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Diastereoselectivity in the Addition of Grignard Reagents to Ketones Controlled by the 1,3-Dithiane 1-Oxide Asymmetric Building Block

Philip C. Bulman Page,* Jeremy C. Prodger, and Donald Westwood

Robert Robinson Laboratories, Department of Chemistry,
University of Liverpool, Oxford Street, Liverpool L69 3BX, England

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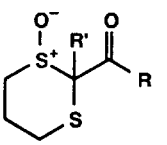
Abstract: 2-Acyl-1,3-dithiane 1-oxides undergo diastereoselective addition of Grignard reagents; the degree of selectivity observed is highly dependent upon the solvent and the halide counter-ion used; very high selectivities have been observed under certain reaction conditions.

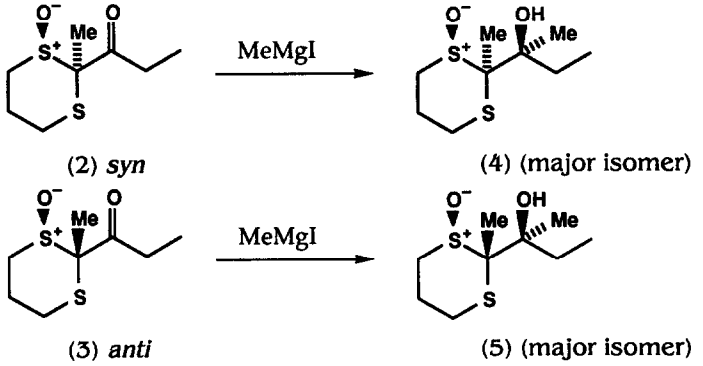
The sulphoxide moiety is pyramidal and highly polarized, and is capable of inducing asymmetry at adjacent centres; methods of asymmetric synthesis which exploit sulphoxide stereochemistry have become extremely useful weapons in the armoury of the synthetic organic chemist.[1] The 1,3-dithiane 1-oxide (DITOX) asymmetric building block falls into this category. We have shown that 2-acyl-1,3-dithiane 1-oxides (1) undergo highly diastereoselective enolate alkylation and amination,[2] Mannich reaction,[3] reduction,[4] cycloaddition,[5] Grignard,[6] and conjugate addition[7] reactions. In our laboratories we have developed asymmetric syntheses of 1,3-dithiane 1-oxide itself[8] and of acyl dithiane oxides[9] in optically pure form and both chiral senses. Additional qualities of the system include the potential for control in tandem reactions and easy removal of the auxiliary to provide synthetically useful functionality. Few asymmetric building blocks can achieve stereocontrol in such a plethora of reaction types and this, coupled with the ease of manipulation, gives the DITOX unit great potential in asymmetric synthesis.



(1)

The addition of Grignard reagents to acyl dithiane oxides occurs in a highly stereoselective manner. Our initial work involved the addition of four equivalents of ethereal methyl magnesium iodide to both *syn-* and *anti-*2-propionyl-2-methyl-1,3-dithiane 1-oxides (2) and (3), in various solvents and at various temperatures.[6] The isomeric purities of the respective products (4) and (5) were measured using analytical hplc techniques or by observation of pairs of methyl singlet resonances in 250 MHz ^{1}H NMR spectra. A selection of relevant results is shown in Table I.

TABLE I. Variation of selectivity with solvent and temperature



(2) *syn* (4) (major isomer)

(3) *anti* (5) (major isomer)

Substrate	Solvent	Temp/°C	Yield/%	Isomer Ratio
syn	THF	25	70	4:1 †
syn	THF	−20	95	*ca.* 25:1 ‡
syn	THF	−78	95	exclusive §
syn	Et_2O	−78	33	1:1 †
anti	THF	−78	95	15:1 ‡
anti	Et_2O	−78	96	3:1 ‡

† Determined by 250 MHz ^1H NMR spectroscopy
‡ Determined by hplc.
§ Minor isomer undetectable by hplc or ^1H NMR spectroscopy

Three observations may be made based upon these early studies. The levels of diastereoselectivity of reactions using THF as solvent are superior to those in diethyl ether; the *syn* 2-methyl substrate (2) induces higher selectivity than the *anti* substrate (3); finally, the levels of selectivity are temperature-dependent.

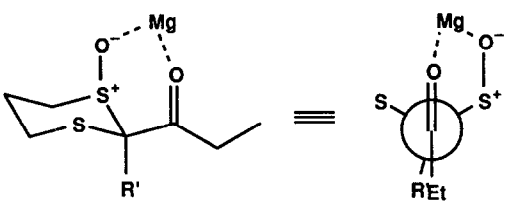


Figure 1

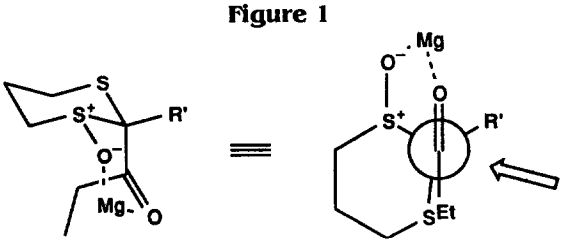


Figure 2

These observations are consistent with the formation of chelated Cram-type[10] transition states, as shown in figures 1 to 4.

For the *syn* substrates (2), chelation of magnesium between the sulphoxide and carbonyl group oxygen atoms can occur. From our model it is apparent that the conformer with axial sulphoxide (Figure 1) would be expected to show low levels of diastereoselectivity. However, when the sulphoxide adopts the equatorial position (Figure 2) the preferred direction of an approaching nucleophile would be determined by the size of the C-2 alkyl substituent *versus* the bulk of the dithiane ring. An inspection of simple molecular models suggests that the reaction should occur as shown by the arrow.

