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Recent advances in the construction of quaternary pseudoanomeric centers in *gem*-*C*,*C*-glycosides: from zaragozic acids to remdesivir

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Gem-*C*,*C*-glycosides—*C*-glycosides characterized by two carbon substituents at the pseudo-anomeric position—constitute a structurally distinctive class of glycomimetics with growing relevance in natural products and drug discovery. These motifs appear in diverse bioactive compounds such as maitotoxin, nogalamycins, zaragozic acids and remdesivir, displaying antimicrobial, anti-inflammatory, and anticancer properties. The unique architectures of *gem*-*C*,*C*-glycosides expand the glycochemical space and hold promise for therapeutic development. In contrast to classical *C*-glycosyl compounds, which benefit from a well-developed synthetic toolbox, the construction of *gem*-*C*,*C*-glycosides remains particularly demanding. This is primarily due to the dual requirement of forming a quaternary center while achieving stereocontrol at a highly congested site. The present review surveys current strategies for constructing quaternary pseudoanomeric centers in *gem*-*C*,*C*-glycosides, highlighting key advances, challenges, and opportunities in this evolving field. Particular attention is given to innovative methodologies that enable direct transformation from carbohydrate precursors, including novel approaches such as metal-hydride hydrogen atom transfer (MHAT) and C–H activation processes.

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1. Introduction

Carbohydrates are among the most structurally diverse natural products, playing key roles in various biological processes, from immune defence to protein folding.[1] Despite recent advancements,[2] translating carbohydrates' therapeutic potential into tangible patient benefits remains a significant challenge. One promising approach towards this end is the use of glycomimetics,[3] which mimic Nature's most effective molecules while overcoming their common drawbacks as credible drugs such as poor oral bioavailability. In addition, structurally modified analogues of carbohydrates may also serve as stable mechanistic probes and have thus the potential to drive groundbreaking advances in glycobiology.[3a] As chiral, densely functionalized molecules, glycomimetics present significant synthetic challenges, inspiring the development of innovative strategies for their synthesis.[3] *C*-Glycosides[4] stand among the most significant and extensively researched classes of glycomimetics.[5,6] The substitution of the exocyclic anomeric oxygen atom by a carbon atom enhances resistance to both chemical and enzymatic hydrolysis, thereby rendering these compounds stable analogues of *O*-glycosides. Within the family of *C*-glycosides, *gem*-*C*,*C*-glycosides are characterized by the presence of two carbon substituents at the pseudo-anomeric position, forming a (stereodefined) quaternary center[7] (Fig. 1a). Over the years, several names have been proposed for this class of compounds. Wilcox first described them as bis-alkylated *C*-glycosides in the early 1980s.[8,9] In the 1990's, Schmidt employed the term *C*-ketosides,[10] while Paquette referred to this class of compounds as bis-*C*,*C*-glycosides.[11]

Recently, the term bis-*C*-glycoside has gained broader usage,[12,13] although it is also applied in a different context to describe structures with two distinct *C*-glycosylation sites, as seen, for example, in *C*-glycosyl flavonoids like 6,8-di-*C*-D-glucosylgenistein (Fig. 1b).[14,15] Indeed, according to IUPAC nomenclature, the prefixes "di" and "bis" do not necessarily imply that the two substituents are attached to the same atom.

Choosing an unambiguous trivial name for a class of compounds is challenging, as it requires a delicate balance between precision and conciseness. Although the prefix "*gem*"

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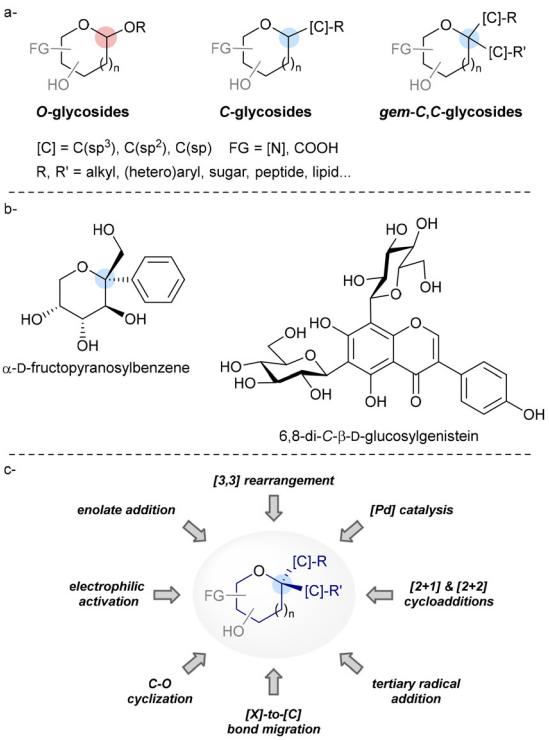

Fig. 1 (a) General structures of *O*-, *C*- and *gem*-*C*,*C*-glycosides. (b) Representative molecular structures of a *C*-ketoside and a bis-*C*-glycoside. (c) General approaches for the synthesis of *gem*-*C*,*C*-glycosides (FG = Functional Group).

conventionally denotes two identical substituents—a limitation shared with "di" and "bis"—we will, for the remainder of this review, use *gem*-*C*,*C*-glycosides to describe glycomimetics with two carbon substituents at the anomeric position, whether or not the groups are identical, as it clearly highlights the presence of two C–C bonds at the pseudo-anomeric position.[16] The term *C*-ketoside appears more appropriate when the parent sugar is clearly identifiable, as exemplified in the *C*-aryl fructopyranoside structure shown in Fig. 1b. Glycomimetic research is predominantly focused on three main classes of compounds, namely iminosugars, carbasugars and *C*-glycosides.[3] Drawing a parallel with D. Trauner's quote on polyketides, one could say that glycomimetics, like any large family, "have prominent members" but also "poor cousins, *i.e.* molecules that have been overlooked because of their [...] unattractive name, unusual shape, or simply because synthetic chemistry was not ready for them".[17] This has certainly been true for carbohydrate mimics featuring a pseudoanomeric center bearing two exocyclic *C*-substituents. From the standpoint of a classical glycochemist, addressing pseudo sugars that lack both glycosidic and anomeric C–H bonds is far from straightforward. By comparison with the parent *C*-glycosyl compounds, *gem*-*C*,*C*-glycosides indeed prove to be underrepresented in chemistry publications. While a wide range of methods have been developed to access *C*-glycosides,[6,7] only a relatively limited number of strategies have been reported for constructing stereodefined quaternary pseudoanomeric carbon in *gem*-*C*,*C*-glycosides (Fig. 1c). The efficient and stereocontrolled introduction of two C–C bonds at the anomeric carbon center of carbohydrates, which contain multiple functional groups and asymmetric centers, remains indeed a significant challenge.

Gem-*C*,*C*-glycosides, with their distinctive structures and notable biological activities, have increasingly captured the interest of synthetic and medicinal chemists over the past decade. These structural motifs are found in a wide range of natural products, from relatively simple molecules like sphydrofuran[18] to more complex compounds such as arenicolide C[19] and maitotoxin,[20] a "molecular Everest" (Fig. 2). A diverse array of naturally occurring compounds and structurally related analogues also feature the *gem*-*C*,*C*-glycosyl moiety. The list includes nogalamycins,[6d,21,22] cinatrins,[23] aurovertins,[24]

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Mathieu Pascaretti

Dr Mathieu Pascaretti earned a first Master's in Organic Chemistry from University of Grenoble Alpes (2018) and a second Master's in preparation for the national chemistry teaching exam (agrégation) at University of Strasbourg (2019). After successfully passing the competitive agrégation national exam in 2021, he completed his PhD in 2024 under the supervision of Profs P. Pale (University of Strasbourg) and V. Dalla (University of Le Havre), focusing on gold(I)-catalyzed alkynylation of glycosides. He is currently a teaching and research assistant (ATER) at ECPM and a member of the SYBIO team (LIMA), where he investigates novel cascade reactions involving exo-glycals.

botcinins,[25] syringolides,[26] zaragozic acids,[27–29] and structurally related compounds (Fig. 2a). The structural diversity of these natural products is matched by a broad array of biological activities, underscoring their therapeutic potential as anti-inflammatory, antimicrobial, and anticancer agents. The distinctive *gem-C,C*-glycoside structures, featuring a quaternary pseudoanomeric center, open up new avenues for exploring glycochemical and patentable spaces, with the potential to significantly enrich drug discovery pipelines in the years ahead. Among emblematic examples, menogaril, a semisynthetic derivative of nogalamycin (Fig. 2b), was selected for clinical trials on different tumor types due to its reduced cardiotoxicity and improved antitumor activity, compared to the parent compound.[22c] However, challenges such as drug resistance and limited intestinal absorption in non-Hodgkin's lymphoma patients, continue to emphasize the urgent need for more effective analogues. The *gem-C,C*-glycoside scaffolds are also critical components in analogues of synthetic drugs, such as mimics of the antidiabetic Steglatro™ (ertugliflozin).[30] In 2020, the pro-drug Veklury™ (remdesivir), a modified nucleotide, was approved by the FDA as an anti-COVID-19 agent.[31] The unique structural feature of *gem-C,C*-glycosides also offer exciting opportunities for development of stable molecular probes, particularly as selective enzyme inhibitors. As demonstrated by Schmidt *et al.*,[32] the ternary nature of the transition state of glycosyltransferases can be effectively mimicked by bisubstrate inhibitors[33] which combine elements of both substrates – the sugar donor and the acceptor – *C*-linked at the anomeric position (Fig. 2c). Anomeric spirocyclopropyl sugars have been also designed as stable, conformationally constrained glycomimetics displaying inhibitory activities towards glycosidases.[34] In this context, the present review provides an overview of recent developments in the synthesis of *gem-C,C*-glycosides, primarily focusing on the past decade (since 2015).[35,36] The goal is not to be exhaustive, but to offer a critical summary of key synthetic studies. Structures discussed were selected based on the following criterion: when a position within a glycomimetic can be intuitively recognized as corresponding to the anomeric center of a related carbohydrate, the compound is classified as a *gem-C,C*-glycoside if two carbon substituents occupy this site, thereby mimicking the structural role of the anomeric carbon. For example, in the Steglatro™ analog depicted in Fig. 2b, the pseudo-anomeric center is inferred based on the position of the characteristic hydroxymethyl group, which serves as a structural marker commonly found in D-hexopyranoses, such as D-glucose (highlighted in red for clarity). In contrast, in Steglatro™ itself,[30] the anomeric center is unambiguously defined by the ketosidic linkage and the position of the hydroxymethyl group. Here, two carbon substituents are now positioned at C-5 rather than at the anomeric C-1 position – based on the structure of the parent D-glucoside derivative (Fig. 2b) – placing Steglatro™ outside the scope of *gem-C,C*-glycosides as defined in this review.

The appeal of *gem-C,C*-glycosides has been further amplified by the potential to develop new synthetic methods and strategies, which can be applied to the construction of relevant analogues for drug discovery. By showcasing a selection of key examples, we aim to inspire further research in this underexplored, yet highly promising class of carbohydrate mimics. The review will be structured into two main parts. The first one will focus on the total synthesis of bioactive natural products and their analogues, highlighting the strategies used to construct the pivotal quaternary pseudoanomeric center within the *gem-C,C*-glycoside motif (sections 2 and 3).[37] The second part will discuss innovative synthetic methods developed specifically for the direct construction of this center from carbohydrate starting materials (sections 4 to 7). To achieve this, synthetic chemists must innovate and move beyond tra-

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Dr Damien Tardieu obtained his Master's degree in 2017 from the University of Montpellier, where he conducted research on the total synthesis of natural isoprostanes. He then moved to Strasbourg to pursue a PhD under the supervision of Prof. P. Compain and Dr N. Kern, where he developed novel synthetic methods for gem-C,C-glycosides via metal-catalyzed hydrogen atom transfer (MHAT) strategies. In 2021, he joined SpiroChem AG, a Swiss contract research organization, as a research chemist. His current work focuses on route scouting and early process development to support drug discovery. His research interests include synthetic strategy design and the development of scalable routes to structurally complex molecules.

Nicolas Kern

Dr Nicolas Kern obtained his PhD in 2014 under the supervision of Dr A. Blanc and Prof. P. Pale, studying the reactivity of strained aza-heterocycles in homogenous gold catalysis. He undertook postdoctoral studies at the University of Manchester with Prof. D. J. Procter, developing asymmetric samarium(II) radical chemistry, then with Prof. P. Compain, working on diverse aspects of carbohydrate chemistry. In 2018 he was appointed as a Chargé de Recherche at CNRS, developing new methodologies towards original carbohydrate mimetics. His current interests focus on reactivity-driven research in radical and organometallic chemistry, targeting bioactive compounds and analogs via atom-economic approaches.

ditional *C*-glycosylation methods, developing processes that enable the stereocontrolled introduction of not one, but two exocyclic *C*-substituents at the pseudoanomeric center. A variety of synthetic approaches have been adopted from the organic chemists' arsenal to achieve this goal, ranging from cationic rearrangements to metal-catalyzed hydrogen atom transfer (MHAT) reactions (Fig. 1c). The final section of this review will focus on specific classes of *gem*-*C*,*C*-glycosides of biological interest, namely strained anomeric spirocyclic *C*-glycosides (section 8).

