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Synthesis of Medium-Sized Lactones by the Copper(I)Chloride/2,2'-Bipyridine-Catalyzed Cyclization of Di- and Trichloroacetates

Frank O. H. Pirrung, Henk Hiemstra* and W. Nico Speckamp*

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

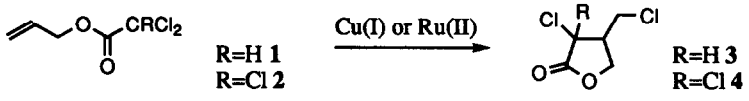
Bernard Kaptein and Hans E. Schoemaker

DSM Research, P. O. Box 18, 6160 MD Geleen, The Netherlands

Abstract. Medium-sized lactones (eight- to eleven-membered rings) are efficiently formed by Cu(bpy)Cl catalyzed cyclization of various alkenyl di- and trichloroacetates at temperatures between 80 and 190 °C in 1,2-dichloroethane or benzene as solvents. The mechanism of the alkene addition reaction is best understood as a chlorine atom transfer process through radical type intermediates. Exclusive *endo*-cyclization is observed in all cases. Ten and eleven-membered lactones are only accessible by the 'rigid chain' approach, in which an alkyne or alkene function is incorporated in the chain connecting the reaction centres, thus reducing the flexibility of the molecule.

INTRODUCTION

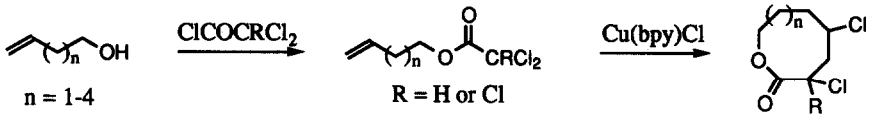
The synthesis of medium-sized lactones (8- to 12-membered ring systems) has recently received considerable attention[1] because these lactones occur in the basic structure of various natural products with interesting biological activities.[2] Among the methods developed, radical based techniques for the formation of lactones and other heterocycles are scarce.[3] The so-called radical transfer process mediated by transition metal catalysts is successfully applied for the formation of 5-membered lactones and lactams from allyl di- and trichloroacetates and amides by a radical *exo*-cyclization onto a double bond.[4] A number of C-C bond formations of this type is described using $RuCl_2(PPh_3)_3$,[4a,5b] CuCl in acetonitrile[6] and Cu(bpy)Cl.[4b] The successful Cu(I) and Ru(II) catalyzed *exo*-cyclizations of allyl chloroacetates **1** and **2** to the 5-membered lactones **3** and **4** are representative examples:[4a]



In addition, Fe and Mo complexes are known to catalyze the formation of C-C bonds between activated halogen compounds and alkenes.[4a,5b] This type of reaction is applied in industrial processes to produce herbicides of general application.[7]

We set out to examine the activity of the Cu(bpy)Cl catalyst towards ω-alkenyl chloroacetates to form 8-, 9-, 10- and 11-membered lactones in view of our earlier successful work on intramolecular additions of glycine

derived radicals by this catalyst.[8] Our strategy is outlined in Scheme 1. We concentrated on the use of di- and trichloroacetates of various ω-alkenols, readily obtained by simple esterification via the acid chlorides. The esters were then treated with the Cu-catalyst under an appropriate set of conditions to yield cyclization products.[9]



n = 1-4 R = H or Cl

Scheme 1. Synthetic strategy

In this paper we report on the formation of 8- to 11-membered lactones by Cu(bpy)Cl catalyzed atom transfer cyclization of ω-alkenyl di- and trichloroacetates. We show that 8- and 9-membered rings are readily accessible from various unsubstituted and methyl- or phenyl-substituted alkenyl esters. For the larger rings it appears necessary to introduce a rigid element into the functional group connecting chain to reduce its flexibility.

RESULTS

Synthesis of the cyclization precursors

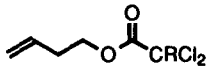
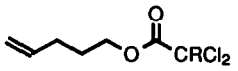
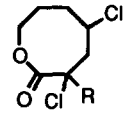
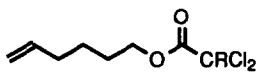
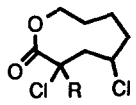
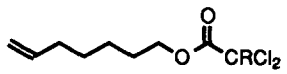
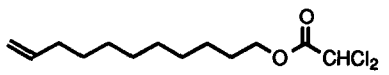
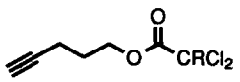
The di- and trichloroacetates **5-34** (Tables 1, 2 and 4) were prepared by esterification of the alkenols by using 1.0 to 1.5 equiv of di- or trichloroacetyl chloride and 2.0 equiv of Et_3N in CH_2Cl_2 at 0 °C for 2 h.[10] The products could be easily isolated and purified by flash chromatography and were obtained in high yields (Tables 1, 2 and 4).

Many of the alkenols were commercially available. The remaining alkenols were synthesized as follows: 6-Hepten-1-ol (entries 13, 14, Table 1) was prepared from 6-heptenoic acid by $LiAlH_4$ reduction (100%). Racemic 1-phenyl- and 1-methyl-4-penten-1-ol[11] (entries 1, 2, Table 2), as well as 2-methyl-5-hexen-2-ol[12] (entry 3, Table 2) were obtained by Grignard addition of 1-bromo-3-butene to benzaldehyde, acetaldehyde or acetone, respectively. 2,2-Dimethyl-4-penten-1-ol[13] (entries 4, 5, Table 2) was prepared by $LiAlH_4$ reduction of the commercially available 2,2-dimethyl-4-pentenal. Following a literature procedure 3,3-dimethyl-4-penten-1-ol[14] (entries 6, 7, Table 2) was prepared by Claisen orthoester rearrangement of 3-methyl-2-buten-1-ol, followed by reduction of the resulting ethyl ester by $LiAlH_4$. 4-Methyl-4-penten-1-ol[15] (entries 8, 9, Table 2) was obtained by a Wittig reaction on ethyl levulinate, followed by $LiAlH_4$ reduction. 5-Methyl-4-hexen-1-ol[16] (entries 12, 13, Table 2) was prepared by copper mediated alkylation of ethyl acetate with 1-bromo-3-methyl-2-butene and subsequent reduction of the resulting ethyl ester by $LiAlH_4$. 6-Hepten-3-yn-1-ol (entries 1, 2, Table 4) and 7-octene-4-yn-1-ol (entries 5, 6, Table 4) were prepared by Cu-catalysed alkylation of 3-butyn-1-ol and 4-pentyn-1-ol with allyl bromide.[17] Reduction to (*Z*)-hepta-3,6-dien-1-ol (entries 3, 4, Table 4) was accomplished by $NaBH_4$ with catalytic $PdCl_2$ in polyethylene glycol 200 at -10 °C.[18]

Cyclization of substrates with unsubstituted chains

The 3-butenyl chloroacetates **5** and **6** were treated with 0.3 equiv of Cu(bpy)Cl in refluxing 1,2-dichloroethane (DCE, bp 83.5 °C) for 18 h (entries 1 and 2, Table 1). However, their cyclization in either the 6-*exo* or the 7-*endo* mode failed completely. Only telomerization products could be detected in the crude reaction mixtures. The failure of these cyclizations might be related to the unwillingness of the ester group to adopt the s-*trans*-conformation during the cyclization reaction.[3d,19]

Table 1: Cyclizations of substrates with unsubstituted chains

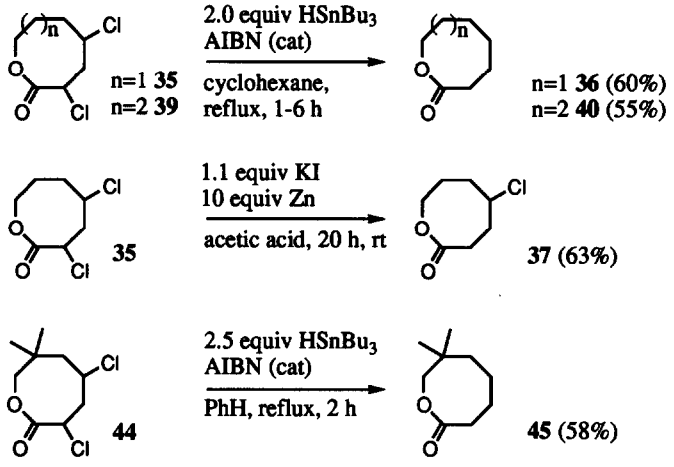
entry	precursor (yield from the alcohol)	conditions[a]	products, yield (diastereomeric ratio *cis:trans*)
			
1	R=H **5** (98%)	Cu*, DCE, reflux, 18 h	telomers
2	R=Cl **6** (87%)	Cu*, DCE, reflux, 18 h	telomers
			
3	R=H **7** (100%)	Cu*, DCE, reflux, 18 h	**35a,b** 75% (70:30)[b]
4		Cu*, PhH, reflux, 18 h	**35a,b** 92% (70:30)[b]
5		Cu*, PhH, 140 °C, 2 h	**35a,b** 90% (70:30)[b]
6	R=Cl **8** (100%)	Cu*, DCE, reflux, 18 h	**38** 60%
7		Cu*, PhH, reflux, 20 h	**38** 39%
8		Cu*, DCE, 130 °C, 2.5 h	**38** 58%
9		CuCl/MeCN, 130 °C, 3 d	**38** 24% (63% of s.m.)
10		$RuCl_2(PPh_3)_3$, PhH, 140 °C, 5 h	**38** 21%
			
11	R=H **9** (85%)	Cu*, DCE, reflux, 18 h	**39a,b** 57% (70:30)[b]
12	R=Cl **10** (86%)	Cu*, DCE, 190 °C, 2 h	**41** 59%
			
13	R=H **11** (94%)	Cu*, DCE, reflux	telomers
14	R=Cl **12** (66%)	Cu*, DCE, reflux	telomers
			
15	**13** (85%)	Cu*, DCE, reflux	telomers
			
16	R=H **14** (87%)	Cu*, DCE, reflux to 190 °C	starting material and telomers
17	R=Cl **15** (92%)	Cu*, DCE, reflux to 190 °C	starting material and telomers

a) Cu*: 0.3 equiv of Cu(bpy)Cl was employed. b) inseparable mixture.

On the contrary, 4-pentenyl dichloroacetate (**7**) cyclized under identical reaction conditions to give the 8-membered lactone **35** in 75% yield (entry 3, Table 1) as an inseparable (by column chromatography) mixture of diastereomers (70:30). The major isomer **35a** was assigned by ^1H NMR as the thermodynamically favoured *cis*-isomer for an 8-membered lactone in a crown conformation.[20] The cyclization yield could be improved to 92% by using refluxing benzene as solvent (entry 4). Alternatively, at higher temperature and with shorter

reaction time (140 °C, sealed tube, 2 h, entry 5) an almost identical yield (90%) was obtained. Other solvents could be used (THF, acetonitrile, CH_2Cl_2, acetone, toluene, xylene), but led to much lower yields (<50%). When ethers (THF, diglyme) were used, the monochloroacetate (22-26%) could be detected in the reaction mixture. This latter product most probably arises if the rate of hydrogen abstraction from the solvent can compete with cyclization.[5b]

The structure of **35** was proven beyond doubt by reduction of the diastereomeric mixture to the known unsubstituted derivative **36**[22] (60%) with $HSnBu_3$/AIBN (Scheme 2). Treatment of **35** with Zn dust in acetic acid[23] led to the monochloro derivative **37** (Scheme 2).



Scheme 2. Reduction of lactones

The trichloroacetate **8** (entry 6, Table 1) cyclized to the 8-membered lactone **38** in 60% isolated yield, when treated with 0.3 equiv of the catalyst in refluxing DCE for 18 h. Alternatively the reaction was complete in 2.5 h at 130 °C in DCE (58%, entry 8). In all cases, significant amounts of telomers were formed. This problem could not be suppressed by applying higher dilution.

Substrate **8** was also treated with 0.3 equiv of CuCl in acetonitrile at 130 °C for 3 d without the bipyridine ligand (entry 9). This procedure led to only 24% of the desired 8-membered lactone **38** with 63% of starting ester remaining, showing the importance of the bipyridine ligand in the catalyst for the enhancement of the reaction rate. Similarly, **8** was treated with $RuCl_2(PPh_3)_3$ (entry 10), producing only 21% of **38**, together with an extensive amount of telomeric side products. This Ru-catalyst has been used for the formation of 5-membered rings from trichloroacetates.[5] The present result indicates that it is not suited for the efficient formation of medium-sized lactones.

Reaction of the 5-hexenyl chloroacetates **9** and **10** with Cu(bpy)Cl (entries 11 and 12) afforded the corresponding 9-membered rings. The dichloroacetate **9** reacted in a refluxing solution of DCE for 20 h to **39** in 57% yield as an inseparable mixture of the two diastereomers **39a** and **39b** in a *cis*:*trans* ratio of 70:30. Lactone **39** was treated with $HSnBu_3$/AIBN to yield the parent nine-membered lactone **40**[22] (Scheme 2). Again, exclusive *endo*-cyclization occurred, no trace of the alternative 8-*exo* product being detectable. Similarly, the cyclization reaction of the corresponding trichloroacetate **10** proceeded at 190 °C in 2 h to give lactone **41**

(59%) as a single regioisomer. At 80 °C in DCE for 18 h, comparable yields could be obtained. In the case of nine-membered rings more telomeric material was formed than in the case of eight-membered systems.

Next, we subjected the heptenyl chloroacetates **11** and **12** to our cyclization conditions (entries 13 and 14). In both cases only telomerization products were formed by treatment with Cu(bpy)Cl in DCE at reflux. Undecenyl dichloroacetate **13** (entry 15) also led exclusively to telomers. As a rationale for these results, we assume that unfavourable entropy effects are more important when the chain is elongated. This conclusion can also be inferred from the larger amount of telomers formed in the case of nine-membered lactones.

To complete this study of unsubstituted chains we subjected the 4-pentynyl chloroacetates **14** and **15** to our standard conditions (entries 16 and 17). The starting materials were left untouched or gave telomeric material, showing that alkynes are unsuitable substrates for this type of cyclization.

Cyclization of substrates with alkyl substituted chains

In order to further study the scope of the cyclization reaction methyl- and phenyl-substituted pentenyl acetates were used. The presence of substituents on the alkyl chain of the cyclization precursor should affect the conformation of the cyclization substrates, and thus the cyclization process.

Dichloroester **16** cyclized to eight-membered lactone **42** in 68% (see Table 2, entry 1) as a non-separable mixture of three diastereomers in the ratio of 70:20:10. The *cis*-dichloro isomer **42a** was the major compound as implied from the characteristic signals of the C-4 methylene group in the ^{1}H NMR spectrum (*vide infra* and see Table 3). For this ring closure a reaction temperature of 130 °C was necessary. At lower temperatures the starting material remained unchanged.

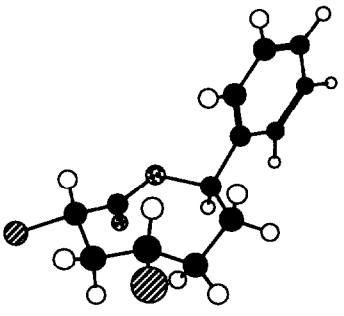


Figure 1. Crystal structure of **43a** (Chem 3D™ view)

The phenyl-substituted dichloroacetate **17** (entry 2), upon treatment at 180 °C for 2 h with Cu(bpy)Cl, cyclized to a 68:18:13 mixture of diastereomers of the eight-membered lactone **43** in 51% yield. No reaction took place at 80 °C. No seven-membered product by *exo*-closure was detected. The major isomer **43a** could be obtained pure by crystallization from the product mixture (mp 71-76 °C) and was subjected to an X-ray analysis[24] (Figure 1, Table 5). The crystal structure determination proved the oxocan-2-one skeleton and revealed the *cis*-relationship between the chlorine substituents. The phenyl substituent was found *trans* with respect to the two chlorine substituents. The plane of the aromatic ring is oriented perpendicular with respect to a plane through the eight-membered lactone ring. The lactone ring adopts a chair-chair (or crown) conformation and an *s-trans*-lactone geometry (dihedral angle 142°, Figure 2).[20] In this way the three substituents can adopt *pseudo*-equatorial positions, which reflects the thermodynamically most stable product.

The 1,1-dimethyl substituted precursor **18** (entry 3) failed to cyclize to the desired lactone product, even at high temperatures (180 °C) for several hours. The harsh conditions necessary for the 1-substituted precursors and the failure of the cyclization of **18** points to steric hindrance by these substituents during the ring closure.

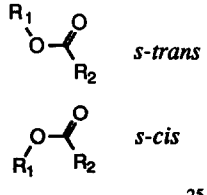


Figure 2. Ester geometries[25]

Following the above procedure the 2,2-dimethyl substituted dichloroacetate **19** afforded 81% of a diastereomeric mixture (75:25) of the eight-membered lactone **44** (entry 4). The mixture of diastereomers of lactone **44** was treated with $HSnBu_3$/AIBN to yield the 7,7-dimethyl substituted oxocan-2-one **45** (Scheme 2). The *cis*-isomer **44a** could be obtained pure by crystallization and was subjected to X-ray analysis[9a,24] (Figure 3, Table 5). The data show that the eight-membered ring has a crown conformation an *s-trans*-lactone geometry (dihedral angle 143°) and *pseudo*-equatorial positions of the *cis*-chlorine atoms.

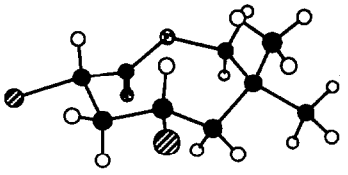


Figure 3. Crystal structure of **44a** (Chem 3D™ view)

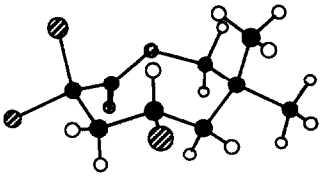


Figure 4. Crystal structure of **46** (Chem 3D™ view)

The corresponding trichloroacetate **20** gave the eight-membered lactone **46** (67%) as a crystalline product (entry 5). The X-ray structure of this compound[24] (Figure 4, Table 5) shows a crown conformation of the eight-membered ring almost identical to the corresponding dichlorolactone (Figure 3). The C-5 chlorine atom adopts the *pseudo*-equatorial position and the ring an *s-trans*-lactone geometry (dihedral angle 140°).

The ^1H NMR data of the *cis*-isomers **35a**, **39a**, **42a**, **43a** and **44a** of the lactones exhibit a striking resemblance, especially in the splitting pattern of the C-4 methylene hydrogens (see Table 3).

