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High Stereocontrol in Aldol Reaction with Ketones: Enantioselective Synthesis of β-Hydroxy γ-Ketoesters by Ester Enolate Aldol Reactions with 2-Acyl-2-alkyl-1,3-dithiane 1-Oxides

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The asymmetric aldol reaction of 1,2-diketones, masked as nonracemic 2-acyl dithiane oxides, with lithium enolates derived from several esters and lactones, proceeds with a high degree of stereocontrol at both carbonyl and enolate prochiral centers, the stereocontrol mainly determined by the configuration of the sulfoxide sulfur atom. The sense of induced stereochemistry observed for ester enolates is different from that seen for lactone enolates. Hydrolysis of the dithiane oxide units of the major diastereoisomerically pure aldol products affords enantiomerically pure tertiary α-substituted β-hydroxy-γ-ketoesters.

Introduction

The diastereoselective generation of neighboring quaternary and tertiary asymmetric centers by carbon−carbon bond formation is often a difficult problem in synthesis. A number of methods for the construction of quaternary asymmetric centers in polyfunctional molecules have been developed.[1] One attractive approach for the preparation of nonracemic tertiary alcohols is the asymmetric aldol reaction involving ketones as electrophiles, resulting in diastereofacial selectivity, where one or both partners is enantiomerically pure. Most of the published work on this topic is, however, limited to the use of aldehydes as electrophiles.[2] Stereoselective aldol reactions with acyclic ketones appear to be relatively uncommon, although a few such reports have recently been published.[3]

Several groups have developed the use of the sulfinyl moiety as a stereo- and enantiocontrolling element and chiral auxiliary.[4] In particular, β-ketosulfoxides have been successfully used to direct asymmetric addition to a carbonyl group with a wide range of nucleophiles.[5] In preceding papers, we have described the asymmetric aldol reaction between lithium enolates derived from esters and enantiomerically pure α-sulfinyl cyclohexanones **1**,[6] giving the corresponding β-hydroxyesters in good yields and with high levels of diastereoselection at the hydroxylic center. Application of this methodology to acyclic β-ketosulfoxides proved less satisfactory due to the ready enolization of these substrates resulting from the presence of strongly acidic protons at the α-position, suggesting that substrates lacking these acidic protons might be successful in asymmetric aldol reactions.

The 1,3-dithiane 1-oxide (DiTOX) unit, when acylated at the 2-position, has been used successfully as a chiral auxiliary for acyl group reactions.[7] When disubstituted at C-2 by an alkyl and an acyl group, it may also be regarded as a chiral masked acyclic 1,2-diketone, and

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(1) For a recent review see: Fuji, K. *Chem. Rev.* **1993**, 9*3*, 2307.

(2) Recent reviews of the aldol reaction: (a) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 111. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem*. **1982**, *13*, 1. (c) Heathcock, C. H.; Kim, B. M.; Williams, S. F.; Masamure, S.; Paterson, I.; Genari, C. In *Comprehensive Organic Synthesis*; Trost B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2. (d) Mukaiyama, T. *Org. React.* **1982**, 28, 203. (e) Mukaiyama, T. *Tetrahedron* **1999**, *55*, 8609. (f) Franklin, A. S. *J. Chem. Soc., Perkin Trans. 1* **1998**, *1*, 2451. (g) Franklin, A. S.; Paterson, I. *Contemp. Org. Synth.* **1996**, 317. (h) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041.

(3) Asymmetric aldol reactions. (1) Chiral enolates with achiral ketones: (a) Bartroli, J.; Turmo, E.; Belloc, J.; Forn, J. *J. Org. Chem.* **1995**, *60*, 3000. (b) Jacobson, I. C.; Reddy, G. P. *Tetrahedron Lett.* **1996**, *37*, 8263. (c) Judge, T. M.; Phillips, G.; Morris, J. K.; Lovasz, K. D.; Romines, K. R.; Luke, G. P.; Tulinsky, J.; Tustin, J. M.; Chrusciel, R. A.; Dolak, L. A.; Mizsak, S. A.; Watt, W.; Morris, J.; van der Velde, S. L.; Strohbach, J. W.; Gammill, R. B. *J. Am. Chem. Soc.* **1997**, *119*, 3627. (d) Soloshonok, V. A.; Avilov, D. V.; Kukhar, V. P. *Tetrahedron* **1996**, *52*, 12443. (2) Achiral enolates with chiral ketones: (e) Akiyama, T.; Ishikawa, K.; Ozaki, S. *Synlett* **1994**, 275. (f) Sakito, Y.; Asami, M.; Mukaiyama, T. *Chem. Lett.* **1980**, 455. (g) Guanti, G.; Riva, R. *Tetrahedron Lett.* **1995**, *36*, 3933. (h) Reetz, M. T.; Hüllmann, M. *J. Chem. Soc., Chem. Commun.* **1986**, 1600. (3) Chiral plus chiral: (i) Sato, H.; Nakamura, S.; Watanabe, N.; Hashimoto, S. *Synlett* **1997**, 451. (4) Chiral catalyst: recent reviews: (j) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357. (k) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (l) Sawamura, M.; Ito, Y. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; p 367. Articles: (m) Gröger, H.; Vogl, E. M. Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137. (n) Evans, D. A.; Kozlowsky, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893. (o) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859. (p) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686.

(4) Reviews: (a) Solladié, G. *Synthesis* **1981**, 185. (b) Barbachyn, M. R.; Johnson, C. R. In *Asymmetric Synthesis*; Morrison, J. D., Scott, J. W., Eds.; Academic Press: New York, 1984; Vol. 4, p 227. (c) Posner, G. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, p 225. (d) Solladié, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, p 133. (e) García Ruano, J. L. *Phosphorus, Sulfur, Silicon* **1993**, *74*, 233. (f) Solladié, G.; Carreño, M. C. In *Organosulphur Chemistry. Synthethic Aspects*; Page, P. C. B., Ed.; Academic Press: New York, 1995; Chapter 1, pp 1−47. (g) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 185. (h) García Ruano, J. L.; Cid, B. In *Topics in Current Chemistry, Vol. 204: Organosulfur Chemistry I.* Page, P. C. B., Ed; Springer, Berlin, 1999; pp 1−126.

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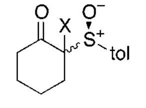

1, X = H, SR, SAr

thus has potential for use as an asymmetric building block. Aldol reactions have not been reported with these substrates. *β*-Ketosulfoxides lacking acidic protons at C-α when available with high ee seemed ideal for our purpose. We report here the results obtained from stereocontrolled aldol reactions of enantiomerically enriched 2-alkyl-2-acetyl-DiTOX[8] with several lithium ester enolates, producing after hydrolysis α-alkyl-substituted acyclic *β*-hydroxy-*γ*-ketoesters with high ee. To our knowledge, access to such systems by diastereofacially selective aldol addition to chiral monoprotected acyclic 1,2-diketones has not previously been reported;[9] however, Evans has recently described a chiral catalytic system allowing the enantioselective addition of thioester enolates to 1,2-unsymmetrical diketones.[3]

Results and Discussion

The *syn*- and *anti*-2-alkyl-2-acetyl-1,3-dithiane 1-oxides **2** (R = Me) and **3** (R = Et) were both first prepared in racemic form according to our previously described procedures,[7,8,10] to determine which of the syn or anti diastereoisomers and which C-2 alkyl substituent results in the highest stereoselectivity in the aldol reaction.

