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Preparation of various enantiomerically pure (benzotriazol-1-yl)- and (benzotriazol-2-yl)-alkan-2-ols

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Abstract—(*S*)-(−)-(Benzotriazol-1-yl)- and (*S*)-(−)-(benzotriazol-2-yl)-alkan-2-ols **7a**–**9a**, **7b**–**9b** and their (*R*)-(+)-acetates **10a**–**12a** and **10b**–**12b** were prepared in high enantiomeric excess via lipase from *Pseudomonas fluorescens* (Amano AK) catalyzed enantioselective acetylation of racemic alcohols **4a**–**6a** and **4b**–**6b** with vinyl acetate in *tert*-butyl methyl ether or toluene at 23 °C. The enantioselectivity of this transformation was dependent on the length of the alkyl chain with *E*-values ranging from 30 to 57. Several benzotriazole substituted ketones **1a**–**3a** and **1b**–**3b** were synthesized from 1*H*-benzotriazole and corresponding haloketones. These compounds were stereoselectively reduced with Baker's yeast in water or in organic solvent containing 5% v/v of water at 30 °C to give the (*S*)-(−)-alcohol. Better stereoselectivity was observed in the kinetic resolution of racemic alcohols **4a**–**6a** and **4b**–**6b** (ee = 69–92% at 44–52% conversion) compared to reduction of corresponding prochiral ketones **1a**–**3a** and **1b**–**3b** with Baker's yeast (ee = 40–67% at 39–89% conversion). Enhanced enantioselectivities were observed at lower temperatures.

1. Introduction

Recently, many 1*H*- and 2*H*-benzotriazole derivatives have attracted considerable attention because of their possible application in medicine,[1–4] agriculture,[5–7] and industry[8] (Fig. 1). As has been reported, they exhibit various pharmaceutical activities, for example, 5- and 6-chloro-1-aroylbenzotriazoles **A** as well as (aminoalkoxy)-benzotriazoles **B** were reported to show analgesic, anti-inflammatory, and central nervous system depressant activities. Some 1-alkylbenzotriazoles, as well as their 4-nitro derivatives are of particular interest as herbicides, insecticides, and

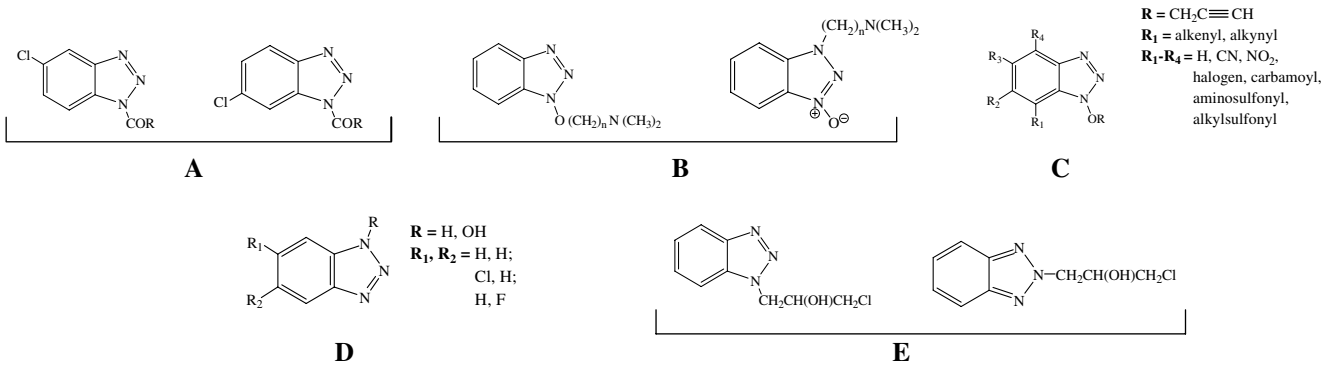

Figure 1.

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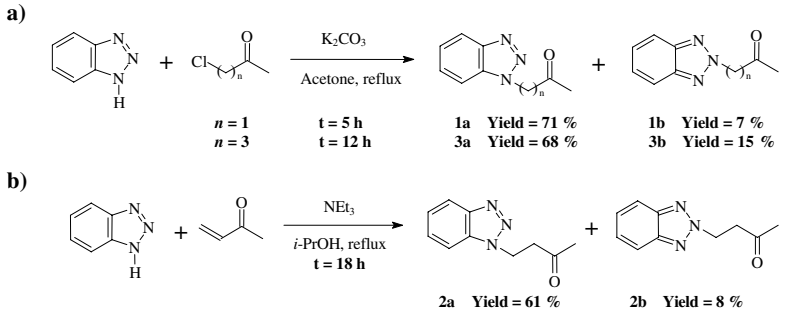
acaricides **C**. Besides their biological activity, some other important industrial applications of benzotriazoles are known, including dyestuffs, fluorescent compounds, corrosion inhibitors **D**, and photostabilizers. It is interesting to note that until now, no natural products containing benzotriazole moieties have been isolated. Therefore only classical functionalization of the easily available and inexpensive benzotriazole is considered as a potential source of new auxiliaries and synthons for asymmetric synthesis. Considering various applications of benzotriazole derivatives and their miscellaneous biological activities, which in the case of chiral compounds, depend on the configuration of the stereogenic center, our attention was focused on the search for a simple method of preparation of some alcohols, **4a–6a** and **4b–6b** (Scheme 2) in enantiomerically pure form, since, for instance, racemic *N*-1- and *N*-2-(chlorohydroxypropyl)-benzotriazoles **E** useful as antineoplastic agents have been described in the literature[2] (Fig. 1). To the best of our knowledge, chiral benzotriazole analogues have not been described in optically active form. Therefore, in continuation of our investigations dealing with bioconversions,[9–13] we tried to obtain benzotriazol-1-yl- and benzotriazol-2-yl-alkan-2-ols **4a–6a** and **4b–6b** in enantiomerically pure form via lipase-catalyzed acetylation with enol esters. There are some examples in the literature in which racemic alcohols with heterocyclic groups were separated into their enantiomers by lipase-catalyzed acetylation.[14] Alternatively, a stereoselective reduction of a prochiral ketone, can yield an optically active alcohol quantitatively. In recent years Baker's yeast (*Saccharomyces cerevisiae*) has gained increasing importance in view of applications in asymmetric synthesis.[15,16] Among the numerous enzymes in Baker's yeast, oxidoreductases play an important role for reductions of ketones with chloro-,[17] bromo-,[18] perfluoroalkyl-,[19] nitro-,[20,21] hydroxyl-,[22,23] dithianyl-,[24] and even silyl-[25] and germyl-[26] moieties. Thus, we also report our results on the Baker's yeast mediated stereoselective reduction of the ketones **1a–3a** and **1b–3b** (Scheme 1) as another possible route to optically active alcohols **7a–9a** and **7b–9b** (Scheme 3).

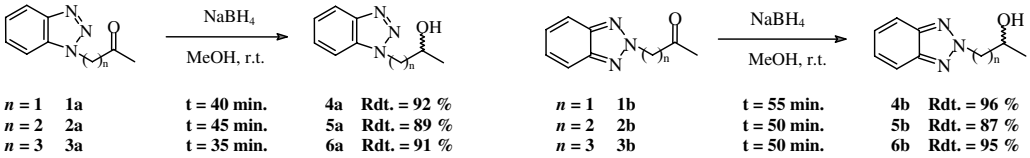
2. Results and discussion

2.1. Synthesis of ketones 1a–3a and 1b–3b and racemic alcohols 4a–6a, 4b–6b

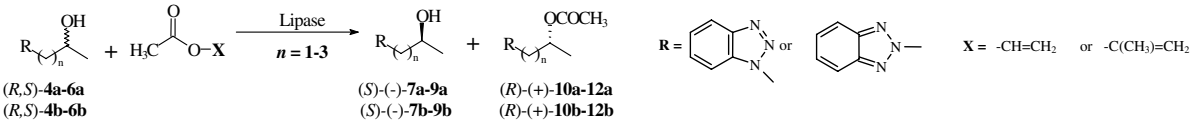
Ketones **1a**, **3a** and **1b**, **3b** were prepared in acceptable yields by the direct N-alkylation of 1*H*-benzotriazole with appropriate haloketones in the presence of K_2CO_3 in acetone[27–29] (Scheme 1a). Ketones **2a** and **2b** were obtained in reasonable yield by the Michael addition[30] between 1*H*-benzotriazole and methyl vinyl ketone in the presence of triethylamine in isopropanol (Scheme 1b). All the reactions were performed under reflux. Racemic alcohols **4a–6a** and **4b–6b** were obtained in high yields (87–96%) by simple reduction of appropriate ketones with sodium tetrahydroborate ($NaBH_4$) in methanol at 25 °C (Scheme 2).



Scheme 1.



Scheme 2.



Scheme 3.

2.2. Kinetic resolution of (±)-4a–6a and (±)-4b–6b by lipase-catalyzed transesterification

The conditions for the lipase-catalyzed acetylation of racemic (benzotriazol-1-yl)-alkan-2-ols (±)-**4a**–**6a** and (benzotriazol-2-yl)-alkan-2-ols (±)-**4b**–**6b** were optimized according to the conventional method (Scheme 3).[31] The effects of lipase, solvent, acyl donor, temperature, additive (e.g., crown ethers and thiacrown ethers) and length of the alkyl chain were evaluated on reactivity and selectivity of enzymatic acetylation.

In a first series of experiments, the efficiency of different commercially available lipases to catalyze the transesterification of chiral alcohols **4a**–**6a**, **4b**–**6b** was investigated. For this purpose, racemic (±)-**4a** and (±)-**4b** taken as model substrates, were treated at room temperature (ca. 23 °C) with 3 equiv of vinyl acetate in *tert*-butyl methyl ether in the presence of a microbial lipase. In control experiments, it was shown that the reaction did not proceed in the absence of enzyme. The main results are given in Table 1. The enantiomeric excesses of **7a**, **7b** and **10a**, **10b** were determined by HPLC using a chiral column. The absolute configuration of the products, alcohols **7a**, **7b** and acetates **10a**, **10b** were determined by the modified Mosher's method as described by Riguera et al.[33,34] According to our investigation, the unchanged alcohol **7a**, **7b** and its acetate **10a**, **10b** have the (*S*)-(−) and (*R*)-(+) configurations, respectively. This assignment agrees well with the Kazlauskas-rule.[35]

The results presented in Table 1, show that for most of the tested lipases, the (*S*)-(−)-alcohol reacts slower than the (*R*)-(+)-enantiomer and the best results with regard to enantioselectivity ($E = 28$–43) and reaction rate (47–55% of conversion within 17–21 h) were obtained with two preparations of lipase from *Pseudomonas fluorescens* (Amano AK and Amano AK-20) and three preparations of lipase from *Pseudomonas cepacia* (Amano PS, Amano P and Amano PS on diatomite). Notably lower enantioselectivities and slightly lower reactivities were obtained, for **4a** and **4b**, with Novozym® SP 435. For another preparation of lipase from *Candida antarctica*-fraction *B*, the enantioselectivities were similar for all cases and were good enough for practical use ($E > 20$). On the other hand, the preparations of lipase from *Burkholderia cepacia*, formerly *P. cepacia*, (Chirazyme® L-1, lyo. and Chirazyme® L-1, c.-f., lyo.) showed significantly higher reaction rates and exhibited promising enantioselectivities for both substrates tested, **4a** and **4b**. The other examined lipases showed no or poor enantioselectivities ($E = 1$–12) and exhibited a poor reaction rate after 4–7 days. It is important to note, that changing the substrate from **4a** to **4b** did not alter the reaction rate and enantioselectivity, with regard to all lipases tested.

