Transition metal-catalysed chlorine transfer radical cyclizations of 2-(3-alken-1-oxy)-2-chloroacetates; formal total synthesis of avenaciolide and isoavenaciolide.


Published in: Journal of Organic Chemistry

DOI: 10.1021/jo00087a011

Transitional Metal-Catalyzed, Chlorine-Transfer Radical Cyclizations of 2-(3-Alken-1-oxo)-2-chloroacetates. Formal Total Synthesis of Avenaciolide and Isoavenaciolide

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Received September 28, 1993

A novel method for the synthesis of functionalized tetrahydrofurans is described. This method involves the treatment of 2-(3-alken-1-oxo)-2-chloroacetates 1 with a catalytic amount of Cu(bpy)Cl in refluxing 1,2-dichloroethane to give good yields of 3-(1-chloroalkyl)-2-tetrahydrofuran carboxylic esters 2. The stereochemical course of the radical cyclizations shows a preference for the formation of 2,3-cis-substituted tetrahydrofurans in all cases. This selectivity is exploited in the formation of bicyclic lactones which form spontaneously upon ester hydrolysis. As an application of this methodology a formal total synthesis of avenaciolide (28) and isoavenaciolide (29) is described.

Introduction

Transition-metal-catalyzed radical cyclizations have received considerable attention in organic synthesis. The atom-transfer cyclization of ω-haloolefins is currently emerging as a valuable tool for the construction of carbon- and heterocyclic molecules. 1, 2

Recently, 3 we reported a novel Cu(bpy)Cl-catalyzed process for the preparation of 2-carbomethoxy-3-(1-chloroalkyl)tetrahydrofurans 2 via chlorine-transfer radical cyclization reactions of methyl 2-(3-alken-1-oxo)-2-chloroacetates 1a (Scheme 1). This new method was developed as an improvement of the BuSnH-mediated radical cyclizations of the corresponding phenyl sulfides 4 1b to tetrahydrofurans 3, in which the last step is a reduction by BuSnH, because the atom-transfer method results in a cyclization product containing a halogen functionality. It was shown that the choice of ligand for the copper complex was very important for the regiochemical outcome of the cyclization reactions. 3b Thus, chloride 1a (R1=H, Scheme 2) gave the desired tetrahydrofuran 2 as the main product when 2,2'-bipyridine (bpy) was used as a ligand, 3b while the use of 6,6'-substituted bpy's (such as 2,2'-biquinoline and 6,6'-dimethyl-bpy) afforded only 6-endo-trig cyclization product 4. This was explained in terms of a change in the nature of the copper complex promoting either the chlorine transfer process via radical A or the Lewis-type reaction via carbocation B. The latter process is more readily achieved by using the usual Lewis acids like SnCl4.

In this paper, we wish to report on the use of Cu(bpy)Cl as an effective catalyst in the formation of new C-C bonds in chlorine-transfer radical cyclizations of 2-(3-alken-1-oxo)-2-chloroacetates. As an application of this methodology, a formal total synthesis of avenaciolide (28) and isoavenaciolide (29) will be described.

Results and Discussion

Synthesis of Precursors. The radical cyclization precursors 5-13 (Table 1) were prepared from the corresponding alcohols as shown in Scheme 3. Synthesis of the acetates of the glyoxylate adducts from the alcohols has already been published. 5 The acetates thus obtained were converted into the required chlorides after treatment with excess acetyl chloride and hydrogen chloride in ether. 6 Evaporation of the volatiles gave the novel chlorides 5-13 as virtually pure oils (according to NMR).

Copper-Catalyzed Radical Cyclizations. The radical cyclization precursors 5-13 were carried out in 1,2-dichloroethane solutions under a nitrogen atmosphere. The reactions were conducted in the presence of 30 mol % of a 1:1 molar mixture of copper(I) chloride and bpy in 0.3 M solutions with respect to the substrate. Cyclization conditions were optimized for the cyclization of the parent compound 5 (Table 1, entry 1). In refluxing 1,2-dichloroethane, cyclization of 5 with 30 mol % Cu(bpy)Cl took 18 h to reach full conversion. Longer reaction times


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tetrahydrofurans showed a small to moderate preference for the cis products in all cases. This result is in agreement with the rules advanced by Beckwith and co-workers, assuming as the most favorable situation a quasi-equatorial orientation of the ester substituent in a chainlike transition state of cyclization (23). The transition-state structures leading to the minor trans-3-substituted tetrahydrofuran derivatives may contain either a boatlike arrangement or a quasi-axial orientation of the ester substituent. Further research is needed to resolve this point.

Both 16a and 16b were formed as about 1:1 mixtures of their diastereomers, showing little stereoselectivity in the delivery of the chlorine radical by the copper(II) intermediate. Cyclization to the bicyclic systems 17 and 18 showed high stereoselectivity for the formation of the products with the chlorine substituent on the convex side of the molecule (although a trace of a third, unknown isomer of 18 was present in the reaction mixture). This implies a delivery of the chlorine atom by the copper complex from the least hindered side of the molecule.