Scheme 1

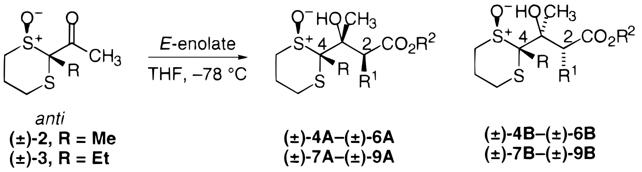

Table 1. Addition of (*E*)-Lithium Ester Enolates to Racemic *anti*-Acyldithiane Oxides 2 and 3

entry	*anti*-DiTOX	ester	aldol	A:B	yield, %
1	(±)-**2**, R = Me	ethyl acetate	**4**	85:15	70
2		ethyl propanoate	**5**	77:23	82
3		*γ*-butyrolactone	**6**	20:80	60
4	(±)-**3**, R = Et	ethyl acetate	**7**	73:27	85
5		ethyl propanoate	**8**	95:5	70
6		*γ*-butyrolactone	**9**	8:92	68

Scheme 2

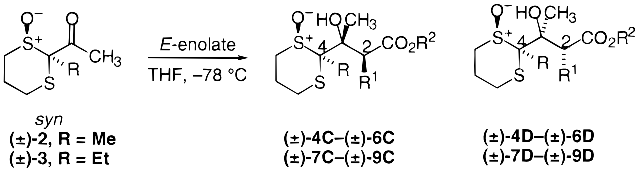

Table 2. Addition of (*E*)-Ester Enolates to Racemic *syn*-Acyldithiane Oxides 2 and 3

entry	*syn*-DiTOX	ester	aldol	C:D	yield, %
1	(±)-**2**, R = Me	ethyl acetate	**4**	57:43	72
2		ethyl propanoate	**5**	72:28	78
3		*γ*-butyrolactone	**6**	26:74	69
4	(±)-**3**, R = Et	ethyl acetate	**7**	52:48	85
5		ethyl propanoate	**8**	72:28	70
6		*γ*-butyrolactone	**9**	18:82	68

We were pleased to find that the addition of three molar equivalents of the lithium enolates[11] of ethyl acetate, ethyl propanoate, and *γ*-butyrolactone to the acetyl dithiane oxides *syn*- and *anti*- (±)-**2** and (±)-**3** in THF solution afforded racemic aldol products **4**−**9** as mixtures of pairs of diastereoisomeric hydroxyesters only, **A** + **B** from *anti*-DiTOX (Scheme 1, Table 1), and **C** + **D** from *syn*-DiTOX (Scheme 2, Table 2). Each pair was subsequently shown to differ in the configuration at *both* of the two new asymmetric centers generated during the reaction, relative to the dithiane 2-position and the sulfoxide unit.

It is particularly fascinating that, while reactions with ester enolates give diastereoisomers **A** and **C** as the major product isomers from *anti*- and *syn*-DiTOX respectively, reactions with lactone enolates give diastereoisomers **B** and **D** as the major products. We have also observed a different stereochemical behavior of cyclic and acyclic enolates in our work on asymmetric ester enolate addition to 2-(4-tolylsulfinyl)cyclohexanone.[6]

The data in Tables 1 and 2 reveal that for prochiral enolates, *anti*-DiTOX isomers (±)-**2** and (±)-**3** afford higher induction than do syn isomers and, among these, the best results are obtained with (±)-*anti*-**3** (R = Et) (Table 1, entries 5 and 6).[12] Lower stereoselectivities were

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(5) Reduction: (a) Carreño. M. C.; García Ruano, J. L.; Martín, A. M.; Pedregal, C.; Rodriguez, J. H.; Rubio, A.; Sánchez, J.; Solladié, G. *J. Org. Chem.* **1990**, *55*, 2120. (b) Barros, D.; Carreño, M. C.; García Ruano, J. L.; Maestro, M. C. *Tetrahedron Lett.* **1992**, *33*, 2733. (c) Sánchez-Obregón, R.; Ortiz, B.; Walls F.; Yuste, F.; García Ruano, J. L. *Tetrahedron: Asymmetry* **1999**, *10*, 10947. Alkylation: (d) Bueno, A. B.; Carreño, M. C.; Fischer, J.; García Ruano, J. L.; Peña, B.; Peñas, L.; Rubio, A. *Tetrahedron Lett.* **1991**, 32, 3191. (e) García Ruano, J. L.; García Paredes, C. *Tetrahedron Lett.* **2000**, *41*, 261 and references therein. (f) Solladié, G.; Hanquet, G.; Izzo, I.; Crumbie, R. *Tetrahedron Lett.* **1999**, *40*, 3071. Hydrocyanation: (g) García Ruano, J. L.; Martín A. M.; Rodríguez, J. H. *J. Org. Chem.* **1992**, 57, 7235. (h) García Ruano, J. L.; García Paredes, C.; Hamdouchi, C. *Tetrahedron*: *Asymmetry* **1999,** *10*, 2935.

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(9) Examples of enolate addition to chiral α-ketoesters yielding α-hydroxyesters (see ref 3e) and to chiral masked α-formyl ketones to afford hydroxy formylesters (see ref 3f) are known.

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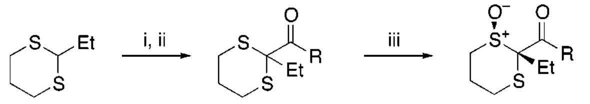
(11) (a) We refer to the stereoisomeric enolates as *Z* or *E*, assigning to the OLi group a higher priority than the OR group. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (c) Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157.

(12) This trend has been observed in other addition reactions: Page, P. C. B.; Allin, S. M.; Collington, E. W.; Carr, R. A. E. *J. Org. Chem.* **1993**, *58*, 6902.

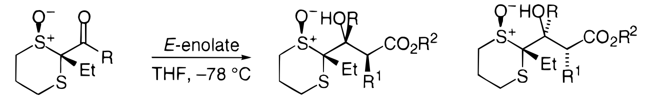
Scheme 3



i. BuLi; RCHO, −78 °C; H_2O
ii. DMSO, TFAA, Et_3N, −78 °C
iii. $Ti(OiPr)_4$, cumene hydroperoxide, H_2O (+)-DET, −30 °C

(+)-3, R = Me, 69%, 92% ee
(+)-10, R = Et, 65%, 94% ee
(+)-11, R = $PhCH_2CH_2$, 81%, ≥98% ee
(+)-12, R = $PhCH_2$, 64%, 94% ee
(+)-13, R = t-$BuCH_2$, 66%, 90% ee

Scheme 4



anti
(+)-3, (+)-10, (+)-11

A

B

Table 3. Addition of (*E*)-Lithium Ester Enolates to *anti*-Acyldithiane Oxides (+)-3, (+)-10, and (+)-11

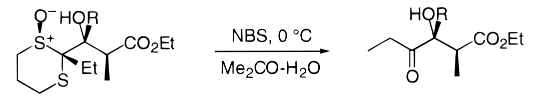
entry	*anti*-DiTOX	ester	aldol	A:B	yield, %
1	**3**, R = Me	ethyl acetate	**7**	73:27	85
2	**3**, R = Me	ethyl propanoate	**8**	95:5	70
3	**3**, R = Me	γ-butyrolactone	**9**	8:92	68
4	**10**, R = Et	ethyl acetate	**14**	82:18	72
5	**10**, R = Et	ethyl propanoate	**15**	81:19	20
6	**11**, R = CH_2CH_2Ph	ethyl acetate	**16**	83:17	71
7	**11**, R = CH_2CH_2Ph	ethyl propanoate	**17**	94:6	86
8	**11**, R = CH_2CH_2Ph	γ-butyrolactone	**18**	10:90	68

obtained with the enolate derived from ethyl acetate, the most selective substrate in this case being (±)-*anti*-**2** (R = Me) (Table 1, entry 1**)**.

With these results in hand, several enantiomerically enriched *anti*-2-acyl-2-ethyl-1,3-dithiane 1-oxides with different acyl groups, including acetyl (+)-**3**, propanoyl (+)-**10**, 2-phenylpropanoyl (+)-**11**, phenylacetyl (+)-**12**, and *tert*-butylacetyl (+)-**13**, were prepared following the established procedures, and using the asymmetric sulfoxidation described by Kagan as the source of chirality, to produce the *R* configuration at the sulfoxide sulfur atoms (Scheme 3).[8]

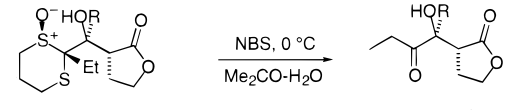
Acyl DiTOX systems (+)-**3** and (+)-**11** successfully underwent aldol reaction (Scheme 4, Table 3), and showed consistent behavior with each enolate. As in the racemic series, the higher selectivities were obtained with propanoate enolate (de > 88%, entries 2 and 7). This is also true for the reaction of compound (+)-**10**, but lower yields were obtained (entries 4 and 5). The major products from these two propanoate reactions, compounds **8A** and **17A**, were obtained in diastereoisomerically pure form by column chromatography on silica gel. Reactions with lactone enolates (entries 3 and 8) showed a high but opposite stereoselectivity, yielding **9B** and **18B** as the major products, easily obtained in diastereoisomerically pure form by crystallization.[13] The two other anti acyl DiTOX systems prepared, (+)-**12** and (+)-**13**, gave poor yields of aldol products or failed to react,[14] despite several modifications to the reaction conditions.[15]

