The economies of synthesis†

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Introduction

Since the dawn of organic chemistry, the synthesis of complex natural products has been the testing ground of methods and strategies in synthesis and in doing so defines the frontiers of the field.[1] Endeavours in complex molecule total synthesis often have a way of yielding enormous dividends in the form of fundamental insight into selectivity principles and the outright invention of new chemistry in order to reach the target. With increasing capabilities in the power of organic synthesis the perception of what constitutes a complex target structure has changed accordingly, be it from acetic acid to adamantane to strychnine to erythronolide to maitotoxin and so on. The last century has witnessed a breathtaking development of synthetic methods and celebrated epochal syntheses of terrifyingly complex target compounds,[1] and in doing so has pushed the capabilities of synthetic methodology to its limits. One culmination point was the total synthesis of palytoxin, **1**,[2] a compound with 64 stereogenic centres (Scheme 1).

Palytoxin, **1**, was assembled from seven building blocks in 39 steps. The synthesis of the seven building blocks has not been published yet in detail, but it can be safely guessed that this required more than 140 steps. Hence it is obvious what enormous effort, manpower, and logistics were involved.

Due to economic considerations, eventually society will not be able to support such an endeavour, unless it is of utmost importance such as the penicillin synthesis project during World War II. In that effort more than 1000 chemists in 39 laboratories joined forces.[3a] The synthetic strategies and methods of the 20th century reach their limits with molecules such as palytoxin, when the number of synthetic steps significantly exceeds 100. In a manufacturing setting, the production plant synthesis of Roche's Fuzeon with 106 steps[3b] may well hold the record for decades to come. It must be the goal of the 21st century to accomplish *more with less*, and in order to do so, one has to analyse the factors that are limiting in traditional organic synthesis.

From the discussion above one realises that the number of steps in a synthesis has a paramount influence on the feasibility and practicality of a synthesis project, as it determines

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† Part of the rapid formation of molecular complexity in organic synthesis themed issue.

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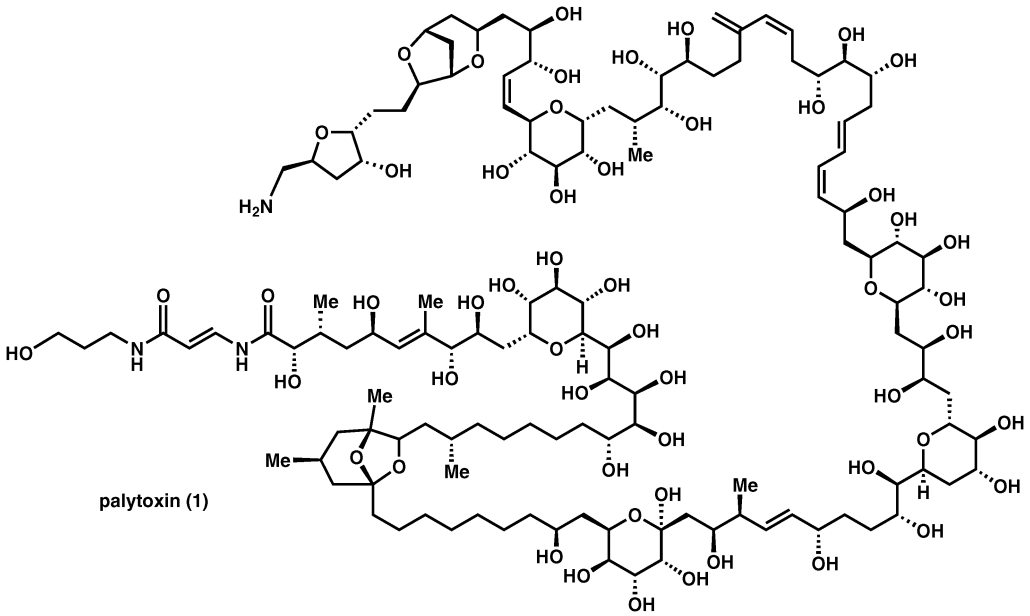

Scheme 1 Palytoxin (**1**).

the manpower input, the material input, the logistics involved as well as the amount of waste and byproducts that are handled. It is for this very good reason that Wender *et al.* emphasise the "step economy" of synthesis projects.[4] Yet this appeal has to be translated into clear guidance on how to reduce the step count, *i.e.* to simplify or streamline complex target syntheses.

This leads to the fundamental question: which steps in a synthesis sequence are essential and, hence, indispensable? This question has been answered by Hendrickson in 1975, when he addressed "the ideal synthesis:"[5]

"*The ideal synthesis creates a complex molecule... in a sequence of only construction reactions involving no intermediary refunctionalisations, and leading directly to the target, not only its skeleton but also its correctly placed functionality*."

Reinhard W. Hoffmann

Reinhard W. Hoffmann studied chemistry from 1951 to 1958 at the University of Bonn, finishing with a doctorate under the guidance of Professor B. Helferich. Two years of postdoctoral studies at the Pennsylvania State University were followed by a second postdoctorate with Professor G. Wittig at the University of Heidelberg. There he started his independent research that led to his habilitation in 1964. Three years later he was appointed as Dozent at the Technische Hochschule Darmstadt. Since 1970 he has held a position as professor of organic chemistry at the Universität Marburg (emeritus status since 2001).

Hendrickson postulates that the skeleton forming steps are the only essential steps in synthesis. If the skeleton forming steps are executed correctly, one should be able to simultaneously set up the functionality needed for the final target or the next step, including the requisite stereocentres. All other refunctionalisation steps (*e.g.* protecting group management steps, non-strategic redox manipulations, *etc.*) should be minimised in order to simplify complex target synthesis. Indeed, the simplification of synthesis with respect to reducing the number of steps and redox manipulations, as well as molecular waste, is imperative. However, one must not forget the overall goal of increased efficiency and should keep in mind the importance of molecular yield. A balance between brevity of sequence and overall yield is critically important.

To understand how far we are away from Hendrickson's ideal synthesis, take for example the assembly line of Kishi's palytoxin synthesis. It involved 11 skeleton forming steps, 15 refunctionalisation steps, and 13 protecting group management steps. Kishi's palytoxin synthesis can be used as a ruler for the state of natural product synthesis at the end of the last century. To generalise from this single example, this reveals that roughly two thirds of the steps of a synthesis are ones that reflect our inability to achieve the Hendrickson "ideal." This is a consequence of the fact that the most sophisticated methods for many skeleton-forming reactions have not yet been developed. The current set of methods are not chemoselective enough to allow for the elimination of non-skeleton building steps.[6] While new methodology is enabling in the synthesis of complex natural products, thinking about the logic and strategy required to reach the "ideal synthesis" is essential.[7]

The economies of synthesis are a useful conceptual framework from which to design and analyse syntheses. What follows below is a brief description of the "economic principles" underlying synthesis logic and a series of synthesis vignettes, which illustrate such economic considerations.

