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The stereospecific synthesis of reserpine

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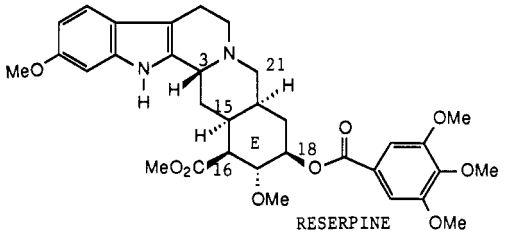
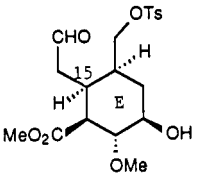
Abstract. A stereospecific synthesis of reserpine in its correct absolute stereochemistry was achieved by constructing a system which has the five asymmetric centers present in ring E. At this point, we were left with the problem of the stereochemistry of the C_3 center. This long-satnding problem has now been solved, in a generally applicable manner, so that it is now possible to produce, at will, either the more stable arrangement (equatorial indole) or the less stable (axial indole) at the C_3 center. This latter arrangement corresponds to that in reserpine.

The construction of reserpine[1] which we outline here starts with the synthesis of ring E of the molecule, as is illustratd below. The particular choice of a ring E bearing a primary carbinol tosylate, as a means of making connection with the tryptamine nitrogen, rather than a carboxaldehyde, as was used in Woodward's original synthesis, was dictated by two considerations.



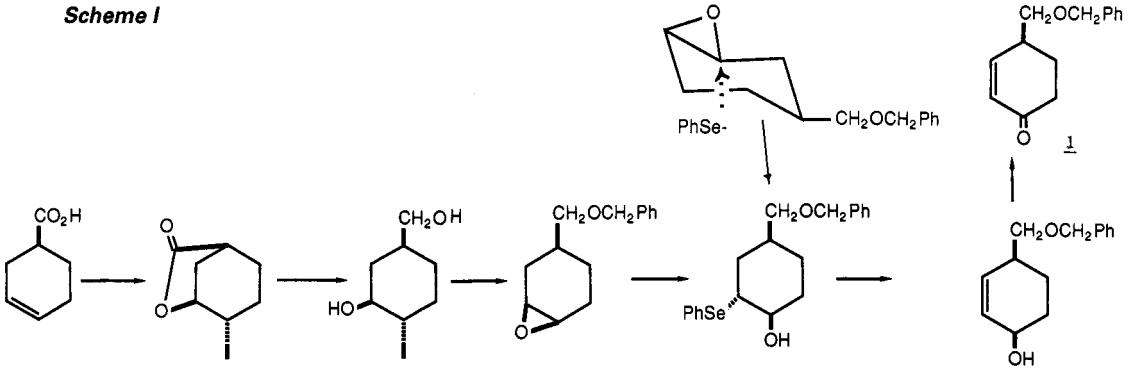


First, connection via an aldehyde has the potential problem of equilibration at the adjacent C_{20} asymmetric center. Conversely, the particular approach to the control of C_3 stereochemistry which we intended to use (vide infra) required that the C_3 center originate from an acetaldehyde fragment at C_{15}.

CONSTRUCTION OF THE E RING IN THE CORRECT ABSOLUTE STEREOCHEMISTRY

The readily available optically pure 3-cyclohexenecarboxylic acid[2] was converted to the required 4-benzyloxymethylcyclohexenone, as shown in scheme I.