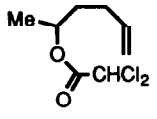
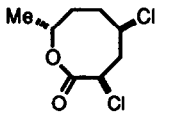
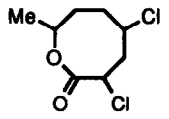
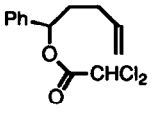
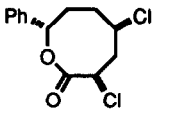
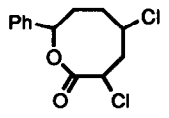
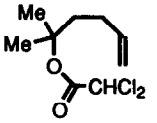
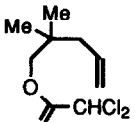
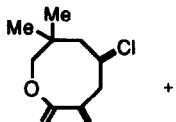
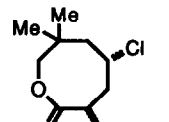
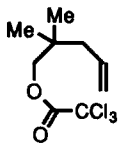
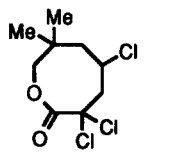
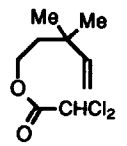
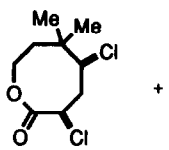
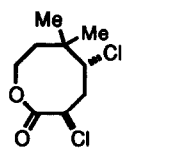
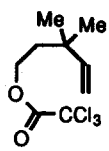
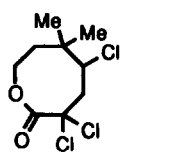
Table 3: Selected ^1H NMR data of H-3, H-4ax and H-4eq of chloro substituted oxocanones

compound	H-3 ppm[a]	H-4ax ppm[a]	H-4eq ppm[a]
35a	4.48 (dd, 6.2, 11.5)	2.57 (ddd, 11.1, 11.5, 14.0)	2.91(ddd, 1.2, 5.8, 14.0)
35b	4.68 (dd, 4.4, 6.5)	2.63 (ddd, 2.8, 6.6, 14.1)	2.88 (ddd, 4.4, 9.1, 14.1)
39a	4.46 (dd, 6.0, 11.8)	2.42 (ddd, 9.0, 11.8, 14.3)	2.75 (ddd, 1.8, 5.8, 14.4)
39b	4.55 (dd, 3.2, 5.6)	2.62 (ddd, 3.2, 5.6, 15.4)	2.72 (ddd, 3.2, 8.0, 15.4)
42a	4.50 (dd, 6.5, 11.5)	2.55 (dt, 11.3, 13.6)	2.90 (dd, 6.4, 13.5)
43a	4.62 (dd, 6.5, 11.2)	2.66 (dt, 11.4, 13.6)	3.01 (dd, 6.4, 13.6)
44a	4.52 (dd, 6.4, 11.7)	2.47 (dt, 11.5, 13.4)	2.90 (dd, 6.3, 13.4)
44b	4.50-4.53 (m)	2.70-2.75 (m)	2.70-2.75 (m)
47a	4.55 (dd, 5.4, 12.0)	2.45 (ddd, 7.9, 12.0, 15.3)	2.71 (ddd, 1.0, 5.4, 15.3)
47b	4.44 (dd, 3.0, 5.1)	2.60 (ddd, 4.7, 7.1, 15.2)	2.70 (ddd, 1.7, 8.9, 15.2)
49a	4.28 (dd, 4.7, 11.4)	2.92 (dd, 11.5, 13.8)	2.67 (dd, 4.7, 13.9)
49b	4.74 (dd, 4.2, 9.9)	2.56 (dd, 9.9, 14.6)	2.71 (dd, 4.2, 14.6)

a) measured in $CDCl_3$, *J* in Hz.

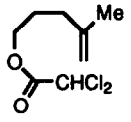
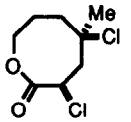
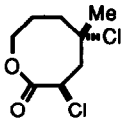
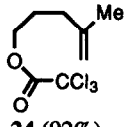
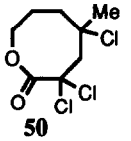
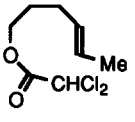
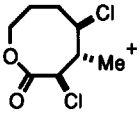
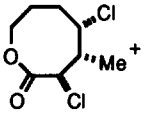
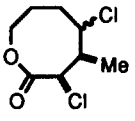
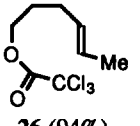
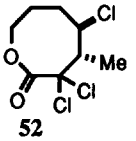
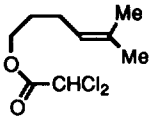
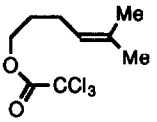
The *pseudo*-axial H-4 is found around 2.50 ppm as a double triplet or ddd with a geminal coupling of ca. 13.5 Hz and two vicinal couplings of ca. 11 Hz. The *pseudo*-equatorial H-4 usually shows a double doublet at 2.70-2.90 ppm with the geminal coupling of ca. 13.5 Hz and one vicinal coupling of ca. 6 Hz with H-3 (alternatively a ddd with an extra small vicinal coupling with H-5 of ca. 1.5 Hz). Furthermore H-3 is a

Table 2: Cyclizations of substrates with alkyl substituted chains

entry	precursor (yield from the alcohol)	conditions[a]	products (diastereomeric ratio) yield		
1	 **16** (84%)	PhH, 130 °C, 5 h	 **42a** (70)	+  **42b, 42c** (20:10)[b]	68%
2	 **17** (100%)	PhH, 180 °C, 1.75 h	 **43a** (69)	+  **43b, 43c** (18:13)[b]	51%
3	 **18** (95%)	PhH, 180 °C, 5 h	no cyclization		
4	 **19** (100%)	PhH, 180 °C, 1.5 h	 **44a** (75)	+  **44b** (25)	81%
5	 **20** (99%)	DCE, 125 °C, 2 h	 **46**		67%
6	 **21** (87%)	PhH, 120 °C, 18 h	 **47a** (70)	+  **47b** (30)	75%
7	 **22** (85%)	DCE, 110 °C, 18 h	 **48**		50%

a) 0.3 equiv of Cu(bpy)Cl was employed. b) inseparable mixture.

Table 2 (continued)

entry	precursor (yield from the alcohol)	conditions[a]	products (diastereomeric ratio) yield	
8	 **23** (87%)	PhH, 150 °C, 1 h	 **49a** (73) +  **49b** (27)	52%
9	 **24** (92%)	DCE, 120 °C, 2 h	 **50**	57%
10	 **25** (94%)	PhH, 120 °C, 20 h	 **51a** (60) +  **51b** (20) +  **51c, 51d** (10:10)[b]	48%
11	 **26** (94%)	DCE, 170 °C, 20 h	 **52**	33%
12	 **27** (93%)	PhH, 120-170 °C	no cyclization	
13	 **28** (95%)	DCE, 120-170 °C	no cyclization	

a) 0.3 equiv of Cu(bpy)Cl was employed. b) inseparable mixture.

characteristic double doublet around 4.50 ppm. In the C-3/C-5 *trans*-isomers (e.g. **35b**, **39b** and **44b**) the signals of the two C-4 hydrogens are less separated from each other. The vicinal couplings in the *cis*-isomers were in good agreement with the data from the Karplus equation for a solution conformation similar to the crown shaped conformation in the crystals. The pattern of the C-4 methylene group hydrogens therefore may be used for the assignment of the relative stereochemistry of the various diastereomers of the 8-membered dichlorolactones in a crown conformation.

The dichloroacetate **21** having two methyl substituents at the 3-position of the alkenyl chain gave the eight-membered lactone **47** (75%, entry 6) as an inseparable mixture of the two diastereomers with a *cis:trans* ratio of 70:30. The trichloroacetate **22** cyclized to the trichlorooxocan-2-one **48** as a single crystalline product (50%, entry 7). In both cases, reaction temperatures of 110-120 °C were employed to achieve complete

conversion in 18 h.

The dichloroacetate **23** cyclized readily at 150 °C in 1 h to a diastereomeric mixture (73:27) of the eight-membered lactone **49** (entry 8). The relative low yield of 52% probably reflects the steric hindrance at the introduction of the chlorine atom on the tertiary C-5 of the product. The major isomer **49a** showed upon irradiation of the C-5 methyl substituent a NOE effect on H-3 and on one of the C-4 protons. Assuming a crown conformation, this means that the methyl substituent takes a *pseudo*-axial and the chlorine substituent on C-3 a *pseudo*-equatorial position, reflecting the *cis*-diastereomer of **49**. The trichloroacetate **24** (entry 9) cyclized at 120 °C to lactone **50** in a 57% yield in which the methyl substituent occupies the *pseudo*-axial position in a crown shaped ring, as inferred from a NOE experiment. The splitting patterns in the ^{1}H NMR of the *cis*- and *trans*-isomers of lactones **47** and **49** show similar features as described above (see Table 3) for the other lactones.

(*E*)-4-Hexenyl dichloroacetate **25** cyclized in a slow process at 120 °C in 20 h to 48% of a mixture of the four possible diastereomers of the eight-membered lactone **51** (entry 10). The major isomer **51a** could be isolated from this mixture by crystallization and was characterized from NOE experiments as *pseudo*-all-equatorial having the chlorine atoms in a relative *cis*-relationship to each other, and the methyl substituent *trans*.

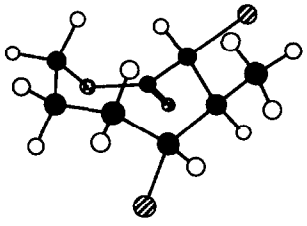


Figure 5: Crystal structure of **51a** (Chem 3D™ view)

Remarkably the crystal structure of **51a** (Figure 5, Table 5)[24] did not show a crown conformation in the solid state, but instead a chair-boat arrangement in which C-5 is bent out of the crown leading to an *s-cis*-lactone geometry (dihedral angle 4°) and an axial C-5 chlorine substituent. The other two substituents on C-3 and C-4 occupy equatorial positions. In solution however, a crown conformation was observed: The vicinal coupling constant for the H-3/H-4 and the H-4/H-5 pairs were both 9.7 Hz, which is expected for a crown conformation where the angles between these two hydrogen pairs are similar. In the crystal structure, however, these dihedral angles were 179° and 74° respectively. The isomer **51b** could be separated by chromatography and was characterized as an epimer of the first diastereomer at C-3, leading to a relative *trans*-relationship between the chlorine substituents. The coupling constants of the H-3/H-4 pair is 3.5 Hz, and for the H-4/H-5 pair 8.8 Hz. By NOE experiments on the C-4 methyl subtituent effects were observed on H-3, H-4, and H-5, respectively. In a crown shaped ring the small coupling constant for H-3/H-4 is obtained for a *cis*-relationship between the chloro and the methyl substituents (small dihedral angle) and the larger coupling constant for H-4/H-5 for a relative *trans*-relationship between the respective substituents (large dihedral angle). The other two inseparable diastereomers possess an eight-membered ring structure as seen from their ^{1}H NMR data. Of the two possibilities for ring closure only 8-*endo* cyclization took place.

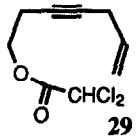
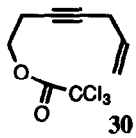
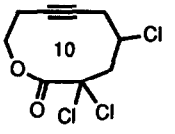
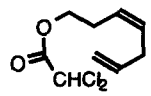
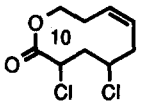
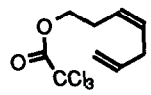
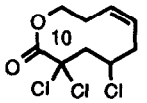
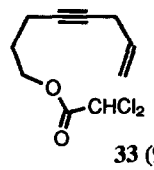
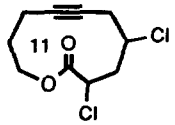
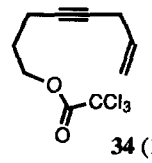
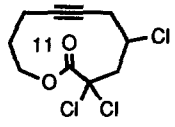
This regioselective ring closure is also found in the cyclization of the corresponding trichloroacetate **26** (entry 11). Only one diastereomer is formed in a yield of 33%, characterized by NOE as the *trans*-isomer: Irradiation of the methyl group showed an enhancement of H-4 and H-5 (equatorial methyl group in a crown shaped ring). The coupling constant for H-4/H-5 is 10.0 Hz, which corresponds to a *trans*-relationship between H-4 and H-5 (large dihedral angle) and an equatorial C-5 chlorine substituent. No seven-membered product was observed in agreement with the results of the cyclization of **25**. The latter two cyclizations (entries 10 and 11) proceeded much slower as compared to the terminally unsubstituted alkenes.

The dimethyl substituted alkenyl di- and trichloroacetates **27** and **28** were also treated with Cu(bpy)Cl. In both cases at temperatures between 120 and 170 °C, the starting materials remained unchanged (entries 12 and 13). Terminal alkene substituents thus substantially reduce the cyclization rate and terminal disubstitution apparently renders the ring closure impossible.

The application of the rigid chain approach

The failure of the cyclization of the 6-heptenyl di- and trichloroacetates **11** and **12** as well as the 10-undecenyl dichloroacetate **13** (see Table 1) necessitated the development of a different strategy. The flexibility of the long carbon chain probably favours intermolecular addition over intramolecular reaction via entropy effects. Therefore a rigid element in the carbon chain might suppress such effects.

Table 4: The rigid chain approach

entry	precursor (yield from the alcohol)	conditions[a]	products (diastereomeric ratio), yield	
1	 **29** (100%)	PhH, 80-160 °C	no cyclization	
2	 **30** (100%)	DCE, 120 °C, 2 h		**53**, 36%
3	 **31** (65%)	PhH, 175 °C, 8 h		**54**, 13%
4	 **32** (62%)	DCE, reflux, 3 d		**55**, 37%
5	 **33** (98%)	PhH, reflux, 18 h		**56**, 51% (67:33)[b]
6	 **34** (100%)	DCE, 175 °C, 3 h		**57**, 10%

a) 0.3 equiv of Cu(bpy)Cl was employed in all cases. b) inseparable mixture.

For this purpose an alkyne functionality was introduced into the alkenyl chain. Dichloroacetate **29** was treated with Cu(bpy)Cl (entry 1, Table 4). However, the starting material remained unchanged at temperatures between 80 and 160 °C.

At 120 °C the more reactive trichloroacetate **30** (entry 2) cyclized in the *endo*-mode to a ten-membered system **53** in 36% isolated yield. The desired product was accompanied by various telomers, making purification by flash chromatography laborious. Higher dilution of the reaction mixture (0.03 M, 10 h at 120 °C) did not suppress telomerization, but only 17% of the ten-membered ring could be isolated from an incomplete reaction.

The dichloroacetate **31**, having a (*Z*)-alkene functionality cyclized to the ten-membered lactone **54** (entry 3). In addition, extensive telomerization took place. Only one diastereomer could be isolated from the reaction mixture. Its relative stereochemistry was assigned as *cis*, as could be inferred from the characteristic splitting pattern of H-4ax (dt, J = 11.9, 13.8 Hz) in the ^{1}H NMR. Similar patterns were obtained for the 8- and 9-membered lactones (see Table 3). At lower temperatures the starting material remained unchanged.

The trichloroacetate **32** afforded after reflux for 3 days 74% of crude cyclic material but only 37% of the ten-membered lactone **55** after purification. Attempts to cyclize **32** at temperatures between 125 and 140 °C were unsuccessful as only telomers were formed.

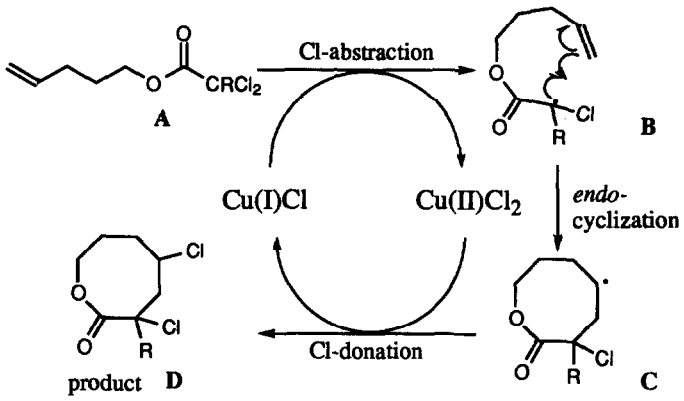
Dichloroacetate **33** was treated with 0.3 equiv of Cu(bpy)Cl at various temperatures. Reflux in PhH gave 51% of a mixture of two diastereomers of the eleven-membered lactone **56** in the ratio of 67:33, separated by chromatography. The relative stereochemistry of the two diastereomers could not be established by NMR techniques. Higher reaction temperatures (up to 175 °C) led to a decrease in yield and increasing telomer formation.

The trichloroacetate **34** led to an eleven-membered system **57** at 175 °C, although the yield was poor. Telomerization was the predominant process. At reflux in DCE for 4 days the starting material remained unchanged.

Although the yields of the cyclizations collected in Table 4 are rather low, 10- and 11-membered rings are accessible by incorporating a rigid element into the alkenyl chain. For this purpose alkyne and alkene functionalities are suitable. All products formed are the result of *endo*-cyclization of the acetate precursor.

DISCUSSION

The catalyst Cu(bpy)Cl is prepared *in situ* from equimolar amounts of CuCl and the 2,2'-bipyridine ligand. Upon simple mixing of the two components in the reaction vessel containing solvent and reactant, an active catalyst is formed. It is assumed that this catalyst consists of a Cu(I) species which formally abstracts a chlorine atom from the starting material **A** (see Scheme 3) to furnish a carbon radical **B** and a Cu(II) species.[6b] The carbon radical **B** is stabilized by the captodative effect, which is a characteristic of our previous work and is believed to be crucial for its success.[26] This stabilized radical attacks onto the alkene functionality leading to a new unstabilized carbon radical **C**, which abstracts a chlorine atom from the previously formed Cu(II) complex to give the product **D** (lactone) and a Cu(I) species which can undergo another catalytic cycle.



Scheme 3. Catalytic cycle (R = H or Cl)

The combination of equimolar amounts of CuCl and 2,2'-bipyridine in a solvent containing a dichloroacetate leads to the formation of a red-brown solution (probably due to the soluble Cu(bpy)Cl complex), which rapidly turns to a transparent green solution, when the reaction mixture is heated to 80 °C. On cyclization of trichloroacetates, the initial red-brown colour cannot be observed. The reaction mixture turns green immediately at room temperature, due to the higher reactivity of this type of ester. When a solution of the catalyst in DCE is heated without substrate, the solution keeps its red-brown colour. The colour change can be ascribed to the Cu(I) → Cu(II) oxidation by chlorine atom abstraction from the starting material. A few minutes after the addition of the catalyst a bright green insoluble material begins to precipitate, but no decrease of catalytic activity can be observed at this stage (the reaction mixture mainly contains starting material). The application of degassed solvents or an argon atmosphere does not prevent the formation of this green solid. Therefore, the formation of the green solid is not caused by O_2, as reported earlier[4a] and higher yields can not be achieved by working with carefully degassed solvents.

