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Principles for Synthetic Efficiency and Expansion of the Field

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Today, the field of natural product total synthesis, which was once a dominant sub-discipline of organic chemistry, has lost its prime position. Even with the renaissance of natural products as drug candidates, and the recent recognition of the value and contribution of natural product-based drugs to societies by the Nobel Prize in Physiology or Medicine 2015, the situation has changed. As we have mentioned in the Introduction, "it is estimated that half of the top 100 best-selling medications will soon be biologics." According to Dirk Trauner, "the field is currently under fire, at least in societies that have traditionally supported it."[1a] To address these challenges, we need to significantly improve efficiency of the synthesis,[1b] expand the field of total synthesis, and address the concerns of society. In this chapter, the efforts by chemists from these dimensions will be summarized with a focus on concepts.

1.1 Concepts for Efficiency in the Total Synthesis of Natural Products

As we have pointed out in the previous sections, the total synthesis of natural products is facing with many challenges. The key to tackle these problems is to improve the synthetic efficiency, which involves selectivity, economy of synthesis, and green chemistry. Over the last five decades, many concepts have been advanced by the leading scientists in the field. It is expected that the new concepts will become new criteria for total synthesis.

Efficiency in Natural Product Total Synthesis, First Edition. Edited by Pei-Qiang Huang, Zhu-Jun Yao, and Richard P. Hsung.

1.1.1 Ideal Synthesis

1.1.1.1 Hendrickson's Definition (1975)

The concept of ideal synthesis was first advanced by J. B. Hendrickson in 1975:

> The synthesis would start from available small molecules so functionalized as to allow constructions linking them together directly, in a sequence only of successive construction reactions involving no intermediary refunctionalizations, and leading directly to the structure of the target, not only its skeleton but also its correctly placed functionality. If available, such a synthesis would be the most economical, and it would contain only construction reactions.[2]

1.1.1.2 Wender's Definition (1996)

A more comprehensive definition of ideal synthesis was given by P. A. Wender in 1996.[3a]

> An ideal (the ultimate practical) synthesis is generally regarded as one in which the target molecule (natural or designed) is prepared from readily available, inexpensive starting materials in one simple, safe, environmentally acceptable, and resource-effective operation that proceeds quickly and in quantitative yield.[3]

Wender also indicated two general ways[3a] for approaching the ideal synthesis (i.e., achieving maximum relevant complexity increase while minimizing step count):

1) The use of strategy-level reactions such as the Diels–Alder reaction or multistep processes such as tandem and domino sequences that allow for a great increase in target-relevant complexity in one operation.
2) The design and development of new reactions and reaction sequences that allow for a great increase in target-relevant complexity.

1.1.1.3 Baran's Quantification of the Ideal Synthesis

To furnish a numerical expression for Hendrickson's conception of an ideal synthesis, P. S. Baran gave the following metric definition: "ideality is the percentage of the sum of construction reactions and strategic redox reactions divided by number all synthetic steps."[4]

Construction reactions are skeletal bond (C–C and C-heteroatom) forming reactions; and **strategic redox reactions** are functionality installation reactions (direct introduction of the correct functionality found in the final product) that belong to the construction reaction.

1.1.2 Selectivity

Although the importance of selectivity in organic synthesis is well known, B. M. Trost was the first to give a systematic analysis and take it as a goal for achieving synthetic efficiency.[5] He categorized selectivity according to chemical reactivity (chemoselectivity), orientation (regioselectivity), and spatial arrangement (diastereoselectivity and enantioselectivity), and indicated the increased role of main group and transition metals in enhancing selectivity.[5a] **Chemoselectivity** refers to the preferential reaction of a chemical reagent with one of two or more different functional groups within a molecule. The term is also applied to reacting molecules or intermediates that exhibit selectivity toward chemically different reagents. The controlled reaction of a functional group (e.g., ester, amide) to a product of an intermediate oxidation state (e.g., ketone/aldehyde, ketone/aldehyde/imine) constitutes another type of chemoselective reaction.

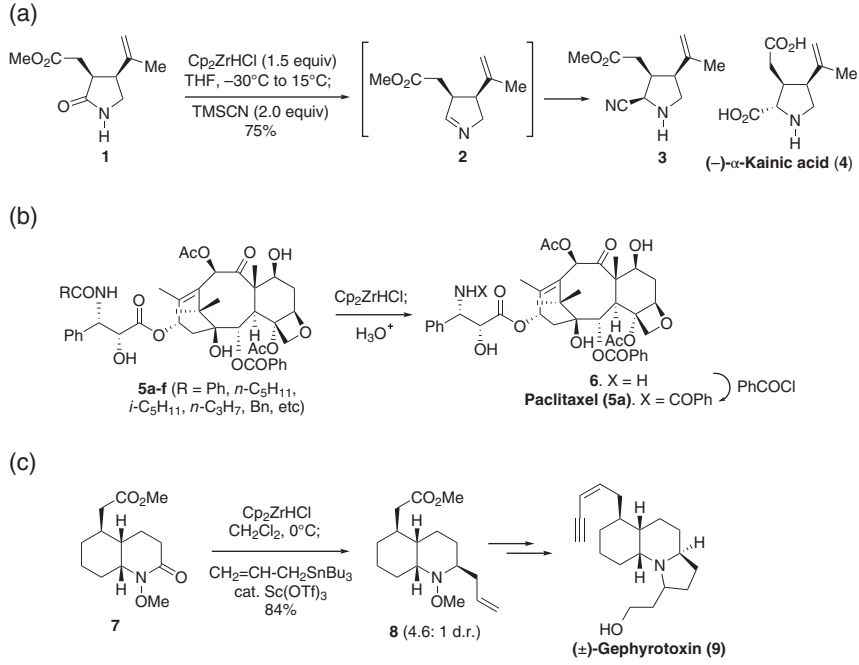
While P. S. Baran views chemoselectivity as both the greatest obstacle to complex molecule synthesis and the mother of invention in total synthesis,[6a] A. K. Yudin, states that achieving high levels of chemoselectivity has been the Achilles heel of chemical synthesis.[6b]

Chemoselectivity is highly depend on reagents. Kagan's reagent (samarium(II) diiodide)[7] is a mild single-electron reductant enabling many chemoselective transformations.[7] The Kagan reagent-mediated efficient total syntheses are presented in Chapter 6.

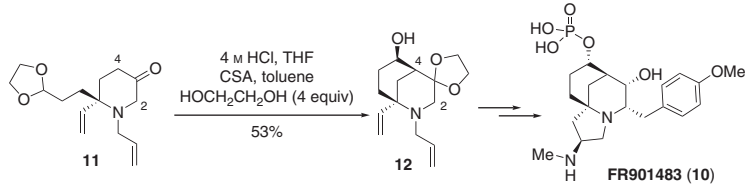
Amides are the least reactive carboxylic acid derivatives. Performing the chemoselective reaction at an amide group in the presence of an ester group is challenging. The pioneering work of B. Ganem showed that Schwartz's reagent (Cp_2ZrHCl)[8] can serve as a chemoselective reducing agent to convert a secondary amide/lactam group in the presence of an ester group to an imine.[9] Using this methodology, they have developed a concise asymmetric total synthesis of (−)-α-kainic acid (**4**, Scheme 1.1a).[9b] The exceptional chemoselectivity of the amide-to-imine reduction was applied to the synthesis of **6** by the selective removal of the amide acyl side chains from the highly functionalized substrates **5a–f**, which are a mixture of primary taxanes extracted from the yew trees growing on Michigan's Upper Peninsula (Scheme 1.1b).[9c] This legendary chemoselective reduction paved a way for efficient commercial semisynthesis production of paclitaxel through semisynthesis by Natural Pharmaceuticals, Inc. (NPI).[9c, 10]

Recently, Chida extended Ganem's chemistry to the reductive functionalization of secondary amides/lactams,[11] leading to (Scheme 1.1c) the most concise and efficient total synthesis of (±)-gephyrotoxin (**9**) to date (14 steps, 9.4 overall yield).[11c]

Chemoselectivity is not only critical for total synthesis but also an important issue in chemical biology,[12a–c] and in protein chemical synthesis.[12d]



Scheme 1.1 Ganem's and Chida's chemoselective transformations based on Schwartz's reagent.



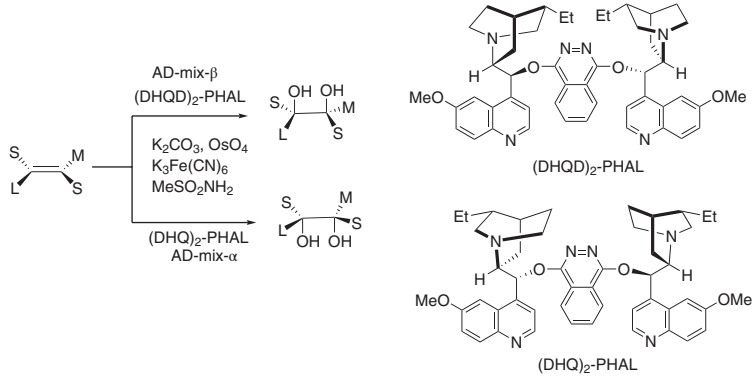
Scheme 1.2 Key C4 regioselective aldol reaction in the total synthesis of FR901483.

