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Xanthate Transfer Cyclization of Glycolic Acid-Derived Radicals. 
Synthesis of Five- to Eight-Membered Ring Ethers

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A novel method for the preparation of functionalized five- to eight-membered ring ethers is described. This method involves the xanthate transfer radical cyclization of 2-(alken-1-oxo)-2-(ethoxythio-carbonyl)sulfanyl|acetic acid methyl esters 6 to give good yields of xanthate-substituted five- to eight-membered ethers 7 and/or 8, depending on the length of the carbon chain. These cyclic ethers are usually obtained as mixtures of diastereomers. The cyclizations are performed at 150-160 °C in tert-butylbenzene with di-tert-butyl peroxide as the initiator. This group-transfer radical cyclization was successfully applied in a total synthesis of lauthian (44). The use of benzoyl xanthate (56) as a catalyst allows a visible light-induced xanthate transfer cyclization to a tetrahydrofuran in high yield.

Introduction

The prevalence of the tetrahydropyran subunit in polyether natural products has stimulated the development of synthetic methods for this heterocycle. The preparation of oxygen heterocycles by cyclization reactions of methyl Group-transfer radical cyclizations of the corresponding phenyl sulfides6,7 1b to tetrahydrofurans 3, since the atom transfer method results in a cyclization product containing a halogen functionality.

While the copper catalyst is highly effective for radical cyclizations to tetrahydrofurans, it failed to promote 6-exo radical cyclization of higher homologues of 1a to provide functionalized tetrahydrofurans.5 Similarly, the Bu3SnH-method failed to bring about 6-exo radical cyclization of the nonactivated alkene 4 (Scheme 2), and only quenching of the incipient radical by Bu3SnH, leading to 5, was observed.6 Apparently, 6-exo cyclization for 4 is too slow to be of use for this radical cyclization method, even under the high dilution (0.07 M) conditions employed for this reaction.

In order to extend the scope of the cyclization reaction of α-alkoxy α-ester radicals, we searched for effective methods to promote 6-exo radical cyclization to tetrahydrofurans or to prepare even larger ring systems. Attention was focussed on atom- or group-transfer cyclization reactions other than the metal-promoted chlorine transfer ring closures studied thus far.8 A method which might be advantageous in this respect is the xanthate transfer radical cyclization technique. Zard and co-workers9-14 employed dithiocarboxates in group-transfer additions of acyl and acyl radicals to olefins. Recently, we reported successful xanthate transfer radical additions of a glycine radical equivalent to alkynes, leading to various novel α-amino acid derivatives.15

In this paper, we wish to report on the successful use of the xanthate transfer radical cyclization method in the synthesis of five- to eight-membered ring ethers. Thus,
it will be shown that xanthates 6 (Scheme 3) are not only suitable for 5-exo radical cyclization (n = 1), but also for six-, seven-, and eight-membered ring formation (n = 2 and n = 3), leading to the xanthate transfer cyclization products 7 and/or 8.

Results and Discussion

Synthesis of the Precursors. The precursors 9–14 (Table 1) for the radical cyclizations were prepared from the corresponding alcohols as outlined in Scheme 4. Treatment of the appropriate alcohol with methyl glyoxylate in CH₂Cl₂, followed by acetylation of the unstable hemiacetal with Ac₂O in pyridine, gave a stable acetate, which was treated with AcCl and HCl(g) to give the corresponding chloride in high yield as a sensitive oil. Substitution of the chlorine substituent with a xanthate group was achieved by treatment of the chloride with commercially available potassium O-ethyl dithiocarbonate in CH₂Cl₂ for 20 min. In this way the xanthates 9–14 were prepared in yields ranging between 74 and 91%.

The synthesis of the chlorides used for the preparation of xanthates 9, 11, and 13 has already been published. The alcohols used for the preparation of 10 and 14 were commercially available, while alcohol 25 used for the preparation of xanthate 13 was obtained from (Z)-3-hexenol as outlined in Scheme 5. Reaction of commercially available (Z)-3-hexenol with methanesulfonyl chloride, followed by a reaction with NaCN impregnated on alumina, gave cyanide 24 in 97% yield. Hydrolysis of the cyanide with NaOH in methanol, followed by reduction with LiAlH₄, gave the desired alcohol 25 in 50% yield.

Xanthate Transfer Cyclizations. The results of the radical cyclization reactions are summarized in Table 1. As the radical initiator, di-tert-butyl peroxide (DTBP) was applied. When heated at temperatures above 130 °C, this peroxide generates two molecules of acetone and two methyl radicals, with a half-life time of 1 h. It was expected that these methyl radicals would initiate a radical chain reaction through addition to the thiocarbonyl group. All reactions were run at 150–160 °C and were monitored by thin layer chromatography. The solvent tert-butylbenzene was used, which is inert and permits high reaction temperatures at normal pressure (bp 169 °C).