The use of 0.3 equiv of Cu(bpy)Cl is essential for the success of the cyclization, as lower yields of product are obtained by lowering the amount of catalyst, which may be due to its gradual decomposition. The reaction is preferably carried out in a 0.07 to 0.2 M solution (standard 0.1 M) in order to suppress telomerization processes due to intermolecular additions. At higher concentration more telomers are obtained. More dilute reaction mixtures (up to 0.01 M) show suppression of telomerization, but considerable amounts of starting material remain unchanged and very low yields of products are isolated. In the latter case the concentration of catalytically active species is significantly lower and cyclization is not complete before total catalyst decomposition has taken place. In general, trichloroacetates tend to be more reactive towards telomerization, expressed in the lower yield of medium-sized lactones isolated compared to the dichloroacetates, and the larger amount of telomers detected.

At temperatures below 80 °C cyclization becomes very slow and incomplete even after several hours of stirring. When the temperature is raised to 180 °C two effects are important: Firstly, the reaction is more rapid, reducing the reaction time from 18 h at 80 °C to about 1 h at temperatures above 160 °C. Secondly, the higher temperature facilitates the reactions of sterically hindered chloroacetates. All starting esters subjected to temperatures of up to 180 °C were thermally stable. Moreover, we did not observe decomposition of lactone **46** when it was treated with the Cu-catalyst under standard conditions at 180 °C.

The *endo*-mode of the cyclizations is supported by earlier observations and calculations on the radical ring closure to 8-membered carbocycles.[21] On the other hand we were unable to cyclize **7** using genuine free radical conditions. Thus, treatment of **7** with 1.1 equiv of $HSnBu_3$ and a catalytic amount of AIBN in refluxing PhH[8a] gave 34% of starting material **7**, 32% of reduced **7** (monochloroacetate) as well as telomeric material. We could not detect any lactone formation by using this cyclization technique.

Pyridyl amines and various 2,2'-bipyridines disubstituted at the 4-positions with methoxy, methoxycarbonyl and carboxylic acid groups were unsuccessful as ligands in the cyclization or gave very low yields of product. Without the bipyridine ligand present, no products could be observed in 1,2-dichloroethane.

The formation of C-C bonds catalyzed by the Cu(bpy)Cl system is generally believed to proceed through free or metal coordinated[27] radicals, called 'radical-pairs', in which a radical interacts strongly with the metal centre. Thus the incipient radical can be bonded to the Cu(II) which is formed after formal oxidation of the catalyst by chlorine atom abstraction.

Assuming radical-pairs the substrate is bonded intimately to the catalyst and therefore carbon-carbon bond formation takes place very close to or within the co-ordination sphere of the metal complex causing the carbon chain to fold in accord with the geometry of the complex. The following observations support this proposal of a template effect:

1) the extremely selective *endo*-mode cyclization of the various alkenyl acetates. In this series the exclusive *endo*-cyclizations of **25** and **26** are remarkable.

2) the inability to achieve 8-membered ring formation of dichloroacetate **7** applying reductive radical cyclization with $HSnBu_3$.

3) the slower reaction rate in the cyclizations of substituted alkyl chains, which results in higher temperatures necessary for lactone formation. The failure to cyclize the 1,1-disubstituted precursor **18** even at high temperatures is remarkable. The substituents probably interact sterically with the Cu-complex. This interaction becomes larger when the substituents are located closer to the ester function.

4) best results are obtained for 8- and 9-membered lactones. The synthesis of 10- and 11-membered rings is possible by the introduction of a rigid element into the alkenyl chain, presumingly due to a better fit in the catalyst complex by decreasing the flexibility of the chain.

In conclusion, the Cu(I) mediated cyclization of substituted alkenyl di- and trichloroacetates is a versatile tool for the construction of 8- to 11- membered lactone systems. The cyclization is regioselective for *endo*-ring closure and the products obtained are often formed in good yields.

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EXPERIMENTAL

General information. All reactions were carried out under an inert atmosphere of dry nitrogen. Standard syringe techniques were applied to transfer dry solvents. Infrared (IR) spectra were obtained from $CHCl_3$ solutions using a Perkin-Elmer 1310 spectrophotometer and wavelengths (ν) are reported in cm^{-1}. Proton nuclear resonance (^1H NMR) spectra were determined in $CDCl_3$, unless indicated otherwise using a Bruker AC 200 (200 MHz), a Bruker WM 250 (250 MHz), a Bruker AMX 300 (300 MHz) or a Bruker AMX 400 (400 MHz) spectrometer. These instruments were also used for ^{13}C NMR (APT) spectra (50, 63, 75.5 and 100.6 MHz respectively) in $CDCl_3$ (unless indicated otherwise). Chemical shifts (δ) are given in ppm downfield from tetramethylsilane. Mass spectra and accurate mass measurements were carried out using a Jeol SX/SX 102 A Tandem Mass Spectrometer, a Varian MAT 711 or a VG Micromass ZAB-2HF instrument. Elemental analysis were performed by Dornis u. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. R_f values were obtained by using thin-layer chromatography (TLC) on silica gel-coated plastic sheets (Merck silica gel 60 F_{254}) with the indicated solvent mixture of ethyl acetate and hexanes of the given ratio (EtOAc:hexanes). Chromatographic purification refers to flash chromatography[28] (fc) using a solvent mixture of ethyl acetate and hexanes in the given ratio and Janssen Chimica silica gel (0.030-0.075 mm). Melting points are uncorrected. CH_2Cl_2 and $(CH_2Cl)_2$ were distilled from P_2O_5 and stored over MS 3Å under an atmosphere of dry nitrogen. Benzene was distilled from P_2O_5 and stored over sodium-wire. Dry THF and Et_2O were distilled from sodium benzophenone ketyl prior to use. CuCl was purified.[29] Reactions 'in sealed tubes' were carried out in thick-walled glass tubes (3 to 15 cm long and 0.5 to 4 cm wide) equipped a thread, which could be screwed tight with a plastic cap.

General procedure A for the esterification of alkenols to di- and trichloroacetates:[10] A solution of di- or trichloroacetyl chloride (usually 1,0-1.3 equiv) in a 0.3 M solution of CH_2Cl_2 was cooled in an ice bath. The alkenol (1 equiv) was added in one portion, followed by dropwise addition of Et_3N (2 equiv) as a 3 M solution in CH_2Cl_2 over 20 minutes. The r.m. was stirred for 1 h at 0 °C and then poured into an equal volume of 2 M HCl(aq). The organic phase was separated, and the aqueous phase was extracted with 3 portions of CH_2Cl_2. The combined organic phases were dried on $MgSO_4$ or Na_2SO_4, concentrated *in vacuo* and the residue was purified by fc.

General procedure B for the Cu-catalyzed cyclization of di- and trichloroacetates to medium-sized lactones: The di- or trichloroacetate was dissolved in 1,2-dichloroethane or benzene (0.1 M solution) in a flask under a N_2 atmosphere. Catalytic amounts of CuCl (0.3 equiv) and of 2,2-bipyridine (0.3 equiv) were added simultaneously, and the mixture was immediately heated to reflux (80 °C). When the reaction was carried out at temperatures between 80 and 190 °C a sealable tube was used, charged with acetate and solvent, equipped with a stirring bar, placed under a N_2 atmosphere, and closed after addition of the two ingredients of the catalyst. It was immersed into an oil bath preheated at the desired temperature and stirred for several hours. When the conversion was complete (TLC-check, the tube was cooled in a water bath to r.t. prior to opening and rinsed with N_2 before closing the tube to continue the reaction), the reaction mixture was concentrated *in vacuo* and the green residue was directly purified by flash chromatography without further workup. The lactone products were sensitive to humidity and were therefore kept under a N_2 atmosphere.

Dichloroacetic acid but-3-enyl ester (5)[30]: According to the general procedure A, a solution of dichloroacetyl chloride (1.0 g, 6.7 mmol, 1.0 equiv) and 3-buten-1-ol (483 mg, 6.7 mmol) in 20 mL of CH_2Cl_2 was treated with Et_3N (1.36 g, 13.4 mmol, 2 equiv) in 5 mL of CH_2Cl_2. The r.m. was stirred at 0 °C for 1 h. Work-up and fc (1:10) afforded **5** (1.20 g, 6.6 mmol, 98%) as a colourless oil. R_f (1:8) 0.80; IR ν 3180, 3000, 2980, 1760, 1740, 1635, 1460; ^1H NMR (200 MHz) δ 2.47 (dq, 2 H, J = 1.3, 6.7 Hz, 2 H-2), 4.32 (t, 2 H, J = 6.7 Hz, 2 H-1), 5.05-5.20 (m, 2 H, 2 H-4), 5.70-5.90 (m, 1 H, H-3), 5.94 (s, 1 H, $CHCl_2$).

Trichloroacetic acid but-3-enyl ester (6)[30]: According to the general procedure A, a solution of trichloroacetyl chloride (689 mg, 3.79 mmol, 1.1 equiv) and 3-buten-1-ol (248 mg, 3.44 mmol) in 10 mL of CH_2Cl_2 was treated with Et_3N (694 mg, 6.88 mmol, 2 equiv) in 2 mL of CH_2Cl_2. The r.m. was stirred at 0 °C for 1 h. Work-up and fc (1:10) afforded **6** (650 mg, 2.99 mmol, 87%) as a colourless oil. R_f (1:10) 0.90; IR ν 3080, 2960, 1760, 1635, 1445, 1375, 1240, 1015, 980, 915, 865, 825;

^{1}H NMR (200 MHz) δ 2.52 (q, 2 H, J = 6.7 Hz, 2 H-2), 4.41 (t, 2 H, J = 6.7 Hz, 2 H-1), 5.10-5.25 (m, 2 H, 2 H-4), 5.81 (ddt, 1 H, J = 6.7, 10.3, 17.1 Hz, H-3).

Dichloroacetic acid pent-4-enyl ester (7)[30]: According to the general procedure A, a solution of dichloroacetyl chloride (1.0 g, 6.7 mmol, 1.0 equiv) and 4-penten-1-ol (577 mg, 6.7 mmol) in 20 mL of CH_2Cl_2 was treated with Et_3N (1.36 g, 13.4 mmol, 2 equiv) in 5 mL of CH_2Cl_2. The r.m. was stirred at 0 °C for 1 h. Work-up and fc (1:10) afforded **7** (1.32 g, 6.7 mmol, 100%) as a colourless oil. R_f (1:4) 0.80; IR ν 3180, 3020, 2960, 2940, 2840, 1760, 1740, 1635, 1460, 1445; ^{1}H NMR (200 MHz) δ 1.82 (quintet, 2 H, J = 6.7 Hz, 2 H-2), 2.10-2.25 (m, 2 H, 2 H-3), 4.28 (t, 2 H, J = 6.5 Hz, 2 H-1), 4.95-5.10 (m, 2 H, 2 H-5), 5.70-5.90 (m, 1 H, H-4), 5.94 (s, 1 H, $CHCl_2$); ^{13}C NMR (50 MHz) δ 27.1 (CH_2), 29.3 (CH_2), 64.1 ($CHCl_2$), 66.5 (C-1), 115.4 (C-5), 136.6 (C-4), 164.1 (CO).

Trichloroacetic acid pent-4-enyl ester (8)[30]: According to the general procedure A, a solution of trichloroacetyl chloride (6.3 g, 34.8 mmol, 1.0 equiv) and 4-penten-1-ol (3.0 g, 34.8 mmol) in 100 mL of CH_2Cl_2 was treated with Et_3N (7.03 g, 69.6 mmol, 2 equiv) in 25 mL of CH_2Cl_2. The reaction was stirred for 3 h at rt. Work-up and fc (1:20) afforded **8** (8.06 g, 34.8 mmol, 100%) as a colourless oil. R_f (1:6) 0.95; IR ν 3070, 2940, 2840, 1760, 1630, 1460, 1440, 1250, 970, 820; ^{1}H NMR (200 MHz) δ 1.88 (quintet, 2 H, J = 6.6 Hz, 2 H-2), 2.19 (q, 2 H, J = 7.3 Hz, 2 H-3), 4.38 (t, 2 H, J = 6.5 Hz, 2 H-1), 5.00-5.15 (m, 2 H, 2 H-5), 5.81 (ddt, 1 H, J = 6.6, 10.3, 17.0 Hz, H-4); ^{13}C NMR (50 MHz) δ 27.1 (CH_2), 29.4 (CH_2), 68.3 (C-1), 89.8 (CCl_3), 115.8 (C-5), 136.4 (C-4), 161.5 (CO).

Dichloroacetic acid hex-5-enyl ester (9): According to the general procedure A, a solution of dichloroacetyl chloride (1.0 g, 6.7 mmol, 1.0 equiv) and 5-hexen-1-ol (671 mg, 6.7 mmol) in 20 mL of CH_2Cl_2 was treated with Et_3N (1.36 g, 13.4 mmol, 2 equiv) in 5 mL of CH_2Cl_2. The reaction was stirred 1 h at 0 °C. Work-up and fc (1:10) afforded **9** (1.20 g, 5.7 mmol, 85%) as a colourless oil. R_f (1:8) 0.65; IR ν 3080, 3020, 2940, 2860, 1760, 1740, 1635, 1465, 1455, 1435, 1386; ^{1}H NMR (200 MHz) δ 1.40-1.50 (m, 2 H, 2 H-3), 1.60-1.80 (m, 2 H, 2 H-2), 2.00-2.15 (m, 2 H, 2 H-4), 4.26 (t, 2 H, J = 6.5 Hz, 2 H-1), 4.90-5.05 (m, 2 H, 2 H-6), 5.65-5.85 (m, 1 H, H-5), 5.93 (s, 1 H, $CHCl_2$); ^{13}C NMR (50 MHz) δ 24.8 (CH_2), 27.7 (CH_2), 33.1 (CH_2), 64.3 ($CHCl_2$), 67.5 (C-1), 115.1 (C-6), 138.0 (C-5), 164.1 (CO).

Trichloroacetic acid hex-5-enyl ester (10): According to the general procedure A, a solution of trichloroacetyl chloride (798 mg, 4.39 mmol, 1.1 equiv) and 5-hexen-1-ol (400 mg, 3.99 mmol) in 12 mL of CH_2Cl_2 was treated with Et_3N (806 mg, 7.98 mmol, 2 equiv) in 3 mL of CH_2Cl_2. The reaction was stirred for 1 h at 0 °C. Work-up and fc (1:10) afforded **10** (848 mg, 3.45 mmol, 86%) as a colourless oil. R_f (1:10) 0.75; IR ν 3080, 2940, 2860, 1760, 1635, 1245, 990, 910, 825; ^{1}H NMR (200 MHz) δ 1.45-1.60 (m, 2 H, 2 H-3), 1.70-1.90 (m, 2 H, 2 H-2), 2.05-2.20 (m, 2 H, 2 H-4), 4.37 (t, 2 H, J = 6.4 Hz, 2 H-1), 4.90-5.10 (m, 2 H, 2 H-5), 5.79 (ddt, 1 H, J = 6.6, 10.2, 17.0 Hz, H-4); ^{13}C NMR (50 MHz) δ 24.6 (CH_2), 27.4 (CH_2), 32.8 (CH_2), 69.0 (C-1), 89.8 (CCl_3), 115.0 (C-6), 137.6 (C-5), 161.5 (CO).

Dichloroacetic acid hept-6-enyl ester (11): To a suspension of 455 mg of $LiAlH_4$ (12 mmol, 8 equiv) in 5 mL of dry Et_2O was added dropwise of 6-heptenoic acid (200 mg, 1.5 mmol) in 15 mL of Et_2O at r.t. The r.m. was refluxed for 6 h and quenched by addition of 2 mL of MeOH, followed by 30 mL of 5% H_2SO_4 and extraction of the aqueous layer with 4 portions of 20 mL of Et_2O. The combined organic phases were dried on $MgSO_4$ and concentrated *in vacuo*. The crude product was essentially pure 6-hepten-1-ol (171 mg, 100%). According to the general procedure A, a solution of dichloroacetyl chloride (221 mg, 1.5 mmol, 1.0 equiv) and 6-hepten-1-ol (190 mg, 1.5 mmol) in 5 mL of CH_2Cl_2 was treated with Et_3N (303 mg, 3.0 mmol, 2 equiv) in 1 mL of CH_2Cl_2. The reaction was stirred 1 h at 0 °C. Work-up and fc (1:6) afforded **11** (316 mg, 1.4 mmol, 94%) as a colourless oil. R_f (1:6) 0.90; ^{1}H NMR (200 MHz) δ 1.35-1.55 (m, 4 H, 2 CH_2), 1.65-1.85 (m, 2 H, CH_2), 2.00-2.15 (m, 2 H, 2 H-5), 4.27 (t, 2 H, J = 6.6 Hz, 2 H-1), 4.90-5.07 (m, 2 H, 2 H-7), 5.65-5.85 (m, 1 H, H-6), 5.94 (s, 1 H, $CHCl_2$); ^{13}C NMR (50 MHz) δ 25.0 (CH_2), 28.1 (CH_2), 28.3 (CH_2), 33.5 (CH_2), 64.3 ($CHCl_2$), 67.6 (C-1), 114.6 (C-7), 138.4 (C-6), 164.4 (CO).

Trichloroacetic acid hept-6-enyl ester (12): According to the general procedure A, a solution of trichloroacetyl chloride (627 mg, 3.54 mmol, 1.1 equiv) and 6-hepten-1-ol (368 mg, 3.23 mmol) in 10 mL of CH_2Cl_2 was treated with Et_3N (651 mg, 6.45 mmol, 2 equiv) in 2 mL of CH_2Cl_2. The reaction was stirred for 1 h at 0 °C and 18 h at rt. Work-up and fc (1:20)

afforded **12** (556 mg, 2.14 mmol, 66%) as a colourless oil. R_f (1:10) 0.60; IR ν 3010, 2970, 2930, 2850, 1760, 1630, 1220; ^{1}H NMR (200 MHz) δ 1.35-1.50 (m, 4 H, 2 CH_2), 1.70-1.90 (m, 2 H, CH_2), 2.00-2.15 (m, 2 H, 2 H-5), 4.36 (t, 2 H, J = 6.6 Hz, 2 H-1), 4.90-5.07 (m, 2 H, 2 H-7), 5.79 (ddt, 1 H, J = 6.9, 10.2, 17.0 Hz, H-6); ^{13}C NMR (50 MHz) δ 24.8 (CH_2), 27.9 (CH_2), 28.1 (CH_2), 33.3 (CH_2), 69.3 (C-1), 89.9 (CCl_3), 114.6 (C-7), 138.2 (C-6), 161.8 (CO).

