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Organic Synthesis

A brief history through some important milestones in total synthesis & their protagonists![‡]

Sridhar R. Iyer *

This article largely depicts the evolution of organic synthesis (till around mid-2000s) largely through some of the important milestones in total synthesis of natural products or molecules that have historical context. Many other aspects of organic chemistry which are equally important are either not discussed or are just touched upon, e.g., atomic theory, molecular theory, development of new reactions, techniques of structural elucidation, methods of isolation & purification, physical organic chemistry & theoretical organic chemistry. Suffice to say without these, organic synthesis would not be in the current position that it is now. The aforementioned topics and their evolution and impact on organic synthesis is a larger subject. As such we will not discuss or analyse the synthetic route's/scheme's in this article. It must also be mentioned that many of the themes in this article and the evolution of organic synthesis has already been comprehensively summarised by Prof. K C Nicolaou in various articles/ reviews/ books[1] and this article has borrowed and adapted many points from his articles/ reviews/ books. Having defined the scope of the present article, let's jump into the important events that characterised synthetic organic chemistry. In 1828, Wöhler synthesised urea and this was the starting point of organic synthesis. Until then, it was considered that organic compounds could not be synthesised in lab (the theory of vitalism!). With this important milestone the theory of vitalism was laid to rest. Later in 1845, Kolbe synthesised acetic acid-another organic compound. The famed British chemist William Perkin Sr.'s synthesis of Mauveine in 1865 (while attempting to synthesise quinine!) and then Alizarin in 1869 (Alizarin was independently synthesised at around the same time by German chemists Graebe & Liebermann who however patented the same just one day before Perkin!) along with the synthesis of Indigo by Adolf von Baeyer in 1870 started the dye industry in Europe (FIGURE-1) which was the genesis of the pharmaceutical industry later.[1]

[‡] This article is dedicated to the memory of Dr. S. Y. Pandey who recently passed away

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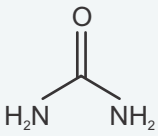
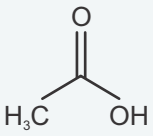


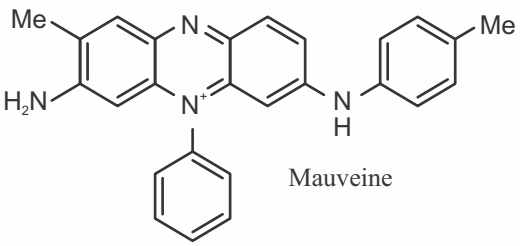
Urea
Wöhler
1828



Acetic Acid
Kolbe
1845

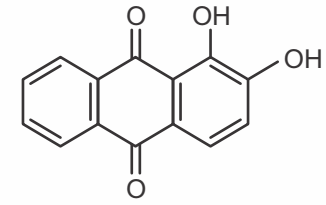
Figure 1

Starting Point of the Dye Industry....

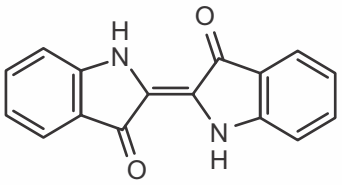


Mauveine

Perlkin Sr., 1865 & 1869



Alizarin



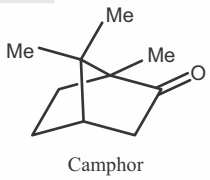
Indigo

Adolf von Baeyer, 1870

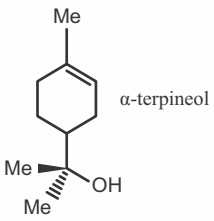
One of the great scientists of all time Emil Fischer made important contributions to organic chemistry & organic synthesis. He did seminal work in glucose chemistry (including the first synthesis of glucose in 1890, unravelling the stereo-chemical configuration of sugars using van't Hoff's & Le Bel's concepts, Fischer projections) and purine chemistry. He has several great achievements to his credit including discovering the reaction to synthesise indoles (Fischer-Indole synthesis), first synthesis of caffeine (1895/1897), contributing to the concept of stereochemistry in organic compounds and was the first to suggest the concept of "lock and key" in the context of enzyme action.

