The Art and Science of Total Synthesis

Grignard   Wittig   Diels-Alder   Brown

The Art and Science of Total Synthesis at the Dawn of the Twenty-First Century**

K. C. Nicolaou,* Dionisios Vourloumis, Nicolas Winssinger, and Phil S. Baran

Dedicated to Professor E. J. Corey for his outstanding contributions to organic synthesis

At the dawn of the twenty-first century, the state of the art and science of total synthesis is as healthy and vigorous as ever. The birth of this exhilarating, multifaceted, and boundless science is marked by Wöhler's synthesis of urea in 1828. This milestone event—as trivial as it may seem by today's standards—contributed to a "demystification of nature" and illuminated the entrance to a path which subsequently led to great heights and countless rich dividends for humankind. Being both a precise science and a fine art, this discipline has been driven by the constant flow of beautiful molecular architectures from nature and serves as the engine that drives the more general field of organic synthesis forward. Organic synthesis is considered, to a large extent, to be responsible for some of the most exciting and important discoveries of the twentieth century in chemistry, biology, and medicine, and continues to fuel the drug discovery and development process with myriad processes and compounds for new biomedical breakthroughs and applications. In this review, we will chronicle the past, evaluate the present, and project to the future of the art and science of total synthesis. The gradual sharpening of this tool is demonstrated by considering its history along the lines of pre-World War II, the Woodward and Corey eras, and the 1990s, and by accounting major accomplishments along the way. Today, natural product total synthesis is associated with prudent and tasteful selection of challenging and preferably biologically important target molecules; the discovery and invention of new synthetic strategies and technologies; and explorations in chemical biology through molecular design and mechanistic studies. Future strides in the field are likely to be aided by advances in the isolation and characterization of novel molecular targets from nature, the availability of new reagents and synthetic methods, and information and automation technologies. Such advances are destined to bring the power of organic synthesis closer to, or even beyond, the boundaries defined by nature, which, at present, and despite our many advantages, still look so far away.

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1. Prologue

"Your Majesty, Your Royal Highnesses, Ladies and Gentlemen.

In our days, the chemistry of natural products attracts a very lively interest. New substances, more or less complicated, more or less useful, are constantly discovered and investigated. For the determination of the structure, the architecture of the molecule, we have today very powerful tools, often borrowed from Physical Chemistry. The organic chemists of the year 1900 would have been greatly amazed if they had heard of the methods now at hand. However, one cannot say that the work is easier; the steadily improving methods make it possible to attack more and more difficult problems and the ability of Nature to build up complicated substances has, as it seems, no limits.

In the course of the investigation of a complicated substance, the investigator is sooner or later confronted by the problem of synthesis, of the preparation of the substance by chemical methods. He can have various motives. Perhaps he wants to check the correctness of the structure he has found. Perhaps he wants to improve our knowledge of the reactions and the chemical properties of the molecule. If the

[*] K. C. Nicolaou, D. Vourloumis, N. Winssinger, P. S. Baran
Department of Chemistry
and The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
and
Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, CA 92093 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu

substance is of practical importance, he may hope that the synthetic compound will be less expensive or more easily accessible than the natural product. It can also be desirable to modify some details in the molecular structure. An antibiotic substance of medical importance is often first isolated from a microorganism, perhaps a mould or a germ. There ought to exist a number of related compounds with similar effects; they may be more or less potent, some may perhaps have undesirable secondary effects. It is by no means, or even probable, that the compound produced by the microorganism—most likely as a weapon in the struggle for existence—is the very best from the medicinal point of view. If it is possible to synthesize the compound, it will also be possible to modify the details of the structure and to find the most effective remedies.

The synthesis of a complicated molecule is, however, a very difficult task; every group, every atom must be placed in its proper position and this should be taken in its most literal sense. It is sometimes said that organic synthesis is at the same time an exact science and a fine art. Here nature is the uncontested master, but I dare say that the prize-winner of this year, Professor Woodward, is a good second."[1]

With these elegant words Professor A. Fredga, a member of the Nobel Prize Committee for Chemistry of the Royal Swedish Academy of Sciences, proceeded to introduce R. B. Woodward at the Nobel ceremonies in 1965, the year in which Woodward received the prize for the art of organic synthesis. Twenty-five years later Professor S. Gronowitz, then a member of the Nobel Prize Committee for Chemistry, concluded

K. C. Nicolaou   D. Vourloumis   N. Winssinger   P. S. Baran

K.C. Nicolaou, born in Cyprus and educated in England and the US, is currently Chairman of the Department of Chemistry at The Scripps Research Institute, La Jolla, California, where he holds the Darlene Shiley Chair in Chemistry and the Aline W. and L. S. Skaggs Professorship in Chemical Biology as well as Professor of Chemistry at the University of California, San Diego. His impact on chemistry, biology, and medicine flows from his works in organic synthesis described in nearly 500 publications and 70 patents as well as his dedication to chemical education, as evidenced by his training of over 250 graduate students and postdoctoral fellows. His recent book titled "Classics in Total Synthesis",[3] which he co-authored with Erik J. Sorensen, is used around the world as a teaching tool and source of inspiration for students and practitioners of organic synthesis.

Dionisios Vourloumis, born in 1966 in Athens, Greece, received his B.Sc. degree from the University of Athens and his Ph.D. from West Virginia University under the direction of Professor P. A. Magriotis, in 1994, working on the synthesis of novel enediyne antibiotics. He joined Professor K. C. Nicolaou's group in 1996, and was involved in the total synthesis of epothilones A and B, eleutherobin, sarcodictyins A and B, and analogues thereof. He joined Glaxo Wellcome in early 1999 and is currently working with the Combichem Technology Team in Research Triangle Park, North Carolina.

Nicolas Winssinger was born in Belgium in 1970. He received his B.Sc. degree in chemistry from Tufts University after conducting research in the laboratory of Professor M. D'Alarcao. Before joining The Scripps Research Institute as a graduate student in chemistry in 1995, he worked for two years under the direction of Dr. M. P. Pavia at Sphinx Pharmaceuticals in the area of molecular diversity focusing on combinatorial chemistry. At Scripps, he joined the laboratory of Professor K. C. Nicolaou, where he has been working on methodologies for solid-phase chemistry and combinatorial synthesis. His research interests include natural products synthesis, molecular diversity, molecular evolution, and their application to chemical biology.

Phil S. Baran was born in Denville, New Jersey in 1977. He received his B.Sc. degree in chemistry from New York University while conducting research under the guidance of Professors D. I. Schuster and S. R. Wilson, exploring new realms in fullerene science. Upon entering The Scripps Research Institute in 1997 as a graduate student in chemistry, he joined the laboratory of Professor K. C. Nicolaou where he embarked on the total synthesis of the CP molecules. His primary research interest involves natural product synthesis as an enabling endeavor for the discovery of new fundamental processes and concepts in chemistry and their application to chemical biology.

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his introduction of E. J. Corey, the 1990 Nobel prize winner, with the following words:

"…Corey has thus been awarded with the Prize for three intimately connected contributions, which form a whole. Through retrosynthetic analysis and introduction of new synthetic reactions, he has succeeded in preparing biologically important natural products, previously thought impossible to achieve. Corey's contributions have turned the art of synthesis into a science…"[2]

This description and praise for total synthesis resonates today with equal validity and appeal; most likely, it will be valid for some time to come. Indeed, unlike many one-time discoveries or inventions, the endeavor of total synthesis[3–6] is in a constant state of effervescence and flux. It has been on the move and center stage throughout the twentieth century and continues to provide fertile ground for new discoveries and inventions. Its central role and importance within chemistry will undoubtedly ensure its present preeminence into the future. The practice of total synthesis demands the following virtues from, and cultivates the best in, those who practice it: ingenuity, artistic taste, experimental skill, persistence, and character. In turn, the practitioner is often rewarded with discoveries and inventions that impact, in major ways, not only other areas of chemistry, but most significantly material science, biology, and medicine. The harvest of chemical synthesis touches upon our everyday lives in myriad ways: medicines, high-tech materials for computers, communication and transportation equipment, nutritional products, vitamins, cosmetics, plastics, clothing, and tools for biology and physics.[7]

But why is it that total synthesis has such a lasting value as a discipline within chemistry? There must be several reasons for this phenomenon. To be sure, its dual nature as a precise science and a fine art provides excitement and rewards of rare heights. Most significantly, the discipline is continually being challenged by new structural types isolated from nature's seemingly unlimited library of molecular architectures. Happily, the practice of total synthesis is being enriched constantly by new tools such as new reagents and catalysts as well as analytical instrumentation for the rapid purification and characterization of compounds.

Thus, the original goal of total synthesis during the first part of the twentieth century to confirm the structure of a natural product has been replaced slowly but surely with objectives related more to the exploration and discovery of new chemistry along the pathway to the target molecule. More recently, issues of biology have become extremely important components of programs in total synthesis. It is now clear that as we enter the twenty-first century both exploration and discovery of new chemistry and chemical biology will be facilitated by developments in total synthesis.

In this article, and following a short historical perspective of total synthesis in the nineteenth century, we will attempt to review the art and science of total synthesis during the twentieth century. This period can be divided into the pre-World War II Era, the Woodward Era, the Corey Era, and the 1990s. There are clearly overlaps in the last three eras and many more practitioners deserve credit for contributing to the evolution of the science during these periods than are

mentioned. The labeling of these eras is arbitrary—not withstanding the tremendous impact Woodward and Corey had in shaping the discipline of total synthesis during their time. As in any review of this kind, omissions are inevitable and we apologize profusely, and in advance, to those whose brilliant works were omitted as a result of space limitations.

2. Total Synthesis in the Nineteenth Century

The birth of total synthesis occurred in the nineteenth century. The first conscious total synthesis of a natural product was that of urea (Figure 1) in 1828 by Wöhler.[8] Significantly, this event also marks the beginning of organic synthesis and
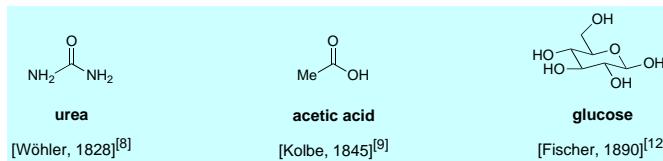

Figure 1. Selected nineteenth century landmark total syntheses of natural products.

the first instance in which an inorganic substance (NH_4CNO:ammonium cyanate) was converted into an organic substance. The synthesis of acetic acid from elemental carbon by Kolbe in 1845[9] is the second major achievement in the history of total synthesis. It is historically significant that, in his 1845 publication, Kolbe used the word "synthesis" for the first time to describe the process of assembling a chemical compound from other substances. The total syntheses of alizarin (1869) by Graebe and Liebermann[10] and indigo (1878) by Baeyer[11] spurred the legendary German dye industry and represent landmark accomplishments in the field. But perhaps, after urea, the most spectacular total synthesis of the nineteenth century was that of (+)-glucose (Figure 1) by E. Fischer.[12] This total synthesis is remarkable not only for the complexity of the target, which included, for the first time, stereochemical elements, but also for the considerable stereochemical control that accompanied it. With its oxygen-containing monocyclic structure (pyranose) and five stereogenic centers (four controllable), glucose represented the state-of-the-art in terms of target molecules at the end of the nineteenth century. E. Fischer became the second winner of the Nobel Prize for chemistry (1902), after J. H. van't Hoff (1901).[13]

3. Total Synthesis in the Twentieth Century

The twentieth century has been an age of enormous scientific advancement and technological progress. To be sure, we now stand at the highest point of human accomplishment in science and technology, and the twenty-first century promises to be even more revealing and rewarding. Advances

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in medicine, computer science, communication, and transportation have dramatically changed the way we live and the way we interact with the world around us. An enormous amount of wealth has been created and opportunities for new enterprises abound. It is clear that at the heart of this technological revolution has been science, and one cannot deny that basic research has provided the foundation for this to occur.

Chemistry has played a central and decisive role in shaping the twentieth century. Oil, for example, has reached its potential only after chemistry allowed its analysis, fractionation, and transformation into myriad of useful products such as kerosene and other fuels. Synthetic organic chemistry is perhaps the most expressive branch of the science of chemistry in view of its creative power and unlimited scope. To appreciate its impact on modern humanity one only has to look around and recognize that this science is a pillar behind pharmaceuticals, high-tech materials, polymers, fertilizers, pesticides, cosmetics, and clothing.[7] The engine that drives forward and sharpens our ability to create such molecules through chemical synthesis (from which we can pick and choose the most appropriate for each application) is total synthesis. In its quest to construct the most complex and challenging of nature's products, this endeavor—perhaps more that any other—becomes the prime driving force for the advancement of the art and science of organic synthesis. Thus, its value as a research discipline extends beyond providing a test for the state-of-the-art. It offers the opportunity to discover and invent new science in chemistry and related disciplines, as well as to train, in a most rigorous way, young practitioners whose expertise may feed many peripheral areas of science and technology.[6]

3.1. The Pre-World War II Era

The syntheses of the nineteenth century were relatively simple and, with a few exceptions, were directed towards benzenoid compounds. The starting materials for these target molecules were other benzenoid compounds, chosen for their resemblance to the targeted substance and the ease by which the synthetic chemist could connect them by simple functionalization chemistry. The twentieth century was destined to bring dramatic advances in the field of total synthesis. The pre-World War II Era began with impressive strides and with increasing molecular complexity and sophistication in strategy design. Some of the most notable examples of total synthesis of this era are α-terpineol (Perkin, 1904),[14] camphor (Komppa, 1903; Perkin, 1904),[15] tropinone (Robinson, 1917; Willstätter, 1901),[16–17] haemin (H. Fischer, 1929),[18] pyridoxine hydrochloride (Folkers, 1939),[19–20] and equilenin (Bachmann, 1939)[21] (Figure 2). Particularly impressive were Robinson's one-step synthesis of tropinone (1917)[16] from succindialdehyde, methylamine, and acetone dicarboxylic acid and H. Fischer's synthesis of haemin[18] (1929). These total syntheses are among those which will be highlighted below. Both men went on to win a Nobel Prize for Chemistry (Fischer, 1929; Robinson, 1947).[13]
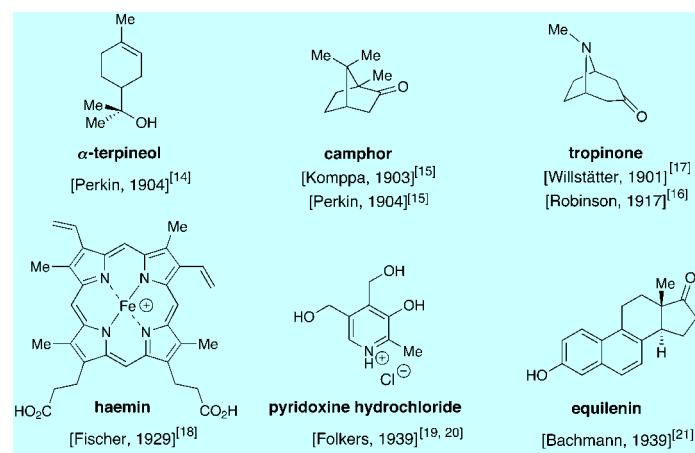

Figure 2. Selected landmark total syntheses of natural products from 1901 to 1939.

3.2. The Woodward Era

In 1937 and at the age of 20 R. B. Woodward became an assistant professor in the Department of Chemistry at Harvard University where he remained for the rest of his life. Since that time, total synthesis and organic chemistry would never be the same. A quantum leap forward was about to be taken, and total synthesis would be elevated to a powerful science and a fine art. Woodward's climactic contributions to total synthesis included the conquest of some of the most fearsome molecular architectures of the time. One after another, diverse structures of unprecedented complexity succumbed to synthesis in the face of his ingenuity and resourcefulness. The following structures (some are shown in Figure 3) are amongst his most spectacular synthetic achievements: quinine (1944),[22] patulin (1950),[23] cholesterol and cortisone (1951),[24] lanosterol (1954),[25] lysergic acid (1954),[26] strychnine (1954),[27] reserpine (1958),[28] chlorophyll a (1960),[29] colchicine (1965),[28b] cephalosporin C (1966),[30] prostaglandin $F_{2\alpha}$ (1973),[31] vitamin B_{12} (with A. Eschenmoser) (1973),[32] and erythromycin A (1981).[33] Some of these accomplishments will be briefly presented in Section 3.5.

Woodward brought his towering intellect to bear on these daunting problems of the 1940s, 1950s, and 1960s with distinctive style and unprecedented glamour. His spectacular successes were often accompanied by appropriate media coverage and his lectures and seminars remained legendary for their intellectual content, precise delivery, and mesmerizing style, not to mention their colorful nature and length! What distinguished him from his predecessors was not just his powerful intellect, but the mechanistic rationale and stereochemical control he brought to the field. If Robinson introduced the curved arrow to organic chemistry (on paper), Woodward elevated it to the sharp tool that it became for teaching and mechanistic understanding, and used it to explain his science and predict the outcome of chemical reactions. He was not only a General but, most importantly, a generalist and could generalize observations into useful theories. He was master not only of the art of total synthesis, but also of structure determination, an endeavor he cherished
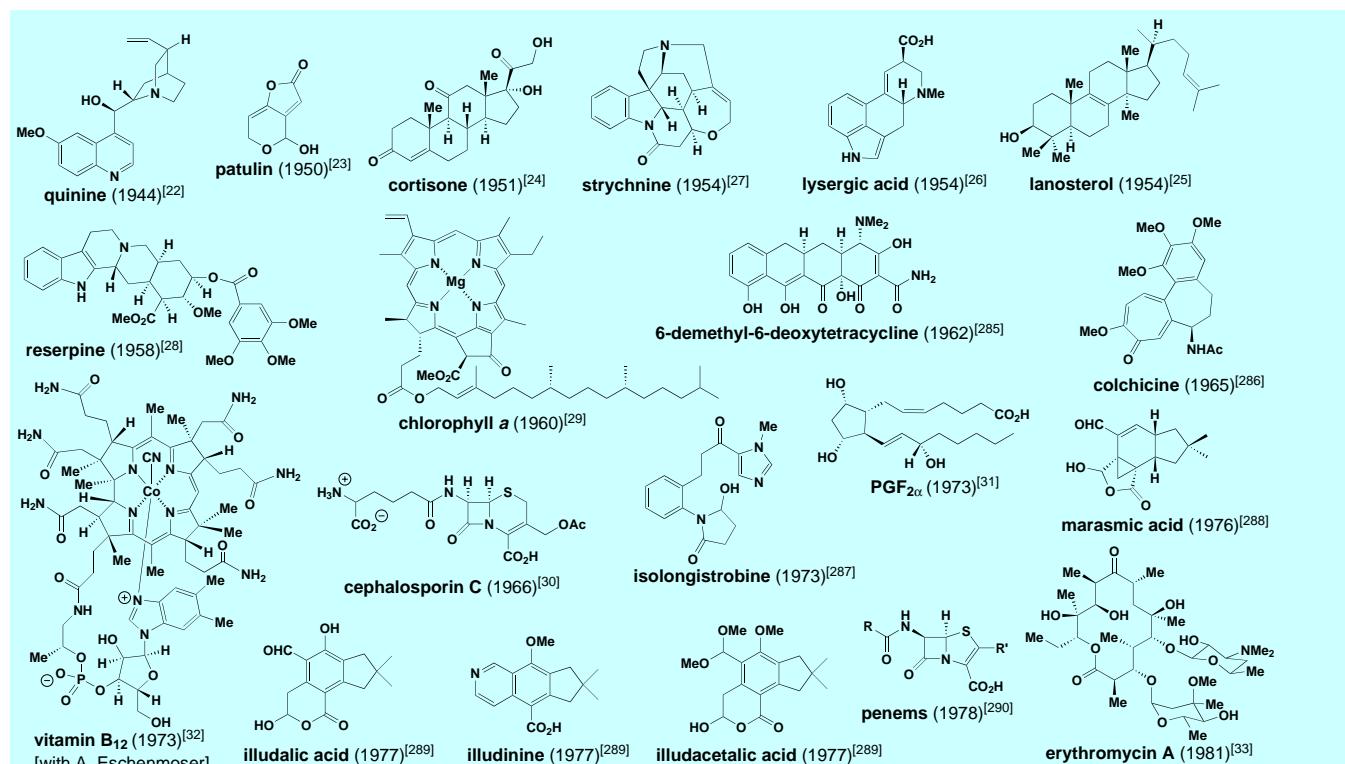
Figure 3. Selected syntheses by the Woodward Group (1944–1981).

throughout his career. He clearly influenced the careers of not only his students, but also of his peers and colleagues, for example, J. Wilkinson (sandwich structure of ferrocene), K. Block (steroid biosynthesis), R. Hoffmann (Woodward and Hoffmann rules), all of whom won the Nobel Prize for chemistry.[13]

His brilliant use of rings to install and control stereochemical centers and to unravel functionality by rupturing them is an unmistakable feature of his syntheses. This theme appears in his first total synthesis, that of quinine,[22] and appears over and over again as in the total synthesis of reserpine,[28] vitamin B$_{12}$,[3, 32] and, remarkably, in his last synthesis, that of erythromycin.[33] Woodward's mark was that of an artist, treating each target individually with total mastery as he moved from one structural type to another. He exercised an amazing intuition in devising strategies toward his targets, magically connecting them to suitable starting materials through elegant, almost balletlike, maneuvers.

However, the avalanche of new natural products appearing on the scene as a consequence of the advent and development of new analytical techniques demanded a new and more systematic approach to strategy design. A new school of thought was appearing on the horizon which promised to take the field of total synthesis, and that of organic synthesis in general, to its next level of sophistication.

3.3. The Corey Era

In 1959 and at the age of 31 E. J. Corey arrived at Harvard as a full professor of chemistry from the University of Illinois,

Urbana-Champaign. His dynamism and brilliance were to make him the natural recipient of the total synthesis baton from R. B. Woodward, even though the two men overlapped for two decades at Harvard. Corey's pursuit of total synthesis was marked by two distinctive elements, retrosynthetic analysis and the development of new synthetic methods as an integral part of the endeavor, even though Woodward (consciously or unconsciously) must have been engaged in such practices. It was Corey's 1961 synthesis of longifolene[34] that marked the official introduction of the principles of retrosynthetic analysis.[4] He practiced and spread this concept throughout the world of total synthesis, which became a much more rational and systematic endeavor. Students could now be taught the "logic" of chemical synthesis[4] by learning how to analyze complex target molecules and devise possible synthetic strategies for their construction. New synthetic methods are often incorporated into the synthetic schemes towards the target and the exercise of the total synthesis becomes an opportunity for the invention and discovery of new chemistry. Combining his systematic and brilliant approaches to total synthesis with the new tools of organic synthesis and analytical chemistry, Corey synthesized hundreds of natural and designed products within the thirty year period stretching between 1960 and 1990 (Figure 4)—the year of his Nobel Prize.

Corey brought a highly organized and systematic approach to the field of total synthesis by identifying unsolved and important structural types and pursuing them until they fell. The benefits and spin-offs from his endeavors were even more impressive: the theory of retrosynthetic analysis, new synthetic methods, asymmetric synthesis, mechanistic proposals, and important contributions to biology and medicine. Some of

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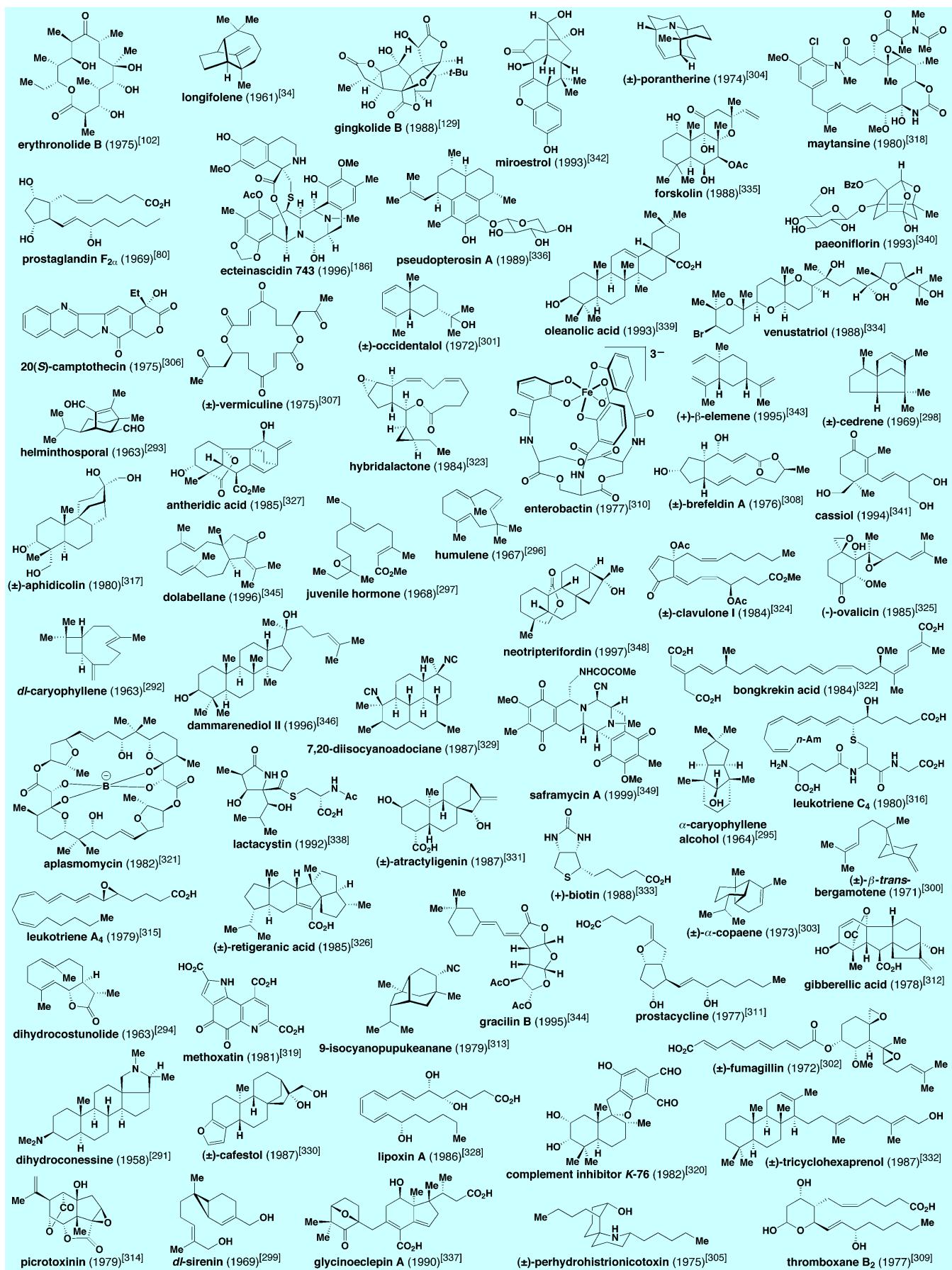
Figure 4. Selected syntheses by the Corey Group (1961–1999).

his most notable accomplishments in the field are highlighted in Section 3.5.

The period of 1950–1990 was an era during which total synthesis underwent explosive growth as evidenced by inspection of the primary chemical literature. In addition to the Woodward and Corey schools, a number of other groups contributed notably to this rich period for total synthesis[3–5] and some continue to do so today. Indeed, throughout the second half of the twentieth century a number of great synthetic chemists made significant contributions to the field, as natural products became opportunities to initiate and focus major research programs and served as ports of entry for adventures and rewarding voyages.

Among these great chemists are G. Stork, A. Eschenmoser, and Sir D. H. R. Barton, whose sweeping contributions began with the Woodward era and spanned over half a century. The Stork–Eschenmoser hypothesis[35] for the stereospecific course of biomimetic–cation cyclizations, such as the conversion of squalene into steroidal structures, stimulated much synthetic work (for example, the total synthesis of progesterone by W. S. Johnson, 1971).[36] Stork's elegant total syntheses (for example, steroids, prostaglandins, tetracyclins)[37–39] decorate beautifully the chemical literature and his useful methodologies (for example, enamine chemistry, anionic ring closures, radical chemistry, tethering devices)[40–43] have found important and widespread use in many laboratories and industrial settings.

Similarly, Eschenmoser's beautiful total syntheses (for example, colchicine, corrins, vitamin B_{12}, designed nucleic acids)[44–47] are often accompanied by profound mechanistic insights and synthetic designs of such admirable clarity and deep thought. His exquisite total synthesis of vitamin B_{12} (with Woodward), in particular, is an extraordinary achievement and will always remain a classic[3] in the annals of organic synthesis. The work of D. H. R. Barton,[48] starting with his contributions to conformational analysis and biogenetic theory and continuing with brilliant contributions both in total synthesis and synthetic methodology, was instrumental in shaping the art and science of natural products synthesis as we know it today. Among his most significant contributions are the Barton reaction, which involves the photocleavage of nitrite esters[49] and its application to the synthesis of aldosterone-21-acetate,[50] and his deoxygenation reactions and related radical chemistry,[51] which has found numerous applications in organic and natural product synthesis.

It seemed for a moment, in 1990, that the efforts of the synthetic chemists had conquerred most of the known structural types of secondary metabolites: prostaglandins, steroids, β-lactams, macrolides, polyene macrolides, polyethers, alkaloids, porphyrinoids, endiandric acids, palitoxin carboxyclic acid, and gingkolide; all fell as a result of the awesome power of total synthesis. Tempted by the lure of other unexplored and promising fields, some researchers even thought that total synthesis was dead, and declared it so. They were wrong. To the astute eye, a number of challenging and beautiful architectures remained standing, daring the synthetic chemists of the time and inviting them to a feast of discovery and invention. Furthermore, several new structures were soon to be discovered from nature that offered unprecedented challenges and opportunities. To be sure, the final decade of the twentieth century proved to be a most exciting and rewarding period in the history of total synthesis.

3.4. The 1990s Era

The climactic productivity of the 1980s in total synthesis boded well for the future of the science, and the seeds were already sown for continued breakthroughs and a new explosion of the field. Entirely new types of structures were on the minds of synthetic chemists, challenging and presenting them with new opportunities. These luring architectures included the enediynes such as calicheamicin and dynemicin, the polyether neurotoxins exemplified by brevetoxins A and B, the immunosuppressants cyclosporin, FK506, rapamycin, and sanglifehrin A, taxol and other tubulin binding agents, such as the epothilones eleutherobin and the sarcodictyins, ecteinascidin, the manzamines, the glycopeptide antibiotics such as vancomycin, the CP molecules, and everninomicin 13,384-1 (see Section 3.5).

Most significantly, total synthesis assumed a more serious role in biology and medicine. The more aggressive incorporation of this new dimension to the enterprise was aided and encouraged by combinatorial chemistry and the new challenges posed by discoveries in genomics. Thus, new fields of investigation in chemical biology were established by synthetic chemists taking advantage of the novel molecular architectures and biological action of certain natural products. Besides culminating in the total synthesis of the targeted natural products, some of these new programs expanded into the development of new synthetic methods as in the past, but also into the areas of chemical biology, solid phase chemistry, and combinatorial synthesis. Synthetic chemists were moving deeper into biology, particularly as they recognized the timeliness of using their powerful tools to probe biological phenomena and make contributions to chemical and functional genomics. Biologists, in turn, realized the tremendous benefits that chemical synthesis could bring to their science and adopted it, primarily through interdisciplinary collaborations with synthetic chemists. A new philosophy for total synthesis as an important component of chemical biology began to take hold, and natural products continued to be in the center of it all. In the next section we briefly discuss a number of selected total syntheses of the twentieth century.

3.5. Selected Examples of Total Syntheses

The chemical literature of the twentieth century is adorned with beautiful total syntheses of natural products.[3–5] We have chosen to highlight a few here as illustrative examples of structural types and synthetic strategies.

Tropinone (1917)

Perhaps the first example of a strikingly beautiful total synthesis is that of the alkaloid (±)-tropinone (**1** in Scheme 1) reported as early as 1917 by Sir R. Robinson.[5, 16] In this elegant synthesis—called biomimetic because of its resem-

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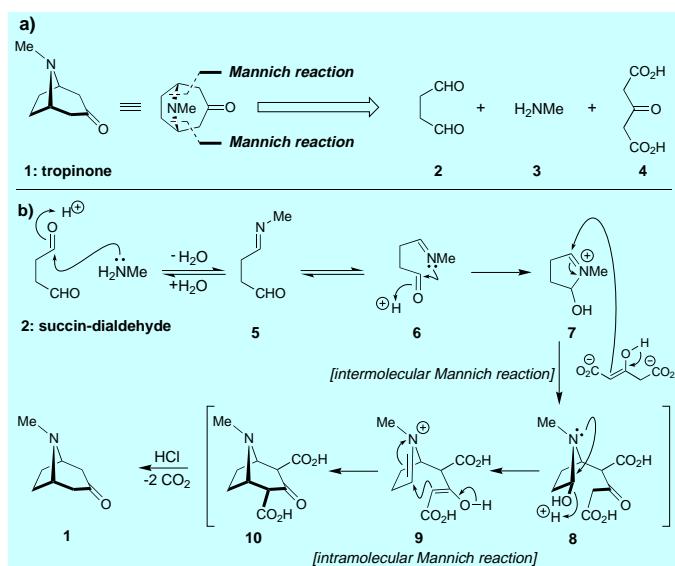
Scheme 1. a) Strategic bond disconnecions and retrosynthetic analysis of (±)-tropinone and b) total synthesis (Robinson, 1917).[16]

blance to the way nature synthesizes tropinone—Robinson utilized a tandem sequence in which one molecule of succindialdehyde, methylamine, and either acetone dicarboxylic acid (or dicarboxylate) react together to afford the natural substance in a simple one-pot procedure. Two consecutive Mannich reactions are involved in this synthesis, the first one in an inter- and the second one in an intramolecular fashion. In a way, the total synthesis of (±)-tropinone by Robinson was quite ahead of its time both in terms of elegance and logic. With this synthesis Robinson introduced aesthetics into total synthesis, and art became part of the endeavor. It was left, however, to R. B. Woodward to elevate it to the artistic status that it achieved in the 1950s and to E. J. Corey to make it into the precise science that it became in the following decades.

Haemin (1929)

Haemin (**1** in Scheme 2), the red pigment of blood and the carrier of oxygen within the human body, belongs to the porphyrin class of compounds. Both its structure and total synthesis were established by H. Fischer.[5, 18] This combined program of structural determination through chemical synthesis is exemplary of the early days of total synthesis. Such practices were particularly useful for structural elucidation in the absence of today's physical methods such as NMR spectroscopy, mass spectrometry, and X-ray crystallography. In the case of haemin, the molecule was degraded into smaller fragments, which chemical synthesis confirmed to be substituted pyrroles. The assembly of the pieces by exploiting the greater nucleophilicity of pyrrole's 2-position, relative to that of the 3-position, led to haemin's framework into which the iron cation was implanted in the final step. Among the most remarkable features of Fischer's total synthesis of haemin are the fusion of the two dipyrrole components in succinic acid at 180–190 °C to form the cyclic porphyrin skeleton in a single step by two C–C bond-forming reactions, and the unusual way in which the carbonyl groups were reduced to hydroxyl groups

prior to elimination of the latter functionalities. In contrast to the rather brutal reagents and conditions used in this porphyrin's synthesis, the tools of the "trade" when Woodward faced chlorophyll *a*, approximately thirty years later, were much sharper and selective.

Equilenin (1939)

The first sex hormone to be constructed in the laboratory by total synthesis was equilenin (**1** in Scheme 3). The total synthesis of this first steroidal structure was accomplished in
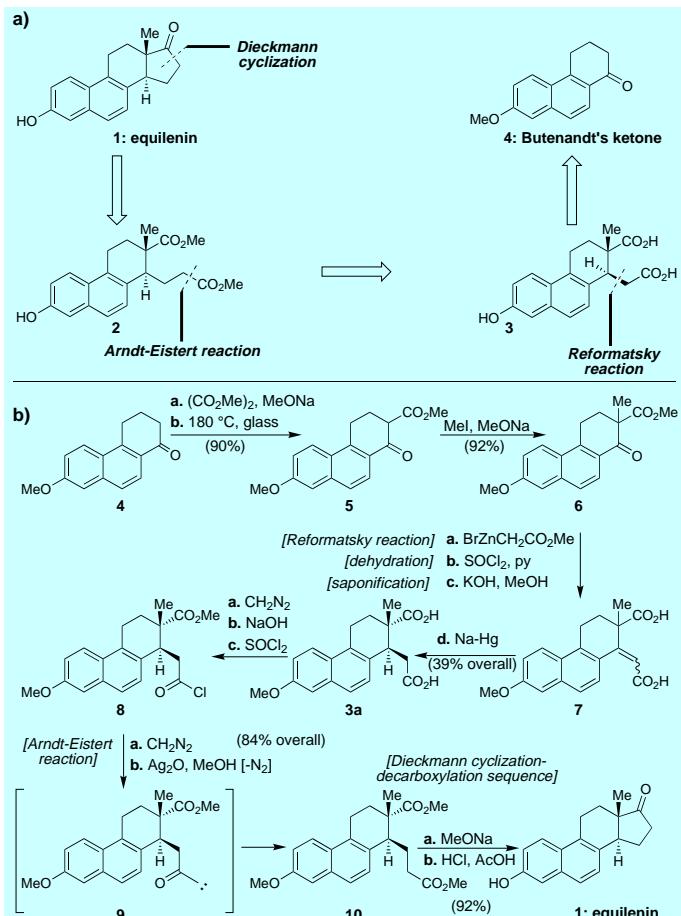
Scheme 3. a) Strategic bond disconnections and retrosynthetic analysis of equilenin and b) total synthesis (Bachmann et al., 1939).[21]

1939 by Bachmann and his group at the University of Michigan.[21, 52] This synthesis featured relatively simple chemistry as characteristically pointed out by the authors: "The reactions which were used are fairly obvious ones…"[21] Specifically, the sequence involves enolate-type chemistry, a Reformatsky reaction, a sodium amalgam reduction, an Arndt–Eistert homologation, and a Dieckmann cyclization–decarboxylation process to fuse the required cyclopentanone ring onto the pre-existing tricyclic system of the starting material. As the last pre-World War II synthesis of note, this example was destined to mark the end of an era; A new epoch was about to begin in the 1940s with R. B. Woodward and his school of chemistry at the helm.

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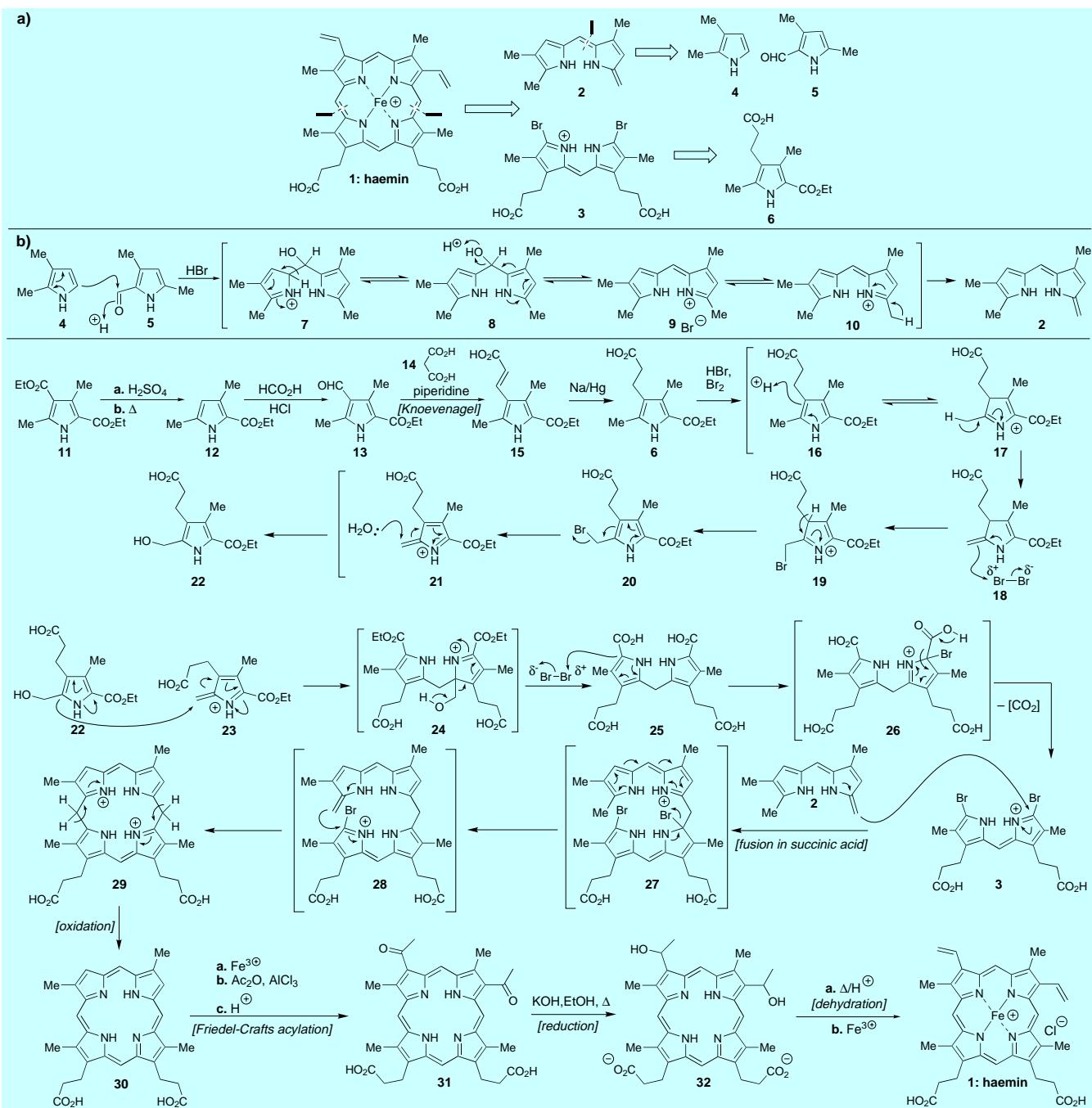
Scheme 2. a) Strategic bond disconnections and retrosynthetic analysis of haemin and b) total synthesis (Fisher, 1929).[18]

Before we close this era of total synthesis and enter into a new one, the following considerations might be instructive in atempting to understand the way of thinking of the pre-World War II chemists as opposed to those who followed them. The rather straightforward synthesis of equilenin is representative of the total syntheses of pre-World War II era—with the exception of Robinson's unique tropinone synthesis. In contemplating a strategy towards equilenin, Bachmann must have considered several possible starting materials before recognizing the resemblance of his target molecule to Butenand's ketone (4 in Scheme 3). After all, three of equilenin's rings are present in 4 and all he needed to do was fuse the extra ring and introduce a methyl group onto the

cyclohexane system in order to accomplish his goal. The issue of stereochemistry of the two stereocenters was probably left open to chance in contrast to the rational approaches towards such matters of the later periods. Connecting the chosen starting material 4 with the target molecule 1 was apparently obvious to Bachmann, who explicitly stated the known nature of the reactions he used to accomplish the synthesis.

