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Enolate Bromination in 2-Acyl-1,3-dithiane 1-Oxides

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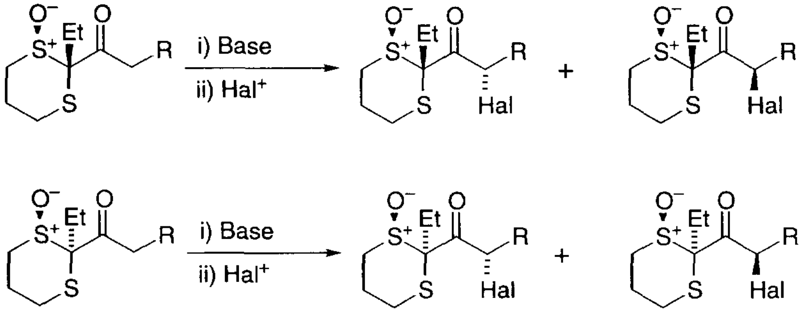
Abstract: Enolates derived from 2-acyl-2-ethyl-1,3-dithiane 1-oxides react readily and diastereoselectively with *N*-bromosuccinimide to give α-bromoketones. In addition, halide displacement by treatment with nitrogen nucleophiles has been briefly investigated, but induces loss of stereochemical integrity by equilibration under the reaction conditions.

INTRODUCTION

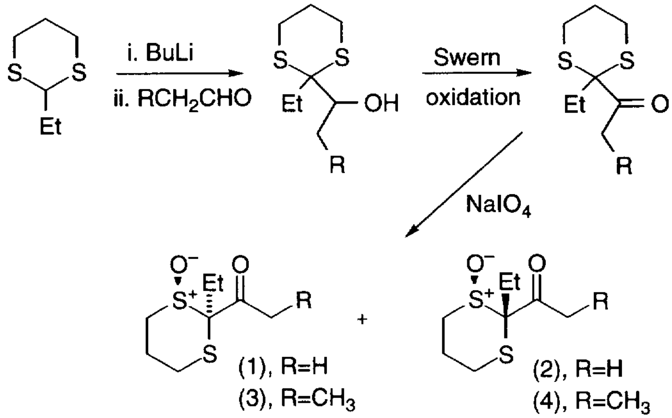
We are developing the uses of simple 1,3-dithiane 1-oxide (DiTOX) derivatives for the enantiocontrol of a range of organic reactions. β-Keto sulfoxides are well known stereocontrol elements,[1] and indeed we have been able to obtain very high levels of induced diastereoselectivity in several different types of carbonyl group reaction using acyl dithiane oxides as substrates.[2-8] In many cases stereoselectivity is sufficiently high that the minor isomer is not detected by 400 MHz ^{1}H nmr spectroscopy. A simple chelation-control model of the reactivity of these systems allows us to forecast which product isomer will be formed in kinetically-controlled transformations.[8] we are able to prepare the acyl dithiane oxide systems and the 2-substituted dithiane oxide starting materials enantioselectively in up to optical purity, both enantiomers being available in all cases.[2] The DiTOX unit may be removed from 2-acyl-2-alkyl-1,3-dithiane 1-oxides by treatment with base;[2,9] alternatively hydrolysis to give the corresponding diketone is readily accomplished by treatment with NBS in aqueous acetone.[9]



Scheme 1

α-Haloketones are useful synthetic intermediates and may be derived from enolates by treatment with sources of electrophilic halogen. We have investigated the diastereoselective halogenation of enolates derived from acyl dithiane oxide derivatives (Scheme 1), and now wish to report our progress in this area. Evans[10] and Oppolzer[11] have both described asymmetric halogenation of ketone enolates directed by chiral auxiliaries, followed by azide displacement, as an approach to α-aminoacids.

