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Asymmetric Induction in the Thio-Claisen Rearrangement. Creation of three Contiguous Stereogenic Centres from α-Hydroxy Ketene Dithioacetals

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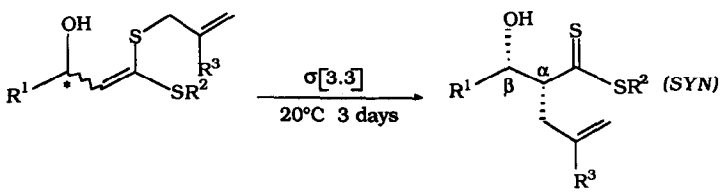
Abstract: *Syn β-hydroxy γ-methyl dithioesters were deprotonated with two equivalents of LDA. A subsequent S-alkylation of the resulting dianions yielded α-hydroxy S-allyl ketene dithioacetals. A single isomer was observed, arising from a selective cis deprotonation. These dithioacetals underwent a rapid and highly diastereoselective thio-Claisen rearrangement at an ambient temperature. Syn-syn α-allyl β-hydroxy γ-methyl dithioesters were mainly formed. The syn-syn/anti-syn ratios ranged from 85 : 15 to 99 : 1. The selectivity observed originates from asymmetric induction with a noteworthy stereoelectronic effect of the hydroxyl group. Configurations were assigned by a spectroscopic method using previously reported ^{13}C NMR rules and then confirmed by a syn-syn diastereoselective aldol reaction. This novel and efficient method for the creation of frameworks with three contiguous stereogenic centres, involves two diastereoselective steps : an aldol reaction followed by a thio-Claisen rearrangement.*

Introduction

Achieving stereocontrol in the construction of acyclic systems is a particularly challenging goal in organic synthesis.[1] The Claisen rearrangement and its variants[2] have been gainfully employed in addressing this challenge, with the aid of relative[2,3] and/or internal[2,4] asymmetric induction. Recently a new Claisen protocol, involving stereocontrol by an asymmetric centre appended to the pericyclic nucleus has appeared.[5-7] This latter strategy has been largely exemplified in the cyclic series[3,5] but it remains scarcely exploited with acyclic systems.[6-7]

In connection with our long standing interest in acyclic stereocontrol chemistry,[8] we reported in a previous paper an example of this acyclic stereocontrol process, dealing with the highly diastereoselective thio-Claisen rearrangement of α-hydroxy ketene dithioacetals (Scheme 1).[9]

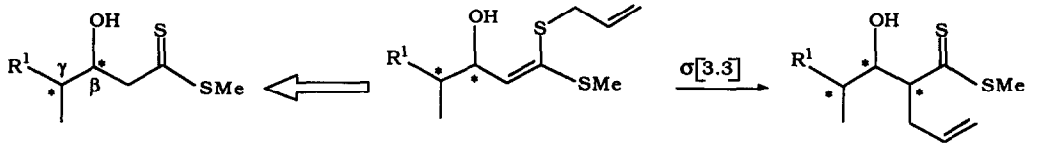


Scheme 1

This sigmatropic shift affords *syn* α-allyl β-hydroxydithioesters with *syn/anti* ratios ranging from 85 : 15 to 100 : 0 (Scheme 1). This novel method regulates the introduction of two contiguous chiral centres on an acyclic framework. The major *syn* relative configuration ($C_\alpha C_\beta$) uniformly observed arises neither from the ketene geometry nor from the S-allylic and alkylthio SR^2 fragments. A chairlike transition state model and a remarkable stereoelectronic effect of the hydroxyl group on the inductive centre have been invoked to rationalize these results.[9]

Such a *syn* ($C_\alpha C_\beta$) configuration is not attainable with the oxygenated version[7] of this rearrangement. It occurs under chelation control and an exclusive formation of *anti* products is observed.

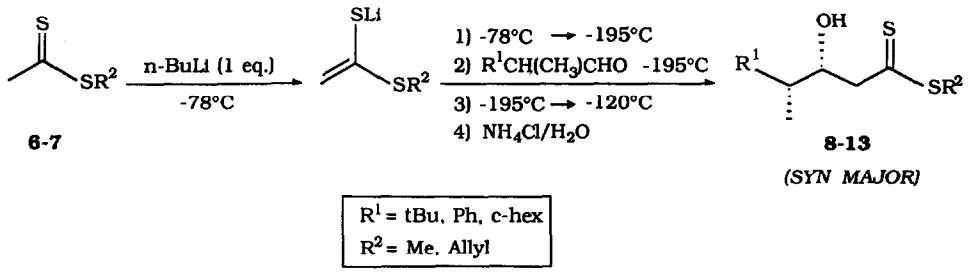
We now disclose our new results concerning the use of this diastereoselective thio-Claisen rearrangement for the creation of three adjacent chiral centres from α-hydroxy ketene dithioacetals bearing an additional asymmetric carbon issued from β-hydroxy γ-methyldithioesters easily available only in the syn configuration (Scheme 2).



Scheme 2

Synthesis of β-Hydroxy γ-Methyl Dithioesters

The starting materials are syn β-hydroxy γ-methyl dithioesters **8-13**. They include two asymmetric carbons in *beta* and *gamma* positions. They were conveniently prepared in THF, under Meyers' "freeze-thaw" conditions,[10] by aldol condensation between enethiolates[11] derived from S-methyl and S-allyl dithioacetates **6** and **7** and the racemic α-methyl aldehydes **3-5** (Scheme 3).



Scheme 3

The ratios of *syn* and *anti* isomers[12] formed were determined by HPLC or ^{13}C NMR analysis of crude products. The control originates from a diastereofacial selectivity[8b,10,13] exhibited by the enethiolate towards the chiral aldehyde. Based on Meyers' results[10] and the predictions of Cram's rules[14], the *syn* configuration was assigned in each case to the main component (Scheme 3). Results are summarized in Table 1.

