Preparation of TADOOH, a Hydroperoxide from TADDOL, and Use in Highly Enantioface- and Enantiomer-Differentiating Oxidations

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Replacement of one OH group in TADDOL (= $\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolane-4,5-dimethanol) by an OOH group gives a stable, crystalline chiral hydroperoxy alcohol TADOOH (= {(4*R*,5*R*)-5-[(hydroperoxydiphenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}diphenylmethanol) **3**, the crystal structure of which resembles those of numerous other TADDOL derivatives (*Fig. 2*). The new hydroperoxide was tested as chiral oxidant in three types of reactions: the epoxidation of enones with base catalysis (*Scheme 2*), the sulfoxidation of methyl phenyl sulfide (*Scheme 3*), and the *Baeyer-Villiger* oxidation of bicyclic and tricyclic cyclobutanones, *rac*-**10a**–**d** with kinetic resolution (*Scheme 4*, *Fig. 3*, and *Table*). Products of up to 99% enantiomer puritiy were isolated (the highest values yet observed for oxidations with a chiral hydroperoxide!). Mechanistic models are proposed for the stereochemical courses of the three types of reactions (*Schemes 5* and *6*, and *Fig. 4*). Results of AM1 calculations of the relative transition-state energies for the anionic rearrangements of the *exo Criegee* adducts of TADOOH to the enantiomeric bicyclo[3.2.0]heptan-6-ones are in qualitative agreement with the observed relative rates (*Table* and *Fig. 5*).

1. Introduction. – Besides C,C-bond-forming reactions, oxidations, and reductions/hydrogenations are the corner stones of organic synthesis. Enantioselective versions of essentially all synthetic transformations in which chiral products arise from achiral precursors are now available, and spectacular examples of enantioselective catalysis continue to appear in the literature. Thus, in the field of oxidations, there are the *Sharpless* epoxidation, dihydroxylation, and aminohydroxylation [1], the *Julia* epoxidation of enones [2], the *Jacobsen-Katsuki* epoxidation [3], the *Kagan* sulfoxidation [4], and enantioselective *Baeyer-Villiger* oxidations [5].

On the other hand, the use of chiral hydroperoxides for enantioselective oxidations has, so far, met with little success[2]). The chiral hydroperoxides [8–10] and peracids [11] employed have been obtained by chromatographic resolution [8] or by enzymatic kinetic resolution [9] of racemic mixtures, or by derivatization of natural products, such as carbohydrates, with H_2O_2 [10] (see the *Formulae* in *Fig. 1*). It is probably fair to state that no selectivites above 50% ee (enantioselectivity 75% es) have generally been obtained in oxidations with chiral hydroperoxides[3]).

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[1]) Postdoctoral Fellow at ETH-Zürich (1999–2000), under the auspices of the *Japan Society for the Promotion of Science* (*JSPS*).

[2]) For enantioselective hydroxylations with chiral dioxiranes and oxaziridines (mainly of enol derivatives), see [6][7].

[3]) For a discussion of enone epoxidations and an example in which 95% es was observed with a special substrate, see [12].

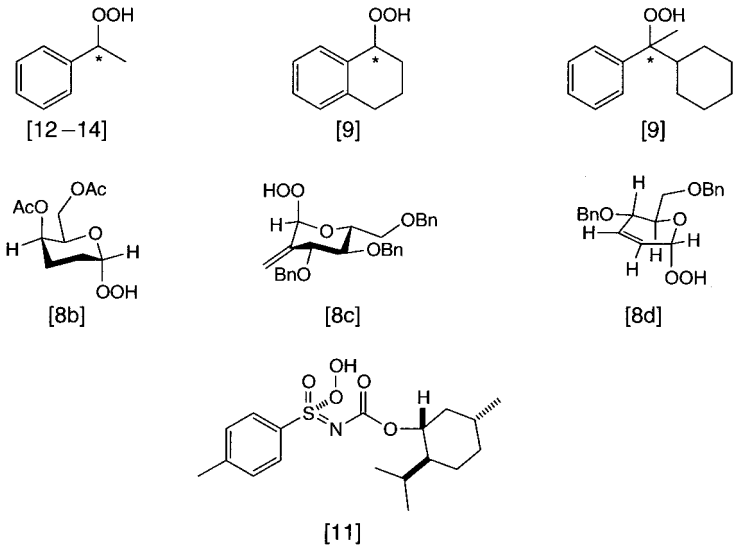


Fig. 1. *Some chiral hydroperoxides obtained by chromatographic or enzymatic* (kinetic) *resolution, or from suitable chiral precursors and* H_2O_2. Some of these compounds have been tested as stoichiometric reagents for enone epoxidation [12], for epoxidation of allylic alcohols [8b–d][14], or for sulfoxidation [8c,d][13]. The imino-sulfonyl-peracid shown was generated *in situ* [11].

We now report a new type of chiral hydroperoxide that is readily prepared from H_2O_2 and a TADDOL, that can be regenerated after use, and that can be used for several enantioselective and 'enantiodifferentiating'[4]) oxidations with selectivities above 90%[5]).

2. Results and Discussion. – 2.1. *Preparation and Structure of TADOOH* **3**. Substitution reactions with replacement of TADDOL OH groups are facile and surprisingly clean, considering the fact that they must occur by the S_N1 mechanism, and that the intermediate cation(s) could undergo various reactions, besides being trapped by a nucleophile[6]). Thus, both OH groups of TADDOL **1** are replaced by Cl with $SOCl_2$ in 82% yield [18], while the *Appel* reaction stops cleanly at the stage of the monochloride **2**, which is isolated in 72% yield [19]. The subsequent replacement of Cl by OOH (**2** → **3** in *Scheme 1*) has been achieved in various ways[7]). In the simplest procedure, the urea·H_2O_2 complex is employed in dimethylformamide (DMF) solution, producing the hydroperoxy alcohol **3** at 50° in almost 90% yield (after chromatography), on a 15-mM scale. Compound **3** ($[\alpha]_D^{r.t.} = -116.5$ in CH_2Cl_2) is

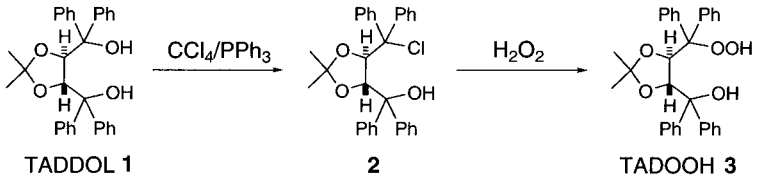
[4]) For the terminology of stereochemistry, see *Helmchen*'s introduction to the *Houben-Weyl*, Vol. E21a [15]. For the term *enantiodifferentiating*, see the definitions by *Izumi* [15][16].

[5]) We use the terms enantioselectivity (% es), enantiomer ratio (er), and enantiomer purity (% ep), and avoid enantiomeric excess (% ee); for a list of stereochemical terms not to be used, see [17].

[6]) TADDOL Ethers are cleaved under acid catalysis in solutions containing H_2O.

[7]) Reaction of **2** with a $MgSO_4$-dried solution of H_2O_2 in THF also leads to formation of **3**, which can be separated chromatographically (SiO_2) from accompanying TADDOL **1**.

Scheme 1. *Preparation of the Hydroperoxide* **3** *from TADDOL*



surprisingly stable under the actual working conditions[8]). Like TADDOLs[9]), the hydroperoxy derivative tends to form inclusion compounds with H-bond acceptors, and it is not surprising that we obtained crystals suitable for X-ray structure analysis with DMF as guest molecules (*Fig. 2*).

As in the structures of all non-symmetrical TADDOL derivatives[9]) capable of forming intramolecular H-bonds [20][21], the more acidic XH group (OOH in **3**) acts as the H-bond donor and the less-acidic ŸH group (OH in **3**) as the H-bond acceptor: there is an eight-membered H-bonded ring in the crystal structure of hydroperoxy alcohol **3**; otherwise, the propeller-like arrangement in **3** of two Ph groups (upper right and lower left side) in a *quasi-axial* and two in a *quasi-equatorial* position is the same as in dozens of other structures of TADDOLs and their derivatives.

2.2. *Epoxidation of Enones by TADOOH* **3**. We first tested the new hydroperoxy alcohol **3** for epoxidations of enones, and we chose the standard substrate chalcone to optimize conditions (*Scheme 2*). This reaction has been carried out previously under numerous conditions, with achiral and chiral hydroperoxides, by base catalysis[10]).

We found that treatment of TADOOH **3** with various bases in THF and addition of 1,3-diphenylprop-2-en-1-one at temperatures between -75 and $+20°$ led to formation of the epoxy ketone **4** in high yield and with excellent enantioselectivities. Two types of conditions were found to give the best results. *i*) Conversion of the hydroperoxide to the Li salt by treatment with a sub-stoichiometric amount of BuLi and reaction with the enone at low temperature (*Entries 7–15* in *Scheme 2*): under these conditions, enantioselectivities of up to 98.5% (GC analysis), with formation of the (−)-(2*R*,3*S*)-epoxy ketone **4**, were obtained (*Entry 10*), the absolute configuration being assigned by optical comparison [2a]. *ii*) The need to activate the enone and at the same time deprotonate the hydroperoxide (to increase its nucleophilicity) was also met by applying what has been called *bifunctional catalysis* [22–24] (*Entries 12–15* in *Scheme 2*): a catalytic amount of LiCl/DBU, a non-self-annihilating *Lewis* acid/base pair, gave an enantioselectivity at 0° (*Entry 15*) comparable to that observed with the Li peroxide.

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[8]) Hydroperoxy alcohol **3** is stable up to *ca.* 130° when it begins to melt with decomposition. A dynamic DSC thermostability test of **3** (carried out at a scan rate of 4°/min) showed the beginning of a strong spontaneous exothermic decomposition reaction above *ca.* 130° when *ca.* 435 kJ/kg are released. This energy would cause a theoretical adiabatic rise in temperature of *ca.* 365° (the estimated heat capacity of the investigated sample is $C_p = 1200$ J/(kg·K)).

[9]) For an extensive review article, covering all aspects of TADDOL chemistry and applications, see [20].

[10]) For reviews, see [2f–i].

