Pergamon

Tetrahedron 54 (1998) 859–874

TETRAHEDRON

Chemoenzymatic Deracemization of (±)-2,2-Disubstituted Oxiranes

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Received 10 September 1997; accepted 5 November 1997

Abstract: The preparation of vicinal diols in up to 98% e.e. and 98% yield from the corresponding (±)-2,2-disubstituted epoxides was achieved *via* an enantioconvergent two-step hydrolysis: Thus, enantioselective enzymatic hydrolysis of the (*S*)-epoxide proceeded with retention of configuration furnishing the corresponding (*S*)-diol. In a subsequent step, the remaining (*R*)-oxirane was hydrolyzed during workup under acid catalysis with complete inversion of configuration yielding the (*S*)-diol. A detailed study of the latter reaction revealed that the experimental conditions have to be carefully chosen with respect to (i) nature of the acid, (ii) the solvent, and (iii) its water content to avoid racemization.

Introduction

Chiral vicinal diols are important intermediates for the asymmetric synthesis of a wide range of bioactive compounds. Several methods to prepare these diols are currently available to the synthetic chemist. A direct and powerful method is the osmium catalyzed asymmetric dihydroxylation of olefins.[1] Although the product e.e.'s achieved by this method are high (up to 95%), the reaction is restricted to relatively simple olefins of *trans* geometry.[1] Furthermore, heavy metal catalysts are ecologically unsound, particularly on an industrial scale. An alternative way of preparing chiral vicinal diols is the selective hydrolysis of enantiopure epoxides. However, this sets the problem to the preparation of optically pure oxiranes. Among the chemical asymmetric epoxidation procedures most widely used, the Sharpless epoxidation[2] of olefins is limited to allylic alcohols and Jacobsen catalysts[3a,b] give mainly good results with *cis* olefins. Only recently, the latter group reported a kinetic resolution of racemic primary epoxides *via* catalytic hydrolysis using chiral cobalt based complexes.[3c] This approach might become a useful method for the preparation of enantiomerically enriched terminal epoxides and 1,2-diols.

In addition to the aforementioned chemical approaches, regio- and enantioselective biocatalytic hydrolysis of racemic epoxides using epoxide hydrolases [EC 3.3.2.X] has been shown to be a powerful alternative. For biotransformations on the preparative scale, epoxide hydrolases from fungal or bacterial sources have been shown to be advantageous over mammalian enzymes. They are (i) highly selective, (ii) cofactor independent, (iii) sufficiently available by fermentation and (iv) their production does not require sophisticated enzyme induction.[4] As a consequence, these biohydrolyses can be easily performed on a multigram scale.

However, the enzymic hydrolyses of epoxides reported so far operate *via* a classic kinetic resolution pattern and provide the enantioenriched vicinal diol and enantiopure epoxide both in 50% theoretical yield. This is often regarded as drawback and methods that would offer a solution to this intrinsic problem of kinetic resolutions are highly desirable.[5] In this study, we aimed at the development of a simple process to transform a racemic epoxide into the corresponding vicinal diol in 100 % theoretical yield and 100% e.e.

0040-4020/98/$19.00
PII: S0040-4020(97)10338-6

Opening of oxiranes involving nucleophilic attack at the less substituted carbon is generally denoted as „normal opening" whereas attack at the more substituted carbon is termed as „abnormal opening".[6] For racemic 2,2-disubstituted oxiranes, the enzymic hydrolysis using bacterial epoxide hydrolases was shown to proceed *via* attack at the less substituted („normal") carbon atom with excellent regioselectivity, [7] thus leading to complete *retention* of configuration at the stereogenic center. If this process could be followed by a selective chemical hydrolysis of the remaining mirror image epoxide enantiomer with *inversion* at the stereogenic („abnormal") center, one could overcome the classical kinetic resolution pattern by producing a single enantiomerically enriched vicinal diol in 100 % theoretical yield. The regio- and/or stereoselectivity of such a hydrolysis of an epoxide ring is very dependent on the reaction conditions.[8] Under basic or neutral conditions, attack on the „normal" position is nearly always the major (if not the only) process occurring. Under acidic conditions, the reaction with most nucleophiles (including water) is considerably facilitated due to initial protonation of the oxirane oxygen. The so-formed conjugate acid shows a marked tendency to open at the „abnormal" carbon atom which is better suited to accomodate a positive charge during the transition state.[9] Furthermore, nucleophilic attack of water *via* an S_N2 mechanism involves the desired inversion of configuration, while an S_N1 mechanism (proceeding through a carbonium ion) in the worst scenario leads to a racemic product.[9] Thus, in order to accrue a maximum in optical yield, the acid catalyzed hydrolysis should ideally proceed *via* a S_N2-like (borderline) process.

Isolated reports on the selective acid catalyzed hydrolysis of chiral trisubstituted,[10a,b] 2,3-disubstituted,[10b] or monosubstituted[10c] oxiranes have been previously published. However, in this paper we present a detailed study on the stereochemical outcome of the reaction depending on the conditions and we discuss some of the mechanistic implications involved. Furthermore, it was anticipated that the sequential combination of bio- and chemocatalysis[11a] might lead to an enantioconvergent hydrolysis of racemic epoxides yielding the corresponding vicinal diols as the sole products in 100% theoretical chemical and optical yield. Preliminary results[11b] on such a resolution-inversion sequence, involving acyclic 2,2-disubstituted oxiranes, were recently reported. Here we want to describe the full details and the merits of this useful procedure.

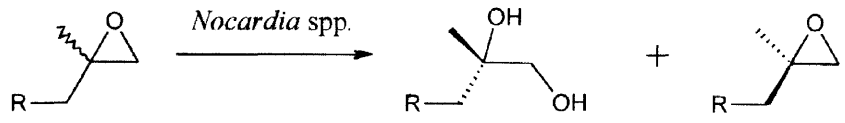
Results and Discussion

Biocatalytic Hydrolysis

2,2-Disubstituted epoxides **1a, 1b** and **1d** were prepared in racemic form as previously described.[12] Substrate **1c** was synthesized as follows. Addition of a Grignard reagent prepared from methylallyl chloride to 1,3-dibromopropane in THF afforded 6-bromo-2-methyl hexene.[13] After work-up, the crude material was epoxidized with *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 and (±)-**1c** was obtained in good yield.

Racemic epoxides **1a-d** were resolved *via* biohydrolysis using lyophilized whole cells of *Nocardia* spp. EH1 or H8,[12c] bacterial strains exhibiting strong epoxide hydrolase activity (Scheme 1). The reactions were

monitored by TLC and GC and the optical purities of the product diols **2a-d** as well as those of the residual enantioenriched epoxides **1a-d** were determined by GC on a chiral stationary phase.[12] The results are presented in Table 1. With R being *n*-pentyl (**1a**), 4-pentenyl (**1b**), or 4-bromobutyl (**1c**) the selectivity was found to be virtually absolute showing an enantiomeric ratio (*E*) of >200 (entries 1-3, Table1). In case of the benzyl substituted substrate (±)-**1d** (entry 4, Table 1) the selectivity was slightly reduced (*E* = 123) but still in a preparatively useful range.



(±)-**1a-d** (*S*)-**2a-d** (*R*)-**1a-d**

a: R = $-(CH_2)_3CH_3$
b: R = $-(CH_2)_2CH{=}CH_2$
c: R = $-(CH_2)_3Br$
d: R = $-C_6H_5$

Scheme 1

Table 1. Kinetic Resolution of Racemic 2,2-Disubstituted Oxiranes **1** *via* Biohydrolysis.

