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INTRAMOLECULAR METAL CATALYZED KHARASCH CYCLIZATIONS OF OLEFINIC α-HALO ESTERS AND ACIDS

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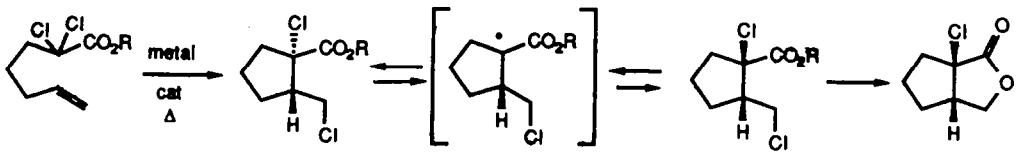
ABSTRACT Functionalized carbocyclic compounds are produced by intramolecular Kharasch radical cyclization reactions catalyzed by various transition metal complexes. Several unsaturated mono-α-haloesters and acids can be efficiently transformed to γ-halocarboxyl and γ-lactone carbocycles via exo closure of a 5-hexenyl type radical intermediate. The cyclization methodology is useful for synthesis of both fused and bridged carbocycles.

Introduction

In recent publications, we have described a new approach to highly functionalized carbocyclic systems which is based upon the intramolecular transition metal promoted cyclization of unsaturated α,α-dichloroesters, acids and nitriles.[1] One representative example of this methodology is outlined in Scheme 1. Treatment of α,α-dichloroester 1 with a metal catalyst such as $RuCl_2(PPh_3)_3$ or $FeCl_2[P(OEt)_3]_3$ gives α,γ-dichloroester cyclization products 2a and 4a in good yield. The ratio of 2a to 4a is highly dependent upon catalyst concentration and reaction time, with 4a being the kinetic and 2a the thermodynamic product. We believe that the catalyst is involved in interconversion of epimeric compounds 2a and 4a via carboxylate radical 3a. If cyclization is performed with $[CpMo(CO)_3]_2$ and ester 1, α-chloro-γ-lactone 5 is the primary product. With acid 2 as substrate, both the ruthenium and iron catalysts produce lactone 5 in excellent yields, presumably via equilibrating α,γ-dichloroacids 2b and 4b. This methodology works equally well to form bridged and fused polycyclic systems.[1]

We have recently been interested in determining whether systems like 1 bearing a single α-halo group will undergo this cyclization chemistry. Although intermolecular Kharasch reactions[2] of tri- and dichloroacetates with alkenes are well known,[3,4] mono α-chloro esters do not seem to have previously been used.[5] We therefore decided to establish experimentally whether transition metals, in this so-called "redox catalytic" process,[6,7] could effectively promote ring closure of some olefinic α-haloesters and acids. Since this methodology might be of use in complex terpene synthesis, we were particularly interested in exploring the scope and stereochemistry of these cyclizations in a structurally diverse group of compounds.

Scheme 1

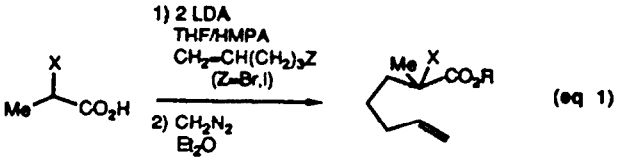


1 2 3 4 5

a) R = Et b) R = H

Cyclization Studies

Initial cyclization experiments were carried out with unsaturated α-chloroacid 8, α-chloroester 9 and α-bromoester 10, which were easily prepared as shown in eq 1. Alkylation of the dianion of 2-chloropropanoic acid (6) with 5-bromo-1-pentene gave α-chloroacid 8,[8,9] which could be methylated with diazomethane to afford ester 9. Similarly, 2-bromopropanoic acid dianion was alkylated with 5-iodo-1-pentene and esterified to yield α-bromoester 10.



