Pergamon

Tetrahedron 56 (2000) 9683–9695

TETRAHEDRON

Electrophilic Amination of Ketone Enolates Mediated by the DiTOX Asymmetric Building Block: Enantioselective Formal Synthesis of α-Aminoacids

Philip C. Bulman Page,[a,*] Michael J. McKenzie,[a] Steven M. Allin[a] and Derek R. Buckle[b]

[a]*The Department of Chemistry, Loughborough University, Loughborough, Leicestershire LE11 3TU, UK*
[b]*SmithKline Beecham Pharmaceuticals, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ, UK*

Received 24 July 2000; revised 13 September 2000; accepted 28 September 2000

Abstract—Diastereoselective electrophilic amination of enolates derived from 2-acyl-1,3-dithiane 1-oxides is used as the key step for an enantioselective synthesis of two α-hydrazido carboxylic acids, well-known precursors of α-amino acids.

Introduction

1,3-Dithiane 1-oxide (DiTOX) derivatives can act as combined chiral auxiliaries and asymmetric building blocks. Asymmetric sulfur oxidation allows access to both enantiomers of the acyl dithiane unit with excellent enantioselectivities.[1] Previously we have shown that 2-acyl substituted DiTOX derivatives undergo a variety of transformations with excellent diastereoselectivities, including reactions of the derived enolates with electrophiles.[2] A chelation control model of these systems allows us to predict the stereochemical outcome of these reactions. We describe here the stereoselective electrophilic amination of enolates using the DiTOX unit as the stereocontrolling element, and application to an enantioselective formal synthesis of α-amino acids via α-hydrazido carboxylic acids.

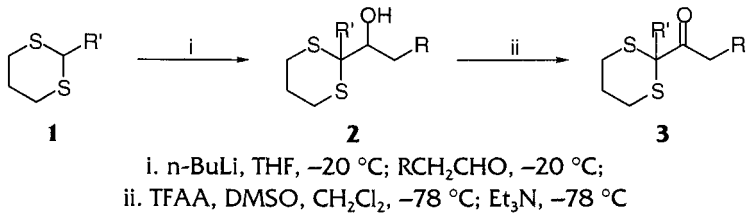
Discussion

The synthesis of non-racemic amino acids, natural and unnatural, has received considerable attention in the literature.[3] Among the many methods developed, electrophilic amination of enolates is one of the most important. Many electrophilic aminating reagents have been employed, including sulfonyl azides,[4] diazonium salts,[5] *O*-substituted hydroxylamines,[6] nitrosyl chloride,[7] (*N*-tosylimino)-phenyliodinane,[8] *N*-alkoxycarbonyl oxaziridines,[9] lithium *tert*-butyl-*N*-tosyloxycarbamate,[10] the aminating reagent of Sharpless,[11] ceric ammonium nitrate/sodium azide,[12] and azodicarboxylate esters; indeed, the electrophilic amination of diethylmalonate with azodicarboxylates was reported as far back as 1924.[13]Oppolzer[14] and Gennari[15] independently reported the asymmetric amination of chiral silyl ketene acetals with di-*tert*-butylazodicarboxylate (DBAD). In the same year, Evans[16,17] and Vederas[18] both published enantioselective approaches to α-amino acids using chiral *N*-acyloxazolidinone enolates and DBAD. DBAD has a number of advantages over other electrophilic aminating reagents: Vederas has established that, of a series of azodicarboxylate esters, the *tert*-butyl derivative gives some of the highest levels of diastereofacial selectivity on reaction with various chiral enolates: methods for the removal of the *tert*-butyloxycarbonyl protecting groups under mild, non-racemizing conditions are well established and are complementary to known methods for N–N bond cleavage; DBAD is a stable, crystalline solid; it is available commercially. Since then, DBAD has been used extensively as an aminating reagent for chiral enolates,[19] and recently Evans has developed a chiral magnesium bis(sulfonamide) complex as a catalyst for the concomitant enolization and enantioselective amination of *N*-acyloxazolidinones.[20] Vederas has also synthesised chiral diazenedicarboxylate esters[21] and a chiral azodicarboxamide[22] for the electophilic amination of achiral ester and amide enolates.

α-Hydrazinocarboxylic acids are useful intermediates for use in the synthesis of enzyme inhibitors and peptidomimetics.[23] We report here in full the diastereoselective amination of enolates derived from *syn* and *anti* 2-acyl-2-alkyl-1,3-dithiane 1-oxides with DBAD,[24] and we describe the application of this process to an enantioselective synthesis of α-hydrazido carboxylic acids and an enantioselective formal synthesis of α-amino acids.

Keywords: asymmetric synthesis; aminoacid; chiral auxiliary; enolate.
* Corresponding author. Tel. +1509-222581; fax: +1509-223926; e-mail: p.c.b.page@lboro.ac.uk

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00923-6



Scheme 1.

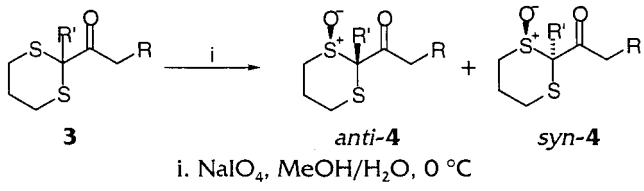
Table 1. Acylation of 2-alkyl-1,3-dithianes

R	R′	Alcohol	Yield/%	Ketone	Yield/%
H	Et	**2a**	80	**3a**	77
Me	Me	**2b**	92	**3b**	48
Me	Et	**2c**	65	**3c**	67
Me	Ph	**2d**	65	**3d**	68
Bn	Et	**2e**	74	**3e**	98
Ph	Et	**2f**	52	**3f**	81
i-Pr	Et	**2g**	76	**3g**	82
t-Bu	Et	**2h**	97	**3h**	88

Eight substrates were chosen for study and were prepared using standard transformations from 2-alkyl-1,3-dithianes **1**: Deprotonation of **1** and treatment with the corresponding aldehydes gave the secondary alcohols **2a**–**h**. Swern oxidation produced the ketones **3a**–**h** in excellent yields (Scheme 1, Table 1). 2-Acetyl derivative **3a** was also prepared in comparable yield by acylation of the 2-ethyl-1,3-dithiane anion with excess ethyl acetate.[1]

Mono-sulfoxidation of four of these acyl dithianes **3a**–**d** was carried out by treatment with sodium periodate in methanol to give the corresponding racemic *anti* and *syn* dithiane oxides **4a**–**d** in excellent yields and with varying diastereoselectivities in favour of the *anti* isomers (Scheme 2, Table 2).

Four of the acyl dithianes having R′=Et were selected for asymmetric sulfur oxidation using the Kagan procedure,[25] which took place smoothly to give the (+)-*anti* (*R*)-1-oxides **4e**–**h**, again in excellent yields and with very high enantiomeric excesses (Scheme 3, Table 3).



Scheme 2.

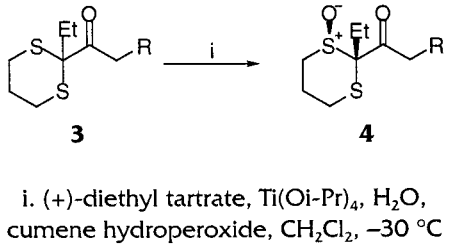
Table 2. Achiral sulfoxidation of 2-acyl-2-alkyl-1,3-dithianes

R	R′	Substrate	Product:	Yield of (±)-*anti*-**4**/%	Yield of (±)-*syn*-**4**/%
H	Et	**3a**	**4a**	39	28
Me	Me	**3b**	**4b**	28	17
Me	Et	**3c**	**4c**	39	27
Me	Ph	**3d**	**4d**	36	20

Asymmetric electrophilic amination was next examined. The lithium enolate of (±)-*anti* 2-ethyl-2-propanoyl-1,3-dithiane 1-oxide (±)-*anti*-**4c** was generated using LHMDS (1.1 equiv.) in dry THF at −78°C and transferred via cannula to a pre-cooled solution of DBAD (1.1 equiv.) in THF solution at −78°C. The solution was allowed to reach room temperature over 12 h before quenching with aqueous ammonium chloride and normal work-up. The desired aminated product (±)-*anti*-**5c** was isolated as a 2: 1 mixture of inseparable diastereoisomers in 52% yield (Scheme 4).[27] The ^{1}H NMR spectra observed at 20°C were to a large degree uninterpretable due to signal broadening. This effect is presumably a result of hindered rotation about the BOC groups, and, as observed by Evans,[16] spectra obtained at higher temperatures (47–52°C) were much improved.

The reaction was repeated under identical conditions but, after allowing ca 5–15 min for reaction with DBAD at −78°C, by which time the persistent yellow colour of the DBAD had disappeared, acetic acid was added at −78°C, and the reaction was allowed to reach room temperature. A similar yield of (±)-*anti*-**5c** was observed, but with a much improved diastereoselectivity of ≥99:1, only one product isomer being detectable by 400 MHz ^{1}H NMR spectroscopy (Scheme 4, R=Me, R′=Et). As expected, the major isomer proved to have the same stereochemistry for both −78°C quench and for room temperature quench. The low temperature acetic acid quench presumably prevents loss of stereochemical integrity at the new asymmetric centre which otherwise occurs at a higher temperature.

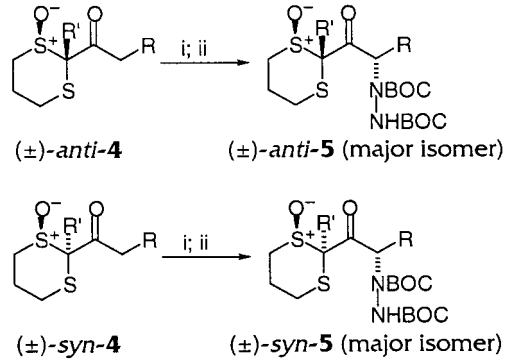
The sense of induced stereochemistry was ultimately proven



Scheme 3.

Table 3. Asymmetric sulfoxidation of 2-acyl-2-ethyl-1,3-dithianes

R	R′	Substrate	Product	Yield/%	ee/%[26]
Bn	Et	**3e**	(+)-*anti*-**4e**	81	>98
Ph	Et	**3f**	(+)-*anti*-**4f**	64	94
i-Pr	Et	**3g**	(+)-*anti*-**4g**	65	89
t-Bu	Et	**3h**	(+)-*anti*-**4h**	66	90



Scheme 4.

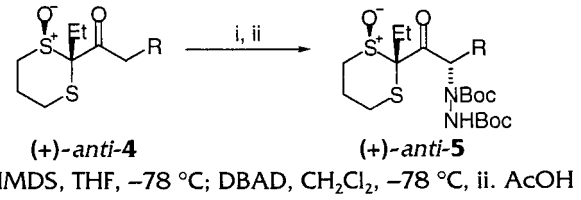
Table 4. Diastereoselectivity of electrophilic amination of (±)-2-acyl-2-alkyl-1,3-dithiane 1-oxide enolates using DBAD

R	R′	Substrate	Product	Isomer ratio[a]	Yield/%
H	Et	***anti*-4a**	***anti*-5a**	–	72
H	Et	***syn*-4a**	***syn*-5a**	–	89
Me	Me	***anti*-4b**	***anti*-5b**	2:1	69
Me	Me	***syn*-4b**	***syn*-5b**	3:1	76
Me	Et	***anti*-4c**	***anti*-5c**	≥99:1[b]	48
Me	Et	***syn*-4c**	***syn*-5c**	12:1	42
Me	Ph	***anti*-4d**	***anti*-5d**	2:1	37

[a] Determined by 400 MHz ^{1}H NMR spectroscopy.[27]
[b] Minor isomer not detected.

to be that shown by conversion of two other examples into known α-hydrazido acids in the non-racemic series (vide infra).

In common with our earlier work, variation of 2-alkyl substituent was expected to exert a dramatic effect upon diastereoselectivity. A selection of the results obtained by variation of the 2-substituent is given in Table 4 and closely parallels those observed during our investigations of enolate alkylation and other reactions of acyl dithiane oxides,[28] optimum diastereoselection being obtained with a 2-ethyl substituent. The sense of induced stereochemistry and the pattern of diastereoselectivity may be rationalized on the basis of a chelation-control model of acyl dithiane oxide reactivity successful for other reactions;[29] additional interaction of the metal counter-ion with the reagent is also a possibility. It is also conceivable that some loss of stereochemical integrity by equilibration may still be occurring under the reaction conditions in some cases. Readers are referred to our investigation of Mannich reactions for a full discussion.[30]



Scheme 5.

