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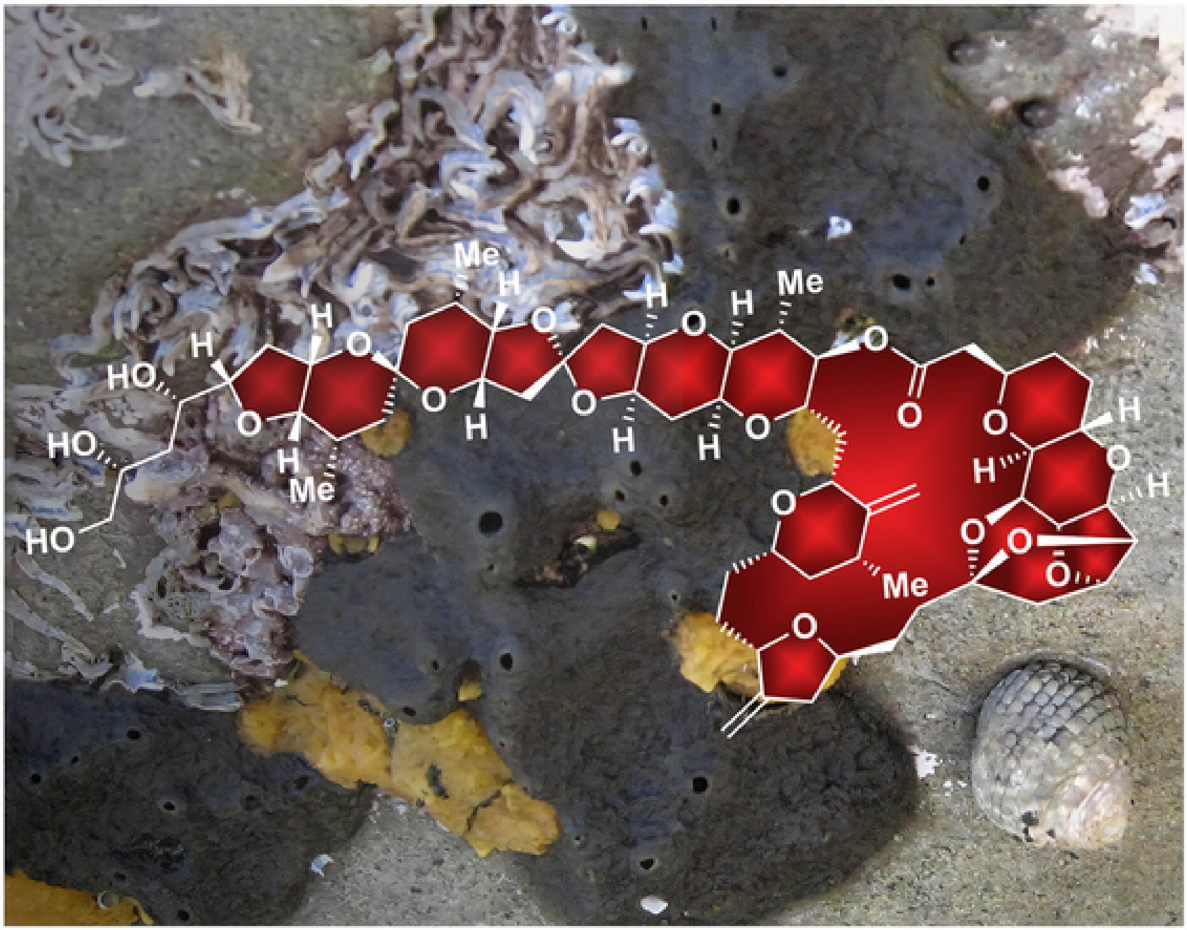
Classics in Total Synthesis IV

New Targets, Strategies, Methods



Classics in Total Synthesis IV

New Targets, Strategies, Methods

K. C. Nicolaou
Ruocheng Yu
Stephan Rigol

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Classics in Total Synthesis IV

K. C. Nicolaou
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New Targets, Strategies, Methods

With a Foreword by
E. J. Corey

WILEY-VCH

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Foreword

It is both an honor and a pleasure to pen the foreword for the fourth volume of *Classics in Total Synthesis*, as I did for the three previous volumes. This series has emerged as a guiding light in the ever-expansive realm of total synthesis. As we embark on this intellectual journey, it is essential to reflect on the profound impact that the preceding volumes have had on our understanding of the total synthesis of complex molecules.

Classics IV seamlessly joins its predecessors, weaving together the threads of scientific discovery, challenge, and intellectual pursuit. This series has proven to be not only a chronicle of synthetic triumphs but also a celebration of the inherent complexity and beauty, which are inherent to total synthesis endeavours.

As I delve into the prepublication draft of this volume, I find the presented synthetic research remarkably clear and vivid and find each of the chapters exerting a captive force. The collection of synthetic triumphs within these pages invites readers to traverse the great complexity and variety that is characteristic for total synthesis journeys. The challenges presented verge on the impossible, demanding not only mental and practical rigor but also unwavering dedication, persistence, and hard work.

