Aust. J. Chem., 1993, **46**, 157–170

Sir Robert Price Lecture, 1992*

The Trouble with Synthesis

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Abstract

Chemical synthesis is defined as the intentional construction of molecules by means of chemical reactions. The motives of chemists for engaging in synthesis are discussed, together with desirable developments in the art of synthesis and in the publication of its results.

I am honoured to give this lecture, named after my good friend Jerry Price. On two important occasions he has given kind help to our researches; and I will do the best I can with this thank-offering. It isn't the first time that I have given a lecture named after a living man; but the previous one was for my teacher Robert Robinson and I was very apprehensive about what he might say afterwards.

Chemists have been using the word 'synthesis' for more than 250 years, so that it predates not only the idea of molecular structure but even Dalton's atomic theory. It comes from the Greek and it means putting together. As with many other terms that we use, including organic and inorganic, we have been saddled with a not too appropriate word to describe an activity. If we took the word seriously we would apply it only to addition reactions like the diene synthesis or catalytic hydrogenation; and if we ever demote 'synthesis' in favour of some less limiting word like 'construction', the category of addition reactions might not be a bad home for it. In truth, nearly all our syntheses depend as much on breaking old bonds as on forming new ones.

There are very few words that don't acquire new meanings as they grow older, and synthesis is no exception. It does not mean making new compositions of matter, new molecules; for it happens that Nature and especially living Nature has exhibited to the chemist a very large variety of molecules. They are there, they are not new; but if we can make them from something else we say that we have synthesized them. And sometimes we proudly call our synthesis a total synthesis.

* Presented at the Division of Chemicals and Polymers, CSIRO, Clayton, Victoria, on 17 September 1992 [jointly sponsored by the Division of Chemicals and Polymers, CSIRO, and the Organic Chemistry Group (Victorian Branch), RACI].

Manuscript received 9 November 1992 0004-9425/93/020157$05.00

Briefly, we are then claiming that, if we were given adequate supplies of all the chemical elements composing our compound, we could make a specimen of the compound totally derived from the matter supplied. In practice, nobody ever executes a total synthesis and few of the raw materials used have in fact been made from their elements. Nineteenth-century chemists, notably Berthelot, have shown the way from the elements to the simpler and more abundantly available compounds (often in miserable yields and quite unpractical conditions) and the vast network of transformations relieves the modern chemist even of the need to verify that there is a notional connection between the raw materials and their constituent elements.

But synthesis of compounds from elements is not peculiar to human beings. Other organisms can assimilate elemental hydrogen, nitrogen, oxygen and sulfur, and incorporate them into a wide variety of compounds. So if we claim to have made the first total synthesis of a natural product we are reduced to the rather feeble defence that no organism is known to assimilate elemental carbon (or phosphorus). I would not bet very heavily against the discovery of an organism that will eat buckminsterfullerene, which is undoubtedly elemental carbon; and as for phosphorus it combines spontaneously with oxygen to form compounds that many organisms will certainly assimilate. It is better to admit at once that total synthesis is by restriction a human activity.

This rejection of competition, or even help, from other organisms in the execution of chemical synthesis is another nineteenth-century legacy. The first and slightly dubious synthesis of a natural product—Wöhler's urea—was considered important as a demonstration that compounds produced by living things are in no way different when human beings produce them with no help from other organisms. The doctrine of vitalism, with its idea of a mysterious force pervading living matter and differentiating it from the non-living, is still alive and vocal; even among scientists it died hard.

For example, one might have thought that Louis Pasteur's lovely experiment with racemic acid, when by intelligent inspection of one of its salts he was able to separate the crystals of 'natural' tartrate from those of its mirror image, would have persuaded him that optical activity in the disperse state is not a prerogative of life. Alas, he thought that racemic acid *was* a product of life. His racemic acid had come from grape juice via a factory where some of the tartaric acid in the juice had been racemized by boiling it down in copper pans. When presented with a truly synthetic racemic specimen of malic acid, he would not even try to resolve it, though by that time he had a method which would certainly have worked. Again, he made beautiful experiments to show that, as he put it, 'fermentation is life without oxygen'; but his vitalistic prejudice was probably what prevented him from making Buchner's experiment[1] and showing, 30 years earlier, that lifeless filtrates could also ferment.

We need no more demonstrations that the molecules of life are the same, and have the same biological actions, however they were made. So that excuse for indulging in chemical synthesis has long lost its plausibility. Indeed, with our present knowledge of the chemistry of living things and its essential unity with the chemistry that we practise, I can see no reason why we should not welcome

[1] Buchner, E., *Ber. Dtsch. Chem. Ges.*, 1897, **30**, 117, 1110.

enzymes and microbes as friends and colleagues. Since they work for even less money than graduate students, perhaps we should at least acknowledge them in publications. Nevertheless, synthesis directed by the human mind remains a most popular and respected activity among chemists, so what other excuses can we offer?

