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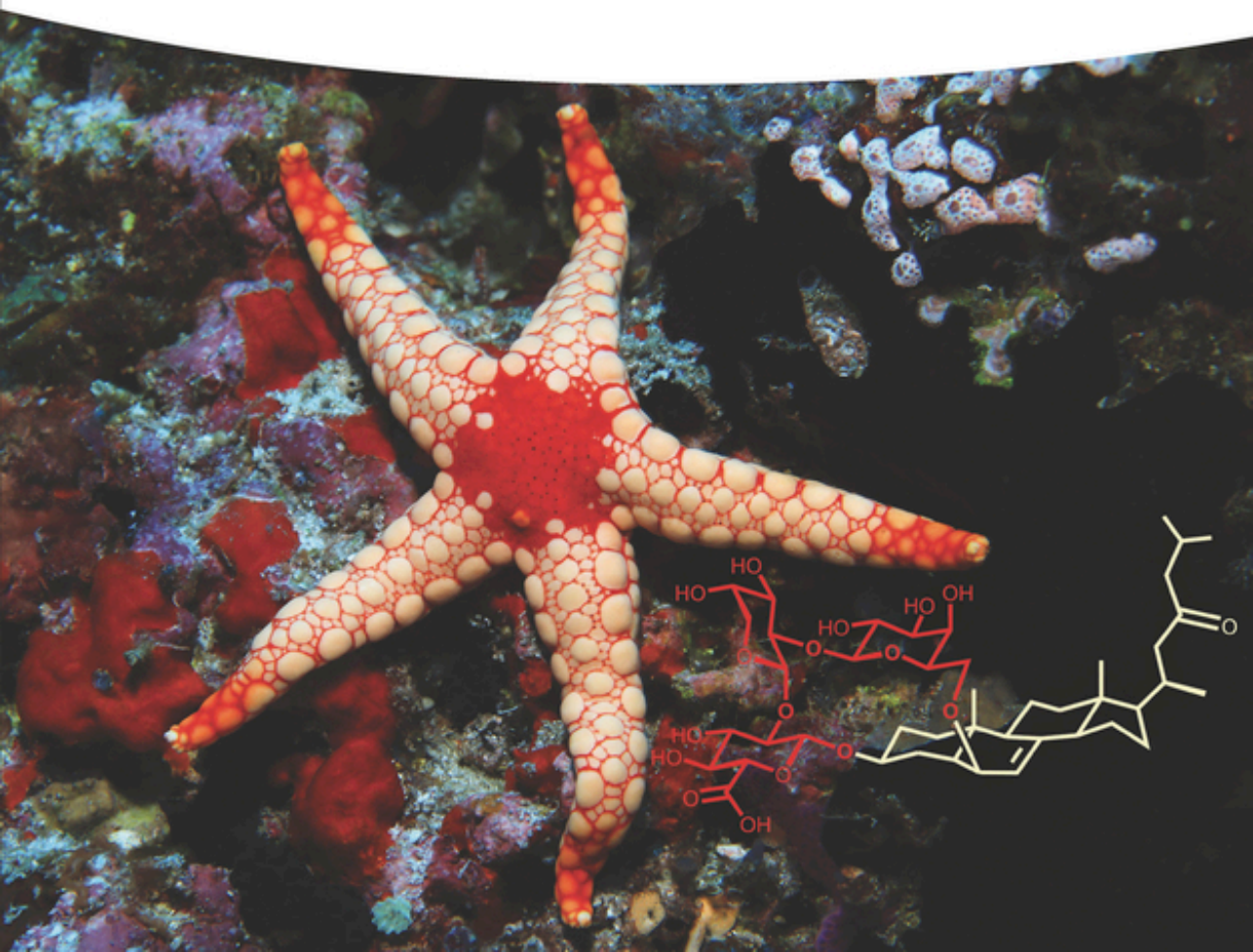

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Contents

Preface

Naturally occurring glycosides are prevalent in plants, microorganisms, and low animals, where they primarily function as signaling and defense agents. These compounds, spanning various categories of natural products such as polyketides, steroids, triterpenes, flavonoids, alkaloids, peptides, and lipids, are produced by stepwise glycosylation under the catalysis of diverse glycosyltransferases. Boasting a wide spectrum of pharmacological activities, including antitumor, anti-infective, and immunomodulatory effects, some glycosides, especially antibiotics, nucleosides, and cardiac glycosides, have found extensive use as therapeutic agents, while many others persist in folkloric usage. The saccharide residues in these compounds play an essential role in shaping their pharmacophore and significantly influence their pharmacokinetic and pharmacodynamic properties.

Given the microheterogeneity and the limited availability of naturally occurring glycosides, chemical synthesis emerges as a practical approach to the availability of these compounds, especially when conducting structure–activity relationship studies for pharmaceutical development. Consequently, the synthesis of natural glycosides has garnered significant research interest. Although it falls into the discipline of total synthesis of natural products, the total synthesis of naturally occurring glycosides encompasses an additional content that involves the installation of the saccharide residues with various glycosylation tactics and methods and protecting group manipulations. While certain elegant total synthesis of naturally occurring glycosides are included in books of natural product synthesis, to the best of our knowledge, no monograph is available that comprehensively discusses the total synthesis of naturally occurring glycosides, especially focusing on the carbohydrate chemistry involved in the total syntheses.

