39. Enantiomeric Purities of (*R*)- and (*S*)-Camphors from the Chiral Pool and High Enantiomeric Purities in General

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The commercially available camphor enantiomers are extensively used in several important areas of chemical research, and it seems that they are often considered to be enantiomerically pure (the meaning of the term is discussed); there are certainly no enantiomeric purities (e.p.) on record. By standard GLC on a modified cyclodextrin column, we have now found five commercial (*R*)-camphors to have the same high but imperfect e.p., (99.62 ± 0.02)% (*R*), a sixth a slightly higher e.p., (99.76 ± 0.06)% (*R*), and three (*S*)-camphors to have different and lower e.p. Nailing down these e.p. is useful by itself and puts into focus the sensitivity of present day GLC, and how little is known about high e.p. in general.

1. Introduction. – Investigations dealing with the structure, synthesis, reactions, derivatizations, transformations, *etc.*, of the camphors make up a truly fundamental chapter of organic chemistry, and the commercially available camphor enantiomers are extensively used in several important areas of research. It seems that these enantiomers are often considered to be enantiomerically pure[1]), and there are certainly no exact enantiomeric purities[1]) (e.p.) on record. The development of modified cyclodextrin columns for GLC permits the determination of e.p. with unprecedented sensitivity and accuracy. By this method, we have now found five commercial (*R*)-camphors to have the same high, but imperfect e.p., (99.62 ± 0.02)% (*R*), a sixth a slightly higher e.p., (99.76 ± 0.06)% (*R*), and three (*S*)-camphors to have different and lower e.p. Response to this in discussion is always strong but contradictory: surprise and disbelief, or we are making a mountain out of a mole-hill. In particular, it seems that GLC specialists consider imperfect e.p. trivial, but that other chemists are often not aware of this. Nailing down these e.p. is useful by itself and puts into focus the sensitivity of present day GLC, and how little is known about e.p. in general. Enantiomeric purities (e.p.), especially very high ones, are something of a grey zone everywhere, and we now provide what may be the first thorough analysis. We suspect that high e.p. will turn out to be similar everywhere else, that this is due to biosynthetic errors, and that GLC has now simply become sensitive enough to detect the errors. If these conjectures turn out to be correct, then they are of considerable importance. To be able to make the conjectures and to show why the camphors are a good case in point, a substantial background must be given and discussed. This paper is, therefore, topheavy in background and speculation.

[1]) For convenience, the enantiomeric purities (e.p.) of the (*R*)-**1** *and* (*S*)-**1** are expressed as the percentages of (*R*)-**1**, thus on the same scale ranging from 0% (enantiomerically pure (*S*)-**1**) to 100% (enantiomerically pure (*R*)-**1**), *via* 50% (racemate (*RS*)-**1**). In principle, enantiomerically pure means that the enantiomeric purity is 100% (see *Sect. 2.3.4*).

2. Background. – 2.1. *Production.* Commercial (+)-(*R*)-camphors ((*R*)-**1**) [1][2])[3]) come from plantation-grown camphor trees (*Cinnamomum camphora*). There are many other higher plants that produce (*R*)-**1** but also some that produce (–)-(*S*)-camphors ((*S*)-**1**), and some that have even been reported to produce the racemate (*RS*)-**1**[4]). None of these latter sources are exploited commercially. Unlike in the case of (*R*)-**1**, the origins of commercial (*S*)-**1** are undisclosed, but it is certain that they are made from some natural terpene ((–)-(1*S*)-borneol [2]?). Commercial (*RS*)-**1** are made from scalemic α-pinenes, and the reason why they are racemic is at the origin and heart of carbocation chemistry [3]. The heyday of camphor production was when they were used as plasticizers for celluloid and photographic film. At present, much less is produced and much more (*RS*)-**1** than (*R*)-**1**, (*S*)-**1** being a research chemical. The prices are in that order, and (*RS*)-**1** and some (*R*)-**1** are used industrially, mainly in pharmaceutics and perfumery.