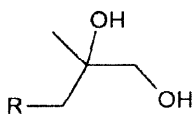
Entry	Substrate[a]	Microorganism	Time [h]	Conversion [%]	Epoxide (e.e.[%])	Diol (e.e.[%])	Selectivity (*E*)
1	(±)-**1a**	*Nocardia* EH1	24	50	*(R)*-**1a** (>99)[b]	*(S)*-**2a** (>99)[b]	>200
2	(±)-**1b**	*Nocardia* EH1	24	40	*(R)*-**1b** (96)[b]	*(S)*-**2b** (97)[b]	>200
3	(±)-**1c**	*Nocardia* H8	20	50	*(R)*-**1c** (>99)[c]	*(S)*-**2c** (>99)[d]	>200
4	(±)-**1d**	*Nocardia* EH1	48	39	*(R)*-**1d** (81)[b]	*(S)*-**2d** (96)[b]	123

[a] Biocatalytic reactions were performed on a gram scale (see experimental part). [b] The absolute configuration of this compound was established by known methods and was in full agreement with those previously reported.[12] [c] The absolute configuration of *(R)*-**1c** was elucidated as follows: Optically active **1c** was hydrolyzed with aqueous NaOH to give **2c**. Then, the bromide functionality was removed with $LiAlH_4$ in THF to yield 2-methyl-1,2-hexanediol. The absolute configuration of the latter was determined *via* coinjection on GC with an independently synthesized enantiopure sample, which was obtained *via* the procedure of Hosokawa *et al.*[12a,14] [d] $LiAlH_4$ reduction of the bromide afforded enantiopure 2-methyl-1,2-hexanediol, whose absolute configuration was determined as described in note c.

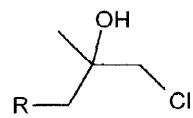
Acidic Hydrolysis

After extractive work-up and chromatographic separation from the (*S*)-diols, the remaining epoxides *(R)*-**1a-d** were treated with acid. In order to determine the reaction conditions best suited for the selective epoxide hydrolysis, a range of different mineral acids was investigated under varying conditions. To obtain comparable data, all compounds were subjected to 0.18 M of mineral acid in water or dioxane[15] at room temperature by maintaining a reaction time of 15 min in all cases. Thus, a rough estimate of the relative reaction rates could be obtained by comparing the quantities of recovered starting material. Careful analysis of all of the products obtained (Chart 1) afforded detailed mechanistic information from which optimal conditions for selective hydrolysis (without racemization) could be concluded. The results of this study are summarized in Table 2 and 3.

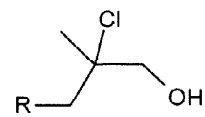
When the *(R)*-oxiranes **1** were treated with hydrochloric acid (Table 2, entries 1-8), chlorohydrin formation was the main process observed, except for 4-bromobutyl oxirane **1c** which gave a complex product mixture (entries 3 and 7, respectively). In dioxane, *(R)*-**1a** and *(R)*-**1b** gave mainly the respective regio-isomeric chlorohydrins **3** and **4** in a 1:1 ratio (62% and 76%, respectively; entries 1 and 2). Under the same conditions, *(R)*-**1d** produced exclusively and with good regioselectivity a 9:1 mixture of **3d** and **4d** in 94% yield (entry 4). The presence of the chloride atom in compounds **3** and **4** was concluded from their MS data, which showed a typical 3:1 ratio of the M^+ signal in each case. The position, C(1)–Cl or C(2)–Cl, could be elucidated from the ^1H NMR spectra. Thus, in case of **3**, the C(2)–CH_3 proton signals appear at δ 1.24-1.29, whereas these methyl protons appear at δ 1.44-1.49 in the ^1H NMR spectra of compounds **4**. Together with other NMR data this confirms the structural assignment of the regio-isomeric chlorohydrins. The reactions in dioxane yielded a small amount of the *E*-configurated olefins **7** (26%, from **1a**; 2%, from **1b**; entries 1 and 2, respectively; *vide infra*) indicating that an elimination process is also operating. In water such elimination processes were not observed, but small amounts of diols **2a, 2b,** and **2d** (7-11%) could be found, although selectivity was only moderate (entries 5, 6, and 8, respectively). Though less pronounced, in water chlorohydrin formation is the major process (34-44%). In comparison the reactions in dioxane were found to be complete whilst those reactions run in water showed varying amounts of residual *(R)*-epoxides (40-56%).



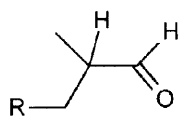
2a-d



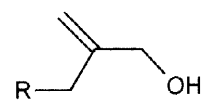
3a,b,d



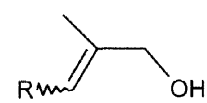
4a,b,d



5a,b,d



6a-d



7a-d

a: R = $-(CH_2)_3CH_3$
b: R = $-(CH_2)_2CH{=}CH_2$
c: R = $-(CH_2)_3Br$
d: R = $-C_6H_5$

Chart 1

Treatment of *(R)*-oxiranes **1a,b,d** with perchloric acid (Table 2, entries 9-16) resulted in the formation of racemic aldehydes **5a,b,d**[16] and/or diols **2a,b,d**. Again, **1c** was an exception and produced only a complex product mixture that was not further examined. In dioxane, no diols were formed and aldehydes were the only products (75-94%, entries 9, 10, and 12). On the other hand, hydrolysis in water gave in addition to the aldehydes (11-21%; entries 13, 14, and 16), considerable amounts of diols **2a,b,d** (22-36%). However, the selectivity of the diol formation was low. From the reactions performed in dioxane only minor amounts

(14%) of starting material were regained. In contrast, aqueous reactions yielded considerable amounts of *(R)*-**1a-d** (41-49%).

Table 2. Acid Catalyzed Hydrolysis of Oxiranes **1** using Hydrochloric, Perchloric, or Phosphoric Acid.

Entry	Epoxide[a] (*R*)	Condi-tions[b]	Solvent	Products					Recovered Startmat. [%][c]
				Diol (*S*)	Yield [%][c]	e.e. [%][d]	Other[e]	Yield [%][c]	
1	**1a**	HCl	dioxane[f]	-			**3a:4a** (1:1)	62	-
							7a (*E*)	26	
2	**1b**	HCl	dioxane[f]	-			**3b:4b** (1:1)	76	-
							7b (*E*)	2	
3	**1c**	HCl	dioxane[f]	-			-[g]		-
4	**1d**	HCl	dioxane[f]	-			**3d:4d** (9:1)	94	-
5	**1a**	HCl	H_2O	**2a**	11	65	**3a:4a** (1:1)	36	40
6	**1b**	HCl	H_2O	**2b**	7	67	**3b:4b** (1:1)	34	56
7	**1c**	HCl	H_2O	-			-[g]		51
8	**1d**	HCl	H_2O	**2d**	8	61	**3d:4d** (1:2)	44	42
9	**1a**	$HClO_4$	dioxane[h]	-			**5a**	75	14
10	**1b**	$HClO_4$	dioxane[h]	-			**5b**	94	-
11	**1c**	$HClO_4$	dioxane[h]	-			-[g]		-
12	**1d**	$HClO_4$	dioxane[h]	-			**5d**	81	14
13	**1a**	$HClO_4$	H_2O	**2a**	36	44	**5b**	11	41
14	**1b**	$HClO_4$	H_2O	**2b**	28	48	**3b**	19	46
15	**1c**	$HClO_4$	H_2O	-			-[g]		44
16	**1d**	$HClO_4$	H_2O	**2d**	22	49	**5d**	21	49
17	**1a**	H_3PO_4	dioxane[i]	-			**6a**	31	15
							7a (*E*:*Z*=7:1)	36	
18	**1b**	H_3PO_4	dioxane[i]	-			**6b**	36	12
							7b (*E*:*Z*=6:1)	41	
19	**1c**	H_3PO_4	dioxane[i]	-	-	-	**6c**	41	-
							7c (*E*:*Z*=7:1)	43	
20	**1d**	H_3PO_4	dioxane[i]	-			**6d**	43	-
							7d (*E*)	45	
21	**1a**	H_3PO_4	H_2O	**2a**	8	25	**6a**	3	32
							7a (*E*:*Z*=6:1)	32	
22	**1b**	H_3PO_4	H_2O	**2b**	11	27	**6b**	4	29
							7b (*E*:*Z*=6:1)	36	
23	**1c**	H_3PO_4	H_2O	**2c**	12	30	**6c**	7	31
							7c (*E*:*Z*=7:1)	29	
24	**1d**	H_3PO_4	H_2O	**2d**	17	34	**6d**	9	31
							7d (*E*)	28	

[a] [*(R)*-oxirane] = 0.0145 M. [b] [Acid] = 0.18 M. [c] GC-yields. [d] Determined by GC on a chiral stationary phase. [e] Ratios in parenthesis were determined by NMR, GC or HPLC. [f] [H_2O] = 0.63 M. [g] Complex product mixture. [h] [H_2O] = 0.42 M. [i] [H_2O] = 0.17 M.