Scheme I

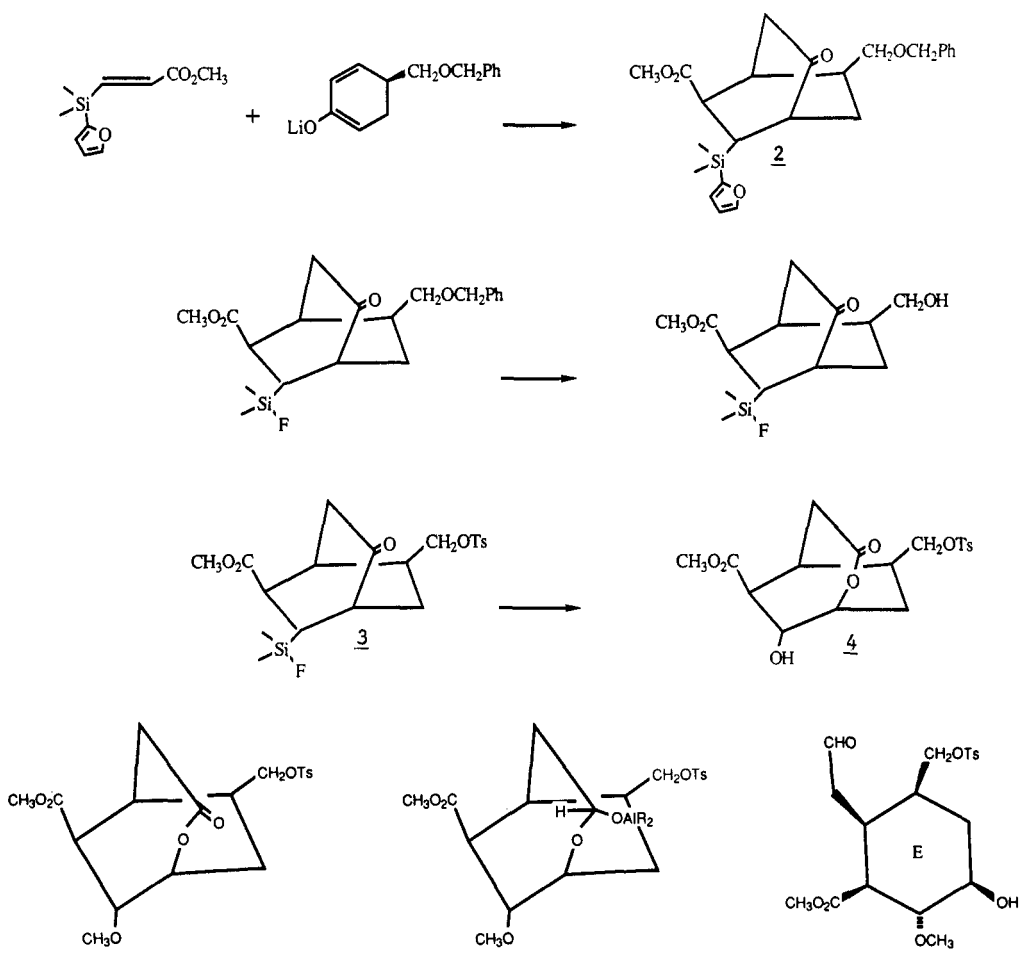


The main point of interest here is that the benzyloxymethyl group is sufficient to define a particular chair which then leads, via the anticipated axial opening to the correct regiochemistry of the eventual cyclohexenonone 1.

CONSTRUCTION OF THE E RING

This is shown in Scheme II. Points of note are 1) that the double Michael reaction, a reaction much used in recent years, especially by the Kametani group,[3] leads immediately to all five chiral centers in their proper form, thus increasing the asymmetric complexity from the one asymmetric center in the starting cyclohexenone 1 to the five asymmetric centers of the product bicyclo 2-2-2-octanone 2, in over 80% yield. The furyldimethyl silyl group was devised by us to allow mild transformation into the fluorodimethylsilyl group (accomplished by simple heating with tetrabutylammonium fluoride in THF). This is required to transform the silicon substituent into the necessary hydroxyl via the Tamao-Kuwajima[4] reaction. The synthetic route is designed so that the result of the peracid treatment which converts the fluorodimethylsilyl group to a hydroxyl simultaneously converts the ketone to a lactone, as shown in 3 to 4. Methylation of the secondary hydroxyl and DIBALH reduction of the lactone now completes the stereospecific synthesis of ring E with the required tosyloxymethyl and adjacent acetaldehyde chain. The construction only required seven steps from the starting 4-benzyloxymethyl cyclohexenone 1.

