.30 (br s, 1H, OH, D_2O exchangeable), 1.08 (s, 3H); ^{13}C NMR δ 129.0, 127.9, 112.5, 77.9, 74.1, 71.3, 54.8, 52.8, 51.6, 38.2, 30.4, 29.5; IR (KBr) 3400, 2900, 1590, 1420, 1240 cm^{-1}. Anal. Calcd for $C_{12}H_{16}Cl_4O_3$: C, 41.17; H, 4.61. Found: C, 41.23; H, 4.64.

2-(1,4,5,6-Tetrabromo-7,7-dimethoxy-bicyclo[2.2.1]hept-5-en-2-yl)-propan-2-ol (7b): yield 76%, colorless solid, mp 72−74 °C; ^{1}H NMR δ 3.63 (s, 3H), 3.60 (s, 3H), 2.68 (dd, 1H, J = 9.2, 4.8 Hz), 2.47 (dd, 1H, J = 11.2, 9.3 Hz), 2.17 (dd, 1H, J = 11.4, 4.9 Hz), 1.52 (s, 3H), 1.15 (s, 3H); ^{13}C NMR δ 125.1, 124.3, 112.7, 71.9, 71.7, 67.8, 56.0, 53.3, 51.7, 40.2, 30.4, 30.1; IR (KBr) 3300, 2900, 1560, 1450, cm^{-1}. Anal. Calcd for $C_{12}H_{16}Br_4O_3$: C, 27.30; H, 3.05. Found: C, 27.23; H, 3.09.

2-(1,4,5,6-Tetrachloro-7,7-dimethoxy-3-methyl-bicyclo[2.2.1]hept-5-en-2-yl)-propan-2-ol (7c): yield 79%; obtained as a viscous liquid; ^{1}H NMR δ 3.52 (s, 3H), 3.48 (s, 3H), 2.26 (d, 1H, J = 5.6 Hz), 2.13−2.10 (m, 1H), 1.48 (br s, 1H, OH), 1.39 (s, 3H), 1.35 (d, 3H, J = 7.1 Hz), 1.19 (s, 3H); ^{13}C NMR δ 130.2, 128.5, 112.7, 78.1, 77.8, 72.0, 61.3, 52.5, 51.4, 42.3, 31.0, 30.0, 16.8; IR (neat) 3500, 2900, 1600, 1450, 1190 cm^{-1}. Anal. Calcd for $C_{13}H_{18}Cl_4O_3$: C, 42.89; H, 4.98. Found: C, 42.93; H 5.07.

2-(5,6-Dibromo-7,7-dimethoxy-bicyclo[2.2.1]hept-5-en-2-yl)-propan-2-ol (7d): yield 74%, colorless solid, mp 76−78 °C; ^{1}H NMR δ 3.16 (s, 3H), 3.14 (s, 3H), 3.05 (dd, 1H, J = 3.4, 2.3 Hz), 2.97 (dd, 1H, J = 4.1, 2.3 Hz), 2.36 (ddd, 1H, J = 8.9, 5.4, 3.4 Hz), 1.94 (ddd, 1H, J = 11.9, 8.9, 4.1 Hz), 1.41 (dd, 1H, J = 11.9, 5.4 Hz), 1.31 (s, 3H), 1.20 (br s, 1H, OH), 1.12 (s, 3H); ^{13}C NMR δ 122.3, 119.4, 117.0, 70.9, 56.3, 54.9, 52.2, 49.5, 48.7, 29.6, 29.4, 25.7; IR (KBr) 3250, 2950, 1590, 1110 cm^{-1}. Anal. Calcd for $C_{12}H_{18}Br_2O_3$: C, 38.95; H, 4.90. Found: C, 38.89; H, 4.86.

General Procedure for the Cleavage of α-Ketohemiacetals and α-Diketones. Method A. To a stirred solution of the α-keto hemiacetal (0.17 mmol) in MeOH (1 mL) and benzene (2 mL) was added $Pb(OAc)_4$ (102 mg, 0.23 mmol) in portions over a period of 30 min at room temperature. After the mixture stirred for the required time, dilute $NaHCO_3$ (2 mL) was added and extracted with ethyl acetate. The combined organic layer was washed once with brine and dried over anhydrous Na_2SO_4. Concentration followed by silica gel chromatography of the crude yielded the pure γ-lactone-fused cyclopentanes.

