FROM BIOSYNTHESSES TO TOTAL SYNTHESSES: AN INTRODUCTION

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1.1 FROM PRIMARY TO SECONDARY METABOLISM: THE KEY BUILDING BLOCKS

1.1.1 Definitions

The primary and secondary metabolisms are traditionally distinguished by their distribution and utility in the living organism network. Primary metabolites include carbohydrates, lipids, nucleic acids, and proteins (or their amino acid constituents) and are shared by all living organisms on Earth. They are transformed by common pathways, which are studied by biochemistry (Fig. 1.1). Secondary metabolites are structurally diverse compounds usually produced by a limited number of organisms, which synthesize them for a special purpose, like defense or signaling, through specific biosynthetic pathways. They are studied by natural product chemistry. This distinction is not always so obvious and some compounds can be studied in the context of both primary and secondary metabolisms. This is especially true nowadays with the use of genetic and biomolecular tools, which tend to make natural product sciences more and more integrative. However, an important point to remember is that the primary metabolism furnishes key building blocks to the secondary metabolism. It would be difficult to describe in detail the full biosynthetic pathways in this section. We tried to organize the discussion as a *vade mecum*, synthetically gathering information from extremely useful sources, which will be cited at the end of this chapter.

1.1.2 Energy Supply and Carbon Storing at the Early Stage of Metabolisms

The sunlight is essential to life except in some part of the deep oceans. It provides energy for plant photosynthesis that splits molecules of water into protons and electrons and releases O₂ (Scheme 1.1). A proton gradient inside the plant chloroplasts then drags a transmembrane ATP synthase complex that produces adenosine triphosphate (ATP) while electrons released from water are transferred to the coenzyme reducer nicotinamide adenine dinucleotide phosphate hydride (NADPH). A major function of chloroplasts is to fix CO₂ as a combination to ribulose-1,5-bisphosphate (RuBP) performed by RuBP carboxylase (rubisco), forming an instable “C₆” β-ketoacid. This is cleaved into two molecules of 3-phosphoglycerate (3-PGA), which is then reduced into 3-phosphoglyceraldehyde (3-PGAL, a “C₃” triose phosphate) during the Calvin cycle. This is one of the major metabolites in the biosynthesis of carbohydrates like glucose and a biochemical mean for storing and retaining carbon atoms in the living cells.

1.1.3 Glucose as a Starting Material Toward Key Building Blocks of the Secondary Metabolism

Glucose-6-phosphate arises from the phosphorylation of glucose. It is the starting material of glycolysis, an important process of the primary metabolism, which consists in eight enzymatic reactions leading to pyruvic acid (PA)
Important intermediates for the secondary metabolism are produced during glycolysis. Glucose, glucose-6-phosphate, and fructose-6-phosphate can be converted to other hexoses and pentoses that can be oligomerized and enter in the composition of heterosides. Additionally, fructose-6-phosphate connects the pentose phosphate pathway, leading to erythrose-4-phosphate toward shikimic acid, which is a key metabolite in the biosynthesis of aromatic amino acids (phenylalanine, tyrosine, or C₆C₃ units) and C₆C₁ phenolic compounds. The next important intermediate in glycolysis is 3-PGAL, which can be redirected toward methylerithritol-4-phosphate (MEP) in the
chloroplast. MEP is a starting block in the biosynthesis of terpenes through C5 isoprene units (isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP)), especially those in C10, C20, and C40 terpenes. 3-PGA is a precursor of serine and other amino acids, while phosphoenolpyruvate (PEP), the precursor of PA, is also an intermediate toward the previously mentioned shikimic acid. Lastly, PA is not only a precursor of the fundamental “C2” acetyl coenzyme A (AcCoA) unit but also an intermediate toward aliphatic amino acids and MEP.

AcCoA is the building block of fatty acids, polyketides, and mevalonic acid (MVA), a cytosolic precursor of the C5 isoprene units for the biosynthesis of terpenes in the C15 and C30 series (mind it is different from the MEP pathway, in product, and in cell location). Finally, AcCoA enters the citric acid or Krebs cycle, which leads to several precursors of amino acids. These are oxaloacetic acid, precursor of aspartic acid through transamination (thus toward lysine as a nitrogenated C4N linear unit and methionine as a methyl supplier), and 2-oxoglutaric acid, precursor of glutamic acid (and subsequent derivatives such as ornithine as a nitrogenated C4N linear unit). All these amino acids are key precursors in the biosynthesis of many alkaloids.