Step economy

The precepts of step economy teach organic chemists that minimising the number of steps leads to an efficient multistep synthesis in terms of cost and time expended to obtain the desired target. While designing and executing a target-oriented synthesis, the structure cannot be modified to accommodate the current state of the art in organic synthesis, rather "the goal structure is very clear and stubbornly inflexible."[8] Thus, the conceptual framework of step economy brings about the conclusion that achieving a total synthesis requires innovation in the form of strategy, tactics and method invention. Alternatively, in cases where there is not a goal structure, but rather a goal function, such as in some biological, medicinal or materials studies, the target can be chemically simplified to the extent that it requires a fewer number of steps to access. The judicious choice and development of reactions or sequences of reactions allows for the step-economical synthesis of a given target structure.[9]

Atom economy

A traditional perspective on the development of novel chemical transforms prioritises synthetic efficiency in terms of mole percent by the maximisation of theoretical product yield with respect to chemo-, regio-, diastereo-, and enantioselective control. A modification of this ideological perspective came with Trost's concept of atom economy,[10] which places an additional restriction on synthetic methodology—that is to maximise the mass efficiency of a reaction with respect to all of the reactants. When viewing organic reactions with an atom economy "filter," the ideal reaction incorporates all of the atoms of the starting materials into the desired product by the merger of chemical building blocks, using only catalytic quantities of reagents. For example, the Diels–Alder reaction proceeds with 100% atom economy. Multiple features of a reaction come under scrutiny, including stoichiometric reagents and high molecular weight byproducts. The importance of this perspective becomes clear given the cost of pharmaceutical and material production, as well as the increasing importance of green chemistry within the context of sustainable development.[11]

Redox economy

Accounting for redox manipulations over the course of a synthesis can be a powerful tool to shorten the pathway to a given target molecule. The basic goal of redox economy is to minimise non-strategic redox manipulations in order to achieve an isohypsic synthesis—one which has no redox steps. When oxidation or reduction operations are used, the oxidation state of the intermediates should not fluctuate, but rather increase or decrease steadily (or exponentially) in the construction of complex molecules. The natural consequence of this is a step economic synthesis.[12] Additionally, due to a lack of chemoselective methodologies, the avoidance of oxidation and reduction steps frequently results in a more atom economic synthesis, as these reactions (relative to redox neutral reactions) tend to be less atom economical. For example, in the Dess–Martin-mediated oxidation of an alcohol, a reagent with a molecular weight of 424 is used to remove 2 hydrogen atoms.

Illustrative syntheses

Methyl homodaphniphyllate and *proto*-daphniphylline (Heathcock)

One of the most time-tested approaches to achieving an efficient synthesis is through employing a biomimetic strategy.[13] These strategies frequently have the natural consequence of reducing the number of functional group interconversions necessary to achieve the desired level of complexity. An overwhelming example of how this can be a successful strategy is in Heathcock and Piettre' synthesis of *proto*-daphniphylline, **10**. They use a purely abiotic "network analysis" (standard retrosynthetic analysis) to methyl homodaphniphyllate, **6** (Scheme 2A), and another approach draws heavily from the presumed biosynthesis (Scheme 2B).

The first approach builds the skeleton layer by layer using network analysis and must address several refunctionalisation steps of the type Hendrickson teaches us to avoid. In contrast, the use of a biomimetic Michael, Diels–Alder, aza-Prins cascade leads to the most efficient synthesis of the natural product. In a single isohypsic cascade (**7** → **10**), two C–N bonds, four C–C bonds, and five rings are generated, underscoring the power of redox neutral (isohypsic) reactions in synthesis. This rapid generation of complexity demonstrated in Heathcock's second-generation synthesis not only allows for a general strategy for the synthesis of a diverse family of alkaloids, but also minimises the use of protecting groups. The biomimetic strategy was later applied to a number of family members, including methyl homodaphniphyllate, **6**.

While protecting groups cannot always be completely eliminated in the synthesis of complex molecules, minimisation of their use is advantageous from the perspectives of both step and atom economy. The pros and cons of protecting group chemistry have recently been reviewed.[6]

Torreyanic acid (Porco)

Another broadly applicable biomimetic Diels–Alder strategy has been employed by Porco and co-workers in their elegant syntheses of epoxyquinoid natural products.[14] One example of this Diels–Alder dimerisation event is shown in Scheme 3 with the total synthesis of torreyanic acid (**17**). While protecting group interchanges are employed in the synthesis of the monomer, **16**, the final step proceeds with all of the functionality present in the dimeric natural product. In this convergent approach, the number of steps required is greatly diminished, relative to a hypothetical alternative strategy, as the monomeric components are identical and do not require separate syntheses.

Typical of pericyclic reactions (sigmatropic rearrangements, electrocyclisations, group transfer reactions, and cycloadditions) is their atom-economical nature with all of the atoms in the starting materials typically present in the product or with loss of low molecular weight materials (CO_2, N_2, *etc.*). In a spectacular show of atom economy, no other reactants

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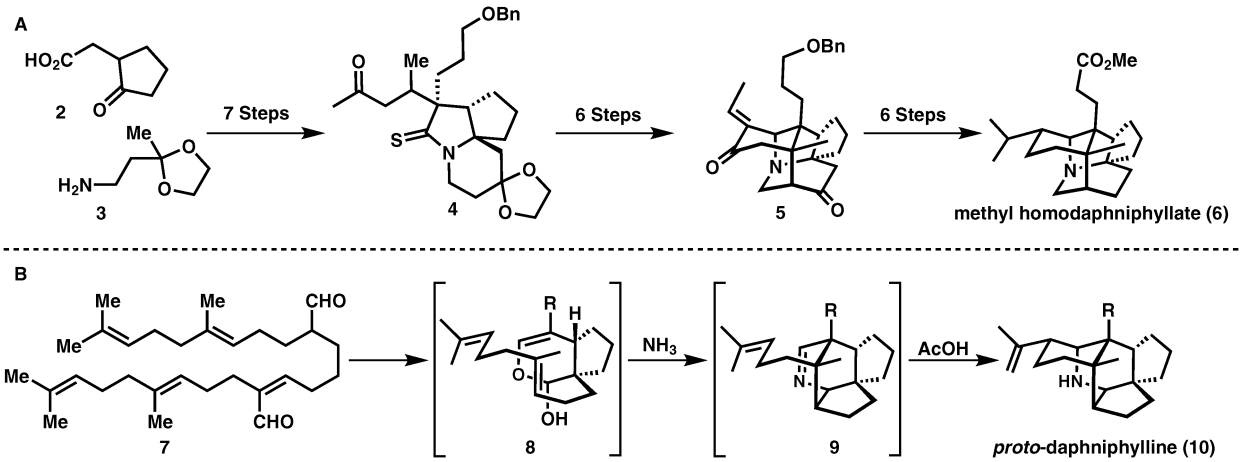
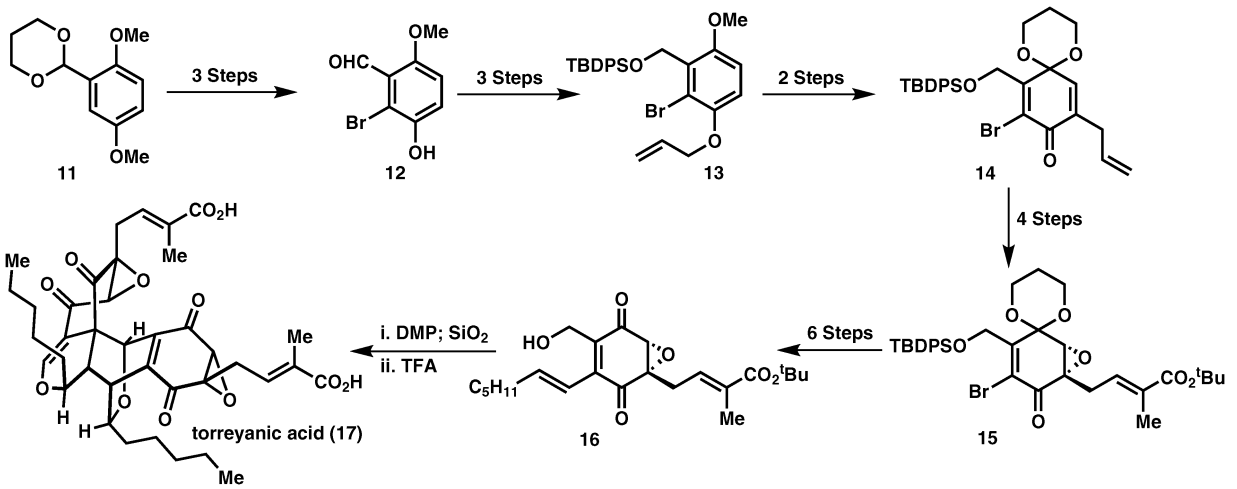