2.2. *Uses.* (*R*)-**1** could well be the oldest known organic chemical and pharmaceutical. Consequently, an incredible number of investigations of many kinds have been carried out with it, and medical use has been important and still continues to a limited extent. Uses and investigations, pioneering, fundamental, routine, abstruse, were at first motivated by the unique availability of (*R*)-**1**. In chemistry, availability still counts today, when (*R*)-**1** and (*S*)-**1** are used very extensively as chiral building blocks [4f] [5] or to test new reagents, and to make resolving agents [4], shift reagents [6], and chiral auxiliaries [4f] [7], but history has given them a special stature, which makes using them doubly attractive, if only because so much is already known about them.

2.3. *Enantiomeric Purities.* In particular, one gets the impression that the natural (*R*)-**1** and (*S*)-**1** were and are often considered to be enantiomerically pure[1])[5]), *i.e.* that the e.p. are also known (in that sense), although accurate e.p.[1]) are certainly not on record. This is so – is part of the stature – although it is also well-known that many other commercial terpenes of natural origin are *not* enantiomerically pure [8][5]), but e.p. are then often not very high (and this can be measured relatively easily).

2.3.1. *Purification.* This belief in perfect (or very high) enantiomeric purity can be traced to two kinds of arguments. One is practical: there is a (usually unstated) rule of thumb that, for an already enantiomerically enriched sample, high constitutional purity (c.p., the purity with respect to impurities other than the minor enantiomer, often also called chemical purity) goes with high e.p. This is so, because purification tends to remove

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[2]) According to the *IUPAC* rules: (1*R*,4*R*)-**1**; also called Japan or Chinese camphor, to distinguish it from, but formerly often confused with, Borneo camphor (+)-(1*R*)-borneol and Ngai camphor (–)-(1*S*)-borneol.

[3]) There are so many important texts that deal with the camphors that we list a representative selection without detailing where the information (largely contained in several or all of them) in *Sect. 2* comes from.

[4]) Proving that a compound is truly racemic is just as difficult as proving that a compound is truly enantiomerically pure. The analytical method was polarimetry, and it is, therefore, not established that the camphors in question were racemic. It is more likely that they were near-racemic mixtures (*cf. Sect. 2.3.5* [16i]), if only because their being racemic would require the antipodal enzymes to be present in a genetically fixed 1:1 ratio (*Sect. 4.1*).

[5]) [8c]: 'The author has found that a surprising number of chemists believe that *all* chiral compounds isolated from nature are 100% one enantiomer'; and 'Nature does not always make just one enantiomer and not the other, although there are many instances in which only one enantiomer has been found'. However, [8d]: 'the only safe principle is to assume, until shown otherwise by a methodology other than optical rotation, that the chiral building blocks are not enantiomerically pure'. Even in the cases where e.p. are known to be imperfect, these are often not well-documented. For a case that is, because a method has been found to increase the e.p., see that of the α-pinenes [8e].

both constitutional impurities and the minor enantiomer, *i.e.*, the minor enantiomer usually behaves just like any other impurity. Now the camphors do have extraordinary crystallinity and volatility and are, therefore, easily obtained in high c.p. (this is of course also why they have been known and available for so long), and this implies an exceptionally high e.p. by the above rule, but, exceptionally, the rule essentially fails with them. The classical method for further purification is recrystallization [4e], and the classical criteria for both c.p. and e.p. are constant maximum m.p. and rotations after repeated crystallizations, but in the case of the camphors, the m.p. criterium is invalid with respect to e.p. and likewise this method of purification with respect to enantiomer enrichment (but not with respect to increasing the c.p.). The reason for this is that (*RS*)-**1** and scalemic mixtures crystallize as a continuous series of ideal solid solutions ((*RS*)-**1**, any scalemic **1**, (*R*)-**1**, and of course (*S*)-**1**, all have the same m.p.!), but this was only reported in 1981 (in a fundamental book [4e]) and is probably not common knowledge. Only crystallization of derivatives that do not form ideal solid solutions may have worked. To what extent other methods of purification function(ed) is a difficult question, but it is likely that the solid solutions always cause(d) problems. Zone melting and zone refining [4e] [9], for example, should also fail.

2.3.3. *Are Natural Products Enantiomerically Pure?* The other arguments are theoretical. First, there is the widespread belief that enzymes are perfect[5]). To our knowledge, the fundamental question[6]) of how efficient enzymes really are was only recently posed by *Cornforth* [10] and by *Koppenhoefer* [11]. Both have concluded that enzymes are not perfect, but even if they were, this argument would not be valid, because it is also well-known that plants often have two so-called antipodal enzymes, of which one produces one enantiomer and the other the other enantiomer.

