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Synthesis and biocatalytic resolution of a new atropisomeric thiobiphenyl: (2,2′,6,6′-tetramethoxybiphenyl-3,3′-diyl)dimethanethiol

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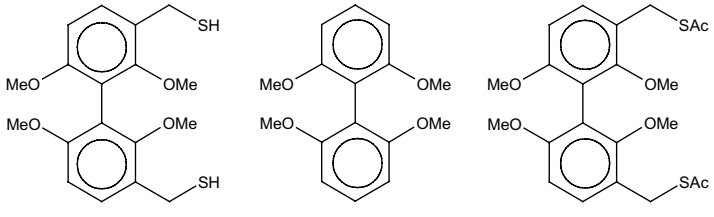
Abstract—Both atropisomers of racemic thiobiphenyl (±)-**1** were obtained in enantiopure form using lipase catalysed procedures. The esterification reaction of (±)-**1** in the presence of vinyl acetate gave in a one-pot reaction (+)-**1** and (−)-**1** via a lipase assisted dynamic kinetic resolution of epimerizing hemithioacetal intermediates. The alcoholysis of the diacetylthioester, (±)-**5**, is an alternative strategy for access to the enantiomers of **1** with high enantiomeric excess.

1. Introduction

Atropisomeric biphenyls are well established as one of the most important classes of ligands in asymmetric synthesis.[1] What is notably promising is their emerging use in the design of self-assembled monolayers on surfaces relevant as biosensors. In this context, biphenyl thio derivatives are particularly attractive due to their easy anchorage to Au and Ag substrates[2] as well as frameworks to build up macropolycyclic devices with a cavity able to complex sulfur-affinity metals.[3] Different papers have reported the effect of the structural features of these atropisomeric molecules on the orientation and packing, and this influence is more marked and better tunable when chiral biphenyls are considered.[4] In general, the preparation of enantiopure axially chiral biphenyl is a demanding task and in this context enzymatic resolution of racemic mixtures could be an effective method, making it possible to access both enantioforms. Although lipases have been used to catalyse the enantioselective esterification of different atropisomeric binaphthyls successfully,[5] little attention has been paid to biphenyls. Only one case has been reported to date, by us, regarding the use of four different *Pseudomonas cepacia* preparations to obtain the kinetic resolution of 6,6′-dimethoxybiphenyl-2,2′-diol.[6]

In our ongoing research program aimed at the synthesis of hydroxylated biphenyls, we have now considered the synthesis of a new C_2-symmetric atropisomeric methanethiol biphenyl the (2,2′6,6′-tetramethoxybiphenyl-3,3′-diyl)dimethanethiol, (±)-**1**, and its resolution. This



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last objective has been realised using two different biocatalytic strategies: the first resorting to the direct esterification of (±)-**1**, in an organic solvent, catalysed by lipase from *P. cepacea* (PS-D) in the presence of vinyl acetate as the acylating agent, while the second method is the alcoholysis of the corresponding acetate derivative (±)-**5** employing the same enzyme and *n*-butanol as nucleophile.

2. Results and discussion

2.1. Synthesis of (±)-1

In the synthesis of (±)-**1**, we have resorted to a well proved established strategy, by exploiting as the starting material the tetramethoxyderivative **2**, obtained in high yield by known literature procedures.[7] Substitution at the 3 and 3′ positions allows the desymmetrisation of this prochiral biphenyl, supplying a couple of atropisomers. In order to introduce two methanethiol groups in the first step, **2** was directly subjected to bromomethylation in the presence of 33% HBr in acetic acid and paraformaldehyde at 50 °C. The use of catalytic amounts of benzyltriethylammonium tribromide [BTEA·Br_3] allowed us to reduce the reaction time and temperature with respect to the usual conditions (Scheme 1).[8]

The course of the reaction occurred with complete regioselectivity, giving in high yield the desired racemic (±)-**3**. Treatment of (±)-**3** with thiourea in water under reflux for 7 h, gave biphenyl dimethanethiol (±)-**1** in quantitative yield.[9] Biphenyl (±)-**1**, solid and air stable, was further exploited without purification. No disulfide derivatives were detected during the reaction time.

