Pergamon

Tetrahedron 55 (1999) 3791–3802

TETRAHEDRON

New Radical Reactions of *S*-Alkoxycarbonyl Xanthates. Total Synthesis of (±)-Cinnamolide and (±)-Methylenolactocin[†]

Judith E. Forbes,[a] Radomir N. Saicic,[a] and Samir Z. Zard[a,b*]

a) Institut de Chimie des Substances Naturelles, CNRS,
91198 Gif sur Yvette, France

b) Laboratoire de Synthese Organique associe au CNRS, Ecole Polytechnique,
91128 Palaiseau, France

Received 29 July 1998; accepted 27 October 1998

Abstract: Irradiation with visible light of *S*-alkoxycarbonyl xanthates derived from various alcohols gives rise to alkoxycarbonyl radicals with bifurcate reactivity: loss of carbon dioxide leads to deoxygenated derivatives (i.e. alkyl xanthates) whereas intramolecular addition to a suitably located double bond produces lactones; these new reactions were applied to the total synthesis of (±)-cinnamolide and (±)-methylenolactocin. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: radical reactions; xanthates; lactones; terpenes

The development of efficient methods for the selective generation of radical intermediates is a prerequisite for a wider application of radical reactions in synthesis and still represents an interesting challenge to synthetic organic chemists.[1] Comparatively few methods allow, for example, the use of the hydroxyl group - a ubiquitous functionality in natural products and in synthetic intermediates- as a source of carbon radicals,[2] the most prominent and useful being by far the Barton-McCombie reaction.[2a] Alkoxycarbonyl radicals, also derived from alcohols, have also been seldom exploited; yet their intramolecular addition to suitably located alkenes constitutes a direct route to esters or lactones (corresponding to step **B** in Scheme 1 and its intramolecular version). In most cases, cyclisations to lactones have been performed reductively using stannane technology, with the loss of alkene functionality inherently accompanying C-C bond formation.[3] Given the wide distribution of unsaturated lactone subunit in natural products, the development of new methods that would allow for alkenyloxycarbonyl radical cyclization with the retention of functionality would be of interest. As part of our work on the chemistry of xanthates, we now give a full account of our studies on *S*-alkoxycarbonyl dithiocarbonates. These are easily accessible from alcohols and turn out to be a flexible source of both alkyl and alkoxycarbonyl radicals.[4]

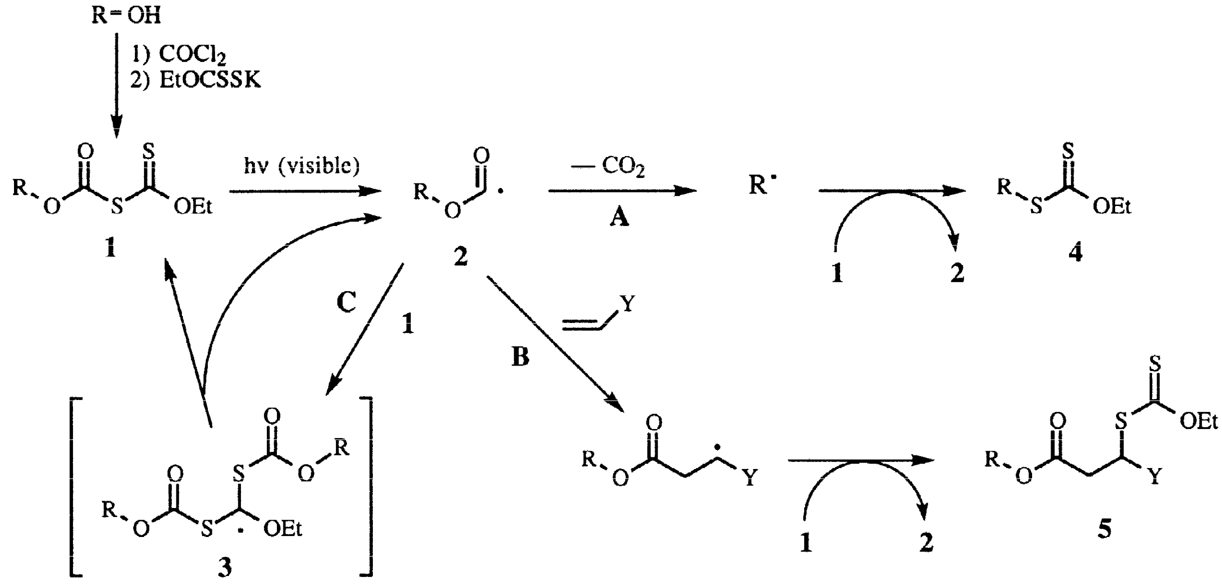
The mechanistic grounds for such an approach are outlined in Scheme 1. By analogy with *S*-acyl xanthates,[5] irradiation with visible light (or in the presence of a suitable chemical initiator)*S*-alkoxycarbonyl xanthates **1** are expected to afford the corresponding alkoxycarbonyl radicals **2**, whose further fate may involve in principle three different reaction pathways (**A**, **B**, or **C**) but only two (**A** and **B**) actually lead to a product: (1) decarboxylation (path **A**), which gives rise to an alkyl radical, is favourable when R is stabilized (e.g. for **2**, R=*t*-Bu, k~10^5-10^6 s^{-1} at 60°C);[6] (2) inter- or intramolecular addition to alkenes leading to esters or lactones (path **B**,

---

[†] *This paper is dedicated with profound respect and affection to the memory of Professor Sir Derek Barton, with remembrance of the wonderful time and chemistry he allowed us to share with him.*

PII: S0040-4020(98)01184-3

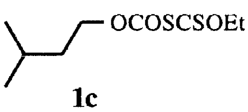
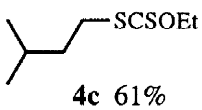
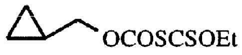
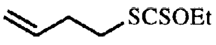
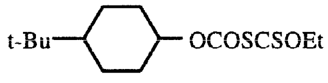
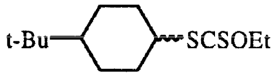
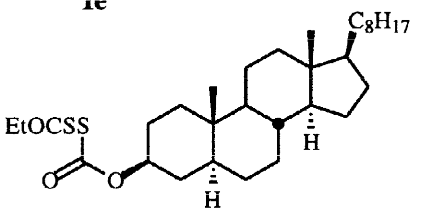
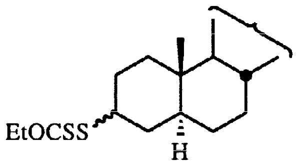
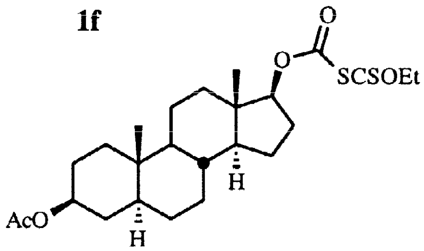
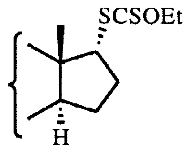
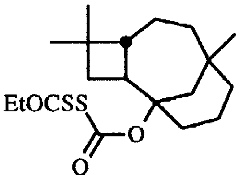
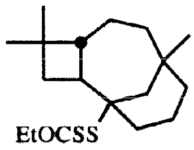
for clarity, only the intermolecular version is shown).[3,7] Paths **A** and **B** are thus in competition. Which route will prevail depends of course on the rate of decarboxylation versus the efficiency of the olefin as a radical trapping agent. While these possibilities reflect the reactivity pattern inherent in alkoxycarbonyl radicals, the synthetic efficiency of either process strongly depends on the reaction conditions, i.e. on the nature of the transfer agent. The overall process displayed in Scheme 1 represents a formal group-transfer cycle; no external transfer agent is thus needed. Unwanted radical-radical and/or radical-solvent reactions are curtailed by the fast addition of the radical intermediates to the thiono group of the precursor. In the case of the initial radical **2**, this reaction is *reversible and degenerate* (path **C**): a symmetric intermediate **3** is formed, which can only collapse to give back the same alkoxycarbonyl radical **2** and starting compound **1** (fragmentation by rupture of the strong O-Et bond is unlikely). Therefore, *the chain transfer reaction does not compete with synthetically more useful propagation steps*, allowing the radical intermediates sufficient lifetime to undergo even relatively slow reactions. This is in sharp contrast to organotin hydride mediated transformations of alkoxycarbonyl radicals, where the slow reactions of **2** — for example the loss of carbon dioxide— are suppressed by a fast, irreversible, and nonselective reduction of all radical intermediates.[2b]



