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-oxy)-2-[(ethoxythiocarbonyl)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 lauthisan (**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, involving free radical chain processes, is currently a topic of great interest.[1-4]

Recently,[5] we reported a novel Cu(bpy)Cl-catalyzed process for the preparation of 2-carbomethoxy-3-(1-chloroalkyl)tetrahydrofurans **2** via chlorine transfer radical cyclization reactions of methyl 2-(3-alken-1-oxy)-2-chloroacetates (**1a**, Scheme 1). This new method was developed as a modification of the reductive Bu_3SnH-mediated radical cyclizations of the corresponding phenyl sulfides[6,7] **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 tetrahydropyrans.[5] Similarly, the Bu_3SnH-method failed to bring about 6-*exo* radical cyclization of the nonactivated alkene **4** (Scheme 2), and only quenching of the incipient radical by Bu_3SnH, 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 tetrahydropyrans 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 coworkers[9-14] employed dithiocarbonates in group-transfer additions of alkyl and acyl radicals to olefins. Recently, we reported successful xanthate transfer radical additions of a glycine radical equivalent to alkenes, 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,

[⊗] Abstract published in *Advance ACS Abstracts,* October 1, 1994.

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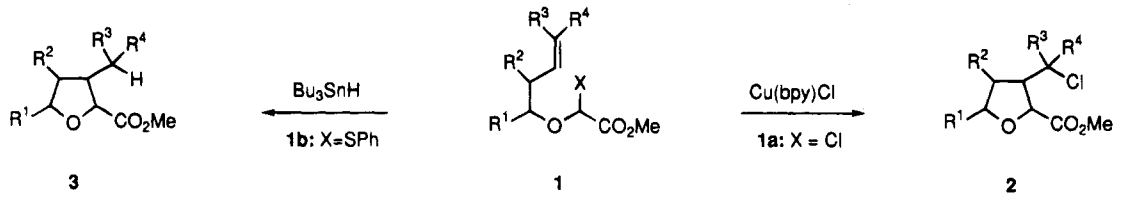
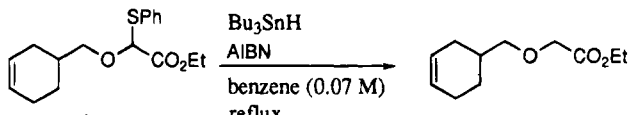
Scheme 1



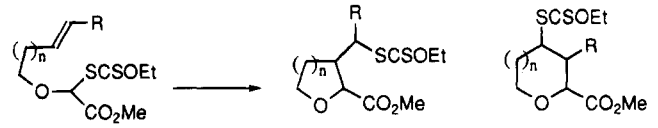
3 1 2

Scheme 2



4 5 64%

Scheme 3



6 7 and / or 8

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[16] in CH_2Cl_2, followed by acetylation of the unstable hemiacetal with Ac_2O in pyridine, gave a stable acetate, which was treated with AcCl and HCl(g)[17] 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 CH_2Cl_2 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.[5d] 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,[18] gave cyanide **24** in 97% yield. Hydrolysis of the cyanide with NaOH in methanol,[19] followed by reduction with $LiAlH_4$,[20,21] 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.[8a] It was expected that these methyl radicals would initiate a radical chain reaction through addition to the thiocarbonyl group.[9-15] 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 Bu_3SnH-mediated cyclization[6] and the Cu(bpy)Cl-catalyzed cyclization[5] of the 2-oxa-5-hexenyl radical derived from **9** have been reported to give similar regio- and stereochemistries.

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 alkene **10** shows that 7-*endo* radical cyclization can compete with 6-*exo* radical cyclization, similar to the all-carbon system.[8a] 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 Bu_3SnH (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* tetrahydropyrans. The Bu_3SnH-mediated analogous cyclization of the 2-oxa-6-heptenyl radical derived from **10** has been reported by Burke and Rancourt[7] and gave comparable regio- and stereoselectivity, although in that case more of the seven-membered ring ether was produced.

Similarly, Bu_3SnH-mediated reduction of the crude mixture of four diastereomers of **19** (Scheme 7) gave a 35:65 mixture of tetrahydropyrans **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* tetrahydrofuran **15** (Table 1) compared well to the

(16) Generated from the commercially available methyl hemiacetal of methyl glyoxylate through distillation from phosphorus pentoxide (cf. Hook, J. M. *Synth. Commun.* **1984**, *14*, 83).

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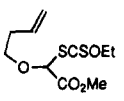
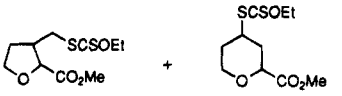
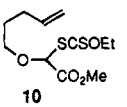
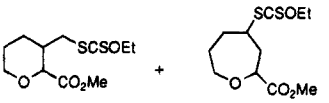
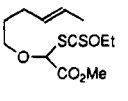
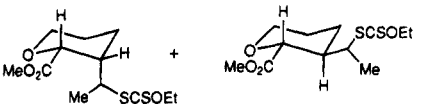
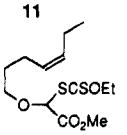
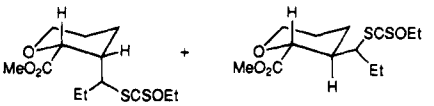
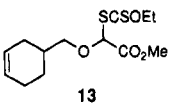
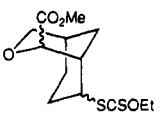
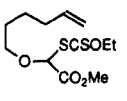
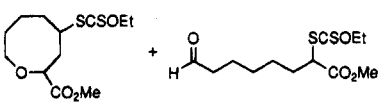
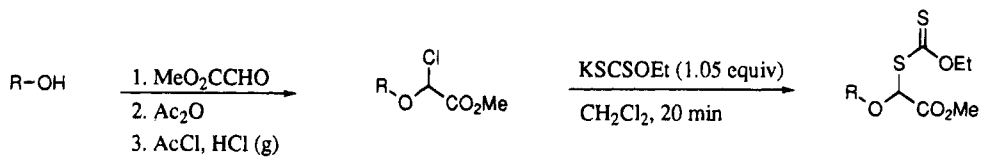
Table 1. Xanthate Transfer Radical Cyclization of Precursors 9–14

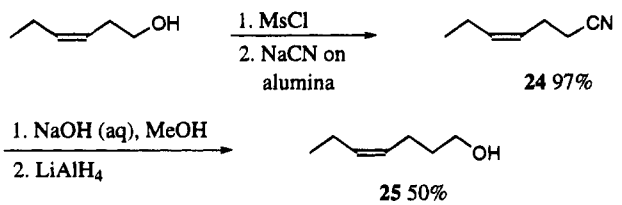
entry	substrate	time / initiator	yield	products (isomer ratio)[c]
1	 **9**	0.3 h 0.3 equiv	71%	 **15a,b** 95 : 5 **16a,b** (50:50) *cis/trans* = 56:44
2	 **10**	0.5 h 0.3 equiv	84%	 **17** **18**
3	 **11**	0.5 h 0.3 equiv	91%	 **19a** **19b**
4	 **12**	0.5 h 0.3 equiv	71%	 **20a** 25 : 75 **20b**
5	 **13**	2 h 0.2 equiv	80%	 **21** (4 diastereomers)
6[b]	 **14**	2.5 h 0.1 equiv	68%	 **22** (75:25) 79 : 21 **23**

[a] *Reaction conditions*: $(t\text{-BuO})_2$ (0.3 equiv), *tert*-butylbenzene (0.5 M), 150-160 °C. [b] Concentration 0.1 M.
[c] Both **18**, **19a**, **19b**, **20a** and **20b** were formed as approximately 1:1 mixtures of diastereomers.

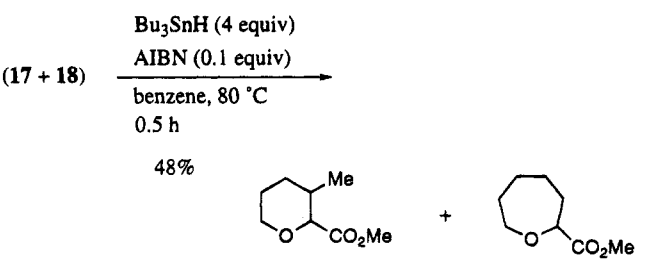
Scheme 4



Scheme 5



Scheme 6



corresponding chlorides obtained from the copper-catalyzed cyclizations.[5] 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 ^{13}C NMR signals for C-2, C-4, and C-6, which compared well with the corresponding chlorides obtained from ionic cyclization reactions.[22] 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

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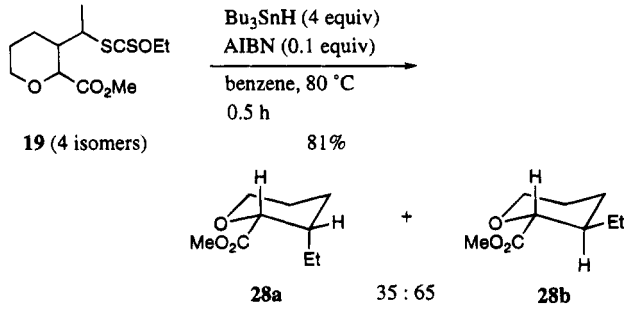
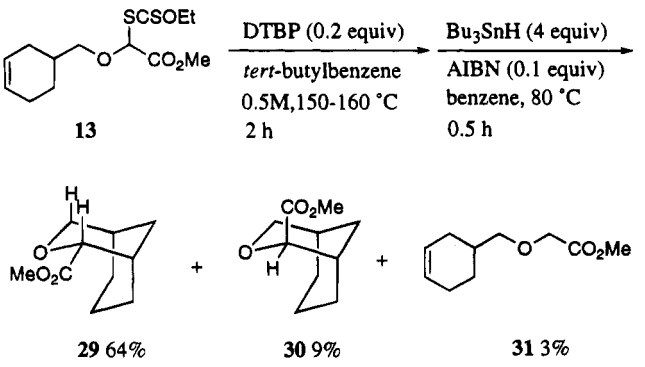
Scheme 7



