DOI: 10.1002/ejoc.200700096

Enzyme-Catalyzed Kinetic Resolution of 1,3-*anti*-Diol Monoesters – Efficient Preparation of Enantiomerically Highly Enriched and Unsymmetrically Substituted 1,3-*anti*-Diols

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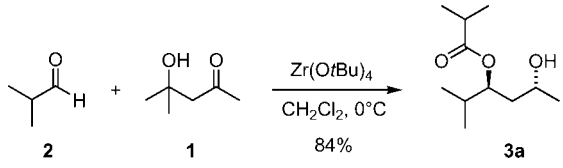
Keywords: Aldol-Tishchenko reaction / Enzyme catalysis / Kinetic resolution / Lipase / 1,3-Diols

Candida antarctica Lipase B (CALB) catalyzed the highly enantioselective acetylation of 1,3-*anti*-diol monoesters which have been obtained through a zirconium-catalyzed aldol-Tishchenko reaction. The product 1,3-*anti*-diol diesters were formed in yields close to 50 % and >98 % *ee*. Separation from the unreactive enantiomers and subsequent hydrolysis furnished both enantiomers of unsymmetrically substituted 1,3-*anti*-diols in high optical purities. Alternatively, the kinetic resolution process can be performed on the free 1,3-*anti*-diols even more rapidly with equally good results. A slow acyl migration during the reaction slightly deteriorated the enantiomeric excess of the unreactive enantiomers.

Introduction

The 1,3-diol motif is a ubiquitous structural feature in natural products of polyketide origin.[1] In the context of natural product synthesis a great wealth of synthetic methodology has been accumulated for their stereoselective preparation.[2] Among the most valuable strategies is a sequence comprising a stereoselective aldol reaction followed by a diastereoselective β-hydroxy ketone reduction giving access to 1,3-*syn*- and 1,3-*anti*-diols, respectively, depending upon the reductant employed. Alternatively, this sequence may be executed in one step employing an aldol-Tishchenko reaction of a ketone with 2 equiv. of an aldehyde one of which is used as the coupling partner in the aldol reaction while the second one is used as hydride donor for the Tishchenko reduction.[3]

We have recently devised a conceptually novel strategy for the aldol-Tishchenko process relying on the facile retro-aldol tendency of ketone aldols. With zirconium alkoxides as catalysts (10 mol-%) ketone aldols such as diacetone alcohol (**1**) undergo rapid retro-aldol cleavage furnishing ketone enolates in situ which react with the aldehydes **2** (2 equiv.) in an aldol-Tishchenko reaction giving rise to 1,3-*anti*-diol monoesters **3** in typically high yields and complete 1,3-*anti* diastereocontrol (Scheme 1).[4] Subsequently, we have shown that chiral zirconium complexes with either TADDOL-[5a] or BINOL-ligands[5b] catalyzed enantioselective aldol-Tishchenko reactions and furnished products **3** with up to 60 % *ee*.



2 **1** **3a**

Scheme 1. Zirconium-catalyzed aldol-Tishchenko reaction of diacetone alcohol (**1**).

In a complementary study we have now investigated the enzyme-catalyzed kinetic resolution of 1,3-*anti*-diol monoesters **3**. Lipases are well established synthetic tools for the enantiomer-differentiating acylation of racemic secondary alcohols with activated acyl derivatives such as vinyl acetate. Among the lipases most frequently employed *Candida antarctica* Lipase B (CALB) occupies a prominent position and has been immobilized on macroporous acrylic resin facilitating its use (Novozym 435 by Novozymes).[6] The three-dimensional structure of the enzyme's active site has been determined and the enzyme's mode of action elucidated.[7] Thus, a catalytic triad comprising the amino acid residues Asp^{187}, His^{224}, and Ser^{105} reacts with the acyl donor and forms a serine ester in the oxyanion hole of the enzyme. The steric environment in the enzyme's active site now only allows *R*-alcohols to selectively add to this intermediate furnishing the product esters with selectivity factors of greater than 200.[8]

A large number of simple secondary alcohols have been shown to be readily resolved using CALB or other lipases.[9] In addition, Williams,[10] Bäckvall,[11] Kim and Park,[12] and more recently Berkessel et al.[13] developed very interesting dynamic kinetic resolutions of secondary alcohols in a pro-

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cess comprising a fast metal-catalyzed racemization and enzyme-catalyzed kinetic resolution. Examples of more highly functionalized alcohols, however, are less frequent.