(eq 1)

6 X = Cl
7 X = Br

8 X = Cl, R = H
9 X = Cl, R = Me
10 X = Br, R = Me

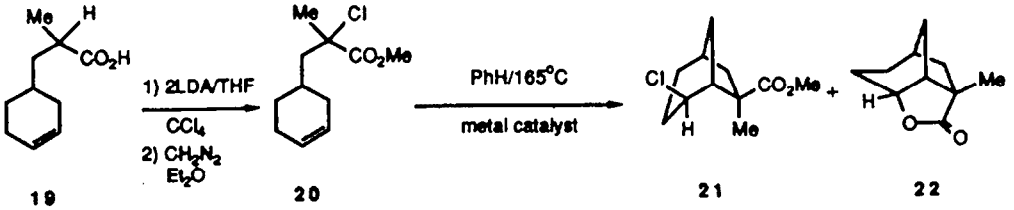
Cyclization experiments with 8, 9 and 10 were performed in benzene at 165°C (sealed tube) using several metal catalysts and the results are shown in the Table. Treatment of α-chloroester 9 with $RuCl_2(PPh_3)_3$ gave a mixture of cyclopentanoid α-chloroesters 11 and 12 which result from the exo closure of a 5-hexenyl type radical.[10] Lactone 13 was produced in smaller amounts along with traces of a single endo closure product 14 (stereochemistry undetermined). Very similar results were obtained with the ferrous chloride/triethyl phosphite catalyst, which was generated in situ.[11] Using $[CpMo(CO)_3]_2$ as catalyst, larger amounts of lactone 13 were produced at the expense of cis-α-chloroester 12. With acid 8, analogous results were observed.

The stereochemistry of 12 was proven by its $AgNO_3$ induced closure[12] to known lactone 13,[13] while epimer 11 did not lactonize under the same conditions. In general, the ratios of stereoisomeric products 11 to 12/13 for the different runs were similar and did not vary significantly from 1:1. We did find that overall these cyclizations were slower than the α,α-dichloroester system shown in Scheme I, probably due to slower formation of the initial α-carboxylate-stabilized radical.

Cyclization of α-bromoester 10 was also investigated.[14] In this case we avoided chlorine containing catalysts in order to eliminate halogen exchange with the products. Using $[CpMo(CO)_3]_2$ and $Fe(CO)_5$,[14] only α-bromoester 18 and lactone 13 were obtained. With this substrate the cyclizations were generally faster than with the chlorinated ones. However, since yields for the bromo compound were not significantly better, the more readily available chloroesters were used in subsequent studies.

This methodology has been extended to synthesis of more complex ring systems. Acid 19, which was prepared by a standard malonic ester synthesis (see Experimental Section), was converted to its

Scheme 2



19 20 21 22

	21	22
$FeCl_2/3P(OEt)_3$ (9.7%) 29h	56%	32%
$RuCl_2(PPh_3)_3$ (4.9%) 132h	38%	37%
$[CpMo(CO)_3]_2$ (5.2%) 95h	57%	21%

Table. Cyclizations of α-Haloesters 9, 10 and α-Chloroacid 8.[a]

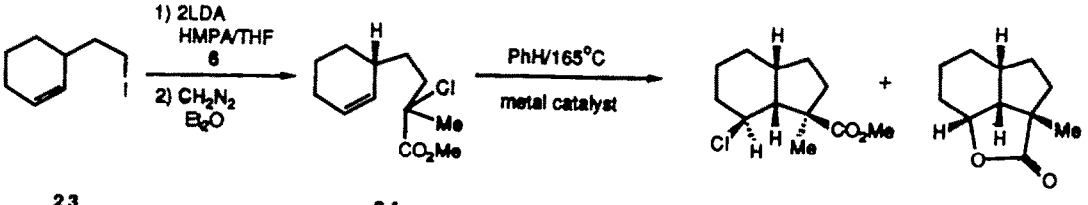
Entry	Substrate	Catalyst	mol%	Time (h)	Cyclization Products (% Yield)[b] 11 R = Me, X = Cl; 15 R = H, X = Cl; 18 R = Me, X = Br	12 R = Me, X = Cl; 16 R = H, X = Cl	13	14 R = Me; 17 R = H
1	9	$RuCl_2(PPh_3)_3$	6.3	132	46	25	14	—
2			10	75.5[e]	35	24	10	5
3		$FeCl_2/3P(OEt)_3$[c]	5.2	37	39	29	16	5
4			13	13.5	42	21	30	5
5		$[CpMo(CO)_3]_2$	4.7	49	31	4	23	5
6			4.9	23	30	4	27	5
7			8	80.5	35	13	25	13
8	8[d]	$RuCl_2(PPh_3)_3$	4.5	96	47	3	24	—
9		$FeCl_2/3PPh_3$[c]	4.9	42	25	3	20	4
10	10	$[CpMo(CO)_3]_2$	4.9	13	31	—	28	—
11		$Fe(CO)_5$	7.3	20	35	—	31	—

