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Lipase catalyzed enantioselective desymmetrization of a prochiral pentane-1,3,5-triol derivative

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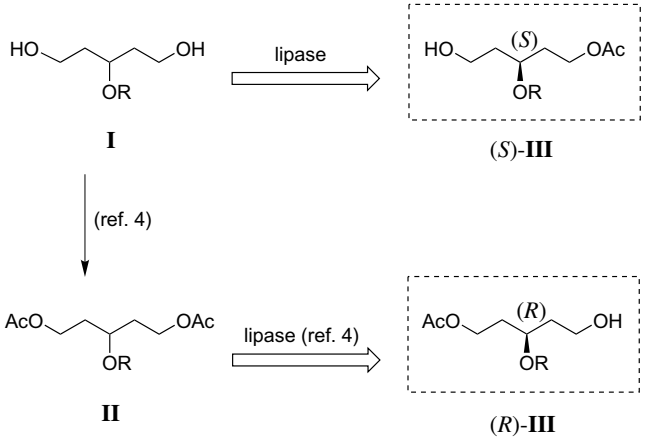
Dedicated to Prof. Dr. Dr. h. c. Gottfried Blaschke on the occasion of his 70th birthday

Abstract—The enantioselective desymmetrization of the prochiral 3-*O*-silyl protected pentanetriol derivative **3** was carefully investigated. At −10 °C, the bacterial lipase from *Burkholderia cepacia* immobilized on ceramic particles led to monoacetate (*S*)-**4** in 52% yield and >99.9% ee. At a reaction temperature of −40 °C the yield and enantioselectivity were even higher, but the reaction time was very long. Theoretical simulations of the reaction progress indicated an enantioselectivity of 25:1 at −10 °C and 35:1 at −40 °C. (*S*)-**4** was converted into the enantiomerically pure building block 5-azidopentane-1,3-diol (*S*)-**7** in two steps. The absolute configuration of (*S*)-**7** was determined by exciton-coupled circular dichroism (ECCD) of diester (*S*)-**8**.

1. Introduction

The development of pharmacologically interesting drugs is currently performed only with enantiomerically pure compounds. There are several methods to produce drugs with high enantiomeric purity. Often the chiral information is derived from enantiomerically pure building blocks available from the chiral pool of Nature. These building blocks are enzymatically synthesized by various organisms. As a result, enzymes also serve as suitable catalysts to synthesize enantiomerically pure building blocks in the laboratory, which are not available from Nature. Whereas Nature has optimized enzymes for a particular transformation over millions of years, in the laboratory, the reaction conditions have to be optimized to gain the desired product in high enantiomeric purity using a given enzyme. The enzymatic production of new synthons is the subject of numerous publications.[1–3]

Herein, we report the enantioselective desymmetrization of a prochiral pentane-1,3,5-triol derivative using various lipases. In contrast to the enzymatic resolution of racemates, the enantioselective desymmetrization of prochiral compounds leads to enantiomerically pure products in 100% yield, theoretically. Soriente et al have described the enantioselective hydrolysis of prochiral diacetate **II** (R = $SiMe_2tBu$) using the lipase of *Pseudomonas fluorescens* (Scheme 1).[4] However, only the (*R*)-configured synthon (*R*)-**III** is available by this method. Therefore, we investigated the direct lipase catalyzed acetylation of a prochiral diol **I** to afford the (*S*)-configured monoacetate (*S*)-**III**. In order to analyze the development of the transformation



Scheme 1. Strategy to obtain (*S*)- and (*R*)-pentane-1,3,5-triol derivatives.

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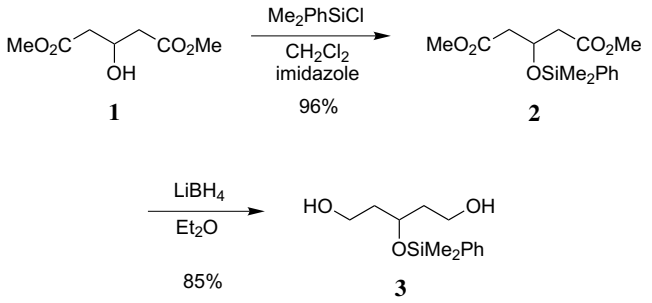
and the enantiomeric excess by HPLC the protecting group R should contain a UV absorbing moiety.

2. Results and discussion

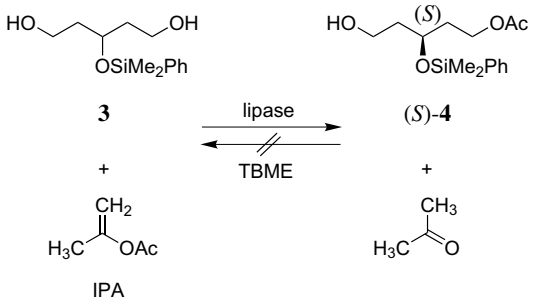
2.1. Synthesis

The synthesis was started from prochiral diester **1**, which was silylated with chloro-dimethyl-phenyl-silane and imidazole in CH_2Cl_2.[5] The resulting silyl ether **2** was reduced by $LiBH_4$ to give prochiral pentanediol **3** (Scheme 2).



Scheme 2. Synthesis of prochiral diol **3**.

The key step for the introduction of chirality is the enantioselective acetylation of prochiral diol **3** using various lipases. In order to achieve irreversibility, a transesterification with isopropenyl acetate (IPA) was carried out (Scheme 3). Generally, *tert*-butyl methyl ether (TBME) was used as the solvent.

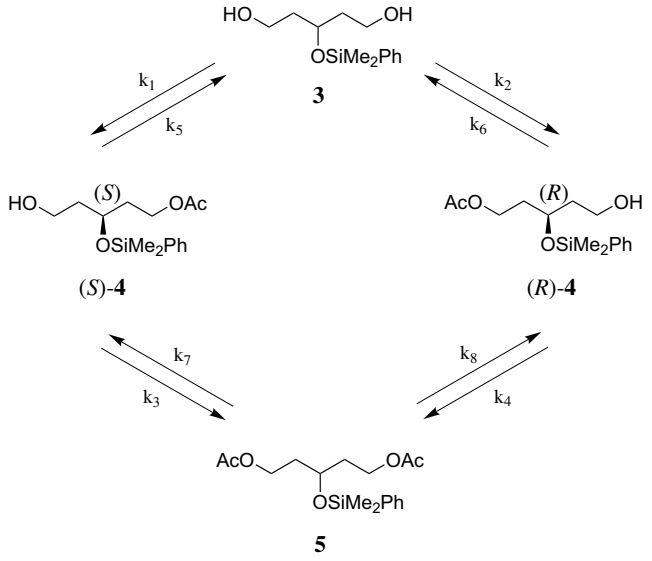


Scheme 3. Lipase catalyzed enantioselective, irreversible acetylation.

