Chem Soc Rev

REVIEW ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Soc. Rev.*, 2018, **47**, 7985

Received 14th May 2018

DOI: 10.1039/c8cs00399h

rsc.li/chem-soc-rev

Enabling strategies for step efficient syntheses

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The field of natural product total synthesis has reached the point where synthetic efficiency has become more important than merely defining a viable (yet less ideal) route to the target molecule. Synthetic efficiency is best represented by the number of steps it takes to finish the target molecule from readily available starting materials, as by reducing the number of steps, all other factors of synthetic efficiency are influenced positively. By comparing several total syntheses from the recent years, the most successful strategies for step efficient syntheses will be highlighted. Each synthesis will be presented using a color-coded synthetic flowchart, in which each step is categorized by a colored box. Five categories of transformations are defined and rated according to their synthetic value. Each class will be signified by different colors so that the reader can quickly see which parts of the synthesis are productive and those that are not.

Introduction

In their pioneering book "The Logic of Chemical Synthesis" Corey and Cheng outlined a general concept for the synthesis of complex molecules.[1,2] Retrosynthetic analysis is a recursive technique that simplifies a given molecule (the target) into commercially available building-blocks. When restricting to the topology, a disconnection can either cleave a ring or split the molecule into precursors (synthons). The possibilities generated from number of different bonds present are best reflected in a tree-like graph (retrosynthetic tree) where each node represents a potential precursor. The Corey work provided a compass to navigate in this network and identify a pathway that a chemical synthesis can proceed through in reverse direction.

Almost 30 years later, chemists still design syntheses according to those guidelines – very recently supported by computer programs.[3,4] With a growing arsenal of synthetic methods available to today's chemist, the emphasis has shifted from how to make a target molecule towards how to make it in the most "efficient" way. Whether a synthesis is regarded as efficient depends on the objective – a process chemist trying to make a compound on scale will have other priorities than a medicinal chemist aiming to cover a broad chemical space or a PhD student trying to synthesize a natural product using innovative transformations – and several reviews and essays have been published to give an

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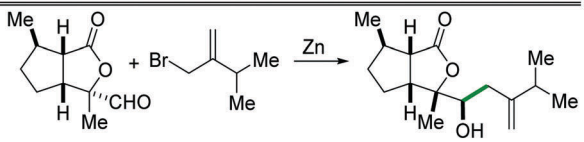
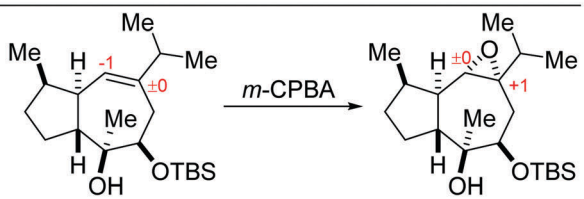
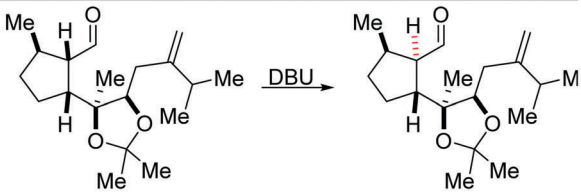
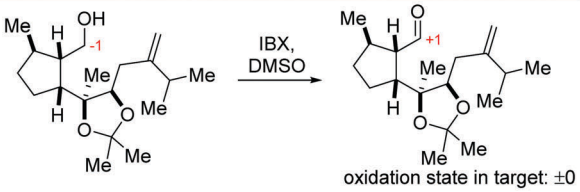
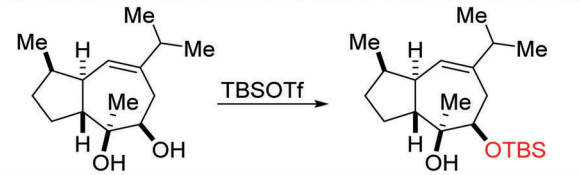
answer to this question.[5–15] This review however is aimed at providing a simple tool to compare different synthetic strategies. By representing synthetic routes as colored flowcharts, we want to visualize strategic differences and aid the reader in evaluating their own synthetic plans. By comparing different syntheses of the same target, we have been able to identify similarities within the shortest approaches which will be summarized at the end of the review.

Rulebook of reaction classification

In order to dissect syntheses into synthetic steps one must first define what is considered a step. This seemingly trivial question has erupted in controversial discussions in recent years.[16,17] The IUPAC defines an elementary reaction step as the pathway between two local minima on the reaction ordinate.[18] This definition however is not very useful in the context of multistep synthesis as functional interconversions may contain several isolable intermediates. A more practical definition considers a step as the sum of all transformations that happen within the same flask and that is terminated by a purification procedure.[15,19] This way of counting can be skewed by the telescoping of single transformations into one-pot procedures in order to improve the efficiency of a synthetic sequence. The main disadvantage of a longer synthetic sequences, the exponential drop in yield, cannot be overcome by telescoping.[6] For the purpose of this review, the definition of a single step will lie in between these two extremes. A single step is defined as the conversion of one particular functional group into another. For example, a Swern oxidation is considered as one-step operation since it converts a hydroxyl group into a carbonyl group, even though it proceeds through several intermediates. The silylation of an alcohol followed by a Swern oxidation of

Table 1 Reaction classifications

Class	Color	Definition	Example[a]
C–C bond formations		forms C–C bonds present in the target	
C-Het bond formations / strategic redox reactions		forms C-Het bonds present in target molecule / oxidation state is altered towards oxidation state present in target	
isomerization / functional group interconversions		One functional group is converted to another - not present in target, includes isomerizations	
non-strategic redox reactions		oxidation state is altered away from the oxidation state present in target	
protecting group manipulations		protection or deprotection of functional groups	

Good

Avoid

[a] All examples are taken from the total synthesis of (−)-englerin A by Christmann.[20]

another alcohol are considered as two steps even if both transformations are conducted as one-pot procedure. Cascade reactions on the other hand will be counted as single steps since upon initiation no further reagents are added. Reactions in which a single set of conditions and reagents transforms two independent functional groups will also be counted as one step (*e.g.* global deprotection). Transformations that occur upon workup (*e.g.* deprotection of an acid-labile TMS-group) are not counted as individual steps. The overall step count will be defined as the sum of steps in the longest linear sequence (LLS) starting from the first commercially available compound.

