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Preparation and stereochemical integrity of certain thioesters of 2-arylpropionic acids and related compounds

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Abstract

2-Arylpropionate thioesters **5**, **6a**/**6b** and **7a/7b**, 2-aryloxypropionate thioesters **8a/8b** and 2-alkoxy-2-arylacetate thioesters **9a/9b** were prepared from thiol **4** and the corresponding carboxylic acids. Thioesters **6a/6b**, **7a/7b**, **8a/8b** and **9a/9b** were monitored for evidence of inter-conversion between epimers in acetonitrile solvent at 40°C, by optical activity in the cases of **6a/6b** and **7a/7b**, and by ^{1}H NMR spectroscopy in the cases of **8a/8b** and **9a/9b**. Only in the case of thioesters **9a/9b** was significant inter-conversion between epimers observed.

Introduction

Several of the 2-arylpropionic acid (2-APA), or profen, class of non-steroidal anti-inflammatory drugs (NSAIDs) undergo a well-known chiral metabolic inversion process with significant pharmacokinetic and toxicological implications (Hutt & Caldwell 1983; Caldwell et al 1988). For the 2-APAs, this process results in conversion of the generally less active (*R*)-enantiomers into the generally more active (*S*)-enantiomers. A similar chiral metabolic inversion has been observed for the 2-aryloxypropionic acid class of herbicides (Buser & Müller 1997). The most accepted proposed mechanism for these inversions involves enantioselective formation of 2-APA co-enzyme A thioesters (Hutt & Caldwell 1983; Knihinicki et al 1991; Tracy & Hall 1992) (Figure 1). In this proposed pathway, the (*R*)-enantiomers are converted into co-enzyme A thioesters, which undergo subsequent epimerisation and hydrolysis; whereas the (*S*)-enantiomers do not undergo conversion into co-enzyme A thioesters. As ATP is required for the co-enzyme A thioester formation step, it has been further proposed, at least in the case of ibuprofen, that the stereoselectivity resides in the selective formation of 2-APA adenylate ester precursors to the co-enzyme A thioesters (Menzel et al 1994). Epimerase enzymes have been proposed for the interconversion between the diastereoisomeric co-enzyme A thioesters, and active enzyme material has been isolated (Shieh & Chen 1993). It has also been realised that the methine protons of 2-APA thioesters are likely to be significantly more acidic than those of the 2-APA free acids, and that conditions may exist in which spontaneous chemical epimerisation of 2-APA co-enzyme A thioesters could be possible (Hutt & Caldwell 1983). Hydrogen/deuterium exchange studies on model 2-APA thioesters have shown that, while thioester hydrolysis is the dominant process in polar aqueous media, methine proton exchange may proceed faster than hydrolysis in solvent systems of lower polarity (Mayer et al 1988), leaving open the possibility that 2-APA co-enzyme A thioesters may be capable of chemical epimerisation in lipophilic sites.

The therapeutic actions of NSAIDs (including the 2-APAs) are associated with cyclooxygenase inhibition. This mode of action is also associated with a number of well-known adverse effects, such as gastro-intestinal ulceration (Vane & Botting 1995). As the unidirectional chiral inversion of the (*R*)-enantiomers constitutes a form of activation, chiral inversion can also enhance the toxic effects of 2-APAs. The issue of whether chiral inversion of 2-APA metabolites can occur without enzymatic mediation is significant. Inter-species variation in enzyme expression can result in corresponding

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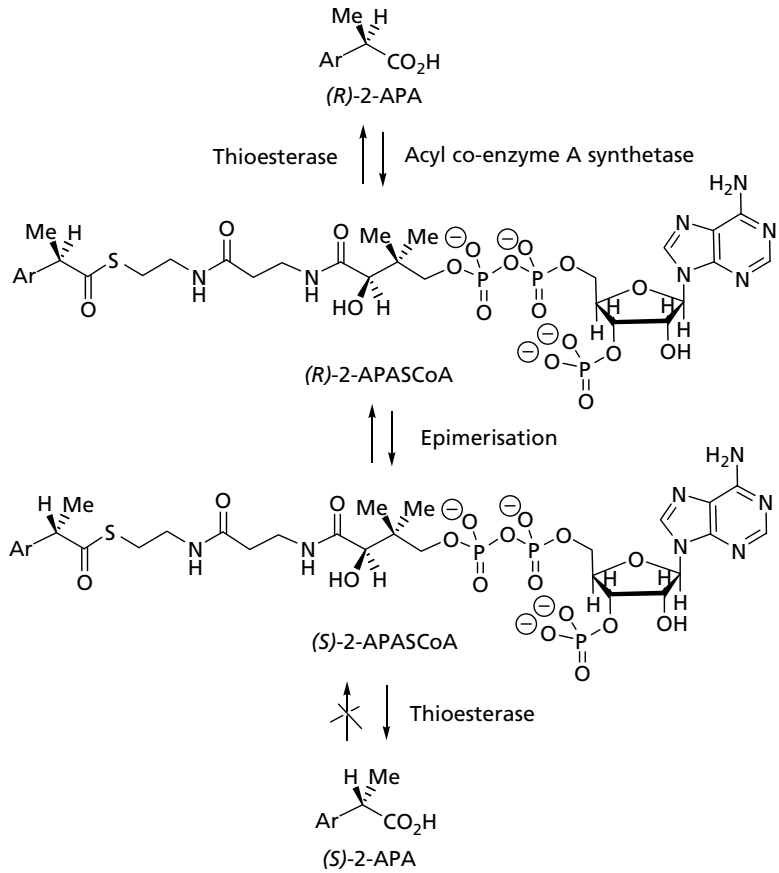


Figure 1 Proposed mechanism for the chiral metabolic inversion inversion of 2-arylpropionic acids (2-APAs) via formation of 2-APA co-enzyme A thioesters.

variation in the occurrence of toxic side-effects. However, a spontaneous or chemical inversion process could be expected to be less affected by inter-species variation, or to affect the appearance of inter-species variation. In addition, co-enzyme A thioesters are not the only type of thioester metabolite which 2-APAs can form. 2-APA thioester conjugates of, for instance, cysteine, glutathione or acyl carrier proteins could also potentially undergo loss of chiral purity if 2-APA thioesters were susceptible to epimerisation under certain conditions. Another feature of the chiral metabolic inversion of 2-APAs is its similarity to dynamic kinetic resolution methods of converting racemic samples of chiral pharmaceutical entities into samples of single enantiomers (Caddick & Jenkins 1996). These generally involve rapid equilibration between enantiomers or diastereoisomers, coupled with a slower stereoselective discriminatory step. In the case of chiral metabolic inversion of 2-APAs, the stereoselective discriminatory step would appear to be co-enzyme A thioester formation, while the equilibration step is epimerisation of diastereoisomeric 2-APA co-enzyme A thioesters. Our aim in this study was to prepare diastereoisomeric thioesters of certain 2-APAs and related compounds, and to observe the extent of epimerisation of these thioesters in systems of moderate polarity. This information would help to establish the feasibility of chemical epimerisation of 2-APA co-enzyme A thioesters in non-polar media, such as lipophilic sites. We were also interested in the possibility of such systems forming the basis for bio-mimetic dynamic kinetic resolutions of 2-APA and related thioesters. Non-racemic *exo*-2-boranethiol (**4**) was selected for conjugation to the 2-APAs and related compounds as this thiol was reportedly obtainable in the chiral non-racemic form from either chiral non-racemic camphor (Dagonneau et al 1973) or borneol (Blanco et al 1990), and as the bornyl 1,7,7-trimethylbicyclo[2.2.1]heptan ring system would constitute a robust chiral auxiliary and stereochemical label with no possibility of itself undergoing inversion of stereocentres. In addition, the resulting thioesters would be non-polar products that could be easily purified and handled.

