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Lipase mediated kinetic resolution of benzimidazolyl ethanols

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Abstract—Enantioselective *trans*-acylation of the racemic benzimidazolyl ethanols was achieved via enzymatic kinetic resolution. A range of commercially available lipases were screened and Novozyme-435 was established as the optimal catalyst. N-Protection was found to be mandatory for effective transesterification. However, electron-withdrawing substituents reduced the enantioselectivity to some extent when compared to the other substituents.

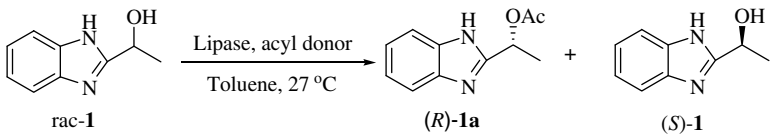
1. Introduction

The high biological potential of benzimidazole derivatives has been well established.[1] Their physiological action include respiratory, analgesic, spasmolytic, anti-inflammatory and antihypertensive activity, which makes them important therapeutic agents to combat human and veterinary diseases.[2] As stereochemistry in a drug molecule governs its biological activity, chirality is a key issue in pharmaceutical research. Of the two enantiomers of 2-(α-hydroxybenzyl) benzimidazole derivatives, the (*R*)-enantiomer is more active and selective than the (*S*)-enantiomer, as demonstrated by QSAR studies and biological tests.[3] Such findings make the synthesis of chiral benzimidazole derivatives an interesting area of research.

The application of enzymes as biocatalysts to obtain chiral compounds in enantiomerically pure forms is quite well known.[4] Lipases have been successfully used in many biotransformations owing to their excellent regio- and stereoselectivities.[5] Their wide substrate specificity, stability, recyclability, non-requirement of co-factors, low cost and applicability to diverse reactions such as esterification, transesterification, amidation and hydrolysis make them popular biocatalysts in organic synthesis.[6] They have been frequently utilized for the kinetic resolution of diastereomeric and enantiomeric mixtures of primary, secondary and allylic alcohols.[7]

2. Results and discussion

Herein, we report the lipase mediated kinetic resolution of benzimidazolyl ethanols. Preliminary studies were performed on benzimidazolyl ethanol *rac*-**1** with various acetates as functionalized acyl donors (Scheme 1). The acetates employed were vinyl acetate, isoprenyl acetate and *p*-chlorophenyl acetate. Vinyl acetate was chosen as the acetate of choice, since with the other two acetates the reactions were found to be sluggish. The substrate was prepared by a standard procedure as reported in the literature.[8] The lipases examined herein were *Pseudomonas cepacia*



rac-**1** (*R*)-**1a** (*S*)-**1**

Scheme 1.

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Table 1. Observed enantiomeric excess of various lipases for *rac*-**1**

Entry	Enzyme	ee[a] (acetate)
1	Lipase PS-B	30
2	Lipase PS-C	50
3	Novozyme-435	70

[a] Based on chiral HPLC.

Table 2. Observed conversion rates of various lipases for *rac*-**2**

Entry	Enzyme	ee[a] (acetate)
1	Lipase PS-B	40
2	Lipase PS-C	60
3	Novozyme-435	97

[a] Based on chiral HPLC.

Table 3. Solvent studies for kinetic resolution of *rac*-**2**

Entry	Solvent	Reaction time (h)	ee (**2a**)[a]	ee (**2**)[a]
1	Hexane	48	92	90
2	Toluene	24	97	93

[a] Based on chiral HPLC.

lipases PS-B and PS-C, and *Candida antarctica* lipase B (Novozyme-435). It was observed that none of the chosen lipases gave ee >70% for this substrate (Table 1).

However, the N-methylated derivative *rac*-**2** gave significantly better results with Novozyme-435 leading to a substantial increase in the enantiomeric excess by ~27% (Table 2).

