Studies on the role of the 2-oxonia Cope rearrangement in p-cyclizations of a-methoxycarbonyl oxycarbenium ions.

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Studies on the Role of the 2-Oxonia Cope Rearrangement in $\pi$-Cyclizations of $\alpha$-Methoxycarbonyl Oxycarbenium Ions

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Abstract: The 2-oxonia Cope rearrangement is shown to play an important role in Lewis acid-induced $\pi$-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 $\pi$-nucleophile and the substitution pattern of the oxycarbenium ion intermediate. The absolute stereochemistry is retained in the cyclization of the enantiopure substrates.

INTRODUCTION

The $\alpha$-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. 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 $\pi$-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 $R^3$.

Both sigmatropisomers A and B can cyclize in a 5-exo and a 6-endo fashion. The mode of $\pi$-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 R1, R2 and R3. 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. Typical examples are the anionic oxy-Cope rearrangement and the 2-azonia-Cope rearrangement. The latter type of reaction has been extensively investigated in combination with a Mannich cyclization by Overman and coworkers. 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. Interestingly, the mechanism of the oxygen variant is believed to be different from the nitrogen case on the basis of stereochemical arguments. 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. 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 R2 and R3 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 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 3-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. However, the alternative mechanism involving cyclization of C to D followed by Wagner-Meerwein ring contraction cannot be excluded. Formation of the cis-compound as a single stereoisomer is best understood assuming a chair-like transition state conformation.
The 2-oxonia Cope rearrangement

Table I Cyclization of Chain-Substituted Precursors

<table>
<thead>
<tr>
<th>Precursor</th>
<th>Reaction Conditions</th>
<th>Products (Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Me&lt;sub&gt;2&lt;/sub&gt;−OAc)</td>
<td>SnCl&lt;sub&gt;4&lt;/sub&gt; (2 equiv)</td>
<td>5 (60%)</td>
</tr>
<tr>
<td>2: R&lt;sup&gt;-&lt;/sup&gt; = Et, R&lt;sup&gt;2&lt;/sup&gt; = H (49%)</td>
<td>SnCl&lt;sub&gt;4&lt;/sub&gt; (4 equiv)</td>
<td>6e (9%)</td>
</tr>
<tr>
<td>3: R&lt;sup&gt;-&lt;/sup&gt; = Me, R&lt;sup&gt;2&lt;/sup&gt; = Pr (45%)</td>
<td>SnCl&lt;sub&gt;4&lt;/sub&gt; (3 equiv)</td>
<td>7 (61%)</td>
</tr>
</tbody>
</table>

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

Compound 2<sup>9</sup> 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<sup>10</sup> 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.

Table II Selected <sup>1</sup>H NMR Data (ppm, J in Hz, CDCl<sub>3</sub>)

<table>
<thead>
<tr>
<th>Compound</th>
<th>O-CH—CO&lt;sub&gt;2&lt;/sub&gt;Me</th>
<th>HC—Cl</th>
<th>HC—O</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>4.50 (t, 7.9)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6c</td>
<td>4.66 (dd, 8.8, 4.1)</td>
<td>4.2 (t, 8.6, 4.2)</td>
<td>4.86 (t, 5.0)</td>
</tr>
<tr>
<td>6t</td>
<td>4.60 (dd, 11.4, 2.3)</td>
<td>4.68 (quintet, 3.0)</td>
<td>4.60 (dd, 11.4, 2.3)</td>
</tr>
<tr>
<td>7</td>
<td>4.20 (d, 10.2)</td>
<td>3.7 (m)</td>
<td>4.55 (dd, 9.1, 2.5)</td>
</tr>
<tr>
<td>8 (C&lt;sub&gt;6&lt;/sub&gt;D&lt;sub&gt;6&lt;/sub&gt;)</td>
<td>3.78 (dd, 12.0, 2.4)</td>
<td>3.60 (tt, 12.0, 4.6)</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>4.49 (d, 7.7)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>4.73 (quintet, 2.7)</td>
<td>-</td>
<td>4.03 (m)</td>
</tr>
<tr>
<td>17a</td>
<td>4.55 (bd, 5.3)</td>
<td>4.00 (tt, 12.0, 4.3)</td>
<td>3.43 (dd, 11.5, 6.0, 1.8)</td>
</tr>
<tr>
<td>17c</td>
<td>3.94 (dd, 11.8, 2.1)</td>
<td>4.01 (tt, 11.8, 4.5)</td>
<td>3.06 (dd, 11.2, 6.8, 1.7)</td>
</tr>
<tr>
<td>17t</td>
<td>4.50 (dd, 11.4, 2.4)</td>
<td>4.65 (quintet, 3.0)</td>
<td>3.60 (dd, 10.8, 7.3, 2.1)</td>
</tr>
<tr>
<td>18</td>
<td>4.54 (dd, 11.4, 2.4)</td>
<td>4.66 (quintet, 3.0)</td>
<td>obscured</td>
</tr>
</tbody>
</table>

