24.3. Anal. ($C_{15}H_{20}OS$) C, H.

2-((Phenylthio)methyl)cyclododecanone (9e): IR ($CHCl_3$) 1703, 1583, 1481, 1470, 1440 cm^{-1}; ^1H NMR δ 7.45–7.18 (m, 5 H), 3.20 (dd, J = 7.5, 13.0 Hz, 1 H), 2.87 (dd, J = 6.9, 13.0 Hz, 1 H), 2.89–2.80 (m, 1 H), 2.80–2.70 (m, 1 H), 2.39–2.28 (m, 1 H), 1.94–1.74 (m, 3 H), 1.64–1.47 (m, 1 H), 1.40–1.10 (m, 14 H); ^{13}C NMR δ 212.4, 136.2, 129.8, 129.0, 126.3, 50.9, 38.3, 34.4, 29.0, 26.2, 26.0, 24.1, 23.7, 23.4, 22.4, 21.9, 21.8. Anal. ($C_{19}H_{28}OS$) C, H.

2-((Phenylthio)methyl)-5-methylcyclohexanone (11): trans/cis = 81/19; IR (neat) 1706, 1584, 1482, 1438 cm^{-1}; ^1H NMR δ 7.32–7.10 (m, 5 H), 3.45 (dd, J = 4.6, 13.4 Hz, 1 H) [3.36 (dd, J = 5.2, 13.1 Hz, 1 H) for cis], 2.69 (dd, J = 8.0, 13.4 Hz, 1 H) [2.79 (dd, J = 8.2, 13.4 Hz, 1 H) for cis], 2.55–2.08 (m, 3 H), 2.03–1.53 (m, 3 H), 1.34 (m, 2 H), 0.99 (d, J = 6.1 Hz, 3 H) [0.94 (d, J = 7.0 Hz, 3 H) for cis]. Anal. ($C_{14}H_{18}OS$) C, H.

2-((Phenylthio)methyl)-1,5-cyclohexanedione 5-(ethylene acetal) (13): IR (neat) 1708, 1584, 1482, 1440 cm^{-1}; ^1H NMR δ 7.14–7.35 (m, 5 H), 3.95 (m, 4 H), 3.51 (dd, J = 4.6, 13.7 Hz, 1 H), 2.73 (dd, J = 8.5, 13.7 Hz, 1 H), 2.63 (s, 2 H), 2.48 (m, 1 H), 2.32 (m, 1 H), 1.95 (m, 2 H), 1.53 (m, 1 H); ^{13}C NMR δ 206.2, 136.2, 129.0, 128.9, 126.0, 110.2, 64.8, 64.6, 51.4, 49.1, 34.3, 32.8, 26.4. Anal. ($C_{15}H_{18}O_3S$) C, H.

4-(Nitromethyl)-4-(phenylthio)-3-hydroxycyclohexanone ethylene acetal (14): ratio of two diastereomers (A vs B), 73:27; IR (neat) 3460 (br), 1550, 1477, 1440 cm^{-1}; ^1H NMR δ 7.67–7.27 (m, 5 H), 5.10 (d, J = 10.7 Hz, 1 H) [4.71 (d, J = 12.2 Hz, 1 H), for B], 4.32 (d, J = 10.7 Hz, 1 H) [4.54 (d, J = 12.2 Hz, 1 H) for B], 4.15 (m, 1 H), 3.97 (m, 4 H), 2.70–2.42 (m, 1 H), 2.37–2.05 (m, 2 H), 2.05–1.82 (m, 1 H), 1.75–1.58 (m, 3 H). Anal. ($C_{15}H_{19}O_5NS$) C, H, N.

3-(2-Hydroxyethoxy)-6-((phenylthio)methyl)-2-cyclohexen-1-one (15): IR ($CHCl_3$) 3430 (br), 1650, 1614, 1482, 1455 cm^{-1}; ^1H NMR δ 7.38–7.14 (m, 5 H), 5.37 (s, 1 H), 3.92 (m, 4 H), 3.70 (dd, J = 3.4, 13.4 Hz, 1 H), 2.78 (dd, J = 9.8, 13.4 Hz, 1 H), 2.52–2.40 (m, 2 H), 2.40–2.28 (m, 1 H), 2.20 (br, 1 H), 1.91–1.73 (m, 2 H); ^{13}C NMR δ 199.2, 177.3, 136.1, 128.9, 125.9, 102.5, 69.8, 60.4, 44.8, 35.6, 28.2, 25.7. Anal. ($C_{15}H_{18}O_3S$) C, H.

1-((Phenylthio)methyl)-2-oxo-1,2,3,4-tetrahydronaphthalene (17): IR (neat) 1710, 1579, 1478, 1440, 1434 cm^{-1}; ^1H NMR δ 7.40–7.08 (m, 5 H), 3.72 (dd, J = 5.2, 7.1 Hz, 1 H), 3.62 (dd, J = 5.2, 12.9 Hz, 1 H), 3.40 (dd, J = 7.1, 12.9 Hz, 1 H), 3.17 (dt, J = 15.6, 6.5 Hz, 1 H), 3.04 (dt, J = 15.6, 6.5 Hz, 1 H), 2.61 (t, J = 6.5 Hz, 2 H); ^{13}C NMR δ 210.1, 136.9, 136.2, 135.3, 129.5, 129.0, 127.9, 127.3, 126.9, 126.3, 52.6, 37.8, 35.2, 27.9. Anal. ($C_{17}H_{16}OS$) C, H.

1-(Phenylthio)-2-phenyl-3-butanone (19): IR (neat) 1710, 1595, 1580, 1490, 1476, 1450, 1433 cm^{-1}; ^1H NMR δ 7.39–7.16 (m, 5 H), 3.89 (dd, J = 6.3, 8.1 Hz, 1 H), 3.64 (dd, J = 8.05, 13.3 Hz, 1 H), 3.15 (dd, J = 6.3, 13.3 Hz, 1 H); ^{13}C NMR δ 206.4, 137.5, 136.2, 129.6, 129.1, 129.0, 128.2, 127.9, 126.3, 59.0, 35.7, 29.4. Anal. ($C_{16}H_{16}OS$) C, H.

1-(Phenylthio)-2-methyl-4-phenyl-3-butanone (21): IR (neat) 1710, 1583, 1495, 1480, 1453, 1438 cm^{-1}; ^1H NMR δ 7.33–7.10 (m, 5 H), 3.71 (s, 2 H), 3.19 (dd, J = 6.5, 12.4 Hz, 1 H), 2.92 (tq, J = 6.5, 7.0 Hz, 1 H), 2.84 (dd, J = 6.5, 12.4 Hz, 1 H), 1.16 (d, J = 7.0 Hz, 3 H); ^{13}C NMR δ 210.0, 136.0, 133.8, 133.0, 130.0, 129.1, 128.8, 127.2, 126.4, 49.5, 44.8, 36.7, 16.9. Anal. ($C_{17}H_{18}OS$) C, H.

1-Nitro-2-methyl-2-(phenylthio)-3-hydroxy-4-phenylbutane (22). The ratio of two diastereomers (A vs B) was 64:36.