Table 5. Amination of (+)-2-acyl-2-ethyl-1,3-dithiane 1-oxides

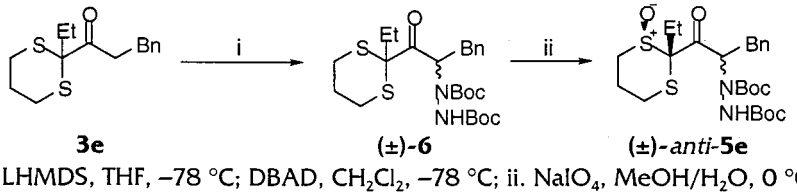
R	Substrate	Product	Yield/%
Bn	(+)-*anti*-**4e**	(+)-*anti*-**5e**	93
Ph	(+)-*anti*-**4f**	(+)-*anti*-**5f**	85
i-Pr	(+)-*anti*-**4g**	(+)-*anti*-**5g**	89
t-Bu	(+)-*anti*-**4h**	(+)-*anti*-**5h**	91

Electrophilic amination of the lithium enolates derived from *syn* and *anti* 2-acetyl-2-ethyl-1,3-dithiane 1-oxides **4a** with DBAD under our standard conditions also proceeded smoothly and in good yields. The (achiral) products are of interest as potential synthons for chiral α-aminoacid synthesis.

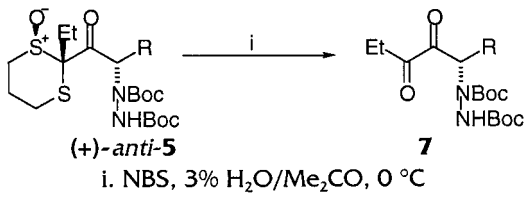
The four non-racemic acyl dithiane oxides *anti*-**4e–h** were next investigated, and underwent deprotonation and amination with DBAD smoothly under similar conditions to give the α-hydrazido ketones *anti*-**5e–h** in excellent yields (Scheme 5, Table 5).

Although the reactions proceeded smoothly and in high yields, in these cases we were unable to determine the diastereoselectivities of the reactions. Acceptable ^{1}H NMR spectra could not be recorded at any temperature; in $CDCl_3$ the spectra were still broad at 55°C and in higher boiling point solvents decomposition of the compounds occurred before the spectra became acceptable. We believe the systems are too sterically congested to allow free rotation even at these high temperatures. Efforts to separate the diastereoisomers by chromatographic methods including chiral HPLC, normal and reverse phase HPLC and GC were all in vain.

In a further effort to determine diastereoselectivity we synthesised one of the compounds by an alternative route. The enolate derived from acyl dithiane **3e** was aminated with DBAD to give α-hydrazido ketone (±)-**6**, which was then oxidised with sodium periodate to give (±)-*anti*-**5e**, as shown in Scheme 6. We believed that the oxidation step would prove unselective, and so produce a mixture of observable diastereoisomers. Attempts to separate or distinguish the isomers of this mixture were, however, again unsuccessful.



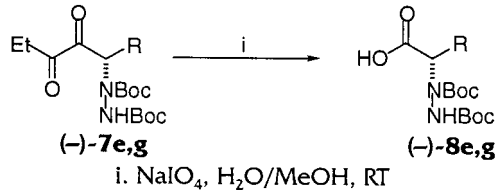
Scheme 6.



Scheme 7.

Table 6. Hydrolysis of α-hydrazido acyl dithiane 1-oxides

R	Substrate	Diketone	Yield/%	$[\alpha]_D^{20}$
Bn	(+)-*anti*-**5e**	(−)-**7e**	85	−42
Ph	(+)-*anti*-**5f**	(+)-**7f**	72	+80
i-Pr	(+)-*anti*-**5g**	(−)-**7g**	72	−64
t-Bu	(+)-*anti*-**5h**	(+)-**7h**	54	+54

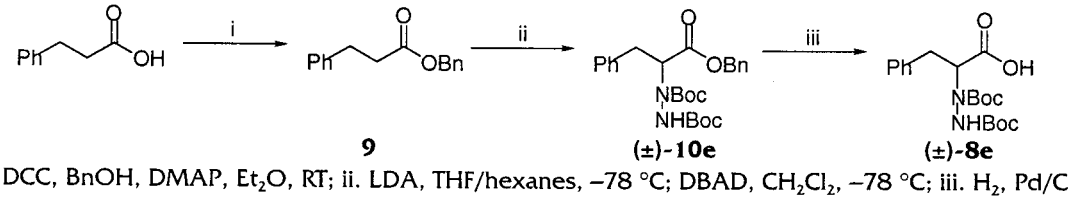


Scheme 8.

cleaved with sodium periodate to give the corresponding carboxylic acids with negligible loss of stereochemical integrity.[31] To convert the α-hydrazido diketones **7** into the carboxylic acids, they were therefore treated with sodium periodate in aqueous methanol (Scheme 8). Unfortunately, the reactions did not take place as smoothly as in the α-arylpropanoic acid series.[31] The diketone (−)-**7e** was oxidised cleanly overnight to the acid (−)-**8e** in 85% yield. Diketone (−)-**7g** was also oxidised to the acid (−)-**8g**, but the reaction required two days to reach completion and was lower yielding. The remaining two diketones (+)-**7f** and (+)-**7h** proved resistant to cleavage, even at elevated temperatures. Treatment of (+)-**7h** with lead tetraacetate, a more powerful oxidant, was also unsuccessful.

In order to determine the ees of our α-hydrazido acids, we first synthesised acid **8e** in racemic form for comparison. Dihydrocinnamic acid was esterified with benzyl alcohol under standard coupling conditions to give **9** in 84% yield.[32] Deprotonation of **9** with LDA and amination with DBAD gave (±)-**10e** in an extremely capricious reaction. Removal of the benzyl ester with palladium on charcoal under a hydrogen atmosphere gave racemic α-hydrazido acid (±)-**8e** in 94% yield (Scheme 9).

Attempts to separate acid (±)-**8e** by chiral HPLC using a variety of conditions were unsuccessful. Also unsuccessful were many attempts to differentiate the enantiomers by a



Scheme 9.

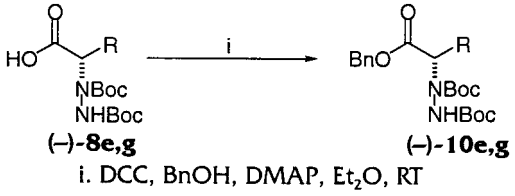
Despite the lack of stereochemical analysis, we decided to take our non-racemic material further through the synthesis, and to check the ee at a later stage, following removal of the sulfoxide moiety. During the DiTOX-mediated enantioselective synthesis of α-aryl propanoic acis,[31] we found aqueous *N*-bromosuccinimide (NBS) to be an effective reagent for hydrolysis of the dithiane oxide grouping in acylated derivatives containing an asymmetric centre at the α-position, allowing isolation of the corresponding 1,2-diketones with negligible loss of stereochemical integrity. Accordingly, we treated the hydrazido acyl dithiane oxides (+)-*anti*-**5e**–**h** with the same reagent system to access the diketones **7** in good yields as bright yellow oils or glasses (Scheme 7, Table 6).

Fortunately the ^{1}H NMR spectra of the diketones could be resolved at elevated temperatures, and furthermore the compounds all possessed significant optical rotations, supporting our contention that the initial enolate aminations were diastereoselective.

We have previously shown that 1,2-diketones containing an asymmetric centre at the α-position may be oxidatively

variety of chiral ^{1}H NMR shift reagents. We next turned our attention to benzyl ester (±)-**10e** and the methyl ester (±)-**11** derived from (±)-**8e**. Unfortunately the enantiomers of these esters were also inseparable and indistinguishable. Evans has reported the optical rotations for the benzyl esters of acids **8e** and **8g** with >99% ee.[16] Acids (−)-**8e** and (−)-**8g** were therefore converted into their corresponding benzyl esters (−)-**10e** and (−)-**10g**, again under standard dehydrating conditions (Scheme 10).

Analysis of their optical rotations indicates formation of the (*S*) esters with ees of 69% and 72% for compounds (−)-**10e** and (−)-**10g**, respectively. The (*S*) configuration is indeed



Scheme 10.

that predicted to be the major isomer according to our usual rules of thumb for reactions of dithiane oxide enolates.[2] The conversion of these compounds into the corresponding amino acids has been demonstrated.[14–16]

An enantioselective synthesis of two α-hydrazido acids has thus been successfully achieved, albeit with limited ee, in contrast to the results observed in our parallel synthesis of α-arylpropanoic acids. We cannot however determine whether this limitation in the ees is a result of poor diastereoselectivity in the key amination step, or of a degree of racemization subsequently.

Experimental

General experimental details

Purification of reagents. Commercially available reagents were used as supplied unless otherwise stated. Butyllithium 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. *N*-Bromosuccinimide was recrystallized from water. Diethyl tartrate was distilled under reduced pressure and stored over 4 Å molecular sieve.

Purification of solvents. Petroleum ether refers to petroleum ether, bp 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. Dichloromethane was distilled from calcium hydride.

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 sulfate and the solvents removed in vacuo 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) were used as eluent, unless otherwise stated.

Procedures

2-(1-Hydroxyethyl)-2-ethyl-1,3-dithiane 2a. 1,3-Dithiane (11.18 g, 92.98 mmol) was dissolved in dry THF (400 mL) and cooled to −20°C. A solution of *n*-butyllithium (64.05 mL, 102.48 mmol) was added slowly via syringe and stirring continued at −20°C for 40 min before cooling to −78°C. Iodoethane (7.45 mL, 93.14 mmol) was added and the reaction mixture allowed to reach room temperature over 2 h before recooling to −20°C prior to further addition of a solution of *n*-butyllithium (64.05 mL, 102.48 mmol). The reaction mixture was stirred at this temperature for 1 h, cooled to −78 °C and acetaldehyde (10.42 mL, 186.40 mmol) added. The reaction mixture was stirred and allowed to reach room temperature overnight. Normal work-up followed by flash column chromatography (5–15% ethyl acetate/petroleum ether) gave **2a** as a viscous, yellow oil (14.30 g, 80%); found: C, 50.38; H, 8.57; $C_8H_{16}OS_2$ requires C, 49.96; H, 8.38%; ν_{max} (film) 3465 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.15 (3H, t, J=7.6 Hz), 1.37 (3H, d, J=6.9 Hz), 1.60–2.13 (4H, series m), 2.56–2.65 (1H, m), 2.65–2.71 (1H, m), 2.81 (1H, s), 2.92–3.08 (2H, m), and 4.28 (1H, dq, J=6.5, 1.8 Hz); *m/z* (EI) 192.0644 (M^+), $C_8H_{16}OS_2$ requires 192.0643.

2-(1-Hydroxypropyl)-2-methyl-1,3,-dithiane 2b. 1,3-Dithiane (5 g, 41.58 mmol) was dissolved in dry THF (200 mL) and cooled to −20°C. A solution of *n*-butyllithium (28.58 mL, 45.73 mmol) was added slowly via syringe and stirring continued at −20°C for 40 min before cooling to −78°C. Iodomethane (2.59 mL, 41.60 mmol) was added and the reaction mixture allowed to reach room temperature over 2 h before recooling to −20°C prior to further addition of a solution of *n*-butyllithium (28.58 mL, 45.73 mmol). The reaction mixture was stirred at this temperature for 1 h, cooled to −78°C and propanal (6.00 mL, 83.16 mmol) added. The reaction mixture was stirred and allowed to reach room temperature overnight. Normal work-up followed by flash column chromatography (15% ethyl acetate/petroleum ether) gave **2b** as a pale yellow oil (7.38 g, 92%); found: C, 50.95; H, 8.68; $C_8H_{16}OS_2$ requires C, 49.96; H, 8.38%; ν_{max} (film) 3460 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.12 (3H, t, J=7.4 Hz), 1.40 (3H, s), 1.75–2.20 (4H, m), 2.55–2.70 (2H, m), 2.81 (1H, s), 2.90–3.10 (2H, m), and 3.85 (1H, br d, J=10.9 Hz); *m/z* (EI) 192.0643 (M^+), $C_8H_{16}OS_2$ requires 192.0643.

