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Selective lipase-catalyzed acylation of epimeric α-sulfinyl alcohols: an efficient method of separation

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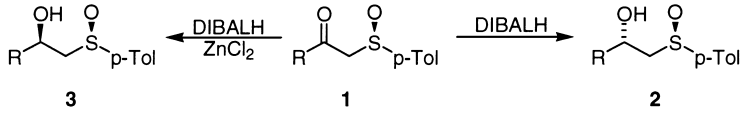
Abstract

A facile and efficient separation of mixtures of epimeric α-sulfinyl alcohols **2**:**3** can be accomplished by selective lipase-catalyzed acylation with neat vinyl acetate. *Pseudomonas cepacia* and *Candida rugosa* lipase showed opposite epimer differentiation in the esterification.

1. Introduction

Enantiomerically pure sulfoxides are now widely used to bring about numerous asymmetric transformations.[1,2] In particular, the diastereocontrolled reduction of α-sulfinyl ketones, which leads to enantiomerically pure alcohols after elimination of the sulfinyl group, has been frequently reported. By applying this strategy, Solladié was able to synthesize several natural compounds.[1] In addition to their application as building blocks, α-sulfinyl alcohols are also effective chiral proton sources for the enantioselective protonation of prochiral enolates.[3,4] The most suitable method for preparing enantiopure α-sulfinyl alcohols is the stereoselective reduction of α-sulfinyl ketones **1** with DIBALH or DIBALH/$ZnCl_2$[5] to yield the diastereomers **2** or **3**, respectively (Scheme 1).



3 **1** **2**

a, R:Me; **b**, R: Et; **c**, R: Pr; **d**, R:Allyl

Scheme 1. Preparation of α-sulfinyl alcohols.

The utility of this method depends on a highly diastereoselective reduction (d.e. >95%), since mixtures of α-sulfinyl alcohols **2** and **3** are very difficult to separate. The degree of diastereoselection achieved in

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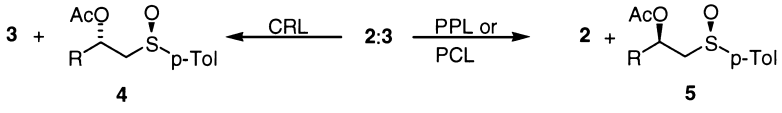
the reduction with DIBALH is highly dependent on the nature of the R group bonded to the carbonyl carbon. When R is a non-branched or a small group, reduction with DIBALH gives d.e. values of about 80%, whereas with DIBALH/$ZnCl_2$, diastereoselection fails with α-sulfinyl ketones bearing coordinating groups.[6] Consequently, this methodology could be greatly improved if a straightforward and efficient procedure for separating the sulfinyl alcohol diastereoisomers **2** and **3** was found.

The lipase-catalyzed transesterification of hydroxylated substrates in organic solvents is now a well-established method that has been extensively used to prepare enantiomerically pure chiral compounds.[7] This prompted us to apply this enzyme method to obtain enantiopure α-sulfinyl alcohols by kinetic separation of the mixture of diastereoisomers obtained in the reduction of α-sulfinyl ketones.

2. Results and discussion

In the course of our studies on the enantioselective protonation reaction of enolates with α-sulfinyl alcohols, we needed to prepare α-sulfinyl alcohols **2a**–**d**.[3] Reduction of the corresponding α-sulfinyl ketones **1a**–**d** with DIBALH was performed according to previous literature,[8,9] with only partial stereoselection, leading to the major diastereomer **2** along with the inseparable minor epimer **3**. Attempts to purify alcohols **2a**–**d** by crystallization gave unsatisfactory yields (~60%), and preparation of the corresponding acetates did not allow chromatographic purification. On the other hand, we achieved efficient epimer separation by using lipase-catalyzed acylation reactions that enabled the selective conversion of **2** and **3** to their corresponding acetates **4** and **5** (Scheme 2). Acetylation was assayed with three commercially available lipases: porcine pancreatic lipase (PPL), *Pseudomonas cepacia* lipase (PCL) and *Candida rugosa* lipase (CRL).