For nearly three decades, we (the Yu group) have dedicated our efforts to the total synthesis of naturally occurring glycosides and successfully accomplished the synthesis of a large variety of natural glycosides, such as landomycin A, periploside A, and luzonicosides A. Throughout the course of our research, it becomes evident that a comprehensive book focusing on the carbohydrate chemistry involved in the total synthesis should be of big value to those interested in this topic and, more generally, in the synthetic carbohydrate chemistry. When approached by Dr. Lifen Yang to explore the idea of documenting those research in a book, the notion immediately resonated with us. Having gone through difficulties in compiling a book, including

those unexpectedly presented by the COVID-19 pandemic, it ultimately took us six years to make a conclusion. Within its pages, we have detailed the comprehensive evolution of carbohydrate chemistry for the total synthesis of naturally occurring glycosides, categorizing the development across ten different types of aglycones to which saccharide residues are assembled. Our aim for this book is to provide readers with a comprehensive and clear understanding of the progress in the total synthesis of naturally occurring glycosides, from simple to complex molecules and from intricate strategies to highly efficient and economical methodologies. We anticipate that this book will serve as a valuable handbook for new researchers entering the field of carbohydrate synthesis, where they can find widely utilized assembly tactics, glycosylation methods, and information on temporary and permanent protecting groups essential for the synthesis of specific types of glycosides.

We express our sincere gratitude to the Wiley group for affording us this invaluable opportunity to author this book and for their enduring patience and unwavering support. Specifically, we extend our deep appreciation to Dr. Lifen Yang for her steadfast management of this project as well as to Pinky Sathishkumar, Katherine Wong, Katrina Maceda, and Shwathi Srinivasan, each of whom served as managing editor during different periods. We are also grateful to Ashok Ravi for his meticulous proofreading of the manuscript. Lastly, we wish to convey our heartfelt thanks to our coworkers and our families for their exceptional patience and unwavering support, which has been indispensable in making the completion of this book possible.

December 2023

Dr. Biao Yu
Dr. Xiaoyu Yang
Shanghai

List of Abbreviations

Ac	acetyl
AIBN	azodiisobutyronitrile
All	allyl
Alloc	allyloxycarbonyl
AzMB	*o*-azidomethylbenzoyl
Bn	benzyl
Boc	*t*-butoxycarbonyl
Bom	benzyloxymethyl
b.r.s.m.	based on recovered starting material
BSTFA	bis(trimethylsilyl)trifluoroacetamide
Bz	benzoyl
CAN	cerium(IV) ammonium nitrate
Cbz	carbobenzyloxy
ClAc	chloroacetyl
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DBAD	dibenzyl azodicarboxylate
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	1,2-dichloro-4,5-dicyanobenzoquinone
DEAD	diethyl azodicarboxylate
DEIPS	diethylisopropylsilyl
DHQD	dihydroquinidine
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIPEA	ethyldiisopropylamine
DMA	*N*,*N*′-dimethyl-1,2-ethanediamine
DMAP	4-*N*,*N*-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide

DMP	Dess–Martin periodinane
DMS	dimethyl sulfide
DMSO	dimethylsulfoxide
DNP-Br	2,4-di-nitrophenylbromide
dr	diastereomeric ratio
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
DTT	DL-1,4-dithiothreito
EDCI	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
ee	enantiomeric excess
FDPP	perfluorophenyl diphenylphosphinate
Fmoc	fluorenylmethyloxycarbonyl
HFIP	hexafluoroisopropanol
HMPA	hexamethylphosphoramide
LDA	lithium diisopropylamide
Lev	levulinyl
HATU	2-(1*H*-7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	bis(trimethylsilyl)amide
HOAt	1-hydroxy-7-azabenzotriazole
LiDBB	lithium 4,4′-ditert-butyl-1,1′-biphenyl
MBz	4-methoxybenzoyl
mCPBA	*m*-chloroperoxybenzoic acid
MMTr	4-methoxtrityl
MOM	methoxymethyl
Ms	methanesulfonyl
MS	molecular sieve
Nap	2-naphthylmethy
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
OTf	trifluoromethanesulfonate
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Phth	phthaloyl
Piv	pivaloyl
PMB	para-methoxybenzyl
PMP	para-methoxyphenyl
pNs	para-nitrobenzenesulfonyl
PPTS	pyridinium *p*-toluenesulfonate
Pyr	pyridine
RCM	ring-closing metathesis
rt	room temperature
S-Phos	2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
TASF	tetra-*n*-butylammonium fluoride-sulfur tetrafluoride

TBAB	tetrabutylammonium bromide
TBAI	tetrabutylammonium iodide
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*t*-butyldimethylsilyl
TDS	hexyldimethylsilyl
TEA	triethylamine
TES	triethylsilyl
Teoc	2-(trimethylsilyl)ethoxycarbonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl group
TMU	tetramethylurea
Tol	toluene
Ts	toluenesulfonyl
TTBP	2,4,6-tri-*tert*-butylpyrimidine

1

Introduction

Glycosides occur ubiquitously in nature, being especially abundant in plants, microorganisms, and low animals, which are evolved as secondary metabolites to function mainly as signal and defense chemicals [1–3]. A recent survey concluded that about 16.2% of the reported natural products are glycosides [4]. The aglycones comprise all types of natural products, such as polyketides, steroids, triterpenes, flavonoids, nucleobases, peptides, and lipids (Figure 1.1). The sugar moieties are usually added onto the aglycones and elongated subsequently via stepwise glycosylation under the action of various glycosyltransferases [5, 6]. Depending on the type of aglycones, the saccharide parts are highly characteristic and conservative in monosaccharide composition and glycosidic linkages. Enormous microheterogeneity occurs due to the tolerance of the glycosyltransferases for variation of the monosaccharide units and the aglycones, the incompleteness of the enzymatic reactions, as well as the subsequent modifications, such as acylation, oxidation, and degradation.