We then investigated the proper choice of the solvent. It is important to note that solvent variation in many cases of lipase-catalyzed kinetic resolutions can influence the enantiomeric or enantiotopic selectivity as well as the reaction rate.[36,37] Therefore, we next investigated the proper choice of solvent for finding a correlation between the enantioselectivity of reaction and any physicochemical characteristics of the solvent such as hydrophobicity or dielectric constant.[38] Acetylations of *rac*-**4a** or *rac*-**4b** with vinyl acetate at 23 °C in the presence of lipase Amano AK were performed in various non-polar organic solvents.

Table 1. Lipase-catalyzed kinetic resolutions of *rac*-**4a** and *rac*-**4b** by transesterification[a]

Entry	Lipases[d]	Substrate	Amount of lipase (mg)	Time (h)	Conv.[b] (%)	Alcohol (*S*)-**7a** or **7b** ee_s (%)[c]	Ester (*R*)-**10a** or **10b** ee_p (%)[c]	E[b]
1	**Amano AK**	**4a**	**180**	**20**	**52**	**92**	**86**	**43**
2	**Amano AK**	**4b**	**180**	**21**	**52**	**91**	**85**	**39**
3	**Amano AK-20**	**4a**	**180**	**17**	**47**	**78**	**87**	**34**
4	**Amano AK-20**	**4b**	**180**	**20**	**55**	**96**	**80**	**35**
5	**Amano PS**	**4a**	**180**	**18**	**49**	**80**	**85**	**30**
6	**Amano PS**	**4b**	**180**	**17**	**48**	**78**	**86**	**32**
7	**Amano P**	**4a**	**180**	**21**	**50**	**84**	**83**	**28**
8	**Amano P**	**4b**	**180**	**20**	**49**	**80**	**85**	**30**
9	**Amano PS on diatomite**	**4a**	**120**	**17**	**52**	**93**	**84**	**39**
10	**Amano PS on diatomite**	**4b**	**120**	**17**	**53**	**95**	**84**	**42**
11	Chirazyme® L-1, lyo.	**4a**	5.6	11	56	89	70	17
12	Chirazyme® L-1, c.-f., lyo.	**4a**	200	13	51	80	77	19
13	Novozym® SP 435	**4a**	50	22	49	78	82	24
14	Chirazyme® L-2, c.-f., lyo.	**4a**	50	19	52	85	79	23
15	Chirazyme® L-2, c.-f., C2, lyo.	**4a**	50	30	50	79	79	20
16	Chirazyme® L-2, c.-f., C3, lyo.	**4a**	50	24	50	80	79	21

[a] Conditions: (±)-**4a**, **4b** (175 mg, 1 mmol), vinyl acetate (258 mg, 3 mmol), and *tert*-butyl methyl ether (10 mL) at 23 °C.

[b] Conversions and *E*-values were calculated from the enantiomeric excess of substrate **7a** or **7b** (ee_s) and of product **10a** or **10b** (ee_p) using the usual formula: $E = \ln[(1 - ee_s)(ee_p/(ee_s + ee_p))]/\ln[(1 + ee_s)(ee_p/(ee_s + ee_p))]$, Conv. $= ee_s/(ee_s + ee_p)$; according to Ref. 32.

[c] Determined by chiral HPLC analysis using Chiracel OD-H column.

[d] *Pseudomonas fluorescens* (Amano AK and Amano AK-20), *Pseudomonas cepacia* (Amano PS, Amano P, and Amano PS immobilized on diatomite), *Burkholderia cepacia* formely *Pseudomonas cepacia* (Chirazyme® L-1, lyo. and Chirazyme® L-1, c.-f. lyo.), *Candida rugosa* (Sigma L1754), *Candida rugosa* formely *Candida cylindracea* (Chirazyme® L-3, lyo. and Chirazyme® L-3, purified, lyo.), *Candida antarctica-fraction B* (Novozym® SP 435, immobilized Chirazyme® L-2, c.-f., lyo., Chirazyme® L-2, c.-f., C2, lyo. and Chirazyme® L-2, c.-f., C3, lyo.), *Candida antarctica-fraction A* (Chirazyme® L-5, lyo.), *Pseudomonas* species (Chirazyme® L-6, lyo.), porcine pancreas lipase (Chirazyme® L-7, lyo.), *Thermomyces* species, formely *Humicola* species (Chirazyme® L-8, lyo.), *Alcaligines* species (Chirazyme® L-10, lyo.), lipase from thermophilic microorganism (Chirazyme® L-12, lyo.).

Table 2. Transesterification of vinyl acetate with (±)-**4a** and (±)-**4b** in various solvents[a]

Entry	Substrate	Solvent	Time (h)	Log P[d]	Conv.[b] (%)	Alcohol (*S*)-**7a** or **7b** ee_s (%)[c]	Ester (*R*)-**10a** or **10b** ee_p (%)[c]	E[b]
1	**4a**	None	22	—	53	78	69	13
2	**4a**	*n*-Hexane	18	3.5	52	83	76	19
3	**4a**	**Toluene**	**43**	**2.5**	**51**	**90**	**85**	**38**
4	**4b**	**Toluene**	**47**	**2.5**	**50**	**83**	**84**	**30**
5	**4a**	**Benzene**	**51**	**2.0**	**48**	**82**	**89**	**43**
6	**4b**	**Benzene**	**51**	**2.0**	**48**	**80**	**86**	**33**
7	**4a**	**^{t}BuOMe**	**20**	**1.3**	**52**	**92**	**86**	**43**
8	**4b**	**^{t}BuOMe**	**21**	**1.3**	**52**	**91**	**85**	**39**
9	**4a**	CH_2Cl_2	100	0.6	30	36	83	15
10	**4a**	THF	98	0.49	54	89	76	21
11	**4a**	Acetone	150	−0.23	50	71	70	12
12	**4a**	Acetonitrile	96	−0.33	28	28	72	8
13	**4a**	Dioxane	130	−1.1	35	47	86	21

[a] Conditions: (±)-**4a**, **4b** (175 mg, 1 mmol), vinyl acetate (258 mg, 3 mmol), Amano AK lipase (180 mg) and solvent (10 mL) at 23 °C.
[b,c] See Table 1.
[d] Log P = The logarithm of the partition coefficient of a given solvent between 1-octanol and water.

The main results are given in Table 2. As shown in Table 2, the activity of *P. fluorescens* (Amano AK) lipase in transesterification of **4a** and **4b** is higher in solvents of low polarity as judged by their log P (the logarithm of the partition coefficient of a given solvent between 1-octanol and water). With *n*-hexane, toluene, benzene, and *tert*-butyl methyl ether ($\log P = 1.3$–3.5), the reaction rates were generally higher than for dichloromethane, THF, acetone, acetonitrile and dioxane ($\log P = -1.1$–0.6). In general, for two substrates tested, **4a** and **4b**, enzyme selectivity was sufficient for practical use in all of the used solvents ($E = 21$–43) except *n*-hexane, dichloromethane, acetone, and acetonitrile. Among the solvents tested, *tert*-butyl methyl ether when used as the standard solvent gave the best results with regards to enantioselectivity and reaction rate. Figures 2 and 3 show the course of the conversion of (±)-**4a** and (±)-**4b** in selected solvents and in solvent-free conditions with time. In general, changing the substrate from **4a** to **4b** did not alter the reaction rate and enantioselectivity significantly.

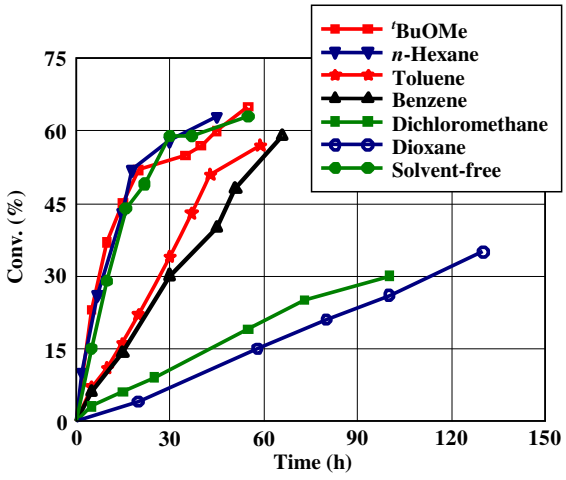


Figure 2. Conversion versus time for Amano AK lipase-catalyzed transesterification of vinyl acetate with (±)-**4a** at 23 °C in selected solvents.

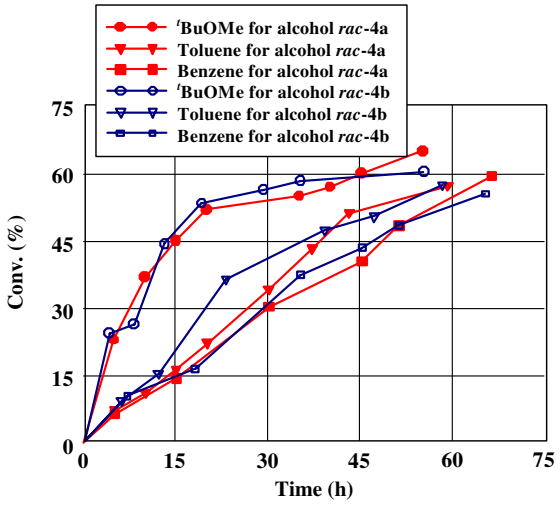


Figure 3. Comparison of conversion versus time for acetylation of (±)-**4a** and (±)-**4b** with vinyl acetate by using Amano AK lipase in ^{t}BuOMe, toluene or benzene at 23 °C.

