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Lipase-Catalyzed Transesterification of meso-Cyclopentane Diols[1]

Fritz Theil*[a], Hans Schick[a], Gabriele Winter[b], and Günter Reck[b]

[a]Central Institute of Organic Chemistry, [b]Analytical Center of the Central Institute of Physical Chemistry, Rudower Chaussee 5, O-1199 Berlin-Adlershof, Federal Republic of Germany

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Abstract The lipase-catalyzed transesterification of the *meso*-cyclopentane diols **1a** - **6a** with vinyl acetate in tetrahydrofuran/triethylamine in the presence of lipases of different origin has been investigated Depending on the structure of the substrate and the origin of the lipase chiral cyclopentane derivatives with high enantiomeric excess could be obtained in good to excellent chemical yields

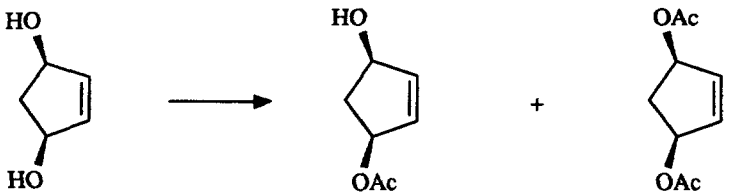
INTRODUCTION

Enzyme-catalyzed transformations are suitable ways to obtain homochiral building blocks[2-4] An attractive way for organic chemists represent the lipase-catalyzed esterifications and transesterifications in organic solvents[5,6] The success of an enantioselective transformation of a given substrate depends on the availability of a suitable lipase that accepts the substrate and the selection of the reaction conditions (enzyme and solvent engineering)[6]

In continuation of our work on the enantioselective transformation of the diol **1a** with Pancreatin[7,8] or with the lipase from *Mucor sp* [9] which allows to prepare enantiomerically pure monoacetate **1b** (Scheme 1) we treated the *meso*-diol **1a** and the derived diols **2a** - **6a** (Scheme 2) with vinyl acetate in tetrahydrofuran in the presence of lipases of different origin

The aim of this investigation was to prepare optically active building blocks and to collect some information on the effect of structural changes in the substrate on enzyme enantioselectivity as well as to compare the different lipases on reactivity and enantioselectivity in the reaction with a given substrate under standard conditions

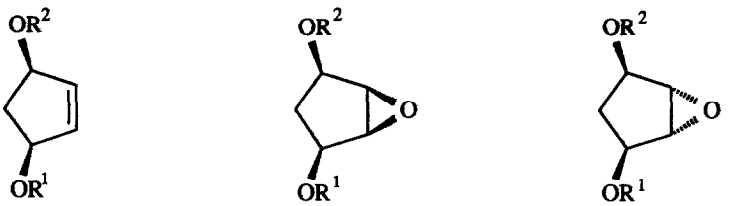
Enantiomerically pure **1b** or its enantiomer are starting materials for the synthesis of prostaglandins[10-18] and other cyclopentanoid natural products[19,20] The diols **2a** and **3a** are starting materials for cyclitols[21-23] and prostaglandins[24,25] The chiral monoacetate **6b** also serves as a starting material for prostaglandin synthesis[26]



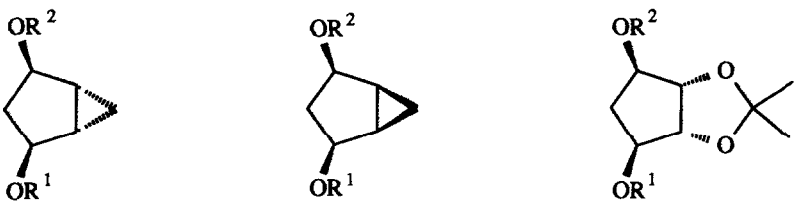
1a **1b** **1c**

Scheme 1.

1a - 6a ⟶ **1b - 6b** + **1c - 6c**



1a-c **2a-c** **3a-c**



4a-c **5a-c** **6a-c**

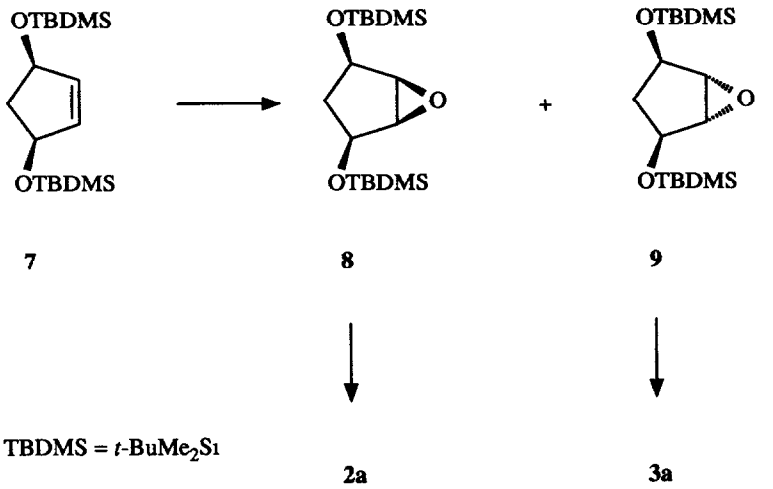
a $R^1 = R^2 = H$, **b** $R^1 = Ac$, $R^2 = H$, **c** $R^1 = R^2 = Ac$

Scheme 2.

PREPARATION OF THE STARTING MATERIALS

The diols **1a**[27], **2a**[28], and **6a**[26] were prepared according to literature procedures For the synthesis of **2a** *m*-chloroperbenzoic acid was used instead of perbenzoic acid[28] In contrast to the epoxidation of **1a** which exclusively affords the *syn*-epoxydiol **2a** the reaction of the corresponding bis-*tert*-butyldimethylsilyl derivative **7** with *m*-chloroperbenzoic acid yielded a mixture of the epoxides **8** and **9** in a ratio of 3 7

Desilylation of **9** afforded the *anti*-epoxydiol **3a** and desilylation of **8** yielded the known compound **2a**, respectively (Scheme 3)



Scheme 3.