These naturally occurring glycosides have shown various pharmacological activities, especially antitumor, anti-infective, and immunomodulatory effects [7]. Some have been long and widely used as therapeutic agents, including, most importantly, antibiotics, nucleosides, and cardiac glycosides [8]. Many others still remained in folkloric usage, such as the saponin extracts from ginseng, licorice, ivy leaves, primula roots, and senega roots [9]. The saccharide residues can be an indispensable part of the pharmacophore or contribute critically to the pharmacokinetic and pharmacodynamic properties of the glycosides.

Chemical synthesis of a glycoside demands integration of the synthetic chemistry of the particular aglycone and the saccharide, involving especially a condensation of the two distinct parts and an overall protecting-group arrangement. Based on the stage at which the glycosidic bond between the saccharide and the aglycone is constructed, five tactics can be applied to the synthesis (Figure 1.2) [10]. The most straightforward and convergent tactic is a direct late-stage glycosylation of the aglycone with a prefabricated saccharide donor, followed by global deprotection (Tactic I). Glycosylation of the aglycone with a fully developed oligosaccharide donor might be problematic; then, the sugar units can be assembled in a linear manner (Tactic II). This tactic could warrant a stereospecific and high-yielding formation of the glycosidic bond to the aglycone but demands manipulation of temporary

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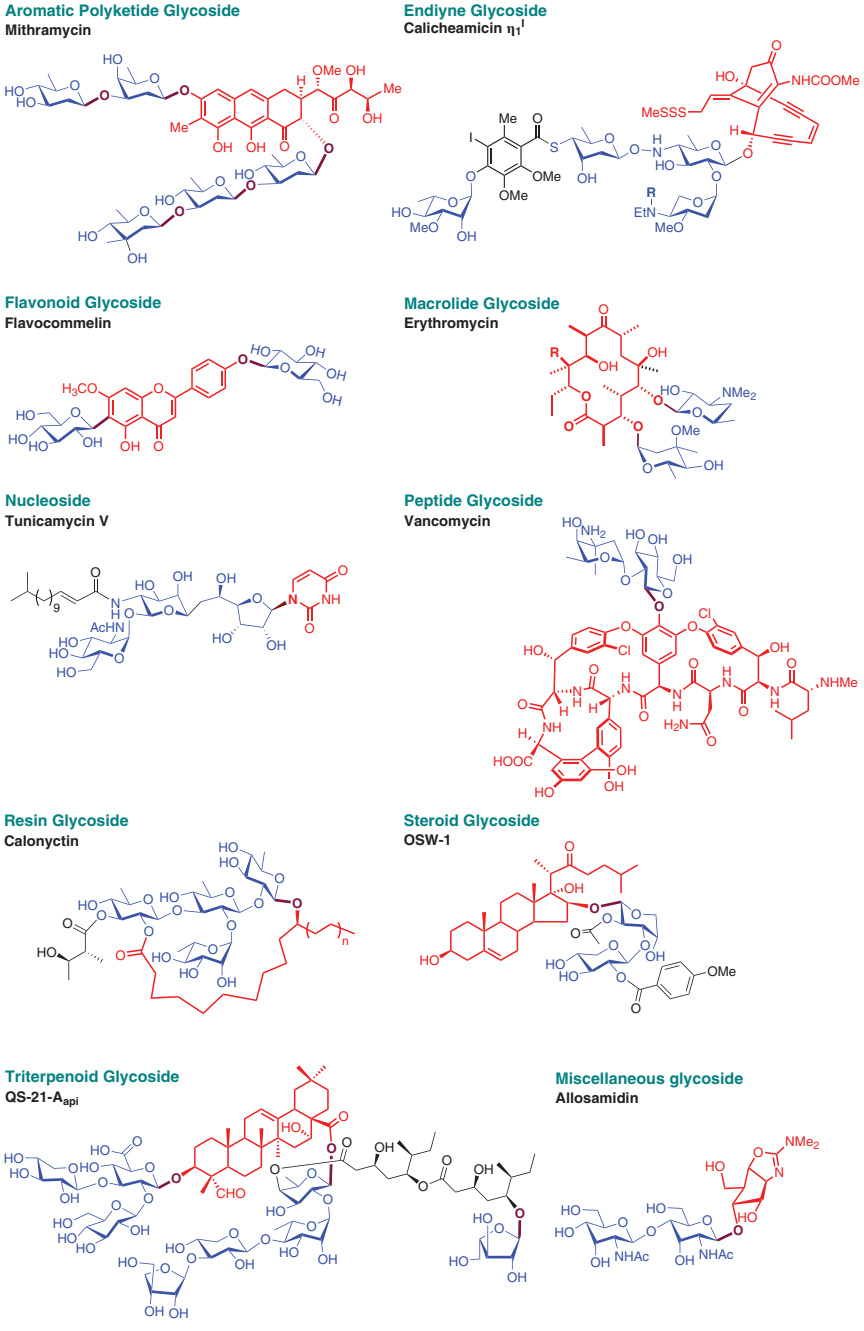

Figure 1.1 Representative molecules in the major categories of the naturally occurring glycosides, which have been synthesized. In red are the algycones, and in blue are the sugar residues.