Materials and Methods

General experimental

Toluene and diethyl ether were pre-dried by stirring for 24 h over calcium hydride, followed by distillation from sodium/benzophenone under a nitrogen atmosphere before use. Hexane, dichloromethane and chloroform

were distilled from calcium hydride and stored over 3 Å molecular sieves. Acetonitrile was stirred over calcium hydride for 24 h, distilled from calcium hydride, then from phosphorous pentoxide and stored over 3 Å molecular sieves. Ethyl acetate was stirred over potassium carbonate for 24 h and then distilled onto 4 Å molecular sieves. Silica gel chromatography was carried out using Silica gel 60 (Fluka). Thin-layer chromatography was performed on silica gel pre-coated on thin-layer aluminium sheets (Merck silica gel 60 F_{254}). All other materials were purchased from Sigma-Aldrich and used without further purification. Melting points were obtained on a Reichet microscope hot-stage melting-point apparatus and are uncorrected. All infra-red spectra were obtained using a Perkin-Elmer Spectrum One FTIR spectrometer in the range 4000–500 cm^{-1}. Liquid samples were examined as thin films interspersed between sodium chloride plates. Solid samples were examined as pressed potassium bromide plates. NMR spectra were recorded on a Bruker-AVANCE 300 MHz spectrometer. All mass spectrometry data was obtained using a Waters Micromass Q-Tof *micro* mass spectrometer, equipped with an electrospray ionisation LockSpray source, using the positive electrospray ionisation mode. Phosphoric acid was used as internal reference compound for accurate mass determination. Samples were dissolved in dichloromethane and further diluted in dichloromethane–methanol–0.1 M ammonium acetate (5:4:1 v/v).

Preparation of (1*S*,4*S*)-*exo*-2-bornanethiol (4)

*From (1S,4S)-exo-2-bornylisothiouronium p-toluenesulphonate (**2**)*

(1*S*,4*S*)-*exo*-2-Bornyl-isothiouronium *p*-toluenesulphonate (**2**) (Blanco et al 1990) (10.54 g, 30.0 mmol) was added to a solution of potassium metabisulphite (14.28 g, 64.0 mmol, 2.5 equiv.) in 4.0 N sodium hydroxide solution (50 mL). The solution was heated to reflux for 3 h. The white material that lined the condenser was washed out with hexane. The solvent was removed under vacuum and the resultant material was re-crystallised from the minimum amount of hot water to afford the title compound (**4**) as a colourless crystalline solid (4.08 g, 80%, 24–26°C, lit. mp 24–26°C (Blanco et al 1990)). ν_{max}/cm^{-1} (KBr): 3044 (s), 2891 (m), 1670 (m), 1601 (m), 1430 (m), 1389 (m), 1223 (s), 1166 (s), 1124 (s), 1030 (s), 813 (s), 683 (vs.); δ_H ($CDCl_3$, 300 MHz, Me_4Si): 0.84 (3H, s, $C_{(1)}H_3$), 0.97 (3H, s, $C_{(7)}(CH_3)_2$), 1.02 (3H, s, $C_{(7)}(CH_3)_2$), 1.10–1.17 (2H, m, $C_{(5)}H_{endo}$, $C_{(6)}H_{endo}$), 1.66–1.75 (3H, m, $C_{(4)}H$, $C_{(5)}H_{exo}$, $C_{(6)}H_{exo}$), 1.78 (1H, d, -S-*H*, $J_{SH,\ 2endo} = 6.96$ Hz), 1.86 (1H, m, $C_{(3)}H_{exo}$), 2.29 (1H, m, $C_{(3)}H_{endo}$), 2.94–3.00 (1H, ddd, $C_{(2)}H_{endo}$, $J_{2endo,3endo} = 9.0$ Hz, $J_{2endo,\ SH} = 7.0$ Hz, $J_{2endo,3exo} = 6$ Hz).

*Via (1S,4S)-exo-2-bornyl N,N-dimethyldithiocarbamate (**3**)*

Zinc *N, N*-dimethyldithiocarbamate (7.24 g, 23.7 mmol) was added to a stirred solution of triphenylphosphine (33.0 g, 126 mmol) and (1*S*,4*S*)-*endo*-2-borneol (**1**) (6.10 g, 39.6 mmol) in anhydrous toluene (50 mL). The flask protected from light and the solution was cooled to 0°C under nitrogen. Diisopropylazodicarboxylate (25 mL, 126.0 mmol) was added slowly to the stirred solution over one hour. The solution was left to stir overnight. The resultant brown solution was loaded directly on to a flash column (30 g silica), eluting first with hexane (500 mL), then with a 10% ethyl acetate–hexane solution to yield compound (**3**) as a red oil (5.71 g, 56%); ν_{max}/cm^{-1} (film): 3040 (s), 2888 (m), 1673 (m), 1600 (m), 1419 (m), 1389 (m), 1220 (s), 1166 (s), 1124 (s), 1090 (s) 1030 (s), 886 (w), 821 (s), 683 (vs.); δ_H($CDCl_3$, 300 MHz, Me_4Si): 0.81 (3H, s, $C_{(1)}H_3$), 0.96 (3H, s, $C_{(7)}(CH_3)_2$), 1.00 (3H, s, $C_{(7)}(CH_3)_2$), 1.10–1.17 (2H, m, $C_{(5)}H_{endo}$, $C_{(6)}H_{endo}$), 1.66–1.75 (3H, m, $C_{(4)}H$, $C_{(5)}H_{exo}$, $C_{(6)}H_{exo}$), 1.86 (1H, m, $C_{(3)}H_{exo}$), 2.29 (1H, m, $C_{(3)}H_{endo}$), 3.30 (3H, bs, NCH_3), 3.47 (3H, bs, NCH_3), 4.11–4.16 (1H, dd, $C_{(2)}H_{endo}$, $J_{2endo,3endo} = 9.0$ Hz, $J_{2endo,3exo} = 6$ Hz).

Lithium aluminium hydride (3.75 g. 0.1 mol) was added with caution to a stirred solution of (1*S*,4*S*)-*exo*-2-bornyl dithiocarbamate (**3**) (4.29 g, 16.6 mmol) in dry diethyl ether (150 mL). The resulting solution was heated to reflux temperature under an inert nitrogen atmosphere overnight. The solution was then cooled to 0 °C and the excess lithium aluminium hydride was quenched using wet diethyl ether, followed by the careful addition of water. The suspension was filtered over celite. The aqueous layer was removed and the organic layer was dried over magnesium sulphate. The solvent was removed under reduced pressure and the crude material was purified by column chromatography (hexane). The material was re-crystallised from the minimum amount of water to afford the title compound (**4**) as a white solid. (2.52 g, 88%, 24–26°C, lit. mp 24–26°C (Blanco et al 1990)); ν_{max} and δ_H as above.

