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Studies on the Role of the 2-Oxonia Cope Rearrangement in π-Cyclizations of α-Methoxycarbonyl Oxycarbenium Ions

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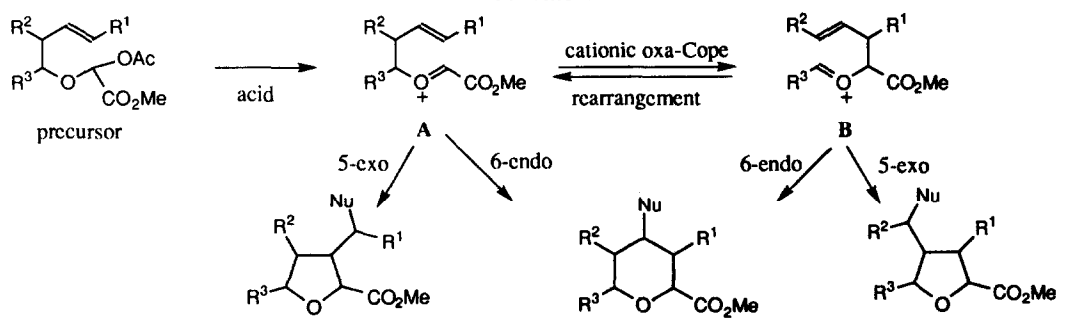
Dedicated with best personal congratulations to Professor L. Ghosez, a good collegue and friend

Abstract: The 2-oxonia Cope rearrangement is shown to play an important role in Lewis acid-induced π-cyclization reactions of a variety of methyl 2-acetoxy-2-(3-alken-1-oxy)acetates to 5- and 6-membered ring ethers. The influence of this [3,3]-sigmatropic rearrangement on the regio- and stereochemical outcome of the cyclization is evaluated by studying three types of substrates, namely (1) four chain-substituted precursors, (2) three silicon-substituted precursors (allyl- and vinylsilanes) and (3) two enantiopure precursors. Controlling factors are the nature of the π-nucleophile and the substitution pattern of the oxycarbenium ion intermediate. The absolute stereochemistry is retained in the cyclization of the enantiopure substrates.

INTRODUCTION

The α-methoxycarbonyl oxycarbenium ion (**A**, Scheme I) is a highly electrophilic carbocation. Its synthetic utility is apparent from the ease of cyclization onto a CC double or triple bond to give a 5- or 6-membered oxygen heterocycle.[1] To determine the possible role of the cationic oxa-Cope rearrangement of **A** to **B** (see Scheme I; a 2-oxonia [3,3]-sigmatropic rearrangement) in this type of π-cyclization a detailed study of the process was carried out and is described herein. In the presence of an acidic mediator the precursor leads to the incipient oxycarbenium ion **A**. If the equilibration to **B** is fast compared to cyclization, the ratio of **A** and **B** depends on their relative stability, which is determined by the nature of the substituents R^1, R^2 and R^3.

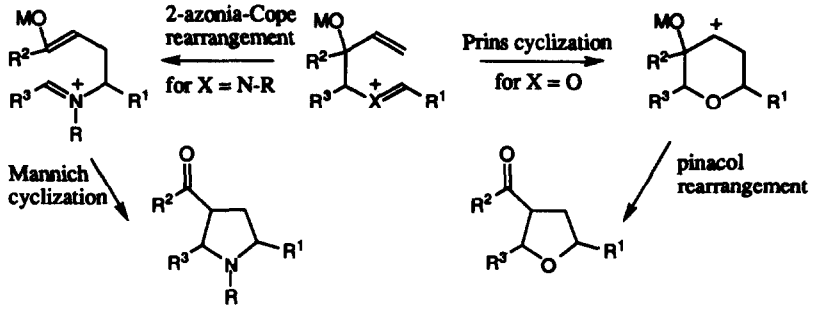
Scheme I



Both sigmatropisomers **A** and **B** can cyclize in a 5-exo and a 6-endo fashion. The mode of π-cyclization will strongly depend on the electronic bias of the olefinic double bond, *i.e.* the nature of the substituents R^1 and

R^2. The 6-endo cyclization mode leads to the same tetrahydropyran structure from both **A** and **B**. The eventual ratio of products will be determined by the relative concentration of **A** and **B** and the relative rates of cyclization. The product (ratio) will thus provide important information on the mechanistic details of the chemistry of Scheme I. In this paper the results are described of the Lewis acid-mediated cyclization of several precursors with different substituents R^1, R^2 and R^3. Moreover, the subtle stereochemical details will be addressed by using enantiopure substrates.

Scheme II



It is well-known that the introduction of a charged atom leads to a large increase of the rate of a [3,3]-sigmatropic rearrangement.[2] Typical examples are the anionic oxy-Cope rearrangement[3] and the 2-azonia-Cope rearrangement.[4,5] The latter type of reaction has been extensively investigated in combination with a Mannich cyclization by Overman and coworkers.[6] The so-called aza-Cope-Mannich reaction (Scheme II) constitutes an elegant synthesis of 3-acylpyrrolidines which has proven highly useful in alkaloid total synthesis. The oxygen analog of this reaction sequence (Scheme II) leading to 3-acyltetrahydrofurans has also been studied in detail by the Overman group.[6] Interestingly, the mechanism of the oxygen variant is believed to be different from the nitrogen case on the basis of stereochemical arguments.[7] Thus, the oxycarbenium cyclization is assumed to proceed via a Prins cyclization-pinacol rearrangement mechanism and not via a 2-oxonia-Cope aldol cyclization pathway. In this paper we present clear evidence that the 2-oxonia-Cope does proceed in certain cases and may drastically influence the outcome of the intended oxycarbenium ion cyclization process.

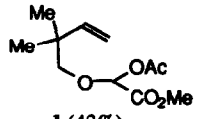
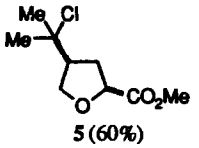
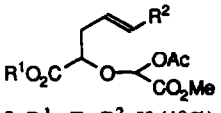
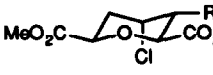
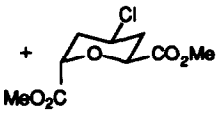
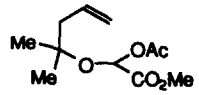
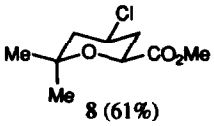
RESULTS AND DISCUSSION

The precursors for the cyclizations were prepared from the appropriate 3-alken-1-ols in a two-step procedure as described before.[1] The alkenol was first treated with methyl glyoxylate and the resulting crude hemiacetal immediately acylated with acetic anhydride. The cyclization precursors (see Tables I, III and IV) were purified by using flash chromatography.

Cyclizations of chain-substituted precursors

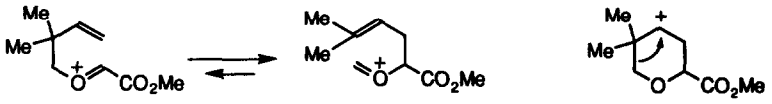
The influence of substituents R^2 and R^3 on the chain (see Scheme I) was studied first. The results of the cyclizations of four different chain-substituted precursors are shown in Table I. Cyclization of substrate **1**[8] containing two allylic methyl groups gave tetrahydrofuran **5** as the only product and as a single isomer. The regiochemistry of this cyclization can be explained by assuming a fast oxa-Cope equilibrium between **C** and **D**, the latter being the more stable sigmatropisomer. Moreover, the 5-exo π-cyclization of **D** onto the more nucleophilic trisubstituted olefin is expected to be much faster than the 6-endo ring closure of **C**.[4] However, the alternative mechanism involving cyclization of **C** to **D'** followed by Wagner-Meerwein ring contraction cannot be excluded.[7] Formation of the *cis*-compound as a single stereoisomer is best understood assuming a chair-like transition state conformation.

