

# Woodward's Synthesis of Vitamin B<sub>12</sub>

*Adil Ghani Khan and S V Eswaran*

Adil Ghani Khan is a final year student of BSc (Honours) in Chemistry at St. Stephen's College, Delhi University.

S V Eswaran is an accomplished Organic Chemist and principal of Deshbandhu College, Delhi University.

**The synthesis of this molecule was a landmark in organic synthesis. It involved the masterful control of shapes of molecules to create 9 chiral centres with known absolute and relative configurations. The concepts of absolute and induced asymmetric synthesis are here explained.**

Robert B. Woodward was one of the greatest Organic Chemists of the 20 th century. Sir Derek Barton, Nobel laureate, in his autobiography, describes him as, "a precocious young man... (who) had taught himself more Chemistry by the age of 18 than the Professors at MIT had acquired in their lifetimes." He may fairly be described as a pioneer and a revolutionary in his field, consistently demonstrating the powerful use of logical reasoning where it was customary to abandon such approaches. Barton further says, "We were taught to think that mechanism had nothing to do with 'real' Chemistry. With one lecture, Woodward showed us the contrary."

Vitamin B<sub>12</sub> is a large and complex molecule (*Figure 1*), containing 9 chiral centres (marked with an asterix), with 6 of the chiral centres linked together in a chain! Even the synthesis of molecules containing just a few chiral centres poses difficulties. This molecule thus presented an unparalleled challenge.

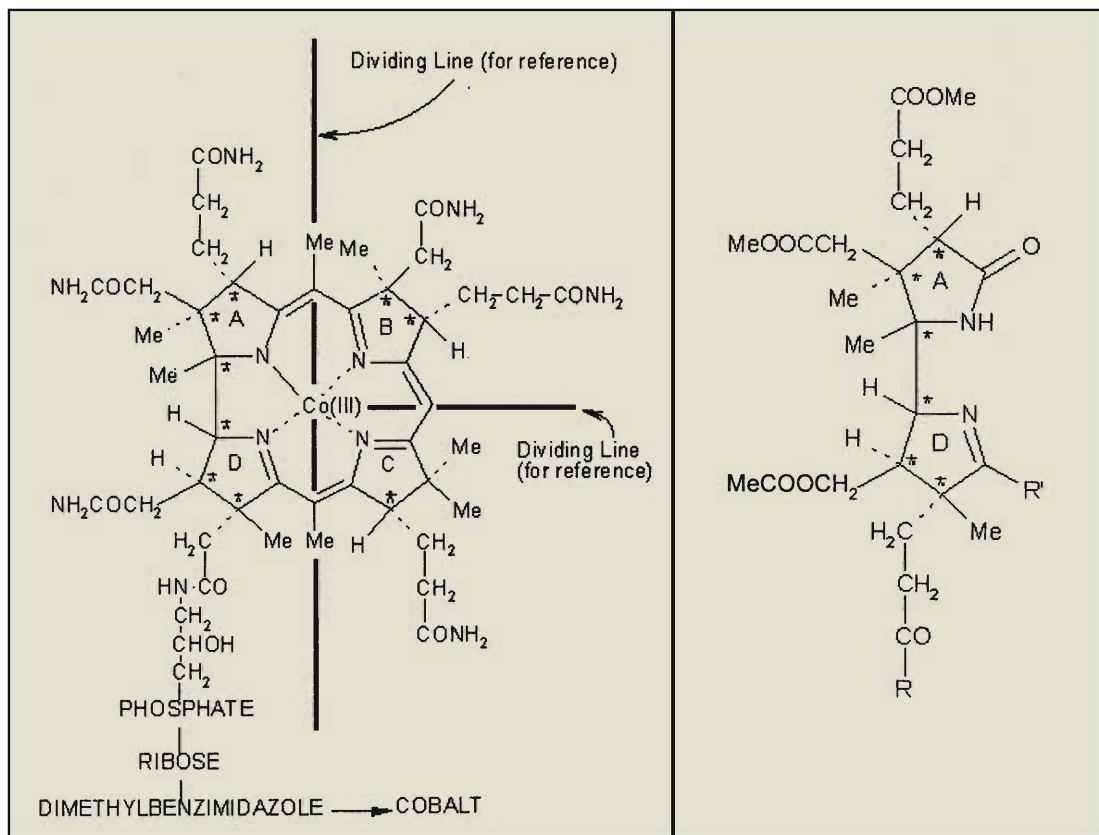
Before describing the synthesis, it is to be stressed that this is an attempt to examine the stereochemical problems posed and the way they were tackled and not a study of the mechanisms of the individual steps involved. One also wishes to get an idea of how such large syntheses are planned.