A limited number of acyclic, but symmetrical 1,3-*anti*-diols have been kinetically resolved through an enzymatic acylation process by the groups of Sih,[14] Norin,[15] and Rabiller et al.[16] Bäckvall et al. employed their Ru-enzyme-coupled process and converted a racemic and diastereomeric mixture of 1,3-diols into enantiomerically pure 1,3-*syn*-diol diacetates in good yields and diastereoselectivity.[17] A single symmetrical 1,3-*anti*-diol diacetate was obtained in high *ee* and excellent yield and diastereoselectivity by the same group using a similar procedure.[18] More recently, Sung et al. reported the *Candida rugosa* Lipase-catalyzed kinetic resolution of 1-phenyl-1,3-butanediol which proceeded in good enantioselecitivity only for the unreactive diol enantiomer.[19]

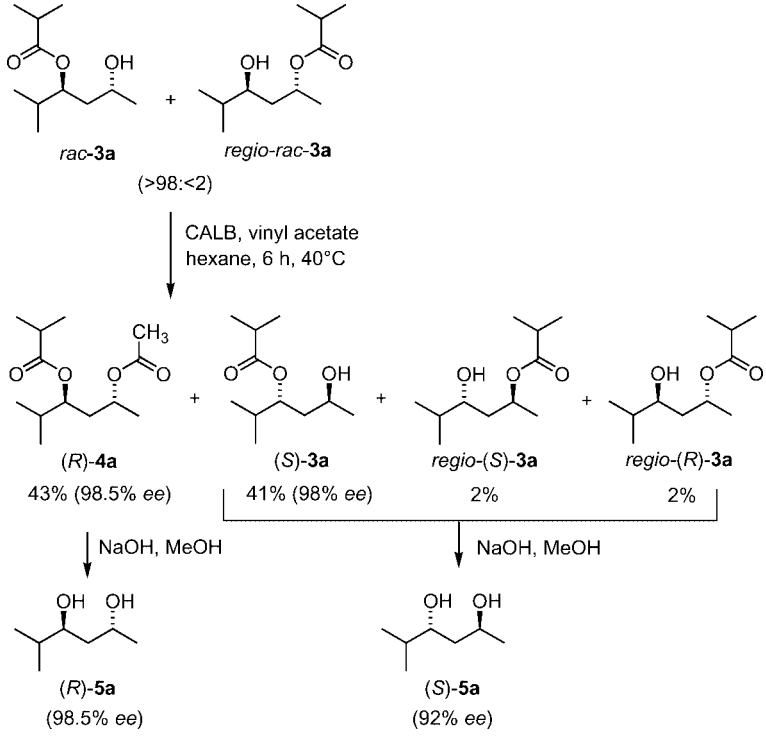
Results and Discussion

As a model we chose aldol-Tishchenko product *rac*-**3a** which was obtained in excellent yield and diastereoselectivity through the zirconium alkoxide-catalyzed aldol-Tishchenko reaction previously developed in our laboratory.[4] When *rac*-**3a** was treated with CALB and vinyl acetate (4 equiv.) in hexane at 40 °C, complete conversion of the *R*-carbinol was observed within 6 h and 1,3-*anti*-diol diester (*R*)-**4a** was isolated in 43% yield and 98.5% *ee* (Scheme 2). The unreactive (*S*)-**3a** was recovered along with small amounts of the enantiomeric regioisomers in a combined yield of 41% and 98% *ee*.

The enantiomeric excess of (*R*)-**4a** and (*S*)-**3a** was directly analyzed through GC on a chiral stationary phase (FS-Hydrodex^R β-3P). The free 1,3-*anti*-diols (*R*)-**5a** and (*S*)-**5a** were then obtained quantitatively through alkaline methanolysis and their respective enantiomeric excesses were determined on the corresponding UV-active bis(*p*-bromobenzoyl) derivatives with HPLC on a chiral OD-phase. Whereas no change in *ee* was observed for the *R*-carbinol enantiomer (98.5% *ee* for (*R*)-**4a** as well as (*R*)-**5a**), the *ee* had dropped from 98% *ee* measured for (*S*)-**3a** to 92% *ee* for (*S*)-**5a**. At first sight surprising this decrease of enantiomeric excess was based upon a slow and apparently enzyme-catalyzed acyl migration in both enantiomers.

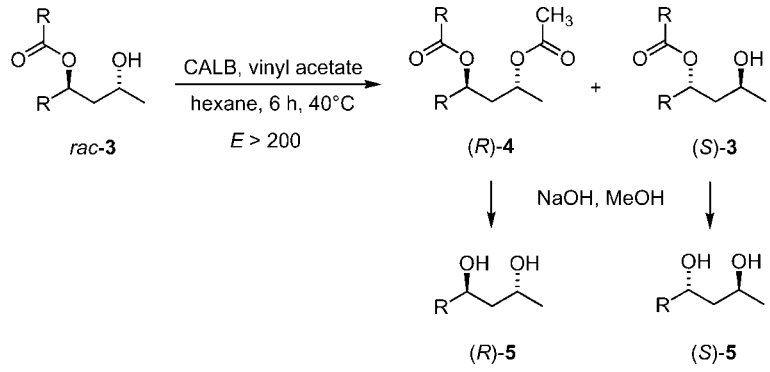
At the start of the kinetic resolution the ratio of *rac*-**3a** to its regioisomer was >98:2, i.e. the minor regioisomer could not be detected by 400-MHz ^{1}H NMR spectroscopy. After the kinetic resolution this ratio had changed to (*R*)-**4a**/(*S*)-**3a**/regioisomers = 10:10:1. Upon chromatographic separation of the desired product (*R*)-**4a** the remaining mixture comprised 1,3-diol monoesters (*S*)-**3a**, *regio*-(*S*)-**3a**, and *regio*-(*R*)-**3a** in a ratio of ca. 20:1:1 which was hydrolyzed to eventually yield the product 1,3-*anti*-diol (*S*)-**5a** in 92% *ee*. The proportion of regioisomers increased sharply towards the end of the kinetic resolution. Whereas after ca. 40% conversion the amount of regioisomers relative to the unreactive enantiomer (*S*)-**3a** was still just 3%, it increased to 10% after the resolution had been completed at 50% conversion.