4 5

Scheme 2. Selective enzyme mediated acylation of α-sulfinyl alcohols

The preparation of α-sulfinyl alcohol (*S*,*R*s)-**2a** in a enantiomerically pure form has been reported previously, and involves the diastereoselective oxidation of the corresponding chiral *p*-tolylthio alcohol to give a (2:1) diastereomeric mixture of (*S*,*R*s)-**2a**:(*S*,*S*s)-**3a**.[10] Using a complex protocol of crystallization, the isolation of (*S*,*R*s)-**2a** from this mixture in 51% yield has been described. By contrast, our procedure, which is based on enzyme-catalyzed acylation using lipases and vinyl acetate (VA) allows us to obtain readily (*S*,*R*s)-**2a** with a better yield and also a high enantiomeric excess. α-Sulfinyl ketone **1a** was reduced with DIBALH to give a 90:10 mixture of **2a**:**3a**. This mixture was allowed to react with neat VA in the presence of PPL (2 mg/mg of alcohol) at room temperature for 3 days, and the lipase was renewed every 24 h (entry 1). Under these conditions, complete conversion of (*R*,*R*s)-**3a** into the acetate derivative (*R*,*R*s)-**5a** took place with high selectivity, while nearly optically pure (*S*,*R*s)-**2a** was recovered in 93% yield (72% yield from α-sulfinyl ketone). The reaction time could be shortened by increasing the temperature to 40°C without any loss of selectivity (entry 2). A faster and also highly selective conversion of (*R*,*R*s)-**3a** to (*R*,*R*s)-**5a** was achieved by using VA and PCL (1 mg/mg of alcohol) instead of PPL (entry 3). When acylation was catalyzed by CRL (2 mg/mg alcohol), (*S*,*R*s)-**2a** reacted rapidly, and the corresponding derivative (*S*,*R*s)-**4a** was obtained in 70% yield and >90% d.e. (entry 4). No improvement in the yield of (*S*,*R*s)-**4a** was achieved with longer reaction times (entry 5). The reverse selectivity showed by CRL and PCL towards **2a** and **3a**, respectively, reflected the general trend followed by all the α-sulfinyl alcohols in the series; CRL preferentially acylated alcohol **2** while PCL preferably acylated its

epimer **3**. This result is opposite many examples found in the literature, where these lipases are reported to show the same selectivity.[11]

The enzymatic acylation reaction was also applied to the mixture of α-sulfinyl alcohols epimers **2b**:**3b**. When PPL was used, longer reaction times were required (five days) than in the separation of the mixture **2a**:**3a**. On the other hand, the acylation reaction was even more selective, since no formation of the (*S*,*R*s)-**4b** derivative could be detected (entries 6 and 7). The results in the acylation of the mixture **2b**:**3b** with PCL and CRL were comparable to those obtained in the separation of the mixture **2a**:**3a** (entries 8 and 9).

PPL was not effective for promoting the acylation of alcohol (*R*,*R*s)-**3c**, probably because of the greater size of the R group, and the mixture **2c**:**3c** was recovered unchanged after prolonged heating at 40°C (entries 10 and 11). However, when the mixture **2c**:**3c** was treated with VA and PCL (1 mg/mg alcohol) for 64 h, (*R*,*R*s)-**3c** could be converted into the acetate (*R*,*R*s)-**5c** with high yield and d.e., while the alcohol (*S*,*R*s)-**2c** was recovered unchanged (entry 12). No appreciable reduction in the reaction time (24 h) was observed by using 2 mg of lipase/mg alcohol (entry 13). On the other hand, CRL promoted the acylation of (*S*,*R*s)-**2c** with VA to give (*S*,*R*s)-**4c** with high diastereoselectivity (entry 14).

Lipase-catalyzed acylation was also successfully applied to the mixture of α-sulfinyl alcohols **2d**:**3d**, which are precursors of allylic alcohols. When VA/PPL or PCL were used, acylation of alcohol (*R*,*R*s)-**3d** took place, but the reaction proceeded very slowly (entries 15–17). CRL required long reaction times also to transform the alcohol (*S*,*R*s)-**2d** into the ester (*S*,*R*s)-**4d**. Despite the relatively long reaction time required, purification of this mixture by diastereoselective acetylation appears to be the procedure of choice for these alcohols due to the difficulty of obtaining optically pure crystalline products by fractional crystallization.