1.1.4 Reactions Involved in the Construction of Secondary Metabolites

Most reactions occurring in the living cells are performed by specialized enzymes, which have been classified in an international nomenclature defined by an enzyme commission (EC) number. There are six classes of enzymes depending on the biochemical reaction they catalyze: EC-1, oxidoreductases (catalyzing oxidoreduction reactions); EC-2, transferases (catalyzing the transfer of functional groups); EC-3, hydrolases (catalyzing hydrolysis); EC-4, lyases (breaking bonds through another process than hydrolysis or oxidation, leading to a new double bond or a new cycle); EC-5, isomerases (catalyzing the isomerization of a molecule); and EC-6, ligases (forming a covalent bond between two molecules). Many subclasses of these enzymes have been described, depending on the type of atoms and functional groups involved in the reaction and, if any, on the cofactor used in this reaction. For example, several cofactors can be used by dehydrogenases like NAD(P)/NAD(P)H, FAD/FADH2, or FMN/FMNH2. For a description of this classification, the reader can refer to specialized Internet websites like ExplorEnz [1]. What is important to realize is that most enzymes are substrate specific and have been selected during
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Evolution to perform specific transformations, making natural products with often and yet unknown functions.

Secondary metabolites arise from specific biosynthetic pathways, which use the previously defined building blocks. The bunch of organic reactions involved in these biosyntheses allows the construction of natural product frameworks, which are finally diversified through “decoration” steps (Scheme 1.3). It is not the purpose of this introductive chapter to describe in detail all biosynthetic pathways and the reader can refer to excellent books and articles, which have been published elsewhere [2, 3].

The reactions involved in the construction of natural product skeletons will be described later for representative classes of compounds. The identification of the building block footprint in the natural product skeleton will be emphasized as much as possible, sometimes referring to biogenetic speculations [4].

After the framework construction, the decoration steps will involve as diverse reactions as aliphatic C─H oxidations (e.g., involving a cytochrome P450 oxygenase) occasionally triggering a rearrangement, heteroatom alkylations (e.g., methylation by S-adenosylmethionine) or allylation (by DmAPP), esterifications, heteroatom or C-glycosylations (leading to heterosides), radical couplings (especially for phenols), alcohol oxidations or ketone reductions, amine/ketone transaminations, alkene dihydroxylations or epoxidations, oxidative halogenations, Baeyer–Villiger oxidations, and further oxygenation steps. At the end of the biosynthesis, such transformations may totally hide the primary building block origin of natural products.

1.1.5 Secondary Metabolisms

1.1.5.1 Polyketides Polyketides (or polyacetates) are issued from the oligomerization of C₂ acetate units performed by polyketide synthases (PKS) and leading to (C₂)n linear intermediates [5, 6]. If the (C₂)n intermediates arise from successive Claisen reactions performed by ketosynthase domains (KS, in nonreducing PKS), a highly reactive poly-β-ketoacyl intermediate H─(CH₂C═O)ₙ─OH is formed, leading to phenolic and aromatic products through further intramolecular Claisen condensations. Furthermore, highly reducing PKSs are made of specialized enzymatic subunits working in line or iteratively to functionalize each C₂ linker bond as CH(OH)CH₂ (by ketoreductases (KR)), then as HC═CH (by dehydratases (DH)), and as CH₂CH₂ (by enoyl reductases (ER)), leading to a high degree of functionalization of the final product (Fig. 1.2). By these iterative sequences, highly reduced polyketides, which can be either linear, macrocyclized, or polycyclized depending on the reactivity of the biosynthetic intermediates, can be formed [7].

Moreover, the PKS enzyme can be hybridized with non-ribosomal peptide synthetase (NRPS) domains (see also “NRPS metabolites and peptides” in the “Alkaloids” section), leading to the acylation of an amino acid by the (C₂)n acyl intermediate. As previously, the functionalization of the acyl chain depends on the PKS enzyme, and the PKS/NRPS products are also extremely diversified (e.g., hirsutellone B; Fig. 1.2) [8].

1.1.5.2 Terpenes Terpenes are derived from the oligomerization of the C₅ isoprene units DMAPP and IPP. Both precursors are prompt to generate either an allylic cation (the diphosphate is a good leaving group) or a tertiary carbocation, respectively, which makes the IPP easy to react with DMAPP (Scheme 1.4). This reaction happens in the active site of a terpene synthase, which activates the departure of the diphosphate group from DmAPP, thanks to Lewis acid activation (a metal like Mg²⁺, Mn²⁺, or Co²⁺ is present in the enzyme active site [9]). This leads to geranyl (C₁₀, monoterpene precursor) or farnesyl (C₁₅, sesquiterpene precursor) diphosphate, depending on the location of the enzyme (chloroplast for the MEP pathway or cytosol for the MVA pathway). Geranylgeranyl (C₂₀, diterpene) and...
farnesylfarnesyl (C_{30}, triterpene precursor) diphosphates can also be obtained by further additions of IPP, leading to longer linear intermediates.