Dichloroacetic acid undec-10-enyl ester (13): According to the general procedure A, a solution of dichloroacetyl chloride (1.0 g, 6.7 mmol, 1.0 equiv) and 10-undecen-1-ol (1.14 g, 6.7 mmol) in 20 mL of CH_2Cl_2 was treated with Et_3N (1.36 g, 13.4 mmol, 2 equiv) in 5 mL of CH_2Cl_2. The reaction was stirred 1 h at 0 °C. Work-up and fc (1:10) afforded **13** (1.60 g, 5.7 mmol, 85%) as a colourless oil. R_f (1:10) 0.70; IR ν 3070, 2920, 2850, 1760, 1740, 1635, 1460; ^{1}H NMR (250 MHz) δ 1.20-1.45 (m, 12 H, 6 CH_2), 1.62-1.78 (m, 2 H, CH_2), 1.95-2.08 (m, 2 H, 2 H-9), 4.25 (t, 2 H, J = 6.7 Hz, 2 H-1), 4.85-5.00 (m, 2 H, 2 H-11), 5.70-5.90 (m, 1 H, H-10), 5.92 (s, 1 H, $CHCl_2$); ^{13}C NMR (50 MHz) δ 25.3 (CH_2), 28.0 (2 CH_2), 28.6 (CH_2), 28.8 (2 CH_2), 29.1 (CH_2), 33.5 (CH_2), 64.1 ($CHCl_2$), 67.2 (C-1), 113.9 (C-11), 138.6 (C-10), 164.1 (CO).

Dichloroacetic acid pent-4-ynyl ester (14): According to the general procedure A, a solution of dichloroacetyl chloride (483 mg, 3.3 mmol, 1.0 equiv) and 4-pentyn-1-ol (276 mg, 3.3 mmol) in 10 mL of CH_2Cl_2 was treated with Et_3N (668 mg, 6.6 mmol, 2 equiv) in 2 mL of CH_2Cl_2. The reaction was stirred for 1 h at 0 °C. Work-up and fc (1:4) afforded **14** (562 mg, 2.9 mmol, 87%) as a light yellow oil. R_f (1:3) 0.60; IR ν 3300, 2960, 2930, 2840, 2110, 1760, 1740, 1460, 1440, 1430, 1385, 1370, 810; ^{1}H NMR (200 MHz) δ 1.85-2.05 (m, 3 H, 2 H-2, H-5), 2.34 (dt, 2 H, J = 2.6, 7.0 Hz, 2 H-3), 4.40 (t, 2 H, J = 6.2 Hz, 2 H-1), 5.95 (s, 1 H, $CHCl_2$); ^{13}C NMR (50 MHz) δ 14.7 (C-3), 26.9 (C-2), 64.1 ($CHCl_2$), 65.7 (C-1), 69.3 (C-4), 82.2 (C-5), 164.2 (CO).

Trichloroacetic acid pent-4-ynyl ester (15): According to the general procedure A, a solution of trichloroacetyl chloride (1.43 g, 7.8 mmol, 1.1 equiv) and 4-pentyn-1-ol (600 mg, 7.13 mmol) in 24 mL of CH_2Cl_2 was treated with Et_3N (1.44 g, 14.3 mmol, 2 equiv) in 8 mL of CH_2Cl_2. The reaction was stirred for 1.5 h at 0 °C. Work-up and fc (1:8) afforded **15** (1.51 g, 6.56 mmol, 92%) as a colourless oil. R_f (1:8) 0.65; IR ν 3300, 3030, 2960, 2840, 1760, 1460, 1440, 1430, 1245, 1020, 820; ^{1}H NMR (200 MHz) δ 1.90-2.07 (m, 3 H, 2 H-2 and H-5), 2.37 (dt, 2 H, J = 2.6, 6.9 Hz, 2 H-3), 4.49 (t, 2 H, J = 6.1 Hz, 2 H-1); ^{13}C NMR (50 MHz) δ 14.8 (C-3), 26.9 (C-2), 67.5 (C-1), 69.6 (C-4), 82.0 (C-5), 89.7 (CCl_3), 161.7 (CO).

Dichloroacetic acid 1-methyl-pent-4-enyl ester (16): A suspension of 531 mg of magnesium chips (22.1 mmol, 1.1 equiv) in 3 mL of dry Et_2O was treated with of 5-bromo-1-pentene (3.0 g, 20.1 mmol) in 30 mL of Et_2O and the resulting Grignard reagent was refluxed for 1 h. At 10 °C a solution of 10.9 g of acetaldehyde (0.25 mol, 12 equiv) in 10 mL of Et_2O was added dropwise over 30 minutes, the reaction mixture was stirred for 2 h at rt and poured into ice/15% H_2SO_4. The aqueous layer was extracted with Et_2O (3 x 50 mL), the combined organic phases were dried ($MgSO_4$), concentrated *in vacuo* and purified by fc (1:5). This yielded 913 mg (10.8 mmol, 54%) of 5-hexen-2-ol. According to the general procedure A, a solution of dichloroacetyl chloride (1.09 g, 7.15 mmol, 1.0 equiv) and 5-hexen-2-ol (602 mg, 7.15 mmol) in 20 mL of CH_2Cl_2 was treated with Et_3N (1.44 g, 14.3 mmol, 2 equiv) in 4 mL of CH_2Cl_2. The reaction was stirred for 18 h at r.t.. Work-up and fc (1:3) afforded **16** (1.27 g, 6.0 mmol, 84%) as a colourless oil. R_f (1:3) 0.75; IR ν 3080, 2980, 2940, 2850, 2240, 1750, 1670, 1390, 1380, 1170, 900; ^{1}H NMR (200 MHz) δ 1.33 (d, 3 H, J = 6.2 Hz, CH_3), 1.57-1.90 (m, 4 H, 2 H-3 and 2 H-4), 2.20 (sextet, 1 H, J = 6.5 Hz, H-2), 4.95-5.05 (m, 2 H, 2 H-6), 5.75 (ddt, 1 H, J = 6.6, 10.1, 17.0 Hz, H-5), 5.92 (s, 1 H, $CHCl_2$).

Dichloroacetic acid 1-phenyl-pent-4-enyl ester (17): A suspension of 396 mg of magnesium chips (16.3 mmol, 1.1 equiv) in 5 mL Et_2O was treated with a solution of of 4-bromo-1-butene (2.0 g, 14.8 mmol) in 50 mL of Et_2O. The resulting Grignard reagent was refluxed for 1 h, then cooled down to -10 °C, followed by the slowly addition of benzaldehyde (1.65 g, 1.05 equiv, 15.5 mmol) keeping the temperature below -5 °C. The r.m. was slowly brought to r.t. and poured into 100 g of ice and 15 mL of H_2SO_4. 1-Phenyl-4-penten-1-ol[11] was obtained by extraction with Et_2O (3 x 50 mL), drying on Na_2SO_4, concentration *in vacuo* and purification by fc (1:3.5) as a colourless oil (1.49 g, 9.18 mmol, 62%). R_f (1:3.5) 0.40, IR ν 3600, 3440, 3070, 3000, 2930, 2850, 1630, 1490, 1445, 910; ^{1}H NMR (200 MHz) δ 1.63 (bs, 1 H, OH), 1.70-2.00 (m, 2 H, 2 H-2), 2.00-2.25 (m, 2 H, 2 H-3), 4.70 (dd, 1 H, J = 5.9, 7.3 Hz, H-1), 4.95-5.12 (m, 2 H, 2 H-5), 5.75-5.95 (m, 1 H, H-4), 7.20-7.40 (m, 5 H, Ar). According to the general procedure A, a solution of dichloroacetyl chloride (770 mg, 5.2 mmol, 1.2 equiv) and 1-phenyl-4-penten-1-ol (705

mg, 4.3 mmol) in 15 mL of CH_2Cl_2 was treated with Et_3N (870 mg, 8.6 mmol, 2 equiv) in 5 mL of CH_2Cl_2. The reaction was stirred for 2 h at 0 °C. Work-up and fc (1:8) afforded **17** (745 mg, 2.7 mmol, 63%) as a colourless oil. From the r.m. 280 mg of starting alcohol was isolated, corrected for starting material the yield of esterification was 100%. R_f (1:8) 0.75; IR ν 3060, 3000, 2940, 1755, 1630, 1490, 1445, 910, 790; ^1H NMR (200 MHz) δ 1.90-2.25 (m, 4 H, 2 H-2 and 2 H-3), 4.95-5.15 (m, 2 H, 2 H-5), 5.70-5.95 (m, 2 H, H-1 and H-4), 5.95 (s, 1 H, $CHCl_2$), 7.25-7.45 (m, 5 H, Ar); ^{13}C NMR (50 MHz) δ 29.4 (C-3), 35.0 (C-2), 64.4 ($CHCl_2$), 78.9 (C-1), 115.7 (C-5), 126.3, 126.3, 128.4, 128.5, 128.5, 136.7 (C-4), 138.7, 163.5 (CO).

Dichloroacetic acid 1,1-dimethyl-pent-4-enyl ester (18): According to the preparation of **17**, 396 mg of magnesium chips (16.3 mmol, 1.1 equiv) in 5 mL of Et_2O were treated with of 4-bromo-1-butene (2.0 g, 14.8 mmol) in 15 mL of Et_2O, followed by 30 minutes of reflux. At r.t. 1.72 g of dry acetone (29.6 mmol, 2 equiv, 2.2 mL) in 10 mL of Et_2O was added slowly to the r.m. and stirred for 5 h. After work-up 2-methyl-5-hexen-2-ol[12] (974 mg, 8.53 mmol, 52%) was obtained by fc (1:4) as a light yellow oil. According to the general procedure A, a solution of dichloroacetyl chloride (940 mg, 6.4 mmol, 1.0 equiv) and 2-methyl-5-hexen-2-ol (731 mg, 6.4 mmol) in 20 mL of CH_2Cl_2 was treated with Et_3N (1.3 g, 12.8 mmol, 2 equiv) in 5 mL of CH_2Cl_2. The reaction was stirred for 1 h at 0 °C. Work-up and fc (1:6) afforded **18** (727 mg, 3.2 mmol, 50%) as a colourless oil. From the r.m. 345 mg of starting alcohol was isolated, the corrected yield for starting material was 95%. R_f (1:6) 0.90; IR ν 3170, 2980, 2920, 2850, 1800, 1750, 1635, 1450, 1380, 1365, 910; ^1H NMR (200 MHz) δ 1.52 (s, 6 H, 2 CH_3), 1.85-2.00 (m, 2 H, 2 H-2), 2.10-2.25 (m, 2 H, 2 H-3), 4.95-5.10 (m, 2 H, 2 H-5), 5.70-5.95 (m, 1 H, H-4), 5.83 (s, 1 H, $CHCl_2$); ^{13}C NMR (50 MHz) δ 25.3 (2 CH_3), 27.8 (C-3), 39.5 (C-2), 65.1 ($CHCl_2$), 86.7 (C-1), 114.7 (C-5), 137.6 (C-4), 163.2 (CO).

Dichloroacetic acid 2,2-dimethyl-pent-4-enyl ester (19): According to the preparation of **11**, 3.87 g of 2,2-dimethyl-4-penten-1-al (34.5 mmol) in 77 mL of Et_2O was treated with of $LiAlH_4$ (1.96 g, 51.8 mmol, 1.5 equiv). The r.m. was refluxed for 2 h and stirred overnight at r.t. Excess $LiAlH_4$ was treated with 5 mL of MeOH, 200 mL of 5% H_2SO_4 was added to the mixture and extracted by Et_2O (3 x 100 mL), the organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. 2,2-Dimethyl-4-penten-1-ol[13] was obtained essentially pure (3.53 g, 30.9 mmol, 90%). According to the general procedure A, a solution of dichloroacetyl chloride (567 mg, 3.85 mmol, 1.1 equiv) and 2,2-dimethyl-4-penten-1-ol (400 mg, 3.51 mmol) in 10 mL of CH_2Cl_2 was treated with Et_3N (709 mg, 7.0 mmol, 2 equiv) in 2 mL of CH_2Cl_2. The reaction was stirred for 10 minutes at 0 °C. Work-up and fc (1:20) afforded **19** (790 mg, 3.51 mmol, 100%) as a light yellow oil. R_f (1:8) 0.65; IR ν 3070, 2960, 1760, 1740, 1640, 1300, 1160, 990, 910, 810; ^1H NMR (200 MHz) δ 0.96 (s, 6 H, 2 CH_3), 2.09 (d, 2 H, J = 7.5 Hz, 2 H-3), 3.99 (s, 2 H, 2 H-1), 5.01 (m, 2 H, 2 H-5), 5.85 (m, 1 H, H-4), 5.97 (s, 1 H, $CHCl_2$).

Dichloroacetic acid 2,2-dimethyl-pent-4-enyl ester (20): According to the general procedure A, a solution of trichloroacetyl chloride (5.76 g, 31.5 mmol, 1.2 equiv) and 2,2-dimethyl-4-penten-1-ol (3.0 g, 26.3 mmol) in 90 mL of CH_2Cl_2 was treated with Et_3N (5.3 g, 52.6 mmol, 2 equiv) in 7 mL of CH_2Cl_2. The reaction was stirred for 1.5 h at 0 °C. Work-up and fc (1:10) afforded **20** (6.78 g, 26.1 mmol, 99%) as a colourless oil. R_f (1:10) 0.90; IR ν 3070, 2960, 1760, 1635, 1460, 1390, 1365, 1250, 990, 835, 820; ^1H NMR (300 MHz) δ 0.99 (s, 6 H, 2 CH_3), 2.10 (d, 2 H, J = 7.5 Hz, 2 H-3), 4.06 (s, 2 H, 2 H-1), 5.03-5.15 (m, 2 H, 2 H-5), 5.80 (ddt, 1 H, J = 7.6, 10.3, 16.8 Hz, H-4); ^{13}C NMR (50 MHz) δ 23.9 (2 CH_3), 34.6 (CH_2), 43.1 (CH_2), 76.3 (C-1), 90.0 (CCl_3), 118.3 (C-5), 133.6 (C-4), 161.8 (CO).

Dichloroacetic acid 3,3-dimethyl-pent-4-enyl ester (21): According to the general procedure A, a solution of dichloroacetyl chloride (1.26 g, 8.6 mmol, 1.1 equiv) and 3,3-dimethyl-4-penten-1-ol[14] (700 mg, 7.8 mmol) in 26 mL of CH_2Cl_2 was treated with Et_3N (1.58 g, 15.6 mmol, 2 equiv) in 5 mL of CH_2Cl_2. The reaction was stirred for 2 h at 0 °C. Work-up and fc (1:10) afforded **21** (1.52 g, 6.7 mmol, 87%) as a light yellow oil. R_f (1:10) 0.55; IR ν 3080, 2960, 2920, 2860, 1760, 1630, 1460, 1410, 1380, 1360, 1300, 1160, 1000, 970, 915, 810; ^1H NMR (400 MHz) δ 1.06 (s, 6 H, 2 CH_3), 1.73 (t, 2 H, J = 7.3 Hz, 2 H-2), 4.26 (t, 2 H, J = 7.3 Hz, 2 H-1), 4.96 (dd, 1 H, J = 1.0, 17.3 Hz, H-5 *trans*), 4.98 (dd, 1 H, J = 1.0, 10.3 Hz, H-5 *cis*), 5.77 (dd, 1 H, J = 11.0, 17.2 Hz, H-4), 5.91 (s, 1 H, $CHCl_2$).

Trichloroacetic acid 3,3-dimethyl-pent-4-enyl ester (22): According to the general procedure A, a solution of trichloroacetyl chloride (1.56 g, 8.6 mmol, 1.1 equiv) and 3,3-dimethyl-4-penten-1-ol[14] (700 mg, 7.8 mmol) in 26 mL of CH_2Cl_2 was treated with Et_3N (1.58 g, 15.6 mmol, 2 equiv) in 5 mL of CH_2Cl_2. The reaction was stirred for 2 h at 0 °C. Work-up and fc

(1:10) afforded **22** (1.71 g, 6.6 mmol, 85%) as a colourless oil. R_f (1:10) 0.75; IR ν 3080, 2960, 2920, 2860, 1760, 1635, 1455, 1410, 1380, 1360, 1240, 1000, 980, 915, 820, 680; ^{1}H NMR (400 MHz) δ 1.08 (s, 6 H, 2 CH_3), 1.79 (t, 2 H, J = 7.2 Hz, 2 H-2), 4.34 (t, 2 H, J = 7.2 Hz, 2 H-1), 4.98 (d, 1 H, J = 17.4 Hz, H-5 *trans*), 4.99 (d, 1 H, J = 10.7 Hz, H-5 *cis*), 5.78 (dd, 1 H, J = 11.1, 17.1 Hz, H-4); ^{13}C NMR (50 MHz) δ 26.9 (2 CH_3), 35.6 (CH_2), 39.8 (CH_2), 67.1 (C-1), 89.9 (CCl_3), 111.7 (C-5), 146.5 (C-4), 161.9 (CO).

Dichloroacetic acid 4-methyl-pent-4-enyl ester (23): According to the general procedure A, a solution of dichloroacetyl chloride (224 mg, 1.53 mmol, 1.1 equiv) and 4-methyl-4-penten-1-ol[15] (139 mg, 1.39 mmol) in 5 mL of CH_2Cl_2 was treated with Et_3N (281 mg, 2.78 mmol, 2 equiv) in 1 mL of CH_2Cl_2. The reaction was stirred for 1 h at 0 °C. Work-up and fc (1:10) afforded **23** (255 mg, 1.21 mmol, 87%) as a colourless oil. R_f (1:10) 0.55; IR ν 3060, 2960, 2930, 2840, 1760, 1640, 1440, 1370, 1300, 1160, 1035, 980, 890, 810; ^{1}H NMR (400 MHz) δ 1.73 (s, 3 H, CH_3), 1.86 (quintet, 2 H, J = 6.9 Hz, 2 H-2), 2.12 (t, 2 H, J = 7.7 Hz, 2 H-3), 4.28 (t, 2 H, J = 6.6 Hz, 2 H-1), 4.71 (s, 1 H, H-5), 4.76 (s, 1 H, H-5'), 5.94 (s, 1 H, $CHCl_2$).

Trichloroacetic acid 4-methyl-pent-4-enyl ester (24): According to the general procedure A, a solution of trichloroacetyl chloride (356 mg, 1.97 mmol, 1.1 equiv) and 4-methyl-4-penten-1-ol[15] (180 mg, 1.79 mmol) in 5 mL of CH_2Cl_2 was treated with Et_3N (362 mg, 3.59 mmol, 2 equiv) in 1 mL of CH_2Cl_2. The reaction was stirred for 1 h at 0 °C. Work-up and fc (1:20) afforded **24** (405 mg, 1.65 mmol, 92%) as a colourless oil. R_f (1:10) 0.60; IR ν 3070, 2920, 2840, 1760, 1640, 1460, 1440, 1370, 1245, 980, 820, 675; ^{1}H NMR (200 MHz) δ 1.74 (s, 3 H, CH_3), 1.92 (quintet, 2 H, J = 6.5 Hz, 2 H-2), 2.16 (t, 2 H, J = 7.0 Hz, 2 H-3), 4.37 (t, 2 H, J = 6.5 Hz, 2 H-1), 4.73 (s, 1 H, H-5), 4.78 (s, 1 H, H-5'); ^{13}C NMR (50 MHz) δ 22.0 (CH_3), 25.9 (CH_2), 33.3 (CH_2), 68.6 (C-1), 89.8 (CCl_3), 111.0 (C-5), 143.5 (C-4), 161.6 (CO).

