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SYNTHESIS OF OPTICALLY ACTIVE COMPOUNDS: A LARGE SCALE PERSPECTIVE

JOHN CROSBY
ICI Fine Chemicals Manufacturing Organisation, Process Technology Department, PO Box 42, Hexagon House, Manchester M9 3DA, U.K.

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CONTENTS

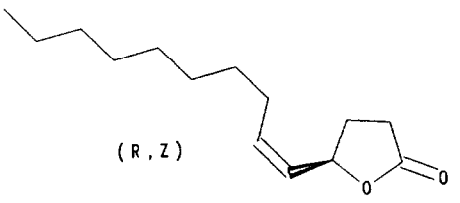
1. INTRODUCTION

The importance of obtaining optically pure materials hardly requires restatement. Manufacture of chemical products applied either for the promotion of human health or to combat pests which otherwise adversely impact on the human food supply is now increasingly concerned with enantiomeric purity. A large proportion of such products contain at least one chiral centre.

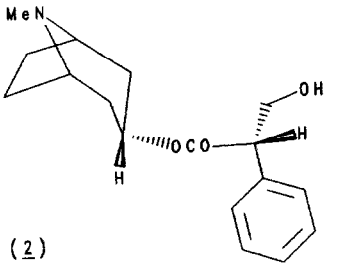
Both the DL and (*RS*), Cahn-Ingold-Prelog, descriptors are used herein. The older DL convention is still in widespread use for amino acids and carbohydrates

The desirable reasons for producing optically pure materials include: (i) biological activity is often associated with only one enantiomer; (ii) enantiomers may exhibit very different types of activity, both of which may be beneficial or one may be beneficial and the other undesirable; production of only one enantiomer allows separation of the effects; (iii) the unwanted isomer is at best 'isomeric ballast'[1] gratuitously applied to the environment; (iv) the optically pure compound may be more than twice as active as the racemate because of antagonism, for example the pheromone of the Japanese beetle (**1**) where as little as 1% of the (*S*, *Z*)-isomer inhibits the (*R*, *Z*)-isomer;[2] (v) registration constraints;[3] production of materials as the required enantiomer is now a question of law in certain countries, the unwanted enantiomer being considered as an impurity; (vi) where the switch from racemate to enantiomer is feasible, there is the opportunity to effectively double the capacity of an industrial process; alternatively where the optically active component of the synthesis is not the most costly, it may allow significant savings to be made in some other achiral but very expensive process intermediate; (vii) improved cost-efficacy; (viii) the physical characteristics of enantiomers versus racemates may confer processing or formulation advantages.

That the shape of a molecule has considerable influence on its physiological action has been recognised for a long time.[4] For example, in the early 1900s Cushney demonstrated that one member of a pair of optical isomers could exhibit greater pharmacological activity than the racemate: (−) hyoscyamine (**2**) was approximately twice as potent as the racemate (atropine) in its effect on pupil



(1)



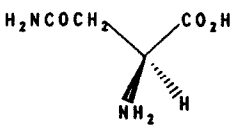
(2)

nerve endings.[5] Examples of property differentiation within enantiomer pairs are numerous and often dramatic. A selection is given in Table 1 which emphasises the reasons for commercial interest and the incentive for producing enantiomerically pure materials by methods applicable to at least multikilogramme amounts and in many cases to hundreds or thousands of tonnes.

All conceivable methods for the production of optically pure chiral materials are being actively researched. The field is served by a steady stream of monographs, reviews[7] and specialist conferences[8] and new journals dedicated to the topic have appeared.[9] The perspective of this article is essentially an industrial one. The topic is approached from the standpoint of the person with an interest in producing at least a few kilogrammes of an enantiomerically pure material for initial field trials or toxicology studies during the development of a new pesticide or therapeutic agent and who may ultimately have to consider how to obtain tonne quantities by the most economic route and within tight time constraints. The aim has been to survey the methods available for producing optically active materials, how they have been applied to targets of commercial interest, and their suitability for producing, at least, multikilogramme amounts. However, it is also hoped to draw the attention of readers, for whom pursuit of the most cost-effective methods is not of overriding priority, to facets of 'large scale thinking' which may nonetheless be useful.

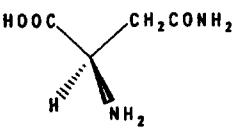
The subject could be addressed either by reference to a selection of target molecules and examining the approaches brought to bear on the problems, or by systematic reference to sources

Table 1.

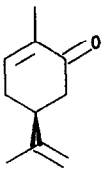


ASPARAGINE

(S) bitter taste

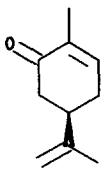


(R) sweet taste

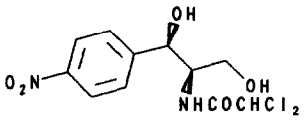


CARVONE

(S) caraway flavour

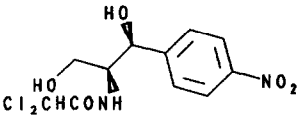


(R) spearmint flavour

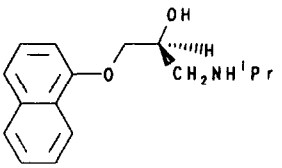


CHLORAMPHENICOL

(R,R) antibacterial

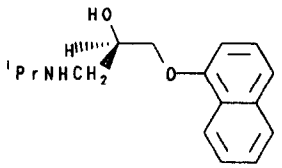


(S,S) inactive



PROPRANOLOL

(S) β-blocking agent
ca 100 x activity of (R)



(R)

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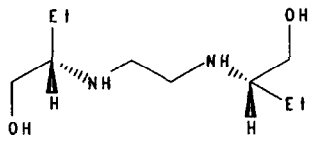
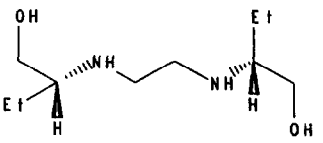
Table 1 *continued*

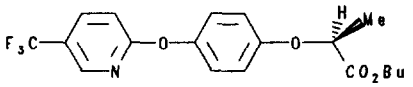


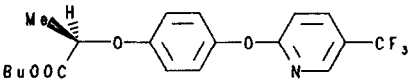


ETHAMBUTOL

(S,S) tuberculostatic

(R,R) causes blindness

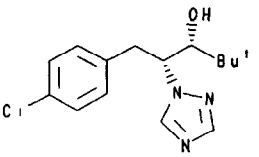


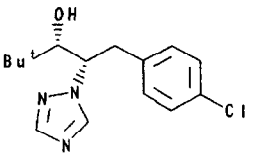


FLUAZIFOP BUTYL

(S) inactive

(R) herbicide

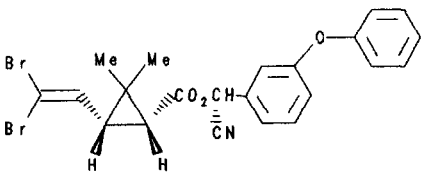




PACLOBUTRAZOL[6]

(2R,3R) fungicide

(2S,3S) plant growth regulato



(S,S,R) inactive

DELTAMETHRIN

(R,R,S) potent insecticide

of, or techniques for, the generation of optically active compounds. The latter has been adopted because it allows the merits of the various approaches to be kept in better perspective. However, because it is felt to be instructive, in one case the range of methods brought to bear on a structure of considerable commercial significance has also been presented (Section 3.1.4).

Excluding the isolation of natural products, the production of optically pure materials has generally presented a significant challenge bearing in mind that, to be of practical large scale use, enantiomeric excesses (*ee*'s) ought to be at least 70% and preferably greater than 80% for the crude material which is initially produced.

Approaches which may be applied are: (i) utilisation of chiral pool materials; (ii) separation of racemates; (iii) creation from prochiral precursors.

2. METHODS FOR OBTAINING OPTICALLY ACTIVE COMPOUNDS

2.1. *The chiral pool*

The chiral pool customarily refers to relatively inexpensive, readily available optically active natural products. Materials, the commercial availability of which generally falls in the range 10^2–10^5 tonnes per annum; representative materials are listed in Table 2. There is, however, as a result of the pressures to produce an ever-growing number of commercial products as single enantiomers, an increasing and still largely unrecognised and unexploited source of new materials which should justifiably be added to the traditional pool. These materials, industrial end products and process intermediates, are often produced in very significant quantities, 10^2–10^3 tonnes per annum. They have a diversity which must soon exceed that of the natural counterparts if this is not already the case. Although in many instances output of these substances exactly matches consumption it is important to recognise they exist, that necessary technology to produce them exists, and that more could be made if the demand was there.

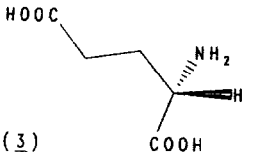
This section is concerned primarily with use of chiral pool substances as building blocks. They are incorporated into the target structure with any necessary modification in order to achieve the desired chiral features.

Table 2.

	Approx. price (US dollars kg^{-1})
Ascorbic acid	13
(+)-Calcium pantothenate	16
(−)-Carvone	23
Anhydrous dextrose	1.2
Ephedrine hydrochloride	62
(+)-Limonene	3
L-Lysine	3.2
Mannitol	7 5
Monosodium glutamate	2
Norephedrine hydrochloride	24
Quinidine sulphate	130
Quinine sulphate	75
Sorbitol	1.7
L-Threonine	12–50 depending on grade
L-Tryptophan	68

Data from *Chemical Marketing Reporter*, Schnell Publishing Company Inc., New York, 13 April (1990); reproduced by permission of the editor

2.1.1. *Amino acids.* α-Amino acids are readily available, in bulk, usually with high *ee*'s and are one of the oldest sources of optical activity. Crystalline glutamic acid (3) was isolated from gluten



(3)

hydrolysate in 1866.[10] The development in Japan in the early 20th century of monosodium L-glutamate as a flavour enhancer laid the foundation for an amino acid industry still dominated by Japanese companies. Other major producers tend to have a primary capability in cyanide chemistry and make racemic α-amino amides by the Strecker synthesis[11] (Scheme 1) and then resolve enzymically (Section 2.2.3.3) or, in some instances, classically (Section 2.2.1).

All the proteinogenic L-amino acids are available commercially on scales ranging from 10 to 10^5 tonnes per annum.[12] L-Lysine (ca 70000 tpa) and monosodium L-glutamate (ca 350000 tpa)[13,14] are produced on scales which rank with petrochemicals. Although in the past it has been the natural, L-series acids, which have been available, D-amino acids are now becoming increasingly available as a result of being needed as components of materials of industrial interest. (Chart 1). Peptide

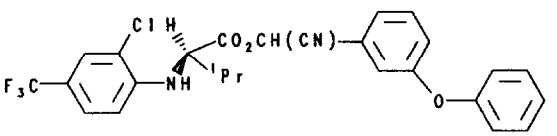
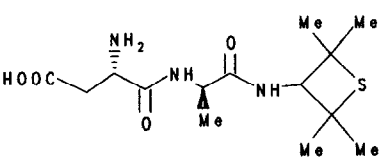
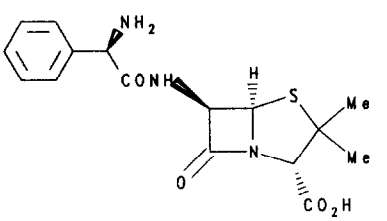
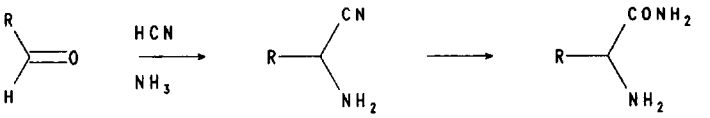
Amino acid	Product	Ref.
D-valine	 FLUVALINATE: insecticide	(15)
D-serine	PyroGlu-His-Trp-Ser-Tyr-D-Ser(Bu^t)-Leu-Arg-Pro-NHEt BUSERELIN (4): prostatic cancer treatment	(16)
D-alanine	 ALITAME (5): synthetic sweetener	(17)
D-phenylglycine	 AMPICILLIN: antibiotic	

Chart 1



Scheme 1.

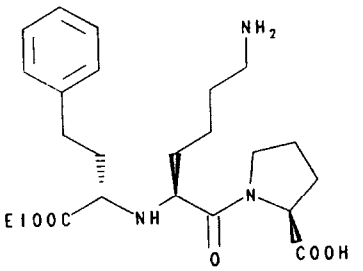
drugs such as buserelin (**4**) often incorporate D-amino acids to thwart proteolytic cleavage at positions where this is otherwise most likely to occur.

Pfizer's new dipeptide sweetener alitame (**5**) required D-alanine, not hitherto widely available; but, as with any potentially important new product, supply was stimulated. In the same area Searle's sweetener, aspartame, had already stimulated sources of L-phenylalanine. D-Alanine is now being advertised by several sources.[18] In the case of L-phenylalanine world demand grew from <50 tpa in 1980 to >3000 tpa by 1985 and more than thirty companies have been involved in process route development.[19]

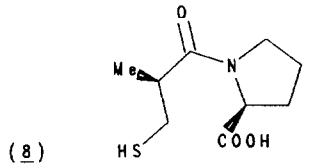
It should not be overlooked that D-amino acids are in principle, usually, just as cheap and abundant as their L-enantiomers. The method of direct crystallisation, which generates L and D with equal facility, is applicable to most amino acids or to simple derivatives thereof (Section 2.2.2). The aminopeptidase and hydantoinase routes (Section 2.2.3.3.) furnish D-amino acids.

In addition to the examples in Chart 1 a selection of other products which derive optical activity from amino acids are given below. In most cases the chemistry by which the acids are incorporated is obvious and straightforward.

Synthetic peptides include some important drugs. The angiotensin-converting enzyme (ACE) inhibitors, lisinopril (**6**), enalapril (**7**), and captopril (**8**), all incorporate L-proline. A synthesis of (**7**)



(6)



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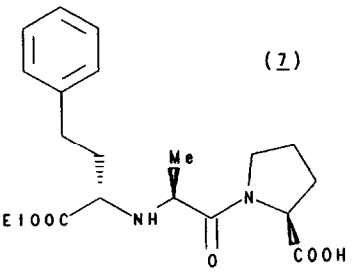
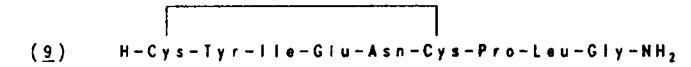


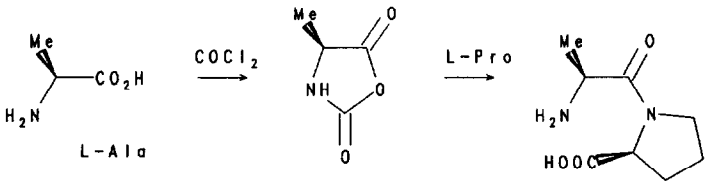
(7)

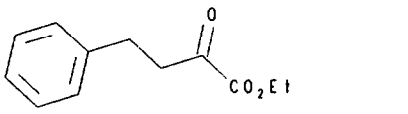
is shown in Scheme 2. A key step here is the Raney Ni reduction which gives 87% of the product as the required (*S*, *S*, *S*) isomer.[7a]

Oxytocin (**9**), used for induction of labour, is representative of other peptide drugs composed of a small number of amino acid residues.



(9) H-Cys-Tyr-Ile-Glu-Asn-Cys-Pro-Leu-Gly-NH_2





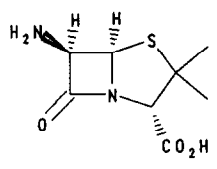
(7)

(i) condense (ii) H_2/Roney Ni
(iii) purify by crystallisation of maleic acid salt

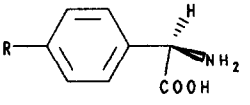
Scheme 2

Syntheses of carbapenem antibiotics have been developed which, variously, utilise the chirality of L-threonine,[20] L-glutamic acid[21] and L-aspartic acid.[22]

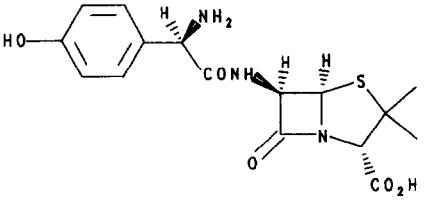
In addition to the proteinogenic amino acids, 6 APA (**10**), D(−)-phenylglycine (**11**) and D(−)-4-hydroxyphenylglycine (**12**) are all produced in large quantities. 6-APA is produced on a scale of around 4000 tonnes per annum by enzymic cleavage of penicillin-V. Compound **11** is also made on a 1000 tonne scale for semisynthetic β-lactam antibiotics such as ampicillin (Chart 1). Compound **12** is a building block for amoxicillin, **13**, and other antibiotics.



(10)



(11) R = H
(12) R = OH



(13)

2.1.2. *Hydroxy acids.* The principal hydroxy acid sources are shown in Chart 2.

Lactic acid. Both enantiomers are produced commercially by fermentation and a significant outlet for the 'unnatural'[23] (*R*)-enantiomer has been as a source of esters of (*S*)-2-chloropropionic acid used for the large tonnage aryloxypropionate herbicides such as fluazifop-butyl (**14**) and mecoprop-P (**15**) (Scheme 3). However (*S*)-2-chloropropionic acid is now available directly (Section 2.2.3.3) without the need for (*R*)-lactic acid.

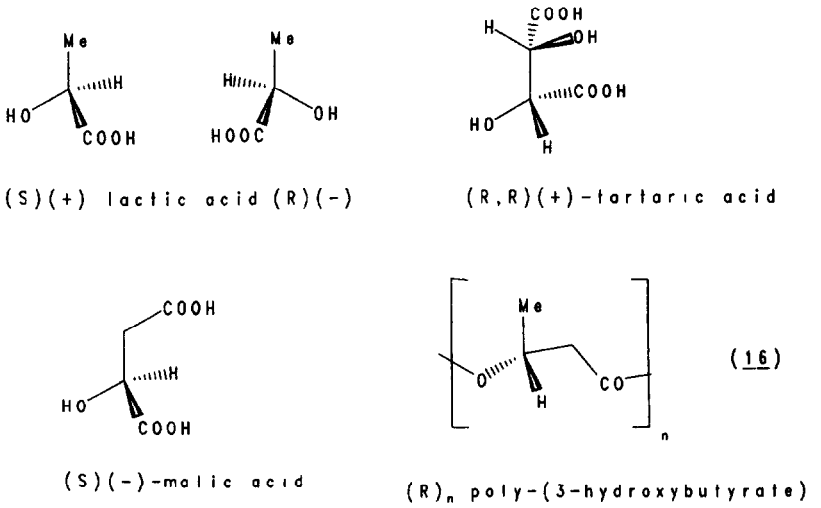
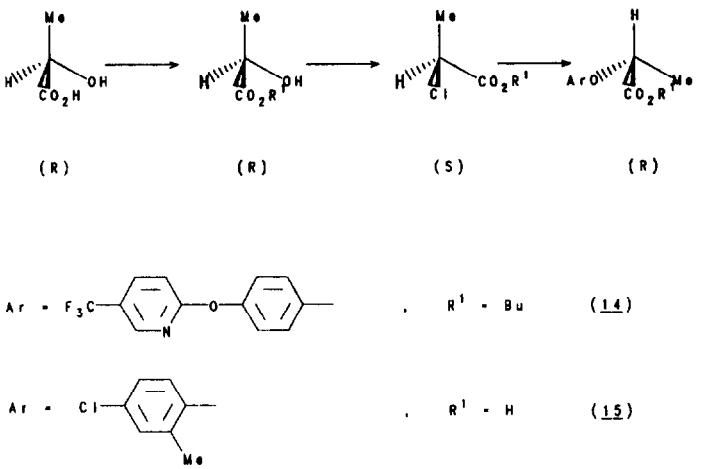


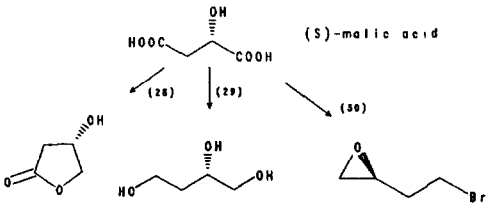
Chart 2



Scheme 3

Tartaric acid. Tartaric acid has an ancient history within organic stereochemistry. It was isolated by Scheele in 1769, its optical activity was recognised by Biot in 1832[24] and it had been resolved both biologically, using a mould, and chemically, via an alkaloid salt by Pasteur as early as 1858.[25] Despite its abundance and long standing availability it has found relatively little application as a chiral building block and industrially finds more use as a resolving agent (Section 2.2.1). Of fifteen applications cited in *Pharmazeutische Wirkstoffe*[26] fourteen are resolutions. The other important outlet for optically active tartaric acid is as a source of chirality in catalysts for asymmetric synthesis (Section 2.3.1).

Malic acid. (*S*)-Malic acid is available by fermentation and more recently by asymmetric synthesis[27] (Section 2.3.1). It may be converted to a range of other C_4 chiral synthons (Scheme 4) but like tartaric acid has found relatively little use as a chiral building block.