Since the motivations for total synthesis were strongly tied to the proof of structure, one needed a high degree of confidence that the proposed transformations did indeed lead to the proposed structure. Furthermore, the limited arsenal of chemical transformations did not entice much creative deviation from the most straightforward course. This high degree of

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confidence that synthetic chemists had in their designed strategies was soon to decrease as the complexity of newly discovered natural products increased, thus catalyzing the development of novel strategies and new chemistry in subsequent years. In addition, advances in theoretical and mechanistic organic chemistry as well as new synthetic tools were to allow much longer sequences to be planned with a heightened measure of confidence and considerable flexibility for redesign along the way.

Strychnine (1954)

As the most notorious poison[53] of the *Strychnos* plant species, strychnine (**1** in Scheme 4) occupied the minds of

structural chemists for a rather long time. Its gross structure was revealed in 1946[54] and was subsequently confirmed by X-ray crystallographic analysis.[55] In 1952, Sir Robert Robinson commented that strychnine: "For its molecular size it is the most complex substance known."[56] This estimation had not, apparently, escaped R. B. Woodward's attention who had already been fully engaged in strychnine's total synthesis. In 1948 Woodward put forth the idea that oxidative cleavage of electron-rich aromatic rings might be relevant in the biogenesis of the *strychnos* alkaloids.[57] This provocative idea was implemented in his 1954[27] synthesis of strychnine, which established Woodward as the undisputed master of the art at the time. The total synthesis of (−)-strychnine by Woodward (Scheme 4) ushered in a golden era of total synthesis and
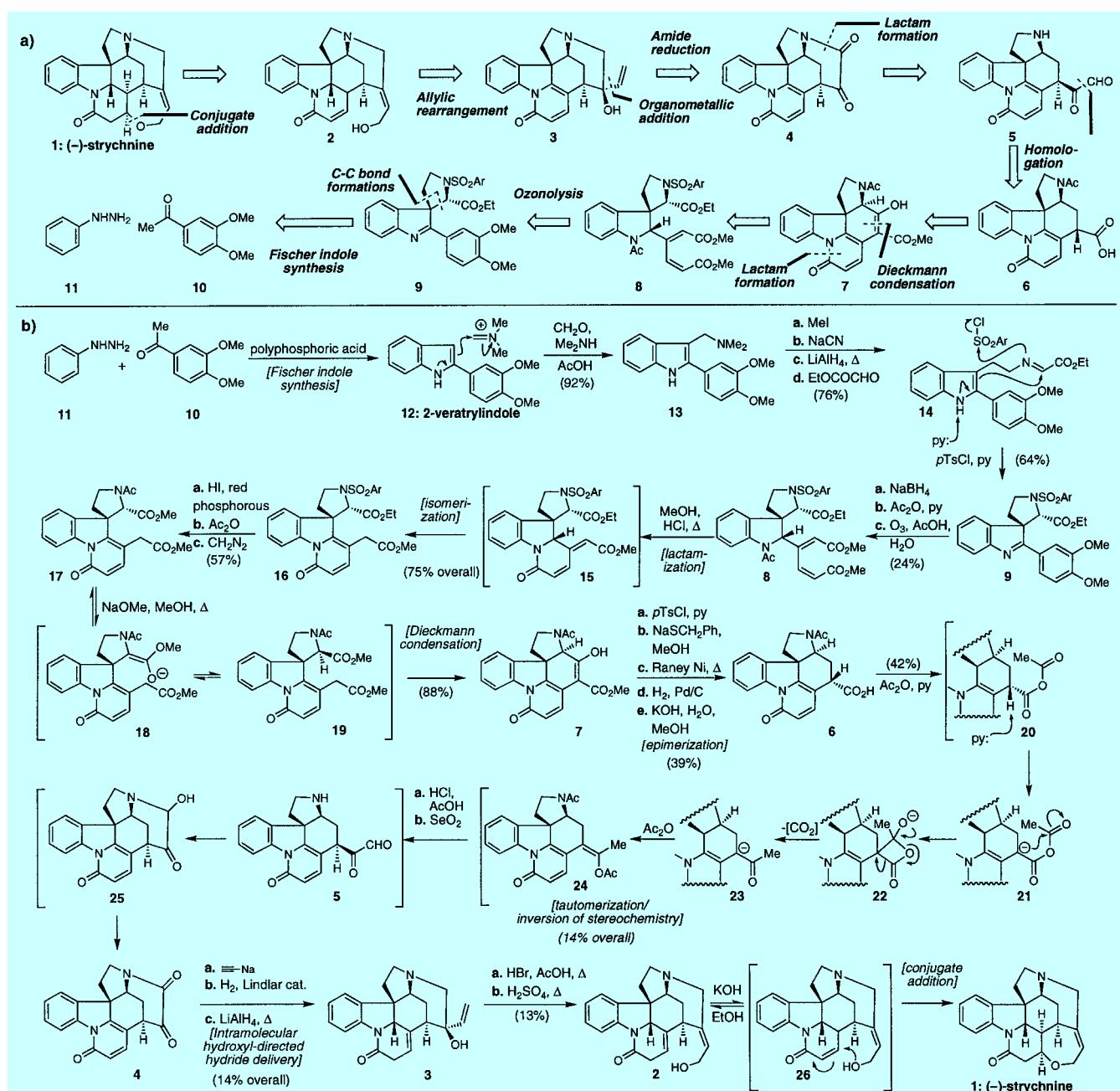
Scheme 4. a) Strategic bond disconnections and retrosynthetic analysis of (−)-strychnine and b) total synthesis (Woodward et al., 1954).[27]

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installed unprecedented confidence in, and respect for, the science of organic synthesis. Although several of its steps were beautifully designed and executed, perhaps the most striking feature is its reliance on only the simplest of reagents to carry out what seemed to be rather complex chemical transformations. With its challenging molecular structure, the molecule of strychnine continued to occupy the minds of several subsequent practitioners of the art and several other total syntheses have since appeared in the literature.[58, 59]

Penicillin (1957)

Few discoveries of the twentieth century can claim higher notoriety than that of penicillin (**1** in Scheme 5). Discovered in 1928 by Alexander Fleming[60] in the secretion of the mold *Penicillium notatum*, penicillin was later shown to possess remarkable antibacterial properties by Chain and Florey.[61] Following a massive development effort known as the Anglo–American penicillin project[62, 63] the substance was

introduced as a drug during World War II and saved countless lives. Its molecular structure containing the unique and strained β-lactam ring was under the cloud of some controversy until Dorothy Crowfoot-Hodgkin confirmed it by X-ray crystallographic analysis.[64]

Not surprisingly, penicillin immediately became a highly priced synthetic target attracting the attention of major players in total synthesis of the time. Finally, it was Sheehan and Henery-Logan[65] at the Massachusetts Institute of Technology who delivered synthetic penicillin V by total synthesis of the "enchanted" molecule, as Sheehan later called it.[66] Their synthesis, reported in 1957 and summarized in Scheme 5, was accompanied by the development of the phthalimide and *tert*-butyl ester protecting groups and the introduction of an aliphatic carbodiimide as a condensing agent to form amide bonds and—in the event—penicillin's fragile β-lactam ring. With this milestone, another class of natural products was now open to chemical manipulation and a new chapter in total synthesis had begun.

Reserpine (1958)

Reserpine (**1** in Scheme 6), a constituent of the Indian snakeroot *Rauwolfia serpentina* BENTH., is an alkaloid substance with curative properties[67] for the treatment of hypertension, as well as nervous and mental disorders.[68] Reserpine was isolated in 1952 and yielded to structural elucidation in 1955 (Schlittler and co-workers)[69] and to total synthesis in 1958 (Woodward et al.).[28] The first total synthesis of reserpine (Scheme 6), considered by some as one of Woodward's greatest contributions to synthesis, inspires admiration and respect by the manner in which it exploits molecular conformation to arrive at certain desired synthetic objectives. During this synthesis, Woodward demonstrated brilliantly the power of the venerable Diels–Alder reaction to construct a highly functionalized 6-membered ring, to control stereochemistry around the periphery of such a ring, and most importantly, to induce a desired epimerization by constraining the molecule into an unfavorable conformation by intramolecular tethering. All in all, Woodward's total synthesis of reserpine remains as brilliant in strategy as admirable in execution. It was to be followed by several others.[70]

The synthesis of reserpine appropriately represents Woodward's approach to total synthesis. Even though Woodward did not talk about retrosynthetic analysis, he must have practiced it subconsciously. In his mind, reserpine consisted of three parts: the indole (the AB unit, see Scheme 6), the trimethoxybenzene system, and the highly substituted E-ring cyclohexane. Given the simplicity of the first two fragments and their obvious attachment to fragment **3**, Woodward concerned himself primarily with the stereoselective construction of **3** and the stereochemical problem encountered in completing the architecture of the CD ring system. He brilliantly solved the first problem by employing the Diels–Alder reaction to generate a cyclic template onto which he installed the required functionality by taking advantage of the special effects of ring systems on the stereochemical outcomes of reactions. He addressed the second issue, that of the last stereocenter to be set at the junction of rings C and D, by
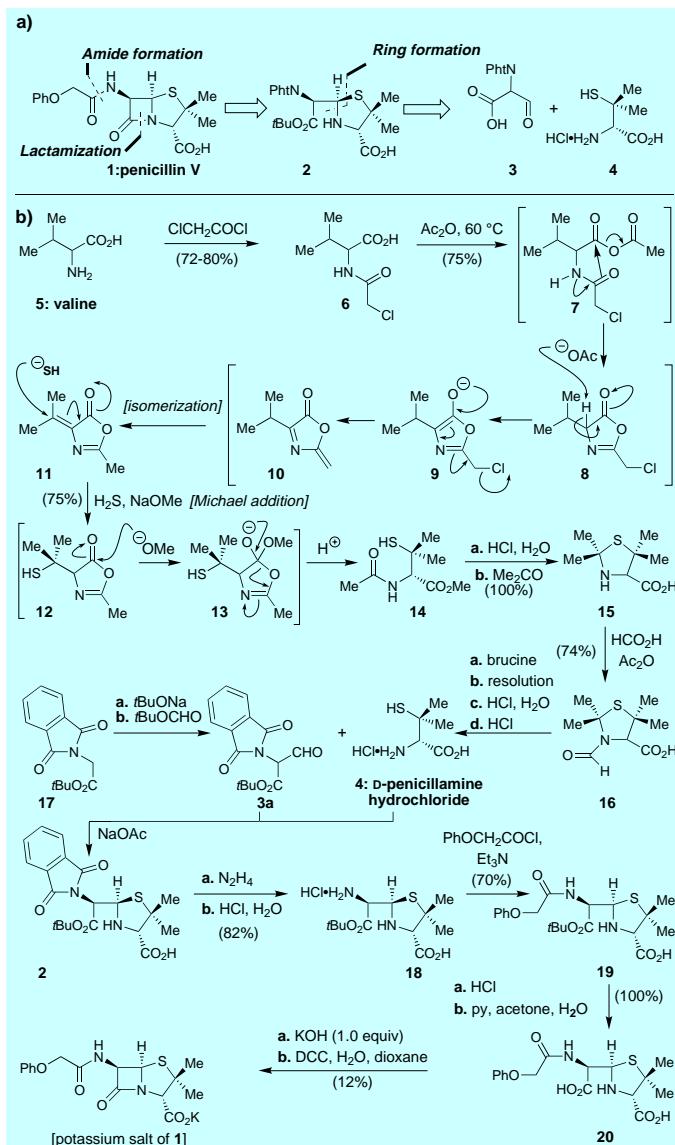
Scheme 5. a) Strategic bond disconnections and retrosynthetic analysis of penicillin V and b) total synthesis (Sheehan et al., 1957).[65]

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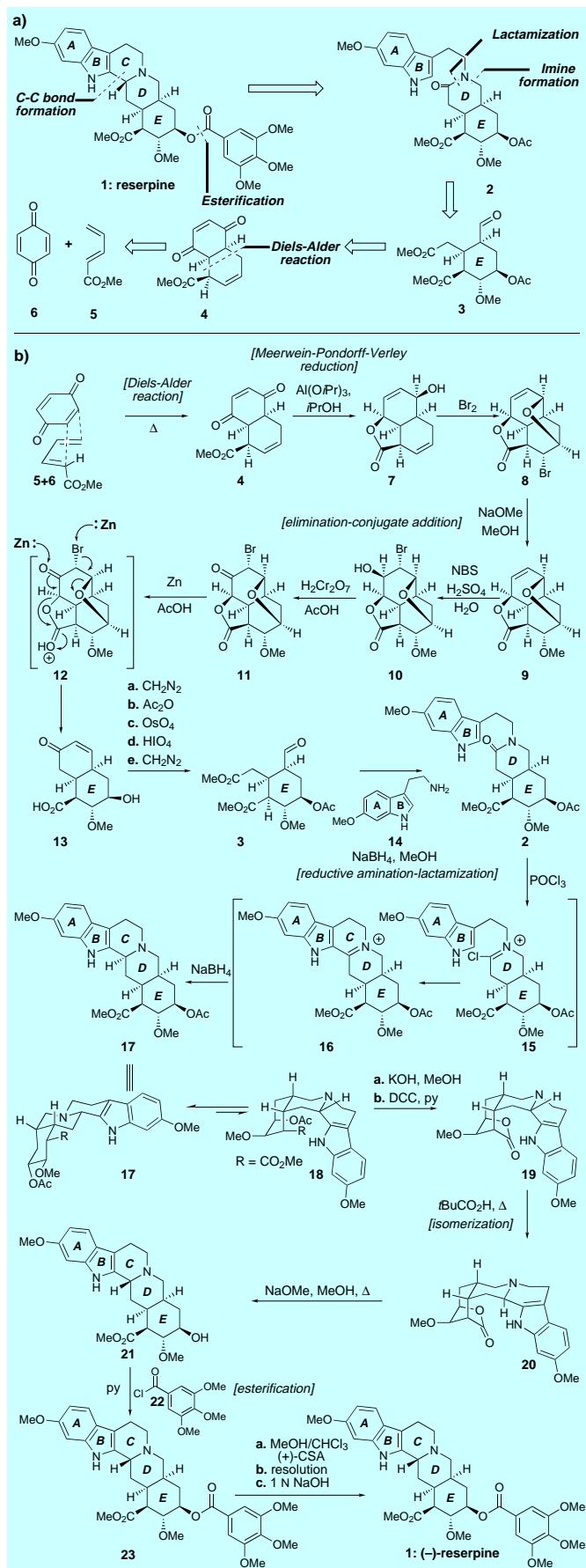
Scheme 6. a) Strategic bond disconnections and retrosynthetic analysis of reserpine and b) total synthesis (Woodward et al., 1958).[28]

cleverly coaxing his polycycle into an unfavorable conformation (through intramolecular tethering), which forced an isomerization to give the desired stereochemistry.

These maneuvers clearly constituted unprecedented sophistication and rational thinking in chemical synthesis design. While this rational thinking was to be further advanced and formalized by Corey's concepts on retrosynthetic analysis, the stereocontrol strategies of this era were to dominate synthetic planning for some time before being complemented and, to a large degree, eclipsed by acyclic stereoselection and asymmetric synthesis advances which emerged towards the end of the century.

Chlorophyll a (1960)

Chlorophyll a (1 in Scheme 7), the green pigment of plants and the essential molecule of photosynthesis, is distinguished from its cousin molecule haemin by the presence of two extra hydrogen atoms (and, therefore, two chiral centers) in one of its pyrrole rings, the presence of the phytyl side chain, and the encapsulation of a magnesium cation rather than an iron cation. Its total synthesis by R. B. Woodward et al. in 1960[29] represents a beautiful example of bold planning and exquisite execution. This synthesis includes improvements over Fischer's routes to porphyrin building blocks and, most importantly, a number of clever maneuvers for the installment of the three stereocenters and the extra five-membered ring residing on the periphery of the chlorin system of chlorophyll a. The chemical synthesis of chlorophyll a is a significant advance over Fischer's total synthesis of haemin,[18] and must have given Woodward the confidence, and prepared the ground, for his daring venture towards vitamin B$_{12}$ in which he was to be joined by A. Eschenmoser (see p. 61).

Longifolene (1961)

The publication of the total synthesis of longifolene (1 in Scheme 8) in 1961 by Corey et al.[34] is of historical significance in that in it Corey laid out the foundation of his systematic approach to retrosynthetic analysis. Our thinking about synthetic design has been profoundly affected and shaped by the principles of retrosynthetic analysis ever since, and the theory is sure to survive for a long time to come. Corey's longifolene synthesis[34] exemplifies the identification and mental disconnection of strategic bonds for the purposes of simplifying the target structure. The process of retrosynthetic analysis unravels a retrosynthetic tree with possible pathways and intermediates from which the synthetic chemist can choose the most likely to succeed and/or most elegant strategies. The total synthesis of longifolene itself, shown in Scheme 8, involves a Wittig reaction, an osmium tetroxide-mediated dihydroxylation of a double bond, a ring expansion, and an intramolecular Michael-type alkylation to construct the longifolene skeleton. This synthesis remains a landmark in the evolution of the art and science of total synthesis.
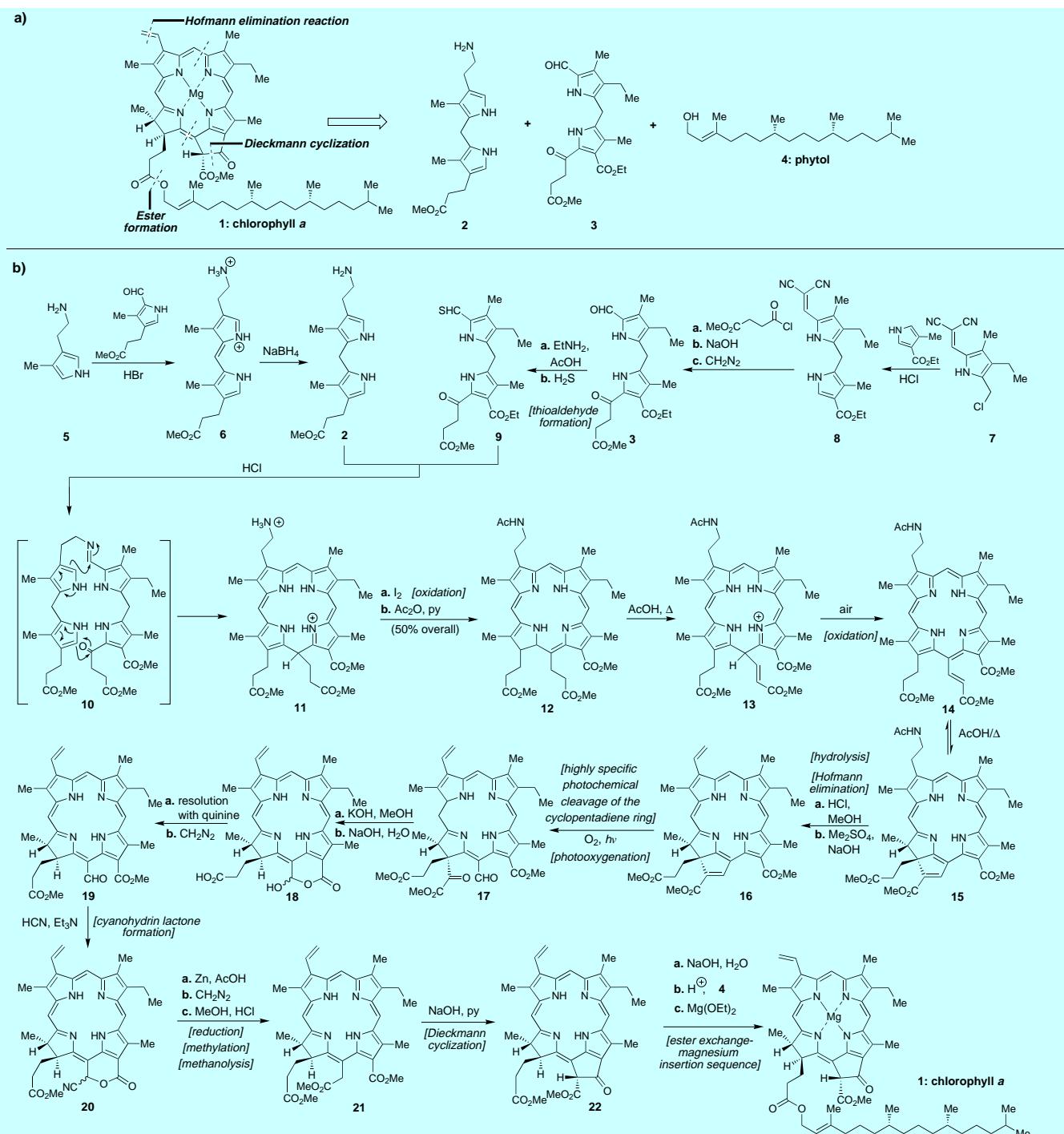
Scheme 7. a) Strategic bond disconnections and retrosynthetic analysis of chlorophyll *a* and b) total synthesis (Woodward et al., 1960).[29] The locking of **2** and **9** together through formation of a schiff base forces the cyclization to proceed with the desired regioselectivity.

Lycopodine (1968)

Lycopodine (**1** in Scheme 9), first isolated in 1881, is the most wildly distributed alkaloid from the genus *lycopodium*.[71] In addition to the great challenge of synthesizing this novel polycyclic framework in a stereocontrolled manner, one must effectively address the challenge posed by the C13 quaternary center, which is common to all four rings. Gilbert Stork was one of the first to successfully complete the total synthesis of lycopodine.[72] This masterfully executed synthesis features a unique "aza-annulation" strategy which utilizes the Stork enamine methodology[73] (a generally useful strategy to generate and trap enolates regiospecifically) to construct quinolone systems, a stereospecific cationic cyclization to establish the C13 quaternary center, and a series of functional group manipulations to elaborate the resulting aromatic ring into ring D. Several syntheses of lycopodine have since appeared,[74] each featuring a unique strategy complementary to Stork's beautiful synthesis.

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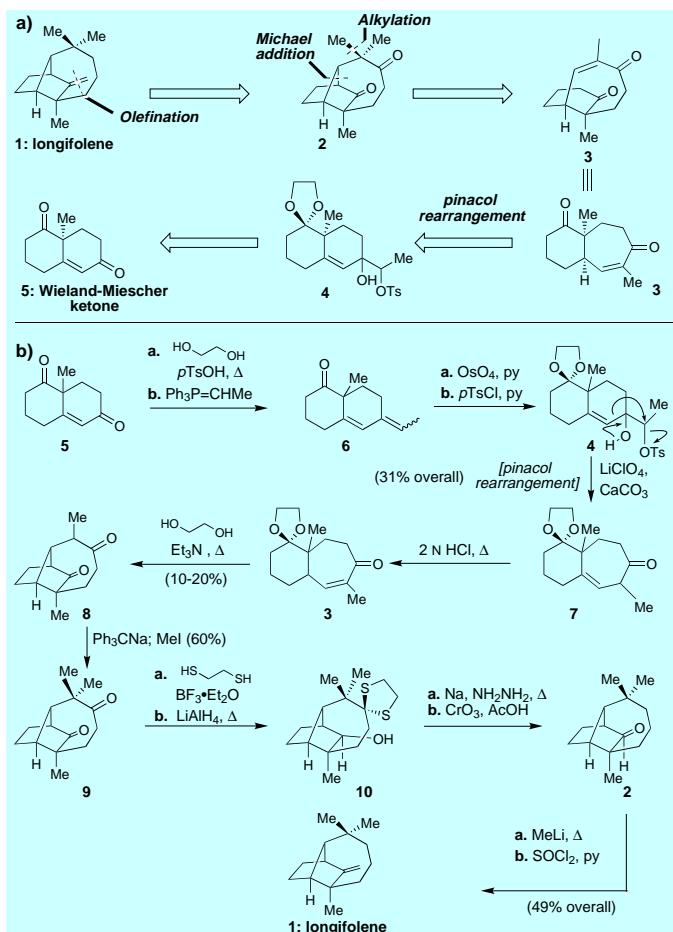
Scheme 8. a) Strategic bond disconnections and retrosynthetic analysis of longifolene and b) total synthesis (Corey et al., 1961).[34]

Cephalosporin C (1966)

Cephalosporin C (**1** in Scheme 10) was isolated from *Cephalosporium acremonium* in the mid-1950s[75] and was structurally elucidated by X-ray crystallographic analysis in 1961.[76] Reminiscent of the penicillins, the cephalosporins represent the second subclass of β-lactams, several of which became legendary antibiotics in the latter part of the twentieth century. Having missed the opportunity to deliver penicillin, the Woodward group became at once interested in the synthesis of cephalosporin C and, by 1965, they completed the first total synthesis of the molecule.[30]

This total synthesis of cephalosporin C was the sole topic of Woodward's 1965 Nobel lecture in Stockholm. Indeed, in a move that broke tradition, R. B. Woodward described on that occasion for the first time, and in a breathtaking fashion, the elegant synthesis of cephalosporin C. Highlights of this synthesis, which is summarized in Scheme 10, include the development of the azodicarboxylate-mediated functionalization of the methylene group adjacent to the sulfur atom of L-cysteine, the aluminum-mediated closure of the aminoester to the β-lactam functionality, the brilliant formation of cephalosporin's sulfur-containing ring, and the use of the β,β,β-trichloroethyloxy moiety to protect the hydroxyl group. This total synthesis stands as a milestone accomplishment in the field of natural product synthesis.
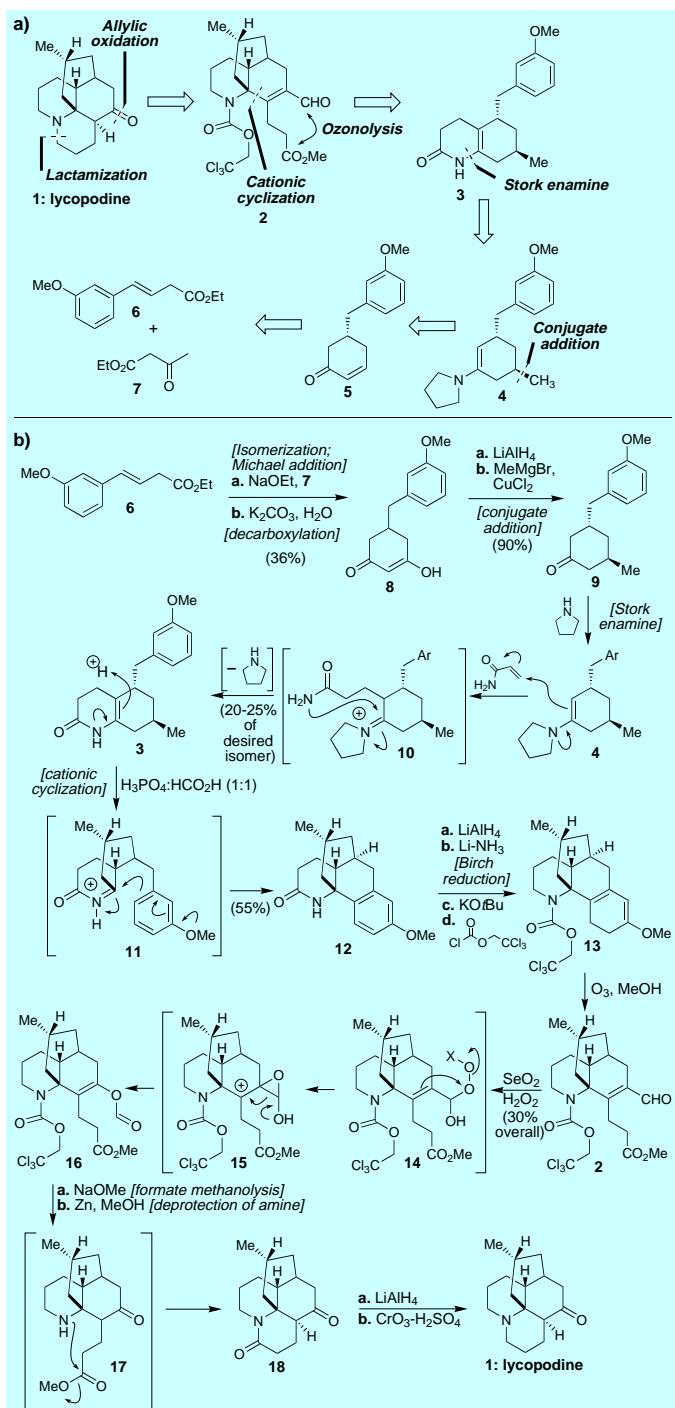
Scheme 9. a) Strategic bond disconnections and retrosynthetic analysis of (±)-lycopodine and b) total synthesis (G. Stork et al., 1968).[72]

Prostaglandins F$_{2\alpha}$ and E$_2$ (1969)

The prostaglandins were discovered by von Euler in the 1930s[77] and their structures became known in the mid-1960s primarily as a result of the pioneering work of Bergström and his group.[78] With their potent and important biological activities and their potential applications in medicine,[79] these scarce substances elicited intense efforts directed at their chemical synthesis. By 1969 Corey had devised and completed his first total synthesis of prostaglandins F$_{2\alpha}$ (**1** in Scheme 11) and E$_2$.[80] These syntheses amplified brilliantly Corey's

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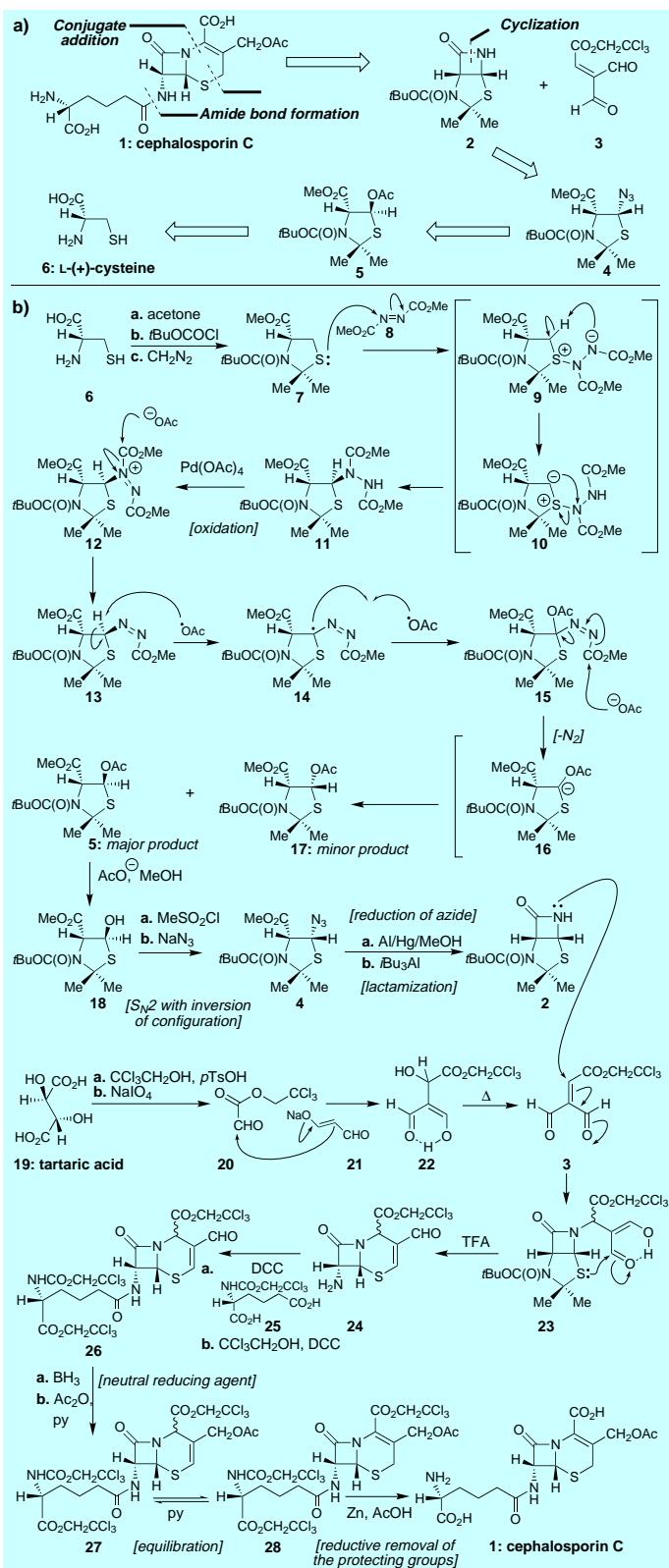
Scheme 10. a) Strategic bond disconnections and retrosynthetic analysis of cephalosporin C and b) total synthesis (Woodward et al., 1966).[30]

retrosynthetic analysis concepts and demonstrated the utilization of the bicycloheptane system derived from a Diels–Alder reaction as a versatile key intermediate for the synthesis of several of the prostaglandins. A large body of
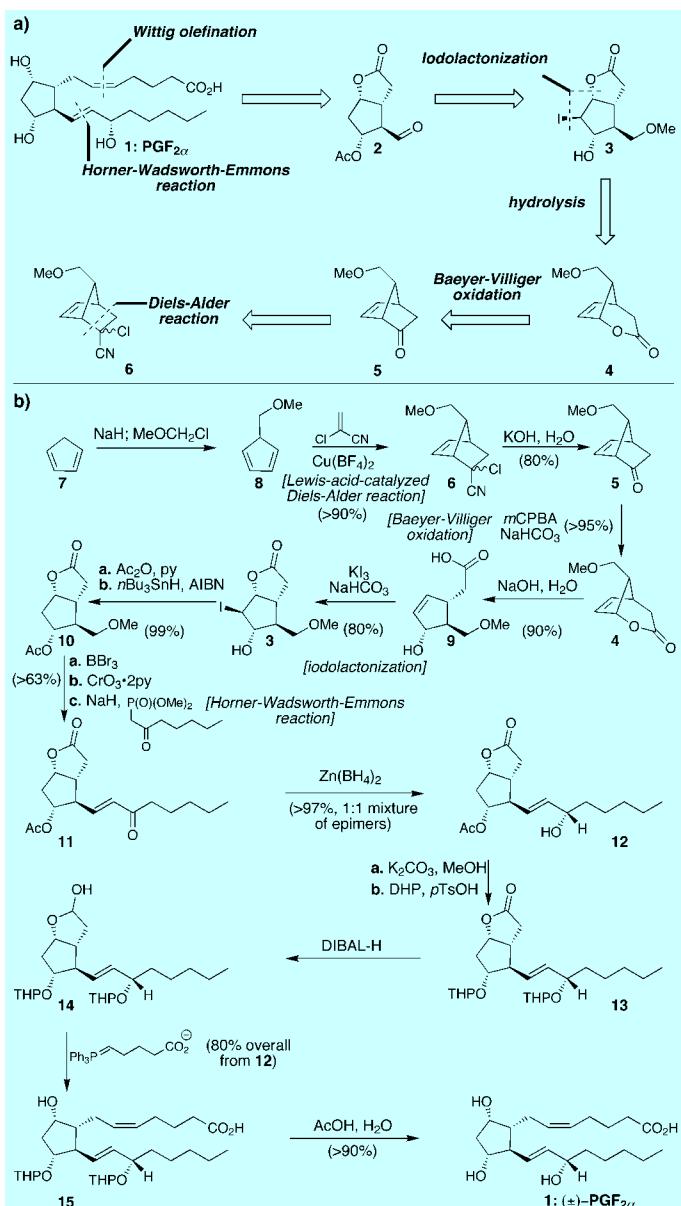
Scheme 11. a) Strategic bond disconnections and retrosynthetic analysis of (±)-PGF$_{2\alpha}$ and b) the total synthesis (Corey et al., 1969).[80]

synthetic work[81–83] followed the initial Corey synthesis and myriad prostaglandin analogues have since been synthesized, aiding both biology and medicine tremendously.

Corey's original strategy evolved alongside the impressive developments in the field of asymmetric catalysis, many of which he instigated, which culminated by the 1990s, in a refined, highly efficient and stereocontrolled synthesis of the prostaglandins.[84] Thus, in its original version, the Corey synthesis of prostaglandins F$_{2\alpha}$ and E$_2$ was nonstereoselective and delivered the racemate and as a mixture of C15 epimers. Then, in 1975, came a major advance in the use of a chiral auxiliary to control the stereochemical outcome of the crucial Diels–Alder reaction to form the bicyclo[2.2.1]heptane system in its optically active form.[85] The theme of chiral auxiliaries to control stereochemistry played a major role in the development of organic and natural products synthesis in the latter part of the century. In addition to the contributions

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of Corey, those of A. I. Myers,[86] D. A. Evans,[87] W. Oppolzer,[88] and H. C. Brown[89] as well as many others helped shape the field.

Finally came the era of catalyst design and here again the prostaglandins played a major role in providing both a driving force and a test. In a series of papers, Corey disclosed a set of chiral aluminum- and boron-based[90, 91] catalysts for the Diels–Alder reaction (and several other reactions) that facilitated the synthesis of an enantiomerically enriched intermediate along the route to prostaglandins. And, finally, the problem of stereoselectivity at C15 was solved by the introduction of the oxazaborolidine catalyst (CBS) by Corey in 1987.[92] These catalysts not only refined the industrial process for the production of prostaglandins, but also found uses in many other instances both in small scale laboratory operations and manufacturing processes of drug candidates and pharmaceuticals. For a more in-depth analysis of the Corey syntheses of prostaglandins $F_{2\alpha}$ and E_2 and other advances on asymmetric catalysis, the reader is referred to ref. [4] and other appropriate literature sources.

### Progesterone (1971)

Progesterone (1 in Scheme 12), a hormone that prepares the lining of the uterus for implantation of an ovum, is a member of the steroid class of compounds that is found ubiquitously in nature. Its linearly fused polycyclic carbon framework is characteristic of numerous natural products of steroidal or triterpenoid structures. A daring approach to progesterone's skeleton by W. S. Johnson[93] was inspired by the elucidated enzyme-catalyzed conversion[94] of squalene oxide into lanosterol or to the closely related plant triterpenoid dammaradienol. This biomimetic strategy was also encouraged by the Stork–Eschenmoser hypothesis, which was proposed in 1955[35] to rationalize the stereochemical outcome of the biosynthetic transformation of squalene oxide to steroid. According to this postulate it was predicted that polyunsaturated molecules with *trans* C=C bonds, such as squalene oxide, should cyclize in a stereospecific manner, to furnish polycyclic systems with *trans,anti,trans* stereochemistry at the ring fusion.

This brilliant proposition was confirmed by W. S. Johnson and his group through the biomimetic total synthesis of progesterone (Scheme 12). A tertiary alcohol serves as the initiator of the polyolefinic ring-closing cascade, in this instance, but other groups have also been successfully employed (for example, acetal, epoxide). The methylacetylenic group performed well as a terminator of the cascade in the original work. A number of new terminating systems have since been successfully employed (for example, allyl or propargyl silanes, vinyl fluoride). The work of W. S. Johnson was complemented by that of van Tamelen[95] and others[3, 4] who also explored such biomimetic cascades.