[a] Reactions were run in benzene at 165 °C (see Experimental Section)
[b] Yields were determined by GLC. All compounds were isolated in pure form and were characterized spectrally.
[c] Catalyst generated in situ
[d] Acid products were treated with excess CH_2N_2 before GLC analysis.
[e] Starting material (24%) remained

dianion and chlorinated with CCl_4[15] to afford cyclization substrate 20 (Scheme 2). Cyclization of 20 with three different catalysts produced the mixtures of bridged [3.2.1.]-γ-chloroester 21 and the γ-lactone 22 shown in the scheme. The structure of 21 was proven by X-ray crystallography. Interestingly, the chloro epimer of 21 was not found. The ratios of 21/22 are somewhat variable as one changes catalyst, but since these additions presumably involve "metal coordinated radicals"[6,7] perhaps these differences are not too surprising.

It is also possible to use the methodology for efficient preparation of fused ring systems as depicted in Scheme 3. The dianion of 2-chloropropanoic acid (6) could be alkylated with iodide 23 to yield, after esterification, cyclization precursor 24. Both the ruthenium and iron complexes induced cyclization of 24 to cis-fused bicyclic chloroester 25 and tricyclic α-lactone 26 in the GLC yields shown in the scheme. The structure and stereochemistry of 25 and 26 were secured by proton NMR couplings and NOE[16] analysis of purified compounds, and by the fact that the former compound does not lactonize upon treatment with $AgNO_3$.[12]

Scheme 3



$FeCl_2/3P(OEt)_3$ (12.6%)	15h	48%	36%
$FeCl_2/3P(OEt)_3$ (14%)	20h	39%	33%
$RuCl_2(PPh_3)_3$ (4.9%)	72h	50%	38%

Conclusion

We have demonstrated that α-monohalo esters smoothly undergo intramolecular metal promoted radical cyclizations to afford a variety of functionalized carbocyclic systems. The starting materials for these cyclizations can be easily prepared via short, simple synthetic routes. These reactions, although somewhat slower than similar cyclizations with α,α-dichlorocarboxylate substrates,[1] efficiently provide carbocycles of potential use in natural product synthesis. We are currently exploring extensions and applications of this methodology.

Experimental Section

Melting points were measured on a Fisher-Johns apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer model 197 or model 1310 spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 60 MHz on a Varian EM-360 NMR spectrometer, at 200 MHz on a Bruker WP-200 instrument and 300 MHz on a Bruker AM 300 spectrometer. Carbon-13 magnetic resonance spectra (^{13}C NMR) were recorded at 50 MHz on a Bruker WP-200 instrument. Low-resolution mass spectra (MS) were obtained at 50-70 eV by electron impact on a Kratos MS9/50 double-focusing mass spectrometer. Combustion analyses were performed by Microtech Laboratories (Skokie, IL). Both analytical and preparative thin-layer chromatography (TLC) were performed using E. M. Merck silica gel PF-254. Flash chromatography was done using Baker silica gel (25-40 μm) according to the procedure of Still.[17] Gas liquid chromatography (GLC) was done on a Varian model 3700 instrument equipped with a thermal conductivity detector using a 6 ft x 1/8 in. stainless steel 3% SE 30 on 80/100 Supelcoport column, 10 ft x 1/8 in. stainless steel 10% Carbowax 20M on 80/100 Chromosorb WAW column, or an Alltech 10 m x 0.53 mm FSOT Superox polyethylene glycol column. Preparative gas liquid chromatography was performed on a Varian model 920 instrument equipped with a thermal conductivity detector using a 5 ft x 1/4 in. 10% SP2100 on 80/100 Supelcoport column. High performance liquid chromatography (HPLC) was performed using a Beckman 10 mm x 25 cm 5μ Ultrasphere column on a Waters model 590 pump equipped with a R401 differential refractometer and a UK6 injector.

