Enantioselective synthesis of α-arylpropanoic acids

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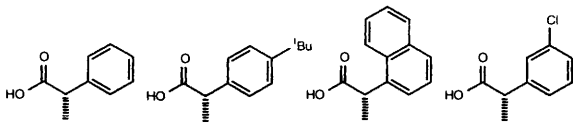
A range of (+)-α-arylpropanoic acids has been prepared in high enantiomeric excesses using 1,3-dithiane 1-oxide (DiTOX) units as the stereocontrolling elements and sources of chirality.

α-Arylpropanoic acids are an important class of compounds well known for their anti-inflammatory activity; a number of methods for their racemic and asymmetric synthesis have been developed and are well covered in the literature by some excellent reviews.[1] Several are successfully marketed, with



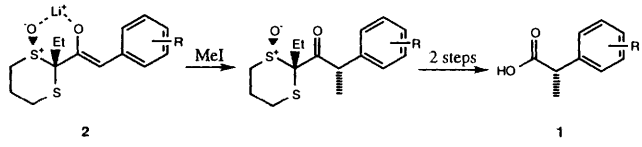
1a **1b** **1c** **1d**

perhaps the most well known example being ibuprofen. 2-Phenylpropanoic acid **1a** has anti-inflammatory, analgesic and antipyretic properties;[2] the *p-tert*-butyl and *m*-chloro derivatives **1b** and **1d** display anti-inflammatory activity;[3] and the 1-naphthyl derivative **1c** is a growth regulator.[4] We report here the enantioselective synthesis of each of these α-arylpropanoic acids **1a–d** using 1,3-dithiane 1-oxide units as the stereocontrolling elements and sources of chirality.

1,3-Dithiane 1-oxide (DiTOX) derivatives can act as chiral auxiliaries or asymmetric building blocks for the enantioselective control of a wide range of reactions. For example, in the past we have shown that 2-acyl-2-alkyl-1,3-dithiane 1-oxides undergo highly diastereoselective enolate alkylation,[5,6] carbonyl group reduction,[7] Grignard reagent addition,[8] Mannich reaction,[9] heterocycloaddition[10] and conjugate additions.[11] The acyl dithiane oxides are available enantioselectively, with both enantiomers available as the chirality is introduced using a catalytic asymmetric sulfoxidation reaction.[12] A chelation control model of the reactivity of these systems allows us to rationalize and, in many cases, predict the stereochemical outcome of the reactions studied. The work has concentrated on diastereoselective reactions, although we have previously reported the enantioselective synthesis of the natural product derivative (*R*)-(−)-2,6-dimethylheptanoic acid using our chemistry.[6] We are now pleased to report the use of DiTOX chemistry in the enantioselective synthesis of α-arylpropanoic acids, a more challenging prospect due to the more ready racemization of the asymmetric centre. The route chosen highlights an alternative method of removal of the DiTOX units proceeding through α-diketone intermediates, remarkably without racemization taking place.

We envisaged that methylation of chiral acyl dithiane oxide enolates **2** followed by removal of the DiTOX unit would lead to optically enriched acids **1** (Scheme 1). The 2-ethyl DiTOX system was selected as it has shown the greatest diastereoselectivity in our previous studies of enolate alkylation.[5]

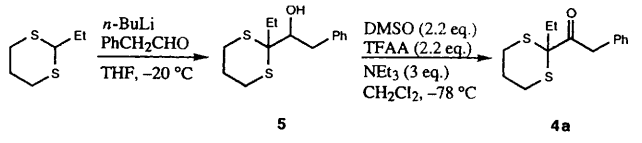
The acyl dithiane oxide substrates **3** were prepared through either two- or three-step procedures. In both methods the final



2 **1**

Scheme 1 Synthetic plan

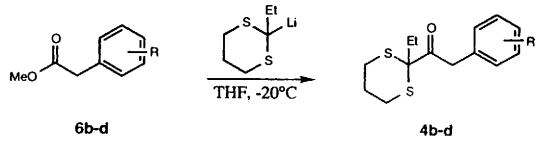
step was an asymmetric sulfur oxidation.[12,13] The acyl dithiane **4a** was prepared by the reaction of the 2-lithio derivative of 2-ethyl-1,3-dithiane with phenylacetaldehyde to give the alcohol **5** which was oxidized using Swern conditions (Scheme 2). The acyldithianes **4b–d** were constructed by the reaction of



5 **4a**

Scheme 2 Preparation of the acyldithiane **4a**

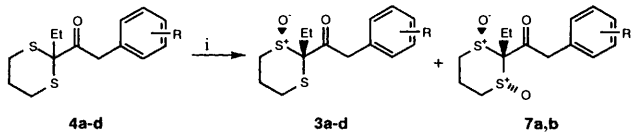
2-lithio-2-ethyl-1,3-dithiane with the corresponding methyl esters **6b–d** (Scheme 3).



