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trans-1,3-Dithiane-1,3-Dioxide; a Chiral Acyl Anion Equivalent. Enantioselective Synthesis of α-Hydroxy- Carboxylic Acids, Esters, Amides and Ketones

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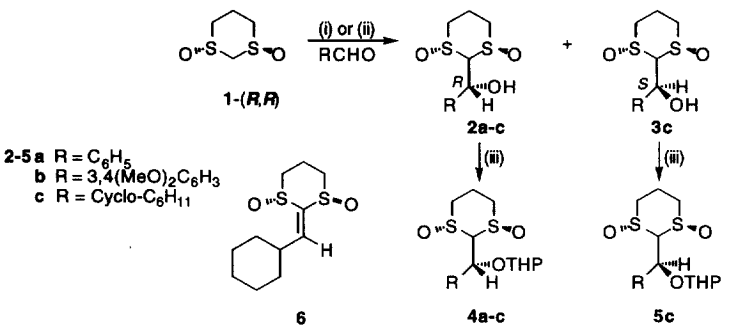
Abstract: The reaction of (*R*,*R*)-(+)-1,3-dithiane-1,3-dioxide with aldehydes has been carried out and the dithiane dioxide moiety elaborated further. (*R*,*R*)-(+)-1,3-Dithiane-1,3-dioxide gave highly diastereoselective addition products with benzaldehyde and 3,4-dimethoxybenzaldehyde and single diastereomers were isolated in 84 and 76% purified yields respectively. Under similar conditions cyclohexane carboxaldehyde gave an easily separable mixture of diastereomers in 86% total isolated yield. The adducts were transformed into protected S-ethyl α-hydroxythioesters in 95-100% ee *via* a Pummerer reaction and subsequent trans-thioesterification protocol using LiSEt. Using LiSEt little racemisation occurred even with aryl substituted thioesters. Further transformations of thioesters to various α-hydroxy carboxylic acid derivatives (acids, esters, amides) without racemisation have been achieved. The approach resulted in the synthesis of the dimethyl ether of (*R*)-(−)-3,4-dihydroxymandelic acid in its naturally occurring form. Addition of dibutyl cuprate (derived from BuMgBr and Cu(I)Br) to the thioester gave the corresponding ketone in high yield and again without racemisation. © 1997 Elsevier Science Ltd.

The use of chiral enolates in reactions with carbonyl compounds or imines for control of stereochemistry in the synthesis of β-substituted carbonyl compounds is well established.[1-6] However, it is more difficult to achieve stereochemical control using chiral nucleophiles in carbon-carbon bond disconnections of α-substituted carbonyl compounds. A number of chiral auxiliaries and chiral reagents for this type of transformation have been developed. Eliel[7] has used the addition of 1,3-oxathianes to aldehydes to access secondary and tertiary α-hydroxy acids; the diastereoselectivity of aldehyde addition is poor, but high diastereoselectivities are obtained after Swern oxidation and re-reduction of the adducts. A chiral dibromoolefin has been used as a carbonyl anion equivalent by Braun[8] who achieved high diastereoselectivity in additions to prochiral sulfonylimines to provide precursors to N-protected α-amino aldehydes. Corey has developed a chiral allenyl anion and obtained high diastereoselectivity in addition reactions with aldehydes.[9] Ozonolysis of the allenyl group then furnishes α-hydroxy carbonyl compounds. We have previously shown that addition of 1,3-dithiane-*trans*-1,3-dioxide to aromatic aldehydes proceeds with high diastereoselectivity.[10] In this paper we describe a method for converting the adducts into α-hydroxythioesters and subsequent transformations of the α-hydroxythioesters into α-hydroxyesters, -acids, -amides and -ketones without racemisation even with particularly sensitive substrates.[11]

The reaction of (+)-*trans*-1,3-dithiane-1,3-dioxide **1** (readily available in two steps[12]) with selected aldehydes is shown in Scheme 1 and Table 1. As expected high diastereoselectivity was obtained with aromatic aldehydes (entries 1, 2) using NaHMDS as base under equilibrating conditions but only poor

selectivity was obtained with cyclohexane carboxaldehyde.[10] However, in the latter case a significant amount of elimination product **6** was also isolated in the NaHMDS mediated reaction. This was avoided using LiHMDS and higher yields of the adducts were obtained, but still with low diastereoselectivity (entry 3).[10] The diastereomers **2c** and **3c** could be easily separated by column chromatography and both were utilised for further transformations.



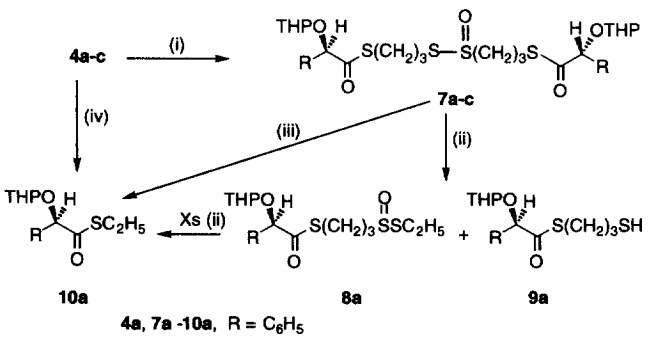
Scheme 1. Reagents and conditions: (i) NaHMDS, Py, THF, 0°C; (ii) LiHMDS, Py, THF, –78- -50°C; (iii) 3,4-DHP, PTSA, CH_2Cl_2, 0°C-rt.

Table 1: Reaction of *trans*-1,3-dithiane-1,3-dioxide with aldehydes

Entry	R	Base	Diastereomeric ratio (**2** : **3**)	Yield %
1	C_6H_5	NaHMDS	>98 : 2	84[a]
2	3,4-$(CH_3O)_2C_6H_3$	NaHMDS	>97 : 3	76[a]
3	Cyclo-C_6H_{11}	LiHMDS	47 : 53	86[b]

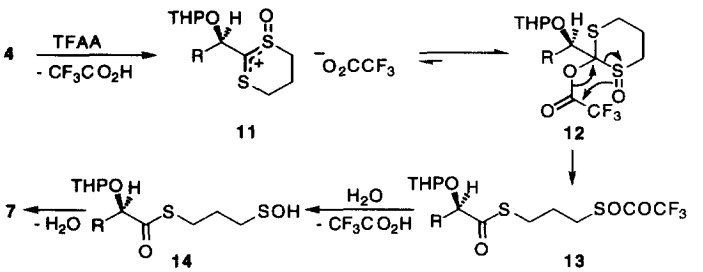
[a]Isolated yield of pure diastereomer **3**; [b]Total isolated yield of diastereomers **2** (40%) and **3** (46%).

The adduct **2a** was protected as the tetrahydropyranyl ether[13] **4a**, which was found to be the best protecting group for our synthetic transformations although the NMR spectrum, as expected, was complicated due to the formation of diastereoisomers. This product was subjected to a Pummerer reaction[14] using trifluoroacetic anhydride (TFAA) in CH_2Cl_2[15] and a rapid reaction occurred giving thiosulfinate **7a** as a mixture of isomers in nearly quantitative yield.



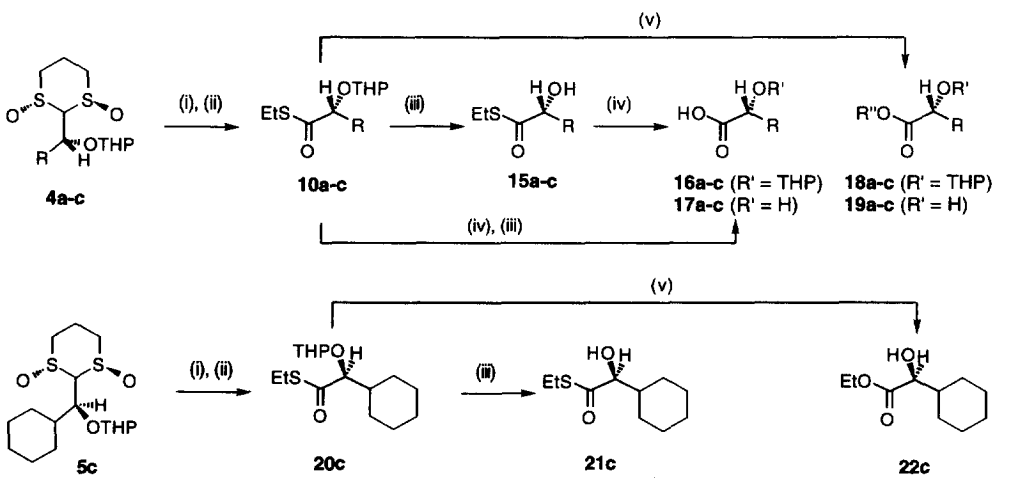
Scheme 2. Reagents and conditions: (i) TFAA, Py, CH_2Cl_2, 0°C; (ii) EtSH, NaSEt, THF; (iii) EtSH, LiOH.H_2O, aq. THF, 0°C, 1.5 h, (iv) TFAA, THF, Py, then EtSH, LiOH.H_2O.