He not only trained many chemists but also contributed to the advancement of organic chemistry in Germany and Europe. His work laid the foundation for bio-chemistry. It is interesting to note Fischer's philosophy wherein he insisted his co-workers not to be influenced by theory before conducting an experiment[2]! He was the first organic chemist to receive the Nobel Prize in Chemistry in 1902. The other notable achievements during that time were the synthesis of Camphor & α-terpineol by Perkin Jr. in 1904 (FIGURE-2).[1]

Figure 2

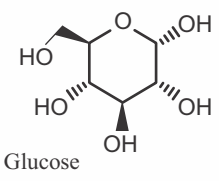


Camphor

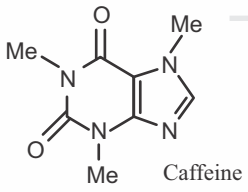


α-terpineol

Perkin Jr., 1904



Glucose



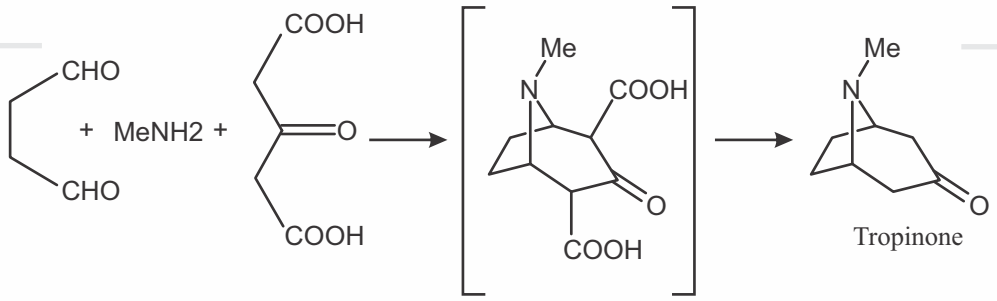
Caffeine

Emil Fischer, 1890 & 1895/1897

Next began the era of another giant of organic chemistry-Sir Robert Robinson. Amongst his notable achievements are his contributions to the structural elucidation of alkaloids-Morphine & Strychnine which are representative examples of complex alkaloids that he worked on. He is well known for his discovery of the reaction called 'Robinson annulation' which has been widely used in synthetic chemistry. He also contributed to reaction mechanism including the usage of curly arrow to show movement of electrons[3] (with regards to the contribution in reaction mechanism/ physical organic chemistry his controversy with another extraordinary chemist C K Ingold is well documented in literature but this is a story in itself and would recommend an excellent article by none other than D H R Barton touching upon this rivalry[4a]!).

However from a synthetic point of view, he is most remembered for his synthesis of tropinone[4b] which was the first of its kind where it was proved that a rational design to synthesise a molecule is possible. Robinson used the double Mannich reaction inspired by a biomimetic approach and synthesised tropinone (FIGURE-3). Thus, this combination of retrosynthetic logic and biomimetic approach is considered as a landmark in organic synthesis. It was far ahead of its time. Robinson was a controversial figure in terms of his personality. He was unusually competitive and had his share of controversy with C K Ingold in particular and also a rivalry with R B Woodward, another great synthetic chemist whom we will discuss next. Robinson was also an avid chess player. He had been the President of British Chess Federation, 1950 - 1953.

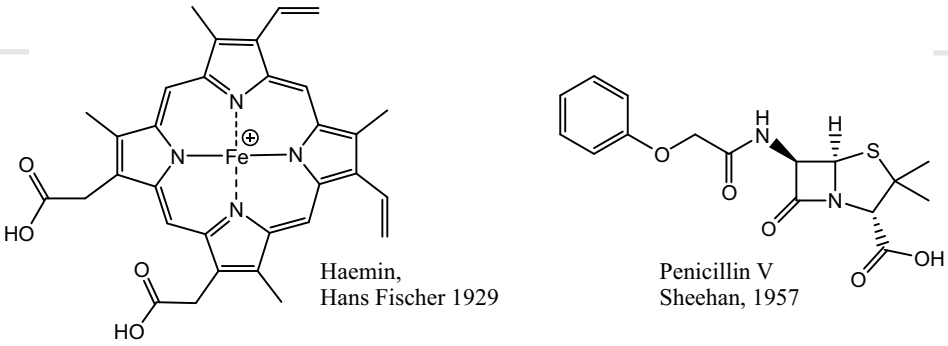
Figure 3



Robinson's landmark synthesis of Tropinone (1917)

