

Efficient Lipase-Catalyzed Kinetic Resolution and Dynamic Kinetic Resolution of β -Hydroxy Nitriles. Correction of Absolute Configuration and Transformation to Chiral β -Hydroxy Acids and γ -Amino Alcohols

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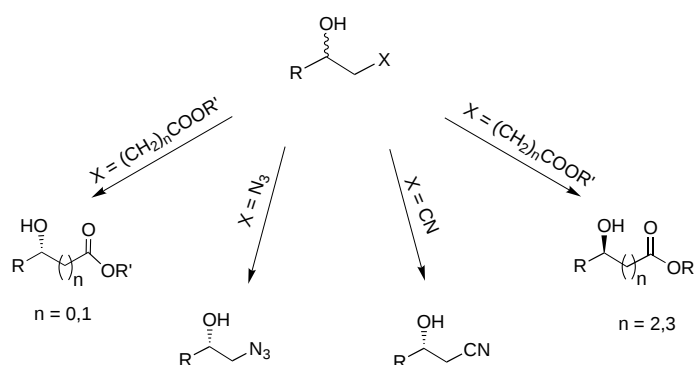
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Received: May 21, 2002; Accepted: July 4, 2002

Dedicated to Roger A. Sheldon on the occasion of his 60th birthday.

Abstract: Chemoenzymatic dynamic kinetic resolution of β -hydroxy nitriles **1** has been carried out using *Candida antarctica* lipase B and a ruthenium catalyst. The use of a hydrogen source to depress ketone formation in the dynamic kinetic resolution yields the corresponding acetates **2** in good yield and high enantioselectivity. It is shown that the ruthenium catalyst and the enzyme can be recycled when used in separate reactions. We also report on the preparation of various enantiomerically pure β -hydroxy acid derivatives and γ -amino alcohols from **1** and **2**. The latter compounds were also used to establish the correct absolute configuration of **1** and **2**.

Keywords: γ -amino alcohols; dynamic kinetic resolution; β -hydroxy acids; kinetic resolution; ruthenium



Scheme 1. Dynamic kinetic resolution of functionalized alcohols with efficient use of all racemate.

In a recent publication^[5d] we reported on the kinetic resolution (KR) of β -hydroxy nitriles (Scheme 1, $X = CN$) and gave a few examples of dynamic kinetic resolution (DKR). These compounds are potentially valuable for the synthesis of natural products and biologically active compounds. During the course of our studies on further functionalization of these enantiomerically pure nitriles we found that the absolute configuration of the β -hydroxy nitriles **1** and β -acetoxy nitriles **2** obtained *via* the lipase-catalyzed esterification were erroneously assigned.^[6] We now report on the determination of the correct stereochemistry for **1** and **2** and provide a complete study of the DKR reaction with additional examples and new protocols. We also report on the preparation of various enantiomerically pure β -hydroxy acid derivatives **8** and γ -amino alcohols **9** from the corresponding β -hydroxy nitriles.

Results and Discussion

Kinetic Resolution and Dynamic Kinetic Resolution

The kinetic resolutions of various β -hydroxy nitriles **1** using the acyl donor *p*-chlorophenyl acetate **3** and

Introduction

During the last decade dynamic kinetic resolution (DKR) has become an active and important area of research in organic synthesis.^[1] DKR is a powerful tool to prepare enantiomerically enriched compounds in high yields that overcomes the limitation of the maximum 50% yield in the traditional kinetic resolution (KR).^[2] We have recently developed a simple approach to perform DKR of alcohols in which the traditional enzymatic kinetic resolution is combined with an *in situ* racemization of the substrate using a ruthenium-based hydrogen transfer catalyst.^[3]

The importance of optically active amino alcohols and hydroxy acid derivatives as versatile building blocks in both asymmetric synthesis and medicinal chemistry is well established.^[4] Recently, we have applied our DKR approach to the preparation of these valuable compounds (Scheme 1).^[5]

Table 1. Lipase-catalyzed kinetic resolution of *rac*-**1**.^[a]

$$\text{(rac)-1a-k} \xrightarrow[\text{Toluene}]{\text{3 / N-435}} \text{2a-k} + \text{1a-k}$$