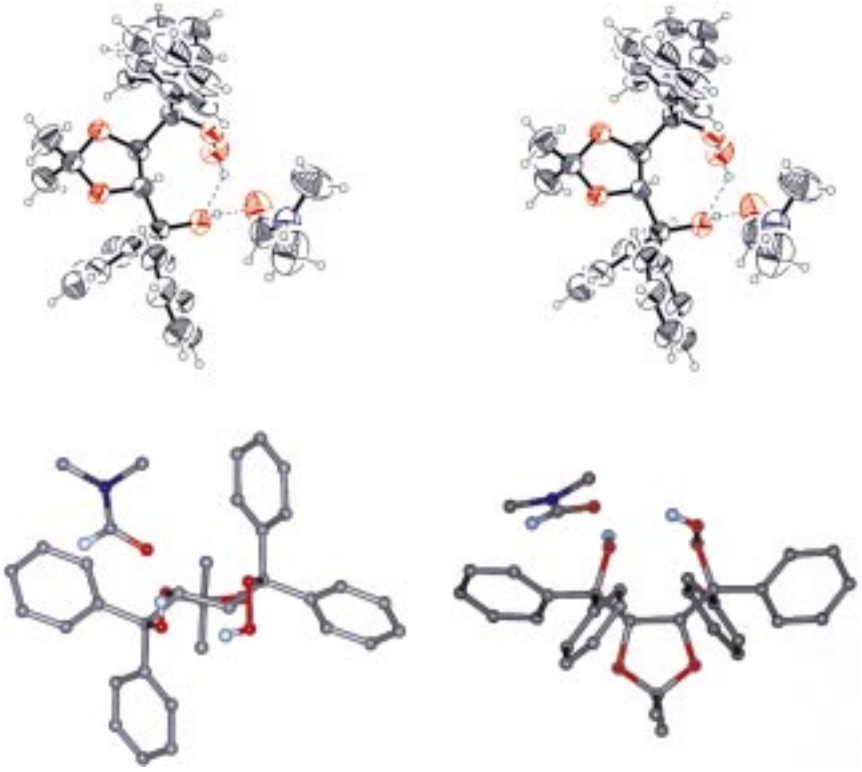


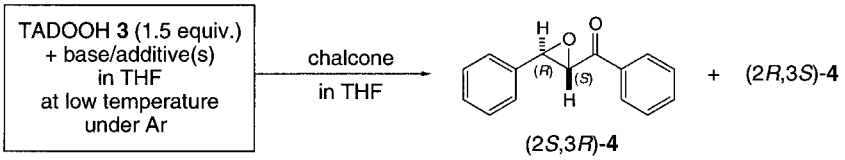
Fig. 2. *X-Ray crystal structure of the TADOOH·DMF inclusion compound* **3**·*O*=*CH*–*NMe*$_2$. *Top:* ORTEP stereoplot with 50% probability level. *Bottom:* front and top view of the 1:1 complex in an *Insight II* (version 98.0) presentation. The X-ray analysis included measurement of the *Bijvoet* pairs, *i.e.*, the absolute configuration (*R*,*R*), as shown here, was determined.

Other enones were also subjected to epoxidation by the new chiral hydroperoxide in high yield and with variable enantioselectivities (see the epoxy ketones **5**–**8** in *Scheme 2*); these reactions were carried out under the standard TADOOH/BuLi conditions, and they have not been optimized.

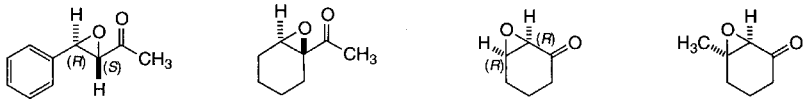
2.3. *Sulfoxidation of Methyl Phenyl Sulfide by* **3**. Another standard substrate for testing an enantioselective oxidation is methyl phenyl sulfide (MeSPh) [4][25][26]. Besides the sulfoxide **9**, there is usually sulfone **10** formed by overoxidation, and there is the interesting implication that a chiral oxidant will react faster with one of the enantiomeric sulfoxides than with the other, so that a kinetic resolution of the primarily formed sulfoxide (which may be cooperative or counterproductive) can complicate assignment of the enantioselectivity of the actual sulfoxidation step.

As outlined in *Scheme 3*, TADOOH **3** oxidizes MeSPh without any catalysis. Under optimized conditions (1.5 equiv. of **3**, 3 d at $-30°$ then 1 d at $+20°$, in THF) the laevorotatory (*S*)-sulfoxide **9** is formed in 73% yield, with an enantiomer purity of 93%. Reaction of *rac*-**9** with **3** at room temperature, with 8% conversion to the sulfone **10**, leads to recovery of the laevorotatory sulfoxide (*S*)-**9**. Thus, the sulfoxide

Scheme 2. *Epoxidation of 1,3-Diphenylprop-2-en-1-one and of Other Enones with Hydrogenperoxy Alcohol* **3**. The equivalents of **3** and of the base refer to 1 equiv. of chalcone. The optimization experiments were carried out with 0.5-mM amounts of chalcone. Enantiomer ratios (er) were determined on chiral GC columns. Yields after FC are given. The absolute configurations of **4** (2*S*,3*R*), **5** (2*S*,3*R*), and **7** (2*R*,3*R*) as shown in the *Formulae* are derived from optical comparison with literature data (see *Exper. Part*); those of the epoxides **6** and **8** are tentatively assigned by analogy (see also *Sect. 6*).



Entry	Base [equiv.]	Additive(s) [equiv.]	Temp. [°]	Reaction time [h]	**4** Yield [%]	**4** (2*S*,3*R*)/(2*R*,3*S*)
1	—	—	–78 → r.t.	7	—	—
2	1.1 Et_3N	—	–78 → r.t.	7	—	—
3	1.1 DMAP	—	–78 → r.t.	7	—	—
4	1.1 KOH	—	–78 → r.t.	7	96	33 : 67
5	1.1 NaOH	—	–78 → r.t.	7	86	46 : 54
6	1.1 LiOH	—	–78 → r.t.	7	95	80 : 20
7	1.1 BuLi	—	–78 → r.t.	7	85	95 : 5
8	1.1 BuLi	—	0	4	94	90 : 10
9	1.1 BuLi	—	–30	24	92	95 : 5
10	1.1 BuLi	—	–78	120	80	98.5 : 1.5
11	1.1 Et_3N	1.1 LiCl	–78 → r.t.	7	—	—
12	1.1 DMAP	1.1 LiCl	–78 → r.t.	7	65	77 : 23
13	1.1 DBN	1.1 LiCl	–78 → r.t.	7	96	88 : 12
14	1.1 DBU	1.1 LiCl	–78 → r.t.	7	89	86 : 14
15	0.11 DBU	0.11 LiCl	–78 → r.t.	7	98	84 : 16

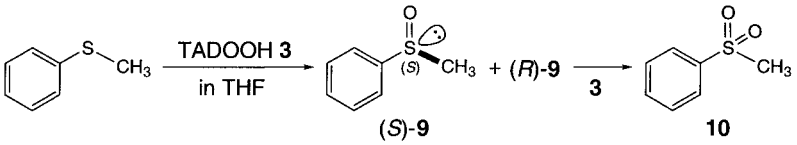


5 (2*S*,3*R*)/(2*R*,3*S*) 89 : 11 | **6** er 70 : 30 | **7** (*R*,*R*)/(*S*,*S*) 55 : 45 | **8** er 91 : 9

enantiomer that is formed faster in the sulfoxidation step is converted to the sulfone more slowly (ratio of rates *ca.* 5 : 1). At $-30°$, sulfone formation is negligible (less than 1%).

2.4. *Enantiomer-Differentiating* Baeyer-Villiger *Oxidation of Bicyclic and Tricyclic Cyclobutanone Derivatives.* Another classical peroxide oxidation is the *Baeyer-Villiger* reaction converting ketones to esters or lactones [5][27][28]. It is known that, for the strained cyclobutanones, base-catalyzed oxidative ring enlargement to γ-lactones occurs with H_2O_2 or RO_2H [29], while the normally employed oxidant is a peracid [30].

Scheme 3. *Oxidation of MeSPh by the Hydrogenperoxy Alcohol* **3**. Reactions were carried out with a 1:1.5 molar ratio of MeSPh and **3**. Yields were detected by GC, enantiomer ratios were determined on a chiral GC column (see *Exper. Part*).



Entry	Temp [°]	Reaction time [h]	**9** Yield [%]	**9** (*S*)/(*R*)	Yield [%] of **10**
1	r.t.	4	91	82 : 18	6
2	r.t.	24	72	88 : 12	27
3	–30	72	61	90 : 10	<1
4	–30 → r.t.	72 + 24	73[a])	93 : 7	23

[a]) Yield of product purified by FC.

Baeyer-Villiger reactions also take place in biological systems, catalyzed by peroxidases [31], and a number of enzymes from various sources have been employed for enantiomer- or enantiotopos-differentiating oxidations [32]. With *racemic* mixtures of cyclobutanone derivatives, the peroxidases (from *Acinetobacter* or from *Cunninghamella echinulata*) can either induce kinetic resolution [33], or else formation of the *normal* lactone from one enantiomer and of the *abnormal* lactone from the other [34][11]), an enantiomer-differentiating regioselective oxidation[12]).

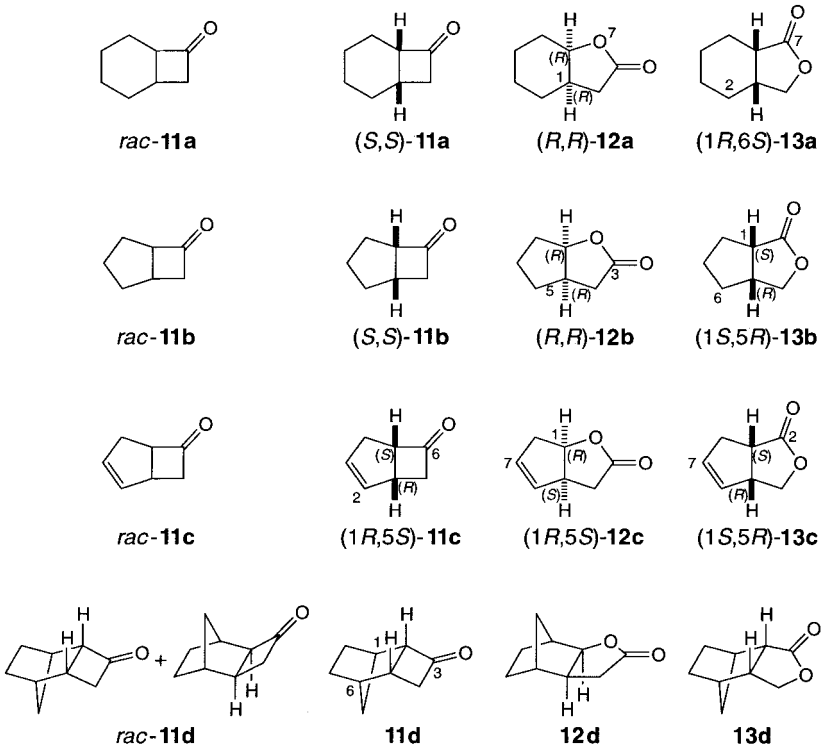
For *Baeyer-Villiger* oxidations with TADOOH **3**, we chose cyclobutanones as substrates, so that we could employ the base-catalysis conditions that worked so well with the enone epoxidations (*vide supra*, *Sect. 2.2*). The cyclobutanones are readily available by dichloroketene cycloaddition to olefins and subsequent reductive dechlorination[13]). Of the *rac*-cyclobutanones **11a**–**d**, the unsaturated compound **11c** is commercially available, and hydrogenation gives the saturated bicyclo[3.2.0]heptanone **11b** (see reference in *Exper. Part*). Following the literature procedures (see *Exper. Part*), we prepared the bicyclo[4.2.0]octanone **11a** and the tricyclic derivative **11d** from cyclohexene and norbornene, respectively. Samples of *racemic* lactones formed as *normal* (see **12**) and as *abnormal* (see **13**) products of *Baeyer-Villiger* oxidation were prepared, and suitable columns for analysis of enantiomer ratios by gas chromatography (GC) for the three series of compounds **11**, **12**, and **13** were chosen. The absolute configurations of lactones **12a**, **12c** were assigned by optical comparison with literature data, the saturated (*i.e.*, **11b**, **12b**, **13b**) and the unsaturated (*i.e.*, **11c**, **12c**, **13c**) series of

11) *Bolm* and *Schlingloff* have shown that a chiral Cu complex exhibits the same behavior when used as a catalyst in the reaction of *rac*-cyclobutanone derivatives with O_2 in the presence of *t*-BuCHO [35].

