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Electrosynthesis

CHIRAL ELECTROSYNTHESIS FOR THE PHARMACEUTICAL INDUSTRY

by Norman L. Weinberg

The pharmaceutical industry, with annual worldwide sales of more than $200 billion, has for many years provided a wealth of opportunities for organic electrosynthesis of high value added intermediates[1]. Many of these are now commercial. The most exciting R&D is occurring in electrosynthesis of chiral drug intermediates. These are enantiomerically pure single isomers of a mixture of possible diastereomers.

Chiral drugs represent a rapidly growing industry segment: $50 billion in sales, with an estimated annual growth rate of >25%[2]. The reasons for the existence of such an impressive market for chiral drugs include: (a) they are generally safer, more effective and faster acting compared to the diastereomeric mixture; (b) usually one half or less of the dosage of the chiral form is used; (c) the chiral form of the drug offers an increase in patent protection (20 years in the USA); and, (d) if the diastereomeric mixture has already passed costly, time-consuming testing and government approvals and has been on the market, the entry into the marketplace of the chiral isomer is significantly easier.

Examples of the remarkable differences in pharmaceutical activity of chiral drugs abound: R-albuterol is an antiasthmatic, the S-form constricts airways; R,R-chloramphenicol is an antibacterial, the S,S-form is inactive; S-ibuprofen is the well known anti-inflammatory, the R-form has side effects; and S-thalidomide, the infamous teratogen of the 1960s, holds promise in the R-form for treating AIDS, leprosy and other diseases. The following article reviews progress in electrochemical methods for producing chiral intermediates.

There are at least six electrochemical routes to chiral products:

(1) Electrolysis of chiral starting materials to make new chiral products

(2) Electrolysis of non-chiral starting materials in chiral solutions

(3) Indirect electrolysis with chiral redox mediators

(4) Electrolysis of non-chiral starting materials at chiral electrodes

(5) Electrolysis of substrates with attached recyclable chiral pendant groups

(6) Electrolysis of chiral or prochiral starting materials in presence of enzymes

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Electrolysis of chiral starting materials to make new chiral products

Electrochemical transformations of this kind have been successfully demonstrated on many kinds of substrates, even complex multifunctional compounds (Fig. 1). Here, electrochemical oxidation or reduction may be the method of choice over conventional routes because of milder reaction conditions (e.g., electrolysis can be carried out near ambient temperature) and because products, in most cases, are formed with no losses resulting from racemization. At the Electrosynthesis Company we have shown this statement to be true for converting the amino acid, L-cystine to L-cysteine[3], the carbohydrate, D-gluconate to D-arabinose, the steroid, 11-ketorockogenin to a ketotigogenin precursor[4], as well as several antibiotic intermediates.

Figure 1: Electrochemical Synthesis. (a) L-Cysteine; (b) D-Arabinose; (c) Reduction of 11-Ketorockogenin; (d) Reductive Amination of Ketoavermectin; (e) Reduction of Glutaroyl-7-ACA Sulfoxide.

$$(\text{-SCH}_2\text{CH(NH}_2\text{)CO}_2\text{H})_2 + 2\text{H}^+ + 2\text{e} \longrightarrow 2\text{HSCH}_2\text{CH(NH}_2\text{)CO}_2\text{H}$$

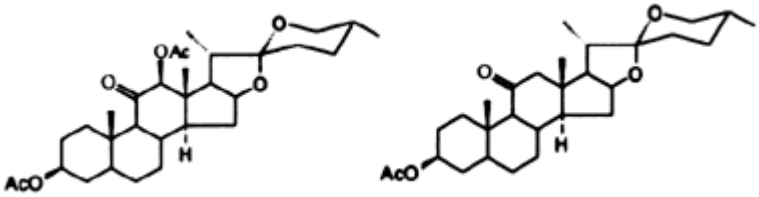
(L-cystine L-cysteine)

(a)

