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Lipase-catalyzed enantioseparation of alcohols containing a tetrazole ring

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ABSTRACT

A simple chemoenzymatic method for the preparation of optically active (5-aryltetrazolyl-2)-4-butan-2-ol, (5-aryltetrazolyl-2)-propan-2-ol, and their acetates has been developed. The starting compounds (5-aryltetrazolyl-2)-4-butan-2-one and (5-aryltetrazolyl-2)-propan-2-one were obtained by a Michael-type addition of 5-aryl substituted tetrazoles to methyl vinyl ketone, and alkylation of 5-aryl substituted tetrazoles with chloroacetone, respectively. Their reduction with sodium borohydride afforded racemic mixtures of (5-aryltetrazolyl-2)-4-butan-2-oles and (5-aryltetrazolyl-2)-propan-2-oles.

1. Introduction

Tetrazoles and their derivatives constitute an interesting subclass of heterocycles, with a wide number of applications. They are used in coordination chemistry as chelating agents,[1] in agriculture as plant growth regulators,[2] and in the explosives industry[3] as useful highly energetic materials and propellants. Moreover, some tetrazole derivatives play an important role in biochemistry and medicinal chemistry.[4–8] Such a wide range of applications is the result of their unique structure and ability to serve as bioisosters of the carboxyl group. It is known that the replacement of a carboxyl group in biologically active compounds with a similarly acidic tetrazolyl fragment, may affect their biological activity. In particular, 5-substituted tetrazole derivatives, with anti-hypertensive activity, are used as pharmacologically active drugs; for example Losartan,[9–12] Candesartan,[11,12] Zolarsartan,[11,12] and Valsartan.[10] Moreover, there are many known tetrazole derivatives involved in hyperlipoproteinemia and associated atherosclerotic diseases.[13–15] Other tetrazole derivatives exhibit antiallergic,[16,17] antiinflammatory,[18–20] antibacterial,[21,22] and antifungal[22] properties. Among the antibacterial and antifungal agents, are 5-thio-substituted tetrazole derivatives such as 1-benzyl-5-[(3-bromopropyl)thio]-1*H*-tetrazole and 5,5′-[1,3-propanediylbis(thio)]bis(1-benzyl-1*H*-tetrazole), with activities similar to the standards ampicillin and intraconazole.[22] The application of tetrazole derivatives is highly diverse, because of their ability to inhibit the action of many enzymes for example, human liver glycosidase,[23] human liver α-mannosidase,[24] aromatase,[25] protein tyrosine phosphatases,[26] HCV NS3 protease,[27] cyclooxygenase-2,[28] and others.[29,30] Therefore, some tetrazole derivatives are used as chemotherapeutic agents in certain types of cancer,[31–33] and in the treatment of AIDS.[34,35] Moreover, there are known tetrazole analogues of natural amino acids, which exist as constituents of enzyme-modifier complexes with higher activities than the free enzyme, for example modifier complex of carboxypeptidase A.[36]

These findings suggest an unpredictable behavior for tetrazole derivatives in enzyme catalyzed reactions, and even total enzyme inhibition may be expected. We were unable to find any information on the use of tetrazole derivatives in lipase-catalyzed reactions in spite of the many papers on the reactions of other azoles.[37–40] Herein we report our findings on the specific properties of the tetrazole moiety.

2. Results and discussion

Herein, we describe a simple chemoenzymatic procedure for the preparation of some new optically active 2,5-disubstituted tetrazoles. The chemical step involves the synthesis of the necessary substrates: ketones and alcohols, while the enzymatic step employs lipases as the chiral catalysts for the enantioseparation. Two groups of alcohols, different in nature of the substituent at the 2-position of the tetrazole ring, were prepared. One group was (5-aryltetrazolyl-2)-4-butan-2-ols **3a–d**. These compounds were obtained from the appropriate 5-substituted tetrazoles **1a–d** in a two step reaction. The first step involved the Michael type addition of the appropriate 5-substituted tetrazoles **1a–d** to methyl vinyl ketone, yielding (5-aryltetrazolyl-2)-4-butan-2-ones **2a–d**. The reaction was carried out in 2-propanol in the presence of triethylamine at reflux (Scheme 1).

According to the literature data,[41] the reaction took place regioselectively to solely give 2,5-disubstituted isomers **2a–d**. The reflux times and yields of the reaction depended on the benzene-ring substituent and are summarized in Table 1. In the second step, the required racemic alcohols **3a–d** were obtained in high yields (94–96%), by reduction of the appropriate ketones **2a–d** with sodium borohydride in methanol at room temperature.

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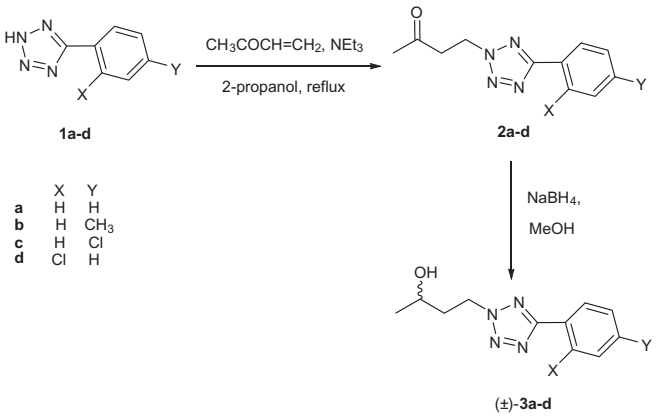


Scheme 1.

Table 1
The reaction times and yields of ketones **2a–d**

Entry	X	Y	Reaction time (h)	Yield (%)
a	H	H	3	85
b	H	CH_3	4	90
c	H	Cl	6	94
d	Cl	H	3	81

The racemic mixtures of alcohols (±)-**3a–d** were then used as the substrates in a lipase-catalyzed acetylation. The influence of the lipase type as well as the substituent on the aromatic ring on the enantioselectivity of the reaction was estimated by determining the reaction enantioselectivity. The catalytic efficiency of three commercially available lipases: Amano AK from *Pseudomonas fluorescens,* Amano PS from *Pseudomonas cepacia*, and Novozym SP 435 from *Candida antarctica* were investigated as catalysts of the reactions carried out at room temperature in *tert*-butyl methyl ether (TBME) with vinyl acetate as an acyl donor (Scheme 2). The control experiment revealed that the reaction did not proceed in the absence of the enzyme.