Elimination is the main process when *(R)*-oxiranes **1a-d** were treated with phosphoric acid (Table 2, entries 17-24). In dioxane as solvent, this is the only pathway (entries 17-24, 67-88%) whereas the analogous treatment in water (entries 21-24) gave small amounts of diols **2a-d** (8-17%, e.e. <34%), next to elimination products (35-40%).

Overall, the elimination process results in a complex mixture of olefins. Thus, in dioxane, the ratio between the $\Delta^{2,3}$ olefins **6a-d** and their $\Delta^{2,4}$ isomers **7a-d** is about 1:1. When water is used as the solvent, the ratio considerably increases in favour of the $\Delta^{2,4}$ product (**6**:**7** ratio up to 1:10). Furthermore, in both solvents the *E*/*Z*-ratio for **7a-c** is more or less equal (ca. 6:1), whereas for the benzylic derivative **7d**, only the *E*-isomer was detected.[17] The position of the C=C bond could be established after careful analysis of the NMR data. Thus, the ^{13}C NMR spectra of **6a-d** typically show a triplet at around 110 ppm whereas the isomers **7a-d** reveal a doublet between δ 125 and 130. About 30% of the starting epoxides could be regained after reaction with phosphoric acid in aqueous medium. Again, when the same conditions were applied in dioxane almost complete reactions were observed.

Table 3. Acid Catalyzed Hydrolysis of Oxiranes **1** using Nitric or Sulfuric Acid.

Entry	Substrate[a]	Conditions[b]	Solvent	Products					Recovered Startmat. [%][c]
				Diol	Yield [%][c]	e.e. [%][d]	Other[e]	Yield [%][c]	
1	**1a**	HNO_3	dioxane[f]	**2a**	87	65	**5a**	5	7
2	**1b**	HNO_3	dioxane[f]	**2b**	93	67	-	-	-
3	**1c**	HNO_3	dioxane[f]	**2c**	78	69	-	-	11
4	**1d**	HNO_3	dioxane[f]	-			-[g]		-
5	**1a**	HNO_3	H_2O	**2a**	45	45	-	-	40
6	**1b**	HNO_3	H_2O	**2b**	56	41	-	-	36
7	**1c**	HNO_3	H_2O	**2c**	54	45	-	-	35
8	**1d**	HNO_3	H_2O	**2d**	25	44	-	-	61
9	**1a**	H_2SO_4	dioxane[h]	**2a**	90	84	-	-	-
10	**1b**	H_2SO_4	dioxane[h]	**2b**	87	87	-	-	-
11	**1c**	H_2SO_4	dioxane[h]	**2c**	55	93	-[g]		-
12	**1d**	H_2SO_4	dioxane[h]	**2d**	45	77	**6d**:**7d**[i](1:1)	41	-
13	**1a**	H_2SO_4	dioxane[j]	**2a**	95	98	-	-	-
14	**1b**	H_2SO_4	dioxane[j]	**2b**	98	98	-	-	-
15	**1c**	H_2SO_4	dioxane[j]	**2c**	74	98	-[g]		-
16	**1d**	H_2SO_4	dioxane[j]	**2d**	90	87	-	-	-
17	**1a**	H_2SO_4	dioxane[k]	**2a**	71	77	-	-	25
18	**1b**	H_2SO_4	dioxane[k]	**2b**	77	76	-	-	19
19	**1c**	H_2SO_4	dioxane[k]	**2c**	55	71	-[g]		26
20	**1d**	H_2SO_4	dioxane[k]	**2d**	43	69	**6d**:**7d**[i](1:3)	22	21
21	**1a**	H_2SO_4	H_2O	**2a**	43	32	-	-	48
22	**1b**	H_2SO_4	H_2O	**2b**	45	36	-	-	45
23	**1c**	H_2SO_4	H_2O	**2c**	55	29	-	-	41
24	**1d**	H_2SO_4	H_2O	**2d**	21	58	-	-	67

[a] [*(R)*-oxirane] = 0.0145 M. [b] [Acid] = 0.18 M. [c] GC-yields. [d] Determined by GC on a chiral stationary phase. [e] Ratios in parenthesis were determined by NMR, GC or HPLC. [f] [H_2O] = 0.43 M. [g] Complex product mixture. [h] [H_2O] = 0.02 M. [i] Only the *E* isomer was detected. [j] [H_2O] = 0.07 M. [k] [H_2O] = 0.23 M.

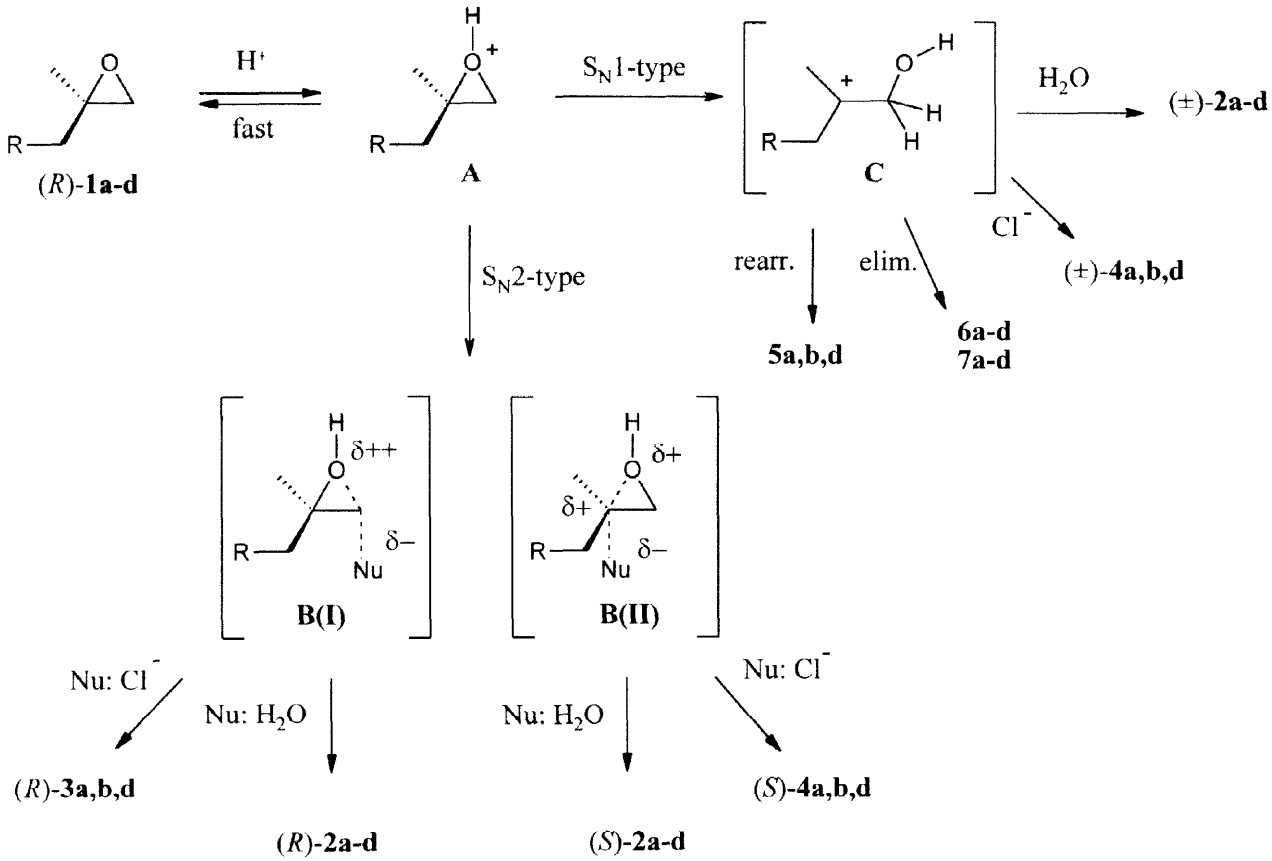
(R)-oxiranes **1a-d** showed a broad range of different reactions upon treatment with hydrochloric, perchloric, and phosphoric acid run in dioxane or water as the solvent. In contrast, the reaction pattern of these oxiranes in the same solvents with nitric, or sulfuric acid were much simpler (Table 3). In general, the latter acids led

