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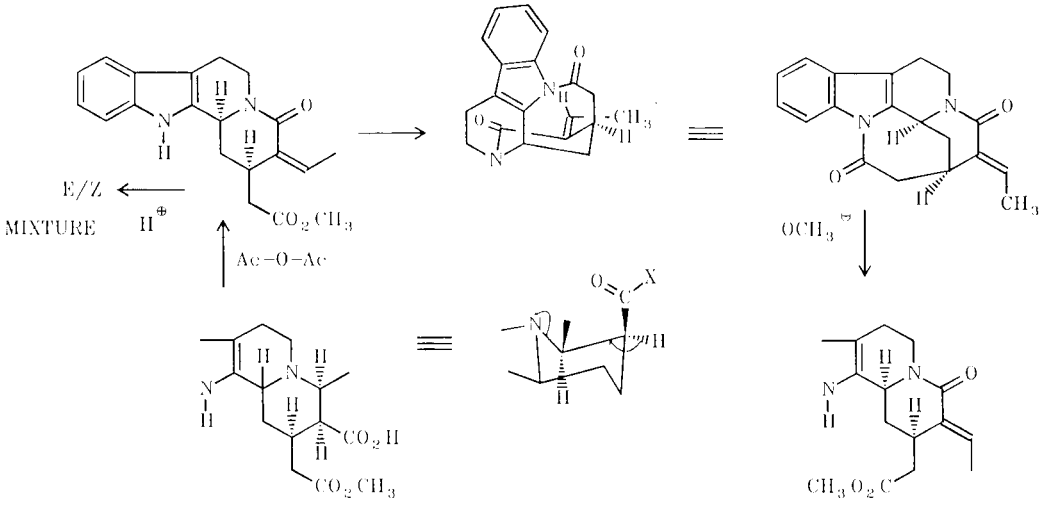
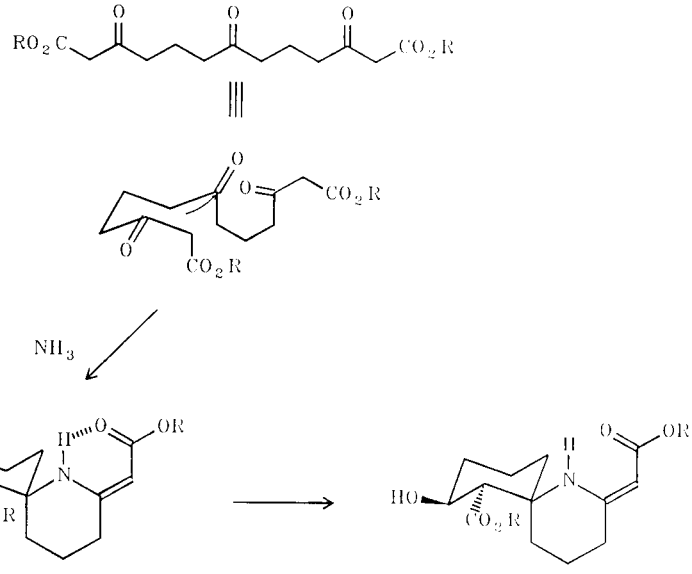
As directed and predictable stereoselectivity is of high importance for an efficient synthesis of pure diastereomers and enantiomers, this approach is of particular importance for synthetic operations aiming at a wide selection of stereoisomers in both series of absolute configurations. Investigations of this type are generally necessary, whenever the relationship between a biological activity and the relative or absolute configuration of the corresponding chemical compound has to be elaborated and one is also very often