Now that a single step is defined, we can distinguish between desirable steps: C–C bond formations, C–heteroatom formations/strategic redox reactions, and steps that should be avoided if possible: protecting group manipulations, non-strategic redox reactions and functional group interconversions[23] as defined by Hendrickson[24] in 1975 and Baran[13] in 2010 (Table 1). Each synthesis discussed will be presented using a color-coded synthesis flowchart, in which each step is categorized by a colored box (Fig. 1). Intermediates are depicted as circles where the number inside the circle represents the number of carbon atoms (excluding carbons of protection groups). The classes of transformations are color-coded, so that the reader can quickly distinguish productive (green) and less productive steps (yellow, orange and red). If two or more steps are performed in one-pot fashion, those steps will be framed. Steps in between two categories will be assigned to the more favorable category, *e.g.* a cascade reaction initiated by a deprotection followed by a C–Het bond formation will be regarded as a C–Het bond formation and not as a protecting group manipulation. Defunctionalizations, in which heteroatoms are substituted by hydrogens, will generally be regarded as non-strategic redox reactions, although they often lead to the correct oxidation state and could therefore also be regarded as strategic redox reactions. Without going into detail, in case of the two englerin syntheses, it can be easily seen that the Chain synthesis is more efficient. This is mainly due to an efficient construction of the C15 sesquiterpene core and the avoidance of protecting group manipulations.

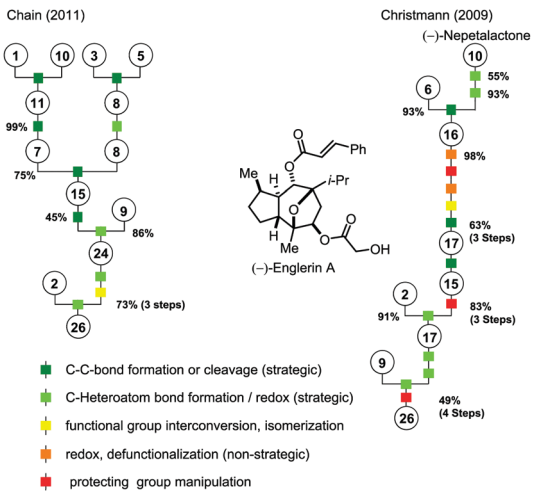


Fig. 1 Flowchart presentation of the synthesis of (–)-englerin A by Christmann compared to the synthesis of Chain.[21,22] The Chain synthesis is more step efficient since it minimizes functional group interconversions and protecting group manipulations.

Selected examples for the step efficient synthesis of natural products

Prostaglandin $F_{2\alpha}$

Prostaglandins have been known to play a key role in regulating many physiological activities in humans since their discovery in 1930.[25] Their investigation culminated in the development of many important prostaglandin-inspired pharmaceuticals. Due to their wide range of biological activities and structural complexity, the early prostaglandin syntheses are regarded as milestones of organic chemistry in the 1950s and 60s. Even though these structures have been known for over 80 years, they continue to inspire chemists to find novel approaches to synthesize them – as for example the seven-step total synthesis of prostaglandin $F_{2\alpha}$ by Aggarwal[26] (2012), published 43 years after Corey's landmark total synthesis (1969).[27] Both syntheses are shown in Fig. 2. As evidently from the flowchart, the step-count of the Corey synthesis is increased by two linear sequences of an 8- and a 15-carbon intermediate without C–C-bond forming reactions. Aggarwal's shorter approach benefits from an enantioselective organocatalytic dimerization of succinaldehyde (2xC4) to generate the central 8C-cyclopentane. Many classic aldol reactions first require activation of the carbonyl group by preforming a reactive enol or even the installation (and later removal) of chiral auxiliaries. In contrast, this direct organocatalyzed aldol reaction enabled the direct formation of two C–C bonds and two chiral centers without the need for preactivation.[28] Owing to a large number of side reactions and polymerizations, this reaction required extensive optimization and was initially reported with 14% yield. Very recently, this step was optimized to 29%.[29] Due to the good availability of the starting material, the reaction was scalable, and the route delivered over 1 gram of the target molecule in a single campaign. Surprisingly, the overall yield (OY) of Corey's synthesis is higher than that of the much shorter Aggarwal route (12% OY compared to 8% OY). Taking into account the limited available methodology of the late 60s, (before the advent of acyclic stereocontrol), the Corey synthesis constitutes a prime example of cyclic stereocontrol and synthesis design.

When weighing longer against shorter sequences in the planning stage, the latter should be preferred.

The advantage of a short synthetic sequence is also that low yielding individual steps can be tolerated much better than in longer sequences – thus when planning a synthesis, the reliability of a certain method becomes less important compared to a longer sequence where individual yields below 50% often deem a project unsuccessful.