The mechanism for the formation of the thioester **7a** is depicted in Scheme 3 and follows from the known chemistry of sulfenic acids to self condense and form thiosulfinates.[16] It should be noted that as an alternative, aqueous hydrolysis of **12** (water during work-up) would give **14** directly.



Scheme 3

The dimeric thioester **7a** was found to be unsuitable for some of our synthetic transformations; it was sensitive even to mild acidic and basic conditions due to the thiosulfinate moiety. We therefore had to remove this group and considered carrying out a trans-thioesterfication reaction.[17] Initial attempts using a stoichiometric (2 eq.) amount of sodium ethanethiolate[18] and excess EtSH in THF resulted in the formation of *S*-ethyl thiosulfinate **8a**, as well as a small amount of the desired thioester **10a** (Scheme 2). However, using an excess of NaSEt (8 eq.) gave the desired thioester **10a** in 92% yield. The adduct **4a** could also be transformed to **10a** in a one-pot operation by carrying out the Pummerer reaction in THF and subsequent direct sulfinylation with excess sodium ethanethiolate. However, **10a** obtained using excess sodium ethanethiolate was only 90% ee[19] indicating that a degree of racemisation had occurred during one of the transformations. Since there are several literature examples of Pummerer reactions occurring without loss of optical purity on substrates bearing readily epimerisable protons,[15,20-24] we assumed that the subsequent basic transthioesterification step was responsible for the partial racemisation. We also recognised that in attempting to manipualte a thioester bearing an aromatic ring we had a substrate that was highly sensitive towards



Scheme 4. Reagents and conditions: (i) TFAA, Py, CH_2Cl_2, 0°C; (ii) EtSH, LiOH.H_2O, aq. THF, 0°C, 1.5 h; (iii) PPTS, EtOH, 60°C, 6 h; (iv) H_2O_2, THF-H_2O, O°C, 0.5 h; (v) $Hg(OCOCF_3)_2$, $BF_3.OEt_2$, MeOH or EtOH reflux, 1 h.

Table 2: Formation and Interconversion of Thioesters

		thioesters		thioesters		acids		esters	
entry	substrate[a]	product	yield	product	yield (ee)	product	yield (ee)	product	yield (ee)
1	**4a**	**10a**	86%	**15a**	100% (98%[b])	**17a**	86% (97%[c])	**19a** (R"=Me)	90% (97%[b])
2	**4b**	**10b**	89%	**15b**	98% (95%[d])	**17b**	89% (94%[d])	**19b** (R"=Me)	83% (95%[d])
3	**4c**	**10c**	77%	**15c**	96% (98%[b])	**17c**	90% (97%[c])	**19c** (R"=Et)	78% (98%[b])
4	**5c**	**20c**	75%	**21c**	98% (100%[b])	-	-	**22c**	79% (100%[b])

[a] Substrate used for subsequent Pummerer reaction. [b] ee determined by chiral HPLC. [c] ee determined after conversion to methyl ester. [d] ee determined by NMR using TFAE in $CHCl_3$.

racemisation.[25] After considerable experimentation we found that using an excess of the less basic LiSEt, racemisation could indeed be suppressed and good yields of the corresponding thioester obtained. The other adducts **4b, c,** and **5c** were similarly converted to thioesters without racemisation (Scheme 4, Table 2).

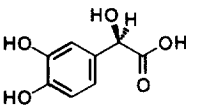
Thioesters are excellent intermediates, suitable for functional group manipulations and C–C bond constructions by displacement of the alkylthio group. We have realised these goals using selected transformations and the results are described below.

We initially attempted transesterification of **10a** to the methyl ester **18a** (Scheme 3) but only obtained poor yields and/or mixtures of products using literature conditions[26-30] e.g. $Hg(OCOCF_3)_2$[27] or $HgCl_2$[26] in methanol gave only partial conversion to the ester even after 24 h at reflux. In addition, partial loss of the THP group in both starting material and product occurred giving rise to a very complex mixture. The problem was circumvented by modifying the conditions using $Hg(OCOCF_3)_2$ in combination with $BF_3.OEt_2$. The reaction was extremely fast and directly delivered the hydroxy ester **18a** in 90% isolated yield. The $BF_3.OEt_2$ evidently assists the transesterification process in addition to catalysing the hydrolysis of the THP group. Unlike the basic reaction conditions, acidic reaction conditions were well tolerated and virtually no racemisation was detected with any of the thioesters **10b, c** and **20c** (Table 2).

The thioester **10a** was hydrolysed to the carboxylic acid **16a** in good yield with lithium hydroperoxide in aq. THF using Evans' hydrolysis conditions of carboximides.[31] However, conversion of **16a** to **17a** gave an unacceptably low yield but reversing the reaction sequence (deprotection of the THP group followed by hydrolysis) gave (*R*)-(–)mandelic acid **17a** in 86% isolated yield and 97% optical purity as determined by the HPLC analysis of its methyl ester. Again this was applied to the other thioesters **10b, c** (Table 2).

One reason for choosing 3,4-dimethoxybenzaldehyde as one of the test aldehydes was because of the common occurrence of the 3,4-dihydroxylated aryl ring (or their corresponding ethers) in compounds with potent β-adrenoceptor agonist activity. [32] (*R*)-(–)-3,4-Dihydroxymandelic acid **23** is a naturally occurring compound and has similar biological activity to DOPA, dopamine, epinephrine and normetanephrine[33] but

has not been synthesised in enantiomerically pure form although derivatives have been resolved.[32] Our route provides the (*R*)-(–)-acid **17b** in 56% overall yield from **2b** in 94% enantiomeric purity. At the present time we have not yet been able to cleave the methoxy groups.



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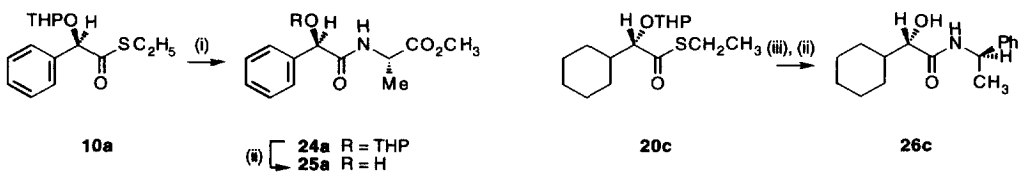
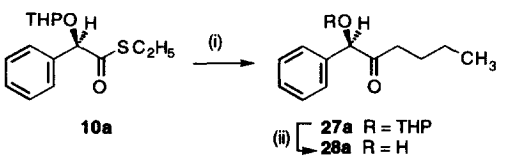
We have successfully utilised thioesters for the synthesis of α-hydroxyamides through a Ag(I) mediated coupling process.[34,35] Thus, reaction of thioester **10a** with L-alanine methylester in the presence of $AgOCOCF_3$ in acetonitrile for 16 h afforded the THP amide **24a** in 89% isolated yield. THP ether cleavage of **24a** using PPTS in EtOH afforded the hydroxy amide **25a** in quantitative yield and without any further racemisation (Scheme 5). Thioester **20c** was coupled in a similar manner to (+)-α-methylbenzylamine thus demonstrating the broad reactivity of different thioesters with different amines (including relatively non-nucleophilic amines).



Scheme 5. Reagents and conditions: (i) $AgOCOCF_3$, (L)-(–)-methylalanate, CH_3CN, 50°C, 16 h; (ii) PPTS, EtOH, 60°C, 6 h, 100%; (iii) *R*-(+)-α-methylbenzylamine, $AgOCOCF_3$, CH_3CN, 70°C, 20 h.