Method B. To a stirred solution of α-keto hemiacetal or α-diketone (0.35 mmol) in methanol (3 mL) was added 30% H_2O_2 (0.25 mL) followed by slow addition of 6 N NaOH solution (0.13 mL). After the mixture stirred at room temperature (~20 °C) for 1−2 h, 5% HCl (10 mL) was added and extracted with ethyl acetate (3 × 5 mL). The combined ethyl acetate layer was washed once with brine and dried over Na_2SO_4. The crude carboxylic acid obtained after concentration of the ethyl acetate layer was treated with excess diazomethane in ether/methanol (1:1) at 0 °C. After quenching excess diazomethane with acetic acid, the solution was concentrated, and silica gel column chromatography afforded the pure product in the specified yields.

Methyl 5,6a-Dichloro-6,6-dimethoxy-1-oxo-hexahydrocyclopenta[*c*]furan-5-carboxylate (5a): colorless solid; mp 118−120 °C; ^{1}H NMR δ 4.61 (t, 1H, J = 9.0 Hz), 4.14 (dd, 1H, J = 9.3, 3.6 Hz), 3.86 (s, 3H), 3.78 (s, 3H), 3.49 (dtd, 1H, J = 9.0, 9.0, 3.6 Hz), 3.32 (s, 3H), 2.82 (dd, 1H, J = 14.5, 9.0 Hz), 2.66 (dd, 1H, J = 14.5, 9.0 Hz); ^{13}C NMR δ 171.1, 167.7, 110.0, 74.0, 73.8, 70.6, 54.3, 53.5, 51.5, 46.3, 41.8; IR (KBr) 2850, 1740 (br), 1180 cm^{-1}. Anal. Calcd for $C_{11}H_{14}Cl_2O_6$: C, 42.19; H, 4.51. Found: C, 42.36; H, 4.79.

Methyl 5,6a-Dibromo-6,6-dimethoxy-1-oxo-hexahydrocyclopenta[*c*]furan-5-carboxylate (5b): colorless solid; mp 112−113 °C; ^{1}H NMR δ 4.55 (t, 1H, J = 9.5 Hz), 4.11 (dd, 1H, J = 9.5, 2.7 Hz), 3.81 (s, 3H), 3.76 (s, 3H), 3.57 (m, 1H), 3.30 (s, 3H), 2.79 (dd, 1H, J = 14.6, 10.2 Hz), 2.64 (dd, 1H, J = 14.6, 8.8 Hz); ^{13}C NMR δ 171.5, 168.1, 109.2, 69.9, 64.9, 63.4, 54.7, 53.4, 52.3, 47.5, 43.0; IR (KBr) 2900, 1760, 1720, 1160 cm^{-1}. Anal. Calcd for $C_{11}H_{14}Br_2O_6$: C, 32.86; H, 3.51. Found: C, 33.36; H, 3.66.

Methyl 3a,5-Dichloro-4,4-dimethoxy-1,1-dimethyl-3-oxo-hexahydro-cyclopenta[*c*]furan-5-carboxylate (9a): colorless solid, mp 118−120 °C; ^{1}HNMR δ 3.79 (s, 3H), 3.71 (s, 3H), 3.14 (dd, 1H, J = 11.6, 8.5 Hz), 2.81 (dd, 1H, J = 14.0, 11.6 Hz), 2.23 (dd, 1H, J = 14.0, 8.5 Hz), 1.61 (s, 3H), 1.24 (s, 3H); ^{13}C NMR δ 169.9, 167.8, 109.8, 82.9, 75.6, 73.8, 55.6, 54.3, 53.5, 51.5, 36.6, 30.9, 23.7; IR (KBr) 2900, 1730 (br), 1160 cm^{-1}. Anal. Calcd for $C_{13}H_{18}Cl_2O_6$: C, 45.76; H, 5.32. Found: C, 45.80; H, 5.46.