Regioselectivity refers to the preferential reaction of a chemical reagent at one direction (position) over all other possible directions (positions) of a molecule. In Huang's enantioselective synthesis of the potent immunosuppressant FR901483 (**10**), a regioselective aldol reaction at C4 of **11** was required.[13a] Under carefully defined conditions, the key aldol reaction proceeded regioselectively at C4 to deliver compound **12** as the sole regio- and diastereoisomer (Scheme 1.2).[13a] The regioselective (and enantioselective) enzymatic $\Delta^{2,3}$ epoxidation of polyene squalene (**46**) to yield (3*S*)-2,3-oxidosqualene (**47**) (see Scheme 1.14 later) is an excellent model of regioselective reaction. Sometimes, reactivity among the same kind of functional groups is referred as site-selectivity, which can be achieved by a variety of methods.[13b–d]

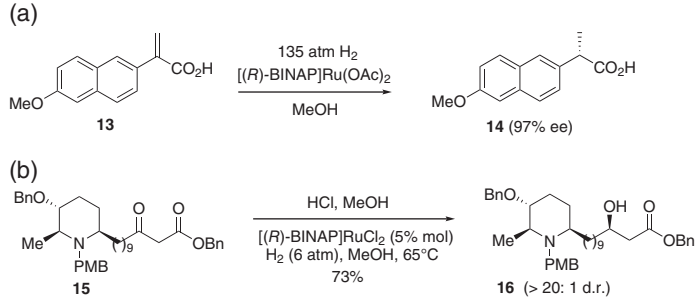
Stereoselectivity includes diastereoselectivity and enantioselectivity. In a diastereoselective reaction one diastereoisomer is formed as preferential to other possible ones. An enantioselective reaction refers to a reaction that leads to preferent formation of one enantioisomer (enantiomers) over another one.

The Sharpless asymmetric epoxidation (of allylic alcohols, AE) and asymmetric dihydroxylation (of alkenes, AD)[14] (Scheme 1.3) are enantioselective reactions. Because of their reliable and predictable enantioselectivity, these two reactions have found widespread applications in the total synthesis of natural products.

R. Noyori and coworkers have developed several BINAP – Ru(II)-based chiral catalysts for enantioselective reduction of alkenes[15a] (Scheme 1.4a) and ketones.[15b] When chiral piperidinyl β-ketone ester **15** was employed as a substrate, the Noyori reaction proceeded diastereoselectively to give the secondary alcohol **16** (Scheme 1.4b).[16]



Scheme 1.3 Sharpless enantioselective (asymmetric) dihydroxylation of alkenes.



Scheme 1.4 Enantioselective (a) and diastereoselective (b) reductions by Noyori's catalysts.

1.1.3 Green Synthesis

In 1991, the concept of green chemistry was put forward with the "Twelve Principles of Green Chemistry" as a scientific approach for environmental protection.[17a–f] One of the principles states that it is better to prevent waste rather than to treat or clean up waste after it is formed. Anastas and coworkers have also demonstrated that catalysis can be used as a primary tool for achieving the principles of green chemistry. For chemical process in pharmaceutical industry, seven important elements[17g] and eight criteria[17h] that define a good chemical manufacturing process have been suggested.[17i,j] In parallel, sustainable practices in medicinal chemistry have been reviewed and some potential future developments have been recently highlighted.[17k]

1.1.4 Atom Economy

The concept of atom economy[18, 19] was advanced by B. M. Trost in 1991.[18a] He suggested that in addition to selectivity,[5] efficient synthetic methods should be economical at atom level with maximum incorporation of atoms of reactants into the desired products. This concept focuses on minimizing both the use of chemical reagents and additives, and waste production in the form of by-products.[18] Cycloaddition reactions such as the Diels–Alder reaction are a class of highly atom-economical reactions. Methods that involve combining building blocks and catalytic amounts of promotors can reach high atom economy. He also suggested the approaching of the selective and economical synthesis by using transition metal catalysis. In 2008, C.-J. Li and B. M. Trost drew our attention to the design of new synthetic processes that can simplify operations in chemical productions and to the use of greener solvents.[18d]

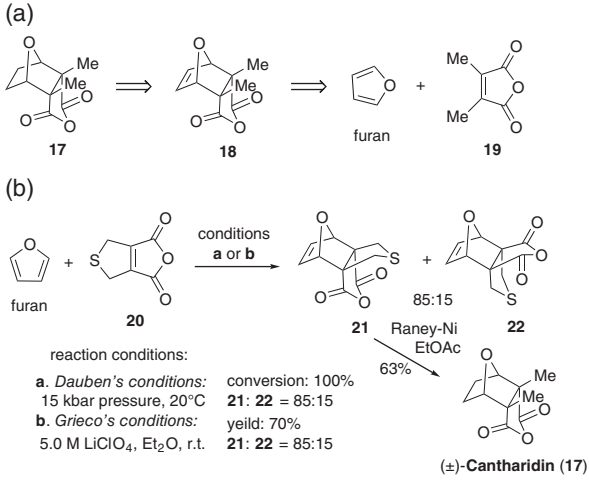
1.1.5 E Factors

In 1992, Sheldon introduced the concept of the E(nvironmental) Factor[20] to relate the mass of waste to the mass of product formed (E Factor = kg waste/kg product).[19b] In that article, Sheldon also provided a figure for the E factors of the main chemical industrial sectors. According to the list, pharmaceutical industry is the sector with the highest E factor (25 ~ 100 compared with <0.1 for the petroleum refining sector). This reflects that most of the synthetic transformations currently used in pharmaceutical industry are multistep syntheses and employing stoichiometric instead of catalytic amount of reagents. In addition, Sheldon also suggested the concept of atom utilization[20a] and atom efficiency,[20c] which emphasized the importance of catalytic processes in achieving high atom efficiency.

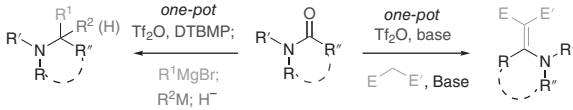
1.1.6 Step Economy

Since the first introduction of the concept of step economy by P. A. Wender in 2006,[21] this brief term has become increasingly popular among the synthetic community. As an approach toward the ideal synthesis, step economy is the drive to increase the efficiency of a synthesis by minimizing synthetic steps, which should cover redox-economy (*vide infra*), quick generation of molecular complexity, and protect group-free synthesis (*vide infra*). However, the intention of Wender was dual.[21c] On one hand, he called for the development of new reactions and new synthetic strategies that allow for shorter routes to a (complex) target, and on the other hand, the design and synthesis of less complex targets while maintaining or enhancing molecular function, namely, function-oriented synthesis (FOS, *vide infra*).[21c–e] The synthesis of the potent vesicant cantharidin (**17**) by Dauben[22] demonstrates the importance of novel synthetic technologies in achieving step economy. Retrosynthetically, the intermediate **18** could be synthesized by a Diels–Alder reaction between furan and dimethyl maleic anhydride (**19**) (Scheme 1.5a). However, this ideal synthesis is difficult to achieve due to the low reactivity of the diene and the dienophile.

Dauben and coworkers overcame these difficulties by employing the high pressure technique and the use of 2,5-dihydrothiophene-3,4-dicarboxylic anhydride (**20**) as a surrogate of the dimethyl maleic anhydride (**19**). Thus, the Diels–Alder reaction of furan with **20** (prepared in three steps from commercially available compound) at 15 kbar pressure yielded quantitatively adducts **21** and **22** in a ratio of 85:15. The former was treated with Raney nickel to



Scheme 1.5 Step-economical synthesis of racemic cantharidin (**17**).



Scheme 1.6 Step-economic transformations of common amides.

produce cantharidin (**17**) in 63% (Scheme 1.5a).[22a] Further improvement by the same group allowed the reaction of >10 g of dihydrothiophene anhydride **20**.[22b] Alternatively, by taking advantage of dramatic rate accelerations of Diels–Alder reactions in 5 M lithium perchlorate-diethyl ether, the Diels–Alder reaction of furan with **20** proceeded smoothly at ambient temperature and pressure to give diastereomeric cycloadducts **21** and **22** in an 85:15 ratio with a 70% combined yield (Scheme 1.5b).[22c]

Amides are a class of versatile compounds found widespread applications in the total synthesis of alkaloids. However, due to their high stability, multistep methods[23] are used for their transformations to compounds at a lower oxidation state with C-C bond formation. By *in situ* amide activation with triflic anhydride (Tf_2O), P.-Q. Huang and coworkers developed a series of step-economic methods for the direct transformations of common amides (Scheme 1.6).[24]

1.1.7 Pot Economy and PASE (Pot, Atom, and Step Economy)

The concepts of both pot economy and its combination with atom and step economy (PASE) were proposed by Clarke in 2007.[25] Although the concept of pot economy overlaps to some extent with step economy, the former addresses the problem of minimizing solvent utilization and waste generation during work-up and product isolation and purification process. During a synthesis, it is the product isolation and purification procedures instead of the reaction itself that consume the most solvents and materials (including solvents, silica gel, or related substances), and generate the most waste (including contaminated aqueous waste from extraction, cleaning equipment, glassware, etc.). Yujiro Hayashi is an outstanding practitioner of pot-economy.[26a] His research group has achieved the elegant, pot economical enantioselective total syntheses of several bioactive natural products using organocatalysis.[26] To achieve a significant "greener" synthesis for molecules of medium complexity, the combination of PASE was further suggested by Clarke.[25]

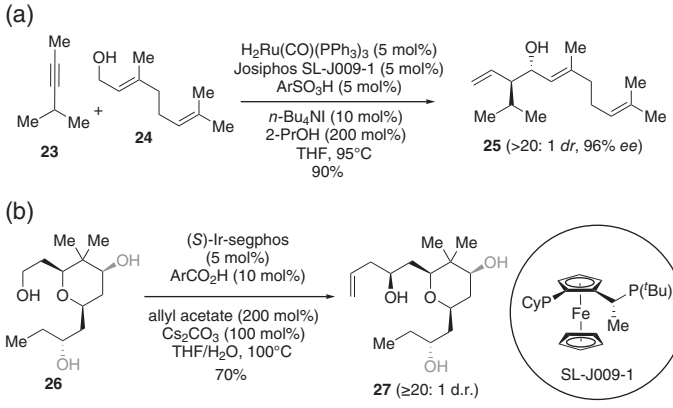
1.1.8 Redox Economy

In a tutorial review article published in 2009, P. S. Baran, R. W. Hoffmann and N. Z. Burns put forward the concept of redox economy.[27] This concept, "which is an ignored strategy," points out the importance of minimizing the use of redox steps in achieving highly efficient multistep organic synthesis. Redox

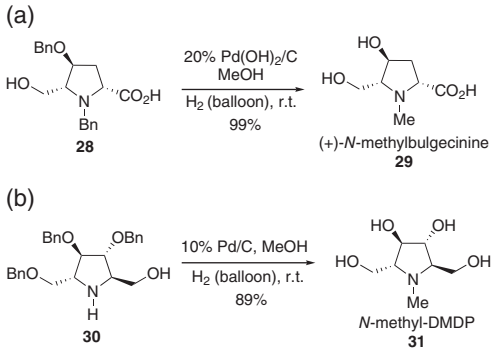
economy can be achieved by two approaches: through the design of redox economical reactions, and redox economical synthetic strategies. Several total syntheses of high redox economy will be illustrated in Chapter 2.