Scheme 8

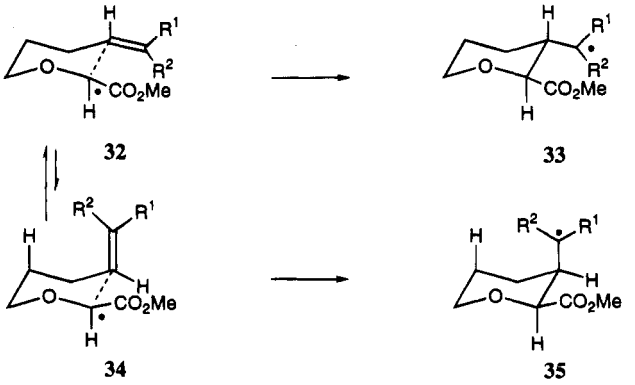


of 0.3 equiv of the initiator gave low yields of the desired product and led to the formation of substantial amounts of byproducts, which could not be separated from **21**. In the presence of 0.2 equiv of the radical initiator, thin layer chromatography indicated full consumption of the substrate after 2 h. Workup afforded the desired 3-oxabicyclo[3.3.1]nonane **21** in 80% 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 Bu_3SnH-reduction of the crude reaction mixture, gave a 73% yield (from **13**) of an 88:12 mixture of **29** and **30**, along with a trace of reduced starting material **31** (3%). Flash chromatography allowed separation of these 3-oxabicyclo[3.3.1]-nonanes (although **31** could not be separated from **30**). The equatorial position of the ester group in **29** was inferred from the clear NOE effect of the OCH methine hydrogen atom with the axial OCH_2 hydrogen atom, while **30** did not show such an effect.

The 2-oxa-6-heptenyl radical cyclizations of xanthates **10**–**12** showed a preference for the formation of the *trans* 2,3-disubstituted tetrahydropyrans. This result may be explained by considering chair-like transition states for 6-*exo* ring closure (Scheme 9),[8a] and assuming as the most favorable situation the alkene and the ester in a pseudo-equatorial orientation as in **32**, leading to *trans* 2,3-disubstituted radical **33**. The minor *cis* isomer may originate from radical **34**, with the alkene in a pseudo-axial position leading to **35**. For large substituents R^2, the transition state **34** may be expected to be even more unfavorable through an increased 1,3-diaxial interaction. Indeed, the *Z*-alkene **12** gave a slightly higher *trans*-selectivity than the *E*-alkene **11**. Burke and Rancourt[7] showed that the use of a bulky trimethylsilyl group situated on the terminal side of the *Z*-alkene strongly increases this effect and gives only the *trans* 6-*exo* cyclization product.

With satisfactory results in hand for both 5-*exo*- and 6-*exo* xanthate transfer radical cyclizations of α-alkoxy

Scheme 9



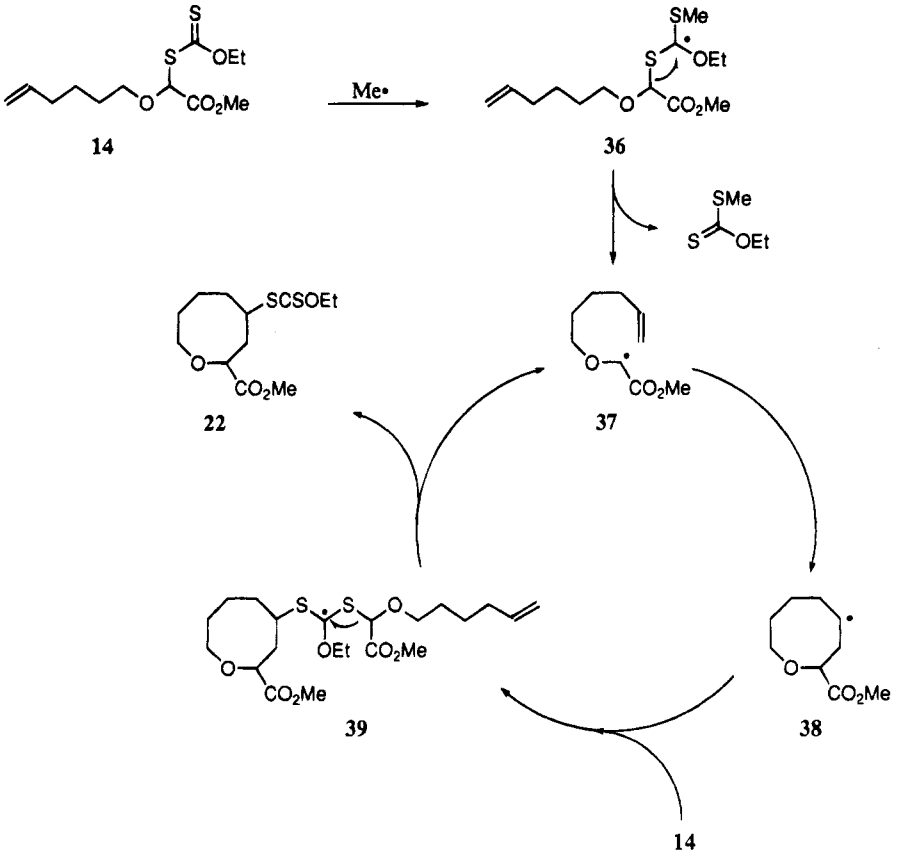
α-ester radicals, the ring closure of the corresponding 2-oxa-7-octenyl radical to an eight-membered ring ether was investigated (Table 1, entry 6). Treatment of xanthate **14** with 0.1 equiv of DTBP in a 0.1 M solution of *tert*-butylbenzene gave after 2.5 h of heating at 150–160 °C a 79:21 mixture 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 *inter*molecular 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-*exo* 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 ^{13}C NMR spectrum at 202 ppm.

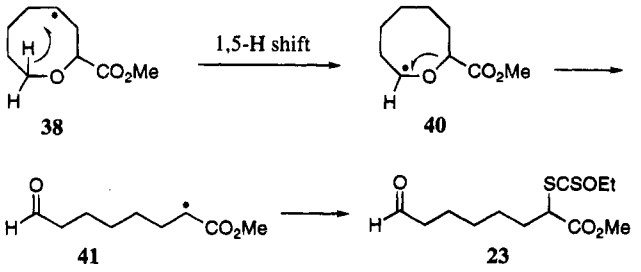
Mechanism of the Xanthate Transfer Radical Cyclization. The mechanism of the xanthate transfer radical cyclization reactions of xanthates **9**–**14** in the synthesis of cyclic ethers is supposed to involve a chain reaction as shown in Scheme 10 for the cyclization of xanthate **14** to oxocane **22**. Initiation of the chain occurs after the generation of methyl radicals by thermal decomposition of DTBP.[8a] 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.[23] 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

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

Scheme 10



Scheme 11



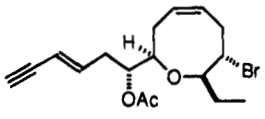
heteroatoms similar to radical **36**. Homolysis of the carbon–sulfur bond as shown in Scheme 10 leads to the desired xanthate transfer cyclization product **22** and the captodative radical **37**. In order to obtain a good yield of the xanthate transfer radical cyclization product, the reaction should be performed with as little initiatior 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]

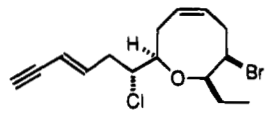
Synthesis of Lauthisan. Recently, synthetic efforts toward the construction of "medium-sized" ethers and lactones attracted increasing interest. Due to the intrinsic difficulties associated with the formation of medium rings,[25] the total synthesis of these molecules remains a challenge. A variety of 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

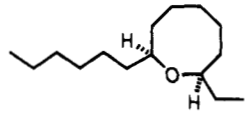
(24) Barton, D. H. R.; Morgan, L. R. *J. Chem. Soc.* **1962**, 622.
(25) Moore, J. A.; Anet, F. A. L. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 7, Chapt. 5.19, p 635.
(26) (a) Erickson, K. L. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1983; Vol. V, p 131. (b) Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 251, 551; **1986**, *3*, 1; **1987**, *4*, 539; **1988**, *5*, 613.
(27) (a) Blunt, J. W.; Lake, R. J.; Munro, M. H. G.; Yorke, S. C. *Aust. J. Chem.* **1981**, *34*, 2393. (b) Blunt, J. W.; Lake, R. J.; Munro, M. H. G. *Aust. J. Chem.* **1984**, *37*, 1545.
(28) For preparation from laurencin, see: Fukazawa, A.; Masamune, T. *Tetrahedron Lett.* **1981**, *22*, 4081.
(29) (a) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron Lett.* **1965**, 1091. (b) Cameron, A. F.; Cheung, K. K.; Erguson, G.; Robertson, J. M. *J. Chem. Soc., Chem. Commun.* **1965**, 638. (c) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron* **1968**, *24*, 4193.
(30) Fukuzawa, A.; Masamune, T. *Tetrahedron Lett.* **1981**, *22*, 4081.
(31) Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Veale, C. A.; Furst, G. T. *J. Am. Chem. Soc.* **1987**, *109*, 2504.



laurencin (42)



laurepinnacin (43)



lauthisan (44)

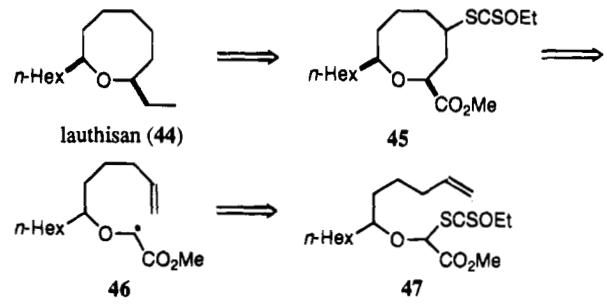
xanthate transfer cyclization method of α-alkoxy α-ester radicals. A retrosynthetic analysis is shown in Scheme 12. In the projected synthesis of lauthisan, the ester group of **45** should serve as a handle to prepare the desired ethyl substituent of lauthisan. Oxocane **45** was envisioned to arise 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[34] 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 38% 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.[35] 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 **45** 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 Bu_3SnH, 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 $LiAlH_4$, 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,[33] 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

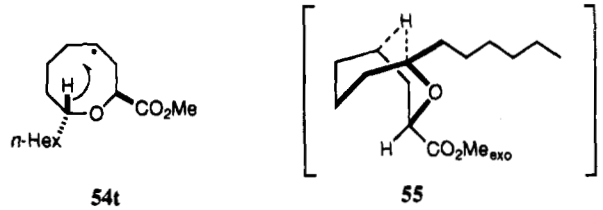
Scheme 12



lauthisan (44) 45 46 47

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 ^{13}C 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 **38** generated from xanthate **14**. Of these, only the *trans* radical **54t** 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 **54c** cannot undergo the 1,5-H shift and so undergoes xanthate capture to form **45**.



