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Resolution, chiral synthesis or what? Studies in alkaloid chemistry*

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Abstract: Experiences show that important biological activities of chiral natural products are related with their absolute configuration therefore the methods providing single enantiomers are of utmost importance. The question is, what are the best known methods to produce them? To try to answer that essential question the lecture is going to present some experiences gained while working on the total synthesis of several important alkaloids.

Chiral natural products are usually found as single enantiomers. That is the case with alkaloids as well. A total synthesis can be regarded as complete, only after the appropriate enantiomer is in our hand. Experiences show that important biological activities usually are also related to the absolute configuration of a given chemical entity, therefore the methods providing them are of utmost importance also in the pharmaceutical industry.

> 'We have witnessed a growth in the value of single enantiomer drugs from less than US$5 billion in 1985 to over 55 billion in 1997. This value is projected to grow 100 billion by the year of 2000. As a percentage of total pharmaceutical sales, single enantiomer drugs have grown from less then 10% in 1985 to 25% in 1995' [1]

The question is, what are the best known methods to produce single enantiomers? Resolution, enantioselective synthesis or what? Before answering that important question I should like to quote some of our experiences gained during our synthetic efforts in the alkaloid field.

SYNTHESIS OF IPECACHUANA ALKALOIDS

Among the *Ipecacuanha* alkaloids emetine is the most important, which has been used for treatment of amoebic dysentery and other ailments since the beginning of this century. Its commercially feasible total synthesis is therefore an attractive goal. In this respect especially the work of Brossi, and Openshaw & Whittaker should be emphasized.

We found an easy way to synthesize the intermediate benzoquinolizidine ketone (Scheme 1). This is the first chiral entity in the synthetic sequence which one has to deracemize in order to perform an economic approach. Boiling it with natural tartaric acid in acetone an asymmetric induction of the second kind occurs and we obtain the required enantiomer in over 90% yield [2]. This is a very rare case of an asymmetric induction of the second kind where two stereogenic centres change at the same time.

SYNTHESIS OF YOHIMBINE ALKALOIDS

When a similar reaction to that depicted in Scheme 1 was performed using 3,4-dihydro-β-carboline instead of dyhidroiso-quinoline, indoloquinizidines were obtained.

In order to build up the yohimbine skeleton, another functionality at the side chain was needed. Thus we used a ketoester derivative as the appropriate precursor. Using similar technique as in the case of emetine

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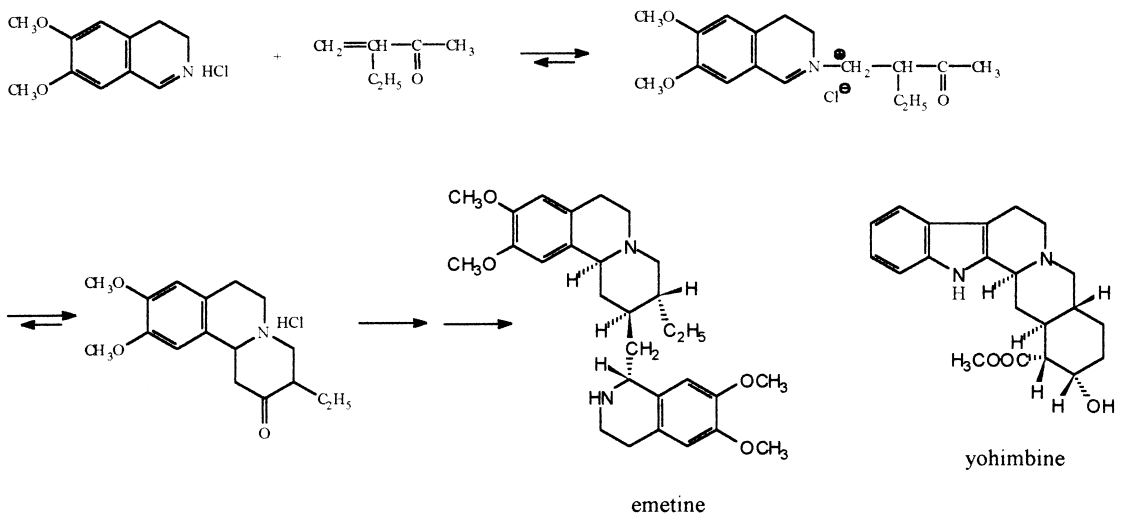