Methyl 2-Chloro-4-(2-cyclohexenyl)-2-methylbutanoate (24). Butyllithium (7.9 mL of a 1.18M solution in hexane, 9.3 mmol) was added to a solution of diisopropylamine (1.4 mL, 1.0 g, 10 mmol) in 40 mL of dry THF at 0°C and the mixture was stirred for 40 min. The mixture was then cooled to -78°C and a solution of 2-chloropropanoic acid (6, 0.39 mL, 0.46 g, 4.25 mmol) in 5 mL of dry THF was added dropwise, followed by HMPA (1.5 mL, 8.6 mmol). The solution was stirred for 10 min and 2-(2-cyclohexenyl)-1-iodoethane (23, 1.00 g, 4.24 mmol) in 5 mL of dry THF was added. The temperature was maintained at -78°C for 1 h and the mixture was allowed to warm to 25°C. Water (25 mL) was added followed by 5% HCl (25 mL) and ether (50 mL). The organic layer was washed with 5% HCl (4 x 25 mL), brine, dried and evaporated to an oil which was purified by flash chromatography (3:1 hexane-EtOAc) to give 858 mg (93%) of 2-chloro-4-(2-cyclohexenyl)-2-methylbutanoic acid as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.00 (1H, s), 5.7-5.6 (1H, m), 5.5 (1H, m), 2.1-1.2 (11H, m), 1.75 (3H, s); IR (film) 3010, 2930, 2860, 1765, 1715, 1450, 1280, 1215, 1180, 1125, 1110, 725 cm^{-1}.

The above unsaturated α-chloroacid (250 mg, 1.15 mmol) was methylated at 25°C with an excess of an ethereal solution of diazomethane to give after purification by flash chromatography (9:1 hexane-EtOAc) 209 mg (79%) of methyl 2-chloro-4-(2-cyclohexenyl)-2-methylbutanoate (24) as a colorless oil which was a mixture of diastereomers: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.7-5.6 (1H, m), 5.52 (1H, m), 3.80 (3H, s), 2.1-1.2 (11H, m), 1.75 (3H, s); IR (film) 3020, 2930, 2860, 1745, 1450, 1380, 1280, 1210, 1175, 1120, 1100 cm^{-1}.

2-Chloro-2-methyl-6-heptenoic Acid (8). Following the above alkylation procedure, 2-chloropropanoic acid (6, 0.36 mL, 0.43 g, 3.9 mmol) was alkylated with 5-bromo-1-pentene (0.46 mL, 0.58 g, 3.9 mmol) to give, after purification by flash chromatography (3:1:0.008 hexane-EtOAc-AcOH) and distillation, 0.58 g (84%) of 2-chloro-2-methyl-6-heptenoic acid (8) as a yellow oil: bp 85°C (<0.1 Torr, bulb to bulb); ^{1}H NMR (200 MHz $CDCl_3$) δ 11.86 (1H, s), 5.8-5.7 (1H, m), 5.1-5.0 (2H, m),

2.1-2.0 (4H, m), 1.78 (3H, s), 1.56 (2H, m); IR (film) 3070, 2970, 2930, 1710, 1635, 1455, 1410, 1380, 1270, 910 cm^{-1}. Anal. Calcd for $C_8H_{13}O_2Cl$: C, 54.40; H, 7.71. Found: C, 54.40; H, 7.42.

Methyl 2-Chloro-2-methyl-6-heptenoate (9). 2-Chloro-2-methyl-6-heptenoic acid (8) was methylated with an excess of an ethereal solution of diazomethane to give, after purification on silica gel (3:1 hexane-EtOAc) a 90% yield of methyl 2-chloro-2-methyl-6-heptanoate (9) as a colorless oil: bp 90°C (30 Torr, bulb to bulb) ^1H NMR (200 MHz, $CDCl_3$) δ 5.8-5.7 (1H, m), 5.1-4.9 (1H, m), 3.78 (3H, s), 2.1-2.0 (4H, m), 1.73 (3H, s), 1.50 (2H, m); IR (film) 3090, 2960, 1745, 1645, 1450, 1270, 920 cm^{-1}. Anal. Calcd for $C_9H_{15}O_2Cl$: C, 56.70; H, 8.10. Found: C 56.69; H, 7.93.