Attempts to prepare **5a** by Simmons-Smith-reaction[29] failed totally Therefore we used the palladium(II)-catalyzed cyclopropanation[30] of **1a** with diazomethane (Scheme 4) expecting to obtain **5a** in analogy to the Simmons-Smith reaction, although the stereochemical course of the transition metal-catalyzed cyclopropanation of cyclic allylic alcohols has not been investigated so far[31]

In contrast to our expectation, reaction of **1a** and **1c** with diazomethane in the presence of a catalytic amount of bis(benzonitrile)palladium(II) chloride afforded exclusively the *anti*-cyclopropyl derivatives **4a** and **4c**, respectively The *syn*-derivatives **5a** and **5c** could not be isolated from the reaction mixture

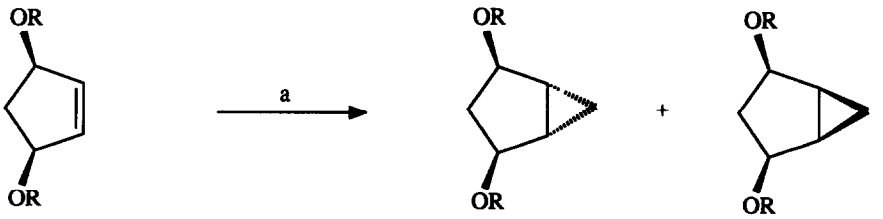
Diacetate **4c** prepared from **1c** corresponds in every respect with **4c** prepared by acetylation (Ac_2O, pyridine) of **4a**

The synthesis of **5a** could be realized by cyclopropanation of the bis-*t*-butyldimethylsilyl derivative **7** under the above described conditions yielding a mixture of **4d** and **5d** in a ratio of 6 4 Desilylation of this mixture afforded **4a** and **5a** (Scheme 4)

The configuration of **4a** has been assigned on the observation of a vicinal coupling constant of 3 0 Hz between C_1-H and C_2-H The coupling constant between C_1-H and C_2-H in **5a** was found to be 7 5 Hz indicating *syn*-configuration This assignment has been confirmed unambiguously by X-ray structure analysis (Fig 1) of **4c**[32]

RESULTS AND DISCUSSION

Lipase-catalyzed transesterifications of the substrates **1a** - **6a** with vinyl acetate were performed in tetrahydrofuran/triethylamine as standard conditions which we have already used advantageously in the



1a, c, 7 **4a, c, d** **5a, c, d**

4d b **4a**

5d b **5a**

a R = H, **c** R = Ac, **d** R = *t*-BuMe$_2$Si

Scheme 4. Reaction conditions a. CH_2N_2, $PdCl_2(C_6H_5CN)_2$, THF, CH_2Cl_2, 0°C, b HOAc, THF, H_2O

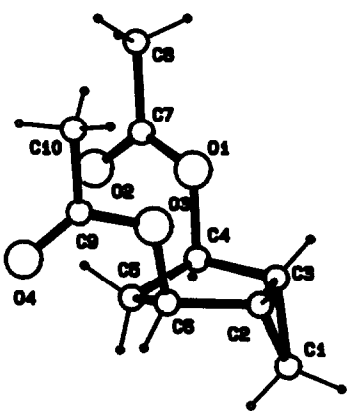


Fig. 1. X-ray structure of **4c**

preparation of **1b**[7-9] and for the selective functionalization of other substrates [33,34].

The lipase-catalyzed transformations were usually stopped when the starting diol was consumed For the different substrates the same amount of one kind of lipase was used. So it was possible to compare the reactivity of the different substrates towards the different kinds of lipase. Concerning the reactivity the diols

1a, **2a**, **4a**, and **5a** are suitable substrates for most of the lipases which were tested These diols could be transformed into mixtures of the monoacetates/diacetates **1b/1c**, **2b/2c**, **4b/4c**, and **ent-5b/5c** in an appropriate time (Tables 1, 2, 4, 5) Diol **6a** was no substrate under the reaction conditions for all lipases tested.

With respect to chemical yield and to enantiomeric purity of the chiral monoacetates **1b**, **2b**, **3b**, **4b**, and **ent-5b** there is no general superior lipase for all the substrates tested In most cases, exclusive of **2a**, Lipozyme was unable to catalyze the transformation of the diols **1a**, **3a**, **4a**, **5a**, and **6a** under selected reaction conditions

For the diol **1a** Pancreatin[8] and the lipase from *Mucor sp* [9] were the enzymes of choice (Table 1)

The most selective enzymes for the *syn*-epoxydiol **2a** were found to be the lipases from *Yarrowia sp 181 H* and from *Candida sp 382* (Table 2)

Under the same reaction conditions the *anti*-epoxydiol **3a** shows a significantly lower reactivity than the other diols Only with the lipases from *Mucor sp* and *Candida sp 382* it could be transformed into **3b** in a very long reaction time besides unreacted **3a** (Table 3)

The *anti*-cyclopropane diol **4a** was transformed with a very high selectivity into the monoacetate **4b** using lipases tested (exclusive of Lipozyme) High chemical yield and excellent enantioselectivity was observed in general (Table 4)

Table 1 Lipase-Catalyzed Transesterification of the Diol **1a**

lipase	reaction time (h)	yield of **1b** (%)	$[\alpha]_D^{20}$ c 1, $CHCl_3$	yield of **1c** (%)	e e (%)	configu-ration
Pancreatin	2 5	65	-66 0°	32	>99	S-OAc
Mucor sp	4	85	-62 0°	10	94	S-OAc
Amano PS	3 75	97	-33 0°	0	50	S-OAc
	0 5[a]	68	-54 1°	35	86	S-OAc
Lipozyme	8	<5	-	-	-	-
Yarrowia	24	63	-54 2°	30	84	S-OAc
Sp 382	2	53	-65 0°	40	>99	S-OAc

[a] fivefold amount of lipase was used

By contrast with the diols **1a** - **4a**, the *syn*-cyclopropane diol **5a** was acetylated preferentially at its R-hydroxy group affording **ent-5b** Exclusive of Pancreatin, the other lipases showed low enantioselectivity (Table 5)