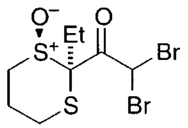
An ethyl group was chosen as 2-substituent in our acyl dithiane oxide substrates as this substituent confers extremely high diastereoselectivity in the corresponding enolate alkylation reactions. Readers are referred to our earlier publications for a full discussion.[8] The *syn* (1) and *anti* (2) 2-ethyl-2-acetyl-1,3-dithiane 1-oxide and the *syn* (3) and *anti* (4) 2-ethyl-2-propanoyl-1,3-dithiane 1-oxide substrates were easily prepared using one of our routine procedures (Scheme 2).[9,12]



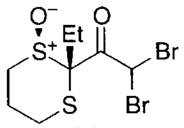
Scheme 2

RESULTS & DISCUSSION

The dithiane oxide substrates were deprotonated at –78 °C in THF solution using lithium hexamethyl disilazide. Addition to solid *N*-bromosuccinimide followed by simple work-up[10] is efficient for the acetyl substrate (1), but leads only to dibrominated material (5) in *ca.* 75% yield. Addition of NBS to solutions of the enolates derived from (1) and (2) gave mixtures of mono and dibrominated materials. Monobromination occurs for the propanoyl substrates (3) and (4), but the diastereoselectivities were disappointing, perhaps due to poor diastereoselectivity or to partial equilibration of the products induced by excess base: treatment of isomer (9) prepared from the *anti* substrate (4) with a solution of LHMDS at –78 °C for 2 hours gave a 1:1 mixture. Addition of boron enolates, generated from the lithium enolates by addition of dibutyl boron triflate at –78 °C followed by stirring for 30 minutes at room temperature, to solid NBS at –78 °C gave improved yields and higher diastereoselectivities, but in the opposite sense.[13] The diastereoisomeric mixtures of α-haloketone products were generally separable by column chromatography. A selection of results is summarized in Table I.

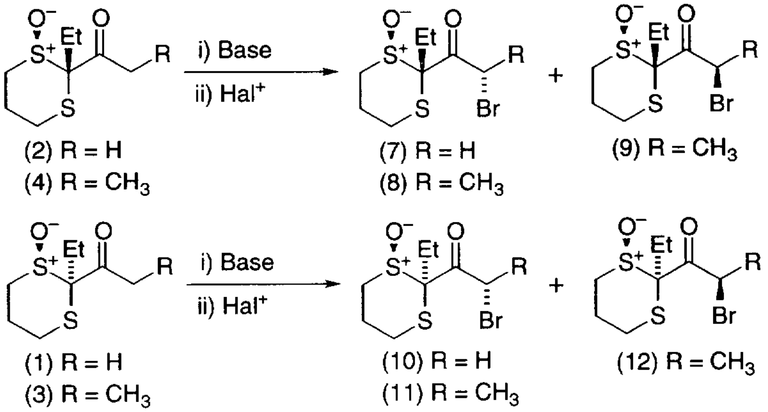


(5)



(6)

Table I. Diastereoselective Halogenation of 2-Acyl-2-ethyl-1,3-dithiane 1-Oxides



(2) R = H
(4) R = CH_3

(7) R = H
(8) R = CH_3

(9) R = CH_3

(1) R = H
(3) R = CH_3

(10) R = H
(11) R = CH_3

(12) R = CH_3

Substrate	Metal	Reagent	Yield/%	Isomer ratio †
syn (1)	Li	NBS	75%‡	~
anti (2)	Li	NBS	69%‡	~
syn (3)	Li	NBS	59%	1:2.5
anti (4)	Li	NBS	73%	1:1
syn (1)	B	NBS	33%, 18%‡	~
anti (2)	B	NBS	71%	~
syn (3)	B	NBS	87%	1.67:1
anti (4)	B	NBS	92%§	5.5:1 §

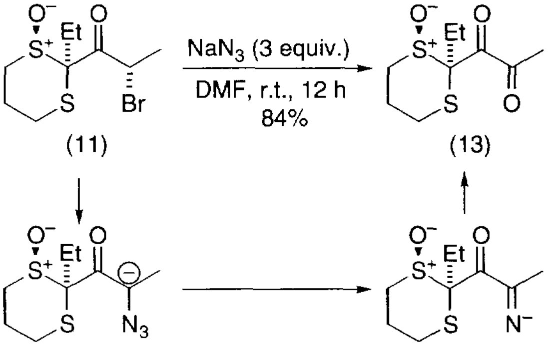
† determined by ^{1}H NMR spectroscopy
‡ dibrominated product § *syn* material; see text

The sense of induced stereoselectivity for all reactions carried out on each substrate was assessed in each series on the basis of ^{1}H NMR evidence.[14] The structure of the minor isomer (11) from the bromination of the lithium enolate derived from (3) was determined by X-ray crystallographic analysis; the relative stereochemistry is as shown. The changes in stereoselectivity observed upon the change of counter ion may result simply from the butyl groups carried on the boron atom altering the reacting conformation or the sterically-controlled approach of the electrophile.

