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

Jan H. Udding, Kees (C.) J. M. Tuijp, Marco N. A. van Zanden, Henk Hiemstra,* and W. Nico Speckamp*

Laboratory of Organic Chemistry, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

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-oxy)-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 carbo- 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-oxy)-2-chloroacetates 1a (Scheme 1). This new method was developed as an improvement of the Bu_3SnH-mediated radical cyclizations of the corresponding phenyl sulfides[4] 1b to tetrahydrofurans 3, in which the last step is a reduction by Bu_3SnH, 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 (R^{1-4} = 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 $SnCl_4$.[5]

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-oxy)-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 cyclizations of 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

• Abstract published in *Advance ACS Abstracts,* February 1, 1994.

(1) For reviews of radical cyclizations including atom-transfer methods, see: (a) Giese, B. *Radicals in Organic Synthesis: formation of carbon-carbon bonds*; Pergamon: Oxford, 1986. (b) Curran, D. P. *Synthesis* **1988**, 489. (c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (d) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, pp 715–832.

(2) For recent references to atom-transfer cyclizations, see: (a) Jolly, R. S.; Livinghouse, T. *J. Am. Chem. Soc.* **1988**, *110*, 7536. (b) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1989**, *111*, 6265. (c) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140. (d) Mori, M.; Kubo, Y.; Ban, Y. *Heterocycles* **1990**, *31*, 433. (e) Nagashima, H.; Seki, K.; Ozaki, N.; Wakamatsu, H.; Itoh, K.; Tomo, Y.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 985. (f) Lee, G. M.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 1281. (g) Curran, D. P.; Chang, C.-T. *Tetrahedron Lett.* **1990**, *31*, 933. (h) Curran, D. P.; Seong, C. M. *J. Am. Chem. Soc.* **1990**, *112*, 9410. (i) Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746. (j) Belvisi, L.; Gennari, C.; Poli, G.; Scolastico, C.; Salom, B.; Vassallo, M. *Tetrahedron* **1992**, *48*, 3945. (k) Nagashima, H.; Wakamatsu, H.; Ozaki, N.; Ishii, T.; Watanabe, M.; Tajima, T.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 1682. (l) Pirrung, F. O. H.; Steeman, W. J. M.; Hiemstra, H.; Speckamp, W. N.; Kaptein, B.; Boesten, W. H. J.; Schoemaker, H. E.; Kamphuis, J. *Tetrahedron Lett.* **1992**, *33*, 5141. (m) Seijas, J. A.; Vázquez-Tato, M. P.; Castedo, L.; Estévez, R.; Onega, M. G.; Ruíz, M. *Tetrahedron* **1992**, *48*, 1637. (n) Nagashima, H.; Ozaki, N.; Ishii, M.; Seki, K.; Washiyama, M.; Itoh., K. *J. Org. Chem.* **1993**, *58*, 464. (o) Ishibashi, H.; Uemura, N.; Nakatani, H.; Okazaki, M.; Tatsunori, S.; Nakamura, N.; Ikeda, M. *J. Org. Chem.* **1993**, *58*, 2360.

(3) Part of these results has appeared in our earlier papers; (a) Udding, J. H.; Hiemstra, H.; van Zanden, M. N. A.; Speckamp, W. N. *Tetrahedron Lett.* **1991**, *32*, 3123. (b) Udding, J. H.; Hiemstra, H.; Speckamp, W. N. *J. Chem. Soc., Perkin Trans. 2*, **1992**, 1529. (c) Udding, J. H.; Fraanje, J.; Goubitz, K.; Hiemstra, H.; Speckamp, W. N.; Kaptein, B.; Schoemaker, H. E.; Kamphuis, J. *Tetrahedron: Asymmetry* **1993**, *4*, 425.

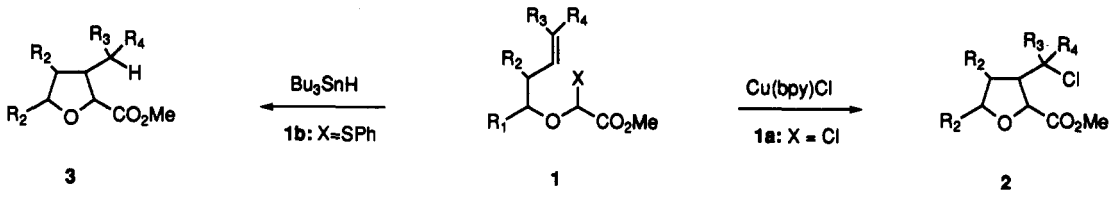
(4) (a) Lolkema, L. D. M.; Hiemstra, H.; Al Ghouch, A. A.; Speckamp, W. N. *Tetrahedron Lett.* **1991**, *32*, 1491. (b) Burke, S. D.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 2335.

(5) (a) Lolkema, L. D. M.; Hiemstra, H.; Mooiweer, H. H.; Speckamp, W. N. *Tetrahedron Lett.* **1988**, *29*, 6365. (b) Lolkema, L. D. M. Ph.D. Thesis, University of Amsterdam, 1993.

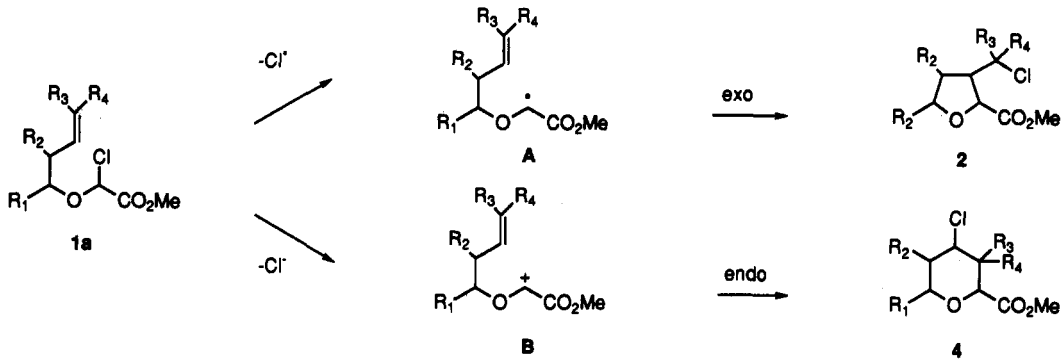
(6) For a recent application of this procedure, see: Myrvold, S.; Reimer, L. M.; Pompliano, D. L.; Frost, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1861.

0022-3263/94/1959-1993$04.50/0

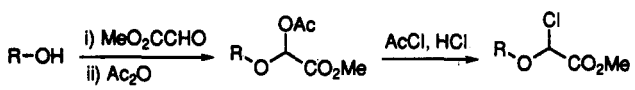
Scheme 1



Scheme 2



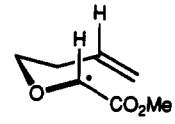
Scheme 3



were required when the reaction was performed in CH_2Cl_2 at 40 °C (48 h: **14** (76%), **15** (7%)) or at room temperature (144 h: **14** (45%), **15** (4%)). Stereoselectivities were similar in all cases. No reaction was observed at temperatures of 0 °C or lower. The reaction was also carried out in a variety of other solvents. Tetrahydrofuran, dimethoxyethane, and methyl acetate were also suitable media for the cyclization but gave rise to the formation of substantial amounts of undesired reduced cyclization product **3** (R^{1-4} = H). Apparently, abstraction of a hydrogen atom from the solvent by the cyclized radical is competing with the delivery of a chlorine atom by the copper complex when the latter solvents are employed.[7]

The results of the cyclization reactions are summarized in Table 1. In general, the product of 5-*exo* cyclization was obtained, as might be expected for this radical cyclization.[4a,8] Only **5** and **10** gave small amounts of the 6-*endo* product. Cu(bpy)Cl-catalyzed cyclization of the parent glycolic acid derivative **5** proceeded with a 5-*exo*/6-*endo* ratio of 11:1, with tetrahydrofuran **14** as the main product. It seems most likely that **15** is formed in a true radical cyclization via intermediate **A**, but it cannot be excluded that this six-membered ring is the product of ionic cyclization via oxycarbenium ion **B** as in the copper catalysis with 6,6′-substituted bpy as a ligand.[3b]

Electronically unbiased, 1,2-disubstituted alkenes **6–9** underwent exclusive 5-*exo* cyclization in good yields. The geometry of the double bond (*E* in **6** and *Z* in **7**) appeared inconsequential for the result, as is the ring size in **8** and **9**. The stereochemical course of the 2-oxa-5-hexenyl radical cyclizations (precursors **5–9**) in the formation of 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,[8] 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.



23

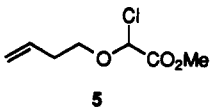
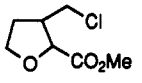
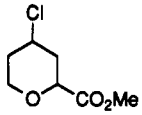
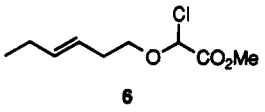
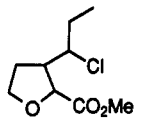
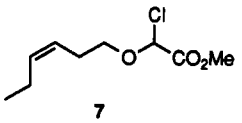
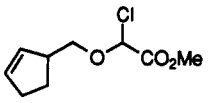
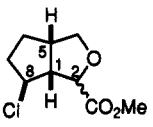
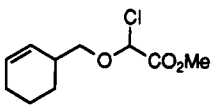
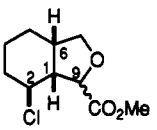
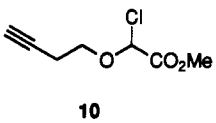
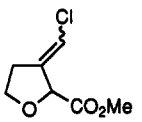
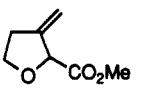
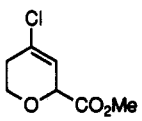
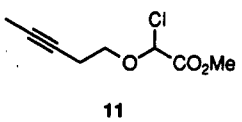
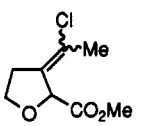
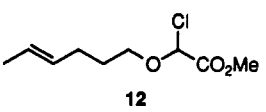
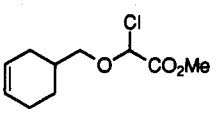
Both **16a** and **16b** were formed as about 1:1 mixtures of their diastereomers, showing little stereoselectivity in the delivery of the chlorine radical by the copper(II) intermediate. Cyclization to the bicyclic systems **17** and **18** showed high stereoselectivity for the formation of the products 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-*endo* cyclization products **15a** and **15b** were already known from ionic cyclization reactions.[5] 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

(7) A similar abstraction of hydrogen atoms from the solvent is described by Weinreb and co-workers in the Ru(II)-catalyzed radical cyclization of ethyl 2,2-dichloro-6-heptynoate with toluene or cumene as a solvent, see: Hayes, T. K.; Villani, R.; Weinreb, S. M. *J. Am. Chem. Soc.* **1988**, *110*, 5533.

(8) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.

Table 1. Cu(bpy)Cl-Catalyzed Cyclization of Radical Precursors 5–13

entry	substrate	products (yield)			
1	 **5**		**14a,b** (75%) cis/trans = 64:36		**15a,b** (7%)[a] cis/trans = 8:92
2	 **6**		**16a,b** (87%) cis/trans = 57:43		
3	 **7**		**16a,b** (95%) cis/trans = 58:42		
4	 **8**		**17a,b** (95%) α/β = 82:18		
5	 **9**		**18a,b** (80%) α/β = 65:35		
6	 **10**		**19a,b** (64%)[b] E:Z = 70:30	 **20** (trace)[b]	 **21** (9%)[b]
7	 **11**		**22a,b** (80%) E:Z = 68:32		
8	 **12**				
9	 **13**				

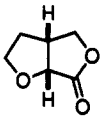
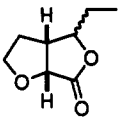
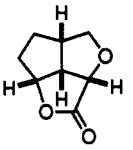
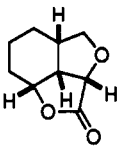
[a] Compound 15 could not be separated from 14. [b] Compounds 19–21 formed an inseparable mixture.