First, the radical cyclization of xanthate 9 was investigated (Table 1, entry 1). In the presence of 0.3 equiv of DTBP, a 0.5 M solution of xanthate 9 in tert-butylbenzene was heated at 150–160 °C in an oil bath. TLC showed that virtually all of the starting material 9 was consumed in 20 min. Flash chromatography afforded the desired cyclization products 15 and 16 in 71% yield, with the 5-exo product 15 prevailing over the 6-endo product 16 (exo/endo = 95:5%). Both the Bu₃SnH-mediated cyclization and the Cu(bpy)Cl-catalyzed cyclization of the 2-oxa-5-hexenyl radical derived from 9 have been reported to give similar regio- and stereosequences.

Similar conditions were applied for the xanthate transfer cyclization of the 2-oxa-6-heptenyl radical precursors 10–12, although slightly longer reaction times were necessary (0.5 h). Thus, xanthates 10–12 gave the cyclized products 17–20 in 71–91% yield. In the case of the disubstituted alkenes 11 and 12, only the 6-exo cyclization products 19 and 20 were formed as inseparable mixtures. The cyclization of the monosubstituted alkenes 10 shows that 7-endo radical cyclization can compete with 6-exo radical cyclization, similar to the all-carbon system. Thus, a mixture of 6-exo cyclization product 17 and 7-endo cyclization product 18 was obtained. The stereochemistry of the cyclization products of 10 was further determined after treatment of the mixture of 17 and 18 with Bu₃SnH (Scheme 6), assuming that the reductive removal of the xanthate group is equally efficient for all isomers. In this way, an inseparable 50:50 mixture of 26 and the seven-membered ring ether 27 was obtained, with 26 present as a 25:75 mixture of cis and trans tetrahydropryanas. The Bu₃SnH-mediated analogous cyclization of the 2-oxa-6-heptenyl radical derived from 10 has been reported by Burke and Rancourt and gave comparable regio- and stereoselectivity, although in that case more of the seven-membered ring ether was produced.

Similarly, Bu₃SnH-mediated reduction of the crude mixture of four diastereomers of 19 (Scheme 7) gave a 35:65 mixture of tetrahydropryans 28a and 28b in 81% yield, with the trans isomer predominating.

The structural assignment of the cyclization products 15 and 17–20 was straightforward. The coupling constants for the OCH methine hydrogen atom in cis and trans tetrahydrofurans 15 (Table 1) compared well to the
Table 1. Xanthate Transfer Radical Cyclization of Precursors 9-14

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>time / initiator</th>
<th>yield</th>
<th>products (isomer ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>0.3 h 0.3 equiv</td>
<td>71%</td>
<td>SCSEOEt + CO2Me</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>0.5 h 0.3 equiv</td>
<td>84%</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>0.5 h 0.3 equiv</td>
<td>91%</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>0.5 h 0.3 equiv</td>
<td>71%</td>
<td>19a + 19b</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>2 h 0.2 equiv</td>
<td>80%</td>
<td>20a + 20b</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>2.5 h 0.1 equiv</td>
<td>68%</td>
<td>21 (4 diastereomers)</td>
</tr>
</tbody>
</table>

* Reaction conditions: (t-BuO)2 (0.3 equiv), 2,2,6,6-tetramethyl-1-piperidinyloxy (0.3 M) 150-160 °C. * Concentration 0.1 M.

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** a,b were formed as approximately 1:1 mixtures of diastereomers.

Scheme 4

\[
\begin{align*}
\text{R-OH} & \xrightarrow{1. \text{Me}_2\text{CCCHO}} \text{R-Cl} \xrightarrow{2. \text{Ac}_2\text{O}} \text{R-CO}_2\text{Me} \\
\text{HO-C} & \xrightarrow{1. \text{Me}_2\text{CCH}} \text{CN} \xrightarrow{2. \text{NaCN on alumina}} \text{OH} \\
\text{NaOH (aq), MeOH} & \xrightarrow{2. \text{LiAIH}_4} \text{H} \\
\end{align*}
\]

Scheme 5

Corresponding chlorides obtained from the copper-catalyzed cyclizations. Thus, the cis 2,3-disubstituted tetrahydrofuran 15a showed for H-2 a doublet at lower field and with a larger coupling constant than for the trans substituted tetrahydrofuran 15b. The minor 6-endo cyclization products 16a,b could not be separated from 15. They were identified by comparison of the isolated 13C NMR signals for C-2, C-4, and C-6, which compared well with the corresponding chlorides obtained from ionic cyclization reactions. Tetrahydropyrans 20, 26, and 28 were identified by the characteristic chemical shift and coupling constants for the H-2 methine hydrogen atom in their 1H NMR spectra. The cis 2,3-disubstituted tetrahydropyrans absorbed at relatively low field and showed relatively small coupling constants as compared to the trans tetrahydropyrans.

