Synthesis of Enantiopure 9-Oxabicyclononanediol Derivatives by Lipase-Catalyzed Transformations and Determination of Their Absolute Configuration

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Dedicated to Professor Manfred Mühlstädt on the occasion of his 75th birthday

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Mixtures of *endo*,*endo*-9-oxabicyclo[4.2.1]nonane-2,5-diol (*meso*-**2**) and *endo*,*endo*-9-oxabicyclo[3.3.1]nonane-2,6-diol [(±)-**3**] were prepared from cycloocta-1,5-diene (**1**) upon treatment with peracids by transannular *O*-heterocyclization and subsequent saponification of the formed diol monoesters such as (±)-**4** and (±)-**5**. The corresponding diacetates, *meso*-**6** and (±)-**7**, were formed by acetylation of either *meso*-**2** and (±)-**3** or (±)-**4** and (±)-**5** with acetic anhydride/pyridine. These diacetates were enantioselectively hydrolyzed by microbial enzymes such as the lipases from *Candida antarctica* (CAL) or *Candida rugosa* (CRL). The corresponding enantiomers were formed by lipase-catalyzed acetylation of the diols *meso*-**2** and (±)-**3** with vinyl acetate. The skeletal isomers can also be separated in this way because the enantiopure monoacetates **4** were formed from the *meso*-compounds **2** or **6**, while one enantiomer of the racemic diacetate (±)-**7** [or the diol (±)-**3**] was transformed into the enantiopure diol **3** (or the enantiopure diacetate **7**, respectively) via the corresponding enantiomers of the monoacetate **5**. The other enantiomer remained untouched in both cases. The lipases reacted enantioselectively to give the *R* isomer. Cycloocta-1,5-diene (**1**) was also used to synthesize 2-oxa-6-thiatricyclo[3.3.1.1^{3,7}]decane-4,8-diol [(±)-**11**] in a four-step sequence. This racemic diol was also acetylated selectively (*R* isomer) with vinyl acetate and CRL. Reductive desulfuration of (±)-**11** gave *exo*,*exo*-9-oxabicyclo[3.3.1]nonane-2,6-diol [(±)-**12**], which was acetylated selectively (*S* isomer) with CRL under the same conditions. The similarity in size and particularly in shape is responsible for the observed stereoselectivity of the lipases for the racemic *endo*,*endo* compounds (±)-**3** and (±)-**7** on the one hand and the *exo*,*exo* compound (±)-**12** on the other hand. The absolute configuration and crystal packing of the products was determined by X-ray structural analysis.

Introduction

Small enantiopure molecules, due to their versatile potential as starting materials in the synthesis of natural products, are favored targets for enzymatic desymmetrization of prochiral compounds or resolution of racemates.[1−5] Moreover, such molecules gain interest as auxiliaries or as a source of ligands for catalytically active metal complexes for asymmetric synthesis.[6−10] Consequently, new ways to synthesize such compounds are desirable. In this context we became interested in several enantiopure polycyclic diols, which are available from cycloocta-1,5-diene (**1**).

There are several alternatives described in the literature to produce the diols **2** and **3** from the diene **1** by treatment with peracids and subsequent transformation of the primary products.[11−15] The ratio of the two skeletal isomers, which are formed by transannular *O*-heterocyclization, can be influenced slightly by the nature of the applied reagents. Thus, treatment of compound **1** with performic acid formed in situ from formic acid and 30% hydrogen peroxide gave a 38:62 mixture of *meso*-**2** and (±)-**3** in 70% combined yield,[11,14] whereas a 1:1 mixture of these products was obtained from **1** by treatment with peracetic acid and subsequent saponification, although with a rather low yield of 28%.[13] A third alternative pathway by acid-catalyzed ring opening of the bis-epoxide of **1** and transannular *O*-heterocyclization gave a mixture of *meso*-**2** and (±)-**3** in 55% overall yield based on **1**.[15] Unfortunately, separation of the isomeric diols *meso*-**2** and (±)-**3** or the corresponding diacetates *meso*-**6** and (±)-**7** by either crystallization or column chromatography was very difficult on a preparative scale. Consequently, we designed a lipase-catalyzed separation: acetylation with hydrolytic enzymes as catalysts transformed *meso*-**2** into the enantiopure monoester **4**. Similarly, one enantiomer of (±)-**3** should give the corresponding diester **7**, while the other should remain untouched. Starting from the diacetates *meso*-**6** and (±)-**7** the other enantiomers should be available in each case. Several reviews on lipase-catalyzed desymmetrizations and kinetic resolutions have been published.[16−19]

Recently, we communicated the application of *Candida rugosa* lipase (CRL) for this purpose,[20] and we now report

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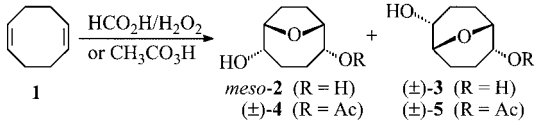
the results with alternative hydrolases, the assignment of the absolute configuration of the products and the crystal packing of the enantiopure compounds. In forthcoming papers, these chiral compounds will be applied as building blocks.

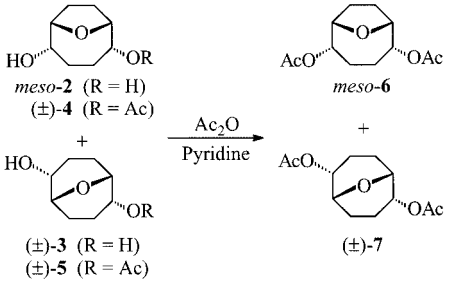
Results and Discussion

It has already been mentioned that compounds *meso*-**2** and (±)-**3** can be synthesized by different methods. According to the protocol of Eaton and Millikan[14] we obtained a 40:60 mixture of the diols *meso*-**2** and (±)-**3** in 65% yield, while we also improved the yield of Ganter's[13] procedure of reaction of **1** with 32% peracetic acid. A 64:36 mixture of the monoacetates (±)-**4** and (±)-**5** was obtained in 38% yield (Scheme 1).



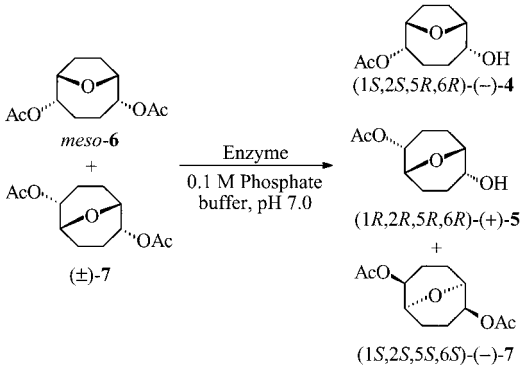
Scheme 1

Hydrolytic enzymes such as esterases and lipases have traditionally been employed for ester hydrolysis in buffer systems. Thus, mixtures of the diols *meso*-**2** and (±)-**3** (40:60) or mixtures of corresponding monoacetates (±)-**4** and (±)-**5** (64:36) were first transformed into the diacetates *meso*-**6** and (±)-**7** by reaction with acetic anhydride/pyridine (Scheme 2). The mixture of these diacetates, in contrast to the diols *meso*-**2** and (±)-**3** or the monoacetates (±)-**4** and (±)-**5**, could be partially separated by repeated recrystallization[13] or extensive column chromatography.



Scheme 2

Subsequently, the activity and selectivity of different lipases and esterases were tested in the hydrolysis of mixtures of diacetates *meso*-**6** and (±)-**7**, employed in different ratios depending on the mode of synthesis (Scheme 3).



Scheme 3

The reaction with porcine pancreatic lipase (PPL) showed only 6% conversion of the diacetates after two weeks and this line of investigation was therefore stopped. Porcine liver acetone powder (PLAP, Sigma, mostly porcine liver esterase[21,22]) was much more active and showed 53% conversion of the diacetates after 36 hours (Table 1). However, only the enantiomeric excess of (−)-**4** (92% *ee*) was satisfactory.

Hydrolysis of a 64:36 mixture of *meso*-**6** and (±)-**7** with *Candida antarctica* lipase B (CAL-B) after 48 hours showed a 36:9:10:45 mixture of (−)-**4** (80% *ee*), (+)-**5** (94% *ee*), *meso*-**6** and (−)-**7** (88% *ee*). The enantiomeric excesses were determined by ^{1}H NMR shift experiments using Eu(hfc)$_3$ (see Supporting Information). The minor amounts of diols that were also formed could not be extracted from the buffer system under the applied conditions.

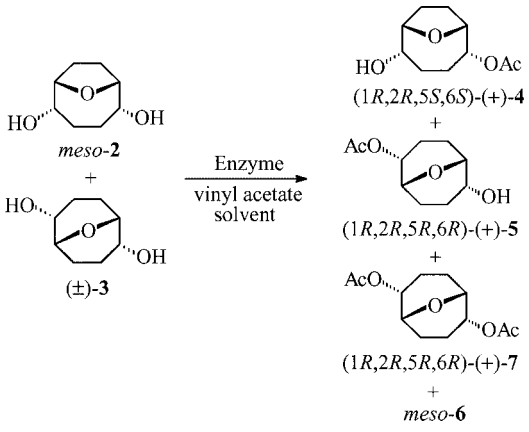
The best result with slightly enhanced enantioselectivity was obtained with *Candida rugosa* lipase (CRL): after 46 hours a conversion of 52% of the diacetates was reached and a 42 (94% *ee*):10 (>98% *ee*):9:39 (92% *ee*) mixture of the mentioned mono- and diesters was obtained. However, the separation of the skeletal isomers was not optimal in these transformations, although quite high enantiomeric excesses were obtained; the minor amounts of diols formed could also not be isolated, even by continuous extraction.