Following the procedure described above various other 1,3-*anti*-diol monoesters *rac*-**3** obtained through the aldol-Tishchenko reaction were submitted to the CALB-catalyzed



Scheme 2. CALB-catalyzed kinetic resolution of 1,3-*anti*-diol monoester *rac*-**3a** with vinyl acetate.

Table 1. CALB-catalyzed kinetic resolution of 1,3-*anti*-diol monoesters *rac*-**3** with vinyl acetate.



rac-**3** (*R*)-**4** (*S*)-**3** (*R*)-**5** (*S*)-**5**

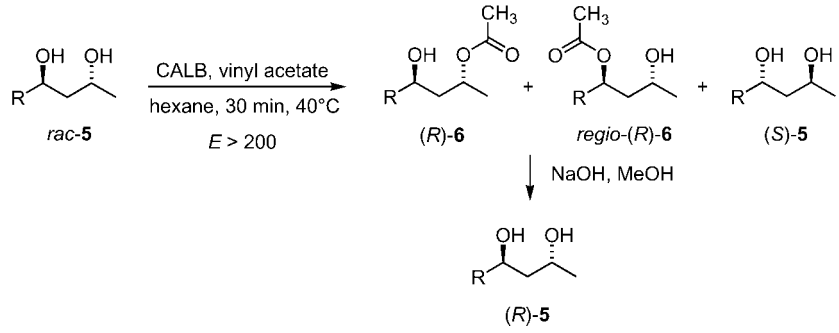
Entry	Substrate	R	Product (*R*)-**4**	Yield [%][a]	*ee* [%][b]	Product (*S*)-**3**	Yield [%][a,c]	*ee* [%][b]
1	*rac*-**3a**	*i*Pr	(*R*)-**4a**	43	98.5	(*S*)-**3a**	41 (10:1)	92 (98)[d]
2	*rac*-**3b**	*c*Pent	(*R*)-**4b**	44	99	(*S*)-**3b**	50 (12:1)	86
3	*rac*-**3c**	*c*Hex	(*R*)-**4c**	45	98.5	(*S*)-**3c**	45 (17:1)	91
4	*rac*-**3d**	1-Et-C_3H_6	(*R*)-**4d**	44	>99	(*S*)-**3d**	47 (30:1)	77
5	*rac*-**3e**	2-Ph$(CH_2)_2$	(*R*)-**4e**	49	99	(*S*)-**3e**	48 (11:1)	92 (97)[e]

[a] Isolated yield after flash column chromatography over silica gel. [b] Determined by chiral HPLC analysis on the bis(*p*-bromobenzoyl) derivative of diols **5** (see text). [c] Values in brackets refer to ratio of regioisomers (*S*)-**3** relative to the sum of *regio*-(*S*)-**3** and *regio*-(*R*)-**3** as determined by ^{1}H NMR spectroscopy. [d] Value in brackets refers to *ee* of (*S*)-**3a** determined directly by chiral GC analysis. [e] Value in brackets refers to *ee* of (*S*)-**3e** determined directly by chiral HPLC analysis.

esterification and yielded the corresponding 1,3-*anti*-diol diesters (*R*)-**4** in 43–49% yield and 98.5 to >99% *ee* from which the corresponding 1,3-*anti*-diols (*R*)-**5** were obtained in essentially quantitative yields and identical enantiomeric excesses (Table 1). The selectivity factors of this kinetic resolution were calculated as $E > 200$ for all examples investigated.[20] Whereas all compounds shared the methyl group at the C(2)-carbinol center to fit in the enzyme's active site the C(4)-carbinol substituent was quite variable including straight-chain alkyl groups, α-branched alkyl groups, and cyclic alkyl groups. Thus, the enzymatic kinetic resolution of aldol-Tishchenko products obtained in one step constitutes a valuable method to furnish highly enantiomerically enriched and unsymmetrically substituted 1,3-*anti*-diols.