to exclusive hydrolysis forming the vicinal diols **2a-d** as products. Decomposition was only observed in dioxane for **1d** with nitric acid (entry 4), whereas minor side reactions were observed for the treatment of **1c** with sulfuric acid (entries 11, 15, and 19). When water was used as the solvent, the stereoselectivity of the hydrolysis (e.e. of diol <58%) as well as the rate (recovery of **1a-d** = 35-67%) was found to be modest or low (entries 5-8 and 21-24). However, in dioxane the reaction rates were considerably increased, which is reflected in the small amount of starting material that could be detected (entries 1-4 and 9-20). Only when employing 70% sulfuric acid some starting material was regained (entries 17-20). In addition, also the stereoselectivity was considerably enhanced, although the e.e. values of diols **2a-d** were still modest (e.e. <78%, entries 1-4) when nitric acid was used. However, treatment of *(R)*-epoxides **1a-d** with concentrated sulfuric acid in dioxane gave the desired high selectivity: Thus, high e.e.'s and excellent yields of the product diols (entries 9-16) were obtained. In particular, optimal conditions were found by using concentrated sulfuric acid in dioxane containing a minimum amount of water (entries 13-16), which afforded *(S)*-diols **2a-d** without detectable racemization.

These results show clearly that specific features of the different mineral acids have profound effects on the reaction course for *(R)*-oxiranes **1a-d**. Nitric and sulfuric acid show high chemoselectivity toward hydrolysis (Table 3), whereas other pathways (such as rearrangement and/or elimination) are observed upon treatment with hydrochloric, perchloric, or phosphoric acid (Table 2). Furthermore, it is demonstrated that the product composition and also the reaction rate depend on the nature of the solvent employed. In general, reactions performed in dioxane were found to be always considerably faster than those performed in water. Most importantly, the results show clearly that the stereoselectivity of the hydrolysis with respect to inversion of configuration of the stereogenic center increases significantly when the reactions are run in dioxane. Additionally, the experiments with sulfuric acid indicate that the concentration of the nucleophile (*i.e.* water) in the organic solvent has a profound influence on the extent of racemization during hydrolysis.

Nucleophilic cleavage of an epoxide under acidic conditions comprises of two idealized steps (Scheme 2). First, protonation of the oxirane oxygen takes place to form **A**. It is now generally accepted that this initial step is a fast and reversible process.[18] The chemical consequence of this latter step is ring opening,[18a] which can proceed *via* two limiting mechanistic pathways: Either a one-stage concerted opening of the carbon–oxygen bond with simultaneous formation of the carbon–nucleophile bond (proceeding through transition states **B**), or a two-stage unimolecular break of the epoxide ring to form an intermediate carbonium ion (**C**), followed by reaction with the nucleophile.[8,18] Reactions involving intermediates **C** would result in the formation of „abnormal" ring-opening products, albeit with low stereoselectivity since either side of the carbocationic sp^2-center is equally accessible. Both „abnormal" and „normal" products would be the result of reactions *via* S_N2-like transition states **B**. One the one hand, steric restrictions would favor **B(I)**, whereas electronic factors favor transition states resembling **B(II)**.[8] Reactions *via* these transition states would

proceed in a stereoselective fashion since the approach of the nucleophile is directed to only one side of the molecule. With the above mechanistic view, most of the experimental findings can be explained as follows. In general, solvation has considerable influence on the rate and the direction of chemical reactions. The acid-base equilibrium constant (pK_a) is influenced by solvent,[19] which consequently effects the rate of protonation to form **A**. However, the rate-limiting step is the opening of the protonated (charged) intermediate (**A**). According to the Hugh-Ingold theory a change to a solvent of greater "solvating power" will cause a decrease in the rate of the reaction.[9] Hence, the reaction rates observed in water are decreased as compared to the rates in dioxane.



Scheme 2

Reactions of *(R)*-**1a-d** with hydrochloric, perchloric and phosphoric acid performed in water always shows considerable amounts of hydrolysis products **2a-d** (Tables 2 and 3). Water, as the nucleophile, is available in vast excess (55 M) and competes effectively with chlorohydrin formation, rearrangement and elimination. In contrast, when dioxane is used as a solvent, water as a nucleophile is less readily available and therefore the specific properties[20] connected with these three acids become more significant and hence the direction of the reactions changes towards non-hydrolysis products. Chlorohydrin formation with hydrochloric acid can be attributed to attack of chloride ion on the protonated epoxides **A**. It is known that chloride attack can become competitive with other reaction pathways, such as hydrolysis, due to special properties associated with the

chloride ion.[21,22] Nucleophilic attack at the less hindered oxirane carbon atom leads to the „normal" chlorohydrins **3a,b,d**, operating *via* intermediates **B(I)**. On the other hand, attack at the electronically more favored tertiary center [intermediates **B(II)** and/or **C**] accounts for the formation of „abnormal" chlorohydrins **4a,b,d**. It was not possible to determine their e.e.'s and absolute configurations, hence it is unclear whether their formation proceeds through carbonium ions **C**, or the more S_N2-like transition states **B(II)** (or both).

Racemic aldehydes **5a,b,d** are predominantly formed under catalysis of perchloric acid. It has been observed before that in media containing perchlorate anions rearranged products, such as aldehydes, are readily formed.[18,23] This behavior is attributed to a propensity of the perchlorate ion (a large ion of low charge density[20]) to associate preferentially with carbonium ions.[24] Consequently, charged intermediates like **C** would be favored and a subsequent 1,2-H shift from either side of the plane accounts for the formation of *racemic* aldehydes **5a,b,d**. In a related fashion, the elimination pathway to form allylic alcohols is also best explained by proceeding *via* **C**. In particular reactions with phosphoric acid show a preference for elimination.[18b,c] Of the mineral acids investigated, phosphoric acid is the weakest, *i.e.* it has the highest pK_a value. This implies that its conjugate base is relatively better able to abstract a proton from intermediates **C**, which ultimately results in the formation of one of the olefinic products. The nature of the microenvironment would direct the carbonium ion toward the different elimination paths, thus determining the ratio of **6**:**7** as well as the *E/Z*-ratio in **7**. Furthermore, it is well known[18,23] that phosphate anions show no signifcant nucleophilic attack on protonated epoxides like **A**, which explains the absence of substitution products.

Hydrolysis to give vicinal diols **2a-d** is the (almost) exclusive reaction observed when nitric or sulfuric acid were used. Anions of high charge density, like SO_4^{2-} and NO_3^-,[20] favor reactions that proceed *via* a S_N2-like pathway through transition states **B(I)** and/or **B(II)**. From the results in Table 3 it becomes clear that each of the hydrolyses of *(R)*-**1a-d** results in diols **2a-d** possessing *(S)*-configuration. Consequently, regardless which acid and whether water or dioxane is used, the pathway *via* **B(II)** is preferentially followed, though not always to the same extent. After initial protonation of the oxirane oxygen the positive charge in intermediate **A** is more effectively dissipated to the tertiary center, which becomes then more prone to backside attack of a water nucleophile available.[18c] However, when water is abundantly present (or even the solvent, entries 17-24, Table 3), charged species are better stabilized and the pathway *via* **C** becomes dominant. As a consequence, addition of water may occur to either side of the flat sp^2-center and the stereoselectivities of these hydrolyses are only modest. On the other hand, when water is only sparcely available in an aprotic, apolar solvent like dioxane, every water molecule is needed to solvate the acid-anion. The steric demands of this solvated species[23] directs attack more toward the „normal" oxirane carbon atom [*via* **B(I)**], which accounts for the small degree of racemization in reactions performed with neat concentrated sulfuric acid (entries 9-12, Table 3). However, a minimum amount of added water (entries 13-16, Table 3) - just enough to have water nucleophiles available in solution, but not enough to stabilize

intermediates **C** - provides the optimal conditions for stereoselective addition of water *via* **B(II)** to form enantiopure *(S)*-diols **2a-d** from *(R)*-**1a-d** without racemization.