Methyl 3a,5-Dibromo-4,4-dimethoxy-1,1-dimethyl-3-oxo-hexahydro-cyclopenta[*c*]furan-5-carboxylate (9b): colorless solid, mp 106−109 °C; ^{1}H NMR δ 3.85 (s, 3H), 3.80 (s, 3H), 3.38 (dd, 1H, J = 10.0, 8.5 Hz), 3.31 (s, 3H), 2.90 (dd, 1H, J = 14.8, 11.5 Hz), 2.34 (dd, 1H, J = 14.4, 8.4 Hz), 1.67 (s, 3H), 1.43 (s, 3H); ^{13}C NMR δ 170.4, 168.3, 109.1, 82.9, 65.6, 64.9, 56.4, 54.7, 53.4, 52.1, 38.1, 30.4, 24.1; IR (KBr) 2850, 1760, 1720, 1420 cm^{-1}. Anal. Calcd for $C_{13}H_{18}Br_2O_6$: C, 36.30; H, 4.22. Found: C, 36.43; H, 4.31.

Methyl 3a,5-Dichloro-4,4-dimethoxy-1,1,6-trimethyl-3-oxo-hexahydro-cyclopenta[*c*]furan-5-carboxylate (9c): viscous liquid; ^{1}H NMR δ 3.85 (s, 3H), 3.79 (s, 3H), 3.28 (s, 3H), 3.21 (qd, 1H, J = 10.4, 6.4 Hz), 2.70 (d, 1H, J = 10.4 Hz), 1.59 (s, 3H), 1.52 (s, 3H), 1.21 (d, 3H, J = 6.4 Hz); ^{13}C NMR δ 169.9, 167.6, 109.9, 83.1, 79.1, 75.4, 62.8, 54.4, 53.5, 51.3, 39.8, 31.9, 23.2, 15.2; IR (neat) 2850, 1750, 1720, 1160 cm^{-1}. Anal. Calcd for $C_{14}H_{20}Cl_2O_6$: C, 47.34; H, 5.67. Found: C, 47.42; H, 5.59.

Methyl 4,4-Dimethoxy-1,1-dimethyl-3-oxo-hexahydro-cyclopenta[*c*]furan-5-carboxylate (9d): yield 58%, colorless solid, mp 101−102 °C; ^{1}H NMR δ 3.70 (s, 3H), 3.43 (s, 3H), 3.36 (s, 3H), 3.34 (d, 1H, J = 10.0 Hz), 3.07 (t, 1H, J = 7.6 Hz), 2.73 (m, 1H), 2.30 (m, 1H), 1.99 (td, 1H, J = 14.1, 8.8 Hz), 1.47 (s, 3H), 1.40 (s, 3H); ^{13}C NMR δ 172.2, 171.7, 110.8, 83.2, 53.2, 52.0, 51.95, 50.3, 49.6, 46.8, 30.2, 27.4, 23.6; IR (KBr) 2950, 1740, 1720, 1430 cm^{-1}. Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 57.29; H, 7.36.

Methyl 3a,5-Dibromo-1-hydroxy-4,4-dimethoxy-3-oxo-hexahydro-cyclopenta[*c*]furan-5-carboxylate (11): yield 69%, mp 100−102 °C (dec); ^{1}H NMR δ 5.72 (s, 1H), 4.62 (s, 1H, OH, D_2O exchangeable), 3.85 (s, 3H), 3.78 (s, 3H), 3.49 (t, 1H, J = 9.8 Hz), 3.30 (s, 3H), 2.84 (dd, 1H, J = 14.5, 10.5 Hz), 2.72 (dd, 1H, J = 14.5, 9.3 Hz); ^{13}C NMR δ 171.2, 168.2, 109.4, 100.8, 64.0, 63.1, 55.3, 54.6, 53.6, 52.2, 40.1; IR (KBr) 3350, 2900, 1750, 1710, 1420, 1220 cm^{-1}. Anal. Calcd for $C_{11}H_{14}Br_2O_7$: C, 31.61; H, 3.38. Found: C, 31.53; H, 3.31.

