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Stereoselective Synthesis of Hydroxy-ketenedithioacetals from Aldehydes

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Abstract: The reaction of Garner's aldehyde with dithioacetate enethiolates followed by alkylation of the intermediate aldolate gives hydroxy-ketenedithioacetals with a moderate *anti* selectivity. This methodology was applied to the synthesis of various other ketene dithioacetals with high *E* or *Z* stereoselectivity. © 1998 Elsevier Science Ltd. All rights reserved.

The chemistry of the enethiolates derived from dithiocarboxylates has received much attention during the last twenty years.[1] They are ambident nucleophiles which can form carbon-carbon bonds or carbon-sulfur bonds when they react with electrophiles. Of particular interest are the reactions creating C-C bonds. This is the case for the reaction of enethiolates with aldehydes (aldol condensation)[2,3] and enones (Michael addition).[4] The stereochemistry of both these reactions has been investigated.[1-4] On the other hand, C-S bond forming reactions, such as the reaction of enethiolates with alkyl halides[5,6] and epoxides,[7] give ketenedithioacetals. These compounds can in turn be used for the formation of C-C bonds.[8] In this paper, we report our results concerning the reaction of enethiolates with Garner's aldehyde **1** (Scheme 1). A one pot procedure, allowing the formation of both a C-C and a C-S bond will be presented.[9] It is a two carbon homologation procedure, transforming an aldehyde (RCHO) into an allylic hydroxy-ketenedithioacetal (RCHOHCH=C(SR)$_2$).

Condensation of dithioester enethiolates with Garner's aldehyde

Serine is one the most useful proteic aminoacids available in the chiral pool. Of special interest are the protected derivatives of the corresponding aldehyde ('serinal'), and among them, the most commonly used is the 4-formyl-1,3-oxazolidine **1**.[10] This aldehyde, often referred to as Garner's aldehyde, has been used in a lot of total syntheses of natural products. The stereochemistry of its condensation with many nucleophiles has been thoroughly studied.[11] Good diastereoselections have been described for allylmetallation reactions,[12] and for some aldol condensations.[13,14] As it was known that enethiolates sometimes gave better results than enolates,[1,3] we decided to test the reaction of aldehyde **1** with dithioesters.

The dithioesters **2a,b** were deprotonated by LDA in dry THF at -78°C.[2] Garner's aldehyde **1** was added to the obtained enethiolates and the reaction mixture was stirred for 45mn at -78°C before quenching by NH_4Cl/H_2O. Classical work up, followed by column chromatography over silica gel gave the expected β-hydroxydithioesters **3a** (62% yield) and **3b** (59%). ^{1}H NMR analysis of the isolated compounds **3a,b** clearly

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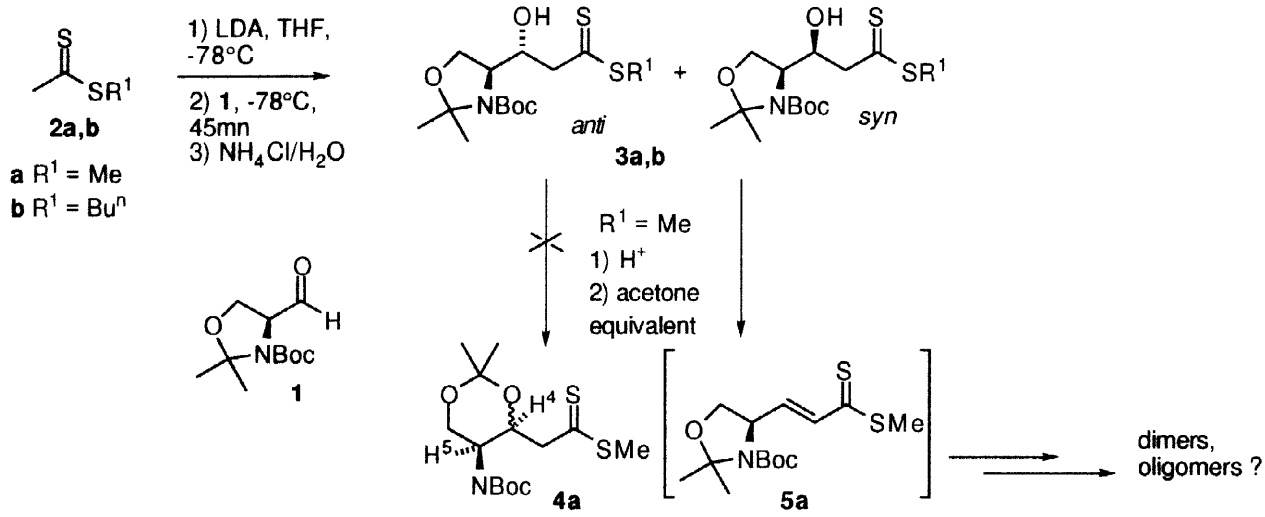
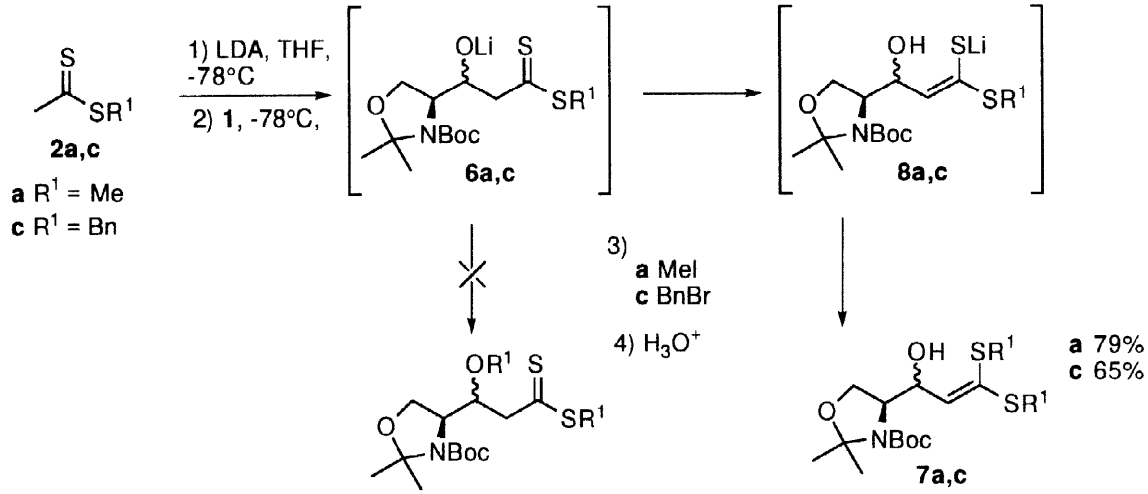