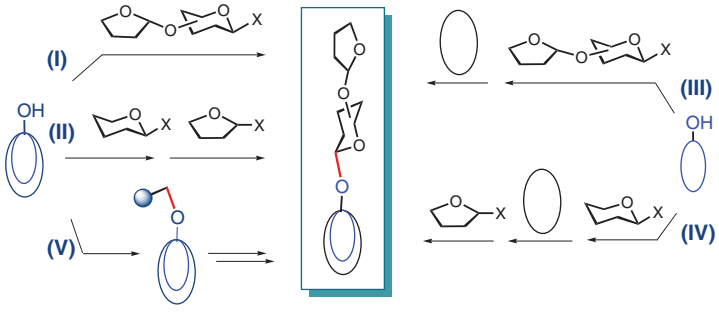

Figure 1.2 Five general tactics for the synthesis of complex glycosides based on the stage of incorporating the saccharide onto the aglycone.

protecting groups in between each glycosylation step. When glycosylation of the aglycone, even with a compromised monosaccharide donor, is unsuccessful, then this glycosidic linkage should be built before elaboration of the full aglycone (Tactic III). The fourth alternative for the assembly of a complex glycoside involves the elaboration of both the aglycone and the glycan after the construction of the glycosidic linkage (Tactic IV). Tactic V involves de novo synthesis of the sugar residue on the aglycone so as to bypass the glycosylation reaction [11, 12].

Installation of a saccharide onto an aglycone usually demands judicious choice of a glycosylation reaction. Numerous glycosylation protocols employing a wide variety of glycosyl donors have been developed (Figure 1.3). The major types that have been applied in the synthesis of natural glycosides include glycosyl bromides [13], fluorides [14], iodides [15], trichloroacetimidates [16, 17], *N*-phenyl trifluoroacetimidates [18, 19], thioglycosides [20–22], sulfoxides [23], heteroaryl thioglycosides [24, 25], 1-hydroxyl sugars [26, 27], 1-*O*-acetates [28], and *ortho*-alkynylbenzoates [29, 30]. Listed are also the commonly used promoters for each type of donor, which are determined by the nature of the leaving groups. It should be noted that the reactivity of a donor is also dependent on the sugar type and protecting group pattern.

Besides the coupling yield, another critical issue for a glycosylation reaction is stereoselectivity. In general, activation of a glycosyl donor by a promoter yields a continuum of species relevant to the sugar oxocarbenium intermediate (Figure 1.4) [31–35]. Each of these interconvertible species can react with an acceptor (an *O*-, *N*-, *S*-, or *C*-nucleophile) to give the glycoside, but with a different stereo-preference. Thus, the relative abundance of these transient species and their kinetic preference for glycosylation determine the overall outcome of the stereoselectivity. Usually, 1,2-*trans*-glycosides can be confidently synthesized with donors equipped with a neighboring (or remote) participating group (path a). This also constitutes a reliable approach to the synthesis of 2-deoxy-glycosides, in that the neighboring participating group needs to be removed afterwards [36–38]. Glycosylation through path b (via the oxocarbenium species) erodes the stereoselectivity. Direct stereoselective synthesis of the 1,2-*cis*-glycosides and the 2-deoxy-glycosides must resort to

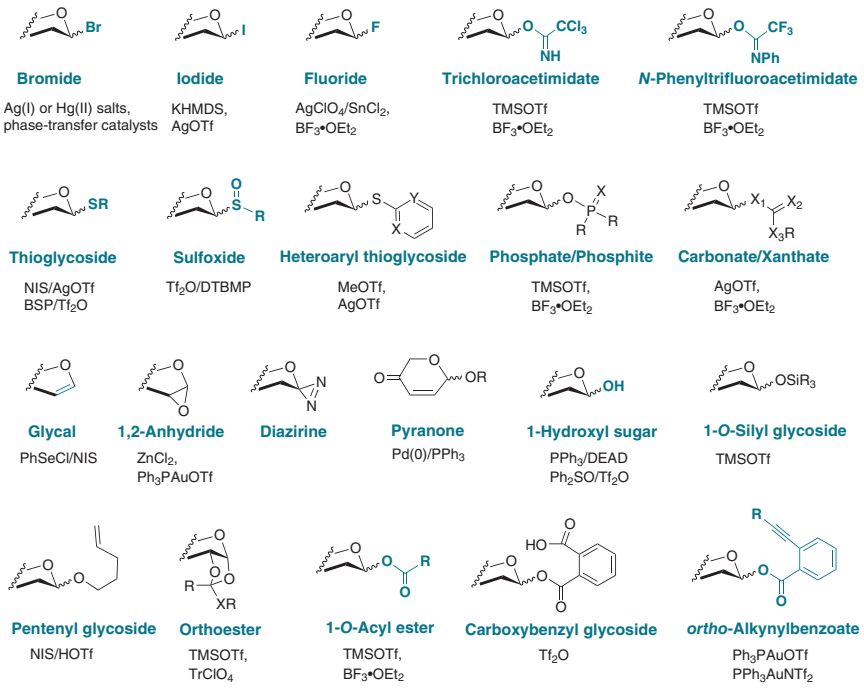

Figure 1.3 The major types of glycosyl donors and their promoters.