The acetylation of prochiral diol **3** can occur at either of the OH groups to afford the monoacetates (*S*)-**4** and (*R*)-**4** or at both OH groups to provide the prochiral diacetate **5** (Scheme 4). In order to obtain monoacetate (*S*)-**4** in a high yield and enantiomeric purity, the lipase catalyzed acetylation of diol **3** was carefully optimized.

2.2. Lipase screening

The most important feature for the production of monoacetate (*S*)-**4** with high enantiomeric purity is the catalyst (lipase). In order to find the most suitable lipase, some commercially available preparations from various sources (four bacterial, four fungal, one mammalian lipase) were investigated (Table 1).



Scheme 4. Lipase catalyzed acetylation of prochiral diol **3**.

Table 1. Investigated lipases

Lipase	Product	Origin
A	Amano AK	*Pseudomonas fluorescens*
B	Amano PS	*Burkholderia cepacia*
C	Amano PS-CII[a]	*Burkholderia cepacia*
D	Chirazyme L-2	*Candida antarctica B*
E	Chirazyme L-3 pur.	*Candida rugosa*
F	Chirazyme L-5	*Candida antarctica A*
G	Chirazyme L-7	*Porcine pancreas*
H	Fluka Lipase	*Candida rugosa*
I	Fluka Lipozyme[a]	*Mucor miehei*

[a] Immobilized.

For a better comparison of the catalytic activity and enantioselectivity of the lipases considered, the esterification of **3** was performed using the following standard conditions: in a 50 mL round-bottomed flask, a given amount of diol **3** was dissolved in 30 mL of a 50:1 TBME/IPA mixture and the given amount of lipase was added (Table 2). The reactions were carried out at a temperature of +40 °C and stirred with a magnetic bar. The reaction progress was controlled by thin layer chromatography (TLC) and stopped after the given time. For this purpose the lipase was filtered off and the filtrate was concentrated in vacuo.

The composition of the resulting mixture was analyzed with HPLC methods 1 and 2. HPLC method 1 is an achiral method (RP-18), which was employed for the determination of the transformation. The ratio of enantiomers (*S*)-**4**:(*R*)-**4** was analyzed by HPLC method 2 using the chiral Daicel Chiralpak AD-H stationary phase.

Table 2 shows the results of the lipase screening. Obviously the lipase from *Candida rugosa* (E, H) is not suitable for this reaction, since even after 144 h or 91 h at 40 °C, the transformation was very low. On the other hand, the lipase from *Candida antarctica B* (D) led to a very fast, but not selective acetylation resulting in large amounts of diacetate **5**.

Table 2. Screening of lipases using standard conditions: 30 mL of TBME/IPA 50:1 at +40 °C

Lipase	*m* (lipase) [mg]	*m* (**3**) [mg]	Time (h)	HPLC method 1			HPLC method 2	
				n (**3**) [%]	*n* (**4**) [%]	*n* (**5**) [%]	*n* ((*S*)-**4**) [%]	*n* ((*R*)-**4**) [%]
A	101.1	273.3	51	2.1	43.1	54.8	98.0	2.0
B	51.7	265.4	72	48.9	47.0	4.1	92.0	8.0
C	157.0	277.6	23	0.2	13.3	86.5	99.9	0.1
D	25.3	236.8	18	0.2	0.0	99.8	—	—
D	30.1	258.3	1	11.4	15.5	73.1	39.3	60.7
E	185.9	279.8	144	97.4	2.5	0.1	—	—
F	164.7	267.2	25	49.0	46.5	4.5	72.8	27.2
G	153.1	248.3	24	59.8	37.2	3.0	37.1	62.9
H	308.0	300.0	91	96.3	3.6	0.1	44.3	55.7
I	122.2	270.4	21	0.2	46.3	53.4	99.4	0.6

m (*X*) [mg] = amount of substance [mg]; *n* (*X*) [%] = amount of substance [%] = *n* (*X*) [mol]/*n* (∑) [mol].

Nevertheless, the enzymatic acetylation of diol **3** to afford diacetate **5** is more convenient than acetylation with acetic anhydride, since the transformation is nearly quantitative and the work-up is easier.[4] Therefore, the *C. antarctica B* lipase will be used for the synthesis of diacetate **5**, which is required for the synthesis of the enantiomeric monoacetate (*R*)-**4** by lipase catalyzed enantioselective hydrolysis.

According to Table 2, most of the lipases investigated provided the (*S*)-configured monoacetate (*S*)-**4**. Only the lipases from *C. antarctica B* (D), *C. rugosa* (H) and *Porcine pancreas* (G) led to a low excess of the (*R*)-configured monoacetate (*R*)-**4**.

The most promising enantioselectivity was attained using the bacterial lipases from *P. fluorescens* (A), *B. cepacia* (B, C) and *Mucor miehei* (I). We decided to further optimize the reaction with Amano PS-CII, a lipase from *B. cepacia* (C), which is immobilized on ceramic particles. In the screening, Amano PS-CII led to the highest enantiomeric excess. Moreover, immobilization on ceramic particles allows the direct analysis of the reaction mixture without cumbersome work-up procedures.

2.3. Optimization of the reaction conditions using Amano PS-CII lipase

In order to find the best reaction conditions, the composition of the reaction mixture and the (*S*)-**4**:(*R*)-**4**-ratio were determined periodically. The general procedure was as follows. In a 50 mL two-necked flask, about 280 mg of diol **3** were dissolved in 30 mL of TBME and 0.50 wt equiv of Amano PS-CII lipase were added. To avoid damage of the ceramic particles, the reaction mixture was stirred with a KPG-stirrer (100 rpm). The reaction temperature was adjusted by a cryostat and the reaction was started by the addition of the respective amount of isopropenyl acetate (IPA). In order to analyze the transformation, samples of 100 μL taken from the reaction mixture were filtered through a membrane filter (0.45 μm) and the solvent was evaporated in a nitrogen stream over 2 min. The residue was dissolved in 100 μL of acetonitrile for HPLC method 1 and in 100 μL of a *n*-hexane/propan-2-ol 9:1 mixture for HPLC method 2. The amount of substances **3**, **4** and **5** (*n* [%]) determined by means of HPLC method 1 was charted in relation to the reaction time to give the diagrams depicted on the left side in Figures 1, 2 and 4 top. The ratio of the enantiomeric monoacetates (*S*)-**4** and (*R*)-**4** was determined by means of HPLC method 2. The development of the enantiomeric excess during the reaction time is shown on the right side in Figures 1, 2 and 4 top.