Scheme 1

showed that they were obtained as mixtures of non separable stereoisomers. However, the spectra at room temperature were complicated by the hindered rotation of the Boc protective group.[15] Recording of the spectrum of **3a** at 70°C in C_6D_6 allowed us to estimate a diastereoisomeric ratio of 75/25 (based on the SMe integrations). This ratio was confirmed by HPLC. In the case of **3b**, only HPLC could be used and gave a 78/22 ratio.

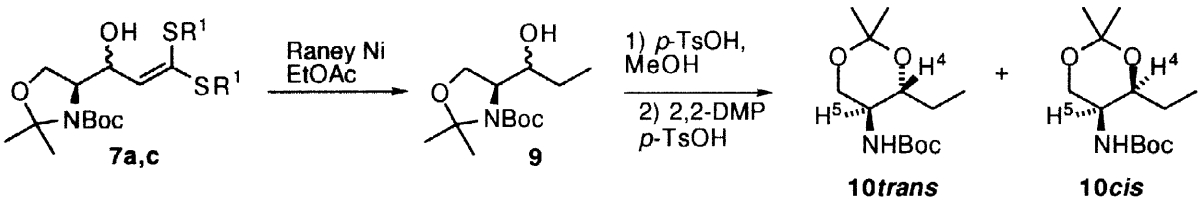
In order to determine the configuration of the major isomer, we tried to transform the oxazolidine **3a** into the dioxane **4a**. In this type of six membered ring compound, the coupling constant J_{H4H5} is characteristic of the configuration : J_{H4H5} = 1-2 Hz for *cis* dioxanes (resulting from a *syn*-selective addition), whereas J_{H4H5} = 7-10 Hz for *trans* dioxanes (resulting from an *anti*-selective addition).[16,17] Various experimental conditions were tried. However in no case the dioxane **4a** could be isolated. Instead of **4a**, a complex mixture was obtained. The ^1H NMR spectrum of this mixture showed ethylenic signals between 5 and 6 ppm. These signals could arise from the formation of the unsaturated dithioester **5a** resulting from acid catalyzed dehydration of **3a**.[18] As other α-ethylenic dithioesters,[19] **5a** is probably unstable and gave rise to a mixture of dimers and/or oligomers, explaining the complex spectrum obtained.



Scheme 2

As the instability of **3a** was probably due to the presence of the hydroxy group, we decided to try to alkylate it. The aldol reaction directly leading to an alcoholate **6a** (Scheme 2), we tried to trap it *in situ* by methyl iodide, rather than to regenerate an alcoholate from the isolated β-hydroxydithioester. Thus, the enethiolate of **2a** was allowed to react with aldehyde **1** at -78°C for 1h. Then 1.5 eq. of MeI was added and the reaction mixture was stirred for another 2h at -78°C before quenching. The ^{1}H NMR spectrum of the obtained product showed no methoxy singlet, but two doublets corresponding to ethylenic protons were observed at 5.74 (major) and 5.63 ppm (minor), as well as methylthio groups (two major singlets at 1.85 and 1.79 ppm). These observations clearly pointed to the ketene dithioacetal structure **7a**, rather than to the expected *O*-methylated compound. As expected, **7a** was obtained as a mixture of stereoisomers in the ratio 75/25, in accordance with the ratio observed for the corresponding dithioester **4a**. This result shows that the alcoholate **6a** was transformed into the enethiolate **8a**. Whether this transformation is complete or equilibrated is not clear.[20] If it is under thermodynamic control, the equilibrium would be displaced by the preferred *S*-alkylation of the highly nucleophilic enethiolate. As shown in Scheme 2, the same procedure was repeated from benzyl dithioacetate **2c** and using benzylbromide as the alkylating reagent. In this case the corresponding di-*S*-benzylated compound **7c** was isolated in 65% yield (two isomers, ratio: 65/35).

The oxazolidine-to-dioxane rearrangement was then attempted on the ketene dithioacetal **7a**. However, in this case also, like with dithioester **3a**, no clear result could be obtained. Here also, loss of H_2O can explain this bad result. In order to get rid of this problem, we first treated **7a** and **7c** by Raney nickel (Scheme 3) in ethyl acetate.[21] Loss of sulfur and hydrogenation of the double bond was observed, giving rise from **7a,c** to the same saturated compound **9**. Finally, treatment of **9** by *p*-toluenesulfonic acid (cleavage of the isopropylidene group), followed by treatment of the free diol by 2,2-dimethoxypropane gave the dioxane **10**.

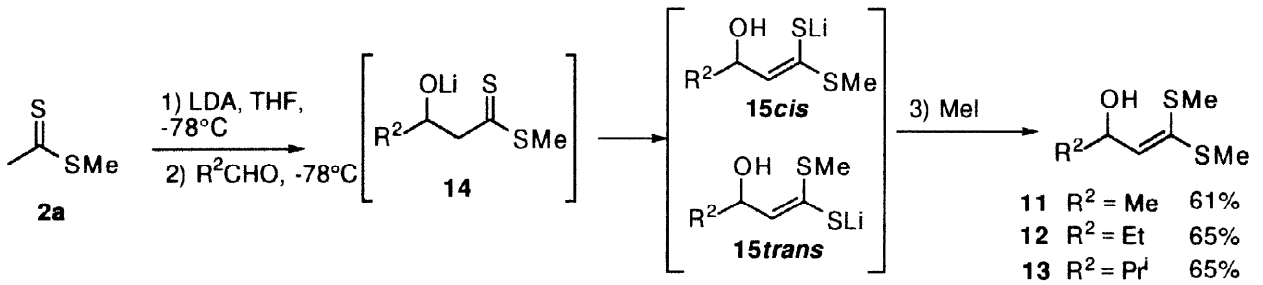


Scheme 3

10 was obtained as a mixture of two stereoisomers which were separated by liquid chromatography. The coupling constants J_{H4H5} were determined : major isomer, J_{H4H5} = 9.5 Hz (**10*trans***) ; minor isomer, J_{H4H5} = 1.7 Hz (**10*cis***).[16,17] These results indicate that, like in the case of enolates, the major isomer obtained by condensation of a dithioacetate enethiolate with the aldehyde **1** has an *anti* configuration. Even though the observed stereoselectivity is mediocre in the three tested examples, ranging from 65/35 to 78/22 (to be compared with 88/12[13] and 80/20[14]), this study allowed us to discover that it is possible to create in one pot a C-C and a C-S bond from a dithioester. This observation has been extended to a series of aldehydes.