A particularly curious but entirely reproducible result is that obtained from the boron enolate derived from the *anti* propanoyl substrate. In this case only, the halogenated products isolated both have the *syn* configuration around the dithiane moiety, only a trace of *anti* materials remaining. An isomerization from *anti* to *syn* has therefore taken place under the reaction conditions, perhaps the result of an equilibration process. *anti* To *syn* isomerization could not however be induced to take place under a range of conditions, including treatment with NBS,[19] in either the starting material (4) or brominated *anti* material (8, 9) prepared using a lithium enolate. We have previously observed *syn* to *anti* equilibration in acyl dithiane oxides upon treatment with trifluoroacetic anhydride.[20]

α-Haloketones are themselves useful synthetic intermediates,[15] and, given the ready conversion of acyl dithiane oxides into the corresponding carboxylic acids,[9] these 2-ethyl-2-(2-haloacyl)-1,3-dithiane 1-oxides can be regarded as protected α-halo carboxylic acids, compounds which have found use in the synthesis of a variety of products including herbicides and pharmaceuticals.[16] One potential synthetic application of our halogenated materials would lie in a synthetic approach to α-amino acids through halide displacement with nitrogen nucleophiles. We have briefly investigated this possibility, with limited success, using the isolated isomers of *syn* and *anti* 2-ethyl-2-(2-bromopropanoyl)-1,3-dithiane 1-oxides as substrates.

A range of nitrogen nucleophiles was examined. Ammonia, benzylamine and tetramethyl guanidinium azide are all unsuccessful as sources of nucleophilic nitrogen, resulting either in racemization at the halogenated chiral centre or protiodebromination of the substrate. Further, we were surprised to isolate in excellent yield the 1,2-diketone (13) from the attempted sodium azide displacement of one diastereoisomer (11) of *syn* 2-ethyl-2-(2-bromopropanoyl)-1,3-dithiane 1-oxide. The reaction may proceed through initial azide displacement followed by deprotonation, loss of nitrogen, and hydrolysis (Scheme 3); such transformations have previously been reported in the literature.[17]

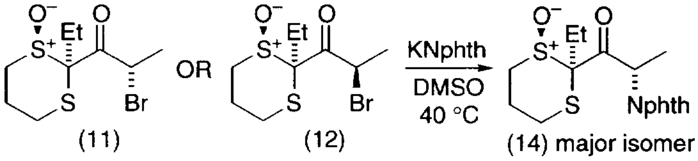


Scheme 3

After some experimentation we were pleased to find that use of three molar equivalents of potassium phthalimide in DMSO solution at 30-40 °C over 12 to 18 hours resulted in successful nucleophilic displacement reactions with *syn* 2-ethyl-2-(2-bromopropanoyl)-1,3-dithiane 1-oxides; no reaction took place at room temperature. From the results, a selection of which is shown in Table II, it is clear that we observe a dramatic change in stereochemistry in the isolated product mixtures: the ratio of isomers in each case has fallen to *ca.* 2:1, and the *same* isomer predominates regardless of the stereochemistry of the starting material at the brominated centre. We interpret this observation as a result of equilibration of the asymmetric centre through enolization resulting from deprotonation after displacement by excess phthalimide anion under the reaction conditions, or through attack by displaced bromide ion.[21] We believe that the relative stereochemistry of the major products is as shown on the basis of comparison of ^{1}H NMR data with that of other α-substituted acyl-1,3-dithiane 1-oxides.[18] It should be noted that a variety of methods exist for the hydrolysis of phthalimide residues to provide deprotected amine functions, for example hydrazinolysis.

All attempts to accelerate the displacement process by the addition of zinc or silver salts resulted in complete loss of stereochemical integrity of the α-bromoketone substrates at the halogenated postion without displacement. One could imagine that chelation of the metal atom with the sulphoxide and acyl group oxygen atoms may restrict the conformation of the 2-(2-bromopropanoyl)-2-ethyl-1,3-dithiane 1-oxide substrates and hence disfavour displacement of the halide, resulting in preferential deprotonation at the halogenated centre.