Finally we have attempted ketone synthesis through the displacement of ethylthio group using carbon nucleophiles. Several examples of the conversion of thioesters to ketones *via* a Fe(III) catalyzed Grignard reaction[36-38] or by an organocuprate reaction have been reported.[39-41] We initially attempted the ketone synthesis *via* an organocuprate reaction.[39] The reaction of **10a** with dibutylcuprate generated from *n*-butyllithium and $CuBr.S(CH_3)_2$ at -60°C afforded the hydroxy protected ketone **27a** in 93% isolated yield but with only 42% ee (determined by HPLC analysis of the alcohol **28a**). As cuprates are widely regarded as non-basic reagents, we assumed that alkoxides (derived from commercial *n*-butyllithium) were responsible for the partial racemisation observed. We therefore focused on the application of the Fe(III) catalysed Grignard reaction. However, we could not effect ketone formation using *n*-butylmagnesium bromide solution in the presence of 10 mol-% $Fe(acac)_3$ at 0°C.[36] We therefore considered the use of an organocuprate-catalysed addition with a Grignard reagent.[39] Whilst no reaction occurred at -78°C, at -15°C the ketone was obtained in 92% yield and in 95% ee (Scheme 6).[42] The results show that racemisation in the synthesis of ketone can be avoided if *Grignard* reagents are used in the cuprate addition.



Scheme 6. Reagents and conditions: (i) BuMgBr, $Me_2S.CuBr$, THF, – 15°C, 0.4 h, 92%; (ii) PPTS, EtOH, 60°C, 6 h, 90%.

In conclusion, we have developed a new and efficient synthesis of chiral thioesters bearing a protected α-hydroxy functionality using enantiomerically pure 1,3-dithiane-1,3-dioxide. The thioesters have been successfully transformed into a range of functional groups including acids, esters, amides and ketones without racemisation even with aryl substituted substrates.

Acknowledgements: We thank Sheffield University for support.

Experimental

General: (+)-*Trans*-dithane dioxide **1** was prepared as previously described[12] and all aldehydes were freshly distilled.

General method for NaHMDS induced addition of dithiane dioxide to aldehydes: Synthesis of (1*R*,3*R*)-1,3-Dithiane-1,3-dioxide-2-[(1*R*)-1-phenyl]methanol 2a: To a stirred solution of (+)-*trans*-dithane dioxide **1** (912 mg, 6.0 mmol) in a dry pyridine (50 ml)-THF (30 ml) mixture under nitrogen at 0°C was added 1.0*M* NaHMDS in THF (6.5 ml, 6.5 mmol). After 0.5 h at 0°C freshly distilled benzaldehyde (0.65 ml, 678 mg, 6.4 mmol) was added neat and further stirred for 0.5 h to give a clear pale brown homogeneous solution. The reaction was quenched with precooled 10% solution of 2.0*M* HCl in EtOH (120 ml). The solvents were evaporated under reduced pressure and the residue was taken up in EtOH and preadsorbed on silica gel. Column chromatography on silica gel using neat acetone as eluent gave 1.30 g (84%) of the alcohol **2a** as a single diastereoisomer. Analytically pure sample was prepared by recrystallisation from MeOH-EtOAc as white needles, mp 166-167°C; ν_{max} (KBr) ca. 3201 (br), 2913, 1494, 1058, 1012 cm^{-1}; δ_H (250 MHz, DMSO-d_6) 7.54-7.24 (m, 5H), 6.07 (d, J = 5.6 Hz, 1H), 5.52 (dd, J = 5.6, 4.2 Hz, 1H), 4.18 (d, J = 4.2 Hz, 1H), 3.61-3.49 (m, 1H), 3.18-3.02 (m, 1H), 2.92-2.76 (m, 2H), 2.65-2.43 (m, 1H), 2.30-2.13 (m, 1H); δ_C (63 MHz, DMSO-d_6) 141.91, 128.66, 127.95, 126.98, 79.32, 68.14, 51.44, 46.21, 15.55; Anal. Calcd for $C_{11}H_{14}O_3S_2$: C, 51.14, H, 5.46; S, 24.82. Found: C, 51.33; H, 5.60; S, 24.98; EIMS *m/z* 259 (M^++1, 2%), 153 (85), 107 (100), 105 (60).

(1*R*,3*R*)-1,3-Dithane-1,3-dioxide-2-[(1*R*)-1-(3,4-dimethoxyphenyl)]methanol 2b. According to the above procedure, **1** (608 mg, 4.0 mmol) was reacted with 3,4-dimethoxybenzaldehyde (700 mg, 4.21 mmol) for 2 h at 0°C and afforded, after column chromatography (15% EtOH in $CHCl_3$), 822 mg of the alcohol **2b** (76% based on the consumed SM) and 91 mg (15%) of unreacted SM **1**. Recrystallisation from MeOH-acetone gave **2b** as colourless needles (mp 186-187°C); ν_{max} (KBr) ca. 3226 (br), 2933, 1521, 1012 cm^{-1}; δ_H (250 MHz, DMSO-d_6) 7.06-6.93 (m, 3H), 5.98 (brs, 1H), 5.44 (d, J = 4.2 Hz, 1H), 4.14 (d, J = 4.2 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.61-3.48 (m, 1H), 3.19-2.75 (m, 3H), 2.64-2.43 (m, 1H), 2.31-2.16 (m, 1H); δ_C (63 MHz, DMSO-d_6) 149.02, 148.63, 134.07, 119.06, 111.99, 110.61, 79.34, 67.95, 56.02, 55.97, 51.28, 46.22, 15.50; Anal. Calcd for $C_{13}H_{18}O_5S_2$: C, 49.04; H, 5.70; S, 20.14. Found: C, 48.98; H, 5.88; S, 20.23; EIMS *m/z* 318 (M^+, 9%), 284 (47), 236 (100), 165 (86).

LiHMDS mediated addition: (1*R*,3*R*)-1,3-Dithiane-1,3-dioxide-2-[(1*R*)-1-cyclo-hexyl]methanol 2c and (1*R*,3*R*)-1,3-Dithiane-1,3-dioxide-2-[(1*S*)-1-cyclohexyl]methanol 3c To a well stirred solution of dithiane dioxide **1** (760 mg, 5.0 mmol) in pyridine (40 ml) and THF (25 ml) under a nitrogen atmosphere was added

1.0*M* LiHMDS in THF (5.2 ml, 5.2 mmol) at 0°C. Lithiation was indicated by the immediate formation of a white curdy precipitate. The mixture was cooled to -78°C and cyclohexane carboxaldehyde (0.63 ml, 583 mg, 5.2 mmol) was added. The reaction mixture was warmed to ca. –50°C over an hour. At this temperature a clear homogeneous solution was observed indicative of completion of the reaction. The reaction mixture was quenched with 10% solution of 2.0*M* HCl in EtOH (100 ml) at the same temperature and worked up as in the general procedure. Careful column chromatography on silica gel using 10% EtOH in $CHCl_3$ gave the less polar diastereoisomer **3c** (602 mg, 46%) as white crystals (CH_2Cl_2-hexane); mp 168-169°C; ν_{max} (KBr) 3432, 2922, 1421, 1018 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 4.33 (ddd, J = 9.3, 4.3, 4.1 Hz, 1H), 3.94 (d, J = 4.1 Hz, 1H), 3.73 (d, J = 4.3 Hz, 1H), 3.61-3.45 (m, 1H), 3.43-3.30 (m, 1H), 3.22-2.98 (m, 2H), 2.69-2.42 (m, 2H), 2.03-1.58 (m, 6H), 1.42-0.98 (m, 5H); δ_C (63 MHz; $CDCl_3$) 73.92, 72.74, 46.33, 43.88, 41.14, 29.28, 28.06, 26.09, 25.88, 25.62, 12.41; Anal. Calcd for $C_{11}H_{20}O_3S_2$: C, 49.97; H, 7.62; S, 24.25. Found: C, 50.01; H, 7.80; S, 24.06; EIMS *m/z* 264 (M^+, 29%), 247 (39), 181 (48), 123 (88), 83 (100). Further elution afforded the more polar diastereoisomer **2c** (533 mg, 40%) as white crystals (acetone-hexane); mp 199-200°C; ν_{max} (KBr) ca. 3268 (br), 2923, 1449, 1046, 1021 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 4.25 (ddd J = 10.0, 9.8, 5.1 Hz, 1H), 3.67-3.54 (m, 1H), 3.57 (d, J = 5.1 Hz, 1H), 3.41 (d, J = 10.0 Hz, 1H), 3.36-3.23 (m, 1H), 3.14-2.68 (m, 3H), 2.52-2.37 (m, 1H); 2.28-2.16 (m, 1H), 2.04-1.51 (m, 5H), 1.41-1.00 (m, 5H); δ_C (63 MHz, DMSO-d_6) 75.85, 70.38, 51.58, 45.73, 41.87, 29.55, 28.26, 26.38, 26.05, 25.92, 15.56; Anal. Calcd for $C_{11}H_{20}O_3S_2$: C, 49.97; H, 7.62; S, 24.25. Found: C, 49.83; H, 7.72; S, 24.02; EIMS *m/z* 264 (M^+, 13%), 247 (19), 181 (57), 123 (100).