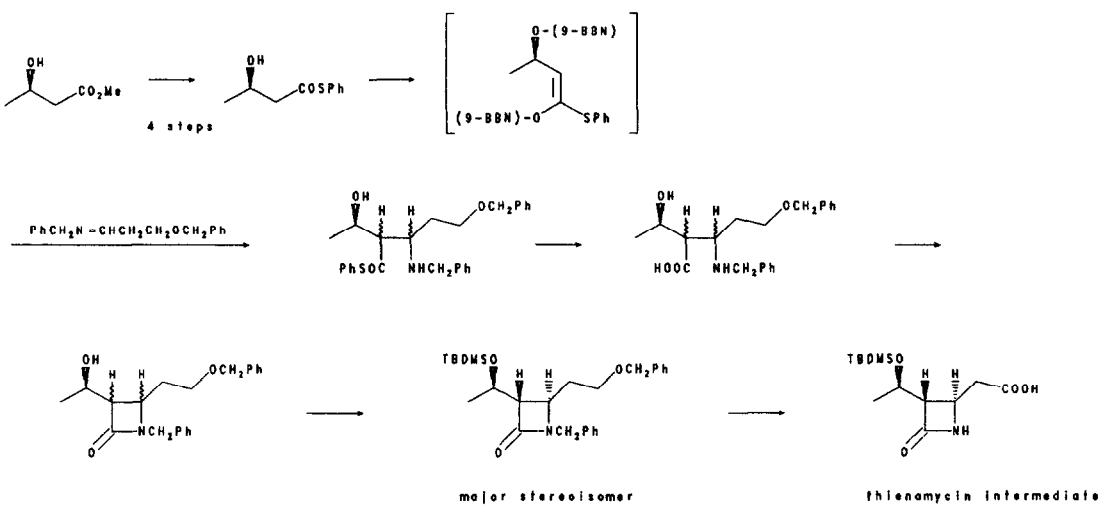


Scheme 4

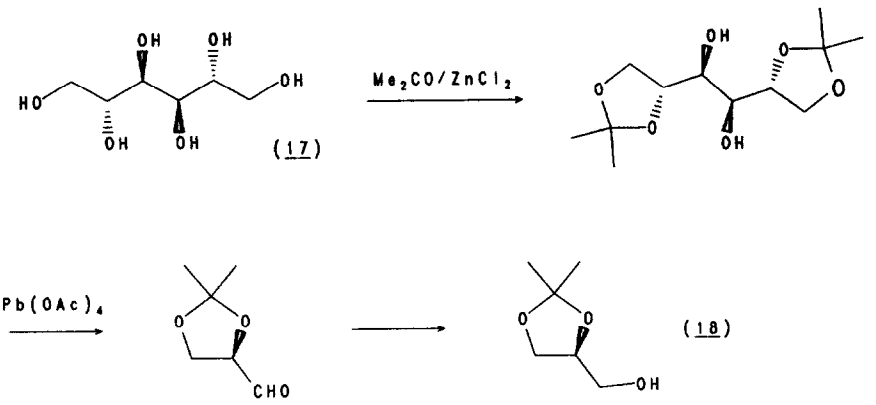
3-*Hydroxybutyric acid.* Poly-((*R*)-3-hydroxybutyrate), (**16**) is a more recent addition to the chiral pool. It is produced in bulk by ICI.[31] Monomeric esters are readily made from it by heating with the corresponding alcohol in the presence of a catalyst.[32] Biological production of the polymer, generated by *Alcaligenes eutrophus* bacteria at up to 80% of its dry weight, can be controlled to give varying proportions of (*R*)-3-hydroxyvalerate as copolymer; depolymerisation and distillation thus also provides access to esters of (*R*)-3-hydroxyvaleric acid. An example of the utility of **16** is in the synthesis of carbapenem antibiotics. One of the routes, investigated by workers at Sagami, is shown in Scheme 5.[33] (*S*)-3-Hydroxybutyric acid is also readily obtained, by yeast reduction of acetoacetates[32] (Section 2.3.2).

2.1.3. *Carbohydrates and derivatives.* Carbohydrates are renewable, often cheap, and abundantly available but as chiral building blocks they rarely bear close structural relation to a target. They suffer from a profusion of chirality. The carbon chains are generally too long necessitating costly transformation to smaller, more useful species. Mannitol is an exception; the symmetry of the molecule permits cleavage to two identical, and still chiral, subunits. This is utilised in the synthesis of (*S*)-solketal (**18**)[34] from the D-isomer (**17**) (Scheme 6). Another disadvantage of carbohydrates is that they are generally only available in one enantiomeric form.

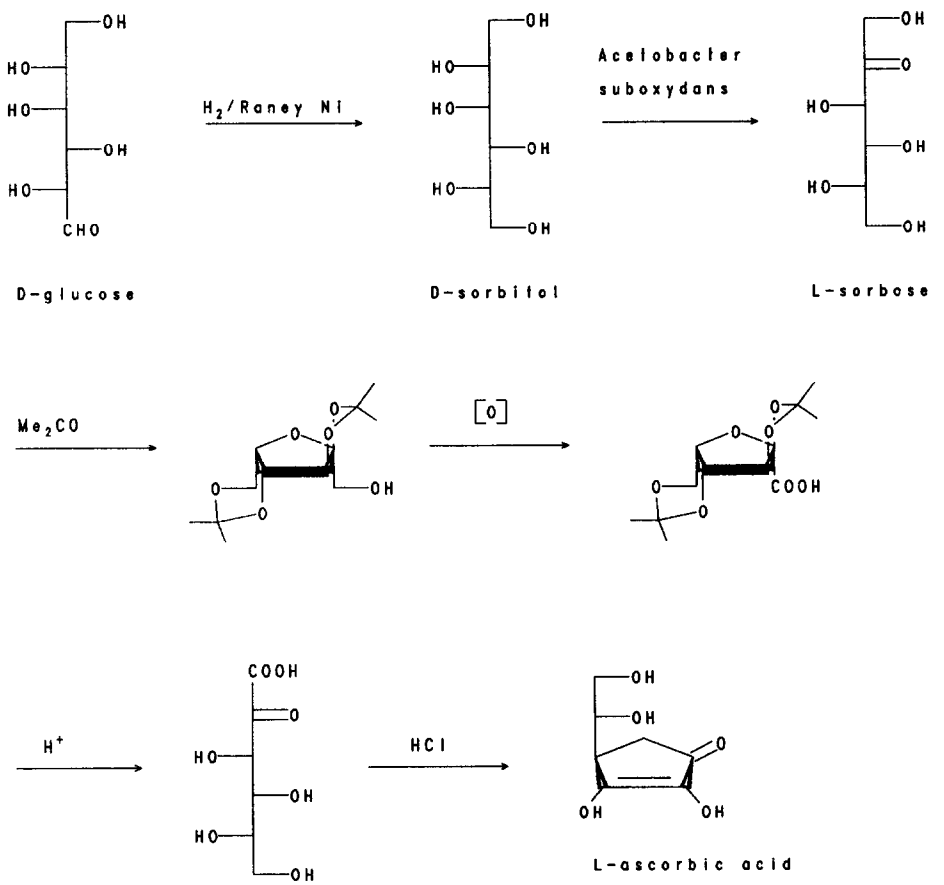
Utilisation of D-glucose in the classic Reichstein–Grussner process for ascorbic acid (Scheme 7) is a major, and one of the earliest, industrial examples of a chiral pool substance being used in synthesis, albeit for the production of another 'pool' material. The process was developed in the 1920s and, currently, is used to produce >35 000 tonnes per annum. These levels of production



Scheme 5



Scheme 6

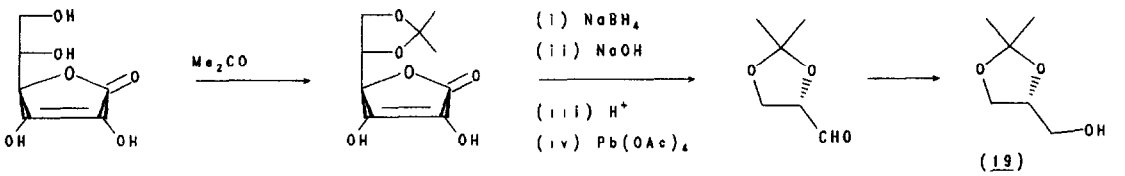


Scheme 7.

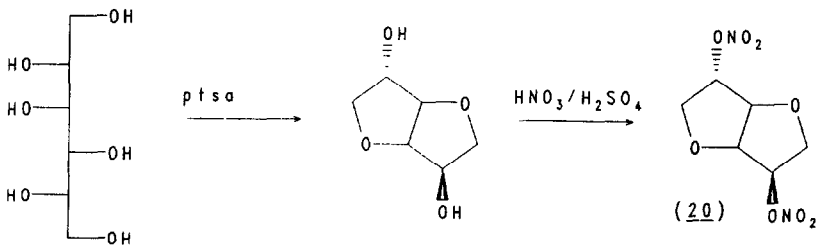
place L-ascorbic acid and D-sorbitol in the class of major chiral pool materials; the latter being produced independently for a large number of other industrial applications such as resins and surfactants.

L-Ascorbic acid may be converted (Scheme 8) to the useful C_3 synthon (*R*)-solketal (**19**)[35] which can be employed in the synthesis of (*S*)-β-blockers. An efficient use of D-sorbitol is its conversion to the coronary vasodilator isosorbide dinitrate (**20**) (Scheme 9).[36]

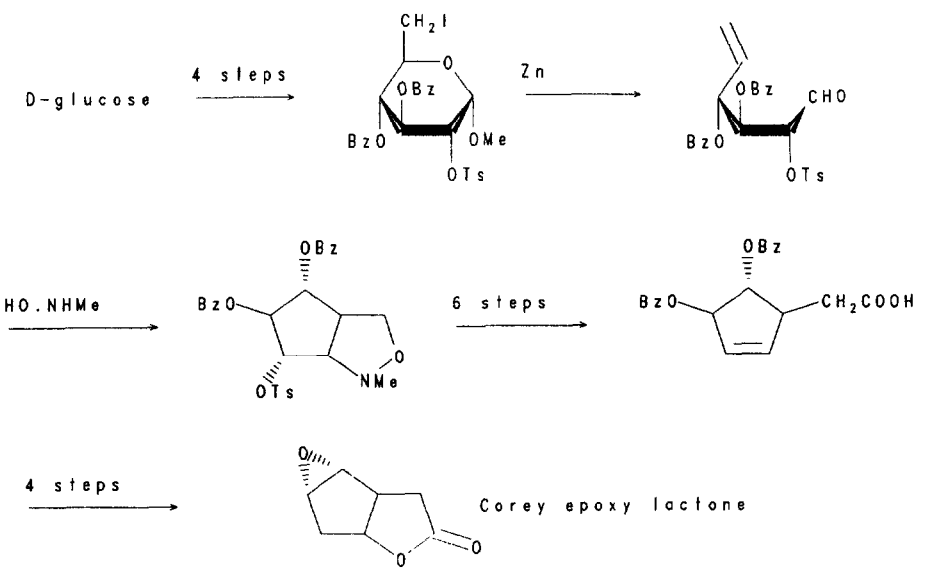
An example of a multistep conversion, in order to use a carbohydrate material, is shown in Scheme 10.[37] A synthesis of this length can only be contemplated when the target is of high value;



Scheme 8

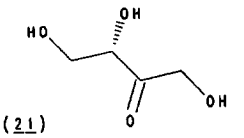


Scheme 9



Scheme 10.

in this case a key prostaglandin intermediate. A recently developed C_4 carbohydrate building block is L-erythrulose (**21**)[38] which can be transformed into the drug *gamma*-amino-*beta*-hydroxybutyric

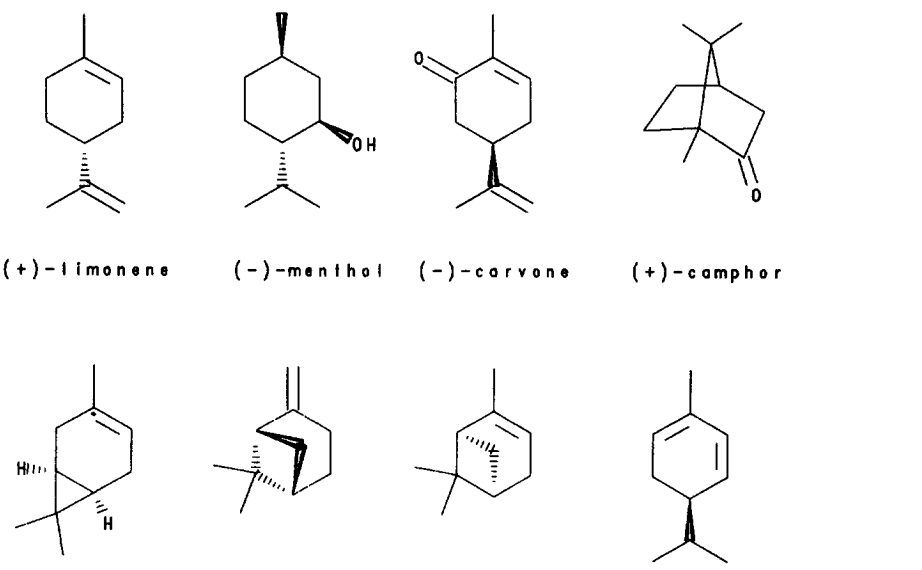


(21)

acid (GABOB), biotin or the C_3 synthon (*S*)-1-glyceraldehyde, and thence into β-blockers or prostaglandins.

2.1.4. *Terpenes.* Some of the available, optically active, terpenes are shown in Chart 3. In general, terpenes do not lend themselves to direct incorporation as building blocks and find their main outlets as precursors for resolving agents and as the source of chirality in catalysts for asymmetric synthesis. Not all are available in both enantiomeric forms and they are not always available with high chemical and optical purities. Purification to high *ee* is not always easy. Most are liquids and are generally devoid of suitable functionality for simple purification via derivatives.

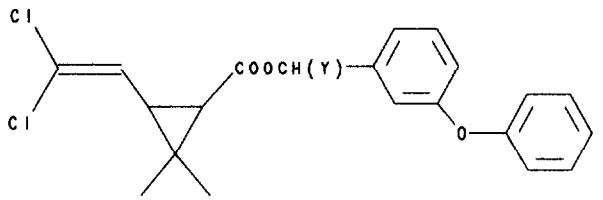
A structural feature of terpenes which has invited attention is the occurrence of geminal dimethyl groups in conjunction with optical activity; the stimulus has been synthetic pyrethroid insecticides,



(22) (23)

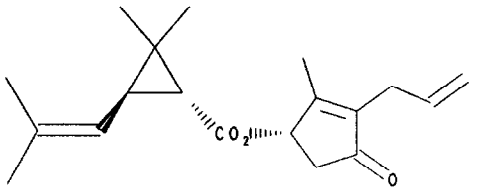
Chart 3.

examples of which are in Chart 4. Many hundreds of tonnes of these potent insecticides are produced worldwide and the quest for higher activity and best cost efficacy has directed much effort to procedures which provide the most active isomers. Perhaps not surprisingly a lot of work has been carried out in Indian Laboratories since (+)-3-carene (**22**) of high *ee* comprises about 60% of Indian turpentine the production of which is in the region of 6000–9000 tonnes per annum;[39] **22** is present

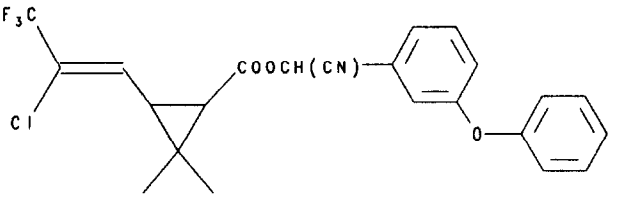


PERMETHRIN (Y = H)

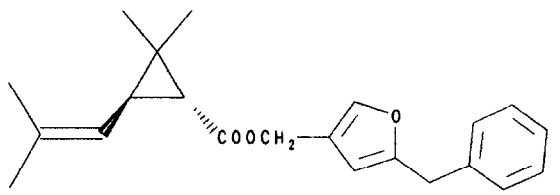
CYPERMETHRIN (Y = CN)



BIOALLETHRIN



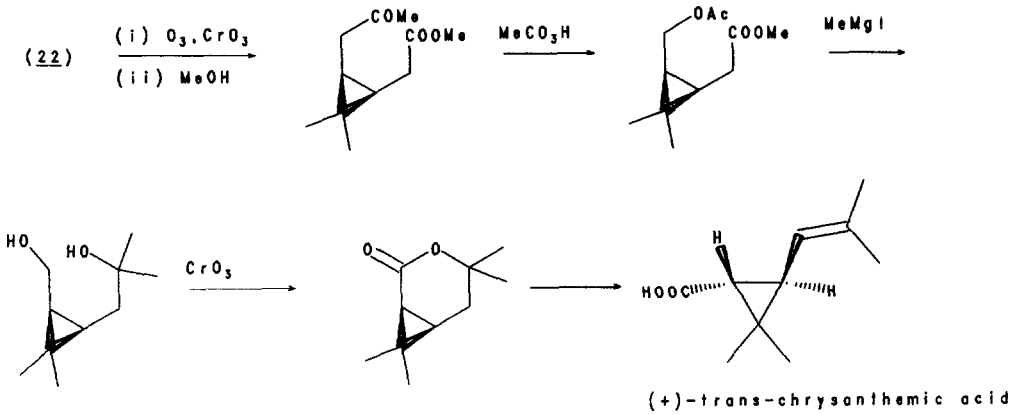
CYHALOTHRIN



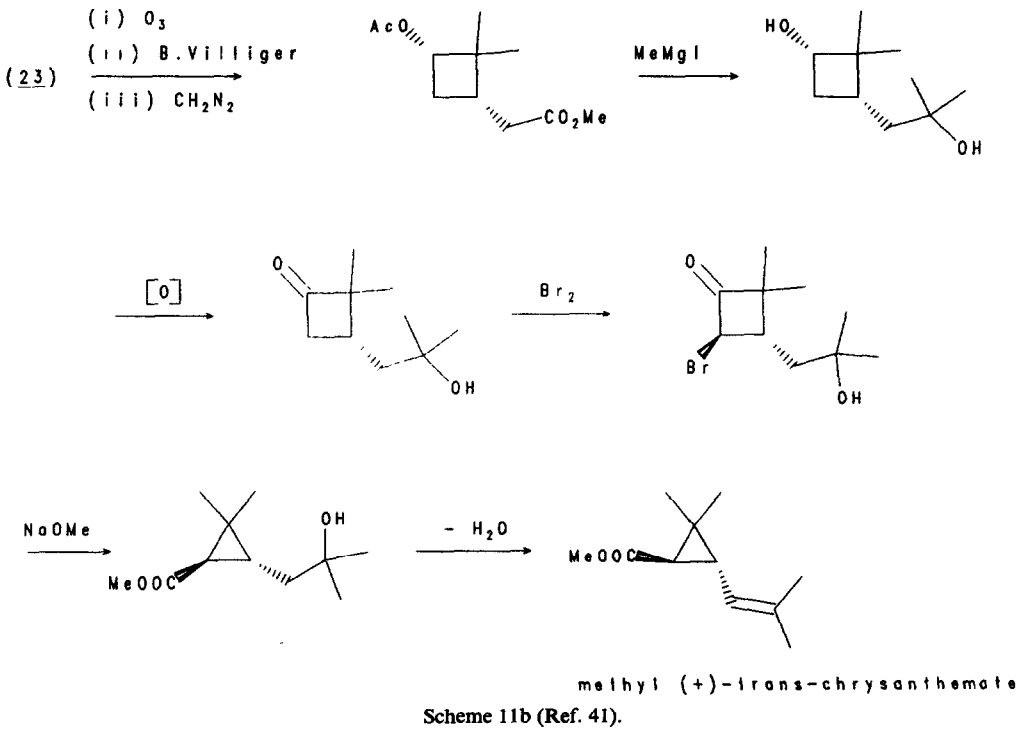
BIORESMETHRIN

Chart 4

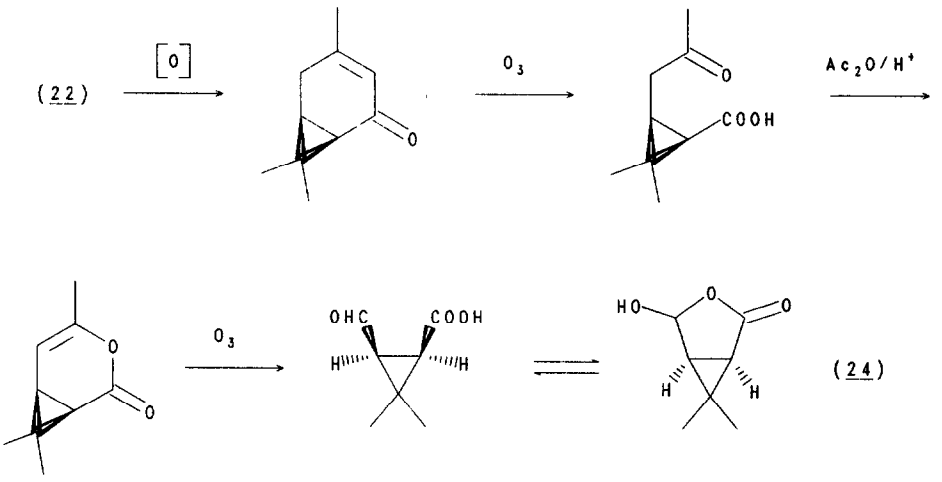
in other turpentines at lower but still commercially interesting levels. Schemes 11 a–c outline some of the approaches which have been considered for exploiting terpenes in pyrethoid synthesis. Caronaldehyde (**24**) permits the synthesis of the highly active (1*R*, *cis*)-isomers of the halovinyl series (Scheme 12). Terpenes also find use as starting materials for other terpenes. Menthol has been manufactured from (*R*)-(−)-α-phellandrene and (+)-3-carene (Section 3.1.3).



