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Enantioselective Synthesis of α-Methyl Carboxylic Acids using a DiTOX Chiral Auxiliary

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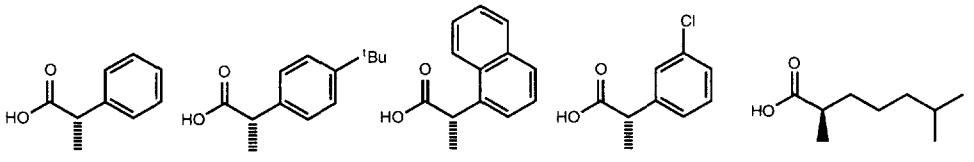
Abstract: Five α-methyl carboxylic acids have been prepared with high e.e.s using 1,3-dithiane 1-oxide (DiTOX) units as the stereocontrolling elements and sources of chirality.

Introduction

α-Methyl carboxylic acids are an important class of compounds well known for their anti-inflammatory and other biological activity; a number of methods for their racemic and asymmetric synthesis have been developed, one of the best involving asymmetric homogeneous catalysis in the hydrogenation of unsaturated carboxylic acids in the presence of BINAP-Ru(II) complexes,[1] and some excellent reviews have appeared.[2] Several are successfully marketed, perhaps the most well known example being ibuprofen. 2-Phenylpropanoic acid **1a** has anti-inflammatory, analgesic and antipyretic properties;[3] the *para*-*t*-butyl and *meta*-chloro derivatives **1b** and **1d** display anti-inflammatory activity;[4] and the 1-naphthyl derivative **1c** is a growth regulator.[5]



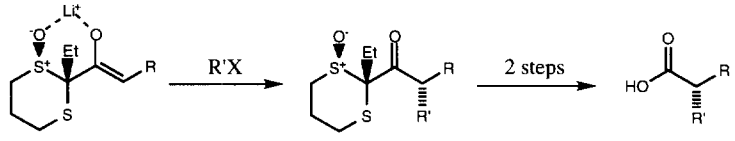
1a **1b** **1c** **1d** **1e**

We report herein full details of the enantioselective synthesis of each of these α-arylpropanoic acids **1a-d**[6] and of the aliphatic natural product derivative *R*-(–)-2,6-dimethylheptanoic acid **1e**[7] by stereoselective enolate alkylation, using 1,3-dithiane 1-oxide (DiTOX) units as the stereocontrolling elements and sources of chirality. The α-aryl examples provide a more challenging prospect due to the more ready racemization of the asymmetric centre. The routes chosen highlight two methods of removal of the DiTOX units, each proceeding through α-diketone intermediates, remarkably, without racemization taking place.

1,3-Dithiane 1-oxide derivatives can act as chiral auxiliaries or asymmetric building blocks for the enantioselective control of a wide range of reactions. For example, 2-acyl-2-alkyl-1,3-dithiane 1-oxides undergo highly diastereoselective inter- and intramolecular enolate alkylation, carbonyl group reduction, Grignard reagent addition, Mannich reaction, heterocycloaddition and conjugate addition reactions.[6-9] The acyl dithiane oxides are available enantioselectively, with both enantiomers available as the chirality is introduced using catalytic asymmetric sulfoxidation reactions.[10] A chelation control

model of the reactivity of these systems allows us to rationalise and in many cases predict the stereochemical outcome of the reactions studied.

We reasoned that stereocontrolled alkylation of chiral acyl dithiane oxide enolates **2** of high ee followed by removal of the DiTOX unit without racemization would lead to optically enriched acids **1** (Scheme 1). In the case of **1e**, this would involve enolate alkylation of a simple 2-propanoyl dithiane oxide system with 4-methyl-1-iodopentane, but for the other cases **1a-d** would require incorporation of the aryl unit into the enolate structure, which would then undergo methylation to give the desired products. These two routes would result in opposite absolute stereochemistry at the methyl group for the same chirality at sulfur, as required. The *anti*-2-ethyl-DiTOX system was selected as this system has shown the greatest diastereoselectivity in our previous studies of enolate alkylation.[6-8]



2 **1**

Scheme 1

A possible simple chelation-control model using steric approach control for acyl dithiane oxide reactivity is illustrated in figure 1. While this is certainly an oversimplification of the reaction process, it has provided a powerful predictive rule of thumb for many of the reaction types studied by us. For *anti* substrates such as these, the sulfoxide can only adopt a chelated conformation if the 2-substituent is axial, and the sulfoxide and acyl groups are equatorial, reasonable except for very large groups. One face of the enolate is then partially shielded by the 2-alkyl substituent, the bulk of the dithiane ring is distant from the reacting centre, and stereoselectivity is expected to be governed principally by the size of the 2-alkyl substituent. Stereoselectivity is therefore expected to improve as the relative size of the 2-alkyl substituent is increased, an effect indeed observed in our enolate alkylation studies.[8]

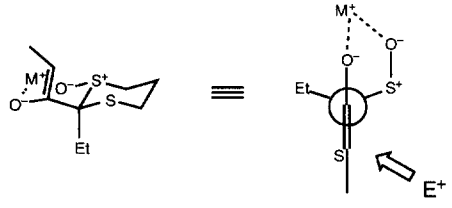
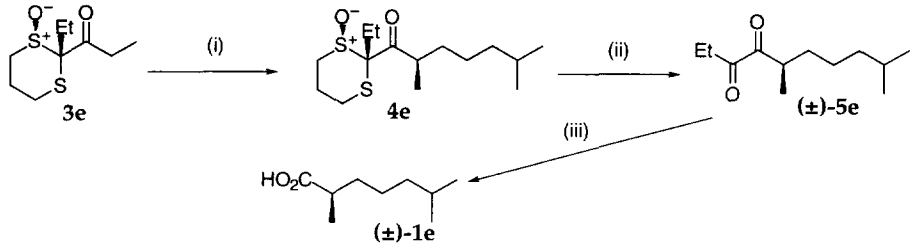


Figure 1

Initially, a synthesis of **1e** was completed in the racemic series. Preparation of (±)-**1e** requires alkylation of the enolate (±)-**2e** derived from (±)-*anti*-2-ethyl-2-propanoyl-1,3-dithiane 1-oxide (±)-**3e**. Deprotonation of **3e** under our usual conditions for this substrate,[8] with lithium hexamethyldisilazide at –78 °C in THF solution, and subsequent addition of 1-iodo-4-methylpentane, prepared from the alcohol *via* the bromide, was unsuccessful. Generation of the enolate under similar conditions, but in the presence of DMPU, resulted however in a very highly diastereoselective reaction upon treatment with 1-iodo-4-methylpentane, to give (±)-**4e** with no trace of the minor diastereoisomer at the alkylated centre visible in the 400 MHz ^{1}H NMR spectrum. The relative stereochemistry assigned to **4e** corresponds to preferential attack of the alkyl iodide at the least

hindered face of the chelated *Z*-enolate, as predicted, and was ultimately shown to be correct by unambiguous synthesis of (R)-(–)-**1e**, described below.[6-8] Cleavage to give the acid (±)-**1e** was accomplished through ready hydrolysis to the diketone (±)-**5e** by treatment with an excess of NBS in acetone–water (97:3) over 20 minutes,[11] followed by oxidative cleavage using aqueous sodium periodate in methanol (Scheme 2).[12]

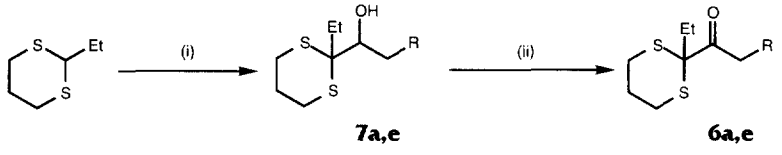


(i) LHMDS (1.1 eq), DMPU (10 eq), THF, –78 °C; 4-methyl iodopentane, –78 °C;
(ii) NBS (6 eq); Me_2CO-H_2O (97:3), 20 °C; (iii) $NaIO_4$ (aq), (2.2 eq), MeOH, 20 °C

Scheme 2

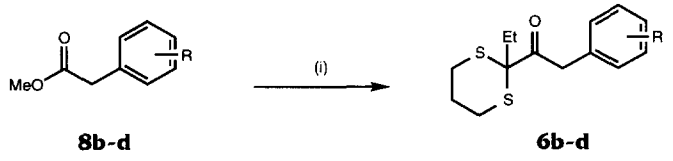
Synthesis of *anti*-1*R*,2*R*-2-acyl-2-ethyl-1,3-dithiane 1-oxides 3

Non-racemic acyl dithiane oxide substrates **3a-e** were prepared through either two or three step procedures. In both methods the final step was an asymmetric sulfur oxidation.[10] Acyl dithianes **6a** and **6e** were prepared by the reaction of the 2-lithio derivative of 2-ethyl-1,3-dithiane with phenylacetaldehyde and propanal respectively, to give alcohols **7a,e** which were oxidized using Swern conditions (Scheme 3). Acyl dithianes **6b-d** were constructed by the reaction of 2-lithio-2-ethyl-1,3-dithiane with the corresponding methyl esters **8b-d** (Scheme 4).



