Acylation of Tropane Alkaloids Displaying Reversed Diastereoselectivities under Enzymatic *versus* Chemical Conditions

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Dedicated to Professor Dieter H. Wolf on the occasion of his 65th birthday

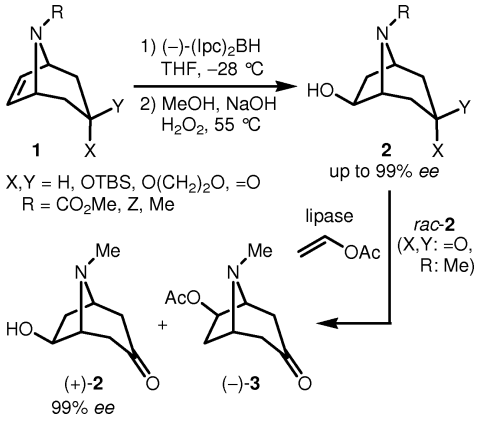
Lipase-mediated monoacetylation of 6,7-dihydroxytropinones **4** gave acetates **5**, *ent*-**5** which were analyzed as Mosher esters **9a**, **b** by ^{1}H NMR spectroscopy. However, the hydroxy groups in **4** were not differentiated by lipases. Reduction of the keto function and subsequent silylation afforded a mixture of *endo/exo*-TBS ethers **11**, which were dihydroxylated to give the corresponding diols *endo/exo*-**12**. In chemical acetylation a change of the *endo/exo* ratio in favor of the *endo*-derivative *endo*-**13** was observed, whereas the formation of the *exo*-acetate *exo*-**13** dominated in lipase-catalyzed acylation reactions. A mechanistic proposal is given.

Key words: Desymmetrization, 3,4-Dihydroxytropinone Derivatives, Lipases, Monoacetylation, Mosher Esters

Introduction

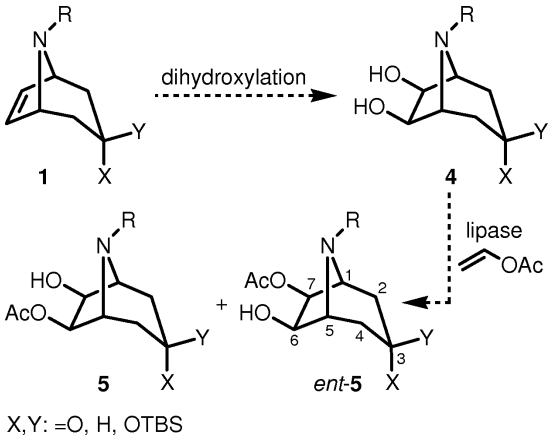
Tropane alkaloids possess a broad spectrum of biological activities and thus a decent amount of work has been devoted to their synthesis and functionalization [1, 2]. In most cases either scopolamine has been used as starting material or a *de novo* route was pursued [1, 2]. Only few reports utilized tropanone or tropenone **1** (Scheme 1) as a scaffold for further manipulations. For example, Simpkins achieved a desymmetrization of tropanone derivatives *via* enantioselective deprotonation by employing a chiral base [3]. We have previously shown that tropenones (**1**, X, Y: =O) can be desymmetrized by enantioselective hydroboration and subsequent oxidative workup to furnish 6-hydroxytropinones **2** [4]. Enantiomerically pure 6-hydroxytropinones **2** were available either by enzymatic resolution with lipases [5] or *via* Mannich-type reaction starting from *tert*-butyl (*R*)-3-hydroxypentenoate as chiral synthon [6].

6,7-Dihydroxytropinones **4** are envisaged as possible building blocks for chiral ligands (Scheme 2). They might be suitable for enzymatic desymmetrization to give the monoacetates **5** and *ent*-**5**, in which the hydroxy groups at C-6 and C-7 could be manipulated separately. In contrast to the many examples of enzymatic resolution of alcohols [7], surprisingly few cases deal



Scheme 1. Desymmetrization of tropenone **1**.

with the lipase-mediated monoacetylation of 1,2-diols and particularly *cis*-1,2-diols. For example, Bosetti described the resolution of terminal 1,2-diols with *Pseudomonas cepacia* lipase [8]. The desymmetrization of cyclic *cis*-1,2-diols with various lipases was recently reported by Nicolosi [9]. Based on our results with 6-hydroxytropinones **2** we were interested to investigate the ability of lipases to differentiate between the two enantiotopic hydroxy groups in the tropinone skeleton. However, we faced unexpected difficulties and finally ended up with conditions which allowed diastereose-



Scheme 2. Possible lipase-assisted desymmetrization of tropinone diols **4**.

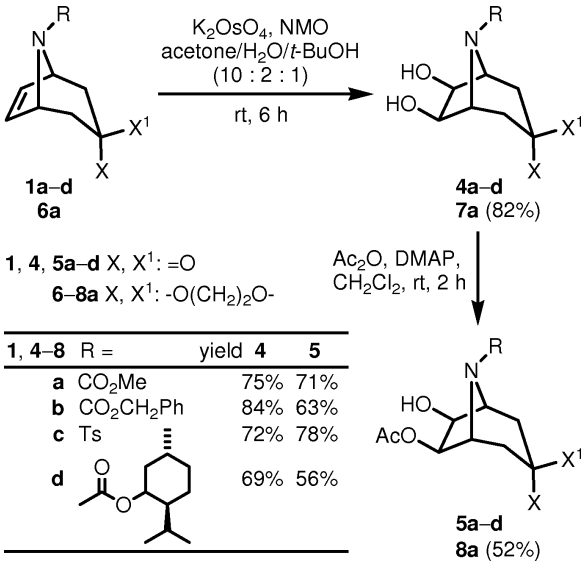
lective acylations of diols **4** with reversed diastereoselectivities under enzymatic and chemical conditions. The results towards this end are discussed below.

Results and Discussion

At the outset of our experiments we realized that the analytical separation of the enantiomers might be the most critical issue and therefore we first prepared racemic monoacetates *rac*-**5** as reference compounds (Scheme 3). Considering a facilitated separation of diastereromers, the novel (–)-menthyloxycarbonyl tropenone **1d** was synthesized in 40 % yield from the corresponding *N*-protected pyrrole and tetrabromoacetone in the presence of diethylzinc and subsequent debromination with Zn/Cu couple [10] analogously to our published procedure for compounds **1a**–**c** [4].

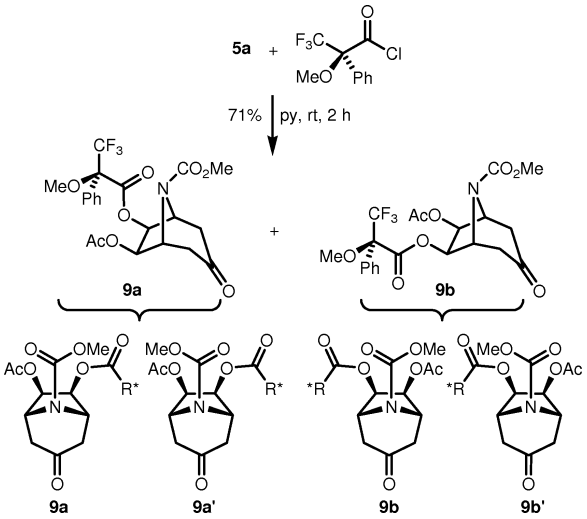
Following a method by Vogel [11], ketones **1a**–**d** and the *O*-protected derivative **6a** [4, 12] were treated with K_2OsO_4 in the presence of NMO in a mixture of acetone/H_2O/*t*-BuOH (10 : 2 : 1) at r. t. to give the diols **4a**–**d** and **7a** in 69–84 % yield (Scheme 3). Monoacetylation with acetic anhydride in the presence of DMAP in CH_2Cl_2 at r. t. to the acetates **5a**–**d** and **8a** proceeded eventless. Unfortunately, neither monoacetates **5a**–**d** nor the enantiomers of acetal **8a** could be resolved by chiral GC on modified cyclodextrine and polyamide phases or HPLC using Chiralcel OD and OJ phases.

Due to these problems with the analytical resolutions we investigated the NMR spectroscopic separation of diastereomers following the method by Mosher [13]. As a typical example, the carbamate-protected



1, 4–8	R =	yield 4	5
a	CO_2Me	75%	71%
b	CO_2CH_2Ph	84%	63%
c	Ts	72%	78%
d		69%	56%

Scheme 3. Preparation of tropenone derived diols **4** and **7a** and their monoacetylation to derivatives **5** and **8a**.



Scheme 4. Derivatization of acetate **5a** with Mosher's reagent; configuration at C-6 and C-7 in diastereomers **9a** and **9b** was arbitrarily assigned.

acetate **5a** was derivatized with (*S*)-MTPACl and the diastereomeric Mosher esters **9a**, **b** were analyzed by ^{1}H NMR spectroscopy (arbitrary configurations are depicted in Scheme 4) [13].

A first inspection of the NMR spectra of the esters **9a**, **b** revealed an additional set of signals besides those of the diastereomeric mixture of **9** (55 : 45) due to the presence of rotamers (Scheme 4). Because the ^{1}H NMR spectrum was only poorly resolved at r. t.

