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Resolution of limonene 1,2-epoxide diastereomers by mercury(II) ions

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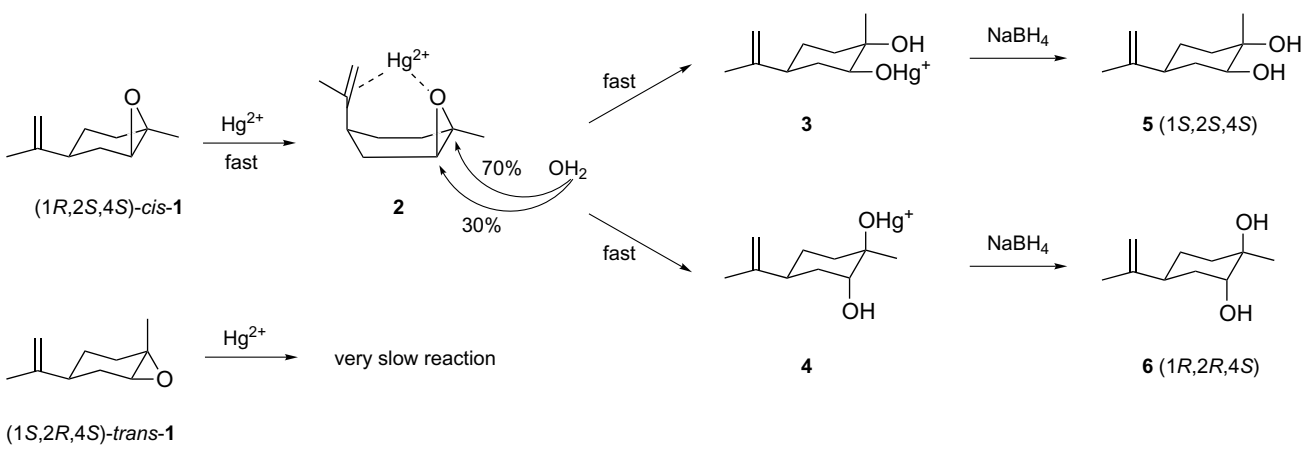
Abstract—When $HgCl_2$ was added to a diastereomeric mixture of *cis*- and *trans*-(4*S*)-limonene 1,2-epoxide, the Hg(II) ions stereoselectively complexed to the *cis* epoxide, enabling ring opening by water. The resulting mercuric salt could be demetalated by treatment with $NaBH_4$, giving a mixture of diastereomeric (1*S*,2*S*,4*S*)- and (1*R*,2*R*,4*S*)-diols. The remaining *trans*-(4*S*)-epoxide was obtained in >98% d.e. and 40% yield. For reactions on a larger scale, the most convenient reaction system was $Hg(OAc)_2$ in 50% acetone/tris-HCl buffer pH 7.0. The reaction rate was affected by the pH, with pH 6–8 as optimum.

Optically pure epoxides are versatile building blocks for the synthesis of optically pure bioactive compounds. Both biological[1–3] and chemical[3,4] methods for the production of optically pure epoxides have been described. Kinetic resolution is an attractive method because racemic epoxides are easily accessible.[5] In recent years, many reports have appeared in which eukaryotic and bacterial epoxide hydrolases (EH) have been employed (Refs. 6, 7 and 8 and papers cited therein). Only recently an efficient chemical kinetic resolution method was developed, using chiral Co(salen) complexes as the catalysts, for the production of enantiopure epoxides.[9]

Limonene is a chiral natural product, of which the enantiomers are readily available in optically pure form. Their 1,2-epoxides are also commercially available, but the pure isomers of the (+)-(4*R*)-epoxides are expensive and the (−)-(4*S*)-epoxides can only be obtained as a mixture of diastereomers. Searching for inhibitors of limonene 1,2-epoxide hydrolase from



Scheme 1.