Preparation of thioesters

For the general preparation of thioesters, (1*S*,4*S*)-*exo*-2-bornanethiol (**4**) (0.9 mmol) and 4-(*N, N*-dimethylamino)-pyridine (10 mol%) in dichloromethane (5 mL) were added to a solution of acid (0.9 mmol) in dichloromethane (25 mL) at 0°C under an inert nitrogen atmosphere, after which *N, N*'-dicyclohexylcarbodiimide (0.195 g, 1.0 mmol, 1.05 equiv.) in dichloromethane (5 mL) was added via syringe and the reaction was left to stir for 5 min at 0°C. The reaction was then left to equilibrate to room temperature for 7 h. The precipitate formed was removed by filtration (using a small-pore sintered glass funnel) and the solvent was removed under vacuum. The residue was taken up in dichloromethane (20 mL) and filtered again. The solution was washed with 0.5 N hydrochloric acid (2×30 mL), followed by a washing with saturated sodium bicarbonate solution (30 mL). The solution was dried over anhydrous sodium sulphate and the solvent is removed under vacuum. The residue was purified by silica gel chromatography using dichloromethane as eluant.

*[(1S,4S)-exo-2-Thiobornyl] phenylacetate (**5**)*

(1*S*,4*S*)-*exo*-2-Bornanethiol (**4**) (1.70 g, 10.0 mmol), 4-(*N, N*-dimethylamino)pyridine (100 mg, 10 mol%), phenylacetic acid (1.36 g, 10.0 mmol) and *N, N*'-dicyclohexylcarbo-

diimide (2.166 g, 10.5 mmol, 1.05 equiv.) gave (**5**) as a pale yellow viscous oil (2.34 g, 81%); ν_{max}/cm^{-1} (film): 2984 (m), 2954 (vs), 2879 (m), 1687 (vs), 1454 (m); δ_H ($CDCl_3$, 300 MHz, Me_4Si): 0.82 (6H, s, $C_{(7)}(CH_3)_2$), 0.84 (3H, s, $C_{(1)}(CH_3)_2$), 0.97–1.39 (3H, m), 1.65–1.93 (4H, m), 3.64 (1H, dd, *H*-C-SR, $J_1 = 15$Hz, $J_2 = 6$ Hz), 3.79 (2H, s, Ar-CH_2-C = O), 7.23–7.52 (5H, Ar-*H*); HRMS calculated for $C_{18}H_{24}OS$ m/z 288.1548, found 288.1548.

*[(1S,4S)-exo-2-Thiobornyl] (2R)-phenylpropionate (**6a**) and [(1S,4S)-exo-2-thiobornyl] (2S)-phenylpropionate (**6b**)*

(1*S*,4*S*)-*exo*-2-Bornanethiol (**4**) (0.1537 g, 0.9 mmol), 4-(*N, N*-dimethylamino)pyridine (10 mg, 10 mol%), (*R*/*S*)-phenylpropionic acid (0.135 g, 0.9 mmol, 0.12 mL) and *N, N′*-dicyclohexylcarbodiimide (0.195 g, 1.0 mmol, 1.05 equiv.) gave **6a** and **6b** as a pale-coloured viscous oil (0.2101 g, 95%, determined to be a 1:1 mixture of diastereoisomers from the ^{1}H NMR spectrum). ν_{max}/cm^{-1} (film): 2953 (s), 2878 (s), 1683 (vs), 1584 (m), 1494 (s), 1453 (s), 1390 (m), 996 (m), 949 (s), 928 (s), 735 (m), 735 (m), 698 (s), 555 (m); δ_H ($CDCl_3$, 300 MHz, Me_4Si): 0.84 (6H, s, $C_{(7)}(CH_3)_2$), 0.86 (3H, s, $C_{(1)}CH_3$), 1.06–1.47 (3H, m), 1.51 (3H, d, J = 6 Hz, (diastereoisomer A)-[H-C-(CH_3)]), 1.52 (3H, d, J = 6 Hz, (diastereoisomer B)-[H-C-(CH_3)]), 1.65–1.93 (4H, m), 3.64 (1H, dd, *H*-C-SR), 3.86 (1H, q, J = 6 Hz, (diastereoisomer B)-[*H*-C-(CH_3)]), 3.88 (1H, q, J = 6 Hz, (diastereoisomer A)-[*H*-C-(CH_3)]), 7.22–7.39 (5H, m, Ar-*H*); HRMS: calculated for $C_{19}H_{26}OS$ m/z 302.1704, found 302.1704.

*[(1S,4S)-exo-2-Thiobornyl] (2R)-phenylpropionate (**6a**)*

(1*S*,4*S*)-*exo*-2-Bornanethiol (**4**) (0.129 g, 0.8 mmol), 4-(*N, N*-dimethylamino)pyridine (10 mg, 10 mol%), (*R*)-phenylpropionic acid (0.1149 g, 0.8 mmol, 0.102 mL) and *N, N′*-dicyclohexylcarbodiimide (0.165 g, 0.8 mmol, 1.05 equiv.) gave **6a** as a pale-coloured viscous oil (0.1977 g, 86% 11:1 ratio of diastereoisomers). ν_{max}/cm^{-1} (film): 2955 (s), 2878 (s), 1684 (vs), 1595 (m), 1584 (m), 1494 (s), 1454 (s), 1390 (m), 1260 (m), 998 (m), 949 (s), 928 (s), 737 (m), 698 (s); δ_H($CDCl_3$, 300 MHz, Me_4Si): 0.84 (6H, s, $C_{(7)}(CH_3)_2$), 0.86 (3H, s, $C_{(1)}(CH_3)_2$), 1.06–1.47 (3H, m), 1.51 (3H, d, J = 6 Hz, (minor diastereoisomer)-[H-C-(CH_3)]), 1.52 (3H, d, J = 6 Hz, (major diastereoisomer)-[H-C-(CH_3)]), 1.65–1.93 (4H, m), 3.64 (1H, dd, *H*-C-SR), 3.87 (1H, q, J = 6 Hz, (major diastereoisomer)-[*H*-C-(CH_3)]), 3.88 (1H, q, J = 6 Hz, (minor diastereoisomer)-[*H*-C-(CH_3)]), 7.22–7.39 (5H, m, Ar-*H*); HRMS calculated for $C_{19}H_{26}OS$ m/z 302.1704, found 302.1704.

*[(1S,4S)-exo-2-Thiobornyl] (2S)-phenylpropionate (**6b**)*

(1*S*,4*S*)-*exo*-2-Bornanethiol (**4**) (0.1537 g, 0.9 mmol), 4-(*N, N*-dimethylamino)pyridine (10 mg, 10 mol%), (*S*)-phenylpropionic acid (0.135 g, 0.9 mmol, 0.12 mL) and *N, N′*-dicyclohexylcarbodiimide (0.195 g, 1.0 mmol, 1.05 equiv.) gave **6b** as a pale-coloured viscous oil (0.1626 g, 70%, 10:1 ratio of diastereoisomers). ν_{max}/cm^{-1} (film): 2953 (s), 2878 (s), 1683 (vs), 1584 (m), 1494 (s), 1453 (s), 1390 (m), 996 (m), 949 (s), 928 (s), 735 (m), 735 (m), 698 (s), 555 (m). δ_H ($CDCl_3$, 300 MHz, Me_4Si): 0.78 (6H, s, $C_{(7)}(CH_3)_2$), 0.86 (3H, s, $C_{(1)}(CH_3)_2$), 1.06–1.36 (3H, m), 1.51 (3H, d, J = 6 Hz, (major diastereoisomer)-[H-C-(CH_3)]), 1.52 (3H, d, J = 6 Hz, (minor diastereoisomer)-[H-C-(CH_3)]), 1.65–1.93 (4H, m), 3.64 (1H, dd, *H*-C-SR), 3.86 (1H, q, J = 6 Hz, (minor diastereoisomer)-[*H*-C-(CH_3)]), 3.88 (1H, q, J = 6 Hz, (major diastereoisomer)-[*H*-C-(CH_3)]), 7.22–7.39 (5H, m, Ar-*H*); HRMS calculated for $C_{19}H_{26}OS$ m/z 302.1704, found 302.1704.

