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Stereospecific Thio-Claisen Rearrangement of S-Crotylic α-Hydroxy Ketene Dithioacetals. Creation of three Contiguous Stereogenic Centres.

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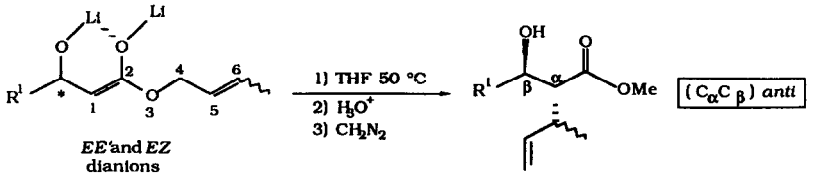
Abstract *All four diastereoisomeric S-crotylic α-hydroxy ketene dithioacetals (ZE', ZZ', EE' and EZ') were prepared uniquivocally from S-methyl or S-crotyl (Z or E) β-hydroxy dithioesters by a tandem cis-deprotonation with LDA and S-alkylation These dithioacetals underwent, in a refluxing cyclohexane solution, an easy thio-Claisen rearrangement into dithioesters, containing three contiguous chiral centres The rearrangement is stereospecific Furthermore each of the four system led to the formation of a different major diastereoisomer, thus making all of the four possible isomers (anti-anti, syn-syn, anti-syn and syn-anti) accessible A relationship between the main component configuration and the starting dithioacetal geometry has been ruled out The observed stereospecificity originates from two independant stereocontrols, an internal and an external one The former is in aggreement with the classical internal control obtained with a [3 3] sigmatropic shift The latter is a result of an asymmetric induction but surprisingly, is dependent on the S-crotylic double bond geometry All the results were rationalised by transition state models and the configurations proven by chemical correlations transformation into known esters and Swern oxidation*

Introduction

The Claisen rearrangement has been used extensively for the stereoselective construction of cyclic and acyclic frameworks [1] Several types of stereocontrol may be involved The internal control of the stereochemistry results in either stereospecificity[1,2] and/or a 1,3 or 1,4-chirality transfer[1,3] More recently, chiral centres directly attached to the pericyclic array on the terminal carbons have also been used to induce asymmetry[4-8], thus giving the possibility of an external control Some of these latter results have been compiled by Kahn and Hehre[5] and interpreted in terms of stereoelectronic control

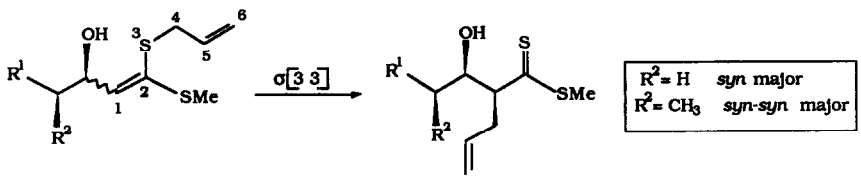
In a chelated version of the anionic enolate Claisen rearrangement, the stereochemistry was governed by an external hydroxy substituted centre on carbon 1 and hence aldols with a (CαCβ) *anti* configuration were stereoselectively formed (Scheme 1) [6] It is worth noting that for the starting dianions only (*EE'*) and (*EZ'*) systems are available



*EE'*and *EZ* dianions

Scheme 1

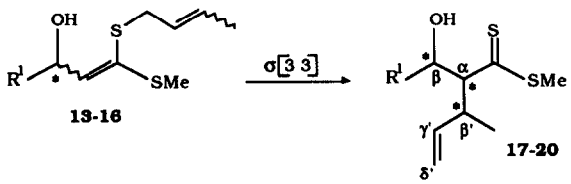
The corresponding sulphur analogue, using ketene dithioacetals, do not suffer such limitations, due to the availability for use of both double bond geometries. Thus, we have previously reported a diastereoselective asymmetric induction *via* the thio-Claisen rearrangement of the neutral S-allyl α-hydroxy ketene dithioacetals [7a,b] This resulted mainly in formation of *syn* α-allyl β-hydroxy dithioesters, independent of the geometry of the ketene double bond (Scheme 2, $R^2 = H$)



Scheme 2

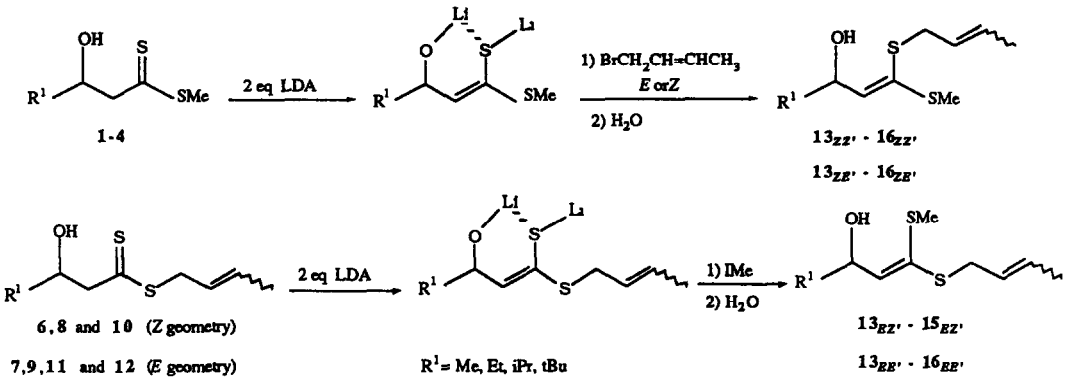
More recently with ketene dithioacetals including two vicinal centres, a quasi total stereocontrol on three contiguous centres has been observed (Scheme 2, $R^2 = CH_3$) [7c] Interestingly, diastereoselectivity has been also reported by P Metzner in a parallel investigation on similar systems.[8] In this case, the asymmetric induction was governed by a C-substituted asymmetric centre on carbons 1 or 6 or an O-substituted asymmetric centre on carbon 6 (see Scheme 2 for the numerotation of the carbons on the pericyclic nucleus)

We now disclose our new results concerning the thio-Claisen rearrangement of S-crotylic α-hydroxy ketene dithioacetals **13-16** into diastereoisomeric α-allyl β-hydroxy β'-methyl dithioesters **17-20** (Scheme 3) This is another method for the creation of three contiguous stereogenic centres [7c] In such a rearrangement, there is a combined use of a classic internal control and an external control The relative configuration (CαCβ') correlates with the two double bond geometries of the pericyclic nucleus and the (CαCβ) configuration depends on the external control by the chiral hydroxy centre For this purpose, all of the four diastereoisomeric S-crotylic α-hydroxy ketene dithioacetals are needed with pure geometric integrity



Scheme 3

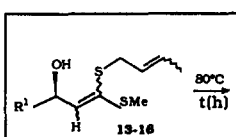
Owing to the particular reactivity of dithioesters, namely the S-alkylation of the corresponding thioenolates with retention of configuration,[9] the access to each of the desired diastereoisomeric ketene dithioacetals has been successfully achieved From our preliminary results, deprotonation of β-hydroxy dithioesters occurs readily and gives pure "*cis*" thioenolates [7] Their *in-situ* S-alkylation gives ketene dithioacetals with retention of the double bond geometry Thus the deprotonation of S-methyl β-hydroxy dithioesters **1-4** followed by an S-alkylation with (*E*) or (*Z*)-crotyl bromide opens the route to (*Z*)-ketene dithioacetals (formation of (*ZE'*) and (*ZZ'*) diastereoisomers[10] respectively) (Scheme 4) The corresponding (*EE'*)and (*EZ'*) isomers are then avalaible by a similar procedure deprotonation of (*E*) or (*Z*) S-crotyl β-hydroxy dithioesters **6-12** and S-alkylation with methyl iodide (Scheme 4)