At first, the progress of the reactions carried out at different temperatures with 5.0 equiv of the acylating agent IPA was recorded. A comparison of the reactions carried out at +20 °C (Fig. 1 top) and at −10 °C (Fig. 1 bottom) shows that the enantioselectivity of the lipase was increased by a reduction in temperature. The yield of monoacetate (*S*)-**4** in sample A (Fig. 1 top, arrow) was 48.3% with 99.53% ee. Sample B (Fig. 1 bottom, arrow) contained 57.0% yield of monoacetate (*S*)-**4** with 99.92% ee. However, the transformation at −10 °C was considerably slower: Point B in Figure 1 was achieved after only 65 h.

Next the influence of the IPA amount on the reaction progress was investigated. The lipase catalyzed acetylation was performed at −10 °C employing 2.0 equiv (Fig. 2 top) or 15.0 equiv (Fig. 2 bottom) of IPA. Obviously a larger IPA amount increased the enantiomeric excess: Sample C taken from the reaction carried out with 2.0 equiv of IPA at the indicated time (Fig. 2 top, arrow) consisted of 63.7% yield of monoacetate (*S*)-**4** with 99.67% ee. In Figure 2 bottom, the marked position D represents a sample, which contained a yield of 65.3% monoacetate (*S*)-**4** with 99.84% ee. However, raising the IPA amount to 50 equiv led to deterioration of the transformation, probably due to the higher polarity of the solvent.

Small amounts of IPA (2.0 equiv) resulted in a maximum of the enantiomeric excess (99.82% ee) after 92.6 h. Afterwards, the ee-value decreased due to the partial racemization of monoacetate (*S*)-**4**. This partial racemization was caused by lipase catalyzed transesterification of diol **3**, monoacetate **4** and diacetate **5**. Thus, in the presence of low amounts of acylating agent IPA, the lipase uses monoacetate **4** and diacetate **5** instead of IPA as an acetyl group donor. This transacetylation leads to a reversibility of the conversion with a decline in the enantiomeric excess.

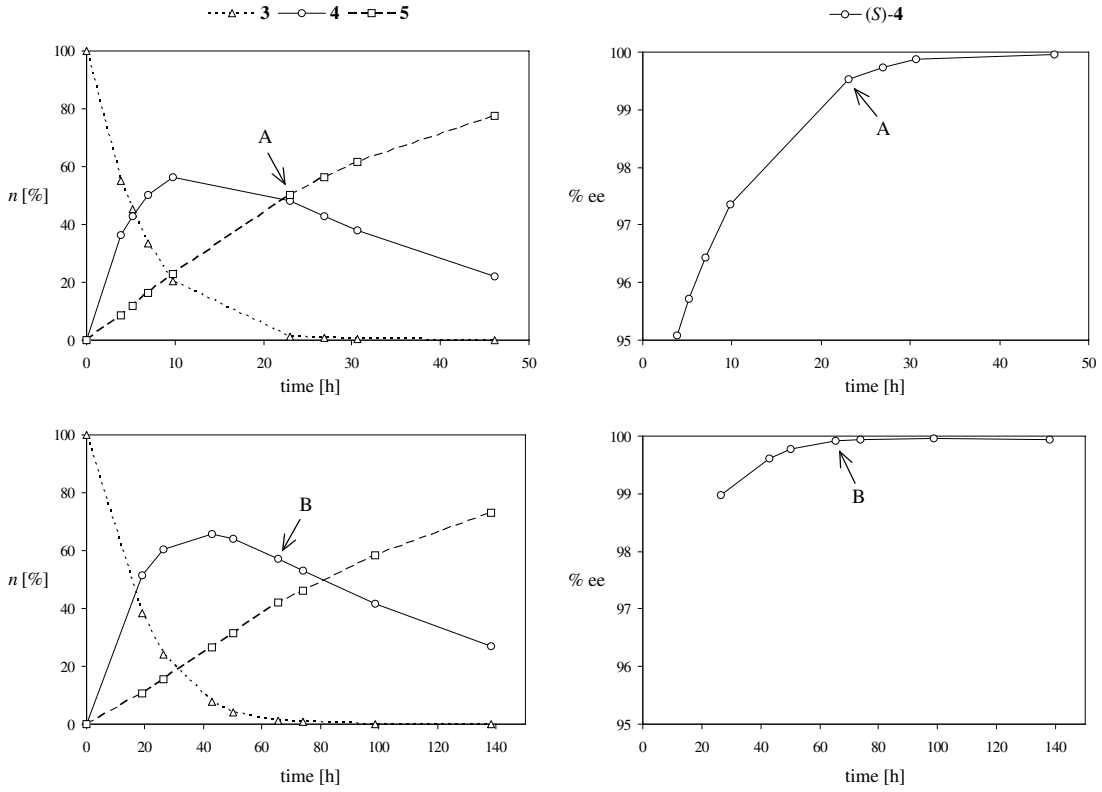


Figure 1. Progress of the reaction using 5 equiv of IPA; left: amount of compounds **3**, **4** and **5** (*n* [%]); right: enantiomeric excess of (*S*)-**4** (% ee); top: carried out at +20 °C; Sample A (23.0 h): (*S*)-**4**: yield: 48.3%, 99.53% ee; bottom: carried out at −10 °C; Sample B (65.4 h): (*S*)-**4**: yield: 57.0%, 99.92% ee.