54t 55

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 **56**[36] (Scheme 14) as a catalyst in a light-induced radical process might be beneficial in this respect. Barton and co-workers[36] 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.

(32) Kotsuki, H.; Ushio, Y.; Kadota, I.; Ochi, M. *J. Org. Chem.* **1989**, *54*, 5153.
(33) (a) Carling, R. W.; Holmes, A. B. *J. Chem. Soc., Chem. Commun.* **1986**, 565. (b) Carling, R. W.; Clark, J. S.; Holmes, A. B. *J. Chem. Soc., Perkin Trans. 1* **1992**, 83.
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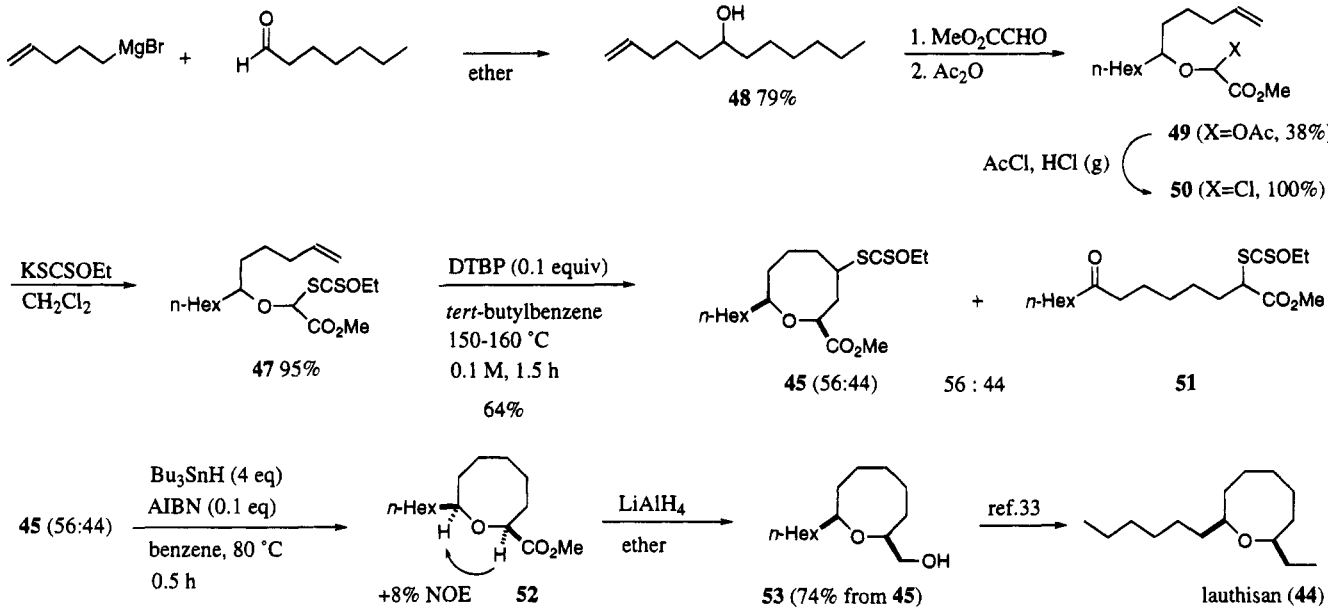
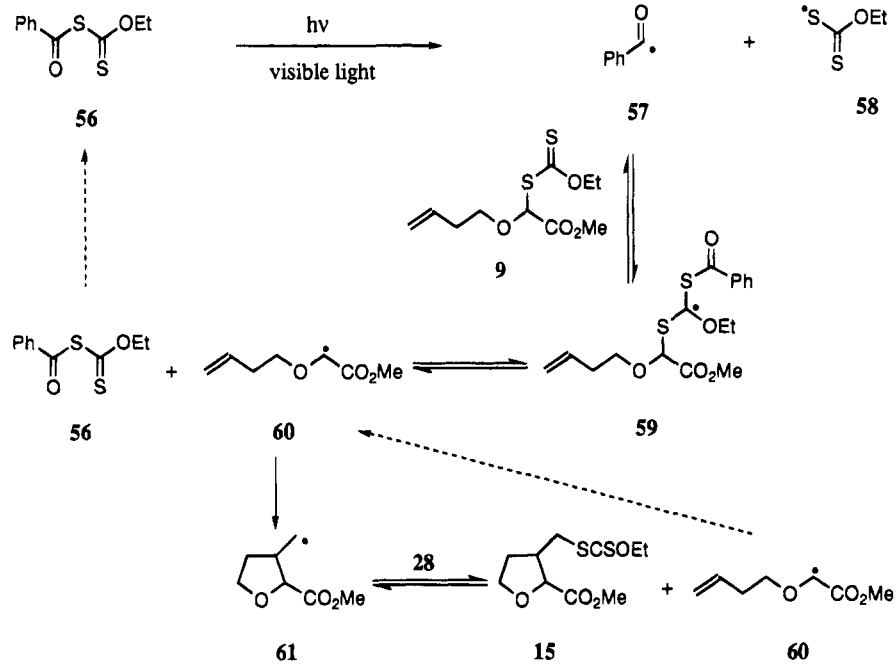
(35) Lolkema, L. D. M. Ph.D. Thesis, University of Amsterdam, 1993.
(36) Barton, D. H. R.; George, M. V.; Tomoeda, M. *J. Chem. Soc.* **1962**, 1967.

Scheme 13



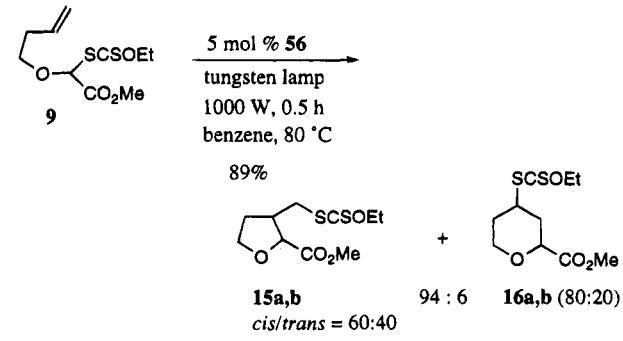
Scheme 14



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[10] 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**.[36] 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[23] 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-

Scheme 15



ther research is needed to test if this light-induced radical process with the benzoyl xanthate catalyst is also of use for the preparation of larger ring systems.

Conclusions

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 Bu_3SnH-method and the Cu(bpy)Cl-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 use of benzoyl xanthate as a catalyst allows a visible light-induced xanthate transfer cyclization to a tetrahydrofuran in high yield.

Experimental Section

General Information. Experimental techniques and analytical measurements were applied as previously described.[5c] NaCN impregnated on alumina was prepared according to a literature procedure.[18] Methanesulfonic acid hex-3(*Z*)-enyl ester,[37] dithiocarbonic acid *S*-benzoyl ester *O*-ethyl ester[36] (**56**), (but-3-enyloxy)chloroacetic acid methyl ester,[5d] chloro(hex-4-enyloxy)acetic acid methyl ester,[5d] and chloro(cyclohex-3-enylmethoxy)acetic acid methyl ester[5d] were prepared according to literature procedures. Chloride **50** 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*)-enenitrile (24). To a solution of methanesulfonic acid hex-3(*Z*)-enyl ester (1.0 g, 5.6 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 light brown oil: IR ($CHCl_3$) 2950, 2930, 2860, 2230, 1450, 1420; ^1H NMR (400 MHz) δ 0.99 (t, J = 7.5 Hz, 3H), 2.07 (d quintet, J = 1.3, 7.4 Hz, 2H), 2.34–2.42 (m, 4H), 5.31–5.35 (m, 1H), 5.52–5.59 (m, 1H); ^{13}C NMR (100 MHz) δ 14.06, 17.51, 20.53, 23.10, 119.38, 124.37, 135.11.

Hept-4(*Z*)-enoic acid. 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 washed with brine and dried (Na_2SO_4), and the solvent was removed in vacuo to give hept-4(*Z*)-enoic acid as a yellow oil (8.37 g, 65.4 mmol, 83%): IR ($CHCl_3$) 3500, 3400–2500 (broad), 2960, 1705, 1410; ^1H NMR (250 MHz) δ 0.95 (t, J = 7.5 Hz, 3H), 2.05 (quintet, J = 7.4 Hz, 2H), 2.31–2.41 (m, 4H), 5.26–5.34 (m, 1H), 5.37–5.45 (m, 1H), 9.80 (broad s, 1H); ^{13}C NMR (63 MHz) δ 14.21, 20.50, 22.44, 34.20, 126.35, 133.44, 179.35.

