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DIASTEREOFACIAL SELECTIVITY VIA ALDOL REACTIONS USING ETHYL DITHIOACETATE AND ETHYL DITHIOPROPIONATE ENOLATES

A. I. Meyers* and Robert D. Walkup
Department of Chemistry
Colorado State University
Fort Collins, Colorado 80523

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Abstract: The lithium enolate of ethyl dithioacetate reacts with α-methyl aldehydes to yield the aldol products in which the syn configuration in the positions β and γ to the thiocarbonyl of the product is favored over the anti configuration. This selectivity is solvent-dependent, and is enhanced at lower temperatures. In most cases, syn:anti product ratios obtained under these conditions varied from 57:43 to >99:1, depending upon the structure of the α-methyl aldehyde. When the lithium enolate of ethyl dithiopropionate was allowed to react with α-methyl aldehydes, only two out of the four possible diastereomers were detected in the product mixtures.

INTRODUCTION

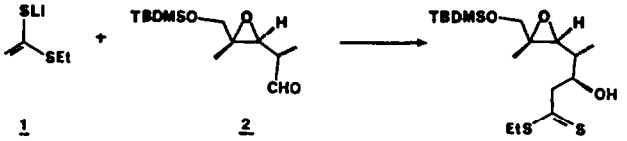
Among the strategies utilized to control the stereochemistry of acylic organic molecules the aldol reaction of an enolate anion and an aldehyde has enjoyed particular success. Several recent reviews have discussed the progress which has been made in this area and take note of two types of stereoselectivity attainable via the aldol reaction.[1] One is simple diastereoselectivity, in which the relative configurations of the two carbons being joined by the aldol addition reaction are selectively controlled (equation 1). A second type of stereoselectivity, diastereofacial stereoselectivity, involves the selective formation of diastereomers having relative configurations at the β and γ positions of the aldol product (equation 2). The goal of simple diastereoselection

(eq. 1)

(eq. 2)

is now attainable using a variety of strategies. However, the attainment of diastereofacial selection using currently-known methods is less certain,[1] and the results from several recently reported natural products syntheses which have utilized aldol reactions requiring such selectivity indicate a need for a better understanding of factors influencing the aldol diastereofacial selection.[2] One recent report has described the Lewis acid-mediated aldol reaction between chiral aldehydes and silyl enol ethers which exhibits good diastereofacial selectivity.[3] It was found during the course of the recently-completed[4] synthesis of (-)-maysine that the lithium enolate of ethyl dithioacetate, 1, reacted with the α-methyl aldehyde 2 to yield the aldol product 3 in a 91:9 syn:anti ratio.[5] This potentially general diastereofacial selectivity, plus the known synthetic versatility of the dithioester functional group present in the aldol products[6] justified further investigation into the scope of the stereoselectivity of the

addition reaction between the dithioenolate and a variety of α-methyl aldehydes. The results of this investigation are described herein, as well as those from related investigations into 1) the temperature dependence of aldol diastereofacial selectivity, 2) the comparative diastereofacial selectivities of the enolates of a variety of acetate equivalents, 3) the simple and diastereofacial selectivities of the enolate of ethyl dithiopropionate, and 4) the diastereofacial selectivity of the aldol-like 1,4-addition of a dithioenolate to an enone.



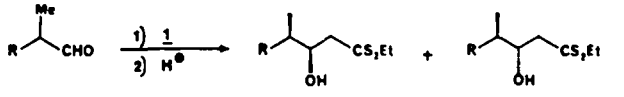
1 2 3

RESULTS AND DISCUSSION

Diastereofacial Selectivity of the Enolate of Ethyl Dithioacetate

Ethyl dithioacetate reacts instantaneously at -78°C with lithium diisopropylamide (LDA) in ethereal solvents to form a colorless solution of the lithium dithioenolate. During the course of this study, it was found that the dithioester reacts equally well with n-butyllithium to form the same enolate species. This dithioenolate decomposes above 0° C to form deep orange polar (polymeric?) products. When an aldehdye is added, an exothermic reaction occurs instantaneously (<1 minute) to form the bright yellow aldol adduct. In spite of the apparently clean conversion to the aldol product, conventional silica gel chromatography of the reaction mixtures resulted in some decomposition of the product, thus allowing isolated yields of only 40-60%.

As an initial probe of the factors involved in the reaction of the lithium enolate 1 with α-methyl aldehydes, we studied the reaction with 2-phenylpropanal 4a (Table 1, entry a). The resulting aldol product mixture was analyzed by HPLC, then separated chromatographically into the two aldol products 5a and 6a. Cram's rule[7] predicts that

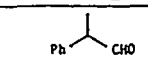
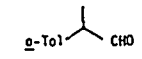
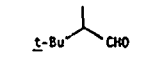
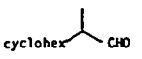
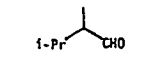
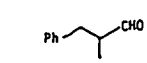
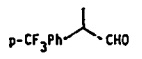
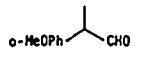
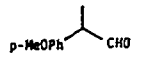
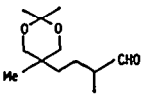


4a 5a 6a

the major product for this reaction would be the syn aldol 5a. The selectivity which the enolate 1 exhibited toward the aldehyde 4a was observed to improve modestly when the reaction temperature was lowered. The results of a study of the effect of the reaction temperature upon the syn:anti ratio in the product mixture indicate that the ratio improves slightly from 85:15 at -78°C to 89:11 at -120°C. It was also found that by allowing the added aldehyde solution to freeze into a layer over a frozen solution of the enolate at -195°C, then slowly warming the frozen mixture to melting point (-120°C) resulted in a 94:6 syn:anti product mixture. This increase in selectivity (89:11 to 94:6) reflects a rather small change in the $\Delta\Delta G^{\ddagger}$ (0.6 kcal/mol), but is believed to be significant in view of its reproducibility (S.D. = ±2.0% over 11

experiments) and the greater synthetic utility of an enhanced selectivity. It is, at this time, not clear why the stereoselectivity increases in the frozen mixture but we have observed virtually no product formation at -195° C until the reaction temperature nears the melting point of the solvent (about -120 C, indicated by the appearance of a yellow color in the slowly thawing mixture). Furthermore, much lower ratios are observed

TABLE 1. Addition of Lithiodithioacetate to α-Methyl Aldehydes

Entry	Aldehyde, 4	Syn:Anti Ratios (5:6) Additions at: -120°C	Syn:Anti Ratios (5:6) Additions at: -195 → -120°C	HPLC Ret. Time (min)[a] (Syn/Anti)
a		89:11	96:4	6.6/5.6[b]
b		94:6	98:2	7.7/6.4[b]
c		>99:1	>99:1	8.0/--[c]
d		74:26	84:16	7.5/7.2[b]
e		77:23	76:24	18.8/18.2[d]
f		50:50	57:43	13.4/12.8[b,e]
g		78:22	84:16	13.1/9.1[b]
h		78:22	85:15	-f-
i		82:18	69:31	-f-
j		72:28	81:19	-g-

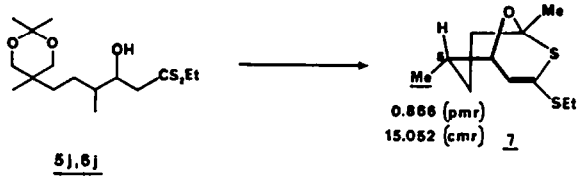
a) HPLC performed using μ-Porasil column. b) Hexane-ethyl acetate (95:5). c) Hexane-ethyl acetate (98:2). d) Hexane-ethyl acetate (99:1). e) Using Dupont Zorbaxsil column (5μ). f) Could not be separated-converted to methyl ester[8] to give indicated ratios, R.T. (hexane-ethyl acetate, 90:10) syn:, 13.8 min, anti:, 15.9 min. g) Determined by HPLC on bicyclic derivatives 7, R.I. (hexane-ethyl acetate, 99:1): 7, 5.2 min; 8, 4.4 min.

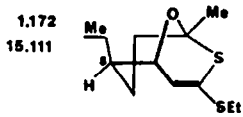
under the "freeze-thaw" conditions when ether (77:23 5a:6a) or pentane (73:27 5a:6a) are used as the solvent; only tetrahydrofuran (THF) or 4:1 THF:ether gives the observed 94:6 syn:anti ratio. These latter two observations suggest that the phase change during the reaction, not the -195° C temperature, and the nature of the solvent, may be important to the selectivity. Obviously, further studies are necessary to elucidate the reason for this observed temperature/solvent effect.