Radical cyclization of xanthate 13 proved more difficult (Table 1, entry 5). Initial experiments in the presence of 13 showed that the reaction did not proceed quantitatively. The major product from the reaction was a mixture of diastereomers, and the minor product was isolated as a diastereomeric mixture.

of 0.3 equiv of the initiator gave low yields of the desired product and led to the formation of substantial amounts of byproducts, which could not be separated from 21. In the presence of 0.2 equiv of the radical initiator, thin layer chromatography indicated full consumption of the substrate after 2 h. Workup afforded the desired 3-oxabicyclo[3.3.1]nonane 21 in 86% yield as a mixture of four diastereomers. In order to establish the stereoselectivity of this cyclization reaction, a separate experiment was carried out (Scheme 8). Cyclization of 13 in the presence of DTBP, followed by Bu3SnH-reduction of the crude reaction mixture, gave a 73% yield (from 21) of 0.2 equiv of the radical initiator, thin layer chromatography indicated full consumption of the substrate after 2 h. Workup afforded the desired 3-oxabicyclo[3.3.1]nonane 21 in 86% yield as a mixture of four diastereomers. In order to establish the stereoselectivity of this cyclization reaction, a separate experiment was carried out (Scheme 8). Cyclization of 13 in the presence of DTBP, followed by Bu3SnH-reduction of the crude reaction mixture, gave a 73% yield (from 21) of 0.3 equiv of the initiator. Addition of a methyl radical did not lead to shorter reaction times, but gave lower yields of 22 and 23 with increased formation of byproducts. The reaction was run at a relatively low concentration in comparison to precursors 9–13, as higher concentrations (0.5 M) gave lower yields of 22 and 23 with the formation of considerable amounts of byproducts (possibly intermolecular coupling products).

Oxocane 22 was obtained as a mixture of two diastereomers. Their relative stereochemistry was not established. The 1H NMR spectrum of 22 showed characteristic absorptions for H-2 with clear vicinal couplings with two hydrogen atoms, excluding a 7-endo cyclization. The aldehyde 23 was identified by its simple 1H NMR spectrum, showing a characteristic absorption for the aldehyde hydrogen atom at 9.74 ppm. The aldehyde carbon atom was clearly present in the 13C NMR spectrum at 202 ppm.

Mechanism of the Xanthate Transfer Radical Cyclization. The mechanism of the xanthate transfer radical cyclization reactions of xanthates 9–14 in the synthesis of cyclic ethers is supposed to involve a chain reaction as shown in Scheme 10 for the cyclization of xanthate 14 to oxocane 22. Initiation of the chain occurs after the generation of methyl radicals by thermal decomposition of DTBP.14 Addition of a methyl radical to the thiocarbonyl group of 14 gives the carbon-centered radical 36, which is stabilized by three heteroatoms. The preferred addition of alkyl radicals to xanthates rather than hydrogen atom abstraction is apparent from the work of Zard and co-workers.9–14 The carbon-centered radical 37 arising from carbon–sulfur bond homolysis in 36 enjoys captodative stabilization by geminal donor and acceptor groups.28 Therefore, the formation of 37 will be highly favored compared to the formation of a nonstabilized ethyl radical via homolysis of the carbon–oxygen bond in 36. With the formation of 37, the radical chain propagation sequence is entered. Cyclization of 37 in an 8-endo-mode leads to the secondary, nonstabilized alkyl radical 38. Addition to the thiocarbonyl group of xanthate 14 gives radical 39, which is stabilized by three α-ester radicals, the ring closure of the corresponding 2-oxa-7-octenyl radical to an eight-membered ring ether was investigated (Table 1, entry 6). Treatment of xanthate 14 with 0.1 equiv of DTBP in a 0.1 M solution of tert-butylbenzene gave after 2.5 h of heating at 150–160 °C a 79:21 mixture of the desired oxocane 22 and the unexpected aldehyde 23 (vide infra) in 68% yield. The use of more radical initiator (0.3 equiv instead of 0.1 equiv) did not lead to shorter reaction times, but gave lower yields of 22 and 23 with increased formation of byproducts. The reaction was run at a relatively low concentration in comparison to precursors 9–13, as higher concentrations (0.5 M) gave lower yields of 22 and 23 with the formation of considerable amounts of byproducts (possibly intermolecular coupling products).