Selection of the appropriate solvent is a critical factor for biocatalysis,[9] as organic solvents are known to change the enzyme activity[10] and enantioselectivity[11] governing the enzyme conformation by interacting with the hydration layer essential for catalysis and by altering hydrophobic or H-bonding in the core of the protein as well as protein solvation sites.[12] *n*-Hexane and toluene were considered as suitable solvents and studied for the domino reaction. Polar solvents did not give the expected conversions. Thus, it was observed that the most effective resolution occurred in toluene at 25 °C (Table 3). The configuration of the remaining alcohol (*S*)-**1** was determined by comparing the rotation values. Alcohol (*S*)-**1** has $[\alpha]_D = -27.4$ (*c* 0.9, CH_3OH) while the reported[8] (*S*)-**1** has $[\alpha]_D = -34.1$ (*c* 0.01, CH_3OH) thus accounting for 80% ee. Conversely, the resolved acetate **1a** was assigned an (*R*)-configuration.

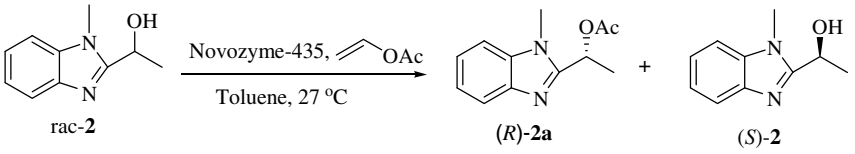
After the initial screening of commercial lipases and solvents (Tables 2 and 3) for *rac*-**2**, we observed that Novozyme-435 effectively catalyzed the kinetic resolution of *rac*-**2** in toluene at 27 °C (Scheme 2).

The higher enantioselectivity observed in the case of *rac*-**2** as compared to *rac*-**1** inspired us to investigate the enzyme compatibility for various substituents (Scheme 3) (Table 2). To study the effects of diverse substituents, various derivatives *rac*-**3**, *rac*-**4**, *rac*-**5** and *rac*-**6** were synthesized[13] and subjected to enzymatic kinetic resolution (Scheme 3). The results obtained are shown in Table 4.

The absolute stereochemistry of the newly created centre was determined by comparing the $[\alpha]_D$ values with the literature for (*S*)-**1a**.[8] The configurations of the resulting ester and the remaining alcohol for all the other examples were assigned as (*R*)- and (*S*)-, respectively, by analogy. It is noteworthy that certain substitutions on the nitrogen enhanced the enantioselectivity. Thus, the ee was found to be lower in case of electron-withdrawing substituents such as benzoyl or *p*-toluene sulfonyl as compared to methyl and benzyl substituents.

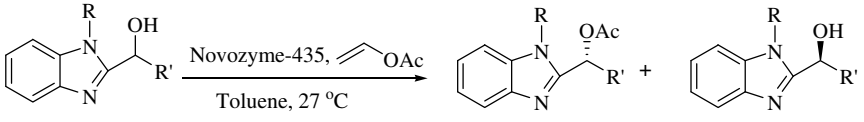
3. Conclusion

In conclusion, enzymatic transesterification was established as an efficient technique for the kinetic resolution of



rac-**2** (*R*)-**2a** (*S*)-**2**

Scheme 2.

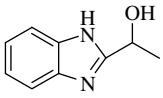
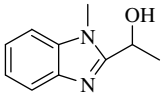
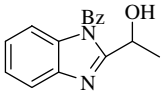
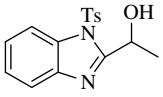
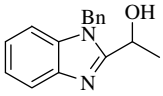
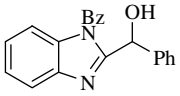


(*R*)-**3a-6a** (*S*)-**3-6**

rac-**3**, R = Bz, R' = Me
rac-**4**, R = Ts, R' = Me
rac-**5**, R = Bn, R' = Me
rac-**6**, R = Bz, R' = Ph

Scheme 3.