A perfect enzyme would lead to truly enantiomerically pure[1]) products. However, just as enzymes are not perfect and, therefore, do not lead to enantiomerically pure products – and because of that – is it highly unlikely that there are truly enantiomerically pure compounds in macroscopic reality (*Sect. 4*); conversely, it is just as unlikely that we would be able to prove that it is enantiomerically pure, if we had one in hand.

2.3.4. *Operational Meaning of the Term Enantiomerically Pure.* The abstract meaning of the term enantiomerically pure is sharply defined, but its macroscopic meaning in the real world is fuzzy[7]), to use the term of *Mislow* and *Bickart* [12], just as is the meaning of 'pure' in general. Now, at least in the case of the (*R*)-**1** (see below), it was either thought that they were truly enantiomerically pure, or that their e.p. were too high to be measured; the latter is now evident: the minor enantiomer could not be detected but now can.

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[6]) Reference [11a] provides a review and describes several experimental approaches, which are otherwise still essentially unpublished.

[7]) The real-world, *macroscopic* meanings of the terms pure, enantiomerically pure, enantiomer, racemate, even compound, and of the descriptors (*R*), (*S*), and (*RS*) are all fuzzy, but (*R*) and (*S*) (not (*RS*)) primarily have a sharply defined, *microscopic*, molecular meaning. For example, in the present text, we call samples with different c.p. and different, imperfect e.p. (compounds that are manifestly not enantiomerically pure) (*R*)-**1** and (*S*)-**1**, as is common usage; this is why we use (*R*)-**1** and (*S*)-**1** (and (*RS*)-**1**) in the plural). Moreover, we would call them (*R*)-**1**/(*S*)-**1** mixtures and scalemic rather than not enantiomerically pure, if our viewpoint were different. Thus, the following conviction expressed in the present paper can be expressed in the following two ways: all enantiomers (in the macroscopic sense) are not enantiomerically pure – and – all enantiomers (in the macroscopic sense) are scalemic.

In the latter view, it made and makes sense to consider a compound to be enantiomerically pure within the limits of the available analytical methods, *i.e., as long as one detects only one enantiomer*[5]) (further on are described two earlier analyses where this was the case). The same view is, of course, accepted with respect to c.p., but the e.p. of natural products were and are apparently thought to be different[5])[8]).

2.3.5. *Analytical Methods.* The basic, but insensitive analytical tool was of course polarimetry [4e] [6b] [8c]. Innumerable optical rotations are on record, and those that can be compared, of course, vary. This can be due to varying e.p., varying c.p., and polarimetric errors. In particular, handbooks and suppliers list $[\alpha]_D$'s, and suppliers also approximate c.p., but not e.p. However, the $[\alpha]_D$'s do often clearly indicate that the e.p. of the (*S*)-**1** must be somewhat lower than those of the (*R*)-**1**. Before the arrival of GLC methods, but only relatively recently, a new principle and a number of important new methods for measuring e.p. were established: *Horeau*'s principle [13][9]), NMR methods, the isotope-dilution method, and the radioactive tracer method [4e] [6] [8c] [11] [14]. These are all not routine, and only the last (and perhaps the first) are sensitive enough to handle the e.p. reported herein. Of these, only analysis by ^{1}H-NMR using a shift reagent has been demonstrated with the camphors (stature!), but with weighed-in samples with e.p. $\leq 90\%$ [15].