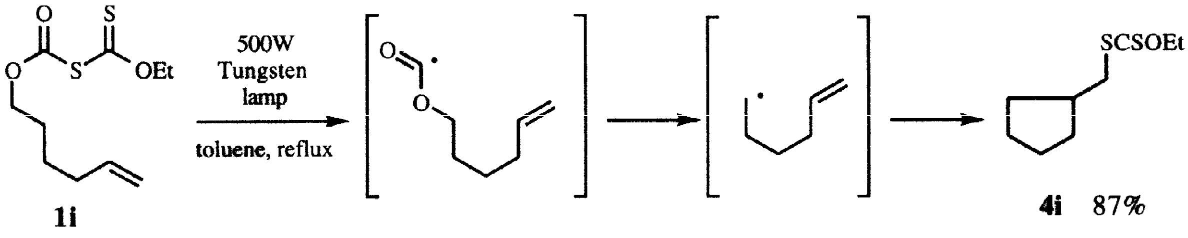
Scheme 1

To test the above mechanistic considerations, we prepared a number of S-alkoxycarbonyl xanthates (**1a-h**) from various alcohols by treating the corresponding chloroformate with potassium *O*-ethylxanthate. Upon exposure of these yellow coloured derivatives to visible light in an inert solvent (heptane, toluene) at reflux, a smooth rearrangement took place affording the expected products **4a-h** in good yield. No reaction takes place in the absence of light. The results are summarized in the Table: tertiary, secondary, and even primary alcohols were all transformed cleanly into alkyl xanthates by this procedure. In the absence of an effective trap (i. e. when path **B** is inoperative) and because path **C** is degenerate, decarboxylation (path **A**) must occur even if it is relatively slow as in the case of alkoxycarbonyl radicals derived from primary or secondary alcohols. Cyclopropylmethyl precursor **1d** afforded 3-butenyl derivative **4d**, through the intermediacy of the well known cyclopropylcarbinyl radical, thus confirming the free radical nature of the reactive intermediates. Overall, the C-O bond in the original alcohol has been replaced by a C-S bond, and this opens up possibilities for further transformations based on sulfur chemistry, including reductive desulfurisation which would represent an alternative to the Barton-McCombie deoxygenation.[2]

Table. Decarboxylative rearrangement of *S*-alkoxycarbonyl xanthates **1**.

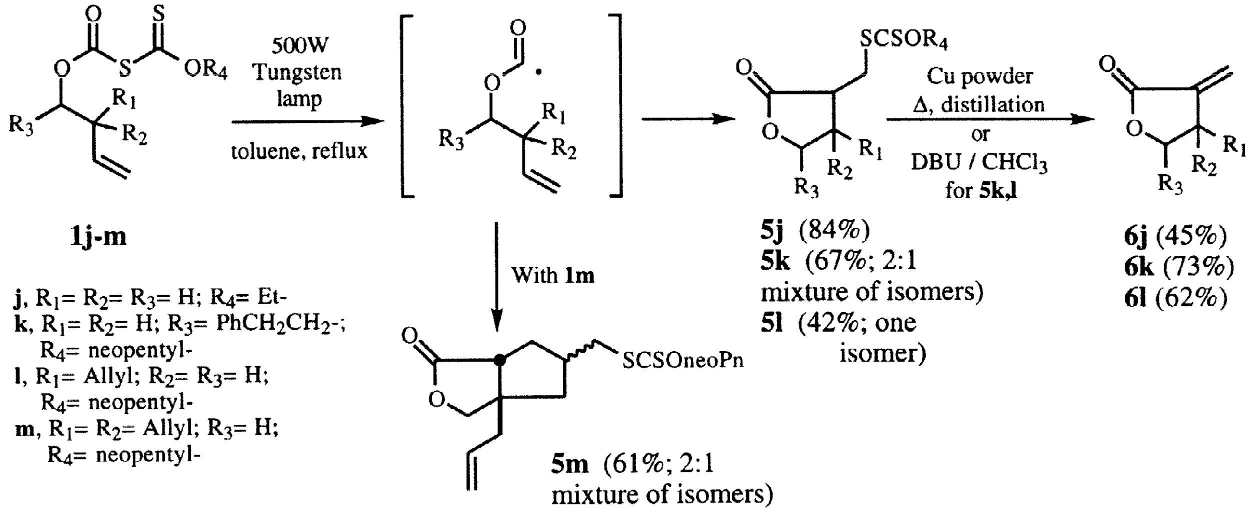
S-Alkoxycarbonyl xanthate	Reaction time (h)	Product and yield
Et−OCOSCSOEt **1a**	2.5	Et−SCSOEt **4a** 59%
$C_{16}H_{33}$−OCOSCSOEt **1b**	2.0	$C_{16}H_{33}$−SCSOEt **4b** 73%
 **1c**	2.5	 **4c** 61%
 **1d**	4.5	 **4d** 59%
 **1e**	1.0	 **4e** 52% (cis:trans = 2:1)
 **1f**	1.0	 **4f** 71% (α:β = 4:1)
 **1g**	2.5	 **4g** 83% (only 17α)
 **1h**	1.25	 **4h** 92%

The synthetic applications of this radical generating system are not restricted to the functional transformations of alcohols, as the propagation sequence can be broadened, allowing additional steps to intervene between alkyl radical formation and the chain transfer step. Thus, when 5-hexenyloxycarbonyl xanthate **1i** was submitted to the same reaction conditions, cyclopentane derivative **4i** was isolated in 87% yield (Scheme 2). Comparable yields were obtained when the reaction was performed in lower boiling cyclohexane; the possibility of obtaining cleanly, at this comparatively low temperature, a primary radical from a primary alcohol through its alkoxycarbonyl xanthate contrasts very favorably with previous work involving alkoxycarbonyl radicals, and highlights the advantages of this approach.[8]



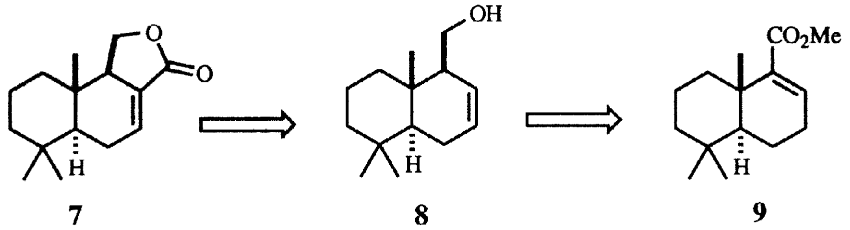
Scheme 2

We next turned our attention towards the second aforementioned possibility — C-C bond formation with the alkoxycarbonyl radicals themselves (Scheme 1, path B) — with the aim of capturing the intermediate alkenyloxycarbonyl radical **2** by a 5-exo-cyclization.[3] To our delight, irradiation of xanthate **1j** derived from 3-buten-1-ol in refluxing heptane (0.01 M) furnished butanolide **5j** in excellent yield (84%). *S*-Alkoxycarbonyl xanthates **1j-m** behaved similarly, affording the corresponding lactones in all cases. The results of these experiments are summarized in Scheme 3. Example **5k** shows that secondary derivatives undergo cyclization as well. Somewhat surprisingly diene **1l** afforded the monocyclic allyl derivative **5l**, while triene **1m** underwent tandem cyclization with the formation of the expected bicyclic product **5m** in 61% yield, as a 2:1 mixture of isomers, tentatively assigned a *cis* ring junction. The non-reductive character of this radical cyclization sequence was further exploited through the ready β–elimination of the xanthate group: heating **5j** with copper powder under vacuum caused the elimination of the xanthate group, and provided the known *exo*-methylene lactone **6j** (also called tulipalin A) in 45% yield. This transformation can also be effected at room temperature, as illustrated by the base catalyzed conversions of **5k** and **5l** to **6k** and **6l**, respectively.