(i) BuLi (1.1 eq), THF, –20 °C; RCH_2CHO (1.1 eq), THF, –20 °C
(ii) DMSO (2.2 eq); TFAA (2.2 eq), NEt_3 (3 eq), CH_2Cl_2, –78 °C

Scheme 3

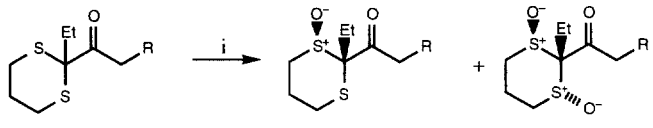


(i) 2-lithio-2-ethyl-1,3-dithiane (1.1 eq), THF, –20 °C

Scheme 4

For the enantiomerically pure series, 1*R*,2*R*-(+)-*anti*-2-ethyl-2-propanoyl-1,3-dithiane 1-oxide,

1*R*,2*R*-(+)-**3e**, predicted by our usual rule of thumb to lead to the correct absolute stereochemistry in the final product **1e**, was prepared by asymmetric sulfur oxidation of **6e** under the conditions of Kagan[13] at –30 °C using (+)-diethyl tartrate as chiral ligand, followed by crystallization to enantiomeric purity. Use of (+)-tartrate in these oxidations of our 2-acyl-DiTOX derivatives leads to the *R* configuration at the sulfoxide sulfur atom. Similar asymmetric sulfur oxidation of **6a-d** at –30 °C, again using (+)-diethyl tartrate as chiral ligand, proceeded cleanly in each case to give monosulfoxides 1*R*,2*R*-**3a-d** with excellent enantiomeric excesses without recrystallization (Scheme 5, Table 1). These oxidations were also highly diastereoselective, with only *anti* sulfoxides observed in all five examples. Some minor over-oxidation to the 1,3-dioxides **9a,b**, easily removed during purification by flash column chromatography, occurred with **6a,b**.



6a-e **3a-e** **9a,b**

(i) $Ti(O^iPr)_4$ (1.1 eq), (+)-diethyl tartrate (2.2 eq), H_2O (1 eq.), cumene hydroperoxide (1.5 eq); CH_2Cl_2, –30 °C

Scheme 5

Table 1. Asymmetric Sulfur Oxidation of Acyl Dithianes **6**

Substrate	R	Yield **3**/%	ee/%[a]	Yield **9**/%	ee/%[a]
6a	Ph	64	94	14	86
6b	4-tBu-C_6H_4	74	90	13	83
6c	1-naphthyl	72	94	0	–
6d	3-Cl- C_6H_4	63	88	0	–
6e	4-methylpentyl	56	≥99	0	0

[a] Determined by ^{1}H NMR shift experiments at 400 MHz in the presence of 5 to 10 mol. equiv. *R*-(–)-2,2,2-trifluoro-1-(9-anthryl) ethanol

Asymmetric enolate alkylation

Enolate generation from and alkylation of 1*R*,2*R*-(+)-**3e** exactly as described above for the racemic material led to enantiomerically pure 1*R*,2*R*,2'*R*-(+)-**4e** in 57% yield in an equally highly diastereoselective reaction (Scheme 2).

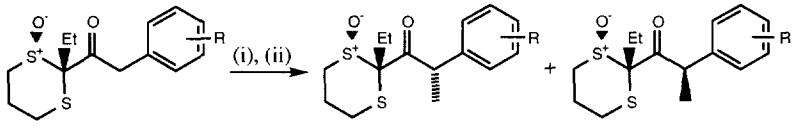
For the α-aryl series, a preliminary study of enolate methylation was first conducted using the simplest substrate **3a** (Scheme 6). Several bases and a range of counter-ions and temperatures of enolate generation and reaction were investigated. A selection of results for alkylation at –78 °C is given in Table 2, and shows that a wide range of diastereoselectivity was observed. Lithium proved to be the most suitable counter-ion, sodium and potassium giving very poor diastereoselectivities. No advantage in either stereoselectivity or yield was gained by reducing the temperature of enolate generation below –78 °C. In each case, the major diastereoisomer obtained was **4a**, again corresponding to preferential attack at the least hindered face of a chelated *Z* enolate, as expected.

Table 2. Deprotonation and Asymmetric Alkylation of **3a**

Base	Temp./°C	Ratio **4a**:**10a**[a]	Yield **4a**+**10a**/%
LHMDS	−100	17:1	82
LHMDS	−78	17:1	82
NHMDS	−78	2:1	75
KHMDS	−78	1:1	87
KO^{t}Bu	20	1.15:1	72

[a] Ratio determined by 400 MHz ^{1}H NMR spectroscopy

The stereochemistry of **4a** was confirmed by single crystal X-ray crystallographic analysis. Similar generation and alkylation of the chiral lithium enolates derived from **3b,c** at −78 °C with methyl iodide provided greater stereoselectivity than did the reaction with **3a**, presumably because the larger substituent groups exert a greater influence over the approach of the electrophile. We were however unable to generate the lithium enolate of **3d** under these conditions, but were pleased to find after some experimentation that the enolate generated using sodium hydride still resulted in moderate diastereoselectivity upon alkylation (Scheme 6; Table 3). In all cases the diastereoisomers **4** & **10** could be readily separated by flash column chromatography on silica gel.



3a-d **4a-d** **10a-d**

(i) LHMDS (**3a-c**) or NaH (**3d**) (1.1 eq); (ii) MeI (1.5 eq); THF −78 °C

Scheme 6

Table 3. Deprotonation and Asymmetric Alkylation of **3a-d**

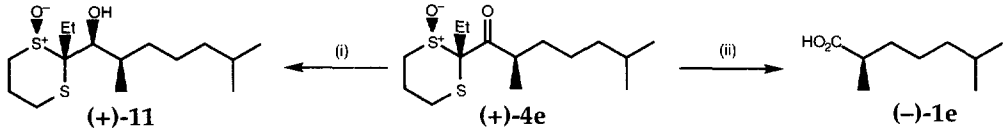
Substrate	R	Base	Temp/°C	Ratio **4**:**10**[a]	Yield of **4**/%
3a	H	LHMDS	−78	17:1	77
3b	4-tBu	LHMDS	−78	20:1	84
3c	2,3-(C_4H_4)	LHMDS	−78	exclusive[b]	80
3d	3-Cl	NaH	−78	7:1	70

[a] Ratio determined by 400 MHz ^{1}H NMR spectroscopy
[b] Minor isomer not observed by 400 MHz ^{1}H NMR spectroscopy

α-Methyl carboxylic acids

For the aliphatic system **1e**, in the case of nonracemic material, we had originally wished to avoid using the two-step procedure for conversion into acid *R*-(−)-**1e** *via* the α-diketone successful for the racemate, as this was expected to lead to racemization through ready enolization. Reduction of (+)-**4e** proceeded in good yield, again with very high diastereoselectivity,[9,14] thus introducing a second new contiguous asymmetric centre, but unfortunately the resulting alcohol 1*R*,2*R*,1'*S*,2'*R*-(+)-**11** proved resistant to hydrolysis to the keto alcohol. We therefore returned to simple base-mediated deacylation of (+)-**4e**, a technique also used by us [15] and others [16] to prepare non-racemic dithiane

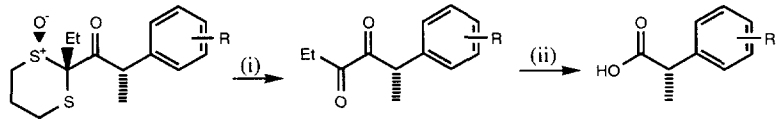
derivatives. Fortunately, this led directly to *R*-(–)-**1e**, we believe without loss of stereochemical integrity,[17] in 39% yield. The synthesis thus proceeds to give essentially optically pure *R*-(–)-**1e** in two steps from **3e**. Furthermore, the 2-ethyl-1,3-dithiane 1-oxide auxiliary is recoverable in optically pure form (Scheme 7).



(i) DIBAL (1.1 eq), $ZnCl_2$ (1.1 eq) THF, –78 °C; (ii) NaOH (10% aq)-EtOH (1:2), Δ, 3h

Scheme 7

For the α-aryl systems, base-mediated cleavage of the 1,3-dithiane 1-oxide units of **4a-d** to give the carboxylic acids in a similar way could not be accomplished, as such treatment led to racemization at best. Transformation into the carboxylic acids was eventually achieved by a return to the two-step procedure employed earlier, *via* the α-diketones, despite our trepidation concerning ready racemization. Hydrolysis of **4a-d** using NBS as before over 15-30 minutes at 0 °C furnished the α-diketones **5a-d** as bright yellow oils (Scheme 8).