12) The peroxidases are usually not stable enough to allow for high turnover numbers, so that their use in organic synthesis has been quite limited [36], in comparison to other types of enzymes (see the two volumes on *Enzyme Catalysis in Organic Synthesis* cited in [32a]).

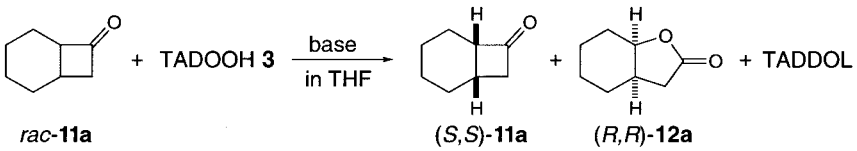
13) For exhaustive treatises of the chemistry of cyclobutanes, see the corresponding *Houben-Weyl* volumes [37][38].

compounds are correlated by hydrogenation, and, for the tricyclic derivatives (*i.e.*, **11d**, **12d**, **13d**), the assignment is based on analogy (structure analogy, signs of $[\alpha]_D^{r.t.}$; see *Exper. Part* and refs. cit. therein).



For the kinetic resolutions by the enantiomer-differentiating power of TADOOH **3**, we first used the bicyclo[4.2.0]octanone *rac*-**11a** as the substrate (see *Scheme 4* and *Fig. 3*). The reaction is clearly base-catalyzed; without a base, or with the *Lewis* acid LiCl alone (*Entry 1* in *Scheme 4*), no reaction took place in THF. With an amount of BuLi (*Entry 2*) or DBU/LiCl (*Entries 3–5*) equivalent to that of the hydroperoxy alcohol **3**, the cyclobutanone was oxidized to give lactone **12a**, the *normal* product exclusively. The (*R*,*R*)-form of **11a** reacts faster (by a factor of 15 at 0°; see *Fig. 3*), and, of course [39], unreacted ketone (*S*,*S*)-**11a** of increasing enantiomer purity can be recovered with increasing degree of conversion. Thus, with 70% conversion at −30° (DBU/LiCl) the unreacted ketone (*S*,*S*)-**11a** is isolated (26% yield) in an enantiomer purity of 99%, while the lactone product (*R*,*R*)-**12a** (66% yield) has an enantiomer purity of 75% (*Entry 1* in *Scheme 4* and *Table*). Interestingly, the other three ketones **11b–d**, containing the cyclobutanone ring annelated to a five-membered ring, gave both the normal (**12b–d**) and the abnormal (**13b–d**) products of the *Baeyer-Villiger* oxidation. Under the standard conditions (as optimized for the bicyclooctanone **11a**, *i.e.*, 70% conversion with DBU/LiCl at −30° in THF), the bicycloheptanone **11b** and bicycloheptenone **11c** gave almost identical results: 30% of unreacted ketone (*S*,*S*)-**11b** and (1*R*,5*S*)-**11c** of 99 and 95% ep and a total of 60–70% of lactones in a 3:1 ratio of

Scheme 4. Baeyer-Villiger *Oxidation of Bicyclo[4.2.0]octan-7-one by the Hydroperoxy Alcohol* **3**. The enantiomer ratio was determined with a chiral GC column (see *Exper. Part*). Conversions were detected by GC.



Entry	**3**	Base	Additive(s)	Temp.	Reaction time	Conversion	**11a** (*S*,*S*)/(*R*,*R*)	**12a** (*R*,*R*)/(*S*,*S*)
	[equiv.]	[equiv.]	[equiv.]	[°]	[h]	[%]		
1	0.7	—	0.7 LiCl	0	30	0	50 : 50	—
2	0.6	0.6 BuLi	—	0	30	60	65 : 35	72 : 28
3	0.6	0.6 DBU	0.6 LiCl	0	30	60	95 : 5	83 : 17
4	0.7	0.7 DBU	0.7 LiCl	–30	60	70	99 : 1	75 : 25
5	1.2	1.2 DBU	1.2 LiCl	–70	30	43	88 : 12	91 : 9

normal to *abnormal* products **12** and **13**, with the former consisting mainly (84 and 90% ep) of the homochiral (*R*,*R*)-**12b** and (1*S*,5*R*)-**12c** and the latter being enantiomerically pure (≥ 99% ep) **13b** and **13c**, respectively (*Entries 2* and *3* in the *Table*). The tricyclic ketone **11d** reacts somewhat less selectively (*Entry 5*).

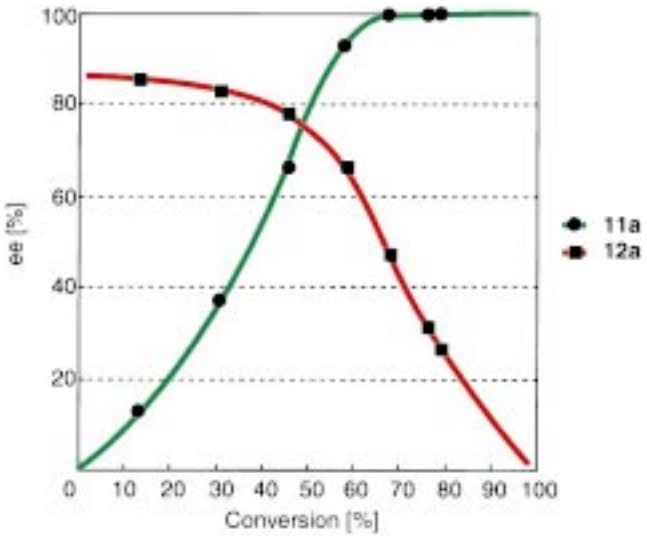


Fig. 3. *Enantiomer excess* (% ee) *of unreacted bicyclooctanone (+)-*(S,S)-**11a** *and of the lactone product (–)-*(R,R)-**12a** *as functions of % conversion in the oxidation of* rac-**11a** *with the hydroperoxy alcohol* **3** (LiCl/DBU, THF, 0°). The ratio of rates with which (*R*,*R*)-**11a** and (*S*,*S*)-**11a** react with **3** under these conditions is 15 : 1 (23 : 1 at –75°).

Table. *Kinetic Resolution of Bicyclic Cyclobutanone Derivatives by TADOOH* **3**, *DBU, and LiCl*. Reactions were carried out with the ketone, **3**, DBU, and LiCl in a 1 : 0.7 : 0.7 : 0.7 molar ratio for 1 h at $-30°$. Yields are given after FC. Enantiomer purity (ep) was determined with a chiral GC column (see *Exper. Part*).

Entry	*rac*	Ketone	Unreacted ketone **11**		Lactones **12** and **13**			
	11	mmol	Yield [%]	ep [%] (configuration)	Total yield [%]	Ratio **12**/**13**	ep of **12** [%] (conf.)	ep of **13** [%] (conf.)
1	**a**	1	26	99 (*S*,*S*)	66	> 99 : 1	75 (*R*,*R*)	–
2	**b**	2	30[a])	99 (*S*,*S*)	70	73 : 27	84 (*R*,*R*)	99 (1*S*,5*R*)
3	**c**	2	30	95 (1*R*,5*S*)	62	75 : 25	90 (1*R*,5*S*)	99 (1*S*,5*R*)
4	**c**	10	26	90 (1*R*,5*S*)	64	72 : 28	93 (1*R*,5*S*)	99 (1*S*,5*R*)
5	**d**	1	23	59	71	63 : 37	88	99

[a]) Yield determined by GC.

Thus, TADOOH **3** turns out to be an enantiomer-differentiating, and also regioselective, stoichiometric oxidant in the *Baeyer-Villiger* reaction of cyclobutanones.

2.5. *Mechanistic Considerations.* The three oxidations with the chiral hydroperoxy alcohol studied by us occur by different mechanisms. All three are well-known standard reactions of organic synthesis or parts of useful synthetic transformations (such as α-sulfenylation, sulfoxidation, and elimination for converting carbonyl compounds to enones or enoates [40–43]), and two of them are name reactions: the *Weitz-Scheffer* oxidation of enones by alkaline H_2O_2 [44], and the *Baeyer-Villiger* oxidation of ketones to ester or lactones [27][45]. Besides the numerous applications of these reactions, there are extensive investigations of their mechanisms to which we will refer in the following brief discussions of mechanistic models for oxidations with TADOOH **3**.

The so-called epoxidation of electron-deficient olefins can be carried out under a variety of conditions[14]). The classical method is treatment with alkaline H_2O_2 (or RO_2H), and the mechanism consists of a conjugate nucleophilic addition of the peroxy anion, followed by cyclization in an intramolecular nucleophilic attack of the enolate formed on the O–O bond, as indicated in *Scheme 5* for the reaction of an enone. If we assume that the conjugate addition is the rate- and stereoselectivity-determining step[15]), an approach of the lithium peroxide (TADOOLi) to the enone as pictured in *Scheme 5* would lead to formation of the major product(s) observed (see *Scheme 2*). The important role played by the counter ion is, of course, not rationalized by this model: with *tert*-amines alone, no reaction takes place ($R_3NH^{\oplus}$ counter ion; *Entries 2* and *3* in *Scheme 2*); from KOH through NaOH to LiOH, there is a reversal of the stereochemical course (30 : 70, 45 : 55, 80 : 20 ratio of enantiomers, *Entries 4–6* in *Scheme 2*); only with $Li^{\oplus}$ counterion under totally aprotic conditions do we observe the highest stereoselectivity (98.5 : 1.5).

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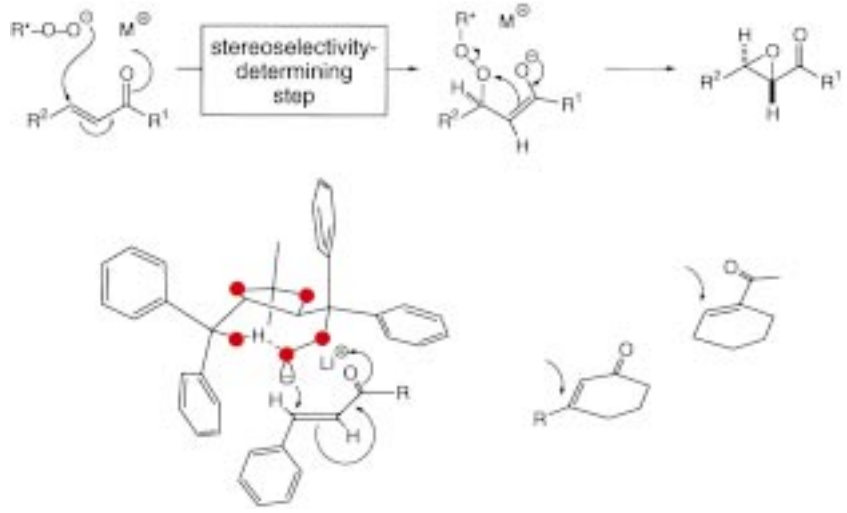
14) These include transition-metal and lanthanide catalysis, phase-transfer catalysis, and polypeptide catalysis. For a recent review article, see [2i].

15) With this assumption, we follow specialists in the field; see the recent article by *Adam et al.* [12], and refs. cit. therein.