It is well worth looking at the proposition that chemical synthesis is an art form, needing no justification because it permits self-expression in its creators and produces aesthetic pleasure in those who examine its products. The greatest of synthetic chemists, Robert Burns Woodward, won the Nobel prize in 1965 for—I quote—his contributions to the art of organic synthesis. He accepted the description at the time, but there was no mistaking the Committee's undertone that synthesis may be more of an art than a science, and it is a fact that the prize has been awarded specifically for synthesis only four times during the 92 years since the first prize was awarded, if one excludes the Bosch–Haber ammonia synthesis which was not original.

If chemical synthesis is an art, which recognized arts are nearest to it? I think, in their different ways, architecture and chess. An architect's constructive imagination works under constraints imposed by the materials and labour that must be used. A grandmaster of chess creates masterpieces in the face of tough and tenacious opposition. The chemist has materials, an imperfect knowledge of their possibilities and limitations, and an opponent—the truth—who sometimes changes during the work into a teacher and friend.

There are others who think of synthesis as a manifestation of human arrogance—though they usually call it aspiration or endeavour. Elaborate expeditions are launched for the essentially useless feats of treading on the top of a high mountain or on the surface of the moon, or synthesizing a vitamin that will always be easier to get from microbes. Woodward certainly had that feeling very strongly; when he and Eschenmoser had completed the epic synthesis of Vitamin B_{12}, he insisted on completing the final steps with totally synthetic material, though they had already been executed by partial synthesis.[2] And Robert Robinson, no mean mountaineer, certainly had the climber's approach to many of his syntheses.

Comparisons apart, there is no doubt that chemical synthesis can be an immensely challenging, endlessly frustrating, totally stimulating exercise. Art, science or sport, it holds its devotees; and because it is a rather expensive activity they have to offer what inducements they can to those who alone can provide the money. Such providers usually insist that the synthesis should have some purpose: the situation is perhaps the same as that of the old alchemists who really wanted to get on with their science—they called it the hermetic art, by the way—but who had to dangle the prospect of unlimited gold in front of the medieval prince or baron who then filled the role of the research councils.

A pretext popular in the early years of this century claimed that synthesis was the final proof of structure. I can remember Robert Robinson advancing it when I asked him why he wanted to synthesize cholesterol. The trouble about that excuse was that structures in those days were deduced mainly by interpreting chemical degradations. The reactions used in synthesis were subject to the same interpretation and to similar mistakes. Nowadays, there are many

[2] Woodward, R. B., in 'Vitamin B_{12}' (Eds B. Zagalak and W. Friedrich) (Walter de Gruyter: New York 1979).

examples of natural products that cannot be crystallized so as to allow the—not quite—infallible method of X-ray diffraction to be used, and the structure is derived from computer analysis of pulsed n.m.r. spectra. In some of these cases, synthesis has indeed provided final proof that the structures deduced were wrong. So the old excuse can be usefully revived on suitable occasions.

A different line of persuasion, and rather easier to sell, is the notion that by solving a difficult problem of synthesis the chemist is likely to be forced to invent new methods. Robinson would not have invented the ring extension that bears his name;[3] I would not have invented the reduction of 2-methoxynaphthalenes to 2-tetralones;[4] and Birch would not have extended this reduction to the much more generally useful methoxybenzenes,[5] if we had not all been working on the synthesis of steroids. The triggering event for Woodward's generalizations on orbital symmetry was a reaction in the B_{12} synthesis that did not go in the sense expected.[6] But the truth is that invention, with its attendant uncertainty, is a last resort for most synthetic chemists whose goal is a natural product. The more reactions we discover, the truer this becomes; and if in the future we entrust the planning of syntheses to computer programs we shall be absolutely dependent on known reactions, the more reliable the better. The reactions we know now were, and still are, largely discovered by accident; and in the days when structures were deduced by chemistry, instead of by spectra, natural product chemistry was a very fertile source. Now, new reactions are quite often found by speculative but not purposeless search in particular areas of chemistry. Corey is the master of this genre, but there are many others now.

That brings me to the distinction between a reaction and a synthesis, and the best example I can think of comes from the first half of this century. Richard Willstätter wanted to make cyclooctatetraene to compare its properties with those of benzene. That, in 1905, was a novel and indeed pioneering excuse for synthesis: making a molecule for its theoretical interest. This pretext has been magnificently extended in recent years to create what might be called the chemistry of funny shapes: prismane, cubane and dodecahedrane are only the more symmetrical examples among a host of bizarre and practically useless molecules that have exacted hard labour from a much larger host of postgraduate and postdoctoral students. But to make cyclooctatetraene was at the time a genuinely valuable exercise. Willstätter wisely chose the line of least effort (Fig. 1) and started from an alkaloid provided by the bark of the pomegranate tree. By already known chemistry he arrived at *N*-methylgranatenine, and to this he applied the long-known techniques of exhaustive methylation, addition of bromine, and alkylation of amines. The final exhaustive methylation gave him his product.