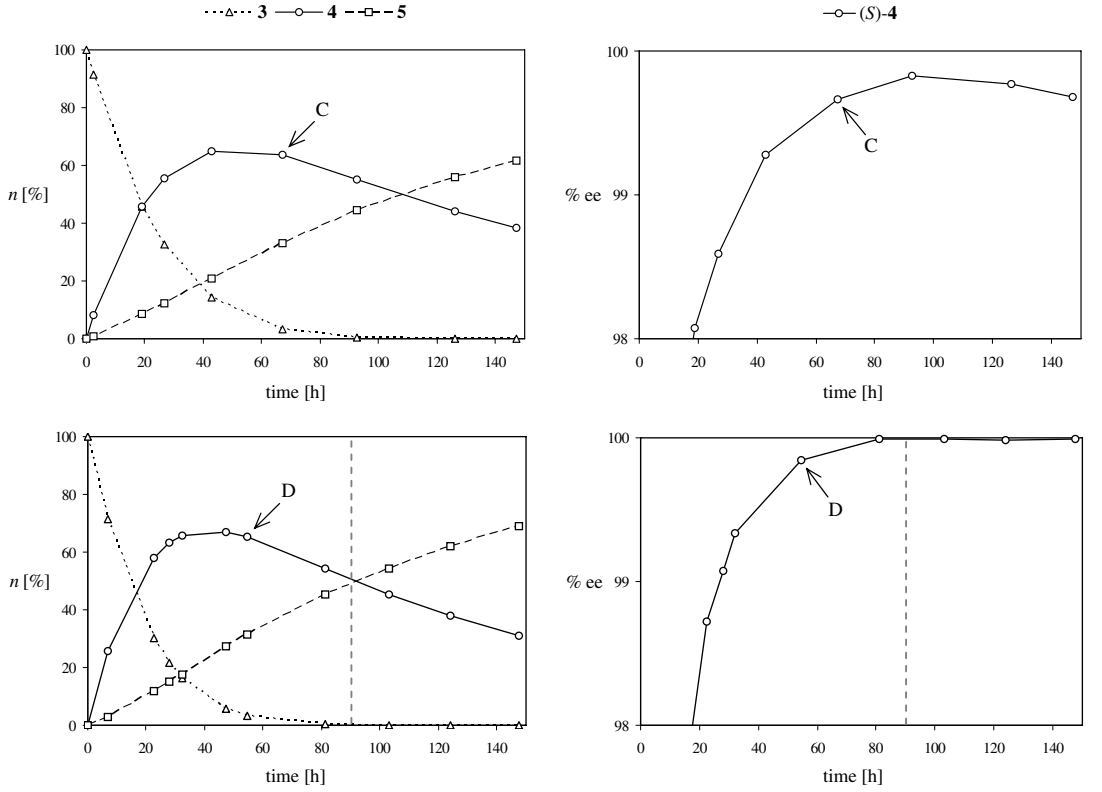


Figure 2. Progress of the reaction carried out at −10 °C; left: amount of compounds **3**, **4** and **5** (*n* [%]); right: enantiomeric excess of (*S*)-**4** (% ee); top: 2.0 equiv of IPA; Sample C (67.2 h): (*S*)-**4**: yield: 63.7%, 99.67%; bottom: 15.0 equiv of IPA; Sample D (54.4 h): (*S*)-**4**: yield: 65.3%, 99.84% ee. The grey dotted lines indicates the time (90 h) reactions should be stopped to get the best yield of (*S*)-**4** with >99.9% ee.

Recently we have published a facile mathematical system for the simulation of catalytic reactions.[6] Based on the theoretically possible equilibria (Scheme 4), the development of the transformation can be calculated using given values for the rate constants k_1 to k_8 and the lipase activity **a**. In Figure 3 the simulated reaction courses and the corresponding enantiomeric excess are displayed. For these calculations the ratio of rate constants ($k_1/k_5 = k_2/k_6 = k_3/k_7 = k_4/k_8$) was set at $1{:}10^{-3}$ (Fig. 3 top) and at $1{:}10^{-6}$ (Fig. 3 bottom) on the product side. The outcome corresponds to the experimental data shown in Figure 2 and proves the assumption that racemization can be prohibited by suppressing the backward reactions. Hence, a sufficient excess of the acylating agent IPA has to be applied to produce monoacetate (*S*)-**4** with high enantiomeric purity.

Finally, the lipase catalyzed acetylation of diol **3** was performed at an extraordinarily low temperature of −40 °C. In this experiment, the amount of lipase was raised from 0.5 to 1.0 wt equiv because its activity was strongly reduced at −40 °C. It can be seen from Figure 4 that lowering the temperature from −10 to −40 °C further increased the enantioselectivity of the transformation. Compound (*S*)-**4** in sample E (Fig. 4 top, arrows) has about the same enantiomeric purity (99.86% ee) as (*S*)-**4** in sample D (99.84% ee) (Fig. 2). However, the yield of monoacetate (*S*)-**4** was considerably higher for sample E (74.2%) than for sample D (65.3%). Despite of the increased amount of catalyst, the reaction rate was dramatically reduced by lowering the reaction temperature: sample D was taken after 54.4 h, sample E after 290.5 h. Overall the reaction was run for about 860 h (about 36 d) at −40 °C. During the reactions (*S*)-**4** reached an excellent enantiomeric purity (>99.99% ee), whereas the yield of (*S*)-**4** was still very high (>60%) (Fig. 4 top).

At the bottom of Figure 4, the computational simulation of this reaction is shown. The use of the rate constants given in Figure 4 resulted in curves, which are nearly identical to the experimentally determined curves shown at the top of Figure 4. A crucial feature for the enantioselectivity of the reaction is the ratio $k_1/k_2 = k_4/k_3 = k_5/k_6 = k_8/k_7$, which is set at 35:1 in the simulation. A comparison of this ratio at −40 °C (35:1) (Fig. 4 bottom) with the corresponding ratio for the reaction at −10 °C of 25:1 (Fig. 3 bottom) supports the higher enantioselectivity of the lipase at a temperature of −40 °C. The rate ratio of the transformations of diol **3** to monoacetate **4** and of monoacetate **4** to diacetate **5** was not altered by lowering the reaction temperature. The simulations shown in Figures 3 and 4 bottom, were calculated with the ratio $k_4/k_1 = k_3/k_2 = k_8/k_5 = k_7/k_6 = 4{:}1$.

To the best of our knowledge, this is one of the first experiments,[7] which employed an enzyme at −40 °C. It was surprising that the *B. cepacia* lipase still worked at such a low temperature. The increased enantioselectivity and yield

