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Advances in AIDS Chemotherapy: The Asymmetric Synthesis of CRIXIVAN®

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Abstract. The discovery and development of an efficient, practical asymmetric synthesis of the HIV Protease inhibitor CRIXIVAN® is described. Particular emphasis is placed on the selective installation of each of the five stereogenic centers as well as design strategies associated with the preparation of a complex pharmaceutical agent needed in multiton quantities.

The orally active HIV Protease inhibitor CRIXIVAN® (Indinavir Sulfate, MK-0639) [1] is one of an exciting class of new drugs for the treatment of AIDS. The five stereogenic centers permit the statistical possibility of 2^5 or 32 stereoisomers of which a single, pure enantiomer must be produced (Scheme 1). The convergent strategy of using a three carbon linker to join the 'western' piperazine fragment with the 'eastern' indanolamide has proved quite successful, especially on the multiton scale required. In order to avoid the formation of diastereomers, each fragment must be prepared in nonracemic form!

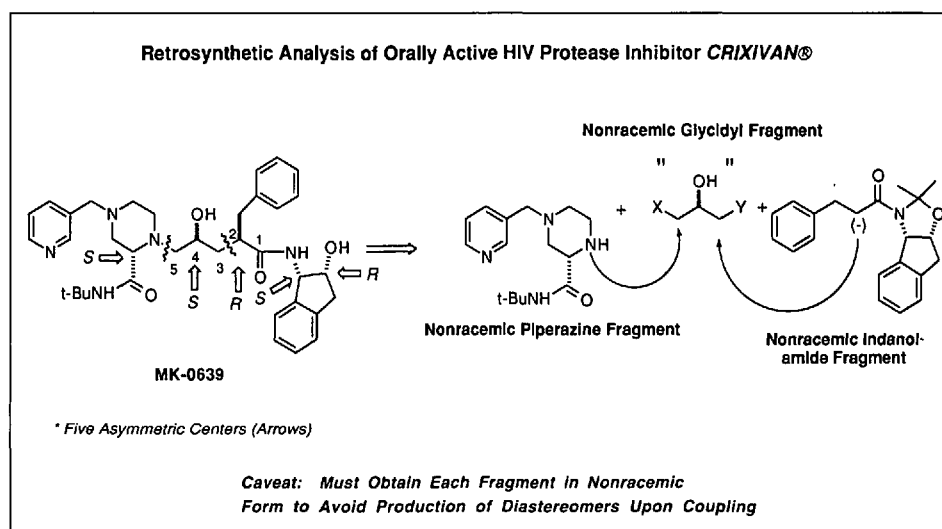
In addition, synthesis on this scale requires a thoughtful choice of starting materials with availability assured at a level typically unheard of in the pharmaceutical industry. While not quite forcing us back to earth, air, fire, and water, the retrosynthetic analysis (Scheme 2) centers around two enantiomerically pure building blocks: (–)-*cis*-Aminoindanol and the (*S*)-piperazine-1-carboxamide. The three carbon linker comes from allyl bromide.

A great deal of work has been done in developing practical syntheses of (–)-*cis*-(1*S*,2*R*)-1-aminoindan-2-ol [(–)-CAI]. Scheme 3 depicts the conversion of indene to indene oxide (87% ee) via the Jacobsen (*S,S*)-Mn(II)-salen catalyst [2] as well as the biotransformation of indene to optically pure indan-1,2-diol. Both the epoxide and the diol undergo a unique Ritter reac-

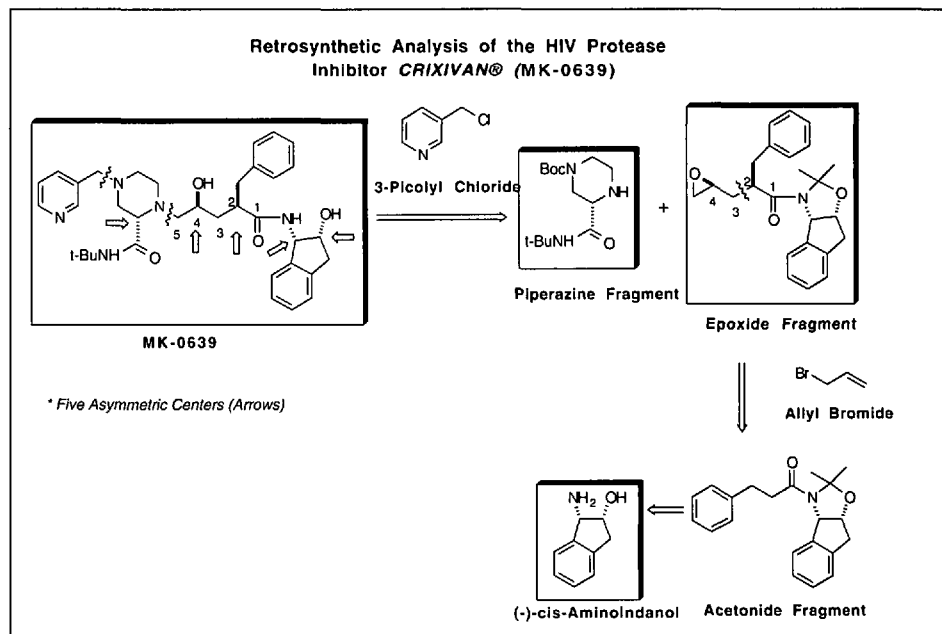
tion [3] with acetonitrile to produce the *cis*-aminoindanol while completely retaining their enantiomeric purity.