Table 2 Lipase-Catalyzed Transesterification of the Diol **2a**

lipase	reaction time (h)	yield of **2b** (%)	$[\alpha]_D^{20}$ c 1, $CHCl_3$	yield of **2c** (%)	e e (%)	configu-ration
Pancreatin	0 5	38	-30 0°	57	>99	S-OAc
Mucor sp	24	48	-23 0°	40	74	S-OAc
Amano PS	2	75	-29 2°	25	94	S-OAc
Lipozyme	72	55	-22 3°	13[a]	76	S-OAc
Yarrowia	1 25	71	-29 0°	20	>99	S-OAc
Sp. 382	24	82	-31 2°	9	>99	S-OAc

[a] 32% of diol **2a** were recovered

Table 3 Lipase-Catalyzed Transesterification of the Diol **3a**

lipase	reaction time (h)	yield of **3b** (%)	$[\alpha]_D^{20}$ c 1, $CHCl_3$	yield of **3c** (%)	e e (%)	configu-ration
Pancreatin	8	<5	-	-	-	-
Mucor sp	144	60	-15 0°	0[a]	82	S-OAc
Amano PS	8	<5	-	-	-	-
Lipozyme	8	<5	-	-	-	-
Yarrowia	8	<5	-	-	-	-
Sp 382	168	56	-11 0°	0[a]	52	S-OAc

[a] 35% of diol **3a** were recovered

For the determination of the absolute configuration of the monoacetate **2b** enantiomerically pure **1b** was epoxidized using *m*-chloroperbenzoic acid affording pure **2b** with a negative optical rotation indicating that the lipases selectively catalyze the acetylation of the *syn*-epoxydiol **2a** at its S-hydroxy group The absolute configuration of **3b** was determined as follows treatment of enantiomerically pure **1b** with *tert*-butyldimethylsilyl chloride and epoxidation of this unsymmetrically protected intermediate afforded a mixture of the epoxides **10** and **11** After separation of **10** and **11** the desilylation of the *anti*-epoxy derivative **11** yielded **3b** with a negative optical rotation proving that the lipases preferentially catalyze the acetylation of the *anti*-epoxydiol **3a** at its S-hydroxy group Desilylation of **10** afforded **2b** (Scheme 5)

Table 4 Lipase-Catalyzed Transesterification of the Diol **4a**

lipase	reaction time (h)	yield of **4b** (%)	$[\alpha]_D^{20}$ c 1, $CHCl_3$	yield of **4c** (%)	e e (%)	configu-ration
Pancreatin	32	94	-13 9°	4	>99	S-OAc
Mucor sp	163[a]	85	-11 0°	10	90	S-OAc
Amano PS	24[b]	87	-16 0°	12	>99	S-OAc
Lipozyme	8	<5	-	-	-	-
Sp 382	24	89	-13 2°	7	92	S-OAc

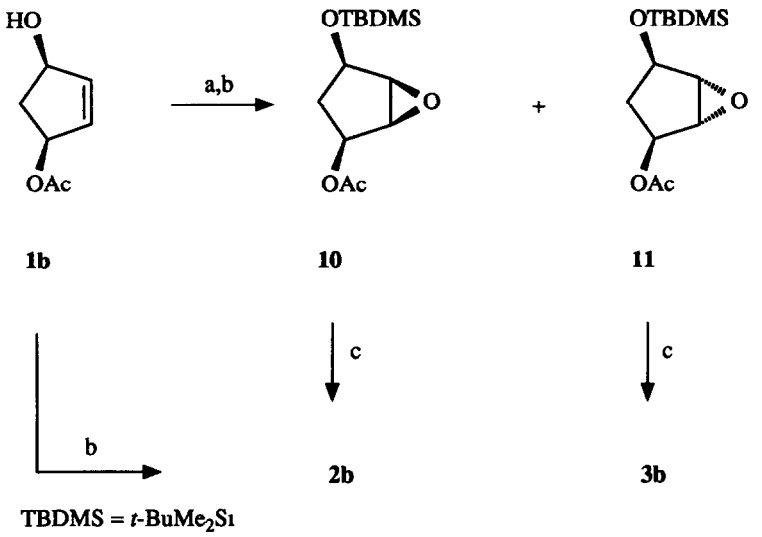
[a] after 96 h 500 mg of lipase were added, [b] twofold amount of lipase was used

Table 5 Lipase-Catalyzed Transesterification of the Diol **5a**

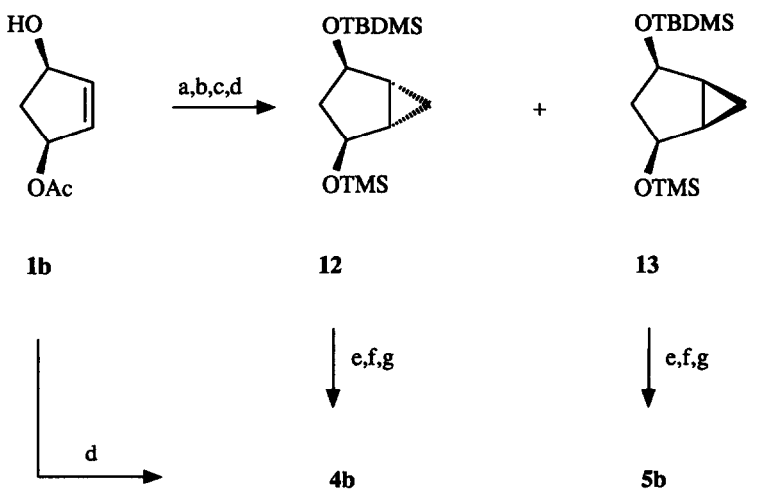
lipase	reaction time (h)	yield of **ent-5b** (%)	$[\alpha]_D^{20}$ c 1, $CHCl_3$	yield of **5c** (%)	e e (%)	configu-ration
Pancreatin	12	75	+41 3°	20	86	R-OAc
Mucor sp	139[a]	69	+1 0°	24	4	R-OAc
Amano PS	16	63	+2 0°	32	10	R-OAc
Lipozyme	8	<5	-	-	-	-
Sp 382	24	55	+20 2°	40	44	R-OAc