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Rhodococcus erythropolis,[10] an unexpected phenomenon was observed when $HgCl_2$ was tested. Even in the absence of enzyme, the diastereoselective conversion of (4*S*)-limonene 1,2-epoxide [(4*S*)-**1**] was observed. In this report we describe this reaction in more detail, since it can be used for the preparative separation of limonene 1,2-epoxide diastereomers.

Commercially available (4*S*)-**1** is a diastereomeric mixture of 57% (1*R*,2*S*,4*S*)-*cis*-**1** and 43% (1*S*,2*R*,4*S*)-*trans*-**1**, corresponding to an d.e. of 14%. When a solution of (4*S*)-**1** in a phosphate buffer (pH 7.0) was incubated with $HgCl_2$, *cis*-(1*R*,2*S*,4*S*)-**1** was converted preferentially, leaving unreacted *trans*-(1*S*,2*R*,4*S*)-**1** (Scheme 1).[11]

The yield and diastereomeric excess of the *trans*-(4*S*)-**1** remaining depended on the amount of $HgCl_2$ added. If the amount of $HgCl_2$ added was equimolar to the amount of *cis*-(4*S*)-**1** present, *trans*-(4*S*)-**1** remained in >98% d.e. and 40% yield (=93% of the maximal theoretical yield).

The stereoselectivity of this reaction was due to the difference in reaction rates of the two diastereomers of (4*S*)-**1** with the Hg(II) ions. If <57 mol% $HgCl_2$ was added, the reaction occurred instantaneous; samples taken after 1 minute showed the same yield as those of samples incubated for 2 h at 30°C. However, if more than 57 mol% $HgCl_2$ was added, the *trans*-epoxide reacts too, although it takes 2 h of incubation to reach maximal conversion (see Table 1).

No product was detected when the reaction mixture was extracted with ethyl acetate and analyzed by GC. Also when the reaction mixture was treated with an equimolar amount of EDTA before extraction, no product was detected by GC analysis of the ethyl acetate phase. This indicates that Hg^{2+} ion forms a tight, water-soluble adduct with (4*S*)-**1**. When the reaction mixture was treated with $NaBH_4$, two 1,2-diols were formed as a 7:3 diastereomeric mixture of the (1*S*,2*S*,4*S*) diequatorial diol **5** and the (1*R*,2*R*,4*S*) diaxial diol **6**.[12]

The following mechanism is proposed for this reaction. Just like in the well-known oxymercuration reaction,[13–15] the first step is the formation of a complex of Hg(II) with the π-orbital of the olefin.[16,17] In the oxymercuration reaction, this π-complex is attacked by a nucleophile from the back side, leading to a covalent organomercuric species. In our case, ligation of the oxygen atom of the epoxide to the mercuric ion is faster, giving a bridged complex in which the cyclohexane ring is presumably in the boat formation (structure **2**, Scheme 1). This bridged π-complex is more readily formed with (4*S*)-*cis*-**1** than with (4*S*)-*trans*-**1**, since these groups are quite close to each other in the *cis* isomer whereas they are remote in the *trans* isomer. Similar steric restrains have been reported for the bromoetherification of **1**[18] and the iodoetherification of carveol.[19] The Lewis acid Hg^{2+} polarizes the carbon–oxygen bonds of the epoxide, enabling rapid ring opening by water which leads to the mercuric salts **3** and **4**. Reduction of the Hg^{2+} ion with $NaBH_4$ breaks up **3** and **4** and releases the diastereomeric diols **5** and **6**, respectively.