The progress of the reactions was monitored on TLC plates; acetates (−)-**4a–d** and unreacted alcohols (+)-**3a–d** were separated by silica gel column chromatography. The enantiomeric excess of the remaining alcohols (+)-**3a–d** were determined by HPLC analysis using a chiral column. In order to determine the enantiomeric excess of the esters formed, acetates (−)-**4a–d** were hydrolyzed to the appropriate optically active alcohols (−)-**3a–d**, since applied Chiracel OD-H column was inappropriate for acetate enantiomers resolution. The hydrolysis was performed in methanol with 1 M NaOH solution at room temperature. It seems reasonable to assume that the enantiomeric excess of acetates (−)-**4a–d** were the same or even higher than the alcohols prepared from them. The results are summarized in the Table 2. The absolute configurations of the products, that is, alcohol (−)-**3a** [obtained by the hydrolysis of ester (−)-**4a**], and acetate (−)-**4a**, were determined by a modified Mosher's method.[42] The assignments arose from the comparison of ^{1}H NMR chemical shifts recorded for diastereomeric esters prepared from the enantiomerically enriched alcohol and the (*R*)- or (*S*)-enantiomer of methoxyphenylacetic acid as shown in the Experimental. Our investigations indicated that the alcohol (−)-**3a** had an (*R*)-configuration. This means that alcohols (+)-**3a–d** and acetates (−)-**4a–d** have (*S*)- and (*R*)-configurations, respectively. This is in agreement with Kazlauskas' rule.[43]

Among the three lipases tested, the best enantioselectivities (*E* = 38–102) were obtained with Amano AK as the catalyst. Amano PS and Novozym SP 435 showed poor selectivities (*E* = 0–7). In addition, reactions catalyzed by lipase from *Pseudomonas cepacia* (Amano PS) were very sluggish (7–12 days). Considering the results of the reactions catalyzed by Amano AK, substituents in the benzene ring affect the rate and the enantioselectivity of the reaction. The highest enantioselectivity (*E* = 102) was noted for compound **3a** without any substituent on the benzene ring. In comparison, 4-methyl, 4-chloro, and 2-chloro substituents diminished the enantioselectivity of the reaction. The results presented in Table 2 also show that the acetylation of **3d** proceeded four times slower than the other reactions investigated.

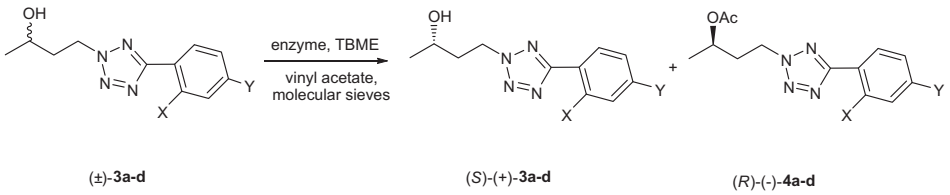
It also seemed worthwhile to investigate if the distance between the hydroxy group (center of the enzymatic reaction) and the tetrazole ring significantly influenced the reaction course. For this purpose, (5-aryltetrazolyl-2)-propan-2-ols **6a–d** were prepared from the appropriate ketones obtained by *N*-alkylation of 5-substituted tetrazoles **1a–d** with chloroacetone. This procedure is often used[37] in the synthesis of other heterocyclic ketones. The reaction was carried out in acetone, in the presence of K_2CO_3 at reflux (Scheme 3).

The results are summarized in Table 3. The yields of the reactions (38–58%) are acceptable, but significantly lower than in preparations of ketones **2a–d**. Extending the reflux did not improve the yields. Both reactions (Scheme 1 and Scheme 3) took place regioselectively to give only one isomer.

The racemic mixtures of alcohols **6a–d** were also prepared by chemical reduction of ketones **5a–d**. The progress of the reaction was monitored by thin-layer chromatography (TLC), and the reaction was stopped when the conversion reached 100%. Regardless of the substituent type, all of the alcohols were obtained in a short reaction time (1–3 h) and with excellent yields ranging between 90.5% and 95%.

The kinetic separation of enantiomers (±)-**6a–d** was carried out only with the Amano AK lipase. The progress of each reaction was monitored by TLC and the reaction was stopped at approximately 50% conversion of the substrate (Scheme 4).

The enantiomeric excess of the remaining alcohols (+)-**6b–d** and acetates prepared (+)-**7c–d** was directly determined by HPLC analysis using a chiral column. The enantiomeric excess of ester (+)-**7b** was assigned after its hydrolysis to the corresponding alcohol. The enantiomeric excess of alcohol (+)-**6a** and ester (+)-**7a** was not determined. The absolute configurations of the alcohols and esters were determined by the modified Mosher's method[42] and indicated an (*S*)-configuration for alcohol (+)-**6d**, and an (*R*)-configuration for acetate (+)-**7d**. The parameters and results of the reaction, enantiomeric purities of the products, and enantioselectivities

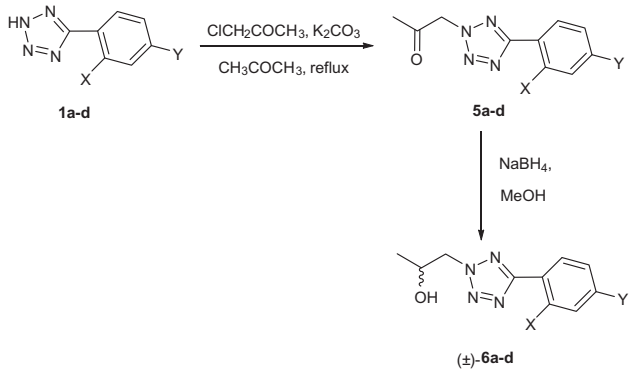


Scheme 2.

Table 2
The results of the lipase-catalyzed transesterifications of alcohols (±)-**3a–d** with vinyl acetate

Entry	X	Y	Enzyme	Time (h)	c (%)[a]	ee_{sub}[b] (%)	ee_{prod}[b] (%)	E[a]
a	H	H	Amano AK	24	42	70	96	102
	H	CH_3		24	43.5	72	93	59
	H	Cl		27	39	59	91	38
	Cl	H		96	55	98	80	40
b	H	H	Amano PS	168	30	30	69	7
	H	CH_3		168	19	15	65	5
	H	Cl		192	33	26	52	4
	Cl	H		288	Very low conversion, products were not isolated			
c	H	H	Novozym SP 435	29	59	10	7	1
	H	CH_3		27.5	53	34	30	2.5
	H	Cl		24	72.5	65	26	3
	Cl	H		24	38.5	rac	rac	0

[a] Conversion (c) and E values were calculated from the enantiomeric excess of the substrate (+)-**3a–d** (ee_{sub}) and the product (−)-**4a–d** (ee_{prod}) using the formula: $E = \ln[(1-ee_{sub})(ee_{prod}/(ee_{sub}+ee_{prod}))]/\ln[(1+ee_{sub})(ee_{prod}/(ee_{sub}+ee_{prod}))]$, $c = ee_{sub}/(ee_{sub}+ee_{prod})$.
[b] Determined by HPLC analysis using a Chiracel OD-H column.



Scheme 3.

Table 3
The refluxing times and yields of ketones **5a–d**

Entry	X	Y	Reflux time (h)	Yield (%)
a	H	H	2	55
b	H	CH_3	5	54
c	H	Cl	2	38
d	Cl	H	1	58

of the reactions are presented in Table 4. The highest enantioselectivity, $E = 47$, was obtained for the acetylation of alcohol (±)-**6c**.

Comparison of the data presented in Table 2 and Table 4 led us to conclude that the length of the alkyl chain between the hydroxy group and the tetrazole ring significantly affects the lipase catalyzed reaction time, but only slightly affects the enantioselectivity of the reaction.