This disadvantage could be overcome by the use of organic solvents (Scheme 4). Moreover, in several cases the lipases exhibited better enantioselectivity in organic sol-

Table 1. Results of enzyme-catalyzed hydrolyses of the diacetates *meso*-**6** and (±)-**7**

Entry	Enzyme	Ratio of starting materials		Ratio of products		*ee*		Combined yield	Ratio of remaining substrates		*ee*	Combined yield
		meso-(**6**)	(±)-**7**	(−)-**4**	(+)-**5**	(−)-**4**	(+)-**5**	(%)	*meso*-(**6**)	(−)-**7**	(−)-**7**	(%)
1	PPL	68	32	n.d.		n.d.		6	64	36	n.d.	93
2	PLAP	53	47	84	16	92	28	53	24	76	n.d.	20
3	CAL-B	64	36	80	20	80	94	45	18	82	88	27
4	CRL	64	36	80	20	94	>98	52	19	81	92	26

vents than in aqueous systems.[23−27] Thus, we first investigated the transformation of a 40:60 mixture of *meso*-**2** and (±)-**3** with CAL-B and CRL with different acyl donors in different solvents (see Supporting Information). The transformations were shown to be most efficient and selective in pure vinyl acetate. In addition to the two lipases of *Candida sp.* the lipase of *Pseudomonas cepacia* (PCL) was also tested, because this lipase has been shown to transform other substituted and even heterocyclic alcohols to the corresponding esters with high enantioselectivity.[28−31]



Scheme 4

In the case of the acetylation of a 40:60 mixture of *meso*-**2** and (±)-**3** the optimal conversion was reached when the *meso*-[4.2.1]isomer **2** was quantitatively transformed to the monoacetate **4** and one enantiomer of the diol (±)-**3** was completely acetylated to one enantiomer of **5**. However, the latter monoacetate **5** is only an intermediate, and was further acetylated to the corresponding diacetate **7**. Unfortunately, the monoacetates (±)-**4** and (±)-**5** could not be separated by GC. Thus, it was difficult to follow up the conversion of the mixture of diols *meso*-**2** and (±)-**3**; the value of 70% consumption of the diols **2** and **3** was used as a criterion for the desired conversion. However, the reaction with PCL was stopped at the point when 66% (GC) of the diols had been consumed after three weeks of reaction (Table 2).[32]

For the remaining diol (−)-**3** (14% isolated yield, 3% impurity of *meso*-**2**) an enantiomeric excess of more than 98% was determined by chiral GC (E value > 200[33]). Moreover, a 48:52 mixture (^{1}H NMR) of the monoacetates (+)-**4** (28% *ee*) and (+)-**5** (60% *ee*) was isolated with 56% yield; 12% of a 21:79 mixture of the *meso*-diacetate **6** and the diacetate (+)-**7** (82% *ee*) was isolated. Thus, only the diol (−)-**3** was prepared as a pure skeletal isomer in enantiopure form. The other compounds exhibited low enantiomeric excesses and low chemical purity. This seems to be due to the fact that the monoacetates are acetylated to the corresponding diacetates *meso*-**6** or (+)-**7** very slowly. The esterification of the second OH group of **4** and **5** started only when about 60% of the diol mixture had already been monoacetylated. We therefore did not continue the investigations with this enzyme.

Next we used CAL-B, immobilized on a porous support and sold under the trade name Novozym®435 by Novo Nordisk. With vinyl acetate as the acylation reagent and solvent the acetylation stopped after 22% conversion of the diols *meso*-**2** and (±)-**3**. A 5:1 mixture of *tert*-butyl methyl ether (MTBE) and vinyl acetate was found to be more useful. The reaction of a 40:60 mixture of *meso*-**2** and (±)-**3** was stopped after six days. At this stage 57% conversion of the diols had occurred and a 13:87 mixture of the diols *meso*-**2** and (−)-**3** (>98% *ee*) was isolated from the product mixture by crystallization. Column chromatography of the mother liquor gave a 4:1 mixture of (+)-**4** (>98% *ee*) and (+)-**5** (95% *ee*) in 38% isolated yield; 18% of (+)-**7** (>98% *ee*, contaminated with 1% of *meso*-**6**) was also isolated. Although this lipase was able to transform the diols *meso*-**2** and (±)-**3** into the monoacetates with very high enantioselectivity (E value > 200), the reaction was very slow. Thus, we decided to apply CRL, which has been used for the esterification of secondary alicyclic alcohols, even sterically demanding ones.[34]

Initially, different solvents, different acetylation reagents, such as vinyl acetate, isopropenyl acetate and acetic anhydride, as well as different amounts of acetylation reagent and lipase were evaluated for the transformation of a 40:60 mixture of *meso*-**2** and (±)-**3** (see Supporting Information). With solvents such as toluene, *n*-heptane or cyclohexane the reaction stopped after 10−25% conversion of the diols after one week. In MTBE in the presence of two, three or four equivalents of vinyl acetate relative to the total amount of the diols *meso*-**2** and (±)-**3**, the reaction stopped after 32%, 53% or 63% conversion, respectively, after one week. Thus, we decided to use vinyl acetate as the acylation reagent and as the solvent. In contrast to the reaction with CAL-B, the acetylation was very fast in the case of the reaction of a 40:60 mixture of *meso*-**2** and (±)-**3**. After six hours, 67% of

Table 2. Results of enzyme-catalyzed acetylations of diols *meso*-**2** and (±)-**3** in vinyl acetate

Entry	Enzyme	Ratio of starting materials		Conversion of **2** and **3**	Ratio and *ee* (%) of products		Comb. yield of **4** and **5**	Ratio and *ee* (%) of products		Comb. yield of **6** and **7**	Ratio and *ee* (%) of remaining substrates		Comb. yield of **2** and **3**
		meso-(**2**)	(±)-**3**	(%)	(+)-**4**	(+)-**5**	(%)	*meso*-**6**	(+)-**7**	(%)	*meso*-(**2**)	(−)-**3**	(%)
1	PCL	40	60	66	48 (28)	52 (60)	56	21	79 (82)	12	3	97 (>98)	14
2	CAL-B	40	60	57	80 (>98)	20 (95)	38	1	99 (>98)	18	13	87 (>98)	23
3	CRL	40	60	67	68 (>98)	32 (80)	40	6	94 (>98)	10	0	100 (>98)	14

the total content of the diols had been consumed. After work up, three fractions of products were isolated; 14% of (−)-**3** (>98% *ee*) was isolated by crystallization as a pure skeletal isomer (E value >200). This compound was used to determine the absolute configuration (vide infra). A 68:32 mixture of the monoesters (+)-**4** (>98% *ee*) and (+)-**5** (80% *ee*) was isolated in 38% yield by column chromatography. Additionally, the diacetate (+)-**7** (>98% *ee*, contaminated with 6% of *meso*-**6**) was separated in 10% yield.

In summary, three practically enantiopure compounds of both enantiomeric series were produced either by lipase-catalyzed hydrolysis of the mixture of diacetates *meso*-**6** and (±)-**7** or by acetylation of the mixture of diols *meso*-**2** and (±)-**3**. However, the absolute configuration of these compounds remained to be determined.

From the literature[35−37] it is known that CRL according to Kazlauskas' rule prefers the enantiomer shown in Figure 1. This is the (*R*)-enantiomer in cases where the larger substituent has also the higher priority according to the Cahn−Ingold−Prelog (CIP) rule.[38,39] This is true for the acetylation of *meso*-**2** and (±)-**3**, and was observed earlier also in hydrolysis of *endo*,*endo*-2,6-diacetoxybicyclo-[3.3.1]nonane.[40]

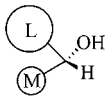


Figure 1. Enantiomer preferably transferred by CRL according to Kazlauskas' rule[36,37] (adapted to the investigated diols)

In order to determine the absolute configuration of the products the diol (−)-**3**, which remained unchanged in the CRL-catalyzed acetylation of the mixture of the diols *meso*-**2** and (±)-**3**, was recrystallized and excellent crystals were grown for X-ray structural analysis. Due to the very small error in the enantiopole parameter, the absolute configuration of (−)-**3** could be determined directly to be (1*S*,2*S*,5*S*,6*S*)-(−)-9-oxabicyclo[3.3.1]nonane-2,6-diol (Figure 2). Consequently, the absolute configuration of the monoacetylation product must be (1*R*,2*R*,5*R*,6*R*)-(+)-**5** and that of the diacetate must be (1*R*,2*R*,5*R*,6*R*)-(+)-**7**. Since in all acetylation experiments with CRL, CAL-B or PCL the same sign of optical rotation was found for the corresponding compounds, all these lipases must be (*R*)-selective with these substrates.

