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Resolution of (4*RS*,5*RS*)-4,5-diphenylimidazolidine-2-thione using pentafluorophenyl active esters

Anna Andreou, Najla Al Shaye, Hannah Brown, Jason Eames *

Department of Chemistry, University of Hull, Cottingham Road, Kingston upon Hull HU6 7RX, UK

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ABSTRACT

(4*RS*,5*RS*)-4,5-Diphenylimidazolidine-2-thione is resolved efficiently by treatment with NaHMDS and an enantiomerically pure pentafluorophenyl active ester. The levels of diastereocontrol were excellent (up to 90% de).

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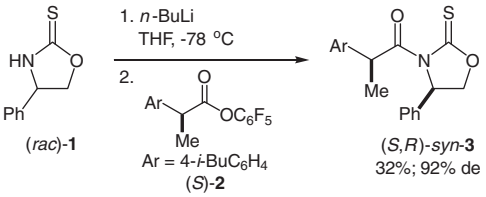
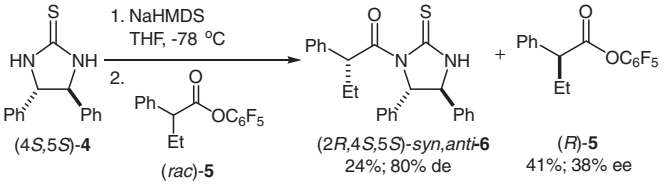
The separation of enantiomeric substrates[1] using parallel resolution is becoming an increasingly popular method.[2] Over the last few years, we have been interested in the kinetic resolution of oxazolidine-2-ones[3] and oxazolidine-2-thiones,[4] such as 4-phenyloxazolidine-2-thione (*rac*)-**1**, using an enantiomerically pure ibuprofen-derived active ester, 2-(4-isobutylphenyl)propanoate (*S*)-**2**, to give the corresponding oxazolidine-2-thione adduct (*S*,*R*)-*syn*-**3** in 32% yield with 92% de (Scheme 1).[3] The levels of diastereocontrol were found to be excellent for a wide range of structurally related profen-based active esters. This methodology has more recently been applied to the resolution of racemic alcohols, such as 1-phenylethanol,[5] and carboxylic acids.[6]

Using our standard protocol,[3] we were interested in studying the resolution of C_2-symmetric 4,5-diphenylimidazolidine-2-thione (4*RS*,5*RS*)-**4**, as this substrate contained all the essential features[7] for efficient molecular recognition with our profen-based pentafluorophenyl active esters.[8] We first studied the resolution of pentafluorophenyl 2-phenylbutanoate (*rac*)-**5** using the enantiomerically pure 4,5-diphenylimidazolidine-2-thione (4*S*,5*S*)-**4** (Scheme 2). Treatment of (4*S*,5*S*)-**4** (1 equiv) with sodium hexamethyldisilazane (NaHMDS; 1.1 equiv) in THF at −78 °C, followed by the addition of pentafluorophenyl 2-phenylbutanoate (*rac*)-**5** (1.1 equiv) gave, after stirring for 2 h, the corresponding 4,5-diphenylimidazolidine-2-thione (2*R*,4*S*,5*S*)-*syn*,*anti*-**6** in 24% yield with 80% de (Scheme 2). The stereochemical outcome of this resolution was confirmed through stereospecific synthesis,[9] and the diastereoselectivity was determined by 400 MHz ^{1}H NMR spectroscopy.[10] Formation of this product, 4,5-diphenylimidazolidine-2-thione (2*R*,4*S*,5*S*)-*syn*,*anti*-**6**, is intrinsically low yielding (~25% yield)[11] due to its being more acidic than its starting 4,5-diphenylimidazolidine-2-thione, (4*S*,5*S*)-**4**, and the inherent enantiomeric composition of the active ester (*rac*)-**5**.[12] The remaining pentafluorophenyl 2-phenylbutanoate (*rac*)-**5** was recovered in 41% yield with 38% ee.[13]