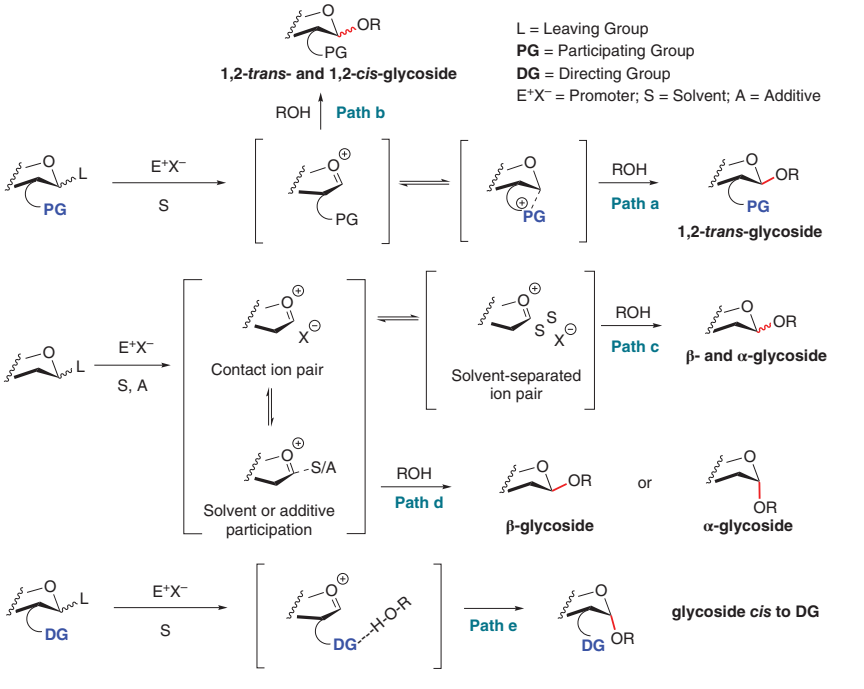

Figure 1.4 A general mechanistic scheme for the stereochemical outcomes in the glycosylation reactions.

fine-tuning of the reaction parameters, to force the glycosylation to proceed via a contact ion pair or a solvent-participating intermediate (path d) [39, 40]. Glycosylation through path c (via the solvent-separated ion pair) usually leads to a mixture of α/β glycosides; however, controlling the conformation of the sugar oxocarbenium intermediate (mainly by the protecting groups) could also lead to stereoselective glycosylation [41–44]. Recently, some directing groups have been developed, which could deliver stereoselective glycosylation via a H-bonding intermediate (path e) [45–47]. It is noteworthy that the inherent stereochemistry of the aglycone would influence strongly the stereoselectivity of the glycosylation reaction. In addition, the glycosidic linkages, especially the abundantly occurring deoxy-glycosides, might undergo anomerization or cleavage under acidic conditions.

In this book, we compile the successful synthesis of the representative and complex natural glycosides. These syntheses are presented in 10 chapters based on the types of target glycosides, namely, aromatic polyketide glycosides, enediyne glycosides, flavonoid glycosides, macrolide glycosides, nucleosides, peptide glycosides, resin glycosides, steroid glycosides, triterpenoid glycosides, and miscellaneous glycosides (Figure 1.1). For each glycoside, a brief introduction has been provided about its origin, structural features, and biological activities. In each synthesis, we focus on the glycosylation steps, especially the step for the construction of the glycosidic bond connecting to the aglycone. The glycosylation yields and stereoselectivity are given and highlighted. The subsequent transformations toward the final targets are also depicted; those include elongation of the glycans, elaboration of the aglycone, and/or manipulation of the protecting groups. Especially, the steps and yields for the final cleavage of the protecting groups are highlighted. These late-stage synthetic steps demonstrate the compatibility of the chemical transformations demanded in the presence of the complex aglycone and the saccharide residues.

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2

Aromatic Polyketide Glycosides

Aromatic polyketides are a diverse family of natural products with considerable structural variation [1, 2]. The majority of these compounds contain highly substituted, fused-ring polyphenols that are derived from poly-β-ketone precursors and decorated with deoxysaccharide residues via *C*- and *O*-linkages (Figure 2.1). The aglycones exhibit three key structural features, including the number of rings, the cyclization pattern dictated by the regioselective cyclization of the linear polyketide precursors, and the ring topology resulting from oxidative rearrangement reactions. Consequently, aromatic polyketides fall into different categories, such as the anthracycline family (e.g. doxorubicin **1**) [3], angucycline family (e.g. landomycin A **2**) [4–6], tetracycline family (e.g. SF2575 **3**), and aureolic acids family (e.g. mithramycin **4**), among others. Many members of the aromatic polyketide family have potent activities, such as antibiotic, immunosuppressive, antiparasitic, cholesterol-lowering, and antitumor activities. Clinical use is seen for some of these compounds, such as doxorubicin (adriamycin, **1**) and mithramycin (**4**), as anticancer drugs.

Landomycin A

The landomycins represent the largest subfamily of angucycline antibiotics, which were initially isolated from *Streptomyces cyanogenus* by Rohr and coworkers in 1990 [7]. Landomycin A (**2**) is the most significant member of this group (Figure 2.2), which features an angular tetracyclic core containing a dearomatized B-ring and a hexasaccharide composed of two repeat trisaccharide, i.e. (α-L-rhodinose-(1 → 3)-β-D-olivose-(1 → 4)-β-D-olivose). It exhibits potent antitumor activities by inhibiting DNA synthesis and G_1/S cell cycle progression, although the precise mechanism of action remains unclear. Structure–activity relationship (SAR) studies indicate that the cytotoxic activity of landomycins depends on the length of the glycan, and landomycin A with the longest sugar chain is the most active congener. Due to its unique structure and potent antitumor activities, there has been significant interest in the total synthesis of landomycin A among organic chemists. Indeed, several research groups have achieved the synthesis of the hexasaccharide fragment of landomycin A using various glycosylation

