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Enantioselective organocatalytic aldehyde–aldehyde cross-aldol couplings. The broad utility of α-thioacetal aldehydes

R. Ian Storer and David W. C. MacMillan*

Division of Chemistry and Chemical Engineering, California Institute of Technology, 1200 E California Blvd; Pasadena, CA 91125, USA

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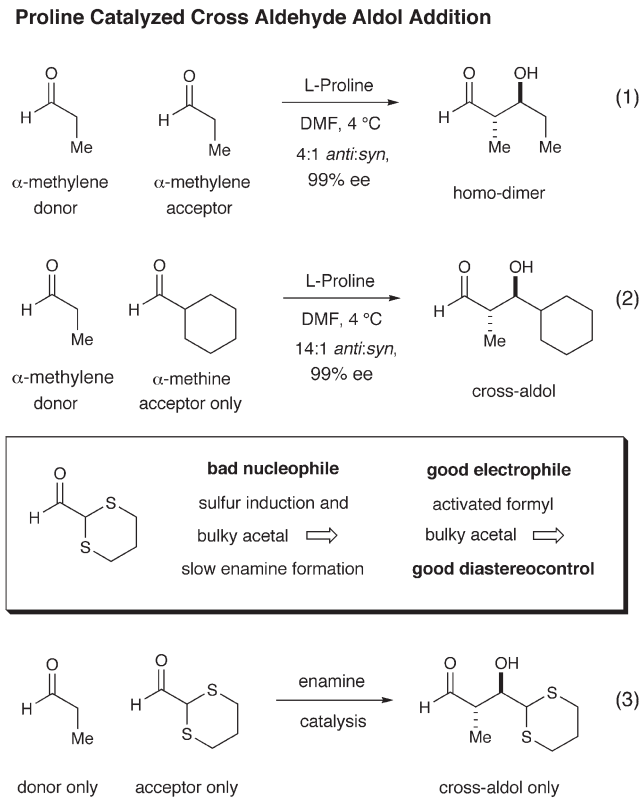
This manuscript is dedicated to Professor D. Seebach for his pioneering work in the area of asymmetric synthesis

Abstract—An asymmetric proline catalyzed aldol reaction with α-thioacetal aldehydes has been developed. Thioacetal bearing aldehydes readily participate as electrophilic cross-aldol partners with a broad range of aldehyde and ketone donors. High levels of reaction efficiency as well as diastereo- and enantiocontrol are observed in the production of *anti*-aldol adducts.

1. Introduction

The aldol reaction is widely considered to be one of the most important technologies for carbon–carbon bond formation in chemical synthesis.[1] Over the last thirty years, seminal research from the laboratories of Evans,[2] Heathcock,[3] Masamune[4] and Mukaiyama[5] have established this venerable reaction as the principal chemical method for the stereoselective construction of complex polyol architecture. Recently, studies by Barbas,[6] Evans,[7] List,[8] Shair,[9] Shibasaki,[10] and Trost[11] have outlined the first examples of enantioselective direct aldol reactions, an important class of metal or proline catalyzed transformation that does not require the pregeneration of enolates or enolate equivalents. With these remarkable advances in place, a fundamental goal for asymmetric aldol technology has become the development of catalytic methods that would allow the direct coupling of aldehyde substrates.[12] In this context, our laboratory has recently reported the first example of a direct enantioselective aldehyde–aldehyde cross-aldol reaction using small molecule catalysts (Scheme 1).[13] Subsequently, we described the enantioselective dimerization and cross coupling of α-oxygenated aldehydes to provide erythrose architecture of broad utility for the construction of hexose carbohydrates.[14] In this report, we further advance this enamine catalysis concept to describe a highly stereoselective protocol for the cross coupling of aldehydes and ketones with α-thioacetal aldehydes. Importantly, the successful introduction of α-thioacetal functionality in this enantioselective cross coupling allows access to highly oxidized, stereodefined synthons of broad versatility. Moreover, the observed reactivity profile of 'viable-electrophile, non-nucleophile' has established α-thioacetal aldehydes as



Scheme 1. Proline-catalyzed cross aldehyde aldol.

Keywords: Aldol; Catalysis; Diastereoselection; Enantioselective; Organocatalysis; Proline.
* Corresponding author. Tel.: +1-626-395-6044; fax: +1-626-795-3658; e-mail address: dmacmill@caltech.edu

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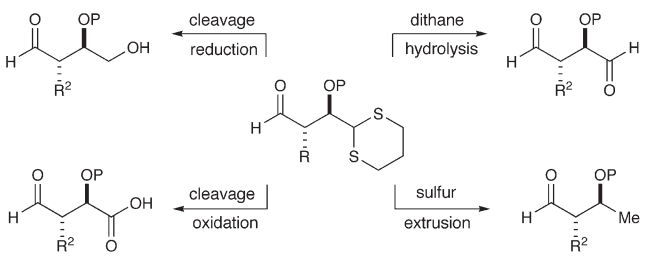
preeminent substrates for highly selective cross aldol reactions with prototypical aldehyde and ketone donors.

Traditionally, the enantioselective aldol coupling of non-equivalent aldehydes has been viewed as a formidable synthetic challenge on account of (i) the propensity of aldehydes to polymerize under metal catalyzed conditions and (ii) the mechanistic requirement that non-equivalent aldehydes must selectively partition into two discrete components, a nucleophilic donor and an electrophilic acceptor. In our recent studies, however, we have established that enamine catalysis can provide good levels of chemo-differentiation and stereocontrol with non-equivalent aldehydes, thereby establishing the aldehyde cross-aldol as an operationally useful transformation. More specifically, we have found that aldehydes containing a methylene carbon (CH_2R_2) adjacent to the carbonyl have a strong propensity to dimerize, via participation as both nucleophile and electrophile (Scheme 1, Eq. 1).[13] In contrast, aldehydes that incorporate an α-methine carbon (CHR_3) generally do not homo-dimerize when exposed to proline, instead behaving as electrophilic acceptors exclusively (Scheme 1, Eq. 2). In this latter case, it is presumed that the kinetic inaccessabilty of the α-methine proton and the thermodynamic instability of the corresponding enamine effectively prohibit nucleophile formation. As a consequence, chemoselective partitioning of α-methylene and α-methine aldehydes into nucleophilic and electrophilic partners respectively can be accomplished via slow addition of the enamine precursor to the α-methine aldehyde in the presence of catalyst. With respect to stereoselectivity, it should be noted that the bulky α,α-disubstituted aldehyde acceptors consistently provide superior levels of *anti*-diastereocontrol in crossed aldehyde aldol reactions in comparison to their α-methylene counterparts (Scheme 1, cf. Eqs. 1 and 3). This improvement in diastereocontrol as a function of increasing steric demand of the electrophile is in accord with a chair-like Zimmerman–Traxler transition state that has been proposed for enamine aldol reactions.