The stereochemical assignment of the cyclization products 14–18 was usually straightforward. The 6-endocyclization products 15a and 15b were already known from ionic cyclization reactions. The relative stereochemistry of the ester in tetrahydrofuran derivatives 14 and 16–18 was derived from the relative chemical shifts and coupling constants of the methine hydrogen at the carbon atom bearing the ester function, in combination with NOESY. The vicinal coupling constant of this hydrogen was always larger in the cis than in the trans isomer. This assignment was proved by using NOESY in the case of 16–18, showing convincing vicinal NOE effects for the already mentioned methine hydrogen in the cis isomers but not for the corresponding trans isomers. Both ester and chlorine substituents in 17b and 18b are situated on the convex side of the molecule. This was concluded from the NOE effects of H-2 on H-8 in 17b and H-9 on H-2 in 18b. On...
Table 1. Cu(bpy)Cl-Catalyzed Cyclization of Radical Precursors 6-13

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>products (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>14a,b (75%) cis/trans = 64:36</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>16a,b (97%) cis/trans = 57:43</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>16a,b (95%) cis/trans = 58:42</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>17a,b (95%) α/β = 82:18</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>18a,b (80%) α/β = 65:35</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>19a,b (64%)b E:Z = 70:30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 (trace)b XORCO2Me</td>
</tr>
<tr>
<td>7</td>
<td>11</td>
<td>22a,b (80%) E:Z = 68:32</td>
</tr>
</tbody>
</table>

* Compound 15 could not be separated from 14. * Compounds 19-21 formed an inseparable mixture.

The basis of the clear NOE effects between the three cis-substituted methine protons in 17a and 18a, it was concluded that in these two bicyclic systems, the ester group is situated on the concave side of the molecule. The stereochemistry of the chlorine substituent in 18a was further established through an X-ray crystal structure determination (Figure 1). The stereochemistry of the chlorine substituent in 17a could only be tentatively assigned by using NOESY: 17a showed only a weak NOE effect of H-1 on H-8, suggesting a trans relationship between the two protons. This stereochemistry has been confirmed in the lactonization reactions (vide infra).

Chlorine-transfer radical cyclization of 2-(3-alkyn-1-oxo)-2-chloroacetates was also effectively catalyzed by Cu(bpy)Cl. The copper-catalyzed cyclization of acetylene 10 led predominantly to the formation of the 5-exo-dig cyclization product 19. The formation of the minor 6-endo cyclization product 21 might be the result of an ionic cyclization: this compound has already been prepared via tin tetrachloride-induced cyclization of the corresponding acetate of 10, via the corresponding oxycarbenium ion. A true 6-endo-dig radical cyclization cannot be excluded, and might occur because it avoids generation of the instable primary vinylic radical in the formation of 19. The reactivity of this primary vinylic radical is probably reflected in the formation of a trace of 20, which is the result of capture of a hydrogen radical by the intermediate primary vinylic radical.

As expected, regioselectivity for the cyclization of the 1,2-disubstituted acetylene 11 is much higher, with only
5-exo-dig cyclization to 22. The stereoselectivity in the formation of both 19 and 22 was in favor of the $E$ isomers, which implies a preferred delivery of the chlorine atom by the copper catalyst from the sterically least hindered side of the molecule. The $E$ and $Z$ isomers of 19 and 22 could be easily distinguished by using NOE $^1$H NMR, showing clear NOE effects between H-2 and the vinylic proton or methyl group for the $E$ isomers 19a and 22a, respectively. The other isomers 19b and 22b did not show such an effect.

While the copper catalyst is highly effective for radical cyclizations to tetrahydrofurans, it failed to promote a 6-exo radical cyclization. So, cyclizations of the 2-oxa-6-heptenyl analogues 12 and 13 with the copper catalyst under the same conditions were not successful. Only uncyclized compounds, still containing the alkene function, were detected in the crude reaction mixture. This failure of cyclization may be explained in terms of a slower rate of cyclization for the 2-oxa-6-heptenyl radicals derived from 12 and 13 as compared to the 2-oxa-5-hexenyl radicals derived from 5-9. A similar difference in the rates of cyclization was also observed in the Bu$_3$SnH-mediated radical cyclizations of the corresponding phenylthio analogues of precursors 5-7 and 13.44

**Lactonization Reactions.** The cyclization products 14a, 16a, 17a, and 18a were selected for hydrolysis experiments for two reasons, namely, for further confirmation of their stereochemistry and to demonstrate the synthetic utility of the chlorine substituent in the molecule. After alkaline hydrolysis (Table 2), lactones 24–27 were formed in moderate to good yields.3 Late anion on the carbon atom bearing the chlorine atom. The formation of the tricyclic system 26 in high yield strongly indicates an exo orientation of the chlorine substituent in 17a, allowing a facile $S_2$ substitution reaction. The yield for the tricyclic lactone 27 was considerably lower. This may be a result of the less favorable orientation of the ester group with respect to C-4 (see Figure 1), thus retarding the formation of the lactone.

**Synthesis of Avenaciolide and Isoavenaciolide.** The structure of the bicyclic lactone 25 resembles the basic skeletons of avenaciolide (28)10 and isoavenaciolide (29)11 two antifungal metabolites from Aspergillus avenaceus. We envisioned that a total synthesis of these two natural products may be achieved by using our copper-catalyzed cyclization to a functionalized tetrahydrofuran as a key step. As a model compound, we selected chlorine 30 bearing an additional stereocenter to study the regio- and stereoselectivity of the copper-catalyzed cyclization. The extra ester substituent (with respect to the parent

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(3) The enzyme-mediated enantioselective lactonization of chloride 14a has been described in an earlier paper, see ref 9c.