The reactions of 1 with other α-methyl aldehydes were studied and the results of this study are shown in Table 1. In most cases, the ratios of the diastereomers formed could be determined from HPLC analysis. Based on the predictions of Cram's rules, the syn configuration was assigned to the major product in each case. Entries a-f in Table 1 indicate that, despite the temperature dependency of the aldol reaction discussed above, the selectivity of the addition is still dictated significantly by the steric bulk of the α-methyl aldehyde. Increasing the bulkiness relative to 2-phenylpropanal (entries b and c) resulted in virtually complete diastereoselectivity, with little or

no temperature dependence, in favor of the syn product. Decreasing the bulk (entries d,e,f) resulted in a lower diastereoselectivity, although the selectivities with aldehydes 4d and 4f could be improved by using "freeze-thaw" conditions.

Entries g, h and i reflect electronic effects upon the diastereoselectivity of the reaction. Electron-donating substituents on the phenyl ring of 2-phenylpropanal should stabilize, and thus favor, the desired transition state geometry for the aldol reaction, relative to the unsubstituted case, by lowering the energy of the aldehyde's π^*_{CO} orbital via overlap between the σ^* orbital of the C_2-$C_{1'}$ bond and the π^*_{CO} bond, in accordance with Anh's theoretical calculation[7e,7f]. Conversely, an electron-withdrawing group would be expected to have an opposite effect. Indeed, the para-trifluoromethyl-substituted aldehyde 4g exhibited a lower selectivity (Table 1, entry g) as expected for an electron-withdrawing group. An ortho or a para methoxy group on the phenyl ring also resulted in a decreased selectivity (Table 1, entries h and i). This can be attributed to the fact that the inductive effect of a methoxy group is that of an electron-withdrawing group[9], therefore the diastereofacial selectivity should be diminished by the inductive effects of these groups, as observed. An unfavorable effect upon through-space interactions between the π^* orbitals of the aromatic ring and the π^*_{CO} orbital[7e] may also account for these results. No present explanation is offered for the apparently anomalous temperature effect on the selectivity of aldehyde 4i shown in Table 1. The 5h:6h and 5i:6i ratios were determined, respectively by the HPLC and ^1H nmr analyses of the methyl ester derivatives,[8] thus some error in these determinations may have been introduced by the added experimental manipulations needed for these analyses.





Entry j in Table 1 shows the results from the aldehyde 4j, a simple analog of the aldehyde used in two syntheses of calcimycin.[2a,2b] The high syn:anti ratio observed, relative to the ratio from the benzyl propanal 4f, indicates a possible positive chelation effect of the ketal oxygens δ to the aldehyde carbonyl. The diastereomeric aldols 5j and 6j could not be distinguished by HPLC. However, brief treatment with a trace of acid yielded the separable oxathianes 7 and 8 in high yield. The assignment of the major product as the presumed syn-derived endo isomer 7 was supported by the nmr chemical shifts (^1H and ^{13}C) of its 5-methyl group occurring upfield from those of the minor

anti-derived exo isomer 8, as expected because of the greater spatial distance between this methyl group and the bridgehead oxygen in the endo isomer.

Diastereofacial Selectivity With Other Acetate Equivalents

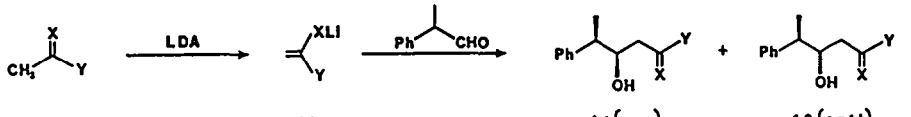
The question of the uniqueness of this stereoselectivity, particularly under the "freeze-thaw" reaction conditions, was considered with other enolates. Table 2 lists

TABLE 2. Addition of Various Lithioenolates to 2-Phenylpropanal

Entry	Enolate Precursor, 9	Syn:Anti Ratios (11:12) Additions at: -120°C	-195 → -120°C	HPLC Ret. Time (min)[a] Syn/Anti
a	CH_3CS_2Et	89:11	96:4	6.6/5.6[b]
b	$CH_3C(=S)OEt$	87:13	90:10	7.5/7.0[b]
c	$CH_3C(=O)SEt$	73:27	75:25	14.2/13.1[b]
d	CH_3CO_2Et	75:25	76:24	12.7/11.9
e	CH_3CONMe_2	79:21	82:18	8.8/10.3[c]
f	PhCOMe	67:33	61:39	-d-
g		83:17	84:16	13.1/12.8[c]
h	CH_3CN	82:18	83:17	18.4/17.8[e]

a) Performed on a μ-Porasil column. b) Hexane-ethylacetate (95:5). c) Hexane-ethylacetate (50:50). d) Ratios determined by ^{1}H-nmr of product mixture by integration of doublets at δ1.406 (syn) and 1.361 (anti). e) Hexane-ethylacetate (90:10).

the erythro:threo aldol ratios obtained when 2-phenylpropanal (4a) was treated with the lithium enolates 10 of a variety of acetate equivalents 9. As with the dithioester aldol products (Table 1), the syn:anti ratios 11:12 could, in most cases, be determined from the HPLC analysis of the product mixture. The assignment of the syn and anti configurations to the major and minor products, respectively, is again based upon precedent. For each case studied, the ^{13}C chemical shift of the hydroxy-bearing C-3 carbon was downfield in the syn (major) product relative to that in the anti (minor) product.



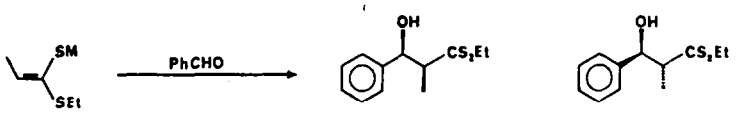
9 10 11(syn) 12(anti)

Table 2 indicates that the acetate equivalents 9b-9h exhibit moderately good diastereofacial selectivity (61:39 to 90:10 syn:anti). However, only in the case of O-ethyl thioacetate (9b) is the selectivity nearly as high as ethyl dithioacetate (9a). The acetyl precursors 9c-9f, the oxazoline 9g, and acetonitrile (9h) exhibited significantly lower selectivities. All acetate equivalents except acetophenone (9f) showed a slightly

higher aldol stereoselectivity under the "freeze-thaw" conditions. The anomalous behavior of acetophenone may be due to unusual electronic or steric factors imposed by the phenyl ring of the enolate upon the transition state of the aldol reaction. Since the linear lithioacetonitrile exhibits selectivity on a par with larger enolates, factors other than the steric bulkiness of the enolates may be involved. It has been observed that, in nucleophilic additions to carbonyls, "soft" nucleophiles give the highest stereoselectivity in their approach.[7f] Evidence from theoretical calculations has indicated that when the counterion of the enolate chelates to the aldehyde oxygen, the selectivity of the direction of the approach by the nucleophile to the aldehyde is not as high as in the uncomplexed case.[7e, 7f] In the present example (Table 2), it appears that the "soft" sulfide-bearing enolate ions from 9a and 9b, which would not be very tightly bound to the "hard" lithium ion, do not allow such a deleterious complexation between the lithium and the aldehyde during the aldol reaction. The enolates from the acetate equivalents 9c-9h, on the other hand, bear "hard" oxygen or nitrogen anionic centers, and probably form tight complexes with their lithium counterions, thus allowing the lithium to interact more intimately with the aldehyde.

Stereoselectivity of the Lithio Ethyl dithiopropionate

The aldol stereoselectivity of the enolate of ethyl dithiopropionate, 13, was also investigated. Initially, the simple diastereoselectivity of 13 was assayed by reacting the lithium enolate, (generated by reaction of ethyl dithiopropionate with either LDA or n-butyllithium at -78° C) with benzaldehyde. The configurations of the resulting separated aldol products 14 and 15 could be assigned on the basis of their ^{1}H nmr spectra. The chromatographically more mobile product exhibited a vicinal coupling constant between the α and β protons of 4.8 cps, implying the syn configuration 14, and the less mobile aldol product exhibited a coupling constant of 8.1 cps, for the anti configuration 15.[2] As shown, the reaction using lithio-13 exhibited very little simple diastereoselectivity, despite the reported specific Z geometry of the lithium enolate of dithiopropanoate.[10] Selectivity for the syn diastereomer improved as the temperatures were lowered to -195°C. Using the bis(cyclopentadienyl)chlorozirconium (IV) enolate of 13, formed from the lithium enolate,[11] the syn:anti ratio was substantially improved.