2. Natural *gem*-*C*,*C*-glycosides and closely related analogues

The synthetic strategies described in this section involve the formation of the quaternary pseudoanomeric center either directly through *gem*-*C*,*C*-glycosylation or *via* a stepwise synthesis of the carbohydrate motif.

This section will also include compounds derived from natural products and closely related to them structurally.

2.1. Nogalamycins

Nogalamycin, an anthracycline antibiotic produced by *Streptomyces nogalater*, was discovered in the 1960s at The Upjohn Company (Scheme 1).[22a,b] This natural product is a prototypical example of anthracycline subclass V (Fig. 2a), which includes potent antitumor natural products, such as arugomycin and decilorubicin.[6d] As a member of the anthracycline class with promising therapeutic potential, nogalamycin has been the focus of extensive research.[22,38,39] However, clinical trials were never initiated due to severe toxicity.[22b] Menogaril (7-con-*O*-methylnogarol), a semisynthetic derivative of nogalamycin (Fig. 2b), was advanced to clinical trials for various tumor types, owing to its reduced cardiotoxicity and improved antitumor activity compared to the parent compound.[22b–d,38] However, challenges such as limited intestinal absorption in non-Hodgkin's lymphoma patients, underscore the ongoing need for more effective analogues. Nogalamycin and its congeners are synthetically compelling due to their unique and intricate structures, where the aglycone aromatic moiety is connected to the sugar residue through both *O*- and *C*-glycosidic bonds, resulting in the formation of a distinctive epoxybenzoxocin ring system (Fig. 2a and Scheme 1). The difficulty in stereocontrolling the formation of the densely functionalized, carbohydrate-bridged DEF-ring system of nogalamycin partly explains why its total synthesis has remained an elusive goal for so many years. Despite numerous attempts by synthetic teams worldwide, including those of Hauser, Terashima, Thomson, VanNieuwenhze or Weinreb, a total synthesis of nogalamycin has yet to be achieved.[39,40–43] Recent studies on the biosynthesis of nogalamycin have revealed that the formation of the crucial *C*-aryl glycoside linkage proceeds through a glycosyl radical intermediate, with the key carbocyclization step being catalyzed by the α-ketoglutarate and nonheme iron-dependent enzyme SnoK (Scheme 1a).[44–46] Both past and recent approaches to the DEF-ring system of nogalamycin have primarily focused on anionic reactions.[39,40–43] In the late 2010s, VanNieuwenhze's group reported three different strategies for the total synthesis of nogalamycin.[47,48] One approach building on Terashima's work on menogaril,[40a] involved the addition of an aryl lithium reagent to a methyl ketone derived from D-arabinose, taking advantage of the chirality within its structure (Scheme 1b).[47b]

A chelate-controlled addition with the α-benzyloxy group was expected to yield the desired tertiary alcohol diastereomer with high stereocontrol. However, the reaction exhibited low selectivity, likely due to the electron-withdrawing β-azido substituent, which, according to Evans' nonchelated model, preferentially stabilized the formation of the undesired diastereomer. A second approach from D-arabinose was developed by the same group by way of a Suzuki–Miyaura reaction as the key step, which coupled the EF-ring segment with the D-ring to give a 1,1-disubstituted alkene (Scheme 1c).[47a] After further manipulation, the coupling product was treated with *m*CPBA to afford the desired epoxide as a single diastereoisomer, although the absolute configuration of the new stereocenter was not determined. Regioselective ring opening by LAH afforded the corresponding tertiary alcohol with concomitant loss of the TBS group. Interestingly, the absence of TBS-deprotection and reductive ring opening with DIBAL and superhydride, showed clearly that lower steric hindrance of the reagent played a key role in this process. Subsequent treatment under acidic conditions afforded the expected DEF-ring fragment of nogalamycin. ^{1}H NMR coupling constants indicated that the F-ring adopts a chair conformation, consistent with the stereochemical preferences imposed by the anomeric effect. In a third strategy developed by VanNieuwenhze's group,[48] the carbohydrate-bridged DEF-ring system is con-

Philippe Compain

Pr Philippe Compain has been Professor of Molecular Chemistry at the University of Strasbourg since 2008. His research ranges from synthetic methodology to the design of biologically relevant glycomimetics. In 1998, he was awarded the Dina Surdin Prize by the French Chemical Society for his PhD research on alkaloid synthesis (UCBL, Lyon). After a postdoctoral stay at Montreal with Prof. S. Hanessian, he was appointed as a Chargé de Recherche at CNRS (ICOA, Orléans). Prof. Compain is an honorary member of the Institut Universitaire de France. He recently served as the 25th President of the Groupe Français des Glycosciences (GFG, the French network in Glycosciences).

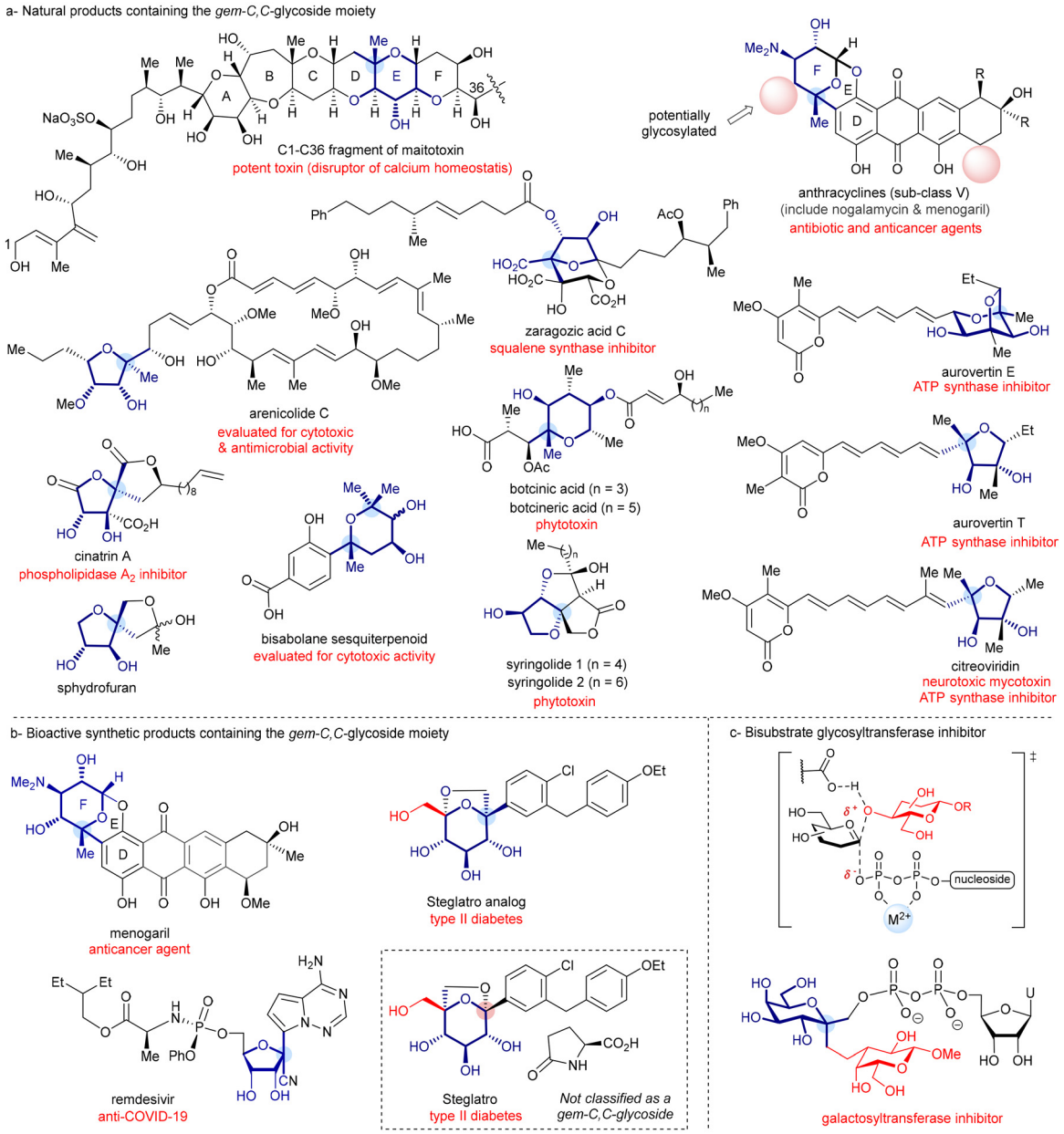
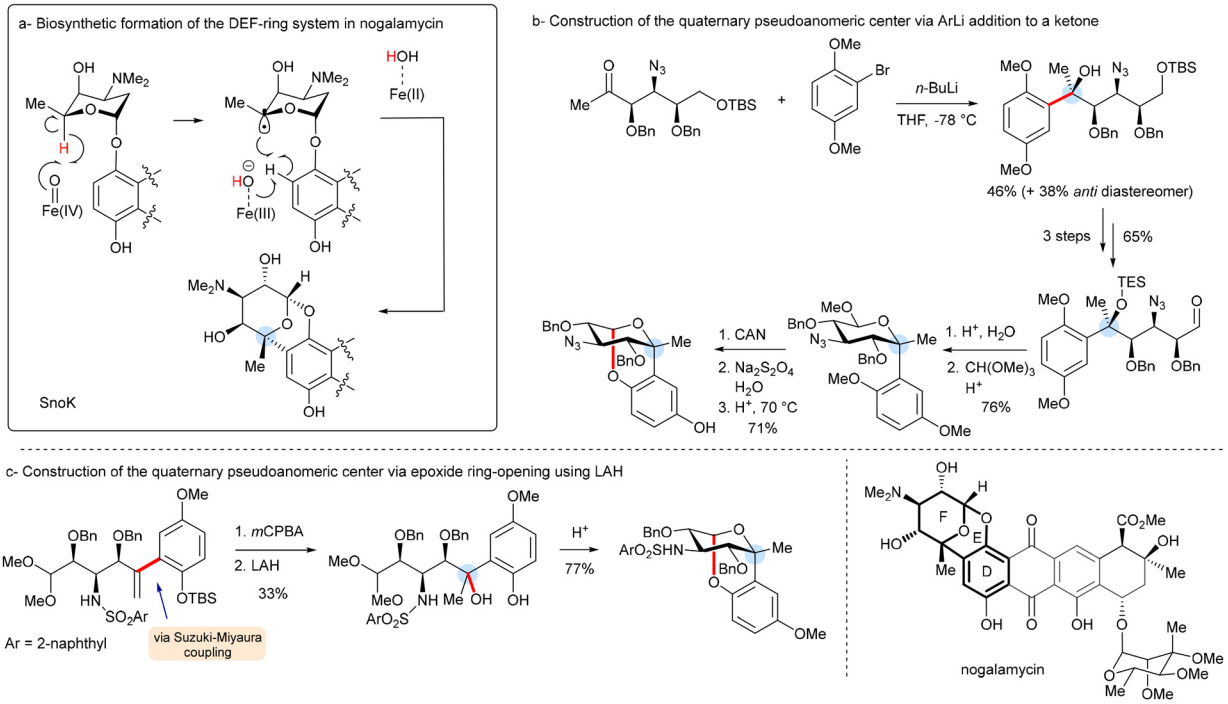


Fig. 2 Selected natural and synthetic bioactive products containing the *gem*-*C*,*C*-glycosyl moiety.

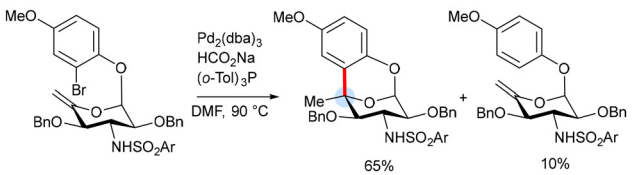
structed by way of a reductive intramolecular Heck reaction from a bifunctional *exo*-glycal intermediate (Scheme 2). Previous attempts to achieve the desired cyclization on related substrates by activating the exocyclic double bond, either under Friedel–Crafts conditions or through an intramolecular radical approach, led to undesired side products and failed to produce the targeted epoxybenzoxocin skeleton.[49] In contrast to most approaches towards nogalamycin and its analogues,[39,40–43,47] these strategies first established the *O*-glycosidic bond, followed by the introduction of the *C*-glycosidic bond to complete the DEF-ring system of nogalamycin. The objective was to exploit the stereoelectronic preference induced by the anomeric effect to construct the quaternary pseudoanomeric center with the desired stereochemistry. Building on optimized Heck conditions identified in a previous model study using synthetically more accessible bifunctional *exo*-glucals,[48b] VanNieuwenhze's group obtained the desired tricyclic product in 65% yield along with a small amount of the protodebrominated product.