Table 1
Diastereofacial selectivity of aldol condensation with dithioacetates **6-7** *and chiral aldehydes* **3-5**

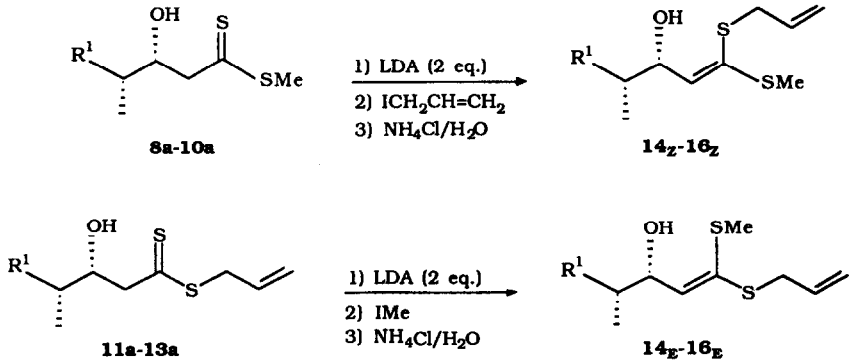
Entry	R^1	R^2	Starting dithioacetate	Aldehyde	*syn/anti* ratio	Yield %	Resulting aldol*
1	tBu	Me	**6**	**3**	>99 : 1	51	**8a-b**
2	Ph	Me	**6**	**4**	91 : 9	78	**9a-b**
3	c-hex	Me	**6**	**5**	89 : 11	44	**10a-b**
4	tBu	Allyl	**7**	**3**	>99 : 1	55	**11a-b**
5	Ph	Allyl	**7**	**4**	94 : 6	58	**12a-b**
6	c-hex	Allyl	**7**	**5**	89 : 11	43	**13a-b**

* *Syn* diastereoisomer with letter a and *anti* diastereoisomer with letter b

The selectivity of the aldol reaction is governed significantly by the steric bulk of the α-methyl aldehyde.[15] With both examples run with 2,3,3-trimethylbutanal **3** (Table 1; entries 1 and 4), only *syn* diastereoisomers **8a** and **11a** were detected, as a consequence of an increased discrimination of the chiral centre substituents.[15] With the two other aldehydes **4** and **5**, mixtures of *syn* and *anti* epimers **9**, **10**, **12** and **13** were obtained (Table 1; entries 2, 3, 5 and 6). A separation of these *syn* and *anti* diastereoisomers by medium-pressure liquid chromatography was effective only in the case of compounds **9** and **12** (R^1 = Ph). The diastereoisomeric pairs **10** and **13** (R^1 = c-hex) were inseparable and were further used as an 89 : 11 *syn/anti* mixture.

Formation of Ketene Dithioacetals and Thio-Claisen Rearrangement

Pure *syn* aldols **8a**, **9a**, **11a** and **12a** and *syn/anti* mixtures of aldols **10** and **13** were treated with two equivalents of LDA at -78°C in THF. The *in situ* S-alkylation[16] of these dianions by methyl or allyl iodides gave rise to the desired α-hydroxy ketene dithioacetals $\mathbf{14_Z}$-$\mathbf{16_Z}$ and $\mathbf{14_E}$-$\mathbf{16_E}$ (Scheme 4).

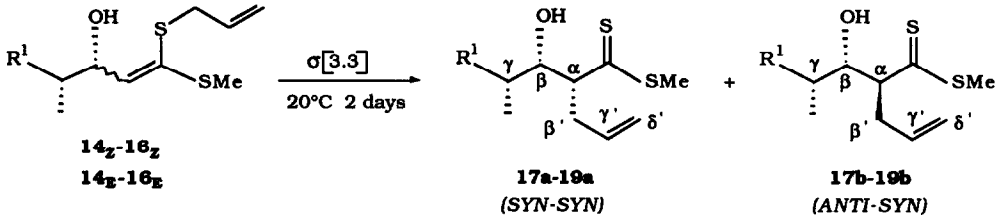


Scheme 4

The ketene geometry was determined on the basis of systematic investigation of ^{1}H NMR spectra: the chemical shift of the proton of the (*E*)-ketene occurs downfield from that of its (*Z*)-isomer.[9] As a combined result of an intramolecular coordination in the dianion[17] and geometry retention with S-alkylation,[8a] (*Z*)-isomers **14$_Z$-16$_Z$** were obtained from S-methyl aldols **8a-10a** and (*E*)-isomers **14$_E$-16$_E$** from S-allyl aldols **11a-13a**.

It is worth noting the spectacularly easy occurrence of the thio-Claisen rearrangement.[9,18] From ^{1}H NMR spectra of crude products, the rearrangement had already begun at room temperature just after quenching and workup.

The rearrangement attained completion after two days at ambient temperature in ethereal solution, furnishing the expected α-allyl β-hydroxydithioesters **17-19** (Scheme 5). Their diastereoisomeric distributions were determined by HPLC analysis (see results in Table 2). For comparison , the already reported results of case R^1 = CH$_3$ appeared in entry 7 and 8.



14$_Z$-16$_Z$
14$_E$-16$_E$

17a-19a
(SYN-SYN)

17b-19b
(ANTI-SYN)

Scheme 5

Dithioacetals **14$_Z$**, **14$_E$**, **15$_Z$** and **15$_E$** were formed respectively from pure *syn* aldols **8a**, **9a**, **11a** and **12a** (entries 1-4). Only two rearranged diastereoisomers were detected. This indicates that no epimerization had occured during the double deprotonation and S-alkylation steps.

With dithioacetals **16$_Z$** and **16$_E$** obtained from impure *syn* aldols **10a** and **13a** (*syn*-*anti* ratio 89 : 11), three of the four possible diastereoisomers were observed (entries 5-6; notes [a] and [b]). The amounts of the fourth and minor diastereoisomer derived from the contaminating *anti* aldols **10b** and **13b** are probably too small for a significant detection.