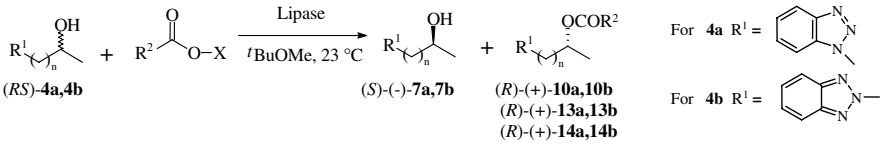
Next, the influence of the amount of Amano AK lipase on the reaction rate and enantioselectivity was investigated. The reaction of (±)-**4a** or (±)-**4b** was carried out with vinyl acetate in *tert*-butyl methyl ether at 23 °C. The amount of enzyme used in all assays was changed in the range 10–180 mg/mmol of substrate. It can be seen clearly from Table 3 that the use of lipase Amano AK in the amounts ranging from 50 to 180 mg/mmol of substrate resulted in good conversions in reasonable times, without significant changes in enantioselectivity ($E = 39$–43), for both substrates tested. Decreasing the amount of enzyme further to 10–25 mg/mmol of substrate led to only a slight decrease of the enantioselectivity ($E = 34$–38) but the reaction proceeded at a slower rate.

The influence of the nature of the acyl donor on the enantioselectivity of lipase-catalyzed transesterification reaction has been well documented by Ema et al.[39] Generally, among the various types of acyl donors examined, enol

Table 3. Influence of the amount of *Pseudomonas fluorescens* lipase (Amano AK) on the transesterification of vinyl acetate with (±)-**4a** and (±)-**4b**[a]

Entry	Substrate	Amount of lipase (mg)	Time (h)	Conv.[b] (%)	Alcohol (*S*)-**7a** or **7b** ee_s (%)[c]	Ester (*R*)-**10a** or **10b** ee_p (%)[c]	*E*[b]
1	**4a**	**180**	**20**	**52**	**92**	**86**	**43**
2	**4b**	**180**	**21**	**52**	**91**	**85**	**39**
3	**4a**	**50**	**43**	**47**	**80**	**89**	**42**
4	**4b**	**50**	**46**	**51**	**90**	**86**	**41**
5	**4a**	25	60	51	87	85	35
6	**4b**	25	59	49	83	87	38
7	**4a**	10	72	43	67	89	35
8	**4b**	10	77	47	78	86	34

[a] Conditions: (±)-**4a**, **4b** (175 mg, 1 mmol), vinyl acetate (258 mg, 3 mmol) and *tert*-butyl methyl ether (10 mL) at 23 °C.
[b,c] See Table 1.



Scheme 4.

Table 4. *Pseudomonas fluorescens* (Amano AK) lipase-catalyzed acetylation of (±)-**4a** and (±)-**4b** by use of various enol esters[a]

Entry	Enol ester	Substrate	R^2	X	Time (h)	Conv.[b] (%)	Alcohol (*S*)-(−) ee_s (%)[c]		Ester (*R*)-(+) ee_p (%)[c]		*E*[b]
1	Vinyl acetate	**4a**	C_4H_9	$CH{=}CH_2$	**20**	**52**	**7a**	**92**	**10a**	**86**	**43**
2	Vinyl acetate	**4b**	C_4H_9	$CH{=}CH_2$	**21**	**52**	**7b**	**91**	**10b**	**85**	**39**
3	Vinyl pentanoate	**4a**	C_4H_9	$CH{=}CH_2$	42	49	**7a**	86	**13a**	89	48
4	Vinyl pentanoate	**4b**	C_4H_9	$CH{=}CH_2$	42	47	**7b**	79	**13b**	89	42
5	Vinyl hexanoate	**4a**	C_5H_{11}	$CH{=}CH_2$	59	45	**7a**	74	**14a**	90	42
6	Vinyl hexanoate	**4b**	C_5H_{11}	$CH{=}CH_2$	59	44	**7b**	72	**14b**	91	46
7	Isopropenyl acetate	**4a**	CH_3	$C(CH_3){=}CH_2$	21	40	**7a**	61	**10a**	93	51
8	Isopropenyl acetate	**4b**	CH_3	$C(CH_3){=}CH_2$	21	43	**7b**	70	**10b**	92	50

[a] Conditions: (±)-**4a**, **4b** (175 mg, 1 mmol), 180 mg of lipase from *Pseudomonas fluorescens* (Amano AK), 3 mmol of enol ester and *tert*-butyl methyl ether (10 mL) at 23 °C.
[b,c] See Table 1.

esters are considered to be the most suitable for kinetic resolution by transesterification.[40] Consequently, the influence of various acyl donors was screened for the Amano AK lipase-catalyzed transesterification of *rac*-**4a** or *rac*-**4b** in *tert*-butyl methyl ether at 23 °C (Scheme 4); the results are shown in Table 4.

As shown in Table 4 and Figure 4, the best results with regard to enantioselectivity and reaction rate were obtained when acetylations of *rac*-**4a** and *rac*-**4b** catalyzed by lipase Amano AK were carried out with vinyl acetate ($E = 43$ and $E = 39$ in 20 and 21 h for 52% conversions, respectively). The length of the alkyl chain of the vinyl esters has only a small effect on the enantioselectivity of this reaction, but important decrease in the reaction rate. On the other hand, as can be seen from the conversion versus time curves in Figure 4 and Table 4, changing the vinyl acetate to isopropenyl acetate notably prolonged the reaction time but led to a noticeable increase in the enantioselectivity. In order to investigate whether the enantioselectivity of Amano AK lipase-catalyzed acetylation of *rac*-**4a** with vinyl acetate in *tert*-butyl methyl ether at 23 °C changes during the

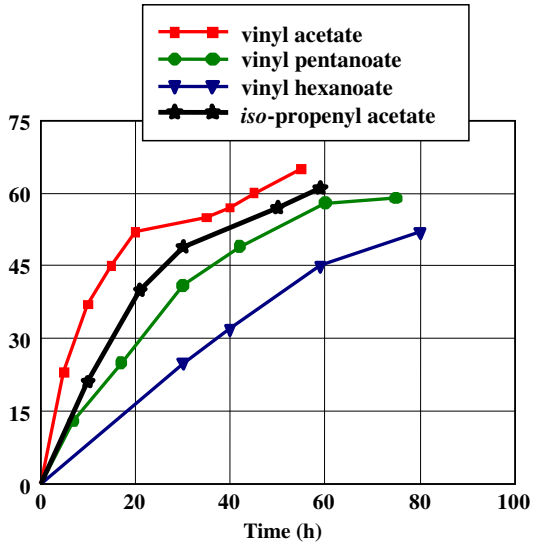


Figure 4. Conversion versus time for *Pseudomonas fluorescens* (Amano AK) lipase-catalyzed acetylation of *rac*-**4a** with tested enol esters.

reaction time we measured the enantiomeric purities of products (*S*)-**7a** and (*R*)-**10a** over time. The dependence of the enantiomeric purities of the alcohol and acetate products on the conversion in this reaction is shown in Figure 5.

The addition of certain additives, such as triethylamine,[41] crown ethers,[42] and some thiacrown ethers[43] in small amounts, has been reported to improve the efficiency of hydrolytic enzymes in several cases. Therefore, in the next step, the influence of selected additives was screened for the Amano AK lipase-catalyzed acetylation of (±)-**4a** and (±)-**4b** with vinyl acetate in *tert*-butyl methyl ether at 23 °C (Table 5). It is obvious from Table 5, that the use of selected additives in acetylation of (±)-**4a** and (±)-**4b** has a negative effect on both the reaction rate (except triethylamine) and the enantioselectivity. Without any additive, the reaction proceeded with higher enantioselectivity giving a good conversion in a reasonable time. The addition of the triethylamine (14 mol %) induces a notable acceleration of the reaction rate, but the enantiomeric ratio was significantly decreased. On the other hand, the addition of crown ethers (18–6 and 15–5) and TDA-1 significantly increased the reaction time, but has only a slight effect on the enantioselectivity of the reaction. It is important to note, that addition of 5 mol % of thiacrown ethers (TTCTD and TTCHD-D) only slightly increased the reaction time and enantioselectivity. Generally, for all the additives tested, changing the substrate from (±)-**4a** to (±)-**4b** did not alter the reaction rate and enantioselectivity considerably.

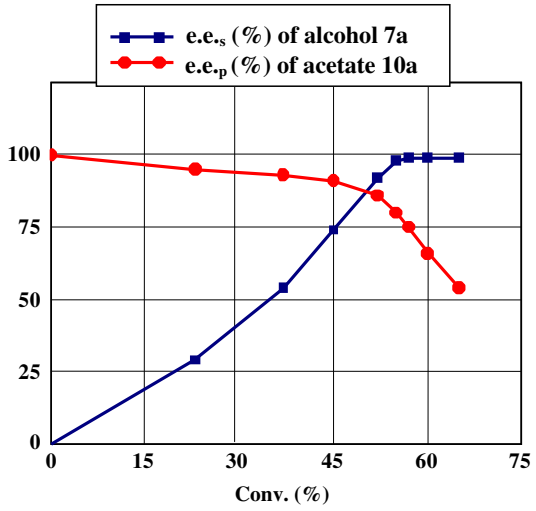


Figure 5. Dependance of enantiomeric purities of **7a** and **10a** on the conversion of (±)-**4a** in Amano AK lipase-catalyzed acetylation with vinyl acetate in *tert*-butyl methyl ether at 23 °C.

Sakai et al.[44] described that the lipase from *P. cepacia* (Amano PS) exerts its function at a very low temperature with markedly enhanced enantioselectivity. Consequently, we have investigated the *P. fluorescens* (Amano AK) lipase-catalyzed acetylation of (±)-**4a** and (±)-**4b** with vinyl acetate under the conditions described in Table 6 at temperatures ranging from 35 to −18 °C (Table 6, Fig. 6). Also, we tested the influence of temperature on Novozym® SP 435 catalyzed acetylation of (±)-**4a** with isopropenyl acetate at temperatures ranging from 4 to 80 °C (Table 6, Fig. 7). It is important to note that the Novozym® SP 435 is thermostable with a maximum activity in the range of 70–90 °C.[45] In this case we examined the possible effect of microwave irradiation[46–54] at 70 °C in toluene as well as under solvent-free conditions (Table 6).

The results in Table 6 show that lipase Amano AK remains active even at −18 °C. Lowering of the temperature from 35 to −18 °C enhances the lipase enantioselectivity, but decreases significantly the reaction rate. From these experiments, performed with lipase Amano AK, it appears clearly that temperatures between 16 and 23 °C are good

Table 5. Additive effects on the acetylation of (±)-**4a** and (±)-**4b** with vinyl acetate using *Pseudomonas fluorescens* lipase (Amano AK) in *tert*-butyl methyl ether at 23 °C[a]

Entry	Additive	Substrate	Amount of additive (mg)	Time (h)	Conv.[b] (%)	Alcohol (*S*)-**7a** or **7b** ee_s (%)[c]	Ester (*R*)-**10a** or **10b** ee_p (%)[c]	E[b]
1	**None**	**4a**	—	**20**	**52**	**92**	**86**	**43**
2	**None**	**4b**	—	**21**	**52**	**91**	**85**	**39**
3	NEt_3	**4a**	20	15	50	79	80	22
4	NEt_3	**4b**	20	12	49	76	78	18
5	15-Crown-5	**4a**	20	38	46	73	86	29
6	18-Crown-6	**4a**	22	43	51	89	85	37
7	TDA-1	**4a**	14	40	44	69	89	35
8	TTCTD[d]	**4a**	12	25	45	70	87	30
9	TTCHD-D[d]	**4a**	12	24	47	78	89	40

[a] Conditions: (±)-**4a**, **4b** (175 mg, 1 mmol), vinyl acetate (258 mg, 3 mmol), 180 mg of lipase from *Pseudomonas fluorescens* (Amano AK), 14 mol % of triethylamine or 5 mol % additive and *tert*-butyl methyl ether (10 mL) at 23 °C.
[b,c] See Table 1.