2.2. Meayamycins

FR901464, a natural antitumor antibiotic first reported in 1996,[50] was isolated by Fujisawa Pharmaceutical Company from *Pseudomonas* sp. no. 2663 (Fig. 3). Notably, Koide's group later discovered that replacing the anomeric hydroxyl group with a methyl group, forming a *gem*-*C*,*C*-glycoside motif, not



Scheme 1 Formation of the DEF-ring system of nogalamycin *via* biosynthetic and synthetic approaches.



Scheme 2 Construction of the DEF-ring system *via* reductive Heck cyclization.

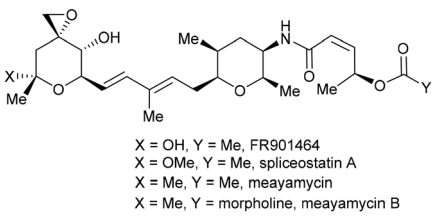
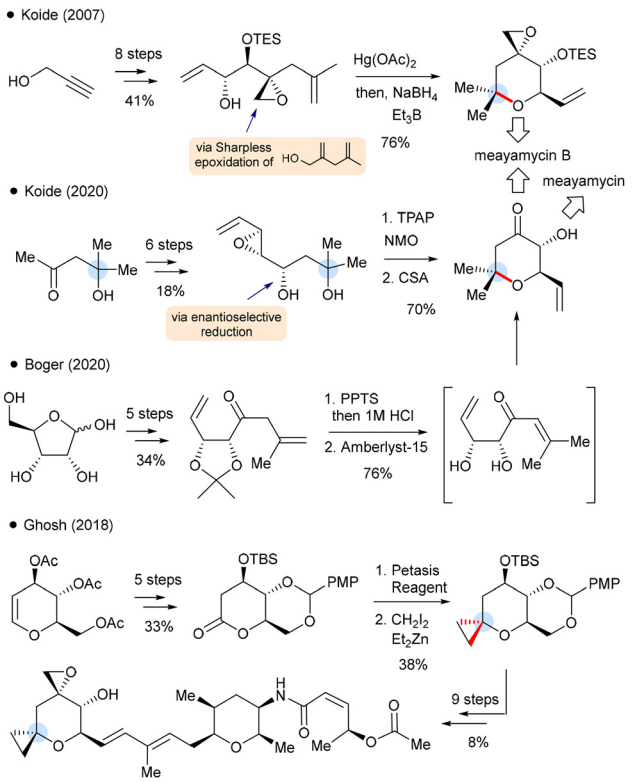


Fig. 3 FR901464 and representative examples of meayamycins.

only prevented rapid degradation but also enhanced biological potency by up to 100-fold.[51–53] Among these synthetic analogues, known as meayamycins, meayamycin B stands out as the most potent splicing modulator reported to date.[52]

The synthesis of meayamycin B by the group of Koide reported in the late 2000s suffered from different drawbacks that limited its availability for biological studies.[53] Notably, the formation of the *gem*-*C*,*C*-glycoside motif through an oxymercuration-demercuration sequence required stoichiometric amounts of $Hg(OAc)_2$ (Scheme 3). In an effort to develop a more concise and environmentally friendly synthesis, Koide *et al.* designed in 2020 a strategy from a tertiary alcohol starting material in which the *gem*-dimethyl motif is already present. The pivotal tetrahydropyran ring was formed under acidic conditions from the corresponding γ-hydroxy epoxide *via* a 6-*endo*-*tet* cyclization.[54] In the two *de novo* syntheses of meayamycin B reported by Koide, the formation of enantiopure key intermediates relies on the use of enantioselective reactions, such as Sharpless epoxidation (Scheme 3). The same year, the group of Boger[55] reported the synthesis of meayamycin from D-ribose which provides two stereogenic centers of the key *gem*-*C*,*C*-glycoside intermediate. This intermediate was obtained in 76% yield following a sequence that included acid-catalyzed acetonide deprotection, alkene isomerization, and 6-*endo*-trig cyclization of the distal alcohol. Initial optimization revealed that treatment of the acetonide with pyridinium *p*-toluenesulfonate (PPTS) at 60 °C predominantly yielded the corresponding diol. Subsequent addition of aqueous 1 M HCl at 60 °C completed the isomerization of the double bond. Treatment with Amberlyst-15 completed the oxa-Michael-type reaction. A spirocyclopropyl carbohydrate analogue of meayamicin was synthesized by the group of Ghosh in 2018 from tri-*O*-acetyl-D-glucal (Scheme 3).[34,56] The cyclopropyl moiety was introduced by first treating the corresponding lactone with Petasis reagent, yielding the corresponding enol-ether in 90% yield. Simmons–Smith cyclopropanation of the resulting *exo*-glycal intermediate with methylene diiodide and diethylzinc provided the desired spirocyclopropyl carbohydrate derivative in a modest 42% yield. The spirocyclopropyl analogue of meayamycin showed significant biological activity in human



Scheme 3 Construction of the *gem-C,C*-glycoside fragment of meayamycins.

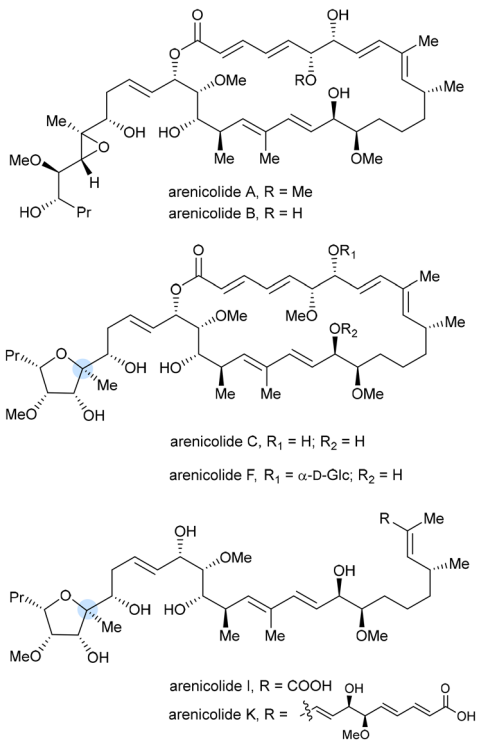
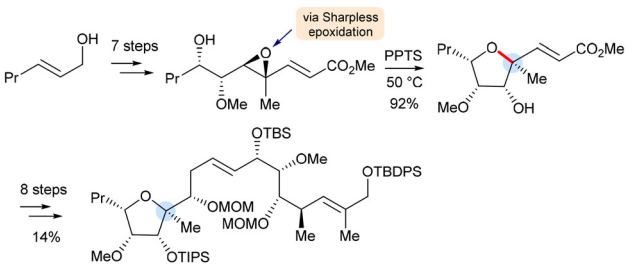


Fig. 4 Selected representative examples of arenicolides, highlighting key structural features.



Scheme 4 Construction of the *gem-C,C*-furanoside fragment of arenicolide C.

cells as an RNA splicing inhibitor, with efficacy comparable to that of spliceostatin A.[56]

2.3. Biomimetic synthesis of the furan ring in arenicolide C

Arenicolides A–C[19] are 26-membered ring macrolides first isolated in 2007 from the marine actinomycete *Salinispora arenicola* (Fig. 4). At that time, arenicolide C was the only known member of the family featuring a furan ring in place of the epoxy group. Initial biological evaluation revealed that arenicolide A exhibits moderate cytotoxicity against the human colon adenocarcinoma cell line.[19b] In the ongoing search for novel anti-tuberculosis agents, a new series of arenicolides bearing a *gem-C,C*-furanoside motif were identified in 2025 from black oil beetle gut bacterium *Micromonospora* sp. GR10, along with arenicolide A and related derivatives resulting from macrolactone ester bond cleavage.[57] Antimicrobial studies revealed that arenicolide A exhibited the most potent *in vitro* activity, underscoring how the absence of an epoxide group, as well as linear modifications of the macrocycle, can influence anti-tuberculosis efficacy.[57] Synthetic efforts directed towards the synthesis of arenicolide C were reported by Nagumo's group in 2015, using a biomimetic epoxide-to-tetrahydrofuran transformation (Scheme 4).[19a] This cyclization process has been observed in the biosynthetic pathways of related natural products, such as lasalocid A.[58] Recent studies have proposed similar pathways for the biosynthesis of arenicolides C, F, G, I and K.[57]

Recalling Koide's synthetic approach to meayamycin B (Scheme 3),[54] the tetrahydrofuran ring was formed under acidic conditions from the corresponding *γ*-hydroxy unsaturated epoxide *via* a Nicolaou-type cyclization.[19a] Treatment with PPTS resulted in efficient 5-*endo-tet* cyclization, yielding the desired *gem-C,C*-furanoside intermediate in excellent yield (Scheme 4). Subsequent synthetic elaboration enabled the successful construction of an advanced fragment of arenicolide C.

2.4. Zaragozic acid C

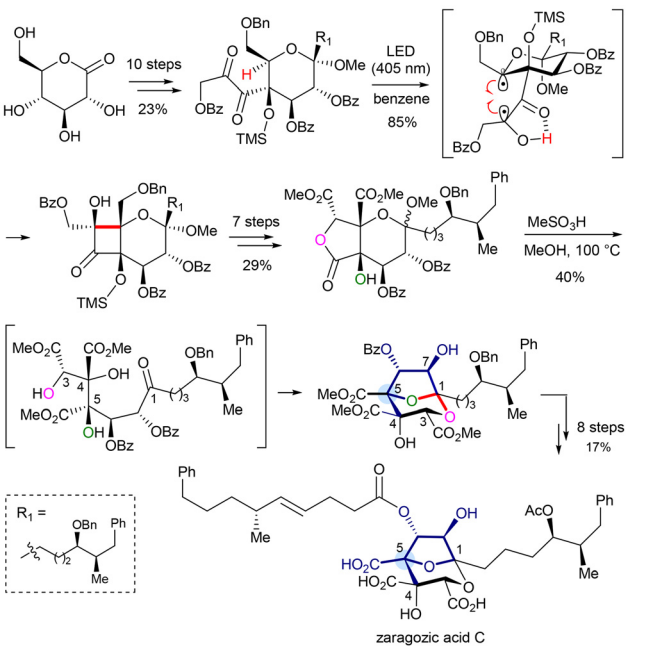
Zaragozic acids,[29] also known as squalestatins, were independently discovered in the early 1990s by researchers from Merck,[59] Glaxo[60] and Mitsubishi Chemical.[61] Zaragozic acid C is a representative member of this family of structurally related fungal metabolites. Their potent inhibitory activity against

mammalian squalene synthase makes then promising lead structures for the development of cholesterol-lowering drugs.[27] Zaragozic acid C features a densely oxygenated 2,8-dioxabicyclo[3.2.1]octane acid core adorned with six stereogenic centers. Despite the complexity of this structure, the organic chemist's trained eye can readily pinpoint the embedded *gem-C,C*-furanoside fragment. Moreover, the three fully substituted carbons at C1, C4, and C5 pose an additional, compelling challenge for its chemical synthesis. Not surprisingly, zaragozic acid C has captured the imagination of many synthetic chemistry groups, resulting in the development of numerous innovative synthetic strategies.[27,28,62–66] The first total synthesis was reported in 1994 by Du Bois and Carreira, shortly followed by the synthesis from Evans' group.[64] Significant contributions to the synthesis of zaragozic acids have also been made by the research groups of Armstrong, De Riccardis, Johnson, Hashimoto, Heathcock, Metz, Nakai and Nicolaou.[27,28] The key steps of these strategies were directed towards the stereocontrolled construction of the hindered tetrasubstituted C4 and C5 centers. Many approaches were employed including osmylation of tri- or tetrasubstituted alkenes, pericyclic reactions or asymmetric aldolizations.[27,28,62–66] in 2017, the group of Inoue proposed an exciting approach based on a Norrish–Yang reaction to generate the precursor of the tetrasubstituted C4 carbon of zaragozic acid C (Scheme 5).[62] The densely functionalized 1,2-diketone precursor for the photoinduced process was synthesized in 10 steps from a D-gluconolactone derivative. Irradiation with purple light (405 nm LED) delivered the desired fused bicyclic ketone in high yield with excellent regio- and stereoselectivity. 1,5-Hydrogen abstraction following ketone sensitization furnished the key 1,4-biradical pair. Regioselectivity of the γ-hydrogen abstraction was directed by the strategic protection of both other hydroxyl moieties with electron-withdrawing benzoyl groups, biasing the reaction toward polarity-matched HAT at the electron-rich pseudoanomeric site. The cyclization is favored by the radical anomeric effect,[67] which stabilizes the reactive α-radical intermediate. The second key step of the synthesis is a remarkable acid-promoted cascade reaction that transforms a bicyclic lactone precursor into the 2,8-dioxabicyclo[3.2.1]octane skeleton of zaragozic acid C (Scheme 5). While various Lewis and both weaker and stronger Brønsted acids proved unsuccessful, treatment with $MeSO_3H$ in MeOH at 100 °C provided the desired bicyclic acetal advanced intermediate in 40% yield with deprotection of the hydroxyl group at C7.[62] This impressive, complex cascade sequence involves methanolysis of the lactone, departure of the anomeric methoxy group and formation of the new acetal motif through the successive nucleophilic additions of the hydroxyl groups at C3 and C5 to the electrophilic carbon center at C1.