Based on our knowledge of the chemo- and stereo-differentiating features of the enamine cross aldol, we recently sought to devise a new and generally useful class of aldehyde cross coupling partner. Specifically we focused upon the design of aldehydic reagents that would (i) selectively function as aldol donors or acceptors, (ii) engender high levels of diastereocontrol, and (iii) contain chemical functionality that is readily elaborated and synthetically versatile. In this context, we selected α-thioacetal aldehydes with the expectation that they would be highly electrophilic yet sterically and electronically deactivated towards enamine formation (Scheme 1 Eq. 3). Moreover, the substantial steric demand of the α-dithane was expected to enforce high levels of absolute and relative stereocontrol in the aldol event. Lastly, the synthetic utility of thioacetals as latent carbonyl and alkyl equivalents has been widely established.[15] Indeed, a variety of conditions have been elucidated to transform dithianes to aldehydes, alcohols or carboxylic acids. Alternatively, the reductive extrusion of sulfur using transition metals is commonly utilized for the conversion of thioacetals to saturated alkyl substituents (Scheme 2).[15] With regard to operational advantages, it is important to note that α-thioacetal aldehydes are readily accessible on large scale and can be easily handled and stored.[16]

Dithiane Aldol Adducts: Latent Functionality

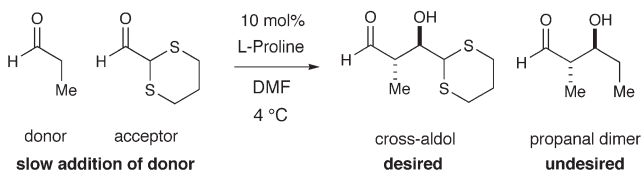


Scheme 2. Manipulation of dithianes.

2. Results and discussion

The proposed organocatalytic cross aldol was first examined using equimolar quantities of propanal and [1,3]-dithane-2-carbaldehyde[16] in the presence of catalytic proline (Table 1, entry 1). Preliminary studies revealed that this aldol reaction was indeed possible to provide the cross aldehyde adduct in 99% ee, however small quantities of the propanal dimer were observed. Gratifyingly, the aldol union can be

Table 1. Enantioselective direct cross-aldol reaction: preliminary studies



Entry	Donor (equiv.[a])	Acceptor (equiv.)	% Cross[b] (desired)	% Dimer[b] (undesired)	% ee Cross
1	1.0	1.0	90	10	99
2	2.0	1.0	65	35	99
3	1.0	2.0	100	0	99
4	1.0	4.0	100	0	99
5[c]	1.0	2.0	90	10	99
6	0	1.0	no thioacetal dimer	—	—

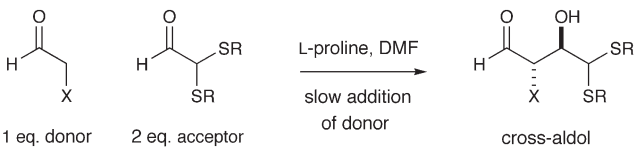
[a] Donor added by syringe pump over 24 h.
[b] Ratio of products determined by ^{1}H NMR integration of reaction crude.
[c] Donor and acceptor premixed.

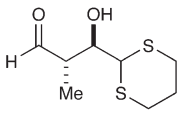
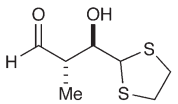
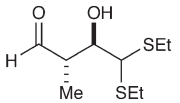
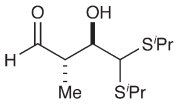
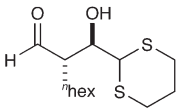
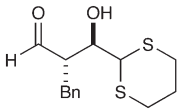
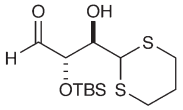
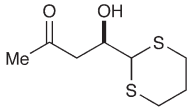
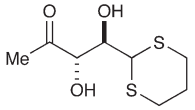
comprehensively partitioned to a cross aldol mechanism via the slow addition of propanal to an excess of the electrophilic aldehyde (entries 3 and 4).

In these cases the corresponding cross aldol adduct was obtained with excellent levels of *anti* diastereoselectivity and enantiocontrol (entry 3, 16:1 *anti–syn*, 99% ee) without production of dimeric propanal. As revealed in entries 3 and 5, the slow addition of the donor component is critical to the kinetic circumvention of the undesired dimerization pathway. The superior levels of cross-aldol selectivity, asymmetric induction and efficiency obtained via slow addition of the donor with excess dithiane acceptor (2 equiv.) prompted us to select these catalytic conditions for further exploration.

Experiments that probed the scope of the dithiane moiety and the donor aldehyde are summarized in Table 2. In all cases, slow addition of the donor aldehyde to a series of thioacetal aldehydes in the presence of proline effectively suppressed homodimerization, whilst providing good to excellent yields of the desired cross-aldol products (entries

Table 2. Enantioselective direct cross-aldol reaction: scope studies



Entry	Temperature (°C)	Mol% cat.	Product	% Yield	*anti–syn*[a]	% cc
1	4	10		85	16:1	>99[b]
2	4	10		77	8:1	99[b]
3	23	10		70	10:1	97[b]
4	23	10		41	8:1	98[b]
5[c]	4	10		75	>20:1	97[b]
6	23	10		73	>20:1	97[b]
7	23	20		52	13:1	70[b]
8[d]	23	20		91	—	96[e]
9[d,f]	23	10		88	>20:1	>99[e]

[a] Ratio determined by ^{1}H NMR analysis of the crude reaction mixtures.
[b] Enantiomeric excess determined by chiral HPLC analysis of the 2,2-dimethyl-1,3-propanediol acetal derivatives.
[c] Ratio of donor–acceptor was 1:1.5.
[d] An excess of ketone donor was used.
[e] Enantiomeric excess determined by chiral HPLC analysis.
[f] Relative and absolute stereochemistry was confirmed by X-ray analysis.[17]

1–7). Considerable variation in the steric demand of the thioacetal substituent is possible without loss in enantiocontrol (entries 1–4, 97 to 99% ee).[16] However, couplings performed with cyclic thioacetal aldehydes (Table 1, entries 1–2) were found to proceed more efficiently than with the acyclic examples (Table 1, entries 3–4). In these cases, we presume that the inherent reactivity of the acceptor decreases with the relative steric demands of the proximal acetal. To our delight, this chemo- and enantioselective cross aldol is also tolerant to a wide range of donor systems (entries 5–9, 97–99% ee). In the context of aldehyde donors, propanal, octanal and hydrocinnamaldehyde provide cross coupled adducts with [1,3]-dithane-2-carbaldehyde in 70–85% yield, >20:1 dr and 95–99% ee (Table 2, entries 1,5,6). Moreover, the silyloxy glycoaldehyde donor enables the rapid construction of latent erythrose architecture (entry 7, 95% yield, 13:1 *anti*–*syn*, 70% ee).

In accord with the studies of Hajos–Parrish[18] and Barbas[6]–List,[7] ketone donors can also be accommodated without loss in reaction efficiency or stereocontrol (Table 2, entries 8 and 9). More specifically, the rapid addition of acetone to [1,3]-dithane-2-carbaldehyde in the presence of proline at room temperature resulted in the corresponding cross aldol adduct in 91% yield and 96% ee (entry 8). Of particular note was the coupling of acetol in 88% yield, >20:1 dr, >99% ee (entry 9) and the silyloxy glycoaldehyde donor (entry 7). The successful implementation of these α-oxy substrates in this cross aldol sequence should allow facile and rapid access to biologically important polyol architectures, such as hexose carbohydrates.

Lastly, it is important to note that this dithiane-aldehyde class provides the highest levels of diastereocontrol that have been observed in aldehyde–aldehyde couplings to date. As revealed in Table 2, formation of the *anti*-isomer is accomplished with excellent selectivity for a range of aldehyde donors and thio-acetal acceptors (entries 1–7, 8 to 20:1 *anti*–*syn*). The relative and absolute stereochemistry observed is in accord with the previously proposed models for proline catalyzed reactions.[14,19]

In summary, we have shown α-thioacetal aldehydes to be versatile acceptor units for direct proline catalyzed aldol reactions with a range of aldehyde and ketone donors. Significantly, this reaction permits highly diastereoselective and enantioselective access to β-hydroxy and α,β-dihydroxy aldehydes and ketones. Work is continuing to apply these units in the synthesis of desymmetrized *meso*-tartrate derivatives, hexose and pentose carbohydrates, and to the total synthesis of polypropionate and polyacetate natural products. A full account of these studies will be presented in due course.