A: IR (neat) 3550 (br), 1550, 1493, 1472, 1453, 1438, 1375, 900, 725 cm^{-1}; ^1H NMR δ 7.76–7.04 (m, 5 H), 4.66 (d, J = 12.9 Hz, 1 H), 4.50 (d, J = 12.9 Hz, 1 H), 3.86 (dd, J = 5.1, 10.3 Hz, 1 H), 3.40 (d, J = 13.6 Hz, 1 H), 2.64 (dd, J = 10.3, 13.6 Hz, 1 H), 2.34 (d, J = 5.1 Hz, 1 H), 1.33 (s, 3 H); ^{13}C NMR δ 138.5, 138.1, 137.9, 130.0, 129.4, 129.2, 128.7, 126.7, 81.0, 75.3, 54.8, 38.0, 19.5. Anal. ($C_{17}H_{19}NO_3S$) C, H, N.

B: IR ($CHCl_3$) 1550, 1495, 1455, 1438, 1372 cm^{-1}; ^1H NMR δ 7.74–7.00 (m, 5 H), 5.10 (d, J = 11.0 Hz, 1 H), 4.39 (d, J = 11.0 Hz, 1 H), 4.00 (m, 1 H), 3.04 (m, 2 H), 2.20 (d, J = 4.4 Hz, 1 H), 1.38 (s, 3 H); ^{13}C NMR δ 138.1, 130.0, 129.5, 129.2, 128.8, 126.9, 81.5, 75.4, 55.1, 38.3, 21.7. Anal. ($C_{17}H_{19}NO_3S$) C, H, N.

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Registry No. **7a**, 107454-82-0; **7b**, 107454-83-1; **7c**, 107454-84-2; **7d**, 107454-85-3; *cis*-**7e**, 107537-33-7; *trans*-**7e**, 107454-86-4; **9a**, 51679-33-5; **9b**, 51679-32-4; **9c**, 51679-34-6; **9d**, 124155-48-2; **9e**, 124155-49-3; **10** (isomer 1), 124223-44-5; **10** (isomer 2), 124155-35-7; *cis*-**11**, 124155-31-3; *trans*-**11**, 124155-36-8; **12**, 124155-37-9; **13**, 124155-38-0; *cis*-**14**, 124155-33-5; *trans*-**14**, 124155-39-1; **15**, 124155-40-4; **16**, 124155-41-5; **17**, 124155-42-6; *trans*-**18**, 124155-43-7; *cis*-**18**, 124155-50-6; **19**, 124155-44-8; *trans*-**20**, 124155-45-9; *cis*-**20**, 124155-51-7; **21**, 124155-46-0; (*R**,*R**)-**22**, 124155-32-4; (*R**,*S**)-**22**, 124155-47-1; $NO_2CH_2C(Ph)=CHCH_3$, 124155-53-9; $PhCH_2CH=C(CH_3)CH_2NO_2$, 124155-54-0; 1-(nitromethyl)cyclopentene, 2562-42-7; 1-(nitromethyl)cyclohexene, 5330-61-0; 1-(nitromethyl)cycloheptene, 52315-51-2; 1-(nitromethyl)cyclooctene, 90608-54-1; 1-(nitromethyl)cyclododecene, 124155-34-6; 1-(nitromethyl)-4-methylcyclohexene, 90087-63-1; 1-(nitromethyl)-cyclohexen-4-one ethylene acetal, 124155-52-8; 1-(nitromethyl)-3,4-dihydronaphthalene, 104489-04-5.

A New and Efficient Approach to Macrocyclic Keto Lactones

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A new and efficient method for macrolactonization has been developed. The intramolecular nucleophilic displacement of chloride from the highly electrophilic α-chloro ketone moiety in **15** by a remote carboxylate nucleophile resulted in the clean formation of the 11-membered keto lactone **1**. Relatively high substrate concentrations (up to 18 mM) could be employed without formation of dimeric or oligomeric byproducts. The slow mixing of substrate and base was not required. This macrolactonization reaction was studied in various solvents at a number of substrate concentrations and reaction temperatures in order to evaluate its scope and limitations. A low-temperature Ti(III) ion/peroxide induced radical addition reaction has also been developed. The lowering of the reaction temperature from 0 °C to −78 °C consistently afforded a dramatic increase in product yield from such reactions. This lowering of the reaction temperature proved essential when the highly functionalized acetoxymethyl vinyl ketone was employed as the radical acceptor.

During the past 15 years, a plethora of macrocyclic lactones (macrolides) have been isolated from natural sources. Many of these have been found to possess important and potentially useful biological properties[1] or to

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have attractive odiferous properties.[2] For example, erythromycin is one member of a large family of macrolide antibiotics that are of immense pharmacological importance.[3] Avermectin and some related macrolides are currently employed as antiparasitics,[4] while several of the closely related milbemycin family of macrolides have been shown to possess significant antibiotic and insecticidal activity.[5] The semisynthetic macrolide Ivermectin is currently being utilized to treat "river blindness" in west Africa.[6]

Due in part to these important pharmacological properties, a number of synthetic approaches for the construction of macrocyclic lactones have been developed.[7] A direct ring closure reaction from an acyclic precursor is conceptually the most appealing strategy for macrolactonization. One of the most direct approaches of this type involves the intramolecular S_N2 reaction of a sodium, potassium, cesium, or silver carboxylate nucleophile with a remote alkyl halide.[8] Strategically related macrolactonization reactions include the intramolecular Mitsunobu reaction, where triphenylphosphine oxide is displaced by carboxylate,[9] and the fluoride-induced macrolactonization of 2-(trimethylsilyl)ethyl ω-mesyloxy carboxylates.[10] However, several disadvantages are commonly associated with such approaches. For example, the direct closure of a medium-sized or large ring is disfavored entropically. In addition, enthalpic problems due to bond angle deformations, transannular interactions, and eclipsing interactions along the ring disfavor the formation of medium-sized rings.[11] As a result, competitive intermolecular reactions can occur, leading to dimeric and oligomeric products. Such intermolecular reactions can commonly be avoided by carrying out the macrolactonization reaction at high effective dilution.

Kinetic studies, examining the synthesis of medio- and macrocyclic lactones via cyclization of the corresponding ω-bromo acids, have shown that these reactions are first-order at low concentrations, with a minimum reaction rate for the formation of 8- and 9-membered rings.[12] However, to date only very simple naturally occurring macrolides, such as exaltolide and ambrettolide, have been prepared using this approach.[13] The requisite high reaction temperatures (100 °C), high-dilution conditions, and long reaction times, have discouraged the general use of this methodology in complex molecule synthesis, and a number of other strategies have been developed.[7] However, many of these alternate methods also have similar inherent drawbacks. Therefore, Cameron and Knight recently were moved to reconsider the direct S_N2 displacement of halide by carboxylate as a viable method for macrolactonization.[14] They extended this methodology to the intramolecular S_N2 attack by carboxylate on a remote allylic chloride. One problem with their approach was the lack of regioselectivity observed during the preparation of the allylic chloride precursor for lactonization. However, macrolactonization (K_2CO_3/DMSO) proceeded cleanly via an S_N2 mechanism. To our knowledge, this is the only reported example of macrolactonization via the nucleophilic displacement of halide by carboxylate that did not use a simple primary alkyl halide as the electrophilic partner.

It seemed to us that this general macrolactonization strategy had not been fully developed. In particular, it was apparent that some of the disadvantages of the reactions involving alkyl and allyl halides as electrophilic partners in the macrolactonization reaction could be overcome by using highly electrophilic α-halo ketones. In this paper we describe our studies in this area and demonstrate that the intramolecular attack by carboxylate on a remote α-halo ketone has considerable promise as a synthetically useful macrolactonization protocol.