3. Conclusion

A series of new optically active 2,5-disubstituted tetrazole derivatives were prepared. The alkylation of 5-aryl substituted tetrazoles with chloroacetone, as well as a Michael-type addition of 5-aryl substituted tetrazoles to methyl vinyl ketone proceeded regioselectively at the 2-position of the tetrazole ring. The resulting ketones were reduced to their corresponding alcohols. All reactions proceeded with high yields under mild conditions. The lipase-catalyzed transesterification of the alcohols with vinyl acetate as the acyl donor was found to be a useful method for the preparation of the corresponding optically active alcohols and esters. The highest enantioselectivities of the reactions ($E = 36–102$) were obtained in the presence of lipase Amano AK from *Pseudomonas fluorescens* as the catalyst.

Table 4
Results of amano AK catalyzed acetylation of alcohols (±)-**6a–d**

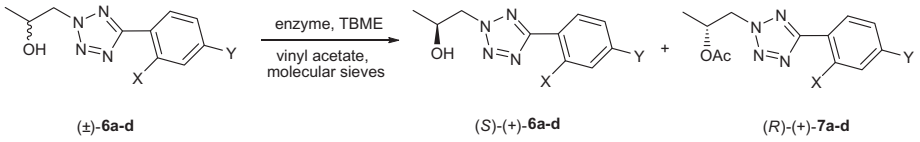
Entry	X	Y	Time (h)	c[a](%)	ee_{sub}[b] (%)	ee_{prod}[b] (%)	E[a]
a	H	H	47	—	ND[c]	ND[c]	—
b	H	CH_3	46	46	77	88	36
c	H	Cl	45	45	74	91	47
d	Cl	H	56	56	99	78	41

[a] Conversion (c) and E values were calculated from the enantiomeric excess of substrate (+)-**6b–d** (ee_{sub}) and product (−)-**7b–d** (ee_{prod}) using the formula: $E=\ln[(1-ee_{sub})(ee_{prod}/(ee_{sub}+ee_{prod}))]/\ln[(1+ee_{sub})(ee_{prod}/(ee_{sub}+ee_{prod}))]$, $c = ee_{sub}/(ee_{sub}+ee_{prod})$.
[b] Determined by HPLC analysis using Chiracel OD-H column.
[c] ND-not determined.

4. Experimental

4.1. General

^1H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Varian Mercury 400 MHz spectrometer in $CDCl_3$ solution; chemical shifts (δ) are reported in ppm; J values are given in Hertz. IR Spectra were taken on a Carl Zeiss Specord M80 instrument. MS spectra were recorded on a Micro-mass ESI Q-ToF Premier instrument. Ee's of the alcohols **3a–d**, **6b–d,** and esters **7c–d**, were determined by HPLC analysis, which were performed on a Shimadzu CTO-10ASV equipped with UV detector STD-20A and chiral column Chiralcel OD-H (Diacel) (in hexane:*iso*-propanol 95:5; 0.8 ml/min



Scheme 4.

for alcohols **3a–d**, **6c–d**, and esters **7c–d;** in hexane:*iso*-propanol 97:3, 0.8 ml/min for alcohol **6b**) using the corresponding racemic compounds as references. The retention times (t_R/min) were as follows for alcohols: **3a** 34.47 (*S*) and 40.79 (*R*), **3b** 40.85 (*S*) and 56.96 (*R*), **3c** 28.36 (*S*) and 35.41 (*R*), **3d** 27.92 (*S*) and 29.83 (*R*), **6b** 52.24 (*S*) and 54.22 (*R*), **6c** 25.74 (*R*) and 28.49 (*S*), **6d** 30.18 (*R*) and 34.26 (*S*) and were as follows for esters: **7c** 18.97 (*S*) and 24.37 (*R*) **7d** 18.38 (*R*) and 19.10 (*S*). Optical rotations were measured with an AP-300 automatic polarimeter (ATAGO). The reactions were monitored by TLC on silica gel 60 (230–400 mesh) plates. The 5-substituted tetrazoles **1a–d** were prepared in high yields (64–91%) from commercially available nitriles, NaN_3, and NH_4Cl in DMF according to the described method.[44] Amano AK, Amano PS were purchased from Amano Co. and Novozym SP 435 (immobilized *C. antarctica*-B lipase) was kindly granted by Novo-Nordisk. Solvents, reagents, and chemicals were purchased from POCH, Merck, Fluka, and Aldrich.

4.2. General procedure for the synthesis of (5-aryltetrazolyl-2)-4-butan-2-ones 2a–d

To a solution of 5-substituted tetrazole **1a–d** (0.04 mol) in 2-propanol (120 mL), triethylamine (0.03 mol, 4.17 mL) and methyl vinyl ketone (0.08 mol, 6.5 mL) were added. The resulting reaction mixture was refluxed for the time indicated in Table 1. The progress of the reaction was monitored by TLC with hexane–ethyl acetate (1:1 v/v) as the eluent. After the appropriate time, the reaction was stopped by filtering off the solid. The solvent was evaporated under reduced pressure. The residue and earlier obtained solid were recrystallized from ethanol.

4.2.1. (5-Phenyltetrazolyl-2)-4-butan-2-one 2a

Colorless crystals, mp 61–63 °C (lit.[41] 62–63 °C), yield 85%. ^{1}H NMR ($CDCl_3$): δ ppm: 2.25 (s, 3H, CH_3), 3.37 (t, 2H, CH_2CO, J = 7.2 Hz), 4.90 (t, 2H CH_2N, J = 7.2 Hz), 7.45–7.47 (m, 3H, C_6H_5), 8.09–8.12 (m, 2H, C_6H_5). ^{13}C NMR ($CDCl_3$): δ ppm: 30.05, 41.59, 47.56, 126.74, 127.23, 128.83, 130.29, 165.06, 204.04. IR (Nujol, cm^{-1}) 1705, 1530, 1168, 930, 790, 760, 735, 699. MS $[M+H]^+$ m/z calcd for $C_{11}H_{13}N_4O^+$ 217,1011, found 217,0770.

4.2.2. (5-(4-Methylphenyl)tetrazolyl-2)-4-butan-2-one 2b

Colorless crystals, mp 83–85 °C, yield 90%. ^{1}H NMR ($CDCl_3$): δ ppm: 2.25 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.26 (t, 2H, CH_2CO, J = 7.2 Hz), 4.88 (t, 2H CH_2N, J = 7.2 Hz), 7.25–7.28 (m, 2H, C_6H_4), 7.97–8.00 (m, 2H, C_6H_4). ^{13}C NMR ($CDCl_3$): δ ppm: 21.42, 30.05, 41.61, 47.50, 124.42, 126.65, 129.52, 140.45, 165.15, 204.09. IR (Nujol, cm^{-1}) 1700, 1615, 1040, 830, 750. MS $[M+H]^+$ m/z calcd for $C_{12}H_{15}N_4O^+$ 231,1168, found 231,0700.