Now this was a classic synthesis. It followed a preconceived plan; it used known reactions; it gave a miserable overall yield; and it took nearly 10 years to finish.[7] It also proved its point: benzene and cyclooctatetraene have completely different properties.

[3] Du Feu, E. C., McQuillin, F. J., and Robinson, R., *J. Chem. Soc.*, 1937, 53.
[4] Cornforth, J. W., Cornforth, R. H., and Robinson, R., *J. Chem. Soc.*, 1942, 689.
[5] Birch, A. J., *J. Chem. Soc.*, 1944, 430.
[6] Woodward, R. B., in 'Aromaticity', Spec. Publ. No. 21, p. 217 (The Chemical Society: London 1967).
[7] Willstätter, R., and Waser, E., *Ber. Dtsch. Chem. Ges.*, 1911, **44**, 3423.

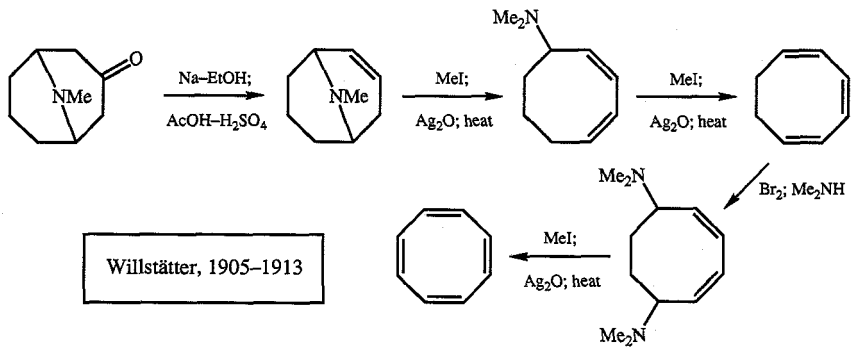


Fig. 1. Synthesis of cyclooctatetraene.

In 1940, J. W. Reppe and his team were studying industrially useful reactions of acetylene, taking advantage of techniques for handling safely this potentially explosive gas. When acetylene was pressed into a warm suspension of nickel cyanide and calcium carbide in tetrahydrofuran (thf), the product was cyclooctatetraene in up to 90% yield[8] (Fig. 2).

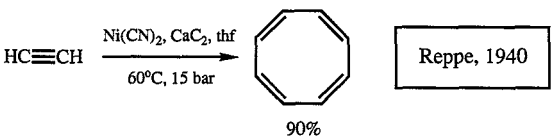


Fig. 2. A reaction of acetylene.

Was this a synthesis? Technically, it fulfils the most rigorous criteria. It can even be called a total synthesis, which Willstätter's was not; indeed, it is only two steps from the elements, since acetylene can be made from carbon and hydrogen. Also, both steps are pure additions: it is truly a putting together. But I will bet that Reppe thought of it as a reaction of acetylene, and I would disqualify it as a synthesis because there was no *purpose* to make cyclooctatetraene.

From some points of view it is no disgrace to have a reaction rather than a synthesis. Turning again to the list of Nobel prizes in chemistry, we find half a dozen laureates—Grignard, Sabatier, Diels, Alder, Brown, Wittig—whose citations refer to the discovery of reactions, and a larger number who studied their mechanisms or stereochemistry.

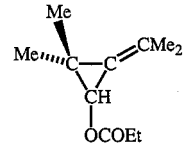
I think we have come far enough now to attempt a modern definition of chemical synthesis as *the intentional construction of molecules by means of chemical reactions*. And it is my purpose now to show the intentions and the reactions interfering with each other. The Why and the How, in other words, are inseparable except in those syntheses that are purely artistic or sporting and therefore have any How and no Why.

A nice example comes from the 1960s. A team in the United States was studying the sex attractant of the female American cockroach. Warm air was passed over a very large number of these animals and then through a cold trap. By further refining a minute amount of active material was obtained

[8] Reppe, J. W., Schlichting, O., Klager, K., and Toepel, T., *Justus Liebigs Ann. Chem.*, 1948, **560**, 1.

and a structure was proposed[9] on the basis of physical measurements (Fig. 3). There were then, as now, a considerable number of chemists looking hungrily for an excuse to synthesize something, and the effect of this structure was rather like that of a dead horse dropped into a lake of piranha fish. Here was a small molecule asking for the application of up-to-date reactions, and the excuse for synthesizing it was most grantworthy: an adequate supply of the stuff, obviously not available from natural sources, might plausibly play its part in controlling a noxious pest. Within 3 years, six approaches were reported, all most ingenious. Two of them[10,11] were successful, the others were honourable near misses. So the molecule was well and truly synthesized and the compound became readily available. There was only one snag—the proposed structure was wrong and the synthetic material inactive. A lady I know remarked at the time that, although this molecule wasn't very good at attracting male cockroaches, it certainly attracted a lot of organic chemists.... but perhaps it would be kinder to say that synthesis here was the final proof of non-structure. And there are happier endings to many another story of this kind, for example in the fields of perfumes and flavours where a component present only in traces may have a dominant effect. In such cases the versatility and power of modern synthetic methods, acting on information provided by modern analytical methods and motivated by the economic or biological importance of the target, can be invaluable.