The field has been revolutionized by the development of highly efficient columns for capillary GLC and HPLC [8c] [11] [16] and, today, enantiomer separations by GLC can be achieved almost routinely. However, the emphasis has so far been on the separations, and the method has yet been little used to actually determine e.p. All of this has notably been documented with the camphors[10]), again in line with their stature. The first separation, which still required derivatization to the oximes, was reported by *König et al.* in 1982 [16h]. They used a capillary column coated with *XE-60*-(*S*)-valine-(*S*)-α-phenylethylamide and noted that the formation of the oximes of (*R*)-**1** (*Fluka*) did not entail (a highly unlikely) racemization[11]), which suggests that they did not detect the enantiomers. The same group described the separation of the camphors ((*RS*)-**1**) directly on an octakis(3-*O*-butyryl-2,6-di-*O*-pentyl)-γ-cyclodextrin column in 1989 [16i] and, in 1990, the identification of nearly racemic **1** in a rosemary oil and of (*R*)-**1** (at low sensitivity) in a peppermint oil [16j] but did not deal with the e.p. of the *Fluka* and peppermint (*R*)-**1**. In 1991, *Keim et al.* published a long list of separations, among which that of the camphors on a heptakis(3-*O*-acetyl-2,6-di-*O*-methyl)-β-cyclodextrin column [16k], again without

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[8]) A leftover from vitalism?

[9]) A referee suggested that *Horeau*'s duplication principle be mentioned 'because it does not require an enantiomerically pure standard'. The fundamental problem with polarimetry is that it does, in principle, require such a standard. No standard is needed once enantiomer separation (GLC, HPLC, *etc.*) is achieved, *and* in *Horeau*'s method, in which the substrate is 'dimerized' somehow and the ratio of the scalemic [(*RR*) + (*SS*)] dimer and the *meso*-(*RS*)-dimer determined (GLC, HPLC, NMR, *etc.*). The beautiful trick of making dimers allows one to determine diastereoisomer ratios instead of enantiomer ratios without use of a chiral spectator reagent. This unique method was very important – but little used – before enantiomer separations became possible and has another important consequence, but enantiomer separation – once it is achieved – is simpler.

[10]) This literature is difficult to find: we were kindly helped by *B. Koppenhoefer*, who made a search in the database Chirabase/GC (Universität Tübingen, D-7400 Tübingen).

[11]) Racemization occurs in strong acid [5a] but is very unlikely under these conditions (pyridine/CH_2Cl_2, $NH_2OH \cdot HCl$, 100°).

dealing with e.p. That question had been addressed earlier, in the investigations of camphor biosynthesis by *Croteau*'s group (*Sect. 5*), using *König*'s separation of the oximes. They checked the e.p. of a tansy leaf (*S*)-**1**, detected only (*S*)-**1**, and concluded that it was 'essentially' enantiomerically pure [17c].

3. Results. – 3.1. *Enantiomeric Purities.* In the course of an investigation of the potassium-in-liquid-ammonia reduction of (*R*)-**1**, (*S*)-**1**, (*RS*)-**1**, and various scalemic **1** [18], we checked the e.p. of the (*R*)-**1** and (*S*)-**1** employing GLC using a commercial octakis(3-*O*-butyryl-2,6-di-*O*-pentyl)-γ-cyclodextrin column and an integrator in parallel with GLC/MS, and found that neither was quite enantiomerically pure. As this met with some disbelief, we then determined the e.p. of every camphor in stock at the *Firmenich* laboratories and subjected these e.p. to statistical analysis. All of the e.p., expressed as the percentages of (*R*)-**1**[1]), are now presented in the *Table*. In addition, the *Figure* shows chromatograms of an (*RS*)-**1** and one of the (*R*)-**1**.

Table. *Enantiomeric and Constitutional Purities of Ten Camphors, and Five* $[\alpha]_D$'s

Camphor[a])	Mean enantiomeric purity ($\overline{\text{e.p.}}$) [% (*R*)-**1**][b])			Constitutional purity (c.p.) [% (*R*)-**1** + (*S*)-**1**]	$[\alpha]_D^{25}$ $[\alpha]_D^{20}$ (in EtOH)
	n_i[c])		$s(\overline{\text{e.p.}})$[d])		
A	5	99.76	0.05(5)	98.8[e])	
B	5	99.63	0.01(2)	98.4	
C	8	99.69	0.02(8)	98.2	
D	7	99.57	0.04(9)	99.2	
D[f])[g])	2	99.52	0.01(5)	99.4	+44.7 (c = 10.0)
E	4	99.67	0.02(1)	98.2	
E[g])				99.9	+44.4 +44.1 (c = 3.7 and 10.0)
F	3	99.51	0.05(8)	97.7	
B–F	29	99.62	0.01(6)		
G	3	10.69	0.09(5)	96.3	
H	4	3.60	0.03(6)	94.6	
I[f])	1	1.70		> 99[f])[h])	−43.7 (c = 10.0)
J[f])	2	50.05	0.03(0)	99.5	0.0 (c = 10.0)

