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Preparation of the four stereoisomers of 3-bromo-2-butanol or their acetates via lipase-catalysed resolutions of the racemates derived from *dl*- or *meso*-2,3-butanediol

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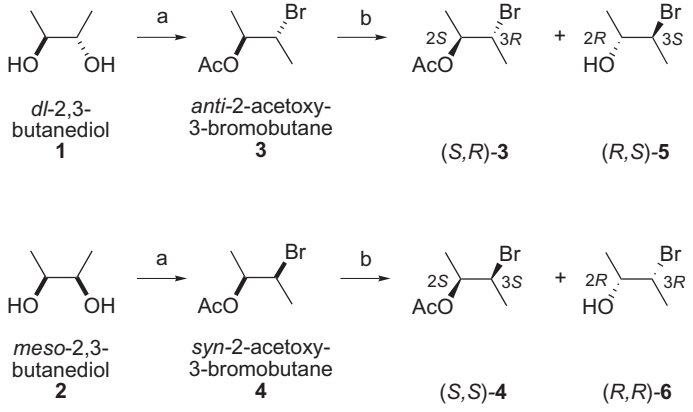
Abstract—The four stereoisomeric 3-bromo-2-butanols and/or their acetates were prepared via lipase-catalysed kinetic resolution by hydrolyses of the acetates of the (±)-*syn*- and (±)-*anti*-3-bromo-2-butanols, or via esterifications of the alcohols. The diastereomeric bromoacetates were obtained by syntheses from the *dl*- and *meso*-2,3-butanediols, respectively. On a preparative scale, the four stereoisomers, either as the free alcohols or as their acetates, were obtained in >95% ee, and in 35–40% yield (based on the starting racemates).

1. Introduction

Enantiomerically pure halohydrins are important as convenient precursors of non-racemic chiral epoxides, which are useful building blocks in enantioselective syntheses.[1] Various enantiomerically pure halohydrins can be prepared by asymmetric chemical syntheses,[2] by microbial asymmetric reduction of haloketones,[3] and by lipase-catalysed resolution of haloalcohols and/or esters.[1,4] The pure enantiomers of *anti*- and *syn*-3-bromo-2-butanol (*R*,*S*)-**5** and (*R*,*R*)-**6**, respectively (Scheme 1) and their esters (*S*,*R*)-**3** and (*S*,*S*)-**4** have, however,



Scheme 1. Pure stereoisomers of 3-bromo-2-butanols (*R*,*S*)-**5** and (*R*,*R*)-**6** and 2-acetoxy-3-bromobutane (*S*,*R*)-**3** and (*S*,*S*)-**4** obtained by lipase catalysed hydrolysis of racemic *anti*- or *syn*-2-acetoxy-3-bromobutanes **3** and **4** obtained from *dl*- or *meso*-2,3-butanediol, **1** and **2**, respectively. Reagents and conditions: (a) HBr in acetic acid, 0 °C, 30 min, 45 °C, 1 h (75–90%) and (b) CALB, Amano PS, or CRL, hexane–water, 1/1, 0.8–12 h.

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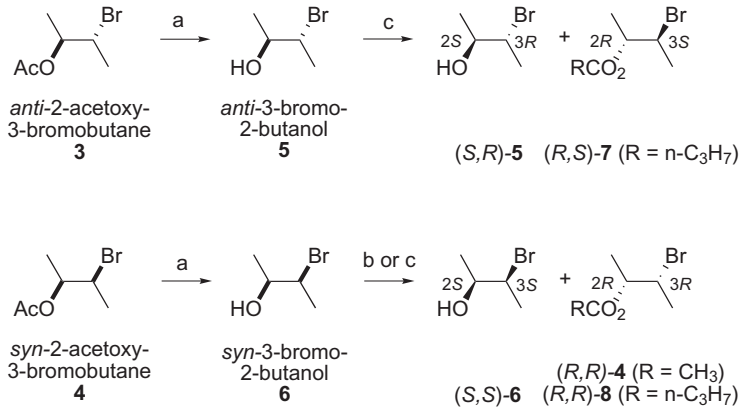