The enantiomeric 1,3-*anti*-diols (*S*)-**5** were obtained in 41–50% yield and 77–92% *ee* upon separation and hydrolysis of the unreactive enantiomers (*S*)-**3**. The small amount of regio-(*R*)-**3** formed again through acyl migration of (*R*)-

Table 2. CALB-catalyzed kinetic resolution of 1,3-*anti*-diols *rac*-**5** with vinyl acetate.



rac-**5** (*R*)-**6** *regio*-(*R*)-**6** (*S*)-**5** (*R*)-**5**

Entry	Substrate	R	Product (*R*)-**6**	Yield (%)[a,b]	*ee* (%)[c]	Product (*S*)-**5**	Yield [%][a]	*ee* (%)[c]
1	*rac*-**5a**	*i*Pr	(*R*)-**6a**	41 (11:1)	96	(*S*)-**5a**	48	>99
2	*rac*-**5c**	*c*Hex	(*R*)-**6c**	42 (30:1)	97.5	(*S*)-**5c**	38	96
3[d]	*rac*-**5f**	Et	(*R*)-**6f**	41 (30:1)	92.5	(*S*)-**5f**	41	99
4	*rac*-**5g**	*n*Hex	(*R*)-**6g**	46 (20:1)	94	(*S*)-**5g**	48	>99

[a] Isolated yield after flash column chromatography over silica gel. [b] Values in brackets refer to ratio of regioisomers (*R*)-**6** and *regio*-(*R*)-**6** as determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC analysis on the bis(*p*-bromobenzoyl) derivative of diols **5** (see text). [d] The selectivity factor *E* was calculated to be 140.

3 was not converted by the enzyme and hence was isolated and hydrolyzed along with (*S*)-**3** thereby deteriorating the enantiomeric excess of (*S*)-**5**.

In an effort to overcome the difficulties associated with the acyl migration of the 1,3-diol monoesters we attempted the enzyme-catalyzed kinetic resolution of some 1,3-*anti*-diols *rac*-**5** which turned out to be a much more rapid process and was completed within just 30–45 min at 40 °C with 4 equiv. of vinyl acetate. The regioisomeric 1,3-*anti*-diol monoesters (*R*)-**6** and *regio*-(*R*)-**6** were obtained in 41–46% yield, 92.5–97.5% *ee*, and 11–30:1 ratio (Table 2). Since CALB is known to readily accept as substrates only secondary alcohols with one substituent being as small as methyl or ethyl it is unlikely that a direct esterification of the "wrong" carbinol had taken place. Apparently, again an acyl migration accounts for the formation of *regio*-(*R*)-**6** which in contrast to the situation discussed above did not deteriorate the enantiomeric excess of the product because both regioisomers shared the same absolute configuration and were subsequently hydrolyzed to the identical 1,3-*anti*-diol (*R*)-**5**. The unreactive diols (*S*)-**5** were recovered in 38–48% yield and 96 to >99% *ee* (Table 2).

Conclusions

A practical method for the synthesis of highly enantiomerically enriched and unsymmetrically substituted 1,3-*anti*-diols has been developed based upon an enzymatic kinetic resolution of 1,3-*anti*-diol monoesters **3**. The substrates **3** were easily available in one step and complete diastereocontrol through the zirconium-catalyzed aldol-Tishchenko reaction of diacetone alcohol and aldehydes. *Candida antarctica* Lipase B effectively catalyzed the acetylation of the *R*-carbinol enantiomer with vinyl acetate and furnished the 1,3-*anti*-diol diesters **4** in yields close to 50% and 98 to >99% *ee* from which the free 1,3-*anti*-diols **5** were obtained through alkaline hydrolysis in identical *ee*. The unreactive (*S*)-1,3-*anti*-diol enantiomers **5** were obtained in slightly lower enantiomeric excess due to a slow acyl migration in the substrates. Alternatively, the free 1,3-*anti*-diols **5** were resolved with CALB and vinyl acetate even more rapidly and furnished both enantiomers in high enantiomeric excesses.

Experimental Section

General: All reactions were carried out in flame-dried glassware with magnetic stirring under nitrogen. The solvents were dried by standard procedures, distilled, and stored under nitrogen. Flash chromatography was carried out with Merck silica gel 60 (40–63 μm). All ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at ambient temperature with Varian Gemini 200, 300, and Mercury 400 spectrometers. Chemical shifts are reported relative to tetramethylsilane as internal standard or residual solvent signals. IR spectra were obtained with a Mattson/Unicam FT-IR spectrometer. Mass spectra were measured with a Bruker APEX II FT-ICR (ESI). Elemental analyses were obtained from the microanalytical laboratory of the Dept. of Chemistry at the University of Leipzig. Optical rotation values were measured with a Schmidt & Haensch Polartronic-D digital polarimeter. The 1,3-*anti*-diol monoesters **3** were prepared according to the literature procedure[4b] and carefully purified by flash chromatography using diethyl ether/pentane (1:3) i.e. minor amounts of the respective regioisomers could not be detected by 400 MHz ^{1}H NMR spectroscopy. The spectroscopic and analytical data of the 1,3-*anti*-diols **5** were reported in a previous publication.[4b] The lipase *Candida antarctica* Lipase B (Novozym 435) was provided by Novozymes and used without further purification. Enantiomeric excesses (*ee*) of 1,3-*anti*-diols **5** were measured on the corresponding bis(*p*-bromobenzoyl) derivatives by HPLC using a Chiralcel OD column with 2-propanol/*n*-hexane as the eluent and for **3a** and **4a** by GC-FID using a FS-Hydrodex β-3P column (25 m × 0.25 mm; 0.25 μm film thickness).