(i) NBS (8 eq), acetone/water (97:3), 0 °C; (ii) $NaIO_4$ (2 eq), MeOH, 20 °C

Scheme 8

Table 4. Preparation of α-Arylpropanoic Acids **1a-d**

Substrate	R	Yield of **5**/%	Yield of **1**/%	ee/%
9a	H	96	80	93 [a]
9b	4-tBu	98	77	90 [a]
9c	2,3-(C_4H_4)	81	68	87 [b]
9d	3-Cl	97	79	81 [b]

[a] Determined by ^1H NMR shift experiments at 400 MHz in the presence of (+)-Eu(hfc)$_3$ (0.3 equiv) using the derived methyl esters
[b] Determined by chiral HPLC using a Chiralpak AD column and comparisons with racemic samples

Following work-up, immediate treatment of **5a-d** with aqueous sodium periodate in methanol proceeded smoothly to yield the α-arylpropanoic acids **1a-d** with excellent enantiomeric excesses (Table 4). It is perhaps remarkable that the α-diketones had largely retained their stereochemical integrity throughout the hydrolysis procedure and the subsequent oxidative cleavage.

Conclusions

We have demonstrated the utility of DiTOX units as stereocontrol elements in the synthesis of α-methyl carboxylic acids. The retention of stereochemical integrity in the intermediate α-diketones under the conditions used is noteworthy.

Acknowledgments

This investigation has enjoyed the support of the EPSRC, SmithKline Beecham Pharmaceuticals Ltd, and Glaxo Wellcome Research and Development Ltd.

EXPERIMENTAL SECTION

General experimental details

Purification of Reagents

Commercially available reagents were used as supplied unless otherwise stated. Butyl lithium was purchased from the Aldrich chemical company in 100 ml bottles as a 2.5 M solution in hexane; the molarity was determined by titration against a solution of diphenylacetic acid. Lithium hexamethyldisilazide was purchased from the Aldrich chemical company in 100 ml bottles as a 1 M solution in THF. Aldehydes were distilled and stored over 4Å molecular sieve. Dimethyl sulphoxide was heated at 50 °C for 3 h over calcium hydride prior to distillation and storage over 4Å molecular sieve. (+)-Diethyl tartrate was distilled using a Büchi Kugelrohr apparatus and stored over 4Å molecular sieve. *N*-Bromosuccinimide was recrystallized from water.

Purification of Solvents

Petroleum ether refers to petroleum ether, b.p. 40-60 °C, unless otherwise stated. Ethyl acetate and petroleum ether were distilled prior to use. Tetrahydrofuran was freshly distilled under argon from the sodium/benzophenone ketyl radical before use or was purchased in anhydrous condition from the Aldrich chemical company in 1000 ml bottles. Isohexane was purchased as HPLC grade.

Preparation of glassware

All organometallic reactions were carried out in round bottom flasks which were either baked at 150 °C for a minimum of four hours or dried in a Bunsen burner flame. The flasks were allowed to cool in a desiccator over self indicating silica gel, and were purged with argon prior to being stoppered with septum caps. Other apparatus such as syringes, needles, cannulas and magnetic stirrer bars were also dried as above and allowed to cool in a desiccator. Reactions were maintained under a slight static positive pressure of nitrogen and reagents and solvents introduced *via* syringe or using cannula techniques, through a septum cap.

Normal work-up procedures

After reaching room temperature, the reaction mixture was poured onto saturated aqueous ammonium chloride and extracted into dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulphate and the solvents removed under reduced pressure to yield the crude products.

Purification of Products

Flash column chromatography was carried out using Merck art. 9385 Kieselgel 60 (230-400 mesh) or ICN Silica 32-63 60 Å, using hand-bellows or an air line to apply pressure to the column. Mixtures of ethyl acetate and petroleum ether (bp 40-60 °C) or isohexane were used as eluent, unless otherwise stated. Thin layer chromatography was carried out using glass-backed plates coated

with a 0.25 mm layer of silica gel 60H containing fluorescer, using mixtures of ethyl acetate and petroleum ether (bp 40-60 °C) or isohexane as eluent unless otherwise stated. UV-inactive compounds were visualized by spraying with either dodecamolybdophosphoric acid (15% w/v in ethanol), or a solution of potassium permanganate (10 g) and sodium carbonate (5 g) in water (2000 ml) followed in both cases by charring where appropriate. Preparative layer chromatography was carried out using 20 x 20 cm glass-backed plates coated with a 2 mm layer of silica gel 60H containing fluorescer (Merck art. 13792), using mixtures of ethyl acetate and petroleum ether (bp 40-60 °C) or isohexane as eluent unless otherwise stated.

Spectroscopy and other data

Infrared spectra were recorded in the range 4000-600 cm^{-1}, and were calibrated against the 1602 cm^{-1} absorption of polystyrene. Solid samples were run as nujol mulls and liquids as thin films. ^1H NMR spectra were recorded using Bruker ACE200, Jeol 270, or Bruker AMX400 instruments using deuteriochloroform or perdeuterio DMSO solutions and tetramethylsilane as internal reference. ^{13}C NMR spectra were recorded using Jeol 270 or Bruker AMX400 instruments using deuteriochloroform solutions and tetramethylsilane or chloroform as internal reference. Mass spectra were obtained on VG Micromass 7070E or AEI MS 902 mass spectrometers. Microanalyses were performed using a Carlo Erba elemental analyser at the University of Liverpool, Department of Chemistry microanalytical laboratory. Melting points were determined on a Reichert hot stage apparatus and are uncorrected.

Procedures

2-Ethyl-1,3-dithiane

To a stirring solution of 1,3-dithiane (50 g, 417 mmol) in THF (500 mL) at –20 °C was added a 2.3 M solution of *n*-butyllithium (1.1 eq, 199.3 mL, 458 mmol). After 1 hour ethyl iodide (1.1 eq, 36.66 mL, 458 mmol) was added and the reaction mixture allowed to reach 25 °C over 17 hours. Normal work-up procedure followed by distillation (65°C, 0.25 mmHg) gave the title compound as a pale yellow oil (57.4 g, 93%), ν_{max} (neat) 2897 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.07 (3H, t, J = 7.2 Hz), 1.72-1.95 (3H, m), 2.05-2.18 (1H, m), 2.76-2.89 (4H, m), and 4.00 (1H, t, J = 6.9 Hz); *m/z* 148.03761 (M^+); $C_6H_{12}S_2$ requires 148.03806. Found: C, 48.60; H, 8.19; $C_6H_{12}S_2$ requires C, 48.45; H, 8.16%.

2-(1-Hydroxy-2-phenylethyl)-2-ethyl-1,3-dithiane 7a

To a stirring solution of 1,3-dithiane (10 g, 83.3 mmol) in THF (350 mL) at –20 °C was added a 2.3 M solution of *n*-butyllithium in hexanes (1.1 eq, 39.90 mL, 91.6 mmol). After 1 hour, the reaction mixture was cooled to –78 °C and ethyl iodide (1.1 eq, 7.33 mL, 91.6 mmol) added. The reaction mixture was allowed to reach 25 °C over 1.5 hours, recooled to –20 °C and a solution of *n*-butyllithium in hexanes (1.1 eq, 39.90 mL, 91.6 mmol) added. After 1 hour the reaction mixture was cooled to –78 °C, phenylacetaldehyde (1.1 eq, 10.25 mL, 91.6 mmol) added, and allowed to reach 25 °C over 17 hours. Normal work-up procedure followed by flash column chromatography using 5% ethyl acetate/petroleum ether as eluent furnished **7a** as a colourless oil (11.71 g, 52%): ν_{max} (neat) 3469 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.14 (3H, t, J = 7.4 Hz), 1.66-2.07 (4H, m), 2.51-3.10 (6H, m), 3.30-3.36 (1H, m), 4.13-4.18 (1H, m), and 7.17-7.36 (5H, m); *m/z* 268.09546 (M^+); $C_{14}H_{20}OS_2$ requires 268.09555. Found: C, 62.73; H, 7.53; $C_{14}H_{20}OS_2$ requires: C, 62.64; H, 7.51%.