Scheme 5



(+)-8A, R = Me
(+)-17A, R = CH_2CH_2Ph

(−)-19, R = Me, 85%
(−)-20, R = CH_2CH_2Ph, 80%



(+)-9B, R = Me
(+)-18B, R = CH_2CH_2Ph

(+)-21, R = Me, 80%
(+)-22, R = CH_2CH_2Ph, 77%

Finally, hydrolysis of the DITOX moieties was effected by treatment of the diastereoisomerically pure adducts (+)-**8A**, (+)-**17A**, (+)-**9B**, and (+)-**18B** with NBS in a 9:1 acetone−water mixture, as previously described for related systems,[16] affording the corresponding enantiomerically enriched β-hydroxy γ-ketoesters (−)-**19**, (−)-**20**, (+)-**21**, and (+)-**22** (Scheme 5).[17]

To explain the stereochemical course of these reactions, in each case, the dithiane unit is assumed to exist in a chair conformation throughout, with the acyl substituent in an equatorial position and the sulfinyl and carbonyl oxygen atoms of the substrate chelated by the enolate metal (Schemes 6 and 7).[7]

We suggest that, in the ester enolate series, the aldol reactions proceed through a cyclic transition state in which additional interaction of the sulfoxide oxygen atom with the lithium counterion, coupled with steric interaction between the bulk of the dithiane ring and the ester unit, favor the boat conformations (**23bt/24bt**) in the transition states in preference to chair (**23ch/24ch**). *anti*-DiTOX would then give preferentially diastereoisomer **A** (Scheme 6) and *syn*-DiTOX diastereoisomer **C** (Scheme 7), as observed. The higher relative stability of **23bt** with respect to **24bt**, the result of reduced steric interactions, would explain the more stereoselective evolution of *anti*-acyl DiTOX compounds. This stereochemical course is similar to that proposed in our preceding study with 2-(4-tolylsulfinyl)cyclohexanone,[6] involving tricoordinated lithium species as intermediates of the aldol reaction.

Conversely, in a possible explanation of the results obtained in the lactone enolate series, the additional bulk of the lactone ring would raise the energy of both the boat and chair aldol transition state conformations **23**/**24**, favoring the less crowded transition states **25/26**, involving the participation of a second molecule of lithium enolate associated with the carbonyl oxygen atom: one associated with the sulfoxide and aldehyde oxygen atoms, and the second in a Zimmerman−Traxler aldol transition state. *anti*-DiTOX would then preferentially give diastereoisomer **B** (Scheme 8) and *syn*-DiTOX substrates to diastereoisomer **D** (Scheme 9), as observed.

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[13] Major propanoate adducts are also obtained in diastereoisomerically pure form by column chromatography on silica gel.

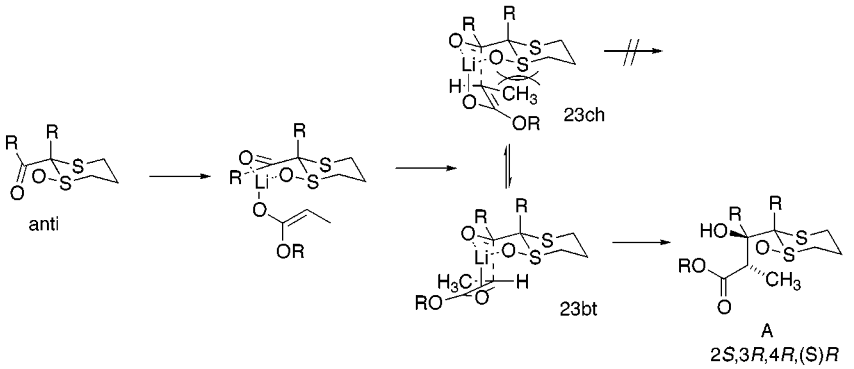
[14] We believe that the compound with R=Bn may be enolized under the reaction conditions, as evidenced by formation of a yellow coloured solution when it is added to the enolate at −78 °C. This is not observed for the compound with R = $CH_2{}^tBu$.

[15] Opening of the DiTOX ring system by enolate attack at the sulfoxide sulfur atom was observed when the reaction temperature was increased. Ring opened products can also be also formed by Grignard reagent attack, see ref 10a.

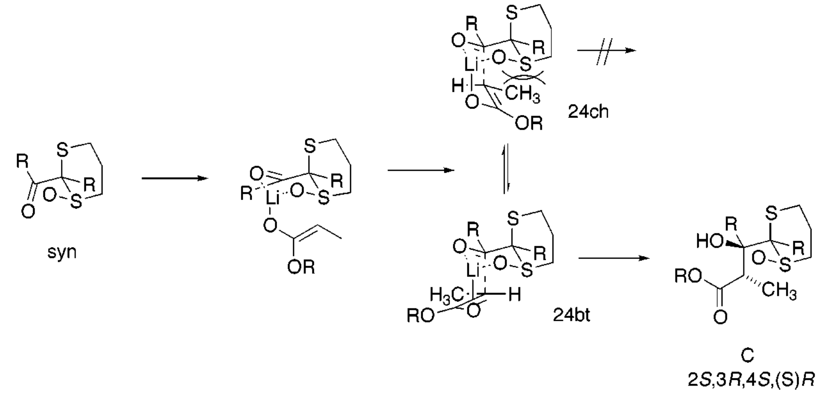
[16] Corey, E. J.; Erickson, *J. Org. Chem.* **1971**, *36*, 3553. Page, P. C. B.; Graham, A. E.; Park, B. K. *Tetrahedron* **1992**, *48*, 7265 and ref 8e above.

[17] The ratio of enantiomers was determined by ^1H NMR spectroscopy in the presence of chiral lanthanide shift reagents; 0.1−0.3 equiv of $Eu(hfc)_3$ was necessary in order to achieve complete separation of signals corresponding to the ester ethoxy group.

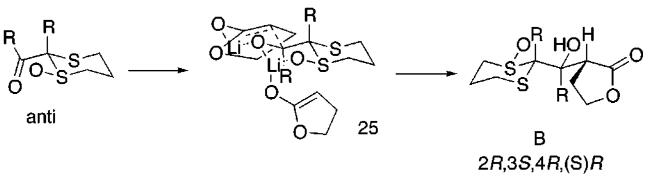
Scheme 6



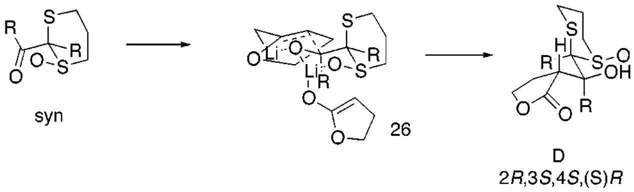
Scheme 7



Scheme 8



Scheme 9



Configurational Assignment

To prove the configurational relationships of diastereoisomers **A** and **B**, we effected hydrolysis of the DiTOX unit in a mixture of **(±)-8A** and **(±)-8B** using NBS/acetone−water (9:1), as previously described for related systems. The corresponding racemic α-hydroxyketone **(±)-19** was obtained in 85% yield as a single diastereoisomer, showing that, as expected for an aldol reaction, **A** and **B** have the same relative configuration between the two new asymmetric centers C-2 and C-3, and that no racemization takes place during the hydrolysis stage (Scheme 10). Importantly, similar hydrolysis of a mixture of **(±)-8C** and **(±)-8D** also gave **(±)-19** as a single diastereoisomer, showing that **C** and **D** *also* have the same relative configuration between the two new asymmetric centers.

Single-crystal X-ray analysis of enantiomerically enriched (+)-**8A**[18] demonstrated that the absolute stereochemistry of this aldol product was (2*S*,3*R*,4*R*,(S)*R*)[19] according to the numbering system depicted in Schemes 1 and 2. We may therefore assign configuration (2*R*,3*S*,4*S*,(S)*R*) to compound **8B**. The same stereochemical assignment is assumed for the **A** and **B** diastereoisomers derived from other acyclic enolates (Scheme 1).[20]

The relative stereochemistry of the major aldol product (±)-**9B** (Scheme 1), derived from γ-butyrolactone enolate and (±)-*anti*-**3**, was unequivocally established as (2*R**,3*S**,4*R**,(S)*R**) by X-ray analysis of the racemic sample. This fact allowed us to confirm that the relative stereoselectivity of the aldol reaction with the lactone enolates was the opposite to that observed from acyclic ester enolates.