With this information in hand, we next investigated the complementary resolution of racemic 4,5-diphenylimidazolidine-2-thione (4*RS*,5*RS*)-**4** using enantiomerically pure pentafluorophenyl 2-phenylbutanoate (*R*)-**5**, formed in 78% yield by DCC coupling of (*R*)-2-phenylbutanoic acid with pentafluorophenol (Scheme 3). Deprotonation of racemic 4,5-diphenylimidazolidine-2-thione (4*RS*,5*RS*)-**4** (1 equiv) with NaHMDS (1.1 equiv) in THF at −78 °C, followed by the addition of pentafluorophenyl 2-phenylbutanoate (*R*)-**5** (1.1 equiv) gave, after 2 h at −78 °C, 4,5-diphenylimidazolidine-2-thione (2*R*,4*S*,5*S*)-*syn*,*anti*-**6** in 28% yield with 78% de. The resolved 4,5-diphenylimidazolidine-2-thione (4*R*,5*R*)-**5** was recovered



Scheme 1. Resolution of oxazolidine-2-thione (*rac*)-**1** using active ester (*S*)-**2**.



Scheme 2. Resolution of active ester (*rac*)-**5** using 4,5-diphenylimidazolidine-2-thione (4*S*,5*S*)-**4**.

* Corresponding author. Tel.: +44 1482 466401; fax: +44 1482 466410.
E-mail address: j.eames@hull.ac.uk (J. Eames).

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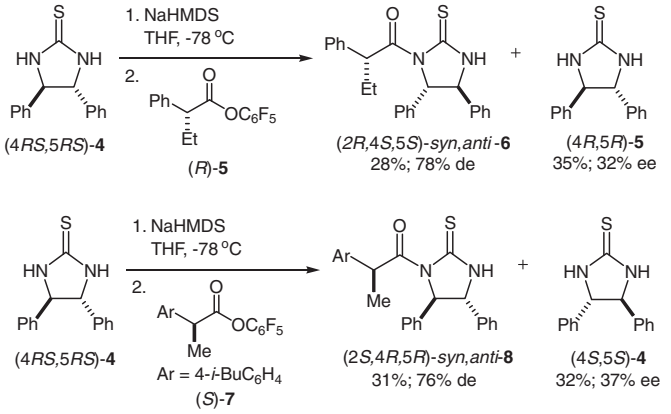
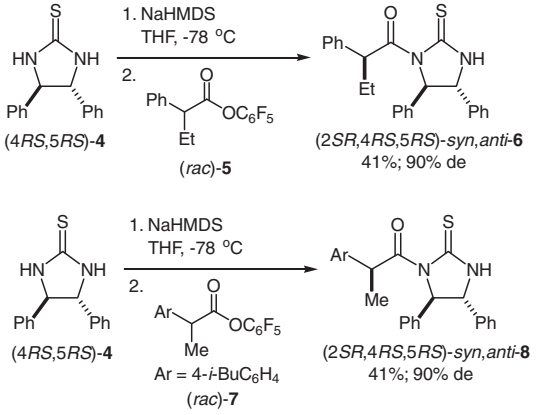


Scheme 3. Kinetic resolution of 4,5-diphenylimidazolidine-2-thione (4*RS*,5*RS*)-**4** using active esters (*R*)-**5** and (*S*)-**7**.



Scheme 4. Mutual resolution of 4,5-diphenylimidazolidine-2-thione (4*RS*,5*RS*)-**4** using active esters (*rac*)-**5** and (*rac*)-**7**.

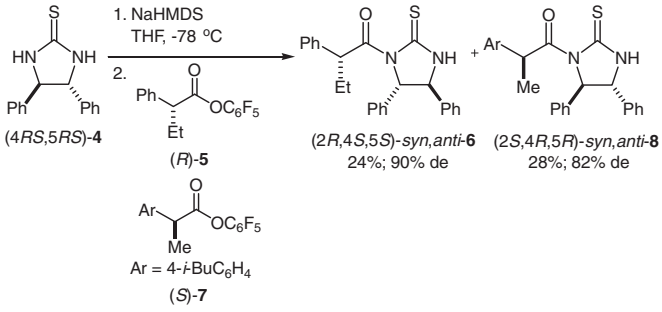
with the predicted stereochemistry in 35% yield with 32% ee (Scheme 3). The enantiomeric 4,5-diphenylimidazolidine-2-thione (4*S*,5*S*)-**4** was synthesised in 32% yield with 37% ee by treatment of the parent 4,5-diphenylimidazolidine-2-thione (4*RS*,5*RS*)-**4** (1 equiv) with NaHMDS (1.1 equiv), followed by the addition of pentafluorophenyl 2-(4-isobutylphenyl)propanoate (*S*)-**7** (1.1 equiv) (Scheme 3). The complementary 4,5-diphenylimidazolidine-2-thione adduct (2*S*,4*R*,5*R*)-*syn*,*anti*-**8** was formed in 31% yield with 76% de (Scheme 3).

