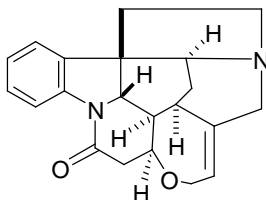
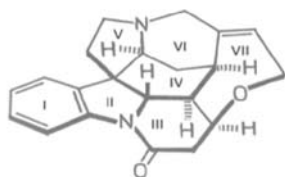


The Total Synthesis of Strychnine

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Either we make Strychnine or take Strychnine.

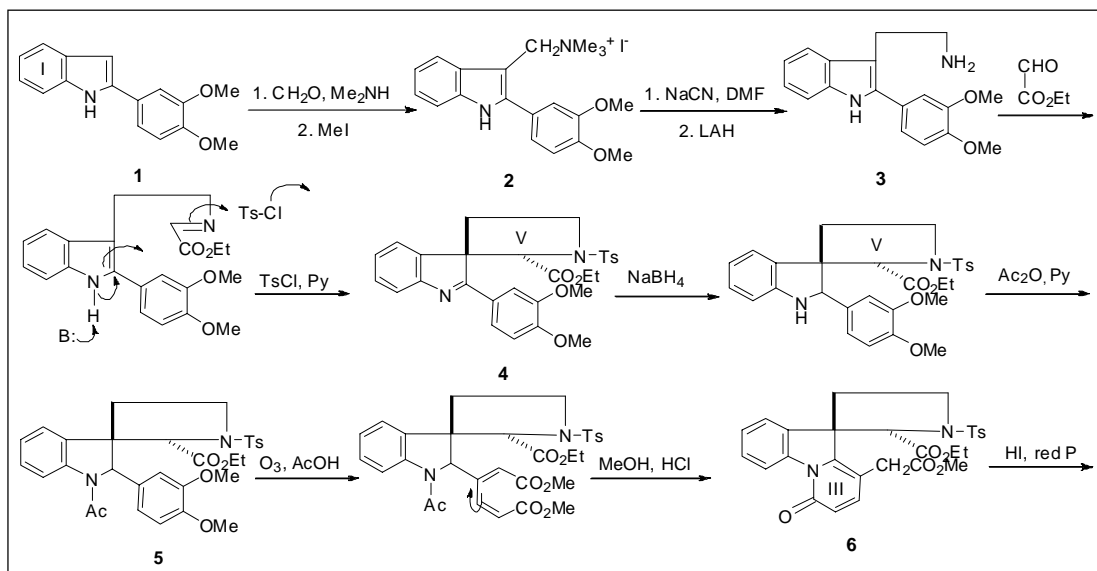
– R B Woodward

Strychnine! No other molecule has captured the popular imagination as strychnine, perhaps because thousands of writers of fiction have used it to dispatch the recipient and then several have made thrillers using ingenious deduction to catch the perpetrator! Known since the 16th century from the forests including the Coramandal Coast of India, it was isolated in a pure form in 1818 and the structure established in 1947! Unlike the 181 atoms scattered in space as in vitamin B₁₂, strychnine, having six asymmetric centres and 7 rings is packed with a mere 24 skeleton atoms!

2-Veratryl indole (**1**) readily prepared by Fischer indole synthesis from acetoveratrone was transformed to tryptamine **3**, whose Schiff's base with CHOCOOEt underwent smooth cyclization with TsCl/Py to generate the spiro ring-V, **4** which was transformed to **5**. Ozonolysis followed by treatment with MeOH/HCl generated the critical pyridone **6** (ring-III) (*Scheme 1*). Initial efforts to effect a Dieckman condensation of the two ester groups were thwarted by the highly electrophilic Ts group present, forming in preference, the Schiff's base. The Ts group was removed (HI, red P) and replaced by Ac (Ac₂O, Py), esterified (CH₂N₂). The resulting **7** underwent smooth Dieckman condensation to give **8**, generating ring-IV.

The enormous reach of R B Woodward in the design and synthesis of carbon constellations is further exemplified with the total synthesis of strychnine (p.641), which even when viewed from the vantage of ensuing significant developments in organic synthesis is an amazing feat! This is followed by the total synthesis of chlorophyll (p.645), where RB pledged the entire efforts on an untested porphyrin to purpurin change, an essential transformation to achieve the total synthesis. The third additional example is the total synthesis of cephalosporin C (p.649), The Nobel Lecture delivered by RB, above all, reflects the fact that in all these creations, he identified an anchor from which he never wavered – in this case the simple molecule cysteine.