2.5. Natural glycoconjugate analogues

Ganglioside GM3 is a key glycosphingolipid that plays a critical role in regulating diverse biological processes within membrane microdomains (Fig. 5).[68] However, its metabolic instability – particularly its susceptibility to sialidase-mediated cleavage – has impeded both the investigation of its biological functions and its development as a therapeutic agent. To overcome this limitation, sialidase-resistant analogues of ganglioside GM3 have been designed and synthesized over the past decades. Substitution of the cleavable *O*-sialoside linkage has resulted in the development of *S*-sialoside and *C*-sialoside analogues, leading to minimal structural modifications of the parent natural product.[69]

In order to mimic the conformational behaviour of the native GM3 more closely, the group of Sodeoka recently reported the synthesis of analogues incorporating a monofluoromethylene-linked sialoside (Fig. 5).[70] The stereocontrolled construction of the CHF-sialoside unit was achieved *via* an Ireland-Claisen rearrangement, enabling formation of the quaternary pseudoanomeric center (Scheme 6). In the same study, GM3 analogues featuring CF_2- and CH_2- linkage were also synthesized, using SiaGal building blocks prepared through the same rearrangement.[70,71] Proliferation assays in Had-1 cells, combined with NMR-based conformational ana-



Scheme 5 Total synthesis of zaragozic acid by Inoue *et al*.

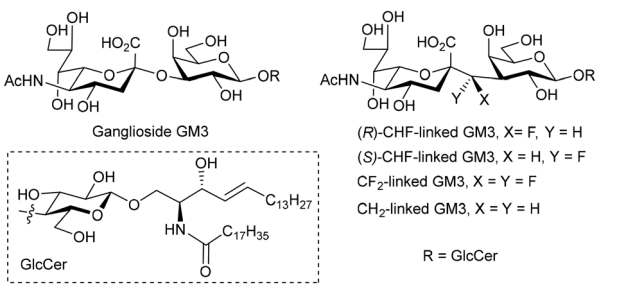
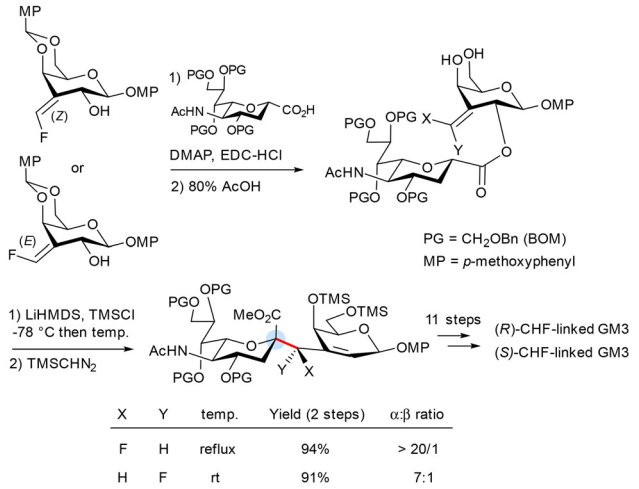


Fig. 5 Structures of ganglioside GM3 and *C*-sialoside analogues.



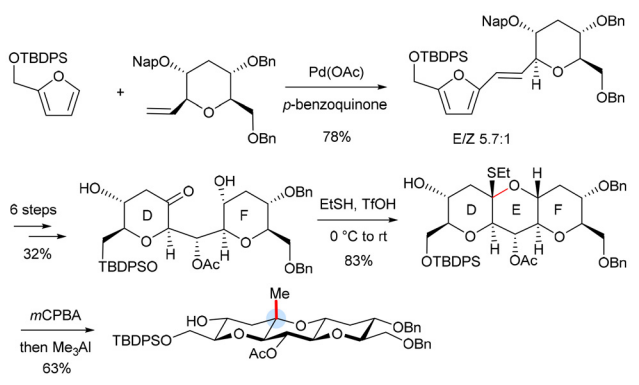
X	Y	temp.	Yield (2 steps)	α:β ratio
F	H	reflux	94%	> 20/1
H	F	rt	91%	7:1

Scheme 6 Synthesis of key CHF-sialoside intermediates *via* Ireland-Claisen rearrangement.

lysis, revealed that the (*S*)-CHF-linked GM3 analogue with an *exo*-gauche conformation was the most potent. Had-1 cells, a murine mammary tumor cell line with a glycosylation defect, serve as a sensitive model for evaluating the biological activity of synthetic GM3 analogues. These findings therefore not only highlight the enhanced stability of *C*-sialoside analogues but also emphasize the crucial role of the *exo*-anomeric conformation in modulating GM3's biological activity.[70]

2.6. DEF-ring system of maitotoxin

Maitotoxin is the largest and most potent secondary metabolite identified to date. Its ladder-like polyether framework, comprising over 30 cyclic ether rings, illustrates the exceptional structural complexity characteristic of marine secondary metabolites. This unique architecture, coupled with its potent biological activity, has established maitotoxin as both a formidable synthetic target and a valuable molecular probe in chemical and biological research.[20] The group of Oishi has recently proposed a furan-based strategy for the synthesis of the DEF-ring system of maitotoxin (Scheme 7).[72] The coupling of the furan-based D-ring precursor with a *C*-vinyl pyranoside, serving as the F-ring precursor, was accomplished *via* a Fujiwara–Moritani reaction in the presence of $Pd(OAc)_2$ and 1,4-benzoquinone. The next steps involved D-ring construction from the furan derivatives *via* the Achmatowicz reaction. Construction of the E ring was then pursued. Treatment of the key δ-ketol with EtSH and triflic acid furnished the corresponding cyclic *S*,*O*-acetal in 83% yield. Subsequent installation of the axial methyl group was achieved *via* *m*CPBA-mediated oxidation of the sulfur atom to the sulfoxide, followed by Me_3Al-promoted methylation,[73] affording the DEF fragment of maitotoxin in 63% yield as a single stereoisomer.



Scheme 7 Synthesis of the DEF-fragment of maitotoxin.

2.7. Recently isolated *gem*-*C*,*C*-glycosides

Over the past decade, several novel natural products bearing the *gem*-*C*,*C*-glycosyl moiety have been isolated, yet their total syntheses remain unreported. The majority of these compounds belongs to the aurovertins family.[24] The list includes aurovertin T (Fig. 2) and aurovertin U (Fig. 6) isolated from *Calcarisporium arbuscula*.

Evaluation of the cytotoxic activities of these compounds against triple-negative breast cancer cell line revealed that aurivertin U exhibits activity comparable to the positive control, Taxol.[78] Interestingly, the ineffectiveness of aurovertin T underscores the critical role of the 2,6-dioxabicyclo[3.2.1]octane system for anti-cancer activity.[74] In contrast, two other previously undescribed polyketides, namely aurovertins V and W (Fig. 6), isolated from the fungus *Aspergillus aureoterreus*, show no cytotoxicity against various human cancer cell lines, includ-

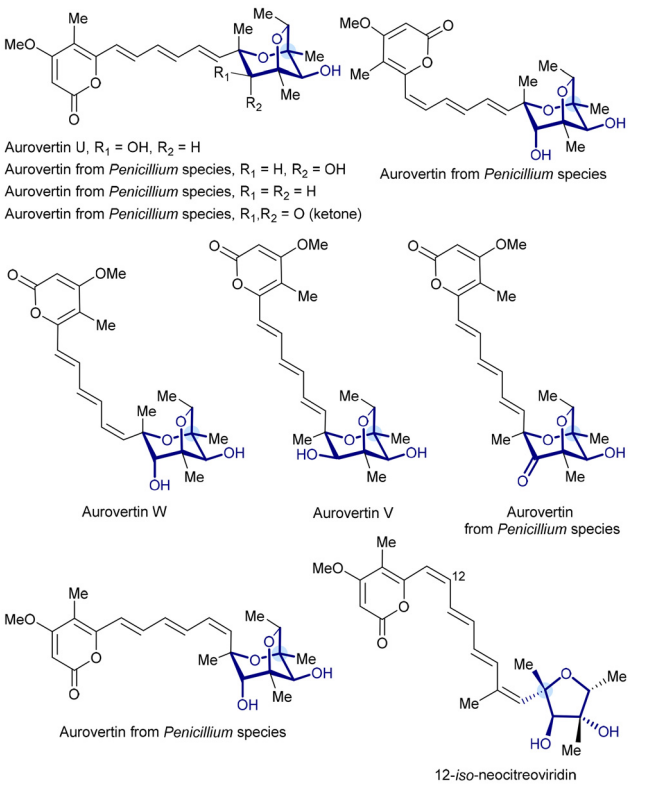
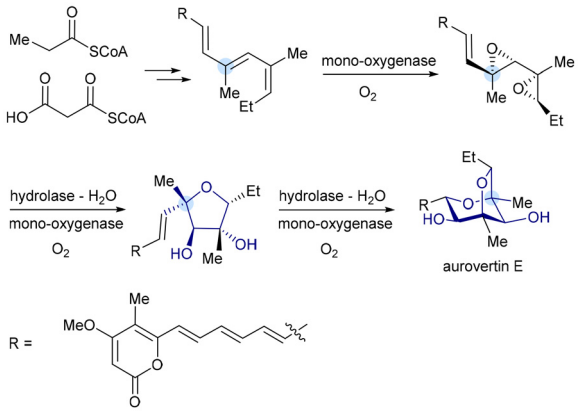


Fig. 6 Recently isolated members of the aurovertin family.



Scheme 8 Proposed biosynthetic pathway for the construction of the 2,6-dioxabicyclo[3.2.1]octane core of aurovertin E.

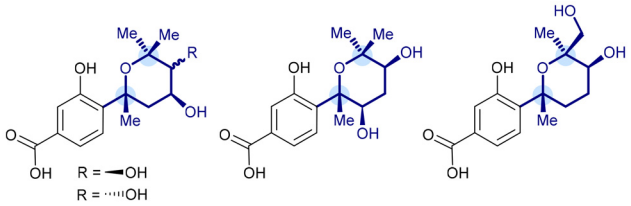


Fig. 7 Structures of newly discovered phenolic bisabolane-type sesquiterpenoids.

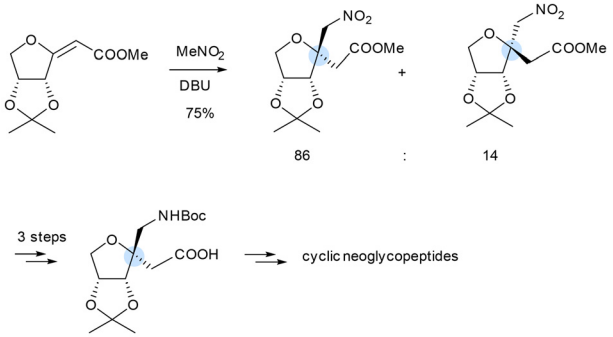
ing HL-60 and U266.[75] Very recently, the marine-derived *Penicillium* sp. OUCMDZ-5930 was identified as prolific source of aurovertins, resulting in the isolation of seven new members of this family including 12-iso-neocitreoviridin.[76] Unfortunately, no antimicrobial or cytotoxicity activity was observed with these compounds to date. The biosynthetic formation of the *gem-C,C*-glycosyl moiety in aurovertins is proposed to proceed *via* regioselective oxidation of a polyene precursor, followed by sequential bis-epoxide ring openings.[24a] For example, in the biosynthesis of aurovertin E, a flavin-dependent mono-oxygenase (AurC) and an epoxide hydrolase (AurD) are thought to act iteratively on the terminal triene segment of the precursor, converting it into the characteristic 2,6-dioxabicyclo[3.2.1]octane core of aurovertins *via* the corresponding dihydroxylated tetrahydrofuran ring (Scheme 8).[77,78]

In 2023, the group of Cheng reported the isolation of four *gem-C,C*-glycoside-containing bisabolane-type sesquiterpenoids from the deep-sea-derived fungus *Aspergillus versicolor* YPH93 (Fig. 7).[79] None of the compounds displayed cytotoxic or inhibitory activity against ferroptosis.[79]

3. Synthetic *gem-C,C*-glycosides of biological interest

3.1. Sugar amino acids

Sugar amino acids (SAAs) are carbohydrate-derived building blocks bearing amino and carboxylic acid functionalities,



Scheme 9 Synthesis of *gem-C,C*-furanoside building blocks.