In an attempt to improve the efficiency of this resolution, we next chose to resolve 4,5-diphenylimidazolidine-2-thione (4*RS*,5*RS*)-**4** in parallel[2,14] using two complementary *quasi*-enantiomeric[15] pentafluorophenyl active esters, (*R*)-**5** and (*S*)-**7**. As a preliminary model study, we first investigated the mutual resolution of 4,5-diphenylimidazolidine-2-thione (4*RS*,5*RS*)-**4**, using the racemic active esters, (*rac*)-**5** and (*rac*)-**7** (Scheme 4). Deprotonaton of racemic 4,5-diphenylimidazolidine-2-thione (4*RS*,5*RS*)-**4** (1 equiv) with NaHMDS (1.1 equiv) in THF at −78 °C, followed by addition of racemic active esters, (*rac*)-**5** (1.1 equiv) and (*rac*)-**7** (1.1 equiv), gave the 4,5-diphenylimidazolidine-2-thione adducts (2*SR*,4*RS*,5*RS*)-*syn*,*anti*-**6** (in 41% yield with 90% de) and (2*SR*,4*RS*,5*RS*)-*syn*,*anti*-**8** (in 41% yield with 90% de), respectively (Scheme 4). In both cases, the diastereoselectivity for these mutual resolutions was higher[2] than their corresponding kinetic resolutions; 90% de for both (*rac*)-**5** and (*rac*)-**7** versus 78% de for (*R*)-**5** and 76% de for (*S*)-**7** (Schemes 3 and 4).

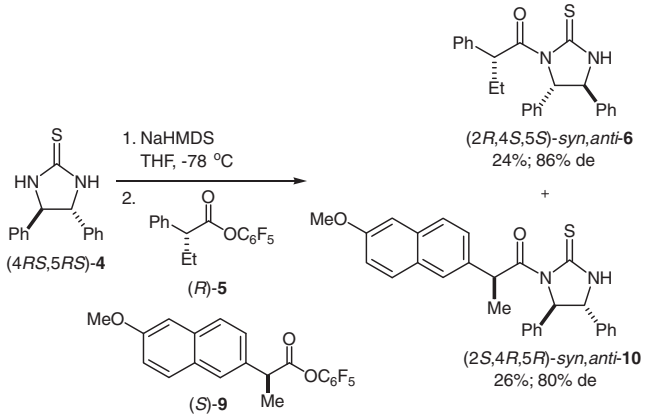
We next turned our attention to the parallel resolution of racemic 4,5-diphenylimidazolidine-2-thione (4*RS*,5*RS*)-**4** using a combination of *quasi*-enantiomeric active esters (*R*)-**5** and (*S*)-**7** (Scheme 5). Deprotonation of (4*RS*,5*RS*)-**4** (1 equiv) using NaHMDS (1.1 equiv) in THF at −78 °C followed by the addition of an equivmolar amount of *quasi*-enantiomeric active esters (*R*)-**5** (0.55 equiv) and (*S*)-**7** (0.55 equiv) gave, after 2 h, a mixture of two *quasi*-enantiomeric 4,5-diphenylimidazolidine-2-thiones (2*R*,4*S*,5*S*)-*syn*,*anti*-**6** and (2*S*,4*R*,5*R*)-*syn*,*anti*-**8** in 24% and 28% yields, with 90% de and 82% de, respectively (Scheme 5).