Fig. 3. An attractive molecule.



All this is just part of the ballet between Chemistry and Nature that has been danced now for more than a hundred years. Nature produces something that humanity wants or needs, but doesn't make enough of it; or, if she does, makes it too expensive to extract or makes it in a country whose people charge too much for it. Europe once imported indigo and madder, both ancient dyestuffs from plants, from the East and Middle East. Chemistry found out how to make both from coal tar, a by-product of the coke ovens and the old gasworks; in fact, the fraction of coal tar containing anthracene came to be called 'Turkey Red oil'. The old indigo syntheses have some fascinating chemistry that is a little obscure even now. In that case, Chemistry won. What it did, of course, was to use dead plants—coal—instead of live ones. But sometimes, Chemistry switches from one live plant to another, as when the turpentine from pine trees becomes the raw material for making the perfumes of flowers.

It was my lot to take part in several of these dances; but the most enthralling was the first: penicillin. My wife and I were graduate students at Oxford when the first concentrates from Fleming's fungus were painfully got together at the School of Pathology and when the first trials with human patients were made at the Radcliffe Infirmary. At the Dyson Perrins Laboratory, Robinson accepted

[9] Jacobson, M., Beroza, M., and Yamamota, R. T., *Science*, 1963, **139**, 48.
[10] Day, A. C., and Whiting, M. C., *Proc. Chem. Soc., London*, 1964, 368.
[11] Wakabayashi, N., *J. Org. Chem.*, 1967, **32**, 489.

the chemical challenge and the nucleus of the team was formed: Ted Abraham and Ernst Chain from Pathology, and Wilson Baker with Robert from the Dyson Perrins. By 1943, when we joined the team, the scene was set. Here was a chemical substance—we didn't know then what it was—enormously effective against bacterial infections including some that sulfonamides could not cure, and obtainable only in traces and with great labour from the broth in which an obscure mould had grown. Chemistry had scored a notable success in the fight against bacterial disease when it developed the sulfonamides. Perhaps it could find out the structure of penicillin and then synthesize it. In time of war, even a costly synthesis, if it could produce enough, would serve.

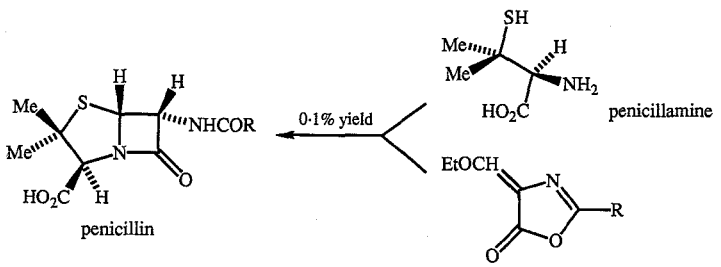


Fig. 4. The first synthesis of penicillin.

The carbon in penicillin (Fig. 4) occurs in three blocks. During 1943, they were all identified and the variability of the side chain was established. I guessed the structure of another part—penicillamine—and did the synthesis and optical resolution in 6 weeks. Before the year's end, synthesis could be concentrated on two different but almost equivalent structures. The international effort that extended over the next 3 years is recorded in 'The Chemistry of Penicillin',[12] published in 1949. There was so much work, and it was so badly abstracted, that rediscoveries of some of it were being made 20 years later, and for all I know still are. But the limit of success was a synthesis in about 0·1% yield.

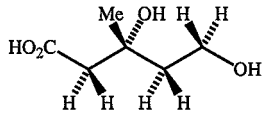
Meanwhile, Nature with human aid was not idle. Better nutrient media were found for the mould, techniques were perfected for growing it in deep tanks instead of in anything shallow that could be sterilized and plugged. Better still, another species of *Penicillium* was found to outperform the Fleming strain; and best of all, when mutants were induced and selected, the yields went up by three orders of magnitude. With more penicillin in the broth, extraction procedures became simpler: penicillin became cheap as well as abundant. Even penicillamine, when it turned out to be useful in lead poisoning and in some other disturbances of metal metabolism, was easier to make by degrading natural penicillins than by synthesis. And when, in 1957, John Sheehan's persistence produced a rational synthesis of penicillin,[13] this was far from viable economically. Thus far, Nature had won hands down; but the balance was restored in a rather curious way.

It was discovered that certain conditions of fermentation could produce a penicillin with no side chain, and that this could be provided by chemistry with

[12] Clarke, H. T., Johnson, J. R., and Robinson, R., (Eds) 'The Chemistry of Penicillin' (Princeton University Press, 1949).
[13] Sheehan, J. C., and Henery-Logan, K. R., *J. Am. Chem. Soc.*, 1959, **81**, 3089.

any side chain desired.[14] And some of these side chains gave penicillins with superior properties. At present, most of the penicillins used in medicine are hybrids, half natural and half synthetic. So the ballet has finished in a triumphal *pas de deux*. But with many, not all, of the useful antibiotics, Nature is still supreme, though that has not prevented chemists from trying to synthesize them.