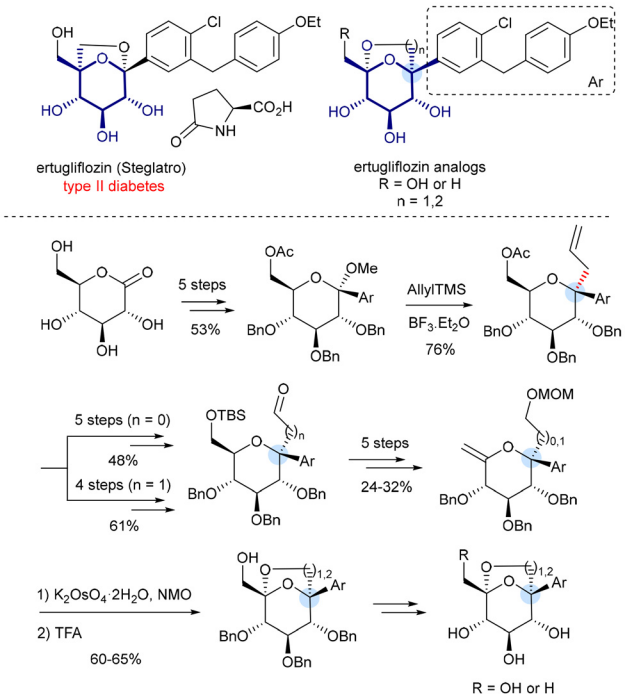
widely used in the synthesis of peptidomimetics, enzyme inhibitors, and non-natural folded polymers known as foldamers.[80] Notably, when incorporated into cyclic peptidomimetics, SAAs can influence molecular conformation in distinct and predictable ways. Recently, Pellegrini-Moïse *et al.* expanded the foldamer monomer repertoire by introducing geminally β,β-disubstituted γ-amino acids, in which the β-carbon corresponds to the pseudoanomeric center of the sugar ring.[81] The key *gem-C,C*-furanoside intermediates were synthesized from the corresponding *exo*-glycals *via* a stereoselective Henry-Michael-type reaction of nitromethane in the presence of DBU (Scheme 9).

In the major diastereomer, the nitro group occupies the less hindered face of the sugar, likely due to thermodynamically driven equilibration involving reversible ring opening and closure. The target Boc-protected γ-amino acid building block was obtained through subsequent reduction of the nitro group.

3.2. Ertugliflozin analogues

Ertugliflozin (MK8835) is an orally active inhibitor of sodium–glucose co-transporter 2 (SGLT2), approved for the treatment of type 2 diabetes (Scheme 10).[82,83] It received FDA approval in December 2017 and EU approval in 2018. Initially discovered by Pfizer and later developed in collaboration with Merck, it is marketed under the names Segluromet, Steglatro, and Steglujan. In 2016, a series of novel *C*-aryl glucoside analogues of ertugliflozin were synthesized and evaluated for their inhibitory activity against human SGLT2.[30]

The synthesis of *gem-C,C*-glycoside analogues of Steglatro involved the construction of two (pseudo) anomeric centers positioned on either side of the endocyclic oxygen atom. The aromatic aglycon part was introduced *via* nucleophilic addition of the corresponding aryllithium reagent to TMS-protected D-gluconolactone.[30] The quaternary anomeric center thus formed was converted into the key *gem-C,C*-glycoside intermediate with high diastereoselectivity upon treatment with allylsilane in the presence of $BF_3{\cdot}Et_2O$. The absolute configuration of the newly generated asymmetric center is consistent with the conformational model proposed by Woerpel.[84] The two *exo*-glycal precursors of the [3.2.1] and [3.3.1] bicyclic

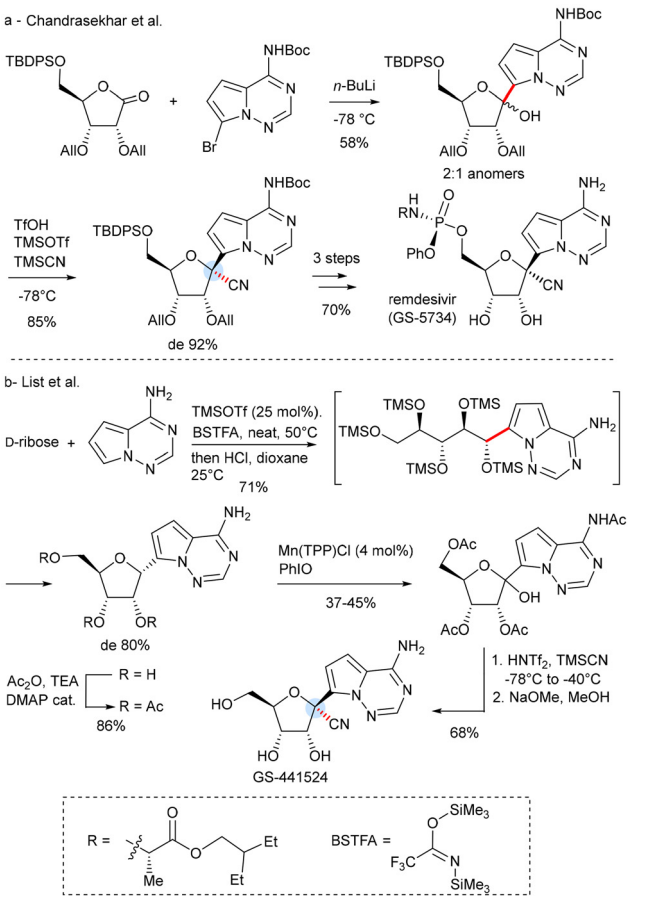


Scheme 10 Synthesis of ertugliflozin analogs.

skeletons were synthesized from the allylated intermediate in respectively five or four steps, including a Pd-catalyzed double bond migration in the case of the former. Subsequent Sharpless dihydroxylation, followed by acid-promoted one-pot MOM deprotection and stereoselective intramolecular trapping of the putative oxocarbenium ion intermediate, furnished both the desired [3.2.1] and [3.3.1] bicyclic frameworks. Further functionalization and deprotection yielded the four targeted ertugliflozin analogues. Among these analogues, the compound most structurally related to ertugliflozin exhibited moderate SGLT2 inhibitory activity, with an IC_{50} value of 700 nM.

3.3. Remdesivir analogues

Remdesivir, a phosphoramidate prodrug nucleotide developed by Gilead Sciences as GS-5734 in 2009, was initially aimed at treating hepatitis C (Fig. 2).[31,85,86] It was later found to be effective against a range of viruses, including Ebola, SARS, and MERS, blocking viral infection at low micromolar concentrations with a high selectivity index.[31] Supported by these favorable bioactivity data and existing safety profiles, it was granted FDA approval as a repurposed treatment for severe COVID-19 infections, becoming the first approved therapy that specifically targets the virus. 1′-Substituted *C*-nucleosides are uncommon among nucleoside analogues. In remdesivir, the 1′-cyano (1′-CN) group, attached to a quaternary pseudo-anomeric carbon, plays a critical role in its antiviral action.[85] Once metabolized to its active triphosphate, remdesivir mimics ATP and is efficiently incorporated into SARS-CoV-2 RNA. The 1′-CN group induces polymerase stalling and also reduces the efficiency of incorporation as a GTP analogue. While 1-CN doesn't protect remdesivir from being excised by viral proofreading enzymes, its presence in RNA may disrupt downstream viral processes like transcription and translation. As several synthetic strategies toward remdesivir and analogues have already been thoroughly reviewed in the recent literature[86] only the most recent developments and advancements in the field are presented here. In most synthetic approaches, a protected D-ribono-1,4-lactone derivative is subjected to *C*-glycosylation with a heteroaryl-lithium or -magnesium reagent.[86,87] A notable example of this strategy was reported in 2022 by the group of Chandrasekhar (Scheme 11a).[88] The cyanation of the resulting lactol was performed under standard conditions (TfOH, TMSOTf)[86] to afford the *gem*-*C*,*C*-glycoside motif. The stereochemical outcome of this transformation was rationalized by invoking a nonbonding interaction of the allyl ether oxygen in the oxocarbenium cation intermediate with the silicon atom in TMSCN, thereby directing preferential delivery of the cyanide ion from the α-face.[89] The use of a silyl/allyl protected D-ribono-1,4-lactone as the starting material streamlined protecting group manipulations compared to the original synthetic route developed by Gilead Sciences.[86,87] In 2022, List *et al.* reported a novel, practical approach to remdesivir (Scheme 11b).[90] The first step involved direct addition of

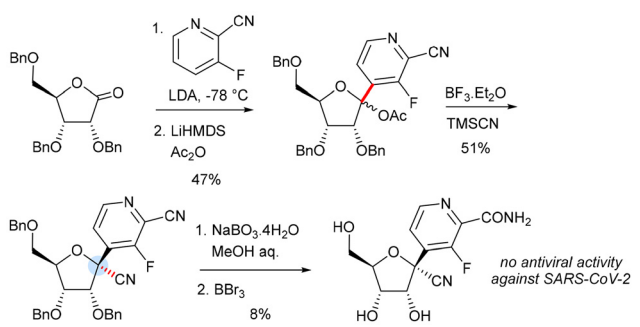


Scheme 11 . Total syntheses of remdesivir nucleoside.

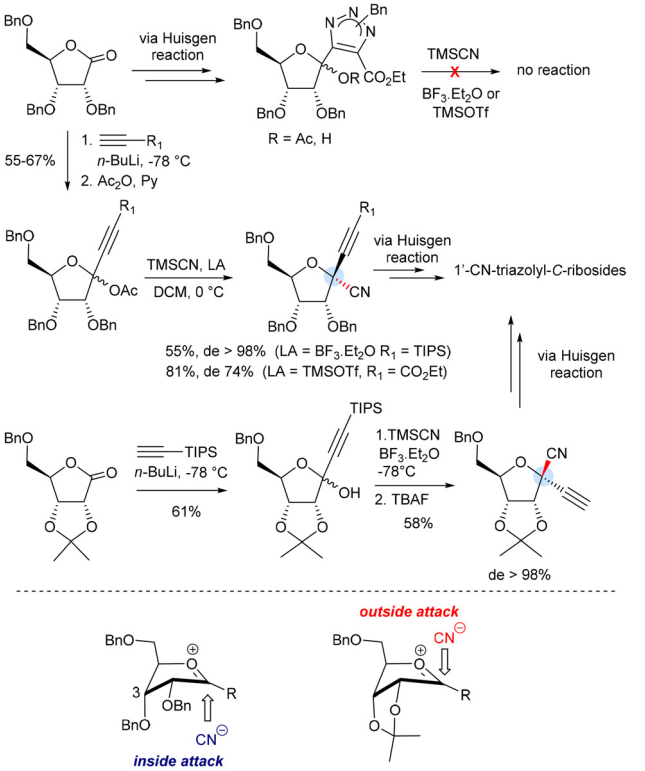
pyrrolo[2,1-*f*][1,2,4]triazin-4-amine to free D-ribose in the presence of catalytic amount of TMSOTf, which is regenerated upon protodesilylation of the innocuitous silyl cation source *N*,*O*-bis(trimethylsilyl)trifluoro acetamide (BSTFA). Remarkably, during the transformation, the dynamic mixture of isomers converged to a single TMS-protected *C*-glycosylation product. Acidic treatment at 25 °C afforded the α-nucleoside with high diastereoselectivity, whereas heating to 50 °C led to formation of the thermodynamically favored β-anomer. The key lactol intermediate was obtained in 37–45% yield *via* Mn-catalyzed benzylic C–H oxidation. Owing to the presence of acetate protecting groups, standard cyanation conditions were modified: the TfOH/TMSOTf mixture was replaced with the stronger Brønsted acid $HNTf_2$ to generate $TMSNTf_2$ *in situ*.