Methyl 2-Bromo-2-methyl-6-heptenoate (10). Using the above alkylation procedure, 2-bromopropanoic acid (7, 0.22 mL, 2.4 mmol) was alkylated with 5-iodo-1-pentene (100 mg, 0.51 mmol). The crude product was methylated with an excess of ethereal diazomethane to give after purification by flash chromatography (9:1 hexane-EtOAc) 56 mg (46%) of methyl 2-bromo-2-methyl-6-heptenoate (10) as a colorless oil: bp 64°C (<0.1 Torr, bulb to bulb); ^1H NMR (300 MHz, $CDCl_3$) δ 5.8-5.7 (1H, m), 5.1-5.0 (2H, m), 3.80 (3H, s), 2.2-2.1 (4H, m), 1.90 (3H, s), 1.6-1.4 (2H, m); IR (film) 3080, 2950, 1740, 1640, 1440, 1265, 1240, 1205, 1175, 1160 cm^{-1}.

3-(3-Cyclohexenyl)-2-methylpropanoic Acid (19). A solution of NaOEt was prepared by addition of Na metal (0.506 g, 22.0 mmol) to absolute ethanol (16 mL) at 0°C under argon. After the sodium had dissolved, the solution was allowed to warm to 25°C, and diethyl methylmalonate (3.8 mL, 3.8 g, 22 mmol) was added dropwise.[18] The mixture was stirred for 15 min, followed by dropwise addition of (3-cyclohexenyl)-iodomethane (4.42 g, 20.0 mmol). The solution was refluxed for 3 h and the solvent was evaporated in vacuo. The residue was diluted with water (40 mL) and extracted with EtOAc (3 x 40 mL). The organic extract was washed with brine, dried with Na_2SO_4 and evaporated to a yellow oil, which was purified by flash chromatography (95:5 hexane-EtOAc) and then distilled (135-140°C, <1 Torr, bulb to bulb) to give 4.35 g (81%) of diethyl 3-(3-cyclohexenyl)-2-methylpropanoate-2-carboxylate as a colorless oil: ^1H NMR (200 MHz, $CDCl_3$) δ 5.6 (2H, m), 4.13 (4H, q, J = 7.1 Hz), 2.0-1.5 (9H, m), 1.40 (3H, s), 1.21 (6H, t, J = 7.1 Hz); IR (film) 3030, 2990, 2930, 2840, 1735, 1470, 1450, 1380, 1270, 1250, 1190, 1115, 1050, 1030, 860, 660 cm^{-1}.

The above diester (21.65 g, 80.9 mmol), LiCl (6.87 g, 0.162 mol), DMSO (300 mL) and water (3 mL) were refluxed for 21.5 h.[19] The mixture was added to H_2O (300 mL) and was extracted with a solution of Et_2O:EtOAc (2:1, 2 x 300 mL). The organic layer was washed with brine, dried with Na_2SO_4 and evaporated to a dark oil which was filtered through silica gel eluting with 95:5 hexane-EtOAc to remove polar material. The filtrate was evaporated leaving a yellow oil which was distilled (91-95°C, <1 Torr) to give 14.05 g (88%) of the monoester as a light yellow oil: ^1H NMR (200 MHz, $CDCl_3$) δ 5.7 (2H, m), 4.13 (2H, q, J = 7.1 Hz), 2.6 (1H, m), 2.1-1.2 (9H, m), 1.25 (3H, t, J = 7.2 Hz), 1.17, 1.13 (3H, s); IR (film) 3020, 2980, 2920, 2840, 1735, 1460, 1380, 1255, 1195, 1165, 1030, 1100, 1080, 1050, 1030, 660 cm^{-1}.

This ester (2.71 g, 13.8 mmol) was added to a solution of KOH (1.39 g, 24.8 mmol) in 95% ethanol (180 mL) and the mixture was refluxed for 3 h. Most of the ethanol was evaporated in vacuo and H_2O (15 mL) was added to the residue. The mixture was acidified with 5% H_2SO_4 and was extracted with EtOAc (3 x 70 mL). The extract was washed with brine, dried with Na_2SO_4 and evaporated. Acid **19**, which was a mixure of diastereomers, was distilled (80°C, <1 Torr, bulb to bulb); ^1H NMR (200 MHz, $CDCl_3$) δ 9.23 (1H, s), 5.7 (2H, m), 2.6 (1H, m), 2.2-1.2 (9H, m), 1.21, 1.18 (3H, s); IR (film) 3025, 2975, 2925, 2825, 1710, 1650, 1460, 1440, 1420, 1380, 1290, 1270, 1240, 1230, 1200 cm^{-1}.

