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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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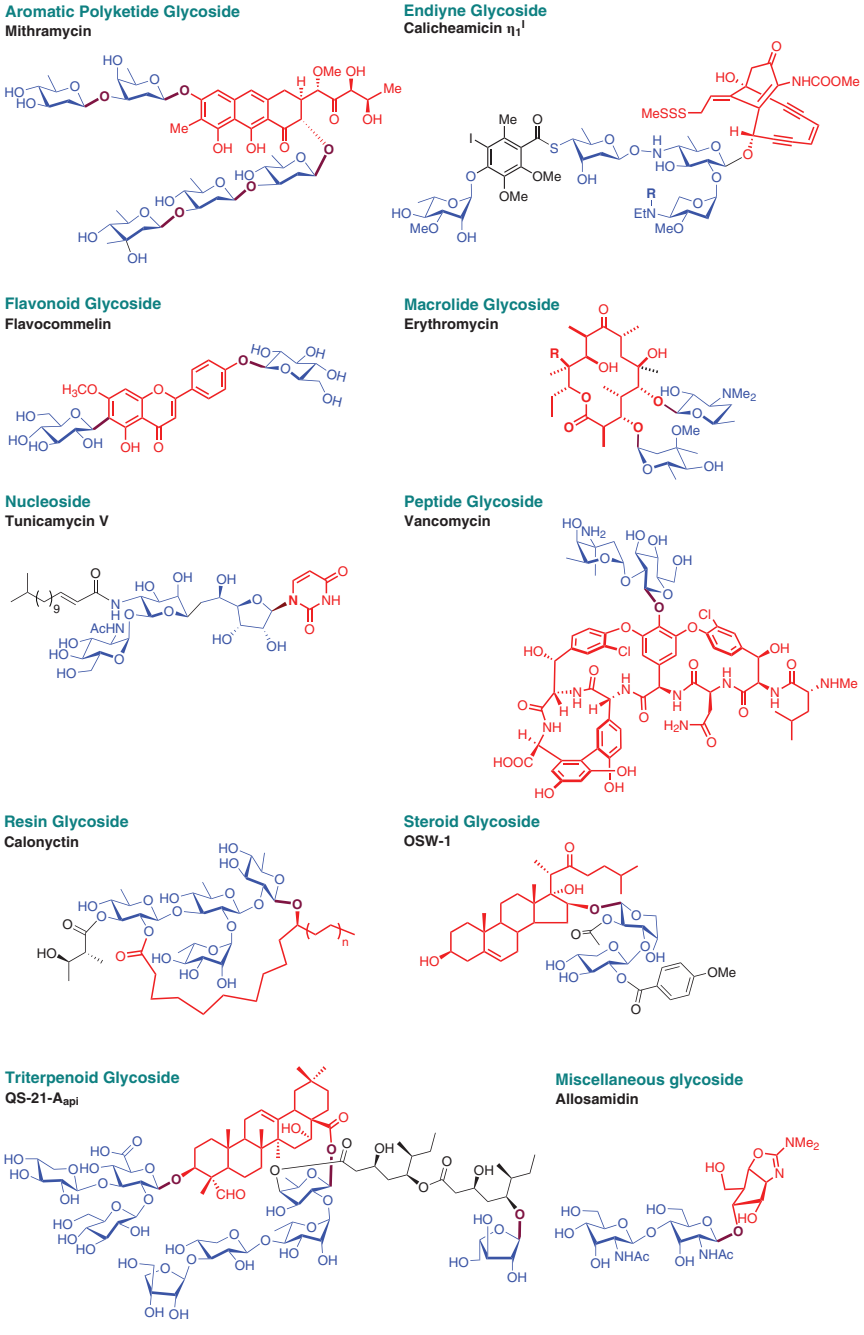

Figure 1.1 Representative molecules in the major categories of the naturally occurring glycosides, which have been synthesized. In red are the algycones, and in blue are the sugar residues.

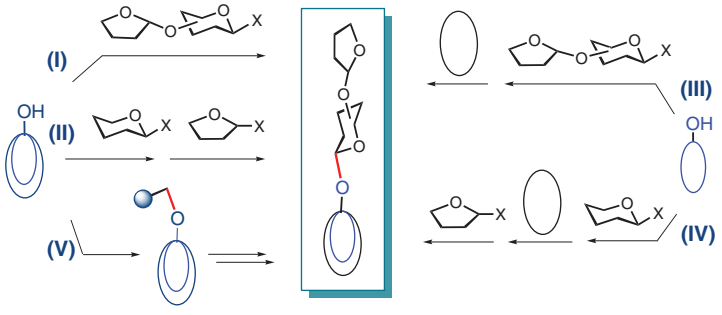

Figure 1.2 Five general tactics for the synthesis of complex glycosides based on the stage of incorporating the saccharide onto the aglycone.