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**Table 2. Lactonization of Cyclization Products**

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>products</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14a</td>
<td><img src="1" alt="Image" /></td>
<td>98%</td>
</tr>
<tr>
<td>2</td>
<td>16a (30:70 mixture of isomers)</td>
<td><img src="2" alt="Image" /></td>
<td>95%</td>
</tr>
<tr>
<td>3</td>
<td>17a</td>
<td><img src="3" alt="Image" /></td>
<td>85%</td>
</tr>
<tr>
<td>4</td>
<td>18a</td>
<td><img src="4" alt="Image" /></td>
<td>46%</td>
</tr>
</tbody>
</table>

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Figure 1. ORTEP diagram of 18a.
Synthesis of Avenaciolide and Isoavenaciolide

The preparation of avenaciolide (28) and isoavenaciolide (29) was anticipated to serve as a handle to obtain the second lactone ring.

Under the usual conditions (30 mol % Cu(bpy)Cl, 80 °C, 2 days), the atom-transfer radical cyclization took place to give the desired 2,3-cis-substituted tetrahydrofurans 31a and 31b as the major products as a 1:1 mixture of C-5 isomers (Scheme 4). The 2,3-trans-substituted product 31c was isolated as a single diastereomer. This latter selectivity may be explained by assuming a six-membered ring transition state with the methyl ester in a pseudoaxial position and the ethyl ester in a pseudoequatorial position (32). The formation of 31a,b is readily explained by assuming a six-membered ring transition state with the methyl ester in a pseudoequatorial position (34) and the ethyl ester in a pseudoaxial position leading to 31a. All three diastereomers could be separated by using flash chromatography (although 31b was contaminated with a fourth diastereomer), and NOESY allowed the assignment of their stereochemistry. Both 31a and 31b showed clear NOE effects between H-2 and H-3, but only 31b showed a NOE effect of H-3 on H-5. For 31c, irradiation of H-2 gave a clear NOE effect on the chloromethyl protons but not on H-3, and irradiation of H-3 showed a clear NOE effect on H-5.

With satisfactory results with model systems in hand, we embarked on the synthesis of avenaciolide and isoavenaciolide as follows. α-Hydroxy ester 35 (Scheme 5) was prepared in one step from 1-undecene and methyl glyoxylate in an ene reaction at low temperature, giving 35 in 76% yield as a ca. 95:5 mixture of E- and Z-alkenes. Treatment with methyl glyoxylate in the usual way and further reaction with acetic anhydride in pyridine afforded the desired acetate in 62% yield (2:1 mixture of isomers). Conversion to chloride 36 was established after treatment with excess acetyl chloride and hydrogen chloride gas for 6 days, to give 36 in 78% yield (4:1 mixture of diastereomers). Chlorine-transfer radical cyclization in the presence of 30 mol % of the copper catalyst (80 °C, 2 days) afforded a mixture of the tetrahydrofurans 37a and 37b in 95% yield. As expected on the basis of the results obtained with model compound 30, a 13C-NMR spectrum of the crude reaction mixture showed the presence of six isomers. To determine the stereoselectivity of cyclization for the tetrahydrofuran ring, the chlorine atoms were removed by reduction with Bu3SnH (Scheme 6). This gave the expected three isomers 42a-c, again with the desired 2,3-cis-substituted tetrahydrofurans 42a and 42b as the major product as a 60:40 mixture of C-5 isomers. All three diastereomers could be separated by using flash chromatography (although 42b was contaminated with a fourth diastereomer), and NOESY allowed assignment of their stereochemistry. The NOE effects for compounds 42a-c were similar to those obtained with the model compounds 31a-c. From the crude mixture of chlorides 37, three diastereomers of 37a were obtained virtually pure by using flash chromatography. These were used for the final part of the synthesis.

The synthesis was now carried on by basic lactonization of 37a, which produced 38 in high yield (89–97%). The second lactone ring was obtained by treatment of the carboxylic acid 38 with Pb(OAc)4, which furnished the corresponding acetates 39 in 67% yield. Oxidation with m-CPBA afforded the two bislactones 40 and 41, which are known intermediates for the synthesis of both avenaciolide (28) and isoavenaciolide (29), respectively. Both spectral and analytical data for normethyleneavenaciolide and normethyleneisoavenaciolide were in complete agreement with those reported in literature.

Comparison of the Cu(I)-Catalyzed Cyclization with the Bu3SnH-Mediated Radical Cyclization. The Bu3SnH-mediated cyclization has been reported for the phenylthio analogues of 5-7, 9, and 11 (although ethylesters instead of methyl esters were employed in those cases).4 The regioselectivity was comparable to the copper-mediated radical cyclization with the exclusive formation of 5-exo cyclization products. The stereoselectivity was similar in the cyclization of the analogues of 5 and 7, but for the phenylthio analogues of 6 and 9 the trans isomers slightly prevailed and for 11 a 1:1 mixture of E- and Z-alkenes was found.