(*E*)-Dichloroacetic acid hex-4-enyl ester (25): According to the general procedure A, a solution of dichloroacetyl chloride (1.13 g, 7.69 mmol, 1.1 equiv) and (*E*)-4-hexen-1-ol (700 mg, 6.99 mmol) in 20 mL of CH_2Cl_2 was treated with Et_3N (1.41 g, 14.0 mmol, 2 equiv) in 5 mL of CH_2Cl_2. The reaction was stirred for 2 h at 0 °C. Work-up and fc (1:6) afforded **25** (1.39 g, 6.59 mmol, 94%) as a colourless oil. R_f (1:8) 0.55; IR ν 3010, 2960, 2940, 2920, 2850, 1760, 1460, 1445, 1435, 1385, 1375, 1250, 1165, 960, 810; ^{1}H NMR (300 MHz) δ 1.65 (dd, 3 H, J = 0.8, 5.8 Hz, CH_3), 1.77 (quintet, 2 H, J = 6.7 Hz, 2 H-2), 2.09 (q, 2 H, J = 6.8 Hz, 2 H-3), 4.27 (t, 2 H, J = 6.6 Hz, 2 H-1), 5.35-5.52 (m, 2 H, H-4 and H-5), 5.94 (s, 1 H, $CHCl_2$); ^{13}C NMR (50 MHz) δ 17.7 (C-6), 27.8 (CH_2), 28.3 (CH_2), 64.2 ($CHCl_2$), 66.9 (C-1), 126.1 (CH=), 129.2 (CH=), 164.4 (CO).

(*E*)-Trichloroacetic acid hex-4-enyl ester (26): According to the general procedure A, a solution of trichloroacetyl chloride (1.40 g, 7.69 mmol, 1.1 equiv) and (*E*)-4-hexen-1-ol (700 mg, 76.99 mmol) in 20 mL of CH_2Cl_2 was treated with Et_3N (1.41 g, 14.0 mmol, 2 equiv) in 5 mL of CH_2Cl_2. The reaction was stirred for 2 h at 0 °C. Work-up and fc (1:6) afforded **26** (1.62 g, 6.6 mmol, 94%) as a colourless oil. R_f (1:8) 0.75; IR ν 2960, 2940, 2920, 2850, 1760, 1460, 1445, 1435, 1375, 1250, 1070, 990, 910, 825; ^{1}H NMR (300 MHz) δ 1.65 (dd, 3 H, J = 0.8, 5.8 Hz, CH_3), 1.83 (quintet, 2 H, J = 6.7 Hz, 2 H-2), 2.12 (q, 2 H, J = 6.8 Hz, 2 H-3), 4.36 (t, 2 H, J = 6.5 Hz, 2 H-1), 5.35-5.55 (m, 2 H, H-4 and H-5); ^{13}C NMR (50 MHz) δ 17.5 (C-6), 27.6 (CH_2), 28.1 (CH_2), 68.4 (C-1), 89.7 (CCl_3), 126.1 (CH=), 128.9 (CH=), 161.6 (CO).

Dichloroacetic acid 5-methyl-hex-4-enyl ester (27): According to the general procedure A, a solution of dichloroacetyl chloride (570 mg, 3.9 mmol, 1.1 equiv) and 5-methyl-4-hexen-1-ol (400 mg, 3.5 mmol) in 10 mL of CH_2Cl_2 was treated with Et_3N (707 mg, 7.0 mmol, 2 equiv) in 2 mL of CH_2Cl_2. The reaction was stirred for 1 h at 0 °C. Work-up and fc (1:10) afforded **27** (732 mg, 3.25 mmol, 93%) as a light yellow oil. R_f (1:10) 0.55; IR ν 2960, 2920, 2840, 1755, 1440, 1370, 1300, 1160, 980, 905, 810; ^{1}H NMR (400 MHz) δ 1.60 (s, 3 H, CH_3), 1.70 (s, 3 H, CH_3), 1.75 (quintet, 2 H, J = 7.3 Hz, 2 H-2), 2.09 (q, 2 H, J = 7.3 Hz, 2 H-3), 4.26 (t, 2 H, J = 6.6 Hz, 2 H-1), 5.09 (tt, 1 H, J = 1.3, 7.3 Hz, H-4), 5.94 (s, 1 H, $CHCl_2$); ^{13}C NMR (50 MHz) δ 17.4 (CH_3), 23.8 (CH_2), 25.5 (CH_3), 28.2 (CH_2), 64.2 ($CHCl_2$), 66.9 (C-1), 122.5 (C-4), 132.8 (C-5), 164.3 (CO).

Trichloroacetic acid 5-methyl-hex-4-enyl ester (28): According to the general procedure A, a solution of trichloroacetyl chloride (709 mg, 3.9 mmol, 1.1 equiv) and 5-methyl-4-hexen-1-ol (400 mg, 3.5 mmol) in 10 mL of CH_2Cl_2 was treated with Et_3N (707 mg, 7.0 mmol, 2 equiv) in 2 mL of CH_2Cl_2. The reaction was stirred for 1 h at 0 °C. Work-up and fc

(1:10) afforded **28** (858 mg, 3.31 mmol, 95%) as a colourless oil. R_f (1:10) 0.75; IR ν 2960, 2920, 2840, 1760, 1440, 1370, 1250, 980, 900, 825, 670; ^{1}H NMR (400 MHz) δ 1.61 (s, 3 H, CH_3), 1.70 (s, 3 H, CH_3), 1.80 (quintet, 2 H, J = 6.9 Hz, 2 H-2), 2.12 (q, 2 H, J = 7.2 Hz, 2 H-3), 4.35 (t, 2 H, J = 6.4 Hz, 2 H-1), 5.10 (t, 1 H, J = 7.1 Hz, H-4); ^{13}C NMR (50 MHz) δ 17.4 (CH_3), 23.8 (CH_2), 25.5 (CH_3), 28.1 (CH_2), 68.6 (C-1), 89.9 (CCl_3), 122.4 (C-4), 132.9 (C-5), 161.6 (CO).

Dichloroacetic acid hept-6-en-3-ynyl ester (29): To a solution of 3-butyn-1-ol (2.36 g, 33.7 mmol) in 5.5 mL of DMF were added CuCl (152 mg, 1.53 mmol, 0.05 equiv), K_2CO_3 (6.34 g, 45.9 mmol, 1.5 equiv) and *n*-Bu_4NCl (861 mg, 3.1 mmol, 0.1 equiv) and under vigorous stirring at r.t., allylbromide (3.7 g, 30.6 mmol, 1.0 equiv) was added dropwise by syringe. The yellow r.m. was stirred for 18 h at r.t., as it turned green slowly. Et_2O (30 mL) was added and the green suspension was filtered over Celite. The filter was rinsed with 50 mL of Et_2O and the filtrate was washed with 50 mL of NaCl(aq), dried (Na_2SO_4), concentrated *in vacuo* and purified by fc (1:2.5) to afford hept-6-en-3-yn-1-ol[17] (3.49 g, 31.6 mmol, 94%) as a light yellow oil. R_f (1:2) 0.40; IR ν 3580, 3440, 3080, 3000, 2940, 2880, 1635, 1415, 910; ^{1}H NMR (200 MHz) δ 1.91 (bs, 1 H, OH), 2.47 (m, 2 H, 2 H-2), 2.95 (m, 2 H, 2 H-5), 3.70 (t, 2 H, J = 6.2 Hz, 2 H-1), 5.10 (dd, 1 H, J = 1.4, 9.9 Hz, H-7 *cis*), 5.30 (dd, 1 H, J = 1.5, 16.9 Hz, H-7 *trans*), 5.83 (ddt, 1 H, J = 5.3, 9.9, 16.9 Hz, H-6); ^{13}C NMR (75.5 MHz) δ 22.6 (CH_2), 22.7 (CH_2), 60.9 (C-1), 78.1 (C-alkyne), 78.9 (C-alkyne), 115.5 (C-7), 132.7 (C-6). According to the general procedure A, a solution of dichloroacetyl chloride (411 mg, 2.79 mmol, 1.0 equiv) and hept-6-en-3-yn-1-ol (307 mg, 2.79 mmol) in 5 mL of CH_2Cl_2 was treated with Et_3N (564 mg, 5.58 mmol, 2 equiv) in 2 mL of CH_2Cl_2 at 0 °C. The reaction was stirred for 18 h at r.t.. Work-up and fc (1:10) afforded **29** (617 mg, 2.79 mmol, 100%) as a yellow oil. R_f (1:10) 0.45; IR ν 3080, 3000, 2900, 1760, 1635, 1460, 1415, 910; ^{1}H NMR (200 MHz) δ 2.60-2.70 (m, 2 H, 2 H-2), 2.90-3.10 (m, 2 H, 2 H-5), 4.36 (t, 2 H, J = 6.9 Hz, 2 H-1), 5.10 (dq, 1 H, J = 1.6, 9.9 Hz, H-7 *cis*), 5.30 (dq, 1 H, J = 1.7, 17.0 Hz, H-7 *trans*), 5.80 (dt, 1 H, J = 4.9, 10.1, 17.0 Hz, H-6), 5.97 (s, 1 H, $CHCl_2$).

Trichloroacetic acid hept-6-en-3-ynyl ester (30): According to the general procedure A, a solution of trichloroacetyl chloride (495 mg, 2.72 mmol, 1.0 equiv) and hept-6-en-3-yn-1-ol (300 mg, 2.72 mmol) in 9 mL of CH_2Cl_2 was treated with Et_3N (549 mg, 5.44 mmol, 2 equiv) in 2 mL of CH_2Cl_2 at 0 °C. The reaction was stirred for 1 h at 0 °C. Work-up and fc (1:10) afforded **30** (617 mg, 2.79 mmol, 100%) as a yellow oil. R_f (1:6) 0.75; IR ν 3080, 2980, 2920, 1760, 1630, 1420, 1240, 1005, 990, 820; ^{1}H NMR (200 MHz) δ 2.60-2.75 (m, 2 H, 2 H-2), 2.90-3.00 (m, 2 H, 2 H-5), 4.44 (t, 2 H, J = 6.9 Hz, 2 H-1), 5.10 (dq, 1 H, J = 1.7, 9.9 Hz, H-7 *cis*), 5.30 (dq, 1 H, J = 1.7, 17.0 Hz, H-7 *trans*), 5.80 (ddt, 1 H, J = 5.2, 9.9, 17.0 Hz, H-6).

(Z)-Dichloroacetic acid hepta-3,6-dienyl ester (31): To powdered $NaBH_4$ (2.2 g, 58.1 mmol, 8 equiv) and $PdCl_2$ (121 mg, 0.68 mmol, 0.08 equiv) was slowly added 145 g of dry polyethylene glycol 200[18], followed by 80 mL of CH_2Cl_2. The mixture was cooled to -10 °C, when hept-6-en-3-yn-1-ol (800 mg, 7.26 mmol, 1 equiv) in 1 mL of CH_2Cl_2 was added in one portion and stirred for 2 h allowing the temperature to rise slowly to r.t. in 2 h. The dark grey r.m. was poured into 300 mL of H_2O and extracted with CH_2Cl_2 (3 x 80 mL). The organic phases were dried ($MgSO_4$), concentrated and purified by fc (1:2) to afford (Z)-hepta-3,6-dien-1-ol (780 mg, 6.95 mmol, 96%) as a colourless oil. R_f (1:2) 0.40; IR ν 3600, 3470, 3080, 3000, 2950, 2930, 2870, 1630, 1045, 995, 910; ^{1}H NMR (300 MHz) δ 2.29 (q, 2 H, J = 6.7 Hz, 2 H-2), 2.45 (bs, 1 H, OH), 2.80 (t, 2 H, J = 6.8 Hz, 2 H-5), 3.59 (t, 2 H, J = 6.4 Hz, 2 H-1), 4.95 (dt, 1 H, J = 1.5, 10.2 Hz, H-7 *cis*), 5.02 (dq, 1 H, J = 1.7, 17.1 Hz, H-7 *trans*), 5.40-5.57 (m, 2 H, H-3 and H-4), 5.78 (ddt, 1 H, J = 6.2, 10.2, 16.9 Hz, H-6); ^{13}C NMR (75.5 MHz) δ 30.5 (CH_2), 31.4 (CH_2), 61.9 (C-1), 114.7 (C-7), 126.4 (CH=), 129.6 (CH=), 132.8 (C-6). According to the general procedure A, a solution of dichloroacetyl chloride (434 mg, 2.94 mmol, 1.1 equiv) and (Z)-hepta-3,6-dien-1-ol (300 mg, 2.67 mmol) in 9 mL of CH_2Cl_2 was treated with Et_3N (539 mg, 5.3 mmol, 2 equiv) in 2 mL of CH_2Cl_2 at 0 °C. The reaction was stirred for 1 h at 0 °C. Work-up and fc (1:10) afforded **31** (388 mg, 1.74 mmol, 65%) as a colourless oil. R_f (1:8) 0.65; IR ν 3080, 3020, 2960, 2920, 2850, 1760, 1635, 1445, 1300, 1165, 990; ^{1}H NMR (200 MHz) δ 2.48 (q, 2 H, J = 6.8 Hz, 2 H-2), 2.82 (t, 2 H, J = 6.0 Hz, 2 H-5), 4.28 (t, 2 H, J = 6.8 Hz, 2 H-1), 5.00 (d, 1 H, J = 11.6 Hz, H-7 *cis*), 5.04 (d, 1 H, J = 17.1 Hz, H-7 *trans*), 5.40-5.65 (m, 2 H, H-3, H-4), 5.81 (ddt, 1 H, J = 6.1, 10.1, 17.1 Hz, H-6), 5.94 (s, 1 H, $CHCl_2$).

(Z)-Trichloroacetic acid hepta-3,6-dienyl ester (32): According to the general procedure A, a solution of trichloroacetyl chloride (534 mg, 2.94 mmol, 1.1 equiv) and (Z)-hepta-3,6-dien-1-ol (300 mg, 2.67 mmol) in 9 mL of CH_2Cl_2 was treated with Et_3N (539 mg, 5.34 mmol, 2 equiv) in 2 mL of CH_2Cl_2 at 0 °C. The reaction was stirred for 1 h at 0 °C. Work-up and

fc (1:10) afforded **32** (424 mg, 1.64 mmol, 62%) as a colourless oil. R_f (1:8) 0.80; IR ν 3080, 3020, 2960, 2920, 2850, 1760, 1630, 1460, 1250, 1170, 990, 820; ^{1}H NMR (200 MHz) δ 2.53 (q, 2 H, J = 6.8 Hz, 2 H-2), 2.84 (t, 2 H, J = 6.6 Hz, 2 H-5), 4.36 (t, 2 H, J = 6.8 Hz, 2 H-1), 5.00 (dd, 1 H, J = 1.5, 10.0 Hz, H-7 *cis*), 5.05 (dd, 1 H, J = 1.5, 16.7 Hz, H-7 *trans*), 5.40-5.65 (m, 2 H, H-3 and H-4), 5.81 (ddt, 1 H, J = 6.2, 10.4, 16.9 Hz, H-6).

Dichloroacetic acid oct-7-en-4-ynyl ester (33): According to the preparation of **29**, a solution of 4-pentyn-1-ol (2.0 g, 23.8 mmol), CuCl (118 mg, 1.12 mmol, 0.05%), K_2CO_3 (4.93 g, 35.7 mmol, 1.5 equiv) and TBACl (661 mg, 2.38 mmol, 0.1 equiv) in 4 mL of DMF was treated with allylbromide (2.61 g, 21.6 mmol, 0.9 equiv) and stirred at r.t. for 2 days.[17] After work-up and fc (1:4) oct-7-en-4-yn-1-ol was obtained (2.65 g, 21.34 mmol, 90%) as a light yellow oil. R_f (1:2) 0.40; IR ν 3610, 3440, 3080, 3000, 2950, 2880, 1635, 1430, 1415, 1395, 1050, 990, 910; ^{1}H NMR (200 MHz) δ 1.59 (bs, 1 H, OH), 1.76 (quintet, 2 H, J = 6.5 Hz, 2 H-2), 2.25-2.40 (m, 2 H, 2 H-3), 2.80-3.00 (m, 2 H, 2 H-6), 3.76 (t, 2 H, J = 6.1 Hz, 2 H-1), 5.09 (dd, 1 H, J = 1.5, 10.0 Hz, H-8 *cis*), 5.30 (dd, 1 H, J = 1.6, 17.0 Hz, H-8 *trans*), 5.80 (ddt, 1 H, J = 5.2, 10.0, 17.0 Hz, H-7). According to the general procedure A, a solution of dichloroacetyl chloride (261 mg, 1.77 mmol, 1.1 equiv) and oct-7-en-4-yn-1-ol (200 mg, 1.6 mmol) in 5 mL of CH_2Cl_2 was treated with Et_3N (323 mg, 3.2 mmol, 2 equiv) in 1 mL of CH_2Cl_2 at 0 °C. The reaction was stirred for 2 h at 0 °C. Work-up and fc (1:8) afforded **33** (368 mg, 1.56 mmol, 98%) as a colourless oil. R_f (1:10) 0.35; IR ν 3080, 2960, 2840, 1760, 1740, 1635, 1460, 1415, 1385, 1350, 1300, 1165, 1015, 990, 910, 810; ^{1}H NMR (200 MHz) δ 1.92 (quintet, 2 H, J = 6.6 Hz, 2 H-2), 2.25-2.40 (m, 2 H, 2 H-3), 2.90-3.00 (m, 2 H, 2 H-6), 4.39 (t, 2 H, J = 6.4 Hz, 2 H-1), 5.10 (dq, 1 H, J = 1.7, 9.9 Hz, H-8 *cis*), 5.29 (dq, 1 H, J = 1.8, 16.9 Hz, H-8 *trans*), 5.83 (ddt, 1 H, J = 5.3, 9.9, 16.9 Hz, H-7), 5.95 (s, 1 H, $CHCl_2$).