Our interest in macrolactonization stemmed from a program aimed at the development of conceptually new synthetic approaches to medium-sized carbocyclic rings,[15] where the efficient synthesis of macrocyclic keto lactones such as **1** was required. Initial approaches to the keto lactone **1**, proceeding via the hydroxy keto acid **2** and employing the Corey–Nicolaou "double activation" method,[16] were rather disappointing. Therefore, α-halo keto acids were considered as alternate substrates for lactonization. The basic strategy called for the regio- and chemoselective attack of the remote carboxylate group in compounds of general structure **3** at the α-carbon of the α-halo ketone moiety. Displacement of halide would then provide the requisite keto lactone **4**. The only previous

3 **4**

approach to keto lactones of this type had proceeded via unstable allene oxide intermediates and had afforded the keto lactones as one of two major products.[17] The utilization of an α-halocarbonyl electrophile in such macrolactonization reactions would be expected to afford very large rate enhancements when compared to the analogous

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Table I. Effect of Temperature on Titanium(III) Ion/Peroxide Induced Radical Addition Reactions

entry	R	solvent	temp, °C	product	% yield[a,b]
1	H	acetone	0	**5**	24
2	H	acetone	−78	**5**	40 (30)[c]
3	H	MeOH	0	**7**	40
4	H	MeOH	−78	**7**	62
5	OAc	MeOH	0	**10**	0
6	OAc	MeOH	−78	**10**	55

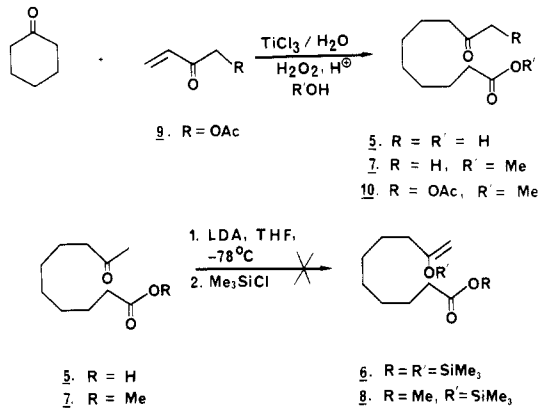
[a] Isolated yields after purification. [b] Yields are based on the amount of hydrogen peroxide (the limiting reagent) employed, in accord with the method employed by Citterio and Vismara[21] to calculate the yields of related reactions. [c] The yield in parentheses is based on consumed cyclohexanone; 32% of the cyclohexanone employed in this reaction could be recovered by distillation. Due to the inexpensive nature of cyclohexanone, this recovery was only carried out for one example.

reaction of simple alkyl halides.[18] This is due, at least in part, to a decreased steric inhibition to the approach of the nucleophile, together with a stabilizing electronic interaction at the transition state of the reaction. The increased rigidity imparted in the substrate by the sp^2-hybridized carbonyl carbon should also favor macrolactonization over competitive intermolecular processes.

α-Halo ketones have never been examined as electrophilic partners in macrolactonization reactions. Indeed, few studies involving the intermolecular displacement of halide from α-halo ketones by carboxylate under basic conditions have been reported.[19,20] However all reactions of this type have resulted in the chemo- and regioselective formation of a single product that is the result of direct displacement of halide by carboxylate. Therefore, it was anticipated that a highly chemo- and regioselective macrolactonization reaction between an α-halo ketone moiety and a remote carboxylate nucleophile should be possible.

Results and Discussion

The focus of our efforts to date has involved the synthesis of macrocyclic keto lactone **1**. Our initial approach to this compound required access to hydroxy keto acid **2** as the precursor for macrolactonization. It was envisioned that this compound would be accessible from 9-oxodecanoic acid (**5**). Therefore, compound **5** was prepared according to a literature procedure, via a titanium(III) ion/peroxide induced radical addition reaction.[21] An acetone solution of cyclohexanone and hydrogen peroxide was added to an aqueous solution of titanium(III) chloride and 2-butenone at 0–5 °C. Under these conditions, 9-oxodecanoic acid was isolated in 24% yield after purification by chromatography (Table I, entry 1). By lowering the reaction temperature to −78 °C, we were able to isolate 40% of this product (Table I, entry 2). Such improvements in product yield by carrying out the radical addition reactions at low temperature have proved quite general (see later; cf. other entries in Table I). The next step called for the regioselective introduction of a hydroxyl group at the C-10 position of compound **5**. However treatment of 9-oxodecanoic acid (**5**) with 2 equiv of LDA in THF at −78 °C, followed by treatment of the presumed kinetic enolate with MoO_5·py·HMPA complex (MoOPH), failed to afford any of the desired 10-hydroxy-9-oxodecanoic acid (**2**).[22] An alternate procedure, involving oxidation of silyl enol ether **6** with mCPBA followed by rearrangement under acidic conditions, also failed, due to difficulties encountered in the preparation of **6**.[23,24] In order to circumvent any problems that might be caused by the presence of the carboxylic acid group, methyl 9-oxodecanoate (**7**) was chosen as an alternate substrate for α-hydroxylation. Compound **7** was prepared via a similar procedure to that described for the preparation of 9-oxodecanoic acid, except that methanol was employed as the solvent. At 0 °C, methyl 9-oxodecanoate was obtained in 40% isolated yield, while at −78 °C this product was isolated in 62% yield (see Table I, entries 3 and 4). However, treatment of methyl 9-oxodecanoate with 1 equiv of LDA at −78 °C, followed by addition of chlorotrimethylsilane, gave only 23% by GC of the desired silyl enol ether **8**, while internal quenching of the enolate with chlorotrimethylsilane afforded no silyl enol ether.



Since the kinetic silyl enol ether was apparently inaccessible in a clean manner via this α-hydroxylation protocol, our strategy for introducing the hydroxyl group was changed. Instead of using methyl vinyl ketone as the radical acceptor in our initial radical addition reaction, acetoxymethyl vinyl ketone (**9**) was considered as an alternate candidate. A successful radical addition reaction should then afford a product bearing the requisite hydroxyl functionality at the desired C-10 position in protected form, and so no subsequent α-hydroxylation protocol would be required. However, functionalized radical acceptors of this type had never previously been examined as substrates in titanium(III) ion/peroxide induced radical addition reactions. It was of interest to see whether such radical acceptors could be successfully utilized in these reactions, since this would allow the one-step preparation of multifunctionalized long-chain carboxylic acids and esters from simple precursors. Acetoxymethyl vinyl ketone (**9**) was prepared in two steps from butyne-1,4-diol according to a literature procedure.[25] Simple distillation afforded **9** contaminated by small amounts of acetic acid. This material was used without further purification in the subsequent radical addition reaction, since storage overnight led to extensive polymerization. When a methanolic solution of cyclohexanone and hydrogen peroxide was

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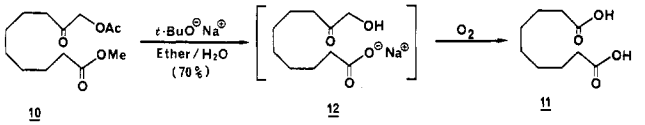
added to acetoxymethyl vinyl ketone in the presence of aqueous titanium(III) chloride at 0 °C, none of the desired acetoxy keto ester **10** was obtained (see Table I, entry 5). However, when the reaction temperature was lowered to −78 °C, 55% of compound **10** was isolated after purification by chromatography (see Table I, entry 6). Acetoxymethyl vinyl ketone is highly susceptible to polymerization. Therefore, one effect of lowering the reaction temperature might be to increase the lifetime of this radical acceptor, which in turn would allow the desired radical addition reaction to occur. A number of other highly functionalized radical acceptors have subsequently been examined as substrates in this titanium(III) ion/peroxide induced C–C bond formation reaction. These studies will be the subject of a future report.