4.2.3. (5-(4-Chlorophenyl)tetrazolyl-2)-4-butan-2-one 2c

Colorless crystals, mp 91–93 °C, yield 94%. ^{1}H NMR ($CDCl_3$): δ ppm: 2.26 (s, 3H, CH_3), 3.27 (t, 2H, CH_2CO, J = 6.8 Hz), 4.89 (t, 2H CH_2N, J = 6.8 Hz), 7.43–7.45 (m, 2H, C_6H_4), 8.03–8.05 (m, 2H, C_6H_4). ^{13}C NMR ($CDCl_3$): δ ppm: 30.05, 41.53, 47.62, 125.74, 128.04, 129.14, 136.31, 164.20, 203.95. IR (Nujol, cm^{-1}) 1710, 1600, 1080, 1000, 840, 750. MS $[M+H]^+$ m/z calcd for $C_{11}H_{12}ClN_4O^+$ 251,0621, found 251,0348.

4.2.4. (5-(2-Chlorophenyl)tetrazolyl-2)-4-butan-2-one 2d

Oil, yield 81%. ^{1}H NMR ($CDCl_3$): δ ppm: 2.26 (s, 3H, CH_3), 3.28 (t, 2H, CH_2CO, J = 7.2 Hz), 4.94 (t, 2H CH_2N, J = 7.2 Hz), 7.36–7.40 (m, 2H, C_6H_4), 7.50–7.52 (m, 1H, C_6H_4), 7.90–7.93 (m, 1H, C_6H_4). ^{13}C NMR ($CDCl_3$): δ ppm: 30.08, 41.48, 47.70, 126.33, 126.88, 130.77, 131.07, 131.27, 132.93, 163.23, 204.01. IR (film, cm^{-1}) 1720, 1600, 1170, 1065, 1040, 750. MS $[M+H]^+$ m/z calcd for $C_{11}H_{12}ClN_4O^+$ 251,0621, found 251,0232.

4.3. General procedure for the synthesis of (5-aryltetrazolyl-2)-propan-2-ones 5a–d

To a solution of 5-substituted tetrazole **1a–d** (0.059 mol) and grounded K_2CO_3 (0.073 mol, 10.1 g) in acetone (85 mL), chloroacetone (0.067 mol, 5.5 mL) was added dropwise with stirring at room temperature for 15 min. Then the reaction mixture was refluxed (55–59 °C) for the time indicated in Table 3. The progress of the reaction was monitored by TLC with chloroform–methanol (9:1 v/v) as the eluent. After completion of the reaction, the precipitate was filtered off, washed with acetone (3 × 50 mL) and the solvent and washings were evaporated under reduced pressure. To the residue, 100 mL of water was added and the resulting solid was collected by filtration. The product was recrystallized from methanol.

4.3.1. (5-Phenyltetrazolyl-2)-propan-2-one 5a

Colorless crystals, mp 132–134 °C, yield 55%. ^{1}H NMR ($CDCl_3$): δ ppm: 2.24 (s, 3H, CH_3), 5.47 (s, 2H, CH_2), 7.47–7.50 (m, 3H, C_6H_5), 8.13–8.16 (m, 2H, C_6H_5). ^{13}C NMR ($CDCl_3$): δ ppm: 27.05, 60.86, 126.87, 126.93, 128.88, 130.50, 165.63, 197.83. IR (Nujol, cm^{-1}) 1719, 1070, 1040, 725, 680. MS $[M+H]^+$ m/z calcd for $C_{10}H_{11}N_4O^+$ 203,0855, found 203,0644.

4.3.2. (5-(4-Methylphenyl)tetrazolyl-2)-propan-2-one 5b

Colorless crystals, mp 139–140 °C, yield 54%. ^{1}H NMR ($CDCl_3$): δ ppm: 2.23 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 5.46 (s, 2H, CH_2), 7.28–7.30 (m, 2H, C_6H_4), 8.02–8.04 (m, 2H, C_6H_4). ^{13}C NMR ($CDCl_3$): δ ppm: 21.45, 27.05, 60.84, 124.14, 126.80, 129.58, 140.74, 165.75, 197.97. IR (Nujol, cm^{-1}) 1720, 1175, 1040, 820, 745. MS $[M+H]^+$ m/z calcd for $C_{11}H_{13}N_4O^+$ 217,1011, found 217,0716.

4.3.3. (5-(4-Chlorophenyl)tetrazolyl-2)-propan-2-one 5c

Colorless crystals, mp 180–182 °C, yield 38%. ^{1}H NMR ($CDCl_3$): δ ppm: 2.27 (s, 3H, CH_3), 5.48 (s, 2H, CH_2), 7.46–7.48 (m, 2H, C_6H_4), 8.08–8.10 (m, 2H, C_6H_4). ^{13}C NMR ($CDCl_3$): δ ppm: 27.13, 60.93, 125.48, 128.22, 129.23, 136.61, 164.84, 197.57. IR (Nujol, cm^{-1}) 1725, 1175, 1085, 1040, 995, 832, 750. MS $[M+H]^+$ m/z calcd for $C_{10}H_{10}ClN_4O^+$ 237,0465, found 237,0298.

4.3.4. (5-(2-Chlorophenyl)tetrazolyl-2)-propan-2-one 5d

Colorless crystals, mp 99–101 °C, yield 58%. ^{1}H NMR ($CDCl_3$): δ ppm: 2.25 (s, 3H, CH_3), 5.53 (s, 2H, CH_2), 7.38–7.42 (m, 2H, C_6H_4), 7.52–7.54 (m, 1H, C_6H_4), 7.96–7.98 (m, 1H, C_6H_4). ^{13}C NMR ($CDCl_3$): δ ppm: 27.09, 60.96, 126.05, 126.93, 130.81, 131.27, 131.38, 133.02, 163.78, 197.66. IR (Nujol, cm^{-1}) 1728, 1205, 1175, 1060, 1030, 795, 750. MS $[M+H]^+$ m/z calcd for $C_{10}H_{10}ClN_4O^+$ 237,0465, found 237,0241.

4.4. General procedure for the synthesis of alcohols (±)-3a–d and (±)-6a–d

In a typical experiment, sodium borohydride (56 mmol, 2.12 g) was added portionwise to a cooled (16 °C) and stirred mixture of the appropriate ketone **2a–d** or **5a–d** (14 mmol) dissolved in 60 mL of methanol. The reaction mixture was stirred at room temperature. The progress of the reaction was monitored by TLC, using toluene–ethyl acetate (5:1 v/v) as the eluent. After completion of the reaction (approximately 2.5 h), the solvent was evaporated and to the resulting crude product, 40 mL of H_2O was added. The mixture was extracted with Et_2O (3 × 50 mL) and the organic layer was washed with water (3 × 50 mL), dried over anhydrous $MgSO_4$, and evaporated.

4.4.1. (5-Phenyltetrazolyl-2)-4-butan-2-ol 3a

Oil, yield 94%. ^{1}H NMR ($CDCl_3$): δ ppm: 1.26 (d, 3H, CH_3, J_{CH3CH} = 6 Hz), 2.08–2.12 (m, 1H, CH_aH_b), 2.20–2.25 (m, 2H,

CH_aH_b + OH), 3.80–3.90 (m, 1H, CH), 4.78–4.85 (m, 2H, CH_2N), 7.46–7.48 (m, 3H, C_6H_5), 8.11–8.13 (m, 2H, C_6H_5). ^{13}C NMR ($CDCl_3$): δ ppm: 23.61, 38.02, 50.14, 64.66, 126.74, 127.26, 128,81, 130.28, 165.02. IR (film, cm^{-1}) 3400, 2980, 1520, 1445, 1130, 1015, 725, 688. MS $[M+H]^+$ m/z calcd for $C_{11}H_{15}N_4O^+$ 219,1168, found 219,0780.