Scheme 5. *Two-Step Mechanism of Enone Epoxidation by $RO_2^{\ominus}$ and Mechanistic Model Compatible with the Stereochemical Outcome of the Epoxidations with TADOOH* **3**. For conditions, see *Scheme 2*.



The uncatalyzed sulfoxidation[16]) by TADOOH **3** (*Scheme 3*) must be formulated as nucleophilic attack of the sulfide S-atom on the O–O bond as pictured in *Fig. 4*. The linear arrangement of S:--O–O was chosen such that the initially formed TADDOLate anion would be stabilized by the H-bonding. Minimal *van der Waals* interaction is expected with the substituents on sulfone turned away from the neighboring axial Ph group, and the smaller substituent (Me) near an equatorial Ph group[17]).

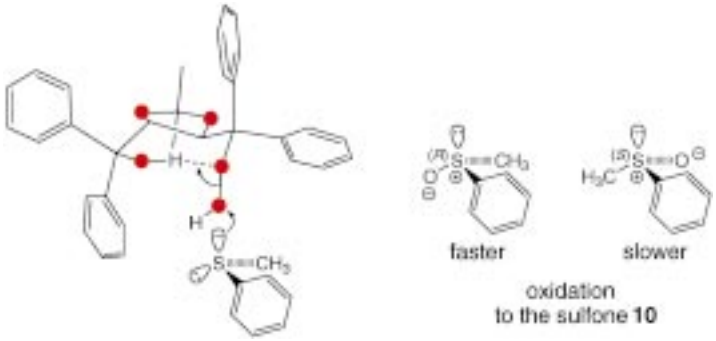


Fig. 4. *Mechanistic model rationalizing preferential formation of (*S*)-methyl phenyl sulfoxide* (**9**) *from methyl phenyl sulfide*, and TADOOH **3**, as well as *faster 'overoxidation' to the sulfone* **10** *of (*R*)-sulfoxide*[17])

The *Baeyer-Villiger* oxidation of ketones is a two-step reaction in which the hydroperoxide or peracid first adds to the C=O group to give a tetrahedral intermediate (*Criegee* adduct [47][48]) that then undergoes rearrangement to the

16) For articles on 'asymmetric sulfoxidation' with seminal referencing, see [4d][13][46].

17) Disregarding polar effects and H-bonding effects in the oxidation of the sulfoxide **9** to the sulfone **10**, the O-atom would have to be considered smaller than the Me group (see the right-hand side of *Fig. 4*).

ester or lactone[18]). Both the formation of the tetrahedral intermediate and the rearrangement are catalyzed by acid and by base, and either step may be rate-determining. Without detailed kinetic measurements, as in the present case, a mechanistic discussion is bound to be rather speculative[19]). For the reactions of the cyclobutanones with TADOOH **3**, we make the following assumptions: *i*) the *Criegee* adducts are formed rapidly (cyclobutanones are highly reactive carbonyl compounds[13])[20]); *ii*) only the *exo*-adducts (*cf.* diastereoisomers **A** and **B** in *Scheme 6*) are considered (TADOO is a very bulky peroxy group[9]); *iii*) the product-determining step is the base-catalyzed rearrangement, as depicted in **C** and **D**[21])[22]) for the *normal* and *abnormal* routes starting from bicycloheptanone **11b**; *iv*) under the conditions specified in the *Table*, the (*R*,*R*,*R*,*R*)-adduct **B** reacts *ca.* 15 times faster than the (*R*,*R*,*S*,*S*)-form, and the approximate product distribution after 70% conversion is as shown in *Scheme 6*.

We were unable to rationalize the observed product distribution by simple inspections of models of the *Criegee* intermediates **A** and **B**, for each of which two preferred conformations must exist, leading to the *normal* and *abnormal* products (*S*,*S*)-**12b**/(*R*,*R*)-**12b** and (1*S*,5*R*)-**13b**/(1*R*,5*S*)-**13b**, respectively. Thus, we calculated the geometries of lowest free energy of activation $\Delta G^{\ddagger}$ for the four anionic[22])[23])[24]) transition states, using *Dewar*'s semiempirical AM1 method [54]. The resulting numbers, shown in *Fig. 5*, are qualitatively in agreement with the experimental results: the two major products (*R*,*R*)-**12b** and (1*S*,5*R*)-**13b** correspond to the lowest activation energies, and the minor products (*S*,*S*)-**12b** and (1*R*,5*S*)-**13b** to the higher ones.

3. Concluding Remarks. – In the era of enantioselective catalysis[25]), it may look like a step backwards to study stoichiometric oxidations by a chiral hydroperoxide: the products obtained (epoxides of enones, sulfoxides, γ-lactones) are, indeed, also accessible in high enantiomer purities by catalytic processes, with H_2O_2, hydroperoxides, peroxides (including dioxiranes), peracids, or O_2 and chiral catalysts

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[18]) Formally, a sigmatropic 1,2-shift (or a *sextett*-rearrangement) to an electron-pair-deficient O-center, with retention of configuration on a migrating stereogenic center, see general textbooks of Organic Chemistry and [5][28b].

[19]) For an excellent treatise about all mechanistic aspects of the *Baeyer-Villiger* reaction, see the 'minireview' by *Renz* and *Meunier* [28b].

[20]) Simple mixing of **3** with *rac*-**11c** in (D_8)-THF at ambient temperature does not lead to a *Criegee* adduct, according to ^{1}H-NMR analysis.

[21]) Maximum stereoelectronic assistance [49–51] is assumed in **C** and **D**, with the three breaking bonds parallel.

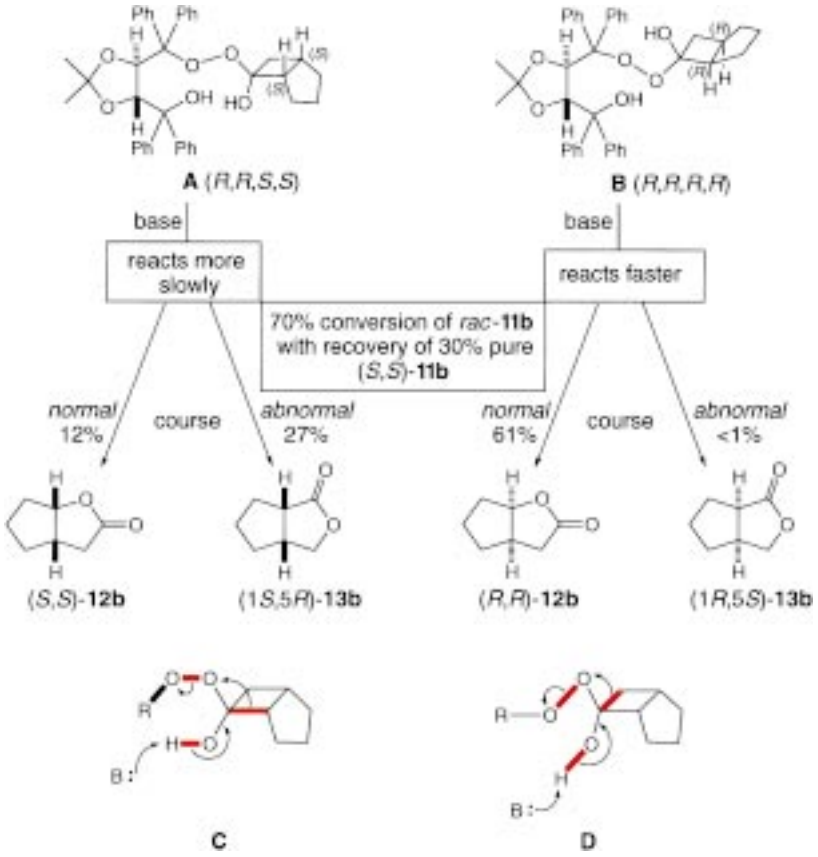
[22]) Of course, the deprotonation and the C–C bond shift need not be concerted: an additional intermediate would then be the deprotonated *Criegee* adduct with an $O^{\ominus}$ group on the cyclobutanone ring. Such an intermediate is used for AM1 calculations (see *Fig. 5*).

[23]) For calculations of the transition-state structure of the *Baeyer-Villiger* rearrangement of acetone with performic acid, see [53].

[24]) For rearrangement of the neutral *Criegee* adducts **A** and **B**, much higher free energies ($\geq$15 kcal/mol) of activation are calculated for the formation of the four lactones. The results of our calculations should be considered with due caution, because they have been performed with anionic transition states, not including the counter-ion $Li^{\oplus}$.

[25]) A recent issue of *Acc. Chem. Res.* was dedicated to the topic 'enantioselective catalysis' and contains two lucid editorials [55].

Scheme 6. *The Two Diastereoisomeric* Criegee *Intermediates* **A** *and* **B**, *the Yields of* Normal *and* Abnormal *Products of* Baeyer-Villiger *Oxidation after 70% Conversion, and Two Geometries* **C** *and* **D** *for* Normal *and* Abnormal *Rearrangement of (*S,S*)*-**11b** *under Stereoelectronic Control*. The numbers for the relative rates with which the enantiomers (*R*,*R*)-**11b** and (*S*,*S*)-**11b** react are taken from the *Table*.



(including peptides and enzymes; see the literature cited in the *Introduction* and in *Sect. 2.5*). However, in these catalytic transformations chiral peroxy compounds are formed *in situ*, and often in tiny amounts to evade identification, so that the detailed mechanisms of their action are very difficult to elucidate (*cf.* the *Sharpless* epoxidation of allylic alcohols by *t*-BuOOH/diethyl tartrate/$Ti(OCHMe_2)_4$ [1a–c]); the same is true of biological processes in which peroxides play an important role. Thus, studies with isolable chiral peroxides of well-defined structures, such as TADOOH **3**, can be instrumental in deepening our understanding of mechanistic details of such oxidations, and it is hoped that the results described here are a step towards this goal. The hitherto reported enantioselectivities of stoichiometric oxidations by chiral peroxides are mostly too low to justify meaningful mechanistic interpretations (a 75:25 ratio of products at 300 K corresponds to a difference ΔE_a between two competing transition states of first-order reactions of merely 0.65 kcal/mol!), and much higher values, such