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 <sup>1</sup>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.

Assuming a mechanism involving equatorial attack of chloride 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 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 showed a remarkable result. Tetrahydropyran 8 was isolated as the only product and as a single isomer. In contrast to all previous cyclizations 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 sigmatropicomer 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 gave tetrahydrofuran 12 as a single isomer. 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.
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.

<table>
<thead>
<tr>
<th>precursor (yield(^{ab}))</th>
<th>reaction conditions</th>
<th>products (yield(^{b}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 (70%)</td>
<td>SnCl(_2) (2 equiv)</td>
<td>12 (75%)</td>
</tr>
<tr>
<td></td>
<td>-78 °C → rt, 3 h</td>
<td></td>
</tr>
<tr>
<td>10: E:Z = 1:6 (51%)</td>
<td>BF(_3)OEt(_2) (2 equiv)</td>
<td>13 (59%)</td>
</tr>
<tr>
<td></td>
<td>-78 °C → rt, 17 h</td>
<td></td>
</tr>
<tr>
<td>11 (40%)</td>
<td>BF(_3)OEt(_2) (2 equiv)</td>
<td>14 (67%)</td>
</tr>
<tr>
<td></td>
<td>-78 °C → rt, 17 h</td>
<td></td>
</tr>
</tbody>
</table>

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

Cyclization of vinylsilane 10\(^{14}\) gave a good yield of dihydropyran 13 upon treatment with boron trifluoride etherate. This 5,6-dihydro-(2H)-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.

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 O, 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\textsuperscript{10} (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)\textsubscript{3}. Treatment of the racemic products prepared from racemic 15 with Eu(hfc)\textsubscript{3} led to a doubling of the methyl ester singlet in each case. Treatment of the reaction product (+)-17a with Eu(hfc)\textsubscript{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 than 87\%,\textsuperscript{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>
<thead>
<tr>
<th>precursor (yield\textsuperscript{a,b})</th>
<th>reaction conditions</th>
<th>products (yield\textsuperscript{b})</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 (69%)</td>
<td>SnCl\textsubscript{4} (2 equiv) (-78^\circ\text{C} \rightarrow rt, 3\ h)</td>
<td>17a (31%) ([\alpha]^{20}<em>{D} = +16.6\ (c 0.97, CHCl\textsubscript{3})) 17c (44%) ([\alpha]^{20}</em>{D} = -11.3\ (c 0.65, CHCl\textsubscript{3})) 17t (18%) ([\alpha]^{20}_{D} = -6.9\ (c 0.53, CHCl\textsubscript{3}))</td>
</tr>
<tr>
<td>16 (50%)</td>
<td>SnCl\textsubscript{4} (2.5 equiv) (-78^\circ\text{C} \rightarrow 20^\circ\text{C}, 5\ h; CH\textsubscript{2}(OMe)\textsubscript{2}\textsubscript{(excess)} \rightarrow -40^\circ\text{C} \rightarrow -10^\circ\text{C}, 15\ min)</td>
<td>18 (32%) ([\alpha]^{20}_{D} = +15.4\ (c 0.68, CHCl\textsubscript{3})) 19 (15%)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Isolated yield of purified product. \textsuperscript{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.\textsuperscript{5}
Ring closure of 16 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 tetrahydropryan 18 obtained in a yield of 32% as a single crystalline isomer (mp 61-62 °C with [α]_D^20 +15.4 (c 0.68, CHCl₃). 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 an 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-butenolic acid.

