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Conference Paper

Louis Pasteur and Modern Industrial Stereochemistry*

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In the context of a brief discussion of the career of Louis Pasteur (who died 100 years ago), the applications of »Pasteurian Resolutions« to modern sterochemistry, especially in its industrial applications, will be presented.

It is a great pleasure for me to dedicate this article to Professor V. Prelog on the occasion of his 90th birthday.[1] I have had the privilege of knowing him for over half of his life[2] (and, of course, more than half of mine), ever since he visited the University of Notre Dame as Reilly Lecturer in 1950. I consider him one of my teachers who deepened my interest and understanding of stereochemistry and, jointly with Professor D. H. R. Barton, is largely responsible for my having devoted most of my own career to this subject.[3] For this I am deeply grateful to him.

I have chosen as the subject of this article Louis Pasteur,[4] another pioneer of stereochemistry, who died 100 years ago as of this writing. Pasteur was and is a folk hero, not only in his native France, but also in many other countries, including the United States. (In looking at some of his biographies in our university library, I was astonished to find that many of them had been checked out by students and faculty within the last year!) Not surprisingly, when Pasteur died in 1895, he was given a state funeral which, among others, was attended by the then French President Francois Fauré. He was offered burial in the Panthéon, that resting place of other French heroes,

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Dedicated to Professor Vladimir Prelog on his 90th birthday.

but his family opted instead to have him interred in a mausoleum inside the Institut Pasteur which had been built for him in 1888 with funds contributed by a grateful public all over the world. It must be said however, that his fame rested largely on his later applied work on microbiology and immunology rather than his early fundamental work in stereochemistry.

Louis Pasteur was born in Dôle, in the French Jura or Franche Compté, near Besançon on December 27, 1822, the son of a tanner. When he was 3, his family moved to Marnoz near Salin and two years later, in 1827, to nearby Arbois which Pasteur considered his home. Pasteur attended the collège in Arbois and, at the age of 15, was sent to Paris to complete his school education. However, he became violently homesick and had to return home within the month. He completed his school education at the nearby Royal College of Besançon, receiving his baccalauréat in 1840 but stayed on for two years as a tutor to get his second high school diploma in science in 1842 at the age of 19. His grade in physics was »passable« and his chemistry grade »mediocre«. He then took the entrance examinations of both the Ecole Normale and the Ecole Polytechnique, but placed only 15 out of 22 in the former and failed the latter. Although admitted to the Ecole Normale he decided not to go but instead to continue his education at the Barbet Boarding School in Paris where he came under the influence of Jean-Baptiste Dumas. In 1843 he passed the entrance examination a second time, ranking 4th, and entered upon a course of university study at the Ecole Normale, working with Antoine Jérome Balard and obtaining the equivalent of a doctorate in 1847. He presented two theses, one in physics dealing with the rotatory polarization of liquids and one in chemistry on potassium, sodium and ammonium arsenate for which latter he received the grade of »excellent«.

It was but a year later, in 1848, that Pasteur made his first major discovery, the resolution of a racemate into its enantiomers by the manual separation of visually distinct enantiomorphous (mirror image) crystals.[5] Pasteur, having found that many of the salts of (+)-tartaric acid are hemihedric, *i.e.* not superposable with their mirror image, examined crystals of salts of paratartaric acid (the much less common racemic form) and, to his surprise,* found that some of these salts also formed hemihedric crystals. When he then looked at crystals of the sodium ammonium salt under the microscope, he realized that the hemihedry of its crystals was of two kinds:

* Pasteur's curiosity was peaked by the (as it turned out, erroneous) reports by de La Provostaye[6] and Mitscherlich[7] that the crystals of (+)-tartaric acid and (racemic) paratartaric acid were identical; these investigators had missed observing the hemihedry, perhaps because their crystals were not as well formed as Pasteur's. Since Pasteur associated the hemihedry he found in salts of (+)-tartaric acid with optical rotation (*i.e.* he correctly associated optical activity with crystal and, ultimately, molecular dissymmetry) he was unable to accept that crystals of salts of the inactive acid could exhibit the same hemihedry he had observed in salts of the (+)-acid.