*[(1S,4S)-exo-2-Thiobornyl] (2R)-(6-methoxynaphth-2-yl)propionate (**7a**) and [(1S,4S)-exo-2-thiobornyl] (2S)-(6-methoxynaphth-2-yl)propionate (**7b**)*

(1*S*,4*S*)-*exo*-2-Bornanethiol (**4**) (0.146 g, 0.9 mmol) and 4-(*N, N*-dimethylamino)pyridine (10 mg, 10 mol%) in chloroform (5 mL), (*R*/*S*)-2-(6-methoxynaphth-2-yl)-propionic acid (naproxen) (0.200 g, 0.9 mmol) in chloroform (25 mL) and *N, N′*-dicyclohexylcarbodiimide (0.230 g, 1.1 mmol, 1.05 equiv.) gave **7a** and **7b** as a pale viscous oil (0.2071g, 63%, 1:1 ratio of diastereoisomers). ν_{max}/cm^{-1} (film): 2955 (s), 2878 (s), 1685 (vs), 1584 (m), 1494 (s), 1454 (s), 1398 (s), 1260 (m), 1097 (w), 998 (m), 949 (s), 928 (s), 737 (m), 698 (s); δ_H ($CDCl_3$, 300 MHz, Me_4Si): 0.83 (6H, s, $C_{(7)}(CH_3)_2$), 0.87 (3H, s, $C_{(1)}(CH_3)_2$), 1.06–1.47 (3H, m), 1.51 (3H, d, J = 6 Hz, (diastereoisomer A)-(H-C-CH_3), 1.52 (3H, d, J = 6 Hz, (diastereoisomer B)-(H-C-CH_3) 1.65–1.93 (4H, m), 3.62 (1H, dd, *H*-C-SR), 3.83–3.90 (1H, m, *H*-C(R_2)-CH_3), 3.91 (3H, s, Ar-OCH_3), 7.11–7.16 (2H, m, Ar-*H*), 7.36–7.43 (1H, m, Ar-*H*), 7.68–7.72 (3H, m, Ar-*H*); HRMS calculated for $C_{24}H_{30}O_2S$ m/z 382.1967, found 382.1966.

*[(1S,4S)-exo-2-Thiobornyl] (2R)-(6-methoxynaphth-2-yl)propionate (**7a**)*

(1S,4*S*)-*exo*-2-Bornanethiol (**4**) (0.146 g, 0.9 mmol), 4-(*N, N*-dimethylamino)pyridine (10 mg, 10 mol%) in chloroform (5 mL), (*R*)-2-(6-methoxynaphth-2-yl)-propionic acid (naproxen) (0.200 g, 0.9 mmol) in chloroform (25 mL) and *N, N′*- dicyclohexylcarbodiimide (0.230 g, 1.1 mmol, 1.05 equiv.) gave **7a** as a pale-coloured viscous oil (0.1907 g, 58%, 22:1 ratio of diastereoisomers). ν_{max}/cm^{-1} (film): 2955 (s), 2875 (s), 1685 (vs), 1584 (m), 1494 (s), 1454 (s), 1400 (s), 1260 (m), 1097 (w), 1031 (w), 998 (m), 949 (s), 928 (s), 737 (m), 698 (s); δ_H ($CDCl_3$, 300 MHz, Me_4Si): 0.83 (6H, s, $C_{(7)}(CH_3)_2$), 0.87 (3H, s, $C_{(1)}(CH_3)_2$), 1.06–1.47 (3H, m), 1.51 (3H, d, J = 6 Hz, minor diastereoisomer -(H-C-CH_3), 1.52 (3H, d, J = 6 Hz, major diastereoisomer-(H-C-CH_3), 1.65–1.93 (4H, m), 3.62 (1H, dd, *H*-C-SR), 3.85–3.90 (1H, m, *H*-C(R_2)-CH_3), 3.91 (3H, s, Ar-OCH_3), 7.11–7.16 (2H, m, Ar-*H*), 7.36–7.43 (1H, m, Ar-*H*), 7.68–7.72 (3H, m, Ar-*H*); HRMS calculated for $C_{24}H_{30}O_2S$ m/z 382.1967, found 382.1966.

*[(1S,4S)-exo-2-Thiobornyl] (2S)-(6-methoxynaphth-2-yl)propionate (**7b**)*

(1*S*,4*S*)-*exo*-2-Bornanethiol (**4**) (0.146 g, 0.9 mmol), 4-(*N, N*-dimethylamino)pyridine (10 mg, 10 mol%) in chloroform (5 mL), (*S*)-2-(6-methoxynaphth-2-yl)-propionic acid

(naproxen) (0.200 g, 0.9 mmol) in chloroform (25 mL) and *N, N*-dicyclohexylcarbodiimide (0.230 g, 1.1 mmol, 1.05 equiv.) gave **7b** as a pale-coloured viscous oil (0.2301 g, 70%, 20.3:1 ratio of diastereoisomers). ν_{max}/cm^{-1} (film): 2955 (s), 2875 (s), 1685 (vs), 1584 (m), 1494 (s), 1454 (s), 1398 (s), 1260 (m), 998 (m), 949 (s), 928 (s), 737 (m), 698 (s); δ_H ($CDCl_3$, 300 MHz, Me_4Si): 0.83 (6H, s, $C_{(7)}(CH_3)_2$), 0.87 (3H, s, $C_{(1)}(CH_3)_2$), 1.06–1.47 (3H, m), 1.51 (3H, d, J = 6 Hz, major diastereoisomer -(H-C-CH_3), 1.52 (3H, d, J = 6 Hz, minor diastereoisomer-(H-C-CH_3)1.65–1.93 (4H, m), 3.62 (1H, dd, *H*-C-SR), 3.85–3.90 (1H, m, *H*-C(R_2)-CH_3), 3.91 (3H, s, Ar-OCH_3), 7.11–7.16 (2H, m, Ar-*H*), 7.36–7.43 (1H, m, Ar-*H*), 7.68–7.72 (3H, m, Ar-*H*); HRMS calculated for $C_{24}H_{30}O_2S$ m/z 382.1967, found 382.1966.