Single-crystal X-ray analysis of (±)-**9D**, obtained as the major isomer from the reaction of *syn*-DiTOX derivative (±)-**3** with the lactone enolate, shows that the relative stereochemistry (2*R**,3*S**,4*S**,(S)*R**) is identical to that of (±)-**9B** at the asymmetric carbon atoms C-2 and C-3, generated in the aldol reaction (i.e., **9B** and **9D** differ only in the relative stereochemistry of the DiTOX moiety). By assuming that aldol products obtained from acyclic and cyclic enolates from *syn*-DiTOX derivatives also have

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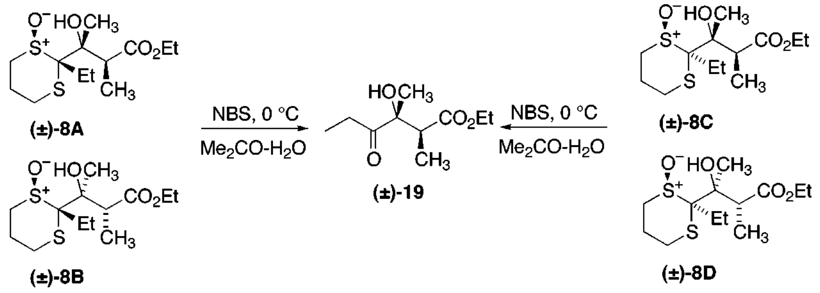
[18] The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

[19] For clarity in the discussion we have adopted the numbering indicated from Schemes 1 and 2 (C-2, C-3 and C-4 for the α-position, hydroxylic and dithiane carbon atoms respectively). Numbering in the Experimental Section is according to the correct compound name.

[20] The ^{1}H NMR signal corresponding to the OH signal in major aldol isomers from reactions with propanoate appears at higher field than that for minor isomers ($\Delta\delta \cong 0.3$ ppm), whereas the shift of H-1′ (hydrogen alpha to the ester) of the minor isomers appears at higher field ($\Delta\delta \cong 0.1-0.4$ ppm). This trend is reversed for the OH signal in the case of lactone adducts, where the OH signal appears at higher field for the major isomer.

Scheme 10



opposite configurations, and taking into account that the hydrolysis of a mixture of (±)-**8C** and (±)-**8D** also gave (±)-**19** as a single diastereoisomer, we may assign the configurations depicted in Scheme 2 for **C** and **D** diastereoisomers of compounds **4**−**9**.

The relative configuration between the two new asymmetric centers generated in the aldol reaction of the major adducts and the sulfoxide is the same in both *syn*- and *anti*-DiTOX systems for reactions of the same enolates, indicating that the diastereofacial selectivity in the reaction is effected principally by the configuration at the sulfoxide sulfur atom (1,3-asymmetric induction), rather than by the asymmetric carbon center of the thiane unit (1,2-asymmetric induction).

Conclusions

In summary, we have described the asymmetric aldol reactions of 1,2-diketones, masked as nonracemic 2-acyl dithiane oxides, with lithium enolates derived from several esters and lactones, which proceed with complete regioselection and high levels of stereoselectivity. The reactions take place with a high degree of stereocontrol at both carbonyl and enolate prochiral centers, and the separation of diastereoisomers is trivial. The sense of induced stereochemistry observed for ester enolates is different from that seen for lactone enolates. The hydrolysis of the dithiane oxide units is successful under very mild conditions and affords functionalized enantiomerically enriched or pure tertiary α-substituted β-hydroxy-γ-ketoesters. The chemistry demonstrates the value of the DiTOX moiety as a stereocontrolling building block inducing high levels of stereoselectivity in aldol reactions with acyclic ketones.

Experimental Section

General Methods. All reagents were commercial and were used without further purification unless stated otherwise. Column chromatography was carried out on flash silica gel (Merck 9385, 230−400 mesh). All reactions were monitored by TLC, which was performed on precoated sheets of silica gel plates 60 (F_{254}). The apparatus for inert atmosphere experiments was dried by flaming in a stream of dry argon. THF was distilled from sodium/benzophenone under argon, and diisopropylamine was distilled from potassium hydroxide. ^{1}H and ^{13}C NMR spectra were recorded at 200 or 300 MHz. Chemical shifts (δ) and coupling constants are given in ppm and Hz, respectively. Diastereoisomeric aldol product ratios were established by integration of well-separated signals of the diastereoisomers in the crude reaction mixtures and are listed in Tables 1−3. Mass spectra and elemental analysis were provided by the Servicio Interdepartamental de Investigacion (SIdI) at UAM (Madrid), and were obtained in the electron impact mode (EI) at 70 eV unless stated otherwise. The synthesis of the 2-acyl-2-alkyl-1,3-dithiane *S*-oxides (**2**, **3** **10**, and **11**) both in racemic form and as enantiomerically enriched compounds was carried out according to the methods previously described by our group.[7]

Aldol Condensation of Lithium Ester Enolates and 2-Acyl-2-alkyl-1,3-dithiane 1-Oxide. General Procedure A. A solution of *n*-BuLi (4.5 mL, 2.5 M in hexane, 10.5 mmol) was slowly added to a cooled solution (−78 °C) of diisopropylamine (1.7 mL, 12.6 mmol) in THF (45 mL) under a nitrogen atmosphere. After 30 min, a THF (30 mL) solution of ethyl acetate or ethyl propanoate (10.5 mmol) was slowly added (γ-butyrolactone enolate was prepared using a 0.3 M THF solution of LHMDS). After the solution was stirred for 30 min at the same temperature, a THF solution (20 mL) of the corresponding 2-acyl-2-alkyl-1,3-dithiane 1-oxide (3 mmol) was added dropwise via syringe and the mixture stirred (5 min). Saturated aqueous NH_4Cl was added and the aqueous layer extracted with CH_2Cl_2 (3 × 50 mL), the organic phases were collected, washed with brine, and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified either by flash chromatography or by crystallization, as indicated below. The ratio of the diastereoisomers was determined directly from the ^{1}H NMR spectrum of the crude reaction mixture.

(±)-Ethyl 3-Hydroxy-3-(2′-methyl-1′-oxo-1′,3′-dithian-2′-yl)butanoates ((±)-4A and (±)-4B). Reaction of (±)-*anti*-**2** (576 mg, 3 mmol) with the lithium enolate of ethyl acetate (10.5 mmol) was carried out following general procedure A. The crude mixture was purified by column chromatography (ethyl acetate−hexane, 4:1) affording a 85:15 mixture of **4A:4B** as a colorless oil (617 mg, 70%): MS (EI) *m/z* 280(0.2) M$^+$, 262 (64), 235 (11), 216 (22), 123 (100), 90 (99); HRMS calcd for $C_{11}H_{20}S_2O_4$ (M$^+$) 280.080303, found 280.081330.

For **(±)-[2′*R**,3*R**,(S)*R**]-4A**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.53 (br s, 1H), 4.17 (q, *J* = 7.1, 2H), 3.17 (d, *J* = 17, 1H), 2.57 (d, *J* = 17, 1H), 3.2−2.0 (m, 6H), 1.68 (s, 3H), 1.51 (s, 3H), 1.20 (t, *J* = 7.1, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 78.6, 66.8, 60.8, 43.4, 41.4, 25.4, 23.8, 18.5, 18.1, 14.1.

For (±)-[2′***R**,3*S**,(S)*R**]-4B**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.23 (br s, 1H), 4.09 (q, *J* = 7.1, 2H), 3.12 (d, *J* = 16.5, 1H), 2.74 (d, *J* = 16.5, 1H), 3.2−2.0 (m, 6H), 1.54 (s, 3H), 1.18 (t, *J* = 7.1, 3H), 1.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 77.6, 61.1, 60.8, 44.4, 41.7, 24.6, 23.6, 18.7, 16.2, 14.1.