Entry	Substrate	R	Time [h]	% Conv. of 1 ^[b]	% ee of 2 ^[c]	% ee of 1 ^[c]	<i>E</i> ^[d]
1	1a	Ph	24	50	> 99 (<i>R</i>)	> 99 (<i>S</i>)	> 1000
2	1b	<i>p</i> -MeO-C ₆ H ₄	16	50	> 99 (<i>R</i>)	> 99 (<i>S</i>)	> 1000
3	1c	<i>p</i> -NO ₂ -C ₆ H ₄	12	50	> 99 (<i>R</i>)	> 99 (<i>S</i>)	> 1000
4	1d	2-Naphthyl	36	50	99 (<i>R</i>)	> 99 (<i>S</i>)	> 1000
5 ^[e]	1e	2-Furyl	60	43	89 (<i>R</i>)	77 (<i>S</i>)	40 ± 1
6	1f	3-Pyridyl	20	51	97 (<i>R</i>)	> 99 (<i>S</i>)	220 ± 10
7	1g	Benzyl	6	49	91 (<i>S</i>)	88 (<i>R</i>)	61 ± 2
8 ^[e]	1h	PhOCH ₂	6	52	95 (<i>R</i>)	99 (<i>S</i>) ^[f]	197 ± 7
9 ^[e]	1i	1-Naphthyl-OCH ₂	3	49	96 (<i>R</i>)	98 (<i>S</i>)	225 ± 15
10	1j	Cyclohexyl	36	49	> 99 (<i>R</i>)	97 (<i>S</i>)	840 ± 40
11	1k	CH ₃ -(CH ₂) ₇ -	6	51	94 (<i>S</i>)	98 (<i>R</i>)	148 ± 6

^[a] Conditions: 0.2 mmol of *rac*-**1**, 0.6 mmol of **3**, 20 mg of *Candida antarctica* lipase B (N-435) and 2 mL toluene at 60 °C.

^[b] % conversion measured by NMR.

^[c] Enantiomeric excess determined by GC or HPLC. Absolute configuration shown in parenthesis.

^[d] Enantiomeric ratio.

^[e] *T* = 30 °C.

Novozym 435 (*Candida antarctica* lipase B) are given in Table 1. The experimental details for this procedure is given in ref. [5d]. The correct absolute configurations, established *via* derivatization (*vide infra*) are given in Table 1.

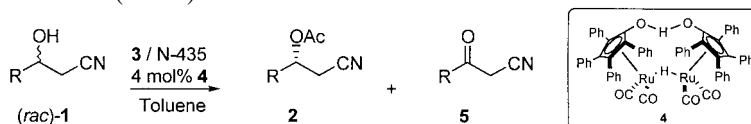
The dynamic kinetic resolutions were carried out at 100 °C using ruthenium catalyst **4** as racemization chemocatalyst, Novozym 435 (N-435) as transesterification biocatalyst, and *p*-chlorophenyl acetate **3** as acyl donor.^[7] The DKR of various β-cyano-α-phenethyl alcohols **1a–c** gave the corresponding acetates **2** in good yields and enantioselectivities (Table 2, entries 1–3). The DKR of 3-hydroxy-3-(2-naphthyl)-propanenitrile **1d** under these conditions also gave enantiopure acetoxynitrile **2d** in high enantioselectivity (entry 4). However, the formation of large amounts of the corresponding ketone **5**, formed during the hydrogen transfer process, was observed for substrates **1a–d**. For the 3-hydroxyundecanenitrile **1k**, the DKR under the conditions used for **1a–d** (i.e., 100 mg N-435/mmol product, 100 °C, 4 mol % **4**) gave the acetates in good yields and enantioselectivity (Table 2, entry 7). However, for the 3-hydroxy-4-(aryloxy)-butanenitriles **1h** and **1g** low enantioselectivity was achieved (Table 2, entries 5 and 6). This is attributed to the lower enantioselectivity of the enzyme for these substrates at this temperature.