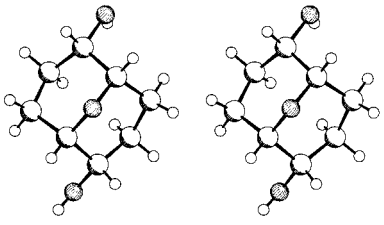


Figure 2. Stereoview of (1*S*,2*S*,5*S*,6*S*)-(−)-9-oxabicyclo[3.3.1]nonane-2,6-diol [(−)-**3**]

In order to determine the absolute configuration of the monoacetate (+)-**4** and to separate impurities of (+)-**5**, several derivatives such as the mesylates, the *N*-phenylcarbamates, the (1*S*)-camphor-10-sulfonates and the carbamates with (*R*)-(+)-phenylethyl isocyanate were synthesized (see Supporting Information). However, these derivatives could not be isolated as pure skeletal isomers, and therefore were not suitable for the determination of the absolute configuration of (+)-**4**. In a different context, the (1*R*,2*R*,5*S*,6*S*)-configuration of (+)-**4** was indirectly determined by X-ray structural analysis of a tricyclic 1,4-dithiepane derivative produced from (+)-**4** by selective oxidation of the hydroxy group and subsequent reaction of the formed ketone with propane-1,3-dithiol.[41]

The X-ray analysis of (1*S*,2*S*,5*S*,6*S*)-(−)-**3** allowed interesting insights into the crystal packing of this compound. The elemental cell along the *y*-axis (Figure 3) shows a layer structure. The diameter of one layer is about 4.2 Å. The layers are linked to each other with hydrogen bonds between the OH groups. The OH···O contact is about 1.91 Å, the O···O distance is about 2.74 Å and the O−H−O angle is about 174°.

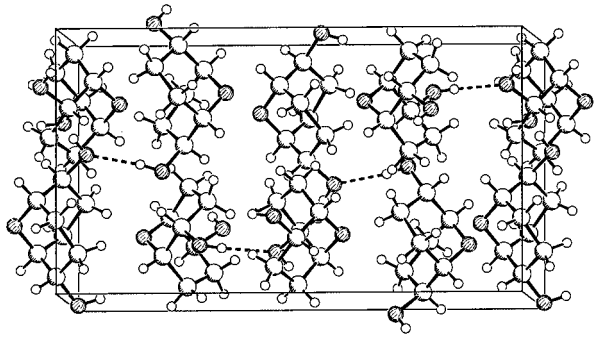


Figure 3. View of the elemental unit of (1*S*,2*S*,5*S*,6*S*)-(−)-9-oxabicyclo[3.3.1]nonane-2,6-diol (−)-**3** along the *y*-axis

The view in the direction of the *z*-axis (Figure 4) shows a supramolecular structure with two types of channels. The

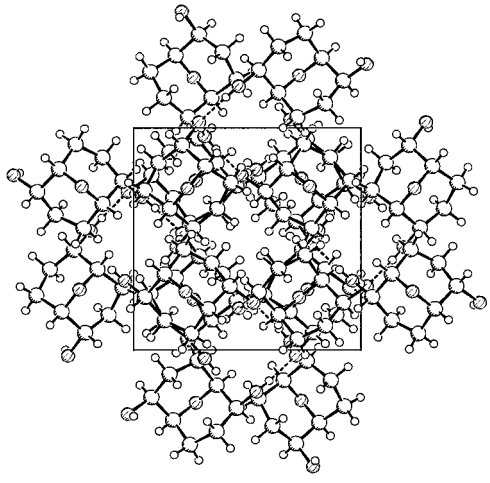
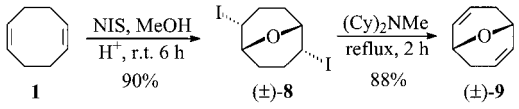


Figure 4. View of the elemental unit of (1*S*,2*S*,5*S*,6*S*)-(−)-9-oxabicyclo[3.3.1]nonane-2,6-diol (−)-**3** along the *z*-axis

non-polar type (center) is coated with the equatorial protons at C-3 and C-7. In the second, more polar and bigger (8.8 Å in diameter) channel, OH groups are involved. It is noteworthy that a 4_3 helical axis causes a permutation of one upon the other molecules.

A similar observation has also been made for racemic *exo*,*exo*-2,6-dimethyl-9-oxabicyclo[3.3.1]nonane-2,6-diol.[42−44] For this compound, which has an opposite orientation of the OH groups compared to **3**, additional hydrogen bonds were observed.[43] Moreover, the channels in the crystalline state were shown to be much bigger, and hence inclusion compounds were formed with a variety of small organic molecules.[44] Because of the smaller cavities, the *endo*,*endo*-diol (−)-**3** could not be co-crystallized with chiral molecules and hence could not be used for racemate resolution. In order to elucidate whether bigger cavities could be obtained from the diastereomer, we next synthesized *exo*,*exo*-9-oxabicyclo[3.3.1]nonane-2,6-diol (**12**) in enantiopure form.

This compound cannot be synthesized by an S_N2 reaction, for example from the tosylate or mesylate of (−)-**3**, for steric reasons. However, for the racemic compound a synthesis has been reported.[13] We modified and optimized this synthetic sequence. First *endo*,*endo*-2,6-diiodo-9-oxabicyclo-[3.3.1]nonane [(±)-**8**] was synthesized from diene **1**, according to our procedure,[45] by transannular *O*-heterocyclization with *N*-iodosuccinimide (NIS) and methanol in 90% isolated yield as a pure skeletal isomer (Scheme 5). Other protocols for transannular *O*-heterocyclization reactions using different electrophiles have, in most cases, led to mixtures of skeletal isomers.[46−58]



Scheme 5

X-ray analysis (Figure 5) shows that any S_N2 replacement of iodine is impossible. From the drawing it becomes obvious as well that HI elimination, which must be the next step in the synthesis, will need a conformational change because the *anti*-periplanar arrangement of H and I necessary for an E2 process is not possible in the most stable chair-chair conformation of compound (±)-**8**.

However, such an arrangement is possible in a boat conformation. Thus, treatment of (±)-**8** with KOH in ethanol

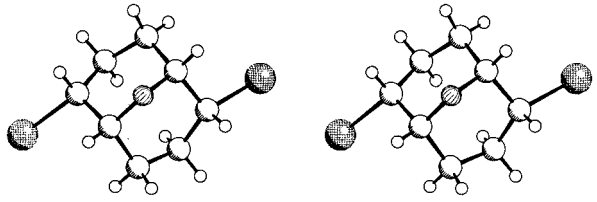


Figure 5. Stereoview of *endo*,*endo*-(±)-2,6-diiodo-9-oxabicyclo-[3.3.1]nonane [(±)-**8**]

at 120 °C in an autoclave for 96 hours[59] gave 40% of the diene (±)-**9**. By modification of a protocol of Stetter and Heckel,[60,61] we obtained the diene (±)-**9** as a crystalline compound in 88% yield by refluxing the diiodide (±)-**8** with dicyclohexylmethylamine.

X-ray analysis of this diene (Figure 6) showed that the double bonds can approach each other and therefore they are suitable for another transannular heterocyclization.

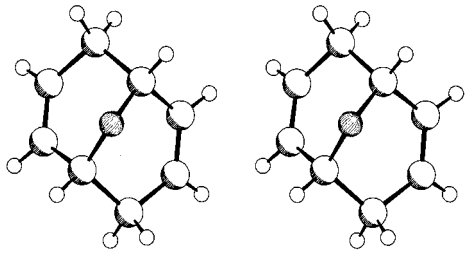
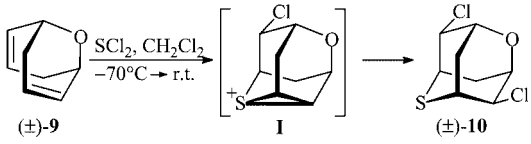


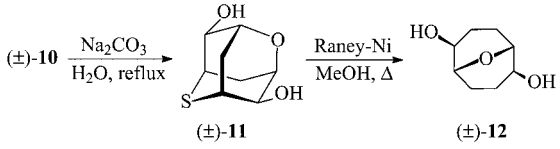
Figure 6. Stereoview of (±)-9-oxabicyclo[3.3.1]nona-2,6-diene [(±)-**9**]

Such a transannular *S*-heterocyclization was reported almost simultaneously by Stetter et al.[59] and by Ganter and Wicker more than three decades ago.[62] According to the published procedure,[59] treatment of the diene (±)-**9** with dichlorosulfane gave, after chromatographic purification, 4,8-dichloro-2-oxa-6-thiaadamantane [(±)-**10**] as a single diastereomer in 45% yield via the episulfonium ion **I** (Scheme 6).



Scheme 6

The X-ray structure of compound (±)-**10** (see Supporting Information) shows that nucleophilic substitution of chlorine by an oxygen function is favored by anchimeric assistance of sulfur, again giving the episulfonium ion **I**, which, in turn, can be opened by an oxygen nucleophile. Thus, refluxing of compound (±)-**10** with concentrated aqueous sodium carbonate[62] gave the diol (±)-**11** in 59% isolated yield (Scheme 7).