One of the remarkable aspects of the *Classics in Total Synthesis* series has been its ability to transcend disciplinary boundaries. While rooted in chemistry, the series establishes strong connections with biology and medicine. This interdisciplinary approach highlights the relevance of synthetic chemistry at a fundamental level to human well-being, health, and education.

The educational approach employed by the authors is enormously valuable and effective. The careful balance between historical context, comments on the molecules' impact to humankind, and the design and execution aspects of each synthesis creates a narrative that is not only clear but also intellectually stimulating. It is a sheer delight to revisit each synthetic success guided by the insightful analyses found throughout *Classics IV*.

As mentioned in the Forewords of the earlier volumes, the enormous number of achievements in total synthesis is so large that capturing them all in a single collection is an impossible task. However, *Classics in Total Synthesis* has risen to this challenge with grace, presenting a carefully made selection that not only represents outstanding achievements, namely the construction of highly complex natural products, but also covers a diverse set of synthetic methodologies.

The question arises: Have we reached a plateau in scientific or intellectual discovery within the field of synthetic organic chemistry? The answer, as echoed by the authors, is a resounding no. The opportunities for new developments and discoveries are as vast as the

synthetic targets that remain to be uncovered, chased, and conquered. Today's total synthesis is not a culmination but a prelude to a future that promises continued dynamic development, relentlessly pushing the boundaries of what we perceive as possible.

In crafting this Foreword, I thank K. C. Nicolaou, Ruocheng Yu, and Stephan Rigol for their work in sustaining the heritage of *Classics in Total Synthesis*. May the publication of *Classics IV* be met with the same enthusiasm and admiration as it was rightly the case with its predecessors. I am confident that studying the *Classics* will empower upcoming generations of chemists, fostering a profound comprehension and appreciation for the significance of total synthesis. This endeavour will instill in them a deep understanding of the value and importance of natural products through showcasing the appealing beauty inherent to their molecular architectures and such insights will serve as catalyst, inspiring these aspiring chemists to embark on their own transformative journeys of exploration, discovery, and innovation.

E. J. Corey
Harvard University
23 January 2024

Preface

As we embark on the journey into the pages of this fourth volume in the *Classics in Total Synthesis* series, we find ourselves standing at the precipice of a new chapter in the evolving narrative of organic synthesis. This series, conceived with the dual purpose of documenting historical milestones and serving as an educational beacon, has traversed through the annals of synthetic chemistry, illuminating the paths carved by the practitioners of our field.

In the preceding volumes (*Classics I*, *Classics II*, and *Classics III*), we witnessed the meticulous unraveling of nature's complexity through ingenious synthetic strategies. *Classics I* laid the groundwork, introducing us to the profound philosophy and purpose of total synthesis. Building upon these foundational principles, *Classics II* expanded our horizons with a focused exploration of the transformative potential that the 21st century holds for synthetic chemistry. *Classics III* brought us up to speed with the rapid advancements of the recent era, showcasing the elegance, brevity, and environmental consciousness that characterize the latest synthetic frontiers.

As we delve into the rich tapestry of *Classics IV*, our aim remains steadfast—to chronicle the evolving landscape of total synthesis. This volume encapsulates the culmination of new methodologies, emerging trends, and a selection of significant total syntheses undertaken from 2009 to 2022 while additionally including two earlier syntheses from 1979 and 1992 for comparison and to highlight the development of organic synthesis over the past decades. In the spirit of its predecessors, *Classics IV* seeks to inspire and educate, weaving together the historical context, the intricacies of retrosynthetic analysis, and the tactical brilliance in execution.

From the complex architectures of natural products to the streamlined synthesis of functional molecules, each Chapter in *Classics IV* unfolds a unique story. The interplay of mechanisms, reactivity, selectivity, and stereochemical aspects is thoroughly examined, echoing the pedagogical format that has become synonymous with this series. Clear Schemes and Figures accompany the text, providing a visual guide to the sophisticated dance of atoms that is initiated by organic chemists, breaking bonds between some of them and forming new ones between others to build the molecules of Nature and their designed analogues in the laboratory.

The creation of *Classics IV* has been a collaborative endeavour, made possible by the dedication and insights of numerous individuals. Besides all scientists involved in the presented synthetic journeys, we extend our deepest gratitude to Janise L. Petrey for her careful editing, ensuring a seamless reading experience and bringing clarity to complex concepts; Jenna L. Kripal for her valuable assistance in creating stimulating and engaging frontispieces for each Chapter;

and the Editorial staff from Wiley-VCH for their professional and straightforward handling of our manuscript and its translation to the finished book that you are holding in your hands now.

We dedicate *Classics IV* to the continued legacy of organic synthesis and recognize the responsibility that lies ahead. To the students, researchers, and practitioners who hold these pages, we impart the torch of innovation and the quest for knowledge. May this volume inspire the next generation of synthetic organic chemists, just as its predecessors have done, to further sharpen the art and science of organic synthesis in general and total synthesis in particular for the betterment of humankind.