Addition to the thiocarbonyl group of xan- thate gives radical 11, which is stabilized by three heteroatoms. The preferred addition of alkyl radicals to xanthates rather than hydrogen atom abstraction is apparent from the work of Zard and co-workers.9–14 The carbon-centered radical 37 arising from carbon–sulfur bond homolysis in 36 enjoys captodative stabilization by geminal donor and acceptor groups.28 Therefore, the formation of 37 will be highly favored compared to the formation of a nonstabilized ethyl radical via homolysis of the carbon–oxygen bond in 36. With the formation of 37, the radical chain propagation sequence is entered. Cyclization of 37 in an 8-endo-mode leads to the secondary, nonstabilized alkyl radical 38. Addition to the thiocarbonyl group of xanthate 14 gives radical 39, which is stabilized by three α-ester radicals, the ring closure of the corresponding 2-oxa-7-octenyl radical to an eight-membered ring ether was investigated (Table 1, entry 6). Treatment of xanthate 14 with 0.1 equiv of DTBP in a 0.1 M solution of tert-butylbenzene gave after 2.5 h of heating at 150–160 °C a 79:21 mixture of the desired oxocane 22 and the unexpected aldehyde 23 (vide infra) in 68% yield. The use of more radical initiator (0.3 equiv instead of 0.1 equiv) did not lead to shorter reaction times, but gave lower yields of 22 and 23 with increased formation of byproducts. The reaction was run at a relatively low concentration in comparison to precursors 9–13, as higher concentrations (0.5 M) gave lower yields of 22 and 23 with the formation of considerable amounts of byproducts (possibly intermolecular coupling products).
heteroatoms similar to radical 36. Homolysis of the carbon–sulfur bond as shown in Scheme 10 leads to the desired xanthate transfer cyclization product 22 and the captodative radical 37. In order to obtain a good yield of the xanthate transfer radical cyclization product, the reaction should be performed with as little initiator as possible, because the addition of a methyl radical to the substrates actually consumes the substrate. In this respect, the use of 0.3 equiv of DTBP in combination with short reaction times gave good yields in the case of xanthates 9–12. For more demanding cyclizations like in the case of 13 and 14, a prolonged reaction time in combination with less initiator gave the best results.

The rather surprising formation of the aldehyde 23 as a side product may be explained as follows (Scheme 11). After cyclization, radical 38 may undergo a 1,5-hydrogen shift to give the oxygen-stabilized radical 40. Subsequent homolysis of the ester-bearing carbon–oxygen bond generates the ester-stabilized radical 41, containing the aldehyde group. Capture of a xanthate group gives 23. So, the acyclic product 23 originates from the cyclic intermediate 38. The intramolecular abstraction of a hydrogen atom by carbon-centered radicals is a well-known phenomenon in radical chemistry. Especially 1,5-hydrogen shifts in alkyl radicals have been reported to be very effective, probably as a result of an optimal alignment and distance of the radical and the hydrogen atom in a chair-like six-membered ring transition state.24

**Synthesis of Lauthisan.** Recently, synthetic efforts toward the construction of “medium-sized” ethers and lactones attracted increasing interest. Due to the intrinsic difficulties associated with the formation of medium rings,28 the total synthesis of these molecules remains a challenge. A variety of eight-membered ring cyclic ethers have been isolated from marine organisms, particularly from the genus *Laurencia.*26 As a target we chose the saturated ether lauthisan (44),27,28 whose structure represents the basic skeleton present in a number of these naturally occurring non-terpenoid eight-membered ring ethers like laurencin (42)29 and laurepinnacin (43).30 This molecule has served several times as the testing ground for the efficacy of oxocane construction.31–33

We envisioned a total synthesis of lauthisan via the...

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xanthate transfer cyclization method of α-alkoxy α-ester radicals. A retrosynthetic analysis is shown in Scheme 12. In the projected synthesis of lauthisan, the ester group of 45 should serve as a handle to prepare the desired ethyl substituent of lauthisan. Oxocane 45 was envisioned to arise from 8-endo cyclization of radical 46 via xanthate transfer cyclization of 47. In comparison to the radical precursor for the synthesis of the parent oxocane 14 (Table 1, entry 6), 47 contains an n-hexyl group.

Scheme 13 shows the synthesis of lauthisan via the xanthate transfer method. Addition of 4-pentenylmagnesium bromide to heptanal gave alcohol 48 in 79% yield after distillation. Addition of this secondary alcohol to methyl glyoxylate appeared difficult, and gave after acetylation the desired acetate 49 in only 58% yield, along with acetylated starting material in 48% yield, which may be recycled. Low yields for the addition of secondary alcohols to methyl glyoxylate have been reported before. It might be a result of the increased steric hindrance as compared to primary alcohols. Conversion of the acetate to the xanthate 47 was carried out very effectively by treatment of 49 with AcCl and HCl(g) to give chloride 50 in 100% yield. Subsequent reaction with potassium O-ethyl dithiocarbonate gave 47 in 95% yield as a yellow oil.

The 8-endo cyclization of xanthate 47 required similar conditions to those for the parent compound 14 (Table 1), albeit with a somewhat shorter reaction time. Surprisingly, a 56:44 mixture of oxocane 45 and ketone 51 was obtained in 64% yield after flash chromatography. The eight-membered ring ether was a 56:44 mixture of only two of the four possible diastereomers. The stereochemistry of these two diastereomers was elucidated after removal of the xanthate group with Bu3SnH, which afforded 52 as a single isomer. The clear NOE-effect of H-2 on H-8 proved the cis-relationship between the substituents on C-2 and C-8, which is also present in lauthisan. This stereochemistry was confirmed after reduction of 52 with LiAlH4, which gave the known alcohol 53 as a single product in 74% yield from 45. The conversion of this alcohol to lauthisan has been described by Holmes and co-workers, so that the synthesis of 53 constitutes a formal total synthesis of lauthisan.