(±)-Ethyl 3-Hydroxy-3-(2′-methyl-1′-oxo-1′,3′-dithian-2′-yl)butanoates ((±)-4C and (±)-4D). Reaction of (±)-*syn*-**2** (576 mg, 3 mmol) with the lithium enolate of ethyl acetate (10.5 mmol) was carried out following general procedure A. The crude mixture was purified by column chromatography (ethyl acetate−hexane, 1:4) affording a 57:43 mixture of **4C:4D** as a colorless oil (635 mg, 72%), mp 73−74 °C (CH_2Cl_2−hexane). Anal. Calcd for $C_{11}H_{20}S_2O_4$: C, 47.13; H, 7.20; S, 22.83. Found: C, 47.02; H, 7.20; S, 22.78.

For **(±)-[2′*S**,3*R**,(S)*R**]-4C**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.81 (br s, 1H), 4.17 (q, *J* = 7.3, 2H,), 3.42 (d, *J* = 17, 1H), 2.77 (d, *J* = 17, 1H), 3.0−1.8 (m, 6H), 1.63 (s, 3H), 1.62 (s, 3H), 1.26 (t, *J* = 7.3, 3H,); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 78.6, 66.8, 60.8, 43.4, 41.4, 25.4, 23.8, 18.5, 18.1, 14.1.

For **(±)-[2′*S**,3*S**,(S)*R**]-4D**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.92 (br s, 1H), 4.12 (q, *J* = 7.2, 2H), 3.37 (d, *J* = 14.5, 1H), 2.62 (d, *J* = 14.5, 1H), 3.0−1.8 (m, 6H), 1.62 (s, 3H), 1.54 (s, 3H), 1.24 (t, J = 7.2, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 77.6, 61.1, 60.8, 44.4, 41.7, 24.6, 23.6, 18.7, 16.2, 14.1.

(±)-Ethyl 3-Hydroxy-2-methyl-3-(2′-methyl 1′-oxo-1′,3′-dithian-2′-yl)butanoates ((±)-5A and (±)-5B). Reaction of (±)-*anti*-**2** (576 mg, 3 mmol) with the lithium *E*-enolate of ethyl propanoate (10.5 mmol) was carried out following general procedure A. The crude mixture was purified by column chromatography (ethyl acetate−hexane, 1:2) affording a 77:23 mixture of **5A**:**5B** as a colorless oil (723 mg, 82%). Anal. Calcd for $C_{12}H_{22}S_2O_4$: C, 48.96; H, 7.54; S, 21.74. Found: C, 48.86; H, 7.46; S, 21.34.

For **(±)-[2′R*,2S*,3R*,(S)R*]-5A**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.23 (d, J = 0.9 Hz, 1H), 4.15 (q, J = 7.1, 2H), 3.06 (q, J = 7.2 Hz, 1H), 3.1−2.0 (m, 6H), 1.68 (s, 3H), 1.48 (s, 3H), 1.17 (t, J = 7.1, 3H), 1.14 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 74.8, 70.0, 60.3, 46.7, 44.2, 28.5, 25.0, 20.9, 15.2, 13.7, 9.8.

For **(±)-[2′R*,2R*,3S*,(S)R*]-5B**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.68 (br s, 1H), 3.9 (q, J = 7.1, 2H), 3.42 (q, J = 6.9 Hz, 1H), 3.1−2.0 (m, 6H), 1.63 (s, 3H), 1.38 (s, 3H), 1.16 (t, J = 7.1, 3H), 1.16 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 79.6, 69.0, 60.5, 47.5, 46.4, 25.7, 25.4, 20.2, 14.9, 12.1, 9.8.

(±)-Ethyl 3-Hydroxy-2-methyl-3-(2′-methyl-1′-oxo-1′,3′-dithian-2′-yl)butanoates ((±)-5C and (±)-5D). Reaction of (±)-*syn*-**2** (576 mg, 3 mmol) with the lithium *E*-enolate of ethyl propanoate (10.5 mmol) was carried out following general procedure A. The crude mixture was purified by column chromatography (ethyl ether−hexane, 5:1) affording a 72:28 mixture of **5C:5D** as a colorless oil (688 mg, 78%). Anal. Calcd for $C_{12}H_{22}S_2O_4$: C, 48.96; H, 7.54; S, 21.74. Found: C, 48.66; H, 7.34; S, 21.94.

For **(±)-[2′S*,2S*,3R*,(S)R*]-5C**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (d, J = 0.9 Hz, 1H), 4.18 (q, J = 7.1, 2H), 3.42 (q, J = 7.0, 1H), 3.1−2.3 (m, 6H), 1.60 (s, 3H), 1.51 (d, J = 0.9, 3H), 1.28 (t, J = 7.1, 3H), 1.27 (d, J = 7.0, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 79.9, 68.2, 60.8, 45.1, 42.7, 24.4, 19.7, 18.0, 15.3, 15.0, 14.1.

For **(±)-[2′S*,2R*,3S*,(S)R*]-5D**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.92 (br s, 1H), 4.15 (q, J = 7.0, 2H), 3.19 (q, J = 7.1, 1H), 3.1−2.3 (m, 6H), 1.63 (s, 3H), 1.61 (s, 3H), 1.28 (t, J = 7.0, 3H), 1.24 (t, J = 7.1, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 77.3, 70.3, 60.7, 44.9, 43.7, 25.3, 19.2, 17.5, 15.3, 15.0, 14.1.

(±)-3-[1′-Hydroxy-1-(2″-methyl-1″-oxo-1″,3″-dithian-2″-yl)ethyl]tetrahydrofuran-2-ones ((±)-6A and (±)-6B). Reaction of (±)-*anti*-**2** (576 mg, 3 mmol) with the lithium enolate of γ-butyrolactone (10.5 mmol) was carried out following general procedure A. The crude 20:80 mixture of two diastereoisomers **6A**:**6B** was purified by column chromatography (ethyl acetate−hexane, 6:1) affording pure **(±)-6B** as a colorless solid (500 mg, 60%). The minor isomer **(±)-6A** was analyzed from an enriched diastereoisomer mixture.

For **(±)-[2″R*,1′R*,3S*,(S)R*]-6A**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.27 (br s, 1H), 4.41 (dt, J = 8.0, 0.9, 1H), 4.18 (m, 1H), 3.47 (dd, J = 13.0, 4.2, 1H), 3.36 (m, 1H), 2.8−2.1 (m, 7H), 1.54 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.6, 79.0, 69.0, 66.0, 47.4, 46.5, 27.4, 25.8, 22.0, 20.3, 10.1.

For **(±)-[2″R*,1′S*,3R*,(S)R*]-6B**: mp 169−172 °C (acetone: hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.67 (d, J = 1.2 Hz, 1H), 4.41 (dt, J = 9.0, 1.2, 1H), 4.17 (ddd, J = 11.1, 9.0, 6.3, 1H), 3.62 (dd, J = 12.3, 8.7, 1H), 3.17 (ddd, J = 12.9, 4.4, 1.0, 1H), 2.8−2.1 (m, 7H), 1.67 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.8, 77.6, 70.4, 66.5, 48.0, 46.9, 28.7, 27.7, 25.2, 20.5, 14.7. Anal. Calcd for $C_{11}H_{18}S_2O_4$: C, 47.47; H, 6.52; S, 23.00. Found: C, 46.91; H, 6.41; S, 22.6.

(±)-3-[1′-Hydroxy-1-(2″-methyl-1″-oxo-1″,3″-dithian-2″-yl)ethyl]tetrahydrofuran-2-ones ((±)-6C and (±)-6D). Reaction of (±)-*syn*-**2** (576 mg, 3 mmol) with the lithium enolate of γ-butyrolactone (10.5 mmol) was carried out following general procedure A. The crude 26:74 mixture of two diastereoisomers **6C**:**6D** was purified by column chromatography (ethyl acetate: hexane, 6:1) affording pure **(±)-6D** as a colorless solid (579 mg, 69%). The minor isomer **(±)-6C** was analyzed from an enriched diastereoisomeric mixture.

For **(±)-[2″S*,1′S*,3R*,(S)R*]-6C**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.75 (br s, 1H), 4.35 (dt, J = 8.2, 0.8, 1H), 4.23−4.15 (m, 1H), 3.47 (dd, J = 13.0, 4.2, 1H), 3.41−3.31 (m, 1H), 2.92−2.78 (m, 1H), 2.8−2.0 (m, 5H), 1.63 (s, 3H), 1.43 (s, 3H).