2-(2-Phenylacetyl)-2-ethyl)-1,3-dithiane 6a

To a stirring solution of DMSO (2.2 eq, 6.58 mL, 92.6 mmol) in dichloromethane (70 ml) at –78 °C was added a solution of trifluoroacetic anhydride (1.5 eq, 8.93 mL, 63.2 mmol) in CH_2Cl_2 (40 mL). After stirring at –78 °C for 30 minutes, a solution of **7a** (11.29 g, 42.1 mmol) in CH_2Cl_2 (40 mL) was added dropwise and stirring continued at –78 °C for 1.5 hours. Triethylamine (3 eq, 17.61 mL, 126.3 mmol) was added and the mixture allowed to reach 25 °C over 1.5 hours. The mixture was poured onto 5% aqueous hydrochloric acid (300 mL) and the organic phase collected, washed with

aqueous sodium hydrogen carbonate (2x50 mL), dried over $MgSO_4$ and concentrared *in vacuo* to yield an orange solid. Washing with petroleum ether gave **6a** as a colourless crystalline solid (9.12 g, 81%), mp 85-86 °C; ν_{max} (nujol) 1702 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.03 (3H, t, *J* = 7.1 Hz), 1.70-2.18 (4H, m), 2.53-2.60 (2H, m), 2.80-2.93 (2H, m), 3.96 (2H, s), and 7.26-7.33 (5H, m); *m/z* 266.07979 (M^+); $C_{14}H_{18}OS_2$ requires 266.07990. Found: C, 62.83; H, 6.78; $C_{14}H_{18}OS_2$ requires: C, 63.12; H, 6.81%.

2-(2-(4-*t*-Butylphenyl)acetyl)-2-ethyl-1,3-dithiane 6b

To a stirring solution of 2-ethyl-1,3-dithiane (5.96 g, 40.3 mmol) in THF (200 mL) at –20 °C was added a 2.3 M solution of *n*-butyllithium in hexanes (1.1 eq, 19.26 mL, 43.3 mmol). After 1 hour, methyl 4-*t*-butylphenylacetate **8b** (1 eq, 8.30 g, 40.3 mmol) in THF (10 mL) was added and the reaction mixture allowed to reach 25 °C over 17 hours. Normal work-up procedure followed by trituration with petroleum ether gave **6b** as an off-white crystalline solid (6.78 g, 52%), mp 110-111 °C; ν_{max} (nujol) 1706 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.05 (3H, t, *J* = 7.4 Hz), 1.31 (9H, s), 1.75-1.85 (1H, m), 2.00-2.04 (1H, m), 2.14 (2H, q, *J* = 7.4 Hz), 2.59 (2H, dt, *J* = 12.0 and 3.8 Hz), 2.91 (2H, m), 3.95 (2H, s), 7.21 (2H, d, *J* = 8.4 Hz), and 7.34 (2H, d, *J* = 8.4 Hz); *m/z* 322.14222 (M^+); $C_{18}H_{26}OS_2$ requires 322.14249. Found: C, 67.07; H, 8.15; $C_{18}H_{26}OS_2$ requires: C, 67.03; H, 8.13%.

2-(2-(1-Naphthyl)acetyl)-2-ethyl-1,3-dithiane 6c

See reference 6 for details.

Methyl 3-chlorophenylacetate 8d

A solution of 3-chlorophenylacetic acid (10 g, 58.6 mmol) and concentrated sulphuric acid (1 mL) in methanol (70 mL) was heated under reflux for 1 hour. The reaction was allowed to cool to 25 °C, washed with saturated aqueous sodium hydrogen carbonate (30 mL) and extracted into CH_2Cl_2. Drying over $MgSO_4$ and concentration *in vacuo* gave **8d** as a yellow oil (10.81 g, 100%): ν_{max} (neat) 1739 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.60 (2H, s), 3.70 (3H, s), 7.14-7.18 (1H, m), and 7.22-7.28 (3H, m); *m/z* 184.0289 (M^+); $C_9H_9ClO_2$ requires 184.0291.

2-(2-(3-Chlorophenyl)acetyl)-2-ethyl-1,3-dithiane 6d

To a stirring solution of 2-ethyl-1,3-dithiane (6.79 g, 45.9 mmol) in THF (200 mL) at –20 °C was added a 2.4 M solution of *n*-butyllithium in hexanes (21.03 mL, 50.5 mmol). After 1 hour, methyl 3-chlorophenylacetate **8d** (1 eq, 8.46 g, 45.9 mmol) was added and the reaction allowed to reach 25 °C over 2 hours. Normal work-up procedure followed by distillation to remove 2-ethyl-1,3-dithiane gave **6d** as a yellow oil (6.95 g, 51%), ν_{max} (neat) 1712 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 1.04 (3H, t, *J* = 7.6 Hz), 1.71-1.88 (1H, m), 1.97-2.06 (1H, m), 2.12 (2H, q, *J* = 7.6 Hz), 2.55-2.63 (2H, m), 2.80-2.92 (2H, m), 3.94 (2H, s), and 7.23-7.33 (4H, m); *m/z* 300.0406 (M^+); $C_{14}H_{17}ClO$ requires 300.0409.

Asymmetric Oxidations

Tartaric acid work-up

The reaction mixture was allowed to reach 25 °C and concentrated *in vacuo*. The crude residue was dissolved in diethyl ether (100 mL) and cooled to –10 °C before addition of saturated aqueous tartaric acid (100 mL). After 1.5 hours at –10 °C, the mixture was allowed to reach 25 °C and the ether layer separated. The aqueous layer was extracted with ether (3x75 mL) and CH_2Cl_2 (3x75 mL), the organic fractions combined, dried over $MgSO_4$ and concentrated *in vacuo*.

(+)-1*R*,2*R*-*anti*-2-(2-Phenylacetyl)-2-ethyl-1,3-dithiane 1-oxide 3a and (+)-1*R*,2*R*,3*R*-2-(2-phenylacetyl)-2-ethyl-1,3-dithiane 1,3-dioxide 9a

To a stirring solution of (+)-diethyl tartrate (2.2 eq, 11.33 mL, 66.2 mmol) in CH_2Cl_2 (75 mL) at room temperature was added titanium isopropoxide (1.1 eq, 9.84 mL, 33.1 mmol). After 5 minutes, water (1 eq, 0.54 mL, 30.1 mmol) was added and the solution stirred for 30 minutes before cooling to –30 °C. A solution of **6a** (8.00g, 30.1 mmol) in CH_2Cl_2 (50 mL) was added after 15

minutes, and a cooled solution of cumene hydroperoxide (1.5 eq, 8.33 mL, 45.2 mmol) added dropwise over 20 minutes. After 3 days at –26 °C, tartaric acid work-up and flash column chromatography using ethyl acetate/petroleum ether 1:1 as eluent gave **3a** (5.44 g, 64%) and **9a** (1.2 g, 14%) as colourless crystalline solids.

For **3a**: mp 112-113 °C, ν_{max} (nujol) 1697 and 1040 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.07 (3H, t, *J* = 7.5 Hz), 1.66-1.70 (1H, m), 1.87-1.97 (1H, m), 2.20-2.30 (1H, m), 2.34-2.50 (3H, m), 2.96-3.38 (2H, m), 3.82 (1H, d, *J* = 15.5 Hz), 4.31 (1H, d, *J* = 15.5 Hz), and 7.27-7.38 (5H, m); δ_C (100 MHz, $CDCl_3$) 8.3, 14.8, 26.3, 26.8, 43.7, 44.5, 75.5, 127.5, 128.9, 130.0, 133.4, and 206.1; *m/z* 282.07515 (M^+); $C_{14}H_{18}O_2S_2$ requires 282.07483. Found: C, 59.30; H, 6.41%; $C_{14}H_{18}O_2S_2$ requires: C, 59.54; H, 6.42. $[\alpha]_D^{25}$ = +251.4 ° (c = 0.7, $CHCl_3$).

For **9a**: mp 131-132 °C, ν_{max} (nujol) 1686 and 1054 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.25 (3H, t, *J* = 7.4 Hz), 2.26-2.31 (1H, m), 2.60-2.82 (2H, m), 2.89-2.96 (2H, m), 3.09-3.14 (1H, m), 3.25-3.27 (1H, m), 3.40-3.47 (1H, m), 3.91 (1H, d, *J* = 18.2 Hz), 4.25 (1H, d, *J* = 18.2 Hz), 7.17-7.20 (2H, m), and 7.27-7.36 (3H, m); *m/z* 298.07034 (M^+); $C_{14}H_{18}O_3S_2$ requires 298.06973. Found: C, 56,40; H, 6.24; $C_{14}H_{18}O_3S_2$ requires: C, 56.35: H, 6.08%. $[\alpha]_D^{25}$ = +280.0 ° (c = 0.60, $CHCl_3$).