3. Experimental

3.1. General

Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[20] Non-aqueous reagents were transferred under nitrogen via syringe or cannula. dimethylformamide (DMF) was purified according to the method of Grubbs.[21] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32–64 mesh silica gel 63 according to the method of Still.[22] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatograms was performed by ultraviolet irradiation (254 nm) or stained using anisaldehyde or aqueous acidic ammonium molybdate. ^{1}H NMR spectra were recorded in $CDCl_3$, at ambient temperature on a Varian 300 spectrometer, at 300 MHz, with residual protic solvent $CHCl_3$ as the internal reference (δ_H=7.26 ppm); Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (J) are given in Hertz (Hz). The proton spectra are reported as follows: chemical shift (δ/ppm) (multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, sept=septet, m=multiplet), coupling constant (J/Hz), number of protons, assignment). ^{13}C NMR spectra were recorded in $CDCl_3$ at ambient temperature on the same spectrometer at 75 MHz, with the central peak of $CHCl_3$ as the internal reference (δ_C=77.3 ppm). Data for ^{13}C NMR are reported in terms of chemical shift. Two dimensional COSY and HMQC NMR spectroscopy were used where appropriate, to aid in the assignment of signals in the ^{1}H NMR spectra. Where a compound has been characterized as an inseparable mixture of diastereoisomers, the NMR data for the major isomer has been reported. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the California Institute of Technology Mass Spectral facility by electron ionisation, chemical ionisation or fast atom/ion bombardment techniques. Optical rotations were measured on a Jasco P-1010 polarimeter, and $[\alpha]_D$ values are reported in 10^{-1} deg cm2 g^{-1}; concentration (c) is in g/100 mL. High performance liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series chromatographs using a Chiralcel AD column (25 cm) and AD guard (5 cm), a Chiralcel OJ column (25 cm) and OJ guard (5 cm), a Chiralcel AS column (25 cm) and AS guard (5 cm), or a Chiralcel ODH column (25 cm) and ODH guard (5 cm) as noted. Syringe pump additions were made using a 10 syringe parallel pump (in all cases the syringe needle tip was submerged below the surface of the liquid in the receiver vessel to ensure continuous mixing).

3.2. Synthesis and characterization

3.2.1. [1,3]Dithiane-2-carbaldehyde. The title compound was obtained from 1,3-dithiane and ethyl formate using the procedure outlined by Page.[16b] The product was initially purified by flash chromatography (3:1 pentane–diethyl ether) to remove any residual 1,3-dithiane and yield a pale yellow oil. The aldehyde was then purified by distillation in vacuo (78 °C, 0.15 mm Hg, 135 °C bath temp.)[16a] to yield a colorless oil. The aldehyde could be successfully stored under anhydrous conditions at ca. −20 °C (mp <0 °C) as a white crystalline solid.

3.2.2. (2*S*,3*R*)-3-[1,3]Dithiane-2-yl-3-hydroxy-2-methylpropionaldehyde (Table 2, entry 1). A solution of freshly

distilled propionaldehyde (100 μL, 1.35 mmol) in 1.35 mL DMF pre-cooled to 4 °C was added slowly over the course of 24 h to a stirring suspension of [1,3]dithiane-2-carbaldehyde (400 mg, 2.70 mmol), L-proline (16 mg, 0.139 mmol) and 1.35 mL DMF at 4 °C. After 46 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were extracted with five portions of ethyl acetate. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Analysis of the crude reaction mixture by ^1H NMR revealed a 16:1 *anti*–*syn* mixture of diastereoisomers. Flash chromatography (1:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 85% yield (236 mg, 1.15 mmol). The enaniomeric excess (ee) was measured by HPLC analysis of the acetal derived from 2,2-dimethylpropane-1,3-diol (see below). IR (film) 3456, 2902, 1717, 1422, 1277, 986, 908, 783 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (d, J=1.2 Hz, 1H, C*H*O), 4.24 (dd, J=7.2, 4.8 Hz, 1H, C*H*OH), 3.87 (d, J=7.2 Hz, 1H, SC*H*S), 3.05–2.78 (m, 3H, C*H*CH_3, SC$H_2$$CH_2CH_2$S), 2.74–2.60 (m, 2H, SC$H_2$$CH_2CH_2$S), 2.15–1.95 (m, 2H, SCH_2C$H_2$$CH_2$S), 1.25 (d, J=7.5 Hz, 3H, CH_3), no OH signal observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.4, 73.7, 48.5, 47.9, 27.7, 26.9, 25.4, 10.4; HRMS (EI+) exact mass calcd for $[M]^+$ ($C_8H_{14}O_2S_2$) requires m/z 206.0435, found m/z 206.0432; $[\alpha]_D$=−15.3 (c=1.0, $CHCl_3$).

3.2.3. (1*R*,2*S*)-2-(5,5-Dimethyl-[1,3]dioxan-2-yl)-1-[1,3]dithian-2-yl-propan-1-ol. A solution of 2,2-dimethylpropane-1,3-diol (21.0 mg, 0.202 mmol) and pyridinium *p*-toluenesulfonate (5 mg, 0.02 mmol) in acetonitrile (0.2 mL) were added to a solution of (2*S*,3*R*)-3-[1,3]dithiane-2-yl-3-hydroxy-2-methyl-propionaldehyde (17.0 mg, 0.083 mmol) in acetonitrile (0.2 mL) at room temperature. The mixture was stirred for 16 h before filtration through a pad of silica (2:1 pentane–diethyl ether) and concentration in vacuo. Flash chromatography (5:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 82% yield (20 mg, 0.068 mmol) 99% ee. The product ee was measured by chiral HPLC (OJ column, 2% EtOH in hexanes) relative to a racemic sample; (1*R*,2*S*) *anti* isomer t_r=39.3 min, (1*S*,2*R*) *anti* isomer t_r=33.7 min, *syn* isomers t_r major=25.1 min, t_r minor=21.4 min. IR (film) 3446, 2954, 1471, 1394, 1108, 1081, 1040, 983 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.60 (d, J=3.6 Hz, 1H, OC*H*O), 4.17 (d, J=4.2 Hz, 1H, SC*H*S), 4.00–3.90 (m, 1H, C*H*OH), 3.63 (d, J=11.1 Hz, 2H, OCH_2C$(CH_3)_2$CH_2O), 3.42 (d, J=11.1 Hz, 2H, OCH_2C$(CH_3)_2$CH_2O), 3.02–2.70 (m, 4H, SC$H_2$$CH_2CH_2$S), 2.21 (qdd (app. pd), J=7.2, 7.2, 4.2 Hz, 1H, C*H*CH_3), 2.15–1.86 (m, 2H, SCH_2C$H_2$$CH_2$S), 1.18 (s, 3H, C$H_3$$CCH_3$), 0.87 (d, J=7.2 Hz, 3H, CHCH_3), 0.72 (s, 3H, CH_3CCH_3), no OH signal observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.2, 77.7, 77.5, 76.2, 51.9, 40.1, 30.7, 30.6, 29.8, 26.4, 23.3, 22.1, 12.0; HRMS (FAB+) exact mass calcd for $[M-H]^+$ ($C_{13}H_{23}O_3S_2$) requires m/z 291.1089, found m/z 291.1098; $[\alpha]_D^{22}$=−13.5 (c=1.0, $CHCl_3$).

