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Novel 1,4-Homofragmentation via an α-Lactone

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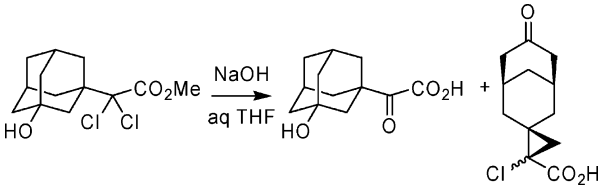
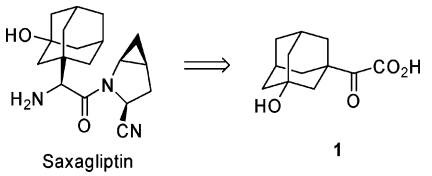


Conversion of an α,α-dichloroester to the corresponding α-keto acid was unexpectedly complicated by a novel 1,4-homofragmentation. Investigation of the kinetics of this reaction revealed a mechanism involving an α-lactone intermediate, which can lead to both the desired α-keto acid and the 1,4-homofragmentation, with the product distribution being dependent upon reaction conditions. This information allowed development of a process that affords the α-keto acid exclusively and should be generally applicable to the preparation of α-keto acids from α,α-dichloroesters or acids.

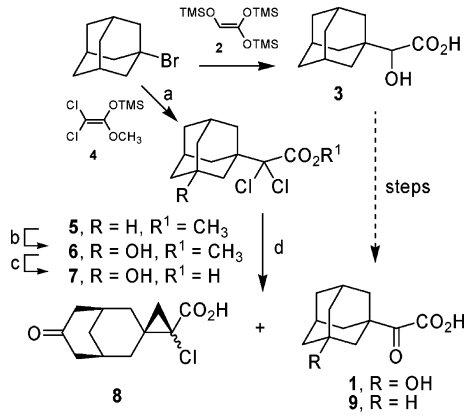
Saxagliptin[1] is a highly potent, long-acting dipeptidyl peptidase IV inhibitor currently undergoing clinical trials for the treatment of type 2 diabetes mellitus. In an improved process[2] for the preparation of saxagliptin, the adamantylglycine fragment is prepared by an enzyme-mediated, asymmetric reductive amination of α-keto acid **1** (Scheme 1). The preparation of substantial quantities of **1** required the development of an efficient, cost-effective, and scalable synthesis.

Lewis acid-mediated α-*tert* alkylation of the tris-silylated form of glycolic acid **2** with 1-bromoadamantane, as reported by Reetz and Heimbach,[3] provides **3**, which could be used for the synthesis of **1** (Scheme 2). However, conversion of **3** to **1** would require esterification, oxidation of the hydroxyl group, hydroxylation of the adamantane ring, and finally, ester hydrolysis. Three of these four steps involve protection/deprotection or oxidation state manipulation, and thus this route was considered inefficient for large-scale work. The $ZnCl_2$-promoted addition of 1,2-diethoxy-1,2-bis(trimethylsiloxy)ethylene to tertiary alkyl halides[4] provides a more direct route to α-keto esters but, unfortunately, did not appear particularly suitable for large-scale work.[5] The hydrolysis of α,α-dichloroesters or acids to the corresponding α-keto acids has been reported in several isolated examples and generally requires relatively harsh conditions.[6] Nevertheless, the recent report of Imashiro and Kuroda[7] on the preparation of α,α-dichloroketene silyl acetal **4** from inexpensive starting materials [methyl trichloroacetate, zinc powder, and chlorotrimethylsilane (TMSCl)] prompted our investigation into the use of **4** as a means to directly introduce the side chain at the oxidation state of an α-keto ester. With modifications[8] of the literature procedure, **4** was prepared and could be used without distillation. Treatment of 1-bromoada-

SCHEME 1



SCHEME 2 [a]



[a] Reagents and conditions: (a) $ZnCl_2$ (0.1 equiv), CH_2Cl_2, rt (92%); (b) (1) 10 N HNO_3, concd H_2SO_4, 2 to ∼34 °C; (2) EtOAc, H_2O, urea (99% crude, 90% recrystallized); (c) (1) NaOH (1.35 equiv), H_2O, MeOH, 5 °C to room temperature; (2) H_2O, concd HCl (99%); (d) NaOH, H_2O, THF, 65 °C.

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(5) The use of Na/K alloy and reported low yield (∼25%) of 1,2-diethoxy-1,2-bis(trimethylsiloxy)ethylene made this approach unattractive for work on large scale.