some crystals had their slanted facets inclined to the left, others to the right, in mirror image fashion. When Pasteur picked apart the two types of (enantiomorphous) crystals and separately dissolved them in water, he found that the solution of one enantiomorph rotated the plane of polarized light to the right, that of the other to the left. He communicated this result to the aged Jean-Baptiste Biot, the original discoverer of the optical rotation of certain naturally occurring substances, who repeated the experiment and was much excited by the result. Pasteur's reputation was thus established and he was soon offered a chair in Dijon. He apparently accepted this chair because it was near his home but soon found out that there was no opportunity for experimental work in Dijon. Fortunately he was able to move on the Strasbourg the same year (1848), where he stayed for 6 years and was able to develop his research.

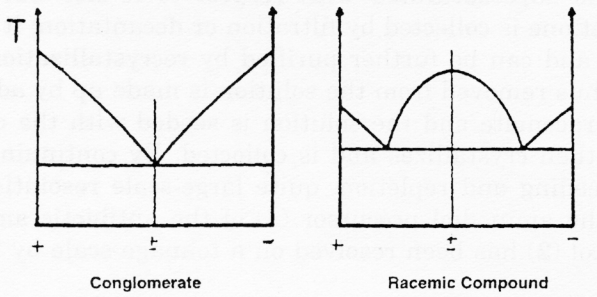
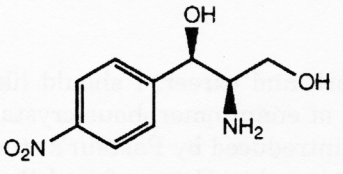


Figure 1. Melting point phase diagrams for conglomerates and racemic compounds.

Before continuing to follow Pasteur's work and career, I should like to point out that, while the manual separation of enantiomorphous crystals is rarely feasible, a modification of the method introduced by Pasteur's student Gernez[8] is still used on a large industrial scale today. Gernez found that by seeding a saturated solution of racemic Pasteur's salt [sodium ammonium (±)-tartrate] with a crystal of one of the enantiomers, an additional amount of the same enantiomer will crystallize. To understand this phenomenon, it is necessary to examine phase diagrams. Rather than to look at solubility diagrams, which are relatively complex, we shall consider melting point diagrams (Figure 1). With a few exceptions (cases in which the enantiomers form solid solutions) these plots may be divided into two classes, one in which the enantiomers form a conglomerate or racemic mixture of enantiomorphous crystals, in which the racemate is a eutectic and has a minimum melting point, and the other where they form a racemic compound in which the two enantiomers pair up in the unit cell of the crystal to form a dimeric (or sometimes tetrameric or even octameric) compound which may have a

melting point higher or lower than that of the pure enantiomers. It is only in the case of conglomerate formation that spontaneous separation of enantiomorphous crystals can occur. It was fortunate for Pasteur that the sodium ammonium salt of racemic tartaric acid forms a conglomerate (fewer than 10% of neutral organic substances and perhaps 20% of salts do so)[9] and that the climate in Paris tends to be cool (Pasteur's salt turns into a racemic compound above 28 °C).[10]

The modern version of this separation process is called the »method of entrainment«[11,12] and proceeds as follows: A saturated solution of the (racemic) conglomerate is seeded with crystals of one of the enantiomers. More crystals of the same enantiomer then form since, as seen in Figure 1, the solution is supersaturated with respect to that enantiomer. (The higher the melting point, other things being equal – as they are in enantiomers – the lower the solubility.) Before the other enantiomer begins to crystallize (the solution is supersaturated with respect to it also but there are no seeds), the first one is collected by filtration or decantation; it will generally be quite pure and can be further purified by recrystallization. The weight of substance thus removed from the solution is made up by adding an equal weight of the racemate and the solution is seeded with the opposite enantiomer which then crystallizes and is collected. By continuing this process of alternate seeding and repletion, quite large-scale resolutions can be effected. Thus the aminodiol precursor (**1**) of the antibiotic amide (*R*,*R*)-(+)-chloramphenicol (**2**) has been resolved on a tonnage scale by this method.[13]