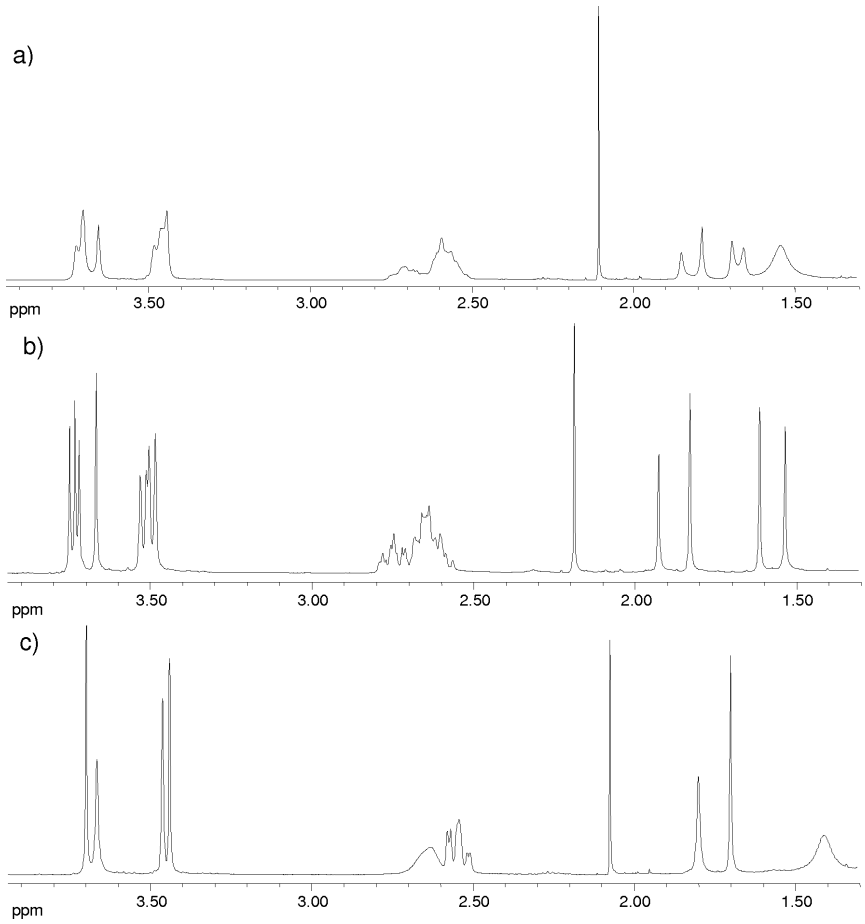
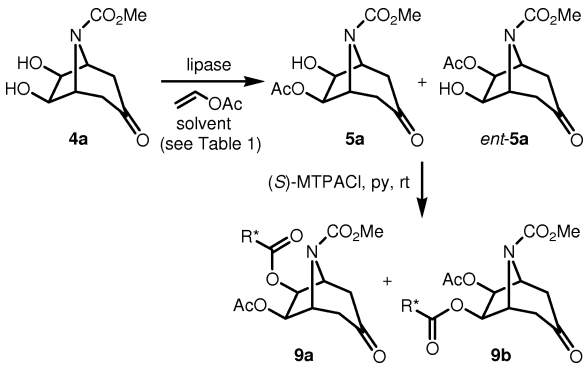


Fig. 1. ^{1}H NMR spectra of the diastereomeric mixture **9a**, **b** in $CDCl_3$ at a) room temperature, b) 215 K, and c) 330 K.



Scheme 5. Lipase-mediated acetylation of diol **4a** with vinyl acetate.

(Fig. 1a), a variable temperature ^{1}H NMR experiment was carried out.

At 215 K (Fig. 1b) the acetyl signals of diastereomer **9a** and its rotamer **9a**′ appear at $\delta = 1.53$ and 1.56 ppm, those of the other diastereomer **9b** and its rotamer **9b**′ appear at $\delta = 1.83$ and 1.92 ppm. The signals of the Mosher ester methoxy group can be seen at $\delta = 3.50$ (**9a**), 3.51 (**9a**′) and 3.48 (**9b**), 3.53 ppm (**9b**′) and the signals of the *N*-carbamate group are visible at $\delta =$ 3.73 (**9a**), 3.75 (**9a**′), and 3.67 (**9b**), 3.71 ppm (**9b**′). Upon increasing the temperature to 330 K (Fig. 1c) the signals for the rotamers disappear and only the signals for the diastereomeric acetyl, methoxy, and carbamate groups were detected.

It should be noted that the diastereomers display slightly different ratios of rotamers. Due to interactions of the *N*-carbamate group with the two acyl groups in its neighborhood free rotation around the N–CO bond is hindered.

With the Mosher esters as an analytical tool in hand, lipase-mediated acylations of ketone **4a** were carried out (Scheme 5).

First, several lipases were screened for monoacetylation and the crude products **5a** were directly con-

Table 1. Enzymatic acetylation of diol **4a** with various lipases[a,b].

Entry	Enzyme	Source	Time [h]	Conversion [%][c]
1	Chirazyme L-1	*Pseudomonas* sp.	3	40
2	Chirazyme L-6	*Pseudomonas* cep.	6	55
3	Chirazyme L-6	*Pseudomonas* cep.	48	70
4	Chirazyme L-5	*Candida antarctica*	24	39
5	Lipase R-10	*Penicillium soqueforti*	48	–
6	Lipase G	*Penicillium camenberti*	21	4
7	Lipase P	*Pseudomonas fluorescence*	48	8
8	Lipase D-20	*Rhizopus oryzae*	48	1
9	Novozyme 435	*Candida antarctica*	16	23
10	Novozyme 435	*Candida antarctica*	12[d]	16
11	Novozyme 435	*Candida antarctica*	7[e]	75
12	Novozyme 435	*Candida antarctica*	7[f]	50

[a] Reaction conditions: vinyl acetate, lipase, CH_2Cl_2, 40 °C; [b] the crude acetate **5a** was directly converted into Mosher esters **9a**, **b** and analyzed by ^{1}H NMR at 330 K, showing in all cases only a racemic mixture; [c] conversions were determined by capillary GC; [d] in acetone; [e] in Et_2O/CH_2Cl_2; [f] in toluene/CH_2Cl_2.

verted to the Mosher esters **9a**, **b** (Table 1). While lipases G, P, and D-20 gave only low conversion (entries 6 – 8), lipases Chirazyme L-1, L-6, and L-5 resulted in moderate to good conversions up to 70 % (entries 1 – 4). Lipase R-10 did not react (entry 5). However, in all cases only racemic mixtures of **5a** were obtained. Also with Novozyme 435 (lipase B from *Candida antarctica*), which is known for its good resolution ability towards secondary alcohols [14], no enantioselectivity was observed regardless of the solvent (entries 9 – 12). A certain improvement concerning conversion was achieved by solvent mixtures (entries 11, 12). Less polar solvents such as toluene, diethyl ether, diisopropyl ether, or TBME could not be used due to the high polarity of the starting material.

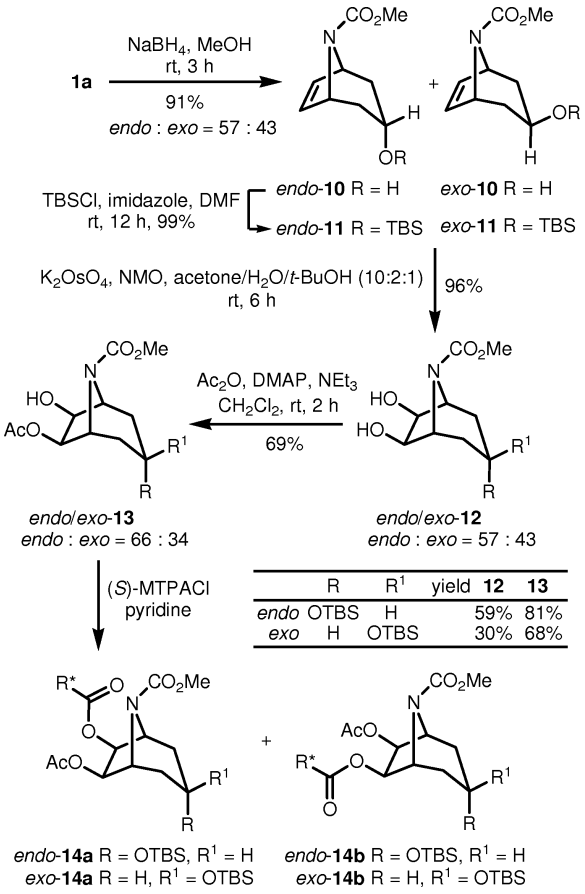
The active site of lipases is known to be rather hydrophobic [7a] and therefore we anticipated that the complete failure of differentiation between the enantiotopic hydroxy groups of the *meso* diol **4a** might be due to the poor binding of the polar tropinone. Consequently, the ketone moiety was converted into a protected alcohol (Scheme 6).

Ketone **1a** was treated with $NaBH_4$ in MeOH at r. t. to give 91 % of a 57 : 43 diastereomeric mixture of *endo*- and *exo*-alcohol **10**, respectively, which was silylated to the corresponding TBS ethers *endo*/*exo*-**11** in 99 % total yield (Scheme 6). After dihydroxylation of the diastereomeric mixture of TBS ethers **11**, a mixture of *endo*- and *exo*-diols **12** were obtained in 96 % yield. Monoacetylation of **12** to *endo*- and *exo*-acetates **13** and esterification of the latter with Mosher's acid

Table 2. Chemical and enzymatic acetylation of *endo*/*exo*-diols **12** (*endo* : *exo* = 57 : 43)[a].