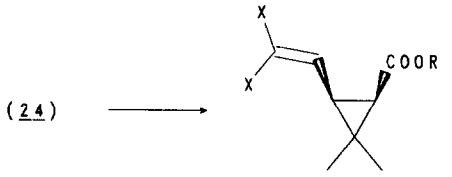
Scheme 11a (Ref. 40).



Scheme 11b (Ref. 41).



Scheme 11c (Ref. 39).



Scheme 12 (Ref. 42).

2.1.5. *Alkaloids*. By far the most useful alkaloids for production of optically active materials are the cinchona bases (Chart 5). They are moderately expensive (Table 2), and very unlikely to find application as building blocks. They are, however, most valuable chiral auxiliaries[43] (Section 2.3.1) and much used as resolving agents on the small scale. For large scale resolutions, a highly efficient recycle is imperative. The four cinchona bases comprise two pairs of diastereomers but the critical

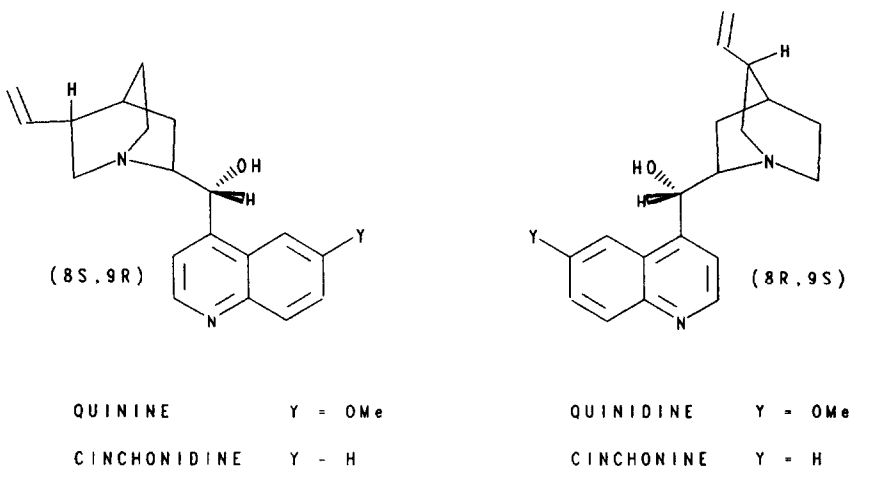


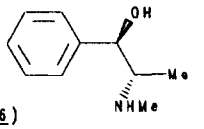
Chart 5

β-hydroxyamino segments are enantiomeric and they behave as such in many applications. Their toxicity is also low compared with, for example, nicotine, brucine and strychnine, the large scale use of which could only be considered in closely controlled circumstances.

2.1.6. *The new pool.* The whole gamut of industrially produced chiral products is available for consideration. Some such as 6-APA (**10**) are not particularly new, having been made on tonnage scales for 20–30 years, but they do not feature in any conventional listing.

Consideration should also be given to by-products which are normally recycled, such as L-phenylglycine in the manufacture of D-phenylglycine[44] and D(+)-α-amino-ε-caprolactam (**25**) in the manufacture of L-lysine (Scheme 31).

In addition, many conventional pool materials such as ephedrine (**26**), menthol and L-phenylalanine have had their availability considerably augmented by manufacture.



(26)

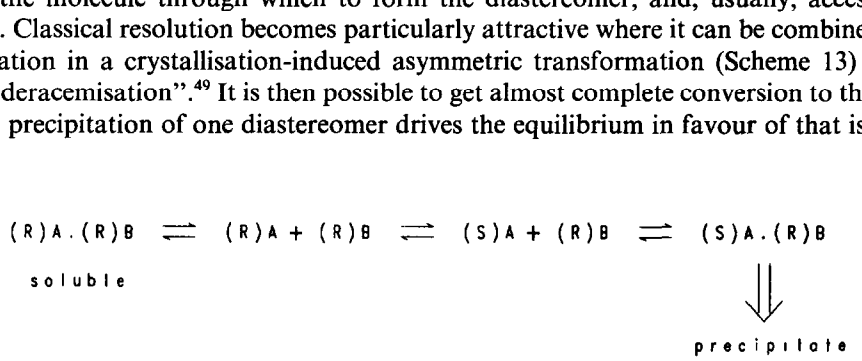
2.2. *Separation of racemates*

2.2.1. *Classical resolution.* Despite its 'low technology' image, classical resolution via diastereoisomer crystallisation is widely used industrially and in particular furnishes a large proportion of those optically active drugs which are not derived from natural products. Examination of a representative group of such drugs[45] shows 65% owe their optical activity to classical resolution. There are clearly many instances where resolution is both economically viable and the method of choice.

It is a technique which is sometimes viewed as owing too much to empiricism to be worthy of serious consideration. However, Wilen *et al.*[46] have provided guidelines which permit a rational approach with a high probability of success. There is still much on offer for the industrial practitioner or anyone requiring kilogrammes of a product and where some effort spent in system optimisation can be justified. It has been said that success is never guaranteed[47] but it is probably more guaranteed than, for example, asymmetric synthesis is at present.

This Report is not concerned with detailed appraisal of the many and well-known reagent-functional group combinations which may be employed to obtain the necessary diastereomers. Likewise the methodology, principles of the technique and criteria for good resolving agents have been well described elsewhere.[48]

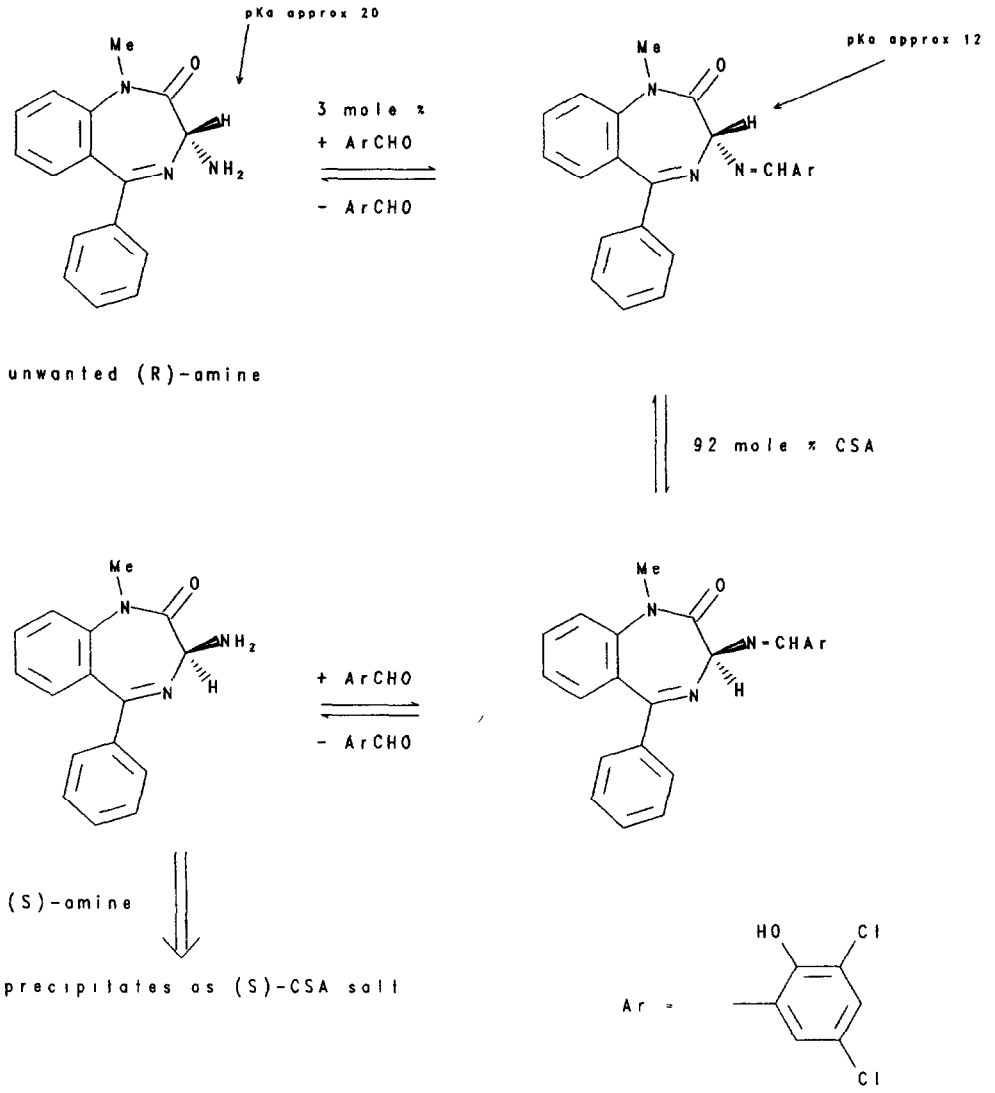
Attractions of classical resolution include wide applicability, providing there is suitable functionality in the molecule through which to form the diastereomer, and, usually, access to both enantiomers. Classical resolution becomes particularly attractive where it can be combined with *in-situ* racemisation in a crystallisation-induced asymmetric transformation (Scheme 13) a process designated "deracemisation".[49] It is then possible to get almost complete conversion to the required enantiomer; precipitation of one diastereomer drives the equilibrium in favour of that isomer. An



Scheme 13.

elegant example comes from the Merck company[50] (Scheme 14) in which a catalytic amount of an aldehyde facilitates racemisation in solution at ambient temperature via the imine and the desired (*S*)-amine continuously crystallises as its (+)-camphor-10-sulphonic acid salt. Racemisation is presumed to be effected by the small amount of amine present as the free-base. This efficient, one-pot resolution–racemisation process has been operated on a 6 kg scale to produce an intermediate for a candidate cholecystokinin antagonist.

Despite the wide applicability of classical resolution, molecules devoid of suitable functionality present difficulties. The problem may in principle be tackled by the formation of inclusion complexes. Compound **27** forms crystalline 1 : 1 inclusion complexes which allow the resolution of molecules such as **28–30** giving products of high *ee*.[51] However, despite the commercial interest[51b,c] which

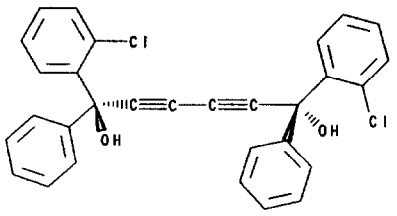


(pKa's calculated by the CAMEO© programme)

Scheme 14

appears directed towards resolved glycidyl compounds, reagents such as **27** are clearly not cheap. The reagent (**27**) is made by oxidative coupling of pure **31** which in turn has to be resolved by forming inclusion complexes with alkaloids.

As with the chiral pool there has been a tendency to think of resolving agents as naturally occurring materials coming from the pool, or derivatives thereof. In reality these have for some time included materials such as 1-phenylethylamine (**32**); which is now widely used since it was shown to be simply resolved with tartaric acid.[52]



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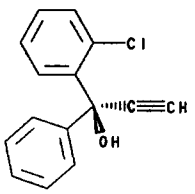

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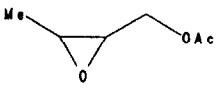

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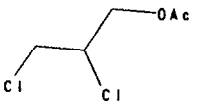

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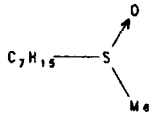

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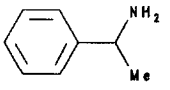
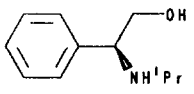


(32)



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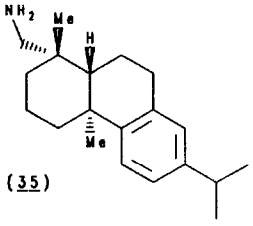
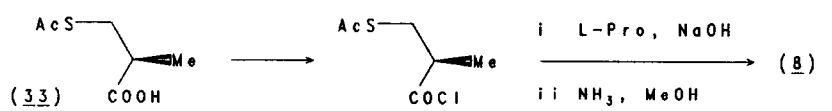


(35)

Existing tonnage products, and their intermediates, should not be overlooked as potential resolving agents. Consider for example D(+)-α-amino-ε-caprolactam **25**, a readily accessible and cheap potential by-product of L-lysine manufacture (Scheme 31). This compound (**25**) has been patented for the resolution of N-acylamino acids.[53]

Commercial targets provide the driving force for many useful advances in the synthesis of optically active materials. Attempts to resolve the intermediate **33** for the ACE inhibitor, captopril **8** (Scheme 15), led to the discovery of the new chiral amine, (*S*)-N-isopropyl(phenylalaninol) (**34**).[54] This reagent was developed when several naturally occurring alkaloids and other commercially available chiral amines proved ineffective. Its development emphasises the value of a systematic study of physical parameters. The solubility ternary phase diagram was determined in order to find optimal conditions for purification of the crude salt.

Captopril intermediate **33** has also been resolved using Amine D™, (+)-dehydroabietylamine (**35**).[55] Derived from wood rosin, it is of interest because of its abundance and cheapness: one of its

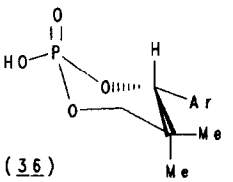
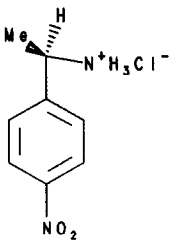
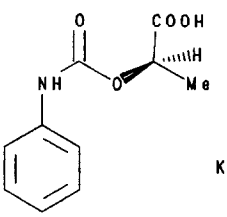


Scheme 15.

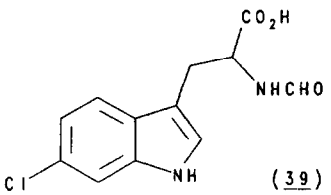
major uses is to promote adhesion of stone aggregates in road construction! It was introduced in 1964[56] but has not been used very often. Amine D™ is approximately 50% pure with about 20% each of the di- and tetrahydroabietylamine analogues.[57] Whilst it may be readily purified via the acetate,[58] it is the author's experience that it may be used satisfactorily in its crude state,[59] particularly in conjunction with lower alkanols as solvents. It forms salts with carboxylic acids which are soluble in organic solvents. Disadvantages are its availability in only one enantiomeric form and its high mole wt. However, it is still approximately three times cheaper per mole than resolved **32** when purchased in bulk.

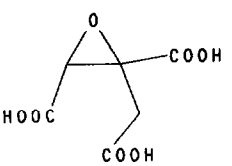
A steady stream of new, tailor-made resolving agents are being offered commercially (Table 3). The phosphoric acids (**36**)[63] extend the range of available strong acid resolving agents. Their pK_a's of 2–3 permit resolution of amines and underivatised amino acids. They are also thermally stable and of low water solubility allowing easy recycle.

Table 3

	Supplier
 (36)	Andeno[60]
 (37)	Chiron[61]
 (38)	Kiralchem[62]

The derivative **37** allows resolution of the acids **39–41** which are not resolved by α-methylbenzylamine.


(39)


(40)

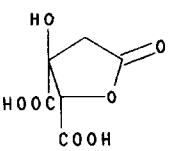
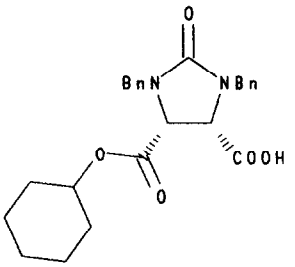
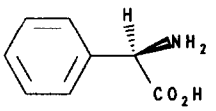
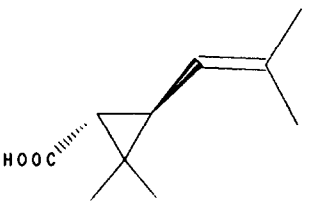
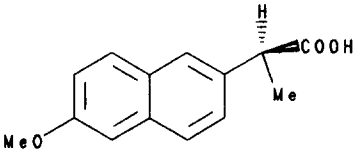
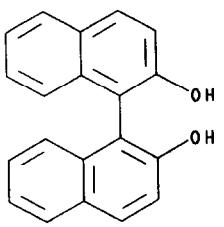

(41)

Table 4.

Resolution product	Reagent	Ref.
 D-biotin intermediate enantiomer recycled via anhydride	(+)-ephedrine	(65)
	camphor-10-sulphonic acid	(7a)
 trans-crysanthemic acid	chloramphenicol base	(66)
 (S)-naproxen (43)	cinchonidine	(67)

Examples of resolutions which have been, or are, of industrial importance are shown in Table 4. It is also of interest to note some of the potential interrelations and the possibility of using the unwanted isomer from one resolution in another (Chart 6).

A recently reported useful application of an unwanted enantiomer is where (*R*)-2-aminobutanol, from ethambutol manufacture (cf. Table 1) has been used for the resolution of 1,1′-binaphthalene-2,2′-diyl hydrogen phosphate. This provides a practical preparative route to pure enantiomers of the valuable chiral auxiliary, 2,2′-dihydroxy-1,1′-binaphthalene (**42**).[64]



(42)

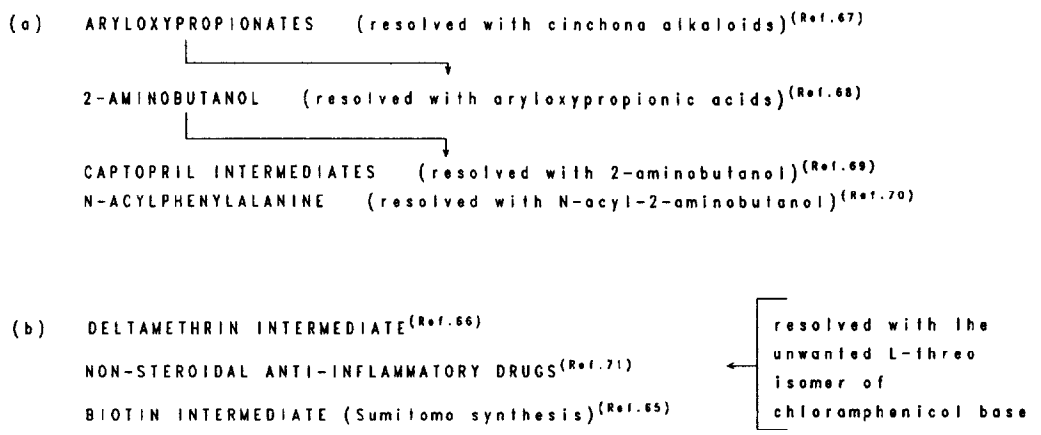


Chart 6.

Factors which need to be appraised when aiming for an economic process:

(i) *The resolving agent.* This should be cheap, available, preferably of low molecular weight to maximise volumetric productivity, optically pure and chemically and optically stable (vis-à-vis multiple recycles). It should be easy to recycle and, to avoid excessive reiteration, should permit >80% recovery of the required enantiomer in 90% *ee* in a single crystallisation. Be alert to the possibility that a cheap racemate exists, enantiomers of which may furnish a suitable resolving agent. The principle of reciprocal resolution is not guaranteed[48b] but it does frequently succeed allowing the process to, periodically, be run in reverse using the target enantiomer to generate resolving agent. There is also the possibility of involving a third material to resolve the desired resolving agent but this becomes operationally cumbersome for a large scale.

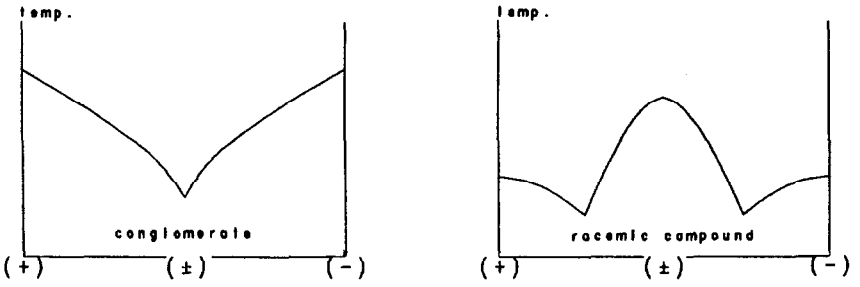
(ii) *Recycle of the unwanted enantiomer.* To avoid multi-stage recycles, aim to recycle at the point in the synthesis at which resolution occurs. Most ideally, aim for *in-situ* racemisation and the achievement of a crystallisation-induced asymmetric transformation.

2.2.2. *Resolution by direct crystallisation.* This is an attractive but infrequently used method; auxiliaries and reagents, other than a solvent are not required. The excellent treatise by Jacques *et al.*[48d] gives a detailed exposition of the theory. In simple terms it depends on the occurrence of some substances as crystalline conglomerates (racemic mixtures) rather than racemic compounds. Although in bulk a conglomerate is optically neutral, individual crystals contain only one enantiomer; whereas in a racemic compound individual crystals contain equal amounts of both enantiomers. Conglomerate formation is a pre-requisite for resolving by direct crystallisation.