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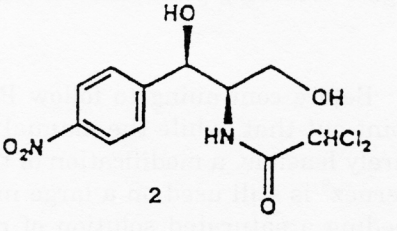

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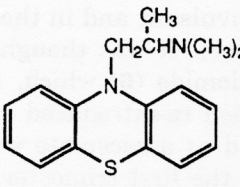
Before continuing the discussion of Pasteur and resolution, let us take a look as to why resolution has taken on such practical importance in the last few years, especially in the area of pharmaceuticals but also in agricultural and flavor chemicals.

The interaction of a drug with its receptor may be likened to the interaction of a glove with a hand. By way of an analogy, if the receptor is right-handed, only the drug shaped like a right-handed glove will be effective. In molecular terms, only one of the two enantiomers of a chiral drug (the so-called »eutomer«) will usually be active; the other enantiomer, the so-called



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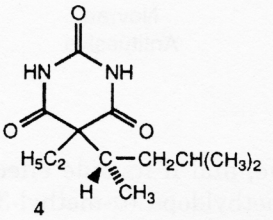
»distomer« will generally be inactive. [There are exceptions, one of them being promethazine (**3**) where the active site may be distant from the chiral center.[14, 15]] Since the distomer may have undesirable side-effects, or simply because – on account of minor toxicity which is seen in many pharmaceuticals – a drug should be given in the smallest dose possible, it is often preferable to administer the single active enantiomer of the drug. (For reviews, see Ref. 16–18.) In practice, pure enantiomers can be obtained in one of three ways: a) By resolution (and, as we have seen or shall see, nearly all resolutions are based on Pasteur's pioneering work) b) by synthesis from enantiomerically pure (usually naturally occurring) starting materials and c) by enantioselective (»asymmetric«) synthesis. (Methods b and c[19] will not be discussed further in this paper.)



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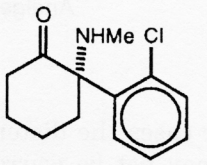

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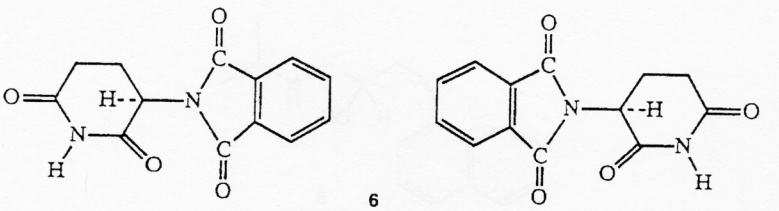
Cases where the distomer is noxious and clearly needs to be removed are those of 5-(1,3-dimethylbutyl)-5-ethylbarbituric acid (**4**)[20] and ketamine (**5**)[21]. In both cases the eutomers are anesthetics whereas the distomer in the case