Entry	Conditions	Method	Solvent	Time [h]	Conv. [%]	*endo* : *exo* **13**
1	Ac_2O, DMAP, NEt_3, rt	A	CH_2Cl_2	2	100	66 : 34[b]
2	Ac_2O, py, rt	B	–	48	80	56 : 44
3	AcCl, NEt_3, rt	C	CH_2Cl_2	5 min	70	56 : 44
4	HOAc, DCC, DMAP	D	CH_2Cl_2	3	100	64 : 36
5	Chirazyme L-1		Et_2O	20	56	15 : 85
6	Chirazyme L-5		Et_2O	24	40	35 : 65
7	Chirazyme L-6		Et_2O	48	33	17 : 83

[a] Conversion and *endo*/*exo* ratios of the crude products were determined by capillary GC; [b] isolated in 69 % yield.



	R	R^1	yield **12**	**13**
endo	OTBS	H	59%	81%
exo	H	OTBS	30%	68%

Scheme 6. Preparation of acetates **13**. Diols **12**: isolated yields after chromatographic separation of the *endo*/*exo*-mixture; acetates **13**: 81 % from *endo*-**12**, 68 % from *exo*-**12**.

chloride (*S*)-MTPACl proceeded in good yields. During acetylation of the *endo*/*exo* mixture of diols **12** we noticed a change of the diastereomeric ratio *endo* : *exo* from 57 : 43 (for diols **12**) to 66 : 34 (for acetates **13**)

Table 3. Chemical acetylation of separated *endo*- and *exo*-diol **12**[a].

Entry	Diol **12**	Method	Time [min]	Conv. [%]	Acetate **13**
1	*endo*	A	15	100	*endo*[b, c]
2	*exo*	A	15	100	*exo*[b, c]
3	*endo*	B	24 h	83	*endo*
4	*exo*	B	24 h	86	*exo*
5	*endo*	C	10	90	*endo*[b]
6	*exo*	C	10	98	*exo*[b, c]
7	*endo*	D	10	69	*endo*
8	*endo*	D	30	93	*endo*
9	*exo*	D	10	72	*exo*
10	*exo*	D	30	97	*exo*

[a] Conversions of the products were determined by capillary GC; [b] isolated yields: 81 % (entry 1), 68 % (entry 2), 84 % (entry 5), 78 % (entry 6); [c] the diacetate as a byproduct: 8 % (entry 1), 13 % (entry 2), 3 % (entry 6).

even when any enrichment during chromatographic purification or other workup was strictly avoided. We therefore studied other acylation conditions in comparison with enzymatic acylation in more detail (Table 2).

Whereas acetic anhydride in pyridine or acetyl chloride/triethylamine produced the same *endo/exo* ratio as was found in the starting diol **12** (entries 2, 3), the use of acetic anhydride/DMAP and acetic acid/DCC/DMAP resulted in a change of the *endo/exo* ratio in favor of the *endo* acetate *endo*-**13** (entries 1, 4). Surprisingly, enzymatic acylation gave reversed *endo/exo* ratios independently of the lipase (entries 5 – 7), *i. e.*, now favoring the formation of the *exo* acetate *exo*-**13** up to 85 % (entry 5).

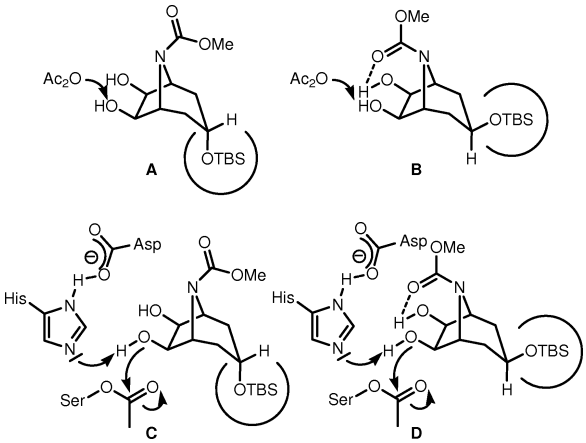
To find out whether both diols **12** display different acylation rates, *endo*- and *exo*-diols **12** were separated from the diastereomeric mixture by column chromatography and isolated in 59 % and 30 % yield, respectively. Subsequently they were acylated in parallel reactions. The results of the chemical acylation are summarized in Table 3.

As can be seen from Table 3, both diastereomers **12** reacted with similar rates to give the corresponding acetates **13**. However, this behavior changed in the lipase-mediated reaction (Table 4). When parallel enzymatic acylations were carried out with *endo*- and *exo*-diol **12**, respectively, the *exo*-diol **12** reacted much faster than the *endo*-diol **12** regardless of time and lipase. The most pronounced effects were seen for Chirazyme L-1 (entries 4, 6) and Novozyme 435 (entries 10, 12). With both lipases the conversion of *endo*-**12** was only 2 % after 24 h, whereas more than 90 % of the *exo*-diol **12** have reacted. Thus, the change of the *endo/exo* ratio during enzymatic acylations is probably

Table 4. Enzymatic acetylation of separated *endo*- and *exo*-diol **12** in diethyl ether[a].

Entry	Diol **12**	Enzyme	Time [h]	Conv. [%]	Acetate **13**
1	*endo*	Chirazyme L-5	27	3	*endo*
2	*exo*	Chirazyme L-5	27	14	*exo*
3	*endo*	Chirazyme L-1	1.5	0.4	*endo*
4	*endo*	Chirazyme L-1	24	2	*endo*
5	*exo*	Chirazyme L-1	1.5	16	*exo*
6	*exo*	Chirazyme L-1	24	93	*exo*[b]
7	*endo*	Chirazyme L-6	23	9	*endo*
8	*exo*	Chirazyme L-6	23	39	*exo*
9	*endo*	Novozyme 435	4	1	*endo*
10	*endo*	Novozyme 435	24	1.5	*endo*
11	*exo*	Novozyme 435	4	30	*exo*
12	*exo*	Novozyme 435	24	92	*exo*[b]

[a] Conversions of the products were determined by capillary GC; [b] isolated yield: 87 % (entry 6), 75 % (entry 12).



Scheme 7. Mechanistic proposal for the different behavior of *endo*- and *exo*-diol **12** in chemical and enzymatic acylations.

caused by the kinetic preference for acylation of the *exo*-diol **12**.

It should be noted that the conversion of the crude acetates **13** from the lipase reaction into the corresponding Mosher esters *endo*-**14a**, **b** and *exo*-**14a**, **b** did not show any enantioselectivity (Scheme 6).

From the above results we propose the following mechanistic hypothesis for the difference in acylation reactions (Scheme 7).

For highly reactive acylation agents such as acetyl chloride there is almost no difference between the *endo*- and *exo*-diol **12**. For less reactive acylating agents such as the system acetic anhydride/DMAP/NEt_3 attack from the *exo* face is possible because the carbamate moves into distant position. In contrast, the bulky *exo* TBS ether forces the carbamate into the opposite direction, resulting in an intramolecular hydrogen bond with the hydroxy group. Thus, both the re-

activity and the empty space for the incoming electrophile are reduced (**A** *versus* **B**). The catalytic mechanism of all lipases known so far is based on a "catalytic triad" Ser–His–Asp, which is linked *via* hydrogen bonds [7a]. The active site of the lipase seems to favor the more lipophilic *endo* face of the tropane skeleton. However, in the *endo*-diol **12** the bulky TBS group presumably inhibits binding of the catalytic triad Asp–His–Ser [7a] thus making an approach from the *endo* face less favorable as compared to the *endo*-attack in the *exo*-diol **12** (**C** *versus* **D**). In all cases, the relative configuration of the TBS ether in the tropinone diol **12** therefore effectively controls the diastereoselectivity of the acetylation process.

In conclusion, the lipase-catalyzed acylation of dihydroxytropinones **4** with vinyl acetate was investigated after establishing the NMR spectroscopic resolution of Mosher esters derived from racemic monoacetates **5** as the analytical tool. However, none of the lipases tested differentiate between the enantiotopic hydroxy groups. Due to the proposed poor binding of **4** to the enzyme active site, tropenone **1a** was converted into the *endo/exo* (57 : 43) TBS ethers *endo/exo*-**11**. During chemical acetylation a change of the *endo/exo* ratio to 66 : 34 was observed. In contrast, the lipase-mediated acylation of *endo/exo*-**12** clearly favored the formation of *exo*-**13** independently of the enzyme. *exo*-Diol **12** reacted much faster than *endo*-**12**. As the lipase is assumed to favor the *endo*-face of **12**, the position of the OTBS group appears to control the diastereoselectivity.

Experimental Section

General information

(2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 1*H*-pyrrole-1-carboxylate was prepared according to a literature procedure [15]. Commercial reagents were used without further purification unless otherwise indicated. All solvents were distilled prior to use. Reactions were performed in oven-dried glassware. Flash chromatography was performed on silica gel Fluka 60 (230 – 400 mesh). The following spectroscopic and analytical instruments were used. IR: Bruker Vector 22 FTIR. – NMR: Bruker Avance 500 (^{1}H: 500.15 MHz, ^{13}C: 125.76 MHz). For ^{1}H spectra, TMS was used as internal standard. Signal assignments are based on DEPT and COSY experiments. – Melting points: Büchi SMP 20, m. p. are uncorrected. – Mass spectrometry: Finnigan MAT 95 and Varian MAT 711. – GC: Hewlett-Packard HP 6890, column HP 5TA (30 m × 0.32 mm), temperature program: 16 °C min^{-1} gradient from 80 °C to 300 °C; Finnigan Trace GC 2000 Ultra, column trifluoroacetyl-γ-cyclodextrine (30 m × 0.25 mm), Lipodex E, Bondex un-β, Bondex un-α, Bondex un-$\alpha+\beta$, Amidex P2210. – HPLC: Jasco PU 980 with detector Jasco 875 UV, column Chiralcel OD-H and OJ-H (250 × 4.6 mm).