General Procedure for the CALB-Catalyzed Acetylation of 1,3-*anti*-Diol Monoesters 3 (GP 1): Immobilized *Candida antarctica* lipase B (Novozym 435) (260 mg) and vinyl acetate (0.32 mL, 4.00 mmol) were added at 40 °C to a solution of 1,3-*anti*-diol monoester **3** (1.00 mmol) in *n*-hexane (10 mL). After stirring the mixture for 6 h at 40 °C, the enzyme was filtered off and washed with *n*-hexane and diethyl ether. The solvents were removed in vacuo and the residue was purified by flash chromatography over silica gel with mixtures of diethyl ether and pentane. For the purpose of *ee*-determination **3** was hydrolyzed with NaOH/MeOH and the resulting 1,3-*anti*-diols **5** were converted with *p*-bromobenzoyl chloride, NEt_3 (2 equiv. each) and DMAP (5 mol-%) in CH_2Cl_2 into the bis(*p*-bromobenzoyl) derivatives.

1,3-Diol Diester (*R*)-4a: 1,3-*anti*-Diol monoester **3a** (195 mg, 1.00 mmol) was kinetically resolved with CALB and vinyl acetate according to the general procedure to furnish 105 mg of 1,3-diester (*R*)-**4a** (43%) as a colorless oil (98.5% *ee* by HPLC). R_f (E/PE, 1:1) = 0.68. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.88 (d, J = 6.9 Hz, 6 H, 6-H_3, 7-H_3), 1.14, 1.16 (2×d, J = 7.0 Hz, 3 H, 10-H_3, 11-H_3), 1.21 (d, J = 6.3 Hz, 3 H, 1-H_3), 1.62–1.85 (m, 3 H, 3-H_2, 5-H), 2.04 (s, 3 H, 13-H_3), 2.60 (sept, J = 7.0 Hz,1 H, 9-H), 4.78–4.91 (m, 2 H, 2-H, 4-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 17.7, 18.3, 19.1, 19.3, 20.7, 21.4 (C-1, C-6, C-7, C-10, C-11, C-13), 32.0, 34.4 (C-5, C-9), 37.4 (C-3), 67.3 (C-2), 73.6 (C-4), 170.7 (C-12), 178.7 (C-8) ppm. MS (ESI_{pos}, MeOH): m/z = 267 $[M + Na]^+$. IR (film): $\tilde{\nu}$ = 2972, 2936, 2878, 1738, 1470, 1372, 1240, 1192, 1158, 1119 cm^{-1}. $C_{13}H_{23}O_4$ (244.5) calcd. C 64.18, H 9.52; found C 63.97, H 9.83. GC-FID [FS-Hydrodex β-3P, 60 °C (4 min), 10 °C min^{-1}, 100 °C (0 min), 5 °C min^{-1} 115 °C (20 min)]: t_R[(1*S*,3*S*)-**4a**] = 24.7 min; t_R[(1*R*,3*R*)-**4a**] = 25.0 min. HPLC [Chiracel OD, *n*-hexane/2-propanol (97:3), 20 °C, 1.0 mL min^{-1}]: t_R[(1*S*,3*S*)] = 5.6 min; t_R[(1*R*,3*R*)] = 6.9 min. $[\alpha]_D^{25}$ = –33.4 (c = 0.72, $CHCl_3$).

1,3-Diol Diester (*R*)-4b: 1,3-*anti*-Diol monoester **3b** (254 mg, 1.00 mmol) was kinetically resolved with CALB and vinyl acetate according to the general procedure to furnish 112 mg of 1,3-diester (*R*)-**4b** (44%) as a colorless oil (99% *ee* by HPLC). R_f (E/PE, 1:1) = 0.73. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.22 (d, J = 6.2 Hz, 3 H, 1-H_3), 1.47–2.1 (m,19 H, 3-H_2, cyclopentyl-CH_2, cyclopentyl-CH, 5-H_2), 2.03 (s, 3 H, 8-H), 2.65–2.75 (m, 1 H, 6-H), 4.84 (ddq, J = 9.9, 6.2, 3.5 Hz, 1 H, 2-H), 5.00 (ddd, J = 10.2, 7.2, 3.0 Hz, 1 H, 4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 20.7 (C-8), 21.4 (C-1), 25.4, 25.7, 25.8, 25.8, 28.5, 29.0, 30.0, 30.3 (cyclopentyl-CH_2), 40.0 (C-3), 44.3, 44.6 (cyclopentyl-CH), 67.2 (C-2), 72.7 (C-4), 170.7 (C-7), 176.4 (C-5) ppm. MS (ESI_{pos}, MeOH): m/z = 615 $[2M + Na]^+$, 319 $[M + Na]^+$, 297 $[M + H]^+$. IR (film): $\tilde{\nu}$ = 3445, 2956, 2870, 1738, 1451, 1372, 1243, 1183, 1149, 1111, 1031, 973, 804, 607 cm^{-1}. $C_{17}H_{28}O_4$ (296.3) calcd. C 68.90,