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mantane with **4** in dry CH_2Cl_2 in the presence of a catalytic amount of $ZnCl_2$ gave the desired α,α-dichloroester **5** in excellent yield. Hydroxylation of the adamantane ring of **5**, presumably via a nitronium ion mediated hydride abstraction,[9] was readily accomplished by treatment with aqueous HNO_3 in concentrated H_2SO_4 followed by an aqueous workup containing urea[10] to afford **6** in near-quantitative yield.[11] Finally, treatment of **6** with NaOH in aqueous THF at elevated temperature was expected to afford the desired α-keto acid **1** by hydrolysis of the ester with concomitant unmasking of the ketone functionality. The desired transformation was accomplished; however, a significant amount of a byproduct, identified as **8**, was also formed.[12] The formation of **8** can be viewed as a 1,4-homofragmentation[13] and, to the best of our knowledge, is the first example of this type of fragmentation to involve an adamantane ring system. Hydrolysis of **5**, under similar conditions, gave **9** as the sole product in near-quantitative yield and therefore provides a more practical synthesis of this material.[14] Hydrolysis of **6** at room temperature with NaOH in aqueous MeOH followed by acidification allowed the direct isolation of α,α-dichloroacid **7** in near-quantitative yield simply by filtration.[15] With **7** in hand, the unmasking of the ketone functionality could now be investigated separately from the ester hydrolysis.

Greater insight into the factors affecting the desired hydrolysis and/or homofragmentation of α,α-dichloroacid **7** was revealed by study of the effects of base concentration and temperature in addition to the kinetics of the reaction. The product distribution varied nonlinearly with base concentration; higher concentrations resulted in increased amounts of homofragmentation (Figure 1). In 1 N NaOH solution, increasing temperature resulted in an increased amount of homofragmentation (Figure 2).

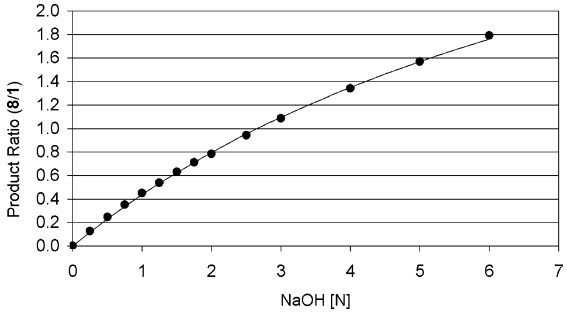

FIGURE 1. Plot of product ratio (**8**/**1**) vs [NaOH] at 70 °C. The curve depicts the results of an unweighted least-squares fit to $\text{ratio}_{obs} = a[\text{NaOH}]/(1 + b[\text{NaOH}])$ ($a = k_4/k_2 = 0.480$, $b = k_3/k_2 = 0.104$; Supporting Information).

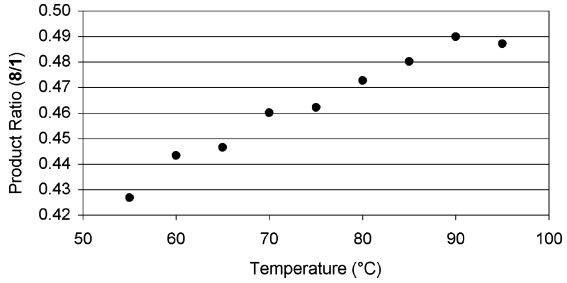

FIGURE 2. Plot of product ratio (**8**/**1**) vs temperature in 1 N NaOH.

TABLE 1. Reaction Rates at 71.7 °C[a]

base	additive	k ($\times 10^{-4}$ s^{-1})
1 N NaOH (42 equiv)	none	3.074
0.25 N NaOH (42 equiv)	$NaClO_4$	3.050
$NaHCO_3$ (4 equiv)	$NaClO_4$	3.044
NaOH (4 equiv)	NaCl	2.925

[a] All reactions were performed at constant ionic strength.

The kinetic measurements of the reaction were performed at 71.7 °C and constant ionic strength, obtained by addition of a nonparticipating salt ($NaClO_4$) as necessary, and followed the disappearance of **7** relative to an internal standard by HPLC (Table 1). In all reactions, the disappearance of substrate followed first-order behavior and the rate was independent (zero-order) of base concentration, even when the product distribution varied (0.25 vs 1 N NaOH). Addition of a participating salt (NaCl) resulted in a slower reaction rate (vide infra).