The remdesivir nucleoside (GS-441524) precipitated as a single diastereoisomer during the subsequent methanolysis step. Activation of the anomeric position for cyanation has also been applied for the synthesis of remdesivir nucleoside analogues. For example, an acetyl-protected riboside was employed in the preparation of a hybrid molecule combining structural features of remdesivir and favipiravir, an antiviral agent approved for influenza treatment in Japan (Scheme 12).[91]

In the continuous effort toward the discovery of broad-spectrum antiviral agents, Lubin-Germain *et al.* synthesized 1′-CN-triazolyl-*C*-ribosides.[92] The presence of the triazole ring at the anomeric center was found to hinder cyanation, whereas introducing the cyano group prior to triazole installation *via* the Huisgen reaction proved to be effective (Scheme 13). Additionally, the choice of protecting groups on the ribose was found to influence the stereochemical outcome, with the isopropylidene acetal favoring β-selectivity. This observation aligns with the conformational model proposed by Woerpel.[84,92] According to this model, formation of the 1,3-*cis* products can be rationalized by a stereoelectronically controlled inside attack of the cyanide on the lowest-energy conformer of the oxocarbenium ion intermediate—specifically, the ^3E conformation, in which the C-3 alkoxy group adopts a pseudoaxial orientation to maximize favorable electrostatic interactions. With the isopropylidene acetal hindering inside attack, outside attack is favoured, leading to preferential formation of the β-anomer (Scheme 13).



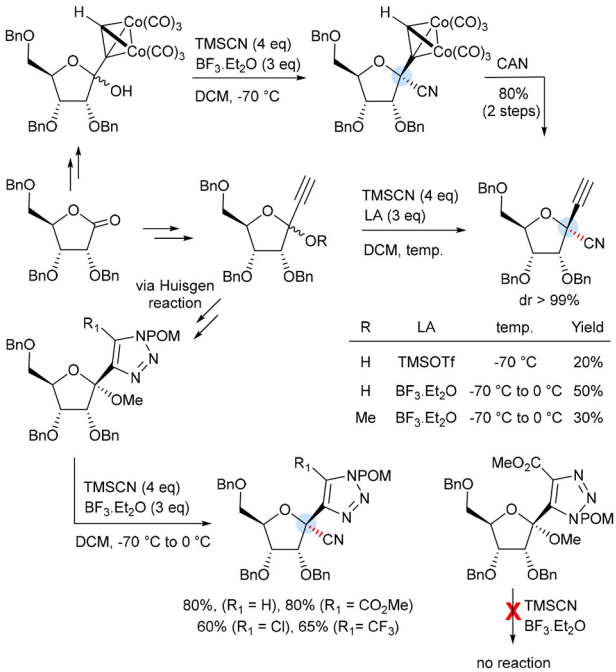
Scheme 12 Synthesis of a remdesivir nucleoside analogue.



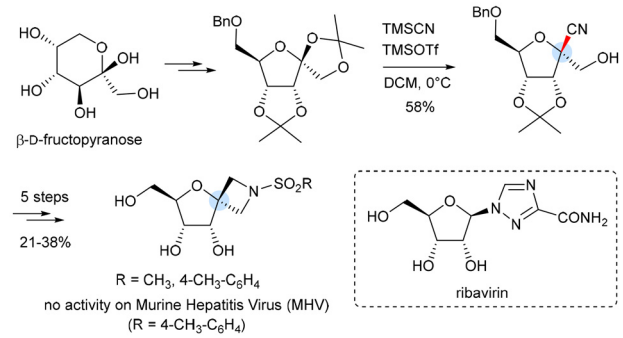
Scheme 13 Synthesis of 1′-CN-triazolyl-*C*-riboside.

A related study was independently reported by the Lebreton group during the same period.[93] The presence of terminal alkynes was detrimental to the efficiency of the cyanation reaction (Scheme 14). Activation of the alkynyl ketose derivatives towards propargylic substitution with dicobalt-octacarbonyl substantially improved the yield of the desired *gem*-*C*,*C*-furanoside. To circumvent the use of toxic cobalt reagents, an improved route featured cyanation after installation of the triazole moiety. Azido-methyl pivalate ($POMN_3$) was selected for the Huisgen reaction, anticipating orthogonal deprotection of the POM group with a methanolic ammonia solution in the presence of the anomeric cyano group. In contrast with the findings of Lubin-Germain *et al.* (Scheme 13),[92] the triazole moiety at the anomeric center had no impact on the efficiency of the cyanation reaction. However, a pronounced difference of reactivity was noted between the 1,5- and 1,4-adducts derived from alkynyl ester derivatives, likely due to increased steric hindrance at the anomeric center in the 1,4-regioisomer (Scheme 14). Late stage modifications of remdesivir and GS-441524 derivatives have been also conducted to develop more potent anti-viral agents.[94]

The biological activity of nucleosides can be fine-tuned by modifying the sugar conformation. The spirocyclic scaffold is a crucial modification for influencing the sugar conformation and enhancing the properties of nucleosides.[95] In 2018, Cobb *et al.* employed a cyanation reaction to access spirocyclic analogues of ribavirin[96] featuring an azetidine scaffold.[97] The desired *gem*-*C*,*C*-furanoside product was obtained in 58% yield



Scheme 14 Synthesis of 1′-CN-triazolyl-*C*-ribosides.



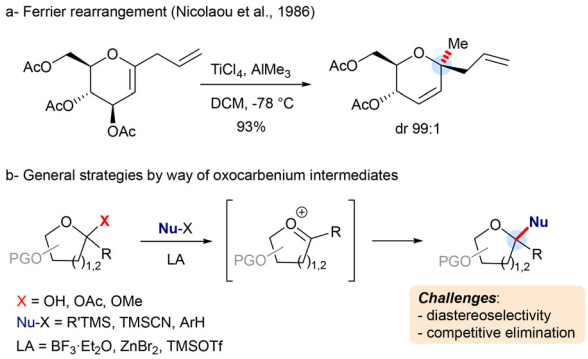
Scheme 15 Synthesis of 1′-CN-triazolyl-*C*-ribosides.

from the corresponding β-D-psicofuranoside derivative using TMSCN and TMSOTf (Scheme 15).

The spirocyclic *N*-sulfonyl azetidines were subsequently obtained through functional group transformations, cyclization and deprotection. Owing to its similarity with ribavirin,[96] a well-known agent for the treatment of chronic hepatitis C, the antiviral properties of the *N*-tosyl derivative were evaluated using Murine Hepatitis Virus (MHV) as a model; however, no significant activity was observed.

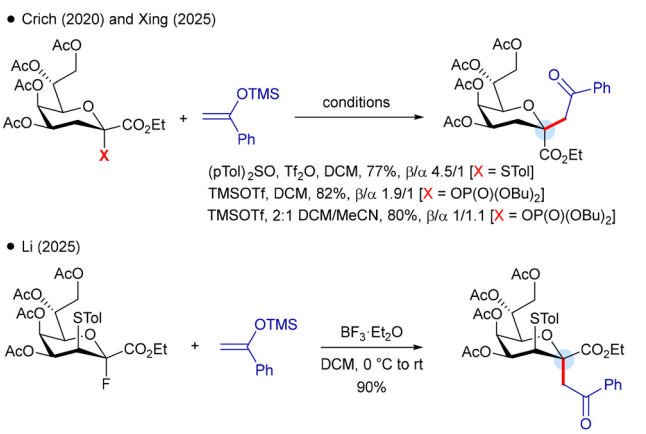
4. Specific methods for the synthesis of *gem*-*C*,*C*-glycosides through glycosyl electrophilic species

C-Glycosylation *via* the generation of oxocarbenium cation intermediates has been extensively investigated as a key strategy for the synthesis of *C*-glycosides.[5a,b] This approach has also proven effective in the construction of *gem*-*C*,*C*-glycosides (Scheme 16). For instance, in 1986 Nicolaou *et al.* reported the synthesis of 1,1-dialkyl glycosides using a Ferrier rearrangement (Scheme 16a).[98] Another notable early example was reported by Wilcox *et al.*, involving the activation of a pseudo-anomeric acetate in a furanoside scaffold using $ZnBr_2$ as the Lewis acid.[8] Following these seminal contributions, a wide array of *C*-glycosylation protocols have emerged, utilizing diverse nucleophiles, Lewis acids, and anomeric leaving groups (Scheme 16b).[86,99,100] Key challenges in these methodologies include achieving anomeric stereocontrol and suppressing competing elimination pathways that lead to glycal formation. This strategy has been applied to the synthesis of *gem*-*C*,*C*-glycosides of biological interest as discussed in section 3 (Schemes 10–15).

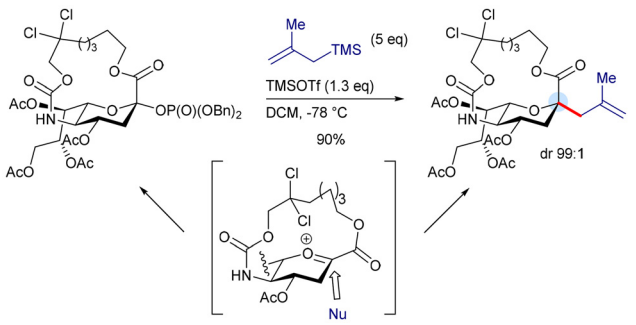


Scheme 16 Strategies for the synthesis of *gem*-*C*,*C*-glycosides *via* an oxocarbenium intermediate.

More recently, the groups of Crich, Xing and Li reported the synthesis of 3-deoxy-D-*manno*-oct-2-ulosonic acid (KDO) *C*-glycosides *via* *C*-glycosylation of dibutylphosphate precursors or thioglycosides (Scheme 17).[101–103] Diastereoselectivity varied with reaction conditions, but complete α-selectivity was achieved upon introduction of a *p*-tolyl sulfide at C3, consistent with the involvement of an episulfonium intermediate.[104]



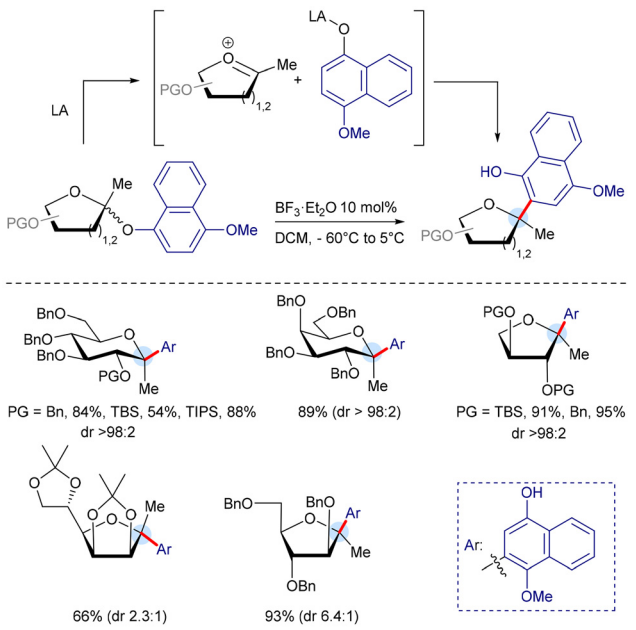
Scheme 17 Synthesis of KDO derivatives.



Scheme 18 Selective α-glycosidation using macrobicyclic sialic acid donors.