Scheme 2 A dramatic cascade reaction en route to daphniphyllum alkaloids.



Scheme 3 Biomimetic Diels–Alder reaction in the synthesis of epoxyquinoid natural products.

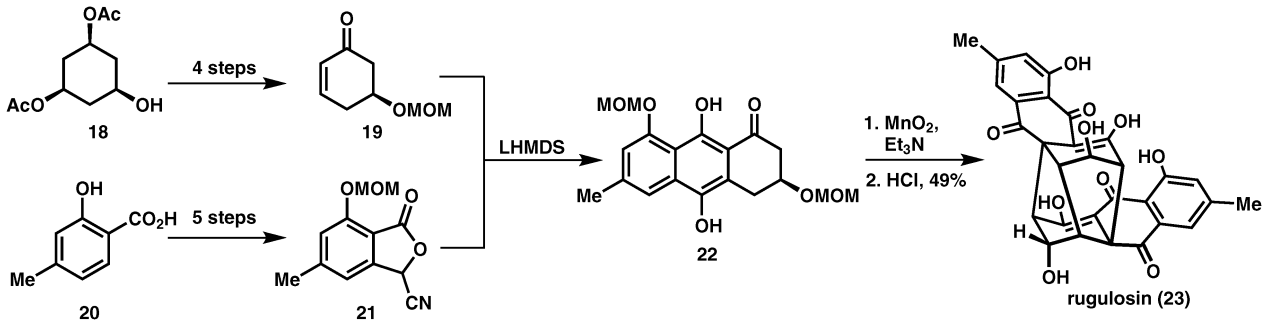
(catalyst, solvent, *etc.*) are necessary to effect Porco's Diels–Alder cycloaddition. Also typical of pericyclic reactions is that the starting materials' oxidation state usually does not change (cycloadditions and ene reactions with singlet-oxygen are obvious exceptions to this rule). Thus, striving for a redox neutral strategy can naturally guide a chemist to consider pericyclic reactions in retrosynthetic analysis.

Rugulosin (Nicolaou)

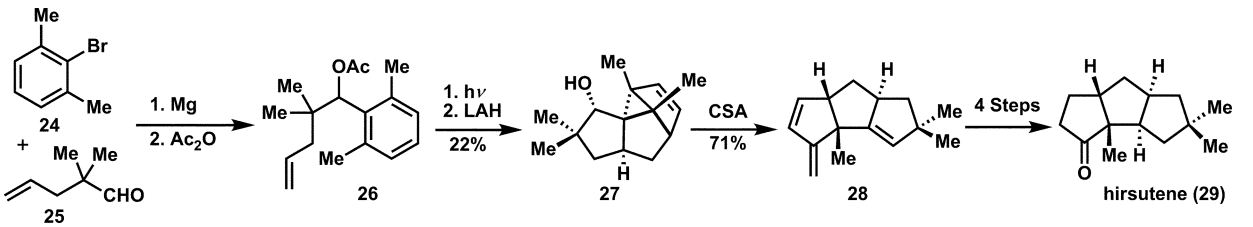
Another beautiful example of biomimetic cascade reactions is seen in Nicolaou's total synthesis of rugulosin, **23**, and related family members (Scheme 4).[15] Nicolaou and co-workers were attracted to these targets by their highly congested core structures and were intrigued by the possibility of re-enacting their biosynthesis. This was ultimately achieved by first synthesising a suitably protected monomer, **22**, which upon exposure to basic, oxidative conditions underwent the desired oxidative dimerisation, Michael, Michael cascade reaction. As with all biomimetic dimerisation reactions, the synthetic route is of a highly step and atom economic nature. This synthesis also provocatively shows how a daring late-stage oxidation strategy can be successful in the synthesis of complex molecules.

Hirsutene (Wender and Mehta)

The arene–olefin cycloaddition reaction, popularised by Wender and coworkers,[16a] is another example of a pericyclic reaction, which has been used to generate complexity in target-oriented synthesis (Scheme 5). In the synthesis of hirsutene, **29**, a photoinduced, formal [3 + 2] cycloaddition, followed by [1,3] diradical recombination, provides a useful tetracycle, **27**, after deacetylation, proceeding in 22% yield along with three other diastereomers (9%). A second redox neutral transformation, a cationic dehydration event, fragments the recently formed cyclopropane to afford the hirsutene core, **28**, in short order. In the final steps of the synthesis, a few refunctionalisations are necessary, deviating from the otherwise isohypsic synthesis. The combined two-step strategy of an arene–olefin cycloaddition with a strategic cyclopropane fragmentation is atom economical, in that all three rings of the carbocyclic core of hirsutene are formed with only the loss of water from the starting materials. While there is one protecting group interchange, the sequence is highly step economic.



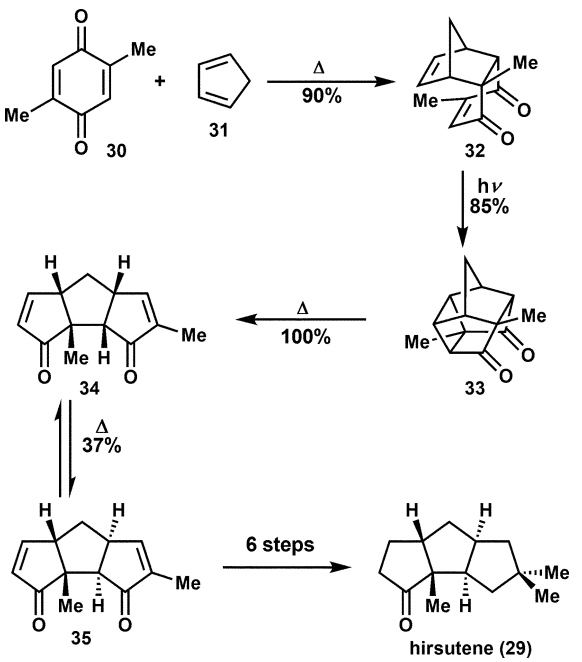
Scheme 4 Biomimetic oxidative dimerisation in the synthesis of rugulosin.