Combined Chemoenzymatic Hydrolysis

Biohydrolysis of 2,2-disubstituted oxiranes, was shown to proceed *via* attack of a formal [OH⁻] at the „normal" oxirane carbon atom while the absolute configuration at the chiral tertiary center is retained.[7] In a complementary fashion, acidic hydrolysis using the conditions described above, involves stereoselective attack of water at the „abnormal" oxirane carbon with concomitant inversion of the stereogenic center. Combination of both hydrolysis methods in a resolution-inversion sequence provides a convenient and useful procedure for the preparation of chiral vicinal diols *(S)*-**2a-d** in an enantioconvergent fashion.

Table 4. Deracemization of (±)-Oxiranes **1**.[a]

Entry	Substrate	Product	Yield (%)[b]	ee (%)
1	(±)-**1a**	*(S)*-**2a**	98	98
2	(±)-**1b**	*(S)*-**2b**	97	99
3	(±)-**1c**	*(S)*-**2c**	71	98
4	(±)-**1d**	*(S)*-**2d**	94	92

[a] Deracemization was performed on a gram scale. [b] Isolated yields.

Thus, enzymic hydrolyses of (±)-**1a-d** were carried out as the initial step and the crude reaction mixtures were directly treated with H_2SO_4 in dioxane containing trace amounts of added water as described above. In this way, racemic epoxides could be directly converted to the respective enantiomerically enriched *(S)*-diols **2a-d** in good yields and excellent e.e.'s, even on a preperative scale (Table 4). The selectivities achieved in the resolution of (±)-**1a-c** with *Nocardia* spp. is virtually absolute which is indicated by the fact that the reaction automatically terminates at 50% conversion, when the faster reacting *(S)*-epoxide is consumed. Then the remaining *(R)*-enantiomer is chemically hydrolyzed under inversion. The selectivity for (±)-**1d** reached at best an *E*-value of 123. Based on the recently published[25] mathematical description of the kinetics of such a resolution-inversion sequence, the bioresolution was allowed to proceed slightly beyond the 50% limit before the acidic hydrolysis was started. In this way, the maximum obtainable e.e. of the final product diol **2d** was achieved.

Concluding Remarks

Optically pure vicinal diols were produced in high chemical yields *via* a two-step resolution-inversion sequence. Thus, racemic 2,2-disubstituted epoxides resolved with a highly selective biocatalyst showing epoxide hydrolase activity (lyophilized cells of *Nocardia* spp.) afforded the enantiopure *(R)*-epoxide and the corresponding vicinal *(S)*-diol. In a subsequent step, the remaining *(R)*-epoxide was hydrolyzed with sulfuric

acid under carefully controlled conditions to the same *(S)*-diol. Careful mechanistic analysis of the results of acid catalyzed hydrolysis using different solvents and mineral acids made it possible to select conditions - concentrated sulfuric acid in dioxane containing a minimum amount of water - that led to the formation of the *(S)*-diol without notable racemization. Furthermore, the biocatalytic and acidic hydrolyses could be successfully combined in a preperative scale procedure. The method described in this study overcomes the intrinsic drawback of a classic kinetic resolution pattern, and it is generally applicable on a large scale.

Experimental Part

General

Bacterial strains of *Nocardia* spp. were a kind gift of J. de Bont (Wageningen, The Netherlands) and C. Syldatk (Stuttgart, Germany). The strains were grown as previously described.[15b,26] ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ unless otherwise noted on a Bruker MSL 300 at 300 and 75.47 Mhz, respectively. Chemical shifts are relative to TMS (δ 0.00) with $CHCl_3$ as internal standard [δ 7.23 (^{1}H) and δ 76.90 (^{13}C)] and coupling constants are given in Hz. ^{13}C NMR multiplicities are determined by using a DEPT pulse sequence. Low resolution MS data were determined at 70 eV *via* DI-EI on a KRATOS-profile spectrometer. FT-IR (in ν/cm^{-1}) spectra were recorded on a Bomem-Michelson M100 spectrometer as a neat film on a NaCl disc, unless otherwise noted. Optical rotation values were measured on a Perkin-Elmer 341 polarimeter at 589 nm (Na line) in a 1 dm cuvette. TLC plates were run on silica gel Merck 60 F_{254} or aluminium oxide 150 F_{254} neutral (type T), compounds were visualized by spraying with vanillin/H_2SO_4 conc. (5 g/l), Mo-reagent [$(NH_4)_6Mo_7O_{24}\bullet 4H_2O$ (1.1 g/L), $Ce(SO_4)_2\bullet 4H_2O$ (4g/L) in H_2SO_4 (10%)] or $KMnO_4$ reagent [$KMnO_4$ (2.5 g/L), Na_2CO_3 (20 g/L) in H_2O]. GC analyses were carried out on a Shimadzu GC-14A equipped with FID and a RSL 1701 capillary column (30m, 0.25 mm, 0,25 μm film, H_2). Enantiomeric excesses were analyzed on the same gas chromatograph equipped with FID, using a CP-Chirasil-DEX CB column (25m, 0.32 mm, 0.25 μm film, H_2). HPLC analyses were performed on a JASCO system containing a 880-PU pump with UV detection, and equipped with a CHIRALPAK AD column (eluent heptane / 2-propanol 95:5). Flash chromatography was performed on silica gel Merck 60 (230-400 mesh). Petroleum ether had a boiling range of 60-90 °C.

Solvents were dried and freshly distilled by standard techniques. For dry reactions, flasks were dried at 150 °C and flushed with dry argon, just before use, and reactions were carried out under argon. Mineral acids (37% HCl, 70% $HClO_4$, 85% H_3PO_4, 60% HNO_3, 98% H_2SO_4) were obtained from commercial sources and used without further purification. Product solutions were dried over Na_2SO_4, and then the solvent was evaporated under reduced pressure. Compounds **1a**,[12a] **1b**,[12c] **1c**,[13, 27a] **1d**,[12b] **2a**,[12a] **2b**,[12c] **2d**,[27b] **3a**,[27c] **5a**,[27d] **5b**,[27e] **5d**,[27f] **6a**,[27g] **6b**,[27h] **6d**,[27i] **7a**,[27j] **7b**,[27k] and **7d**[27l] have been synthesized previously.

(±)-2-(4-Bromobutyl)-2-methyl oxirane (1c).[13] To a vigorously stirred mixture of 50 mL of dry THF and 14.03 g (577.1 mmol) of activated[28] magnesium turnings, cooled to 0 °C, was added dropwise a solution of 18.25 g (201.5 mmol) of 3-methylallyl chloride in 150 mL of dry THF. After the addition was complete, the mixture was stirred at 0 °C for an additional 2 h and then allowed to warm to r.t. The resulting Grignard reagent was filtered under argon atmosphere and then added dropwise to a solution of 36.71 g (181.8 mmol) of 1,3-dibromopropane in 450 mL of dry THF. The reaction mixture was stirred at r.t. for 20 h, after which the excess of Grignard reagent was cautiously destroyed by addition of saturated aqueous NH_4Cl at 0 °C. After dilution with 150 mL of water, the two phases were separated and the aqueous layer was extracted with three 100-mL portions of CH_2Cl_2. The combined organic layers were washed with 150 mL of brine, dried, and partially evaporated at 15 °C. The crude product was used directly for the next reaction in order to reduce losses due to the volatility of the product.