Tetrodotoxin (1972)

Tetrodotoxin (1 in Scheme 13) is the poisonous compound of the Japanese puffer fish and its structure was elucidated by
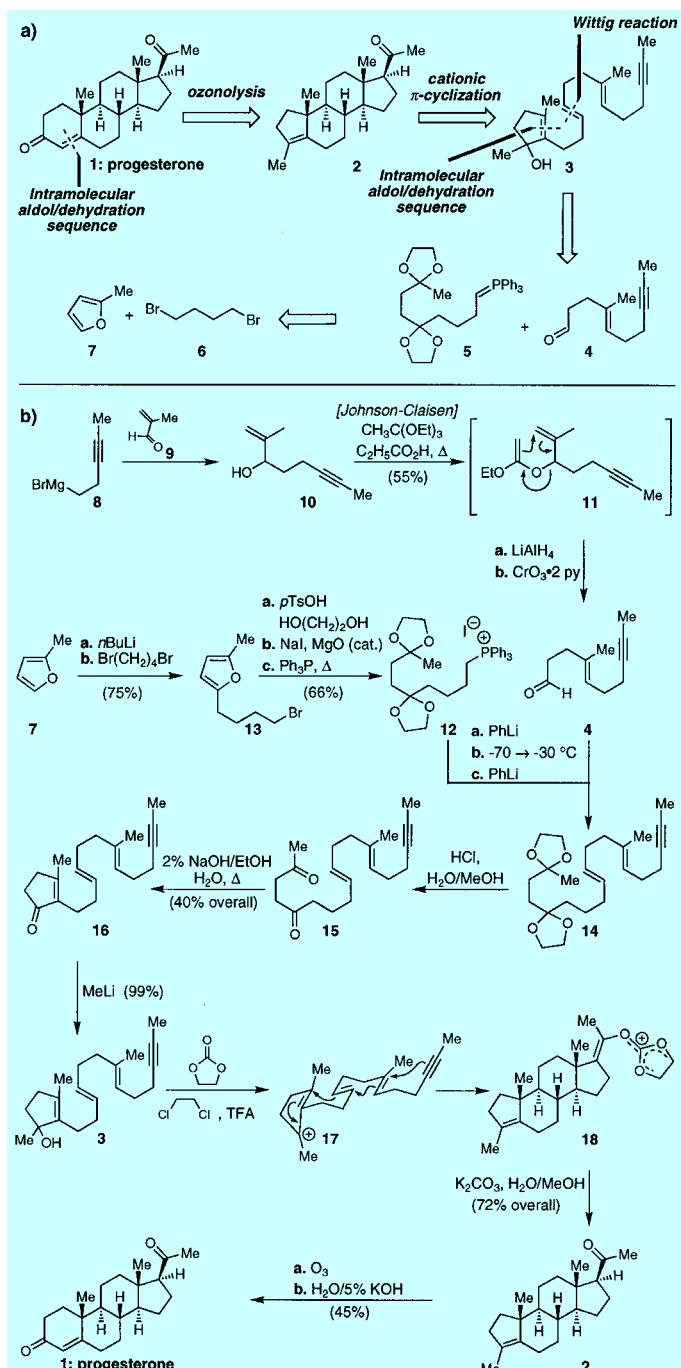
Scheme 12. a) Strategic bond disconnections and retrosynthetic analysis of progesterone and b) total synthesis (Johnson et al., 1971).[93]

Woodward in 1965.[96] By 1972 Kishi and his group had published the total synthesis[97] of this highly unusual and challenging structure. This outstanding achievement from Japan was received at the time with great enthusiasm and remains to this day as a classic in total synthesis. The target molecule was reached through a series of maneuvers which included a Diels–Alder reaction of a quinone with butadiene, a Beckman rearrangement to install the first nitrogen atom, stereoselective reductions, strategic oxidations, unusual functional group manipulations, and, finally, construction of the guanidinium system. As a highly condensed and polyfunc-
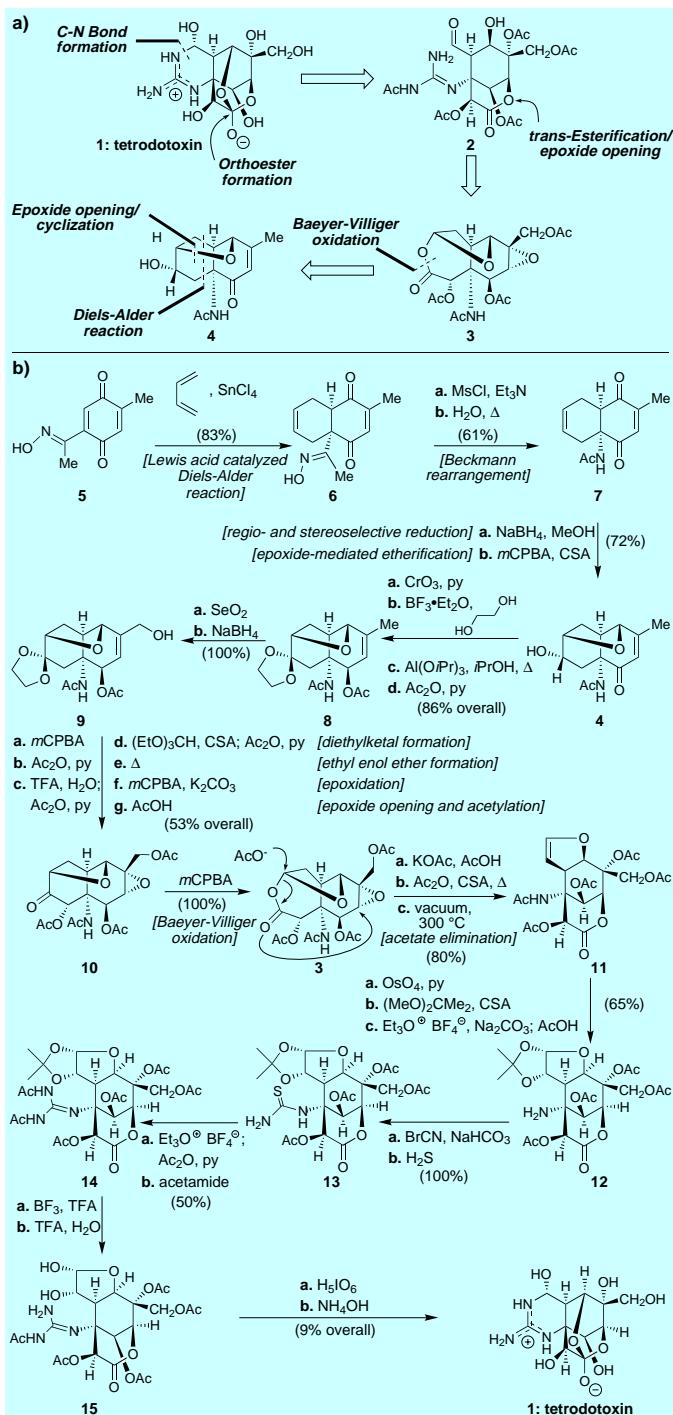
Scheme 13. a) Strategic bond disconnections and retrosynthetic analysis of tetrodotoxin and b) total synthesis (Kishi et al., 1972).[97]

Rarely before has a synthetic project yielded so much knowledge, including: novel bond-forming reactions and strategies, ingenious solutions to formidable synthetic problems, biogenetic considerations and hypotheses, and the seeds of the principles of orbital symmetry conservation known as the Woodward and Hoffmann rules.[98] The structure of vitamin B$_{12}$ was revealed in 1956 through the elegant X-ray crystallographic work of Dorothy Crowfoot-Hodgkin.[99] The escalation of molecular complexity from haemin to chlorophyll *a* to vitamin B$_{12}$ is interesting not only from a structural point of view, but also in that the total synthesis of each molecule reflects the limits of the power of the art and science of organic synthesis at the time of the accomplishment.

One of the most notable of the many elegant maneuvers of the Woodward–Eschenmoser synthesis of vitamin B$_{12}$ is the photoinduced ring closure of the corrin ring from a pre-organized linear system wrapped around a metal template, which was an exclusive achievement of the Eschenmoser group. The convergent approach defined cobyric acid (**2** in Scheme 14) as a landmark key intermediate, which had previously been converted into vitamin B$_{12}$ by Bernhauser et al.[100] The synthesis of vitamin B$_{12}$ defined the frontier of research in organic natural product synthesis at that time. For an in depth discussion of this mammoth accomplishment, the reader is referred to ref. [4].

tional molecule, tetrodotoxin was certainly a great conquest and elevated the status of both the art and the practitioner, and at the same time was quite prophetic of things to come.

Vitamin B$_{12}$ (1973)

The total synthesis of vitamin B$_{12}$ (**1** in Scheme 14), accomplished in 1973 by a collaboration between the groups of Woodward and Eschenmoser,[3, 32] stands as a monumental achievement in the annals of synthetic organic chemistry.

Erythronolide B (1978)

The macrolide antibiotics, of which erythromycin is perhaps the most celebrated, stood for a long time as seemingly unapproachable by chemical synthesis. The origin of the initial barriers and difficulties was encapsulated in the following statement made by Woodward in 1956, "Erythromycin, with all our advantages, looks at present hopelessly complex, particularly in view of its plethora of asymmetric centers."[101] In addition to the daunting stereochemical problems of erythromycin and its relatives, also pending was the issue of forming the macrocyclic ring. These challenges gave impetus to the development of new synthetic technologies and strategies to address the stereocontrol and macrocyclization problems.

The brilliant total synthesis of erythronolide B[102] (**1** in Scheme 15), the aglycon of erythromycin B, by Corey et al. published in 1979, symbolizes the fall of this class of natural products in the face of the newly acquired power of organic synthesis. Additionally, it provides further illustration of the classical strategy for the setting of stereocenters on cyclic templates. The synthesis began with a symmetrical aromatic system that was molded into a fully substituted cyclohexane ring through a short sequence of reactions in which two bromolactonizations played important roles. A crucial Baeyer–Villiger reaction then completed the oxygenated stereocenter at C6 and rendered the cyclic system cleavable to an open chain for further elaboration.

As was the case in many of Corey's syntheses, the total synthesis of erythronolide B was preceded by the invention of a new method, namely the double activation procedure for the formation of macrocyclic lactones employing 2-pyridinethiol esters.[103] This landmark invention allowed the synthesis of

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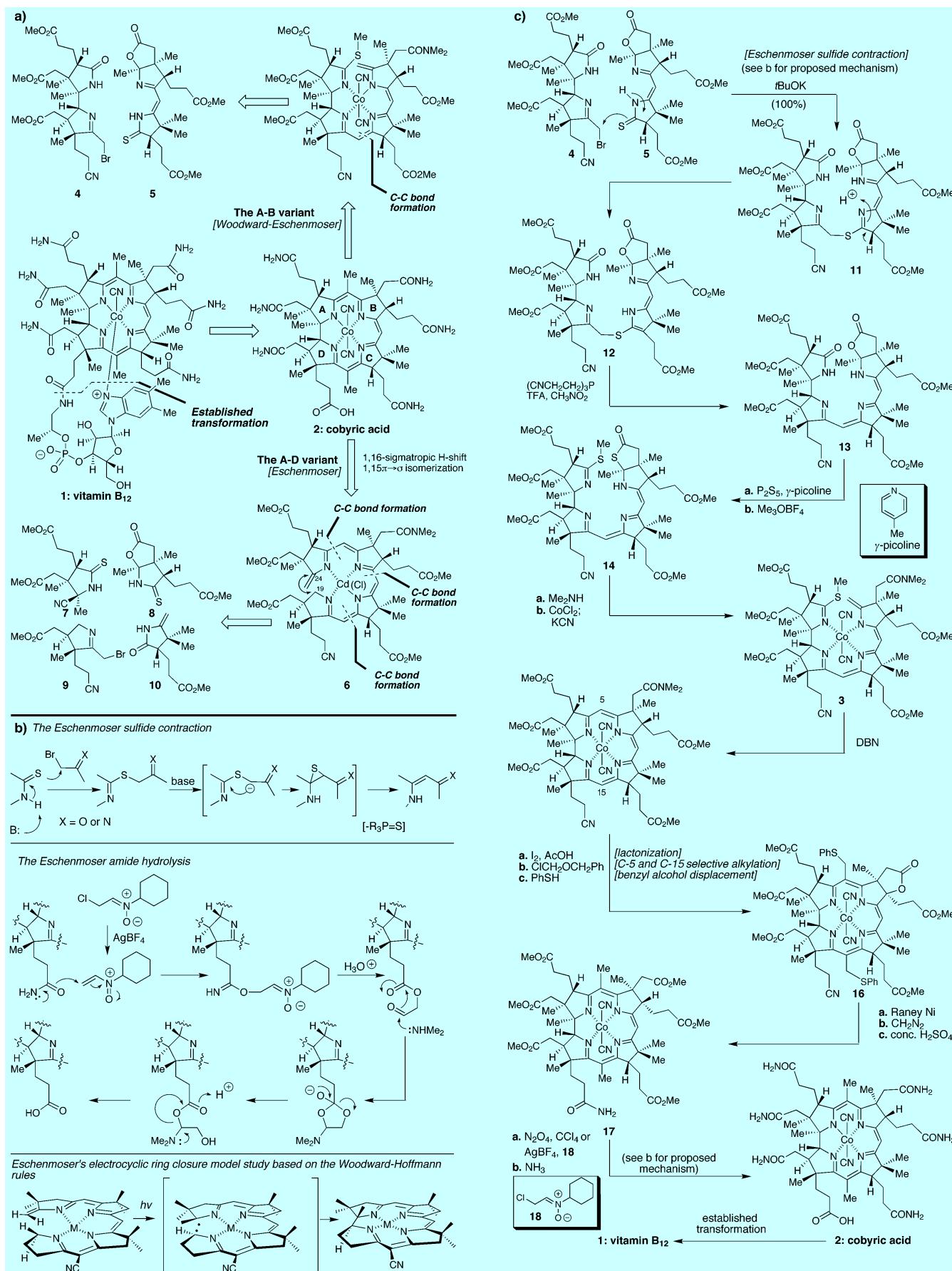
Scheme 14. a) Strategic bond disconnections and retrosynthetic analysis of (−)-vitamin B$_{12}$, b) key synthetic methodologies developed in the course of the total synthesis, c) and final synthetic steps in the Woodward-Eschenmoser total synthesis of vitamin B$_{12}$ (Woodward–Eschenmoser, 1973).[32]

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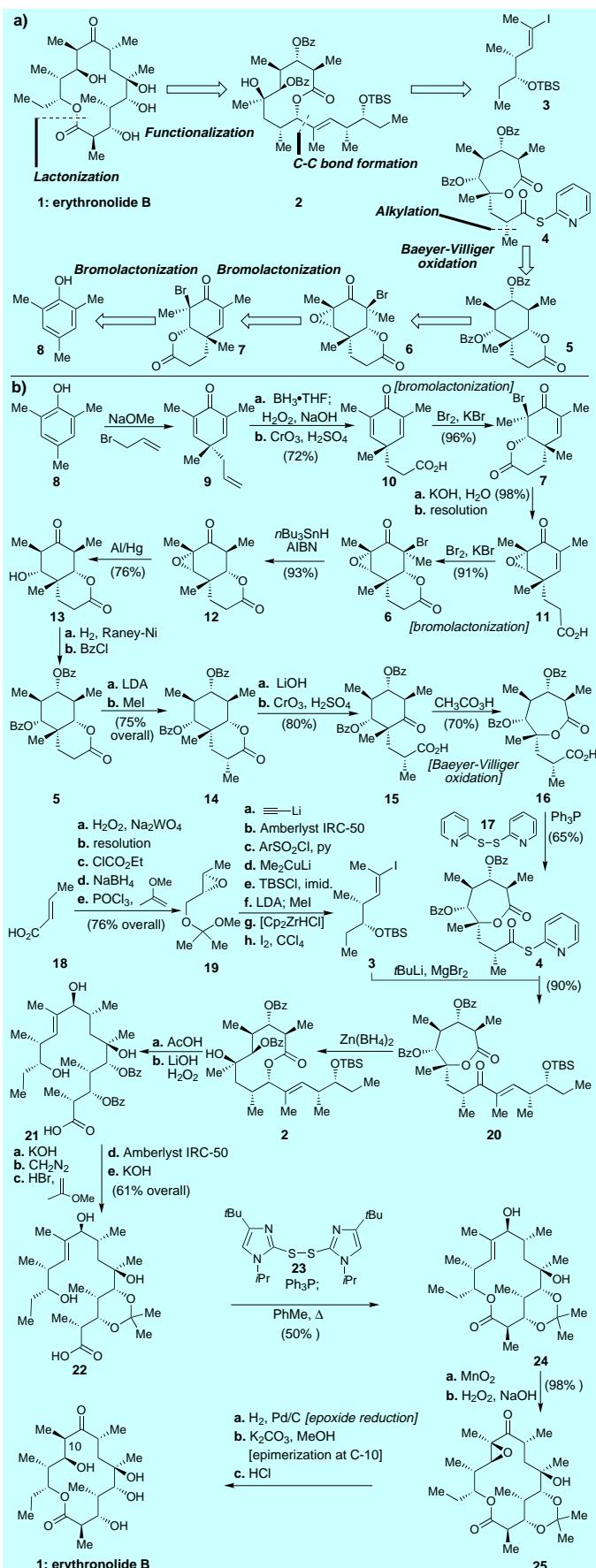
Scheme 15. a) Strategic bond disconnections and retrosynthetic analysis of erythronolide B and b) total synthesis (Corey et al., 1978).[102]

several macrolides including erythronolide B and, most significantly, catalyzed the development of several improvements and other new methods for addressing the macrocyclization problem.[104] Soon to follow Corey's synthesis of erythronolide B was Woodward's total synthesis of erythromycin A.[33]

Monensin (1979, 1980)

Monensin[105] (**1** in Scheme 16), isolated from a strain of *Streptomyces cinamonensis*, is perhaps the most prominent member of the polyether class of antibiotics. Also known as ionophores, these naturally occurring substances have the ability to complex and transport metals across membranes, thus exerting potent antibacterial action.[106, 107] These structures are characterized by varying numbers of tetrahydropyran, tetrahydrofuran, and/or spiroketals. Kishi's total synthesis of monensin,[108] which followed his synthesis of the simpler ionophore lasalocid,[109] represents a milestone achievement in organic synthesis (Scheme 16). This accomplishment demonstrates the importance of convergency in the total synthesis of complex molecules and is one of the first examples of stereoselective total synthesis through acyclic stereocontrol, and elegantly marked the application of the Cram rules within the context of natural-product synthesis. By unraveling the spiroketal moiety of the molecule Kishi was able to adopt an aldol-based strategy to couple monensin's two segments. A series of daring reactions (for example, hydroborations, epoxidations) on acyclic systems with pre-existing stereocenters allowed the construction of the two heavily substituted fragments of the molecule which were then successfully coupled and allowed to fold into the desired spiroketal upon deprotection. Kishi's beautiful synthesis of monensin also provided a demonstration of the importance of 1,3-allylic strain in acyclic conformational preferences, which in turn can be exploited for the purposes of stereocontrolled reactions (for example, epoxidation).

A second total synthesis of monensin was accomplished in 1980 by W. C. Still and his group (Scheme 17).[110] Just as elegant as Kishi's synthesis, the Still total synthesis of monensin demonstrates a masterful application of chelation-controlled additions to the carbonyl function. A judicious choice of optically active starting materials as well as a highly convergent strategy that utilized the same aldol – spiroketalization sequence as in Kishi's synthesis allowed rapid access to monensin's rather complex structure.

Endiandric Acids (1982)

The endiandric acids (Scheme 18) are a fascinating group of natural products discovered in the early 1980s in the Australian plant *Endiandra introsa* (Lauraceae) by Black et al.[111] Their intriguing structures and racemic nature gave rise to the so called "Black hypothesis" for their plant origin, which involved a series of non-enzymatic electrocyclizations from acyclic polyunsaturated precursors (see Scheme 18). Intrigued by these novel structures and Black's hypothesis for their "biogenetic" origin, we directed our attention towards their total synthesis. Two approaches were followed, a

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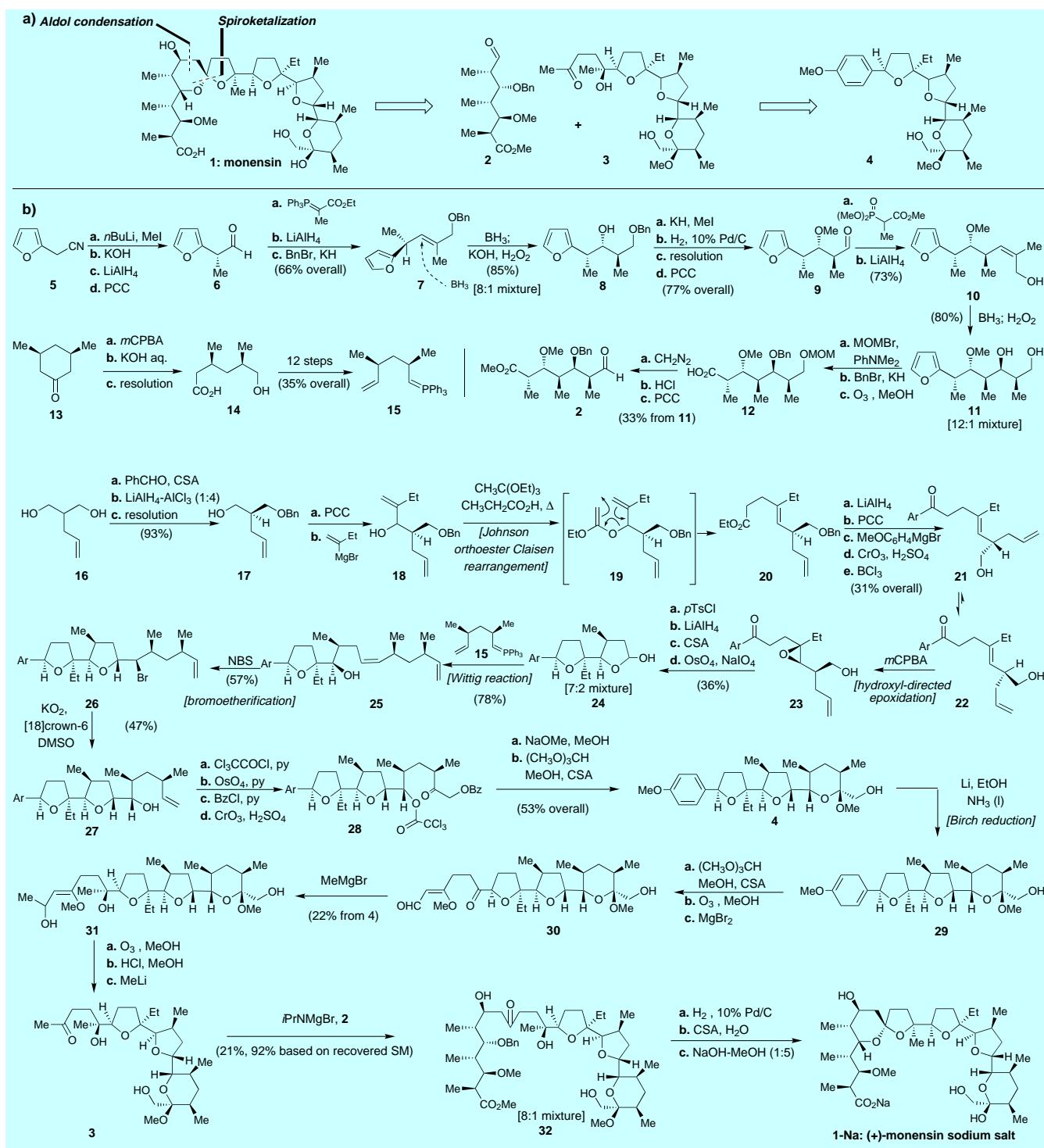
Scheme 16. a) Strategic bond disconnections and retrosynthetic analysis of monensin and b) total synthesis (Kishi et al., 1979).[108]

stepwise (Scheme 19b) and a direct one-step strategy (Scheme 19c). Both strategies involve an 8-π-electron electrocyclization, a 6-π-electron electrocyclization, and a Diels–Alder-type [4+2] cycloaddition reaction to assemble the polycyclic skeletons of endiandric acids. The total synthesis[112] of these architecturally interesting structures demonstrated a number of important principles of organic chemistry and verified Black's hypothesis for their natural origin. In particular, the "one-pot" construction of these target molecules from acyclic precursors from the endiandric acid cascade is remarkable, particularly if one considers the stereospecific formation of no less than four rings and eight stereogenic centers in each final product.

Efrotomycin (1985)

Efrotomycin (**1** in Scheme 20; see p. 67), the most complex member of the elfamycin class of antibiotics[113] that includes
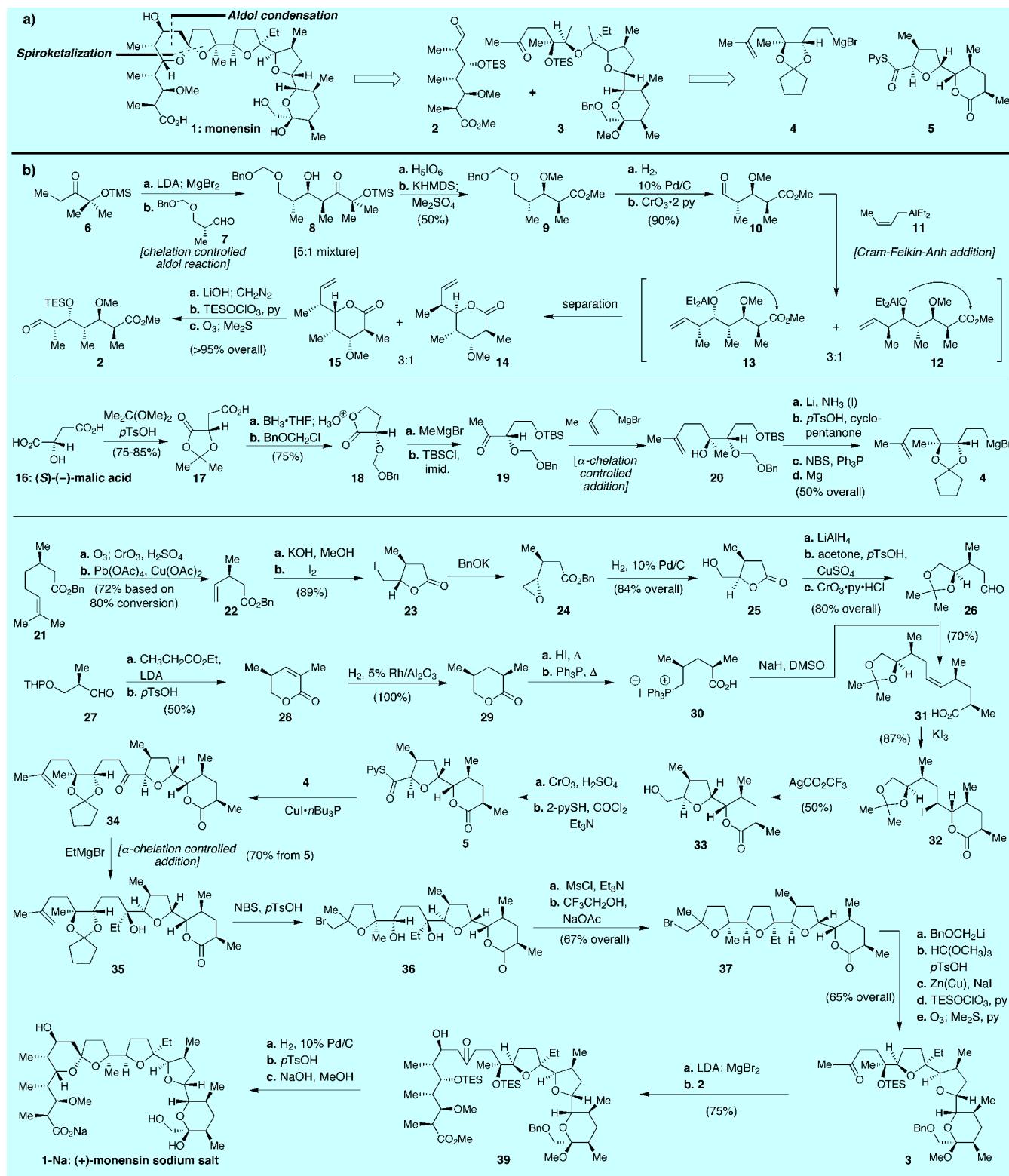
Scheme 17. a) Strategic bond disconnections and retrosynthetic analysis of monensin and b) total synthesis (Still et al., 1980).[110]

aurodox, was isolated from *Nocardia lactamdurans*. [114] Its molecular structure, which contains nineteen stereocenters and seven geometrical elements of stereochemistry, presented considerable challenge to the synthetic chemists of the 1980s, particularly in regard to the oligosaccharide domain and the all-*cis*-tetrasubstituted tetrahydrofuran system. The total syn-

thesis of efrotomycin, accomplished in 1985 in our laboratories,[115] addressed both problems by devising new methodologies for the stereoselective construction of glycosides and tetrahydrofurans. Scheme 20 summarizes this total synthesis in which the two-stage activation procedure for the synthesis of oligosaccharides utilizing thioglycosides and glycosyl

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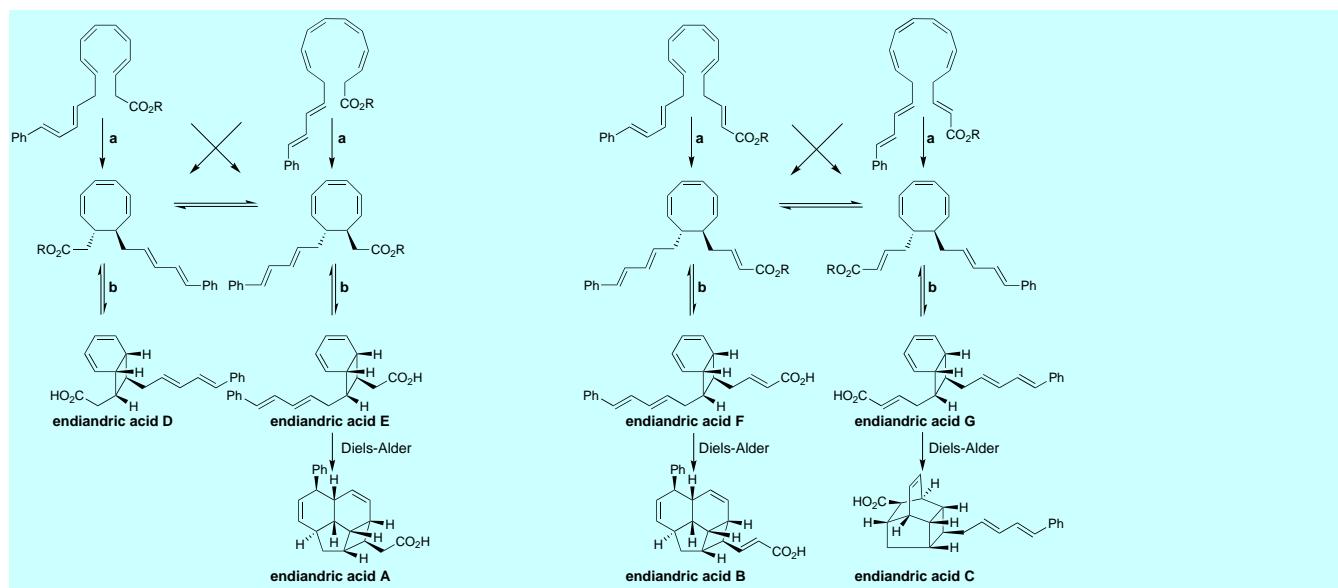
Scheme 18. The endiandric acid cascade (Black et al., R = Me, H). a) Conrotatory 8-π-electron cyclization; b) disrotatory 6-π-electron cyclization.[111]
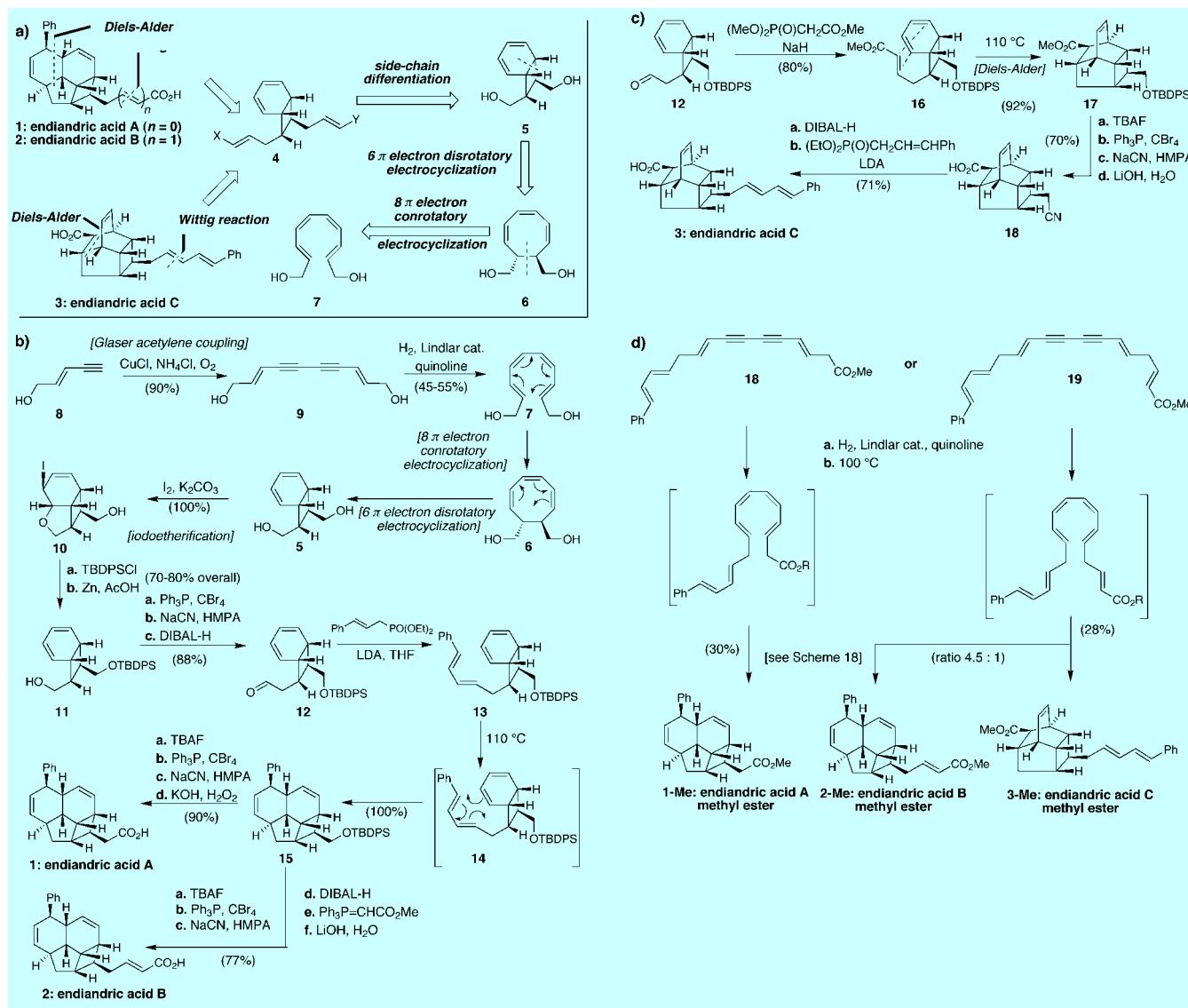
Scheme 19. a) Strategic bond disconnections and retrosynthetic analysis of endiandric acids A – C, b, c) total synthesis, and d) "biomimetic" synthesis of endiandric acid methyl esters A – C (Nicolaou et al., 1982).[112]

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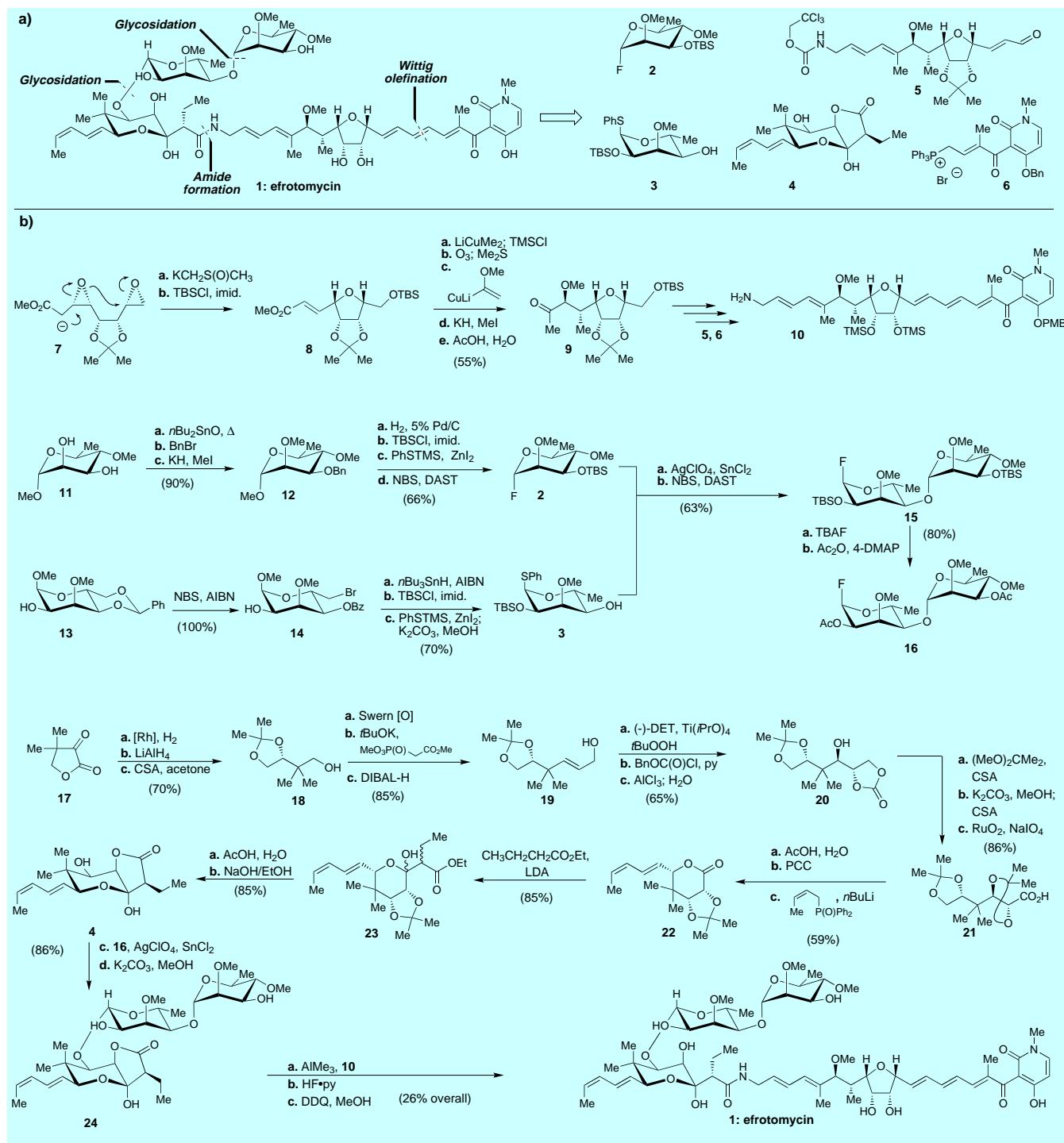
Scheme 20. a) Strategic bond disconnections and retrosynthetic analysis of efrotomycin and b) total synthesis (Nicolaou et al., 1985).[115]

fluorides[116] as well as the base-induced zip-type diepoxide opening were highlighted as powerful methods for organic synthesis. Numerous applications and extensions of these synthetic technologies have since followed.[117]

Okadaic acid (1986)

Okadaic acid[118] (1 in Scheme 21) is a marine toxin isolated from *Halichondria Okadai*. Besides its shellfish toxicity,

okadaic acid exhibits potent inhibition of certain phosphatases and is a strong tumor promotor. With its three spiroketal moieties and seventeen stereogenic centers, the molecule's polycyclic structure presented a serious challenge to synthetic chemistry. The first total synthesis of okadaic acid was achieved in 1984 by the Isobe group in Japan[119] and was followed by those of Forsyth[120] and Ley.[121] The Isobe synthesis of okadaic acid, summarized in Scheme 21, highlights the use of sulfonyl-stabilized carbanions in synthesis, the

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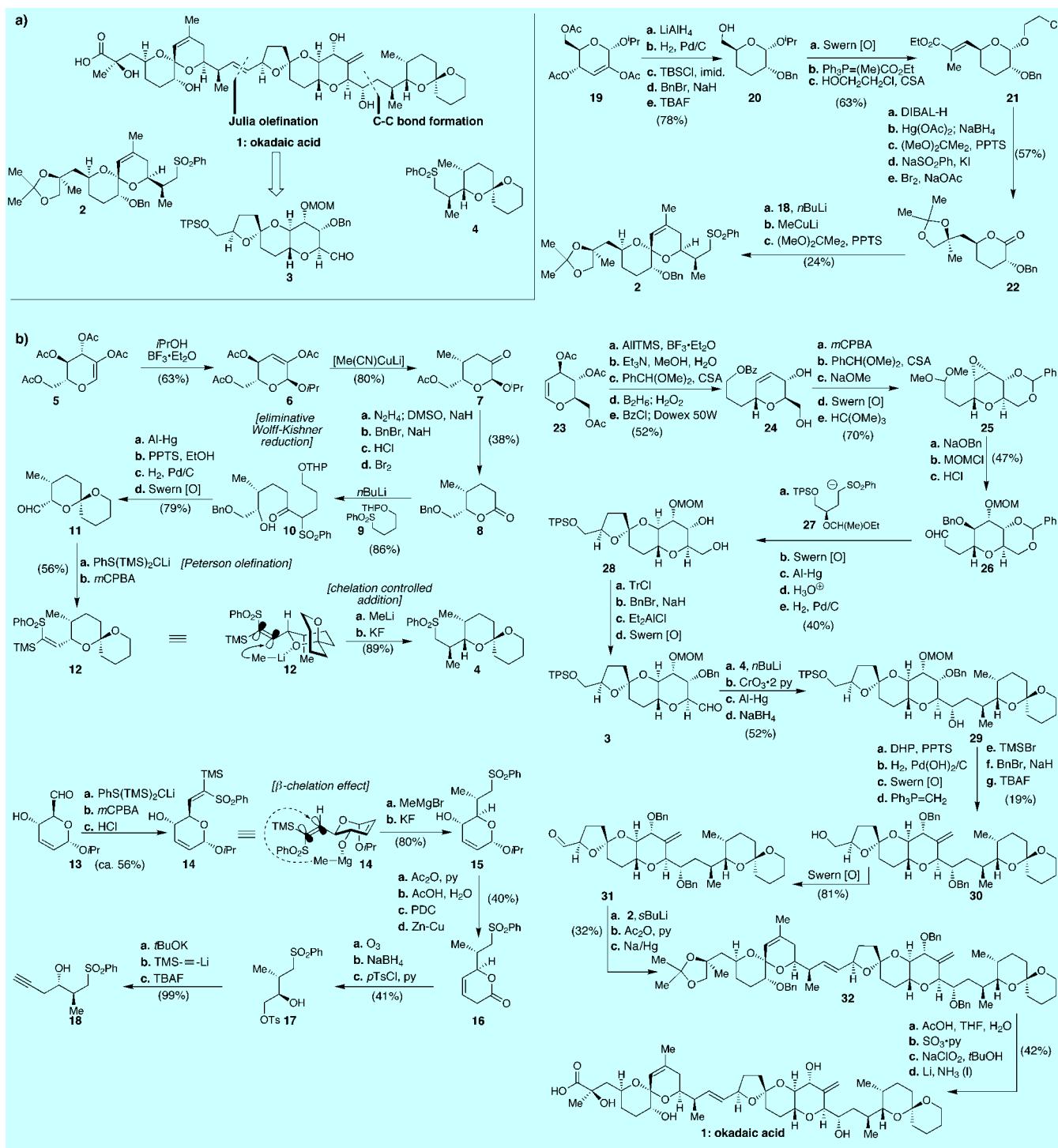
Scheme 21. a) Strategic bond disconnections and retrosynthetic analysis of okadaic acid and b) total synthesis (Isobe et al., 1986).[119]

control of stereochemistry through chelation, and the power of the anomeric effect to exert stereocontrol in spiroketal formation.