The structural assignment of oxocanes 45, 52, and 53 was straightforward. The NMR data were similar to those of the simple oxocane 43 (Table 1), showing for H-2 vicinal coupling with two protons, thus excluding 7-exo cyclization. For ketone 51, H-2 showed a similar signal as in aldehyde 23, and the ketone carbonyl was found in the 13C NMR spectrum at 211 ppm.

The exclusive formation of the 2,8-cis-disubstituted oxocane 45 along with ketone 51 may be explained as follows. Two stereoisomeric intermediate radicals can arise from xanthate 47, in contrast to the single comparable species generated from xanthate 14. Of these, only the trans radical 54c undergoes the 1,5-H shift, via TS 55, precluding formation of the trans isomer of 45, and allowing the sequence of steps to ketone 51. The other, 2,8-cis-disubstituted intermediate radical 54e cannot undergo the 1,5-H shift and so undergoes xanthate capture to form 45.

Light-Induced Radical Cyclization. The use of di-tert-butyl peroxide as a radical initiator in the xanthate transfer radical cyclizations allows the synthesis of a variety of five- to eight-membered ring ethers. In spite of its good performance, we felt the need for a different initiator, because DTBP actually consumes the substrate during initiation via an irreversible reaction of a methyl radical with the xanthate to give methyl O-ethyl dithiocarbonate as an inert product. It was envisioned that the use of benzoyl xanthate (Scheme 14) as a catalyst in a light-induced radical process might be beneficial in this respect. Barton and co-workers showed that irradiation of a solution of 56 with visible light produces benzoyl radical 57 and xanthate radical 58. We expected that the benzoyl radical would initiate the xanthate transfer cyclization chain.

Indeed, when a solution of xanthate 9 in benzene was irradiated with visible light from a tungsten lamp at 80 °C for 0.5 h in the presence of 5 mol % of 56, the expected cyclization products 15 and 16 were obtained in a combined yield of 89% after flash chromatography (Scheme 15). This yield is better than the 71% yield obtained from the cyclization of this xanthate at 150 °C with di-tert-butyl peroxide (0.3 equiv) as a radical initiator (see Table 1, entry 1). Both regio- and stereochemistry for these reactions are comparable, with the 5-exo cyclization product 15 prevailing and a slight preference for the 2,3-cis-disubstituted tetrahydrofuran 15a in both cases.

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The mechanism for the light-induced xanthate transfer radical cyclization of 9 in the presence of a catalytic amount of benzoyl xanthate is shown in Scheme 14. This mechanism is based on the work of Zard on light-induced intermolecular xanthate transfer additions to alkenes in the presence of this catalyst. Irradiation of a solution of 56 in benzene with visible light generates benzoyl radicals 57 and xanthate radicals 58. Addition of 57 to xanthate 9 gives radical 59, which undergoes a homolytic cleavage of the glycolic C–S bond to give the captodative radical 61 and benzoyl xanthate 56. In this step, the catalyst 56 is regenerated. Radical 60 may cyclize to the primary radical 61, which may react with 9 to the desired xanthate transfer radical cyclization product 15 and the captodative radical 60 which carries the chain.

Clearly, the catalyst 56 does not consume the substrate, because the initiator for the xanthate transfer radical cyclization is regenerated during the initiation steps (57 to 59 to 60), in contrast to the consumption of xanthate by the methyl radicals which gives methyl xanthate. This is a distinct advantage of the benzoyl xanthate-catalyzed light-induced radical cyclization. Fur-
The development of the xanthate transfer cyclization technique for the cyclization of α-alkoxy α-ester radicals markedly improves the synthetic utility of these radical intermediates. This method appears to be more effective than the known Bu₃SnH-method and the Cu(bpy)Cl₂-method, allowing not only the synthesis of five-membered ring ethers, but also six-, seven-, and eight-membered ring ethers. This group-transfer radical cyclization is successfully applied in a total synthesis of lauthisan. The group-transfer radical cyclization is light-induced xanthate transfer cyclization to a tetraester, use of benzoyl xanthate as a catalyst allows a visible process with the benzoyl xanthate catalyst is also of use for the preparation of larger ring systems.

Experimental Section

General Information. Experimental techniques and analytical measurements were applied as previously described. NaCN impregnated on alumina was prepared according to a literature procedure. Methanesulfonic acid hex-3(Z)-eny1 ester,27 diithiocarbamic acid S-benzoyl ester O-ethyl ester,28 (but-3-enyloxy)chloroacetic acid methyl ester,29 chloro(hex-4-enyloxy)acetic acid methyl ester, and chloro(hex-3-enyloxy)acetic acid methyl ester were prepared according to literature procedures. Chloroform and the chlorides used for the preparation of xanthates 9-14 were quite sensitive. Therefore, these compounds were used immediately after their preparation, without further purification.