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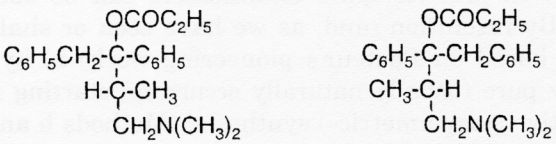
of the barbituric acid is a convulsant and in the case of ketamine causes excitory and psychic disturbances. It was thought, for a time, that a similar situation pertained in thalidomide (**6**) which, at one time, was used as a sedative and has recently been re-introduced in the management of AIDS. The drug was originally used as a racemate with disastrous effects: When given to pregnant women in the first trimester, it acted as a teratogen, *i.e.* caused the development of infants with stunted or deformed arms and legs. It was later shown (in mice and rats) that the sedative action resides in the *R*-(+) enantiomer and the teratogenic property in the (*S*)-(–)[22] and that the tragedy might have been prevented if only the (*R*) eutomer had been administered. However, this is probably not so, since the drug appears to be enantiomerized (racemized) in the body[23] so that the *R*-enantiomer, even if administered as such, is converted to the unwanted *S*; both enantiomers are teratogenic in rabbits.[24]

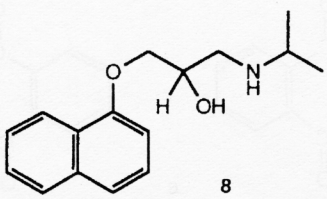


(2*S*,3*R*)-(+)- (2*R*,3*S*)-(-)-

Darvon Novrad
Analgesic Antitussive

7

In other cases the distomer is inactive, and if its side effects are minor resolution may not be warranted. (*S*)-α-methyldopa (α-methyl-3,4-dihydroxyphenylalanine) may be in this category.[25] A more interesting case is that where both enantiomers have desirable, but quite different pharmacological properties, an example being the analgesic (pain reliever) Darvon (**7**) whose enantiomer, appropriately called »Novrad«, is an antitussive (cough suppressant).[26] Yet another example is propranolol (**8**) which controls blood pressure by blocking the so-called β-receptors; the enantiomer in this case, while not



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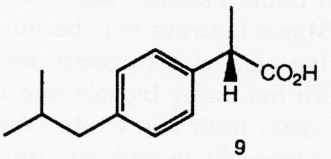
a β-blocker, also seems to have beneficial effects.[27] An interesting situation is also exhibited by the anti-flammatory drug ibuprofen (**9**). This is another case of facile enantiomerization and it was therefore initially not deemed worth while to separate the *in vitro* pharmacologically active (*S*)-(+) eutomer[28] in as much as the (*R*)-(–) distomer is converted, *in vivo*, into the (*S*)-(+).[29] However, it is now believed that this transformation is slow in relation to the speed of action of the drug and that, by administering the pure (*S*)-(+) enantiomer, a faster-acting drug might be produced.



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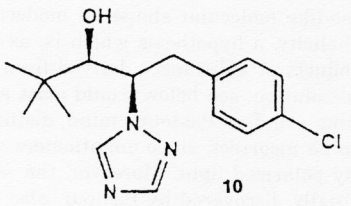
Finally, there are also cases where the distomer should be removed because it antagonizes (blocks) the beneficial effect of the eutomer.[15]

It must be said here that considerations of pharmacodynamics – *i.e.* preferred drug-receptor interaction – are not the only ones to be considered. Pharmacokinetics – the rate at which the drug arrives at the receptor – must also be considered; for example relative permeation of enantiomers through a (chiral) cell membrane, relative efficacy of plasma binding, relative rate of excretion and last but not least relative degradation of enantiomers in a first pass through the liver.[18]

The matter of enantiomerism in drugs has attracted enough general interest to merit an article »Lifting the Side Effect Out of the Drug« in the November 9, 1995 issue of the *Wall Street Journal*! But pharmaceuticals are not the only area where enatiomers may differ: In the case of Paclobutrazol (**10**) the (2*R*,3*R*)-(+) enantiomer is used in agriculture as a fungicide whereas the (2*S*,3*S*)-(–) enantiomer is a growth regulator.[30] And there are several similar situations with flavor chemicals, a typical case being that of the carvones (**11**) where the (*R*)-(–) isomer has the odor of spearmint and the (*S*)-(+) isomer that of caraway seed.[31]