Table 2
Thio-Claisen rearrangement of ketene dithioacetals **14$_Z$-16$_Z$** *and* **14$_E$-16$_E$**

Entry	R^1	Dithioacetal	*syn-syn/anti-syn*	Yield %	Dithioester
1	tBu	**14$_Z$**	85 : 15	54	**17**
2	tBu	**14$_E$**	94 : 6	47	**17**
3	Ph	**15$_Z$**	99 : 1	92	**18**
4	Ph	**15$_E$**	99 : 1	91	**18**
5	c-hex	**16$_Z$**	89 : 11[a]	74	**19**
6	c-hex	**16$_E$**	98 : 2 [b]	64	**19**
7	Me[9]	Z	96/4 (syn/anti)	65	
8	Me[9]	E	87/13 (syn/anti)	64	

[a] Calculated ratio from a 16 : 9 : 75 mixture of three diastereoisomers (elution order)
[b] Calculated ratio from a 12 : 2 : 86 mixture of three diastereoisomers (elution order)

In order to determine the relationship between the starting *syn* aldols **10a** and **13a** and their two rearranged products, the rearrangement has been carried out with an *anti* enriched mixture[19] of aldol **13** (*syn/anti* 79 : 21) (Table 3). It is thus ascertained that the chromatographically more mobile isomer, whose percentage increases from 12 to 19%, derivates from the "wrong" *anti* aldol **13b** (Table 3). It is also possible to adjust the real diastereoisomeric ratios of rearrangement products from pure *syn* aldols **10a** and **13a** (Table 2; entries 5 and 6).

Table 3
Thio-Claisen rearrangement with syn/anti mixtures of aldol **13**

Starting aldol **13a-b** *syn/anti*	Resulting aldol **19** Isomer ratio (elution order)
89 : 11	12 : 2 : 86
79 : 21	19 : 2 : 79

The present thio-Claisen rearrangement proceeds with a high level of diastereoselectivity. The *syn-syn/anti-syn* ratios[20] range from 85 : 15 (R^1 = tBu) to 99 : 1 (R^1 = Ph). Best results are obtained from (*E*)-dithioacetals (see Table 2; entries 1, 2 and 5, 6) in contrast to entry 7 and 8 ($R^1 = CH_3$).

Configuration Assignment

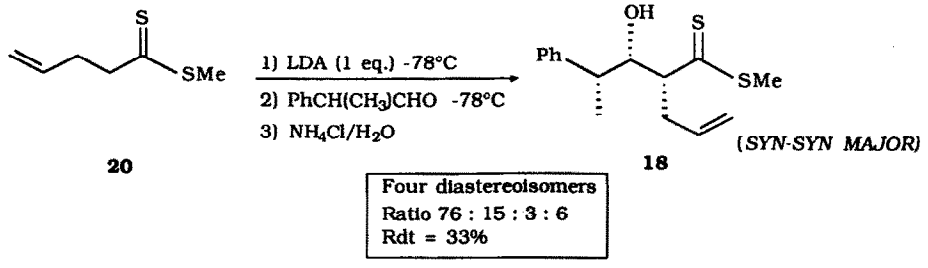
As no epimerization has been detected (*vide supra*), the ($C_\beta C_\gamma$) configuration of both rearrangement products must be *syn*, similar to the ($C_\beta C_\gamma$) configuration of their starting aldol (Schemes 4 and 5).

For each diastereoisomeric pair **17-19**, a ^{13}C NMR relationship between carbon chemical shifts of the major and the minor isomer has been established: δ(C-β' *min*) > δ(C-β' *maj*); δ(C-γ' *maj*) > δ(C-γ' *min*); δ(C-δ' *min*) > δ(C-δ' *maj*); δ(C-α *maj*) > δ(C-α *min*) (see Scheme 5 for the carbon identification). By a comparison using ^{13}C NMR rules put forth in a previous paper,[9] a *syn* ($C_\alpha C_\beta$) configuration was assigned to the main rearrangement isomer and an *anti* ($C_\alpha C_\beta$) configuration to the minor rearrangement isomer.

So the configuration must be *syn-syn* for the major product and *anti-syn* for the minor one.

These attributions have been further confirmed by an unequivocal synthesis of *syn-syn* aldol using a *syn-syn* diastereoselective aldol condensation[10] with double asymmetric induction.[21]

The condensation of methyl 4-pentenedithioate **20** with 2-phenylpropanal **4** under standard conditions[22] gave rise to a 76 : 15 : 3 : 6 mixture of the four diastereoisomers **18** (chemical yield 33%) (Scheme 6).



Scheme 6

From HPLC analysis, the *syn-syn* major product (76%) rigorously matched the major thio-Claisen rearrangement product while the next major isomer (15%), whose structure should be *anti-syn* in agreement with Meyers' results,[10] precisely matched the minor thio-Claisen rearrangement product.

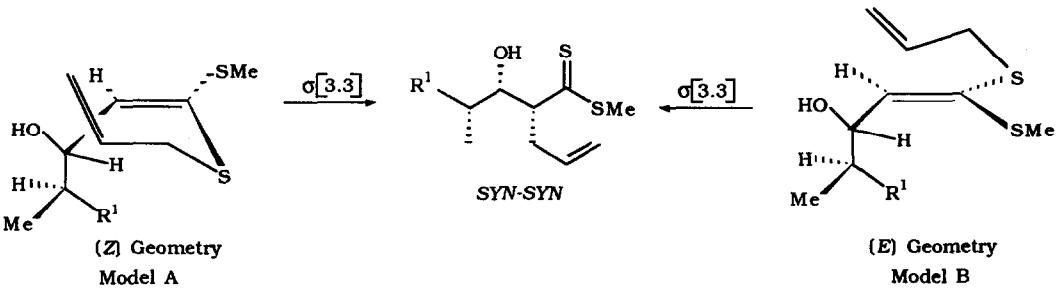
The same aldol reaction was unsuccessful with the aldehydes **3** and **5**.

From the above results the thio-Claisen rearrangement method seems to be superior to the method making use of aldol reactions for an easy diastereoselective synthesis of α-allyl β-hydroxydithioesters.

Discussion

Three pairs of *E*, *Z* isomeric dithioacetals were rearranged under smooth conditions. Each compound gave *syn-syn* dithioesters preferentially (Table 2). *Syn-syn/anti-syn* ratios were between 85 : 15 (R^1 = tBu) and 99 : 1 (R^1 = Ph) when (*Z*)-dithioacetals were used. The (E)-dithioacetals furnished the same rearranged products with *syn-syn/anti-syn* selectivities ranging from 94 : 6 (R^1 = tBu) to 99 : 1 (R^1 = Ph). Each *E* isomer rearranged more selectively than its *Z* isomer. The **syn stereoselectivity was enhanced** when $R^1 = CH_3$ was replaced by bulkier substituents as Ph, t-Bu, C-hex in the starting **E** dithioacetals and **was lowered** to a small extent with **Z** dithioacetals except in entry 3 (R^1 = Ph).