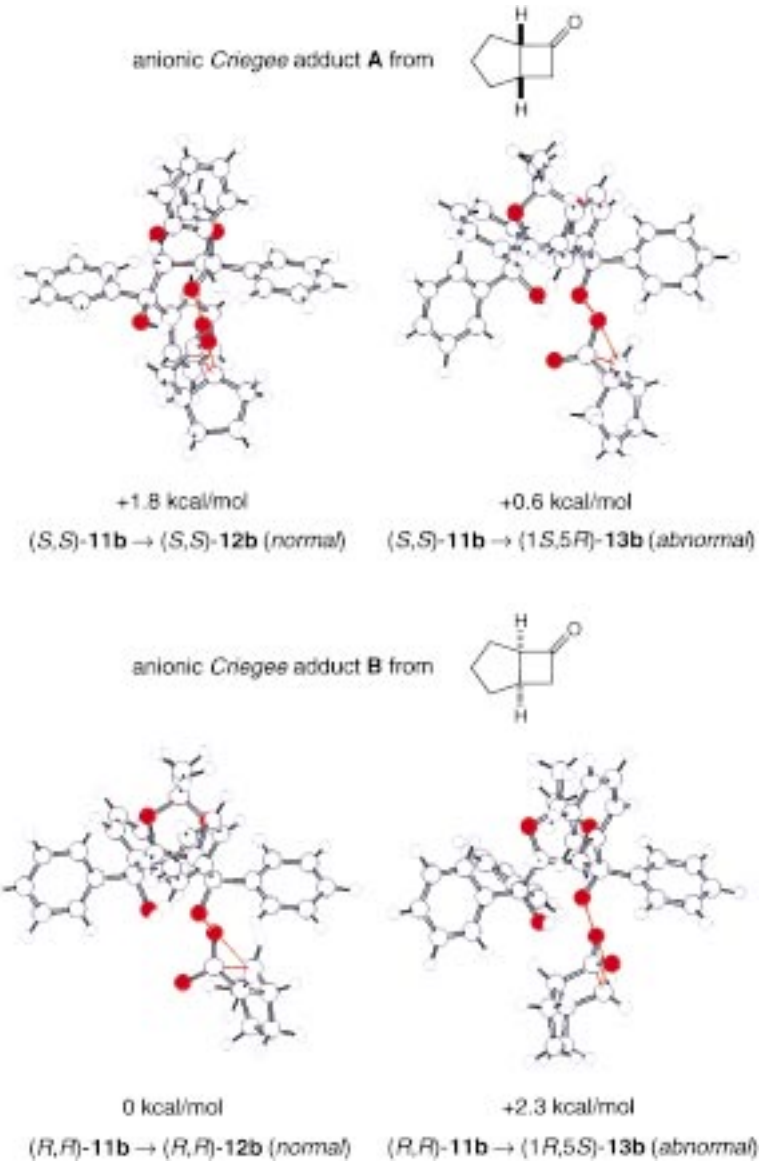


Fig. 5. *Geometries and relative free energies for transition states of the anionic* (base catalyzed) *rearrangement of the* Criegee *adducts* **A** *and* **B** (*cf. Scheme 6*) *with formation of the* normal (*i.e.*, **12b**) *and of the* abnormal (*i.e.*, **13b**) *lactones as calculated by the AM1 software package* Spartan [52]. The transition state of lowest energy ((*R*,*R*)-**10b**$^{\ominus}$ → (*R*,*R*)-**11b** + TADDOLate$^{\ominus}$) is arbitrarily set equal to *zero*.

as some of those observed with TADDOH **3**, are a promising prerequisite for valid mechanistic conclusions. More work is, however, required to start interpretations beyond the simple models proposed here.

We thank the *Japanese Society for the Promotion of Science* for a stipend granted to *M.A.* We thank Dr. *V. Gramlich* for the determining the X-ray crystal structure of **3**, and *Novartis Pharma AG*, Basel, for continuing financial support, and for a safety test of TADOOH.

Experimental Part

1. *General.* Abbreviations: DBN: 1,5-diazabicyclo[4.3.0]non-5-ene, DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP: 4-(dimethylamino)pyridine, FC: flash chromatography, UHP: urea/hydrogen peroxide adduct, t_R: retention time, er: enantiomer ratio, % es: enantioselectivity, percent of the major enantiomer formed, % ep: enantiomer purity, percent of the major enantiomer in a non-racemic mixture. THF (for epoxidation of enone) was freshly distilled over K under Ar before use. DMF was distilled over CaH_2 (*Fluka*), Et_3N over NaOH (*Fluka*). Et_2O was distilled over NaOH and $FeSO_4$ (*Fluka*). LiCl (*Fluka*) was dried at 150° before use. AcOH, bicyclo[2.2.1]hept-2-ene, BuLi (1.6M in hexane), CCl_4, CH_2Cl_2, 1,3-diphenylprop-2-en-1-one, cyclohexene, cyclohex-2-en-1-one, DBU, DMAP, AcOEt, hexane, KOH, LiOH, 3-methylcyclohex-2-en-1-one, MeSPh, NaOH, pentane, Pd/C, (*E*)-4-phenylbut-3-en-2-one, pyridine, Ph_3P, THF (for sulfoxidation and *Baeyer-Villiger* oxidation), Cl_3CCOCl, UHP, and Zn (powder) were used as purchased from *Fluka*, DBN as purchased from *Bayer*, bicyclo[3.2.0]hept-2-en-6-one and 30% H_2O_2 as purchased from *Merck*, H_2 gas as purchased from *GasPan*. 1-(Cyclohex-1-enyl)ethanone was used as purchased from *Aldrich*. TADDOL **1** [18] and the monochloride **2** [19] were prepared according to literature procedures. Bicyclo[4.2.0]octan-7-one [56] and *exo*-tricyclo[4.2.1.$0^{2,5}$]nonan-3-one [57] were obtained from the corresponding olefins (cyclohexene and norbornene (= bicyclo[2.2.1]hept-2-ene)) by [2 + 2] cycloaddition of dichloroketene (generated *in situ* from Cl_3CCOCl and Zn powder, with ultrasound activation, according to literature procedures [58]), followed by dechlorination (Zn powder and AcOH [59]). Bicyclo[3.2.0]heptan-6-one [60] was obtained from bicyclo[3.2.0]hept-2-en-6-one by catalytic hydrogenation (H_2, atmospheric pressure, 10% Pd/C, AcOEt [34]). All long-time reactions at −78° were carried out using a *Lauda Ultra Kryomat® RUK90*, all long-time reactions at −30° with a *Frigomix® S*. TLC: *Macherey-Nagel Alugram® SIL G/UV$_{254}$* or *Merck 60F$_{254}$* silica-gel plates; detection by $UV_{254\,nm}$ light or I_2, or by dipping in/spraying with phosphomolybdic acid solution (phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot 4\,H_2O$ (10 g), H_2SO_4 (60 ml), H_2O (940 ml)). FC: *Fluka* silica gel *60* (40–63 μm), at *ca.* 0.3 bar. GC: *GC 8000^{TOP}* (*CE Instruments*); column: *Alpha Dex 120*, 30 m × 0.25 mm (*Supelco*) or *Beta Dex 120*, 30 m × 0.25 mm (*Supelco*); injection temp. 200°, detection temp. 250°, split ratio 26:1, pressure 100 kPa H_2. M.p.: *Büchi-510* apparatus, uncorrected. Optical rotations: *Perkin-Elmer 241* polarimeter (10 cm, 1 ml cell), at r.t. IR spectra: *Perkin-Elmer 1620-FT-IR* spectrometer, in cm^{-1}. NMR Spectra: *Bruker AMX 400* (^{1}H: 400 MHz, ^{13}C: 100 MHz), *Varian Gemini 300* (^{1}H: 300 MHz, ^{13}C: 75 MHz) or *Gemini 200* (^{1}H: 200 MHz, ^{13}C: 50 MHz); chemical shifts (δ) in ppm downfield from TMS ($\delta = 0.0$) as internal standard; *J* values in Hz; unless otherwise stated, $CDCl_3$ solutions. MS: *Finnigan MAT-TSQ 7000* (ESI) spectrometer; in *m*/*z* (% of basic peak). Elemental analyses were performed by the Microanalytical Laboratory of the Laboratorium für Organische Chemie, ETH Zürich.

2. *Preparation of {(4*R,5R*)-5-[Hydroperoxydiphenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}diphenylmethanol* (TADOOH **3**). A 50-ml, dry two-necked round-bottomed flask containing a *Teflon*-coated stirring bar was charged with **2** (8.00 g, 14.6 mmol), UHP (24.0 g, 164 mmol), and anh. DMF (60 ml) under Ar. The colorless soln. was stirred for 24 h at 50°. The resulting heterogeneous mixture was filtered, and washed with H_2O and pentane to give 10.47 g of crude product, which was dissolved in CH_2Cl_2 and washed twice with H_2O, dried (Na_2SO_4), and chromatographed (50 g of SiO_2, CH_2Cl_2). The solvent was evaporated under reduced pressure to give a colorless amorphous material, which was triturated with hexane (20 ml) for 10 min at r.t. to yield **3** (6.88 g, 14.3 mmol, 87%). M.p. 142–143° (dec.)[8]). R_f 0.49 (CH_2Cl_2). $[\alpha]_D^{r.t.} = -116.5$ ($c = 1.0$, CH_2Cl_2); $[\alpha]_D^{r.t.} = -135.2$ ($c = 1.0$, MeOH). IR ($CHCl_3$) 3673, 3578, 3462, 3299, 3089, 3062, 2935, 2874, 1956, 1891, 1813, 1672, 1601, 1495, 1447, 1382, 1166, 1079, 1053, 1033, 1013, 885, 644, 600. ^{1}H-NMR (300 MHz): 0.63 (*s*, Me); 0.93 (*s*, Me); 3.57 (*s*, OH); 5.04 (*d*, *J* = 7.2, CH); 5.14 (*d*, *J* = 7.2, CH); 7.23–7.51 (*m*, 20 arom. H); 9.66 (*s*, OOH). ^{13}C-NMR (75 MHz): 27.15 (Me); 27.62 (Me); 77.81; 79.77; 81.17; 89.57; 110.81; 127.03; 127.33; 127.41; 127.58; 127.66; 127.75; 127.90; 128.30; 128.58; 128.93; 129.42; 139.74; 142.36; 143.20; 145.90. Anal. calc. for $C_{31}H_{30}O_5$ (482.58): C 77.16, H 6.27; found: C 76.98, H 6.41.

3. *Enantioselective Epoxidation of 1,3-Diphenylprop-2-en-1-one at −78°. General Procedure 1* (*GP 1*). A dry 10-ml *Schlenk* tube containing a *Teflon*-coated stirring bar was charged with **3** (180.9 mg, 0.375 mmol), base (*Scheme 2*, *Entries 2–10*; 0.275 mmol) or LiCl/*tert*-amine (LiCl (0.275 mmol, 11.9 mg), *tert*-amine (0.275 mmol); *Scheme 2*, *Entries 11–15*), and THF (1.0 ml) under Ar. The mixture was cooled to −78°, then 1,3-diphenylprop-2-en-1-one (52.1 mg, 0.25 mmol) in THF (0.5 ml) was added. The mixture was stirred at −78°

for 3 h, at 0° for 2.5 h, and at r.t. for 1 h. The resulting yellow soln. was combined with sat. NH_4Cl soln. (0.5 ml), stirred for 10 min at r.t., and extracted three times with Et_2O. The combined org. phases were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residue was purified by FC (30 g of SiO_2; hexane/Et_2O 5:1) to yield **4** as colorless oil. The er was determined by GC analysis. GC (column: *Alpha Dex 120*, 30 m × 0.25 mm; column temp., 180°: t_R ((2*S*,3*S*)-**4**) 41.1 min; t_R ((2*R*,3*R*)-**4**) 42.2 min.

4. *Enantioselective Epoxidation of α,β-Enones at −30°. General Procedure 2* (*GP 2*). A dry 10-ml *Schlenk* tube containing a *Teflon*-coated stirring bar was charged with **3** (361.9 mg, 0.75 mmol) and THF (1.5 ml) under Ar. The mixture was cooled to −30°, then BuLi (1.6M, 0.34 ml, 0.55 mmol) was added (*cf. Entries 7–10* in *Scheme 2*). After 10-min stirring, the enone (0.50 mmol) in THF (0.5 ml) was added. The mixture was stirred for 1 d at −30°. The resulting yellow soln. was combined with sat. NH_4Cl soln. (0.5 ml), stirred for 10 min at r.t., and extracted three times with Et_2O. The combined org. phases were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residue was purified by FC or bulb-to-bulb distillation.