Alcohols are routinely synthesized by addition of organometallic reagents to aldehydes. The latter in turn are synthesized by oxidation of simpler alcohols. Thus, direct use of alcohols as the surrogates of aldehydes constitute a class of redox-economical reactions. However, such reactions are challenging. In this context, the conceptually novel "C–C bond forming hydrogenations," "C–C bond forming transfer hydrogenations" (Scheme 1.7a), and related reactions (Scheme 1.7b),[28] invented by M. J. Krische and coworkers, represent important breakthroughs in both concept and synthetic methodology. In addition to being redox economical, the reactions also displayed excellent regio-, diastereo-, and enantio-selectivities. Moreover, as can be seen from Scheme 1.7b, the reaction took place chemoselectively at the primary alcohol in the presence of free secondary alcohols allowing a protecting group-free synthesis (*vide infra*). The power of these revolutionary methodologies has been demonstrated by the efficient enantioselective total syntheses of several structurally complex natural products[28a–f] including cyanolide A, which will be discussed in Chapter 2. This chemistry has also been applied by A. Fürstner to the total synthesis of mandelalide A (the proposed structure).[28g]

To overcome the problem of over *N*-alkylation with alkyl halides, the traditional method for the synthesis of tertiary/secondary amines from the corresponding secondary/primary amines consists of reductive *N*-alkylation of secondary/primary amines with aldehydes. Direct use of an alcohol as an alkylating reagent for the *N*-alkylation represents another type of redox-economical method.[27] The Pd/C or $Pd(OH)_2$/C-catalyzed *N*-methylation reactions with



Scheme 1.7 Krische reactions for the redox-economical, diastereo-, and enantioselective synthesis of functionalized alcohols.



Scheme 1.8 Huang's redox-economical and chemoselective amine *N*-methylation.

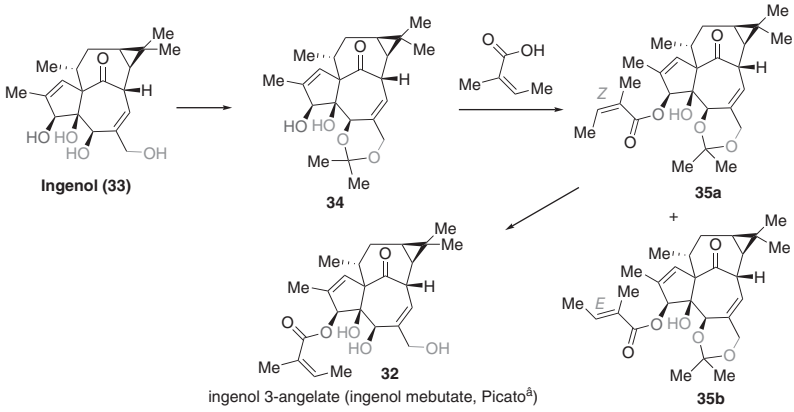
methanol outlined in Scheme 1.8 turned out to be a synthetically useful redox-economical reaction.[29] Under mild reaction conditions (at r.t., 1 atm H_2), *N*-,*O*-debenzylations and *N*-methylation took place sequentially and chemoselectively in one pot, and in the presence of unprotected hydroxyl and carboxyl groups.[29a]

1.1.9 Protecting-Group-Free Synthesis

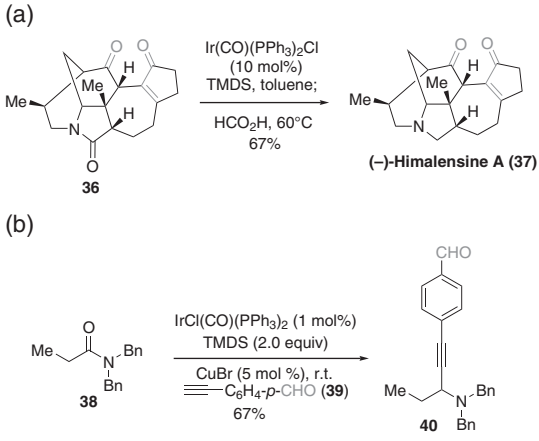
Natural products are generally multifunctionalized compounds. Thus the use of cumbersome protecting groups are indispensable for achieving selective transformations.[30] The semisynthesis of ingenol angelate (**32**) developed by the scientists of Leo Pharma in Denmark is a typical example (Scheme 1.9).[31a] The protection of the two hydroxyl groups in the form of a cyclic acetal ensued the selective esterification of the allylic hydroxyl group at the cyclopentene ring. This semisynthesis provided enough material for clinical trials, and was the basis for the approval of ingenol angelate (**32**) by the US Food and Drug Administration (FDA) in 2012 as a drug for the treatment of AK.[31b] However, the use of a protecting group generally brings about two additional steps to a synthesis, which reduces dramatically the efficiency of the synthesis. Moreover, at the last step of the synthesis, chemists often suffer from frustration at being unable to cleave the protecting groups without destroying the whole molecule. Thus, organic synthesis without using protecting groups (protecting group-free synthesis)[32] has become an attractive approach to achieving step economy.

There are two tactics to develop protecting group-free syntheses. Protecting groups are used to direct a reaction to take place at a specific functional group or position. Thus, the first approach is to developing chemo-, regio-, and stereoselective reactions and methods (*vide supra*).

The last step of the total synthesis of (–)-himalensine A (**37**) (Scheme 1.10a), reported very recently by D. J. Dixon and coworkers,[33a] provides an example of this approach. Amide (lactam) is a highly stable functional group that serves as



Scheme 1.9 Leo Pharma's semisynthesis of Picato (**32**).



Scheme 1.10 On substrate and on nucleophile protecting-group-free syntheses.

the protected form of the corresponding amine. The last step requires the selective reduction of the lactam in compound **36** in the presence of two more reactive ketone and enone functional groups. The conventional method resides in the protection of the more reactive ketone and enone groups before the reduction of the less reactive lactam. And after lactam reduction, it needs to cleave the two protecting groups. Instead, Dixon employed a new chemoselective method that consisted of partial reduction of the lactam group with Vaska's catalyst/TMDS (1,1,3,3-tetramethyldisiloxane) followed by further reduction in hot formic acid to deliver (–)-himalensine A (**37**). This protecting-group-free reduction not only significantly increased the synthetic efficiency, but also ensued the success of the total synthesis.

By means of Ir and Cu(I) bis-metal sequential catalysis, reductive alkynylation of tertiary amides (e.g., **38**) proceeded under mild conditions to afford propargylic amines (e.g., **40**, Scheme 1.10b).[33b] The reaction exhibits exceptional chemoselectivity and functional group tolerance even for sensitive functional groups such as aldehyde, cyano, ester, and nitro groups on either the amide or alkyne partners. For example, acetylene derivative **39** bearing an unprotected aldehyde group underwent smooth reaction with **38** to afford the desired amino aldehyde **40**.

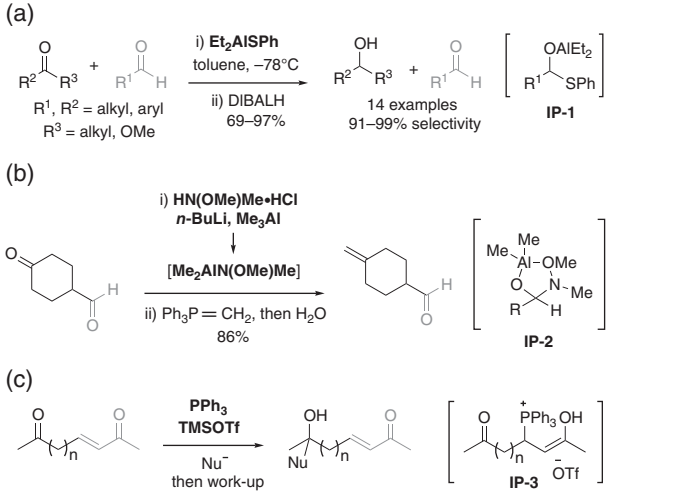
Now, even unprotected polyhydroxylated carbohydrates can serve as starting materials in organic synthesis.[34]

The second tactic to develop protecting-group-free syntheses is the strategic design of a synthetic route to avoid situations where selectivity is a problem. Many highly efficient total syntheses are protecting group free, and some will be discussed in Chapter 2.