6b-d **4b-d**

Scheme 3 Preparation of the acyldithianes **4b–d**

Asymmetric sulfur oxidation of **4a–d** under the conditions of Kagan[13] at −30 °C proceeded cleanly in each case to give the oxides **3a–d** with excellent enantiomeric excesses (Scheme 4,



4a-d **3a-d** **7a,b**

Scheme 4 Asymmetric sulfur oxidation of acyldithianes **4**. *Reagents and conditions:* i, $Ti(OPR^i)_4$ (1.1 equiv.), (+)-diethyl tartrate (2.2 equiv.), H_2O (1 equiv.), cumene hydroperoxide (1.5 equiv.); CH_2Cl_2, −30 °C.

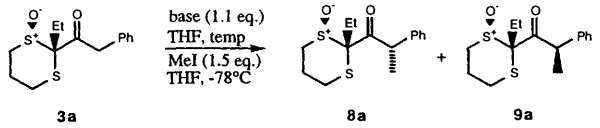
Table 1). The oxidation was also highly diastereoselective, with only *anti* sulfoxide observed in all four examples. Some minor over oxidation to the 1,3-dioxides **7a,b** occurred with **4a,b**. The dioxides were easily removed during purification by flash column chromatography.

Table 1 Asymmetric sulfur oxidation of acyldithianes **4**

Substrate	Yield of **3** (%)	ee (%)[a]	Yield of **7** (%)	ee (%)[a]
4a	64	94	14	86
4b	74	90	13	83
4c	72	94	0	—
4d	63	88	0	—

[a] Determined by ^{1}H NMR shift experiments at 400 MHz in the presence of 5–10 mol equiv. (*R*)-(−)-1-(9-anthryl)-2,2,2-trifluoroethanol.[16]

Table 2 Deprotonation and asymmetric alkylation of **3a**



3a **8a** **9a**

Base*	Temp. (°C)	Ratio **8a**:**9a**[a]	Total yield (%)
LHMDS	−78	17:1	82
LHMDS	−100	17:1	82
NHMDS	−78	2:1	75
KHMDS	−78	1:1	87
KOBu^t	20	1.15:1	72

[a] Ratio determined by 400 MHz ^{1}H NMR spectroscopy. * LHMDS = lithium bis(trimethylsilyl)amide, NHMDS = sodium bis(trimethylsilyl)-amide and KHMDS = potassium bis(trimethylsilyl)amide.

Table 3 Deprotonation and asymmetric alkylation of **3a–d**

Substrate	Base	Temp. (°C)	Ratio **8**:**9**[a]	Yield of **8** (%)
3a	LHMDS	−78	17:1	77
3b	LHMDS	−78	20:1	84
3c	LHMDS	−78	exclusive[b]	80
3d	NaH	−78	7:1	70

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

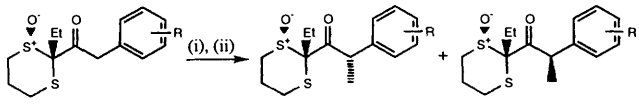
Initial enolate methylation studies were conducted using the simplest substrate **3a** (R = H). A range of counter-ions, and methods and temperatures of enolate generation and reaction were investigated; a selection of results for alkylation at −78 °C are given in Table 2. A wide range of diastereoselectivity was observed. Lithium proved to be the most suitable counter-ion, with sodium and potassium giving poor diastereoselectivities. No advantage was seen on reducing the temperature of enolate generation below −78 °C. In each case, the major diastereoisomer obtained was **8**. The sense of asymmetric induction, as expected,[5,11] corresponds to preferential attack of methyl iodide at the least hindered face of the chelated *E*-enolate. The stereochemistry of **8a** was confirmed by single crystal X-ray crystallographic analysis.