Houston, TX
September 2024

K. C. Nicolaou
Ruocheng Yu
Stephan Rigol

About the Authors

K. C. Nicolaou was born in Cyprus and educated in the United Kingdom and United States. He currently holds the Harry C. and Olga K. Wiess Chair in Natural Sciences at Rice University. His previous appointments include positions at the University of Pennsylvania and joint positions as the Darlene Shiley Chair in Chemistry and the Aline W. and L. S. Skaggs Chair in Chemical Biology at The Scripps Research Institute and as Distinguished Professor of Chemistry at the University of California, San Diego. The impact of his work in chemistry, biology, and medicine flows from his contributions to chemical synthesis as described in over 800 publications. He is the recipient of numerous Prizes, Awards, and Honors (e.g., Nemitsas Prize, Wolf Prize, and the Robert Koch Gold Medal) and has been elected to several Academies, such as the New York Academy of Sciences; the American Academy of Arts and Sciences; the American Philosophical Society; the Royal Society of London; the National Academy of Sciences (USA); the Royal Society of Chemistry (UK); the Cyprus Academy of Sciences, Letters and Arts; and the German Academy of Sciences Leopoldina.

Ruocheng Yu studied chemistry at Peking University, China, as an undergraduate student under the supervision of Zhen Yang and Jiahua Chen. After receiving his bachelor's degree in 2012, he went on to pursue his doctoral studies under the guidance of K. C. Nicolaou at The Scripps Research Institute and later Rice University. In the Nicolaou lab, he completed the total syntheses of several natural and designed molecules, including gukulenin B. He is currently a postdoctoral fellow in the laboratory of Emily Balskus.

Stephan Rigol received his higher education at Leipzig University, Germany, where he obtained his undergraduate degrees, and received his doctorate in 2013 after carrying out research in the fields of synthetic organic and medicinal chemistry under the guidance of Athanassios Giannis. He then moved to the United States to join the group of K. C. Nicolaou at Rice University where he is currently conducting research in the field of natural products chemistry with a particular focus on molecules with antibacterial and anticancer activities.

Abbreviations

18-crown-6	1,4,7,10,13,16-hexaoxacyclo-octadecane
4CzIPN	1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene
9-BBN	9-borabicyclo[3.3.1]nonane
A	adenine
Ac	acetyl
acac	acetoacetate
Ad	adamantane
AD	asymmetric dihydroxylation
ADC	antibody–drug conjugate
ADP	adenosine diphosphate
AIBN	2,2′-azobisisobutyronitrile
AIDS	acquired immunodeficiency syndrome
αKG	α-ketoglutaric acid disodium salt dihydrate
AK	actinic keratosis
Alloc	allyloxycarbonyl
amphos	di-*tert*-butyl(4-dimethylamino-phenyl)phosphine
aq.	aqueous
AQN	anthraquinone
ar **or** Ar	aryl
ATP	adenosine triphosphate
ATCC	American Type Culture Collection
ax	axial
AZADO	2-azaadamantane-*N*-oxyl
BAIB	bis(acetoxy)iodobenzene
BAr_F	tetrakis[3,5-bis(trifluoromethyl)-phenyl]borate
BDE	bond dissociation energy
BHT	2,6-di-*tert*-butyl-4-methylphenol
BINAP	([1,1′-binaphthalene]-2,2′-diyl)bis-(diphenylphosphane)
BINOL	2,2′-dihydroxy-1,1′-binaphthyl
BIPHEP	2,2′-bis(diphenylphosphino)-1,1′-biphenyl
Bn	benzyl
BNAH	1-benzyl-1,4-dihydronicotinamide
Boc	*tert*-butoxycarbonyl
BOM	benzyloxymethyl
BOP	bis(2-oxo-3-oxazolidinyl) phosphinic
bpy	2,2′-bipyridine
bpz	2,2′-bipyrazine
brsm	based on recovered starting material
Bu	butyl
Bz	benzoyl
C	cytosine
CAN	ceric ammonium nitrate
Cap	caproyl
Cas9	CRISPR associated protein 9
cat.	catalytic **or** catalyst
Cbz	benzyloxycarbonyl
CD	cluster of differentiation
CDI	1,1′-carbonyldiimidazole
CFL	compact fluorescent light
CIPE	complex-induced proximity effect
Cit	L-citrulline
Cl_4NHPI	tetrachloro-*N*-hydroxyphthalimide
CMD	concerted metalation–deprotonation
CNS	central nervous system
CoA	coenzyme A
cod	1,5-cyclooctadiene
coe	cyclooctene
Cp	cyclopentadienyl
CRISPR	clustered regularly interspaced short palindromic repeats
CSA	10-camphorsulfonic acid
CV	cyclic voltammetry
cy **or** Cy	cyclohexyl
Δ	heat
dab	2,9-bis(*p*-anisyl)-1,10-phenan-throline
DABCO	1,4-diazabicyclo[2.2.2]octane
DAST	(diethylamino)sulfur trifluoride
dba	(*E*,*E*)-dibenzylideneacetone
DBB	di-*tert*-butylbiphenylide
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DDT	dichlorodiphenyltrichloroethane
DEAD	diethyl azodicarboxylate
DERA	2-deoxy-D-ribose-5-phosphate aldolase