For **(±)-[2″S*,1′R*,3S*,(S)R*]-6D**: mp 175−177 °C (acetone−hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.62 (br s, 1H), 4.37 (dt, J = 8.3, 0.8 1H), 4.17 (ddd, J = 11.2, 8.9, 6.0, 1H), 4.20−4.12 (m, 1H), 3.50−3.40 (m, 1H), 2.96 (ddd, J = 8.3, 6.2, 3.4, 1H), 2.8−2.1 (m, 5H), 1.57 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.5, 82.3, 77.2, 66.5, 46.8, 46.0, 28.2 (2C), 28.0, 21.9, 21.5. Anal. Calcd for $C_{11}H_{18}S_2O_4$: C, 47.47; H, 6.52; S, 23.00. Found: C, 47.45; H, 6.48; S, 22.42.

Ethyl 3-(2′-Ethyl-1′-oxo-1′,3′-dithian-2′-yl)-3-hydroxybutanoates (7A and 7B). Reaction of (+)-*anti*-**3** (618 mg, 3 mmol) with the lithium enolate of ethyl acetate (10.5 mmol) was carried out following general procedure A. The crude 73:27 mixture of two nonracemic diastereoisomers **7A**:**7B** was purified by column chromatography (ethyl acetate−hexane, 1:3) to give a colorless oil (750 mg, 85%). Anal. Calcd for $C_{12}H_{22}S_2O_4$: C, 48.96; H, 7.54; S, 21.74. Found: C, 48.76; H, 7.40; S, 21.65.

For **[2′R,3R,(S)R]-7A**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.59 (br s, 1H), 4.11 (q, J = 7.4, 2H), 3.14 (d, J = 16.5, 1H), 2.70 (d, J = 16.5, 1H), 3.1−1.8 (m, 6H), 2.20−2.00 (m, 2H), 1.52 (s, 3H), 1.21 (t, J = 7.4, 3H), 1.20 (t, J = 7.5, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 77.1, 73.2, 60.9, 47.3, 42.9, 27.8, 25.5, 24.7, 16.4, 14.0, 9.1.

For **[2′R,3S,(S)R]-7B**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.42 (br s, 1H), 4.10 (q, J = 7.4, 2H), 2.90 (d, J = 16.5, 1H), 2.65 (d, J = 16.5, 1H), 3.1−1.8 (m, 6H), 2.40−1.80 (m, 2H), 1.54 (s, 3H), 1.21 (t, J = 7.4, 3H), 1.20 (t, J = 7.5, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 76.5, 72.7, 60.8, 47.2, 41.3, 26.2, 24.8, 24.4, 17.7, 14.0, 9.3.

Racemic **7A** and **7B** were also synthesized from (±)-**3** following the same procedure.

(±)-Ethyl 3-(2′-Ethyl-1′-oxo-1′,3′-dithian-2′-yl)-3-hydroxybutanoates ((±)-7C and (±)-7D). Reaction of (±)-*syn*-**3** (618 mg, 3 mmol) with the lithium enolate of ethyl acetate (10.5 mmol) was carried out following general procedure A. The crude 52:48 mixture of two diastereoisomers **7C**:**7D** was purified by column chromatography (ethyl ether−hexane, 6:1) affording **(±)-7C** as a colorless solid (361 mg, 41%) and **(±)-7D** as a colorless oil (344 mg, 39%).

For **(±)-[2′S*,3R*,(S)R*]-7C**: mp 82−83 °C (CH_2Cl_2−hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.88 (br s, 1H), 4.12 (q, J = 7.3, 2H), 3.45 (d, J = 14.9, 1H), 2.17 (d, J = 14.9, 1H), 3.8−2.0 (m, 6H), 2.80−2.00 (m, 1H), 2.00−1.80 (m, 1H), 1.65 (s, 3H), 1.23 (t, J = 7.3, 3H), 1.15 (t, J = 7.5, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 82.3, 69.6, 60.9, 47.3, 41.0, 26.8, 26.6, 26.5, 25.6, 14.1, 9.2; MS (EI) m/z 294 (0.7) (M^+); HRMS calcd for $C_{12}H_{22}S_2O_4$ 294.09595, found 294.09720. Anal. Calcd for $C_{12}H_{22}S_2O_4$: C, 48.96; H, 7.54; S, 21.74. Found: C, 49.10; H, 7.50; S, 21.30.

For **(±)-[2′S*,3S*,(S)R*]-7D**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.98 (br s, 1H), 4.14 (q, J = 7.1, 2H), 3.94 (d, J = 15.5, 1H), 2.58 (d, J = 15.5, 1H), 3.6−2.2 (m, 6H), 2.30−2.00 (m, 1H), 1.82−1.60 (m, 1H), 1.55 (s, 3H), 1.12 (t, J = 7.1, 3H), 1.04 (t, J = 7.6, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 82.0, 70.3, 60.9, 45.5, 43.0, 29.7, 26.0, 24.7, 21.8, 14.1, 9.6; MS (EI) m/z 294(0.7) (M^+); HRMS calcd for $C_{12}H_{22}S_2O_4$ 294.09595, found 294.09708.

(+)-Ethyl [2′R,2S,3R,(S)R]-3-(2′-ethyl-1′-oxo-1′,3′-dithian-2′-yl)-3-hydroxy-2-methylbutanoate ((+)-8A). Reaction of (+)-*anti*-**3** (618 mg, 3 mmol) with the lithium *E*-enolate of ethyl propanoate (10.5 mmol) was carried out following general procedure A. The crude 95:5 mixture of two diastereoisomers **8A**:**8B** was purified by column chromatography (ethyl acetate−hexane, 6:1) affording (+)-**8A** as a colorless solid that was further purified by crystallization from hexane (647 mg, 70%): mp 87−89 °C (hexane); $[\alpha]^{25}_D$ +103 (c = 1.4, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.97 (br s, 1H), 4.11 (q, J = 7.1, 2H), 3.26 (ddd, J = 11.0, 3.4, 7.7, 1H), 3.13 (q, J = 7.5 Hz, 1H), 3.00−2.80 (m, 1H), 2.5−1.7 (m, 6H), 1.38 (s, 3H), 1.23 (t, J = 7.1, 3H), 1.22 (d, J = 7.5, 3H), 1.18 (t, J = 7.2, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.4, 80.7, 73.0, 60.8, 46.5, 44.6, 26.1, 23.1, 21.9, 20.7, 15.0, 13.8, 9.7; MS (EI) m/z 308(2) (M^+), 290 (64), 167(84), 147 (71), 123 (69), 90 (64), 73 (89); HRMS calcd for $C_{13}H_{24}S_2O_4$ 308.1110, found 308.1116. Anal. Calcd for $C_{13}H_{24}S_2O_4$: C, 50.60; H, 7.85; S, 20.75. Found: C, 50.77; H, 7.49; S, 20.78.

The minor isomer **8B** was not isolated. Racemic **8A** was also synthesized from (±)-**3** following the same procedure.

(±)-Ethyl 3-(2′-Ethyl-1′-oxo-1′,3′-dithian-2′-yl)-3-hydroxy-2-methylbutanoates ((±)-8C and (±)-8D). Reaction of (±)-*syn*-**3** (618 mg, 3 mmol) with the lithium *E*-enolate of ethyl propanoate (10.5 mmol) was carried out following general procedure A. The crude 72:28 mixture of two diastereoisomers **8C**:**8D** was purified by column chromatography (ethyl acetate−hexane, 6:1) to give a colorless solid (647 mg, 70%) but isomer separation was not achieved, mp 128−131 °C (CH_2Cl_2−hexane). Anal. Calcd for $C_{13}H_{24}O_4S_2$: C, 50.60; H, 7.85; S, 20.75. Found: C, 50.67; H, 7.81; S, 20.98.

For **(±)-[2′S*,2S*,3R*,(S)R*]-8C**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.21 (br s, 1H), 4.14 (q, J = 7.1, 2H), 3.48 (q, J = 7.1 Hz, 1H), 3.3−1.8 (m, 8H), 1.50 (s, 3H), 1.27 (d, J = 7.1, 3H), 1.26 (d, J = 7.1 3H), 1.15 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 75.6, 81.5, 72.1, 60.6, 45.3, 43.7, 25.0, 24.5, 22.0, 16.4, 15.2, 13.9, 9.9.