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 in 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-oxy)-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.[5] 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.[7]

As expected, regioselectivity for the cyclization of the 1,2-disubstituted acetylene **11** is much higher, with only

Table 2. Lactonization of Cyclization Products

entry	substrate	products	yield
1	**14a**	 **24**	98%
2	**16a** (30:70 mixture of isomers)	 **25** (α/β = 30:70)	95%
3	**17a**	 **26**	85%
4	**18a**	 **27**	46%

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_3SnH-mediated radical cyclizations of the corresponding phenylthio analogues of precursors **5-7** and **13**.[4a]

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.[9] Lactone **25** was formed as a 30:70 mixture of C-6 diastereomers, which clearly demonstrates a S_N2 substitution reaction of the carboxylate 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_N2 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.

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

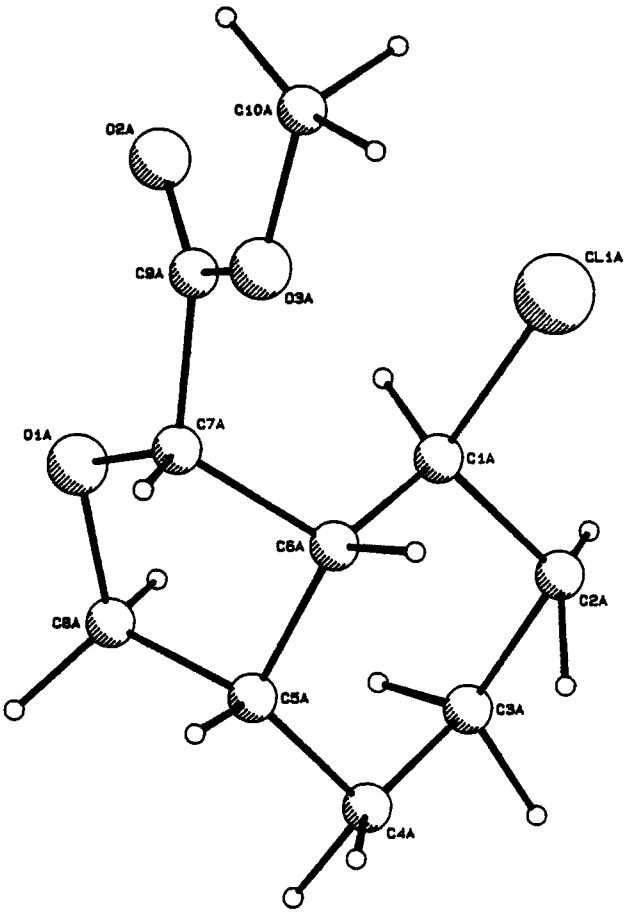
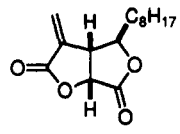


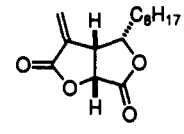
Figure 1. ORTEP diagram of **18a**.

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

(10) Isolation and structure of avenaciolide: (a) Brookes, D.; Tidd, B. K.; Turner, W. B. *J. Chem. Soc.* **1963**, 5385. (b) Ellis, J. J.; Stodola, F. H.; Vesonder, R. F.; Glass, C. A. *Nature (London)* **1964**, *203*, 1382. (c) Brookes, D.; Sternhell, S.; Tidd, B. K.; Turner, W. B. *Aust. J. Chem.* **1967**, *18*, 373. Synthesis of avenaciolide: (d) Parker, W. L.; Johnson, F. *J. Org. Chem.* **1973**, *38*, 2489; *J. Am. Chem. Soc.* **1969**, *91*, 7208. (e) Anderson, R. C.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1975**, *97*, 3870; *J. Org. Chem.* **1985**, *50*, 4781. (f) Herrmann, J. L.; Berger, M. H.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1979**, *101*, 1544; **1973**, *95*, 7923. (g) Schreiber, S. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1984**, *106*, 7200. (h) Kallmerten, J.; Gould, T. J. *J. Org. Chem.* **1985**, *50*, 1128. (i) Mikami, K.; Shimizu, M.; Nakai, T. *J. Org. Chem.* **1991**, *56*, 2952. (j) Burke, S. D.; Pacofsky, G. J.; Piscopio, A. D. *J. Org. Chem.* **1992**, *57*, 2228. (k) Snider, B. B.; McCarthy, B. A. *Tetrahedron* **1993**, *49*, 9447.



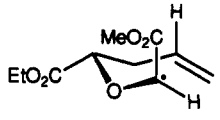
28
avenaciolide



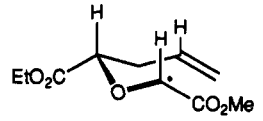
29
isoavenaciolide

compound **5**) was anticipated to serve as a handle to obtain the second lactone ring.

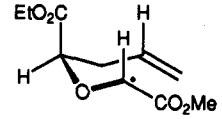
Under the usual conditions (30 mol % Cu(bpy)Cl, 80 °C, 2 days), the atom-transfer radical cyclization took place to give the desired 2,3-*cis*-substituted tetrahydrofurans **31a** and **31b** as the major products as a 1:1 mixture of C-5 isomers (Scheme 4). The 2,3-*trans*-substituted product **31c** was isolated as a single diastereomer. This latter selectivity may be explained by assuming a six-membered ring chair 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 chair transition state with the methyl ester in a pseudoequatorial position (**34**) and the ethyl ester in a pseudoequatorial position (**33**) leading to **31b**, or with 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 an 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.



32



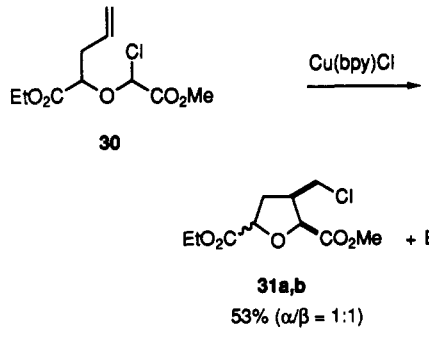
33



34

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,[10i,12] 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

Scheme 4



30

31a,b
53% (α/β = 1:1)

31c
25%

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 ^{13}C-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 Bu_3SnH (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 $Pb(OAc)_4$,[11e] which furnished the corresponding acetates **39** in 67% yield. Oxidation with *m*-CPBA[10g,13] (69–87% yield) 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[10d,f,g] (**40**) and normethyleneisoavenaciolide[11b–f] (**41**) were in complete agreement with those reported in literature.

Comparison of the Cu(I)-Catalyzed Cyclization with the Bu_3SnH-Mediated Radical Cyclization. The Bu_3SnH-mediated cyclization has been reported for the phenylthio analogues of **5-7**, **9**, and **11** (although ethyl esters 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.

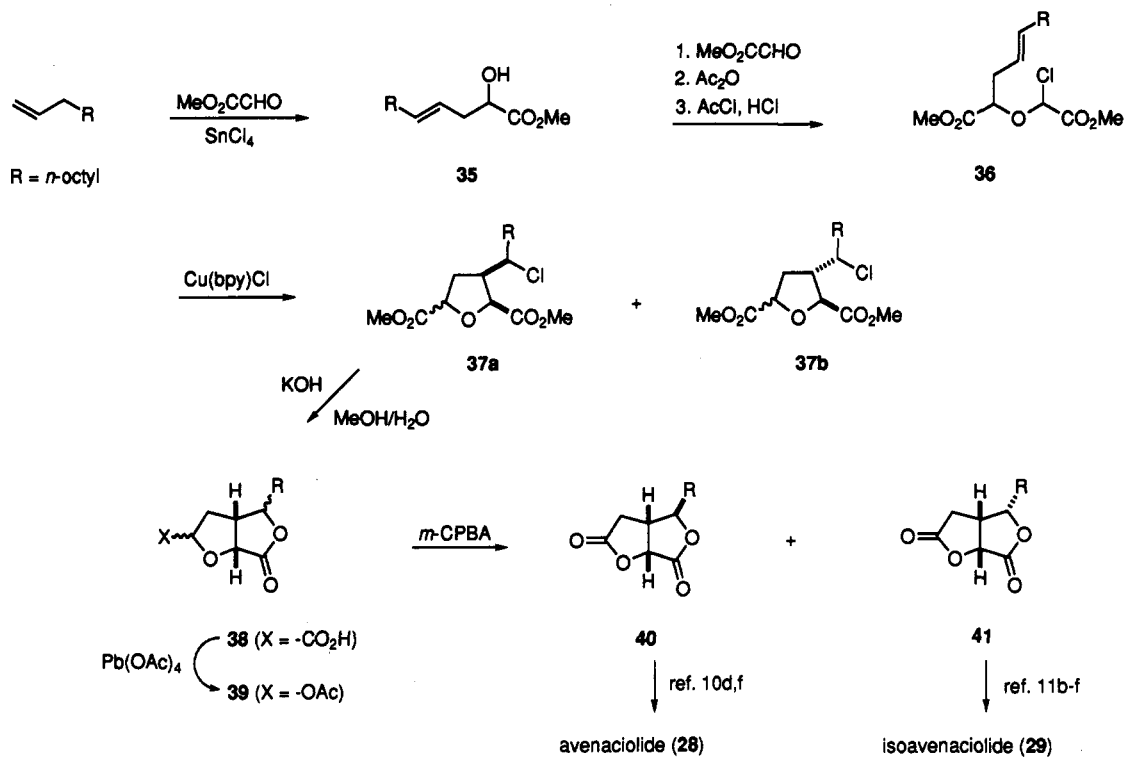
The great similarities in regiochemistry and stereochemistry for both types of cyclization strongly suggest that the mechanistic course of transition metal-catalyzed

(11) Isolation and structure of isoavenaciolide: (a) Aldridge, D. C.; Turner, W. B. *J. Chem. Soc. C* **1971**, 2431. Synthesis of isoavenaciolide: (b) Yamada, K.; Kato, M.; Iyoda, M.; Hirata, Y. *J. Chem. Soc., Chem. Commun.* **1973**, 499. (c) Damon, R. H.; Schlessinger, R. H. *Tetrahedron Lett.* **1975**, 4551. (d) Anderson, R. C.; Fraser-Reid, B. *Tetrahedron Lett.* **1977**, 2865; *J. Org. Chem.* **1985**, *50*, 4781. (e) Murai, A.; Takahashi, K.; Taketsuru, H.; Masamune, T. *J. Chem. Soc., Chem. Commun.* **1981**, 221. (f) Wee, A. G. H. *Tetrahedron* **1990**, *46*, 5065.

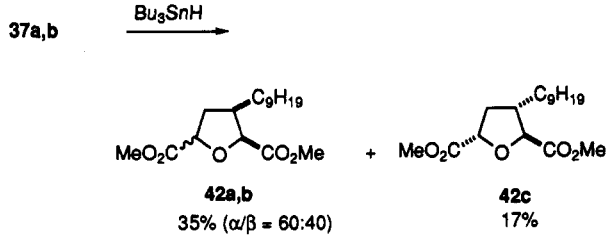
(12) Whitesell, J. K.; Bhattacharya, A.; Buchanan, C. M.; Chen, H. H.; Deyo, D.; James, D.; Liu, C-L.; Minton, M. A. *Tetrahedron* **1986**, *42*, 2993.