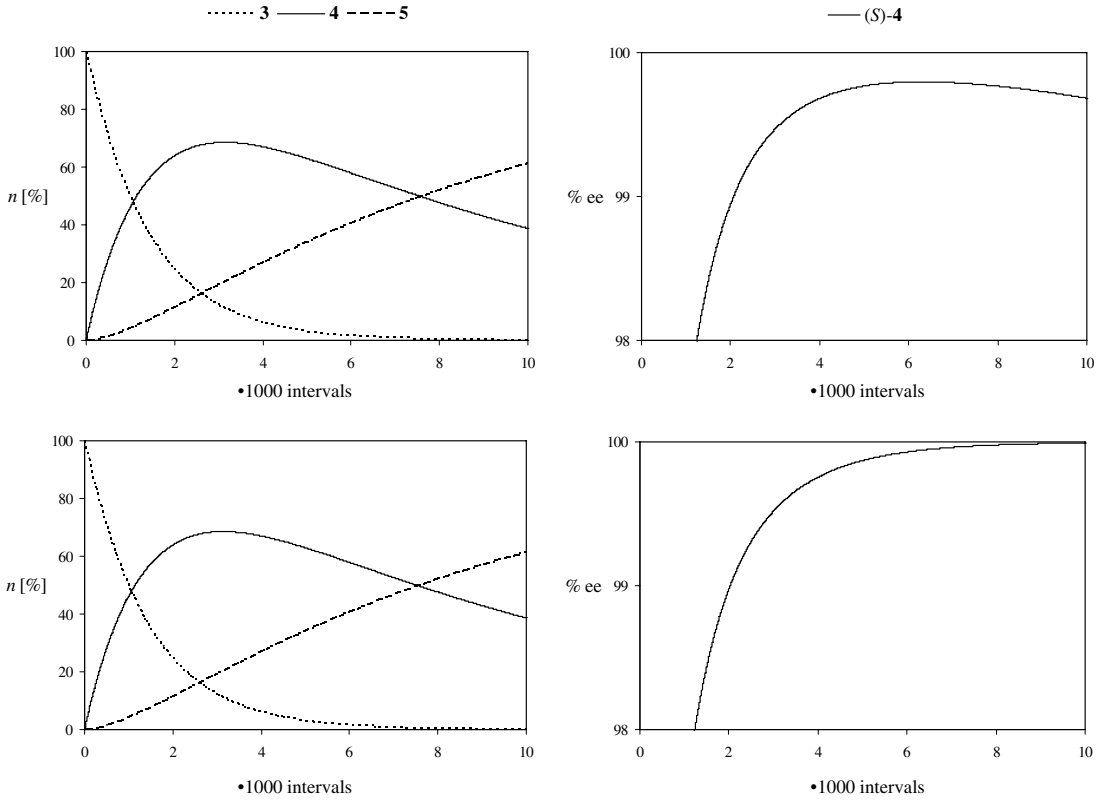


Figure 3. Simulated[6] progress of the reaction using a constant lipase activity **a** = 0.0035. The rate constants k_1 to k_8 are defined in Scheme 4; left: amount of compounds **3**, **4** and **5** (*n* [%]); right: enantiomeric excess of (*S*)-**4** (% ee); top: $k_1 = 25$, $k_2 = 1$, $k_3 = 4$, $k_4 = 100$, $k_5 = 25 \times 10^{-3}$, $k_6 = 1 \times 10^{-3}$, $k_7 = 4 \times 10^{-3}$, $k_8 = 100 \times 10^{-3}$; bottom: $k_1 = 25$, $k_2 = 1$, $k_3 = 4$, $k_4 = 100$, $k_5 = 25 \times 10^{-6}$, $k_6 = 1 \times 10^{-6}$, $k_7 = 4 \times 10^{-6}$, $k_8 = 100 \times 10^{-6}$.

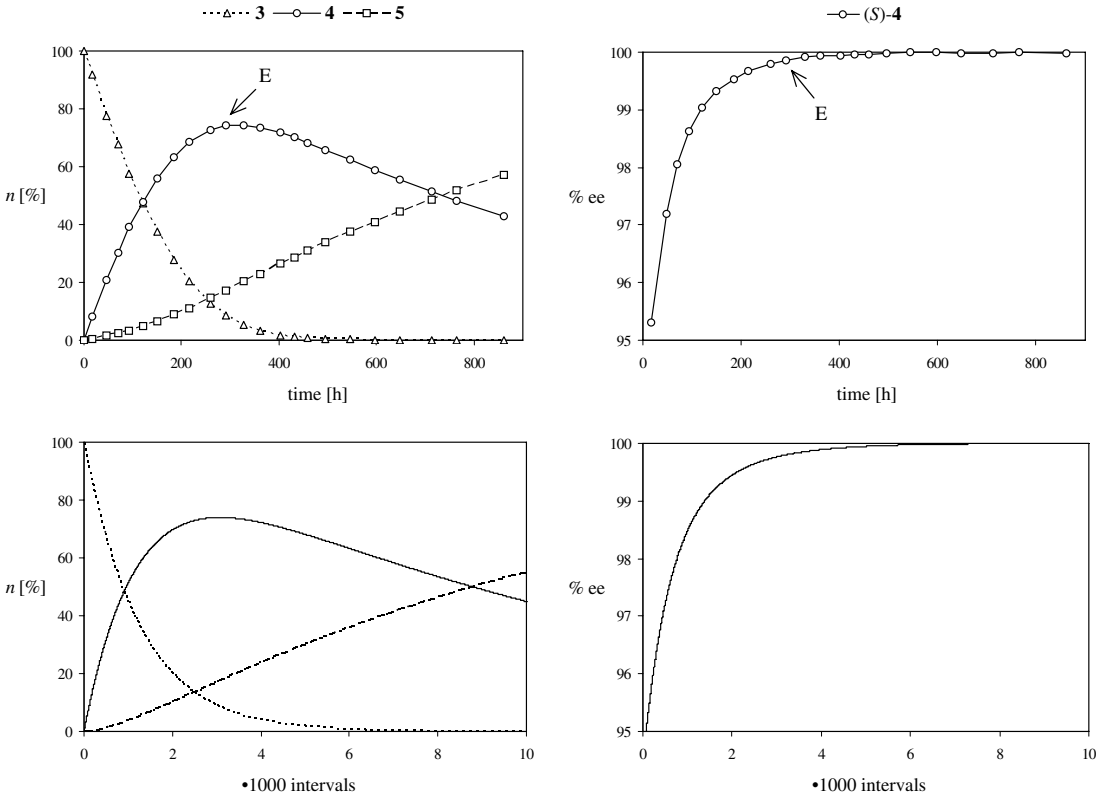


Figure 4. Measured and simulated[6] progress of the reaction at −40 °C; left: amount of compounds **3**, **4** and **5** (*n* [%]); right: enantiomeric excess of (*S*)-**4** (% ee); top: reaction carried out using 15 equiv of IPA; bottom: Simulation[6] of the reaction using a constant lipase activity **a** = 0.004. The rate constants k_1 to k_8 are defined in Scheme 4; $k_1 = 35$, $k_2 = 1$, $k_3 = 4$, $k_4 = 140$, $k_5 = 35 \times 10^{-6}$, $k_6 = 1 \times 10^{-6}$, $k_7 = 4 \times 10^{-6}$, $k_8 = 140 \times 10^{-6}$.

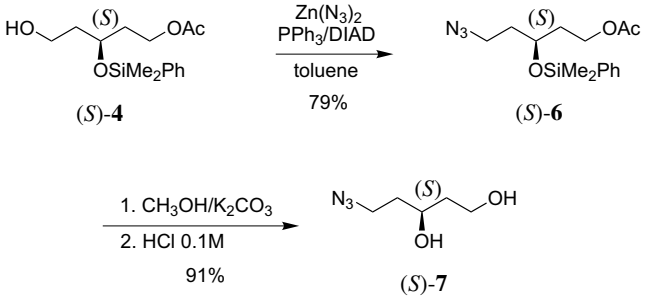
have prompted us to explore further lipase catalyzed transformations at similar unphysiological temperatures.