Typical procedure for the preparation of THP ether: (1*R*)-Tetra-hydropyran-(2*RS*)-2-yl [(1*R*,3*R*)-1-(1,3-dithane-1,3-dioxide-2-yl)-1-phenyl]-methyl ether 4a. The alcohol **2a** (1.20 g, 4.65 mmol), was suspended in dry CH_2Cl_2 (25 ml) under nitrogen atmosphere at 0°C. 3,4-Dihydropyran (0.73 ml, 673 mg, 8.0 mmol) and PTSA (12 mg, 0.063 mmol) were added and stirred at 0°C-RT for 2 h. The reaction mixture was poured into aqueous saturated $NaHCO_3$ solution (50 ml) and extracted with CH_2Cl_2 (3 x 20 ml). Combined organic extracts were washed with brine (50 ml), dried (Na_2SO_4) and evaporated to give **4a** as colourless solid (1.50 g, 94%). Recrystallisation from CH_2Cl_2-hexane afforded analytically pure sample, mp 185-188°C; ν_{max} (KBr) 2922, 1061, 1017 cm^{-1}; δ_H (250 MHz, $CDCl_3$) (1:1 diastereomers) 7.58-7.23 (m, 5H), 5.67 (d, J = 5.0 Hz, 0.5 H), 5.58 (d, J = 5.0 Hz, 0.5H), 5.13 (brt, J = 3.2 Hz, 0.5 H), 4.65 (brt, J = 3.2 Hz, 0.5 H), 4.23-4.09 (m, 0.5H), 3.76-3.47 (m, 2H), 3.44 (d, J = 5.0 Hz, 0.5H), 3.40 (d, J = 5.0 Hz, 0.5H), 3.36-3.24 (m, 0.5 H), 3.21-3.06 (m, 1H), 3.01-2.78 (m, 2H), 2.73-2.54 (m, 1H), 2.46-2.25 (m, 1H), 2.13-1.30 (m, 6H); δ_H (63 MHz, $CDCl_3$) (diastereomeric signals) 139.12, 136.84, 128.93, 128.70, 128.28, 127.79, 126.97, 100.03, 94.33, 81.75, 80.94, 73.04, 70.87, 62.14, 61.64, 50.88, 45.73, 45.47, 30.08, 29.90, 25.45, 25.21, 18.78, 18.30, 14.07; Anal. Calcd for $C_{16}H_{22}O_4S_2$: C, 56.12; H, 6.47; S, 18.72. Found: C, 56.29; H, 6.55; S, 18.56; EIMS *m/z* 342 (M^+, 1%), 193 (55), 85 (100).

(1*R*)-Tetrahydropyran-(2*RS*)-2-yl [(1*R*,3*R*)-1-(1,3-dithane-1,3-dioxide-2-yl)-1-(3,4-dimethoxyphenyl)]-methyl ether 4b. According to the above procedure the alcohol **2b** (800 mg, 2.51 mmol) and DHP (0.46 ml, 424 mg, 5.0 mmol) were reacted in the presence of PTSA (10 mg, 0.053 mmol) for 2 h at 0°C-rt. Normal work-up and isolation gave 940 mg (93%) of **4b** as white gummy solid . Analytically pure sample was prepared by recrystallisation from CH_2Cl_2-hexane as white amorphous solid (mp 156-158°C; ν_{max} (KBr) 2935, 1518, 1040 1018 cm^{-1}; δ_H (250 MHz, $CDCl_3$) (4:1 diastereomers) 7.10-6.84 (m, 3H), 5.60 (d, J = 5.4

Hz, 0.8H), 5.52 (d, J = 5.4 Hz, 0.2 H), 5.10 (brt, J = 4.2 Hz, 0.2H), 4.65 (brt, J = 4.2 Hz, 0.8H), 4.21-4.06 (m, 1H), 3.88 (s, 6H), 3.75-3.54 (m, 2H), 3.44 (d, J = 5.4 Hz, 0.2 Hz), 3.40 (d, J = 5.4 Hz, 0.8H), 3.24-3.11 (m, 1H), 3.01-2.59 (m, 3H), 2.46-2.30 (m, 1H), 2.05-0.91 (m, 6H); δ_C (63 MHz; $CDCl_3$) 157.16, 156.88, 139.21, 136.77, 128.17, 127.13, 119.05, 118.90, 118.25, 117.86, 107.73, 102.42, 101.99, 89.51, 88.69, 80.68, 78.53, 70.72, 70.05, 69.42, 63.82, 63.71, 58.44, 53.42, 53.23, 38.49, 37.94, 37.72, 33.25, 33.03, 27.55, 26.63, 26.13, 21.82, 21.75; Anal. Calcd for $C_{18}H_{26}O_6S_2$: C, 53.71; H, 6.51; S, 15.93. Found: C, 53.46; H, 6.69, S, 15.88; EIMS m/z 402 (M^+, 1%), 300 (4), 85 (28), 55 (100).

(1*R*)-Tetrahydropyran-(2*RS*)-2-yl [1-cyclohexyl-(1*R*,3*R*)-1-(1,3-dithiane-1,3-dioxide-2-yl)]methyl ether 4c. According to the typical procedure the alcohol **2c** (480 mg, 1.82 mmol), DHP (0.40 ml, 370 mg, 4.40 mmol) and PTSA (9.0 mg, 0.047 mmol) were stirred together at 0°C-rt for 3 h. Work-up and isolation as in the general procedure afforded 607 mg (96%) of **4c.** Recrystallisation from CH_2Cl_2-hexane gave **4c** as white amorphous solid: mp 190-192°C; ν_{max} (KBr) 2922, 1452, 1028 cm^{-1}; δ_H (250 MHz, $CDCl_3$) (7:3 diastereomers) 4.94-4.87 (m, 0.7H), 4.73 (brt, J = 3.9 Hz, 0.3H), 4.53 (dd, J = 5.1, 3.0 Hz, 0.7H), 4.38 (dd, J = 5.1, 3.0Hz, 0.3H), 4.23-4.10 (m, 0.3H), 3.97-3.84 (m, 0.7H), 3.77-3.63 (m, 1H), 3.58-3.44 (m, 1H), 3.40-3.30 (m, 1H), 3.18-2.57 (m, 4H), 2.42-2.25 (m, 1H), 2.03-1.40 (m, 13H), 1.33-0.89 (m, 4H); δ_C (63 MHz, $CDCl_3$) (diastereomeric signals) 100.08, 99.23, 78.11, 77.93, 74.52, 73.75, 63.72, 62.69, 54.30, 53.78, 47.15, 46.45, 43.11, 41.83, 30.41, 30.33, 29.51, 28.93, 28.58, 26.21, 26.06, 25.98, 25.42, 25.34, 20.08, 19.01, 15.33, 15.26; Anal. Calcd for $C_{16}H_{28}O_4S_2$: C, 55.14; H, 8.10; S, 18.40. Found: C, 55.10; H, 8.28; S, 18.25; EIMS m/z 348 (M^+, 6%), 331 (36), 265 (50), 248 (61), 123 (96), 55 (100).

(1*S*)-Tetrahydropyran-(2*RS*)-2-yl [1-cyclohexyl-(1*R*,3*R*)-1-(1,3-dithiane-1,3-dioxide-2-yl)]methyl ether 5c. Using the same procedure as was used for the preparation of **4c**, **3c** gave **5c** as colourless amorphous solid (94%); mp 182-185°C (CH_2Cl_2-hexane); ν_{max} (KBr) 2925, 2856, 1448, 1024 cm^{-1}; δ_H (250 MHz, $CDCl_3$) (2:3 diastereomers) 4.91-4.84 (m, 0.4H), 4.57-4.49 (m, 0.6H), 4.94 (dd, J = 5.3, 3.3 Hz, 0.6H), 4.31 (dd, J = 5.3, 3.3 Hz, 0.4H), 3.98-3.83 (m, 1H), 3.72-3.35 (m, 3H), 3.22-2.78 (m, 3H), 2.72-2.38 (m, 2H), 2.05-0.90 (m, 17H); δ_C (63 MHz, $CDCl_3$) (diastereomeric signals) 101.98, 99.60, 77.96, 75.07, 73.32, 73.11, 65.58, 63.56, 47.87, 47.48, 44.85, 44.77, 43.12, 41.78, 31.48, 30.62, 29.27, 28.84, 28.54, 28.21, 26.31, 25.98, 25.24, 25.07, 21.49, 20.09, 14.99, 13.48; Anal. Calcd for $C_{16}H_{28}O_4S_2$: C, 55.14, H, 8.10, S, 18.40, Found: C, 54.96, H, 8.01, S, 18.19; EIMS m/z 348 (M^+, 2%), 264 (26), 181 (37), 123 (62), 55 (100).