During the period of which I have been speaking, biochemists began to learn about the actual chemical processes of life. This development was generated partly by better methods of separating and identifying small amounts of material, but above all it owed its impetus to the availability of stable and radioactive isotopes and of the analytical techniques to detect and measure them. It became possible to study the actual workings of a living cell, and I well remember the excitement of reading Rudolf Schoenheimer's little book, 'The Dynamic State of Body Constituents', in which he shows that throughout our lives we have little more stability or permanence than a flame. More to the present point, it became possible to put loaded questions to a living organism or to one of its functional systems, by presenting it with an isotopically labelled version of something that it would eat. And the more that was understood about the chemistry of the organism, the more subtle became these questions, and organic synthesis began to play an ever more useful part in loading them.



(3*R*)-mevalonic acid

Fig. 5. Mevalonic acid.

For work of this kind, synthesis is often delimited by which isotopes are wanted for labelling, and at which positions. I have had a long love affair with mevalonic acid, the precursor of terpenoids (Fig. 5). Altogether, we labelled this molecule in 17 different ways using 10 different syntheses, eight of them novel at the time; and very recently we added an eleventh synthesis for an eighteenth labelling mode. There were compelling reasons for choosing each of these syntheses, but I have time for only one example. Here, the label had to be ^{13}C and a high proportion of molecules had to have isotopic atoms at both labelling positions.[15]

The reason behind this requirement was a skeletal rearrangement occurring when lanosterol, a precursor of cholesterol, is formed from squalene, or rather, as is now known, from squalene epoxide. The question to answer was whether the rearranged methyl group in lanosterol came from position *A* or position *B* in squalene (Fig. 6). Six molecules of mevalonic acid go to make one molecule of squalene and the pattern of incorporation was known. Ordinary isotopic labelling of the migrating group would not distinguish between the two modes of rearrangement, because of the symmetry of the squalene molecule about its midpoint. The same symmetry would defeat ordinary double labelling at both the migrating group and its receptor position. But if the statistical distribution

[14] Batchelor, F. R., Doyle, F. P., Nayler, J. H. C., and Rollinson, G. N., *Nature (London)*, 1959, **183**, 257.
[15] Cornforth, J. W., Cornforth, R. H., Pelter, A., Horning, M. G., and Popják, G., *Tetrahedron*, 1959, **5**, 311.

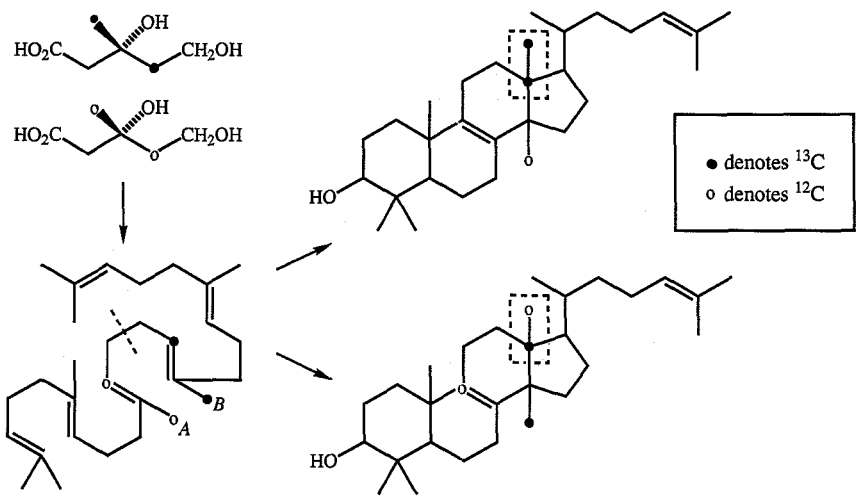


Fig. 6. Labelled mevalonic acid and its incorporation into lanosterol via squalene.

of the two labels was skewed by dilution with non-isotopic mevalonic acid, an intramolecular rearrangement within a group of atoms originating from one mevalonic acid molecule would produce an excess of lanosterol doubly isotopic at adjacent positions, and chemical degradation of this lanosterol to separate those two carbon atoms would allow measurement of that excess. That was the basis of the experiment and the imperative for synthesis (Fig. 7).

