Absolute Configuration of α-Methylstyrene Oxide: The Correct Absolute Configuration/Optical Rotation Correlation

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The accurate determination of the absolute configuration of chiral molecules has always been a highly crucial problem for organic chemists. Apart from the Bijvoet X-ray method, which allows a direct (crystallographic) determination, all the strategies employed to reach this goal imply a correlation of the concerned compound with another molecule of previously established absolute configuration. Most of the time, this correlation is based on the comparison of optical rotation values and sign, whenever these data are available. If it is not, tentative attributions were also based on other arguments like supposed similarity of chemical mechanism as compared to a structurally similar compound, presumed stereochemical integrity of a chemical reaction (retention or inversion of absolute configuration), supposed identical stereoselectivity of an enzyme as compared to an "almost identical" substrate, similarity of the chromatographic elution order in GC or HPLC analysis, etc. Although in most cases these arguments led to a correct conclusion, it unfortunately appears that, due to various reasons, an erroneous result was sometimes proposed in the literature. Since this was taken later on as a (wrong) reference by other authors, this led over time to quite puzzling and conflicting conclusions concerning the correct absolute configuration of a particular molecule.

In the course of our current work[1] of biocatalyzed resolution of various racemic epoxides using "new" enzymes, i.e., epoxide hydrolases, we have recently experienced this problem in the case of α-methylstyrene oxide **1**. Thus, we have observed that conflicting optical rotation signs, and therefore opposite absolute configurations, were described by different authors for the enantiomers of **1**. Careful examination of the experimental parts of these publications indicated, however, that the solvents used for measuring the optical rotation value were often different. Therefore, since it is well documented that the nature of the solvent can, in certain cases, lead to inversion of the optical rotation sign,[2] we suspected this was the most probable explanation to these puzzling results. We describe in this paper the chemical correlation studies we have achieved in order (a) to clarify this point and (b) to unambiguously establish the absolute configuration/optical rotation sign correlation for the enantiomers of **1**.

Bibliographic Results

Examination of the literature indicates that three initial publications describe an absolute configuration/optical rotation sign correlation for **1**. The first one has been achieved in 1965 by Mitsui et al. via reduction of the ethyl ester of (*S*)-atrolactic acid into the corresponding (*S*)-2-phenyl-1,2-propanediol **3**, followed by intramolecular cyclization into (*S*)-**1**.[3] These authors describe a *negative* $[\alpha]_D$ value ($[\alpha]^{11}_D$ −20) for the epoxide thus obtained, a measurement which was achieved by using the *neat* product. Interestingly, they observed an *inversion* of the optical rotation sign when the product was dissolved in ethanol ($[\alpha]^{11}_D$ +2.9, *c* 8.3). In 1968, Johnson et al. proposed a "tentative" absolute configuration for the same product, obtained by reaction of acetophenone with a chiral ylide.[4] This was based on a "probable similarity" of the reaction stereoselectivity with the one observed during formation of (*R*)-styrene oxide from benzaldehyde following the same route. The supposed (*R*)-configuration of **1** was, in this case, correlated to a *positive* optical rotation sign ($[\alpha]_D$ +1.9, temperature not mentioned) measured in acetone solution (with no indication of the solution concentration). To the contrary, Fujisama and colleagues described, in 1990, the synthesis of optically active **1**, which showed a *negative* optical rotation when measured in acetone ($[\alpha]^{23}_D$ −2.7, *c* 0.7).[5] The (*R*) absolute configuration was attributed to this enantiomer by comparison with an authentic sample, correlated chemically (in the course of a previous work[6]) by transformation of this optically active **1** into known (−)-(*S*)-2-phenyl-2-butanol **4** (via a regioselective opening of the oxirane cycle with a methyl Grignard reagent). Unfortunately, this work referred to a previous publication by the same group, where no experimental conditions (i.e., wavelength, concentration, etc.) and in particular no indication of the solvent used to achieve these optical rotation measurements were described.

From these various results it appears (a) that the optical rotation sign of (*S*)-**1** was observed to be reversed from negative to positive when measured neat or in ethanol solution but (b) that two conflicting results were described (by two distinct research teams) for the optical rotation sign of (*R*)-**1** measured in acetone solution. Despite this incoherence, several further studies were based on one or another of these results in order to deduce the absolute configuration of an enantiomer of **1.** Obviously, this led to conflicting results, thus enhancing the confusion, as illustrated in Table 1 (compare for instance entries 2 and 5 or entries 3 and 6). Therefore, to clarify this puzzling situation, we decided (a) to control the possible solvent-dependent switch of the optical rotation sign of optically active **1** (b) to ascertain the absolute configuration of **1** following two "crossed" approaches, thus avoiding any possible mistake.