In the case of *anti* substrates (3) with axial sulphoxide conformation (Figure 3), no chelation can occur between the metal ion and the carbonyl and sulphoxide group oxygen atoms, but in this case chelation of the metal atom between the carbonyl group oxygen atom and the nucleophilic sulphur atom of the dithiane ring is possible. In the equatorial sulphoxide conformation (Figure 4), chelation of the metal ion between the sulphoxide and carbonyl group oxygen atoms can occur. The steric bulk of the C-2 alkyl substituent would then direct nucleophilic attack at the ketone. Again, inspection of simple molecular models suggests that addition will occur as shown by the arrow.

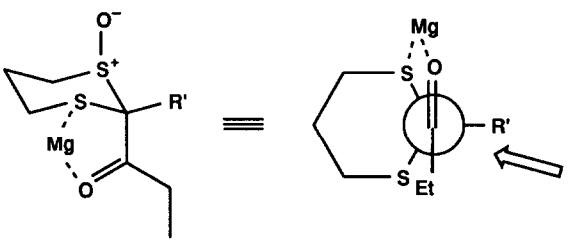


Figure 3

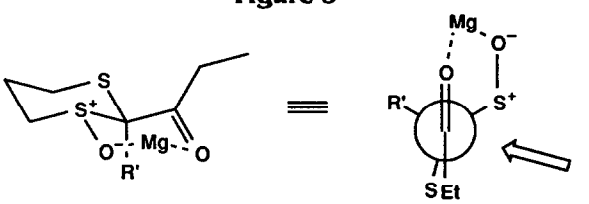
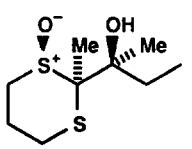


Figure 4

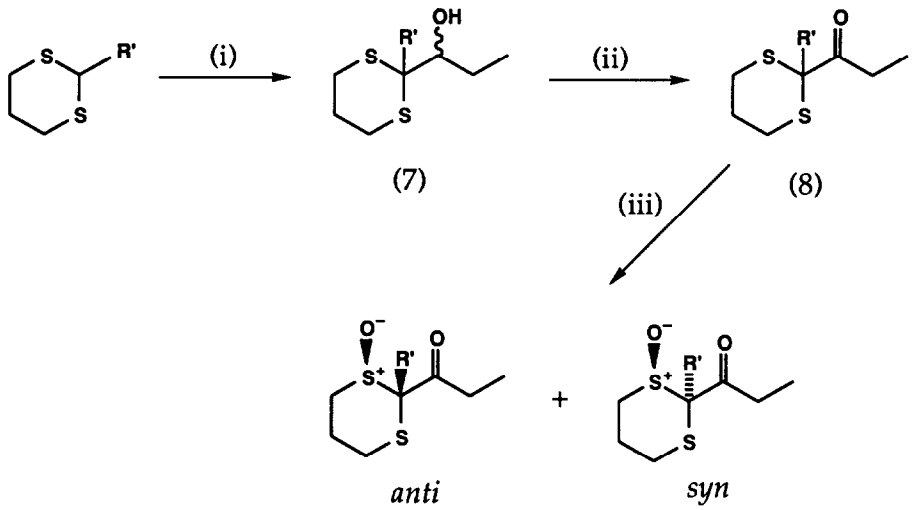
The structure of the major diastereoisomer (6) generated by the reaction of *syn*-2-methyl-2-propionyl-1,3-dithiane 1-oxide with four equivalents of methyl magnesium iodide in THF at –78 °C was confirmed by an X-ray crystal structure determination, and conforms to our predictive model. Products from the *anti* series, although crystalline, were not amenable to X-ray study.



(6)

Clearly, in both *syn* (2) and *anti* substrates (3) the size of the alkyl group at the 2-position of the dithiane 1-oxide ring should, to some extent, determine both the level of stereoselectivity attained through each reactive conformation and the equilibrium concentrations of each of these conformations. In addition, stereoelectronic factors such as the gauche effect and anomeric considerations might be important. To address some of these issues further work in our laboratories involved studying the effect of altering the size and shape of the alkyl 2-substituent R of the substrates (1) and changing the nature of the halide associated with the Grignard reagent.

A range of *syn* and *anti* 2-substituted 2-propionyl-1,3-dithiane 1-oxide substrates were prepared according to Scheme 1. The appropriate 2-substituted 1,3-dithiane 1-oxide was deprotonated at low temperature using butyl lithium and the resulting anion quenched with propionaldehyde to give the alcohols (7). Swern oxidation gave the ketones (8), and finally sulphur oxidation using sodium metaperiodate gave mixtures of *syn* and *anti* substrates, easily separated using flash column chromatography on silica gel.[11]



Reagents : (i) BuLi, THF, –78 °C; CH_3CH_2CHO;
(ii) DMSO, $(CF_3CO)_2O$, CH_2Cl_2, –78 °C, Et_3N; (iii) $NaIO_4$

Scheme 1

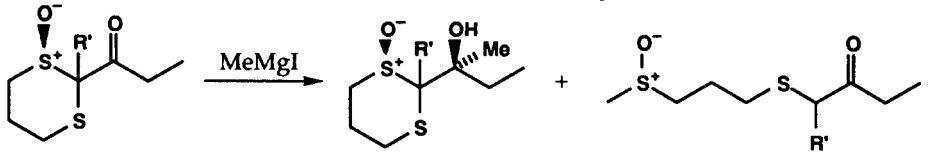
Grignard reagent additions were performed using standard conditions to provide the corresponding carbinols, generally in good yields (Table II).