(+)-1*R*,2*R*-*anti*-2-(2-(4-*t*-Butylphenyl)acetyl)-2-ethyl-1,3-dithiane 1-oxide 3b and (+)-1*R*,2*R*,3*R*-2-(2-(4-*t*-butylphenyl)acetyl)-2-ethyl-1,3-dithiane 1,3-dioxide 9b

To a stirring solution of (+)-diethyl tartrate (2.2 eq, 4.68 mL, 26.5 mmol) in CH_2Cl_2 (35 mL) at 25 °C was added titanium isopropoxide (1.1 eq, 4.06 mL, 13.2 mmol). After 5 minutes, water (1 eq, 0.22 mL, 12.0 mmol) was added and the solution stirred for 30 minutes before cooling to –30 °C. A solution of **6b** (4.00 g, 12.0 mmol) in CH_2Cl_2 (20 mL) was added, and after 15 minutes a cooled solution of cumene hydroperoxide (1.5 eq, 3.45 mL, 18.1 mmol) added dropwise over 20 minutes. After 3 days at –30 °C, tartaric acid work-up and flash column chromatography using ethyl acetate/petroleum ether 1:1 as eluent gave **3b** (3.12 g, 74%) and **9b** (0.56 g, 13%) as colourless crystalline solids.

For **3b**: mp 132-134 °C, ν_{max} (nujol) 1706 and 1051 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.07 (3H, t, *J* = 7.4 Hz), 1.32 (9H, s), 1.67-1.71 (1H, m), 1.88-1.97 (1H, m), 2.20-2.29 (1H, m), 2.38-2.49 (3H, m), 3.02-3.06 (2H, m), 3.79 (1H, d, *J* = 16.0 Hz), 4.29 (1H, d, *J* = 16.0 Hz), 7.22 (2H, d, *J* = 8.4 Hz), and 7.37 (2H, d, *J* = 8.4 Hz); δ_C (100 MHz, $CDCl_3$) 8.5, 14.9, 26.5, 27.0, 31.7, 34.9, 43.9, 44.2, 76.7, 125.9, 129.8, 130.4, 150.5, and 206.6; *m/z* 338.13698 (M^+); $C_{18}H_{26}O_2S_2$ requires 338.13742. Found: C, 63.71; H, 7.76; $C_{18}H_{26}O_2S_2$ requires: C, 63.86; H, 7.74%. $[\alpha]_D^{25}$ = +253.0 ° (c = 0.20, $CHCl_3$).

For **9b**: mp 123-124 °C, ν_{max} (nujol) 1685 and 1059 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.26 (3H, t, *J* = 7.4 Hz), 1.31 (9H, s), 2.27-2.35 (1H, m), 2.74-2.98 (4H, m), 3.11-3.15 (1H, m), 3.33-3.37 (1H, m), 3.45-3.53 (1H, td, *J* = 14.0 and 4.0 Hz), 3.90 (1H, d, *J* = 18.4 Hz), 4.20 (1H, d, *J* = 18.4 Hz), 7.12 (2H, d, *J* = 8.0 Hz), and 7.36 (2H, d, *J* = 8.0 Hz); *m/z* 354.13188 (M^+); $C_{18}H_{26}O_3S_2$ requires 354.13232. Found: C, 60.93; H, 7.42; $C_{18}H_{26}O_3S_2$ requires: C, 60.98; H, 7.39%. $[\alpha]_D^{25}$ = +264.5 ° (c = 0.31, $CHCl_3$).

(+)-1*R*,2*R*-*anti*-2-(2-(1-Naphthyl)acetyl)-2-ethyl-1,3-dithiane 1-oxide 3c

See reference 6 for details.

(+)-1*R*,2*R*-*anti*-2-(2-(3-Chlorophenyl)acetyl)-2-ethyl-1,3-dithiane 1-oxide 3d

To a stirring solution of (+)-diethyl tartrate (2.2 eq, 4.34 mL, 24.2 mmol) in CH_2Cl_2 (30 mL) at 25 °C was added titanium isopropoxide (1.1 eq, 3.77 mL, 12.1 mmol). After 5 minutes, water (1 eq, 0.21 mL, 11.0 mmol) was added and the solution stirred for 30 minutes before cooling to –30 °C. A solution of **6d** (3.47 g, 11.0 mmol) in CH_2Cl_2 (25 mL) was added, and after 15 minutes a cooled solution of cumene hydroperoxide (1.2 eq, 2.57 mL, 13.2 mmol) added dropwise over 20 minutes. After 3 days, tartaric acid work-up and flash column chromatography using ethyl acetate/isohexane 1:1 as eluent gave **3d** as a colourless viscous oil (2.31 g, 63%); ν_{max} (neat) 1697 and 1040cm^{-1}; δ_H (270 MHz, $CDCl_3$) 1.07 (3H, t, *J* = 7.6 Hz), 1.67-1.75 (1H, m), 1.83-1.97 (1H, m), 2.20-2.53 (4H, m), 3.00-3.05 (2H, m), 3.78 (1H, d, *J* = 15.7 Hz), 4.30 (1H, d, *J* = 15.7 Hz), 7.16-7.20 (1H, m), and 7.27-

7.31 (3H, m); δ_C (67.5 MHz, $CDCl_3$) 7.9, 14.5, 25.8, 26.5, 43.5, 43.6, 74.9, 127.4, 127.9, 129.7, 134.3, 134.9, and 204.9; *m/z* 316.0356 (M^+); $C_{14}H_{17}ClO_2S_2$ requires 316.0359. Found: C, 53.18; H, 5.37; $C_{14}H_{17}ClO_2S_2$ requires: C, 53.07: H, 5.41%. $[\alpha]_D^{25}$ = +215 ° (c = 1.10, $CHCl_3$).

(+)-1*R*,2*R*-*anti*-2-(2*S*-Phenylpropanoyl)-2-ethyl-1,3-dithiane 1-oxide 4a

To a stirring solution of **3a** (1g, 3.55 mmol) in THF (150 mL) at –78 °C was added a 1 M solution of LHMDS in THF (1.1 eq, 0.33 mL, 3.90 mmol). After 20 minutes, methyl iodide (1.5 eq, 0.33 mL, 5.33 mmol) was added and the solution allowed to reach 25 °C over 17 hours. Normal work-up gave **4a** and **10a** as a mixture of diastereoisomers (17:1 by ^1H NMR spectroscopy). Flash column chromatography using ethyl acetate/petroleum ether 1:1 as eluent gave **4a** as a colourless solid (0.81 g, 77%), mp 113-114 °C; ν_{max} (nujol) 1693 and 1054 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.50 (3H, t, *J* = 7.5 Hz), 1.53 (3H, d, *J* = 6.9 Hz), 1.73-1.82 (2H, m), 1.97-2.06 (1H, m), 2.45-2.56 (2H, m), 2.62-2.70 (1H, m), 3.06-3.09 (2H, m), 4.73 (1H, q, *J* = 6.9 Hz), and 7.24-7.37 (5H, m); *m/z* 296.09066 (M^+); $C_{15}H_{20}O_2S_2$ requires 296.09048. $[\alpha]_D^{25}$ = +276.5° (c = 0.24, $CHCl_3$).

(+)-1*R*,2*R*-*anti*-2-(2*S*-(4-*t*-Butylphenyl)propanoyl)-2-ethyl-1,3-dithiane 1-oxide 4b

To a stirring solution of **3b** (0.10 g, 0.296 mmol) in THF (5 mL) at –78 °C was added a 1 M solution of LHMDS in THF (1.1 eq, 0.33 ml, 0.325 mmol). After 20 minutes, methyl iodide (1.5 eq, 0.04 mL, 0.444 mmol) was added and the reaction allowed to reach 25 °C over 2 hours. Normal work-up gave **4b** and **10b** as a mixture of diastereoisomers (20:1 by ^1H NMR spectroscopy). Flash column chromatography using ethyl acetate/petroleum ether 1:1 as eluent gave **4b** as a colourless crystalline solid (0.087 g, 84%), mp 131-132 °C; ν_{max} (nujol) 1683 and 1045 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.49 (3H, t, *J* = 7.2 Hz), 1.29 (9H, s), 1.52 (3H, d, *J* = 7.2 Hz), 1.75-1.81 (2H, m), 1.97-2.03 (1H, m), 2.51-2.70 (3H, m), 3.06-3.09 (2H, m), 4.70 (1H, q, *J* = 7.2 Hz), and 7.26-7.33 (4H, m); δ_C (100 MHz, $CDCl_3$) 8.1, 15.2, 22.2, 27.0, 27.6, 31.9, 35.1, 44.2, 47.4, 76.7, 126.4, 128.3, 137.0, 151.3, and 210.1; *m/z* 352.1528 (M^+); $C_{19}H_{28}O_2S_2$ requires 352.1531. Found: C, 64.49; H, 8.04; $C_{19}H_{28}O_2S_2$ requires: C, 64.73; H, 8.00%. $[\alpha]_D^{25}$ = +280.9 ° (c = 0.24, $CHCl_3$).

(+)-1*R*,2*R*-*anti*-2-(2*S*-(1-Naphthyl)propanoyl)-2-ethyl-1,3-dithiane 1-oxide 4c

See reference 6 for details.