2.2. Preparation of enantiopure (−)-1 and (+)-1 by biocatalytic procedures

2.2.1. Esterification of (±)-1. In order to have the synthesised thiobiphenyl enantiomerically pure we first considered the enantiomeric separation of (±)-**1** synthesised direct esterification, exploiting its free –SH functions, using *tert*-butyl methyl ether (*t*-BME) and vinyl acetate as acyl donor in the presence of lipase from *P. cepacia* adsorbed on kaolin mineral (PS-D), already used in our previous work.[6] After a 24 h reaction time, several products were detected in the reaction medium, all of which were different from the synthetic standards previously prepared by conventional acetylation of (±)-**1**. In seven days the total conversion of the substrate was observed, with TLC analysis of the crude reaction mixture showing only two spots of comparable intensity. The chromatographic purification of the reaction mixture afforded two compounds, **1a** and **1b**, whose NMR analyses showed very similar signal patterns, and a limited number of resonances, justified by a molecular C_2 symmetry for both products. The occurrence of one singlet resonance consistent with the presence of an acetyl group together with one doublet and one quartet, respectively, at 1.54 and 6.10 ppm, for compound **1a**, and 1.54 and 6.06 for **1b**, consistent with a –$CHCH_3$ group, indicated the formation of acetylated hemithioacetal groups in both compounds. These spectral properties in association with the observation that the chemical hydrolysis of **1a** and **1b** provided (−)-**1** (ee 91%) and (+)-**1** (ee 96%), respectively,[10] highlighted that the reaction had resulted in the formation of two diastereoisomers each containing two new homochiral stereogenic centres (Scheme 2).

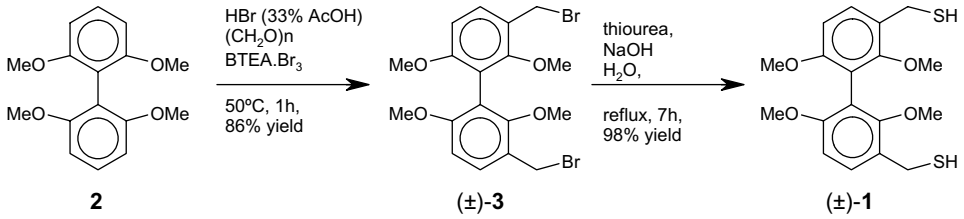
The absolute configuration of (+)-**1** and (−)-**1** was assigned as a*S* and a*R*, respectively, by comparison of their CD Cotton effects with that observed for the known biphenyl sulphide (+)-**4**[11] (Fig. 1).

The observed results prove that the thiol groups considered are weak nucleophiles to suffer acetylation by the acyl-enzyme species and the direct esterification of (±)-**1** does not occur.[12] On the other hand the presence of acetaldehyde in the solution, produced by the vinyl acetate in the primary step of the reaction (see Scheme 3), allows the formation of the corresponding hemithioacetal suitable for further esterification.