H 9.51; found C 68.67, H 9.81. HPLC [Chiracel OD, *n*-hexane/2-propanol (97:3), 20 °C, 1.0 mL min^{-1}]: t_R[(1*S*,3*S*) = 5.6 min; t_R[(1*R*,3*R*)] = 6.5 min. $[\alpha]_D^{25}$ = –28.7 (*c* = 0.56, $CHCl_3$).

1,3-Diol Diester (*R*)-4c: 1,3-*anti*-Diol monoester **3c** (282 mg, 1.00 mmol) was kinetically resolved with CALB and vinyl acetate according to the general procedure to furnish 146 mg of 1,3-diester (*R*)-**4c** (45%) as a colorless oil (98.5% *ee* by HPLC). R_f = 0.72 (E/PE, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.88–2.04 (m, 23 H, 3-H_2, cyclohexyl-CH_2, cyclohexyl-CH), 1.21 (d, *J* = 6.2 Hz, 3 H, 1-H_3), 2.08 (s, 3 H, 8-H_3) 2.34 (tt, *J* = 7.1, 3.6 Hz, 1 H, 6-H), 4.79–4.91 (m, 2 H, 2-H, 4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7, 21.4 (C-1, C-8), 25.6, 25.7, 25.9, 26.2, 26.3, 26.5, 28.1, 29.0, 29.1, 29.4 (cyclohehyl-CH_2), 37.7 (C-3), 42.1, 43.7 (cyclohexyl-CH), 67.2 (C-2), 73.0 (C-4), 170.7 (C-8), 175.7 (C-5) ppm. MS (ESI_{pos}, MeOH): *m*/*z* = 671 [2M + Na]$^+$, 347 [M + Na]$^+$. IR (film): $\tilde{\nu}$ = 3444, 2930, 2854, 1736, 1450, 1372, 1312, 1247, 1169, 1145, 1132, 1028, 972, 958, 894, 844, 788, 762, 607 cm^{-1}. $C_{19}H_{32}O_4$ (324.4) calcd. C 70.39, H 9.93; found C 70.09, H 9.97. HPLC [Chiralcel OD, *n*-hexane/2-propanol (97:3), 20 °C, 1.0 mL min^{-1}]: t_R[(1*S*,3*S*)] = 10.3 min; t_R[(1*R*,3*R*)] = 11.3 min. $[\alpha]_D^{25}$ = –26.2 (*c* = 0.30, $CHCl_3$).

1,3-Diol Diester (*R*)-4d: 1,3-*anti*-Diol monoester **3d** (258 mg, 1.00 mmol) was kinetically resolved with CALB and vinyl acetate according to the general procedure to furnish 105 mg of 1,3-diester (*R*)-**4d** (44%) as a colorless oil (>99% *ee* by HPLC). R_f = 0.75 (E/PE, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.89–0.94 (m, 12 H, 7-H_3, 9-H_3, 13-H_3, 15-H_3), 1.19 (d, *J* = 6.2 Hz, 3 H, 1-H_3), 1.28–1.72 (m, 11 H, 3-H_2, 5-H, 6-H_2, 8-H_2, 12-H_2, 14-H_2), 2.02 (s, 3 H, H-17), 2.23 (tt, *J* = 8.3, 5.7 Hz, 1 H, 11-H), 4.82 (m_c, 1 H, 2-H), 5.11 (m_c, 1 H, 4-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 11.9, 12.0, 12.2 (C-7, C-9, C-13, C-15), 20.7 (C-17), 21.3 (C-1), 22.2, 22.6 (C-6, C-8), 24.8, 25.0 (C-12, C-14), 36.6 (C-3), 45.0 (C-5), 49.3 (C-11), 67.7 (C-2), 71.4 (C-4), 170.6 (C-16), 177.9 (C-10) ppm. MS (ESI_{pos}, MeOH): *m*/*z* = 623 [2M + Na]$^+$, 323 [M + Na]$^+$, 301 [M + H]$^+$. IR (film): $\tilde{\nu}$ = 3444, 2964, 2935, 2877, 1732, 1461, 1372, 1325, 1242, 1179, 1145, 1115, 1078, 1023, 985, 958, 912, 801, 608 cm^{-1}. $C_{17}H_{32}O_4$ (300.3) calcd. C 67.98, H 10.73; found C 68.55, H 10.23. HPLC [Chiralcel OD, *n*-hexane/2-propanol (97:3), 20 °C, 1.0 mL min^{-1}]: t_R[(1*S*,3*S*)] = 5.1 min; t_R[(1*R*,3*R*)] = 5.9 min. $[\alpha]_D^{25}$ = –37.4 (*c* = 0.59, $CHCl_3$).