Scheme 5 Arene–olefin cycloaddition reaction in the synthesis of hirsutene.

It is also instructive to note that compound **27** might be considered more complex than the final target. Such "overbred skeletons" are only desirable when they can be generated and converted to the target in a rapid fashion.

Mehta and co-workers[16b] later reported an extremely atom-economical synthesis of the tricyclic hirsutene core, **35** (Scheme 6). A remarkable sequence of events, requiring only heat, light, and solvent as reagents, transpired to assemble the core structure in an isohypsic fashion. Beginning with a benzoquinone, **30**, and cyclopentadiene a thermal Diels–Alder gives **32**. This is followed by photochemical [2 + 2] to afford **33** and thermal cyclobutane fragmentation provides **34**. Finally, a double epimerisation (*via* olefin isomerisation) sets the required stereochemistry to deliver the core, **35**, in four steps and 28% overall yield, in the near absence of any reagents. To complete the synthesis, a mere six steps were then required to adjust the functionality present to that of hirsutene, **29**.



Scheme 6 Synthesis of the hirsutene core in the near absence of reagents.

Pentalenene (Paquette)

Paquette and co-workers have developed two syntheses[17] of pentalenene (**37**), separated by 20 years (Scheme 7). The first of these is a traditional approach proceeding in over 20 steps and involving several corrective refunctionalisations. The second-generation synthesis used only two skeletal building operations and a total of eight steps. This remarkable simplification of the synthesis was due to a cascade process in which the complex tricyclic structure, **43**, was generated in one stroke from a monocyclic starting material, **38**, in a sequence of electrocyclic reactions and an aldol addition. In this way a remarkably rapid increase in complexity was attained.

Cascade reactions are still restricted to rather special situations, yet their application in complex target synthesis is steadily increasing,[18] because they provide a truly powerful tool to rapidly generate complexity.

Methylphenidate (Matsumura and Davies)

In the total synthesis of methylphenidate (Ritalin), **48**, Davies and co-workers demonstrate excellent atom, step and redox economy by the use of a C–H activation reaction (Scheme 8).[19] One previous asymmetric route relied on the use of a chiral auxiliary in an aldol reaction (**46** → **47**), which provided material with excellent diastereoselectivity.[20] However, the use of this stoichiometric reagent is costly from the perspective

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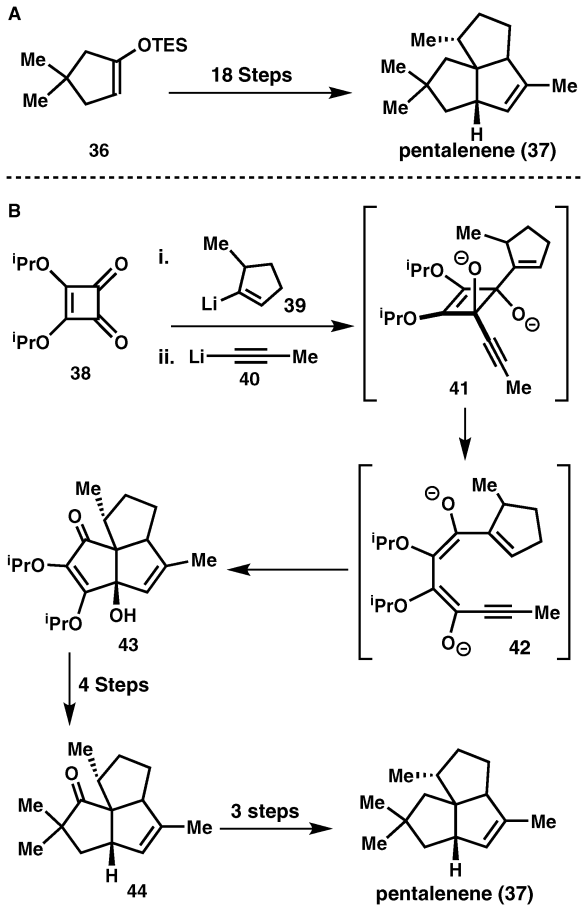
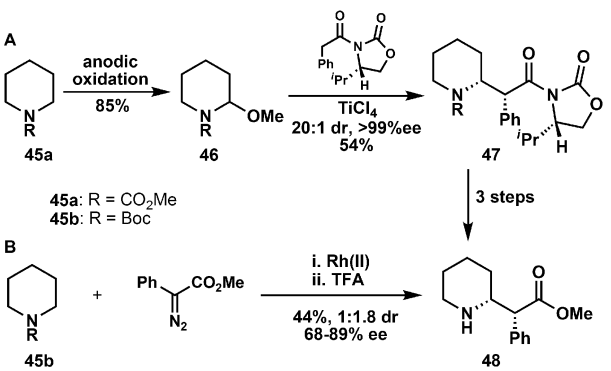


Scheme 7 Squarate ester cascade reaction enables a rapid pentalenene synthesis.

of atom economy and requires a number of steps to install and then later remove. An abbreviated synthesis utilised an enantioselective, rhodium(II)-catalysed intermolecular C–H insertion with phenyldiazoacetate to directly afford methylphenidate, **48**, after Boc deprotection. While the diastereoselectivity is notably lower, the direct nature of this synthesis greatly enables the rapid synthesis of a diversity of analogs. When used strategically, the logic of C–H functionalisation can dramatically shorten sequences and, in some cases, even solve seemingly insurmountable challenges.



Scheme 8 Strategic C–H oxidation in the synthesis of methylphenidate (**48**).

Miyakolide C_6–C_{13} fragment (Masamune and White)

The last decade has seen major advances in the field of allylic oxidation methodology, especially palladium catalysed oxidation of alkenes to allylic alcohols and amines. The benefit of linear increase of oxidation state with simultaneous functional group installation can be illustrated by comparison of parts A and B in Scheme 9. The original synthesis[21a] of the intermediate **52** starts from 1,4-butanediol, **49**, and subsequent differentiation of the hydroxyl groups requires a sequence involving a total of four protecting group steps.

The alternative strategy[21b] in Scheme 9B starts from alcohol **53**, having a terminal double bond as profunctionality for the other alcohol function. This allowed for the generation of the allylic alcohol at the end of the reaction sequence by a palladium catalysed oxidation (*i.e.* **55** → **56**). Since this functionality was now generated after all the other steps had been completed, the differentiation problem did not exist as one alcohol was masked as an olefin. While desymmetrisation of a late-stage intermediate can be a powerful tool (*vide infra*), in the case of Scheme 9A the use of a symmetrical starting material brought no advantage, because the desymmetrisation required a large number of steps. Hence, the alternative strategy (Scheme 9B) turned out to be more effective. Thus, as seen in the previous section C–H functionalisation can allow for significant shortening of synthetic sequences.