2-(1-Hydroxypropyl)-2-ethyl-l,3-dithiane 2c. 1,3-Dithiane (10 g, 83.17 mmol) was dissolved in dry THF (300 mL) and cooled to −20°C. A solution of *n*-butyllithium (57.17 mL, 91.47 mmol) was added slowly via syringe and stirring continued at −20°C for 40 min before cooling to −78°C. Iodoethane (6.66 mL, 83.27 mmol) was added and the reaction mixture allowed to reach room temperature over 2 h before recooling to −20°C prior to further addition of a solution of *n*-butyllithium (57.17 mL, 91.47 mmol). The reaction mixture was stirred at this temperature for 1 h, cooled to −78°C and propanal (9.02 mL, 125.08 mmol) added. The reaction mixture was stirred and allowed to reach room temperature overnight. Normal work-up followed by flash column chromatography (5–15% ethyl acetate/petroleum ether) gave **2c** as a viscous, clear oil which solidified to colourless crystals on application of a high vacuum (11.16 g, 65%); mp 41–43°C; found: C, 52.19; H, 8.77; $C_9H_{l8}OS_2$ requires C, 52.38; H, 8.79%; ν_{max} (film) 3440 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.06 (3H, t, J=7.4 Hz), 1.08 (3H, t, J=7.2 Hz), 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, 1.8 Hz); *m/z* (EI) 206.0800 (M^+), $C_9H_{18}OS_2$ requires 206.0799.

2-(1-Hydroxypropyl)-2-phenyl-1,3-dithiane 2d. 2-Phenyl-1,3-dithiane (5 g, 25.47 mmol) was dissolved in dry THF (200 mL) and cooled to –20°C. A solution of *n*-butyllithium (17.50 mL, 28 mmol) was added slowly via syringe and stirring continued at −20°C for 40 min before cooling to

−78°C. Propanal (3.67 mL, 50.89 mmol) was added and the reaction mixture allowed to reach room temperature overnight. Normal work-up followed by flash column chromatography (15% ethyl acetate/petroleum ether) gave **2d** as a viscous, clear oil which solidified to colourless crystals on trituration with petroleum ether (4.20 g, 65%); mp 68–70°C; found: C, 60.63; H, 7.13; $C_{13}H_{18}OS_2$ requires C, 61.38; H, 7.13%; ν_{max} (film) 3465 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.90 (3H, t, J=7.2 Hz), 1.09–1.33 (1H, m), 1.51–1.72 (1H, m), 1.87–2.00 (2H, m), 2.13 (1H, d, J=5.4 Hz), 2.65–2.81 (4H, m), 3.68–3.79 (1H, m), 7.26–7.46 (3H, m), and 7.92–8.00 (2H, m); m/z (EI) 254.0796 (M^+), $C_{13}H_{18}OS_2$ requires 254.0799.

2-(1-Hydroxy-3-phenylpropyl)-2-ethyl-1,3-dithiane 2e. A solution of *n*-butyllithium in hexanes (21.7 mL, 52.0 mmol) was added to a stirred solution of 2-ethyl-1,3-dithiane (7.0 g, 47.3 mmol) in THF (150 mL) at −20°C. After 1 h, dihydrocinnamaldehyde (7.61 mL, 52.0 mmol) was added, and the mixture allowed to reach room temperature over 1 h. Normal work-up, extraction with dichloromethane, drying over magnesium sulfate, and column chromatography using 5% ethyl acetate/hexane as eluent gave **2e** as a colourless oil (9.91 g, 74%); ν_{max} 3200–3600 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 1.06 (3H, t, J=7.4 Hz), 1.60–1.98 (4H, m), 2.25–2.38 (1H, m), 2.47–3.01 (8H, m), 3.96 (1H, d, J=10.2 Hz), and 7.18–7.30 (5H, m); m/z (EI) 282.1112 (M^+); $C_{15}H_{22}OS_2$ requires 282.1111.

2-(1-Hydroxy-2-phenylethyl)-2-ethyl-1,3-dithiane 2f. A solution of *n*-butyllithium in hexanes (39.9 mL, 91.6 mmol) was added to a stirred solution of 1,3-dithiane (10 g, 83.3 mmol) in THF (350 mL) at −20°C. After 1 h, the reaction mixture was cooled to −78°C and ethyl iodide (7.33 mL, 91.6 mmol) added. The mixture was allowed to reach room temperature over 1.5 h, then recooled to −20°C, and a solution of *n*-butyllithium in hexanes (39.9 mL, 91.6 mmol) added. After 1 h, the mixture was cooled to −78°C, phenylacetaldehyde (10.25 mL, 91.6 mmol) added, and the mixture allowed to reach room temperature over 17 h. Normal work-up procedure followed by flash column chromatography using 5% ethyl acetate/petroleum ether as eluent furnished **2f** as a colourless oil (11.71 g, 52%); ν_{max} 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 268.0955 (M^+); $C_{14}H_{20}OS_2$ requires 268.0956. Found: C, 62.73; H 7.53%. Calcd for $C_{14}H_{20}OS_2$: C, 62.64; H 7.51%.

2-(1-Hydroxy-3-methylbutyl)-2-ethyl-1,3-dithiane 2g. A solution of *n*-butyllithium in hexanes (15.5 mL, 37.1 mmol) was added to a stirred solution of 2-ethyl-1,3-dithiane (5.0 g, 33.8 mmol) in THF (100 mL) at −20°C. After 1 h, isovaleraldehyde (3.99 mL, 37.1 mmol) was added, and the mixture allowed to reach room temperature over 2 h. Normal work-up and column chromatography using 10% ethyl acetate/hexane as eluent gave **2g** as a colourless oil (6.02 g, 76%); ν_{max} 3479 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 0.96 (3H, d, J=5.5 Hz), 0.99 (3H, d, J=5.8 Hz), 1.08 (3H, t, J=7.4 Hz), 1.38–1.48 (1H, m), 1.63–1.74 (2H, m), 1.76–1.96 (3H, m), 1.99–2.12 (1H, m), 2.44–2.53 (1H, m), 2.60–2.69 (2H, m), 2.91–3.04 (2H, m), and 4.08 (1H, dd, J=10.1 and 1.7 Hz); m/z (CI) 234.1112 (M^+); $C_{11}H_{22}OS_2$ requires 234.1112. Found: C, 56.78; H, 9.72%. Calcd for $C_{11}H_{22}OS_2$: C, 56.36; H, 9.46%.

2-(1-Hydroxy-3,3-dimethylbutyl)-2-ethyl-1,3-dithiane 2h. A solution of *n*-butyllithium in hexanes (17.5 mL, 37.1 mmol) was added to a stirred solution of 2-ethyl-1,3-dithiane (5.4 g, 36.5 mmol) in THF (100 mL) at −20°C. After 1 h, 3,3-dimethylbutyraldehyde (5.00 mL, 40.2 mmol) was added, and the mixture allowed to reach room temperature over 0.5 h. Normal work-up and column chromatography using 10% ethyl acetate/ isohexane as eluent gave **2h** as a colourless oil (8.73 g, 97%); ν_{max} 3480 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 1.01 (9H, s), 1.09 (3H, t, J=7.4 Hz), 1.31 (1H, dd, J=14.1 and 8.5 Hz), 1.57–1.71 (1H, m), 1.76–1.96 (3H, m), 2.01–2.11 (1H, m), 2.57–2.66 (2H, m), 2.76–2.78 (1H, m), 2.92–3.04 (2H, m), and 4.11 (1H, d, J=8.8 Hz); m/z (FAB) 248.1268 (M^+); $C_{12}H_{24}OS_2$ requires 248.1269. Found: C, 58.29; H, 10.08%. Calcd for $C_{12}H_{24}OS_2$: C, 58.01; H, 9.74%.

2-Acetyl-2-ethyl-1,3-dithiane 3a. A 2 M solution of oxalyl chloride (28.65 mL, 57.30 mmol) in dry CH_2Cl_2 was added to a solution of DMSO (8.13 mL, 114.57 mmol) in dry CH_2Cl_2 (100 mL) via cannula at −78°C. After stirring at −78°C for 30 min, **2a** (10 g, 51.99 mmol) was added as a solution in dry CH_2Cl_2 (100 mL) via cannula and stirring continued for a further 2 h. Triethylamine (36.30 mL, 260.44 mmol) was added and the reaction mixture allowed to reach 0°C overnight. The mixture was poured onto 5% aqueous HCl (100 mL) and shaken thoroughly. The organic phase was washed with saturated aqueous sodium hydrogen carbonate, dried over magnesium sulfate, and the solvents removed under reduced pressure. Flash column chromatography (15% ethyl acetate/petroleum ether) gave **3a** as a yellow oil (7.65 g, 77%); found: C, 50.78; H, 7.50; $C_8H_{14}OS_2$ requires C, 50.49; H, 7.41%; ν_{max} (film) 1737 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.00 (3H, t, J=7.5 Hz), 1.70–1.90 (1H, m), 1.95–2.10 (3H, m), 2.33 (3H, s), 2.55–2.75 (2H, m), and 2.90–3.05 (2H, m); m/z (EI) 190.0489 (M^+), $C_8H_{14}OS_2$ requires 190.0486.

2-Propanoyl-2-methyl-1,3-dithiane 3b. A 2 M solution of oxalyl chloride (10.31 mL, 20.62 mmol) in dry CH_2Cl_2 was added to a solution of DMSO (2.93 mL, 41.29 mmol) in dry CH_2Cl_2 (10 mL) via cannula at −78°C. After stirring at −78°C for 30 min, **2b** (3.56 g, 18.72 mmol) was added as a solution in dry CH_2Cl_2 (50 mL) via cannula and stirring continued for a further 2 h. Triethylamine (7.84 mL, 56.25 mmol) was added and the reaction mixture allowed to reach 0°C overnight. The mixture was poured onto 5% aqueous HCl (50 mL) and shaken thoroughly. The organic phase was washed with saturated aqueous sodium hydrogen carbonate, dried over magnesium sulfate, and the solvents removed under reduced pressure. Flash column chromatography (15% ethyl acetate/petroleum ether) gave **3b** as a yellow oil (1.70 g, 48%); found: C, 51.39; H, 7.64; $C_8H_{14}OS_2$ requires C, 50.49; H, 7.41%; ν_{max} (film) 1710 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.04 (3H, t, J=7.2 Hz), 1.60 (3H, s), 1.63–1.84 (1H, m), 1.98–2.10 (1H, m), 2.50–2.61 (2H, m), 2.64 (2H, q, J=7.14 Hz), and 2.97–3.12 (2H, m); m/z (EI) 190.0484 (M^+), $C_8H_{14}OS_2$ requires 190.0486.

2-Propanoyl-2-ethyl-1,3-dithiane 3c. A 2 M solution of oxalyl chloride (6.41 mL, 12.82 mmol) in dry CH_2Cl_2 was added to a solution of DMSO (1.82 mL, 25.65 mmol) in dry CH_2Cl_2 (10 mL) via cannula at −78°C. After stirring at −78°C for 30 min, **2b** (2.4 g, 11.63 mmol) was added as a solution in dry CH_2Cl_2 (50 mL) via cannula and stirring continued for a further 2 h. Triethylamine (8.12 mL, 58.26 mmol) was added and the reaction mixture allowed to reach 0°C overnight. The mixture was poured onto 5% aqueous HCl (50 mL) and shaken thoroughly. The organic phase was washed with saturated aqueous sodium hydrogen carbonate, dried over magnesium sulfate, and the solvents removed under reduced pressure. Flash column chromatography (15% ethyl acetate/petroleum ether) gave **3b** as a yellow oil (1.60 g, 67%); found: C, 51.93; H, 7.84; $C_9H_{16}OS_2$ requires C, 52.90; H, 7.89%; ν_{max} (film) 1700 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.02 (3H, t, J=7.5 Hz), 1.15 (3H, t, J=7.3 Hz), 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), 2.85–3.10 (2H, m); m/z (EI) 204 (M^+).