1,3-Diol Diester (*R*)-4e: 1,3-*anti*-Diol monoester **3e** (326 mg, 1.00 mmol) was kinetically resolved with CALB and vinyl acetate according to the general procedure to furnish 160 mg of 1,3-diester (*R*)-**4e** (49%) as a colorless oil (99% *ee* by HPLC). R_f = 0.70 (E/PE, 1:1). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.21 (d, *J* = 6.2 Hz, 3 H, 1-H_3), 1.72–1.90 (m, 4 H, 3-H_2, 5-H_2), 2.00 (s, 3 H, 11-H_3), 2.50–2.64 (m, 4 H, 6-H_2, 8-H_2), 2.90–2.98 (t, *J* = 7.5 Hz, 2 H, 9-H_2), 4.90 (m_c, 1 H, 2-H), 5.07 (m_c, 1 H, 4-H), 7.10–7.32 (m, 10 H, phenyl-H_5) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 20.6 (C-11), 21.4 (C-1), 31.0 (C-6), 31.6 (C-9), 36.0 (C-8), 36.5 (C-5), 40.6 (C-3), 67.1 (C-2), 70.2 (C-4), 126.1, 126.4 (*p*-phenyl-CH), 128.4, 128.4, 128.5, 128.6 (*m*-, *o*-phenyl-CH), 140.7, 141.5 (phenyl-C), 170.7, 174.3 (C-7) ppm. MS (ESI_{pos}, MeOH): *m*/*z* = 391 [M + Na]$^+$, 369 [M + H]$^+$. IR (film): $\tilde{\nu}$ = 3443, 3062, 3027, 2977, 2932, 2863, 1736, 1603, 1496, 1454, 1373, 1244, 1148, 1121, 1078, 1029, 954, 788, 751, 699 cm^{-1}. $C_{23}H_{28}O_4$ (368.3) calcd. C 74.98, H 7.65; found C 74.63, H 7.72. HPLC [Chiralcel OD, *n*-hexane/2-propanol (99.5:0.5), 20 °C, 1.0 mL min^{-1}]: t_R[(1*S*,3*S*)] = 53.0 min; t_R[(1*R*,3*R*)] = 56.2 min. $[\alpha]_D^{25}$ = –14.1 (*c* = 0.71, $CHCl_3$).

General Procedure for the CALB-Catalyzed Acetylation of 1,3-*anti*-Diols 5 (GP 2): Immobilized *Candida antarctica* lipase B (Novozym 435) (260 mg) and vinyl acetate (0.32 mL, 4.00 mmol) were added at 40 °C to a solution of 1,3-*anti*-diol **5** (1.00 mmol) in *n*-hexane (10 mL). The mixture was stirred at 40 °C for 30–45 min whereupon the product 1,3-*anti*-diol monoesters **6** were isolated and their enantiomeric excesses determined as described above in **GP 1**.

1,3-Diol Monoester (*R*)-6a: Yield: 41% (96% *ee* by HPLC). R_f = 0.42 (E/PE, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.91 (d, *J* = 6.7 Hz, 3 H, 6-H_3), 0.92 (d, *J* = 6.7 Hz, 3 H, 7-H_3, 7-H_3) 1.27 (d, *J* = 6.3 Hz, 3 H, 1-H_3), 1.50–1.67 (m, 3 H, 3-H_2, 5-H), 2.06 (s, 3 H, 9-H), 3.28 (ddd, *J* = 7.8, 5.4, 2.3 Hz, 1 H, 4-H), 5.18 (ddq, *J* = 9.6, 6.3, 2.8 Hz,1 H, 2-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 17.8, 18.8 (C-6, C-7), 20.9 (C-9), 21.3 (C-1), 33.7 (C-5), 41.1 (C-3), 68.7 (C-2), 72.2 (C-4), 171.8 (C-8) ppm. MS (ESI_{pos}, MeOH): *m*/*z* = 197 [M + Na]$^+$. IR (Film): $\tilde{\nu}$ = 3453, 2961, 2876, 1737, 1716, 1669, 1463, 1374, 1248, 1147, 1129, 1045, 1023, 988, 954, 915, 865, 821, 802, 635, 611 cm^{-1}. HRMS for [M + Na]$^+$ calcd. 197.11482; found 197.11497. HPLC [Chiralcel OD, *n*-hexane/2-propanol (97:3), 20 °C, 1.0 mL min^{-1}]: t_R[(1*S*,3*S*)] = 5.6 min; t_R[(1*R*,3*R*)] = 6.9 min. $[\alpha]_D^{25}$ = –22.0 (*c* = 0.55, $CHCl_3$).