Before we talk of R B Woodward and his achievements, it is important to note two other milestones in the field of total synthesis. First is the synthesis of Haemin by Hans Fischer in 1929. This feat and his work on chlorophyll fetched him the Nobel Prize in 1930. Second is the synthesis of penicillin V by Sheehan (FIGURE-4).[1]

Figure 4



One can see the molecular complexity in Haemin (FIGURE-4) and structurally related Chlorophyll a[5a] & Vitamin B12[5c] (FIGURE-5). The latter two were synthesised by R B Woodward considered by many as the most accomplished organic chemist of our times. A sample list of the total synthesis completed by Woodward apart from the already mentioned Chlorophyll a & vitamin B12 are complex natural products like Strychnine, Reserpine & Cephalosporin C[6] to name a few. The synthesis of Vitamin B12 was accomplished in collaboration with Eschenmoser (ETH Zurich) and spanned more than a decade with around 100 chemists having worked on this project at both Cambridge and Zurich. But this is not all that he achieved in organic chemistry. He was a pioneer in using physical methods to connect them with structural features of an organic molecule (Woodward-Fieser Rules)[7], he worked on structural elucidation of many complex molecules (including Ferrocene in which he collaborated with Wilkinson[8] which triggered a great deal of interest in the chemistry of organotransition metals-Wilkinson in 1973 won a Nobel Prize for his contributions in the field of organometallic compounds) and the Woodward-Hoffmann rules[9a] for pericyclic reactions for which Roald Hoffmann a theoretical chemist who collaborated with Woodward to devise these rules got a Nobel Prize, along with Fukui (Fukui actually started thinking on these lines long before the experimental results in Woodward's lab[9b]). By the time, of course, Woodward had already passed away or else he might have got his second Nobel Prize. The debate of VB Theory vs MO Theory was at that time tending in favour of MO theory and the contributions of Fukui & the Woodward-Hoffmann rules further tilted this debate favourably towards MO theory. The starting point of the Woodward-Hoffmann rules was an unexpected reaction in the hands of Prof. S Ranganathan (working as a postdoc in Woodward's lab)[9c] wherein he was trying an intramolecular Michael Addition which failed. While further just heating the compound, he was able to cyclise the compound with unexpected stereochemical consequence. On further investigations a whole new set of experimental data was obtained which needed rationalisation. Woodward then collaborated with R Hoffmann a theoretical chemist to find a theoretical rationale. It may be mentioned that it was William Moffitt[9c] who supposedly introduced Woodward to MO Theory during the course of their investigation of the so called octant rule (along with Carl Djerassi). However Moffitt died early ending the collaboration of Woodward and Moffitt. While we are with this topic it may be mentioned that the synthesis of the birth

control pill (a steroid molecule, an oral contraceptive pill) was achieved by Carl Djerassi and his team and is also an important moment in the history of organic synthesis. Carl Djerassi is, hence, often referred to as the "father of the birth control pill". Carl Djerassi was a multifaceted personality. Apart from his seminal contribution in the field of steroids and optical rotation (octant rule) he was also a play writer, a novelist, and a poet especially in his later part of life! He shared the same passion as Roald Hoffmann who also is a play writer, a novelist, a poet, and has a deep interest in art and humanities. In fact together Hoffmann and Djerassi also wrote a play called "Oxygen"[9d]. Hoffmann is also involved in popularising/ educating chemistry among general public (an apt thing to do considering the image of chemistry not being very good in the recent times!). Before moving on with total synthesis, it is important to mention here the work of D H R Barton whose paper on the conformation analysis of steroids[10a] had a deep impact on organic chemistry. It introduced the concept of conformation to organic chemists (six membered ring with a chair conformation and later the boat conformation). Barton along with Hassel got a Nobel Prize in 1969 "for their contributions to the development of the concept of conformation and its application in chemistry".[10b]