*[(1S,4S)-exo-2-Thiobornyl] (2R)-phenoxypropionate (**8a**) and [(1S,4S)-exo-2-thiobornyl] (2S)-phenoxypropionate (**8b**)*

(1*S*,4*S*)-*exo*-2-Bornanethiol (**4**) (0.204 g, 1.2 mmol), 4-(*N, N*-dimethylamino)pyridine (15 mg, 10 mol%), (*R*/*S*)-2-phenoxypropionic acid (0.200 g, 1.2 mmol) and *N, N*′-dicyclohexylcarbodiimide (0.260 g, 1.3 mmol, 1.05 equiv.) gave **8a** and **8b** as a pale-coloured viscous oil (0.28 g, 76%, 1:1 ratio of diastereoisomers). ν_{max}/cm^{-1} (film): 2955 (s), 2878 (s), 1684 (vs), 1595 (m), 1584 (m), 1494 (s), 1454 (s), 1390 (m), 1260 (m), 998 (m), 949 (s), 928 (s), 737 (m), 698 (s); δ_H ($CDCl_3$, 300 MHz, Me_4Si): 0.84 (6H, s, $C_{(7)}(CH_3)_2$), 0.86 (3H, s, $C_{(1)}(CH_3)_2$), 1.06–1.47 (3H, m), 1.61 (3H, d, J = 6 Hz, (diastereoisomer A)-[H-C-(CH_3)]), 1.62 (3H, d, J = 6 Hz, (diastereoisomer B)-[H-C-(CH_3)]), 1.65–1.93 (4H, m), 3.64 (1H, dd, *H*-C-SR), 4.87 (1H, q, J = 6 Hz, (diastereoisomer A)-[*H*-C-(CH_3)]), 4.88 (1H, q, J = 6 Hz, (diastereomer B)-[*H*-C-(CH_3)]), 7.22–7.39 (5H, m, Ar-*H*); HRMS calculated for $C_{19}H_{20}O_2S$ m/z 318.1654, found 318.1729.

*[(1S,4S)-exo-2-Thiobornyl] (R)-α-methoxyphenylacetate (**9a**) and [(1S,4S)-exo-2-thiobornyl] (S)-α-methoxyphenylacetate (**9b**)*

(1*S*,4*S*)-*ex*o-2-Bornanethiol (**4**) (0.204 g, 1.2 mmol), 4-(*N, N*-dimethylamino)pyridine (15 mg, 10 mol%), (±)-α-methoxyphenylacetic acid (0.200 g, 1.2 mmol) and *N, N*′-dicyclohexylcarbodiimide (0.260 g, 1.3 mmol, 1.05 equiv.) gave **9a** and **9b** as a pale-coloured viscous oil (0.36 g, 95%, 1:1 ratio of diastereoisomers). ν_{max}/cm^{-1} (film): 2985 (s), 2953 (vs), 2879 (s), 1676 (vs), 1493 (m), 1455s (s), 1389 (m), 1281 (m), 1257 (m), 1200 (s), 1114 (s), 1065 (s), 989 (m), 703 (s), 627 (m); δ_H ($CDCl_3$, 300 MHz, Me_4Si): 0.80 (3H, s, $C_{(7)}(CH_3)_2$), 0.82 (3H, s, $C_{(7)}(CH_3)_2$), 0.84 (3H, s, $C_{(1)}(CH_3)$), 1.06–1.36 (3H, m), 1.65–1.93 (4H, m), 3.46 (3H, s, (diastereoisomer A)-[H-C-OCH_3]), 3.47 (3H, s, (diastereoisomer B)-[H-C-OCH_3]) 3.64 (1H, dd, $J^1 = 21$ Hz, $J^2 = 9$ Hz, *H*-C-SR), 4.73 (1H, s, (diastereoisomer A)-[*H*-C-OCH_3]), 4.75 (1H, s, (diastereomer B)-[*H*-C-OCH_3]), 7.24–7.37 (5H, m, Ar-*H*); HRMS calculated for $C_{19}H_{20}O_2S$ m/z 318.1654, found 318.1732.

*[(1S,4S)-exo-2-Thiobornyl] (R)-α-methoxyphenylacetate (**9a**)*

(1*S*,4*S*)-*exo*-2-Bornanethiol (**4**) (0.204 g, 1.2 mmol), 4-(*N, N*-dimethylamino)pyridine (15 mg, 10 mol%), (*R*)-α-methoxy-phenylacetic acid (0.200 g, 1.2 mmol) and *N, N*′-dicyclohexylcarbodiimide (0.260 g, 1.3 mmol, 1.05 equiv.) gave **9a** as a pale viscous oil (0.36 g, 95%, 13:1 ratio of diastereoisomers). ν_{max}/cm^{-1} (film): 2985 (s), 2953 (vs), 2879 (s), 1675 (vs), 1493 (m), 1455s (s), 1389 (m), 1281 (m), 1257 (m),1200 (s), 1114 (s), 1065 (s), 989 (m), 703 (s), 627 (m); δ_H($CDCl_3$, 300 MHz, Me_4Si): 0.81 (3H, s, $C_{(7)}(CH_3)_2$), 0.82 (3H, s, $C_{(7)}(CH_3)_2$), 0.84 (3H, s, $C_{(1)}(CH_3)$), 1.06–1.36 (3H, m), 1.65–1.93 (4H, m), 3.46 (3H, s, (minor diastereoisomer)-[H-C-OCH_3]), 3.47 (3H, s, (major diastereoisomer)-[H-C-OCH_3]) 3.64 (1H, dd, $J^1 = 21$ Hz, $J^2 = 9$ Hz, *H*-C-SR), 4.73 (1H, s, (minor diastereoisomer)-[*H*-C-OCH_3]), 4.75 (1H, s, (major diastereoisomer)-[*H*-C-OCH_3]), 7.24–7.37 (5H, m, Ar-*H*); HRMS calculated for $C_{19}H_{20}O_2S$ m/z 318.1654, found 318.1732.

*[(1S,4S)-exo-2-Thiobornyl] (S)-α-methoxyphenylacetate (**9b**)*

(1*S*,4*S*)-*exo*-2-Bornanethiol (**4**) (0.204 g, 1.2 mmol), 4-(*N, N*-dimethylamino)pyridine (15 mg, 10 mol%), (*S*)-α-methoxy-phenylacetic acid (0.200 g, 1.2 mmol) and *N, N*′-dicyclohexylcarbodiimide (0.260 g, 1.3 mmol, 1.05 equiv.) gave **9b** as a pale viscous oil (0.36 g, 95%, 16:1 ratio of diastereoisomers). ν_{max}/cm^{-1} (film): 2985 (s), 2953 (vs), 2879 (s), 1676 (vs), 1493 (m), 1455s (s), 1389 (m), 1281 (m), 1257 (m), 1200 (s), 1114 (s), 1065 (s), 989 (m), 703 (s), 627 (m); δ_H ($CDCl_3$, 300 MHz, Me_4Si): 0.80 (3H, s, $C_{(7)}(CH_3)_2$), 0.82 (3H, s, $C_{(7)}(CH_3)_2$), 0.84 (3H, s, $C_{(1)}(CH_3)$), 1.06–1.36 (3H, m), 1.65–1.93 (4H, m), 3.46 (3H, s, (major diastereoisomer)-[H-C-OCH_3]), 3.47 (3H, s, (minor diastereoisomer)-[H-C-OCH_3]), 3.64 (1H, dd, $J^1 = 21$ Hz, $J^2 = 9$ Hz, *H*-C-SR), 4.73 (1H, s, (major diastereoisomer)-[*H*-C-OCH_3]), 4.75 (1H, s, (minor diastereoisomer)-[*H*-C-OCH_3]), 7.24–7.37 (5H, m, Ar-*H*); HRMS calculated for $C_{19}H_{20}O_2S$ m/z 318.1654, found 318.1731.

Optical activity

All optical rotation studies were carried out using a Perkin Elmer 341 Polarimeter at 20°C, maintained by a Julabo F25-ED refrigerated and heating circulator using a wavelength of 598 nm (Sodium-D line) and a cell of 100 mm path length. Thioester solutions were prepared in 10-mL volumetric flasks to give concentrations of 1.5–3.5 g per 100 mL of solvent. The solutions were incubated at 40°C using a Heidolph MR3001 K heater/stirrer with thermostat control, and rotation values were taken at regular intervals. All optical rotation values quoted are ± 0.05° (3 replicates).