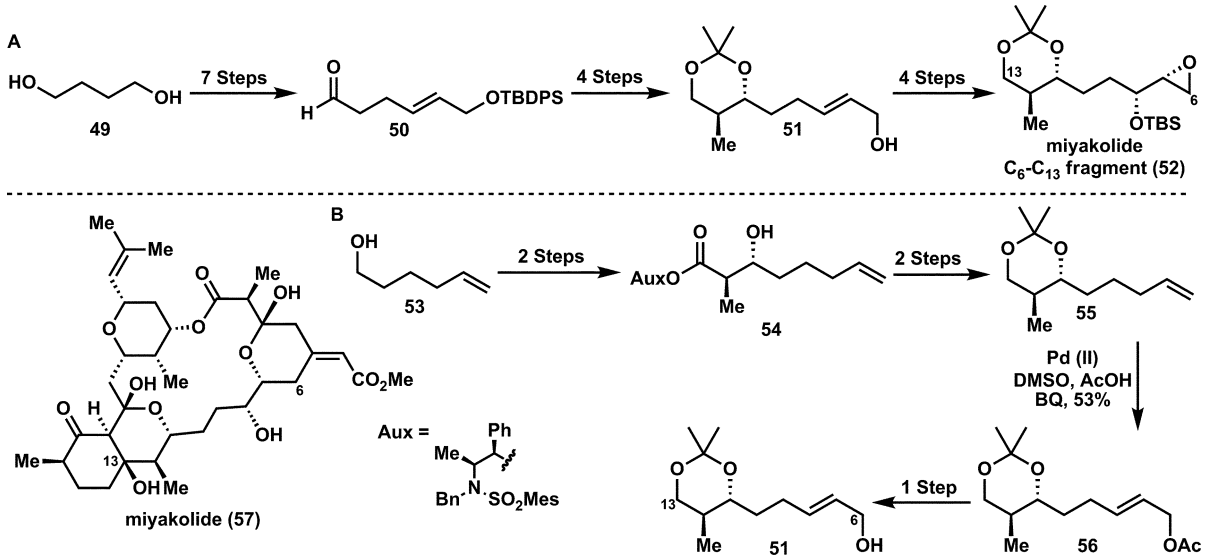
Davanone (Honda–Tsuchihashi and Vosburg)

A recent total synthesis of (+)-davanone, **61**, from Vosburg and co-workers[22] achieves step, atom and redox economy through careful synthetic design (Scheme 10). Using Bode's thiazolium catalyst, a redox isomerisation is first used for the synthesis of a β-hydroxyester, **63**. The resulting alcohol, **63**, then participates in a Tsuji–Trost reaction to form the desired tetrahydrofuran, **64**. After conversion of the ethyl ester to a Weinreb amide, reaction with prenyl magnesium chloride affords the enantiopure natural product, **61**. The four successive isohypsic transformations provide a successful strategy for a step economic synthesis relative to the previous enantioselective synthesis (20 steps from commercial material). Protecting groups are avoided, further simplifying the synthesis. Additionally, the reaction sequence involves two catalytic reactions, which are highly atom economical, producing only minimal byproducts.

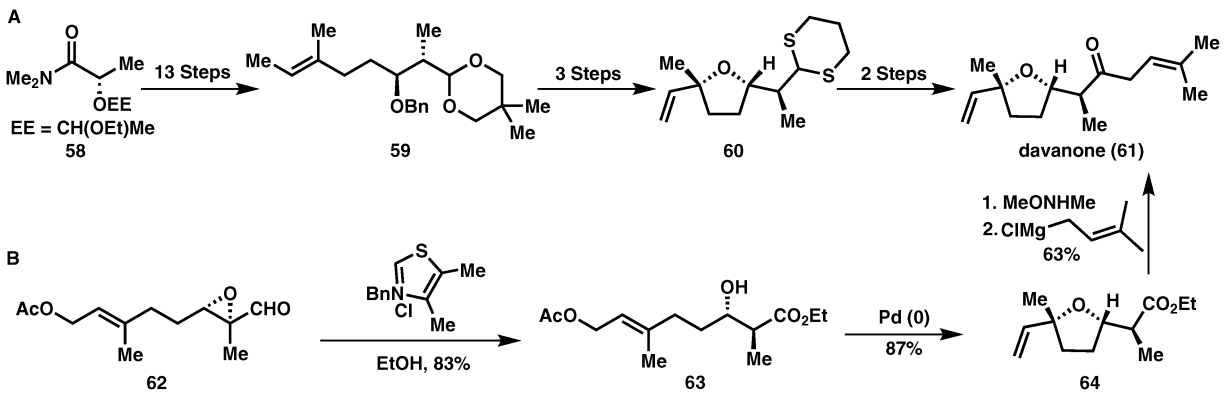
Platencin (Rutjes and Mulzer)

While transition-metal processes are powerful opportunities to maximise synthesis economy, judicious reaction selection is still necessary. This can be seen by comparing the final steps of two formal syntheses of platencin, **70**.[23] In Rutjes' synthesis in Scheme 11A the authors chose to form the skeletal bond by a samarium iodide reductive coupling reaction. This required protection and later deprotection of the enone, **65**, as well as ozonolytic cleavage of both double bonds. Refunctionalisation of diol **66** then requires an additional three steps to reach Nicolaou's intermediate **67** for the synthesis of platencin **70**.

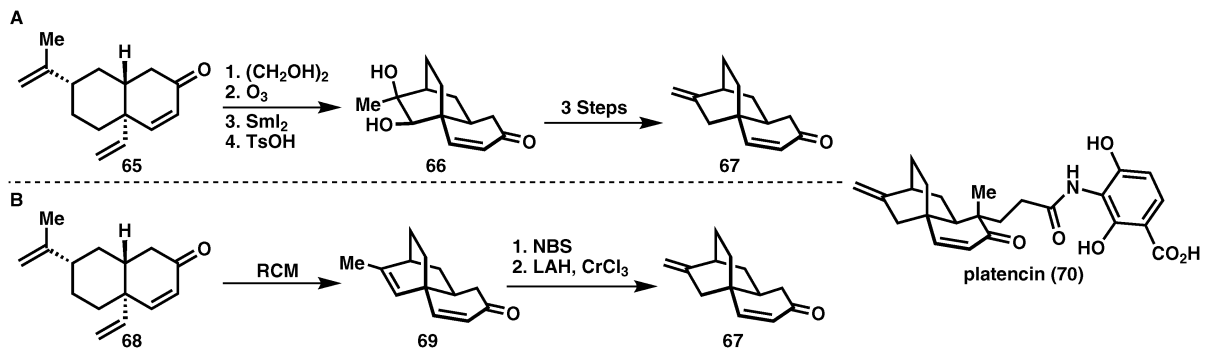
By opting to use ring-closing metathesis as the transition-metal catalysed bond-forming reaction (Scheme 11B), protecting groups are no longer necessary and the overall transformation



Scheme 9 C–H oxidation used in the synthesis of the miyakolide C_6–C_{13} fragment (**51**).