(+)-1*R*,2*R*-*anti*-2-(2*S*-(3-Chlorophenyl)propanoyl)-2-ethyl-1,3-dithiane 1-oxide 4d and (+)-1*R*,2*R*-*anti*-(2*R*-(3-chlorophenyl)propanoyl)-2-ethyl-1,3-dithiane 1-oxide 10d

Sodium hydride (1.1 eq, 0.130 g, 3.23 mmol) was washed with THF (2x5 mL) and added with stirring to THF (25 mL) at 0 °C. A solution of **3d** (0.932 g, 2.94 mmol) in THF (25 mL) was added dropwise. After 5 minutes at 0 °C, the reaction mixture was cooled to –78 °C and stirred for 1 hour. Methyl iodide (1.5 eq, 0.27 mL, 4.41mmol) was added and the reaction allowed to reach 25 °C. After 30 minutes, normal work-up gave **4d** and **10d** as a mixture of diastereoisomers (7:1 by ^1H NMR spectroscopy). Column chromatography using ethyl acetate as eluent gave **4d** (0.68 g, 70%) and **10d** (0.103 g, 11%) as colourless oils.

For **4d**: ν_{max} (neat) 1691 and 1057 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 0.65 (3H, t, *J* = 7.4 Hz), 1.62 (3H, d, *J* = 7.2 Hz), 1.83-1.91 (2H, m), 2.09-2.20 (1H, m), 2.57-2.75 (3H, m), 3.16-3.21 (2H, m), 4.77 (1H, q, *J* = 7.2 Hz), 7.34-7.36 (3H, m), and 7.47 (1H, s); δ_C (67.5 MHz, $CDCl_3$) 7.6, 14.7, 21.9, 26.0, 27.0, 43.6, 46.8, 75.7, 126.1, 127.8, 128.0, 130.1, 134.7, 141.6, and 208.6; *m/z* 330.0514 (M^+); $C_{15}H_{19}ClO_2S_2$ requires 330.0515.

For **10d**: ν_{max} (neat) 1693 and 1059 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 1.20 (3H, t, *J* = 7.6 Hz), 1.56 (3H, d, *J* = 7.2 Hz), 1.52-1.63 (2H, m), 1.98-2.08 (2H, m), 2.22-2.52 (2H, m), 2.79-2.91 (1H, m), 3.06-3.12 (1H, m), 4.55 (1H, q, *J* = 7.2 Hz), 7.31-7.39 (2H, m), 7.43-7.49 (1H, m), and 7.57 (1H, s); δ_C (67.5 MHz, $CDCl_3$) 8.3, 13.8, 20.9, 26.5, 42.9, 47.3, 76.1, 126.4, 127.6, 128.3, 129.9, 134.4, 142.3, and 209.6; *m/z* 330.0517 (M^+); $C_{15}H_{19}ClO_2S_2$ requires 330.0515.

General procedure for hydrolysis of 2-acyl-1,3-dithiane 1-oxides 4a-d to give diketones 5a-d

To a stirring solution of *N*-bromosuccinimide (8 eq) in acetone/water (97:3) at 0 °C was added a solution of the acyl dithiane oxide **4** in acetone. The solution was stirred for an appropriate time (15-30 min) and quenched with saturated aqueous sodium sulphite. The mixture was extracted three times with CH_2Cl_2, and the organic fractions combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product **5** was purified by flash column chromatography using 10% ethyl acetate/petroleum ether as eluent.

(+)-2*S*-Phenylhexan-3,4-dione 5a

Compound **4a** (0.250 g, 0.845 mmol) was treated with *N*-bromosuccinimide (8 eq, 1.2 g, 6.76 mmol) in acetone/water (30 mL) as described above to give **5a** as a bright yellow oil (0.153 g, 96%); ν_{max} (neat) 1711 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.92 (3H, t, J = 7.3 Hz), 1.43 (3H, d, J = 7.0 Hz), 2.45 (1H, dq, J = 18.7 and 7.3 Hz), 2.83 (1H, dq, J = 18.7 and 7.3 Hz), 4.61 (1H, q, J = 7.0 Hz), 7.20-7.26 (3H, m), and 7.29-7.33 (2H, m); *m/z* 190.09943 (M^+); $C_{12}H_{14}O_2$ requires 190.09937. $[\alpha]_D^{25}$ = +231.4 ° (c = 0.35, $CHCl_3$).

(+)-2*S*-(4-*t*-Butylphenyl)hexan-3,4-dione 5b

Compound **4b** (0.784 g, 2.23 mmol) was treated with *N*-bromosuccinimide (8 eq, 3.14 g, 17.8 mmol) in acetone/water (40 mL) as described above to give **5b** as a bright yellow oil (0.536 g, 98%); ν_{max} (neat) 1712 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.93 (3H, t, J = 7.2 Hz), 1.29 (9H, s), 1.42 (3H, d, J = 7.2 Hz), 2.44 (1H, dq, J = 18.8 and 7.2 Hz), 2.82 (1H, dq, J = 18.8 and 7.2 Hz), 4.60 (1H, q, J = 7.2 Hz), 7.12-7.15 (2H, m), and 7.30-7.33 (2H, m); δ_C (100 MHz, $CDCl_3$) 7.4, 17.2, 31.2, 31.9, 45.1, 112.4, 126.6, 128.7, 135.3, 151.0, 199.8, and 202.0;); *m/z* 246.16194 (M^+); $C_{16}H_{22}O_2$ requires 246.16199. $[\alpha]_D^{25}$ = +216.8 ° (c = 0.74, $CHCl_3$).

(+)-2*S*-(1-Naphthyl)hexan-3,4-dione 5c

See reference 6 for details.

(+)-2*S*-(3-Chlorophenyl)hexan-3,4-dione 5d

Compound **4d** (0.50 g, 1.51 mmol) was treated with *N*-bromosuccinimide (8 eq, 2.16 g, 12.1 mmol) in acetone/water (40 mL) as described above to give **5d** as a bright yellow oil (0.392 g, 97%); ν_{max} (neat) 1716 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 0.97 (3H, t, J = 7.2 Hz), 1.42 (3H, d, J = 7.2 Hz), 2.51 (1H, dq, J = 18.8 and 7.2 Hz), 2.83 (1H, dq, J = 18.8 and 7.2 Hz), 4.61 (1H, q, J = 7.2 Hz), 7.08-7.12 (1H, m), and 7.20-7.28 (3H, m); *m/z* 224.0604 (M^+); $C_{12}H_{13}ClO_2$ requires 224.0604.

General procedure for oxidative cleavage of α-diketones 5a-d to give carboxylic acids 1a-d

To a stirring solution of diketone **5** in methanol at room temperature was added dropwise a solution of sodium periodate (2 eq) in water. After an appropriate time (12-24 h), the solution was filtered and the filtrate concentrated *in vacuo*. Extraction with CH_2Cl_2 (3 portions), drying over $MgSO_4$ and concentration *in vacuo* gave the crude product. Flash column chromatography using ethyl acetate/petroleum ether 1:1 as eluent gave the purified acid **1**.

(+)-2*S*-Phenylpropanoic acid 1a

Treatment of diketone **5a** (0.199 g, 1.05 mmol) in methanol (15 mL) with $NaIO_4$ (2 eq, 0.45 g, 2.10 mmol) in water (7 mL) as described above gave **1a** as a colourless oil (0.125 g, 80%); ν_{max} (neat) 2600-3600 and 1703 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, J = 7.0 Hz), 3.59 (1H, q, J = 7.0 Hz), 7.18-7.23 (5H, m), and 10.47 (1H, br s); *m/z* 150.06823 (M^+); $C_9H_{10}O_2$ requires 150.06808. $[\alpha]_D^{25}$ = +65.5 ° (c = 0.55, $CHCl_3$); lit[18] $[\alpha]_D^{25}$ = +76.2 °; lit[19] $[\alpha]_D^{25}$ = +72 ° (c = 1.6, $CHCl_3$).

(+)-2*S*-(4-*t*-Butylphenyl)propanoic acid 1b

Treatment of diketone **5b** (0.540 g, 2.20 mmol) in methanol (30 mL) with $NaIO_4$ (2 eq, 0.94 g, 4.40 mmol) in water (10 mL) as described above gave **1b** as a colourless crystalline solid (0.350 g, 77%), mp 100-101 °C; ν_{max} (nujol) 2600-3600 and 1695 cm^{-1}; δ_H (200 MHz, DMSO) 1.24 (9H,

s), 1.370 (3H, d, *J* = 7.0 Hz), 3.62 (1H, q, *J* = 7.0 Hz), 7.17-7.22 (2H, m), 7.32-7.36 (2H, m), and 12.27 (1H, br s); δ_C (100 MHz, $CDCl_3$) 18.7, 32.0, 35.1, 45.5, 126.3, 127.9, 137.3, 150.9, and 181.6; *m/z* 206.13081 (M^+); $C_{13}H_{18}O_2$ requires 206.13068. Found: C, 75.55; H, 8.82; $C_{13}H_{18}O_2$ requires: C, 75.69; H, 8.79%. $[\alpha]_D^{25}$ = +129.0 ° (c = 0.25, $CHCl_3$).