There are 4 rings in the molecule, labelled A, B, C and D. Of these, A and D with six chiral centres are on the left hand side (LHS) and B and C having three chiral centres on the right hand side (RHS). These were to be built separately and then joined.

Keywords

Asymmetric synthesis, chiral.

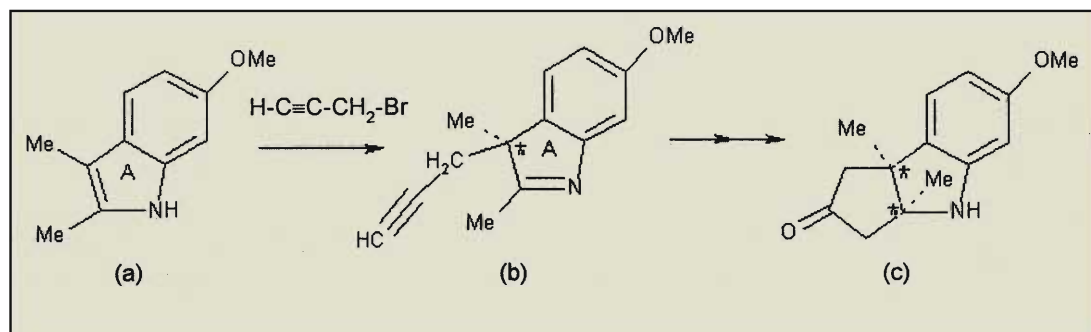


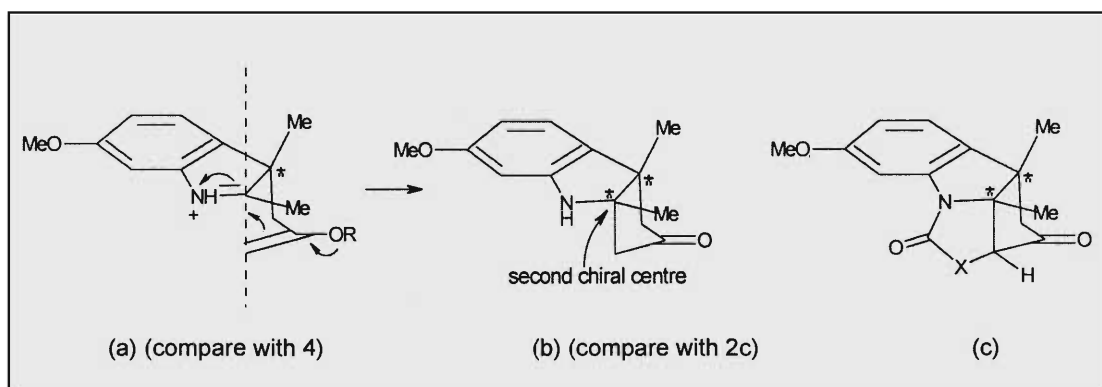


The largest and most challenging block was the LHS. Woodward started with the relatively simple molecule 3-methoxy-7,8-dimethylindole, *Figure 2a*. When this was treated with propargyl bromide ( $\text{HC}\equiv\text{C}-\text{CH}_2-\text{Br}$ ), it attacked the double bond to give *Figure 2b*. This provided the first chiral centre (in fact obtained as a racemic mixture). This was then cyclised to give *Figure 2c*.

*Figure 1. Vitamin B<sub>12</sub>.*

*Figure 2.*





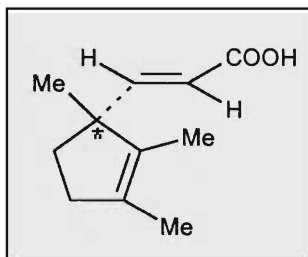
**Figure 3.**

The interesting feature is that the chain undergoing cyclisation is on one side of the flat part of *Figure 3a*, and when cyclisation occurs, it does so from the same side as from where the first attack took place. It can be seen from *Figure 3a* that the chain can't stretch around the molecule and attack from the other side. Thus the two methyl groups were on the same side of the molecule and the second chiral centre (shown in *Figure 3b*) was produced with known stereochemistry. Woodward called this Induced Asymmetric Synthesis, that is, the creation of a new asymmetric centre stereo-specifically under the influence of asymmetry already present.