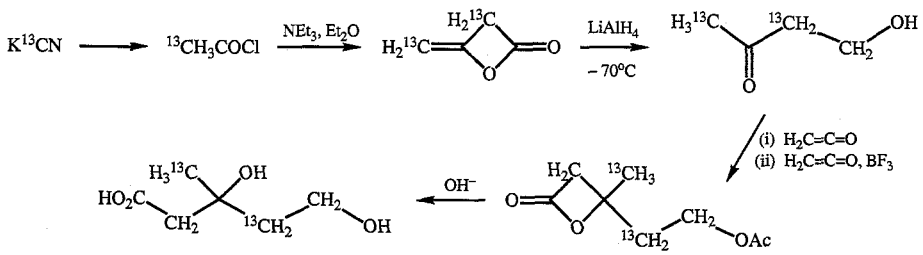


Fig. 7. Synthesis of doubly isotopic mevalonic acid.

One interesting effect of isotopic synthesis is to take us back closer to the classic ideal of synthesis from the elements. Here, we had to start from isotopic potassium cyanide. By one-carbon chemistry this was turned into methyl-labelled acetyl chloride, which was treated, in ether, first with triethylamine at reflux and then with lithium aluminium hydride at −70°C. In this three-step reaction ketene is formed first and dimerizes to diketene, which is reduced to 4-hydroxybutan-2-one labelled at positions 1 and 3. To skew the distribution of isotopic species, this was diluted with about an equal weight of unlabelled 4-hydroxybutan-2-one, then treated twice with ketene: once to acetylate the hydroxy group, then in the presence of boron trifluoride to form a β-lactone which yielded the labelled mevalonic acid on hydrolysis. Curiously, this synthesis resembles quite closely the

biosynthesis of mevalonic acid, with ketene taking the place of acetyl-coenzyme A; but we could not have claimed it as a biomimetic synthesis since that horrible word had yet to be invented. As it happens, this is also one of the best ways to make unlabelled mevalonic acid in quantity, if the hydroxybutanone is prepared less exotically.

I should not leave the subject of isotopic synthesis without mentioning tachosynthesis, in which the 20-minute half-life of the positron-emitting carbon-11 has forced the development of a fascinating branch of chemistry requiring an ion accelerator, a radiochemical laboratory, and a hospital in close proximity to each other, and subordinating all other considerations to one imperative—speed.[16]

Probably, most of the chemical synthesis done today is carried out in industrial laboratories, much of it aimed to produce new pharmaceuticals, agrochemicals, additives and materials of many uses. One major reason for aiming at a particular type of molecule is that a competitor has, or is suspected of having, a successful product of that type, and this generates what I call interstitial synthesis—trying to find loopholes, in a patent for example. Again, industrial laboratories usually have screening programs designed to review large numbers of compounds in search of some desired property. When one compound is so detected—and rather seldom has it been made with that particular property in view—a program of synthesis may be directed to variations on the theme compound. The synthesis, unlike the screening, is not entirely random; but above all, the object is to maximize the number of compounds made and to minimize the time taken. This puts a premium on known and reliable synthetic methods and it discourages both innovation and the exploitation of unexpected findings. In contrast, when a candidate for commercial development arises some very interesting synthesis is often initiated, since the object here is to find the shortest, cheapest, cleanest route to the target. Innovation becomes desirable, bold short cuts are tried, and some of these syntheses are among the neatest pieces of chemistry I know. The synthesis of Nylon 6–6 from propene, ammonia, air, hydrogen and water (Fig. 8) is beautiful in its seeming simplicity, but our academic standards would disqualify it because all of it was not found out by the same people.

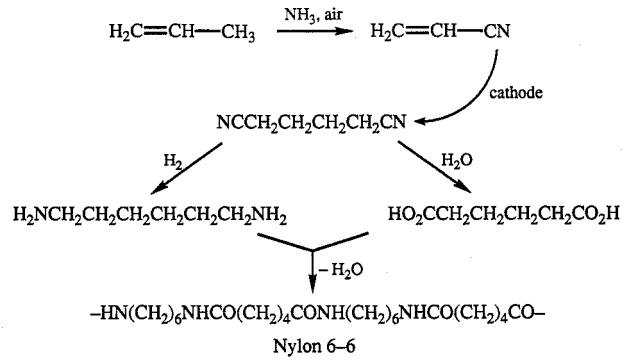


Fig. 8. Industrial synthesis of Nylon 6–6.

[16] Långström, B., *et al.*, in 'Biomedical Imaging' (Academic Press: London 1985).

The larger the scale, and the cheaper the product has to be, the more factors must be taken into consideration when choosing the winning method—or, not infrequently, for rejecting them all. Problems about pollution from the by-products of a process are nowadays taken into consideration in the planning, not tackled retrospectively. And no nonsense about the pure ideal of total synthesis limits the choice of raw materials or methods. Anyone who has helped to plan an industrial synthesis tends to pity the poverty of the criteria that an academic synthesis must meet. Work of this sort ought to be held in greater respect and published more often than, alas, it is.