3. Conclusions

Since α-sulfinyl ketones are readily obtained by reacting α-sulfinyl carbanions with esters, the diastereoselective reduction of α-sulfinyl ketones with DIBALH is a suitable method for obtaining α-sulfinyl alcohols **2**. However, in some instances where the diastereoselectivity of the reduction is only moderate, the simultaneous formation of the diastereomer **3** limits the scope of this method. The lipase-catalyzed acylation of the mixture of alcohols **2** and **3** allows us to overcome this drawback. In addition, provided that PCL and CRL show the opposite selectivity for each diastereomer, this method can be applied in all cases in which the diastereoselectivity in the reduction of the corresponding ketone is not complete, and allows us to obtain alcohols **2** or **3** of high optical purity as desired. This method has considerable advantages regarding yields and optical purity and allows us to isolate the products while avoiding cumbersome time-consuming derivatization or crystallization procedures.

4. Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-250 with tetramethylsilane as an internal reference and $CDCl_3$ as a solvent. Melting points were determined with a Cambridge Instruments apparatus and are uncorrected. Optical rotation measurements were determined on a Perkin–Elmer 241 polarimeter at room temperature. High resolution mass spectra (HRMS) were recorded on a Fisons VG Autospec instrument. Lipases were purchased from Sigma (PPL and CRL) and Amano (PCL). Ketones **1a**–**d** were prepared as described in previous literature.[8,9,12]

Table 1
Enzymatic selective acylation of α-sulfinyl alcohols with VA

Entries	**2**:**3** (ratio)	Lipase[a]	T(°C)/ t(h)	Major Product (% yield) (% d.e.)[b]	Minor Products (ratio)
1	**2a**:**3a** (90:10)	PPL[c]	r.t./ 72	**2a** (93) (>90)	**4a**:**5a** (8:92)
2	**2a**:**3a** (90:10)	PPL[c]	40/ 36	**2a** (90) (>90)	**4a**:**5a** (15:85)
3	**2a**:**3a** (90:10)	PCL[d]	r.t./ 8	**2a** (90) (>90	**4a**:**5a** (8:92)
4	**2a**:**3a** (90:10)	CRL	r.t/ 14	**4a** (75) (>90)	**2a**:**3a** (38:62)
5	**2a**:**3a** (90:10)	CRL	r.t. /10	**4a** (75) (>90)	**2a**:**3a** (34:66)
6	**2b**:**3b** (88:12)	PPL[c]	r.t./ 110	**2b** (92) (>90)	**4b**:**5b** (>5:95)
7	**2b**:**3b** (88:12)	PPL[c]	40/ 79	**2b** (88) (>90)	**4b**:**5b** (>5:95)
8	**2b**:**3b** (88:12)	PCL[d]	r.t./ 10	**2b** (97) (>90)	**4b**:**5b** (>5:95)
9	**2b**:**3b** (88:12)	CRL	r.t./ 21	**4b** (80) (>90)	**2b**:**3b** (45:55)
10	**2c**:**3c** (89:11)	PPL[c]	r.t./ 264	-	-
11	**2c**:**3c** (89:11)	PPL[c]	40./ 192	-	-
12	**2c**:**3c** (89:11)	PCL[d]	r.t./ 64	**2c** (90) (>90)	**4c**:**5c** (10:90)
13	**2c**:**3c** (89:11)	PCL	r.t./ 48	**2c** (81) (>90)	**4c**:**5c** (19:81)
14	**2c**:**3c** (89:11)	CRL[c]	r.t./ 72	**4c** (89) (>90)	**2c**:**3c** (45:55)
15	**2d**:**3d** (90:10)	PPL[c]	r.t./ 144	**2d** (90) (85)	**4d**:**5d** (5:95)
16	**2d**:**3d** (90:10)	PPL[c]	40/ 120	**2d** (90) (88)	**4d**:**5d** (5:95)
17	**2d**:**3d** (90:10)	PCL[e]	40/ 240	**2d** (92) (>90)	**4d**:**5d** (>5:95)
18	**2d**:**3d** (90:10)	CRL[c]	r.t./120	**4d** (55)(>90)	**2d**:**3d** (21:79)

a: 2 mg of lipase/mg alcohol were used otherwise noted.
b: Determined by ^{1}H-NMR; (>90) means that no other diastereoisomer could be even detected.
c: Lipase was renewed each 24 h.
d: 1mg of lipase/mg alcohol.
e: Lipase was renewed each 120 h.