Scheme 1

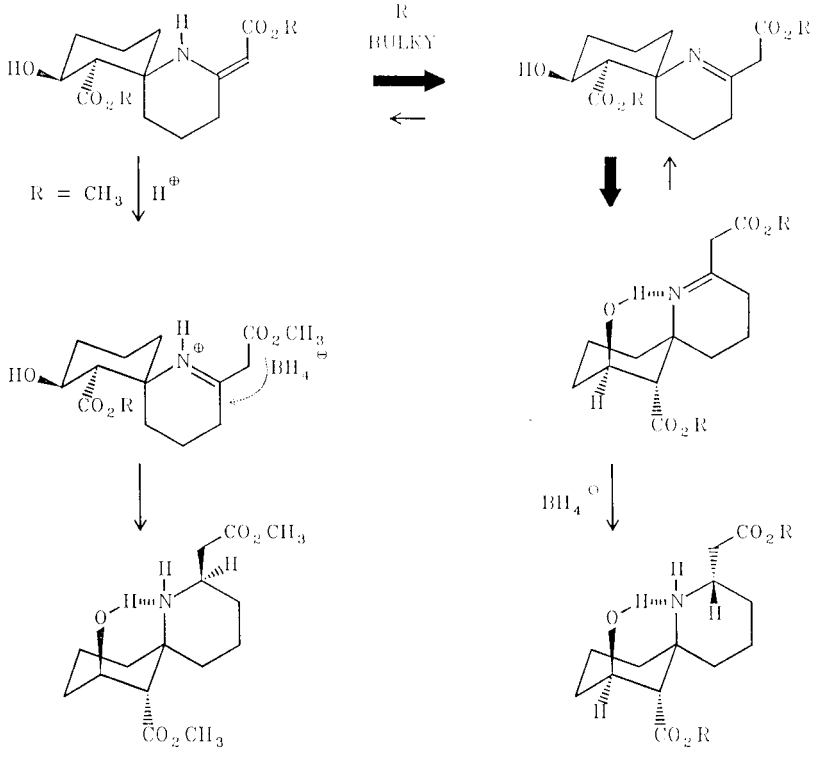



Scheme 2

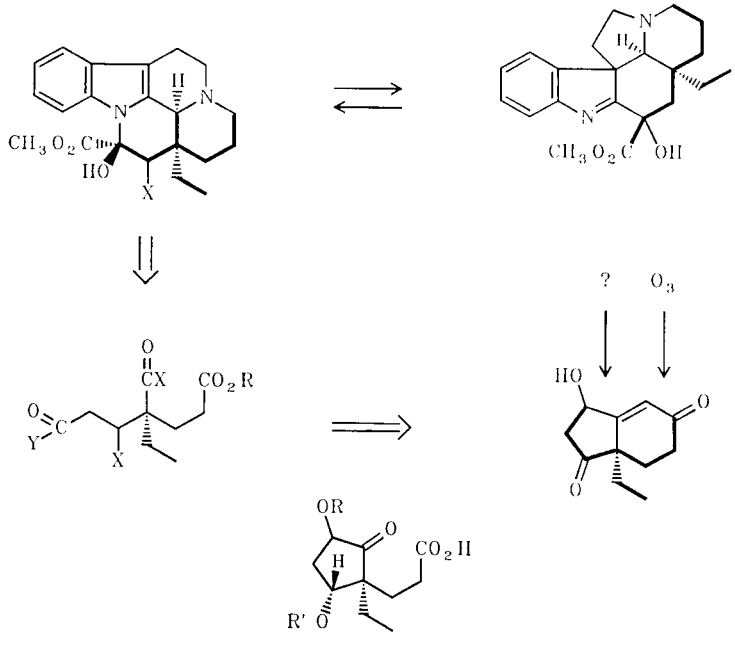


confronted with this problem in natural product synthesis as in many cases nature provides quite a range of diastereoisomers in a given series of natural products. Just as an introduction and to illustrate the problem the lecture starts with two examples from our earlier work in alkaloid synthesis. We decided to introduce the exocyclic double bond, which is very typical for the corynanthe series, at the lactam stage, as indoloquinolizidones of this type are much more stable than the corresponding quinolizidines and as

Scheme 3



Scheme 4



assignment of double bond configuration is particularly easy with these intermediates (nmr spectroscopy). A very simple approach to these intermediates makes use of the methylene-lactam rearrangement (see **Scheme 1**) starting from the corresponding amino acid and if one operates under kinetic control the Z-configuration will of course be highly favored.