3.2.4. [1,3]Dithiolane-2-carbaldehyde.[16c] A solution of DIBAL-H (1.0 M hexanes, 14.1 mL, 14.0 mmol) was added dropwise to a stirred solution of [1,3]dithiolane-2-carboxylic acid ethyl ester (2.5 g, 14.0 mmol) in CH_2Cl_2 (21 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h, quenched with MeOH (2 mL) and allowed to slowly warm to room temperature. A solution of Rochel salts (20 mL) and CH_2Cl_2 (30 mL) were added and stirring continued for 3 h. The mixture was extracted three times with CH_2Cl_2. The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated to yield a pale yellow oil. Purification by flash chromatography (4:1 pentane–diethyl ether) yielded a colorless clear oil in 85% yield (1.59 g, 11.9 mmol). The title aldehyde could be successfully stored under anhydrous conditions below 0 °C (−78 °C for long term storage).

3.2.5. (2*S*,3*R*)-[1,3]Dithiolane-2-yl-3-hydroxy-2-methyl-propionaldehyde (Table 2, entry 2). A solution of freshly distilled propionaldehyde (123 μL, 1.69 mmol) in 1.75 mL DMF pre-cooled to 4 °C was added slowly over the course of 24 h to a stirring suspension of [1,3]dithiolane-2-carbaldehyde (453 mg, 3.38 mmol), L-proline (19.5 mg, 0.169 mmol) and 1.75 mL DMF at 4 °C. After 28 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were extracted with five portions of ethyl acetate. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Analysis of the crude reaction mixture by ^1H NMR revealed an 8:1 *anti*–*syn* mixture of diastereoisomers. Flash chromatography (2:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 77% yield (251 mg, 1.31 mmol). The ee was measured by HPLC analysis of the acetal derived from 2,2-dimethylpropane-1,3-diol (see below). IR (film) 3440, 2972, 2928, 2877, 2730, 1715, 1456, 1423, 1380, 1279, 1101, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.80 (d, J=2.1 Hz, 1H, C*H*O), 4.71 (d, J=5.7 Hz, 1H, SC*H*S), 3.74 (ddd, J=5.7, 5.7, 4.5 Hz, 1H, C*H*OH), 3.40–3.14 (m, 4H, SC$H_2$$CH_2$S), 2.85 (d, J=4.4 Hz, 1H, O*H*), 2.78–2.66 (m, 1H, C*H*CH_3), 1.19 (d, J=7.2 Hz, 3H, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9, 76.6, 57.3, 50.3, 39.3, 38.5, 11.4; HRMS (EI+) exact mass calcd for $[M]^+$ ($C_7H_{12}O_2S_2$) requires m/z 192.0279, found m/z 192.0279; $[\alpha]_D^{22}$=−2.4 (c=1.0, $CHCl_3$).

3.2.6. (1*R*,2*S*)-2-(5,5-Dimethyl-[1,3]dioxan-2-yl-1-[1,3]dithiolan-2-yl-propan-1-ol. A solution of 2,2-dimethylpropane-1,3-diol (10.8 mg, 0.104 mmol) and pyridinium *p*-toluenesulfonate (5 mg, 0.02 mmol) in acetonitrile (0.2 mL) were added to a solution of (2*S*,3*R*)-[1,3]dithiolane-2-yl-3-hydroxy-2-methyl-propionaldehyde (10.0 mg, 0.052 mmol) in acetonitrile (0.2 mL) at room temperature. The mixture was stirred for 26 h before filtration through a pad of silica (2:1 pentane–diethyl ether) and concentration in vacuo. Flash chromatography (4:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 76% yield (11 mg, 0.04 mmol) 99% ee. The product ee was measured by chiral HPLC (ODH column, 2% EtOH in hexanes) relative to a racemic sample; (1*R*,2*S*) *anti* isomer t_r=22.2 min, (1*S*,2*R*) *anti* isomer t_r=40.6 min, *syn* isomers t_r major=16.6 min, t_r minor=18.7 min. IR (film) 3487, 2954, 2860, 1471, 1394, 1108, 1017, 990, 924 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.80 (d, J=5.7 Hz, 1H, SC*H*S), 4.63 (d, J=3.3 Hz, 1H, OC*H*O), 3.64 (m, 1H, C*H*OH), 3.62 (d,

J=11.0 Hz, 2H, $CH_2C(CH_3)_2CH_2$), 3.42 (d, J=11.0 Hz, 2H, $CH_2C(CH_3)_2CH_2$), 3.34–3.13 (m, 4H, SCH_2CH_2S), 2.09 (qdd, J=6.9, 6.6, 3.0 Hz, 1H, $CHCH_3$), 1.17 (s, 3H, CH_3CCH_3), 1.06 (d, J=6.9 Hz, 3H, $CHCH_3$), 0.71 (s, 3H, CH_3CCH_3), no OH signal observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.5, 77.5, 77.4, 57.8, 41.6, 39.2, 38.8, 30.5, 23.3, 22.0, 12.0, one signal obscured; HRMS (EI+) exact mass calcd for $[M-H]^+$ ($C_{12}H_{22}O_3S_2$) requires m/z 277.0932, found m/z 277.0919; $[\alpha]_D^{24}$=+17.6 (c=1.0, $CHCl_3$).

3.2.7. Bis-ethylsulfanyl-acetaldehyde (Table 2, entry 3). The title compound was obtained from glyoxal and ethane thiol using the procedure outlined by Bates.[16d] The product can be purified by flash chromatography (40:1 pentane–diethyl ether) or by vacuum distillation (60 °C, 0.1 mm Hg) to yield a colorless clear oil. The title aldehyde could be successfully stored under anhydrous conditions below 0 °C (−78 °C for long term storage).

3.2.8. (2*S*,3*R*)-4,4-Bis-ethylsulfanyl-3-hydroxy-2-methyl-butyraldehyde. A solution of freshly distilled propionaldehyde (98 mg, 123 μL, 1.69 mmol) in 1.75 mL DMF was added slowly over the course of 24 h to a stirring suspension of bis-ethylsulfanyl-acetaldehyde (554 mg, 3.38 mmol), L-proline (19.5 mg, 0.17 mmol) and 1.75 mL DMF room temperature. After 38 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were extracted with five portions of ethyl acetate. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Analysis of the crude reaction mixture by ^{1}H NMR revealed an 10:1 *anti*–*syn* mixture of diastereoisomers. Flash chromatography (3:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 70% yield (262 mg, 1.18 mmol). The ee was measured by HPLC analysis of the acetal derived from 2,2-dimethylpropane-1,3-diol (see below). IR (film) 3468, 2970, 2929, 2872, 2728, 1722, 1455, 1455, 1377, 1266, 1108, 1051, 976 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80 (d, J=1.5 Hz, 1H, CHO), 3.93 (d, J=6.3 Hz, 1H, $CH(SEt)_2$), 3.86 (dd, J=6.3, 7.2 Hz, 1H, $CHOH$), 3.17 (br s, 1H, $CHOH$), 2.93 (qdd, J=7.2, 7.2, 1.5 Hz, 1H, $CHCH_3$), 2.80–2.50 (m, 4H, $S(CH_2CH_3)_2$), 1.27 (t, J=7.2 Hz, 3H, SCH_2CH_3), 1.26 (t, J=7.2 Hz, 3H, SCH_2CH_3), 1.19 (d, J=7.2 Hz, 3H, $CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 74.5, 56.3, 48.8, 25.8, 24.7, 14.9, 14.7, 11.1; HRMS (FAB+) exact mass calcd for $[M]^+$ ($C_9H_{18}O_2S_2$) requires m/z 222.0748, found m/z 222.0758; $[\alpha]_D^{21}$=+23.3 (c=1.0, $CHCl_3$).