4.4.2. (5-(4-Methylphenyl)tetrazolyl-2)-4-butan-2-ol 3b

Colorless crystals, mp 47–49 °C, yield 95%. ^1H NMR ($CDCl_3$): δ ppm: 1.26 (d, 3H, CH_3, J_{CH3CH} = 6 Hz), 2.07–2.13 (m, 1H, CH_aH_b), 2.17–2.23 (m, 2H, CH_aH_b + OH), 2.40 (s, 3H, CH_3), 3.84–3.86 (m, 1H, CH), 4.77–4.84 (m, 2H, CH_2N), 7.26–7.29 (m, 2H, C_6H_4), 7.99–8.01 (m, 2H, C_6H_4). ^{13}C NMR ($CDCl_3$): δ ppm: 21.43, 23.60, 38.02, 50.07, 64.67, 124.46, 126.67, 129.53, 140.44, 165.11. IR (Nujol, cm^{-1}) 3470, 1115, 1062, 1040, 818, 740. MS MS $[M+H]^+$ m/z calcd for $C_{12}H_{17}N_4O^+$ 233,1324, found 233,0893.

4.4.3. (5-(4-Chlorophenyl)tetrazolyl-2)-4-butan-2-ol 3c

Colorless crystals, mp 70–73 °C, yield 96%. ^1H NMR ($CDCl_3$): δ ppm: 1.27 (d, 3H, CH_3, J_{CH3CH} = 6 Hz), 2.06–2.12 (m, 2H, CH_aH_b + OH), 2.19–2.23 (m, 1H, CH_aH_b), 3.84–3.89 (m, 1H, CH), 4.74–4.88 (m, 2H, CH_2N), 7.43–7.46 (m, 2H, C_6H_4), 8.04–8.08 (m, 2H, C_6H_4). ^{13}C NMR ($CDCl_3$): δ ppm: 23.68, 37.98, 50.22, 64.71, 125.80, 128.05, 129.16, 136.31, 164.18. IR (Nujol, cm^{-1}) 3465, 1608, 1120, 1090, 1070, 833, 755. MS $[M+H]^+$ m/z calcd for $C_{11}H_{13}ClN_4O^+$ 253,0778, found 253,0589.

4.4.4. (5-(2-Chlorophenyl)tetrazolyl-2)-4-butan-2-ol 3d

Oil, yield 95%. ^1H NMR ($CDCl_3$): δ ppm: 1.26 (d, 3H, CH_3, J_{CH3CH} = 6.4 Hz), 2.02 (s, 1H, OH), 2.06–2.15 (m, 1H, CH_aH_b), 2.20–2.28 (m, 1H, CH_aH_b), 3.86–3.90 (m, 1H, CH), 4.84–4.90 (m, 2H, CH_2N), 7.37–7.41 (m, 2H, C_6H_4), 7.52–7.54 (m, 1H, C_6H_4) 7.92–7.95 (m, 1H, C_6H_4). ^{13}C NMR ($CDCl_3$): δ ppm: 23.62, 38.01, 50.29, 64.73, 126.40, 126.92, 130.80, 131.09, 131.29, 132.99, 163.23. IR (film, cm^{-1}) 3420, 2985, 1460, 1125, 1065, 1030, 745. MS $[M+H]^+$ m/z calcd for $C_{11}H_{13}ClN_4O^+$ 253,0778, found 253,0719.

4.4.5. (5-Phenyltetrazolyl-2)-propan-2-ol 6a

Colorless crystals, mp 53–55 °C, yield 95%. ^1H NMR ($CDCl_3$): δ ppm: 1.34 (d, 3H, CH_3, J_{CH3CH} = 6.4 Hz), 3.02 (s, 1H, OH), 4.43–4.47 (m, 1H, CH), 4.57 and 4.61 (dd, 1H, C*Ha*HbN, J_{HaCH} = 7.6 Hz, J_{HaHb} = 13.6 Hz), 4.66 and 4.69 (dd, 1H, CHa*Hb*N, J_{HbCH} = 3.6 Hz), 7.45–7.47 (m, 3H, C_6H_5), 8.06–8.09 (m, 2H, C_6H_5). ^{13}C NMR ($CDCl_3$): δ ppm: 20.22, 59.78, 66.18, 126.77, 126.93, 128.85, 130.41, 165.06. IR (Nujol, cm^{-1}) 3325, 1125, 1060, 840, 775, 725, 685. MS $[M+H]^+$ m/z calcd for $C_{10}H_{13}N_4O^+$ 205,1011, found 205,0980.

4.4.6. (5-(4-Methylphenyl)tetrazolyl-2)-propan-2-ol 6b

Colorless crystals, mp 85–87 °C, yield 92.5%. ^1H NMR ($CDCl_3$): δ ppm: 1.33 (d, 3H, CH_3, J_{CH3CH} = 6.4 Hz), 2.40 (s, 3H, C*H3*C_6H_4), 3.01 (s, 1H, OH), 4.42–4.46 (m, 1H, CH), 4.56 and 4.59 (dd, 1H, C*Ha*HbN, J_{HaCH} = 7.6 Hz, J_{HaHb} = 13,6 Hz), 4.64 and 4.68 (dd, 1H, CHa*Hb*N, J_{HbCH} = 3.6 Hz), 7.25–7.27 (m, 2H, C_6H_4), 7.96–7.98 (m, 2H, C_6H_4). ^{13}C NMR ($CDCl_3$): δ ppm: 20.20, 21.45, 59.73, 66.19, 124.14, 126.70, 129.55, 140.61, 165.16. IR (Nujol, cm^{-1}) 3330, 1135, 1070, 928, 828, 749. MS $[M+H]^+$ m/z calcd for $C_{11}H_{15}N_4O^+$ 219,1168, found 219,0672.

4.4.7. (5-(4-Chlorophenyl)tetrazolyl-2)-propan-2-ol 6c

Colorless crystals, mp 100–103 °C, yield 90.5%. ^1H NMR ($CDCl_3$): δ ppm: 1.35 (d, 3H, CH_3, J_{CH3CH} = 6.4 Hz), 2.79 (s, 1H, OH), 4.42–4.49 (m, 1H, CH), 4.58 and 4.61 (dd, 1H, C*Ha*HbN, J_{HaCH} = 7.6 Hz, J_{HaHb} = 13,6 Hz), 4.66 and 4.69 (dd, 1H, CHa*Hb*N, J_{HbCH} = 3.6 Hz), 7.42–7.45 (m, 2H, C_6H_4), 8.01–8.04 (m, 2H, C_6H_4). ^{13}C NMR ($CDCl_3$): δ ppm: 20.29, 59.87, 66.21, 125.47, 128.06, 129.18, 136.50, 164.23. IR (Nujol, cm^{-1}) 3200, 1415, 1195, 1090, 935, 840, 755, 735. MS $[M+H]^+$ m/z calcd for $C_{10}H_{12}ClN_4O^+$ 239,0621, found 239,0238.