The methylation of the chiral lithium enolates derived from **3b,c** at −78 °C exhibited greater selectivity than that derived from **3a**, presumably because the larger R groups exert a greater influence over the approach of the electrophile. We were unable to generate the lithium enolate of **3d**; however, we were pleased to find that the enolate generated using sodium hydride still exerted moderate diastereoselectivity (Scheme 5; Table 3). In all cases the diastereoisomers **8** and **9** could be readily separated by flash chromatography on silica gel.

Table 4 Preparation of α-arylpropanoic acids **1a–d**

Substrate	Yield of **10** (%)	Yield of **1** (%)	ee (%)
9a	96	80	93[a]
9b	98	77	90[a]
9c	81	68	87[b]
9d	97	79	81[b]

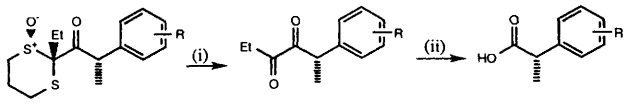
[a] Determined at ^{1}H NMR shift experiments at 400 MHz in the presence of (+)-Eu(hfc)$_3$ (0.3 equiv.) using the corresponding methyl esters. [b] Determined by chiral HPLC using a Chiralpack AD column and comparisons with racemic samples.



3a-d **8a-d** **9a-d**

Scheme 5 Deprotonation and asymmetric alkylation of **3a–d**. *Reagents and conditions:* i, LHMDS (**3a–c**) or NaH (**3d**) (1.1 equiv.); ii, MeI (1.5 equiv.); THF −78 °C.

Removal of the 1,3-dithiane 1-oxide units of **8a–d** to reveal the carboxylic acids could not be accomplished using the base-induced cleavage employed previously,[6,12] but was achieved through a two-step procedure. Hydrolysis of **8a–d** using an excess of *N*-bromosuccinimide in acetone–H_2O (97:3) over 15–30 min at room temperature furnished the α-diketones **10a–d** as bright yellow oils (Scheme 6, Table 4).[14] We were pleased



8a-d **10a-d** **1a-d**

Scheme 6 Preparation of α-arylpropanoic acids **1a–d**. *Reagents and conditions:* i, NBS (8 equiv.), acetone–water (97:3), RT; ii, $NaIO_4$ (2 equiv.), MeOH, 20 °C.

to find that, remarkably, the α-diketones retained their stereochemical integrity throughout this procedure and the subsequent oxidative cleavage. Treatment of **10a–d** with aqueous sodium periodate in methanol[15] proceeded smoothly to yield the α-arylpropanoic acids **1a–d** with excellent enantiomeric excesses (Scheme 6, Table 4).

Experimental †

The following are sample procedures

2-Ethyl-2-[2-(1-naphthyl)acetyl]-1,3-dithiane 4c

To a stirred solution of 2-ethyl-1,3-dithiane (5 g, 33.8 mmol) in THF (150 cm^3) at −20 °C was added a 2.3 mol dm^{-3} solution of butyllithium in hexanes (1.1 equiv., 16.16 cm^3, 37.2 mmol). After 1 h, methyl 1-naphthylacetate (1.1 equiv., 6.50 cm^3, 37.2 mmol) was added to the reaction mixture which was then allowed to reach 25 °C over 17 h. After reaching room temperature, the reaction mixture was poured onto saturated aqueous ammonium chloride and extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to yield the crude products, trituration of which with light petroleum and recrystallization from

† *J* Values in Hz and $[\alpha]_D$ values in 10^{-1} deg cm^2 g^{-1}.

methanol gave **4c** as a colourless crystalline solid (6.50 g, 61%), mp 129–130 °C; ν_{max}(Nujol)/cm^{-1} 1699; δ_H(400 MHz, $CDCl_3$) 1.18 (3 H, t, *J* 7.6), 1.79–1.86 (1 H, m), 1.97–2.02 (1 H, m), 2.26 (2 H, q, *J* 7.6), 2.59–2.64 (2 H, m), 2.94–3.02 (2 H, m), 4.47 (2 H, s), 7.34 (1 H, d, *J* 6.8), 7.41–7.51 (3 H, m), 7.79 (1 H, d, *J* 8.0), 7.84–7.87 (1 H, m) and 8.02–8.05 (1 H, m); δ_C(100 MHz, $CDCl_3$) 9.9, 25.3, 28.3, 31.9, 40.3, 62.1, 124.7, 126.0, 126.3, 126.7, 128.6, 128.9, 129.4, 131.8, 133.2, 134.5 and 201.4 (Found: C, 68.1; H, 6.4%; M^+, 316.095 36. $C_{18}H_{20}OS_2$ requires C, 68.31; H, 6.37%; M^+ 316.095 55).