Hept-4(*Z*)-en-1-ol (25). A solution of hept-4(*Z*)-enoic acid (1.0 g, 7.8 mmol) in anhydrous diethyl ether (24 mL) was added during 15 min to a stirred solution of $LiAlH_4$ (0.33 g, 8.6 mmol) in anhydrous diethyl ether (9 mL) at 0 °C. After heating under reflux for 0.5 h, water (0.32 mL), 20% NaOH (0.24 mL), and water (1.1 mL) were added in succession. Water (50 mL) was added, and the resulting solution was extracted with ether (four times 30 mL). The organic extract was washed with brine and dried ($MgSO_4$) and the solvent was removed in vacuo to give **25** (530 mg, 4.64 mmol, 60%) as a colorless oil: IR ($CHCl_3$) 3610, 3440 (broad), 2990, 2960, 2930, 2870, 1455; ^1H NMR (200 MHz) δ 0.90 (t, J = 7.5 Hz, 3H), 1.57 (broad s, 1H), 1.63 (quintet, J = 7.4 Hz, 2H), 1.98–2.17 (m, 4H), 3.66 (t, J = 6.5, 2H), 5.27–5.47 (m, 2H); ^{13}C NMR (63 MHz) δ 14.22, 20.43, 23.43, 32.60, 62.44, 128.22, 132.27; HRMS calcd for $C_7H_{14}O$ 114.1045, found 114.1033.

Acetoxy(pent-4-enyloxy)acetic Acid Methyl Ester. 4-Pentenol (2.46 g, 28.6 mmol) was treated with methyl glyoxylate (4.16 g, 47.3 mol, 1.65 equiv) in 12 mL of dichloromethane. After stirring for 2 h, the mixture was concentrated in vacuo and treated with DMAP (0.17 g, 1.4 mmol) and acetic anhydride (5.4 mL, 57 mmol) in 28 mL of pyridine for 3 h. Evaporation with toluene (three times) and flash chromatography gave acetoxy(pent-4-enyloxy)acetic acid methyl ester (4.916 g, 22.74 mmol, 80%) as a colorless oil: R_f 0.50 (EtOAc/hexane 1:4); IR 3020, 2950, 1750, 1635, 1435, 1370; ^1H NMR (250 MHz) δ 1.64–1.75 (m, 2H), 2.06–2.13 (m, 2H), 2.13 (s, 3H), 3.58–3.80 (m, 2H), 3.78 (s, 3H), 4.93–5.04 (m, 2H), 5.67–5.81 (m, 1H), 5.93 (s, 1H); MS FAB 217 ($(M + H)^+$).

Acetoxy(hept-4(*Z*)-enyloxy)acetic Acid Methyl Ester. Alcohol **25** (1.04 g, 9.11 mmol) was treated with methyl glyoxylate (1.60 g, 18 mmol) in 5 mL of dichloromethane. After stirring for 18 h, the mixture was concentrated in vacuo and treated with DMAP (110 mg, 0.9 mmol) and acetic anhydride (1.7 mL, 18 mmol) in 9 mL of pyridine for 3 h. Evaporation with toluene (three times) and flash chromatography gave acetoxy(hept-4(*Z*)-enyloxy)acetic acid methyl ester (1.143 g, 4.68 mmol, 51%) as a colorless oil: R_f 0.45 (EtOAc/hexane 1:4); IR ($CHCl_3$) 2990, 2950, 2870, 1750, 1435, 1370; ^1H NMR (400 MHz) δ 0.93 (t, J = 7.5 Hz, 3H), 1.67 (quintet, J = 7.4 Hz, 2H), 1.99–2.15 (m, 4H), 2.14 (s, 3H), 3.64 (dt, J = 9.4, 6.6 Hz, 1H), 3.73 (dt, J = 9.4, 6.6 Hz, 1H), 3.79 (s, 3H), 5.25–5.29 (m, 1H), 5.36–5.40 (m, 1H); ^{13}C NMR (100 MHz) δ 14.22, 20.41, 20.76, 23.19, 29.27, 52.71, 69.79, 92.68, 127.62, 132.65, 166.31, 170.05 .

Acetoxy(hex-5-enyloxy)acetic Acid Methyl Ester. 5-Hexenol (2.047 g, 20.44 mol) was treated with methyl glyoxylate (3.6 g, 40.9 mmol) in 10 mL of dichloromethane. After stirring for 3 h, the mixture was concentrated in vacuo and treated with DMAP (cat.) and acetic anhydride (3.9 mL, 41 mmol) in 20 mL of pyridine for 3 h. Evaporation with toluene (three times) and flash chromatography gave acetoxy-(hex-5-enyloxy)acetic acid methyl ester (3.155 g, 14.73 mmol, 72%) as a colorless oil: R_f 0.55 (EtOAc/hexane 1:2); IR 3070, 3020, 2950, 1750, 1630, 1435, 1370; ^1H NMR (200 MHz) δ 1.38–1.55 (m, 2H), 1.57–1.72 (m, 2H), 2.00–2.15 (m, 2H), 2.15 (s, 3H), 3.59–3.80 (m, 2H), 3.80 (s, 3H), 4.91–5.03 (m, 2H), 5.67–5.88 (m, 1H), 5.95 (s, 1H).

General Procedure for the Synthesis of α-Chloro Ethers. Freshly distilled acetyl chloride (at least 20 equiv) was added to a 0.5 M solution of the acetate in ether (dry) at 0 °C. Hydrogen chloride gas was passed through this solution at 0 °C for 0.5 h, and the reaction mixture was concentrated in vacuo. This afforded essentially pure chlorides, which were immediately used in the next reaction.

Chloro(pent-4-enyloxy)acetic Acid Methyl Ester. A solution of acetoxy(pent-4-enyloxy)acetic acid methyl ester (3.027 g, 14.00 mmol) in 20 mL of ether and 20 mL of acetyl chloride was treated with hydrogen chloride gas at 0 °C for 0.5 h. Evaporation of the volatiles gave chloro(pent-4-enyloxy)-acetic acid methyl ester (2.493 g, 12.95 mmol, 92.5%) as a light yellow oil: IR 2950, 1760, 1635, 1435; ^1H NMR (250 MHz) δ 1.69–1.81 (m, 2H), 2.05–2.19 (m, 2H), 3.58 (dt, J = 9.5, 6.6 Hz, 1H), 3.82 (s, 3H), 3.96 (dt, J = 9.5, 6.6 Hz, 1H), 4.94–5.04 (m, 2H), 5.67–5.84 (m, 1H), 5.79 (s, 1H).

Chloro(hept-4(*Z*)-enyloxy)acetic Acid Methyl Ester. A solution of acetoxy(hept-4(*Z*)-enyloxy)acetic acid methyl ester (1.096 g, 4.487 mmol) in 6.5 mL of ether and 6.5 mL of acetyl chloride was treated with hydrogen chloride gas at 0 °C for 0.5 h. Evaporation of the volatiles gave chloro(hept-4(*Z*)-enyloxy)acetic acid methyl ester (0.984 g, 4.33 mmol, 97%) as a colorless oil: IR ($CHCl_3$) 2990, 2950, 2870, 1755, 1435, 1295; ^1H NMR (250 MHz) δ 0.91 (t, J = 7.5 Hz, 3H), 1.71 (quintet, J = 7.0 Hz, 2H), 1.93–2.14 (m, 4H), 3.56 (dt, J = 9.4, 6.6 Hz, 1H), 3.82 (s, 3H), 3.94 (dt, J = 9.4, 6.5 Hz, 1H), 5.23–5.40 (m, 2H), 5.78 (s, 1H, CHCl); ^{13}C NMR (63 MHz) δ 14.19, 20.44, 23.23, 28.64, 53.03, 70.10, 88.59, 127.33, 132.84, 165.64.

Chloro(hex-5-enyloxy)acetic Acid Methyl Ester. A solution of acetoxy(hex-5-enyloxy)acetic acid methyl ester (2.034 g, 9.49 mmol) in 14 mL of ether and 13.5 mL of acetyl

(37) Esch, P. M.; Boska, I. M.; Hiemstra, H.; De Boer, R. F.; Speckamp, W. N. *Tetrahedron* **1991**, *24*, 4039.

chloride was treated with hydrogen chloride gas at 0 °C for 0.5 h. Evaporation of the volatiles gave chloro(hex-5-enyloxy)-acetic acid methyl ester (1.7011 g, 8.23 mmol, 87%) as a light yellow oil: IR ($CHCl_3$) 2950, 1760, 1635, 1435; ^1H NMR (200 MHz) δ 1.40–1.55 (m, 2H), 1.61–1.77 (m, 2H), 2.01–2.15 (m, 2H), 3.60 (dt, J = 9.5, 6.5 Hz, 1H), 3.84 (s, 3H), 3.97 (dt, J = 9.5, 6.7 Hz, 1H), 4.92–5.04 (m, 2H), 5.67–5.88 (m, 1H), 5.81 (s, 1H).

(But-3-enyloxy)[(ethoxythiocarbonyl)sulfanyl]acetic Acid Methyl Ester (9). To a solution of (but-3-enyloxy)-chloroacetic acid methyl ester (110 mg, 0.618 mmol) in CH_2Cl_2 (1.24 mL) was added potassium *O*-ethyl dithiocarbonate (104 mg, 0.65 mmol). After stirring for 20 min, the mixture was subjected to flash chromatography to give **9** as a yellow oil (145 mg, 0.548 mmol, 89%): R_f 0.55 (EtOAc/hexane 1:6); IR 3075, 2990, 2950, 1750, 1635, 1435; ^1H NMR (250 MHz) δ 1.40 (t, J = 7.2 Hz, 3H), 2.40 (qt, J = 6.7, 1.2 Hz, 2H), 3.61 (dt, J = 9.4, 6.7 Hz, 1H), 3.72–3.79 (m, 1H), 3.76 (s, 3H), 4.65 (q, J = 7.2 Hz, 2H), 4.98–5.10 (m, 2H), 5.69–5.82 (m, 1H), 6.06 (s, 1H); ^{13}C NMR (63 MHz) δ 13.59, 33.45, 52.81, 68.95, 70.69, 86.52, 116.83, 134.00, 167.53, 210.80; HRMS calcd for $C_{10}H_{16}O_4S_2$ 264.0470, found 264.0480.