4.4.8. (5-(2-Chlorophenyl)tetrazolyl-2)-propan-2-ol 6d

Oil, yield 91%. ^1H NMR ($CDCl_3$): δ ppm: 1.35 (d, 3H, CH_3, J_{CH3CH} = 6.4 Hz), 2.67 (s, 1H, OH), 4.45–4.48 (m, 1H, CH), 4.63 and 4.66 (dd, 1H, C*Ha*HbN, J_{HaCH} = 8 Hz, J_{HaHb} = 14 Hz), 4.74 and 4.78 (dd, 1H, CHa*Hb*N, J_{HbCH} = 3.2 Hz), 7.39–7.425 (m, 2H, C_6H_4), 7.52–7.54 (m, 1H, C_6H_4), 7,96–7.98 (m, 1H, C_6H_4). ^{13}C NMR ($CDCl_3$): δ ppm: 20.19, 59.80, 66.21, 126.09, 126.96, 130.86, 131.23, 131.28, 133.02, 163.30. IR (film, cm^-) 3420, 2985, 1595, 1455, 1125, 1060, 1030, 940, 775, 745. MS $[M+H]^+$ m/z calcd for $C_{10}H_{12}ClN_4O^+$ 239,0621, found 239,081.

4.5. General procedure for the enzyme-catalyzed transesterification of alcohols (±)-3a–d and (±)-6a–d

In a typical experiment, the appropriate alcohol (±)-**3a–d** or (±)-**6a–d** (2 mmol) was dissolved in 10 mL of TBME. Then vinyl acetate (2 mmol, 0.18 mL), molecular sieves 4 Å (200 mg), and 40 mg of enzyme were added. The mixture was stirred at room temperature (20–25 °C) and the conversion monitored by TLC with toluene–ethyl acetate (5:1 v/v) as the eluent. After the appropriate time, the reaction was stopped by filtering off the enzyme and molecular sieves. The solvent was evaporated under reduced pressure. The mixture of acetate and unchanged alcohol was separated by column chromatography on silica gel with a toluene–ethyl acetate (5:1 v/v) mixture as the eluent. The enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel OD-H column. NMR spectra of the enantiomerically enriched alcohols (*S*)-(+)-**3a–d** were identical with those of (±)-**3a–d**. The specific rotations were measured in MeOH solution for the enantiomerically enriched alcohols and are as follows:

(*S*)-(+)-**3a**: $[\alpha]_D^{22} = +20.2$ (*c* 2.43, CH_3OH), ee = 70%;
(*S*)-(+)-**3b**: $[\alpha]_D^{22} = +20.2$ (*c* 2.52, CH_3OH), ee = 72%;
(*S*)-(+)-**3c**: $[\alpha]_D^{22} = +13.75$ (*c* 2.91, CH_3OH), ee = 59%;
(*S*)-(+)-**3d**: $[\alpha]_D^{24} = +22.2$ (*c* 2.12, CH_3OH), ee = 98%;
(*S*)-(+)-**6b**: $[\alpha]_D^{29} = +36.4$ (*c* 2.35, CH_3OH), ee = 68%;
(*S*)-(+)-**6c**: $[\alpha]_D^{26} = +34.5$ (*c* 2.42, CH_3OH), ee = 74%;
(*S*)-(+)-**6d**: $[\alpha]_D^{25} = +43.1$ (*c* 1.95, CH_3OH), ee = 99%.

4.5.1. (*R*)-(−)-(5-Phenyltetrazolyl-2)-4-butan-2-yl acetate 4a

Oil, yield 81.5%. ^1H NMR ($CDCl_3$): δ ppm: 1.29 (d, 3H, CH_3, J_{CH3CH} = 6.4 Hz), 2.01 (s, 3H, CH_3CO), 2.29–2.35 (m, 2H, CH_2), 4.70–4.73 (m, 2H, CH_2N), 4.96–5.00 (m, 1H, CH), 7.45–7.50 (m, 3H, C_6H_5), 8.11–8.14 (m, 2H, C_6H_5). ^{13}C NMR ($CDCl_3$): δ ppm: 19.85, 21.11, 35.13, 49.66, 67.94, 126.75, 127.30, 128.84, 130.26, 165.11, 170.36. IR (film, cm^{-1}) 1730, 1445, 1370, 1235, 1065, 728, 690. MS $[M+H]^+$ m/z calcd for $C_{13}H_{17}N_4O_2^+$ 261,1273, found 261,0687. $[\alpha]_D^{22} = -22.6$ (*c* 2.19, CH_3OH) ee = 96%.

4.5.2. (*R*)-(−)-(5-(4-Methylphenyl)tetrazolyl-2)-4-butan-2-yl acetate 4b

Oil, yield 86%. ^1H NMR ($CDCl_3$): δ ppm: 1.29 (d, 3H, CH_3, J_{CH3CH} = 6.0 Hz), 2.01 (s, 3H, CH_3CO), 2.23–2.37 (m, 2H, CH_2), 2.40 (s, 3H, CH_3), 4.69–4.72 (m, 2H, CH_2N), 4.94–5.02 (m, 1H, CH), 7.26–7.29 (m, 2H, C_6H_4), 8.00–8.02 (m, 2H, C_6H_4). ^{13}C NMR ($CDCl_3$): δ ppm: 19.85, 21.12, 21.45, 35.13, 49.62, 67.99, 124.49, 126.67, 129.54, 140.43, 165,10, 170.37. IR (film, cm^{-1}) 1735, 1460, 1370, 1235, 1040, 825, 750. MS $[M+H]^+$ m/z calcd for $C_{14}H_{19}N_4O_2^+$ 275,1430, found 275,0847. $[\alpha]_D^{22} = -20.2$ (*c* 2.35, CH_3OH) ee = 93%.

4.5.3. (*R*)-(−)-(5-(4-Chlorophenyl)tetrazolyl-2)-4-butan-2-yl acetate 4c

Colorless crystals, mp 46–48 °C, yield 97%. ^1H NMR ($CDCl_3$): δ ppm: 1.29 (d, 3H, CH_3, J_{CH3CH} = 6 Hz), 2.01 (s, 3H, CH_3CO), 2.29–2.34 (m, 2H, CH_2), 4.69–4.73 (m, 2H, CH_2N), 4.93–5.01 (m, 1H,

CH), 7.44–7.46 (m, 2H, C_6H_4), 8.05–8.07 (m, 2H, C_6H_4). ^{13}C NMR ($CDCl_3$): δ ppm: 19.86, 21.11, 35.11, 49.74, 67.87, 125.80, 128.05, 129.16, 136.30, 164.25, 170.34. IR (Nujol, cm^{-1}) 1720, 1605, 1240, 1085, 1060, 1040, 1010, 948, 830, 750. MS $[M+H]^+$ m/z calcd for $C_{13}H_{16}ClN_4O_2^+$ 295,0884 found 295,0381. $[\alpha]_D^{22} = -24.9$ (c 2.38, CH_3OH) ee = 91%.