EXPERIMENTAL

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

General procedure for the synthesis of the precursors. Method A: Methyl glyoxylate hydrate (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 calc for both alcohol and glyoxyate) and DMAP (0.2 equiv). After being stirred for 16 h at rt, the reaction mixture was evaporated with benzene (3 ×) and CH₂Cl₂ (3 ×). The residue was chromatographed. Method B: Anhydrous methyl glyoxylate (ca. 2 equiv) was added to a 1.5 M solution of the alcohol in dry CH₂Cl₂. 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 called for both alcohol and glycolate) and a catalytic amount of DMAP. After being stirred for 16 h at rt, the reaction mixture was evaporated with benzene (3 ×) and CH2Cl2 (3 ×). The residue was chromatographed.

Methyl 2-acetoxy-2-(2,2-dimethyl-3-buten-1-oxo)acetate (1). Method B: 2,2-Dimethyl-3-buten-1-ol9 (415 mg, 4.2 mmol) in 5 mL of dry CH2Cl2 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. Rf 0.90 (EtOAc:hexanes = 1:7). IR 1755 (C=O). 1H NMR (200 MHz, mixture of two diastereoisomers) 1.01 (s, 6 H, CH3), 2.16 (s, 3 H, CH3), 3.46 (m, 2 H, CH2), 3.81 (s, 3 H, OCH3), 5.80 (dd, J = 10.9, 1.2 Hz, 1 H, =CH2), 5.78 (dd, J = 17.3, 1.2 Hz, 1 H, =CH2), 5.78 (dd, J = 17.5, 10.8 Hz, 1 H, CH3), 5.96 (s, 1 H, OCH).

Methyl 2-acetoxy-2-(1-carbomethoxy-3-buten-1-oxo)acetate (2). Method B: Ethyl 2-hydroxy-4-pentenoate (455 mg, 3.2 mmol) in 5 mL of dry CH2Cl2 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. Rf 0.38 (EtOAc:hexanes = 1:3). IR 1750 (C=O). 1H NMR (200 MHz, mixture of two diastereoisomers) 1.27 (t, J = 7.1 Hz, 3 H, CH3), 2.13 and 2.16 (s, 3 H, CH3), 2.54 (m, 2 H, CH2), 3.80 and 3.83 (s, 3 H, OCH3), 4.17 (m, 2 H, OCH2), 4.36 (m, 1 H, CHC2Et), 5.12 (m, 2 H, =CH2), 5.80 (m, 1 H, CH=), 6.03 and 6.05 (s, 1 H, CHOAc). 13C NMR (62.9 MHz) 14.07 (CH2CH3), 20.58 (CH3), 36.54 (CH2), 52.68 (OCH3), 61.26 (OCH2), 77.09 (CHCO2Et), 91.36 (CHOAc), 118.16 (=CH2), 132.22 (CH=), 165.79 (C=O), 169.73 and 170.44 (CO2Me and CO2Et).