(13) Grieco, P. A.; Oguri, T.; Yokoyama, Y. *Tetrahedron Lett.* **1978**, *5*, 419.

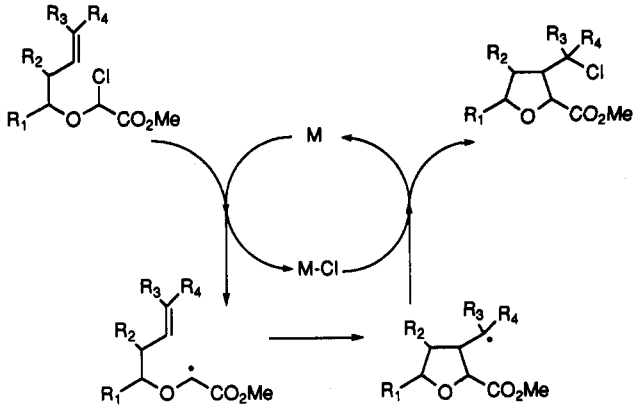
Scheme 5



Scheme 6



Scheme 7



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[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,[2e] resulting in relatively mild cyclization conditions.

Conclusions

In conclusion, we have shown that, when heated with Cu(bpy)Cl, 2-(3-alken-1-oxy)-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.[3c] 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.[15] 2,2'-Bipyridine (bpy) was commercially available. 3-Pentynol and (*E*)-4-hexenol were commercially available. 3-(Hydroxymethyl)cyclopentene was prepared according to a literature procedure.[16] The acetates used for the preparation of chlorides **5-7**, **9**, **10**, **13**, and **30** were prepared as described in our earlier papers.[5] 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 (1.25 g, 12.8 mmol) was treated with methyl glyoxylate[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)

(14) Viehe, H. G.; Janousek, Z.; Merényi, R. *Acc. Chem. Res.* **1985**, *18*, 148.

(15) Keller, R. N.; Wycoff, H. D. *Inorg. Synth.* **1946**, *2*, 1.

(16) Chapman, O. L.; Mattes, K. C.; Sheridan, R. S.; Klun, J. *J. Am. Chem. Soc.* **1978**, *100*, 4878.

(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.

and acetic anhydride (1.81 mL, 19.1 mmol) in 13 mL of pyridine for 3 h. The reaction mixture was evaporated with toluene (3 times) and the residue was chromatographed to give methyl 2-[(cyclopent-2-enylmethyl)oxy]-2-acetoxyacetate (1.831 g, 8.03 mmol, 63%) as a colorless oil: R_f 0.35 (EtOAc/hexane 1:6); IR ($CHCl_3$) 3020, 2950, 1750, 1435, 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); ^{13}C NMR (50 MHz, mixture of two diastereomers) 20.8, 26.4, 31.8, 45.7, 45.8, 52.7, 74.0, 74.1, 92.8, 130.96, 130.98, 132.71, 132.75, 166.3, 169.9.

Methyl 2-(3-Pentyn-1-oxy)-2-acetoxyacetate. 3-Pentynol (1.50 g, 17.8 mmol) was treated with methyl glyoxylate[17] (2.20 g, 25 mmol) in 9 mL of dichloromethane. After stirring for 18 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 with toluene (3 times) and the residues was chromatographed to give methyl 2-(3-pentyn-1-oxy)-2-acetoxyacetate (2.85 g, 13.3 mmol, 75%) as a colorless oil: R_f 0.40 (EtOAc/hexane 1:3); IR ($CHCl_3$) 3020, 2950, 1750, 1435, 1370; ^1H NMR (200 MHz) 1.71 (t, J = 2.5 Hz, 3H), 2.11 (s, 3H), 2.35–2.50 (m, 2H), 3.75 (s, 3H), 3.60–3.85 (m, 2H), 5.95 (s, 1H).

Methyl 2-((*E*)-4-Hexen-1-oxy)-2-acetoxyacetate. (*E*)-4-Hexenol (1.20 g, 12 mmol) was treated with methyl glyoxylate[17] (2.11 g, 24 mmol) in 6 mL of dichloromethane. After stirring for 1.5 h, the mixture was concentrated in vacuo and treated with DMAP (147 mg, 1.2 mmol) and acetic anhydride (2.27 mL, 24 mmol) in 10 mL of pyridine for 3 h. The reaction mixture was evaporated with toluene (3 times) and the residue was chromatographed to give methyl 2-((*E*)-4-hexen-1-oxy)-2-acetoxyacetate (1.716 g, 7.45 mmol, 62%) as a colorless oil: R_f 0.50 (EtOAc/hexane 1:4); IR ($CHCl_3$) 3020, 2950, 1755, 1435, 1370; ^1H NMR (200 MHz) 1.60-1.71 (m, 5H), 1.98–2.10 (m, 2H), 2.14 (s, 3H), 3.59–3.78 (m, 2H), 3.78 (s, 3H), 5.28–5.50 (m, 2H), 5.93 (s, 1H).

General Procedure for the Synthesis of α-Chloro Ethers. Freshly distilled acetyl 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 in the cyclization reactions.

Methyl 2-(3-Buten-1-oxy)-2-chloroacetate (5). A solution of methyl 2-(3-buten-1-oxy)-2-acetoxyacetate (1.184 g, 5.86 mmol) in 12 mL of ether and 12 mL of acetyl chloride was treated with hydrogen chloride gas at 0 °C for 0.5 h. Evaporation of the volatiles gave 5 (1.040 g, 5.84 mmol, 100%) as a light yellow oil: IR ($CHCl_3$) 3075, 2950, 1760, 1635, 1435, 1295; ^1H NMR (200 MHz) 2.37 (q, J = 6.8 Hz, 2H), 3.60 (dt, J = 9.5, 6.9 Hz, 1H), 3.77 (s, 3H), 3.95 (dt, J = 9.5, 6.9 Hz, 1H), 4.98–5.10 (m, 2H), 5.66–5.80 (m, 1H), 5.78 (s, 1H); ^{13}C NMR (50 MHz) 32.8, 52.9, 69.5, 88.2, 117.2, 133.4, 165.4.

Methyl 2-((*E*)-3-Hexen-1-oxy)-2-chloroacetate (6). A solution of methyl 2-((*E*)-3-hexen-1-oxy)-2-acetoxyacetate (1.173 g, 5.10 mmol) in 15 mL of ether and 40 mL of acetyl chloride was treated with hydrogen chloride gas at 0 °C for 0.5 h. Evaporation of the volatiles gave 6 (1.044 g, 5.06 mmol, 100%) as a light yellow oil: IR ($CHCl_3$) 3020, 2955, 2870, 1750, 1455, 1435, 1295; ^1H NMR (250 MHz) 0.94 (t, J = 7.4 Hz, 3H), 1.92–2.07 (m, 2H), 2.36 (qd, J = 6.8, 0.7 Hz, 2), 3.59 (dt, J = 9.5, 7.1 Hz, 1H), 3.84 (s, 3H), 3.95 (dt, J = 9.5, 7.1 Hz, 1H), 5.31–5.43 (m, 1H), 5.50–5.63 (m, 1H), 5.82 (s, 1H).

Methyl 2-((*Z*)-3-Hexen-1-oxy)-2-chloroacetate (7). A solution of methyl 2-((*Z*)-3-hexen-1-oxy)-2-acetoxyacetate (1.621 g, 7.048 mmol) in 15 mL of ether and 15 mL of acetyl chloride was treated with hydrogen chloride gas at 0 °C for 0.5 h. Evaporation of the volatiles gave 7 (1.303 g, 6.31 mmol, 90%) as a light yellow oil: IR ($CHCl_3$) 2960, 2880, 1760, 1455, 1435, 1300; ^1H NMR (250 MHz) 0.95 (t, J = 7.6 Hz, 3H), 1.97-2.12 (m, 2H), 2.42 (q, J = 7.0 Hz, 2H), 3.57 (dt, J = 9.5, 7.1 Hz, 1H), 3.84 (s, 3H), 3.95 (dt, J = 9.4, 7.1 Hz, 1H), 5.25–5.35 (m, 1H), 5.44–5.52 (m, 1H), 5.82 (s, 1H).

Methyl 2-[(Cyclopent-2-enylmethyl)oxy]-2-chloroacetate (8). A solution of methyl 2-[(cyclopent-2-enylmethyl)oxy]-2-acetoxyacetate (678 mg, 2.97 mmol) in 4.2 mL of ether and 4.2 mL of acetyl chloride was treated with hydrogen chloride gas at 0 °C for 0.5 h. Evaporation of the volatiles gave 8 (608.2 mg, 2.97 mmol, 100%) as a light yellow oil: IR ($CHCl_3$) 3020, 2950, 2850, 1755, 1435, 1295; ^1H NMR (200 MHz, mixture of two diastereomers) 1.48–1.62 (m, 1H), 1.96–2.15 (m, 1H), 2.25–2.50 (m, 2H), 2.95–3.15 (m, 1H), 3.47 (dt, J = 9.1, 6.6 Hz, 1H), 3.82–3.92 (m, 1H), 3.84 (s, 3H), 5.61–5.68 (m, 1H), 5.81–5.84 (m, 1H), 5.81 (s) and 5.82 (s, 1H).

Methyl 2-[(Cyclohex-2-enylmethyl)oxy-2-chloroacetate (9). A solution of methyl 2-[(cyclohex-2-enylmethyl)oxy]-2-acetoxyacetate (1.110 g, 4.581 mmol) in 7 mL of ether and 6.5 mL of acetyl 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 light yellow oil: IR ($CHCl_3$) 3020, 2930, 1760, 1435, 1295; ^1H NMR (200 MHz, mixture of two diastereomers) 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), 5.75–5.83 (m, 1H), 5.83 (s) and 5.84 (s, 1H); ^{13}C NMR (50 MHz, mixture of two diastereomers) 20.18, 20.34, 24.95, 24.96, 25.29, 25.47, 34.56, 34.80, 52.92, 74.10, 74.19, 88.51, 88.61, 126.45, 126.50, 129.35, 129.45, 165.46.

Methyl 2-(3-Butyn-1-oxy)-2-chloroacetate (10). A solution of methyl 2-(3-butyn-1-oxy)-2-acetoxyacetate (700 mg, 3.50 mmol) in 7 mL of ether and 6.3 mL of acetyl chloride was treated with hydrogen chloride gas at 0 °C for 0.5 h. Evaporation of the volatiles gave 10 (565.0 mg, 3.20 mmol, 91%) as a light yellow oil: IR ($CHCl_3$) 3300, 3020, 2955, 2115, 1755, 1435, 1295; ^1H NMR (200 MHz) 1.99 (t, J = 2.7 Hz, 1H), 2.53 (td, J = 7.0, 2.6 Hz, 2H), 3.70 (dt, J = 9.5, 7.1 Hz, 1H), 3.79 (s, 3H), 4.01 (dt, J = 9.6, 6.8 Hz, 1H), 5.84 (s, 1H).

Methyl 2-(3-Pentyn-1-oxy)-2-chloroacetate (11). A solution of methyl 2-(3-pentyn-1-oxy)-2-acetoxyacetate (700 mg, 3.27 mmol) in 6.5 mL of ether and 5.85 mL of acetyl chloride was treated with hydrogen chloride gas at 0 °C for 0.5 h. Evaporation of the volatiles gave 11 (604.2 mg, 3.17 mmol, 97%) as a light yellow oil: IR ($CHCl_3$) 3020, 2950, 1760, 1435, 1295; ^1H NMR (200 MHz) 1.75 (t, J = 2.5 Hz, 3H), 2.45–2.55 (m, 2H), 3.69 (dt, J = 9.5, 7.4 Hz, 1H), 3.84 (s, 3H), 4.01 (dt, J = 9.5, 6.9 Hz, 1H), 5.88 (s, 1H).