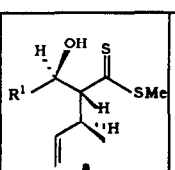


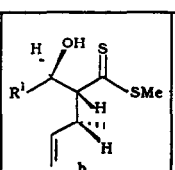
Scheme 4

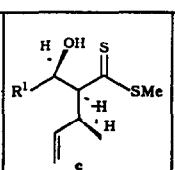
Results

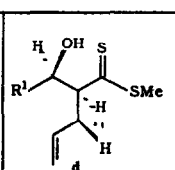
The synthesis of all four pure diastereoisomeric S-crotylic ketene dithioacetals was achieved using the chemistry described (Scheme 4) Starting dithioesters **1-4** have been prepared by an aldol condensation[11] between S-methyl dithioacetate and ethanal, propanal, isopropanal and trimethylacetaldehyde (*Z*)-Dithioesters **6, 8** and **10** and (*E*)-dithioesters **7, 9, 11** and **12** have been formed from S-crotyl dithioacetates 5_Z and 5_E respectively and the same aldehydes A deprotonation of dithioesters **1-4** with LDA at -78°C and a subsequent S-alkylation by pure (*Z*) or (*E*)-crotyl bromide afforded quantitatively and respectively pure ketene dithioacetals $13_{ZZ'}$-$16_{ZZ'}$ and $13_{ZE'}$-$16_{ZE'}$ By a same stereoselective deprotonation of (*Z*)-dithioesters **6, 8** and **10** and (*E*)-dithioesters **7, 9,11** and **12**, followed by an *in-situ* S-methylation, ketene dithioacetals $13_{EZ'}$-$15_{EZ'}$ and $13_{EE'}$-$16_{EE'}$ were obtained











Entry	R1	N°	Geo-metry	t (hr)	N°	*anti-anti* %	*anti-syn* %	*syn-syn* %	*syn-anti* %	%
1	Me	13	*ZE'*	2 5	17	**63**	3	7	27	85
2			*ZZ'*	5		3	17 5	**77**	2 5	98
3			*EE'*	3 5		9	**37**	29 5	24 5	78
4			*EZ'*	6		24	1	3	**72**	79
5	Et	14	*ZE'*	4	18	**70.5**	2	6	21 5	91
6			*ZZ'*	4 5		3	17	**78**	2	96
7			*EE'*	4 5		17	**36.5**	25	21,5	69
8			*EZ'*	8		18,5	1	5	**75.5**	88
9	iPr	15	*ZE'*	8	19	**73**	0 5	7 5	19	87
10			*ZZ'*	13		1	17	**79**	3	97
11			*EE'*	16		11	**42**	24	23	73
12			*EZ'*	12		15	0	10	**75**	90
13	tBu	16	*ZE'*	15	20	**94**	0	2 5	3 5	52
14			*ZZ'*	28		28	19	**51**	2	60
15			*EE'*	24		25	**55**	8	12	38

Table 1 Diastereoselectivity of the Rearrangement

The ^{1}H NMR spectra for each pair of (*E*) and (*Z*)-ketene dithioacetals exhibited the previously observed difference of chemical shift $\delta(CH=)_E > \delta(CH=)_Z$ and allowed us to ascertain the geometric purity of the ketene [7]

The rearrangement of these S-crotylic ketene dithioacetals into aldols **17-20** occured more slowly than that of the S-allylic analogues [7] several monthes at room temperature are required for the reaction to go to completion Hence, it was run at 80 °C in a cyclohexane solution without any change in the diastereoisomeric distribution The rearrangement times were ranging from 2 5 to 28 hours (Table 1)

Ketene Dithioacetal Geometry	Major Aldol Configuration
ZE'	*anti-anti*
ZZ'	*syn-syn*
EE'	*anti-syn*
EZ'	*syn-anti*

Table 2 Stereospecificity of the Rearrangement

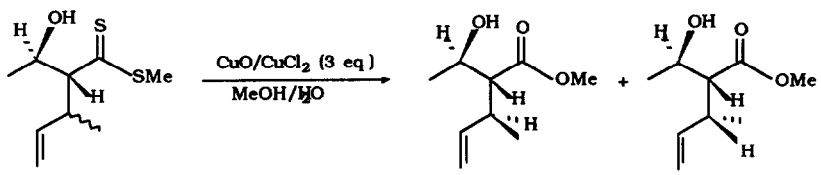
All the four possible diastereoisomeric dithioesters **17-20**, detected in HPLC analysis, were uniformly formed with quite acceptable yield except in the case of R^1 = tBu (Table 1, Entries 13-15) The rearrangement is stereospecific. the configuration of the major diastereoisomer correlates with the ketene dithioacetal configuration as summarized[12] in Table 2

However the diastereospecificity level is better with (*ZE'*), (*ZZ'*) and (*EZ'*) geometries relative to the (*EE'*) geometry. So the stereospecificity increases with the number of double bonds with a (*Z*) geometry (Table 1, Compare entries 2, 6, 10 with 4, 8, 12 and 1, 5, 9 and 3, 7, 11).

From the HPLC analysis, the four diastereoisomers **a b, c** and **d** are eluted in two well separated series. Each constitute a couple of (**a** + **b**) and (**c** + **d**) isomers with the *anti-anti, anti-syn, syn-syn* and *syn-anti* configuration respectively By purification by MPLC of each crude mixture of diastereoisomeric aldols **17-20**, dithioesters **17a** *anti-anti*, **17b** *anti-syn*, **19c** *syn-syn* and **19d** *syn-anti* have been isolated as pure products The others have been collected as mixtures of *syn-syn* and *syn-anti* isomers (**17c** + **17d**), (**18c** + **18d**), (**20c** + **20d**) and (*anti-anti* + *anti-syn*) isomers (**18a** + **18b**), (**19a** + **19b**), (**20a** + **20b**) respectively

Configuration Assignment

The configurations have been established only with the diastereoisomers **17a-d** (R^1 = Me) by a chemical correlation with the analoguous esters previously described by Kurth *et al* [6a,b] Thus the 95 5 mixture of **17a** and **17b** were reacted with $CuCl_2/CuO$ in methanol [13] Methanolysis resulted in a 95 5 mixture of two diastereoisomeric esters (Scheme 5)



17a-17b **21a** *anti-anti* **21b** *anti-syn*

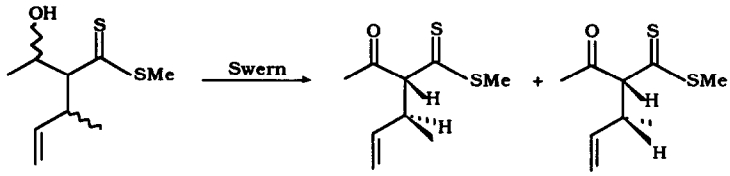
17a /17b = 95 5 **21a /21b** = 95 5

Scheme 5

These two esters were identified as the known esters with an *anti-anti* configuration for the major diastereoisomer (95%) and *anti-syn* configuration for the minor one (5%) Thus an *anti-anti* and *anti-syn* configuration have been assigned to the precursors **17a** and **17b** respectively A similar methanolysis applied to the mixture of diastereoisomers **17c** and **17d** failed Nevertheless, **17c** and **17d** must have a *syn* (CαCβ) configuration

The *syn* or *anti* (CαCβ') configuration has been unambiguously determined after Swern oxidations[14] of β-hydroxy dithioesters **17a-d** into *syn* and *anti* β-oxo dithioesters (Scheme 6) During this process the

asymmetry at the carbon in the β-position has been lost. The oxidation has been successively applied to pure isomers **17a** and **17b** and two different mixtures of the other isomers **17c** and **17d**: a 96 4 mixture of **17c+17d**, obtained from the rearrangement of dithioacetal $\mathbf{13_{ZZ'}}$ (Table 1, Entry 2) and a 4 96 mixture issued from $\mathbf{13_{EZ'}}$ (Table 1; Entry 4)



17a-17d **22** *anti* **23** *syn*

Aldol	**22 /23**
Pure **17a**	100 0
Pure **17b**	0 100
17c/17d ratio 96 4	15 85
17c/17d ratio 4 96	90 10

Scheme 6

Oxidation of *anti-anti* **17a** gave pure *anti* β-oxo dithioester **22** and oxidation of *anti-syn* **17b** pure *syn* β-oxo dithioester **23** (Scheme 6) On the other hand, the 96 4 mixture of (**17c+17d**) was converted in a 15 85 mixture of (**22+23**) and the 4 96 mixture provided a 90 10 mixture of (**22+23**) So a *syn-syn* and a *syn-anti* configuration has been assigned to **17c** and **17d** respectively

The same trends in the diastereoisomeric ratio are observed with dithioesters **18-20** as shown in the table 1 The same configuration assignements were then extended to diastereoisomers **18a-d**, **19a-d** and **20a-d** So all four diastereoisomeric rearranged dithioesters **17**, **18**, **19** and **20** may be formed predominantly by a judicious choice of the starting S-crotylic ketene dithioacetal (Table 1)

Discussion

Internal Control

The (CαCβ') configurations result from the internal control of the Claisen rearrangement and correlate to the double bond geometries The level of this control, quantified by the (*anti-syn* + *syn-syn*) (*anti-anti* + *syn-anti*) ratio for each diastereiosomeric mixture **17-20**, is quite high except for (*EE'*)-ketene dithioacetals (see Table 3 for the particular case of dithioacetals **13**)