Once the stereochemical information is established in (–)-CAI, it is then used to control the two central stereogenic centers. A single-pot amidation and acetone formation (Scheme 4) is used to generate an amide whose enolate can be stereospecifically allylated to produce a latent equivalent of the desired epoxide (Scheme 5) [4]. The newly formed center has the desired (pro-2*R*)-configuration. Careful conversion of the pendant olefin to an iodohydrin occurs with yet another efficient transfer of stereochemical information. This permits establishment of the desired (*S*)-configuration of the C(4)–OH (Scheme 6). Conversion of the iodohydrin to the homo-chiral epoxide is virtually quantitative.

Scheme 1

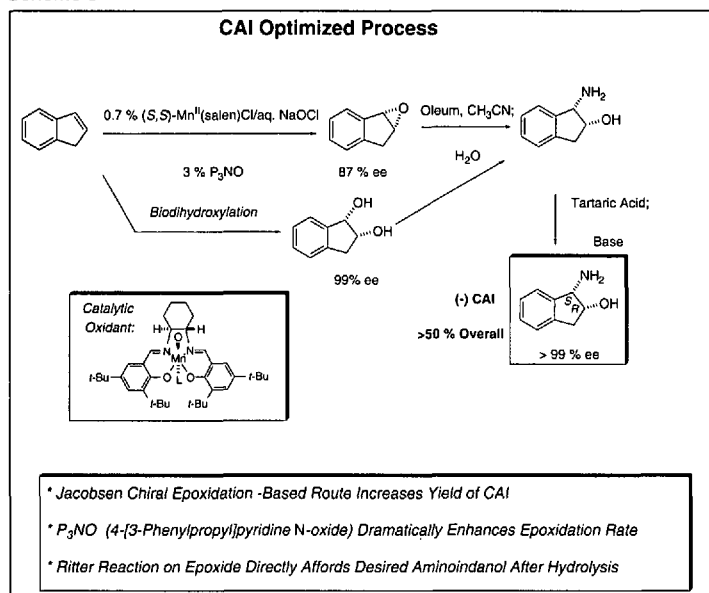


Scheme 2

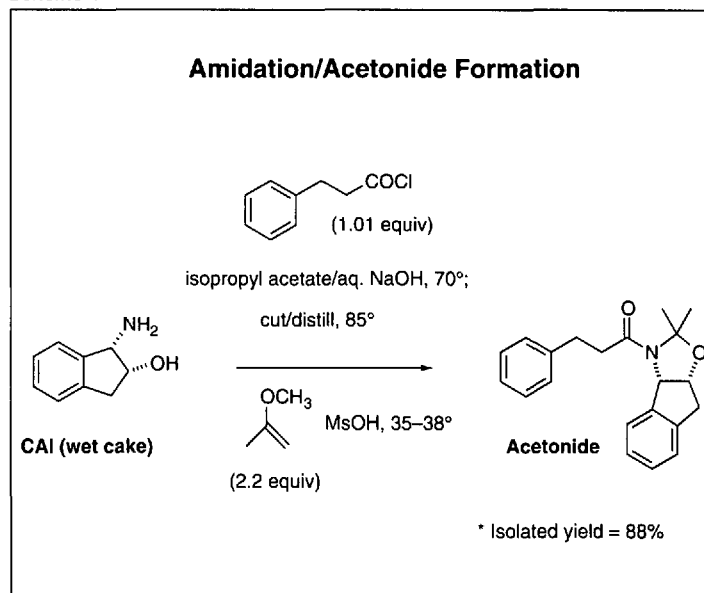


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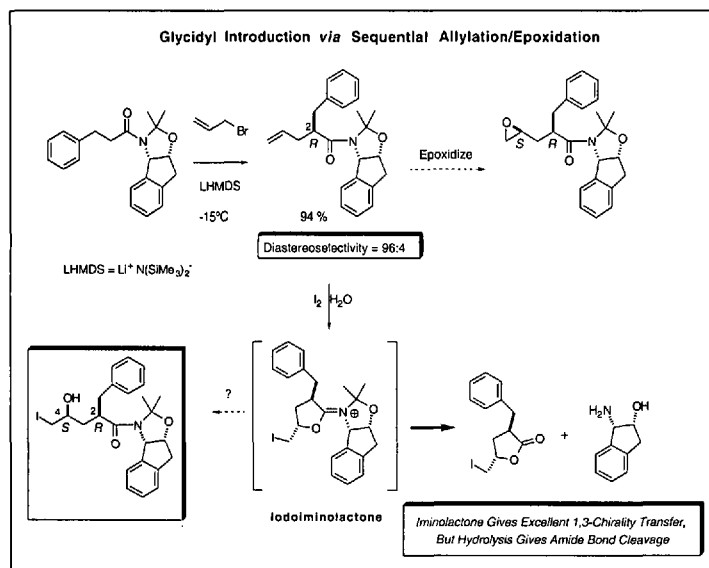
Scheme 3