In order to produce large amounts of (*S*)-**4** in a reasonable period of time, the lipase catalyzed acetylation of diol **3** was performed at −10 °C with 15 equiv of IPA. The reaction was stopped as soon as the ratio of monoacetate **4** to diacetate **5** was about 1:1, according to HPLC method 1 (Fig. 2 bottom, grey dotted lines). Upon flash chromatography, (*S*)-**4** was obtained in >99.9% ee and 52% yield.

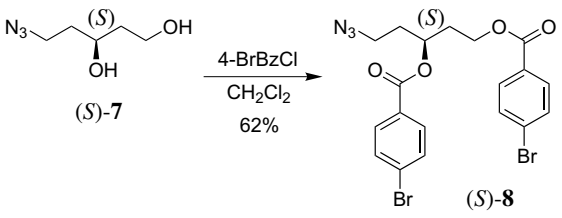
2.4. Absolute configuration

According to our plan the enantiomerically pure monoacetate (*S*)-**4** should be transformed into the chiral building block 5-azidopentane-1,3-diol (*S*)-**7**. Diol (*S*)-**7** should also be used for the determination of the absolute configuration of (*S*)-**4**. Thus, monoacetate (*S*)-**4** was reacted in a Mitsunobu reaction[8] with $Zn(N_3)_2$, PPh_3 and diisopropyl azodicarboxylate (DIAD) to afford azide (*S*)-**6**, which was hydrolyzed to yield azidodiol (*S*)-**7** (Scheme 5). Enantiomerically pure azidodiol (*S*)-**7** represents an interesting building block, since the positions 1, 3 and 5 of the pentane scaffold can be modified selectively.

In order to determine the absolute configuration of monoacetate (*S*)-**4**, azidodiol (*S*)-**7** was acylated with 4-bromobenzoyl chloride to provide dibenzoate (*S*)-**8** (Scheme 6).



Scheme 5. Synthesis of (*S*)-5-azidopentane-1,3-diol (*S*)-**7**.



Scheme 6. Synthesis of bis(bromobenzoyl) derivative (*S*)-**8** for determination of the absolute configuration (4-BrBzCl = 4-bromobenzoyl chloride).

At first the enantiomeric purity of dibenzoate (*S*)-**8** was investigated with HPLC method 3 using a Daicel Chiralpak IB column. According to this analysis, the dibenzo-

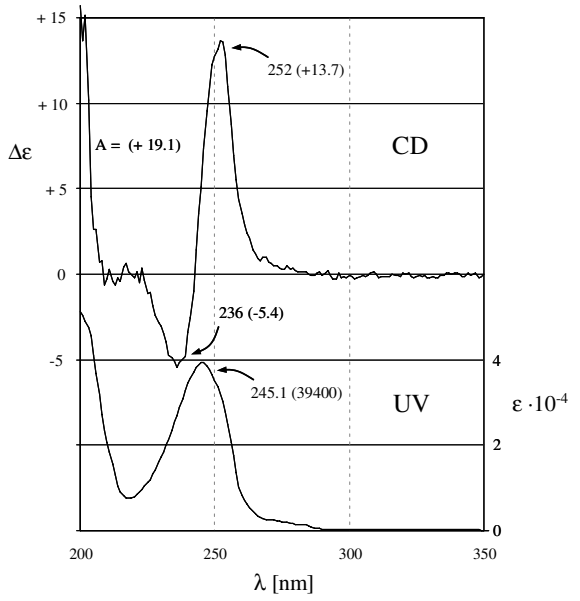


Figure 5. CD and UV spectra of (*S*)-**8** in *n*-hexane.

ate used for recording the CD spectrum had an enantiomeric purity of 99.84% ee. The CD spectrum was recorded in *n*-hexane and arises from exciton-coupling between the electric transition moments of the benzoyl chromophores (Fig. 5). The $\pi \rightarrow \pi^*$ transitions (245 nm) couple with each other and reveal a bisignate curve: the Cotton effect with lower energy is positive (252 nm) and the one with higher energy negative (236 nm), which proves the (*S*)-configuration of the stereogenic centre.[4,9,10]

3. Conclusions

Prochiral diol **3** was enantioselectively monoacetylated by transesterification with isopropenyl acetate to obtain enantiomerically pure monoacetate (*S*)-**4** (>99.9% ee) using the immobilized lipase from *B. cepacia*. The reaction conditions were carefully optimized. Lowering of the reaction temperature led to an increased enantioselectivity. Even at −40 °C, the lipase catalyzed the transesterification but with a low reaction rate. In order to avoid partial racemization, 15 equiv of the acylating agent isopropenyl acetate should be used. Large amounts of monoacetate (*S*)-**4** were synthesized with 15 equiv of IPA at −10 °C. The conversion of (*S*)-**4** into enantiomerically pure pentane derived building blocks was demonstrated by the synthesis of 5-azidopentane-1,3-diol (*S*)-**7**.

4. Experimental

4.1. General

Thin layer chromatography (TLC): silica gel 60 F_{254} (E. Merck); Flash chromatography (fc): Silica gel 60, 40–63 μm (E. Merck);[11] HPLC equipment: Merck Hitachi, UV-Detector L-7400, Autosampler L-7200, Pump L-7100, data acquisition HSM-Software; Melting points: Melting point apparatus SMP 3 (Stuart Scientific), and are uncorrected; Optical rotation: Polarimeter 341 (Perkin Elmer), 1.0 dm tube, concentration *c* (g/100 mL), temperature 20 °C, the unit [deg mL dm^{-1} g^{-1}] is omitted; IR: IR spectrophotometer 480Plus FT-ATR-IR (Jasco); ^1H NMR (400 MHz): Unity Mercury Plus 400 NMR spectrometer (Varian), δ in parts per million related to tetramethylsilane; MS: MAT GCQ (Thermo-Finnigan), TSQ 7000 (Thermo-Finnigan), LCQ MAT (Thermo Finnigan), EI = electron impact; Elemental analysis: Vario EL (Elementaranalysesysteme GmbH).

4.2. HPLC analysis

Method 1

column:	Merck LiChrospher 100 RP-18e (5 μm); 125—4 mm;
mobile phase:	acetonitrile/water 50:50; 1 mL/min;
detection:	$\lambda = 264$ nm for 16 min;
retention times (rt):	rt (**3**) = 1.9 min; rt (**4**) = 4.1 min; rt (**5**) = 12.4 min;
scaling factors (sf):	sf (**3**) = sf (**4**) = sf (**5**) = 1.00 [*n* (%)/area (%)].