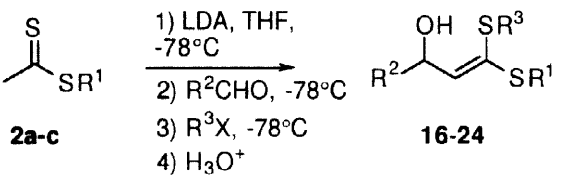
One pot synthesis of ketene dithioacetals from dithioacetates and aldehydes

Hydroxyketene dithioacetals[22] have been previously obtained by reduction of the corresponding ketones (no C-C nor C-S bond formation)[23,24] and by double deprotonation of β-hydroxydithioesters followed by *S*-alkylation (with a C-S bond formation).[25] Our method will allow the one-pot formation of a C-S and a C-C bond.



Scheme 4

The results obtained using methyl dithioacetate **2a**, various aldehydes and methyl iodide as the alkylating reagent are presented in Scheme 4. As discussed before, formation of the dithioacetals **11-13** must result from the transformation of the alcoholate **14** obtained from the condensation of the starting enethiolate with the aldehyde, into a hydroxylated enethiolate **15**. Such enethiolate may be *cis* or *trans*. However, as **15*cis*** could be stabilized by the formation of a O-H-S hydrogen bond and/or a S-Li-O chelation and that no such intramolecular stabilization is possible for **15*trans***, we postulated that the *cis* isomer should predominate. If this is true, it must be possible to synthesize stereoselectively *Z* and *E* ketene dithioacetals by an appropriate choice of R^1 and R^3 (Scheme 5). Our results are summarized in the Table. As expected, in each case one of the isomers largely predominate. The *Z*/*E* ratios were determined by ^1H NMR. Confirmation of the stereochemistry was obtained by comparison of our NMR data for compounds **16*Z*** and **16*E*** with those reported by Beslin and Perrio.[25]



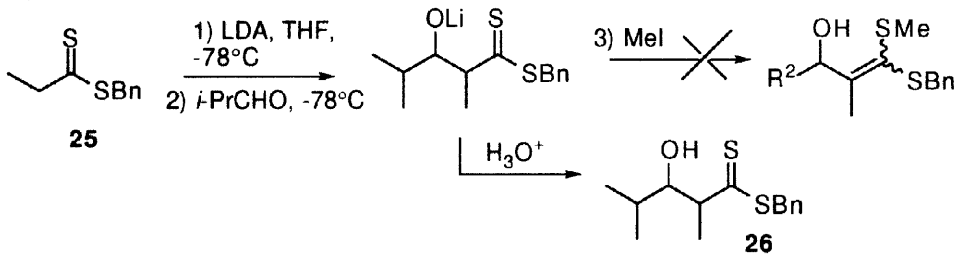
Scheme 5

product§	R^1	R^2	$R^{3\#}$	*Z*/*E*	yield
16*Z*	Me	Me	Bn	99/1	67%
16*E*	Bn	Me	Me	4/96	58%
17*E*	*n*-Bu	Me	Me	4/96	74%
18*Z*	*n*-Bu	Me	Bn	97/3	71%
19*Z*	Me	Et	Bn	96/4	72%
19*E*	Bn	Et	Me	3/97	70%
20*E*	*n*-Bu	Et	Me	1/99	72%
21*Z*	*n*-Bu	Et	Bn	99/1	80%
22*Z*	Me	*i*-Pr	Bn	98/2	71%
22*E*	Bn	*i*-Pr	Me	4/96	69%
23*E*	*n*-Bu	*i*-Pr	Me	1/99	81%
24*Z*	*n*-Bu	*i*-Pr	Bn	99/1	71%

§ Major isomer indicated. # Used alkylating agent : MeI or BnBr

Table

In an attempt to generalize this reaction, we have treated the alcoholate obtained by condensation of benzyl propanedithioate **25** and isobutyraldehyde with methyl iodide (Scheme 6). However, in this case no *S*-alkylated product was observed. We were able to identify the β-hydroxydithioester **26**[2] in the obtained crude mixture. It seems that the proton α to the C=S double bond in the intermediate alcoholate is not acidic enough to allow the alcoholate to enethiolate transformation to take place.[20] This limits the scope of this method to dithioacetates.



Scheme 6

Experimental section

All the reactions were carried out under a slightly positive pressure of nitrogen. Anhydrous THF was obtained by distillation over sodium wires in the presence of benzophenone after the blue color of sodium diphenyl ketyl persisted. Elemental analyses were performed by the "service central d'analyse du CNRS" at Vernaison. NMR spectra were recorded using Bruker AC200 or AM300 apparatus. The attribution of the ^{13}C signals were confirmed by DEPT experiments. The IR spectra were recorded on a Nicolet impact 400 apparatus. Mass spectra (MS) were obtained from a Nermag R10 10H spectrometer. HPLC analyses were performed on a Shimadzu system equiped with a diode array detector and a Kromasil C18 column (eluent : mixtures of water and CH_3CN). The dithioesters **2a-c** were prepared by known methods.[26] For the synthesis of the aldehyde **1** we used the procedure described by Garner and Park.[10,27] All the new products were isolated as oils.