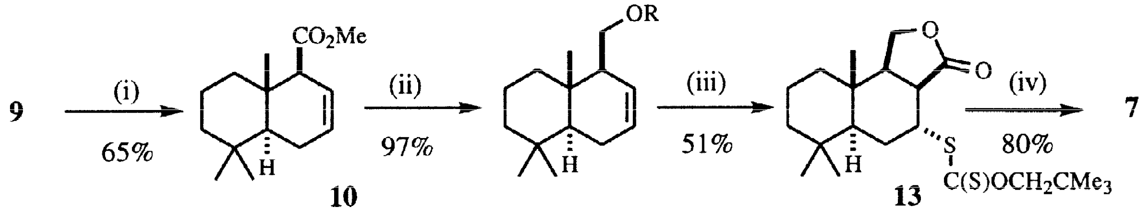
Scheme 3

Having explored briefly the potential of alkoxycarbonyl xanthates as a convenient source of alkyl and alkoxycarbonyl radicals, it seemed interesting to further demonstrate their synthetic potential by the total synthesis of two natural products: (±)-cinnamolide **7** and (±)-methylenolactocin **19**, representing two common structural patterns found in naturally occuring butenolides.[9]



Scheme 4

Cinnamolide **7**, isolated from the bark of *Cinnamosma fragrans*,[10] is a member of the drimane class of terpenoids.[11] Three syntheses have been reported.[12] Our retrosynthetic dissection of this molecule is outlined in Scheme 4. The application of the *4-butenol tobutenolide* transform simplifies the target to the unsaturated alcohol **8** structurally related to the known ester **9**.[13] This plan was put into practice as shown in Scheme 5. Ester **9**, prepared as previously described,[13] was isomerised to **10** by a kinetically controlled protonation of the corresponding ester enolate. Reduction of **10** with lithium aluminum hydride afforded the desired unsaturated alcohol **8**, which was converted into xanthate derivative **12** via chloroformate **11**, thus setting up the stage for the xanthate mediated cyclization. Upon irradiation with visible light in refluxing toluene, a clean reaction took place affording lactone **13** as a single diastereoisomer in 51% isolated yield. Treatment of **13** with DBU gave (±)-cinnamolide as a colourless crystalline compound in 80% yield (mp 83-5°C, lit.[12a]: 85-85.5°C, spectral properties identical with those previously reported).[10]



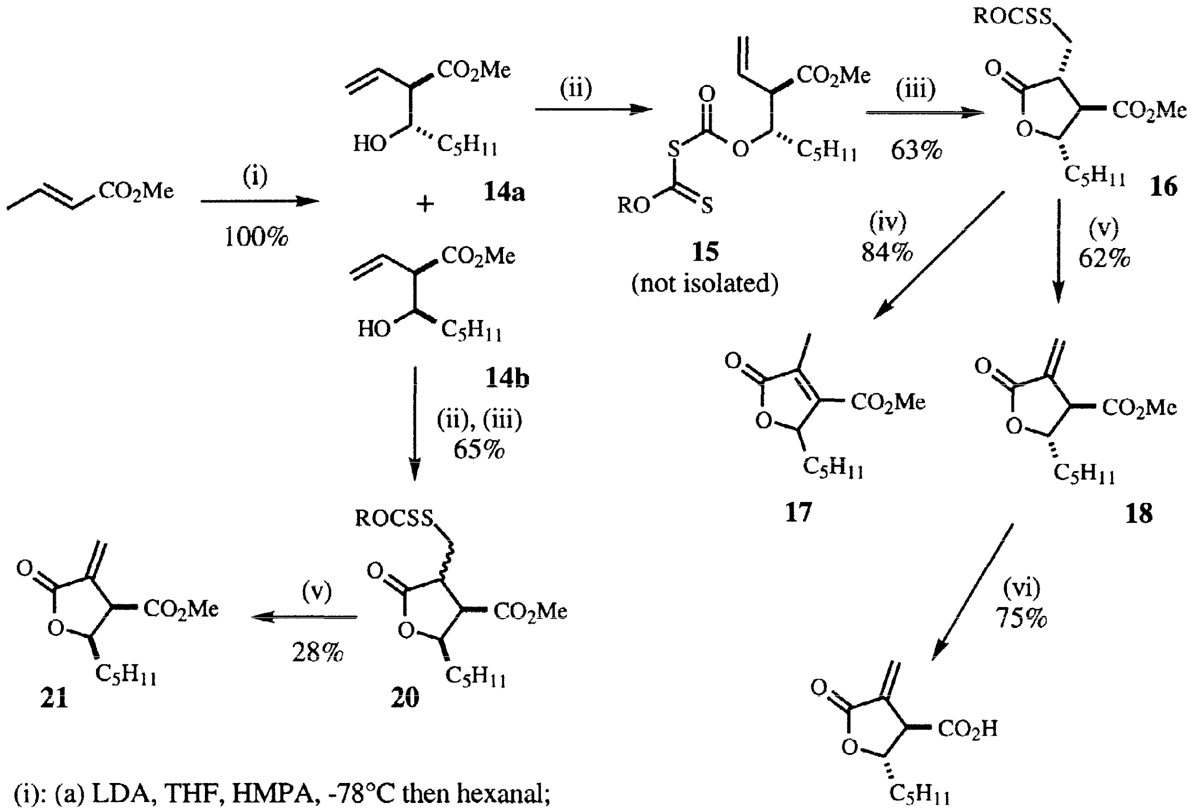
8, R = H
11, R = COCl
12, R = $C(O)SC(S)OCH_2CMe_3$

(i): (a) LDA, THF, HMPA, -78°C; (b) HCl aq. (ii): $LiAlH_4$; (iii): (a) $COCl_2$, toluene, THF; (b) $NaSC(S)OCH_2CMe_3$, acetone; (c) hν, toluene, reflux; (iv) DBU, $CHCl_3$.

Scheme 5

Methylenolactocin **19**, isolated from the culture filtrate of *Penicillium* sp.,[14] belongs to the large group of α-methylene-γ-butyrolactone antibiotics. Its antitumor and selective antibacterial activity,[14] along with its relatively high level of functionalization and proclivity towards isomerisation make this small molecule an interesting synthetic target. Several total and formal syntheses have been reported.[15] A retrosynthetic analysis similar to that for cinnamolide indicated unsaturated alcohol **14a** as a suitable precursor for the application of the xanthate protocol; this compound could be obtained in a single step by an aldol reaction between methyl crotonate and hexanal (Scheme 6).

Indeed, addition of methyl crotonate anion to hexanal gave a quantitative yield of **14a** and **14b** as a 1:1 mixture.[16] No attempt was made to optimize the stereoselectivity of the reaction, as the chromatographic separation of the isomers was reasonably effective. Treatment of **14a** with phosgene, followed by sodium S-neopentyl xanthate afforded radical precursor **15** which upon irradiation with visible light yielded the crystalline cyclic xanthate derivative **16** as a single diastereoisomer (63% from **14a**, Scheme 6). It is interesting in this respect to note that when isomer **14b** was subjected to the same sequence of reactions (ii, iii), a 2:1 mixture of diastereoisomers **20** was obtained. The relative stereochemistry of intermediates **14a**, **14b**, **16** and **20** was deduced after transformation into methylenolactocin methyl ester **18** and *epi*-methylenolactocin methyl ester **21**, whose configurations were established by NOE experiment, and also by comparison of the NMR spectra of **18** with the literature data.[15f] The stereochemical outcome of the two cyclizations can be explained by assuming a chair-like transition state with strong preference for all substituents to adopt pseudoequatorial positions.[17] In this way, a single all-*trans* isomer **16** is obtained from **14a** via **22**, whereas conformational equilibrium between **23a** and **23b** gives rise to the mixture of diastereoisomers **20** (Scheme 7).