Several attempts to increase the efficiency of the process by reducing the amount of ketone for substrates **1a–d** have been carried out. Thus, hydrogen gas and 2,4-dimethyl-3-pentanol **6** were tested as hydrogen sources with the aim to push the equilibrium back to the alcohol

1. The addition of 0.5 equivalents of 2,4-dimethyl-3-pentanol **6** to the reaction mixture reduced the amount of ketone **5a** considerably (11%), moreover it improved the yield of acetate **2a** (entry 8). The use of hydrogen gas (1 bar) inhibited the formation of ketone almost completely (4%), but the DKR under these conditions gave the acetate in low enantioselectivity (87% ee, entry 9). This is mainly due to a decrease of the racemization rate under 1 bar of hydrogen gas.

In previous studies we have shown that by reducing the enzyme/ruthenium catalyst ratio the enzymatic acylation becomes the rate-determining step and the enantioselectivity can therefore substantially improved.^[5c] Therefore, the DKR of 3-hydroxy-4-(phenyloxy)-butanenitrile **1h** using 5 mg N-435/mmol product and 4 mol % **4** at 100 °C improved the enantioselectivity (entry 13).^[8]

We then turned our attention to investigate the possibility of recycling both the catalyst **4** and the enzyme. To study the reuse of enzyme, the recovered enzyme from the DKR of **1a** (Table 2, entry 7) was employed in a KR of **1a** under the conditions described in Table 1. Only traces of acetate **2a** were observed on the GC after 24 h. However, the recovered enzyme from the KR (Table 1, entry 1) could be reused in the KR of **1a** more than three times.^[9] To study the reuse of catalyst **4**, we applied the catalyst **4** in the repetitive racemization process of (*S*)-**1a**. On completion of the racemization of (*S*)-**1a**, the reaction was cooled, additional aliquots of (*S*)-**1a** and proton source **6** were added, and racemization was repeated. Up to 3 cycles were carried out without addition of more catalyst. From these results, it

Table 2. Dynamic kinetic resolution (DKR) of *rac*-**1**.^[a]

Entry	Substrate	R	Time [h]	% of 2 ^[b]	% ee of 2 ^[c]	% of 5 ^[b]
1	1a	Ph	36	74	97 (<i>R</i>)	23
2	1b	<i>p</i> -MeO-C ₆ H ₄	36	81	99 (<i>R</i>)	19
3	1c	<i>p</i> -NO ₂ -C ₆ H ₄	36	72	96 (<i>R</i>)	26
4	1d	2-Naphthyl	36	78	94 (<i>R</i>)	21
5	1h	PhOCH ₂	36	98	36 (<i>R</i>)	2
6	1g	1-Naphthyl-OCH ₂	36	95	44 (<i>R</i>)	3
7	1k	CH ₃ -(CH ₂) ₇ -	36	93	92 (<i>S</i>)	4
8 ^[d]	1a	Ph	36	85	97 (<i>R</i>)	11
9 ^[e]	1a	Ph	36	72	87 (<i>R</i>)	4
10 ^[d]	1b	<i>p</i> -MeO-C ₆ H ₄	36	86	97 (<i>R</i>)	8
11 ^[d]	1c	<i>p</i> -NO ₂ -C ₆ H ₄	36	80	94 (<i>R</i>)	13
12 ^[d]	1d	2-Naphthyl	36	82	91 (<i>R</i>)	14
13 ^[f]	1h	PhOCH ₂	36	73	74 (<i>R</i>)	1

^[a] Conditions: 0.2 mmol of *rac*-**1a**, 0.6 mmol of **3**, 20 mg of *Candida antarctica* lipase B (N-435), 4 mol % of **4** and 2 mL toluene at 100 °C.

^[b] % yield measured by NMR.

^[c] Optical purity measured by GC or HPLC. Absolute configuration shown in parenthesis.

^[d] 0.1 mmol of **6** added.