Table II. Nitrogen nucleophile displacements in 2-(2-bromoacyl)-2-ethyl-1,3-dithiane 1-oxides



Substrate (isomer)	Yield/%	Isomer ratio[a]
Syn (Major) (10)	91	2 : 1
Syn (Minor) (11)	95	2 : 1

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

Overall this chemistry does provide the nucleus of a high yielding approach to chiral α-aminoketones, but the reduction in stereochemical integrity following the nitrogen displacement step inevitably limits the synthetic application, and may highlight a general drawback of α-amino ketone generation by halide displacement.[21]

Acknowledgment

These investigations have enjoyed the support of Glaxo Group Research Ltd. (studentship to SMA). We are also indebted to the SERC Service for Very High Field NMR Spectroscopy at the University of Warwick for their help and patience.

EXPERIMENTAL SECTION

General experimental details

Purification of Reagents

Commercially available reagents were used as supplied unless otherwise stated. Butyl lithium was purchased from Aldrich in 500 ml bottles as a 1.65 M solution in hexane. The molarity was determined by titration against a solution of diphenylacetic acid. 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.

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.

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 in 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 a saturated solution of 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 diasteroisomeric 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.

Purification of Products

Flash column chromatography was carried out using Merck 9385 Kieselgel 60 (230-400 mesh), 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 eluant, unless otherwise stated. Thin layer chromatography was carried out using aluminium-backed plates coated with a 0.25mm layer of silica gel 60H containing fluorescer, using mixtures of ethyl acetate and petroleum ether (bp 40-60 °C) 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 (2 l) followed in both cases by charring where appropriate.

Spectroscopy and other data

Infrared spectra were recorded in the range 4000-600 cm^{-1} using a Perkin Elmer 298 spectrophotometer, and were calibrated against the 1602 cm^{-1} absorption of polystyrene. Solid samples were run as nujol mulls or potassium bromide disks and liquids as thin films. ^{1}H NMR spectra were recorded using Bruker ACE200, Bruker WM250, or Bruker AMX400 instruments using deuteriochloroform solutions and tetramethylsilane as internal reference. ^{13}C nmr spectra were recorded using Bruker WM 250 (62.8 MHz) or Bruker AMX400 (100.62 MHz) 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

General procedure for generation of lithium enolates of *syn* or *anti* 2-acyl-2-ethyl-1,3-dithiane 1-oxide substrates

A stirred solution of the 2-acyl-2-ethyl-1,3-dithiane 1-oxide substrate in THF (*ca.* 25 ml/g) was cooled to –78 °C and a 1 M solution of LHMDS (1.1 equiv.) added *via* syringe. After stirring for 10-15 minutes at –78 °C the lithium enolate was ready for subsequent reaction.

General procedure for generation of boron enolates of *syn* or *anti* 2-acyl-2-ethyl-1,3-dithiane 1-oxide substrates

A stirred solution of the 2-acyl-2-ethyl-1,3-dithiane 1-oxide substrate in THF (*ca.* 25 ml/g) was cooled to –78 °C and a 1 M solution of LHMDS (1.1 equiv.) added *via* syringe. After stirring for 10-15 minutes at –78 °C, a 1 M solution of dibutylboron triflate (1.1 equiv.) was introduced and the reaction mixture allowed to reach room temperature over 30 minutes; the boron enolate was then recooled to –78 °C before subsequent reaction.

Lithium mediated reactions

(±)-2-(2,2-Dibromoacetyl)-2-(*R*)-ethyl-1,3-dithiane 1-(*R*)-oxide (6)

The lithium enolate was generated from *anti* 2-acetyl-2-ethyl-1,3-dithiane 1-oxide (0.17 g, 0.825 mmol) as described above and added by cannula to solid NBS (0.22 g, 1.24 mmol) at –78 °C. The reaction mixture was allowed to reach room temperature overnight. Normal work-up procedure gave the title compound as a crystalline solid (0.032 g, 11%); ν_{max} 1709 and 1055 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.18 (3H, t, *J* = 7.4 Hz), 1.71-1.94 (2H, m), 2.11-2.30 (1H, m), 2.40-2.62 (2H, m), 2.76-3.17 (3H, m), and 6.70 (1H, s); *m/z* (EI) found 361.86368 (M^+); $C_8H_{12}S_2O_2Br_2$ requires 361.86455.