Methyl 2-Chloro-3-(3-cyclohexenyl)-2-methylpropanoate (20). Butyllithium (21 mL of a 1.6 M solution in hexane, 34 mmol) was added to a solution of diisopropylamine (5.6 mL, 4.0 g, 40 mmol) in 30 mL of dry THF at 0°C and the mixture was stirred for 40 min. The LDA solution was cooled to -25°C and a solution of 3-(3-cyclohexenyl)-2-methylpropanoic acid (**19**, 2.53 g, 15.0 mmol) in 30 mL of dry THF was added dropwise. The solution was warmed over 1 h to 50°C and maintained at this temperature for 7 h. The mixture was cooled to -78°C and carbon tetrachloride (7.2 mL, 12 g, 75

mmol) in 30 mL of dry THF was added rapidly. The solution was allowed to warm to 25°C over several hours, was cooled to 0°C, acidified with 1 N HCl, and extracted with ether (4 x 100 mL). The combined ether extract was washed with brine, dried with Na_2SO_4 and evaporated. The crude product was first distilled (80°C, < 0.1 Torr, bulb to bulb), then further purified by flash chromatography (8.5:1.5; 7:3 hexane-EtOAc) to give 1.90 g (63%) of 2-chloro-3-(3-cyclohexenyl)-2-methylpropanoic acid as a yellow oil: ^{1}H NMR (200 MHz) δ 5.61 (2H, m), 3.77 (3H, s), 2.1-2.0 (5H, m), 1.76 (3H, s), 1.7-1.2 (4H, m); IR (film) 3030, 3000, 2920, 2850, 1745, 1455, 1440, 1300, 1270, 1240, 1215, 1185, 1120, 1105, 660 cm^{-1}.

The above acid was methylated at 25°C with an excess of ethereal diazomethane to give, after purification by flash chromatography (3:1 hexane-EtOAc), a 90% yield of methyl 2-chloro-3-(3-cyclohexenyl)-2-methylpropanoate (**20**) as a colorless oil which was a mixture of diastereomers: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.61 (2H, m), 3.77 (3H, s), 2.1-2.0 (5H, m), 1.76 (3H, s), 1.7-1.2 (4H, m); IR (film) 3030, 3000, 2920, 2850, 1745, 1455, 1440, 1300, 1270, 1240, 1215, 1185, 1120, 1105, 660 cm^{-1}. Anal. Calcd for $C_{11}H_{17}O_2Cl$: C, 61.01; H, 8.09. Found: C, 60.97; H, 7.91.

Transition Metal Promoted Cyclization of Olefinic α-Chloroester 24. A mixture of anhydrous $FeCl_2$ (14.4 mg, 0.114 mmol), triethyl phosphite (58μL, 56 mg, 0.34 mmol), methyl 2-chloro-4-(2-cyclohexenyl -2-methylbutanoate (**24**, 209 mg, 0.910 mmol) and dry benzene (3.2 mL) in a heavy-walled pyrex tube was cooled in liquid nitrogen, degassed by multiple freeze-thaw cycles at <0.1 Torr, and sealed under vacuum. The tube was heated in an oil bath at 165°C for 15 h with stirring. Hexane (3 mL) and benzene (2 mL) were added to the reaction solution and the mixture was filtered through Florisil, eluting with benzene:hexane (2:3, 20 mL) and then EtOAc (20 mL). The total filtrate was evaporated to an oil and purified by flash chromatography (9:1 hexane-ether). GLC yields of products **25** and **26** are given in Scheme 3. Data for the purified compounds are reported below:

Methyl 9β-Chloro-2β-methylbicylo[4.3.0]nonane-2α-carboxylate (25): colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.0-3.9 (1H, ddd, J = 4.3, 8.8, 9.8 Hz), 3.70 (3H, s), 2.60 (1H, m), 2.4-1.3 (11H, m), 1.37 (3H, s); IR (film) 2960, 2880, 1735, 1460, 1440, 1240, 1210, 1160, 1100 cm^{-1}; MS, m/z (relative intensity) 232 (0.2), 230 (0.5), 135 (100), 94 (63), 28 (49). No lactone was formed when this compound was heated in a $AgNO_3/H_2O$/dioxane solution.[12]