The major *syn* ($C_\alpha C_\beta$) configuration is similar to the configuration previously reported for the rearrangement of α-hydroxy ketene dithioacetals containing only one remote chiral centre.[9] This stereochemical outcome is consistent with the same "electrostatic" chairlike transition state[9] where the hydroxyl group lies in the outside position[23]. The bond formation between the allylic terminal carbon and the prochiral ketene carbon takes place *anti*[23] to the alkyl group $R^1CH(Me)$, on the top side, the more electron-rich ketene face (Scheme 7; models A and B).



Scheme 7

The better *syn* selectivity observed for (*E*)-dithioacetals (Table 2) may be interpreted in term of a less strained pseudocyclic intermediate state B compared to state A.

The enhanced *syn* selectivity in the order $R^1 = CH_3$, tBu, c-hex and Ph (Table 2 for E acetals) may be a result of a more difficult formation of the corresponding minor ($C_\alpha C_\beta$) *anti* compounds. These minor isomers are probably formed by an anti attack to the hydroxyl group, on the bottom face.

When R^1= Ph, the staggered conformation of the second asymmetric centre $R^1CH(Me)$, pictured in models A and B, is particularly favoured because of a potent π-stacking[24] of the phenyl group with the ketene double bond. Consequently, a bottom side approach is prevented.

With a more sterically demanding alkyl group[15] (R^1 = tBu), the gauche interaction tBu ⟷ ketene moiety become higher. The alkyl centre may adopt another conformation, resulting in a clockwise rotation (120°) along C-C axis. This new conformation releases the bottom face and allows, to some extent, the formation of an *anti-syn* product.

Conclusion

The thio-Claisen rearrangement of ketene dithioacetals with two remote asymmetric centres with a *syn* relative configuration proceeds smoothly. It allows the diastereoselective formation of *syn-syn* α-allyl β-hydroxy γ-methyl dithioesters independently of the dithioacetal geometry. The diastereoselectivity levels are high, ranging from 85 : 15 to 99 : 1 The (*E*)-dithioacetals rearranged more selectively than the (*Z*)-isomers.

This stereocontrol results from asymmetric induction and is improved by using R^1 group bulkier than Me and E acetal geometry.

An application in optically active series is envisioned, starting from optically pure α-methyl aldehydes.[25]

These results illustrate the specificity of thiocarbonyl reactivity. To our knowledge, such a *syn* ($C_\alpha C_\beta$) configuration formation is not feasible *via* a Claisen rearrangement of similar oxygenated intermediates. [7] This Claisen version proceeds under chelation control and esters with an *anti* ($C_\alpha C_\beta$) configuration would be obtained.

We are presently proceeding with the study of this thio-Claisen rearrangement with the aim to create three contiguous stereogenic centres, starting from α-hydroxy S-crotylic ketene dithioacetals.

EXPERIMENTAL SECTION

General

All reactions were run under a positive nitrogen pressure. THF was distilled over sodium benzophenone ketyl. Preparative liquid chromatographs were performed on a Jobin-Yvon Chromatospac Prep 10 chromatograph or by flash chromatography. The column was prepared with a suspension of silica gel in the eluting solvent: a mixture of cyclohexane and ethyl acetate in the ratio indicated. 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. ^1H NMR 60 MHz spectra were run on a Varian EM 360 spectrometer and ^1H NMR 200 Hz on a JEOL JNM-FX 200. The products were dissolved in the mentioned solvent. Significant data are quoted in order: chemical shift in ppm, multiplicity (s, singulet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant, assignment. ^{13}C NMR spectra were determined at 20,15 MHz with a Bruker WP 80 spectrometer operating with broad band ^1H decoupling. The solvent used is $CDCl_3$. IR absorption spectra were run on a Perkin-Elmer 257 and 684 instrument and the compound was dissolved in CCl_4. Mass spectra were obtained at 70 eV with Varian Mat CH5 or with Nermag spectrometers and the data tabulated as m/e and relative intensities in percent. Elemental analyses were performed by Service Central d'Analyse of CNRS at Vernaison. The results are described as percentages.

Starting Materials

2-Phenylpropanal **4** was purchased from Aldrich Chemical Company and was redistilled before use.

2,3,3-Trimethylbutanal **3** and 2-cyclohexylpropanal **5** were obtained according to the procedure described in reference[26], *via* alcohols **1** and **2** respectively.

***1-Ethoxy-2,3,3-trimethyl-2-butanol* 1**

Prepared from pinacolone (15 g; 0.15 mol) in 46% yield according to reference[26]. Colourless oil. Bp_{12} 63°C. ^1H NMR (60 MHz, CCl_4) δ 0.95 (s, 9 H, tBu), 1.12 (s, 3 H, CH_3), 1.22 (t, J = 6.5 Hz, 3 H, CH_3 of OEt), 2.17 (s, 1 H, OH), 3.21 and 3.38 (AB, J = 10 Hz, 2 H, CH_2), 3.5 (q, J = 6 Hz, 2 H, CH_2 of OEt). IR: 3570 cm^{-1} (OH).

***2,3,3-Trimethylbutanal* 3**

Dehydratation of alcohol **1** (10.7 g; 0.07 mol) was carried out as described.[26] Yield 62%. Colourless oil. Bp_{12} 28°C. The physical and spectroscopic properties matched those previously reported.[25]

***2-Cyclohexyl-1-ethoxy-2-propanol* 2**

Prepared from cyclohexyl methyl ketone (16.5 g; 0.13 mol) in 55% yield according to reference[26]. Colourless oil. Bp_{22} 107-108°C. ^1H NMR (60 MHz, CCl_4) δ 0.93 to 1.93 (m, 11 H, c-hex), 0.97 (s, 3 H, CH_3), 1.18 (t, J = 7 Hz, 3 H, CH_3 of OEt), 2.05 (br s, 1 H, OH), 3.10 and 3.23 (AB, J = 9 Hz, 2 H, CH_2), 3.47 (q, J = 7 Hz, 2 H, CH_2 of OEt). IR: 3580 cm^{-1} (OH).