Dithioacetals **13** Geometry	(CαCβ') *syn/anti* ratio
ZE'	10 90
ZZ'	94 5 5 5
EE'	66 5 33 5
EZ'	4 96

Table 3 Internal Control with Ketene Dithioacetals **13**

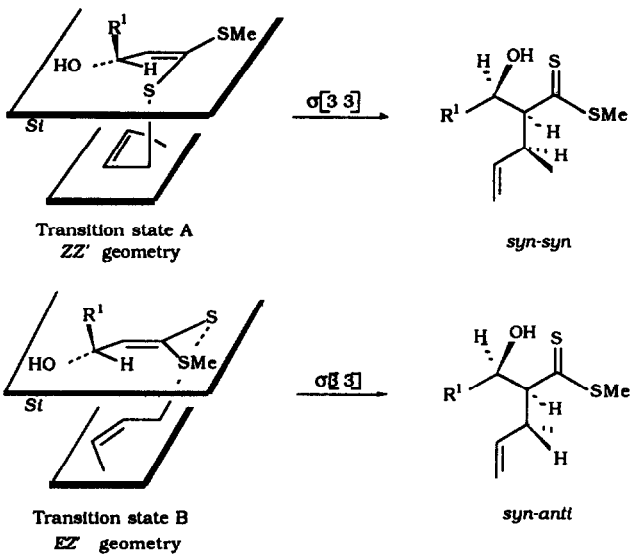
Changing only one of the geometries of the hexadienic system induces a (CαCβ') relative configuration inversion Conversely, changing the geometry of both double bonds gives retention of (CαCβ') configuration Usual correlations between (CαCβ') configurations and double bond geometries are effective and may be rationalized by the classic pseudo chair transition state [1,15]

External Control

Obviously, a (*Z*) geometry for the S-crotylic double bond favoures a *syn* (CαCβ) configuration and a (*E*)geometry favoures an *anti* (CαCβ) configuration It is noteworthy that, in our precedent related study, S-allylic ketene dithioacetals always rearranged into *syn* (CαCβ) diastereoisomers [7] So this difference for the major (CαCβ) configuration originates from the introduction of the methyl group on the terminal carbon of the S-allylic chain This behaviour contrasts with Kurth's results obtained with the dianionic analogue with

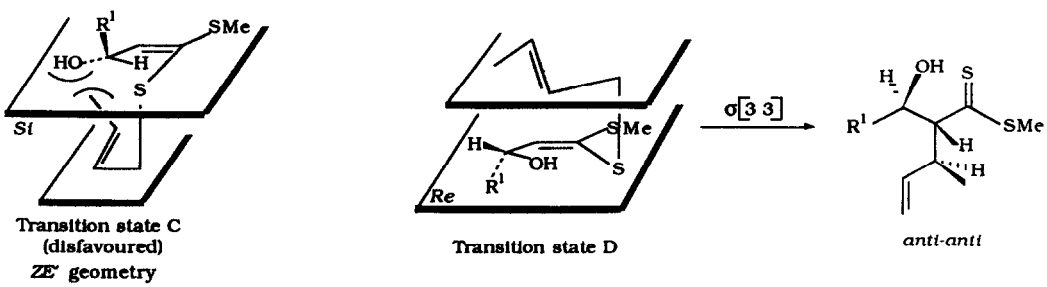
oxygenated precursors (Scheme 1) These results showed the exclusive formation of *anti* (CαCβ) β-hydroxy esters, regardless of bond geometry

According to these correlations between the major (CαCβ) configuration and the S-crotylic double bond geometry, a transition state model, similar to that proposed for S-allylic α-hydroxy ketene dithioacetal rearrangement, is not suitable for a total interpretation and can only be used to explain a *syn* (CαCβ) configuration. Correspondingly, with (*ZZ'*) and (*EZ'*) dithioacetals a *Si*-approach (on the bottom face) fits adequately with the observed (CαCβ) *syn* configuration of the rearranged dithioesters (Scheme 7)



Scheme 7

When the crotylic double bond of the dithioacetal possesses (*E*) geometry, an opposite asymmetric induction is observed which probably is due to the approach mode differing In a *Si*-approach pictured as transition state C, severe steric interactions between the terminal methyl group and the encumbered asymmetric centres disfavour the C-C single bond formation (Scheme 8) The stereochemical facial differenciation must then occur *via* a *Re* approach (on the top face) as pictured in transition state model D with the OH group lying in an "inside" position[16] and the hydrogen in an "outside"position [16] The approach occurs *anti* to the alkyl group R^1 on the less congested face Such a conformation has been recently put forward in a stereocontrol interpretation of some electrophilic reaction results [17]



Scheme 8

For (*EE'*)-ketene dithioacetals where the observed selectivities are lower, the two types of *Re* and *Si* approaches may be accessible and this may account for the diastereoisomeric ratio of dithioesters **17-20**

Conclusion

Various S-crotylic α-hydroxy ketene dithioacetals were prepared efficiently and with pure geometric integrity from β-hydroxy dithioesters by a stereoselective double deprotonation, followed by a S-alkylation of the resulting dianions Their thio Claisen rearrangement in a refluxing cyclohexane solution afforded dithioesters with three contiguous chiral centres (four diastereoisomers are possible) Stereospecificity is observed· in each case one of the four possible diastereoisomers is selectively formed and its stereochemistry correlates with the geometry of the dithioacetal This stereocontrol is a result of two different controls an internal and an external one Transition state models were suggested to rationalise the results

Work is in progress to extend these original results to the creation of four contiguous stereogenic centres from β-hydroxy dithioesters bearing one more stereogenic centre in a γ-position The influence of other heteroatoms on the chiral centre is also under investigation

EXPERIMENTAL SECTION

General

All reactions were conducted under a positive pressure of nitrogen THF was distilled over sodium benzophenone ketyl Preparative liquid chromatography was performed on a Jobin-Yvon Chromatospac Prep 10 chromatograph or by flash chromatography HPLC was performed with a UV (254 nm) detector on a Waters HPLC pump and a 40 mm x 25 cm silica column (Merck SI 60, 5μ) equiped with a Perisorb A S I 60 precolumn ^{1}H NMR 60 MHz spectra were run on a Varian EM 360 spectrometer and ^{1}H NMR 200 Hz on a JEOL JNM-FX 200 ^{13}C NMR spectra were determined at 20 15 MHz with a Bruker WP 80 spectrometer IR absorption spectra were run on a Perkin-Elmer 257 and 684 instruments Mass spectra were obtained at 70 eV with Varian Mat CH5 or with Nermag spectrometers Elemental analyses were performed by Service Central d'Analyse of CNRS at Vernaison

(*E*)-2-Buten-1-ol was purchased from Aldrich Chemical Company (*Z*)-2-Buten-1-ol was prepared from commercial 2-butyn-1-ol (Aldrich) by hydrogenation over Lindlar catalyst, following the procedure described [18] (*E*)-1-Bromo-2-butene was prepared by the reaction of (*E*)-2-buten-1-ol with CBr_4 in the presence of PPh_3 in dry acetonitrile under standard conditions [19] (*Z*)-1-Bromo-2-butene was obtained by the reaction of (*Z*)-2-Buten-1-ol with PBr_3 in ether [20] The synthesis of methyl 3-hydroxybutanedithioate **1**, methyl 3-hydroxypentanedithioate **2**, methyl 3-hydroxy-4-methylpentanedithioate **3** and methyl 3-hydroxy-4,4-dimethylpentanedithioate **4** were previously described by us [7b] (*E*)-2-butenyl dithioacetate was prepared by a classical condensation of CS_2 with methylmagnesium iodide, followed by an alkylation with (*E*)-1-bromo-2-butene [21] (*Z*)-2-butenyl dithioacetate was obtained from dithioacetic acid[21] and (*Z*)-2-buten-1-ol according to a published method [22]

General Procedure for the Aldol Reaction

n-Butyllithium (1 1 eq) was added dropwise to a cooled (-20 °C) solution of diisopropylamine (1 1 eq) in THF and the solution was stirred at this temperature for 30 min The resulting solution of LDA was cooled to -78 °C and a solution of 2-butenyl dithioacetate **5** (1 1 eq) in THF was added dropwise and stirred for 25 min at -78 °C to give a colourless solution A solution of the required aldehyde (1 1 eq) in THF was added in one aliquot at -78 °C and the solution turned orange immediately The reaction mixture was stirred at -78 °C (each reaction time is indicated below for each compound), quenched with a saturated NH_4Cl solution, allowed to warm to room temperature and extracted with ether The organic extract was washed with saturated brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford crude aldols **6-12** The products were then purified by flash chromatography Their geometric purity was determined by ^{13}C NMR analysis