Scheme 10 Two approaches for the total synthesis of (+)-davanone (**61**).



Scheme 11 Ring-closing metathesis to synthesise platencin (**70**).

to intermediate **67** can be performed in a mere three steps as opposed to seven. Overall, the Mulzer synthesis of platencin takes place in nine steps and is a profound example of step, atom, and redox economy in action.

Hemibrevetoxin B (Nakata and Nelson)

Another dramatic example of step reduction is the Nelson approach[24] to hemibrevetoxin B, **79**. The advanced key intermediate **72**, which can be converted to **79**, was synthesised by the Nakata group through an approach involving sequential ring formation requiring 29 steps (Scheme 12A). With the importance of this intermediate apparent, Nelson's approach, which proceeds *via* bidirectional synthesis, followed by late-stage desymmetrisation (Scheme 12B), significantly simplified the pathway to **79**. This approach relies on an acid-catalysed epoxide opening to simultaneously form both tetrahydropyran rings in **75**. Net two-carbon homologation and epoxidation

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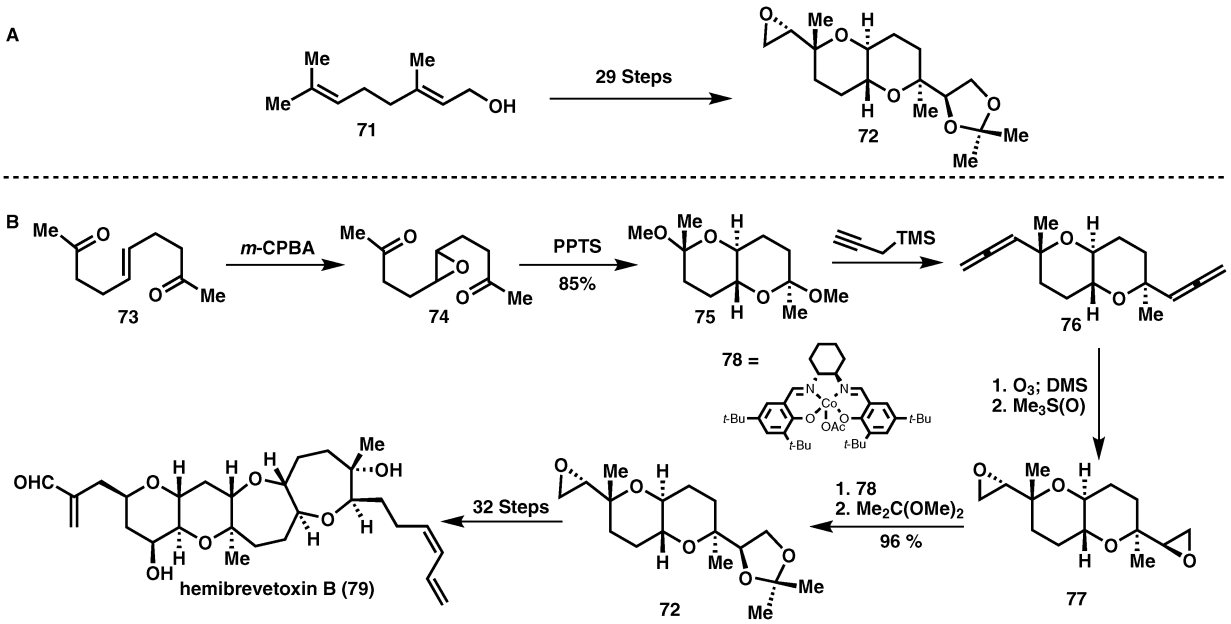


Scheme 12 Desymmetrisation of a diepoxide en route to hemibrevetoxin B (**79**).

furnishes the key intermediate **77**. Jacobsen's epoxide opening then acts to desymmetrise **77** and after acetonide formation affords **72**. This approach results in a four-fold reduction in the total number of steps required to synthesise this important intermediate, **72**. The approach is guided by linearly increasing oxidation state and a general avoidance of protecting groups, leading to a highly efficient synthesis.

Rifamycin (Kishi and Harada–Oku)

As demonstrated in Scheme 12, a valuable strategy to reduce the number of skeleton forming steps in a synthesis is to find a hidden symmetry in the target or a precursor intermediate: such symmetry permits a bidirectional elaboration of the skeleton with an attendant reduction in the skeleton building steps.[25] This can be illustrated with regard to rifamycin S, **80**, in the synthesis of a portion of its ansa chain, **82**. The pioneering synthesis by Nagaoka and Kishi[25a] synthesised the key intermediate **82** from the aldehyde **81** by chain extension (Scheme 13A). The skeleton was extended in a *sequential* manner, amounting to four skeleton building steps (accompanied by one strategic and eight corrective redox-operations and eight protecting group steps).

A key to an improvement is the direct use of the *latent symmetry* in the intermediate **82**. This provided the opportunity to elaborate the skeleton in a symmetrical manner from a central building block **83** (Scheme 13B). Two-fold simultaneous chain extension by addition of crotylboronate to **83** is the single skeleton building reaction in this novel synthesis[25b] of **82**. Symmetry is maintained throughout a number of refunctionalisation steps until tetraol **86**. At this point the symmetry of the prochiral compound **86** is broken by differentiation with the aid of a chiral auxiliary (TMS-enol ether of menthone, **87**). The resulting monoacetal is then readily converted into the enantiomerically pure target **82**. Note that this synthesis of **82** has only one skeleton building step, but the remaining 10 refunctionalisation steps (redox manipulations and protecting group interchanges) detract from the otherwise elegant approach.

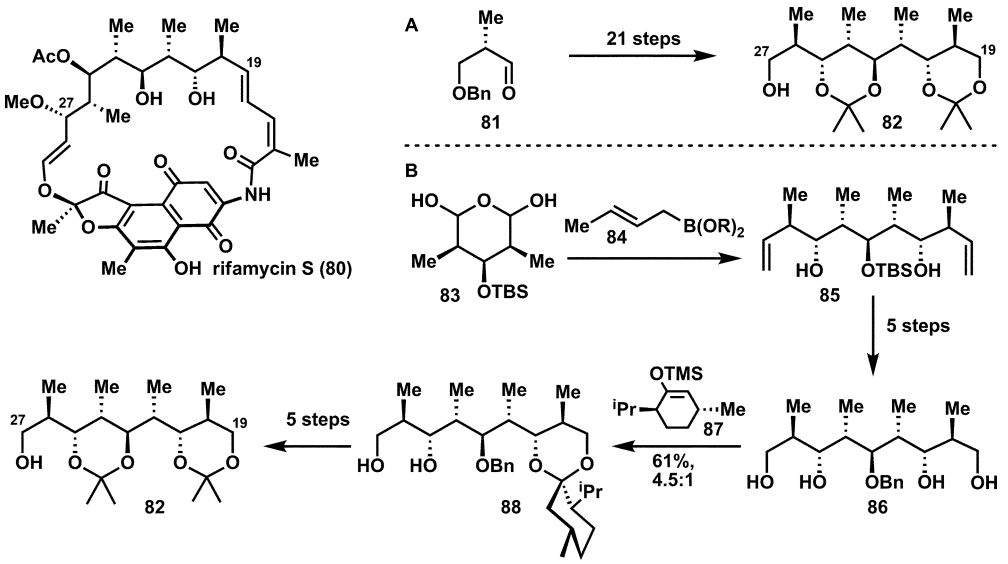
Spirastrellolide A methyl ester (Paterson)