[(Ethoxythiocarbonyl)sulfanyl](pent-4-enyloxy)-acetic Acid Methyl Ester (10). To a solution of chloro(pent-4-enyloxy)acetic acid methyl ester (2.47 g, 12.83 mmol) in CH_2Cl_2 (26 mL) was added potassium *O*-ethyl dithiocarbonate (2.16 g, 13.5 mmol). After stirring for 20 min, the mixture was subjected to flash chromatography to give **10** as a yellow oil (2.825 g, 10.15 mmol, 79%): R_f 0.65 (EtOAc/hexane 1:4); IR 3070, 2990, 2950, 2870, 1745, 1635, 1435; ^1H NMR (200 MHz) δ 1.44 (t, J = 7.1 Hz, 3H), 1.73 (q, J = 6.7 Hz, 2H), 2.06–2.17 (m, 2H), 3.60 (dt, J = 9.3, 6.4 Hz, 1H), 3.68–3.80 (m, 1H), 3.80 (s, 3H), 4.68 (q, J = 7.2 Hz, 2H), 4.93–5.06 (m, 2H), 5.68–5.90 (m, 1H), 6.07 (s, 1H); ^{13}C NMR (75 MHz) δ 13.66, 28.27, 29.94, 52.91, 69.10, 70.76, 86.60, 115.06, 137.64, 167.70, 210.89; HRMS calcd for $C_{11}H_{18}O_4S_2$ 278.0646, found 278.0659.

[(Ethoxythiocarbonyl)sulfanyl](hex-4-enyloxy)-acetic Acid Methyl Ester (11). To a solution of chloro(hex-4-enyloxy)acetic acid methyl ester (1.503 g, 7.28 mmol) in CH_2Cl_2 (15 mL) was added potassium *O*-ethyl dithiocarbonate (1.225 g, 7.64 mmol). After stirring for 20 min, the mixture was subjected to flash chromatography to give **11** as a yellow oil (1.874 g, 6.41 mmol, 88%): R_f 0.60 (EtOAc/hexane 1:4); IR 2990, 2950, 1745, 1435; ^1H NMR (250 MHz) δ 1.42 (t, J = 7.1 Hz, 3H), 1.61 (d, J = 4.8 Hz, 3H), 1.60–1.72 (m, 2H), 1.98–2.06 (m, 2H), 3.57 (dt, J = 9.2, 6.5 Hz, 1H), 3.73 (dt, J = 9.3, 6.4 Hz, 1H), 3.79 (s, 3H), 4.67 (q, J = 7.1 Hz, 2H), 5.35–5.46 (m, 2H), 6.05 (s, 1H); ^{13}C NMR (75 MHz) δ 13.64, 17.84, 28.76, 28.88, 52.84, 52.89, 69.21, 70.70, 86.60, 86.66, 125.58, 130.10, 167.73, 210.95; HRMS calcd for $C_{12}H_{20}O_4S_2$ 292.0803, found 292.0799.

[(Ethoxythiocarbonyl)sulfanyl](hept-4(*Z*)-enyloxy)-acetic Acid Methyl Ester (12). To a solution of chloro(hept-4(*Z*)-enyloxy)acetic acid methyl ester (0.908 g, 4.11 mmol) in CH_2Cl_2 (8 mL) was added potassium *O*-ethyl dithiocarbonate (0.679 g, 4.23 mmol). After stirring for 20 min, the mixture was subjected to flash chromatography to give **12** as a yellow oil (1.148 g, 3.75 mmol, 91%): R_f 0.50 (EtOAc/hexane 1:4); IR ($CHCl_3$) 2990, 2950, 2860, 1750, 1435; ^1H NMR (400 MHz) δ 0.93 (t, J = 7.6 Hz, 3H), 1.43 (t, J = 7.1 Hz, 3H), 1.68 (quintet, J = 7.0 Hz, 2H), 1.97–2.12 (m, 4H), 3.58 (dt, J = 9.3, 6.5 Hz, 1H), 3.75 (dt, J = 9.3, 6.6 Hz, 1H), 3.79 (s, 3H), 4.67 (q, J = 7.1 Hz, 2H), 5.25–5.34 (m, 1H), 5.35–5.39 (m, 1H), 6.06 (s, 1H); ^{13}C NMR (100 MHz) δ 13.62, 14.23, 20.41, 23.36, 29.08, 52.88, 69.26, 70.71, 86.74, 127.72, 132.52, 167.75, 211.04; HRMS calcd for $C_{13}H_{22}O_4S_2$ 306.0960, found 306.0946.

(Cyclohex-3-enylmethoxy)[(ethoxythiocarbonyl)-sulfanyl]acetic Acid Methyl Ester (13). To a solution of chloro(cyclohex-3-enylmethoxy)acetic acid methyl ester (1.567 g, 7.19 mmol) in CH_2Cl_2 (14.4 mL) was added potassium *O*-ethyl dithiocarbonate (1.210 g, 7.55 mmol). After stirring for 30 min, the mixture was subjected to flash chromatography to give **13** as a yellow oil (1.627 g, 5.34 mmol, 74%): R_f 0.65 (EtOAc/hexane 1:4); IR 3000, 2910, 2830, 1745, 1435, 1230; ^1H NMR (200 MHz, mixture of two diastereomers) 1.22–1.38 (m, 1H), 1.44 (t, J = 7.1 Hz, 3H), 1.60–2.20 (m, 6H), 3.44–3.53 (m, 1H), 3.58–3.68 (m, 1H), 3.81 (s, 3H), 4.69 (q, J = 7.1 Hz, 2H), 5.60–5.75 (m, 2H), 6.07 (s), 6.08 (s); ^{13}C NMR (75 MHz, mixture of two diastereomers) 13.68, 24.30, 24.36, 25.28, 25.31, 28.15, 28.24, 33.37, 33.40, 52.93, 70.76, 74.30, 74.43, 86.79, 86.83, 125.61, 126.95, 127.02, 167.78, 211.01; HRMS calcd for $C_{13}H_{20}O_4S_2$ 304.0803, found 304.0830.

[(Ethoxythiocarbonyl)sulfanyl](hex-5-enyloxy)-acetic Acid Methyl Ester (14). To a solution of chloro(hex-5-enyloxy)acetic acid methyl ester (1.701 g, 8.23 mmol) in CH_2Cl_2 (16.5 mL) was added potassium *O*-ethyl dithiocarbonate (1.39 g, 7.31 mmol). After stirring for 20 min, the mixture was subjected to flash chromatography to give **14** as a yellow oil (2.137 g, 7.31 mmol, 89%): R_f 0.45 (EtOAc/hexane1:4); IR 3070, 2990, 2940, 2860, 1750, 1635, 1435; ^1H NMR (200 MHz) δ 1.42 (t, J = 7.2 Hz, 3H), 1.35–1.55 (m, 2H), 1.55–1.70 (m, 2H), 1.98–2.09 (m, 2H), 3.58 (dt, J = 9.2, 6.4 Hz, 1H), 3.67–3.78 (m, 1H), 3.78 (s, 3H), 4.66 (q, J = 7.1 Hz, 2H), 4.89–5.01 (m, 2H), 5.65–5.86 (m, 1H), 6.05 (s); ^{13}C NMR (63 MHz) δ 13.58, 25.09, 28.51, 33.21, 52.78, 69.65, 70.60, 86.61, 114.53, 138.29, 167.66, 210.90; HRMS calcd for $C_{12}H_{20}O_4S_2$ 292.0803, found 292.0786.

Cyclization of 9. To a solution of **9** (110.5 mg, 0.418 mmol) in *tert*-butylbenzene (0.84 mL) was added DTBP (18 mg, 0.13 mmol). The reaction mixture was heated at 150–155 °C for 20 min. Filtration through a short silica column (eluting with EtOAc/hexane 1:3) afforded a mixture of **15** and **16** as a light yellow oil (78 mg, 0.295 mmol, 71%). According to ^1H NMR, **15a**:**15b**:**16a**:**16b** = 50:40:5:5. Careful flash chromatography (hexane, then EtOAc/hexane 1:6) gave samples of **15a** and **15b**, while **16a** and **16b** could not be isolated. **(2*R**,3*R**)-3-[[(Ethoxythiocarbonyl)sulfanyl]methyl]tetrahydrofuran-2-carboxylic Acid Methyl Ester (15a)**: R_f 0.25 (EtOAc/hexane 1:4); IR ($CHCl_3$) 2990, 2950, 2880, 1740, 1435; ^1H NMR (250 MHz) δ 1.40 (t, J = 7.1 Hz, 3H), 1.86 (dq, J = 12.1, 8.0 Hz, 1H), 2.09–2.22 (m, 1H), 2.75–2.90 (m, 1H), 3.00 (dd, J = 13.6, 9.1 Hz, 1H), 3.22 (dd, J = 13.6, 5.9 Hz, 1H), 3.75 (s, 3H), 3.89 (q, J = 7.8 Hz, 1H), 4.18 (dt, J = 4.5, 8.3 Hz, 1H), 4.50 (d, J = 7.2 Hz, 1H), 4.62 (q, J = 7.1 Hz, 2H); ^{13}C NMR (50 MHz) δ 13.67, 30.63, 35.63, 41.82, 51.80, 68.28, 70.12, 79.41, 171.62, 213.95; HRMS calcd for $C_{10}H_{16}O_4S_2$ 264.0490, found 264.0475. **(2*R**,3*S**)-3-[[(Ethoxythiocarbonyl)sulfanyl]methyl]-tetrahydrofuran-2-carboxylic Acid Methyl Ester (15b)**: R_f 0.20 (EtOAc/hexane 1:4); IR ($CHCl_3$) 2990, 2950, 2880, 1740, 1435; ^1H NMR (250 MHz) δ 1.41 (t, J = 7.1 Hz, 3H), 1.76 (dq, J = 12.5, 7.4 Hz, 1H), 2.11–2.19 (m, 1H), 2.68–2.80 (m, 1H), 3.17 (dd, J = 13.6, 8.4 Hz, 1H), 3.49 (dd, J = 13.7, 6.1 Hz, 1H), 3.75 (s, 3H), 3.98–4.04 (m, 2H), 4.20 (d, J = 5.4 Hz, 1H), 4.64 (q, J = 7.1 Hz, 2H); ^{13}C NMR (63 MHz) δ 13.74, 31.42, 38.85, 43.25, 52.14, 68.71, 70.20, 81.04, 172.60, 213.78; HRMS calcd for $C_{10}H_{16}O_4S_2$ 264.0490, found 264.0470. Data for **4-[(ethoxythiocarbonyl)sulfanyl]tetrahydropyran-2-carboxylic acid methyl ester (16a and 16b)** derived from the enriched fractions: **16a**: ^1H NMR (250 MHz) δ 4.23 (dd, J = 9.0, 3.5 Hz, 1H, H-2); ^{13}C NMR (63 MHz) δ 30.36 and 33.20 (C-3 and C-5), 43.50 (C-4), 64.45 (C-6), 72.80 (C-2). **16b**: ^1H NMR (250 MHz) δ 2.43–2.53 (m, 1H), 3.58 (dt, J = 3, 11 Hz, 1H); ^{13}C NMR (63 MHz) δ 44.76 (C-4), 67.55 (C-6), 72.62 (C-2).