dF(CF_3)ppy	2-(2,4-difluorophenyl)-5-trifluoromethylpyridine
DG	directing group
DHPR	dihydropyridine receptor
DHQ	dihydroquinine
DIAD	diisopropyl azodicarboxylate
DIANANE	*endo*,*endo*-2,5-diaminonorbornane
DIBAL-H	diisobutylaluminium hydride
dibm	diisobutyrylmethane
DMAP	4-dimethylaminopyridine
DMDO	3,3-dimethyldioxirane
DME	ethylene glycol dimethyl ether
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DoM	directed *ortho*-metalation
DPBS	Dulbecco's phosphate-buffered saline
dpm	dipivaloylmethanato
DPPA	diphenylphosphoryl azide
dppb	1,4-bis(diphenylphosphino)butane
dppf	diphenylphosphinoferrocene
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
dtbbpy	4,4′-di-*tert*-butyl-2,2′-bipyridine
DTBM	di-*tert*-butyl-4-methoxyphenyl
dtbpy	4,4′-di-*tert*-butyl-2,2′-bipyridine
EBX	ethynylbenziodoxolone
EC_{50}	half maximal effective concentration
ECC	excitation–contraction coupling
EDCI	1-ethyl-3-(3-dimethylamino-propyl)carbodiimide
ee	enantiomeric excess
ep	error-prone
eq	equatorial
equiv	equivalent(s)
esp	*α*,*α*,*α*′,*α*′-tetramethyl-1,3-benzenedipropionic acid
ETP	epipolythiodiketopiperazine
EWG	electron-withdrawing group
Fc	ferrocenyl
FDPP	furanyldiketopyrrolopyrrole
FMO	frontier molecular orbital
fod	1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate
G	guanine
G2	gap 2
gen.	generation
Glc	glucose
GlyR	glycine receptors
GOase	galactose oxidase
HAT	hydrogen atom transfer
hfacac	hexafluoroacetylacetonate
HFIP	hexafluoroisopropanol
HIV	human immunodeficiency virus
HLF	Hofmann–Löffler–Freytag
HMDS	hexamethyldisilazane
HMG	3-hydroxy-3-methylglutaryl
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hsp	heat shock protein
HWE	Horner–Wadsworth–Emmons
hv	light
IBX	*o*-iodoxybenzoic acid
IC_{50}	50% inhibitory concentration
IC_{70}	70% inhibitory concentration
imid.	imidazole
Ipc	isopinocampheyl
i-Pr	isopropyl
IR	infrared
ISC	intersystem crossing
k	reaction rate constant
KHMDS	potassium hexamethyldisilazide
LA	Lewis acid
LBA	Lewis acid-assisted chiral Brønsted acid
LD_{50}	50% lethal dose
LDA	lithium diisopropylamide
LED	light-emitting diode
LG	leaving group
LiHMDS	lithium hexamethyldisilazide
liq.	liquid
LLG-5	*Linckia laevigata* ganglioside 5
LLS	longest linear sequence
LSF	late-stage functionalization
M	molar
M	mitosis
Mal	maleimido
MC	metal-centered
m-CPBA	*m*-chloroperoxybenzoic acid
MDR	multi-drug resistance