2-Propanoyl-2-phenyl-1,3-dithiane 3d. A 2 M solution of oxalyl chloride (9.09 mL, 18.18 mmol) in dry CH_2Cl_2 was added to a solution of DMSO (2.60 mL, 36.64 mmol) in dry CH_2Cl_2 (10 mL) via cannula at −78°C. After stirring at −78°C for 30 min, **2d** (4.20 g, 16.51 mmol) was added as a solution in dry CH_2Cl_2 (50 mL) via cannula and stirring continued for a further 2 h. Triethylamine (6.92 mL, 49.65 mmol) was added and the reaction mixture allowed to reach 0°C overnight. The mixture was poured onto 5% aqueous HCl (50 mL) and shaken thoroughly. The organic phase was washed with saturated aqueous sodium hydrogen carbonate, dried over magnesium sulfate, and the solvents removed under reduced pressure. Flash column chromatography (15% ethyl acetate/petroleum ether) gave **3d** as colourless crystals on trituration with petroleum ether (2.83 g, 68%); mp 78–80°C; found: C, 61.87; H, 6.39; $C_{13}H_{16}OS_2$ requires C, 61.82; H, 6.38%; ν_{max} (film) 1710 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.98 (3H, t, J=7.3 Hz), 1.73–1.96 (1H, m), 1.98–2.15 (1H, m), 2.36 (2H, q, J=7.4 Hz), 2.63–2.78 (2H, m), 3.03–3.20 (2H, m), 7.25–7.42 (3H, m), 7.45–7.55 (2H, m); m/z (EI) 252.0638 (M^+), $C_{13}H_{16}OS_2$ requires 252.0643.

2-(3-Phenylpropan-1-oyl)-2-ethyl-1,3-dithiane 3e. TFAA (6.00 mL, 42.4 mmol) was added to a stirred solution of DMSO (4.42 mL, 62.2 mmol) in CH_2Cl_2 (75 mL) at −78°C. After 30 min, a solution of **2e** (8.0 g, 28.3 mmol) in CH_2Cl_2 (30 mL) was added dropwise, and stirring continued at −78°C for 1.5 h. Triethylamine (11.93 mL, 84.8 mmol) was added, and the mixture allowed to reach room temperature over 1 h. The mixture was poured into 5% aqueous hydrochloric acid (200 mL), extracted into CH_2Cl_2, and the organic phase collected, washed with aqueous sodium hydrogen carbonate, dried over magnesium sulfate, and concentrated in vacuo. Column chromatography using 10% ethyl acetate/hexane as eluent gave **3e** as a colourless solid (7.78 g, 98%); ν_{max} 1704 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 0.91 (3H, t, J=7.6 Hz), 1.61–1.86 (1H, m), 1.99 (2H, q, J=7.6 Hz), 1.95–2.16 (1H, m), 2.53–2.61 (2H, m), 2.81–3.06 (6H, m), and 7.15–7.31 (5H, m); m/z (EI) 280.0956 (M^+); $C_{15}H_{20}OS_2$ requires 280.0957. Found: C, 64.36; H, 7.22%. Calcd for $C_{15}H_{20}OS_2$: C, 64.24; H, 7.19%.

2-(2′-Phenylacetyl)-2-ethyl-1,3-dithiane 3f. A solution of TFAA (8.93 mL, 63.2 mmol) in CH_2Cl_2 (40 mL) was added to a stirred solution of DMSO (6.58 mL, 92.6 mmol) in CH_2Cl_2 (70 mL) at −78°C. After stirring at −78°C for 30 min, a solution of **2f** (11.29 g, 42.1 mmol) in CH_2Cl_2 (40 mL) was added dropwise, and stirring continued at −78°C for 1.5 h. Triethylamine (17.61 mL, 126.3 mmol) was added, and the mixture allowed to reach room temperature over 1.5 h. The mixture was poured into 5% aqueous hydrochloric acid (300 mL), and the organic phase collected, washed with aqueous sodium hydrogen carbonate (2×50 mL), dried over magnesium sulfate and concentrated in vacuo to yield an orange solid. Trituration with petroleum ether gave **3f** as a colourless crystalline solid (9.12 g, 81%), mp 85–86°C; ν_{max} 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 266.0798 (M^+); $C_{14}H_{18}OS_2$ requires 266.0799. Found: C, 62.83; H, 6.78%. Calcd for $C_{14}H_{18}OS_2$: C, 63.12; H, 6.81%.

2-(3-Methylbutan-1-oyl)-2-ethyl-1,3-dithiane 3g. TFAA (5.34 mL, 38.1 mmol) was added to a stirred solution of DMSO (3.94 mL, 55.9 mmol) in CH_2Cl_2 (50 mL) at −78°C. After stirring at −78°C for 30 min, a solution of **2g** (5.90 g, 25.4 mmol) in CH_2Cl_2 (50 mL) was added dropwise, and stirring continued at −78°C for 1.5 h. Triethylamine (10.54 mL, 76.3 mmol) was added, and the mixture allowed to reach room temperature over 1 h. The mixture was poured into 5% aqueous hydrochloric acid (150 mL), extracted into CH_2Cl_2, and the organic phase collected, washed with aqueous sodium hydrogen carbonate, dried over magnesium sulfate and concentrated in vacuo. Column chromatography using 10% ethyl acetate/hexane as eluent gave **3g** as a colourless oil (4.80 g, 82%); ν_{max} 1702 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 0.95 (6H, d, J=6.9 Hz), 1.01 (3H, t, J=7.4 Hz), 1.74–1.91 (1H, m), 2.03 (2H, q, J=7.4 Hz), 2.03–2.13 (1H, m), 2.16–2.32 (1H, m), 2.59 (2H, d, J=6.9 Hz), 2.60–2.68 (2H, m), and 2.95–3.06 (2H, m); m/z (CI) 233.1035 (M^++H); $C_{11}H_{21}OS_2$ requires 233.1034. Found: C, 56.73; H, 8.58%. Calcd for $C_{11}H_{20}OS_2$: C, 56.85; H, 8.67%.

2-(3,3-Dimethylbutan-1-oyl)-2-ethyl-1,3-dithiane 3h. TFAA (7.26 mL, 51.4 mmol) was added to a stirred solution of DMSO (5.35 mL, 75.4 mmol) in CH_2Cl_2 (75 mL) at −78°C. After stirring at −78°C for 30 min, a solution of **2h** (8.50 g, 34.3 mmol) in CH_2Cl_2 (75 mL) was added dropwise, and stirring continued at −78°C for 1.5 h. Triethylamine (14.33 mL, 102.8 mmol) was added, and the mixture allowed to reach room temperature over 1 h. The mixture was poured into 5% aqueous hydrochloric acid (200 mL), extracted into CH_2Cl_2, and the organic phase collected, washed with aqueous sodium hydrogen carbonate, dried over magnesium sulfate and concentrated in vacuo. Column chromatography using 10% ethyl acetate/hexane as eluent gave **3h** as a colourless oil (7.38 g, 88%); ν_{max} 1706 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 1.02 (3H, t, J=7.4 Hz), 1.07 (9H, s), 1.74–1.89 (1H, m), 2.02 (2H, q, J=7.4 Hz), 2.03–2.12 (1H, m), 2.61–2.68 (2H, m), 2.63 (2H, s), and 2.95–3.06 (2H, m); m/z (FAB) 246.1111 (M^+); $C_{12}H_{22}OS_2$ requires 246.1112. Found: C, 58.17; H, 9.20%. Calcd for $C_{12}H_{22}OS_2$: C, 58.49; H, 9.00%.

General procedure for the achiral sulfoxidation of 2-acyl-2-alkyl-1,3 dithianes to the corresponding sulfoxides

Using sodium metaperiodate. A solution of sodium metaperiodate (1 equiv.) in water (ca. 10 mL/g) was added dropwise to a solution of the substrate in methanol (ca. 50 mL/g of substrate) at 0°C over 0.5 h. The mixture was stirred at this temperature overnight and then allowed to reach room temperature. The precipitate was removed by filtration and washed thoroughly with CH_2Cl_2. The filtrate was evaporated to half its original volume and partitioned between water and CH_2Cl_2. The aqueous layer was twice washed with CH_2Cl_2, the combined organic extracts were dried over magnesium sulfate and the solvents removed under reduced pressure to yield a crude mixture of diastereoisomeric sulphoxides. These were separated by flash column chromatography using 50–100% ethyl acetate/petroleum ether solvent systems as eluent.

Tartaric acid work-up. The reaction mixture was allowed to reach room temperature, and concentrated in vacuo. The crude material was dissolved in diethyl ether (100 mL) and cooled to −10°C before addition of saturated aqueous tartaric acid (100 mL). After stirring for 1.5 h at −10°C, the mixture was allowed to reach room temperature and the ether layer separated. The aqueous layer was extracted with diethyl ether (3×75 mL) and CH_2Cl_2 (3×75 mL), and the organic fractions combined, dried over magnesium sulfate, and concentrated in vacuo.

(±)-*syn* and *anti* 2-Acetyl-2-ethyl-1,3-dithiane 1-oxides 4a. Treatment of ketone **3a** (2.50 g, 13.14 mmol) as described above with sodium metaperiodate (2.81 g, 13.14 mmol) in water (20 mL) and methanol (125 mL) furnished the diastereoisomeric sulfoxides, separated to yield the *syn* and *anti* diastereoisomers, both as colourless crystalline solids after application of a high vacuum.

For *syn*-**4a**: (0.76 g, 28%), mp 57–58°C; found: C, 46.76; H, 6.87; $C_8H_{14}O_2S_2$ requires C, 46.57; H, 6.84%; ν_{max} (soln) 1701 and 1041 cm^{-1}; δ_H (200 MHz, $CDCl_3$), 1.10 (3H, t, J=7.9 Hz), 2.00–2.20 (1H, m), 2.30–2.45 (3H, m), 2.45 (3H, s), 2.50–2.70 (1H, m), and 2.85–3.30 (3H, m); *m/z* (EI) 206.0437 (M^+), $C_8H_{l4}O_2S_2$ requires 206.0435.

For *anti*-**4a**: (1.07 g, 39%), mp 40–41°C; found: C, 46.53; H, 6.87; $C_8H_{14}O_2S_2$ requires C, 46.57; H, 6.84%; ν_{max} (soln) 1694 and 1055 cm^{-1}; δ_H (200 MHz, $CDCl_3$), 1.05 (3H, t, J=7.7 Hz), 1.70–1.90 (2H, m), 2.10–2.30 (1H, m), 2.45 (3H, s), 2.45–2.70 (3H, m), and 3.05–3.15 (2H, m); *m/z* (EI) 206.0439 (M^+), $C_8H_{14}O_2S_2$ requires 206.0435.

(±)-*syn* and *anti* 2-Propanoyl-2-methyl-1,3,dithiane 1-oxides 4b. Treatment of ketone **3b** (1.70 g, 8.93 mmol) as described above with sodium metaperiodate (1.92 g, 8.98 mmol) in water (20 mL) and methanol (100 mL) furnished the diastereoisomeric sulfoxides, separated to yield the *syn* and *anti* diastereoisomers as colourless crystalline solids.

For *syn*-**4b**: (0.31 g, 17%), mp 40–42°C; found: C, 46.55; H, 6.87; $C_8H_{14}O_2S_2$ requires C, 46.57; H, 6.84%; ν_{max} (soln) 1705 and 1040 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.08 (3H, t, J=7.3 Hz), 1.84 (3H, s), 2.20–2.50 (3H, m), 2.50–2.90 (2H, m), and 3.0–3.30 (3H, m); *m/z* (EI) 206.0436 (M^+), $C_8H_{14}O_2S_2$ requires 206.0435.

For *anti*-**4b**: (0.52 g, 28%), mp 56–57°C; found: C, 46.62; H, 6.85; $C_8H_{14}O_2S_2$ requires C, 46.57; H, 6.84%; ν_{max} (soln) 1695 and 1040 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.13 (3H, t, J=7.4 Hz), 1.68 (3H, s), 1.79–1.89 (1H, m), 2.36–2.74 (4H, m), 2.9–3.06 (2H, m), 3.18–3.26 (1H, m); *m/z* (EI) 206.0439 (M^+); $C_8H_{14}O_2S_2$ requires 206.0435.