4.5.4. (*R*)-(−)-(5-(2-Chlorophenyl)tetrazolyl-2)-4-butan-2-yl acetate 4d

Colorless crystals, mp 42–44 °C, yield 96.5%. ^{1}H NMR ($CDCl_3$): δ ppm: 1.29 (d, 3H, CH_3, J_{CH3CH} = 6.4 Hz), 2.01 (s, 3H, CH_3CO), 2.31–2.38 (m, 2H, CH_2), 4.74–4.78 (m, 2H, CH_2N), 4.96–5.01 (m, 1H, CH), 7.35–7.42 (m, 2H, C_6H_4), 7.51–7.53 (m, 1H, C_6H_4), 7.91–7.94 (m, 1H, C_6H_4). ^{13}C NMR ($CDCl_3$): δ ppm: 19.83, 21.12, 35.10, 49.81, 67.92, 126.40, 126.88, 130.77, 131.04, 131.28, 132.97, 163.30, 170.34. IR (Nujol, cm^{-1}) 1721, 1245, 1060, 750. MS $[M+H]^+$ m/z calcd for $C_{13}H_{16}ClN_4O_2^+$ 295,0884 found 295,0191. $[\alpha]_D^{24} = -16.7$ (c 3, CH_3OH) ee = 80%.

4.5.5. (*R*)-(+)-(5-Phenyltetrazolyl-2)-propan-2-yl acetate 7a

Oil, yield 95%. ^{1}H NMR ($CDCl_3$): δ ppm: 1.36 (d, 3H, CH_3, J_{CH3CH} = 6.4 Hz), 2.01 (s, 3H, CH_3CO), 4.77–4.79 (m, 2H, CH_2N), 5.42–5.47 (m, 1H, CH), 7.46–7.50 (m, 3H, C_6H_5), 8.13–8.15 (m, 2H, C_6H_5). ^{13}C NMR ($CDCl_3$): δ ppm: 17.43, 20.89, 56.27, 67.84, 126.79, 127.19, 128.86, 130.35, 165.21, 170.03. IR (film, cm^{-1}) 1745, 1450, 1370, 1235, 790, 730, 690. MS $[M+H]^+$ m/z calcd for $C_{12}H_{15}N_4O_2^+$ 247,1117 found 247,0660.

4.5.6. (*R*)-(+)-(5-(4-Methylphenyl)tetrazolyl-2)-propan-2-yl acetate 7b

Oil, yield 79%. ^{1}H NMR ($CDCl_3$): δ ppm: 1.35 (d, 3H, CH_3, J_{CH3CH} = 6.8 Hz), 2.00 (s, 3H, CH_3CO), 2.40 (s, 3H, CH_3), 4.73 and 4.76 (dd, 1H, CHaHbN, J_{HaCH} = 2.4 Hz, J_{HaHb} = 14 Hz), 4.77 and 4.80 (dd, 1H, CHaHbN, J_{HbCH} = 1.6 Hz), 5.41–5.46 (m, 1H, CH), 7.26–7.29 (m, 2H, C_6H_4), 8.00–8.03 (m, 2H, C_6H_4). ^{13}C NMR ($CDCl_3$): δ ppm: 17.43, 20.89, 21.45, 56.21, 67.86, 124.39, 126.71, 129.54, 140.52, 164.20, 170.03. IR (film, cm^{-1}) 1740, 1615, 1460, 1370, 1235, 825, 750. MS $[M+H]^+$ m/z calcd for $C_{13}H_{17}N_4O_2^+$ 261,1273 found 261,0865. $[\alpha]_D^{29} = +7.3$ (c 2.18, CH_3OH) ee = 83%.

4.5.7. (*R*)-(+)-(5-(4-Chlorophenyl)tetrazolyl-2)-propan-2-yl acetate 7c

Colorless crystals, mp 66–68 °C, yield 96%. ^{1}H NMR ($CDCl_3$): δ ppm: 1.35 (d, 3H, CH_3, J_{CH3CH} = 6.4 Hz), 2.00 (s, 3H, CH_3CO), 4.72–4.81 (m, 2H, CH_2N), 5.40–5.46 (m, 1H, CH), 7.43–7.47 (m, 2H, C_6H_4), 8.05–8.08 (m, 2H, C_6H_4). ^{13}C NMR ($CDCl_3$): δ ppm: 17.45, 20.88, 56.37, 67.79, 125.70, 128.09, 129.16, 136.38, 164.36, 170.00. IR (Nujol, cm^{-1}) 1740, 1600, 1225, 1082, 1055, 1040, 839, 750. MS $[M+H]^+$ m/z calcd for $C_{12}H_{14}ClN_4O_2^+$ 281,0727 found 281,0343. $[\alpha]_D^{26} = +5.2$ (c 2.31, CH_3OH) ee = 91%.

4.5.8. (*R*)-(+)-(5-(2-Chlorophenyl)tetrazolyl-2)-propan-2-yl acetate 7d

Oil, yield 96%. ^{1}H NMR ($CDCl_3$): δ ppm: 1.37 (d, 3H, CH_3, J_{CH3CH} = 6.8 Hz), 2.01 (s, 3H, CH_3CO), 4.78 and 4.81 (dd, 1H, CHaHbN, J_{HaCH} = 6.8 Hz, J_{HaHb} = 14 Hz), 4.84 and 4.87 (dd, 1H, CHaHbN, J_{HbCH} = 4.4 Hz), 5.41–5.49 (m, 1H, CH), 7.35–7.42 (m, 3H, C_6H_5), 7.50–7.55 (m, 1H, C_6H_4), 7.92–7.96 (m, 1H, C_6H_4) .^{13}C NMR ($CDCl_3$): δ ppm: 17.43, 20.88, 56.40, 67.86, 126.32, 126.88, 130.78, 131.10, 131.29, 133.04, 163.39, 170.01. IR (film, cm^{-1}) 1740, 1455, 1370, 1230, 1060, 745. MS $[M+H]^+$ m/z calcd for $C_{12}H_{14}ClN_4O_2^+$ 281,0727 found 281,0220. $[\alpha]_D^{26} = +8.8$ (c 2.85, CH_3OH) ee = 78%.

4.6. General procedure for the synthesis of racemic mixtures of acetates (±)-4a–d and (±)-7a–d

A mixture of the appropriate alcohol **3-a–d** or **6a–d** (1 mmol) and anhydrous pyridine (0.63 mL) in acetic anhydride (0.63 mL) was stirred at room temperature for 24 h. The progress of the reaction was monitored by TLC with toluene–ethyl acetate (5:1 v/v) as the eluent. After completion of the reaction the mixture was cooled in an ice bath. The product was extracted with ethyl acetate (3 × 10 mL), and the organic layer was washed with 5% HCl solution (3 × 10 mL), with $NaHCO_3$ solution (3 × 10 mL), and dried over anhydrous $MgSO_4$. The product was purified by chromatography on a short silica gel column with toluene–ethyl acetate (5:1 v/v).