***2-Cyclohexylpropanal* 5**

Dehydratation of alcohol **2** (13.3 g; 0.07 mol) was carried out as described.[26] Yield 70 %. Colourless Oil. Bp_{10} 74-76°C. The physical and spectroscopic properties matched those previously reported.[25]

The preparation of dithioacetates **6** and **7** was carried out as described in the literature.[27] Boiling points and spectra data were in agreement with those reported in the literature (Reference[27a] for methyl dithioacetate **6** and reference[28] for allyl dithioacetate **7**).

Methyl 4-pentenedithioate **20** was obtained by thio-Claisen rearrangement according to reference[29]. Some spectroscopic and physical properties of this compound **20** were reported in reference[30].

General Procedure for Aldol Reaction between Dithioacetates 6-7 and Aldehydes 3-5

Dithioacetate **6** or **7** (1 eq.) diluted in THF was added dropwise at -78°C under nitrogen to a solution in THF of n-butyllithium (1,2 eq.). After stirring for 15 min., the resulting colourless enethiolate solution was cooled to -195°C in a liquid nitrogen bath. The mixture froze immediately. A solution of aldehydes **3-5** (1,2 eq.) in THF was then added *via* syringe at -195°C. The frozen solution was allowed to warm to -120°C by adding a pentane/isopropanol/acetone solution 4 : 1 : 1 (v/v/v) to the liquid nitrogen bath. Around -120°C the solution began to become liquid and to go orange. After melting completely, the reaction mixture was quenched with a saturated NH_4Cl solution, allowed to warm to room temperature and extracted with ether. The organic extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Crude aldols **8-13** were isolated as mixtures of *syn* and *anti* isomers. The *syn/anti* ratios were assessed by HPLC or ^{13}C NMR analysis. Aldols **8-13** were further purified by MPLC. The separation of the diastereoisomeric pairs was successful in the case of compounds **9** and **12**.

***Methyl 3-hydroxy-4,5,5-trimethylhexanedithioate* 8**

From the reaction between dithioacetate **6** (0.53 g; 5 mmol) and 2,3,3 trimethylbutanal **3**. Yield 51%. *syn/anti* ratio >99 : 1<. HPLC: only *syn* isomer was detected (n-heptane/EtOAc, 95 : 5).

***Syn* isomer 8a:**

Orange oil. TLC R_f 0.18 (c-hexane/EtOAc, 95 : 5). ^1H NMR (60 MHz, CCl_4) δ 0.97 (s, 9 H, tBu), 1.00 to 1.33 (m, 4 H, CH_3-4 and H-4), 2.3 (d, J = 3 Hz, 1 H, OH), 2.62 (s, 3 H, SCH_3), 2.9 to 3.17 (m, 2 H, H-2), 4.2 to 4.53 (m, 1 H, H-3). IR: 3605 and 3465 cm^{-1} (OH). ^{13}C NMR ($CDCl_3$) δ 8.12 (CH_3-4), 20.10 (SCH_3), 28.43 (tBu), 33.59 (C-5), 47.47 (C-4), 59.06 (C-2), 71.91 (C-3), 238.03 (C=S). MS: 57 (67), 59 (26), 85 (100), 91 (23), 99 (32), 113 (58), 135 (16), 172 (32), 220 (14). Anal. Calcd for $C_{10}H_{20}OS_2$: C, 54.50; H, 9.15; S, 29.09. Found: C, 55.25; H, 9.21; S, 29.22.

***Methyl 3-hydroxy-4-phenylpentanedithioate* 9**

From the reaction between dithioacetate **6** (0.43 g; 4 mmol) and 2-phenylpropanal **4**. Yield 78%. *syn/anti* ratio 91 : 9. HPLC: *anti* isomer was eluted first (n-heptane/EtOAc, 95 : 5).

***Syn* isomer 9a:**

Orange oil. TLC R_f 0.08 (c-hexane/EtOAc, 95 : 5). ^1H NMR (60 MHz, CCl_4) δ 1.35 (d, J = 7 Hz, 3 H, CH_3-4), 2.58 (s, 3 H, SCH_3), 2.6 to 3.13 (m, 2 H, OH and H-4), 2.98 (d, J = 6 Hz, 2 H, H-2), 4 to 4.5 (m, 1 H, H-3), 7.28 (m, 5 H, H-Ar). IR: 3590 and 3420 cm^{-1} (OH), 3020 3055 and 3075 cm^{-1} (=C-H of Ar), 1600, 1490 and 1450 cm^{-1} (C=C of Ar). ^{13}C NMR ($CDCl_3$) δ 17.16 (CH_3-4), 19.86 (SCH_3), 45.65 (C-4), 56.39 (C-2), 76.02 (C-3), 126.65, 127.84, 128.59 and 143.98 (Ar), 237.64 (C=S). MS: 43 (46), 59 (41), 77 (41), 91 (97), 105 (100), 134 (53), 222 (32), 240 (3). Anal. Calcd for $C_{12}H_{16}OS_2$: C, 59.96; H, 6.71; S, 26.67. Found: C, 59.86; H, 6.72; S, 25.65.

***Anti* isomer 9b:**

Orange oil. TLC R_f 0.12 (c-hexane/EtOAc, 95 : 5). ^{13}C NMR ($CDCl_3$) δ 17.56 (CH_3-4), 19.86 (SCH_3), 45.49 (C-4), 56.17 (C-2), 75.86 (C-3), 126.75, 127.84, 128.59 and 142.73 (Ar), 237.59 (C=S).

***Methyl 4-cyclohexyl-3-hydroxypentanedithioate* 10**

From the reaction between dithioacetate **6** (0.53 g; 5 mmol) and 2-cyclohexylpropanal **5**. Yield 44%. *syn/anti* ratio 89 : 11. HPLC: no separation of diastereoisomers. The *syn/anti* ratio was determined by a ^{13}C NMR analysis.

Orange oil. TLC R_f 0.18 (c-hexane/EtOAc, 95 : 5).