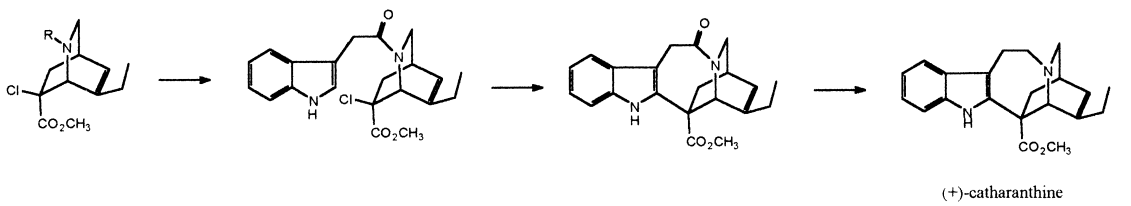
Scheme 1

synthesis, the racemic ketoester was transformed in a procedure applying asymmetric transformation of the second kind into optically active product (enantiomer excess 90%) with the help of (+)-tartaric acid. The obtained ketoester has the correct absolute configuration for all of yohimbines (Scheme 1).

SYNTHESIS OF ALKALOIDS FROM *CATHARANTHUS ROSEUS*

The alkaloid vinblastine and vincristine are widely used in the chemotherapy of cancer. They are presumably synthesized in the plant through a coupling of the alkaloids catharanthine and vindoline. The total synthesis of these alkaloids has been realized by the outstanding achievements of Potier, Kutney, Kuehne, Atta-ur-Rahman and other excellent scientists, mainly through the coupling of the monomeric alkaloids. Since the vindoline content of the plant is far higher than that of catharanthine, the total synthesis of the latter was an important challenge to solve.

At the outset 3-ethylpyridine was reduced and acylated followed by a Diels–Alder reaction with α-chloro-acryloyl chloride. After esterification, deprotection and acylation, the desired amide was obtained. The latter compound was transformed by irradiation to the cyclized product, which was reduced by $NaBH_4/BF_3$ system in one step and in almost quantitative yield to racemic catharanthine (Scheme 2).

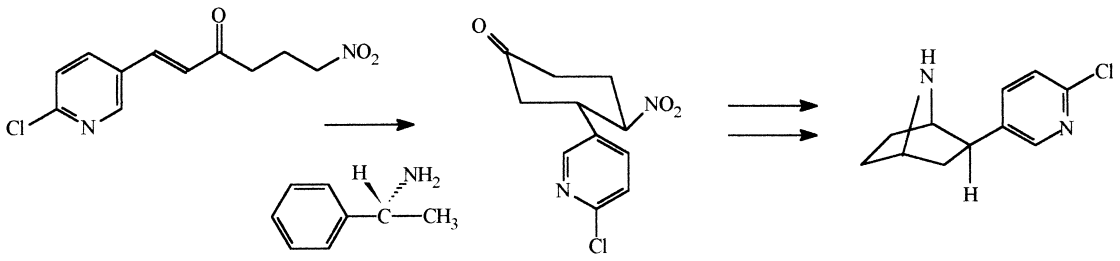


Scheme 2

In this particular case the resolution proved to be the most practical, which was performed at an early stage, i.e. before the indole part was introduced, in good yield, with the isoquinuclidine base using (+)-dibenzoyl-D-tartaric acid. By this short sequence the first total synthesis of the natural, optically active (+)-catharanthine was achieved.

SYNTHESIS OF EPIBATIDINE

Epibatidine was isolated from the skin extract of an Ecuadoran poison frog *Epipedobates tricolor* in 1992 by Dali *et al*. and proved to be several hundred times more potent as analgesic than morphine and operates *via* a nonopiod mechanism (Scheme 3).