Table I Cyclization of Chain-Substituted Precursors

precursor (yield[a,b])	reaction conditions	products (yield[a])
 1 (43%)	$SnCl_4$ (2 equiv) -78 °C → rt, 3 h	 5 (60%)
 2: R^1= Et, R^2=H (49%) 3: R^1= Me, R^2= Pr (45%)	(2) $SnCl_4$ (4 equiv) -78 °C → rt, 3 h; MeOH, HCl (cat), rt, 24 h (3) $SnCl_4$ (4 equiv) -78 °C → rt, 3 h	 6t (65%) 7 (61%) +  6c (9%)
 4 (46%)	$SnCl_4$ (3 equiv) -78 °C → rt, 16 h	 8 (61%)

a) Isolated yield of purified product. b) Overall yield from the corresponding alcohol, see ref. 1.

Compound **2**[9] was prepared to investigate the outcome of the π-cyclization in the case of an (almost) degenerate cationic oxa-Cope rearrangement and to probe the influence of the ester function in the presence of a second ester group. Substrate **3**[10] with a propyl-substituted double bond served as a reference compound for the net *cis*- or *trans*-addition to the carbon-carbon double bond. The low overall yields of precursors **2** and **3** are not surprising in view of the low nucleophilicity of the hydroxyl function due to the proximity of the electron-withdrawing ester group.



C D D'

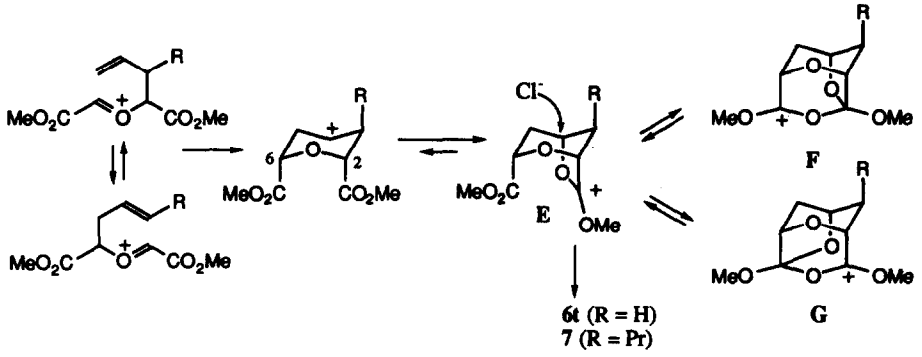
Table II Selected ^{1}H NMR Data (ppm, *J* in Hz, $CDCl_3$)

compound	O-C*H*-CO_2Me	*H*C-Cl	*H*C6-O
5	4.50 (t, 7.9)	-	-
6c	4.66 (dd, 8.8, 4.1)	4.2 (tt, 8.6, 4.2)	4.86 (t, 5.0)
6t	4.60 (dd, 11.4, 2.3)	4.68 (quintet, 3.0)	4.60 (dd, 11.4, 2.3)
7	4.20 (d, 10.2)	3.7 (m)	4.55 (dd, 9.1, 2.5)
8 (C_6D_6)	3.78 (dd, 12.0, 2.4)	3.60 (tt, 12.0, 4.6)	-
12	4.49 (d, 7.7)	-	-
13	4.73 (quintet, 2.7)	-	4.03 (m)
17a	4.55 (bd, 5.3)	4.00 (tt, 12.0, 4.3)	3.43 (ddd, 11.5, 6.0, 1.8)
17c	3.94 (dd, 11.8, 2.1)	4.01 (tt, 11.8, 4.5)	3.06 (ddd, 11.2, 6.8, 1.7)
17t	4.50 (dd, 11.4, 2.4)	4.65 (quintet, 3.0)	3.60 (ddd, 10.8, 7.3, 2.1)
18	4.54 (dd, 11.4, 2.4)	4.66 (quintet, 3.0)	obscured

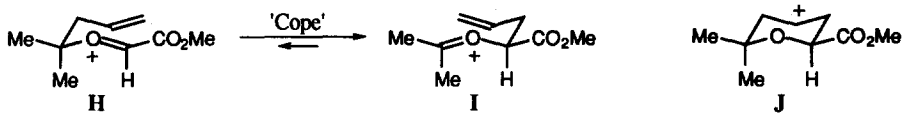
Cyclization of **2** (followed by transesterification to a dimethyl ester) gave two tetrahydropyran isomers. The determination of the structures followed from the coupling constants in the ^{1}H NMR spectra which are

shown in Table II. The major isomer (**6t**) appeared to be symmetric according to NMR, having two equatorial ester functions and an axial chlorine atom. The minor isomer (**6c**) had the ester functions in a *trans*-relationship and the chlorine in an equatorial orientation. Cyclization of **3** proceeded in a similar fashion as **2** and gave product **7** as a single isomer. The propyl group adopts an equatorial position (Table II), indicating a net *cis*-addition of carbocation and chloride to the carbon-carbon double bond.

Scheme III



Assuming a mechanism involving equatorial attack of chloride[1] both ester groups of **2** need to adopt a quasi axial orientation in the transition state of formation of products **6t** and **7**. Moreover, the *n*-propyl group of **3** must also assume an axial position in order to provide **7**. The participation of both ester functions[1] may be the reason for these surprising transition state geometries (Scheme III). The cyclic carbenium ion at C4 can be trapped by one of the ester functions to form dioxycarbenium ion **E**. The second ester function may then also participate to form the tricyclic intermediates **F** and/or **G** from **E**. In the mechanism of formation of **6c** the second ester function probably adopts an equatorial orientation. It must be added here that the details of the mechanism of cyclization as shown in Scheme III remain speculative and require further scrutiny.



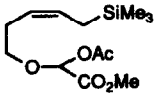
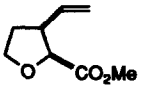
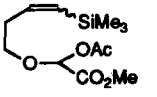
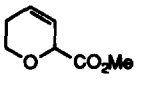
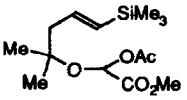
Cyclization of the alternative dimethyl precursor **4**[11] showed a remarkable result. Tetrahydropyran **8** was isolated as the only product and as a single isomer. In contrast to all previous cyclizations[1] the product had an equatorial chlorine substituent (Table II). The explanation for this result probably lies in a steric effect of the two methyl functions. The incipient oxycarbenium ion **H** may easily undergo the oxa-Cope rearrangement to form the much more stable sigmatropisomer **I**. The chair-chair interconversion of either **I** or **J** is unlikely, because the alternative chair would show an unfavourable 1,3-diaxial interaction between the ester and a methyl group. Thus, the ester function is forced to adopt the quasi equatorial orientation in this particular cyclization. Equatorial attack of chloride results in the formation of product **8**. The stereochemical outcome of this cyclization supports the idea that the ester participation is responsible for the formation of 2,4-*trans*-products (*i.e.* net *cis*-addition).

Cyclization of silicon-substituted precursors

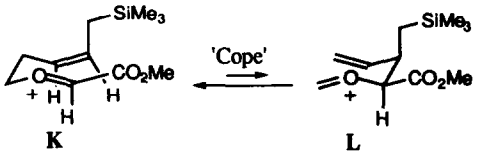
The role of the oxa-Cope rearrangement in the π-cyclization of α-ester oxycarbenium ions was further studied by using vinyl- and allylsilanes as π-nucleophiles. The results of the cyclizations of precursors **9**-**11** are summarized in Table III. Allylsilane **9**[12] gave tetrahydrofuran **12** as a single isomer.[13] The structure of **12** was proved to be the *cis*-compound by irradiation of H2, which gave an nOe on H3. It is obvious that this cyclization onto the activated double bond suggests a direct ring closure of the incipient oxycarbenium ion **K**. A

chair-like transition state (**K**) explains the *cis*-stereochemistry. The oxa-Cope rearrangement would lead to **L**. If present, **L** would cyclize much more slowly than **K** because of its less nucleophilic double bond.

Table III Cyclization of Silicon-Containing Precursors.