We anticipated, on the basis of our transition state model, that the steric bulk of the 2-substituent R′ should have a marked effect upon the degree of stereoselectivity achieved using our system. For *syn* and *anti* substrates the transition states shown in figures 1 and 4 will only be tolerated for small C-2 alkyl substituents R′. In the case of the *syn* substrates a large R′ group will favour reaction *via* the stereoselective transition state shown in figure 2. However, increasing the bulk of group R′ will decrease the steric discrimination between the two faces of the carbonyl group, and will therefore reduce the levels of stereoselectivity achieved through this transition state. We should therefore expect to see an optimum size of C-2 alkyl substituent. Indeed, inspection of Table II demonstrates that in the *syn* series a 2-methyl substituent induces greater selectivity than

a 2-ethyl.

For the *anti* substrates, increasing the bulk of the 2 substituent will disfavour reaction *via* the stereoselective transition state shown in figure 4; however, selectivity within this transition state will be favoured by large R'. Taking this into account we again expect to observe an optimum size of 2-substituent, and from Table II it appears that this is provided by an ethyl group.

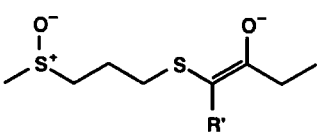
Table II. Variation of selectivity with R'



Substrate	R'	Solvent	Temp/°C	Alcohol yield/%	Ratio †	(9) yield/%
syn	Me	THF	−78	95	exclusive ‡	0
syn	Et	THF	−78	15	9.5:1	18
syn	^{i}Pr	THF	−78	0	—	60
syn	Ph	THF	25	0	—	78
syn	Ph	THF	−78	0	—	51
syn	Ph	Et_2O	25	80	2:1	0
anti	Me	THF	−78	95	15:1	0
anti	Et	THF	−78	75	23:1	0
anti	^{i}Pr	THF	−78	0	—	33
anti	Ph	THF	25	0	—	70
anti	Ph	THF	−78	0	—	71
anti	Ph	Et_2O	25	80	10:1	0

† Determined by 250 MHz ^{1}H NMR spectroscopy
‡ Minor isomer undetectable by hplc or ^{1}H NMR spectroscopy

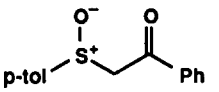
For reactions in THF solvent, increasing the size of the C-2 alkyl substituent also has the effect of favouring the formation of ring opened products (9). Evidently attack by Grignard reagent at the sulphoxide sulphur atom is responsible for thioacetal ring cleavage and expulsion of enolate (10), and hence the appearance of these materials.



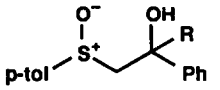
(10)

It is possible that increasing the bulk of the group R' increases the steric hindrance around the carbonyl group, thus favouring nucleophilic attack at sulphur. For the 2-phenyl substrates, reaction in tetrahydrofuran gave only ring opened products, but, interestingly,

when the reaction was performed in diethyl ether only alcohol products were formed (Table II). Of more interest than the modest levels of stereoselectivity achieved in these reactions is the remarkable change in chemoselectivity when the solvent is changed from THF to diethyl ether. A study of the literature reveals few examples of additions of Grignard reagents to β-keto sulphoxides. Nokami has published one example where an acidic proton is sited between the sulphoxide and carbonyl groups of a β-ketosulphoxide; in this case addition of one equivalent of ethereal Grignard reagent to (11) resulted in deprotonation as would be expected. The resulting anion (12) could be successfully reacted with a variety of electrophiles, however this was only possible in diethyl ether solvent — the anion (12) is quite unreactive in THF.[12]



(11)



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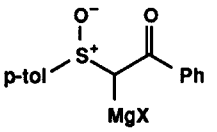
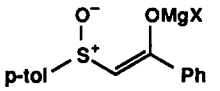


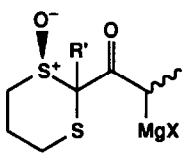
a

(12)



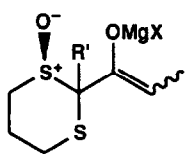
b

Nokami further showed that addition of two equivalents of Grignard reagent to (11) in diethyl ether results in a high yield of the alcohol (13). The same reaction in THF solvent gave a complex product mixture, including products of displacement at the sulphoxide sulphur atom. Nokami made the unusual proposal that the species (12) exists as the carbanion (12a) in diethyl ether, but as the enolate (12b) in THF. Reaction *via* (12a) allows further attack by Grignard reagent at the carbonyl group resulting in the formation of alcohol products (13), while reaction *via* (12b) allows Grignard reagent attack at the sulphoxide group only, resulting in the complex product mixture observed. Unconventional though this suggestion may be, our own results do parallel those of Nokami in that the solvent dependence of the chemoselectivity observed is similar. In our case, when the C-2 alkyl group is large the Grignard addition process may be hindered to such an extent that deprotonation to give (14) becomes the more favourable process.



a

(14)



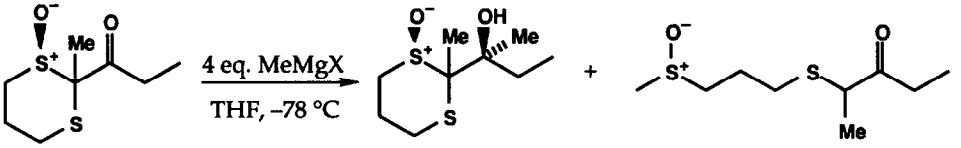
b

According to the Nokami explanation, in diethyl ether the predominant species would be C-metallated (14a), through which further Grignard reagent attack at the carbonyl group is possible, resulting in the formation of the observed alcoholic products; while in THF O-metallated species (14b) would be present, in which further Grignard reagent attack is only possible at the sulphoxide group, giving rise to ring opened materials.