(2S,3R)-2,3-Epoxy-1,3-diphenylpropan-1-one (**4**). (*E*)-1,3-Diphenylprop-2-en-1-one (104 mg, 0.50 mmol) was allowed to react with **3** in the presence of BuLi, according to *GP 2*. The crude product was purified by FC (30 g of SiO_2; pentane/Et_2O 5:1) to yield **4** (110.5 mg, 0.49 mmol, 98%) as colorless oil; 95% es (GC analysis). GC (column: *Alpha Dex 120*, 30 m × 0.25 mm; column temp, 180°: t_R ((2*R*,3*S*)-**4** (minor)) 41.0 min; t_R ((2*S*,3*R*)-**4** (major)) 42.2 min. $[\alpha]_D^{r.t.} = +209.0$ ($c = 0.86$, CH_2Cl_2) ([2a][61]: (2*R*,3*S*)-**4**: $[\alpha]_D^{r.t.} = -214$ ($c = 2.72$, CH_2Cl_2)). ^{1}H-NMR (300 MHz): 4.06 (*d*, *J* = 1.9, CH); 4.29 (*d*, *J* = 1.9, CH); 7.35–7.39 (*m*, 5 arom. H); 7.43–7.49 (*m*, 2 arom. H); 7.57–7.63 (*m*, 1 arom. H); 7.97–7.99 (*m*, 1 arom. H); 8.00–8.01 (*m*, 1 arom. H). ^{13}C-NMR (75 MHz): 59.26 (OCH); 60.86 (OCH); 125.68; 128.22; 128.66; 128.77; 128.95; 133.90; 135.31; 135.34; 192.95 (C=O). All anal. data were in accordance with the literature values [62].

(3S,4R)-3,4-Epoxy-4-phenylbutan-2-one (**5**). (*E*)-4-Phenylbut-3-en-2-one (146.2 mg, 1.0 mmol) was allowed to react with **3** in the presence of BuLi, according to *GP 2*. Crude product was purified by bulb-to-bulb distillation (123–125°/11 Torr) to yield **5** (120.0 mg, 0.74 mmol, 74%) as colorless oil; 89% es (GC analysis). GC (column: *Beta Dex 120*, 30 m × 0.25 mm; initial column temp, 110° (15 min); heating rate, 5°/min (to 150°)): t_R ((3*S*,4*R*)-**5** (major)) 23.9 min; t_R ((3*R*,4*S*)-**5** (minor)) 24.1 min. $[\alpha]_D^{r.t.} = +70.2$ ($c = 1.0$, $CHCl_3$) ([63]: (3*S*,4*R*)-**5** $[\alpha]_D^{r.t.} = +75.5$ ($c = 2.2$, $CHCl_3$, 98% ee)). ^{1}H-NMR (300 MHz): 2.19 (*s*, Me); 3.49 (*d*, *J* = 1.9, OCH); 4.00 (*d*, *J* = 1.9, OCH); 7.26–7.38 (*m*, 5 arom. H); 9.66 (*s*, 1 H). ^{13}C-NMR (75 MHz): 24.82 (Me); 57.85 (CO); 63.60 (CO); 125.97; 128.97; 129.30; 135.32; 204.14 (C=O). All anal. data were in accordance with the literature values [64].

1-(1,2-Epoxycyclohexyl)ethanone (**6**). 1-(Cyclohex-1-enyl)ethanone (62.1 mg, 0.50 mmol) was allowed to react with **3** in the presence of BuLi, according to *GP 2*. Crude product was purified by FC (15 g of SiO_2; pentane/Et_2O 3:1) followed by bulb-to-bulb distillation (42–43°/2.5 Torr) to yield 56.5 mg of a 47:53 mixture of starting material (1-(cyclohex-1-enyl)ethanone, 24.8 mg, 0.20 mmol, 40%) and **6** (31.7 mg, 0.23 mmol, 46%) as colorless oil; 70% es (GC analysis). GC (column: *Beta Dex 120*, 30 m × 0.25 mm; initial column temp, 80° (10 min); heating rate, 2°/min (to 150°)): t_R(**6** (minor)) 20.6 min; t_R (**6** (major)) 21.6 min. The optical activity of the mixture (calculated for the concentration of **6**) was $[\alpha]_D^{r.t.} = -9.5$ ($c = 0.21$, $CHCl_3$). ^{1}H-NMR (300 MHz) of **6**: 1.21–1.54 (*m*, 4 H); 1.62–1.93 (*m*, 2 H); 2.05 (*s*, Me); 1.92–2.31 (*m*, 1 H); 2.47–2.61 (*m*, 1 H); 3.29–3.31 (*m*, OCH). ^{13}C-NMR (75 MHz) of **6**: 18.84; 19.36; 22.12; 23.34; 24.34; 57.02 (OCH); 63.10 (OC); 208.62 (O=C). The spectroscopic data were in accordance with the literature values [65].

(R,R)-2,3-Epoxycyclohexan-1-one (**7**). Cyclohex-2-en-1-one (96.1 mg, 1.0 mmol) was allowed to react with **3** in the presence of BuLi, following *GP 2*. Crude product was purified by FC (30 g of SiO_2; pentane/Et_2O 3:1) followed by bulb-to-bulb distillation (70–80°/10 Torr) to yield **7** (50.0 mg, 0.45 mmol, 45%) as colorless oil; 55% es (GC analysis). GC (column: *Beta Dex 120*, 30 m × 0.25 mm, initial column temp., 80° (2 min); heating rate, 2°/min (to 100°)): t_R ((*S*,*S*)-**7** (minor)) 13.4 min; t_R ((*R*,*R*)-**7** (major)) 13.6 min. $[\alpha]_D^{r.t.} = +6.6$ ($c = 1.0$, MeOH) ([66]: (*R*,*R*)-**7**: $[\alpha]_D^{r.t.} = +90.5$ ($c = 0.60$, MeOH; 87.5% es)). ^{1}H-NMR (300 MHz): 1.65–1.73 (*m*, 1 H); 1.83–2.14 (*m*, 3 H); 2.23–2.31 (*m*, 1 H); 2.51–2.59 (*m*, 1 H); 3.22 (*d*, *J* = 4.0, CH); 3.58–3.61 (*m*, CH). ^{13}C-NMR (75 MHz): 16.94; 22.79; 36.31; 55.06 (OCH); 55.89 (OCH); 205.98 (C=O). The anal. data were in accordance with the literature values [62].

3-Methyl-2,3-epoxycyclohexan-1-one (**8**). 3-Methylcyclohex-2-en-1-one (55.1 mg, 0.50 mmol) was allowed to react with **3** in the presence of BuLi, according to *GP 2*. Crude product was purified by FC (15 g of SiO_2; pentane/Et_2O 5:1), followed by bulb-to-bulb distillation (60–65°/5 Torr) to yield **8** (46.6 mg, 0.37 mmol, 74%) as colorless oil; 91% es (GC analysis). GC (column: *Beta Dex 120*, 30 m × 0.25 mm; column temp, 100°): t_R (**8** (minor)) 8.7 min; t_R (**8** (major)) 9.3 min. $[\alpha]_D^{r.t.} = +101.0$ ($c = 1.0$, MeOH) ([66]: $[\alpha]_D^{r.t.} = -122.6$ ($c = 0.51$, MeOH)). ^{1}H-NMR (300 MHz): 1.46 (*s*, Me); 1.61–1.68 (*m*, 1 H); 1.82–2.16 (*m*, 4 H); 2.45–2.55 (*m*, 1 H); 3.08 (*s*, CH). ^{13}C-NMR (75 MHz): 17.11; 22.17; 28.33; 35.63; 61.94 (OCH); 62.37 (OC); 206.75 (C=O). The NMR data were in accordance with the literature values [62].

5. *Enantioselective Sulfoxidation of MeSPh. (*S*)-Methyl Phenyl Sulfoxide* (**9**). A 10-ml round-bottomed flask containing a *Teflon*-coated stirring bar was charged with **3** (180.9 mg, 0.35 mmol) and THF (1.5 ml). The mixture was cooled to $-30°$, then MeSPh (31.1 mg, 0.25 mmol) was added. This mixture was stirred for 3 d at $-30°$ then for 1 d at r.t. The solvent was evaporated under reduced pressure. The residue was purified by FC (15 g of SiO_2; Et_2O) to yield **9** (25.5 mg, 0.18 mmol, 73%) as a colorless oil; 93% es (GC analysis). GC (column: *Alpha Dex 120*, 30 m × 0.25 mm; initial column temp, 110° (40 min); heating rate, 2°/min (to 150°)): t_R ((*S*)-**9** (major)) 30.7 min; t_R ((*R*)-**9** (minor)) 31.4 min. $[\alpha]_D^{r.t.} = -154.8$ ($c = 2.1$, $CHCl_3$) ([67]: (*S*)-**9**: $[\alpha]_D^{r.t.} = -131.0$ ($c = 0.53$, $CHCl_3$, 81% ee)). ^{1}H-NMR (300 MHz): 2.73 (*s*, Me); 7.50–7.57 (*m*, 3 arom. H); 7.63–7.68 (*m*, 2 arom. H). ^{13}C-NMR (75 MHz): 43.91 (Me); 123.43; 129.31; 130.97; 145.66. The spectroscopic data were in accordance with the literature values [26c].

6. *Kinetic Resolution of* rac-*Methyl Phenyl Sulfoxide* (**9**). A 10-ml round-bottomed flask containing a *Teflon*-coated stirring bar was charged with **3** (24.1 mg, 0.050 mmol), *rac*-**9** (35.1 mg, 0.25 mmol), and THF (1 ml). The mixture was stirred for 7 h at r.t. An aliquot was withdrawn from the mixture and analyzed by GC: 8% conversion and 53% ep (**9**). GC (column: *Alpha Dex 120*, 30 m × 0.25 mm; initial column temp, 110° (40 min); heating rate, 2°/min (to 150°)): t_R ((*S*)-**9** (major)) 30.7 min; t_R ((*R*)-**9** (minor)) 31.4 min; t_R (**10**) 48.5 min.

7. *Kinetic Resolution of Bicyclo[4.2.0]octan-7-one at 0°*. A 25-ml, round-bottomed flask containing a *Teflon*-coated stirring bar was charged with *rac*-bicyclo[4.2.0]octan-7-one (0.15 mmol), DBU (27.4 mg, 0.18 mmol), LiCl (7.6 mg, 0.18 mmol), and THF (15 ml). The mixture was cooled to 0°, **3** (92.0 mg, 0.18 mmol) was added in eight portions (each 11.5 mg, 0.0225 mmol) every 30 min. After each addition, a small sample of the mixture was withdrawn by syringe, quenched with sat. NH_4Cl/hexane, and analyzed by GC. The results are shown in *Scheme 4* and in *Fig. 3*.

8. *Kinetic Resolution of Cyclobutanone Derivatives. General Procedure 3* (*GP 3*). A 25-ml, round-bottomed flask containing a *Teflon*-coated stirring bar was charged with cyclobutanone derivative (1.0 mmol), DBU (106.6 mg, 0.70 mmol), LiCl (29.7 mg, 0.70 mmol), and THF (15 ml). The mixture was cooled to $-30°$, then **3** (337.8 mg, 0.70 mmol) was added, and stirring was continued at $-30°$ for 1 h. The resulting soln. was combined with sat. NH_4Cl soln. (15 ml), stirred for 10 min at r.t., extracted with Et_2O (4 × 10 ml). The combined org. phases were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residue was purified by FC.