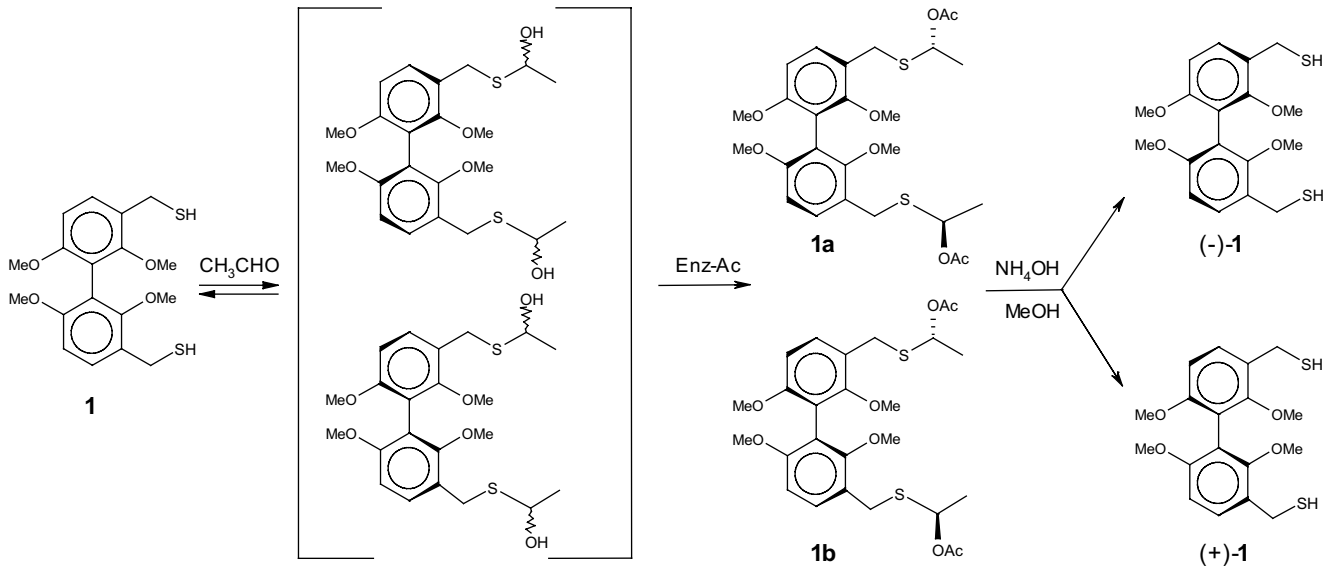
The known high *R*-stereoselectivity in the PS-D central chirality recognition (supposed also in this case) and the reversible nature of the reaction between the thiol and aldehyde, generate a dynamic resolution of the new stereogenic centres with a final result in which **1a** and **1b** were the favoured products.

This mechanism, also observed by Brand et al.[13] in the biocatalytic resolution of an epimerising hemithioacetal, was confirmed by two additional experiments in our case. In the first one, performed using isopropenyl acetate instead of vinyl acetate, no appearance of the product was detected; in the second experiment, in which acetaldehyde was added at the start, a significant enhancement of the reaction rate was observed with the formation of **1a** and **1b**.

In terms of molecular recognition it is noteworthy that lipase PS-D showed very poor selectivity regarding the



Scheme 1. Synthesis of (±)-(2,2′,6,6′-tetramethoxybiphenyl-3,3′-diyl)dimethanethiol], (±)-**1**.



Scheme 2. PS-D-catalysed dynamic resolution of (±)-**1** in the presence of vinyl acetate in *t*-BME.

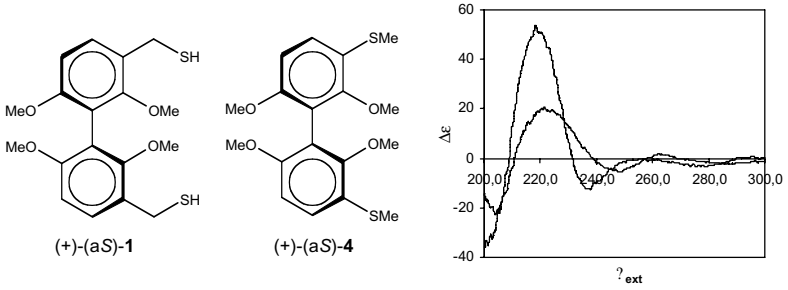
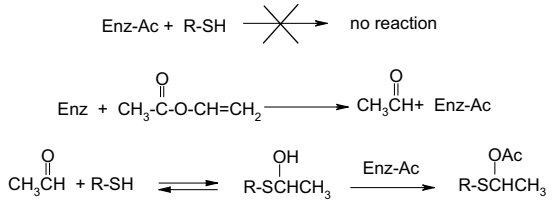


Figure 1. CD spectra of (+)-(a*S*)-**1** (line) and reference compound (a*S*)-2,2′,6,6′-tetramethoxy-3,3′-bis(methylsulfanyl)biphenyl (+)-**4**[11] (bold).