[a]) *A*: (+)-Camphor, *Fluka 21300, purum, natural*, > 97% (GC), $[\alpha]_D^{20} = +43.5 \pm 1$ (c = 10, EtOH) 1990. *B*: (+)-(1*R*)-Camphor, *Aldrich 85,730-0*, 99%, $[\alpha]_D^{25} = +44.1$ (c = 10, EtOH), 1988. *C*: Camphor, *The British Drug House Ltd.*, BDH microanalytical reagent, 10–20 y old. *D*: Camphora Ph. H.V. pulv., *Siegfried*, D-Campher rein, 1971(?). *E*: Refined Camphor, *The Nippon Camphor Co. Ltd.*, 10–20 y old. *F*: origin unknown, 10–20 y old. *G*: (−)-Camphor, *Aldrich C35-2*, tech., $[\alpha]_D^{20} = -30.7$ (c = 11.8, MeOH), age unknown. *H*: (−)-Camphor, *Fluka 21295, purum*, ~ 95% (GC), $[\alpha]_D^{20} = -40 \pm 2$ (c = 10, EtOH), 1989. *I*: gift from *W. Oppolzer* (1989), made from (−)-(1*S*)-borneol (*Aldrich*; specifications unknown) according to [2]. *J*: Camphre synthétique, *Lotti* (Genève), 1975.

[b]) Remainder is (*S*)-**1**.

[c]) Number of GLC analyses.

[d]) Standard errors of the mean enantiomeric purities $s(\overline{\text{e.p.}}) = s(\text{e.p.})_i/\sqrt{n_i}$; $s(\text{e.p.})_i$ = standard deviations for each individual analysis of a given sample; common s(e.p.) for *all* samples = 0.096 ≈ 0.10; calculated from

$$s(\text{e.p.})^2 = \left[\sum_{i=1}^{k} (n_i - 1)s(\text{e.p.})_i^2\right]/(N-k); \quad (k = 10, N = 43).$$

[e]) Single GLC analyses; we assume that the standard deviations are about the same as for the enantiomeric purities, ± 0.1.

[f]) From [18].

[g]) Purified by flash chromatography and then bulb-to-bulb distillation.

[h]) Earlier, less sensitive GLC analysis.

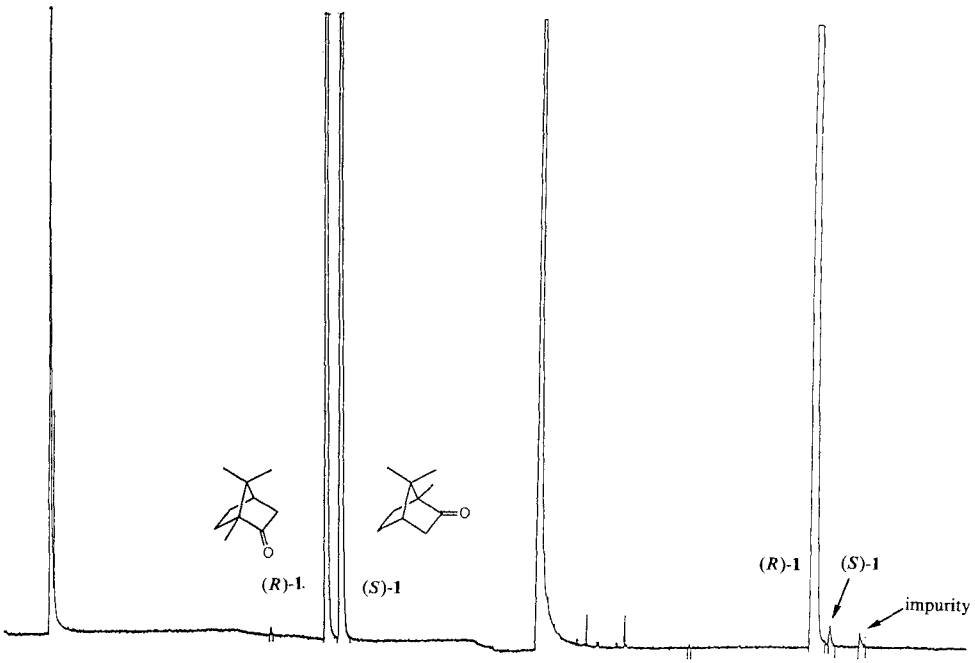

Fig. *Two chromatograms:* left: *of an* (RS)-**1**, *sample* J (see the *Table*); right: *of an* (R)-**1**, *sample* B