Amphotericin B (1987)

The polyene macrolide family of natural products is a subgroup of the macrolide class, which poses formidable challenges to synthetic organic chemistry. Among them,

amphotericin B[122] (**1** in Scheme 22), isolated from *Strepto-myces nodosus*, occupies a high position as a consequence of its complexity and medical importance as a widely used antifungal agent. Its total synthesis[123] in 1987 by our group represented the first breakthrough within this class of complex molecules. This total synthesis featured the recognition of subtle symmetry elements within the target molecule that allowed the utilization of the same starting material to construct two, seemingly unrelated, intermediates and the

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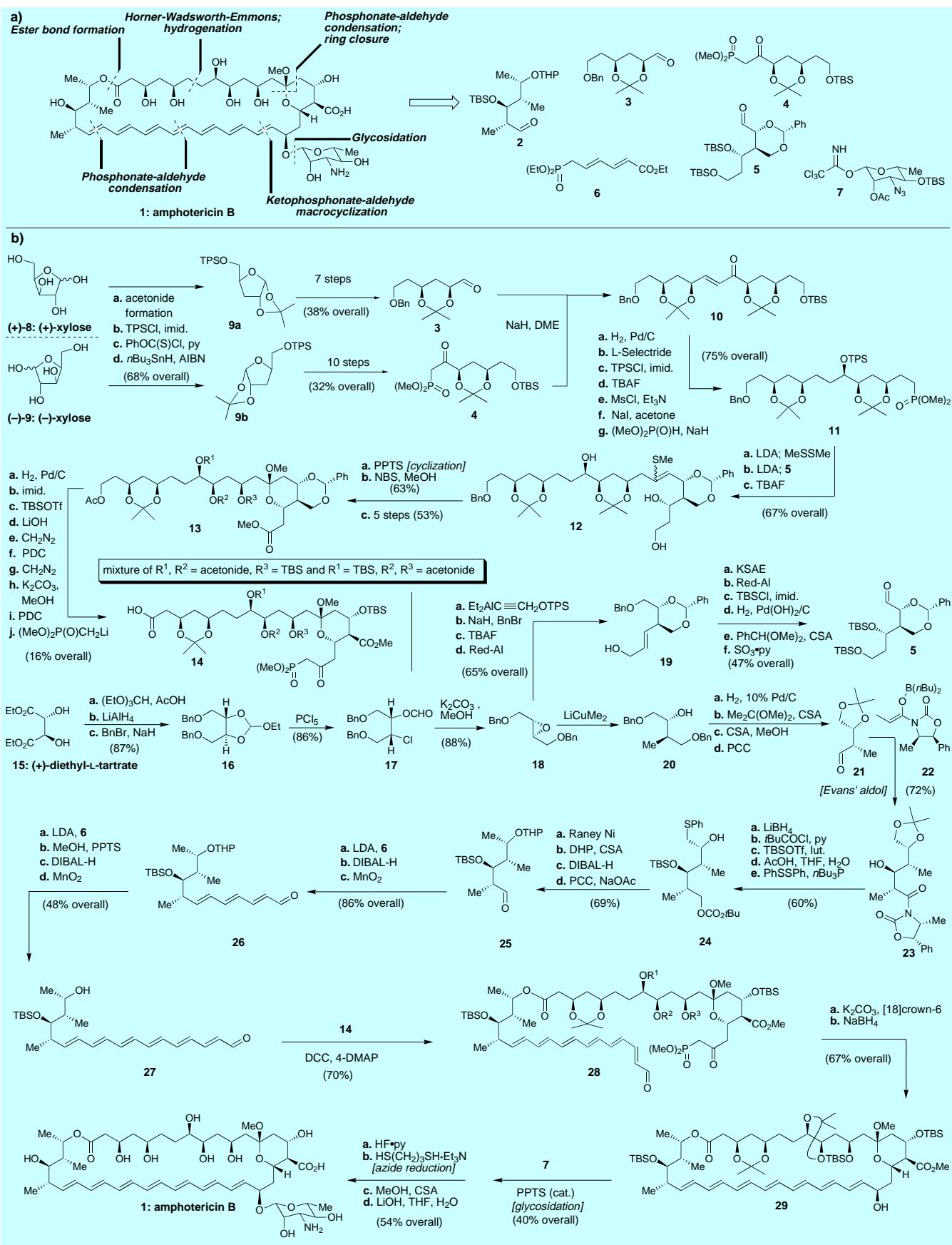
Scheme 22. a) Strategic bond disconnections and retrosynthetic analysis of amphotericin B and b) total synthesis (Nicolaou et al., 1987).[123]

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employment of the then newly discovered Sharpless asymmetric epoxidation reaction[124] to stereoselectively construct the 1,3-diol systems.

The Horner-Wadsworth-Emmons process[125] emerged as the most valuable reaction of the synthesis, having been utilized five times to construct carbon–carbon double bonds. Particularly striking was the application of an intramolecular ketophosphonate–aldehyde condensation to construct the 38-membered ring of amphotericin B. A further, notable feature within this total synthesis is the strategy through which the carbohydrate moiety was installed stereoselectively on a derivative of amphoteronolide B to construct the challenging β-1,2-*cis*-glycoside bond of the target molecule. Important in this field is also Masamune's elegant synthesis of 19-dehydroamphoteronolide B.[126]

Ginkgolide B (1988)

Ginkgolide B (**1** in Scheme 23) is a highly functionalized natural substance isolated from the *Ginkgo biloba* tree, widely known for its medicinal properties.[127] The structural elucidation of ginkgolide B in 1967 was a major accomplishment of the Nakanishi group.[128] Its total synthesis by the Corey group in 1988[129] stands as a landmark achievement in organic synthesis. Despite its relatively small size, ginkgolide B proved to be stubborn in its defiance to chemical synthesis, primarily because of its highly unusual bond connectivity. Among its most striking structural features are the *tert*-butyl group which occurs rather rarely in nature, the eleven stereogenic centers of which two are quaternary, and its six five-membered rings. The Corey synthesis of ginkgolide B abounds with brilliant strategies and tactics, but most impressive is, perhaps, the intramolecular [2+2] ketene cycloaddition reaction, which contributed substantially to the construction of the required carbon framework by delivering two of the most challenging rings.

Palitoxin (1989, 1994)

Isolated from soft corals of the *Palythoa* genus, palitoxin (**1** in Scheme 24) is endowed with toxic properties exceeded only by a few other substances known to man.[130] Both its structural elucidation and total synthesis posed formidable challenges to chemists. While the gross structural elucidation of palitoxin was reported independently by the groups of Hirata[131] and Moore[132] in 1981, its total synthesis had to await several more years of intense efforts. Finally, after heroic efforts from Kishi and his group the synthesis of palitoxin carboxylic acid was published in 1989[133] and that of palitoxin itself in 1994[134] (see Scheme 24). The synthesis of palitoxin holds a special place in the history of total synthesis in that palitoxin is the largest secondary metabolite to be synthesized in the laboratory, both in terms of molecular weight and number of stereocenters. Most importantly, this mammoth endeavor led to the discovery and development of a number of useful synthetic reactions. Amongst them are the improvement of the NiCl$_2$/CrCl$_2$-mediated coupling reaction
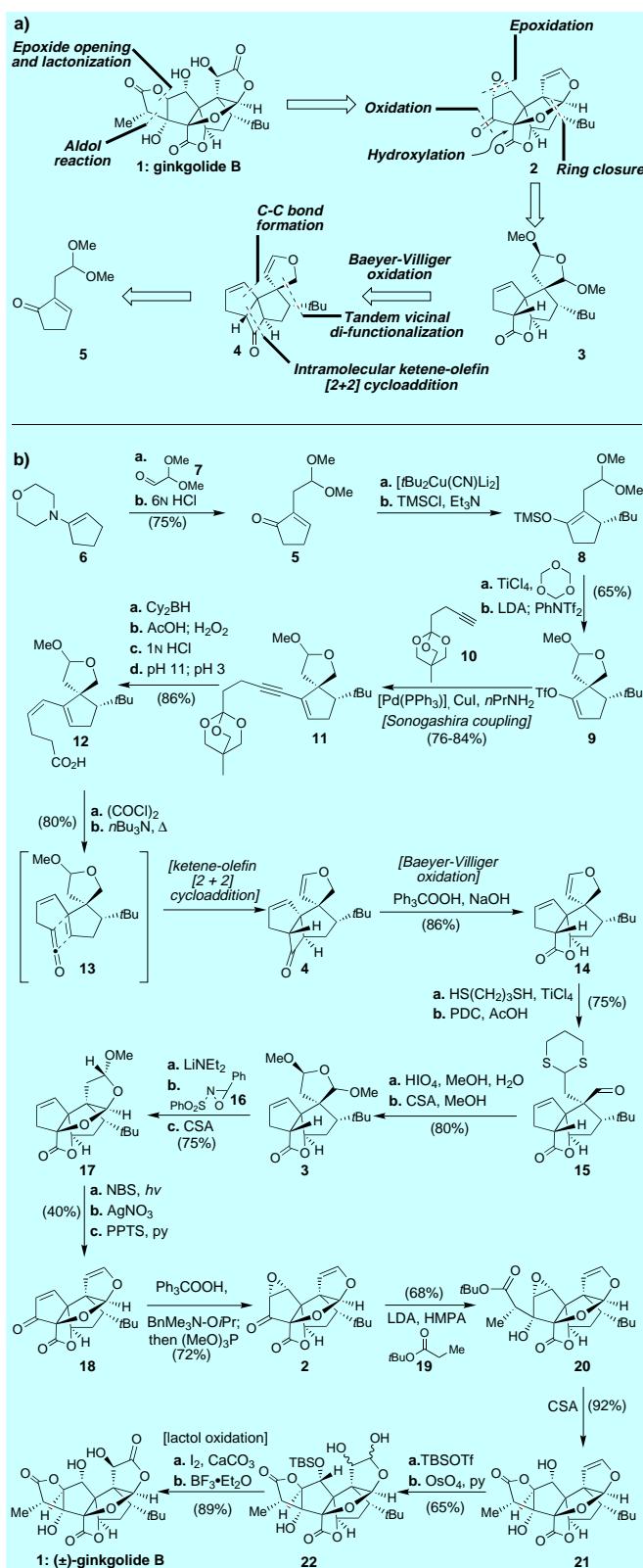

Scheme 23. a) Strategic bond disconnections and retrosynthetic analysis of ginkgolide B and b) total synthesis (Corey et al., 1988).[129]

between iodo-olefins and aldehydes, a modified, refined method for the Suzuki palladium-catalyzed coupling reaction leading to conjugated dienes, and a new synthesis of *N*-acyl ureas.
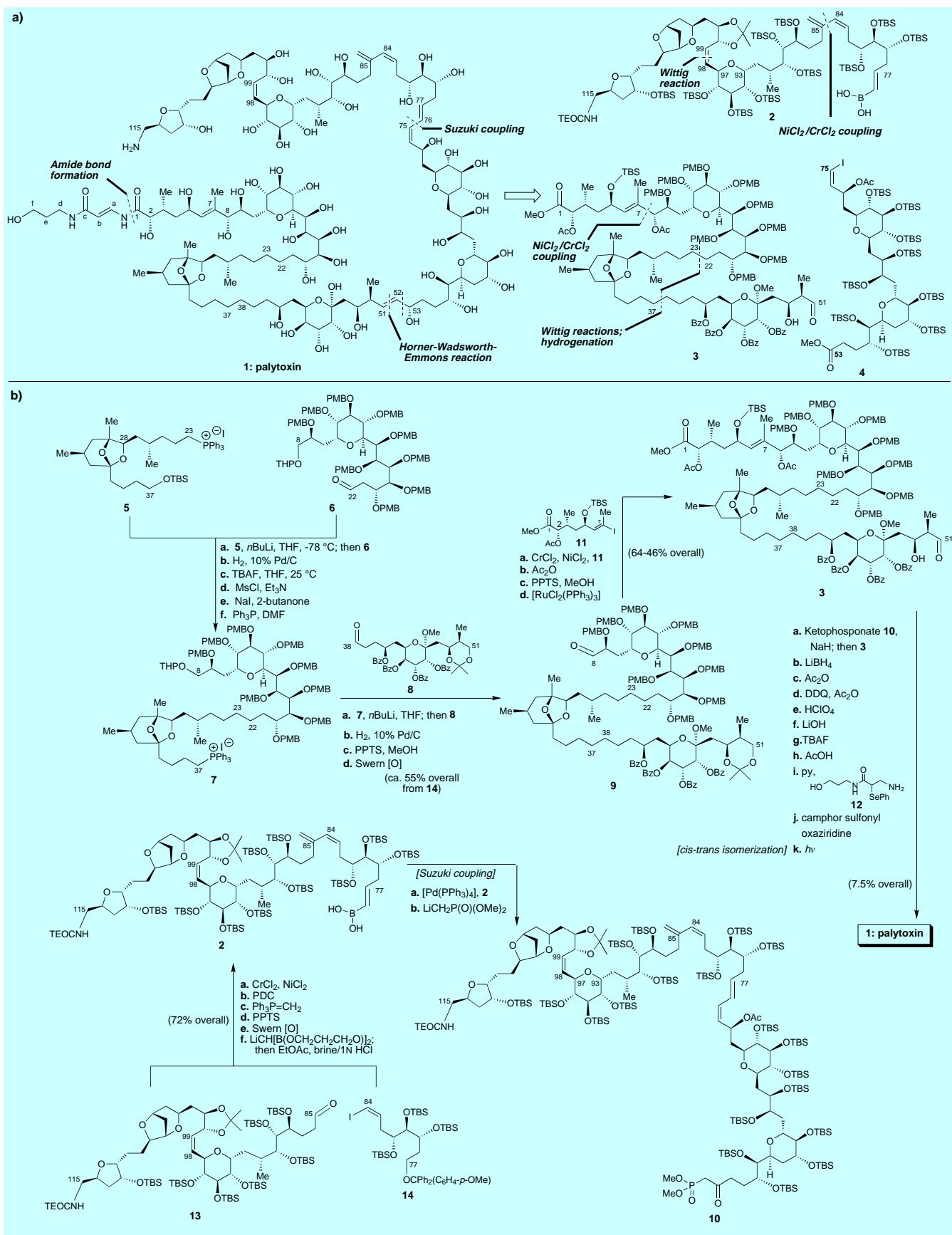
Scheme 24. a) Strategic bond disconnections and retrosynthetic analysis of palytoxin and b) highlights of the total synthesis (Kishi et al. 1989, 1994).[133, 134]

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Cytovaricin (1990)

Cytovaricin (**1** in Scheme 25) is a 22-membered macrolide, isolated from *Streptomyces diastatochromogenes* in 1981,[135]

which is endowed with impressive antineoplastic activity and complex molecular architecture. Possessing seventeen stereogenic centers on its main framework, a spiroketal, and a glycoside moiety with four additional stereocenters, cytovar-
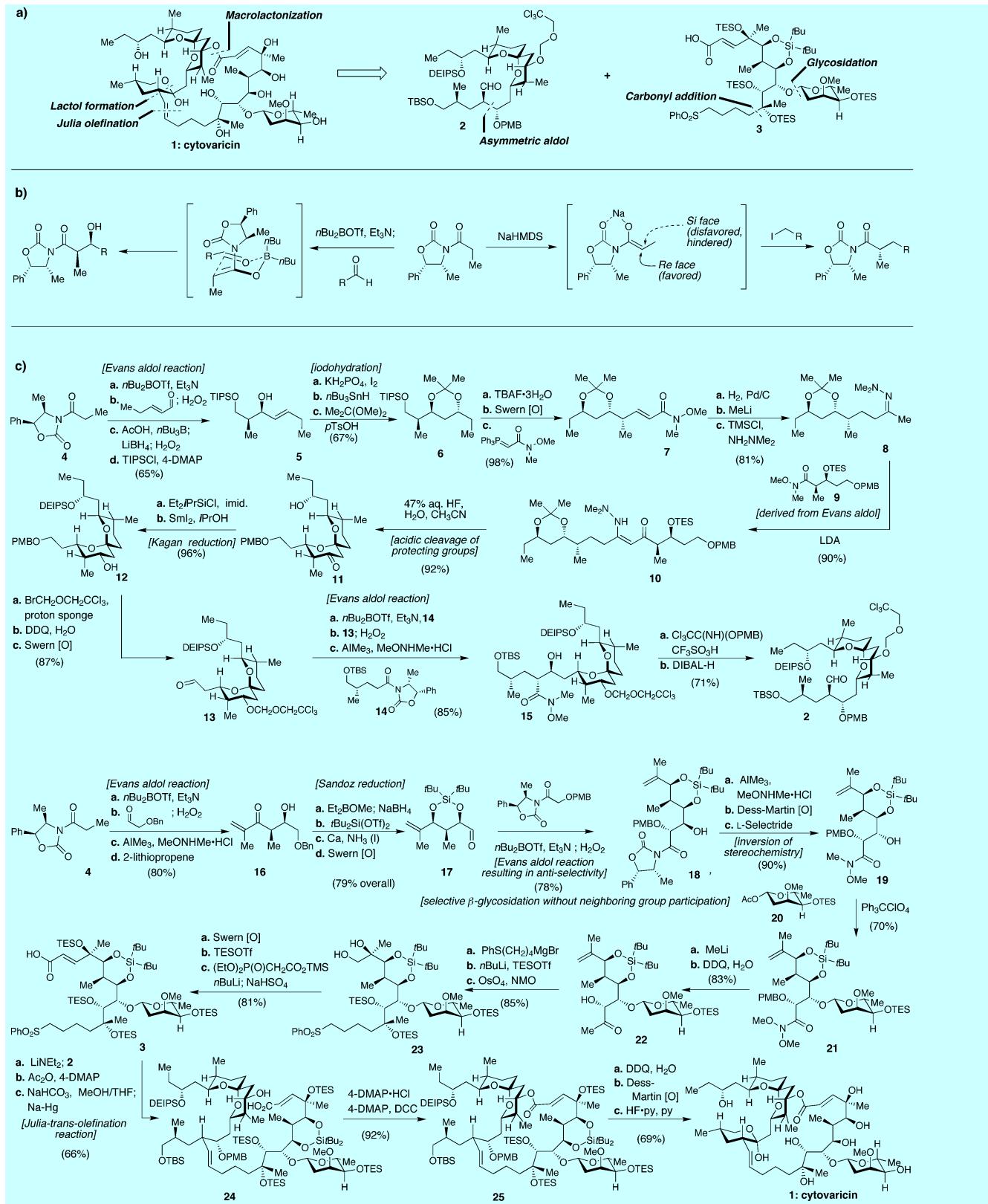
Scheme 25. a) Strategic bond disconnections and retrosynthetic analysis of cytovaricin, b) key asymmetric alkylation and aldol reactions, and c) outline of the total synthesis (Evans et al., 1990).[137]

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icin presented a considerable challenge to synthetic chemistry in the 1980s. Its structural elucidation by X-ray crystallographic analysis in 1983[136] opened an opportunity for Evans et al. to apply their elegant alkylation and aldol methodology for acyclic stereoselection to the solution of the cytovaricin problem. Indeed, by 1990 the group reported a beautiful total synthesis[137] that clearly demonstrated the new concepts of stereochemical control by acyclic stereoselection as opposed to the classical methods applied previously to solve such problems. It is instructive to compare this synthesis to the cyclic-template strategy used by Corey,[102] Woodward,[33] and Stork[138] to achieve stereochemical control in their syntheses of the erythromycin macrolide framework. This impressive use of acyclic stereocontrol through the use of the Evans chiral oxazolidone certainly propelled the area of polyketide synthesis, a class of compounds that are rather readily accessible synthetically by today's standards.

Calicheamicin γ_1^I (1992)

The arrival of calicheamicin $\gamma_1^{I\,[139]}$ (**1** in Scheme 26) and its relatives, collectively known as the enediyne anticancer antibiotics,[140] on the scene in the 1980s presented an entirely new challenge to synthetic organic chemistry. Isolated from *Micromonospora echinospora ssp* calichensis, this fascinating natural product provided a unique opportunity for discovery and invention in the areas of chemistry, biology, and medicine. Its novel molecular structure is responsible for its powerful biological properties, which include strong binding to duplex DNA, double-strand cleavage of the genetic material by formation of a benzenoid diradical, and—as a consequence—potent antitumor and antibiotic activity.

The structure of calicheamicin γ_1^I is comprised of a carbohydrate domain and an enediyne core carrying a trisulfide moiety that acts as a triggering device for the cascade of events which leads, via a Bergman cycloaromatization,[141] to the diradical species and DNA rupture. The oligosaccharide domain of calicheamicin γ_1^I is endowed with high affinity for certain DNA sequences, and acts as the delivery system of the molecule to its biological target. The highly strained 10-membered enediyne system, the novel oligosaccharide fragment, and the trisulfide unit are but some of the unusual and challenging features of calicheamicin γ_1^I. Even more challenging, of course, was the chartering of the proper sequence for assembling all these functionalities into the final structure. Two groups rose to the challenge, ours (1992)[142] and that of S. J. Danishefsky (1994).[143]

Notable features of our total synthesis of calicheamicin γ_1^I (Scheme 26) are the installment of the sulfur atom in the carbohydrate domain through a stereospecific [3,3]-sigmatropic rearrangement and the [3+2] olefin–nitrile oxide cycloaddition reaction employed in the construction of the enediyne core. That a molecule of such complexity could be assembled in the laboratory in less than five years after its structural elucidation in 1987 is an accurate reflection of the high level of the state-of-the-art in the early 1990s. Just as impressive is Danishefsky's synthesis of calicheamicin, which can be found in the original literature.[143]

Strychnine (1993)

Although (−)-strychnine had succumbed to the ingenuity of Woodward in 1954 (see Scheme 4) it can still be considered a target of choice to demonstrate the application of new reactions and novel strategies by virtue of its abundant stereochemical features densely packed in a heptacyclic framework. Almost 40 years after Woodward's seminal synthesis, Overman's synthesis of strychnine[58] (Scheme 27; see p. 76) stands as a testimony to the evolution of organic synthesis. Indeed, powerful palladium-mediated reactions were used to expedite the assembly of the crucial intermediate **13** (Scheme 27) in a stereospecific fashion, thereby setting the stage for the key tandem aza-Cope rearrangement and Mannich reaction. This tandem reaction proved to be particularly efficient and well-suited to afford an advanced tricyclic system with concomitant formation of the quaternary center stereospecifically, under mild conditions, and in nearly quantitative yield. The sophisticated sequence of reactions which ultimately led to Overman's (−)-strychnine synthesis deserves special mention for its elegance.

Rapamycin (1993)

Rapamycin (**1** in Scheme 28; see p. 77) is an important molecule within the field of immunosuppression that was first isolated in 1975[144] from *Streptomyces hygroscopicus*, a bacterial strain found in soil collected in Rapa Nui (Easter Island), and structurally elucidated in 1978.[145] Its potent immunosuppressive properties are reminiscent of those of cyclosporin and FK506, whose biological and medical importance, particularly in the field of organ transplants, became evident in the 1980s.[146] Although the structures of rapamycin and FK506 possess striking similarities, the former is considerably more complex and attracted serious attention from the synthetic chemists in the late 1980s and early 1990s. By 1995 there were four total syntheses of rapamycin,[147–150] the first being reported from this group in 1993 (Scheme 28).[147] This asymmetric synthesis of rapamycin is an example of high convergency and acyclic stereoselection, and is perhaps known best for the way in which the macrocyclic ring was formed. A palladium-catalyzed reaction based on Stille's chemistry allowed a "stitching cyclization" process to proceed, to furnish the required conjugated triene system concurrently as it formed the 29-membered ring of the target molecule.[151]

Taxol (1994)

Taxol (**1** in Scheme 29; see p. 78), one of the most celebrated natural products, was isolated from the Pacific yew tree and its structure was reported in 1971.[152] Its arduous journey to the clinic took more than 20 years, being approved by the Food and Drug Administration (FDA) in 1992 for the treatment of ovarian cancer.[153] Synthetic chemists were challenged for more than two decades as taxol's complex molecular architecture resisted multiple strategies toward its construction in the laboratory. Finally, in 1994, two essentially simultaneous reports[154, 155] described two distinctly different

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total syntheses of taxol. These first two syntheses, by our group[154] and that of Holton,[155] were followed by those of Danishefsky,[156] Wender,[157] Mukaiyama,[158] and Kuwajima.[159] All these syntheses, which are characterized by novel strategies and brave tactics, contributed enormously to the advancement of total synthesis and enabled investigations in biology and medicine.

Amongst the most notable features of our total synthesis of taxol (Scheme 29) are the boron-mediated Diels–Alder reaction to construct the highly functionalized C ring, the application of the Shapiro and McMurry coupling reactions, and the selective manner in which the oxygen functionalities were installed onto the 8-membered ring of the molecule. Because of the great drama associated with cancer, this and the other syntheses of taxol received headliner publicity. The art and science of total synthesis was once again brought to the attention of the general public.

Zaragozic Acid (1994)

A new natural product with unprecedented molecular architecture often gives impetus to synthetic endeavors directed at its total synthesis. Such was the case with zaragozic acid A (**1** in Scheme 30; see p. 79) whose structure was released essentially simultaneously in 1992 by groups from Merck[160] and Glaxo[161] (the latter naming the compound squalestatin S 1).[162] Isolated from a species of fungi, zaragozic acid A exhibits impressive in vitro and in vivo inhibition of cholesterol biosynthesis by binding to squalene synthase.[163] Zaragozic acid A, like its many relatives, possesses an unusual tricarboxylic acid core, whose highly oxygenated nature added to its novelty and complexity as a synthetic target. The distinguishing features of our synthesis[164] of zaragozic acid A (Scheme 30) include the utilization of the Sharpless asymmetric dihydroxylation reaction[165] to install the first two oxygen-bearing stereocenters onto a complex prochiral diene system and a multi-step, acid-catalyzed rearrangement to secure the zaragozic acid skeleton.

The synthesis of zaragozic acid was also accomplished and reported at approximately the same time as ours by the groups of Carreira (zaragozic acid C)[166] and Evans (zaragozic acid C).[167] In addition, Heathcock et al.[168] reported another total synthesis of zaragozic acid A in 1996.

Swinholide A (1994)

Swinholide A (**1** in Scheme 31; see p. 80), a marine natural product with antifungal and antineoplastic activity, was originally isolated from the Red Sea sponge *Theonella swinhoei*.[169a] Its structure was fully established in the late 1980s by X-ray cystallographic analysis.[169b] The structure of swinholide A has C_2 symmetry and is distinguished by two conjugated diene systems, two trisubstituted tetrahydropyran systems and two disubstituted dihydropyran systems, a 44-membered diolide ring, and thirty stereogenic centers. Its challenging molecular architecture coupled with its scarcity
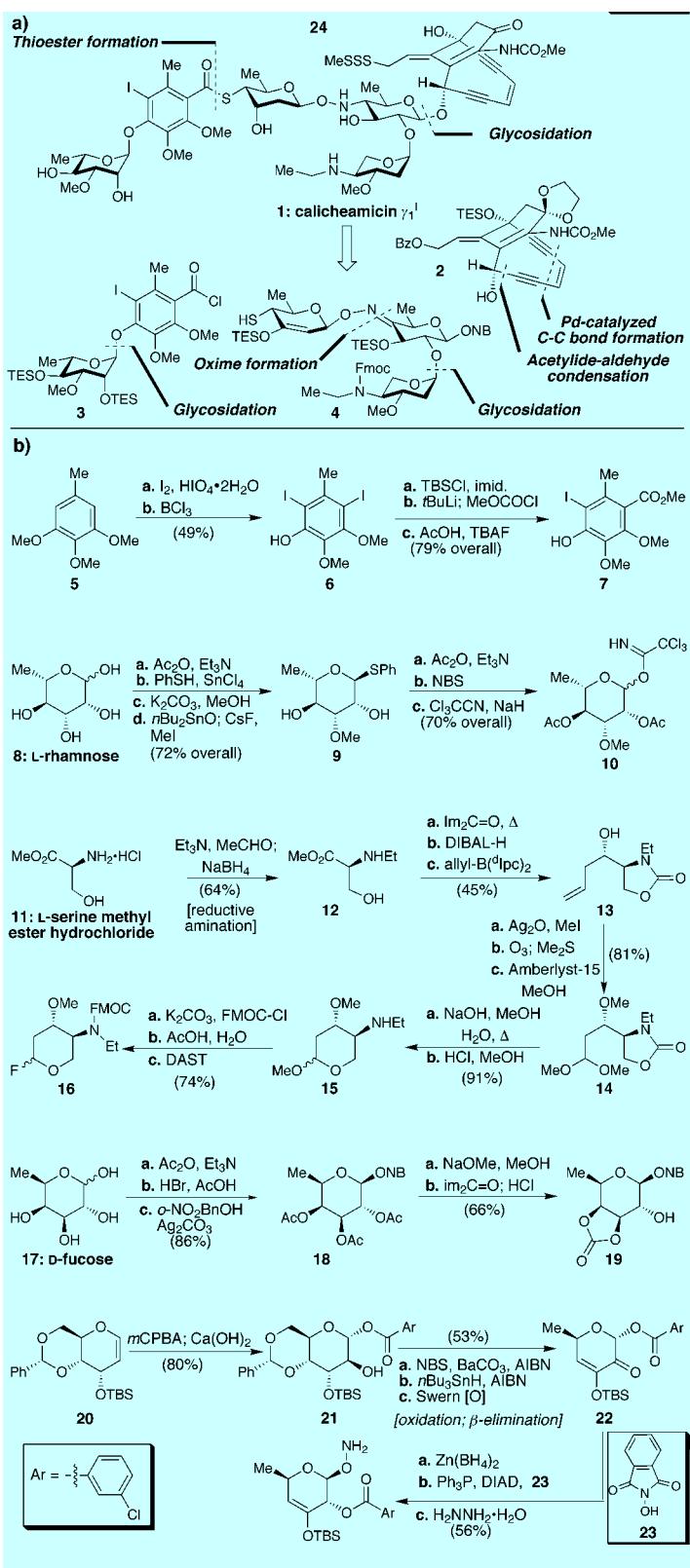
Scheme 26. a) Strategic bond disconnections and retrosynthetic analysis of calicheamicin γ_1^I and b) total synthesis (Nicolaou et al., 1992).[142]

and biological action prompted several groups to undertake synthetic studies towards its total synthesis. Two laboratories, that of I. Paterson at Cambridge[170] and ours[171] have succeeded in the task.

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Scheme 26. (Continued)

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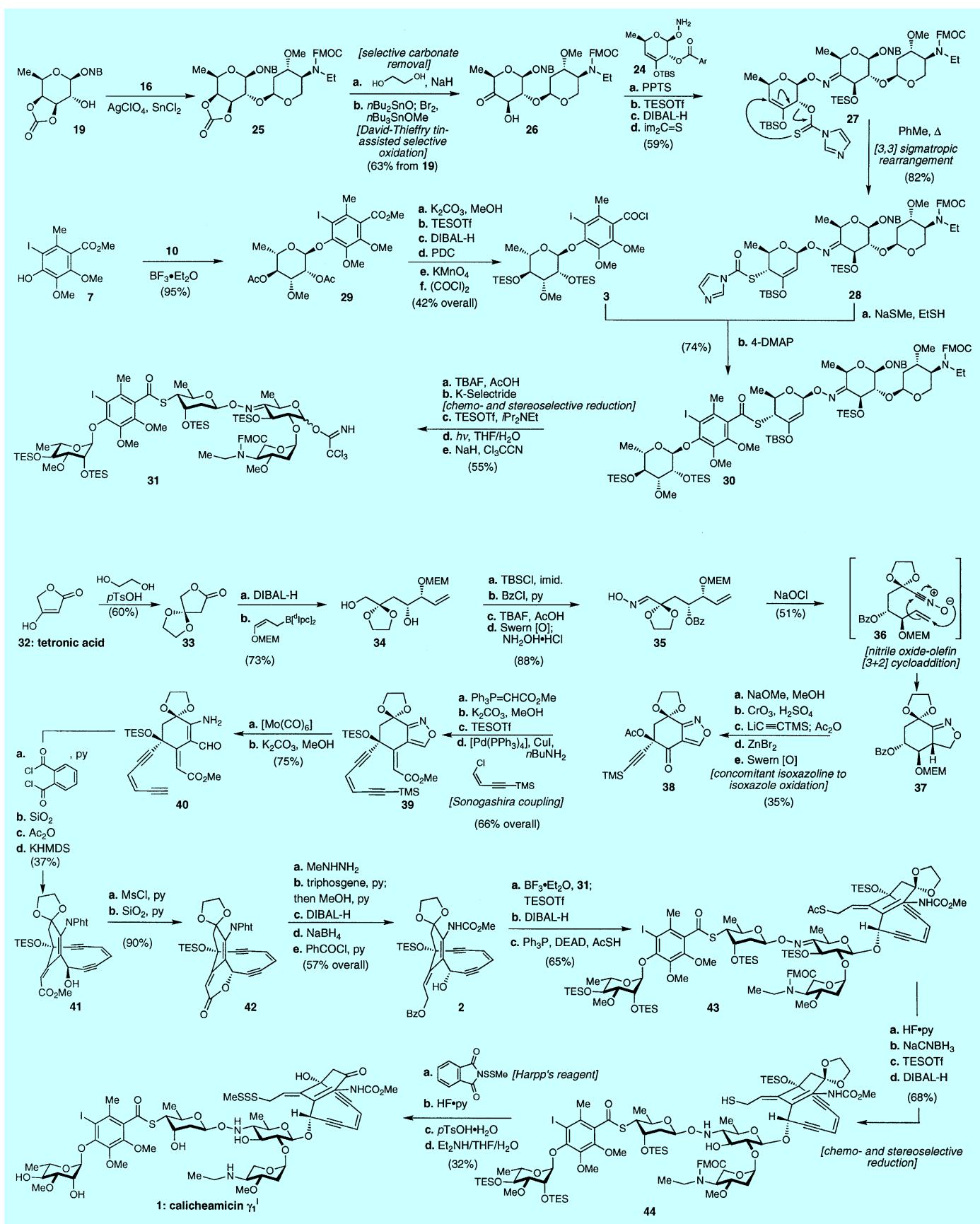
Paterson's total synthesis,[170] shown in Scheme 31 (see p. 80), came first and was accompanied by the development and application of a number of various types of asymmetric boron-mediated aldol reactions to form key C–C bonds. Indeed, this new aldol methodology[172] was utilized to install three contiguous chiral centers in two steps with high diastereoselectivity (**9** → **12** in Scheme 31), and represents a most welcomed progress in acyclic stereocontrol. Our total synthesis of swinholide A[171] (Scheme 32; see p. 81) featured two relatively new, at the time, methods for C–C bond construction in complex-molecule synthesis, namely the Ghosez cyclization[173] to form α,β-unsaturated β-lactones from orthoester sulfones and epoxides, and the dithiane-stabilized anion opening of cyclic sulfates.[174] The macro-lactonization was performed by the Yamaguchi reagent[175] in both strategies. Both total syntheses are highly convergent and demonstrated the power of the art in acyclic stereo-selection and large-ring construction and stand as important achievements in the field of macrolide synthesis.

Brevetoxin B (1995)

Brevetoxin B (**1** in Scheme 33; see p. 82), an active principle of the poisonous waters associated with the "red tide" phenomena,[176] was the first structure of its kind to be

elucidated (1981).[177] The beauty of brevetoxin's molecular architecture, which accommodates eleven rings and twenty-three stereogenic centers, attracted immediate attention from the synthetic community. This neurotoxin, whose mechanism of action involves the opening of sodium channels, shows remarkable regularity in its structure. Thus, all rings are *trans*-fused and each contains an oxygen atom. All ring oxygens are separated by a C–C bond and each is flanked by two *syn*-arranged hydrogen or methyl substituents—except for the first which carries a carbonyl to its "left" and the last which is flanked by two *anti*-oriented hydrogens. With its imposing structure, brevetoxin B presented a formidable and daunting problem to synthetic organic chemistry. Not only did new methods need to be developed for the construction of the various cyclic ether moieties residing within its structure, but, most importantly, the "right strategy" had to be devised for the global assembly of the molecule.