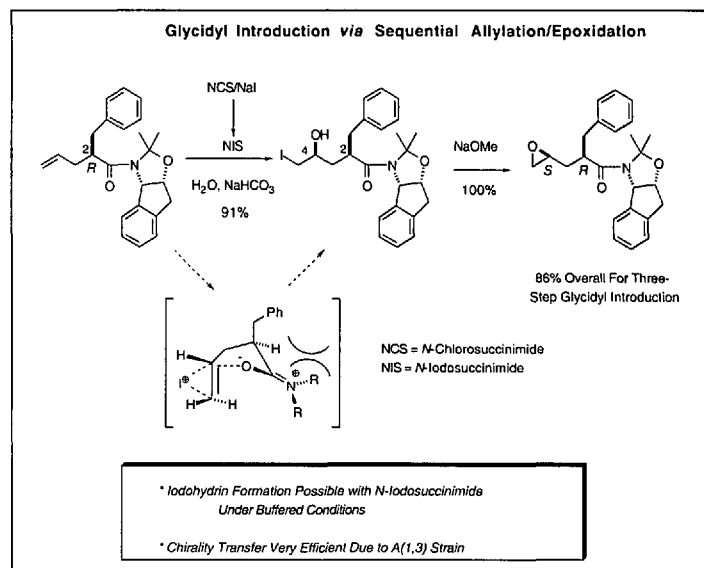
Scheme 4



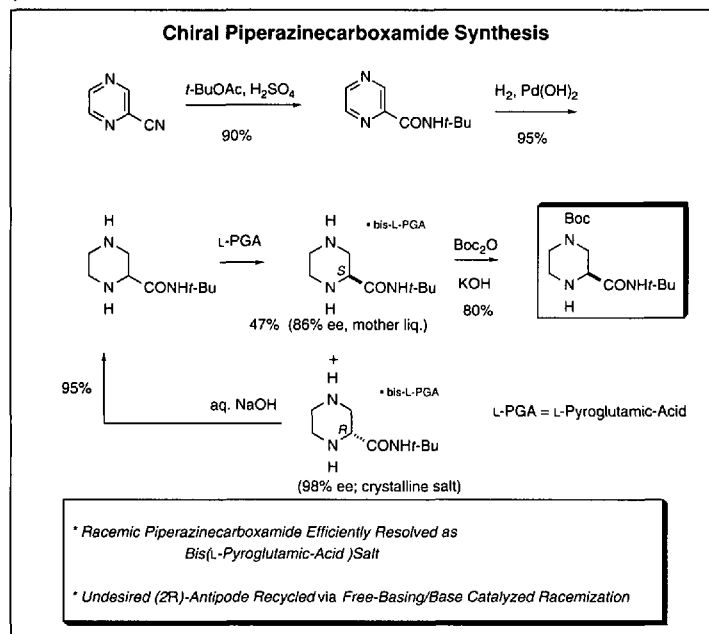
Scheme 5



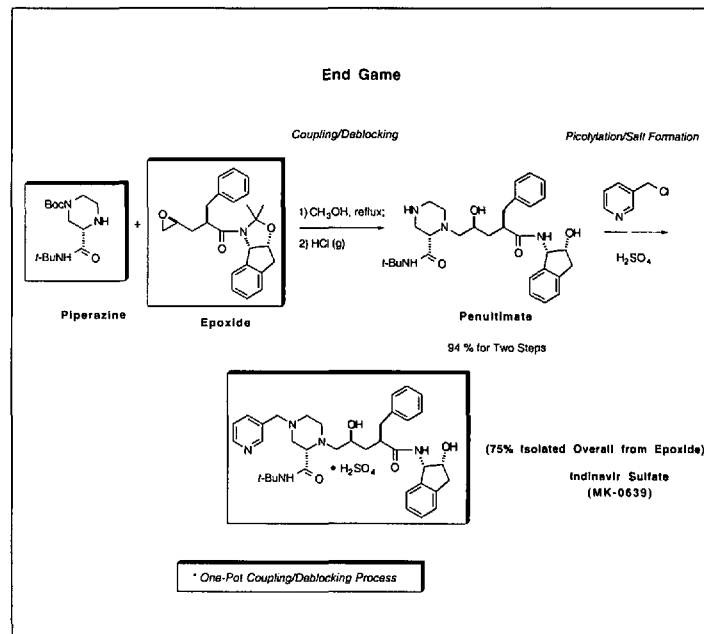
Scheme 6



Scheme 7



Scheme 8



The western piperazine fragment is derived from a readily available pyrazine by reduction of the aromatic ring. While we have had success with both asymmetric catalytic reduction and enzymatic routes to the required (*S*)-piperazinecarboxamide, the method of choice is a classical resolution/racemization. Resolution is achieved by crystallization of the bis(*L*-pyroglutamic-acid) salt. The undesired enantiomer is then racemized with base and recycled. Selective acylation (Boc_2O) at the distal nitrogen yields the piperazine ready for coupling (Scheme 7).

Simply heating the two key fragments (piperazine + epoxide) followed by removal of the Boc group from the distal nitrogen produces the penultimate inter-

mediate in 94% yield. Alkylation with picolyl chloride and sulfate salt formation give Indinavir Sulfate, the active ingredient of *CRIXIVAN*[®] with greater than 99% enantiomeric and chemical purity (Scheme 8).

The chemistry described here is the work of an heroic team of scientists whom I have the honor to represent. I would especially like to acknowledge the team leaders from Merck's Process Research Department: Drs. David Askin, Thomas R. Verhoeven, and R.P. (Skip) Volante; they and their colleagues have much to be proud of.

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Application of Enzymes in Industrial Organic Synthesis

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Abstract. Aminopeptidase- and amidase-based methods for the production of enantiomerically pure amino acids, intermediates for pharmaceuticals and agrochemicals, are discussed. Furthermore, enzymatic syntheses of the dipeptide sweetener aspartame and semisynthetic antibiotics (such as ampicillin, amoxicillin, cephalexin, and cefadroxil) are highlighted.