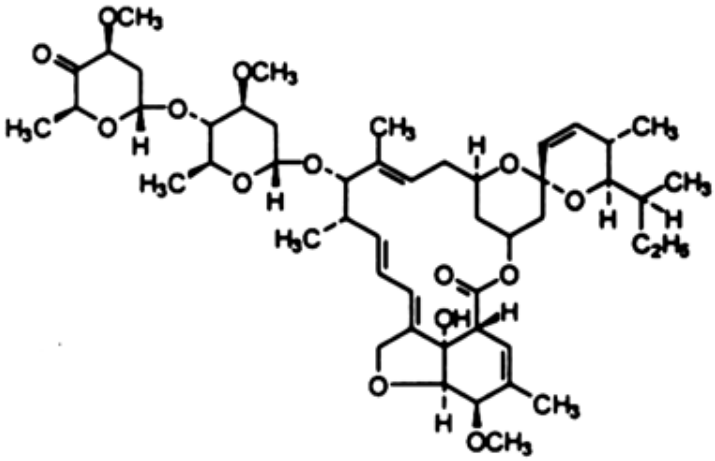
$$\text{C}_6\text{H}_{12}\text{O}_7 \longrightarrow \text{C}_5\text{H}_{10}\text{O}_5 + \text{CO}_2 + 2\text{H}^+ + 2\text{e}$$

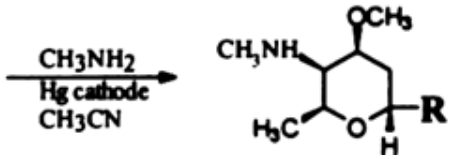
(D-gluconic acid D-arabinose)

(b)

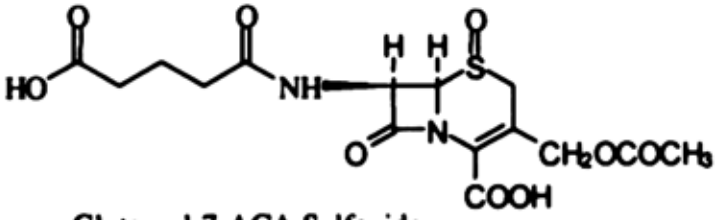


(c)

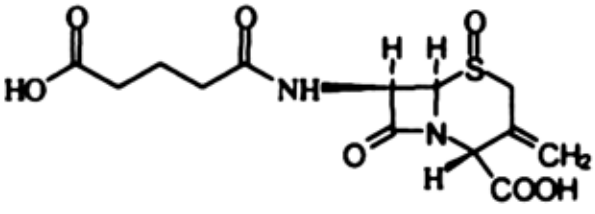




(d)



Glutaroyl-7-ACA Sulfoxide



Exomethylenecepham Sulfoxide

(e)

Workers at Merck have demonstrated electrochemical reductive amination of multifunctional ketoavermectin as well as oxidative decarboxylation of azetidinone carboxylic acid to produce an intermediate to the antibiotic thienamycin[5], both in good yield. Schering-Plough in conjunction with other groups recently reported the electrochemical reduction of cephalosporin C derivatives to valuable exomethylenecephams, which are needed to access antibiotics such as ceftibuten and cefaclor[6].

Electrolysis of non-chiral starting materials in chiral solutions

Chiral products can be made by providing a chiral additive or supporting electrolyte in solution. These additives induce chirality by coadsorption, hydrogen bonding, complexed redox reaction or other mechanism so that subsequent cathodic reduction or anodic oxidation of the starting material leads to chiral products. To date, this method has been investigated by many workers with only limited success and generally with enantiomeric excesses reported in the <20% range; however, indications are that a much better understanding of the reaction variables (concentrations of reactants, temperature, pH, electrode material, and electrode potential, etc.) could lead to greatly improved results. An encouraging example of this kind (Fig. 2) is reduction of 4-methylcoumarin in presence of a catalytic amount of the chiral alkaloid yohimbine. The dihydrocoumarin is formed in 55% yield and 60-70% enantiomeric excess at pH 2 and a cathode potential of -1.5V *vs.* SCE, along with the dimer (5% yield); whereas at higher pH and more negative potential, the yield of the dihydrocoumarin was 57%, but with only 12% enantiomeric excess[7].

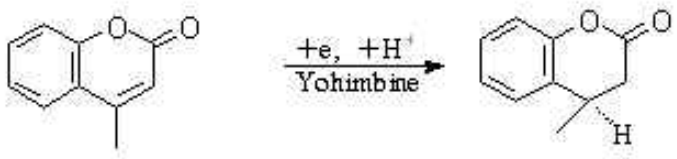


Figure 2: Enantioselective cathodic reduction of 4-methylcoumarin.

