Some thoughts on the total synthesis of natural products

Are there still important challenges?

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Résumé **Quelques réflexions sur la synthèse totale de produits naturels. Reste-t-il encore des défis importants ?**
La synthèse totale de produits naturels demeure l'une des aventures les plus excitantes et les plus difficiles de la chimie organique. Ce bref article présente quelques réflexions personnelles sur les succès, les difficultés et les défauts de la synthèse totale et propose quelques futurs défis aux chimistes de synthèse.

Mots-clés **Synthèse totale, produits naturels, méthodologies, efficacité, groupes protecteurs.**
Key-words **Total synthesis, natural products, methodology, efficiency, protecting groups.**

The total synthesis of complex natural products still remains the most formative, exciting and daunting endeavour in organic chemistry, requiring not only a broad knowledge of chemistry but also inspiration, dedication, patience, innovative ideas and creative artistic qualities. For decades, the total synthesis of natural products has occupied a cardinal position in the discovery of novel transformations and in the development and optimisation of useful and widely applicable reactions. The fall-out of organic synthesis have radically altered our vision of chemistry, bringing in new theoretical concepts that have expanded and better rationalised our understanding of chemistry whilst at the same time stimulating the development and use of modern physical and spectroscopic techniques. The enormous impact of total synthesis on the advancement of chemistry in general is exquisitely illustrated by the Eschenmoser-Woodward synthesis of vitamin B12. This formidable endeavour took 11 years to reach completion and involved over 100 co-workers. Novel bond-forming strategies, elegant solutions to daunting synthetic predicaments, new biosynthetic hypotheses and the principles of orbital symmetry conservation have all evolved from this synthetic venture and have deeply altered our vision and knowledge of our science.

The sizes and complexities of the natural products being synthesised today bear little resemblance to the substrates that were investigated at the beginning of this century. The construction of such architecturally complex targets has emulated the search for powerful synthetic methodologies aimed at the rapid and efficient assembly of structures of undreamed complexities.

The enormous success of organic synthesis has sadly led to a feeling of self-satisfaction and to the growing belief that « no natural product was beyond the reach of a capable organic chemist provided time, manpower and money were made available ». In other words, organic synthesis is believed by some of us to have now reached maturity and to become a decaying science in the future.

Whilst the argumentation that any natural product could be prepared nowadays might bear some truth, it is beside the point and the real question should not be « can we synthesise this molecule? », but rather « how can we synthesise it efficiently, in a minimum number of steps, with optimum convergency, with as little as possible functional group transformations, few, if any, protecting group manipulations, little or no by-products and maximum atom-efficiency? Which new reaction(s) or concept(s) can be derived from this endeavour? ». Obviously, such a philosophical attitude towards total synthesis is far broader ranging than the shear assembly of a natural product at all cost. In this regard, I am always fascinated by the elegancy, the conciseness and the apparent simplicity of the synthesis of Reserpine by R.B. Woodward. The ingenuity of this « great master » in taking advantage of the shape and functionalities of the very first synthetic intermediate to derive, after only a few steps, the properly substituted ring E of Reserpine is simply magnificent.

All to often nowadays, the total synthesis of complex natural products embodies the skilful use of well-established methodologies and protecting groups compatibility and consists more in a race towards the final objective than in attempting to widen our general knowledge of chemistry by providing the chemical community with novel transformations or innovative concepts. In this context, it is always instructive to read the accounts of visionary chemists such as K. Wiesner, who synthesised several times the same but amazingly complex natural product. However, every second and third generation synthesis would embrace novel transformations, shortcut some steps and improve the overall route to the final product. Only by comparing the ultimate approach with the initial synthesis, could one really appreciate the exquisite level of elegancy achieved and the breathtaking advances that were realised by this iterative process.

Being the first one to assemble a natural product is, of course, a laudable enterprise of paramount importance since the subsequent strategies often benefit from the successes and failures observed during this initial venture. However, many of the key-problems that generally hamper our ability to efficiently construct these complex structures are simply being ignored in this approach. Thus, the key-question should not be: « Can we synthesise Taxol? », but rather: « How can we synthesise Taxol in, let's say, 10 steps? » Of course, one will strongly object that this proposal is ridiculous and that no-one can assemble Taxol in 10 steps. True… for the moment, that is. Indeed, let's remember that Willstätter prepared Tropinone in 21 steps in 1901 and that this was a landmark achievement at that time. Only a few years later, Robinson obtained the same natural product in only three steps. Thus, our inability to assemble Taxol in 10 steps stems from the paucity of suitable methodologies. The development of novel and efficient methods for the rapid construction of complex structures should therefore be strongly encouraged.

Most of today's syntheses of complex natural products are rather long and tedious and proceed with poor overall yields. These are typically due to the necessity to append and remove, with great selectivity and often repetitively, various protecting groups and to effect regularly a number of delicate functional group interconversions. Of paramount importance for organic chemistry in general, would therefore be the development of novel strategies that would obviate the need for selective protecting groups and that would allow the efficient construction of the product's backbone without interfering with the various functionalities already present in their correct oxidation levels. Clearly, such an ideal approach is well beyond our reach nowadays and it would require significant efforts from numerous research groups throughout the world to provide suitable solutions to these formidable problems.

Besides the necessary and cumbersome use of protecting groups and functionalities interconversions, the greatest toll paid in a total synthesis often arises from our long-standing inability to create the desired carbon-carbon bonds at will. Sequential assembly is typically required if control is to be exercised. The recent advent of multicomponent condensation reactions or cascade-type processes, that form multiple C-C bonds or ring systems in a single operation, raises exciting promises and there is little doubt that a growing number of them shall be used in the future, though much work still remains to widen their synthetic scope and functional group tolerance.

These are only but a few examples of the challenges that awaits a modern synthetic chemist. In contrast to the previous – and a little self-indulgent – claims, I believe wholeheartedly that the total synthesis of complex natural products is in its infancy. Like a child, we have learned to stand on our feet and to slowly walk, one step after another. It is now time to gather how to run, drive a car and fly a plane or a rocket. However, these far-reaching objectives will require asking the correct questions and solving the most challenging and daunting problems. The future of organic synthesis is at that price.

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