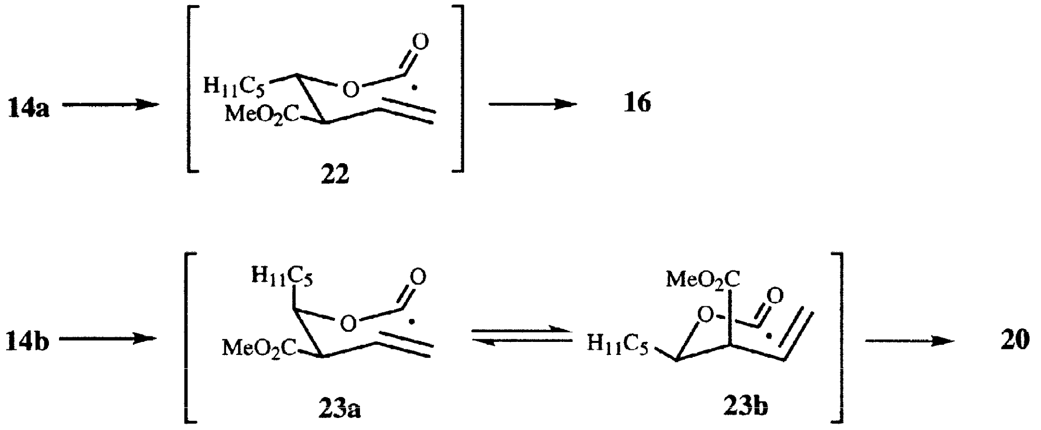


19 (±) Methylenolactocin

(i): (a) LDA, THF, HMPA, -78°C then hexanal;
(ii): (a) $COCl_2$, toluene, THF; (b) $NaSC(S)OCH_2CMe_3$, acetone; (iii) hν, toluene, reflux; (iv) DBU, $CHCl_3$;
(v) Cu / Δ, distillation; (vi) HCl, butanone, reflux.
R in **15**; **16**; and **20** = Me_3CCH_2-

Scheme 6

Unfortunately, all our attempts to accomplish the xanthate elimination from lactone **16** under basic conditions as in the case of compounds **5k,l** and in the cinnamolide synthesis were unsuccessful: we invariably obtained regioisomer **17** as the only product. It appeared that methyl ester **18** was much too base labile to survive the reaction conditions. Fortunately, pyrolytic elimination proved feasible in this case and, after some experimentation, we found that heating **16** in presence of copper powder and distillation of the product as formed afforded methylenolactocin methyl ester **18** in 62% isolated yield. Similarly, pyrolysis of **20** gave *epi*-methylenolactocin methyl ester, albeit in lower yield (28%, not optimized). Finally, acidic hydrolysis of **18** under conditions described previously [15f] furnished crystalline (±)-methylenolactocin **16** (mp 54-6°C, recryst. from ethyl acetate-hexane, lit.[15g]: oil), with ^{1}H and ^{13}C NMR spectra identical to published data.[14]



Scheme 7

In summary, we have accomplished perhaps the shortest synthesis of (±)-methylenolactocin; our approach also demonstrates the applicability of the xanthate based radical process for the construction of delicate lactone containing structures. More generally, the transformations implying alkoxycarbonyl radicals described above illustrate two advantageous features of the xanthate method, namely a relatively long lifetime given to the radical intermediates, and the non-reductive character of the last propagation step, which enables further manipulation of the adducts.

EXPERIMENTAL

Unless otherwise stated, nmr spectra were recorded on a Bruker 200MHz instrument; chemical shifts are given in ppm using trimethylsilane as reference and coupling constants are in Hertz. IR spectra were recorded on a Nicolet FT instrument. Melting points are uncorrected. $[\alpha]_D$ are for chloroform solutions (c=1). Reagents and solvents were purified according to standard procedures. Compound **1a** was prepared following the literature procedure;[18] xanthates **4a** and **4b** are known.[19]

General procedure for the preparation of S-alkoxycarbonyl xanthates (1b-m) from the corresponding alcohols according to scheme 1 : THF (4 ml) was added to a toluene solution of phosgene (3.7 ml of a commercial 1.9 M solution; 7 mmol), followed by dropwise addition of the solution of the alcohol (1 mmol) in THF (4 ml). The reaction mixture was stirred at room temperature for an additional 0.5-4 h (TLC monitoring). Evaporation of the excess phosgene and solvent *in vacuo* afforded the crude alkyl chloroformate in virtually quantitative yield; this was used in the next step without further purification.

A solution of potassium *O*-ethyl xanthate or sodium *O*-neopentyl xanthate (0.9-1 mmol) in acetone (5 ml) was added dropwise with stirring to a solution of the alkyl chloroformate (0.9-1 mmol) in acetone (5 ml) at room temperature.[20] After additional stirring (0.5-2 h) at the same temperature (TLC monitoring), most of the acetone was evaporated under reduced pressure and the reaction mixture was partitioned between water and dichloromethane. The organic layer was then washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* afforded *S*-alkoxycarbonyl xanthates **1** as bright-yellow oils in most cases; these were used without further purification, except for **1f,g,h** which were crystalline and could be further purified for microanalysis.

S-Alkoxycarbonyl xanthate (1f). This pale yellow solid was prepared from cholestanol according to the general procedure in 79% yield; m.p. 88-89.5°C (from acetone); $[\alpha]_D$ +9.7; ν_{max} (nujol): 1740, 1725 cm^{-1}; ^{1}H NMR: δ_H 4.70 (*q*, J = 7.1, 2H), 4.84 (m, 1H). Anal. Calc. for $C_{31}H_{52}O_3S_2$: C, 69.40; H, 9.70%. Found: C, 69.42; H, 9.85%.

S-Alkoxycarbonyl xanthate (1g). This pale yellow solid was prepared from 1β-acetoxy-17β-hydroxy-androst-5-ene according to the general procedure in 52% yield; m.p. 77.5-79.5°C (from acetone); $[\alpha]_D$

-31; ν_{max} (nujol): 1740, 1712 cm^{-1}; ^{1}H NMR: δ_H 0.82 (*s*, 3H), 1.03 (*s*, 3H), 1.49 (*t*, J = 7.1, 3H), 2.03 (*s*, 3H), 4.60 (*m*, 1H), 4.70 (*m*, 1H), 4.72 (*q*, J = 7.1, 2H), 5.41 (*bd*, J = 4.8, 1H). Anal. Calc. for $C_{25}H_{36}O_5S_2$: C, 62.50; H, 7.50%. Found: C, 62.59; H, 7.43%.

S-Alkoxycarbonyl xanthate (1h). A solution of phosgene (0.68 mmol) in toluene was added dropwise to a solution of β-caryophyllene alcohol (0.45mmol) and pyridine (0.81 mmol) in dry ether (10 ml) at 0°C and the mixture stirred at 0°C for 2 hours. The ether was blown off with a stream of nitrogen at 0°C and the residue dissolved in cold acetone (100 ml). A solution of potassium *O*-ethyl xanthate (0.45 mmol) was added dropwise and the mixture stirred at 0°C for 1 hour. Most of the acetone was removed *in vacuo*, and the residue treated with water and extracted with dichloromethane. The combined extracts were dried, concentrated, and the residue purified by column chromatography (ether / pentane 1:20) to give **1h** as a yellow solid (0.2 mmol, 45%; of the starting alcohol was also recovered); m.p. 133-134°C (from acetone); $[\alpha]_D$ +38; ν_{max} (nujol): 1735 cm^{-1}; ^{1}H NMR: δ_H 0.88-2.50 (*m*, 16H), 0.92 (*s*, 3H), 0.98 (*s*, 3H), 1.06 (*s*, 3H), 1.47 (*t*, J = 7.1, 3H), 4.69 (*q*, J = 7.1, 2H). Anal. Calc. for $C_{19}H_{30}O_3S_2$: C, 61.62; H, 8.11%. Found: C, 61.43; H, 8.12%.

General procedure for the photochemically induced transformation of S-alkenyloxycarbonyl xanthates: *S*-Alkenyloxycarbonyl xanthates **1a-m** (1 mmol) were dissolved in degassed heptane or toluene (10 ml), and irradiated with a 500 W tungsten filament lamp, under reflux in an argon atmosphere. The progress of the reaction, indicated by the fading of the initially bright-yellow colour of the solution, was further monitored by TLC. After the reaction was complete (2.5-9 h), the solvent was evaporated *in vacuo*, and the product purified by flash chromatography on silica gel.