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

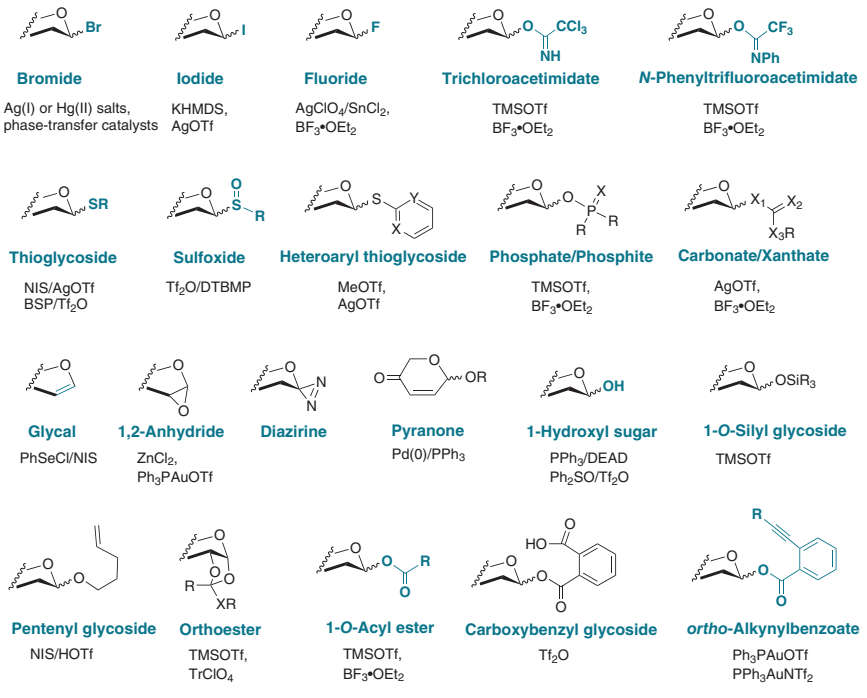

Figure 1.3 The major types of glycosyl donors and their promoters.

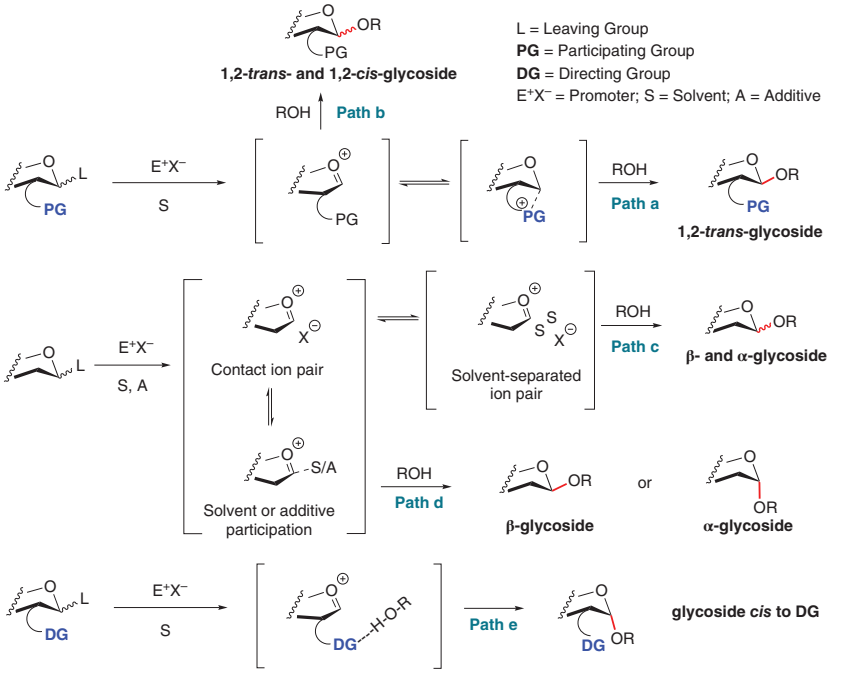

Figure 1.4 A general mechanistic scheme for the stereochemical outcomes in the glycosylation reactions.

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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