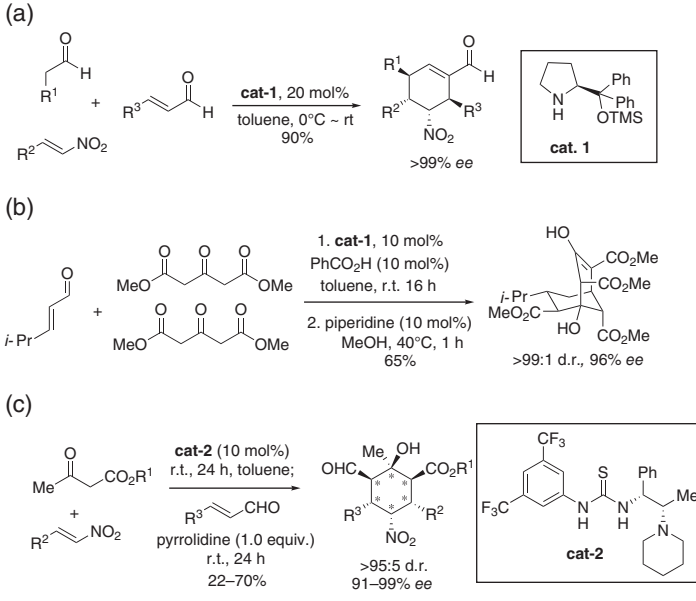
If the use of protecting groups is unavoidable, one should try to economize one step from either protection or deprotection via a one-pot reaction. The reaction showcased in Scheme 1.8 can illustrate this tactic. Because *N,O*-deprotection and *N*-methylation took place in one pot, no additional step is required for the deprotection.[29a] Another tactic for the manipulation of less reactive carbonyl groups in the presence of more reactive aldehyde/ketone groups is through the *in situ* protection of the former. Reagents such as diethylaluminum benzenethiolate (Et_2AlSPh),[35a] the combination HN(OMe)Me·HCl/*n*-BuLi/Me_3Al,[35b] and PPh_3/trifluoromethanesulfonic acid trialkylsilyl esters (R_3SiOTf) have been employed by Markó, Colby, and Fujioka, respectively, for the discrimination of different carbonyl compounds/groups (Scheme 1.11a, b). Notably, H. Fujioka's PPh_3/R_3SiOTf system is able to undergo conjugate addition with *α,β*-enones, leading to the *in situ* protection of *α,β*-enones[35d, e] (Scheme 1.11c).

1.1.10 Multicomponent Reactions and One-Pot Reactions

In a multicomponent reaction (MCRs) at least three different starting materials react in a programed sequence to yield, in one pot, the final product, which incorporated most of the atoms of the starting materials.[36] MCRs is a highly efficient methodology because at least two bonds are formed in one pot. Many classical MCRs are named reactions, including the Mannich reaction (M-3CR), Biginelli reaction (B-3CR), and Ugi reaction (U-4CR). Up to eight component reactions have been reported.[37] The high convergence of the MCRs rend them particularly useful for the construction of compound libraries. Merging MCRs with organocatalysis paves an avenue for the asymmetric multicomponent reactions (AMCRs).[38] In this context, Enders and coworkers achieved the control of four stereocenters in a diphenylprolinol silyl ether-mediated asymmetric three-component reaction (Scheme 1.12a).[39a] After this breakthrough, organocatalytic



Scheme 1.11 *In situ* protection of aldehydes (a and b) and α,β-enone (c).



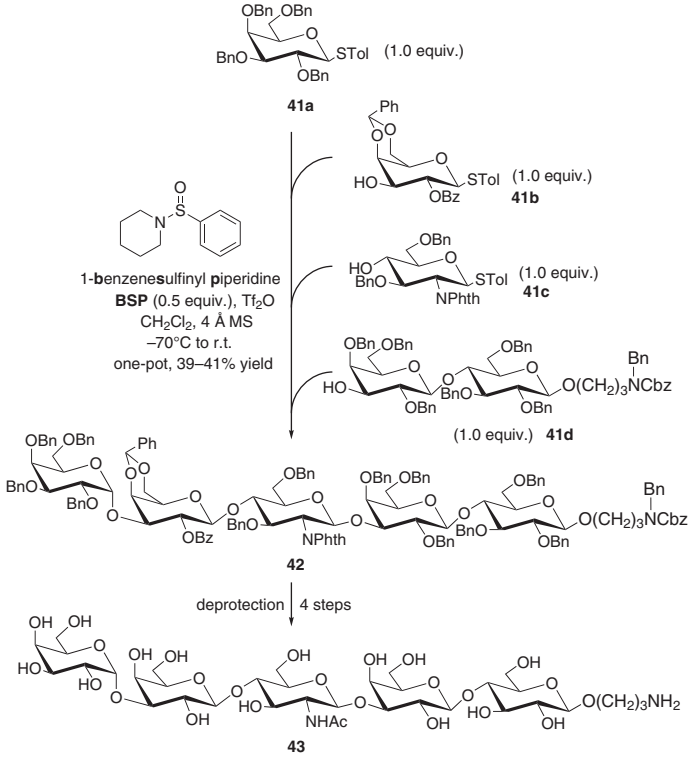
Scheme 1.12 Organocatalytic, asymmetric multicomponent reactions.

one-pot formation of 1 out of 64 (2^6) possible stereoisomers have been achieved by K. A. Jørgensen (Scheme 1.12b)[39b] and D. Enders (Scheme 1.12c),[39c] respectively.

In 2004, Xin-Shan Ye and coworkers reported a four-component reaction of easily available common saccharide building blocks to give, in one pot, the fully protected α-Gal pentasaccharide (**42**), which was further converted in four steps to yield α-Gal pentasaccharide (**43**) (Scheme 1.13).[40] Note that it was reported that α-Gal pentasaccharide (**43**) plays an important role in the interaction with human anti-Gal antibodies and may be useful in the research of xenotransplantation and immunotherapy.

1.1.11 Scalability

The total synthesis of structurally complex natural products generally ends with only milligrams of the final product. Thus scale up of a lengthy multistep total synthesis presents a huge challenge. Nevertheless, to be able to provide sufficient amount of a compound in a reasonable time is crucial for



Scheme 1.13 Four-component one-pot synthesis of α-Gal pentasaccharide (**43**).

investigating the function of the molecule. Thus the scalability become an important issue not only for the total synthesis of natural products, but also for organic reactions and synthetic methods. This issue began to attract the attention of synthetic organic chemists. In a recent review article entitled: "Natural Product Synthesis in the Age of Scalability,"[41a] P. S. Baran and coauthors illustrated the gram-scale total syntheses of natural products and kilogram syntheses in pharmaceutical company disclosed in recent years, and emphasized the importance to develop simple, scalable synthetic routes.

Very recently, Allred and coauthors reviewed the state-of-the-art of the production of structurally complex natural product-based drug candidates on scales sufficient to drive human drug trials.[41b]

1.1.12 Convergent Synthesis

Convergent synthesis is a classical yet efficient strategy in total synthesis.[42a,b] Many highly efficient total syntheses employing this strategy will be presented in Chapter 2. The building-block-based convergent strategy can forge practical synthesis for medicinal chemistry. This has been nicely demonstrated by Andrew G. Myers in the context of antibacterial drug discovery (see Section 1.4). In addition, recently, M. Inoue,[42c] J. Šenda,[42d] and coworkers have independently outlined many elegant examples employing convergent strategies for efficient synthesis of structurally complex natural product.[42] Recently, M. Inoue summarized the radical-based convergent strategies for total syntheses of densely oxygenated natural products.[42e]

1.2 Biomimetic Synthesis

In the field of total synthesis of natural products, the structure of the target is usually complex with structure containing multifunctionality and multistereocenters. Hence, multistep synthesis is common, which makes ideal total synthesis and fully atom-economical total synthesis difficult to achieve. A more appropriate approach would be one that imitates nature. Indeed, we admire the biosynthesis of natural products of living organism, which proceeds in an efficient, selective, economical, and environmental friendly manner.

In the literature, when a new natural product is reported, very often the authors suggest a plausible biosynthetic route. Such proposals are generally not confirmed by experimental data and can be incorrect. Even Robinson and Woodward made mistakes on this issue.[43a] In fact, only a small portion of biosynthetic routes have been elucidated. For example, although the biosynthesis of tropane alkaloids has been investigated since the time of Robinson, its exact biogenesis (biosynthetic route) remained unsolved for 100 years.[43b] Biogenetic speculative seems to be a general methodology according to Robert Thomas in

a review entitled: "Biogenetic Speculation and Biosynthetic Advances."[43a] He indicated that: "A prerequisite of the experimental investigation of any biosynthetic pathway is the formulation of a hypothetical scheme for the transformation of candidate precursors based on plausible reaction mechanisms" and emphasized the importance of biogenetic speculation.

Moreover, as can be seen from the following examples, in so-called "biomimetic synthesis" only a key strategy, a key intermediate, or a key step but not the whole synthetic sequence is imitated under nonenzymatic conditions.[44] As such, it may be more appropriate to define this type of synthesis as *bio-inspired synthesis*.[45] Thus, it is important to be aware of the basic principles and strategies that nature follows. Although the biosynthesis of many natural products of different origin remains a "black box," general schemes of biosyntheses in plants are known.[46] From these known schemes the following basic principles, key features, and basic strategies of a biosynthesis can be figured out.