The cyclization of linear precursors is achieved by specialized cyclases, which generate a poorly functionalized natural product framework [10, 11]. Auxiliary enzymes such as oxygenases then increase the complexity and the diversity of compounds by further functionalization (Scheme 1.3b) [12]. A high degree of oxidation can be observed in compounds like thapsigargin, paclitaxel, or bilobalide (Fig. 1.3). The biosynthesis of this last compound, for example, involves a high oxygenation pattern, two Wagner–Meerwein rearrangements, and several oxidative cleavages leading to the loss of five carbons. The resulting natural products can
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Thus be extremely modified, with structures whose biogenetic origin is far from being obvious at first sight and cannot be determined without further experiments such as isotopic labeling.

1.1.5.3 Flavonoids, Resveratrols, Gallic Acids, and Further Polyphenolics

We have previously discussed the polyketide origin of some phenolic compounds based on the \( \text{(C}_2\text{)}_n \) motif. Other polyphenols like gallic acids are directly derived by the aromatization of shikimic acid (\( \text{C}_6\text{C}_1 \) building block; Scheme 1.2) [13]. The \( \text{C}_6\text{C}_3 \) building blocks are available from the conversion of phenylalanine and tyrosine into cinnamic and \( \text{p} \)-coumaric acids, respectively, and then by further hydroxylation steps (Scheme 1.5). These can dimerize into lignans (e.g., podophyllotoxin) [14, 15] through radical processes or converted to low molecular weight compounds like eugenol, coumarins, or vanillin [16]. The coenzyme A thioesters of these \( \text{C}_6\text{C}_3 \) acids can be used as initiator units by specialized ketosynthases for an elongation by two acetyl units, leading to aromatic polyketides like styrylpyrones or diarylheptanoids (e.g., curcumin) [17]. Important compounds from this metabolism are flavonoids (\( \text{C}_6\text{C}_3\text{C}_6 \)) [18] and stilbenes (\( \text{C}_6\text{C}_2\text{C}_6 \)) (a decarboxylation occurs during the aryl cyclization) [19], which are synthesized by chalcone synthase and stilbene synthase, respectively. Flavonoids (e.g., catechin) and stilbenes (e.g., resveratrol) are present in large amounts in fruits and vegetables and may exert their radical scavenging properties in vivo.

1.1.5.4 Alkaloids

Alkaloids are nitrogen-containing compounds. The nitrogen(s) can be involved in an amine function, conferring basicity to the natural product (like “alkali”), or in less or nonbasic functions such as an amide, a nitrile, an isonitrile, or an ammonium salt (quaternary amines). For amines, protonation often occurs at physiological pH and may condition their biological activity. In many cases, the nitrogen is biogenetically derived from an amino acid. We will thus discuss alkaloids according to their amino acid origin.

Alkaloids Derived from the Krebs Cycle (Lysine and Ornithine Derived) As shown previously (Scheme 1.2), the Krebs cycle is a crucial metabolic process, which leads to \( \alpha \)-ketoacids (oxaloacetic and \( \text{2-oxoglutaric} \) acids). Their enzymatic transamination affords the two amino acids—aspartic acid and glutamic acid—which are the direct biosynthetic precursors of amino acids lysine and ornithine, respectively. These in turn produce cadaverine, a “\( \text{C}_5\text{N} \)” unit, and putrescine, a “\( \text{C}_4\text{N} \)” unit, which are major components for the biosynthesis of important alkaloids, as will be discussed later (Scheme 1.6). Additionally, ornithine is a precursor of arginine, another important amino acid.