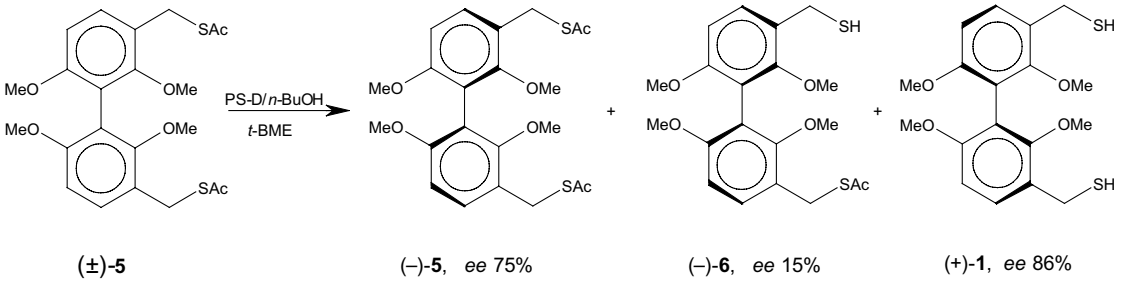
Scheme 3. Lipase-catalysed formation and esterification of a hemithioacetal group.

axial chirality, as evidenced by the low ee value (18%) measured for the unreacted substrate in an esterification reaction stopped about 50% conversion. This low atropo-discrimination operated from PS-D on the enantiomers of (±)-**1**, can be understood by the distance between the new generated –OH groups from the asymmetric axis. Conversely the high steric recognition of the enzyme for the central chirality is supported by the presence of two single reaction products both possessing molecular C_2 symmetry.

2.2.2. Alcoholysis of (±)-5. Alcoholysis of acetate derivative (±)-**5** was considered as an alternative way to have access to enantiopure **1** assuming a more favourable atropo-discrimination of the lipase, due to a greater influence of the molecular asymmetry on the enzymatic recognition.

Thus diacetylthioester (±)-**5**, prepared from (±)-**1** by conventional acetylation, was subjected to treatment with *n*-BuOH in *t*-BME in the presence of PS-D (Scheme 4).

The reaction gave a conversion of 47% in 72 h and a 48% ee value measured for the residue (−)-**5**, showing a low axial enantioselectivity ($E = 5$)[14] for PS-D in this process. Considering that the alcoholysis of (±)-**5** to give (+)-**1** involves two different steps, we have also investigated the alcoholysis of the racemic (±)-**6**. This had a slower reaction rate with respect to the alcoholysis of (±)-**5**, associated with a comparable enantioselectivity ($E = 4$). In spite of these results, the use of the alcoholysis of (±)-**5** for the preparative resolution of biphenyl (±)-**1** is possible by kinetic control of the reaction. So in a preparative experiment, by prolonging the alcoholysis until 66% substrate conversion, unreacted (−)-**5** was isolated with 75% ee, monoester (−)-**6** with 15% ee and thiol (+)-**1** with 86% ee. Chemical hydrolysis of (−)-**5** and successive crystallisation of the obtained thiols from *t*-BME allowed us to recover enantiopure (+)-**1** and (−)-**1** from the mother liquor.



Scheme 4. PS-D catalysed alcoholysis of (±)-**5** in the presence of *n*-BuOH in *t*-BME.

With the aim of obtaining a catalyst with higher selectivity immobilised lipases from different sources, *Mucor miehei* (Lipozyme®) and *Candida antarctica* (Novozyme 435) were considered as catalysts in the alcoholysis reaction of (±)-**5**. In these experiments no significant improvement in the enantiomeric ratio of the process with respect to PS-D was observed. Conversely, an axial *R* stereopreference was evidenced for both these enzymes. Considering that in the central chiral recognition of secondary alcohols both lipases from *P. cepacia* and from *Mucor miehei* are reported to have the same stereopreference, this result appears interesting and will be further investigated.

3. Conclusions

In summary, we have synthesised a new C_2-symmetric chiral thiomethanebiphenyl in racemic form and developed two enzymatic procedures, based on esterification and alcoholysis, to obtain the single enantiomers. Although PS-D was not able to carry out direct esterification of free –SH groups, the enantiomeric separation of thiol (±)-**1** has been achieved by a dynamic kinetic resolution of epimerising hemithioacetal moieties spontaneously generated in the presence of vinyl acetate used as acyl donor. Conversely, PS-D catalysed alcoholysis of diacetylthioester gave (±)-**5** with low enantioselectivity, although by kinetic control of the reaction, enantiomers (+)-**1** and (−)-**1** were obtained in satisfactory enantiomeric excess.

