Eschenmoser Approach to Vitamin $\text{B}_{12}$ by A/D Strategy
An Unexpected Journey

G Wayne Craig

East is East, West is West, The twain shall never meet.

– Rudyard Kipling

They can indeed meet if there is a will!

The Woodward–Eschenmoser collaboration across the seas broadened the mural of organic synthesis as never before! The left-hand side of $\text{B}_{12}$ harboring six contiguous centres (AB) was crafted by RB as a single piece whereas Eschenmoser generated all the rings A, B, C, D from a single dilactone! The great irony is that the Woodward–Hoffmann rules, whose origins came directly during the vitamin $\text{B}_{12}$ synthesis by RB was brilliantly used by Eschenmoser for a correct photo-induced union of A and D rings.

In the following pages Dr. G W Craig provides a gripping account of the endeavours from Zurich, which has not received as much attention as it deserves. We are immensely grateful to him for this comprehensive and painstaking effort.

S Ranganathan

Human subtlety will never devise an invention more beautiful, more simple or more direct than does Nature because in her inventions nothing is lacking, and nothing is superfluous.

– Leonardo Da Vinci

Introduction

The American chemist, Robert Burns Woodward (1917–1979) intellectualized the synthesis of complex molecules based on a paramount mechanistic rationale and a sense of Nature culminating in an impressive list of chemical achievements. Although Woodward received the Nobel Prize in Chemistry in 1965, his more prestigious accomplishments were forthcoming. Joining forces with the Swiss chemist and corrin expert, Albert
Eschenmoser (b. 1925), they orchestrated and conquered the highest synthetic pinnacle imaginable at that time, the total synthesis of vitamin B\textsubscript{12}.

Their collaborative Harvard–ETH approach, termed the A/B strategy, was based on Eschenmoser’s east-west synthesis of an early corrin model. However, during the synthesis of the east-fragment, Eschenmoser recognized that an A/D strategy to synthesize vitamin B\textsubscript{12} was theoretically attainable, in accord with the principles of orbital symmetry conservation elucidated by Woodward and Roald Hoffmann (b.1937). These post-Nobel Prize accomplishments, the Woodward–Hoffmann (W–H) rules (1965–1969) and the synthesis of vitamin B\textsubscript{12} (1972–1976) respectively, were to become the major hallmark of Woodward’s crowning legacy in his ‘meritorious achievements to the art of organic chemistry’.

**A Competitive Challenge**

Before Woodward had completed the total synthesis of chlorophyll-a (1) (*Figure 1*) in 1960, he had already set his sights on an exceedingly more complex tetrapyrrole, vitamin B\textsubscript{12} (2) (*Figure 2*). Between 1960 and 1961, Woodward began synthetic investigations into the west wing (8) of vitamin B\textsubscript{12}. However, Eschenmoser at the ETH, had already initiated corrin model studies in 1959 which

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**Figure 1 (left).** Chlorophyll-a, (1) red, aromatic chlorin chromophore.

**Figure 2 (right).** Vitamin B\textsubscript{12}, (2) red, nonaromatic corrin chromophore.

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