CHIMIA 50 (1996) Nr. 9 (September)

Chimia 50 (1996) 418–419

ISSN 0009–4293

Biocatalytic *vs.* Chemical Synthesis of Enantiomerically Pure Compounds

Roger A. Sheldon*

Introduction

In the last decade the growing awareness of the importance of chirality in conjunction with biological activity has led to a burgeoning demand for efficient methods for the industrial synthesis of enantiomerically pure compounds [1–6]. The commercial importance of this trend in pharmaceuticals, *e.g.*, is underscored by the fact that the combined sales of the 'chiral top ten' in 1994 were in excess of 16 billion dollars (*Table*). Eight of these top-ten drugs are marketed as optically pure compounds.

Basically, enantiomerically pure compounds are derived from three different sources: *a*) the rich diversity of chiral molecules, *e.g.* carbohydrates and terpenes, that occur naturally as pure enantiomers, *b*) *de novo* fermentation of cheap carbohydrate raw materials, *e.g.* sucrose or molasses and *c*) synthesis from optically inactive raw materials. *De novo* fermentation is an important source of both relatively simple primary metabolites, such as L-amino acids and lactic acid, as well as a variety of complex substances, such as antibiotics, hormones and vitamins. However, many chiral molecules are not naturally occurring and cannot be made *via de novo* fermentation, which leaves synthesis as the only choice.

Synthetic Methodology

Synthetic methods can be broadly divided into two types based on the type of substrate used: a racemate or a prochiral molecule (*Fig.*). Racemates can be resolved *via* direct preferential crystallization, diastereomeric salt crystallization or *via* kinetic resolution.

Traditionally, crystallization techniques were widely used for the industrial synthesis of pure enantiomers [7]. Alternatively, racemates can be resolved by kinetic resolution, which depends on the fact that the different enantiomers react at different rates with another chiral molecule. The enantioselective conversion of a prochiral substrate to an optically active substrate, by reaction with a chiral addend, is called an asymmetric synthesis. In both cases, the chiral addend should, for obvious economic reasons, be employed in catalytic quantities, *e.g.* as a chiral metal complex or an enzyme. Although the choice of chemo- *vs.* biocatalytic methods applies to both kinetic resolutions and asymmetric synthesis, in practice, enzymatic methods generally involve hydrolytic processes and are kinetic resolutions while asymmetric syntheses usually employ chemocatalysts. Hence, in the majority of cases it comes down to a choice between three methods: separation of a racemate by crystallization, enzymatic kinetic resolution of a racemate and catalytic asymmetric synthesis with chiral metal complexes.

Asymmetric Synthesis *vs.* Kinetic Resolution

A major disadvantage of kinetic resolution compared to asymmetric synthesis is that the former has a maximum theoretical yield of 50% and requires (at least) one extra (racemization) step to fully utilize the starting material. However, this is frequently compensated by the fact that the enzymatic kinetic resolution is a simpler process with a higher productivity (space-time yield) than the corresponding asymmetric synthesis. In some cases the problem is circumvented by employing conditions under which the unwanted isomer undergoes spontaneous *in situ* ra-

Table. *The Chiral Top Ten*

Drug	Therapeutic Class	Sales[a]) $ mio/year
Amoxycillin	Antibiotic	2200
Enalapril	Antihypertensive	2100
Ampicillin	Antibiotic	2000
Captopril	Antihypertensive	1800
Pravastatine	Antihypercholesteremic	1700
Diltiazem	Antihypertensive	1500
Ibuprofen[b])	Antiinflammatory	1500
Lovastatin	Antihypercholesteremic	1300
Naproxen	Antiinflammatory	1200
Fluoxetine[b])	Antidepressant	1200

[a]) Bulk formulated drug.
[b]) Marketed as the racemate.