4. Experimental

4.1. General methods

Lipase preparation PS-D (lipase from *P. cepacia* immobilised on kaolin mineral) was obtained from Amano International Enzyme Co; Lipozyme® (lipase from *M. miehei* immobilised on a macroporous ion-exchange resin) and Novozyme 435 (lipase from *Candida antarctica* immobilised on acrylic resin) were purchased from Fluka and Aldrich, respectively.

Thin-layer chromatography (TLC) was carried out on Merck silica gel 60-F_{254} precoated glass plates and the compounds detected by charring with molybdophosphoric acid. Preparative liquid chromatography was performed using LiChroprep® Si 60 (25–40 μm) or LiChroprep® DIOL (25–40 μm) from Merck.

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance™ 400 instrument at 400.13 and 100.03 MHz, respectively. Chemicals shifts (δ) are reported in ppm relative to TMS and coupling constants (J) in hertz. Optical rotations were recorded on a DIP 135 JASCO instrument using a $\varnothing 3.5 \times 100$ mm cell. The enantiomeric excess of **5** was determined by chiral HPLC analysis using a Chiralcel® OD (Daicel Chemical Industries) column eluting with 98.5:1.5 *n*-hexane:ethanol mixture at 0.4 ml/min flow rate: t_R/min = 40.16 for the (*R*)-enantiomer and 43.07 for (*S*)-enantiomer. The enantiomeric excesses of **6** and **1** were determined by chiral HPLC analysis after exhaustive chemical acetylation with standard procedure of the isolated compounds. CD spectra were registered at room temperature in CH_3CN (0.1 cm cell length) on a JASCO J-810 spectropolarimeter.

4.2. Synthesis of (±)-2,2′,6,6′-tetramethoxybiphenyl-3,3′-diyl)dibromomethane, (±)-3

To a solution of 2,2′,6,6′-tetramethoxy-1,1′-biphenyl **2** (2.1 g, 7.75 mmol) in acetic acid (10 ml) was added with vigorous magnetic stirring, HBr (33% in acetic acid, 32.15 mmol, 2.60 g), benzyltriethylammonium tribromide (0.16 mmol, 0.05 g) and paraformaldehyde (0.48 g, 16.07 mmol). The solution was stirred at 50 °C for 1 h, then water (100 ml) and a saturated aqueous solution of $Na_2S_2O_5$ (50 ml) added to the mixture. The organic phase was dried over Na_2SO_4 and evaporated to afford a colourless solid that was purified by flash chromatography using a 1:1 mixture of ethyl acetate: petroleum, as eluent to give (±)-**3** as a colourless solid (3.03 g, yield 86%); mp 214–215 °C. ^{1}H NMR δ 3.47 (s, 6H), 3.76 (s, 6H), 4.53 (d, J = 12.8, 2H), 4.76 (d, J = 12.8, 2H), 6.75 (d, J = 11.2, 2H), 7.41 (d, J = 11.2, 2H); ^{13}C NMR δ 29.59, 55.95, 60.81, 106.82, 117.40, 123.74, 131.41, 157.66, 159.19. Anal. Calcd for $C_{18}H_{20}Br_2O_4$: C, 46.98; H, 4.38. Found: C, 46.81; H, 4.19.

4.3. Synthesis of (±)-(2,2′,6,6′-tetramethoxybiphenyl-3,3′-diyl)dimethanethiol, (±)-1

To a solution of (±)-**3** (1.13 g, 2.45 mmol) in water (50 ml), thiourea (0.56 g, 7.37 mmol) was added in one pot. The reaction mixture was stirred at reflux for 6 h. A solution of NaOH (0.4 g, 10 mmol) in water (10 ml) was then added and the solution refluxed for 1 h. Water was added and the solution then extracted with CH_2Cl_2.