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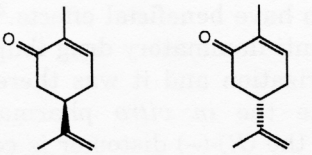

(*R*)-(-) (*S*)-(+)

(spearmint) (caraway)

11

Let us return now to Louis Pasteur, both his life and his chemistry. In 1849 he was married to Marie Laurent who became his steadfast companion throughout his life, serving also as his private secretary and sometimes his assistant. She put up with his many travels and his long hours of work; in a letter to her daughter years later she wrote »Your father, very busy as always, says little to me, sleeps little and gets up at dawn«. When, on occasion, she got restless, he told her that »he would lead her into posterity«. (In fact, she is buried next to him in the mausoleum of the Pasteur Institute.) The Pasteurs had 5 children of whom, however, only 2, a son and a daughter, lived to adulthood. The son had no offspring; the daughter was married to René Vallery-Radot; the latter, as well as Pasteur's grandson, Pasteur Vallery-Radot, wrote biographies of Louis Pasteur, embellished, no doubts by the close relationship and by the fact that Pasteur himself edited his son-in-law's writing.

Around 1850, Pasteur's supply of racemic tartaric acid seems to have run out and he traveled all over Europe to find new sources, with limited success. He therefore studied the racemization of the abundant (+)-tartaric acid; in 1853 he succeeded in this endeavor (Figure 2) by heating tartaric acid with cinchona alkaloids which, in the process, were themselves transformed chemically, for example cinchonine into chinchonicine (cinchotoxine) (Figure 2).[32] As is obvious from Figure 2, the enantiomerization (racemization) of (+)-tartaric acid must proceed *via meso*-tartaric acid which was indeed isolated by Pasteur; fortunately thermodynamics favors the racemic isomer which was thus the major product. However, Pasteur also found the non-resolvable meso-tartaric acid which he called the untwisted (»détordu«) isomer.* But there was a third,

* Pasteur had the idea, expostulated in his 1860 lectures,[33] that optically active substances had a twisted, spiral, staircase-like molecular shape; in modern terms we would say that he attributed optical activity to helicity, a hypothesis which is, as we know partially correct. He also felt that only natural products or substances derived from them (*e.g.* by chemical transformation or by their use in resolution, see below) could exist as single enantiomers; this hypothesis persisted for a long time – and, in Pasteur's mind, distinguished living from non-living matter – but is now known to be incorrect, since enantiomers can be generated by photochemical synthesis with circularly polarized light. Moreover, the »spontaneous resolution« observed in conglomerates, and actually discovered by Pasteur, also militates against his theory.

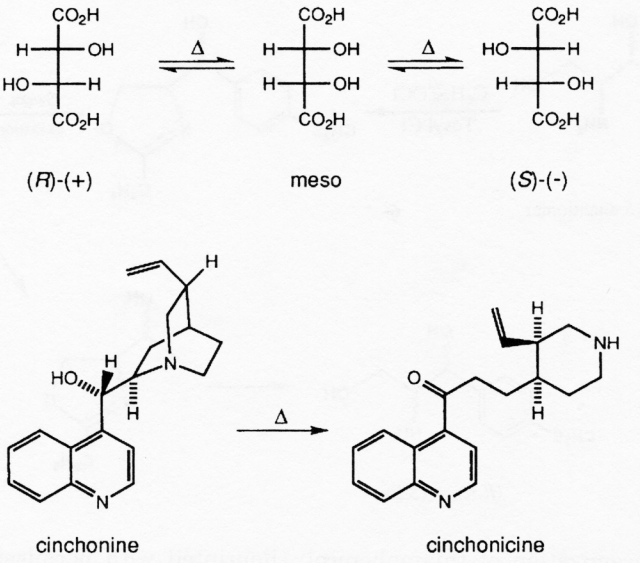

Figure 2. Epimerization and racemization of (*R*)-(+)-tartaric acid.

even more important discovery that resulted from the same experiment: the chinchotoxin salts of the two enantiomers of racemic tartaric acid were separable, being diastereomers. This, of course, forms the basis of large numbers of resolutions performed since Pasteur's time and even today. The fact that Pasteur was able to draw three major conclusions, two of them unanticipated, from a single experiment designed to achieve racemization points to his superior powers of observation which he had already demonstrated in his 1848 publication.