(+)-2*S*-(1-Naphthyl)propanoic acid 1c

Treatment of diketone **5c** (0.30 g, 1.25 mmol) in methanol (20 mL) with $NaIO_4$ (2 eq, 0.53 g, 2.50 mmol) in water (7 mL) as described above gave **1c** as a colourless solid (0.171 g, 68%), mp 68-69 °C; ν_{max} (nujol) 2600-3400 and 1705 cm^{-1}; δ_H (270 MHz, DMSO) 1.51 (3H, d, *J* = 7.2 Hz), 4.46 (1H, q, *J* = 7.2 Hz), 7.42-7.60 (4H, m), 7.82-7.85 (1H, m), 7.93-7.96 (1H, m), 8.12-8.15 (1H, m), and 12.42 (1H, br s); δ_C (100 MHz, $CDCl_3$) 18.5, 41.7, 123.7, 125.3, 126.2, 126.4, 127.1, 128.7, 129.7, 132.0, 134.7, 136.7, and 180.9; m/z 200.08405 (M^+); $C_{13}H_{12}O_2$ requires 200.08374. Found: C, 78.08; H, 6.14; $C_{13}H_{12}O_2$ requires: C, 77.98; H, 6.04%. $[\alpha]_D^{25}$ = +125.7 ° (c = 0.35, $CHCl_3$); lit[5] $[\alpha]_D^{25}$ = +133.9 °.

(+)-2*S*-(3-Chlorophenyl)propanoic acid 1d

Treatment of diketone **5d** (0.300 g, 1.34 mmol) in methanol (10 mL) with $NaIO_4$ (2 eq, 0.57 g, 2.68 mmol) in water (10 mL) as described above gave **1d** as a colourless oil (0.24 g, 79%); ν_{max} (neat) 3000-3400 and 1713 cm^{-1}; δ_H (270 MHz, DMSO) 1.36 (3H, d, *J* = 7.2 Hz), 3.72 (1H, q, *J* = 7.2 Hz), 7.23-7.40 (4H, m), and 12.49 (1H, br s); δ_C (100 MHz, $CDCl_3$) 18.0, 45.1, 125.9, 127.7, 127.9, 129.9, 134.5, 141.6, and 180.2; *m/z* 184.0290 (M^+); $C_9H_9ClO_2$ requires 184.0291. $[\alpha]_D^{25}$ = +41.0 ° (c = 1.0, $CHCl_3$); lit[20] $[\alpha]_D^{20.5}$ = +100 ° (c = 1.7, $CHCl_3$).

(+)-2*S*-Methyl phenylpropanoate

To a stirring solution of acid **1a** (0.044 g, 0.293 mmol) in THF/methanol (2 mL/1 mL) was added a 2 M solution of trimethylsilyldiazomethane in hexanes (4 eq, 0.59 mL, 1.17 mmol) at 25 °C. After 1.5 hours the reaction was concentrated *in vacuo* and purified by preparative TLC to give methyl ester as a pale yellow oil (0.035 g, 73%); δ_H (400 MHz, $CDCl_3$) 1.50 (3H, d, *J* = 7.2 Hz), 3.66 (3H, s), 3.73 (1H, q, *J* = 7.2 Hz), and 7.20-7.35 (5H, m); *m/z* 164.08335 (M^+); $C_{10}H_{12}O_2$ requires 164.08374.

(+)-2*S*-Methyl (4-*t*-butylphenyl)propanoate

To a stirring solution of acid **1b** (0.033 g, 0.160 mmol) in THF/ methanol (2 mL/1 mL) was added a 2 M solution of trimethylsilyldiazomethane in hexanes (4 eq, 0.32 mL, 0.64 mmol) at 25 °C. After 1 hour the reaction was concentrated *in vacuo* and purified by preparative TLC to give methyl ester as a pale yellow oil (0.035 g, 99%); ν_{max} (neat) 1737 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.31 (9H, s), 1.49 (3H, d, *J* = 7.7 Hz), 3.66 (3H, s), 3.71 (1H, q, J = 7.7 Hz), 7.20-7.26 (2H, m), and 7.31-7.37 (2H, m); *m/z* 220.14603 (M^+); $C_{12}H_{20}O_2$ requires 220.14633.

(±)-2-(1-Naphthyl)propanoic acid

To a solution of diisopropylamine (2 eq, 1.50 mL, 10.0 mmol) in THF (10 mL) at 0 °C was added a 2.4 M solution of *n*-butyllithium in hexanes (2 eq, 4.48 mL, 10.0 mmol). After 30 minutes, the solution was cooled to –78 °C and 1-naphthylacetic acid (1.0 g, 5.00 mmol) in THF (10 mL) added. After a further 30 minutes, methyl iodide (1.1 eq, 0.37 mL, 5.50 mmol) was added and the solution allowed to reach 25 °C. Normal work-up, extraction with CH_2Cl_2, washing with dilute aqueous HCl and drying over $MgSO_4$ gave the crude acid. Recrystallization from ethanol gave the racemic acid as a colourless solid (0.82 g, 76%), mp 149-150 °C; ν_{max} (nujol) 2600-3200 and 1703 cm^{-1}; δ_H (270 MHz, DMSO) 1.52 (3H, d, *J* = 6.9 Hz), 4.47 (1H, q, *J* = 6.9 Hz), 7.42-7.60 (4H, m), 7.82-7.85 (1H, m), 7.93-7.96 (1H, m), 8.12-8.15 (1H, m), and 12.40 (1H, br s); *m/z* 200.0836 (M^+); $C_{13}H_{12}O_2$ requires 200.0837. Found: C, 78.04; H, 6.03; $C_{13}H_{12}O_2$ requires: C, 77.98; H, 6.04%.

(±)-2-(3-Chlorophenyl)propanoic acid

To a solution of diisopropylamine (2 eq, 1.65 mL, 11.7 mmol) in THF (10 mL) at 0 °C was added a 2.4 M solution of *n*-butyllithium in hexanes (2 eq, 4.89 mL, 11.7 mmol), After 30 minutes, the solution was cooled to –78 °C and 3-chlorophenylacetic acid (1.0 g, 5.87 mmol) in THF (10 mL) added. After a further 30 minutes, methyl iodide (1.1 eq, 0.40 mL, 6.46 mmol) was added and the reaction allowed to reach 25 °C. Normal work-up, extraction with CH_2Cl_2, washing with dilute aqueous HCl, and drying over $MgSO_4$ gave the crude acid. Column chromatography using ethyl acetate/isohexane 1:1 as eluent gave the racemic acid as a colourless solid (0.84 g, 78%), mp 74-76 °C; ν_{max} (neat) 2600-3400 and 1713 cm^{-1}; δ_H (270 MHz, DMSO) 1.36 (3H, d, *J* = 7.2 Hz), 3.72 (1H, q, *J* = 7.2 Hz), 7.24-7.39 (4H, m), and 12.45 (1H, br s); *m/z* 184.0292 (M^+); $C_9H_9ClO_2$ requires 184.0291. Found: C, 58.44; H, 4.94; $C_9H_9ClO_2$ requires: C, 58.55; H, 4.91%.

4-Methyl bromopentane

4-Methyl pentanol (4.0g, 39.15 mmol) was added over 1 hour to phosphorus tribromide (1.93 ml, 20.32 mmol) containing 3 drops of concentrated hydrobromic acid while maintaining the temperature at 10-15 °C. The reaction was stirred at 10 °C for a further 45 minutes, then at room temperature for 2 days. The reaction mixture was poured onto ice water (20 ml) and extracted into dichloromethane (3 x 25ml). The combined organic extracts were washed with aqueous sodium bicarbonate, dried over $MgSO_4$ and the solvents removed under reduced pressure to give a colourless oil. Flash column chromatography using 15% ethyl acetate/ petroleum ether as eluent gave the title compound as a colourless oil (4.10g, 63%), ν_{max} (film) 2959, 2872, 1469, 1368 and 1255 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.90 (6H, d, *J* = 6.5 Hz), 1.25-1.40 (2H, m), 1.50-1.70 (1H, m), 1.77-1.95 (2H, m), and 3.40 (2H, t, *J* = 6.9 Hz); *m/z* 166.01828 (M^+), $C_6H_{13}Br$ requires 166.0801. Found: C, 43.92; H, 8.05; $C_6H_{13}Br$ requires C, 43.66, H, 7.94%.