S-2-Methylpropyl-O-ethyl dithiocarbonate (4c). This colourless liquid was prepared from S-alkoxycarbonyl xanthate **1c** according to the general procedure in 61% yield; ν_{max} (film): 1200, 1100, 1045 cm^{-1}; ^{1}H NMR: δ_H 1.01 (*d*, J = 6.6, 6H), 1.42 (*t*, J = 7.1, 3H), 1.97 (*m*, 1H), 3.03 (*d*, J = 6.7, 2H), 4.65 (*q*, J = 7.1, 2H).

S-3-Butenyl-O-ethyl dithiocarbonate (4d). This colourless liquid was prepared from S-alkoxycarbonyl xanthate **1d** according to the general procedure in 59% yield; ν_{max} (film): 1625, 1200, 1100, 1040 cm^{-1}; ^{1}H NMR: δ_H 1.42 (*t*, J = 7.1, 3H), 2.45 (*dt*, J = 7.3 and J'= 14.3, 2H), 3.19 (*t*, J = 7.3, 2H), 4.65 (*q*, J = 7.1, 2H), 5.05-5.16 (*m*, 2H), 5.72-5.89 (*m*, 1H).

S-4-t-Butylcyclohexyl-O-ethyl dithiocarbonate (4e). This colourless liquid was prepared from S-alkoxycarbonyl xanthate **1e** according to the general procedure in 52% yield; it consisted of a 2:1 mixture of *cis*- and *trans*- isomers; ν_{max} (film): 1200, 1100, 1040 cm^{-1}; ^{1}H NMR: δ_H 0.84 (*s*, 9H), 0.94-2.23 (*m*, 9H), 1.42 (*t*, J = 7.1, 3H), 3.49 (*m*, 0.33H), 4.12 (*br s*, 0.66H) 4.64 (*q*, J = 7.1, 2H). Anal. Calc. for $C_{13}H_{24}OS_2$: C, 60.00; H, 9.23%. Found: C, 60.05; H, 9.37%.

S-(Cholestan-3β-yl)-O-ethyl dithiocarbonate (4f). This compound was obtained from *S*-alkoxycarbonyl xanthate **1f** according to the general procedure as a 4:1 mixture of epimers in 71% yield; recrystallisation from acetone gave the major 3α-isomer as a white solid; m.p. 103-106°C; $[\alpha]_D$ +30; ν_{max} (nujol): 1200, 1095, 1045 cm^{-1}; ^{1}H NMR: δ_H 4.15 (br s, equatorial hydrogen on C-3; in the minor isomer the corresponding hydrogen appears as a broad *m* at 3.59), 4.63 (*q*, J = 7.1, 2H). Anal. Calc. for $C_{30}H_{52}OS_2$: C, 73.17; H, 10.57%. Found: C, 72.91; H, 10.68%.

S-(1β-Acetoxy-androst-5-en-17α-yl)-O-ethyl dithiocarbonate (4g). This white crystalline solid was prepared from *S*-alkoxycarbonyl xanthate **1g** according to the general procedure in 83% yield; m.p. 185-186°C (from acetone); $[\alpha]_D$ -26; ν_{max} (nujol): 1720, 1235, 1200, 1090, 1035 cm^{-1}; ^{1}H NMR: δ_H 0.94 (*s*, 3H), 1.02 (*s*, 3H), 1.42 (*t*, J = 7.1, 3H), 2.03 (*s*, 3H), 3.92 (*dd*, J = 2.1 and J'= 8.8, 1H), 4.6 (*m*, 1H), 4.62 (*q*, J = 7.1, 2H), 5.37 (*bd*, J = 4.8, 1H). Anal. Calc. for $C_{24}H_{36}O_3S_2$: C, 66.00; H, 8.25%. Found: C, 65.97; H, 8.22%.

Dithiocarbonate (4h). This colourless oil was prepared from *S*-alkoxycarbonyl xanthate **1h** according to the general procedure in 92% yield; $[\alpha]_D$ +57; ν_{max} (film): 1210, 1100, 1030 cm^{-1}; ^{1}H NMR: δ_H 0.82-2.49 (*m*, 16H), 0.86 (*s*, 3H), 0.98 (*s*, 6H), 1.44 (*t*, J = 7.1, 3H), 4.5-4.7 (2*q*, J = 7.1, 2H).

S-Cyclopentylmethyl-O-ethyl dithiocarbonate (4i). This colourless oil was prepared from *S*-alkoxycarbonyl xanthate **1i** according to the general procedure in 87% yield after silica gel chromatography (petroleum ether); ν_{max} (film): 1195, 1095, 1035 cm^{-1}; ^{1}H NMR: δ_H 0.88-2.18 (*m*, 9H), 1.42 (*t*, J = 7.1, 3H), 3.15 (*d*, J = 7.3, 2H), 4.64 (*q*, J = 7.1, 2H). Anal. Calc. for $C_9H_{16}OS_2$: C, 53.15; H, 7.83%. Found: C, 52.94; H, 7.84%.

Lactone (5j). This colourless liquid was prepared from *S*-alkoxycarbonyl xanthate **1j** according to the general procedure in 84% yield after silica gel chromatography (petroleum ether); ν_{max} (film): 1780, 1230, 1160, 1125, 1062, 1035 cm^{-1}; ^{1}H NMR: δ_H 1.44 (*t*, J = 7.1, 3H), 2.07-2.23 (*m*, 1H), 2.41-2.52 (*m*, 1H), 2.95-3.15 (*m*, 2H), 3.27 (*dd*, J = 8.2 and J'= 14.1, 1H), 3.73 (*dd*, J = 8.8 and J'= 14.1, 1H), 4.14-4.27 (*m*, 1H), 4.35-4.44 (*m*, 1H), 4.67 (*q*, J = 7.1, 2H). This compound was used without further purification for the synthesis of tulipalin A **6j**.

Lactone (5k). According to the general procedure and starting from 823 mg (4.67 mmol) of alcohol **4j**, after purification by flash chromatography (eluent: 2% EtOAc in toluene), 804 mg (67 %) of **7k** was obtained as a colourless oil; IR (film): 1773, 1226, 1195, 1067 cm^{-1}; ^{1}H NMR (min = minor isomer; maj = major isomer): 7.4-7.05 (*m*, 5H); 4.6-4.5 (*m*, 1H, C*H*-OC=O, min); 4.4-4.2 (*m*, 1H, C*H*-OC=O, maj); 4.26 (*s*, 2H, C*H*$_2$-O); 3.75 (*dd*, J_1=14, J_2=4.9, 1H, *H*CHSC(S), maj); 3.7 (*dd*, J_1=14, J_2=4.8, 1H, *H*CHSC(S), min); 3.27 (*dd*, J_1=14, J_2=7.2, 1H, HC*H*SC(S), min); 3.23 (*dd*, J_1=14, J_2=7, 1H, HC*H*SC(S), maj); 3.2-3.0 (*m*, 1H, *H*C-C=O); 2.9-2.7 (*m*, 2H, *H*$_2$CPh); 2.5-1.9 (*m*, 4H); 1.1 (*s*, 9H); ^{13}C NMR: 214 (C=S; maj); 213.88 (C=S, min); 176.64 (C=O, min); 176.38 (C=O; maj); 140.53 (C-*Ar*; maj); 140.43 (C-*Ar*, min); 128.55 (CH-*Ar*); 128.39 (CH-*Ar*); 126.21 (CH-*Ar*); 83.83 (^{t}BuC*H*$_2$O, min); 83.76 (^{t}BuC*H*$_2$O, maj); 77.87 (*H*COC=O, maj); 77.74 (*H*COC=O, min); 40.85 (*CH*-C=O, maj); 38.87 (*CH*-C=O, min); 37.15 (CH_2, min); 37.0 (CH_2, maj); 35.81 (CH_2, min); 35.35 (CH_2, maj); 34.5 (CH_2, maj); 32.49 (CH_2, min); 31.82 (CMe_3, both isomers); 31.5 (CH_2, both isomers); 26.5 (C*Me*$_3$, both isomers). This compound was used without further purification for the preparation of **6k**.