Returning to the rarefied atmosphere of academic synthesis, we can identify some different constraints. For the most part, synthesis in university laboratories is executed by learners: graduate students and inexperienced postdoctorals. It has become accepted that the supervisor's role is to plan and inspire, not to participate. As one who has been a bench worker almost continuously for 60 years and who has been learning all that time about the best ways to carry out chemical experiments I find this sad, though I know the constraints on the supervisors. The effect has been to stereotype practical methods and to limit the choice available. I am far from decrying the value of chemical synthesis as intellectual training, but I know that in its practice the hands and brain must work together as in few other disciplines. Every experiment is a new experiment, no matter how often others—and you—may have done it before. To put it no higher, the use of stereotyped procedures tends to add to the expense of research as well a being of less benefit to the trainee.

Perhaps this is the place to comment on the publication of chemical syntheses. It has become customary—I blame Bob Woodward more than any other for making it so—to report a synthesis in a preliminary note or in a sequence of notes, and to defer full publication with proper description of intermediates and methods for years or for ever. Some of Woodward's best syntheses were never reported in detail, and never will be. And if in the beginning this was principally a disease of multistep synthesis, it has spread to the reporting of new reactions and of the increasing number of compounds that are synthesized for specific purposes such as catalysis or complexation. These are useful activities; but as time goes on the value of a chemical paper tends to reside more and more in what was actually done and made, not in why it was done. As it is, there are now thousands of claims to novel compounds that are verifiable only by repetition of the work, because it cannot be done by comparison or analysis of published properties. It is a poor tribute to chemical synthesis to say that it has been pouring a large volume of unpurified sewage into the chemical literature, but that is too near the truth for comfort. I do not know what can be done about this, though I would support a conspiracy of editors to refuse to publish a preliminary note if the full publication from a previous note was still outstanding after an agreed interval.

Now, what of the future of chemical synthesis? There is no doubt that it remains a most popular activity: picking up at random a recent *Chemical Communications* I found that 40% of the articles had to do with synthesis or synthetic methods. Clark Still has pointed out that there is practically no imaginable small molecule of reasonable stability that cannot be made by existing methods in sufficient quantity to examine its properties—given enough time,

money and effort. Advances in photochemistry, in free-radical chemistry, and in the use of auxiliary elements, notably silicon, offer an almost embarrassingly wide choice of procedures; and Corey[17] has pioneered effective, programmable rules for combining them into strategies for synthesis. Much attention is rightly being given to stereospecific synthesis and the control of chirality. Success here has come from better understanding of preferred conformations during reactions, from the now predictable stereochemistry of electrocyclic reactions, and from the much greater use of transition and other elements to hold reactants in desired conformations or to coordinate reagents on the same metal atom.

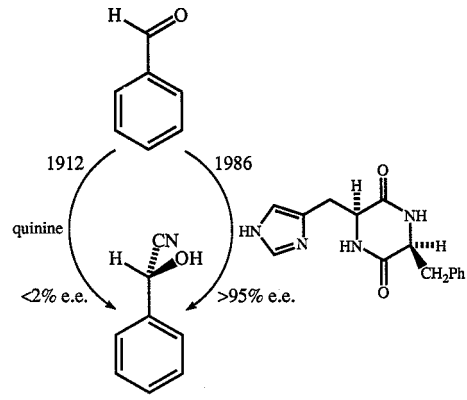


Fig. 9. Asymmetric synthesis of mandelonitrile.

To illustrate the advance of chiral catalysis over the years one can go back to the original example of absolute asymmetric synthesis (Fig. 9). Bredig[18] found in 1912 a small anisochirality* in mandelonitrile formed from benzaldehyde and hydrogen cyanide in the presence of what seems to have been a crude preparation of cinchona alkaloids. The industrial importance of a related mandelonitrile stimulated a search for more efficient chiral catalysts and the best of them gave an impressive result[19] even when applied to benzaldehyde rather than the targeted 3-phenoxybenzaldehyde, which was still better. One could only wish it possible to find such catalysts by prediction but, alas, our powers in this direction are still infantile.

Other advances have nearly perfected the art of the protecting group. Name any functional group that you want to shield temporarily from your operations on another part of the molecule, and there is a menu of reagents, artfully tuned for ease of attachment and selectivity of removal. Add to these the selective reagents that discriminate between similar functional groups, and you have so many acronyms that you already need a glossary to sort them out.

So far, so good. Now let us look at the other face of the coin. We are in danger of being limited by our own powers. In the chemistry of natural products

* I take this opportunity of proposing that the terms *monochiral* (one-handed), *isochiral* (equal-handed), and *anisochiral* (unequal-handed) should be used in place of homochiral, racemic, and scalemic respectively.

[17] Corey, E. J., and Cheng, Xue-Min, 'The Logic of Chemical Synthesis' (Wiley Interscience: 1989).

[18] Bredig, C., *Chem. Ztg*, 1912, **35**, 324.