Table 4. Kinetic resolution of various benzimidazolyl ethanols

Entry	Substrate	Reaction time (h)	ee[a] (acetate)	ee[a] (alcohol)	% Conversion[b]	E[c]
rac-**1**		24	70	80	53	14
rac-**2**		24	97	93	49	225
rac-**3**		24	79	88	53	25
rac-**4**		24	75	86	53	19
rac-**5**		24	95	97	51	165
rac-**6**		24	77	87	53	22

[a] Based on chiral HPLC.

[b] The % conversion was calculated from the enantiomeric excess of the starting material (ee_s) and the product (ee_p) according to % conversion $= ee_s/(ee_s + ee_p)$.

[c] The enantioselectivity E can be expressed in terms of ee_s and $ee_p$by $E = \ln[1 - ee_s/1 + (ee_s/ee_p)]/\ln[1 + ee_s/1 + (ee_s/ee_p)]$.

benzimidazolyl ethanols. These enantiopure benzimidazolyl ethanols have proven to be valuable synthons for various biologically active compounds.

4. Experimental

4.1. General methods

Solvents were dried over standard drying agents and freshly distilled prior to use. Chemicals were purchased and used without further purification. The enzymes were purchased from Ms. Amano Enzyme Co. Japan. All column chromatographic separations were performed using silica gel (Acme's, 60–120 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C in vacuo. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured with a Bruker Avance 300 MHz with tetramethylsilane as internal standard for solutions in deuteriochloroform. J values are given in Hertz. IR spectra were recorded on a Perkin–Elmer IR-683 spectrophotometer with NaCl optics. Optical rotations were measured with JASCO DIP 300 digital polarimeter at 25 °C. Mass spectra were recorded on CEC-21-11013 or Fannigan Mat 1210 double focusing mass spectrometers operating at a direct inlet system or LC/MSD Trap SL (Agilent Technologies). The enantiomeric excess of resulting esters and alcohols was determined by HPLC analysis which was conducted by using chiral-OD column, 225 nm, *i*-PrOH/*n*-hexane solvent system. All chromatographic separation and purification of final products were carried out on silica gel columns (60–120 mesh).

4.2. General procedure for the lipase-catalyzed transesterification of racemic alcohols

All racemic allylic alcohols were subjected to enzymatic transesterification according to the same procedure. The enzyme/substrate ratio of 50 mg of enzyme/mmol of substrate was kept constant in all the cases. To a stirred mixture of alcohol (0.1 mmol) and toluene (0.33 mL), vinyl acetate (16 μL) and Novozyme-435 (5 mg) were added and stirred at room temperature for 24 h. The reaction was then filtered and concentrated in vacuo. Column chromatography of the crude product with a 20% ethyl acetate in *n*-hexane as eluant gave enantiomerically pure alcohol in 32–43% yields.

4.2.1. Enzymatic resolution of (±)-1-(1*H*-benzo[*d*]imidazol-2-yl)ethanol 1. To a stirred mixture of alcohol **1** (0.16 g, 0.1 mmol) and toluene (0.33 mL), vinyl acetate (16 μL) and Novozyme-435 (5 mg) were added and stirred at room temperature for 24 h. The reaction was then filtered and concentrated in vacuo. Column chromatography of the crude product with a 1:1 EtOAc/*n*-hexane mixture as eluant gave ester (*R*)-**1a** in 38% yield and 80% ee and alcohol (*S*)-**1** with 33% yield and 90% ee. (*R*)-**1a**: $[\alpha]_D = +59.4$ (*c* 0.9, CH_3OH), HPLC (column, chiral-OD, 225 nm, 3% *i*-PrOH/*n*-hexane); t_R (major): 3.71 min; t_R (minor): 4.31 min; IR (neat): 3100, 1738, 1025 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.73 (br s, 1H), 7.96–7.44 (m, 2H),