Hept-4(Z)-enynitrile (24). To a solution of methanesulfonic acid hex-3(Z)-eny1 ester (1.0 g, 5.5 mmol) in benzene (10 mL) was added NaCN impregnated on alumina (8.4 g). The mixture was heated at reflux for 16 h. The cyanide was isolated by filtering the mixture and removing the solvent under reduced pressure to yield 24 (0.594 g, 5.45 mmol, 97%) as a colorless oil. The crude material was used immediately in the next reaction.

Hept-4(Z)-enoic acid (25). A solution of 34 (8.56 g, 78.5 mmol) and 342 mL of 25% aqueous NaOH in 170 mL of methanol was stirred at reflux for 16 h. After concentration in vacuo, water was added, and the solution was acidified to pH 5 with concentrated aqueous HCl. The water layer was extracted with EtOAc (three times 250 mL), the organic extract was concentrated in vacuo and the chlorides (8.37 g, 65.4 mmol, 83%) were quite sensitive. Therefore, these compounds were used immediately after their preparation, without further purification.

Experimental Section

General Information. Experimental techniques and analytical measurements were applied as previously described. NaCN impregnated on alumina was prepared according to a literature procedure. Methanesulfonic acid hex-3(Z)-eny1 ester, diithiocarbamic acid S-benzoyl ester O-ethyl ester, (but-3-enyloxy)chloroacetic acid methyl ester, chloro(hex-4-enyloxy)acetic acid methyl ester, and chloro(hex-3-enyloxy)acetic acid methyl ester were prepared according to literature procedures. Chloroform and the chlorides used for the preparation of xanthates 9-14 were quite sensitive. Therefore, these compounds were used immediately after their preparation, without further purification.
The text is a scientific journal article discussing the synthesis and characterization of xanthate transfer cyclization of glycolic acid-derived radicals. The article includes detailed chemical reactions, spectral data, and analytical methods. It describes the synthesis of various acetylic esters, including some with specific functionalities like ethoxythiocarbonyl sulfanylacetic acid methyl ester (1) and related compounds. The text also mentions the use of chromatography and spectroscopy (e.g., IR and NMR) to characterize the products. The article concludes with cyclization reactions, highlighting the formation of new compounds with potential applications in organic chemistry.
Cyclization of 11. To a solution of 11 (182.6 mg, 0.624 mmol) in tert-butylbenzene (1.3 mL) was added DTBP (27 mg, 0.20 mmol). The reaction mixture was heated at 150–155 °C for 0.5 h. Filtration over a short silica column (eluting with EtOAc/hexane 1:4) gave a 9:1 mixture of four diastereomers, Rf 0.20 and 0.10 (EtOAc/hexane 1:4); IR (CHCl3) 2990, 2930, 2850, 1745, 1435; 1H NMR (60 MHz, mixture of four diastereomers) 1.35–2.25 (m, 8H), 1.60–1.85 (m, 5H), 2.14 (dq, J = 13.1, 2.6 Hz, 2H), 2.50 (s) and 3.75 (s), 3.85 (s) and 3.95 (s, 3H), 3.95 (s) and 4.01 (d, J = 9.5 Hz, 0.25 H); 13C NMR (63 MHz, mixture of four diastereomers) major diastereomer: 13.67, 21.34, 21.39, 26.81, 28.57, 31.02, 43.65, 52.22, 52.66, 70.38, 74.28, 77.21, 72.26, 213.26; minor diastereomer: 19.24, 22.01, 34.67, 45.21, 51.46, 67.51, 69.62, 69.65, 72.91, 73.59, 74.28, 77.21, 77.71, 72.18, 213.26; HRMS calcd for C20H32O5S2: 340.0803, found 340.0795.

Cyclization of 14. To a solution of 14 (179.7 mg, 0.615 mmol) in tert-butylbenzene (0.2 mL) was added DTBP (17 mg, 0.13 mmol). The reaction mixture was heated at 150–155 °C for 2.5 h. Flash chromatography (hexane, followed by EtOAc/hexane 1:4) gave three fractions. The first fraction consisted of a 75:25 mixture of diastereomers of 4-[(ethoxythiocarbonyl)sulfanyl]oxoacene-2-carboxylic acid methyl ester (22) as a colorless oil (91.0 mg, 0.311 mmol, 71%).