The experimental data presented above are consistent with the mechanism proposed in Scheme 3 for the hydrolysis of **7** to α-keto acid **1** and formation of homofragmentation product **8**. Formation of α-lactone **11**, as a common intermediate, from sodium salt **10** is the rate-determining step with the ultimate fate of **11** dependent upon the reaction conditions. Addition of water (k_2) or hydroxide (k_3[NaOH]) to α-lactone **11** would be expected to afford **12**, which, upon subsequent loss of HCl, would afford α-keto acid **1**. However, proton abstraction from the hydroxyl group of **11** by hydroxide (k_4[NaOH]) can lead to

(8) In our hands, zinc dust, with or without activation, gave variable induction periods with the potential for an uncontrollable reaction; however, zinc flake (−325 mesh, Alfa Aesar), without activation, gave uniformly reproducible and controllable reactions. We also found that slow addition of a mixture of chlorotrimethylsilane and methyl trichloroacetate to the zinc flake in THF allows for an addition-controlled reaction with less potential for an uncontrollable reaction.

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(10) Urea is used to scavenge nitrous acid and the nitrite ester of **6**, which are formed in the reaction. Workup without a nitrous acid scavenger gave crude **6**, which would release a brown gas (NO_2) upon standing at room temperature. 1-Adamantyl nitrite is reported to behave similarly; see ref 9c. For a comparison of the reactivity of nitrous acid scavengers, see Fitzpatrick, J.; Meyer, T. A.; O'Neill, M. E.; Williams, D. L. H. *J. Chem. Soc., Perkin Trans. 2* **1984**, 927−932.

(11) The nitrate ester of **6** is often observed in small amounts (<1% by HPLC) and is of no consequence since it is converted to α-keto acid **1** during the subsequent hydrolysis. For the reported solvolysis of 1-adamantyl nitrate, see Kevill, D. N.; Hawkinson, D. C. *J. Org. Chem.* **1990**, *55*, 5394−5399.

(12) Compound **8** underwent "spontaneous resolution" during crystallization, giving a conglomerate mixture of homochiral crystals since only a single enantiomer was evident in the unit cell. Crystallographic data (excluding structure factors) for **8** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 602449. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax +44 1223 336033; e-mail deposit@ccdc.cam.ac.uk).

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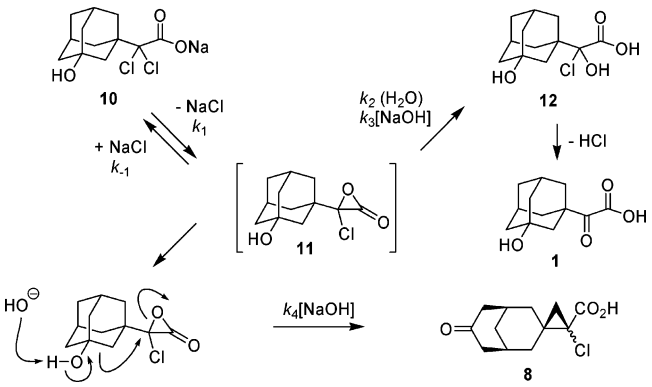
(15) For examples of the saponification of alkyl α,α-dichloroesters to the corresponding α,α-dichloroacids, see (a) Reference 6g. (b) Hayes, T. K.; Villani, R.; Weinreb, S. M. *J. Am. Chem. Soc.* **1988**, *110*, 5533−5543. (c) Snider, B. B.; Walner, M. *Tetrahedron* **1989**, *45*, 3171−3182. (d) Benedetti, M.; Forti, L.; Ghelfi, F.; Pagnoni, U. M.; Ronzoni, R. *Tetrahedron* **1997**, *53*, 14031−14042. (e) Ghelfi, F.; Bellesia, F.; Forti, L.; Ghirardini, G.; Grandi, R.; Libertini, E.; Montemaggi, M. C.; Pagnoni, U. M.; Pinetti, A. *Tetrahedron* **1999**, *55*, 5839−5852.