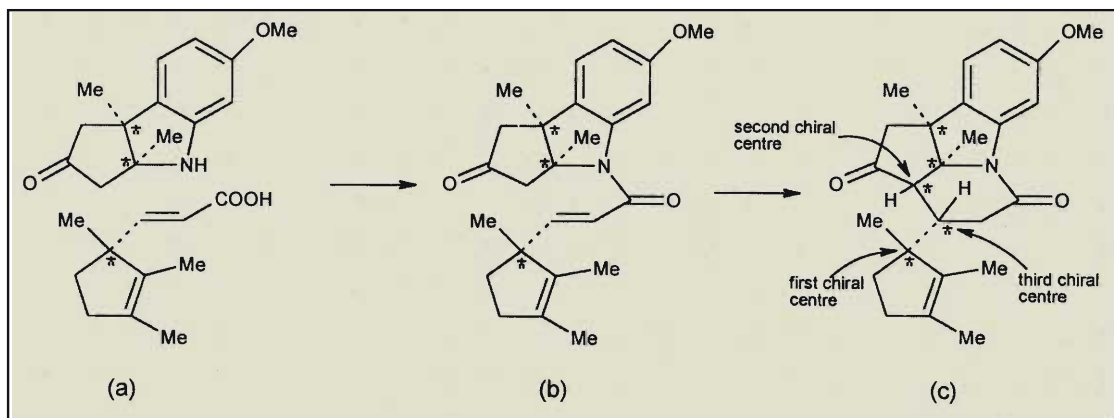
Since the product obtained, *Figure 2c*, was racemic, it was then resolved and their absolute configuration established. The correct antipode was processed further.

The tri-cyclic ketone (*Figure 2c* = *Figure 3b*) was a very useful molecule as it contained a replaceable hydrogen atom on N where a suitable chain could be added. Moreover, the shape of the molecule is concave as seen clearly in *Figure 3b* and thus any attachment to N could bring about cyclisation by attacking the molecule only from 'behind' it as seen in *Figure 3c*. This could create yet another chiral centre with known configuration, another example of induced asymmetric synthesis.

**Figure 4.**



The structure to be attached to the N atom for this purpose was *Figure 4*, a compound derived from (–) camphor, which is a

**Figure 5.**

naturally occurring substance containing one asymmetric carbon atom of known configuration. The trans arrangement of the two larger groups about the double bond should be noted.

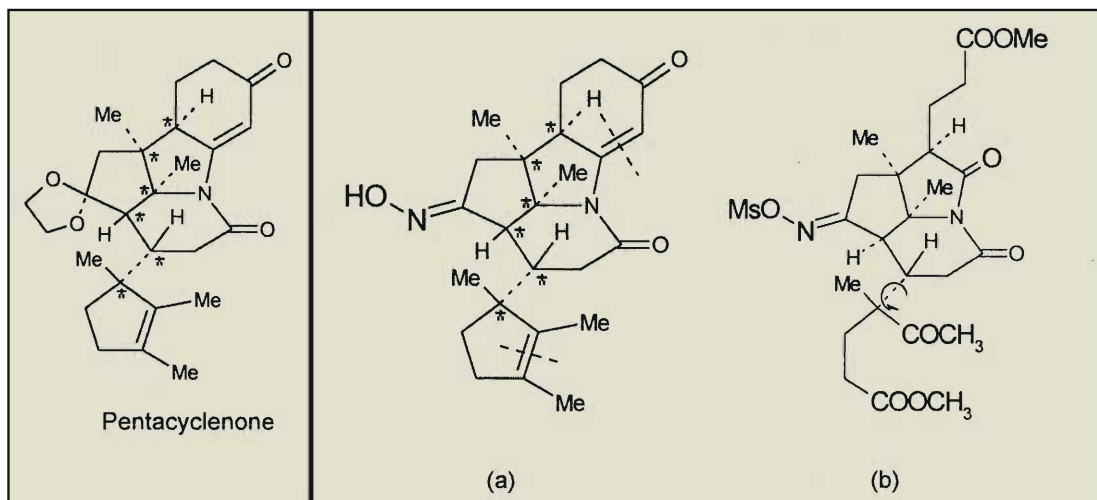
This group is attached to the N atom and made to undergo cyclisation as described earlier (*Figures 5*). Three new chiral centres are created at this stage (as shown in *Figure 5c*).