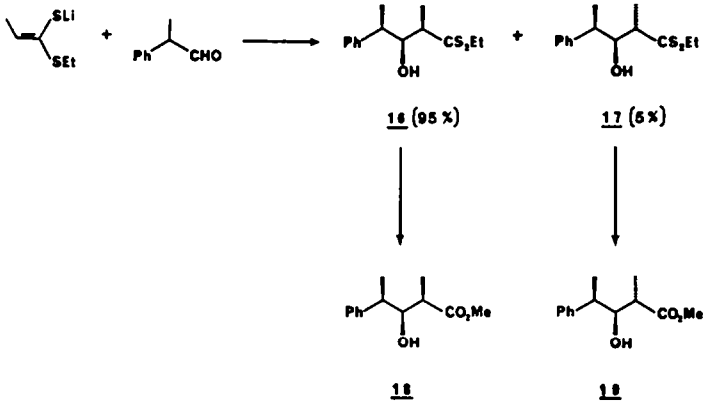


13 14 (syn) 15 (anti)

M	Ratio (14:15) -78°C	-120°C	-195° → -120°C
Li	46:54	52:48	59:41
$ZrCp_2Cl$	81:19	84:16	84:15
Ph_3Sn		N.R.	
Bu_3B		N.R.	

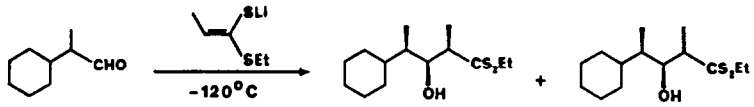
Interestingly, an attempt at performing this reaction using the reportedly selective triphenyltin (IV) enolate of 13, (from the lithium enolate and triphenyltin (IV) chloride[12]), failed because of the apparent stability of the tin enolate. In addition, attempts to form and react the selective dibutylboron enolates of dithioesters failed because of the reaction of the dithioesters with dibutylboron triflate[13] to form intractable tars.

The reaction of 13 (M=Li) with 2-phenylpropanal was also examined. It was surprising to discover that even the lithium enolate, at -120° C, yielded a mixture of only two out of the four possible diastereomers, 16 and 17, in a 95:5 ratio respectively. Using "freeze-thaw" conditions or the zirconium enolate did not change the product ratio from 95:5. The products, 16 and 17, were separated chromatographically and ^{13}C nmr spectroscopy attested to their stereochemical purities. The structure of each was assigned by first converting them to the corresponding methyl esters using copper (II)-mediated methanolysis[8] and then comparing them chromatographically with the reaction mixture obtained from the Reformatsky reaction of methyl-2-bromopropionate and 2-phenylpropanal. Matsumoto[14] has rigorously deduced the structures of all four diastereomers produced by this Reformatsky reaction, and found that the major diastereomers had the 2,3-syn, 3,4-syn configuration (18) and his next major diastereomer had the 2,3-anti, 3,4-syn configuration (19).[14] The HPLC retention time of



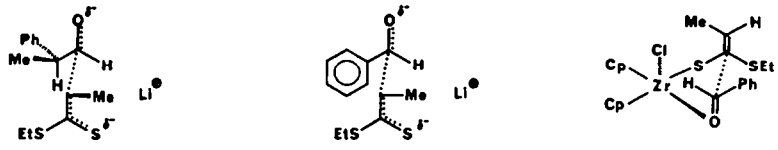
the methyl ester of the major dithioester aldol product precisely matched that of the major Reformatsky reaction product, 18, while the ester from the minor dithioester aldol product precisely matched the next major diastereomer from the Reformatsky products, 19. Using these results, structures 16 and 17 were assigned to the major and minor dithioester aldol products, respectively.

These results indicate that the enolate of ethyl dithiopropionate exhibits very high (>99:1) diastereofacial selectivity and high (95:5) simple diastereoselectivity with 2-phenylpropanal. When the dithiopropionate was treated with 2-cyclohexylpropanal only two diastereomers were obtained, in an 84:16 ratio. These aldol products, after chromatographic separation, yielded the pure diastereomers as ascertained by ^{13}C nmr and we have assigned the structures 20 and 21 for the major and minor diastereomers, respectively, based upon the precedent set by the reaction with 2-phenylpropanol.



20 (84%) 21 (16%)

The two examples of simple diastereoselection/diastereofacial selection studied above suggest that the introduction of a methyl group in the enolate results in a substantial improvement in the diastereofacial selectivity. These results also indicate that the lithium enolate of 13 exhibits favorable simple diastereoselectivity with the α-methyl aldehydes studied. We suspect that the reason for this rests on the basis that the reaction occurs via a non-cyclic transition state, as shown with 2-phenylpropanal in 22, and with benzaldehyde in 23. In both cases it is assumed that electronic and steric repulsion will favor the approach shown, with the (Z)-enolate's[10] anionic sulfur anti to the aldehyde C_1-C_2 bond, and the enolate carbonyl carbon anti to the carbonyl oxygen.[15] In the case of the α-methyl aldehydes, the substituents on the sp^3 α-carbon of the aldehyde project out from the plane of the carbonyl sufficiently to favor the less hindered approach by the enolate shown in 22. This approach would yield the α,β-syn product. However, in the case of benzaldehyde the sp^2 α-carbon (phenyl group) of the aldehyde does not exert as great a steric bulk as an sp^3 α-carbon (alkyl group), and thus does not demand the syn-producing anti transition state 23 as strongly as an sp^3 α-carbon. Use of the bis(cyclopentadienyl)chlorozirconium(IV) enolate, however, would involve coordination of both the enolate sulfur and the aldehyde carbonyl to the transition metal, thus changing the nature of the favored transition state to one such as 24, which would yield the syn aldol product.[2]

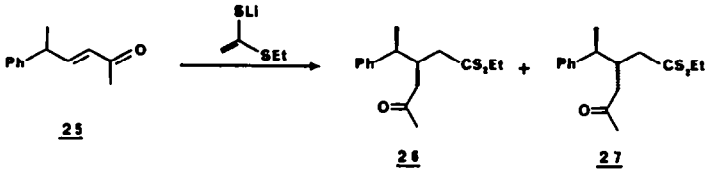


22 23 24

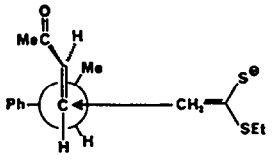
Diastereofacial Selectivity in the Addition of the Ethyl Dithioacetate Enolate to an Enone

Two recent reports have indicated the proclivity of dithioester enolates to undergo 1,4-additions to α,β-unsaturated ketones[16]. Since such a 1,4-addition can be considered to be a homolog to an aldol addition, it was decided to test the diastereofacial selectivity of the addition of the enolate 1 to the enone 25.[17] The reaction occurred readily at -50° C to yield the 1,4-addition adducts 26 and 27 in an 84:16 ratio (66% isolated yield) with none of the 1,2-addition product observed. The structure of the major product was assigned to the threo diastereomer 26 on the basis of the approach vector depicted by 28 which is expected to be favored in analogy with the aldol reaction transition state geometry. However, it was not possible to obtain evidence from the spectra of the separated adducts 26 and 27 which would rigorously substantiate this assignment. Lowering the reaction temperature for this addition to

-78° C slightly increased the diastereomeric ratio to 89:11, however the yield dropped to 42%, and at reaction temperatures of -120° C and below no reaction occurred.



25 26 27



28

Conclusions

The results presented herein indicate that the dithioenolates have the potential for yielding high diastereofacial selectivity when reacted with α-methyl aldehydes. The stereoselectivity exhibited by these species appears to be highly dependent upon the structure of the aldehyde reactant and upon the conditions of the reaction. Nevertheless, the results show that the dithioacetate exhibits diastereofacial selectivity superior to that of other acetates and we suspect that this superiority is due to the thioenolate being a "softer" anion than the other enolates. The "softness" of the thioenolate may be responsible for both the promising simple diastereoselectivity and the diastereofacial selectivity observed. The weak association of the thioenolate anion with the lithium counterion contributes to formation of an acyclic transition state (see 22) which dictates the simple diastereoselectivity, and the weak association of the enolate's lithium counterion to the aldehyde in the transition state appears to be responsible for the diastereofacial selectivity.[7e,7f] While some synthetically useful transformations have been made using heterogeneous conditions,[18] the concepts of using frozen solutions as the "solid support" and using heterogeneous conditions to achieve diastereofacial selectivity are novel.[19]

The ready conversion of the dithioester functional group in the product to other groups via Raney nickel reduction, thiophilic or carbophilic Grignard or organolithium additions, and solvolysis reactions[6,8] should make the products from these additional processes quite useful in organic synthesis.*

*After this manuscript was submitted, a report by Beslin (Beslin, P., Vallee, Y. Tetrahedron 1985, 41, 2691) appeared which described the reaction of Z-enolates of dithiopropionates with aldehydes showing poor diastereoselectivity. However, use of chelating alkyl groups or large alkyl groups, indeed, improved the simple diastereoselectivity (i.e. 14, 15). Another study reported after submission of this manuscript (Gennari, et al., Tetrahedron Letters 1985, 26 797) described high levels of simple diastereoselectivity using thioester ketene silyl acetals.