Methyl 2-((*E*)-4-Hexen-1-oxy)-2-chloroacetate (12). A solution of methyl 2-((*E*)-4-hexen-1-oxy)-2-acetoxyacetate (0.460 g, 2.0 mmol) in 4 mL of ether and 4 mL of acetyl chloride was treated with hydrogen chloride gas at 0 °C for 1 h. Evaporation of the volatiles gave 12 (0.408 g, 1.98 mmol, 100%) as a light yellow oil: IR ($CHCl_3$) 2940, 1755, 1435, 1295; ^1H NMR (200 MHz) 1.63 (d, J = 4.9 Hz, 3H), 1.65–1.79 (m, 2H), 2.01–2.11 (m, 2H), 3.58 (dt, J = 9.5, 6.6 Hz, 1H), 3.84 (s, 3H), 3.96 (dt, J = 9.5, 6.6 Hz, 1H), 5.30–5.55 (m, 2H), 5.81 (s, 1H).

Methyl 2-[(Cyclohex-3-enylmethyl)oxy]-2-chloroacetate (13). A solution of methyl 2-[(cyclohex-3-enylmethyl)oxy]-2-acetoxyacetate (1.19 g, 4.91 mmol) in 10 mL of ether and 9 mL of acetyl chloride was treated with hydrogen chloride gas at 0 °C for 0.5 h. Evaporation of the volatiles gave 13 (1.07 g, 4.91 mmol, 100%) as a light yellow oil: IR ($CHCl_3$) 3020, 2920, 2830, 1760, 1435, 1295; ^1H NMR (200 MHz, mixture of two diastereomers) 1.20–1.45 (m, 1H), 1.65–2.25 (m, 6H), 3.42–3.52 (m, 1H), 3.84 (s, 3H), 3.81–3.90 (m, 1H), 5.65 (br s, 2H), 5.81 (s) and 5.82 (s, 1H).

General Procedure for the Cuprous Chloride-Catalyzed Cyclization. To a solution of the precursor in 1,2-dichloroethane (0.3 M) in a dry nitrogen atmosphere were added first 0.3 equiv of 2,2′-bipyridine (bpy) and then 0.3 equiv of CuCl. The resulting clear, reddish brown solution was heated under reflux for at least 18 h. The crude reaction mixture was directly brought on a column for flash chromatography.

Cyclization of 5. To a solution of 5 (10.84 g, 60.90 mmol) in 120 mL of 1,2-dichloroethane were added bpy (2.85 g, 18.3 mmol) and CuCl (1.81 g, 18.3 mmol). The reaction mixture was heated under reflux for 2 days and concentrated in vacuo. The residue was chromatographed to give two fractions.

The first fraction consisted of an 83:17 mixture (according to ^1H NMR) of **(2*R**,3*R**)- and (2*R**,3*S**)-2-carbomethoxy-3-(chloromethyl)tetrahydrofuran (14a and 14b)** as a colorless oil (5.42 g, 30.4 mmol, 50%): R_f 0.30 and 0.25 (EtOAc/hexane 1:6); IR ($CHCl_3$) 2950, 2890, 1745, 1435. Careful flash chromatography gave a sample of **14a**: IR 2950, 2880, 1740, 1435, 1370, 1290; ^1H NMR (200 MHz) 1.98 (dq, J = 12.5, 7.9 Hz, 1H), 2.23

(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), 4.51 (d, J = 7.5 Hz, 1H); ^{13}C NMR (63 MHz) 29.77, 43.40, 45.06, 51.83, 68.13, 78.58, 171.11; HRMS calcd for $C_7H_{11}O_3Cl$ 178.0397, found 178.0395. Spectroscopic data derived from the mixture of diastereomers for **14b**: ^{1}H NMR (200 MHz) 1.79–1.96 (m, 1H), 2.12–2.20 (m, 1H), 2.66–2.84 (m, 1H), 3.59 (dd, J = 11.1, 6.7 Hz, 1H), 3.71 (dd, J = 11.1, 6.0 Hz), 3.76 (s, 3H), 3.98–4.05 (m, 2H), 4.29 (d, J = 5.6 Hz, 1H); ^{13}C NMR (63 MHz) 29.99, 45.96, 46.16, 52.16, 68.70, 79.28, 172.56.

The second fraction consisted of a 78:22 mixture (according to ^{1}H NMR) of **14** and **2-carbomethoxy-4-chlorotetrahydropyran**[5] **(15)** (3.43 g, 19.3 mmol, 32%). According to ^{1}H NMR, **14a:14b** = 27:73. Compound **15** consisted of a mixture of **(2*R**,4*S**)-2-carbomethoxy-4-chlorotetrahydropyran**[5] **(15a)** and **(2*R**,4*R**)-2-carbomethoxy-4-chlorotetrahydropyran**[5] **(15b)**. According to ^{1}H NMR, **15a:15b** = 8:92.

Cyclization of 6. To a solution of **6** (564 mg, 2.73 mmol) in 9.1 mL of 1,2-dichloroethane were added bpy (128 mg, 0.819 mmol) and CuCl (81.1 mg, 0.819 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 ^{1}H NMR) of diastereomers of **(2*R**,3*R**)-2-carbomethoxy-3-(1-chloropropyl)tetrahydrofuran (16a)** as a colorless oil (281.3 mg, 1.36 mmol, 50%): R_f 0.30 (EtOAc/hexane 1:4); IR ($CHCl_3$) 2970, 2950, 2890, 1740, 1455, 1435; ^{1}H NMR (200 MHz, mixture of two diastereomers) 1.05 and 1.06 (2 × t, J = 7.2 Hz, 3H), 1.62–2.30 (m, 4H), 2.69–2.88 (m, 1H), 3.75 (s, 3H), 3.71-4.05 (m, 2H), 4.20–4.30 (m, 1H), 4.48 (d, J = 8.1 Hz, 0.60H), 4.61 (d, J = 7.4 Hz, 0.40H); ^{13}C NMR (63 MHz, mixture of two diastereomers) 10.23, 10.91, 28.71, 28.77, 30.03, 31.13, 49.61, 50.68, 51.60, 51.83, 63.52, 64.05, 68.42, 69.02, 78.13, 79.34, 171.58, 171.63; HRMS calcd for $C_9H_{15}O_3Cl$ 206.0710, found 206.0729.

The second fraction consisted of a 56:44 mixture (according to ^{1}H NMR) of diastereomers of **(2*R**,3*S**)-2-carbomethoxy-3-(1-chloropropyl)tetrahydrofuran (16b)** as a colorless oil (211.7 mg, 1.02 mmol, 37%): R_f 0.20 (EtOAc/hexane 1:4); IR ($CHCl_3$) 2970, 2950, 2875, 1740, 1455, 1435; ^{1}H NMR (200 MHz, mixture of two diastereomers) 1.07 (t, J = 7.3 Hz, 3H), 1.67–2.23 (m, 4H), 2.58–2.71 (m, 0.56H), 2.74–2.91 (m, 0.44H), 3.75 (s) and 3.77 (s, 3H), 3.85–4.12 (m, 3H), 4.38 (d, J = 6.8 Hz, 0.56H), 4.48 (d, J = 5.1 Hz, 0.44 H); ^{13}C NMR (63 MHz, mixture of two diastereomers) 10.94, 11.24, 27.58, 29.59, 30.03, 30.47, 49.93, 51.97, 65.91, 66.63, 68.95, 79.00, 79.11, 172.86, 173.04; HRMS calcd for $C_9H_{15}O_3Cl$ 206.0710, found 206.0712.

Cyclization of 7. To a solution of **7** (547 mg, 2.65 mmol) in 8.8 mL of 1,2-dichloroethane were added bpy (124 mg, 0.795 mmol) and CuCl (78.7 mg, 0.795 mmol). The reaction mixture was heated under reflux for 18 h. Flash chromatography gave two fractions.

The first fraction consisted of a 59:41 mixture (according to ^{1}H NMR) of diastereomers of **16a** as a colorless oil (301 mg, 1.46 mmol, 55%): R_f 0.30 (EtOAc/hexane 1:4). The second fraction consisted of a 53:47 mixture (according to ^{1}H NMR) of diastereomers of **16b** as a colorless oil (216.8 mg, 1.05 mmol, 40%): R_f 0.20 (EtOAc/hexane 1:4).

Cyclization of 8. To a solution of **8** (236.1 mg, 1.155 mmol) in 3.85 mL of 1,2-dichloroethane were added bpy (54.1 mg, 0.347 mmol) and CuCl (34.3 mg, 0.347 mmol). The reaction mixture was heated under reflux for 2 days. Flash chromatography gave two fractions.

The first fraction consisted of a 62:38 mixture (according to ^{1}H NMR) of **(1*R**,2*R**,5*R**,8*R**)-2-carbomethoxy-8-chloro-3-oxabicyclo[3.3.0]octane (17a)** and **(1*R**,2*S**,5*R**,8*R**)-2-carbomethoxy-8-chloro-3-oxabicyclo[3.3.0]octane (17b)** as a colorless oil (107 mg, 0.524 mmol, 45%): R_f 0.25 and 0.20 (EtOAc/hexane 1:6). Careful flash chromatography (EtOAc/hexane 1:10) of this mixture gave a sample of **17b**: R_f 0.25 (1:6); IR ($CHCl_3$) 2950, 2870, 1740, 1435; ^{1}H NMR (200 MHz) 1.54–1.62 (m, 1H), 1.93–2.35 (m, 3H), 2.93–3.09 (m, 2H), 3.68 (dd, J = 3.1, 9.1 Hz, 1H), 3.76 (s, 3H), 4.11 (d, J = 3.8 Hz, 1H), 4.16 (dd, J = 6.8, 9.1 Hz, 1H), 4.27–4.33 (m, 1H); ^{13}C NMR (50 MHz) 30.01, 35.83, 42.28, 52.18, 59.65, 64.83, 76.17, 81.63, 171.98; HRMS calcd for $C_9H_{13}O_3Cl$ 204.0553, found 204.0540.

The second fraction consisted of **17a** as a colorless oil (117 mg, 0.577 mmol, 50%): R_f 0.20 (EtOAc/hexane 1:6); IR ($CHCl_3$) 2950, 2870, 1745, 1435; ^{1}H NMR (300 MHz) 1.43–1.54 (m, 1H), 1.75–1.84 (m, 1H), 2.02–2.23 (m, 2H), 2.86–2.96 (m, 1H), 3.08 (ddd, J = 4.7, 7.0, 9.0, 1H), 3.72 (dd, J = 6.8, 9.3 Hz, 1H), 3.77 (s, 3H), 3.81 (dd, J = 2.6, 9.2 Hz, 1H), 3.99 (dt, J = 6.4, 5.0 Hz, 1H), 4.27 (d, J = 7.0 Hz, 1H); ^{13}C NMR (50 MHz) 30.40, 37.42, 42.64, 51.78, 56.86, 60.68, 74.76, 79.45, 169.73; HRMS calcd for $C_9H_{13}O_3Cl$ 204.0553, found 204.0516.