The great similarities in regiochemistry and stereochemistry for both types of cyclization strongly suggest that the mechanistic course of transition metal-catalyzed
Scheme 5

radical cyclizations is similar to that of free radical cyclizations. This implies the generation of an incipient free radical which cyclizes unaffected by the copper complex. The catalyst acts as carrier of the chlorine atom by way of a redox reaction between Cu(I) and Cu(II), as shown in Scheme 7.

The presence of a pair of captodatively stabilizing substituents\(^\text{14}\) probably facilitates the formation of the incipient radical. The bidentate nitrogen ligand further enhances the ability of the copper center to abstract a chlorine atom,\(^\text{26}\) resulting in relatively mild cyclization conditions.

Conclusions

In conclusion, we have shown that, when heated with Cu(bpy)Cl, 2-(3-alken-1-oxyl)-2-chloroacetates undergo chlorine-transfer radical cyclization to give 2-carbomethoxy-3-(1-chloroalkyl)-substituted tetrahydrofurans. The chlorine substituent incorporated into the cyclization product allows for the introduction of functionality required for the synthesis of natural products. Further applications of group transfer radical cyclization are under investigation.

Experimental Section

General Information. Experimental techniques and analytical measurements were applied as previously described.\(^\text{26}\) IR spectral data are reported in cm\(^{-1}\) and NMR chemical shifts in ppm (solvent CDCl\(_3\), unless indicated otherwise). CuCl was purified according to a literature procedure.\(^\text{16}\) 2,2'-Bipyridine (bpy) was commercially available. 3-Pentynol and 4-hexenol were commercially available.

3-(Hydroxymethyl)cyclopentene was prepared according to a literature procedure.\(^\text{16}\) The acetates used for the preparation of chlorides 5-7, 9, 10, 13, and 30 were prepared as described in our earlier papers.\(^\text{6}\) While 30 and 35 appeared to be stable at 4 °C for several months, 5-13 were quite sensitive. Therefore, these compounds were used immediately after their preparation, without further purification.

Methyl 2-[(Cyclopent-2-enylmethyl)oxy]-2-acetoxyacetate. 3-(Hydroxymethyl)cyclopentene (1.65 g, 12.8 mmol) was treated with methyl glyoxylate\(^\text{17}\) (1.60 g, 18 mmol) in 7 mL of dichloromethane. After stirring for 18 h, the mixture was concentrated in vacuo and treated with DMAP (159 mg, 1.3 mmol)


\(^{17}\) Generated from the commercially available methyl hemiacetal of methyl glyoxylate through distillation from phosphorus pentoxide (cf. Hook, J. M. Synth. Commun. 1984, 14, 83.)
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and acetic anhydride (1.81 mL, 19.1 mmol) in 13 mL of pyridine for 3 h. The reaction mixture was evaporated to toluene (3 times) and the residue was chromatographed to give methyl 2-((cyclopent-2-enylmethylene)-2-oxo-2-acetooctate (1.831 g, 5.03 mmol, 65%) as a colorless oil: Rf 0.36 (EtOAc/hexane 1:5); IR (CHCl₃) 3020, 2950, 2870, 1750, 1455, 1435, 1295; ¹H NMR (200 MHz) 1.95-2.10 (m, 1H), 2.14 (s, 3H), 2.80-2.95 (m, 2H), 3.47-3.87 (m, 2H), 3.79 (s, 3H), 5.62-5.67 (m, 1H), 5.78-5.82 (m, 1H), 5.96 (s, 1H); ¹³C NMR (50 MHz, mixture of two diastereomers) 20.8, 26.4, 31.8, 45.7, 45.8, 52.7, 74.0, 74.1, 92.5, 130.96, 130.98, 132.71, 132.75, 166.3, 169.9.

Methyl 2-(3-Pentyn-1-0xy)-2-acetooctate. 3-Pentynol (1.50 g, 17.8 mmol) was treated with methyl glyoxylate (2.20 g, 20.8 mmol) in 9 mL of dichloromethane. After stirring for 1.5 h, the mixture was concentrated in vacuo and treated with DMAP (249 mg, 2.0 mmol) and acetic anhydride (2.9 mL, 31 mmol) in 20 mL of pyridine for 3 h. The reaction mixture was evaporated to toluene (3 times) and the residues was chromatographed to give methyl 2-(3-pentyn-1-0xy)-2-acetooctate (2.56 g, 13.3 mmol, 75%) as a colorless oil: Rf 0.40 (EtOAc/hexane 1:5); IR (CHCl₃) 3020, 2950, 2870, 1760, 1435, 1370; ¹H NMR (200 MHz) 1.71 (t, J = 2.5 Hz, 3H), 2.11 (s, 3H), 3.25-3.50 (m, 2H), 3.76 (s, 3H), 5.39-5.48 (m, 2H), 5.95 (s, 1H). General Procedure for the Synthesis of α-Chloro Ethers. A solution of methyl chloride (at least 20 equiv) was added to a 0.5 M solution of the acetate in ether (dry) at 0 °C. Hydrogen chloride gas was passed through this solution at 0 °C for 0.5 h, and the reaction mixture was concentrated in vacuo. This afforded essentially pure chlorides, which were immediately used for the next steps.