Scheme 7

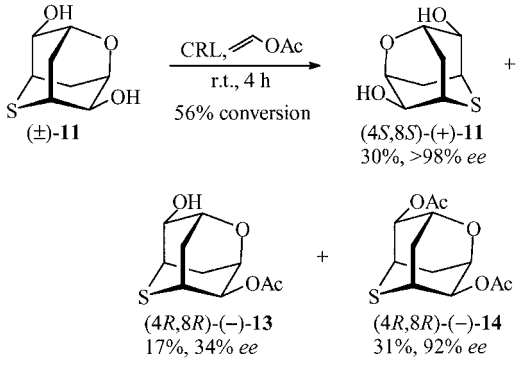
An alternative two-step procedure, involving refluxing of the dichloride (±)-**10** with potassium acetate in DMF and subsequent saponification of the formed diacetate, did not improve the yield of (±)-**11**. The relative configuration of

product (±)-**11** was proven by X-ray structural analysis (see Supporting Information).

The synthesis of compound (±)-**12** was completed by reductive desulfuration with Raney-nickel, which gave the desired *exo*,*exo*-9-oxabicyclo[3.3.1]nonane-2,6-diol [(±)-**12**] in 63% yield. This diol was contaminated with 5% of the *endo*,*exo*-diol showing that the nucleophilic substitution of chlorine with oxygen was not completely diastereoselective (see Supporting Information). The corresponding dihydroxyoxathiaadamantane could not be isolated from the reaction mixture of the nucleophilic substitution step.

With the racemic diols (±)-**11** and (±)-**12** in hand, we now investigated the lipase-catalyzed acetylation in order to compare the enantioselectivity of the lipase of *Candida rugosa* towards these compounds. Comparing the molecular geometry of the corresponding enantiopure diols **3** and **11** (cf. Figure 10) their similarity in size becomes obvious. Thus, we also expected (*R*)-selectivity of the CRL (see discussion in ref.[20]).

This lipase reacted very fast with the racemic tricyclic diol (±)-**11** to give the monoacetate (−)-**13** and the diacetate (−)-**14**: after four hours 56% of racemic (±)-**11** had already been consumed (Scheme 8).



Scheme 8

The remaining diol (+)-**11** (31% isolated yield) had more than 98% *ee* (*E* value 34). A second fraction isolated in 17% yield by column chromatography contained the monoacetate (−)-**13** (34% *ee*). The third fraction, the diacetate (−)-**14** (92% *ee*), was isolated in 31% yield. Single crystals of the diol (+)-**11** were grown and an X-ray crystal structural analysis was performed. The presence of the sulfur atom allowed us to determine the absolute configuration of this compound to be (1*S*,2*S*,4*S*,5*S*,7*S*,8*S*)-(+)-2-oxa-6-thiaadamantane-4,8-diol [(+)-**11**] (Figure 7). Thus, (*R*)-selectivity of the lipase was also observed for this tricyclic heterocycle.

Compound (1*S*,2*S*,4*S*,5*S*,7*S*,8*S*)-(+)-(**11**) crystallized in the orthorhombic space group $P2_12_12_1$, with hydrogen bonds between the hydroxyl groups attached to C-4 and C-8 contributing to the high symmetry of the crystal system; large channels were not found in the crystal packing.

Next we investigated the CRL-catalyzed acetylation of the C_2-symmetric *exo*,*exo*-diol (±)-**12**. According to the investigations of Griengl et al.[63] bicyclo[2.2.1]- and bicyclo-

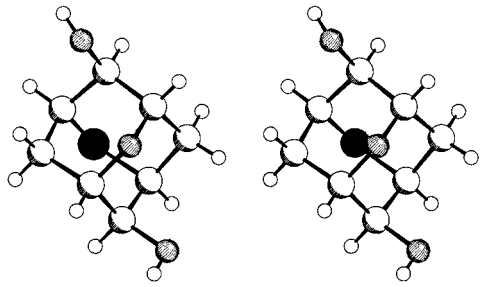
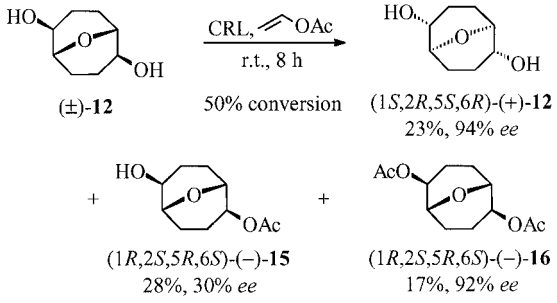


Figure 7. Stereoview of (1*S*,2*S*,4*S*,5*S*,7*S*,8*S*)-(+)-2-oxa-6-thiaadamantane-4,8-diol (+)-(**11**)

[2.2.2]alkanols bearing an OH group in the *exo*-position are not acetylated with CRL. In our case, under the conditions mentioned for the reactions of the diols (±)-**3** and (±)-**11**, one enantiomer of the *exo*,*exo*-diol (±)-**12** was acetylated, although with a lower reaction rate than the other abovementioned diols. After a reaction time of eight hours 50% conversion of the racemate was detected and three compounds were found in the reaction mixture (Scheme 9).



Scheme 9

This mixture was separated by column chromatography. The diol (+)-**12** (94% *ee*, *E* value 115) eluted as the last compound from the column and was isolated in 23% yield. For the monoacetate (−)-**15**, isolated in 28% yield, a quite low enantiopurity of only 30% *ee* was detected. The diacetate (−)-**16** (92% *ee*) was isolated in 17% yield.

The diol (+)-**12** was recrystallized from acetone and single crystals were obtained. X-ray crystallography showed a tetragonal space group $P4_12_12$ (Figure 8). No big cavities were found in the packing scheme of this compound (see Supporting Information).

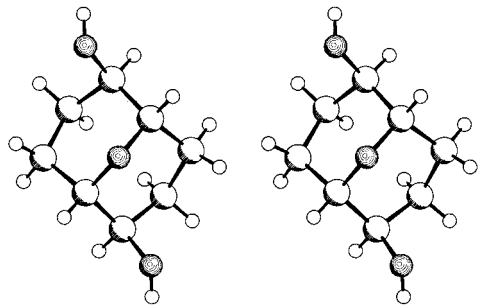
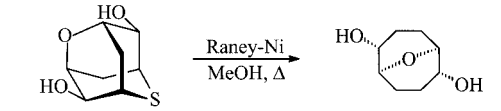


Figure 8. Stereoview of (1*S*,2*R*,5*S*,6*R*)-(+)-9-oxabicyclo[3.3.1]nonane-2,6-diol [(+)-**12**]

The assignment of the absolute configuration was not possible in a direct way due to the absence of a heavy atom and a too big error of the enantiopole parameter, but was successful indirectly. Reductive desulfuration of the enantiopure (1*S*,2*S*,4*S*,5*S*,7*S*,8*S*)-(+)-2-oxa-6-thia-adamantane-4,8-diol [(+)-**11**] with Raney nickel gave enantiopure (1*S*,2*R*,5*S*,6*R*)-(+)-9-oxabicyclo[3.3.1]nonane-2,6-diol [(+)-**12**] (Scheme 10).



(1*S*,2*S*,4*S*,5*S*,7*S*,8*S*)-(+)-**11** (1*S*,2*R*,5*S*,6*R*)-(+)-**12**

Scheme 10

This product exhibited the same sign of optical rotation as the non-acetylated product in the kinetic resolution of (±)-**12** with CRL. As expected, the value of the specific rotation was slightly bigger ($[\alpha]_D^{20}$ = +25.4), due to the higher enantiomeric excess (>98% *ee*) in relation to +24.5 (94% *ee*) obtained for the diol (+)-**12** not acetylated in the resolution reaction. Thus, CRL acetylates the *exo*,*exo*-diol (±)-**12** (*S*)-selectively.

Comparing the acetylation of the three C_2-symmetric diols **3**, **10** and **12** it is noteworthy to mention that all compounds were transformed with very high enantioselectivity; *endo*,*endo*-2,6-diacetoxybicyclo[3.3.1]nonane can also be hydrolyzed with high enantioselectivity.[40] In order to find an explanation for the opposite stereoselectivity of the lipase in the transformation of *exo*,*exo*-diol (±)-**12**, in addition to the X-ray structures, the most stable conformations of these compounds were calculated (AM1) to exclude steric distortions caused by packing effects. The calculated conformations did not differ from the structures found in the crystal (Figure 9).

While the (*R*,*R*)-enantiomers of the *endo*,*endo*-diol (±)-**3** and the tricyclic diol (±)-**11** were acetylated, as expected from Kazlauskas' rule,[36] the enzyme prefers the (*S*,*S*)-enantiomer of *exo*,*exo*-diol (±)-**12**. A comparison of the molecular geometry of all the faster-acetylated enantiomers indicates that the shape of these molecules is very similar (Figure 9); the (*R*)-selectivity in the CRL-catalyzed hydrolysis of the diacetates of racemic bicyclo[3.3.1]nonane-2,6-diol[40] also fits into this picture.