Strychnine

Another classic target in natural product synthesis is strychnine, the most famous member of strychnos alkaloids which has

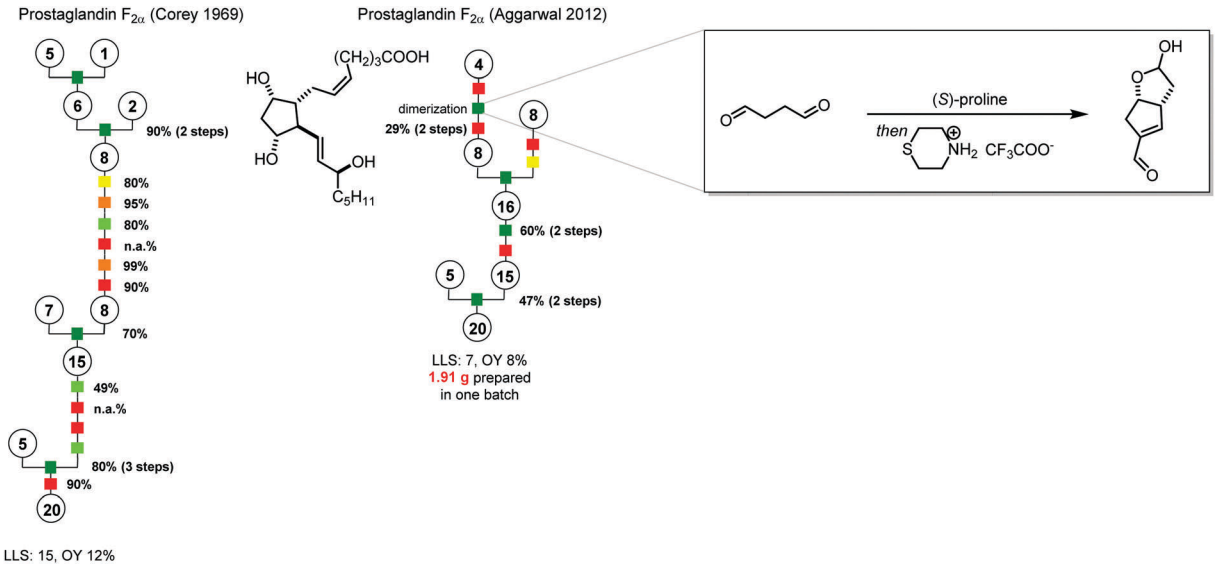


Fig. 2 Flow scheme representation of the total synthesis of prostaglandin $F_{2\alpha}$.

been synthesized more than a dozen times.[30] Its structure was elucidated in 1946[31] – at the time it was regarded "for its molecular size the most complex substance known."[32] Only nine years later, Woodward presented its synthesis[33,34] – long before retrosynthetic analysis was formulated. His 28-step synthesis (Fig. 3) dwells on an oxidative cleavage of an electron-rich benzene derivative

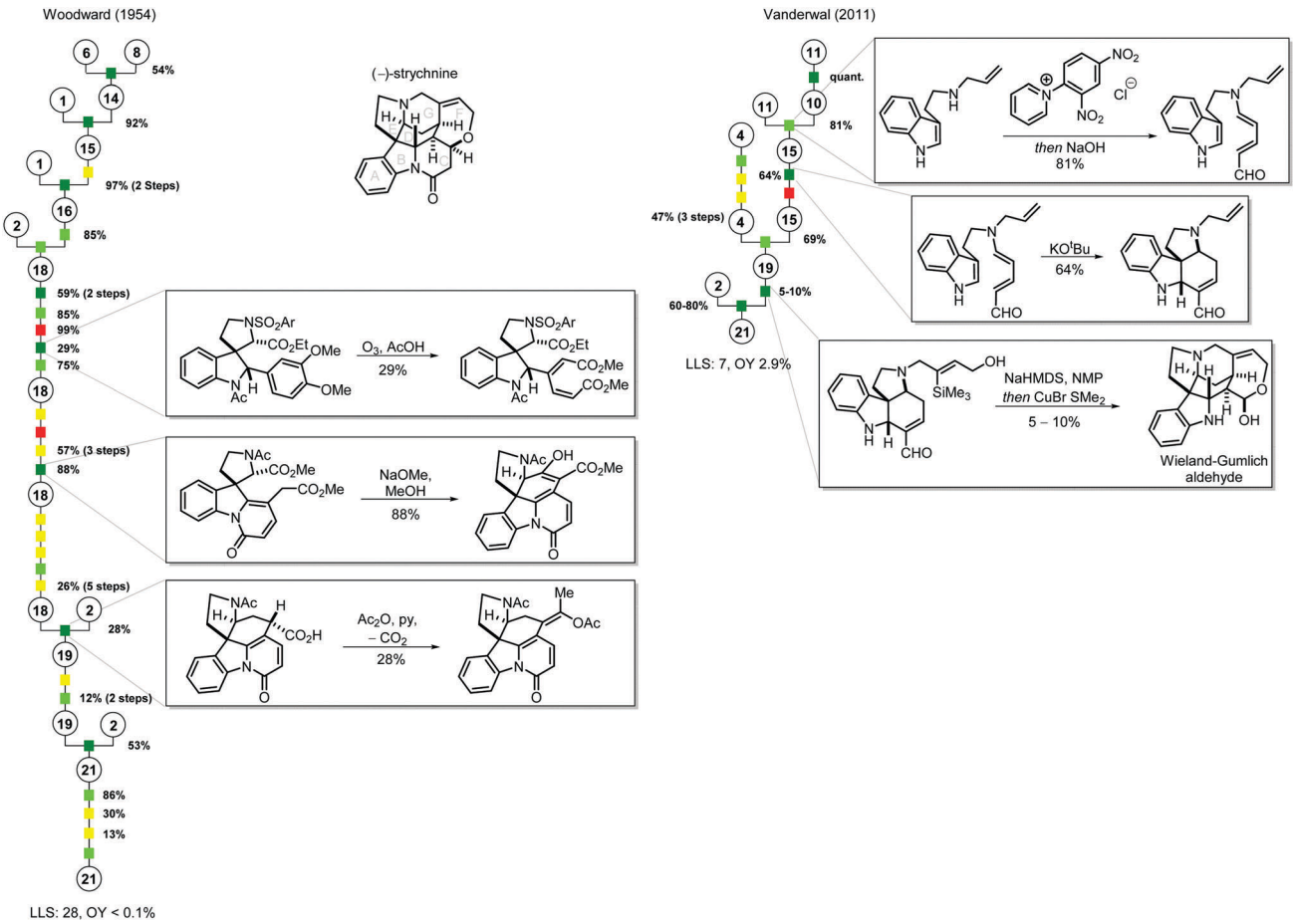


Fig. 3 Strychnine total synthesis by Woodward and Vanderwal.