EXPERIMENTAL

General. Pure 2-phenylpropanal was separated from the attendant aceto-phenone in the commercial material by flash chromatography (silica gel, 95:5 hexane:ethyl acetate). Ethyl dithioacetate and ethyl dithiopropionate were prepared according to Meijer.[20] O-ethyl thioacetate (9b) was prepared according to Ohno.[21] Cooling baths employed in this study, and their approximate temperatures, are as follows: water/ice, 0°C; 28% aqueous $CaCl_2$/dry ice, -20°C; acetonitrile/dry ice, -35°C; chloroform/dry ice, -55°C; acetone/dry ice, -78°C; absolute methanol/liquid nitrogen, -100°C; 4:1:1 (v/v/v) pentane:isopropanol:acetone/liquid nitrogen, -120°C; isopentane/liquid nitrogen, -160°C; liquid nitrogen, -195°C. "Flash chromatography" refers in all cases to air pressure-driven solvent elution on 230-400 mesh silica gel.[22] Medium pressure liquid chromatography (MPLC) refers in all cases to chromatography through a 75cm x 28mm (ID) column packed with 230-400 mesh silica gel using the apparatus previously described.[23] All ^1H and ^{13}C spectra were recorded in deuteriochloroform at 100 MHz and 25 MHz respectively.

Ethanethiol acetate (9c). To a cooled stirring solution of ethanethiol (14.6 ml, approximately 0.2 mol) in 70 ml dichloromethane containing 28 ml (approximately 0.2 mol) of dry triethylamine (distilled from CaH_2) under a $CaCl_2$-filled drying tube, was added dry acetyl chloride (14.0 ml, approximately 0.2 mol) dropwise. The resulting mixture was stirred at room temperature for 4 h, then carefully mixed with 75 ml of water. The aqueous phase was extracted with dichloromethane (50 ml), and the combined organic phases were washed with saturated NaCl, dried (Na_2CO_3), filtered, and distilled to yield 12.3 g (60%) of pure ethanethiol acetate, b.p. 109-111°C. ^1H-Nmr: 2.85 (q,2H), 2.35 (s,3H), 1.28 (t,3H). IR: 1690cm^{-1} Aldehydes 4b, 4d, 4g, 4h, and 4i. These were prepared by acid hydrolysis[24] of the enol ethers derived from the corresponding methyl ketones by the procedure of Earnshaw, et al.,[25] and were purified by flash chromatography, and used without further purification.

2-(2-methylphenyl)propanal (4b). 53% yield. ^1H-Nmr: 9.55 (d,1H), 7.10 (m,4H), 3.80 (d (J=1.5) of q(J=7, 1H), 2.40 (s, 3H), 1.40 (d, J=7, 3H). IR: 2700, 1715 cm^{-1}.

2-Cyclohexylpropanal (4d). 44% yield. ^1H-Nmr: 9.60 (d,1H), 2.15 (br q, 1H), 1.01-1.08 (br m, 11H), 1.05 (d, J=7, 3H). IR: 2690, 1725 cm^{-1}. This aldehyde has been reported in the literature,[26] but no spectroscopic data was given.

2-(4-Trifluoromethylphenyl)-propanal (4g). 39% yield. ^1H-Nmr: 9.68 (d,1H), 7.60 (d,2H), 7.28 (d,2H), 3.72 (d of q,1H), 1.52 (d,3H). IR: 2710, 1725, 1620 cm^{-1}.

2-(2-Methoxyphenyl)-propanal (4h). 18% yield. ^1H-Nmr: 9.65 (s,1H), 7.0 (m,4H), 3.90 (q,1H), 3.85 (s,3H), 1.45 (d,3H). IR: 2700, 1718 cm^{-1}.

2-(4-Methoxyphenyl)-propanal (4i). 64% yield. ^1H-Nmr: 9.55 (d,1H), 7.08 (d,2H), 6.83 (d,2H), 3.80 (q,1H), 3.60 (s,3H), 1.38 (d,3H). IR: 2710, 1720, 1610 cm^{-1}.

2,3,3-Trimethylbutanal (4c). Methyl 3,3-dimethylbutanoate (2.01 g, 15.4 mmol) in 10 ml THF was added dropwise to a cooled (-78°C) solution of 23 ml of LDA in THF, and the solution was stirred for 1 h. Iodomethane (1.91 ml, 30.7 mmol), in 13.4 ml (77 mmol) HMPA was then added dropwise and the mixture was stirred at -78°C for 3.5 h. The mixture was then quenched with water (20 ml) and extracted with ether (3 x 50 ml). The combined extracts, after aqueous acid and brine washes and then drying ($MgSO_4$) gave 1.75 g (79%) of the pure α-methyl ester (^1H-Nmr: 3.62, 2.30 (q), 1.15 (d), 1.00. IR: 1740 cm^{-1}). This material was added, in 10 ml THF, to a stirring mixure of 0.30 g (7.9 mmol) of lithium aluminum hydride in 35 ml THF. After stirring at room temperature overnight, the mixture, upon workup, yielded 1.107 g (78%) of pure 2,3,3-trimethylbutanol (^1H-Nmr: 3.80 (d of d), 3.30 (d of d), 2.45 (D_2O-exchangeable), 1.30 (m), 0.94 (d), 0.85 (s). IR: 3340, 1470, 1370 cm^{-1}. Oxidation of this alcohol by the Swern procedure[27] followed by bulb-to-bulb distillation yielded 0.69 g (64%) of the aldehyde 4c. ^1H-Nmr: 9.75 (d), 2.15 (br m), 1.05 (d), 1.02 (s). IR: 2720, 1730 cm^{-1}. This aldehyde has been reported in the literature[28c,29], although no spectroscopic data were given.

2,3-Dimethylbutanal (4e). This aldehyde was prepared via the α-methylation of N-cyclohexyl-3-methylbutanimine according to the procedure of Stork and Dowd[30] followed by acidic hydrolysis to yield, upon workup and distillation, a 19% yield of the volatile aldehyde 4e. ^1H-Nmr: 9.60 (d), 2.1 (br m), 1.05 (d), 1.03 (d), 0.95 (d). IR: 2650, 1730 cm^{-1}. This aldehyde has been reported,[28] but no spectroscopic data was given.

2-Methyl-3-phenylpropanal (4f). Lithium aluminum hydride (0.42 g, 11 mmol) was stirred in 25 ml THF at 0°C while 1.032 g (7 mmol) of α-methyl cinnamaldehyde in 15 ml THF was added dropwise. About 0.5 g (3.8 mmol) of anhydrous aluminum chloride were then cautiously added, and the mixture was heated to reflux overnight. Upon cooling, workup,

and flash chromatography (80:20 hexane:ethyl acetate), 1.04 g (98%) of 2-methyl-3-phenylpropanol was obtained. Oxidation by the Swern procedure[27] yielded 0.46 g (94%) of the unstable aldehyde 4f. ^{1}H-Nmr: 9.70 (d), 7.20 (s), 2.9 (br m), 1.15 (d). IR: 2700, 1725 cm^{-1}.