Epimerisation studies by NMR

^{1}H NMR spectra were recorded at 300 MHz on a Bruker-AVANCE 300 MHz spectrometer on solutions of thioesters in 75:25 CD_3CN–$CDCl_3$ at 40°C probe temperature.

Results and Discussion

Quantities of (1*S*,4*S*)-*exo*-2-bornanethiol (**4**) could be prepared in good quantity and purity from commercially avail-

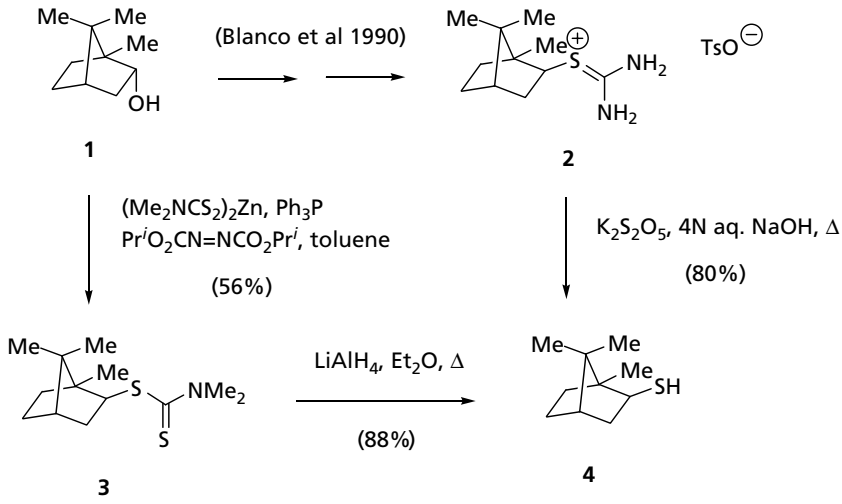
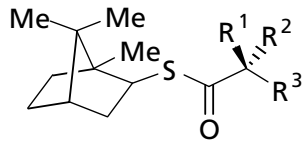


Figure 2 Preparative routes to (1*S*,4*S*)-*exo*-2-bornanethiol (**4**).

able (1*S*,4*S*)-*endo*-2-borneol (**1**) by either of the two routes shown in Figure 2. (1*S*,4*S*)-*exo*-2-Bornyl-isothiouronium *p*-toluenesulphonate (**2**) was prepared as described by Blanco et al (1990). Hydrolysis of the thiouronium salt **2** to thiol **4** was more conveniently achieved by treatment with potassium metabisulphite in aqueous base (Cai et al 2002) than by the method originally described by Blanco et al (1990). Alternatively, thiol **4** could be obtained by application of a method described by Rollin (1986) as follows. Mitsunobu-type reaction of borneol (**1**) with zinc dimethyldithiocarbamate gave the dithiocarbamate (**3**), which gave thiol **4** upon lithium aluminium hydride reduction. In our hands, an alternative route to thiol **4** from camphor by conversion into thiocamphor and subsequent reduction (Dagonneau et al 1973) was found to give mixtures of both thiol **4** and its 2-*endo* epimer. Thioesters **5**–**9** (Figure 3) were obtained by *N, N*′-dicyclohexylcarbodiimide (DCC)-mediated coupling of thiol **4** with the appropriate acid in the presence of 4-(*N, N*-dimethylamino)pyridine (DMAP). This method gave the thioesters in yields of 58–95% after purification by silica gel chromatography. Samples of the thioester derived from phenylacetic acid (i.e. thioester **5**) were prepared to optimise the DCC/DMAP methodology.

Samples of racemic 2-phenylpropionic acid, optically pure (*R*)-2-phenylpropionic acid and optically pure (*S*)-2-phenylpropionic acid were subjected to the same reaction conditions, giving thioesters **6a** and **6b** as an equal mixture of diastereoisomers, as largely diastereosiomer **6a** and as largely diastereoisomer **6b**, respectively. In the ^{1}H NMR spectra of these samples, the 2-phenylpropionyl α-methyl groups resonated as doublets in the range 1.51–1.52 ppm, while the α-methine protons were assigned to quartet resonances in the region 3.86–3.91 ppm. It was clear from the ^{1}H NMR spectra of the sample of predominantly thioester **6a** and from that consisting predominantly of its epimer **6b** that both samples contained observable amounts of the other diastereoisomer, estimated at 8–9% from the ^{1}H NMR spectra, despite being prepared from optically pure samples of the corresponding 2-phenylpropionic acids, implying that a significant amount of epimerisation occurs under the conditions of thioester formation and isolation. This is not surprising as both DCC and, especially, DMAP are basic reagents. Silica



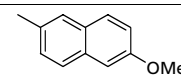
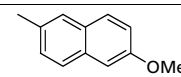
	R^1	R^2	R^3
5	H	H	Ph
6a	H	Me	Ph
6b	Me	H	Ph
7a	H	Me	
7b	Me	H	
8a	H	Me	OPh
8b	Me	H	OPh
9a	H	MeO	Ph
9b	MeO	H	Ph

Figure 3 Structural formulae of thioesters **5**–**9**.

gel, used for product purification by chromatography, is Lewis acidic, and could also feasibly induce some epimerisation. This observation could be taken in support of the relative ease of epimerisation of the thioesters, even in a non-polar medium such as dichloromethane. However, epimerisation of a reaction intermediate, rather than of the product thioesters, cannot be ruled out. While the α-methyl and α-methine proton resonances of thioesters **6a** and **6b** were sufficiently well resolved to allow reasonable estimation of the relative abundance of both epimers in freshly prepared samples, loss of resolution was observed in samples kept in solution over time; hence ^{1}H NMR spectroscopy could not be used to follow the inter-conversion of **6a** and **6b**. The reason for this loss of resolution is unclear to us. Contamination by 2-phenylpropionic acid arising from hydrolysis appears a likely explanation, although no quantities of this could be detected in samples by chromatography. The loss of resolution could suggest that some epimerisation is occurring in solution over time, but this is not supported by the optical activity experiments discussed below. Loss of resolution in NMR spectra can be a consequence of a number of experimental factors, such as presence of fine particles in the sample, difficulty in maintaining the homogeneity of the magnetic field, the development of concentration gradients within the sample and other factors. All reasonable precautions were carried out to maintain the quality of the NMR samples (e.g. filtering to remove fine particles). However, the α-methyl and α-methine proton resonances were finely resolved even in fresh samples prepared with great care. We were unable to prevent the resolution of these samples degrading over time. The diastereoisomeric integrity of (**6a**) and (**6b**) were instead examined by determination of optical activity in acetonitrile as solvent at 40°C. Acetonitrile was selected as it is a moderately polar aprotic solvent with some inherent basicity, and as it was found to be a good medium for H/D exchange in 2-APA thioesters by Mayer et al (1988). Optical rotations of samples of 1:1 mixtures of **6a** and **6b**, of predominantly **6a**, and of predominantly **6b**, in acetonitrile at 40°C were recorded for periods of greater than 20 days. No significant variations in optical activity were observed during this time, suggesting that no epimerisation was occurring. To determine whether any equilibration between **6a** and **6b** could be achieved under more basic conditions, the experiments were repeated in acetonitrile containing 5% v/v diisopropylethylamine, again at 40°C. Under these conditions, samples of 1:1 mixtures of **6a** and **6b** gave optical rotations of 28.43° and did not vary over the duration of the experiments. Samples of thioester **6a**, prepared as described above, gave initial rotations of −18.43°, gradually changing to −12.80° over 14 days; while samples of **6b** gave initial rotations of 65.93°, gradually changing to 48.77° over 14 days. Little further change was observed after 14 days; suggesting that even in a polar aprotic medium of some basicity, equilibration between thioesters **6a** and **6b** is relatively minor and incomplete.