4-Methyl Iodopentane

4-Methyl bromopentane (1.5g, 9.09 mmol) was added to a solution of potassium iodide (4.09g, 24.64 mmol) in acetone (60 ml) and the mixture heated under reflux for 30 minutes. Approximately 40 ml of solvent was removed by evaporation and the resulting solution cooled in an ice bath prior to addition of water (50 ml). The organic phase was extracted into ether (2 x 25 ml) and the combined organic extracts washed with saturated aqueous sodium bisulfite solution, dried over $MgSO_4$, and the solvents removed under reduced pressure. Flash column chromatography using 15% ethyl acetate/ petroleum ether as eluent gave the title compound as a colourless oil (1.06g, 55%), ν_{max} (film) 2960, 2920, 2890, 1415 and 1270 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.90 (6H, d, *J* = 6.6 Hz), 1.20-1.34 (2H, m), 1.48-1.77 (1H, m), 1.75-1.92 (2H, m), and 3.18 (2H, t, *J* = 7.1 Hz); *m/z* 212 (M^+). Found: C, 33.95; H, 6.28; $C_6H_{13}I$ requires C, 33.98, H, 6.18%.

2-(1-Hydroxypropyl)-2-ethyl-1,3-dithiane 7e

A 1.6 M solution of n-butyllithium in hexanes (1.1 eq, 57.17 ml, 91.47 mmol). was added to a stirring solution of 1,3-dithiane (10g, 83.17 mmol) in THF (300 ml) at –20 °C. After 1 hour the reaction mixture was cooled to –78 °C and iodoethane (1 eq, 6.66 ml, 83.3 mmol) added. The reaction mixture was allowed to reach room temperature over 2 hours before recooling to –20 °C prior to further addition a 1.6 M solution of n-butyllithium in hexanes (1.1 eq, 57.17 ml, 91.47 mmol). The reaction mixture was stirred at this temperature for 1 hour, cooled to –78 °C, propanal (1.5 eq, 9.02 ml, 125.1 mmol) added, and the mixture allowed to reach room temperature overnight. Normal work-up procedure followed by flash column chromatography using 15% ethyl acetate/ petroleum ether as eluent gave **7e** as a colourless crystalline solid (11.16g, 65%), mp 41-43 °C; ν_{max} 3440 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.06 (3H, t, *J* = 7.4 Hz), 1.08 (3H, t, *J* = 7.2Hz), 1.30-1.55 (1H, m), 1.55-2.10 (5H, series m), 2.55-2.70 (2H, m), 2.73 (1H, t, *J* = 2.2 Hz), 2.88-3.08 (2H, m), and 3.90 (1H, dt, *J* = 10.8 and 1.8 Hz); *m/z* 206.08002 (M^+), $C_9H_{18}OS_2$ requires 206.07991. Found: C, 52.19; H, 8.77; $C_9H_{18}OS_2$ requires C, 52.38, H, 8.79%.

2-Propanoyl-2-ethyl-1,3-dithiane 6e

A 2 M solution of oxalyl chloride (1.1 eq, 6.41 ml, 12.82 mmol) in dichloromethane was added To a stirring solution of DMSO (2.2 eq, 1.82 ml, 25.65 mmol) in dichloromethane (10 ml) at -- 78 °C. After stirring at –78 °C for 30 minutes, a solution of **7e** (2.40g, 11.63 mmol) in dichloromethane (50 ml) was added dropwise and stirring continued for a further 2 hours. Triethylamine (5 eq, 8.12 ml, 58.26 mmol) was added and the mixture allowed to reach 25 °C over 1.5 hours. The mixture was poured onto 5% aqueous hydrochloric acid (50 ml), partitioned between water and dichloromethane and the organic phase washed with aqueous sodium bicarbonate solution. Drying over $MgSO_4$, removal of the solvent under reduced pressure and flash column chromatography using 15% ethyl acetate/ petroleum ether as eluent gave **6e** (1.60g, 67%), ν_{max} 1700 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.02 (3H, t, *J* = 7.5 Hz), 1.15 (3H, t, *J* = 7.3Hz), 1.70-1.90 (2H, m), 2.10 (2H, q, *J* = 7.4 Hz), 2.58-2.70 (2H, m), 2.70 (2H, q, *J* = 7.2 Hz), and 2.85-3.10 (2H, m); *m/z* 204 (M^+). Found: C, 51.93; H, 7.84; $C_9H_{16}OS_2$ requires C, 52.90, H, 7.89%.

(+)-1R,2R-*anti*-2-Propanoyl-2-ethyl-1,3-dithiane 1-oxide 3e

Titanium tetraisopropoxide (1.1 eq, 1.60 ml, 5.4 mmol) was added to a stirring solution of (+)-diethyl tartrate (2.2 eq, 1.84 ml, 10.7 mmol) in dichloromethane (50 ml) at room temperature. After 5 minutes, water (1 eq, 0.09 ml, 5.3 mmol) was added and the solution stirred for 30 minutes before cooling to –30 °C. A solution of **6e** in dichloromethane was added over 15 minutes, and a cooled solution of cumene hydroperoxide (2 eq, 1.81 ml, 9.8 mmol) then added dropwise over 20 minutes. After 3 days at –20 °C, tartaric acid work-up and flash column chromatography using ethyl acetate as eluent gave **(+)-3e** as a colourless crystalline solid. Recrystallization from petroleum ether gave **3e** (0.60g, 56%) in enantiomerically pure form, mp 61-63 °C; δ_H (400 MHz, $CDCl_3$) 1.01 (3H, t, *J* = 7.2 Hz), 1.12 (3H, t, *J* = 7.2Hz), 1.71-1.85 (2H, m), 2.12-2.24 (1H, m), 2.40-2.52 (2H, m), 2.52-2.68 (2H, m), and 2.97-3.10 (3H, m). Found: C, 49.29; H, 7.34; $C_9H_{16}O_2S_2$ requires C, 49.06, H, 7.32%. $[\alpha]_D^{20}$ = +280.8 ° (c = 1, $CHCl_3$).

(+)-1R,2R-*anti*-2-(2-(R)-6-Dimethylheptanoyl)-2-ethyl-1,3-dithiane 1-oxide 4e

A 1 M solution of LHMDS in THF (1.1 eq, 1.1 ml) was added to a stirring solution of **3e** (0.215g, 0.98 mmol) in THF (3 ml) and DMPU (1.18 ml, 9.8 mmol) at –78 °C. After 20 minutes, 4-methyl iodopentane (1.5 eq, 0.31g, 1.46 mmol) was added and the reaction allowed to reach room temperature overnight. Normal work-up procedure gave **(+)-4e**, a single diastereoisomer by 400 MHz ^1H NMR spectroscopy, as a yellow oil (0.17g, 57%), ν_{max} 1689 and 1056 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.879 (3H, d, *J* = 6.4 Hz), 0.882 (3H, d, *J* = 6.4 Hz), 1.08 (3H, t, *J* = 7.4 Hz), 1.12 (3H, d, *J* = 6.6 Hz), 1.14-1.22 (2H, m), 1.23-1.37 (1H, m), 1.39-1.59 (3H, m), 1.62-1.80 (2H, m), 1.84-1.94 (1H, m), 2.13-2.19 (1H, m), 2.44-2.66 (3H, m), 3.05-3.10 (2H, m), and 3.18-3.29 (1H, m); δ_C (100 MHz, $CDCl_3$) 8.4, 14.8, 16.8, 22.4, 22.6, 24.6, 25.9, 27.0, 27.8, 35.0, 38.6, 41.0, 43.8, 75.0, and 212.8; *m/z* 304.15334 (M^+); $C_{15}H_{28}O_2S_2$ requires 304.15307. $[\alpha]_D^{20}$ = +166.80 ° (c = 1, $CHCl_3$).

(R)-(–)-2,6-Dimethylheptanoic acid 1e

A solution of **4e** (0.05g, 0.164 mmol) in ethanol (10 ml) was heated under reflux with a 10% aqueous sodium hydroxide (5 ml) for 3 hours. The reaction mixture was then neutralized by addition of dilute aqueous hydrochloric acid, extracted into dichloromethane (2 x 25 ml) and ether (1 x 25 ml). The combined organic extracts were dried over $MgSO_4$ and the solvents removed under reduced pressure. Flash column chromatography using 75% ethyl acetate/ petroleum ether as eluent gave **(–)-1e** as a colourless oil (0.01g, 39%), ν_{max} 3400, 1707 and 1140 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.86 (6H, d, *J* = 6.6 Hz), 1.18 (3H, d, *J* = 7.0 Hz), 1.25-1.45 (5H,series m), 1.48-1.59 (1H, m), 1.60-1.73 (1H, m), 2.40-2.51 (1H, m), and 12.34 (1H, s); *m/z* 176.16540 ($M+NH_4^+$); $C_9H_{22}O_2N$ requires 176.16505. $[\alpha]_D^{20}$ = –18.21 ° (c = 1.01, $CHCl_3$); lit[17] $[\alpha]_D^{20}$ = –17.5 °.

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