Ando *et al.* introduced a distinct approach to stereocontrol, reporting that *C*-glycosylation of conformationally restricted sialic acid donors afforded exclusively the α-isomer—an otherwise challenging selectivity for this substrate class (Scheme 18).[105]

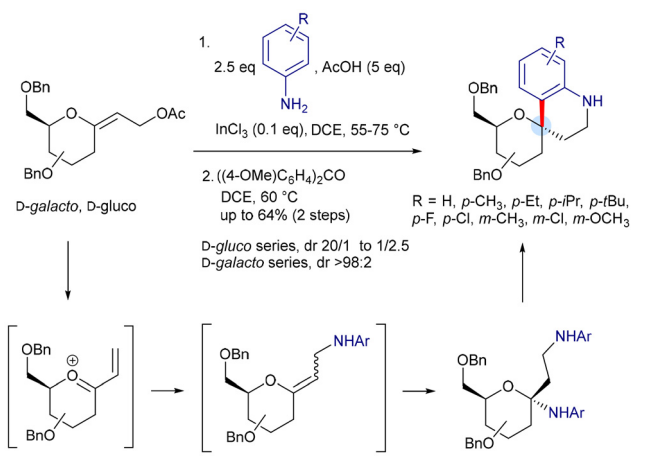
As part of our ongoing efforts to develop new strategies for constructing the DEF system of nogalamycin (see Fig. 2),[46,106] we recently reported the synthesis of *C*-naphthyl ketosides *via* a Fries-type rearrangement (Scheme 19).[107] In this approach, *O*-aryl ketosides[46] were activated with a Lewis acid, generating the corresponding oxocarbenium and naphtholate derivative. These intermediates subsequently underwent a regioselective Friedel–Crafts-type coupling, leading to the desired products.[106a,107] High β-selectivity was achieved in the D-hexopyranose and L-threo series, whereas low to modest diastereoselectivity was observed for 5-membered *O*-ketosides. Although this methodology is currently limited to *C*-naphthyl ketosides, it represents the first example of constructing a quaternary pseudoanomeric center *via* a Fries-type rearrangement.[106a]



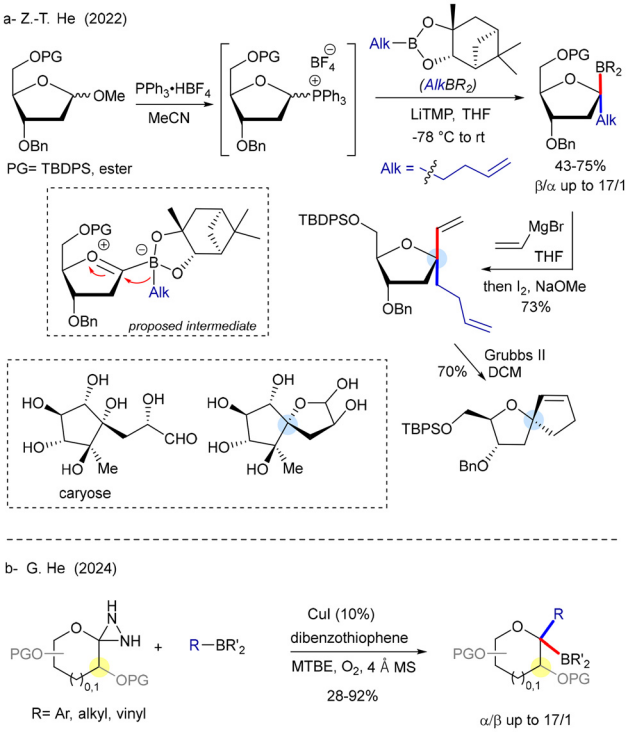
Scheme 19 Synthesis *C*-naphthyl ketosides *via* Fries type rearrangement.

Another example involving an intramolecular Friedel–Crafts reaction was reported by Lin *et al.*[108] In this approach spiro[pyran-4-quinolines] were synthesized in a two-step sequence from *exo*-glycals using $InCl_3$ as the Lewis acid (Scheme 20). The first step involved an "*exo*-Ferrier"-type rearrangement generating a vinyloxonium undergoing facile 1,4 addition of anilines, resulting in a formal substitution of the acetate followed by *N*-glycosylation affording the corresponding *C*,*N*-glycosides. The resulting intermediates were subsequently converted into the spirosugar through treatment with $InCl_3$ and 4,4′-dimethoxybenzophenone, which facilitated the departure of the *N*-aryl group as a benzophenone imine to form the oxocarbenium intermediate.[108] Interestingly, in the *exo*-galactal series the reaction directly leads to spiro compounds in the presence of $InCl_3$ by increasing the temperature to 75 °C without requiring further treatment with the ketone.

Recently, the group of Z.-T. He described the *gem*-*C*,*B*-glycosylation of furanose and pyranose derivatives through 1,2 boronate migration (Scheme 21a).[16a] In this methodology, 2-methoxy glycosides were initially converted into the corresponding glycosylphosphoniums, which were then deprotonated to generate phosphonium ylides. Reaction with various boronic esters afforded boro-ketosides in moderate to high yields and excellent diastereoselectivity. These compounds can be further transformed into *gem*-*C*,*C*-glycosides[16a] using Zweifel olefination conditions, which involve treatment of the boronic esters with a vinyl Grignard reagent, followed by the addition of iodine and sodium methoxide.[109] This approach is exemplified by the ring-closing metathesis-based synthesis of a spirofuranose derivative,[110] whose core structure is related to that of natural *gem*-*C*,*C*-glycosides derived from caryose. It is worth noting that the methodology developed by Z.-T. He is limited to 2-deoxy precursors, likely due to the susceptibility of 2-oxygenated derivatives towards elimination under strongly basic conditions (see section 5). Boro-ketosides can also be



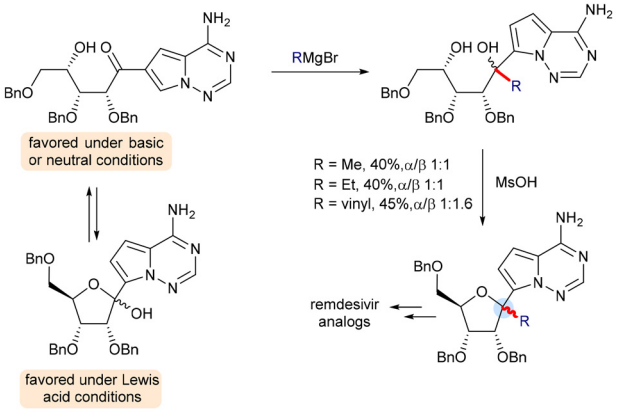
Scheme 20 Synthesis of spiro[pyro-4-quinolines].



Scheme 21 Synthesis of boro-ketosides and application to the formation of *gem*-*C*,*C*-glycosides.

obtained from glycosylidene diazirines through the generation of carbenes, which then insert into the C–B bond of boronic ester reagents (Scheme 21b).[111,112] According to G. He *et al.*, a 1,2 migration from a zwitterionic intermediate generated from the glycosylidene carbene is also involved in this sequence.[111] Remarkably, these conditions tolerate the presence of *O*-substituents at C-2. The resulting *C*,*B*-anomeric products can also be transformed into *gem*-*C*,*C*-glycosides *via* vinylation.[111]

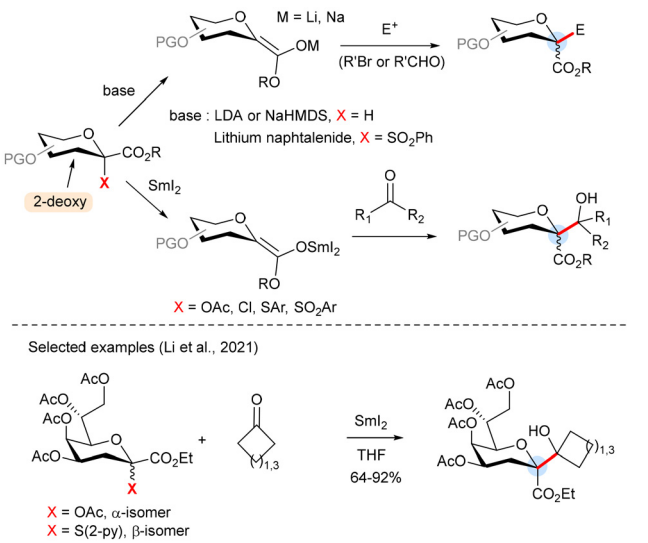
The addition of anionic species to carbonyl precursors followed by cyclization is another strategy for constructing *gem*-*C*,*C*-glycosides. This method has been successfully applied to the synthesis of complex structures, such as the DEF core of nogalamycin (see Scheme 1b)[40a,47b] and the antidiabetic drug Steglatro™.[113] Aldrich *et al.* have recently developed a method to introduce diverse substituents at the 1′ position of *C*-nucleosides related to remdesivir (Scheme 22).[114] Their methodology is based on the observation that the hemiketal formed upon the addition of the appropriate heteroaryllithium reagent to the corresponding ribolactone (see Scheme 11a) exists in equilibrium with the hydroxyketone tautomer, depending on the reaction conditions. In the presence of Lewis acids, the hemiketal is the predominant tautomer and may participate in electrophilic activation (see section 3 and Scheme 17). In contrast, under neutral or basic conditions, the hydroxyketone tautomer is favored. When exposed to a Grignard reagent, the hydroxyketone form yields a mixture of diastereoisomers, which cyclize into *C*-nucleosides upon treatment with methanesulfonic acid. At this point, the isomers can be separated and deprotected.[114] The same strategy has also been applied to introduce difluoromethyl and fluoromethyl substituents.[114]



Scheme 22 Synthesis of remdesivir analogs.

5. Specific methods for the synthesis of *gem*-*C*,*C*-glycosides through glycosyl anionic species

Glycosyl anions have been employed as intermediates in the synthesis of *C*-glycosides; however, this strategy remains significantly less explored than approaches relying on electrophilic glycosyl intermediates.[5,115] The main strategies for generating glycosyl anions involve halogen–lithium exchange from chloro- or bromo-glycosides, as well as lithiation of *endo*-glycals.[5,115] However, these methods are not well suited for the synthesis of *gem*-*C*,*C*-glycosides, due, for example, to the limited accessibility of tertiary anomeric halides. An alternative



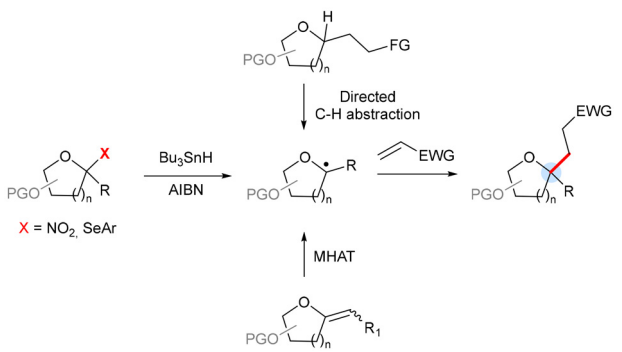
Scheme 23 Synthesis of *gem*-*C*,*C*-glycosides *via* an enolate intermediate.

strategy involves the generation of an anomeric exocyclic enolate from an ester functional group at the C1 position (Scheme 23).[69c,120–122] Enolates derived from lithium or sodium have been reacted with a variety of electrophiles,[116] although samarium enolates remain the most widely used for such transformations.[69c,116,117] However, these methodologies are generally limited to 2-deoxy substrates, as β-elimination may readily occur in the presence of C2 hydroxyl groups. This strategy has been applied to the synthesis of neuraminic and ulosonic acid derivatives, as well as KDO *C*-glycosides, as recently demonstrated by Li *et al.*[118]

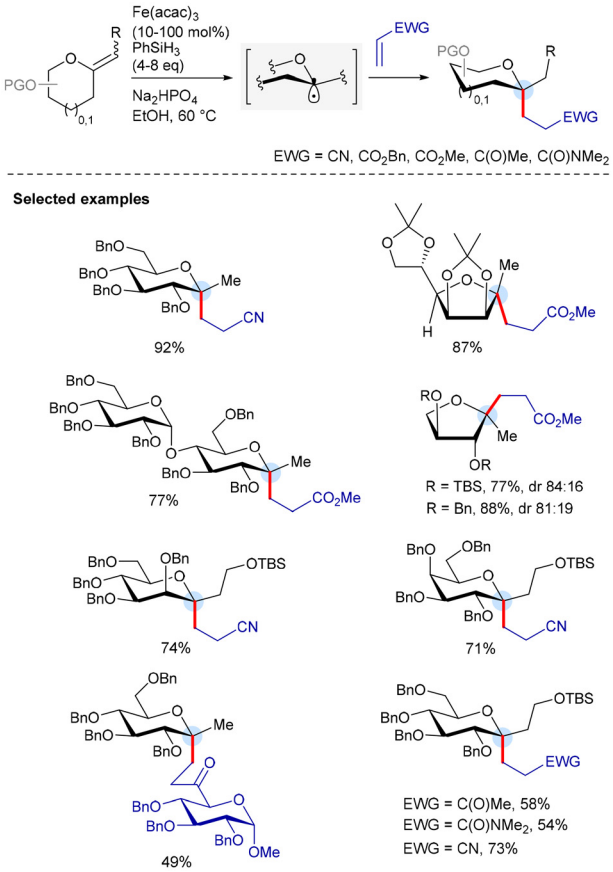
6. Specific methods for the synthesis of *gem*-*C*,*C*-glycosides through glycosyl radical species

Given the limitations associated with the synthesis of *gem*-*C*,*C*-glycosides *via* anionic or oxocarbenium-based strategies—such as substrate incompatibility under strongly acidic or basic conditions, and the restriction of anionic approaches to 2-deoxy precursors—the generation of anomeric radicals and their subsequent trapping with various electrophiles has emerged as a promising alternative.[5c,119] Since the pioneering work of Giese *et al.*, several methods for generating tertiary pseudo anomeric radicals have been reported (Scheme 24).[120–125] In Giese's original report, electron transfer from a stannyl radical to a nitro group at the anomeric position generates a tertiary radical, which subsequently reacts with acrylonitrile.[120] A similar strategy has been applied to anomeric selenide precursors.[121] More recently, generation of tertiary radicals *via* Metal-hydride-induced Hydrogen Atom Transfer (MHAT)[122,123] or photocatalyzed hydrogen atom abstraction and subsequent addition to Michael acceptors has been reported.[124]