Finally, in order to study the effects of changing the nature of the halide ion

associated with the reagent, methyl Grignard reagent was utilized with three different counter-ions (Cl^-, Br^-, and I^-), and each was added to both *syn*- and *anti*- 2-methyl-2-propionyl-1,3-dithiane 1-oxides (Table III). For the *syn* substrate, only methyl magnesium iodide gave isolable products. For the *anti* substrates, both yields and selectivities were very poor for reagents with bromide or chloride as counter-ion. These results are difficult to rationalize, but are perhaps connected with the differing Lewis acidities of the three reagents, or with reagent oligomerization.[13]

Table III. Variation of selectivity with counter-ion



(major isomer) (9)

Substrate	Counterion	Alcohol yield/%	Ratio †	(9) yield/%
syn	I	95	exclusive ‡	0
syn	Br	—	—	—
syn	Cl	—	—	—
anti	I	95	15:1	0
anti	Br	40	2:1	50
anti	Cl	14	1:1	18

† Determined by 250 MHz ^1H NMR spectroscopy
‡ Minor isomer undetectable by hplc or ^1H NMR spectroscopy

Acknowledgment

This investigation has enjoyed the support of the SERC. We are indebted to the SERC Very High Field NMR Service at the University of Warwick for their help and patience.

EXPERIMENTAL

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 2.5 M solution in hexane. The molarity was determined by titration against a solution of diphenyl acetic acid. Methyl magnesium iodide was prepared as a 0.6 M solution in ether by the addition of methyl iodide (3.85 g, 27.08 mmol) to magnesium turnings (0.50 g, 20.83 mmol) in ether (33.0 ml). This solution could be stored under argon for 2-3 days. Methyl magnesium bromide was purchased from Aldrich in 100 ml bottles as a 3 M solution in THF. Methyl magnesium chloride was purchased from Aldrich as a 3 M solution in THF. Aldehydes were distilled and stored over 4Å molecular sieve. Dimethyl sulphoxide was heated at 50 °C for 3 h over calcium hydride prior to distillation and storage over 4Å molecular sieve.

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 and ether (diethyl ether) were 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 dessicator 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 dessicator. Reactions were maintained in under a slight static positive pressure of argon and reagents and solvents introduced *via* syringe or using cannula techniques, through a septum cap.

Normal work-up procedures

Organometallic reactions were usually worked up by the addition of a saturated solution of ammonium chloride, followed by extraction of the aqueous phase into dichloromethane. The combined organic extracts were washed with water and dried over anhydrous magnesium sulphate which was later removed by filtration. The solvents were removed under reduced pressure, and the crude products purified by chromatography or distillation.

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) in proportions ranging from 1:1 to 1:10 were used as eluant, unless otherwise stated. Dry flash column chromatography was carried out using Merck 15111 silica gel using petroleum ether (bp 40-60 °C) containing an increasing proportion of ethyl acetate as eluant. 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 eluant 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. A Büchi Kugelrohr oven was used as the heat source for bulb to bulb distillations; boiling points quoted refer to the oven temperature.

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 Perkin Elmer R34, Bruker WM250, Bruker ACE200, 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 Carlos Ebra elemental analyser at the University of Liverpool, Department of Chemistry microanalytical laboratory. Melting points were determined on a Reichert hot stage apparatus and are uncorrected.

Procedures

2-Phenyl-1,3-dithiane

Hydrogen chloride gas was bubbled through a solution of benzaldehyde (21.2 g, 200 mmol) and 1,3-propanedithiol (21.6 g, 200 mmol) in chloroform (50 ml) at 6 °C until the solution became saturated (*ca.* 5 min). The mixture was stirred at 6 °C for 1 hour and allowed to reach room temperature. The solution was washed successively with water (2x50 ml), 10% aqueous potassium hydroxide (3x50 ml), and water (2x50 ml). The organic layer was dried over magnesium sulphate and the solvent removed under reduced pressure to give an off-white solid; one recrystallization from methanol provided 2-phenyl-1,3-dithiane as a colourless solid (33.5 g, 85%), m.p. 71.5-72.5 °C; δ_H (220 MHz, $CDCl_3$) 1.80-2.00 (1H, m), 2.05-2.2 (1H, m), 2.80-3.10 (4H, m), 5.10 (1H, s), 7.25-7.35 (3H, m) and 7.40-7.50 (2H, m); *m/z* (EI) 196 (M^+).