8.1. *Kinetic Resolution of Bicyclo[4.2.0]octan-7-one: (*S,S*)-Bicyclo[4.2.0]octan-7-one* (**11a**) *and (*R,R*)-7-Oxabicyclo[4.3.0]nonan-8-one* (**12a**). *rac*-Bicyclo[4.2.0]octan-7-one (124.2 mg, 1.0 mmol) was allowed to react with **3** in the presence of DBU and LiCl, according to *GP 3*. The crude product was purified by FC (15 g of SiO_2; hexane/Et_2O 10:1 → 5:1 → 1:2) to yield **11a** (32.7 mg, 0.263 mmol, 26.3% yield) and **12a** (92.5 mg, 0.660 mmol, 66.0% yield) as colorless oils.

Data of **11a**: 99% ep (GC analysis). GC (column: *Beta Dex 120*, 30 m × 0.25 mm; initial column temp., 85° (25 min); heating rate, 10°/min (to 150°)): t_R ((*R*,*R*)-**11a** (minor)) 22.8 min; t_R ((*S*,*S*)-**11a** (major)) 23.3 min. $[\alpha]_D^{r.t.} = +18.1$ ($c = 1.00$, $CHCl_3$). ^{1}H-NMR (300 MHz): 1.04–1.28 (*m*, 3 H); 1.37–1.59 (*m*, 3 H); 1.94–1.98 (*m*, 1 H); 2.12–2.18 (*m*, 1 H); 2.43–2.52 (*m*, 2 H); 3.10–3.19 (*m*, 1 H); 3.25–3.30 (*m*, 1 H). ^{13}C-NMR (100 MHz): 21.06; 22.21; 22.34; 22.43; 29.32; 52.02; 56.55; 210.19 (C=O). Anal. data were in accordance with the literature values [56]. Judging from the absolute configuration of **12a** formed in this kinetic resolution, the abs. configuration of **11a** must be (*S*,*S*).

Data of **12a**: 75% ep (GC analysis). GC (column: *Beta Dex 120*, 30 m × 0.25 mm; initial column temp., 85° (25 min); heating rate, 10°/min (to 150°)): t_R ((*R*,*R*)-**12a** (major)) 36.4 min; t_R ((*S*,*S*)-**12a** (minor)) 36.7 min. $[\alpha]_D^{r.t.} = +29.1$ ($c = 1.00$, $CHCl_3$) ([68]: (*S*,*S*)-**12a**: $[\alpha]_D^{r.t.} = -40.3$ ($c = 8$, $CHCl_3$)). ^{1}H-NMR (300 MHz): 1.23–1.31 (*m*, 2 H); 1.43–1.55 (*m*, 2 H); 1.62–1.77 (*m*, 3 H); 2.03–2.12 (*m*, 1 H); 2.24 (*dd*, $J = 2.6$, 16.8, O=CH); 2.34–2.44 (*m*, CH); 2.62 (*dd*, $J = 6.8$, 16.8, O=CH); 4.52 (*dt*, $J = 4.1$, 4.4, OCH). ^{13}C-NMR (100 MHz): 19.53; 22.45; 26.78; 27.43; 34.50; 37.15; 78.83 (OCH); 177.31 (C=O). All anal. data were in accordance with the literature values [68].

8.2. *Kinetic Resolution of Bicyclo[3.2.0]heptan-6-one: (*S,S*)-Bicyclo[3.2.0]heptan-6-one* (**11b**), *(*R,R*)-2-Oxabicyclo[3.3.0]octan-3-one* (**12b**), *and (1*S,5R*)-3-Oxabicyclo[3.3.0]octan-2-one* (**13b**). *rac*-Bicyclo[3.2.0]-heptan-6-one (220.3 mg, 2.0 mmol) was allowed to react with **3** in the presence of DBU and LiCl, following *GP 3*. A small aliquot of the mixture was withdrawn and analyzed by GC to provide the degree of conversion; after 70% conversion, the crude product was isolated and purified by FC (30 g of SiO_2; hexane/Et_2O 10:1 → 5:1 → 1:2) to yield a 2:1 mixture **12b**/**13b** (174.8 mg, 1.39 mmol, 69.5% yield) as a colorless oil, as well as a soln. of **11b**. Because of its volatility, **11b** was not separated from the solvent. The isomeric lactones **12b** and **13b** could

not be separated by FC. Thus, their mixture was analyzed on a chiral column to afford the ratio of (*R*,*R*)-**12b**/(*S*,*S*)-**12b**/(1*S*,5*R*)-**13b**/(1*R*,5*S*)-**13b**. For configurational assignments, as given here, see *Sect. 9*.

Data of **11b**: 99% ep (GC analysis). GC (column: *Beta Dex 120*, 30 m × 0.25 mm; column temp, 85°): t_R ((*R*,*R*)-**11b** (minor)) 10.3 min; t_R ((*S*,*S*)-**11b** (major)) 10.6 min. ^{1}H-NMR (300 MHz): 1.50–1.92 (*m*, 5 H); 2.02–2.06 (*m*, 1 H); 2.49 (*ddd*, *J* = 3.4, 4.4, 18.4, O=CH); 2.84–2.94 (*m*, CH); 3.19 (*ddd*, *J* = 4.4, 8.4, 9.3, O=CH); 3.51–3.59 (*m*, CH). ^{13}C-NMR (100 MHz): 24.60; 28.79; 29.70; 51.44; 64.79 (CH); 214.91 (C=O). The spectroscopic data were in accordance with the literature values [61].

Data of **12b**/**13b**: **12b**: 84% ep, **13b**: 99% ep (GC analysis). GC (column: *Alpha Dex 120*, 30 m × 0.25 mm; column temp, 95°): t_R ((*R*,*R*)-**12b** (major)) 30.7 min; t_R ((*S*,*S*)-**12b** (minor)) 31.0 min; t_R ((1*S*,5*R*)-**13b** (major)) 28.6 min; t_R ((1*R*,5*S*)-**13b** (minor)) 29.0 min. The optical activity of the mixture of lactones **12b** and **13b** was $[\alpha]_D^{r.t.} = +45.6$ (*c* = 1.00, $CHCl_3$). The literature values are $[\alpha]_D^{r.t.} = -59$ (*c* = 1, MeOH) for (*S*,*S*)-**12b** [69], and $[\alpha]_D^{r.t.} = +96.9$ (*c* = 1, $CHCl_3$) for (1*S*,5*R*)-**13b** [70]; if we assume that the specific rotation of **12b** in MeOH and in $CHCl_3$ do not differ a lot, we can calculate the $[\alpha]_D^{r.t.}$ value for the mixture of 12% (*S*,*S*)-**12b** + 61% (*R*,*R*)-**12b** + 27% (1*S*,5*R*)-**13b** + < 1% (1*R*,5*S*)-**13b** (*cf. Table* and *Scheme 6*) to be + 55°, which is not very different from the measured value + 45.6°.

The NMR spectrum of the **12b**/**13b** mixture could be interpreted, and all the signals assigned by comparison with the spectrum of *rac*-**12b** (90%)/*rac*-**13b** (10%), as obtained from *rac*-**11b** and *m*-chloroperbenzoic acid. ^{1}H-NMR (300 MHz): **12b**: 1.52–2.08 (*m*, 6 H); 2.29 (*dd*, *J* = 1.6, 17.1, O=CCH); 2.86–2.89 (*m*, 2 H); 5.01 (*m*, OCH); **13b**: 1.51–3.00 (*m*, 8 H); 3.94 (*dd*, *J* = 3.1, 9.3, OCH); 4.47 (*dd*, *J* = 7.8, 9.3, OCH). ^{13}C-NMR (100 MHz): **12b**: 23.24; 33.32; 33.45; 35.89; 37.75; 86.29 (CO); 177.71 (C=O); **13b**: 25.34; 30.55; 33.61; 38.79; 44.34; 73.51 (CO); 181.03 (C=O). These data were in accordance with literature values reported for **12b** [71] and **13b** [70].

8.3. *Kinetic Resolution of Bicyclo[3.2.0]hept-2-en-6-one: (1*R,5S*)-Bicyclo[3.2.0]hept-2-en-6-one* (**11c**), *(1*R,5S*)-2-Oxabicyclo[3.3.0]oct-6-en-3-one* (**12c**), *and (1*S,5R*)-3-Oxabicyclo[3.3.0]oct-6-en-2-one* (**13c**). *rac*-Bicyclo[3.2.0]hept-2-en-6-one (1.08 g, 10 mmol) was allowed to react with **3** in the presence of DBU and LiCl, according to *GP 3*. The crude product was purified by FC (100 g of SiO_2; pentane/Et_2O 10:1 → 5:1 → 1:2) to yield **11c** (275.4 mg, 2.55 mmol, 25.5%) as a colorless oil and a 7:3 mixture **12c**/**13c** (not separable by FC; 797.2 mg, 6.42 mmol, 64.2%) as a colorless oil.

Data of **11c**: 90% ep (GC analysis); for assignment of abs. configuration, see *Sect. 9*. GC (column: *Beta Dex 120*, 30 m × 0.25 mm; initial column temp, 85°): t_R ((1*S*,5*R*)-**11c** (minor)) 8.5 min; t_R ((1*R*,5*S*)-**11c** (major)) 8.9 min. $[\alpha]_D^{r.t.} = +34.7$ (*c* = 1.00, CH_2Cl_2). ^{1}H-NMR (300 MHz): 2.84 (*dddd*, *J* = 1.9, 4.1, 9.7, 17.4, O=CCH); 2.65–2.75 (*m*, 2 H); 3.33 (*ddd*, *J* = 2.9, 8.4, 17.4, C=CCH); 3.44–3.53 (*m*, 1 H); 3.84–3.92 (*m*, 1 H); 5.78–5.81 (*m*, C=CH); 5.83–5.87 (*m*, C=CH). ^{13}C-NMR (100 MHz): 34.82; 36.77; 54.20; 61.84; 132.17 (C=C); 132.80 (C=C); 213.18 (C=O). The spectroscopic data were in accordance with the literature values [72].