Racemization – or epimerization, the corresponding process in structures with more than one chiral center – is, of course, a highly undesirable occurrence in a stereoselective synthesis. Yet it is an all-important process on an industrial scale in as much as resolution necessarily (but see below) leaves one with 50% of the undesirable enantiomer, which causes both an economic and an environmental problem. If the undesired enantiomer can be racemized, the resulting racemate can again be subjected to resolution, so that there is no net loss. An example is the racemization of thiamphenicol *via* a phenyloxazoline derivative (Figure 3);[34] this is a particularly tricky case since inversion of configuration at both chiral center is required.

Sometimes racemization and resolution can be combined in a process called »asymmetric transformation of the second kind« or, perhaps better, »crystallization-induced asymmetric transformation«.[35] The principle of the process is shown in Figure 4; the species to be resolved, X, must contain a

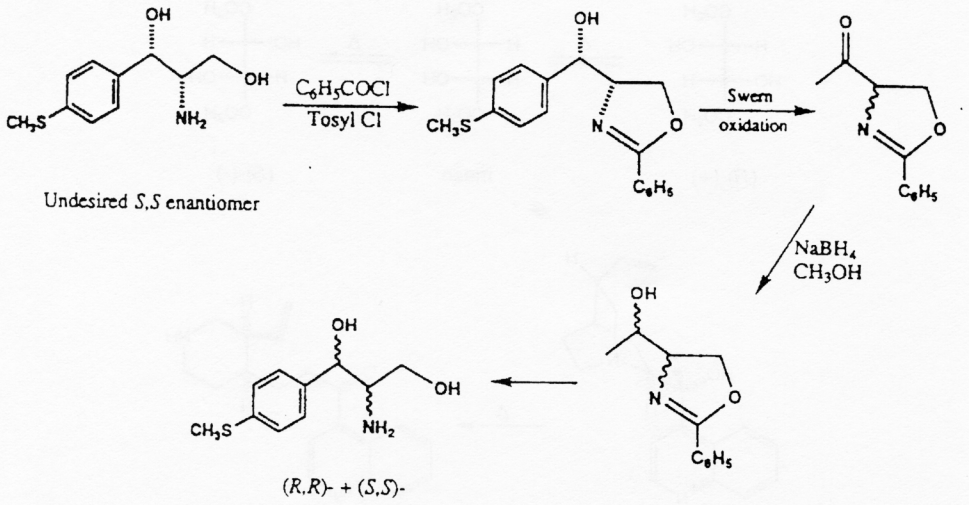

Figure 3. Racemization of thiamphenicol. (Reprinted with permission from E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994. Copyright John Wiley & Sons, Inc., 1994.)

chiral center which is readily enantiomerized (racemized); sometimes this requires making a derivative of the compound to be so resolved (Figure 5). A resolving agent, (*S*)-Y is added and the less soluble diastereomer, say (*S*)-X.(*S*)-Y crystallizes out in the usual manner according to the method (resolution *via* diastereomer formation) discovered by Pasteur in 1853. However, the residual, more soluble diastereomer (*R*)-X.(*S*)-Y is simultaneously epimerized to a mixture of (*R*)-X.(*S*)-Y and (*S*)-X.(*S*)-Y (since X contains a stereochemically labile chiral center) and the resolution then proceeds until the entire amount of racemic X is converted into crystalline (*S*)-X.(*S*)-Y whose yield may therefore approach 100% instead of the usual 50%. An example

Equilibration of diastereomers in solution.
Useful only if one diastereomer crystallizes out.
Can get 100% of the less soluble
diastereomer:

$$(R)\text{-X} + (S)\text{-Y} \rightarrow (R)\text{-X.}(S)\text{-Y}$$
$$\Downarrow\Uparrow$$
$$(S)\text{-X} + (S)\text{-Y} \rightarrow \underline{(S)\text{-X.}(S)\text{-Y}}$$
$$\downarrow$$

Figure 4. Crystallization-induced asymmetric transformation: Principle.