After several abortive attempts, brevetoxin B was finally conquered, and the total synthesis was reported in 1995 from these laboratories (Scheme 33).[178] Along with the accomplishment of the total synthesis, this twelve-year odyssey[179] yielded a plethora of new synthetic technologies for the construction of cyclic ethers of various sizes. Prominent among them are (see Scheme 33b): a) the regio- and stereo-selective routes to tetrahydrofuran, tetrahydropyran, and
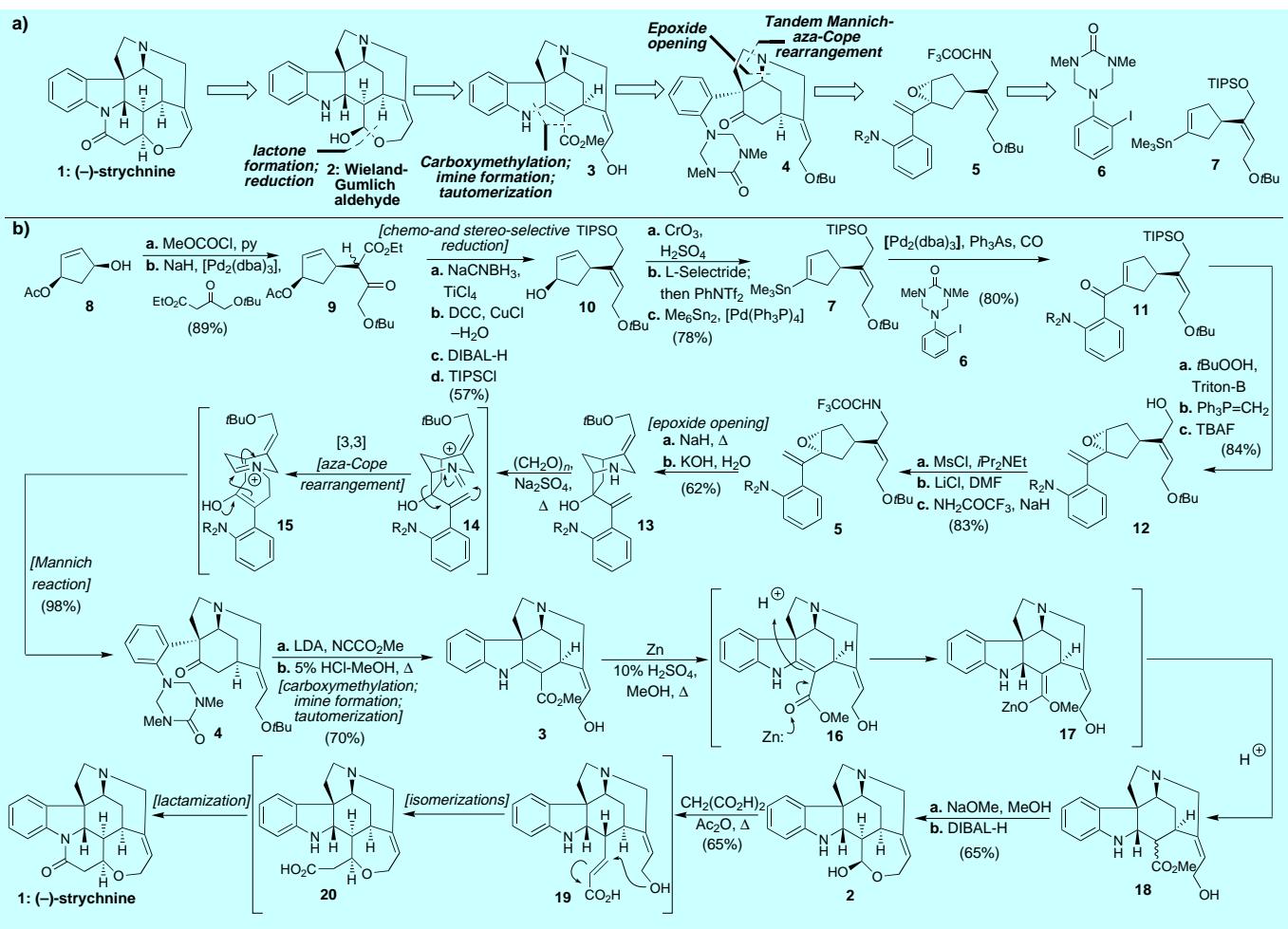
Scheme 27. a) Strategic bond disconnections and retrosynthetic analysis of (−)-strychnine and b) total synthesis (Overman et al., 1993).[58]

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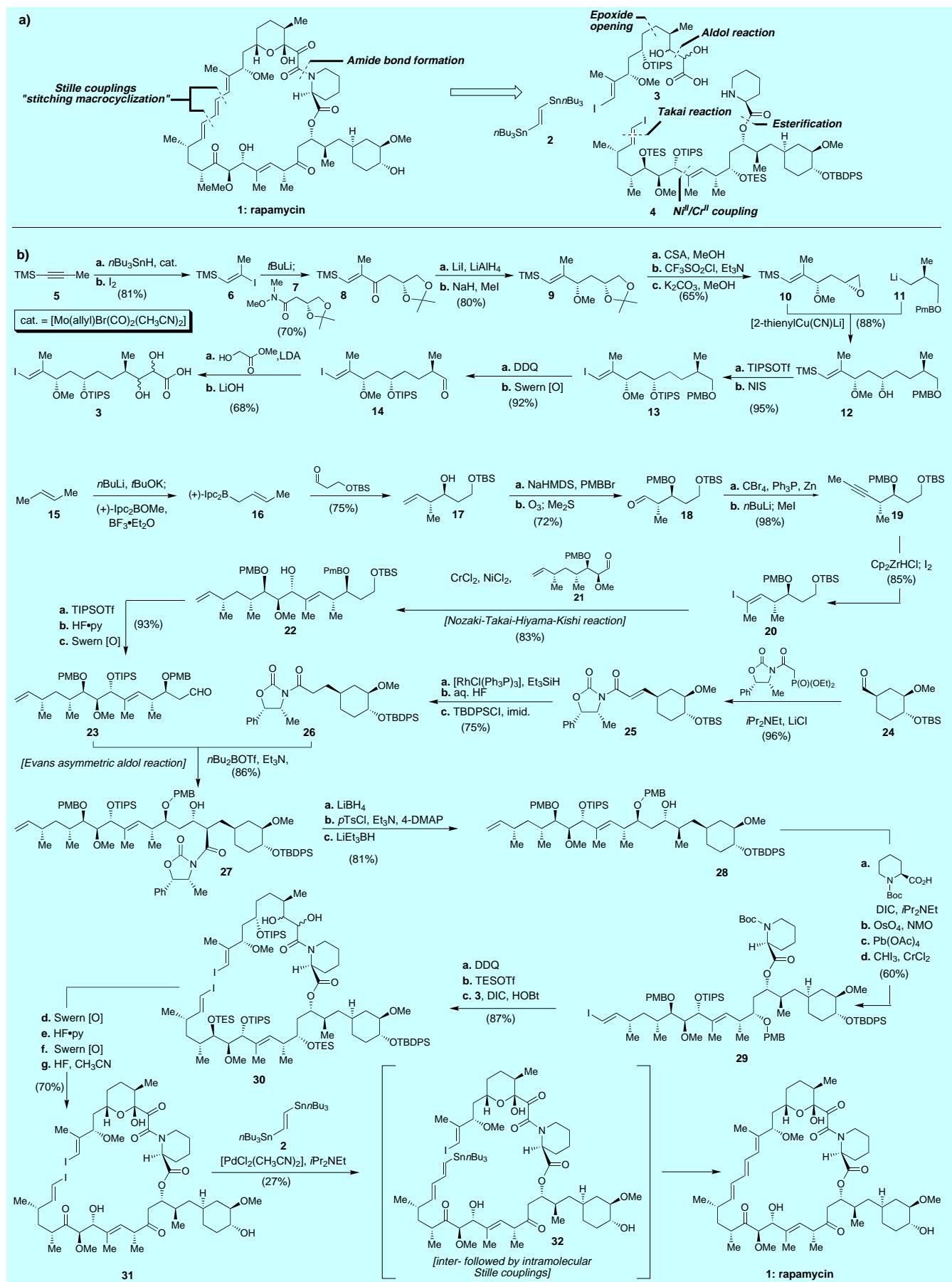
Scheme 28. a) Strategic bond disconnections and retrosynthetic analysis of rapamycin and b) highlights of the total synthesis (Nicolaou et al., 1993).[147]
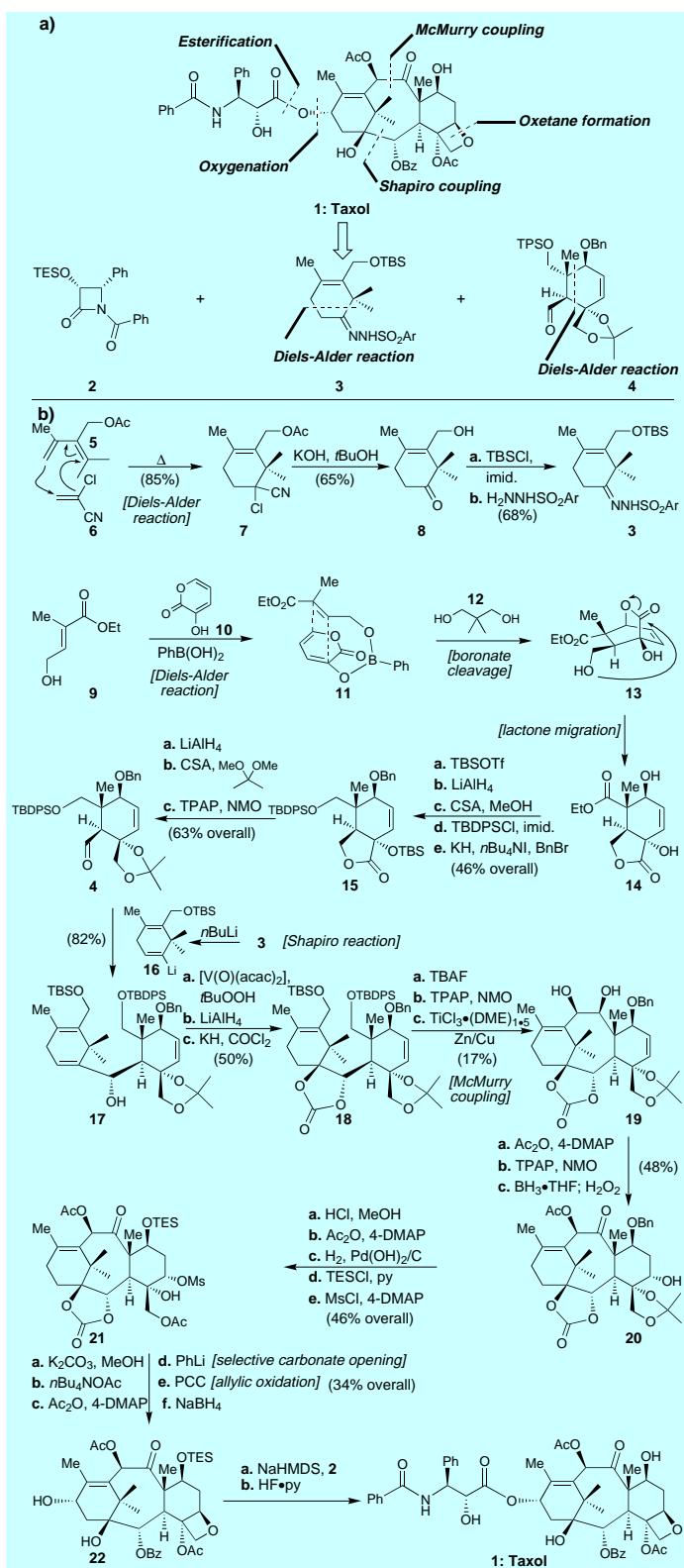
Scheme 29. a) Strategic bond disconnections and retrosynthetic analysis of taxol and b) total synthesis (Nicolaou et al., 1994).[154]

oxepane systems employing specifically designed hydroxy epoxides; b) the silver-promoted hydroxy dithioketal cyclization to didehydrooxocanes; c) the remarkable radical-mediated bridging of bis(thionolactones) to bicyclic systems; d) the photoinduced coupling of dithionoesters to oxepanes; e) the

silicon-induced hydroxy ketone cyclization to oxepanes; f) nucleophilic additions to thiolactones as an entry to medium and large ring ethers; g) thermal cycloadditions of dimethyl acetylene dicarboxylate with cyclic enol ethers as an entry to medium size oxocyclic systems; and h) the novel and unprecedented chemistry of dithiatopazine. For a more detailed analysis of this total synthesis, the reader should consult ref. [3].

Dynemicin A (1995)

Dynemicin A[180] (1 in Scheme 35; see page 84), a dark blue substance with strong antitumor properties and a member of the enediyne class of antitumor antibiotics that includes calicheamicin γ_1^I (Scheme 26), possesses a striking molecular architecture.[140, 181] Isolated from *Micromonospora chersina*, dynemicin includes in its structure a highly strained 10-membered enediyne ring, and a juxtaposition of epoxide, imine, and anthraquinone functionalities. The lure provided by this fascinating DNA-cleaving molecule resulted in intense synthetic studies directed towards its total synthesis. In 1993 Schreiber et al. first reported the total synthesis of di- and trimethoxy derivatives of dynemicin methyl ester (1 in Scheme 34; see p. 84).[182] This synthesis relies on the powerful intramolecular Diels–Alder reaction to construct the complex enediyne region of the molecule and a series of selective follow-up reactions to reach the methylated dynemicin targets.

Myers et al. reported the first total synthesis of dynemicin itself in 1995.[183] Their synthesis, summarized in Scheme 35, highlights a stereoselective introduction of the ene–diyne bridge, the use of a quinone imine as the dienophile in a regio- and stereoselective Diels–Alder reaction, and a number of other novel steps to complete the total synthesis. The second total synthesis of dynemicin was reported from the Danishefsky laboratory[184] (Scheme 36; see p. 85) and features a double Stille-type coupling in its assembly of the enediyne grouping. All three syntheses project admirable elegance and sophistication.

Ecteinascidin 743 (1996)

A marine-derived natural substance, ecteinascidin (1 in Scheme 37) possesses an unusual molecular architecture and extremely potent antitumor properties. Isolated from the tunicate *Ecteinascidia turbinata*, ecteinascidin 743 is comprised of eight rings, including a 10-membered heterocycle, and seven stereogenic centers.[185] Prompted by its attractive molecular architecture, impressive biological action, and low natural abundance, Corey et al. embarked on its total synthesis, and in 1996 they published the first total synthesis[186] of ecteinascidin 743 based on a brilliant strategy (Scheme 37; see p. 86).

The plan was inspired, at least in part, by the proposed biosynthesis of the natural product. Of the many powerful transformations in Corey's total synthesis of ecteinascidin 743, at least three stand out as defining attributes; an intramolecular Mannich bisannulation sequence was instrumental in establishing the bridging aromatic core to the
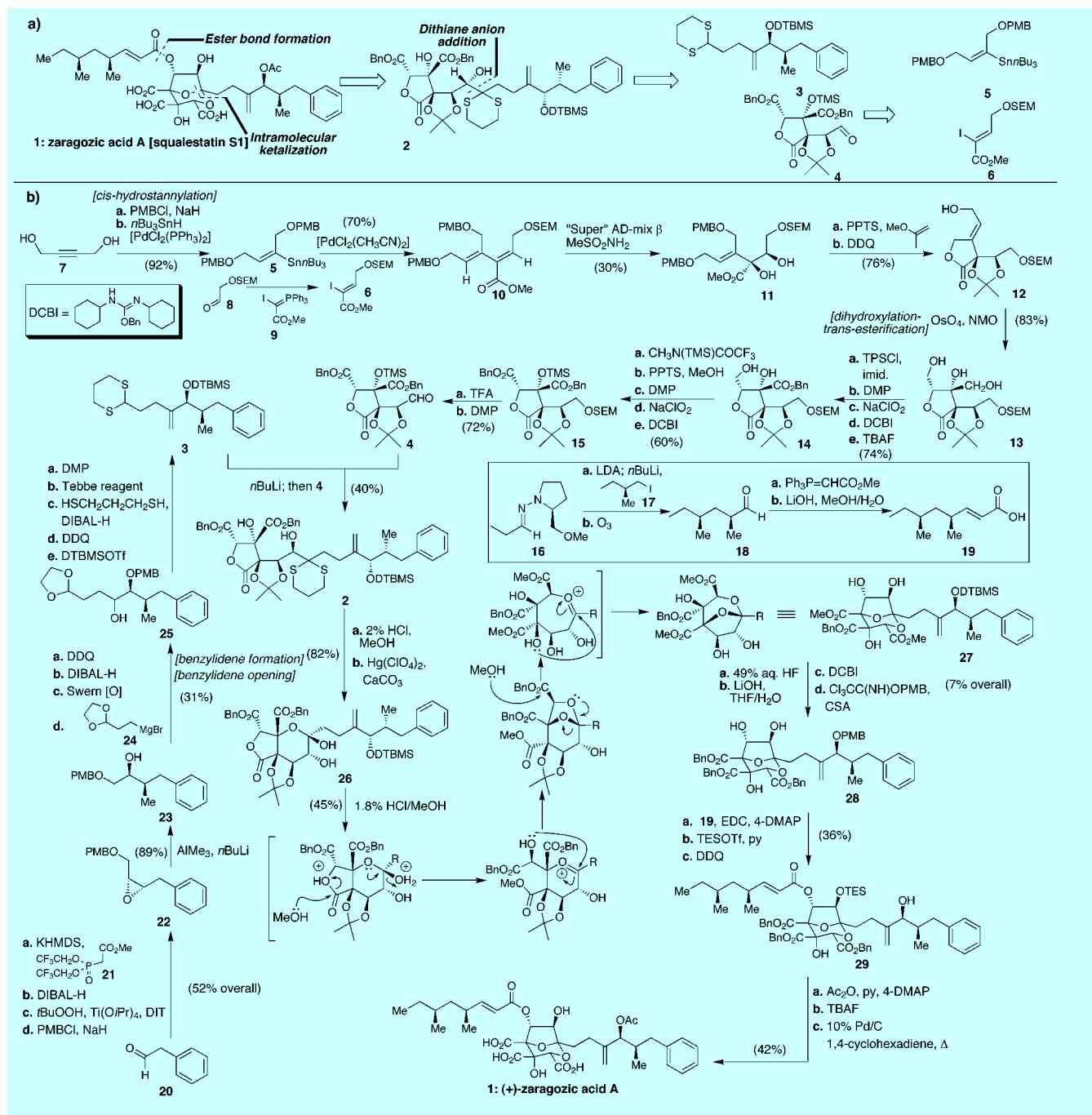
Scheme 30. a) Strategic bond disconnections and retrosynthetic analysis of zaragozic acid A and b) total synthesis (Nicolaou et al., 1994).[164]

piperazine ring, which allowed the formation of the desired aminal functionality, while two asymmetric Pictet–Spengler reactions played key roles in forming the isoquinoline rings. The centerpiece of the synthesis is, however, the generation and biomimetic quinone methide capture by the sulfur atom to construct the 10-membered lactone bridge. The masterful use of substrate topology to predict reactivity, inflict asymmetry, and achieve selectivity is amply demonstrated throughout Corey's synthesis.

Finally, the success in recognizing subtle retrosynthetic clues left by nature and applying them in the context of a chemical synthesis elevates this total synthesis to a unique level of brilliance. This impressive accomplishment also speaks for the efficiency that total synthesis has reached and the complex natural product analogues which can be synthesized in large quantities.[187]

Epothilone A (1997)

Appearing in the mid-1990s, epothilones A (1 in Scheme 38; see p. 87) and B[188] stimulated intense research activities in several laboratories.[189] The impetus for their total synthesis came not so much from their modestly complex macrolide structures but more so from their potent tubulin-

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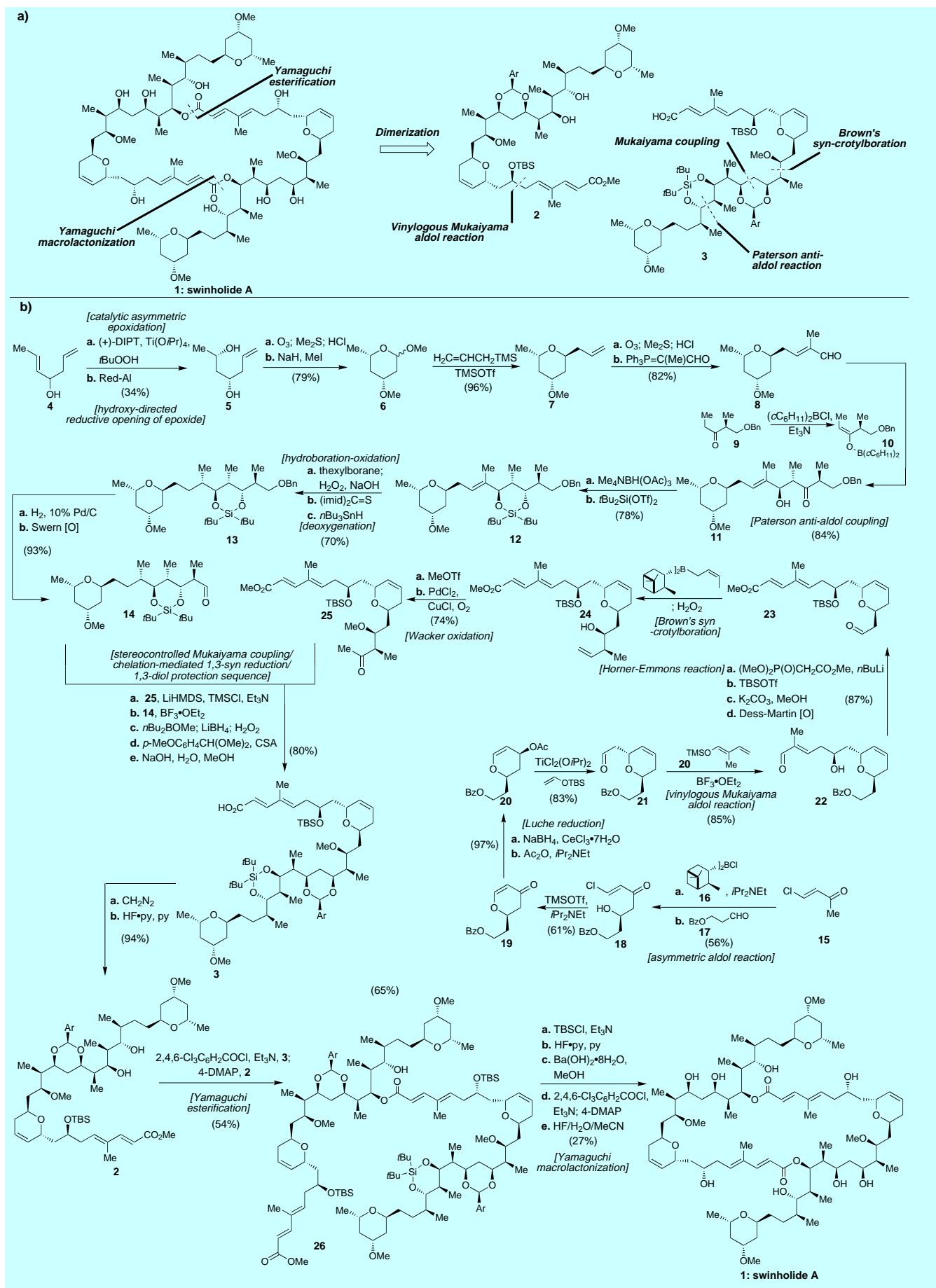
Scheme 31. a) Strategic bond disconnections and retrosynthetic analysis of swinholide A and b) total synthesis (Paterson et al., 1994).[170]

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a)

Yamaguchi esterification

Yamaguchi macrolactonization

1: swinholide A

Dimerization

Enders alkylation

Dithiane-cyclic sulfate coupling

2

Mukaiyama aldol

Ghosez lactonization

3

b)

a. Ac₂O, Et₃N, 4-DMAP
b. CH₂=CHCH₂TMS, BF₃·OEt₂, TMSOTf
c. NaOMe, MeOH
(74%)

5: L-rhamnose

6

a. nBu₂SnO; CsF, MeI
b. NaH, CS₂; MeI
c. nBu₃SnH, AIBN
[selective methylation/ Barton-McCombie deoxygenation sequence]
(35%)

7

a. O₃; NaBH₄
b. I₂, Ph₃P, imid.
c. LDA, **8**
d. O₃
[Enders alkylation]
(67%)

9

TiCl₄, Et₃N
4
(68%)
[aldol condensation]

10

a. PhCHO, SmI₂
b. TBSOTf
[1,3 anti-reduction; Evans-Hoveyda modification of the Tishchenko reduction]
(77%)

11

a. H₂, 10% Pd/C
b. SOCl₂, Et₃N
c. RuCl₃, NaIO₄
(94%)

12

a. TiCl₂(OiPr)₂, **20**
b. TBSOTf
c. K₂CO₃, MeOH
d. Swern [O]
e. TiCl₄, SH SH
f. DIBAL-H
g. TBSOTf
(50%)

21

a. tBuLi, HMPA;
b. H₂SO₄
(72%)

a. DIBAL-H
b. BF₃·OEt₂, TMS
c. BzCl, Et₃N
d. OsO₄, NMO; Pb(OAc)₄
(60%)

19

a. NaH, MeI
b. PhSO₂ **17**, DMPU, nBuLi; H₂SO₄; pTsOH; Et₃N, DBU
(84%)
[Ghosez lactonization]

18

16

K₂CO₃, MeOH
(52% overall)

22

[cleavage of dithiane functionality]
[syn 1,3-selective reduction]
(68% overall)
[selective desilylation]

a. NBS, AgClO₄
b. nBu₃B; NaBH₄; H₂O₂, NaOH
c. p-MeO-C₆H₄CH(OMe)₂, CSA
d. DIBAL-H
e. HF·py, py

a. PMBCO(NH)CCl₃, CSA
b. DIBAL-H
c. (+)-Ipc₂B(allyl); NaOH, H₂O₂
(74%)

13

14

nBuLi; CO₂; I₂

15

23

(92% overall)

a. MnO₂
b. (MeO)₂P(O)CH₂CO₂Me, nBuLi

2

(82%)

a. NaOH, MeOH/THF/H₂O
b. TMSOTf, iPr₂NEt

3

[Yamaguchi esterification]
a. 2,4,6-Cl₃C₆H₂COCl, Et₃N, **2**, 4-DMAP
b. PPTS, MeOH
c. Ba(OH)₂·8H₂O
d. 2,4,6-Cl₃C₆H₂COCl, Et₃N; 4-DMAP
e. HF/H₂O/MeCN
[Yamaguchi macrolactonization]
(7% overall)

1: swinholide A

Scheme 32. a) Strategic bond disconnections and retrosynthetic analysis of swinholide A and b) total synthesis (Nicolaou et al., 1995).[171]

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binding properties and their potential to overshadow taxol as superior anticancer agents. The first total synthesis of epothilone A came from the Danishefsky laboratories in 1996[190] and was followed shortly thereafter by syntheses from our laboratories[191] and from those of Schinzer.[192] Danishefsky's first total synthesis of epothilone A (Scheme 38) featured a Suzuki coupling reaction to form a crucial C–C bond and an intramolecular enolate–aldehyde condensation to form the 16-membered macrocyclic lactone. This method as well as others allowed the Danishefsky group to synthesize several additional natural and designed members of the epothilone family, including epothilone B,[193] for extensive biological investigations.

Chemical biology was also on our minds in devising a solution and a solid-phase total synthesis[194] of epothilone A (**1**). As shown in Scheme 39 (see p. 87) this new solid-phase paradigm of complex molecule total synthesis relied on a novel olefin metathesis strategy.[195] Of special note is the cyclorelease mechanism of this approach by which the 16-membered epothilone ring was constructed with simultaneous cleavage from the resin. Most importantly, this solid-phase strategy allowed the application of Radiofrequency Encoded Chemistry (REC; IRORI technology)[196] to the construction of combinatorial epothilone libraries[197] for chemical biology studies. The power of chemical synthesis of the 1990s in delivering large numbers of complex structures for biological screening was clearly demonstrated by this example of total synthesis, marking, perhaps, a new turn for the science.

Eleutherobin (1997)

A marine natural product of some note, eleutherobin (**1** in Scheme 40; see p. 88) includes in its structure a number of unique features. Isolated from an *Eleutherobia* species of soft corals and reported in 1995,[198] this scarce natural product elicited immediate attention from the synthetic community as a result of its novel molecular architecture and tubulin binding properties. Among the challenges posed by the molecule of eleutherobin are its oxygen-bridged 10-membered ring and its glycoside bond. Solutions to these problems were found in our 1997 total synthesis[199] as well as in Danishefsky's total synthesis,[200] which followed shortly thereafter. Scheme 40 summarizes our strategy to eleutherobin from (+)-carvone. Highlights include the intramolecular acetylide–aldehyde condensation to give the desired 10-membered ring and the spontaneous intramolecular collapse of an in situ generated hydroxycyclodecenone to form eleutherobin's bicyclic framework. This total synthesis exemplified the power of chemical synthesis in delivering scarce natural substances for biological investigations.

Sarcodictyin A (1997)

Sarcodictyins A and B (**1** and **2** in Scheme 41; see p. 88) are two marine natural products discovered in 1987 in the Mediterranean stoloniferan coral *Sarcodictyon roseum*.[201]
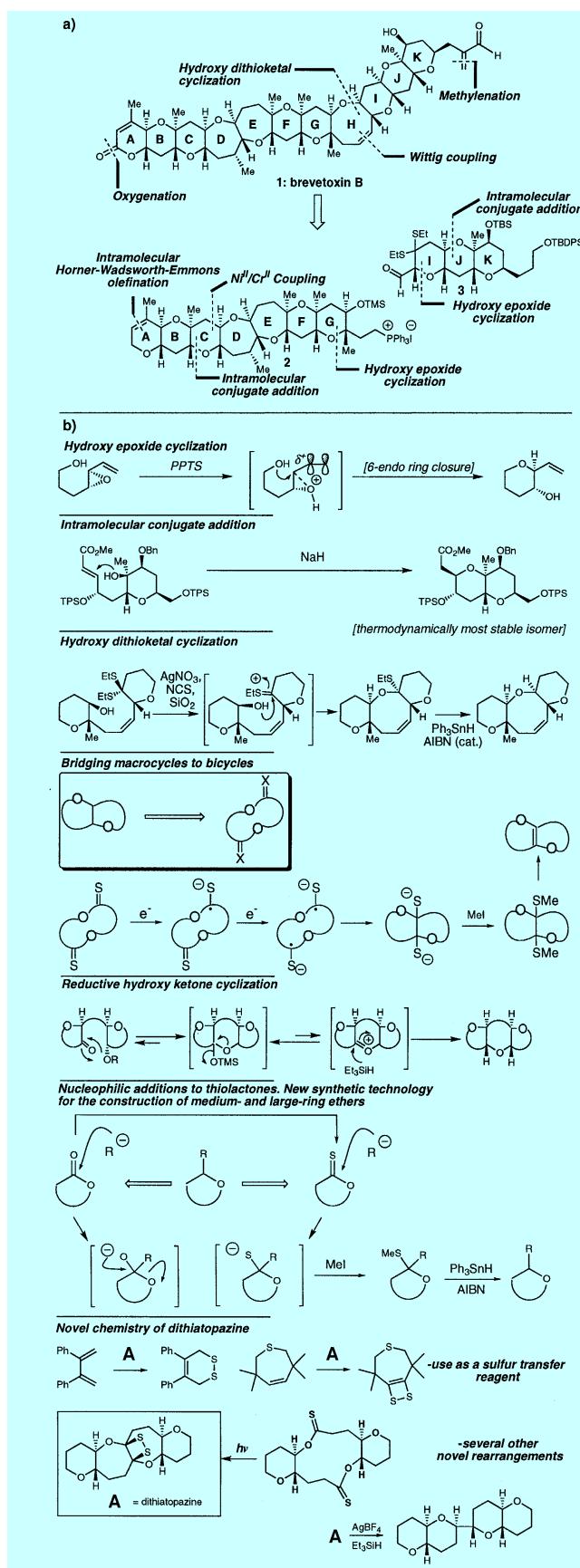
Scheme 33. a) Strategic bond disconnections and retrosynthetic analysis of brevetoxin B, b) key synthetic methodologies developed for the formation of polycyclic ethers and fundamental discoveries, and c) total synthesis of brevetoxin B (Nicolaou et al., 1995).[178]

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Scheme 33. (Continued)

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83

a)

b)
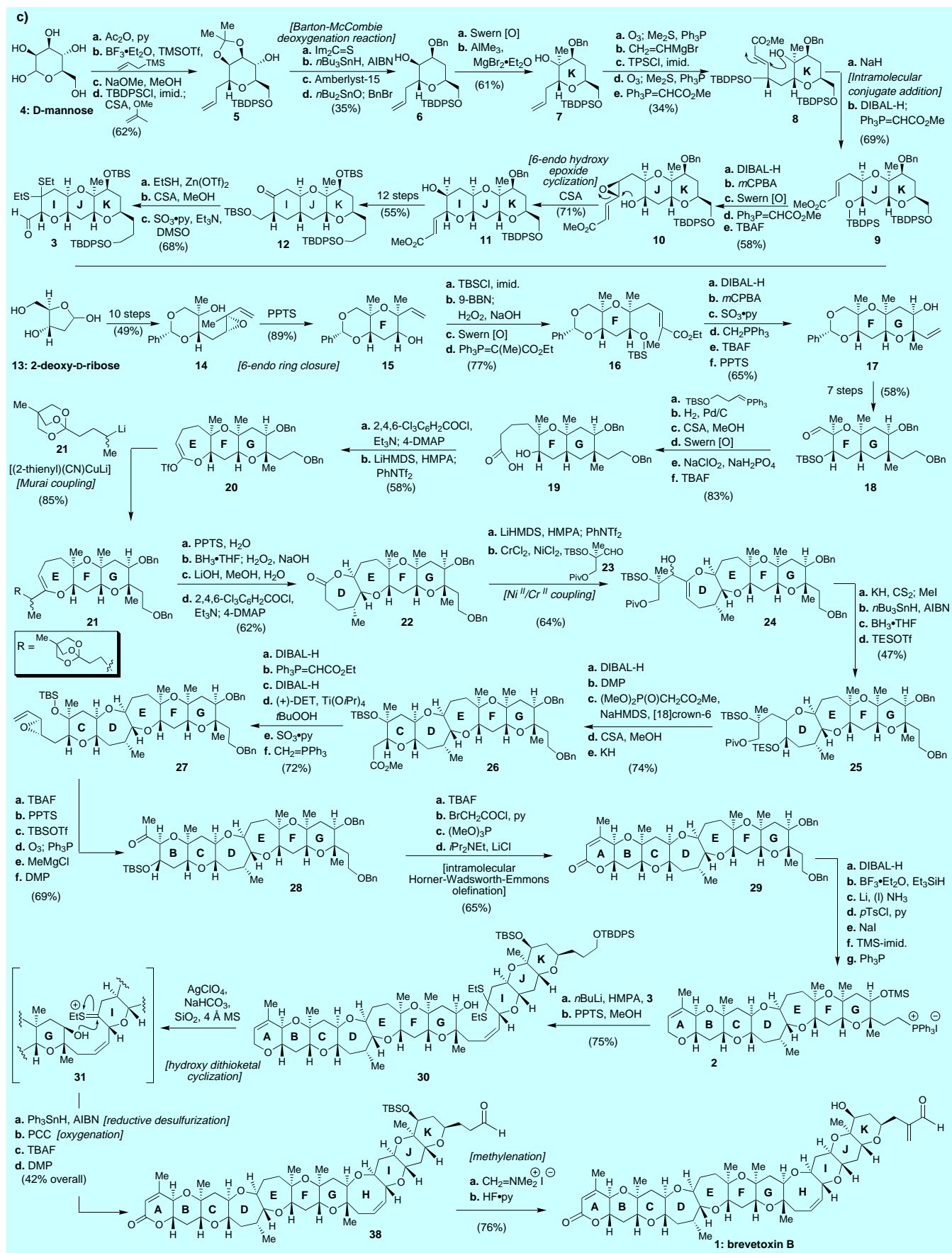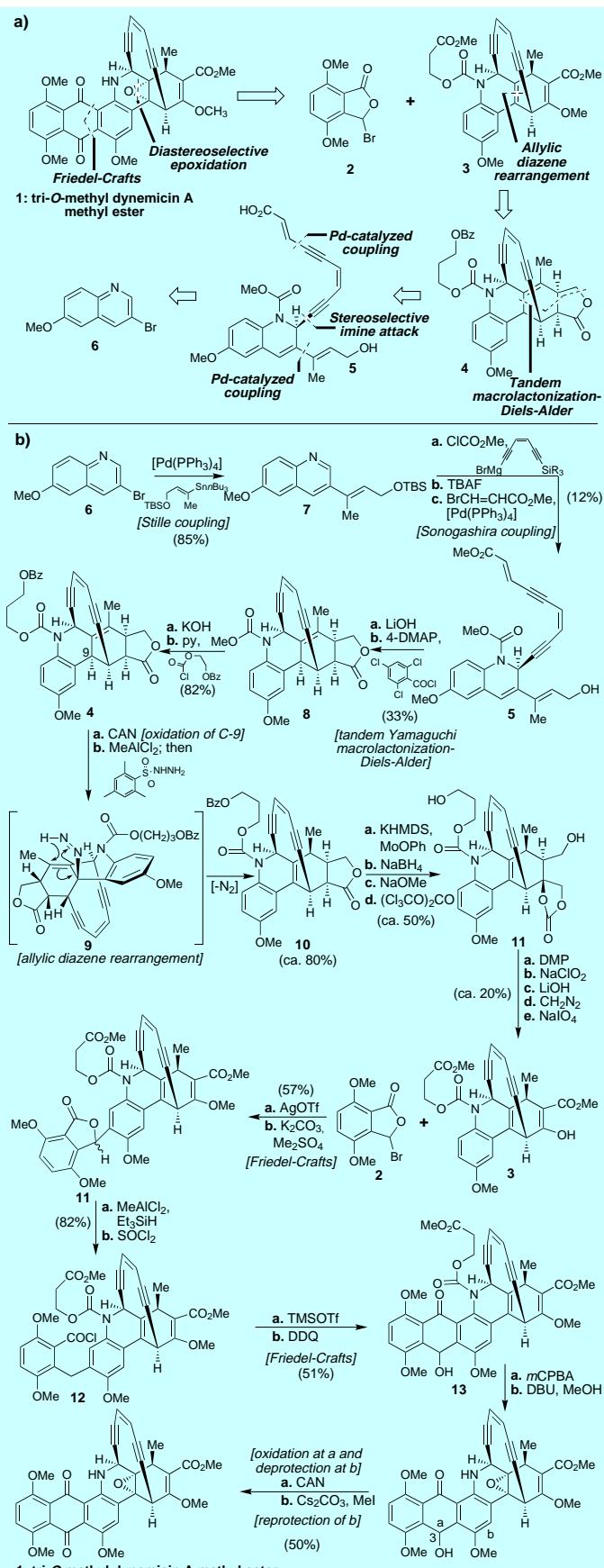
Scheme 34. a) Strategic bond disconnections and retrosynthetic analysis of tri-*O*-methyl dynemicin A methyl ester and b) total synthesis (Schreiber et al., 1993).[182]

a)

b)
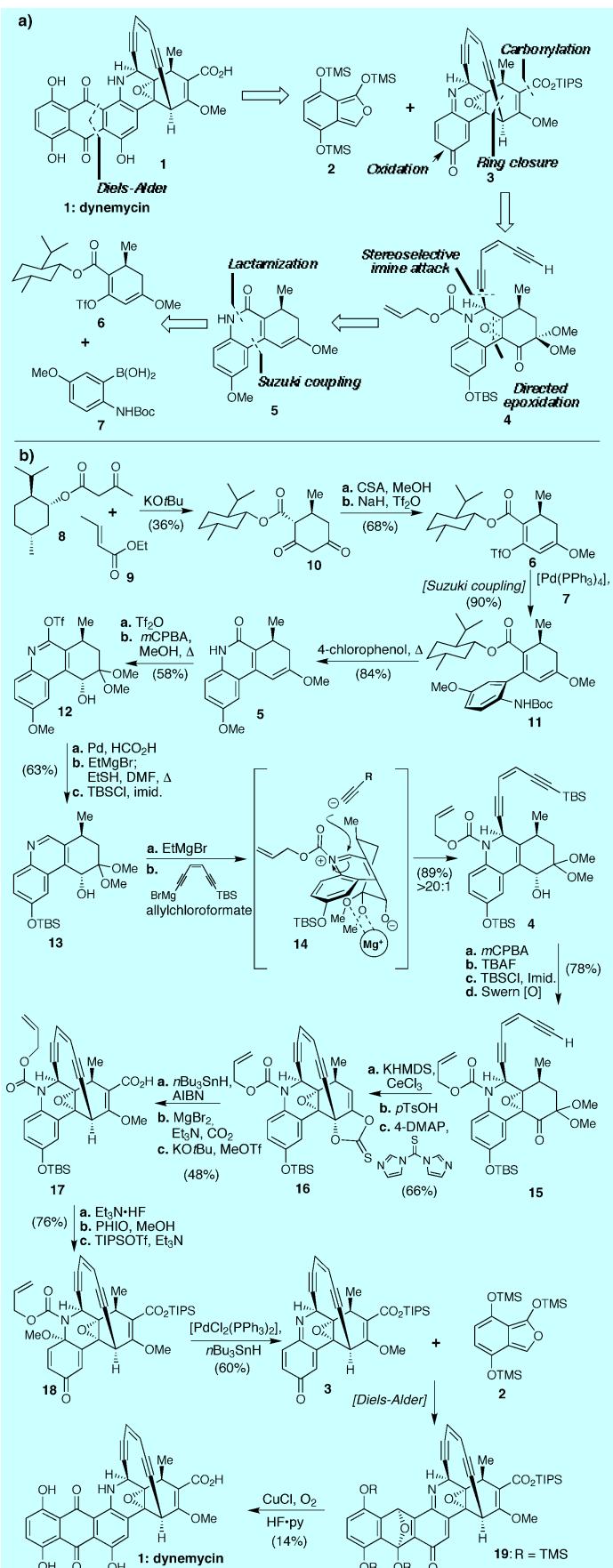
Scheme 35. a) Strategic bond disconnections and retrosynthetic analysis of dynemicin A and b) total synthesis (Myers et al., 1995).[183]

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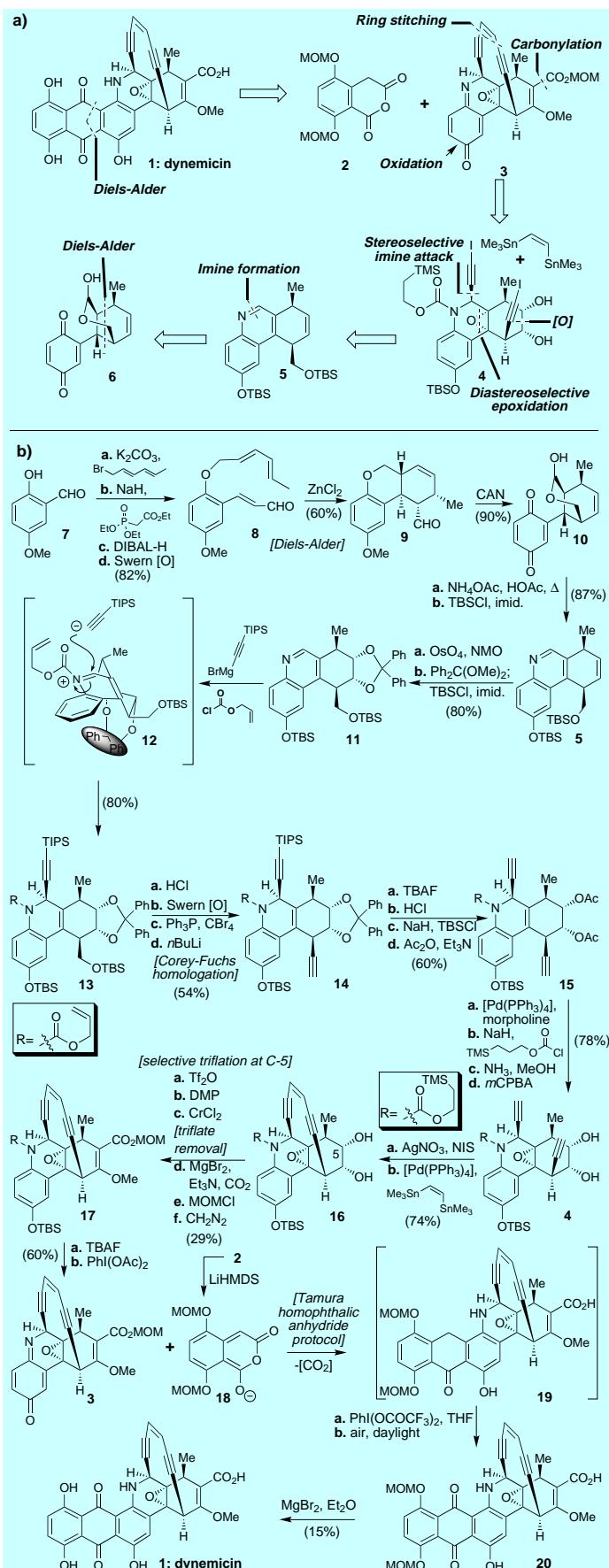
Scheme 36. a) Strategic bond disconnections and retrosynthetic analysis of dynemicin A and b) total synthesis (Danishefsky et al., 1996).[184]

Their potent antitumor properties are due, at least in part, to their tubulin-binding properties, resembling both eleuthero-bin and taxol in this regard.[202, 203] While the structural similarities of the sarcodictyins to eleutherobin are apparent, the correspondence of these molecules to taxol is not so obvious.[203] Nevertheless, the excitement generated from their taxol-like properties, coupled with their scarcity, led to the launching of programs directed toward their total synthesis.