Cyclization of 9. To a solution of **9** (922 mg, 4.22 mmol) in 14.1 mL of 1,2-dichloroethane were added bpy (198 mg, 1.27 mmol) and CuCl (126 mg, 1.27 mmol). The reaction mixture was heated under reflux for 18 h. Flash chromatography gave three fractions.

The first fraction consisted of **(1*R**,2*R**,6*R**,9*S**)-9-carbomethoxy-2-chloro-8-oxabicyclo[4.3.0]nonane (18b)** (238 mg, 1.09 mmol, 26%), contaminated with a third isomer. **18b**: R_f 0.25 (EtOAc/hexane 1:4); IR ($CHCl_3$) 3000, 2950, 2850, 1740, 1445, 1435; ^{1}H NMR (200 MHz) 1.23–1.82 (m, 5H), 2.04–2.17 (m, 1H), 2.47–2.70 (m, 2H), 3.72 (t, J = 8.1 Hz, 1H), 3.76 (s, 3H), 3.99–4.08 (m, 1H), 4.09 (t, J = 7.9 Hz, 1H), 4.53 (d, J = 3.4 Hz, 1H); ^{13}C NMR (50 MHz) 20.26, 23.20, 33.60, 36.97, 52.09, 52.34, 58.78, 71.55, 79.78, 172.84; HRMS calcd for $C_{10}H_{15}O_3Cl$ 218.0710, found 218.0732. Characteristic signals for the third isomer: ^{1}H NMR (200 MHz) 4.46 (d, J = 8.7 Hz, OCH); ^{13}C NMR (50 MHz) 24.03, 25.46, 31.98, 41.17, 48.83, 52.18, 57.91, 75.08, 76.77, 173.15.

The second fraction consisted of a 73:27 mixture (according to ^{1}H NMR) of **18a** and **18b** (57 mg, 0.261 mmol, 6%) as a colorless oil.

The third fraction consisted of **(1*R**,2*R**,6*R**,9*R**)-9-carbomethoxy-2-chloro-8-oxabicyclo[4.3.0]nonane (18a)** (439 mg, 2.01 mmol, 48%) as a white solid. Recrystallization from diispropyl ether gave white crystals, mp 87.5–88 °C: R_f 0.15 (EtOAc/hexane 1:4); IR ($CHCl_3$) 3000, 2950, 2890, 2860, 1740, 1470, 1445, 1435; ^{1}H NMR (200 MHz) 1.40–1.75 (m, 5H), 2.05–2.16 (m, 1H), 2.59–2.80 (m, 2H), 3.76 (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); ^{13}C NMR (50 MHz) 20.26, 23.22, 35.47, 39.41, 50.99, 52.10, 55.97, 69.97, 79.65, 171.04. Anal. Found: C, 54.77; H, 6.95. Calcd for $C_{10}H_{15}O_3Cl$: C, 54.92; H, 6.86. The X-ray crystal structure of this major isomer was determined (see Figure 1).[18]

Cyclization of 10. To a solution of **10** (556 mg, 3.15 mmol) in 10.5 mL of 1,2-dichloroethane were added bpy (147.6 mg, 0.94 mmol) and CuCl (93.5 mg, 0.94 mmol). The reaction mixture was heated under reflux for 18 h. Flash chromatography afforded an inseparable mixture of **2-carbomethoxy-3-(chloromethylene)tetrahydrofuran (19) and 2-carbomethoxy-4-chloro-5,6-dihydro-2*H*-pyran**[5] **(21)** as a colorless oil (404 mg, 2.29 mmol, 73%), which contained a trace of **2-carbomethoxy-3-methyleneterahydrofuran (20)**. According to ^{1}H NMR, **19:21** = 87:13 and **19a:19b** = 70:30. R_f: 0.36 (EtOAc/hexane 1:4). IR ($CHCl_3$): 3080, 3010, 2955, 2890, 1745, 1660, 1435, 1340.

Data derived from this mixture for **19a**: ^{1}H NMR (250 MHz) 2.66–2.79 (m, 2H), 3.74 (s, 3H), 4.04–4.31 (m, 2H), 4.87 (d, J = 1.6 Hz, 1H), 6.27 (dt, J = 2.2, 2.6 Hz, 1H); ^{13}C NMR (50 MHz) 30.42, 52.23, 68.21, 77.90, 112.40, 140.17, 170.39.

Data derived from this mixture for **19b**: ^{1}H NMR (250 MHz) 2.55–2.80 (m, 2H), 3.73 (s, 3H), 4.00–4.15 (m, 2H), 5.01 (s, 1H), 6.10 (dt, J = 2.0, 2.1 Hz, 1H); ^{13}C NMR (50 MHz) 31.18, 52.02, 68.90, 78.20, 120.43, 140.13, 169.9.

Data derived from this mixture for **21**: ^{1}H NMR (250 MHz, in agreement with ref 5) 2.30–2.45 (m, 2H), 3.74 (s, 3H), 3.80–4.00 (m, 2H), 4.73 (q, J = 2.7 Hz, 1H), 5.98 (dt, J = 3.1, 1.6 Hz, 1H); ^{13}C NMR (50 MHz) 32.00, 52.12, 62.71, 72.88, 111.85, 150 (C=O not observed).

Characteristic signals for **20**: ^{1}H NMR (250 MHz) 4.79 (bs, 1H, OCH), 5.14 (q) and 5.23 (q, J = 2.2 Hz, 2H, =CH_2); ^{13}C NMR (50 MHz) 107.73 (=CH_2), 131 (*C*=CH_2).

Cyclization of 11. To a solution of **11** (480 mg, 2.52 mmol) in 8.4 mL of 1,2-dichloroethane were added bpy (118 mg, 0.76 mmol) and CuCl (75.2 mg, 0.76 mmol). The reaction mixture

(18) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

was heated under reflux for 18 h. Flash chromatography gave two fractions.

The first fraction consisted of **(*E*)-2-carbomethoxy-3-(1-chloroethylidene)tetrahydrofuran (22a)** as a colorless oil (245 mg, 1.29 mmol, 51%): R_f 0.35 (EtOAc/hexane 1:4); IR ($CHCl_3$) 3000, 2950, 2895, 1735, 1680, 1435, 1380, 1325; ^1H NMR (200 MHz) 2.17–2.20 (m, 3H), 2.60–2.80 (m, 2H), 3.75 (s, 3H), 4.03–4.14 (m, 1H), 4.23 (q, J = 8.0 Hz, 1H), 4.95 (s, 1H); ^1H NMR (C_6D_6, 200 MHz) 1.88–1.91 (m, 3H), 2.38–2.47 (m, 2H), 3.16 (s, 3H), 3.68–3.79 (m, 1H), 4.16 (q, J = 8.1 Hz, 1H), 4.77 (s, 1H); ^{13}C NMR (63 MHz) 23.61, 31.88, 51.98, 68.45, 77.83, 125.47, 133.59, 170.85; HRMS calcd for $C_8H_{11}O_3Cl$ 190.0397, found 190.0379.

The second fraction consisted of a 12:88 mixture (according to ^1H NMR) of **22a and 22b** as a colorless oil (141 mg, 0.740 mmol, 29%): IR ($CHCl_3$) 2950, 1735, 1685, 1430, 1275, 1240; HRMS calcd for $C_8H_{11}O_3Cl$ 190.0397, found 190.0379. Data derived from this mixture for **(*Z*)-2-carbomethoxy-3-(1-chloroethylidene)tetrahydrofuran (22b)**: R_f 0.30 (EtOAc/hexane 1:4); ^1H NMR (200 MHz) 2.14 (q, J = 1.4 Hz, 3H), 2.60–2.75 (m, 2H), 3.76 (s, 3H), 4.05–4.16 (m, 1H), 4.27 (q, J = 8.0 Hz, 1H), 4.99 (s, 1H); ^1H NMR (C_6D_6, 200 MHz) 1.61 (d, J = 1.3 Hz, 3H), 1.80–1.96 (m, 1H), 2.06–2.25 (m, 1H), 3.33 (s, 3H), 3.72 (td, J = 8.1, 5.0 Hz, 1H), 4.15 (q, J = 7.8 Hz, 1H), 5.16 (s, 1H); ^{13}C NMR (63 MHz) 23.69, 30.82, 52.00, 69.37, 79.64, 123.52, 133.71, 170.57.

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 bpy (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 ^1H-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.

Attempted Cyclization of 13. To a solution of **13** (141.8 mg, 0.65 mmol) in 2.16 mL of 1,2-dichloroethane were added bpy (33.5 mg, 0.21 mmol) and CuCl (25.0 mg, 0.25 mmol). The reaction mixture was heated under reflux for 18 h. A ^1H-NMR spectrum of the crude reaction mixture (110 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 **(1*R**,5*R**)-2,7-dioxabicyclo[3.3.0]oct-8-one (24)** as a colorless oil (31.6 mg, 0.504 mmol, 98%): IR ($CHCl_3$) 2980, 2910, 2870, 1775, 1475, 1445, 1375; ^1H 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), 3.96–4.07 (m, 1H), 4.13 (dd, J = 3.1, 9.8 Hz, 1H), 4.50 (dd, J = 7.6, 9.8 Hz, 1H), 4.63 (d, J = 8.1 Hz, 1H); ^{13}C NMR (50 MHz) 32.87, 38.50, 68.78, 71.43, 77.63, 175.20; HRMS calcd for $C_6H_8O_3$ 128.0473, found 128.0463.

Saponification of 16a. A 30:70 mixture (according to ^1H NMR) of chlorine 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 a 30:70 mixture (according to ^1H NMR) of **(1*R**,5*R**,6*R**)-6-ethyl-2,7-dioxabicyclo[3.3.0]oct-8-one (25a) and (1*R**,5*R**,6*S**)-6-ethyl-2,7-dioxabicyclo[3.3.0]oct-8-one (25b)** as a colorless oil (87.9 mg, 0.563 mmol, 95%): IR ($CHCl_3$) 2970, 2870, 1770, 1460, 1370, 1355, 1190, 1085, 965, 905; ^1H NMR (200 MHz, mixture of two diastereomers) 1.01 (t, J = 7.4 Hz) and 1.05 (t, J = 7.7 Hz, 3H), 1.59–2.03 (m, 3H), 2.14–2.33 (m, 1H), 2.75–2.87 (m, 0.70H, **25b** H-5), 3.07–3.14 (m, 0.30H, **25a** H-5), 3.73–4.07 (m, 2H), 4.21 (dt, J = 3.5, 6.4 Hz, 0.60H, **25b** H-6), 4.45 (dt, J = 8.0, 6.0 Hz, 0.30H, **25a** H-6), 4.63 (d, J = 7.9 Hz, 0.70H, **25b** H-1), 4.76 (d, J = 8.0 Hz, 0.30H, **25a** H-1); ^{13}C NMR (50 MHz, mixture of two diastereomers) **25a** 10.00, 24.69, 25.40, 42.69, 69.72, 79.42, 79.92, 175.19; **25b** 9.13, 29.36, 32.72, 44.06, 68.61, 78.45, 85.85, 174.80; HRMS calcd for $C_8H_{12}O_3$ 156.0786, found 156.0790.