*4.1. General procedure for the lipase-catalyzed acylation of alcohols **2**:**3***

To a solution of alcohols **2**:**3** in neat VA was added the appropriate lipase (1 or 2 mg/mg alcohol). The reaction mixture was vigorously stirred for the time and temperature shown in Table 1. The reaction was stopped by enzyme filtration and purified by column chromatography.

*4.2. (*S,R*s)-(+)-1-(4-Methylphenylsulfinyl)-2-propanol **2a***

Yield 93%; m.p. 130–131°C (lit.[10] 128°C); $[\alpha]_D$=+258.0 (c=1, ethanol) (lit.[10] +314.5); ^{1}H NMR, δ 1.24 (d, 3H, J=7.5 Hz), 2.43 (s, 3H), 2.62 (dd, 1H, J=12.5 and 1.8 Hz), 3.08 (dd, 1H, J=12.5 and 10 Hz), 4.07 (bb, 1H), 4.35–4.45 (m, 1H), 7.36 (d, 2H, J=7.5 Hz), 7.53 (d, 2H, J=7.5 Hz); ^{13}C NMR, δ 21.3 (q), 23.2 (q), 62.5 (t), 63.4 (d), 123.9 (d), 130.0 (d), 139.4 (s), 141.5 (s); HRMS analysis (EI, M^+): 198.0708, calcd ($C_{10}H_{14}O_2S$) 198.0714.

*4.3. (*S,R*s)-(+)-1-(4-Methylphenylsulfinyl)-2-butanol **2b***

Yield 97%; m.p.: 70–71°C. $[\alpha]_D$=+305.9 (c=2, $CHCl_3$). ^{1}H NMR, δ 0.90 (t, 3H, J=7.5 Hz), 1.44–1.65 (m, 2H), 2.43 (s, 3H), 2.65 (dd, 1H, J=12.5 and 2.5 Hz), 3.06 (dd, 1H, J=12.5 and 10 Hz), 3.75 (bb, 1H), 4.04–4.17 (m, 1H), 7.36 (d, 2H, J=7.5 Hz), 7.53 (d, 2H, J=7.5 Hz); ^{13}C NMR, δ 9.5 (q), 21.2 (q), 29.9 (t), 63.1 (t), 66.9 (d), 123.8 (d), 129.8 (d), 139.8 (s), 141.2 (s); HRMS analysis (EI, M^+): 212.0874, calcd ($C_{11}H_{16}O_2S$) 212.0871.

*4.4. (*S,R*s)-(+)-1-(4-Methylphenylsulfinyl)-2-pentanol* ***2c***

Yield 90%; m.p. 84–85°C; $[\alpha]_D$=+282.2 (c=2, $CHCl_3$); ^{1}H NMR, δ 0.88 (t, 3H, J=7.5 Hz), 1.29–1.62 (m, 4H), 2.42 (s, 3H), 2.75 (dd, 1H, J=13.2 and 2 Hz), 2.95 (dd, 1H, J=13.2 and 10 Hz), 4.15–4.31 (m, 1H), 4.61 (d, 1H, J=4 Hz), 7.33 (d, 2H, J=8 Hz), 7.53 (d, 2H, J=8 Hz); ^{13}C NMR, δ 13.7 (q), 18.3 (q), 21.3 (t), 39.1 (t), 63.1 (t), 65.6 (d), 123.8 (d), 129.9 (d), 139.7 (s), 141.3 (t); HRMS analysis (EI, M^+): 226.1032, calcd ($C_{12}H_{18}O_2S$) 226.1027.

*4.5. (*S,R*s)-(+)-5-(4-Methylphenylsulfinyl)-2-penten-4-ol* ***2d***

Yield 92%; m.p. 64–66°C; $[\alpha]_D$=+270 (c=2, $CHCl_3$); ^{1}H NMR, δ 1.67 (d, 3H, J=6.2 Hz), 2.42 (s, 3H), 2.74 (dd, 1H, J=13.2 and 2 Hz), 3.01 (dd, 1H, J=13.2 and 9.7 Hz), 4.01 (bb, 1H), 4.52–4.70 (m, 1H), 5.49 (ddd J=16.8, 6.3 and 1.5 Hz), 5.68–5.82 (m, 1H), 7.34 (d, 2H, J=8 Hz), 7.53 (d, 2H, J=8 Hz); ^{13}C NMR, δ 17.4 (q), 21.1 (q), 63.5 (t), 66.5 (d), 123.7 (d), 127.3 (d), 129.8 (d), 131.3 (d), 139.7 (s), 141.2 (s); HRMS analysis (EI, M^+): 224.0873, calcd ($C_{12}H_{16}O_2S$) 224.0871.