This act of assembling two asymmetrical molecules of known configuration in a manner that the relative chiralities have the desired character is what is called Absolute Asymmetric Synthesis.

The second chiral centre was created by induced asymmetric synthesis as described earlier.

The third chiral centre is generated with the known configuration, because the H atom can project only in the direction shown due to the great amount of crowding in the concave part of the molecule (which can be seen in *Figure 3c*). Five chiral atoms are created in a chain with complete stereo-specificity as shown in *Figure 5c*.

Till now the aromatic ring, which we started with, had been acting as a stable platform on which this elaborate construction was carried out. When needed no longer, it was destroyed, but in a manner that enabled it to become a part of the final product.

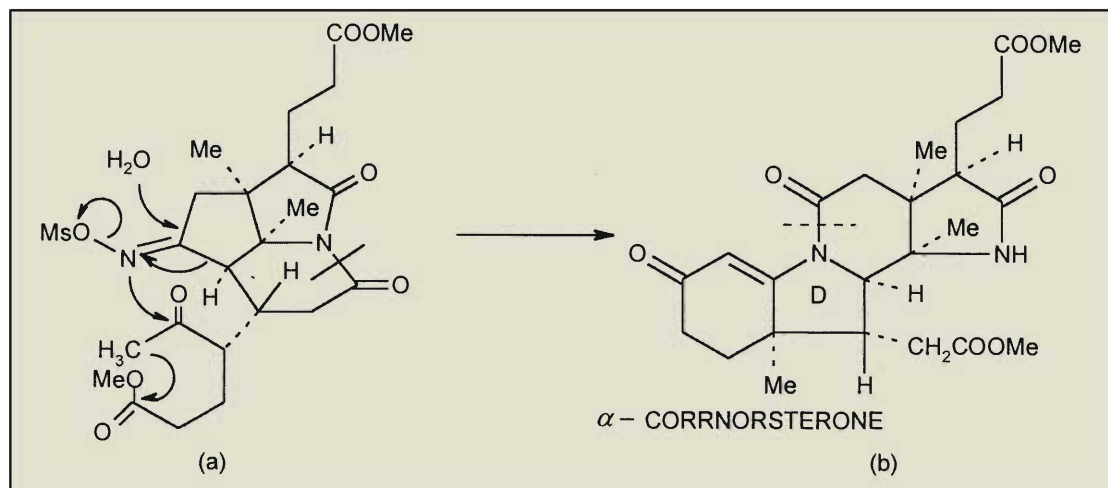


**Figure 6 (Left).**  
**Figure 7 (right).**

Incidentally, this modification leads to the creation of the final chiral centre, albeit *with unknown configuration*, *Figure 6*.

One would observe at this stage the need to introduce a second N atom in the molecule. This was done by the formation of an oxime, *Figure 7a*. A stereochemical point of significance here is that the hydroxyl group is oriented only in the shown direction, because of steric hindrance on the other possible side. Some modifications were made by the cleavages as shown in *Figure 7a* to get *Figure 7b*. (Note the way the erstwhile aromatic ring has now become  $\alpha$ - $\text{CH}_2\text{CH}_2\text{COOMe}$  group, which is very much a part of the target molecule).

The Beckmann Rearrangement of oxime mesylite, a difficult task due to the great amount of crowding at the pertinent area, was eventually achieved on refluxing at 170 °C for 2 hours. This refluxing not only placed the second N atom in its correct position with respect to the first, it also led to a couple of other useful changes (*Figure 8a*). The diacylamine system was cleaved as shown by the dotted line, which was good since the cyclic system was not required. Further, a bond was also formed by the attack of the newly placed N atom on the electrophilic C=O group 5 atoms removed from it. Further, a cyclisation in the lower left part of the molecule as shown in *Figure 8a* was also



realised. This whole shuffling around results in *Figure 8a*, which was named  $\alpha$ -cornnorsterone (which means ‘cornerstone’ in Danish) and has a new steroid profile.