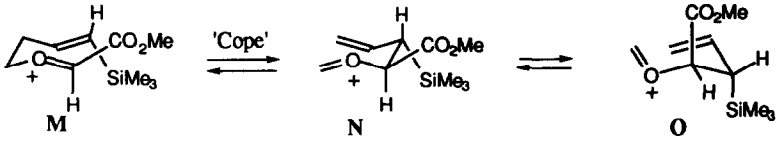
precursor (yield[a,b])	reaction conditions	products (yield[a])
 **9** (70%)	$SnCl_4$ (2 equiv) -78 °C → rt, 3 h	 **12** (75%)
 **10**: *E*:*Z* = 1:6 (51%)	$BF_3{\cdot}OEt_2$ (2 equiv) -78 °C → rt, 17 h	 **13** (59%)
 **11** (40%)	$BF_3{\cdot}OEt_2$ (2 equiv) -78 °C → rt, 17 h	 **14** (67%)

a) Isolated yield of purified product. b) Overall yield from the corresponding alcohol, see ref. 1.



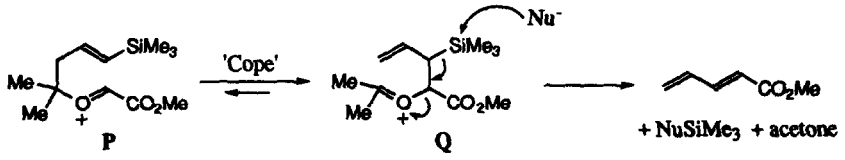
K **L**

Cyclization of vinylsilane **10**[14] gave a good yield of dihydropyran **13** upon treatment with boron trifluoride etherate. This 5,6-dihydro-(2*H*)-pyran appeared to be somewhat unstable on a silica gel column, due to a facile shift of the double bond to form the conjugated system. A reasonable mechanism for the cyclization of **10** involves the oxa-Cope rearrangement of the incipient cation **M** to sigmatropisomer **N** which contains a more reactive allylsilane π-nucleophile. This allylsilane is most reactive if the trimethylsilyl function is in the pseudo axial orientation, so that cyclization is expected to occur after chair-chair interconversion. However, direct cyclization of vinylsilane **M** is expected to lead to the same product.



M **N** **O**

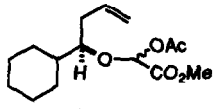
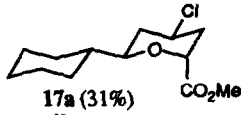
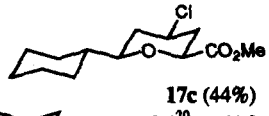
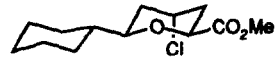
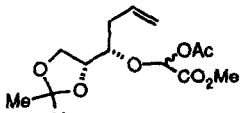
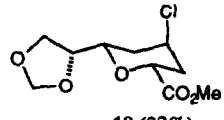
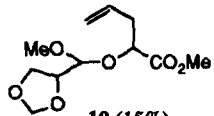
Vinylsilane precursor **11**[15] showed entirely different behaviour. Treatment of **11** with 2 equiv of boron trifluoride etherate gave methyl pentadienoate (**14**) as the only isolated product. Presumably, the 2-oxonia-Cope rearrangement now favours the rearranged ion **Q**, which contains a tertiary oxycarbenium ion. Not surprisingly, this relatively stable intermediate is rather slow to cyclize onto the olefin, so that the β-elimination of $NuSiMe_3$ and acetone can successfully compete. In this case the oxa-Cope rearrangement clearly plays a decisive role in the outcome of the attempted cyclization. Comparison of the behaviour of **10** and **11** nicely indicates the influence of the presence of the gem-dimethyl function. Furthermore, comparison of substrates **4** and **11** illustrates the dramatic effect of the presence of silicon.



Cyclization of enantiopure substrates

To study the influence of the oxa-Cope rearrangement on a stereogenic centre in more detail we prepared the enantiopure precursors **15** and **16**. Cyclization of **15**[16] (Table IV) with 2 equiv of tin tetrachloride gave a mixture of three isomeric tetrahydropyrans in excellent total yield. The stereochemistry of **17a**, **17c** and **17t** followed from the ^{1}H NMR spectra. The coupling patterns for H2, H4 and H6 were most diagnostic (Table II). All three products showed optical activity, indicating that no (complete) racemization had occurred. To determine whether or not partial racemization had occurred, we measured the ^{1}H NMR spectra of the products in the presence of the chiral shift reagent Eu(hfc)$_3$. Treatment of the racemic products prepared from racemic **15** with Eu(hfc)$_3$ led to a doubling of the methyl ester singlet in each case. Treatment of the reaction product (+)-**17a** with Eu(hfc)$_3$ also gave two signals for the methyl ester singlet, but now with very different intensities. From integration of these signals the ee was determined to be 83%. Starting with an ee for the alcohol of less then 87%,[17] it is clear that in the mechanistic pathway of formation of **17a** little or no loss of stereochemical integrity occurs. The same appeared to hold for the products **17c** and **17t**. In these cases the methyl signals of the two enantiomers overlapped with other signals, so that the ee's could not be precisely determined, but were estimated to be higher than 75% in both cases. These results show that the cyclization of **22** occurs with retention of configuration at the stereocentre (or with complete inversion).

Table IV Cyclization of Enantiopure Precursors.

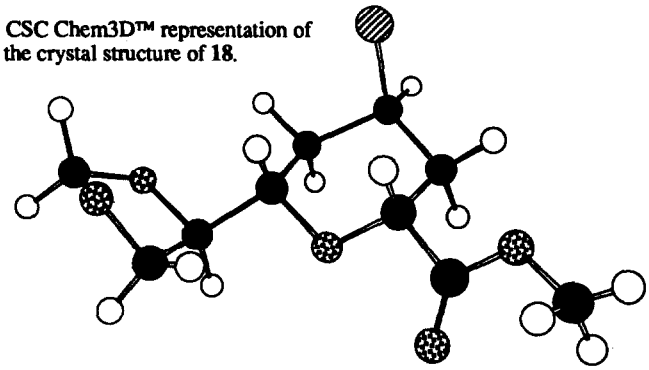
precursor (yield[a,b])	reaction conditions	products (yield[a])
 **15** (69%) $[\alpha]^{20}_D$ = -1.0 (c 1.04, $CHCl_3$)	$SnCl_4$ (2 equiv) -78 °C → rt, 3 h	 **17a** (31%) $[\alpha]^{20}_D$ = +16.6 (c 0.97, $CHCl_3$) +  **17c** (44%) $[\alpha]^{20}_D$ = -11.3 (c 0.63, $CHCl_3$) +  **17t** (18%) $[\alpha]^{20}_D$ = -6.9 (c 0.53, $CHCl_3$)
 **16** (50%) $[\alpha]^{20}_D$ = +22.3 (c 1.51, $CHCl_3$)	$SnCl_4$ (2.5 equiv) -78 °C → -20 °C, 5 h; $CH_2(OMe)_2$ (excess) -40 °C → -10 °C, 15 min	 **18** (32%) $[\alpha]^{20}_D$ = +15.4 (c 0.68, $CHCl_3$) +  **19** (15%)

a) Isolated yield of purified product. b) Overall yield from the corresponding alcohol, see reference 1.