***Syn* isomer 10a:**

^1H NMR (60 MHz, CCl_4) δ 0.73 to 1.9 (m, 15 H, CH_3, H-4 and c-hex), 2.4 (br s, 1 H, OH), 2.6 (s, 3 H, SCH_3), 3.02 (d, J = 6 Hz, 2 H, H-2), 3.83 to 4.33 (m, 1 H, H-3). IR: 3620 and 3480 cm^{-1} (OH). ^{13}C NMR ($CDCl_3$) δ 10.45 (CH_3-4), 19.95 (SCH_3), 26.72, 26.82, 29.86 and 31.50 (c-hex), 40.40 (C-4), 43.54 (c-hex), 57.43 (C-2), 73.02 (C-3), 238.18 (C=S). MS: 41 (100), 55 (83), 58 (39), 69 (59), 84 (45), 111 (46), 139 (37), 140 (15), 198 (44), 246 (20). Anal. Calcd for $C_{12}H_{22}OS_2$: C, 58.49; H, 9.00; S, 26.02. Found: C, 59.09; H, 9.03; S, 26.14.

***Anti* isomer 10b:**

^{13}C NMR ($CDCl_3$) δ 11.43 (CH_3-4), 19.95 (SCH_3), 26.51, 26.72, 28.57 and 31.72 (c-hex), 38.76 (C-4), 43.54 (c-hex), 55.36 (C-2), 73.39 (C-3), 238.47 (C=S).

***Allyl 3-hydroxy-4,5,5-trimethylhexanedithioate* 11**

From the reaction between dithioacetate **7** (0.77 g; 5.8 mmol) and 2,3,3-trimethylbutanal **3**. Yield 55%. *syn/anti* ratio >99 : 1<. HPLC: only *syn* isomer was detected (n-heptane/EtOAc, 95 : 5).

***Syn* isomer 11a:**

Orange oil. TLC R_f 0.15 (c-hexane/EtOAc, 95 : 5). ^1H NMR (60 MHz, CCl_4) δ 0.8 to 1.4 (m, 4 H, H-4 and CH_3), 0.95 (s, 9 H, tBu), 2.21 (s, 1 H, OH), 2.9 to 3.17 (m, 2 H, H-2), 3.91 (d, J = 6.83 Hz, 2 H, SCH_2), 4.23 to 4.5 (m, 1 H, H-3), 5.03 to 6.21 (m, 3 H, $CH=CH_2$). IR: 3610 and 3465 cm^{-1} (OH), 3080 cm^{-1} (=C-H), 1635 cm^{-1} (C=C). ^{13}C NMR ($CDCl_3$) δ 7.92 (CH_3-4), 28.26 (tBu), 33.39 (C-5), 39.36 (SCH_2), 47.26 (C-4), 58.88 (C-2), 71.68 (C-3), 119.56 (=CH_2), 130.53 (CH=), 236.08 (C=S). MS: 43 (96), 45 (22), 57 (99), 58 (36), 59 (57), 71 (15), 85 (100), 99 (51), 113 (63), 246 (0.03). Anal. Calcd for $C_{12}H_{22}OS_2$: C, 58.49; H, 9.00; S, 26.02. Found: C, 58.27; H, 8.92; S, 25.79.

***Allyl 3-hydroxy-4-phenylpentanedithioate* 12**

From the reaction between dithioacetate **7** (0.77 g; 5.8 mmol) and 2-phenylpropanal **4**. Yield 58%. *syn/anti* ratio 95 : 5. HPLC: *anti* isomer was eluted first (n-heptane/EtOAc, 95 : 5).

***Syn* isomer 12a:**

Orange oil. TLC R_f 0.1 (c-hexane/EtOAc, 95 : 5). ^1H NMR (60 MHz, CCl_4) δ 1.33 (d, J = 7 Hz, 3 H, CH_3-4); 2.6 to 3.00 (m, 2 H, OH and H-4), 2.88 (d, J = 6 Hz, 2 H, H-2), 3.83 (d, J = 6 Hz, 2 H, SCH_2), 4 to 4.38 (m, 1 H, H-3), 5.03 to 6.2 (m, 3 H, $CH=CH_2$), 7.25 (m, 5 H, Ar). IR: 3595 and 3455 cm^{-1} (OH), 3075, 3055 and 3020 cm^{-1} (=C-H of Ar), 1635 cm^{-1} (C=C), 1600, 1490 and 1450 cm^{-1} (C=C of Ar). ^{13}C NMR ($CDCl_3$) δ 17.12 (CH_3-4), 39.27 (SCH_2), 45.62 (C-4), 56.42 (C-2), 75.96 (C-3), 119.57 (=CH_2), 126.64, 127.81 and 128.58 (Ar), 130.41 (=C-H), 143.91 (Ar). MS: 41 (43), 77 (33), 91 (23), 105 (100), 117 (14), 134 (78), 161 (5), 225 (7), 248 (6), 266 (2). Anal. Calcd for $C_{14}H_{18}OS_2$: C, 63.11; H, 6.81; S, 24.07. Found: C, 63.20; H, 6.88; S, 23.55.

***Anti* isomer 12b:**

Orange oil. TLC R_f 0.14 (c-hexane/EtOAc, 95 : 5). ^{13}C NMR ($CDCl_3$) δ 17.52 (CH_3-4), 39.42 (SCH_2), 45.51 (C-4), 56.21 (C-2), 75.80 (C-3), 119.57 (=CH_2), 126.79, 127.81 and 128.58 (Ar), 130.41 (=C-H), 143.94 (Ar), 236.17 (C=S).

***Allyl 4-cyclohexyl-3-hydroxypentanedithioate* 13**

From the reaction between dithioacetate **7** (0.77 g; 5.8 mmol) and 2-cyclohexylpropanal **5**. Yield 43%. *syn/anti* ratio 89 : 11. From aldol reaction at -78°C under standard conditions.[8a,22] Yield 43%. *syn/anti* ratio 79 : 21.

HPLC: *anti* isomer was eluted first (n-heptane/EtOAc, 98 : 2). Orange oil. TLC R_f 0.16 (c-hexane/EtOAc, 95 : 5).