Scheme 2. Pure stereoisomers of 3-bromo-2-butanols (*S*,*R*)-**5** and (*S*,*S*)-**6** and either 2-acetoxy-3-bromobutane (*S*,*S*)-**4** or 2-butanoyloxy-3-bromobutanes (*R*,*S*)-**7** and (*R*,*R*)-**8** obtained by lipase catalysed acylation of racemic *anti*- or *syn*-3-bromo-2-butanols **5** and **6** obtained by chemical hydrolysis of racemic *anti*- or *syn*-2-acetoxy-3-bromobutane **3** or **4**. Reagents and conditions: (a) HCl (aq, 8 M), 24 h, 75%, (b) CALB, vinyl acetate, CH_2Cl_2, rt, 22 h and (c) CALB, vinyl propionate, CH_2Cl_2, rt, 72 h.

attracted limited attention.[5] Although the enantiomers of the *anti*-esters **3** are easily accessible from the pure *d*- and *l*-enantiomers of the 2,3-butanediol **1**,[5e] the enantiomers of the *syn*-esters **4** are not readily available. The enantiomers of the *anti*-esters **3** are useful precursors of enantiomerically pure (*S*,*S*)- or (*R*,*R*)-2,3-dimethyloxirane,[5e] which, due to their C_2-symmetry, are useful building blocks. As a result they react with nucleophiles to give a single product, whereas *meso*- or unsymmetrical epoxides tend to give mixtures of products.[6] The aim of this work was to efficiently resolve either the (±)-*anti*- and (±)-*syn*-2-acetoxy-3-bromobutanes, **3** and **4**, respectively, or the corresponding alcohols, (±)-*anti*- and (±)-*syn*-3-bromo-2-butanol, **5** and **6**, by enzyme-catalysed hydrolysis (Scheme 1) or esterification (Scheme 2).

The racemic bromoacetates **3** and **4** are easily prepared from the appropriate 2,3-butanediol diastereomers **1** and **2**, respectively.[5e,7] Both *dl*- and *meso*-2,3-butanediol **1** and **2** are accessible in high diastereomeric purity using previously published procedures.[8] Thus, commercially available 2,3-butanediol as a *meso*-/*dl*-mixture [dr (diastereomeric ratio) = 85/15] gives *meso*-2,3-butanediol **2** (dr = 99/1) after crystallisation while the *dl*-form **1** (dr ≈ 95/5) is obtained from commercially available *dl*-/*meso*-mixtures after epimerisation.[8] The two racemic diastereomers of the *anti*- and *syn*-bromoacetates **3** and **4** are then prepared from the respective diol diastereomers **1** and **2** by treatment with hydrogen bromide in acetic acid.[7]

The lipase-catalysed kinetic resolution by hydrolysis of the two diastereomeric racemic acetates **3** and **4** of the 3-bromo-2-butanols **5** and **6** was then studied (Scheme 1).

2. Enzyme catalysed kinetic resolution of racemic 2-acetoxy-3-bromobutanes

2.1. Preparation of the racemic *anti*- and *syn*-2-acetoxy-3-bromobutanes

Both *dl*- and *meso*-2,3-butanediol[8] **1** and **2** (Scheme 1) were treated with a saturated solution of hydrogen bromide in acetic acid (4.1 M) at 0 °C for 30 min and then at 45 °C for 1 h, which furnished both *anti*- and *syn*-2-acetoxy-3-bromobutanes **3** and **4** in 75–90% yield. According to the known mechanism of the reaction,[7] complete Walden inversion should take place at the carbon atom bearing the bromine. Thus, the *dl*-diol **1** gave (±)-*anti*-2-acetoxy-3-bromobutane **3**, whereas the *meso*-diol **2** furnished (±)-*syn*-2-acetoxy-3-bromobutane **4**. In the latter case, however, we observed a slight decrease in the diastereomeric ratio. Thus a sample of *meso*-diol **2** with 99/1 dr, gave *syn*-ester **4** with 95/5 dr. In contrast, samples of *dl*-diol **1** (99.5/0.5 and 91/9 dr) provided the *anti*-ester **3** with preserved diastereomeric ratios.