As mentioned above, the absolute configuration of the *endo*,*endo*-monoacetate (+)-**4** — the product of acetylation of *meso*-**2** by CRL — could not be determined directly. According to Kazlauskas' rule, this compound with CRL/vinyl acetate should be acetylated at the (*R*)-center. This assumption is supported by the following consideration: Comparison of the projections of the (*R*)-center and the (*S*)-center of *meso*-**2** with the (*R*)-center of the diol (*R*,*R*)-**3** suggests strongly that the environments of the (*R*)-centers of **2** and **3** are much more similar (Figure 10). By comparison of these two projections the (*R*)-center of **2** should also be transformed selectively. As mentioned above, this assumption was proven by X-ray structural analysis of a derivative obtained after Jones oxidation of (2*R*,5*S*)-(+)-**4** and subsequent treatment of the formed ketone with 1,3-propanethiol.[41]

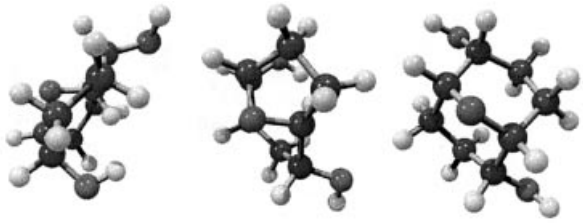


Figure 10. Comparison of the projections of the (5*S*)- and the (2*R*)-centers of *meso*-**2** with (2*R*,6*R*)-**3**

Conclusion

A very simple one-pot reaction of the bulk chemical cycloocta-1,5-diene (**1**) with peracids gave mixtures of *endo*,*endo*-9-oxabicyclo[4.2.1]nonane-2,5-diol (**2**) and *endo*,*endo*-9-oxabicyclo[3.3.1]nonane-2,6-diol [(±)-**3**] by transannular *O*-heterocyclization and hydrolysis. Applying (*R*)-selective lipases, simultaneous separation of the skeletal isomers, desymmetrization of *meso*-**2** and kinetic resolution of (±)-**3**, three practically enantiopure compounds, namely (1*S*,2*S*,5*S*,6*S*)-(−)-9-oxabicyclo[3.3.1]nonane-2,6-diol (−)-**3**, (1*R*,2*R*,5*S*,6*S*)-(+)-2-acetoxy-9-oxabicyclo[4.2.1]nonan-5-ol (+)-**4** [contaminated with 20% of (+)-**5**] and (1*R*,2*R*,5*R*,6*R*)-(+)-2,6-diacetoxy-9-oxabicyclo[3.3.1]-nonane (+)-**7** were isolated. The enantiomers of these com-

Figure 9. View of the four C_2-symmetric substrates preferentially transformed by the lipase of *Candida rugosa* (CRL): (a) (1*R*,2*R*,5*R*,6*R*)-(+)-9-oxabicyclo[3.3.1]nonane-2,6-diol [(+)-**3**], (b) (1*R*,3*R*,4*R*,5*R*,7*R*,8*R*)-(−)-2-oxa-6-thiaadamantane-4,8-diol [(−)-**11**], (c) (1*R*,2*S*,5*R*,6*S*)-(−)-9-oxabicyclo[3.3.1]nonane-2,6-diol [(−)-**12**], (d) (1*S*,2*R*,5*S*,6*R*)-(+)-2,6-diacetoxybicyclo[3.3.1]nonane

pounds were available using the same lipases to catalyze the hydrolysis of the corresponding diacetates *meso*-**6** and (±)-**7**. *Candida rugosa* lipase (CRL) was shown to be the most efficient for both types of reaction. Analogously, 2-oxa-6-thiatricyclo[3.3.1.1^{3,7}]decane-4,8-diol [(±)-**11**] and *exo*,*exo*-9-oxabicyclo[3.3.1]nonane-2,6-diol [(±)-**12**] were resolved by CRL-catalyzed acetylation. While the diols *meso*-**2**, (±)-**3** and (±)-**11** or the diacetates (±)-**5** and *meso*-**6** were transformed (*R*)-selectively, the *exo*,*exo*-diol (±)-**12** was acetylated with (*S*)-selectivity by the same lipase under similar conditions. The similarity of the shape of the molecules is responsible for the observed stereoselectivity. The absolute configuration of the products and crystal packing were determined by X-ray crystallography. Forthcoming papers will describe synthetic applications of the thus-formed enantiopure building blocks.

Experimental Section

General Remarks: ^{1}H NMR (300.1 MHz) and ^{13}C NMR (75.5 MHz), if not otherwise stated, were recorded from ca. 20% solutions in $CDCl_3$ on a 300-MHz spectrometer. Chemical shifts are reported as δ values (ppm) relative to TMS (for ^{1}H as internal standard; for ^{13}C, $CDCl_3$, δ = 77.0 ppm was used as internal standard). The multiplicity of the ^{13}C signals was determined by the DEPT technique. Mass spectra (electron impact ionization, 70 eV) were recorded by GC/MS coupling. The conversion of substrates during enzymatic transformations was followed by GC on quartz capillary columns (25 m × 0.33 mm, 0.52 μm HP-5 and 30 m × 0.32 mm, 0.25 μm SPB-1, temperature program, 50 °C → 180 °C with 5 °C/min then from 180 °C → 280 °C with 30 °C/min heating rates with N_2 as the carrier gas). The ratio of compounds was determined by integration of the peak area and was not corrected. The products of enzymatic transformations were separated by column chromatography (silica gel, Merck 60, 70−230 mesh). The solvents are mentioned in the corresponding procedures. The enantiomeric excesses of the diols were determined by chiral GC on a β-cyclodextrin column (30 m × 0.25 mm, 0.25 μm, Beta-Dex™ 120, isotherm 170 °C for compounds **3** and **12**, and 190 °C for compound **11**; N_2 as carrier gas). The enantiomeric excesses of the mono- and diacetates were determined by ^{1}H NMR spectroscopy using Eu(hfc)$_3$ as a chiral shift-reagent. Optical rotations were measured with a polarimeter (Na_D line, λ = 589 nm). Microanalyses were carried out by the "Mikroanalytisches Laboratorium, Organische Chemie", University of Münster using a CHN-O analyzer. X-ray data sets were collected with CAD4 diffractometers. Programs used: data collection EXPRESS (Nonius B.V., 1994), data reduction MolEN (K. Fair, Enraf−Nonius B.V., 1990), structure solution SHELXS-97,[64] structure refinement SHELXL-97,[65] graphics SCHAKAL.[66]

Chemicals were purchased from Acros, Aldrich, Fluka, Sigma or Merck. Cycloocta-1,5-diene was kindly donated by Degussa-Hüls, Marl, Germany. The lipase from *Pseudomonas cepacia* (Amano PS) was a kind gift of Amano Pharmaceutical Co., Ltd., Nagoya, Japan. The lipase *Candida antarctica* (Novozym435®) was kindly donated by Novo Nordisk A/S, Copenhagen, Denmark. The lipase of *Candida rugosa* and porcine liver esterase (acetone powder, PLAP) were purchased from Sigma. According to a given protocol,[14] a 40:60 mixture of the diols **2** and **3** (31.0 g, 65%) was synthesized. Complete spectroscopic data of all prepared compounds are given in the Supporting Information.

Reaction of Cycloocta-1,5-diene (1) with Peracetic Acid: Similar to a known procedure,[13] a 32% peracetic acid solution in acetic acid (58.9 g, 242 mmol) was cooled to −5 °C and stirred vigorously. A solution of cycloocta-1,5-diene (**1**; 11.5 g, 106 mmol) in acetic acid (22 mL) was added dropwise over a period of 2 hours, and the temperature was kept between −5 °C and 0 °C. This mixture was stirred at this temperature for two more hours and then allowed to warm up slowly, while stirring was continued for 18 hours. The reaction mixture was then treated with 10% aqueous sodium hydroxide until pH 7 was reached. Subsequently, this mixture was extracted continuously with ethyl acetate (200 mL) for 15 hours. The organic layer was stirred with a solution of $FeSO_4$ (50 g) in brine (100 mL) and dried over $MgSO_4$. After evaporation of the solvent a 64:36 mixture of the monoacetates (±)-**4** and (±)-**5** was isolated as a yellowish oil. Yield: 8.12 g (38%). The product ratio varied between 64:36 and 55:45 depending on the reaction temperature and work-up conditions. The mixture could not be separated by column chromatography. The spectroscopic data agree with published values.[13]

***endo*,*endo*-2,5-Diacetoxy-9-oxabicyclo[4.2.1]nonane (*meso*-6) and *endo*,*endo*-2,6-Diacetoxy-9-oxabicyclo[3.3.1]nonane [(±)-7]:** The 64:36 mixture of (±)-*endo*,*endo*-2-acetoxy-9-oxabicyclo-[4.2.1]nonan-5-ol (*meso*-**4**) and (±)-*endo*,*endo*-2-acetoxy-9-oxabicyclo[3.3.1]nonan-6-ol [(±)-**5**] (4.51 g, 22.6 mmol), was stirred with acetic anhydride (10.2 g, 100 mmol) and pyridine (9.5 g, 120 mmol) at room temperature for 18 hours. The solvents were then evaporated in vacuo to dryness. The brownish solid was filtered through a silica gel column (cyclohexane/acetone, 2:1). After evaporation of the solvent, a colorless solid was isolated. Yield: 4.98 g (92%). M.p. 65 °C. The spectroscopic data agree with published values.[13]