Methyl 6a-Chloro-5-hydroxy-6,6-dimethoxy-1-oxo-hexahydro-cyclopenta[*c*]furan-5-carboxylate (18): yield 91% (64% conversion), colorless solid, mp 72−74 °C; ^{1}H NMR δ 4.59 (t, 1H, J = 8.8 Hz), 4.16 (dd, 1H, J = 9.0, 2.0 Hz), 3.81 (s, 3H), 3.75 (s, 3H), 3.50 (br s, 1H, OH, D_2O exchangeable), 3.39 (s, 3H), 3.15−3.12 (m, 1H), 3.04 (t, 1H, J = 12.5 Hz), 1.80 (dd, 1H, J = 13.9, 2.7 Hz); ^{13}C NMR δ 171.5, 171.3, 107.7, 82.8, 72.1, 71.0, 54.0, 53.1, 50.9, 45.3, 37.5; IR (KBr) 3350, 2900, 1730, 1150 cm^{-1}. Anal. Calcd for $C_{11}H_{15}ClO_7$: C, 44.83; H, 5.13. Found: C, 44.79; H, 5.08.

General Procedure for Sodium Borohydride Reduction of α-Keto Hemiacetals. A solution of α-keto hemiacetal (0.5 mmol) in MeOH (5 mL) was cooled to 0 °C, and $NaBH_4$ (0.75 mmol) was added to it. After the mixture stirred at 0 °C for 1 h, dilute HCl (3 mL) was added and extracted with ethyl acetate (3 × 5 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Concentration followed by purification of the crude by silica gel column chromatography afforded the pure diols.

1,7-Dichloro-8,8-dimethoxy-4-oxa-tricyclo[4.2.1.0^{3,7}]-nonane-2,3-diol (19a): yield 88%, colorless solid, mp 133−134 °C; ^{1}H NMR δ 4.31 (br s, 1H, OH, D_2O exchangeable), 4.26 (ddd, 1H, *J* = 8.5, 3.3, 1.0 Hz), 3.69 (d, 1H, *J* = 8.5 Hz), 3.67 (s, 3H), 3.65 (m, 2H), 3.64 (s, 3H), 2.75−2.67 (m, 2H), 1.77 (m, 1H); ^{13}C NMR δ 106.3, 105.5, 83.0, 75.1, 70.4, 68.4, 52.1, 51.2, 44.9, 39.4; IR (KBr) 3300, 2900, 1200 cm^{-1}. Anal. Calcd for $C_{10}H_{14}Cl_2O_5$: C, 42.13; H, 4.95. Found: C, 42.23; H, 5.01.

1,7-Dichloro-8,8-dimethoxy-4-oxa-tricyclo[4.2.1.0^{3,7}]-nonane-2,3-diol (19b): yield 8%, colorless solid, mp 119−120 °C; ^{1}H NMR δ 4.27 (dd, 1H, *J* = 6.3, 2.4 Hz), 4.23 (dd, 1H, *J* = 8.3, 3.9 Hz), 3.71 (d, 1H, *J* = 8.3 Hz), 3.65 (s, 3H), 3.63 (s, 3H), 3.45 (br s, 1H, OH, D_2O exchangeable), 3.06 (d, 1H, *J* = 6.5 Hz, OH, D_2O exchangeable), 2.73 (ddd, 1H, *J* = 11.0, 3.9, 2.2 Hz), 2.44 (ddd, 1H, *J* = 12.5, 11.0, 2.4 Hz), 2.08 (dd, 1H, *J* = 12.5, 2.2); ^{13}C NMR δ 105.3, 102.2, 78.8, 77.1, 71.0, 70.5, 51.6, 51.2, 45.5, 35.7; IR (KBr) 3300, 2850, 1200 cm^{-1}. Anal. Calcd for $C_{10}H_{14}Cl_2O_5$: C, 42.13; H, 4.95. Found: C, 42.05; H, 4.91.