2.2. *Candida antarctica* lipase B-catalysed hydrolysis

The diastereomeric *anti*- and *syn*-2-acetoxy-3-bromobutanes **3** and **4** were only slightly soluble in water. The partition coefficient between identical volumes of hexane and the aqueous buffer solution used below was found to be 97/3 for both of the bromoesters **3** and **4** (Scheme 1), while the partition coefficients of the *anti*- and *syn*-3-bromo-2-butanols **5** and **6** (Scheme 2) were approximately 30/70. Thus, in an enzyme-catalysed hydrolysis reaction in a hexane–water system, the substrate, either the *anti*- or *syn*-2-acetoxy-3-bromobutane **3** or **4** was almost completely dissolved in the hexane phase, whereas the main part of the product, 3-bromo-2-butanol, was found in the water phase.

Of the enzymes screened, lipase B from *Candida antarctica* (CALB, see Table 1, footnote a) was found to be best both in terms of rate and enantiomeric ratio (*E*) in the resolution of both of the acetates **3** and **4**.

The kinetic resolutions of the two *syn*- and *anti*-2-acetoxy-3-bromobutanes **4** and **3** were carried out by lipase-catalysed hydrolyses in biphasic systems consisting of hexane (1.5–2.0 mL/mmol of ester **4** or **3**) and 0.2 M sodium or potassium phosphate buffer solution (aq, pH 7.5, 1.5 mL/mmol of **4** or **3**) at ambient temperature. After equilibration of the reaction mixture

Table 1. Hydrolysis of the racemic 2-acetoxy-2-bromobutanes **3** and **4** catalysed by various lipases[a]

Entry	Substrate (2-acetoxy-3-bromobutane)	dr[b]	Enzyme[a]	Reaction time (h)	Conversion (%)[b]	Product (3-bromo-2-butanol)			Remaining substrate (2-acetoxy-3-bromobutane)			E[c] ± SD
						ee_p[b] (%)	Prod dr[b] (conf.)	$[\alpha]_D^{20}$[b]	ee_s[b] (%)	dr[b] (conf.)	$[\alpha]_D^{25}$[b]	
1	**4**	*syn*/*anti* 95/5	CALB	0.75	43	97	(*R*,*R*)-**6** 100/0 (2*R*,3*R*)	−20.2 (*c* 2, $CHCl_3$)[d]	75	94/6 (2*S*,3*S*)		
2	**4**	*syn*/*anti* 95/5	CALB	4	54	84	(*R*,*R*)-**6** 97/3 (2*R*,3*R*)		99.5	94/6 (2*S*,3*S*)	−2.2 (neat)[d]	110 ± 10
3	**3**	*anti*/*syn* 99.5/0.5	CALB	2	44	95	(*R*,*S*)-**5** ≈ 99.5/0.5 (2*R*,3*S*)	+13.2 (neat)[e]	75	>99.5/0.5 (2*S*,3*R*)		
4	**3**	*anti*/*syn* 99.5/0.5	CALB	11	54	84	(*R*,*S*)-**5** ≈ 99.5/0.5 (2*R*,3*S*)		99	>99.5/0.5 (2*S*,3*R*)	−16.6 (neat)[e]	65 ± 8
5	**3**	*anti*/*syn* 91/9	CALB	7	55	79	(*R*,*S*)-**5** 90/10 (2*R*,3*S*)		96	92/8 (2*S*,3*R*)		41 ± 11
6	**3**	*anti*/*syn* 91/9	PS	120	55	78	(*R*,*S*)-**5** 93/7 (2*R*,3*S*)		96	91/9 (2*S*,3*R*)		37 ± 6
7	**3**	*anti*/*syn* 91/9	CRL	240	87	—	—		89	91/9 (2*S*,3*R*)		3

[a] *Candida antarctica* lipase B (commercial product Chirazyme® lipase L-2, c.-f., C3, lyo Roche) *Pseudomonas cepacia* lipase (commercial product Amano PS). *Candida rugosa* lipase (commercial product Chirazyme® lipase L-3, Roche).