MeOH	methanol
MES	mesityl (2,4,6-trimethylphenyl)
MIC	minimum inhibitory concentration
MLCT	metal-to-ligand charge transfer
MMPP	magnesium monoperoxyphthalate hexahydrate
MMTrCl	4-methoxytriphenylmethyl
MNBA	2-methyl-6-nitrobenzoic anhydride
modp	bis(1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentanedionato) [i.e., 4-[5,5-dimethyl-2,4-di(oxo-κ*O*)-1-oxohexyl]morpholinato]
mol.	molecular
MOM	methoxymethyl
MoOPH	oxodiperoxymolybdenum-(pyridine)(hexamethylphosphoric triamide)
MPAA	mono-*N*-protected amino acid
MPO	4-methylpyridine *N*-oxide
Ms	methanesulfonyl
MS	molecular sieves
MVK	methyl vinyl ketone (butenone)
MW	microwave
N	normal (equivalent concentration)
NAD^+	nicotinamide adenine dinucleotide (oxidized form)
NADH	nicotinamide adenine dinucleotide (reduced form)
$NADP^+$	nicotinamide adenine dinucleotide phosphate (oxidized form)
NADPH	nicotinamide adenine dinucleotide phosphate (reduced form)
NaHMDS	sodium hexamethyldisilazide
Nap	naphthalenide **or** naphthalenyl
NBS	*N*-bromosuccinimide
NCIMB	National Collection of Industrial, Food and Marine Bacteria
NCS	*N*-chlorosuccinimide
Nf	nonafluorobutanesulfonyl
NHC	*N*-heterocyclic carbene
NHK	Nozaki–Hiyama–Kishi
NIR	near-infrared
NIS	*N*-iodosuccinimide
NMM	*N*-methylmorpholine
NMO	4-methylmorpholine *N*-oxide
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Ns	nitrobenzenesulfonyl
Nu	nucleophile
ox	oxalate
PABC	*p*-aminobenzyloxycarbonyl
PAF	platelet-activating factor
PAFR	platelet-activating factor receptor
PanK	pantothenate kinase
PBR	peripheral benzodiazepine receptor
Pc	phthalocyanine
PCC	pyridinium chlorochromate
PCR	polymerase chain reaction
PDC	pyridinium dichromate
PDP	2-({(*S*)-2-[(*S*)-1-(pyridin-2-ylmethyl)pyrrolidin-2-yl]pyrrolidin-1-yl}methyl)pyridine
PdPc	palladium(II) octabutoxyphthalocyanine
PET	positron emission tomography **or** photoinduced electron transfer
PG	protecting group
Ph	phenyl
phen	1,10-phenanthroline
PHOX	2-[2-(diphenylphosphino)phenyl]-2-oxazoline
pin	pinacolato
PIPES	piperazine-*N*,*N*′-bis(2-ethane-sulfonic acid)
Piv	pivaloyl
PKC	protein kinase C
PKS	polyketide synthase
PMB	4-methoxybenzyl
PMP	4-methoxyphenyl **or** 1,2,2,6,6-pentamethylpiperidine
PNP	*p*-nitrophenol **or** purine nucleoside phosphorylase
PPM	phosphopentomutase
PPO	pyrophosphate
PPTS	pyridinium 4-toluenesulfonate
ppy	2-phenylpyridine
PS-BEMP	polystyrene-bound 2-*tert*-butyl-imino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine
py	pyridine
PyOX	2-(pyridin-2-yl)-4,5-dihydrooxazole
quant.	quantitative
RCM	ring-closing metathesis
Red-Al	sodium bis(2-methoxyethoxy)aluminium hydride
RHF	restricted Hartree–Fock model

RNA	ribonucleic acid
rsm	recovered starting material
RyR	ryanodine receptor
Sal	salen
SAR	structure–activity relationship
SCE	saturated calomel electrode
SET	single-electron transfer
Sia	siamyl
SP	sucrose phosphorylase
sp.	species
T	thymine
TAS-F	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBADT	tetra-*n*-butylammonium decatungstate
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBD	triazabicyclodecene
TBDPS	*tert*-butyldiphenylsilyl
TBDPSCl	*tert*-butyldiphenylchlorosilane
TBHP	*tert*-butyl hydroperoxide
TBOx	tethered bis(8-quinolinolato)
TBS	*tert*-butyldimethylsilyl
TCAI	trichloroacetimidate
TCPTAD	adamantan-1-yl-(4,5,6,7-tetra-chloro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)acetate
TDAE	tetrakis(dimethylamino)ethylene
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy, free radical
Teoc	2-(trimethylsilyl)ethoxycarbonyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
tfb*	tetrafluorobenzobarrelene
TFMS	zinc trifluoromethanesulfinate
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
Tle	*tert*-leucine
TMEDA	*N*,*N*,*N′*,*N′*-tetramethylethylene-diamine
TMP	2,2,6,6-tetramethylpiperidide
tmphen	3,4,7,8-tetramethyl-1,10-phenanthroline
TMS	trimethylsilyl
TMTU	tetramethylthiourea
tol **or** Tol	tolyl
TPAP	tetra-*n*-propylammonium perruthenate
TPCP	1,2,2-triphenylcyclopropane-carboxylate
TPP	tetraphenylporphyrin
Tris	2,4,6-triisopropylbenzenesulfonyl
Ts	4-toluenesulfonyl
TS	transition state
Txn	trioxacarcin
UHP	urea hydrogen peroxide complex
USSR	Union of Soviet Socialist Republics
UV	ultraviolet
vs.	versus