Methyl 2-acetoxy-2-(1-carbomethoxy-3-(E)-hepten-1-oxo)acetate (3). Method B: Methyl 2-hydroxy-4-(E)-octenoate9 (3.44 g, 20.0 mmol) in 20 mL of dry CH2Cl2 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. Rf 0.49 (EtOAc:hexanes = 1:3). IR 1750 (C=O). 1H NMR (200 MHz, mixture of two diastereoisomers) 0.85 (t, J = 7.3 Hz, 3 H, CH2CH3), 1.33 (sextet, J = 7.3 Hz, 2 H, CH2CH3), 1.94 (q, J = 7.2 Hz, 2 H, CH2Et), 2.08 and 2.11 (s, 3 H, CH3), 2.48 (t, J = 6.6 Hz, 2 H, CH2), 3.67 and 3.69 (s, 3 H, OCH3), 3.74 and 3.78 (s, 3 H, OCH3), 4.28-4.38 (m, 1 H, CHC2Et), 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-oxo)acetate (4). Method B: 2-Methyl-1-pentene9 (1.83 g, 18.3 mmol) in 6 mL of dry CH2Cl2 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. Rf 0.49 (EtOAc:hexanes = 1:3). IR 1750 (C=O). 1H NMR (200 MHz) 1.25 (s, 6 H, CH3), 2.12 (s, 3 H, CH3), 2.31 (d, J = 7.2 Hz, 2 H, CH2), 3.78 (s, 3 H, OCH3), 5.013 (m, 2 H, =CH2), 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 CH2Cl2 at -78 °C was added a 1.2 M solution of SnCl4 in CH2Cl2 (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 iced water and an excess of NaHCO3 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 CH2Cl2. After the layers were separated, the water layer was extracted (3 ×) with CH2Cl2 (35 mL). The combined organic layers were dried (MgSO4) and concentrated in vacuo. The residue was chromatographed to give 5 (222 mg, 1.1 mmol, 60%) as a colourless oil. Rf 0.20 (EtOAc:hexanes = 1:3). IR 1740 (C=O). 1H NMR (200 MHz) 1.53 (s, 3 H, CH3), 1.56 (s, 3 H, CH3), 2.06 (m, 1 H, H3), 2.40 (m, 1 H, H3), 2.60 (quintet, J = 6.6 Hz, 1 H, H4), 3.75 (s, 3 H, OCH3), 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). 13C NMR (50.3 MHz) 31.12 and 31.23 (CH3), 32.28 (C3), 51.61 and 51.84 (C4 and OCH3), 69.71 and 70.07 (C5 and C6), 77.00 (C2), 174 (C=O). MS (EI, 70 eV) 207 (M+H, 2), 147/149 (M+CO2Me and CO2Et).

2,6-Dicarbomethoxy-4-chlorotetrahydropyran (6). To a solution of precursor 2 (1.27 g, 4.6 mmol) in 40 mL of dry CH2Cl2 at -78 °C was added a 1.2 M solution of SnCl4 in CH2Cl2 (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 iced water and an excess of NaHCO3 was added. The resulting mixture was stirred for 30 min at rt and then filtered over celite. The residue was rinsed with 230 mL of CH2Cl2. After the layers were separated, the water layer was extracted (3 ×) with CH2Cl2 (40 mL). The combined organic layers were dried (MgSO4) 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 NaHCO₃ 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). Rf 0.19 (EtOAc:hexane = 1:3). IR 1750 (C=O). 1H NMR (200 MHz) 2.00-2.40 (m, 4 H, H3 and H5), 3.78 (s, 6 H, CH3). After filtration, the filtrate was concentrated in vacuo and the residue was chromatographed to give two fractions. The second fraction consisted of 6e (98 mg, 0.4 mmol, 9%, colourless oil). Rf 0.10 (EtOAc:hexanes = 1:3). 1H NMR (200 MHz) 2.01-2.59 (m, 4 H, H3 and H5), 3.79 (s, 6 H, CH3), 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+CO₂Me, 67/24), 183 (M+CO₂Me-HCl, 35). Accurate mass 191.0921 (calcd for C₉H₁₅O₃Cl C, 52.30; H, 7.32).