Increased separation of the 4,5-diphenylimidazolidine-2-thione adducts can be achieved using two *quasi*-enantiomeric active esters, (*R*)-**5** and (*S*)-**9**, which have different polarity.[16] Treatment of 4,5-diphenylimidazolidine-2-thione (4*RS*,5*RS*)-**4** (1 equiv) with NaHMDS (1.1 equiv) in THF at −78 °C, followed by the addition of an equimolar amount of (*R*)-**5** (0.55 equiv) and (*S*)-**9**[17] (0.55 equiv) gave the 4,5-diphenylimidazolidine-2-thiones (2*R*,4*S*,5*S*)-*syn*,*anti*-**6** and (2*S*,4*R*,5*R*)-*syn*,*anti*-**10**[18] in 24% yield with 86% de and 26% yield with 80% de, respectively (Scheme 6). These adducts were easily separated by column chromatography; ΔR_F [CH_2Cl_2] = 0.10.[19]

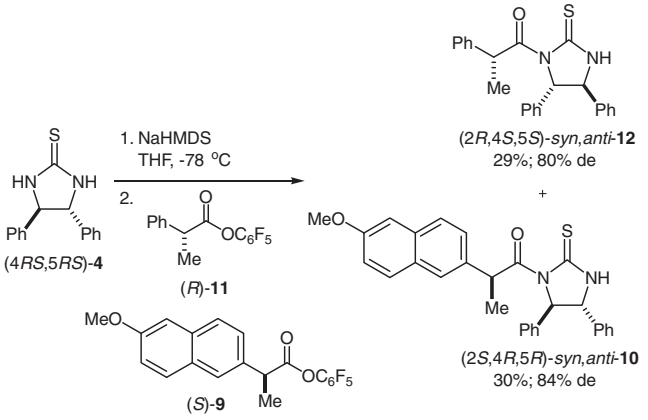
However, attempts at separating the enantiomers of (4*RS*,5*RS*)-**4** using a pair of *quasi*-enantiomeric pentafluorophenyl propanoates, (*R*)-**11**[20] and (*S*)-**9**, gave the corresponding 4,5-diphenylimidazolidine-2-thiones (2*R*,4*S*,5*S*)-*syn*,*anti*-**12**[21] and (2*S*,4*R*,5*R*)-*syn*,*anti*-**10** in higher yields, 29% and 30%, respectively, but with decreased levels of diastereoselectivity, 80% de and 84% de, respectively (Scheme 7). These pentafluorophenyl propanoates, (*R*)-**11** and (*S*)-**9**, were less diastereoselective than the pentafluorophenyl



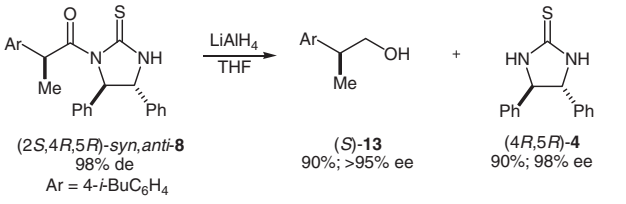
Scheme 5. Parallel resolution of 4,5-diphenylimidazolidine-2-thione (4*RS*,5*RS*)-**4** using active esters (*R*)-**5** and (*S*)-**7**.



Scheme 6. Parallel resolution of 4,5-diphenylimidazolidine-2-thione (4*RS*,5*RS*)-**4** using active esters (*R*)-**5** and (*S*)-**9**.



Scheme 7. Parallel resolution of 4,5-diphenylimidazolidine-2-thione (4*RS*,5*RS*)-**4** using active esters (*R*)-**11** and (*S*)-**9**.



Scheme 8. $LiAlH_4$ reduction of 4,5-diphenylimidazolidine-2-thione (2*S*,4*R*,5*R*)-**8**.

butanoate (*R*)-**7**, due to their increased electrophilicity and less sterically demanding nature.

Access to the resolved parent 4,5-diphenylimidazolidine-2-thione, such as (4*R*,5*R*)-**4**, was achieved by $LiAlH_4$ reduction of 4,5-diphenylimidazolidine-2-thione (2*S*,4*R*,5*R*)-*syn*,*anti*-**8** (Scheme 8). Addition of $LiAlH_4$ to a stirred solution of (2*S*,4*R*,5*R*)-*syn*,*anti*-**8** in THF at RT, and stirring the resulting solution for 2 h, gave the required enantiomerically pure 4,5-diphenylimidazolidine-2-thione (4*R*,5*R*)-**4**[22] in 90% yield with 98% ee and the primary alcohol (*S*)-**13**[5b,6] in 90% yield with >95% ee (Scheme 8).