Ornithine-derived alkaloids (incorporating the \( \text{C}_4\text{N} \) unit) Putrescine is derived from the decarboxylation of ornithine and is a precursor of linear polyamines like spermine. After enzymatic methylation of one amine of putrescine...
in the presence of S-adenosylmethionine, transamination of the other affords $\gamma$-(N-methylamino)aldehyde [20]. The resulting cyclic iminium is a key intermediate in the formation of many medicinally important alkaloids such as the plant-derived compounds cocaine, atropine, or the calystegines [21, 22]. Indeed, this iminium is a Mannich acceptor, which can react with various nucleophiles, the first of those being the carbanion of acetyl-CoA. Thus, after a stepwise
elongation by two AcCoA units, either decarboxylation can occur, leading to the acetonylpiprylolidine hygrine, or a second Mannich reaction by the intramolecular attack of the acetooacetate anion onto an oxidation-derived pyrrolinium, leading to the tropane skeleton (tropinone). The acetoacetyl-CoA intermediate can also react intermolecularly with another pyrrolinium cation, leading to cuscohygrine after decarboxylation. Finally, the pyrrolizidine alkaloids [23] are derived from homospermidine, which, when submitted to terminal oxidative deamination, leads to the bicyclic skeleton of retronecine and further Senecio alkaloids. We can mention herein that ornithine is a biosynthetic precursor of arginine, bearing a guanidine function, which is an intermediate toward the toxic compounds tetrodotoxin and saxitoxin (not shown).

**Lysine-Derived Alkaloids (Incorporating the C₅N Unit)** From lysine to piperidine alkaloids, the biosynthetic steps parallel the one previously described from ornithine. Indeed, the oxidative deamination of cadaverine affords a δ-amino aldehyde, which cyclizes through imine formation into piperidine. Protonation results in a Mannich acceptor, which is able to react with various nucleophiles such as β-ketothioester anions. The first product of these reactions is pelletierine, which can further react through an intramolecular Mannich reaction leading to pseudopelletierine. Quinolizidines [24] can also be formed, first from the Mannich reaction of the piperideine acceptor with the corresponding enamine nucleophile and then after additional transformation steps, leading, for example, to lupinine, sparteine, or cytisine.

Indolizidine alkaloids [15] such as castanospermine and swainsonine are formed from pipecolic acid, an amino acid derived from lysine, which can be elongated by malonyl-CoA followed by ring closure. When protonated, these alkaloids are oxonium mimics strongly inhibiting glycosidases.

**Tyrosine- and Phenylalanine-Derived Alkaloids** Tyrosine and phenylalanine amino acids are bearing the phenylethylamine moiety of many medicinally relevant alkaloids. Further hydroxylations on the aromatic carbocycle or on the aliphatic part can be observed. Methylation can occur on phenolic oxygens and on the amine, leading to catecholamines (adrenaline, noradrenaline, dopamine). Arylethylamines are also usual to react with endogenous aldehydes through Pictet–Spengler reactions [25], leading to important biosynthetic intermediates (Scheme 1.7) like:

- Reticuline from the reaction with 4-hydroxyphenylacetalddehyde toward benzyltetrahydroisoquinoline alkaloids;

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**SCHEME 1.7** Tyrosine-derived alkaloid biosynthetic pathways (double head arrows figure bond cleavages during biosynthetic processes).
morphine, berberine, tubocurarine, isoboldine, or the highly modified aristolochic acid [26, 27]

- Automnaline from the reaction with 3-(4-hydroxyphenyl)propanal toward phenylethyltetrahydroisoquinoline alkaloids: colchicine, cephalotaxine, or shelhammericine [28, 29]

- Ipecoside from the reaction of dopamine with secologanan toward terpene tetrahydroisoquinoline alkaloids: ipecoside or emetine

Lastly, norbelladine (top of Scheme 1.7) is issued from the reductive amination of 3,4-dihydroxybenzaldehyde (derived from phenylalanine) with tyramine (derived from tyrosine) and constitutes a biosynthetic node leading to Amaryllidaceae alkaloids such as galantamine, crinine, or lycorine depending on the topology of phenolic couplings. In all these biosynthetic routes, radical phenolic couplings are key reactions for C–C and C–O bond formations and rearrangements [30, 31].

**Tryptophan-Derived Indole and Indole Monoterpene Alkaloids**

As for alkaloids derived from tyrosine and phenylalanine, those derived from tryptophan are formed after decarboxylation of the amino acid (into tryptamine) and possible hydroxylation of the aromatic carbocycle (e.g., serotonin) and N-methylation (e.g., psilocin). As previously, tryptamine can also react through Pictet–Spengler reactions to form tetrahydro-β-carbolines, which can be aromatized, for example, into harmine (Scheme 1.8) [16].