Paterson's first approach to the C_{26}–C_{40} bis-spiroacetal subunit of spirastrellolide A, **97**, while only 11 linear steps, was plagued by a low yielding acetonide deprotection and spirocyclisation step (**92** → **93**) as a result of the propensity of the five-membered lactone, **92**, to undergo elimination and aromatisation (Scheme 14A).[26] The first generation route also suffers from the use of high molecular weight, stoichiometric reagents (DMP, $[Ph_3PCuH]_6$, *etc.*). An alternative strategy was employed,[26] which both avoids these problems and allows for greater material throughput.

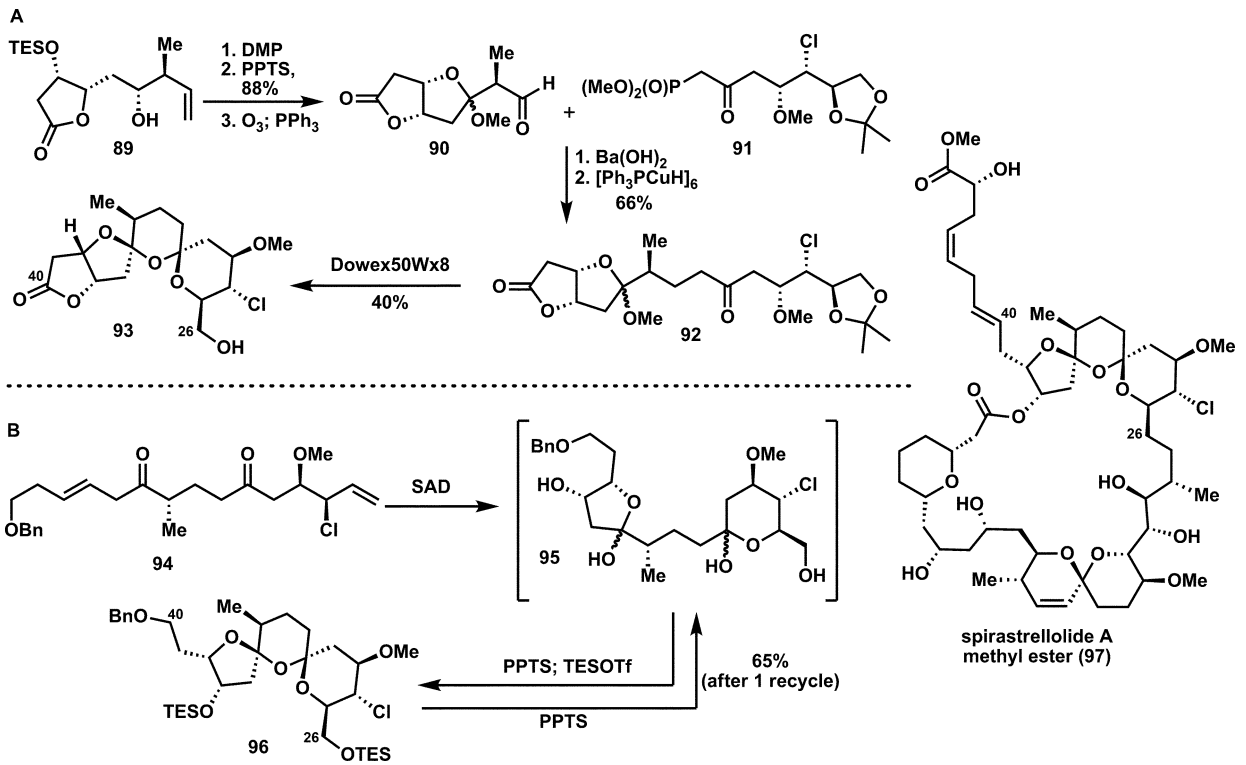
In Paterson's landmark total synthesis of spirastrellolide A methyl ester, **97**,[26] an exponential increase in oxidation state *via* a double dihydroxylation event is accompanied by an exponential increase in complexity (Scheme 14B). This approach allows for the rapid formation of the tricyclic bis-spiroacetal subunit, **96**, from a linear carbon chain precursor, **94**, containing the requisite functionality necessary for synthesis of the natural product. While a mixture of isomers is obtained, the undesired isomers can be conveniently recycled to afford a predominance of the desired product. While the step economy of the two routes is identical, the second-generation route leads to a dramatic increase in redox and atom economy—thus a greater supply of material can be obtained.

Oseltamivir phosphate (Roche, Corey and Hayashi)

The synthetic challenge of the H5N1 influenza treatment, oseltamivir phosphate, largely relates to the development of a process-friendly route, which can directly impact the current supply problem.[27] Roche has previously disclosed a highly



Scheme 13 Desymmetrisation of a *meso* tetraol in the synthesis of rifamycin S (**80**).



Scheme 14 Double spirocyclisation in the total synthesis of spirastrellolide A methyl ester (**97**).

efficient process scale route (12–13 steps, 39% overall yield) shown in Scheme 15A. However, this route has the Achilles heel of requiring a starting material, shikimic acid, **98**, which is not readily available for manufacturing scale production. A number of subtle features, which are generally overlooked, become major players in the chemistry of drug production. Thus, as with most process routes to medicinal agents, the Roche process route is a masterpiece of design, engineering, and execution.

Following the potential for a life-threatening influenza epidemic in 2005, the global supply of Tamiflu came into question due to the limited available quantities of **98**. While Corey's alternative strategy[27] reported in 2006, depicted in Scheme 15B is less efficient in terms of overall yield (22%), the greater availability of the starting materials makes this route more attractive. Another fantastic route reported in 2009 by Hayashi *et al.*[27] requires only three pots from relatively cheap materials to afford the target in 57% overall yield. However