*4.6. (*S,R*s)-(+)-1-(4-Methylphenyl)sulfinylmethylethyl acetate* ***4a***

Yield 75%, $[\alpha]_D$=+178.6 (c=2, $CHCl_3$); ^{1}H NMR, δ 1.38 (d, 3H, J=6.5 Hz), 2.07 (s, 3H), 2.42 (s, 3H), 2.91–3.00 (m, 2H), 5.30–5.44 (m, 1H), 7.34 (d, 2H, J=8Hz), 7.55 (d, 2H, J=8 Hz); ^{13}C NMR, δ 19.9 (q), 20.2 (q), 21.1 (q), 63.7 (t), 65.2 (d), 123.6 (d), 129.8 (d), 140.5 (s), 141.4 (s), 169.7 (s); HRMS analysis (CI, MH^+): 241.0888, calcd ($C_{12}H_{17}O_3S$) 241.0898.

*4.7. (*S,R*s)-(+)-1-(4-Methylphenyl)sulfinylmethylpropyl acetate* ***4b***

Yield 80%, $[\alpha]_D$=+156.2 (c=2, $CHCl_3$); ^{1}H NMR, δ 0.92 (t, 3H, J=7.5 Hz), 1.68–1.81 (m, 2H), 2.08 (s, 3H), 2.42 (s, 3H), 2.85–3.01 (m, 2H), 5.21–5.33 (m, 1H), 7.34 (d, 2H, J=8 Hz), 7.54 (d, 2H, J=8 Hz); ^{13}C NMR, δ 8.8 (q), 20.6 (q), 21.0 (q), 26.8 (t), 61.9 (t), 69.2 (d), 123.5 (d), 129.7 (d), 140.5 (s), 141.3 (s), 169.7 (s); HRMS analysis (CI, MH^+): 255.1053, calcd ($C_{13}H_{19}O_3S$) 255.1054.

*4.8. (*S,R*s)-(+)-1-(4-Methylphenyl)sulfinylmethylbutyl acetate* ***4c***

Yield 89%, $[\alpha]_D$=+150.2 (c=2, $CHCl_3$); ^{1}H NMR, δ 0.82 (t, 3H, J=7.2 Hz), 1.15–1.31 (m, 2H), 1.49–1.67 (m, 2H), 1.99 (s, 3H), 2.32 (s, 3H), 2.75–2.92 (m, 2H), 5.15–5.31 (m, 1H), 7.25 (d, 2H, J=8 Hz), 7.46 (d, 2H, J=8 Hz); ^{13}C NMR, δ 13.5 (q), 17.9 (q), 20.7 (q), 21.1 (t), 36.0 (t), 62.5 (t), 68.2 (d), 123.7 (d), 129.8 (d), 140.5 (s), 141.5 (s), 169.9 (s); HRMS analysis (CI, MH^+): 269.1214, calcd ($C_{14}H_{21}O_3S$) 269.1211.

*4.9. (*S,R*s)-(+)-1-(4-Methylphenyl)sulfinylmethyl-2-butenyl acetate* ***4d***

Yield 55%; m.p. 94–96°C; $[\alpha]_D$=+208.5 (c=2, $CHCl_3$); NMR, ^{1}H δ 1.62 (dd, 3H, J=6.5 and 1.2 Hz), 2.01 (s, 3H), 2.35 (s, 3H), 2.90–2.94 (m, 2H) 5.31–5.42 (m, 1H), 5.55 (dd, 1H, J=13.5 and 7 Hz), 5.70–5.84 (m, 1H), 7.26 (d, 2H, J=8 Hz), 7.47 (d, 2H, J=8 Hz); NMR, ^{13}C δ 17.6 (q), 21.0 (q), 21.3 (q), 62.6 (t), 68.9 (d), 123.9 (d), 127.1 (d), 129.9 (d), 131.1 (d),140.6 (s), 141.6 (s), 169.5(s); HRMS analysis (EI, M^+) 266.0980, calcd ($C_{14}H_{18}O_3S$) 266.0976.

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