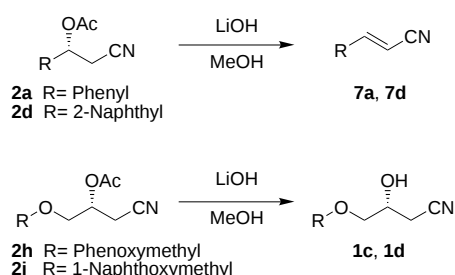
^[e] Reaction performed under 1 bar of hydrogen gas.

^[f] 5 mg of enzyme used.

is easy to envisage the synthesis of a wide range of β -acetoxy nitriles **2** from the corresponding β -hydroxy nitriles **1** in a two-step manner by combining the racemization of **1** at 100 °C with the enzymatic KR at lower temperature without sacrificing the enzyme.^[10]

Hydrolysis of β -Acetoxy Nitriles

In a first set of experiments we studied the hydrolysis of compounds **2a**, **2d**, **2h** and **2i** using LiOH in methanol. As expected the reaction with substrates **1a** and **1d** led predominantly to the elimination of the acetate group to form exclusively 3-phenyl- and 3-naphthyl-2-propenenitriles **7**, respectively. However, the reaction proceeds smoothly for substrates **2h** and **2i** and with total retention of configuration (Scheme 2).

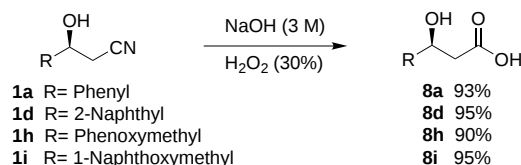
**Scheme 2.**

The hydrolysis of enantiomerically pure acetate **2a** could be achieved by using NaHCO₃/MeOH and KCN/MeOH. However, in both cases small amounts of elimination product (5–10%) were obtained. Surprisingly, the enantiopurity dropped considerably. We then decided to use the lipase-catalyzed hydrolysis of acetate **2a** using different lipases (PS-C, N-435, AK) under the conditions described by Itoh et al. (pH = 7, 35 °C).^[6] To our surprise, the enantiopurity of the alcohol obtained dropped considerably, i.e., **1a** was obtained in quantitative yield and 86% ee by using lipase-AK.

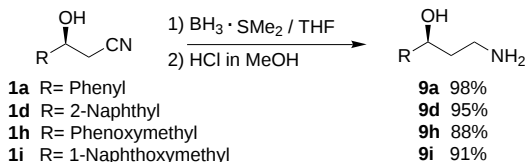
Synthesis of β -Hydroxy Acids and β -Amino Alcohols

In a first set of experiments, the basic hydrolysis of the β -hydroxy nitriles **1** was carried out using NaOH in H₂O/EtOH. Under these conditions, the reaction proceeded fast, but several by-products were observed by NMR. The addition of H₂O₂ inhibited the formation of the byproducts, yielding the corresponding β -hydroxy acids **8** in good yields (Scheme 3). Compounds **8h** and **8i** can also be obtained from the corresponding β -acetoxy nitriles **2h** and **2i**, since under these conditions the acetate is also hydrolyzed.

A series of β -amino alcohols **9** were prepared by borane reduction of the corresponding nitriles **1** (Scheme 4).



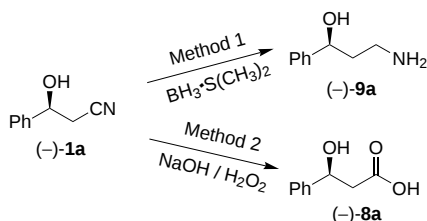
Scheme 3.



Scheme 4.

Determination of the Absolute Configuration

The absolute configuration of the optically active products **1a** and **2a** was determined, on the basis of the recovered unreacted alcohol from the kinetic resolution of (*rac*)-**1a**, by two independent methods (Scheme 5).

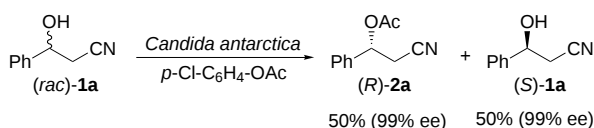


Scheme 5.