3.2.9. (2*R*,3*S*)-3-(5,5-Dimethyl-[1,3]dioxan-2-yl)-1,1-bis-ethylsulfanyl-butan-2-ol. A solution of 2,2-dimethyl-propane-1,3-diol (20.0 mg, 0.193 mmol) and pyridinium *p*-toluenesulfonate (5 mg, 0.02 mmol) in acetonitrile (0.2 mL) were added to a solution of (2*S*,3*R*)-4,4-bis-ethylsulfanyl-3-hydroxy-2-methyl-butyraldehyde (21.4 mg, 0.096 mmol) in acetonitrile (0.2 mL) at room temperature. The mixture was stirred for 36 h before filtration through a pad of silica (10:1 pentane–diethyl ether) and concentration in vacuo. Flash chromatography (10:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 81% yield (24 mg, 0.078 mmol) 97% ee. The product ee was measured by chiral HPLC (ODH column, 2% EtOH in hexanes) relative to a racemic sample; (2*R*,3*S*) *anti* isomer t_r=8.0 min, (2*S*,3*R*) *anti* isomer t_r=13.6 min, *syn* isomers t_r major=5.4 min, t_r minor=6.5 min. IR (film) 3490, 2957, 2929, 2870, 2852, 1455, 1393, 1265, 1154, 1108, 1080, 1018, 976, 923 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65 (d, J=3.0 Hz, 1H, $OCHO$), 3.94 (d, J=3.3 Hz, 1H, $CH(SEt)_2$), 3.91–3.83 (m, 1H, $CHOH$), 3.62 (d, J=11.1 Hz, 2H, CH_2O), 3.44 (d, J=10.8 Hz, 1H, CH_2O), 3.43 (d, J=10.5 Hz, 1H, CH_2O), 2.80–2.60 (m, 4H, $(SCH_2CH_3)_2$), 2.28 (qdd, J=7.2, 7.2, 3.0 Hz, 1H, $CHCH_3$), 1.27 (t, J=7.8 Hz, 6H, $(SCH_2CH_3)_2$), 1.18 (s, 3H, CH_3CCH_3), 0.99 (d, 3H, J=7.2 Hz, $CHCH_3$), 0.71 (s, 3H, CH_3CCH_3), no OH signal observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.7, 77.6, 77.5, 75.4, 55.9, 40.6, 30.6, 25.8, 25.3, 23.3, 22.0, 14.9, 14.8, 11.3; HRMS (FAB+) exact mass calcd for $[M]^+$ ($C_{14}H_{28}O_3S_2$) requires m/z 308.1480, found m/z 308.1490; $[\alpha]_D$=−33.2 (c=1.0, $CHCl_3$).

3.2.10. Bis-isopropylsulfanyl-acetaldehyde (Table 2, entry 4). A biphasic mixture of an aqueous 40% solution of glyoxal (12.5 g solution, ca. 5 g glyoxal, 86 mmol), isopropanethiol (13.1 g, 16.0 mL, 172 mmol) and 2 N HCl (10 mL) in CH_2Cl_2 was stirred vigorously for 24 h. The phases were separated and the aqueous phase extracted two times with CH_2Cl_2. The organic phases were combined, washed once with an aqueous solution of Na_2CO_3, dried over $MgSO_4$, and concentrated to yield a pale yellow oil. The product was purified by flash chromatography (10:1 pentane–diethyl ether) to yield the title compound as a colourless clear oil in 38% yield (6.4 g, 33 mmol). The title aldehyde could be successfully stored under anhydrous conditions below 0 °C (−78 °C for long term storage). IR (film) 2963, 2927, 2867, 2813, 2707, 1715, 1590, 1455, 1384, 1367, 1247, 1155, 1128, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.07 (d, J=5.6 Hz, 1H, CHO), 4.18 (dd, J=5.6, 0.6 Hz, 1H, $CH(S^iPr)_2$), 3.05 (sep, J=6.9 Hz, 2H, $(CH(CH_3)_2)_2$), 1.32 (d, J=6.6 Hz, 6H, $CH_2(CH_3)_2$), 1.28 (d, J=6.6 Hz, 6H, $CH_2(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.5, 53.6, 36.2, 23.8, 23.6; HRMS (EI+) exact mass calcd for $[M]^+$ ($C_8H_{16}OS_2$) requires m/z 192.0643, found m/z 192.0636.

3.2.11. (2*S*,3*R*)-3-Hydroxy-4,4-bis-isopropylsulfanyl-2-methyl-butyraldehyde. A solution of freshly distilled propionaldehyde (20 mg, 25 μL, 1.69 mmol) in 0.35 mL DMF was added slowly over the course of 24 h to a stirring suspension of bis-isopropylsulfanyl-acetaldehyde (130 mg, 0.68 mmol), L-proline (3.9 mg, 0.034 mmol) and 0.35 mL DMF room temperature. After 40 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were extracted with five portions of ethyl acetate. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Analysis of the crude reaction mixture by ^{1}H NMR revealed an 8:1 *anti*–*syn* mixture of diastereoisomers. Flash chromatography (3:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 41% yield (34.2 mg, 0.14 mmol). The ee was measured by HPLC analysis of the acetal derived from 2,2-dimethylpropane-1,3-diol (see below). IR (film) 3470, 2962,

2927, 2864, 1723, 1454, 1367, 1243, 1154, 1051 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.80 (d, J=1.8 Hz, 1H, C*H*O), 4.01 (d, J=5.4 Hz, 1H, C*H*(S^iPr)$_2$), 3.86 (dd (app. t), J=5.7, 5.7 Hz, 1H, C*H*OH), 3.23 (br s, 1H, CHO*H*), 3.22–3.04 (m, 2H, (SC*H*(CH_3)$_2$)$_2$), 2.93 (qdd, J=7.5, 5.7, 1.8 Hz, 1H, C*H*CH_3), 1.32 (d, J=6.6 Hz, 3H, SCH(CH_3)$_2$), 1.31 (d, J=6.6 Hz, 3H, SCH(CH_3)$_2$), 1.30 (d, J=6.6 Hz, 3H, SCH(CH_3)$_2$), 1.27 (d, J=6.6 Hz, 3H, SCH(CH_3)$_2$), 1.17 (d, J=7.5 Hz, 3H, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.4, 74.7, 54.5, 48.7, 35.6, 35.3, 24.1, 24.0, 23.7, 23.5, 11.0; HRMS (FAB+) exact mass calcd for $[M]^+$ ($C_{11}H_{22}O_2S_2$) requires m/z 250.1061, found m/z 250.1071; $[\alpha]_D^{22}$=−8.2 (c=1.0, $CHCl_3$).