With respect to the mechanism of cyclization of **15**, let us assume equatorial attack of chloride for all three products. Isomer **17c** must then have arisen via a transition state with both the ester and the cyclohexyl function in a quasi equatorial position, isomer **17a** via a transition state with the ester group in a quasi axial position and the minor isomer **17t** via a transition state with both the ester and the cyclohexyl group in a quasi axial position. The experimental result of retention of configuration in this particular cyclization reaction is an important observation of synthetic relevance. However, from this result no indication for the occurrence of an oxa-Cope rearrangement during the cyclization is obtained.[5]

Ring closure of **16**[16,18] was not as straightforward as the cyclizations described before, because the process was thwarted by the loss of the acid labile acetonide protecting group. This problem was solved by quenching the reaction at low temperature with dimethoxymethane to *in situ* protect the diol system again. In this way, 15% of a diacetal was isolated characterized as **19**, the oxa-Cope rearranged oxycarbenium ion trapped with methanol. The main product was tetrahydropyran **18** obtained in a yield of 32% as a single crystalline isomer (mp 61-62 °C) with $[\alpha]^{20}_D$ +15.4 (c 0.68, $CHCl_3$). According to the coupling patterns in the ^1H NMR spectrum (Table II), the ester function in **18** is in an equatorial position and the chlorine atom in an axial position. The signal for H6 overlapped with other signals so that the coupling constants could not be determined. To prove the structure of **18** beyond doubt an X-ray crystal structure determination was carried out. The X-ray analysis of **18** confirmed that the absolute configuration for C6 remained unchanged (Figure 1). Thus, the cyclization of **16** proceeded without epimerization and two new stereocenters were formed in a diastereoselective way, albeit in a low chemical yield. The occurrence of an oxa-Cope rearrangement was proved through the isolation of **19**, although it is not certain that **18** is formed via such a pathway.

Figure 1. CSC Chem3D™ representation of the crystal structure of **18**.



In conclusion, we have shown that the cationic oxa-Cope rearrangement may play a important role in π-cyclization reactions of α-methoxycarbonyl oxycarbenium ions. The preference of the ester function for the quasi axial orientation in the transition state is probably the main reason for the surprising formation of the 2,4-*trans*-disubstituted products. In the cyclization of two enantiopure precursors, the stereochemical integrity was preserved.

ACKNOWLEDGEMENTS

We thank K. Goubitz and J. Fraanje of the Laboratory of Crystallography for the X-ray crystal structure determination. F. O. H. Pirrung is kindly acknowledged for providing 2,2-dimethyl-3-butenoic acid.[8]

EXPERIMENTAL

General information. See reference 1. Optical rotations were measured with a Perkin Elmer 241 polarimeter. Combustion analyses were performed by Dornis u. Kolbe, Mülheim a. d. Ruhr, Germany.

General procedure for the synthesis of the precursors. Method A: Methyl glyoxylate hydrate[1,19] (ca. 2 equiv) was added to a 0.1-0.2 M solution of the alcohol in benzene. The reaction mixture was refluxed for 16 h in the presence of a Dean-Stark trap. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in pyridine (0.5-1.0 M) and treated with acetic anhydride (1.5 equiv calcd for both alcohol and glyoxylate) and DMAP (0.2 equiv). After being stirred for 16 h at rt, the reaction mixture was evaporated with benzene (3 ×) and CH_2Cl_2 (3 ×). The residue was chromatographed. Method B: Anhydrous methyl glyoxylate[1,20] (ca. 2 equiv) was added to a 1.5 M solution of the alcohol in dry CH_2Cl_2. After being stirred overnight at rt,

the reaction mixture was concentrated *in vacuo*. The residue was dissolved in pyridine (0.5-1.0 M) and treated with acetic anhydride (1.5 equiv calcd for both alcohol and glyoxylate) and a catalytic amount of DMAP. After being stirred for 16 h at rt, the reaction mixture was evaporated with benzene (3 ×) and CH_2Cl_2 (3 ×). The residue was chromatographed.

Methyl 2-acetoxy-2-(2,2-dimethyl-3-buten-1-oxy)acetate (1). Method B: 2,2-Dimethyl-3-buten-1-ol[8] (415 mg, 4.2 mmol) in 5 mL of dry $CH_2Cl_2$was treated with anhydrous methyl glyoxylate (0.85 mL, 11.6 mmol). The crude hemiacetal was dissolved in 5 mL of pyridine and treated with acetic anhydride (2.0 mL, 21.7 mmol) and a catalytic amount of DMAP to give 1 (407 mg, 1.8 mmol, 43%) as a colourless oil. R_f 0.19 (EtOAc:hexanes = 1:7). **IR** 1755 (C=O). **^{1}H NMR** (200 MHz) 1.04 (s, 6 H, CH_3), 2.16 (s, 3 H, CH_3), 3.46 (m, 2 H, CH_2), 3.81 (s, 3 H, OCH_3), 5.00 (dd, J = 10.9, 1.2 Hz, 1 H, =CH_2), 5.02 (dd, J = 17.3, 1.2 Hz, 1 H, =CH_2), 5.78 (dd, J = 17.5, 10.8 Hz, 1 H, CH=), 5.96 (s, 1 H, OCH).

Metyl 2-acetoxy-2-(1-carboethoxy-3-buten-1-oxy)acetate (2). Method B: Ethyl 2-hydroxy-4-pentenoate[9] (455 mg, 3.2 mmol) in 5 mL of dry CH_2Cl_2 was treated with anhydrous methyl glyoxylate (0.6 mL, 8.2 mmol). The crude hemiacetal was dissolved in 5 mL of pyridine and treated with acetic anhydride (1.8 mL, 19.1 mmol) and a catalytic amount of DMAP to give 2 (429 mg, 1.6 mmol, 49%) as a colourless oil. R_f 0.38 (EtOAc:hexanes = 1:3). **IR** 1750 (C=O). **^{1}H NMR** (200 MHz, mixture of two diastereoisomers) 1.27 (t, J = 7.1 Hz, 3 H, CH_3), 2.13 and 2.16 (s, 3 H, CH_3), 2.54 (m, 2 H, CH_2), 3.80 and 3.83 (s, 3 H, OCH_3), 4.17 (m, 2 H, OCH_2), 4.36 (m, 1 H, $CHCO_2Et$), 5.12 (m, 2 H, =CH_2), 5.80 (m, 1 H, CH=), 6.03 and 6.05 (s, 1 H, CHOAc). **^{13}C NMR** (62.9 MHz) 14.07 (CH_2CH_3), 20.58 (CH_3), 36.54 (CH_2), 52.68 (OCH_3), 61.26 (OCH_2), 77.09 ($CHCO_2Et$), 91.36 (CHOAc), 118.16 (=CH_2), 132.22 (CH=), 165.79 (C=O), 169.73 and 170.44 (CO_2Me and CO_2Et).

Methyl 2-acetoxy-2-(1-carbomethoxy-3-(*E*)-hepten-1-oxy)acetate (3). Method B: Methyl 2-hydroxy-4-(*E*)-octenoate[10] (3.44 g, 20.0 mmol) in 20 mL of dry CH_2Cl_2 was treated with anhydrous methyl glyoxylate (3.2 mL, 43.6 mmol). The crude hemiacetal was dissolved in 25 mL of pyridine and treated with acetic anhydride (5.9 mL, 62.6 mmol) and a catalytic amount of DMAP to give 3 (2.72 g, 9.0 mmol, 45%) as a colourless oil. R_f 0.49 (EtOAc:hexanes = 1:3). **IR** 1750 (C=O). **^{1}H NMR** (200 MHz, mixture of two diastereoisomers) 0.85 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 1.33 (sextet, J = 7.3 Hz, 2 H, CH_2CH_3), 1.94 (q, J = 7.2 Hz, 2 H, CH_2Et), 2.08 and 2.11 (s, 3 H, CH_3), 2.48 (t, J = 6.6 Hz, 2 H, CH_2), 3.67 and 3.69 (s, 3 H, OCH_3), 3.74 and 3.78 (s, 3 H, OCH_3), 4.28-4.38 (m, 1 H, $CHCO_2Me$), 5.36-5.49 (m, 2 H, CH=CH), 5.98 and 5.99 (s, 1 H, CHOAc).

Methyl 2-acetoxy-2-(1,1-dimethyl-3-buten-1-oxy)acetate (4). Method B: 2-Methyl-4-penten-2-ol[11] (1.83 g, 18.3 mmol) in 6 mL of dry CH_2Cl_2 was treated with anhydrous methyl glyoxylate (2.42 g, 27.5 mmol). The crude hemiacetal was dissolved in 20 mL of pyridine and treated with acetic anhydride (7.5 mL, 67 mmol) and a catalytic amount of DMAP to give 4 (1.58 g, 8.42 mmol, 46%) as a colourless oil. R_f 0.50 (EtOAc:hexanes = 1: 3.5). **^{1}H NMR** (200 MHz) 1.25 (s, 6 H, CH_3), 2.12 (s, 3 H, CH_3), 2.31 (d, J = 7.2 Hz, 2 H, CH_2), 3.78 (s, 3 H, OCH_3), 5.08 (m, 2 H, =CH_2), 5.82 (m, 1 H, CH=), 6.10 (s, 1 H, CHOAc).