- Method 1: The unreacted enantiomerically pure (*S*)-**1a** was reduced using borane·methyl sulfide complex to the corresponding (*S*)-3-phenyl-3-hydroxypropylamine [(*S*)-**9a**] (*vide supra*). The product obtained was compared with a sample of enantiomerically pure (*S*)-(*S*)-**9a** obtained from (*R*)-styrene oxide by regioselective epoxide ring opening with cyanide followed by borane reduction.^[11]

- Method 2: The unreacted enantiomerically pure (*S*)-**1a** was converted into the corresponding hydroxy acid (*S*)-3-hydroxy-3-phenylpropanoic acid [(*S*)-**8a**] by treatment with NaOH (3 M) and H₂O₂ (30%) (*vide supra*). The optical rotation was compared with commercially available (*S*)-(*S*)-**8a**.^[12]

Thus, in accordance with the Kazlauskas rule^[2] the *R*-enantiomer of the alcohol reacts faster than the *S*-enantiomer (Scheme 6) yielding, for hydroxy nitrile **1a**,



Scheme 6. Lipase-catalyzed transesterification of β -hydroxy nitrile **1a**.

enantiomerically pure (*R*)-2-cyano-1-phenylethyl acetate (*R*)-**2a**, [α]_D²³: +69.9 (c 1.1, CHCl₃)^[13] and unreacted the *S*-(*S*)-**1a**, [α]_D²³: -57.9 (c 2.6, EtOH), lit.^[14] [α]_D²⁰: -57.7 (c 2.6, EtOH, 96% ee).

Conclusion

A complete study of the chemoenzymatic DKR of β -hydroxy nitriles using *Candida antarctica* lipase B (CALB) as transesterification biocatalyst and ruthenium catalyst **4** as racemization chemocatalyst has been carried out. The study indicates that the efficiency of the process can be increased by: (i) using 2,4-dimethyl-3-pentanol **6** as a mild hydrogen source to depress ketone formation during the DKR of aryl-substituted β -hydroxy nitriles, and (ii) reducing the enzyme/ruthenium catalyst ratio to improve the enantioselectivity for substrates for which the enzyme shows low enantiomeric ratio. The absolute configuration of the β -hydroxy and β -acetoxy nitriles, established by transformation to enantiomerically pure β -hydroxy acid derivatives **8** and γ -amino alcohols **9**, shows that the enzymatic reactions follow Kazlauskas' rule^[2] with CH₂CN being accepted as the small group by CALB.

Experimental Section

General Remarks

Solvents were purified by standard procedures. All other reagents are commercially available and were used without further purification. ¹H and ¹³C NMR spectra were recorded in CDCl₃ at 400 and 100 MHz, respectively. Solvents for extraction were technical grade and distilled before use. Kinetic resolution and dynamic kinetic resolution of compounds **1** were carried out as described in ref. [5d].

Racemization of (*S*)-**1a**

To a solution of (*S*)-**1a** (29.4 mg, 0.2 mmol), **6** (14 μ L, 0.1 mmol) in toluene (2 mL) ruthenium catalyst **4** (10.85 mg, 4 mol %) was added. The resulting reaction mixture was stirred at 100 °C for 30 h under argon.

General Procedure for the Hydrolysis of **2c** and **2d**

In a typical experiment, LiOH (19 mg, 0.8 mmol) was added to a solution of 2-cyano-1-(phenoxymethyl)ethyl acetate **2c** (75 mg, 0.4 mmol) in methanol (2 mL). The mixture was stirred for 1 h, and then saturated ammonium chloride solution (10 mL) was added. The mixture was evaporated, and then extracted with diethyl ether (3 $\times$ 25 mL). The combined ether phases were dried over Na₂SO₄ and evaporated to give alcohol **1c** as a colorless oil; yield: 58 mg (99%).