2-(1-(1-Hydroxypropyl))-2-methyl-1,3-dithiane

To a solution of 1,3-dithiane (5 g, 41.6 mmol) in THF (250 ml) at –20 °C was added a solution of butyllithium in hexane (1 equiv.). The resulting pale yellow anion was stirred for one hour at –20 °C before cooling to –78 °C. Methyl iodide (2.6 ml, 41.6 mmol) was added and the mixture allowed to reach room temperature. After stirring for two hours the mixture was recooled to –20 °C. A solution of butyllithium (1 equiv.) was added and the yellow/brown anion stirred at –20 °C for three hours before cooling to –78 °C. Propanal (3 ml, 41.6 mmol) was added and the mixture allowed to reach to room temperature overnight. Normal work-up and flash column chromatography using 10% ethyl acetate/petroleum ether as eluant gave the alcohol as a colourless oil (8 g, 82 %); ν_{max} 3500-3300 cm^{-1}; δ_H (220 MHz, $CDCl_3$) 1.10 (3H, t, *J* 7.5 Hz), 1.30-1.50 (1H, m), 1.40 (3H, s), 1.90-2.20 (3H, m), 2.60-2.75 (2H, m), 2.85 (1H, br s), 3.00 (2H, dt, *J* 1.5 and 13.5 Hz) and 3.8 (1H, d, *J* 11 Hz); *m/z* (CI, NH_3) 210 (M^++18). Found: C, 49.90; H, 8.56; $C_8H_{16}OS_2$ requires C, 49.96; H, 8.39%.

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

Treatment of 1,3-dithiane (5 g, 41.6 mmol) in THF (250 ml) with a solution of butyllithium (2 equiv.), ethyl bromide (3.1 ml, 41.6 mmol) and propanal (3.1 ml, 41.6 mmol) as described above gave the alcohol (8 g, 80%) as a colourless solid, m.p. 40-43 °C; ν_{max} 3500 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.80-2.20 (12H, m), 2.40-3.20 (5H, m) and 3.90 (1H, d, *J* 10 Hz); *m/z* (CI, NH_3) 207 (M^++1). Found: C, 52.50; H, 8.93; $C_9H_{18}OS_2$ requires C, 52.38; H, 8.79%.

2-(1-(1-Hydroxypropyl))-2-(2-propyl)-1,3-dithiane

Treatment of 1,3-dithiane (5 g, 41.6 mmol) in THF (250 ml) with a solution of butyllithium (2 equiv.), 2-iodopropane (4.2 ml, 41.6 ml) and propanal (3.1 ml, 41.6

mmol) as described above gave the alcohol (5 g, 60%) as a colourless oil; ν_{max} 3470 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.30-1.90 (9H, m), 1.40-2.20 (5H, m), 2.50-2.70 (2H, m), 2.90-3.10 (3H, m) and 4.00 (1H, d, *J* 9 Hz); *m/z* (CI, NH_3) 221 (M^++1). Found: C, 54.47; H, 9.31; $C_{10}H_{20}S_2O$ requires C, 54.50; H, 9.15%.

2-(1-(1-Hydroxypropyl))-2-phenyl-1,3-dithiane

To a solution of 2-phenyl-1,3-dithiane (10.0 g, 51.0 mmol) in THF (200 ml) at –30 °C was added a solution of butyllithium (1 equiv.). The resulting pale yellow anion was stirred for two hours at –30 °C. The mixture was cooled to –78 °C, treated with propanal (3.26 g, 56 mmol), and allowed to reach room temperature. The mixture was subjected to normal work-up and flash column chromatography using 10% ethyl acetate/petroleum ether as eluant to give the alcohol as a colourless crystalline solid (11.4 g, 89%); m.p. 76-78 °C; ν_{max} 3500 cm^{-1}; δ_H (220 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.5 Hz), 1.10-1.15 (1H, m), 1,55-1.60 (1H, m), 1.90-2.00 (2H, m), 2.15 (1H, br s), 2.65-2.80 (4H, m), 3.70-3.80 (1H, m), 7.25-7.45 (3H, m) and 7.95-8.05 (2H, m); *m/z* (CI) 272 (M^++18). Found: C, 61.13; H, 7.19; $C_{13}H_{18}S_2O$ requires C, 61.38; H, 7.13%.

2-(1-(Propan-1-oyl))-2-methyl-1,3-dithiane

To a solution of dimethyl sulphoxide (5.6 g, 72 mmol) in dry dichloromethane (60 ml) at –78 °C was added trifluoroacetic anhydride (7.6 ml, 54.0 mmol). After stirring for 30 minutes at –78 °C a solution of 2-(1-(1-hydroxypropyl))-2-methyl-1,3-dithiane (6.12 g, 36 mmol) in dichloromethane (20 ml) was added dropwise. Stirring was continued at –78 °C for one hour while triethylamine (14 ml, 100 mmol) was slowly added. The solution was allowed to reach room temperature and washed with 5% aqueous hydrochloric acid (2x100 ml). The organic phase was separated, washed with saturated aqueous sodium hydrogen carbonate (2x100 ml), and dried over magnesium sulphate. The solvent was removed under reduced pressure and the residue purified by flash column chromatography using 5% ethyl acetate/ petroleum ether as eluant. The ketone was isolated as a pale yellow oil (3.15 g, 80%); ν_{max} 1710 cm^{-1}; δ_H (220 MHz, $CDCl_3$) 1.10 (3H, t, *J* 7.5 Hz), 1.60 (3H, s), 1.65-1.85 (1H, m), 2.00-2.20 (2H, m), 2.60-3.10 (3H, m), and 3.10 (2H, dt, *J* 1 and 12 Hz); *m/z* (EI) 190.048609 (M^+); $C_8H_{14}S_2O$ requires 190.048609.