Light-Induced Cyclization of 9. To a solution of **9** (238.9 mg, 0.9037 mmol) in benzene (4.5 mL) was added **dithiocarbonic acid *S*-benzoyl ester *O*-ethyl ester (56)** (41 mg, 0.18 mmol). The reaction mixture was irradiated with a 1000 W tungsten lamp under reflux for 0.5 h. Flash chromatography afforded three fractions. The first fraction consisted of **15a** (12 mg, 0.045 mmol, 5%) as a light yellow oil. The second fraction consisted of a 62:32:6 mixture of **15a**, **15b**, and **16a** (170.5 mg, 0.646 mmol, 72%). The third fraction consisted of a 2:90:8 mixture of **15a**, **15b**, and **16b** (27.9 mg, 0.106 mmol, 12%).

Cyclization of 10. To a solution of **10** (187.0 mg, 0.6717 mmol) in *tert*-butylbenzene (1.3 mL) was added DTBP (30 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 1:5) gave a mixture of four diastereomers of **3-[[(ethoxythiocarbonyl)sulfanyl]methyl]tetrahydropyran-2-carboxylic acid methyl ester (17)** and **4-[(ethoxy-**

thiocarbonyl)sulfanyl]oxepane-2-carboxylic acid methyl ester (18) (157 mg, 0.564 mmol, 84%): R_f 0.35, 0.25, and 0.20 (EtOAc/hexane 1:4); IR ($CHCl_3$) 2980, 2950, 2850, 1740, 1435; ^1H NMR (250 MHz, mixture of four diastereomers, characteristic signals) δ 1.36 (t, J = 7.2 Hz, 3H), 3.68 (s), 3.69 (s), 3.74 (s, 3H), 4.58 (q, J = 7.2 Hz, 2H); ^{13}C NMR (63 MHz, mixture of four diastereomers, characteristic signals) δ 13.65 (OCH_2CH_3), 35.45 and 37.47 (**17** C-3), 47.20 and 47.66 (**18** C-4), 66.93, 67.36, 68.48, 68.73 (**17** C-6 and **18** C-7), 69.60, 69.71, 69.88 and 70.00 (OCH_2CH_3), 75.50, 75.94, 78.26, and 80.25 (C-2); HRMS calcd for $C_{11}H_{18}O_4S_2$ 278.0647, found 278.0669.

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 on a short silica column (eluting with EtOAc/hexane 1:4) gave a 33:67 mixture of **(2*R**,3*R**)-3-[1-[(ethoxythiocarbonyl)sulfanyl]ethyl]tetrahydropyran-2-carboxylic acid methyl ester (19a)** and **(2*R**,3*S**)-3-[1-[(ethoxythiocarbonyl)sulfanyl]ethyl]tetrahydropyran-2-carboxylic acid methyl ester (19b)** as a colorless oil (167 mg, 0.571 mmol, 91%), with both **19a** and **19b** present as approximately 1:1 mixtures of their diastereomers: R_f 0.25 and 0.20 (EtOAc/hexane 1:4); IR ($CHCl_3$) 2940, 2850, 1735, 1435, 1370; ^1H NMR (250 MHz, mixture of four diastereomers) δ 1.20–2.20 (m, 8H), 1.37 (t, J = 7.2 Hz, 3H), 3.32–3.45 (m, 0.67H), 3.50–4.05 (m, 3H), 3.70 (s), 3.71 (s), 3.73 (s) and 3.79 (s, 3H), 4.26–4.33 (m, 0.33H, **19a** H-2), 4.50–4.65 (m, 2H); ^{13}C NMR (63 MHz, mixture of four diastereomers, characteristic signals) δ 13.75, 14.87, 18.90, 19.38, 19.85, 40.26, 41.93, 42.23, 42.89, 45.77, 45.80, 46.70, 46.75, 66.51, 67.79, 67.82, 69.68, 69.75, 69.84, 69.90, 76.31, 77.03, 79.17, 79.53, 170.51, 170.81, 170.90, 171.08, , 213.30, 213.39, 213.60; HRMS calcd for $C_{12}H_{20}O_4S_2$ 292.0803, found 292.0822.

Cyclization of 12. To a solution of **12** (162.4 mg, 0.530 mmol) in *tert*-butylbenzene (1.1 mL) was added DTBP (23 mg, 0.16 mmol). The reaction mixture was heated at 150–155 °C for 0.5 h. Flash chromatography gave a 25:75 mixture of **(2*R**,3*R**)-3-[1-[(ethoxythiocarbonyl)sulfanyl]propyl]-tetrahydropyran-2-carboxylic acid methyl ester (20a)** and **(2*R**,3*S**)-3-[1-[(ethoxythiocarbonyl)sulfanyl]propyl]-tetrahydropyran-2-carboxylic acid methyl ester (20b)** as a colorless oil (115 mg, 0.375 mmol, 71%), with both **20a** and **20b** present as approximately 1:1 mixtures of their diastereomers: R_f 0.35 and 0.30 (EtOAc/hexane 1:4); IR ($CHCl_3$) 2960, 2850, 1740, 1450, 1435; ^1H NMR (400 MHz, mixture of four diastereomers) 0.80–1.00 (m, 3H), 1.333–2.30 (m, 7H), 1.37 (t, J = 7.1 Hz, 3H), 3.34–3.41 (m, 0.75 H), 3.55–4.05 (m, 3H, including **20b** H-2: 3.95 (d, J = 9.6) and 4.01 (d, J = 9.8 Hz)), 3.70 (s), 3.71 (s), 3.72 (s) and 3.80 (s, 3H), 4.31–4.34 (m, 0.25H, **20a** H-2), 4.52–4.65 (m, 2H); ^{13}C NMR (100 MHz, mixture of four diastereomers) **20b**: 11.88 (CH_3), 13.70, 21.85, 24.37, 24.84, 25.14, 25.24, 26.18, 40.50, 42.90, 52.09, 52.22, 53.33, 53.97, 67.86, 67.91, 69.97, 79.22, 79.43, 170.59, 170.68, 213.93, 214.06. **20a** characteristic signals: 39.44 (C-3), 51.84, 53.97 (CHS), 65.86 and 66.35 (C-6), 75.96 and 76.99 (C-2), 171.02 and 171.08 (C=O), 214.36 (C=S); HRMS calcd for $C_{13}H_{22}O_4S_2$ 306.0960, found 306.0948.

Cyclization of 13. To a solution of **13** (262.5 mg, 0.862 mmol) in *tert*-butylbenzene (1.7 mL) was added DTBP (25 mg, 0.17 mmol). The reaction mixture was heated at 150–155 °C for 2 h. Filtration over a short silica column (eluting with EtOAc/hexane 1:4) gave a mixture of four diastereomers of **8-[(ethoxythiocarbonyl)sulfanyl]-3-oxabicyclo[3.3.1]-nonane-2-carboxylic acid methyl ester (21)** (211 mg, 0.693 mmol, 80%): R_f 0.20 and 0.10 (EtOAc/hexane 1:4); IR ($CHCl_3$) 2990, 2930, 2850, 1745, 1435; ^1H NMR (200 MHz, mixture of 4 diastereomers) 1.20–2.65 (m, 10H), 2.75–3.05 (m, 1H), 3.65–4.45 (m, 4H, including 4.35 (d, J = 2.5 Hz, major isomer H-4), 3.75 (s), 3.77 (s) and 3.85 (s, 3H), 4.55–4.70 (m, 2H); ^{13}C NMR (63 MHz, mixture of 4 diastereomers, characteristic signals) 69.37 (major diastereomer), 69.43, 69.51 and 69.57 (OCH_2CH_3), 73.77, 77.09, 78.85 and 79.43 (C-4); HRMS calcd for $C_{13}H_{20}O_4S_2$ 304.0803, found 304.0791. Flash chomatography (EtOAc/hexane 1:10 to 1:4) gave a 9:1 mixture (according to both ^1H NMR and ^{13}C NMR) of the major diastereomer **21a** and a second diastereomer **21b** as a colorless oil (112 mg, 0.368 mmol, 43%): R_f 0.20 (EtOAc/hexane 1:4); IR ($CHCl_3$) 2990, 2930, 2850, 1745, 1435. Spectral data derived from this mixture for **21a**: ^1H NMR (250 MHz) δ 1.38 (t, J = 7.1 Hz, 3H), 1.60–1.85 (m, 5H), 2.14 (dq, J = 13.1, 2.6 Hz, 1H), 2.34 (broad s, 1H), 2.80–2.95 (m, 1H), 3.68–3.83 (m, 1H), 3.81 (s, 3H), 4.01 (broad d, J = 6.0 Hz, 1H), 4.09 (d, J = 10.7 Hz), 4.32 (d, J = 2.5 Hz, 1H), 4.60 (q, J = 7.1 Hz, 2H); ^{13}C NMR (63 MHz) δ 13.73, 27.58, 27.76, 28.18, 29.48, 35.59, 48.73, 52.08, 69.62, 73.23, 79.14, 170.65, 213.69. Spectral data derived from this mixture for **21b**: ^1H NMR (250 MHz) δ 3.74 (s, 3H), 4.26 (broad s, 1H); ^{13}C NMR (63 MHz) δ 21.43, 28.78, 30.57, 31.54, 33.63, 79.73; HRMS calcd for $C_{13}H_{20}O_4S_2$ 304.0803, found 304.0795.