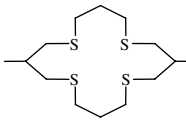
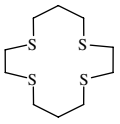
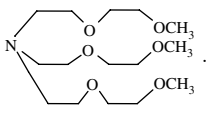
[d] TTCHD-D: 1,5,9,13-tetrathiacyclohexadecane-3,11-diol  , TTCTD: 1,4,8,11-tetrathiacyclotetradecane  , TDA-1: tris-(3,6-dioxaheptyl)amine  .

Table 6. Temperature influence in the Amano AK or Novozym® SP 435-catalyzed acetylation of (±)-**4a**[a]

Entry	Enzyme, solvent, enol ester	Activation mode[d]	Temp. (°C)	Time (h)	Conv.[b] (%)	Alcohol (*S*)-**7a** ee_s (%)[c]	Ester (*R*)-**10a** ee_p (%)[c]	E[b]
1	Amano AK, ^{t}BuOMe, vinyl acetate	Δ	35	11	48	73	80	20
2	Amano AK, ^{t}BuOMe, vinyl acetate	**Δ**	**23**	**20**	**52**	**92**	**86**	**43**
3	Amano AK, ^{t}BuOMe, vinyl acetate	**Δ**	**16**	**28**	**53**	**97**	**86**	**55**
4	Amano AK, ^{t}BuOMe, vinyl acetate	Δ	4	74	51	94	91	75
5	Amano AK, ^{t}BuOMe, vinyl acetate	Δ	−10	134	49	91	93	88
6	Amano AK, ^{t}BuOMe, vinyl acetate	Δ	−18	240	47	83	95	101
7	Novozym® SP 435, toluene, isopropenyl acetate	**Δ**	**4**	**58**	**42**	**68**	**93**	**36**
8	Novozym® SP 435, toluene, isopropenyl acetate	**Δ**	**16**	**25**	**54**	**93**	**80**	**30**
9	Novozym® SP 435, toluene, isopropenyl acetate	**Δ**	**23**	**17**	**49**	**80**	**83**	**26**
10	Novozym® SP 435, toluene, isopropenyl acetate	Δ	40	4	48	72	79	18
11	Novozym® SP 435, toluene, isopropenyl acetate	Δ	70	1 h 30 min	47	62	70	10
12	Novozym® SP 435, toluene, isopropenyl acetate	Δ	80	40 min	51	62	59	7
13	Novozym® SP 435, toluene, isopropenyl acetate	MW 240 W	80	40 min	55	76	61	9
14	None solvent	Δ	80	40 min	53	70	63	9
15	None solvent	MW 240 W	80	40 min	47	59	68	9

[a] Conditions: (±)-**4a** (175 mg, 1 mmol), enol ester (3 mmol), 180 mg of lipase from *Pseudomonas fluorescens* (Amano AK) or 500 mg of lipase from *Candida antarctica* fraction-*B* (Novozym® SP 435) and 10 mL of solvent.
[b,c] See Table 1.
[d] MW = microwave irradiation, Δ = classical heating.

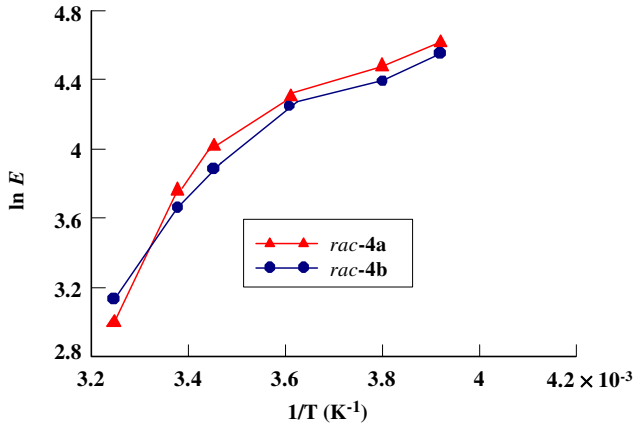


Figure 6. Correlation between $\ln E$ versus the inverse of temperature [$1/T$ (K^{-1})] for Amano AK lipase-catalyzed transesterification of *rac*-**4a** and *rac*-**4b** with vinyl acetate in *tert*-butyl methyl ether.

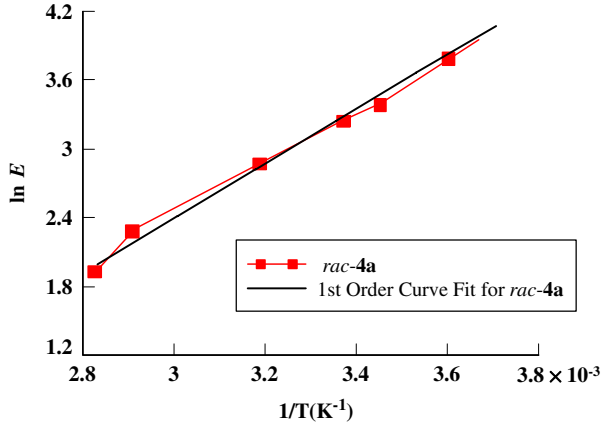
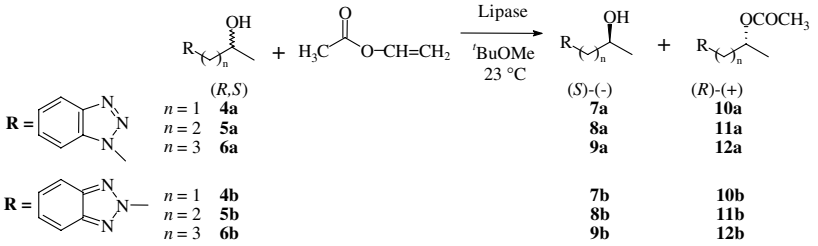


Figure 7. Correlation between $\ln E$ versus the inverse of temperature [$1/T$ (K^{-1})] for Novozym® SP 435-catalyzed transesterification of *rac*-**4a** with isopropenyl acetate in toluene.

compromise for achieving the preparation of both (*S*)-**7a** and (*R*)-**10a** in terms of enantioselectivity ($E = 43$–55) and reaction time (52–53% conversion within 20–28 h). The results listed in Table 6 are used to plot $\ln E$ as a function $1/T$ (K^{-1}) (Fig. 6). We found that, in the case of lipase Amano AK catalyzed acetylation of *rac*-**4a** and *rac*-**4b**, the correlation of $\ln E$ as a function of $1/T$ (K^{-1}) is non-linear (Fig. 6). In fact, this correlation was not in agreement with the theoretical calculations: $\ln E = \Delta\Delta S^{\ddagger}/R - \Delta\Delta H^{\ddagger}/(RT)$.[55]

On the other hand, for the reaction performed by using Novozym® SP 435 under temperatures between 4 and 23 °C are good compromise for achieving the preparation of both (*S*)-**7a** and (*R*)-**10a** in terms of enantioselectivity ($E = 26$–36) and reaction time (42–54% conversion within 17–58 h). The results listed in Table 6 were used to plot $\ln E$ as a function of $1/T$ (K^{-1}) (Fig. 7). We found that, the observed straight line of this correlation was in agreement with the theoretical calculations.[55] Concerning acetylations performed by use of Novozym® SP 435 in non-classical conditions, it is obvious from Table 6, that we cannot observe for *rac*-**4a** any advantages of microwave irradiation (MW) in terms of reaction rates and enantioselectivity when compared to classical heating (Δ).

Finally, in order to investigate the influence of the length of the alkyl chain, six different racemic alcohols (±)-**4a**–**6a** and (±)-**4b**–**6b** were used as substrates in a kinetic resolution by a lipase-catalyzed acetylation. All acetylations were carried out in *tert*-butyl methyl ether or toluene with vinyl acetate, by using Amano AK lipase at 23 °C (Scheme 5). The results are collected in Table 7. The enantiomeric excesses of the unreacted alcohol **7a**–**9a** and **7b**–**9b** and the acetate product **10a**–**12a** and **10b**–**12b** were determined by chiral HPLC analysis. To the best of our knowledge no data are available for the absolute configurations of **8a**–**9a**, **8b**–**9b** and **11a**–**12a**, **11b**–**12b** or their derivatives. For these compounds, the absolute configurations were



Scheme 5.

Table 7. Transesterification of *rac*-**4a**–**6a** and *rac*-**4b**–**6b** with vinyl acetate using lipase Amano AK in toluene or *tert*-butyl methyl ether at 23 °C[a]

Entry	Substrate	*n*	Solvent	Time (h)	Conv.[b] (%)	Alcohol (*S*)-**7**, **8**, **9** ee_s (%)[c]	Ester (*R*)-**10, 11, 12** ee_p (%)[c]	*E*[b]
1	**4a**	1	Toluene	43	51	90	85	38
2	**5a**	**2**	**Toluene**	**45**	**50**	**89**	**90**	**57**
3	**6a**	3	Toluene	47	47	80	89	41
4	**4a**	1	^{t}BuOMe	20	52	92	86	43
5	**5a**	**2**	**^{t}BuOMe**	**23**	**48**	**84**	**91**	**56**
6	**6a**	3	^{t}BuOMe	26	46	78	90	45
7	**4b**	1	Toluene	47	50	83	84	30
8	**5b**	2	Toluene	48	48	82	85	32
9	**6b**	3	Toluene	48	49	77	86	31
10	**4b**	1	^{t}BuOMe	21	52	91	85	39
11	**5b**	2	^{t}BuOMe	23	44	69	89	36
12	**6b**	3	^{t}BuOMe	28	46	74	87	36

[a] Conditions: (±)-**4a**–**6a** or (±)-**4b**–**6b** (1 mmol), vinyl acetate (258 mg, 3 mmol), lipase from *Pseudomonas fluorescens* (Amano AK) (180 mg) and solvent (10 mL) at 23 °C.
[b,c] See Table 1.

assigned by comparison of the sign of the specific rotation with the data for (*S*)-(−)-**7a**, (*S*)-(−)-**7b** and (*R*)-(+)-**10a**, (*R*)-(+)-**10b**. On this basis, in all cases the unreacted alcohols **7a**–**9a**, **7b**–**9b**, and their acetates **10a**–**12a**, **10b**–**12b** had the (*S*)-(−)- and (*R*)-(+)-configurations, respectively.