DCC/DMAP coupling of thiol (**4**) with samples of racemic naproxen, optically pure (*R*)-naproxen, and optically pure (*S*)-naproxen gave thioesters **7a** and **7b** as an equal mixture of diastereoisomers, as predominantly diastereosiomer **7a** and as predominantly diastereoisomer **7b**, respectively. In the ^{1}H NMR spectra of freshly prepared samples, the α-methyl group of **7a** was assigned to a doublet resonating at 1.52 ppm, while the α-methyl group of **7b** was assigned to a doublet resonating at 1.51 ppm. As in the case of **6a**/**6b**, ^{1}H NMR spectra of samples of thioesters **7a** and **7b** freshly prepared from batches of the corresponding optically pure chiral non-racemic naproxens indicated the presence of amounts of the other diastereoisomer in ratios of 20–22:1. Again, this may be a consequence of a lability of thioesters **7a**/**7b** to interconversion, at least under the coupling and isolation conditions, but may also arise from loss of stereochemical integrity of reaction intermediates. Again, as in the case of thioesters **6a**/**6b**, resolution of diastereospecific resonances in the ^{1}H NMR spectra was lost in samples kept in solution over time; hence epimerisation between **7a** and **7b** could not be observed by ^{1}H NMR spectroscopy. As in the case of compounds **6a**/**6b** above, the α-methyl (but not the α-methine) proton resonances of **7a**/**7b** were finely resolved in fresh samples prepared for NMR with all reasonable precautions. However, we were unable to prevent loss of this resolution in these samples kept over time. No observable change in the optical activity of samples of **7a**/**7b** in acetonitrile at 40°C was observed over periods of several days.

As chiral metabolic inversions have also been observed for certain of the 2-aryloxypropionic acid class of herbicides, we wished to examine the thioester of 2-phenoxypropionic acid as a model for the aryloxypropionic acid herbicides. DCC/DMAP coupling of thiol **4** and racemic 2-phenoxypropionic acid gave a 1:1 mixture of thioesters **8a** and **8b**. As optically pure samples of the non-racemic 2-phenoxypropionic acids were not readily available, only the racemic acid was used in this case. In the ^{1}H NMR spectrum of **8a** and **8b**, the α-methyl protons were assigned to doublet resonances observed at 1.61 and 1.62 ppm, and the α-methine protons to quartets observed at 4.87 and 4.88 ppm. These samples retained sufficient resolution over time to allow continued observation of these resonances. No change in the ratio of **8a** to **8b** was observed in the ^{1}H NMR spectra of samples at 40°C over time. As it would be expected that epimerisation between **8a** and **8b** would likely result in an unequal mixture at equilibrium, lack of variation in the ratio of epimers suggests that equilibration is unlikely to occur.

As neither the 2-arylpropionate thioesters **6a/6b** and **7a/7b** nor the 2-aryloxypropionate thioesters **8a/8b** underwent significant equilibration between epimers in acetonitrile at 40°C, we finally selected the α-methoxypropionate thioesters **9a** and **9b** as compounds that combine contributions from both aryl and alkoxy groups α- to the thioester carbonyl group. DCC/DMAP coupling of thiol **4** with samples of racemic α-methoxy-phenylacetic acid, optically pure (*R*)-α-methoxy-phenylacetic acid, and optically pure (*S*)-α-methoxy-phenylacetic acid gave thioesters **9a** and **9b** as an equal mixture of diastereoisomers, as predominantly diastereosiomer **9a** and as predominantly diastereoisomer **9b**, respectively. Diastereospecific ^{1}H NMR resonances

for the methoxy and α-methine protons of **9a** were observed at 3.47 ppm and 4.75 ppm, respectively; and for the corresponding protons of **9b** at 3.46 ppm and 4.73 ppm, respectively. As with thioesters **6a/6b** and **7a/7b**, the presence of amounts of the other diastereoisomers, in ratios of 13–16:1, were observed in ^{1}H NMR spectra of samples of **9a** and **9b** prepared from samples of the optically pure non-racemic α-methoxy-phenylacetic acids. The methoxy resonances of thioesters **9a/9b** remained sufficiently well resolved in solution over time to allow observation of equilibration between epimers **9a** and **9b** by ^{1}H NMR spectroscopy. This was very much helped by the fact that in the case of **9a/9b**, the diastereospecific resonances were singlets rather than quartets or doublets. Experiments were preformed using a 75:25 mix of D3-acetonitrile and D-chloroform as solvent, the chloroform being necessary to maintain the solubility of the thioesters. The α-methoxy resonances of solutions of predominantly thioester **9a** and of predominantly thioester **9b** were monitored for 60 h at 40 °C. Over this time, the intensity of the α-methoxy resonance at 3.47 ppm of the solution initially consisting of predominantly thioester **9a** (93% **9a**, 7% **9b**) steadily decreased, while the resonance at 3.46 ppm (i.e. that arising from the α-methoxy group of **9b**) steadily increased, giving a proportion of 63% **9a** and 37% **9b** after 60 h. As compounds **6**, **7** and **8**, discussed above, were found to be on the whole inert towards epimerisation, lengthy observation periods over several day were allowed in those cases to ensure that any epimerisation occurring was detected. The observation period of 60 h was sufficient to show that compound **9a** was clearly more susceptible to epimerisation than any of the compounds discussed above, although that time was probably insufficient to allow the system to reach equilibrium. Similarly, the intensity of the α-methoxy resonance at 3.46 ppm in the solution initially consisting of predominantly thioester **9b** (6% **9a**, 94% **9b**) steadily decreased, while the resonance at 3.47 ppm steadily increased, giving a proportion of 24% **9a** and 76% **9b** after 60 h. As with **9a**, observation over 60 h was sufficient to show that thioester **9b** was susceptible to epimerisation without the system necessarily reaching equilibrium. No resonances arising from hydroylsis products (i.e. thiol **4** or α-methoxy-phenylacetic acid) were observed, nor were any hydrolysis products detected chromatographically. These observations suggest that equilibration between epimers **9a** and **9b** is occurring in acetonitrile at 40°C.