[a] after 96 h 500 mg of lipase were added

Cyclopropanation[30] of enantiomerically pure **1b** yielded the *anti*-cyclopropyl derivative **4b** with a negative optical rotation proving selective S-acetylation of **4a** under lipase catalysis In a more complicated reaction sequence enantiomerically pure **1b** was converted into a mixture of the cyclopropyl derivatives **12** and **13** which could be separated By further functional group manipulation **13** was converted into **5b** with a negative optical rotation By this way it was clearly demonstrated that the monoacetyl derivative **ent-5b** with its positive optical rotation was formed by a preferred acetylation of **5a** at its R-hydroxy group **12** was transformed into **4b** (Scheme 6)



Scheme 5. Reaction conditions a TBDMS-Cl, imidazole, DMF, 20°C, b 3-Cl-$C_6H_4CO_3H$, $NaHCO_3$, CH_2Cl_2, 20°C, c $(n\text{-}C_4H_9)_4NF$, THF, 20°C



Scheme 6. Reaction conditions a TBDMS-Cl, imidazole, DMF, 20°C, b Wofatit SBW (OH^-), MeOH, 20°C, c TMS-Cl, pyridine, 20°C, d CH_2N_2, $PdCl_2(C_6H_5CN)_2$, THF, CH_2Cl_2, 0°C, e Wofatit KPS (H^+), MeOH, 20°C, f Ac_2O, pyridine, 20°C, g $(n\text{-}C_4H_9)_4NF$, THF, 20°C

EXPERIMENTAL

Tetrahydrofuran was dried over sodium wire Triethylamine was distilled from and stored over potassium hydroxide. T l c. was carried out on plates precoated with silica gel 60 (Merck) For visualization the plates were treated with 3 5 % of molybdato phosphoric acid in ethanol and heated to 150°C Flash chromatography was performed on silica gel 60 (0 063 - 0 040 mm) ^{1}H n.m r spectra were recorded at 80 MHz on a Tesla BS 587 4 instrument if not indicated otherwise or at 300 MHz on a Gemini 300 instrument, and ^{13}C n m r. spectra at 75 MHz on a Gemini 300 instrument (Varian) with hexamethyldisiloxane as internal standard ^{19}F n m r spectra were measured at 282 MHz on a Gemini 300 instrument in $CDCl_3$ with $CFCl_3$ as internal standard All chemical shifts are reported in δ values. Electron impact mass spectra were obtained on the GC/MS-Datensystem HP 5985 B I.r spectra were recorded on a Specord 75 IR spectrometer (Carl Zeiss Jena) Optical rotations were measured with the photoelectric polarimeter Polamat A (Carl Zeiss Jena) at 546 and 578 nm and extrapolated to 589 nm

The following lipases were used

Pancreatin 6xNF· Fa. Belger, Kleinmachnow, FRG

Lipase from *Mucor sp* : Institute of Biotechnology, Leipzig, FRG

Amano PS Amano Pharmaceutical Co Ltd , Nagoya, Japan

Lipozyme M20 Novo Industri A/S, Copenhagen , Denmark

Lipase from *Yarrowia sp H 181* Institute of Biotechnology, Leipzig , FRG

Lipase from *Candida sp 382* Novo Industri A/S, Copenhagen , Denmark

The enantiomeric excess (e e) of the monoacetates **1b** - **4b** and **ent-5b** was determined by ^{19}F n m r spectroscopy of the corresponding (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid esters (Mosher esters) The Mosher esters were prepared according to ref [8] The racemic monoacetates **rac-1b** - **rac-5b** were prepared in the usual manner by treating of the diols **1a** - **5a** with one equivalent of acetic anhydride in pyridine

Preparation of the Starting Materials

cis-1,4-bis(t-Butyldimethylsilyl)cyclopent-2-ene-1,4-diol (7)

Imidazole (12 5 g, 187 5 mmol) and *tert*-butyldimethylsilyl chloride (20 8 g, 125 mmol) were added to a solution of diol **1a** (5.0 g, 50 mmol) in pyridine (100 ml) After stirring at room temperature for 1 5 h the mixture was diluted with diethyl ether (200 ml) This mixture was washed with a 1*N* solution of sodium bicarbonate (50 ml) and with water (2 x 50 ml) The organic phase was dried ($MgSO_4$) The solvents were distilled off under reduced pressure Distillation of the residue afforded pure **7** (14 75 g, 90 %)

B p 90 - 95°C (0 67 Pa).

(1RS,2RS,4SR,5SR)-6-Oxa-2,4-bis(*t*-butyldimethylsilyl)-bicyclo[3 1 0]hexane-2,4-diol (**8**) and (1SR,2RS,4SR,5RS)-6-oxa-2,4-bis(*t*-butyldimethylsilyl)-bicyclo[3 1 0]hexane-2,4-diol (**9**)

m-Chloroperbenzoic acid (23 05 g, 133 mmol) and sodium bicarbonate (11 2 g, 133 mmol) were added to a solution of **7** (12 5 g, 38 mmol) in dichloromethane (140 ml) The mixture was stirred at room temperature for 30 h The suspension was filtered through silica gel The filtrate was washed with a 1*N* solution of sodium bicarbonate (50 ml) and water (2 x 50 ml) The organic phase was dried ($MgSO_4$) and the solvents were distilled off under reduced pressure The residue was separated by flash chromatography on silica gel (400 g) with hexane - diethyl ether (40 1 → 30 2) and yielded **8** (3 25 g, 25 %) and **9** (7 74 g, 60%)

8 M p 46 - 48°C, ^{1}H n m r ($CDCl_3$) 0 00 and 0 02 (12H, 2s, $SiMe_3$), 0 84 (18H, s, *t*-Bu), 1 06 - 2 06 (2H, m, CH_2), 3 28 (2H, s, CH-O), 3 99 (2H, dd, J 12 and 8 Hz, CH-OSi), ^{13}C n m r ($CDCl_3$) -4 66, 18 11, 25 84, 34 57, 57 28, 70 58, m s 287 (M - C_4H_9, 45), 147 (35), 73 (100), calcd C 59 24, H 10 53, found C 58 91, H 10 73