Trichloroacetic acid oct-7-en-4-ynyl ester (34): According to the general procedure A, a solution of trichloroacetyl chloride (644 mg, 3.54 mmol, 1.1 equiv) and oct-7-en-4-yn-1-ol (400 mg, 3.2 mmol) in 10 mL of CH_2Cl_2 was treated with Et_3N (646 mg, 6.4 mmol, 2 equiv) in 2 mL of CH_2Cl_2 at 0 °C. The reaction was stirred for 2 h at 0 °C. Work-up and fc (1:8) afforded **34** (862 mg, 3.2 mmol, 100%) as a colourless oil. R_f (1:8) 0.55; IR ν 3080, 2960, 2840, 1760, 1635, 1455, 1415, 1380, 1350, 1245, 1015, 990, 910, 895, 820; ^{1}H NMR (200 MHz) δ 1.97 (quintet, 2 H, J = 6.6 Hz, 2 H-2), 2.30-2.45 (m, 2 H, 2 H-3), 2.90-3.00 (m, 2 H, 2 H-6), 4.48 (t, 2 H, J = 6.3 Hz, 2 H-1), 5.10 (dq, 1 H, J = 1.7, 9.9 Hz, H-8 *cis*), 5.29 (dq, 1 H, J = 1.8, 16.9 Hz, H-8 *trans*), 5.83 (ddt, 1 H, J = 5.2, 9.9, 16.9 Hz, H-7).

(3*R,5*R**)- and (3*R**,5*S**)-3,5-Dichloro-oxocan-2-one (35)**: According to the general procedure B, acetate **7** (40 mg, 0.203 mmol) in 2 mL of benzene was treated with 0.3 equiv of CuCl (6.1 x 10^{-5} mol, 6.0 mg) and 0.3 equiv of 2,2-bipyridine (6.1 x 10^{-5} mol, 9.5 mg) and refluxed for 18 h. Concentration *in vacuo* and purification by fc (1:6) afforded **35** (37 mg, 0.188 mmol, 92%) as a colourless oil. This consisted of an inseparable mixture of the *cis* and *trans* diastereomers in the ratio of 70:30. R_f (1:6) 0.40; IR ν 3000, 2960, 1760, 1740, 1460, 1435; MS (EI, 70 eV) *m/z* (relative intensity) 197 (M^++1, 39), 196 (M^+, 3), 181 (8), 179 (16), 163 (17), 161 (54), 143 (10), 125 (100), 115 (29), 103 (51), 100 (59), 79 (55), 69 (23), 68 (37), 41 (28); HRMS calcd for $C_7H_{10}O_2Cl_2$ 196.0058, found 196.0055, calcd for $C_7H_{11}O_2Cl_2$ (M^++1) 197.0136, found 197.0137. **(3*R**,5*R**)-35a** (*cis*): ^{1}H NMR (300 MHz) δ 1.83-2.15 (m, 3 H), 2.33-2.45 (m, 1 H), 2.57 (ddd, J = 11.1, 11.5, 14.0 Hz, H-4), 2.91 (ddd, J = 1.2, 5.8, 14.0 Hz, H-4), 4.10 (ddd, J = 4.1, 4.9, 11.1 Hz, H-8), 4.17-4.27 (m, H-8), 4.48 (dd, J = 6.2, 11.5 Hz, H-3), 4.75-4.88 (m, H-5); ^{13}C NMR (50 MHz) δ 29.3 (CH_2), 37.7 (CH_2), 50.0 (C-4), 54.6 (CH), 58.6 (CH), 68.0 (C-8), 170.3 (C-2). **(3*R**,5*S**)-35b** (*trans*): ^{1}H NMR (300 MHz) δ 1.83-2.15 (m, 4 H, 2 CH_2), 2.63 (ddd, 1 H, J = 2.8, 6.6, 14.1 Hz, H-4), 2.88 (ddd, 1 H, J = 4.4, 9.1, 14.1 Hz, H-4'), 4.34-4.45 (m, 2 H, 2 H-8), 4.68 (dd, 1 H, J = 4.4, 6.5 Hz, H-3), 4.45-4.50 (m, 1 H, H-5); ^{13}C NMR (50 MHz) δ 26.7 (CH_2), 34.1 (CH_2), 46.8 (C-4), 54.3 (CH), 56.6 (CH), 69.0 (C-8), 170.3 (C-2).

Oxocan-2-one (36)[22]: To a refluxing solution of $HSnBu_3$ (148 mg, 0.5 mmol, 2 equiv) in 1.5 mL of cyclohexane was slowly added a solution of **35** (50 mg, 0.25 mmol) and AIBN (0.01 equiv, 0.4 mg) in 1 mL of cyclohexane. The r.m. was refluxed for 1 h, concentrated *in vacuo* and purified by fc (1:6). This afforded **36** (20 mg, 1.44 mmol, 60%) as a colourless oil. R_f (1:6) 0.25. The spectroscopic data were in agreement with the literature.

5-Chloro-oxocan-2-one (37): Oxocan-2-one **35** (281 mg, 1.43 mmol) was dissolved in 7 mL of absolute acetic acid. To this mixture was added at r.t. KI (261 mg, 1.57 mmol, 1.1 equiv), followed by Zn dust (935 mg, 14.3 mmol, 10 equiv) in small

portions over 2 h. The r.m. was stirred for 20 h at r.t., poured into 50 mL of H_2O and neutralized by slow addition of 200 mL of $NaHCO_3$(aq). The aqueous phase was extracted with CH_2Cl_2 (3 x 70 mL), the combined organic phases were dried ($MgSO_4$), concentrated *in vacuo* and purified by fc (1:2) to afford **37** (147 mg, 0.904 mmol, 63%) as a colourless oil. R_f (1:4) 0.15; IR ν 2990, 2940, 2850, 1715, 1480, 1440, 1385, 1360, 1350, 1330, 1265, 1135, 1120, 1095, 1085, 1005; ^{1}H NMR (300 MHz) δ 1.90-2.00 (m, 2 H, CH_2), 2.00-2.10 (m, 2 H, CH_2), 2.20-2.40 (m, 2 H, 2 H-4), 2.48 (ddd, 1 H, *J* = 4.1, 7.6, 13.3 Hz, H-3), 2.80 (ddd, 1 H, *J* = 4.1, 9.9, 13.3 Hz, H-3), 4.20-4.35 (m, 2 H, 2 H-8), 4.44 (ddd, 1 H, *J* = 3.7, 8.6, 13.0 Hz, H-5); ^{13}C NMR (75.5 MHz) δ 27.4 (CH_2), 28.1 (CH_2), 32.0 (CH_2), 36.8 (CH_2), 59.1 (C-5), 67.2 (C-8), 175.2 (C-2); MS (EI, 70 eV) *m/z* (relative intensity) 134 (10), 132 (M^+-OCH_2, 32), 127 (16), 126 (17), 116 (10), 98 (13), 97 (16), 90 (5), 85 (6), 81 (9), 68 (31), 55 (100), 41 (26), 27 (14).

3,3,5-Trichloro-oxocan-2-one (38): According to the general procedure B, acetate **8** (324 mg, 1.40 mmol) in 20 mL of DCE (0.07 M) was treated with 0.3 equiv of CuCl (0.42 mmol, 41.6 mg) and 0.3 equiv of 2,2-bipyridine (0.42 mmol, 65.6 mg) and heated in a sealed tube at 130 °C for 2.5 h. Concentration *in vacuo* and purification by fc (1:10) afforded **38** (187 mg, 0.808 mmol, 58%) as a colourless oil. R_f (1:10) 0.50; IR ν 2960, 1760, 1590, 1460, 1445, 1420, 1180, 1170, 1010; ^{1}H NMR (300 MHz, d_6-acetone) δ 1.70-2.20 (m, 4 H, 2 CH_2), 3.07 (dd, 1 H, *J* = 3.6, 15.4 Hz, H-4), 3.22 (dd, 1 H, *J* = 8.4, 15.4 Hz, H-4'), 3.70 (t, 2 H, *J* = 6.2 Hz, 2 H-8), 4.40-4.50 (m, 1 H, H-5); ^{13}C NMR (75.5 MHz) δ 26.5 (C-7), 34.9 (C-6), 56.1 (C-5), 56.9 (C-4), 70.8 (C-8), 80.9 (C-3), 168.7 (C-2).

(3*R,5*R**)- and (3*R**,5*S**)-3,5-Dichloro-oxonan-2-one (39)**: According to the general procedure B, acetate **9** (123 mg, 0.58 mmol) in 6 mL of DCE was treated with 0.3 equiv of CuCl (0.17 mmol, 17 mg) and 0.3 equiv of 2,2-bipyridine (0.17 mmol, 27 mg) and refluxed for 18 h. Concentration *in vacuo* and purification by fc (1:10) afforded **39** (70 mg, 0.33 mmol, 57%) as a colourless oil. This consisted of a mixture of the *cis* and *trans* diastereomers in the ratio of 70:30. R_f (1:6) 0.40; MS (EI, 70 eV) *m/z* (relative intensity) 211 (M^++1, 15), 175 (26), 157 (11), 139 (27), 121 (7), 97 (18), 93 (17), 83 (43), 82 (100), 81 (30), 67 (35), 55 (52), 54 (40), 41 (27); HRMS calcd for $C_8H_{12}O_2Cl_2$ 210.0214, found 210.0210, calcd for $C_8H_{13}O_2Cl_2$ (M^++1) 211.0293, found 211.0287; **(3*R**,5*R**)-39a** (*cis*): IR ν 3010, 2940, 2860, 1760, 1460, 1445, 1175, 1160; ^{1}H NMR (400 MHz) δ 1.30-1.50 (m, 1 H), 1.65-2.05 (m, 4 H), 2.42 (ddd, 1 H, *J* = 9.0, 11.8, 14.3 Hz, H-4), 2.75 (ddd, 1 H, *J* = 1.8, 5.8, 14.4 Hz, H-4'), 4.04 (dt, 1 H, *J* = 4.0, 11.0 Hz, H-9), 4.25-4.33 (m, 1 H, H-9'), 4.46 (dd, 1 H, *J* = 6.0, 11.8 Hz, H-3), 4.70-4.85 (m, 1 H, H-5); ^{13}C NMR (63 MHz) δ 21.2 (CH_2), 26.6 (CH_2), 39.8 (CH_2), 46.5 (CH_2), 54.4 (CH), 55.0 (CH), 65.8 (C-9), 169.7 (C-2); **(3*R**,5*S**)-39b** (*trans*): IR ν 2940, 1730, 1460, 1370, 1280, 1175, 1040, 990, 905; ^{1}H NMR (400 MHz) δ 1.40-1.50 (m, 1 H), 1.60-1.70 (m, 1 H), 1.80-1.90 (m, 2 H), 1.94 (q, 2 H, *J* = 6.2 Hz), 2.62 (ddd, 1 H, *J* = 3.2, 5.6, 15.4 Hz, H-4), 2.72 (ddd, 1 H, *J* = 3.2, 8.0, 15.4 Hz, H-4'), 4.33-4.40 (m, 1 H, H-5), 4.43-4.50 (m, 2 H, 2 H-9), 4.55 (dd, 1 H, *J* = 3.2, 5.6 Hz, H-3); ^{13}C NMR (63 MHz) δ 19.5 (CH_2), 26.6 (CH_2), 37.8 (CH_2), 43.0 (C-4), 55.0 (CH), 55.7 (CH), 65.5 (C-9), 169.6 (C-2).

Oxonan-2-one (40)[22]: According to the preparation of **36**, the nine-membered lactone **39** (37 mg, 0.18 mmol) was treated with $HSnBu_3$ (2 equiv, 0.36 mmol) and AIBN (5%) in 1 mL of refluxing cyclohexane for 6 h. Work-up and fc (1:10) yielded **40** (14 mg, 0.1 mmol, 55%). R_f (1:10) 0.50. The spectroscopic data were in agreement with the literature.

3,3,5-Trichloro-oxonan-2-one (41): According to the general procedure B, acetate **10** (100 mg, 0.41 mmol) in 6.7 mL of DCE (0.06 M) was treated with 0.3 equiv of CuCl (0.12 mmol, 12.1 mg) and 0.3 equiv of 2,2-bipyridine (0.12 mmol, 18.7 mg) and heated in a sealed tube at 190 °C for 2 h. Concentration *in vacuo* and purification by fc (1:12) afforded **41** (59 mg, 0.24 mmol, 59%) as a colourless oil. R_f (1:10) 0.40; IR ν 3030, 2980, 2890, 1770, 1470, 1440, 1385, 1300, 1270; ^{1}H NMR (300 MHz) δ 1.70-1.95 (m, 5 H), 2.00-2.15 (m, 1 H), 3.05 (dd, 1 H, *J* = 3.7, 15.1 Hz, H-4), 3.14 (dd, 1 H, *J* = 8.4, 15.1 Hz, H-4'), 4.35-4.47 (m, 2 H, 2 H-9), 4.50-4.60 (m, 1 H, H-5); ^{13}C NMR (75.5 MHz) δ 19.0 (CH_2), 26.4 (CH_2), 37.5 (CH_2), 54.2 (C-4), 55.2 (C-5), 67.1 (C-9), 81.6 (C-3), 165.8 (C-2).

(3*R,5*R**,8*R**)-, (3*R**,5*S**,8*R**)- and (3*R**,5*R**,8*S**)-3,5-Dichloro-8-methyl-oxocan-2-one (42)**: According to the general procedure B, acetate **16** (100 mg, 0.47 mmol) in 6 mL of DCE (0.08 M) was treated with 0.3 equiv of CuCl (0.14 mmol, 14.0 mg) and 0.3 equiv of 2,2-bipyridine (0.14 mmol, 21.9 mg) and heated in a sealed tube at 130 °C for 4 h. Concentration *in vacuo* and purification by fc (1:5) afforded **42** (67 mg, 0.32 mmol, 68%) as a light yellow oil, which solidified

upon standing. The product consisted of a mixture of three diastereomers in the ratio of 70:20:10. R_f (1:5) 0.40; IR ν 2920, 1755, 1440, 1110, 990, 840; (**3*R**,5*R**,8*R**)-**42a** (major isomer): ^{1}H NMR (300 MHz) δ 1.33 (d, 3 H, *J* = 6.3 Hz, CH_3), 1.70-2.00 (m, 3 H, 2 H-6, H-7), 2.39 (ddd, 1 H, *J* = 1.3, 7.5, 10.0 Hz, H-7'), 2.55 (dt, 1 H, *J* = 11.3, 13.6 Hz, H-4), 2.90 (dd, 1 H, *J* = 6.4, 13.5 Hz, H-4'), 4.18 (ddt, 1 H, *J* = 1.7, 6.7, 11.1 Hz, H-5), 4.50 (dd, 1 H, *J* = 6.5, 11.5 Hz, H-3), 5.16 (ddq, 1 H, *J* = 3.7, 6.3, 10.1 Hz, H-8); ^{13}C NMR (75.5 MHz) δ 19.8 (CH_3), 37.4 (CH_2), 38.0 (CH_2), 51.2 (C-4), 54.8 (CHCl), 59.0 (CHCl), 76.3 (C-8), 171.6 (C-2); (**3*R**,5*S**,8*R**)-**42b** (second isomer): ^{1}H NMR (300 MHz) δ 1.37 (d, 3 H, *J* = 6.2 Hz, CH_3), 2.67 (dd, 1 H, H-4), 5.00-5.10 (m, 1 H, H-8), rest of the signals obscured; ^{13}C NMR (75.5 MHz) δ 20.0 (CH_3), 31.7 (CH_2), 32.6 (CH_2), 47.7 (C-4), 55.5 (CHCl), 57.2 (CHCl), 76.7 (C-8), 171.6 (C-2); (**3*R**,5*R**,8*S**)-**42c** (minor isomer): ^{1}H NMR (300 MHz) δ 1.43 (d, 3 H, *J* = 6.2 Hz, CH_3), 4.75 (dd, 1 H, H-3), rest of the signals obscured; ^{13}C NMR (75.5 MHz) δ 20.2 (CH_3), 35.1 (CH_2), 36.0 (CH_2), 45.7 (C-4), 53.4 (CHCl), 56.4 (CH), 78.4 (C-8), 171.6 (C-2).

Table 5: Selected data of the crystal structures of lactones **43a**, **44a**, **46** and **51a**

lactone	**43a**	**44a**	**46**	**51a**
crystal type	monoclinic	monoclinic	monoclinic	monoclinic
space group	C2/c	$P2_1/a$	$P2_1/n$	$P2_1/n$
a (Å)	29.605(3)	10.3946(8)	6.3772(9)	6.467(3)
b (Å)	5.7972(6)	9.9835(6)	11.3992(8)	10.862(2)
c (Å)	19.787(1)	11.469(2)	16.139(1)	13.464(2)
β (°)	128.610(5)	111.933(8)	92.139(9)	95.47(2)
V (Å^3)	2653.6(4)	1104.0(2)	1172.0(2)	941.5(5)
Z	8	4	4	4
calcd density (gcm^{-3})	1.37	1.35	1.47	1.49
μ (CuKα) (cm^{-1})	43.9	51.5	70.44	60.01
F(000)	1136	472	536	440
T (K)	293	253	247	247
final R	0.058	0.061	0.049	0.061
observed reflections	2184	1705	2231	1519
dihedral angle (°)				
(C3)-(C2)-(O1)-(C8)	142	143	140	4

(3*R,5*R**,8*S**)-, (3*R**,5*S**,8*S**)- and (3*R**,5*R**,8*R**)-3,5-Dichloro-8-phenyl-oxocan-2-one (43)**: According to the general procedure B, acetate **17** (100 mg, 0.37 mmol) in 1.8 mL of benzene (0.2 M) was treated with 0.3 equiv of CuCl (0.11 mmol, 10.9 mg) and 0.3 equiv of 2,2-bipyridine (0.11 mmol, 17.3 mg) and heated in a sealed tube at 180 °C for 1.75 h. Concentration *in vacuo* and purification by fc (1:8) afforded **43** (50.8 mg, 0.186 mmol, 51%) as a yellow solid, which consisted of three diastereomers in the ratio of 69:18:13. R_f (1:8) 0.45; IR ν 3060, 3010, 2950, 2920, 1760, 1490, 1445, 1350; The major *cis*-dichloro, *trans*-phenyl isomer could be isolated by crystallization from hexane. (**3*R**,5*R**,8*S**)-**43a** (major isomer): light yellow crystals, mp 71-76 °C (hexane); a sample of these crystals was subjected to an X-ray analysis (Figure 1, Table 5)[24]; ^{1}H NMR (300 MHz) δ 2.0-2.15 (m, 2 H, 2 H-6), 2.15-2.25 (m, 1 H, H-7), 2.45-2.55 (m, 1 H, H-7), 2.66 (dt, 1 H, *J* = 11.4, 13.6 Hz, H-4), 3.01 (dd, 1 H, *J* = 6.4, 13.6 Hz, H-4'), 4.31 (ddt, 1 H, *J* = 6.5, 11.2 Hz, H-5), 4.62 (dd, 1 H, *J* = 6.5, 11.5 Hz, H-3), 6.05 (dd, 1 H, *J* = 7.0, 7.6 Hz, H-8), 7.30-7.45 (m, 5 H, Ar); ^{13}C NMR (50 MHz) δ 37.9 (CH_2), 38.3 (CH_2), 51.5 (C-4), 54.7 (CH), 59.2 (CH), 80.6 (C-8), 125.9, 125.9, 128.3, 128.5, 138.0, 171.3 (C-2). MS (EI, 70 eV) *m/z* (relative intensity) 272 (M^+, 25), 237 (5), 200 (2), 169 (16), 168 (18), 167 (25), 166 (27), 140 (24), 138 (80), 117 (74), 105 (60), 91 (30), 77 (22), 67 (9), 55 (100), 41 (13); HRMS calcd for $C_{13}H_{14}O_2Cl_2$ 272.0371, found 272.0370; Anal. Calcd. for $C_{13}H_{14}O_2Cl_2$: C, 57.16; H, 5.17; Cl, 25.96. Found C, 57.13; H, 5.26; Cl, 26.15; (**3*R**,5*S**,8*S**)-**43b** (second isomer): ^{1}H NMR (300 MHz) δ 2.00-2.20 (m, 3 H), 2.82 (m, 1 H), 2.65-3.01 (m, 2 H, 2 H-4), 4.30 (m, 1 H, H-5), 4.85 (dd, 1 H, *J* = 4.5, 6.7 Hz, H-3), 5.96 (dd, 1 H, *J* = 3.5, 9.2 Hz, H-

8), 7.30-7.45 (m, 5 H, Ar); ^{13}C NMR (50 MHz) δ 35.7 (CH_2), 36.9 (CH_2), 48.2 (C-4), 54.0 (CH), 57.3 (CH), 80.7 (C-8), 125.7, 125.9, 128.3, 128.5, 138.0, C-2 not observed; **(3*R**,5*R**,8*R**)-43c** (minor isomer): ^{1}H NMR (300 MHz) δ 2.00-2.20 (m, 3 H), 2.80-2.90 (m, 1 H), 2.65-3.01 (m, 2 H, 2 H-4), 4.05 (m, 1 H, H-5), 4.80-4.90 (m, 1 H, H-3), 5.80 (dd, 1 H, *J* = 3.4, 9.7 Hz, H-8), 7.30-7.45 (m, 5 H, Ar); ^{13}C NMR (50 MHz) δ 33.2 (CH_2), 2 CH_2 obscured, 52.0 (CH), 56.3 (CH), 82.6 (C-8), 125.9, 126.1 128.3, 128.5, 138.0, C-2 not observed.