When the aldehyde partner of the Pictet–Spengler reaction with tryptamine is the terpene secologanan, strictosidine is formed as an entry toward the vast monoterpene indole alkaloids [32, 33]. Hydrolysis of the glucosidic part releases the strictosidine aglycone bearing an aldehyde, while iminium formation and further cyclization and reduction can lead to ajmalicine (from oxocyclization) or yohimbine (from carbocyclization). These alkaloids are referred to as from the Corynanthe type, with the monoterpene carbon skeleton unmodified. Although it misses one carbon and has a very

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**SCHEME 1.8** Tryptophan-derived alkaloid biosynthetic pathways (gray parts: monoterpenic units).
different structure, strychnine is related to the Corynanthe alkaloids, incorporating two carbons from acetyl-CoA. Highly modified monoterpene skeletons are derived from the Corynanthe core through C–C bond breaking and reorganization, leading to Iboga-type (e.g., catharanthine) and Aspidosperma-type (e.g., vindoline) alkaloids. The anticancer drug vinblastine is a heterodimer resulting from the nucleophilic attack of vindoline on a Mannich acceptor resulting from catharanthine, found in Madagascar periwinkle (Catharanthus roseus). The heteroaromatic compounds ellipticine, camptothecin, and quinine are also derived from a Corynanthe-type precursor, although in this case the biosynthetic relationship may not be obvious due to deep modifications of the skeleton.

Finally, two important classes of compounds have to be mentioned since they have inspired many synthetic chemists. The pyrroloindole alkaloids result from the cyclization of tryptamine, as found in physostigmine (formed by a cationic mechanism after methylation in position 3 of the indole; not shown) or in chimonanthine (presumably formed by a radical coupling mechanism; Scheme 1.8). The ergot alkaloids are derived from the 3,3-dimethylallylation on position 4 of the indole in tryptophan whose further cyclization and oxidation processes afford the natural products (e.g., lysergic acid, Scheme 1.8, and ergotamine), which have had important medical applications [34].

**NRPS Metabolites and Peptides**

NRPS enzymes assemble amino acids, including nonproteinogenic ones, into oligopeptides. The enzymes contain several modules, and especially an adenylation domain (A), which specifically selects and activates the amino acid to be transferred as a thioester on the nearby peptidyl carrier protein (PCP) [2]. A condensation module (C) then catalyzes the formation of the peptide bonds between the newly introduced amino acyl-PCP (bearing a free amine) and the elongated peptidyl-PCP thioester. At the end of the elongation, a cyclization can occur into cyclopeptides, but the peptide can also be transferred to auxiliary enzymes like methyltransferases, glycosyltransferases, or oxidases (vancomycins are typical products of such functionalizations) [35, 36]. The formation of heterocycles is also frequently encountered in this metabolism, as in penicillins that are derived from the tripeptide α-aminoadipoyl-cysteinyln-valine or telomestatin (Fig. 1.4) [2].

**Other Alkaloid Origins**

There are many other nitrogen sources involved in alkaloid biosyntheses, for example, nicotinic acid (originated from aspartic acid and intermediate in nicotine and anabasine biosyntheses) and anthranilic acid (originated from tryptophan and intermediate toward acridines or aurachins). The amination reaction (e.g., through transamination of carbonyl compounds) is also a way to introduce nitrogens in natural products, for example, from fatty acids, steroids (toward Solanum alkaloids or cyclopamines), or other terpenoids (aconitine and atisine have diterpene skeletons, while Daphniphyllum alkaloids are triterpene derivatives). Finally, nucleic acids can also be precursors of alkaloids like the well-known caffeine.

**1.2 FROM BIOSYNTHESIS TO TOTAL SYNTHESIS: STRATEGIES TOWARD THE NATURAL PRODUCT CHEMICAL SPACE**

**1.2.1 The Chemical Space of Natural Products**

Natural products occupy an important place in human communities as demonstrated by their vast use from ancient times to nowadays, like dyes, fibers, oils, perfumes, agrochemicals, or drugs. Broadly, both primary and secondary metabolites could be classified as natural products, while the latter, as discussed previously, are usually regarded as the “natural products” owing to their complexity and diversity arising from a variety of biosynthetic pathways. The structural chemical diversity found among

![FIGURE 1.4 Structural diversity of nonribosomal peptide compounds (AAA, α-aminoadipic acid).](image-url)
all living organisms, defining the chemical space of natural products [37], is the consequence of their evolution, occurring as an adaptation of organisms to their environment. It is commonly believed that secondary metabolites are produced as messengers by living organisms or as weapons against enemies, and thus they should have certain biological activities in a medicinal point of view [38]. Indeed, natural products are regarded as one of the main sources of medicines (Fig. 1.5). From the traditional medicinal extracts to every single bioactive molecule, the methods of extraction, purification, identification, and biological investigation of natural products have been well established. Their complex structures and interesting properties have attracted synthetic chemists to accomplish their total syntheses and that of medicinally relevant analogs, sometimes in the industrial context [39]. Thus, targeting the chemical space of natural products has never been more relevant than today. Although the discovery of natural products demands time and labor-consuming manipulations, it is worth to notice that the knowledge on this chemical space is still continually growing while biological advances allow for discovering and understanding potential targets. However, increasing the chemical space of human-made compounds based on natural products should benefit from transdisciplinary collaborations such as the use of coupled biosynthetic and chemical synthetic methods to design original “unnatural natural products” [40].