For **(±)-[2′S*,2R*,3S*,(S)R*]-8D**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.02 (br s, 1H), 4.14 (q, J = 7.1, 2H), 3.11 (q, J = 7.1, 1H), 3.6−2.2 (m, 8H), 1.79 (s, 3H), 1.26 (d, J = 7.1, 3H), 1.21 (t, J = 7.1, 3H), 1.14 (t, J = 7.6, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 84.2, 72.0, 60.7, 46.0, 45.4, 27.0, 26.4, 23.8, 22.1, 14.3, 13.9, 9.6.

(+)-[2″*R*,1′*S*,3*R*,(S)*R*]-3-[1′-(2″-Ethyl-1″-oxo-1″,3″-dithian-2″-yl)-1′-(hydroxy)ethyl]tetrahydrofuran-2-one ((+)-9B). Reaction of (+)-*anti*-**3** (618 mg, 3 mmol) with the lithium enolate of γ-butyrolactone (10.5 mmol) was carried out following general procedure A. The crude 8:92 mixture of two diastereoisomers **9A**:**9B** was purified by crystallization from ethyl acetate−hexane affording (+)-**9B** as a colorless solid (595 mg, 68%): mp 129−130 °C (acetone−hexane); $[\alpha]^{25}_{D}$ +79 (c = 1.3, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.73 (br s, 1H), 4.3−4.1 (m, 2H), 3.43 (dd, J = 11.9, 8.9, 1H), 3.14 (dt, J = 5.6, 1.1, 1H), 3.11 (dt, J = 6.3, 1.8, 1H), 2.9−2.0 (m, 8H), 1.53 (s, 3H), 1.31 (t, J = 7.1, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 180.0, 78.9, 74.1, 48.0, 46.1, 28.4, 27.8, 24.8, 22.5, 16.5, 14.0, 9.4. Anal. Calcd for $C_{12}H_{20}O_4S_2$: C, 49.30; H, 6.90; S, 21.89. Found: C, 49.28; H, 6.88; S, 21.76.

The minor isomer **9A** was not isolated. Racemic **9B** was also prepared from (±)-anti-**3** following the same procedure.

(±)-[2″S*,1′S*,3R*,(S)R*]-3-[1′-(2″-Ethyl-1″-oxo-1″,3″-dithian-2″-yl)-1-(hydroxy)ethyl]tetrahydrofuran-2-one ((±)-9D). Reaction of (±)-*syn*-**3** (618 mg, 3 mmol) with the lithium enolate of γ-butyrolactone (10.5 mmol) was carried out following general procedure A. The crude 18:82 mixture of two diastereoisomers **9C**:**9D** was purified by crystallization from ethyl acetate affording **(±)-9D** as a colorless solid (595 mg, 68%): mp 183−184 °C (acetone−hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.58 (s, 1H), 4.36 (t, J = 9.0, 1H), 4.17 (ddd, J = 11.7, 8.9, 6.0, 1H), 4.10−3.90 (m, 1H), 3.90 (dd, J = 12.9, 8.6, 1H), 3.30−3.15 (m, 1H), 3.15−3.00 (m, 1H), 2.80−2.50 (m, 1H), 2.70−2.50 (m, 5H), 1.90−1.30 (m, 1H), 1.57 (s, 3H), 1.15 (t, J = 7.5, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.2, 83.0, 70.3, 66.3, 48.5, 46.8, 28.3, 26.3, 25.4, 23.7, 21.5, 9.6. Anal. Calcd for $C_{12}H_{20}S_2O_4$: C, 49.30; H, 6.90; S, 21.89. Found: C, 48.85; H, 6.87; S, 21.69.

The minor isomer **9C** was not isolated.

Ethyl 3-Hydroxy-3-(2′-ethyl-1′-oxo-1′,3′-dithian-2′-yl)-pentanoates (14A and 14B). Reaction of (+)-*anti*-**10** (618 mg, 3 mmol) with the lithium enolate of ethyl acetate (10.5 mmol) was carried out following general procedure A. The crude 82:18 mixture of two nonracemic diastereoisomers **14A**:**14B** was purified by column chromatography (ethyl ether−hexane−CH_2Cl_2, 3:1:1) to give a colorless low melting point solid (665 mg, 72%).

For **[2′*R*,3*R*,(S)*R*-14A]**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.17 (br s, 1H), 4.18 (q, J = 7.2, 2H), 3.27 (m, 1H), 3.05 (d, J = 15.9, 1H), 2.73 (d, J = 15.9, 1H), 3.0−1.5 (m, 9H), 1.28 (t, J = 7.1, 3H), 1.27 (t, J = 7.2, 3H), 0.97 (t, J = 7.6, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.8, 79.7, 74.3, 61.2, 47.4, 39.4, 31.0, 25.4, 24.8, 19.1, 13.9, 9.5, 8.6.

For **[2′*R*,3*S*,(S)*R*]-14B**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.50 (br s, 1H), 4.14 (q, J = 7.2, 2H), 3.27 (m, 1H), 3.22 (d, J = 16.1, 1H), 2.69 (d, J = 16.1, 1H), 3.0−1.5 (9H, m), 1.27 (t, J = 7.1, 3H), 1.25 (t, J = 7.2, 3H), 0.94 (t, J = 7.4, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.8, 78.0, 75.0, 61.2, 47.1, 38.0, 32.2, 27.8, 24.8, 16.7, 14.0, 9.3, 8.2.

(+)-Ethyl [2′*R*,2*S*,3*R*,(S)*R*]-3-(2′-Ethyl-1′-oxo-1′,3′dithian-2′-yl)-3-hydroxy-2-methyl butanoate ((+)-15A). Reaction of (+)-*anti*-**10** (663 mg, 3 mmol) with the lithium *E*-enolate of ethyl propanoate (10.5 mmol) was carried out following general procedure A. The crude 91:9 mixture of two diastereoisomers **15A**:**15B** was purified by column chromatography (ethyl ether−CH_2Cl_2−hexane, 3:1:1) to give (+)-**15A** as a colorless solid of low mp (193 mg, 20%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.32 (br s, 1H), 4.18 (q, J = 7.2, 2H), 3.26 (q, J = 7.2, 1H), 3.27−3.22 (m, 1H), 3.0−1.5 (m, 11H), 1.27 (t, J = 7.1, 3H), 1.19 (t, J = 7.2, 3H), 1.21 (d, J = 7.2, 3H), 1.14 (d, J = 7.6, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.8, 79.7, 74.3, 61.2, 47.4, 45.4, 31.0, 25.4, 24.8, 19.1, 13.9, 12.8, 9.5, 8.6.

The minor isomer **15B** was not isolated.

Ethyl 3-(2′-Ethyl-1′-oxo-1′,3′-dithian-2′-yl)-5-phenyl-3-hydroxypentanoates (16A and 16B). Reaction of (±)-*anti*-**11** (849 mg, 3 mmol) with the lithium enolate of ethyl acetate (10.5 mmol) was carried out following general procedure A. The crude 83:17 mixture of two diastereoisomers **16A**:**16B** was purified by column chromatography (ethyl ether−hexane−CH_2Cl_2, 2:1:1) to give a colorless solid (818 mg, 71%), but isomer separation was not achieved.

For **[2′*R*,3*R*,(S)*R*]-16A**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.26−7.16 (m, 5H), 5.19 (br s, 1H), 4.21 (J = 7.1, 2H), 3.14 (d, J = 17, 1H), 2.91 (d, J = 17, 1H), 3.5−1.1 (m, 12H), 1.31 (t, J = 7.1, 3H), 1.07 (t, J = 7.1, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 141.8, 128.3 (4C), 125.8, 79.2, 73.8, 61.3, 47.1, 40.3, 40.1, 30.5, 25.5, 25.3, 18.6, 13.9, 9.6.

For **[2′*R*,3*S*,(S)*R*]-16B**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.26−7.16 (m, 5H), 5.49 (br s, 1H), 4.21 (q, J = 7.3, 2H), 3.35 (d, J = 16, 1H), 2.11 (d, J = 16, 1H), 3.5−1.1 (m, 12H), 1.27 (t, J = 7.3, 3H), 1.07 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 141.8, 128.3 (4C), 125.8, 78.4, 73.4, 61.3, 47.3, 40.8, 39.7, 30.8, 28.5, 25.3, 23.0, 15.8, 9.5; HRMS calcd for $C_{19}H_{28}S_2O_4$ 384.12725, found 384.12692.