***cis*-2-Carbomethoxy-4-(1-chloro-1-methyl)ethyltetrahydrofuran (5).** To a solution of precursor 1 (406 mg, 1.8 mmol) in 15 mL of dry CH_2Cl_2 at -78 °C was added a 1.2 M solution of $SnCl_4$ in CH_2Cl_2 (2.9 mL, 3.5 mmol). The reaction mixture was allowed to warm up to rt and stirred at rt for 3 h. Then the reaction mixture was poured into icewater and an excess of $NaHCO_3$ was added. The resulting mixture was stirred for 30 min at rt and then filtered over celite. The residue was rinsed with 200 mL of CH_2Cl_2. After the layers were separated, the water layer was extracted (3 ×) with CH_2Cl_2 (35 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed to give 5 (222 mg, 1.1 mmol, 60%) as a colourless oil. R_f 0.20 (EtOAc:hexanes = 1:3). **IR** 1740 (C=O). **^{1}H NMR** (200 MHz) 1.53 (s, 3 H, CH_3), 1.56 (s, 3 H, CH_3), 2.06 (m, 1 H, H3), 2.40 (m, 1 H, H3), 2.60 (quintet, J = 8.6 Hz, 1 H, H4), 3.75 (s, 3 H, OCH_3), 3.92 (t, J = 8.7 Hz, 1 H, H5), 4.04 (t, J = 8.2 Hz, 1 H, H5), 4.50 (t, J = 7.9 Hz, 1 H, H2). **^{13}C NMR** (50.3 MHz) 31.12 and 31.23 (CH_3), 32.28 (C3), 51.61 and 51.84 (C4 and OCH_3), 69.71 and 70.07 (C5 and CCl), 77.00 (C2), 174 (C=O). **MS** (EI, 70 eV) 207 (M^++H, 2), 147/149 (M^+-CO_2Me, 100/41), 111 (M^+-CO_2Me-HCl, 57), 83 (54).

2,6-Dicarbomethoxy-4-chlorotetrahydropyran (6). To a solution of precursor 2 (1.27 g, 4.6 mmol) in 40 mL of dry CH_2Cl_2 at -78 °C was added a 1.2 M solution of $SnCl_4$ in CH_2Cl_2 (14.6 mL, 17.5 mmol). The reaction mixture was allowed to warm up to rt and stirred at rt for 3 h. Then the reaction mixture was poured into icewater and an excess of $NaHCO_3$ was added. The resulting mixture was stirred for 30 min at rt and then filtered over celite. The residue was rinsed with 250 mL of CH_2Cl_2. After the layers were separated, the water layer was extracted (3 ×) with CH_2Cl_2 (40 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in 50 mL of methanol and treated with a catalytic amount of HCl.

After being stirred at rt for 24 h, the reaction mixture was neutralized (pH ~ 7) with a saturated solution of $NaHCO_3$ in water and concentrated *in vacuo*. The residue was vigorously stirred with 50 mL of EtOAc to dissolve the product. After filtration, the filtrate was concentrated *in vacuo* and the residue was chromatographed to give two fractions. The first fraction consisted of **6t** (707 mg, 3.0 mmol, 65%, colourless oil). R_f 0.19 (EtOAc:hexanes = 1:3). **IR** 1750 (C=O). ^{1}**H NMR** (200 MHz) 2.00-2.40 (m, 4 H, H3 and H5), 3.78 (s, 6 H, CH_3), 4.60 (dd, J = 11.4, 2.3 Hz, 2 H, H2 and H6), 4.68 (quintet, J = 3.0 Hz, 1 H, H4). ^{13}**C NMR** (50.3 MHz) 35.42 (C3 and C5), 52.45 (CH_3), 54.52 (C4), 71.23 (C2 and C6), 170.30 (C=O). The second fraction consisted of **6c** (98 mg, 0.4 mmol, 9%, colourless oil). R_f 0.10 (EtOAc:hexanes = 1:3). ^{1}**H NMR** (200 MHz) 2.01-2.59 (m, 4 H, H3 and H5), 3.79 (s, 6 H, CH_3), 4.2 (tt, J = 8.6, 4.2 Hz, 1 H, H4), 4.66 (dd, J = 8.8, 4.1 Hz, 1 H, H2), 4.86 (t, J = 5.0 Hz, 1 H, H6). **MS** (EI, 70 eV, ethyl methyl ester of **6t**) 191/193 (M^+-CO_2Me, 67/24), 177/179 (M^+-CO_2Et, 100/33).

***rel*-(2*R*,3*S*,4*R*,6*S*)-2,6-Dicarbomethoxy-4-chloro-3-propyltetrahydropyran (7).** To a solution of precursor **3** (1.00 g, 3.3 mmol) in 20 mL of dry CH_2Cl_2 at -78 °C was added a 1.2 M solution of $SnCl_4$ in CH_2Cl_2 (11.0 mL, 13.2 mmol). The reaction mixture was allowed to warm up to rt and stirred at rt fot 3 h. Then the reaction mixture was poured into icewater and an excess of $NaHCO_3$ was added. The resulting mixture was stirred for 30 min at rt and then filtered over celite. The residue was rinsed with 200 mL of CH_2Cl_2. After the layers were separated, the water layer was extracted (3 ×) with CH_2Cl_2 (40 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed to give **7** (561 mg, 2.0 mmol, 61%) as a colourless oil. R_f 0.37 (EtOAc:hexanes = 1:3). **IR** 1745 (C=O). ^{1}**H NMR** (200 MHz) 0.84-2.25 (m, 9 H, H3, $CH_2CH_2CH_3$ and H5), 2.38 (dt, J = 14.4, 2.8 Hz, 1 H, H5), 3.60-3.75 (m, 1 H, H4), 3.76 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 4.20 (d, J = 10.2 Hz, 1 H, H2), 4.55 (dd, J = 9.1, 2.5 Hz, 1 H, H6). ^{13}**C NMR** (50.3 MHz) 13.59 (CH_3), 18.39 (CH_2Me), 29.03 (CH_2Et), 36.29 (C5), 41.54 (C3), 51.99 and 52.14 (OCH_3), 58.19 (C4), 70.55 and 76.77 (C2 and C6), 169.51 and 170.08 (C=O). **MS** (EI, 70 eV) 279/281 (M^++H, 7/2), 219/221 (M^+-CO_2Me, 100/33), 183 (M^+-CO_2Me -HCl, 35). Accurate mass 278.0941 (calcd for $C_{12}H_{19}O_5{}^{35}Cl$ 278.0921).