2-(3-Formylbutyl)-2,5,5-trimethyl-1,3-dioxane (4j). 5-Ketohexanoic acid (1.226 g, 9.7 mmol), trimethyl orthoformate (1.12 g, 10.6 mmol) and 2,2-dimethyl-1,3-propanediol (1.10 g, 10.6 mmol) were stirred together in 15 ml dichloromethane with 1-2 mg of p-toluenesulfonic acid for 3.5 h. The solution was partitioned between water and dichloromethane, and the organic phases were washed (brine), dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting crude oil was then dissolved in ether and treated with an excess of ethereal diazomethane. Concentration of this reaction mixture, followed by flash chromatography (95:5 hexane:ethyl acetate) yielded 1.27 g (57%) of 2-(3-carbomethoxypropyl)-2,5,5-trimethyl-1,3-dioxane (^{1}H-Nmr: 3.65 (s), 3.55 (s), 3.50 s), 2.40 (m), 1.80 (m), 1.40 (s), 1.05 (s), 0.95 (s). IR: 1745, 1440, 1375 cm^{-1}). Treatment of 1.25 g (5.4 mmol) of this material with LDA followed by iodomethane in HMPA in the same manner used above for the preparation of 4c yielded, after nonacidic workup and flash chromatography (95:5 hexane:ethyl acetate), 1.00 g (76%) of the α-methyl ester ^{1}H-nmr: 3.65 (s), 3.55 (s), 3.50 (s), 2.40 (br m), 1.70 (br m), 1.35 (s), 1.17 (d), 1.05 (s), 0.95 (s). IR: 1745, 1465, 1380 cm^{-1}. Reduction of this material with lithium aluminum hydride (0.132 g, 3.35 mmol), ether (room temperature overnight) yielded, upon workup, 0.80 g (90%) of pure 2-(4-hydroxy-3-methylbutyl)-2,5,5-trimethyl-1,3-dioxane; ^{1}H-Nmr: 3.45 (s), 3.40 (s), 1.6 (br m), 1.35 (s), 1.05 (s), 0.92 (d), 0.87 (s). IR: 3415, 1480, 1470, 1400 cm^{-1}. Oxidation of 0.40 g (1.85 mmol) of this alcohol using the Swern procedure[27] yielded, upon workup and flash chromatography (90:10 hexane:ethyl acetate), 0.329 g (99%) of the pure aldehyde 4j. ^{1}H-Nmr: 9.58 (d), 3.42 (s), 3.48 (s), 2.30 (br m), 1.70 (br m), 1.40 (s), 1.10 (d), 1.05 (s), 0.88 (s). IR: 2710, 1730, 1480, 1460, 1400, 1380 cm^{-1}. This material was used without purification.

General Procedure for all Dithioenolate Addition Reactions. Ethyl dithioacetate (or ethyl dithiopropionate) (1.2-1.5 equivalents)[31] was stirred at -78°C in 4:1 (v/v) THF:ether (4 ml/mmol dithioester), and an equimolar amount of n-butyllithium (in hexane) was added via syringe. Within 15 minutes of this addition, the colorless enolate solution was cooled to the desired temperature and a solution of 1.0 equiv of the aldehyde (or enone), in 4:1 THF:ether (1 ml/mmol of aldehyde), cooled to the same temperature as the enolate,[32] was added via canula. The reaction mixture was then stirred for 30 minutes. For those reactions initiated below -120°C the reaction vessel was placed in a -120°C bath and thus allowed to warm to -120°C over 30 minutes. (CAUTION: When the enolate solution is initially cooled to -195°C under argon, significant condensation of argon occurs in the reaction vessel. Subsequent warming to -120°C will cause a rapid evaporation of this condensed gas. Precautions (i.e. adequate venting of the flask) should be taken to allow for the release of the pressure caused by this evaporation from the reaction vessel in order to prevent excess pressure build-up in the inert gas line.) The reaction mixture was then quenched with dilute $NaHCO_3$ solution, allowed to warm to 0°C, and extracted with ether. The ether extract was then washed (brine), dried (K_2CO_3), filtered, and concentrated in vacuo to yield the crude dithioester aldol products. In all cases, thin layer chromatography and HPLC analysis of the crude reaction mixtures indicated that the aldol reaction succeeded to the extent of 80-90%, with the remaining 10-20% as unreacted aldehyde. However, silica gel chromatography resulted in 50-60% yields of the purified aldol products. Analysis of the crude reaction mixtures (see Table 1) gave the ratios of diastereomers. In all cases the dithioester products were bright yellow oils or waxy solids.

General Procedure for Other Enolate Additions. The enolates of the acetate equivalents 11b-11h were generated by the addition of the precursor in 4:1 THF:ether to a -78°C solution of an equimolar amount of LDA. The resulting enolate solutions were stirred at -78°C for 30 minutes and their reactions with 2-phenylpropanal, and subsequent workups, were carried out in a manner identical to that described above for the dithioester enolate addition reactions. Yields of the aldol products in each case were 50-60% after chromatography.

General Procedure for the Conversion of Dithioesters to Esters.[8] A solution of the dithioester in absolute alcohol (methanol or ethanol) was stirred with 3 equivalents each of cupric oxide and cupric chloride monohydrate at room temperature for 3-12 h. The mixture was then diluted with 3 volumes of ether, filtered, washed (brine), dried ($MgSO_4$), again filtered, and concentrated to give the crude esters (85-90% yields after flash chromatography).

Syn- and Anti-Ethyl 3-hydroxy-4-phenyldithiopentanoate (5a,6a). Medium pressure liquid chromatography of the diastereomeric mixture (95:5 hexane:ethyl acetate, 10 ml/min) yielded the separate diastereomers. See Table 3 for ^{1}H and ^{13}C Nmr data. IR (identical for both diastereomers): 3430, 1590, 1488, 1150 cm^{-1}. Mass spectrum

(identical for both diastereomers): m/e 254 (2.3%, M^+), 236 (14%), 192 (5%), 134 (32%), 120 (12%). Anal. Calcd. for $C_{13}H_{18}OS_2$: C, 61.37; H, 7.13. Found: C 61.31; H. 7.24.

Syn- and Anti-Ethyl 3-hydroxy-4-(2-methylphenyl)dithiopentanoate (5b, 6b). Flash chromatography (98:2 hexane: ethyl acetate) yielded the separate diastereomers. See Table 3 for ^1H and ^{13}C-Nmr data. IR (identical for both diastereomers): 3440, 1490, 1455, 1150 cm^{-1}. Anal. Calcd. for $C_{14}H_{20}OS_2$: C, 62.64; H, 7.51. Found: C, 62.52; H.7.80.

Syn-Ethyl 3-hydroxy-4,5,5-trimethyldithiohexoate (5c). Flash chromatography (98:2 hexane: ethyl acetate) yielded the pure aldol product. See Table 3 for ^1H and ^{13}C-Nmr data. IR: 3460, 1160 cm^{-1}. Anal. Calcd. for $C_{11}H_{22}OS_2$: C, 56.36; H, 9.46. Found: C, 56.30; H, 9.63.

Syn- and Anti-Ethyl 4-cyclohexyl-3-hydroxydithiopentanoate (5d, 6d). Medium pressure liquid chromatography (98:2 hexane: ethyl acetate, 13 ml/min) yielded the separate diastereomers. See Table 3 for ^1H and ^{13}C-Nmr data. IR (identical for both diastereomers): 3440, 1450, 1160 cm^{-1}. Anal. Calcd. for $C_{13}H_{24}OS_2$: C, 59.95; H, 9.29. Found: C, 60.30; H, 9.60.

Syn- and Anti-Ethyl 4,5-dimethyl-3-hydroxydithiohexanoate (5e, 6e). The two diastereomers could not be separated from each other, so the mixture was purified by flash chromatography (99:1 hexane: ethyl acetate). See Table 3 for ^1H and ^{13}C Nmr data. This aldol product mixture could not be sufficiently purified for satisfactory elemental analysis.

Syn- and Anti-Ethyl 3-Hydroxy-4-methyl-5-phenyldithiopentanoate (5f, 6f). The diastereomeric mixture could not be separated into the component diastereomers. ^1H and ^{13}C Nmr data[33] for the mixture are given in Table 3. IR: 3440, 1600, 1500, 1455, 1155 cm^{-1}. Anal. Calcd. for $C_{14}H_{20}OS_2$: C, 62.64; H, 7.51. Found: C, 63.00; H, 7.82.

Syn- and Anti-Ethyl 3-hydroxy-4-(4-trifluoromethylphenyl)dithiopentanoate (5g, 6g). Medium pressure liquid chromatography (95:5 hexane: ethylacetate at 13 ml/min), followed by preparative HPLC (μ-Porasil column, 95:5 hexane: ethyl acetate at 1.5 ml/min) allowed the separate diastereomers to be obtained. ^1H and ^{13}C-Nmr data are given in Table 3. IR (identical for both diastereomers): 3425, 1620, 1450, 1420, 1325, 1160, 1120 cm^{-1}. Anal. Calcd. for $C_{14}H_{17}F_3OS_2$: C, 52.17; H, 5.32. Found: C, 53.11; H, 5.67.