The reaction of Hg^{2+} with (4*S*)-**1** was observed only at neutral pH (6–9) (Table 1). The type of buffer used did not affect the stereoselectivity of the reaction. At pH-values >9 the conversion rate decreased dramatically (Table 1), probably due the formation of insoluble HgO hydrates.[20]

The reaction system investigated is rather dilute and therefore inconvenient for scale-up. However, simply increasing the concentration of (4*S*)-**1** and Hg(II) led to decreased selectivity, probably due to the two-phase system formed. The addition of cosolvents increases the

Table 1. Effect of pH, buffer, Hg(II), and incubation time on the conversion of (4*S*)-**1**

Buffer	pH	10 min 30°C				2 h 30°C			
		+57 mol% Hg(II)		no Hg(II)		+57 mol% Hg(II)		no Hg(II)	
		d.e. (4*S*)-**1** (%)	Yield (4*S*)-**1** (%)	d.e. (4*S*)-**1** (%)	Yield (4*S*)-**1** (%)	d.e. (4*S*)-**1** (%)	Yield (4*S*)-**1** (%)	d.e. (4*S*)-**1** (%)	Yield (4*S*)-**1** (%)
None		–	0	18	100	–	0	44	82
Citrate	4.0	>98	1	>98	49	–	0	>98	13
	5.0	>98	24	28	86	–	0	>98	51
	6.0	>98	35	15	97	>98	22	27	89
KP_i	6.0	>98	36	14	98	>98	20	27	89
	7.0	>98	37	15	100	>98	34	20	98
	8.0	>98	38	15	100	>98	36	19	99
Tris	7.0	>98	40	15	100	>98	20	20	98
	8.0	79	47	15	100	>98	39	18	100
	9.0	53	55	15	100	>98	40	18	100
Glycine	9.0	62	52	15	100	>98	38	18	100
	10.0	−9	94	15	100	21	66	18	100
	11.0	−11	94	15	100	−4	83	18	100

solubility of the limonene epoxide but decreases the solubility of the Hg(II) salt. After much experimentation, reproducible results on a 3 g scale were obtained using $Hg(OAc)_2$ in 50% acetone/tris-buffer pH 7.0 during a very short time.[21]

At pH-values lower than 6, the acid-catalyzed hydrolysis of (4*S*)-**1** competes with the formation of the Hg(II)-(4*S*)-**1** complex, and as a consequence yields were lower. However, under acidic conditions, the diaxial (1*R*,2*R*,4*S*)-diol **6** is formed as the major (>85%) reaction product and the (1*R*,2*S*,4*S*)-*cis*- rather than the (1*S*,2*R*,4*S*)-*trans*-isomer of (4*S*)-**1** (>98% e.e.) remained in 49% yield (=86% of the maximal theoretical yield). (Table 1). This reaction has been reported previously.[22,23]

Also (4*R*)-**1** was stereoselectively converted by both Hg(II) and low pH. The reaction of Hg(II) with (4*R*)-**1** resulted in >99% pure (1*R*,2*S*,4*R*)-*trans*-**1**, while the incubation of (4*R*)-**1** in citrate buffer pH 4 resulted in >99% pure (1*S*,2*R*,4*R*)-*cis*-**1**.

The stereoselective conversion of **1** was previously described using different catalysts. The biological kinetic resolution of **1** has been described using whole cells of *Rhodotorula glutinis*[24] and limonene 1,2-epoxide hydrolyze from *Rhodococcus erythropolis*.[25] With both epoxide hydrolase activities, the (1*S*,2*R*)-isomers of (4*S*)-**1** and (4*R*)-**1** remained. Davies et al.[18] have reported on the bromine-induced stereoselective cyclization of (4*R*)-**1,** leaving optically pure (1*R*,2*S*,4*R*)-**1** after the addition of 50 mol% bromine.[26] Our method avoids the use of bromine and carbon tetrachloride and has superior yields. We have not found any previous reports on the stereoselective conversion of epoxides by Hg(II), although the ring opening of cyclopropanes by Hg(II) is a known reaction.[27]

In conclusion, the method described in this paper in combination with the published one[22,23] provides a feasible access to all enantiopure stereoisomers of limonene 1,2-epoxide. The Hg(II) system preferentially converts the *cis*-isomers of **1**, leaving enantiopure (1*S*,2*R*,4*S*)-*trans*-**1** and (1*R*,2*S*,4*R*)-*trans*-**1** from (4*S*)-**1** and (4*R*)-**1**, respectively. The complementary, enantiopure (1*R*,2*S*,4*S*)-**1** and (1*S*,2*R*,4*R*)-**1** (i.e. (4*S*)-*cis*-**1** and (4*R*)-*cis*-**1**), can be obtained by incubating (4*S*)-**1** or (4*R*)-**1**, respectively, at pH values <5.

