Diastereocontrol of Thio-Claisen Rearrangement induced by an Adjacent Hydroxy-substituted Chiral Centre

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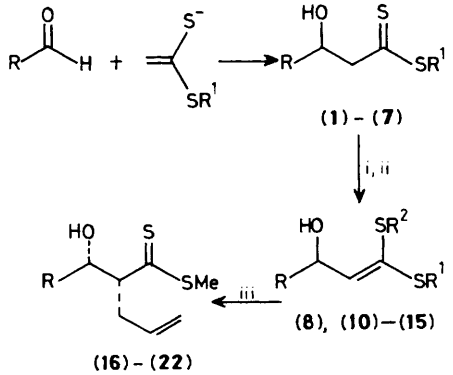
S-Allyl α-hydroxy ketene dithioacetals smoothly rearrange into α-allyl β-hydroxydithioesters with a high level of *syn*-diastereoselectivity, with the *syn* : *anti* ratio ranging from 24 : 1 to 6 : 1, independently of the geometry of the ketene double bond.

The Claisen rearrangement has been widely used in stereocontrolled formation of double and single bonds and in 1,3 and 1,4 chirality transfer.[1,2] Although less studied, asymmetric induction by a remote chiral centre appended to the pericyclic array has recently been demonstrated.[2] Chirality transmission has been achieved successfully in the chelation controlled ester enolate Claisen[3] rearrangement of various allylic α-or β-hydroxy-substituted esters.[4—6] The dianionic rearrangement of allylic 3-hydroxybutanoates has been reported by two independent groups with opposite stereoselectivities.[5,6] The *anti*-configuration of the allylic aldol formed has subsequently been confirmed.[5] In the absence of chelation control, the stereoselectivity was inverted.[6]

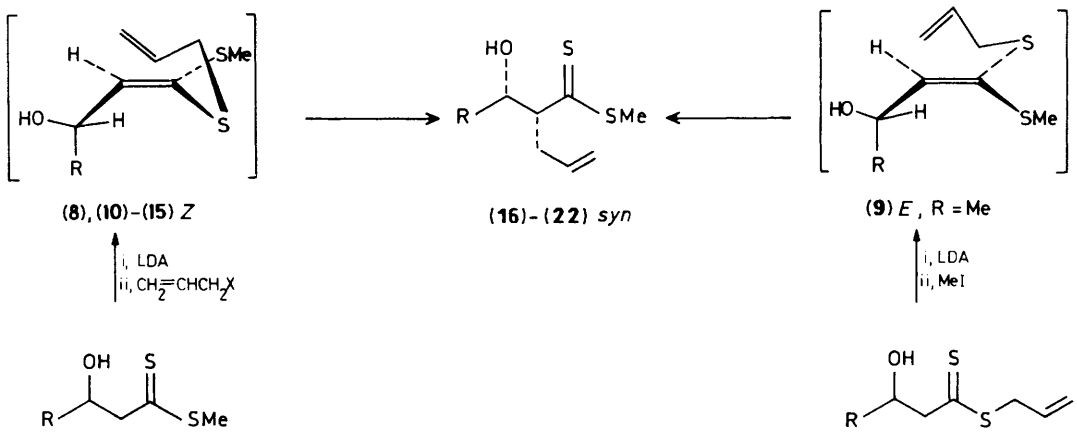
Here we disclose our results on the thio-Claisen rearrangement of *S*-allyl α-hydroxy ketene dithioacetals. It was expected, as is known for simple *S*-allyl ketene dithioacetals,[7,9]



Scheme 1. *Reagents and conditions:* i, LDA (2 equiv.) tetrahydrofuran (THF), −78 °C; ii, CH_2=$CHCH_2X$, −78 °C; iii, 25 °C, 3 days.

Table 1. Thio-Claisen rearrangement diastereoselectivity.

Entry	Hydroxydithioester		Ketene dithioacetal			Rearranged product		
	R		R^2	R^1		*syn* : *anti* ratio		Yield (%)
1	Me	(**1**)	Allyl	Me	(**8**)	9 : 1	(**16**)	73
2			Me	Allyl	(**9**)	10 : 1	(**16**)	68
3	Et	(**2**)	Allyl	Me	(**10**)	13 : 1	(**17**)	45
4	Pr	(**3**)	Allyl	Me	(**11**)	16 : 1	(**18**)	57
5	Pr^i	(**4**)	Allyl	Me	(**12**)	24 : 1	(**19**)	65
6	Bu^t	(**5**)	Allyl	Me	(**13**)	>24 : 1	(**20**)	42
7	Ph	(**6**)	Allyl	Me	(**14**)	6 : 1	(**21**)	34
8	$PhCH_2$	(**7**)	Allyl	Me	(**15**)	24 : 1	(**22**)	28



Scheme 2

that such a rearrangement would occur easily providing diastereoisomeric α-allyl β-hydroxydithioesters (see Scheme 1).