*(2S,5R)-2-Isopropyl-5-methylcyclohexyl 3-oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (**1d**)*

Preparation according to literature procedures [4, 10] from menthylpyrrole (1.20 g, 4.82 mmol) and tetrabromoacetone (3.2 g, 7.22 mmol) in toluene (100 mL), a 1 M solution of Et_2Zn in hexane (8.67 mL, 8.67 mmol), and Cu/Zn (4 g) in saturated NH_4Cl/MeOH (25 mL), yield: 590 mg (1.93 mmol, 40 %), brown oil. – $R_f = 0.28$ (EtOAc/hexanes = 1 : 5). – $[\alpha]_D^{20} = -63.5°$ ($c = 1.0$, $CHCl_3$). – IR (ATR): $\tilde{\nu} =$ 2953, 2868, 1698 (CO), 1404, 1298, 1096, 986, 734, 631 cm^{-1}. – ^{1}H NMR (500.15 MHz, $CDCl_3$): $\delta = 0.78$ (d, $J = 7.0$ Hz, 3 H, CH(CH_3)$_2$), 0.86 – 0.91 (m, 1 H, 4′-H$_{ax}$), 0.93 (d, $J = 7.0$ Hz, 6 H, CH(CH_3)$_2$, 5′-CH$_3$), 0.95 – 1.02 (m, 1 H, 6′-H$_{ax}$), 1.04 – 1.14 (m, 1 H, 3′-H$_{ax}$), 1.36 – 1.42 (m, 1 H, 2′-H), 1.46 – 1.55 (m, 1 H, 5′-H), 1.64 – 1.71 (m, 2 H, 3′-H$_{eq}$, 4′-H$_{eq}$), 1.87 – 1.91 (m, 1 H, CH(CH$_3$)$_2$), 2.03 – 2.06 (m, 1 H, 6′-H$_{eq}$), 2.36 (br d, $J = 16.2$ Hz, 2 H, 2-H, 4-H), 2.59 – 2.80 (m, 2 H, 2-H, 4-H), 4.63 (dt, $J = 10.9$ Hz, $J = 4.4$ Hz, 1 H, 1′-H), 4.83 (br, 2 H, 1-H, 5-H), 6.22 (br s, 2 H, 6-H, 7-H). – ^{13}C{^{1}H} NMR (125.76 MHz, $CDCl_3$): $\delta = 16.6$ (CH(*C*H$_3$)$_2$), 21.2 (CH(*C*H$_3$)$_2$), 22.4 (CH$_3$), 24.1 (C-3′), 26.9 (*C*H(CH$_3$)$_2$), 31.8 (C-5′), 34.7 (C-4′), 41.9 (C-6′), 45.6, 46.1 (C-2, C-4), 47.8 (C-2′), 56.5 (C-1, C-5), 75.9 (C-1′), 134.1, 134.3 (C-6, C-7), 153.2 (COO), 206.1 (C-3). – MS (EI, 70 eV): m/z (%) = 305 (5) [M$^+$], 167 (80), 123 (30), 97 (15), 83 (100), 55 (30). – $C_{18}H_{27}NO_3$ (305.2): calcd. C 70.7, H 8.91, N 4.59; found C 69.41, H 8.80, N 4.18.

*Methyl 6,7-dihydroxy-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (**4a**)*

To a stirred solution of **1a** (565 mg, 3.12 mmol) in a solvent mixture of acetone/water/*t*-BuOH (50 mL/10 mL/5 mL) was added NMO (1.1 g, 9.40 mmol) and a solution of potassium osmate dihydrate (5 mg) in CCl_4 (2 mL). After stirring for 6 h, a solution of Na_2SO_3 (1 g) in water (10 mL) was added and the reaction mixture stirred for a further 1 h. The aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. Purification by flash chromatography on SiO_2 with EtOAc ($R_f = 0.30$) gave **4a** as a colorless solid (502 mg, 2.33 mmol, 75 %). – M. p. 126 °C. – IR (ATR): $\tilde{\nu} =$ 3474, 3339 (OH), 2961, 1705 (CO), 1659 (CO), 1470, 1403, 1195, 1118, 1085, 1006, 764 cm^{-1}. – ^{1}H NMR (500.15 MHz, $CDCl_3$): $\delta = 2.48$ (br d, $J = 16.4$ Hz, 2 H, 2-H, 4-H), 2.60 – 2.67 (m, 2 H, 2-H, 4-H), 3.45 (br, 2 H, OH), 3.78 (s, 3 H, CH$_3$), 4.07 (s, 2 H, 6-H, 7-H), 4.42 (br, 2 H, 1-H, 5-H). – ^{13}C{^{1}H} NMR (125.76 MHz, $CDCl_3$): $\delta = 45.3$,

45.8 (C-2, C-4), 53.1 (CH_3), 61.3 (C-1, C-5), 73.9, 74.8 (C-6, C-7), 155.4 (CO), 205.4 (C-3). – MS (EI, 70 eV): m/z (%) = 215.1 (25) [M^+], 155.1 (100), 127.1 (85). – $C_9H_{13}NO_5$ (215.1): calcd. C 50.23, H 6.09, N 6.51; found C 50.32, H 6.01, N 6.46.

*Benzyl 6,7-dihydroxy-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (**4b**)*

Yield: 396 mg (1.36 mmol, 84 %), colorless solid. – M. p. 104 °C. – R_f = 0.30 (EtOAc/hexanes = 1 : 1 → EtOAc). – IR (ATR): $\tilde{\nu}$ = 3356 (OH), 2943 (C-H), 1683 (CO), 1425, 1333, 1112, 1082, 1000, 694 cm^{-1}. – ^{1}H NMR (500.15 MHz, $CDCl_3$): δ = 2.45 (d, J = 16.4 Hz, 2 H, 2-H, 4-H), 2.54 – 2.69 (m, 2 H, 2-H, 4-H), 3.45 (br, 1 H, OH), 3.58 (br, 1 H, OH), 4.03 (s, 2 H, 6-H, 7-H), 4.44 (d, J = 11.3 Hz, 2 H, 1-H, 5-H), 5.18 (d, J = 9.8 Hz, 2 H, CH_2Ar), 7.32 – 7.37 (m, 5 H, Ar). – ^{13}C{^{1}H} NMR (125.76 MHz, $CDCl_3$): δ = 45.4, 45.8 (C-2, C-4), 61.4 (C-1, C-5), 67.7 (CH_2Ar), 73.8, 74.7 (C-6, C-7), 127.9, 128.4, 128.7 (Ar), 136.0 (Ar), 154.8 (COO), 205.4 (C-3). – MS (EI, 70 eV): m/z (%) = 291.1 (15) [M^+], 156 (35), 91 (100) [$C_7H_7^+$]. – $C_{15}H_{17}NO_5$ (291.1): calcd. C 61.85, H 5.88, N 4.81; found C 61.72, H 5.91, N 4.74.

*6,7-Dihydroxy-8-[(4-methylphenyl)sulfonyl]-8-azabicyclo[3.2.1]octan-3-one (**4c**)*

Yield: 120 mg (0.39 mmol, 72 %), colorless solid. – M. p. 170 °C. – R_f = 0.3 (EtOAc/hexanes = 4 : 1). – IR (ATR): $\tilde{\nu}$ = 3483, 3392 (OH), 2918 (C-H), 1689 (CO), 1345, 1153, 1092, 813, 660, 278 cm^{-1}. – ^{1}H NMR (500.15 MHz, [D$_6$]DMSO): δ = 2.37 – 2.42 (m, 2 H, 2-H, 4-H), 2.39 (s, 3 H, CH_3), 2.59 (br d, J = 5.1 Hz, 1 H, 2-H), 2.60 (br d, J = 5.1 Hz, 1 H, 4-H), 3.90 (d, J = 2.6 Hz, 2 H, 6-H, 7-H), 4.05 (br d, J = 4.9 Hz, 2 H, OH), 5.01 (br d, J = 2.6 Hz, 2 H, 1-H, 5-H), 7.37 – 7.39 (m, 2 H, Ar), 7.81 – 7.82 (m, 2 H, Ar). – ^{13}C{^{1}H} NMR (125.76 MHz, [D$_6$]DMSO): δ = 20.9 (CH_3), 45.4 (C-2, C-4), 63.1 (C-1, C-5), 73.8 (C-6, C-7), 127.06, 129.5 (C-2′, C-3′), 138.1 (C-1′), 143.2 (C-4′), 205.0 (C-3). – MS (EI, 70 eV): m/z (%) = 311.1 (15) [M^+], 251 (50), 156 (35), 96 (85), 91 (98) [$C_7H_7^+$], 54 (100). – $C_{14}H_{17}NO_5S$ (311.1): calcd. C 54.01, H 5.50, N 4.50, S 10.30; found C 53.92, H 5.53, N 4.41, S 10.06.