Method 2

column:	Daicel Chiralpak AD-H (5 μm); 250—4.6 mm;
mobile phase:	*n*-hexane/propan-2-ol 51:1; 1 mL/min;
detection:	$\lambda = 264$ nm for 40 min;
retention times (rt):	rt ((*S*)-**4**) = 25.0 min; rt ((*R*)-**4**) = 27.5 min; the rt can be increased by using *n*-hexane/propan-2-ol 54:1 to rt ((*S*)-**4**) = 27.5 min; rt ((*R*)-**4**) = 32.5 min;
scaling factors (sf):	sf ((*S*)-**4**) = sf ((*R*)-**4**) = 1.000 [*n* (%)/area (%)].

Method 3

column:	Daicel Chiralpak IB (5 μm); 250—4.6 mm;
mobile phase:	*n*-hexane/2-propanol 20:1; 1 mL/min;
detection:	$\lambda = 245$ nm for 30 min;
retention times (rt):	rt ((*S*)-**8**) = 17.7 min; rt ((*R*)-**8**) = 19.3 min;
scaling factors (sf):	sf ((*S*)-**8**) = sf ((*R*)-**8**) = 1.000 [*n* (%)/area (%)].

4.3. Dimethyl 3-(dimethylphenylsilyloxy)glutarate 2

$Me_2PhSiCl$ (11.1 g, 65.0 mmol) was dissolved in CH_2Cl_2 (100 mL) and imidazole (10 g, 147 mmol) was added. A

solution of dimethyl ester **1** (10.0 g, 56.8 mmol) in CH_2Cl_2 (50 mL) was added dropwise and the reaction mixture stirred for 22 h at room temperature. Afterwards, water (120 mL) was added, and the aqueous layer was separated and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with water (100 mL), dried over K_2CO_3 and concentrated in vacuo. The residue was purified by fc (∅ 8 cm; *h* 20 cm; 7:1 petroleum ether/EtOAc; fractions 30 mL; R_f 0.30); colourless oil; yield 17.0 g (96%); IR (ATR, neat): ν (cm^{-1}) = 3070 (C–$H_{arom.}$), 2953 (C–H), 1735 (C=O); ^1H NMR ($CDCl_3$): δ (ppm) = 0.38 (s, 6H, –Si(CH_3)$_2$), 2.53 (d, J = 6.2 Hz, 4H, –CH_2–CH–CH_2–), 3.58 (s, 6H, 2 × –CO_2CH_3), 4.61 (quint, J = 6.3 Hz, 1H, –CH_2–C*H*–CH_2–), 7.31–7.37 (m, 3H, $H_{arom.}$), 7.51–7.55 (m, 2H, $H_{arom.}$); EIMS *m*/*z* (rel int.): 310 (M, 12), 233 (M−Ph, 97), 77 (Ph, 11); $C_{15}H_{22}O_5Si$ (310.4).

4.4. 3-(Dimethylphenylsilyloxy)pentane-1,5-diol 3

$LiBH_4$ (6.6 g, 300 mmol) was added to a solution of **2** (15.4 g, 50 mmol) in Et_2O (700 mL) and the reaction mixture was stirred for 17 h at room temperature. A saturated solution of NH_4Cl (200 mL) was added to destroy excess $LiBH_4$. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over K_2CO_3, concentrated in vacuo and the residue was purified by fc (∅ 8 cm; *h* 20 cm; EtOAc; fractions 30 mL; R_f 0.30); colourless oil; yield 10.8 g (85%); IR (ATR, neat): ν (cm^{-1}) = 3340 (O–H), 3070 (C–$H_{arom.}$), 2949, 2882 (C–H); ^1H NMR ($CDCl_3$): δ (ppm) = 0.44 (s, 6H, –Si(CH_3)$_2$), 1.65–1.79 (m, 4H, –CH_2–CH–CH_2–), 1.93 (s, 2H, 2 × –O*H*), 3.59–3.70 (m, 4H, 2 × –CH_2–OH), 4.11 (quint, J = 5.8 Hz, 1H, –CH_2–C*H*–CH_2–), 7.36–7.43 (m, 3H, $H_{arom.}$), 7.58–7.61 (m, 2H, $H_{arom.}$); EIMS *m*/*z* (rel int.): 254 (M, 2), 177 (M−Ph, 5), 135 (Me_2PhSi, 8), 77 (Ph, 68); $C_{13}H_{22}O_3Si$ (254.4).

4.5. (*S*)-[3-(Dimethylphenylsilyloxy)-5-hydroxypentan-1-yl] acetate (*S*)-4 and [3-(Dimethylphenylsilyloxy)pentane-1,5-diyl] diacetate 5

Diol **3** (3.03 g, 11.9 mmol) was dissolved in TBME (400 mL) and amano PS-CII lipase (3 g) was added. The suspension was stirred with a KPG-stirrer and cooled to −10 °C. The reaction was started by the addition of isopropenyl acetate (19.5 mL, 179 mmol; −10 °C). After 42.5 h of stirring at −10 °C the KPG-stirrer was removed. The reaction mixture was warmed to room temperature within about 2 min in a water bath and filtered immediately. The filtrate was concentrated in vacuo and purified by fc (∅ 8 cm; *h* 20 cm; 1:1 cyclohexane/EtOAc; fractions 30 mL).

Data for (*S*)-**4**: R_f 0.29; colourless oil; yield 1.84 g (52%); $[\alpha]_D^{20}$ = +9.5 (*c* 0.64, THF); 99.91% ee (HPLC method 2); IR (ATR, neat): ν (cm^{-1}) = 3454 (O–H), 3070 (C–$H_{arom.}$), 1738 (C=O); ^1H NMR (DMSO-d_6): δ (ppm) = 0.45 (s, 3H, –Si–CH_3), 0.46 (s, 3H, –Si–CH_3), 1.67–1.90 (m, 4H, –CH_2–CH–CH_2–), 2.06 (s, 3H, CH_3–COO–), 4.04–4.16 (m, 4H, 2 × –CH_2–O–), 4.51 (t, J = 4.7 Hz, 1H, –CH_2–C*H*–CH_2–), 7.47–7.54 (m, 3H, $H_{arom.}$), 7.66–7.69 (m, 2H, $H_{arom.}$); EIMS *m*/*z* (rel int.): 296 (M, 11), 219 (M−Ph, 24), 135 (Me_2PhSi, 13), 77 (Ph, 97). Anal. Calcd for $C_{15}H_{24}O_4Si$ (296.4): C 60.78, H 8.16. Found: C 60.41, H 8.42.