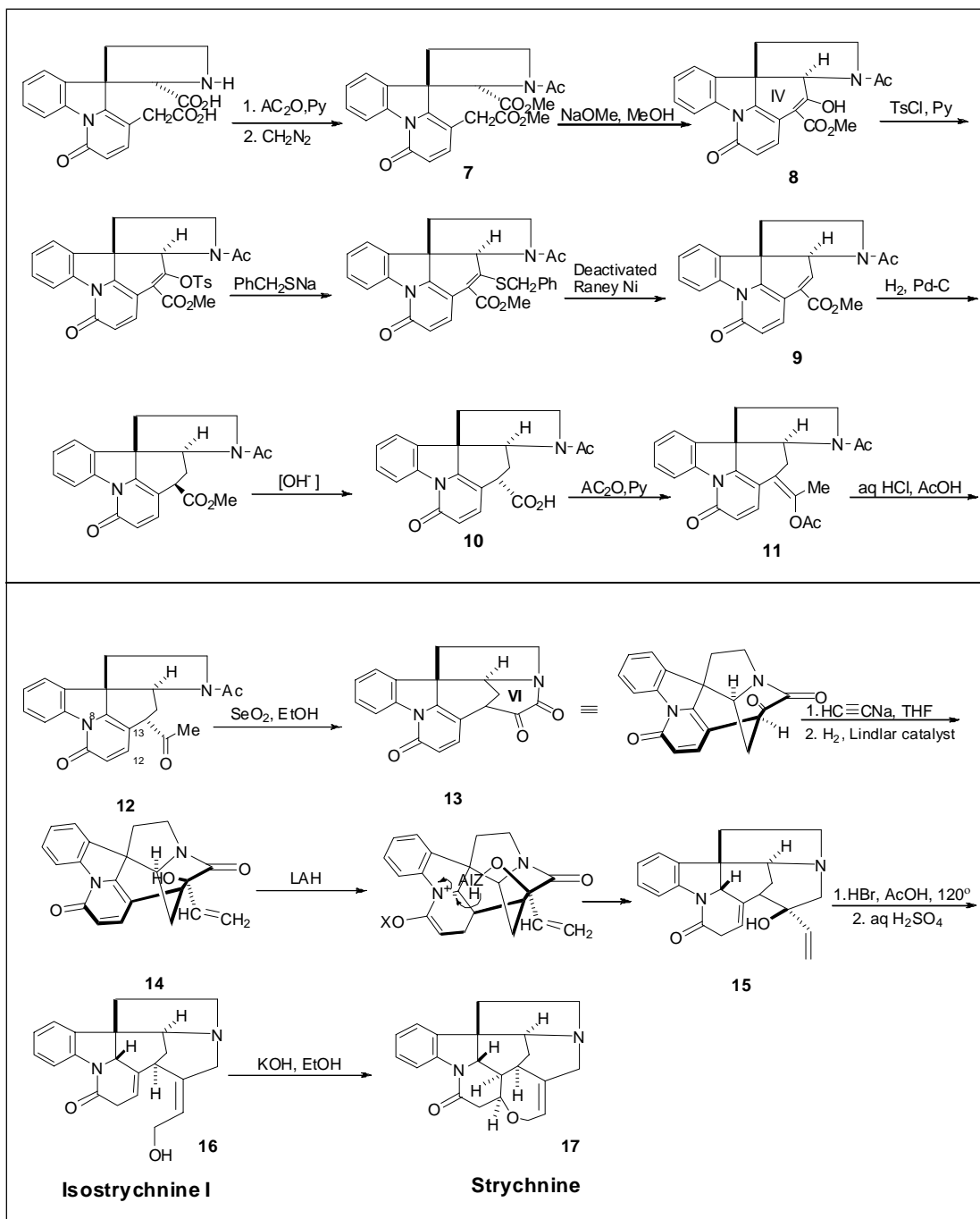
Keywords
Strychnine.



Scheme 1.

The enol ester group in **8** was transformed to acrylate **9** and then subjected to reduction. This process creates another chiral centre where the major product turned out to be unwanted β -ester which was readily epimerised to the more stable α -acid, **10**. The structure of compound **10** was conformed from a sample secured from natural strychnine. For this purpose **10** was readily resolved using quinidine and esterified to the methyl ester corresponding to **10** which was identical to that obtained from the natural sources. This enabled further transformations with the more readily obtained material from the natural sources. The linking of the α -carboxyl group in **10** to the nitrogen that would generate ring-VI necessitated the inversion of this centre; this was achieved in an unusual manner by treatment of **10** with Ac_2O and pyridine to form the enol acetate **11** (Scheme 2).

The formation of **11** could be rationalized by the initially formed anhydride, that undergoes nucleophilic acyl transfer, decarboxylation and acylation of the thus generated enolate! Vigorous acid hydrolysis of **11** afforded **12** (Scheme 3). The protonation of the enolate takes place from the β -side. Thus **12** is not disposed for linking with the *trans*-NH. Woodward did not consider this as an impediment because of the ready epimerisation of this centre.



Scheme 2 (top).
Scheme 3 (bottom).

Indeed this turned out to be true! Treatment of **12** with SeO_2 -EtOH gave **13** with the generation of ring-VI. The 3D representation of **13** clearly shows that the epimerization has indeed taken place!

The pathway to strychnine now involves addition of two carbon atoms and creation of chiral centres at 8, 13 and 12 positions (**12**) (*Scheme 3*). At this stage compound **13** is highly concave and the carbon at 8 rests at the bottom of it. To deliver an H to this carbon is the kind of challenge that Nature often posed and Woodward overcame this using an Al-courier! Compound **13** was treated with sodium acetylide in THF and the acetylinic moiety was reduced to provide **14**. Compound **14** when reacted with LAH in refluxing ether effected the reduction of the amide present in ring-VI and delivered the hydrogen to the most inaccessible carbon-8 to form **15**. Compound **15** is related to isostrychnine **16** where the allyl alcohol is isomerised to provide a hydroxy methyl isomer. This transformation proved exceptionally difficult. Eventually, treatment of **15** with HBr/AcOH at 120°C , and the resulting mixture of halo compounds on hydrolysis in boiling aq. H_2SO_4 generated the desired **16**, isostrychnine! The action of ethanolic KOH led to the closure of the 7-membered oxide ring-VII, which also generated the chiral centre at 12 and 13 in a correct order.

Even in the light of significant developments in organic synthesis during the intervening six decades, Woodward's synthesis of strychnine defies the imagination of chemists! Here again Woodward had to overcome the problems raised by Nature in placing one of the Hs inside the bowl with 4 outside!

Suggested Reading

- [1] R B Woodward, M P Cava, W D Ollis, A Hunger, H U Daeniker and K Schenker, *Tetrahedron*, Vol.19, p.247, 1963.