2-Methylenecyclohexyl-1,3-Dithane 1,3-dioxide 6. Colourless solid, mp 202-203°C; ν_{max} (KBr) 2928, 2856, 1050, 1032 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 6.52 (d, J = 11.0 Hz, 1H), 3.69-3.56 (m, 1H), 3.28-2.96 (m, 2H), 2.89-2.51 (m, 3H), 2.41-2.26 (m, 1H), 1.91-1.62 (m, 4H), 1.52-1.10 (m, 6H); δ_C (63 MHz; $CDCl_3$) 145.54, 142.66, 55.52, 49.37, 38.45, 32.90, 32.33, 25.35, 25.28, 25.05, 14.85; Anal. Calcd for $C_{11}H_{18}O_2S_2$ C, 53.62; H, 7.36; S, 26.02. Found: C, 53.41; H, 7.13, S, 25.92; EIMS m/z 246 (M^+, 45%), 229 (100), 181 (55), 123 (70).

General procedure for Pummerer reaction: Synthesis of *S*-[[(1*R*)-1-Phenyl-1-tetrahydropyran-(2*RS*)-2-yloxy]thioacetyl]-*S*-propyl[[(1*R*)-1-phenyl-1-tetrahydropyran-(2*RS*)-2-yloxy]thioacetyl]-*S*-propane-thiosulfinate 7a. To a stirred solution of THP ether **4a** (1.45 g, 4.23 mmol) in dry CH_2Cl_2 (50 ml) at 0°C under a nitrogen atmosphere were successively added dry pyridine (0.80 ml, 782 mg, 10.0 mmol) and freshly

distilled TFAA (0.85 ml, 1.26 g, 6.0 mmol) and stirred for 15 minutes. The reaction mixture was quenched with cold water and diluted with CH_2Cl_2 (50 ml). The layers were separated and the organic layer was washed with water (2 x 60 ml) and brine (60 ml), dried (Na_2SO_4) and evaporated to give the crude thiosulfinate ester **7a** as viscous gummy liquid (1.34 g, 95%): ν_{max} ($CHCl_3$) 2941, 1740, 1688, 1030 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.53-7.20 (m, 10H), 5.30-5.14(m, 2H), 5.02-4.84 (m, 1.2H), 4.64-4.51 (m, 0.8H), 4.11-3.73 (m, 2H), 3.71-3.34 (m, 2H), 3.25-2.53 (m, 4H), 3.07 (t, J = 6.9 Hz, 2H), 2.24 (quint, J = 7.0 Hz, 2H), 2.14-1.37 (m, 16 H).

***S*-Ethyl [[(1*R*)-1-phenyl-1-tetrahydropyran-(2*RS*)-2-yloxy]thioacetyl]-*S*-propanethiosulfinate 8a.** Colourless viscous liquid, ν_{max} (film) 2943, 1688, 1119, 1033 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.53-7.27 (m, 5H), 5.27 (s, 0.4H), 5.25 (s, 0.6 H), 4.93 (brt, J = 3.6 Hz, 0.4 H), 4.65 (brt, J = 3.6 Hz, 0.6H), 4.05-3.93 (m, 2H), 3.70-3.89 (m, 2H), 2.91 (q, J = 7.2 Hz, 2H), 2.74-2.59 (m, 4H), 2.09-1.49 (m, 8H), 1.27(t, J = 7.2 Hz, 3H), δ_C (63 MHz; $CDCl_3$) 201.62, 200.07, 136.91, 136.45, 128.85, 128.75, 128.69, 128.61, 128.48, 128.31, 127.55, 126.99, 126.73, 98.07, 95.45, 82.11, 81.74, 77.62, 62.01, 61.95, 37.62, 37.55, 32.71, 30.16, 29.97, 28.81, 26.87, 25.41, 25.23, 18.55, 14.45; Anal. Calcd for $C_{18}H_{26}O_4S_3$: C, 53.70; H, 6.51; S, 23.89. Found: C, 53.96; H, 6.59; S, 23.70; EIMS *m/z* 386 (M^+–16, 2%), 302 (10), 191 (33), 107 (55), 85 (100).

Typical procedure for transthioesterification of thiosulfinate ester 7a: Synthesis of (1*R*)-*S*-Ethyl [1-phenyl-1-tetrahydropyran-(2*RS*)-2-yloxy]-thioacetate 10a. Lithium hydroxide monohydrate (235 mg, 5.59 mmol) was added to a stirred solution of crude **7a** (700 mg, 1.05 mmol) and ethane thiol (0.75 ml, 629 mg, 10.13 mmol) in ca. 3% aqueous THF (20 ml) at 0°C. The heterogeneous solution was stirred at 0°C for 1 h and the resulting pale brown solution was diluted with Et_2O (50 ml) and water (50 ml). The layers were separated. The aqueous layer was extracted with Et_2O (2 x 25 ml) and the combined organic extracts were washed with brine (25 ml), dried (Na_2SO_4) and evaporated. The crude product was purified over silica gel using 4% EtOAc in petrol as eluent to afford 482 mg (86%) of **10a** as colourless oil: ν_{max} (film) 2933, 1688, 1452, 1033 cm^{-1}; δ_H (250 MHz, $CDCl_3$) (2:3 diastereomers) 7.53-7.23 (m, 5H), 5.27 (s, 0.4H), 5.25 (s, 0.6H), 4.93 (brt, J = 3.6 Hz, 0.6H), 4.65 (brt, J = 3.6 Hz, 0.4H), 4.05-3.93 (m, 0.4H), 3.70-2.89 (m, 1.6H), 2.83 (overlapping q, J = 7.2 Hz, 2H), 2.13-1.42 (m, 6H), 1.27 (overlapping t, J = 7.2 Hz, 3H), δ_C (63 MHz, $CDCl_3$) (diastereomeric signals) 201.95, 200.35, 137.07, 136.59, 128.57, 128.44, 128.23, 127.59, 126.76, 98.04, 95.33, 82.12, 81.70, 61.94, 30.16, 29.97, 25.43, 25.25, 22.67, 18.59, 18.51, 14.36, 14.32; Anal Calcd for $C_{15}H_{20}O_3S$: C, 64.26; H, 7.19. Found: C, 64. 42; H, 7.21; EIMS *m/z* 280 (M^+, 30%), 149 (60), 113 (60), 71 (75), 57 (100).

(1*R*)-*S*-Ethyl [1-(3,4-dimethoxyphenyl)-1-tetrahydropyran-(2*RS*)-2-yloxy]-thioacetate 10b. Pummerer reaction of **4b** (750 mg, 1.86 mmol) as in the general procedure for **4a** using pyridine (0.40 ml, 395 mg, 5.0 mmol) and TFAA (0.30 ml, 446 mg, 2.12 mmol) and standard work up afforded the thiosulfinate **7b** as gummy viscous liquid (696 mg, 95%). The crude product (600 mg, 0.76 mmol) was subjected to trans-thioesterification using $LiOH.H_2O$ (160 mg, 3.80 mmol) and EtSH (0.60 ml, 503 mg, 8.10 mmol) as described above for 2 h at 0°C. Column chromatography of the residue on silica gel using 10% EtOAc in petrol gave 462 mg (89%) of **10b** as viscous liquid: ν_{max} ($CHCl_3$) 2944, 1688, 1518 cm^{-1}; δ_H (250 MHz, $CDCl_3$) (3:7 diastereomers) 7.07-6.80 (m, 3H), 5.19 (s, 0.3H), 5.16 (s, 0.7H), 4.90 (brt, J = 3.6 Hz, 0.3 H), 4.64 (brt, J = 3.6 Hz, 0.7H), 4.05-3.91 (m, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.71-3.40 (m, 1H), 2.84

(overlapping q, J = 7.0 Hz, 2H), 2.10-1.46 (m, 6H), 1.22 (overlapping t, J = 7.0 Hz, 3H); δ_C (63 MHz, $CDCl_3$) (diastereomeric signals) 201.95, 200.34, 149.37, 149.13, 149.03, 148.88, 129.60, 128.90, 120. 44, 119.37, 110.94, 110.28, 109.88, 98.07, 95.07, 81.91, 81.47, 62.03, 61.91, 55.89, 30.17, 29.97, 25.42, 25.23, 22.69, 18.66, 18.53, 14.39, 14.33; Anal Calcd for $C_{17}H_{24}O_5S$: C, 59.98; H, 7.11. Found: C, 60.26; H, 7.23; EIMS *m/z* 340 (M^+, 2%), 256 (14), 167 (85), 139 (80), 83 (100).