***(Z)-2-Butenyl 3-hydroxybutanedithioate* 6**

From the reaction between dithioacetate $\mathbf{5_Z}$ (0 2 g, 1 4 mmol) and acetaldehyde for 1 min Yield 49% Orange oil TLC R_f 0 36 (c-hexane/EtOAc 80 20) δ_H (60 MHz, CCl_4) 1 18 (d, J = 6, 3H, CH_3), 1 6 to 1 8 (m, 3H, =CH-$\underline{CH_3}$), 3 02 (d, J = 6, 2H, H-2), 3 27 (br s, 1H, OH), 3 77 to 4 00 (m, 2H, SCH_2), 4 25 (sextet, J = 6, 1H, H-3), 5 23 to 6 00 (m, 2H, CH=CH) ν_{max} 3 618 and 3 456 cm^{-1} (OH), 3 020 cm^{-1} (=C-H) δ_C ($CDCl_3$) 13 08 (CH_3), 22 54 (CH_3), 33 98 (SCH_2), 59 71 (C-2), 67 88 (C-3), 121 98 (=$\underline{CH}$-CH_3), 130 19 (SCH_2-$\underline{CH}$=), 236 24 (C=S) *M/Z* 43 (100), 55 (87), 58 (19), 85 (16), 91 (18), 101 (29), 135 (36), 175 (15), 190 (8) Anal Calcd for $C_8H_{14}OS_2$ C, 50 49, H, 7 41, S, 33 69 Found C, 50 64, H, 7 36, S, 33 59

***(E)-2-Butenyl 3-hydroxybutanedithioate* 7**

From the reaction between dithioacetate $\mathbf{5_E}$ (1 46 g, 10 mmol) and acetaldehyde for 1 min Yield 56% Orange oil TLC R_f 0 2 (c-hexane/EtOAc 80 20) δ_H (60 MHz, CCl_4 and D_2O) 1 18 (d, J = 6, 3H, CH_3), 1 57 to 1 83 (m, 3H, =CH-$\underline{CH_3}$), 3 00

(d, J = 6, 2H, H-2), 3 7 to 3 97 (m, 2H, SCH_2), 4 23 (sextet, J = 6, 1H, H-3), 5 13 to 6 02 (m, 2H, CH=CH) ν_{max} 3 620 and 3 470 cm^{-1} (OH), 3 020 cm^{-1} (=C-H) δ_C ($CDCl_3$) 17.86 (=CH-$\underline{CH_3}$), 22 61 (CH_3), 39 09 (SCH_2), 59 81 (C-2), 67 91 (C-3), 122 99 (=$\underline{CH}$-CH_3), 131 48 (SCH_2-$\underline{CH}$=), 235 97 (C=S) *M/Z* 43 (60), 45 (47), 55 (100), 87 (16), 101 (27), 134 (12), 135 (46), 175 (16), 190 (5) Anal Calcd for $C_8H_{14}OS_2$ C, 50 49, H, 7 41, S, 33 69 Found C, 50 89, H, 7 36, S, 33 58

***(Z)-2-Butenyl 3-hydroxypentanedithioate* 8**

From the reaction between dithioacetate **5Z** (0.2 g, 1 4 mmol) and propanal for 45 s Yield 47% Orange oil TLC R_f 0 27 (c-hexane/EtOAc 90 10) δ_H (60 MHz, CCl_4) 0 98 (t, J = 6 5, 3H, CH_3), 1 21 to 1 5 (m, 2H, H-4), 1 65 to 1 83 (m, 3H, =CH-$\underline{CH_3}$), 2 92 (br s, 1H, OH), 2 95 to 3 15 (m, 2H, H-2), 3 73 to 4 25 (m, 3H, SCH_2 and H-3), 5 23 to 6 06 (m, 2H, CH=CH) ν_{max} 3 620 and 3 470 cm^{-1} (OH), 3 020 cm^{-1} (=C-H) δ_C ($CDCl_3$)· 9 78 (CH_3), 13 07 (=CH-$\underline{CH_3}$), 29 56 (C-4), 34 02 (SCH_2), 57 95 (C-2), 72 98 (C-3), 121 97 (=$\underline{CH}$-CH_3), 130 17 (SCH_2-$\underline{CH}$=), 236 63 (C=S) *M/Z* 55 (77), 57 (100), 59 (52), 87 (24), 115 (11), 149 (48), 175 (14), 189 (13), 204 (11) Anal Calcd for $C_9H_{16}OS_2$ C, 52 90, H, 7 89, S, 31 38 Found C, 53 58, H, 8 11, S, 31 55

***(E)-2-Butenyl 3-hydroxypentanedithioate* 9**

From the reaction between dithioacetate **5E** (0 365 g, 2 5 mmol) and propanal for 45 s Yield 57% Orange oil TLC R_f 0 37 (c-hexane/EtOAc 80 20) δ_H (60 MHz, CCl_4 and D_2O) 0 97 (t, J = 6 5, 3H, CH_3), 1 2 to 1 5 (m, 2H, H-4), 1 6 to 1 77 (m, 3H, =CH-$\underline{CH_3}$), 2 9 to 3 07 (m, 2H, H-2), 3 63 to 4.13 (m, 3H, SCH_2 and H-3), 5 1 to 6 00 (m, 2H, CH=CH) ν_{max} 3 680 and 3 480 cm^{-1} (OH), 3 030 cm^{-1} (=C-H) δ_C ($CDCl_3$) 9 82 (CH_3), 17 77 (=CH-$\underline{CH_3}$), 29 56 (C-4), 39 05 (SCH_2), 58 01 (C-2), 72 96 (C-3), 122 96 (=$\underline{CH}$-CH_3), 131 39 (SCH_2-$\underline{CH}$=), 236 35 (C=S) *M/Z* 43 (11), 55 (68), 57 (100), 71 (19), 117 (9), 149 (22), 175 (6), 189 (6), 204 (4) Anal Calcd for $C_9H_{16}OS_2$ C, 52 90, H, 7 89, S, 31 38 Found C, 52 82, H, 7 94, S, 31 22

***(Z)-2-Butenyl 3-hydroxy-4-methylpentanedithioate* 10**

From the reaction between dithioacetate **5Z** (0 2 g, 1 4 mmol) and isobutyraldehyde for 30 s Yield 33% Orange oil TLC R_f 0 32 (c-hexane/EtOAc 95 5) δ_H (60 MHz, CCl_4) 0 95 (d, J = 6, 6H, 2 CH_3 of iPr), 1 16 to 1 57 (m, 1H, H-4), 1 6 to 1 8 (m, 3H, =CH-$\underline{CH_3}$), 2 67 (br s, 1H, OH), 2 9 to 3 1 (m, 2H, H-2), 3 73 to 4 00 (m, 3H, SCH_2 and H-3), 5 23 to 6 00 (m, 2H, CH=CH) ν_{max} 3 600 and 3 460 cm^{-1} (OH), 3 020 cm^{-1} (=C-H) δ_C ($CDCl_3$) 13 10 (=CH-$\underline{CH_3}$), 17 49 and 18 69 (2 CH_3 of iPr), 33 54 (C-4), 34 10 (SCH_2), 55 81 (C-2), 76 42 (C-3), 122 01 (=$\underline{CH}$-CH_3), 130 19 (SCH_2-$\underline{CH}$=), 237 44 (C=S) *M/Z* 43 (54), 55 (62), 71 (100), 87 (18), 91 (16), 113 (10), 131 (11), 163 (23), 218 (5) Anal Calcd for $C_{10}H_{18}OS_2$ C, 55 00, H, 8 31, S, 29 36 Found C, 55 49, H, 8 40, S, 28 25