Contents Overview

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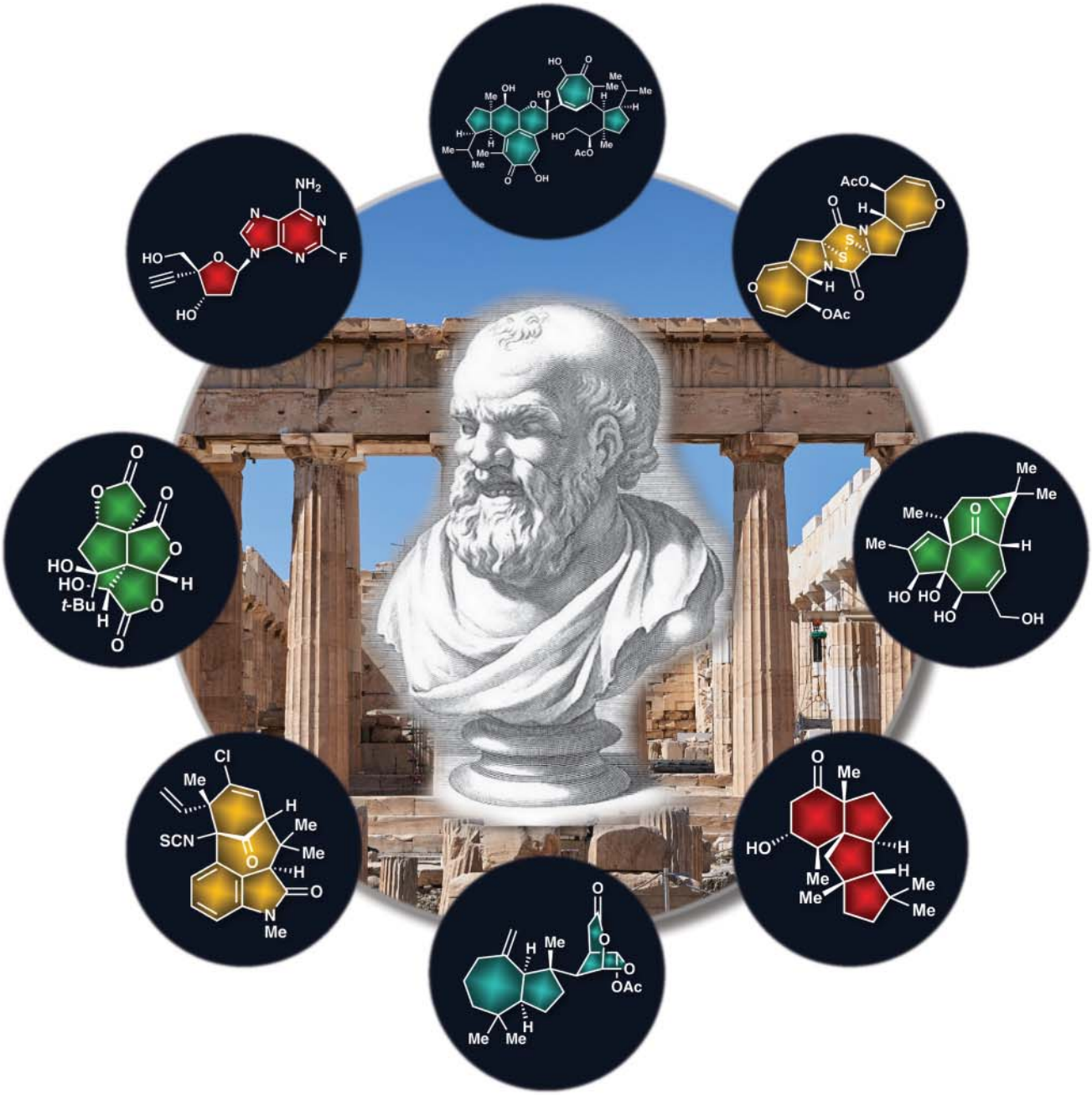
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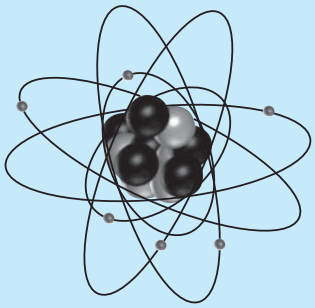

1

Introduction: Total Synthesis Marching on with New Methods and Strategies and with Molecules for Biology and Medicine

With its power constantly increasing, the essence of total synthesis remains the same. What changes is its purpose. Originally, it was to confirm a proposed structure of a natural product, then it became a means to produce natural products in bulk as a means to fulfill a need for society. From here it turned into a practice to demonstrate intellect and elegance, along with an opportunity to discover and develop new synthetic methods, to test the applicability of newly discovered methods, and to fill voids where existing methods failed. The ability of biochemists and other chemists to isolate minute amounts of natural products and determine their structures created the need to render them readily available for biological investigations. This challenge was taken up by synthetic chemists in the last decades of the 20th century, who delivered, through total synthesis, not only the targeted scarce natural products but also their designed analogues for extensive biological studies. Today, total synthesis endeavours blend all these aspects of the art and science of this discipline with

Classics in Total Synthesis IV: New Targets, Strategies, Methods, First Edition.
K. C. Nicolaou, Ruocheng Yu, and Stephan Rigol.

constant new additions. In its modern paradigm, and with mission, total synthesis is gathering momentum as a harmonious endeavour aiming not only for its own advancement but also as a partner to biology and medicine in a systematic way. It has a profound impact on the sciences of chemistry, biology, and medicine, specifically interfacing and facilitating chemical biology, medicinal chemistry, and the drug discovery and development process in general.