1.2.1 Basic Logic of Biosynthesis

1.2.1.1 Basic Principles of Biosynthesis

1) Economy (of materials, energy, time, etc.)
2) Rapid generation of molecular complexity
3) Environmentally benign and sustainable
4) Function-oriented synthesis (of bioactive molecules)

1.2.1.2 Key Features and Basic Strategies of Biosynthesis

1) Aqueous phase synthesis
2) The building blocks strategy
3) The cascade reaction strategy
4) The C–H functionalization strategy
5) The divergent synthesis, collective synthesis
6) The (multi)enzyme catalysis (multidomain protein)
7) The highly selective (chemo-, regio-, and stereoselective) synthesis
8) The protecting-group-free synthesis
9) The small quantity synthesis
10) The umpolung tactic
11) The oligomerization tactic
12) The repetitive tactic

1.2.2 Tandem, Cascade, and Domino Reactions – One-Pot Reactions

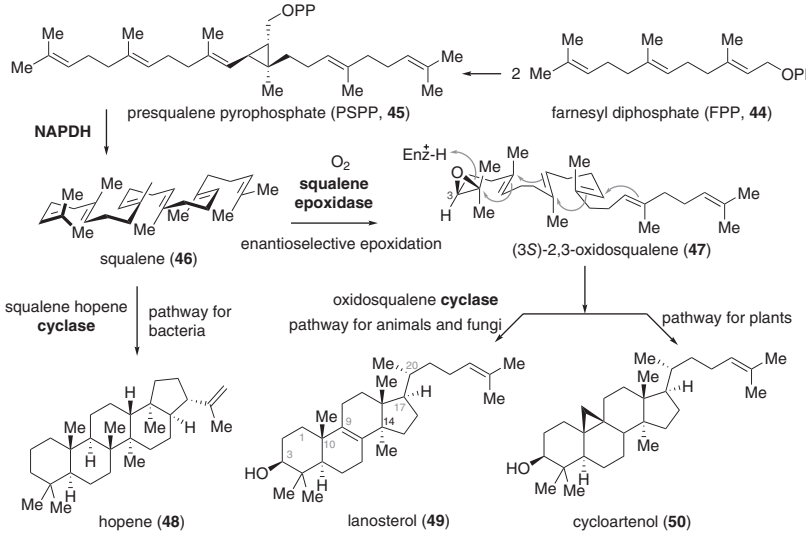
Among the biosynthetic strategies that fascinate chemists the most are undoubtedly the one-pot cascade reactions/sequences because they allow

rapid generation of molecular complexity, leading to high synthetic efficiency in an elegant manner. Depending on the complexity of the molecule, it may involve a tandem or a cascade/ domino reaction sequence.

The first one-pot reaction can be traced back to the well-known Robinson's tropinone synthesis developed 100 years ago (see Chapter 2, Section 2.1.1). This synthesis is inspirational for synthetic efficiency. The synthesis was achieved through a multicomponent reaction, which involves tandem (sequential) Mannich reactions, and bis-decarboxylation in one pot.

A general view[47] of terpene and sterol biosynthesis is depicted in Scheme 1.14. Central to this scheme is the regio- and enantioselective epoxidation of squalene (**46**) to give (3*S*)-2,3-oxidosqualene (**47**) and the subsequent oxidosqualene cyclase-catalyzed polycyclization to yield a specific product. A plant triterpenoid is built through an all-chair folding, whereas a sterol precursor adopts a chair-boat-chair folding (see **47**) (followed by generation of a chair-boat-chair proto structure, which then undergoes methyl-hydrogen migration and proton loss). The chemical principles of these polyolefin cyclizations are Barton's conformational analysis-based Stork–Eschenmoser hypothesis (rationalization on stereoelectronic grounds). It is fascinating that nature is able to convert the achiral molecule squalene, in just two steps, into a single stereoisomer with 4–5 rings and no less than seven asymmetric centers out of 128 possible stereoisomers!

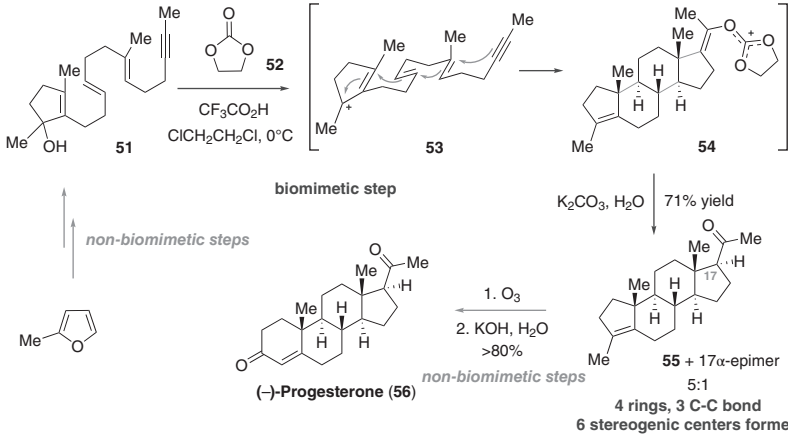
In light of the Stork–Eschenmoser hypothesis, in 1971 W. S. Johnson and coworkers achieved the biomimetic synthesis of (±)-progesterone (**56**).[48]



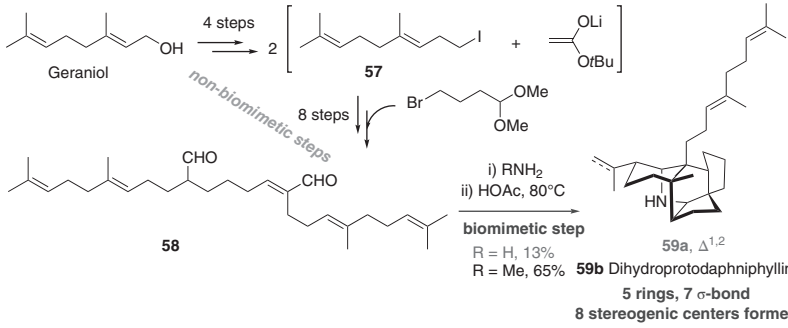
Scheme 1.14 Key steps in terpene and sterol biosynthesis.

The nonenzymatic, stereospecific (except C17), cationic polyolefin cyclization of cyclopentenol derivative **51** afforded, in a one-pot, polycyclic framework **55** with an all-*trans* ("natural") configuration (Scheme 1.15).

Heathcock's biomimetic synthesis of (±)-dihydroprotodaphniphylline (**59b**) (Scheme 1.16) represents another legendary classic in the history of biomimetic synthesis.[49a–c] It was inspired by a possible biosynthesis of one of the alkaloids.[49e] For the key biomimetic step, reaction of *E*-dialdehyde **58** with ammonia/NEt_3-HCl followed by treating with HOAc resulted in the formation of pentacyclization product **59a** at a 13% yield. However, by replacing ammonia with methylamine, (±)-dihydroprotodaphniphylline (**59b**) was obtained at a 65% yield! Interestingly, this spectacular result stemmed from a serendipitous discovery during an early investigation where a bottle of "ammonia" was actually methylamine. In this marvelous reaction,



Scheme 1.15 Johnson's biomimetic synthesis of (±)-progesterone (**56**).



Scheme 1.16 Heathcock's biomimetic synthesis of (±)-dihydroprotodaphniphylline (**59b**).

pentacyclization occurred in a stereospecific manner to form five rings and seven σ-bonds including four carbon-carbon bonds, two carbon-nitrogen bonds, and one carbon-hydrogen bond.[49]

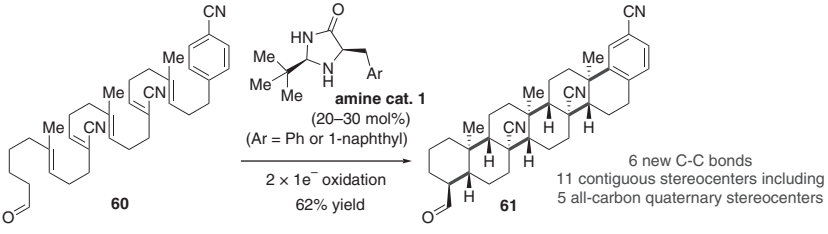
The success of this synthesis led to a concrete proposal about the biosynthesis of the alkaloids.[49b] It is worth mentioning that, in this 13-step synthesis, only the last step is biomimetic.[49b]

After these landmark accomplishments, many cascade polycyclizations have been developed for the total synthesis of natural products,[50] and the one-pot reaction methodology including tandem reactions, cascade reactions, and domino reactions is gaining popularity within the synthetic comminity.[50,51]

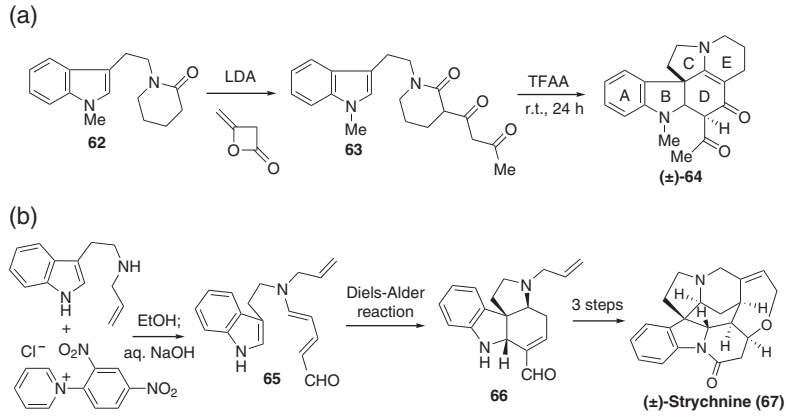
In recent years, organocatalytic asymmetric cascade reactions have emerged as a new tool in total synthesis.[52] In this regard, in 2010 D. W. C. MacMillan and S. Rendler developed SOMO catalysis to accomplish polyene tricyclization. Application of this concept to polyenal **60** resulted in the enantioselective formation of a hexacyclization adduct **61** as a single diastereomer at a 62% yield, which translates to an average yield of 92% per bond formed (Scheme 1.17). The level of enantiocontrol was assumed to be similar to those observed for the lower homologs of **61** (92% *ee*). In this remarkable chiral imidazolidinone catalyzed cascade reaction sequence, a total of 11 contiguous stereocenters including five all-carbon quaternary centers, were formed from the acyclic starting material **60**.[52e]

One-pot reaction methodology, in particular cascade polycyclizations, constitutes an important strategy for the rapid generation of molecular complexity.[53] In recent years, diverse strategies providing rapid access to molecular complexity have appeared.[54] In this context, Kagan's reagent (SmI_2) turned out to be a versatile reagent for a range of transformations, which will be illustrated in Chapter 6. Recently, David J. Procter has summarized the development of complexity-generating cascades by Sm(II)-mediated electron transfer to carboxylic acid derivatives.[54d]

A. H. Jackson's approach to the pentacyclic indole derivative **64**, which was related to *Aspidosperma* alkaloids, represents a typical example of rapid generation of molecular complexity from easily available starting materials (**62** and **63**) and under simple reaction conditions (Scheme 1.18a).[55a] Scheme 1.18(b) highlights C. D. Vanderwal's complexity-generating transformation to access



Scheme 1.17 MacMillan's enantioselective polyene cyclization via organocatalysis.