Aldol reaction with Garner's aldehyde

The dithioester (1 mmol) was added dropwise at -78°C to a solution of LDA in THF (1.1 mmol, prepared from diisopropylamine and *n*-BuLi at -20°C). The reaction mixture was stirred for 10mn, before Garner's aldehyde (1 mmol) was added dropwise. The reaction mixture was then stirred for another 45mn, before quenching with a saturated solution of NH_4Cl in water. The aqueous phase was extracted twice with diethyl ether. The collected organic layers were dried over anhydrous $MgSO_4$, filtered and the solvents were evaporated under reduced pressure. The obtained residue was purified by chromatography over silica gel (column or preparative layer chromatography). The β-hydroxydithioesters were obtained as orange oils. The *syn* and *anti* isomers were not separated.

Starting with methyl dithioacetate a mixture of *syn* and *anti* **3a** was obtained in 62% yield (*anti*/*syn* = 75/25)

3a : ^1H NMR (300 MHz, 343 K, C_6D_6) major isomer 4.51-4.39 (m, 1H, C<u>H</u>OH), 4.63 (broad s, 1H, OH), 3.96-3.85 (m, 2H, CH_2O), 3.72-3.60 (m, 1H, CHN), 3.24 (d, J = 5.9 Hz, 2H, CH_2CS_2), 2.20 (s, 3H, SCH_3), 1.76-1.34 (m, 15H, $(CH_3)_3C$ and $(CH_3)_2C$). The minor *syn* isomer was characterized by a singlet at 2.18 (SCH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) : 223.50 (<u>C</u>S_2), 153.50 and 152.25 (<u>C</u>O_2t-Bu), 95.00 and

94.19 ($(CH_3)_2\underline{C}$), 81.10 and 80.05 ($(CH_3)_3\underline{C}$), 73.91 (CHOH), 64.95 (CHN), 61.66 and 60.42 ($\underline{C}H_2O$), 55.10 ($\underline{C}H_2CS_2$), 28.19 ($(\underline{C}H_3)_3C$), 26.65, 25.83, 23.75 and 22.50 ($(\underline{C}H_3)_2C$), 19.96 ($S\underline{C}H_3$).

Starting with *n*-butyl dithioacetate a mixture of *syn* and *anti* **3b** was obtained in 59% yield (*anti/syn* = 78/22) **3b** : ^{1}H NMR (200 MHz, $CDCl_3$) major isomer 4.35-3.86 (m, 5H), 3.24 (t, J = 8 Hz, 2H, SCH_2), 3.14 (d, J = 6.4 Hz, 2H, CH_2CS_2), 1.78-1.40 (m, 19H, $(CH_3)_3C$, $(CH_3)_2C$ and 2 CH_2), 0.87 (t, J = 8 Hz, 3H, CH_3). The minor isomer could not be clearly characterized by NMR. The *anti/syn* ratio was determined by HPLC.

Synthesis of ketenedithioacetals from Garner's aldehyde

The procedure was similar to that reported for the aldol condensations, excepted that an alkylating reagent (methyl iodide or benzyl bromide) was added to the reaction mixture after the formation of the aldolate. The reaction mixture was then stirred for 2h at -78°C before quenching with NH4Cl/water.

Starting with methyl dithioacetate and using MeI as the alkylating reagent, a mixture of *anti* and *syn* **7a** was isolated in a 79% yield. **7a** : ^{1}H NMR (300 MHz, 343 K, C_6D_6) major isomer 5.74 (d, J = 8.7 Hz, 1H, HC=C), 5.08-5.00 (m, 1H, OH), 4.77 (dd, J = 4.4 and 8.8 Hz, 1H, CHO), 3.72 (dd, J = 2.3 and 8.9 Hz, 1H, CHN), 3.45 (dd, J = 2.7 and 6.2 Hz, 2H, CH_2O), 1.85 and 1.79 (2s, 6H, 2 SCH_3), 1.24-1.07 (m, 15 H, $(CH_3)_3C$ and $(CH_3)_2C$). The minor isomer was characterized by the following signals : 5.63 (d, J = 8.8 Hz, HC=C), 1.86 and 1.74 (2s, 6H, 2 SCH_3).^{13}C NMR (50.3 MHz, $CDCl_3$) : 154.20 ($\underline{C}O_2t$-Bu), 138.8 ($\underline{C}(SCH_3)_2$), 129.63 ($H\underline{C}$=C) 94.43 ($(CH_3)_2\underline{C}$), 81.08 ($(CH_3)_3\underline{C}$), 70.70 (CHO), 65.05 ($\underline{C}H_2O$), 62.21 (CHN), 28.12 ($(\underline{C}H_3)_3C$), 26.02 ($\underline{C}H_3$), 24.45 ($\underline{C}H_3$), 17.09 and 16.02 (2 $S\underline{C}H_3$). IR (film) : 3450, 2981, 2931, 2882, 1697, 1394, 1370, 1258, 1178, 1092, 1073, 857 cm^{-1}. MS (CI, NH_3 + isobutane) m/z : 332 ($MH^+ - H_2O$, 100), 276 (28), 264 (11). Elemental analysis : calc. for $C_{15}H_{27}O_4NS_2$: C% = 51.55, H% = 7.79, S% = 18.35 ; found : C% = 51.35, H% = 7.80, S% = 18.06.

Starting with benzyl dithioacetate and using BnBr as the alkylating reagent, a mixture of *anti* and *syn* **7c** was isolated in a 65% yield. **7c** : ^{1}H NMR (300 MHz, 343 K, C_6D_6) major isomer 7.05-6.72 (m, 10 H, 2 C_6H_5), 5.96 (d, J = 8.7 Hz, 1H, HC=C), 4.81-4.73 (m, 1H, OH), 4.62-4.55 (m, 1H, CHO), 3.85-3.42 (m, 5H), 3.27 (dd, J = 2.4 and 6.6 Hz, 2H, CH_2O), 1.51-1.05 (m, 15 H, $(CH_3)_3C$ and $(CH_3)_2C$). The minor isomer was characterized a doublet at 5.85 ppm (d, J = 8.7 Hz, HC=C). ^{13}C NMR (50.3 MHz, $CDCl_3$) : 153.90 ($\underline{C}O_2t$-Bu), 138.18, 136.96, 136.16, 133.32, 128.96, 128.44, 127.14 ($H\underline{C}$=C, $\underline{C}(SBn)_2$ and 2 $\underline{C}_6H_5$), 94.16 ($(CH_3)_2\underline{C}$), 80.70 ($(CH_3)_3\underline{C}$), 70.61 (CHOH), 64.66 ($\underline{C}H_2O$), 61.32 (CHN), 37.69 (2 $\underline{C}H_2Ph$), 28.34 ($(\underline{C}H_3)_3C$), 26.39 and 24.58 ($(\underline{C}H_3)_2C$). Elemental analysis : calc. for $C_{27}H_{35}O_4NS_2$: C% = 64.64, H% = 7.03, S% = 12.78 ; found : C% = 64.51, H% = 6.99, S% = 12.50.