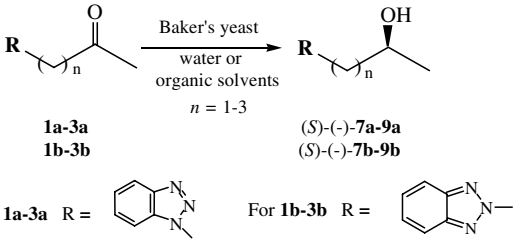
It is obvious from Table 7 that increasing the length of the alkyl chain of alcohols **4a**–**6a** produces an important effect on the enantioselectivity of this reaction, but only a marginal effect on the reaction rate. Concerning the two solvents tested, in the case of compound **5a** ($n = 2$, Scheme 5), the enantioselectivities were significantly higher when compared to the values determined for **4a** and **6a**. Moreover, for compounds **4a**–**6a**, the reaction rates observed in toluene were about twice as small as in *tert*-butyl methyl ether. On the other hand, in the case of alcohols **4b**–**6b** no noticeable differences for enantioselectivity and reaction rates were observed, concerning the two solvents tested. For these compounds, the reaction rates were similar when compared to those observed in the case of compounds **4a**–**6a**. It can be clearly seen from Table 7, that it is possible to run the acetylation of racemic alcohols (±)-**4a**–**6a** and (±)-**4b**–**6b** in a reasonable time and with good enantioselectivities [$E = 30$–57] when the number of carbon atoms in the alkyl chain is increased from $n = 1$ to $n = 3$ (Scheme 5).

2.3. Baker's yeast mediated reduction of ketones 1a–3a and 1b–3b in water and in selected organic solvents

One of the most widely used methods of effecting stereoselective reductions of various ketones is through the use of the yeast in water.[15–26] Recently, Smallridge et al.,[56] North,[57] and Rotthaus et al.[58] have shown that similar reductions are possible using non-fermenting yeast in an organic solvent. Finally, we would like to report our results concerning the reduction of six ketones **1a**–**3a** and **1b**–**3b** utilizing Baker's yeast/water or Baker's yeast/organic solvent reaction system (Scheme 6). All reductions of selected ketones were performed by using instant dry yeast Fermipan brown (Gist brocades) at 30 °C.

The enantiomeric excesses of the products, alcohols **7a**–**9a** and **7b**–**9b** were determined by chiral HPLC analysis. For these compounds the absolute configurations were assigned by the comparison of the sign of the specific rotation with the data for (*S*)-(−)-**7a** and (*S*)-(−)-**7b**, prepared previously via lipase-catalyzed enantioselective acetylation. It is important to note that in all cases, the isolated alcohols **7a**–**9a**, **7b**–**9b** had the (*S*)-(−)-configurations. This assignment agrees well with the Prelog's-rule.[16a,59]

It can be seen from Table 8, that it is possible to run the stereoselective reduction of prochiral ketones **1a**–**3a** and



Scheme 6.

Table 8. Reduction of ketones **1a**–**3a** and **1b**–**3b** by Baker's yeast in selected organic solvents[f] or in water[e]

Entry	Substrate	Solvent	*n*	Time (days)	Conv.[a,b] (%)	Yield[c] (%)	Alcohol (*S*)-(−)[d]ee (%)	
1	**1a**	Water[e]	1	4	57	43	**7a**	51
2	**2a**	Water[e]	2	4	39	29	**8a**	46
3	**3a**	Water[e]	3	4	55	39	**9a**	54
4	**1a**	Toluene[f]	1	2	89	76	**7a**	67
5	**2a**	Toluene[f]	2	2	48	40	**8a**	55
6	**3a**	Toluene[f]	3	2	85	73	**9a**	62
7	**1a**	^{t}BuOMe[f]	1	2	81	65	**7a**	61
8	**2a**	^{t}BuOMe[f]	2	2	43	38	**8a**	49
9	**3a**	^{t}BuOMe[f]	3	2	79	62	**9a**	58
10	**1b**	Water[e]	1	4	56	45	**7b**	58
11	**2b**	Water[e]	2	4	48	36	**8b**	49
12	**3b**	Water[e]	3	4	52	42	**9b**	40
13	**1b**	Toluene[f]	1	2	87	67	**7b**	60
14	**2b**	Toluene[f]	2	2	69	53	**8b**	57
15	**3b**	Toluene[f]	3	2	50	40	**9b**	41
16	**1b**	^{t}BuOMe[f]	1	2	80	69	**7b**	63
17	**2b**	^{t}BuOMe[f]	2	2	71	61	**8b**	56
18	**3b**	^{t}BuOMe[f]	3	2	49	39	**9b**	49

[a] Determined by GC and ^{1}H NMR.
[b] Complement to 100% is an unreacted ketone.
[c] Yields calculated after purification and separation by chromatography on silica gel 60.
[d] Determined by chiral HPLC analysis using Chiracel OD-H column.
[e] Conditions: 0.75 g (5.676 mmol) of $(NH_4)_2SO_4$, 0.38 g (1.726 mmol) of $K_2Na_2HPO_4$, 56 mg (0.275 mmol) of $MgCl_2{\cdot}6H_2O$ in 200 mL of water and 10 g of instant dry Fermipan brown yeast (*Saccharomyces cerevisiae*) was shaken at 30 °C for 4 h, with free access of air. Next, 6 mmol of ketone **1a**–**3a** or **1b**–**3b**, impregnated on silica gel 60, was added and the mixture was shaken at 30 °C.
[f] Conditions: the same like precedently, but the reactions were performed in the mixture containing 10 mL of water and 190 mL of an organic solvent.

1b–**3b** by using instant dry yeast Fermipan brown in water, as well as in an organic solvent containing 5% v/v of water. However, for all ketones tested, the reduction proceeded with a poor or moderate degree of stereoselectivity (ee = 40–67%). It is important to note that in the case of ketones **1a**–**3a**, the enantiomeric excess of the corresponding alcohol varied slightly with the lengthening in the alkyl chain, concerning the organic solvent and water. On the other hand, in the case of ketones **1b**–**3b**, increasing the length of the alkyl chain led to a noticeable decrease in stereoselectivity. Generally, in the case of all ketones tested, **1a**–**3a** and **1b**–**3b**, the reaction rates of the reduction were similar to that in toluene as well as in *tert*-butyl methyl ether while they were significantly higher than those reported for reduction in water. It is important to note that for all the ketones tested, the reactions were incomplete within the times indicated in Table 8 and the starting materials were isolated as complement to 100% of conversion. The longer reaction times than those indicated in Table 8 do not lead to an increased conversion due to a significant decrease in yeast reductase activity.

3. Conclusion

We have presented a general method to realize enantioselective acetylations of various (benzotriazol-1-yl)-alkan-2-ols **4a**–**6a** and (benzotriazol-2-yl)-alkan-2-ols **4b**–**6b**. Reasonably high enantioselectivities [$E = 30$–57] were obtained using *P. fluorescens* (Amano AK) lipase and vinyl acetate in toluene or *tert*-butyl methyl ether at 23 °C. Additionally we have also reported preliminary results concerning the Baker's yeast mediated stereoselective reduction of corresponding ketones **1a**–**3a**, **1b**–**3b** in water or in an organic solvent. However, for all the ketones tested the results obtained, concerning the yield and enantiomeric excess of isolated (*S*)-(−)-alcohols **7a**–**9a**, **7b**–**9b**, were poor or moderate (yield = 29–76% and ee = 40–67%) and not sufficient for practical use. Finally, the kinetic resolution of racemic alcohols is a simple, efficient and, to the best of our knowledge, is the first procedure for the preparation of enantiomerically pure alcohols **7a**–**9a**, **7b**–**9b** and their acetates.

4. Experimental

4.1. General

Lipases from *P. cepacia* and *P. fluorescens* were purchased from Amano Pharmaceutical Co., Ltd (Nagoya, Japan). Novozym® SP 435 was kindly gifted by Novo Nordisk (Bagsvaerd, Denmark). Chirazyme® Lipases & Esterases, Screening Set Industrial Enzymes 2 was kindly gifted by Roche Molecular Biochemicals (Mannheim, Germany). The instant dry *S. cerevisiae* yeasts were generously supplied by the producer: Gist brocades. All the commercially available chemicals were obtained from Aldrich and Fluka. Solvents of analytical-grade quality were purchased from Lab Scan Ltd. and Aldrich. The racemic acetates were synthesized from the corresponding alcohols and acetyl chloride or acetic anhydride according to the usual procedures [e.g., 10 mmol of (±)-**4a**–**6a** or (±)-**4b**–**6b**, 15 mmol of acetyl chloride, 15 mmol of pyridine in CH_2Cl_2 (30 mL) at 25 °C].

4.2. Analytical methods

Microanalyses were performed by the Laboratoire Central de Microanalyse du CNRS, Gif sur Yvette, France. ^{1}H (200 or 250 MHz) and ^{13}C (62.9 or 100.6 MHz) NMR spectra were recorded on Bruker AC-200 or 250 spectrometer in $CDCl_3$ with TMS as the internal standard. Chemical shifts (δ) are given in parts per million. Optical rotation measurements were recorded on a DiP-370 JASCO polarimeter. The specific rotations were as follows for (*S*)-(−)-alcohols and their (*R*)-(+)-acetates: **7a**: $[\alpha]_D^{24} = -28.6$ (*c* 1.46, MeOH); ee = 98%; **8a**: $[\alpha]_D^{24} = -32.1$ (*c* 1.33, MeOH); ee = 95%; **9a**: $[\alpha]_D^{24} = -24.6$ (*c* 1.51, MeOH); ee = 96%; **7b**: $[\alpha]_D^{24} = -19.4$ (*c* 1.33, MeOH); ee = 95%; **8b**: $[\alpha]_D^{24} = -25.1$ (*c* 1.28, MeOH); ee = 97%; **9b**: $[\alpha]_D^{24} = -33.3$ (*c* 1.49, MeOH); ee = 96%; **10a**: $[\alpha]_D^{24} = +29.3$ (*c* 1.55, MeOH); ee = 94%; **11a**: $[\alpha]_D^{24} = +39.2$ (*c* 1.49, MeOH); ee = 98%; **12a**: $[\alpha]_D^{24} = +21.9$ (*c* 1.39, MeOH); ee = 96%; **10b**: $[\alpha]_D^{24} = +18.9$ (*c* 1.49, MeOH); ee = 97%; **11b**: $[\alpha]_D^{24} = +27.1$ (*c* 1.22, MeOH); ee = 93%; **12b**: $[\alpha]_D^{24} = +19.9$ (*c* 1.35, MeOH); ee = 98%. Gas chromatographic analyses were run on a 6000 Vega Series instrument equipped with a FID detector and Spectra-Physics SP 4290 integrator and an OV_1 column (15 m). The detector and the injector temperatures were set at 300 and 290 °C, respectively. Column temperature was programmed in the range 80–250 °C (10 °C min^{-1}). The retention times (t_R/min) were as follows for racemic alcohols: **4a**: 9.12; **5a**: 10.41; **6a**: 11.86; **4b**: 6.81; **5b**: 8.07; **6b**: 10.02 and were as follows for their racemic acetates: **10a**: 10.02; **11a**: 11.91; **12a**: 12.96; **10b**: 9.57; **11b**: 10.12; **12b**: 10.76. HPLC analyses were run on a Thermo-Separation Products P-100 instrument. Enantiomeric excess of unreacted (*S*)-(−)-(benzotriazol-1-yl)-alkan-2-ols (*S*)-(−)-**7a**–**9a**, (*S*)-(−)-(benzotriazol-2-yl)-alkan-2-ols (*S*)-(−)-**7b**–**9b** and their acetates (*R*)-(+)-**10a**–**12a**, (*R*)-(+)-**10b**–**12b** were controlled by HPLC analysis on a chiral column Chiracel OD-H and directly determined using racemic compounds as references. The conditions were: 43 bar, 254 nm, 22 °C and *n*-hexane/isopropanol = 95:5 v/v (1 mL/min) for compounds **7a**–**9a**, **7b**–**9b**, **10b**–**12b** and 43 bar, 254 nm, 22 °C and *n*-hexane/isopropanol = 98:2 v/v (1 mL/min) for compounds **10a**–**12a**. The retention times (t_R/min) were as follows for alcohols: **7a**: 22.18 (*R*), 23.40 (*S*); **8a**: 37.87 (*R*), 38.56 (*S*); **9a**: 45.15 (*R*), 47.88 (*S*); **7b**: 12.88 (*R*), 13.75 (*S*); **8b**: 14.92 (*R*), 15.67 (*S*); **9b**: 21.03 (*R*), 21.69 (*S*) and were as follows for their acetates **10a**: 44.03 (*R*), 58.52 (*S*); **11a**: 47.04 (*R*), 62.86 (*S*); **12a**: 49.55 (*R*), 65.09 (*S*); **10b**: 9.10 (*R*), 17.74 (*S*); **11b**: 10.93 (*R*), 19.03 (*S*); **12b**: 17.08 (*R*), 26.34 (*S*). Column chromatography was performed on Merck silica gel 60 (230–400 mesh). TLC was carried out using glass sheets pre-coated with silica gel 60 F_{254} prepared by Merck. The reactions under microwave irradiations were performed in a monomode microwave reactor (Synthewave 402 from Prolabo), fitted with a stirring system and an IR temperature detector, which indicates the surface temperature.