early in the synthesis. The C- and D-rings are then formed consecutively by lactamization and Dieckmann condensation. A homologation of a carboxylic acid with acetic anhydride and consecutive lactamization completed the G-ring and finally, an allylic rearrangement followed by an oxa-michael addition furnished the F-ring. The successful synthesis of strychnine established Woodward's reputation as master of total synthesis. A remarkable feature of the reported route is the lack of chromatography during the work up. From the 28 reported steps, only the last step required chromatography, all other intermediates where either crystallized or used without further purification. In 2011, Vanderwal reported a 7-step synthesis of (±)-strychnine, the shortest route so far.[35] To build a molecule as complex as strychnine using as little as 7 steps, the synthesis must only use desirable transformations – as evident by the flow-chart, there is only one deprotection step in the LLS, all other reactions are either C–C or C–Het-bond formations. By making use of an intramolecular Diels–Alder reaction, ring D and E are formed in a single step. Rings G and F are also formed in a single step – a Brook-rearrangement followed by conjugate addition and acetalization yields the Wieland–Gumlich aldehyde and completes the formal synthesis of (±)-strychnine.

Jiadifenolide

The sesquiterpene jiadifenolide was isolated along with jadifenoxolane A and B from the pericarps of *Illicium jiadifengpi* in 2009 and displayed promising biological activity as a promoter of neurite outgrowth in rat neurons.[36] Its biological

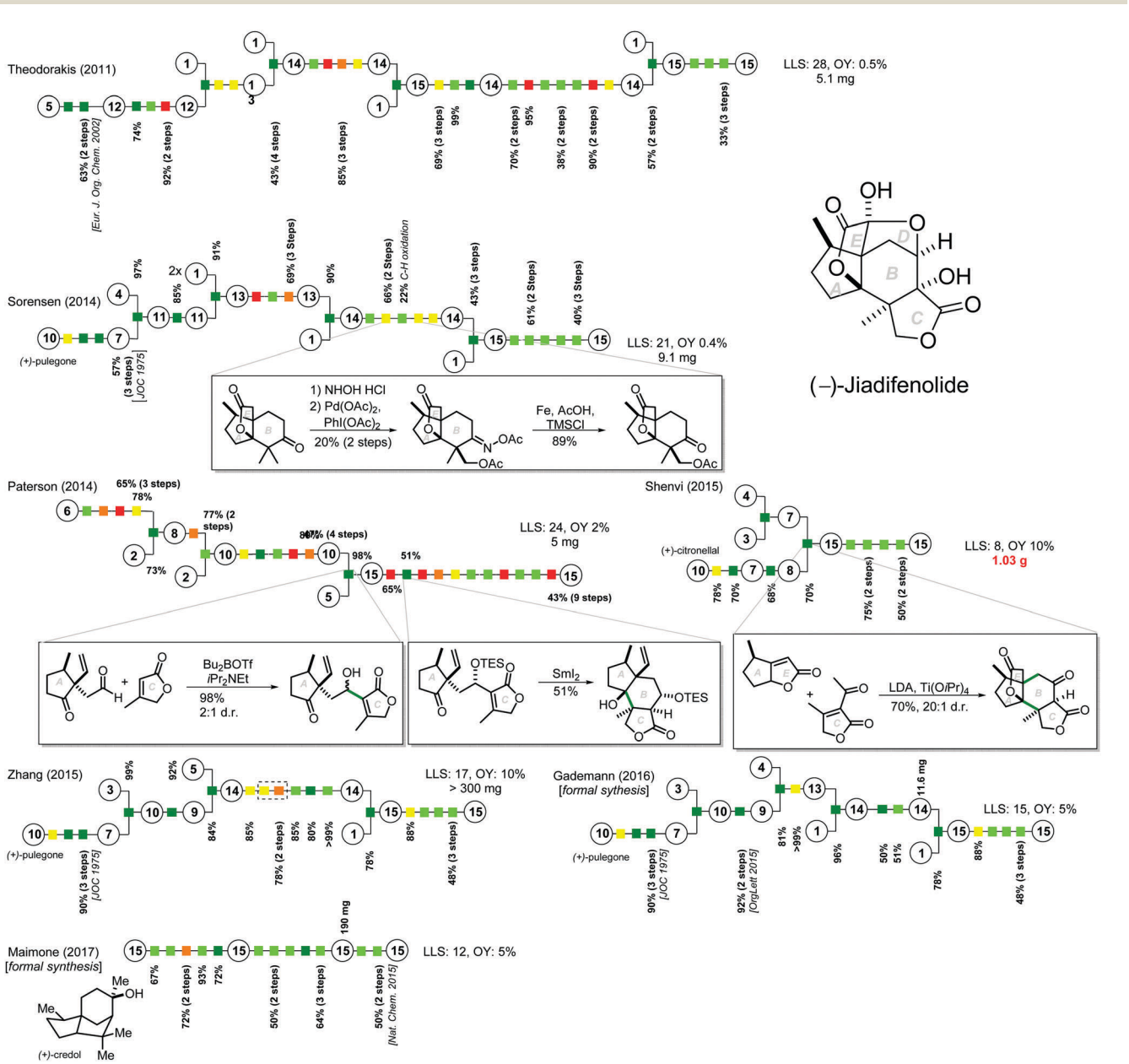


Fig. 4 Comparison of jiadifenolide syntheses.