Determination of the stereochemistry of the isomers of 7a and 7c

Reduction step

To a solution of the dithioacetal (**7a** or **7c**, 1 mmol) in ethyl acetate (5 ml) was added Raney nickel (1.25 g). The resulting mixture was stirred under reflux for 3 h before cooling to room temperature. The nickel was filtered off and washed with several portions of ethyl acetate. The collected EtOAc fractions were evaporated under reduced pressure and the obtained residue was rapidly purified by liquid chromatography over silica gel using a 4/1 mixture of pentane and EtOAc as the eluant. No attempts at obtaining an analytically pure sample of **9** was made. Compound **9** was isolated in 55% yield from **7a**, and 60% yield from **7c**. The absence of any SMe or SBn groups, and of any ethylenic protons was checked by ^{1}H NMR. **9** : ^{1}H NMR

(200 MHz, $CDCl_3$) : 4.20-3.52 (m, 7H), 2.00-1.41 (m, 15 H, $(CH_3)_3C$ and $(CH_3)_2C$), 1.12 (t, J = 8.3 Hz, 3H, CH_3).

cleavage of the isopropylidene group

A solution of the alcohol **9** (100 mg, 0.39 mmol) and PTSA (9 mg, 0.05 mol) in MeOH (3.3 ml) was stirred for 3 h at room temperature. An aqueous solution of $NaHCO_3$ (15 ml) and ethyl acetate (20 ml) were then added. The aqueous layer was extracted with EtOAc (2 x 20 ml), and the mixed organic phases were dried over $MgSO_4$, filtered, and the solvent was evaporated under reduce pressure. The obtained residue was used without further purification.

formation of the 1,3-dioxane ring

To a solution of the crude diol (40 mg, 0.18 mmol) in 2,2-dimethoxypropane (1.9 ml) was added PTSA (2.6 mg, 0.014 mmol). The reaction mixture was stirred for 6 h at room temperature. After a classical work up ($NaHCO_3/H_2O$, EtOAc), the dioxanes **10*trans*** and **10*cis*** were separated by liquid chromatography. The global yield from **9** (two steps) was 61%.

10*trans* : ^1H NMR (300 MHz, 343 K, C_6D_6) : 4.88 (broad s, 1H, NHBoc), 3.77 (dd, J = 5 and 11.5 Hz, 1H, 1H from CH_2O), 3.57 (ddd, J = 5, 8.5 and 9.5 Hz, CHN), 3.27 (dd, 2H, J = 8.5 and 11.5, 1H, 1H from CH_2O), 3.25-3.15 (m partly masked by the preceding dd, 1H, CHO), 1.53-1,36 (m, 2H, $C\underline{H}_2CH_3$), 1.40 (s, 9H, $(CH_3)_3C$), 1.36 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 0.94 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) : 155.16 ($\underline{C}O_2t$-Bu), 98.71 ($(CH_3)_2\underline{C}$), 79.63 ($(CH_3)_3\underline{C}$), 72.92 ($\underline{C}HO$), 63.45 ($\underline{C}H_2O$), 49.22 ($\underline{C}HN$), 28.28 ($(\underline{C}H_3)_3C$), 27.89 ($CH_3\underline{C}H_2$), 25.52 and 24.73 ($(\underline{C}H_3)_2C$), 9.44 ($\underline{C}H_3CH_2$). IR (film) : 3308, 2969, 2932, 2857, 1672, 1536, 1456, 1370, 1308, 1240, 1172, 1013 cm^{-1}. MS (CI, NH_3 + isobutane) : m/z : 260 (MH^+, 52), 204 (40), 160 (100), 146 (59).

10*cis* : ^1H NMR (200 MHz, $CDCl_3$) : 5.28 (d, J = 10.3 Hz, 1H, NHBoc), 4.05 (dd, J = 2.1 and 12 Hz, 1H, 1H from CH_2O), 3.84 (dt, J = 1.7 and 6.5 Hz, 1H, CHO), 3.75 (dd, J = 2.1 and 12 Hz, 1H, 1H from CH_2O), 3.59-3.40 (m, 1H, CHN), 1.63-1.42 (m, 17 H, $C\underline{H}_2CH_3$, $(CH_3)_3C$ and $(CH_3)_2C$), 0.92 (t, J = 7.6 Hz, 3H, CH_3).

Synthesis of ketene dithioacetals 11-13 and 16-24

The experimental procedure is analogous to the one reported for the synthesis of compounds **7a,c**. The obtained ketene dithioacetals were purified by liquid chromatography over silica gel (column or preparative layer chromatography). They were isolated as colorless or slightly yellow oils.

4,4-dimethylthio-but-3-en-2-ol (11) : yield 61%. ^1H NMR (200 MHz, $CDCl_3$) : 5.77 (d, J = 7.9 Hz, 1H, CH), 4.94 (dq, 1H, J = 6.5 and 7.8 Hz, 1H, CHO), 2.34 (s, 3H, SCH_3), 2.29 (s, 3H, SCH_3), 2.04 (s, 1H, OH), 1.29 (d, J = 6.5 Hz, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) : 134.90 ($\underline{C}(SR)_2$), 134.11 ($H\underline{C}$=C), 66.89 ($\underline{C}HO$), 23.11 ($\underline{C}H_3$), 17.02 and 16,37 (2 $S\underline{C}H_3$).