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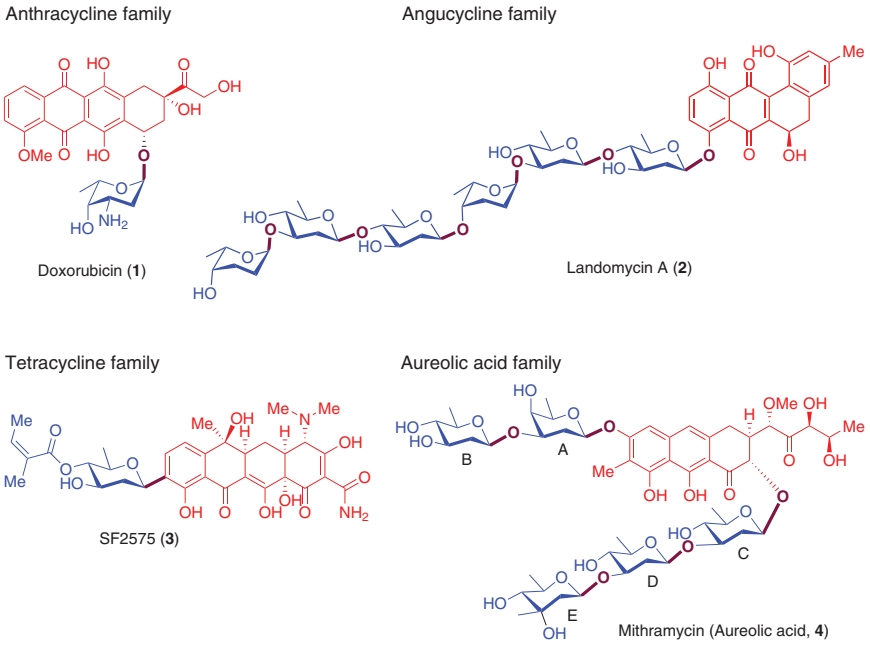


Figure 2.1 Representative aromatic polyketide glycosides.

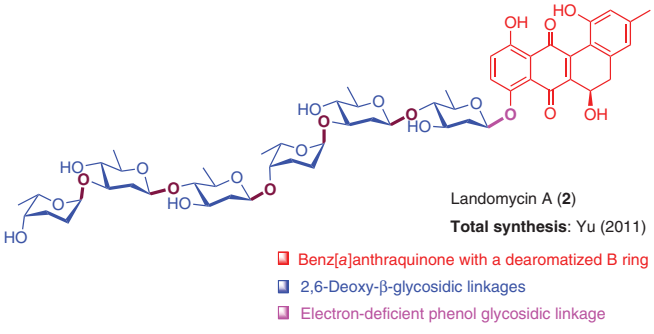
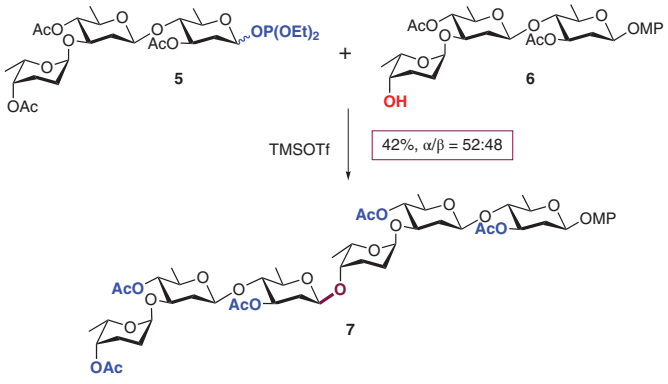


Figure 2.2 Landomycin A (**2**) and its structural features.

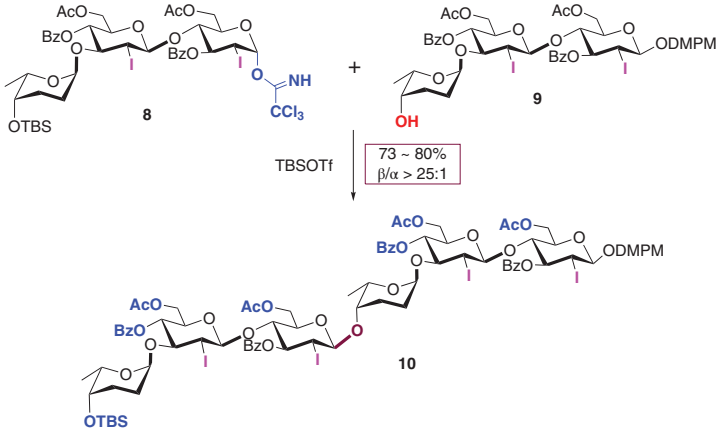
methods. Nevertheless, only Yu and coworkers accomplished the total synthesis of landomycin A in 2011 [8].

In 1997, Sulikowski and coworkers reported the first approach to the synthesis of the hexasaccharide fragment of landomycin A (Scheme 2.1) [9]. The desired hexasaccharide **7** was obtained in a moderate yield of 42% and a β/α stereoselectivity of ~1 : 1 through a late-stage coupling of trisaccharide acceptor **6** with 2-deoxy-trisaccharide phosphite **5** under the catalysis of TMSOTf.