Data of **12c**/**13c**: **12c**: 93% ep; **13c**: 99% ep (GC analysis); for assignment of abs. configuration, see *Sect. 9*. GC (column: *Alpha Dex 120*, 30 m × 0.25 mm; column temp., 105°): t_R((1*R*,5*S*)-**12c** (major)) 17.6 min; t_R ((1*S*,5*R*)-**12c** (minor)) 17.9 min; t_R ((1*S*,5*R*)-**13c** (major)) 16.6 min; t_R ((1*R*,5*S*)-**13c** (minor)) 16.8 min. Optical activity of the **12c**/**13c** 7:3: $[\alpha]_D^{r.t.} = +65.2$ (*c* = 1.00, MeOH) ([73]: (1*S*,5*R*)-**12c**: $[\alpha]_D^{r.t.} = -104$ (*c* = 1.2, MeOH); [34][74]: (1*R*,5*S*)-**13c**: $[\alpha]_D^{r.t.} = -67.9$ (> 95% ee; *c* = 2.3, $CHCl_3$)); with the same assumption made for the **12b**/**13b** mixture above, we calculated + 83° for the optical activity of the mixture of 67% (1*R*,5*S*)-**12c**, + 5% (1*S*,5*R*)-**12c**, + 28% (1*S*,5*R*)-**13c**, + < 1% (1*R*,5*S*)-**13c** (*cf. Entry 4* in the *Table*). The NMR spectra of **12c** and **13c** were interpreted by comparison with the spectrum of *rac*-**12c** (96%)/*rac*-**13c** (4%), as obtained from *rac*-**11c** and H_2O_2/HOAc (see *Sect. 9*). ^{1}H-NMR (300 MHz): **12c**: 2.40–2.82 (*m*, 4 H); 3.48–3.56 (*m*, 1 H); 5.11–5.16 (*m*, OCH); 5.57–5.61 (*m*, C=CH); 5.78–5.82 (*m*, C=CH); **13c**: 2.70–2.79 (*m*, 2 H); 3.11–3.17 (*m*, 1 H); 3.50–3.66 (*m*, 1 H); 4.25 (*dd*, *J* = 1.6, 9.3, OCH); 4.43 (*dd*, *J* = 7.0, 9.3, OCH); 4.65–5.69 (C=CH); 5.85–5.89 (C=CH). ^{13}C-NMR (100 MHz): **12c**: 33.01; 39.27; 45.34; 82.91 (CO); 129.61 (C=C); 131.26 (C=C); 176.79 (C=O); **13c**: 36.28; 41.44; 46.21; 71.35 (CO); 130.61 (C=C); 132.30 (C=C); 180.96 (C=O). The NMR data were in accordance with the literature values reported for **12c** [72] and **13c** [74].

8.4. *Kinetic Resolution of* exo-*Tricyclo[4.2.1.0^{2,5}]nonan-3-one: (+)*-exo-*Tricyclo[4.2.1.0^{2,5}]nonan-3-one* (**11d**), *3-Oxatricyclo[5.2.1.0^{2,6}]decan-4-one* (**12d**), *and 4-Oxatricyclo[5.2.1.0^{2,6}]decan-3-one* (**13d**). *rac-exo*-Tricyclo[4.2.1.0^{2,5}]nonan-3-one (136.2 mg, 1.0 mmol) was allowed to react with **3** in the presence of DBU and LiCl, according to *GP 3*. The crude product was purified by FC (15 g of SiO_2; hexane/Et_2O 10:1 → 5:1 → 1:2) to yield **11d** (30.6 mg, 0.225 mmol, 22.5%) as a colorless oil and a 6:4 mixture **12d**/**13d** (not separable by FC; 108.1 mg, 0.710 mmol, 71.0%) as a colorless oil of $[\alpha]_D^{r.t.} = +25.5$ (*c* = 1.00, $CHCl_3$).

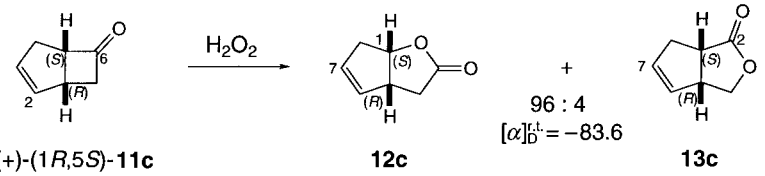
Data of **11d**: 59% ep (GC analysis). GC (column: *Alpha Dex 120*, 30 m × 0.25 mm; column temp., 100°): t_R ((+)-**11d** (major)) 12.8 min; t_R ((−)-**10d** (minor)) 13.1 min. $[\alpha]_D^{r.t.} = +43.1$ (*c* = 1.00, $CHCl_3$). ^{1}H-NMR

(300 MHz): 1.07–1.27 (*m*, 3 H); 1.44–1.67 (*m*, 3 H); 2.23–2.30 (*m*, 1 H); 2.39–2.43 (*m*, 2 H); 2.49–2.57 (*m*, 1 H); 2.98–3.02 (*m*, 1 H); 3.07–3.10 (*m*, 1 H). ^{13}C-NMR (100 MHz): 26.57; 28.18; 31.10; 32.23; 37.14; 39.44; 50.21; 68.02; 212.94 (C=O). The NMR data were in accordance with the literature values [57].

Data of **12d**/**13d**: **12d**: 88% ep; **13d**: 99% ep (GC analysis). GC (column: *Beta Dex 120*, 30 m × 0.25 mm; initial column temp., 85° (11 min); heating rate, 10°/min (to 150°)); t_R (**12d** (major)) 30.9 min; t_R (**12d** (minor)) 31.3 min; t_R (**13d** (major)) 29.5 min; t_R (**13d** (minor)) 29.7 min. The abs. configurations shown in the *formulae* for **11d**, **12d**, and **13d** in *Sect. 5* of the general part have been drawn by analogy with the series of bicyclic compounds **11a**, **12a**/**11b**, **12b**, **13b**/**11c**, **12c**, **13c**, without any experimental evidence! The NMR spectrum of the 6 : 4 **12d**/**13d** mixture could be interpreted, and the signals assigned by comparison with published spectra of **12d** [75] and **13d** [76]. ^{1}H-NMR (300 MHz): **12d**: 1.08–1.78 (*m*, 6 H); 2.08–2.78 (*m*, 5 H); 4.46–4.49 (*m*, OCH); **13d**: 1.08–1.78 (*m*, 6 H); 2.08–2.78 (*m*, 4 H); 3.90 (*dd*, *J* = 3.7, 9.6, OCH); 4.42 (*d*, *J* = 9.6, OCH). ^{13}C-NMR (100 MHz): **12d**: 23.17; 27.88; 31.28; 33.29; 40.86; 41.84; 47.99; 86.40 (CO); 178.11 (C=O); **13d**: 27.14; 27.78; 33.38; 40.47; 41.63; 41.70; 42.59; 72.81 (CO); 179.49 (C=O).

9. *Determination of the Absolute Configuration of* **11b**, **11c**, **12b**, **12c**, **13b**, **13c**. Compound (+)-**11c** (90% ep, 90.0 mg, 0.83 mmol; from the kinetic resolution of *rac*-**11c**) was oxidized with 30% H_2O_2 in AcOH according to the procedure in [77]. The crude product was purified by FC (10 g of SiO_2; pentane/Et_2O 4 : 1) to yield a 96 : 4 mixture of *normal* lactone **12c** and *abnormal* lactone **13c** (50.0 mg, 0.403 mmol, 48.6%) as a colorless oil. **12c**: 90% ep; **13c**: 90% ep (GC analysis). GC (column: *Alpha Dex 120*, 30 m × 0.25 mm; column temp., 105°: t_R (**12c** (minor)) 17.6 min; t_R (**12c** (major)) 17.9 min; t_R (**13c** (major)) 16.6 min; t_R (**13c** (minor)) 16.8 min. Optical activity of the 96 : 4 mixture **12c**/**13c** $[\alpha]_D^{r.t.} = -83.6$ (*c* = 1.00, MeOH). Optical comparison with literature values and comparison of the t_R values of **12c** and **13c** from the kinetic resolution and from the oxidation of (+)-(1*R*,5*S*)-**11c** (see *Scheme 7*) led to the assignments as given in the procedure, above, in the *Table*, and in *Scheme 6*.

Scheme 7. *The Absolute Configuration of* **11c**, **12c**, *and* **13c** *by Independent Formation of* **12c** *and* **13c** *from the Product* **11c** *of Kinetic Resolution*



(90% (1*R*,5*S*) + 10% (1*S*,5*R*))(90% (1*S*,5*R*) + 10% (1*R*,5*S*))(90% (1*S*,5*R*) + 10% (1*R*,5*S*))
([73]: (1*S*,5*R*)-**12c** $[\alpha]_D^{r.t.} = -104$)
([74]: (1*R*,5*S*)-**13c** $[\alpha]_D^{r.t.} = -67.9$)

Compound (+)-(1*R*,5*S*)-**11c** (90% ep; as obtained from a kinetic resolution experiment; see *Entry 4* in the *Table*) was hydrogenated (H_2, atmospheric pressure, 10% Pd/C, AcOEt) to give (*S*,*S*)-**11b**, 90% es (GC analysis). GC (column: *Beta Dex 120*, 30 m × 0.25 mm; column temp, 85°: t_R ((*R*,*R*)-**11b** (minor)) 10.3 min; t_R ((*S*,*S*)-**11b** (major)) 10.6 min. Thus, the unsaturated (**11c**) and the saturated (**11b**) bicyclo[3.2.0]heptanone, as recovered from the kinetic resolutions, are correlated by chemical conversion (**11c** → **11b**) and by comparison of the t_R values of the major and the minor enantiomers on a chiral column.

The 96 : 4 mixture (1*S*,5*R*)-**12c**/(1*S*,5*R*)-**13c**, both of 90% ep (see above, and *Scheme 7*), was hydrogenated (H_2, atmospheric pressure, 10% Pd/C, AcOEt) to give a 96 : 4 mixture (*S*,*S*)-**12b**/(1*S*,5*R*)-**13b**, both of 90% ep (GC analysis). GC (column: *Alpha Dex 120*, 30 m × 0.25 mm; column temp, 95°): t_R ((*R*,*R*)-**12b** (minor)) 30.7 min; t_R ((*S*,*S*)-**12b** (major)) 31.0 min; t_R ((1*S*,5*R*)-**11b** (major)) 28.6 min; t_R ((1*R*,5*S*)-**13b** (minor)) 29.0 min. With the known absolute configurations of the enantiomers of **12c** and of **13c** (see above and *Scheme 7*) and by comparison of the t_R values of major and minor enantiomer components from the products of kinetic resolution and of H_2O_2 oxidation of (1*R*,5*S*)-**11c**, we can thus assign the absolute configurations of **12b** and **13b** as given in the procedures above, in the *Table*, and in *Scheme 6*.

10. *X-Ray Crystal-Structure Determination of TADOOH* **3** · *DMF Complex* (see *Fig. 1*). From a crystal of size 0.30 × 0.10 × 0.10 mm, 1605 reflections were measured on an *Enraf Nonius CAD-4* Diffractometer with CuK_α radiation (graphite monochromator, $\lambda = 1.54184$ Å). For determination of the absolute configuration, the

Friedel pair of every reflection was measured as well. The structure was solved by direct methods with SIR97 [78]. The non-H-atoms were refined anisotropically with SHELXL-97 [79]. The H-atoms were calculated at idealized positions and included in the structure factor calculation with fixed isotopic displacement parameters. $C_{34}H_{37}NO_6$, Mol.-wt. 555.65, crystallized from DMF/Et_2O/hexane, temp. 293(2) K, orthorhombic, space group $P2_12_12_1$, $a = 9.790(10)$ Å, $b = 11.781(13)$ Å, $c = 26.00(3)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 2999(6)$ Å^3, $Z = 4$, $\rho_{calc.} = 1.231$ g·cm^{-3}, $\mu = 0.677$ mm^{-1}, $F(000) = 1184$. Number of reflections collected 1605 (ω scan, $3.40 < \theta < 47.46$), 1605 independent reflections, 1605 reflections observed, criterion $I > 2\sigma(I)$, final $R = 3.45\%$, $wR_2 = 8.84\%$, goodness of fit 1.097, $\Delta\rho$ (max, min) 0.131 eÅ^{-3}, -0.125 eÅ^{-3}. Crystallographic data (excluding structure factors) for the structure of **3** have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-148646. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ UK (fax: +44(1233)336033; e-mail: deposit@ccdc.cam.ac.uk).

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