9 B p 170 - 190°C (bath temperature/0 67 Pa), ^{1}H n m r ($CDCl_3$) 0 00 and 0 02 (12 H, 2s, $SiMe_3$), 0 83 (18H, s, *t*-Bu), 1 04 - 2 00 (2H, m, CH_2), 3 37 (2H, s, CH-O), 4 24 (2H, d, J 5 5 Hz, CH-OSi), ^{13}C n m r ($CDCl_3$) -4 83, 17 92, 25 68, 42 26, 59 61, 71 44, m s 287 (M - C_4H_9, 3), 147 (100), 73 (55), calcd C 59 24, H. 10 53, found C 59.05, H 10 48

(1RS,2RS,4SR,5SR)-6-Oxabicyclo[3 1 0]hexane-2,4-diol (**2a**)

Acetic acid (15 ml) and water (5 ml) were added to a solution of **8** (3 0 g, 9 mmol) in tetrahydrofuran (15 ml) After standing at 50°C for 48 h the solvents were removed by co-distillation with toluene under reduced pressure affording **2a** (1 1 g, 95 %)

M p 78 - 82°C (ethyl acetate)(ref [28] m p 83 - 83 5°C), ^{1}H n m r (DMSO-d_6) 1 02 (1H, dt, J 12 and 8 Hz, CH_2), 1 78 (1H, dt, J 12 and 8 Hz, CH_2), 3 24 (2H, s, CH-O), 3 80 (2H, m, CH-OH), 4.80 (2H, d, J 5 Hz,

OH, exchangeable), ^{13}C n m r (D_2O) 34 52, 60 67, 71 45, m s 116 (M, 1), 73 (67), 60 (100), i r (KBr) 3600 - 3000, 1330, 1120, 1095, 1070, 1035, 895, 850, 610

(1SR,2RS,4SR,5RS)-6-Oxabicyclo[3.1.0]hexane-2,4-diol (**3a**)

Acetic acid (30 ml) and water (10 ml) were added to a solution of **9** (7 5 g, 22 8 mmol) in tetrahydrofuran (30 ml) After standing at 50°C for 48 h the solvents were removed by co-distillation with toluene under reduced pressure The residue was purified by flash chromatography on silica gel (50 g) with ethyl acetate yielding **3a** (2.2 g, 84 %) as a waxy hygroscopic compound

M.p 37 - 39°C (capillary), ^1H n m.r (DMSO-d_6). 1 23 - 1 95 (2H, m, CH_2), 3.36 (2H, s, CH-O), 4 00, 2H, d after H/D-exchange, J 5.5 Hz, CH-OH), 4.61 (2H, br d, OH, exchangeable), ^{13}C n m r. (D_2O) 41 41, 61 53, 72 45, m s 116 (M, 15), 98 (7), 97 (13), 73 (80), 69 (64), 60 (70), 43 (100), i r (KBr) 3600 - 3100, 1080, 845; calcd C 51 72, H 6 94; found C: 50 51, H 6 98

(1RS,2RS,4SR,5SR)-Bicyclo[3.1 0]hexane-2,4-diol (**4a**)

A solution of **1a** (2 5 g, 25 mmol) in tetrahydrofuran/dichloromethane (60 ml, 1 1) was treated at 0°C with bis(benzonitrile)palladium(II) chloride (48 mg, 0 125 mmol) and then under t l c. control with a solution of diazomethane (CAUTION) in diethyl ether The excess of diazomethane was destroyed by adding a few drops of glacial acetic acid The reaction mixture was filtered through Celite and the solvents were removed under reduced pressure The residue was purified by flash chromatography on silica gel (100 g) with ethyl acetate yielding **4a** (1 1 g, 40%)

Colourless hygroscopic oil: b p 140 - 150°C (bath temp./1 5 Pa), ^1H n m.r ($CDCl_3$, 300 MHz) -0 19 - (-0 14) (1H, m, cycloPr), 0.46 (1H, dt, J 15 0 Hz and 8 0 Hz, cycloPr), 1 46 - 1 65 (4H, m, CH and CH_2), 2 82 (2H, br s, OH), 4 17 (2H, d, J 3 5 Hz, CH-OH); ^{13}C n.m r (acetone-d_6) 6 90, 24 63, 40 48, 74 02, m s 96 (M - H_2O, 42), 67 (75), 57 (100), i r (film) 3600 - 3100, 3075, 3040, 3000, 2950, 2900, 1465, 1425, 1350, 1110, 1080, 1000, 845, calcd C 63 13, H 8 83, found C 62 51, H 9 14

(1RS,2RS,4SR,5SR)-Bicyclo[3 1 0]hex-2,4-diyl diacetate (**4c**)

In analogy **4c** was prepared from **1c** (0 5 g, 4 4 mmol) Flash chromatography on silica gel (50 g) with hexane - ethyl acetate (4 . 1) yielded **4c** (0 68 g, 78 %)

M p 72 - 73°C (hexane - diethyl ether); ^1H n.m r ($CDCl_3$, 300 MHz) - 0 07 - (-0 04) (1H, m, cycloPr), 0 61 (1H, dt, J 15.0 and 8 3 Hz, cycloPr), 1 67 (1H, dd, J 3 5 and 8 3 Hz, CH_2), 1 79 (1H, dd, J 3 0 and 3 5 Hz, CH_2), 2 01 (6H, s, OAc), 5 07 (2H, dd, J 3.0 and 2 9 Hz, CHOAc), ^{13}C n m.r ($CDCl_3$) 6 07, 21 37, 22 00, 36 07, 76 05, 170 71), m s.. 198 (M, 8), 157 (30), 139 (100), 96 (65), 79 (75), 67 (55), i r (KBr) 1730, 1720, 1380, 1360, 1250, 1065, 1030, 825, calcd C 60 59, H 7 12, found C 60.07, H 7 27

(1SR,2RS,4SR,5RS)-Bicyclo[3 1 0]hexane-2,4-diol (**5a**)

In ananlogy to the above desribed cyclopropanation procedure **7** (8 25 g, 25 mmol) was treated with diazomethane yielding a mixture of **4d** and **5d** A solution of **4d/5d** in tetrahydrofuran (30 ml) was treated with acetic acid (30 ml) and water (10 ml) After standing at 50°C for 20 h the solvents were removed by co-distillation with toluene under reduced pressure The mixture was separated by flash chromatography on silica gel (300 g) with ethyl acetate - ethanol (9 1) yielding **4a** (1 6 g, 54 %) and **5a** (1 2 g, 38 %)