[b] Conversions were determined by using dodecane as the internal standard present in the reaction mixtures. Conversion, diastereomeric ratio (dr) and ee were determined by GC-analysis using an HP 5890 chromatograph with a β-DEX 120 capillary chiral column (id = 0.32 mm, 30 m, $d_f = 0.25$ μm) or a Cyclosilb capillary chiral column (id = 0.32 mm, 30 m, $d_f = 0.25$ μm) with He as the carrier gas. Optical rotation was determined with a Perkin Elmer 341LC polarimeter.

[c] $E = \ln[(1 - ee_s)/(1 + ee_s/ee_p)]/\ln[(1 + ee_s)/(1 + ee_s/ee_p)]$. E was also determined from several experimental data points from ee as a function of conversion using the software Simfit.[10] SD = standard deviation.

[d] Literature values for *syn*-compounds: (2*R*,3*R*)-*3-Bromobutan-2-ol* (*R*,*R*)-**6**: $[\alpha]_D = -1.1$,[5a,14] $[\alpha]_D^{23} = -3.4$ (*c* 5, $CHCl_3$) for a sample of 61% ee.[5b] (2*S*,3*S*)-*2-Acetoxy-3-bromobutane* (*S*,*S*)-**4**: $[\alpha]_D = -0.31$.[5a,14]

[e] Literature values for *anti*-compounds: (2*R*,3*S*)-*3-Bromobutan-2-ol* (*R*,*S*)-**5**: $[\alpha]_D^{25} = +13.9$ (neat),[5d] $[\alpha]_D = +18$ (*c* 30, $CHCl_3$)[5f] {for the enantiomer (*S*,*R*)-**5** = −13.2 (*c* 10, Et_2O)[5g]}. (2*S*,3*R*)-*2-Acetoxy-3-bromobutane* (*S*,*R*)-**4**: $[\alpha]_D^{25} = -3.0$.[5a,14] Following the recipe described in Ref. 7, we transformed enantiopure (2*R*,3*R*)-2,3-butanediol into pure (*R*,*S*)-**4** {$[\alpha]_D^{25} = +18.8$ (neat, after chromatography and distillation)}.

by stirring without the enzyme for 1 h, the hydrolytic reactions were started by the addition of 50–80 mg of the lipase powder per mmol of the acetate **4** or **3**. In reactions on a preparative scale (2–5 g of substrate), instead of using the buffer solution, the pH was monitored by a pH-meter and maintained at 7.2–7.7 by the addition of 0.2–1 M NaOH solution.

2.3. Results and discussion

The results of our CALB-catalysed hydrolysis reactions are shown in Table 1. According to previous studies, the (*R*)-enantiomer of 2-acetoxy-1-bromopropane is the preferred substrate with this lipase.[9] We found that both the two racemic 2-acetoxy-3-bromobutanes **3** and **4** reacted with the same (*R*)-enantiopreference. This was confirmed by comparison of the specific rotation of the alcohols produced with the values reported in the literature[5] (Table 1).