1,1-dimethylthio-pent-1-en-3-ol (12) : yield 65%. ^1H NMR (200 MHz, $CDCl_3$) : 5.75 (d, 1H, J = 7.5 Hz, HC=C), 4.71 (dt, 1H, J = 6.7 and 7.5 Hz, 1H, CHO), 2.33 (s, 3H, SCH_3), 2.29 (s, 3H, SCH_3), 1.75-1.42 (m, 2H, $C\underline{H}_2CH_3$), 1.16 (broad s, 1H, OH), 0.92 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) : 134.98 ($\underline{C}(SR)_2$), 134.36 ($H\underline{C}$=C), 65.69 ($\underline{C}HO$), 27.88 ($\underline{C}H_2$), 23.01 ($\underline{C}H_3$), 16.86 and 16.23 (2 $S\underline{C}H_3$). Elemental analysis : calc. for $C_7H_{14}OS_2$: C% = 47.15, H% = 7.91, O% = 8.97 ; found : C% = 47.27, H% = 7.56, O% = 9.23.

4-methyl-1,1-dimethylthio-pent-1-en-3-ol (13) : yield 65%. ^{1}H NMR (300 MHz, $CDCl_3$) : 5.75 (d, J = 7.5 Hz, 1H, HC=C), 4.45 (dd, J = 5.8 and 7.5 Hz, 1H, CHO), 2.32 (s, 3H, SCH_3), 2.29 (s, 3H, SCH_3), 2.14 (broad s, 1H, OH), 1.88-1.62 (m, 1H, C<u>H</u>$(CH_3)_2$), 0.98 (d, J = 6.7 Hz, 3H, CH_3), 0.89 (d, J = 6.7 Hz, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) : 136.04 (<u>C</u>$(SR)_2$), 132.74 (H<u>C</u>=C), 74.45 (<u>C</u>HO), 34.08 (<u>C</u>H$(CH_3)_2$), 18.18 (CH(<u>C</u>$H_3)_2$), 16.92 and 16.45 (2 S<u>C</u>H_3).

(*Z*)-4-benzylthio-4-methylthio-but-3-en-2-ol (16*Z*)[25] : yield 67%. ^{1}H NMR (200 MHz, $CDCl_3$) : 7.34-7.10 (m, 5H, C_6H_5), 5.72 (d, J = 8.2 Hz, 1H, HC=C), 4.51 (dq, J = 6.2 and 8.2 Hz, 1H, CHO), 3.93 (AB, J_{AB} = 13.4 Hz, δ_A-δ_B = 34.3 Hz, SCH_2), 2.29 (s, 3H, SCH_3), 0.99 (d, J = 6.5 Hz, 3H, CH_3), 0.92 (broad s, 1H, OH). ^{13}C NMR (50.3 MHz, $CDCl_3$) : 138.77, 138.47, 132.05, 128.86, 128.41, 127.14 (<u>C</u>$_6H_5$, H<u>C</u>=C and <u>C</u>$(SR)_2$), 65.58 (<u>C</u>HO), 37.89 (S<u>C</u>H_2), 21.92 (<u>C</u>H_3), 16.36 (S<u>C</u>H_3).

(*E*)-4-benzylthio-4-methylthio-but-3-en-2-ol (16*E*)[25] : yield 58%. ^{1}H NMR (200 MHz, $CDCl_3$) : 7.30-6.99 (m, 5H, C_6H_5), 5.76 (d, J = 8 Hz, 1H, HC=C), 4.75 (m, 1H, CHO), 3.78 (AB, J_{AB} = 11.7 Hz, δ_A-δ_B = 27.6 Hz, 2H, SCH_2), 2.18 (s, 3H, SCH_3), 1.03 (d, J = 6.2 Hz, 3H, CH_3), 0.9 (broad s, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$) : 138.93, 137.25, 132.81, 128.99, 128.36, 127.13 (<u>C</u>$_6H_5$, H<u>C</u>=C and <u>C</u>$(SR)_2$), 66.03 (<u>C</u>HO), 38.01 (S<u>C</u>H_2), 22.82 (<u>C</u>H_3), 16.74 (S<u>C</u>H_3).

(*E*)-4-*n*-butylthio-4-methylthio-but-3-en-2-ol (17*E*) : yield 74%. ^{1}H NMR (200 MHz, $CDCl_3$) : 5.96 (d, J = 7.5 Hz, 1H, HC=C), 4.92 (dq, J = 6.5 and 7.5 Hz, 1H, CHO), 2.71 (dt, J = 2.1 and 7.2 Hz, 2 H, SCH_2), 2.33 (s, 3H, SCH_3), 2.05 (broad s, 1H, OH), 1.65-1.34 (m, 4H, $(CH_2)_2$), 1.28 (d, J = 6.5 Hz, 3H, CH_3), 0.92 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) : 138.59 (<u>C</u>$(SR)_2$), 133.62 (H<u>C</u>=C), 66.00 (<u>C</u>HO), 33.39 (<u>C</u>H_2), 30.76 (<u>C</u>H_2), 23.01 (<u>C</u>H_2), 21.80 (<u>C</u>H_3), 16.77 (S<u>C</u>H_3), 13.58 (<u>C</u>H_3). MS (CI, NH_3 + isobutane) m/z : 189 (MH^+ - H_2O, 100), 110 (7).