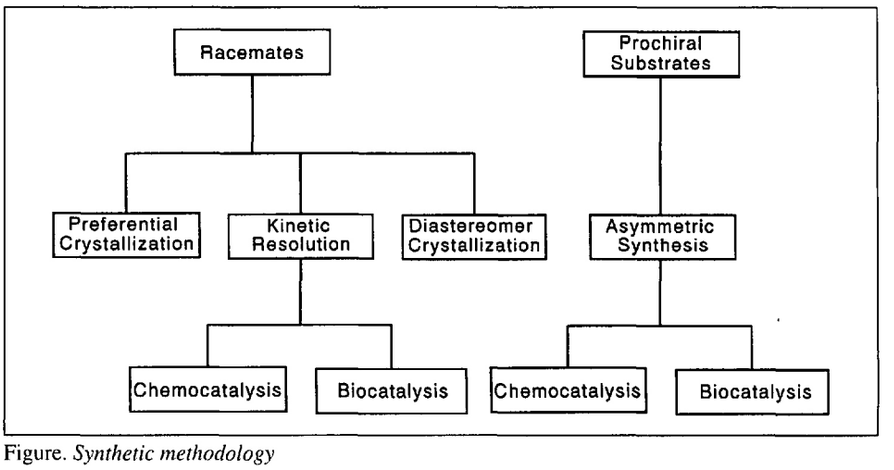
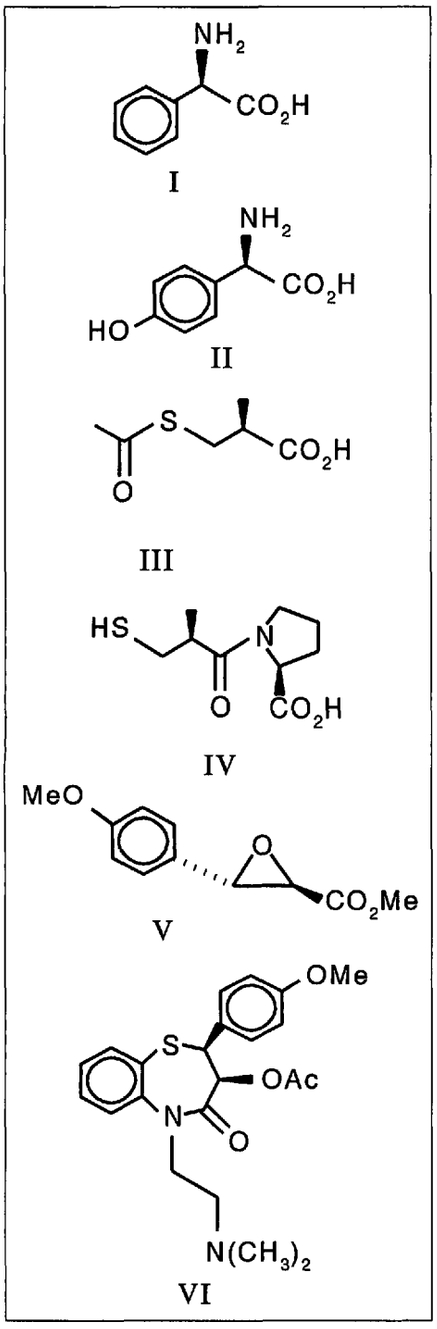


Figure. *Synthetic methodology*

**Correspondence*: Prof. Dr. R.A. Sheldon
Laboratory for Organic Chemistry and Catalysis
Delft University of Technology
Julianalaan 136
NL–2628 BL Delft



cemization. Such a process is referred to as a dynamic kinetic resolution and is equivalent to an asymmetric synthesis.

Factors Effecting Process Economics

Numerous factors are involved in determining the economics of different pathways and the method of choice will vary from one product to another. The substrate costs and availability may influence the choice of a kinetic resolution *vs.* an asymmetric synthesis. The price and ease of recycling of the resolving agent or (bio)-catalyst are obviously critical factors. Many hydrolytic enzymes, *e.g.* lipases, are sufficiently inexpensive that they can often be used on a throw-away basis. In contrast, most chiral metal complexes tend to be very expensive and/or not readily available on a large scale.

The chemical, optical and volume yield (productivity) are obviously important. For an economically viable process, it may be necessary to sacrifice percentage points on chemical or optical yield in order to achieve economically viable productivities. An advantage of many enzymatic kinetic resolutions, employing lipases or esterases, is that they can be performed at high substrate concentrations, sometimes even with neat substrate. Catalytic asymmetric syntheses, on the other hand, generally require relatively high dilutions in order to achieve acceptable enantioselectivities.

The ease of racemization of the unwanted isomer is a critical factor in resolution processes, and it is not generally recognized that the racemization step is often the most difficult one in the overall process. It is remarkable, therefore, that so little attention is devoted to the development of new racemization catalysts.