Before the method may be applied it is obviously necessary to establish the existence of the conglomerate; this may be done in a number of ways:

(i) by selecting small, discrete crystals and subjecting them to any sensitive method for measuring enantiomer excess (polarimetry, chiral LC or GC, NMR with shift reagent, effect on the nematic phase of a liquid crystal);[72] (ii) determination of binary (Fig. 1), or ternary phase diagrams; (iii) effecting resolution by direct crystallisation (more likely to be used as a confirmatory test); (iv) powder X-ray or solid state IR spectra (enantiomers give spectra identical with those of racemic conglomerate but differ for racemic compounds).

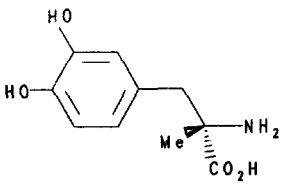
There are a number of variations in the way resolution by direct crystallisation may be effected in practice. In the first method, simultaneous crystallisation of the two enantiomers is carried out in an apparatus of the type shown schematically in Fig. 2. Initially seeds are introduced into the two crystallisation chambers and crystallisation from the supersaturated solution occurs. The depleted



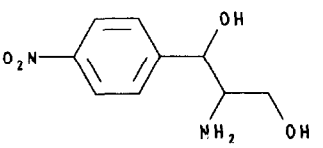
Binary phase diagrams

Fig. 1.

solution is resaturated at a higher temperature in a make-up vessel before recooling to restore the original level of supersaturation required in the crystallisers. This was in essence the method used in the Merck process for the antihypertensive methyldopa (**44**).[73] A 150 ton capacity plant was



(44)



(45)

operated and judged to be more economic than an alternative classical resolution using quinine, even assuming 98% recovery of the resolving agent. The process was operated in water using SO_2 to ensure solubility.

Another successful large scale process was developed by Haarmann and Reimer for (−)-menthol which is separated as an ester.[74] A simple apparatus suitable for laboratory operation has been described by Sato *et al.*[75] who used it to resolve DL-lysine-3,5-dinitrobenzoate.

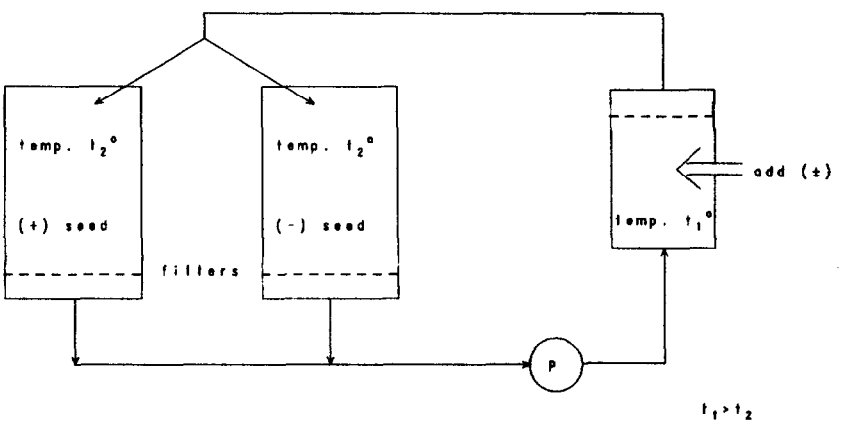
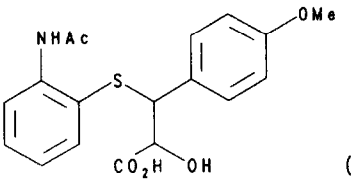


Fig. 2.

Another method consists of taking alternate crops of each of the enantiomers using a single vessel; this is the so-called method of resolution by entrainment.[76] It has its origins in the work of Gernez who in 1866[77] demonstrated that resolution could occur when a supersaturated solution of racemate was seeded with one of the enantiomers. To a supersaturated solution of the racemate initially artificially enriched with, say, the (+)-enantiomer are added seed crystals of the (+)-enantiomer. A crop of (+)-enriched product is collected equal to approximately twice the amount of material used for the original enrichment. An amount of racemate equal to the weight of the (+) crop is then dissolved in the filtrates by warming and the solution is cooled back to the operating temperature to restore the original degree of supersaturation, but now with the (−) enantiomer in excess. The solution is then seeded with the (−) enantiomer and the whole process repeated *ad infinitum*. The main practical limitation on the number of cycles through which such a process can be operated is the build-up of impurities and the tolerance to these of the crystallisation. A highly purified starting racemate may be essential if an economic number of cycles is to be achieved. Such a procedure was used by Amiard *et al.*[78] to resolve chloramphenicol base, DL-*threo*-1-(4-nitrophenyl)-2-aminopropane-1,3-diol (**45**). This process has now been translated to the large scale by Roussel-Uclaf;[79] the product is cropped in 57 kg lots to make 35–40 tonnes per year.

Other examples of this procedure are indicated in patents to Industria Chimica Profarmaco SpA for the resolution of naproxen (**43**) as its ethylamine salt[80] and for 2-hydroxy-3-(4-methoxyphenyl)-3-(2-acetylaminophenylthio)propionic acid (**46**), an intermediate for optically active benzothiazepines.[81]



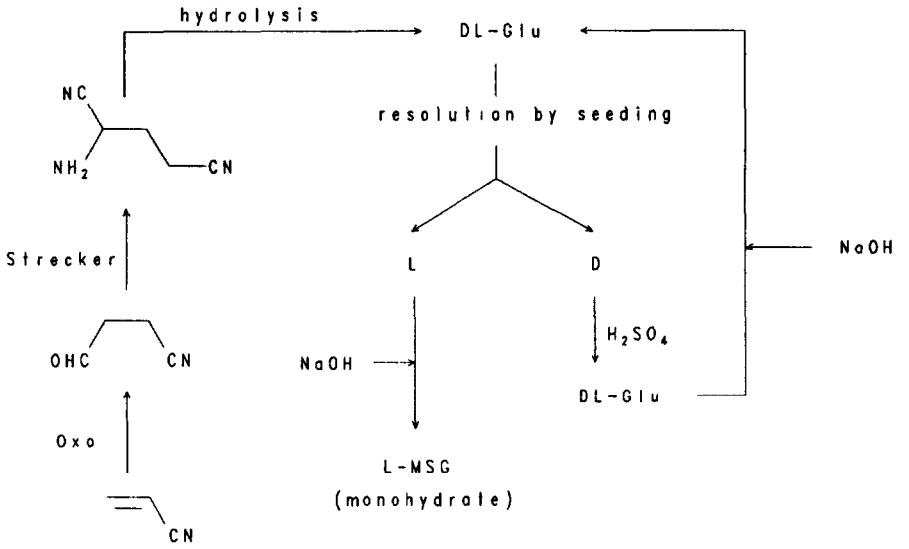
(46)

A further industrially important example of resolution by direct crystallisation was Ajinomoto's process for L-glutamic acid (Scheme 16), introduced in the early 1960s, operated on a scale in excess of 10 000 tpa, and competitively with the fermentation process for MSG.[82]

A more esoteric variant has been reported[83] in which the supersaturated solution of racemate is seeded simultaneously with large crystals of one enantiomer and very small crystals of the other. After crystallisation has occurred the products are separated by sieving.

The ultimate process is a combination of resolution by direct crystallisation with facile *in-situ* racemisation of the unwanted enantiomer. This leads to a so called[84] Second Order Asymmetric Transformation (Fig. 3) and, if achievable, would be expected to be economically competitive with any other procedure for generating optical activity. Such a process, proceeding in the absence of deliberate seeding, is a 'spontaneous resolution' and the enantiomer obtained becomes a matter of chance.

Another attraction of direct crystallisation is that unlike classical resolution it is not necessary for substrates to possess any particular functionality for it to work. However, it is of limited, and unpredictable, applicability. The occurrence of conglomerates has been estimated at perhaps less than 10% of all crystalline racemates.[85] However the frequency amongst salts has been estimated to be two or three times that for covalent compounds;[86] this provides a basis for increasing the chance of discovering a conglomerate. Note, for example, that of the naturally occurring α-amino acids virtually all are resolvable either directly or as derivatives;[87] cf. alanine monomaleate.[88] The technique is clearly amenable to large scale operation but may require very fine temperature control.[74]



Ajinomoto process for L-monosodium glutamate

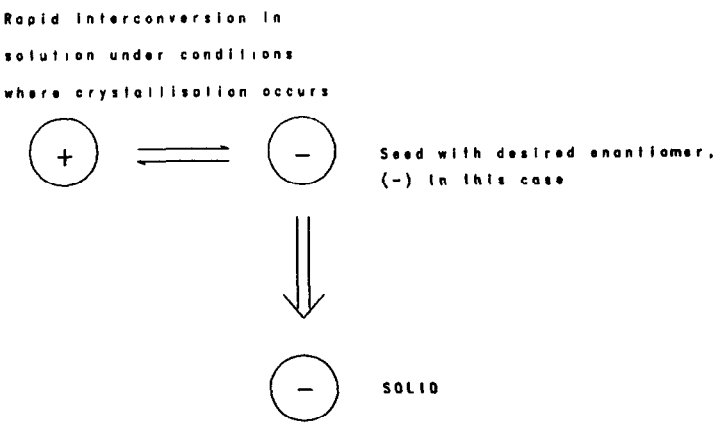
Scheme 16

Uniform quality of feedstock, preferably of high chemical purity, will be required in order to achieve reproducible crystallisations.

2.2.3. *Kinetic resolution.*[89] This is a process in which one of the enantiomers (*A*) of a racemate (*AB*) is more readily converted to product than the other:

$$A \xrightarrow{k_A} y \qquad E = k_A/k_B$$
$$B \xrightarrow{k_B} z$$

The enantiomer ratio, *E*, dictates the efficiency of resolution and is related to the enantiomeric excess of the recovered reactant (ee_R) and of the product (ee_P), at a given degree of conversion (c), by the



The ultimate resolution process

Fig. 3

equations:

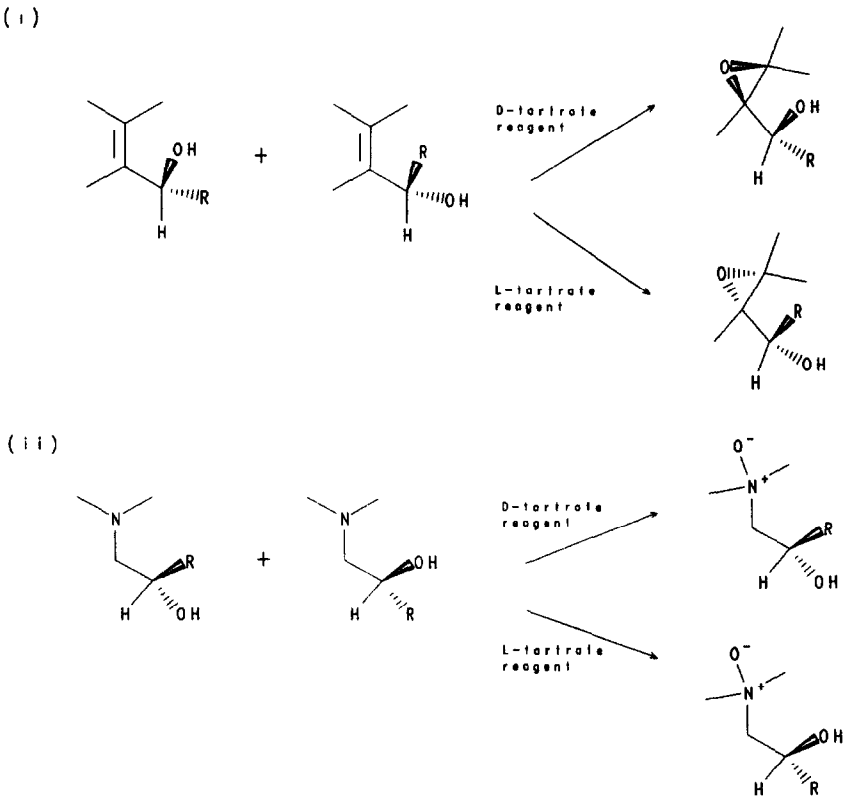
$$E = \ln[(1-c)(1-ee_R)]/\ln[(1-c)(1+ee_R)]$$

$$E = \ln[1-c(1+ee_P)]/\ln[1-c(1-ee_P)]$$

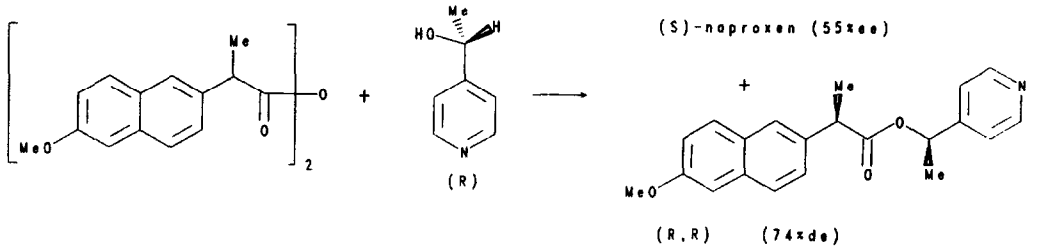
for a derivation of these equations see C. S. Chen and C. J. Sih, *Angew. Chem. Int. Edn.* **1989,** *28*, 695. A useful graphical representation of the dependence of ee_R as a function of c and E has been given by Martin *et al.*[90] The attraction of kinetic resolution is that the *ee* of the residual substrate improves with the degree of conversion and with only modest selectivity it is still possible to recover the substrate with high *ee*. In practice an E value >20 would be sought for a commercially attractive process such that a high *ee* (ca 98%) can be attained at 60% and preferably closer to 50% conversion. The converse being that when E is high (ca 50 or greater) the product, if chiral, is simultaneously obtained with high *ee*; product *ee* deteriorates as c increases and is poor for low E values at the point at which reactant has a satisfactory *ee*. For an economic process it is important to be able to utilise the resolution product; this is more likely to be the case when it also has a high *ee*.

Kinetic resolution may be realised by chemical or enzymic methods, in the former case the reaction may be either catalytic or stoichiometric with respect to the optically active auxiliary; from an economic standpoint catalysis is obviously preferred. Kinetic resolutions and high E values are more commonly found with enzymic than chemical process, this is reflected in the number of commercially relevant examples given below.

2.2.3.1. *Stoichiometric chemical reaction.* The work of Sharpless[90,91] using the original, stoichiometric, version of the epoxidation reagent focused attention on chemical kinetic resolution and the very high *ee*'s which are attainable (cf. examples in Scheme 17). In a different example (Scheme 18),



Scheme 17.



Scheme 18.

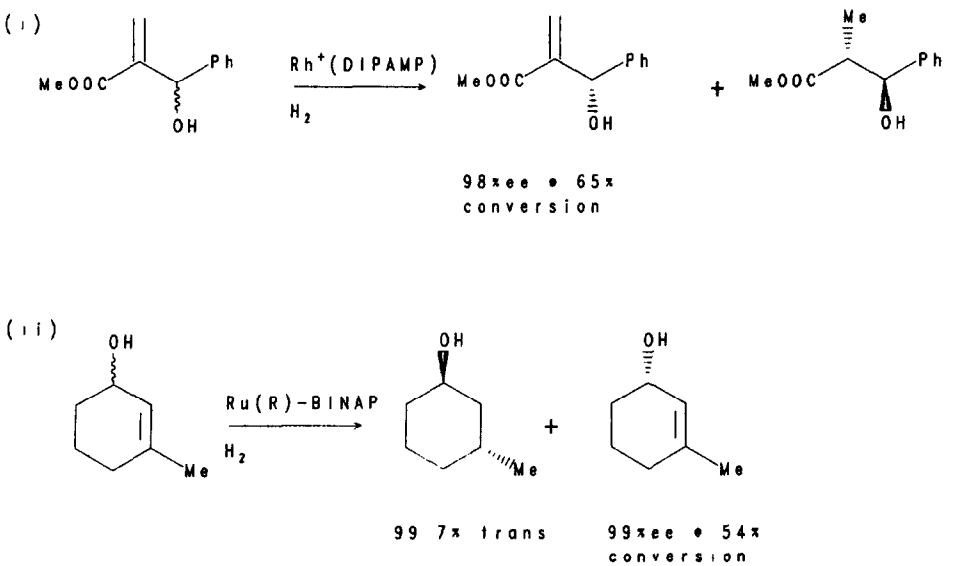
stoichiometric use of an auxiliary has been applied to naproxen synthesis.[92] The anhydride of racemic naproxen is reacted with optically active 1-(4-pyridyl)ethanol giving a product of modest optical purity. The same approach has been used for the resolution of pyrethroid acids[93] and aryloxypropionic acids.[94]

2.2.3.2. *Chemical catalysis.* The area is still relatively new and applications will go hand in hand with the general development of new catalysts for asymmetric synthesis where these can be applied to chiral substrates. Its industrial potential has yet to be realised.

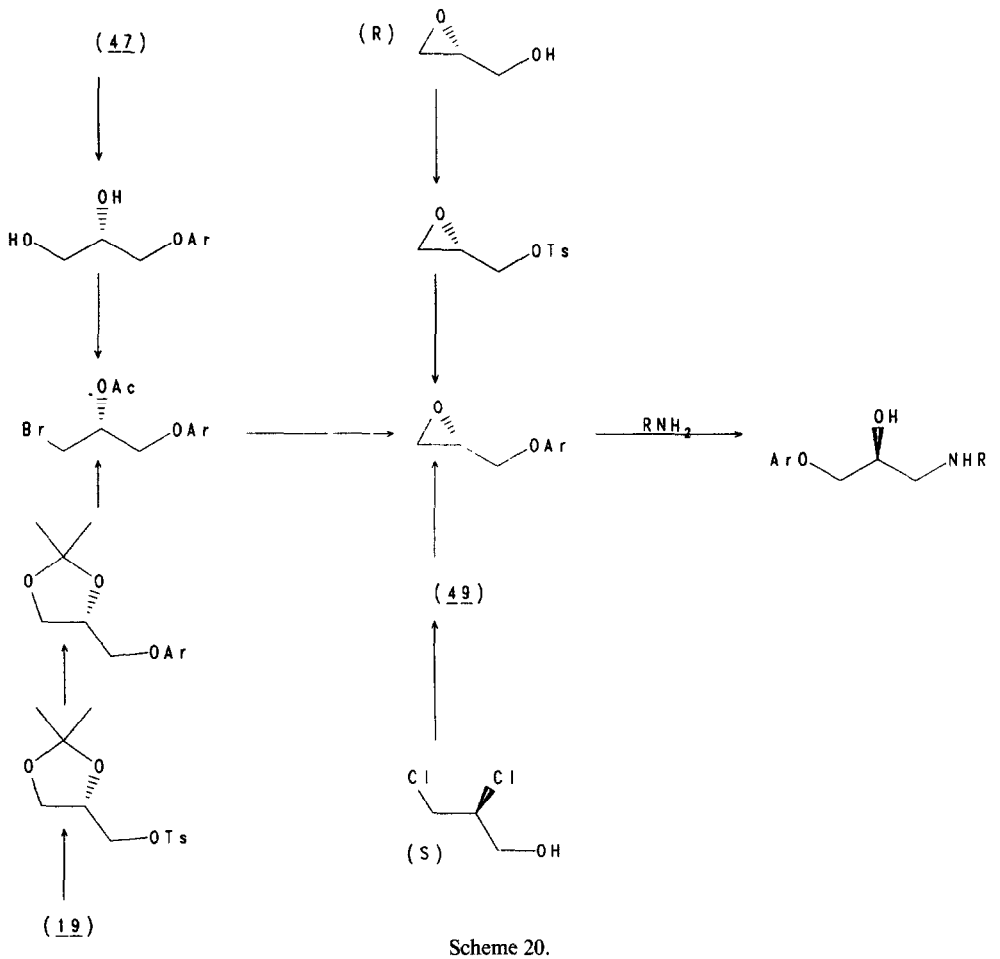
For pointers one can return here to the Sharpless epoxidation (catalytic version).[95] Another major area of asymmetric catalysis, hydrogenation, also provides examples of kinetic resolution. Both rhodium-based catalysts and the Ru-BINAP catalysts of Noyori *et al.* have been used (Scheme 19).[96,97]

2.2.3.3. *Enzymic catalysis.* There are many industrially relevant examples under this heading. Consider first the various approaches to β-blockers (Scheme 20).