With the requisite acetoxy keto ester **10** now in hand, the macrocyclic keto lactone **1** was targeted. The next step required the hydrolysis of the acetoxy keto ester to the corresponding hydroxy keto acid **2**, which was to serve as our precursor for lactonization. When base-catalyzed hydrolysis was attempted with sodium *tert*-butoxide in ether (containing 1.2 molar equiv of water), a single major product was obtained. However, a spectroscopic examination of this compound suggested that the desired hydroxy keto acid **2** had not been produced. Instead, the data were consistent with nonanedioic acid (**11**). This compound was presumably produced via initial hydrolysis of the acetoxy keto ester **10** to the hydroxy keto carboxylate **12**. Subsequent oxidative dehydroxymethylation then

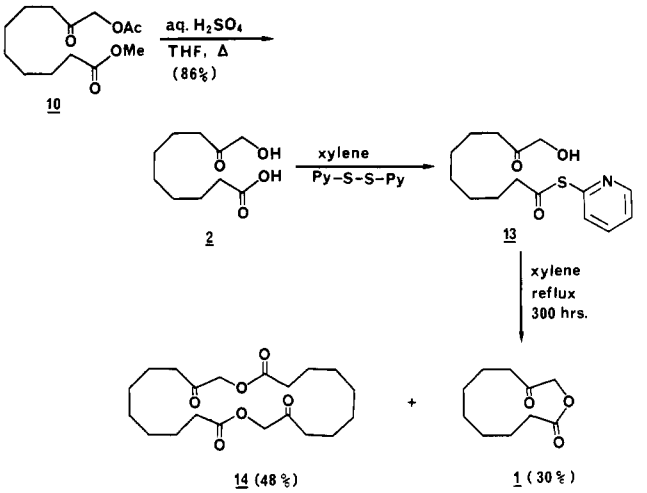


10 **12** **11**

occurred to afford, after workup, nonanedioic acid. This supposition was reinforced by the observation that hydroxy keto acid **2** (prepared by an alternate route, see later) was also converted cleanly to nonanedioic acid under the same reaction conditions. Since no oxidizing agent was deliberately added during the reaction, it seemed likely that adventitious molecular oxygen had effected the oxidative C–C bond cleavage. When this hydrolysis reaction was repeated under stringently oxygen-free conditions, none of the oxidative cleavage product was obtained. Instead, hydroxy keto acid **2** was obtained in 50% isolated yield. To our knowledge, only one example of this kind of oxidative cleavage reaction has previously been reported.[26]

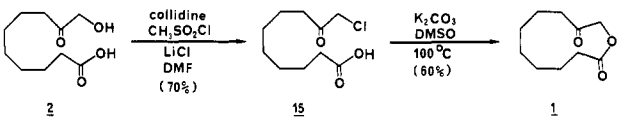
Acid-catalyzed hydrolysis proved a much more effective method for producing the desired hydroxy keto acid **2**. Refluxing acetoxy keto ester **10** for 6 h in the presence of aqueous H_2SO_4 afforded compound **2** cleanly in 86% isolated yield.

With the hydroxy keto acid **2** in hand, our attention was turned to the preparation of the requisite macrocyclic keto lactone **1**. Initial studies involved macrolactonization of the hydroxy keto acid **2** via the Corey–Nicolaou "double activation" method. However, conversion of compound **2** to the thiopyridyl ester **13**, followed by the slow addition of this compound to refluxing xylene, afforded reproducibly low yields of keto lactone **1** (around 30% after chromatography). A considerable amount (48%) of diolide **14** was also obtained. Several inherent drawbacks were apparent with this approach. A high reaction temperature was required, and very high effective dilution conditions had to be maintained by slow addition of the substrate via a syringe pump. The preparation of 256 mg



10 **2** **13** **14** (48%) **1** (30%)

of macrocyclic keto lactone **1** required the slow addition of the thiopyridyl ester **13** to 1.5 L of refluxing xylene over 10 days. Even under these conditions, a considerable amount of the dimeric byproduct **14** was produced! One important reason for these unsatisfactory results is presumably the low nucleophilicity of the hydroxyl group, which is situated α to an electron-withdrawing ketone function. This would be expected to retard the macrolactonization reaction, thus requiring an even slower addition of substrate to the reaction mixture than was carried out in order to maintain sufficiently high effective dilution conditions. Application of a Ag^+-catalyzed version of this reaction[27] might have allowed the more efficient formation of the keto lactone **1**. However, our proposed new macrolactonization strategy, involving nucleophilic attack by carboxylate at the α-position of a remote α-halo ketone, was instead examined at this time as a potentially viable alternate method for the preparation of keto lactone **1**. The presence of the keto group should now accelerate rather than retard the macrolactonization reaction, presumably allowing for the more efficient formation of the desired ketolactone. Hydroxy keto acid **2** was converted to the corresponding mesylate, which in the presence of LiCl afforded the desired chloro keto acid **15** in 70% isolated yield. This was then subjected to lactonization under



2 **15** **1**

high dilution conditions. A solution of the chloro keto acid in DMSO was added slowly to a stirred suspension of K_2CO_3 in DMSO at 100 °C over a period of 6 h. After additional stirring for another 3 h at 100 °C and aqueous workup, the desired keto lactone **1** was obtained in 60% isolated yield. No evidence of diolide **14** or other oligomeric byproducts was observed. The clean formation of this product in reasonable yield, coupled with the facile isolation of the macrolactone product, prompted us to investigate the scope of this reaction in more detail.

Since a quantitative kinetic examination of this macrolactonization methodology was planned, it was important to choose a set of reaction conditions that would be appropriate for such a study. One problem with our initial study was that much of the base (K_2CO_3) was suspended rather than dissolved in the reaction medium. In order to accurately establish the effect of concentration on the reaction, a homogeneous solution was required. Therefore,

(26) Herzig, P. T.; Ehrenstein, M. *J. Org. Chem.* **1951**, *16*, 1050.

(27) Gerlach, H.; Thalmann, A. *Helv. Chim. Acta* **1974**, *57*, 2661.

Table II. Effect of Solvent, Substrate Concentration, and Reaction Temperature on Macrolactonization of Chloro Keto Acid 15 Using Aqueous NaOH as Base

entry	solvent	conc, mM	temp, °C	reaction time, min	% yield[a] lactone 1	% yield[a] diolide 14
1	DMSO	1.1	50	20	100 (72)	0
2	DMSO	18.0	50	20	100 (72)	0
3	DMSO	50.0	50	20	60	40
4	DMSO	1.1	22	30	100 (72)	0
5	DMSO	12.0	22	30	100 (75)	0
6	DMSO	21.0	22	30	69	31
7	DMSO	21.2	50	20	87	13
8	DMF	1.1	50	30	100 (75)	0
9	DMF	12.0	50	30	100 (75)	0
10	DMF	8.8	22	60	100 (75)	0
11	acetone	2.2	22	120	0	0
12	acetone	1.5	56	180	100 (82)	0
13	acetone	11.3	56	180	70	30
14	MeOH	1.2	22	300	0	0
15	MeOH	1.4	65	300	0	0[b]

[a] Crude yields, as determined by GC and ^{1}H NMR analysis, are given, with isolated yields in parentheses. [b] A mixture of methoxy keto acid **16** (20%) and unreacted chloro keto acid **15** (80%) was recovered.