3.2.12. (2*R*,3*S*)-3-(5,5-Dimethyl-[1,3]dioxan-2-yl)-1,1-bis-isopropylsulfanyl-butan-2-ol. A solution of 2,2-dimethylpropane-1,3-diol (14.2 mg, 0.136 mmol) and pyridinium *p*-toluenesulfonate (5 mg, 0.02 mmol) in acetonitrile (0.2 mL) were added to a solution of (2*S*,3*R*)-3-hydroxy-4,4-bis-isopropylsulfanyl-2-methyl-butyraldehyde (17.0 mg, 0.068 mmol) in acetonitrile (0.2 mL) at room temperature. The mixture was stirred for 51 h before filtration through a pad of silica (5:1 pentane–diethyl ether) and concentration in vacuo. Flash chromatography (10:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 83% yield (19.1 mg, 0.057 mmol) 98% ee. The product ee was measured by chiral HPLC (ODH column, 2% ^{i}PrOH in hexanes) relative to a racemic sample; (2*R*,3*S*) *anti* isomer t_r=10.2 min, (2*S*,3*R*) *anti* isomer t_r=11.7 min, *syn* isomers t_r major=8.4 min, t_r minor=9.7 min. IR (film) 3494, 2957, 2928, 2867, 1461, 1393, 1365, 1244, 1154, 1107, 1040, 989, 923 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.69 (d, J=3.3 Hz, 1H, OC*H*O), 4.03 (d, J=3.0 Hz, 1H, SC*H*S), 3.82 (dd, J=8.5, 3.0 Hz, 1H, C*H*OH), 3.61 (d, 2H, CH_2O), 3.51–3.37 (m, 2H, CH_2O), 3.18 (sept, J=6.6 Hz, 1H, SC*H*(CH_3)$_2$), 3.10 (sept, J=6.9 Hz, 1H, SC*H*(CH_3)$_2$), 2.33–2.19 (m, 1H, C*H*CH_3), 1.31 (d, J=6.6 Hz, 3H, CH(CH_3)$_2$), 1.30 (d, J=6.6 Hz, 3H, CH(CH_3)$_2$), 1.28 (d, J=6.6 Hz, 3H, CH(CH_3)$_2$), 1.25 (d, J=6.6 Hz, 3H, CH(CH_3)$_2$), 1.18 (s, 3H, CH_3CCH$_3$), 1.00 (d, J=7.2 Hz, 3H, CHCH_3), 0.71 (s, 3H, CH$_3$CCH_3), no OH signal observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.2, 77.53, 77.47, 74.7, 53.9, 40.3, 35.1, 34.9, 30.6, 24.1, 23.9, 23.5, 23.4, 23.3, 22.0, 10.6; HRMS (FAB+) exact mass calcd for $[M]^+$ ($C_{16}H_{32}O_3S_2$) requires m/z 336.1793, found m/z 336.1794; $[\alpha]_D^{22}$=−42.9 (c=1.0, $CHCl_3$).

3.2.13. (2*S*,2′*R*)-2-([1,3]Dithian-2-yl-hydroxy-methyl)-octanal (Table 2, entry 5). A solution of freshly distilled octanal (65 mg, 79 μL, 0.34 mmol) in 0.35 mL DMF was added slowly over the course of 15 h to a stirring suspension of [1,3]dithiane-2-carbaldehyde (50 mg, 0.34 mmol), L-proline (3.9 mg, 0.034 mmol) and 0.35 mL DMF at room temperature. After 36 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were extracted with five portions of ethyl acetate. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Analysis of the crude reaction mixture by ^1H NMR revealed a >20:1 *anti*–*syn* mixture of diastereoisomers. Flash chromatography (3:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 75% yield (70 mg, 0.25 mmol). The ee was measured by HPLC analysis of the acetal derived from 2,2-dimethylpropane-1,3-diol (see below). IR (film) 3460, 2927, 2856, 1718, 1465, 1422, 1378, 1277, 1244, 1051, 910, 787 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.72 (d, J=2.1 Hz, 1H, C*H*O), 4.20 (ddd, J=8.1, 2.7, 2.1 Hz, 1H, C*H*OH), 3.86 (d, J=8.1 Hz, 1H, SC*H*S), 3.02–2.60 (m, 6H, C*H*C_6H_{13}, O*H*, SCH_2CH_2CH_2S), 2.14–1.94 (m, 2H, SCH$_2$CH_2CH$_2$S), 1.88–1.60 (m, 2H, CH_2(CH$_2$)$_4$CH$_3$), 1.46–1.22 (m, 8H, (CH_2)$_4$CH$_3$), 0.88 (t, J=6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 72.9, 53.3, 48.2, 31.9, 29.6, 27.8, 27.5, 26.7, 26.3, 25.4, 22.8, 14.3; HRMS (EI+) exact mass calcd for $[M]^+$ ($C_{13}H_{24}O_2S_2$) requires m/z 276.1218, found m/z 276.1224; $[\alpha]_D^{22}$=−16.3 (c=1.0, $CHCl_3$).

3.2.14. (1*R*,2*S*)-2-(5,5-Dimethyl-[1,3]dioxan-2-yl)-1-[1,3]dithian-2-yl-octan-1-ol. A solution of 2,2-dimethylpropane-1,3-diol (20.4 mg, 0.20 mmol) and pyridinium *p*-toluenesulfonate (5 mg, 0.02 mmol) in acetonitrile (0.2 mL) were added to a solution of (2*S*,2′*R*)-2-([1,3]dithian-2-yl-hydroxy-methyl)-octanal (27 mg, 0.098 mmol) in acetonitrile (0.2 mL) at room temperature. The mixture was stirred for 49 h before filtration through a pad of silica (5:1 pentane–diethyl ether) and concentration in vacuo. Flash chromatography (4:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 95% yield (33.5 mg, 0.092 mmol) 97% ee. The product ee was measured by chiral HPLC (ODH column, 2% EtOH in hexanes) relative to a racemic sample; (1*R*,2*S*) *anti* isomer t_r=24.7 min, (1*S*,2*R*) *anti* isomer t_r=16.7 min, *syn* isomers t_r major=27.6 min, t_r minor=31.5 min. IR (film) 3490, 2953, 2928, 2855, 1469, 1422, 1394, 1113, 1018 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.71 (d, J=3.3 Hz, 1H, OC*H*O), 4.25 (d, J=6.8 Hz, 1H, SC*H*S), 4.00 (dd, J=6.8, 5.4 Hz, 1H, C*H*OH), 3.63 (d, J=11.0 Hz, 2H, OCH_2C(CH$_3$)$_2$CH_2O), 3.42 (d, J=11.0 Hz, 2H, OCH_2C(CH$_3$)$_2$CH_2O), 2.99–2.72 (m, 4H, SCH_2CH$_2$-CH_2S), 2.19–2.01 (m, 2H, C*H*(C_6H_{13}), CH_2(CH$_2$)$_4$CH$_3$), 2.00–1.85 (m, 1H, CH_2(CH$_2$)$_4$CH$_3$), 1.62–1.46 (m, 2H, SCH$_2$CH_2CH$_2$S), 1.36–1.22 (m, 8H, (CH_2)$_4$CH$_3$), 1.18 (s, 3H, CH_3CCH$_3$), 0.87 (t, J=6.6 Hz, 3H, (CH$_2$)$_5$CH_3), 0.72 (s, 3H, CH$_3$CCH_3), no OH signal observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.4, 77.7, 77.5, 74.0, 51.7, 43.6, 32.0, 30.6, 29.9, 29.8, 29.3, 27.5, 26.4, 26.2, 23.4, 22.9, 22.0, 14.4; HRMS (FAB+) exact mass calcd for $[M]^+$ ($C_{18}H_{34}O_3S_2$) requires m/z 362.1950, found m/z 362.1937; $[\alpha]_D^{22}$=+0.71 (c=1.0, $CHCl_3$).