BusNi-Reduction of 17 and 18. A solution of the mixture of 17 and 18 (129.0 mg, 0.4633 mmol) in refluxing benzene (9.5 mL) was treated with AIBN (7.5 mg, 0.050 mmol) and BuSnH (1.85 mmol, 1.85 mL) for 0.5 h and concentrated in vacuo. The DBU workup procedure(34) was applied as follows: The residue was taken up in ether (2 mL), DBU (0.28 mL, 1.85 mmol) was added, and a 0.1 M solution of Li2 in ether was added to this solution until the iodine color just persisted. After filtration on a short silica column (eluting with ether), the mixture was concentrated in vacuo. The residue was chromatographed to give a 50:50 mixture of 26 and o xoacene-2-carboxylic acid methyl ester (27) (35 mg, 0.221 mmol, 48%). According to 1H NMR, 26 was present as a 1:3 mixture of (2R*,3S*)-3-methyltetrahydropyran-2-carboxylic acid methyl ester (26a) and (2S*,3R*)-3-methyltetrahydropyran-2-carboxylic acid methyl ester (26b): Rf 0.35 and 0.30 (EtOAc/hexane 1:4); IR (CHCl3) 2990, 2930, 2850, 1745, 1435; 1H NMR (200 MHz, mixture of three diastereomers) δ 0.83 (d, J = 6.5 Hz, 26CH2); 0.93 (d, J = 7.0 Hz, 26a CHCH3; 26a 26b = 1.3, 1.5H), 1.10–2.20 (m, 6.5H), 3.30–4.16 (m, 5H), including 3.53 (d, J = 9.7 Hz, 26b-H2) and 4.13 (dd, J = 10.0, 4.7 Hz, 0.5H, 27.2H); 3.69 (s) and 3.71 (s, 3H); 13C NMR (63 MHz, mixture of three diastereomers) δ 12.77 (26a CHCH3; 17.30 (26b CHCH3); 20.75, 25.75, 27.27, 28.58, 30.54, 51.85, 51.83, 57.90, 62.36, 62.69, 77.83, 79.15, 83.35, 71.10, 171.46, 173.41; MS (EI) 99 (M – CH3COO)3; HRMS calcd for C29H26O11: 598.1512, found 598.1515.

BusNi-Reduction of 19. A solution of the mixture of diastereomers of 19 (159.4 mg, 0.5451 mmol) in refluxing

benzene (11 mL) was treated with AIBN (9 mg, 0.065 mmol) and BuSnH (0.59 mL, 2.2 mmol) for 0.5 h and concentrated in vacuo. The DBU workup procedure was applied as follows. The residue was taken up in ether (2.2 mL, DUB (0.33 mL, 2.2 mmol) was added, and 0.1 M solution of Li in ether was added to this solution until the iodine color just persisted. After filtration on a short silica column (eluting with ether), the mixture was concentrated in vacuo. The residue was chromatographed on two fractions. The first fraction consisted of the acid methyl ester (28b) (46.0 mg, 0.267 mmol, 49%) as a colorless oil: Rf 0.35 (EtOAc/hexane 1:4); IR (CHCl3) 2950, 2850, 1740, 3.55–3.83 (m, 1H), 4.90–5.05 (m, 2H), 5.70–5.90 (m, 1H); MS FAB 185 (+M+H+).

Acetoxy[(1-hexyl-5-enyl)oxy]acetic Acid Methyl Ester (49). Alcohol 48 (5.530 g, 30 mmol) was treated with methyl glyoxlate (5.28 g, 60 mmol) in 15 mL of dichloromethane. After refluxing for 20 h, the mixture was concentrated in vacuo and treated with DMAP (37 mg, 0.3 mmol, 1.75% of acid anhydride). The first fraction consisted of a white solid (2.5 mL) in 15% pyridine for 3 h. Evaporation of toluene (three times) and flash chromatography (EtOAc/hexane 1:2–4) gave two fractions. The first fraction consisted of 49 (3.58 g, 11.4 mmol, 38%) as a colorless oil: Rf 0.20 (EtOAc/hexane 1:10); IR 2930, 2850, 1705, 1635, 1455, 1345, 1270; 1H NMR (200 MHz) δ 0.88 (t, J = 6.4 Hz, 3H), 1.27–1.60 (m, 14H), 2.00–2.14 (m, 2H), 2.10–2.14 (m, 1H), 3.62–3.71 (m, 1H), 3.80 (s, 3H), 4.92–5.05 (m, 2H), 5.70–5.90 (m, 1H), 5.99 (s, 1H); HRMS calcd for C17H30O5 314.2093, found 314.2105. The second fraction consisted of acetic acid 1-hexyl-5-enyl ester as a colorless oil (3.23 g, 14.3 mmol, 48%): Rf 0.40 (1:10); IR 3070, 2930, 2850, 1720, 1635, 1455, 1375, 1250; 1H NMR (200 MHz) δ 0.88 (t, J = 6.6 Hz, 3H), 1.26–1.60 (m, 14H), 2.00–2.15 (m, 2H), 2.04 (s, 3H), 4.93 (s, J = 6.2 Hz, 1H), 4.92–5.04 (m, 2H), 5.70–5.90 (m, 1H); MS FAB 227 (+M+H+).