activity combined with the complex and unprecedented pentacyclic framework makes it a target for total synthesis. To date, seven syntheses have been published[37–43] with a step count ranging from 8 to 28 steps (Fig. 4). Upon comparison, the endgames of the syntheses share some similarity since all approaches construct the D-ring as the last step following α-oxidation of the E-ring lactone. In addition, five of the seven syntheses transfer the methyl-substituted C1-stereogenic center in the A-ring from terpene feedstock. In the syntheses of Sorensen, Zhang and Gademann, (+)-pulegone was used and the first steps are identical.[44] Sorensen and Theodorakis constructed the B, C and E ring in a successive manner which results in a rather linear sequence. In order to build the C-ring lactone, Sorensen selectively oxidizes one of two diastereotopic methyl groups. This transformation however requires the introduction and removal of a directing group and is, from a step economic point of view, not ideal. The syntheses of Zhang, Gademann as well as the Paterson synthesis are more convergent as they directly introduce the C-ring lactone into the synthesis. The B-ring is constructed *via* a SmI_2-mediated C–C-bond formation. The shortest syntheses were reported by the groups of Shenvi and Maimone (8 and 12 steps respectively). Interestingly, the two approaches are rather different. Maimone's synthesis consists almost exclusively of strategic oxidations of (+)-credol – a starting material that already contains all 15 carbon atoms of jiadifenolide. In contrast, the synthesis of Shenvi relies on one exceptionally powerful key disconnection of the A, E and C ring so that the oxapropellane core is constructed in a single step. This remarkably short synthesis benefits from introducing the two coupling partners in a high oxidation state thus reducing the need for additional oxidations.

Frondosin B

Frondosin B was isolated from the marine sponge *Dysidea frondosa* in 1997. It was found to inhibit interleukin-8 receptors and protein kinase C in the micromolar range rendering it a lead structure for oncology and inflammatory diseases.[45] The structure was elucidated by NMR spectroscopy and the absolute configuration of the single stereocenter was established as (*R*) *via* total synthesis by Danishefsky in 2001.[46] The second total synthesis by Trauner revised this stereochemical assignment. Remarkably, it was later ascertained by the groups of Ovaska,[47] MacMillan[48] and Davies[49] that the initial assignment by Danishefsky was correct. Apart from the debate about its absolute configuration, the landmark 3-step synthesis by MacMillan makes it a mandatory example in the context of this review (Fig. 5).

Despite its modest complexity, the total synthesis of (+)-frondosin is far from trivial as the first synthesis of Danishefsky and later Trauner required 17 and 20 steps respectively. A shorter synthesis was then achieved by Ovaska (10 steps) in 2009, but none of these syntheses come close to MacMillan's work regarding the number of steps.

As C8 is the only stereocenter in (+)-frondosin, substrate control cannot be used. Methyl-substituted stereogenic centers are difficult to construct and often derived from citronellal or in the context of polyketides from the Roche ester.[50] Flynn's attempt to generate the C8-stereocenter by an asymmetric hydrogenation of a trisubstituted alkene failed.[51] Furthermore, the stereocenter is prone to racemization under a variety of conditions.[49,52] Danishefsky constructs the stereocenter early in the synthesis *via* opening of chiral epoxide with methyl nucleophile. In contrast, MacMillan generates the stereocenter

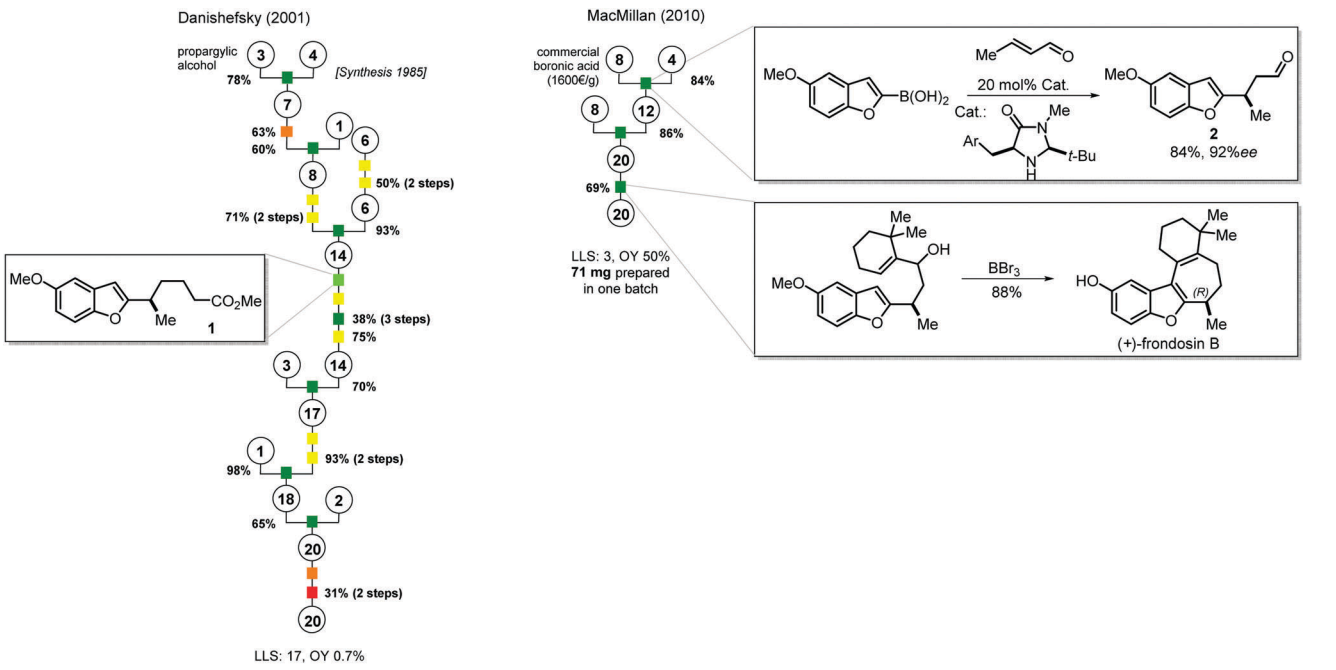


Fig. 5 Frondosin total syntheses.

while simultaneously connecting two large fragment using an organocatalytic Friedel–Crafts alkylation.[53]

At this point is instructive to step back and compare the similar intermediates 1 (Danishefsky) and 2 (MacMillan). The Danishefsky synthesis is completed in another 11 steps following a classic synthesis plan. Intermediate 1 is converted to a diene and the cyclohexene is constructed in a Diels–Alder reaction. In contrast, MacMillan recognized that the 6-membered ring with the geminal dimethyl group can be brought into the synthesis from (commercially available) 2,2-dimethylcyclohexanon *via* Shapiro reaction.