4.3. Typical acetylation procedure for racemic (±)-4a–6a and (±)-4b–6b using Amano AK lipase in toluene or *tert*-butyl methyl ether at 23 °C

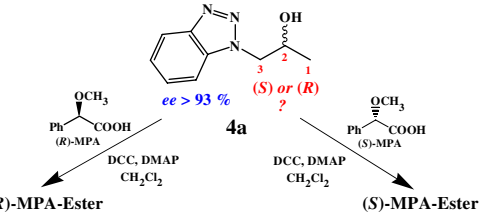
Vinyl acetate (3 mmol, 258 mg) and *P. fluorescens* (Amano AK) lipase (180 mg) were added to a solution of the racemic (benzotriazol-1-yl)-alkan-2-ol (±)-**4a**–**6a** or (benzotriazol-2-yl)-alkan-2-ol (±)-**4b**–**6b** (1 mmol) in 10 mL of toluene or *tert*-butyl methyl ether. The mixture was stirred at 23 °C and monitored by TLC. After the appropriate time (Table 7), the reaction was stopped by filtering off the solid enzyme and the solvent was evaporated under reduced pressure. A crude mixture of acetate (*R*)-(+)-**10a**–**12a**, (*R*)-(+)-**10b**–**12b** and unreacted alcohol (*S*)-(−)-**7a**–**9a**, (*S*)-(−)-**7b**–**9b** was separated by flash chromatography on silica gel with *n*-hexane/ethyl acetate (20:1 v/v) as the eluent. For all of the unreacted alcohols (*S*)-**7a**–**9a**, (*S*)-**7b**–**9b** and their acetates (*R*)-**10a**–**12a**, (*R*)-**10b**–**12b** determination of enantiomeric excess was performed by means of chiral HPLC column chromatography (Chiracel OD-H column).

4.4. Typical reduction procedure for prochiral 1a–3a and 1b–3b using Baker's yeast at 30 °C

To a solution of 0.75 g (5.676 mmol) of $(NH_4)_2SO_4$, 0.38 g (1.726 mmol) of $K_2Na_2HPO_4$, and 56 mg (0.275 mmol) of $MgCl_2{\cdot}6H_2O$ in 200 mL of water [or mixture containing 10 mL of water and 190 mL of toluene or *tert*-butyl methyl ether] in a 500 mL Erlenmayer flask, 10 g of instant dry Fermipan brown yeast (*S. cerevisiae*) was added. The flask was shaken at 30 °C, with free access of air. After 4 h [6 h, respectively], 6 mmol of ketone **1a**–**3a** or **1b**–**3b**, impregnated on silica gel 60, was added. The obtained mixture was shaken at 30 °C and monitored by TLC. After the appropriate time (Table 8), the biomass was filtered off on Celite 445 (20 g) and extracted with 300 mL of ethyl acetate. The resulting solutions were evaporated to dryness and the obtained alcohol **7a**–**9a** or **7b**–**9b** was purified by flash chromatography on silica gel with *n*-hexane/ethyl acetate (15:1 v/v) as the eluent. For all obtained alcohols **7a**–**9a** and **7b**–**9b** determination of enantiomeric excess was possible by means of chiral HPLC analysis using a Chiracel OD-H column. Concerning the impregnation process of ketone, to a solution of 6 mmol of ketone **1a**–**3a** or **1b**–**3b** in 50 mL of diethyl ether, 6 g of silica gel 60 was added and the mixture was stirred for 30 min at room temperature. Next, diethyl ether was evaporated under reduced pressure.

4.5. Assignment of absolute configuration of 7a and 10a

The unreacted enantiomer of alcohol (−)-**7a**, isolated from the reaction of lipase Amano AK catalyzed acetylation of the racemate **4a**, was made to react with enantiomerically pure (*R*)- and (*S*)-enantiomers of methoxyphenylacetic acid (MPA), and ^{1}H NMR spectra of the resulting esters were taken in a $CDCl_3$ solution.



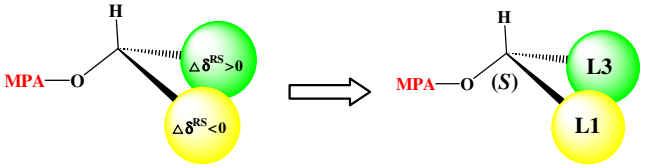
The differences in the chemical shifts ($\Delta\delta^{RS}$) observed in the esters prepared from the (*R*)- and (*S*)-acids, respectively,

were calculated separately for the protons attached to one and the other carbon atom adjacent to the stereogenic center as shown by the following equations:

$$\Delta\delta^{RS}L_1 = \delta^{R}L_1 - \delta^{S}L_1 = 1.20 - 1.37 = -0.17 \text{ ppm}$$

$$\Delta\delta^{RS}L_3 = \delta^{R}L_3 - \delta^{S}L_3 = 4.80 - 4.69 = +0.11 \text{ ppm}$$

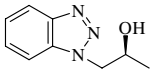
The negative value of $\Delta\delta^{RS}$, which corresponds to the signal of protons of the substituent L_1, and the opposite plus sign resulting for the protons L_3 determine the (*S*)-configuration for unreacted enantiomer (−)-**7a**, according to the drawing:



The same procedure was applied to the second enantiomer of the alcohol isolated after hydrolysis of the acetate, (+)-**10a**. As compared with (*S*)-(−)-**7a**, the respective $\Delta\delta^{RS}$ values are of opposite signs thus indicating the (*R*)-configuration.

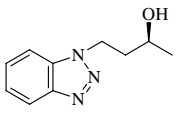
^{1}H and ^{13}C NMR spectra of enantiomeric alcohols **7a**–**9a**, **7b**–**9b** obtained in the kinetic resolution and in the reduction of corresponding ketones by Baker's yeast were identical with those of the racemic alcohols (±)-**4a**–**6a**, (±)-**4b**–**6b** obtained in the classical process. ^{1}H, ^{13}C NMR and MS spectra, IR data as well as micro-analyses of enantiomeric alcohols **7a**–**9a** and **7b**–**9b** are as follows.

4.5.1. (*S*)-(−)-7a: (Benzotriazol-1-yl)-propan-2-ol



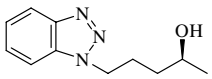
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 1.34 (d, $J = 5.73$ Hz, 3H, CH_3CH), 3.76 (s, 1H, OH), 4.38–4.56 (m, 2H, CH_2N), 4.56–4.72 (m, 1H, CH), 7.26 (t, $J = 7.61$ Hz, 1H, aromatic CH), 7.44 (t, $J = 7.60$ Hz, 1H, aromatic CH), 7.60 (d, $J = 7.98$ Hz, 1H, aromatic CH), 7.79 (d, $J = 8.34$ Hz, 1H, aromatic CH); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 20.58 ($CHCH_3$), 55.18 (NCH_2), 66.85 (*C*H–OH), 109.98, 119.20, 123.93, 127.27, 133.64, 145.19 (*C*–Ar); IR (neat, cm^{-1}): 3415 cm^{-1}: OH; Anal. Calcd for $C_9H_{11}ON_3$ (177.20): C, 61.00; H, 6.26; N, 23.71. Found: C, 60.97; H, 6.23; N, 23.67. MS (electr. impact, 70 eV, *m*/*z*): $(M)^{+\cdot} = 177$ (56.42), $(M-C_2H_4O)^+ = 133$ (11.93), $(M-C_2H_5O)^+ = 132$ (57.50), $(M-C_3H_6ON)^+ = 105$ (59.13), $(M-C_3H_7ON)^+ = 104$ (90.24), $(M-C_3H_6ON_2)^+ = 91$ (24.23), $(M-C_3H_5ON_3)^+ = 78$ (27.12), $(M-C_3H_6ON_3)^+ = 77$ (100), $(M-C_3H_7ON_3)^+ = 76$ (14.29).