2-(1-(Propan-1-oyl))-2-ethyl-1,3-dithiane

Treatment of 2-(1-(1-hydroxypropyl))-2-ethyl-1,3-dithiane (6.5 g, 32 mmol) with dimethyl sulphoxide (4.25 g, 64 mmol), trifluoroacetic anhydride (6.34 ml, 48 mmol) and triethylamine (12 ml, 85 mmol) as described above gave the ketone as a colourless oil (5.09 g, 79%); ν_{max} 1710 cm^{-1}; δ_H (220 MHz, $CDCl_3$) 1.00 (3H, t, *J* 8 Hz), 1.15 (3H, t, *J* 8 Hz), 1.70-2.30 (4H, m), 2.50-2.90 (4H, m) and 2.85-3.20 (2H, m).

2-(1-(Propan-1-oyl))-2-(2-propyl)-1,3-dithiane

Treatment of 2-(1-(1-hydroxypropyl))-2-(2-propyl)-1,3-dithiane (4.7 g, 21.4 mmol) with dimethyl sulphoxide (3.4 g, 42.8 mmol), trifluoroacetic anhydride (4.35 ml, 32.1 mmol) and triethylamine (10 ml, 72 mmol) as described above gave the ketone as a clear oil (4.05 g, 80%); ν_{max} 1705 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.05-1.40 (9H, m), 1.65-2.15 (2H, m), 2.20-2.50 (1H, m) and 2.60-3.12 (6H, m); *m/z* (CI, NH_3) 219 (M^++1). Found: C, 55.07;

H, 8.44; $C_{10}H_{18}OS_2$ requires C, 55.00; H, 8.31%.

2-(1-(Propan-1-oyl))-2-phenyl-1,3-dithiane

Treatment of 2-(1-(1-hydroxypropyl))-2-phenyl-1,3-dithiane (5.07 g, 20 mmol) with dimethyl sulphoxide (3.15 g, 40 mmol), trifluoroacetic anhydride (4.3 ml, 30 mmol) and triethylamine (9.42 ml, 67.3 mmol) as described above gave the ketone as a colourless crystalline solid (3.4 g, 70%), m.p. 78-80 °C; ν_{max} 1710 cm^{-1}; δ_H (220 MHz, $CDCl_3$) 1.05 (3H, t, *J* 7.5 Hz), 1.80-2.00 (1H, m), 2.05-2.15 (1H, m), 2.40 (2H, q, *J* 7.5 Hz), 2.70-2.80 (2H, m), 3.10-3.25 (2H, m), 7.35-7.45 (3H, m) and 7.50-7.60 (2H, m); *m/z* (EI) 252 (M^+). Found: C, 61.97; H, 6.43; $C_{13}H_{16}OS_2$ requires C, 61.87; H, 6.39%.

General procedure for the oxidation of 2-substituted 2-acyl-1,3-dithianes to the corresponding sulphoxides

A solution of sodium metaperiodate (1 equiv.) in water (ca. 10 ml g^{-1}) was added dropwise to a solution of the substrate in methanol (*ca.* 50 ml g^{-1} of substrate) at 0 °C over 0.5 h. The mixture was stirred at this temperature overnight and allowed to reach room temperature. The precipitate was removed by filtration and washed thoroughly with chloroform, and the filtrate evaporated to a slush and partitioned between water and dichloromethane. The aqueous layer was washed twice with dichloromethane and the combined organic fractions dried over magnesium sulphate. The solvent was removed under reduced pressure to give a mixture of diastereoisomeric sulphoxides. Isomers were separated by flash column chromatography using ethyl acetate as eluant. The pure diastereoisomers were recrystallized if necessary.

syn- *and* anti- *2-(1-(Propan-1-oyl))-2-methyl-1,3-dithiane 1-oxides*

Treatment of 2-(1-(propan-1-oyl))-2-methyl-1,3-dithiane (4.5 g, 24 mmol) as described above with sodium metaperiodate (5.07 g, 24 mmol) in water (50 ml) and methanol (200 ml) furnished the *syn* sulphoxide as a clear oil (1.34 g, 28%) and the *anti* sulphoxide as a colourless crystalline solid (2.41 g, 50%). For the *syn* sulphoxide: b.p. 190-192 °C (1.25 mmHg); ν_{max} 1710 and 1050 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.10 (3H, t, *J* 7 Hz), 1.90 (3H, s), 2.20-2.50 (2H, m), 2.60-2.90 (3H, m), 3.00-3.40 (3H, m); *m/z* (EI) 206 (M^+). Found: C, 46.50; H, 6.83; $C_8H_{14}O_2S_2$ requires C, 46.57; H, 6.84%. For the *anti* sulphoxide: m.p. 57-58 °C; ν_{max} 1690 and 1060 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.15 (3H, t, *J* 7 Hz), 1.70 (3H, s), 1.80-2.00 (1H, m), and 2.30-2.80 (4H), 2.90-3.10 (2H, m) and 3.15 (1H, dt, *J* 2 and 12 Hz); *m/z* (EI) 206 (M^+). Found: C, 46.48; H, 6.94; $C_8H_{14}O_2S_2$ requires C, 46.57; H, 6.84%.