Lactone (5l). This compound was obtained as a colourless oil in 42 % yield (eluent: pure toluene); IR (film): 1775, 1223, 1188, 1068 cm^{-1}; ^{1}H NMR: 5.85-5.6 (*m*, 1H, *H*C=CH$_2$); 5.2-5.05 (*m*, 2H, HC=C*H*$_2$); 4.38 (app.*t*, J=8.4, *H*CH-OC=O); 4.27 (*s*, 2H, ^{t}BuC*H*$_2$O); 3.39 (app.*t*, J=8.4, HC*H*-OC=O); 3.65 (*dd*, J_1=14.5, J_2=5.6, 1H, *H*CHSC=S); 3.46 (*dd*, J_1=14.5, J_2=5.6, 1H, HC*H*SC=S); 2.8-2.15 (*m*, 4H); 1.05 (*s*, 9H); ^{13}C NMR: 214; 176.96; 133.76; 118.21; 83.86; 70.96; 44.33; 39.72; 36.15; 34.65; 31.86; 26.38. It was used without further purification for the preparation of **6l**.

Lactone (5m). This compound was obtained as a light yellow oil in 61% yield and as a 2:1 mixture of isomers after Kugelrohr distillation under vacuum (220°/0.08 mmHg); IR (film): 1772 cm^{-1}; ^{1}H NMR: 5.8-5.6 (*m*, 1H); 5.25-5.1 (*m*, 2H); 4.25 (*s*, 2H); 4.2-3.9 (*m*, 2H, -*H*2C-OC=O); 3.19 (app.*d*, J= 6.9; 1H, *H*2C-SC=S); 2.75-1.30 (series of *m*, 8H); 1.05 (*s*, 9H); ^{13}C NMR (for the major isomer): 214.35; 179.7; 132.52; 119.46; 83.31; 75.59; 50.92; 49.12; 42.52; 40.88; 40.20; 38.89; 34.39; 31.73; 26.55. Anal. Calcd. for $C_{17}H_{26}O_3S_2$: C 59.63; H 7.66. Found: C 59.68; H 7.76

Tulipalin A (6j). A mixture of xanthate **5j** (0.22 mmol) and copper powder (1.0 g) was heated in an oven (oven temp. 175-180°C) under vacuum (15 mmHg). Lactone **6j** thus distilled as formed and was obtained as a colourless liquid (0.10 mmol, 46%); ν_{max} (film): 1760, 1666 cm^{-1}; ^{1}H NMR: δ_H 2.99 (*m*, 2H), 4.37 (*t*, J = 7.3, 2H), 5.68 (*t*, J = 2.5, 1H), 6.26 (*t*, J = 2.9, 1H); these were essentially identical with previously reported data for tulipalin A.[21]

3-Methylene-5-(2-phenylethyl)-2-tetrahydrofuranone (6k). DBU (61 mg; 0.40 mmol) was added to a solution of lactone **5k** (60 mg; 0.16 mmol) in chloroform (3 ml), and the reaction mixture stirred for 2 h at room temperature The solution was then diluted with chloroform, washed successively with 1% HCl, aqueous $NaHCO_3$, and water, and the organic layer dried over $MgSO_4$. Concentration under reduced pressure and purification of the residue by flash chromatography (SiO_2; eluent: 10% EtOAc in toluene) gave **6k** as a colourless oil (24 mg, 73%); IR (film): 1758, 1666, 1602 cm^{-1}; ^{1}H NMR: 7.37-7.2 (m, 5H); 6.22 (app. *t*, J=3, 1H, *H*CH=C, *Z* to C=O); 5.62 (app. *t*, J=3, 1H, HC*H*=C, *E* to C=O); 4.51 (*m*, 1H, *H*COC=O); 3.05 (*m*, 1H);

2.78 (*m*, 2H); 2.57 (*m*, 1H); 2.1-1.9 (*m*, 2H); ^{13}C NMR: 170.13; 140.53; 134.45; 128.46; 128.36; 126.11; 122.04; 76.41; 37.96; 33.42; 33.21.

3-Methylene-4-(2-propenyl)-2-tetrahydrofuranone (6l). Lactone **6l** was prepared in the same way as **6k**. Purification by flash chromatography (SiO_2; eluent: 20% EtOAc in hexane) afforded **6l** as a colourless oil in 62% yield; IR (film): 1764, 1666, 1643 cm^{-1}; ^{1}H NMR: 6.3 (*d*, J=2.8, 1H, *H*CH=CC=O *Z* to C=O); 5.83-5.68 (*m*, 1H, *H*C=CH$_2$); 5.66 (*d*, J=2.3, 1H, *H*CH=CC=O *E* to C=O); 5.18-5.1 (*m*, 2H, HC=C*H*$_2$); 4.43 (*dd*, J_1=9.1, J_2=8.3, 1H, *H*CH-OC=O); 4.02 (*dd*, J_1=9.1, J_2=5.42, 1H, HC*H*-OC=O); 3.17 (*m*, 1H); 2.44 (m, 1H); 2.32 (m, 1H); ^{13}C NMR: 172.0; 137.68; 133.54; 122.27; 118.25; 70.31; 37.85; 37.84.

Ester (10). A solution of BuLi in hexane (2 ml of 1.6 M solution; 3.2 mmol) was added at -20°C, under an argon atmosphere, to a solution of diisopropylamine (324 mg; 3.30 mmol) in dry THF (5 ml), and the resulting solution stirred for 20 min at that temperature. The reaction mixture was then cooled to -78°C, HMPA (627 mg; 3.50 mmol) was added and, after stirring for an additional 30 min., a solution of **9**[13] (669 mg; 2.84 mmol) in dry THF (3 ml) was added dropwise. After further stirring for 15 min at -78°C, 5% aqueous HCl (20 ml) was added all at once and the mixture allowed to reach room temperature. Work-up afforded a mixture of **9** and **10** in a 5:1 ratio (584 mg, 77%). Purification by flash chromatography (SiO_2; eluent: toluene) afforded **10** as a colourless oil (283 mg, 42%; 65% based on recovered starting ester **9**); a fraction (234 mg) containing a mixture of **9** and **10** was also isolated; IR (film): 1729 cm^{-1}; ^{1}H NMR: 5.8-5.7 (*m*, 1H); 5.56-5.5 (*m*, 1H); 3.69 (*s*, 3H); 2.98-2.91 (*m*, 1H); 2.15-1.8 (*m*, 2H); 1.6-1.2 (series of *m*, 7H, 3 x CH$_2$ + CH); 0.92 (*s*, 3H); 0.9 (*s*, 3H); 0.89 (*s*, 3H); ^{13}C NMR: 174.14; 128.06; 123.85; 57.29; 51.26; 49.31; 42.20; 40.10; 36.16; 33.12; 23.51; 21.71; 18.67; 14.79. This material was used as such in the next step.

Alcohol (8). A solution of ester **10** (260 mg; 1.10 mmol) was slowly added to a solution of $LiAlH_4$ (44 mg) in THF (1 ml) at room temperature, and the mixture was stirred for 2 h at the same temperature. Work-up as usual afforded alcohol **8** as a white solid (223 mg, 97%) and this was used directly in the next step; IR (in CH_2Br_2): 3354 cm^{-1}; ^{1}H NMR: 5.83-5.75 (*m*, 1H); 5.62 (app. *d*, J=10, 1H); 3.84 (*dd*, J_1=10, J_2=5, 1H, *H*CH-OH); 3.37 (app. *t*, J=10, 1H, HC*H*-OH); 2.15-1.8 (*m*, 3H, allylic); 1.6-1.1 (series of *m*, 7H); 0.91 (*s*, 3H); 0.89 (*s*, 3H); 0.78 (*s*, 3H); ^{13}C NMR: 127.42; 126.6; 62.73; 53.98; 49.71; 42.25; 39.59; 35.12; 33.33; 32.92; 23.85; 21.92; 18.71; 14.28.