(±)-2-(2,2-Dibromoacetyl)-2-(*S*)-ethyl-1,3-dithiane 1-(*R*)-oxide (5)

The lithium enolate was generated from *syn* 2-acetyl-2-ethyl-1,3-dithiane 1-oxide (0.43 g, 2.09 mmol) as described above and added by cannula to solid NBS (0.56 g, 3.15 mmol) at –78 °C. The reaction mixture was allowed to reach room temperature overnight. Normal work-up procedure gave the title compound as a crystalline solid (0.45 g, 75%); ν_{max} 1720 and 1041 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.15 (3H, t, *J* = 7.4 Hz), 2.28-2.47 (4H, m), 2.54-2.63 (1H, m), 2.94-3.07 (2H, m), 3.18-3.21 (1H, m), and 6.71 (1H, s); *m/z* (EI) found 361.86475 (M^+); $C_8H_{12}S_2O_2Br_2$ requires 361.86455.

(±)-2-(2-Bromopropanoyl)-2-(*R*)-ethyl-1,3-dithiane 1-(*R*)-oxides (8, 9)

The lithium enolate was generated from *anti* 2-propanoyl-2-ethyl-1,3-dithiane 1-oxide (0.17 g, 0.773 mmol) as described above and added by cannula to solid NBS (0.21 g, 1.18 mmol) at –78 °C. The reaction mixture was allowed to reach room temperature overnight. Normal work-up procedure gave the title compound together with the isomer at the halogenated position , a 1:1 mixture of diastereoisomers by ^1H NMR spectroscopy, as crystalline solids (0.168 g, 65%).

For the less polar isomer: 0.083 g, 33%; ν_{max} 1691 and 1056 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.04 (3H, t, *J* = 7.7 Hz), 1.80 (3H, d, *J* = 7.1 Hz), 1.71-1.80 (2H, m), 2.12-2.31 (1H, m), 2.42-2.61 (2H, m), 2.90-3.15 (3H, m), 5.13 (1H, q, *J* = 7.1 Hz); *m/z* (EI) found 297.97014 (M^+); $C_9H_{15}S_2O_2Br$ requires 297.96968.

For the more polar isomer: 0.085 g, 33%; ν_{max} 1700 and 1060 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.23 (3H, t, *J* = 7.68 Hz), 1.88 (3H, d, *J* = 6.6 Hz), 1.70-2.28 (3H, m), 2.43-2.53 (3H, m), 2.97-3.08 (2H, m), 5.19 (1H, q, *J* = 6.6 Hz); *m/z* (EI) found 297.96955 (M^+); $C_9H_{15}S_2O_2Br$ requires 297.96968.

(±)-2-(2-(*R*)-Bromopropanoyl)-2-(*S*)-ethyl-1,3-dithiane 1-(*R*)-oxide (12)

The lithium enolate was generated from *syn* 2-propanoyl-2-ethyl-1,3-dithiane 1-oxide (0.21 g, 0.955 mmol) as described above and added by cannula to solid NBS (0.26 g, 1.46 mmol) at –78 °C. The reaction mixture was allowed to reach room temperature overnight. Normal work-up procedure gave the title compound (0.120 g) together with the isomer at the halogenated position (0.048 g), a 2.5:1 mixture of diastereoisomers, as crystalline solids (0.168 g, 59%).

For the major isomer (12): ν_{max} 1707 and 1041 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.20 (3H, t, *J* = 7.42 Hz), 1.77 (3H, d, *J* = 6.6 Hz), 2.20-2.51 (4H, m), 2.58-2.87 (2H, m), 3.11-3.30 (2H, m), and 5.02 (1H, q, *J* = 6.6 Hz); *m/z* (EI) found 297.97043 (M^+); $C_9H_{15}S_2O_2Br$ requires 297.96968.

For the minor isomer (11): ν_{max} 1715 and 1051 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.10 (3H, t, *J* = 7.42 Hz), 1.782 (3H, d, *J* = 6.6 Hz), 2.24-2.56 (5H, m), 2.68-2.84 (1H, m), 3.06-3.17 (1H, m), 3.37-3.51 (1H, m), and 5.15 (1H, q, *J* = 6.6 Hz); *m/z* (EI) found 297.97072 (M^+); $C_9H_{15}S_2O_2Br$ requires 297.96968. The structure of this compound was determined by X-ray crystallographic analysis.