Classics in Total Synthesis IV features a variety of total syntheses that have been published in the literature since 2009 and more. For comparison and perspective reasons, the total syntheses of natural products related to those covered herein are, in certain cases, included. And while the main focus of the book is still the art and science of total synthesis, aspects of new synthetic methods and analogue design, synthesis, and biological investigation are also discussed. The latter underscores the trends in the state of the art of the discipline and emphasizes its importance to the science of organic synthesis in general and its impact on biology and medicine. It is also interesting to note that total synthesis still retains, to this day, its role of structure confirmation or revision, despite the enormous progress in analytical techniques and instrumentation. Statistics based on past total synthesis endeavours originating from the Nicolaou group, which have delivered almost 200 naturally occurring molecules, show that 13% of them contributed, in one way or another, to some structural aspect of the molecule, whether absolute configuration, revision of at least one stereogenic center of the previously assigned structure, or even its total synthesis and prediction of its existence in Nature before it was discovered. These seemingly odd occurrences are still common. However, the errors should not be attributed to the heroes of isolation of natural products. Due to the scarcity of numerous naturally occurring compounds, their characterization is regularly conducted by investigating only minute amounts, which, understandably, sometimes results in inaccuracies concerning their structure. These investigators did not have the privilege of collecting sufficient quantities of their products from their rare sources, a fact denying them the full armamentarium of analytical techniques, including the optimum tool of X-ray crystallography.

1.1 Targets

Nature's molecules are of unimaginable variety, complexity, novelty, and biological activity. This is more impressive if one considers the limited collection of building blocks, reactions, enzymes, and conditions as compared to the vast number of building blocks, ever-growing number of synthetic methods, catalysts, and reaction conditions that synthetic organic chemists enjoy, and yet we still have to surpass Nature's power and beauty when it comes to biosynthesis and novelty of natural products' structures.

Figure 1 highlights a selected number of natural products featured in this book, *Classics IV*, and yet these molecules represent