*(2S,5R)-2-Isopropyl-5-methylcyclohexyl 6,7-dihydroxy-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (**4d**)*

Yield: 207 mg (0.61 mmol, 69 %), colorless oil. – R_f = 0.28 (EtOAc/hexanes = 2 : 1). – $[\alpha]_D^{20} = -56.3°$ (c = 1.0, $CHCl_3$). – IR (ATR): $\tilde{\nu}$ = 3392 (OH), 2953, 2869 (C-H), 1695 (CO), 1667 (CO), 1403, 1304, 1083, 1001, 772, 698 cm^{-1}. – ^{1}H NMR (500.15 MHz, $CDCl_3$): δ = 0.79 (d, J = 6.9 Hz, 3 H, CH(CH_3)$_2$), 0.85 – 0.99 (m, 1 H, 4′-H$_{ax}$), 0.91 (dd, J = 6.8 Hz, J = 1.6 Hz, 6 H, CH(CH_3)$_2$, 5′-CH_3), 1.01 – 1.13 (m, 2 H, 3′-H$_{ax}$, 6′-H$_{ax}$), 1.35 – 1.55 (m, 2 H, 2′-H, 5′-H), 1.65 – 1.71 (m, 2 H, 3′-H$_{eq}$, 4′-H$_{eq}$), 1.85 – 2.08 (br m, 2 H, CH(CH$_3$)$_2$, 6′-H$_{eq}$), 2.47 (br d, J = 16.0 Hz, 2 H, 2-H, 4-H), 2.58 – 2.67 (br m, 2 H, 2-H, 4-H), 3.16 (br, 2 H, OH), 4.07 (br, 2 H, 6-H, 7-H), 4.43 (br, 2 H, 1-H, 5-H), 4.62 (dt, J = 10.8 Hz, J = 4.2 Hz, 1 H, 1′-H). – ^{13}C{^{1}H} NMR (125.76 MHz, $CDCl_3$): δ = 16.5 (CH(CH_3)$_2$), 20.8 (CH(CH_3)$_2$), 22.0 (CH_3), 23.5 (C-3′), 26.5 (CH(CH$_3$)$_2$), 31.4 (C-5′), 34.2 (C-4′), 41.4 (C-6′), 45.5, 45.7 (C-2, C-4), 47.2 (C-2′), 61.3 (C-1, C-5), 74.1, 74.7 (C-6, C-7), 75.7 (C-1′), 155.0 (COO), 205.6 (C-3). – MS (EI, 70 eV): m/z (%) = 339 (5) [M^+], 201 (10), 138 (45), 97 (30), 83 (100), 57 (30), 18 (25). – $C_{18}H_{29}NO_5$ (339.2): calcd. C 63.69, H 8.61, N 4.13; found C 63.83, H 8.80, N 3.94.

*Methyl 6,7-dihydroxy-8H-spiro[8-azabicyclo[3.2.1]octane-3,2′-[1,3]dioxolane]-8-carboxylate (**7a**)*

Yield: 281 mg (1.09 mmol, 82 %), colorless solid. – M. p. 99 °C. – R_f = 0.26 (EtOAc). – IR (ATR): $\tilde{\nu}$ = 3333 (OH), 2919, 2853 (C-H), 1697 (CO), 1443, 1363, 1097, 970, 773, 604 cm^{-1}. – ^{1}H NMR (500.15 MHz, $CDCl_3$): δ = 1.91 – 2.05 (m, 4 H, 2-H, 4-H), 3.10 (br, 2 H, OH), 3.71 (s, 3 H, CH_3), 3.83 – 3.87 (m, 2 H, OCH_2), 3.92 – 3.97 (m, 2 H, OCH_2), 4.16 (br, 1 H, 1-H), 4.21 (br, 1 H, 5-H), 4.50 (d, J = 1.9 Hz, 2 H, 6-H, 7-H). – ^{13}C{^{1}H} NMR (125.76 MHz, $CDCl_3$): δ = 38.3, 38.8 (C-2, C-4), 52.7 (OCH_3), 61.7, 61.9 (C-1, C-5), 63.8, 64.5 (OCH_2), 72.8, 73.5 (C-6, C-7), 106.6 (C-3), 155.4 (C-8). – MS (EI, 70 eV): m/z (%) = 259 (10) [M^+], 199 (20), 127 (20), 99 (100), 18 (25). – $C_{11}H_{17}NO_6$ (259.1): calcd. C 50.96, H 6.61, N 5.40; found C 50.98, H 6.55, N 5.26.

*Methyl 6-(acetyloxy)-7-hydroxy-3-oxo-8-azabicyclo[3.2.1]-octane-8-carboxylate (**5a**)*

Method A: Ac_2O (16 μL, 0.16 mmol) was added to a stirred solution of **4a** (35 mg, 0.16 mmol), DMAP (7 mg, 0.06 mmol) and triethylamine (70 μL, 0.36 mmol) in absolute CH_2Cl_2 (2 mL). The reaction mixture was stirred at r. t. for 0.5 h, concentrated under vacuum and diluted with EtOAc (10 mL). The organic layer was washed with 0.1 N NaOH/H_2O and brine (10 mL each), dried (Na_2SO_4) and concentrated. Purification by flash chromatography on SiO_2 with EtOAC/hexanes (4 : 1) → EtOAc gave in a first fraction (R_f (EtOAc) = 0.42) **5a** (25 mg, 0.10 mmol, 71 %) and in a second fraction unreacted **4a** (4 mg, 0.02 mmol). – IR (ATR): $\tilde{\nu}$ = 3415 (OH), 2959, 2916 (C-H), 1737 (CO), 1688 (CO), 1451, 1393, 1228, 1121, 1008, 631, 536 cm^{-1}. – ^{1}H NMR (500.15 MHz, $CDCl_3$): δ = 2.15 (s, 3 H, $COCH_3$), 2.47 – 2.80 (m, 5 H, 2-H, 4-H, OH), 3.79 (s, 3 H, CH_3), 4.25 (d, J = 6.2 Hz, 1 H, 7-H), 4.46 (br, 2 H, 1-H, 5-H), 4.87 (d, J = 6.2 Hz, 1 H, 6-H). – ^{13}C{^{1}H} NMR

(125.76 MHz, $CDCl_3$): $\delta = 20.5$ (CH_3), 45.2, 45.6 (C-2, C-4), 53.1 (CH_3), 58.8 (C-1, C-5), 75.0, 75.8 (C-7, C-6), 154.3 (COO), 169.8 ($OCOCH_3$), 203.9 (C-3). – MS (EI, 70 eV): m/z (%) = 257 (15) [M^+], 197 (80), 154 (100), 127 (65), 43 (95). – HRMS (EI): calcd. for $C_{11}H_{15}NO_6$ 257.0899; found 257.0898 [M^+]. – $C_{11}H_{15}NO_6$ (257.1): calcd. C 51.36, H 5.88, N 5.44; found C 51.42, H 6.33, N 4.87.

*Benzyl 6-(acetyloxy)-7-hydroxy-3-oxo-8-azabicyclo[3.2.1]-octane-8-carboxylate (**5b**)*

Yield: 26 mg (0.08 mmol, 63 %), colorless oil. – $R_f = 0.37$ (EtOAc/hexanes = 2 : 1). – IR (ATR): $\tilde{\nu} = 3436$ (OH), 3064, 2959 (C-H), 1738 (CO), 1692 (CO), 1415, 1225, 1003, 699, 601 cm^{-1}. – ^1H NMR (500.15 MHz, $CDCl_3$): $\delta = 2.12$ (s, 3 H, $COCH_3$), 2.46 – 2.72 (m, 4 H, 2-H, 4-H), 4.24 (d, $J = 6.2$ Hz, 1 H, 7-H), 4.46 (br, 2 H, 1-H, 5-H), 4.87 (d, $J = 6.2$ Hz, 1 H, 6-H), 5.21 (s, 2 H, CH_2Ar), 7.31 – 7.41 (m, 5 H, Ar). – $^{13}C\{^1H\}$ NMR (125.76 MHz, $CDCl_3$): $\delta = 20.7$ (CH_3), 45.6 (C-2, C-4), 58.7, 61.5 (C-1, C-5), 67.8 (CH_2Ar), 74.4 (C-7), 75.8 (C-6), 128.2, 128.5, 128.7 (Ar), 135.9 (Ar), 154.3 (COO), 170.1 ($OCOCH_3$), 204.6 (C-3). – MS (EI, 70 eV): m/z (%) = 333.1 (5) [M^+], 273 (10), 198 (10), 91 (100) [$C_7H_7^+$], 42.9 (20), 28.0 (20). – $C_{17}H_{19}NO_6$ (333.1): calcd. C 61.25, H 5.75, N 4.20; found C 61.03, H 6.07, N 3.93.