(±)-*syn* and *anti* 2-Propanoyl-2-ethyl-1,3-dithiane 1-oxides 4c. Treatment of ketone **3c** (2.50 g, 12.23 mmol) as above with sodium metaperiodate (2.62 g, 12.25 mmol) in water (20 mL) and methanol (125 mL) furnished the diastereoisomeric sulfoxides, separated to yield the *syn* and *anti* diastereoisomers as colourless crystalline solids, after application of a high vacuum.

For *syn*-**4c**: (0.72 g, 27%), mp 69–71°C; found: C, 48.96; H, 7.29; $C_9H_{l6}O_2S_2$ requires C, 49.06; H, 7.32%; ν_{max} (film) 1710 and 1050 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.09 (3H, t, J=7.4 Hz), 1.15 (3H, t, J=7.1 Hz), 2.01–2.20 (1H, m), 2.20–2.50 (3H, m), and 2.50–3.35 (6H, series m); *m/z* (EI) 220.0593 (M^+), $C_9H_{16}O_2S_2$ requires 220.0592.

For *anti*-**4c**: (1.05 g, 39%), mp 61–63°C; found: C, 49.01; H, 7.25; $C_9H_{l6}O_2S_2$ requires C, 49.06; H, 7.32%; ν_{max} (soln) 1700 and 1060 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.03 (3H, t, J=7.4 Hz), 1.14 (3H, t, J=7.5 Hz), 1.71–1.91 (2H, m), 2.10–2.30 (1H, m), 2.40–2.74 (4H, m), and 2.95–3.13 (3H, m); *m/z* (EI) 220.0593 (M^+), $C_9H_{l6}O_2S_2$ requires 220.0592.

(±)-*syn* and *anti* 2-Propanoyl-2-phenyl-1,3-dithiane 1-oxides 4d. Treatment of ketone **3c** (2.30 g, 9.11 mmol) as above with sodium metaperiodate (1.95 g, 9.12 mmol) in water (20 mL) and methanol (100 mL) furnished the diastereoisomeric sulfoxides, separated to yield the *syn* and the *anti* diastereoisomers as colourless crystalline solids after application of a high vacuum.

For *syn*-**4d**: (0.50 g, 20%), mp 72–74°C; found: C, 58.08; H, 6.01; $C_{13}H_{l6}O_2S_2$ requires C, 58.18; H, 6.01%; ν_{max} (film) 1710 and 1060 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.92 (3H, t, J=7.2 Hz), 1.80–2.05 (1H, s), 2.25–2.40 (6H, series m), 3.05–3.20 (1H, m), 7.30–7.49 (3H, m), and 7.58–7.68 (2H, m); *m/z* (EI) 268.0593 (M^+), $C_{13}H_{l6}O_2S_2$ requires 268.0592.

For *anti*-**4d**: (0.88 g, 36%), mp 125–126°C; found: C, 57.95; H, 5.99; $C_{13}H_{l6}O_2S_2$ requires C, 58.18; H, 6.01%; ν_{max} (film) 1690 and 1050 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.06 (3H, t, J=3 Hz), 1.70–1.90 (1H, m), 2.35–2.60 (2H, m), 2.61–2.90 (3H, m), 3.04–3.15 (1H, m), 3.27–3.45 (1H, m), and 7.45–7.55 (5H, m); *m/z* (EI) 268.0590 (M^+), $C_{13}H_{l6}O_2S_2$ requires 268.0592.

(+)-*anti*-2-(*R*)-(3-Phenylpropanoyl)-2-ethyl-1,3-dithiane 1-(*R*)-oxide (+)-*anti*-4e. Titanium isopropoxide (7.54 mL, 25.3 mmol) was added to a stirred solution of (+)-diethyl tartrate (8.68 mL, 50.7 mmol) in dichloromethane (60 mL)

at room temperature. After 5 min, water (0.41 mL, 23.0 mmol) was added, and the mixture stirred for 30 min. The mixture was cooled to −30°C, and a solution of **3e** (6.45 g, 23.0 mmol) in dichloromethane (50 mL) added. After 5 min, a cooled solution of cumene hydroperoxide (5.13 mL, 27.6 mmol) in dichloromethane (10 mL) was added dropwise over 20 min. After stirring for 3 days at −30°C, tartaric acid work-up and flash column chromatography using 50% EtOAc/hexane as eluent gave (+)-*anti*-**4e** as a colourless solid (5.54 g, 81%), mp 59–60°C; ν_{max} 1696 and 1053 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 0.92 (3H, t, J=7.6 Hz), 1.62–1.83 (2H, m), 2.05–2.49 (4H, m), 2.81–3.07 (5H, m), 3.36–3.58 (1H, m), and 7.17–7.32 (5H, m); *m/z* (CI) 296.0903 (M^+); $C_{15}H_{20}O_2S_2$ requires 296.0905. Found: C, 60.80; H, 6.79%. Calcd for $C_{15}H_{20}O_2S_2$: C, 60.77; H, 6.80%. $[\alpha]_D^{25}$=+177.0 (c=1.02, $CHCl_3$).

(+)-*anti*-2-(*R*)-(2-Phenylacetyl)-2-ethyl-1,3-dithiane 1-(*R*)-oxide (+)-*anti*-4f. Titanium isopropoxide (9.84 mL, 33.1 mmol) was added to a stirred solution of (+)-diethyl tartrate (11.3 mL, 66.2 mmol) in dichloromethane (75 mL) at room temperature. After 5 min, water (0.54 mL, 30.1 mmol) was added, and the mixture stirred for 30 min. The mixture was cooled to −30°C, and a solution of **3f** (8.00 g, 30.1 mmol) in dichloromethane (50 mL) added. After 5 min, a cooled solution of cumene hydroperoxide (8.33 mL, 45.2 mmol) in dichloromethane (10 mL) was added dropwise over 20 min. After stirring for 3 days at −26°C, tartaric acid work-up and flash column chromatography using 50% EtOAc/Petroleum ether as eluent gave (+)-*anti*-**4f** as a colourless crystalline solid (5.44 g, 64%), mp 112–113°C; ν_{max} 1697, 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* 282.0752 (M^+); $C_{14}H_{18}O_2S_2$ requires 282.0748. Found: C, 59.30; H, 6.41%. Calcd for $C_{14}H_{18}O_2S_2$: C, 59.54; H, 6.42%. $[\alpha]_D^{25}$=+251.4 (c=0.7, $CHCl_3$).

(+)-*anti*-2-(*R*)-(3-Methylbutanoyl)-2-ethyl-1,3-dithiane 1-(*R*)-oxide (+)-*anti*-4g. Titanium isopropoxide (6.32 mL, 21.2 mmol) was added to a stirred solution of (+)-diethyl tartrate (7.28 mL, 42.5 mmol) in dichloromethane (50 mL) at room temperature. After 5 min, water (0.35 mL, 19.3 mmol) was added and the mixture stirred for 30 min. The mixture was cooled to −30°C, and a solution of **3g** (4.48 g, 19.3 mmol) in dichloromethane (30 mL) added. After 5 min, a cooled solution of cumene hydroperoxide (4.44 mL, 23.1 mmol) in dichloromethane (10 mL) was added dropwise over 20 min. After stirring for 3 days at −30°C, tartaric acid work-up and flash column chromatography using 50% EtOAc/hexane as eluent gave (+)-*anti*-**4g** as an off-white solid (3.12 g, 65%); ν_{max} 1693, 1059 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 0.98 (6H, d, J=6.9 Hz), 1.04 (3H, t, J=7.4 Hz), 1.71–1.88 (2H, m), 2.12–2.28 (2H, m), 2.42–2.65 (4H, m), 2.96 (1H, dd. J=18.0, 6.9 Hz), and 3.05–3.10 (2H, m); *m/z* (CI) 249.0964 (M^++H); $C_{11}H_{21}O_2S_2$ requires 249.0983. Found: C, 53.08; H, 8.12%. Calcd for $C_{11}H_{20}O_2S_2$: C, 53.19; H, 8.12%. $[\alpha]_D^{25}$=+220.0 (c=1.03, $CHCl_3$).

(+)-*anti*-2-(*R*)-(3,3-Dimethylbutanoyl)-2-ethyl-1,3-dithiane 1-(*R*)-oxide (+)-*anti*-4h. Titanium isopropoxide (8.64 mL, 29.1 mmol) was added to a stirred solution of (+)-diethyl tartrate 9.95 mL, 58.1 mmol) in dichloromethane (75 mL) at room temperature. After 5 min, water (0.48 mL, 26.4 mmol) was added and the mixture stirred for 30 min. The mixture was cooled to −30°C, and a solution of **3h** (6.50 g, 26.4 mmol) in dichloromethane (50 mL) was added. After 5 min, a cooled solution of cumene hydroperoxide (5.88 mL, 31.7 mmol) in dichloromethane (10 mL) was added dropwise over 20 min. After stirring for 3 days at −30°C, tartaric acid work-up and flash column chromatography using 50% EtOAc/hexane as eluent gave (+)-*anti*-**4h** as an off-white solid (4.58 g, 66%); ν_{max} 1692, 1056 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 1.07 (3H, t, J=7.4 Hz), 1.08 (9H, s), 1.71–1.85 (2H, m), 2.07–2.21 (1H, m), 2.39–2.66 (3H, m), 2.46 (1H, d, J=18.7 Hz), 3.04 (1H, d, J=18.7 Hz), and 3.05–3.10 (2H, m); *m/z* (FAB) 262.1070 (M^+); $C_{12}H_{22}O_2S_2$ requires 262.1062. Found: C, 55.09; H 8.45%. Calcd for $C_{12}H_{22}O_2S_2$: C, 54.92; H 8.45%. $[\alpha]_D^{25}$=+179.0 (c=1.03, $CHCl_3$).

General procedure for the generation of lithium enolates of *syn* or *anti* 2-acyl-2-alkyl-1,3-dithiane 1-oxides and their amination with di-*tert*-butylazodicarboxylate

A stirred solution of the 2-acyl-2-alkyl-1,3-dithiane 1-oxide substrate in THF (ca. 25 mL/g substrate) was cooled to −78°C and a 1 M solution of LHMDS (1.1 equiv.) added via syringe. After 10−20 min, the solution was transferred by cannula into a pre-cooled solution of DBAD (1.1 equiv.) in dichloromethane at −78°C, with flushing of the cannula using THF (2 mL). After 5 min, acetic acid (3.0 equiv.) was added, and the reaction allowed to reach room temperature. Normal work-up and column chromatography using 50% ethyl acetate/hexane gave the α-hydrazido ketone products.

Ammonium chloride variant work-up procedure. After reaching room temperature, the reaction mixture was poured onto a solution of saturated aqueous ammonium chloride (ca. 50 mL/mmol substrate) and extracted into dichloromethane (3×25 mL). The combined organic extracts were dried over magnesium sulfate and the solvents removed under reduced pressure to yield the crude diastereoisomeric products which were analysed by 250 or 400 MHz ^{1}H NMR spectroscopy either directly or after flash column chromatography through a short column of silica gel (Merck 9385) using ethyl acetate/petroleum ether solvent systems as eluent.

(±)-*syn*-2-(2-(*N*,*N*′-Bis-(*tert*-butoxycarbonyl)hydrazino)-acetyl)-2-(*S*)-ethyl-1,3-dithiane 1-(*R*)-oxide (±)-*syn*-5a. The lithium enolate of *syn*-2-acetyl-2-ethyl-1,3-dithiane 1-oxide (±)-*syn*-**4a** (0.40 g, 1.94 mmol) was generated as described above and added via cannula to a stirred solution of DBAD (0.49 g, 2.13 mmol) in THF (8 mL) at −78°C. The reaction mixture was allowed to reach room temperature overnight. Normal work-up procedure gave (±)-*syn*-**5a** as a colourless crystalline solid (0.75 g, 89%), mp 57–58°C; found: C, 49.15; H, 7.38; N, 6.43; $C_{18}H_{32}O_6N_2S_2$ requires C, 49.52; H, 7.39; N, 6.42%; ν_{max} (soln) 3244, 1719, 1479, and 1054 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 325 K) 1.11 (3H, t, J=7.2 Hz), 1.45 (18H, s), 2.05–2.15 (1H, m), 2.24–2.45

(2H, m), 2.47–2.61 (1H, m), 2.80–3.30 (4H, series m), 4.50–4.80 (2H, m), and 6.60 (1H, br s); *m/z* (CI, NH_3) 437 (M^++1).