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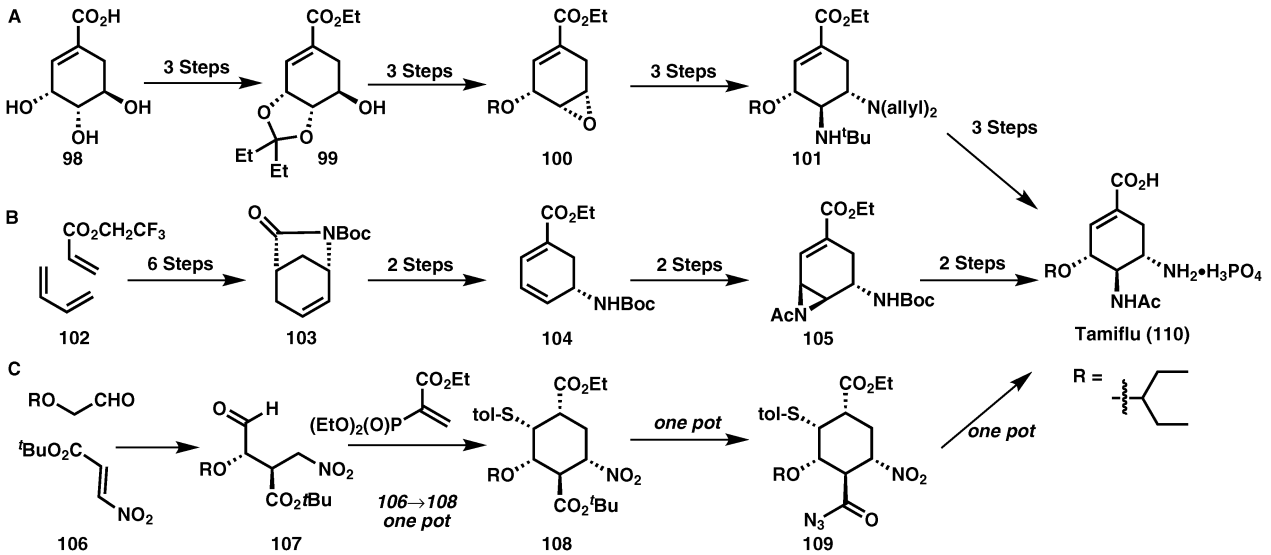


Scheme 15 Addressing the supply problem of Tamiflu (**110**).

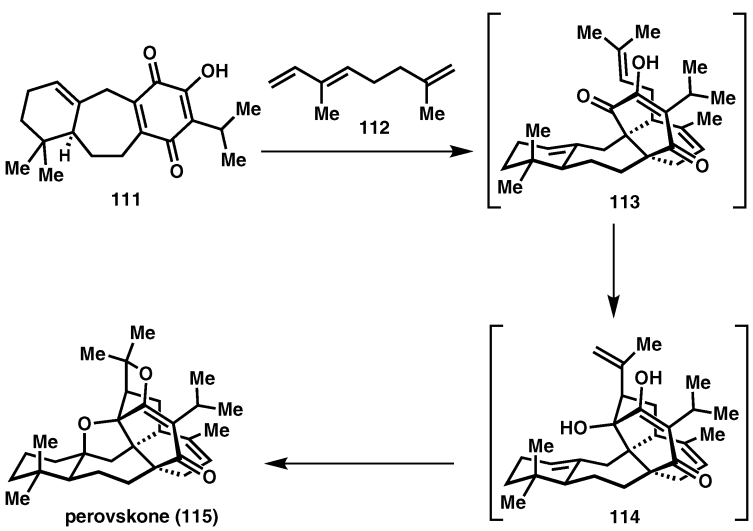
within the context of process chemistry, the use of an acyl azide, **109**, detracts somewhat from this otherwise brilliant approach, as these are potentially dangerous intermediates. Both of the syntheses in Schemes 15B and 15C have the clear advantage over Scheme 15A, as they are not limited by the availability of the starting materials. Several syntheses of Tamiflu have recently emerged and a very insightful review of their relative merits has been published.[28]

Perovskone (Majetich)

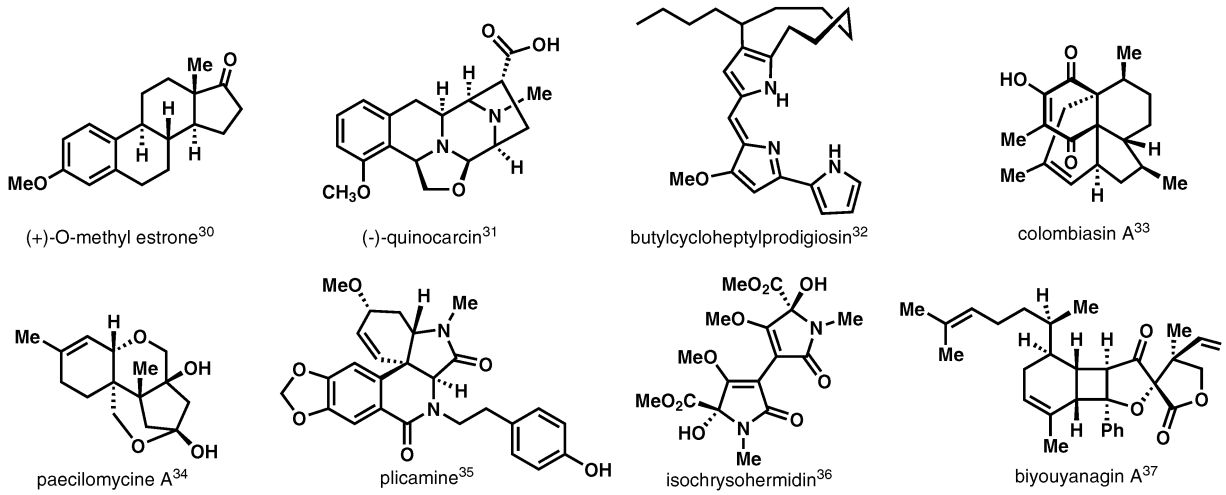
In a total synthesis of perovskone (**115**), Majetich demonstrates atom, step and redox economy with a spectacular biomimetic cascade (Scheme 16). After eleven steps Majetich obtains intermediate **111**, which then undergoes a Diels–Alder cycloaddition with diene **112** and olefin isomerisation to arrive at **113**. This tetracycle then participates in an ene reaction, followed by two acid-catalysed etherifications to afford the natural product, **115**. While the details of the one-pot transformation have not yet been published, the two-pot procedure proceeds with excellent regio-, chemo-, and diastereoselectivity (74% overall). The use of an isohypsic cascade with no refunctionalisations necessary resulted in a highly efficient increase in molecular complexity.[29]

Suggested further reading

As the purpose of this review is to highlight the various aspects of the economies of synthesis in action, it cannot possibly be comprehensive. The interested reader can find several fine monographs on the topic of total synthesis for more examples that can be scrutinised through the economic "filters" delineated herein. Scheme 17 features a number of other excellent examples of syntheses that display striking levels of step, redox, or atom economy.[30–37]



Scheme 16 Majetich rapidly assembles the core of perovskone.



Scheme 17 More examples of economic total synthesis.

Conclusion

"*If all the economists were laid end to end, they would not reach a conclusion*" – George Bernard Shaw.

Indeed, the economies of synthesis are nice guidelines and conceptual frameworks for analysing and even designing syntheses, but that is all they are—apparent concepts to the seasoned practitioner. Thus, while all organic chemists can agree that the goal of minimising steps, waste, and redox fluctuations is an admirable one, the means to achieve this will always be the subject of debate and will always have more than one good answer. With the above quote in mind it can be said that this review does not have a truly satisfying conclusion, but instead these ideas are continuously re-evaluated during the act of organic synthesis. As the examples in this "tutorial" review demonstrate, it is the *act of actual execution* of such syntheses (*i.e.* aiming for the Hendrickson ideal) that will have the greatest impact on the practice of organic synthesis.

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