rel-(2R,3S,4R,6S)-2,6-Dicarbomethoxy-4-chloro-3-propyltetrahydropyran (7). To a solutions of precursor 3 (1.00 g, 3.3 mmol) in 20 mL of dry CH₂Cl₂ at -78 °C was added a 2 M solution of SnCl₄ in CH₂Cl₂ (11.0 mL, 13.2 mmol). The mixture was stirred for 2 h at rt. Then the reaction mixture was poured into ice water and an excess of NaHCO₃ was added. The residue was filtered and then concentrated in vacuo to give 7 (561 mg, 2.0 mmol, 61%) as a white oil. MS (EI, 70 eV) 279/281 (M+H, 7/2), 219/221 (M+CO₂Me, 100/33), 183 (M+CO₂Me-HCl, 35). Accurate mass 279.0941 (calcd for C₉H₁₅O₃Cl 278.0921). 

cis-2-Carbomethoxy-4-chloro-6,6-dimethyltetrahydropyran (8). To a solution of precursor 4 (1.48 g, 4.93 mmol, 70%) as a yellowish oil.

Methyl 2-acetoxy-2-[5-trimethylsilyl-3-(Z)-pent-en-1-oxy]acetate (9). Method A: 5-Trimethylsilyl-3-penten-1-ol (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 product 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 (1.50 g, 10.4 mmol) in 15 mL of dry CH₂Cl₂ was treated with anhydrous methyl glyoxylate (3.9 mL, 53.2 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. Rf 0.25 (EtOAc:hexanes = 1:3). IR 1750 (C=O). 1H NMR (200 MHz, major isomer) 0.11 (s, 9 H, Si(CH₃)₃), 2.16 (s, 3 H, CH3), 2.46 (m, 2 H, CH₂CH₂Si), 128.38 (CH=), 166.21 (C=O), 169.88 (CO₂Me).
Methyl 2-acetoxy-2-[2-methyl-5-trimethylsilyl-4-(E)-penten-2-oxy]acetate (11). Method B: 2-Methyl-5-trimethylsilyl-4-(E)-penten-2-ol 15 (157 mg, 0.9 mmol) in 5 mL of dry CH2Cl2 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 Ac2O (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. 1H NMR (200 MHz) 0.9 (s, 9 H, Si(CH3)3), 1.23 (s, 6 H, CH3), 2.12 (s, 3 H, CH3), 2.36 (d, J = 6.6 Hz, 2 H, CH2CH=), 3.78 (s, 3 H, OCH3), 5.80 (d, J = 18.5 Hz, 1 H, H3), 6.00 (dt, J = 18.5, 6.6 Hz, 1 H, =CH), 6.10 (s, 1 H, OCH). 13C NMR (50.3 MHz) 0.73 (Si(CH3)3), 20.77 (CH3), 25.29 and 25.82 (CH3), 28.22 (CH2CH=), 52.44 (OCH3), 79.68 (CO), 88.52 (OCH), 134.50 (Si(CH3)), 141.10 (CH), 169.77 (CO2Me).
2-Carbomethoxy-4-chloro-6-cyclohexyltetrahydropyran (17). To a solution of precursor (1'R)-18 (185 mg, 0.65 mmol) in 6 mL of dry CH2Cl2 at -78 °C was added a 1.2 M solution of SnCl4 in CH2Cl2 (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 iced water and an excess of NaHCO3 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 CH2Cl2. After the layers were separated, the water layer was extracted with CH2Cl2 (3 x 30 mL). The combined organic layers were dried (MgSO4) and concentrated in vacuo. The residue was chromatographed to give 3 fractions. The first fraction consisted of [3'S,4'R,6'R]-17a (52.0 mg, 0.20 mmol, 31%, colourless oil). Rf 0.50 (EtOAc:hexanes = 1:1.2). [a]20D = +22.3 (c 1.51, CHCl3). IR 1750 (GO). 'H NMR (200 MHz) 0.87-2.16 (m, 15 H, (CH2)5CH, H3 and H5eq), 2.43 (quintet, J = 12.9, 1.9 Hz, 1 H, H3ax), 3.44 (dd, J = 11.1, 3.0 Hz, 2 H, =CHCH2), 3.36 (s, 3 H, CH3), 4.00 (tt, J = 11.0, 4.5 Hz, 1 H, H6), 3.77 (s, 3 H, CH3), 3.94 (dd, J = 11.6, 2.1 Hz, 1 H, H2), 4.02 (tt, J = 11.8, 3.0 Hz, 1 H, H7), 4.01 (tt, J = 11.0, 4.5 Hz, 1 H, H4). 13C NMR (50.3 MHz) 25.72, 25.80 and 26.22 (CH2CH2CH2). 28.14 and 28.88 (CH2CH2CH2). 38.63 and 38.91 (C3 and C5), 42.08 (C1+), 51.89 (CH3). 55.02 (C4), 75.36 (CZ), 81.31 (C2), 170 (C=O), MS (EI, 70 ev) 260 (M+, 2). 224 (M+-HCl, 30). 