***(E)-2-Butenyl 3-hydroxy-4-methylpentanedithioate* 11**

From the reaction between dithioacetate **5E** (0 44 g, 3 mmol) and isobutyraldehyde for 30 s Yield 50% Orange oil TLC R_f 0 31 (c-hexane/EtOAc 90 10) δ_H (60 MHz, CCl_4) 0 95 (d, J = 7, 6H, 2 CH_3 of iPr), 1 5 to 2 1 (m, 4H, H-4 and =CH-$\underline{CH_3}$), 2 5 (br s, 1H, OH), 2 83 to 3 13 (m, 2H, H-2), 3 63 to 4 03 (m, 3H, SCH_2 and H-3), 5 13 to 6 03 (m, 2H, CH=CH) ν_{max} 3 610 and 3 475 cm^{-1} (OH), 3 020 cm^{-1} (=C-H) δ_C ($CDCl_3$) 17 53 (CH_3 of iPr), 17 82 (=CH-$\underline{CH_3}$), 18 73 (CH_3 of iPr), 33 53 (C-4), 39 16 (SCH_2), 55 90 (C-2), 76 41 (C-3), 123 05 (=$\underline{CH}$-CH_3), 131 39 (SCH_2-$\underline{CH}$=), 237 09 (C=S) *M/Z* 43 (82), 53 (13), 55 (100), 71 (91), 73 (21), 87 (20), 131 (13), 163 (24), 203 (5), 218 (5) Anal Calcd for $C_{10}H_{18}OS_2$ C, 55 00, H, 8 31, S, 29 36 Found C, 55 79, H, 8 39, S, 28 35

***(E)-2-Butenyl 3-hydroxy-4,4-dimethylpentanedithioate* 12**

From the reaction between dithioacetate **5E** (0 73 g, 5 mmol) and trimethylacetaldehyde for 30 s Yield 41% Orange oil TLC R_f 0 27 (c-hexane/EtOAc 90 10) δ_H (60 MHz, CCl_4) 0 97 (s, 9H, 3 CH_3 of tBu), 1 6 to 1 83 (m, 3H, =CH-$\underline{CH_3}$), 2 63 (br s, 1H, OH), 2 73 to 3 4 (m, 3H, H-2 and H-3), 3 53 to 3 97 (m, 2H, SCH_2), 5 4 to 5 87 (m, 2H, CH=CH) ν_{max} 3 615 and 3 465 cm^{-1} (OH), 3 020 cm^{-1} (=C-H) δ_C ($CDCl_3$) 17 74 (=CH-$\underline{CH_3}$), 25 81 (3 CH_3 of tBu), 35 07 (C-4), 39 16 (SCH_2), 54 09 (C-2), 79 32 (C-3), 122 96 (=$\underline{CH}$-CH_3), 131 32 (SCH_2-$\underline{CH}$=), 237 85 (C=S) *M/Z* 41 (32), 55 (53), 57 (100), 69 (20), 85 (36), 87 (21), 177 (12), 232 (8) Anal Calcd for $C_{11}H_{20}OS_2$ C, 56 85, H, 8 68, S, 27 59 Found C, 57 00, H, 8 70, S, 26 70

General Procedure for Ketene Dithioacetal Formation and subsequent Thio-Claisen Rearrangement

n-Butyllithium (2 2 eq) was added dropwise to a cooled (-20 °C) solution of diisopropylamine (2 2 eq) in dry THF and the solution was stirred at this temperature for 15 min The resulting solution of LDA was cooled to -78 °C A solution of S-methyl aldols **1-4** or S-2-butenyl aldols **6-12** (1 eq) was added dropwise *via* a syringe The mixture was stirred at -78 °C for 45 min To the colourless resulting solution, the electrophile (1 1 eq of crotyl bromide or methyl iodide) was added at -78 °C in one portion The solution was stirred for 45 min at the temperature indicated below (-20 °C or -78 °C), then allowed to warm to room temperature over 30 min After quenching with a saturated NH_4Cl solution, the colourless reaction mixture was extracted with ether The ethereal extract was washed with sodium thiosulfate and with brine, dried over $MgSO_4$ and filtered Concentration *in vacuo* afford colourless ketene dithioacetals **13-16** Their rearrangements were performed in refluxing cyclohexane and lead to dithioesters **17-20** The diastereoisomeric distribution was determined by an HPLC analysis The dithioesters **17-20** were purified by MPLC In some cases, the separation of the diastereoisomeric mixture was successful (*vide infra*)

***Methyl 2-(1-hydroxyethyl)-3-methyl-4-pentenedithioate* 17**

From the thio-Claisen rearrangement of ketene dithioacetal **13ZE**, formed by the reaction of aldol **1** (0 3 g, 2 mmol) and (*E*)-1-bromo-2-butene at -20°C Rearrangement time 2 5 hrs Yield 85% *anti-anti / anti-syn / syn-syn / syn-anti* ratio 63 3 7 27 From the thio-Claisen rearrangement of ketene dithioacetal **13ZZ**, formed by the reaction of aldol **1** (0 075 g, 0 5 mmol) and (*Z*)-1-bromo-2-butene at -20°C Rearrangement time 5 hrs Yield 98% *anti-anti / anti-syn / syn-syn / syn-anti* ratio 3 17 5 77 2 5 From the thio-Claisen rearrangement of ketene dithioacetal **13EE**, formed by the reaction of aldol **7** (0 076 g, 0 4 mmol) and methyl iodide at -78°C Rearrangement time 3 5 hrs Yield 78% *anti-anti / anti-syn / syn-syn / syn-anti* ratio 9 37 29 5 24 5

From the thio-Claisen rearrangement of ketene dithioacetal $\mathbf{13}_{EZ}$, formed by the reaction of aldol **6** (0 08 g, 0 42 mmol) and methyl iodide at -78°C Rearrangement time 6 hrs Yield 79% *anti-anti / anti-syn / syn-syn / syn-anti* ratio 24 1 3 72

HPLC the elution order is the following one *anti-anti* **17a**, *anti-syn* **17b**, *syn-syn* **17c**, *syn-anti* **17d** (n-heptane/EtOAc 97 3) After MPLC, *anti-anti* isomer **17a** and *anti-syn* isomer **17b** were isolated as pure products and *syn-syn* isomer **17c** and *syn-anti* isomer **17d** as a mixture

***Anti-anti* isomer 17a**

Orange oil TLC R_f 0.16 (c-hexane/EtOAc 95 5) δ_H (200 MHz, $CDCl_3$) 0 95 (d, J = 6 35, 3H, CH_3), 1 16 (d, J = 6 35, 3H, CH_3), 2 67 (s, 3H, SCH_3), 2 95 to 3.15 (m, 2H, H-α and H-β'), 3 34 (d, J = 10 74, 1H, OH), 3 97 to 4 16 (m, 1H, H-β), 5 08 to 5 88 (m, 3H, H-γ and H-δ') ν_{max} 3 430 cm^{-1} (OH), 3 075 cm^{-1} (=C-H), 1 638 cm^{-1} (C=C) δ_C ($CDCl_3$) 18 16, 19 23, 21 89, 40 83 (C–β'), 66 92 (C-α), 71 52 (C–β), 115 83 (C–δ'), 140 94 (C–γ'), 241 09 (C=S) Anal Calcd for $C_9H_{16}OS_2$ C, 52.90, H, 7 89, S, 31 38 Found C, 53 07, H, 7 96, S, 30 34

***Anti-syn* isomer 17b**

Orange oil TLC R_f 0 14 (c-hexane/EtOAc 95 5) δ_H (200 MHz, $CDCl_3$) 1 18 (d, J = 5 86, 3H, CH_3), 1 21 (d, J = 6 35, 3H, CH_3), 2 60 (s, 3H, SCH_3), 2 83 to 3 05 (m, 2H, H-α and H-β'), 3 38 (d, J = 10 49, 1H, OH), 4 1 to 4 2 (m, 1H, H-β), 4 77 to 5 68 (m, 3H, H-γ and H-δ') ν_{max} 3 460 cm^{-1} (OH), 3 075 cm^{-1} (=C-H), 1 638 cm^{-1} (C=C) δ_C ($CDCl_3$) 17 88, 18 91, 21 83, 41 64 (C–β'), 66 38 (C-α), 70 95 (C–β), 114 20 (C–δ'), 140 88 (C–γ'), 240 88 (C=S)

***Syn-syn* isomer 17c**

Orange oil TLC R_f 0 07 (c-hexane/EtOAc 95 5) δ_H (200 MHz, $CDCl_3$) 1 10 (d, J = 7 08, 3H, CH_3), 1 21 (d, J = 6 11, 3H, CH_3), 2 17 (br s, 1H, OH), 2 59 (s, 3H, SCH_3), 2 83 to 3 01 (m, 2H, H-β'), 3 25 (dd, J = 7 57 and 6 11, 1H, H-α), 4 18 to 4 31 (m, 1H, H-β), 4 97 to 6 16 (m, 3H, H-γ and H-δ') ν_{max} 3 540 cm^{-1} (OH), 3 080 cm^{-1} (=C-H), 1 650 cm^{-1} (C=C) δ_C ($CDCl_3$) 18 40, 19 02, 21 41, 39 42 (C–β'), 69 49 (C-α), 72 27 (C–β), 114 31 (C–δ'), 140 91 (C–γ'), 237 78 (C=S) *M/Z* 43 (58), 45 (49), 55 (54), 101 (100), 111 (53), 117 (12), 145 (38), 157 (49), 159 (60), 204 (1)