3.2. *Statistical Analyses.* Each sample was analyzed several (n_i) times and the resulting mean e.p. ($\overline{\text{e.p.}}$) and standard errors $s(\overline{\text{e.p.}})$ are listed for each sample. The $\overline{\text{e.p.}}$ of all six (*R*)-**1** *A* to *F* are clearly very similar. Comparison of these six, two by two by a *Student*'s *t* test and of all six using the test of the smallest significant difference, showed that the $\overline{\text{e.p.}}$ of *B* to *F* can be considered to be identical and that the $\overline{\text{e.p.}}$ of *A* is different. One can then calculate an $\overline{e.p.}$ for *B* to *F* and this is 99.62 with an $s(\overline{\text{e.p.}})$ of 0.02. The $\overline{\text{e.p.}}$ of *A* is slightly higher, 99.76, with an $s(\overline{\text{e.p.}})$ of 0.06. These standard errors of the means $\overline{\text{e.p.}}$ are defined as $s(\overline{\text{e.p.}}) = s(\text{e.p.})_i/\sqrt{n_i}$, where the $s(\text{e.p.})_i$ are the standard deviations for each analysis. According to a χ^2 test on all of the analyses (thus including those of *G* to *J*), these $s(\text{e.p.})_i$ can be taken to be all the same, $s(\text{e.p.}) = 0.10$.

For completeness, we transform the data into the enantiomeric excess scale: the $\overline{\text{ee}}$ for *B* to *F* is 99.24, standard error $s(\overline{ee}) = \sqrt{2s(\overline{\text{e.p.}}(\text{B–F}))^2} = 0.02$, and the $\overline{\text{ee}}$ for A 99.52, $s(\overline{\text{ee}}) = 0.08$. The c.p. of the (R)-**1** all differ somewhat (see the *Table* and below). The three (*S*)-**1** have different and distinctly lower e.p. and also different c.p. *Unless proven otherwise, one must assume that commercial camphors in general had and have e.p. of this kind.*

3.3. $[\alpha]_D$*'s.* We do not have satisfactory $[\alpha]_D$'s. This would require very high c.p., and we only managed to purify three samples to > *ca.* 99.5% c.p., by flash chromatography [19]. Some kind of ultrapurification would be in order. Note that zone melting should increase the c.p. but not the e.p. (*Sect. 2.3.1*), but that other methods could increase both.

3.3.1. *Constitutional Purities.* In principle, the analyses on the cyclodextrin column provide both the e.p. and the c.p., but, since we optimized for the determination of the e.p., it was better to check the c.p. on a normal capillary column. There were a number of

tiny peaks, and these were integrated. We did not identify these impurities, except for the borneols, which were 'major' impurities (before chromatography) in all but one sample (H), and for the isoborneols (minor). The response factors are exactly the same for (*R*)-**1** and (*S*)-**1** and, in principle, different for the constitutional impurities. The latter probably does not affect the integrations too much, but we inevitably also neglect a background of further impurities: these absolute analyses are much more problematic than the relative e.p. analyses (where one focuses only on the two enantiomers). We, therefore, only ran a single, optimized gas chromatogram for each sample and assume that the standard deviations are of about the same order as in the e.p. analyses. The $[\alpha]_D$'s of the purified samples and the c.p. of all the samples are also listed in the *Table*. Since the e.p. and c.p. are of the same order, and the constitutional impurities (possibly contributing to the $[\alpha]_D$) only partly identified, we cannot extrapolate the $[\alpha]_D$'s to 100% e.p. and (necessarily also) c.p.[12]).