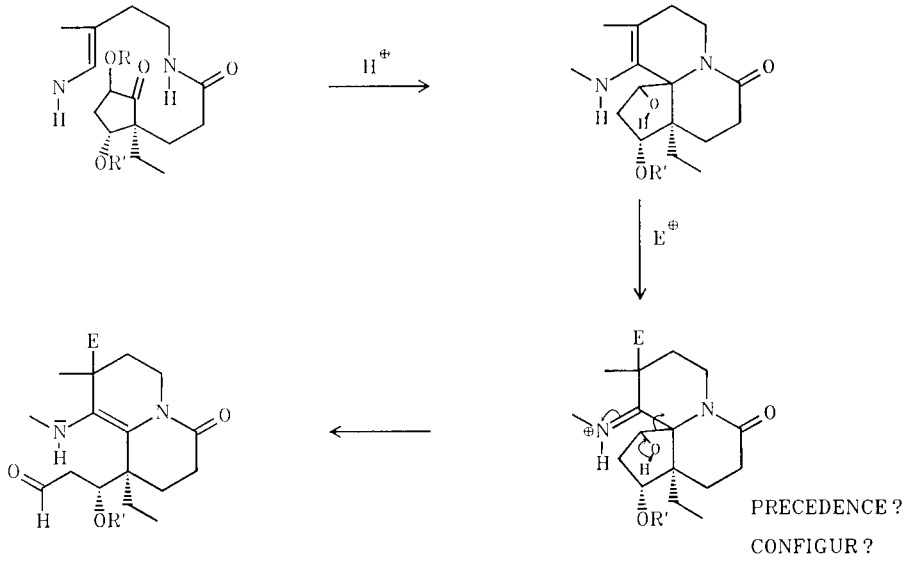
Unfortunately, this configuration is present only in very few and less important alkaloids. When we tried to isomerize to the *E*-configuration under acidic conditions we ended up with a not easily separated *E*/Zmixture. When the compound, however, was forced into the 1,3-diaxal conformation of an acyl indole, thus removing the ester side chain from the plane of the double bond, the desired *E*-configuration was established exclusively. One easily could generate the corresponding indoloquinolizidones by nucleophilic ring opening of the acylindole moiety.

In the second example we deal with the quite important $sp^3$-carbon-2-configuration of the spiropiperidine alkaloids. Synthetically quite flexible spiropiperdines can be easily prepared from 1,5-triketones as demonstrated in **Scheme 2** and as long as the nitrogen has only poor basicity even the alcohol prefers the all-equatorial conformation (no hydrogen bond). Under these conditions reduction of the exocyclic double bond with borohydride needs acid-catalysis and gives rise to α-attack as the frontside is hindered by the equatorial ester group. If the ester group is made very bulky, however, ( *tert*-butyl alcohol, borneol) this large group shifts the vinylogous urethane very much to the side of the imine, thus enhancing the basicity and leading the molecule into the hydrogen bond stabilized conformation which is then of course attacked by the borohydride from the front-side to generate the natural product configuration in this series (**Scheme 3**). Needless to add that this process will not need any acid catalysis which simplifies the former two-stage reduction process.

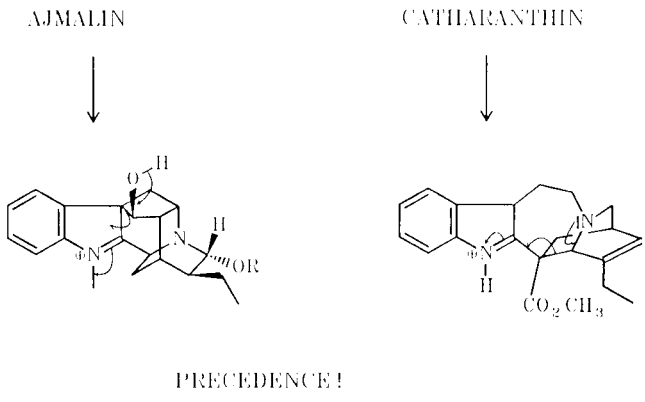
For a more complicated case now let us focus on the enantioselective synthesis of indole alkaloids from easily available hydrindaneones, that were synthesized according to the Hajos-Wiechert protocol for the industrial synthesis of norgestrel. As the iboga structure of the indole alkaloids and the aspidosperma framework can easily be interconverted by rearrangement reations, an approach to the first one also provides access to the second and *vice versa*. As the formula, (**see Scheme 4**), indicates, nearly all the carbon atoms of the diketone will be needed and the only chemical problem is the opening of the rings. This looks easy for the six-membered one (presence of a double bond) but is much less obvious for the cylopentanone. So we were not surprised at all to note that when after the disclosure of the general approach at a Reisenburg Conference in1983 Professor Takano from Japan reported a synthesis along these lines in 1986, the opening of this ring took quite a number of troublesome reactions.