4.7. General procedure for the chemical hydrolysis of acetates (*R*)-(−)-4a–d and (*R*)-(+)-7b

To the appropriate ester (0.4 mmol) dissolved in methanol (2 mL), a solution of 1 M NaOH (2 mL) was added. The mixture was stirred at room temperature for 24 h. The progress of the reaction was monitored by TLC with toluene-ethyl acetate (5:1 v/v) as the eluent. The product was extracted with $CHCl_3$ (4 × 10 mL) and the organic layer washed with water (3 × 50 mL), dried over anhydrous $MgSO_4$, and evaporated. The alcohol was purified by chromatography on a short silica gel column with toluene–ethyl acetate (5:1 v/v) as the eluent. The specific rotations were measured in MeOH solution for the prepared enantiomerically enriched alcohols and are as follows:

(*R*)-(−)-**3a**: $[\alpha]_D^{28} = -29.7$ (c 1.60, CH_3OH), ee = 96%;
(*R*)-(−)-**3b**: $[\alpha]_D^{22} = -25.6$ (c 1.76, CH_3OH), ee = 93%;
(*R*)-(−)-**3c**: $[\alpha]_D^{22} = -22.95$ (c 1.22, CH_3OH), ee = 91%;
(*R*)-(−)-**3d**: $[\alpha]_D^{24} = -21.8$ (c 2.36, CH_3OH), ee = 80%;
(*R*)-(−)-**6b**: $[\alpha]_D^{26} = -52.0$ (c 1.50, CH_3OH), ee = 83%;

NMR Spectra of the enantiomerically enriched alcohols (*S*)-(−)-**3a–d** and (*S*)-(−)-**6b** were identical with those of (±)-**3a–d** and (±)-**6b**.

4.8. Assignment of the absolute configuration of alcohol (−)-3a and its acetate and alcohol (+)-6c and its acetate

The enantiomerically enriched alcohol (−)-**3a** [obtained by hydrolysis of ester (−)-**4a**, isolated from the reaction of lipase Amano AK catalyzed transesterification of the racemate (±)-**3a**], was used in reaction with optically pure (*R*)- and (*S*)-enantiomer of methoxyphenylacetic acid (MPA)[42] (Scheme 5). The ^{1}H NMR spectra of the resulting esters were taken in $CDCl_3$ solution:

(R)–MPA-Ester, δ ppm: 1.31 (d, 3H, CH_3, J_{CH3CH} = 6.4 Hz), 2.17–2.25 (m, 2H, CH_2), 3.42 (s, 3H, CH_3), 4.24–4.30 (m, 2H, CH_2N), 4.77 (s, 1H, CH), 5.01–5.03 (m, 1H, CH), 7.32–7.39 (m, 3H, Ar), 7.45–7.49 (m, 5H, Ar), 8.09–8.11 (m, 2H, Ar);

(S)-MPA-Ester, δ ppm: 1.16 (d, 3H, CH_3, J_{CH3CH} = 6.4 Hz), 2.30–2.35 (m, 2H, CH_2), 3.39 (s, 3H, CH_3), 4.63–4.67 (m, 2H, CH_2N), 4.69 (s, 1H, CH), 5.01–5.09 (m, 1H, CH), 7.33–7.49 (m, 8H, Ar), 8.12–8.14 (m, 2H, Ar).

The differences in the proton chemical shifts ($\Delta\delta RS$) observed for the esters prepared from the (*R*)- and (*S*)-acids, respectively, were calculated separately for the protons bonded to each carbon

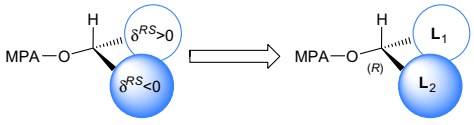
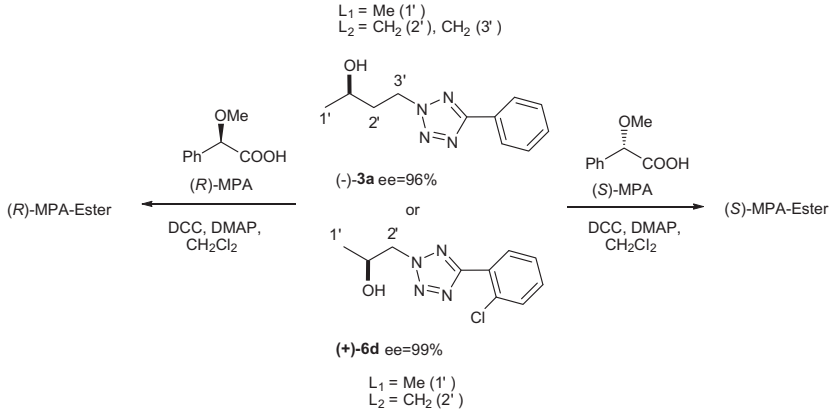


Figure 1.



Scheme 5.

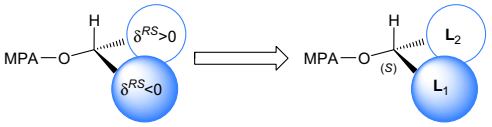


Figure 2.

atom adjacent to the stereogenic center as shown by the following equations:

$$\Delta\delta^{RS}L1 = \delta^{R}L_1 - \delta^{S}L_1 = 1.31 - 1.16 = +0.15ppm$$

$$\Delta\delta^{RS}L2 = \delta^{R}L_2 - \delta^{S}L_2 = (2.21 - 2.32) + (4.27 - 4.65) = (-0.11) + (-0.38) = -0.49ppm$$

The positive value of $\Delta\delta RS$, which corresponds to the signal of the protons of the substituent L_1, and the opposite minus sign for the protons L_2 indicate an (*R*)-configuration for the enantiomer (−)-**3a** according to Figure 1:

The same procedure was applied to the second enantiomer of the alcohol (+)-**6d** isolated from the racemate (±)-**6d** (Scheme 5). ^{1}H NMR spectra of the resulting esters were taken in $CDCl_3$ solution:

(R)–MPA-Ester, δ ppm: 1.25 (d, 3H, CH_3, J_{CH3CH} = 6.4 Hz), 3.34 (s, 3H, CH_3), 4.70 (s, 1H, CH), 4.82–4.88 (m, 2H, CH_2N), 5.49–5.56 (m, 1H, CH), 7.25–7.44 (m, 7H, Ar), 7.53–7.55 (m, 1H, Ar), 7.91–7.93 (m, 1H, Ar).

(S)-MPA-Ester, δ ppm: 1.42 (d, 3H, CH_3, J_{CH3CH} = 6.4 Hz), 3.34 (s, 3H, CH_3), 4.63–4.83 (m, 2H, CH_2N), 4.68 (s, 1H, CH), 5.53–5.56 (m, 1H, CH), 7.12–7.44 (m, 7H, Ar), 7.51–7.55 (m, 1H, Ar), 7.83–7.85 (m, 1H, Ar).

The differences in the chemical shifts ($\Delta\delta RS$) observed for the esters prepared from the (*R*)- and (*S*)-acids, respectively, were calculated separately for the protons attached to two carbons bonded directly to chiral carbon as shown by the following equations:

$$\Delta\delta^{RS}L1 = \delta^{R}L_1 - \delta^{S}L_1 = 1.25 - 1.42 = -0.17ppm$$

$$\Delta\delta^{RS}L2 = \delta^{R}L_2 - \delta^{S}L_2 = 4.85 - 4.73 = +0.12ppm$$

The negative value of $\Delta\delta RS$, which corresponds to the signal of protons of the substituent L_1, and the opposite plus sign resulting for the protons L_2 indicate an (*S*)-configuration for enantiomer (+)-**6d** according to Figure 2.

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