***Syn* isomer 13a:**

^1H NMR (60 MHz, CCl_4) δ 0.7 to 2.0 (m, 15 H, CH_3, H-4 and c-hex), 2.23 (br s, 1 H, OH), 3.05 (d, J = 6 Hz, 2 H, H-2), 3.83 to 4.33 (m, 1 H, H-3), 5.0 to 6.2 (m, 3 H, $CH=CH_2$). IR: 3620 and 3475 cm^{-1} (OH), 3090 cm^{-1} (=C-H), 1640 cm^{-1} (C=C). ^{13}C NMR ($CDCl_3$) δ 10.45 (CH_3-4), 26.76, 29.87 and 31.53 (c-hex), 39.39, 40.42, 43.55, 57.46 (C-2), 73.00 (C-3), 119.61 (=CH_2), 130.54 (=C-H), 236.49 (C=S). MS: 41 (100), 43 (23), 67 (21), 69 (21), 82 (30), 111 (14), 139 (13), 166 (4), 231-(4), 272 (1). Anal. Calcd for $C_{14}H_{24}OS_2$: C, 61.72; H, 8.8; S, 23.53. Found: C, 62.43; H, 8.9; S, 22.24.

***Anti* isomer 13b:**

^{13}C NMR ($CDCl_3$) δ 11.43 (CH_3-4), 28.57, 29.87 and 31.53 (c-hex), 38.78, 40.42, 43.55, 55.43 (C-2), 73.37 (C-3), 119.61 (=CH_2), 130.54 (=C-H), 236.49 (C=S).

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 in an acetone/dry ice bath. A solution of pure *syn* aldol **8a**, **9a**, **11a** or **12a** or a *syn/anti* mixture of aldol **10** or **13** was added dropwise via syringe. The mixture was stirred at -78°C for 30 min. The electrophile (1 eq. of allyl or methyl iodide) was added in one portion to the colourless resulting solution. The solution was stirred at -78°C for 45 min., 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, then dried over $MgSO_4$. The solution went orange quickly and was left at room temperature. After a couple of days the rearrangement was finished. Its progress was monitored by ^1H NMR analysis. Crude dithioesters **17-19** were isolated as a mixture of diastereoisomers after concentration *in vacuo*. The diastereoisomeric distribution was determined by an HPLC analysis. The dithioesters **17-19** were purified by MPLC. In some cases, the separation of the mixture was successful (*vide infra*).

***Methyl 2-allyl-3-hydroxy-4,5,5-trimethylhexanedithioate* 17**

From the thio-Claisen rearrangement of ketene dithioacetal $\mathbf{14_Z}$ formed by the reaction of *syn* aldol **8a** (0.17 g; 0.78 mmol) and allyl iodide. Yield 54%. *syn-syn/anti-syn* ratio 85 : 15.

From the thio-Claisen rearrangement of ketene dithioacetal $\mathbf{14_E}$ formed by the reaction of *syn* aldol **11a** (0.17 g; 0.7 mmol) and methyl iodide. Yield 47%. *syn-syn/anti-syn* ratio 96 : 4.

HPLC: *anti-syn* isomer was eluted first (n-heptane/EtOAc, 95 : 5). The diastereoisomeric pair was separable by MPLC.

***Syn-syn* isomer 17a:**

Orange oil. TLC R_f 0.09 (c-hexane/EtOAc, 95 : 5). ^1H NMR (60 MHz, CCl_4) δ 0.86 (s, 9 H, tBu), 0.92 (d, J = 7.08 Hz, 3 H, CH_3-γ), 1.01 to 1.3 (m, 1 H, H-γ), 1.63 (br s, 1 H, OH), 2.60 (s, 3 H, SCH_3); 2.65 to 2.8 (m, 2 H, H-β'), 3.38 (dt, J = 3.91 and 9.03 Hz, 1 H, H-α), 4.1 to 4.29 (m, 1 H, H-β), 4.9 to 5.78 (m, 3 H, H-γ' and H-δ'). IR: 3630 and 3450 cm^{-1} (OH), 3075 cm^{-1} (=C-H), 1640 cm^{-1} (C=C). RMN ^{13}C: 7.54 (CH_3-γ), 19.13 (SCH_3), 28.12 (tBu), 32.98 (C of tBu), 38.49 (C-β'), 43.79 (C-γ), 65.39 (C-α), 75.17 (C-β), 116.55 (C-δ'), 135.58 (C-γ'), 240.48 (C=S). MS: 56 (71), 70 (20), 84 (95), 90 (71), 96 (100), 98 (77), 130 (53), 145 (65), 146 (64), 260 (24). Anal. Calcd for $C_{13}H_{24}OS_2$: C, 59.95; H, 9.29; S, 24.62. Found: C, 60.11; H, 9.25; S, 23.39.

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

Orange oil. TLC R_f 0.13 (c-hexane/EtOAc, 95 : 5). ^{13}C NMR ($CDCl_3$) δ 8.39 (CH_3-γ), 19.57 (SCH_3), 28.08 (tBu), 33.43 (C of tBu), 38.71 (C-β'), 44.27 (C-γ), 65.00 (C-α), 74.32 (C-β), 117.04 (C-δ'), 134.67 (C-γ'), 242.10 (C=S).

***Methyl 2-(1-hydroxy-2-phenylpropyl)-4-pentenedithioate* 18**

From the thio-Claisen rearrangement of ketene dithioacetal **15Z** formed by the reaction of *syn* aldol **9a** (0.15 g; 0.625 mmol) and allyl iodide. Yield 92%. *syn-syn/anti-syn* ratio 99 : 1.

From the thio-Claisen rearrangement of ketene dithioacetal **15E** formed by the reaction of *syn* aldol **12a** (0.17 g; 0.625 mmol) and methyl iodide. Yield 91%. *syn-syn/anti-syn* ratio 99 : 1.

HPLC: *syn-syn* isomer was eluted first (n-heptane/EtOAc, 95 : 5). Orange oil. TLC R_f 0.2 (c-hexane/EtOAc, 95 : 5). The diastereoisomeric pair was inseparable by MPLC.