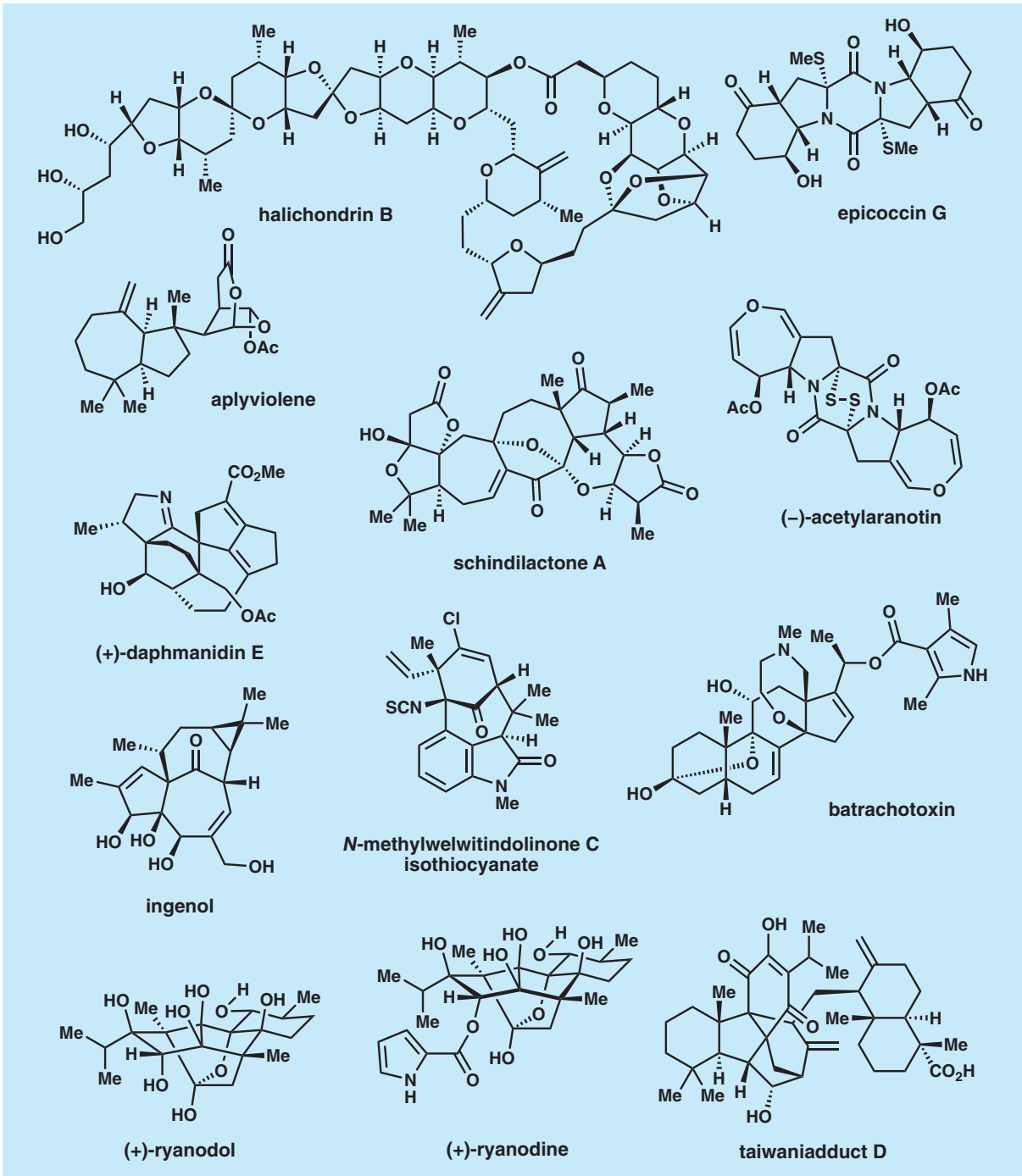

Figure 1. Molecular structures of selected natural products featured.

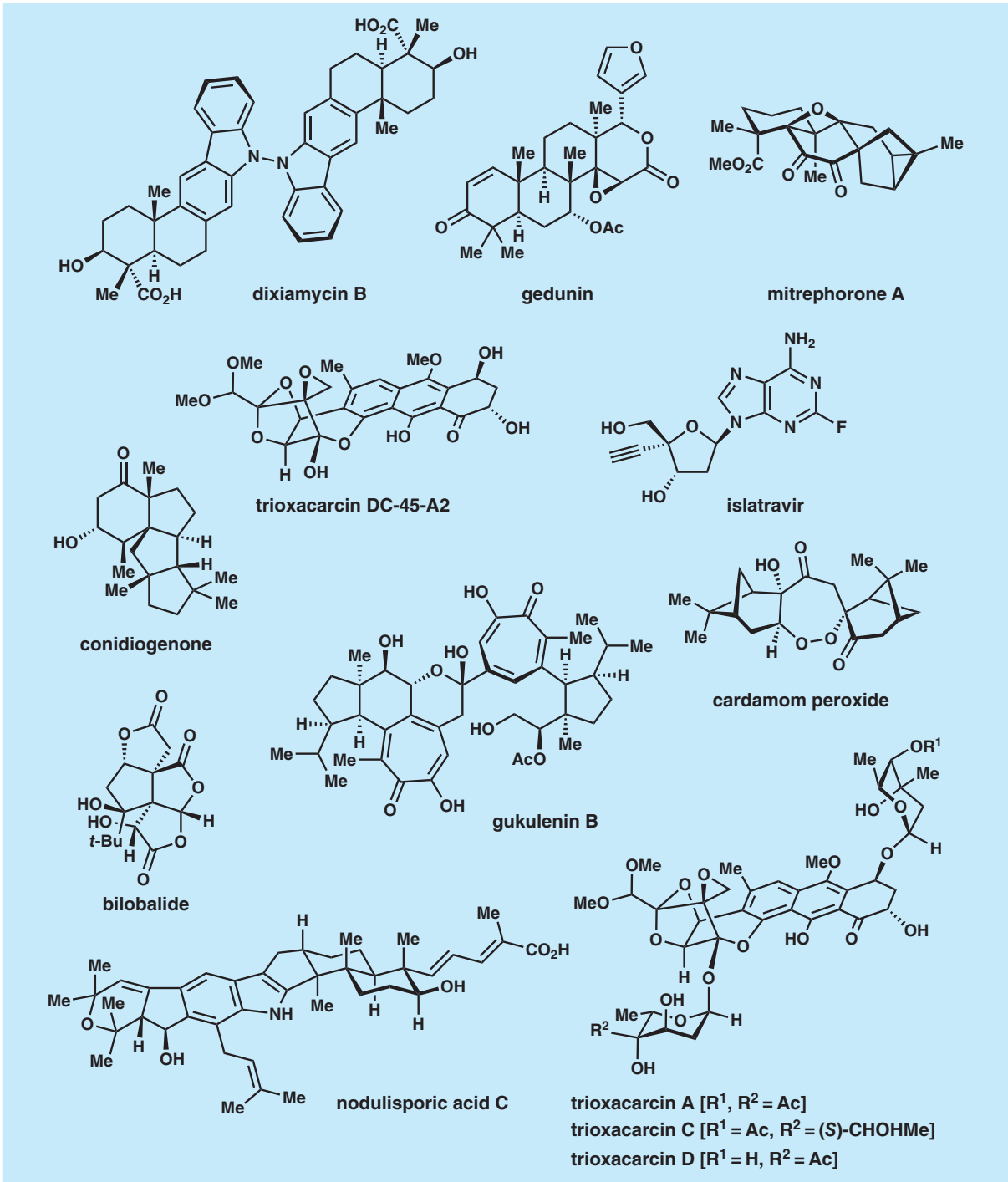

Figure 1. Molecular structures of selected natural products featured (continued).