(i) *(R)-Glycidyl butyrate* (**47**). There is much industrial interest in this compound.[98] Processes for large scale synthesis have been developed using a lipase-catalysed hydrolysis (Scheme 21). The

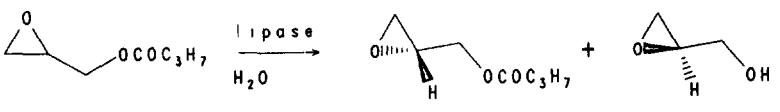


Scheme 19



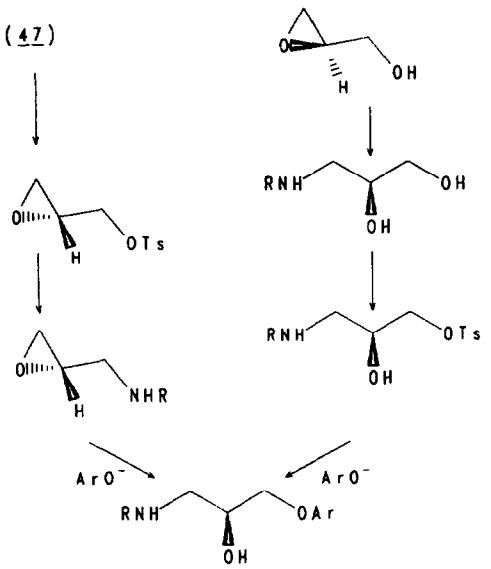
Scheme 20.

reaction was first reported by Ladner and Whitesides.[99] It has been refined and is now operated on a multi-ton scale,[98a] despite the relatively modest enantioselectivity of porcine pancreatic lipase which requires the reaction to be run well beyond 50% conversion to ensure high *ee*. If the process could be operated with higher selectivity, such that the by-product (*R*)-glycidol was also produced with a comparably high *ee* (96–98%), both products could in principle be converted into the desired (*S*)-*β*-blockers (Scheme 22).[100]



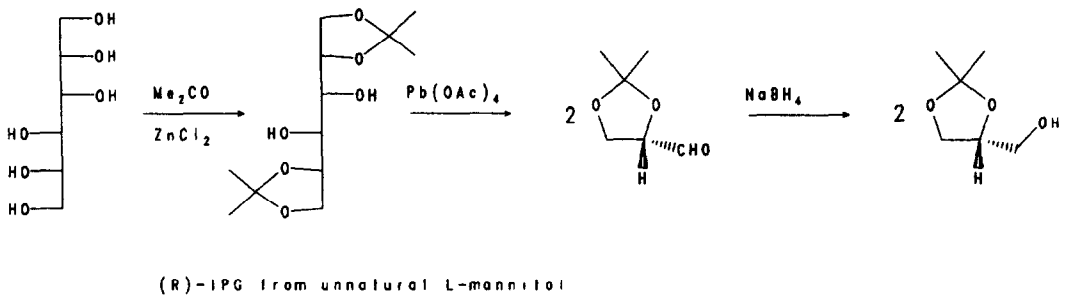
Enzymic resolution of glycidyl butyrate

Scheme 21



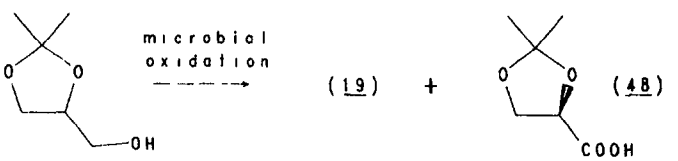
Scheme 22

(ii) (*R*)-*Isopropylideneglycerol* (**19**). This synthon is difficult and expensive to obtain by direct synthesis (Schemes 8, 23).[35,101] International Bio-Synthetics have developed a route in which the resolution is effected by a selective microbial oxidation of the (*S*)-enantiomer into (*R*)-isopropylideneglyceric acid (**48**) (Scheme 24).[102] The *ee* of **19** exceeds 98% whilst that of the product **48** is greater than 90%.[103]



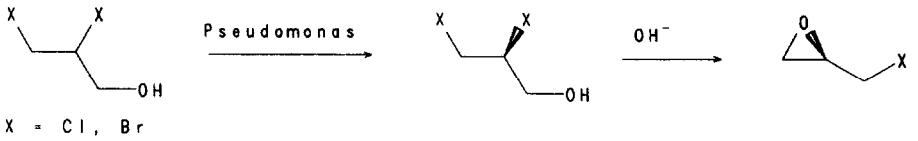
(R)-IPG from unnatural L-mannitol

Scheme 23



Resolution of IPG

Scheme 24.



Generation of (S)-2,3-dihalo-1-propanols through selective microbial degradation of (R) enantiomers

Scheme 25

(iii) (*R*)-*Epichlorohydrin* (**49**). Processes have been patented for the production of (*R*)-enantiomers of both epichlorohydrin and epibromohydrin via the corresponding (*S*)-2,3-dihalo-1-propanols (Scheme 25).[104] Both enantiomers of epichlorohydrin are available from Osaka Soda.
Other, lipase-based, approaches to (*S*)-β-blocker intermediates are shown in Scheme 26.

Intermediates for ACE-inhibitors have also been obtained using enzyme-mediated kinetic resolution (Scheme 27).[108,109] In this case yields are >50% indicating that the substrate enantiomers are continuously equilibrated via the enol-form then the microorganism removes one by reduction. Industrial production of α-amino acids is another area where enzymic resolutions have commanded attention and several large scale processes are being operated.

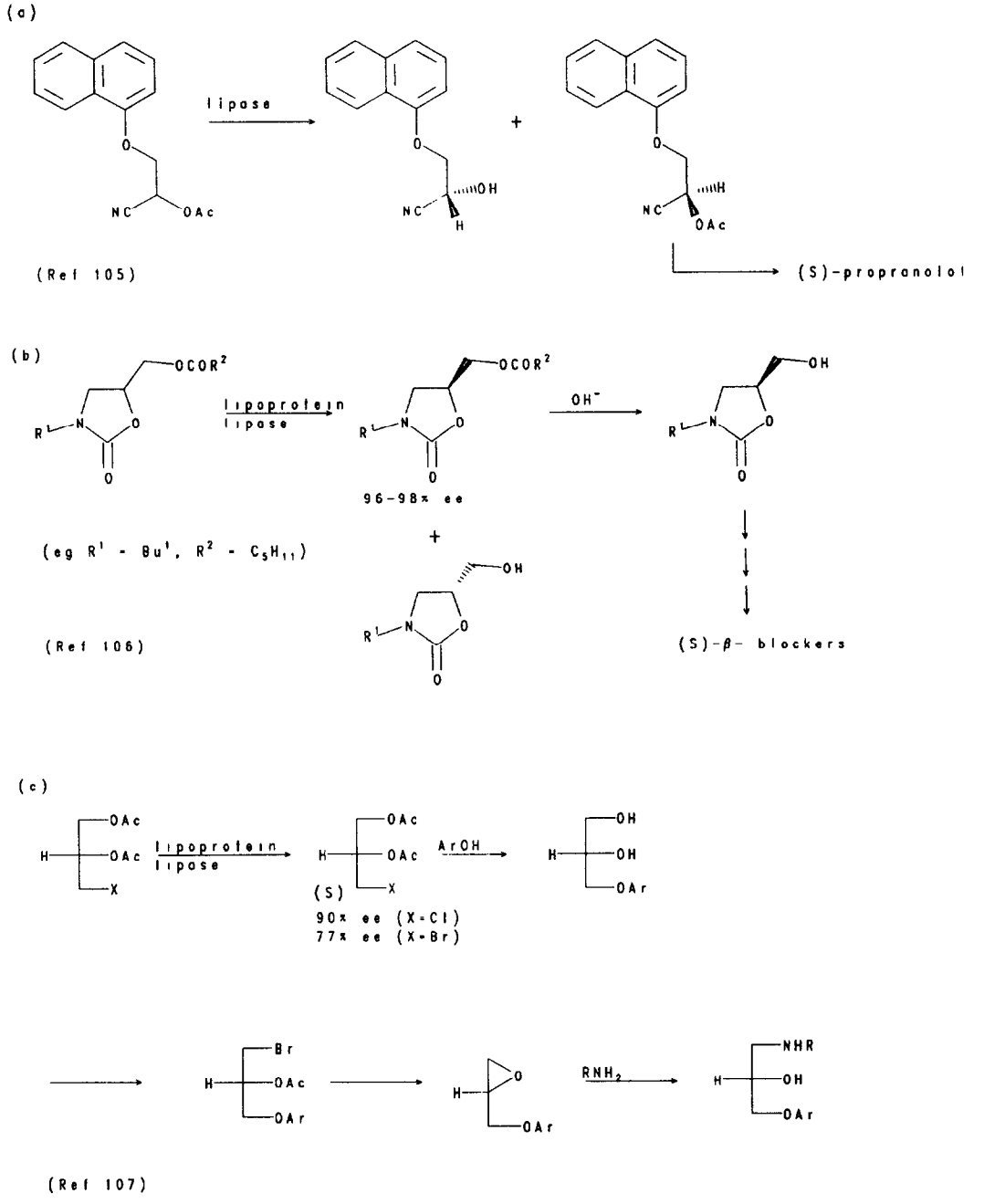
Tanabe have operated a process using an amino acylase immobilised on DEAE-Sephadex,[110] (Scheme 28). This was one of the earliest examples using an immobilised enzyme in commercial production and has been used, *inter alia*, for the production of L-methionine, L-valine and L-phenylalanine.

Scheme 29 shows the DSM process.[111] Depending on which enantiomer is required, recycle is achieved either by treating the D-Schiffs base (**50**) at pH 13 or converting the L-acid (**51**) via its methyl ester to the amide and proceeding via the corresponding L-Schiffs base. An interesting feature of the process is the efficient separation of the L-amino acid from the D-amino acid amide under aqueous conditions using the highly water insoluble Schiff bases formed from the amide and benzaldehyde.

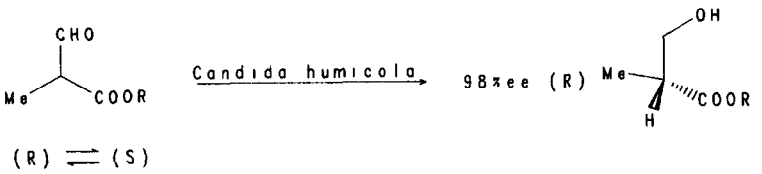
The DSM process accepts a range of substrates, a valuable attribute for a commercial route, and may be used to produce the D-phenylglycine and D-4-hydroxyphenylglycine required for β-lactam antibiotic side chains.

D-4-Hydroxyphenylglycine is made via enzymic kinetic resolution with hydantoinases (Scheme 30) by both the Snamprogetti[112] and the Kanegafuchi[113] companies. Since the hydantoins racemise readily under the conditions of the enzymic hydrolysis this allows virtually quantitative conversion of the racemic hydantoin into the D-amino acid.

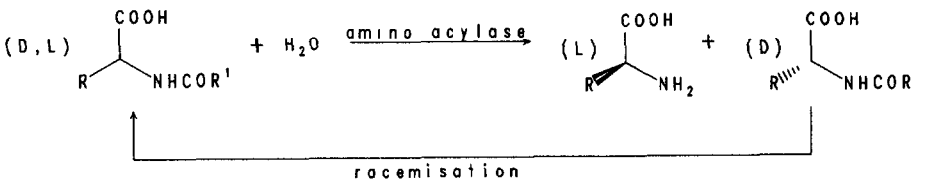
The Toray process for L-lysine (Scheme 31) is a further example of an industrial enzymic kinetic resolution process in which total conversion of the substrate may be achieved. DL-α-Amino-ε-caprolactam (**52**) is hydrolysed with simultaneous racemisation of the unwanted D-isomer (**25**). This transformation may also be effected enzymically.[114] Synthesis of the important optically active 2-halopropionic acids (cf. Section 2.1.2) has also seen the industrial development of enzymic resolutions. The Stauffer Chemical Company investigated the lipase catalysed route shown in Scheme 32[115] whilst ICI have commercialised a dehalogenase-based process on a very large scale (Scheme 33).[116] In the Stauffer procedure it is essential that excess, insoluble ester is present. In aqueous solution non-stereoselective hydrolysis occurs; this process requirement is further enhanced by the presence of added organic solvent.


(a)
lipase
+
(Ref 105)
(S)-propranolol
(b)
lipoprotein lipase
96-98% ee
OH⁻
+
(eg R¹ - Bu¹, R² - C5H11)
(Ref 106)
(S)-β- blockers
(c)
lipoprotein lipase
ArOH
(S)
90% ee (X=Cl)
77% ee (X=Br)
RNH2
(Ref 107)

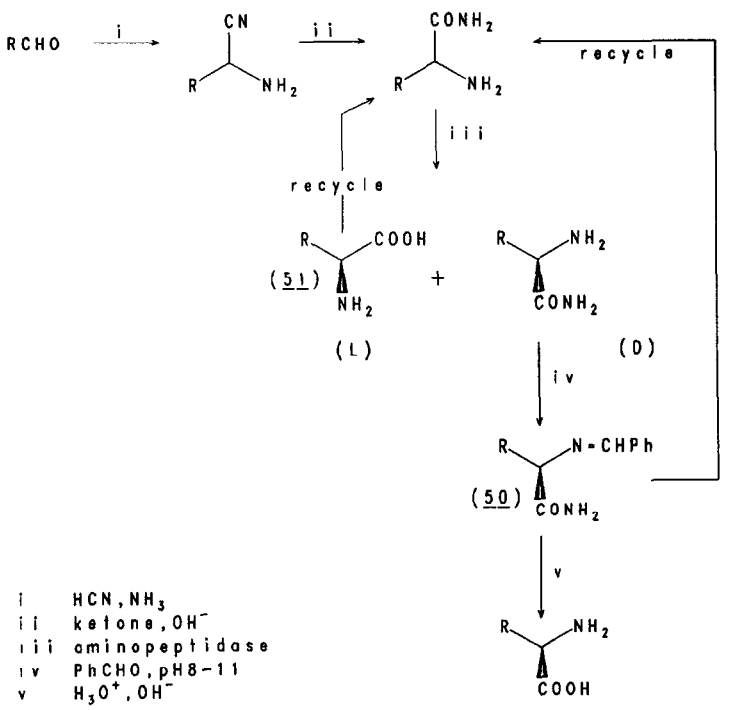
Scheme 26



Scheme 27.

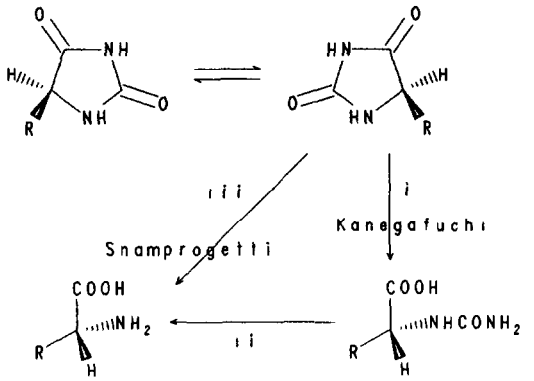


Scheme 28



DSM process for L or D amino acids

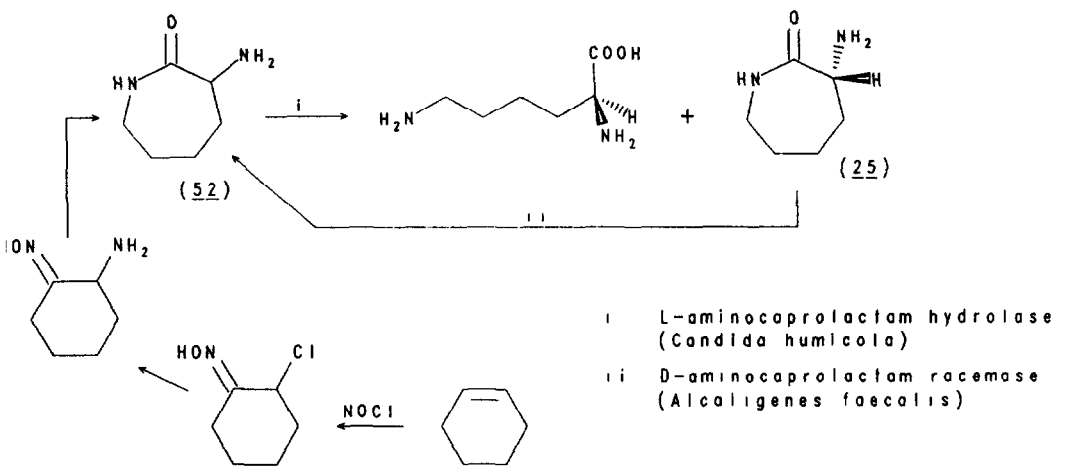
Scheme 29



i H_2O, hydantoinase
ii HNO_2, HCl
iii H_2O, resting cells of Agrobacterium radiobacter (hydantoinase + N-carbamoyl-D-amino acid amidohydrolase)

Hydantoinase routes to D-amino acids

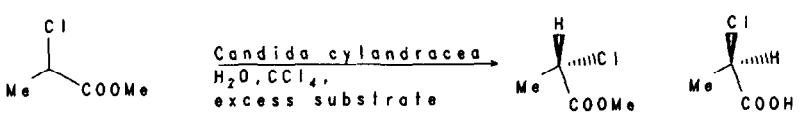
Scheme 30



i L-aminocaprolactam hydrolase (Candida humicola)
ii D-aminocaprolactam racemase (Alcaligenes faecalis)

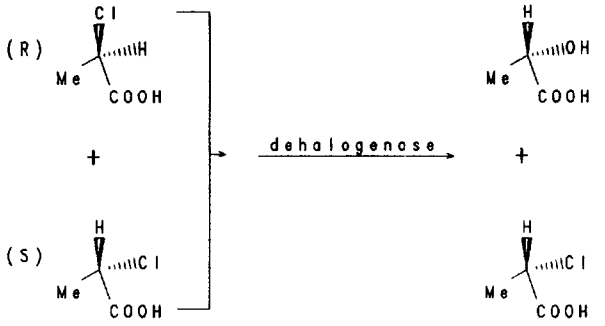
Toray process for L-lysine

Scheme 31



95% ee
30% yield

Scheme 32.



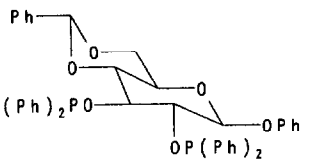
ICI dehalogenase process for (S)-2-chloropropionic acid

Scheme 33.

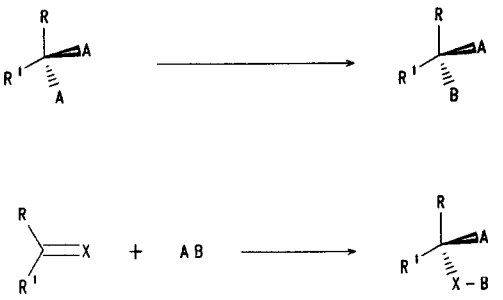
2.3 *From prochiral compounds: asymmetric synthesis*

Acquisition of enantiomerically pure materials through transformation of prochiral substrates (Scheme 34) necessitates the intervention of an optically active agent used either stoichiometrically or catalytically to express its chirality. We shall be concerned here with the latter case which is particularly challenging when non-enzymic catalysts are used.