Experimental Results

Our first approach was to synthesize (*R*)-2-phenyl-1,2-propanediol **3**, known to be obtainable via dihydroxylation of α-methylstyrene **2** by using the well-known

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Table 1. Literature Correlation between Optical Rotation and Absolute Configuration of 1

entry	absol config	sign	solvent	$[\alpha]_D$	*c*	*T*, °C	ref
1	*S*	−	neat	20	neat	11	3
2	*S*	+	EtOH	2.9	8.3	11	
3	*R*	+	acetone	1.90	?	?	4
4	*S*	−	acetone	6.9	0.36	25	11
5	*R*	+	EtOH	2.86	5	20	12
6	*R*	−	acetone	2.7	0.7	23	5
7	*R*	+	?	?	?	?	13
8	*S*	+	EtOH	1.25	2.09	20	1b
9	*R*	+	acetone	1.2	1.28	25	14
10	*S*	−	$CHCl_3$	7.8	3.84	25	15

ADmix-β Sharpless catalyst, as described recently.[7] The (*R*) absolute configuration of this diol was ascertained independently via chemical correlation with atrolactic acid of established absolute configuration.[8] Cyclization of **3**, via a stereochemically unambiguous chemical route (described in Scheme 1) was then performed, thus leading to (*R*)-**1**.

As a second approach, this (*R*)-**1** epoxide was further transformed into (−)-(*S*)-2-phenyl-2-butanol **4** following the way previously described by Fujisawa et al.[6] Due to the reaction mechanism involved, and considering the structure of the obtained product, its absolute configuration can be deduced unambiguously as being (*S*)-**4**. This is also consistent with the previous attribution achieved independently by Cram and colleagues.[9]

To check the coherence of the absolute configuration determinations described in the literature for compounds **1**, **3** and **4**, we then measured the optical rotation for each of these products using at least three different solvents, i.e., ethanol, chloroform, and acetone. The obtained values are indicated in Scheme 1. Interestingly it appears (a) that, for diol **3** as well as for alcohol **4**, no inversion of the optical rotation sign was observed, whatever the solvent used. Therefore, it can be deduced that the absolute configuration claimed for both these products in the literature are correct even if they were deduced from measurements achieved using different solvents. However, this is not the case for epoxide **1**. Indeed, the sign of its optical rotation switched from positive to negative depending on the solvent used. Therefore, the absolute configuration claimed for this product in the recent literature might be incorrect, depending on the optical rotation sign used as a reference by the authors.

Having these results in hands, we considered it was of importance to similarly check the behavior of various other aromatic epoxides derivatives we have recently prepared in the context of our work devoted to the synthesis of enantiopure epoxides using biocatalysis.[10] Comparison of the optical rotation sign for several of these derivatives, measured in acetone on one side and in chloroform on the other, are summarized in Table 2. Interestingly, it appears that three out of seven of these compounds indeed exhibited a switch of their optical rotation sign from one solvent to the other. Apparently, *para*-substituted derivatives do not lead to such an inversion, whereas the others do. This may be a consequence of the different intrinsic electronic distribution implied in each of these molecules, thus favoring or disfavoring intermolecular interactions (i.e., formation of clusters for instance) due to hydrogen bonds occurrence.

From the various above-described results the following conclusions can be drawn: (a) the optical rotation measured for the (*R*)-**1** enantiomer is *negative* in either chloroform or ethanol solution; (b) this sign is inverted to *positive* if the measurement is performed in acetone. It can therefore be deduced (a) that the sign of the optical rotation observed for (*R*)-**1** by Fujisawa[6] should be positive (instead of negative as described) and (b) that two other previously proposed absolute configurations of **1** must be corrected. These are the above cited attributions by (a) Hassine et al.[12] and (b) Janssen and colleagues.[15] Indeed, in this last case, an (*S*)-**1** absolute configuration was deduced from a negative optical rotation in chloroform solution, as compared with a positive value measured in acetone by Johnson and colleagues[4] for the (*R*)-**1** enantiomer. Therefore, it appears that, owing to the above-described solvent-dependent optical rotation sign inversion we have observed, this correlation must be inverted to (*R*).