*Figures 8.*

The required ring D in our target molecule, *Figure 2*, was the N containing ring present in this molecule. One should note here that it contains the required acetic ester side chain and methyl group, properly oriented.

It was now required to cleave the newly formed 6-member lactam ring as shown by the dotted line in *Figure 8*. This cleavage, however, proved to be the trickiest part of the synthesis since the bond was being cleaved only under very severe conditions which resulted in many unwanted side products. Finally it was realised that there exists an isomer of  $\alpha$ -cornnorsterone different only in the configuration of the propionic ester side chain at the first chiral atom from the top in *Figure 9*. One would recall that the configuration at this atom was ambiguous. This isomer was named  $\beta$ -cornnorsterone (*Figure 9*), and the interesting point was that this isomer underwent cleavage very easily.

The reason for this divergence in behaviour becomes clear on seeing the two products of cleavage (*Figure 9*). Cleavage in the  $\alpha$  isomer leads to a structure where the bulky propionic ester side chain and the acetic ester side chain are on the same side of the

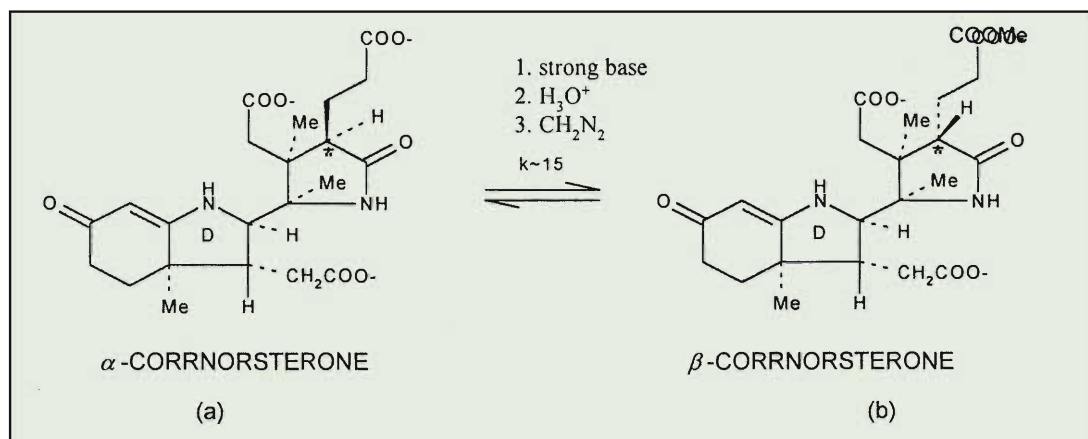


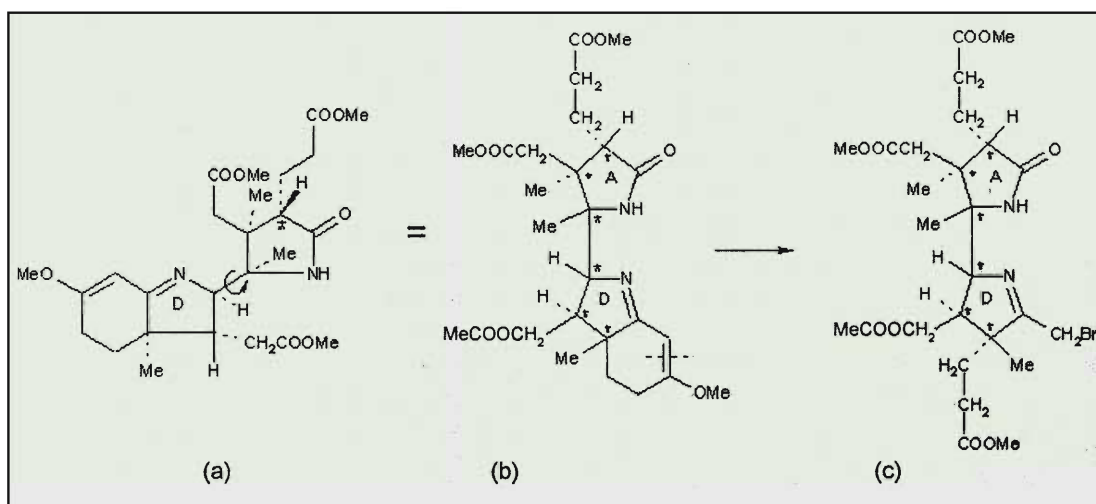
Figure 9.