Boron mediated reactions

(±)-2-(2-Bromoacetyl)-2-(R)-ethyl-1,3-dithiane 1-(R)-oxide (7)

The boron enolate was generated from *anti* 2-acetyl-2-ethyl-1,3-dithiane 1-oxide (0.174 g, 0.845 mmol) as described above and added by cannula to solid NBS (0.226 g, 1.27 mmol) at –78 °C. The reaction mixture was allowed to reach room temperature overnight. Normal work-up procedure gave the title compound as a crystalline solid (0.171 g, 71%). ν_{max} 1705 and 1050 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.08 (3H, t, *J* = 7.4 Hz), 1.73-1.87 (2H, m), 2.15-2.30 (1H, m), 2.43-2.76 (3H, m), 3.04-3.11 (2H, m), 4.28 (1H, d, *J* = 14.0 Hz), and 4.57 (1H, d, *J* = 14.0 Hz); *m/z* (EI) found 283.95464 (M^+), $C_8H_{13}S_2O_2Br$ requires 283.95404. Found: C, 33.82; H, 4.60%. $C_8H_{13}S_2O_2Br$ requires C, 33.69; H, 4.60%.

(±)-2-(2,2-Dibromoacetyl)-2-(S)-ethyl-1,3-dithiane 1-(R)-oxide (5) and (±)-2-(2-Bromoacetyl)-2-(S)-ethyl-1,3-dithiane 1-(R)-oxide (10)

The boron enolate was generated from *syn* 2-acetyl-2-ethyl-1,3-dithiane 1-oxide (0.122 g, 0.592 mmol) as described above and added by cannula to solid NBS (0.158 g, 0.888 mmol) at –78 °C. The reaction mixture was allowed to reach room temperature overnight. Normal work-up procedure gave the title compounds as a crystalline solids.

For (5): 0.039 g, 18%; spectroscopic data given above.

For (10): 0.058 g, 33%; ν_{max} 1707 and 1059 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.09 (3H, t, *J* = 7.4 Hz), 2.05-2.22 (1H, m), 2.32-2.47 (2H, m), 2.54-2.83 (2H, m), 3.09-3.34 (2H, m), 4.31 (1H, d, *J* = 15.9 Hz), 4.59 (1H, d, *J* = 15.9 Hz); *m/z* (EI) found 283.95351 (M^+), $C_8H_{13}S_2O_2Br$ requires 283.95404. Found: C, 33.89; H, 4.62%. $C_8H_{13}S_2O_2Br$ requires C, 33.69; H, 4.60%.

(±)-2-(2-(S)-Bromopropanoyl)-2-(S)-ethyl-1,3-dithiane 1-(R)-oxide (11)

The boron enolate was generated from *syn* 2-propanoyl-2-ethyl-1,3-dithiane 1-oxide (0.120 g, 0.545 mmol) as described above and added by cannula to solid NBS (0.145 g, 0.815 mmol) at –78 °C. The reaction mixture was allowed to reach room temperature overnight. Normal work-up procedure gave the title compound together with the isomer at the halogenated position, a 1.67:1 mixture of diastereoisomers by ^{1}H NMR spectroscopy, as crystalline solids (0.143 g, 87%). Spectroscopic data given above.

(±)-2-(2-(S)-Bromopropanoyl)-2-(S)-ethyl-1,3-dithiane 1-(R)-oxide (11)

The boron enolate was generated from *anti* 2-propanoyl-2-ethyl-1,3-dithiane 1-oxide (0.28 g, 1.27 mmol) as described above and added by cannula to solid NBS (0.34 g, 1.91 mmol) at –78 °C. The reaction mixture was allowed to reach room temperature overnight. Normal work-up procedure gave the title compound (0.296 g) together with the isomer at the halogenated position (0.053 g), a 5.5:1 mixture of diastereoisomers by ^{1}H NMR spectroscopy, as crystalline solids (0.349 g, 92%). Spectroscopic data given above.

Nucleophilic displacements of bromide from *syn* and *anti* 2-(2-bromoacyl)-2-ethyl-1,3-dithiane 1-oxides using nitrogen nucleophiles

(±)-2-(1,2-Diketopropyl)-2-(*S*)-ethyl-1,3-dithiane 1-(*R*)-oxide (13)