1.2.2 The Biosynthetic Pathways as an Inspiration for Synthetic Challenges

1.2.2.1 Precursor-Directed Biosyntheses and Mutasynthetic Strategies to Increase the Chemical Space of Natural Products

As the genetics and biochemistry of natural product biosynthesis are better understood, novel biosynthetic techniques have been developed to study and generate new diversity in natural product analogs (Scheme 1.9). Precursor-directed biosynthesis (PDB) is considered as the earliest example of combining chemical and biological methods for the generation of complex natural product analogs [41, 42]. This approach, compared with the biosynthetic pathway of wild-type metabolites (Scheme 1.9a), involves the feeding of analogs of the natural biosynthetic building blocks to the living organisms (Scheme 1.9b), usually bacteria or fungi, which incorporate the modified precursors into the biosynthesized compound. Mutasynthesis, also termed as mutational biosynthesis (MBS), involves the inactivation of a key step of the biosynthesis in a mutant microorganism (Scheme 1.9c), which can then be fed by various modified or advanced building blocks (mutasynthons; Scheme 1.9d) [43]. These mutasynthons could not be incorporated by the wild type due to specificities of the enzymatic machinery. Build up on PDB, MBS eliminates the natural biosynthetic intermediate, thus generating a less complex mixture of metabolites and making the purification or yield of target products better.
Both approaches can potentially greatly increase the diversity of natural compounds.

1.2.2.2 The Biomimetic Strategy: A Bridge between Biosynthesis and Total Synthesis During the past century, synthetic chemists were endeavoring to discover more efficient strategies to access complex natural products. The chemical synthesis of tropinone by Robinson in 1917 [44], one of the first biomimetic ones, is a fantastic example of an early efficient synthesis, which consisted in a multicomponent process between succinaldehyde, methylamine, and calcium acetonedicarboxylate [45]. Since then, the construction of natural products by chemical methods inspired by nature’s biosynthetic pathways has attracted many synthetic chemists and participated in the progress of organic chemistry. As discussed in the book *Biomimetic Organic Synthesis* coedited by one of us (B.N.), an increasing number of total syntheses have been termed “biomimetic” or “bioinspired” during the last 20 years, meaning the use of a synthetic tactic that follows or mimics a hypothetical or proven biosynthetic pathway. Concomitantly, the biosynthesis of natural products has been more and more understood, thanks to genetic and enzymatic studies. Therefore, as a bridge between biosynthesis and total synthesis, biomimetic synthesis is able to overcome some drawbacks of conventional strategies, as it often relies on the self-assembling properties of a key reactive intermediate [46].

Tremendous works dealing with bioinspired total syntheses of secondary metabolites have thus been achieved, providing new insights in the reactivity of biomimetic precursors and occasionally leading to controversy or unresolved questions [47]. An interesting example goes to hirsutellones, a family of fungal PKS/NRPS compounds (also regarded as alkaloids due to their nitrogen) with intriguing structures and a significant antitubercular activity [7]. Their biosynthesis has been hypothesized by Oikawa who proposed a key linear precursor of the related compounds GKK1032A₂, made from one tyrosine, nine AcCoA, and several methylations by S-adenosylmethionine [48]. We applied this hypothesis to the less methylated hirsutellone in a biomimetic strategy following pathway (a), forming the first cyclohexane ring before the complete tricyclic core of the natural product. Pathway (b) involves the allylic oxidation at the terminal methyl group of the triene to release an allylic alcohol or cation as an “electrophilic tail.” The polycyclization would then be initiated through reverse electronic activation compared to pathway (a), forming the first cyclohexane ring before the IMDA reaction occurs.