Syn- and Anti-Ethyl 3-hydroxy-4-(2-methoxyphenyl)dithiopentanoate (5h, 6h). The diastereomeric mixture could not be separated into its components, so the mixture was purified by flash chromatography (95:5 hexane: ethyl acetate). ^1H and ^{13}C-Nmr data[33] for the mixture are given in Table 3. IR: 3445, 1600, 1585, 1495, 1240 cm^{-1}. Anal. Calcd. for $C_{14}H_{20}O_2S_2$: C, 59.12; H, 7.09. Found: C, 59.15; H, 7.38.

Syn- and Anti-Ethyl 3-hydroxy-4-(4-methoxyphenyl)dithiopentanoate (5i, 6i). The diastereomeric mixture, which could not be separated into its components, was purified by flash chromatography (95:5 hexane: ethyl acetate). ^1H and ^{13}C Nmr data[33] for the mixture are given in Table 3. IR: 3440, 1610, 1515, 1245 cm^{-1}. Anal. Calcd. for $C_{14}H_{20}O_2S$: C, 59.12; H, 7.09. Found: C, 59.50; H, 7.39.

Syn- and Anti-Ethyl 3-hydroxy-4-methyl-6-[2-(2,5,5-trimethyl-1,3-dioxanyl)]dithioocta-noate (5j, 6j). The diastereomeric mixture, which could not be separated into its components, was purified by flash chromatography (95:5 hexane: ethyl acetate). ^1H and ^{13}C Nmr data[33] for the mixture are given in Table 3. IR: 3440, 1450, 1380, 1090 cm^{-1}. This aldol product tended to decompose to the derivatives 7 and 8 upon standing, precluding satisfactory combustion analysis.

Syn- and Anti-Methyl 3-hydroxy-4-(2-methoxyphenyl)pentanoate. The methyl esters were prepared from the dithioesters 5h and 6h using the general procedure, in methanol. Flash chromatography (85:15 hexane: ethyl acetate) yielded an inseparable mixture of the diastereomeric methyl esters. ^1H-Nmr: 7.136 (br d), 6.864 (br t), 4.133 (m), 3.760 (s), 3.598 (s), 3.305 (m), 3.270 (exchanges D_2O), 2.329 (d), 1.318 (d). ^{13}C-Nmr: syn[33]: 173.103, 156.404, 131.765, 127.737, 127.095, 120.439, 110.338, 71.862, 55.047, 51.251, 39.282, 37.939, 15.186; anti[33]: 172.869, 156.755, 130.306, 128.204, 127.095, 120.439, 110.338, 71.044, 55.047, 51.251, 38.815, 37.180, 15.986.

Syn- and Anti-Methyl 3-hydroxy-4-(4-methoxyphenyl)pentanoate. The methyl esters were prepared from the dithioesters 5i and 6i using the general procedure, in methanol. Flash chromatography (85:15 hexane: ethyl acetate) yielded the inseparable mixture of the diastereomeric methyl esters. ^1H-Nmr: 7.100 (d), 6.828 (d), 4.062 (m), 3.770 (s), 3.662 (s, anti), 3.638 (s, syn), 3.182 (br s, exchanges D_2O), 2.719 (pentet), 2.60 (br m), 2.308 (d), 2.295 (d), 1.336 (d, syn), 1.287 (d, anti). ^{13}C-Nmr: syn[33]: 173.03, 157.981, 135.502, 128.321, 113.724, 72.679, 55.047, 51.485, 44.712, 39.282,

17.446; anti[33]: 172.869, 157.981, 135.502, 128.846, 113.607, 72.154, 55.047, 51.485, 44.245, 38.874, 17.213.

Endo and Exo-2,5-Dimethyl-8-thioethoxy-1-oxa-9-thia[3.3.1]bicyclonona-7-ene (7, 8). The diastereomeric mixture of ketal dithioesters 5j and 6j were stirred in acetone with a catalytic amount of p-toluenesulfonic acid (monohydrate) at room temperature for 20 minutes. Saturated aqueous $NaHCO_3$ was then added, and the mixture was extracted with ether. The extract was washed (brine), dried ($MgSO_4$), filtered, and concentrated to yield the pure bicyclic derivative (80-90% yields). Preparative HPLC (μ-Porosil, 99:1 hexane: ethyl acetate at 2.0 ml/min) yielded the two pure diastereomers as colorless oils. ^{1}H-Nmr: syn-derived endo product 7: 6.038 (d), 4.441 (d of d), 2.834 (q), 2.783 (q), 1.93 (br m), 1.6 (br m), 1.629 (s), 1.303 (t), 0.866 (d); anti-derived exo product (10): 6.024 (d), 4.313 (d), 2.842 (q), 2.784 (q), 2.09 (br m), 1.80 (br m), 1.631 (s), 1.298 (t), 1.172 (d). ^{13}C-Nmr: endo (9): 130.831, 121.489, 82.546, 76.007, 42.727, 34.962, 30.700, 27.897, 25.328, 17.621, 15.052; exo (8): 129.547, 124.759, 83.188, 76.474, 36.889, 30.992, 30.875, 27.897, 22.642, 17.329, 15.111. IR (identical for both diastereomers): 1595, 1450, 1375, 1360 cm^{-1}. Mass spectrum (identical for both diaste reomers): m/e 230 (3% M^+), 200 (5%), 183 (5%), 109 (7%), 158 (8%), 143 (11%), 129 (11%), 111 (78%). Anal. Calcd. for $C_{11}H_{18}OS_2$: C, 57.74; H, 7.88. Found: C, 57.66; H, 8.00.

Syn- and Anti-O-Ethyl 3-hydroxy-4-phenylthiopentanoate (11b, 12b). Medium pressure liquid chromatography (90:10 hexane: ethyl acetate, 10 ml/min) yielded the separate diastereomers (the less polar anti isomer required further purification by preparative thin layer chromatography (silica gel, 80:20 hexane: ethyl acetate)). See Table 4 for ^{1}H and ^{13}C-Nmr data. IR (identical for both diastereomers): 3440, 1590, 1490 cm^{-1}. Mass spectrum .pa (identical for both diastereomers): m/e 220 (15%, $M^+ - H_2O$), 134 (24%), 105 (94%). Anal. Calcd. for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61. Found: C, 65.56; H, 7.92.

Syn- and Anti-Ethyl 3-hydroxy-4-phenylthiopentanoate (11c, 12c). Flash chromatography (95:5 hexane: ethyl acetate) yielded the separated diastereomers. See Table 4 for ^{1}H and ^{13}C-Nmr data. IR (identical for both diastereomers): 3445, 1680 cm^{-1}. Anal. Calcd. for $C_{13}H_{18}O_2S$: C, 65.51; H. 7.61. Found: C, 66.17; H, 8.20.

Syn- and Anti-Ethyl 3-hydroxy-4-phenylpentanoate (11d, 12d). Flash chromatography (95:5 hexane: ethyl acetate) yielded the purified syn diastereomer, but could not fully separate the minor anti component. However, treatment of the anti dithioester 6a with $CuO/CuCl_2$/ethanol, using the general procedure described above, yielded an ethyl ester identical chromatographically and spectroscopically to the partially-purified aldol 12d. See Table 4 for ^{1}H and ^{13}C-Nmr data. IR (identical for both diastereomers): 3440, 1730 cm^{-1}. Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16. Found: C, 69.98; H, 8.52.

Syn- and Anti-N,N-Dimethyl-3-hydroxy-4-phenylpentanamide (11e, 12e). Separation of the two diastereomers could not be achieved chromatographically, so the flash chromatographed (70:30 hexane: ethyl acetate) mixture was characterized. See Table 4 for ^{1}H and ^{13}C-Nmr data.[33] IR: 3410, 1630, 1495, 1455, 1400 cm^{-1}. Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65. Found: C, 69.11; H, 9.03.

Syn- and Anti-1,4-Diphenyl-3-hydroxypentane-1-one (11f, 12f). The two diastereomers could not be separated chromatographically, therefore the flash chromatographed (95:5 hexane: ethyl acetate) mixture was characterized. See Table 4 for ^{1}H and ^{13}C-Nmr data[33]. IR: 3380, 1670 cm^{-1}. Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.29; H, 7.13. Found: C, 80.20; H, 7.12.

Syn- and Anti-4,4-Dimethyl-2-(3-hydroxy-3-phenylbutyl)-2-oxazoline (11g, 12g). The product mixture, which tended to decompose to an insoluble white solid upon sitting, could not be separated into its component diastereomers. Therefore the flash chromatographed (50:50 hexane: ethyl acetate) mixture was characterized. See Table 4 for ^{1}H and ^{13}C-Nmr data.[33] IR: 3400, 1670, 1500, 1460, 1370 cm^{-1}. Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56. Found: C, 71.72; H, 9.06.