Saponification of 17a. A mixture of 113.2 mg of **17a** (0.553 mmol) and 46 mg of lithium hydroxide monohydrate in 2.2 mL of methanol and 0.44 mL of water was heated under reflux for 16 h. Workup afforded lactone **26** (72 mg, 0.47 mmol, 85%) as a colorless oil: IR ($CHCl_3$) 2970, 2870, 1775, 1455, 1430, 1350, 1235, 1185, 1110, 1085, 1010, 990, 935; ^1H NMR (250 MHz) 1.49–1.66 (m, 1H), 1.75–1.91 (m, 1H), 2.00 (dt, J = 13.4, 7.2 Hz, 1H), 2.20 (dd, J = 6.4, 14.0 Hz, 1H), 2.83–2.92 (m, 1H), 3.48 (dt, J = 6.6, 9.2 Hz, 1H), 3.84 (dd, J = 2.6, 8.9 Hz, 1H), 3.98 (dd, J = 5.8, 8.9 Hz, 1H), 4.60 (d, J = 9.0 Hz, 1H), 4.98 (t, J = 5.6 Hz, 1H); ^{13}C NMR (63 MHz) 28.48, 35.31, 46.74, 50.55, 75.21, 78.80, 83.78, 174.83; HRMS calcd for $C_8H_{10}O_3$ 154.0630, found 154.0651.

Saponification of 18a. A mixture of 34 mg of **18a** (0.155 mmol) and 13 mg of lithium hydroxide monohydrate in 0.62 mL of methanol and 0.12 mL of water was heated under reflux for 16 h. Workup and flash chromatography afforded lactone **27** as a colorless oil (12 mg, 0.071 mmol, 46%): R_f 0.35 (EtOAc/hexane 2:1); IR ($CHCl_3$) 3000, 2940, 2855, 1770, 1475, 1445, 1430, 1355, 1285, 1190, 1155, 1085, 1030, 980, 950; ^1H NMR (200 MHz) 1.38–1.75 (m, 5H), 2.18–2.28 (m, 1H), 2.35–2.54 (m, 1H), 2.93 (dt, J = 10.0, 7.7 Hz, 1H), 3.31 (dd, J = 9.2, 11.9 Hz, 1H), 3.99 (t, J = 8.6 Hz, 1H), 4.71 (dt, J = 6.9, 2.6 Hz, 1H), 4.88 d, J = 8.3 Hz, 1H); ^{13}C NMR (50 MHz) 12.91, 21.39, 27.34, 34.32, 37.98, 70.90, 74.85, 80.65, 175.86; HRMS calcd for $C_9H_{12}O_3$ 168.0786, found 168.0795.

Methyl 2-(1-carbethoxy-3-buten-1-oxy)-2-chloroacetate (30). According to the general procedure, a solution of methyl 2-[(1-carbethoxy-3-buten-1-oxy]-2-acetoxyacetate (313.6 mg, 1.145 mmol) in 3 mL of ether and 3.25 mL of acetyl chloride was treated with hydrogen chloride gas at 0 °C for 0.5 h. The reaction mixture was stored at 4 °C for 5 days. Evaporation of the volatiles and flash chromatography gave two fractions. The first fraction consisted of **30** (120 mg, 0.481 mmol, 42%) as a light yellow oil: R_f 0.35 and 0.30 (EtOAc/hexane 1:10); IR ($CHCl_3$) 3070, 3020, 2980, 1750, 1635, 1435, 1365, 1295; ^1H NMR (200 MHz, 70:30 mixture of diastereomers) 1.28 (t, J = 7.2 Hz, 3H), 2.50–2.70 (m, 2H), 3.82 (s, minor isomer) and 3.86 (s, major isomer, 3H), 4.16–4.35 (m, 2H), 4.45–4.51 (m, 1H), 5.10–5.21 (m, 2H), 5.70–5.94 (m, 1H), 5.93 (s, 0.7H), 5.95 (s, 0.3H), ^{13}C NMR (50 MHz, mixture of two diastereomers) major isomer 14.1, 36.2, 53.1, 61.5, 75.9, 86.4, 118.6, 131.7, 165.2, 169.6; minor isomer 36.5, 61.3, 77.4, 86.3, 119.1, 131.4. The second fraction consisted of the starting acetate (125 mg, 0.456 mmol, 40%): R_f 0.20 (EtOAc/hexane 1:10).

Cyclization of 30. To a solution of **30** (113.1 mg, 0.4535 mmol) in 1.5 mL of 1,2-dichloroethane were added bpy (21 mg, 0.14 mmol) and CuCl (13.5 mg, 0.14 mmol). The reaction mixture was heated under reflux for 2 days. Flash chromatography (EtOAc/hexane 1:10 to 1:3) gave four fractions.

The first fraction consisted of **(2*R**,3*R**,5*R**)-5-carbethoxy-2-carbomethoxy-3-(chloromethyl)tetrahydrofuran (31a)** as a colorless oil (22.3 mg, 0.089 mmol, 20%): R_f 0.15 (EtOAc/hexane 1:6); IR ($CHCl_3$) 3020, 2980, 2950, 1735, 1435, 1370; ^1H NMR (200 MHz) 1.28 (t, J = 7.1 Hz, 3H), 2.29–2.37 (m, 2H), 2.90–3.10 (m, 1H), 3.38 (dd, J = 8.4, 11.1 Hz, 1H), 3.58 (dd, J = 6.0, 11.1 Hz, 1H), 3.76 (s, 3H), 4.20 (q, J = 7.1 Hz, 2H), 4.77–4.84 (m, 2H); ^1H NMR (C_6D_6, 200 MHz), 0.86 (t, J = 7.1 Hz, 3H), 1.85–2.06 (m, 2H), 2.57–2.82 (m, 1H), 2.92 (dd, J = 8.2, 11.0 Hz, 1H), 3.17 (s, 3H), 3.14–3.20 (m, 1H), 3.86 (q, J = 7.1 Hz, 2H), 4.64 (d, J = 7.6 Hz, 1H), 4.72 (dd, J = 4.7, 7.9 Hz, 1H); ^{13}C NMR (50 MHz), 14.1, 33.6, 42.8, 43.9, 52.1, 61.3, 76.9, 79.4, 170.5, 172.1; HRMS calcd for $C_{10}H_{15}O_5Cl$ 250.0608, found 250.0614.

The second fraction consisted of a 55:45 mixture (according to ^1H NMR) of **31a** and **31c** (12 mg, 0.0479 mmol, 11%) as a colorless oil: R_f 0.15 and 0.10 (EtOAc/hexane 1:6).

The third fraction consisted of **(2*R**,3*S**,5*S**)-5-carbethoxy-2-carbomethoxy-3-(chloromethyl)tetrahydrofuran (31c)** as a colorless oil (23 mg, 0.0918 mmol, 20%): R_f 0.10 (EtOAc/hexane 1:6); IR ($CHCl_3$) 3020, 2970, 2950, 1740, 1435, 1370; ^1H NMR (250 MHz) 1.27 (t, J = 7.1 Hz, 3H), 2.02 (dt, J = 13.1, 6.6 Hz, 1H), 2.57 (dt, J = 13.1, 8.3 Hz, 1H), 2.70–2.84 (m, 1H), 3.58 (dd, J = 7.0, 11.1 Hz, 1H), 3.71 (dd, J = 6.1, 11.1 Hz, 1H), 3.76 (s, 3H), 4.21 (q, J = 7.1 Hz, 2H), 4.53 (d, J = 5.8 Hz, 1H), 4.72 (dd, J =

7.0, 8.2 Hz, 1H); ^{13}C NMR (63 MHz) 14.1, 33.7, 45.2, 45.9, 52.3, 61.3, 77.3, 80.2, 171.5; HRMS calcd for $C_{10}H_{15}O_5Cl$ 250.0608, found 250.0614.

The fourth fraction consisted of **(2*R**,3*R**,5*S**)-5-carbethoxy-2-carbomethoxy-3-(chloromethyl)tetrahydrofuran (31b)** as a colorless oil (31.3 mg, 0.125 mmol, 28%), contaminated with a fourth isomer. **31b**: R_f 0.05 (EtOAc/hexane 1:6); IR ($CHCl_3$) 3020, 2970, 2950, 1735, 1435, 1370; ^{1}H NMR (300 MHz) 1.30 (t, J = 7.1 Hz, 3H), 2.20 (dt, J = 12.9, 8.9 Hz, 1H), 2.56 (dt, J = 12.9, 7.6 Hz, 1H), 2.89–3.00 (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); ^{1}H NMR (C_6D_6, 200 MHz) 0.95 (t, J = 7.2 Hz, 3H), 1.87–1.97 (m, 1H), 2.04–2.28 (m, 2H), 3.10 (dd, J = 7.7, 11.0 Hz, 1H), 3.19 (s, 3H), 3.28 (dd, J = 6.8, 11.0 Hz, 1H), 3.97 (q, J = 7.1 Hz, 2H), 4.19–4.27 (m, 1H), 4.25 (d, J = 7.2 Hz, 1H); ^{13}C NMR (63 MHz) 14.2, 33.1, 42.6, 45.3, 52.1, 61.3, 77.6, 79.5, 170.2, 170.9; MS (EI) 250 (M^+, 2), 249 (5), 209 (9), 193 (18), 177 (10), 149 (15), 135 (34.5), 133 (100); HRMS (M^+ – 1) calcd for $C_{10}H_{14}O_5Cl$ 249.0530, found 249.0518. Characteristic signals derived from this mixture for the fourth diastereomer: ^{1}H NMR (300 MHz) 4.44 (d, J = 6.4 Hz, H-2); ^{13}C NMR (63 MHz) 77.86 and 80.10 (C-2 and C-5).

Methyl (4*E*)-2-Hydroxy-4-tridecenoate (35). To a solution of freshly distilled methyl glyoxylate[17] (5.28 g, 60 mmol) in dichloromethane (300 mL) was added at –78 °C a precooled solution (–78 °C) of 1-undecene (18.52 g, 120 mmol) in dichloromethane (120 mL). Then, freshly distilled tin tetrachloride (7.0 mL, 15.63 g, 60 mmol) was added to the mixture in 15 min. After the solution was stirred at –78 °C for 3 h, ether (200 mL) was added and the reaction mixture was stirred at room temperature for 18 h. The mixture was poured out in a saturated aqueous sodium bicarbonate solution (200 mL). The water layer was extracted with dichloromethane (2 × 200 mL), and the combined organic layers were washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, and concentrated in vacuo. Flash chromatography afforded **35** (11.07 g, 45.69 mmol, 76%) as a colorless oil: R_f 0.45 (EtOAc/hexane 1:4); according to ^{13}C NMR, *E*:*Z* = about 95:5; IR ($CHCl_3$) 3540 (OH), 3000, 2950, 2925, 2850, 1730, 1455, 1435; ^{1}H NMR (200 MHz) 0.85 (t, J = 6.7 Hz, 3H, alkyl-CH_3), 1.25 (bs, 12H, CH_2), 1.91–2.01 (m, 2H), 2.30–2.55 (m, 2H, =CHCH_2CH), 2.88 (d, J = 5.9 Hz, 1H, OH), 3.74 (s, 3H, OCH_3), 4.17–4.23 (m, 1H, C*H*OH), 5.25–5.65 (m, 2H, CH=CH): ^{13}C NMR (63 MHz, mixture of *E* and *Z* isomers) *E* isomer 14.0 (alkyl-CH_3), 22.6, 29.1, 29.2, 29.3, 29.4, 31.8, 32.5 (CH_2), 37.6 (CH_2CHOH), 52.2 (OCH_3), 70.4 (CHOH), 123.3 (=C-alkyl), 135.2 (*C*=C-alkyl), 174.8 (C=O); *Z*-isomer; characteristic signals 122.6 and 133.9; HRMS calcd for $C_{14}H_{26}O_3$ 242.1882, found 242.1891.