SCHEME 3



the homofragmentation product **8** as indicated. Under weakly basic conditions in which this proton abstraction is unlikely, the formation of **8** should not be observed. As expected, treatment of **7** with $NaHCO_3$ (4 equiv) in water at elevated temperature resulted in the exclusive formation of the desired α-keto acid **1**, and at constant ionic strength, the reaction rate was equivalent to that observed with a >10-fold amount of NaOH. This observation obviates an alternative mechanism in which **1** is formed from **11** and **8** is formed directly from **10**. Thus, strong alkali is unnecessary for the hydrolysis of an α,α-dichloroacid to an α-keto acid. The slower reaction rate observed with the addition of NaCl is evidence of reversibility[16] between **10** and **11**. For the homofragmentation to take place, the α-lactone must be in a suitable orientation and this is reflected in the temperature dependency of the product distribution as increasing temperature should increase the probability of the orientation required for homofragmentation. From the temperature dependence of reaction rate (k_{obs}) in 1 N NaOH, the activation enthalpy ($\Delta H^{\ddagger}$) and entropy ($\Delta S^{\ddagger}$) were calculated to be 27.8 ± 0.2 kcal/mol and 5.9 ± 0.4 cal/mol·K, respectively, and these values can reasonably be attributed to the rate-determining step (k_1) of the reaction (Supporting Information). The liberation of bromide ion from bromoacetic acid has been shown to involve the formation of the corresponding α-lactone as the reaction is zero-order with regard to base.[17]

The product distribution is determined by the steps with rate constant k_4, which yields homofragmentation product **8**, and rate constants k_2 and k_3, which yield α-keto acid **1**, in accordance with eq 1. Thus, the nonlinear dependence of product distribution versus base concentration (Figure 1) can be explained by competing parallel reactions involving hydroxide.

$$\frac{[\mathbf{8}]}{[\mathbf{1}]} = \frac{k_4[\mathrm{NaOH}]}{k_2 + k_3[\mathrm{NaOH}]} = \frac{(k_4/k_2)[\mathrm{NaOH}]}{1 + (k_3/k_2)[\mathrm{NaOH}]} = \frac{a[\mathrm{NaOH}]}{1 + b[\mathrm{NaOH}]} \quad (1)$$

With this mechanistic understanding, the hydrolysis of **6** can be performed in a single vessel with proper control of pH *and* temperature to afford α-keto acid **1** exclusively. Treatment of **6** with NaOH (1.35 equiv) in aqueous THF at ambient temperature serves to selectively hydrolyze the ester. Subsequent adjustment of the pH to ~7.4 with HCl and addition of $NaHCO_3$ (2.5 equiv) followed by heating to ~85 °C (4−6 h, with removal of THF by distillation) serves to unmask the ketone moiety. Acidification with concentrated HCl and extraction with EtOAc gave the desired α-keto acid **1** in >99% yield. With modifications to facilitate processing on scale, this chemistry has been used to prepare >600 kg of high-purity α-keto acid **1**.

α-Keto acids continue to be of interest for use in the preparation of chiral α-hydroxy acids and α-amino acids.[18] The alkylation of α,α-dichloroacetic acid or esters[19] in concert with a milder hydrolysis should allow the preparation of structurally diverse α-keto acids. The relatively mild conditions described herein for the conversion of an α,α-dichloroester or acid to an α-keto acid may allow an α,α-dichloroester to serve as a protected form of an α-keto acid in more structurally complex molecules.

Experimental Section

(3-Hydroxytricyclo[3.3.1.1^{3,7}]decan-1-yl)oxoacetic Acid (1). To a suspension of **6** (15 g, 51.16 mmol) in THF (30 mL) and water (30 mL) at room temperature was added 1 N NaOH (69 mL, 69 mmol) over 70 min. After being stirred for 16 h, the mixture was adjusted to pH 7.4 by the addition of 6 N HCl (2.8 mL), followed by the addition of $NaHCO_3$ (11.2 g, 0.133 mol). The temperature of the resulting mixture was slowly (2.5 h) raised to ~85 °C with removal of THF by distillation. After being heated for 5 h, the mixture was cooled and acidified to pH 0.2 by careful (CO_2 evolution) addition of concentrated HCl (11 mL). The resulting mixture was extracted with EtOAc while the aqueous phase was maintained at ~pH 0.2. The organic fractions were combined, dried ($MgSO_4$), and concentrated in vacuo to give **1** as a nearly colorless granular solid (11.42 g, 99.5%). Recrystallization from water gave **1** as colorless needles: mp 164−165 °C; IR (KBr) 3399, 2933, 2861, 1712, 1689 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 14.2 (br s, 1H), 4.55 (br s, 1H), 2.16 (s, 2H), 1.74−1.42 (m 12H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 202.5 (C), 166.1 (C), 66.1 (C), 46.9 (C), 44.7 (CH_2), 44.0 (CH_2), 35.9 (CH_2), 34.6 (CH_2), 29.4 (CH). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.42; H, 7.04.