Xanthate (13). Alcohol **8** (210 mg, 1 mmol) was converted into *S*-alkoxycarbonyl xanthate **12** according to the general procedure. Purification by flash chromatography (SiO_2; 2% EtOAc in toluene) afforded lactone **13** (183 mg, 51%) as a white solid; IR (CH_2Br_2): 1771 cm^{-1}; ^{1}H NMR: 4.59 (*t*, J=2.7, 1H); 4.27 (*s*, 2H); 4.23 (*d*, J= 9.5,1H); 4.13 (*dd*, J_1=9.5, J_2=5.6, 1H); 2.94 (*d*, J=7.3, 1H); 2.25 (*dd*, J_1=6.7, J_2=5.6, 1H); 2.4-1.05 (series of *m*, 9H); 1.03 (s, 9H); 0.89 (*s*, 3H); 0.87 (*s*, 3H); 0.79 (*s*, 3H); ^{13}C NMR: 212.28; 175.62; 83.32; 67.49; 47.80 (two CH superimposed); 44.00; 43.78; 41.49; 39.93; 35.36; 33.09; 32.53; 31.70; 26.47; 24.20; 21.72; 17.83; 14.38. This material was used directly for the next step.

(±)-Cinnamolide (7). DBU (206 mg; 1.35 mmol) was added with stirring to a solution of **13** (175 mg; 0.44 mmol) in chloroform (5 ml) at room temperature. The reaction was complete within 15 min, as indicated by TLC. Work-up as for **6k** followed by purification by flash chromatography (SiO_2; 10% EtOAc in toluene) afforded (±)-cinnamolide **9** as a crystalline white solid (82 mg, 80%) ; m.p. 83-4°C (from hexane; lit.[10] 85-85.5°C); spectral data identical with those reported in the literature.[10b]

3-Carboxymethyl-4-hydroxy-1-nonene (14a) and (14b). A solution of LDA in THF (40 ml), prepared from diisopropylamine (2.27 g; 25 mmol), BuLi (15 ml of 1.6 M solution in hexane; 22 mmol) and HMPA (4.03 g; 22.5 mmol) as described for **10**. A solution of methyl crotonate (2.0 g; 20 mmol) in THF (5 ml) was then added dropwise at -78°C. After stirring for 5 min., a solution of n-hexanal (2.0 g; 10 mmol) in THF (2 ml) was added in one portion. The mixture was allowed to reach -20°C, then cooled again to -70°C and quenched with aqueous NH_4Cl (40 ml), added all at once. Standard work-up afforded alcohol **17** (4.0g; 100%) as a 1:1 mixture of **14a** and **14b**. Flash chromatography (SiO_2; 10% EtOAc in toluene) afforded pure **14a** (1.07 g), a mixture of **14a** and**14b** (1.26 g) and pure **14b** (483 mg); **14a**: IR (film): 3486, 1737, 1639 cm^{-1}; ^{1}H NMR: 6.0-5.85 (*m*, 1H); 5.35-5.2 (*m*, 2H); 3.9 (br. *s*, 1H); 3.73 (*s*, 3H); 3.08 (*dd*, J_1=9.5;J_2=4.6, allylic H); 2.58 (*d*,

J=3.4, 1H); 1.6-1.2 (*m*, 8H); 0.9 (*t*, J=6.5, 3H); ^{13}C NMR: 173.6; 131.79; 120.49; 71.50; 55.82; 52.18; 34.17; 31.80; 25.38; 22.68; 14.12.
14b: IR (film): 3467, 1737, 1639 cm^{-1}; ^{1}H NMR: 5.9-5.75 (*m*, 1H); 5.3-5.2 (*m*, 2H); 3.85 (*m*, 1H); 3.73 (*s*, 3H); 3.12 (app. *t*, J=8, allylic H); 2.65 (br. *s*, 1H)1.6-1.2 (*m*, 8H); 0.9 (*t*, J=6.5, 3H); ^{13}C NMR: 173.68; 133.00; 119.32; 72.35; 57.01; 52.00; 34.52; 31.73; 25.10; 22.62; 14.04.

Lactone (16). Alcohol **14a** (416 mg; 2.08 mmol) was converted into *S*-alkoxycarbonyl xanthate **15** and the latter irradiated according to the general procedure. Purification by flash chromatography (SiO_2; 20% EtOAc in heptane) afforded lactone **16** as a white solid (442 mg; 63%); m.p. 79-81°C (heptane); IR (CH_2Br_2): 1775, 1736 cm^{-1}; ^{1}H NMR: 4.4 (*dt*, J_1=9.15, J_2=4.23, 1H, C*H*OC=O); 4.27 (AB quart., J_1=15.5, J_2=10.4, 2H, ^{t}BuC*H*$_2$O); 3.78 (*s*, 3H); 3.76 (*dd*, J_1=14, J_2=4.75, 1H, *H*CHSC=S); 3.55 (*m*, 1H, SCH$_2$C*H*C=O); 3.43 (*dd*, J_1=14, J_2=6.75, 1H, HC*H*SC=S); 2.93 (*dd*, J_1=11.1, J_2=9.31, 1H, O$_2$C-C*H*); 1.85-1.62 (*m*, 2H); 1.55-1.3 (series of *m*, 6H); 1.0 (*s*, 9H); 0.89 (*t*, J=6.5, 3H); ^{13}C NMR: 213.93; 174.37; 170.81; 83.97 (^{t}Bu*C*H$_2$O); 80.19 (*C*HOC=O); 52.8; 51.21; 44.57; 34.7; 34.53; 31.88; 31.33; 26.51; 24.79; 22.4; 13.91. Anal. Calcd. for $C_{18}H_{30}O_5S_2$: C 55.36; H 7.74. Found: C 55.56; H 7.52

Lactone (20). Alcohol **14b** (416 mg; 2.08 mmol) was transformed into lactone **20** following exactly the same procedure as for **14a**. Purification by flash chromatography (SiO_2; 20% EtOAc in heptane) afforded lactone **20** as a colourless oil (482 mg, 65%); it consisted of a 2:1 mixture of isomers; IR (film): 1783, 1741 cm^{-1}; ^{1}H NMR: 4.7 (app. *t*, 1H, C*H*OC=O); 4.37 (br. *s*, 2H); 3.84-3.68 (*m*+*s*, 4H, OMe + *H*CH-SC=S); 3.63-3.35 (*m*, 2H, HC*H*-SC=S + SCH$_2$C*H*C=O); 3.24 (*dd*, 1H); 1.7-1.2 (series of *m*, 8H); 1.0 (*s*, 9H); 0.9 (br. *s*, 3H); ^{13}C NMR (of the major isomer): 213.75; 174.72; 169.61; 83.91; 77.86; 52.33; 47.82; 41.4; 34.19; 31.42; 31.14; 30.86; 26.36; 25.03; 22.24; 13.77.

2(H)-3-Methyl-4-carboxymethyl-5-pentyl-2,5-dihydrofuranone (17). To a solution of **16** (41 mg; 0.105 mmol) in chloroform (1 ml), DBU (13 mg; 0.105 mmol) was added with stirring at room temperature. TLC indicated the instantaneous consumption of the starting material. Work-up as described for **6k** followed by purification by flash chromatography (SiO_2; 20% EtOAc in hexane) afforded **17** as a colourless oil (20 mg, 84%); IR (film): 1770, 1728, 1664 cm^{-1}; ^{1}H NMR: 5.12-5.07 (*m*, 1H, *H*COC=O); 3.9 (*s*, 3H); 2.2 (*d*, J=2.3, 3H); 2.2-2.04 (*m*, 2H); 1.66-1.25 (series of *m*, 6H); 0.89 (*t*, J=6.5, 3H, Me); ^{13}C NMR: 172.89; 162.64; 147.57; 137.42; 81.34; 52.29; 32.72; 31.33; 24.36; 22.35; 13.89; 10.80.

(±)-Methylenolactocin methyl ester (18). To a solution of lactone **16** (126 mg) in chloroform (7 ml), Cu-powder (2.1 g) was added, and the solvent was removed first on a rotary evaporator, then at 0.05 mmHg. The resulting powder was transferred to a Kugelrohr appartus and heated under vacuum (180°C/1.5 mmHg). Under these conditions, lactone **18** (71 mg) distilled but was still contaminated by minor quantities of starting material **16** and unwanted isomer **17**. Purification by flash chromatography (SiO_2; 20% EtOAc in hexane) afforded pure (±)-methylenolactocin methyl ester as a colourless oil (45 mg; 62%); the ^{1}H and ^{13}C NMR spectra were identical with those previously reported.[15f]

(±)-epi-Methylenolactocin methyl ester (21). Compound **20** (235 mg) was heated with copper powder in the same way as its isomer **16.** This gave lactone **24** as a colourless oil (37 mg, 28%); IR (film): 1770, 1741, 1667 cm^{-1}; ^{1}H NMR: 6.40 (*d*, J=2.3, 1H); 5.83 (*d*, J=2.03, 1H); 4.63 (*ddd*, J_1=11, J_2=8, J_3=4.1, 1H); 4.01 (*dt*, J_1=8, J_2=2.1, 1H); 3.76 (*s*, 3H); 1.7-1.25 (series of *m*, 8H); 0.9 (*t*, 3H);^{13}C NMR: 169.29; 168.75; 133.67; 124.85; 78.18; 52.26; 49.04; 31.42; 31.29; 25.12; 22.34; 13.84.