1,3-Diol Monoester (*R*)-6c: Yield: 42% (97.5% *ee* by HPLC). R_f = 0.44 (E/PE, 1:1). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 0.90–1.93 (m, 13 H, cyclohexyl-CH_2, cyclohexyl-CH, 3-H_2), 1.21 (d, *J* = 6.3 Hz, 3 H, 1-H_3) 2.04 (s, 3 H, 7-H_3), 2.57 (d, *J* = 4.0 Hz, 1 H, OH), 3.27 (m_c, 1 H, 4-H), 5.16 (ddq, *J* = 9.6, 6.3, 3.4 Hz,1 H, 2-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 21.0 (C-7), 21.4 (C-1), 26.3, 26.4, 26.7, 28.3, 29.5 (cyclohexyl-CH_2), 41.3 (C-3), 43.7 (cyclohexyl-CH), 68.7 (C-2), 71.6 (C-4) 171.8 (C-6) ppm. MS (ESI_{pos}, MeOH): *m*/*z* = 441 [2M + Na]$^+$, 419 [2M + M]$^+$, 237 [M + Na]$^+$. IR (film): $\tilde{\nu}$ = 3439, 2926, 2853, 1736, 1449, 1374, 1248, 1181, 1123, 1065, 1042, 956, 892, 788 cm^{-1}. HRMS for [M + Na]$^+$ calcd. 237.14612; found 237.14635. HPLC [Chiralcel OD, *n*-hexane/2-propanol (97:3), 20 °C, 1.0 mL min^{-1}]: t_R[(1*S*,3*S*)] = 10.3 min; t_R[(1*R*,3*R*)] = 11.3 min. $[\alpha]_D^{25}$ = –10.0 (*c* = 0.60, $CHCl_3$).

1,3-Diol Monoester (*R*)-6f: Yield: 41% (92.5% *ee* by HPLC). R_f = 0.45 (E/PE, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.4 Hz 3 H, 7-H_3), 1.24 (d, *J* = 6.3 Hz, 3 H, 1-H_3), 1.39–1.68 (m, 4 H, 3-H_2, 5-H_2), 2.05 (s, 3 H, 8-H_3), 2.73 (br. s, 1 H, OH), 3.37–3.47 (m, 1 H, 4-H), 5.16 (ddq, *J* = 9.6, 6.3, 3.1 Hz, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.7 (C-7), 20.9 (C-8), 21.4 (C-1), 30.1 (C-5), 44.1 (C-3), 68.5, 68.9 (C-2, C-4), 171.9 (C-7) ppm. MS (ESI_{pos}, MeOH): *m*/*z* = 183 [M + Na]$^+$, 161 [M + H]$^+$. IR (Film): $\tilde{\nu}$ = 3435, 2970, 2879, 1737, 1716, 1461, 1374, 1247, 1150, 1118, 1034, 965, 891, 807, 611, 451 cm^{-1}. HPLC [Chiralcel OD, *n*-hexane/2-propanol (99:1), 20 °C, 1.0 mL min^{-1}]: t_R[(1*S*,3*S*)] = 9.2 min; t_R[(1*R*,3*R*)] = 12.6 min. $[\alpha]_D^{25}$ = –28.6 (*c* = 0.28, $CHCl_3$).

1,3-Diol Monoester (*R*)-6g: Yield: 46% (94% *ee* by HPLC). R_f = 0.45 (E/PE, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.86–0.90 (m, 3 H, 10-H_3), 1.20–1.69 (m, 10 H, 3-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2), 1.23 (d, *J* = 6.3 Hz, 3 H, 1-H_3), 2.07 (s, 3 H, 12-H_3), 3.46–3.54 (m, 1 H, 4-H), 4.18 (ddq, *J* = 9.6, 6.3, 3.1 Hz, 1 H, 2-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 14.2 (C-10), 20.9 (C-12), 21.4 (C-1), 22.7 (C-9), 25.8 (C-6), 29.4 (C-7), 31.9 (C-8), 37.4 (C-5), 44.5 (C-3), 67.6 (C-2), 68.5 (C-4), 171.9 (C-11) ppm. MS (ESI_{pos}, MeOH): *m*/*z* = 239 [M + Na]$^+$. IR (film): $\tilde{\nu}$ = 3444, 2930, 2857, 1738, 1716, 1459, 1374, 1246, 1147, 1043, 954, 809, 611 cm^{-1}. HRMS for [M + Na]$^+$ calcd. 239.16177; found 239.16199. HPLC [Chiralcel OD, *n*-hexane/2-propanol (97:3), 20 °C, 1.0 mL min^{-1}]: t_R[(1*S*,3*S*)] = 5.2 min; t_R[(1*R*,3*R*)] = 5.8 min. $[\alpha]_D^{25}$ = –11.6 (*c* = 0.34, $CHCl_3$).

Acknowledgments

Support of this work through the Deutsche Forschungsgemeinschaft is gratefully acknowledged. We would like to thank Novo-

zymes for the generous donation of Novozym 435 and Prof. J.-E. Bäckvall (University of Stockholm) for valuable suggestions.

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Received: February 5, 2007
Published Online: April 23, 2007