Dichlorotricyclo[3.3.1.1^{3,7}]decan-1-ylacetic Acid Methyl Ester (5). To a suspension of zinc flake (100.4 g, 1.54 mol) in anhydrous THF (400 mL), cooled in an 18 °C bath, was added a solution of methyl trichloroacetate (136.7 g, 0.77 mol) and chlorotrimethylsilane (120 mL, 0.946 mol) at a rate to keep the reaction temperature <30 °C (1.75 h required). After being stirred for an additional 2 h, the mixture was diluted with heptane (900 mL) and filtered (under nitrogen) through Celite. The filter cake was washed with additional heptane (500 mL). The combined filtrate was concentrated at reduced pressure (~15 mmHg) with a bath temperature (<25 °C) to give **4** as an oil containing a small amount of solid (172 mL; contains residual $ZnCl_2$, which need not be removed since $ZnCl_2$ is used to catalyze the next reaction). Quantitative ^{1}H NMR indicates 0.512 mol of **4** (66.4%).

To a solution of crude **4** in anhydrous CH_2Cl_2 (200 mL) was added anhydrous $ZnCl_2$ (2.5 g, 18.3 mmol). To this mixture, maintained in an 18 °C cooling bath, was added a solution of 1-bromoadamantane (76.0 g, 0.353 mol) in CH_2Cl_2 (40 mL) over 75 min. After being stirred for an additional 2.5 h, the mixture was diluted with heptane (600 mL), brine (200 mL), and water

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(19) (a) Villieras, J.; Disnar, J. R.; Perriot, P.; Normant, J. F. *Synthesis* **1975**, 524−525. (b) Coutrot, P.; El Gadi, A. *Synthesis* **1984**, 115−117. (c) For additional examples, see ref 15b,c.

(200 mL). The organic phase (upper layer) was washed with water/brine (1:1), 1 N $NaHCO_3$, and brine. After drying ($MgSO_4$), concentration in vacuo and recrystallization from methanol gave **5** as a colorless solid (90.16 g, 92% based on 1-bromoadamantane): mp 76−77 °C; IR (KBr) 2940, 2904, 2850, 1746, 1739, 1243 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.86 (s, 3H), 2.08 (br s, 3H), 1.88, 1.87 (2 s, 6H), 1.66 (ABq, $J = 12.1$ Hz, $\Delta\nu_{AB} = 33.6$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.1 (C), 95.8 (C), 53.9 (CH_3), 44.0 (C), 36.9 (CH_2), 36.3 (CH_2), 28.3 (CH). Anal. Calcd for $C_{13}H_{18}Cl_2O_2$: C, 56.33; H, 6.54; Cl, 25.58. Found: C, 56.41; H, 6.40; Cl, 25.75.

Dichloro-(3-hydroxytricyclo[3.3.1.1^{3,7}]decan-1-yl)acetic Acid Methyl Ester (6). To ice-cold concentrated H_2SO_4 (56 mL) was added 10 N HNO_3 (5.80 mL, 58.0 mmol) dropwise over 30 min. The cold bath was removed and **5** (15.0 g, 54.1 mmol) was added portionwise (1.25 g every 10 min). During this addition, the reaction mixture reached a temperature maximum of 34 °C. The resulting mixture was allowed to stir at room temperature for an additional 22 h. The reaction mixture was quenched by addition, over ∼15 min, to an ice-cold, well-stirred mixture of EtOAc (230 mL), water (250 mL), and urea (8.0 g, 0.133 mol). After 45 min of stirring, the cold bath was removed and the mixture was allowed to warm to room temperature. After the mixture was stirred for an additional 4 h, the aqueous phase was removed and extracted with EtOAc. The organic fractions were combined and washed with water, 1 N $NaHCO_3$, and brine. After drying ($MgSO_4$), concentration in vacuo gave crude **6** as a nearly colorless solid (15.67 g, 98.8%), which can be used in the next reaction without further purification. Recrystallization from aqueous CH_3OH (91% recovery) gave **6** as a colorless, cottonlike solid: mp 114−115 °C; IR (KBr) 3279, 2929, 2910, 2855, 1750, 1737, 1239 cm^{-1}; ^1H NMR ($CDCl_3 + CD_3OD$, 500 MHz) δ OH is exchanged, 3.87 (s, 3H), 2.30 (br s, 2H), 1.82 (s, 2H), 1.80 (s, 4H), 1.66 (ABq, $J = 11.5$ Hz, $\Delta\nu_{AB} = 24.3$ Hz, 4H), 1.58−1.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.9 (C), 94.2 (C), 68.9 (C), 54.1 (CH_3), 47.5 (C), 44.5 (CH_2), 44.0 (CH_2), 35.7 (CH_2), 34.8 (CH_2), 30.1 (CH). Anal. Calcd for $C_{13}H_{18}Cl_2O_3$: C, 53.25; H, 6.18; Cl, 24.18. Found: C, 53.24; H, 6.24; Cl, 24.31.