(±)-*anti*-2-(2-(*N*,*N*′-Bis-(*t*-butoxycarbonyl)hydrazino)-acetyl)-2-(*R*)-ethyl-1,3-dithiane 1-(*R*)-oxide (±)-*anti*-5a. The lithium enolate of *anti* 2-acetyl-2-ethyl-1,3-dithiane 1-oxide (±)-*anti*-**4a** (0.10 g, 0.485 mmol) was generated as described above and added via cannula to a stirred solution of DBAD (0.123 g, 0.534 mmol) in THF (3 mL) at −78°C. The reaction mixture was allowed to reach room temperature overnight. Normal work-up procedure gave (±)-*anti*-**5a** as a colourless crystalline solid (0.153 g, 72%), mp 51–53°C; found: C, 48.97; H, 7.39; N, 6.40; $C_{18}H_{32}O_6N_2S_2$ requires C, 49.52; H, 7.39; N, 6.42%; ν_{max} (soln) 3244, 1719, 1479, and 1054 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 325 K) 1.07 (3H, t, *J*=7.5 Hz), 1.46 (18H, s), 1.69–1.82 (2H, m), 2.13–2.30 (1H, m), 2.40–2.60 (2H, m), 2.70–2.80 (1H, m), 2.90–3.12 (2H, m), 4.50 (1H, m), 5.10 (1H, m), and 6.55 (1H, br s); *m/z* (CI, NH_3) 437 (M^++1).

(±)-*syn*-2-(2-(*S*)-(*N*,*N*′-Bis-(*t*-butoxycarbonyl)hydrazino)-propanoyl)-2-(*S*)-methyl-1,3-dithiane 1-(*R*)-oxide (±)-*syn*-5b. The lithium enolate of *syn* 2-propanoyl-2-methyl-1,3-dithiane 1-oxide (±)-*syn*-**4b** (0.20 g, 0.969 mmol) was generated as described above and added via cannula to a stirred solution of DBAD (0.25 g, 1.09 mmol) in THF (5 mL) at −78°C. The reaction mixture was stirred for 10 min at −78°C before addition of glacial acetic acid (0.28 mL, 4.66 mmol). The reaction mixture was allowed to reach room temperature overnight. Normal work-up procedure gave (±)-*syn*-**5b**, a 3:1 mixture of inseparable product diastereoisomers, as a colourless oil (0.32 g, 76%); found: C, 49.15; H, 7.45; N, 6.58; $C_{18}H_{32}O_6N_2S_2$ requires C, 49.52; H, 7.39; N, 6.42%; ν_{max} (soln) 3301, 1750, 1705, 1454, and 1059 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 325 K) major isomer: 1.35 (3H, d, *J*=6.6 Hz), 1.43 (9H, s), 1.44 (9H, s), 1.90 (3H, s), 2.20–2.39 (2H, m), 2.40–2.50 (1H, m), 2.84–2.95 (1H, m), 3.00–3.09 (1H, m), 3.72 (1H, br t, *J*=12.4 Hz), 5.35 (1H, br s), and 6.85 (1H, br s); characteristic minor isomer signals: 1.87 (s) and 6.70 (br s); *m/z* (CI, NH_3) 437.1771 (M^++1), $C_{18}H_{32}O_6N_2S_2$ requires 437.1780.

(±)-*anti*-2-(2-(*S*)-(*N*,*N*′-Bis-(*t*-butoxycarbonyl)hydrazino)-propanoyl)-2-(*R*)-methyl-1,3-dithiane 1-(*R*)-oxide (±)-*anti*-5b. The lithium enolate of *anti* 2-propanoyl-2-methyl-1,3-dithiane 1-oxide (±)-*anti*-**4b** (0.20 g, 0.969 mmol) was generated as described above and added via cannula to a stirred solution of DBAD (0.25 g, 1.09 mmol) in THF (5 mL) at −78°C. The reaction mixture was stirred for 10 min at −78°C before addition of glacial acetic acid (0.28 mL, 4.66 mmol). The reaction mixture was allowed to reach room temperature overnight. Normal work-up procedure gave (±)-*anti*-**5b**, a 2:1 mixture of inseparable product diastereoisomers, as a pale yellow oil (0.292 g, 69%); found: C, 47.80; H, 7.24; N, 6.80; $C_{18}H_{32}O_6N_2S_2$ requires C, 49.52; H, 7.39%; N, 6.42; ν_{max} (soln) 3300, 1740, 1700, 1460, and 1060 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 325 K) major isomer: 1.34–1.45 (21H, m), 1.78 (3H, s), 2.30–2.55 (3H, m), 2.81–2.95 (2H, m), 3.25 (1H, br s), 5.35 (1H, br s), and 6.40 (1H, br s); characteristic minor isomer signals: 1.47 (d, *J*=6.6 Hz), 1.62 (s), and 5.55 (br s); *m/z* (CI, NH_3) 437 (M^++1).

(±)-*syn*-2-(2-(*S*)-(*N*,*N*′-Bis-(*t*-butoxycarbonyl)hydrazino)-propanoyl)-2-(*S*)-ethyl-1,3-dithiane 1-(*R*)-oxide (±)-*syn*-5c. The lithium enolate of *syn* 2-propanoyl-2-ethyl-1,3-dithiane 1-oxide (±)-*syn*-**4c** (0.20 g, 0.908 mmol) was generated as described above and added via cannula to a stirred solution of DBAD (0.23 g, 0.999 mmol) in THF (5 mL) at −78°C. The reaction mixture was stirred for 10 min at −78°C before addition of glacial acetic acid (0.26 mL, 4.54 mmol). The reaction mixture was allowed to reach room temperature overnight. Normal work-up procedure gave (±)-*syn*-**5c**, a 12:1 mixture of inseparable product diastereoisomers, as a colourless crystalline solid (0.17 g, 42%), mp 139–141°C; found: C, 49.15; H, 7.45; N, 6.58; $C_{19}H_{34}O_6N_2S_2$ requires C, 50.64; H, 7.60; N, 6.22%; ν_{max} (soln) 3568, 1745, 1701, 1478, and 1053 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 325 K) major isomer: 1.08 (3H, t, *J*=7.5 Hz), 1.40–1.55 (21H, m), 2.10–2.30 (2H, m), 2.35–2.54 (3H, bm), 2.74 (1H, br t, *J*=10.8 Hz), 3.00 (1H, br t, *J*=14.5 Hz), 3.60 (1H, br s), 5.40 (1H, br s), and 6.75 (1H, br s); characteristic minor isomer signal 1.39 (d, *J*=6.9 Hz); *m/z* (CI, NH_3) 451 (M^++ 1).

(±)-*anti*-2-(2-(*S*)-(*N*,*N*′-Bis-(*t*-butoxycarbonyl)hydrazino)-propanoyl)-2-(*R*)-ethyl-1,3-dithiane 1-(*R*)-oxide (±)-*anti*-5c. The lithium enolate of *anti* 2-propanoyl-2-ethyl-1,3-dithiane 1-oxide (±)-*anti*-**4c** (0.20 g, 0.908 mmol) was generated as described above and added via cannula to a stirred solution of DBAD (0.23 g, 0.999 mmol) in THF (5 mL) at −78°C. The reaction mixture was stirred for 15 min at −78°C before addition of glacial acetic acid (0.26 mL, 4.54 mmol). The reaction mixture was allowed to reach room temperature overnight. Normal work-up procedure gave (±)-*anti*-**5c**, a single diastereoisomer by ^1H NMR spectroscopy (≥99:1), as a colourless crystalline solid which was recrystallized from diethyl ether (0.20 g, 48%), mp 154–156 °C; found: C, 50.57; H, 7.63; N, 6.23; $C_{19}H_{34}O_6N_2S_2$ requires C, 50.64; H, 7.60; N, 6.22%; ν_{max} (soln) 3401, 1747, 1712, 1455, and 1058 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 325 K) 0.98 (3H, t, *J*=7.5 Hz), 1.46 (9H, s), 1.48 (9H, s), 1.53 (3H, d, *J*=7.3 Hz), 1.65–85 (2H, m), 2.10–2.20 (1H, m), 2.40–2.60 (2H, m), 2.70 (1H, br t, *J*=12.6 Hz), 2.95 (1H, br d, *J*=14.0 Hz), 3.30 (1H, br s), 5.65 (1H, br s), and 6.40 (1H, br s); *m/z* (CI, NH_3) 450.1848 (M^+), $C_{19}H_{34}O_6N_2S_2$ requires 450.1858.

(±)-*anti*-2-(2-(*S*)-(*N*,*N*′-Bis-(*t*-butoxycarbonyl)hydrazino)-propanoyl)-2-(*R*)-phenyl-1,3-dithiane 1-(*R*)-oxide (±)-*anti*-5d. The lithium enolate of *anti* 2-propanoyl-2-phenyl-1,3-dithiane 1-oxide (±)-*anti*-**4d** (0.20 g, 0.792 mmol) was generated as described above and added via cannula to a stirred solution of DBAD (0.188 g, 0.816 mmol) in THF (5 mL) at −78 °C. The reaction mixture was stirred for 15 min at −78°C before addition of glacial acetic acid (0.22 mL, 3.84 mmol). The reaction mixture was allowed to reach room temperature overnight. Normal work-up procedure gave (±)-*anti*-**5d** as a 2:1 mixture of product diastereoisomers by 400 MHz ^1H NMR spectroscopy. The product isomers were separated by flash column chromatography using ethyl acetate as eluent to yield the major isomer (0.099 g, 27%) and the minor isomer (0.038 g,

10%) both as pale yellow oils; found: C, 55.71; H, 6.96; N, 5.13; $C_{23}H_{34}O_6N_2S_2$ requires C, 55.40; H, 6.87; N, 5.62%; ν_{max} (soln) 3590, 1748, 1708, 1534, 1446, and 1051 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 325 K) major isomer: 1.34 (3H, d, J=7.6 Hz), 1.36 (9H, s), 1.44 (9H, s), 1.78–1.87 (1H, m), 2.42–2.55 (1H, m), 2.60–2.80 (2H, m), 3.00–3.10 (1H, m), 3.35 (1H, br t, J=12.9 Hz), 5.24 (1H, br s), 5.78 (1H, br s), 7.36–7.50 (3H, m), and 7.55–7.60 (2H, m); minor isomer: 1.40–1.54 (21H, m), 1.70–1.80 (1H, m), 2.50–2.62 (1H, m), 2.67–2.75 (1H, m), 2.92–3.07 (2H, m), 3.40 (1H, br s), 5.74 (1H, br s), 6.32 (1H, br s), and 7.35–7.50 (5H, m); m/z (CI, NH_3) 499 (M^++1).

(+)-*anti*-2-(2-(*N*,*N*′-Bis-(*tert*-butoxycarbonyl)hydrazino)-3-phenylpropanoyl)-2-(*R*)-ethyl-1,3-dithiane 1-(*R*)-oxide (+)-*anti*-5e. Treatment of (+)-*anti*-**4e** (3.0 g, 10.1 mmol) with a 1 M solution of LHMDS in THF (11.2 mL, 11.2 mmol), DBAD (2.57 g, 11.2 mmol) and acetic acid (1.80 mL, 30.5 mmol) as described above gave (+)-*anti*-**5e** as a colourless powder (4.99 g, 93%), mp 82–83°C; ν_{max} 1735, 1718, 1701 and 1050 cm^{-1}; m/z (CI) 526.2179 (M^+); $C_{25}H_{38}N_2O_2S_2$ requires 526.2172. Found: C, 56.91; H, 7.26; N, 5.26%. Calcd for $C_{25}H_{38}N_2O_6S_2$: C, 57.06; H, 7.28; N, 5.32%. $[\alpha]_D^{25}$=+138 (c=1.0, $CHCl_3$).