syn- *and* anti- *2-(1-(Propan-1-oyl))-2-ethyl-1,3-dithiane 1- oxides*

Treatment of 2-(1-(propan-1-oyl))-2-ethyl-1,3-dithiane (4.7 g, 23 mmol) as described above with sodium metaperiodate (5.0 g, 23 mmol) in water (50 ml) and methanol (200 ml) furnished the *syn* sulphoxide (1.0 g, 20%) and the *anti* sulphoxide (2.91 g, 58%) as colourless crystalline solids. For the *syn* sulphoxide: m.p. 71-74 °C; ν_{max} 1710 and 1060 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.05 (3H, t, *J* 8 Hz), 1.10 (3H, t, *J* 8 Hz) and 2.00-3.40 (10H, m); *m/z* (CI, NH_3) 221 (M^++1). Found: C, 49.07; H, 7.40; $C_9H_{16}O_2S_2$ requires C, 49.06; H, 7.32%. For the *anti* sulphoxide: m.p. 61-63 °C; ν_{max} 1690 and 1050 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.00 (3H, t, *J* 8 Hz), 1.15 (3H, t, *J* 8 Hz), 1.70-2.00 (3H, m), 2.10-2.30 (2H,

m), 2.40-2.80 (3H, m) and 2.95-3.2 (2H, m); *m/z* (CI, NH_3) 221 (M^++1). Found: C, 49.05; H, 7.39; $C_9H_{16}O_2S_2$ requires C, 49.06; H, 7.32%.

syn- *and* anti- *2-(1-(Propan-1-oyl))-2-(2-propyl)-1,3- dithiane 1-oxides*

Treatment of 2-(1-(propan-1-oyl))-2-(2-propyl)-1,3-dithiane (4 g, 18.3 mmol) as described above with sodium metaperiodate (3.9 g, 18.3 mmol) in water (40 ml) and methanol (180 ml) furnished the *syn* sulphoxide as a colourless crystalline solid (1.0 g, 24%) and the *anti* sulphoxide as a waxy solid (1.1 g, 27%). For the *syn* sulphoxide: m.p. 85-88 °C; ν_{max} 1695 and 1050 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.00 (3H, t, *J* 8.3 Hz), 1.10 (3H, t, *J* 8.3 Hz), 1.2 (3H, d, *J* 8.3 Hz) and 2.20-3.50 (9H, m); *m/z* (CI, NH_3) 235 (M^++1). Found: C, 51.05; H, 7.80; $C_{10}H_{18}O_2S_2$ requires C, 51.25; H, 7.74%. For the *anti* sulphoxide: ν_{max} 1695 and 1025 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.10 (3H, t, *J* 8 Hz), 1.20 (3H, t, *J* 8 Hz), 0.80-1.15 (2H, t), 1.60-1.80 (1H, m) and 2.20-3.20 (9H, m); *m/z* (EI) 234.0748 (M^+); $C_{10}H_{18}O_2S_2$ requires 234.0748.

syn- *and* anti- *2-(1-(Propan-1-oyl))-2-phenyl-1,3-dithiane 1-oxides*

Treatment of 2-(1-(propan-1-oyl))-2-phenyl-1,3-dithiane (2.40 g, 9.52 mmol) as described above with sodium metaperiodate (2.24 g, 10.48 mmol) in water (25 ml) and methanol (200 ml) furnished the *syn* sulphoxide as an oil (0.56 g, 22%) and the *anti* sulphoxide as a colourless crystalline solid (1.68 g, 66%). For the *syn* sulphoxide: ν_{max} 1700 and 1050 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.00 (3H, t, *J* 7Hz), 1.90-2.10 (1H, m), 2.40-3.00 (6H, m), 3.10-3.30 (1H, m), 7.74-7.60 (3H, m) and 7.65-7.75 (2H, m); *m/z* (EI) 268 (M^+). Found: C, 58.20; H, 5.99; $C_{13}H_{16}O_2S_2$ requires C, 58.18; H, 6.01%. For the *anti* sulphoxide: m.p. 129-130 °C; ν_{max} 1690 and 1050 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.05 (3H, t, *J* 7 Hz), 1.75-1.85 (1H, m), 2.37-2.56 (2H, m), 2.60-2.85 (3H, m), 3.05-3.15 (1H, m), 3.20-3.45 (1H, m) and 7.40-7.55 (5H, m); *m/z* (EI) 268 (M^+). Found: C, 58.39; H, 6.04; $C_{13}H_{16}O_2S_2$ requires C, 58.18; H, 6.01%.

General procedure for addition of methyl Grignard reagents to 2-substituted 2-acyl-1,3-dithiane 1-oxides.

To a solution of the substrate ketone in THF or ether (*ca.* 25 ml/mmol ketone) at a preset temperature was added the methyl Grignard reagent (4 equiv.) in one slow steady addition. The resulting white suspension was stirred at this temperature for 4-6 h and allowed to reach room temperature overnight. The mixture was poured onto 5% aqueous hydrochloric acid and extracted with dichloromethane. The organic extracts were washed with water and dried over magnesium sulphate. Removal of the solvent and flash column chromatography using ethyl acetate as eluant furnished the diastereoisomeric addition products. Diastereoisomeric ratios were measured by ^1H NMR spectroscopy or hplc techniques.

syn-*2-(2-(2-Hydroxybutyl))-2-methyl-1,3-dithiane 1-oxide*

Isolated as a colourless solid; ν_{max} 3270 and 1025 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.96 (t, *J* 7.4 Hz), 1.37-1.55 (m), 1.51 (s), 1.55 (s), 1.75-1.98 (m), 2.47-3.05 (m) and 4.35 (br s); *m/z* (CI) 223 (M^++1). Found: C, 48.45; H, 8.21; $C_9H_{18}O_2S_2$ requires C, 48.61; H, 8.16%.