The *anti*- and *syn*-acetates **3** and **4** were both hydrolysed with good enantioselectivity with *E*-values of 65 and 110, respectively, on a preparative scale while in small-scale reactions ($\leqslant$100 mg substrate) the *E*-values were higher (>100 for **3** and >200 for **4**). Thus, on a preparative scale, for the *syn*-acetate **4** and for a reaction interrupted at 43% conversion, the hydrolysis product, (2*R*,3*R*)-3-bromo-2-butanol (*R*,*R*)-**6**, was obtained highly enantiomerically pure (97% ee, Table 1, entry 1). On the other hand, the remaining substrate (2*S*,3*S*)-2-acetoxy-3-bromobutane (*S*,*S*)-**4** (99.5% ee, entry 2) could be isolated in reactions interrupted at a higher conversion (54%). Similarly, but with a lower enantioselectivity, (2*R*,3*S*)-3-bromo-2-butanol (*R*,*S*)-**5** (95% ee, entry 3) was obtained at 44% conversion, while the remaining (2*S*,3*R*)-2-acetoxy-3-bromobutane (*S*,*R*)-**3** (99% ee, entry 4) was recovered at 54% conversion.

The activity of *C. antarctica* lipase B working on the two racemic diastereomeric acetates **3** and **4** was notably different. With the *syn*-ester **4** and the *anti*-one **3**, the reactions required on average 0.8 and 2 h, respectively, to reach a conversion of 44% with the same enzyme concentration. Consequently, the diastereomeric ratio (dr) of both the *syn*-ester **4** and the *anti*-ester **3** changed with time in both cases but in opposite directions (Table 1). The dr of the remaining substrate (−)-*syn*-2-acetoxy-3-bromobutane (*S*,*S*)-**4** decreased from 95/5 to 94/6 (entries 1 and 2) while that of (−)-*anti*-2-acetoxy-3-bromobutane (*S*,*R*)-**5** increased slightly (entries 3–5). In addition, the diastereomeric purity of the substrate seemed to play an important role in these enzyme-catalysed resolutions. As shown in entry 5, the enantioselectivity appeared to drop (from $E = 65$ to 41), when the experiment started with *anti*-2-acetoxy-3-bromobutane **3** containing 9% of its *syn*-isomer **4**. This result could be explained by the *syn*-isomer **4** acting as a competitive inhibitor.[11]

We investigated other lipases under the same reaction conditions, in order to study if higher enantioselectivity could be obtained in the resolution of the *anti*-enantiomers. Amano PS (*Pseudomonas cepacia* lipase) and CRL (Chirazyme® lipase L-3, lyophilised, from *Candida rugosa*) were tested (Table 1, entries 6 and 7), but unfortunately, only lipase Amano PS displayed a satisfactory enantioselectivity ($E = 37$), similar to that of CALB. Moreover, under the same general conditions (except for the enzyme used), the Amano PS-reaction required 120 h to reach 55% conversion, compared with only 7 h when CALB was used. CRL gave poor results both in terms of enantioselectivity ($E = 3$) and reaction time (more than 200 h).

In our hands, CALB-catalysed hydrolysis reactions on a preparative scale usually gave a lower *E*-value than that obtained in small-scale reactions. This was probably due to mass transfer limitations caused by the scale-up.[12] The reaction times were virtually unchanged; 4 h for the *syn*-isomer **4** and 11 h for the *anti*-isomer **3** were required to reach 54% conversion in large-scale reactions (Table 1, entries 2 and 4). Slightly longer reaction times were, however, observed for the small-scale reactions with buffer solution. In these reactions, not only could the presence of the phosphates in the buffer affect the rate but also the lack of continuous pH control might cause a lowering of the rate if the buffering capacity is low. Such pH control is important, because it can influence not only the rate but also the enantioselectivity. A low pH might not only make the equilibrium of the hydrolysis shift towards the substrates, but also cause a non-selective acid-catalysed hydrolysis. Conversely, a higher pH might result in an alkaline ester hydrolysis, followed by the formation of epoxides. Despite these expected effects of the lack of continuous pH-control, the enantioselectivity in the small-scale reactions was, as mentioned above, higher than in preparative scale reactions.