Indirect electrolysis with chiral redox mediators

In contrast, use of chiral redox agents in solution has been very promising (Fig. 3). Osmium tetroxide has long been known as an excellent oxidant for converting olefins to diols. Using a chiral ligand with only catalytic quantities of Os (VIII) present and using either ferricyanide or iodine as a co-redox species, olefins have been converted to chiral diols in impressive yield and high enantiomeric excess[8]. Vitamin B_{12}, which is already a chiral redox reagent, non-toxic and inexpensive, has been shown to be a potentially valuable reagent in the electrosynthesis of prostaglandin intermediates[9].

Figure 3: (a) Chiral diols by Os-catalyzed anodic oxidation of olefins; (b) B_{12} catalyzed synthesis of prostaglandin intermediate

(a)

ORGANIC PHASE: $[OsO_4 + L \longrightarrow Complex]$

$[Complex + Olefin \longrightarrow Osmate\ Ester]$

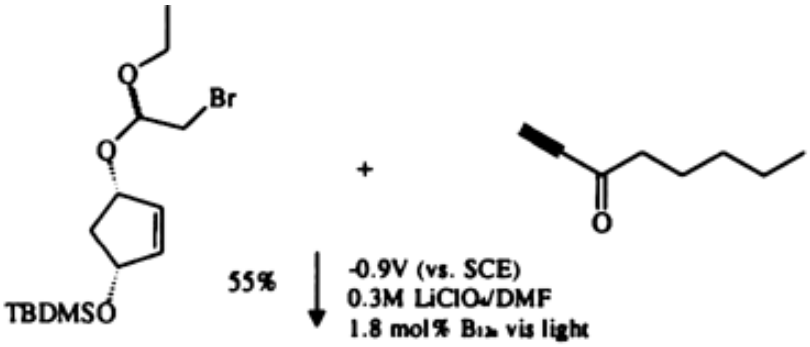
Cyclohexane $\longrightarrow$ $[Osmate\ Ester + 2OH^- \longrightarrow Diol + OsO_4^{2-} + L$

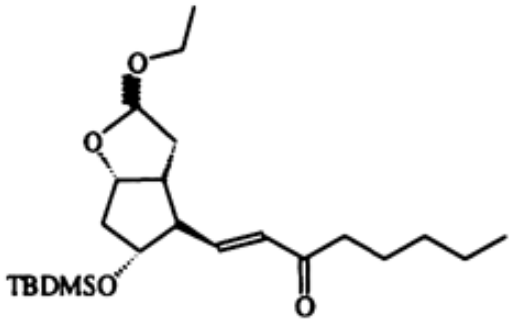
AQUEOUS PHASE: $2[Fe(CN)_6^{3-}] + OsO_4^{2-} \longrightarrow 2[Fe(CN)_6^{4-}] + OsO_4$

At anode: $2[Fe(CN)_6^{4-}] \longrightarrow 2[Fe(CN)_6^{3-}] + 2e$

At cathode: $2H_2O + 2e \longrightarrow H_2 + 2OH^-$

Overall: $Olefin + 2H_2O \longrightarrow diol + H_2$





(b)

Electrolysis of non-chiral starting materials at chiral electrodes

Chiral electrodes have been prepared in a number of ways[10], including by adsorption or by chemical attachment of chiral substances to electrodes. Chiral product enantiomeric excess is so far limited to about 50% or less, so that with some increased understanding of the substrate–electrode interface, the reaction variables and the mechanism of product formation, this method too could be greatly improved.

Electrolysis of substrates with attached recyclable chiral pendant groups

An interesting example of the use of chiral auxiliaries attached to substrates is shown in Fig. 4[11]. The cinnamate ester, electrochemically hydrodimerized in a solution of DMF/Et_4NBr, forms an all trans ester as a 5-membered ring (a result of intramolecular cyclization caused by simultaneous base formation at the cathode), in >95% yield. The nature of the R-group has a remarkable effect on the *ee* value: for R- menthyl, 0%; R- methyl o-cinnamoyl, 44%; and, R- endo-bornyl, >95%. An important added feature of this approach is that the ester groups are removable and recyclable.