syn-2-(2-(2-Hydroxybutyl))-2-ethyl-1,3-dithiane 1-oxide

Isolated as a sticky oil; ν_{max} 3375 and 1025 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.94 (t, *J* 7.0 Hz, major), 1.03 (t, *J* 7.0 Hz, minor), 1.15 (t, *J* 7.5 Hz), 1.30-1.45 (m), 1.57 (s), 1.75-2.03 (m), 2.67-2.73 (m), 2.87-2.93 (m), 3.10-3.20 (m), 4.17 (s), and 4.40 (s); *m/z* (CI, NH_3) 237 (M^++1). Found: C, 50.77; H, 8.65; $C_{10}H_{20}O_2S_2$ requires C, 50.81; H, 8.53%.

syn-2-(2-(2-Hydroxybutyl))-2-phenyl-1,3-dithiane 1-oxide

Isolated as a colourless solid; ν_{max} 3360 and 1070 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.77 (t, *J* 7.0 Hz), 0.97 (t, *J* 7.4 Hz), 1.01 (s), 1.56 (s), 1.62-1.77 (m), 1.88-2.04 (m), 2.20-2.71 (m), 2.82-2.90 (m), 4.04 (s), 4.47 (s), 7.32-7.47 (m) and 7.66-7.80 (m); *m/z* (EI) 284 (M^+).

anti-2-(2-(2-Hydroxybutyl))-2-methyl-1,3-dithiane 1-oxide

Isolated as a colourless solid; ν_{max} 3300 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.86 (t, *J* 8 Hz), 1.10 (s), 1.36 (s), 1.43-1.50 (m), 1.66 (s), 1.69 (s), 1.95-2.10 (m), 2.20-2.35 (m), 2.55-2.73 (m), 2.9-2.95 (m) and 3.32 (s); *m/z* (CI) 223 (M^++1).

anti-2-(2-(2-Hydroxybutyl))-2-ethyl-1,3-dithiane 1-oxide

Isolated as a colourless solid; ν_{max} 3380 and 1025 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.84 (t, *J* 7 Hz), 0.95 (t, *J* 7 Hz), 1.18 (t, *J* 7.8 Hz), 1.35 (s), 1.50-1.62 (m), 1.78-2.10 (m), 2.18-2.52 (m), 2.73-2.82 (m) and 2.90-3.02 (m); *m/z* (CI, NH_3) 237 (M^++1). Found: C, 50.55; H, 8.69; $C_{10}H_{20}O_2S_2$ requires C, 50.81; H, 8.53%.

anti-2-(2-(2-Hydroxybutyl))-2-phenyl-1,3-dithiane 1-oxide

Isolated as a colourless solid, m.p. 142-147 °C; ν_{max} 3300 and 1010 cm^{-1}; δ_H (250 MHz, $(CD_3)_2SO$) 0.74 (t, *J* 7.4 Hz), 0.79 (t, *J* 7.3 Hz), 1.14 (s), 1.32 (s), 1.38-1.52 (m), 2.07-2.14 (m), 2.45-2.50 (m), 2.70-2.81 (m), 2.91-2.97 (m), 5.01 (s), 5.50 (s), 7.35-7.45 (m) and 7.90-8.25 (m); *m/z* (EI) 284 (M^+). Found: C, 58.92; H, 7.04; $C_{14}H_{20}O_2S_2$ requires C, 59.12; H, 7.09%.

8-Methylsulphinyl-4-methyl-5-thiaoctan-3-one

Isolated as a pale yellow oil; ν_{max} 1710 and 1040 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.09 (3H, t, *J* 7.3 Hz), 1.42 (3H, d, *J* 7.0 Hz), 1.96-2.09 (2H, m), 2.58 (3H, s), 2.16-2.70 (4H, m), 2.77 (2H, t, *J* 7.5 Hz) and 3.10 (1H, q, *J* 7.0 Hz); *m/z* (CI) 223 (M^++1).

8-Methylsulphinyl-4-ethyl-5-thiaoctan-3-one

Isolated as a colourless oil; ν_{max} 1715 and 1050 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7 Hz), 1.10 (3H, t, *J* 7 Hz), 0.80-1.40 (4H, m), 1.60-2.20 (5H, m), 2.40-3.0 (2H, m) and 2.60 (3H, s); *m/z* (EI) 236.0902; $C_{10}H_{20}O_2S_2$ requires 236.0905.

8-Methylsulphinyl-4-(2-propyl)-5-thiaoctan-3-one

Isolated as a clear oil; ν_{max} 1700 and 1040 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.95 (6H, d, *J* 8.3 Hz), 0.80-1.30 (5H, m), 1.80-2.20 (3H, m), 2.30-3.00 (5H, m) and 2.60 (3H, s); *m/z* (EI) 250.1059; $C_{11}H_{22}O_2S_2$ requires 250.1061.

8-Methylsulphinyl-4-phenyl-5-thiaoctan-3-one

Isolated as a colourless oil; ν_{max} 1710 and 1040 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.00

(3H, t, *J* 7.4 Hz), 1.95-2.05 (2H, m), 2.45-2.60 (4H, m), 2.55 (3H, s), 2.60-2.70 (2H, m), 4.72 (1H, s) and 7.38 (5H, s); *m/z* (CI) 302 (M^++18).

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11. Assignment of *syn* and *anti* substrate diastereoisomers was made on the basis of nmr evidence and by correlation with our previous work. The *anti* diastereoisomers characteristically display a discrete signal in their ^{1}H nmr spectra at *ca.* δ 1.7-1.9 ppm, corresponding to a dithiane ring proton. This signal appears at lower field for *syn* isomers and is often masked by other resonances. *Anti* diastereoisomers are normally observed to be more polar than *syn* upon thin layer chromatography, enabling efficient separation by column chromatography.
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