5a M.p 83 - 85 °C (acetone - hexane) ^1H n m r ($CDCl_3$, 300 MHz) 0 43 (1H, dt, J 7 7 and 5 5 Hz, cycloPr), 0 86 (1H, dt, J 7 5 and 3.8 Hz, cycloPr), 1 00 (1H, dt, J 13 0 and 9 0 Hz, CH_2), 1 53 (2H, s, OH), 1 58 (2H, dd, J 7 5 and 3.8 Hz, CH), 2 18 (1H, dt, J 13 0 and 7.5 Hz, CH_2), 4 34 (2H, ddd, J 8 0, 7 5, and 3 0 Hz, CH-OH), ^{13}C n m r. (acetone -d_6) 2.01, 23.49, 37 09, 70 63, m.s. 113 (M - 1, 0 3), 96 (24), 95 (36), 67 (80), 57 (100), i r (KBr) 3500 - 3000, 1350, 1090, 1060, 1035, 820, calcd C 63 13, H 8 83, found C 63 05, H 8 99

Lipase-Catalyzed Acetylation of the *meso*-Diols 1a - 5a.

General Procedure. Triethylamine (0.07 g, 0 7 mmol), vinyl acetate (0.6 g, 7 mmol), and the corresponding amount of lipase (see below) were added to a solution of the *meso*-diols **1a - 6a** (1 mmol) in tetrahydrofuran (2 5 ml) The reaction mixture was stirred at room temperature and monitored by t l.c control until the corresponding diol was completely consumed if not indicated otherwise in the Tables 1 - 5 The suspension was filtered through Celite and the filter cake was washed with ethyl acetate (3 x 5 ml) The solvents were distilled off under reduced presssure and the residue was separated by flash chromatography with hexane - ethyl acetate followed by Kugelrohr distillation or recrystallization

The following amounts of lipase were used for 1 mmol of substrate if not indicated otherwise (see Tables 1 - 5). Pancreatin 500 mg, *Mucor sp* 500 mg; Amano PS. 50 mg, Lipozyme 50 mg, *Yarrowia sp* 500 mg, *Sp 382* 50 mg

(1R,2R,4S,5S)-(-)-2-Hydroxy-6-oxabicyclo[3 1 0]hex-4-yl acetate (**2b**)
Colourless oil [**rac-2b** m.p. 45 - 47°C (diethyl ether - hexane)], ^{1}H n m.r ($CDCl_3$) 1 30 (1H, dt, J 12 and 8 Hz, CH_2), 2 03 (3H, s, OAc), 2 33 (1H, dt, J 12 and 8 Hz, CH_2), 2 62 (1H, br s, OH, exchangeable), 3 50 (1H, dd, J 3 and 1 5 Hz, CH-O), 3 60 (1H, dd, J 3 and 1 5 Hz, CH-O), 4 12 (1H, dt, J 8 and 1 5 Hz, CH-OH), 4.90 (1H, dt, J 8 and 1 5 Hz, CH-OAc), ^{13}C n m r. ($CDCl_3$) 20 66, 30 94, 55 43, 57.29, 69 68, 71 66, 170 80, m s 159 (M + 1, 1), 141 (5), 97 (35), 69 (100), 60 (65), i r (KBr) 3500 - 3100, 1750, 1740, 1250, calcd C· 53 16, H 6 37, found C 53 17, H 6 42

(1RS,2RS,4SR,5SR)-6-Oxabicyclo[3 1 0]hex-2,4-diyl diacetate (**2c**)
M p 86 - 88°C (diethyl ether - hexane), ^{1}H n m r ($CDCl_3$) 1 24 - 1 80 (1H, m, CH_2), 2 03 (6H, s, OAc), 2 34 (1H, dt, J 12 and 8 Hz, CH_2), 3 60 (2H, s, CH-O), 4 94 (2H, dd, J 12 and 8 Hz, CH-OAc), ^{13}C n m r ($CDCl_3$): 20 82, 27 90, 54 88, 71.42, 170 69, m.s 141 (M - OAc, 75), 115 (8), 98 (100), 81 (75), 69 (85), i r (KBr)· 1735, 1380, 1365, 1260, 1070, 1030, 880; calcd C 54 00, H 6 04, found C 54 13, H: 6 16

(1S,2R,4S,5R)-(-)-2-Hydroxy-6-oxabicyclo[3.1 0]hex-4-yl acetate (**3b**)
Colourless oil, b p 125 - 130°C (bath temp /0 5 Pa); ^{1}H n m r ($CDCl_3$) 1 52 - 2.21 (3H, m, CH_2 and OH), 2 01 (3H, s, OAc), 3 55 (2H, m, CH-O), 4 29 (1H, br d, J 5 5 Hz, CH-OH), 5 20 (1H, br d, J 5 5 Hz, CH-OAc), ^{13}C n m r ($CDCl_3$) 21 08, 37.68, 56 11, 58 33, 70 79, 73 27, 170 24), m s 141 (M - OH, 0 6), 115 (12), 96 (38), 97(43), 70 (100), i r (film) 3650 - 3100, 1750, 1440, 1385, 1250, 1090, 1050, 850; calcd C 53 16, H 6 37, found C 53 05, H 6 62

(1SR,2RS,4SR,5RS)-6-Oxabicyclo[3 1 0]hex-2,4-diyl diacetate (**3c**)
M p 53 - 54°C (diethyl ether - hexane), ^{1}H n m r ($CDCl_3$) 1 60 - 2 29 (2H, m, CH_2), 2 00 (6H, s, OAc), 3 56 (2H, s, CH-O), 5 16 (2H, d, J 5 5 Hz, CH-OAc), ^{13}C n m r ($CDCl_3$) 20 99, 35 43, 56 64, 72 49, 170 22, m s 200 (M, 1 5), 141 (75), 98 (100), 81 (55), 67 (55), i r (KBr) 1750, 1740, 1380, 1240, 850, calcd C 54 00, H 6 04, found C 53 87, H 6 01)