Cyclization of 14. To a solution of **14** (179.7 mg, 0.615 mmol) in *tert*-butylbenzene (6.2 mL) was added DTBP (9.1 mg, 0.062 mmol). The reaction mixture was heated at 150–155 °C for 2.5 h. Flash chromatography (hexane, followed by EtOAc/hexane1:4) gave three fractions. The first fraction consisted of a 75:25 mixture of diastereomers of **4-[(ethoxythiocarbonyl)sulfanyl]oxocane-2-carboxylic acid methyl ester (22)** as a colorless oil (91.0 mg, 0.311 mmol, 50%): R_f 0.25 (EtOAc/hexane1:4); IR 2990, 2930, 2850, 1740, 1435; ^1H NMR (200 MHz, mixture of two diastereomers) 1.42 (t, J = 7.1 Hz, 3H), 1.59–2.46 (m, 8H), 3.65–4.10 (m, 3H), 3.73 (s) and 3.75 (s, 3H), 4.25 (dd, J = 2.6, 11.1 Hz, 0.75 H), 4.34 (dd, J = 4.1, 9.5 Hz, 0.25 H), 4.64 (q, J = 7.1 H, 2H); ^{13}C NMR (63 MHz, mixture of two diastereomers) major diastereomer: 13.74, 24.34, 27.76, 32.78, 35.85, 48.43, 52.06, 68.72, 69.57, 77.21, 172.26, 213.92; minor diastereomer (characteristic signals) 29.44, 32.61, 33.08, 47.45, 52.01, 68.72, 69.66, 74.26, 172.75, 213.53; HRMS calcd for $C_{12}H_{20}O_4S_2$ 292.0803, found 292.0818. The second fraction consisted of a 1:1 mixture of **22** and **23** as a colorless oil (13 mg, 0.044 mmol, 7%). The third fraction consisted of **2-[(ethoxythiocarbonyl)sulfanyl]-8-oxooctanoic acid methyl ester (23)** (19 mg, 0.065 mmol, 11%) as a colorless oil: R_f 0.20 (1:4); IR 3000, 2940, 2860, 1730, 1435; ^1H NMR (250 MHz) δ 1.40 (t, J = 7.1 Hz, 3H), 1.45–1.75 (m, 6H), 1.78–1.96 (m, 2H), 2.42 (dt, J = 1.6, 7.3 Hz, 2H), 3.73 (s, 3H), 4.35 (t, J = 7.3 Hz, 1H), 4.61 (q, J = 7.1 Hz, 2H), 9.74 (t, J =1.7 Hz, 1H); ^{13}C NMR (50 MHz) δ 13.67, 21.69, 26.81, 28.57, 31.02, 43.65, 52.22, 52.66, 70.38, 171.47, 202.33, 212.15; HRMS calcd for $C_{12}H_{20}O_4S_2$ 292.0803, found 292.0848.

Bu_3SnH-Reduction of 17 and 18. A solution of the four diastereomers of **17** and **18** (129.0 mg, 0.4633 mmol) in refluxing benzene (9.3 mL) was treated with AIBN (7.5 mg, 0.05 mmol) and Bu_3SnH (0.50 mL, 1.85 mmol) for 0.5 h and concentrated in vacuo. The DBU workup procedure[38] 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 I_2 in ether was added to this solution until the iodine color just persisted. After filtration on a 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 **oxepane-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 **(2*R**,3*S**)-3-methyltetrahydropyran-2-carboxylic acid methyl ester (26a)** and **(2*R**,3*R**)-3-methyltetrahydropyran-2-carboxylic acid methyl ester (26b)**: R_f 0.35 and 0.30 (EtOAc/hexane 1:4); IR ($CHCl_3$) 3000, 2950, 2860, 1745, 1435; ^1H NMR (250 MHz, mixture of three diastereomers) δ 0.83 (d, J = 6.5 Hz, **26b** $CHCH_3$) and 0.93 (d, J = 7.0 Hz, **26a** $CHCH_3$, **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** H-2) and 4.13 (dd, J = 10.0, 4.7 Hz, 0.5H, **27** H-2), 3.69 (s) and 3.71 (s, 3H); ^{13}C NMR (63 MHz, mixture of three diastereomers) δ 12.77 (**26a** CCH_3), 17.30 (**26b** CCH_3), 20.37, 25.42, 25.49, 27.27, 29.62, 30.54, 30.91, 31.77, 32.73, 33.29, 51.78, 51.83, 67.90, 68.38, 68.69, 77.83, 79.15, 83.35, 171.10, 171.46, 173.41; MS (EI) 99 ($M - CH_3C(O)O)^+$; HRMS calcd for $C_6H_{11}O$ 99.0810, found 99.0807.

Bu_3SnH-Reduction of 19. A solution of the mixture of four diastereomers of **19** (159.4 mg, 0.5451 mmol) in refluxing

(38) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.

benzene (11 mL) was treated with AIBN (9 mg, 0.055 mmol) and Bu_3SnH (0.59 mL, 2.2 mmol) for 0.5 h and concentrated in vacuo. The DBU workup procedure[38] was applied as follows. The residue was taken up in ether (2.2 mL), DBU (0.33 mL, 2.2 mmol) was added, and a 0.1 M solution of I_2 in ether was added to this solution until the iodine color just persisted. After filtration on a a short silica column (eluting with ether), the mixture was concentrated in vacuo. The residue was chromatographed to give two fractions. The first fraction consisted of **(2*R**,3*R**)-3-ethyltetrahydropyran-2-carboxylic acid methyl ester (28b)** (46.0 mg, 0.267 mmol, 49%) as a colorless oil: R_f 0.35 (EtOAc/hexane 1:4); IR ($CHCl_3$) 2950, 2850, 1740, 1460, 1435; ^1H NMR (250 MHz) δ 0.85 (t, J = 7.3 Hz, 3H), 1.03–1.78 (m, 6H), 1.91–2.01 (m, 1H), 3.39 (dt, J = 3.1, 11.2 Hz, 1H), 3.65 (d, J = 9.7 Hz, 1H), 3.73 (s, 3H), 3.97–4.05 (m, 1H); ^{13}C NMR (63 MHz) δ 10.55, 24.08, 25.14, 27.82, 39.35, 51.92, 67.92, 82.14, 171.47; HRMS calcd for $C_9H_{16}O_3$ 172.1099, found 172.1081. The second fraction consisted of a 87:13 mixture (according to ^1H NMR) of **28a** and **28b** (30.0 mg, 0.174 mmol, 32%) as a colorless oil: IR ($CHCl_3$) 2940, 2850, 1740, 1460, 1435, 1375. Spectral data derived from this mixture for **(2*R**,3*S**)-3-ethyltetrahydropyran-2-carboxylic acid methyl ester (28a)**: ^1H NMR (250 MHz) δ 0.84 (t, J = 7.5 Hz, 3H), 1.10–1.90 (m, 7H), 3.44 (dt, J = 11.3, 2.8 Hz, 1H), 3.71 (s, 3H), 4.04–4.10 (m, 1H), 4.09 (d, J = 2.7 Hz, 1H); ^{13}C NMR (63 MHz) δ 11.81, 19.34, 20.70, 25.46, 37.71, 51.70, 68.53, 79.42, 171.59; MS (EI) 171 $(M - H)^+$; HRMS calcd for $C_9H_{15}O_3$ 171.1021, found 171.1017.

Bu_3SnH-Reduction of 21. To a solution of **13** (178.0 mg, 0.5846 mmol) in *tert*-butylbenzene (1.2 mL) was added DTBP (26 mg, 0.18 mmol). The reaction mixture was heated at 150–155 °C for 2 h. Filtration over a short silica column (eluting with EtOAc/hexane 1:4) gave crude **21** (178.0 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 Bu_3SnH (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-enylmethoxy)acetic acid methyl ester (31)** and **(1*R**,2*R**,5*S**)-3-oxabicyclo[3.3.1]nonane-2-carboxylic acid methyl ester (30)** (13.0 mg, 0.071 mmol, 12% from **13**) as a colorless oil: R_f 0.45 (EtOAc/hexane 1:4); IR ($CHCl_3$) 2990, 2910, 2850, 1735, 1445, 1435. Spectral data derived from this mixture for **30**: ^1H NMR (200 MHz) δ 1.25–2.40 (m, 10H), 3.76 (s, 3H), 3.76–3.83 (m, 1H), 4.25 (dt, J = 11.3, 2.4 Hz, 1H), 4.35 (s, H-2); ^{13}C NMR (63 MHz) δ 21.41, 28.69, 28.80, 30.51, 31.13, 31.73, 51.73, 69.87, 77.98, 173.50. Spectral data derived from this mixture for **31**: ^1H NMR (200 MHz, characteristic signals) δ 3.42 (d, J = 6.4 Hz, $CHCH_2O$, 2H), 4.10 (s, $OCH_2C(O)$), 5.60–5.70 (m, 2H); ^{13}C NMR (63 MHz, characteristic signals) δ 24.47, 25.48, 28.36, 33.80, 68.51, 76.76, 125.81, 127.05; MS (EI) $(M - CH_3C(O)O)^+ = 156$; HRMS calcd for $C_8H_{13}O$ 125.0967, found 125.0978. The second fraction consisted of **(1*R**,2*S**,5*S**)-3-oxabicyclo[3.3.1]nonane-2-carboxylic acid methyl ester (29)** as a colorless oil (69.0 mg, 0.375 mmol, 64% from **13**): R_f 0.25 (EtOAc/hexane 1:4); IR ($CHCl_3$) 2990, 2910, 2850, 1735, 1445, 1435; ^1H NMR (200 MHz) δ 1.40–1.95 (m, 8H), 2.05–2.10 (m, 1H), 2.15–2.35 (m, 1H), 3.76 (s, 3H), 3.82 (dt, J = 11.2, 2.1 Hz, 1H), 4.09 (d, J = 11.3, 1H), 4.29 (broad s, 1H); ^{13}C NMR (63 MHz) δ 21.44, 27.64, 28.80, 30.59, 31.57, 33.65, 51.86, 73.31, 79.76, 171.85; HRMS calcd for $C_{10}H_{16}O_3$ 184.1099, found 184.1070.