It is noteworthy that the impetus for the chemical synthesis of these molecules in the 1990s was provided not only from their structural novelty, but also from the desire to apply organic synthesis as an enabling technology for chemical biology. Thus, the total synthesis of sarcodictyins A and B, accomplished in these laboratories in 1997,[204] went further than delivering the natural substances. It was applied, particularly in its solid-phase version (Scheme 41; see p. 88), to the construction of combinatorial libraries for the purposes of biological screening.[203, 205] That complex natural products such as the sarcodictyins could be synthesized, at least partially, on a solid phase is testament to the power and potential of the recent advances in solid-phase chemistry. Even more telling is the ability of synthetic chemistry at the turn of the century to deliver combinatorial libraries of complex natural or designed products such as those synthe-sized in this program and in the one described above for the epothilones.

Resiniferatoxin (1997)

A structural relative of phorbol ester,[206] resiniferatoxin (1 in Scheme 43; see p. 92)[207] was isolated from the *E. resinifere* cactus species and exhibits—unlike phorbol but like capsai-cin[208]—binding affinity to the vanilloid receptor present in sensory neurons. Besides its potential in biology and medi-cine, resiniferatoxin offers opportunities to the synthetic chemist, among which is the application of new methods of synthesis to the construction of the molecule. The structure of resiniferatoxin contains an ABC ring skeleton with two *trans* fusions. The C-ring carries five contiguous stereocenters, three of which bear hydroxyl groups which are engaged in a benzyl orthoester system. Following their success with phorbol ester[209] the Wender group at Stanford reported the total synthesis of resiniferatoxin in 1997.[210] This synthesis (Scheme 43) brilliantly blends classical synthetic methods with modern methodological advances in a strategy that stands as a hallmark to the progression of natural product synthesis. Highlights include an intramolecular [3+2] dipolar cycloaddition reaction between an oxidopyryllium ion and a terminal olefin to construct the BC framework, and a transition metal-induced ring closure of an eneyne to form the cyclopentane system (ring A).

Brevetoxin A (1998)

Within the polluted "red tide" waters often resides a more powerful neurotoxin, and that is brevetoxin A (1 in Scheme 42; see p. 90). Isolated from the dinoflagellate species *Ptychodiscus brevis Davis* (*Gymnodium breve Davis*), breve-

a)

Spiro tetrahydroisoquinoline formation

Esterification

Mannich bisannulation

Curtius rearrangement

Fl =

1: ecteinascidin 743

2

3

4

5

b)

6

a. *n*BuLi, TMEDA
b. MeI
(87%)

7

a. *n*BuLi
b. DMF
(64%)

8

a. CH₃SO₃H
b. NaH, BnBr
(86%)

9

10

BOPCl;

12

a. piperidine AcOH, 9
b. Pd(PPh₃)₄ Et₃N/HCO₂H
(93%)

13

11

[-N₂]

(PhO)₂P(O)N₃, Et₃N

15

[Curtius rearrangement]

[-N₂]

14

(93%) BnOH

16

[Rh(cod)-(*R,R*)-dipamp)] BF₄
H₂
[asymmetric hydrogenation]
(97%, 96% ee)

17

BF₃•Et₂O, H₂O

3

a. BF₃•Et₂O, 4Å MS
b. H₂, Pd/C
(73%)

18

BF₃•Et₂O, H₂O

3

a. 4 , AcOH, KCN
b. Cs₂CO₃, allylbromide
(53%)

19

a. DIBAL-H
b. KF•2H₂O, MeOH
c. CH₃SO₃H
[Mannich bisannulation]
(55%)

20

21

22

a. Tf₂NPh, Et₃N, 4-DMAP
b. TBDPSCl, 4-DMAP
c. MOMBr, *i*Pr₂NEt
d. [PdCl₂(Ph₃P)₂], *n*Bu₃SnH
e. formalin, NaBH₃CN
f. Me₃Sn, [PdCl₂(Ph₃P)₂],LiCl
(55% overall)

[position-selective angular hydroxylation]

(68%)

a. (PhSeO)₂O
b. TBAF
c. EDC•HCl, 4-DMAP, 2

23

Tf₂O, DMSO; *i*Pr₂NEt; *t*BuOH;
(Me₂N)₂C=N*t*Bu
[deprotects thiol]; Ac₂O
(79%)
[tandem quinodimethane formation, deprotection and cyclization]

24

a. *n*Bu₃SnH, [PdCl₂(Ph₃P)₂]
b. 25 , DBU
(70%)

25

26

a. 5
b. CF₃CO₂H
c. AgNO₃ - H₂O
(high yield)

1: ecteinascidin 743

Scheme 37. a) Strategic bond disconnections and retrosynthetic analysis of ecteinascidin 743 and b) total synthesis (Corey et al., 1996).[186]

toxin A was structurally elucidated in 1986.[211] With its ten fused ring structure and its twenty-two stereocenters, brevetoxin A rivals brevetoxin B in complexity, but as a synthetic target it arguably exceeds the latter in difficulty and challenge because of the presence of the 9-membered ring. Indeed, with rings ranging in size from 5- to 9-membered, all sizes in between included, brevetoxin A can be considered as the ultimate challenge to the synthetic chemist as far as medium-sized ring construction is concerned. After a ten-year campaign, our group reported the total synthesis of brevetoxin A (Scheme 42) in 1998.[212] As in the case of brevetoxin B, this program was rich in new synthetic technologies and strategies, which emerged as broadly useful spin-offs (Scheme 42 c). Amongst the most important synthetic technologies developed during this program was the palladium-catalyzed coupling of cyclic ketene acetal phosphates gen-

erated from lactones with appropriate appendages to afford cyclic enol ether diene systems[213] suitable for a cycloaddition reaction with singlet oxygen (24→26 in Scheme 42). This method provided the crucial turning point in solving the problems associated with the 7-, 8-, and 9-membered rings of the target and opened the gates for the final and victorious drive to brevetoxin A.

Manzamine A (1998)

Manzamine A (**1** in Scheme 44; see p. 93) is a sponge-derived substance (genera *Haliclona* and *Pellina*) with potent antitumor properties. Disclosed in 1986,[214] the structure of manzamine A, and those of its subsequently reported relatives,[215] attracted a great deal of attention from synthetic chemists. The interest in the manzamines as synthetic targets

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a)
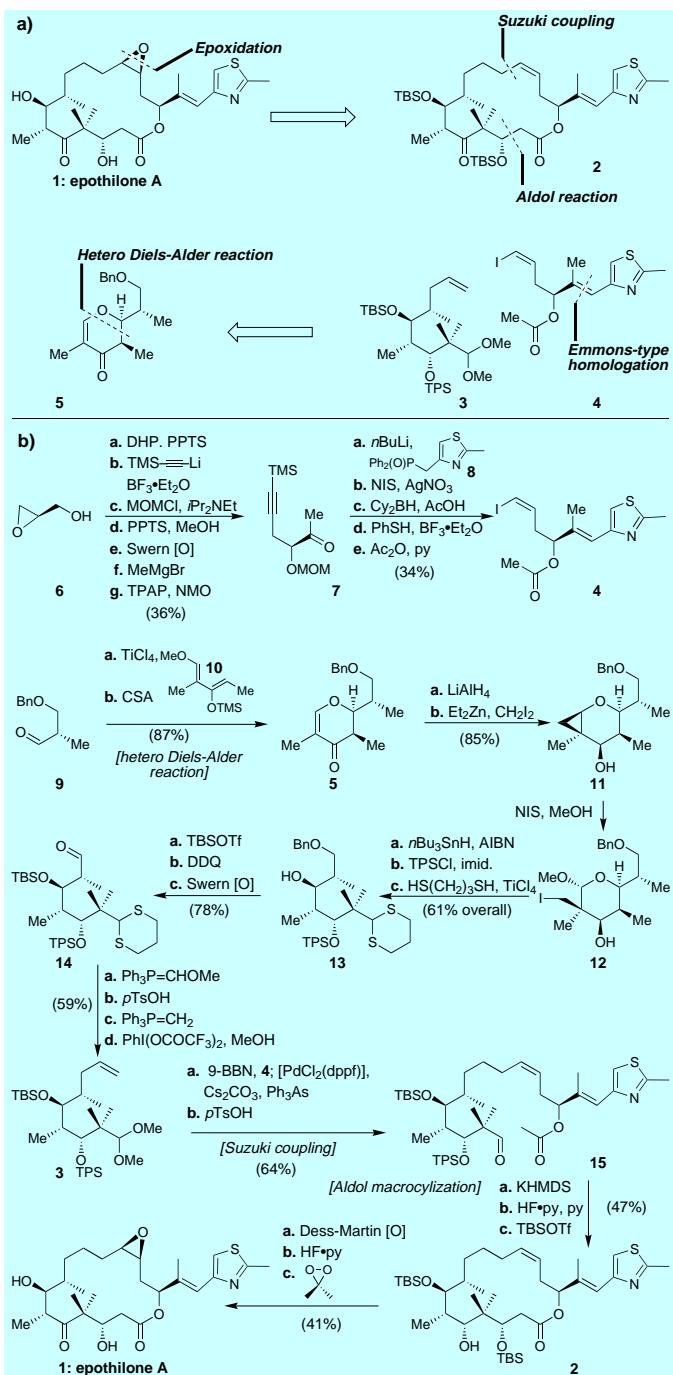
Scheme 38. a) Strategic bond disconnections and retrosynthetic analysis of epothilone A and b) total synthesis (Danishefsky et al., 1996).[190]

was heightened by a hypothesis put forward by Baldwin et al. in 1992 for their biosynthesis.[216] By early 1999 two total syntheses[217, 218] of manzamine A and evidence[219] supporting the biosynthetic hypothesis had been reported.

Baldwin's intriguing hypothesis for the biosynthesis of the manzamine alkaloids postulates four simple starting materials and an intramolecular Diels–Alder reaction as the key process to assemble the polycyclic framework (see Scheme 45). The first total synthesis of manzamine A appeared from the Winkler group in 1998,[217] proceeded through ircinal (2 in Scheme 44), itself a natural product, and involved
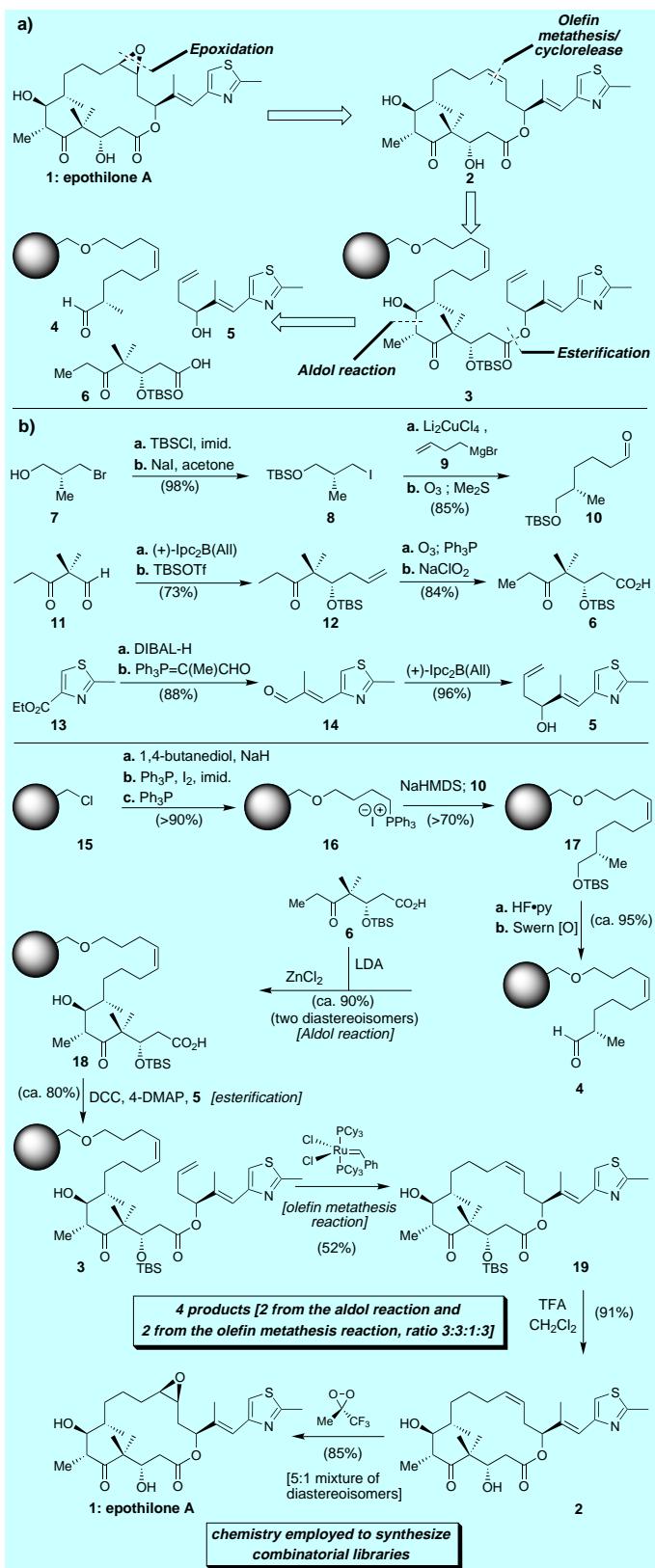
Scheme 39. a) Strategic bond disconnections and retrosynthetic analysis of epothilone A and b) total synthesis (Nicolaou et al., 1997).[194, 197]

a photoinduced [2+2] cycloaddition reaction, a Mannich closure, and an intramolecular N-alkylation to assemble the polycyclic skeleton. In early 1999 the Baldwin group provid-

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87
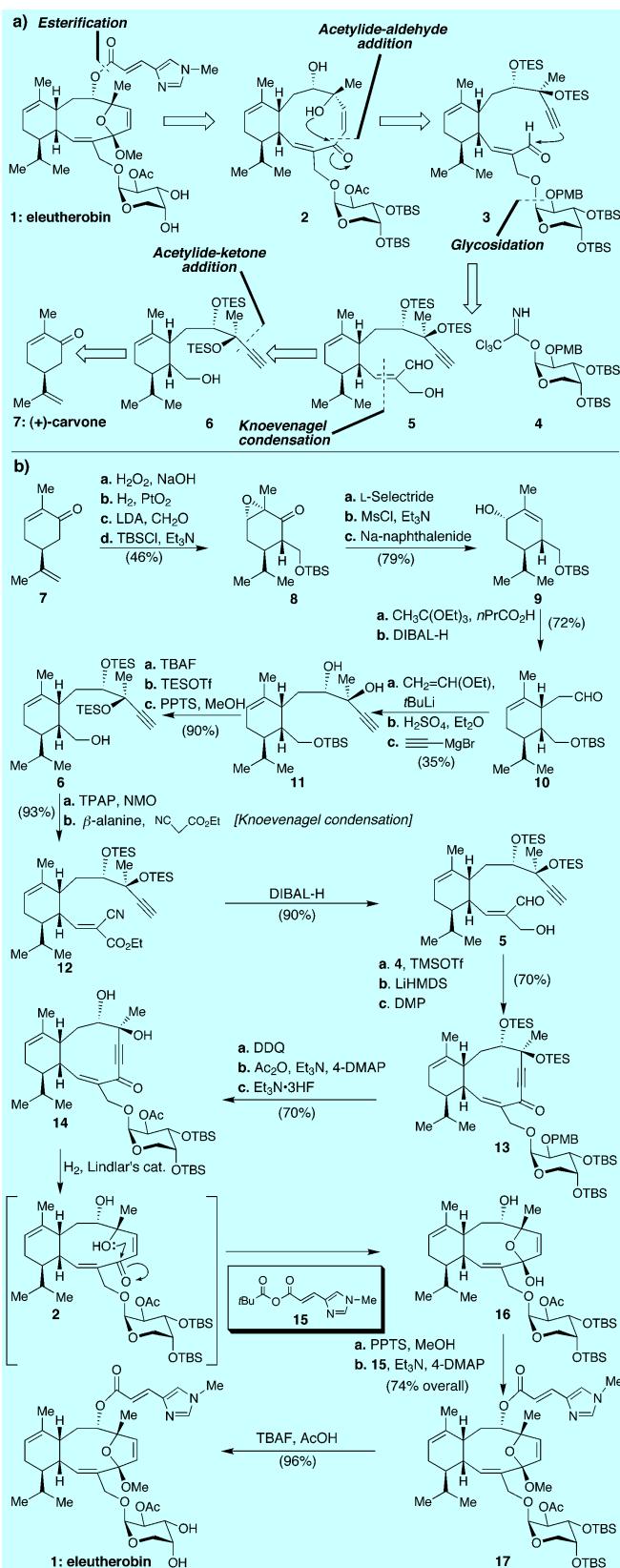
Scheme 40. a) Strategic bond disconnections and retrosynthetic analysis of eleutherobin and b) total synthesis (Nicolaou et al., 1997).[199]

Martin et al. in 1999 (Scheme 46; see p. 94)[218] on the other hand involved an intramolecular Diels – Alder reaction and two olefin metathesis ring closures to construct the pentacyclic framework of the target molecule. All three approaches
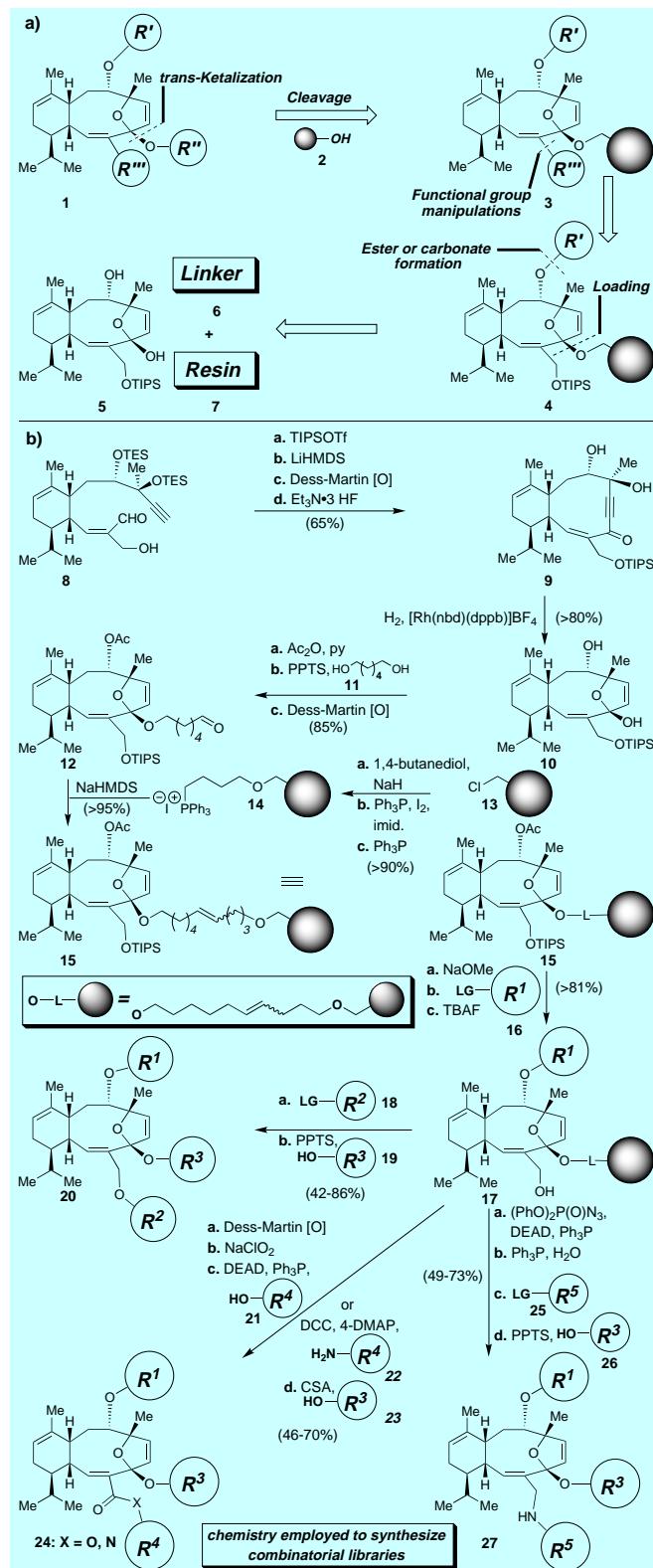
Scheme 41. a) Strategic bond disconnections and retrosynthetic analysis of a solid-phase sarcodictyin library and b) total synthesis (Nicolaou et al., 1998).[205]

ed[219] evidence for their hypothesis through synthetic studies culminating in the synthesis, albeit in low yield, of keramaphidin B (Scheme 45; see p. 93). The synthesis reported by

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are elegant in their conception and brilliant in their execution, demonstrating once again the ability of organic synthesis to swiftly respond to new challenges posed by novel structures from nature.

Vancomycin (1999)

Vancomycin (**1** in Scheme 47 and 48; see p. 95), a representative of the glycopeptide class of antibiotics,[220] was isolated in the 1950s and used for over four decades as a weapon of last resort to combat bacterial disease. Isolated[221] from the actinomycete *Amycolatopsis orientalis*, vancomycin finally yielded to structural elucidation in 1982.[222] Within a few years, it became the subject of synthetic investigations, primarily as a consequence of its novel molecular architecture, important biological action and medical applications, and intriguing mechanism of action. As a synthetic target, vancomycin offered a unique opportunity to synthetic chemists to develop new synthetic technologies and strategies. Among the most intriguing structural features of the molecule were its two 16-membered bisaryl ether macrocycles and its 12-membered bisaryl ring system, each of which is associated with an atropisomerism problem. The attachment of the two carbohydrate moieties onto the heptapeptide aglycon system added to the challenge presented by this target molecule.

By 1998 two groups, that of D. A. Evans[223] and ours,[224] had reported independent total syntheses of the vancomycin aglycon and by early 1999 the first total synthesis[225, 226] of vancomycin itself appeared in the literature followed by another report of the aglycon synthesis by the Boger group.[227] Emanating from these laboratories, the total synthesis of vancomycin is summarized in Scheme 48 (see p. 96). During the vancomycin campaign, a number of new methods and strategies were designed and developed, among which, perhaps, the triazene-driven biaryl ether synthesis[228] is the most prominent. The strategy employed modern asymmetric reactions for the construction of the required amino acid building blocks, which were then assembled into appropriate peptides and cyclized to form the desired framework. While the two biaryl ether macrocycles were formed by the triazene-driven cyclization, the bisaryl ring framework was assembled by a sequential Suzuki coupling and a macrolactamization reaction. Finally, the sugar units were sequentially attached onto an appropriately protected aglycon derivative, which afforded a protected vancomycin system in a stereoselective manner from which free vancomycin was obtained.

The Evans synthesis of vancomycin's aglycon, shown in Scheme 47,[223] featured the stereocontrolled construction of the amino acid building blocks and assembly to the heptapeptide backbone through a vanadium-mediated C−C bond forming reaction to construct the 12-membered biaryl ring system and two nucleophilic aromatic substitutions activated by *o*-nitro groups to form the two bisaryl ether macrocycles. The synthesis of vancomycin's aglycon[227] by Boger et al. (Scheme 50; see p. 100) is distinguished by extensive studies to determine the activation energy required to atropisomerize each macrocycle, thereby allowing selective atropisomerization of the AB ring system in the presence of the COD framework. These total syntheses added yet another distin-

guished chapter to the annals of total synthesis and placed the glycopeptide antibiotics on the list of conquests of synthetic organic chemistry.

CP Molecules (1999)

CP-263,114 and CP-225,917 (**1** and **2**, respectively, in Scheme 49; see p. 98), isolated from an unidentified fungus by Pfizer scientists in 1997,[229] inhibit squalene synthase and ras farnesyl transferase, and as such, represent important new leads for cholesterol-lowering and anticancer drugs. Nature molded within these structures an exotic display of delicate and rare functionalities that beckoned to synthetic chemists worldwide. The total synthesis of these compounds was finally accomplished in 1999 in our laboratories after a relentless campaign through a daunting synthetic labyrinth plagued with manifold and unexpected obstacles.[230] This total synthesis is retrosynthetically blueprinted in Scheme 49 a. A critical disassembly maneuver called upon an intramolecular Diels – Alder reaction to simplify the bicyclic structure **6** of the CP molecules to the open-chain precursor **7**. Although this retrosynthetic analysis serves as a conceptual overview of the synthesis, it should be noted that it is actually the culmination of several unsuccessful retrosyntheses by which the conversion of ketone **6** into the CP molecules was planned.

Commencing with dimethyl malonate (**8**), the synthesis of the CP molecules proceeded smoothly through several intermediates and finally yielded the desired acyclic precursur **7** stereoselectively (Scheme 49 b). When compound **7** was treated with Me_2AlCl in dichloromethane at -20 °C, complete conversion to **6** through a Lewis acid catalyzed intramolecular Diels – Alder reaction was observed within two minutes. The formidable task of stereoselectively installing the remote stereocenter at C7 was addressed by utilizing dithiane chemistry (**6**→**15**). The reason for such a high level of diastereoselectivity (ca. 11:1) could possibly be a consequence of a shielding effect of the CP skeleton. Indeed, the surprisingly close proximity of this side chain to the rest of the molecule was quite apparent throughout the synthesis. The stage was now set for the installation of the fused maleic anhydride moiety. The synthesis of this delicate moiety was in itself a great challenge due to unique environment surrounding ketone **15**. The development of novel chemistry to construct the anhydride was a result of persistence in the face of several failed strategies.[231] Thus, ketone **15** was smoothly converted to the enol triflate followed by palladium-catalyzed carboxymethylation and exchange of the dithiane for a dimethoxy ketal leading to the unsaturated ester **16**.

After reduction with DIBAL-H, a Sharpless hydroxyl-directed epoxidation of the allylic alcohol led to epoxide **17** selectively (ca. 10:1). Introduction of this electrophilic species allowed for the placement of an additional carbon atom with the correct oxidation state for the ensuing cascade sequence. This carbon atom, in the form of a cyanide, was added to epoxide **17** using Et_2AlCN and proceeded with complete regio- and stereospecificity (see **17b**). It was after considerable experimentation that we discovered that it was possible to convert diol **18** in one synthetic operation. Thus, selective mesylation of diol **18**, followed by treatment with base and

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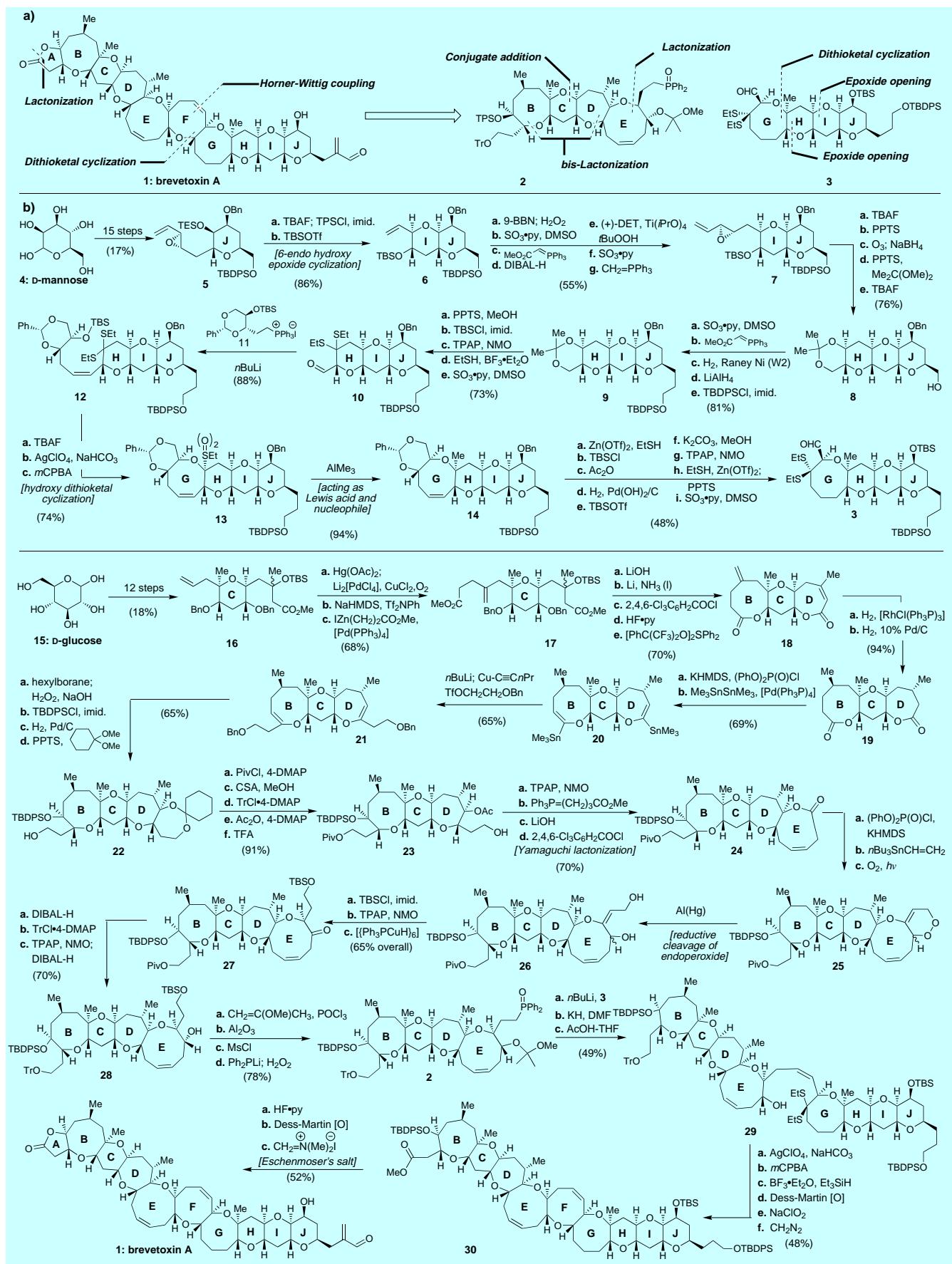
Scheme 42. a) Strategic bond disconnections and retrosynthetic analysis of brevetoxin A, b) total synthesis (Nicolaou et al., 1998),[212] and c) key synthetic methodologies developed in the course of the total synthesis (Nicolaou et al., 1998).[212]

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c) *Cyclic ketene acetal phosphates for the construction of medium and large cyclic ethers*

Enol-phosphates and thioketal-mediated etherification for the construction of the EFGH ring skeleton of brevetoxin A

Novel stereocontrolled synthesis of the nonacene ring system of brevetoxin A. Conformational-reactivity effects in nine-membered rings

Synthesis of N-heterocycles via lactam-derived ketene aminal phosphates. Asymmetric synthesis of cyclic amino acids


Scheme 42. (Continued)

finally acidic workup afforded the maleic anhydride **5**. The course of this dizzying domino sequence undoubtedly involves formation of the unprecedented carbocyclic imino butenolide **21** (a proven intermediate and new chemical entity isolated for the first time) whereupon facile tautomerization to the electron rich and easily oxidizable 2-amino-furan **22** occurs.

Stepwise oxidation of the furan **22** followed by nitrogen extrusion leads to anhydride **5**. The remarkable efficiency with which this reaction takes place (56% overall yield, seven transformations in one operation) is a testament to the utility of tandem reactions in organic synthesis. After some brief protecting group manipulations, the stage was set for the aplication of another cascade reaction. It was found that treatment of **23** with Dess-Martin-periodinane in refluxing benzene led to the desired γ-hydroxy lactonol in 63% yield. This tandem reaction was based on the simple ring–chain tautomerization of hydroxy ketones and permitted the crucial oxidation to take place.[232]

The next key step involved the one-carbon elongation of intermediate **4** by the classic Arndt–Eistert reaction. Because of the extreme steric hindrance of the carboxylic acid derived from **4**, a new method specifically tailored for the preparation of hindered α-diazoketones was developed.[233] This new synthetic technology was based on the expected extreme reactivity of the acyl mesylate species. In the event, acyl mesylate **25** successfully activated the hindered carboxylic acid for attack by diazomethane thus leading to the requisite α-diazoketone for the ensuing Wolff rearrangement. The final stage in the synthesis required conversion of indole **27** into the CP molecules. Although the conversion of **2** into **1** was known, the counterintuitive conversion of the seemingly robust **1** into its hydrated counterpart **2** appeared unlikely. We reasoned that LiOH might be useful for effecting this conversion by virtue of its unique solubility and reactivity. Not only did this LiOH-mediated cascade reaction succeed in hydrolyzing the indole amide of **27** to the corresponding carboxylic acid, it was also able to induce ring opening of the stable pyran motif to provide **2** directly. The conversion of **2** into **1** using acid catalysis proceeded smoothly, thus completing the total synthesis of the CP molecules.

In summary, the first total syntheses of these (racemic) compounds was accompanied by a plethora of fundamental discoveries, cascade reactions, and new synthetic technologies among which the following are, perhaps, most notable (see Scheme 49 c, d): 1) the design and execution of a cascade reaction involving no less than seven steps traversing through previously unknown chemical entities to construct the fused maleic anhydride moiety;[231] 2) the enlistment of another tandem sequence predicated on the ring–chain tautomerization of hydroxy ketones to sculpt the γ-hydroxy lactone moiety onto the bicyclic skeleton;[232] 3) development of a mild and effective method for the construction of extremely hindered diazoketones using acyl mesylates (Scheme 49 d, top);[233] 4) a new paradigm for the two-step construction of strikingly complex natural-productlike heterocycles from commercially available chemicals (Scheme 49 d, middle);[234] 5) a new method for the

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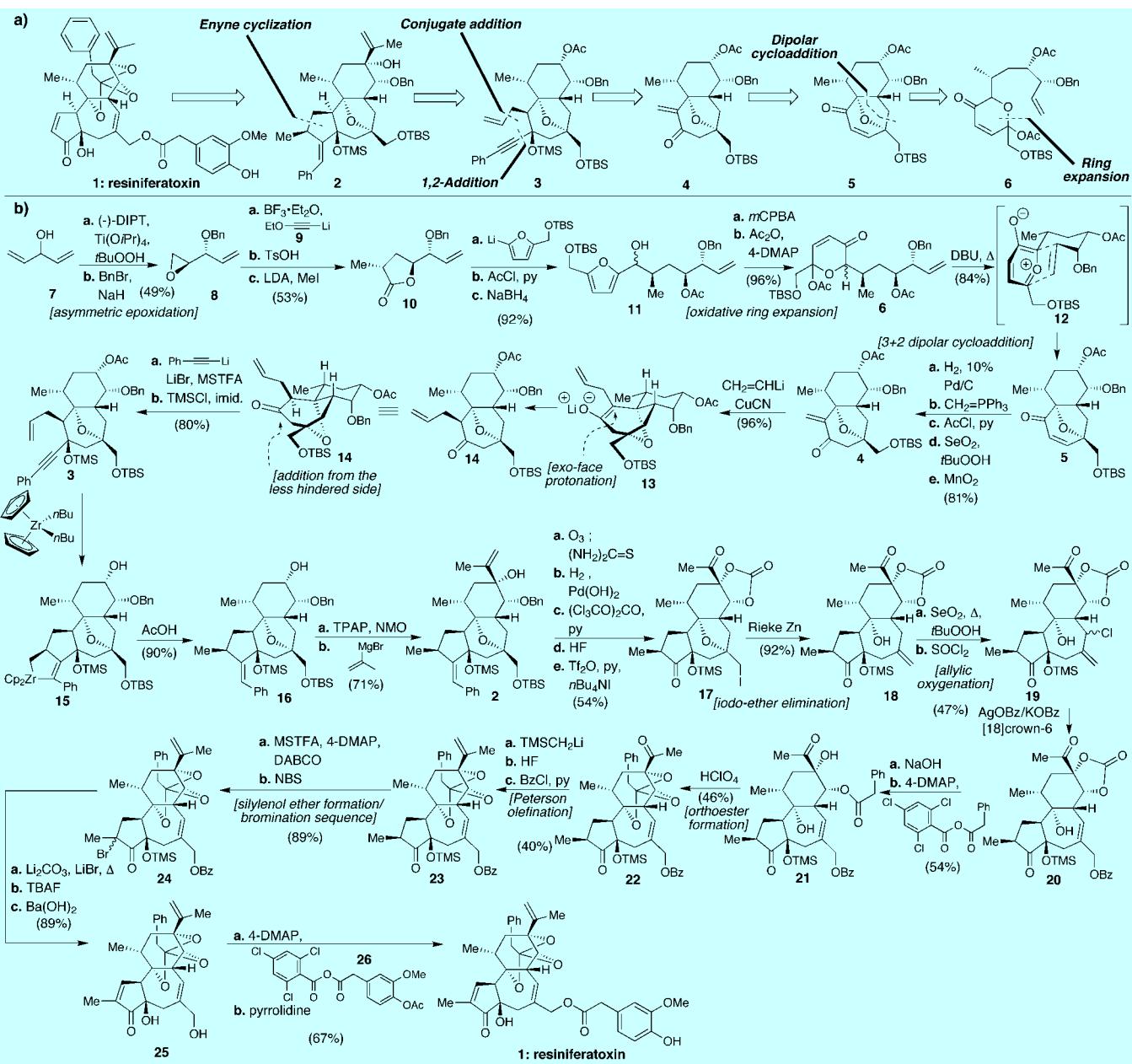
Scheme 43. a) Strategic bond disconnections and retrosynthetic analysis of resiniferatoxin and b) total synthesis (Wender et al., 1997).[210]

one-carbon homologation of hindered aldehydes (Scheme 49 d, bottom);[235] and 6) the daring and counterintuitive conversion of the structurally robust CP molecule **1** into its hydrated CP derivative **2** passing through a multiply-charged intermediate in yet another cascade sequence.[230] The total synthesis of the CP molecules stands as an instructive example of how total synthesis can act as a driving force for the discovery and development of new concepts and methods in chemistry.