General Procedure for the Preparation of β -Hydroxy Acids

(S)-3-Hydroxy-3-phenylpropanoic acid [(S)-8a]: In a two-necked round-bottomed flask equipped with a condenser were placed (S)-3-hydroxy-3-phenylpropanenitrile **1a** (74 mg, 0.5 mmol), 3.7 mL of NaOH (3 M), and 1.3 mL of H₂O₂ (30%). The reaction mixture was heated at 70 °C for 1 h and 1 h at 90 °C and cooled to room temperature. The solution was washed once with ether (3 mL). The aqueous solution was acidified with 2 M HCl (10 mL), and then extracted with dichloromethane (3 $\times$ 20 mL). The combined ether phases were dried over Na₂SO₄ and evaporated to give hydroxy acid (S)-8a as a pale yellow solid; yield: 77 mg (93%). The NMR data are in agreement with those previously reported.^[15] [α]_D²³: –21.9 (c 4, MeOH) [lit.^[10] [α]_D²⁰: –22.5 (c 4, MeOH)].

(S)-3-Hydroxy-3-(1-naphthyl)propanoic acid [(S)-8d]: ¹H NMR: δ = 2.87 (d, 1H, CH₂, ³J_{H-H} = 16.4 Hz, ³J_{H-H} = 4.0 Hz), 2.94 (dd, 1H, CH₂, ³J_{H-H} = 16.4 Hz, ³J_{H-H} = 9.2 Hz), 5.34 (dd, 1H, CH, ³J_{H-H} = 9.2 Hz, ³J_{H-H} = 4.0 Hz), 7.52 (m, 3H, CH=), 7.85 (m, 4H, CH=); ¹³C NMR: δ = 43.0 (CH₂), 70.5 (CH), 123.8 (CH=), 124.8 (CH=), 126.4 (CH=), 126.6 (CH=), 128.0 (CH=), 128.3 (CH=), 128.8 (CH=), 133.3 (C), 133.5 (C), 139.7 (C), 175.9 (CO).

(S)-3-Hydroxy-4-(phenoxy)butanoic acid [(S)-8h]: ¹H NMR: δ = 2.68 (dd, 1H, CH₂, ³J_{H-H} = 16.8 Hz, ³J_{H-H} = 7.5 Hz), 2.76 (dd, 1H, CH₂, ³J_{H-H} = 16.8 Hz, ³J_{H-H} = 5.1 Hz), 3.99 (m, 2H, CH₂-O), 4.43 (m, 1H, CH), 6.89 (m, 2H, CH=), 6.95 (m, 1H, CH=), 7.27 (m, 2H, CH=); ¹³C NMR: δ = 38.1 (CH₂), 66.9 (CH₂-O), 70.1 (CH), 114.7 (CH=), 121.5 (CH=), 129.7 (CH=), 159.3 (C), 176.9 (CO).

(S)-3-Hydroxy-4-(2-naphthoxy)butanoic acid [(S)-8i]: ¹H NMR: δ = 2.85 (d, 1H, CH₂, ³J_{H-H} = 16.4 Hz, ³J_{H-H} = 7.6 Hz), 2.89 (dd, 1H, CH₂, ³J_{H-H} = 16.4 Hz, ³J_{H-H} = 4.4 Hz), 4.20 (m, 2H, CH₂-O), 4.61 (m, 1H, CH-O), 6.81 (d, 1H, CH=, ³J_{H-H} = 7.6 Hz), 7.36 (t, 1H, CH=, ³J_{H-H} = 8.0 Hz), 7.47 (m, 3H, CH=), 7.80 (m, 1H, CH=), 8.22 (m, 1H, CH=); ¹³C NMR: δ = 38.3 (CH₂), 67.0 (CH₂-O), 70.9 (CH), 105.2 (CH=), 121.3 (CH=), 121.9 (CH=), 125.6 (CH=), 125.9 (CH=), 126.7 (CH=), 127.8 (CH=), 134.7 (C), 154.1 (C), 177.1 (CO).