Dodec-1-en-6-ol (48). To a mixture of magnesium (1.800 g, 74.0 mmol) and 7 mL of ether was slowly added a solution of 1-bromo-4-pentene (10.015 g, 67.26 mmol) in 30 mL of dry ether. After stirring for 20 min, freshly distilled heptanal (7.834 g, 68.6 mmol) in 4 mL of ether was added dropwise to this mixture at −5 °C. After stirring at room temperature for 0.5 h, the mixture was poured out on 30 g of ice, 17 mL of 15% sulfuric acid was added, and the layers were separated. After extraction of the water layer with ether (4 × 50 mL), the combined organic layers were dried ($MgSO_4$) and the solvent was removed in vacuo. Distillation (60–65 °C, 0.01 mmHg) afforded **48** as a colorless oil (9.808 g, 53.21 mmol, 79%); IR 3600, 3450 (broad), 3075, 2920, 2850, 1635, 1455, 1435; ^1H NMR (200 MHz) δ 0.88 (t, J = 6.7 Hz, 3H), 1.27–1.58 (m, 14H), 1.72 (broad s, 1H, OH), 2.00–2.10 (m, 2H), 3.55–3.63 (m, 1H), 4.90–5.05 (m, 2H), 5.70–5.90 (m, 1H); MS FAB 185 $((M + H)^+)$.

Acetoxy[(1-hexylhex-5-enyl)oxy]acetic Acid Methyl Ester (49). Alcohol **48** (5.530 g, 30 mmol) was treated with methyl glyoxylate (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%) and acetic anhydride (5.7 mL, 60 mmol) in 30 mL of pyridine for 3 h. Evaporation with toluene (three times) and flash chromatography (EtOAc/hexane 1:24) gave two fractions. The first fraction consisted of **49** (3.58 g, 11.4 mmol, 38%) as a colorless oil: R_f 0.20 (EtOAc/hexane 1:10); IR 2930, 2850, 1750, 1635, 1635, 1455, 1435, 1370; ^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), 2.15 (s, 3H), 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 $C_{17}H_{30}O_5$ 314.2093, found 314.2105. The second fraction consisted of **acetic acid 1-hexylhex-5-enyl ester** as a colorless oil (3.23 g, 14.3 mmol, 48%): R_f 0.40 (1:10); IR 3070, 2930, 2850, 1720, 1635, 1455, 1435, 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 (q, J = 6.2 Hz, 1H), 4.92–5.04 (m, 2H), 5.70–5.90 (m, 1H); MS FAB 227 $((M + H)^+)$.

Chloro[(1-hexylhex-5-enyl)oxy]acetic Acid Methyl Ester (50). A solution of **49** (3.00 g, 9.54 mmol) in 14 mL of ether and 13.6 mL of acetyl chloride was treated with hydrogen chloride gas at 0 °C for 0.5 h. Evaporation of the volatiles gave chloride **50** (2.775 g, 9.54 mmol, 100%) as a light yellow oil: IR 3070, 2950, 2930, 2850, 1760, 1630, 1455, 1435, 1295; ^1H NMR (200 MHz, mixture of two diastereomers) δ 0.88 (t, J = 6.6 Hz, 3H), 1.15–1.55 (m, 14H), 1.95–2.15 (m, 2H, 3.70–3.90 (m, 1H, 3.85 (s, 3H), 4.90–5.10 (m, 2H), 5.65–5.90 (m, 1H), 5.89 (s) and 5.90 (s, 1H).

[(Ethoxythiocarbonyl)sulfanyl][(1-hexylhex-5-enyl)oxy]acetic Acid Methyl Ester (47). To a solution of **50** (1.0673 g, 3.67 mmol) in CH_2Cl_2 (7.4 mL) was added potassium *O*-ethyl dithiocarbonate (0.627 g, 3.85 mmol). After stirring for 20 minutes, the mixture was subjected to flash chromatography to give **47** as a yellow oil (1.31 g, 3.48 mmol, 95%): R_f 0.58 (EtOAc/hexane 1:4); IR 3070, 2930, 2850, 1750, 1635, 1455, 1435; ^1H NMR (250 MHz, mixture of two diastereomers) δ 0.80–0.95 (m, 3H), 1.20–1.70 (m, 14H), 1.43 (t, J = 7.1 Hz, 3H), 1.95–2.15 (m, 2H), 3.60–3.70 (m, 1H), 3.79 (s, 3H), 4.67 (q, J = 7.1 Hz, 2H), 4.90–5.05 (m, 2H), 5.70–5.85 (m, 1H), 6.11 (s, 0.5H), 6.12 (s, 0.5H); ^{13}C NMR (63 MHz, mixture of two diastereomers) δ 13.62, 13.97, 22.49, 22.53, 23.99, 24.68, 24.74, 25.33, 29.16, 29.38, 31.67, 32.59, 33.17, 33.56, 33.71, 33.75, 52.76, 70.53, 79.47, 79.61, 85.85, 114.42, 114.61, 138.33, 138.51, 167.95, 211.54; HRMS calcd for $C_{18}H_{32}O_4S_2$ 376.1742, found 376.1745.

Cyclization of 47. To a solution of **47** (1.0810 g, 2.8705 mmol) in *tert*-butylbenzene (29 mL) was added DTBP (42 mg, 0.29 mmol). The reaction mixture was heated at 150–155 °C for 1.5 h. Flash chromatography (hexane, then EtOAc/hexane 1:6) gave two fractions. The first fraction consisted of a 56:44 mixture of diastereomers of **(2*R**,8*R**)-4-[(ethoxythiocarbonyl)sulfanyl]-8-hexyloxocane-2-carboxylic acid methyl ester (45)** as a light yellow oil (387 mg, 1.03 mmol, 36%): R_f 0.30 (EtOAc/hexane 1:10); IR 2990, 2920, 2850, 1740, 1455, 1435, 1290; ^1H NMR (250 MHz, mixture of two diastereomers) δ 0.86 (t, J = 6.8 Hz, 3H), 1.15–2.45 (m, 18H), 1.40 (t, J = 7.1 Hz, 3H), 3.40–3.60 (m, 1H), 3.72 (s), 3.75 (s, 3H), 3.65–3.90 (m, 0.56H), 4.00–4.10 (m, 0.44H), 4.18 (dd, J = 10.3, 2.3 Hz) and 4.22 (dd, J = 6.8, 5.3 Hz, 1H), 4.61 (q, J = 6.9 Hz, 2H); ^{13}C NMR (50 MHz, mixture of two diastereomers) δ 13.75, 13.78, 14.05, 22.59, 23.96, 25.91, 25.97, 29.21, 31.79, 32.69, 32.75, 33.37, 34.09, 35.15, 36.07, 36.39, 38.41, 46.94, 49.05, 52.03, 52.07, 69.65, 75.92, 79.35, 80.83, 82.54, 172.25, 213.51, 214.25; HRMS calcd for $C_{18}H_{32}O_4S_2$ 376.1742, found 376.1785. The second fraction consisted of **2-[(ethoxythiocarbonyl)sulfanyl]-8-oxotetradecanoic acid methyl ester (51)** (299 mg, 0.794 mmol, 28%) as a light yellow oil: R_f 0.15 (EtOAc/hexane 1:10); IR 2990, 2950, 2930, 2850, 1730, 1705, 1455, 1435; ^1H NMR (250 MHz) δ 0.84 (t, J = 6.9 Hz, 3H), 1.10–1.70 (m, 12H), 1.38 (t, J = 7.1 Hz, 3H), 1.75–2.00 (m, 2H),

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 (q, J = 7.1 Hz, 2H); ^{13}C 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 $C_{18}H_{32}O_4S_2$ 376.1742, found 376.1788.

(2*R,8*R**)-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 Bu_3SnH (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%): R_f 0.35 (EtOAc/hexane 1:10); IR ($CHCl_3$) 2990, 2920, 2850, 1740, 1455, 1435; ^{1}H NMR (250 MHz) δ 0.86 (t, J = 6.8 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); ^{13}C NMR (50 MHz) δ 14.08, 22.62, 24.95, 25.22, 26.11, 26.84, 29.28, 31.86, 32.04, 33.50, 36.35, 51.83, 79.39, 82.04, 173.54.

(8-Hexyloxocan-2-yl)methanol (53). A 56:44 mixture of diastereomers of **45** (345 mg, 0.916 mmol) in refluxing benzene (18 mL) was treated with AIBN (22 mg, 0.14 mmol) and Bu_3SnH (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 $LiAlH_4$ (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 ($MgSO_4$) 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**): R_f 0.15 (EtOAc/hexane 1:10); IR ($CHCl_3$) 3570, 3450 (broad), 2990, 2920, 2850, 1455; ^{1}H 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); ^{13}C 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 $C_{14}H_{28}O_2$ 228.2089, found 228.2106.

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Supplementary Material Available: Copies of ^{1}H and/or ^{13}C 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.