7.28–7.26 (m, 2H), 6.12–6.04 (m, 1H), 2.35 (s, 3H), 1.84 (d, 3H, $J = 6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.32, 141.55, 138.92, 123.05, 115.33, 76.29, 21.97, 19.58; ESIMS (m/z) (%): 227 (M+23): Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.33; H, 6.14; N, 13.83 and (*S*)-**1**: $[\alpha]_D = -13.5$ (*c* 1.1, CH_3OH), HPLC (column, chiral-OD, 225 nm, 4% *i*-PrOH/*n*-hexane); t_R (major): 10.46 min; t_R (minor): 9.54 min; IR (neat): 3400, 3150, 1045 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59–7.54 (m, 2H), 7.22–7.17 (m, 2H), 5.15 (m, 1H), 1.72 (d, 3H, $J = 6$ Hz). ESIMS (m/z) (%): 163 (M+1): Anal. Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.98; H, 6.14; N, 17.37.

4.2.2. Enzymatic resolution of (±)-1-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)ethanol 2. To a stirred mixture of alcohol **2** (0.18 g, 0.1 mmol) and toluene (0.33 mL), vinyl acetate (16 μL) and Novozyme-435 (5 mg) were added and stirred at room temperature for 24 h. The reaction was then filtered and concentrated in vacuo. Column chromatography of the crude product with a 4:1 EtOAc/*n*-hexane mixture as eluant gave ester (*R*)-**2a** in 42% yield and 99% ee and alcohol (*S*)-**2** with 40% yield and 99% ee. (*R*)-**2a**: $[\alpha]_D = +63.6$ (*c* 1.0, CH_3OH), HPLC (column, chiral-OD, 225 nm, 4% *i*-PrOH/*n*-hexane); t_R (major): 26.92 min; t_R (minor): 41.07 min; IR (neat): 1735, 1020 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 7.80–7.85 (m, 1H), 7.35–7.15 (m, 3H), 6.23–6.13 (m, 1H), 3.81 (s, 3H), 2.11 (s, 3H), 1.82 (d, 3H, $J = 5.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.32, 152.27, 123.16, 122.39, 120.10, 109.43, 64.32, 29.96, 20.97, 18.84; ESIMS (m/z) (%): 241 (M+23): Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.88; H, 6.36; N, 12.97 and (*S*)-**2**: $[\alpha]_D = -8.6$ (*c* 1.0, CH_3OH), HPLC (column, chiral-OD, 225 nm, 5% *i*-PrOH/*n*-hexane); t_R (major): 69.75 min; t_R (minor): 56.31 min; IR (neat): 3350, 1047 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74–7.72 (m, 1H), 7.30–7.24 (m, 3H), 5.15–5.10 (m, 1H), 3.81 (s, 3H), 1.73 (d, 3H, $J = 6$ Hz); ESIMS (m/z) (%): 177 (M+1): Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.58; H, 6.54; N, 15.37.