Lipase-Catalyzed Hydrolysis of the Mixture of Diacetates *meso*-6 and (±)-7: A suspension of a 64:36 mixture of the diacetates *meso*-**6** and (±)-**7** (480 mg, 2 mmol) in 0.1 M phosphate buffer (pH 7.1, 45 mL) was treated with 90 mg of CRL and stirred at room temperature for 48 hours. During that time, the liberated acetic acid was neutralized by addition of 0.1 M NaOH. After termination of the reaction by addition of solid NaCl until saturation, the reaction mixture was continuously extracted with diethyl ether (50 mL) for 10 hours. The organic layer was separated, dried over $MgSO_4$ and the solvent was evaporated. The residue was subsequently separated by column chromatography (cyclohexane/ethyl acetate, 2:1). In this way a 19:81 mixture of the diacetates *meso*-**6** and (−)-**7** (127 mg, 26%, 92% *ee*, determined by chiral GC after saponification) was isolated. Furthermore, an 80:20 mixture (207 mg, 52%) of the monoacetates (−)-**4** (94% *ee*, ^{1}H shift NMR) and (−)-**5** (>98% *ee*, ^{1}H shift NMR) was isolated.

The hydrolyses with the other lipases were done analogously. The results are collected in Table 1.

Lipase-Catalyzed Acetylation of a Mixture of Diols *meso*-2 and (±)-3: A 40:60 mixture of the diols *meso*-**2** and (±)-**3** (10.0 g, 63.3 mmol), prepared according to ref.[14] was dissolved in vinyl acetate (250 mL), CRL (2.5 g) was added and the mixture was stirred for 6 hours, after which time 67% of the diol mixture had been consumed. The progress of acetylation was followed by GC. The lipase was then filtered off by passing the reaction mixture through a silica gel column, which was subsequently eluted with acetone (300 mL). The organic layers were combined and the solvent was evaporated in vacuo. The crude product was dissolved in ethyl acetate (60 mL) and subsequently *n*-pentane was added whilst

stirring until all unchanged diol (−)-**3** precipitated. The solid was separated as an analytically pure white powder by filtration. A fraction of the diol was recrystallized from acetone for X-ray analysis.

(1*S*,2*S*,5*S*,6*S*)-(−)-9-Oxabicyclo[3.3.1]nonane-2,6-diol [(−)-3]: Yield 1.44 g (48% of the theoretically possible amount). M.p. 84 °C (M.p. of the racemate 127−128 °C[13]). $[\alpha]_D^{20} = -45.8$ (c = 1.0, ethanol); >98% *ee* (chiral GC). ^{13}C NMR ($CDCl_3/CD_3OD$): δ = 21.8 (t), 28.1 (t), 68.0 (d), 69.9 (d) ppm. The ^{1}H NMR (100 MHz) and mass spectra of the racemate are known.[13]

The solvent was evaporated from the mother liquor and the residue was separated by column chromatography (cyclohexane/ethyl acetate, 1:1) to give the inseparable monoacetates (+)-**4** and (+)-**5** as a light-yellowish oil (5.10 g, 68:32 mixture) and the diacetate (+)-**7** as a sweet-smelling, colorless solid.

(1*R*,2*R*,5*S*,6*S*)-(+)-2-Acetoxy-9-oxabicyclo[4.2.1]nonan-5-ol [(+)-4]: >98% *ee* (^{1}H shift NMR, 100 mol % $Eu(hfc)_3$]. ^{13}C NMR: δ = 21.0 (q), 23.6 (t), 25.2 (t), 25.4 (t), 28.0 (t), 66.4 (d), 71.6 (d), 73.6 (d), 77.5 (d), 170.2 (s) ppm. The ^{1}H NMR (100 MHz) and mass spectra of the racemate are known.[13]

(1*R*,2*R*,5*R*,6*R*)-(+)-2-Acetoxy-9-oxabicyclo[3.3.1]nonan-6-ol [(+)-5]: >80% *ee* [^{1}H shift NMR, 100 mol % $Eu(hfc)_3$]. ^{13}C NMR: δ = 21.0 (q), 21.5 (t), 22.8 (t), 28.2 (t), 30.7 (t), 68.1 (d), 69.6 (d), 70.6 (d), 81.5 (d), 170.2 (s) ppm. The ^{1}H NMR (100 MHz) and mass spectra of the racemate are known.[13]

(1*R*,2*R*,5*R*,6*R*)-(+)-2,6-Diacetoxy-9-oxabicyclo[3.3.1]nonane [(+)-7]: Yield 1.53 g (31% of theoretically possible amount, contaminated with 6% of *meso*-**6**). M.p. 110 °C (cyclohexane/ethyl acetate; m.p. of the racemate 112−113 °C[13]). $[\alpha]_D^{20} = +50.2$ (c = 1.0, ethyl acetate); >98% *ee* (determined by chiral GC after saponification), corrected value of specific rotation for skeletal pure (+)-**7**, $[\alpha]_D^{20} = +53.4$. ^{13}C NMR: δ = 20.7 (q), 22.5 (t), 24.8 (t), 66.1 (d), 70.0 (d), 169.8 (s) ppm. The ^{1}H NMR (100 MHz) and mass spectra of the racemate are known.[13]

(1*S*,2*S*,5*S*,6*S*)-(−)-2,6-Diacetoxy-9-oxabicyclo[3.3.1]nonane [(−)-7]: Enantiopure (1*S*,2*S*,5*S*,6*S*)-(−)-**3** (0.31 g, 2 mmol) was acetylated with acetic anhydride (1.02 g, 10 mmol) and pyridine (0.95 g, 12 mmol) for 18 hours at room temperature. After removal of the volatile material in vacuo, the solid residue was purified by column chromatography (silica gel; cyclohexane/ethyl acetate, 1:1). Yield 0.44 g (93%). M.p. 110 °C (cyclohexane/ethyl acetate). $[\alpha]_D^{20} = -53.7$ (c = 1.0, ethyl acetate); >98% *ee* (chiral GC, after saponification).

***endo*,*endo*-2,6-Diiodo-9-oxabicyclo[3.3.1]nonane [(±)-8]:** According to ref.[45], (±)-**8** was prepared as white crystals from cycloocta-1,5-diene (**1**) (10.80 g, 0.1 mol) and *N*-iodosuccinimide (35.8 g, 0.16 mol) in methanol after recrystallization from methanol. Yield 27.2 g (90%). M.p. 123−124 °C (ref.[46] M.p. 124 °C). The spectroscopic data agree with published values.[45]

9-Oxabicyclo[3.3.1]nona-2,6-diene [(±)-9]: *endo*,*endo*-2,6-Diiodo-9-oxabicyclo[3.3.1]nonane [(±)-**8**] (78.0 g, 0.21 mol) and dicyclohexylmethylamine (88.5 g, 0.5 mol) were refluxed for 2 hours. After cooling to room temperature the reaction cake was dissolved in a mixture of 2 N hydrochloric acid (350 mL) and Et_2O (250 mL). The layers were separated and the aqueous phases was extracted with Et_2O (2 × 100 mL). The combined organic layer was neutralized with 5% aqueous $NaHCO_3$ (100 mL), washed with water (100 mL) and dried over $MgSO_4$. After evaporation of the solvent a light yellowish waxy solid remained. Yield 22.3 g (88%, 96% purity, GC). M.p. 37 °C (*n*-pentane, ref.[59] M.p. 34−36 °C). The spectroscopic data agree with published values.[60] Single crystals for X-ray structural analysis were grown by careful recrystallization from *n*-pentane.

4,8-Dichloro-2-oxa-6-thiatricyclo[3.3.1.1^{3,7}]decane [(±)-10]: Synthesized according to a known procedure[59] from 9-oxabicyclo[3.3.1]nona-2,6-diene [(±)-**9**] (12.5 g, 0.102 mol) and SCl_2 (10.5 g, 0.102 mol) in dry CH_2Cl_2 (250 mL). Purified by column chromatography (cyclohexane/ethyl acetate, 1:1). Yield 10.0 g (43%). M.p. 181 °C (cyclohexane/ethyl acetate), (ref.[59] M.p. 184−185 °C, in a sealed capillary after sublimation). A 100 MHz ^{1}H NMR spectrum of this compound has been published.[62] ^{13}C NMR: δ = 32.3 (t), 36.3 (d), 60.9 (d), 71.0 (d) ppm. MS (GC/MS): *m*/*z* (%) = 227/225/223 (16:94:94), 190/188 (48:100), 157 (16), 155 (49), 145 (10), 125 (9), 117 (14), 115 (30), 97 (10), 91 (26), 85 (16). Single crystals were grown for X-ray structural analysis by recrystallization from acetone.