The crude was dried over Na_2SO_4 and gave a colourless solid that was used in the next reaction without purification (0.88 g, yield 98%). (±)-**1**; mp 135.5 °C. ^{1}H NMR δ 1.84 (t, J = 10.0, 2H), 3.38 (s, 6H), 3.68 (s, 6H), 3.73 (m, 4H), 6.68 (d, J = 11.6, 2H), 7.27 (d, J = 11.6, 2H); ^{13}C NMR δ 23.76, 56.18, 61.10, 106.93, 116.90, 126.97, 129.81, 156.97, 158.05. Anal. Calcd for $C_{18}H_{22}S_2O_4$: C, 58.99; H, 6.05; Found: C, 58.87; H, 5.99.

4.4. PS-D catalysed esterification of (±)-1

To a solution of (±)-**1** (200 mg, 0.54 mmol) in *t*-BME (40 ml) was added enzyme (1 g), acetaldehyde (0.8 ml, 7.1 mmol) and vinyl acetate (1 ml, 10.8 mmol). The suspension was shaken at 300 rpm and 42 °C. The reaction was stopped by filtering-off the enzyme after 5 days. Chromatographic purification on LiChroprep® DIOL eluting with cyclohexane:diisopropyl ether 30:70 gave, Compound **1a**: 87 mg (yield 30%) ^{1}H NMR 1.54 (d, J = 6.5, 6H), 2.05 (s, 6H), 3.38 (s, 6H), 3.72 (s, 6H), 3.84 (d, J = 12.9, 2H), 3.96 (d, J = 12.9, 2H), 6.10 (q, J = 6.5, 2H), 6.70 (d, J = 8.5, 2H), 7.30 (d, J = 8.5, 2H); ^{13}C NMR 21.19, 21.27, 29.51, 55.87, 60.9, 75.68, 106.39, 117.68, 123.14, 130.25, 157.29, 157.99, 170.5. Compound **1b**: 92 mg (yield 32%), ^{1}H NMR 1.54 (d, J = 6.5, 6H), 2.03 (s, 6H), 3.41 (s, 6H), 3.71 (s, 6H), 3.85 (d, J = 12.8, 2H), 3.97 (d, J = 12.8, 2H), 6.06 (q, J = 6.5, 2H), 6.69 (d, J = 8.5, 2H), 7.29 (d, J = 8.5, 2H); ^{13}C NMR 21.18, 21.43, 29.83, 55.89, 60.79, 75.89, 106.39, 117.73, 123.13, 130.19, 157.32, 158.01, 170.42.

Hydrolysis of isolated **1a** was performed in CH_3OH by the addition of NH_4OH at room temperature. After 30 min, CH_2Cl_2 was added to the reaction mixture and the organic phase washed with a saturated NH_4Cl solution. The organic phase was dried and evaporated in vacuo to obtain a white solid (−)-**1** with 91% ee, which after crystallisation from *t*-BME was recovered from the mother liquor in enantiopure form (ee = 96%) $[\alpha]_D^{25} = -40.1$ (c 0.35, $CHCl_3$). Hydrolysis of **1b** performed as above gave (+)-**1** with 96% ee. Crystallisation from *t*-BME gave in the mother liquor (+)-**1** with ee >98% $[\alpha]_D^{25} = +40.9$ (c 0.55, $CHCl_3$). CD: λ_{ext} 291.9 ($\Delta\varepsilon$ +0.18), 277.3 ($\Delta\varepsilon$ −3.21), 25.1 ($\Delta\varepsilon$ −0.36), 235.9 ($\Delta\varepsilon$ −11.96), 219.0 ($\Delta\varepsilon$ +51.66), 201.9 ($\Delta\varepsilon$ −31.68).

The CD spectrum of the reference compound[11] was registered under the same conditions (+)-(a*S*)-2,2′,6,6′-tetramethoxy-3,3′-bis(methylsulfanyl)biphenyl, (+)-**4**, CD: λ_{ext} 290.1 ($\Delta\varepsilon$ −1.86), 262.1 ($\Delta\varepsilon$ +1.79), 247.7 ($\Delta\varepsilon$ −5.24), 220.3 ($\Delta\varepsilon$ +20.31), 203.6 ($\Delta\varepsilon$ −22.60).