(1*R*)-*S*-Ethyl [1-cyclohexyl-1-tetrahydropyran-(2*RS*)-2-yloxy]thioacetate 10c. THP ether **4c** (540 mg, 1.55 mmol) was subjected to a Pummerer reaction as described in the general procedure using pyridine (0.35 ml, 342 mg, 4.33 mmol) and TFAA (0.40 ml, 595 mg, 2.83 mmol) at 0°C for 20 minutes. Standard work up and isolation following the general procedure gave 426 mg (81%) of **7c**. The thiosulfinate **7c** (360 mg, 0.53 mmol) was treated with EtSH (0.5 ml, 420 mg, 6.8 mmol) and $LiOH.H_2O$ (140 mg, 3.33 mmol) for 10 h at rt and worked up as in the general procedure. Column chromatography of the residue on silica gel (elution with 3% EtOAc in petrol) gave 234 mg (77%) of **10c** as a colourless oil: ν_{max} (film) 2918, 2845, 1676, 1446 cm^{-1}; δ_H (250 MHz, $CDCl_3$) (1:1 diastereomers) 4.65 (t, J = 4.3 Hz, 0.5 H) 4.59 (t, J = 4.3 Hz, 0.5 H), 4.04 (d, J = 6.0 Hz, 0.5H), 3.87 (d, J= 6.0 Hz, 0.5 Hz), 4.02-3.83 (m, 1H), 3.55-3.39 (m, 1H), 2.83 (overlapping q, J = 7.0 Hz, 2H), 1.99-1.46 (m, 12H), 1.35-0.98 (m, 5H), 1.24 (overlapping t, J = 7.0 Hz, 3H); δ_C (63 MHz, $CDCl_3$) (diastereomeric signals) 203.48, 202.30, 100.20, 98.07, 86.91, 85.38, 62.90, 62.70, 41.93, 41.77, 30.32, 30.25, 29.36, 29.05, 28.16, 27.85, 26.20, 26.14, 26.02, 25.33, 22.59, 22.39, 19.28, 19.20, 14.63; Anal. Calcd for $C_{15}H_{26}O_3S$: C, 62.90; H, 9.15. Found: C, 62.78; H, 9.18; EIMS *m/z* 286 (M^+, 1%), 258 (2), 197 (14), 85 (100).

Typical procedure for THP ether deprotection: (*R*)-*S*-Ethylthio mandelate 15a. A solution of thioester THP ether **10a** (140 mg, 0.5 mmol) and PPTS (12.6 mg, 0.05 mmol) in ethanol (3 ml) was stirred at 60°C (bath temperature) for 6 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on a silica gel column using 10% EtOAc in petrol to afford pure **15a** (98 mg, 100%); mp 50-51°C; ν_{max} (KBr) ca. 3316 (br), 1688, 1458 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.47-7.29 (m, 5H), 5.18 (d, J = 4.9 Hz, 1H), 3.86 (d, J = 4.9 Hz, 1H), 2.87 (overlapping q, J = 6.9 Hz, 2H), 1.22 (t, J = 6.9 Hz, 3H); δ_C (63 MHz; $CDCl_3$) 202.06, 138.21, 128.84, 128.75, 127.09, 79.93, 23.40, 14.37; Anal. Calcd for $C_{10}H_{12}O_2S$: C, 61.20, H, 6.16. Found: C, 60.98, H, 6.01; EIMS *m/z* 197 (M^++1, 1%), 168 (2), 107 (71), 77(100).

(*R*)-*S*-Ethylthio 3,4-dimethoxymandelate 15b The THP ether **10b** (164 mg, 0.48 mmol) was deprotectd as in the general procedure using PPTS (12 mg, 0.048 mmol) in EtOH (3.5 ml) at 60°C for 5 h. Column chromatography of the residue on silica gel using 30% EtOAc in petrol gave 121 mg (98%) of **15b** as a colourless solid, mp 64-65°C; ν_{max} (KBr) ca. 3460 (br), 3020, 1678, 1516 Cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.97 (dd, J = 8.0, 2.0 Hz, 1H), 6.89 (d, J = 2.0 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H) 5.15 (d, J = 3.8 Hz, 1H), 3.88 (s, 6H), 3.52 (d, J = 3.8 Hz, 1H) 2.90 (dq, J = 7.8 Hz, 2H), 1.23 (t, J = 7.8 Hz, 3H); δ_C (100 MHz; $CDCl_3$) 202.28, 149.43, 149.18, 130.67, 119.87, 111.01, 109.69, 79.62, 55.87, 23.34, 14.37; Anal. Calcd for $C_{12}H_{16}O_4S$: C, 56.23, H, 6.29. Found: C, 56.48; H, 6.23; EIMS *m/z* 256 (M^+, 23%), 167 (98), 139 (100), 124 (59).

(*R*)-*S*-Ethylthio cyclohexylglycolate 15c. Deprotection of **10c** (143 mg, 0.50 mmol) using PPTS (15 mg, 0.06 mmol) in EtOH (3 ml) for 10 h at 70°C as in the typical procedure and column chromatography of the

residue on silica gel using 8% EtOAc in petrol as eluent afforded 97 mg (96%) of **15c** as colourless oil: ν_{max} (film) 3446, 2928, 2850, 1680 1450 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 4.07 (dd, J = 6.3, 3.8 Hz, 1H), 2.93 (q, J = 7.2 Hz, 2H), 2.76 (d, J = 6.3 Hz, 1H), 1.87-1.58 (m, 6H), 1.54-1.43 (m, 1H), 1.42-1.06 (m, 4H), 1.27 (t, J = 7.2 Hz, 3H); δ_C (63 MHz; $CDCl_3$) 203.65, 81.72, 42.73, 29.48, 26.32, 26.00, 25.95, 25.48, 22.94, 14.66; Anal. Calcd for $C_{10}H_{18}O_2S$: C, 59.37; H, 8.97. Found: C, 59.50; H, 9.03; EIMS *m/z* 203 (M^++1, 71%), 176 (58), 143 (56), 92 (100).

General procedure for lithium hydroperoxide mediated hydrolysis of thioesters: (*R*)-(–)-mandelic acid 17a. To a stirred solution of thioester **15a** (60 mg, 0.30 mmol) in 10% aq. THF (1.5 ml) was added 30% aq. H_2O_2 (1.0 ml, ca. 10 mmol) followed by lithium hydroxide monohydrate (20 mg, 0.48 mmol). The resulting mixture was stirred at 0°C for 0.5 h, during which time a colourless solid separated out. The mixture was treated with excess 1.0*N* Na_2S0_3 solution (1.0 ml) to give a clear solution. After acidification (ca. pH 2-3) at 0°C with 10% HCl, the mixture was extracted with EtOAc (3 x 10 ml) and the combined organic extracts were washed with brine (10 ml), dried (Na_2SO_4) and evaporated to give the acid **17a** as a white solid. Recrystallisation from EtOAc-CH_2Cl_2 afforded 40 mg (85%) of **17a** which was identical in all respects with authentic (R)-(–)-mandelic acid: mp 131-132°C [lit.[43] mp 133-134°C], $[\alpha]_D^{25}$ -151.8 (c 0.82, H_2O) [lit.[43] $[\alpha]_D^{25}$ -178.4 (c 0.69, EtOH)].