4. Causes of the Imperfect Enantiomeric Purities. – 4.1. *Antipodal Enzymes.* The first explanation for the imperfect camphor e.p. that comes to mind is that both antipodal enzymes are at work; it is even established that both sage and rosemary have a set of antipodal enzymes [17]. However, this does not explain why the e.p. of five of our six (*R*)-**1**, from different suppliers and of widely different ages, are indistinguishable, and the e.p. of the sixth almost the same, nor why these e.p. are so high. One would expect the distributions of the antipodal enzymes to differ in various parts of the trees and in trees in different locations: the e.p. should depend on how, where, and when the harvesting is done; they should vary. This is the case for the (*S*)-**1**[13]) but not for the(*R*)-**1**.

4.2. *Enzymatic Errors?* – In the case of the (*R*)-**1**, we can think of two explanations, both still speculative. The antipodal cyclases could be there in a genetically fixed ratio, or we already see the efficiency of one sole cyclase. The latter explanation has the virtue of being simpler and may also be sufficient, because our e.p. may already be within the range that one can expect for an enzymatic reaction. However, information on this is only just appearing. *Koppenhöfer*'s results (*Sect. 2.3.3*) are mainly unpublished [11a][6]): he has reported unspecified enzymatic errors that translate into e.p. of 99.80–99.99% [11d], and e.p. of 98.3% for a commercial (*S*)-ethyl lactate [11b] and of 99.97% and 99.83% for two commercial diethyl tartrate enantiomers [11c]. *Armstrong et al.* have reported that even common L-amino acids – commercial ($\geq$ 99.20%) and in human urine (94.9(!)–99.94%) – have imperfect e.p. [20], and *Gil-Av* and coworkers that the D-amino acids accumulate in human teeth [21].

Furthermore, the hypothetical enzymatic errors are particularly easy to account for in our case: the cyclase would once in a while bind the substrate (*Sect. 5*) in the wrong, antipodal helical conformation. The antipodal cyclases may be particularly inefficient enzymes as they bind the same substrate in antipodal helical conformations [17].

5. Enantiomeric Purity of Enzyme-Synthesized Camphors. – As behooves their stature, the biosynthesis of both (*R*)-**1** and (*S*)-**1**, by antipodal geranyl pyrophosphate cyclases, from sage and tansy, respectively, has been investigated extensively by *Croteau*'s

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[12]) If one neglects the c.p.'s and extrapolates only on the basis of the e.p., one does not get the same absolute values.

[13]) Their being made by oxidation of (1*S*)-borneol (*Sect. 2.1*) does not affect the argument.

group [17]. The primary products are the bornyl pyrophosphates, which are then enzymatically dephosphorylated and oxidized. The e.p. were checked at the level of the camphors, as follows. ^{3}H-Labeled geranyl pyrophosphate was transformed into tiny amounts of labeled (*R*)-**1** or (*S*)-**1**, each mixed with unlabeled carrier (*RS*)-**1**, each mixture derivatized with (−)-(2*R*,3*R*)-butane-2,3-diol, the ketals so obtained isolated by TLC and then analyzed by GLC using a ^{3}H-detector and a packed column, and the label only detected in the appropriate ketal [17c]. Our separations are much better, but our method is *not* sensitive enough to detect directly such tiny amounts of (*R*)-**1** and (*S*)-**1**, let alone the minor enantiomers, (*S*)-**1** and (*R*)-**1**, respectively, that could be there as well. This is why *Croteau et al.* also isolated and analyzed an (*S*)-**1** from tansy leaves (*Sect. 2.3.5*).

6. Experimental. – GLC: *Carlo-Erba Mega 6000* chromatograph, split injector, flame ionization detector, *SpectraPhysics Chromjet 700* integrator; e.p.: fused silica *Macherey-Nagel Lipodex E* (oktakis(3-*O*-butyryl-2,6-di-*O*-pentyl)-γ-cyclodextrin) 45 m × 0.25 mm column; c.p.: fused silica *J&W Scientific* chemically-bonded methylsilicone *DB1* 60 m × 0.25 mm column. GLC/MS (identification and homogeneity control of the peaks of both enantiomers in every case): *Carlo-Erba 4160, Finnigan 4500 - INCOS 3.7*, same cyclodextrin column. Polarimetry: *Perkin Elmer 241* polarimeter.

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