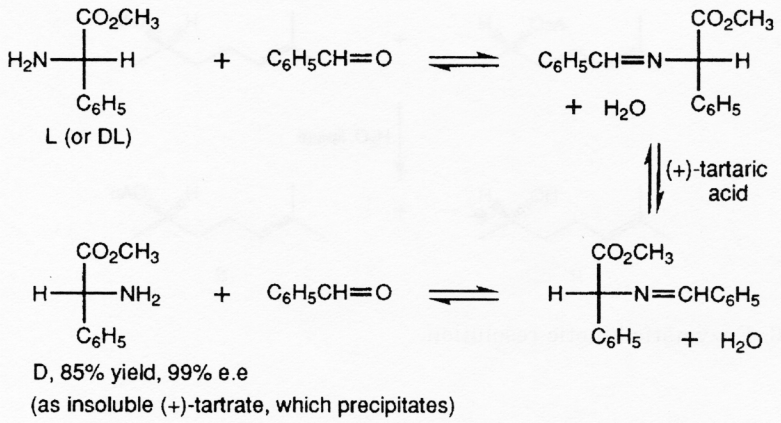

Figure 5. Crystallization-induced asymmetric transformation of racemic or L phenylglycine methyl ester to the D isomer.

involving preparation of D-α-phenylglycine (important as building block of the antibiotic ampicillin, manufactured commercially in multiton quantities) *via* epimerization of the Schiff base derivative is shown in Figure 5.[36]

In 1854 Pasteur moved from Strasbourg to Lille. This move brought him in close contact with the French beer and wine industry which at that time was suffering from poor fermentations resulting in off-taste or even spoilt products. In trying to explain and then successfully cure this problem, Pasteur became interested in microbiology, which, in one form or another, engaged him for the rest of his life. His third (and last) original paper* in the area of stereochemistry dealt with another important method of resolution, this time using enzymes.[38] When he inocculated a solution of ammonium paratartrate (racemic) containing some albuminoid (nitrogenous) material with the microorganism *penicillium glaucum* (obtained from a spontaneous fermentation of calcium (+)-tartrate), he realized, by polarimetric measurement, that the (+)-tartrate was destroyed in the fermentation and the ammonium salt of the (–)-tartrate left behind. This finding is being exploited nowadays in enzymatic resolutions, especially of chiral acids or chiral alco-

* Pasteur did review his work and speculated on its significance in three later lectures, two in 1860[33] and one in 1883.[37] It must be said that his speculations were less spectacular than his experimental work; while he recognized that optical activity was due to molecular dissymetry, he adhered to a vitalistic point of view (see previous footnote), he confused "untwisted" meso forms with racemic compounds and, in his 1883 review, barely mentioned le Bel's work and not at all van't Hoff's. He apparently paid little attention to the structural theories of organic chemistry developed by Couper, Kekulé, Loschmidt, Butlerov, Crum Brown, le Bel and van't Hoff between 1858 and the 1870's.