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11. To 2 ml of a freshly prepared 5 mM solution of diastereomeric (4*S*)-**1** in 50 mM potassium phosphate buffer (pH 7.0) was added 225 μl of a 25 mM $HgCl_2$ solution in water and the reaction mixture was incubated for 10 min at 30°C. One ml of EtOAc was added and the vials were vigorously shaken to accomplish quantitative extraction of the epoxide *trans*-(1*S*,2*R*,4*S*)-**1** (40% yield). $t_R=10.84$ min (α-DEX 120, 100°C). *Trans*-(1*R*,2*S*,4*R*)-**1** was prepared in the same way from a diastereomeric mixture of (4*R*)-**1** (38% yield). $t_R=10.62$ min (α-DEX 120, 100°C). These retention times and the MS-spectra were the same as those of authentic samples of the isomers of *trans*-**1**.
12. To a solution of diastereomeric (4*S*)-**1** (288 mg, 1.83 mmol) in 50 mM tris-HCl buffer (pH 7.0, 250 ml) was added $HgCl_2$ (41.4 ml of a 25 mM solution in water, 281 mg, 1.04 mmol). After 10 min at 30°C, 50 ml EtOAc was added and unreacted (1*S*,2*R*,4*S*)-*trans*-**1** was extracted from the water phase. The water phase was separated and 24 mg of sodium borohydride was added. The solution was stirred for 21 h, after which the solution was extracted with 3 portions of 50 ml of CH_2Cl_2 and thereafter with 3 portions of 50 ml of EtOAc. The collected organic phases were dried over $MgSO_4$, filtered and evaporated till dryness, yielding 180 mg of a solid. The solid consisted of the (1*S*,2*S*,4*S*)-diol **5** and the (1*R*,2*R*,4*S*)-diol **6** as a 7:3 mixture. (1*S*,2*S*,4*S*)-diol **5**: $t_R=15.04$ min (α-DEX 120, 140°C). ^{1}H NMR: δ 1.20 (s, 3H); 1.72 (br s, 3H); 1.21–2.30 (m, 9H); 3.54 (dd $J_{a,a}=11.8$ Hz, $J_{a,e}=4.5$ Hz, 1H); 4.69–4.73 (m, 2H). (1*R*,2*R*,4*S*)-diol **6**: $t_R=16.12$ min (α-DEX 120, 140°C) and its MS- and ^{1}H NMR spectra were identical to that of enzymatically prepared optically pure (1*R*,2*R*,4*S*)-**6**.[25]
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21. To a solution of 3 g (20 mmol) diastereomeric (4*S*)-**1** in 70 ml acetone was added 70 ml 200 mM $Hg(OAc)_2$ in tris-HCl buffer pH 7.0. After stirring the reaction mixture for 20 seconds, 100 ml petroleum ether (40–60) was added and the mixture was stirred for 1 min. The organic phase was separated and the water phase was extracted with 100 ml of petroleum ether. The collected organic fractions were dried over $MgSO_4$, filtered and evaporated till dryness, yielding 1.28 g (43%=99% of the maximal theoretical yield) of unreacted *trans*-(1*S*,2*R*,4*S*)-**1** (d.e.> 98%, $[\alpha]_D^{20}=-38.0°$ ($c=3.5$, $CHCl_3$); lit.[29] −30.4° ($c=0.56$, MeOH).
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