The total number of steps is important for the economics of any process: more steps translate to longer throughput times and lower overall productivities. Generally speaking, researchers focus their attention on the resolution or asymmetric synthesis step and overlook the number of steps that precede or follow it. Hence, in resolution processes, it is important whether or not the required product is formed directly, *i.e.*, an *attractive vs.* a *subtractive* resolution, and whether the substrate is a precursor or a derivative of the racemic product [1].

Finally, the position of the resolution or asymmetric synthesis step in the overall synthetic scheme can have an important bearing on the cost-price. The golden rule is to plan this step as early as possible in the synthesis. This is readily understood when one considers that every step performed on a racemic mixture is carrying 50% isomeric ballast through the process. Removal of this ballast automatically halves the amount of reagents, solvent, reactor volume, *etc.*, required and doubles the productivity. Most of these extra costs are recovered if an efficient reacemization step is available. However, we note that this is generally feasible only when the product contains one stereogenic centre.

Commercially Relevant Examples

The general principles outlined above are illustrated by reference to the industrial synthesis of several products from the chiral top ten (*Table*). The examples are treated in order of increasing complexity.

(*R*)-Phenylglycine (**I**) and (*R*)-(*p*-hydroxyphenyl)glycine (**II**) are the side-chain intermediates of the semi-synthetic penicillins, ampicillin and amoxycillin, respectively. All commercial processes for the synthesis of **I** and **II** involve either resolution of the racemate *via* diastereomeric salt crystallization [4][5] or enzymatic kinetic resolution of, *e.g.*, the racemic hydantoin [8][9]. The relative merits of the various processes are discussed.

The Angiotensin Converting Enzyme (ACE) inhibitor, Captopril (**IV**) contains two stereogenic centres. In commercial processes, one of these is provided by (*S*)-proline, which is readily available from *de novo* fermentation. The synthetic challenge is provided by the other chiral building block, (*R*)-β-(acetylmercapto)isobutyric acid (**III**). The relative merits of the different approaches, involving resolution *via* crystallization or biocatalytic methods are discussed [4][5][10].

The third example concerns the synthesis of the calcium antagonist, diltiazem (**VI**). The various synthetic strategies for the production of the key intermediate (**V**), *e.g.* enzymatic kinetic resolution [11] and catalytic asymmetric epoxidation [12] or dihydroxylation [13], are evaluated.

[1] R.A. Sheldon, 'Chirotechnology', Marcel Dekker, New York, 1993.
[2] R.A. Sheldon, *J. Chem. Biotechnol.* **1996**, in press.
[3] R.A. Sheldon, in 'Problems and Wonders of Chiral Molecules', Ed. M. Simonyi, Akademiai Kiado, Budapest, 1990, pp. 349–386.
[4] R.A. Sheldon, *Drug Information J.* **1990**, *24*, 129.
[5] R.A. Sheldon, *Chem. Ind. (London)* **1990**, 212.
[6] A.N. Collins, G.N. Sheldrake, J. Crosby, Eds., 'Chirality in Industry', Wiley, New York, 1992.
[7] A. Collet, in 'Chiral Separations by HPLC', Ed. A.M. Krstulovic, Ellis Horwood, Chichester, 1989, pp. 81–103.
[8] S. Takahashi, in 'Progress in Industrial Microbiology', Eds. K. Aida, I. Chibata, K. Nakayama, T. Takanami and H. Yamada, Elsevier, Amsterdam, 1986, Vol. 24, pp. 269–279.
[9] R. Olivieri, E. Fascetti, L. Angelini, L. Degen, *Biotechnol. Bioeng.* **1985**, *23*, 2173.
[10] T. Ohashi, J. Hasegawa, in [8], pp. 269–278
[11] L. Hulshof, J.H. Roskam, to Stamicarbon Eur. Pat. Appl. 0343714, 1989.
[12] E.N. Jacobsen, L. Deng, Y. Furukawa, L.E. Martinez, *Tetrahedron* **1994**, *50*, 4323.
[13] K.G. Watson, Y.M. Fung, M. Gredley, G.J. Bird, R. Jackson, B.R. Mathews, *J. Chem. Soc., Chem. Commun.* **1990**, 1018.