2aα-Methyl-3,4,4aα,5,6,7aα,7bα-( )octahydroindeno[7,1-b,c]-furan-2-one (26): mp 53-54°C (recrystallized from hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.57 (1H, m), 2.2-2.0 (4H, m), 1.6-1.3 (8H, m), 1.29 (3H, s); IR (film) 2930, 2860, 1760, 1455, 1260, 1160, 965 cm^{-1}; MS, m/z (relative intensity) 180 (0.68), 121 (100), 94 (43), 86 (40), 84 (61), 79 (45), 49 (91); exact mass calcd for $C_{11}H_{16}O_2$ 180.1150, found 180.1135.

Cyclization of α-Haloesters 9, 10 and α-Chloroacid 8. Using the general procedure for cyclization of **24**, these compounds were cyclized with the catalysts shown in the Table. Unsaturated chloroester **9** and chloroacid **8** (followed by treatment with diazomethane) produced the cyclic esters **11**, **12**, **14** and lactone **13**. The crude mixture was separated by preparative TLC (95:5 hexane-ether) to provide pure lactone **13**. The mixture of cyclized esters **11**, **12** and **14** was then separated by HPLC (95:5 hexane-EtOAc). Data for the purified products are listed below:

Methyl trans-2-(Chloromethyl)-1-methylcyclopentane-1-carboxylate (11): colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.68 (3H, s), 3.61 (1H, dd, J = 6.9, 10.7 Hz), 3.42 (1H, dd, J = 8.4, 10.7 Hz), 2.8-2.6 (1H, m), 2.2-2.0 (2H, m), 1.8-1.4 (4H, m), 1.12 (3H, s); IR (film) 2970, 2890, 1730, 1440, 1265, 1205, 1155, 1130 cm^{-1}. No reaction occurred when this compound was heated with $AgNO_3/H_2O$/dioxane.[12]

Methyl cis-2-(Chloromethyl)-1-methylcyclopentane-1-carboxylate (12):
colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.68 (3H, s), 3.66 (1H, dd, J = 6.0, 9.5 Hz), 3.38 (1H, dd,

J = 9.2, 10.7 Hz), 2.1-1.6 (7H, m), 1.32 (3H, s); IR (film) 2970, 2880, 1735, 1450, 1210, 1160, 1125 cm^{-1}. Lactone **13** was produced when this compound was heated with $AgNO_3/H_2O$/dioxane.[12]

cis-1-Methyl-3-oxa-2-oxobicyclo[3.3.0]octane (13): bp 80°C (30 Torr, bulb to bulb); ^1H NMR (200 MHz, $CDCl_3$) δ 4.43 (1H, dd, J = 8.0, 9.4 Hz), 3.94 (1H, dd, J = 3.5, 9.4 Hz), 2.5-2.4 (1H, m), 2.2-1.5 (6H, m), 1.37 (3H, s); IR (film) 2970, 1770, 1455, 1380, 1130 cm^{-1}; MS, m/z (relative intensity), 140 (2.7), 86 (40), 84 (62), 81 (42), 49 (100); exact mass calcd for $C_8H_{12}O_2$ 140.0848, found 140.0859.

Methyl 3-Chloro-1-methycyclohexane-1-carboxylate (14): colorless oil; ^1H NMR (200 MHz, $CDCl_3$) δ 4.2-4.0 (1H, m), 3.69 (3H, s), 2.3-1.4 (8H, m), 1.22 (3H, s); IR (film) 2960, 2870, 1735, 1460, 1290, 1265, 1200, 1120 cm^{-1}; MS m/z (relative intensity) 192 (0.6), 190 (2.4), 95 (75), 84 (62), 49 (100), 28 (96).