(*Z*)-4-benzylthio-4-*n*-butylthio-but-3-en-2-ol (18*Z*) : yield 71%. ^{1}H NMR (200 MHz, $CDCl_3$) : 7.30-7.10 (m, 5H, C_6H_5), 5.77 (d, J = 7.5 Hz, 1H, HC=C), 4.50-4.25 (m, 1H, CHO), 3.80 (AB, J_{AB} = 9.4 Hz, δ_A-δ_B = 22.3 Hz, 2H, CH_2Ph), 2.88-2.61 (m, 2H, SCH_2), 1.71-1.24 (m, 4H, $(CH_2)_2$), 0.87 (d, J = 6.2 Hz, 3H, CH_3), 0.83 (t, J = 6.2 Hz, 3H, CH_3), 0.79 (broad s, 1H, OH). ^{13}C NMR (50.3 MHz, $CDCl_3$) : 141.88 (<u>C</u>$(SR)_2$), 138.75, 133.80, 128.95, 128.47, 127.17 (<u>C</u>$_6H_5$ and H<u>C</u>=C), 65.73 (<u>C</u>HO), 37.64 (<u>C</u>H_2Ph), 32.34 (<u>C</u>H_2), 30.87 (<u>C</u>H_2), 21.80 (<u>C</u>H_2), 16.77 (<u>C</u>H_3), 13.65 (<u>C</u>H_3). MS (CI, NH_3 + isobutane) m/z : 283 (MH^+,2), 282(M^+, 2) 265 (MH^+ - H_2O, 100), 207 (5), 191 (11), 173 (20). Elemental analysis : calc. for $C_{15}H_{22}OS_2$: C% = 63.79, H% = 7.85, S% = 22.41 ; found : C% = 63.77, H% = 8.15, S% = 22.70

(*Z*)-1-benzylthio-1-methylthio-pent-1-en-3-ol (19*Z*) : yield 72%. ^{1}H NMR (200 MHz, $CDCl_3$) : 7.34-7.21 (m, 5H, C_6H_5), 5.70 (d, J = 8.2 Hz, 1H, HC=C), 4.34-4.21 (m, 1H, CHO), 3.95 (AB, J_{AB} = 13.4 Hz, δ_A-δ_B = 37.4 Hz, 2H, CH_2Ph), 3,00 (broad s, 1H, OH), 2.31 (s, 3H, SCH_3), 1.54-1.13 (m, 2H, CH_2), 0.76 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) : 138.47 (<u>C</u>$(SR)_2$), 137.64, 133.09, 128.89, 128.41, 127.14 (H<u>C</u>=C and <u>C</u>$_6H_5$), 70.94 (<u>C</u>HO), 37.58 (S<u>C</u>H_2), 29.79 (<u>C</u>H_2), 16.06 (S<u>C</u>H_3), 9.44 (<u>C</u>H_3). Elemental analysis : calc. for $C_{13}H_{18}OS_2$: C% = 61.38, H% = 7.13, S% = 25.20 ; found : C% = 61.42, H% = 7.15, S% = 25.01.

(*E*)-1-benzylthio-1-methylthio-pent-1-en-3-ol (19*E*) : yield 70%. ^{1}H NMR (200 MHz, $CDCl_3$) : 7.34-7.21 (m, 5H, C_6H_5), 5.85 (d, J = 7.8 Hz, 1H, HC=C), 4.61 (dt, J = 6.9 and 7.8 Hz, 1H, CHO), 4.05 (broad s, 1H, OH), 3.92 (AB, J_{AB} = 13.4 Hz, δ_A-δ_B = 12.3 Hz, 2H, CH_2Ph), 2.32 (s, 3H, SCH_3), 1.65-

1.39 (m, 2H, CH_2), 0.79 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) : 140.38 ($\underline{C}(SR)_2$), 137.71, 133.5, 128.9, 128.33, 127.03 ($H\underline{C}$=C and $\underline{C}_6H_5$), 70.94 ($\underline{C}HO$), 37.58 ($S\underline{C}H_2$), 29.79 ($\underline{C}H_2$), 16.66 ($S\underline{C}H_3$), 9.44 ($\underline{C}H_3$).

(*E*)-1-*n*-butylthio-1-methylthio-pent-1-en-3-ol (20*E*) : yield 72%. ^1H NMR (200 MHz, $CDCl_3$) : 5.86 (d, J = 7.5 Hz, 1H, HC=C), 4.60 (dt, J = 6 and 7.5 Hz, 1H, CHO), 2.71 (m, 2H, SCH_2), 2.24 (s, 3H, SCH_3), 1.65-1.26 (m, 6H, 3 ($C\underline{H}_2$)), 0.84 (nearly t, J = 7.9 Hz, 6H, 2 CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) : 137.86 ($\underline{C}(SR)_2$), 134.07 ($H\underline{C}$=C), 70.95 ($\underline{C}HO$), 32.31 ($\underline{C}H_2$), 30.77 ($\underline{C}H_2$), 29.92 ($\underline{C}H_2$), 21.72 ($\underline{C}H_2$), 16.69 ($S\underline{C}H_3$), 13.56 ($\underline{C}H_3$), 9.56 ($\underline{C}H_3$).

(*E*)-1-benzylthio-1-*n*-butylthio-pent-1-en-3-ol (21*Z*) : yield 80%. ^1H NMR (200 MHz, $CDCl_3$) : 7.45-7.20 (m, 5H, C_6H_5), 5.88 (d, J = 8.6 Hz, 1H, HC=C), 4.35-4.21 (m, 1H, CHO), 3.93 (AB, J_{AB} = 13.4 Hz, δ_A-δ_B = 35.3 Hz, 2H, CH_2Ph), 2.90-2.61 (m, 2H, SCH_2), 1.67-1,12 (m, 6H, 3 CH_2), 0.93 (m (~t), 4H, CH_3 and OH), 0.74 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) : 141.03 ($\underline{C}(SR)_2$), 138.60, 132.03, 128.93, 128.40, 127.10 ($\underline{C}_6H_5$ and $H\underline{C}$=C), 70.83 ($\underline{C}HO$), 37.58 ($\underline{C}H_2Ph$), 32.31 ($\underline{C}H_2$), 30.86 ($\underline{C}H_2$), 29.62 ($\underline{C}H_2$), 21.87 ($\underline{C}H_2$), 13.65 ($\underline{C}H_3$), 9.50 ($\underline{C}H_3$). MS (CI, NH_3 + isobutane) m/z : 297 (MH^+, 1), 296 (M^+, 1), 279 (MH^+ - H_2O, 100), 205 (6), 189 (31), 173 (12). Elemental analysis : calc. for $C_{16}H_{24}OS_2$: C% = 64.82, H% = 8.16, S% = 21.62 ; found : C% = 65.07, H% = 8.13, S% = 21.73.