(*R*)-(–)-3,4-Dimethoxy mandelic acid 17b. Hydrolysis of thioester **15b** (53 mg, 0.20 mmol) using 30% aq. H_2O_2 (0.80 ml, ca. 8.0 mmol) and lithium hydroxide monohydrate (16 mg, 0.38 mmol) in 10% aq. THF (1.0 ml) at 0°C for 0.5 h, and worked up as described for above to give **17b** as a gummy solid which failed to crystallise. The acid was chromatographed on a silica gel column using $CHCl_3$-MeOH-AcOH-H_2O (150:15:3:2) to afford **17b** (39 mg, 89%) as a colourless solid mp 97-98°C (CH_2Cl_2-CCl_4); $[\alpha]_D^{25}$ -112 (c 0.70 $CHCl_3$); ν_{max} (KBr), 3449, 2945, 2848, 1734, 1598 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.98 (dd, J = 7.9, 2.0 Hz, 1H), 6.93 (d, J = 2.0 Hz, 1H), 6.85 (d, J = 7.9 Hz, 1H), 5.19 (s, 1H), 3.87 (s, 6H); δ_C (100 MHz; $CDCl_3$) 177.37, 149.40, 149.14, 130.00, 119.30, 111.12 109.55, 72.47, 55.92; Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.60, H, 5.70. Found: C, 56.44, H, 5.70; EIMS *m/z* 212 (M^+, 42%), 167 (100), 139 (58).

(*R*)-(–)-Cyclohexylglycolic acid 17c. According to the general procedure thioester **15c** (47 mg, 0.23 mmol) in 10% aq. THF (1.0 ml) was treated with 30% aq. H_2O_2 (1.0 ml, ca. 10 mmol) and lithium hydroxide monohydrate (20 mg, 0.48 mmol). The resulting mixture was stirred at 0°C for 1.0 h, and worked up as described in the general procedure to give the known acid **17c** (33 mg, 90%) as a colourless solid (EtOAc-CH_2Cl_2), mp 130-131°C [Lit.[44] mp 127-129°C], $[\alpha]_D^{25}$ -15.5 (0.40, CH_3OH), [lit.[44] $[\alpha]_D^{25}$ -25.5 (c 1.0 HOAc)].

General procedure for Hg(II)trifluoroacetate assisted transesterification: Synthesis of (*R*)-(–)-Methyl mandelate 19a. To a stirred solution of thioester **10a** (62 mg, 0.22 mmol) in dry MeOH (2 ml) was added $Hg(OCOCF_3)_2$ (100 mg, 0.23 mmol). Freshly distilled $BF_3.OEt_2$ (0.06 ml, ca. 0.50 mmol) was added *via* a microsyringe and the mixture gently refluxed on a preheated oil bath for 1 h. The reaction mixture was cooled, MeOH was removed under reduced pressure and the residue was taken up in diethyl ether (15 ml). Saturated aq. $NaHCO_3$ solution (15 ml) was added and vigorously stirred to neutralise BF_3. The ether layer

was separated and the aqueous layer containing the mercury salts was extracted with ether (2 x 10 ml). The combined organic extracts were washed with brine (15 ml), dried (Na_2SO_4) and evaporated. Flash column chromatography on silica gel (10% EtOAc in petrol) afforded **19a** (33 mg, 90%) as a crystalline solid (dichloromethane-pentane): mp 56-57°C [lit.[45] mp 55°C], $[\alpha]_D^{25}$ -143.9 (c 0.32, MeOH) [lit[45] $[\alpha]_D^{25}$ -174.9 ($CHCl_3$)] which was identical in all respects with authentic (*R*)-(–)-methyl mandelate.

(*R*)-(–)-Methyl 3,4-dimethoxymandelate 19b. Ester **19b** was synthesised as described above from thioester **10b** (54 mg, 0.16 mmol), $Hg(OCOCF_3)_2$ (102 mg, 0.24 mmol) and $BF_3.OEt_2$ (0.06 ml, ca. 0.50 mmol) in MeOH (2.0 ml) for 1 h. Purification by chromatography using 50% EtOAc in petrol affordrd 30 mg (83%) **19b** as colourless semisolid. $[\alpha]_D^{25}$ -102.0 (c 0.93 CH_3OH); ν_{max} ($CHCl_3$) 3482 (br), 2960, 1745, 1518 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.97 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.93 (d, *J* = 2.3 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 5.12 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.76(s, 3H); δ_C (100 MHz; $CDCl_3$) 174.26, 149.01, 148.99, 130.76, 119.25, 111.05, 109.46, 72.69, 55.92, 53.03; Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24; Found: C, 58.59; H, 6.34; EIMS *m/z* 226 (M^+, 41%), 167 (100), 139 (82).

(*R*)-(–)-Ethyl cyclohexylglycolate 19c. The thioester **10c** (40 mg, 0.14 mmol) was transestrified using $Hg(OCOCF_3)_2$ (120 mg, 0.28 mmol) and $BF_3.OEt_2$ (0.05 ml, 0.43 mmol) in EtOH (2.0 ml) at reflux for 2 h. The reaction mixture was processed according to the general procedure and column chromatography on silica gel using 8% EtOAc-petrol gave 21 mg (77%) of **19c** as colourless crystals; mp 40-41°C; lit.[46] 44-45°C; $[\alpha]_D^{25}$ -18.6 (c 2.1, $CHCl_3$) [lit.[47] $[\alpha]_D^{30.5}$ -6.92 (c 39.6, $CHCl_3$); ν_{max} ($CHCl_3$) 3484, 2925, 2852, 1729 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 4.24 (q, *J* = 8.0 Hz, 2H), 3.97 (dd, *J* = 7.8, 4.2 Hz, 1H), 2.72 (d, *J* = 7.8 Hz, 1H), 1.85-1.07 (m, 6H), 1.46-1.38 (m, 1H), 1.28-1.05 (m, 4H), 1.29 (t, *J* = 8.0 Hz, 3H); δ_C (63 MHz; $CDCl_3$) 174.89, 74.81, 61.52, 41.98, 29.08, 26.31, 26.26, 26.03, 25.99, 14.25; EIMS *m/z* 186 (M^+, 15%), 111 (50), 83 (100).

(1*S*)-*S*-Ethyl [1-cyclohexyl-1-tetrahydropyran-(2*RS*)-2-yloxy]thioacetate 20c. Pummerer and trans-thioesterification of adduct **5c** as described for the preparation of **10c** gave **20c** (75%) as colourless oil. Spectral data of this compound was identical in all respects with that of (*R*)-(–) enantiomer **10c**.

(*S*)-*S*-Ethylthio cyclohexylglycolate 21c. Deprotection of **20c** following the procedure used for the preparation of **15c** afforded **21c** (98%) as a colourless oil. Spectral data of this compound was identical in all respects with that of (*R*)-(–) enantiomer **15c**.

(*S*)-(+)-Ethyl cyclohexylglycolate 22c. Esterification of **20c** following the procedure used for the preparation of **19c** afforded **22c** (79%) as a colourless oil. Spectral data of this compound was identical in all respects with that of (*R*)-(–) enantiomer **19c**, $[\alpha]_D^{25}$ +17.7 (c 1.54 $CHCl_3$).

General procedure for Ag(I)trifluoroacetate mediated aminolysis. Synthesis of (2*R*)-Methyl *N*-[2-phenyl-2-tetrahydropyran-(2*RS*)-2-yloxy]acetyl]-L-alaninate 24a. Silver(I)trifluoroacetate (442 mg, 2.0 mmol) was added to a solution of thioester **10a** (140 mg, 0.5 mmol) and L-alanine methyl ester (103 mg, 1.0 mmol) in dry CH_3CN (4.0 ml) and the mixture stirred at 50°C for 16 h under a nitrogen atmosphere. The solvent was evaporated under reduced pressure and the mixture was directly charged onto a silica gel column. Elution with 30% EtOAc in petrol afforded pure amide as a colourless viscous liquid (143 mg, 89%): ν_{max}

(film) 3420, 3329, 1748, 1681 cm^{-1}; δ_H (250 MHz; $CDCl_3$) (3:2 diastereomers) 7.55-7.16 (m, 6H), 5.18 (s, 1H), 4.86 (dist. t, J = 3.6 Hz, 0.6H), 4.61 (overlapping quint, J = 6.3 Hz, 1H), 4.54 (dist. t, J = 3.6 Hz, 0.4H), 3.93-3.78 (m, 1H), 3.75 (s, 1.5H), 3.73 (s, 1.5 H), 3.67-3.36 (m, 2H), 1.97-1.36 (m, 5H), 1.46 (overlapping d, J = 6.7 Hz, 3H); Anal. Calcd for $C_{17}H_{23}O_5N$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.81; H, 7.31; N, 4.66; CIMS *m/z* 266 (M^+– 55, 14%), 238 (80), 220 (41), 85 (100).