α-Bromo-ester **18** from the cyclization of unsaturated α-bromoester **10** was purified by preparative GLC at 160°C. Data for this product are listed below:

Methyl trans-2-(Bromomethyl)-1-methylcyclopentane-1-carboxylate (18): colorless oil; ^1H NMR (200 MHz, $CDCl_3$) δ 3.69 (3H, s), 3.48 (1H, dd, J = 6.3, 9.7 Hz), 3.25 (1H, m), 2.8-2.6 (1H, m), 2.2-2.0 (2H, m), 1.8-1.5 (4H, m), 1.09 (3H, s); IR (film) 2985, 2880, 1730, 1440, 1270, 1200, 1150, 1120 cm^{-1}. No reaction occurred when this compound was heated with $AgNO_3/H_2O$/dioxane.[12]

Cyclization of α-Chloroester 20. Using the procedure for the cyclization of **24**, compound **20** was cyclized with the catalysts shown in **Scheme 2**. Products **21** and **22** were isolated by successive flash chromatography (7:3 hexane-ether, followed by 3:1 hexane-EtOAc). Data for these pure products are listed below:

Methyl exo-3-Chloro-endo-1-methylbicyclo[3.2.1]octane-exo-1-carboxylate (21): mp 54-55°C (recrystallized from hexane); ^1H NMR (200 MHz, $CDCl_3$) δ 4.39 1H, s), 3.68 (3H, s), 2.8-2.7 (2H, m), 2.3-1.3 (8H, m), 1.35 (3H, s); IR (film) 2950, 2880, 2870, 1735, 1470, 1435, 1270, 1240, 1200, 1170, 1155, 1125, 1115 cm^{-1}; ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.4, 60.0, 52.4, 52.1, 49.1, 37.6, 34.0, 33.2, 28.0, 27.7, 19.1; MS, m/z (relative intensity) 218 (13), 216 (42), 121 (66), 101 (100), 80 (52). No lactone was formed when this compound was heated with $AgNO_3/H_2O$/dioxane.[12]

Crystal Structure Determination of α-Chloroester 21. Crystal data: $C_{11}H_{17}O_2Cl$, M = 216.71. Monoclinic, $P2_1/c$, a = 6.820 (5), b = 20.314 (5), c = 8.142 (2) Å, β = 100.19 (3)°, V = 1110.1, $Å^3$, Z = 4, D_c = 1.30 g cm^{-3}, F(000) = 464, MoK_α radiation, λ = 0.71073 Å, μ = 3.15 cm^{-1}. Accurate cell dimensions and a crystal orientation matrix were determined on an Enraf-Nonius CAD4 diffractometer by a least squares refinement of the setting angles of 15 reflections with θ in the range 10-15°. Intensity data were collected by the ω/2θ scan method using monochromatized radiation in the range $2 < \theta < 27°$. The intensities of three reflections, chosen as standards, were monitored at regular intervals and did not show any decay of crystal during data collection. Intensities of 2418 unique reflections were measured, of which 1626 had $I > 3\sigma(I)$, and were used in the structure solution and refinement. Data were corrected for Lorentz and polarization factors and for empirical absorption; maximum and minimum correction factors being 0.9995 and 0.9835 respectively. The structure was solved by the heavy atom method. Refinement[20] of the structure was by full-matrix least squares calculations, initially with isotropic and finally with anisotropic temperature factors for the non-hydrogen atoms which were included in the subsequent cycles of refinement with isotropic thermal parameters. Refinement converged with R = 0.041, $R_w = (\Sigma w\Delta^2/\Sigma F_o^2)^{1/2} = 0.061$, and S = 2.34. In the refinement cycles, weights were derived from the counting statistics. Scattering factors were those of Cromer and Mann[21] and Stewart, Davidson and Simpson[22], and allowance was made for anomalous dispersion.[23] A difference map calculated at the conclusion of the refinement had no chemically significant features.[24]

4-Methyl-2-oxatricyclo[5.2.1.0^{4,9}]decane-3-one (22): colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.8-4.7 (1H, m), 2.57 (1H, dd, J = 4.6, 9.1 Hz), 2.30 (1H, m), 2.0-1.4 (8H, m), 1.27 (3H, s); IR (film) 2940, 2860, 1765, 1260, 1150, 1110, 980, 800 cm^{-1}; MS, m/z (relative intensity) 166 (5), 93 (100), 84 (50), 49 (77); exact mass calcd for $C_{10}H_{14}O_2$ 166.0944, found 166.0992.

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