Nicolaou et al. [49] and Uchiro et al. [50] achieved the total syntheses of hirsutellone B in 2009 and 2011, respectively. We recently described a formal total synthesis by forming the key decahydrofluorene (tricyclic) core of hirsutellone B in a biomimetic strategy following pathway (b) [47]. As for the synthesis of this important synthetic
intermediate with eight stereocenters, Uchiro’s nonbiomimetic strategy took 23 steps from \(R\-(–)\)-citronellene with 1% global yield (Scheme 1.11). In comparison, Nicolaou’s synthetic strategy, involving an Et2AlCl-triggered cascade cyclization, decreased the number of reaction steps to six steps starting from \(R\-(+)\)-citronellal and with 16% overall yield. Although this was not claimed as biomimetic by the authors, this work supports the “tail-to-head” biosynthetic pathway (a) (Scheme 1.10) and nicely reveals the efficiency of biosynthetically related cascade reactions. We reported an alternative biomimetic synthesis of the tricyclic core of hirsutellones by a reverse “head-to-tail” cyclization strategy using nine steps and with 8% brsm global yield (Scheme 1.11) [47]. Interestingly, our strategy supports the biosynthetic pathway (b), thus confirming that both biosynthetic routes are possible. However, thanks to recent biosynthetic experiments using the isotopically labeled precursor (\(^{18}\text{O-phenol})\-L-tyrosine, we demonstrated that the phenolic oxygen is incorporated in analogous natural products, pyrrocidines, thus giving clues to biosynthetic pathway (b) [51].
1.2.3 The Science of Total Synthesis

1.2.3.1 The Evolution of Total Synthesis and Its Significance Today The vast utility of total synthesis and its connections with other research fields can be illustrated by a selection of key words, some of them deeply resonating with current major societal challenges: medicinal chemistry and new drugs, pharmacology, agrochemicals, biosynthetic studies, synthetic methodologies, structure determination, physical organic chemistry, catalysis, green resources, or bioinspiration. Back to the nineteenth century, the first organic synthesis of urea from ammonium cyanate, an inorganic substance, was accomplished by Wöhler in 1828 and raised the curtain of total synthesis. Total synthesis had then, for a time, played an essential role on elucidating the structure of natural products, and it is still the case nowadays when the determination of relative and absolute configurations cannot be achieved by analytic methods. With the improvement of analytical chemistry, and as chemistry and biology are better understood, the role of total synthesis slowly changed. A variety of new reactions, catalysts, and technologies have been developed for total synthesis. Most importantly, total synthesis is playing a key role for new drug discovery, chemical biology, or even material science. As introduced in the former part, a lot of natural products and derivatives were developed to provide new drugs against human diseases (Fig. 1.5), of which total synthesis enabled a larger amount of products available for further studies [52] and challenged optimized strategies for their industrial production [35]. As striking examples, we can cite Paterson’s synthesis of discodermolide at the 60 g scale for anticancer clinical studies by Novartis [53], or the recent industrial production of the antimalarial drug artemisinin by Sanofi, using a semisynthetic strategy starting from a biotechnologically available advanced intermediate [54, 55].

1.2.3.2 Strychnine as a Case Study: A Classic among the Classics Herein, we would like to illustrate the evolution of total synthesis by one of the most famous natural products, strychnine (Scheme 1.12). For decades, strychnine was regarded as one of the most challenging natural products to be synthesized [56]. The correct structure of strychnine was determined by Woodward and Brehm in 1948, one century after its discovery [57]. Since then, this remarkable natural product witnessed the evolution of total synthesis.
The landmark synthesis of strychnine was reported by Woodward and coworkers in 1954, 6 years after its structure determination [58].

Since then, many synthetic chemists have been confronted with strychnine, which is a classic among the classics of total synthesis. Overall, 18 total syntheses of strychnine have been reported so far [58a–r], the shortest one in only 7 linear steps from tryptamine by Vanderwal [58r], to be compared with the earliest total synthesis of Woodward in 29 linear steps from phenylhydrazine [53a]. The efficiency of these works can be evaluated by looking at the overall yields, from 0.00014% [58a] to nearly 10% yield [58e]. For sure, these improvements not only took benefits from Corey’s retrosynthetic “Logic of Chemical Synthesis” but also from those famous chemists’s creativity and from new achievements in synthetic and catalytic methodologies. Indeed, new methodological concepts have arisen by the last 20 years, such as those of ideal synthesis [59], atom economy, step economy, redox economy, and sustainable approaches [60].

The efficiency of total synthesis should then benefit to the growing research efforts in chemical biology and drug discovery in the future, in connection with recently designed strategies like diversity-oriented synthesis (DOS) and function-oriented synthesis (FOS).