***Syn-syn* isomer 18a:**

^{1}H NMR (60 MHz, CCl_4) δ 1.28 (d, J = 6.5 Hz, 3 H, CH_3-γ), 2.4 to 3.33 (m, 5 H, OH, H-β', H-α and H-γ), 2.55 (s, 3 H, SCH_3), 3.83 (dd, J = 6 and 5 Hz, 1 H, H-β), 4.67 to 5.83 (m, 3 H, H-γ' and H-δ'), 7.2 (m, 5 H, H-Ar). IR: 3590 and 3440 cm^{-1} (OH), 3065, 3050 and 3020 cm^{-1} (=C-H of Ar), 1638 cm^{-1} (C=C), 1600, 1490 and 1450 cm^{-1} (C=C of Ar). ^{13}C NMR ($CDCl_3$) δ 16.68 (CH_3-γ), 19.33 (SCH_3), 35.56 (C-β'), 42.89 (C-γ), 62.25 (C-α), 79.09 (C-β), 116.72 (C-δ'), 126.76, 127.77 and 128.80 (Ar), 135.48 (C-γ'), 144.52 (Ar), 243.19 (C=S). MS: 43 (19), 77 (36), 79 (23), 91 (100), 131 (29), 134 (64), 175 (19), 233 (10), 280 (1). Anal. Calcd for $C_{15}H_{20}OS_2$: C, 64.24; H, 7.19; S, 22.86. Found: C, 64.19; H, 7.17; S, 22.70.

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

^{13}C NMR ($CDCl_3$) δ 16.68 (CH_3-γ), 18.43 (SCH_3), 39.70 (C-β'), 44.23 (C-γ), 61.16 (C-α), 78.26 (C-β), 117.44 (C-δ'), 126.72, 127.73 and 128.80 (Ar), 134.78 (C-γ'), 144.85 (Ar), 243.18 (C=S).

***Methyl (2-cyclohexyl-1-hydroxypropyl)-4-pentenedithioate* 19**

From the thio-Claisen rearrangement of ketene dithioacetal **16Z** formed by the reaction of *syn* aldol **10a** (0.19 g; 0.77 mmol) and allyl iodide. This aldol was contaminated by its *anti* isomer **10b** (*syn/anti* ratio 89 : 11). Yield 74%. Three diastereoisomers were detected: *syn-syn/anti-syn/syn-anti* ratio 75 : 9 : 16.

From the thio-Claisen rearrangement of ketene dithioacetal **16E** formed by the reaction of *syn* aldol **13a** (0.2 g; 0.75 mmol) and methyl iodide. This aldol was contaminated by its *anti* isomer **13b** (*syn/anti* ratio 89 : 11). Yield 64%. Three diastereoisomers were detected: *syn-syn/anti-syn/syn-anti* ratio 86 : 2 : 12.

Starting with a mixture of the same aldols **13a** and **13b** in 79 : 21 ratio (This mixture was enriched in diastereoisomer *anti* **13b**), the same three diastereoisomers **19** were detected as before: *syn-syn/anti-syn/syn-anti* ratio 79 : 2 : 19.

HPLC: *syn-anti* isomer was eluted first, then *anti-syn* isomer and finally *syn-syn* isomer (n-heptane/EtOAc, 97 : 3). After MPLC, *syn-anti* isomer was isolated as a pure product and *anti-syn* and *syn-syn* isomers as a mixture.

***Syn-syn* isomer 19a:**

Orange oil. TLC R_f 0.16 (c-hexane/EtOAc, 95 : 5). ^{1}H NMR (60 MHz, CCl_4) δ 0.86 (d, J = 6 Hz, 3 H, CH_3-γ), 0.97 to 2.03 (m, 12 H, H-γ and c-hex), 2.4 to 2.8 (m, 3 H, OH and H-β'), 2.6 (s, 3 H, SCH_3), 3.38 (dt, J = 5 and 8 Hz,1 H, H-α), 3.77 to 4.13 (m, 1 H, H-β), 4.73 to 6.03 (m, 3 H, H-γ' and H-δ'). IR: 3630 and 3470 cm^{-1} (OH), 3080 cm^{-1} (=C-H), 1640 cm^{-1} (C=C). ^{13}C NMR ($CDCl_3$) δ 10.25 (CH_3-γ), 19.19 (SCH_3), 26.80, 29.85, 31.23, 37.52 (C-β'), 40.24, 40.67, 63.90 (C-α), 76.13 (C-β), 116.58 (C-δ'), 135.76 (C-γ'), 241.54 (C=S). Anal. Calcd for $C_{15}H_{26}OS_2$: C, 62.91; H, 9.16; S, 22.35. Found: C, 62.80; H, 9.12; S, 21.10.

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

Orange oil. TLC R_f 0.16 (c-hexane/EtOAc, 95 : 5). ^{13}C NMR ($CDCl_3$) δ 10.5: (CH_3-γ), 19.19 (SCH_3), 26.80, 29.85, 31.23, 38.90 (C-β'), 40.24, 40.67, 63.90 (C-α), 76.13 (C-β), 117.15 (C-δ'), 134.89 (C-γ'), 241. 54 (C=S).

Aldol reaction with 4-pentenedithioate 20

To a solution of LDA (1,1 eq.; 0,72 mmol) in THF cooled to -78°C, a solution of dithioester **20** (1 eq.; 0,71 mmol) in THF was added dropwise. After stirring for 25 min. at -78°C, the solution was colourless. A solution of 2-phenylpropanal **4** in THF at -78°C was added in one dash. The solution went orange immediately. The reaction mixture was stirred at -78°C for 5 min. The reaction was quenched with a saturated NH_4Cl solution, extracted with ether and washed with brine. The ether phase was dried over $MgSO_4$ and evaporated. The resulting product consisted of a mixture of the four diastereoisomers **18** in a ratio 76 : 15 : 3 : 6 (elution order) assessed by HPLC analysis (n-heptane/EtOAc, 95 : 5). The major product (76%) was the *syn-syn* isomer **18a** and the next major product (15%) the *anti-syn* one **18b**. No assignment of the two other isomers (3 and 6%) was attempted. After MPLC no separation of the four isomers was obtained (c-hexane/EtOAc, 95 : 5). Yield 33%. Spectra data of diastereoisomers **18a** and **18b** were given previously.

A reaction under the same conditions was unsuccessful with aldehydes **3** and **5**.

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