General Procedure for the Preparation of β -Amino Alcohols

(S)-3-Amino-1-phenyl-1-propanol [(S)-9a]: Borane · methyl sulfide complex (0.35 mL of 2 M solution in THF, 0.70 mmol) was added to a THF (2 mL) solution of (S)-3-hydroxy-3-phenylpropanenitrile **1a** (74 mg, 0.5 mmol). The methyl sulfide was then distilled off. The resulting THF solution was refluxed for 2 h. The reaction was cooled down, and quenched with methanolic hydrogen chloride. The mixture was then evaporated to dryness. The residue was dissolved in 2 M HCl (10 mL) and extracted with dichloromethane (2 $\times$ 5 mL). The aqueous solution was made alkaline with 3 M NaOH (15 mL), and then extracted with ethyl acetate (3 $\times$ 20 mL). The combined ether phases were dried over Na₂SO₄ and evaporated to give amino alcohol **3a** as a colorless liquid; yield: 73 mg (98%). The NMR data are in agreement with those previously reported.^[9] [α]_D²³: –43.0 (c 1, MeOH) [lit.^[9] [α]_D²⁵: –43.6 (c 1, MeOH)].

(S)-3-Amino-1-(1-naphthyl)-1-propanol [(S)-9d]: ¹H NMR: δ = 1.82 (m, 1H, CH₂), 1.93 (m, 1H, CH₂), 2.97 (m, 1H, CH₂-N),

3.09 (m, 1H, CH₂-N), 5.34 (dd, 1H, CH, ³J_{H-H} = 8.7 Hz, ³J_{H-H} = 3.3 Hz), 7.45 (m, 3H, CH=), 7.83 (m, 4H, CH=); ¹³C NMR: δ = 39.8 (CH₂), 40.8 (CH₂), 75.8 (CH), 124.3 (CH=), 124.4 (CH=), 125.7 (CH=), 126.1 (CH=), 127.8 (CH=), 128.1 (CH=), 128.2 (CH=), 132.9 (C), 133.6 (C), 142.8 (C).

(S)-4-Amino-1-phenoxy-2-butanol [(S)-9h]: ¹H NMR: δ = 1.68 (m, 1H, CH₂), 1.81 (m, 1H, CH₂), 2.79 (bs, 3H, NH₂, OH), 2.94 (m, 1H, CH₂-N), 3.16 (m, 1H, CH₂-N), 3.89 (dd, 1H, CH₂-O, ³J_{H-H} = 9.2 Hz, ³J_{H-H} = 3.6 Hz), 3.94 (dd, 1H, CH₂-O, ³J_{H-H} = 9.2 Hz, ³J_{H-H} = 5.6 Hz), 4.20 (m, 1H, CH), 6.92 (m, 3H, CH=), 7.27 (m, 2H, CH=); ¹³C NMR: δ = 34.3 (CH₂), 40.5 (CH₂), 71.3 (CH₂-O or CH-O), 72.0 (CH₂-O or CH-O), 114.8 (CH=), 121.1 (CH=), 129.7 (CH=), 159.0 (C).

(S)-4-Amino-1-(2-naphthoxy)-2-butanol [(S)-9i]: ¹H NMR: δ = 1.76 (m, 1H, CH₂), 1.89 (m, 1H, CH₂), 2.90 (b, 4H, NH₂, OH, CH₂-N), 3.20 (m, 1H, CH₂-N), 4.05 (dd, 1H, CH₂-O, ³J_{H-H} = 9.3 Hz, ³J_{H-H} = 6.0 Hz), 4.15 (dd, 1H, CH₂, ³J_{H-H} = 9.3 Hz, ³J_{H-H} = 5.1 Hz), 4.37 (m, 1H, CH), 6.82 (d, 1H, CH=, ³J_{H-H} = 7.5 Hz), 7.46 (m, 4H, CH=), 7.78 (m, 1H, CH=), 8.26 (m, 1H, CH=); ¹³C NMR: δ = 34.8 (CH₂), 40.5 (CH₂), 71.4 (CH₂-O or CH-O), 72.23 (CH₂-O or CH-O), 105.1 (CH=), 120.6 (CH=), 122.1 (CH=), 125.4 (CH=), 126.1 (CH=), 126.6 (CH=), 127.7 (CH=), 134.7 (C), 155.0 (C).

Acknowledgements

Financial support from the Swedish Foundation for Strategic Research is gratefully acknowledged.

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