Methyl 2-(3-Buten-1-0xy)-2-chloroacetate (8). A solution of methyl 2-((cyclohex-3-enylmethylene)-2-chloroacetate (1.110 g, 4.58 mmol) in 7 mL of ether and 6.5 mL of acetic chloride was treated with hydrogen chloride gas at 0 °C for 0.5 h. Evaporation of the volatiles gave 8 (602.2 mg, 2.97 mmol, 100%) as a light yellow oil: IR (CHCl₃) 3020, 2950, 2870, 1760, 1455, 1370; ¹H NMR (200 MHz) 1.45-1.65 (m, 1H), 1.93-2.10 (m, 1H), 2.14 (s, 3H), 2.27-2.37 (m, 2H), 2.90-3.10 (m, 1H), 3.47-3.67 (m, 2H), 3.79 (s, 3H), 5.62-5.67 (m, 1H), 5.78-5.82 (m, 1H), 5.96 (s, 1H); ¹³C NMR (50 MHz, mixture of two diastereomers) 20.8, 26.4, 31.8, 45.7, 45.8, 52.7, 74.0, 74.1, 92.5, 130.96, 130.98, 132.71, 132.75, 166.3, 169.9.

Methyl 2-[((cyclopent-2-enyl)methylene]oxy)-2-chloroacetate (9). A solution of methyl 2-((cyclopent-2-enyl)methylene]oxy)-2-acetooctate (1.110 g, 4.58 mmol) in 7 mL of ether and 6.5 mL of acetic chloride was treated with hydrogen chloride gas at 0 °C for 0.5 h. Evaporation of the volatiles gave 9 (994 mg, 4.55 mmol, 99%) as a colorless oil: IR (CHCl₃) 3020, 2950, 2870, 1760, 1455, 1370; ¹H NMR (200 MHz) 1.30-1.90 (m, 4H), 1.95-2.10 (m, 2H), 2.40-2.60 (m, 1H), 3.46 (dt, J = 9.2, 7.4 Hz, 1H), 3.78-3.97 (m, 1H), 3.86 (s, 3H), 5.50-5.62 (m, 1H), 5.75-5.85 (m, 1H), 5.83 (s) and 5.84 (s, 1H); ¹³C NMR (50 MHz, mixture of two diastereomers) 20.8, 26.4, 31.8, 45.7, 45.8, 52.7, 74.0, 74.1, 92.5, 130.96, 130.98, 132.71, 132.75, 166.3, 169.9, 187.4, 194.5.
(ddt, J = 12.5, 7.6, 4.9 Hz, 1H), 2.80-2.98 (m, 1H), 3.40 (dd, J = 11.0, 8.6 Hz, 1H), 3.60 (dd, J = 6.0, 11.0 Hz, 1H), 3.76 (s, 3H), 3.92 (q, J = 7.8 Hz, 1H), 4.21 (dt, J = 4.7, 8.3 Hz, 1H), 4.61 (d, J = 7.5 Hz, 1H); 13C NMR (63 MHz) 29.77, 43.40, 46.06, 51.83, 78.58, 171.11; HRMS calcd for C15H21OCl 178.1397, found 178.1396.

The second fraction consisted of a 72:28 mixture (according to 1H NMR) of diastereomers of (2R,4S)-2-carboxymethoxy-4-chlorotetrahydropyran as a colorless oil (83.5 mg, 0.42 mmol, 26%). 1H NMR (500 MHz) 1.01-1.18 (m, 2H), 1.24-1.48 (m, 1H), 1.50-1.69 (m, 2H), 1.86 (dd, J = 8.8, 3.6 Hz, 1H), 3.59 (m, 1H), 3.77 (s, 3H), 3.79 (m, 1H); 13C NMR (125 MHz) 19.90, 21.40, 22.10, 27.20, 30.46, 40.32, 49.51, 58.72, 70.13, 70.14, 71.00, 78.58, 171.11; HRMS calcd for C14H21OCl 202.1400, found 202.1396.

Cyclization of 6. To a solution of 6 (564 mg, 2.73 mmol) in 9.1 mL of 1,2-dichloroethane were added bpy (326 mg, 0.61 mmol) and CuCl (61.1 mg, 0.81 mmol). The reaction mixture was heated under reflux for 18 h. Flash chromatography gave two fractions.

The first fraction consisted of a 60:40 mixture (according to 1H NMR) of diastereomers of (2R,3R)-2-carboxymethoxy-3-(1-chloropropyl)tetrahydrofuran (15a) as a colorless oil (281.3 mg, 1.36 mmol, 50%): Rf = 0.30 (EtOAc/hexane 1:4); HR (CHCl3) 2970, 2950, 2950, 1740, 1455, 1435; 13C NMR (200 MHz, mixture of two diastereomers) 1.05 and 1.06 (2 × t, J = 7.2 Hz, 3H), 1.66-2.30 (m, 4H), 2.09-2.85 (m, 1H), 3.75 (s, 3H), 3.71-4.05 (m, 3H, J = 7.2 Hz), 3.77 (s, 3H), 3.75 (m, 3H); 1H NMR (200 MHz, mixture of two diastereomers) 10.23, 10.93, 27.81, 27.81, 30.03, 31.39, 46.11, 50.88, 51.50, 61.60, 51.38, 63.52, 64.05, 68.42, 69.02, 78.13, 79.34, 171.58, 171.63; HRMS calcd for C14H21O4Cl 204.0553, found 204.0549.