4.2.3. Enzymatic resolution of (±)-(2-(1-hydroxyethyl)-1*H*-benzo[*d*]imidazol-1-yl)(phenyl) methanone 3. To a stirred mixture of alcohol **3** (0.27 g, 0.1 mmol) and toluene (0.33 mL), vinyl acetate (16 μL) and Novozyme-435 (5 mg) were added and stirred at room temperature for 24 h. The reaction was then filtered and concentrated in vacuo. Column chromatography of the crude product with a 1:4 EtOAc/*n*-hexane mixture as eluant gave ester (*R*)-**3a** in 35% yield and 85% ee and alcohol (*S*)-**3** with 33% yield and 88% ee. (*R*)-**3a**: $[\alpha]_D = +27.8$ (*c* 1.0, CH_3OH), HPLC (column, chiral-OD, 225 nm, 4% *i*-PrOH/*n*-hexane); t_R (major): 8.17 min; t_R (minor): 10.26 min; IR (neat): 1728, 1698, 1038 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06–8.04 (m, 2H), 7.63–7.60 (m, 3H), 7.45–7.39 (m, 2H), 7.27–7.24 (m, 2H), 6.37–6.20 (m, 1H), 2.11 (s, 3H), 1.98 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.24, 133.63, 129.86, 128.50, 123.10, 115.49, 67.22, 18.14; ESIMS (m/z) (%): 309 (M+1). Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 69.85; H, 5.66; N, 8.78 and (*S*)-**3**: $[\alpha]_D = -36.0$ (*c* 1.0, CH_3OH), HPLC (column, chiral-OD, 225 nm, 5% *i*-PrOH/*n*-hexane); t_R (major): 31.23 min; t_R (minor): 27.54 min; IR (neat): 3366, 1692, 1029 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08–8.05 (m, 2H), 7.57–7.46 (m, 2H), 7.44–7.35 (m, 3H), 7.27–7.24 (m, 2H), 6.33–6.29 (m, 1H), 1.99 (d, 3H, $J = 6$ Hz); ESIMS (m/z) (%): 267 (M+1): Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.58; H, 5.54; N, 10.24.

4.2.4. Enzymatic resolution of (±)-1-(1-tosyl-1*H*-benzo[*d*]-imidazol-2-yl)ethanol 4. To a stirred mixture of alcohol **4** (0.33 g, 0.1 mmol) and toluene (0.33 mL), vinyl acetate (16 μL) and Novozyme-435 (5 mg) were added and stirred at room temperature for 24 h. The reaction was then filtered and concentrated in vacuo. Column chromatography of the crude product with a 1:9 EtOAc/*n*-hexane mixture as eluant gave ester (*R*)-**4a** in 39% yield and 82% ee and alcohol (*S*)-**4** with 37% yield and 86% ee. (*R*)-**4a**: $[\alpha]_D = +23.4$ (*c* 0.9, CH_3OH), HPLC (column, chiral-OD, 225 nm, 4% *i*-PrOH/*n*-hexane); t_R (major): 3.74 min; t_R (minor): 8.46 min; IR (neat): 1743, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98–7.68 (m, 4H), 7.38–7.25 (m, 4H), 5.33 (br s, 1H) 3.66 (br s, 1H), 2.37 (s, 3H), 1.54 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.49, 146.22, 141.34, 133.07, 130.29, 126.93, 125.45, 124.99, 120.42, 113.68, 64.31, 29.70, 23.15, 21.66; ESIMS (m/z) (%): 359 (M+1). Anal. Calcd for $C_{18}H_{28}N_2O_4S$: C, 60.32; H, 5.06; N, 7.82. Found: C, 60.25; H, 5.16; N, 7.78 and (*S*)-**4**: $[\alpha]_D = -21.8$ (*c* 0.8, CH_3OH), HPLC (column, chiral-OD, 225 nm, 5% *i*-PrOH/*n*-hexane); t_R (major): 31.32 min; t_R (minor): 27.61 min; IR (neat): 3427, 1023 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87–7.68 (m, 4H), 7.38–7.26 (m, 4H), 5.52–5.48 (m, 1H), 2.38 (s, 3H), 1.76 (d, 3H, $J = 6.2$ Hz); ESIMS (m/z) (%): 317 (M+1): Anal. Calcd for $C_{16}H_{16}N_2O_3S$: C, 60.74; H, 5.10; N, 8.85. Found: C, 60.58; H, 5.08; N, 8.64.