Several β-hydroxydithioesters (**1**)—(**7**) were prepared according to a known procedure[8—10] by condensation of the preformed lithium thioenolate of methyl dithioacetate with aldehydes at −78 °C. The deprotonation stereochemistry of these dithioesters was first defined: *S*-alkylation with benzyl bromide of the chelated dianion formed by double deprotonation with lithium di-isopropylamide (LDA) of methyl 3-hydroxybutanedithioate (**1**) gave a *single*† stereoisomer of the expected ketene dithioacetal, probably of *Z* geometry.‡ The β-hydroxydithioesters (**1**)—(**7**) were then similarly deprotonated with LDA (2 equiv.) and treated with allyl bromide at −78 °C affording after work-up a colourless solution of the desired stereochemically pure *S*-allyl α-hydroxy ketene dithioacetal (*Z*)-(**8**)—(**15**).‡§ When left at room temperature these solutions slowly became orange. After 3 days, a mixture of two diastereoisomeric α-allyl β-hydroxydithioesters (**16**)—(**22**) was isolated with a *syn* : *anti* ratio in the range 6 : 1 to 24 : 1, determined by h.p.l.c. (see Table 1).

Diastereoisomer configurations were deduced from h.p.l.c. comparison with a *syn*-rich mixture of the same diastereoisomers prepared by a *syn*-stereospecific aldol condensation[8] of methyl pent-4-enedithioate with the requisite aldehydes.

Assignment of the *syn*-configuration to the major aldol (**16**) was confirmed by coupling constant measurements[8,11,12] [$J_{2,3}$(*syn*) 4.9 < $J_{2,3}$(*anti*) 5.35 Hz] and by chemical conversion[13] of the aldol mixture (**16**) into the known *syn*- and *anti*-ethyl 2-allyl-3-hydroxybutanoates.[12]

The *syn*-stereoselectivity uniformly observed is independent of the ketene dithioacetal geometry since a *syn* : *anti* ratio of 10 : 1 was obtained after rearrangement of the *S*-allyl α-hydroxy ketene dithioacetal (*E*)-(**9**),‡§ the stereoisomer of (**8**) formed from *S*-allyl β-hydroxybutanedithiolate (see entry 2, Table 1, and Scheme 2).

The *syn*-rich selectivity of this rearrangement does not result from chelation control but rather from a steric or an electronic effect or both. As shown in the transition state model in Scheme 2, the bond formation between the allylic termini and the ketene carbons occurs *anti* to the R group whose A-strain[14] is always larger than that of the hydroxy group.[2] In this transition state the hydroxy group lies in the "outside position"[2] almost in the plane of the ketene owing to steric repulsion and stabilization resulting from a through-space interaction of the oxygen lone pair with the ketene dithioacetal double bond. This prevailing stereoelectronic control may explain the *syn* : *anti* ratio decrease in entry 7 resulting from competition between the phenyl and hydroxy groups for conjugation with the ketene double bond.

† Evidence for the stereochemical purity of this ketene dithioacetal was obtained by comparison of its ^{1}H n.m.r. spectrum with that of the other isomer prepared from benzyl 3-hydroxybutanedithioate: respective signals for the methyl doublets δ 0.88 and 1.05; for the SMe singlets δ 2.2 and 2.23; for the alkene doublets δ 5.67 and 5.87.

‡ Based on the assumption that the dianion (**1**) is chelated and remains so during the alkylation, the *Z* configuration was assigned to (**8**) and, by analogy to (**10**)—(**15**) and the *E* configuration to (**9**).

§ The ^{1}H n.m.r. spectra of (**8**) and (**9**) show respective signals for the methyl doublets at δ 1.2 and 1.23; for the SMe singlets at δ 2.25 and 2.28; for the ketene protons at δ 5.85 and 5.98. By analogy, we assumed that the stereochemistry of (**10**)—(**15**) would be the same as that of (**8**).

Now that we are certain of the *syn*-configuration of the rearranged aldols, work is in progress to create three consecutive asymmetric centres from various *S*-allylic α-hydroxy ketene dithioacetals involving the above induction and the internal Claisen stereospecificity.[3] Starting from enantiomerically pure β-hydroxydithioesters which are easily available,[15] absolute diastereoselective thio-Claisen rearrangement will be also attempted.

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