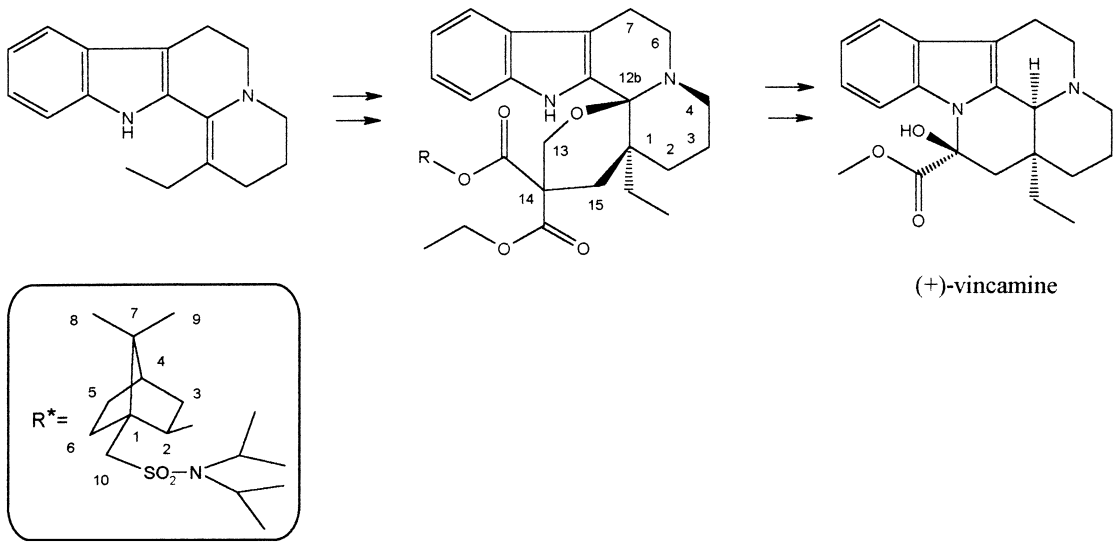


Scheme 3

The main goal of our strategy was to create a practical route to the natural epibatidine on a large scale Hence we used commonly available starting materials, and well controllable chemical transformations. Our enantioselective synthetic approach was based upon the enantioselective intramolecular Michael addition of prochiral precursor, leading to the chiral ketone, induced by chiral bases. Up till now α-phenylethylamine enantiomers have proved to be the best bases to catalyze the enantioselective reaction. The cyclized product was obtained in over 80% enantiomer excess, then transformed into the natural epibatidine [2].

SYNTHESIS OF VINCAMINE

(+)-Vincamine (Scheme 4), an alkaloid, isolated from *Vinca minor,* proved to be a useful pharmaceutical, and is on the market as a specific brain vasodilator agent. One of our approaches started from natural L-tryptophane, which was converted to (+)-vincamine [3]. Another route starts from the achiral but prochiral enamine. The isoborneol derivative, prepared by Oppolzer, was acylated with ethyl malonyl chloride giving rise to the derived compound. The components and formaldehyde were allowed to react in ethanol at ambient temperature. From the clear solution after 3 days the adduct crystallized in 82% yield.



(+)-vincamine

Scheme 4

Catalytic reduction of the latter compound afforded the hydroxymethyl derivative with high diastereoselectivity. Removal of the hydroxymethyl group was easily and quantitatively achieved by treatment with silica gel. Hydrolysis of the ester and partial decarboxylation gave the key precursor of vincamine in 96% enantiomeric purity. The combined chemical yield based on enamine was the excellent 78%. The chiral auxiliary was recovered in good yield [3].

SUMMARY

In the above discussed syntheses we have used the following techniques:

A *Asymmetric induction of the second kind* (Ipecacuanha alkaloids, e.g. (–)-emetine (–)-cephaeline, (–)-protoemetine, Yohimbine alkaloids, e.g. (+)-yohimbine (–)-β-yohimbine),

B *Classical resolution in early stage* (e.g. (+)-catharanthine),

C *Precursor from natural chiral pool* (e.g. (+)-vincamne from L-tryptophan),

D *Applying chiral auxiliary* (e.g. (–)-menthol or bornane derivative for (+)-vincamine),

E *Catalytic enantioselective synthesis* (applying R-α-phenylethylamine for (–)-epibatidine).

We may conclude that almost every special problem has its own individual solution if we take the practicality and economy of the synthesis into account.

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