(1R,2R,4S,5S)-(-)-2-Hydroxybicyclo[3 1 0]hex-4-yl acetate (**4b**)
Colourless oil, b p 100 - 110°C (bath temp /0 5 Pa), ^{1}H n m r ($CDCl_3$) -0 20 - 0 00 (1H, m, cycloPr), 0 38 - 0 73 (1H, m, cycloPr), 1 49 - 1 77 (4H, m, CH_2 and CH-C), 1 94 (1H, br s, OH, exchangeable), 1 99 (3H, s, OAc), 4 12 (1H, m, CH-OH), 5 12 (1H, dd, J 2.5 Hz, CH-OAc), ^{13}C n m r ($CDCl_3$) 6 69, 21.30, 21 43, 24 77, 38 12, 73 55, 76 96, 170 43, m s 139 (M - OAc, 8), 96 (90), 79 (40), 67 (100), i r (film): 3650 - 3100, 3060, 3050, 3000, 2950, 2900, 1735, 1385, 1375, 1250, 1075, 1025, 985, calcd. C 61 52, H 7 74, found C 61 41, H 8 11

(1S,2R,4S,5R)-(+)-4-Hydroxybicyclo[3 1 0]hex-2-yl acetate (**ent-5b**)
Colourless oil, b p 120 - 130°C (bath temp./0 5 Pa), ^{1}H n m r ($CDCl_3$) 0 30 - 0 68 (1H, m, cycloPr), 0 77 - 1 90 (5H, m, CH_2, CH-C, OH, and cycloPr), 1 97 (3H, s, OAc), 2 04 - 2 50 (1H, m, CH_2), 4 40 (1H, dt, J 8 and 4 Hz, CH-OH), 5 12 (1H, dt, J 8 and 4 Hz, CH-OAc), ^{13}C n m r ($CDCl_3$) 2 36, 19 93, 21 00, 22 77, 33 03, 70 14, 73 35, 171 05, m s 139 (M - OH, 100), 95 (43), 79 (92), 67 (65), i.r (film) 3650 - 3100, 3085, 3050, 3020, 2980, 2965, 2900, 1750, 1480, 1390, 1365, 1250, 1085, 1060, 1000; calcd C 61 52, H 7 74, found C 61 64, H 8 19

(1SR,2RS,4SR,5RS)-Bicyclo[3 1 0]hex-2,4-diyl diacetate (**5c**)
Colourless liquid, b p 120 - 125°C (bath temp /15 Pa), ^{1}H n m r ($CDCl_3$) 0 40 - 1 85 (5H, m, CH_2, CH-C, and cycloPr), 1 98 (6H, s, OAc), 2 14 - 2 58 (1H, m, CH_2), 5 16 (2H, br dt, J 8 and 4 Hz, CH-OAc), ^{13}C n m r ($CDCl_3$) 3 36, 20 04, 20 88, 30 06, 72 87, 170 70, m s 139 (M - OAc, 85), 97 (23), 79 (100), 67 (18), i r (film) 3085, 3050, 3010, 2985, 2950, 1750, 1380, 1365, 1250, 1035, 1000, calcd C 60 59, H 7 12, found C 60 57, H 7 24

Determination of the Absolute Configuration of the Monoacetates 2b, 3b, 4b, and ent-5b

2b from **1b**
m-Chloroperbenzoic acid (0 516 g, 3 mmol) and sodium bicarbonate (0 253 g, 3 mmol) were added to a solution of enantiomerically pure **1b** (0 142 g, 1 mmol) in dichloromethane (5 ml) After stirring at room temperature for 50 min the suspension was filtered The filtrate was concentrated under reduced pressure Flash chromatography of the residue on silica gel (20 g) with diethyl ether - hexane (4 1) yielded **2b** (0 131 g, 83 %) as a colourless oil $[\alpha]_D^{20}$ -30 0° (c 1, $CHCl_3$) The ^{1}H n m r spectrum was identical with the spectrum of **2b** from the lipase-catalyzed transesterifications

3b from 11

(1R,2R,4S,5S)-(-)-2-*t*-Butyldimethylsilyloxy-6-oxabicyclo[3.1.0]hex-4-yl acetate (10) and (1S,2R,4S,5R)-(+)-2-*t*-butyldimethylsilyloxy-6-oxabicyclo[3.1.0]hex-4-yl acetate (11)

m-Chloroperbenzoic acid (2.0 g, 11.6 mmol) and sodium bicarbonate (1.0 g, 11.9 mmol) were added to a solution of (1S,4R)-4-*t*-butyldimethylsilyloxycyclopent-2-enyl acetate (0.975 g, 3.5 mmol) {Prepared from **1b** in analogy to the corresponding *trans*-isomer[10]: B.p. 105 - 110°C (bath.temp./20 Pa); $[\alpha]_D^{20}$ +1° (c 10, $CHCl_3$);^{1}H n.m.r. ($CDCl_3$) 0.04 (6H, s, $SiMe_3$), 0.85 (9H, s, *t*-Bu,), 1.56 (1H, dt, J 12 and 5 Hz, CH_2), 1.99 (3H, s, OAc), 2.75 (1H, dt, J 12 and 8 Hz, CH_2), 4.65 (1H, m, CH-OSi), 5.40 (1H, m, CH-OAc), 5.85 (2H, m, CH=CH), ^{13}C n.m.r. ($CDCl_3$) 4.73, 4.78, 17.99, 20.99, 25.71, 41.02, 74.71, 76.77, 131.00, 138.73, 170.65, calcd. C 60.89, H 9.43, found C 60.37, H 9.12} in dichloromethane (10 ml). After stirring at room temperature for 48 h *m*-chloroperbenzoic acid (1.0 g, 5.8 mmol) and sodium bicarbonate (0.5 g, 5.95 mmol) were added. After a further 72 h the reaction mixture was diluted with hexane (50 ml) and filtered. The filtrate was washed with a 1*N* solution of sodium bicarbonate (10 ml) and water (2 x 20 ml). After drying (Na_2SO_4) the organic phase was concentrated under reduced pressure. Flash chromatography of the residue on silica gel (100 g) with hexane - diethyl ether (10 : 1 → 7 : 1) yielded **11** (0.211 g, 23 %) as the less polar product and **10** (0.197 g, 22 %) as the more polar product besides unchanged starting material (0.232 g, 28 %).