***cis*-2-Carbomethoxy-4-chloro-6,6-dimethyltetrahydropyran (8).** To a solution of precursor **4** (144 mg, 0.63 mmol) in 6 mL of dry CH_2Cl_2 at -78 °C was added a 2 M solution of $SnCl_4$ in CH_2Cl_2 (1.0 mL, 2.0 mmol). The reaction mixture was allowed to warm up to rt and stirred at rt for 16 h. Then the reaction mixture was poured into icewater and an excess of $NaHCO_3$ was added. The resulting mixture was stirred for 30 min at rt and then filtered over celite. The residue was rinsed with 200 mL of CH_2Cl_2. After the layers were separated, the water layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed to give **8** (80 mg, 0.39 mmol, 61%) as a white solid. Recrystallization (ether/pentane) gave **8** as white crystals, mp 74-74.5 °C. R_f 0.50 (EtOAc:hexanes = 1:4). **IR** 1750 (C=O). ^{1}**H NMR** (300 MHz) 1.24 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 1.72 (t, J = 12.6 Hz, 1 H, H5ax), 1.76 (q, J = 12.3 Hz, 1 H, H3ax), 2.07 (ddd, J = 13.0, 4.4, 1.9 Hz, 1 H, H5eq), 2.48 (dquintet, J = 12.7, 2.1 Hz, 1 H, H3eq), 3.77 (s, 3 H, OCH_3), 4.2 (m, 1 H, H4), 4.23 (dd, J = 12.0, 2.5 Hz, 1 H, H2). ^{1}**H NMR** (200 MHz, C_6D_6) 0.66 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3), 1.46 (t, J = 12.4 Hz, 1 H, H5ax), 1.61 (ddd, J = 12.8, 4.8, 1.7 Hz, 1 H, H5eq), 1.75 (q, J = 12.3 Hz, 1 H, H3ax), 2.18 (dquintet, J = 12.6, 2.1 Hz, 1 H, H3eq), 3.27 (s, 3 H, OCH_3), 3.60 (tt, J = 12.0, 4.6 Hz, 1 H, H4), 3.78 (dd, J = 12.0, 2.4 Hz, 1 H, H2). ^{13}**C NMR** (50.3 MHz) 22.00 and 31.06 (CH_3), 38.97 and 46.38 (C3 and C5), 52.33 and 52.71 (C4 and OCH_3), 70.08 (C2), 74.46 (C6), 170.80 (C=O). **MS** (EI, 70 eV) 206/208 (M^+, 4/2), 171 (M^+-Cl, 59), 147/149 (M^+-CO_2Me, 60/18). Accurate mass 206.0712 (calcd for $C_9H_{15}O_3{}^{35}Cl$ 206.0710). Combustion analysis C, 52.30; H, 7.46 (calcd for $C_9H_{15}O_3Cl$ C, 52.31; H, 7.32).

Methyl 2-acetoxy-2-[5-trimethylsilyl-3-(*Z*)-penten-1-oxy]acetate (9). Method A: 5-Trimethylsilyl-3-penten-1-ol[12] (1.20 g, 7.06 mmol) was treated with methyl glyoxylate hydrate (1.50 g, 14.12 mmol) in 70 mL of benzene. The crude hemiacetal was treated with acetic anhydride (1.22 g, 11.97 mmol) and DMAP (0.19 g, 1.60 mmol) in 18 mL of pyridine to give **9** (1.48 g, 4.93 mmol, 70%) as a yellowish oil. R_f 0.50 (EtOAc:hexanes = 1:1.8). **IR** 1750 (C=O). ^{1}**H NMR** (200 MHz) 0.02 (s, 9 H, $Si(CH_3)_3$), 1.46 (d, J = 8.6 Hz, 2 H, CH_2Si), 2.14 (s, 3 H, CH_3), 2.33 (m, 2 H, CH_2CH=), 3.66 (m, 2 H, OCH_2), 3.79 (s, 3 H, OCH_3), 5.2 (m, 1 H, CH=), 5.5 (m, 1 H, CH=), 5.97 (s, 1 H, OCH). ^{13}**C NMR** (62.9 MHz) 1.09 ($Si(CH_3)_3$), 18.67 (CH_2Si), 20.73 (CH_3), 27.39 (CH_2CH=), 52.65 (OCH_3), 69.84 (OCH_2), 92.55 (OCH), 121.57 (=$CHCH_2Si$), 128.38 (CH=), 166.21 (C=O), 169.88 (CO_2Me).

Methyl 2-acetoxy-2-(4-trimethylsilyl-3-buten-1-oxy)acetate (10). Method B: 4-Trimethylsilyl-3-buten-1-ol[14] (1.50 g, 10.4 mmol) in 15 mL of dry CH_2Cl_2 was treated with anhydrous methyl glyoxylate (3.9 mL, 53.2 mmol). The crude hemiacetal was dissolved in 15 mL of pyridine and treated with acetic anhydride (9.0 mL, 95.5 mmol) and a catalytic amount of DMAP to give two isomers (*E*:*Z* = 1:6) of **10** (1.45 g, 5.3 mmol, 51%) as a colourless oil. R_f 0.25 (EtOAc:hexanes = 1:5). **IR** 1750 (C=O). ^{1}**H NMR** (200 MHz, major isomer) 0.11 (s, 9 H, $Si(CH_3)_3$), 2.16 (s, 3 H, CH_3), 2.46 (m, 2 H, =$CHCH_2$), 3.72

(m, 2 H, CH_2O), 3.80 (s, 3 H, OCH_3), 5.62 (bd, J = 14.1 Hz, 1 H, =CHSi), 5.97 (s, 1 H, OCH), 6.25 (dt, J = 14.1, 7.1 Hz, 1 H, CH=).

Methyl 2-acetoxy-2-[2-methyl-5-trimethylsilyl-4-(*E*)-penten-2-oxy]acetate (11). Method B: 2-Methyl-5-trimethylsily-4-(*E*)-penten-2-ol[15] (157 mg, 0.9 mmol) in 5 mL of dry CH_2Cl_2 was treated with anhydrous methyl glyoxylate (0.2 mL, 2.7 mmol). The crude hemiacetal was dissolved in 5 mL of pyridine and treated with Ac_2O (0.6 mL, 6.6 mmol) and a catalytic amount of DMAP to give **11** (110 mg, 0.4 mmol, 40%) as a colourless oil.R_f 0.30 (EtOAc:hexanes = 1:6). **IR** 1750 (C=O). **^{1}H NMR** (200 MHz) 0.04 (s, 9 H, $Si(CH_3)_3$), 1.23 (s, 6 H, CH_3), 2.12 (s, 3 H, CH_3), 2.36 (d, J = 6.6 Hz, 2 H, CH_2CH=), 3.78 (s, 3 H, OCH_3), 5.80 (d, J = 18.5 Hz, 1 H, SiCH=), 6.00 (dt, J = 18.5, 6.6 Hz, 1 H, =CH), 6.10 (s, 1 H, OCH). **^{13}C NMR** (50.3 MHz) 0.73 ($Si(CH_3)_3$), 20.77 (CH_3), 25.29 and 25.82 (CH_3), 28.22 (CH_2CH=), 52.44 (OCH_3), 79.68 (CO), 88.52 (OCH), 134.50 (SiCH=), 141.10 (=CH), 166.88 (C=O), 169.77 (CO_2Me).

***cis*-2-Carbomethoxy-3-vinyltetrahydrofuran (12).** To a solution of precursor **9** (167 mg, 0.56 mmol) in 6 mL of dry CH_2Cl_2 at -78 °C was added a 1.2 M solution of $SnCl_4$ in CH_2Cl_2 (0.93m mL, 1.12 mmol). The reaction mixture was allowed to warm up to rt and stirred for 3 h. Then the reaction mixture was poured into icewater and an excess of $NaHCO_3$ was added. The resulting mixture was stirred at rt for 30 min at rt and then filtered over celite. The residue was rinsed with 150 mL of CH_2Cl_2. After the layers were separated, the water layer was extracted (3 ×) with CH_2Cl_2 (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed to give **12** (65 mg, 0.42 mmol, 75%) as a colourless oil. R_f 0.45 (EtOAc:hexanes = 1:1). **IR** 1750 (C=O). **^{1}H NMR** (200 MHz) 1.91-2.20 (m, 2 H, H4), 3.12 (quintet, J = 7.8 Hz, 1 H, H3), 3.68 (s, 3 H, CH_3), 3.69-3.97 (m, 1 H, H5), 4.21 (td, J = 8.1, 4.9 Hz, 1 H, H5), 4.49 (d, J = 7.7 Hz, 1 H, H2), 5.13 (m, 2 H, $=CH_2$), 5.65 (ddd, J = 17.1, 10.0, 8,5 Hz, 1 H, =CH). **^{13}C NMR** (50.3 MHz) 31.10 (C4), 46.62 (C3), 51.36 (CH_3), 68.72 (C5), 80.44 (C2), 117.00 ($=CH_2$), 135.02 (=CH).