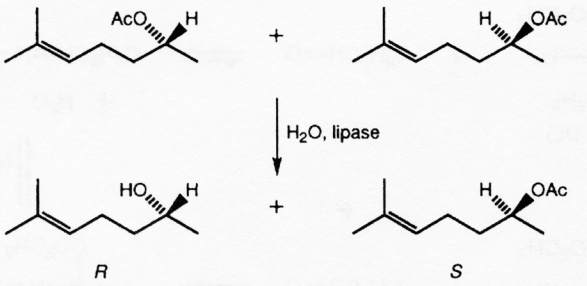

Figure 6. Enzymatic kinetic resolution.

hols.[39] In cleavage of an ester of the racemic acid (or alcohol) by means of a lipase, only one of the two enantiomeric esters will generally be hydrolyzed (Figure 6). The hydrolyzed acid (or alcohol) can be separated from the residual ester to yield one of the enantiomeric products; the other enantiomer can be obtained by saponifying the residual ester in conventional chemical ways. If pure enzymes are used, the process may be highly stereoselective and it may thus be possible to hydrolyze one of the enantiomeric esters quantitatively or nearly so while leaving the other one entirely unchanged, thereby producing nearly enantiomerically pure products in high (near 50%) recovery. This process is an example of a kinetic resolution (Figure 7).[40] An unusual but ingenious modification is shown in Figure 8, wherein a spontaneous racemization of a hydantoin derivative of racemic *p*-hydroxyphenylglycine is combined with a highly stereoselective enzymatic synthesis to convert the entire starting material to D-*p*-hydroxphenylglycine (desired in the manufacture of one of the penicillins) or a derivative thereof.[41]

Resolution of (+)-X using a chiral reagent (*R*)-Y

$$(R)\text{-X} \xrightarrow[k_R]{(R)\text{-Y}} (R)\text{-P (product)}$$

$$(S)\text{-X} \xrightarrow[k_S]{(R)\text{-Y}} (S)\text{-P}$$

Since transition states (*R*)-X.(*R*)-Y and (*S*)-X. (*R*)-Y are diastereomeric, $k_R \neq k_S$
If $k_R \gg k_S$, at 50% reaction nearly all (*R*)-X will be transformed to (*R*)-P and quite pure (*S*)-X is left behind.

Figure 7. Principle of kinetic resolution.

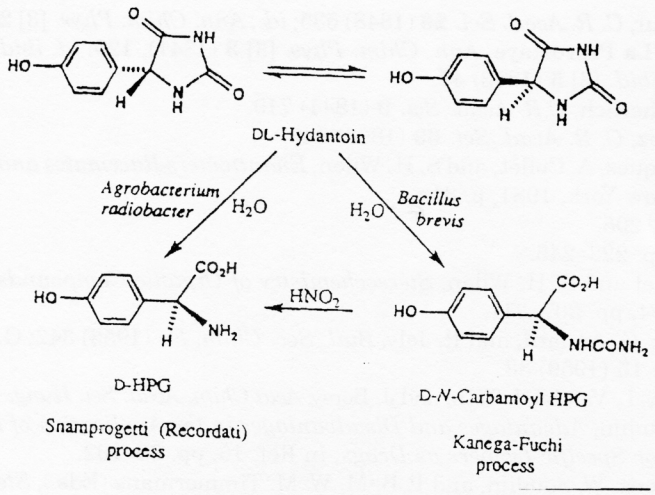

Figure 8. Enzymatic resolution with concommitant asymmetric transformation of D-*p*-hydroxyphenylglycine. (Reprinted with permission form E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994. Copyright John Wiley & Sons, Inc., 1994.)

Pasteur, in 1857, returned to the Ecole Normale as Director of the Science Department* and devoted the rest of his scientific career to microbiology, the treatment of silkworm disease, and the development of animal and human vaccines; that work is widely known and brought him membership in the Académie Française in 1881. It has now become clear, however, that his less well known (at least among the general public) stereochemical work during the first 10 years of his career has both academic and commercial impact comparable with that of his later achievements.

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SAŽETAK

Louis Pasteur i suvremena industrijska stereokemija

Ernest L. Eliel

U sklopu sažetog razmatranja životopisa Louisa Pasteura (koji je umro prije 100 godina) predočena je primjena »*Pasteurskog odvajanja*« na modernu stereokemiju, posebno u industriji.