3.2.15. (2*S*,3*R*)-2-Benzyl-3-[1,3]dithian-2-yl-3-hydroxy-propionaldehyde (Table 2, entry 6). A solution of freshly distilled hydrocinnamaldehyde (45 mg, 45 μL, 0.34 mmol) in 0.35 mL DMF was added slowly over the course of 24 h to a stirring suspension of [1,3]Dithiane-2-carbaldehyde (100 mg, 0.68 mmol), L-proline (3.9 mg, 0.034 mmol) and 0.35 mL DMF at room temperature. After 46 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were extracted with five portions of ethyl acetate. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Analysis of the crude reaction mixture by ^1H NMR revealed a >20:1 *anti*–*syn* mixture of diastereoisomers. Flash chromatography (1:1 pentane–diethyl ether) afforded the title compound as a

mixture of diastereoisomers as a clear, colorless oil in 75% yield (71 mg, 0.25 mmol). The ee was measured by HPLC analysis of the acetal derived from 2,2-dimethylpropane-1,3-diol (see below). IR (film) 3436, 2903, 1719, 1496, 1422, 1049, 747, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.80 (d, J=0.6 Hz, 1H, C*H*O), 7.34–7.16 (m, 5H, Ph), 4.11 (dd, J=9.3, 2.7 Hz, 1H, C*H*OH), 3.88 (d, J=9.3 Hz, 1H, SC*H*S), 3.28 (m, 1H, C*H*Bn), 3.17 (dd, J=13.6, 7.5 Hz, 1H, CH_2Ph), 3.04 (dd, J=13.6, 7.8 Hz, 1H, CH_2Ph), 2.86 (ddd, J=13.1, 8.7, 2.7 Hz, 1H, SCH_2), 2.64–2.50 (m, 3H, SCH_2, SCH_2), 2.10–1.85 (m, 2H, $SCH_2CH_2CH_2S$), no OH signal observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3, 138.6, 129.4, 129.0, 126.9, 71.5, 54.0, 47.8, 32.6, 26.7, 26.1, 25.3; HRMS (FAB+) exact mass calcd for $[M]^+$ ($C_{14}H_{18}O_2S_2$) requires m/z 282.0748, found m/z 282.0762; $[\alpha]_D$=+29.5 (c=1.0, $CHCl_3$).

3.2.16. (1*R*,2*S*)-2-(5,5-Dimethyl-[1,3]dioxan-2-yl)-1-[1,3]dithian-2-yl-3-phenyl-propan-1-ol. A solution of 2,2-dimethylpropane-1,3-diol (25.0 mg, 0.24 mmol) and pyridinium *p*-toluenesulfonate (5 mg, 0.02 mmol) in acetonitrile (0.2 mL) were added to a solution of (2*S*,3*R*)-2-benzyl-3-[1,3]dithian-2-yl-3-hydroxy-propionaldehyde (26 mg, 0.092 mmol) in acetonitrile (0.2 mL) at room temperature. The mixture was stirred for 65 h before filtration through a pad of silica (10:1 pentane–diethyl ether) and concentration in vacuo. Flash chromatography (5:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 90% yield (31 mg, 0.084 mmol) >99% ee. The product ee was measured by chiral HPLC (AD column, 2% EtOH in hexanes) relative to a racemic sample; (1*R*,2*S*) *anti* isomer t_r=40.7 min, (1*S*,2*R*) *anti* isomer t_r=66.7 min, *syn* isomers t_r major=59.6 min, t_r minor=54.0 min. IR (film) 3480, 2955, 2867, 1472, 1422, 1394, 1131, 1096, 1024, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.15 (m, 5H, Ph), 4.61 (d, J=3.0 Hz, 1H, OC*H*O), 4.18 (d, J=6.9 Hz, 1H, SC*H*S), 3.92 (m, 1H, C*H*OH), 3.83 (br s, 1H, O*H*), 3.65 (m, 2H, CH_2O), 3.39 (d, J=11.4 Hz, 1H, CH_2O), 3.38 (d, J=11.4 Hz, 1H, CH_2O), 3.00–2.79 (m, 3H, CH_2Ph, SCH_2), 2.74–2.64 (m, 3H, $SCH_2CH_2CH_2S$), 2.08–1.95 (m, 1H, $SCH_2CH_2CH_2S$), 1.94–1.78 (m, 1H, $SCH_2CH_2CH_2S$), 1.21 (s, 3H, CH_3), 0.71 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.6, 128.7, 126.4, 102.5, 77.5, 77.3, 72.6, 51.3, 45.5, 33.2, 32.6, 30.6, 29.4, 28.8, 26.2, 23.4, 22.0; HRMS (FAB+) exact mass calcd for $[M-H]^+$ ($C_{19}H_{27}O_3S_2$) requires m/z 367.1402, found m/z 367.1416; $[\alpha]_D^{22}$=+16.7 (c=1.0, $CHCl_3$).

3.2.17. (2*S*,3*R*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-3-[1,3]dithian-2-yl-3-hydroxy-propionaldehyde (Table 2, entry 7). A solution of freshly purified (*tert*-butyl-dimethyl-silanyloxy)-acetaldehyde (294 mg, 1.69 mmol) in 0.88 mL DMF was added slowly over the course of 24 h to a stirring suspension of [1,3]dithiane-2-carbaldehyde (500 mg, 3.38 mmol), L-proline (39 mg, 0.34 mmol) and 0.88 mL DMF at room temperature. After 44 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were extracted with five portions of ethyl acetate. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Analysis of the crude reaction mixture by ^1H NMR revealed a 13:1 *anti*–*syn* mixture of diastereoisomers. Flash chromatography (3:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 52% yield (283 mg, 0.88 mmol). The ee was measured by HPLC analysis of the acetal derived from 2,2-dimethylpropane-1,3-diol and confirmed by analysis of the corresponding diol, obtained by reduction of the aldehyde (see below). IR (film) 3468, 2945, 2910, 2892, 2847, 1714, 1466, 1422, 1373, 1253, 1129, 1005, 872, 836, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ; 9.53 (s, 1H, C*H*O), 4.37 (ddd, J=9.5, 2.1, 1.9 Hz, 1H, C*H*OH), 4.33 (d, J=2.1 Hz, 1H, C*H*OTBS), 3.59 (d, J=9.5 Hz, 1H, SC*H*S), 3.07–2.83 (m, 2H, SCH_2), 2.76 (s, 1H, O*H*), 2.55–2.42 (m, 1H, SCH_2), 2.37–2.25 (m, 1H, SCH_2), 2.13–1.88 (m, 2H, $SCH_2CH_2CH_2S$), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.092 (s, 3H, $SiCH_3$), 0.089 (s, 3H, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 78.7, 73.7, 42.7, 26.0, 24.8, 24.7, 24.1, 18.4, −4.5, −4.8; HRMS (EI+) exact mass calcd for $[M]^+$ ($C_{13}H_{26}O_3SiS_2$) requires m/z 322.1063, found m/z 322.1070; $[\alpha]_D^{24}$=−9.9 (c=1.0, $CHCl_3$).

3.2.18. (1*R*,2*S*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-2-(5,5-dimethyl-[1,3]dioxan-2-yl)-1-[1,3]dithian-2-yl-ethanol. A solution of 2,2-dimethylpropane-1,3-diol (102 mg, 0.975 mmol) and pyridinium *p*-toluenesulfonate (10 mg, 0.04 mmol) in acetonitrile (0.3 mL) were added to a solution of (2*S*,3*R*)-3-[1,3]dithiane-2-yl-3-hydroxy-2-methyl-propionaldehyde (31.4 mg, 0.098 mmol) in acetonitrile (0.2 mL) at room temperature. The mixture was stirred for 16 h before filtration through a pad of silica (10:1 pentane–diethyl ether) and concentration in vacuo. Flash chromatography (10:1 pentane–diethyl ether) afforded the title compound as a mixture of diastereoisomers as a clear, colorless oil in 46% yield (18.2 mg, 0.045 mmol) 70% ee. The product ee was measured by chiral HPLC (AD column, 2% EtOH in hexanes) relative to a racemic sample; (1*R*,2*S*) *anti* isomer t_r=6.3 min, (2*S*,3*R*) *anti* isomer t_r=7.7 min, *syn* isomers t_r major=9.8 min, t_r minor=11.7 min. IR (film) 3485.7, 2954, 2927, 2900, 2856, 1470, 1395, 1249, 1124, 1100, 1027, 837, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.52 (d, J=4.4 Hz, 1H, OC*H*O), 4.27 (d, J=3.0 Hz, 1H, SC*H*S), 4.15 (dd, J=7.9, 3.0 Hz, 1H, C*H*OH), 3.87 (dd, J=7.9, 4.4 Hz, 1H, C*H*OTBS), 3.72–3.58 (m, 2H, CH_2O), 3.45–3.35 (m, 2H, CH_2O), 3.10–2.95 (m, 2H, $SCH_2CH_2CH_2S$), 2.90–2.63 (m, 2H, $SCH_2CH_2CH_2S$), 2.12–1.90 (m, 2H, $SCH_2CH_2CH_2S$), 1.19 (s, 3H, $C(CH_3)_2$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.73 (s, 3H, $C(CH_3)_2$), 0.14 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$), no OH signal observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.2, 77.5, 76.5, 72.8, 48.4, 30.7, 30.2, 29.3, 26.3, 26.2, 23.4, 22.1, 18.6, −4.0, −4.5, 1 signal obscured; HRMS (EI+) exact mass calcd for $[M]^+$ ($C_{18}H_{36}O_4SiS_2$) requires m/z 408.1824, found m/z 408.1827; $[\alpha]_D^{24}$=−21.2475 (c=1.0, $CHCl_3$).