(3*R,5*R**)- and (3*R**,5*S**)-3,5-Dichloro-7,7-dimethyl-oxocan-2-one (44)**: According to the general procedure B, acetate **19** (200 mg, 0.89 mmol) in 4.5 mL of benzene (0.2 M) was treated with 0.3 equiv of CuCl (0.27 mmol, 26.3 mg) and 0.3 equiv of 2,2-bipyridine (0.27 mmol, 42.2 mg) and heated in a sealed tube at 180 °C for 1.5 h. Concentration *in vacuo* and purification by fc (1:8) afforded **44** (162.5 mg, 0.72 mmol, 81%) as a white solid, which consisted of two diastereomers in the ratio of 70:30. R_f (1:8) 0.45; The major *cis*-isomer could be isolated by recrystallization from hexane. **(3*R**,5*R**)-44a** (*cis*): white crystals, mp 78-81 °C (hexane), a sample of these crystals was subjected to an X-ray analysis (Figure 3, Table 5)[9a]; IR ν 2960, 2920, 2870, 1750, 1455, 1250, 1140, 1000, 880, 725; ^{1}H NMR (300 MHz) δ 0.86 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.91 (dd, 1 H, *J* = 6.6, 16.4 Hz, H-6), 2.09 (d, 1 H, *J* = 16.4 Hz, H-6'), 2.47 (dt, 1 H, *J* = 11.5, 13.4 Hz, H-4), 2.90 (dd, 1 H, *J* = 6.3, 13.4 Hz, H-4'), 3.59 (d, 1 H, *J* = 11.0 Hz, H-8), 4.35-4.45 (m, 1 H, H-5), 4.52 (dd, 1 H, *J* = 6.4, 11.7 Hz, H-3), 4.58 (d, 1 H, *J* = 11.0 Hz, H-8'); ^{13}C NMR (75.5 MHz) δ 23.6 (CH_3), 26.9 (CH_3), 38.1 (C-7), 51.2 (CH_2), 51.6 (CH_2), 54.0 (CH), 54.5 (CH), 76.3 (C-8), 171.6 (C-2); MS (EI, 70 eV) *m/z* (relative intensity) 225 (M^++1, 10), 207 (26), 206 (38), 191 (33), 189 (100), 170 (15), 153 (61), 152 (67), 134 (48), 107 (38), 99 (100), 95 (40), 81 (36), 69 (44), 55 (70), 43 (56), 41 (47), 36 (42); HRMS calcd for $C_9H_{14}O_2{}^{35}Cl$ (M^+-Cl) 189.0682, found 189.0689, calcd for $C_9H_{14}O_2{}^{37}Cl$ (M^+-Cl) 191.0653, found 191.0649; Anal. Calcd. for $C_9H_{14}O_2Cl_2$: C, 48.02; H, 6.27; Cl, 31.50. Found C, 48.07; H, 6.34; Cl, 31.41; **(3*R**,5*S**)-44b** (*trans*): IR ν 2980, 2860, 1740, 1460, 1365, 1290, 1260, 1155, 1040, 1030, 905, 945, 875; ^{1}H NMR (400 MHz) δ 0.90 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.91 (dd, 1 H, *J* = 7.4, 16.4 Hz, H-6), 2.10 (dd, 1 H, *J* = 1.2, 16.4 Hz, H-6'), 2.70-2.75 (m, 2 H, 2 H-4), 3.82 (d, 1 H, *J* = 11.2 Hz, H-8), 4.48 (d, 1 H, *J* = 11.2, H-8'), 4.50-4.53 (m, 1 H, H-3), 4.56-4.61 (m, 1 H, H-5); ^{13}C NMR (75.5 MHz) δ 23.5 (CH_3), 27.0 (CH_3), 38.3 (C-7), 49.1 (CH_2), 50.8 (CH_2), 52.6 (CH), 54.3 (CH), 76.8 (C-8), 170.9 (C-2).

7,7-Dimethyl-oxocan-2-one (45): To a refluxing solution of **44** (105 mg, 0.47 mmol) in 4.5 mL of benzene was added in small portions via a syringe pump a solution of $HSnBu_3$ (339 mg, 1.17 mmol, 2.5 equiv) and AIBN (3.8 mg, 2.3 x 10^{-5} mol, 0.05 equiv) in 3 mL of benzene over a period of 1 h. After one hour of reflux the solvent was evaporated and the residue taken up in 30 mL of CH_2Cl_2. This solution was shaken with 10 mL of KF(aq), the aqueous layer was separated and washed with CH_2Cl_2 (2 x 10 mL). After drying of the organic layers (Na_2SO_4) and concentration *in vacuo*, the residue was purified by fc (1:3) affording **45** (42 mg, 0.27 mmol, 58%) as a colourless oil. R_f (1:6) 0.20; IR ν 2960, 2930, 2860, 1770, 1480, 1450, 1370, 1330, 1310, 1250, 1150, 1120, 1060; ^{1}H NMR (250 MHz) δ 0.91 (s, 6 H, 2 CH_3), 1.20-1.40 (m, 3 H, 2 H-4 and H-5), 1.45-1.60 (m, 1 H, H-5'), 1.70-1.85 (m, 2 H, 2 H-6), 2.45-2.55 (m, 2 H, 2 H-3), 3.90 (bs, 2 H, 2 H-8); ^{13}C NMR (75.5 MHz) δ 22.1 (C-5), 25.1 (CH_3), 25.2 (CH_3), 27.8 (CH_2), 31.4 (CH_2), 35.6 (C-7), 37.4 (C-3), 75.4 (C-8), 176.1 (C-2).

3,3,5-trichloro-7,7-dimethyl-oxocan-2-one (46): According to the general procedure B, acetate **20** (934 mg, 3.6 mmol) in 18 mL of DCE (0.2 M) was treated with 0.3 equiv of CuCl (1.08 mmol, 107 mg) and 0.3 equiv of 2,2-bipyridine (1.08 mmol, 169 mg) and heated in a sealed tube at 145 °C for 2 h. Concentration *in vacuo* and purification by fc (1:30) afforded a white solid, which was recrystallized from hexane to yield **46** (628 mg, 2.42 mmol, 67%) as white crystals, mp 68-69 °C, a sample of these crystals was subjected to an X-ray analysis (Figure 4, Table 5).[24] R_f (1:10) 0.55; IR ν 3020, 2960, 1760, 1465, 1370, 1250, 1070, 1030; ^{1}H NMR (300 MHz) δ 0.90 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.91 (dd, 1 H, *J* = 6.7, 16.5 Hz, H-6), 2.14 (dd, 1 H, *J* = 1.1, 16.5 Hz, H-6'), 2.98 (dd, 1 H, *J* = 10.7, 14.6 Hz, H-4), 3.23 (dt, 1 H, *J* = 1.3, 14.6 Hz, H-4'), 3.79 (dd, 1 H, *J* = 1.1, 10.7 Hz, H-8), 4.55 (d, 1 H, *J* = 10.7 Hz, H-8'), 4.56 (m, 1 H, H-5); ^{13}C NMR (75.5 MHz, d_6-acetone) δ 24.3 (CH_3), 25.2 (CH_3), 36.3 (C-7), 48.0 (CH_2), 54.8 (CH_2), 56.1 (C-5), 71.2 (C-8), 84.4 (C-3), 166.6 (C-2); Anal. Calcd. for $C_9H_{13}O_2Cl_3$: C, 41.64; H, 5.05; Cl, 40.98. Found C, 41.78; H, 5.17; Cl, 40.88.

(3*R,5*S**)- and (3*R**,5*R**)-3,5-Dichloro-6,6-dimethyl-oxocan-2-one (47)**: According to the general procedure B, acetate **21** (650 mg, 2.89 mmol) in 25 mL of benzene was treated with 0.3 equiv of CuCl (0.87 mmol, 86 mg) and 0.3 equiv of 2,2-bipyridine (0.87 mmol, 136 mg) and heated in a sealed tube at 120 °C for 18 h. Concentration *in vacuo* and purification by fc

(1:20) afforded **47** (487 mg, 2.16 mmol, 75%) of a colourless oil, which consisted of two inseparable diastereomers in the ratio of 70:30. R_f (1:10) 0.25; IR ν 2960, 2920, 1760, 1465, 1445, 1375, 1275, 1165, 1140, 1035, 965, 810; MS (EI, 70 eV) *m/z* (relative intensity) 225 (M^++1, 6), 211 (3), 209 (3), 200 (4), 199 (4), 197 (6), 191 (3), 190 (3), 189 (10), 172 (7), 170 (11), 166 (7), 164 (30), 163 (8), 162 (90), 161 (18), 150 (14), 125 (19), 103 (22), 90 (33), 83 (99), 75 (45), 69 (100), 55 (60), 41 (77), 39 (57); HRMS calcd for $C_9H_{15}O_2Cl_2$ (M^++1) 225.0449, found 225.0438; for $C_9H_{14}O_2Cl$ (M^+-Cl) 189.0683, found 189.0653; (**3*R**,5*S**)-**47a** (*cis*): ^{1}H NMR (400 MHz) δ 1.03 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.35 (dt, 1 H, *J* = 2.0, 16.1 Hz, H-7), 1.96 (ddd, 1 H, *J* = 4.3, 12.7, 16.8 Hz, H-7'), 2.45 (ddd, 1 H, *J* = 7.9, 12.0, 15.3 Hz, H-4), 2.71 (ddd, 1 H, *J* = 1.0, 5.4, 15.3 Hz, H-4'), 4.07 (ddd, 1 H, *J* = 2.1, 11.5, 13.5 Hz, H-8), 4.47 (dd, 1 H, *J* = 3.2, 8.1 Hz, H-5), 4.55 (dd, 1 H, *J* = 5.4, 12.0 Hz, H-3), 4.64 (ddd, 1 H, *J* = 1.8, 4.3, 11.5 Hz, H-8'); ^{13}C NMR (100.6 MHz) δ 25.7 (CH_3), 25.7 (CH_3), 38.2 (C-7), 37.2 (C-6), 43.2 (C-4), 56.4 (CH), 65.7 (C-8), 67.0 (CH), 171.7 (C-2); (**3*R**,5*R**)-**47b** (*trans*): ^{1}H NMR (400 MHz) δ 1.10 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3), 1.30 (dt, 1 H, *J* = 3.2, 15.6 Hz, H-7), 2.29 (ddd, 1 H, *J* = 5.3, 12.0, 16.4 Hz, H-7'), 2.60 (ddd, 1 H, *J* = 4.7, 7.1, 15.2 Hz, H-4), 2.70 (ddd, 1 H, *J* = 1.7, 8.9, 15.2 Hz, H-4'), 4.20 (dd, 1 H, *J* = 1.8, 6.0 Hz, H-5), 4.32 (dt, 1 H, *J* = 3.4, 11.2 Hz, H-8), 4.44 (dd, 1 H, *J* = 3.0, 5.1 Hz, H-3), 4.60-4.65 (m, 1 H, H-8'); ^{13}C NMR (100.6 MHz) δ 24.0 (CH_3), 24.5 (CH_3), 38.6 (C-7), 38.3 (C-6), 41.9 (C-4), 53.4 (CH), 65.3 (C-8), 67.1 (CH), 172.0 (C-2).

3,3,5-Trichloro-6,6-dimethyl-oxocan-2-one (48): According to the general procedure B, acetate **22** (750 mg, 2.90 mmol) in 26 mL of DCE was treated with 0.3 equiv of CuCl (0.87 mmol, 86 mg) and 0.3 equiv of 2,2-bipyridine (0.87 mmol, 136 mg) and heated in a sealed tube at 110 °C for 18 h. Concentration *in vacuo* and purification by fc (1:20) afforded a light yellow solid, which was recrystallized from hexane to yield **48** (371 mg, 1.42 mmol, 50%) as white crystals. R_f (1:10) 0.35; IR ν 2960, 2920, 1760, 1460, 1420, 1390, 1370, 1240, 1180, 1150, 1060, 1040, 995, 975, 920, 895, 845; ^{1}H NMR (400 MHz) δ 1.03 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 1.43 (dt, 1 H, *J* = 2.0, 16.2 Hz, H-7), 1.88 (dt, 1 H, *J* = 3.1, 16.0 Hz, H-7'), 2.86 (dd, 1 H, *J* = 7.7, 16.3 Hz, H-4), 3.05 (d, 1 H, *J* = 16.3 Hz, H-4'), 4.22 (dt, 1 H, *J* = 2.2, 11.5 Hz, H-8), 4.66 (ddd, 1 H, *J* = 2.1, 4.3, 11.4 Hz, H-8'), 4.60-4.70 (m, 1 H, H-5); ^{13}C NMR (100.6 MHz) δ 26.1 (CH_3), 26.1 (CH_3), 38.1 (C-6), 38.4 (C-7), 52.4 (C-4), 65.5 (C-5), 67.2 (C-8), 82.6 (C-3), 167.7 (C-2); Anal. Calcd. for $C_9H_{13}O_2Cl_3$: C, 41.64; H, 5.05; Cl, 40.98. Found C, 41.75; H, 4.99; Cl, 40.82.

(3*R,5*R**)- and (3*R**,5*S**)-3,5-Dichloro-5-methyl-oxocan-2-one (49)**: According to the general procedure B, acetate **23** (164 mg, 0.78 mmol) in 7.8 mL of benzene was treated with 0.3 equiv of CuCl (0.23 mmol, 23 mg) and 0.3 equiv of 2,2-bipyridine (0.23 mmol, 36 mg) and heated in a sealed tube at 150 °C for 1 h. Concentration *in vacuo* and purification by fc (1:25) afforded **49** (84.9 mg, 0.40 mmol, 52%) as a colourless oil, which consisted of two diastereomers in the ratio of 73:27. A pure fraction (47 mg, 0.22 mmol, 28%) of the major isomer could be isolated by fc (1:25). (**3*R**,5*R**)-**49a** (*cis*): colourless oil; R_f (1:10) 0.30; IR ν 3020, 2960, 2920, 2835, 1760, 1745, 1460, 1440, 1375, 1365, 1310, 1260, 1160, 1100, 1040, 1020, 990, 965, 930, 905, 855; ^{1}H NMR (400 MHz) δ 1.72 (s, 3 H, CH_3), 1.92 (tt, 1 H, *J* = 5.9, 9.7 Hz), 2.00-2.10 (m, 2 H), 2.18 (dd, 1 H, *J* = 10.2, 14.5 Hz, H-6), 2.67 (dd, 1 H, *J* = 4.7, 13.9 Hz, H-4), 2.92 (dd, 1 H, *J* = 11.5, 13.8 Hz, H-4'), 4.28 (dd, 1 H, *J* = 4.7, 11.4 Hz, H-3), 4.40-4.50 (m, 2 H, 2 H-8); ^{13}C NMR (100.6 MHz) δ 26.8 (CH_2), 30.8 (CH_3), 40.3 (CH_2), 52.3 (CH_2), 52.6 (C-3), 69.7 (C-8), 70.6 (C-5), 173.0 (C-2); (**3*R**,5*S**)-**49b** (*trans*): R_f (1:10) 0.25; ^{1}H NMR (400 MHz) δ 1.70 (s, 3 H, CH_3), 1.75-1.90 (m, 1 H), 1.92 (ddd, 1 H, *J* = 2.2, 11.0, 16.0 Hz, H-6), 2.07 (ddd, 1 H, *J* = 2.3, 7.2, 15.6 Hz, H-6'), 2.05-2.15 (m, 1 H), 2.56 (dd, 1 H, *J* = 9.9, 14.6 Hz, H-4), 2.71 (dd, 1 H, *J* = 4.2, 14.6 Hz, H-4'), 4.40 (ddd, 1 H, *J* = 4.9, 6.2, 11.3 Hz, H-8), 4.51 (ddd, 1 H, *J* = 4.2, 7.6, 11.7 Hz, H-8'), 4.74 (dd, 1 H, *J* = 4.2, 9.9 Hz, H-3); ^{13}C NMR (100.6 MHz) δ 26.9 (CH_2), 36.1 (CH_3), 38.9 (CH_2), 52.2 (CH_2), 52.7 (C-3), 68.6 (C-8), 70.1 (C-5), 172.9 (C-2).