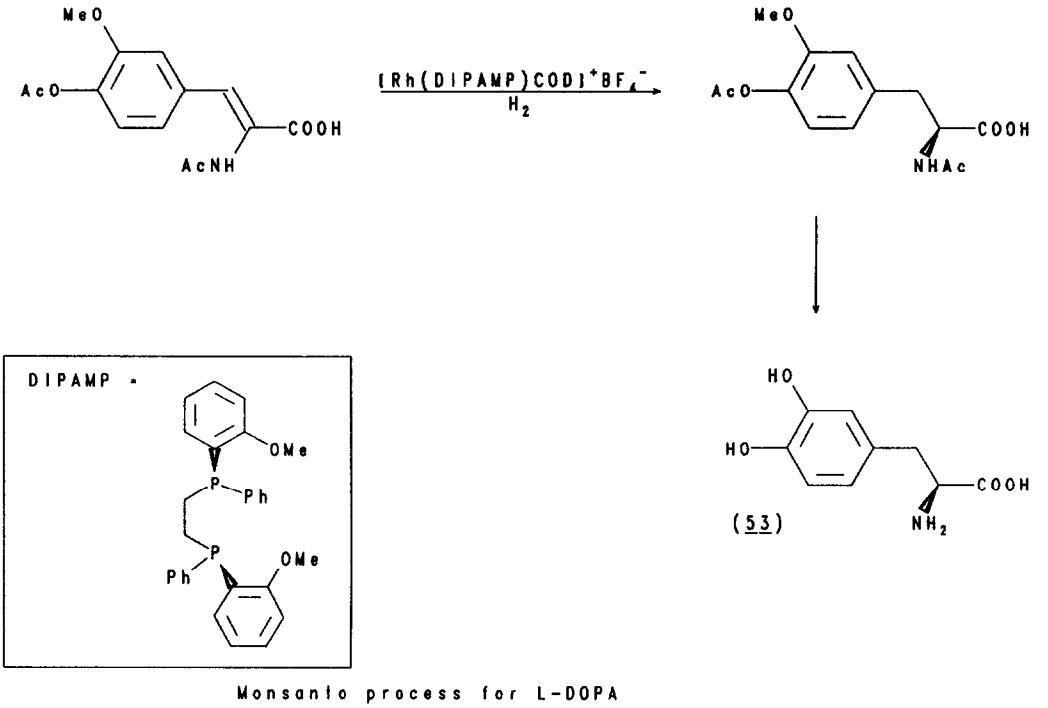
2.3.1. *Non-enzymic methods.*[117] *Asymmetric hydrogenation* has its origins in the soluble Wilkinson catalyst modified with chiral phosphine ligands; this led to the Monsanto process for levodopa (**53**) (Scheme 35), commercialised in the early 1970s. This was a landmark in industrial asymmetric synthesis[118] and a spur for a huge amount of other industry-based research. A similar levodopa process has been developed by VEB Isis-Chemie[119] but uses a catalyst in which **54** is the chiral ligand. Another commercial asymmetric hydrogenation is the Enichem synthesis of (*S*)-phenylalanine.[117b]



(54)



Scheme 34

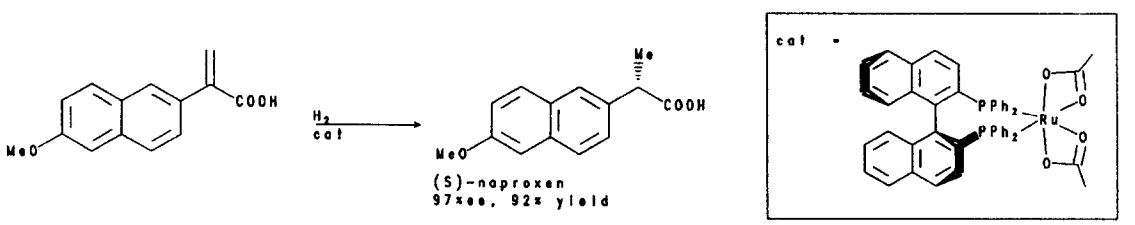


Monsanto process for L-DOPA

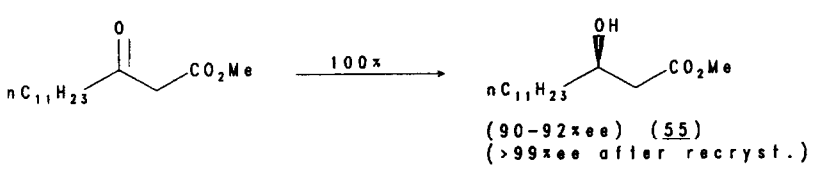
Scheme 35

The important non-steroidal anti-inflammatory group of drugs has stimulated almost every conceivable approach to their synthesis as single enantiomers (Section 3.1.4). One of particular interest under this heading is shown in Scheme 36.[120]

Although asymmetric reductions of ketones are probably still better served by enzymic methods with respect to the diversity of substrates accepted (Table 5), there have been very considerable advances in recent years by Noyori and co-workers[121] through use of BINAP-Ru systems. Tartaric acid—modified Raney nickel was one of the earliest chemical catalysts, for the reduction of β-keto esters and β-diketones, and has been applied on a commercial scale.[7b] It was used by Hoffmann-La



Scheme 36



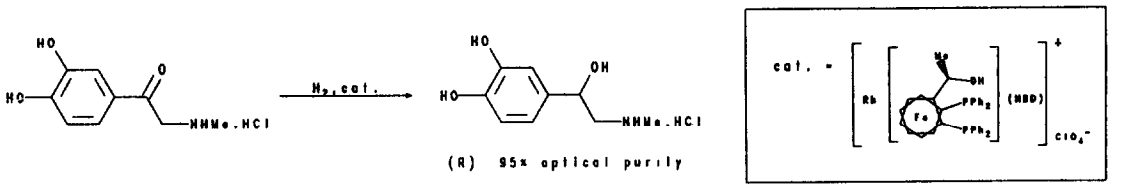
Scheme 37.

Roche for the transformation shown in Scheme 37;[7b] the product **55** was made on a 6–100 kg scale as an intermediate for a pancreatic lipase inhibitor. Synthesis of epinephrine (Scheme 38)[122] and of pantolactone (Scheme 39)[123] are further examples of asymmetric carbonyl group reductions applied to biologically important compounds. In these cases the activities of the catalysts were too low to be the basis for commercial processes.

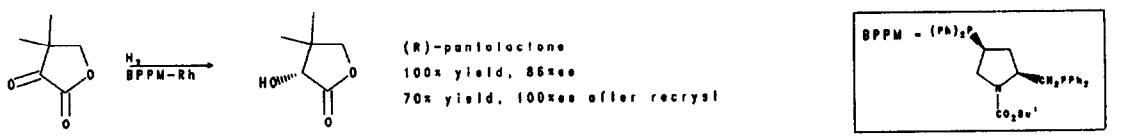
One of the major applications of asymmetric synthesis in industry is the Takasago process for (−)-menthol (Scheme 40)[125] which is based upon a highly efficient *asymmetric isomerisation* of diethylgeranylamine (**56**) to citronellal diethylenamine (**57**). The process has been operated since 1985 to produce about 1000 tonnes per annum of (−)-menthol.

Compound **57** has also been used by workers at Hoffmann-La Roche as a precursor for trimoprostil (**58**) (Scheme 41)[117d] an antiulcerative agent.

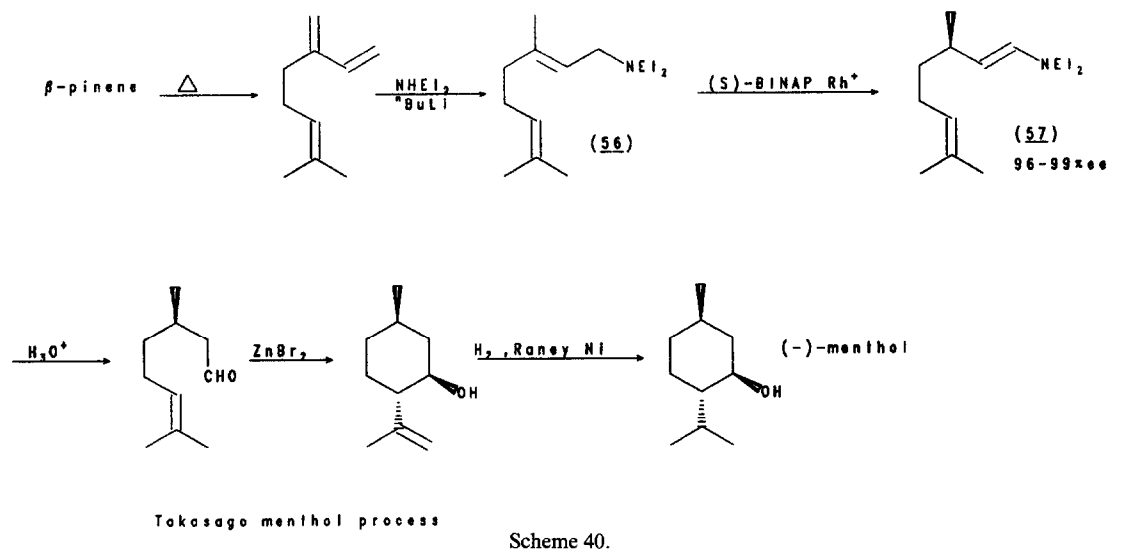
Pre-eminent amongst *asymmetric oxidation* processes is the Sharpless epoxidation which has



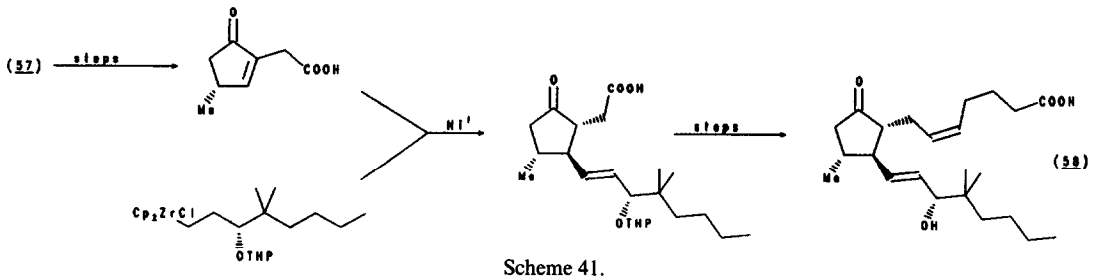
Scheme 38



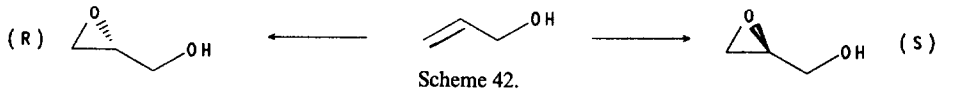
Scheme 39



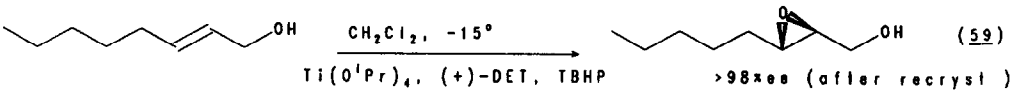
Scheme 40.



Scheme 41.



Scheme 42.

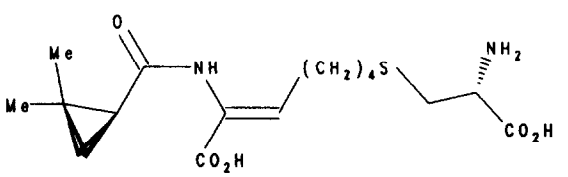


Scheme 43.

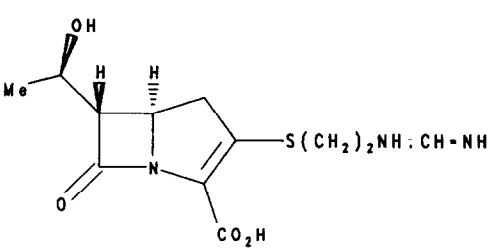
been extensively reviewed.[126] The catalytic version of the process[95,127] has been scaled-up by ARCO for production of both enantiomers of glycidol (Scheme 42)[128] on at least a 600 g mole scale.[129] The process has also been operated on a multi-kilogramme scale by the Upjohn company[130] to give epoxide **59** (Scheme 43). The catalytic version of the process has an appreciably better volume productivity (10% vs <2%) than the stoichiometric version.

Jacobson *et al.*[131] have disclosed details of catalytic asymmetric epoxidation using manganese complexes of chiral Schiff bases which permit epoxidation of a range of alkyl and aryl-substituted olefins (examples in Scheme 44). Preliminary studies indicate that NaOCl is an effective oxidant. Although the reported *ee*'s are still only modest in some cases, these results break significant new ground and must be seen as having industrial potential.

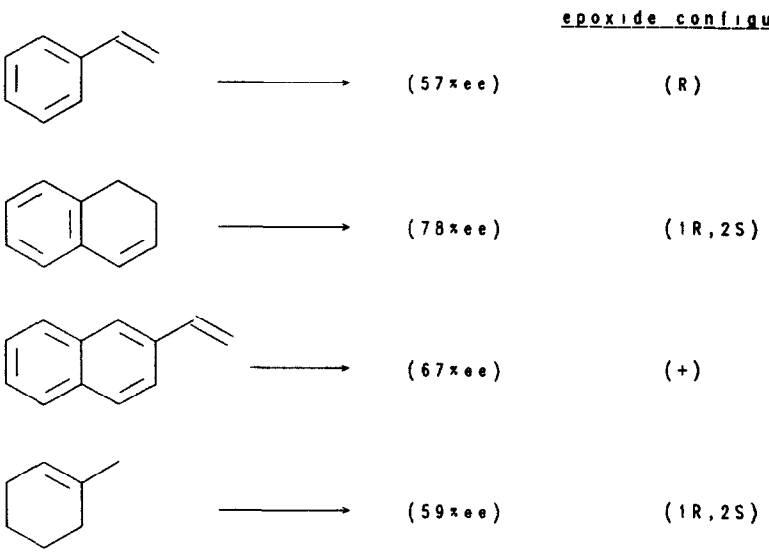
Although much investigated, *asymmetric cyclopropanation* has yet to be applied on a large scale to the potentially most lucrative targets: synthetic pyrethoids. One process that has been scaled up is for (+)-ethyl (1*S*)-2,2-dimethylcyclopropanecarboxylate (**60**) (Scheme 45).[132] Compound **60** is obtained by reaction of isobutene with ethyl diazoacetate using the catalyst **61**; **60** is a key intermediate for cilastatin (**62**), used in conjunction with imipenem (**63**) to suppress hydrolysis of the latter by renal enzymes.



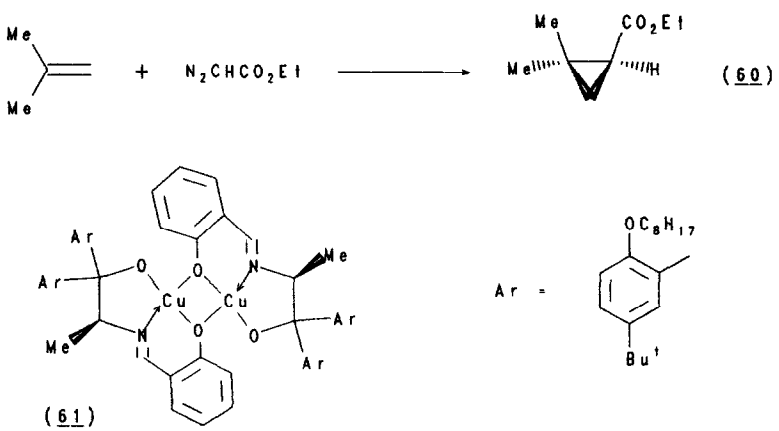
(62)



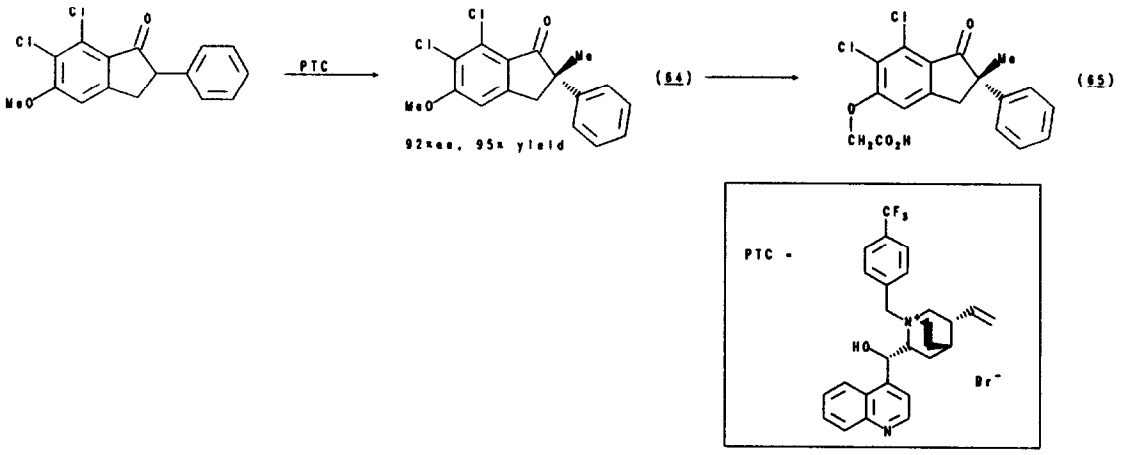
(63)



Scheme 44



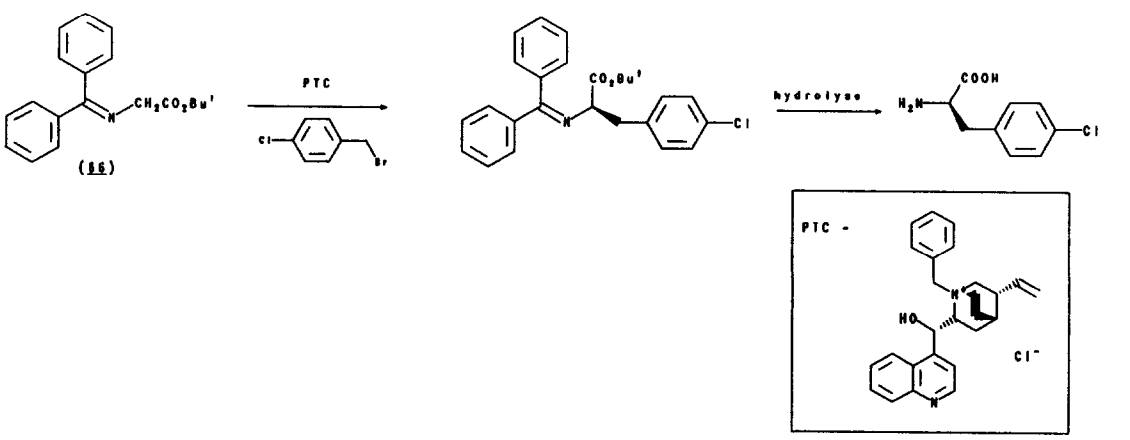
Scheme 45.



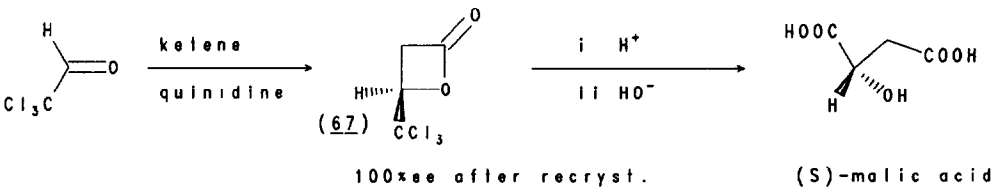
Scheme 46

Asymmetric phase transfer catalysis has proved a difficult area with false dawns[133] before the signal achievement by the Merck Group of Dolling *et al.* who obtained the alkylated indanone **64** (Scheme 46)[134] in 92% *ee* and 95% yield. Compound **64**, an intermediate in a proposed commercial synthesis of *S*(+)-indacrinone (**65**) (MK-0197), was only obtained with high *ee* after painstaking and methodical development work[135] which followed an initial observation of only 6% *ee*. More recently O'Donnell *et al.*,[136] also using a quaternised cinchona alkaloid as the catalyst, alkylated the Schiffs base ester **66** (Scheme 47) to realise an α-amino acid synthesis. Although by most standards the *ee* of the product of the alkylation step would be considered low for a practical synthesis, (66%), recrystallisation leads in one step to optically pure product (in the filtrate); to date this process has only been run on a multigramme scale.

Cycloaddition is another of the select and disparate asymmetric syntheses which have been commercialised[137] and highlights again the value of cinchona alkaloids (Scheme 48).[27] The cyclo-

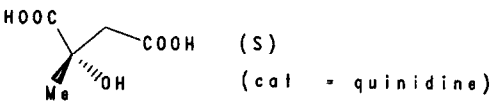


Scheme 47



Scheme 48

addition of ketene and chloral at low temperature in the presence of 1 mol % of the alkaloid proceeds quantitatively to the lactone **67** with high *ee*. Hydrolysis of **67** affords (*S*)-malic acid; the unnatural (*R*)-acid results if quinine is the catalyst. Use of 1,1,1-trichloroacetone in place of chloral

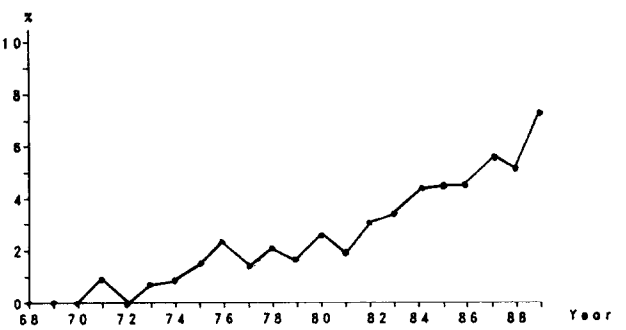


(68)

leads to citramalic acid **68**,[138] a promising synthon for natural products, because of its isoprenoid structure, but not hitherto easily made in optically active form or extensively exploited. The reaction has been extended to a range of other aldehydes and ketones containing 1,1-dichloro substituents.[139] Products from this chemistry are being commercialised by Lonza.

2.3.2. *Enzymic methods.* A rising proportion of syntheses of homochiral materials include enzymic steps (Fig. 4) showing an increasing recognition of the contribution enzymes can make and willingness by the chemical community to employ them.

This section is concerned with use of micro-organisms or isolated enzymes to catalyse single transformations, rather than multi-step sequences from basic feedstocks such as carbohydrates. Those biological systems are included which may be complex in themselves but which can be regarded as sources of, for example, reducing or oxidising power.