To a vigorously stirred solution of the crude product in 500 mL of CH_2Cl_2 was added 29.56 g (213.9 mmol) of K_2CO_3. After the mixture was stirred at r.t. for 1 h and then cooled to 0 °C, *m*-CPBA (36.75 g, 212.9 mmol) was added slowly. The reaction was allowed to warm to r.t. and stirred for an additional 20 h, after

which the white suspension was filtered. The resulting yellowish solution was treated with 250 mL of 10% aqueous $Na_2S_2O_5$ to destroy excess peracid. The two-phase system was stirred for 30 min and then the layers were separated. The organic phase was washed with 100 mL of saturated aqueous $NaHCO_3$, dried, and evaporated. Flash chromatography (gradient from 30:1 to 5:1, petroleum ether/EtOAc) afforded 26.45 g (68%) of (±)-**1c** as a clear liquid. Spectroscopic data are given below.

General Procedure for the Preparative Biohydrolysis of (±)-1a-d. Racemic Epoxides **1a-d** (2.00 g, 10.37-15.87 mmol) were hydrolyzed using rehydrated lyophilized microbial cells (2.00 g) in Tris-buffer (100 mL, 0.05 M, pH 7.5) by shaking the mixture at 30 °C with 120 rpm. The reactions were monitored by TLC and GC and after an appropriate degree of conversion was reached (20-48 h) the mixtures were continuously extracted with CH_2Cl_2. The organic layers were washed with 100 mL of brine, dried, and evaporated. The remaining residues were flash chromatographed (gradient of 10:1 to 5:1, petroleum ether/EtOAc) to give enantiomerically enriched epoxides (*R*)-**1a-d** and the corresponding vicinal diols (*S*)-**2a-d**.
Yields, e.e. values, and optical rotation data for all compounds are listed below. Compounds **1a**, **1b**, **1d**, **2a**, **2b** and **2d** have been characterized before (*vide supra*).[12,27a,b] The enantiomeric excess of these compounds was determined by GC on a chiral stationary phase as previously described.[12] The characteristic data of **1c** and **2c** are shown below.
(R)-**1a**: Yield 45%, e.e. >99%, $[\alpha]^{20}_D$ –4.2 (c 3.6, $CHCl_3$) {Ref.[29a] $[\alpha]^{20}_D$ –7.4 (neat, e.e. 88%)}; *(R)*-**1b**: yield 43%, e.e. 96%, $[\alpha]^{25}_D$ –5.4 (c 1, $CHCl_3$); (*R*)-**1c**: yield 46%, 7.05 (*S*) and 7.24 (*R*) min (90°C iso, 1 bar), e.e. >99%, $[\alpha]^{20}_D$ –14.5° (c 0.5, $CHCl_3$), ^{1}H NMR: 1.30 (s, 3H), 1.51-1.67 (m, 4H), 1.79-1.94 (m, 2H), 2.55 (d, J = 2.65, 1H), 2.65 (d, J = 2.65, 1H), 3.40 (t, J = 6.61, 2H); ^{13}C NMR: 20.86 (q), 23.84 (t), 32.58 (t), 33.58 (t), 35.75 (t), 53.76 (t), 56.69 (q); MS, *m/z* (relative intensity) 193 (M^+-1, 0.5), 191 (M^+-1, 0.5), 111 (55), 99 (12), 85 (100), 43 (59); (*R*)-**1d**: yield 47%, e.e. 81%, $[\alpha]^{25}_D$ –8.2 (c 1, $CHCl_3$).
(S)-**2a**: Yield 47%, e.e. >99%, $[\alpha]^{25}_D$ –1.4 (c 1, $CHCl_3$) {Ref.[29b] $[\alpha]^{20}_D$ –1.8 (c 0.98, $CHCl_3$, e.e. 88%)}; *(S)*-**2b**: yield 40%, e.e. 97%, $[\alpha]^{20}_D$ –2.3 (c 1, EtOH) {Ref.[12c] $[\alpha]^{20}_D$ –2.1 (c 0.92, EtOH, e.e. 94%)}; *(S)*-**2c**: yield 45%, 6.75 (*S*) and 7.02 (*R*) min (145°C iso, 1 bar), e.e. >99%, $[\alpha]^{20}_D$ –3.1° (c 1, EtOH); ^{1}H NMR: 1.15 (s, 3H), 1.41-1.54 (m, 4H), 1.82-1.93 (m, 2H), 2.70 (br s, 2H), 3.39 (d, J = 2.78, 1H), 3.41 (d, J = 2.78, 1H), 3.44 (t, J = 6.64, 2H); ^{13}C NMR: 22.60 (q), 23.40 (t), 33.34 (t), 33.86 (t), 37.79 (t), 69.88 (t), 73.08 (s); MS, *m/z* (relative intensity) 197 (M^+-15, 0.9), 195 (M^+-15, 0.9), 181 (73), 179 (75), 99 (12), 75 (84), 43 (100); *(S)*-**2d**: yield 39%, e.e. 96%, $[\alpha]^{25}_D$ –17.9 (c 0.5, EtOH) {Ref.[12b] $[\alpha]^{20}_D$ –11.7 (c 0.56, EtOH, e.e. 75%)}.

General Procedure for the Acid Catalyzed Hydrolyses of (*R*)-1a-d. Reactions were performed in water or dioxane at a concentration of 0.0145 M of epoxide. Mineral acid was added dropwise until the concentration of acid reached 0.18 M. The water concentration varied between 0.63 M and 0.02 M, and was dependent on which acidic conditions were chosen. The reaction mixture was stirred at r.t. for 15 min, and then the reaction was quenched by neutralization with saturated aqueous $NaHCO_3$. Then EtOAc was added, and the resulting biphasic mixture was stirred vigorously for an additional 30 min. The organic layer was separated, dried and evaporated. Isolation of products, product ratios and yields were obtained by standard chromatographical techniques.
Analytical Scale Reactions of *(R)*-1a-d with Mineral Acids. The general procedure was employed by using 0.0075-0.01 g *(R)*-**1a-d** in ca. 4 mL of solvent and 0.06 mL of 37% aqueous HCl, 0.06 mL of 70% aqueous $HClO_4$, 0.048 mL of 85% aqueous H_3PO_4, 0.052 mL of 60% aqueous HNO_3, 0.04 mL of 98% aqueous H_2SO_4, 0.043 mL of 93% aqueous H_2SO_4, or 0.056 mL of 70% aqueous H_2SO_4. After workup, a sample from the organic layer was directly analyzed by GC and/or HPLC.
Preparative Scale Reactions. In order to obtain pure compounds for characterization and as reference material, as well as to demonstrate the general applicability, several reactions were performed on a preparative scale:
Chlorohydrin Formation. The general procedure was employed by using 0.278 g (2.18 mmol) of *(R)*-**1a** in 150 mL of dioxane and 2.25 mL of 37% aqueous HCl. Workup and flash chromatography (petroleum ether/EtOAc, 1:1) gave (in order of elution) 0.215 g (60%) of a 1:1 (NMR) mixture of chlorohydrins **3a** and **4a**, respectively, and 0.072 (26%) of *(E)*-**7a**. The spectroscopic data for *(E)*-**7a** were identical with those

reported previously.[27j] Careful column chromatography on silica gel (gradient 50:1 to 20:1, petroleum ether/EtOAc) afforded pure samples of **1-chloro-2-methyl heptan-2-ol (3a):** ^{1}H NMR: 0.88 (t, J = 7, 3H), 1.24 (s, 3H), 1.28-1.61 (m, 8H), 2.31 (br s, 1H), 3.45 (d, J = 10.9, 1H), 3.48 (d, J = 10.8, 1H); ^{13}C NMR: 14.12 (q), 22.65 (t), 23.63 (t), 24.52 (q), 32.12 (t), 39.87 (t), 54.41 (t), 76.02 (s); MS, *m/z* (relative intensity) 166 (M^+, 0.5), 164 (M^+, 1.5), 148 (0.3), 146 (0.9), 128 (3), 95 (60), 43 (100), and **2-chloro-2-methyl heptan-1-ol (4a):** ^{1}H NMR: 0.87 (t, J = 7, 3H), 1.19-1.54 (m, 6H), 1.49 (s, 3H), 1.61-1.83 (m, 2H), 2.6 (br s, 1H), 3.61 (d, J = 4.9, 1H), 3.64 (d, J = 4.9, 1H); ^{13}C NMR: 14.12 (q), 22.71 (t), 24.19 (t), 26.26 (q), 32.39 (t), 40.64 (t), 71.18 (t), 72.27 (s); MS, *m/z* (relative intensity) 166 (M^+, 0.7), 164 (M^+, 2.0), 148 (0.9), 146 (0.3), 95 (67), 43 (100).