2-Carbomethoxy-5,6-dihydro-(2*H*)-pyran (13). To a solution of precursor **10** (572 mg, 2.1 mmol) in 15 mL of dry CH_2Cl_2 at -78 °C was added $BF_3{\cdot}OEt_2$ (0.5 mL, 4.9 mmol). The reaction mixture was allowed to warm up to rt and stirred at rt for 17 h. The reaction mixture was poured into icewater and an excess of $NaHCO_3$ was added. The resulting mixture was stirred for 30 min at rt. The layers were separated and the organic layer was washed with 25 mL of a saturated solution of $NaHCO_3$ in water. The water layers were extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed to give **13** (176 mg, 1.2 mmol, 59%) as a colourless oil. R_f 0.23 (EtOAc:hexanes = 1:5). **IR** 1740 (C=O). **^{1}H NMR** (200 MHz) 2.15 (m, 2 H, H5), 3.77 (s, 3 H, CH_3), 3.83 (m, 1 H, H6), 4.03 (m, 1 H, H6), 4.73 (quintet, J = 2.7 Hz, 1 H, H2), 5.9 (m, 1 H, H4), 6.01 (m, 1 H, H3). **^{13}C NMR** (50.3 MHz) 24.35 (C5), 52.04 (CH_3), 62.35 (C6), 72.59 (C2), 123.80 and 127.12 (C3 and C4), 171.06 (C=O). Accurate mass 142.0633 (calcd for $C_7H_{10}O_3$ 142.0630).

Attempt to cyclize 11. To a solution of **11** (1.035 g,3.42 mmol) in 20 mL of dry CH_2Cl_2 at -78 °C was added $BF_3{\cdot}OEt_2$ (0.9 mL, 7.3 mmol). The reaction mixture was allowed to warm up to rt and stirred at rt for 17 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo* to give an oil (257 mg, 2.29 mmol, 67%), which according to its ^{1}H NMR spectrum was virtually pure **methyl (*E*)-2,4-pentadienoate (14).** **^{1}H NMR** (200 MHz) 3.74 (s, 3 H, OCH3), 5.48 (d, 1 H, J = 10 Hz), 5.60 (d, 1 H, J = 16.5 Hz), 5.90 (d, 1 H, J = 15.5 Hz), 6.45 (dt, 1 H, J = 16.5, 10.5 Hz), 7.26 (dd, 1 H, J = 15.5, 10.5 Hz). These NMR data compared well with literature data on the ethyl ester.[21]

(1'*R*)-Methyl 2-acetoxy-2-(1-cyclohexyl-3-buten-1-oxy)acetate (15). Method B: (*R*)-1-Cyclohexyl-3-buten-1-ol[16] (559 mg, 3.63 mmol) in 5 mL of dry CH_2Cl_2 was treated with anhydrous methyl glyoxylate (0.6 mL, 8.18 mmol). The crude hemiacetal was dissolved in 7 mL of pyridine and treated with Ac_2O (1.7 mL, 18.03 mmol) and a catalytic amount of DMAP to give **(1'*R*)-15** (712 mg, 2.50 mmol, 69%) as a colourless oil. R_f 0.32 (EtOAc:hexanes = 1:3). $[\alpha]^{20}_D$ = -1.0 (c 1.04, $CHCl_3$). **IR** 1745 (C=O), 1630 (C=C). **^{1}H NMR** (200 MHz, mixture of two diastereoisomers) 0.92-1.89 (m, 11 H, $(CH_2)_5CH$), 2.13 and 2.14 (s, 3 H, CH_3), 2.32 (m, 2 H, CH_2CH=), 3.49 (m, 1 H, CHO), 3.79 and 3.80 (s, 3 H, OCH_3), 5.07 (m, 2 H, $=CH_2$), 5.83 (m, 1 H, CH=), 5.97 and 6.00 (s, 1 H, OCHOAc).

(2'*R*,3'*S*)-Methyl 2-acetoxy-2-(1,2-*O*-isopropylidene-5-hexene-1,2-diol-3-oxy)acetate (16). Method B: (2*R*, 3*S*)-1,2-*O*-*Iso*-propylidene-5-hexene-1,2,3-triol[16] (589 mg, 3.4 mmol) in 6 mL of dry CH_2Cl_2 was treated with anhydrous methyl glyoxylate (0.6 mL, 8.2 mmol). The crude hemiacetal was dissolved in 8 mL of pyridine and treated with acetic anhydride (1.7 mL, 18.03 mmol) and a catalytic amount of DMAP to give two fractions. The first fraction consisted of **(2*R*,3*S*)-3-**

acetoxy-1,2-*O*-isopropylidene-5-hexene-1,2-diol (317 mg, 1.5 mmol, 43%, yellowish oil). R_f 0.30 (EtOAc:hexanes = 1:3). **^{1}H NMR** (200 MHz) 1.34 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 2.05 (s, 3 H, CH_3), 2.38 (m, 2 H, =CHCH_2), 3.79 (dd, J = 8.2, 6.2 Hz, 1 H, OCH_2), 4.02 (dd, J = 8.2, 6.5 Hz, 1 H, OCH_2), 4.15 (q, J = 6.0 Hz, 1 H, OCH), 4.97-5.14 (m, 3 H, CHOAc and =CH_2), 5.75 (m, 1 H, CH=). The second fraction consisted of **16** (516 mg, 1.7 mmol, 50%, colourless oil). R_f 0.20 (EtOAc:hexanes = 1:3). $[\alpha]^{20}_D$ = +22.3 (c 1.51, $CHCl_3$). **IR** 1750 (C=O), 1630 (C=C). **^{1}H NMR** (200 MHz, mixture of diastereoisomers) 1.32, 1.37 and 1.39 (s, 6 H, CH_3), 2.13 and 2.15 (s, 3 H, CH_3), 2.23-2.51 (m, 2 H, =CHCH_2), 3.78 (s, 3 H, OCH_3), 3.70-4.13 (m, 4 H, OCHCHCH_2O), 5.12 (m, 2 H, =CH_2), 5.84 (m, 1 H, CH=), 6.03 and 6.12 (s, 1 H, CHOAc). **^{13}C NMR** (62.9 MHz, mixture of diastereoisomers) 20.83 and 20.90 (CH_3), 25.31, 25.35, 26.25 and 26.71 (C(CH_3)$_2$), 35.79 and 36.24 (=$CHCH_2$), 52.61 and 52.71 (OCH_3), 64.80 and 66.66 (OCH_2), 76.05, 77.22, 79.80 and 80.10 (OCHCHO), 91.81 and 93.25 (CHOAc), 109.06 and 109.47 (CMe_2), 117.81 and 118.70 (=CH_2), 132.84 and 133.34 (CH=), 166.01 and 166.21 (C=O), 169.87 and 170.04 (CO_2Me). **MS** (EI, 70 eV) 287 (M^+-Me, 40), 185 (M^+-Me-CO_2Me-Ac, 18), 131 (AcOCHCO_2Me, 11), 101 ($C_5H_9O_2$, 70), 43 (Ac, 100).