***Syn-anti* isomer 17d**

Orange oil TLC R_f 0 07 (c-hexane/EtOAc 95 5) δ_H (200 MHz, $CDCl_3$) 0 98 (d, J = 6 35, 3H, CH_3), 1 17 (d, J = 5 86, 3H, CH_3), 2 5 (br s, 1H, OH), 2 62 (s, 3H, SCH_3), 2 83 to 3 03 (m, 1H, H-β'), 3 18 (dd, J = 6 34 and 8 79, 1H, H-α), 4 10 to 4 33 (m, 1H, H-β), 4 96 to 6 18 (m, 3H, H-γ and H-δ') ν_{max} 3 542 cm^{-1} (OH), 3 065 cm^{-1} (=C-H), 1 629 cm^{-1} (C=C) δ_C ($CDCl_3$) 18 40, 19 02, 20 59, 42 00 (C–β'), 70 36 (C-α), 72 48 (C–β), 114 31 (C–δ'), 143 10 (C–γ'), 238 64 (C=S)

***Methyl 2-(1-hydroxypropyl)-3-methyl-4-pentenedithioate* 18**

From the thio-Claisen rearrangement of ketene dithioacetal $\mathbf{14}_{ZE}$, formed by the reaction of aldol **2** (0 246 g, 1 5 mmol) and (*E*)-1-bromo-2-butene at -20°C Rearrangement time 4 hrs Yield 91% *anti-anti / anti-syn / syn-syn / syn-anti* ratio 70 5 2 6 21 5 From the thio-Claisen rearrangement of ketene dithioacetal $\mathbf{14}_{ZZ}$, formed by the reaction of aldol **2** (0 08 g, 0 5 mmol) and (*Z*)-1-bromo-2-butene at -20°C Rearrangement time 4 5 hrs Yield 96% *anti-anti / anti-syn / syn-syn / syn-anti* ratio 3 17 78 2 From the thio-Claisen rearrangement of ketene dithioacetal $\mathbf{14}_{EE}$, formed by the reaction of aldol **9** (0 047 g, 0.22 mmol) and methyl iodide at -78°C Rearrangement time 4 5 hrs Yield 69% *anti-anti / anti-syn / syn-syn / syn-anti* ratio 17 36 5 25 21 5 From the thio-Claisen rearrangement of ketene dithioacetal $\mathbf{14}_{EZ}$, formed by the reaction of aldol **8** (0 06 g, 0 29 mmol) and methyl iodide at -78°C Rearrangement time 8 hrs Yield 88% *anti-anti / anti-syn / syn-syn / syn-anti* ratio 18 5 1 5 75 5

HPLC the elution order is the following one *anti-anti* **18a**, *anti-syn* **18b**, *syn-syn* **18c**, *syn-anti* **18d** (n-heptane/EtOAc 98 2) After MPLC, *anti-anti* isomer **18a** and *anti-syn* isomer **18b** were isolated as a mixture and *syn-syn* isomer **18c** and *syn-anti* isomer **18d** as a mixture

***Anti-anti* isomer 18a**

Orange oil TLC R_f 0 18 (c-hexane/EtOAc 95 5) δ_H (200 MHz, $CDCl_3$) 0 94 (d, J = 5 7, 3H, CH_3-β'), 0 95 (t, J = 7 32, 3H, CH_3), 1 40 (quintet, J = 7 32, 2H, H–γ), 2 66 (s, 3H, SCH_3), 2 92 to 3 09 (m, 2H, H-α and H–β'), 3 3 (d, J = 10 74, 1H, OH), 3 52 to 3 73 (m, 1H, H-β), 4 97 to 5 83 (m, 3H, H-γ and H-δ') ν_{max} 3 430 cm^{-1} (OH), 3 075 cm^{-1} (=C-H), 1 640 cm^{-1} (C=C) δ_C ($CDCl_3$) 10 89 (CH_3), 18 46, 19 57, 29 08 (C_γ), 41 32 (C–β'), 69 86 (C-α), 73 48 (C–β), 115 86 (C–δ'), 141 37 (C–γ'), 242 01 (C=S) *M/Z* 55 (68), 57 (100), 71 (39), 97 (41), 112 (16), 115 (59), 145 (68), 159 (98), 189 (43), 218 (2) Anal Calcd for $C_{10}H_{18}OS_2$ C, 55 00, H, 8 31, S, 29 36 Found C, 55 30, H, 8 24, S, 29 28

***Anti-syn* isomer 18b**

Orange oil TLC R_f 0 18 (c-hexane/EtOAc 95 5) δ_H (200 MHz, $CDCl_3$) 0 95 (t, J = 7 08, 3H, CH_3), 1 18 (d, J = 5 86, 3H, CH_3-β'), 1 3 to 1 5 (m, 2H, H–γ), 2 58 (s, 3H, SCH_3), 2 89 to 3 18 (m, 2H, H-α and H–β'), 3 31 (d, J = 10 74, 1H, OH), 3 61 to 3 81 (m, 1H, H-β), 4 79 to 5 89 (m, 3H, H-γ and H-δ') ν_{max} 3 420 cm^{-1} (OH), 3 070 cm^{-1} (=C-H), 1 638cm^{-1} (C=C) δ_C ($CDCl_3$) 11 04 (CH_3), 18 15, 19 39, 29 13 (C_γ), 41 99 (C–β'), 69 22 (C-α), 72 92 (C–β), 114 48 (C–δ'), 141 15 (C–γ'), 242 13 (C=S)

***Syn-syn* isomer 18c**

Orange oil TLC R_f 0 04 (c-hexane/EtOAc 95 5) δ_H (200 MHz, $CDCl_3$) 0 96 (t, J = 7 08, 3H, CH_3), 1 1 (d, J = 6 84, 3H, CH_3-β'), 1 28 to 1 68 (m, 2H, H-α), 2 23 (br s, 1H, OH), 2 59 (s, 3H, SCH_3), 2 83 to 3 03 (m, 1H, H–β'), 3 31 (dd, J = 6 11 and 7 08, 1H , H-α), 3 84 to 4 04 (m, 1H, H-β), 4 91 to 6 15 (m, 3H, H-γ and H-δ') ν_{max} 3 610 and 3 445 cm^{-1} (OH), 3 065 cm^{-1} (=C-H), 1 632 cm^{-1} (C=C) δ_C ($CDCl_3$) 10 53 (CH_3), 18 75, 19 51, 27 91 (C_γ), 39 52 (C–β'), 70 58 (C-α), 77 88 (C–β), 114 61 (C–δ'), 141 27 (C–γ'), 239 19 (C=S)

***Syn-anti* isomer 18d:**

Orange oil TLC R_f 0 04 (c-hexane/EtOAc 95 5) δ_H (200 MHz, $CDCl_3$) 0.93 (t, J = 7 33, 3H, CH_3), 1 00 (d, J = 6 35, 3H, CH_3-β'), 1.24 to 1.67 (m, 2H, H-γ), 2 62 (s, 3H, SCH_3), 2.65 (br s, 1H, OH), 2 8 to 3.00 (m, 1H, H-β'), 3 24 (dd, J = 6 35 and 8 31, 1H, H-α), 3 73 to 3 99 (m, 1H, H-β), 4 91 to 6 15 (m, 3H, H-γ and H-δ') ν_{max} 3 560 cm^{-1} (OH), 3 070 cm^{-1} (=C-H), 1 630 cm^{-1} (C=C) δ_C ($CDCl_3$) 10 53 (CH_3), 17 75, 19 51, 27 37 (C_γ), 42 02 (C-β'), 71 16 (C-α), 76 32 (C-β), 114 61 (C-δ'), 143 35 (C-γ'), 240 30 (C=S)