Methyl 2-(1-Carbomethoxy-3-dodecen-1-oxy)-2-acetoxyacetate. Alcohol **35** (1.50 g, 6.19 mmol) was treated with methyl glyoxylate[17] (1.01 g, 11.48 mmol) in dichloromethane (3.1 mL). The mixture was heated at reflux for 4 h and stirred at room temperature for 18 h. Treatment with DMAP (84 mg, 1.93 mmol) and acetic anhydride (0.97 mL, 10.3 mmol) in pyridine (6.8 mL) and flash chromatography afforded **methyl 2-[(3*E*)-1-carbomethoxy-3-dodecen-1-oxy]-2-acetoxyacetate** (1.43 g, 3.84 mmol, 62%) as a colorless oil: R_f 0.20 (EtOAc/hexane 1:6); IR ($CHCl_3$) 3020, 2930, 2850, 1755, 1435, 1370; ^{1}H NMR (250 MHz, 2:1 mixture of diastereomers) 0.80 (t, J = 6.9 Hz, 3H, alkyl-CH_3), 1.22 (s, 12H, CH_2), 1.85–2.00 (m, 2H), 2.10 (s, 3H, C(O)CH_3), 2.40–2.55 (m, 2H, CH_2CHO), 3.69 (s, minor isomer) and 3.70 (s, major isomer, 3H, OCH_3), 3.76 (s, minor isomer) and 3.79 (s, major isomer, 3H, OCH_3), 4.25–4.35 (m, 1H), 5.28–5.55 (m, 2H, CH=CH), 6.00 (s, minor isomer) and 6.01 (s, major isomer, 1H, CHOAc); ^{13}C NMR (50 MHz, mixture of two diastereomers) major isomer 14.0 (alkyl-CH_3), 20.6 (C(O)CH_3), 22.6, 29.1, 29.2, 29.3, 29.4, 31.8, 32.5 (CH_2), 35.5 (CH*C*H_2CH=), 52.0 and 52.8 (OCH_3), 77.6 (*C*HOCHOAc), 91.3 (CHO*C*HOAc), 123.2 (=CH-alkyl), 134.8 (*C*H=CH-alkyl), 165.9 (C=O), 169.8 (C=O), 171.2 (C=O); minor isomer 20.4, 35.9, 79.2, 91.9, 122.8, 135.2, 165.7, 168.4, 171.0; MS (EI) (M – $CH_3C(O)O)^+$ = 313.

Methyl 2-(1-Carbomethoxy-3-dodecen-1-oxy]-2-chloroacetate (36). A solution of methyl 2-[(3*E*)-1-carbomethoxy-3-dodecen-1-oxy]-2-acetoxyacetate (6.47 g, 17.38 mmol) in 35 mL of ether and 31 mL of acetyl chloride was treated with hydrogen chloride gas at 0 °C for 0.5 h. The reaction mixture was stored at 4 °C for 6 days. After evaporation of the volatiles, the residue was chromatographed to give **36** (4.71 g, 13.51 mmol, 78%) as a light yellow oil: R_f 0.40 (EtOAc/hexane 1:9); IR ($CHCl_3$) 3020, 2930, 2850, 1750, 1435, 1295; ^{1}H NMR (200 MHz, 4:1 mixture of diastereomers) 0.85 (t, J = 6.6 Hz, 3H, alkyl-CH_3), 1.23 (s, 12H, CH_2), 1.90–2.05 (m, 2H, =CHCH_2-alkyl), 2.45–2.60 (m, 2H, CH_2-CHO), 3.73 (s, 3H, OCH_3), 3.81 (s, minor isomer) and 3.84 (s, 3H, OCH_3, major isomer), 4.38–4.48 (m, 1H), 5.20–5.60 (m, 2H, CH=CH), 5.89 (s, 0.8H), and 5.92 (s, 0.2H, CHCl); ^{13}C NMR (63 MHz, mixture of two diastereomers) 14.1 (alkyl-CH_3), 22.7, 29.1, 29.3, 29.4, 29.5, 31.9, 32.5 (CH_2), 35.4 and 35.5 (=CH*C*H_2CH), 52.2 (OCH_3), 53.2 (OCH_3), 76.7 and 78.0 (CH_2*C*HCO$_2$CH$_3$), 86.4 and 86.6 (CHCl), 122.4 and 122.8 (CH=), 135.2 and 135.9 (CH=), 165.3 and 165.4 (C=), 170.3 and 170.4 (C=O).

Cyclization of 36. To a solution of **36** (4.71 g, 13.50 mmol) in 45 mL of 1,2-dichloroethane were added bpy (633 mg, 4.05 mmol) and CuCl (401 mg, 4.05 mmol). The reaction mixture was heated at reflux for 48 h. Filtration of the reaction mixture through a short silica column (eluting with EtOAc) gave a mixture of **(2*R**,3*R**)-2,5-dicarbomethoxy-3-(1-chlorononyl)tetrahydrofuran (37a) and (2*R**,3*S**)-2,5-dicarbomethoxy)-3-(1-chlorononyl)tetrahydrofuran (37b)** (4.461 g, 12.8 mmol, 95%) as a colorless oil: IR ($CHCl_3$) 3020, 2950, 2930, 2850, 1740, 1450, 1435; ^{1}H NMR (200 MHz, mixture of diastereomers) 0.87 (t, J = 6.7 Hz, 3H), 1.25–3.00 (m, 17H), 3.71 (s), 3.73 (s), 3.74 (s), 3.75 (s), 3.76 (s), 3.77 (s) and 3.79 (s, 6H), 3.75–4.25 (m, 1H), 4.50–4.90 (m, 2H); ^{13}C NMR (63 MHz, mixture of diastereomers) selected signals 48.07, 48.49, 49.52, 49.81, 50.15, 50.62 and 51.08 (C-3), 61.20, 61.35, 61.64, 61.69, 63.02, 63.44, 63.72 and 64.40 (CCl), 77.17, 77.46, 77.67, 77.71, 77.88, 78.09, 78.22, 78.73, 79.18, 79.57, 80.06, 80.17, 80.22 and 80.44 (C-2 and C-5), 170.73, 170.79, 170.90, 171.03, 171.23, 171.34, 171.60, 171.75, 172.12, 172.44, 172.60 (2 × C=O); HRMS calcd for $C_{17}H_{29}O_5Cl$ 348.1704, found 348.1715.

After flash chromatography (EtOAc/hexane 1:9), samples of three diastereomers of **37a** were obtained virtually pure (**37a**1-3).

37a-1: isolated as a colorless oil, R_f 0.27 (EtOAc/hexane 1:6); IR ($CHCl_3$) 3010, 2950, 2930, 2850, 1740, 1450, 1435; ^{1}H NMR (200 MHz) 0.84 (t, J = 6.7 Hz, 3H, alkyl-CH_3), 1.23 (bs, 11H, CH_2), 1.40–1.85 (m, 3H), 2.11–2.44 (m, 2H), 2.75–3.00 (m, 1H, H-3), 3.72 (s, 3H), 3.73 (s, 3H), 3.70–3.85 (m, 1H, CHCl), 4.80 (d, J = 7.4 Hz, 1H, H-2), 4.80–4.86 (m, 1H, H-5); ^{13}C NMR (63 MHz) 13.9 (alkyl-CH_3), 22.5, 25.9, 28.9, 29.1, 29.3, 31.7 and 32.6 (CH_2), 36.8 (CHCl*C*H_2), 49.5 (C-3), 51.8, 52.1, 61.3 (CHCl), 77.7 and 80.4 (C-2 and C-5), 171.0, 172.4; HRMS calcd for $C_{17}H_{29}O_5Cl$ 348.1704, found 348.1700.

37a-2: isolated as a colorless oil, R_f 0.24 (EtOAc/hexane 1:6); IR ($CHCl_3$) 3010, 2950, 2930, 2850, 1740, 1450, 1435; ^{1}H NMR (250 MHz) 0.82 (t, J = 6.8 Hz, 3H, alkyl-CH_3), 1.21 (bs, 11H, CH_2), 1.40–1.85 (m, 3H, CH_2), 2.23–2.50 (m, 2H, H-4), 2.75–2.95 (m, 1H, H-3), 3.69 (s, 3H), 3.70 (s, 3H), 3.75–3.85 (m, 1H, CHCl), 4.69 (d, J = 8.1 Hz, 1H, H-2), 4.82 (dd, J = 9.3, 2.9 Hz, 1H, H-5); ^{13}C NMR (63 MHz) 14.1 (alkyl-CH_3), 22.6, 26.4, 28.9, 29.2, 29.4, 31.8, 32.8 (CH_2), 38.1 (CHCl*C*H_2), 48.6 (C-3), 52.2, 52.3, 61.7 (CHCl), 77.1 and 79.3 (C-2 and C-5), 171.0, 172.7; HRMS calcd for $C_{17}H_{29}O_5Cl$ 348.1704, found 348.1715.

37a-3: isolated as a colorless oil, R_f 0.13 (EtOAc/hexane 1:6); IR ($CHCl_3$) 3010, 2950, 2930, 2850, 1740, 1450, 1435; ^{1}H NMR (200 MHz) 0.86 (t, J = 6.7 Hz, 3H, alkyl-CH_3), 1.25 (bs, 11H, CH_2), 1.45–1.95 (m, 3H, CH_2), 2.33 (td, J = 12.6, 9.8 Hz, 1H), 2.61 (dt, J = 12.7, 7.0 Hz, 1H), 2.70–2.95 (m, 1H, H-3), 3.71 (s, 3H), 3.78 (s, 3H), 3.70–3.85 (m, 1H, CHCl), 4.56 (d, J = 7.7 Hz, 1H, H-2), 4.57–4.66 (m, 1H, H-5).

Bu_3SnH Reduction of 37. A solution of the mixture of diastereomers of **37** (346.4 mg, 0.99 mmol) and AIBN (6.5 mg, 0.04 mmol) in cyclohexane (2 mL) was added to a refluxing solution of Bu_3SnH (0.4 mL, 1.5 mmol) in cyclohexane (2 mL) over 4 h, and the mixture was stirred for 18 h at room temperature. After concentration in vacuo, the DBU workup procedure[2c] was applied as follows. The mixture was taken up in ether (4 mL, 0.25 M), DBU (0.22 mL, 1.5 mmol) was added, and a solution of I_2 in ether (0.1 M) was slowly added until the iodine color just persisted. After filtration over a short silica column (eluting with 50 mL ether), the solution was concentrated in vacuo.

The residue was chromatographed to give three fractions.

The first fraction consisted of **(2R*,3S*,5R*)-2,5-dicarbomethoxy-3-nonyltetrahydrofuran (42a)** (66.8 mg, 0.21mmol, 21%) as a colorless oil: R_f 0.19 (EtOAc/hexane 1:6); IR ($CHCl_3$) 3000, 2920, 2850, 1740, 1460, 1430; ^1H NMR (200 MHz) 0.85 (t, J = 6.7 Hz, 3H, alkyl-CH_3), 1.22 (s, 16H, CH_2), 1.95–2.30 (m, 2H, H-4), 2.35–2.60 (m, 1H, H-3), 3.70 (s, 3H), 3.72 (s, 3H), 4.70 (d, J = 7.8 Hz, 1H, H-2), 4.81 (dd, J = 8.8, 3.7 Hz, 1H, H-5); ^{13}C NMR (50 MHz) 14.0 (alkyl-CH_3), 22.6, 28.3, 29.2, 29.4, 29.5, 31.8, 34.7 (CH_2), 41.5 (C-3), 51.5, 52.1, 77.3 and 81.3 (C-2 and C-5), 171.9, 173.2; HRMS calcd for $C_{17}H_{30}O_5$ 314.2093, found 314.2049.