The second fraction consisted of a 43:57 mixture (according to 1H NMR) of diastereomers of (2R,3S,5R,8S,9S)-9-carboxymethoxy-9-chloro-8-oxabicyclo[4.3.0]nonane (16a) (499 mg, 2.01 mmol, 48%) as a colorless oil. Recrystallization from diisopropyl ether gave white crystals, mp 87.5-88 °C: Rf = 0.15 (EtOAc/hexane 1:4); HR (CHCl3) 3000, 2950, 2950, 2870, 1740, 1470, 1445, 1435; 13C NMR (200 MHz) 1.40-1.75 (m, 5H), 2.05-2.16 (m, 1H), 2.29-2.80 (m, 2H), 3.75 (s, 3H), 3.82 (t, J = 8.8 Hz, 1H), 3.94 (t, J = 8.4 Hz, 1H), 4.06-4.19 (m, 1H), 4.48 (d, J = 4.8 Hz, 1H); 1H NMR (200 MHz) 0.59, 0.95, 2.32, 55.47, 59.41, 59.92, 10.35, 97.97, 97.95, 78.65, 171.04. Anal. Found: C, 54.77; H, 6.85.

Calcld for C23H29O3Cl: C, 54.92; H, 6.86. The X-ray crystal structure of this major isomer was determined (see Figure 1)."
heated under reflux for 18 h. Flash chromatography gave two fractions.

The first fraction consisted of \(\text{(E)\text{-2-carboxamethoxy-3-(1-chloroethylenide)tetrahydrofuran (22a)}}\) as a colorless oil (245 mg, 1.29 mmol, 51%): \(\text{Rf} = 0.35\) (EtOAc/hexane 1:4); IR (CHCl\(_3\)) 3000, 2980, 2935, 1735, 1690, 1455, 1380, 1325; \(\text{H NMR (200 MHz):} 1.07-1.21 (s, 1H), 2.57 (s, 3H), 3.74-3.86 (m, 1H), 4.23 (q, \text{J} = 8.27, 1H), 4.96 (s, 1H); \(\text{H NMR (CDCl}_3, 200 \text{MHz):} 1.08-1.18 (m, 1H), 1.39 (m, 1H), 2.00 (s, 3H), 3.75-3.84 (m, 1H), 4.14 (q, \text{J} = 8.27, 1H), 4.95 (s, 1H); \(\text{H NMR (CF}_3\text{CHCO}_2\text{H, 200 MHz):} 1.08-1.19 (m, 1H), 1.39 (m, 1H), 2.00 (s, 3H), 3.76-3.87 (m, 1H), 4.14 (q, \text{J} = 8.17, 1H), 4.97 (s, 1H); \(\text{H NMR (CDCl}_3, 63 \text{MHz):} 23.61, 31.88, 51.98, 68.45, 77.23, 124.57, 133.59, 170.85; \text{HRMS calcd for C}_{13}\text{H}_{20}\text{O}_2\text{Cl}: 210.1059, found 210.1057. The residue was taken up in ether and dried (MgSO\(_4\)). Concentration of the reaction mixture over a short silica column (eluting with EtOAc). This showed that all starting material was gone, but no cyclization product could be detected in the complex spectrum.

**Attempted Cyclization of 12.** To a solution of 12 (48.2 mg, 0.233 mmol) in 0.8 mL of 1,2-dichloroethane were added dicyclohexylamine (12.3 mg, 0.079 mmol) and CuCl (7.6 mg, 0.077 mmol). The reaction mixture was heated under reflux for 20 h. A \(\text{H-NMR spectrum of the crude reaction mixture (47.2 mg) was obtained after filtration of the reaction mixture over a short silica column (eluting with EtOAc). This showed that all starting material was gone, but no cyclization product could be detected in the complex spectrum.**

**General Procedure for the Lactonization Reactions.** To a 0.2 M solution of the chloride in a 5:1 mixture of methanol and water (v/v) was added lithium hydroxide monohydrate (2 equiv). After being heated under reflux for 16 h, the reaction mixture was acidified with 2 M HCl to pH 1 and concentrated in vacuo. The residue was taken up in ether and dried (MgSO\(_4\)). Concentration in vacuo afforded the desired lactone.

**Saponification of 14a.** A mixture of 45.0 mg of 14a (0.595 mmol) and 22 mg of lithium hydroxide monohydrate in 1.1 mL of methanol and 0.3 mL of water was under reflux for 16 h. Workup afforded \(\text{(1R,5R)-2,7-dioxabicyclo[3.3.0]oct-8-ene (24) as a colorless oil (31.6 mg, 0.504 mmol, 98%): IR (CHCl}_3\) 2980, 2910, 2870, 1775, 1475, 1455, 1375; \(\text{H NMR (200 MHz):} 1.81-1.96 (m, 1H), 2.18-2.36 (m, 1H), 3.11-3.27 (m, 1H), 3.75-3.87 (m, 1H), 3.95-4.07 (m, 1H), 4.00 (m, 1H), 4.73 (d, \text{J} = 8.17, 1H); \(\text{H NMR (CDCl}_3, 63 \text{MHz):} 23.63, 30.82, 62.00, 69.37, 79.64, 123.62, 130.85, 170.57.\)**