1.2.3.3 DOS and FOS: Two Strategies to Optimize Biological Hits and Synthetic Efficacy  Classical combinatorial chemistry has allowed for the synthesis of vast amounts of products, yet poorly overlapping the chemical space of natural products, essentially due to their limited structural diversity and drug-likeness. Chemists are thus searching for ever more efficient ways to generate rapidly more complex and diverse functional compounds. As discussed before, precursor-directed biosynthesis and mutasynthesis have been developed by biochemists and exemplify a biological mean to diversify structures in a natural product series. In addition, organic chemists have designed new strategies for this purpose, such as DOS and FOS.

DOS and Divergent Total Synthesis  DOS, often compared with the classical target-oriented synthesis (TOS), is using forward synthetic analysis with the aim of transforming various building blocks, through planned reactions, to efficiently generate complex and diverse compounds matching with a large portion of the chemical space. To some extent, this is the opposite way as the well-established retrosynthetic analysis of TOS. The strategy of DOS mainly relies on the variation of three parameters [61]: (1) the building blocks, to introduce a vast number of functional groups in the skeleton; (2) the stereochemistry, which can be introduced by various stereoselective reagents; and (3) the molecular skeleton, which could achieve the highest level of structural complexity and diversity by using different synthetic methods, such as multicomponent reactions, combinational synthesis, folding pathway, and branched pathway [62]. In any case, DOS greatly increases the chemical space to enable more biological and pharmaceutical investigation.

Using an analogous strategy, diverse natural products were synthesized through collective natural product synthesis or divergent total synthesis. This powerful concept was applied by MacMillan and coworkers to the asymmetric synthesis of six monoterpene indole alkaloids using organocascade catalysis (strychnine, aspidospermidine, vincadifformine, akuammicine, kopsanone, and kopsinine) [63]. Dai and coworkers exploited the combination of a biosynthetically inspired strategy with such a divergent approach for the synthesis of seven monoterpene indole alkaloids (mersicarepine, leuconodines B and D, leuconoxine, melodidine E, leuconolam, and rhasinilam) [64]. In the taiwaniaquinoid series, four natural products were synthesized by Li and coworkers after two to three steps from a common intermediate prepared on the gram scale [65]. Such collective strategies are more and more encountered in the literature, taking advantage of a common synthetic route leading to key intermediates to access entire families of compounds rather than a sole natural product target.

**FOS**  The common problem encountered with total synthesis is the high complexity of natural products, which often takes many steps to be achieved and lowers overall yields. One way to solve this problem is, as discussed before, to think and design efficient synthetic strategies, for example, using redox or step economy, to shorten the route. Another approach is to design less complex synthetic targets by maintaining or improving selected functions involved in the biological activity, which is the so-called FOS. FOS is based on the study of complex targeted molecules with the aim of shortening the synthetic work to develop diverse simplified but still functional targets, keeping key structural features to effect biological functions [66]. FOS is thus deeply related to drug discovery. Many simplified small compounds can indeed be proposed from structure–activity relationship studies. For example, the famous antimalarial artemisinin gave simplified but functional analogs with potent in vitro antimalarial activities in the same range of IC₅₀ as that of the natural product (Scheme 1.13) [67]. Other than DOS, which focuses on structure complexity and diversity, FOS concentrates more
on the functional groups involved in the biological functions, while both of them are somehow inspired by total synthesis.

1.2.4 Conclusion: A Journey in the Future of Total Synthesis

The future of total synthesis is written in our laboratory notebooks. It will not only be conditioned by new synthetic achievements and new methodologies and technologies improving the efficacy of experiments but also by their applications to answer questions from new horizons. All of us will agree, as it was said by others, that total synthesis is marked by beauty and it has sometimes been compared with art. Not so many fields can respond to such criteria, and it is due to the free creativity we are able to exert. In theory, total synthesis could provide any compound, from the simplest to the most complex ones. But can we provide enough material for deepened studies in other research fields [52]? Indeed, our products, once achieved, are not to be stored indefinitely in tiny flasks. They should lead to new projects, new questions, and new answers.

Thus, how studying in depth the biological, the chemical, and the physical properties of a natural product when its natural source is rare, low producing, and sometimes no more available? This question is in the hand of two scientific communities: the biotechnological and the synthetic chemist ones. Let’s bet that we will still answer many of such questions by continuing to improve qualitatively and quantitatively our productivity by making our syntheses simpler and faster (and thus, as we may say, more “elegant”) and by being the driving forces in building strong interdisciplinary bridges.

Further Reading on Total Synthesis and Biosynthesis

- P. M. Dewick, Medicinal natural products, a biosynthetic approach, Wiley: Chichester (2009)
- The reader interested in biosynthetic pathways can also refer to the interactive KEGG atlas (biosynthetic pathways) available on Internet: http://www.kegg.jp/kegg/atlas/

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