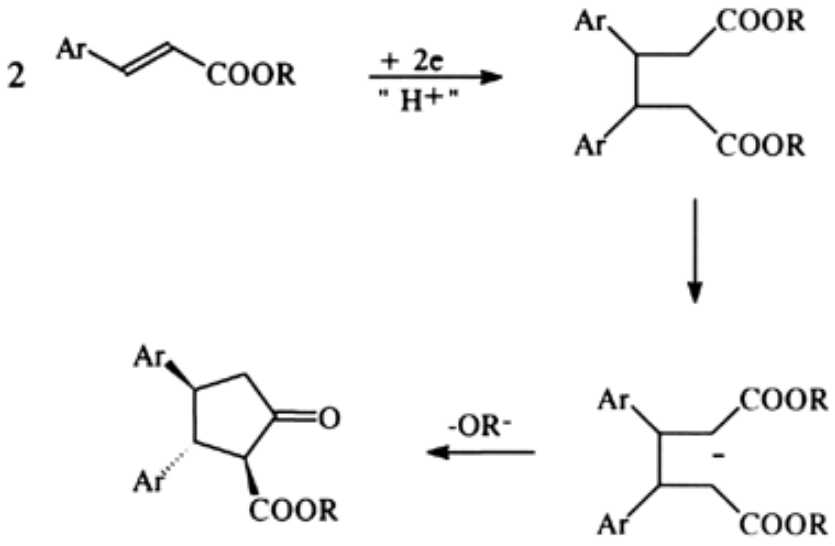


Figure 4: Chiral products via recyclable chiral ester groups.

Figure 4: Chiral products via recyclable chiral ester groups.

Electrolysis of chiral or prochiral starting materials in presence of enzymes

Electroenzymatic processing is a relatively new approach, but is already showing great promise in the research being published[12]. Commercialization is only possible provided production rates (current densities) can be improved and turnover numbers are sufficiently high to enable economical use and regeneration of expensive enzymes and cofactors. The non-electrochemical literature is filled with many useful and important enzymatic reactions, such as chiral formation of alcohols from methyl groups, and epoxides, alcohols, and amines from olefins to name only a few. Many of these transformations have no electrochemical analogy and all proceed in remarkably high yield producing enantiomerically pure

products. The trick is to link the extraordinary capabilities of enzymes with the power of electrochemistry. The rewards include: regiospecific reactions; enantiomerically pure products suitable for drugs; a variety of unusual transformations in high yield from inexpensive substrates; significantly easier separation of products compared to bioenzymatic reactions; and, processes which have fewer environmental problems. Figure 5 shows a few examples of electroenzymatic reactions.

Substrate	**Product**
pyruvic acid (CO_2)	L-lactic acid
pyruvic acid (NH_3)	L-glutamic acid
2-butanol	2-butanone
2-hexen-1-ol	2-hexanol
p-hydroxybenzylalcohol	p-hydroxybenzaldehyde
p-ethylphenol	a -hydroxyethylphenol (99% ee)
ß-D-glucose	D-gluconic acid
sugar alcohols	non-natural L-carbohydrates

Figure 5: Examples of electroenzymatic synthesis.

Conclusions

Organic electrosynthesis is an evolving field, with many commercial examples already in place and many more possibilities under exploration in laboratory and pilot stages. These offer unique synthesis of valuable intermediates, particularly for drugs. The opportunities increase as more sophisticated, off-the-shelf, multipurpose cells become available and as the industry expands its knowledge base, engineering and experience to move quickly from lab to piloting and into commercial production.

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Dr. Weinberg has been intrigued with the beauty, simplicity, and inherent environmentally friendly nature of electrochemistry since his Ph.D. work in 1963 on electrosynthesis. Since then, he has authored many technical papers and reviews and holds many patents in various electrochemical areas. Recent books include *"Electrochemistry for a Cleaner Environment"* co-edited with Dr. David Genders (1992, Electrosynthesis Co.) and *"Electroorganic Synthesis"*, co-edited with Prof. Daniel Little (1991, Dekker).

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