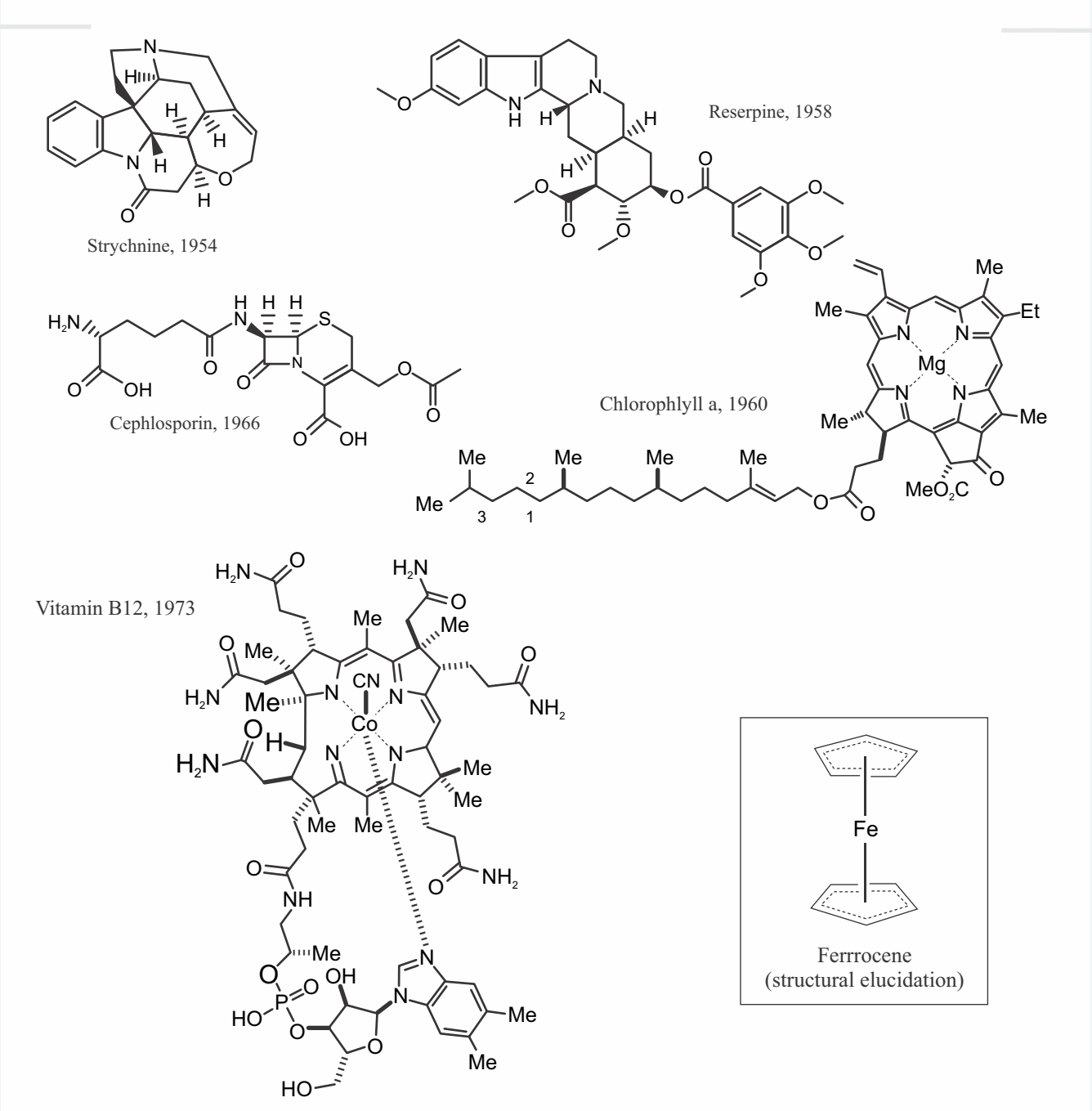


Figure 5 Representative examples of R B Woodwards exploits in organic synthesis

Another pioneer in the field of total synthesis was E J Corey. E J Corey, like R B Woodward, synthesised several complex molecules like Prostaglandins[1], Erythronolide B[1], Ginkgolide B[1], Gibberellic Acid……..(FIGURE-6) the list is too long ! However, his major contribution is the introduction of the concept of "retrosynthetic analysis"[11] which can be used to synthesise complex molecules. The concept is based on the fact that a molecule can be divided into smaller fragments (through bond forming reactions at strategic places based on that chemical bond and the knowledge of reactions) which can then be continued to get a whole set of likely sequence to synthesise the molecule. For the introduction of this concept and his contribution towards the synthesis of many complex molecules, he was awarded the Nobel Prize in 1990. It may be mentioned that the concept of retrosynthetic analysis is so obvious that one can imagine that this sort of thought processes might have been used by many previously mentioned exponents of total synthesis. One can see the genesis of this kind of thinking in the synthesis of tropinone by Robinson and there is a good possibility that R B Woodward could also be using this thought process, while attempting to synthesise complex molecules. However, no one had formalised this concept and therein lies the value of E J Corey's introduction of retrosynthetic analysis. He also elaborated this concept in depth explaining it in much details. It became an invaluable tool in the hands of synthetic chemists, attempting total synthesis of complex molecules (although easily said than done but nevertheless now with this tool, at least, one could attempt to think of a route to synthesise complex molecules). It demystified total synthesis to some extent (again the actual synthesis is always easily said than done!). E J Corey also contributed in discovering many new reagents/ reactions like: Corey Kim oxidation, Corey-Bakshi-Shibata, OTBDMS protection, etc. It is interesting that many of these reagents/ reactions did not require any costly material or reagent but rather were work of very good imagination…..many of these reagents/ reactions could have been discovered even in a less funded laboratory.