(+)-*anti*-2-(2-(*N*,*N*′-Bis-(*tert*-butoxycarbonyl)hydrazino)-2-phenylethanoyl)-2-(*R*)-ethyl-1,3-dithiane 1-(*R*)-oxide (+)-*anti*-5f. Treatment of (+)-*anti*-**4f** (0.60 g, 2.13 mmol) with a 1 M solution of LHMDS in THF (2.34 mL, 2.34 mmol), DBAD (0.54 g, 2.34 mmol) and acetic acid (0.38 mL, 6.38 mmol) as described above gave (+)-*anti*-**5f** as a colourless foam (0.92 g, 85%), mp 52–54°C; ν_{max} 3241, 1745, 1731, 1690 and 1041 cm^{-1}; m/z (FAB) 513.2092 (M^++H); $C_{24}H_{37}N_2O_6S_2$ requires 513.2093. Found: C, 56.09; H, 7.19; N 5.06%. Calcd for $C_{24}H_{36}N_2O_6S_2$: C, 56.22; H, 7.08; N, 5.47%. $[\alpha]_D^{25}$=+210.0 (c=0.23, $CHCl_3$).

(+)-*anti*-2-(2-(*N*,*N*′-Bis-(*tert*-butoxycarbonyl)hydrazino)-3-methylpropanoyl)-2-(*R*)-ethyl-1,3-dithiane 1-(*R*)-oxide (+)-*anti*-5g. Treatment of (+)-*anti*-**4g** (2.28 g, 9.19 mmol) with a 1 M solution of LHMDS in THF (10.1 mL, 10.1 mmol), DBAD (2.32 g, 10.1 mmol) and acetic acid (1.65 mL, 30.3 mmol) as described above gave (+)-*anti*-**5g** as a colourless powder (3.92 g, 89%), mp 144–145°C; ν_{max} 3207, 1729, 1709, 1693 and 1056 cm^{-1}; m/z (FAB) 479.2242 (M^++H); $C_{21}H_{39}N_2O_6S_2$ requires 479.2250. Found: C, 52.28; H, 8.04; N, 5.67%. Calcd for $C_{21}H_{38}N_2O_6S_2$: C, 52.69; H, 8.00; N, 5.85%. $[\alpha]_D^{25}$=+85 (c=0.53, $CHCl_3$).

(+)-*anti*-2-(2-(*N*,*N*'-Bis-(*tert*-butoxycarbonyl)hydrazino)-3,3-dimethylpropanoyl)-2-(*R*)-ethyl-1,3-dithiane 1-(*R*)-oxide (+)-*anti*-5h. Treatment of (+)-*anti*-**4h** (3.00 g, 11.5 mmol) with a 1 M solution of LHMDS in THF (11.6 mL, 11.6 mmol), DBAD (2.90 g, 11.6 mmol) and acetic acid (1.96 mL, 34.7 mmol) as described above gave (+)-*anti*-**5h** as a colourless powder (5.11 g, 91%), mp 126–128°C; ν_{max} 3173, 1707, 1692 and 1056 cm^{-1}; m/z (FAB) 493.2407 (M^++H); $C_{22}H_{41}N_2O_6S_2$ requires 493.2413. Found: C, 53.37; H, 8.23; N, 5.65%. Calcd for $C_{22}H_{40}N_2O_6S_2$: C, 53.63; H, 8.18; N, 5.69%. $[\alpha]_D^{25}$=+22 (c=1.0, $CHCl_3$).

(±)-2-(2-(*N*,*N*′-Bis-(*tert*-butoxycarbonyl)hydrazino)-3-phenylpropanoyl)-2-ethyl-1,3-dithiane (±)-6. A 1 M solution of LHMDS (1.83 mL, 1.83 mmol) in THF was added to a stirred solution of **3e** (0.47 g, 1.7 mmol) in THF (10 mL) at −78°C. After 30 min, the solution was transferred by cannula into a solution of DBAD (0.42 g, 1.83 mmol) in dichloromethane (10 mL) at −78 °C, and the solution allowed to reach room temperature. Normal work-up and column chromatography using 10% ethyl acetate/hexane as eluent gave (±)-**6** as a colourless solid (0.79 g, 93%), mp 55–57°C; ν_{max} 1747, 1713 and 1703 cm^{-1}; δ_H (400 MHz, DMSO-d_6, 370 K) 0.99 (3H, t, J=7.3 Hz), 1.34 (9H, s), 1.42 (9H, s), 1.47–1.53 (1H, m), 1.88–1.92 (2H, m), 2.13–2.21 (2H, m), 2.40–2.48 (1H, m), 2.53–2.59 (1H, m), 2.86–2.89 (1H, m), 3.01–3.06 (1H, m), 3.15–3.21 (1H, m), 5.64 (1H, br s), 7.14–7.19 (1H, m), 7.21–7.29 (4H, m), and 8.35 (1H, br s); m/z (CI) 510.2223 (M^+); $C_{25}H_{38}N_2O_5S_2$ requires 510.2223. Found: C, 58.83; H, 7.70; N, 5.32%. Calcd for $C_{25}H_{38}N_2O_5S_2$: C, 58.80 H, 7.50; N, 5.49%.

(±)-*anti*-2-(2-(*N*,*N*′-Bis-(*tert*-butoxycarbonyl)hydrazino)-3-phenylpropanoyl)-2-ethyl-1,3-dithiane 1-oxide (±)-*anti*-5e. A solution of sodium metaperiodate (0.14 g, 0.65 mmol) in water (5 mL) was added to a stirred solution of (±)-**6** (0.31 g, 0.61 mmol) in methanol (15 mL) at 0°C. After 2 days, the reaction was filtered, the filtrate extracted with dichloromethane, the organic fractions were combined and dried over magnesium sulfate, and the solvents removed in vacuo. Column chromatography using 50% ethyl acetate/hexane gave (±)-**5e** (0.22 g, 70%). Data as above.

General procedure for hydrolysis of 1,3-dithiane 1-oxides to give diketones

A solution of the substrate in acetone was added to a stirred solution of *N*-bromosuccinimide (8.0 equiv.) in acetone/water (97:3) at 0°C. The resulting mixture was stirred at 0°C until completion of the reaction (15–30 min) and then quenched with saturated aqueous sodium sulfite. The reaction mixture was extracted with dichloromethane (×3), the organic fractions combined, dried over magnesium sulfate, and concentrated in vacuo. The crude product was purified by flash column chromatography using dichloromethane as eluent.

(−)-2-(*S*)-(*N*,*N*′-Bis-(*tert*-butoxycarbonyl)hydrazino)-1-phenylhexan-3,4-one (−)-7e. Treatment of (+)-*anti*-**5e** (4.00 g, 7.6 mmol) in acetone (100 mL) with NBS (10.9 g, 60.8 mmol) in aqueous acetone (150 mL) as described above gave (−)-**7e** as a bright yellow glass (2.70 g, 85%); ν_{max} 1718 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 323 K) 1.05 (3H, t, J=7.0 Hz), 1.38 (9H, s), 1.43 (9H, s), 2.68–2.78 (3H, m), 3.11 (2H, br s), 6.25 (1H, br s, NH), and 7.16–7.30 (5H, m); m/z (FAB) 443.2177 (M^++Na); $C_{22}H_{32}NaN_2O_6$ requires 443.2158. Found: C, 62.71; H, 7.64; N, 6.63%. Calcd for $C_{22}H_{32}N_2O_6$: C, 62.83; H, 7.67; N, 6.66%. $[\alpha]_D^{25}$=−42 (c=1.0, $CHCl_3$).

(+)-1-(*S*)-(*N*,*N*′-Bis-(*tert*-butoxycarbonyl)hydrazino)-1-phenylpentan-2,3-one (+)-7f. Treatment of (+)-*anti*-**5f** (0.60 g, 1.17 mmol) in acetone (25 mL) with NBS (1.67 g, 9.37 mmol) in aqueous acetone (35 mL) gave (+)-**7f** as a

bright yellow oil (0.320 g, 72%); ν_{max} 1710, 1682 and 1651 cm^{-1}; δ_H NMR (400 MHz, $CDCl_3$, 323 K) 1.02 (3H, t, J=7.1 Hz), 1.46 (9H, s), 1.50 (9H, s), 2.83 (2H, q, J=7.0 Hz), 6.40 (1H, br s, NH), and 7.28–7.54 (5H, m). $[\alpha]_D^{25}$=+80 (c=1.0, $CHCl_3$).

(−)-3-(S)-(*N*,*N*′-Bis-(*tert*-butoxycarbonyl)hydrazino)-2-methylheptan-4,5-one (−)-7g. Treatment of (+)-*anti*-**5g** (2.30 g, 4.8 mmol) in acetone (75 mL) with NBS (6.85 g, 38.4 mmol) in aqueous acetone (100 mL) gave (−)-**7g** as a bright yellow oil (1.28 g, 72%); ν_{max} 1737, 1721, 1713 and 1699 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 323 K) 0.91 (3H, br d, J=6.4 Hz), 0.98 (3H, d, J=6.4 Hz), 1.10 (3H, t, J=7.2 Hz), 1.44 (9H, s), 1.48–1.52 (9H, m), 2.27–2.37 (1H, m), 2.72–2.81 (2H, m), 5.02 (1H, br s), and 6.21 (1H, br s, NH); *m*/*z* (FAB) 372.2256 (M^+); $C_{18}H_{32}N_2O_6$ requires 372.2261. $[\alpha]_D^{25}$=−64 (c=1.0, $CHCl_3$).

(+)-3-(*S*)-(*N*,*N*'-Bis-(*tert*-butoxycarbonyl)hydrazino)-2,2-dimethylheptan-4,5-one (+)-7h. Treatment of (+)-*anti*-**5h** (2.50 g, 5.1 mmol) in acetone (100 mL) with NBS (7.23 g, 40.7 mmol) in aqueous acetone (100 mL) gave (+)-**7h** as a bright yellow oil (1.06 g, 54%); ν_{max} 1721, 1710 and 1684 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 323 K) 1.01 (3H, t, J=7.0 Hz), 1.06 (9H, s), 1.49 (9H, s), 1.53 (9H, s), 1.46–1.53 (2H, m), and 3.92 (1H, s); *m*/*z* (FAB) 387.2489 (M^++H); $C_{19}H_{35}N_2O_6$ requires 387.2495. Found: C, 58.65; H, 8.92; N, 6.95%. Calcd for $C_{19}H_{34}N_2O_6$: C, 59.04; H, 8.87; N, 7.25%. $[\alpha]_D^{25}$=+54 (c=1.0, $CHCl_3$).

(−)-2-(S)-(*N*,*N*′-Bis-(*tert*-butoxycarbonyl)hydrazino)-3-phenylpropanoic acid (−)-8e. A solution of sodium *meta*-periodate (1.02 g, 4.76 mmol) in water (50 mL) was added to a stirred solution of (−)-**7e** (1.0 g, 2.38 mmol) in methanol (50 mL). After 24 h, the reaction was filtered, the filtrate extracted with dichloromethane, and the organic fractions combined, dried over magnesium sulfate, and concentrated in vacuo. Flash column chromatography using 50% ethyl acetate/dichloromethane as eluent gave (−)-**8e** as a colourless oil (0.770 g, 85%); ν_{max} 3400–2600, 1745 and 1711 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 323 K) 1.47 (18H, s), 3.15 (1H, br s), 3.41 (1H, br d, J=7.4 Hz), 3.46 (1H, br s), 6.19 (1H, br s, NH), and 7.18–7.33 (5H, m); *m*/*z* (FAB) 403.1850 (M^++Na); $C_{19}H_{28}NaN_2O_6$ requires 403.1845. Found: C, 59.98; H, 7.64%. Calcd for $C_{19}H_{28}N_2O_6$: C, 59.98; H, 7.42%. $[\alpha]_D^{20}$=−56 (c=1.0, $CHCl_3$).

(−)-2-(S)-(*N*,*N*′-Bis-(*tert*-butoxycarbonyl)hydrazino)-3-methylbutanoic acid (−)-8g. A solution of sodium *meta*-periodate (1.53 g, 4.86 mmol) in water (25 mL) was added to a stirred solution of (−)-**7g** (0.90 g, 2.42 mmol) in methanol (40 mL). After 48 h, the reaction was filtered, the filtrate extracted with dichloromethane, and the organic fractions combined, dried over magnesium sulfate, and concentrated in vacuo. Flash column chromatography using 50% ethyl acetate/dichloromethane as eluent gave (−)-**8g** as a colourless oil (0.328 g, 41%); ν_{max} 3600–2600, and 1718 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 323 K) 1.01 (3H, d, J=6.8 Hz), 1.08 (3H, d, J=6.8 Hz), 1.47 (9H, s), 1.51 (9H, s), 2.31–2.38 (1H, m), and 6.65 (1H, br s, NH); *m*/*z* (FAB) 355 (M^++Na). $[\alpha]_D^{20}$=−24 (c=1.0, $CHCl_3$).