4.5. Synthesis of (±)-(*S*,*S*′)-[(2,2′,6,6′-tetramethoxybiphenyl-3,3′-diyl)bis(methylene)]diethanethioate, (±)-5

To a solution of (±)-**1** (300 mg, 0.82 mmol) in CH_2Cl_2 (3 ml) was added pyridine (265 μl, 3.28 mmol) and acetic anhydride (309 μl, 3.28 mmol). After 24 h at room temperature, the mixture was washed with water and the organic phase dried, filtered and evaporated in vacuo. The product of the reaction, (±)-**5**, was obtained with 90% yield (332 mg): ^{1}H NMR 2.34 (s, 3H), 3.37 (s, 6H), 3.73 (s, 6H), 4.16 (d, J = 13.5, 2H), 4.21 (d, J = 13.5, 2H), 6.70 (d, J = 8.5, 2H), 7.35 (d, J = 8.5, 2H).

4.6. General procedure for enzymatic alcoholysis of (±)-5

In a general enzymatic alcoholysis reaction 50 mg (0.11 mmol) of (±)-**5** was dissolved in 5 ml of *t*-BME and immobilised enzyme (250 mg) and *n*-BuOH (0.33 mmol) then added. The reactions were shaken at 300 rpm at 42 °C and monitored by TLC analysis. The conversions of substrate were determined by ^{1}H NMR analysis and ee of substrate was measured by HPLC analysis of the reaction mixture.

4.7. Preparative PS-D catalysed alcoholysis of (±)-5

Enzyme (650 mg) and *n*-BuOH (0.87 mmol) were added to a solution of (±)-**5** (130 mg, 0.29 mmol) in 13 ml of *t*-BME. The suspension was shaken at 300 rpm and 42 °C. The reaction was stopped and the enzyme filtered off after 8 days; the substrate conversion (66%) was determined by HPLC analysis and confirmed by methoxyl singlet peaks integration in the ^{1}H NMR spectrum. Chromatographic purification on LiChroprep® Si 60 eluting with pentane: CH_2Cl_2 40:60 mixture to 0:100% furnished: (−)-**5** 38 mg (yield 26%), ee 75%, $[\alpha]_D^{25} = -42.7$ (c 0.62, $CHCl_3$); (+)-**1** 33.0 mg (yield 28%), ee 86% and (a*R*)-(*S*)-[2,2′,6,6′-tetramethoxy-3′-(sulfanylmethyl)biphenyl-3-yl]methylethanethioate (−)-**6** 31 mg (yield 23%), ee 15%, $[\alpha]_D^{25} = -8.8$ (c 0.52, $CHCl_3$), ^{1}H NMR 1.89 (t, J = 7.5, 1H), 2.35 (s, 3H), 3.39 (s, 3H), 3.44 (s, 3H), 3.74 (s, 3H), 3.75 (s, 3H), 3.80 (d, J = 7.5, 2H), 4.17 (d, J = 13.5, 2H), 4.21 (d, J = 13.5, 2H), 6.73 (m, 2H), 7.35 (m, 2H); ^{13}C NMR 23.39, 28.27, 30.34, 55.91, 60.67, 60.83, 106.49, 106.70, 117.32, 117.48, 122.84, 126.75, 129.58, 130.44, 156.74, 157.36, 157.82, 158.12, 195.77.

4.8. Enzymatic alcoholysis of monoacetylthioester (±)-6

Substrate 20 mg (0.05 mmol), obtained by conventional acetylation procedure, was dissolved in *t*-BME (2 ml) and 100 mg of PS-D and *n*-BuOH (0.1 mmol) were added. The reaction mixture was shaken at 300 rpm and 42 °C for 5 d. After this time, the reaction was stopped and the mixture analysed by ^{1}H NMR analysis to determine the conversion of substrate (32%). The enantiomeric excess of (+)-**1** (ee 55%) was determined by chiral HPLC analysis of the product isolated and acetylated.

Acknowledgements

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