Table III. Representative Kinetic Data for Macrolactonization Reactions of Chloro Keto Acid 15 Using Aqueous NaOH as Base

entry	solvent	conc, mM	temp, °C	rate const, k, min^{-1}	half-line, min	correl coeff
1	DMSO	11.5	22	1.3×10^{-1}	3.5	0.9993
2	DMF	11.0	22	6.2×10^{-2}	10.0	0.9996

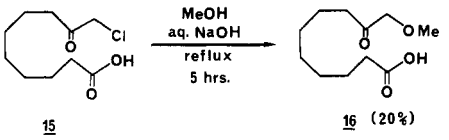
1 M aqueous sodium hydroxide solution was examined as the base, with DMSO as the reaction solvent. In order to accurately evaluate the reaction rate, a rapid mixing of the substrate and the base was also required. Galli and Mandolini showed that macrolactonization of simple ω-halo carboxylates could be achieved without resorting to the slow addition of substrate, so long as reasonably high dilution conditions (up to 0.9 mM for 12-membered lactones) were employed.[12d] However, when a solution of the chloro keto acid **15** in DMSO was added to an aqueous DMSO solution of NaOH in one portion at 50 °C, only 15% (by GC) of the desired keto lactone **1** was observed. One major product (70% by GC) was obtained, which did not correspond to the diolide **14**. A determination of the structure of this compound is currently under active investigation. When an inverse addition procedure was employed, adding aqueous NaOH in one portion to a DMSO solution of the substrate at 50 °C, none of this undesired product was formed, provided that care was taken to ensure the use of only 1 equiv of base. Even at relatively high substrate concentrations (18 mM), 100% conversion to the desired keto lactone was observed by GC analysis, with no traces of unwanted diolide. Isolated yields for the keto lactone **1** were typically around 72%. This is the first reported macrolactonization reaction where such a high substrate concentration has been efficiently utilized without interference from unwanted side reactions. When the substrate concentration was raised to 50 mM, considerable diolide formation was apparent. The effect of substrate concentration on the outcome of this macrolactonization reaction at two different reaction temperatures is summarized in Table II (entries 1–7).

Quantitative kinetic investigations were carried out in order to establish the rate acceleration caused by the presence of the α-keto group. The progress of the reaction was followed by taking aliquots at regular time intervals and measuring the concentration of the released chloride ions using a known electrochemical titration method.[12d] Representative kinetic data is listed in Table III (entry 1). The reaction was shown to be first-order at 22 °C and 50 °C for a range of substrate concentrations (up to 11.5 mM). However, a considerable deviation from first-order kinetics was observed at a substrate concentration of 50 mM. The first-order rate constant k was found to be 1.3×10^{-1} min^{-1} at 22 °C. This value proved to be highly reproducible and independent of the initial substrate concentration, as expected for a first-order process. At 50 °C the rate constant k for this reaction was approximately 3.51 min^{-1}. This compares with a rate constant of 5.22×10^{-2} min^{-1} reported by Galli and Mandolini for the closure of an 11-membered macrolactone via carboxylate attack on a remote alkyl bromide at 50 °C.[12d] Theremore, it can be seen that the presence of the α-keto function significantly increases the rate of macrolactonization. This point is even more dramatic when one considers that bromide is a considerably better leaving group than chloride.

In DMSO the reaction proceeded smoothly to afford the desired keto lactone **1**, so long as an inverse addition technique was used and care was taken to ensure the use of only 1 equiv of base. If an excess of base was employed, a substantial amount of an unwanted product (identical with that obtained from the lactonization reaction where the chloro keto acid **15** was added to the base at 50 °C) could be detected by GC and ^{1}H NMR analysis.

Other reaction solvents were also examined. In DMF, high isolated yields of the keto lactone **1** were obtained at substrate concentrations as high as 12 mM, and no traces of diolide were observed (Table II, entries 8–10). The rate of the reaction was somewhat lower in DMF than in DMSO (Table III, entry 2). Nevertheless, the reaction was complete, at room temperature, in less than 1 h. In acetone, no reaction occurred at room temperature even after stirring for several hours (Table II, entry 11). However, at reflux, the lactone was produced in 82% isolated yield (at a substrate concentration of 1.5 mM, Table II, entry 12). At higher concentrations (11.3 mM) a mixture of lactone **1** and diolide **14** (70:30 ratio as established by NMR analysis) was produced (Table II, entry 13). Isolation of the lactone was considerably easier when the reaction was carried out in acetone rather than in DMF or DMSO. Simple evaporation of the solvent and partitioning between water and ether afforded the keto lactone. In methanol, no lactonization was observed at room temperature or under forcing conditions (Table II, entries 14 and 15).

After refluxing at 65 °C for 5 h, the methoxy keto acid **16** was produced in 20% yield. The rest of the material (80%) was unreacted chloro keto acid.



15 **16** (20%)

In conclusion, a new and efficient method for macrolactonization has been developed. The intramolecular attack by carboxylate at the α-carbon of a remote α-chloro ketone moiety has been established as a viable method for the synthesis of the 11-membered macrocyclic keto lactone **1**. The successful utilization of remarkably high substrate concentrations in a variety of solvents, and under mild reaction conditions, makes this methodology one of the most attractive macrolactonization strategies currently available. Studies designed to evaluate the utility of this synthetic methodology in the construction of other medium- and large-ring macrocyclic keto lactones are underway. The utilization of other α-halocarbonyl groups as electrophilic partners in this type of reaction is also under active investigation. The results of these studies will be reported in due course.

Experimental Section

General Reaction Procedures. Melting points were determined on a Thomas-Hoover capillary melting point apparatus, and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a General Electric GN-300 or Varian FT-80 NMR spectrometer. ^1H NMR chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) using either an internal TMS (0 ppm) or $CHCl_3$ (7.26 ppm) standard. ^{13}C NMR chemical shifts are reported in ppm downfield of TMS using either an internal TMS (0 ppm), $CDCl_3$ (77.0 ppm), or DMSO-d_6 (39.5 ppm) standard. Mass spectra were recorded on a Hewlett-Packard 5995 GC–MS instrument in electron impact ionization mode (1600 eV); only selected ions are reported here. Ion abundances are reported as percentages of the most abundant ion. IR spectra were recorded on an IBM system 9000 FT-IR or Perkin-Elmer 1600 series FT-IR spectrometer. Elemental analyses were performed by Atlantic Microlabs, Inc., P.O. Box 2288, Norcross, GA 30091. Classical column chromatographic separations were carried out on silica gel (70–230 mesh). Flash chromatographic separations were carried out on silica gel (200–425 mesh) according to the procedure of Still.[28] All reactions were followed either by GC (3% OV101 on Gas Chrom Q, $^1/_8$ in. packed column) or TLC (silica) analysis. All solvents were purified according to standard literature procedures.[29] Unless otherwise stated, all reactions were carried out under a dry N_2 atmosphere. Water used in all the kinetic experiments was made free of chloride and carbon dioxide by initial treatment with $KMnO_4$ and NaOH, followed by double distillation.