Data for **5**: R_f 0.55; colourless oil; yield 1.72 g (43%); IR (ATR, neat): ν (cm^{-1}) = 3070 (C–$H_{arom.}$), 1737 (C=O); ^1H NMR (DMSO-d_6): δ (ppm) = 0.45 (s, 6H, –Si(CH_3)$_2$), 1.74–1.90 (m, 4H, –CH_2–CH–CH_2–), 2.06 (s, 6H, 2 × CH_3–COO–), 4.00–4.16 (m, 5H, 2 × –CH_2–O– and –CH_2–C*H*–CH_2–), 7.47–7.55 (m, 3H, $H_{arom.}$), 7.65–7.68 (m, 2H, $H_{arom.}$); EIMS *m*/*z* (rel int.): 338 (M, 5), 135 (Me_2PhSi, 12), 77 (Ph, 94); $C_{17}H_{26}O_5Si$ (338.5).

4.6. (*S*)-[5-Azido-3-(dimethylphenylsilyloxy)pentan-1-yl] acetate (*S*)-6

Monoacetate (*S*)-**4** (3.04 g, 10.3 mmol; 99.86% ee) was dissolved in toluene (60 mL). Then $Zn(N_3)_2$·2Py (2.36 g, 7.7 mmol)[8] and triphenylphosphane (5.37 g, 20.5 mmol) were added. To this suspension, diisopropyl azodicarboxylate (4.0 mL, 20.5 mmol) was added dropwise and the reaction mixture was stirred for 22 h at room temperature. The mixture was transferred to a column without further work-up and purified by fc (∅ 8 cm; *h* 18 cm; 9:1 cyclohexane/EtOAc; fractions 30 mL; R_f 0.23); colourless oil; yield 2.59 g (79%); $[\alpha]_D^{20}$ = −0.2 (*c* 0.88, CH_2Cl_2); IR (ATR, neat): ν (cm^{-1}) = 3071 (C–$H_{arom.}$), 2093 (N=N=N), 1738 (C=O); ^1H NMR (DMSO-d_6): δ (ppm) = 0.46 (s, 3H, –Si–CH_3), 0.47 (s, 3H, –Si–CH_3), 1.72–1.85 (m, 4H, –CH_2–CH–CH_2–), 2.06 (s, 3H, CH_3–COO–), 3.37–3.47 (m, 2H, –CH_2–N_3), 4.00–4.14 (m, 3H, –CH_2–O– and –CH_2–C*H*–CH_2–), 7.48–7.55 (m, 3H, $H_{arom.}$), 7.66–7.68 (m, 2H, $H_{arom.}$); EIMS *m*/*z* (rel int.): 321 (M, 1), 135 (Me_2PhSi, 3), 77 (Ph, 31). Anal. Calcd for $C_{15}H_{23}N_3O_3Si$ (321.5): C 56.05, H 7.21, N 13.07. Found: C 55.62, H 7.35, N 12.84.

4.7. (*S*)-5-Azidopentane-1,3-diol (*S*)-7

Azide (*S*)-**6** (2.54 g, 7.9 mmol) was dissolved in methanol (100 mL). K_2CO_3 (270 mg) was then added and the reaction mixture was stirred for 3 h at room temperature. Afterwards, HCl (1 M, 7.9 mL) was added and the reaction mixture was stirred for a further 2 h at room temperature. Then, it was degassed in an ultrasonic bath, NH_3 (25%, 1.6 mL) was added and the mixture was concentrated to dryness in vacuo. To remove any remaining water, $CHCl_3$ (2 × 70 mL) was added and evaporated in vacuo again. The residue was then heated at reflux in ethanol (70 mL) for 10 min and then cooled overnight (5 °C). The salts were filtered off, washed with ethanol (70 mL) and the filtrate was concentrated in vacuo. The residue was purified by fc (∅ 6 cm; *h* 20 cm; EtOAc; fractions 30 mL; R_f 0.22); pale-yellow oil; yield 1.04 g (91%); $[\alpha]_D^{20}$ = −26.7 (*c* 0.88, CH_2Cl_2); IR (ATR, neat): ν (cm^{-1}) = 3340 (O–H), 2091 (N=N=N); ^1H NMR (CD_3OD): δ (ppm) = 1.71–1.90 (m, 4H, –CH_2–CH–CH_2–), 3.54 (t, J = 7.0 Hz, 2H, –CH_2–N_3), 3.80 (t, J = 6.6 Hz, 2H, –CH_2–OH), 3.94 (tt, J = 4.7/3.9 Hz, 1H, –CH_2–C*H*–CH_2–); EIMS *m*/*z* (rel int.): 146 (MH, 43), 72

(C_5H_{12}, 100). Anal. Calcd for $C_5H_{11}N_3O_2$ (145.2): C 41.37, H 7.64, N 28.95. Found: C 41.69, H 7.91, N 28.38.

4.8. (*S*)-(5-Azidopentane-1,3-diyl) bis-4-bromobenzoate (*S*)-8

NEt_3 (255 μL, 1.84 mmol) and a solution of 4-bromobenzoyl chloride (220 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) were added to azidodiol (*S*)-**7** (45 mg, 0.31 mmol). The reaction mixture was stirred for 45 h at room temperature. Afterwards, a saturated solution of NH_4Cl (50 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over Na_2SO_4, concentrated in vacuo and the residue was purified by fc (∅ 3 cm; *h* 20 cm; 9:1 cyclohexane/EtOAc; fractions 10 mL; R_f 0.17); colourless solid; mp 51–53 °C; yield 99 mg (62%); $[\alpha]_D^{20} = +42.0$ (*c* 0.67, CH_2Cl_2); 99.84% ee (HPLC method 3); IR (ATR, neat): *ν* (cm^{-1}) 3090 (C–$H_{arom.}$); 2096 (N=N=N); 1714 (C=O); ^1H NMR ($CDCl_3$): *δ* (ppm) = 1.95–2.10 (m, 2H, N_3–CH_2–CH_2–CH–), 2.16–2.24 (m, 2H, –O–CH_2–CH_2–CH–), 3.42 (t, 2H, *J* = 7.0 Hz, N_3–CH_2–), 4.34–4.47 (m, –O–CH_2–), 5.42–5.46 (m, 1H, –CH_2–C*H*–CH_2–), 7.51 (d, *J* = 8.6 Hz, 2H, $H_{arom.}$), 7.54 (d, *J* = 8.6 Hz, 2H, $H_{arom.}$), 7.80 (d, *J* = 8.6 Hz, 2H, $H_{arom.}$), 7.84 (d, *J* = 8.6 Hz, 2H, $H_{arom.}$); EIMS *m*/*z* (rel int.): 511 (M, 1), 184 (C_6H_4Br–C≡O, 9); $C_{19}H_{17}Br_2N_3O_4$ (511.2).

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