Aspidophytine (1999)

For over 25 years aspidophytine (**1** in Scheme 51; see p. 101) has remained an unanswered challenge for organic synthesis. Best known for its use as an anticockroach/insecticidal

powder—at least since the Aztec era in parts of Mexico and Central America[236]—its complex structure was not elucidated until 1973 by the groups of M. P. Cava, P. Yates, and D. E. Zacharias.[237] The first total (enantioselective) synthesis of this molecule was finally completed in 1999 by E. J. Corey and co-workers and featured a rapid assembly of the aspidophytine core via a novel cascade sequence.[238] The hallmark of the synthesis is the tandem sequence uniting dialdehyde **3** and indole **2** in a one flask tandem operation. Also notable is the conversion of acid **9** into lactone **11** by attack of the iminium species **10**. It is impressive that all four stereocenters (three quaternary) of **1** are derived from one chiral center secured early in the synthesis using the CBS reduction (see p. 58). Aside from developing a breathtaking new domino sequence to assemble the aspidophytine skeleton, this work raises the
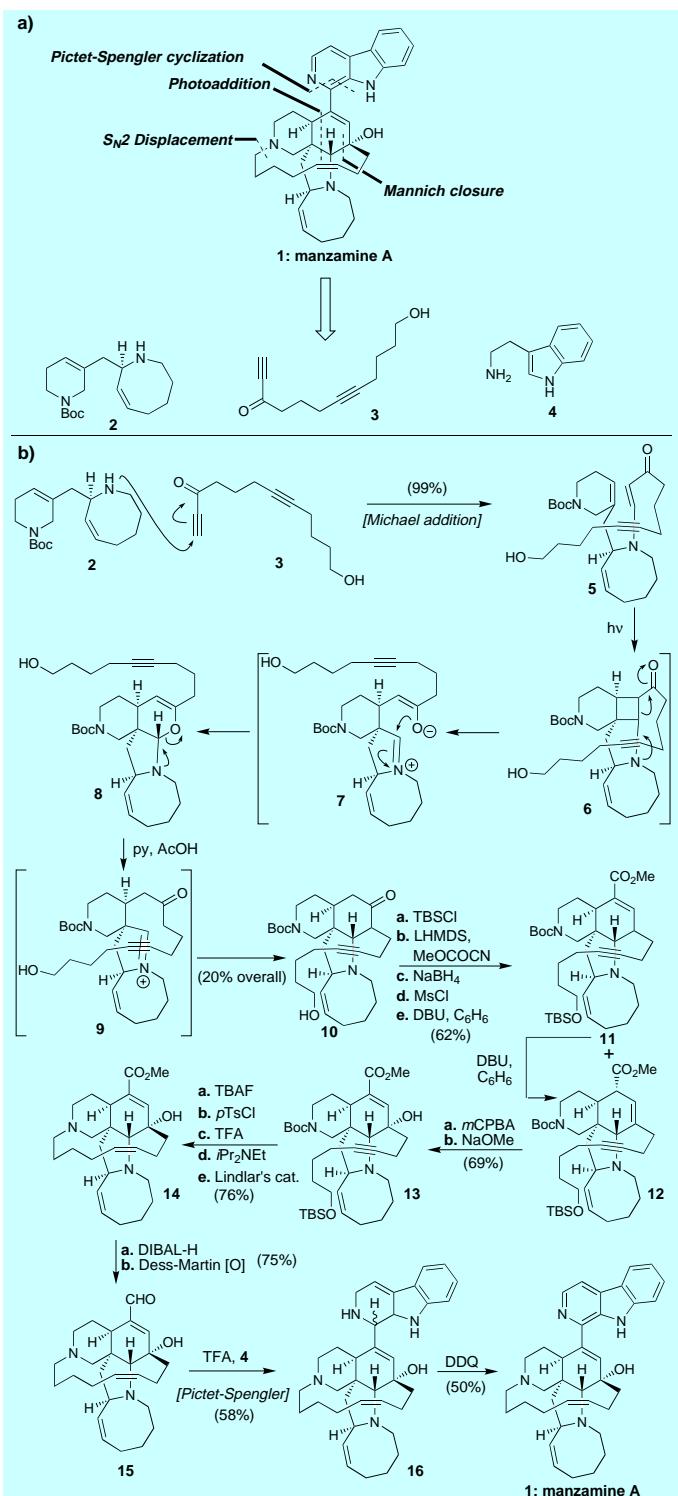
Scheme 44. a) Strategic bond disconnections and retrosynthetic analysis of manzamine A and b) total synthesis (Winkler et al., 1998).[217]

standards for the concise synthesis of extremely complex alkaloids from simple starting materials.

Sanglifehrin A (1999)

Sanglifehrin A (Scheme 53; see p. 104) was originally isolated by a team of Novartis scientists from an actinomycete
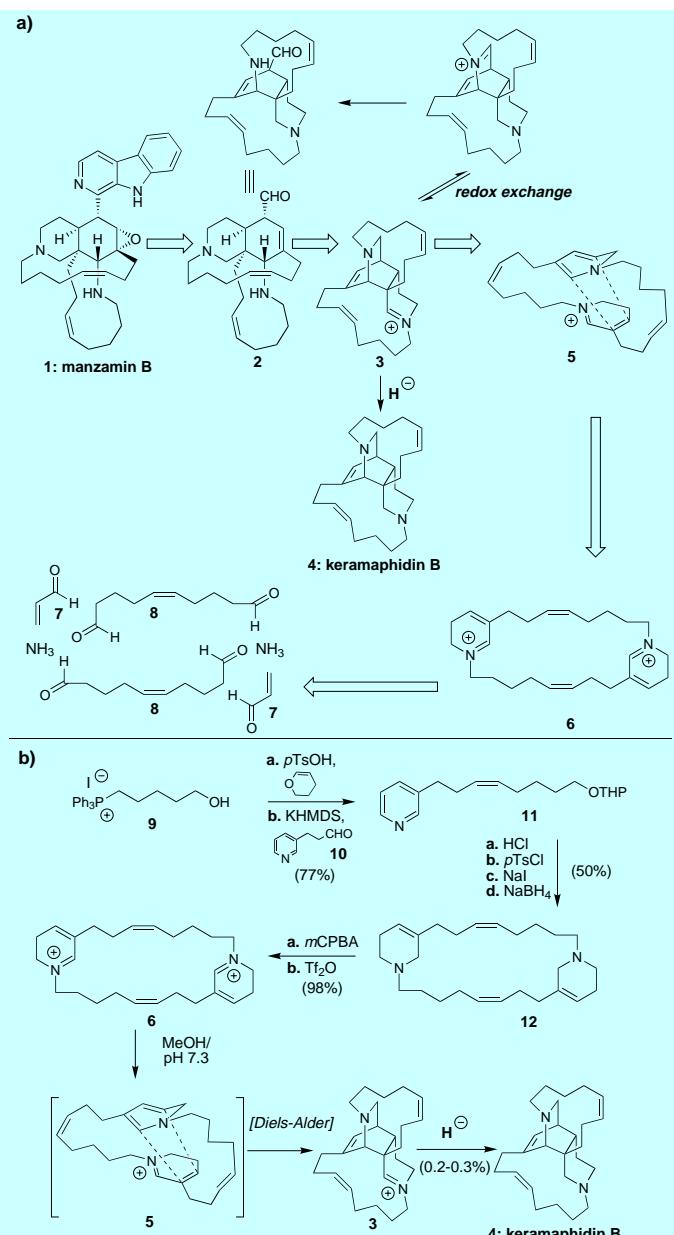
Scheme 45. a) Strategic bond disconnections and retrosynthetic analysis of manzamine B and b) biomimetic total synthesis of keramaphidin B (Baldwin et al., 1998).[219]

strain found in a soil sample collected in Malawi.[239] This molecule was found to display a very strong affinity for cyclophillin A (20-fold higher than cyclosporin A) and significant immunosuppressive activity (10-fold lower than cyclosporin A). Its mode of action seems to differ from other cyclophillin binders such as cyclosporin A and thus it raises a high interest for the understanding of immunosuppression mechanisms.

Sanglifehrin's chimeric structure is formed by a unique [5.5]-spirolactam fragment, linked to a 22-membered macrolactone ring that contains two unusual amino acid residues (piperazic acid and *meta*-tyrosine) as well as L-valine. Its unprecedented molecular features as well as its novel biological properties made sanglifehrin A a prime target for total synthesis. The first total synthesis of sanglifehrin A was

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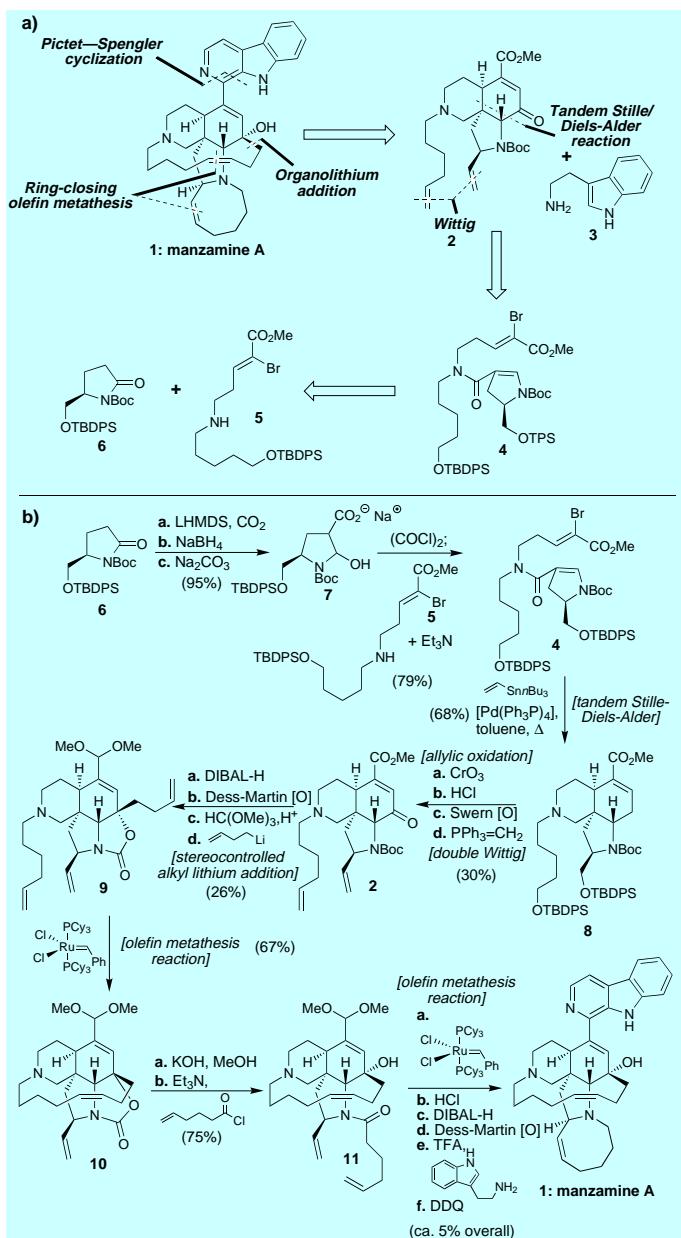
Scheme 46. a) Strategic bond disconnections and retrosynthetic analysis of manzamine A and b) total synthesis (Martin et al., 1999).[218]

achieved in our laboratories in 1999.[240] As indicated in Scheme 53, the two main domains of the molecule were assembled by an intermolecular Stille coupling. The construction of the sensitive iodomacrocycle fragment was performed by an esterification, two peptide couplings, and eventually a regioselective intramolecular Stille coupling. The synthesis of the spirolactam moiety involved the use of Paterson aldol reactions to establish the first five stereocenters, while the spirolactam fragment was formed by intramolecular cyclization of a suitable 9-hydroxy-5-keto-amide precursor. The developed chemistry demonstrated once again the power of the Stille coupling reaction in the synthesis of complex molecules and opened the way for the construction of possible libraries for biological screening purposes.

Everninomicin 13,384-1 (1999)

Everninomicin 13,384-1 (Ziracin; **1** in Scheme 52; see p. 102),[241] a member of the orthosomicin class of antibiotics[242] and currently in clinical trials, is a promising new weapon against drug-resistant bacteria including methicillin-resistant Staphylococci and vancomycin-resistant Streptococci and Enterococci.[243] Isolated from *Micromonospora carbonacea var africana* (found in a soil sample collected from the banks of the Nyiro River in Kenya), everninomicin 13,384-1 possesses a novel oligosaccharide structure containing two sensitive orthoester moieties, a 1,1′-disaccharide bridge, a nitrosugar, several β-mannoside bonds, and terminates with two highly substituted aromatic esters.[244]

As a consequence of its unusual connectivity and polyfunctional and sensitive nature, everninomicin 13,384-1 constituted a formidable challenge to organic synthesis. After several generations of glycosylation and protecting group strategies had been explored and new synthetic methodologies were developed, the total synthesis of everninomicin 13,384-1 was finally completed in our laboratories in 1999.[245] Highlights of this synthesis include: 1) the tin acetal-based stereocontrolled formation of the 1,1′-disaccharide linkage;[246] 2) the 1,2-migration of selenophenyl groups leading to selective orthoester formation based upon a modification of Sinaÿ's method;[247] and 3) the stereocontrolled formation of eight unique glycoside bonds using a variety of techniques including sulfur-, selenium-, and ester-based neighboring group participation.

Additional examples of natural products synthesized in the twentieth century are given in Figures 5–8 (see pp. 105–108),[350–458] but even this listing does not do justice to the science of those whose brilliant contributions are not mentioned here as a result of the limited space available and unintentional oversight. For a more complete picture, the reader should consult the primary literature.

4. What Have We Learned from a Century of Organic and Natural Product Synthesis?

During the twentieth century, we have come, through the electronic theory and understanding of the nature of the chemical bond and mechanistic insights, to adopt the arrow to designate bond making and bond breaking. During this revolutionary period for organic synthesis, we have also come to understand and use conformational analysis, and to use pericyclic reactions, anions and cations, as well as carbenes and radicals in controlled ways to form and break chemical bonds. The Woodward and Hoffmann rules brought understanding and generalization to pericyclic reactions such as the Diels–Alder reaction, the photoinduced [2+2] cycloadditions, and the various 1,3-dipolar cycloaddition reactions.

We have discovered new continents of chemistry and an amazing number of synthetic reactions based on heteroatoms and organometallic reagents and catalysts. Among the former are the chemistries of nitrogen, phosphorous, boron, sulfur, and silicon. Organometallic chemistry came a long way from the sodium and Grignard reagents to cuprates and titanium

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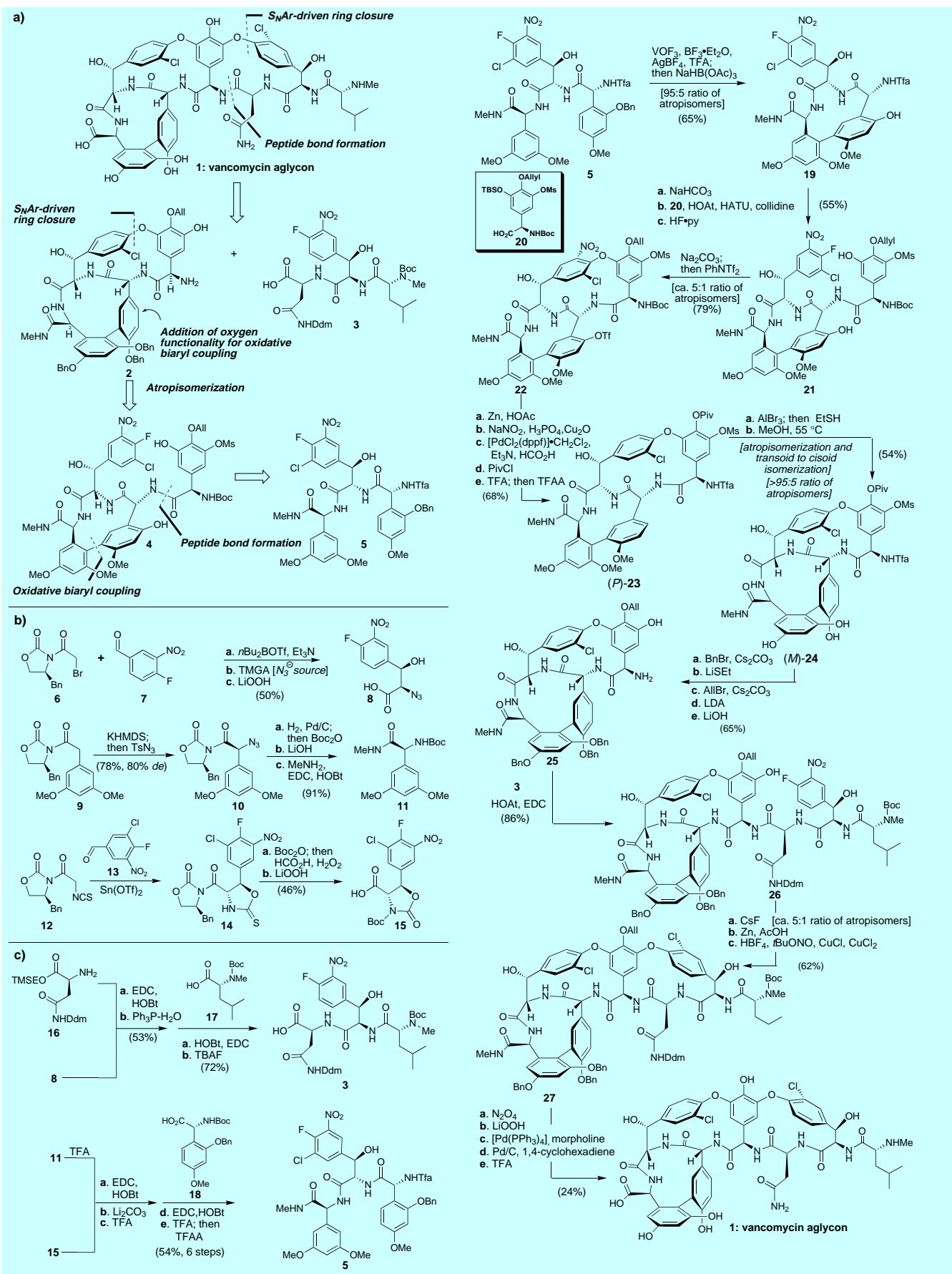
Scheme 47. a) Strategic bond disconnections and retrosynthetic analysis of vancomycin aglycon, b) key methodology for unnatural amino acid synthesis, and c) total synthesis (Evans et al., 1998).[223]

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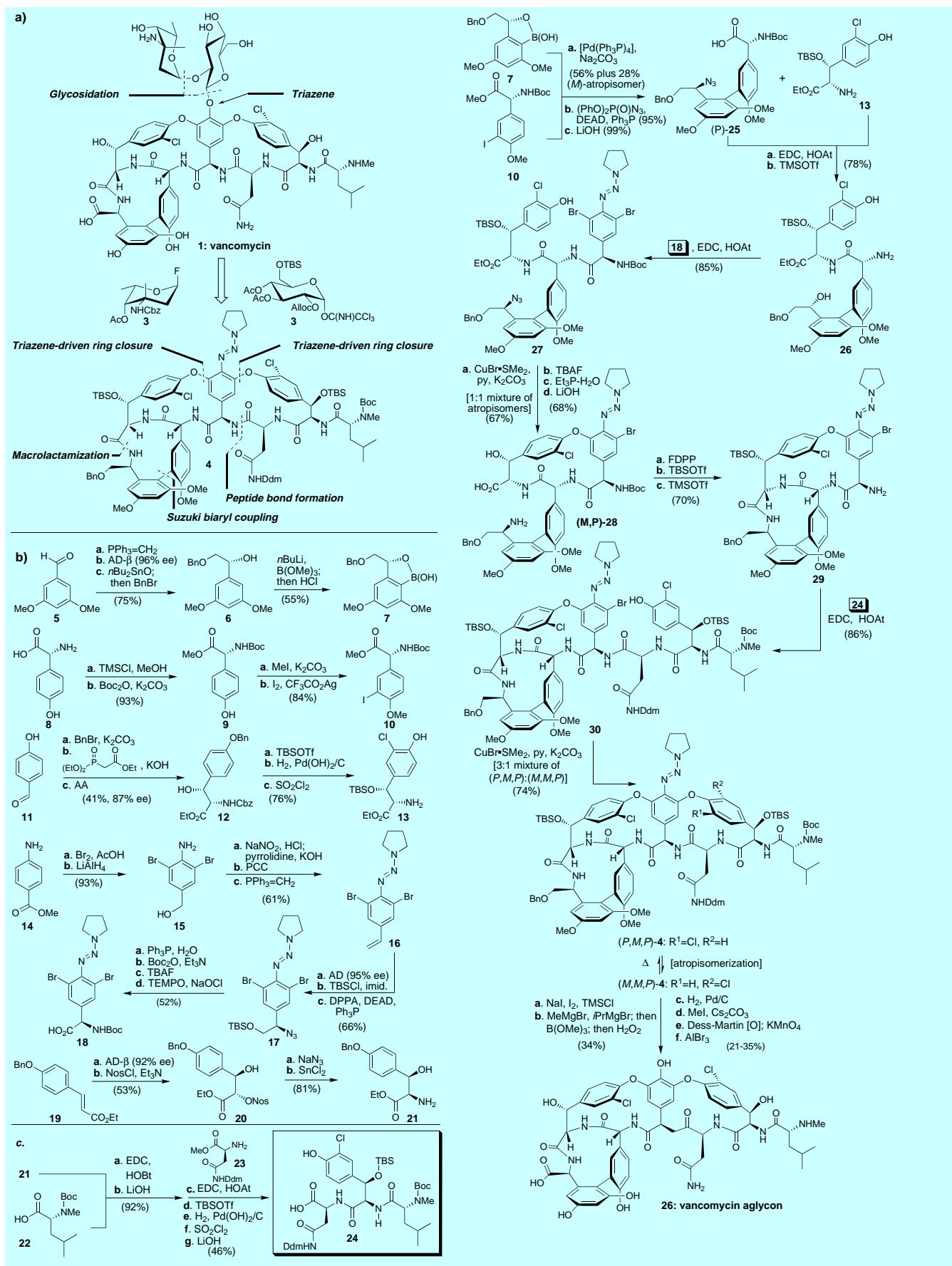
Scheme 48. a) Strategic bond disconnections and retrosynthetic analysis of vancomycin aglycon, b) key methodology for unnatural amino acid synthesis, and c) total synthesis of vancomycin (**1**) (Nicolaou et al., 1999).[224–226]

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c)
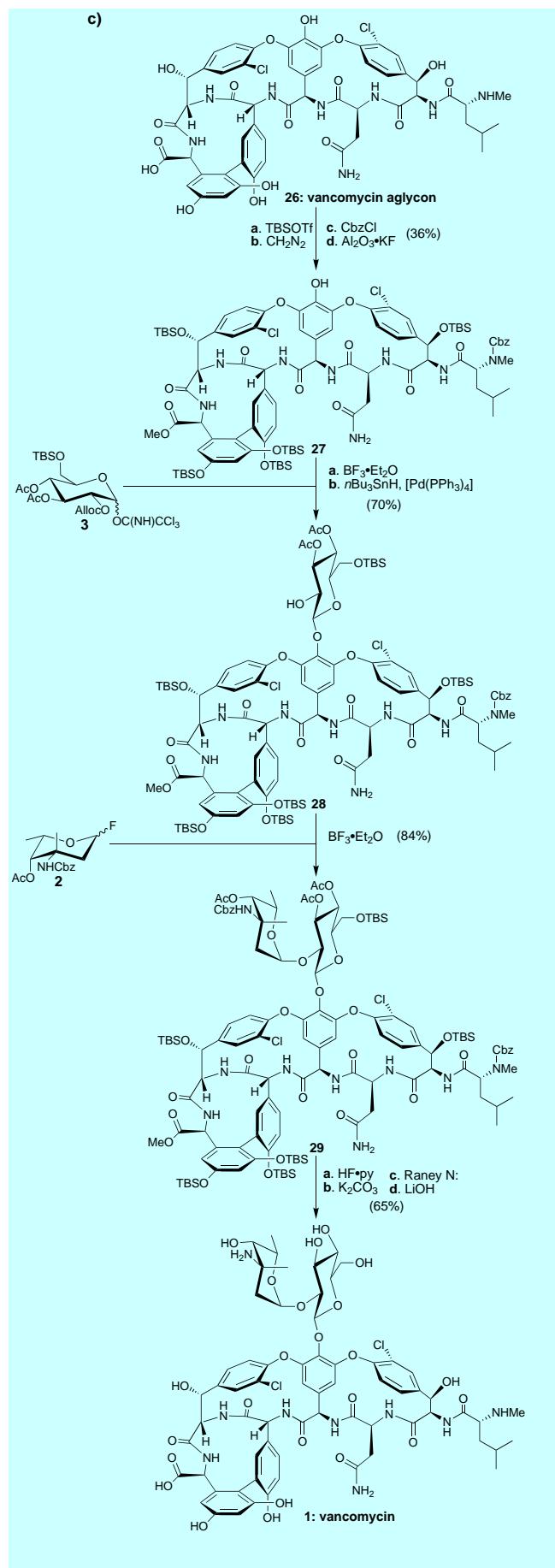
reagents. Of particular importance are the recent advances made in catalysis using transition metals both for the formation of carbon–carbon bonds and for asymmetric synthesis. The retrosynthetic analysis principles introduced by Corey revolutionized strategy design in total synthesis, while the many metal-catalyzed processes discovered during the second half of the century facilitated the construction of complex molecules in impressive ways. Most prominent among these catalytic processes are the various palladium-catalyzed reactions for carbon–carbon bond formation[248] and the olefin metathesis reaction[249] made synthetically useful by the Grubbs[250] (ruthenium) and Schrock[251] (molybdenum) catalysts. During this period, we have also witnessed the introduction of enzymes[252] as important tools for organic synthesis and of catalytic antibodies[253] as promising and useful reagents for synthetic and mechanistic studies, and the application of genetic engineering to total synthesis.[254]

In terms of stereochemical control, a journey through the twentieth century reveals the dramatic progress from stereochemically random reactions to stereocontrolled processes, first carried out in a reliable manner on cyclic templates and later on acyclic systems. Acyclic stereoselection, both via internal chiral auxiliaries and external catalysts, brought us not only to diastereoselective processes, but also to asymmetric synthesis. Particularly impressive have been the advances in asymmetric catalysis by which many building blocks and final targets can nowadays be synthesized at will. Classical optical resolution methods that characterized the early total syntheses are being replaced by stereoselective processes delivering only the desired enantiomer in high enantiomeric excesses. Such processes include the Hajos–Wiechert cycloaldol/dehydration reaction catalyzed by optically active amino acids,[255] the Knowles asymmetric hydrogenation process for the industrial production of L-DOPA employing soluble rhodium catalysts carrying chiral phosphane ligands,[256] the Takasago process for the production of L-menthol via an asymmetric catalytic amino–enamine isomerization employing a rhodium–BINAP catalyst,[257] the Noyori asymmetric catalytic hydrogenation of ketones ((S)- or (R)-[RuBr$_2$(binap)] catalyst),[258] the Katsuki–Sharpless asymmetric catalytic epoxidation ((L)-(+)- or (D)-(−)-diethyl tartrate/Ti(OiPr)$_4$ catalyst),[259] the Sharpless dihydroxylation reaction (OsO$_4$ catalyst),[165] the Corey oxazaborolidine-catalyzed reduction of ketones,[92] and the Shibasaki carbon–carbon bond forming reactions employing bimetallic catalysts.[260]

Cascade reactions in which several transformations are carried out in one reaction vessel in tandem have assumed increasing importance in total synthesis.[261] Such cascades can be defined as one-pot sequences involving fleeting intermediates, each of which leads to the formation of the next until a stable product is formed, or pathways marked with distinct intermediates that can be isolated if so desired, but which are allowed to proceed to the next stage until the desired product is obtained. By expanding the definition of cascade reactions one can include the various one-pot reactions in which a number of reagents and/or components are added sequentially to form a final product without isolation of intermediate

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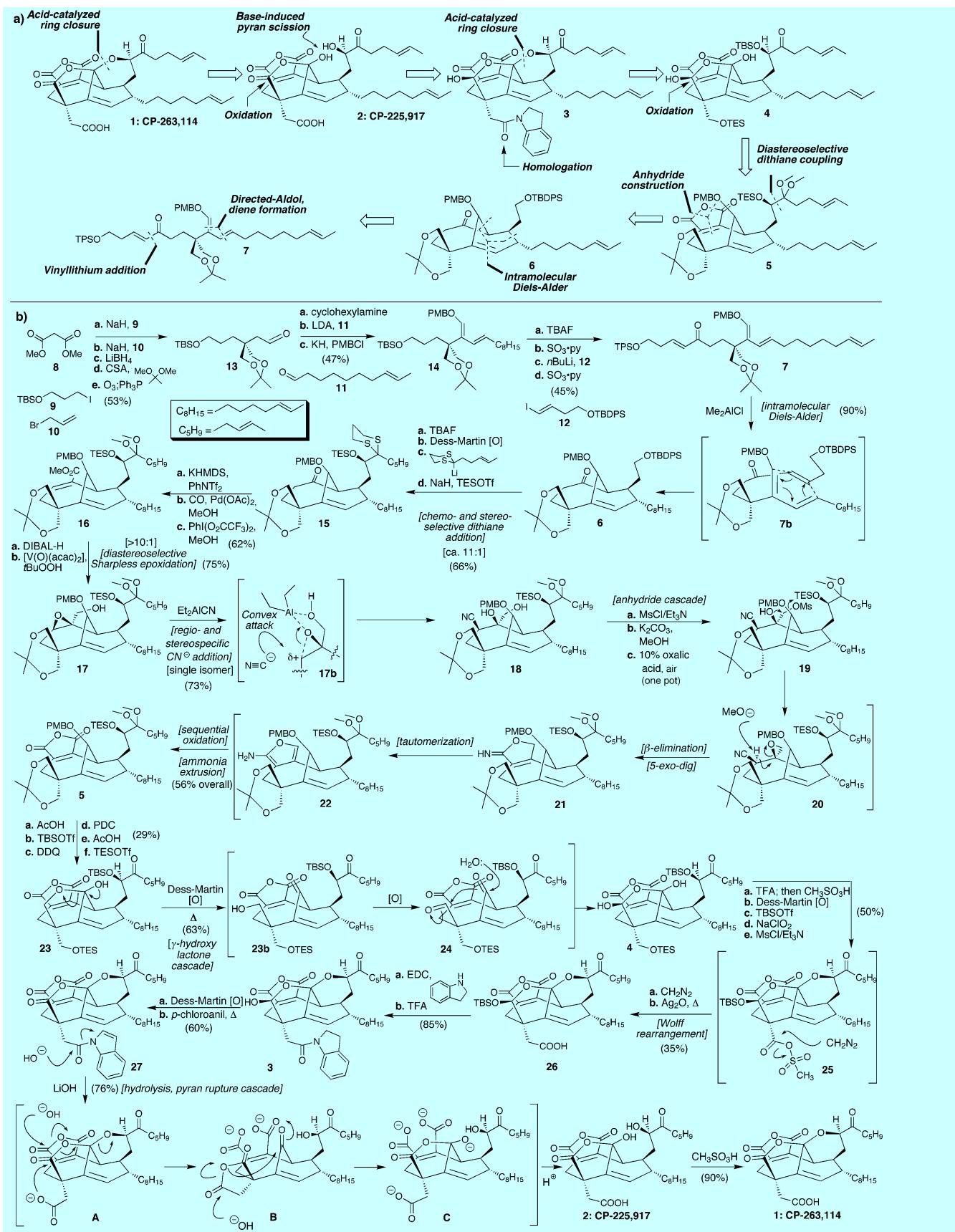
Scheme 49. a) Strategic bond disconnections and retrosynthetic analysis of the CP molecules (**1** and **2**) and b) total synthesis (Nicolaou et al., 1999).[230] c) New cascade reactions: the anhydride cascade, which features the first use of a highly unstable 2-aminofuran in the synthesis. The γ-hydroxylactonal cascade was developed as a mild method to construct the precursor to the fused γ-hydroxylactone moiety, the γ-hydroxylactonal. The pyran rupture cascade traverses through a sequence of intermediates, including the tetraanion **C**. d) New synthetic technologies. (For further information see the text.)

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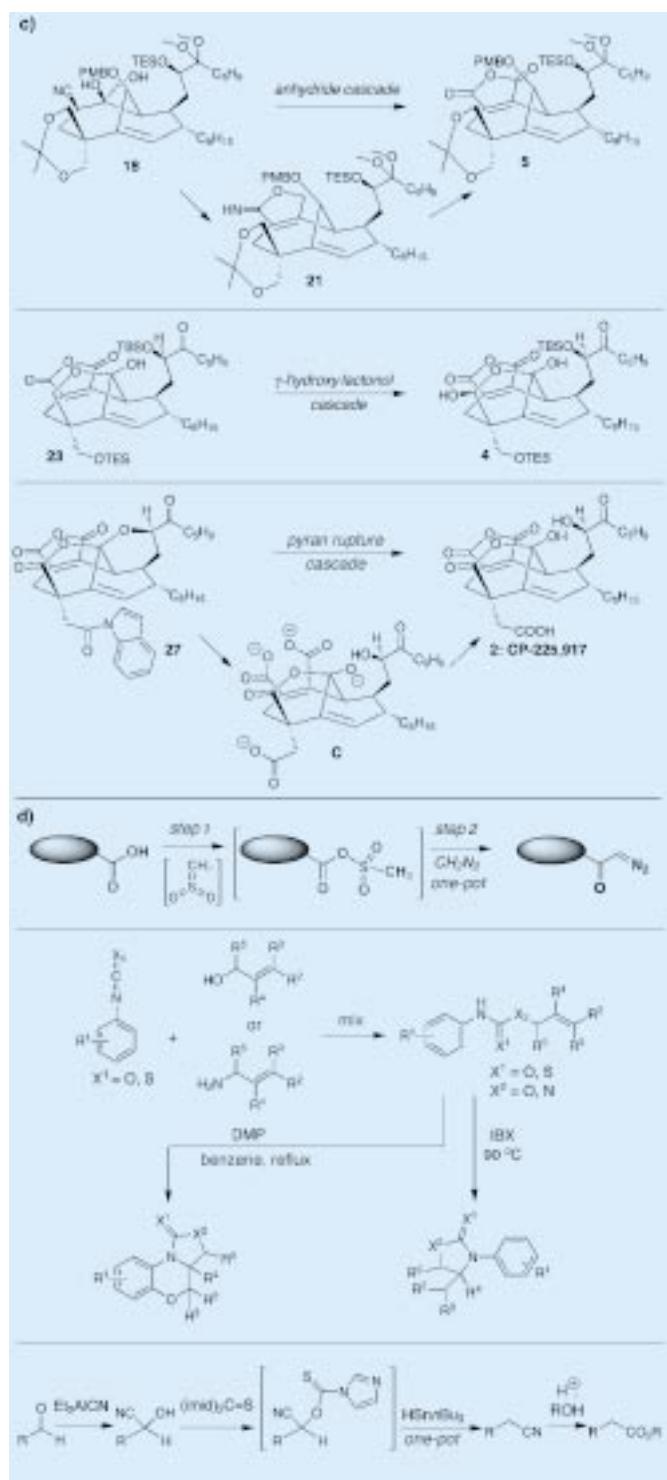
Scheme 49. (Continued)

compounds or work-ups. Examples of cascade reactions include the Robinson synthesis of tropinone,[16] the biomimetic synthesis of steroids,[262] the endriandric acid synthesis,[112] the Ugi three-component reaction,[263] the Vollhardt synthesis of estrone,[358h] the synthesis of the CP molecules and the many radical-based[264] and palladium-catalyzed[265] tandem sequences for the formation of polycyclic carbon frameworks.

5. The Impact of Total Synthesis

In tracing the evolution of organic synthesis and total synthesis to its present state, it is instructive to also consider its impact on other scientific disciplines and on society. Simply stated, this impact has been enormous and it boils down to profoundly shaping our world by providing the myriad synthetic materials we have around us today. To be sure, total synthesis has been aided by its own appeal and advances, but also by developments in analytical and purification techniques and spectroscopic methods.

5.1. Driving and Testing the State-of-the-Art in Organic Synthesis

As the flagship of organic synthesis, total synthesis often guides and demands new synthetic methods and strategies. It also becomes the testing ground where new technologies and strategic concepts are tested and judged for their applicability, efficiency, and practicality. In a way, total synthesis provides the tough and real challenges to new synthetic methods, often before they are passed over to those who use them extensively in their daily research and/or for their manufacturing needs. Indeed, the total synthesis of complex natural products is frequently given as the reason for the need to develop a new synthetic method to achieve a goal unattainable by existing methods. Furthermore, newly appearing synthetic methods become convincingly useful once they have been successfully applied to total synthesis. Examples here include the Diels–Alder reaction,[266] the Wittig reaction,[267] the hydroboration reaction,[268] the Corey dithiane reaction,[269] the Sharpless asymmetric epoxidation reaction,[259] the various palladium-catalyzed coupling reactions,[270] the olefin metathesis reaction,[271] and last but not least, the multitude of protecting groups available to the synthetic chemists.[272]

It is important to note that total synthesis not only drives organic synthesis forward in terms of synthetic technologies and strategies, but also frequently leads to fundamental theories and concepts. Thus, it was within the realm of the total synthesis of natural products that the theories of conformational analysis[273] (Barton and Hassel), the Woodward and Hoffmann rules,[98] and the Corey principles of retrosynthetic analysis[3, 4, 34] crystallized.

Today our desire and ability to make contributions to biology and medicine is driven to a large extent by total synthesis, which can deliver not only scarce natural products but also combinatorial libraries of related substances for biological evaluation purposes.

Total synthesis not only dictates and demands the invention and development of new synthetic strategies, but it also provides opportunities for the discovery of such methods and techniques. Such discoveries are made either through rational pursuit or simply by serendipity. Indeed, some of the most dramatic and influential discoveries of our century are fruits of serendipity. A remark made by Pasteur: "Serendipity, however, appears to be most generous to those positioned to
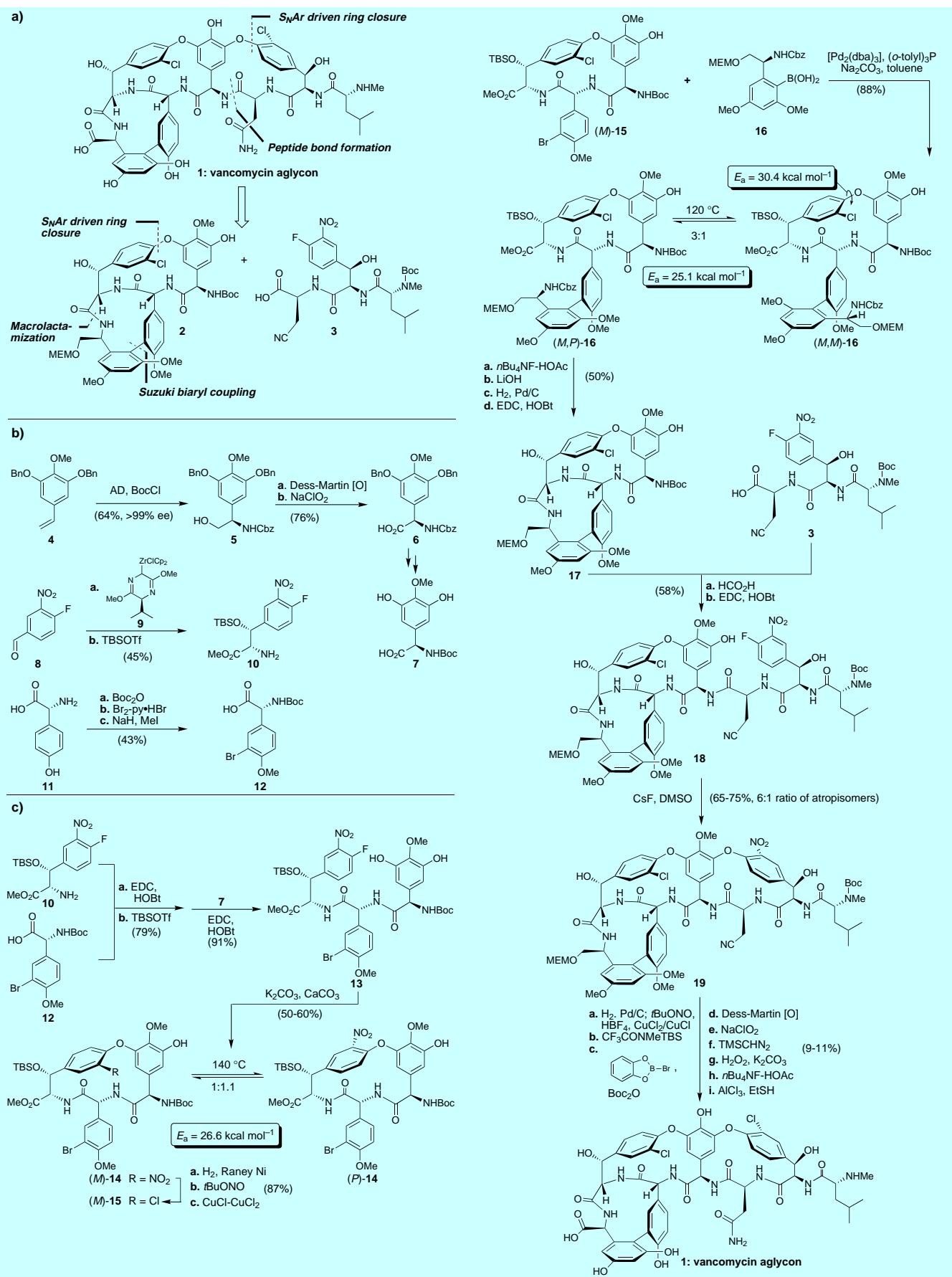
Scheme 50. a) Strategic bond disconnections and retrosynthetic analysis of vancomycin aglycon, b) key methodology for unnatural amino acid synthesis, and c) total synthesis (Boger et al., 1999).[227]

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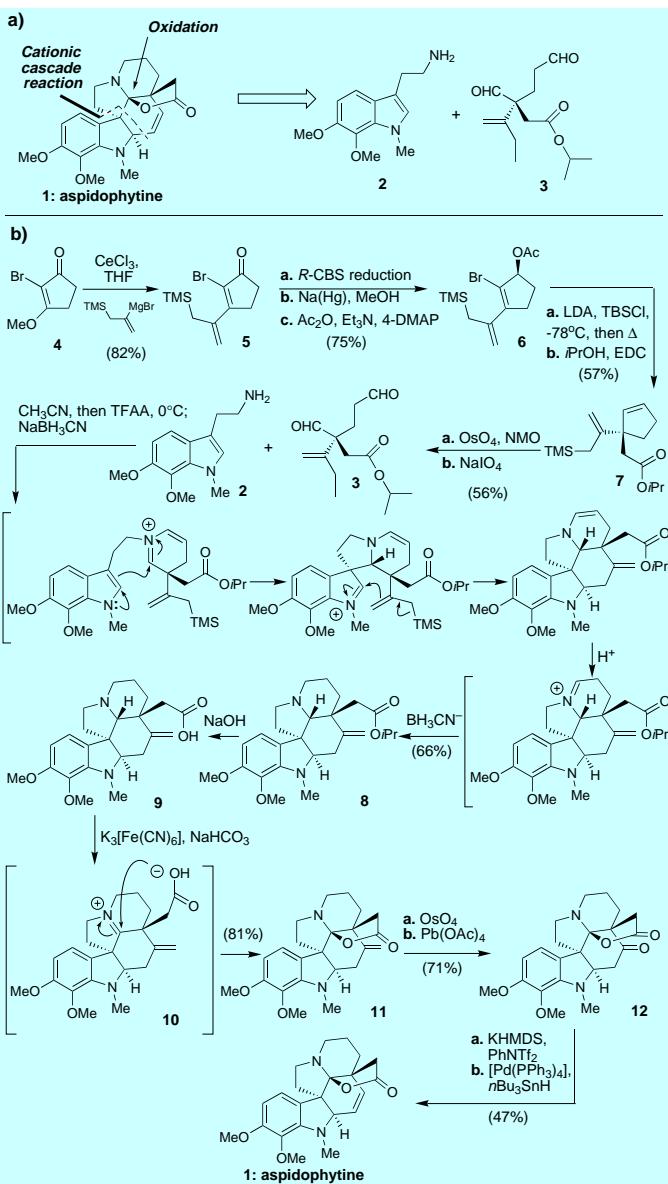
Scheme 51. a) Strategic bond disconnections and retrosynthetic analysis of aspidophytine and b) total synthesis (Corey et al., 1999).[238]

detect and exploit the accidental," is worthy of remembering. Serendipity will, no doubt, continue to be part of our science.