1,7-Dibromo-8,8-dimethoxy-4-oxa-tricyclo[4.2.1.0^{3,7}]-nonane-2,3-diol (20a): yield 71%, colorless solid, mp 146−147 °C; ^{1}H NMR δ 4.30 (dd, 1H, *J* = 8.5, 3.6 Hz), 4.28 (br s, 1H, OH), 3.71 (s, 3H), 3.68 (s, 3H), 3.68−3.63 (m, 3H), 2.81 (t, 1H, *J* = 11.0 Hz), 2.75 (dd, 1H, *J* = 11.7, 3.6 Hz), 1.85 (d, 1H, *J* = 11.2 Hz); ^{13}C NMR δ 106.3, 106.1, 83.7, 70.2, 68.0, 61.5, 52.3, 51.4, 46.8, 40.8; IR (KBr) 3500, 2950, 1200 cm^{-1}. Anal. Calcd for $C_{10}H_{14}Br_2O_5$: C, 32.11; H, 3.77. Found: C, 32.18; H, 3.71.

1,7-Dibromo-8,8-dimethoxy-4-oxa-tricyclo[4.2.1.0^{3,7}]-nonane-2,3-diol (20b): yield 6%, colorless solid, mp 101−102 °C; ^{1}H NMR δ 4.34 (dd, 1H, *J* = 6.5, 2.4 Hz), 4.24 (dd, 1H, *J* = 8.3, 3.9 Hz), 3.69 (s, 3H), 3.68 (s, 3H), 3.67 (d, 1H, *J* = 8.3 Hz), 3.25 (s, 1H, OH, D_2O exchangeable), 2.97 (d, 1H, *J* = 6.4 Hz, OH, D_2O exchangeable) 2.78 (ddd, 1H, *J* = 11.0, 3.9, 2.2 Hz), 2.52 (dt, 1H, *J* = 12.4, 2.4 Hz), 2.17 (dd, 1H, *J* = 12.4, 2.2 Hz); ^{13}C NMR δ 105.6, 102.5, 79.5, 71.3, 70.7, 63.0, 51.9, 51.4, 47.3, 37.2; IR (KBr) 3550, 2950, 1150 cm^{-1}. Anal. Calcd for $C_{10}H_{14}Br_2O_5$: C, 32.11; H, 3.77. Found: C, 32.20; H, 3.80.

5,6a-Dichloro-6,6-dimethoxy-1-oxo-hexahydro-cyclopenta[*c*]furan-5-carbaldehyde (21): procedure is similar to that adopted for the cleavage of α-keto hemiacetals using $Pb(OAc)_4$ (Method A); yield 96%, colorless solid, mp 120−122 °C; ^{1}H NMR δ 9.58 (s, 1H), 4.63 (t, 1H, *J* = 9.2 Hz), 4.13 (dd, 1H, *J* = 9.2, 4.4 Hz), 3.74 (s, 3H), 3.52 (ddt, 1H, *J* = 9.4, 8.6, 4.6 Hz), 3.33 (s, 3H), 2.71 (dd, 1H, *J* = 14.6, 8.0 Hz), 2.47 (dd, 1H, *J* = 14.9, 9.5 Hz); ^{13}C NMR δ 189.4, 170.9, 110.3, 79.7, 73.5, 71.3, 54.0, 53.0, 46.7, 37.7; IR (KBr) 2900, 1750, 1720, 1380 cm^{-1}. Anal. Calcd for $C_{10}H_{12}Cl_2O_5$: C, 42.43; H, 4.27. Found: C, 42.48; H, 4.21.

5,6a-Dibromo-6,6-dimethoxy-1-oxo-hexahydro-cyclopenta[*c*]furan-5-carbaldehyde (22): procedure is similar to that adopted for the cleavage of α-keto hemiacetals using $Pb(OAc)_4$ (Method A); yield 97%, colorless solid, mp 120−122 °C; ^{1}H NMR δ 9.59 (s, 1H), 4.63 (dd, 1H, *J* = 9.3, 8.6 Hz), 4.17 (dd, 1H, *J* = 9.3, 3.4 Hz), 3.75 (s, 3H), 3.66−3.58 (m, 1H), 3.36 (s, 3H), 2.75 (dd, 1H, *J* = 15.0, 8.4 Hz), 2.56 (dd, 1H, *J* = 15.0, 9.3 Hz); ^{13}C NMR δ 187.5, 171.2, 109.1, 73.6, 70.8, 62.7, 54.1, 53.3, 47.8, 38.6; IR (KBr) 2900, 1750, 1690, 1370, 1160 cm^{-1}. Anal. Calcd for $C_{10}H_{12}Br_2O_5$: C, 32.29; H, 3.25. Found: C, 32.21; H, 3.30.