4.5.2. (*S*)-(−)-8a: 4-(Benzotriazol-1-yl)-butan-2-ol



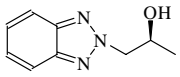
^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 1.25 (d, $J = 6.22$ Hz, 3H, CH_3CH), 1.95–2.31 (m, 2H, CH_2CH), 2.93 (s, 1H, OH), 3.69–3.85 (m, 1H, CH), 4.68–4.98 (m, 2H, CH_2N), 7.36 (t, $J = 7.52$ Hz, 1H, aromatic CH), 7.47 (t, $J = 7.51$ Hz, 1H, aromatic CH), 7.62 (d, $J = 8.26$ Hz, 1H, aromatic CH), 8.03 (d, $J = 8.29$ Hz, 1H, aromatic CH); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 23.79 ($CHCH_3$), 38.44 (CH_2CH), 44.81 (CH_2N), 64.58 (CHOH), 109.47, 119.81, 123.89, 127.25, 133.16, 145.72 (*C*–Ar); IR (neat, cm^{-1}): 3425 cm^{-1}: OH; Anal. Calcd for $C_{10}H_{13}ON_3$ (191.23): C, 62.81; H, 6.85; N, 21.97. Found: C, 62.78; H, 6.82; N, 21.95. MS (electr. impact, 70 eV, *m*/*z*): $(M)^{+\cdot} = 191$ (17.09), $(M-C_3H_6O)^+ = 133$ (58.12), $(M-C_4H_7O)^+ = 120$ (34.19), $(M-C_4H_9O)^+ = 118$ (88.03), $(M-C_4H_9ON)^+ = 104$ (62.39), $(M-C_4H_6ON_2)^+ = 93$ (56.41), $(M-C_4H_8ON_2)^+ = 91$ (100), $(M-C_4H_8ON_3)^+ = 77$ (94.87), $(M-C_4H_9ON_3)^+ = 76$ (24.79), $(M-C_5H_8ON_3)^+ = 65$ (33.33), $(M-C_5H_9ON_3)^+ = 64$ (45.30), $(M-C_5H_{10}ON_3)^+ = 63$ (41.88), $(M-C_6H_6ON_3)^+ = 55$ (60.68).

4.5.3. (*S*)-(−)-9a: 5-(Benzotriazol-1-yl)-pentan-2-ol



^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 1.18 (d, $J = 6.12$ Hz, 3H, CH_3), 1.41–1.57 (m, 2H, CH_2), 2.03–2.31 (m, 2H, CH_2CH), 2.42 (s, 1H, OH), 3.75–3.97 (m, 1H, CH), 4.68 (t, $J = 7.11$ Hz, 2H, CH_2N), 7.29–7.41 (m, 1H, aromatic CH), 7.42–7.61 (m, 2H, aromatic CH), 8.04 (d, $J = 8.32$ Hz, 1H, aromatic CH); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 23.60 ($CHCH_3$), 25.96 (CH_2), 35.71 (CH_2CH), 48.05 (CH_2N), 67.08 (CHOH), 109.34, 119.73, 123.81, 127.15, 132.77, 145.70 (*C*–Ar); IR (neat, cm^{-1}): 3430 cm^{-1}: OH; Anal. Calcd for $C_{11}H_{15}ON_3$ (205.26): C, 64.37; H, 7.37; N, 20.47. Found: C, 64.34; H, 7.34; N, 20.43. MS (electr. impact, 70 eV, *m*/*z*): $(M-C_5H_4O)^+ = 120$ (17.39), $(M-C_5H_{10}O)^+ = 119$ (18.48), $(M-C_5H_{11}O)^+ = 118$ (20.11), $(M-C_5H_9ON)^+ = 106$ (45.65), $(M-C_5H_8ON_2)^+ = 93$ (25.54), $(M-C_5H_9ON_2)^+ = 92$ (11.41), $(M-C_5H_{10}ON_2)^+ = 91$ (35.33), $(M-C_5H_{10}ON_3)^+ = 77$ (57.07), $(M-C_5H_{11}ON_3)^+ = 76$ (14.13), $(M-C_6H_{12}ON_3)^+ = 63$ (14.13).

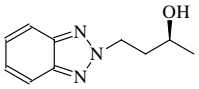
4.5.4. (*S*)-(−)-7b: (Benzotriazol-2-yl)-propan-2-ol



^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 1.30 (d, $J = 6.31$ Hz, 3H, CH_3CH), 3.57 (s, 1H, OH), 4.32–4.53 (m, 1H, CHOH), 4.54–4.87 (m, 2H, CH_2CH), 7.39–7.47 (m, 2H, aromatic CH), 7.79–7.93 (m, 2H, aromatic CH); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 20.09 ($CHCH_3$), 62.79 (NCH_2), 66.62 (*C*H–OH), 117.85, 126.54, 144.06 (*C*–Ar); IR (neat, cm^{-1}): 3425 cm^{-1}: OH; Anal. Calcd for $C_9H_{11}ON_3$ (177.20): C, 61.00; H, 6.26; N, 23.71. Found: C, 60.95; H, 6.25; N, 23.68. MS (electr. impact, 70 eV, *m*/*z*): $(M)^{+\cdot} = 177$ (54.04), $(M-C_2H_3O)^+ = 134$(13.13), $(M-C_2H_4O)^+ = 133$ (100), $(M-C_3H_5O)^+ = 120$ (28.73), $(M-C_3H_6ON)^+ = 105$ (38.99), $(M-C_3H_7ON)^+ = 104$

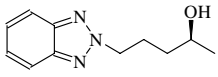
(83.99), $(M-C_3H_5ON_3)^+ = 78$ (51.03), $(M-C_3H_6ON_3)^+ = 77$ (23.28).

4.5.5. (*S*)-(−)-8b: 4-(Benzotriazol-2-yl)-butan-2-ol



^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 1.23 (d, $J = 6.74$ Hz, 3H, CH_3), 2.07 (s, 1H, OH), 2.12–2.45 (m, 2H, CH_2CH), 3.70–3.92 (m, 1H, CH), 4.73–5.12 (m, 2H, CH_2N), 7.28–7.46 (m, 2H, aromatic CH), 7.78–7.93 (m, 2H, aromatic CH); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 23.33 (*C*H_3), 38.69 (*C*H_2CH), 53.37 (*C*H_2N), 64.51 (CHOH), 117.72, 126.24, 144.04 (*C*–Ar); IR (neat, cm^{-1}): 3435 cm^{-1}: OH; Anal. Calcd for $C_{10}H_{13}ON_3$ (191.23): C, 62.81; H, 6.85; N, 21.97. Found: C, 62.77; H, 6.84; N, 21.93. MS (electr. impact, 70 eV, *m*/*z*): $(M)^{+\cdot} = 191$ (4.88), $(M-C_3H_6O)^+ = 133$ (3.61), $(M-C_3H_6O)^+ = 121$ (8.27), $(M-C_4H_7O)^+ = 120$ (100), $(M-C_4H_8O)^+ = 119$ (9.84), $(M-C_4H_9ON)^+ = 104$ (13.56), $(M-C_4H_7ON_2)^+ = 92$ (8.83), $(M-C_4H_8ON_2)^+ = 91$ (15.50), $(M-C_5H_9ON_3)^+ = 64$ (6.00), $(M-C_5H_{10}ON_3)^+ = 63$ (9.95).

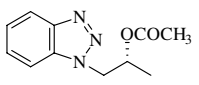
4.5.6. (*S*)-(−)-9b: 5-(Benzotriazol-2-yl)-pentan-2-ol



^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 1.17 (d, $J = 6.23$ Hz, 3H, CH_3), 1.41–1.63 (m, 2H, CH_2), 2.12–2.36 (m, 1H + 2H, OH + CH_2CH), 3.77–3.94 (m, 1H, CH), 4.77 (t, $J = 7.00$ Hz, 2H, CH_2N), 7.31–7.47 (m, 2H, aromatic CH), 7.83–7.98 (m, 2H, aromatic CH); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 23.58 (*C*H_3), 26.34 (*C*H_2), 35.69 (*C*H_2CH), 56.37 (*C*H_2N), 67.25 (CHOH), 117.84, 126.21, 144.14 (*C*–Ar); IR (neat, cm^{-1}): 3415 cm^{-1}: OH; Anal. Calcd for $C_{11}H_{15}ON_3$ (205.26): C, 64.37; H, 7.37; N, 20.47. Found: C, 64.36; H, 7.35; N, 20.44. MS (electr. impact, 70 eV, *m*/*z*): $(M-C_2H_5O)^+ = 160$ (4.60), $(M-C_3H_8O)^+ = 145$ (6.27), $(M-C_4H_8O)^+ = 133$ (11.71), $(M-C_5H_8O)^+ = 121$ (15.80), $(M-C_5H_9O)^+ = 120$ (100) $(M-C_5H_{10}ON)^+ = 105$ (6.02), $(M-C_5H_{11}ON)^+ = 104$ (15.47), $(M-C_5H_9ON_2)^+ = 92$ (10.03), $(M-C_5H_{10}ON_2)^+ = 91$ (11.04), $(M-C_5H_9ON_3)^+ = 78$ (6.02), $(M-C_6H_{11}ON_3)^+ = 64$ (6.94).

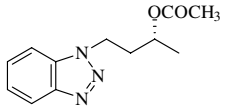
^{1}H, ^{13}C NMR, and MS spectra, IR data as well as microanalyses of enantiomeric acetates **10a**–**12a**, **10b**–**12b** obtained in the kinetic resolution are as follows.

4.5.7. (*R*)-(+)-10a: 2-Acetoxy-1-(benzotriazol-1-yl)-propan-2-ol



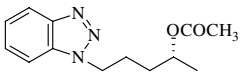
^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 1.34 (d, $J = 5.14$ Hz, 3H, CH_3CH), 1.95 (s, 3H, $COCH_3$), 4.78 (t, $J = 3.99$ Hz, 2H, CH_2N), 5.31–5.46 (m, 1H, CH), 7.38 (t, $J = 6.02$ Hz, 1H, aromatic CH), 7.51 (t, $J = 6.01$ Hz, 1H, aromatic CH), 7.62 (d, $J = 6.62$ Hz, 1H, aromatic CH), 8.07 (d, $J = 6.66$ Hz, 1H, aromatic CH); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 17.53 (CH*C*H_3), 21.01 (CO*C*H_3), 51.86 (N*C*H_2), 69.08 (*C*H–OCOCH$_3$), 109.54, 119.99, 123.92, 127.46, 133.47, 145.84 (*C*–Ar), 170.06 (C=O); IR (neat, cm^{-1}): 1725 (C=O); Anal. Calcd for $C_{11}H_{13}N_3O_2$ (219.23): C, 60.27; H, 5.98; N, 19.17. Found: C, 60.18; H, 5.93; N, 19.16. MS (electr. impact, 70 eV, *m*/*z*): $(M)^{+\cdot} = 219$ (8.44), $(M-C_2H_4O_2)^+ = 159$ (62.93), $(M-C_3H_2O_2)^+ = 149$ (11.48), $(M-C_3H_3O_2)^+ = 148$ (10.37), $(M-C_4H_7O_2)^+ = 132$ (31.26), $(M-C_4H_7O_2)^+ = 131$ (20.06), $(M-C_4H_9O_3)^+ = 130$ (43.57), $(M-C_5H_8O_2N)^+ = 105$ (30.57), $(M-C_5H_9O_2N)^+ = 104$ (50.62), $(M-C_5H_8O_2N_2)^+ = 91$ (17.57), $(M-C_5H_7O_2N_3)^+ = 78$ (15.35), $(M-C_5H_8O_2N_3)^+ = 77$ (100).