Dichloro-(3-hydroxytricyclo[3.3.1.1^{3,7}]decan-1-yl)acetic Acid (7). A solution of methanol (370 mL) and 1 N NaOH (370 mL, 0.37 mol) was cooled to ∼5 °C, followed by the addition of **6** (80.0 g, 0.273 mol). The cold bath was removed and the resulting mixture was stirred at room temperature for 20 h. The resulting solution was diluted with water (1660 mL) followed by acidification by the addition of concentrated HCl (75 mL) over 25 min while a temperature of ∼18 °C was maintained with cooling as necessary. The resulting suspension was cooled in an ice bath and stirred gently for 75 min. Stirring was discontinued and the mixture was allowed to stand at ∼0 °C for 3 h. The solid was collected by filtration, washed with cold water, and dried in vacuo to give **7** as a colorless solid (73.33 g, 98.9%): mp 236−237 °C (decomp); IR (KBr) 3461, 2933, 2911, 1717, 1275 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ OH and CO_2H are exchanged, 4.88 (s, 3H), 2.26 (s, 2H), 1.86 (s, 6H), 1.65 (ABq, $J = 11.5$ Hz, $\Delta\nu_{AB} = 26.7$ Hz, 4H), 1.59−1.52 (m 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 165.9 (C), 96.0 (C), 66.8 (C), 46.2 (C), 44.5 (CH_2), 43.9 (CH_2), 35.6 (CH_2), 34.6 (CH_2), 29.5 (CH). Anal. Calcd for $C_{12}H_{16}Cl_2O_3$: C, 51.63; H, 5.77; Cl, 25.40. Found: C, 51.61; H, 5.64; Cl, 25.33.

(1*R,1′*r*,2′*S**,5*S**)-2′-Chloro-7-oxospiro[bicyclo[3.3.1]nonane-3,1′-cyclopropane]-2′-carboxylic Acid (8).** A mixture of **7** (4.50 g, 16.12 mmol) and 4 N NaOH (100 mL, 0.40 mol) was heated at ∼70 °C for 7 h. The resulting mixture was cooled in an ice bath and acidified by the addition of concentrated HCl (34 mL) to give a white suspension that was diluted with water and extracted with chloroform. The organic fractions were combined, washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo to give **8** as a colorless solid (2.14 g, 54.6%): mp 205−208 °C (aqueous methanol); IR (KBr) 2947, 1729, 1668 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.50 (br s, 1H), 2.64 (s, 1H), 2.59−2.43 (m, 3H), 2.41−2.30 (m, 2H), 2.16 (dd, $J = 13.7$, 3.8 Hz, 1H), 1.97 (d, $J = 13.2$ Hz, 1H), 1.88 (dd, $J = 13.7$, 3.8 Hz, 1H), 1.79 (m, 1H), 1.72 (d, $J = 6.6$ Hz, 1H), 1.56 (dd, $J = 13.7$, 1.6 Hz, 1H), 1.50 (dd, $J = 13.7$, 2.2 Hz, 1H), 1.06 (d, $J = 6.6$ Hz, 1H); ^{13}C NMR (*p*-dioxane-d_8, 125 MHz) δ 208.7 (C), 169.7 (C), 49.2 (C), 47.2 (CH_2), 39.3 (CH_2), 35.9 (CH_2), 33.0 (CH_2), 32.4 (CH_2), 32.3 (CH_2), 32.2 (CH_2), 27.5 (CH). Anal. Calcd for $C_{12}H_{15}ClO_3$: C, 59.39; H, 6.23; Cl, 14.61. Found: C, 59.60; H, 6.44; Cl, 14.42.

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Supporting Information Available: Preparation of compound **9**; experimental details of product distribution and kinetic studies, rate data, and additional kinetic plots; copies of ^1H and ^{13}C NMR spectra of compounds **1** and **5**−**9**; and X-ray structure data (ORTEP drawing and CIF file) for compound **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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