Scheme 1.18 Jackson's and Vanderwal's complexity-generating transformations.

the tetracyclic core (**66**), which is the key intermediate for the short racemic syntheses of norfluorocurarine (five steps), dehydrodesacetylretuline (six steps), valparicine (seven steps), and strychnine (**67**, six steps).[55b]

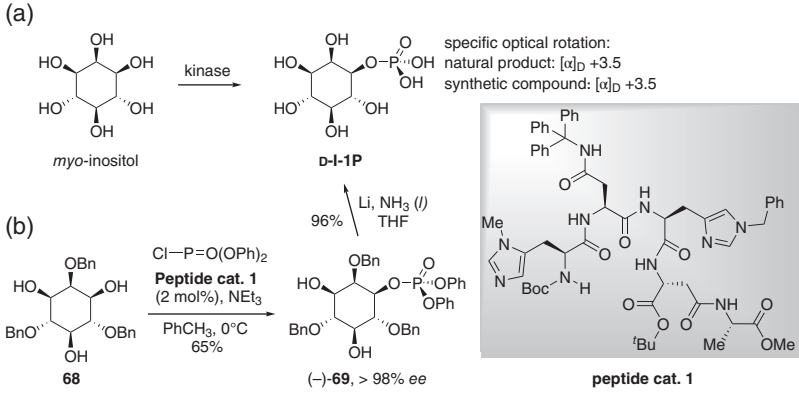
The assessment of molecule complexity would be helpful for planning efficient and convergent synthetic routes.[56a–e] In 2015, Jun Li and Martin D. Eastgate developed an approach for generating a unique complexity index, which is reflective of both intrinsic molecular complexity and extrinsic synthetic complexity. This approach allows for a direct comparison between molecules, the analysis of trends within research programs, and so on.[56f]

1.2.3 Site and Stereoselective Reactions

The beauty and elegance of biosynthesis resides in the highly regio-, chemo-, and stereoselective reaction at a specific functional group among many other reaction sites. The biosynthesis of D-myoinositol-1-phosphate (**D-I-1P**, Scheme 1.19a) provides an example. In the cell, kinases catalyze the transfer of a phosphoryl group (PO_3^{2-}) from an adenosine triphosphate (ATP) to a specific hydroxyl group among several others in a substrate to yield a specific phosphate ester.[57] In 2001, S. J. Miller and B. R. Sculimbrene developed the **peptide cat. 1** as a kinase mimic for the catalytic asymmetric phosphorylation, and achieved a concise enantioselective total synthesis of D-*myo*-inositol-1-phosphate (**D-I-1P**, Scheme 1.19b).[58]

1.2.4 The C—H Bond Functionalization Strategy

The site selective functionalization of an inert C–H bond among many other reaction sites represents another strategy in biosynthesis. In recent years,



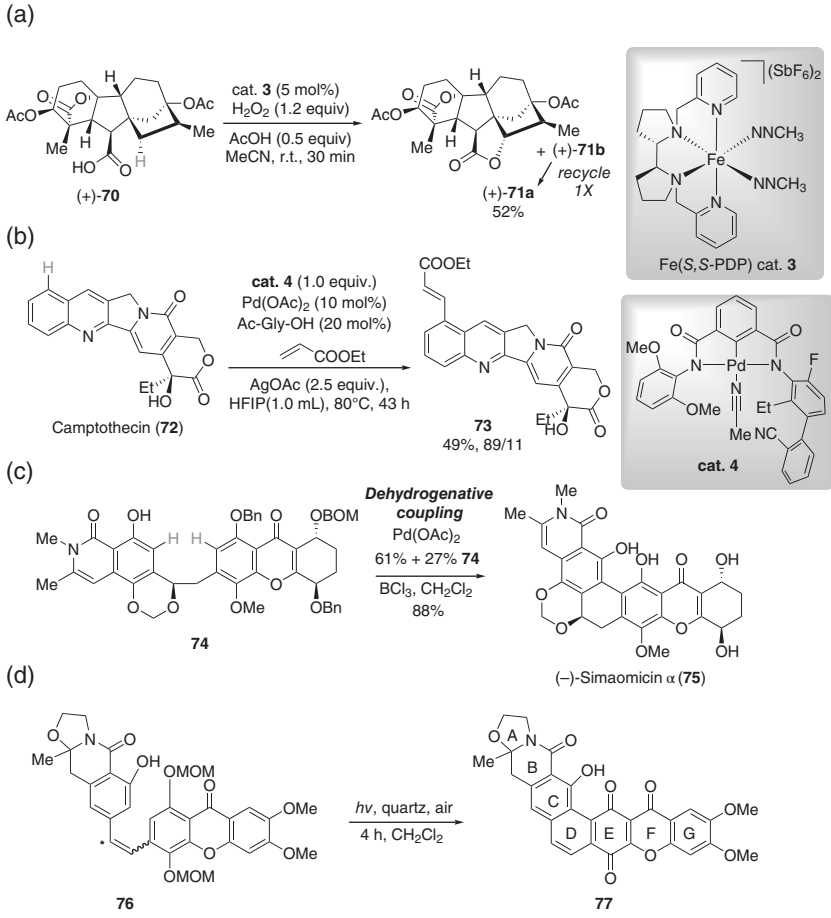
Scheme 1.19 The biosynthetic (a) and S. J. Miller's biomimetic (b) site and enantioselective synthesis of D-*myo*-inositol-1-phosphate (**D-I-1P**).

significant progress has been made on chemical C–H bond functionalization, which is emerging as a powerful tool for organic synthesis.[59] Many applications of C–H bond functionalization to the total synthesis of natural products will be discussed in Chapter 5. Significantly, C–H bond functionalization can also serve as a unique tool for regioselective late-stage modification of agrochemicals such as tetrahydrogibberellic acid analog (+)-**71a** (Scheme 1.20a),[60a] medicinal agents such as the antileukaemic and antitumour alkaloid (+)-camptothecin (**72**) (Scheme 1.20b),[60b] and simaomicin α (**75**), "the most potent natural-occurring anticoccidial agent reported"[60c] (Scheme 1.20c). It is worth mentioning that in 1989, simply by irradiation with medium pressure Hg lamp (quartz), T. Ross Kelly and coworkers achieved the one-pot transformation of **76** to (±)-cervinoymcin A_2 (**77**) at a 36% yield (Scheme 1.20d).[60d] The one-pot transformation involves a cascade of events including regioselective cyclization, cleavage of the MOM ethers, and oxidation.

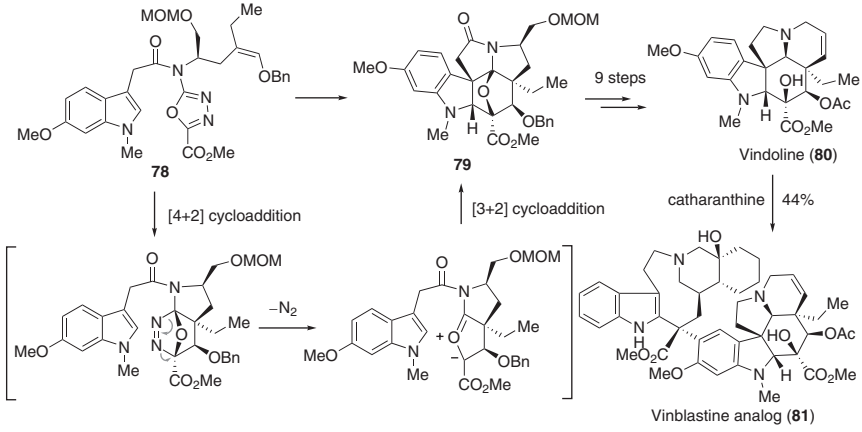
D. L. Boger's tandem intramolecular Diels – Alder/1,3-dipolar cycloaddition cascade of 1,3,4-oxadiazoles (e.g., **78**) represents an elegant methodology for rapidly accessing molecule complexity (Scheme 1.21).[61a] Combining this methodology with late-stage C – H functionalization forged a short route to anticancer alkaloid vinblastine analog (**81**), which proved to be 10 times more potent than vinblastine, displaying an IC_{50} of 600 – 700 pM in the cell growth inhibition assays.[61b,c]

1.2.5 The Building-Block Strategy

The building block is an old concept. Even Stephen Hanessian's well-known concept of the "chiron" (chiral building-block, chiral synthon)[62] has seldom appeared in current literature. The building-block-based strategy may seem to be a low



Scheme 1.20 White's, Yu's, Ready's, and Kelly's late-stage selective C–H bond functionalizations.