Syn- and Anti-3-Hydroxy-4-phenylpentanonitrile (11h, 12h). The two diastereomers could not be separated chromatographically, therefore the flash chromatographed (90:10 hexane: ethyl acetate) mixture was characterized. See Table 4 for ^{1}H and ^{13}C-Nmr data[33]. IR: 3440, 2240, 1495, 1455 cm^{-1}. Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48. Found: C, 74.98; H, 8.05.

Syn- and Anti-Ethyl 3-hydroxy-2-methyl-3-phenyldithiopropanoate (14, 15). Flash chromatography (95:5 hexane: ethyl acetate) yielded the separated diastereomers (HPLC retention times (95:5 hexane: ethyl acetate, 2.0 ml/min): syn (14): 3.6 min., anti (15): 4.5 min. ^{1}H-Nmr: syn (14): 7.217 (s), 4.906 (d), 3.699 (s, exchanges D_2O), 3.503 (d of q), 3.032 (t), 1.272 (d), 1.117 (t); anti (15): 7.308 (s), 4.959 (d of d), 3.566 (A_3BX pattern), 3.210 (t), 2.868 (d, exchanges D_2O), 1.273 (t), 1.095 (d). ^{13}C-Nmr:

syn (14): 141.282, 127.562, 126.919, 126.014, 76.562, 61.089, 29.590, 16.366, 11.724; anti (15): 209.185, 141.633, 128.029, 127.620, 126.569, 78.284, 61.411, 30.057, 20.365, 11.899. IR (identical for both diastereomers): 3440, 1450, 1400, 1190 cm^{-1}. Anal. Calcd. for $C_{12}H_{16}OS_2$: C, 59.96; H, 6.71. Found: C, 59.81; H, 6.98.

2,3-Syn-3,4-Syn and 2,3-Anti-3,4-Syn-Ethyl 3-hydroxy-2-methyl-4-phenyldithiopentanoate (16, 17). Medium pressure liquid chromatography (95:5 hexane: ethyl acetate, 10 ml/min) yielded the two separated diastereomers (HPLC retention times (95:5 hexane: ethyl acetate, 1.0 ml/min): 2,3-syn-3,4-syn (16): 6.9 min,; 2,3-anti-3,4-syn (11): 8.1 min. See Table 5 for ^1H and ^{13}C-Nmr data. Mass spectrum (identical for both diastereomers): m/e 268 (1%, M^+), 250 (1%), 221 (2%), 134 (35%), 105 (93%). Anal. Calcd. for $C_{14}H_{20}OS_2$: C, 62.66; H, 7.51. Found: C, 62.95; H, 7.85.

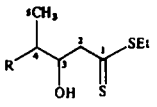
2,3-Syn-3,4-Syn and 2,3-Anti-3,4-Syn Methyl 3-hydroxy-2-methyl-4-phenylpentanoate (18, 19). Treatment of each diastereomer 16 and 17 with CuO/$CuCl_2$/methanol, using the general procedure, yielded the corresponding methyl esters 18 and 19 (HPLC retention times (80:20 hexane: ethyl acetate, 2.0 ml/min): 2,3-syn-3,4-syn (18): 4.4 min, 2,3-anti-3,4-syn (19): 3.9 min). The configuration of 18 was verified by its identical HPLC retention time to the major product produced by the Reformatsky reaction of methyl 2-bromopropionate and 2-phenylpropanal and the diastereomer 19 was likewise identified with the next most major product from the Reformatsky reaction.[14]

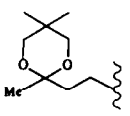
2,3-Syn-3,4-Syn and 2,3-Anti-3,4-Syn-Ethyl 4-cyclohexyl-3-hydroxy-2-methyldithiopentanoate (20, 21). Flash chromatography (95:5 hexane: ethyl acetate) yielded the two separated diastereomers (HPLC retention times (95:5 hexane: ethyl acetate, 1.5 ml/min): 2,3-syn-3,4-syn (20): 5.6 min, 2,3-anti-3,4-syn (21): 4.1 min). See Table 5 for ^1H and ^{13}C-Nmr data. IR (identical for both diastereomers): 3440, 1440, 1180 cm^{-1}. Anal. Calcd. for $C_{14}H_{26}OS_2$: C, 61.26; H, 9.55. Found: C, 61.36; H, 9.57.

5-Phenylhex-3-en-2-one (25). Dimethyl (2-oxopropyl)phosphonate (2.0 g, 12 mmol), in 5 ml dry THF, was added to a 0°C suspension of 0.3 g (12.5 mmol) of sodium hydride in 10 ml dry THF. The mixture was stirred at room temperature for 1 hour then cooled to 0°C, and to it was added 1.51 g (11.2 mmol) of 2-phenylpropanal in 10 ml dry THF. The mixture was then allowed to stir at room temperature for 2.5 hours. Water (20 ml) was then added, and the mixture was extracted with ether (3 x 20 ml). The extracts were then washed (brine), dried ($MgSO_4$), concentrated, and the crude product was flash chromatographed (95:5 hexane: ethyl acetate) to yield 1.32 g (68%) of the enone 25, which was used without further purification. ^1H-Nmr: 7.2 (s), 6.9 (d of d), 6.0 (d of d), 3.6 (pentet), 2.2 (s), 1.4 (d). IR: 1690, 1673, 1620, 1600, 1500 cm^{-1}.

Threo and Erythro Ethyl 2-oxo-3-(1-phenylethyl)dithiohexanoate (26, 27). Flash chromatography (95:5 hexane: ethyl acetate) yielded the purified diastereomers 26 and 27 (66% combined yield) (HPLC retention times (90:10 hexane: ethyl acetate, 1.5 ml/min): major (threo, 26) product: 7.229 (s), 2.937 (br m), 3.175 (q), 2.415 (br m), 2.018 (s), 1.266 (t), 1.236 (d); minor (erythro, 27) product: 7.224 (s), 3.033 (br m), 3.192 (q), 2.378 (br m), 1.952 (s), 1.297 (d), 1.291 (t). ^{13}C-Nmr: major (threo, 26) product: 207.025, 144.202, 128.029, 127.445, 126.044, 53.704, 43.545, 41.735, 40.859, 30.524, 29.999, 16.745, 12.075; minor (erythro, 27) product: 207.550, 144.550, 128.145, 127.737, 126.219, 53.061, 44.479, 42.143, 41.618, 30.816, 30.174, 18.263, 12.075. IR (identical for both diastereomers): 1720, 1600, 1500, 1450, 1160 cm^{-1}. Mass spectrum (identical for both diastereomers): m/e 233 (1%), (M^+-SCH_2CH_3), 174 (2%), 131 (6%), 104 (27%). Anal. Calcd. for $C_{16}H_{22}OS_2$: C, 65.26; H, 7.53. Found: C, 65.17; H, 7.28.