In our own planning an early opening of this bond actually had never been considered as we were convinced that the cyclization product which is available as indicated in **Schemes 8 and 9** should easily undergo a retro-aldol process on attack of electrophiles in the β-position of the indole (**Schemes 5**

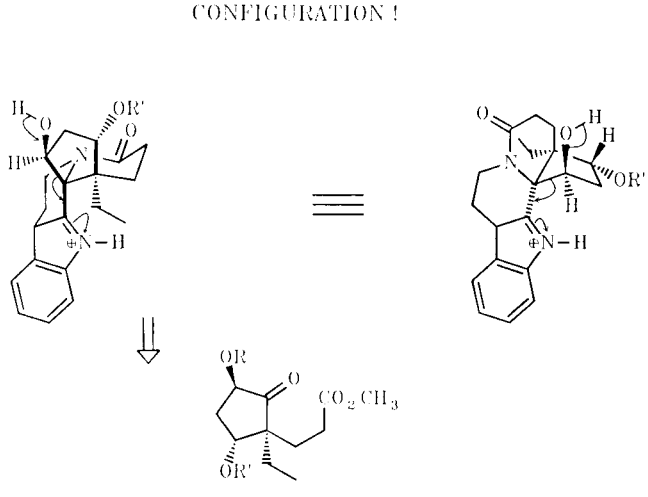
Scheme 5



Scheme 6




Scheme 7

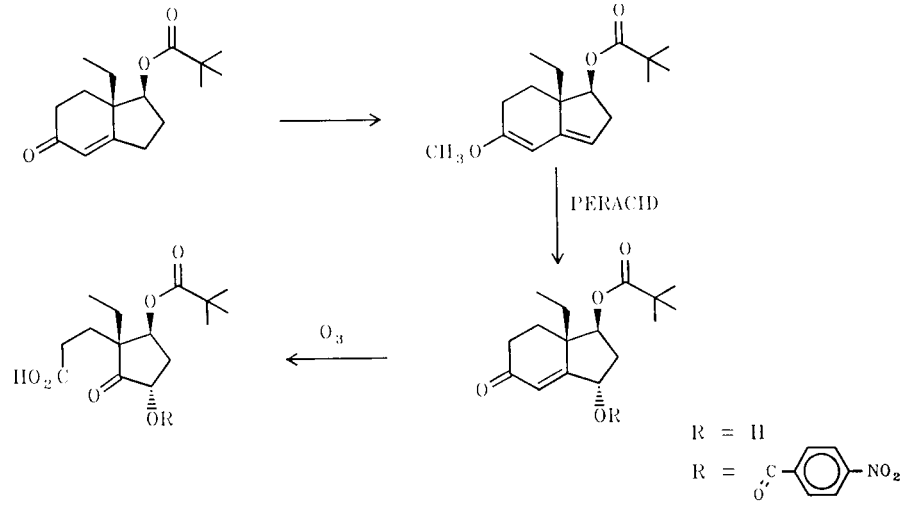



**and 6**), if the correct α-configuration of the free hydroxy group could be provided for maximum overlap (**see Scheme 7**).