2-Oxa-6-thiatricyclo[3.3.1.1^{3,7}]decane-4,8-diol [(±)-11]: Similar to ref.[62] a mixture of 4,8-dichloro-2-oxa-6-thiatricyclo[3.3.1.1^{3,7}]decane [(±)-**10**] (8.5 g, 36.5 mmol), Na_2CO_3 (15.0 g, 141.5 mmol) and water (50 mL) was refluxed for 12 hours. The cold mixture was then neutralized with 2 N aqueous HCl and lyophilized. The crude solid was extracted with ethyl acetate (100 mL), the extract was dried over $MgSO_4$ and concentrated to about 10 mL. This solution was purified by column chromatography (ethyl acetate) to give the diol (±)-**11** as a yellowish solid. Yield 4.07 g (59%). Single crystals were grown for X-ray structural analysis by recrystallization from ethyl acetate. M.p. 312 °C (ethyl acetate, ref.[62] M.p. 316−317 °C). ^{1}H NMR (CD_3OD): δ = 1.99 (dm, ^2J = 12.8 Hz, 2 H), 2.72−2.78 (m, 2 H), 2.88 (dm, ^2J = 12.8 Hz, 2 H), 3.79−3.88 (m, 2 H), 3.95−4.03 (m, 2 H) ppm. A 100 MHz ^{1}H NMR spectrum in $CDCl_3$ has been published,[62] but the assignment of the signals seems not to be conclusive (cf. Supporting Information). ^{13}C NMR (CD_3OD): δ = 32.3 (t), 36.8 (d), 71.1 (d), 72.4 (d) ppm. MS (GC/MS): *m*/*z* (%) = 187 (100) [$M^+ - 1$], 171 (38), 155 (23), 137 (46), 131 (18), 113 (34), 109 (22), 97 (93), 85 (46), 81 (51), 69 (38).

***exo*,*exo*-9-Oxabicyclo[3.3.1]nonane-2,6-diol [(±)-12]:** Similar to ref.[13] 2-oxa-6-thiatricyclo-[3.3.1.1^{3,7}]decane-4,8-diol [(±)-**11**] (6.7 g, 35.6 mmol) in dry ethanol (250 mL) was treated with Raney-nickel (25 g) and refluxed for 24 hours. After cooling to room temperature, the solid was removed by filtration, the filter was washed with ethanol (50 mL), the layers were combined and the solvent was evaporated in vacuo. The remaining white solid was purified by column chromatography (acetone) to give the diol (±)-**12** as the major product. Yield 3.51 g (63%). M.p. 91 °C (acetone, ref.[13] M.p. 85−86 °C after sublimation). ^{13}C NMR ([D_6]DMSO): δ = 21.7 (t), 25.1 (t), 67.3 (d), 72.2 (d) ppm. 60 MHz ^{1}H NMR and mass spectra of this compound are known.[13] Additionally 180 mg (3.4%) of *endo*,*exo*-9-oxabicyclo[3.3.1]nonane-2,6-diol was also isolated (for spectroscopic data see Supporting Information).

Kinetic Resolution of 2-Oxa-6-thiatricyclo[3.3.1.1^{3,7}]decane-4,8-diol [(±)-11]: 2-Oxa-6-thiatricyclo[3.3.1.1^{3,7}]decane-4,8-diol [(±)-**11**] (1.20 g, 6.4 mmol) was partially dissolved in vinyl acetate (45 mL) and CRL (0.72 g) was added. The mixture was stirred at room temperature for 4 hours. The lipase was then separated by filtration through a short silica-gel column and the column was eluted with acetone (200 mL) and ethanol (200 mL). GC analysis of the product mixture showed 45% remaining diol (±)-**11**. After evaporation of the solvent the residue was separated by column chromatography (ethyl acetate).

(1*S*,2*S*,4*S*,5*S*,7*S*,8*S*)-(+)-2-Oxa-6-thiatricyclo[3.3.1.1^{3,7}]decane-4,8-diol [(+)-11]: Yield 0.37 g, (31%). $[\alpha]_D^{20} = +22.5$ (c = 1.0, ethanol),

>98% *ee* (chiral GC, 190 °C, isotherm). All spectroscopic data agree with those given for the racemic compound. Careful recrystallization from acetone gave single crystals suitable for X-ray structural analysis.

(1*R*,2*R*,4*R*,5*R*,7*R*,8*R*)-(−)-4-Acetoxy-8-hydroxy-2-oxa-6-thiatricyclo[3.3.1.1^{3,7}]decane [(−)-13]: Yield 0.26 g (17%). M.p. 144 °C, $[\alpha]_D^{20} = -17.6$ (c = 1.0, ethyl acetate), 34% *ee* (chiral GC after saponification to the diol). ^{1}H NMR: δ = 2.06−2.21 (m, 2 H), 2.17 (s, 3 H), 2.81−2.96 (m, 4 H), 3.92−3.99 (m, 2 H), 4.01−4.07 (m, 1 H), 5.13 (dd, ^3J = 1.7 Hz, 1 H) ppm. ^{13}C NMR: δ = 21.1 (q), 31.3 (t), 31.7 (d), 32.6 (d), 68.5 (d), 69.7 (d), 71.0 (d), 72.0 (d), 170.2 (s) ppm. MS (GC/MS): *m*/*z* (%) = 230 (30), 188 (4), 170 (40), 137 (100), 123 (6), 113 (8), 111 (18), 97 (28), 94 (29), 85 (14), 81 (24), 73 (8), 69 (7). $C_{10}H_{14}O_4S$ (230.3): calcd. C 52.16, H, 6.13; found C 52.31, H 6.28.

(1*R*,2*R*,4*R*,5*R*,7*R*,8*R*)-(−)-4,8-Diacetoxy-2-oxa-6-thiatricyclo-[3.3.1.1^{3,7}]decane [(−)-14]: Yield 0.55 g (31%). $[\alpha]_D^{20} = -55.9$ (c = 1.0, ethyl acetate); 92% *ee* (chiral GC after saponification to the diol). All spectroscopic data agree with those given for the racemate.

Reductive Desulfuration of (1*S*,2*S*,4*S*,5*S*,7*S*,8*S*)-(+)-2-Oxa-6-thiatricyclo[3.3.1.1^{3,7}]decane-4,8-diol [(+)-11]: (1*S*,2*S*,4*S*,5*S*,7*S*,8*S*)-(+)-2-Oxa-6-thiatricyclo[3.3.1.1^{3,7}]decane-4,8-diol [(+)-**11**] (180 mg, 0.95 mmol) was dissolved in ethanol (20 mL), Raney-nickel (3 g) was added and the mixture refluxed for 36 hours. Work-up as described above gave (1*S*,2*R*,5*S*,6*R*)-(+)-9-oxabicyclo[3.3.1]nonane-2,6-diol [(+)-**12**]. Yield 70 mg (47%). $[\alpha]_D^{20} = +25.4$ (c = 1.0, ethanol); >98% *ee* (chiral GC).

Kinetic Resolution of *exo*,*exo*-9-Oxabicyclo[3.3.1]octane-2,6-diol [(±)-12]: *exo*,*exo*-9-Oxabicyclo[3.3.1]octane-2,6-diol [(±)-**12**] (0.8 g, 5.1 mmol) was dissolved in vinyl acetate (32 mL), treated with CRL (0.6 g) and the mixture stirred at room temperature. The progress of the reaction was followed by GC. After 8.5 hours 50% of the diol was consumed and the lipase was separated by filtration through a short silica-gel column with ethyl acetate (200 mL) as eluent. After evaporation of the solvent the residue was separated by column chromatography (ethyl acetate).

(1*S*,2*R*,5*S*,6*R*)-(+)-9-Oxabicyclo[3.3.1]nonane-2,6-diol [(+)-12]: Yield 0.18 g (23%). $[\alpha]_D^{20} = +22.5$ (c = 1.0, ethanol); 94% *ee* (chiral GC). The spectroscopic data agree with those given above for the racemic compound.

(1*R*,2*S*,5*R*,6*S*)-(−)-2-Acetoxy-9-oxabicyclo[3.3.1]nonan-6-ol [(−)-15]: Yield 0.30 g (28%). M.p. 70−71 °C (ethyl acetate). $[\alpha]_D^{20} = -11.7$ (c = 1.0, ethyl acetate); 30% *ee* (chiral GC, after saponification). ^{1}H NMR: δ = 1.36−1.49 (m, 2 H), 1.72−1.80 (m, 2 H), 1.90−2.38 (m, 4 H), 2.06 (s, 3 H), 3.54−3.59 (m, 1 H), 3.83−3.91 (m, 2 H), 4.68−4.76 (m, 1 H) ppm. ^{13}C NMR: δ = 21.1 (t), 21.3 (q), 22.5 (t), 22.6 (t), 25.1 (t), 68.1 (d), 70.0 (d), 70.9 (d), 170.6 (s) ppm. MS (GC/MS): *m*/*z* (%) = 200 (8), 182 (4), 139 (15), 121 (6), 112 (6), 104 (6), 95 (28), 79 (35), 67 (35). $C_{10}H_{16}O_4$ (200.2): calcd. C 59.98, H 8.05; found C 60.13, H 8.11.