4.2.5. Enzymatic resolution of (±)-1-(1-benzyl-1*H*-benzo[*d*]-imidazol-2-yl)ethanol 5. To a stirred mixture of alcohol **5** (0.25 g, 0.1 mmol) and toluene (0.33 mL), vinyl acetate (16 μL) and Novozyme-435 (5 mg) were added and stirred at room temperature for 24 h. The reaction was then filtered and concentrated in vacuo. Column chromatography of the crude product with a 1:4 EtOAc/*n*-hexane mixture as eluant gave ester (*R*)-**5a** in 34% yield and 95% ee and alcohol (*S*)-**5** with 32% yield and 97% ee. (*R*)-**5a**: $[\alpha]_D = +12.2$ (*c* 0.8, CH_3OH), HPLC (column, chiral-OD, 225 nm, 4% *i*-PrOH/*n*-hexane); t_R (major): 3.67 min; t_R (minor): 3.84 min; IR (neat): 1734, 1042 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.26 (m, 6H), 7.03–7.01 (m, 2H), 6.23–6.12 (m, 1H), 5.82–5.38 (m, 2H), 1.80 (s, 3H), 1.72 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.63, 154.27, 138.97, 129.11, 128.76, 125.83, 123.04, 115.39, 69.92, 55.73, 22.95; ESIMS (m/z) (%): 317 (M+23): Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.85; H, 6.08; N, 9.35 and (*S*)-**5**: $[\alpha]_D = -15.1$ (*c* 0.9, CH_3OH), HPLC (column, chiral-OD, 225 nm, 5% *i*-PrOH/*n*-hexane); t_R (major): 15.49 min; t_R (minor): 8.38 min; IR (neat): 3520, 1021 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.16 (m, 6H), 7.15–7.02 (m, 2H), 5.45 (s, 2H), 5.29–5.06 (m, 1H), 3.62 (br s, 1H), 1.69 (d, 3H, $J = 5$ Hz); ESIMS (m/z) (%): 253 (M+1): Anal.

Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found C, 76.28; H, 6.56; N, 11.24.

4.2.6. Enzymatic resolution of (±)-(2-(hydroxy(phenyl)-methyl)-1*H*-benzo[*d*]imidazol-1-yl)(phenyl)methanone 6. To a stirred mixture of alcohol **6** (0.33 g, 0.1 mmol) and toluene (0.33 mL), vinyl acetate (16 μL) and Novozyme-435 (5 mg) were added and stirred at room temperature for 24 h. The reaction was then filtered and concentrated in vacuo. Column chromatography of the crude product with a 1.5:8.5 EtOAc/*n*-hexane mixture as eluant gave ester (*R*)-**6a** in 41% yield and 84% ee and alcohol (*S*)-**6** with 43% yield and 87% ee. (*R*)-**6a**: $[\alpha]_D = +2.5$ (*c* 1.1, CH_3OH), HPLC (column, chiral-OD, 225 nm, 4% *i*-PrOH/*n*-hexane); t_R (major): 3.58 min; t_R (minor): 4.21 min; IR (neat): 1738, 1686, 1039 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.12–7.59 (m, 3H), 7.51–7.37 (m, 3H), 7.36–7.24 (m, 4H), 7.10–7.05 (m, 4H), 6.86 (s, 1H), 2.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.82, 153.45, 141.55, 138.94, 130.87, 129.37, 127.72, 115.36, 72.08; ESIMS (*m*/*z*) (%): 371 (M+1): Anal. Calcd for $C_{23}H_{18}N_2O_3$: C, 74.58; H, 4.90; N, 7.56. Found: C, 73.98; H, 4.66; N, 7.64 and (*S*)-**6**: $[\alpha]_D = -6.6$ (*c* 1.3, CH_3OH), HPLC (column, chiral-OD, 225 nm, 5% *i*-PrOH/*n*-hexane); t_R (major): 17.06 min; t_R (minor): 8.16 min; IR (neat): 3357, 1690, 1023 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.09–8.03 (m, 2H), 7.50–7.43 (m, 3H), 7.34–7.05 (m, 9H), 6.37–6.21 (m, 1H); ESIMS (*m*/*z*) (%): 329 (M+1): Anal. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found C, 76.58; H, 4.96; N, 8.64.

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