The second fraction consisted of **(2R*,3R*,5R*)-2,5-dicarbomethoxy-3-nonyltetrahydrofuran (42c)** as a colorless oil (52 mg, 0.17 mmol, 17%): R_f 0.15 (EtOAc/hexane 1:6); IR ($CHCl_3$) 3000, 2920, 2850, 1740, 1460, 1430. ^1H-NMR (200 MHz) 0.85 (t, J = 6.6 Hz, 3H, alkyl-CH_3), 1.23 (s, 15H), 1.55–1.80 (m, 2H), 2.20–2.40 (m, 1H, H-3), 2.50 (dt, J = 12.2, 7.5 Hz, 1H), 3.73 (s, 6H), 4.28 (d, J = 6.9 Hz, 1H, H-2), 4.68 (t, J = 7.9 Hz, 1H, H-5); ^{13}C NMR (50 MHz) 14.0 (alkyl-CH_3), 22.6, 27.9, 29.2, 29.4, 31.8, 33.0, 36.2 (CH_2), 44.1 (C-3), 52.0, 52.1, 77.6 and 82.7 (C-2 and C-5), 172.4, 172.5; HRMS calcd for $C_{17}H_{30}O_5$ 314.2093, found 314.2043.

The third fraction consisted of **(2R*,3S*,5S*)-2,5-dicarbomethoxy-3-nonyltetrahydrofuran (42b)** (43 mg, 0.13 mmol, 14%), contaminated with a fourth isomer: R_f 0.09 (EtOAc/hexane 1:6); IR ($CHCl_3$) 3000, 2920, 2850, 1740, 1460, 1430; ^1H NMR (200 MHz) 0.86 (t, J = 6.8 Hz, 3H, alkyl-CH_3), 1.24 (s, 16H, CH_2), 1.90–2.10 (m, 1H), 2.30–2.55 (m, 2H), 3.69 (s, 3H), 3.78 (s, 3H), 4.55 (d, J = 7.8 Hz, 1H, H-2), 4.54–4.62 (m, 1H, H-5); ^{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 $C_{17}H_{30}O_5$ 314.2093, found 314.2075. Characteristic signals derived from this mixture for the fourth isomer: ^{13}C NMR (50 MHz) 27.81, 32.95 and 35.36 (CH_2), 42.74 (CH), 77.74 and 83.17 (C-2 and C-5).

(1R*,5R*)-6-*n*-Octyl-2,7-dioxa-8-oxobicyclo[3.3.0]octane-3-carboxylic Acid (38). To a solution of **37a-2** (69.2 mg, 0.20 mmol) in 0.3 mL of water was added 1.4 mL of a 2% solution of KOH in methanol. The reaction mixture was heated under reflux for 18 h. After evaporation in vacuo, water (5.3 mL) was added and the mixture was acidified to pH 1 with 2 M HCl. The water layer was extracted with ether (4 × 3.5 mL), and the combined organic layers were washed with brine (3 mL). The solution was concentrated in vacuo, and the reaction mixture was evaporated with toluene (3 times). In this way, **38b** (55.1 mg, 0.19 mmol, 97%) was isolated as a colorless oil: IR ($CHCl_3$) 3500–2500 (weak, COOH), 3020, 2920, 2850, 1775, 1730, 1465, 1455; ^1H NMR (200 MHz) 0.85 (t, J = 6.6 Hz, 3H, alkyl-CH_3), 1.24 (s, 12H, CH_2), 1.55–1.75 (m, 2H, CH_2), 2.15–2.35 (m, 1H), 2.40–2.60 (m, 1H), 2.85–3.05 (m, 1H, H-5), 4.31 (td, J = 6.4, 3.0 Hz, 1H, H-6), 4.63–4.70 (m, 1H, H-3), 4.88 (d, J = 7.8 Hz, 1H, H-1), 8.19 (bs, 1H, COOH); ^{13}C NMR (63 MHz) 14.0 (alkyl-CH_3), 22.5, 24.9, 29.0, 29.1, 29.3, 31.7, 35.7 and 36.1 (CH_2), 44.0 (C-5), 77.9 (C-6), 79.4 and 84.0 (C-1 and C-3), 173.8, 174.7.

Treatment of a 40:60 mixture (according to ^1H NMR) of **37a-1** and **37a-2** (942 mg, 2.70 mmol) in the same way gave a 40:60 mixture (according to ^1H NMR) of **38a** and **38b** (682 mg, 2.40 mmol, 89%): IR ($CHCl_3$) 3500–2500 (weak, COOH), 3020, 2920, 2850, 1775, 1730, 1465; ^1H NMR (200 MHz, mixture of two diastereomers) characteristic signals for **38a** 3.10–3.35 (m, 1H, H-5), 4.45–4.60 (m, 1H, H-6), 4.60–4.80 (m, 1H, H-3), 5.02 (d, J = 7.6 Hz, 1H, H-1).

(1R*,5R*)-3-Acetoxy-6-*n*-octyl-2,7-dioxabicyclo[3.3.0]octan-8-one (39). To a solution of a 40:60 mixture (according to ^1H NMR) of **38a** and **38b** (249 mg, 1.00 mmol) in benzene (10.0 mL) was added $Pb(OAc)_4$ (889.8 mg, 2.01 mmol). The reaction mixture was heated under reflux for 18 h and concentrated in vacuo. The residue was chromatographed to give two fractions.

The first fraction consisted of **39b** (56.6 mg, 0.190 mmol, 19%): R_f 0.30 (EtOAc/hexane 1:3); IR ($CHCl_3$) 3020, 2930, 2850, 1780, 1750, 1465; ^1H NMR (200 MHz) 0.87 (t, J = 6.6 Hz, 3H, alkyl-CH_3), 1.26 (bs, 12H), 1.55–1.75 (m, 2H), 2.04 (s, 3H, C(O)-CH_3), 2.00–2.15 (m, 1H), 2.42 (dd, J = 13.7, 8.3 Hz, 1H), 3.05 (qd, J = 8.5, 1.9 Hz, 1H), 4.31 (td, J = 6.5, 2.0 Hz, 1H, H-6), 4.84 (d, J = 8.2 Hz, 1H, H-1), 6.41 (d, J = 4.7 Hz, 1H, H-3); ^{13}C NMR (63 MHz) 14.0 (alkyl-CH_3), 21.0 (C(O)CH_3), 22.6, 24.9, 29.1, 29.3, 31.7, 36.4, 37.8 (CH_2), 42.8 (C-5), 78.8 (C-6), 83.4 (C-1), 99.5 (C-3), 169.4, 172.7; MS (EI) (M – $CH_3C(O)O)^+$ = 239.

The second fraction consisted of a 50:17:33 mixture (according to ^1H NMR) of **39a–c** (143.4 mg, 0.481 mmol, 48%): R_f 0.25 (EtOAc/hexane 1:3); IR 3020, 2930, 2850, 1780, 1750, 1465; ^1H NMR (200 MHz, mixture of three diastereomers) **39a** characteristic signals 3.25-3.45 (m, 1H, H-5), 4.50–4.65 (m, 1H, H-6), 4.92 (d, J = 8.1 Hz, 1H, H-1), 6.37 (d, J = 3.8 Hz, 1H, H-3); **39c** characteristic signals 2.30–2.50 (m, 1H), 2.75–2.95 (m, 1H, H-5), 4.40–4.50 (m, 1H, H-6), 4.79 (d, J = 8.6 Hz, 1H, H-1), 6.43 (d, J = 4.9 Hz, 1H, H-3).

(1R*,5R*,6R*)-6-*n*-Octyl-2,7-dioxabicyclo[3.3.0]octane-3,8-dione (40). To a solution of **39b** (45 mg, 0.151 mmol) in dichloromethane (0.5 mL) were added at 0 °C BF_3·OEt_2 (3.8 μL, 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 $Na_2S_2O_3$ 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 **40** as a colorless oil (33.4 mg, 0.131 mmol, 87%): IR ($CHCl_3$) 3020, 2930, 2850, 1780, 1465, 1415, 1355, 1290; ^1H NMR (300 MHz) 0.88 (t, J = 7.0 Hz, 3H alkyl-CH_3), 1.27 (bs, 12H, CH_2), 1.65–1.80 (m, 2H, CH_2), 2.55 (dd, J = 17.9, 3.8 Hz, 1H), 2.95 (dd, J = 17.9, 9.4 Hz, 1H), 3.00–3.10 (m, 1H, H-5), 4.35 (dt, J = 7.2, 5.3 Hz, 1H, H-6), 5.02 (d, J = 7.6 Hz, 1H, H-1); ^{13}C NMR (75 MHz) 14.0 (alkyl-CH_3), 22.6, 24.9, 29.1, 29.3, 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 $C_{14}H_{22}O_4$ 254.1518, found 254.1509.

(1R*,5R*,6S*)-6-*n*-Octyl-2,7-dioxabicyclo[3.3.0]octane-3,8-dione (41). To a solution of a 40:20:40 mixture (according to ^1H NMR) of **39a–c** (46.8 mg, 0.157 mmol) in dichloromethane (0.5 mL) were added at 0 °C BF_3·OEt_2 (3.9 μL, 0.03 mmol) and *m*-CPBA (purity 85%, 35.1 mg, 0.173 mmol). The mixture was stirred for 3 h. Then, ether (4.3 mL) was added and the mixture was subsequently washed with a 10% aqueous $Na_2S_2O_3$ 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. The residue was chromatographed to give two fractions. The first fraction consisted of **40** (12.5 mg, 0.05 mmol, 31%) as a colorless oil: R_f 0.21 (EtOAc/hexane 1:2.5). The second fraction consisted of a 28:72 mixture (according to ^1H NMR) of **40** and **41** (15.2 mg, 0.06 mmol, 38%). Recrystallization from diisopropyl ether afforded **41** (9.5 mg, 0.04 mmol, 24%) as white crystals, mp 83.5-84.5 °C: R_f 0.18 (EtOAc/hexane 1:2.5); IR ($CHCl_3$) 3020, 2930, 2850, 1795, 1465, 1360, 1285; ^1H NMR (300 MHz) 0.89 (t, J = 6.9 Hz, 3H, alkyl-CH_3), 1.20–1.45 (m, 12H), 1.45–1.65 (m, 1H), 1.75–1.90 (m, 1H), 2.65 (d, J = 9.5 Hz, 2H), 3.47 (qd, J = 9.5, 5.7 Hz, 1H, H-5), 4.62 (dt, J = 8.5, 5.4 Hz, 1H, H-6), 5.16 (d, J = 8.3 Hz, 1H, H-1); ^{13}C NMR (50 MHz) 14.1 (alkyl-CH_3), 22.6, 25.5, 26.9, 29.1, 29.2, 29.3, 31.4, 31.8 (CH_2), 39.4 (C-5), 76.9 and 78.7 (C-1 and C-6), 170.2, 173.3. Anal. Found: C, 66.29; H, 8.82. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72.

Acknowledgment. K. Goubitz and J. Fraanje of the Department of Crystallography are kindly acknowledged for the X-ray crystal structure determination of **18a**. These investigations were supported by The Netherlands' Foundation for Chemical Research (SON), with financial support from the Dutch Organization for the Advancement of Pure Research (NWO).

Supplementary Material Available: Copies of ^1H and/or ^{13}C NMR spectra for all new compounds, i.e., **5–14, 16–22, 24–27, 30, 31, 35–39**, the precursors of compounds **8, 11, 12,** and **36**, and for normethyleneavenaciolide (**40**) and normethyleneisoavenaciolide (**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.