3.2.19. (1*R*,2*R*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-1-[1,3]dithian-2-yl-propane-1,3-diol. (A reduction method was used to provide an alternative enantiomeric excess assay). A solution of (2*S*,3*R*)-2-(*tert*-butyl-dimethyl-silanyloxy)-3-[1,3]dithian-2-yl-3-hydroxy-propionaldehyde (19.0 mg, 0.16 mmol) was added dropwise to a stirring suspension of sodium borohydride (15.0 mg, 0.39 mmol) in ethanol at 0 °C. The effervescing mixture was slowly warmed to room temperature and stirred for 30 min. A saturated solution of ammonium chloride was added to quench the reaction, followed by dilution with CH_2Cl_2 and water. The aqueous

layer was washed three times with portions of CH_2Cl_2, and the combined organics dried over $MgSO_4$, filtered and concentrated to yield a colourless oil. Purification by flash chromatography (2:1 pentane–diethyl ether) gave the title product as a colorless oil in 89% yield (17.0 mg, 0.052 mmol), 72% ee. The product ee was measured by chiral HPLC (AD column, 4% EtOH in hexanes) relative to a racemic sample; (1*R*,2*R*) *anti* isomer t_r=23.3 min, (1*S*,2*S*) *anti* isomer t_r=29.1 min. IR (film) 3405, 2954, 2929, 2892, 2847, 1461, 1422, 1253, 1253, 1091, 1040, 836, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.44 (br s, 1H, SC*H*S), 3.99–3.94 (m, *J*=1.8 Hz, 2H, C*H*OH, C*H*OTBS), 3.86–3.66 (m, 2H, CH_2OH), 2.99–2.88 (m, 3H, SCH_2CH$_2$C*H*HS), 2.84–2.72 (m, 1H, SCH$_2$CH$_2$CH_2S), 2.16–1.85 (m, 2H, SCH$_2$-CH_2CH$_2$S), 0.92 (s, 9H, SiC(CH_3)$_3$), 0.17 (s, 3H, SiCH_3), 0.14 (s, 3H, SiCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 76.0, 72.1, 64.3, 50.0, 30.3, 29.4, 26.1, 26.0, 18.3, −4.2, −4.4; HRMS (EI+) exact mass calcd for $[M]^+$ ($C_{13}H_{28}O_3SiS_2$) requires *m*/*z* 324.1249, found *m*/*z* 324.1252.

3.2.20. (*R*)-4-[1,3]Dithian-2-yl-4-hydroxy-butan-2-one (Table 2, entry 8). Acetone (395 mg, 0.5 mL, 6.80 mmol) was added to a suspension of [1,3]dithiane-2-carbaldehyde (37 mg, 0.25 mmol) and L-proline (5.8 mg, 0.05 mmol) in 2.0 mL DMF at room temperature. After stirring at room temperature for 65 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were extracted with five portions of ethyl acetate. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Flash chromatography (1:2 pentane–diethyl ether) afforded the title compound as a clear, colorless oil in 91% yield (47 mg, 0.23 mmol) 96% ee. The product ee was measured by chiral HPLC (ODH column, 5% EtOH in hexanes) relative to a racemic sample; *R*-isomer t_r=28.9 min, *S*-isomer t_r=26.5 min. IR (film) 3438, 2901, 1713, 1422, 1361, 1277, 1164, 1072, 909 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.41–4.32 (m, 1H, C*H*OH), 3.86 (d, *J*=6.0 Hz, 1H, SC*H*S), 3.23 (d, *J*=2.7 Hz, 1H, CHO*H*), 3.00–2.65 (m, 6H, SCH_2CH$_2$CH_2S, CH_2CHOH), 2.19 (s, 3H, CH_3), 2.11–1.87 (m, 2H, SCH$_2$CH_2CH$_2$S); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.2, 68.8, 51.0, 47.5, 31.1, 28.3, 27.9, 25.7; HRMS (EI+) exact mass calcd for $[M]^+$ ($C_8H_{14}O_2S_2$) requires *m*/*z* 206.0435, found *m*/*z* 206.0429; $[\alpha]_D^{21}$=+34.2 (*c*=1.0, $CHCl_3$).

3.2.21. (3*S*,4*R*)-4-[1,3]Dithian-2-yl-3,4-dihydroxy-butan-2-one (Table 2, entry 9). Acetol (541 mg, 0.50 mL, 7.30 mmol) was added to a suspension of [1,3]dithiane-2-carbaldehyde (37 mg, 0.25 mmol) and L-proline (2.9 mg, 0.025 mmol) in 2.0 mL DMF at room temperature. After stirring at room temperature for 12 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were extracted with five portions of ethyl acetate. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo to yield a waxy white solid. Analysis of the crude reaction mixture by ^1H NMR revealed an >20:1 *anti*–*syn* mixture of diastereoisomers. The crude white solid was triturated twice with diethyl ether. Syringe removal of the ether yielded the title compound as a dry white solid 88% yield (46 mg, 0.22 mmol), >20:1 dr, >99% ee. Product ee was measured by chiral HPLC (AD column, 12% EtOH in hexanes) relative to a racemic sample; (3*S*,4*R*) *anti* isomer t_r=108.0 min, (3*R*,4*S*) *anti* isomer t_r=128.3 min, *syn* isomers not detected. The product was recrystallized from boiling acetone. The resulting crystals were analyzed by X-ray crystallogrphy to obtain confirmation of both relative and absolute stereochemistry. IR (film) 3370, 3304, 1673, 1386, 1357, 1262, 1222, 1126, 1060, 1005, 913 cm^{-1}; ^1H NMR (300 MHz, C_2D_6SO) δ 5.81 (d, *J*=5.1 Hz, 1H, C(O)CHO*H*), 5.56 (d, *J*=6.0 Hz, 1H, CH(O*H*)C(S)S), 4.23 (d, *J*=3.6 Hz, 1H, SC*H*S), 4.00 (m, 1H, C(O)C*H*OH), 3.90 (m, 1H, C*H*(OH)CS), 3.00–2.68 (m, 4H, SCH_2CH$_2$CH_2S), 2.16 (s, 3H, CH_3), 1.98 (m, 1H, SCH$_2$CH_2CH$_2$S), 1.82 (m, 1H, SCH$_2$CH_2CH$_2$S); ^{13}C NMR (75 MHz, C_2D_6SO) δ 210.7, 77.9, 76.0, 49.5, 29.5, 28.8, 27.6, 26.7; HRMS (EI+) exact mass calcd for $[M]^+$ ($C_8H_{14}O_3S_2$) requires *m*/*z* 222.0385, found *m*/*z* 222.0382; $[\alpha]_D$=+13.0 (*c*=1.0, EtOH).

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