In conclusion, we have shown[23] that four pentafluorophenyl active esters, (*R*)-**5**, (*S*)-**7**, (*S*)-**9** and (*R*)-**11**, can be used to efficiently resolve racemic 4,5-diphenylimidazolidine-2-thione, (4*RS*,5*RS*)-**4** in good yields. The levels of diastereocontrol were found to be good to excellent (78% de→90% de) favouring formation of the corresponding (2*R**,4*S**,5*S**)-*syn*,*anti*-4,5-diphenylimidazolidine-2-thiones **6**, **8**, **10** and **12**. The nearest analogy to this work is the desymmetrisation of *meso*-(4*R*,5*S*)-diphenylimidazolidine-2-thione[24] using profen-based pentafluorophenyl active esters. The levels of molecular recognition between the PhCHN(Na)C=S motif of *meso*-(4*R*,5*S*)-4,5-diphenylimidazolidine-2-thione and the enantiomerically pure active ester, (*R*)-**5**, were similarly high (92% de). In comparison, formation of the complementary diastereoisomeric *anti*-4,5-diphenylimidazolidine-2-thiones can be achieved using a deprotonation–methylation strategy developed by Davies[25] involving a related C_2-symmetric *N*-propanoyl 4,5-diphenylimidazolidine-2-thione.