Scheme 1.21 Boger's cascade methodology and its combination with late-stage C–H functionalization.

efficient approach and out of fashion. However, the building block is the essential strategy that nature adopted for almost all biosyntheses! From proteins to nucleic acids, and from polysaccharides to secondary metabolites, all are synthesized starting from a limited number of simple (mono-, bi-, and multifunctional) building blocks such as amino acids for nonribosomal peptides, acyl-CoA thioesters for polyketides, isoprenyl diphosphates for terpenes, monosugars (and four bases) for polysaccharides, and DNA by iterative coupling.[63]

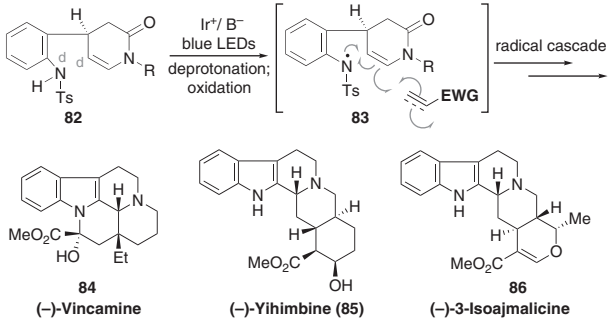
Surprisingly, an analysis of the 39 shortest enantioselective total syntheses, discussed in Chapter 2, revealed that chiral building-block-based approach is still the most commonly adopted (18 out of 39) and reliable strategy. The building-block-based approach is also a biomimetic approach. For these reasons, Chapter 9 is devoted to the total synthesis of natural products based on renewable resource-based building blocks/chirons. In this regard, Thomas J. Maimone and coworkers have very recently illustrated the power of this strategy in modern total synthesis.[64]

In 2014, Martin D. Burke and coworkers reported that it is possible to synthesize most polyene natural product motifs using just 12 building blocks and one coupling reaction.[63a] Their strategy relied on the identification of substructural motifs that are prevalent in natural products and development of suitable bifunctional building blocks and assembly method.[63a] The implementation of this strategy resulted in the first total syntheses of the polyene natural products asnipyrone B, physarigin A, and neurosporaxanthin β-D-glucopyranoside.

1.2.6 The Collective Synthesis Strategy

It is a common phenomenon that secondary metabolites exist collectively as a mixture of many compounds. Thus, the development of synthetic strategies to allow accessing different natural products is another way to increase synthetic efficiency. Many elegant collective syntheses will be discussed in other chapters of this book. Recently, Yong Qin and coworkers disclosed the efficient, enantioselective, collective syntheses of 33 monoterpenoid indole alkaloids belonging to four families[65a] (Scheme 1.22). The method relies on photocatalytic generation of a nitrogencentered radical that leads to umpolung of the reactivity of the nucleophilic amine and triggers radical cascade reactions. The method exhibited excellent chemo-, regio-, and diastereoselectivity.

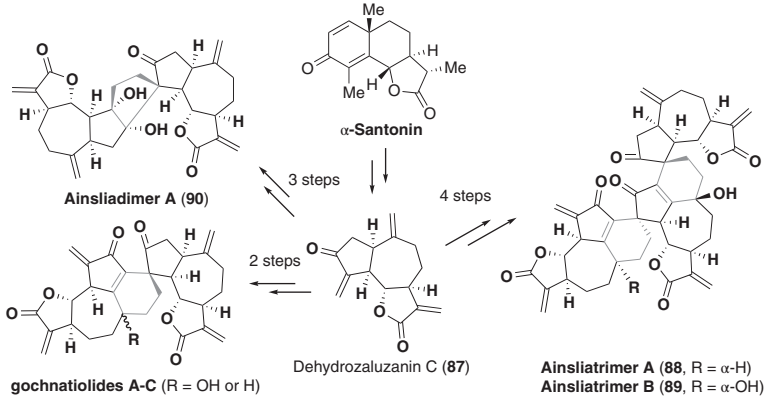
Recent examples of collective syntheses include bioinspired syntheses of iboga-type indole alkaloids (X. G. She),[65b] metathesis-cascade reactions-based synthesis (C. C. Li),[65c,e] synthesis of (−)-mersicarpine and related alkaloids (J. P. Zhu),[65d] organocatalytic [4 + 3] cycloaddition reaction-based synthesis of englerin A and B and related natural terpenes (B.-F. Sun, G.-Q. Lin),[65f] and synthesis of lycopodium alkaloids (X. G. Lei; [65g–i] M. D. Shair[65j]).



Scheme 1.22 Qin's radical cascade-based collective syntheses of indole alkaloids.

1.2.7 The Oligomerization Tactic

Oligomerization (including dimerization and trimerization) is a tactic used by nature to build complexity in short steps. Thus, identifying the inherent yet hidden symmetry (monomer) and developing methods for assembling monomers are both crucial to simplifying synthetic routes for the synthesis of oligomeric natural products. In 2011, Scott A. Snyder and coworkers developed a programmable resveratrol oligomer synthesis based on regioselective reactions.[66] In the same year, they reviewed synthetic approaches to oligomeric natural products.[67a] In 2014, X. Lei provided an overview for the biomimetic syntheses of oligomeric sesquiterpenoids.[67b] By identifying dehydrozaluzanin C (**87**) as the structure motif, they established a four-step transformation into very complicated trimers ainsliatrimer A (**88**) and ainsliatrimer B (**89**) (Scheme 1.23).[68] Very recently, Wen-Ju Bai and Xiqing Wang published an updated review focusing on symmetry.[67c]



Scheme 1.23 Lei's collective synthesis of oligomeric sesquiterpenoids.

1.3 The Expansion of the Field: Chemical Biology/ Chemical Genetics

Chemical biology and chemical genetics are terms used to describe a field that employs the methods of chemistry to study biology. Chemical genetics, which uses small molecules as chemical probes/tools to perturb the function of gene products and allow the systematic dissection of biological processes, and identify small molecules with the ability to induce a biological phenotype or to interact with a particular gene product, is an emerging tool for lead generation in drug discovery.[69]

The studies of FK-506 and rapamycin by S. L. Schreiber and collaborators represent a classical approach of chemical biology in investigating the mechanism of information transfer or signaling through the cytoplasm of the cell, which is one of the great mysteries of cell biology. Cyclosporine A, FK-506, and rapamycin are natural fungal products that possess potent immunosuppressant activity and are capable of specifically inhibit cellular processes. Through chemical biological studies by means of organic synthesis, conformational analysis, and chemical analysis, and in combination with modern techniques in biology such as flow cytometry, they are able to decipher related biological processes at a molecular level.[70] On the other hand, the joint efforts of medicinal chemists, pharmacologists, and chemists from several pharmaceutical companies and universities have also been fruitful, resulting in several approved immunosuppressant and anticancer drugs from rapamycin.[71] Moreover, rapamycin and rapalogs have been shown to increase lifespan and improve other markers of aging in a range of organisms.[71] Table 1.1 shows an overview of these drugs.

1.3.1 Diversity-Oriented Synthesis (DOS)

DOS[72] was conceived as a novel conceptual alternate of combinatorial chemistry for the construction of libraries to study the chemical genetics. The tasks of DOS include the development of efficient pathways to a large amount of skeletal and stereochemical diverse small molecules with defined coordinates in chemical space. In order to achieve the highest levels of structural diversity: The building blocks, stereochemistry, functional groups, and, most importantly, the molecular framework must be varied.[72c]

1.3.2 Function-Oriented Synthesis (FOS)

In view of the difficulty in the efficient synthesis of structurally complex natural products and the uncertainty of the molecule's medicinal profile, the concept of FOS was advanced by Paul A. Wender to achieve function with simple synthetic mimetics.[73] Although such strategy has previously been employed in the

Table 1.1 Drugs developed from immunosuppressant natural products.

Natural Products	Approved Year, Trade Name	Medical Uses
Cyclosporine	1983, Neoral, Sandimmune,	to prevent organ rejection in transplant patients
FK-506	1994, Tacrolimus.	to stave off organ rejection in liver transplants (and other types of organ transplants)
Rapamycin	1999, Rapamune (sirolimus)	to prevent organ transplant rejection;
	2007, Torisel (temsirolimus)	to treat kidney cancer;
	2009, Afinitor (everolimus)	to treat advanced kidney cancer
Approvals for other cancers and for use as an immunosuppressant to prevent rejection of transplanted organs followed.		

pharmaceutical industry, its introduction to academic research is helpful for emphasizing the importance of function,[21c–e] Since simplified targets can be accessed in a step-economic fashion, natural product-based drug discovery can be accelerated. In connection with FOS, very recently, K. Gademann and E. A. Crane reviewed an approach based on natural product derived fragments that can successfully address some of the current challenges in drug discovery.[74] Examples from various stages of the drug development process up to the clinic have been presented.

1.3.3 Biology-Oriented Synthesis (BIOS)

BIOS[75] is a concept advanced by Herbert Waldmann as a structure-based approach to analyze biologically relevant chemical space in view of the use in the development of small molecules for chemical biology and medicinal chemistry research. BIOS is based on structural analysis of the protein and the small-molecule world as well as the combination of structural conservatism and diversity in nature.

1.3.4 Lead-Oriented Synthesis (LOS)

LOS[76] is a concept introduced by Ian Churcher to capture the specific problem of preparing diverse small molecules with lead-like molecular properties[75a] The realization of lead-oriented synthesis requires the development of new synthetic methods and approaches that can deliver large numbers of diverse, lead-like small molecules.