9-Oxodecanoic Acid (5). First, 30% aqueous hydrogen peroxide (5.5 mL, 0.049 mol) was added dropwise, with stirring, to cyclohexanone (9.8 g, 0.1 mol); 69–70% perchloric acid (0.35 mL) was then added dropwise. The temperature of the solution rose to 45 °C, and the mixture separated into two layers. Water (10 mL) was added, and the resulting syrupy two-phase mixture was added dropwise to a stirred, cooled (−78 °C) mixture of 20% aqueous titanium(III) chloride solution (85 mL, 0.104 mol), methyl vinyl ketone (15 mL, 0.18 mol), and acetone (150 mL) over a period of 15 min. The resulting mixture was allowed to stand at room temperature for 2 h, and was then extracted with toluene (5 × 100 mL). The organic extracts were combined and washed with 15% aqueous sodium hydroxide (4 × 50 mL), water (2 × 100 mL), dried over anhydrous Na_2SO_4, and distilled at ambient pressure to recover unreacted cyclohexanone (3.12 g, 32%, bp 150–155 °C). The aqueous washings were acidified with 10% aqueous HCl and extracted with toluene (4 × 100 mL). The combined toluene extracts were washed with water (2 × 100 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting brown oil was purified by crystallization from petroleum ether (30–60 °C) to afford pure 9-oxodecanoic acid (3.75 g, 0.02 mol, 40% based on H_2O_2) as a white solid: mp 47–48 °C (lit.[22] mp 47–48 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (br s, 6), 1.60 (m, 4), 2.14 (s, 3, CH_3COCH_2), 2.34 (t, 2, J = 7.65 Hz, CH_2CH_2COOH), 2.42 (t, 2, J = 7.57 Hz, $CH_2CH_2COCH_3$), 11.33 (s, 1, COOH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.74, 24.62, 28.94, 33.96, 43.68 (C-2 through C-8 and C-10), 179.44 (C-1), 209.13 (C-9).

Methyl 9-Oxodecanoate (7). Two solutions were prepared. Solution A: 30% aqueous hydrogen peroxide (24.0 mL, 0.214 mol) was added with stirring to a cooled solution of 98% sulfuric acid (20 mL) in methanol (500 mL). Cyclohexanone (39.26 g, 0.40 mol) was added, and the homogeneous mixture was allowed to stand for 2 h at room temperature. Solution B (prepared immediately before use): 20% aqueous titanium(III) chloride (360 mL, 0.466 mol) was added with stirring and cooling to methanol (300 mL). Methyl vinyl ketone (60 mL, 0.72 mol) was then added, and the solution was cooled to −78 °C.

Nitrogen was bubbled through solutions A and B for 10 min before they were combined. Then, the cold (−78 °C) solution A was added, dropwise over a period of 1 h via a cooled addition funnel, to the cold (−78 °C) solution B under nitrogen. The resulting mixture was allowed to warm to room temperature and stand for 45 min. The mixture was then extracted with toluene (4 × 100 mL), and the combined toluene extracts were washed with water (2 × 150 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residual liquid was distilled in vacuo to give methyl 9-oxodecanoate (**7**) (28.6 g, 62% based on H_2O_2, bp 95–98 °C/2 mmHg): ^1H NMR (300 MHz, $CDCl_3$) δ 1.3 (br s, 6), 1.6 (m, 4), 2.11 (s, 3, CH_2COCH_3), 2.28 (t, 2, J = 6.81 Hz, $CH_2CH_2COOCH_3$), 2.43 (t, 2, J = 7.29 Hz, $CH_2CH_2COCH_3$), 3.63 (s, 3, $COOCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.85, 24.99, 29.08, 33.97, 43.54 (C-2 through C-8 and C-10), 51.19 (OCH_3), 173.75 (C-1), 208.08 (C-9).

Acetoxymethyl Vinyl Ketone (9). Acetoxymethyl vinyl ketone (**9**) was prepared from 2-butyne-1,4-diol according to a literature procedure.[26] Distillation of the crude product in vacuo afforded acetoxymethyl vinyl ketone (14.0 g, 70%) as a colorless liquid, bp 70–75 °C (6 mmHg), typically contaminated by 5–10% acetic acid: ^1H NMR (80 MHz, $CDCl_3$) δ 2.15 (s, 3, CH_3COO), 4.90 (s, 2, $COCH_2O$), 5.95 (m, 1, CH_2=$CHCO$), 6.36 (m, 2, CH_2=$CHCO$). The product proved to be very unstable and polymerized upon standing for several hours. Therefore, it was immediately used in the next step.

Methyl 10-Acetoxy-9-oxodecanoate (10). Two solutions were prepared. Solution A: 30% aqueous hydrogen peroxide (24 mL, 0.211 mol) was added with stirring to a cooled (0–5 °C) solution of 98% sulfuric acid (20 mL) in methanol (500 mL). Cyclohexanone (39.2 g, 0.10 mol) was then added, and the homogeneous mixture was allowed to stand for 2 h at room temperature. Dry nitrogen was bubbled through the solution for 10 min prior to use. Solution B (prepared immediately before use): 20% aqueous titanium(III) chloride (360 mL) was added with stirring and cooling (−78 °C) to methanol (325 mL). Freshly prepared and distilled acetoxymethyl vinyl ketone (**9**) (60 g, 0.47 mol) was then added. Dry nitrogen was bubbled through the solution for 10 min prior to use.

Solution A was added dropwise over 30 min via a cooled addition funnel to the stirred and cooled (−78 °C) solution B under a nitrogen atmosphere. The reaction mixture was stirred for 2 h while warming to room temperature. The resulting solution was then extracted with toluene (4 × 250 mL), and the combined toluene extracts were washed with water (2 × 200 mL) and dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo to afford a crude residue (50 g). Purification by flash chromatography (1:1 mixture of n-pentane and ether) gave compound **10** (30 g, 0.116 mol, 55%) as a white solid: mp 54–55 °C; IR (Nujol) ν_{max} 2920, 2850, 1735, 1720, 1465 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (m, 6), 1.59 (m, 4), 2.16 (s, 3, CH_3COO), 2.30 (t, 2, J = 7.5 Hz, $CH_2CH_2COOCH_3$), 2.41 (t, 2, J = 7.35 Hz, $CH_2CH_2COCH_2$),

(28) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(29) (a) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon: London, 1980. (b) *Vogel's Textbook of Practical Organic Chemistry*, 4th ed.; Furniss, B. S., et al., Eds.; Longman: London, 1978.

3.66 (s, 3, CH_3O), 4.64 (s, 2, $COCH_2O$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.45, 23.15, 24.81, 28.89, 33.98, 38.68 (C-2 through C-8 and CH_3COO-), 51.40 (CH_3O), 67.93 (C-10), 170.18, 174.14 (C-1 and $OC(O)CH_3$), 203.84 (C-9). Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.47; H, 8.53. Found: C, 60.37; H, 8.56.