***Methyl 2-(1-hydroxy-2-methylpropyl)-3-methyl-4-pentenedithioate* 19**

From the thio-Claisen rearrangement of ketene dithioacetal **15_{ZE}**, formed by the reaction of aldol **3** (0 089 g, 0 5 mmol) and (*E*)-1-bromo-2-butene at -20°C Rearrangement time 8 hrs Yield 87% *anti-anti / anti-syn / syn-syn / syn-anti* ratio 73 0 5 7 5 19 From the thio-Claisen rearrangement of ketene dithioacetal **15_{ZZ}**, formed by the reaction of aldol **3** (0 089 g, 0 5 mmol) and (Z)-1-bromo-2-butene at -20°C Rearrangement time. 13 hrs Yield 97% *anti-anti / anti-syn / syn-syn / syn-anti* ratio 1 17 79 3 From the thio-Claisen rearrangement of ketene dithioacetal **15_{EE}**, formed by the reaction of aldol **11** (0 17 g, 0 75 mmol) and methyl iodide at -78°C Rearrangement time 16 hrs Yield 73% *anti-anti / anti-syn / syn-syn / syn-anti* ratio 11 42 24 23 From the thio-Claisen rearrangement of ketene dithioacetal **15_{EZ}**, formed by the reaction of aldol **10** (0 063 g, 0 29 mmol) and methyl iodide at -78°C Rearrangement time 12 hrs. Yield 90% *anti-anti / anti-syn / syn-syn / syn-anti* ratio 15 0 10 75

HPLC the elution order is the following one *anti-anti* **19a**, *anti-syn* **19b**, *syn-anti* **19d**, *syn-syn* **19c** (n-heptane/EtOAc 99 1) After MPLC, *anti-anti* isomer **19a** and *anti-syn* isomer **19b** were isolated as a mixture and *syn-syn* isomer **19c** and *syn-anti* isomer **19d** as pure products

***Anti-anti* isomer 19a**

Orange oil TLC R_f 0 22 (c-hexane/EtOAc 95 5) δ_H (200 MHz, $CDCl_3$ and D_2O) 0 86 (d, J = 6 43, 3H, CH_3), 0 87 (d, J = 6 43, 3H, CH_3), 0 90 (d, J = 5 93, 3H, CH_3), 1 36 to 1 54 (m, 1H, H-γ), 2 59 (s, 3H, SCH_3), 2 87 to 3 06 (m, 1H, H-β'), 3 19 (dd, J = 2 96 and 9 9, 1H, H-α), 3 27 (dd, J = 2 48 and 9 9, 1H, H-β), 4 69 to 5 72 (m, 3H, H-γ and H-δ') ν_{max} 3 420 cm^{-1} (OH), 3 080 cm^{-1} (=C-H), 1 640 cm^{-1} (C=C) δ_C ($CDCl_3$) 18 60, 19 63, 19 85, 20 04, 32 45 (C_γ), 41 76 (C-β'), 66 79 (C-α), 77 99 (C-β), 115 91 (C-δ'), 141 29 (C-γ'), 242 41 (C=S) *M/Z* 55 (79), 71 (35), 87 (63), 97 (38), 103 (63), 145 (84), 159 (78), 189 (100), 191 (10), 232 (0 5) Anal Calcd for $C_{11}H_{20}OS_2$ C, 56 85, H, 8 675, S, 27 59 Found C, 56 64, H, 8 49, S, 26 37

***Anti-syn* isomer 19b**

Orange oil TLC R_f 0 22 (c-hexane/EtOAc 95 5) δ_H (200 MHz, $CDCl_3$) 0 88 (d, J = 6 93, 3H, CH_3), 0 93 (d, J = 6 43, 3H, CH_3), 1 11 (d, J = 6 93, 3H, CH_3), 1 41 to 1 61 (m, 1H, H-γ), 2 52 (s, 3H, SCH_3), 2 82 to 2 96 (m, 1H, H-β'), 3 18 (dd, J = 2 97 and 9 89, 1H, H-α), 3 32 (dt, J = 2 97 and 10 39, 1H, H-β), 3 48 (d, J = 10 39, 1H, OH), 4 74 to 5 72 (m, 1H, H-γ and H-δ') ν_{max} 3 430 cm^{-1} (OH), 3 085 cm^{-1} (=C-H), 1 640 cm^{-1} (C=C) δ_C ($CDCl_3$) 18 33, 19 33, 19 75, 20 20, 32 55 (C_γ), 42 45 (C-β'), 66 69 (C-α), 77 43 (C-β), 114 35 (C-δ'), 141 21 (C-γ'), 242 28 (C=S)

***Syn-syn* isomer 19c**

Orange oil TLC R_f 0 12 (c-hexane/EtOAc 95 5) δ_H (200 MHz, $CDCl_3$) 0 85 (d, J = 6 93, 3H, CH_3), 0 87 (d, J = 6 92, 3H, CH_3), 1.03 (d, J = 6 93, 3H, CH_3), 1 63 to 1 78 (m, 1H, H-γ), 1 98 (br s, 1H, OH), 2 53 (s, 3H, SCH_3), 2 75 to 2 93 (m, 1H, H-β'), 3 42 (dd, J = 5 44 and 8 41, 1H, H-α), 3 86 (dd, J = 2 97 and 8 41, 1H, H-β), 4 92 to 6 14 (m, 3H, H-γ and H-δ') ν_{max} 3 620 and 3 475 cm^{-1} (OH), 3 060 cm^{-1} (=C-H), 1 630 cm^{-1} (C=C) δ_C ($CDCl_3$) 15 37, 18 69, 19 48, 20 66, 30 18 (C_γ), 39 45 (C-β'), 67 81 (C-α), 78 42 (C-β), 114 64 (C-δ'), 141 27 (C-γ'), 239 30 (C=S)

***Syn-anti* isomer 19d**

Orange oil TLC R_f 0 15 (c-hexane/EtOAc 95 5) δ_H (200 MHz, $CDCl_3$) 0 85 (d, J = 6 93, 3H, CH_3), 0 86 (d, J = 6 92, 3H, CH_3), 0 95 (d, J = 6 43, 3H, CH_3), 1 68 to 1 84 (m, 1H, H-γ), 2 53 (br s, 1H, OH), 2 55 (s, 3H, SCH_3), 2 81 to 2 96 (m, 1H, H-β'), 3 30 (t, J = 6 93, 1H, H-α), 3 78 (dd, J = 3 96 and 6 93, 1H, H-β), 4 94 to 5 97 (m, 3H, H-γ and H-δ') ν_{max} 3 595 and 3 470 cm^{-1} (OH), 3 080 cm^{-1} (=C-H), 1 632 cm^{-1} (C=C) δ_C ($CDCl_3$) 15 92, 18 30, 19 34, 20 56, 30 26 (C_γ), 41 86 (C-β'), 68 26 (C-α), 79 75 (C-β), 114 29 (C-δ'), 143 67 (C-γ'), 240 96 (C=S)

***Methyl 2-(1-hydroxy-2,2-dimethylpropyl)-3-methyl-4-pentenedithioate* 20**

From the thio-Claisen rearrangement of ketene dithioacetal **16_{ZE}**, formed by the reaction of aldol **4** (0 192 g, 1 mmol) and (*E*)-1-bromo-2-butene at -20°C Rearrangement time 15 hrs Yield 52% *anti-anti / anti-syn / syn-syn / syn-anti* ratio 94 0 2 5 3 5 From the thio-Claisen rearrangement of ketene dithioacetal **16_{ZZ}**, formed by the reaction of aldol **4** (0 096 g, 0 5 mmol) and (Z)-1-bromo-2-butene at -20°C Rearrangement time 28 hrs Yield 60% *anti-anti / anti-syn / syn-syn / syn-anti* ratio 28 19 51 2 From the thio-Claisen rearrangement of ketene dithioacetal **16_{EE}**, formed by the reaction of aldol **12** (0 36 g, 1 5 mmol) and methyl iodide at -78°C Rearrangement time 24 hrs Yield 38% *anti-anti / anti-syn / syn-syn / syn-anti* ratio 25 55 8 12

HPLC the elution order is the following one *anti-anti* **20a**, *anti-syn* **20b**, *syn-syn* **20c**, *syn-anti* **20d** (n-heptane/EtOAc 99 1) After MPLC, *anti-anti* isomer **20a** and *anti-syn* isomer **20b** were isolated as a mixture and *syn-syn* isomer **20c** and *syn-anti* isomer **20d** as a mixture