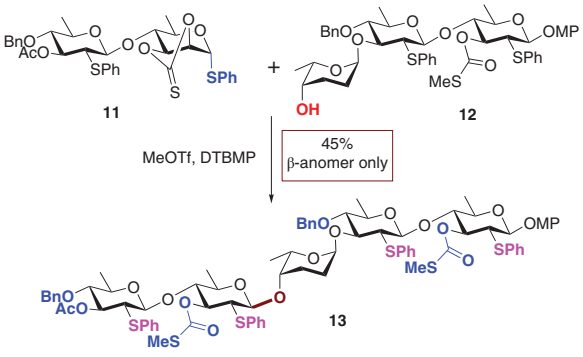
Scheme 2.1 The key glycosylation step employed in the synthesis of landomycin A hexasaccharide by the Sulikowski group.

In 2000, Roush et al. reported a stereoselective synthesis of the hexasaccharide of landomycin A (Scheme 2.2) [10]. The construction of the 2-deoxy-β-glycosidic linkages exhibited excellent stereoselectivity (>95 : 5) using 2-iodo-glycosyl donors, in which the 2-iodo group participated in the glycosylation. Glycosylation of trisaccharide acceptor **9** with trichloroacetimidate donor **8** in the presence of TBSOTf at −78 °C resulted in the desired β-linked hexasaccharide **10** with high selectivity and in yields ranging from 73% to 80%.



Scheme 2.2 The key glycosylation step employed in the synthesis of landomycin A hexasaccharide by the Roush group.

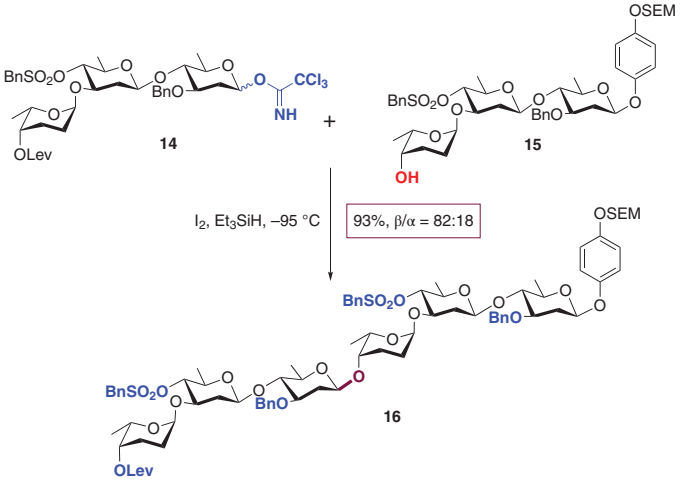
Using phenyl 2,3-*O*-thionocarbonyl-1-thioglycosides as 2-deoxy-β-glycoside precursors, which can undergo a 1 → 2 sulfide migration and concurrent glycosidation, Yu et al. achieved the synthesis of the hexadeoxysaccharide fragment of landomycin A in 2002 (Scheme 2.3) [11]. A late-stage glycosylation of trisaccharide acceptor **12** with disaccharide sulfide donor **11** in the presence of MeOTf and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) yielded pentasaccharide **13** with



Scheme 2.3 The key glycosylation step employed in the synthesis of landomycin A hexasaccharide by the Yu group.

complete stereocontrol and a yield of 45%. The coupling partners, **11** and **12**, were prepared using similar methodologies.

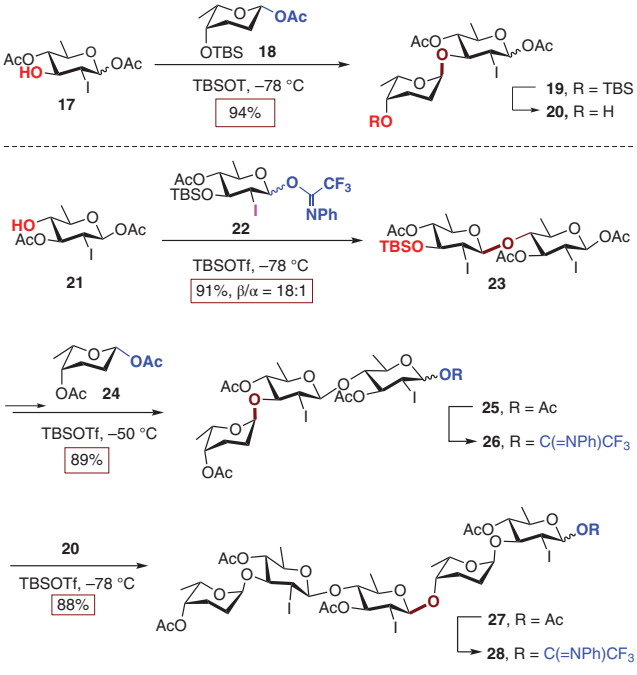
In 2010, Takahashi and coworkers reported a stereoselective synthesis of a panel of deoxyhexasaccharides relevant to the landomycin A glycan, in which the β-selective glycosylation was realized using 2-deoxyglycosyl imidate donors featuring an electron withdrawing sulfonate at the *O*-4 position and being activated with I_2 and Et_3SiH at an extremely low temperature (Scheme 2.4) [12]. Glycosylation of trisaccharide acceptor **15** with trisaccharide imidate donor **14** was performed at −95 °C in the presence of I_2 and Et_3SiH, yielding hexasaccharide **16** in 93% yield and with good β/α selectivity (82 : 18).



Scheme 2.4 The key glycosylation step employed in the synthesis of landomycin A hexasaccharide by the Takahashi group.