Attempted Base-Catalyzed Hydrolysis of Methyl 10-Acetoxy-9-oxodecanoate (10). To a stirred suspension of sodium *tert*-butoxide (7.0 g, 73 mmol) in diethyl ether (125 mL) cooled to 0 °C was added distilled water (0.5 mL, 27.8 mmol). A solution of acetoxy keto ester **10** (2.0 g, 7.75 mmol) in diethyl ether (20 mL) was added dropwise. The cooling bath was removed, and stirring was continued for 4 h at room temperature. The resulting thick brown solution was quenched with ice water (25 mL). The brown aqueous layer was separated and acidified with 1 M aqueous HCl. The resulting cloudy solution was extracted with ether (3 × 50 mL), and the combined ether extracts were washed with water (100 mL) and brine (100 mL) and dried over anhydrous Na_2SO_4. Concentration in vacuo followed by purification by crystallization then afforded nonanedioic acid (**11**) (1.01 g, 70%) as a white solid: mp 106–108 °C (lit.[30] mp 106.5 °C); ^1H NMR (300 MHz, DMSO-d_6) δ 1.31 (m, 6), 1.61 (m, 4), 2.3 (t, 4, J = 6.45 Hz, CH_2CH_2COOH), 11.94 (br s, 2, $COOH$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.35, 28.33, 33.54 (C-2 through C-8), 174.36 (C-1 and C-9).

Base-Catalyzed Hydrolysis of Methyl 10-Acetoxy-9-oxodecanoate (10) under Oxygen-Free Conditions. To a stirred suspension of sodium *tert*-butoxide (300 mg, 3.2 mmol) in diethyl ether (20 mL) cooled to 0 °C was added distilled water (0.1 mL, 5.5 mmol). Any dissolved oxygen was removed from the solution by a freeze–thaw technique while bubbling nitrogen through the solution. This was done four times in order to ensure complete removal of oxygen from the solution. In another flask, acetoxy keto ester **10** (165 mg, 0.64 mmol) was dissolved in diethyl ether (5 mL), and oxygen was removed from the solution as before. After the complete removal of oxygen from both solutions, the sodium *tert*-butoxide solution was cooled to 0 °C and the solution of the acetoxy keto ester was added dropwise under nitrogen. The cooling bath was removed, and stirring was continued for 24 h at room temperature. The resulting light brown solution was quenched with ice water (10 mL). The pale yellow aqueous solution was separated and acidified with 1 M aqueous HCl. The resulting solution was extracted with ether (2 × 30 mL), and the combined extracts were washed with water (25 mL) and brine (15 mL) and dried over anhydrous Na_2SO_4. Concentration in vacuo afforded 10-hydroxy-9-oxodecanoic acid (**2**) (64.5 mg, 50%). This product showed identical chromatographic and spectral characteristics to the sample of **2** obtained via acid-catalyzed hydrolysis of the acetoxy keto ester **10** (see next experiment).

10-Hydroxy-9-oxodecanoic Acid (2). A solution of acetoxy keto ester **10** (1.5 g, 7.42 mmol) and 1 M aqueous sulfuric acid (5 mL) in THF (30 mL) was refluxed for 6 h under nitrogen. Excess sodium bicarbonate (4 g) was added, and the THF was removed in vacuo. The residual solution was extracted with ether (20 mL) to remove any unreacted acetoxy keto ester **10**. The aqueous layer was then acidified with dilute sulfuric acid and extracted with ether (3 × 25 mL). The combined ether extracts were washed with H_2O (2 × 25 mL) and dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo to afford hydroxy keto acid **2** (0.94 g, 86%) as a white solid. This material was sufficiently pure to be used directly in the next step. Analytically pure material was obtained by purification using column chromatography (1:1 mixture of *n*-pentane and diethyl ether). A white crystalline solid, mp 66–68 °C, was obtained: IR (Nujol) ν_{max} 3300, 2920, 2848, 1710, 1691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (m, 6), 1.64 (m, 4), 2.35 (t, 2, J = 7.49 Hz, CH_2CH_2COOH), 2.41 (t, 2, J = 7.46 Hz, $CH_2CH_2COCH_2OH$), 4.24 (s, 2, $C(O)CH_2OH$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.54, 24.54, 28.76, 28.87, 33.95, 38.32 (C-2 through C-8), 68.60 (C-10), 179.62 (C-1), 210.93 (C-9). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.41; H, 8.91. Found: C, 59.50; H, 9.01.

Preparation of 1-Oxacycloundecane-2,10-dione (1) via Corey–Nicolaou Method. A 100-mL three-necked flask was charged with anhydrous xylene (50 mL) and cooled in ice under nitrogen. Triphenylphosphine (2.0 g, 7.6 mmol) was added to the cooled solution and stirred to dissolve. In another flask hydroxy keto acid **2** (0.94 g, 4.65 mmol) was dissolved in anhydrous xylene (30 mL) with warming. This solution was then added to the triphenylphosphine solution at 0 °C, and dry nitrogen was bubbled through the solution to remove all dissolved oxygen. To this clear and colorless solution was added 2,2′-dipyridyldithiol (1.20 g, 6.38 mmol). The resulting clear yellow solution was then stirred at room temperature for 24 h under nitrogen.

Without isolating the resulting thiol ester **13**, the whole reaction mixture was used in the next step. The clear yellow solution was added slowly from a mechanically driven syringe to anhydrous xylene (1500 mL) at reflux under nitrogen over a total period of 225 h. The solution was then stirred for an additional 120 h at reflux. The solvent was subsequently removed under high vacuum. The residue was subjected to column chromatographic separation (8:1 mixture of pentane and ether) to give the following.

(i) 1-Oxacycloundecane-2,10-dione (**1**) (256 mg, 30%) as a colorless liquid: IR (Nujol) ν_{max} 2920, 2845, 1730, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (m, 2), 1.48 (m, 4), 1.65 (m, 2), 1.85 (m, 2), 2.5 (t, 4, J = 6.32 Hz, C-2 and C-8 protons), 4.60 (s, 2, $C(O)CH_2O$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.99 (t), 22.4 (t), 23.15 (t), 25.31 (t), 26.14 (t), 33.25 (t), 36.98 (t) (C-3 through C-9), 67.96 (t, C-11), 172.77 (s, C-2), 208.23 (s, C-10); MS (m/z) 184 (M^+), 154, 126, 98. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.22; H, 8.7. Found: C, 65.04; H, 8.78.

(ii) 1,12-Dioxacyclododecane-2,10,13,21-tetraone (**14**) (410 mg, 48%) as a white solid: mp 71–72 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (m, 12), 1.62 (m, 8), 2.42 (t, 8, J = 6.6 Hz, $CH_2C(O)$ and CH_2COO), 4.62 (s, 4, $C(O)CH_2O$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.78, 24.81, 28.38, 34.03, 38.51 (C-3 through C-9 and C-14 through C-20), 68.106 (C-11 and C-22), 173.032 (C-2 and C-13), 204.887 (C-10 and C-21). Anal. Calcd for $C_{20}H_{32}O_6$: C, 65.22; H, 8.7. Found: C, 65.13; H, 8.78.