The general procedure was employed by using 0.275 g (2.18 mmol) of *(R)*-**1b** in 150 mL of dioxane and 2.25 mL of 37% aqueous HCl. Workup and flash chromatography (petroleum ether/EtOAc, 1:2) gave (in order of elution) 0.266 g (75%) of a 1:1 (NMR) mixture of chlorohydrins **3b** and **4b**, respectively, and 0.005 (2%) of *(E)*-**7b**. The spectroscopic data for *(E)*-**7b** were identical with those reported previously.[27k] Careful column chromatography on silica gel (gradient 100:1 to 25:1, petroleum ether/EtOAc) afforded pure samples of **1-chloro-2-methyl 6-hepten-2-ol (3b):** ^{1}H NMR: 1.21 (s, 3H), 1.31-2.23 (m, 6H), 2.26 (br s, 1H), 3.51 (s, 2H), 4.91-5.06 (m, 2H), 5.67-5.88 (m, 1H); ^{13}C NMR: 23.66 (t), 26.13 (t), 33.71 (q), 38.77 (t), 54.27 (t), 75.62 (s), 114.91 (t), 138.20 (d); MS, *m/z* (relative intensity) 164 (M^+, 0.1), 162 (M^+, 0.3), 146 (0.2), 144 (0.6), 93 (60), 55 (61), 43 (100), and **2-chloro-2-methyl 6-hepten-1-ol (4b):** ^{1}H NMR: 1.19-1.65 (m, 2H), 1.49 (s, 3H), 1.75-1.25 (m, 4H), 2.6 (br s, 1H), 3.61 (d, J = 1.5, 1H), 3.66 (d, J = 1.5, 1H), 4.85-5.16 (m, 2H), 5.47-5.93 (m, 1H); ^{13}C NMR: 23.09 (t), 24.39 (t), 33.98 (q), 39.89 (t), 71.05 (t), 72.07 (s), 115.03 (d), 138.35 (t); MS, *m/z* (relative intensity) 164 (M^+, 1.5), 162 (M^+, 4.5), 146 (0.9), 144 (0.3), 93 (66), 55 (67), 43 (100).

The general procedure was employed by using 0.327 g (2.21 mmol) of *(R)*-**1d** in 150 mL of dioxane and 2.25 mL of 37% aqueous HCl. Workup and flash chromatography (petroleum ether/EtOAc, 1:2) gave 0.371 g (91%) of a 9:1 (HPLC) mixture of chlorohydrins **3d** and **4d**. Careful column chromatography on silica gel (gradient 25:1 to 5:1, petroleum ether/EtOAc) afforded pure samples of **1-chloro-2-methyl-3-phenyl propan-2-ol (3d):** ^{1}H NMR: 1.29 (s, 3H), 2.06 (br s, 1H), 2.90 (d, J = 11.0, 1H), 2.92 (d, J = 11.0, 1H), 3.44 (d, J = 10.3, 1H), 3.47 (d, J = 10.3, 1H), 7.20-7.39 (m, 5H); ^{13}C NMR: 24.79 (q), 45.09 (t), 52.97 (t), 72.40 (s), 126.94 (d), 128.48 (2d), 130.38 (2d), 136.48 (s); MS, *m/z* (relative intensity) 186 (M^+, 0.3), 184 (M^+, 0.9), 171 (0.2), 169 (0.6), 148 (15), 135 (11), 117 (10), 91 (100), 43 (28), and **2-chloro-2-methyl-3-phenyl propan-1-ol (4d):** ^{1}H NMR: 1.51 (s, 3H), 2.26 (br s, 1H), 3.12 (d, J = 13.8, 1H), 3.17 (d, J = 14.0, 1H), 3.59 (s, 1H), 3.63 (s, 1H), 7.11-7.40 (m, 5H); ^{13}C NMR: 26.09 (q), 46.24 (t), 70.01 (t), 74.42 (s), 127.08 (d), 128.22 (2d), 130.89 (2d), 136.08 (s); MS, *m/z* (relative intensity) 186 (M^+, 0.4), 184 (M^+, 1.2), 171 (0.1), 169 (0.3), 148 (15), 135 (12), 117 (9), 91 (100), 43 (31).

Rearrangement. The general procedure was employed by using 0.280 g (2.19 mmol) of *(R)*-**1a** in 150 mL of dioxane and 2.25 mL of 70% aqueous $HClO_4$. The reaction was allowed to stir until completion (25 min). The usual workup and careful evaporation yielded 0.238 g (85%) of crude **2-methyl heptanal (5a)**[16]: IR (KBr): 2922, 2852 (s, C-H), 1728 (s, C=O), 1468 (s, C-H_2/C-H_3), 1372 (m, C-H_3), 718 (s, C-H_2); ^{1}H NMR: δ 1.05 (d, J = 6.7, 3H), 1.09-1.42 (m, 9H), 1.47-1.71 (m, 2H), 2.18-2.36 (m, 1H), 9.55 (d, J = 2.0, 1H). Crude **5a** was stirred with 0.08 g (2.11 mmol) of $NaBH_4$ in 25 mL of MeOH at rt. After completion of the reaction, excess $NaBH_4$ was destroyed with saturated aqueous Na_2SO_4, the organic layer was dried and evaporated. Flash chromatography (petroleum ether/EtOAc, 1:1) afforded 0.230 g (81%) of 2-methyl heptan-1-ol, which spectroscopic data were identical to those reported previously.[30a]

The general procedure was employed by using 0.280 g (2.22 mmol) of *(R)*-**1b** in 150 mL of dioxane and 2.25 mL of 70% aqueous $HClO_4$. The reaction was allowed to stir until completion (15 min). The usual workup and careful evaporation yielded 0.263 g (94%) of crude **2-methyl 6-hepten-1-al (5b)**[16]: IR: 3072 (w, alkenyl C-H), 2927, 2864 (s, C-H), 1708 (s, C=O), 1640 (m, C=C), 1455 (s, C-H_2/C-H_3), 993 (s, alkenyl C-H_2), 910 (s, alkenyl C-H_2); ^{1}H NMR: 0.79-0.91 (m, 2H), 1.06 (d, J = 7.0, 3H), 1.08-1.72 (m, 1H), 1.96-2.09 (m, 2H), 2.23-2.36 (m, 1H), 4.88-5.03 (m, 2H), 5.61-5.84 (m, 1H), 9.57 (d, J = 1.9, 1H). Crude **5b** was stirred with $NaBH_4$ (0.08 g, 2.11 mmol) as described for crude **5a.** Workup and flash chromatography (petroleum ether/EtOAc, 1:1) afforded 0.244 g (87%) of 2-methyl 6-hepten-1-ol, which spectroscopic data were identical to those reported previously.[30b]