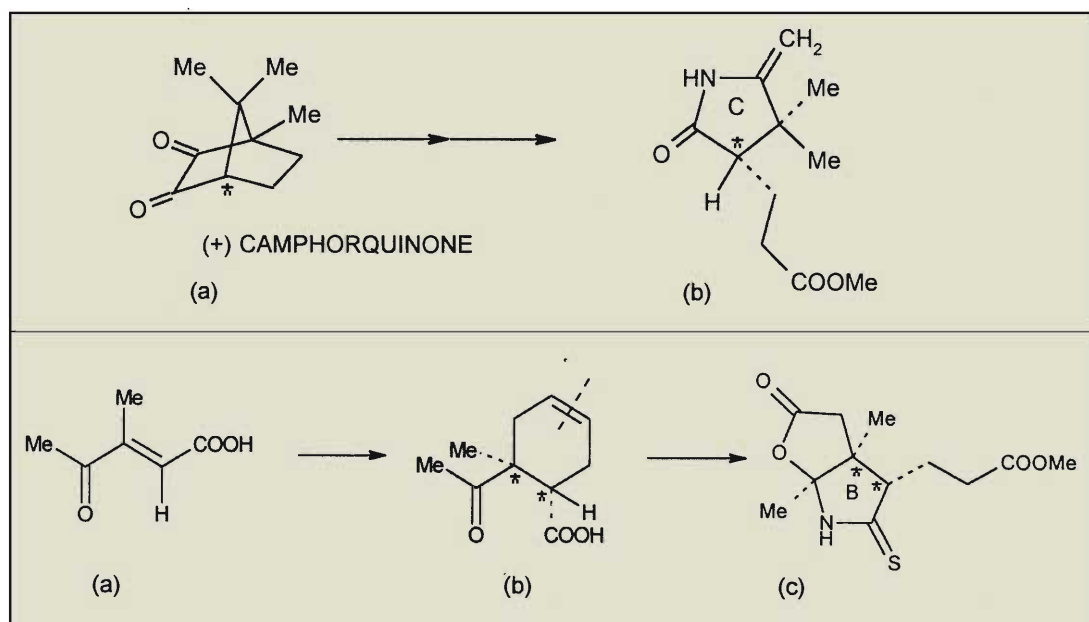
lactam ring, which leads to a high energy transition state due to crowding. In the  $\beta$  isomer product they are on opposite sides, leading to easy cleavage. So the two cleavage products were equilibrated to get the  $\beta$  isomer (Figure 9b), which, incidentally, is the required isomer.

This is modified to get Hesperimine (Figure 10a  $\equiv$  Figure 10b), which is cleaved with ozone and finally modified some more to get the A/D building block, Figure 10c.

Figure 10.

The synthesis of the intermediate representing ring C was relatively simpler. It contained only one chiral centre and this





was provided by the starting material in the required configuration, (+) camphorquinone.

**Figure 11 (top).**  
**Figure 12 (bottom).**

The B block intermediate has two chiral centres and the starting compound, *Figure 12a*, being trans with respect to the two larger groups sets the stereo-chemical stage. A Diels Alder reaction was performed on it and the two chiral centres were created with the required stereo-specificity. A series of reactions followed leading to *Figure 12c*, a complete solution of the B block.

The task left was to join these three blocks, each prepared with known configurations, in the correct way. This was a difficult job as it required C-C bonds to be made between two very bulky groups. The B and C blocks were joined first by bridging them together with a sulphur atom bridge, and then extracting the S atom (*Figures 13a-c*).

Then this and the A/D block were combined in a similar manner to give a thioester which lost S to give *Figure 14b*.

At this stage, all the rings were together in one molecule and final conversions were made which led to the target molecule.