201/203 (M+-CD3, 100/32). 183 (M+-Me, 18). 131 (M+-HCOOMe, 11). 101 (S+CH2=CH2). 77.40 (CH=O), 78.57 (OCH2CHO), 96.56 (OCH20), 97.85 (CHOMe), 117.43 (CH=), 133.47 (CH=), 167.87 (GO). The second fraction consisted of [3'S,4'R,6'R]-17b (31.3 mg, 0.12 mmol, 18%, colourless oil). Rf 0.50 (EtOAc:hexanes = 1:1.2). [a]20D = +15.4 (c 0.68, CHCl3). IR 1750 (C=O). 'H NMR (200 MHz) 0.87-2.24 (m, 15 H, (CH2)5CH, H3 and H5eq), 2.43 (quintet, J = 10.8, 7.3, 2.1 Hz, 1 H, H6), 3.75 (s, 3 H, CH3), 4.50 (dd, J = 11.4, 2.4 Hz, 1 H, H2), 4.65 (quintet, J = 3.0 Hz, 1 H, H4). 13C NMR (50.3 MHz) 25.63, 25.76 and 26.20 (CH2CH2CH2). 38.12 and 28.83 (CH2CH2CH2), 35.38 and 36.09 (C3 and C5), 41.84 (CH3), 51.87 (CH3), 55.93 (C4), 71.12 and 76.03 (C2 and C6), 171.52 (C=O). The third fraction consisted of [3'R,4'R,6'R]-17c (31.3 mg, 0.12 mmol, 18%, colourless oil). Rf 0.50 (EtOAc:hexanes = 1:1.2). [a]20D = -6.9 (c 0.53, CHCl3). IR 1740 (C=O). 'H NMR (200 MHz) 0.84-2.24 (m, 15 H, (CH2)5CH, H3 and H5eq), 2.43 (quintet, J = 10.8, 7.3, 2.1 Hz, 1 H, H6), 3.75 (s, 3 H, CH3), 4.50 (dd, J = 11.4, 2.4 Hz, 1 H, H2), 4.65 (quintet, J = 3.0 Hz, 1 H, H4). 13C NMR (50.3 MHz) 25.63, 25.76 and 26.20 (CH2CH2CH2). 38.12 and 28.83 (CH2CH2CH2), 35.38 and 36.09 (C3 and C5), 41.84 (CH3), 51.87 (CH3), 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 CH2Cl2 at -78 °C was added a 1.2 M solution of SnCl4 in CH2Cl2 (3.0 mL, 3.6 mmol). The reaction mixture was warmed to -20 °C for 5 h, then 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 iced water and NaHCO3 was added. The mixture was filtered over celite and the residue was rinsed with 150 mL of CH2Cl2. After the layers were separated, the water layer was extracted with CH2Cl2 (3 x 30 mL). The organic layers were dried (Na2SO4) and concentrated in vacuo. The residue was chromatographed to give two fractions. The first fraction consisted of 3-(1-carbomethoxy-3-buten-1-oxo)-1,2-O-methylene-3-methoxy-1,2-propanediol (19, 51 mg, 0.21 mmol, 15%, yellowish oil). Rf 0.20 (EtOAc:hexanes = 1:1.2). 'H NMR (200 MHz) 2.42 (m, 2 H, =CHCH2), 3.37 (s, 3 H, OCH3), 3.67 (d, J = 6.0 Hz, 2 H, CH2), 3.79 (s, 3 H, CO2CH3), 3.8 (t, J = 6.6 Hz, 1 H, CHCHO), 4.17-4.37 (m, 2 H, OCHCHOMe), 4.65 (s, 2 H, OCH2O), 5.15 (m, 2 H, =CH2), 5.86 (m, 1 H, CH=). 13C NMR (50.3 MHz) 32.90 (CH2=CH2), 52.25 (COCH22), 55.16 (OCH2), 65.46 (OCH2), 77.40 (CHCOOMe), 78.57 (OCH2CHO), 96.56 (OCH20), 97.85 (CHOMe), 117.43 (CH=O), 133.47 (CH3), 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. Rf 0.10 (EtOAc:hexanes = 1:1.2). [a]20D = +15.4 (c 0.68, CHCl3). IR 1750 (C=O). 'H NMR (200 MHz) 1.73-2.27 (m, 4 H, H3 and H5), 3.75 (s, 3 H, CH3), 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, OCH2O), 5.01 (s, 1 H, OCH2O). 13C NMR (50.3 MHz) 34.88 and 35.82 (C3 and C5), 51.94 (CH3), 54.64 (C4), 67.47 (C8), 70.80 and 72.42 (C6 and C7), 76.32 (C2), 95.21 (OCH2O), 170.72 (C=O), MS...
(El, 70 eV) 250 (M+, 4), 214 (M+ - HCl, 18), 191/193 (M+ - CO2Me, 18/6), 177/179 (M+ - CO2Me - CH2, 100/32). Combustion analysis C, 47.90; H, 6.10 (calcd for C10H5O3Cl C, 47.91; H, 6.03). X-Ray crystal structure determination of (+)-18. C10H5O3Cl, Mw = 250.7, orthorhombic, P21_21_21, a = 8.4683(5), b = 9.5727(6), c = 14.1412(1) Å, V = 1168.3(1) Å3, Z = 4, Dx = 1.43 g cm−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.