The general procedure was employed by using 0.250 g (1.69 mmol) of *(R)*-**1d** in 110 mL of dioxane and 1.75 mL of 70% aqueous $HClO_4$. The reaction was allowed to stir until completion (35 min). The usual workup and careful evaporation yielded 0.199 g (79%) of crude **2-methyl-3-phenyl propanal (5d)**[16]: IR: 3062 (w, aryl C-H), 2933, 2863 (s, C-H), 1728 (s, C=O), 1603 (w, aryl C-H), 1495 (m, aryl C-H), 1454 (s, C-H_2/C-H_3), 742, 700 (s, aryl C-H); ^{1}H NMR: 1.10 (d, J = 6.8, 3H), 2.56-2.78 (m, 2H), 3.11 (dd, J = 4.9, 12.4, 1H), 7.17-7.37 (m, 5H), 9.73 (d, J = 1.4, 1H). Crude **5d** was stirred with $NaBH_4$ (0.05 g, 1.32 mmol) in 20 mL of MeOH as described for **5a**. Workup and flash chromatography (petroleum ether/EtOAc, 1:1) afforded 0.192 g (76%) of 2-methyl-3-phenyl propan-1-ol, which spectroscopic data were identical to those reported previously.[30c]

Elimination. The general procedure was employed by using 0.270 g (2.14 mmol) of *(R)*-**1a** in 150 mL of dioxane and 1.8 mL of aqueous 85% H_3PO_4. Workup and flash chromatography (petroleum ether/EtOAc, 5:1) gave (in order of elution) 0.039 g (14%) of unreacted *(R)*-**1a** and 0.181 g (67%) of a 1:1 (GC) mixture of olefins **6a** and **7a** (*E/Z* ratio 7:1, NMR), respectively. Careful column chromatography on silica gel (gradient 100:1 to 75:1, petroleum ether/EtOAc) afforded a pure sample of **6a**, which showed spectroscopic data identical to those previously reported,[27g] a pure sample of *(E)*-**7a**,[27j] and a 2:1 mixture of *(E)*-**7a** and *(Z)*-**7a**. The presence of *(Z)*-**7a** was proven by comparison of the NMR data with those from the literature.[31]

The general procedure was employed by using 0.285 g (2.26 mmol) of *(R)*-**1b** in 150 mL of dioxane and 1.8 mL aqueous of 85% H_3PO_4. Workup and flash chromatography (petroleum ether/EtOAc, 7.5:1) gave (in order of elution) 0.043 g (15%) of unreacted *(R)*-**1b** and 0.190 g (67%) of a 1:1 (GC) mixture of olefins **6b** and **7b** (*E/Z* ratio 6:1, NMR), respectively. Careful column chromatography on silica gel (gradient 250:1 to 100:1, petroleum ether/EtOAc) afforded 0.097 g of pure **2-methylene 6-hepten-1-ol (6b):** ^{1}H NMR: 1.41-2.33 (m, 6H), 3.76 (br s, 1H), 4.00 (s, 2H), 4.76-5.37 (m, 4H), 5.42-6.01 (m, 1H); ^{13}C NMR: 27.05 (t), 28.75 (t), 33.60 (t), 68.97 (t), 111.72 (t), 114.75 (t), 138.39 (d), 145.79 (s); and 0.116 g of a 6:1 mixture of *(E)*-**7b** and *(Z)*-**7b**, respectively. The identity and the *E/Z* ratio of **7b** was established by comparison of the NMR data with those from the literature.[27k,32]

The general procedure was employed by using 0.420 g (2.18 mmol) of *(R)*-**1c** in 150 mL of dioxane and 1.8 mL of 85% aqueous H_3PO_4. Workup and flash chromatography (petroleum ether/EtOAc, 10.1) gave 0.353 g (84%) of a 1:1 (GC) mixture of olefins **6c** and **7c** (*E/Z* ratio 7:1, NMR), respectively. Careful column chromatography on silica gel (gradient 75:1 to 50:1, petroleum ether/EtOAc) afforded (in order of elution) 0.079 g of pure **6c**, 0.233 g of a 7:9:1 (NMR) mixture of **6c**, *(E)*-**7c**, and *(Z)*-**7c**, respectively, and 0.041 g of **7c** (*E/Z* ratio 3:1). The NMR data are given below.

6-Bromo-2-methylene heptan-1-ol (6c): ^{1}H NMR: 1.29-1.96 (m, 4H), 2.18 (br t, J = 7, 2H), 3.36 (t, J = 6.6, 2H), 4.33 (s, 2H), 5.06 (d, J = 1.4, 1H), 5.14 (d, J = 1.4, 1H); ^{13}C NMR: 25.92 (t), 31.17 (t), 32.27 (t), 32.71 (t), 67.63 (t), 111.72 (t), 146.39 (s).

***(E)*-6-Bromo-2-methyl 2-hepten-1-ol (7c)**: ^{1}H NMR: 1.60 (s, 3H), 1.71-2.27 (m, 4H), 3.36 (t, J = 7.7, 2H), 3.80 (s, 2H), 4.06 (br s, 1H), 5.54 (t, J = 7.4, 1H); ^{13}C NMR: 13.70 (q), 24.47 (t), 32.47 (t), 32.97 (t), 69.00 (t), 123.24 (d), 136.31 (s).

***(Z)*-6-Bromo-2-methyl 2-hepten-1-ol (7c)**: ^{1}H NMR: 1.66 (s, 3H), 1.77-2.27 (m, 4H), 3.26 (t, J = 7.0, 2H), 3.98 (s, 2H), 4.06 (br s, 1H), 5.41 (t, J = 7.3, 1H); ^{13}C NMR: 15.36 (q), 21.47 (t), 32.91 (t), 37.47 (t), 67.20 (t), 126.04 (d), 135.38 (s).

The general procedure was employed by using 0.325 g (2.20 mmol) of *(R)*-**1d** in 150 mL of dioxane and 1.8 mL of 85% aqueous H_3PO_4. Workup and flash chromatography (petroleum ether/EtOAc, 2:1) gave 0.280 g (86%) of of a 1:1 (HPLC) mixture of olefins **6d** and *(E)*-**7d**, respectively. Pure samples of both compounds were obtained after careful column chromatography (gradient 25:1 to 5:1, petroleum ether/EtOAc). The spectroscopic data of **6d**[27i] and *(E)*-**7d**[27l] were identical to those reported previously.

Hydrolysis. The general procedure was employed by using ca. 2.20 mmol of *(R)*-**1a-c** in 150 mL of dioxane and 1.95 mL of 60% aqueous HNO_3. Workup and flash chromatography (petroleum ether/EtOAc, 2:1) gave diols *(S)*-**2a-c** (76%-85%, e.e. ≈ 65%), next to some (≈ 10%) regained epoxide.

The general procedure was employed by using ca. 2.20 mmol of *(R)*-**1a-d** in 150 mL of dioxane and 1.61 mL of 93% aqueous H_2SO_4. Workup and flash chromatography (petroleum ether/EtOAc, 2:1) gave diols *(S)*-**2a-d** (76%-97%, e.e. ≈ 87-98%).

General Method for the Chemoenzymatic Deracemization of Oxiranes (±)-1a-d. The general method for the preparative biohydrolysis (*vide supra*) was employed by using 1.00 g (5.19-7.94 mmol) of (±)-**1a-d** and 1.00 g of rehydrated lyophilized microbial cells in Tris-buffer (50 mL, 0.05 M, pH 7.5). At 50% conversion (GC) or slightly beyond this value,[25] the reaction was quenched by continuous extraction of *(R)*-**1a-d** and *(S)*-**2a-d** using CH_2Cl_2. The resulting bright orange oil (ca.1.2 g) was treated as described in the general procedure for the acidic reactions by using 1.95-2.95 mL of 93% aqueous H_2SO_4 in 180-275 mL dioxane. Workup and flash chromatography (petroleum ether/EtOAc, 2:1) afforded 0.773-1.124 g (71-98%) of optically pure (e.e. >90%) diols (*S*)-**2a-d**.

Acknowledgements

The authors would like to express their thanks to U. Felfer and D.V. Johnson for helpful discussions and critically proofreading the manuscript. Furthermore, we gratefully acknowledge H.J. Weber and C. Illaszewicz for recording the NMR spectra, C. Mirtl for measuring the MS spectra, and W. Kern for recording the IR spectra. This research was performed within the Spezialforschungsbereich Biokatalyse (SFB-A4) and was financed by the Fonds zur Förderung der wissenschaftlichen Forschung (Austrian Ministry of Science, Vienna F104) and the European Commission (BIO4-CT-0005)

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