*7-Hydroxy-8-[(4-methylphenyl)sulfonyl]-3-oxo-8-azabicyclo[3.2.1]oct-6-yl acetate (**5c**)*

Yield: 20 mg (0.05 mmol, 78 %), colorless oil; as byproduct **4c** (5 mg, 0.016 mmol). – M. p. 138 °C. – $R_f = 0.41$ (EtOAc/hexanes = 3 : 1). – IR (ATR): $\tilde{\nu} = 3488$ (OH), 2959, 2893 (C-H), 1734 (CO), 1713 (CO), 1337, 1234, 1151, 1045, 661, 597, 540 cm^{-1}. – ^1H NMR (500.15 MHz, $CDCl_3$): $\delta = 2.07$ (s, 3 H, $COCH_3$), 2.45 (s, 3 H, CH_3), 2.54 (br, 1 H, OH), 2.62 – 2.72 (m, 2 H, 2-H, 4-H), 2.76 – 2.83 (m, 2 H, 2-H, 4-H), 4.21 – 4.26 (m, 2 H, 1-H, 5-H), 4.53 (quint, $J = 2.2$ Hz, 1 H, 7-H), 4.90 (d, $J = 6.3$ Hz, 1 H, 6-H), 7.35 (d, $J = 8.1$ Hz, 2 H, 3′-H), 7.84 (d, $J = 8.2$ Hz, 2 H, 2′-H). – $^{13}C\{^1H\}$ NMR (125.76 MHz, $CDCl_3$): $\delta = 20.6$ (Ar-CH_3), 21.6 (CH_3), 46.1, 46.7 (C-2, C-4), 60.7, 63.7 (C-1, C-5), 75.9 (C-6, C-7), 127.7, 129.9 (C-2′, C-3′), 144.5 (C-1′), 146.7 (C-4′), 169.8 (OCO), 203.7 (C-3). – MS (EI, 70 eV): m/z (%) = 353 (10) [M^+], 150 (30), 198 (70), 155 (40), 91 (100), 54 (65), 43 (90). – $C_{16}H_{19}NO_6S$ (353.1): calcd. C 54.38, H 5.42, N 3.96; found C 54.62, H 5.60, N 3.72.

*(2S,5R)-2-Isopropyl-5-methylcyclohexyl 6-acetoxy-7-hydroxy-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (**5d**)*

Yield: 25 mg (66.0 μmol, 56 %), colorless oil. – $R_f = 0.34$ (EtOAc/hexanes = 1 : 1). – $[\alpha]_D^{20} = -40.5°$ ($c = 0.1$, $CHCl_3$). – IR (ATR): $\tilde{\nu} = 3429$ (OH), 2954, 2869 (C-H), 1740 (CO), 1694 (CO), 1405, 1229, 1090, 1003, 631 cm^{-1}. – ^1H NMR (500.15 MHz, $CDCl_3$): $\delta = 0.80$ (d, $J = 6.5$ Hz, 3 H, $CH(CH_3)_2$), 0.85 – 0.98 (m, 1 H, 4′-H_{ax}), 0.91 (d, $J = 6.6$ Hz, 6 H, $CH(CH_3)_2$, 5′-CH_3), 1.02 – 1.10 (m, 2 H, 3′-H_{ax}, 6′-H_{ax}), 1.37 – 1.56 (m, 2 H, 2′-H, 5′-H), 1.68 – 1.71 (m, 2 H, 3′-H_{eq}, 4′-H_{eq}), 1.85 – 2.09 (br m, 2 H, $CH(CH_3)_2$, 6′-H_{eq}), 2.15 (s, 3 H, $OCOCH_3$), 2.33 (br, 1 H, OH), 2.46 – 2.70 (br m, 4 H, 2-H, 4-H), 4.24 (t, $J = 6.9$ Hz, 1 H, 7-H), 4.48 (br, 2 H, 1-H, 5-H), 4.64 (dt, $J = 10.8$ Hz, $J = 4.4$ Hz, 1 H, 1′-H), 4.87 (d, $J = 6.3$ Hz, 1 H, 6-H). – $^{13}C\{^1H\}$ NMR (125.76 MHz, $CDCl_3$): $\delta = 16.3$ ($CH(CH_3)_2$), 20.7, 20.8 ($CH(CH_3)_2$, $COCH_3$), 22.0 (CH_3), 23.4 (C-3′), 26.6 ($CH(CH_3)_2$), 31.4 (C-5′), 34.2 (C-4′), 41.4 (C-6′), 45.1, 45.6 (C-2, C-4), 47.2 (C-2′), 58.7, 61.3 (C-5, C-1), 74.7, 74.9 (C-6, C-7), 76.2 (C-1′), 154.4 (COO), 170.1 (OCO), 204.9 (C-3). – MS (EI, 70 eV): m/z (%) = 381 (5) [M^+], 321 (10), 184 (15), 138 (65), 83 (100), 57 (30), 28 (15). – $C_{20}H_{31}NO_6$ (381.2): calcd. C 62.97, H 8.19, N 3.67; found C 62.23, H 8.22, N 3.54.

*Methyl 6-(acetyloxy)-7-hydroxy-8H-spiro[8-azabicyclo-[3.2.1]octane-3,2′-[1,3]dioxolane]-8-carboxylate (**8a**)*

Yield: 25 mg (0.083 mmol, 52 %), colorless oil; **7a** as byproduct (4 mg, 0.015 mmol). – $R_f = 0.35$ (EtOAc). – IR (ATR): $\tilde{\nu} = 3435$ (OH), 2959, 2891 (C-H), 1738 (CO), 1688 (CO), 1452, 1219, 1099, 768, 602 cm^{-1}. – ^1H NMR (500.15 MHz, $CDCl_3$): $\delta = 1.88 – 2.13$ (m, 5 H, 2-H, 4-H, OH), 2.13 (s, 3 H, $COCH_3$), 3.73 (s, 3 H, CH_3), 3.84 – 3.88 (m, 2 H, OCH_2), 3.95 – 3.99 (m, 2 H, OCH_2), 4.16 – 4.27 (m, 2 H, 1-H, 5-H), 4.65 (d, $J = 6.2$ Hz, 1 H, 7-H), 5.42 (d, $J = 6.2$ Hz, 1 H, 6-H). – $^{13}C\{^1H\}$ NMR (125.76 MHz, $CDCl_3$): $\delta = 20.9$ ($OCOCH_3$), 37.9, 38.7 (C-2, C-4), 52.7 ($COOCH_3$), 61.7, 61.9 (C-1, C-5), 63.8, 64.5 (OCH_2), 72.8, 73.5 (C-7, C-6), 106.6 (C-3), 155.4 (C-8). – MS (EI, 70 eV): m/z (%) = 301 (15) [M^+], 241 (50), 198 (30), 99 (100), 43 (50). – $C_{13}H_{19}NO_7$ (301.1): calcd. C 51.82, H 6.36, N 4.65; found C 51.88, H 6.73, N 4.42.

*Methyl 3-hydroxy-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (**10**)*

A solution of **1a** (504 mg, 2.78 mmol) in MeOH (5 mL) was added to a stirred solution of $NaBH_4$ (211 mg, 5.56 mmol) in absolute MeOH (2 mL). After stirring for 3 h, the reaction mixture was hydrolyzed with a saturated solution of NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine (80 mL), dried (Na_2SO_4) and concentrated to give **10** as a yellow oil (464 mg, 2.53 mmol, 91 %), *endo* : *exo* = 57 : 43. – $R_f = 0.24$ (EtOAc/hexanes = 3 : 2). – IR (ATR): $\tilde{\nu} =$ 3448, 3075, 2965, 2880, 1667 (CO), 1602, 1459, 1309, 1108, 886, 764 cm^{-1}. – ^1H NMR (500.15 MHz, $CDCl_3$): $\delta = 1.47$ (br t, $J = 10.2$ Hz, 1 H, *exo*, 2-H), 1.59 (br, 1 H, *exo* OH),

1.73 (br, 1 H, *exo*, 4-H), 1.78 (br d, $J = 14.8$ Hz, 2 H, *endo*, 2-H, 4-H), 1.97 (ddd, $J = 12.8$, 6.4, 1.8 Hz, 2 H, *exo*, 2-H, 4-H), 2.18 (br d, $J = 9.5$ Hz, 2 H, *endo*, 2-H, 4-H), 2.26 (br, 1 H, *endo* OH), 3.71 (s, 3 H, *exo*, CH_3), 3.72 (s, 3 H, *endo*, CH_3), 3.89 – 3.96 (m, 2 H, *endo/exo*, 3-H), 4.56 – 4.66 (m, 4 H, *endo/exo*, 1-H, 5-H), 6.02 (d, $J = 12.7$ Hz, 2 H, *exo*, 6-H, 7-H), 6.39 (d, $J = 11.0$ Hz, 2 H, *endo*, 6-H, 7-H). – $^{13}C\{^1H\}$ NMR (125.76 MHz, $CDCl_3$): $\delta = 33.9$, 34.6, 35.1, 35.8 (C-2, C-4), 52.3 (OCH_3), 57.1 (C-1, C-5), 64.8, 65.6 (C-3), 130.7, 131.1 (C-6, C-7), 135.6, 136.0 (C-6, C-7), 152.9, 153.2 (COO). – MS (EI, 70 eV): m/z (%) = 183 (40) [M^+], 138 (100), 126 (30), 102 (45), 94 (80), 80 (30), 59 (15). – $C_9H_{13}NO_3$ (183.1): calcd. C 59.00, H 7.15, N 7.65; found C 58.53, H 7.20, N 7.53.