Acknowledgements

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References and notes

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2. Reviews, see: (a) Eames, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 885; (b) Eames, J. In *Organic Synthesis Highlights*; VCH-Wiley, 2003; Vol. v, Chapter 17; (c) Dehli, J. R.; Gotor, V. *Chem. Soc. Rev.* **2002**, *31*, 365; (d) Dehli, J. R.; Gotor, V. *ARKIVOC* **2002**, *v*, 196.
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6. Al Shaye, N.; Boa, A. N.; Coulbeck, E.; Eames, J. *Tetrahedron Lett.* **2008**, *49*, 4661.
7. For high levels of molecular recognition, the nucleophilic component must contain a PhCH(alkyl)-XM motif, where X is O and N.
8. Addition of racemic sodiated *trans*-4,5-tetramethylene-imidazolidine-2-thione to (*S*)-pentafluorophenyl 2-(4-isobutylphenyl)propanoate leads to the corresponding (4*R*,5*R*)-3-[2*S*-(4-isobutylphenyl)propanoyl]-4,5-tetramethyleneimidazolidine-2-thione in 36% yield with 40% de.
9. The 4,5-diphenylimidazolidine-2-thione (2*R*,4*S*,5*S*)-*syn*,*anti*-**6** was formed in 54% yield by the addition of lithiated 4,5-diphenylimidazolidine-2-thione (4*S*,5*S*)-**4** to (*R*)-2,4-dichlorophenyl 2-(4-isobutylphenyl)propanoate.
10. For 4,5-diphenylimidazolidine-2-thione (2*R*,4*S*,5*S*)-*syn*,*anti*-**6**, the PhCHNC=O doublet is at 5.37 ppm (1H, d, *J* = 5.4). Whereas, for (2*R*,4*R*,5*R*)-*anti*,*anti*-**6**, the PhCHNC=O doublet is at 5.22 ppm (1H, br d, *J* = 2.2).
11. Trace amounts (<2%) of dipropanonyl thioureas can be detected in the crude mixture by ^{1}H NMR spectroscopy.
12. Dipropanonyl thioureas can be formed using an excess of Brønsted base and active ester. Under our standard conditions, treatment of thiourea (4*S*,5*S*)-**4** (1 equiv) with *n*-BuLi (2.2 equiv) and active ester (*rac*)-**7** (4.4 equiv) gave the propanoyl thioureas *syn*,*anti*- and *anti*,*anti*-**8** in 25% yield in a diastereoisomeric ratio of 56:44 and the di-propanoyl thioureas *syn*,*anti*,*syn*-, *syn*,*anti*,*anti*- and *anti*,*anti*,*anti*- in 48% yield with a diastereoisomeric ratio of 35:45:20. The relative ratio of the propanoyl and di-propanoyl thioureas was 38:62 (by ^{1}H NMR spectroscopy).
13. The enantiomeric excess was determined by comparison with the known specific rotation, and through hydrolysis to give the corresponding carboxylic acid. The enantiomeric excess of this carboxylic acid was determined by self-coupling to form the corresponding anhydride, see: Coulbeck, E.; Eames, J. *Tetrahedron: Asymmetry* **2009**, *20*, 635.
14. Recent examples of parallel kinetic resolutions: (a) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1997**, *119*, 2584; (b) Liao, L.; Zhang, F.; Dmitrenko, O.; Bach, R. D.; Fox, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 4490; (c) Davies, S. G.; Garner, A. C.; Long, M. J.; Smith, A. D.; Sweet, M. J.; Withey, J. M. *Org. Biomol. Chem.* **2004**, *2*, 3355.
15. Zhang, Q. S.; Curran, D. P. *Chem. Eur. J.* **2005**, 4866.
16. The 2-(6-methoxynaphthalen-2-yl)propanoyl transfer group, in (*S*)-**9**, is more polar than the 2-phenylbutanoyl transfer group in (*R*)-**7**.
17. The mutual resolution using (*rac*)-**9**, gave (2*RS*,4*SR*,5*SR*)-*syn*,*anti*-**10** in 31% yield with 72% de.
18. (2*S*,4*R*,5*R*)-*syn*,*anti*-**10**; $[\alpha]_D^{25}$ +166.8 (*c* 4.0, $CHCl_3$).
19. (2*R*,4*S*,5*S*)-*syn*,*anti*-**6**: $R_F[CH_2Cl_2]$ 0.66; (2*S*,4*R*,5*R*)-*syn*,*anti*-**10**; $R_F[CH_2Cl_2]$ 0.56.
20. The mutual resolution using (*rac*)-**11**, gave (2*RS*,4*SR*,5*SR*)-*syn*,*anti*-**12** in 35% yield with 80% de.
21. (2*R*,4*S*,5*S*)-*syn*,*anti*-**12**; $[\alpha]_D^{25}$ −134.2 (*c* 2.4, $CHCl_3$).
22. $[\alpha]_D^{25}$ +62.7 (*c* 2.2, $CHCl_3$) {lit. $[\alpha]_D^{25}$ +65.0 (*c* 0.25, $CHCl_3$); Davies, S. G.; Mortlock, A. A. *Tetrahedron* **1993**, *49*, 4419}.
23. Representative experimental procedure: Synthesis of (4*S*,5*S*)-3-[2*R*-phenylbutanoyl]-4,5-diphenylimidazolidine-2-thione (2*R*,4*S*,5*S*)-*syn*,*anti*-**6**; NaHMDS (0.43 mL, 1.0 M in THF, 0.43 mmol) was added to a stirred solution of enantiomerically pure 4,5-diphenylimidazolidine-2-thione (4*S*,5*S*)-**4** (0.1 g, 0.39 mmol) in THF at −78 °C. After stirring for 1 h, a solution of racemic pentafluorophenyl 2-phenylbutanoate (*rac*)-**5** (0.14 g, 0.43 mmol) in THF (5 mL) was added. The resulting mixture was stirred for 2 h at −78 °C. The reaction was quenched with H_2O (10 mL). The organic layer was extracted with Et_2O (2 × 10 mL), dried (over $MgSO_4$) and evaporated under reduced pressure to give a separable mixture of two diastereoisomeric oxazolidine-2-ones (2*R*,4*S*,5*S*)-*syn*,*anti*-**6** and (2*S*,4*S*,5*S*)-*anti*,*anti*-**6** (ratio 90:10). The crude mixture was purified by flash column chromatography on silica gel eluting with light petroleum (bp 40–60 °C)/CH_2Cl_2 (1:9), to give (2*R*,4*S*,5*S*)-*syn*,*anti*-**6** (33 mg, 21%) and (2*S*,4*S*,5*S*)-*anti*,*anti*-**6** (4 mg, 3%) as a separable diastereoisomeric mixture (90:10—*syn*,*anti*-/*anti*,*anti*-); and pentafluorophenyl 2-phenylbutanoate (*R*)-**5** (26 mg, 41%) as a colourless oil with ~38% ee; {$[\alpha]_D^{25}$ +26.4 (*c* 1.0, $CHCl_3$)}; {(*R*)-; >98% ee $[\alpha]_D^{25}$ +69.5 (*c* 5.3, $CHCl_3$)}.
Characterisation data for: (2*S*,4*S*,5*S*)-*anti*,*anti*-6; colourless oil; R_F $[CH_2Cl_2]$ 0.52; ν_{max} ($CHCl_3$) cm^{-1} 3022 (N–H), 1216 (C=S) and 1705 (C=O); $[\alpha]_D^{25}$ +7.4 (*c* 1.1, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 7.42–7.38 (3 H, m, 3 × CH; Ph), 7.30–7.25 (5H, m, 5 × CH; Ph), 7.23–7.18 (5 H, m, 5 × CH; Ph), 6.84 (2 H, d, *J* 8.8, 2 × *CH*; Ph), 6.19 (1H, t, *J* 7.5, PhCHEt), 5.22 (1H, br d, *J* 2.2, PhCHNCO), 4.38 (1H, br s, PhCHN), 2.20–2.10 (1H, ddq, *J* 13.7, 7.5 and 7.3, $CH_AH_BCH_3$), 1.89–1.80 (1H, ddq, *J* 13.7, 7.5 and 7.3, $CH_AH_BCH_3$) and 0.74 (3H, t, *J* 7.3, $CHCH_2CH_3$); δ_C