(±)-Methylenolactocin (19). Acid hydrolysis of **18** (39 mg) as described in the literature[15f] afforded of (±)-methylenolactocin **19** (29 mg, 75%) as a white solid; m.p. 54-6°C (EtOAc/hexane; lit.[15g]: oil); ^{1}H and ^{13}C NMR spectra identical with those previously reported for the natural compound.[14]

References and notes:

1. For comprehensive reviews see: a) Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K.J. and Trach, F. *Org. React.* **1996**, *48*, 301-855; b) Curran, D. P. in: *Comprehensive Organic Synthesis*, Editors: B. Trost and I. Fleming, Pergamon Press, **1991**, *Vol. 4*, p. 715-831.
2. (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc. Perkin Trans. 1*, **1975**, 1574-1585. (b) Pfenniger, J.; Heuberger, C.; Graf, W. *Helv. Chim. Acta* **1980**, *63*, 2328-2337. (c) Dolan, S. C.; MacMillan, J. *J. Chem. Soc. Chem. Commun.* **1985**, 1588-1589. (d) Giese, B.; Gonzalez-Gomez, J. A.; Witzel, T. *Angewandte Chem. Int. Ed. Eng.* **1984**, *23*, 69. (e) Barton, D. H. R.; Crich, D. *J. Chem. Soc. Perkin Trans. 1*, **1986**, 1603-1611.
3. (a) Bachi, M. D.; Bosch, E. *J. Org. Chem.* **1992**, *57*, 4696-4705 and references cited therein. (b) Singh, A. K.; Bakshi, R. K.; Corey, E.J. *J. Am. Chem. Soc.* **1987**, *109*, 6187-6189.
4. (a) For a review of this work, see: Zard, S. Z. *Angew.Chem. Int. Ed. Eng.* **1997**, *36*, 672-685. For preliminary communications on this subject see: (b) Forbes, J. E.; Zard, S. Z. J. *Am. Chem. Soc.* **1990**, *112*, 2034-2035. (c) Saicic, R. N.; Zard, S. Z. *J. Chem. Soc. Chem. Commun.* **1996**, 1631-1632.
5. (a) Delduc, P.; Tailhan, Ç.; Zard, S. Z. *J. Chem. Soc. Chem. Commun.* **1988**, 308-310. (b) Barton, D. H. R.; George, M. V.; Tomoeda, M. *J. Chem. Soc.* **1962**, 1967-1974.
6. (a) Griller, D.; Roberts, B.P. *J. Chem. Soc. Chem.Commun.* **1971**, 1035-1036. (b) Griller, D.; Roberts, B. P. *J. Chem. Soc.Perkin Trans. 2*, **1972**, 747-751. (c) Ingold, K. U.; Maillard, B.; Walton, J. C. *J. Chem. Soc.Perkin Trans. 2*, 1981, 970-974. (d) Ruegge, D.; Fischer, H. Int. *J. Chem. Kinet.* **1986**, *18*, 145-158. (e) Beckwith, A. L. J.; Bowry, V.; Moad, G. *J. Org. Chem.* **1988**, *53*, 1632-1641. (f) Simakov, P. A.; Martinez, F. A.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1998**, *63*, 1226-1232.
7. Urry, W. H.; Huyser, E. S. *J. Am. Chem. Soc.* **1953**, *75*, 4876-4877.
8. Recently a modification of the Barton-McCombie reaction allowing for deoxygenation of primary alcohols at low temperatures was reported: Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. S. *Tetrahedron* **1993**, *49*, 2793-2796.
9. (a) Fraga, B. M. *Nat. Prod. Rep.* **1992**, *9*, 217-241, 557-580. (b) Petragnani, N.; Ferraz, H. M. C.; Silva, G. V. J. *Synthesis* **1986**, 157-183. (c) Knight, D. W. *Contemp. Org. Chem.* **1994**, *1*, 287-315.
10. (a) Canonica, L.; Corbella, A.; Jommi, G.; Krepinsky, J. *Tetrahedron Lett.* **1967**, 2137-2141. (b) Canonica, L.; Corbella, A.; Gariboldi, P.; Jommi, G.; Krepinsky, J.; Ferrari, J.; Casagrande, C. *Tetrahedron* **1969**, *25*, 3895-3902.
11. For a recent review on drimanes see: Jansen, B. J. M.; de Groot, A. *Nat. Prod. Rep.* **1991**, *8*, 309-318, 319-337.
12. (a) Tanis, S. P.; Nakanishi, K. *J. Am. Chem. Soc.* **1979**, *101*, 4398-4900. (b) Yanagawa, H.; Kato, T.; Kitahara, Y. *Synthesis* **1970**, 257-258. (c) Suzuki, T.; Tanemura, M.; Kato, T.; Kitahara, Y. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1268.
13. (a) Danheiser, R. L.; Casebier, D. S.; Firooznia, F. *J. Org. Chem.* **1995**, *60*, 8341-8350. (b) Stadler, P. A.; Nechvatal, A.; Frey, A. J.; Eschenmoser, A. *Helv. Chim. Acta* **1957**, *40*, 1373-1409. (c) Stadler, P. A.; Eschenmoser, A.; Schinz, H.; Stork, G. *Helv. Chim. Acta* **1957**, *40*, 2191-2198. (d) Liapis, M.; Ragousis, V.; Ragousis, N. *J. Chem. Soc. Perkin Trans 1*, **1985**, 815-817.
14. Park, B. K.; Nagasawa, M.; Hirota, A.; Nakayama, M. *J. Antibiot.* **1988**, *41*, 751-758.
15. (a) de Azevedo, M. B. M.; Murta, M. M.; Greene, A.E. *J. Org. Chem.* **1992**, *57*, 4567-4569. (b) Lu, X.; Zhu, G. *Synlett* **1993**, 68-70. (c) Honda, T.; Kimura, N. *J. Chem. Soc. Chem. Commun.* **1994**, 77-78. (d) Zhu, G.; Lu, X. *J. Org. Chem.* **1995**, *60*, 1087-1089. (e) Vaupel, A.; Knochel, P. *Tetrahedron Lett.* **1995**, *36*, 231-232. (f) Mawson, S.; Weavers, R. T. *Tetrahedron* **1995**, *51*, 11257-11270 (g) Maiti, G.; Roy, S. C. *J. Chem. Soc. Perkin Trans 1*, **1996**, 403-404. (h) Sibi, M. P.; Deshpande, P. K.; La Loggia, A. J. *Synlett* **1996**, 343-345.
16. See for example: Galatsis, P.; Millan, S. D.; Nechalka, P.; Ferguson, G. *J. Org. Chem.* **1994**, *59*, 6643-6651. In principle, the starting homoallylic alcohol **17a** can be made in optically pure form through the now well established asymmetric aldol technology: Moon Kim, B.; Williams, S. F. and Masamune, S., in: *Comprehensive Organic Synthesis*, Editors: B. Trost and I. Fleming, Pergamon Press, **1991**, *Vol. 2*, p. 239-275.
17. (a) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925-3942. (b) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959-974.
18. Barany, G.; Fulpius, B. W.; King, T. P. *J. Org. Chem.* **1978**, *43*, 2930-2932.
19. Degani, I.; Fochi, R. *Synthesis* **1978**, 365-368.
20. Inverse order of addition leads to the decomposition of *S*-alkoxycarbonyl xanthate. For the mechanism of this anionic chain reaction see ref. (4a).
21. Murray, A. W.; Reid, R. G. *Synthesis* **1985**, 35-38.