Finally, the last step of the MacMillan reaction combines several transformations (and therefore counted as one step, *vide supra*). Not only does BBr_3 initiate the allylic Friedel–Crafts alkylation, it also cleaves the methoxy ether and the HBr formed in the process isomerizes the double bond to yield (+)-frondosin B in 69% isolated yield.

Enabling methods for step efficient synthesis – swinholide A

Swinholide A, first isolated in 1985 from a marine sponge, shows promising biological activities as it interrupts the assembly of actin during microtubule formation, rendering it cytotoxic in the ng mL^{-1} range. Apart from its biological activity, the complex structure of swinholide A makes it an interesting target for total synthesis. Swinholide A features a symmetric 44-membered macrodiolide and contains no less than 30 chiral centers. As it was shown in the above example, the development of a new C–C-bond-forming reaction has enabled a powerful disconnection between the stereogenic center and the benzofuran. Polyketide synthesis classically involves either aldol chemistry or stoichiometric amounts of preformed organometallic carbon-nucleophiles to form new C–C-bonds. Both transformations utilize carbonyl compounds as the electrophile and exhibit little functional group tolerance. Therefore, iterative polyketide synthesis often requires non-strategic redox reactions and protecting groups.

By merging redox manipulation and C–C bond formation in the transition metal catalyzed transfer hydrogenation, the group of Krische developed several regio- and stereoselective C–C bond formations that selectively couple primary alcohols with allylic acetates or allenes and thus generate polyketides with minimal use of non-strategic redox reactions and protection group manipulations.[15] The potential of this new methodology was demonstrated in a 16-step total synthesis of swinholide A (Fig. 6).[54] Owed to its enormous complexity, only three groups completed a total synthesis since its isolation in 1985. The first two syntheses by the groups of Paterson (1994)[55] and Nicolaou (1996)[56] relied on classic carbonyl chemistry and are comparable in terms of step efficiency (27 and 33 steps LLS, respectively).

On the contrary, the Krische synthesis constitutes of 16 steps in the LLS. The deciding difference is the minimal use of protection group and functional group manipulations. Surprisingly, both the synthesis of Nicolaou and Paterson, use a smaller number of C–C bond formations than Krische. Using chemistry developed in his group, five of the fourteen C–C bonds in the Krische synthesis are formed *via* transition metal catalyzed hydrogen-mediated C–C couplings. Another five C–C bonds are formed *via* olefin metathesis[57,58] and together they account for more than two thirds of all C–C bond formations. Only four C–C bonds are formed without the use of transition metal catalysis. In comparison, neither the synthesis of Nicolaou nor the synthesis of Paterson uses a single late transition metal catalyzed C–C bond formation. While classic carbonyl chemistry is rather limited in terms of functional group tolerance, hydrogen-mediated C–C bond formation and olefin metathesis tolerate many functional groups including free secondary alcohols. In combination, these two methods can be used to rapidly generate large fragments of polyketides. Often, functional group interconversions or protection groups can be avoided. For instance, in the first step of the fragment B synthesis of Krische, a direct allylation of an unprotected diol is performed with high diastereoselectivity and without the need to either oxidize the primary alcohol prior to the C–C coupling nor to protect the secondary alcohol. This protecting group free C–C coupling is enabled by the high site-selectivity of the allylation reaction which leaves the secondary alcohol untouched. Classical methods for reductive carbonyl allylations would require oxidation of the alcohol to the aldehyde and the carbon nucleophile needs to be preformed by metalation and possibly transmetallation protocols. This again relates to the concept of preactivation as described for Aggarwal's organocatalyzed aldol reaction (*vide supra*).[28]

It is instructive to compare the Paterson and Krische synthesis of the A fragment since both approaches target the same C–C bonds for disconnection. Krische forms the intermediate by three consecutive C–C-bond forming reactions (hydrogen mediated C–C-bond formation, olefin metathesis and allylation) followed by ozonolytic cleavage of the terminal alkene. Paterson starts with aldehyde oxidation state and sets the stereogenic center with an asymmetric aldol reaction. Cyclization is followed by reduction and acylation which sets the stage for the formation of the C8–C9 bond *via* S_N2' reaction.

Synthesis of (−)-thapsigargin

Biomimetic approaches are among the most successful strategies for natural product synthesis. In terpene synthesis, cyclases can generate the most complex scaffolds in a single transformation. The core is subsequently oxidized and further elaborated, *e.g. via* esterifications.

Following the general strategy of terpene synthesis, *i.e.* the carbon skeleton is built prior to functionalization *via* C–H oxidations. As a result, functional group interconversions and protecting group manipulations can be avoided since only a few functional groups are present early in the synthesis. With the growing arsenal of C–H oxidation available, two-phase terpene synthesis is gaining importance.[59]

A successful demonstration of the two phase strategy is the 15 step (−)-thapsigargin synthesis by Baran (Fig. 7).[19] This highly oxidized sesquiterpene (every second skeletal carbon atom is bearing an oxygen atom) shows promising biological activities and is currently in late-stage clinical trials for the treatment of a number of cancer types. Prior to the Baran work,