Conclusions

Samples of thioesters **6a/6b**, **7a/7b**, **8a/8b** and **9a/9b** were assessed for evidence of equilibration between diastereoisomers in acetonitrile at 40°C, by monitoring of optical activity in the cases of **6a/6b** and **7a/7b**, and by monitoring for diastereospecific ^{1}H NMR resonances in the cases of **8a/8b** and **9a/9b**. No evidence of significant inter-conversion between epimers was observed for thioesters **6a/6b**, **7a/7b** or **8a/8b** under these conditions. Evidence of some minor inter-conversion between epimers **6a** and **6b** was observed in a significantly more basic medium (acetonitrile containing 5% v/v diisopropylethylamine). Only in the case of thioesters **9a/9b** was significant inter-conversion between epimers observed. These finding do not support the possibility of spontaneous or chemical inter-conversion between diastereoisomeric 2-arylpropionate and 2-aryloxypropionate thioesters in non-polar media. That such inter-conversion is possible is demonstrated by thioesters **9a/9b**, in which the combined electron-withdrawing effects of both the aryl and alkoxy substituents present on the carbon α- to the thioester carbonyl group provide sufficiently high α-methine acidity to allow inter-conversion. Further work on systems of similar acidity to the α-methoxy-phenylacetate thioesters **9a/9b**, such as α-halo- or α-thio-arylacetate thioesters might be of interest from a synthetic viewpoint, but could provide no information on chiral inversion of 2-aryl- or aryloxypropionic acids. Co-enzyme A is a more polar and more conformationally flexible structure than the bornyl system used in this study. It remains possible that in non-polar media, 2-APA co-enzyme A thioesters adopt a conformation in which polar functionalities on the co-enzyme A group assist in the epimerisation process. Such a conformation might be better mimicked by functionalised bornanethiols such as *exo*-3-(sulfhydro)isoborneol (**10**) (Corey et al 1993) or 10-methylthio-*exo*-2-bornanethiol (**11**, Figure 4) (Montenegro et al 1996). These thiols retain the stereochemical robustness of the bornane group while providing polar groups that could participate in the epimerisation process. Further functionalisation of such compounds (e.g. by phosphorylation or by introduction of adenosyl groups) could be used to obtain close conformationally-constrained mimics of co-enzyme A.

It is noteworthy that in the preparations of the individual diastereoisomers of thioesters **6**, **7** and **9** (i.e. of epimers **a** and **b** for each of these), some quantity of the opposite diastereoisomer was always obtained. Also, similar quantities of the opposing diastereoisomers were obtained for each (e.g. preparation of **6a** from thiol **4** and optically pure (*R*)-phenylpropionic acid gave **6a** containing **6b** as a minor component in a ration of 11:1, while preparation of **6b** from **4** and optically pure (*S*)-phenylpropionic acid gave **6b** containing **6a** as a minor component in a ration of 10:1). The corresponding ratios for **7a** and **7b** are 22:1 and 20:1, respectively, and for **9a** and **9b** are 13:1 and 16:1, respectively. It would be tempting to cite the formation of the minor diastereoisomers as evidence in support of thioester epimerisation. Some form of stereochemical inversion must be occurring at the α-CH

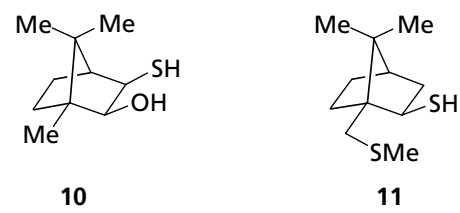


Figure 4 Structural formulae of thiols 10 and 11.

site during the course of these preparations, which gives rise to the minor diastereoisomers. The inverting species could be the thioesters products, which could begin epimerising once formed under the reaction or isolation conditions. Compounds such as DMAP or DCC present in the reaction medium, or silica gel used for product purification/isolation could be capable of facilitating such epimerisation. However, the inertness towards epimerisation subsequently observed for these compounds does not support this conclusion, and inversion of an intermediate formed during the coupling process, such as an *O*-acylisourea, is more likely. Carbodiimide-type coupling conditions, such as we have used, are commonly used in the derivatisation of 2-APAs for purposes of chromatographic determination of enantiomers (Tan et al 1997). The above observations suggest that the possibility of some inversion of configuration at the α-CH site should be allowed for in method validation when using such reagents for that purpose.

References

Blanco, J. M., Caamano, O., Eirín A., Fernández, F., Medina, L. (1990) Synthesis of chiral sulfinic acids: sodium (1*S-exo*)-2-bornanesulfinate. *Synthesis* 584–586

Buser, H.-R., Müller, M. D. (1997) Conversion reactions of various phenoxyalkanoic acid herbicides in soil. 2. Elucidation of the enantiomerization process of chiral phenoxy acids from incubation in a D_2O/soil system. *Environ. Sci. Technol.* **31**: 1960–1967

Caddick, S., Jenkins, K. (1996) Dynamic resolutions in asymmetric synthesis. *Chem. Soc. Rev.* 447–456

Cai, Y., Roberts, B. P., Tocher, D. A. (2002) Carbohydrate-derived thiols as protic polarity-reversal catalysts for enantioselective radical-chain reactions. *J. Chem. Soc. Perkin Trans.* **1**: 1376–1386

Caldwell, J., Hutt, A. J., Fournel-Gigleux, S. (1988) The metabolic chiral inversion and dispositional enantioselectivity of the 2-arylpropionic acids and their biological consequences. *Biochem. Pharmacol.* **37**: 105–114

Corey, E. J., Chen, Z., Tanoury, G. J. (1993) A new and highly enantioselective synthetic route to P-chiral phosphines and diphosphines. *J. Am. Chem. Soc.* **115**: 11000–11001

Dagonneau, M., Paquer, D., Vialle, J. (1973) Composés organiques sulfurés XXXIX. Action des organomagnésiens aliphatiques sur le thiocamphre et la thiofenchone. *Bull. Chim. Soc. Fr.* 1699–1702

Hutt, A. J., Caldwell, J. (1983) The metabolic chiral inversion of 2-arylpropionic acids - a novel route with pharmacological consequences. *J. Pharm. Pharmacol.* **35**: 693–704

Knihinicki, R. D., Day, R. O., Williams, K. M. (1991) Chiral inversion of 2-arylpropionic acid non-steroidal anti-inflammatory drugs - II. *Biochem. Pharmacol.* **42**: 1905–1911

Mayer, J. M., Bartolucci, C., Maître, J.-M., Testa, B. (1988) Metabolic chiral inversion of anti-inflammatory 2-arypropinates: lack of reaction in liver homogenates, and study of methine proton acidity. *Xenobiotica* **18**: 533–543

Menzel, S., Waibel, R., Brune, K., Geisslinger, G. (1994) Is the formation of R-ibuprofen-adenylate the first stereoselective step of chiral inversion? *Biochem. Pharmacol.* **48**: 1056–1058

Montenegro, E., Echarri, R., Claver, C., Castillón, S., Moyano, A., Pericàs, M. A., Riera, A. (1996) New camphor-derived sulfur chiral controllers: synthesis of (2*R-exo*)-10-methylthio-2-bornanethiol and (2*R-exo*)-2,10-bis(methylthio)bornane. *Tetrahedron: Asymmetry* **7**: 3553–3558

Rollin, P. (1986) One-step stereospecific conversion of alcohols into dithiocarbamates: a smooth pathway for the introduction of a sulphur functionality. *Tetrahedron Lett.* **35**: 4169–4170

Sheih, W.-R., Chen C.-S. (1993) Purification and characterisation of novel 2-arylpropionyl-CoA epimerases from rat liver cytosol and mitochondria. *J. Biol. Chem.* **268**: 3487–3493

Tan, S. C., Jackson, S. H. D., Swift, C. G., Hutt, A. J. (1997) Enantiospecific analysis of ibuprofen by high performance liquid chromatography: determination of free and total drug enantiomer concentrations in serum and urine. *Chromatographica* **46**: 23–32

Tracy, T. S., Hall, S. D. (1992) Metabolic inversion of (*R*)-ibuprofen. *Drug Metab. Dispos.* **20**: 322–327

Vane, J. R., Botting, R. M. (1995) New insights into the mode of action of anti-inflammatory drugs. *Inflamm. Res.* **44**: 1–10