1.4 Addressing the Threats that Humans May Face in the Near Future

A re-recognition by both the scientific community and society of the key role the total synthesis of natural products can play in both science and technology requires tremendous efforts from scientists in the field. Prevising and addressing the major challenges that human may have to face is not only an effective approach but also a duty for scientists.

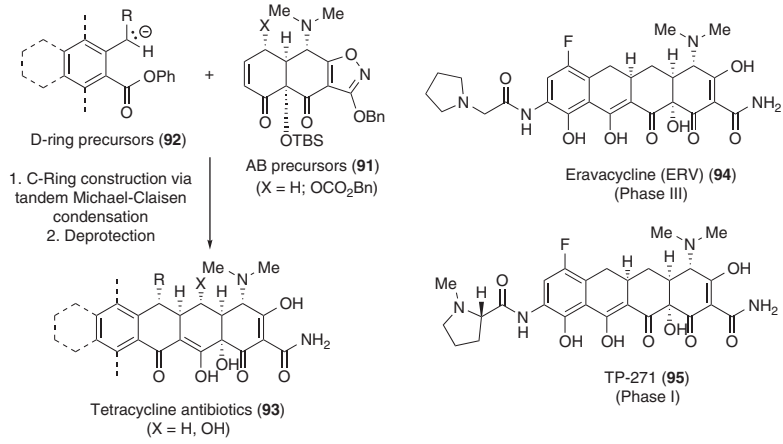
1.4.1 A. G. Myers' Endeavor

In this context, the longstanding efforts of Andrew G. Myers and his team at Harvard University is very respectable. Eco-environmental problems, resource problems, and resistance of bacteria to various antibiotics may be three major threats that humans will face in the near future. In A. G. Myers and coworkers' recent comprehensive review on the 100-year history of antibiotics discovery and development, they presented their deep concern about the risk of humanity returning to a pre-antibiotic era due to the fact that many major pharmaceutical companies have abandoned antibacterial R&D. Importantly, they revealed the essential and evolving role of chemical synthesis throughout the history of antibiotics, and make the point that this is the clearest path forward to discover future generations of life-saving medicines.[77]

> If the funding system for antibiotics research is not strengthened, if the attitude that academia is not the place for practical innovations persists, and if pharmaceutical companies (and venture capitalists) refuse to prime the pump independently, then the consequences for society could be dire.

This is the last sentence of their review, which presented once again their deep concern on the potential social crisis.

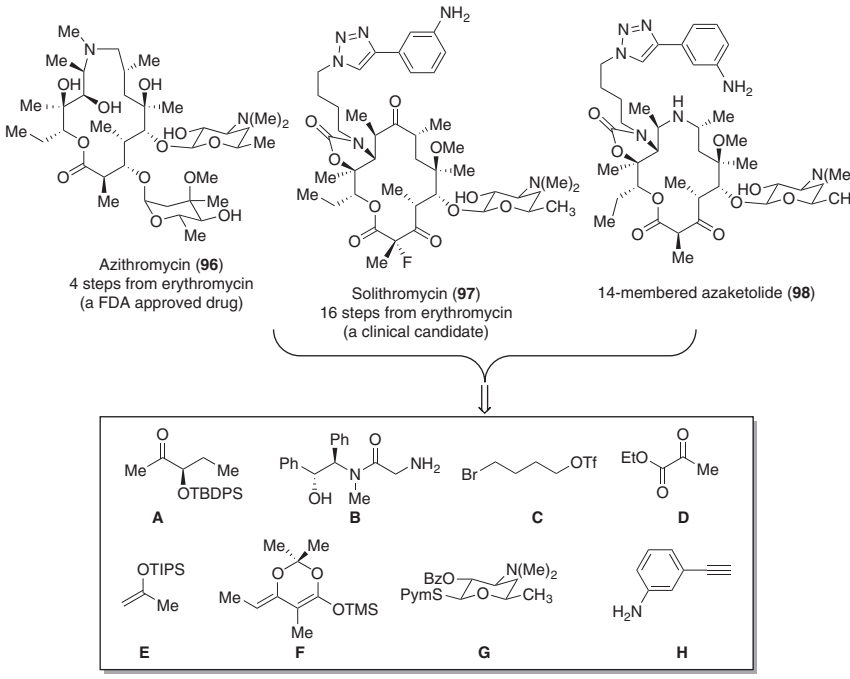
Prior to this review article, in the mid-1990s, A. G. Myers initiated a program aimed at the development of a practical synthetic platform for accessing fully synthetic tetracycline analogs. The motif of this project was to break through the limit of classical approach to antibiotics by semisynthesis or chemical modification of natural antibiotics obtained from fermentation. Via the latter approach, <10 tetracycline antibiotics have been approved over last 60 years, while within the same period of time, for structurally simpler quinolone and β-lactam antibiotics, the approved numbers are >40 and >50, respectively.[78a] Moreover, fully synthetic tetracycline analogs may be helpful in overcome the problems of stability and resistance. After a 12-year of efforts, Myers and coworkers disclosed in 2005 a practical enantioselective synthetic route to a diverse



Scheme 1.24 Myers' *de novo* convergent approach to antibiotic tetracycline analogs.

range of fully synthetic 6-deoxytetracycline antibiotics (**93**),[78b,c] which are inaccessible via the conventional semisynthesis approach (Scheme 1.24). Their method consists of separately constructing an AB-ring precursor (**91**) and a D-ring precursor (**92**) containing much of the essential functionality for binding to the bacterial ribosome. The coupling of D-ring precursors (**92**) with an AB precursor (**91**) via tandem Michael–Claisen condensation reactions proceeded diastereoselectively to form a C-ring and thus forged a convergent approach to an unprecedented series of tetracycline analogs (**93**). On the basis of this first generation technology, more than 3000 fully synthetic tetracycline analogs including the clinical candidates eravacycline (**94**, Phase III) and TP-271 (**95**, Phase I), and a preclinical candidate (TP-6076), have been synthesized.[78c] On the other hand, a company, Tetraphase Pharmaceuticals, was founded in 2006 to commercialize the tetracycline synthetic platform. The continuing efforts of Myers' team at Harvard resulted in the development of two entirely different approaches to the key AB enone (**91**).[78a,c] The second-generation synthesis of AB enone was improved and scaling up by the chemists at Tetraphase Pharmaceuticals to allow the synthesis of >100-kg of the AB enone, which enabled clinical development of eravacycline, TP-271, and TP-6076.[78a]

The success inspired and stimulated the development of safer and more effective anti-infective agents of other antibiotic classes. Since the discovery of erythromycin in 1949 by scientists at Eli Lilly, macrolide antibiotics have proven to be safe and effective for use in treating several human infectious diseases. However, due to their structural complexity, in spite of the accomplishments in both the chemical total synthesis and modified biosynthetic routes,[79] all members of this class approved or in clinical development for use in humans have



Scheme 1.25 Myers' convergent platform to macrolide antibiotics of the erythromycin class.

been manufactured by semisynthesis from erythromycin and steps for the semisynthesis of new analogs increased over the years.[76a] In 2016, Myers and coworkers developed an ingenious approach to macrolide antibiotics of erythromycin class with rich molecular topological (ring size) and functional group diversity.[80] Their synthetic strategy relies simply on the convergent assembly of simple building blocks **A–H** (Scheme 1.25). Through this convergent platform, more than 300 new macrolide antibiotic candidates, including the clinical candidate solithromycin, have been synthesized. Such fully synthetic and functionality diverse analogs are not accessible by traditional semisynthetic approaches. The majority of those molecules exhibited antibiotic activity, some are efficacious against strains resistant to macrolides in current use.[80a]

1.4.2 D. L. Boger's Endeavor

With the increasingly serious problem of antibiotic resistance, vancomycin (see Figure 5 in the Introduction), aglycopeptide antibiotic, isolated in 1956, and approved as an antibiotic by the FDA in 1958, was considered the last weapon made by human beings to fight against bacteria. However, with the discovery of

vancomycin-resistant strains of methicillin-resistant *Staphylococcus aureus* in 1997, there was an urgent need to develop new antibiotics effective against the superbugs. In this connection, the research groups led by D. A. Evans,[81] K. C. Nicolaou,[82] and D. L. Boger[83] achieved the total syntheses of vancomycin aglycon, and its sister antibiotic teicoplanin aglycon,[83a,84] in 1998, and 1999, respectively. In 1999, K. C. Nicolaou's group completed the total synthesis of vancomycin.[85]

Boger's long term endeavor on the total syntheses of vancomycin-related glycopeptide antibiotics and key analogs led to discovery, very recently, of peripheral modified [ψ[CH_2NH]Tpg^4]vancomycin analogs with added synergistic mechanisms of action providing durable and potent antibiotics.[86a] Being "over 25,000 times more potent than its' predecessors in activity, the super antibiotic has been hailed as the answer to antibiotic resistance by scientists."[87] This groundbreaking accomplishment is regarded as a victory in the battle against bacteria.[86b]

The progress in the chemistry and biochemistry of natural product-based antibiotics in general,[88] and vancomycin-related glycopeptide antibiotics and analogs in particular,[89] has been reviewed very recently by William M. Wuest and D. L. Boger, respectively, which serves well as the concluding remarks of this chapter.

Acknowledgements

Financial support from the National Key R&D Program of China (grant No. 2017YFA0207302), the National Natural Science Foundation of China (21332007, 21472153, and 21672176) and the Program for Changjiang Scholars and Innovative Research Team in University of Ministry of Education, China gratefully acknowledged.

We thank Ms. Yan-Jiao Gao for her assistance in the preparation of this manuscript, and thank graduate students Xiao-Gao Wang, Xiu-Ning Hu, Yi Lin, Shu-Ren Wang, and Qian He for their help in drawing schemes/figures.

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