Benzyl-Reduction of 21. To a solution of 18 (178.0 mg, 0.5846 mmol) in tert-butylbenzene (1.2 mL) was added DTBP (26 mg, 0.15 mmol). The reaction mixture was heated at 0.150–155 °C for 0.5 h. Evaporation of the volatiles gave crude 21 (278.0 mg) as a light yellow oil. A solution of crude 21 (178.0 mg) in refluxing benzene (12 mL) was treated with AIBN (10 mg, 0.06 mmol) and BuSnH (0.63 mL, 2.3 mmol) for 0.5 h. Flash chromatography gave two fractions. The first fraction consisted of a 1,3 mixture (according to 1H NMR) of (cyclohex-3-enylmethyl)oxy]acetic acid methyl ester (30) (3.00 g, 9.54 mmol) in CH2Cl2 (7.4 mL) was added potassium chloride gas at 0 °C for 0.5 h. Evaporation of the volatiles gave chloro acid 50 (2.775 g, 9.54 mmol, 100%) as a yellow oil: IR 3070, 2930, 2850, 2870, 1760, 1630, 1455, 1355; 1H NMR (200 MHz, mixture of two diastereomers) δ 0.85–1.05 (m, 3H), 1.15–1.40 (m, 9H), 1.68–2.00 (m, 1H), 1.90–2.45 (m, 3H), 3.15–3.35; IR (KBr) 2273 (M+CO2); MS calcd for C30H46O4 442.3295 (M+Na+), found 442.3300.
2.34 (t, J = 7.4 Hz, 2H), 2.35 (t, J = 7.2 Hz, 2H), 3.71 (s, 3H), 4.32 (t, J = 7.2 Hz, 1H), 4.59 (s, J = 7.1 Hz, 2H); 13C NMR (63 MHz) δ 13.65, 13.95, 22.47, 23.43, 23.86, 26.87, 28.69, 28.92, 31.10, 31.59, 42.43, 42.6, 52.25, 52.56, 70.28, 171.42, 211.03, 212.11; HRMS calcd for C19H34O2S2 376.1742, found 376.1788.

(2R*,8R*)-8-Hexyloxocane-2-carboxylic Acid Methyl Ester (52). A 56:44 mixture of diastereomers of 45 (120 mg, 0.319 mmol) in refluxing benzene (6.4 mL) was treated with AIBN (8 mg, 0.048 mmol) and Bu3SnH (0.34 mL, 1.3 mmol) for 0.5 h. Flash chromatography (hexane to EtOAc/hexane 1:24) gave 52 as a colorless oil (70 mg, 0.27 mmol, 86%): Rf 0.35 (EtOAc/hexane 1:10); IR (CHCl3) 2990, 2920, 2850, 1740, 1455, 1435; 1H NMR (250 MHz) δ 0.86 (t, J = 6.9 Hz, 3H), 1.14-2.00 (m, 20H), 3.40-3.50 (m, 1H), 3.72 (s, 3H), 4.08 (dd, J = 3.4, 9.3 Hz, 1H); 13C NMR (50 MHz) δ 13.08, 22.62, 24.95, 25.22, 26.11, 26.84, 29.28, 31.66, 32.04, 33.50, 36.35, 51.83, 79.39, 82.04, 173.54.

(8-Hexyloxycan-2-yl)methanol (53). A 56:44 mixture of diastereomers of 40 (345 mg, 0.916 mmol) in refluxing benzene (18 mL) was treated with AIBN (22 mg, 0.14 mmol) and Bu3SnH (0.97 mL, 3.7 mmol) for 0.5 h. Filtration over a short silica column (eluting with EtOAc/hexane 1:10) gave crude 52 as a light brown oil (264 mg). To a solution of crude 52 (264 mg) in dry ether (9 mL) was added LiAlH4 (174 mg, 4.58 mmol). The reaction mixture was stirred for 1 h at room temperature and water (4 mL) was added. The resulting gel was taken up in 50 mL of EtOAc and dried (MgSO4) and the volatiles were removed in vacuo. The residue was chromatographed to give 53 as a colorless oil (154 mg, 0.674 mmol, 74% from 45): Rf 0.15 (EtOAc/hexane 1:10); IR (CHCl3) 3570, 3450 (broad), 2990, 2920, 2850, 1455; 1H NMR (250 MHz) δ 0.86 (t, J = 6.9 Hz, 3H), 1.19-1.80 (m, 20H), 2.10 (broad s, 1H, OH), 3.40-3.55 (m, 3H), 3.55-3.63 (m, 1H); 13C NMR (63 MHz) δ 13.93, 22.52, 23.84, 23.89, 26.22, 27.28, 29.34, 30.31, 31.73, 33.93, 36.81, 66.34, 80.06, 80.54; HRMS calcd for C14H28O2 228.2089, found 228.2106.

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Supplementary Material Available: Copies of 1H and/or 13C NMR spectra for all new compounds, i.e. 9-31, 45, 47-53 and of the precursors of compounds 10, 12, 14, and 25 (70 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.