Interestingly enough, this enantiomer was obtained via enantioselective biocatalyzed hydrolysis of α-methylstyrene oxide **1**, using a recombinant epoxide hydrolase from *Agrobacterium radiobacter*. If our assumption was correct, the enantioselectivity of this enzyme should therefore be *opposite* to the one we have ourselves observed on the same substrate using the *Aspergillus niger* enzyme.[1b] To confirm this point, and therefore to ascertain our stereochemical analysis, biohydrolysis of racemic **1** using a sample of the *A. radiobacter* enzyme was checked. Our results indicate that this was the case indeed, the *A. niger* epoxide hydrolase hydrolyzing preferentially the (*R*)-**1** enantiomer (thus leaving the (*S*) enantiomer unreacted), whereas the *A. radiobacter* showed a high preference for hydrolyzing the (*S*)-**1** antipode, leading to the recovery of the (*R*)-**1** enantiomer. Interestingly enough, it therefore appears that, at least for this particular substrate, these two biocatalysts are nicely enantiocomplementary, i.e., allowing preparation, at will, of either enantiomer of **1** in enantiopure form.

Conclusion

In the course of this work, we have unambiguously established the optical rotation/absolute configuration

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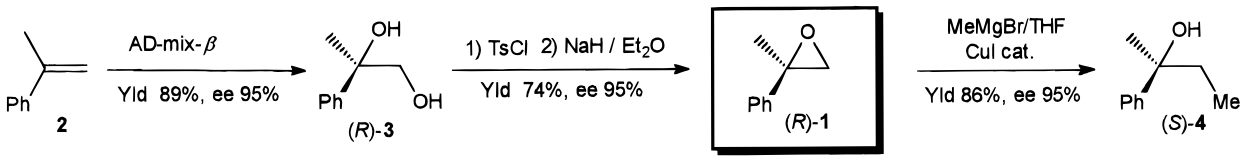
Scheme 1



$[\alpha]_D^{20}$ -5 (c 6.72, EtOH)

$[\alpha]_D^{20}$ -10.6 (c 1.76, $CHCl_3$)

$[\alpha]_D^{20}$ -4.7 (c 1.5, Acetone)

$[\alpha]_D^{20}$ -8.6 (c 1.18, Et_2O)

lit.[8a] (*S*)-**3**: $[\alpha]_D$# +8.4 (c 6.76, Et_2O)

lit.[3] (*S*)-**3**: $[\alpha]_D^8$ +5.4 (c 8.9, EtOH)

$[\alpha]_D^{20}$ -2.5 (c 1.27, EtOH)

$[\alpha]_D^{20}$ -20.1 (c 1.02, $CHCl_3$)

$[\alpha]_D^{20}$ +1.7 (c 1.27, Acetone)

$[\alpha]_D^{20}$ -14.8 (c 1.61, EtOH)

$[\alpha]_D^{20}$ -16.7 (c 1.45, $CHCl_3$)

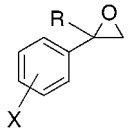
$[\alpha]_D^{20}$ -15.9 (c 1.50, Acetone)

lit.[18] (*S*)-**4**: $[\alpha]_D^{27}$ -15.7 (c 0.8, EtOH)

lit.[19] (*S*)-**4**: $[\alpha]_D^{20}$ -9.2 (c 3.2, $CHCl_3$)

#: temperature not mentioned

Table 2. Optical Rotation Sign of Various Styrene Oxide Derivatives Measured in Acetone and EtOH



X	R	absol config	ee, %	$[\alpha]^{20}_D$	*c*	solvent	ref
H	H	*R*	>99	+5.3	1.58	acetone	16
		R	>99	−24	1	$CHCl_3$	
p-Cl	H	*S*	>99	+1.3	1.53	acetone	1a
		S	>99	+24.9	1.50	$CHCl_3$	
m-Cl	H	*R*	>99	+9.1	1.92	acetone	16
		R	>98	−10.9	1.80	$CHCl_3$	
o-Cl	H	*S*	96	+46.7	1.6	acetone	17
		S	96	+61.5	1.62	$CHCl_3$	
p-Br	H	*S*	98	−38	.955	acetone	1a
		S	98	−41.7	1.46	$CHCl_3$	
p-NO_2	H	*S*	95	+14.2	1.09	acetone	1a
		S	95	+33.9	1.34	$CHCl_3$	
H	Me	*R*	95	+1.8	1.27	acetone	
		R	95	−20.1	1.02	$CHCl_3$	

correlation for the α-methylstyrene oxide **1** enantiomers, and we have observed that the sign of this rotation depends on the solvent used to achieve this measurement. As a general point, this study emphasizes the fact that, to avoid confusing situations, much greater care should be taken in the context of absolute configuration attributions. Interestingly enough, the study we have achieved, following a conflicting absolute configuration attribution to an optically enriched enantiomer of α-methyl styrene oxide **1**, led us to the very interesting observation that the biocatalyzed hydrolysis of **1**, using either *A. niger* or *A. radiobacter* epoxide hydrolases, were enantiocomplementary, thus allowing preparation of both enantiomers of **1**, at will, simply by choosing the appropriate biocatalyst. Further work is in progress in order to check if this observation is valid for other structurally different epoxides.

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