(+)-(1*R*,2*R*)-2-Ethyl-*anti*-2-[2-(1-naphthyl)acetyl]-1,3-dithiane 1-oxide 3c

To a stirred solution of (+)-diethyl tartrate (2.2 equiv., 7.15 cm^3, 41.8 mmol) in CH_2Cl_2 (50 cm^3) at 25 °C was added titanium isopropoxide (1.1 equiv., 6.21 cm^3, 20.9 mmol). After 5 min, water (1 equiv., 0.34 cm^3, 19.0 mmol) was added to the solution which was then stirred for 30 min before being cooled to −30 °C. A solution of **4c** (6 g, 19.0 mmol) in CH_2Cl_2 (25 cm^3) was added to the mixture followed after 15 min by a cooled solution of cumene hydroperoxide (1.5 equiv., 5.28 cm^3, 28.5 mmol), added dropwise over 20 min. After 3 days at −30 °C, the reaction mixture was allowed to reach 25 °C and then concentrated under reduced pressure. The crude residue was dissolved in diethyl ether (100 cm^3) and the solution cooled to −10 °C before addition of saturated aqueous tartaric acid (100 cm^3). After 1.5 h at −10 °C, the mixture was allowed to reach 25 °C when the ether layer was separated and the aqueous layer was extracted with ether (3 × 75 cm^3) and CH_2Cl_2 (3 × 75 cm^3). The combined organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. Flash column chromatography using ethyl acetate–light petroleum 1 : 1 as eluent gave **3c** as a colourless crystalline solid (4.57 g, 72%), mp 131–133 °C; ν_{max}(Nujol)/cm^{-1} 1691 and 1043; δ_H(400 MHz; $CDCl_3$) 1.19 (3 H, t, *J* 7.6), 1.68–1.72 (1 H, m), 2.05–2.11 (1 H, m), 2.30–2.36 (1 H, m), 2.49–2.60 (3 H, m), 3.03–3.06 (2 H, m), 4.22 (1 H, d, *J* 17.0), 4.98 (1 H, d, *J* 17.0), 7.40–7.54 (4 H, m), 7.84 (1 H, d, *J* 8.0), 7.88–7.90 (1 H, m) and 8.03 (1 H, d, *J* 7.2); δ_C(100 MHz, $CDCl_3$) 8.9, 15.3, 26.9, 27.4, 42.1, 44.4, 75.4, 125.4, 126.0, 126.5, 127.1, 129.0, 129.2, 129.6, 130.2, 133.1, 134.7 and 197.7 (Found: C, 64.8; H, 6.05%; M^+, 332.090 98. $C_{18}H_{20}O_2S_2$ requires C, 65.02; H, 6.06%; M^+, 332.090 48); $[\alpha]_D^{25}$ +224.6 (*c* 0.31, $CHCl_3$).

(+)-(1*R*,2*R*)-2-Ethyl-*anti*-2-[2*S*-(1-naphthyl)propanoyl]-1,3-dithiane 1-oxide 8c

To a stirred solution of **3c** (1.0 g, 3.01 mmol) in THF (75 cm^3) at −78 °C was added a 1 mol dm^{-3} solution of LHMDS in THF (1.1 equiv., 3.31 cm^3, 3.31 mmol). After 20 min, methyl iodide (1.5 equiv., 0.28 cm^3, 4.52 mmol) was added to the solution which was then allowed to reach 25 °C over 17 h. After reaching room temperature, the reaction mixture was poured onto saturated aqueous ammonium chloride and extracted with dichloromethane. The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to yield **8c** as a single diastereoisomer (^{1}H NMR). Flash column chromatography using ethyl acetate–light petroleum (1 : 1) as eluent gave **8c** as an off-white solid (0.83 g, 80%), mp 118–119 °C; ν_{max}(Nujol)/cm^{-1} 1692 and 1055; δ_H(400 MHz, $CDCl_3$) 0.30 (3 H, t, *J* 7.2), 1.52–1.57 (1 H, m), 1.61 (3 H, d, *J* 6.8), 1.82–1.89 (2 H, m), 2.46–2.61 (2 H, m), 2.70–2.77 (1 H, m), 3.08–3.22 (2 H, m), 5.72 (1 H, q, *J* 6.8), 7.44 (1 H, t, *J* 7.6), 7.51–7.54 (1 H, m), 7.58–7.63 (2 H, m), 7.78 (1 H, d, *J* 8.0), 7.89 (1 H, d, *J* 8.0) and 8.24 (1 H, d, *J* 8.0); δ_C(100 MHz; $CDCl_3$) 8.0, 15.8, 22.3, 26.4, 27.6, 38.0, 44.4, 76.8, 123.0, 125.9, 126.1, 127.5, 128.8, 130.0, 131.5, 135.0, 135.7 and 194.3 (Found: C, 65.75; H, 6.4%; M^+, 346.1061. $C_{19}H_{22}O_2S_2$ requires C, 65.86; H, 6.40%; M^+, 346.1062); $[\alpha]_D^{25}$ +336.0 (*c* 0.38, $CHCl_3$).