the only reported route to (−)-thapsigargin by Ley required 42 steps, starting from (+)-carvone.[60] The Baran group started their synthesis with a Robinson annulation[61] of (+)-dihydrocarvone and ethyl vinyl ketone introducing all 15 skeletal carbon atoms in the first step. This first step already marks the end of the cyclase phase. Subsequently, a series of oxidations and finally a santonin rearrangement formed the [5,7]-bicyclic framework whilst also introducing the tertiary acylated alcohol. In general, the Baran route introduces all esters present in the natural product shortly after installing the corresponding alcohols using them as protection groups. In contrast, in the Ley synthesis, all esters are formed step-by-step at the end of the synthesis and thus, requiring multiple protection/deprotection steps. The [5,7]-bicyclic framework is constructed *via* RCM of an already highly functionalized diene. It takes another 25 steps to introduce the remaining three skeletal oxygens and three more skeletal carbons. While the three additional carbons are introduced shortly after the olefin metathesis, the introduction of the remaining oxygen atoms accounts for most of the following steps. Hence it is not sufficient to separate C–C bond formations from oxygenations, but equally important to control the timing of the oxidation events. More recently, Evans reported a thirteen-step route to thapsigargin.[62] Similar to Baran, the 15-carbon skeleton is formed early in the synthesis *via* coupling of a (−)-carvone-derivative (C10) with a C5-ketone. The ketone already possesses an increased oxidation level, which makes the synthesis convergent. The [5,7,5]-tricyclic carbon skeleton is then completed *via* a diastereoselective pinacol coupling, forming the two vicinal stereocenters at C6 and C7. Evans' synthesis thus represents a complementary approach compared to Baran's synthesis. Joining highly oxidized coupling partners can remove oxidation steps from the LLS thus leading to high convergency.

Ley's OY of 0.78% over 42 steps (89% average yield per step) is more than double than that of Baran (0.33%, 66% average

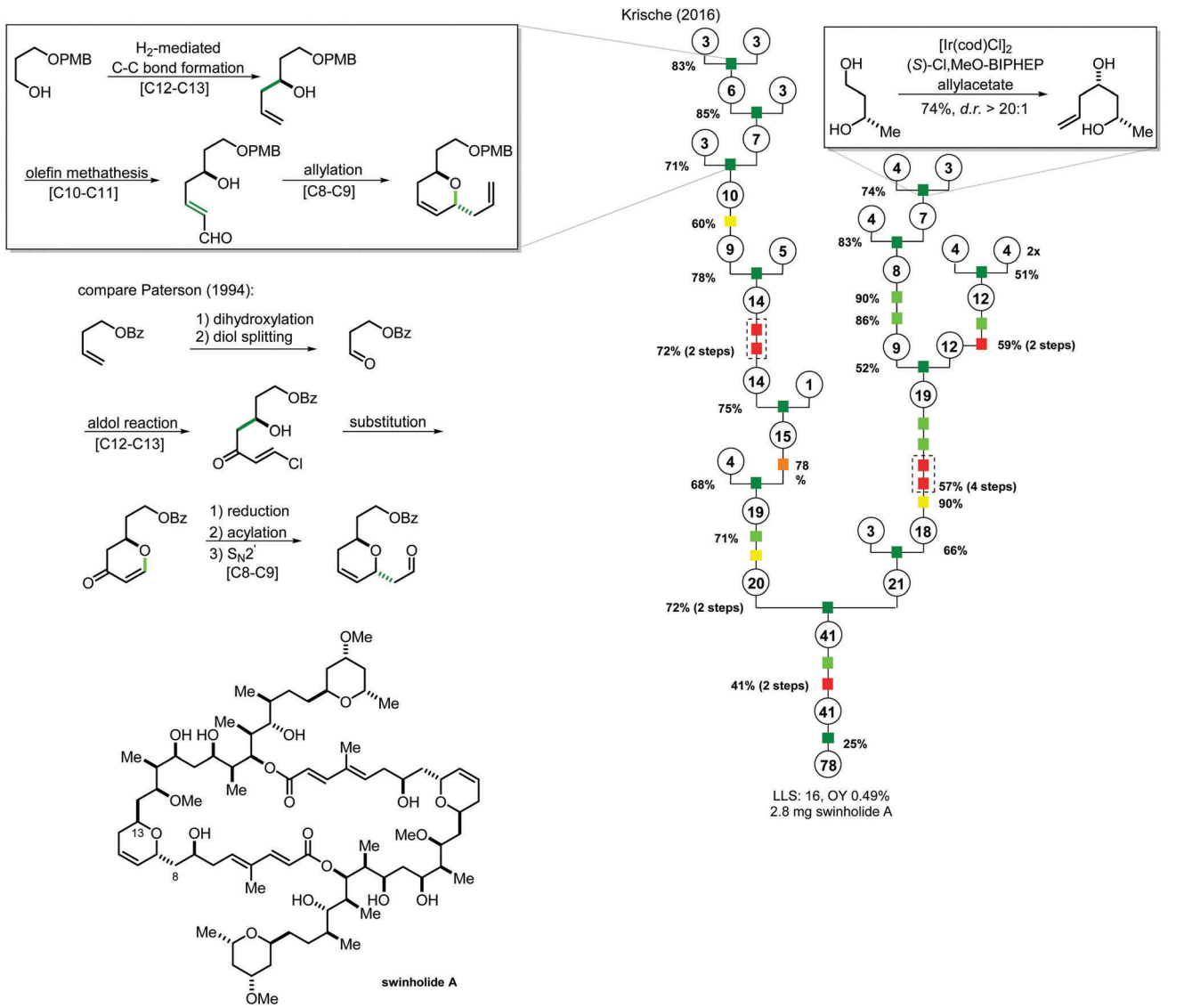


Fig. 6 Swinholide A total synthesis of Krische.[39]