(2*R*)-Methyl *N*-[(2-hydroxy-2-phenyl)acetyl]-L-alaninate 25a. Deprotection of THP ether **24a** (98 mg, 0.30 mmol) using PPTS (8.0 mg, 0.03 mmol) in EtOH (3 ml) at 60°C for 3 h, as described in the general procedure and column chromatography of the residue using 40% EtOAc in petrol afforded 72 mg (100%) of **25a** as colourless viscous oil: ν_{max} ($CHCl_3$) ca. 3480-3061 (br) 1695, 1611 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.41-7.23 (m, 5H), 6.69 (brd, J = 6.2 Hz, 1H), 5.01 (s, 1H), 4.53 (quint, 6.3 Hz, 1H), 3.68 (s, 3H), 1.32 (overlapping d, J = 6.3 Hz, 3H); δ_C (63 MHz; $CDCl_3$) 173.25, 172.46, 139.43, 128.59, 128.38, 126.94, 74.10, 52.49, 47.84, 17.99; Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.52; H, 6.33; N, 5.94; EIMS *m/z* 237 (M^+, 6%), 187 (26), 107 (61), 85 (100).

(2*S*)-2-Cyclohexyl-2-hydroxy-*N*-[(1*R*)-1-phenylethyl]acetamide 26c. Aminolysis of **20c** was carried out as described in the general procedure above using the thioester **20c** (50 mg, 0.17 mmol), silver(I)trifluoroacetate (100 mg, 0.45 mmol) and (*R*)-(+) α-methylbenzylamine (0.08 ml, 75.2 mg, 0.62 mmol) in dry acetonitrile (2.0 ml) at 70°C for 20 h. Most of the solvent was evaporated under reduced pressure and the residue was filtered through a short length silica gel column using 50% EtOAc in petrol to remove excess amine and silver salts. The crude product containing small amounts of unreacted starting material was directly subjected to THP ether cleavage using PPTS (10 mg, 0.40 mmol) in EtOH (2.0 ml) for 6 h at 60°C. Ethanol was evaporated and the residue was column chromatographed on silica gel using 35% EtOAc in petrol to afforded 39 mg (85%) of **26c** as colourless crystals (CH_2Cl_2-pentane), mp 109-110°C; ν_{max} (KBr) 3381, 3273, 2922, 2853, 1646, 1555 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.41-7.20 (m, 5H), 6.70 (d, J = 7.6 Hz, 1H), 5.14 (quint, J = 7.8 Hz, 1H), 3.94 (dd, J = 5.9, 3.2 Hz, 1H), 2.57 (d, J = 5.9 Hz, 1H), 1.90-0.98 (m, 11H), 1.51 (d, J = 7.8 Hz, 3H); δ_C (63 MHz; $CDCl_3$) 172.07, 143.02, 128.67, 127.38, 126.14, 76.20, 48.44, 41.82, 29.60, 26.29, 26.08, 25.94, 25.78, 21.90; Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.58; H, 8.90; N, 5.27; EIMS *m/z* 261 (M^+, 39%), 243 (13), 179 (81), 105 (100).

Reaction of Bu_2CuLi with thioester 10a: (1*R*)-1-Phenyl-1-tetrahydro-pyran-(2*RS*)-2-yloxyhexane-2-one 27a.

Freshly crystallised $(CH_3)_2S{\cdot}CuBr$ (62 mg, 0.3 mmol) (prepared and recrystallised according to *House* et al.[48]) was placed in flame-dried 25 ml nitrogen flask. The flask was evacuated with a vacuum pump and purged with argon. This process was repeated three times. The complex was dissolved in dry dimethyl sulfide (0.15 ml) and THF (1.0 ml). The clear solution was cooled to –78 °C (part of the complex precipitated), and a freshly prepared butylmagnesium bromide solution (ca. 1.0 M in THF; 0.60 ml, 0.60 mmol) was added dropwise, the mixture was warmed to –15 °C, then the thioester solution **10a** (34 mg, 0.12 mmol; 2 diastereomers, diastereomeric ratio 63:37) was added in THF (0.5 ml). Stirring was continued for 30 min, then the mixture was quenched with 3 ml 10% aq. NH_3/90% sat. aq. NH_4Cl at the same temperature and extracted with diethyl ether (3 x 20 ml). The combined organic extracts were washed with brine (25 ml), dried (anhydrous sodium sulfate) and evaporated. Column chromatography of the crude product gave 31 mg (0.11

mmol, 92%; 2 diastereomers, diastereomeric ratio 50:50) of ketone **27a**: ν_{max} (film) 2960, 1724 cm^{-1}; δ_H (250 MHz; $CDCl_3$) (3:2 diastereomers) 7.44-7.20 (m, 5H), 5.20 (s, 0.4H), 5.12 (s, 0.6H), 4.74 (t, J = 3.2 Hz, 0.4H), 4.51(t, J = 3.2 Hz, 0.6H), 3.90-3.77 (m, 0.6H), 3.77-3.11 (m, 0.4H), 3.52-3.34 (m, 1H), 2.69-2.32 (m, 2H), 1.96-1.63 (m, 3H), 1.60-1.34 (m, 5H), 1.26-1.06 (m, 2H), 0.78 (overlapping t, J = 7.8 Hz, 3H); δ_C (63 MHz; $CDCl_3$) (diastereomeric) 209.29, 208.19, 136.56, 136.33, 128.59, 128.28, 128.16, 127.18, 127.02, 97.37, 96.72, 83.18, 82.48, 62.72, 61.95, 37.48, 37.42, 30.50, 30.34, 25.43, 25.31, 22.15, 22.11, 19.53, 18.83, 13.77, 13.70; Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.63; H, 8. 72; EIMS *m/z* 276 (M^+, 1%), 191 (59), 107 (50), 85 (100).

(*R*)-1-Hydroxy-1-phenylhexane-2-one 28a. Deprotection of **27a** (16 mg, 0.058 mmol) according to the general procedure furnished the hydroxy ketone **28a** (11 mg, 90%). ν_{max} (film) 3460, 2964, 1733 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 7.42-7.24 (m, 5H), 5.07 (s, 1H), 4.36 (brs, 1H), 2.33 (dt, J = 7.6, 2.3 Hz, 2H), 1.61-1.35 (m, 2H), 1.17 (sextet, J = 7.6 Hz, 2H), 0.79 (t, J = 7.6 Hz, 3H), δ_C (63 MHz; $CDCl_3$) 209.66, 138.15, 128.96, 128.67, 127.43, 79.68, 37.53, 25.74, 22.08, 13.64; Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.12, H, 8.21; EIMS *m/z* 192 (M^+, 10%), 107 (100), 79 (74).

Table 3: Methods of analysis of all chiral compounds

Compound	Methods & Conditions	UV-(λ) detection	Ret. time (min)/ Elution order	ee(%) & abs. config.
15a	HPLC[a] (i)	235	5.2:7.9 (*S:R*)	98 (*R*)
15b	^{1}H NMR	-	-	95 (*R*)[b]
15c	HPLC[a] (i)	235	5.6:7.0 (*S:R*)	98 (*R*)
17a	c	-	-	97 (*R*)
17b	^{1}H NMR	-	-	94 (*R*)[d]
17c[e]	HPLC[a] (ii)	220	4.6:6.5 (*S:R*)	97 (*R*)
19a	HPLC[a](ii)	254	5.7:9.7 (*S:R*)	97 (*R*)
19b	^{1}H NMR	-	-	95 (*R*)[f]
19c	HPLC[a] (iii)	220	3.6:5.3 (*S:R*)	98 (*R*)
21c	HPLC[a] (ii)	235	8.9 (*S*)	100 (*S*)
22c	HPLC[a] (i)	220	3.8 (*S*)	100 (*S*)
28	HPLC[a](iv)	254	4.5:5.7 (*S:R*)	95 (*R*)

[a]Chiralcel OD column (25 x 4.6 mm id); [b]5.0 mol eq. of (*R*)-(-)-TFAE in $CHCl_3$; [c]Direct ee measurement of acid **17a** by HPLC was unsuccessful. Therefore **17a** was converted into **19a** and ee measured by HPLC. [d]8 mol eq. of (*R*)-(-)-TFAE in $CHCl_3$; [e]Direct ee measurement of **17c** by HPLC was unsuccessful. The ee value quoted is for the methyl ester of **19c** prepared by esterification of **17c** with diazomethane. [f]6.0 mol eq. of (*S*)-(+)-TFAE in $CHCl_3$.

(i) 5.0% iPrOH in petrol, 2.0 cm^3/min; (ii) 5.0% iPrOH in petrol, 2.0 cm^3/min; (iii) 0-20% CH_3CN in H_2O over 20 min, 1.0 cm^3/min; (iv) 5.0% iPrOH in petrol, 2.0 cm^3/min.

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