REFERENCES AND NOTES

8. 2,2-Dimethyl-3-buten-1-ol was obtained by lithium aluminium hydride reduction of 2,2-dimethyl-3-buten-2-01 acid; see Kwart, H.; Miller, R. K. J. Am. Chem. Soc. 1954, 76, 5403.
9. Ethyl 2-hydroxy-4-pentenoate was prepared from ethyl 2-bromo-4-pentenoate (Phillips, D. D. J. Am. Chem. Soc. 1954, 76, 5385) through reaction with silver acetate (AcOH, 100 °C, 6 h, 60%) and liberation of the hydroxyl function [KOH (cat), EtOH, reflux, 1 h, 76%].
11. 2-Methyl-4-penten-2-01 was obtained through Grignard reaction of allylmagnesium chloride with acetone.
17. Specific rotation of the starting alcohol: [α]D20 = +7.6 (c 0.44, EtOH). The literature value, [α]D20 = +8.7 (c 0.54, EtOH), corresponds to 87% ee, see reference 16.
18. Specific rotation of the starting alcohol: [α]D20 = +17.0 (c 1.89, CHCl3). The literature value, [α]D20 = +16.0 (c 1.80, CHCl3), corresponds to 92% de, see reference 16.
20. Methyl glyoxylate was generated from the methyl hemiacetal of methyl glyoxylate through distillation from phosphorus pentoxide, Hook, J. M. Synth. Commun. 1984, 14, 83. The methyl hemiacetal of methyl glyoxylate was obtained from Chemie Linz Ges. m. b. H., Linz, Austria.

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