*Methyl 3-{[tert-butyl(dimethyl)silyl]oxy}-8-azabicyclo-[3.2.1]oct-6-ene-8-carboxylate (**11**)*

A solution of **10** (451 mg, 3.46 mmol) in absolute DMF (2 mL) was added to a solution of *tert*-butyldimethylsilylchloride (500 mg, 3.28 mmol) and imidazole (225 mg, 3.28 mmol) in absolute DMF (2 mL) under nitrogen atmosphere. After stirring for 16 h, the reaction mixture was taken up in CH_2Cl_2 (50 mL) and washed with brine and H_2O (20 mL each). The combined organic layers were dried (Na_2SO_4) and concentrated to give **11** as a colorless oil (728 mg, 2.45 mmol, 99 %), *endo* : *exo* = 57 : 43. – R_f = 0.36 (EtOAc/hexanes = 1 : 4). – IR (ATR): $\tilde{\nu} = 2954$, 2928, 2856, 1711 (CO), 1452, 1106, 1005, 632 cm^{-1}. – ^1H NMR (500.15 MHz, $CDCl_3$): $\delta = -0.03$ (s, 6 H, *exo*, $SiMe_2$), 0.00 (s, 6 H, *endo*, $SiMe_2$), 0.85 (s, 9 H, *exo*, $SiC(CH_3)_3$), 0.86 (s, 9 H, *endo*, $SiC(CH_3)_3$), 1.53 (br t, $J = 10.1$ Hz, 1 H, *exo*, 2-H), 1.56 (br d, $J = 14.6$ Hz, 2 H, *endo*, 2-H, 4-H), 1.65 (br t, $J = 10.1$ Hz, 1 H, *exo*, 4-H), 1.82 (ddd, $J = 13.0$, 6.7, 2.0 Hz, 2 H, *exo*, 2-H, 4-H), 2.09 (d, $J = 12.4$ Hz, 1 H, *endo*, 2-H), 2.20 (d, $J = 12.4$ Hz, 1 H, *endo*, 4-H), 3.71 (s, 3 H, *exo*, CH_3), 3.72 (s, 3 H, *endo*, CH_3), 3.92 (tt, $J = 9.4$, 6.6 Hz, 1 H, *exo*, 3-H), 4.00 (t, $J = 5.5$ Hz, 1 H, *endo*, 3-H), 4.56 (br t, $J = 38.7$ Hz, 4 H, *endo/exo*, 1-H, 5-H), 6.02 (d, $J = 13.8$ Hz, 2 H, *exo*, 6-H, 7-H), 6.11 (d, $J = 15.9$ Hz, 2 H, *endo*, 6-H, 7-H). – $^{13}C\{^1H\}$ NMR (125.76 MHz, $CDCl_3$): $\delta = -4.9$, -4.6 ($SiMe_2$), 17.7, 18.0 ($SiC(CH_3)_3$), 25.7, 25.8 ($SiC(CH_3)_3$), 34.1, 34.9, 35.0, 35.9 (C-2, C-4), 52.1 (OCH_3), 57.2 (C-1, C-5), 65.0, 65.4 (C-3), 130.7, 131.1 (C-6, C-7), 133.4, 133.9 (C-6, C-7), 152.8, 153.3 (COO). – MS (EI, 70 eV): m/z (%) = 297 (10) [M^+], 240 (85), 196 (35), 164 (100), 138 (35), 108 (35), 89 (50). – $C_{15}H_{27}NO_3Si$ (297.1): calcd. C 60.57, H 9.15, N 4.71; found C 60.64, H 9.16, N 4.64.

*Methyl 6,7-dihydroxy-3-{[tert-butyl(dimethyl)silyl]oxy}-8-azabicyclo[3.2.1]octane-8-carboxylate (**12**)*

As described for **4a**, total yield: 96 %; chromatography on SiO_2 with EtOAc/hexanes (1 : 1) gave in a first fraction (R_f = 0.28) *endo*-**12** (447 mg, 1.35 mmol, 59 %) as a colorless solid and in a second fraction a mixture of *endo/exo*-**12** (51 mg, 0.15 mmol, 7 %) and in a third fraction ($R_f = 0.16$) *exo*-**12** (241 mg, 0.73 mmol, 30 %) as a colorless solid.

*endo-**12***

M. p. 173 °C. – IR (ATR): $\tilde{\nu} = 3481$ (OH), 2951, 2927, 2855 (C-H), 1682 (CO), 1461, 1251, 1091, 996, 773, 546 cm^{-1}. – ^1H NMR (500.15 MHz, $CDCl_3$): $\delta = 0.03$ (s, 6 H, $SiMe_2$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 1.75 (br d, J = 16.7 Hz, 2 H, 2-H, 4-H), 1.93 (br d, $J = 18.6$ Hz, 1 H, 2-H), 2.02 (br d, $J = 18.3$ Hz, 1 H, 4-H), 3.08 (br, 1 H, OH), 3.16 (br, 1 H, OH), 3.69 (s, 3 H, CH_3), 3.97 (t, $J = 4.0$ Hz, 1 H, 3-H), 4.06 (br, 1 H, 1-H), 4.15 (br, 1 H, 5-H), 4.67 (br, 2 H, 6-H, 7-H). – $^{13}C\{^1H\}$ NMR (125.76 MHz, $CDCl_3$): $\delta = -5.2$ ($SiMe_2$), 17.8 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 36.3, 36.9 (C-2, C-4), 52.5 (OCH_3), 61.9, 62.3 (C-1, C-5), 64.7 (C-3), 73.3, 73.8 (C-6, C-7), 155.4 (COO). – MS (EI, 70 eV): m/z (%) = 331 (10) [M^+], 274 (100), 230 (15), 171 (25), 140 (35), 89 (40), 73 (40). – $C_{15}H_{29}NO_5Si$ (331.2): calcd. C 54.35, H 8.82, N 4.23; found C 54.33, H 8.75, N 4.17.

*exo-**12***

M. p. 129 °C. – IR (ATR): $\tilde{\nu} = 3481$ (OH), 2951, 2927, 2855 (C-H), 1682 (CO), 1461, 1251, 1091, 996, 773, 546 cm^{-1}. – ^1H NMR (500.15 MHz, $CDCl_3$): $\delta = 0.03$ (s, 6 H, $SiMe_2$), 0.85 (s, 9 H, $SiC(CH_3)_3$), 1.52 (br t, J = 12.1 Hz, 1 H, 2-H), 1.62 (br t, $J = 11.9$ Hz, 1 H, 4-H), 1.92 (ddd, $J = 12.6$ Hz, $J = 5.5$ Hz, $J = 2.3$ Hz, 2 H, 2-H, 4-H), 3.38 (br, 1 H, OH), 3.45 (br, 1 H, OH), 3.65 (sept, $J = 5.6$ Hz, 1 H, 3-H), 3.70 (s, 3 H, CH_3), 4.05 (d, $J = 4.8$ Hz, 2 H, 6-H, 7-H), 4.07, 4.18 (br s, 2 H, 1-H, 5-H). – $^{13}C\{^1H\}$ NMR (125.76 MHz, $CDCl_3$): $\delta = -4.7$ ($SiMe_2$), 18.0 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 37.7, 38.2 (C-2, C-4), 52.7 (OMe), 61.5, 61.8 (C-1, C-5), 64.5 (C-3), 73.2, 74.0 (C-6, C-7), 155.3 (COO). – MS (EI, 70 eV): m/z (%) = 331 (10) [M^+], 274 (100), 230 (15), 171 (25), 140 (35), 89 (40), 73 (40). – $C_{15}H_{29}NO_5Si$ (331.2): calcd. C 54.35, H 8.82, N 4.23; found C 54.45, H 8.85, N 4.18.

*Methyl 6-acetoxy-3-endo-{[tert-butyl(dimethyl)silyl]oxy}-7-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate (endo-**13**)*

Yield: 46 mg (0.12 mmol, 81 %), colorless oil. – M. p. 127 °C. – $R_f = 0.26$ (EtOAc/hexanes = 1 : 1). – IR (ATR): $\tilde{\nu} = 3445$ (OH), 2927, 2857 (C-H), 1744 (CO), 1702 (CO), 1463, 1233, 1093, 775, 683 cm^{-1}. – ^1H NMR (500.15 MHz, $CDCl_3$): $\delta = 0.03$ (s, 6 H, $SiMe_2$), 0.90 (s, 9 H, $SiC(CH_3)_3$), 1.78 (br t, $J = 15.2$ Hz, 2 H, 2-H, 4-H), 1.93 – 2.08 (m, 2 H, 2-H, 4-H), 2.11 (s, 3 H, Ac-CH_3), 2.21 – 2.29 (m, 1 H, OH), 3.71 (s, 3 H, CH_3), 4.00 (br s, 1 H, 3-H), 4.08 – 4.19 (m,

2 H, 1-H, 5-H), 4.80 (t, $J = 7.0$ Hz, 1 H, 7-H), 5.66 (d, $J = 6.1$ Hz, 1 H, 6-H). – $^{13}C\{^1H\}$ NMR (125.76 MHz, $CDCl_3$): $\delta = -5.2$ ($SiMe_2$), 17.8 ($SiC(CH_3)_3$), 20.9 (Ac-CH_3), 25.7 ($SiC(CH_3)_3$), 35.8, 36.0, 36.4, 36.8 (C-2, C-4), 52.5 (OCH_3), 59.2, 59.4, 62.4, 62.5 (C-1, C-5), 64.7 (C-3), 73.8, 74.4 (C-7), 75.9, 76.7 (C-6), 154.8 (COO), 170.3 (OCO). – MS (EI): m/z (%) = 373 (5) [M^+], 358 (40), 316 (100), 256 (80), 182 (35), 140 (40), 117 (70). – $C_{17}H_{31}NO_6Si$ (373.1): calcd. C 54.66, H 8.37, N 3.75; found C 54.74, H 8.32, N 3.66.