(100 MHz; $CDCl_3$) 180.4 (C=S), 175.1 (C=O), 140.5 (*i*-C; Ph), 139.2 (*i*-C; Ph), 139.1 (*i*-C; Ph), 129.3[2] (2C, 2 × CH; Ph), 129.2[2] (2C, 2 × CH; Ar), 128.8[2] (2 × CH; Ph), 128.4[1] (1 × CH; Ph), 128.4[1] (1 × CH; Ph), 128.3[2] (2C, 2 × CH; Ph), 127.1[1] (1 × CH; Ph), 125.4[2] (2C, 2 × CH; Ph), 125.2[2] (2C, 2 × CH; Ar), 71.7 (PhCHNCO), 64.8 (PhCHN), 50.2 (PhCHEt), 27.1 (CH_2CH_3) and 11.9 (CH_2CH_3) (found MH^+, 401.1678; $C_{25}H_{25}O_1N_2S_1^+$ requires MH^+, 401.11682); (2*R*,4*S*,5*S*)-*syn*,*anti*-**6**; colourless oil; R_F [CH_2Cl_2] 0.44; ν_{max} ($CHCl_3$) cm^{-1} 3020 (N–H), 1215 (C=S) and 1705 (C=O); $[\alpha]_D^{25}$ −161.0 (*c* 0.8, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 7.35–7.27 (4H, m, 4 × CH; Ph), 7.23–7.06 (9H, m, 9 × CH; Ph), 6.77 (2H, d, *J* 8.8, 2 × CH; Ph), 6.14 (1H, t, *J* 7.5, PhCHEt), 5.37 (1H, d, *J* 5.4, PhC*H*NCO), 4.42 (1H, d, *J* 5.4, PhCHN), 2.04–1.93 (1 H, ddq, *J* 13.7, 7.5 and 7.3, $CH_AH_BCH_3$), 1.70–1.58 (1H, ddq, *J* 13.7, 7.5 and 7.3, $CH_AH_BCH_3$) and 0.79 (3H, t, *J* 7.3, $CHCH_2CH_3$); δ_C (100 MHz; $CDCl_3$) 180.4 (C=S), 175.2 (C=O), 138.9 (*i*-C; Ph), 138.7 (*i*-C; Ph), 138.4 (*i*-C; Ar), 129.3[2] (2C, 2 × CH; Ph), 129.0[3] (3C, 3 × CH; Ph), 128.8[2] (2C, 2 × CH; Ph), 128.2[2] (2C, 2 × CH; Ph), 128.1[1] (1 × CH; Ph), 126.9[1] (1 × CH; Ar), 125.9[2] (2C, 2 × CH; Ph), 125.7[2] (2C, 2 × CH; Ar), 71.6 (PhCHNCO), 64.9 (PhCHN), 51.2 (PhCHEt), 26.8 (CH_2CH_3) and 12.0 (CH_2CH_3) (found MH^+, 401.1678; $C_{25}H_{25}O_1N_2S_1^+$ requires MH^+, 401.1682).

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