2-Carbomethoxy-4-chloro-6-cyclohexyltetrahydropyran (17). To a solution of precursor **(1'*R*)-15** (185 mg, 0.65 mmol) in 6 mL of dry CH_2Cl_2 at -78 °C was added a 1.2 M solution of $SnCl_4$ in CH_2Cl_2 (1.1 mL, 1.32 mmol). The reaction mixture was warmed to rt and stirred at rt for 3 h. Then the reaction mixture was poured into ice water and an excess of $NaHCO_3$ was added. The resulting mixture was stirred for 30 min at rt and then filtered over celite. The residue was rinsed with 150 mL of CH_2Cl_2. After the layers were separated, the water layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed to give 3 fractions. The first fraction consisted of **(2*R*,4*R*,6*R*)-17a** (52.0 mg, 0.20 mmol, 31%, colourless oil). R_f 0.50 (EtOAc:hexanes = 1:4). $[\alpha]^{20}_D$ = +16.6 (c 0.97, $CHCl_3$). **IR** 1735 (C=O). **^{1}H NMR** (200 MHz) 0.87-2.16 (m, 14 H, $(CH_2)_5$CH, H5 and H3ax), 2.59 (dquintet, J = 13.1, 2.0 Hz, 1 H, H3eq), 3.43 (ddd, J = 11.5, 6.0, 1.8 Hz, 1 H, H6), 3.75 (s, 3 H, CH_3), 4.00 (tt, J = 12.0, 4.3 Hz, 1 H, H4), 4.55 (bd, J = 5.3 Hz, 1 H, H2). **^{13}C NMR** (50.3 MHz) 25.72, 25.80 and 26.22 ($CH_2CH_2CH_2$), 28.02 and 28.33 (CH_2CHCH_2), 36.79 and 38.75 (C3 and C5), 42.31 (CH), 51.84 and 53.23 (C4 and CH_3), 73.05 and 77.18 (C2 and C6), 171.56 (C=O). The second fraction consisted of **(2*S*,4*R*,6*R*)-17c** (74.0 mg, 0.28 mmol, 44%, colourless oil). R_f 0.40 (EtOAc:hexanes = 1:4). $[\alpha]^{20}_D$ = -11.3 (c 0.63, $CHCl_3$). **IR** 1745 (C=O). **^{1}H NMR** (200 MHz) 0.82-2.05 (m, 13 H, $(CH_2)_5$CH, H3ax and H5ax), 2,17 (dquintet, J = 12.9, 1.9 Hz, 1 H, H5eq), 2.43 (dquintet, J = 12.7, 2.1 Hz, 1 H, H3eq), 3.06 (ddd, J = 11.2, 6.8, 1.7 Hz, 1 H, H6), 3.74 (s, 3 H, CH_3), 3.94 (dd, J = 11.8, 2.1 Hz, 1 H, H2), 4.01 (tt, J = 11.8, 4.5 Hz, 1 H, H4). **^{13}C NMR** (50.3 MHz) 25.63, 25.74 and 26.14 ($CH_2CH_2CH_2$), 28.14 and 28.88 (CH_2CHCH_2), 38.63 and 38.91 (C3 and C5), 42.08 (CH), 51.99 (CH_3), 55.06 (C4), 75.38 (C6), 81.31 (C2), 170 (C=O). **MS** (EI, 70 eV) 260 (M^+, 2), 224 (M^+-HCl, 30), 201/203 (M^+-CO_2Me, 100/32), 183/185 (98/32), 141 (80), 113 (61). The third fraction consisted of **(2*S*,4*S*,6*R*)-17t** (31.3 mg, 0.12 mmol, 18%, colourless oil). R_f 0.35 (EtOAc:hexanes = 1:4). $[\alpha]^{20}_D$ = -6.9 (c 0.53, $CHCl_3$). **IR** 1740 (C=O). **^{1}H NMR** (200 MHz) 0.84-2.24 (m, 15 H, $(CH_2)_5$CH, H3 and H5), 3.60 (ddd, J = 10.8, 7.3, 2.1 Hz, 1 H, H6), 3.75 (s, 3 H, CH_3), 4.50 (dd, J = 11.4, 2.4 Hz, 1 H, H2), 4.65 (quintet, J = 3.0 Hz, 1 H, H4). **^{13}C NMR** (50.3 MHz) 25.63, 25.76 and 26.20 ($CH_2CH_2CH_2$), 28.12 and 28.83 (CH_2CHCH_2), 35.38 and 36.09 (C3 and C5), 41.84 (CH), 51.87 (CH_3), 55.93 (C4), 71.12 and 76.03 (C2 and C6), 171.42 (C=O).

(1'*R*,2*R*,4*R*,6*S*)-2-Carbomethoxy-4-chloro-6-(1,2-*O*-methylene-1,2-dihydroxyethyl)-tetrahydropyran (18). To a solution of precursor **16** (430 mg, 1.42 mmol) in 15 mL of dry CH_2Cl_2 at -78 °C was added a 1.2 M solution of $SnCl_4$ in CH_2Cl_2 (3.0 mL, 3.6 mmol). After being stirred at -20 °C for 5 h, the reaction mixture was cooled to -40 °C and dimethoxymethane (2.0 mL, 23 mmol) was added. The mixture was stirred at -10 °C for 15 min and then poured into icewater and $NaHCO_3$ was added. The mixture was filtered over celite and the residue was rinsed with 150 mL of CH_2Cl_2. After the layers were separated, the water layer was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed to give two fractions. The first fraction consisted of **3-(1-carbomethoxy-3-buten-1-oxy)-1,2-*O*-methylene-3-methoxy-1,2-propanediol** (**19**, 51 mg, 0.21 mmol, 15%, yellowish oil). R_f 0.20 (EtOAc:hexanes = 1:1.2). **^{1}H NMR** (200 MHz) 2.42 (m, 2 H, =CHCH_2), 3.37 (s, 3 H, OCH_3), 3.67 (d, J = 6.0 Hz, 2 H, OCH_2), 3.79 (s, 3 H, CO_2CH_3), 3.8 (t, J = 6.6 Hz, 1 H, $CHCO_2$Me), 4.17-4.37 (m, 2 H, OCHCHOMe), 4.65 (s, 2 H, OCH_2O), 5.15 (m, 2 H, =CH_2), 5.86 (m, 1 H, CH=). **^{13}C NMR** (50.3 MHz) 32.90 (CH_2CH=), 52.25 (CO_2CH_3), 55.16 (OCH_3), 65.46 (OCH_2), 77.40 ($CHCO_2$Me), 78.57 (OCH_2CHO), 96.56 (OCH_2O), 97.85 (CHOMe), 117.43 (=CH_2), 133.47 (CH=), 167.87 (C=O). The second fraction consisted of **18** (115 mg, 0.46 mmol, 32%, white solid). Recrystallization from ether/pentane gave white crystals, mp 61.0-62.0 °C. R_f 0.10 (EtOAc:hexanes = 1:1.2). $[\alpha]^{20}_D$ = +15.4 (c 0.68, $CHCl_3$). **IR** 1750 (C=O). **^{1}H NMR** (200 MHz) 1.73-2.27 (m, 4 H, H3 and H5), 3.75 (s, 3 H, CH_3), 3.78-4.03 (m, 4 H, H6, H7 and H8), 4.54 (dd, J = 11.4, 2.4 Hz, 1 H, H2), 4.66 (quintet, J = 3.0 Hz, 1 H, H4), 4.84 (s, 1 H, OCH_2O), 5.01 (s, 1 H, OCH_2O). **^{13}C NMR** (50.3 MHz) 34.88 and 35.82 (C3 and C5), 51.94 (CH_3), 54.64 (C4), 67.47 (C8), 70.80 and 72.42 (C6 and C7), 76.32 (C2), 95.21 (OCH_2O), 170.72 (C=O). **MS**

(EI, 70 eV) 250 (M^+, 4), 214 (M^+-HCl, 18), 191/193 (M^+-CO_2Me, 18/6), 177/179 (M^+-CO_2Me-CH_2, 100/32). Combustion analysis C, 47.90; H, 6.10 (calcd for $C_{10}H_{15}O_5Cl$ C, 47.91; H, 6.03). **X-Ray crystal structure determination of (+)-18.** $C_{10}H_{15}O_5Cl$, M_r = 250.7, orthorhombic, $P2_12_12_1$, a = 8.4683(5), b = 9.5727(6), c = 14.412(1) Å, V = 1168.3(1) $Å^3$, Z = 4, D_x = 1.43 gcm^{-3}, λ(Cu Kα) = 1.5418 Å, μ(Cu Kα) = 29.9 cm^{-1}, F(000) = 528, T = 248 K. Final R = 0.037 for 1097 observed reflections. Refinement of the enantiomorph under the same conditions converged to R = 0.051. The crystal structure is represented in Figure 1. More details of the X-ray structure determination have been deposited at the Cambridge Crystallographic Data Centre.

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