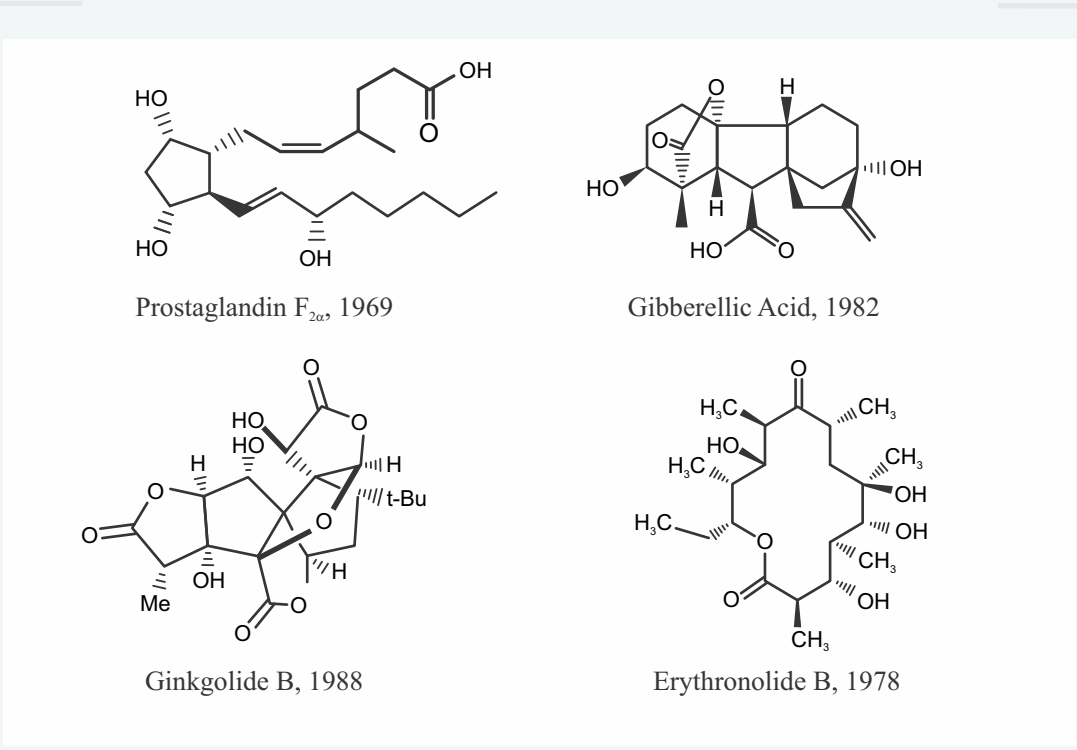
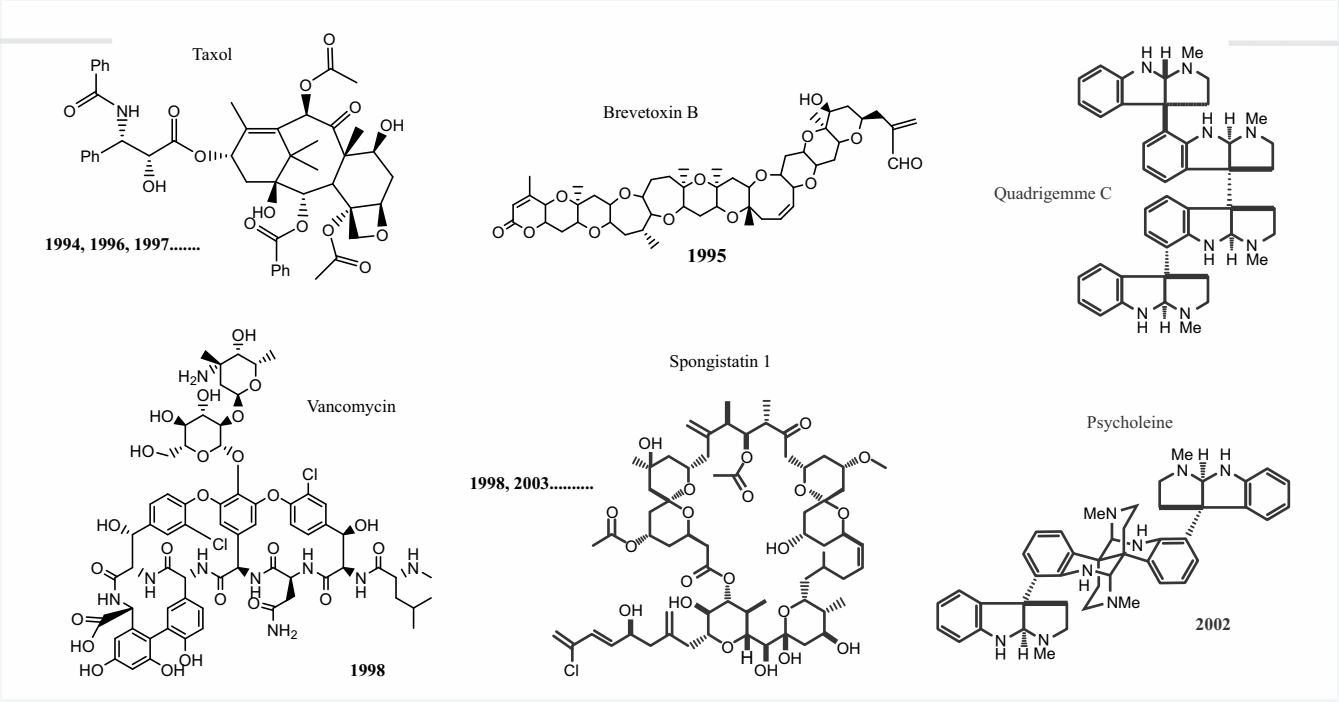