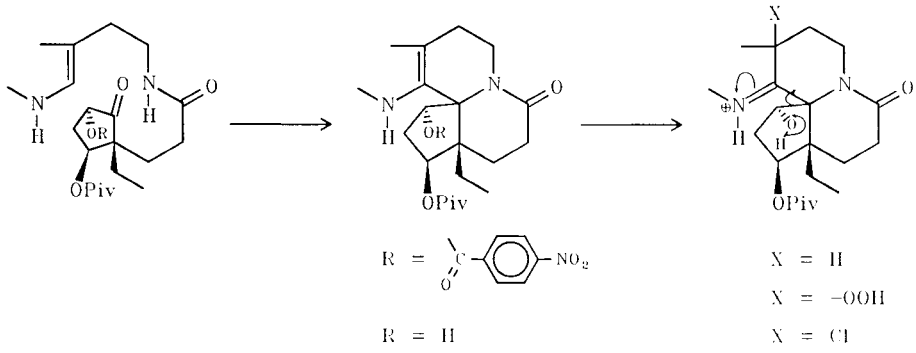
Fortunately, to establish this α-configuration turned out to be very easy (see **Scheme 8**) and as additionally the literature provides well established examples of ring-opening processes of this type (**Scheme 6**) we expected no problems for this transformation. In the event it turned out that the reversible process of protonation (X = H) did not trigger the retro-aldol process but that this step was nicely initiated by an irreversible halogenation reaction (X = Cl, **Scheme 9**). As was easily proven by ir and nmr-spectra the aldehyde group generated, as expected, did immediately combine with the indole nitrogen to form a seven-membered ring (see **Scheme 10**). Having achieved this goal the crucial question arises how to configurational direct the reduction of the acyliminium salt which is formed on extrusion of the halogen atom from the benzylic position. For the non natural α-configuration this poses no problem, whatsoever, as ethyl group and pivalate protect the β-side very efficiently. For the natural β-configuration we made use of the tris-acetoxyborohydride introduced by D. Evans as a purely intramolecular reducing reagent (see **Scheme 11**). This could be brought to bear after a selective hydrolysis of the pivalate and generated the α-*cis*-configuration of the natural product series. As intermediates obtained this way have been converted into indole alkaloids already (see **Scheme 12**), the stereochemical problem is solved this way.

As a second example of directed stereoselectivity we investigated the potential of chiral Diels-Alder adducts with imides (see **Scheme 13**, R = H). On alkylation and diastereoselective cyclization intermediates are obtained that in a thermal retro-Diels-Alder process may be converted into enantiomerically pure