10 ^{1}H n.m.r. ($CDCl_3$): 0.01 and 0.04 (6H, 2s, $SiMe_3$), 0.84 (9H, s, *t*-Bu), 1.14 - 1.62 (1H, m, CH_2), 2.01 (3H, s, OAc), 2.06 - 2.34 (1H, m, CH_2), 3.35 (1H, dd, J 3 and 1.5 Hz, CH-O), 3.48 (1H, dd, J 3 and 1.5 Hz, CH-O), 4.11 (1H, dt, J 8 and 1.5 Hz, CH-OSi), 4.84 (1H, dt, J 8 and 1.5 Hz, CH-OAc), ^{13}C n.m.r. ($CDCl_3$) 4.83, 4.89, 17.98, 20.79, 25.64, 31.05, 54.41, 57.40, 70.23, 57.40, 170.82, $[\alpha]_D^{20}$ -4.5° (c 1, $CHCl_3$).

11 ^{1}H n.m.r. ($CDCl_3$) 0.04 and 0.06 (6H, 2s, $SiMe_3$), 0.86 (9H, s, *t*-Bu), 1.50 - 2.16 (2H, m, CH_2), 2.00 (3H, s, OAc), 3.44 (1H, d, J 2.5 Hz, CH-O), 3.58 (1H, d, J 2.5 Hz, CH-O), 4.28 (1H, d, J 5 Hz, CH-OSi), 5.14 (1H, d, J 5 Hz, CH-OAc), ^{13}C n.m.r. ($CDCl_3$) 4.82, 4.89, 17.87, 20.91, 25.58, 38.52, 56.61, 59.05, 70.82, 73.01, 170.46, $[\alpha]_D^{20}$ +18.6° (c 1, $CHCl_3$).

3b

Tetrabutylammonium fluoride x 3 H_2O (0.540g, 1.7 mmol) was added to a solution of **11** (0.211, 0.82 mmol) in tetrahydrofuran (5 ml) and stirred at room temperature for 30 min. After evaporation of the solvent under reduced pressure the residue was purified by flash chromatography on silica gel (20 g) with ethyl acetate - hexane (2 : 1) affording **3b** (0.080g, 62%) - $[\alpha]_D^{20}$ -21.8° (c 1, $CHCl_3$). The ^{1}H n.m.r. spectrum was identical with the spectrum of **3b** from the lipase-catalyzed transesterifications.

2b

In analogy **10** yielded **2b** - $[\alpha]_D^{20}$ -30.5° (c 1, $CHCl_3$).

4b and 5b from 12 and 13,respectively

A solution of (1S,4R)-4-*t*-butyldimethylsilyloxy-cyclopent-2-enyl acetate (1.85 g, 7.2 mmol) in methanol (25 ml) was treated with Wofatit SBW (OH^-, 2 g) and stirred at room temperature for 5.5 h. After filtration the solvent was removed under reduced pressure. A solution of this t.l.c.-homogeneous product (1.55 g, 7.2 mmol) in pyridine (5 ml) was treated with trimethylsilyl chloride (1.08 g, 10 mmol). The suspension was stirred at room temperature for 15 min. Then the reaction mixture was diluted with hexane (50 ml) and filtered. The filtrate was washed with ice-cold water (3 x 20 ml) and dried (Na_2SO_4). After evaporation of the solvents under reduced pressure the residue was purified by Kugelrohr distillation (90 - 95°C bath temp./8 Pa) yielding a t.l.c.-homogeneous product (1.95 g, 95 %). A solution of this bis-silylether in tetrahydrofuran (5 ml) and dichloromethane (5 ml) was treated with $PdCl_2(C_6H_5CN)_2$ (10 mg). To this solution was added a solution of diazomethane in diethyl ether at 0°C until conversion to **12** and **13** was complete (t.l.c. control). The reaction mixture was filtered through Celite. The solvents were removed under reduced pressure and the residue was separated by flash chromatography on siliga gel (100 g) with hexane - diethyl ether (500 : 2) affording **12** (1.05 g, 51 %) as the less polar product and **13** (0.41 g, 20 %) as the more polar product as colourless liquids. A solution of **13** in methanol (10 ml) was treated with Wofatit KPS (H^+, 0.5 g) and stirred at room temperature for 25 min. Then the mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (10 g) with hexane - ethyl acetate (3 : 1) yielding 0.16 g (52 %) of a t.l.c.-homogeneous liquid. A solution of this liquid in pyridine (2 ml) was treated at room temperature with acetic anhydride (1 ml). After standing at room temperature for 20 h methanol (0.5 ml) was added and the solvents were removed under reduced pressure affording 0.19 g (100 %) of a t.l.c.-homogeneous yellow liquid. A solution of this liquid in tetrahydrofuran (5 ml) was treated with tetrabutylammonium fluoride x 3 H_2O (0.63 g, 2 mmol). After stirring at room temperature for 16 h the reaction mixture was concentrated under reduced pressure. Flash chromatography of the residue on silica gel (20 g) with ethyl acetate - hexane (2 : 1) yielded **5b** (0.10 g, 90 %) as a colourless oil - $[\alpha]_D^{20}$ -47.2° (c 2,

$CHCl_3$) The ^1H n m.r spectra of **5b** and **ent-5b** from the lipase-catalyzed transesterifications were identical

The same sequence starting from **12** yielded **4b** - $[\alpha]_D^{20}$ -12 6° (c 1, $CHCl_3$)

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32 Crystal data for compound **4c** at 293 K $C_{10}H_{14}O_4$, M = 198 2 g mol^{-1}, monoclinic, $P2_1/n$, a = 6 49(15), b = 9 19(11), c = 17.23(6) Å, ß = 97.0(2)°, V = 1027 8 $Å^3$, Z = 4, D_x= 1 291 g cm^{-3}, MoK_α-radiation (0 71073 Å), diffractometer Enraf-Nonius CAD4, temperature of measurement 293 K, ω-2Θ scan mode, $2\Theta_{max}$= 50°, structure solved with MULTAN 11/82, R = 0 12 for 1330 reflections with $I \geq 2\sigma(I)$

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