Figure 6 Representative examples of some of the total synthesis completed by E J Corey

Apart from the aforementioned organic chemists & their achievements, there are many other total synthetic chemists/ organic chemists whose work we have not touched upon (on just made a passing reference here!) like Kishi (palytoxin, considered at that time the Mount Everest of Total synthesis!), G. Stork, A. Eschenmoser, S. Danishefsky, K C Nicolaou, Mukaiyama, Paul Wender, Barry Trost, David Evans, Larry Overman, Amos Smith, Stuart Schreiber, Heathcock, Dale Boger, W S Johnson……FIGURE-7 shows some of the natural products synthesised by some of these organic chemists at the end of the century or in the beginning of the 2000s. From the point of view of total synthesis, some of the milestones worth mentioning are synthesis of progesterone by W S Johnson[12] (which utilised a biomimetic domino reaction), synthesis of Quinine (Woodward-1944 (Formal Synthesis!)[13] & Stork[14]-2001-this synthesis of Quinine is considered a masterpiece in total synthesis/ organic synthesis and is stereo-selective unlike Woodward's synthesis where he synthesised an advanced intermediate which had been reported by Rabe as converted to quinine…. there is a debate here whether the Rabe's conversion is reproducible and/ or synthetically useful) and some recent advances like Protecting Group Free synthesis of natural products by Phil Baran.[15]

Figure 7



We have also not touched upon many who contributed in discovering new reactions/ concepts which have been used widely not only in total synthesis but also in Medicinal chemistry/ organic synthesis/ organic chemistry in general, e.g., Grignard, Wittig, H C Brown, Winstein, Cram, Merrified, Prelog, Diels, Alder, D H R Barton, K B Sharpless, J M Lehn, Suzuki, Heck, Negishi, Noyori, Grubb,…….

So why do scientists indulge in total synthesis / organic synthesis? For the following reasons:

1. It's a final confirmation of their structure (although now with sophisticated analytical technique's no longer is synthesis a necessity for this but in rare cases it is still used!)
2. Discovering new chemistry during the course of synthesis
3. Synthesis of a route such that a lot many analogue's can be synthesized for biological screening
4. Large scale synthesis for the targets that can be useful to society and human beings.

The last point can be exemplified by the fact that the dye industry was started thanks to organic synthesis and many of the chemical companies started off as dye manufacturers-notable examples being BASF and Hoescht. From the dye industry also came the pharmaceutical industry, e.g., Ciba-Geigy (which later became Novartis after merger with Sandoz).

The modern chemotherapy also owes its debt in part to the dye industry (Paul Ehrlich started his experiments using dyes for staining cells and noticed that some of these kill the bacteria. Salvarsan (Arsenic containing dye) was found in 1909 by Ehrlich. Often organic synthesis is described as both art and science. Sir J W Cornforth in his article titled “The trouble with synthesis” says synthesis in spirit is close to both architecture and chess[16]!

In conclusion, synthetic organic chemists have been able to take challenging and complex targets and their toolkit for synthesising these have also increased over the last century. Initially, the very synthesis of a natural product was a challenge, then came a phase where total synthesis was like a race, i.e., who gets to synthesising the molecule first, then synthetic chemists looked at more elegant ways of synthesising the molecule (in terms of developing new chemistry including asymmetric synthesis) and finally, the focus shifted to total synthesis of biologically interesting molecules (of Medicinal significance). Presently the focus is shifting towards synthesising them:

1. Efficiently (atom economy, using new and more sophisticated chemistry-metal catalysis, cascade reactions, CH-functionalisation, etc. & shorter synthetic route's),
2. Using more practical routes (which can be scaled up), and
3. Incorporating the concept of green chemistry (reduction of hazardous chemicals-either their usage or as side products).

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   c)Lecture of RB Woodward on Vit B12: https://www.youtube.com/watch?v=YvEB05xdAy4 (Vit B12 lecture-1); https://www.youtube.com/watch?v=AVi_awjWaP4 (Vit B12 Lecture-2).
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