(+)-Ethyl [2′*R*,2*S*,3*R*,(S)*R*]-3-(2′-Ethyl-1′-oxo-1′,3′-dithian-2′-yl)-5-phenyl-3-hydroxy-2-methylpentanoate ((+)-17A. Reaction of (+)-*anti*-**11** (849 mg, 3 mmol) with the lithium *E*-enolate of ethyl propanoate (10.5 mmol) was carried out following general procedure A. The crude 94:6 mixture of two diastereooisomers **17A**:**17B** was purified by column chromatography (ethyl acetate: acetone−hexane, 4:2:1) affording (+)-**17A** as a colorless solid which was further purified by crystallization from hexane (716 mg, 86%): $[\alpha]^{25}_{D}$ + 3 (c = 1, $CHCl_3$); mp 58−61 °C (hexanes−ethyl ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28−7.22 (m, 5H), 4.87 (br s, 1H), 4.21 (q, J = 7.1, 2H), 3.41 (q, J = 7.1, 1H), 3.29 (ddd, J = 11.1, 7.6, 4.7, 1H), 3.1−1.9 (m, 11H), 1.44 (d, J = 7.1, 3H), 1.32 (t, J = 7.1, 3H), 1.17 (t, J = 7.5, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 142.5, 128.4 (2C), 128.3 (2C), 125.8, 81.9, 74.7, 61.0, 47.2, 45.6, 36.8, 30.1, 26.4, 24.4, 20.2, 15.3, 14.0, 10.3. Anal. Calcd for $C_{20}H_{30}S_2O_4$: C, 60.28; H, 7.59; S, 16.06. Found: C, 59.72; H, 7.34; S, 16.22.

The minor isomer **17B** was not isolated.

(+)-[2″*R*,1±*S*,3*R*,(S)*R*]-3-[1′-(2″-Ethyl-1″-oxo-1″,3″-dithian-2″-yl)-3-phenyl-1-hydroxypropyl]tetrahydrofuran-2-one ((+)-18B). Reaction of (+)-*anti*-**11** (849 mg, 3 mmol) with the lithium enolate of γ-butyrolactone (10.5 mmol) was carried out following general procedure A. The crude 10:90 mixture of two diastereoisomers **18A**:**18B** was purified by crystallization from ethyl acetate affording (+)-**18B** as a colorless solid (780 mg, 68%): mp 168 °C (ethyl acetate); $[\alpha]^{25}_{D}$ +106, (c = 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.5−7.0 (m, 5H), 6.65 (br s, 1H), 4.7−4.1 (m, 2H), 3.17 (dd, J = 10.7, 10.5, 1H), 3.2−2.0 (m, 14H), 1.37 (t, J = 7.1, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.0, 141.2, 128.5 (2C), 128.3 (2C), 125.6, 81.1, 75.5, 66.3, 47.8, 42.2, 38.4, 30.1, 28.6, 27.7, 24.9, 16.5, 9.4. Anal. Calcd for $C_{19}H_{26}S_2O_4$: C, 59.67; H, 6.86; S, 16.73. Found: C, 59.52; H, 6.81; S, 16.39.

The minor isomer **18A** was not isolated.

Thioketal *S*-Oxide Hydrolysis in the Presence of NBS. General Procedure B. To a cooled solution (0 °C) of NBS (27 mmol) in 10 mL of an acetone−water mixture (90:10) was slowly added a 0.3 M solution of the corresponding thioketal S-oxide (3 mmol in acetone) via cannula. During the addition, the reaction mixture developed an orange coloration. After 5 min of stirring, the mixture was poured into a separating funnel containing hexane (60 mL), dichloromethane (60 mL), and a saturated solution of Na_2SO_3 (60 mL). The organic layer was washed with $NaHCO_3$ (60 mL) and brine (60 mL) and dried over $MgSO_4$. The solvent was carefully removed under reduced pressure and the residue purified by flash chromatography using the eluent indicated below.

(−)-Ethyl (2*S*,3*R*)-2,3-Dimethyl-3-hydroxy-4-oxohexanoate ((−)-19). Hydrolysis of (+)-**8A** was carried out following general procedure B. The crude mixture was purified by column chromatography (hexane−CH_2Cl_2, 3:1) to afford (−)-**19** as a colorless oil (515 mg, 85%): $[\alpha]^{25}_{D}$ −22 (*c* = 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 4.08 (q, *J* = 7.1, 2H), 4.06 (br s, 1H), 3.03 (q, *J* = 7.4 Hz, 1H), 2.79 (dq, *J* = 18.3, 7.4 Hz, 1H), 2.63 (dq, *J* = 18.3, 7.1 Hz, 1H), 1.27 (d, *J* = 7.4 Hz, 3H), 1.22 (t, *J* = 7.1, 3H), 1.20 (s, 3H), 1.06 (dd, *J* = 7.4, 7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 215.8, 175.8, 79.7, 70.0, 45.1, 29.4, 22.6, 14.0, 108, 7.3. Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.37; H, 8.98. Found: C, 58.86; H, 8.76.

This hydroxyketone was also prepared as a racemic compound from (±)-**8A** and (±)-**8C**.

(−)-Ethyl (2*S*,3*R*)-3-[2′-(Phenyl)ethyl]-3-hydroxy-2-methyl-4-oxohexanoate ((−)-20). Hydrolysis of (+)-**17A** was carried out following general procedure B. The crude mixture was purified by column chromatography (hexane−CH_2Cl_2, 3:1) to afford (−)-**20** as a colorless oil (700 mg, 80%): $[\alpha]^{25}_{D}$ −52, (*c* = 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ) δ 7.4−7−1 (m, 5H), 4.22 (br s, 1H), 4.08 (q, *J* = 7.1, 2H), 3.07 (q, *J* = 7.3 Hz, 1H), 2.90−2.50 (m, 2H), 2.3−1.7 (m, 4H), 1.28 (d, *J* = 7.3, 3H), 1.23 (t, *J* = 7.1, 3H), 1.11 (t, *J* = 7.2, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ) δ 215.0, 175.3, 141.2, 128.4 (4C), 128.2, 126.1, 82.0, 61.0, 45.2, 37.3, 30.6, 29.4, 13.9, 10.9, 7.5. Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.82; H, 8.28. Found: C, 69.58; H, 8.21.

(+)-(2′*S*,3*R*)-3-(2′-Hydroxy-3′-oxo-pent-2′-yl)tetrahydrofuran-2-one ((+)-21). Hydrolysis of (+)-**9B** was carried out following general procedure B. The crude mixture was purified by column chromatography (hexane−CH_2Cl_2, 3:1) to afford (+)-**21** as a colorless oil (446 mg, 80%): $[\alpha]^{25}_{D}$ +16, (*c* = 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ) δ 4.41 (dt, *J* = 8.8, 3.3, 1H), 4.25 (dt, *J* = 9.0, 7.5, 1H), 4.17 (br s, 1H), 3.17 (t, *J* = 9.6, 1H), 2.9−2.0 (m, 4H), 1.32 (s, 3H), 1.17 (t, *J* = 7.2, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ) δ 212.4, 176.3, 77.8, 67.2, 47.5, 29.4, 24.3, 23.5, 7.7. Anal. Calcd for $C_9H_{14}O_4$: C, 58.08; H, 7.58. Found: C, 57.95; H, 7.30.

This hydroxyketone was also prepared as a racemic compound from (±)-**9B** and (±)-**9D**.

(+)-(3′*S*,3*R*)-3-(1′-Phenyl-3′-hydroxy-4′-oxohex-3′-yl)tetrahydrofuran-2-one ((+)-22). Hydrolysis of (+)-**18B** was carried out following general procedure B. The crude mixture was purified by column chromatography (hexane-CH_2Cl_2, 3:2) to afford (+)-**22** as a colorless oil (638 mg, 77%): $[\alpha]^{25}_{D}$ +48 (*c* = 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.4−7−1 (m, 5H), 4.41 (dt, *J* = 8.8, 3.3, 1H), 4.32 (br s, 1H), 4.23 (dt, *J* = 9.0, 7.3, 1H), 3.17 (t, *J* = 9.6, 1H), 2.9−2.0 (m, 8H), 1.28 (t, *J* = 7.2, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 212.4, 176.3, 141.2, 128.4, 128.2, 126.1, 81.8, 67.2, 47.5, 37.3, 30.6, 29.4, 23.5, 13.9. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.53; H, 7.30. Found: C, 69.71; H, 7.21.

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Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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