3. Enzyme catalysed resolution of the *rac*-3-bromo-2-butanols by esterification

3.1. *Candida antarctica* lipase B-catalysed transesterifications of vinyl esters

We also investigated the scope of the enzyme-catalysed resolution reactions of secondary vicinal bromoalcohols and their esters by studying some CALB-catalysed esterifications of the *anti*- and *syn*-3-bromo-2-butanols **5** and **6** on a small scale (Scheme 2). These alcohols were obtained by acid-catalysed chemical hydrolyses of the *anti*- or *syn*-acetates **3** or **4** by means of an aqueous solution containing 75% concentrated HCl.[13]

The mixture of a racemic *anti*- or *syn*-3-bromo-2-butanol either **5** or **6** (0.3 mmol) and vinyl acetate or vinyl butanoate (0.3 mmol) in dichloromethane (1.2 mL) was incubated for 30 min at ambient temperature. The lipase-catalysed transesterification reaction of the vinyl ester was then initiated by the addition of 15–30 mg of CALB (see footnote a, Table 1).

3.2. Results and discussion

As shown in Table 2, *syn*-3-bromo-2-butanol **6** showed excellent enantioselectivity in CALB-catalysed acylations: $E = 180$ for formation of (*R*,*R*)-**4** from vinyl acetate

Table 2. Transesterifications of vinyl esters with *anti*- or *syn*-bromobutanols **5** and **6** catalysed by *Candida antarctica* lipase B[a]

Substrate (3-bromo-2-butanol)	dr[b]	Reaction time (h)	Acyl donor	Conv. (%)[b]	Product ester ee_p[b] (conf.) (%)	Remaining alcohol ee_s[b] (conf.) (%)	E[b] ± SD
6	*syn*/*anti* 95/5	22	Vinyl butanoate	47	96 (2*R*,3*R*)	86.5 (2*S*,3*S*)	160 ± 15
6	*syn*/*anti* 95/5	22	Vinyl acetate	49	96 (2*R*,3*R*)	93 (2*S*,3*S*)	170 ± 15
5	*anti*/*syn* 99.5/0.5	72	Vinyl butanoate	45	92 (2*R*,3*S*)	76 (2*S*,3*R*)	53 ± 6
5	*anti*/*syn* 99.5/0.5	—	Vinyl acetate	No rx	—	—	—

[a] The reaction conditions were similar to those described in Ref. 9a.
[b] See footnotes b and c in Table 1.

and $E = 160$ for formation of (*R*,*R*)-**8** from vinyl butanoate. In contrast, the *anti*-isomer reacted with vinyl butanoate to give (*R*,*S*)-**7** with a much lower enantioselectivity, $E = 53$. The *syn*-isomer **6** showed higher activity (22 h to give 49% conversion) than the *anti*-isomer (72 h for 45% conversion). Interestingly, *anti*-3-bromo-2-butanol **5** reacted very slowly with vinyl acetate as the acyl donor.

4. Conclusions

Our results show that enantiomerically enriched 3-bromo-2-butanols **5** and **6** and their esters **3** and **4** can indeed be prepared by chemical conversion of either pure *meso*- or pure *dl*-2,3-butanediol, **2** or **1**, and using the products, *rac*-2-acetoxy-3-bromobutane (**4** or **3**) or *rac*-3-bromo-2-butanol (**6** or **5**) in a lipase-catalysed resolution by hydrolysis or acylation. CALB was the best enzyme of those tested and provided excellent enantioselectivity and activity towards both *syn*-acetate **4** and the *syn*-alcohol **6**. A more modest enantioselectivity was observed with the corresponding *anti*-compounds, **3** and **5**. Although Amano PS revealed a similar trend and magnitude of enantioselectivity towards the diastereomers, it required much longer reaction times in the resolutions.

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13. *Rac-anti*-2-acetoxy-3-bromobutane (3.9 g, 20 mmol) and HCl (aq. 8 M, 40 mL) were stirred for 24 h. Extractive work-up and distillation provided *anti*-3-bromo-2-butanol (2.3 g, 15 mmol, 75%) with unchanged dr.
14. The rotation values given in Ref. 5a are, as the authors state, probably too low due to the low enantiomeric excess of the samples.