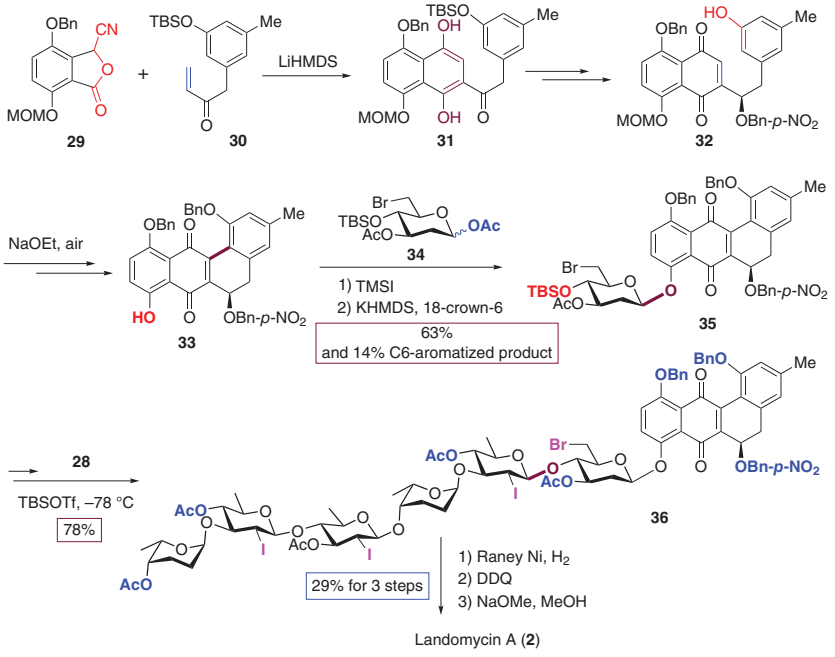
Total synthesis of landomycin A (2) by the Yu group. Although various approaches for synthesizing the hexasaccharide and shorter deoxysaccharides [13–15] of landomycins have been developed, the synthesis of the aglycone was

only achieved by Roush et al. in 2004 [16], and the total synthesis of landomycin A was not achieved until 2011 [8, 17, 18]. Due to the challenging linkage between the landomycin aglycone and the saccharide chain, the glycosylation of aglycone was carried out with monosaccharide donors. The remaining pentasaccharide building block was synthesized as shown in Scheme 2.5. Glycosylation of acceptor **17** with L-rhodinosyl acetate **18** under the catalysis of TBSOTf at −78 °C afforded the thermodynamically favored α-disaccharide **19** in 94% yield. Selective removal of the C4′-*O*-TBS group in **19** provided disaccharide acceptor **20**. Coupling of acceptor **21** with 2,6-dideoxy-2-iodo-glucopyranosyl trifluoroacetimidate **22** under the action of TBSOTf at −78 °C afforded β-disaccharide **23** in excellent yield (91%), along with the corresponding α-disaccharide in ∼5% yield. After removal of the C3-*O*′-TBS group, glycosylation with L-rhodinosyl acetate **24** enabled by TBSOTf at −50 °C gave trisaccharide **25** in a high yield of 89%. Trisaccharide **25** was converted to trifluoroacetimidate **26** in two steps, which was then coupled with disaccharide acceptor **20** under the catalysis of TBSOTf at −78 °C, yielding the desired β-pentasaccharide **27** in a satisfactory yield of 88%. Pentasaccharide acetate **27** was then transformed to trifluoroacetimidate **28** in a similar manner to the **25** → **26** transformation.



Scheme 2.5 Synthesis of pentasaccharide donor **28** by Yu and coworkers.

The synthesis of landomycin aglycone started with the preparation of naphthalene **31** via Hauser annulation between cyanophthalide **29** and aryl enone **30** under basic conditions (Scheme 2.6). Compound **31** was then converted to naphthoquinone **32** by stereoselective reduction of the C-6 carbonyl group,



Scheme 2.6 Total synthesis of landomycin A (**2**) by Yu and coworkers.

protection of the resultant hydroxyl with *p*-nitrobenzyl group, removal of the *O*-TBS group, and oxidation of the hydroquinone. The C-ring was formed via intramolecular Michael addition, followed by oxidation of **32** through treatment with NaOEt and air [16]; subsequent protecting group manipulation provided C8-OH derivative **33**. After extensive studies, glycosylation of aglycone **33** was achieved by using a S_N2-type reaction with the *in situ* generated α-glycosyl iodide from acetate **34** under basic conditions, furnishing β-glycoside **35** in 63% yield, with the corresponding C6-aromatizaed product being isolated in 14% yield. Subsequently, the C4′-*O*-TBS group in landomycinone glycoside **35** was selectively cleaved, and coupling with pentasaccharide trifluoroacetimidate donor **28** was achieved under the catalysis of TBSOTf (3 mol%) at −78 °C, yielding hexasaccharide **36** in a good yield of 78%. Stronger reaction conditions such as greater equivalents of TBSOTf or higher temperature led to cleavage of the 2,3,6-trideoxy-α-glycosidic and the C8-*O*-2′-deoxy-β-glycosidic linkages. Finally, removal of the bromide, iodide, and benzylic protecting groups (with H_2, Raney-Ni), regeneration of the quinone motif (with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone [DDQ]), and removal of the five acetyl groups (with NaOMe/MeOH) accomplished the total synthesis of landomycin A (**2**) in 29% yield for the last three steps.

In 2021, Mong and coworkers reported the total synthesis of landomycin Q and landomycin R, which are the trisaccharide and disaccharide derivatives of the B-ring unsaturated anhydrolandomycinone congeners [19]. The construction of the key linkage between aglycone and the saccharide chain was also achieved using an S_N2-type glycosylation with glycosyl iodide under basic conditions.