*Methyl 6-acetoxy-3-exo-{[tert-butyl(dimethyl)silyl]oxy}-7-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate (exo-**13**)*

Yield: 34 mg (0.10 mmol, 68 %), colorless crystals. – M. p. 130 °C. – $R_f = 0.24$ (EtOAc/hexanes = 1 : 1). – IR (ATR): $\tilde{\nu} = 3415$ (OH), 2953, 2857 (C-H), 1710 (CO), 1686 (CO), 1463, 1255, 1098, 1004, 835, 774, 672 cm^{-1}. – ^1H NMR (500.15 MHz, $CDCl_3$): $\delta = 0.03$ (s, 6 H, $SiMe_2$), 0.85 (s, 9 H, $SiC(CH_3)_3$), 1.55 (br t, $J = 11.9$ Hz, 1 H, 2-H), 1.66 (br t, $J = 11.9$ Hz, 1 H, 4-H), 1.92 – 2.98 (m, 2 H, 2-H, 4-H), 2.13 (s, 3 H, Ac-CH_3), 2.23 (br, 1 H, OH), 3.69 – 3.76 (m, 1 H, 3-H), 3.72 (s, 3 H, CH_3), 4.10 – 4.24 (m, 3 H, 1-H, 5-H, 7-H), 4.92 (br s, 1 H, 6-H). – $^{13}C\{^1H\}$ NMR (125.76 MHz, $CDCl_3$): $\delta = -4.6$ ($SiMe_2$), 18.0 ($SiC(CH_3)_3$), 20.8 (Ac-CH_3), 25.7 ($SiC(CH_3)_3$), 37.3, 38.0 (C-2, C-4), 52.6 (OCH_3), 58.8, 61.9 (C-1, C-5), 64.3 (C-3), 73.6, 74.3 (C-6), 75.5, 76.2 (C-7), 154.7 (COO), 170.6 (OCO). – MS (EI, 70 eV): m/z (%) = 373 (5) [M^+], 358 (40), 316 (100), 256 (80), 182 (35), 140 (40), 117 (70). – $C_{17}H_{31}NO_6Si$ (373.1): calcd. C 54.66, H 8.37, N 3.75; found C 54.85, H 8.35, N 3.72.

*Chemical acetylation of separated endo- and exo-diol **12***

Method B: To stirred solution of *endo*-**12** or *exo*-**12** (10 mg, 30 μmol) in absolute pyridine (0.5 mL) was added Ac_2O (3 μL, 30 μmol). After stirring for 24 h, the reaction mixture was directly analyzed by capillary GC.

Method C: To a stirred solution of *exo*-**12** (30 mg, 89 μmol) and Et_3N (50 μL, 0.36 mmol) in absolute CH_2Cl_2 (1.5 mL) was added AcCl (6.4 μL, 89 μmol). The reaction mixture was stirred at r. t. for 0.5 h, concentrated under vacuum and diluted with EtOAc (10 mL). The organic layer was washed with 0.1 N NaOH/H_2O and brine (10 mL each), dried (Na_2SO_4) and concentrated. Purification by flash chromatography on SiO_2 with EtOAc/hexanes (1 : 1) gave *exo*-**13** (26 mg, 69.6 μmol, 78 %) and the corresponding diacetate as byproduct (1.1 mg, 2.7 μmol, 3 %).

Method D: To a stirred solution of *endo*-**12** or *exo*-**12** (10 mg, 30.2 μmol), DMAP (1 mg, 10 μmol) and DCC (11 mg, 53.4 μmol) in absolute CH_2Cl_2 (0.5 mL) were added 0.5 mL of a solution of AcOH (5.1 mL, 90.6 μmol) in absolute CH_2Cl_2 (1.5 mL), and the reaction mixture was stirred at r. t.. Aliquots were taken after 0.2, 0.5, and 1 h and directly analyzed by capillary GC.

*(R)-(+)-MTPA ester (**9a** and **9b**)*

To a solution of **5a** (12 mg, 46.7 μmol) in absolute pyridine (0.5 mL) was added (*S*)-(+)-MTPACl (15 μL). The reaction mixture was stirred for 2 h, concentrated with toluene (3 × 1 mL), and the residue chromatographed on SiO_2 (EtOAc/hexanes (2 : 1), $R_f = 0.52$) to give the diastereomeric esters **9a** and **9b** (15.7 mg, 33.2 μmol, 71 %) as a colorless solid. – ^1H NMR (500.15 MHz, $CDCl_3$, 215 K)*: $\delta = 1.56$ (s, 3 H, Ac-CH_3, **9a**′), 1.61 (s, 3 H, Ac-CH_3, **9a**), 1.83 (s, 3 H, Ac-CH_3, **9b**), 1.92 (s, 3 H, Ac-CH_3, **9b**′), 2.56 – 2.79 (m, 4 H, 2-H, 4-H), 3.48 (s, 3 H, OMe, **9b**), 3.50 (s, 3 H, OMe, **9a**), 3.51 (s, 3 H, OMe, **9a**′), 3.53 (s, 3 H, OMe, **9b**′), 3.67 (s, 3 H, $COOCH_3$, **9b**), 3.72 (s, 3 H, $COOCH_3$, **9b**′), 3.73 (s, 3 H, $COOCH_3$, **9a**), 3.75 (s, 3 H, $COOCH_3$, **9a**′), 4.44 – 4.62 (m, 2 H, 1-H, 5-H), 4.91 (t, $J = 6.2$ Hz, 2 H, 6-H, 7-H), 5.04 (dd, $J = 13.4$ Hz, $J = 6.4$ Hz, 2 H, 6-H, 7-H), 5.12 (dd, $J = 9.9$ Hz, $J = 6.4$ Hz, 2 H, 6-H, 7-H), 5.26 (dd, $J = 6.4$ Hz, $J = 3.2$ Hz, 2 H, 6-H, 7-H), 7.37 – 7.45 (m, 5 H, Ar). (* Arbitrary numbering of the diastereomers).

*(R)-(+)-MTPA ester (endo-**14a**, endo-**14b**)*

Yield: 23.5 mg (39.9 μmol, 99 %), colorless solid. – $R_f =$ 0.36 (EtOAc/hexanes = 1 : 3). – ^1H NMR (500.15 MHz, $CDCl_3$, 298 K)*: $\delta = 0.09$ (s, 6 H, $SiMe_2$), 0.95 (s, 9 H, $SiC(CH_3)_3$), 1.64 (s, 3 H, Ac-CH_3), 1.69 (s, 3 H, Ac-CH_3), 1.81 (s, 3 H, Ac-CH_3), 1.88 (s, 3 H, Ac-CH_3), 1.84 – 2.11 (m, 4 H, 2-H, 4-H), 3.51 – 3.56 (m, 3 H, OMe), 3.64 (s, 3 H, $COOCH_3$), 3.69 (s, 3 H, $COOCH_3$), 3.70 (s, 3 H, $COOCH_3$), 3.72 (s, 3 H, $COOCH_3$), 4.07 (s, 1 H, 3-H), 4.16 – 4.33 (m, 2 H, 1-H, 5-H), 5.78 (d, $J = 5.9$ Hz, 1 H, 6-H), 5.83 (s, 2 H, 7-H), 5.91 (d, $J = 6.1$ Hz, 1 H, 6-H), 7.37 – 7.45 (m, 5 H, Ar). (* Arbitrary numbering of the diastereomers).

*(R)-(+)-MTPA ester (exo-**14a**, exo-**14b**)*

12.7 mg (21.6 μmol, 80 %), colorless solid. – $R_f = 0.32$ (EtOAc/hexanes = 1 : 3). – ^1H NMR (500.15 MHz, $CDCl_3$, 298 K)*: $\delta = 0.06$ (s, 6 H, $SiMe_2$), 0.86 (s, 9 H, $SiC(CH_3)_3$), 1.64 (s, 3 H, Ac-CH_3), 1.69 (s, 3 H, Ac-CH_3), 1.81 (s, 3 H, Ac-CH_3), 1.88 (s, 3 H, Ac-CH_3), 1.84 – 2.11 (m, 4 H, 2-H, 4-H), 3.50 (s, 3 H, OMe), 3.51 (s, 3 H, OMe), 3.53 (s, 3 H, OMe), 3.56 (s, 3 H, OMe), 3.66 – 3.78 (m, 3 H, $COOCH_3$), 3.76 – 3.82 (m, 1 H, 3-H), 4.19 – 4.37 (m, 2 H, 1-H, 5-H), 5.03 (d, $J = 6.1$ Hz, 1 H, 6-H), 5.11 (t, $J = 7.2$ Hz, 1 H, 7-H), 5.17 (t, $J = 6.9$ Hz, 1 H, 7-H), 5.25 (br, 1 H, 6-H), 7.37 – 7.45 (m, 5 H, Ar). (* Arbitrary numbering of the diastereomers).

Screening procedure for the lipase-catalyzed resolution

To a solution of **4a** (15 mg, 0.07 mmol) or *endo*-**12**, *exo*-**12** (10 mg, 0.03 mmol each) in the respective solvent (Table 1) were added vinyl acetate (13 μL or 10 μL), molecular sieves 4 Å (4 pellets) and the respective enzyme (2000 – 10000 U; units according to the manufacturer's information, respective 2 – 15 mg). The reaction mixture was stirred at 40 °C. At time

intervals from 0.5 to 4 h and sedimentation of the enzyme, aliquots of 30 μL were taken from the supernatant, filtered, diluted with CH_2Cl_2 (300 μL) and directly analyzed by capillary GC. The reaction was terminated after 48 h.

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