[19] Tanaka, K., Mori, A., and Inoue, S., *J. Org. Chem.*, 1990, **55**, 181.

it is becoming rather unusual to carry out any chemistry on a product that you isolate. Spectroscopy or X-ray diffraction gives you the answer to the structural problem and if you need to modify the structure you use well understood reactions. But in the days when it was actually necessary to do some chemistry to solve the structural problem, natural product chemistry was one of the most prolific sources of new reactions. I suggest that this was because the people trying the reactions did not know what to expect. Similarly, if you plan a synthesis and leave its execution to less skilled people who have been told what to expect, you are likely to miss observations and opportunities that you would not miss if you allowed yourself to be taught by the experiments instead of trying to teach Nature how she should behave. And if you boast too loudly that you can devise a synthesis of anything, those who use your work may relegate *you* to the rank of a technician: oil in the machinery, indispensable but expendable. It is better to have good reasons of your own for your syntheses—reasons that others accept but do not choose.

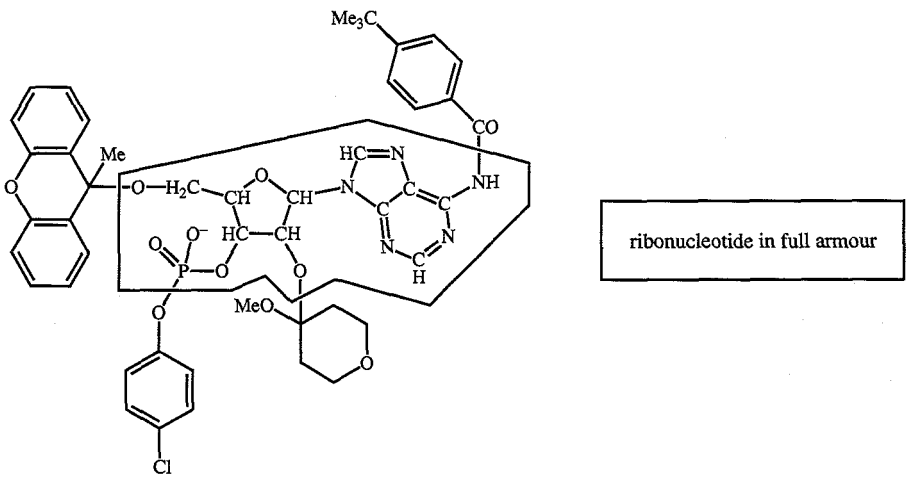


Fig. 10. Protected and activated ribonucleotide.

The infrastructure of knowledge and analytical technique on which we base our present syntheses is highly impressive, but I suspect—indeed, I hope—that in the future it may come to be regarded much as we regard the mechanisms drawn by Heath Robinson or Rowland Emett: quaint. It is nice to have a choice of protecting groups, but using one means two more steps in the synthesis. Also, some protecting groups and some reactions are so expensive that there is no chance of their being used outside a chemical or biochemical laboratory. How much better if we begin to regard their use as an imperfection, an artistic failure if you like, and try to eliminate them. The methods which we use to synthesize the oligopeptides or oligonucleotides (Fig. 10) needed by our friends the biochemists and molecular biologists are by present standards most ingenious, but they do sometimes remind me of a medieval knight buckling on a hundredweight of armour before being hoisted onto a carthorse to go into battle.

We have before us all the time the example of the enzymes, which handle substrates with many unprotected functional groups and select unerringly their

target group because their specific catalysis is based not on obstructing the wrong reaction but enormously accelerating the right one. Perhaps there is a prospect of things to come in Corey's development of the so-called CBS catalysts[20] (Fig. 11). These chiral oxazaborolidines do not themselves reduce carbonyl groups, and diborane in tetrahydrofuran is a poor reductant, but the two together form a complex that reacts fast and with high anisochirality. The analogy of the catalyst to an enzyme and of diborane to a coenzyme is quite close, and the only thing lacking here is further catalysis of the reaction by specific binding of the substrate. As it is, the selectivity is achieved by obstruction, not positive binding.

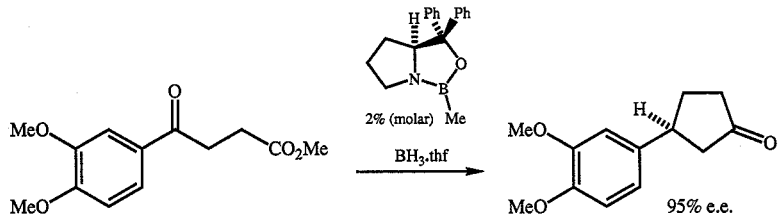


Fig. 11. CBS catalysis.

We have not had as much time as the enzymes to develop their approach to synthesis—not by some seven powers of 10—but we are supposed to be more purposeful. And we have to use the old methods of synthesis to construct the new world of specific catalysis, and we have not at present much idea of what we should be making. We need to know a lot more about intermolecular associations; and enzymes, though they certainly have a lot to teach us, are not very talkative. Still, I suppose we shall learn; and luckily there are many excellent reasons why we should make the attempt: the problem is not How or Why, but What. May I live to see, and better to share, more than the limited success that so far has been achieved.

[20] Corey, E. J., Bakshi, R. K., and Shibata, S., *J. Am. Chem. Soc.*, 1987, **109**, 5551.