**Saponification of 16a.** A 30:70 mixture (according to \(\text{H NMR)}\) of chloride epimers of 16a (123 mg, 0.595 mmol) and 50 mg of lithium hydroxide monohydrate in 3.0 mL of methanol and 0.5 mL of water was heated under reflux for 16 h. Workup afforded \(\text{(1R,5R,5R)-2,7-dioxabicyclo[3.3.0]oct-8-ene (24) as a colorless oil (37.9 mg, 0.663 mmol, 95%): IR (CHCl}_3\) 2970, 2870, 1770, 1460, 1370, 1355, 1085, 965, 905; \(\text{H NMR (200 MHz, mixture of two diastereomers):} 1.01 (t, \text{J} = 7.4 \text{Hz,} 1H), 1.18-1.30 (m, 1H), 1.22 (m, 3H), 2.57-2.59 (m, 1H), 2.69 (m, 2H), 3.57-3.68 (m, 1H), 3.72-3.84 (m, 1H), 4.03 (dd, \text{J} = 8.17, 1H); \(\text{H NMR (CDCl}_3, 63 \text{MHz):} 23.75, 30.57, 47.80, 69.37, 79.64, 123.62, 130.85, 170.57; \text{HRMS calcd for C}_{13}\text{H}_{20}\text{O}_2: 210.1059, found 210.1057.**
The fourth fraction consisted of (2R,3R,5S)-5-carboxethoxy-2-carbomethoxy-3-(chloromethyl)tetrahydrofuran (51b) as a colorless oil. A mixture of diastereomers 1.25 mL of acetyl chloride was treated with hydrogen chloride gas at 0 °C for 0.5 h. The reaction mixture was added at -78 °C a precooled dichloromethane (300 mL) was added at -78 °C (t, J = 7.1 Hz, 3H), 2.20 (dt, J = 12.9, 8.9 Hz, 1H), 2.56 (d, J = 12.9, 7.6 Hz, 1H), 2.28-3.00 (m, 1H), 3.44 (dd, J = 8.5, 11.1 Hz, 1H), 3.61 (dd, J = 6.7, 11.1 Hz, 1H), 3.75 (s, 3H), 4.26 (q, J = 7.1 Hz, 2H), 4.57-4.64 (m, 2H); ^1H NMR (CDCl3, 200 MHz) 0.96 (t, J = 7.2 Hz, 3H), 1.87-1.97 (m, 1H), 2.04-2.28 (m, 2H), 3.10 (dd, J = 7.2, 11.1 Hz, 1H), 3.39 (q, J = 7.1 Hz, 2H), 4.19-4.27 (m, 1H), 4.25 (d, J = 7.2 Hz, 1H); ^13C NMR (63 MHz, mixture of diastereomers) 79.5, 170.2, 170.9; MS (EI) 250 ((M+)^+). Concentrated in vacuo. Flash chromatography afforded 35 (11.07 g, 25% yield) as a colorless oil: IR (CDCl3, 1000-3000 cm^-1) 3010, 2950, 2930, 2850, 1740, 1450, 1435; ^1H NMR (300 MHz, CDCl3) 0.85 (t, J = 6.7 Hz, 3H, alkyl-CH3), 1.25 (bs, 12H, CH2-1, 2H-1); ^13C NMR (125 MHz, mixture of E and Z isomers) 17.78, 77.67, 77.11, 77.88, 78.09, 78.22, 78.75, 78.18, 78.97, 80.17, 80.22 and 80.44 (C-2, C-3, C-4, C-5, C-6, C-7, C-8, C-9, C-10, C-11, C-12) ppm. The mixture for the fourth diastereomer: ^1H NMR (300 MHz) 4.44 (d, J = 6.4 Hz, 2H); ^13C NMR (63 MHz, mixture of diastereomers) 76.10, 80.22 and 80.44 ppm. Flash chromatography (EtOAc/hexane 1:1) afforded 37a (64.7 g, 13.5 mmol) as a light yellow oil: IR (EtOAc) 3080, 2950, 2920, 2850, 1740, 1450; ^1H NMR (200 MHz) 0.85 (t, J = 6.7 Hz, 3H, alkyl-CH3), 1.25 (bs, 12H, CH2-1, 2H-1); ^13C NMR (63 MHz, mixture of diastereomers) 76.10, 80.22 and 80.44 ppm. The mixture for the fourth diastereomer: ^1H NMR (300 MHz) 4.44 (d, J = 6.4 Hz, 2H); ^13C NMR (63 MHz, mixture of diastereomers) 76.10, 80.22 and 80.44 ppm. Flash chromatography (EtOAc/hexane 1:1) afforded 37a (64.7 g, 13.5 mmol) as a light yellow oil: IR (EtOAc) 3080, 2950, 2920, 2850, 1740, 1450; ^1H NMR (200 MHz) 0.85 (t, J = 6.7 Hz, 3H, alkyl-CH3), 1.25 (bs, 12H, CH2-1, 2H-1); ^13C NMR (63 MHz, mixture of diastereomers) 76.10, 80.22 and 80.44 ppm.
The first fraction consisted of (2R*,3S*,5R*)-2,5-dicarboxymethoxy-3-nonyltetrahydrofuran (42a) (66.8 mg, 0.131 mmol, 87%) as a colorless oil: \( R_f 0.15 \) (EtOAc/hexane 1:6); IR (CHCl\(_3\)) 3020, 2930, 2850, 1700, 1460, 1430; \( ^1\)H NMR (200 MHz) 0.86 (t, \( J = 6.8 \) Hz, 3H, alkyl-CH\(_3\)), 1.24 (s, 12H, CH\(_2\)), 1.65-1.80 (m, 2H), 2.40-2.60 (m, 1H, H-5), 4.54-4.62 (m, 1H, H-4), 6.43 (d, \( J = 7.8 \) Hz, 1H, H-2); \(^{13}\)C NMR (50 MHz) 14.0 (alkyl-CH\(_3\)), 22.6, 24.9, 29.2, 31.7, 37.8, and 38.1 (CH\(_2\)), 44.0 (C-5), 77.9 (C-6), 80.3 (C-1), 89.5 (C-6), 124.2 (C-5), 169.4, 172.7; MS (EI) (M\(^+\)) 254.1518, found 254.1509.