Proportion of papers on asymmetric synthesis cited by Chem. Abs. which employ enzymic methods

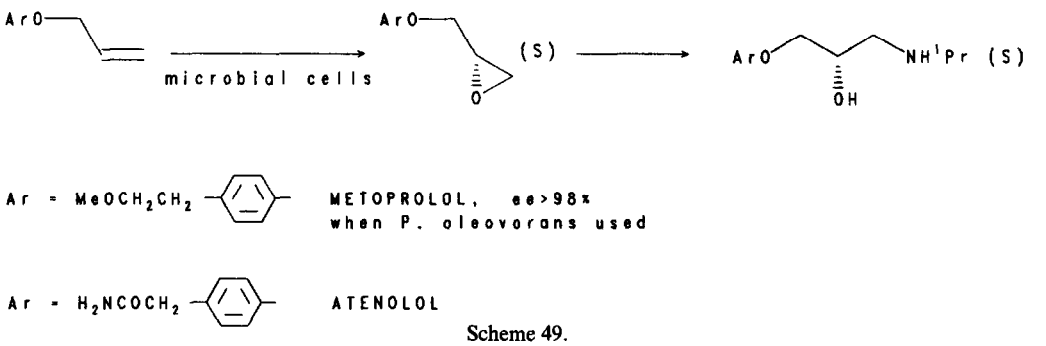
Fig. 4

Oxidation

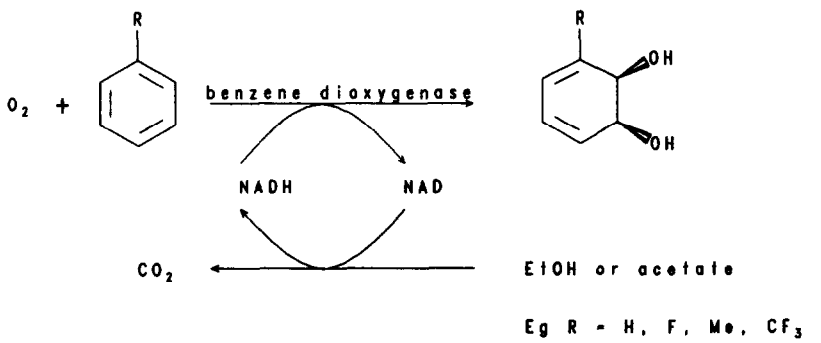
(i) *Chiral epoxides.* Microbial epoxidation dates from 1963[140] and it was in 1973 that the reaction was found to be stereospecific.[141] The Nippon Mining company carried out much of the pioneering work.[142] One of the preferred micro-organisms is *Nocardia corallina* B-276 which accepts a wide range of substrates. Although many epoxide-producing micro-organisms show their epoxidising ability only when grown on hydrocarbons such as lower alkanes, in the case of *N. corallina* glucose or sucrose grown cells are also active. Since growth on hydrocarbons also tends to be lower this makes *N. corallina* more commercially attractive.[142] Production of long chain epoxides[143] is further assisted by their relatively low toxicity to the organism, allowing accumulation without severe product inhibition: e.g. 80 g l^{-1} of 1,2-epoxytetradecane. By 1986 twelve 1,2-epoxyalkanes, C_7–C_{18}, were commercially available from this technology. Aryl glycidyl ethers may also be made and have the (*S*)-configuration required for the pharmacologically active β-blockers (cf. Scheme 49).

Shell and Gist-Brocades have also reported a route to single enantiomer β-blockers using stereoselective microbial epoxidation (Scheme 49).[144,145] These epoxides are produced with a stereochemistry which is consistent with the observed *si* side stereoselectivity for linear olefins.[146] Such routes, at the time, were obviously attractive over earlier lengthy chemical synthesis, involving pre-synthesis of chiral synthons such as (*R*)-isopropylideneglycerol.

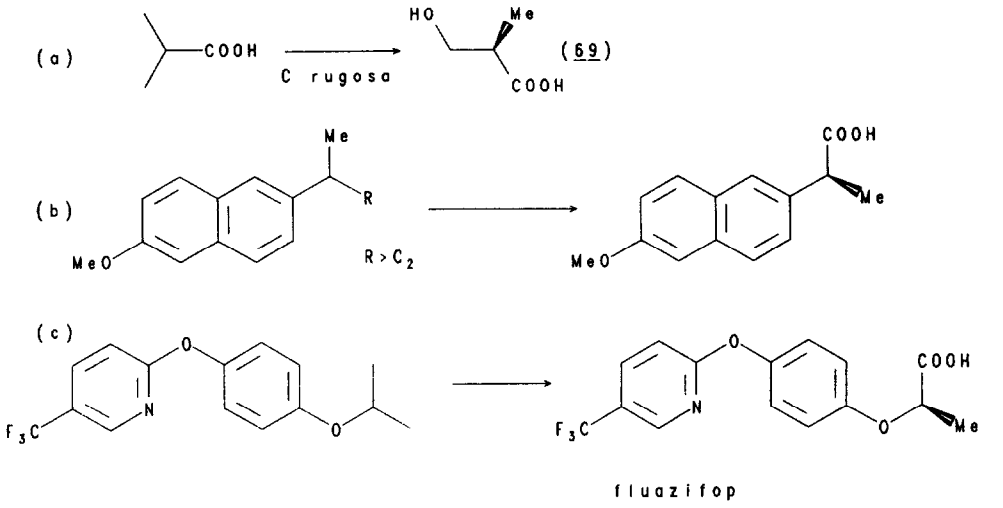
(ii) *Dihydrocatechols.* By the use of a genetically manipulated micro-organism, ICI has developed the process depicted in Scheme 50 which proceeds in high yield and with total selectivity. This process uses intact cells because the isolated dioxygenase enzyme is unstable plus a cosubstrate such



Scheme 49.



Scheme 50.



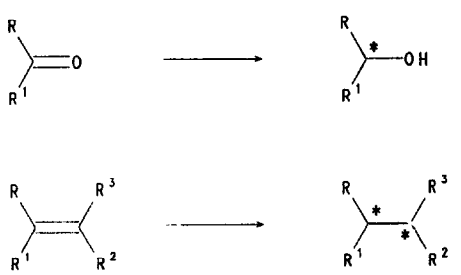
Scheme 51

as ethanol or acetate that can be oxidised to CO_2 to regenerate NADH. Although originally developed with benzene as substrate to produce polymerisation monomers,[147] the process may be applied to a range of substituted benzenes to give the corresponding (*cis*, 1*S*)-1,2-dihydrocatechols. The process was developed in the face of challenging technical hurdles. It employs a catalyst which can be used in standard, non-sterile chemical plant and oxygen is reacted with flammable volatile cytotoxic water-immiscible substrates. These are problems which will be encountered in many of the potentially most useful bio-transformations. The technology has been proved at the tonnage scale.[148]

(iii) *Stereoselective side-chain oxidation.* Examples are shown in Scheme 51. Methods have been patented[149] for the production of (*R*)-(−)-3-hydroxyisobutyric acid[69] required for the Squibb cardiovascular drug, captopril (**8**). Shell–Gist-Brocades have investigated similar oxidation processes to (*S*)-naproxen and the active (*R*)-isomers of the aryloxypropionate herbicides[150,151] ((b) and (c) in Scheme 51).

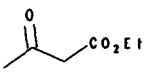
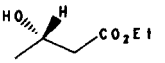
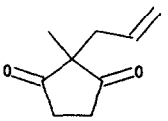
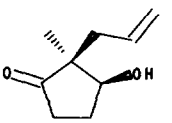
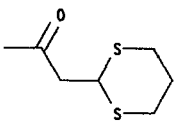
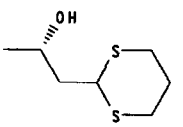
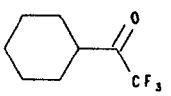
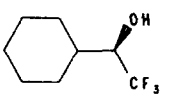
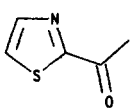
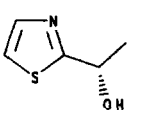
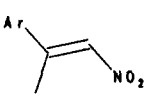
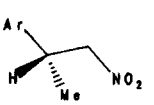
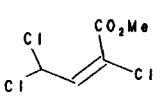
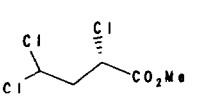
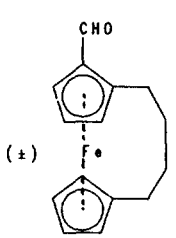
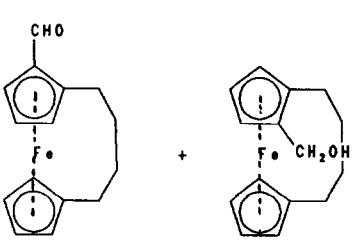
Reduction (Scheme 52)

As far as the bench chemist is concerned, applications are dominated by use of baker's yeast.[152] Its use is largely empirical. Attractions are cheapness, it does not demand elaborate equipment or sterile technique and it is applicable to an extremely diverse range of substrate types (Table 5) often

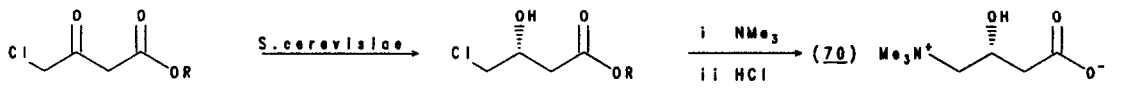


Scheme 52.

Table 5.

Substrate	Product	ee(%)	Ref.
		97	153
		>98	154
		99	155
		99	156
		95	157
		89-98	158
		84-98	159
		89%ee 80%ee	160

Structural diversity of substrates accepted in yeast reductions



Synthesis of L-carnitine

Scheme 53

giving very high *ee*'s. Little attention has been given to problems relevant to very large scale operation. Some of the more obvious disadvantages are the need for high *biomass* : *substrate* ratios and dilution which, for the commercial operator, translate into difficult isolations, serious effluent problems, and poor productivities. For products required in kgs rather than tonnes it is a viable technique.[153b] The transformation shown in the first entry of Table 5 is one which has been demonstrated on a multikilogramme scale; this complements PHB (Section 2.1.2) and makes both enantiomeric forms of 3-hydroxybutyrates easily accessible.

Sih *et al.*[161] have reported an interesting compact synthesis of L-carnitine (**70**) (Scheme 53) using *S. cerevisiae*. Key to the success of this route was 'manipulating' Prelog's rule[162] (Scheme 54); by making the R Group sufficiently large (C_8H_{17}) so that the required (*R*)-stereochemistry was obtained. In contrast use of R = Et leads to the (*S*) product.

Hydrogenation of activated carbon–carbon double bonds has been less extensively exploited but, again, yeasts will carry out such reductions and usually with high stereospecificity (Table 5 and Ref. 163). A group at Hoffmann-La Roche have devised a technical synthesis of (4*R*,6*R*)-4-hydroxy-2,2,6-trimethylcyclohexanone (**71**) (Scheme 55),[164] using baker's yeast reduction of a carbon–carbon double bond; the starting material is readily available oxo-isophorone. The intermediate diketone is a solid which may be strained off whilst continuing to pump-feed the liquid starting material.[164b] Compound **71** is a building block for the synthesis of optically active hydroxy carotenoids and other terpenoid compounds.

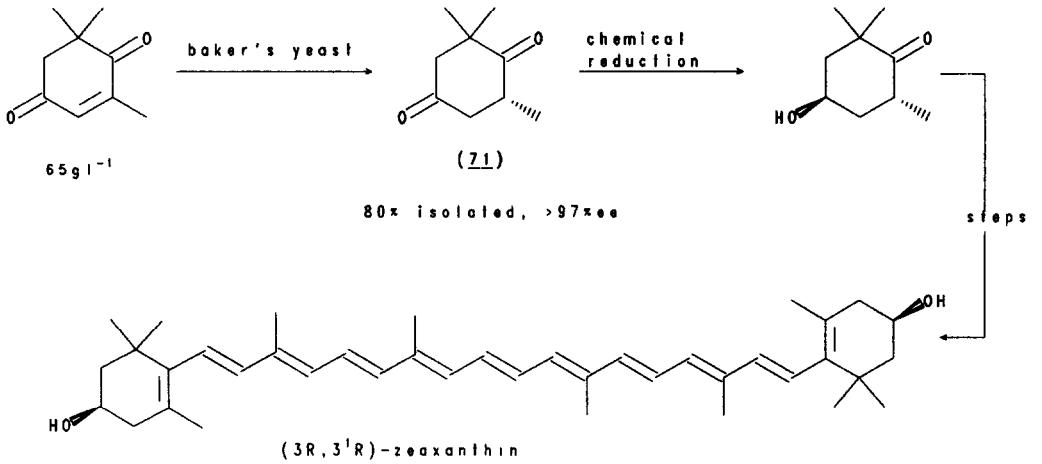
Reductive amination

Scheme 56 shows an interesting example developed by Wandrey at the Institute of Biotechnology, Nuclear Research Centre, Jülich: the process has been commercialised by Degussa. The principles of the reactor system, which had a capacity of about 250 tonnes per year of amino acids (1987),[165] are shown in Fig. 5. Continuous operation is achieved through use of an ultrafiltration membrane to retain the soluble enzyme. The necessary cofactor is also retained by the membranes by binding it to a water soluble polymer (PEG) in order to increase its molecular weight. One of the first

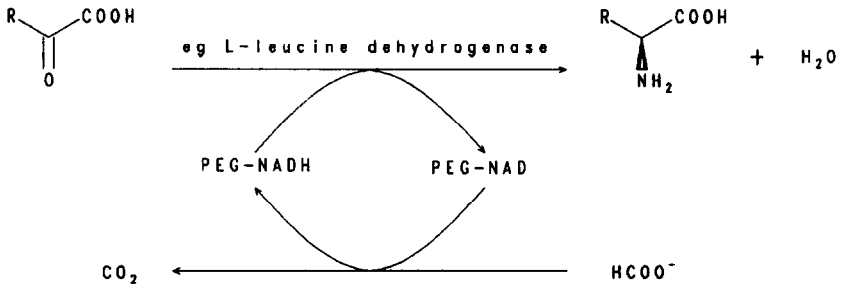
"hydride" delivered to re face, as defined by CPI sequence O>L>S.

"Prelog's Rule" for stereochemistry of yeast reductions

Scheme 54.



Scheme 55.



Scheme 56

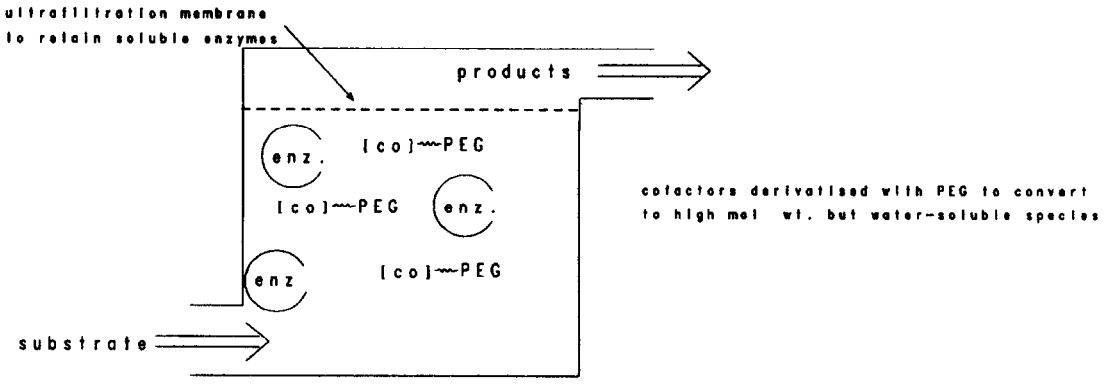
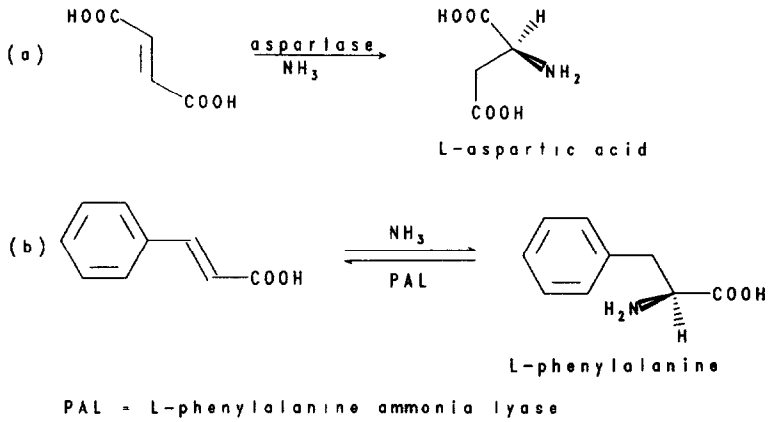


Fig. 5.



Scheme 57

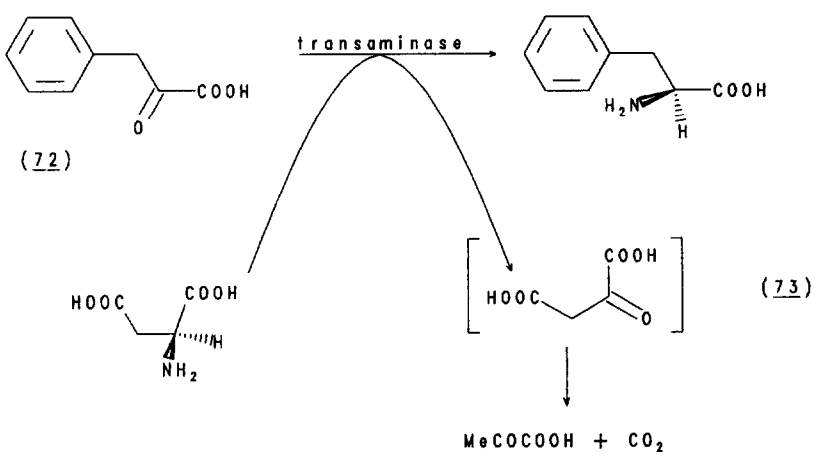
materials to be produced commercially using this technique was L-tertiary leucine in 1986. Over 70 000 recycles of PEG-derivatised cofactor have been achieved and L-leucine was made with a productivity of 200 g l^{-1} day^{-1}.

Ammonia addition

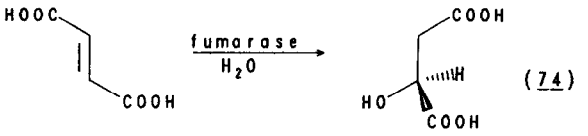
Production of L-aspartic acid (Scheme 57a) is an industrially important example using enzymic addition of ammonia to a prochiral substrate, fumaric acid. The production of pharmaceutical grade material was about 4000 tonnes per annum in 1987.[66] It is possible to immobilise the enzyme and still retain virtually all (97%) of the aspartase activity; the half life of such an immobilised catalyst was estimated at 3–4 years.[66] Commercialisation of a corresponding process to L-phenylalanine (Scheme 57b) was achieved by Genex.[166] This is a more difficult reaction because of low conversion, poor stability of the enzyme, and substrate inhibition.

Transamination

Another large scale (600 tonnes per year) approach to L-phenylalanine, developed by Purification Engineering,[167] is transamination from aspartic acid to phenylpyruvic acid (**72**) (Scheme 58). The initial by-product, **73**, decarboxylates yielding pyruvic acid.

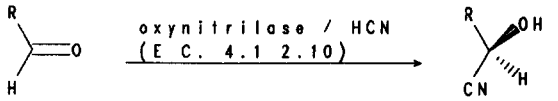


Scheme 58



(74)

Scheme 59.



Scheme 60.

Hydration

A process for the production of (*S*)-malic acid (**74**) (Scheme 59) has been operated by Tanabe since 1974.[168] Citramalic acid, **68**, could be similarly obtained using *Clostridium tetanomorphum*.[169]

Cyanohydrin formation

This is a reaction which has attracted much attention[170a–d] but does not yet seem to have been scaled up.[170e] Cyanohydrin formation is of particular interest for pyrethroid synthesis, Scheme 60 shows an enzymic route from prochiral aldehydes. Use of membrane reactors (Fig. 5)[171] is one of the technologies which could possibly be used.

3. EPILOGUE

3.1. *General remarks*

The task of the industrial process development chemist, who may in the early stages of definition of a route for the manufacture of an optically active material have at least 10 route options of maybe 6–10 stages each, is clearly far from easy. Where and by what means in the overall synthetic scheme should optical activity be introduced? Chirality is an additional, constraining dimension which has to be added to the other chemical and physical considerations not to mention issues such as registration, patents, effluent, toxicity and economics.

It is instructive to consider a number of points: (i) when and how optical activity is generated in a synthesis; (ii) pros and cons of biological versus chemical methods; (iii) historically, how approaches to a commercially important chiral product have evolved; (iv) how the advent of a commercially important new structure stimulates the range of approaches.

3.1.1. *Where and how to introduce optical activity in a multi-stage synthesis.* Any attempt to draw up guidelines is fraught with exceptions. There is no best point to insert optical activity into a synthesis which is predictable; in many instances it is only after experimentation and with a knowledge of physical parameters that this may be determined. Solubility and crystallisation behaviour can be crucial. For example, does a conglomerate exist (Section 2.2.2) or is easy enantiomer purification possible.

On a small laboratory scale it may be advantageous to carry larger amounts of material through a synthesis for ease of manipulation. Large scale process economics favour processing the minimum amount of material.

If a resolution is involved, the stage which allows most efficient recycle of unwanted material is likely to dictate where the optical activity is produced. If an *in-situ* racemisation can be coupled with the resolution, allowing a 'Second Order' process then it will be immaterial where it takes

place. Similarly, when a catalytic asymmetric synthesis is employed, any point in the synthetic sequence is probably acceptable.

All methods are obviously constrained by the requirement that there should be no significant risk of racemisation following the creation of optical activity. It is generally beneficial to have the opportunity for crystallisation after the 'chiral' step to permit *ee* enhancement.

Different route options to a given target may, individually, only be amenable to a particular approach, and be dictated by the means by which the optical activity is created. Comparison of these options becomes part of the wider issue of overall process economics, encompassing capital costs, operating costs, materials costs, environmental costs, etc. All these parameters have to be optimised and the 'chiral' part of the equation may be subordinated to other factors when there are two or more 'chiral' options. Conversely if there is only one credible approach to the target in optically active form this will dictate the route. However, there are usually several possible synthetic routes (see Section 3.1.4).