Introduction

There is an ever increasing demand for enantiomerically pure compounds used as building blocks but also as active ingredients in the pharmaceutical and agrochemical industry. In addition to relying on the existing chiral pool, production methods include resolution processes *via* diastereomeric salt formation, asymmetric homogeneous catalysis, asymmetric synthesis, and kinetic resolution processes with enzymes. In this paper, we will concentrate on the use of amidases and aminopeptidases in (industrial) synthesis. In addition, recent results with further transformations of unsaturated amino acids will be discussed.

Kinetic Resolutions with Aminopeptidases and Amidases

α -H-Amino Acids

Amino acids have proven to be a versatile class of intermediates for a wide variety of enantiomerically pure pharmaceuticals and agrochemicals. Classical exam-

ples include D-phenylglycine and D-(*p*-hydroxyphenyl)glycine, used as building blocks for semisynthetic antibiotics, and L-phenylalanine, one of the constituents of the dipeptide sweetener aspartame. Production capacities for these types of applications typically are in the order of thousands of tons per year. Other amino acids, produced on a somewhat smaller scale, are utilized in various pharmaceutical and agrochemical applications. For example, D-valine is used in the synthesis of the pyrethroid insecticide fluvalinate.

Whereas the naturally occurring amino acids can often be most conveniently produced using microbial production methods (fermentation), synthetic amino acids or amino acids with the nonnatural D-configuration have to be prepared using chemical or chemo-enzymatic techniques. One particularly useful approach, discovered by DSM in 1975, is the use of an aminopeptidase present in *Pseudomonas putida* ATCC 12633 according to Scheme 1.

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Scheme 1