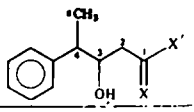
TABLE 3. NMR Spectral Data For 5, 6



R \ Position	Position		$SCH_2\underline{CH_3}$	$S\underline{CH_2}CH_3$	C-2	C-3	C-4	C-CH_3	R
Phenyl	Erythro	^1H	1.241	3.183	3.074, 2.877	4.327	2.820	1.354	7.272
		^{13}C	17.037	56.214	30.408	75.598	45.296	11.841	143.443,128.087, 127.328,126.102
	Threo	^1H	1.263	3.206	2.987, 2.984	4.411	2.945	1.343	7.312
		^{13}C	17.096	55.689	30.291	75.073	44.771	17.666	141.983,127.737, 125.927
o-Tolyl	Erythro	^1H	1.251	3.154	3.068 2.969	4.283	3.00[a]	1.325	2.305,7.112
		^{13}C	16.979	56.156	30.524	75.365	39.983	11.958	142.041,135.152, 130.189,126.044, 125.868,19.840
	Threo	^1H	1.310	3.296	3.143, 3.105	4.314	3.00[a]	1.297	7.136,2.354
		^{13}C	17.388	55.630	30.933	75.715	40.158	12.133	155.820,136.261, 130.364,126.452, 126.219,20.015
t-Butyl	Erythro	^1H	1.325	3.231	3.099, 3.057	4.458	1.22[a]	0.931	0.943
		^{13}C	12.075	58.783	30.700	71.453	47.048	7.988	33.327,28.247
Cyclohexyl	Erythro	^1H	1.325	3.303	3.099	4.231	1.70[a]	0.918	1.70[a],1.20[a],
		^{13}C	12.016	57.207	30.700	72.621	40.041	10.440	43.311,31.342, 29.707,26.729, 26.613
	Threo	^1H	1.335	3.246	3.105,	4.088	1.70[a]	0.868	1.70[a],1.20[a]
		^{13}C	12.133	55.222	30.875	73.088	38.640	11.491	43.545,31.692, 28.481,26.788, 26.613
1-Propyl	(mixture)	^1H	1.332	3.240	3.113	4.164	1.33[a]	0.893	1.738,0958,0.924
	Erythro	^{13}C	12.743	59.218	31.076	74.223	44.738	10.524	29.032 or 21.909, 19.982
	Threo	^{13}C	12.743	57.524	31.484	75.040	45.906	11.341	29.032 or 21.909, 18.523
Benzyl	Erythro	^1H	1.291	3.210	3.106	3.973	1.99	0.894	2.457,2.335,7.200
	(mixture)	^1H	1.278	3.191				0.868	
		^{13}C	15.227	56.039	30.700	74.898	40.450	13.476	140.365,140.348,
	Threo			55.222		73.730	40.275	12.016	128.963,128.846, 127.912,125.518, 30.574,38.348
p-Trifluorophenyl	Erthro	^1H	1.293	3.200	2.955 2.949	4.274	2.924	1.383	7.576,7,355
		^{13}C	16.804	56.039	30.816	75.248	45.296	12.075	128.759,147.938, 128.087,125.226 118.687
	Threo	^1H	1.310	3.222	-a-	4.297	-a-	1.381	7.576,7402
		^{13}C	17.913	55.981	30.875	75.131	45.296	12.133	128.671,125.051
o-Anisyl	(mixture)	^1H	1.232	3.134	3.074	4.336	3.302	1.320	3.750,7.193,7.123, 6.813
	Erthro	^{13}C	15.753	56.506	30.349	74.956	38.115	11.841	156.229,131.765, 126.919,120.332, 110.221,54.988
	Threo	^{13}C	16.337	55.981	30.349	74.606	37.356	11.841	156.521,130.306, 128.321,126.919, 120.332,120.221 54.988
p-Anisyl	(mixture)	^1H	1.259	3.160	3.007 2.938	4.199	2.770	1.334	7.126, 6.825 3.745
	Erythro	^{13}C	17.037	56.214	30.349	75.715	44.362	11.724	157.572,135.444, 128.087,113.432, 54.696
	Threo	^{13}C	17.037	55.864	30.349	75.715	44.012	11.724	157.572,134.042, 128.729,113.432 54.696
	(mixture)	^1H	1.303	3.237	3.148 3.115	4.147	1.67[a]	0.949	3.545,3.397,1.673 1.303,0.977,0.877
	Erythro	^{13}C	14.611	58.284	30.725	75.741	39.308	12.743	99.679,70.836 36.798,31.484, 23.369,21.092, 28.098
	Threo	^{13}C	16.304	57.233	30.375	76.675	40.009	12.743	99.679,70.836, 36.389,31.192, 21.384,28.098, 23.018

a) Signal obscured by other signals; chemicals shift value, if given, is approximate.

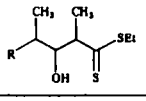
TABLE 4. NMR Spectral Data for 11, 12

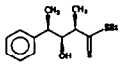
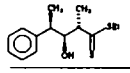
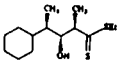
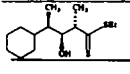


X || C-X' 2 Position			X || C-X' 2	C-2	C-3	C-4	C-CH_3	Phenyl
S || —C—OEt	Erythro	^1H	4.442,1.322	2.700 2.681	4.224[a]	2.857[a]	1.351	7.249
		^{13}C	221.738,68.008, 17,271	51.368	74.139	45.354	13.476	143.618,128.204, 127.503,126.277
	Threo	^1H	4.475,1.345	2,780 2,707	4.368[a]	2.920	1.327	7,283
		^{13}C	221.855,68.359 17,388	51.076	74.022	45.179	13.651	142.567,128,262, 128,145,126.511
O || —C—SEt	Erythro	^1H	2.822,1.185	2.540	4.105	2.746	1.340	7.222
		^{13}C	198.851 48.799,17.096	23.168	72.796	45.471	14.468	143,384,128.204, 127.328,126.277
	Threo	^1H	2.878,1.234	2.683 2.621	4.199	2.76[a]	1.312	7.273
		^{13}C	198.967,48.499, 17.329	23.518	72.737	45.296	14.702	142.275,128.379, 128.087,126.686
O || —C—OEt	Erythro	^1H	4.112,1.222	2.301 2.290	4.11[a]	2.773	1.374	7.249
		^{13}C	172.927,60.652 17.446	39.458	72.621	45.646	14.235	143.559,128.437, 128,087,127,620 126.511
	Threo	^1H	4.100,1.212	2.414 2.354	4.176[a]	2.824	1.300	7.249
		^{13}C	172.402,60.418 17.037	38.990	71.978	45.004	14.060	142.450,128.087, 127.970,127.445, 126.336
O || —C—NMe_2	(mixture of diast.)	^1H	2.889,2702	2.203 2.189	3.940	2.783[a]	1.386	7.197
		^{13}C	172.168,36.889 36.597	34.728	72.562	45.471	18.030	143,968,127.970, 127.095,125.927
	Threo	13C	172.168,36.889 36.597	34.728	71.745	44.420	18.030	142.917,127.737, 127.445,125.460
O || —C—	(mixture of diast.)	^1H	7.805,7.724, 7.394	2.926 2.921	4.283	2.94[a]	1.406 1.361	7.384
	Erythro	^{13}C	200.427,128.321, 127.737,136.495 132.991	43.077	72.329	45.588	17.796	143.910,128.204, 127.445,126.336
		^{13}C	200.077,128.321 127.737,136.611 132.991	42.435	71.745	44.946	17.096	142.742,128.087, 127.445,126.336
Me N Me O	(mixture of diast.)	^1H	3.829,3.807, 1.217	2.150 2.145	3.979	2.770	1.384	7.200
	Erythro	^{13}C	164.637,78.284 66.607,28,189	32.918	72.446	45.705	17.621	143.734,128.087, 127.386,126.102
	Threo	^{13}C	164.627,78.284 66.607,28.189	32.276	71.862	44.829	16.862	142.684,127.854 127.386,126.102
—C≡N	(mixture of diast.)	^1H	-----	2.309 2.264	3.85	2.827	1.364 1.295	7.246
	Erythro	^{13}C	117.928	24.336	71.978	45.471	17.388	142.450,128.554, 127.153,126.744
	Threo	^{13}C	117.811	23.406	71.336	44.771	17.388	141.049,128.321 127.854,126.744

a) signal obsured by other signals; chemical shift value, if given, is approximate.

TABLE 5. NMR Spectral Data for 16, 17, 20, 21



Structure \ Position			$SCH_2\underline{CH_3}$	$S\underline{CH_2}CH_3$	C-2	2-CH_3	C-3	C-4	C-CH_3	R
	16	^1H	1.264	3.150	3.142	1.355	3.969	2.842	1.273	7.249
		^{13}C	17.680	55.806	29.941	15.928	78.459	42.961	11.958	144.143,128.496, 127.328,126.394
	17	^1H	1.340	3.236	3.417	1.311	4.023	2.878	1.306	7.286
		^{13}C	18.964	56.856	30.116	16.512	78.401	42.961	12.133	143.209,128.204, 126.452
	20	^1H	1.318	3.213	3.469	1.351	3.910	1.60[a]	0.918	1.683,1.572, 1.168
		^{13}C	18.088	57.499	31.342	12.133	76.241	40.275	10.498	29.941,29.182, 26.905,26.729
	21	^1H	1.252	3.247	3.427	1.250	4.005	1.70[a]	0.898	1.700,1.134
		^{13}C	20.307	58 199	31.400	12.133	76.416	40.217	10.206	30.233,26.788

a) signal obscured by other signals; chemical shift value, if given, is approximate

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31. Different concentrations of the enolate solution, different amounts of excess enolate used, and different concentrations of aldehyde solution did not significantly affect the yields or stereochemical outcomes of these reactions.

32. For those reactions initiated below -120°C, the aldehyde solution was cooled to -120 C.

33. ^{13}C-Nmr assignments for the major vs. minor diastereomers are based upon relative peak heights in the spectrum of the mixture.

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