10-Chloro-9-oxodecanoic Acid (15). A stirred mixture of hydroxy keto acid **2** (1.0 g, 4.95 mmol) and collidine (3.30 mL, 25 mmol) under nitrogen was treated with lithium chloride (1.062 g, 25 mmol) dissolved in a minimum amount of anhydrous DMF (13 mL). On cooling to 0 °C a suspension was formed, which was treated dropwise with methanesulfonyl chloride (2.0 mL, 25.8 mmol). The suspension rapidly became thick, and magnetic stirring was not possible. The suspension was allowed to stand at this temperature with occasional stirring (using a glass rod). After 2 h no traces of starting material were apparent by TLC analysis. The pale yellow suspension was allowed to warm to room temperature and was quenched with ice water (30 mL). The resulting solution was extracted with ether (3 × 30 mL). The combined ether extracts were washed with saturated aqueous $Cu(NO_3)_2$ (4 × 30 mL) until no further intensification of the blue color of the aqueous $Cu(NO_3)_2$ was observed, indicating complete removal of collidine. The ether extracts were then dried over anhydrous Na_2SO_4, and the solution was concentrated in vacuo. The resulting crude product was purified by column chromatography, using a silica column that had been pretreated with hexane/acetic acid (99:1), and then washed several times with hexane. The crude product was eluted with a hexane–diethyl ether mixture (4:1) to afford pure chloro keto acid **15** (0.723 g, 70%) as white solid: mp 67–68 °C; IR (Nujol) ν_{max} 3400–2500 (br OH), 2930, 2880, 1725 (ketone C=O stretch), 1691 (acid C=O stretch), 1465, 940 (C-Cl stretch) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (m, 6), 1.62 (m, 4), 2.35 (t, 2, J = 7.42 Hz, CH_2CH_2COOH), 2.59 (t, 2, J = 7.3 Hz, $CH_2CH_2C(O)CH_2Cl$), 4.08 (s, 2, $C(O)CH_2Cl$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.286 (t), 24.361 (t), 28.607 (t), 33.834 (t), 39.435 (t) (C-2 through C-8), 48.070 (t, C-10), 180.035 (s, C-1), 202.608 (s, C-9). Anal. Calcd for $C_{10}H_{17}O_3Cl$: C, 54.42; H, 7.71; Cl, 16.1. Found: C, 54.52; H, 7.83; Cl, 15.98.

Preparation of 1-Oxacycloundecane-2,10-dione (1) via Intramolecular Nucleophilic Substitution of Chloride by Carboxylate: (i) Using K_2CO_3 as the Base. A solution of chloro keto acid **15** (300 mg, 1.36 mmol) was added over 2 h via a motor driven syringe to a stirred suspension of anhydrous potassium carbonate (700 mg, 5 mmol) in anhydrous DMSO (250 mL) under nitrogen, which was maintained at 100 °C. After additional stirring for 1 h at 100 °C, the mixture was cooled to room temperature and partitioned between water and *n*-pentane. The combined *n*-pentane extracts were dried over anhydrous Na_2SO_4, and the solution was concentrated in vacuo to afford the crude

(30) *CRC Handbook of Chemistry and Physics*, 66th ed.; Weast, R. C., Ed.; CRC Press: Boca Raton, FL, 1985–86; p C-90 (listed as azeleic acid).

keto lactone 1 as a colorless oil (220 mg). Purification by column chromatography, using *n*-pentane (10)/diethyl ether (1) as the eluting solvent, gave pure 1-oxacycloundecane-2,10-dione (1) (145 mg, 60%) as a clear liquid. This product showed identical physical and spectral characteristics to the sample of 1 obtained via the Corey–Nicolaou method.

(ii) Using NaOH as the Base. Typical preparative procedures are described below.

(a) Lactonization in DMSO by Usual Addition Procedure. A solution of 1 M aqueous NaOH (0.2 mL) in DMSO (8 mL) was heated to 50 °C. After thermal equilibration, a solution of chloro keto acid **15** (26 mg, 0.118 mmol) in DMSO (2 mL) was added in one portion. The clear solution turned yellow immediately after addition of the substrate. Stirring was continued at this temperature for 1 h, and the solution was then allowed to cool to room temperature. The reaction mixture was then partitioned between *n*-pentane and water, and the aqueous layer was extracted with *n*-pentane (3 × 25 mL). The combined *n*-pentane extracts were dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo to afford a crude product (17 mg). GC analysis of this crude product showed the presence of only 15% of the desired keto lactone 1. The major fraction (68%) was unidentified.

(b) Lactonization in DMSO Using Inverse Addition Procedure. A solution of chloro keto acid **15** (36 mg, 0.1633 mmol) in DMSO (15 mL) was heated to 50 °C, and 1 M aqueous NaOH solution (0.17 mL, 0.17 mmol) was added in one portion. Stirring was continued at this temperature for 30 min, and the reaction was then allowed to cool to room temperature. The reaction mixture was partitioned between water and *n*-pentane, and the aqueous layer was extracted with *n*-pentane (3 × 30 mL). The combined pentane extracts were washed with water (2 × 50 mL) and dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo to afford the desired keto lactone 1 (22 mg, 73%) as a colorless oil.

(c) Lactonization in DMF. A solution of chloro keto acid **15** (485 mg, 2.3 mmol) in DMF (250 mL) was stirred at room temperature for 10 min, and then 1 M aqueous sodium hydroxide solution (2.3 mL, 2.3 mmol) was added in one portion. Stirring was continued at room temperature for additional 1.5 h in order to ensure complete reaction. Workup as above afforded the desired keto lactone 1 (332 mg, 82%) as a colorless oil, which solidified upon standing overnight, to afford a white solid, mp 34–35 °C.

(d) Lactonization in Acetone. A solution of chloro keto acid **15** (16.4 mg, 0.074 mmol) in acetone (50 mL) was heated to reflux, and 1 M aqueous NaOH (0.07 mL, 0.07 mmol) was added in one portion. Refluxing was continued for 2.5 h, and the reaction mixture was then allowed to cool to room temperature. The solvent was removed in vacuo, and the residue was partitioned between water and hexane. The hexane layer was washed with water (2 × 50 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo afforded the keto lactone 1 (11 mg, 80%).

(e) Attempted Lactonization in Methanol. A solution of chloro keto acid **15** (16 mg, 0.073 mmol) in methanol (50 mL) was heated to reflux. One equivalent of 1 M aqueous NaOH (0.07 mL, 0.07 mmol) was added in one portion. Soon after this addition, the solution became cloudy. Refluxing was continued for 5 h. After cooling the reaction mixture to room temperature, it was partitioned between water and hexane. The hexane layer was washed with water (2 × 50 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent in vacuo afforded a crude oil (13 mg). ^1H NMR analysis showed this crude product to consist of unreacted chloro keto acid **15** (80%) and methoxy keto acid **16** (20%): ^1H NMR (**16**) δ 1.32 (br s, 6), 1.61 (m, 4), 2.34 (t, 2, J = 7.5 Hz, CH_2CH_2COOH), 2.58 (t, 2, J = 7.5 Hz, $CH_2C(O)CH_2OCH_3$), 3.66 (s, 3, $CH_3OCH_2C(O)$), 4.24 (s, 2, $CH_3OCH_2C(O)$).

Kinetic Experiments. A solution of chloro keto acid **15** in DMSO or DMF of appropriate concentration was thermally equilibrated at the appropriate reaction temperature. Then exactly 1 equiv of 1 M aqueous NaOH was added in one portion by syringe. The resulting concentration change by adding this solution was negligible. Between 15 and 20 samples (12 mL each) were withdrawn at convenient time intervals, quenched with 0.5 M H_2SO_4 (15 mL), and potentiometrically titrated with aqueous $AgNO_3$ (10^{-3}–10^{-4} M) using a standard calomel electrode and a platinum electrode. Best results were obtained when the reference electrode was connected to the titration vessel through a saturated potassium nitrate salt bridge. End points were determined graphically from the second derivative plots.

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