(*Z*)-1-benzylthio-4-methyl-1-methylthio-pent-1-en-3-ol (22*Z*) : yield 71%. ^1H NMR (200 MHz, $CDCl_3$) : 7.35-7.10 (m, 5H, C_6H_5), 5.76 (d, J = 8.5 Hz, 1H, HC=C), 4.20-4.05 (m, 1H, CHO), 3.95 (AB, J_{AB} = 13,4 Hz, δ_A-δ_B = 42.1 Hz, 2H, CH_2Ph), 2.31 (s, 3H, SCH_3), 1.83 (broad s, 1H, OH), 1.68-1.50 (m, 1H, $C\underline{H}(CH_3)_2$), 0.83 (d, J = 6.6 Hz, 3H, CH_3), 0.73 (d, J = 6.6 Hz, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) : 138.41 ($\underline{C}(SR)_2$), 136.37, 135.53, 128.89, 128.38, 127.11 ($\underline{C}_6H_5$ and $H\underline{C}$=C), 74.22 ($\underline{C}HO$), 38.04 ($\underline{C}H_2Ph$), 33.28 ($\underline{C}H(CH_3)_2$), 18.66 ($CH(\underline{C}H_3)_2$), 16.98 ($S\underline{C}H_3$). Elemental analysis : calc. for $C_{14}H_{20}OS_2$: C% = 62.64, H% = 7.51 ; found : C% = 62.62, H% = 7.73.

(*E*)-1-benzylthio-4-methyl-1-methylthio-pent-1-en-3-ol (22*E*) : yield 69%. ^1H NMR (200 MHz, $CDCl_3$) : 7.30-7.15 (m, 5H, C_6H_5), 5.86 (d, J = 8.2 Hz, 1H, HC=C), 4.40 (dd, J = 6.5 and 8.6 Hz, 1H, CHO), 3.91 (AB, J_{AB} = 13 Hz, δ_A-δ_B = 18.5 Hz, 2H, CH_2Ph), 2.30 (s, 3H, SCH_3), 1.89 (broad s, 1H, OH), 1.68-1.54 (m, 1H, $C\underline{H}(CH_3)_2$), 0.82 (d, J = 6.6 Hz, 3H, CH_3), 0.73 (d, J = 6.6 Hz, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) : 139.22 ($\underline{C}(SR)_2$), 137.35, 133.73, 128.83, 128.32, 127.00 ($\underline{C}_6H_5$ and $H\underline{C}$=C), 74.46 ($\underline{C}HO$), 37.52 ($\underline{C}H_2Ph$), 34.02 ($\underline{C}H(CH_3)_2$), 17.92 ($CH(\underline{C}H_3)_2$), 16.63 ($S\underline{C}H_3$). MS (CI, NH_3 + isobutane) m/z : 269 (MH^+, 7), 268 (M^+, 8), 251 (MH^+ - H_2O, 100), 225 (10), 177 (19), 159 (33).

(*E*)-1-*n*-butylthio-4-methyl-1-methylthio-pent-1-en-3-ol (23*E*) : yield 81%. RMN ^1H (200 MHz, $CDCl_3$) : 5.97 (d, J = 8.6 Hz, 1H, HC=C), 4.49 (dd, J = 6.9 and 8.4 Hz, 1H, CHO), 2.85-2.50 (m, 2H, SCH_2), 2.34 (s, 3H, SCH_3), 1.82-1.35 (m, 5H, $C\underline{H}(CH_3)_2$ and $(CH_2)_2$), 2.10 (broad s, 1H, OH), 1.15-0.81 (m, 9H, 3 CH_3). RMN ^{13}C (50.3 MHz, $CDCl_3$) : 136.74 ($\underline{C}(SR)_2$), 134.67 ($H\underline{C}$=C), 74.53 ($\underline{C}HO$), 34.09 ($\underline{C}H(CH_3)_2$), 32.31 ($S\underline{C}H_2$), 30.89 ($\underline{C}H_2$), 21.69 ($\underline{C}H_2$), 18.11 ($CH(\underline{C}H_3)_2$), 16.69 ($S\underline{C}H_3$), 13.56 ($\underline{C}H_3$). MS (CI, NH_3 + isobutane) m/z : 235 (MH^+, 2), 234 (M^+, 2), 217 (MH^+ - H_2O, 40), 191 (100), 145 (37). Elemental analysis : calc. for $C_{11}H_{22}OS_2$: C% = 56.36, H% = 9.46 ; found : C% = 56.64, H% = 9.69.

(*Z*)-1-benzylthio-1-*n*-butylthio-4-methyl-pent-1-en-3-ol (24*Z*) : yield 71%. ^1H NMR (200 MHz, $CDCl_3$) : 7.38-7.10 (m, 5H, C_6H_5), 5.89 (d, J = 8.8 Hz, 1H, HC=C), 4.50 (dd, J = 6.9 and 8.4 Hz, 1H, CHO), 3.97 (AB, J_{AB} = 13.2 Hz, δ_A-δ_B = 29.4 Hz, 2H, CH_2Ph), 2.82-2.60 (m, 2H, SCH_2), 1.68-1.19 (m,

6H, OH, C<u>H</u>$(CH_3)_2$ and $(CH_2)_2$), 0.93 (t, J = 7.9 Hz, 3H, CH_3), 0.71 (d, J = 6.5 Hz, 3H, CH_3), 0.58 (d, J = 6.7 Hz, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) : 138.48 (<u>C</u>$(SR)_2$), 137.39, 131.56, 128.42, 127.95 and 127.06 (H<u>C</u>=C and <u>C</u>$_6H_5$), 74.35 (<u>C</u>HO), 34.09 (<u>C</u>H$(CH_3)_2$), 37.55 (<u>C</u>H_2Ph), 33.23 (S<u>C</u>H_2), 20.98 (<u>C</u>H_2), 18.05 (<u>C</u>H_2), 17.82 (CH(<u>C</u>$H_3)_2$), 14.15 (<u>C</u>H_3). MS (CI, NH_3 + isobutane) m/z : 294 (MH^+-H_2O, 100), 268 (49), 204 (15). Elemental analysis : calc. for $C_{17}H_{26}OS_2$: C% = 65.76, H% = 8.44, S% = 20.65 ; found : C% = 65.99, H% = 8.48, S% = 20.63.

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