Hydrocinnamic acid, benzyl ester 9. Dicyclohexylcarbodiimide (3.03 g, 14.7 mmol), 4-dimethylaminopyridine (0.16 g, 1.3 mmol) and benzyl alcohol (1.52 mL, 14.7 mmol) were added to a stirred solution of dihydrocinnamic acid (2.0 g, 13.3 mmol) in diethyl ether (50 mL). After 4 h, the solution was filtered, the filtrate washed with water (4×50 mL), dried over magnesium sulfate, and concentrated in vacuo. Column chromatography using 10% ethyl acetate/ petroleum ether as eluent gave **9** as a colourless oil (2.70 g, 84%); ν_{max} 1735 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 2.68 (2H, t, J=7.4 Hz), 2.97 (2H, t, J=7.4 Hz), 5.10 (2H, s), and 7.16–7.31 (10H, m); *m*/*z* (EI) 240.1151 (M^+); $C_{16}H_{16}O_2$ requires 240.1150.

(±)-2-(*N*,*N*′-Bis-(*tert*-butoxycarbonyl)hydrazino)-3-phenylpropanoic acid, benzyl ester (±)-10e.[16] A solution of *n*-butyllithium in hexanes (1.04 mL, 2.50 mmol) was added To a stirred solution of diisopropylamine (0.30 mL, 2.29 mmol) in THF (5 mL) at 0°C. After 30 min, the reaction was cooled to −78°C, and a solution of **9** (0.50 g, 2.08 mmol) in THF (3 mL) added. After a further 30 min, a cooled solution of DBAD (0.53 g, 2.30 mmol) in dichloromethane was transferred by cannula into the reaction vessel. The reaction was allowed to reach room temperature before normal work-up. Column chromatography using dichloromethane as eluent gave (±)-**10e** as a colourless viscous oil (0.550 g, 56%); ν_{max} 3325 and 1735 cm^{-1}; δ_H (400 MHz, $CDCl_3$, 323 K) 1.40 (9H, s), 1.42 (9H, s), 3.18 (2H, d, J=7.2 Hz), 5.03 (1H, br s), 5.09 (2H, s), 6.23 (1H, br s, NH), and 7.15–7.32 (10H, m); *m*/*z* (FAB) 493.2304 (M^++Na); $C_{26}H_{34}NaN_2O_6$ requires 493.2315.

(±)-2-(*N*,*N*′-Bis-(*tert*-butoxycarbonyl)hydrazino)-3-phenylpropanoic acid (±)-8e. Palladium on carbon catalyst (0.060 g) was added to a solution of (±)-**10e** (0.500 g, 1.06 mmol) in ethyl acetate (20 mL), and the mixture placed under a slight static positive pressure of hydrogen and rapidly stirred. After 4 h, the reaction was filtered through a pad of celite and the filtrate concentrated to give (±)-**8e** as a colourless foam (0.381 g, 94%). Data as given above.

(−)-2-(*S*) (*N*,*N*′-Bis-(*tert*-butoxycarbonyl)hydrazino)-3-phenylpropanoic acid, benzyl ester (−)-10e.[16] Dicyclohexylcarbodiimide (0.45 g, 2.17 mmol), 4-dimethylaminopyridine (0.024 g, 0.20 mmol) and benzyl alcohol (0.22 mL, 2.17 mmol) were added to a stirred solution of (−)-**8e** (0.75 g, 1.97 mmol) in diethyl ether (20 mL). After 8 h, the solution was filtered, the filtrate washed with water (4×50 mL), dried over magnesium sulfate, and concentrated in vacuo. Column chromatography using 10% ethyl acetate/ dichloromethane as eluent gave (−)-**10e** as a clear colourless glass (0.814 g, 88%). $[\alpha]_D^{20}$=−4.16 (c=2.0, $CHCl_3$), other data as above for racemate.

(−)-2-(*S*) (*N*,*N*′-Bis-(*tert*-butoxycarbonyl)hydrazino)-3-methylbutanoic acid, benzyl ester (−)-10g.[16] Dicyclohexylcarbodiimide (0.068 g, 0.33 mmol), 4-(dimethylamino)pyridine (0.004 g, 0.03 mmol) and benzyl alcohol (0.034 mL, 0.33 mmol) were added to a stirred solution of (−)-**8g** (0.100 g, 0.30 mmol) in diethyl ether (3 mL). After 4 h, the solution was filtered, the filtrate washed with water (4×5 mL), dried over magnesium sulfate, and concentrated in vacuo. Column chromatography using 10% ethyl acetate/ dichloromethane as eluent gave (−)-**10g** as a viscous oil

(0.106 g, 83%). $[\alpha]_D^{20}=-5.09$ ($c=1.9$, $CHCl_3$), other data as above for racemate.

Acknowledgements

This investigation has enjoyed the support of the EPSRC and SmithKline Beecham Pharmaceuticals.

References

1. Page, P. C. B.; Heer, J. P.; Bethell, D.; Collington, E. W.; Andrews, D. M. *Synlett* **1995**, 773; Page, P. C. B.; Heer, J. P.; Bethell, D.; Collington, E. W.; Andrews, D. M. *Tetrahedron: Asymmetry* **1995**, *6*, 2911.
2. Page, P. C. B.; McKenzie, M. J.; Buckle, D. R. *Tetrahedron* **1998**, *54*, 14581, and references therein.
3. Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539; Williams, R. M. *Organic Chemistry Series Volume 7: Synthesis of optically active α-amino acids*; Baldwin, J. E., Magnus, P. D., Eds.; Pergamon: Oxford, 1989.
4. Hennessy, M. J.; Ruckle Jr., R. E.; Taber, D. F. *J. Org. Chem.* **1986**, *51*, 4077.
5. Sakakura, T.; Hara, M.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1545; Sakakura, T.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1309.
6. Sheradsky, T.; Salemnick, G.; Nir, Z. *Tetrahedron* **1972**, *28*, 2833; Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1; Casarini, A.; Dembech, P.; Lazzari, D.; Marini, E.; Reginato, G.; Ricci, A.; Seconi, A. *J. Org. Chem.* **1993**, *58*, 5620; Tamura, Y.; Minamikawa, J.; Sumoto, K.; Fujji, S.; Ikedu, M. *J. Org. Chem.* **1973**, *38*, 1239; Yamada, S.; Oguri, T.; Shiori, T. *J. Chem. Soc., Chem. Commun.* **1972**, 623; Kjaer, A.; Malver, O. *Tetrahedron Lett.* **1982**, *23*, 2687; Colvin, E. W.; Kirby, G. W.; Wilson, A. C. *Tetrahedron Lett.* **1982**, *23*, 3835.
7. Hassner, A.; Rasmussen, J. K. *J. Org. Chem.* **1974**, *39*, 2558.
8. Ahn, K.-H.; Lim, B.-W. *Synth. Commun.* **1996**, *26*, 3407.
9. Collet, A.; Vidal, J.; Damestoy, S. *Tetrahedron Lett.* **1995**, *36*, 1439 and references therein.
10. Zheng, N.; Armstrong, J. D.; McWilliams, J. C.; Volante, R. P. *Tetrahedron Lett.* **1997**, *38*, 2817.
11. Magnus, P.; Lacour, J.; Coldham, I.; Mugrage, B.; Bauta, W. B. *Tetrahedron* **1995**, *51*, 11087.
12. Magnus, P.; Barth, L. *Tetrahedron* **1995**, *51*, 11075.
13. Diels, O.; Behncke, H. *Ber.* **1924**, *57*, 653; Mellor, J. M.; Smith, N. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2927; Fahr, E.; Lind, H. *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 372; Mitsunobu, O. *Synthesis* **1981**, 1; Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem.* **1987**, *52*, 4235; Smissman, E. E.; Makriyannis, A. *J. Org. Chem.* **1973**, *38*, 1652; Meyers, A.; Comins, D. L.; Roland, D. M.; Henning, R.; Shimizu, K. *J. Am. Chem. Soc.* **1979**, *101*, 7104.
14. Oppolzer, W.; Moretti, R. *Tetrahedron* **1988**, *44*, 5541; Oppolzer, W.; Morreti, R. *Helv. Chim. Acta* **1986**, *69*, 1923; Oppolzer, W. *Tetrahedron* **1987**, *43*, 4057; Oppolzer, W. *Pure Appl. Chem.* **1988**, *60*, 39; Oppolzer, W.; Tamura, O. *Tetrahedron Lett.* **1990**, *31*, 991; Oppolzer, W.; Moretti, R. *Helv. Chim. Acta* **1986**, *69*, 1923.
15. Gennari, C.; Bertolini, G.; Colombo, L. *J. Am. Chem. Soc.* **1986**, *108*, 6394.
16. Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria Jr., J. F. *J. Am. Chem. Soc.* **1986**, *108*, 6395.
17. Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria Jr, J. F. *Tetrahedron* **1988**, *44*, 5525; Evans, D. A.; Evrard, D. A.; Rychnovsky, S. D.; Früch, T.; Whittingham, W. G.; DeVries, K. M. *Tetrahedron Lett.* **1992**, *33*, 1189; Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011.
18. Vederas, J. C.; Trimble, L. A. *J. Am. Chem. Soc.* **1986**, *108*, 6397.
19. For examples see. Arya, P.; Ben, R. N.; Qin, H. *Tetrahedron Lett.* **1998**, *39*, 6131; Greck, C.; Ferreira, F.; Genêt, J. P. *Tetrahedron Lett.* **1996**, *37*, 2031; Seebach, D.; Sting, A. R. *Tetrahedron* **1996**, *52*, 279.
20. Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997**, *119*, 6452.
21. Vederas, J. C.; Harris, J. M.; Bolessa, E. A.; Mendonca, A. J.; Feng, S.-C. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1945.
22. Vederas, J. C.; Harris, J. M.; McDonald, R. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2669.
23. Cativiela, C.; Díaz-de-Villegas, M. D.; Gàlvez, J. A. *Tetrahedron: Asymmetry* **1997**, *8*, 1605.
24. Page, P. C. B.; Allin, S. M.; Collington, E. W.; Carr, R. A. E. *Tetrahedron Lett.* **1994**, *35*, 2427.
25. Rebiere, F.; Samuel, O.; Ricard, L.; Kagan, H. B. *J. Org. Chem.* **1991**, *56*, 5991; Page, P. C. B.; Wilkes, R. D.; Witty, M. *J. Org. Prep. Proc. Intl.* **1994**, 702, and references therein.
26. Enantiomeric excesses were determined by ^1H NMR spectroscopy in the presence of (+)- or (−)- trifluoroanthrylethanol and/or by chiral HPLC using a Chiralcel OJ column.
27. The diastereoselectivity of the reactions were determined by 400 MHz ^1H NMR spectroscopy. For example, for the major isomer of (±)-*anti*-**5c** the 2-ethyl group triplet appears at δ 0.98 ppm and for the minor isomer at δ 1.04 ppm.
28. Page, P. C. B.; Westwood, D.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 185; Page, P. C. B.; Klair, S. S.; Westwood, D. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2441; Page, P. C. B.; Shuttleworth, S. J.; Schilling, M.; Tapolczay, D. *Tetrahedron Lett.* **1993**, *34*, 6947.
29. Page, P. C. B.; Namwindwa, E. S.; Klair, S. S.; Westwood, D. *Synlett* **1990**, 457; Page, P. C. B.; Namwindwa, E. S. *Synlett* **1991**, 80; Page, P. C. B.; Gareh, M. T.; Porter, R. A. *Tetrahedron: Asymmetry* **1993**, 2139.
30. Page, P. C. B.; Allin, S. M.; Collington, E. W.; Carr, R. A. E. *J. Org. Chem.* **1993**, *58*, 6902.
31. Page, P. C. B.; McKenzie, M. J.; Buckle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1995**, *21*, 2673.
32. Smith, M.; Moffatt, J. G.; Khorana, H. G. *J. Am. Chem. Soc.* **1958**, *80*, 6204; Balcom, B. J.; Peterson, N. O. *J. Org. Chem.* **1989**, *54*, 1922.