(±)-2-(2-(*S*)-Bromopropanoyl)-2-(*S*)-ethyl-1,3-dithiane 1-(*R*)-oxide (11) (0.15 g, 0.501 mmol) was dissolved in DMF (5 ml) at room temperature. Sodium azide (0.10 g, 1.54 mmol) was added and the reaction mixture stirred overnight at room temperature. Water (50 ml) was added and the mixture extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were washed with water, dried over magnesium sulphate, and the solvents removed under reduced pressure. Flash column chromatography gave the title compound as a yellow oil (0.099 g, 84%); ν_{max} (neat) 1714, 1700, and 1061 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.12 (3H, t, *J* = 7 Hz), 2.19-2.25 (2H, m), 2.39 (3H, s), 2.40-2.58 (2H, m), and 2.92-3.30 (4H, m); δ_C (100 MHz, $CDCl_3$) 10.24, 26.75, 27.58, 28.50, 30.50, 49.05, 77.19, 194.64, and 195.91; *m/z* (CI, NH_3) 235 (M^++H).

(±)-2-(2-(*S*)-Phthalimidopropanoyl)-2-(*S*)-ethyl-1,3-dithiane 1-(*R*)-oxide (14)

(±)-2-(2-(*R*)-Bromopropanoyl)-2-(*S*)-ethyl-1,3-dithiane 1-(*R*)-oxide (0.10 g, 0.334 mmol) was dissolved in DMSO (5 ml). Potassium phthalimide (0.186 g, 1.00 mmol) was added and the reaction mixture stirred at 40 °C overnight. After cooling to room temperature, water (50 ml) was added and the mixture extracted with dichloromethane (3 x 25 ml) and ethyl acetate (3 x 25 ml). The combined organic extracts were washed with water (3 x 10 ml), dried over magnesium sulphate, and the solvents removed under reduced pressure to give a 2:1 mixture of diastereoisomeric products by ^1H NMR spectroscopy. Separation by flash column chromatography gave the title compound (0.077 g, 63%) and the isomer at the nitrogenated position (0.041 g, 28%) as colourless oils; ν_{max} (neat) 1777, 1717, 1623, 1057, and 756 cm^{-1}.

For the major isomer: δ_H (400 MHz, $CDCl_3$) 1.14 (3H, t, *J* = 7.5 Hz), 1.94 (3H, d, *J* = 7.5 Hz), 2.10-2.23 (1H, m), 2.24-2.47 (3H, m), 2.67-2.79 (2H, m), 3.02-3.27 (1H, m), 3.40-3.50 (1H, m), 5.45 (1H, q, *J* = 7 Hz), 7.22-7.75 (2H, m), 7.83-7.88 (2H, m); *m/z* (EI) 365.07554 (M^+); $C_{17}H_{19}O_4NS_2$ requires 365.07555. Found C, 52.50; H, 6.71; N, 3.79; $C_{17}H_{19}O_4NS_2$ requires C, 55.87; H, 5.24; N, 3.83%.

For the minor isomer: δ_H (400 MHz, $CDCl_3$) 1.19 (3H, t, *J* = 7.6 Hz), 1.70 (3H, d, *J* = 7.0 Hz), 2.20-2.55 (5H, m), 2.93-3.05 (1H, m), 3.10-3.16 (1H, m), 3.70-3.79 (1H, m), 5.35 (1H, q, *J* = 7 Hz), 7.69-7.75 (2H, m), 7.81-7.86 (2H, m); *m/z* (EI) 365 (M^+).

(±)-2-(2-(*S*)-Phthalimidopropanoyl)-2-(*S*)-ethyl-1,3-dithiane 1-(*R*)-oxide (14)

(±)-2-(2-(*S*)-Bromopropanoyl)-2-(*S*)-ethyl-1,3-dithiane 1-(*R*)-oxide (0.05 g, 0.167 mmol) was dissolved in DMSO (5 ml). Potassium phthalimide (0.093 g, 0.502 mmol) was added and the reaction mixture stirred at 40 °C overnight. After cooling to room temperature, water (50 ml) was added and the mixture extracted with dichloromethane (3 x 25 ml) and ethyl acetate (3 x 25 ml). The combined organic extracts were washed with water (3 x 10 ml), dried over magnesium sulphate, and the solvents removed under reduced pressure to give a 2:1 mixture of diastereoisomeric products by ^1H NMR spectroscopy. a yellow oil. Separation by flash column chromatography gave the title compound (0.039 g, 64%) and the isomer at the nitrogenated position (0.019 g, 31%) as colourless oils. The sense of stereochemical induction in the major diastereoisomer was judged to be identical to that in the product of the corresponding reaction of potassium phthalimide with the major bromopropanoyl isomer described above. Spectroscopic data as described above.

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