(1*R*,2*S*,5*R*,6*S*)-(−)-2,6-Diacetoxy-9-oxabicyclo[3.3.1]nonane [(−)-16]: Yield 0.22 g (17%). M.p. 111 °C (ethyl acetate, ref.[13] M.p. 113−114 °C for the racemic compound). $[\alpha]_D^{20} = -29.3$ (c = 1.0, ethyl acetate), 92% *ee* (chiral GC after saponification). ^{13}C NMR: δ = 21.2 (q), 21.7 (t), 22.6 (t), 69.6 (d), 70.6 (d), 170.6 (s) ppm. MS (GC/MS): *m*/*z* (%) = 242 (2) [M$^+$], 183 (10), 139 (10), 122 (18), 104 (6), 94 (32), 81 (13), 67 (15), 55 (9), 43 (100). $C_{12}H_{18}O_5$ (242.3): calcd. C 59.49, H 7.49; found C 59.58, H 7.73. A 100 MHz ^{1}H NMR spectrum of the racemate is known in the literature.[13]

X-ray Crystallographic Studies

(1*S*,2*S*,5*S*,6*S*)-(−)-9-Oxabicyclo[3.3.1]nonane-2,6-diol [(−)-3]: $C_8H_{14}O_3$, M = 158.19, colorless crystal 0.40 × 0.25 × 0.15 mm, a = 9.572(1), b = 9.572(1), c = 16.928(1) Å, V = 1551.0(2) Å^3, $\rho_{calcd.}$ = 1.355 g cm^{-3}, μ = 8.46 cm^{-1}, empirical absorption correction (0.728 ≤ T ≤ 0.884), Z = 8, tetragonal, space group $P4_32_12$ (no. 96), λ = 1.54178 Å, T = 223 K, ω/2θ scans, 1804 reflections collected ($-h$, $-k$, $-l$), [(sinθ)/λ] = 0.62 Å^{-1}, 1573 independent (R_{int} = 0.035) and 1478 observed reflections [$I \geq 2\sigma(I)$], 103 refined parameters, R = 0.031, wR^2 = 0.086, Flack parameter −0.03(19), max. residual electron density 0.17 (−0.13) e·Å^{-3}; hydrogen atoms calculated and refined as riding atoms.

***endo*,*endo*-2,6-Diiodo-9-oxabicyclo[3.3.1]nonane [(±)-8]:** $C_8H_{12}I_2O$, M = 377.98, colorless crystal 0.40 × 0.30 × 0.25 mm, a = 19.221(1), b = 5.394(1), c = 12.996(1) Å, β = 128.77(1)°, V = 1050.5(2) Å^3, $\rho_{calcd.}$ = 2.390 g cm^{-3}, μ = 59.37 cm^{-1} empirical absorption correction (0.142 ≤ T ≤ 0.226), Z = 4, monoclinic, space group $C2/c$ (No. 15), λ = 0.71073 Å, T = 223 K, $\omega/2\theta$ scans, 2141 reflections collected ($\pm h$, $-k$, $\pm l$), [(sinθ)/λ] = 0.62 Å^{-1}, 1074 independent (R_{int} = 0.029) and 975 observed reflections [$I \geq 2\sigma(I)$], 52 refined parameters, R = 0.037, wR^2 = 0.097, max. residual electron density 1.87 (−1.27) e·Å^{-3}; hydrogen atoms calculated and refined as riding atoms. An X-ray structure of this compound is already known.[67]

9-Oxabicyclo[3.3.1]nona-2,6-diene [(±)-9]: $C_8H_{10}O$, M = 122.16, colorless crystal 0.60 × 0.55 × 0.40 mm, a = 5.429(1), b = 11.656(2), c = 10.316(1) Å, β = 100.77(1)°, V = 641.3(2) Å^3, $\rho_{calcd.}$ = 1.265 g cm^{-3}, μ = 6.42 cm^{-1}, empirical absorption correction (0.699 ≤ T ≤ 0.783), Z = 4, monoclinic, space group $P2_1/c$ (no. 15), λ = 1.54178 Å, T = 223 K, $\omega/2\theta$ scans, 1381 reflections collected ($\pm h$, $-k$, $-l$), [(sinθ)/λ] = 0.62 Å^{-1}, 1310 independent (R_{int} = 0.035) and 1269 observed reflections [$I \geq 2\sigma(I)$], 83 refined parameters, R = 0.037, wR^2 = 0.097, max. residual electron density 0.21 (−0.15) e·Å^{-3}; hydrogen atoms calculated and refined as riding atoms.

4,8-Dichloro-2-oxa-6-thiatricyclo[3.3.1.1^{3,7}]decane [(±)-10]: $C_8H_{10}Cl_2OS$, M = 225.12, colorless crystal 0.50 × 0.40 × 0.10 mm, a = 12.488(2), b = 9.816(2), c = 7.432(1) Å, β = 96.65(1)°, V = 904.9(3) Å^3, $\rho_{calcd.}$ = 1.652 g cm^{-3}, μ = 81.69 cm^{-1}, empirical absorption correction (0.106 ≤ T ≤ 0.496), Z = 4, monoclinic, space group $C2/c$ (no. 15), λ = 1.54178 Å, T = 223 K, ω/2θ scans, 920 reflections collected ($+h$, $-k$, $\pm l$), [(sinθ)/λ] = 0.62 Å^{-1}, 882 independent (R_{int} = 0.089) and 874 observed reflections [$I \geq 2\sigma(I)$], 57 refined parameters, R = 0.045, wR^2 = 0.126, max. residual electron density 0.45 (−0.42) e·Å^{-3}; hydrogen atoms calculated and refined as riding atoms.

2-Oxa-6-thiatricyclo[3.3.1.1^{3,7}]decane-4,8-diol [(±)-11]: $C_8H_{12}O_3S$, M = 188.24, colorless crystal 0.60 × 0.40 × 0.20 mm, a = 6.465(1), b = 6.957(1), c = 10.139(1) Å, α = 88.64(1)°, β = 74.16(1)°, γ = 71.23(1)°, V = 414.3(1) Å^3, $\rho_{calcd.}$ = 1.509 g cm^{-3}, μ = 31.90 cm^{-1}, empirical absorption correction (0.233 ≤ T ≤ 0.528), Z = 2, triclinic, space group $P\bar{1}$ (No. 2), λ = 1.54178 Å, T = 223 K, $\omega/2\theta$ scans, 1838 reflections collected ($-h$, $\pm k$, $\pm l$), [(sinθ)/λ] = 0.62 Å^{-1}, 1680 independent (R_{int} = 0.044) and 1657 observed reflections [$I \geq 2\sigma(I)$], 112 refined parameters, R = 0.038, wR^2 = 0.102, max. residual electron density 0.46 (−0.26) e·Å^{-3}; hydrogen atoms calculated and refined as riding atoms.

(1*S*,2*S*,4*S*,5*S*,7*S*,8*S*)-(+)-2-Oxa-6-thiatricyclo[3.3.1.1^{3,7}]decane-4,8-diol [(+)-11]: $C_8H_{12}O_3S$, M = 188.24, colorless crystal 0.60 × 0.50 × 0.20 mm, a = 9.122(1), b = 10.207(1), c = 17.925(1) Å, V =

1669.0(3) Å^3, $\rho_{calcd.}$ = 1.498 g cm^{-3}, μ = 31.68 cm^{-1}, empirical absorption correction ($0.236 \leq T \leq 0.530$), Z = 8, orthorhombic, space group $P2_12_12_1$ (no. 19), λ = 1.54178 Å, T = 223 K, $\omega/2\theta$ scans, 1956 reflections collected ($-h$, $-k$, $-l$), [$(\sin\theta)/\lambda$] = 0.66 Å^{-1}, 1956 independent and 1943 observed reflections [$I \geq 2\sigma(I)$], 222 refined parameters, R = 0.049, wR^2 = 0.137, Flack parameter 0.06(3), max. residual electron density 0.74 (-0.55) e·Å^{-3}; hydrogen atoms calculated and refined as riding atoms.

(1*S*,2*R*,5*S*,6*R*)-(+)-9-Oxabicyclo[3.3.1]nonane-2,6-diol [(+)-12]: $C_8H_{14}O_{2.923}S_{0.077}$, M = 159.43, colorless crystal 0.50 × 0.30 × 0.20 mm, a = 11.223(5), c = 6.434(3) Å, V = 810.4(6) Å^3, $\rho_{calcd.}$ = 1.307 g cm^{-3}, μ = 9.87 cm^{-1}, empirical absorption correction ($0.638 \leq T \leq 0.827$), Z = 8, tetragonal, space group $P4_12_12$ (No. 92), λ = 1.54178 Å, T = 223 K, $\omega/2\theta$ scans, 970 reflections collected ($-h$, $+k$, $+l$), [$(\sin\theta)/\lambda$] = 0.62 Å^{-1}, 823 independent (R_{int} = 0.025) and 693 observed reflections [$I \geq 2\sigma(I)$], 59 refined parameters, R = 0.036, wR^2 = 0.096, Flack parameter 0.2(2), max. residual electron density 0.18 (-0.11) e·Å^{-3}. The crystal contained 7.7(3)% of the sulfur-bridged starting material, disorder refined with PART command, hydrogen atoms calculated and refined as riding atoms.

CCDC-215356−215362 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44-1223-336-033: E-mail: deposit@ccdc.cam.ac.uk].

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