***Anti-anti* isomer 20a**

Orange oil TLC R_f 0 17 (c-hexane/EtOAc 98 2) δ_H (200 MHz, $CDCl_3$) 0 90 (s, 9H, 3 CH_3 of tBu), 0 91 (d, J = 6 35, 3H, CH_3), 2.63 (s, 3H, SCH_3), 2 95 to 3.11 (m, 1H, H-β'), 3 29 (dd, J = 1 96 and 10 26, 1H, H-α), 3 56 (dd, J = 1 96 and 9 77, 1H, H-β), 4 10 (d, J = 9 77, 1H, OH), 4.8 to 5 9 (m, 3H, H-γ and H-δ') ν_{max} 3 400 cm^{-1} (OH), 3 070 cm^{-1} (=C-H), 1 635 cm^{-1} (C=C) δ_C ($CDCl_3$) 18 50, 19 44, 26 82 (3 CH_3 of tBu), 36 86 (C_γ), 43 39 (C-β'), 65 19 (C-α), 80 51 (C-β), 116 20

(C–δ'), 141 68 (C–γ'), 243 87 (C=S) *M/Z* 55 (65), 87 (66), 103 (65), 111 (20), 135 (18), 145 (22), 189 (100), 190 (10), 191 (15), 246 (0 8) Anal Calcd for $C_{12}H_{22}OS_2$ C, 58 49, H, 9 00, S, 26 02 Found. C, 58.50, H, 8 90; S, 25 53

***Anti-syn* isomer 20b'**

Orange oil TLC R_f 0 17 (c-hexane/EtOAc 98 2) δ_C ($CDCl_3$) 18 76, 19 11, 26 82 (3 CH_3 of tBu), 36 91 (C_γ), 43 97 (C–β'), 65 19 (C-α), 79 54 (C–β), 114 61 (C–δ'), 140 73 (C–γ'), 243 87 (C=S)

Methanolysis

To methanol (4 cm^3), 0 29 g of $CuCl_2$ (2 13 mmol), 0 17 g of CuO (2 13 mmol), 0 15 g of a 95 5 mixture of dithioesters **17a** and **17b** (obtained from the rearrangement of dithioacetal $\mathbf{13}_{ZZ'}$) (0 71 mmol) and 40 µl of distilled water were successively added. The resulting mixture was stirred at room temperature under an atmosphere of air for 48 hrs and then filtered. The black solid residue was washed with ether and then the resulting ethereal solution was washed with saturated brine, dried over $MgSO_4$ and concentrated under *vacuo* to afford a crude mixture of esters **21a** and **21b** The products were purified by chromatography, but without any separation of both diastereoisomers Yield 88% The diastereoisomeric distribution was assessed by CPV analysis ($T_{Injector}$ 200°C, $T_{Detector}$ 200°C, T_{Oven} 115°C) *anti-anti* / *anti-syn* ratio 95 5 *Anti-anti* isomer **21a** had the shortest retention time. The spectroscopic data were similar to those previouly reported by Kurth *et al* [6b]

Preparation of the Authentic Sample

The authentic sample constituted of *anti-anti* ester **21a** and *anti-syn* ester **21b** was prepared from (*E*)-2-butenyl acetate **24**, *via* (*E*)-2-butenyl 3-hydroxybutanoate **25**.

***(E)-2-Butenyl acetate* 24**

Prepared according to a general procedure[28] from (*E*)-2-buten-1-ol (4.2 cm^3, 50 mmol) and acetyl chloride (3 5 cm^3, 50 mmol) in presence of pyridine (4 45 cm^3, 55.5 mmol) in dry methylene chloride (185 cm^3) Yield 90% Colourless oil Bp_{75} 68-70°C δ_H (60 MHz, CCl_4) 1 62 to 1 82 (m, 3H, =CH-$\underline{CH_3}$), 2 00 (s, 3H, CH_3CO), 4 27 to 4 52 (m, 2H, OCH_2), 5 47 to 5 87 (m, 2H, CH= CH) ν_{max} 1 740 cm^{-1} (C=O)

***(E)-2-Butenyl 3-hydroxybutanoate* 25**

Obtained by an aldol condensation[6a] between ester **24** (1 14 g, 10 mmol) and acetaldehyde Yield 80% Colourless oil TLC R_f 0 49 (c-hexane/EtOAc 50 50) The spectroscopic data matched those previouly reported [6a] δ_C ($CDCl_3$) 17 67(=CH-$\underline{CH_3}$), 22 56 (CH_3), 43 09, 64 37, 65 34, 125 04(=$\underline{CH}$-CH_3), 131 63(OCH_2-$\underline{CH}$=), 172 53 (C=O)

***Methyl 2-(1-hydroxyethyl)-3-methyl-4-pentenoate* 21**

Obtained according to Fujisawa's procedure[6d] by a Claisen rearrangement of the dianion formed from aldol **25** (0 16 g, 1 mmol), followed by an esterification with diazomethane (prepared from diazald[23]) Yield 28% Colourless oil The resulting product was a mixture of two esters, diastereoisomers *anti-anti* **21a** and *anti-syn* **21b** The diastereoisomeric distribution was assessed by CPV analysis ($T_{Injector}$ 200°C, $T_{Detector}$ 200°C, T_{Oven} 115°C) *anti-anti* / *anti-syn* ratio 15 85 *Anti-anti* isomer **21a** had the shortest retention time The spectroscopic data were similar to those previouly reported by Kurth *et al* [6b]

Oxidation of Aldols 17a-d

To a stirred solution of oxalyl chloride (1 1 eq) in CH_2Cl_2 cooled to -70 °C was added a solution of dimethyl sulfoxide (2 2 eq) in CH_2Cl_2 over a period of 5 min The mixture was stirred at -65 °C for 20 min A solution of pure dithioesters **17a-17b** or a mixture of dithioesters **17c-17d** (1 eq) in CH_2Cl_2 was added over a period of 5 min at -50 °C After 20 min, triethylamine (5 eq) was added over a period of 1 min and stirred at -50 °C for 5 min and 10 min at room temperature precisely (to avoid epimerization[24]) The reaction mixture is immediately poured in water, acidified with an aqueous HCl solution (1%) and extracted with CH_2Cl_2. The organic solution is washed with saturated brine, dried over $MgSO_4$, filtered and concentrated The orange residue can't be purified by column chromatography without any degradation The diastereoisomeric ratio was determined by HPLC analysis (n-heptane/EtOAc 98 2) The *anti* β-cetodithioester **22** was eluted first.

From pure *anti-anti* dithioester **17a** (0 4 mmol), only the *anti* β-ketodithioester **22** was detected Crude yield 80% From pure *anti-syn* dithioester **17b** (0 076 mmol), only the *syn* β-ketodithioester **23** was detected Crude yield 92% From a 96 4 mixture of *syn-syn* isomer **17c** and *syn-anti* isomer **17d** (issued from the rearrangement of the dithioacetal $\mathbf{13}_{ZZ'}$) (0 29 mmol), a 15 85 mixture of respectively *anti* β-ketodithioester **22** and *syn* β-ketodithioester **23** was isolated Crude yield 92% From a 4 96 mixture of *syn-syn* isomer **17c** and *syn-anti* isomer **17d** (issued from the rearrangement of the dithioacetal $\mathbf{13}_{EZ'}$) (0 21 mmol), a 90 10 mixture of respectively *anti* β-ketodithioester **22** and *syn* β-ketodithioester **23** was isolated Crude yield 83%

***Methyl 3-methyl-2-(1-oxoethyl)-4-pentenedithioate* 22-23**

Anti isomer 22

δ_H (60 MHz, CCl_4) 0 97 (d, J = 6 5, 3H, CH_3-β'), 2 13 (d, 3H, CH_3CO), 2 65 (s, 3H, SCH_3), 2 9 to 3 63 (m, 1H, H sur C–β'), 4 15 (d, J = 10 5, 1H, H-α), 4 77 to 6 02 (m, 3H, H-γ' and H-δ') δ_C ($CDCl_3$) 17 48, 20 11, 28 53, 41 38 (C–β'), 80 88 (C-α), 115 75 (C–δ'), 140 41 (C–γ'), 201 20 (C=O), 230 47 (C=S)

Syn isomer 23

δ_H (60 MHz, CCl_4) 1 03 (d, J = 6 5, 3H, CH_3-β'), 2 17 (s, 3H, CH_3CO), 2 61 (s, 3H, SCH_3), 2 9 to 3 63 (m, 1H, H–β'), 4 15 (d, J = 10 5, 1H, H-α), 4 77 to 6 02 (m, 3H, H-γ' and H-δ') ν_{max} 3 080 cm^{-1} (=C-H), 1 760 cm^{-1} (C=O), 1640 cm^{-1} (C=C) δ_C ($CDCl_3$) 18 53, 19 97, 28 83, 41 48 (C–β'), 80 55 (C-α), 115 51 (C-δ'), 139 24 (C–γ'), 201 20 (C=O), 230 47 (C=S)

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