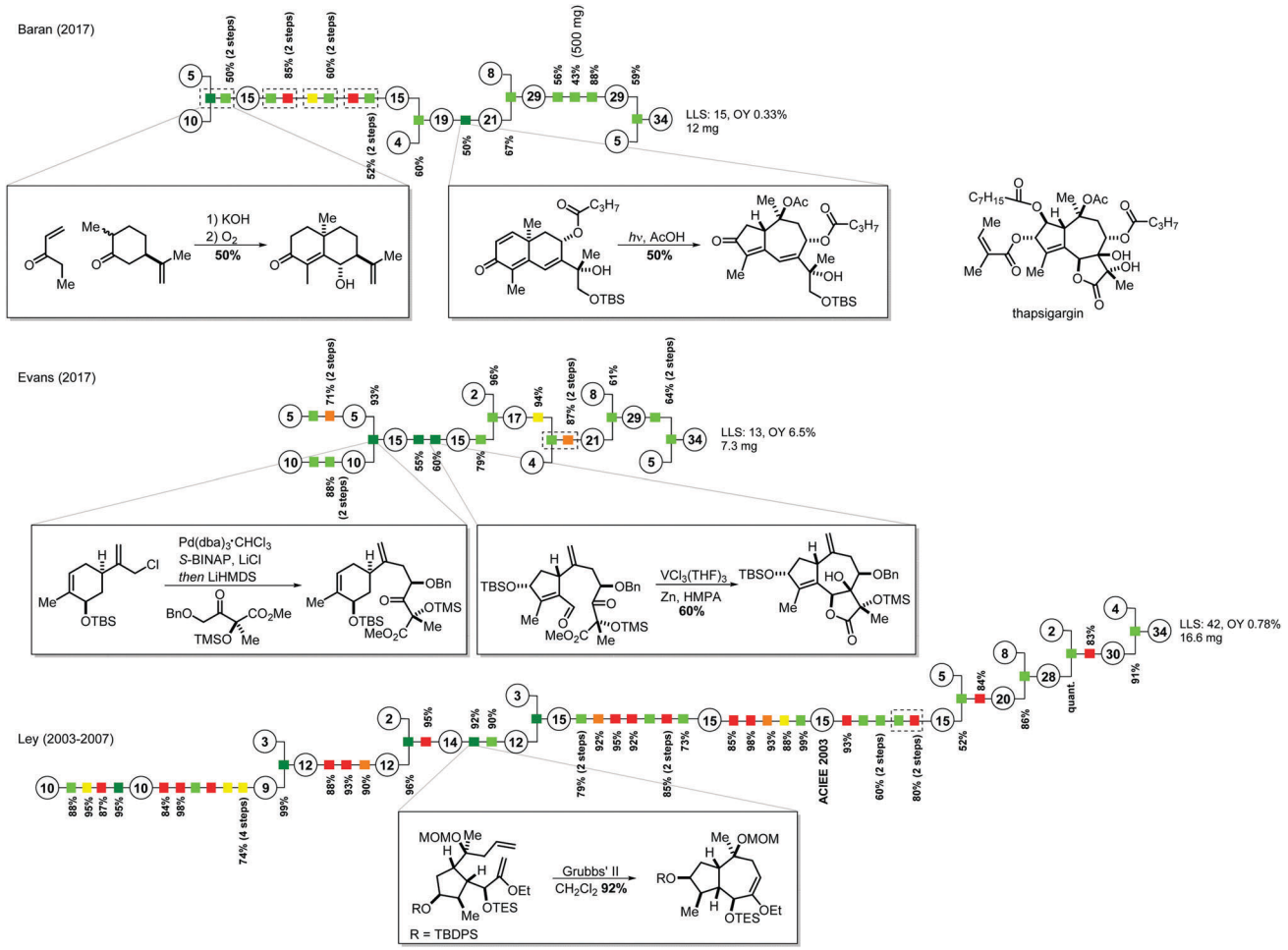


Fig. 7 Thapsigargin syntheses by Baran, Evans and Ley.

yield per step). Surprisingly, again the longer synthetic sequence delivers the better OY (see prostaglandin $F_{2\alpha}$). On the other hand, Baran's short synthesis provides access to ample quantities of the natural product. Due to the high toxicity of thapsigargin, the natural product itself was not prepared on gram scale but 500 mg of a late-stage intermediate was prepared. The highest OY achieved by Evans (6.5%), thus providing a practical access to this promising anti-cancer lead structure. This again underscores the importance of step-efficiency in synthesis. Apart from the OY, the amount of labor is directly proportional to the number of steps. It should be noted the challenging transformations often require extensive optimization. Reducing the risk by relying one established methods can also come with additional time and cost as even those must be tested under a variety of conditions. Again, the amount of material lost during optimizations is proportional to the length of the synthetic sequence.

Conclusions

So which strategies are leading to the shortest syntheses? The approaches to step efficient syntheses highlighted in this article are as different as the natural products they build. However, there are a few common features:

Convergent syntheses using large building blocks are often superior in the construction of complex natural products compared to a rather linear assembly involving the addition of one- or two-carbon fragments. In the retrosynthetic analysis, disconnections should therefore divide the target in fragments of comparable size and complexity. This approach also lowers the number of C–C bond formations.

Rather than relying on classic methods that often come with the cost of low functional group tolerance, milder methods should be applied (and developed!) that possess high functional group tolerance.[6] In this regard, non-strategic functional group interconversions or redox manipulations should be avoided.

Biomimetic approaches often allow for exceptionally short syntheses. If the biosynthesis of a natural product has been proposed, one should consider mimicking Nature's assembly strategy. In terpene synthesis, the separation of the cyclase phase from subsequent oxidative functionalizations provides a blueprint for the chemical synthesis. This two-phase strategy[59] can lead to concise routes with little or no protection group manipulations as in the construction of the carbocyclic terpene core, only few functional groups are present.

Apart from these general guidelines, the flowchart presentation can assist in comparing different routes with respect to step- and redox economy. Following the color code, less efficient parts of a synthesis plan can be easily distinguished from more efficient ones. Although syntheses have been compared using a flow-chart presentation and color coding the yields,[63] the color coding of classes of transformations according to their synthetic value allows for the comparison of different routes in the planning stage.

To compare the efficiency of synthetic routes, the OY of a synthetic route was shown to be less diagnostic than the step count. In all cases shown, the amount of synthesized product was largest with the shortest synthesis although in some cases, significantly longer sequences resulted in a better OY. It should be noted that the OY does not reflect labor, amount of waste (e-factor), atom- and redox economy. Those factors are mainly influenced by the number of steps. Thus, a step-efficient synthesis inherently reduces protecting groups, non-strategic redox operations, functional group interconversions and purification steps.

Conflicts of interest

There are no conflicts to declare.

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