5.2. Drug Discovery and Development

While it is wonderful that total synthesis has made such great leaps from the beginning of the twentieth century, its greatest impact has been on the drug discovery and development process.[274] Indeed, the evolution of the drug discovery and development process parallels closely that of total synthesis. The two disciplines must be considered in unison, for they are very synergistic and complementary. Academic research focuses on organic and natural product synthesis, which provides highly relevant basic knowledge and offers superb education and training to young men and women

wishing to pursue the science of drug discovery and development process.

The pharmaceutical industry applies the knowledge gained to discovering and manufacturing new drugs for the benefit of society. That medicinal and combinatorial chemists have so many tools at their disposal today in their quests for huge numbers of novel and diverse small molecules is primarily the result of the contributions of total synthesis and of organic synthesis as a whole. A reminder of the importance of chemical synthesis as one of the two main arms of the drug discovery process—the other being identification of appropriate biological targets—will help appreciate total synthesis within a larger perspective. Just as advances in molecular biology facilitate drug discovery today by allowing the elucidation of the human genome and proteome, so does progress in total synthesis, which enables the construction of the molecules needed to bind and modulate the function of disease-associated biological targets.

The challenging and rewarding features of total synthesis invite competition, which, like in any other human endeavor, is both inevitable and healthy. Fortunately, and unlike many other sciences, the creative nature of organic and natural product synthesis allows equal opportunity for brilliant contributions to all practitioners, whether they are the first to finish or the last. And there are many things to discover and invent in this science; only our imagination is the limit.

6. Future Perspectives

The science and art of organic synthesis attracts many who practice invention, discovery, and development of new synthetic reactions and reagents for wider use. Such new processes and engineered reactions are of paramount importance to research chemists and manufacturers of chemical products including pharmaceuticals. Other synthetic chemists adopt total synthesis as their main endeavor, with the aim of designing and executing elegant strategies toward complex targets. In judging such accomplishments, one has to give credit not only to the beauty and efficiency of the strategies and tactics, but also to the value of the exercise in providing access to the target molecule and its analogues for, usually but not always, biological studies. Yet, there are others who attempt to combine target-oriented synthesis with the discovery and development of new synthetic technologies. And finally, there are those who aim to incorporate biology into their total synthesis programs as well as methodology development, thus elevating natural products to opportunities for creative science in total synthesis, synthetic methodology, and chemical biology.

All sub-disciplines of organic natural product synthesis are to be equally respected as important to the advancement of knowledge and the benefit of humankind. Furthermore, one can choose which of these dimensions he or she will adopt in their research programs, for all three have their place in science. Indeed, the beauty of total synthesis lies in the challenge and opportunities that it provides to make creative and useful contributions to many other disciplines. It is, therefore, up to the practitioner to imagine new directions and

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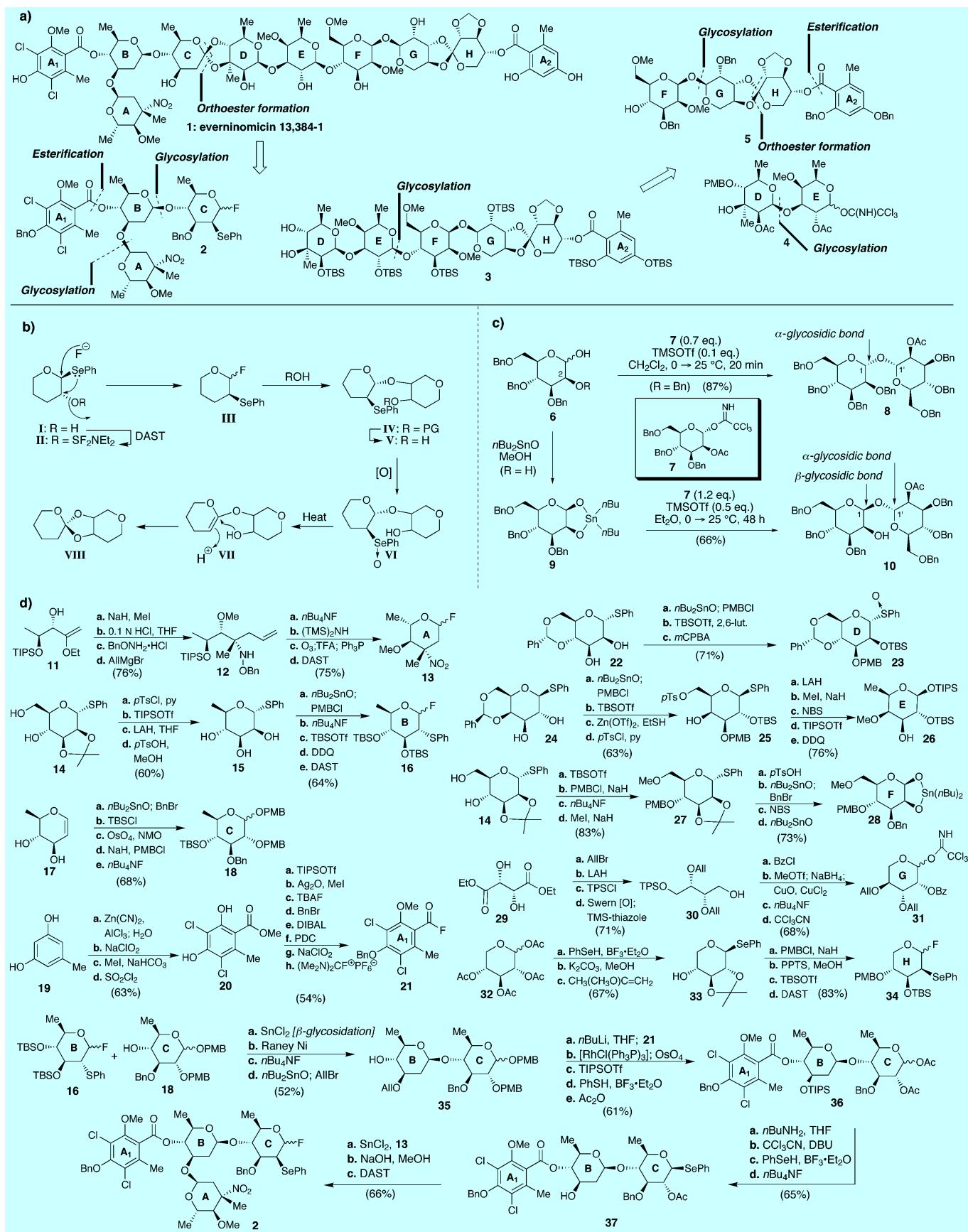
Scheme 52. a) Strategic bond disconnections and retrosynthetic analysis of everninomicin 13,384-1 and b, c)important synthetic methods; b) orthoester formation by 1,2-migration of the phenylselanyl group followed by glycosylation (**I→II→III→IV**), and ring closure after syn-elimination (**V→VI→VII→VIII**); c) stereoselective construction of 1,1′-disaccharides; d) synthesis of the building blocks and completion of the total synthesis of everninomicin 13,384-1 (Nicolaou et al., 1999).[245]

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Scheme 52. (Continued)

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a)

Brown crotylboration

Stille coupling

spirolactamization

1: sanglifehrin A

Stille coupling

amide bond formation

3

5

4

b)
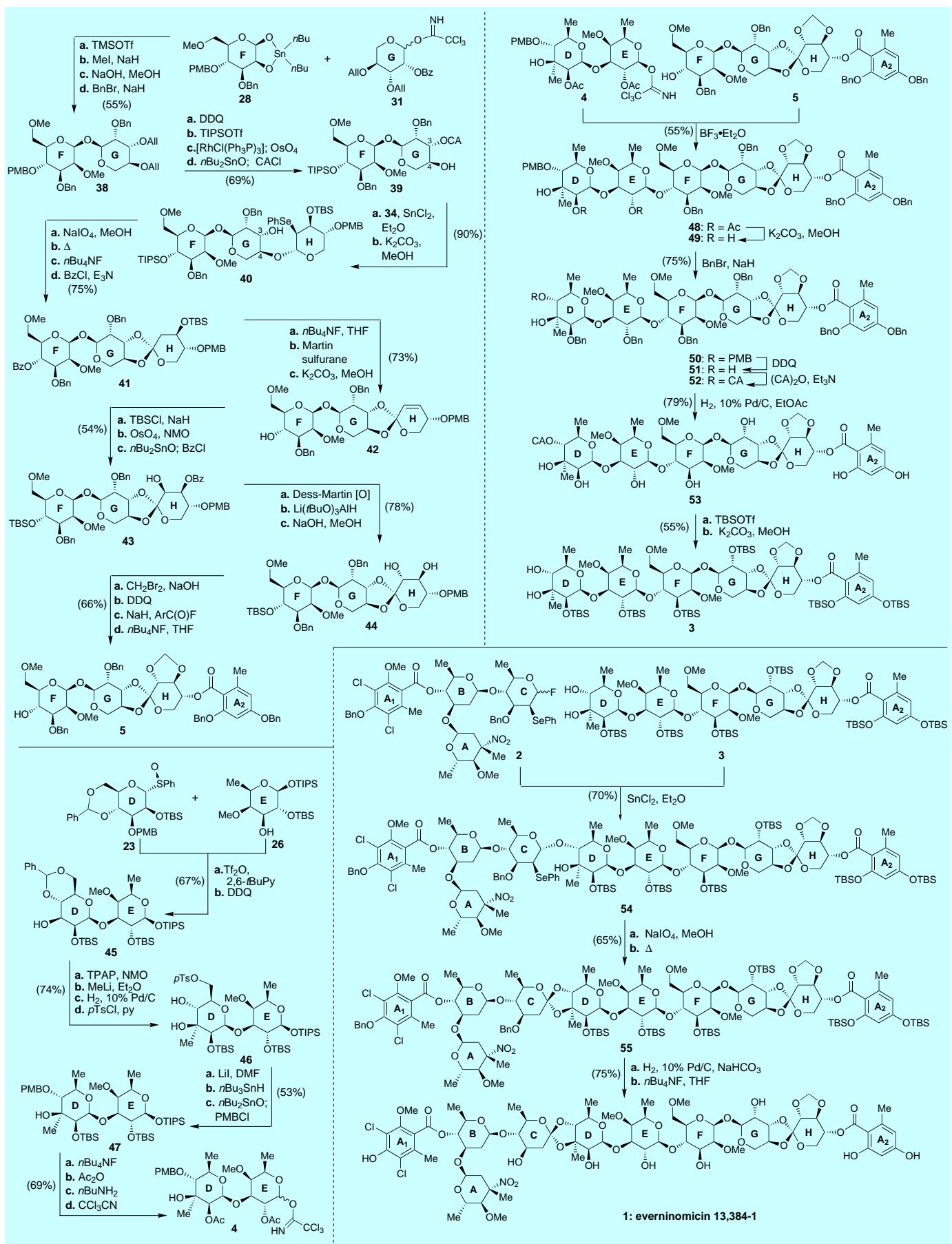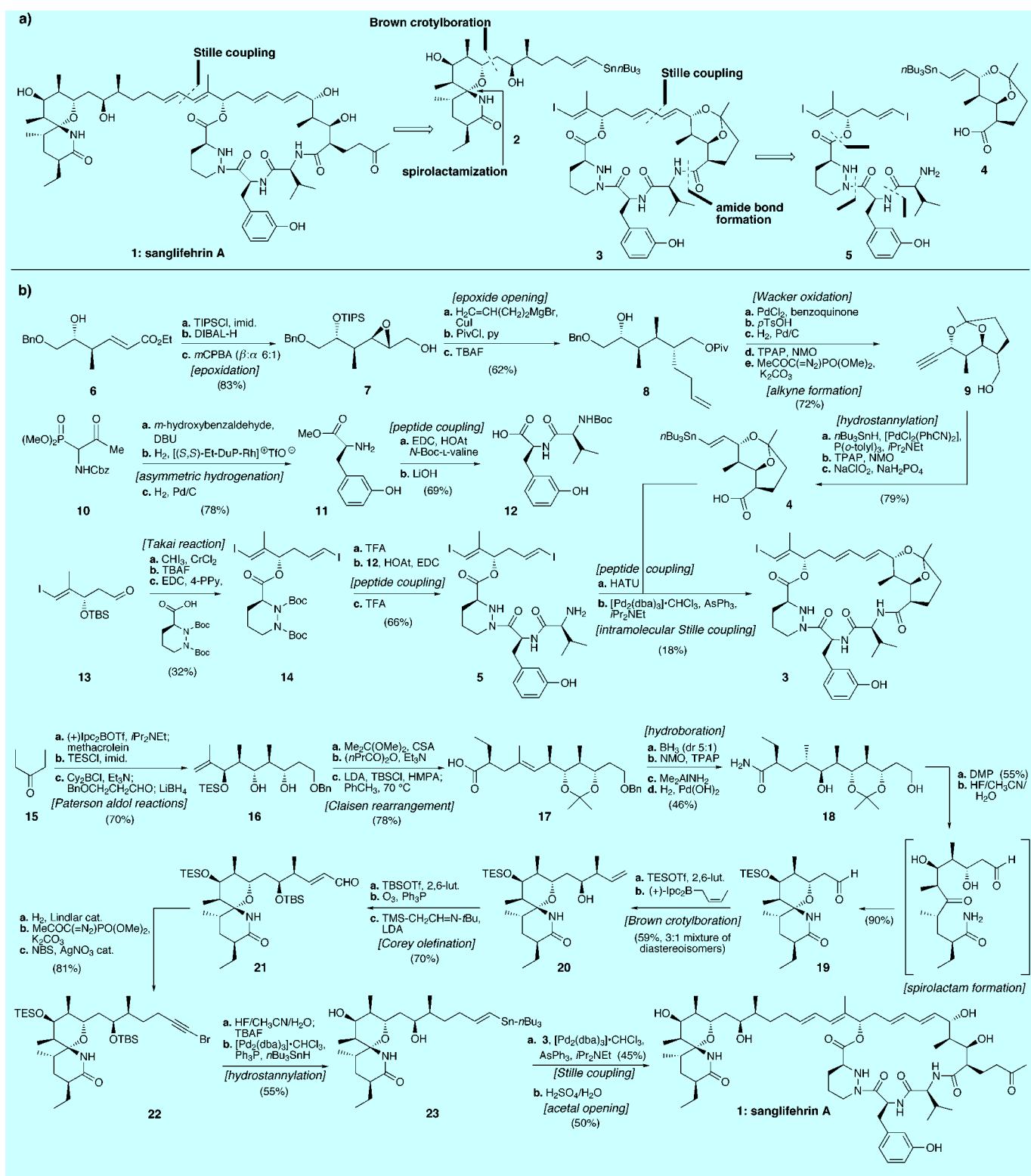
Scheme 53. a) Strategic bond disconnections and retrosynthetic analysis of sanglifehrin A and b) total synthesis (Nicolaou et al., 1999).[240]

to constantly raise the bar to higher and higher expectations for the art and science of organic and natural products synthesis.

Throughout its history the art and science of total synthesis has demonstrated its nature as an aesthetically appealing endeavor and as a scientifically important discipline. As a science and an art, it has attracted some of the most creative

minds of the twentieth century and its impact on society is paramount, if not fully appreciated by the general public. As we close the chapter of the twentieth century and move into the twenty-first century many may be wondering of the fate of total synthesis. The best guides we have are history and the present state-of-the-art. They both speak volumes of the vigor

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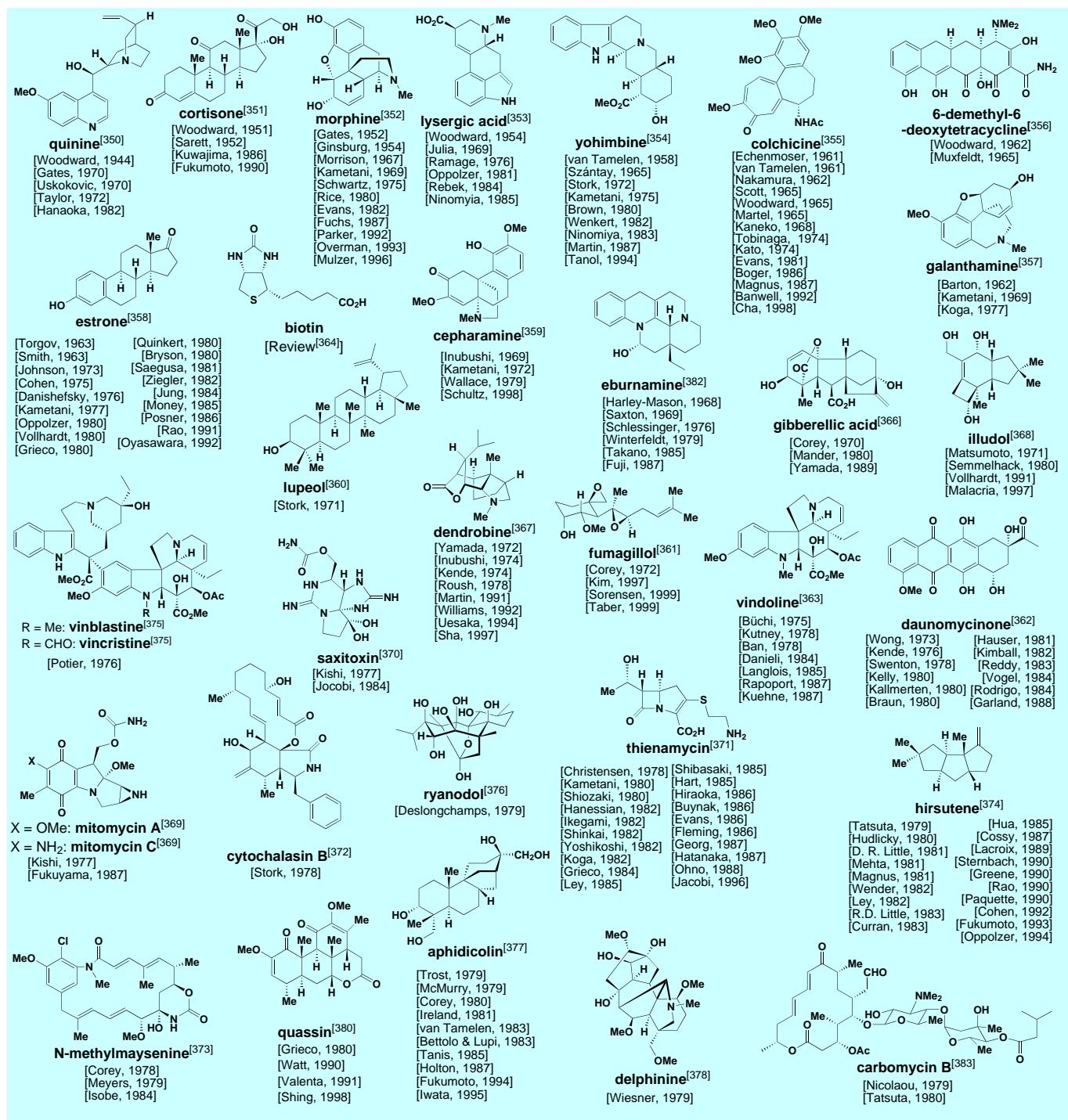
Figure 5. Selected natural product syntheses from the twentieth century.

of this art and science, and of its potential for further advances and contributions. For one, nature has not yet finished revealing its secrets to us, and many more novel, and presently unimaginable, structures are destined to dazzle our eyes, boggle our minds, and challenge our creativity. Furthermore, the state of the art is comparatively only in its early stages of development in light of nature's seemingly magical and powerful biosynthetic schemes. To be sure, the competitive nature of the pharmaceutical and biotechnology industries and their drive to discover and produce new cures for disease

will demand new and sharper tools for organic synthesis. Fueled by these and other industries, the discipline of total synthesis will be there to attract talented individuals as practitioners and to deliver the new tools needed for yet higher efficiencies and selectivities.

Targeting more complex structures will demand more effective reactions in terms of accomplishing bond constructions and functional-group transformations. The overall efficiency has to be pushed higher and so does selectivity. Cascade reactions and other novel strategies will have to be

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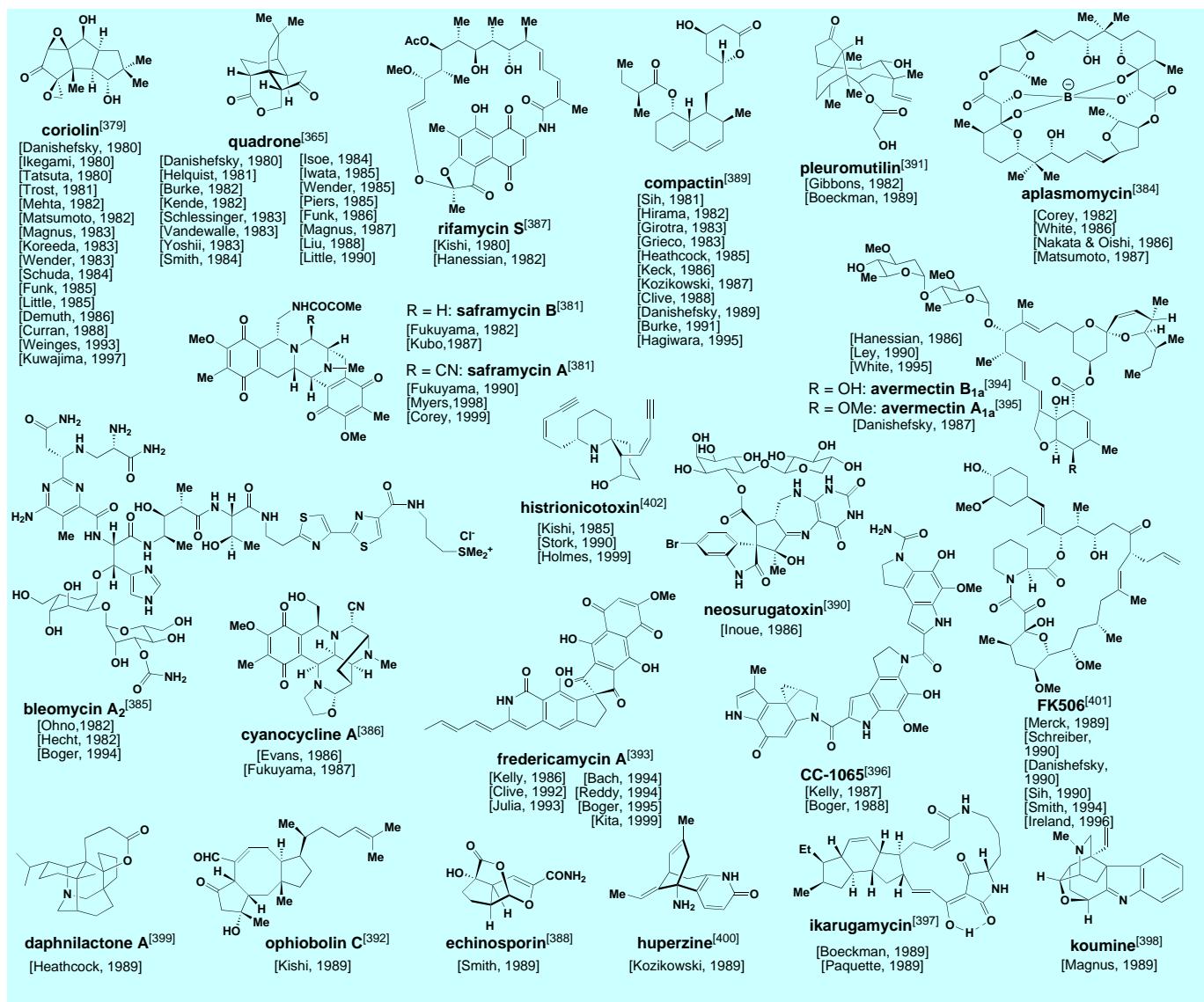
Figure 6. Selected natural product syntheses from the twentieth century.

devised for delivering complex and diverse structures in single operations in order to achieve such goals. New catalysts have to be invented to bring about otherwise difficult or impossible operations. There is little doubt that we can count on mother nature to provide us with the targets and the opportunities to invent and develop such methods in the future.

Solid-phase chemistry[275] is now gathering momentum in natural product synthesis. Traditionally used for the synthesis of peptides[276] and oligonucleotides,[277] this approach is now being applied to construct small organic molecules in large numbers, particularly for the purposes of drug discovery,[278] catalyst development,[279] and material science.[280] Again, new techniques, strategies, and tactics are needed to elevate this endeavor to a higher level of sophistication, applicability, and scope. As we have mentioned above, total synthesis is taking a leading role in spearheading developments in new technologies for solid-phase and combinatorial chemistry. With the strong foundation provided by such advances, automation of synthetic and combinatorial chemistry should also be possible

and forthcoming. Indeed, automation technologies are already entering the realm of chemical synthesis laboratories.[281] Finally, a goal of paramount importance for the ensuing century will undoubtedly involve the development of synthetic strategies for the rapid construction of complex natural products that rival or even surpass the efficiency of nature.

In addition to natural products and their analogues, synthetic chemists are also beginning to target complex and exotic natural productlike structures for the purpose of biological screening.[282] Such endeavors are clearly related to total synthesis and are both inspired and facilitated by advances in the latter field. Particularly enabling are those contributions that include both new synthetic technologies and novel molecular architectures. Examples of such endeavors include those from the Schreiber group,[283a] Sharpless group,[283b] and our own[283c] (Figure 9; see p. 108).

In closing, in surveying the art and science of total synthesis of the twentieth century, one is left with awe at its accomplish-

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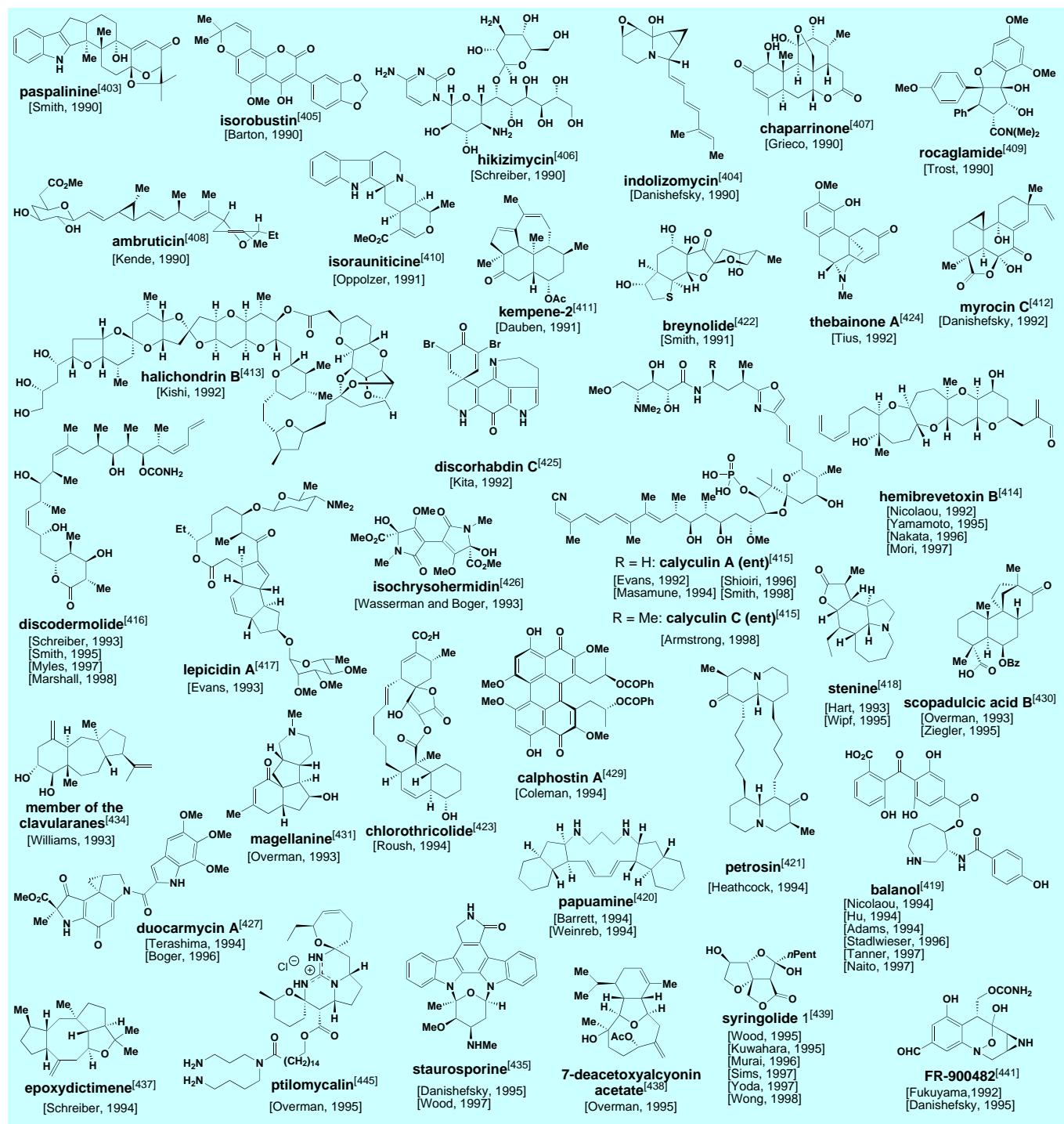
Figure 7. Selected natural product syntheses from the twentieth century.

ments and power. As a practitioner of the art, one is filled with overwhelming pride to be part of such attractive and vigorous endeavors and apprehensive in being responsible for conveying its true meaning and value to society.[284] But, most importantly, the surveyor must be overly excited and optimistic about the future of the discipline and in transferring this enthusiasm to the next generation of chemists. It would, indeed, be of considerable interest to compare the present state-of-the-art with that at the end of the twenty-first century.

Abbreviations

AA	asymmetric aminohydroxylation
Ac	acetyl
acac	acetylacetonyl
AD	asymmetric dihydroxylation
AIBN	2,2′-azobisisobutyronitrile
All	allyl
Alloc	allyloxycarbonyl
9-BBN	9-borabicyclo[3.3.1]nonane

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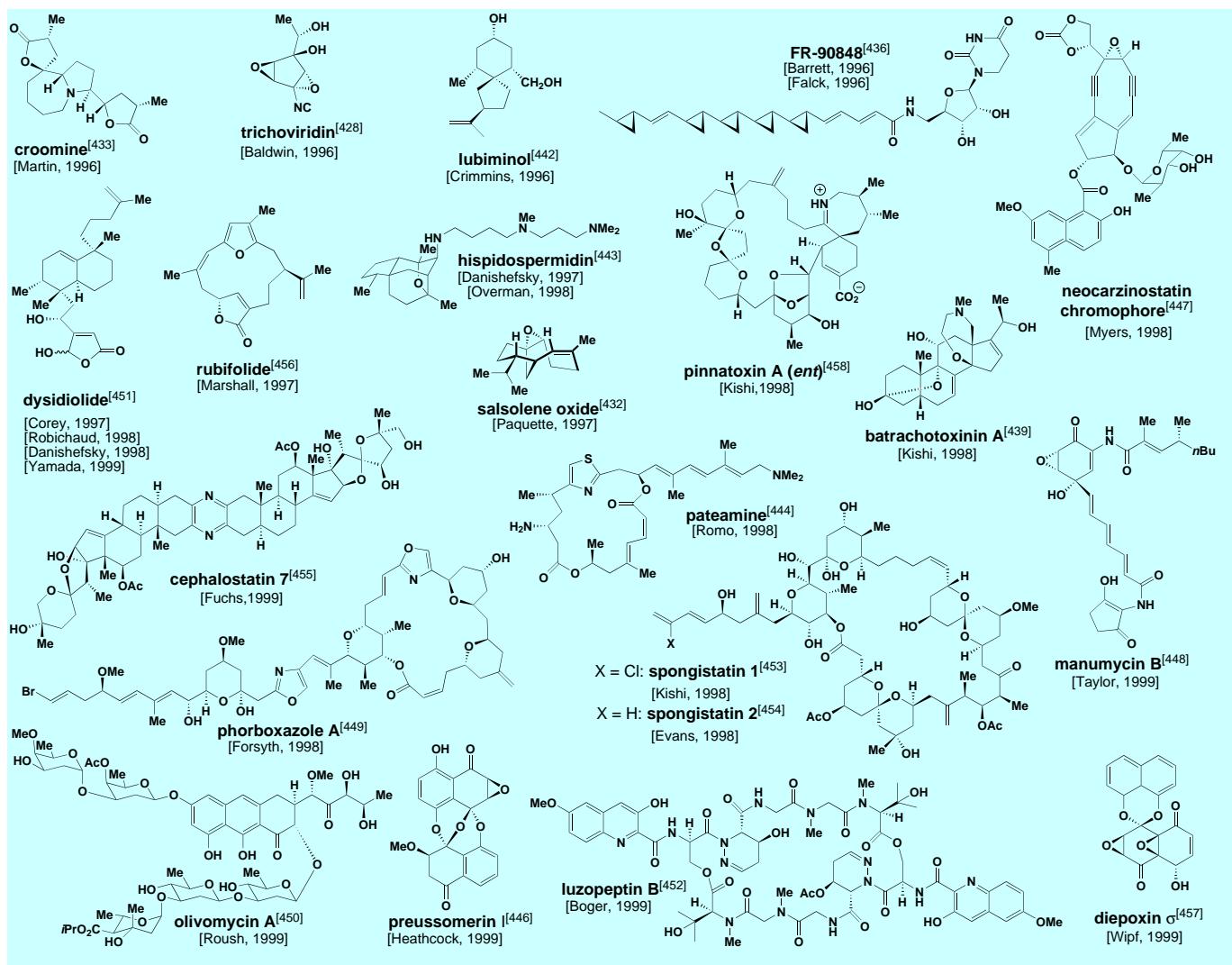
Figure 8. Selected natural product syntheses from the twentieth century.
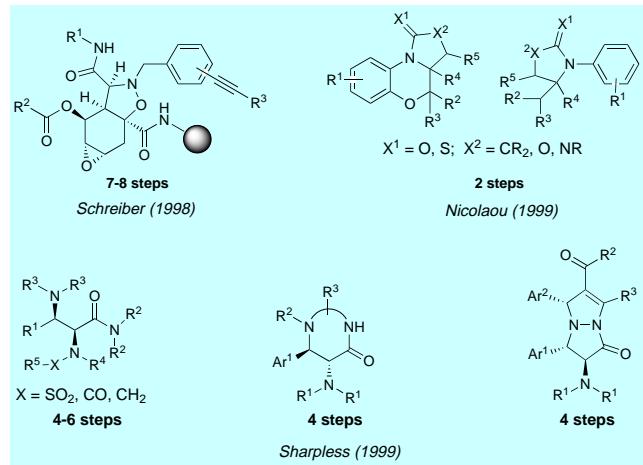
Figure 9. Novel, natural productlike, molecular architectures recently synthesized for biological screening purposes (number of steps from commercially available materials).[283]

BOP	benzotriazol-1-yloxy-tris(dimethylamino)phos-phonium hexafluoride
Bz	benzoyl
CA	chloroacetyl
CAN	cerium ammonium nitrate
Cbz	benzyloxycarbonyl
Cod	cyclooctadiene
Cp	cyclopentadienyl
CSA	10-camphorsulfonic acid
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DAST	(diethylamino)sulfur trifluoride
dba	*trans,trans*-dibenzylideneacetone
DBN	1,5-diazabicyclo[5.4.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCB	3,4-dichlorobenzyl
DCC	*N,N'*-dicyclohexylcarbodiimide
Ddm	4,4'-dimethoxydiphenylmethyl
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DEIPS	diethylisopropylsilyl
DET	diethyl trtrate

BINAP	2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl

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DHP	3,4-dihydro-*2H*-pyran
DIAD	diisopropylazodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIC	5-(3,3-dimethyl-1-triazenyl)-1*H*-imidazole-4-carboximide
DIPT	diisopropyl tartrate
DMA	*N,N*-dimethylacetamide
4-DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin-periodinane
DMPU	*N,N*-dimethylpropyleneurea
DMSO	dimethylsulfoxide
Dopa	3-(3,4-dihydroxyphenyl)alanine
DPPA	diphenyl phosphoryl azide
dppb	1,4-bis(diphenylphosphinyl)butane
dppf	1,1′-bis(diphenylphosphanyl)ferrocene
DTBMS	di-*tert*-butylmethylsilyl
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
FDPP	pentafluorophenyl diphenylphosphinate
Fmoc	9-fluorenylmethoxycarbonyl
HATU	*O*-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate
HBTU	*O*-benzotriazol-1-yl-N,N,N′,N′-tetramethyluronium hexafluorophosphate
HMDS	bis(trimethylsilyl)amide
HMPA	hexamethylphosphoramide
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxybenzotriazole
IBX	*o*-iodoxybenzoic acid
imid.	imidazole
Ipc	isopinocamphenyl
KSAE	Katsuki – Sharpless asymmetric epoxidation
LDA	lithium diisopropylamide
lut.	2,6-lutidine
*m*CPBA	3-chloroperoxybenzoic acid
MOM	methoxymethyl
Ms	methanesulfonyl
MSTFA	*N*-methyl-*N*-(trimethylsilyl) trifluoroacetamide
nbd	norbaranadine (bicyclo[2.2.1]hepta-2,5-diene)
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	4-methylmorpholine-*N*-oxide
Nos	4-nitrobenzolsulfonyl
OTf	trifluoromethanesulfonate
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PG	protecting group
Pht	phthalimidyl
Piv	pivaloyl
PMB	*p*-methoxybenzyl
PPTS	pyridinium 4-toluenesulfonate
*p*Ts	4-toluenesulfonyl
py	pyridine
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
SEM	2-(trimethylsilyl)ethoxymethyl
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl

TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TEOC	trimethylsilylethylcarbonyl
TES	triethylsilyl
Tfa	trifluoroacetyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TMGA	tetramethylguanidinium azide
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
TPS	triphenylsilyl
Tr	trityl

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