3.1.2. *The place of biological methods.* Increasingly, reported syntheses of optically active compounds include biological steps (Fig. 4). The number and variety of large scale enzymic processes is also increasing (see Sections 2.3.2 and 2.2.3.3) demonstrating that in many situations biology offers the most economic solution.

Although many large scale applications employ enzyme reactions which do not require cofactors, cofactor recycle has been successfully addressed as for example in the Wandrey–Degussa membrane reactor (Fig. 5) or, more simply, through the use of intact cells in conjunction with another substrate, to drive the cofactor recycle (cf. Scheme 50).

Enzymes are catalytic proteins which dictates both their capabilities and drawbacks. Advantageous features of biological systems are:

(i) Specificity. The corollary being perhaps limited substrate range but it is disputable whether enzymes are any worse than chemical catalysts in this respect; witness the substrate limitations of the Sharpless epoxidation catalyst and chiral hydrogenation catalysts. Many enzymes are at least as catholic in their acceptance of substrate variation.

(ii) They generally conform to well worked out kinetics. As Whitesides has pointed out,[172] the time spent in measurement of kinetic constants is well rewarded when there is a need to optimise a process by rational control of enzyme activity.

(iii) Most enzymes operate under similar conditions of pH and temperature. This allows consecutive reactions to be run in the same vessel without intermediate product isolation.

(iv) Catalytic properties may be manipulated through the application of protein engineering[173] and the catalyst concentration can be increased through the use of cloning techniques.

(v) Safety. It is possible to avoid the use of reagents which are costly and difficult to handle on the large scale (e.g. highly toxic metal catalysts or pyrophoric reagents).

(vi) Catalyst discovery. Although it can be an empirical process, statistically the chances of success are good because of the large population of organisms from which to choose and the further ability to produce mutants.

(vii) Mild conditions of use. This can permit isolation of products which would not survive traditional chemical processing and also allows for cheaper engineering.

(viii) Biocatalysts are able to perform the equivalent of most known organic reactions. Notable exceptions include the Cope rearrangements and Diels–Alder reactions.[174]

Negative features:

(i) It is not always possible to access either enantiomer as easily as with chemical methods.

(ii) Low volumetric productivity is often a problem but should not be assumed. Some bioprocesses operate at concentrations which match or exceed those commonly encountered in conventional chemical manufacture. A spectacular example is a process being developed by Novo–

Nordisk for sugar-based surfactants.[175] Using a lipase as catalyst, a long-chain fatty acid is esterified with a sugar under solventless conditions to achieve almost 100% product formation.

(iii) The need for cofactors; but this is increasingly amenable to solution.

(iv) Chemical and thermal instability.

(v) Incompatibility with organic solvents, particularly polar ones.

(vi) Often lacking in properties sought by the process engineer: mechanical strength and rheological properties, where application, whole cells or supported enzymes, leads to heterogeneous systems.

(vii) Reactions are often very slow in comparison with chemical processes but this can be a consequence of enzyme concentration rather than reaction rate.

(viii) Subject to inhibition.

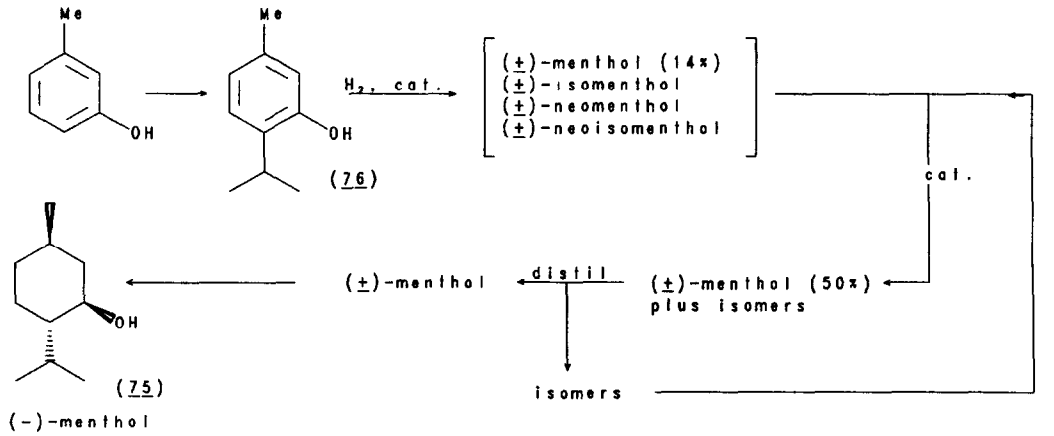
(ix) Phase separation problems during work-up.

(x) Poor substrate: biomass ratios leading to serious effluent problems if whole cells are used (e.g. yeast reduction).

It is debatable whether an ability to operate in an aqueous medium is a plus point. It can often be easier to recycle organic solvents and disposal of aqueous biological waste streams is a problem. Many substrates which are of interest are water soluble and this makes their isolation more difficult.

Reasons for disfavouring biological processes are more concerned with operational features; they score heavily as a means of effecting chiral synthesis. A balanced view must be kept of the bio-option. It does not offer a magical solution any more than do other types of asymmetric catalysis. It may introduce additional unit processes into the flowsheet which add to the cost of an apparently straightforward transformation. Also, successful operation of enzyme processes in the manufacture of fine chemicals depends crucially on an integrated skill base spanning biotechnology–classical organic chemistry–physical chemistry–process engineering. Biocatalyst manufacture is unlikely to be a commercially attractive exercise in its own right.[174]

3.1.3. *Evolution of methods for a commercial product*: (−)-*menthol.* World demand (1988) for (−)-menthol (**75**) is approximately 4000 tonnes.[39] Historically it has been produced from *Mentha arvensis* (Japanese mint) oil by cooling and separating the crystals by centrifugation. This is an inherently unpredictable source, due to climatic variations and competing cash crops, and this has led to the development of many synthetic and semi-synthetic methods. The Haarman and Reimer synthesis (Scheme 61)[74] exemplifies the former. 3-Cresol is converted to thymol (**76**) which is hydrogenated to an eight-isomer mixture; its (±)-menthol content is enhanced by passing over a



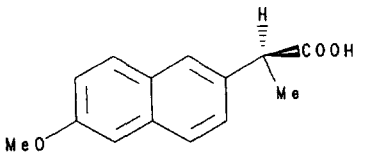
Scheme 61.

heterogeneous catalyst. After separation of racemic menthol by distillation the residue is re-isomerised and recycled. The racemic menthol is then resolved by the method of preferential crystallisation (Section 2.2.2). An esterase method has also been investigated for the resolution of (±)-menthol.[176] A technical process from phellandrene (Scheme 62)[177] illustrates a semi-synthetic approach. Another semi-synthetic process was disclosed in 1978 for the manufacture of (−)-menthol starting from (+)-3-carene and this has since been commercialised.[178] Details of the Malti-Chem process, from (+)-3-carene are in Scheme 63. Based upon this technology, a 120 tonne plant was built in 1982.[39] Most recently we have seen the emergence of the Takasago asymmetric synthesis (Section 2.3.1, Scheme 40) which starts with the initial thermal cracking of β-pinene.

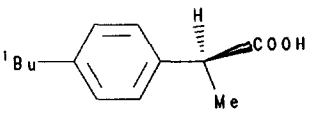
Production of (−)-menthol parallels nicely the development of methods for producing optically active materials. It evolved from the isolation from natural materials to the use of one of the most challenging of techniques, catalytic asymmetric synthesis. It has also encompassed chiral pool methods and the resolution of totally synthetic material.

3.1.4. *The stimulus of a commercially important optically active structure.* Alongside the evolution of methods for production of (−)-menthol, which adopted technologies and techniques as they became available and offered improved methods, it is interesting to review the response to a structural target of more recent origin and which from the outset had a wider range of developed techniques and more advanced chemistry on which to build. This is well illustrated by the non-steroidal, anti-inflammatory, alpha-arylalkanoic acids (examples in Chart 7). The average daily dose for this class of drugs can be from several hundred milligrams to 1–2 grammes and this results in multi-hundred ton requirements. Scheme 64 (a–k) summarises methods which have been considered in relation to the synthesis of naproxen or ibuprofen. *All* the approaches discussed in this review are exemplified at least on the research scale and several have been investigated on a multikilogramme scale. Of particular interest is the stereoconvergent Zambon process, (*k*). Though the bromination is not totally diastereoselective, because in one case rearrangement prevails versus substitution in the other, significant amounts of the (*R,R,R*)-diastereomer (**77**) can be tolerated whilst still obtaining a total conversion to (*S*)-naproxen of high *ee*.

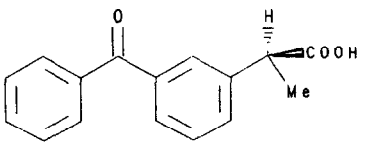
This section could equally well have been illustrated by reference to aryloxypropionate herbicides, pyrethroids, β-blockers, carbapenems, etc., where synthetic and technological ingenuity have been applied to the problem of synthesising them as single enantiomers.



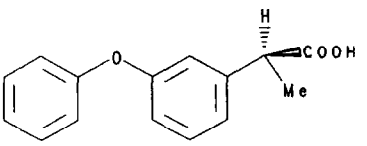
(S)-NAPROXEN



(S)-IBUPROFEN

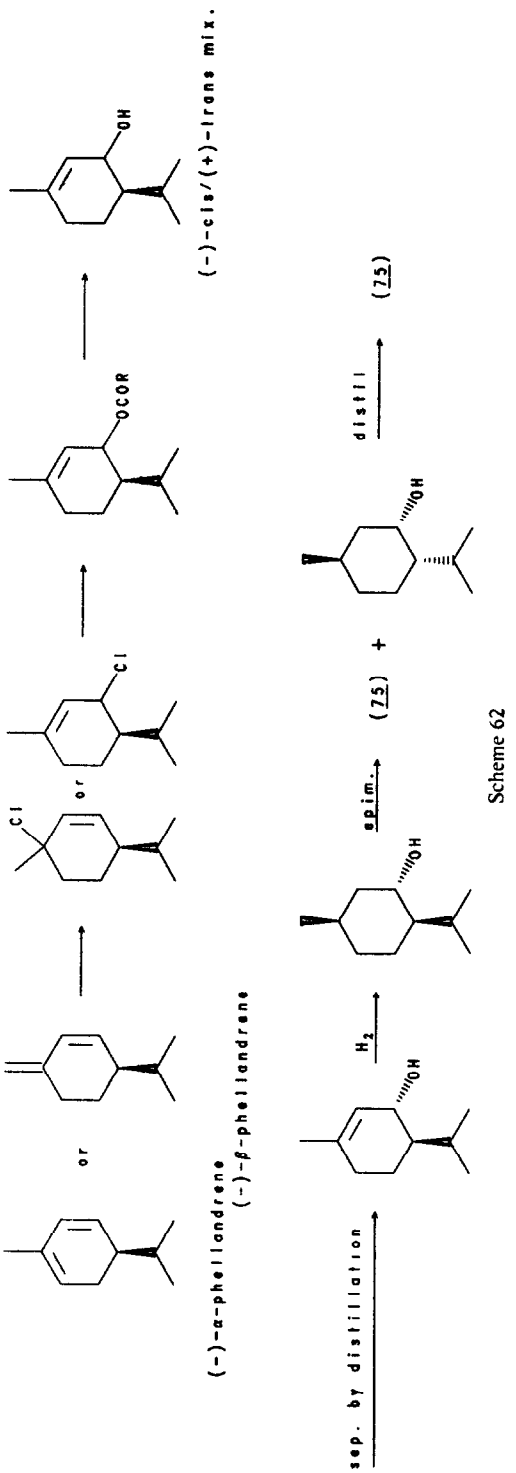


(S)-KETOPROFEN

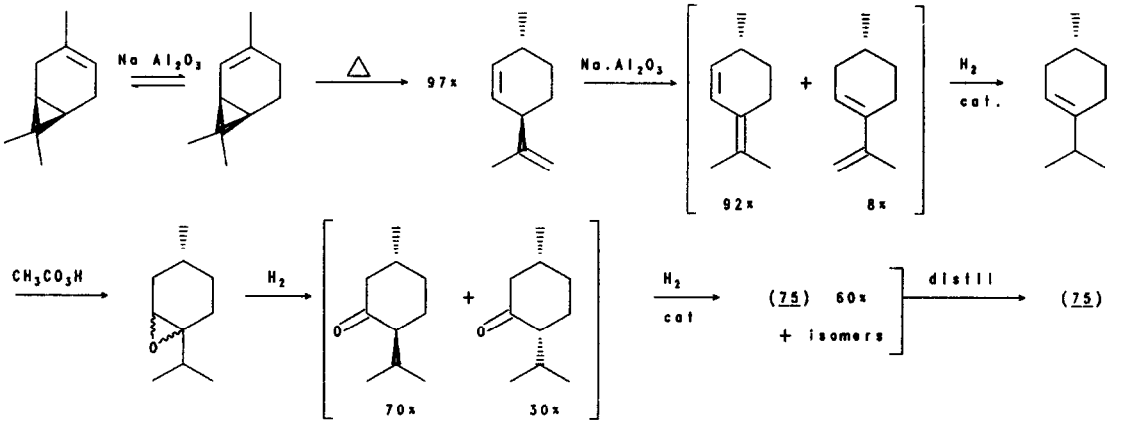


(S)-FENOPROFEN

Chart 7.


(-)-α-phellandrene
(-)-β-phellandrene
or
sep. by distillation
H2
spim.
(75) +
distil
(75)
(-)-cis/(+)-trans mix.
OH
OCOR
Cl
or

Scheme 62



Scheme 63

(a) Classical resolution with cinchonidine [179]

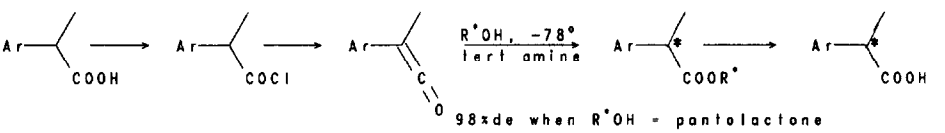
(b) Resolution by direct crystallisation of the ethylamine salt.[80]

(c) Chemical kinetic resolution via anhydride (Scheme 18) [92]

(d) Kinetic resolution of ibuprofen ester using lipase [180]
(membrane reactor)

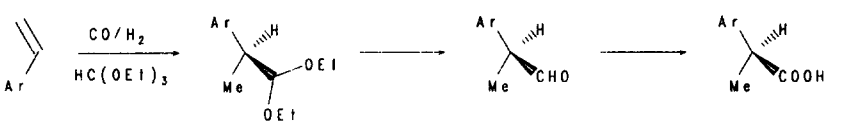
(e) Stereoselective, microbial side chain oxidation (Scheme 51b) [150]

(f) (Ref 181)



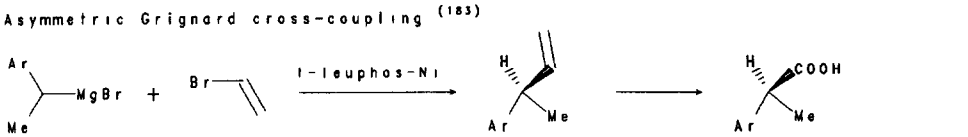
(g) Asymmetric hydrogenation (Scheme36).[7b]

(h) Asymmetric hydroformylation [182]

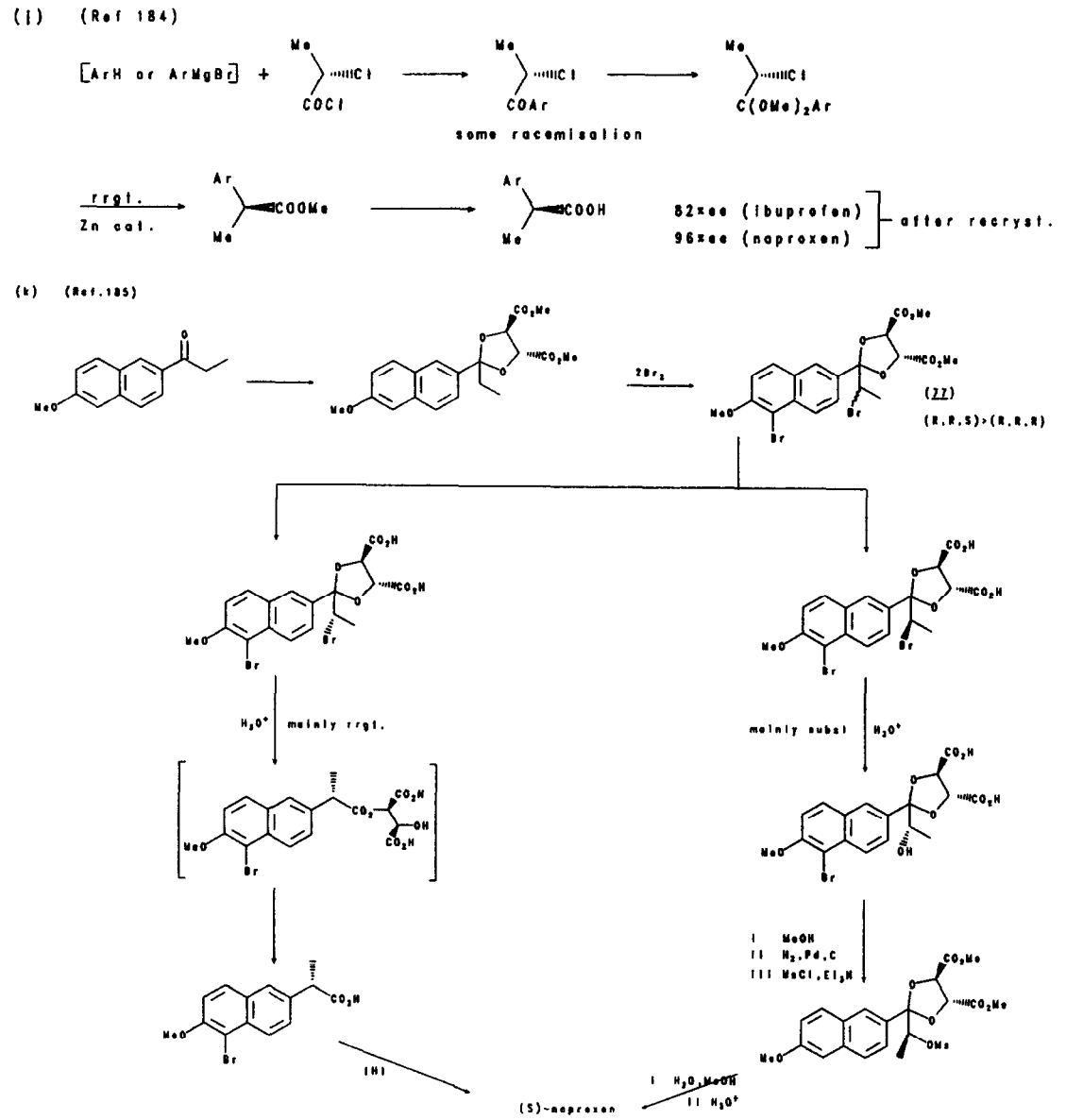


aldehyde is labile under hydroformylation conditions
trapped with orthoformate to prevent racemisation

(i) Asymmetric Grignard cross-coupling [183]



Scheme 64.



Scheme 64 *continued.*

3.2. *Future prospects*

Key commercial targets will continue to provide a major driving force for advances in all aspects of the production of optically active materials. The future will see an interesting race between biology, conventional chemistry and separation technology; between protein engineering, unnatural product chemistry[186] and membrane science.

At present, viewed against a need to deliver multikilogramme amounts quickly and of a quality which, ideally, should be as close as possible to that from long term manufacture, so that registration can proceed rapidly, there is an in-built pressure for the industrial process chemist to use off-the-peg procedures. To start anew and develop, for example, methods of catalytic asymmetric

synthesis for reactions or substrates for which no close parallel exists is unlikely to offer success in the short term. Against the totality of examples of the manufacture of optically active materials, at the industrial level, catalytic asymmetric syntheses are still relatively scarce. Whilst they have received deserved publicity this may have led to a perception of utility which is ahead of its reduction to practice. Significant achievements have, not atypically, required 5–10 years of laboratory scale development (many decades of man years) before it was possible to contemplate scale-up. There are however targets of the 'synthon' type, intermediates for ranges of related compounds, where the commercial chemist can accept the longer timescale.

Biological methods have tended to be oversold as part of the general enthusiasm for 'biotechnology' and there has been a rather blinkered approach to parallel developments in chemistry. On a 10–15 year timescale we can expect conventional chemistry to retake ground from enzymes in the manufacture of bulk fine chemicals with the bonus of "unnatural" capabilities. The day when catalytic antibodies (abzymes)[187] can be expected to make their mark in fine chemicals manufacture still seems some considerable way off.

Crystallisation will continue to have a pivotal role, particularly at a practical level, whether it be in new resolutions by direct crystallisation of conglomerates or to furnish the very high *ee*'s being sought and which otherwise good methods fail to deliver directly.

The field is in an exciting and dynamic state with beneficial rivalry between different approaches, guaranteeing faster progress. Also, there will be synergies between the camps; for example, one method may allow facile production of a chiral auxiliary, not necessarily cheaply, which can then become part of a novel and useful catalyst. One thing that is certain—there will be advances of which we cannot even dream.

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