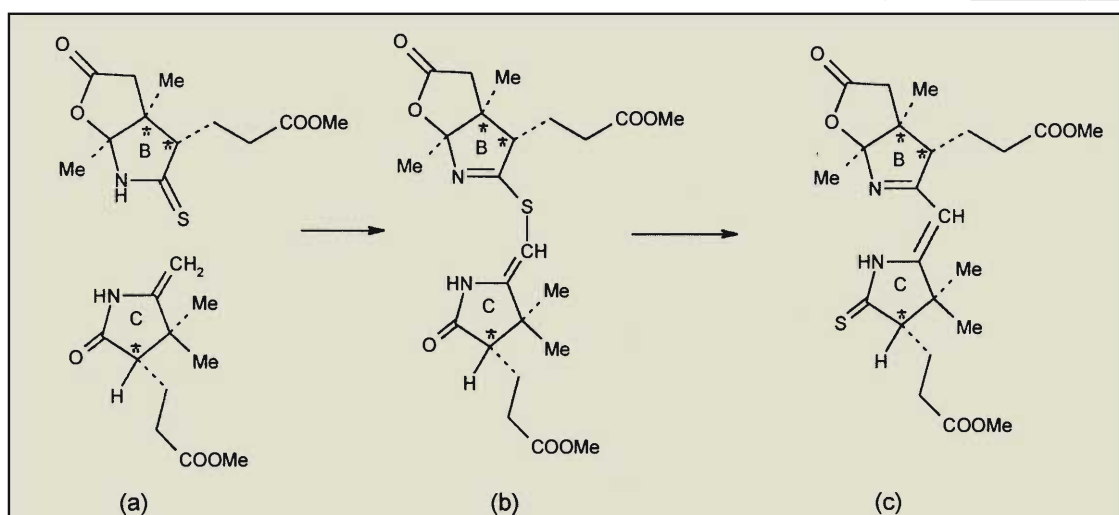


Figure 13

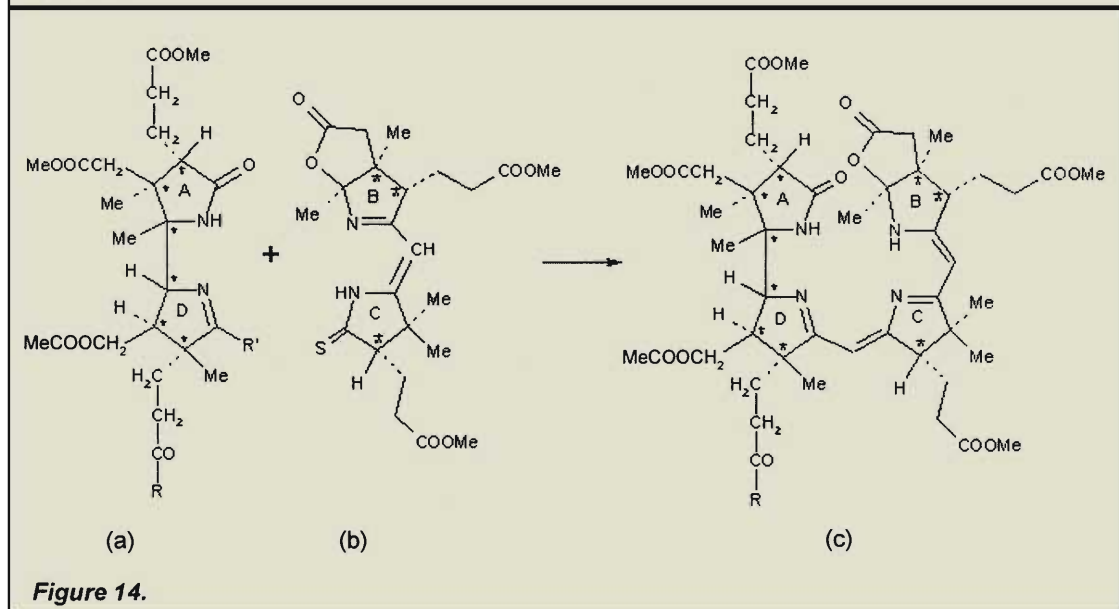


Figure 14.

*Address for Correspondence*

Adil Ghani Khan and  
S V Eswaran

Saman Zaar, Diggri Road  
Aligarh 202 002, India.

Email:adilghani@rediffmail.com

An idea of the enormity of the project is felt when one considers that it took a team of about a hundred co-workers working for 11 years to perform the complete synthesis. It is worth noting that Woodward announced the completion of the synthesis in Delhi in 1972.