(+)-(2*S*)-2-(1-Naphthyl)hexane-3,4-dione 10c

To a stirred solution of *N*-bromosuccinimide (8 equiv., 2.33 g, 13.1 mmol) in acetone–water (97 : 3, 40 cm^3) at 0 °C was added a solution of the acyldithiane oxide **8c** (0.567 g, 1.64 mmol) in acetone. The solution was stirred for 30 min and then quenched with saturated aqueous sodium sulfite. The mixture was extracted with CH_2Cl_2 (× 3) and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography using 10% ethyl acetate–light petroleum as eluent to give **10c** as a bright yellow oil (0.320 g, 81%); ν_{max}(neat)/cm^{-1} 1710; δ_H(400 MHz, $CDCl_3$) 0.88 (3 H, t, *J* 7.2), 1.54 (3 H, d, *J* 6.8), 2.44 (1 H, dq, *J* 18.8 and 7.3), 2.87 (1 H, dq, *J* 18.8 and 7.3), 5.37 (1 H, q, *J* 6.8), 7.19 (1 H, d, *J* 6.8), 7.40 (1 H, t, *J* 7.8), 7.51 (1 H, t, *J* 7.6), 7.56–7.61 (1 H, m), 7.76 (1 H, d, *J* 8.0), 7.86 (1 H, d, *J* 8.0) and 8.26 (1 H, d, *J* 8.0); δ_C(100 MHz, $CDCl_3$) 7.4, 17.4, 31.2, 41.3, 123.8, 125.9, 126.1, 126.7, 127.4, 128.9, 129.7, 131.8, 135.0, 135.7, 200.4 and 201.8; *m/z* 240.115 34 (M^+, $C_{16}H_{16}O_2$ requires 240.115 02); $[\alpha]_D^{25}$ +283.3 (*c* 0.60, $CHCl_3$).

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

To a stirred solution of the diketone **10c** (0.30 g, 1.25 mmol) in methanol (20 cm^3) at room temperature was added dropwise a solution of sodium periodate (2 equiv., 0.53 g, 2.50 mmol) in water (7 cm^3). After 12 h, the solution was filtered, concentrated under reduced pressure, and extracted with CH_2Cl_2 (× 3). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product. Flash column chromatography of this using ethyl acetate–light petroleum (1 : 1) as eluent gave **1c** as a colourless solid (0.171 g, 68%), mp 68–69 °C; ν_{max}(Nujol)/cm^{-1} 2600–3400 and 1705; δ_H(270 MHz, DMSO) 1.51 (3 H, d, *J* 7.2), 4.46 (1 H, q, *J* 7.2), 7.42–7.60 (4 H, m), 7.82–7.85 (1 H, m), 7.93–7.96 (1 H, m), 8.12–8.15 (1 H, m) and 12.42 (1 H, br s); δ_C(100 MHz, $CDCl_3$) 18.5, 41.7, 123.7, 125.3, 126.2, 126.4, 127.1, 128.7, 129.7, 132.0, 134.7, 136.7 and 180.9 (Found: C, 78.1; H, 6.1%; M^+, 200.084 05. $C_{13}H_{12}O_2$ requires C, 77.98; H, 6.04%; M^+, 200.083 74); $[\alpha]_D^{25}$ +125.7 (*c* 0.35, $CHCl_3$).

Acknowledgements

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