The second fraction consisted of (2R*,3S*,5S*)-2,5-dicarboxymethoxy-3-nonyltetrahydrofuran (42c) (33.4 mg, 0.05 mmol, 31%) as a colorless oil: \( R_f 0.21 \) (EtOAc/hexane 1:2.5); IR (CHCl\(_3\)) 3020, 2930, 2850, 1700, 1460, 1430; \( ^1\)H NMR (200 MHz) 0.85 (t, \( J = 7.0 \) Hz, 3H, alkyl-CH\(_3\)), 1.27 (bs, 12H, CH\(_2\)), 1.65-1.80 (m, 2H), 2.55 (m, 1H, H-1), 3.69 (3H, 3.78 (s, 3H), 4.55 (d, \( J = 7.8 \) Hz, 1H, H-2), 4.54-4.62 (m, 1H, H-4), 6.43 (d, \( J = 7.8 \) Hz, 1H, H-2); \(^{13}\)C NMR (50 MHz) 14.0 (alkyl-CH\(_3\)), 22.6, 28.3, 29.1, 29.2, 29.4, 29.5, 31.8 and 33.9 (CH\(_2\)), 43.2 (C-3), 51.5, 52.1, 78.0 and 81.0 (C-2 and C-5), 171.8, 171.9; HRMS calcd for C\(_{17}\)H\(_{29}\)O\(_{6}\) 312.2075, found 312.2075.

Characteristic signals derived from this mixture for the fourth isomer: \( ^1\)H NMR (50 MHz) 27.51, 32.85 and 55.36 (CH\(_2\)), 42.74 (CH\(_2\)), 77.74 and 83.17 (C-2 and C-5).

(1R*,5R*,6R*)-6-N-Octyl-2,7-dioxabicyclo[3.3.0]octane-3,8-dione (41). To a solution of 39b (45 mg, 0.157 mmol) in dichloromethane (0.5 mL) were added at 0 °C BF\(_3\)-Et\(_2\)O (3.9 mg, 0.03 mmol) and m-CPBA (purity 85%, 33.7 mg, 0.166 mmol). The reaction mixture was stirred for 3 h. Then, ether (4.3 mL) was added and the mixture was subsequently washed with a 10% aqueous Na\(_2\)SO\(_4\) solution, a saturated aqueous NaHCO\(_3\) solution, and brine. The combined water layers were extracted with ether, and the combined organic layers were concentrated in vacuo. Filtration through a short silica column (ether) afforded 41 as a colorless oil: IR (CHCl\(_3\)) 3020, 2930, 2850, 1700, 1465, 1415, 1355, 1290; \( ^1\)H NMR (300 MHz) 0.88 (t, \( J = 7.0 \) Hz, 3H, alkyl-CH\(_3\)), 1.28 (bs, 12H, CH\(_2\)), 1.65-1.80 (m, 2H, H-2), 2.55 (m, 1H, H-1), 3.69 (3H, 3.78 (s, 3H), 4.55 (d, \( J = 7.8 \) Hz, 1H, H-2), 4.54-4.62 (m, 1H, H-4), 6.43 (d, \( J = 7.8 \) Hz, 1H, H-2); \(^{13}\)C NMR (75 MHz) 14.0 (alkyl-CH\(_3\)), 22.6, 24.9, 29.1, 29.2, 31.7, 32.8 and 35.4 (CH\(_2\)), 40.1 (C-5), 77.0 and 84.9 (C-1 and C-6), 169.9, 173.7; HRMS calcd for C\(_{17}\)H\(_{29}\)O\(_{4}\) 254.1518, found 254.1509.

Acknowledgment. K. Goubitz and J. Fraanje of the Department of Crystallography are kindly acknowledged for chemical research (SON), with financial support from the Dutch Organization for the Advancement of Pure Research (NWO).

Supplementary Material Available: Copies of \(^1\)H and/or \(^{13}\)C NMR spectra for all new compounds, i.e., 5-17, 19-22, 24-27, 30, 31, 35-39, the precursors of compounds 8, 11, 12, and 36, and for normethyleneasovanicilide (40) and normethylenesosovaenicilide (41) (82 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.