4.5.8. (*R*)-(+)-11a: 2-Acetoxy-4-(benzotriazol-1-yl)-butan-2-ol



^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 1.36 (d, $J = 6.21$ Hz, 3H, CH_3CH), 1.96 (s, 3H, $COCH_3$), 2.22–2.39 (m, 2H, CH_2CH), 4.71 (t, $J = 7.5$ Hz, 2H, CH_2N), 4.88–5.12 (m, 1H, CH), 7.31–7.42 (m, 1H, aromatic CH), 7.45–7.57 (m, 2H, aromatic CH), 8.05 (d, $J = 8.28$ Hz, 1H, aromatic CH); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 19.69 (CH*C*H_3), 20.87 (CO*C*H_3), 35.13 (*C*H_2CH), 44.43 (N*C*H_2), 68.21 (*C*H–OCOCH$_3$), 108.94, 119.68, 123.70, 127.12, 132.59, 145.60 (*C*–Ar), 170.24 (C=O); IR (neat, cm^{-1}): 1720 (C=O); Anal. Calcd for $C_{12}H_{15}N_3O_2$ (233.26): C, 61.79; H, 6.48; N, 18.01. Found: C, 61.73; H, 6.43; N, 17.95. MS (electr. impact, 70 eV, *m*/*z*): $(M)^{+\cdot} = 233$ (11.38), $(M-C_2H_4O_2)^+ = 173$ (21.20), $(M-C_4H_6O_2)^+ = 147$ (19.32), $(M-C_4H_7O_2)^+ = 146$ (82.98), $(M-C_4H_8O_2)^+ = 145$ (70.96), $(M-C_4H_9O_2)^+ = 144$ (100), $(M-C_5H_{11}O_2)^+ = 130$ (66.29), $(M-C_6H_9O_2)^+ = 120$ (40.42), $(M-C_6H_{11}O_2)^+ = 118$ (31.88), $(M-C_6H_{11}O_2N)^+ = 104$ (57.22), $(M-C_6H_{10}O_2N_2)^+ = 91$ (65.32), $(M-C_6H_{10}O_2N_3)^+ = 77$ (81.16), $(M-C_7H_{11}O_2N_3)^+ = 64$ (20.50), $(M-C_7H_{12}O_2N_3)^+ = 63$ (23.46).

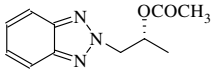
4.5.9. (*R*)-(+)-12a: 2-Acetoxy-5-(benzotriazol-1-yl)-pentan-2-ol



^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 1.23 (d, $J = 6.25$ Hz, 3H, CH_3CH), 1.34–1.66 (m, 2H, CH_2), 1.96 (s, 3H, $COCH_3$), 1.98–2.30 (m, 2H, CH_2CH), 4.54 (t, $J = 7.41$ Hz, 2H, CH_2N), 4.86–5.09 (m, 1H, CH), 7.38–7.45 (m, 1H, aromatic CH), 7.48–7.60 (m, 2H, aromatic CH), 8.03 (d, $J = 6.73$ Hz, 1H, aromatic CH); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 19.57 (CH*C*H_3), 20.99 (CO*C*H_3), 25.41 ($CH_2CH_2CH_2$) 32.22 (*C*H_2CH), 42.86 (N*C*H_2), 69.63 (*C*H–OCOCH$_3$), 108.39, 119.34, 123.59, 126.83, 131.48, 145.43 (*C*–Ar), 170.33 (C=O); IR (neat,

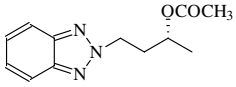
cm^{-1}): 1725 (C=O); Anal. Calcd for $C_{13}H_{17}N_3O_2$ (247.28): C, 63.14; H, 6.93; N, 16.99. Found: C, 63.10; H, 6.89; N, 16.94. MS (electr. impact, 70 eV, *m/z*): $(M-C_2H_3O_2)^+ = 188$ (15.34), $(M-C_2H_4O_2)^+ = 187$ (34.66), $(M-C_4H_5O_2)^+ = 162$ (14.55), $(M-C_4H_6O_2)^+ = 161$ (29.91), $(M-C_4H_7O_2)^+ = 160$ (12.98), $(M-C_5H_9O_2)^+ = 146$ (14.66), $(M-C_5H_{11}O_2)^+ = 144$ (100), $(M-C_6H_{13}O_2)^+ = 130$ (62.13), $(M-C_7H_{11}O_2)^+ = 120$ (33.15), $(M-C_7H_{13}O_2N)^+ = 104$ (54.66), $(M-C_7H_{12}O_2N_2)^+ = 91$ (64.34), $(M-C_7H_{11}O_2N_3)^+ = 78$ (15.44), $(M-C_7H_{12}O_2N_3)^+ = 77$ (88.97).

4.5.10. (*R*)-(+)-10b: 2-Acetoxy-1-(benzotriazol-2-yl)-propan-2-ol



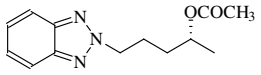
^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 1.35 (d, $J = 2$ 6.42 Hz, 3H, CH_3CH), 1.99 (s, 3H, $COCH_3$), 4.84 (d, $J = 5.83$ Hz, 2H, CH_2N), 5.45–5.67 (m, 1H, CH), 7.31–7.45 (m, 2H, aromatic CH), 7.81–7.92 (m, 2H, aroamtic CH); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 17.58 (CH*C*H$_3$), 20.97 (CO*C*H$_3$), 59.76 (*C*H–OCOCH$_3$), 68.74 (N*C*H$_2$), 118.01, 126.45, 144.40 (*C*–Ar), 170.06 (C=O); IR (neat, cm^{-1}): 1720 (C=O); Anal. Calcd for $C_{11}H_{13}N_3O_2$ (219.23): C, 60.27; H, 5.98; N, 19.17. Found: C, 60.22; H, 5.95; N, 19.10. MS (electr. impact, 70 eV, *m/z*): $(M)^{+\cdot} = 219$ (10.38), $(M-C_2H_3O_2)^+ = 160$ (14.42), $(M-C_2H_4O_2)^+ = 159$ (93.09), $(M-C_2H_5O_2)^+ = 158$ (29.55), $(M-C_4H_6O_2)^+ = 133$ (32.97), $(M-C_4H_9O_3)^+ = 130$ (18.53), $(M-C_5H_8O_2N)^+ = 105$ (11.07), $(M-C_5H_9O_2N)^+ = 104$ (24.93), $(M-C_5H_7O_2N_3)^+ = 78$ (17.38), $(M-C_5H_8O_2N_3)^+ = 77$ (17.81), $(M-C_{11}H_{12}O_2)^+ = 43$ (100), $(M-C_{11}H_{14}O_2)^+ = 41$ (9.83).

4.5.11. (*R*)-(+)-11b: 2-Acetoxy-4-(benzotriazol-2-yl)-butan-2-ol



^{1}H NMR (200 MHz, $CDCl_3$, ppm): δ 1.28 (d, $J = 6.29$ Hz, 3H, CH_3CH), 1.98 (s, 3H, $COCH_3$), 2.31–2.46 (m, 2H, CH_2CH), 4.80 (t, $J = 7.28$ Hz, CH_2N), 4.85–5.05 (m, 1H, CH), 7.31–7.43 (m, 2H, aromatic CH), 7.78–7.92 (m, 2H, aromatic CH); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 19.89 (CH*C*H$_3$), 21.11 (CO*C*H$_3$), 35.79 (*C*H$_2$CH), 52.99 (N*C*H$_2$), 68.20 (*C*H–OCOCH$_3$), 117.87, 128.31, 144.26 (*C*–Ar), 170.46 (C=O); IR (neat, cm^{-1}): 1720 (C=O); Anal. Calcd for $C_{12}H_{15}N_3O_2$ (233.26): C, 61.79; H, 6.48; N, 18.01. Found: C, 61.74; H, 6.45; N, 17.99. MS (electr. impact, 70 eV, *m/z*): $(M)^{+\cdot} = 233$ (15.38), $(M-C_2H_3O)^+ = 190$ (15.72), $(M-C_2H_4O_2)^+ = 173$ (46.63), $(M-C_3H_8O_2)^+ = 158$ (27.66), $(M-C_4H_7O_2)^+ = 146$ (52.73), $(M-C_5H_8O_2)^+ = 133$ (26.16), $(M-C_6H_9O_2)^+ = 120$ (100), $(M-C_6H_{10}O_2N)^+ = 105$ (11.68), $(M-C_6H_{11}O_2N)^+ = 104$ (21.56), $(M-C_6H_{10}O_2N_2)^+ = 91$ (22.77), $(M-C_6H_{10}O_2N_3)^+ = 77$ (18.04).

4.5.12. (*R*)-(+)-12b: 2-Acetoxy-5-(benzotriazol-2-yl)-pentan-2-ol



^{1}H NMR (250 MHz, $CDCl_3$, ppm): δ 1.22 (d, $J = 6.24$ Hz, 3H, CH_3CH), 1.50–1.71 (m, 2H, CH_2), 2.02 (s, 3H, $COCH_3$), 2.11–2.31 (m, 2H, CH_2CH), 4.74 (t, $J = 7.05$ Hz, CH_2N), 4.91–5.01 (m, 1H, CH), 7.32–7.46 (m, 2H, aromatic CH), 7.82–7.94 (m, 2H, aromatic CH); ^{13}C NMR (62.9 MHz, $CDCl_3$, ppm): δ 19.79 (CH*C*H$_3$), 21.18 (CO*C*H$_3$), 25.91 (CH$_2$*C*H$_2$CH$_2$), 32.65 (*C*H$_2$CH), 56.10 (N*C*H$_2$), 69.94 (*C*H–OCOCH$_3$), 117.82, 126.13, 144.17 (*C*–Ar), 170.51 (C=O); IR (neat, cm^{-1}): 1729 (C=O); Anal. Calcd for $C_{13}H_{17}N_3O_2$ (247.28): C, 63.14; H, 6.93; N, 16.99. Found: C, 63.12; H, 6.90; N, 16.96. MS (electr. impact, 70 eV, *m/z*): $(M)^{+\cdot} = 247$ (5.13), $(M-C_2H_4O_2)^+ = 187$ (7.30), $(M-C_4H_5O_2)^+ = 162$ (11.31), $(M-C_4H_7O_2)^+ = 160$ (7.32), $(M-C_5H_9O_2)^+ = 146$ (7.01), $(M-C_5H_{10}O_2)^+ = 145$ (27.06), $(M-C_6H_{10}O_2)^+ = 133$ (9.57), $(M-C_7H_{11}O_2)^+ = 120$ (100), $(M-C_7H_{12}O_2)^+ = 119$ (7.10), $(M-C_7H_{13}O_2N)^+ = 104$ (6.88), $(M-C_7H_{12}O_2N_2)^+ = 91$ (13.26), $(M-C_7H_{11}O_2N_3)^+ = 78$ (8.55), $(M-C_7H_{12}O_2N_3)^+ = 77$ (16.78).

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