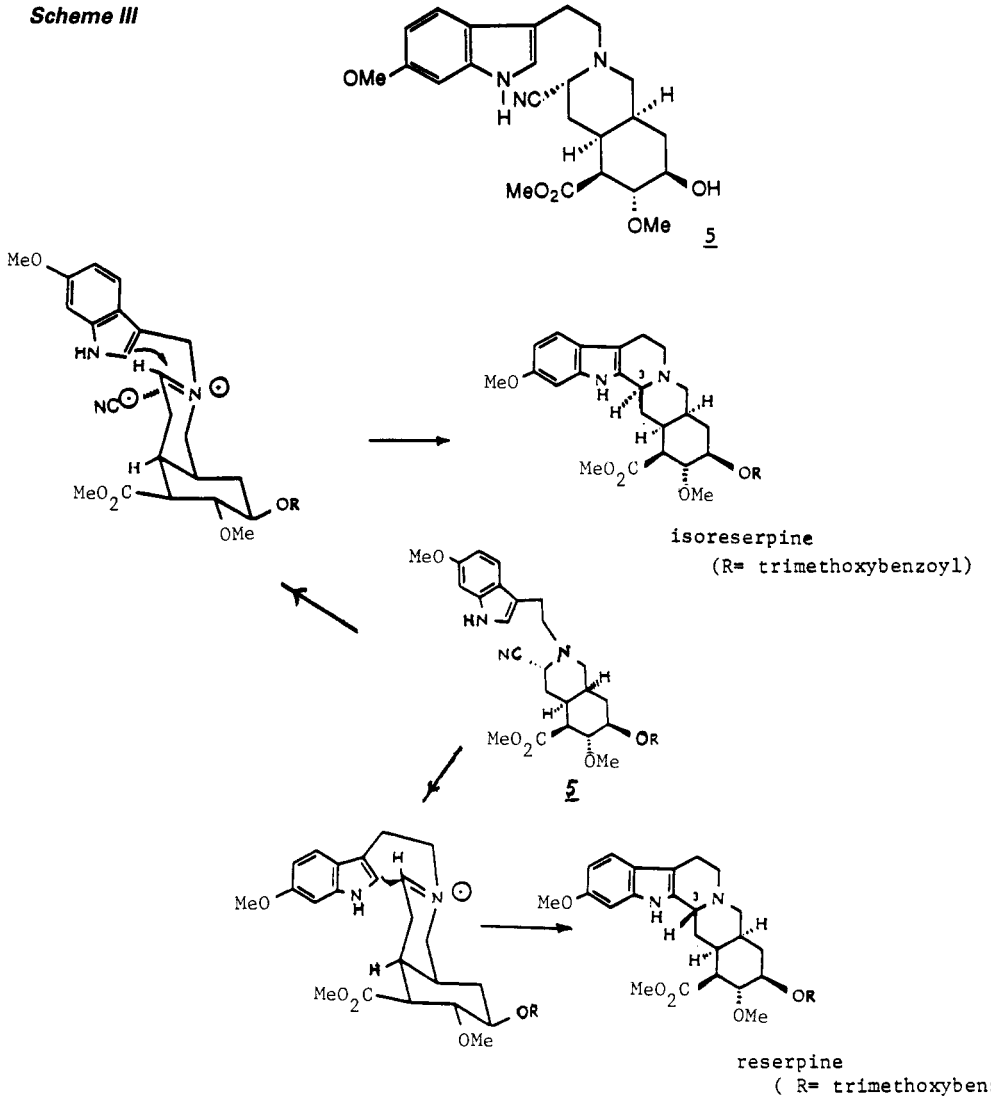
Scheme II



ATTACHMENT TO METHOXYTRYPTAMINE AND THE C_3 CONTROL

The direct regio and stereospecific control of the C3 center has been a serious problem. We have now shown that the product of what is essentially a Strecker reaction, the cyclic cyano amine 5, can be converted to either the more stable isomer, in this case isoreserpine, or to the desired less stable isomer with an axially connected indole ring, in this case the desired reserpine. The success of this approach, illustrated in SCHEME III, is due to the fact that heating 5 in acetonitrile solution converts it to a tight ion pair in which the initially axial cyano group (anomeric effect) blocks the face which would have to be accessed to produce the axial attachment of the indole ring. The result is the formation of isoreserpine. On the other hand, breaking up the ion pair, either by adding silver fluo borate or simply by using a tetrahydrofuran solution containing some aqueous hydrochloric acid, now allows the intermediacy of the immonium salt which should--and does--lead to unimpeded axial-half chair approach of the indole, as required by stereoelectronic considerations, e.g. Dunitz-like approach angle to the endocyclic immonium salt.[5] The product is then the alcohol corresponding to natural reserpine. Esterification with 3,4,5-trimethoxybenzoyl chloride then gave reserpine, identical in all respects with the natural substance.

Scheme III



Acknowledgements The work which is briefly outlined here owes a great debt to Dr. Masahiro Toyota who carried out all the steps leading to the substituted ring E, as summarized in scheme II. A very significant contribution was made by Dr. Peng Cho Tang who unraveled the factors which eventually led to the control of the C_3 stereochemistry. Other, entirely different approaches to reserpine, utilizing more particularly free radical chemistry for the ring E construction, were carried out by Drs. Michael Casey, Peng Cho Tang and Burton Goodman. To all these , I express my gratitude.
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