5,6a-Dichloro-5-hydroxymethyl-6,6-dimethoxy-hexahydro-cyclopenta[*c*]furan-1-one (23). A solution of aldehyde (0.5 mmol) in MeOH (5 mL) was cooled to 0 °C, and $NaBH_4$ (0.5 mmol) was added to it. After the mixture stirred at 0 °C for 15 min, dilute HCl (3 mL) was added and extracted with ethyl acetate (3 × 5 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Concentration followed by purification of the crude by silica gel column chromatography afforded the pure chlorohydrin: yield 88%, colorless solid, mp 120−122 °C; ^{1}H NMR δ 4.59 (t, 1H, *J* = 8.9 Hz), 4.06 (dd, 1H, *J* = 9.3, 3.9 Hz), 3.94 (dd, 1H, *J* = 12.2, 6.8 Hz), 3.84 (dd, 1H, *J* = 12.2, 6.8 Hz), 3.79 (s, 3H), 3.56 (s, 3H), 3.54−3.46 (m, 1H), 2.60 (dd, 1H, *J* = 14.1, 9.3 Hz), 2.35 (t, 1H, *J* = 6.8 Hz, OH, D_2O exchangeable), 2.13 (dd, 1H, *J* = 14.1, 8.8 Hz); ^{13}C NMR δ 171.6, 110.5, 82.4, 74.3, 70.8, 66.4, 54.6, 53.3, 47.1, 41.9; IR (KBr) 3300, 2850, 1730, 1370, 1140 cm^{-1}. Anal. Calcd for $C_{10}H_{14}Cl_2O_5$: C, 42.13; H, 4.95. Found: C, 42.18; H, 5.01.

5,6a-Dibromo-5-hydroxymethyl-6,6-dimethoxy-hexahydro-cyclopenta[*c*]furan-1-one (24): procedure is similar to the one adopted for **23**; yield 87%, viscous liquid; ^{1}H NMR δ 4.57 (dd, 1H, *J* = 9.3, 8.0 Hz), 4.09 (dd, 1H, *J* = 9.5, 2.7 Hz), 3.96 (dd, 1H, *J* = 12.4, 6.8 Hz), 3.86 (dd, 1H, *J* = 12.4, 6.8 Hz), 3.79 (s, 3H), 3.66−3.59 (m, 1H), 3.59 (s, 3H), 2.62 (dd, 1H, *J* = 14.4, 8.8 Hz), 2.42 (t, 1H, *J* = 6.8 Hz, OH), 2.23 (dd, 1H, *J* = 14.4, 9.8 Hz); ^{13}C NMR δ 171.9, 110.0, 78.6, 70.0, 67.2, 63.9, 54.8, 54.2, 48.5, 42.9; IR (neat) 3300, 2850, 1730, 1370, 1140 cm^{-1}. Anal. Calcd for $C_{10}H_{14}Br_2O_5$: C, 32.11; H, 3.77. Found: C, 32.19; H, 3.82.

Spiroepoxide (25): yield 70%, mp 195−198 °C (dec); ^{1}H NMR δ 4.61 (t, 1H, *J* = 8.8 Hz), 4.11 (t, 1H, *J* = 8.1 Hz) 3.49 (s, 6H), 3.45−3.36 (m, 1H), 3.09 (d, 1H, *J* = 5.9 Hz), 2.66 (d, 1H, *J* = 5.9 Hz), 2.14 (dd, 1H, *J* = 13.5, 10.0 Hz), 2.04 (dd, 1H, *J* = 13.5, 5.1 Hz); ^{13}C NMR δ 171.9, 103.0, 73.8, 63.7, 62.8, 51.8, 51.4, 50.5, 45.8, 30.8; IR (KBr) 2900, 1750, 1440, 1360, 1150 cm^{-1}. Anal. Calcd for $C_{10}H_{13}BrO_5$: C, 40.98; H, 4.47. Found: C, 40.91; H, 4.42.

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Supporting Information Available: Experimental procedures for the ruthenium-catalyzed oxidation of **1**, **7**, **10**, and **12**−**14** and spectral data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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