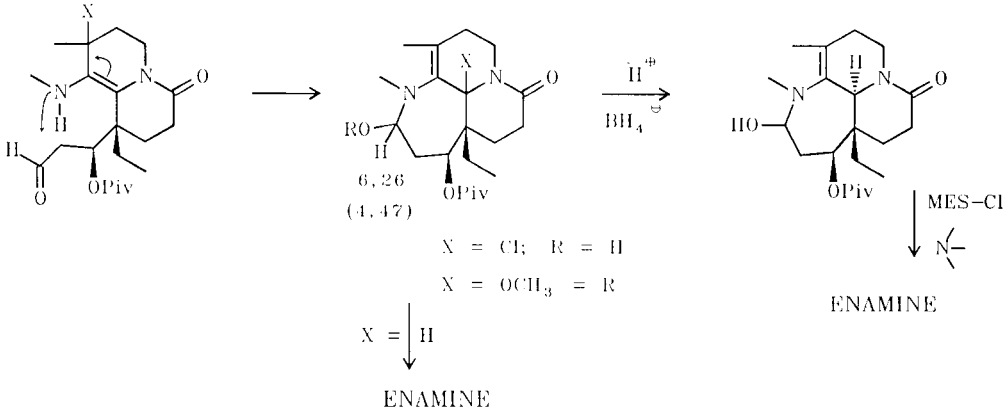
Scheme 8



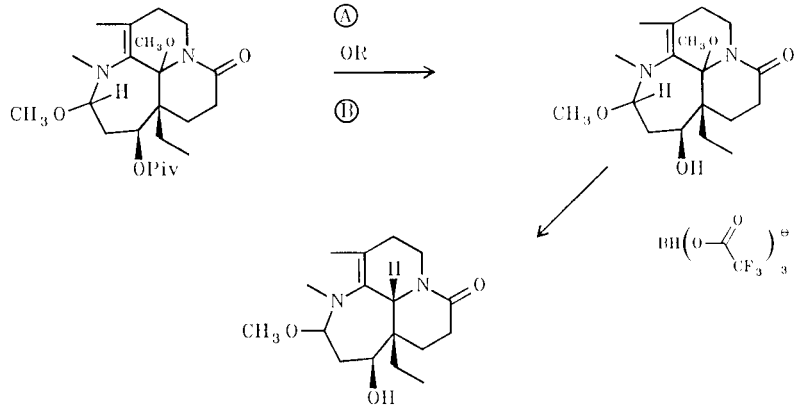
## Scheme 9




## Scheme 10

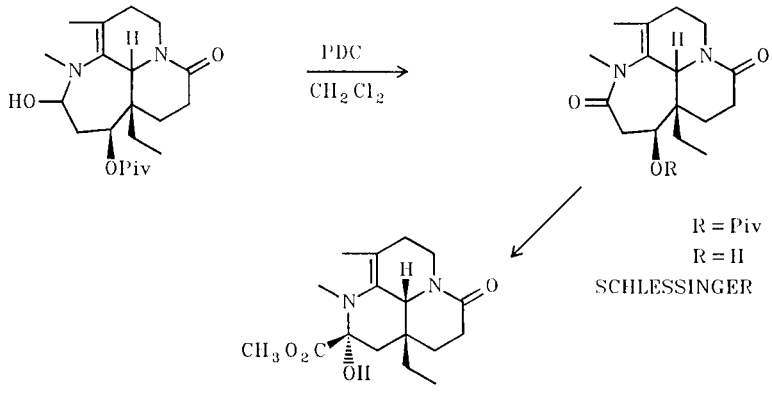



## Scheme 11

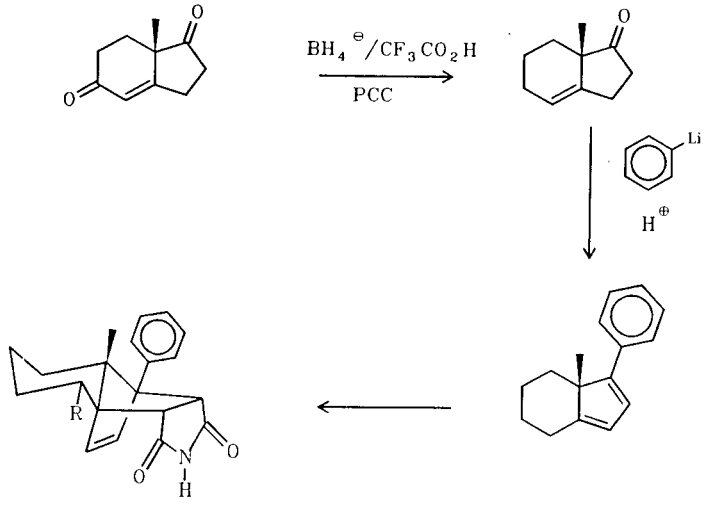



Ⓐ : $OCH_3^{\ominus}$ / $HOCH_3$ ; Ⓑ $LiAlH_4$ THF RT

**Scheme 12**

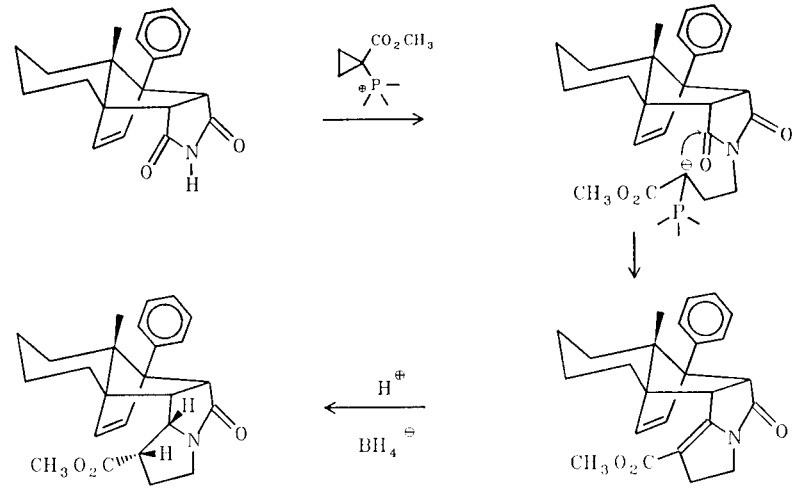



**Scheme 13**

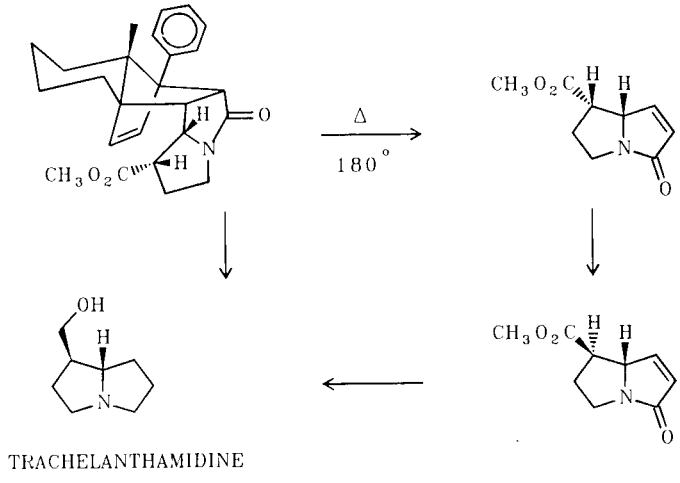



R = H ; R = $CH_3$

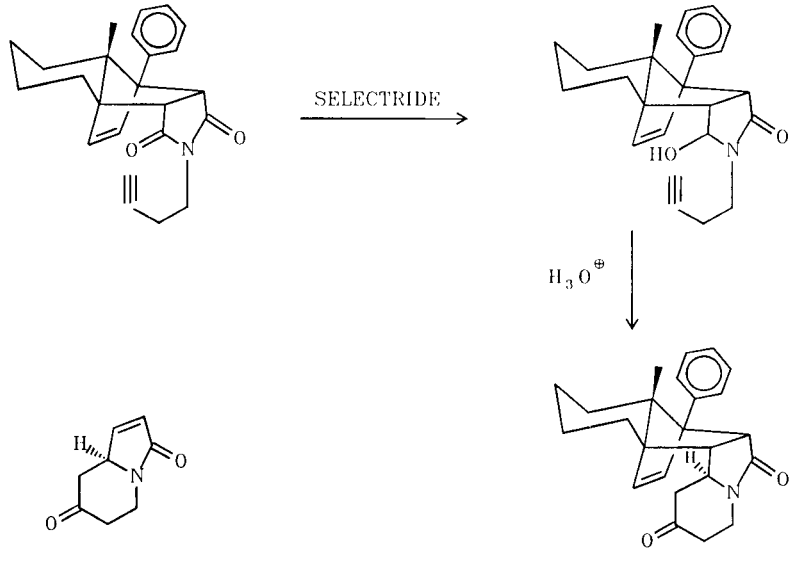
Scheme 14



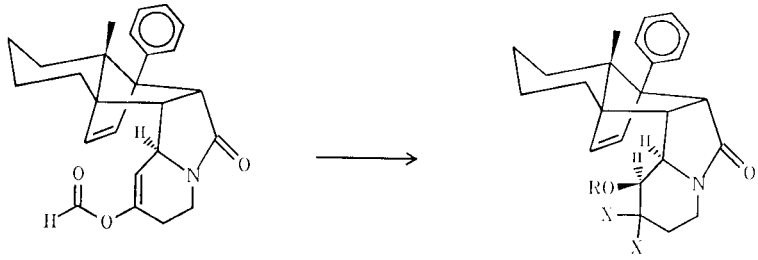
Scheme 15

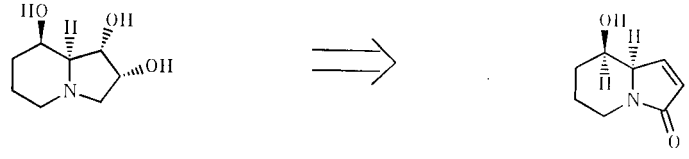



Scheme 16



Scheme 17





9-EPISWAINSONINE

indolizidones or pyrrolizidones (see **Schemes 14-17**), which have been converted into alkaloids too. It is of special interest in this field that minor changes in the constitution of the diene (R = $CH_3$) may lead to a complete change of regioselectivity. As flexibility in regioselectivity amounts to flexibility in absolute configuration of the retro-Diels-Alder product both enantiomers can be prepared in a predictable way.