3,3,5-Trichloro-5-methyl-oxocan-2-one (50): According to the general procedure B, acetate **24** (907 mg, 3.69 mmol) in 36 mL of DCE was treated with 0.3 equiv of CuCl (1.11 mmol, 110 mg) and 0.3 equiv of 2,2-bipyridine (1.11 mmol, 173 mg) and heated in a sealed tube at 120 °C for 2 h. Concentration *in vacuo* and purification by fc (1:20) afforded a colourless oil, which solidified upon standing to yield **50** (516 mg, 2.10 mmol, 57%). R_f (1:10) 0.35; IR ν 2960, 2930, 1760, 1460, 1450, 1380, 1365, 1290, 1250, 1190, 1165, 1150, 1120, 1110, 1090, 1060, 1035, 990, 930, 910, 870, 690; ^{1}H NMR (400 MHz) δ 1.80 (s, 3 H, CH_3), 1.80-1.90 (m, 1 H, H-7), 1.91 (dd, 1 H, *J* = 9.4, 16.5 Hz, H-6), 2.10-2.25 (m, 1 H, H-7'), 2.17 (dd, 1 H, *J* = 6.7, 16.6 Hz, H-6'), 3.14 (d, 1 H, *J* = 14.9 Hz, H-4), 3.51 (d, 1 H, *J* = 14.8 Hz, H-4'), 4.37 (td, 1 H, *J* = 4.4, 14.9 Hz, H-8), 4.67 (dt, 1 H, *J* = 3.5, 10.6 Hz, H-8'); ^{13}C NMR (100.6 MHz) δ 26.1 (CH_2), 33.5 (CH_3), 39.8 (CH_2), 59.5 (C-4), 70.7 (C-5), 71.2

(C-8), 80.2 (C-3), 169.3 (C-2); MS (FAB, 70 eV) *m/z* (relative intensity): 245 (M^++1, 3), 209 (M^+-Cl, 5), 167 (16), 155 (31), 149 (53), 139 (20), 138 (38), 137 (71), 136 (73), 121 (16), 107 (32), 97 (34), 95 (41), 83 (58), 81 (44), 71 (42), 69 (67), 57 (68), 55 (69), 43 (43), 41 (37).

(3*R,4*S**,5*R**)-, (3*R**,4*S**,5*S**)-, (3*R**,4*R**,5*R**)- and (3*R**,4*R**,5*S**)-3,5-Dichloro-4-methyloxocan-2-one (51)**: According to the general procedure B, acetate **25** (135 mg, 0.64 mmol) in 3.2 mL of benzene was treated with 0.3 equiv of CuCl (0.19 mmol, 19 mg) and 0.3 equiv of 2,2-bipyridine (0.19 mmol, 30 mg) and heated in a sealed tube at 120 °C for 20 h. Concentration *in vacuo* and filtration over a short Si-column (1:20) afforded **51** (65 mg, 0.308 mmol, 48%) as a colourless oil, which consisted of four diastereomers in the ratio of 60:20:10:10. The major isomer **51a** could be isolated by recrystallization from hexane. Isomer **51b** could be separated by fc (1:20) (R_f (1:8) 0.25) from the mixture of the two minor isomers **51c** and **51d** (R_f (1:8) 0.22), which could not be separated from each other. **(3*R**,4*S**,5*R**)-51a**: mp 96-98 °C, white crystals, a sample of these crystals was subjected to an X-ray analysis (Figure 5, Table 5)[24]; IR ν 3020, 2970, 2940, 2880, 1760, 1465, 1380, 1365, 1300, 1240, 1160, 1020, 970, 955, 910; ^{1}H NMR (300 MHz) δ 1.40 (d, 3 H, J = 6.6 Hz, CH_3), 1.90-2.10 (m, 3 H), 2.15-2.30 (m, 1 H), 2.43 (tq, 1 H, J = 6.6, 9.7 Hz, H-4), 3.93-4.02 (m, 1 H, H-5), 4.07 (d, 1 H, J = 9.5 Hz, H-3), 4.26 (ddd, 1 H, J = 4.7, 5.1, 11.1 Hz, H-8), 4.78 (dt, 1 H, J = 6.7, 11.1 Hz, H-8'); ^{13}C NMR (75.5 MHz) δ 19.6 (CH_3), 26.8 (CH_2), 35.7 (CH_2), 50.7 (C-4), 60.8 (CH), 65.4 (CH), 68.0 (C-8), 172.2 (C-2); MS (EI, 70 eV) *m/z* (relative intensity) 211 (M^++1, 5), 175 (17), 161 (7), 139 (12), 135 (16), 117 (27), 110 (23), 108 (69), 89 (55), 83 (29), 82 (100), 81 (44), 67 (52), 55 (60), 41 (44); HRMS calcd for $C_8H_{12}O_2Cl_2$ 210.0214, found 210.0249; Anal. Calcd. for $C_8H_{12}O_2Cl_2$: C, 45.52; H, 5.73. Found C, 45.42; H, 5.76; **(3*R**,4*S**,5*S**)-51b** (second isomer): colourless oil; IR ν 3020, 2960, 2940, 1740, 1460, 1450, 1380, 1290, 1265, 1230, 1160, 1130, 1080, 995, 980, 965, 930, 905, 880; ^{1}H NMR (300 MHz) δ 1.29 (d, 3 H, J = 6.8 Hz, CH_3), 1.70-2.30 (m, 4 H, 2 H-6 and 2 H-7), 2.87 (ddq, 1 H, J = 3.5, 6.8, 8.8 Hz, H-4), 4.15 (dt, 1 H, J = 6.4, 8.7 Hz, H-5), 4.35 (dd, 1 H, J = 5.0, 11.7 Hz, H-8), 4.59 (ddd, 1 H, J = 4.1, 8.8, 11.7 Hz, H-8'), 4.85 (d, 1 H, J = 3.5 Hz, H-3); ^{13}C NMR (75.5 MHz) δ 16.4 (CH_3), 25.9 (CH_2), 31.8 (CH_2), 45.7 (C-4), 58.8 (CH), 63.3 (CH), 69.9 (C-8), 172.2 (C-2); **(3*R**,4*R**,5*R**)-51c and (3*R**,4*R**,5*S**)-51d**: ^{1}H NMR (300 MHz) δ 1.25 (d, 3 H, J = 7.0 Hz, CH_3) and 1.32 (d, 3 H, J = 6.9 Hz, CH_3), the rest of the ^{1}H signals was obscured; **(3*R**,4*R**,5*R**)-51c**: ^{13}C NMR (75.5 MHz) δ 17.8 (CH_3), 26.8 (CH_2), 29.6 (CH_2), 48.7 (C-4), 59.2 (CH), 63.6 (CH), 67.4 (C-8), 172.2 (C-2); **(3*R**,4*R**,5*S**)-51d**: ^{13}C NMR (75.5 MHz) δ 20.1 (CH_3), 25.9 (CH_2), 32.4 (CH_2), 49.9 (C-4), 58.9 (CH), 63.3 (CH), 68.0 (C-8), 170.4 (C-2).

(4*R,5*S**)-3,3,5-Trichloro-4-methyl-oxocan-2-one (52)**: According to the general procedure B, acetate **26** (165 mg, 0.64 mmol) in 6.4 mL of DCE was treated with 0.3 equiv of CuCl (0.19 mmol, 19 mg) and 0.3 equiv of 2,2-bipyridine (0.19 mmol, 30 mg) and heated in a sealed tube at 170 °C for 20 h. Concentration *in vacuo* and purification by fc (1:30) afforded **52** (52.2 mg, 0.213 mmol, 33%) as a colourless oil. R_f (1:10) 0.35; IR ν 3000, 2960, 2940, 1760, 1590, 1465, 1450, 1435, 1380, 1370, 1360, 1350, 1300, 1230, 1085, 1073, 1010, 965, 930, 890; ^{1}H NMR (250 MHz) δ 1.55 (d, 3 H, J = 6.4 Hz, CH_3), 1.63 (dd, 1 H, J = 1.4, 6.0 Hz, H-7), 1.70-1.80 (m, 1 H, H-7'), 1.86 (ddd, 1 H, J = 2.6, 9.5, 17.3 Hz, H-6), 2.21 (ddd, 1 H, J = 3.3, 8.9, 17.4 Hz, H-6'), 3.06 (dq, 1 H, J = 6.4, 10.0 Hz, H-4), 3.98 (ddd, 1 H, J = 2.9, 3.9, 10.0 Hz, H-5), 4.35 (ddd, 1 H, J = 1.2, 5.9, 10.9 Hz, H-8), 4.77 (ddd, 1 H, J = 3.5, 11.0, 12.3 Hz, H-8'); ^{13}C NMR (75.5 MHz) δ 15.6 (CH_3), 24.4 (CH_2), 31.7 (CH_2), 51.9 (C-4), 64.0 (C-5), 71.6 (C-8), 86.8 (C-3), 170.6 (C-2).

3,3,5-Trichloro-oxa-7-cyclodecyn-2-one (53): According to the general procedure B, acetate **30** (100 mg, 0.39 mmol) in 3.9 mL of DCE was treated with 0.3 equiv of CuCl (0.12 mmol, 11.6 mg) and 0.3 equiv of 2,2-bipyridine (0.12 mmol, 18.7 mg) and heated in a sealed tube at 120 °C for 20 h. Concentration *in vacuo* and purification by fc (1:10) afforded **53** (36 mg, 0.14 mmol, 36%) as a colourless oil. R_f (1:10) 0.30; IR ν 2980, 2920, 2840, 1745, 1590, 1460, 1420, 1370, 1180, 1075, 1030, 990, 890, 820; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35-2.50 (m, 1 H), 2.53-2.80 (m, 3 H), 3.13 (dd, 1 H, J = 3.5, 15.6 Hz, H-4), 3.42 (dd, 1 H, J = 4.8, 15.6 Hz, H-4'), 4.05-4.15 (m, 1 H, H-5), 4.28 (ddd, 1 H, J = 2.8, 6.5, 10.3 Hz, H-10), 4.95 (dt, 1 H, J = 5.1, 10.2 Hz, H-10'); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.0 (CH_2), 29.2 (CH_2), 52.8 (C-5), 55.2 (C-4), 63.4 (C-10), 81.1 (C-alkyne), 82.6 (C-alkyne), 83.0 (C-3), 165.8 (C-2).

(3*R,5*R**)-3,5-Dichloro-3,4,5,6,9,10-hexahydro-oxecin-2-one (54)**: According to the general procedure B, acetate **31** (141 mg, 0.63 mmol) in 6 mL of benzene was treated with 0.3 equiv of CuCl (0.19 mmol, 18.8 mg) and 0.3 equiv of

2,2-bipyridine (0.19 mmol, 29.7 mg) and heated in a sealed tube at 175 °C for 8 h. Concentration *in vacuo* and purification by fc (1:30) afforded *cis*-**54** (18 mg, 0.08 mmol, 13%) as a colourless oil. R_f (1:10) 0.50; IR ν 3020, 2955, 2925, 2850, 1730, 1450, 1445, 1370, 1320, 1300, 1275, 1265, 1175, 1160, 1150, 1080, 1035, 990, 920, 845; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00-2.20 (m, 1 H, H-9), 2.35-2.50 (m, 2 H, H-9' and H-6), 2.55-2.70 (m, 1 H, H-6'), 2.63 (ddd, 1 H, J = 3.2, 10.8, 15.7 Hz, H-4), 2.77 (dt, 1 H, J = 11.9, 13.8 Hz, H-4'), 3.95-4.10 (m, 1 H, H-10), 4.09 (dd, 1 H, J = 2.8, 11.4 Hz, H-3), 4.15-4.30 (m, 1 H, H-10'), 4.50-4.65 (m, 1 H, H-5), 5.60-5.75 (m, 1 H, CH=), 5.86 (dt, 1 H, J = 4.1, 10.8 Hz, CH=); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.6 (CH_2), 33.1 (CH_2), 43.0 (C-4), 53.9 (CHCl), 57.7 (CHCl), 63.3 (C-10), 127.4 (CH=), 127.5 (CH=), 169.1 (C-2); MS (EI, 70 eV) *m/z* (relative intensity) 222 (M^+, 5), 192 (7), 186 (9), 160 (16), 157 (23), 151 (16), 150 (53), 116 (15), 105 (9), 93 (31), 81 (34), 80 (37), 79 (29), 67 (100), 55 (30), 41 (29), 39 (27); HRMS calcd for $C_9H_{13}O_2Cl_2$ (M^++1) 223.0293, found 223.0286.

3,3,5-Trichloro-3,4,5,6,9,10-hexahydro-oxecin-2-one (55): According to the general procedure B, acetate **32** (106 mg, 0.41 mmol) in 4 mL of DCE was treated with 0.3 equiv of CuCl (0.12 mmol, 12.3 mg) and 0.3 equiv of 2,2-bipyridine (0.12 mmol, 19.4 mg) and refluxed for 3 days. Concentration *in vacuo* and filtration over a short Si-column (1:10) yielded crude **55** (78 mg, 74%), which was purified by fc (1:30) to afford **55** (38 mg, 0.15 mmol, 37%) as a colourless oil. R_f (1:10) 0.50; IR ν 2960, 2930, 2850, 1755, 1450, 1435, 1420, 1370, 1335, 1270, 1255, 1240, 1180, 1070, 1035, 990, 935, 890, 860; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00-2.15 (m, 1 H, H-9), 2.40-2.55 (m, 1 H, H-9'), 2.44 (dd, 1 H, J = 2.8, 10.5 Hz, H-6), 2.75-2.90 (m, 1 H, H-6'), 2.88 (dd, 1 H, J = 2.9, 14.2 Hz, H-4), 3.24 (dd, 1 H, J = 11.7, 14.2 Hz, H-4'), 3.91 (ddd, 1 H, J = 3.0, 10.7, 12.5 Hz, H-10), 4.50-4.60 (m, 1 H, H-5), 4.80 (ddd, 1 H, J = 1.9, 5.1, 10.5 Hz, H-10'), 5.65-5.80 (m, 1 H, CH=), 5.90 (dt, 1 H, J = 5.1, 10.4 Hz, CH=); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.3 (CH_2), 31.8 (CH_2), 51.5 (C-4), 56.7 (C-5), 65.3 (C-10), 82.0 (C-3), 127.4 (CH=), 127.6 (CH=), 165.0 (C-2).

(3*R,5*R**)- and (3*R**,5*S**)-3,5-Dichloro-oxa-7-cycloundecyn-2-one (56)**: According to the general procedure B, acetate **33** (178 mg, 0.76 mmol) in 7.5 mL of benzene was treated with 0.3 equiv of CuCl (0.23 mmol, 22.5 mg) and 0.3 equiv of 2,2-bipyridine (0.23 mmol, 35.5 mg) and refluxed for 18 hours, later 0.3 equiv of CuCl was added as some starting material was still present and the mixture was refluxed for 18 h. Concentration *in vacuo* and purification by fc (1:20) afforded **56** as two separated diastereomers in the ratio of 67:33 in total yield of 51% (90.8 mg, 0.39 mmol). Major isomer of **56**: 60.2 mg (0.26 mmol, 34%), colourless oil R_f (1:10) 0.30; IR ν 3000, 2935, 2925, 2840, 1730, 1460, 1435, 1385, 1350, 1330, 1315, 1295, 1275, 1260, 1220, 1175, 1155, 1085, 1045, 1010, 905; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85-2.55 (3 x m, 3 x 2 H, 2 H-6, 2 H-9, 2 H-10), 2.55-2.63 (m, 1 H, H-4), 3.05 (ddd, 1 H, J = 3.4, 12.2, 15.2 Hz, H-4'), 3.72 (ddt, 1 H, J = 3.5, 6.1, 11.4 Hz, H-5), 4.20 (ddd, 1 H, J = 2.7, 6.6, 11.4 Hz, H-11), 4.33 (dd, 1 H, J = 2.9, 12.1 Hz, H-3), 4.59 (ddd, 1 H, J = 2.5, 8.1, 11.0 Hz, H-11'); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.3 (C-10), 26.7 (CH_2), 29.5 (CH_2), 44.7 (C-4), 54.2 (CHCl), 55.3 (CHCl), 66.4 (C-11), 76.9 (C-alkyne), 84.4 (C-alkyne), 168.2 (C-2); Minor isomer of **56**: 30.6 mg (0.13 mmol, 17%), colourless oil R_f (1:10) 0.25; IR ν 2960, 2925, 2840, 1740, 1455, 1430, 1385, 1360, 1350, 1335, 1325, 1305, 1290, 1220, 1180, 1170, 1160, 1085, 1040, 1020, 990, 905; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80-2.40 (2 x m, 5 H), 2.49 (ddt, 1 H, J = 2.5, 10.3, 16.8 Hz), 2.68 (ddd, 1 H, J = 3.0, 6.5, 15.1 Hz, H-4), 2.81 (ddd, 1 H, J = 4.7, 8.9, 14.9 Hz, H-4'), 4.00 (ddd, 1 H, J = 3.0, 8.1, 11.2 Hz, H-11), 4.17 (ddd, 1 H, J = 4.5, 7.9, 14.8 Hz, H-5), 4.62 (dd, 1 H, J = 3.0, 8.9 Hz, H-3), 4.84 (ddd, 1 H, J = 3.0, 6.8, 11.3 Hz, H-11'); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.9 (C-10), 25.9 (CH_2), 28.5 (CH_2), 42.4 (C-4), 54.3 (CHCl), 55.4 (CHCl), 65.7 (C-11), 76.9 (C-alkyne), 84.5 (C-alkyne), 168.6 (C-2).

3,3,5-Trichloro-oxa-7-cycloundecyn-2-one (57): According to the general procedure B, acetate **34** (193 mg, 0.72 mmol) in 7.2 ml of DCE was treated with 0.3 equiv of CuCl (0.21 mmol, 21.3 mg) and 0.3 equiv of 2,2-bipyridine (0.21 mmol, 33.6 mg) and heated at 175 °C for 3 hours. Concentration *in vacuo* and purification by fc (1:20) to afforded **57** (20.1 mg, 0.075 mmol, 10%) as a colourless oil. R_f (1:10) 0.40; IR ν 3030, 3000, 2960, 2930, 2840, 1745, 1590, 1460, 1430, 1415, 1385, 1360, 1350, 1330, 1320, 1295, 1280, 1235, 1190, 1170, 1080, 1070, 1045, 1030, 995, 890; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.85-2.60 (3 x m, 3 x 2 H, 2 H-6, 2 H-9 and 2 H-10), 3.01 (dd, 1 H, J = 5.7, 15.6 Hz, H-4), 3.49 (dd, 1 H, J = 3.1, 15.7 Hz, H-4'), 3.75-3.90 (m, 1 H, H-11), 4.15-4.40 (m, 1 H, H-11'), 4.75 (ddd, 1 H, J = 3.3, 7.3, 11.1 Hz, H-5); ^{13}C NMR (63 MHz, $CDCl_3$) δ 17.4 (C-10), 26.6 (CH_2), 29.4 (CH_2), 53.9 (C-4), 54.1 (C-5), 68.6 (C-11), 76.7 (C-alkyne), 83.1 (C-alkyne), 83.7 (C-3), 164.8 (C-2).

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