Recently MHAT has emerged as a powerful tool for the hydrofunctionalisation of electron rich alkenes.[126] Building on the iron-mediated Michael–Giese hydroalkylation of olefins reported by Baran,[127] our group has recently developed a method for the synthesis of *gem*-*C*,*C*-glycosides (Scheme 25).[122] We demonstrated that *exo*-glycals can be converted into tertiary



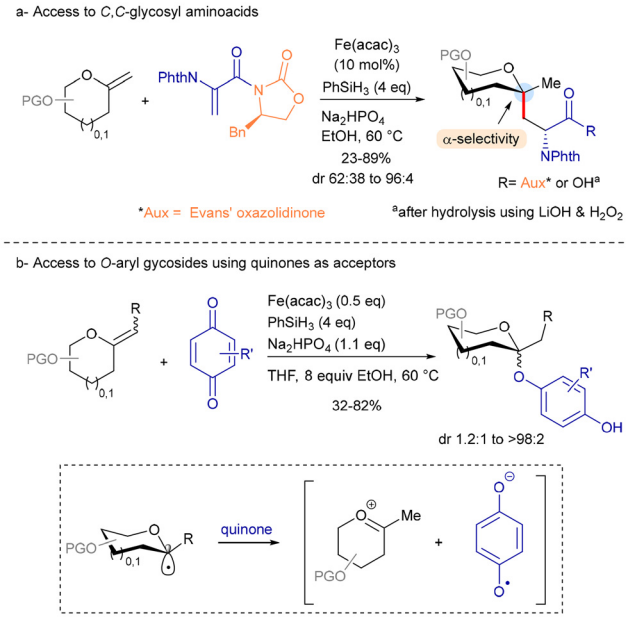
Scheme 24 General approaches to *gem*-*C*,*C*-glycosides *via* the generation of tertiary pseudo anomeric radicals (FG = Functional Group).



Scheme 25 Synthesis of *gem*-*C*,*C*-glycosides from *exo*-glycals by MHAT.

pseudo-anomeric radicals, which then undergo addition to various Michael acceptors in good yields. The reaction proceeds with high α-selectivity in the D-*gluco*, D-*manno* and D-*galacto* series (see also Scheme 5 for another example illustrating the concept of radical anomeric effect).[67] This methodology was successfully applied to trisubstituted *exo*-glycals, whose conversion however required increased catalyst and silane loading to achieve satisfactory yields. Such trend may be due to slower hydrogen atom transfer from the reactive iron(III) hydride to the more sterically demanding olefin (a step typically considered to be fast), thus resulting in catalyst deactivation and (indirect) silane consumption through H_2 evolution.

Our group extended this methodology to the synthesis of *C*,*C*-glycosyl amino acids using *N*-phthalimido-dehydroalanine derivatives as Michael acceptors (Scheme 26a).[123] High levels of dual stereocontrol were achieved through the coupling of *exo*-glycals with an enantiopure dehydroalanine derivative bearing an Evans-type oxazolidinone. Complete stereocontrol could observed at the pseudo-anomeric center, affording exclusively the α-anomer as previously discussed, along with excellent diastereoselectivity at the amino acid stereocenter when a sterically nondemanding methoxymethyl (MOM) protecting group was installed at the 2-position. Direct removal of the auxiliary proceeded conveniently without epimerization nor



Scheme 26 Coupling of *exo*-glycals with challenging acceptors *via* MHAT process.

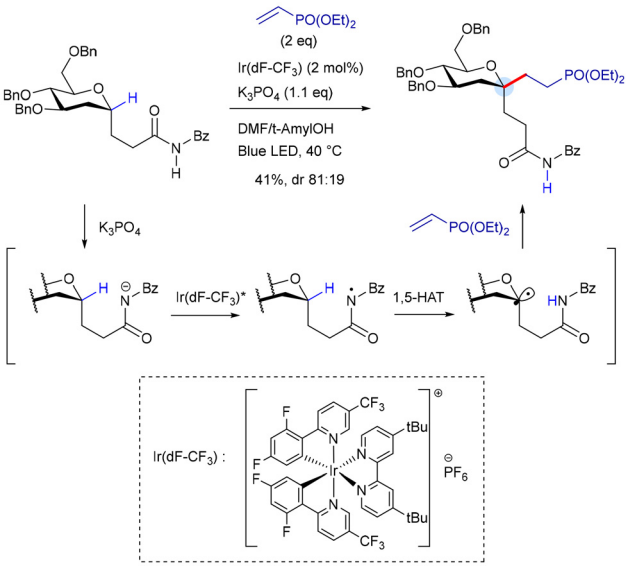
phthalimide opening using carefully controlled amounts of LiOH and H_2O_2. Quinones were also investigated as potentially demanding Michael acceptors considering their redox properties (Scheme 26b).[46] Under MHAT conditions, *O*-aryl ketosides were obtained instead of the corresponding *C*-aryl derivatives. Mechanistic studies indicated that the tertiary pseudoanomeric radical first generated from the *exo*-glycal and iron hydride undergoes subsequent oxidation by the quinone to form an oxocarbenium cation.[46] The latter and the resulting semiquinone radical then combine to give the C–O coupling product following reduction. As seen above, *O*-naphthyl ketosides can be converted into the corresponding *gem*-*C*,*C*-glycosides upon treatment with a Lewis acid (see Scheme 19).[106a]

Recently, Rovis *et al.* developed a methodology for directed hydrogen atom abstraction using photoredox catalysis (Scheme 27).[124] The reaction is initiated by deprotonation of a benzoyl imide, followed by oxidation of the resulting anion to the corresponding nitrogen-centered radical by an excited iridium(III) photocatalyst.

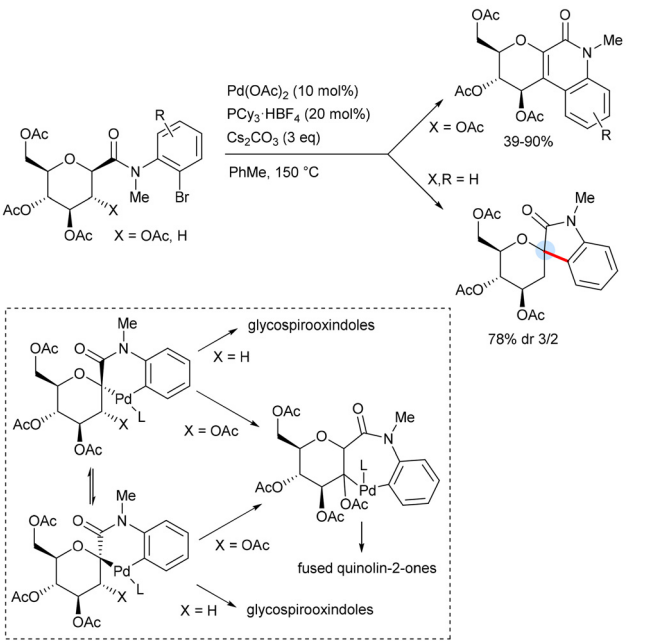
In a representative example involving a 2-deoxy D-glucose derivative, the pseudo-anomeric hydrogen atom is then abstracted *via* a [1,5-HAT] process, generating the corresponding *C*-radical which then undergoes addition to diethylvinylphosphonate.

7. Specific methods for the synthesis of *gem*-*C*,*C*-glycosides through organopalladium intermediates

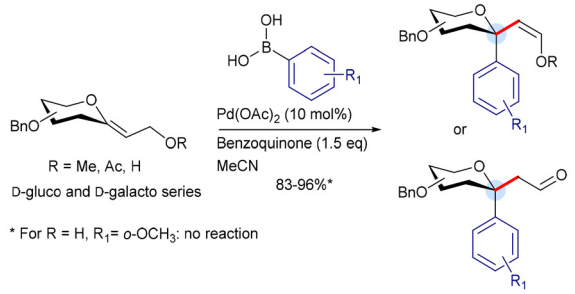
Synthesis of *gem*-*C*,*C*-glucosides *via* C–H bond functionalization approach have been reported by several groups using rhodium or palladium complexes.[128–130] For example, Messaoudi *et al.* described the intramolecular Pd-catalyzed anomeric C–H activation of glycosyl carboxamides (Scheme 28).[129] Notably, depending on the substituent at the C2 position, either fused glycosylquinolin-2-ones or glycosylspirooxindoles were obtained. The authors proposed a mechanistic rationale to explain the pathway divergence: intramolecular C–H activation generates an axially oriented palladium *C*-enolate that exists in equilibrium with its diastereoisomeric equatorial counterpart. When X = H, reductive elimin-



Scheme 27 Synthesis of a *gem*-*C*,*C*-glycoside *via* directed C-H abstraction.



Scheme 28 Anomeric C–H activation of glycosyl carboxamides.



Scheme 29 Heck-type arylation of *exo*-glycals.

ation leads to a diastereomeric mixture of glycosylspirooxindoles, whereas a 1,2-palladium migration occurs when X = OAc, leading to tricyclic fused products.[129]

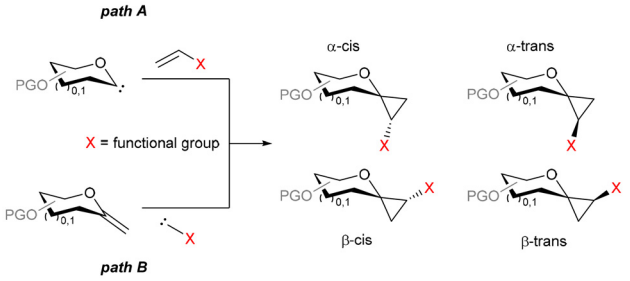
Lin *et al.* described the coupling of arylboronic acids with a trisubstituted *exo*-glycal *via* a palladium-catalyzed Heck-type reaction (Scheme 29).[130] The *C*-arylation products were obtained with exclusive α-selectivity and excellent yields, except when 2- methoxyphenylboronic acid was used, in which case no reaction occurred. A related Heck reaction, leading to the DEF core of nogalamycin, was described by VanNieuwenhze's group (see Scheme 2).[48]

8. Anomeric spirocyclopropyl-*C*-glycosides and analogues

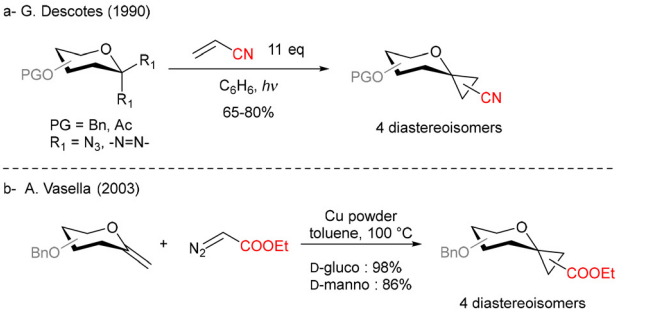
This section will focus on anomeric spirocyclopropyl-*C*-glycosides, a conformationally constrained sub-class of *gem*-*C*,*C*-glycosides, which have demonstrated inhibitory activity against biologically relevant enzymes.[34] The structural features underlying their bioactivity are indeed closely associated with the introduction of a spirocyclopropyl group at the anomeric position, which significantly limits molecular flexibility and reinforces the overall rigidity of the sugar framework. Two principal approaches for their synthesis have been documented in the literature.[34,131] In the first approach (Scheme 30, path A), a glycosylidene carbene is generated and then undergoes cyclopropanation with an activated carbon–carbon double bond. The second approach (path B) relies on the use of *exo*-glycal methylene groups, accessible from the corresponding lactones. These derivatives react with functionalized carbenes or their equivalents, also leading to the formation of the spirocyclopropane motif. A major limitation shared by both synthetic routes is the lack of stereochemical control, which often results in a mixture of the four possible isomers. These isomers are classified based on their configurations: α or β, and *cis* or *trans*.

Descotes' group described the first example of the use of anomeric glycosylidene carbene precursors to generate anomeric spirocyclopropyl sugars (path A),[132] which took advantage of the reactivity of C-1 *gem*-diazido sugars under photolytic conditions (Scheme 31a). This route was subsequently developed further by Vasella and colleagues, who published several studies on the use of diazirines as precursors for 1-spirocyclopropanes.[112d,133] Additionally, this group was the first to synthesize monosaccharide cyclopropanes by metal-catalyzed cyclopropanation of diazo esters of *exo*-glycals (path B) (Scheme 31b).[134] In particular, the copper-catalyzed cycloaddition of ethyl diazoacetate with *exo*-glycal led to the formation of spirocyclopropyl-*C*-glycosides in the D-glucose and D-mannose series in high yields, but low diastereoselectivity.

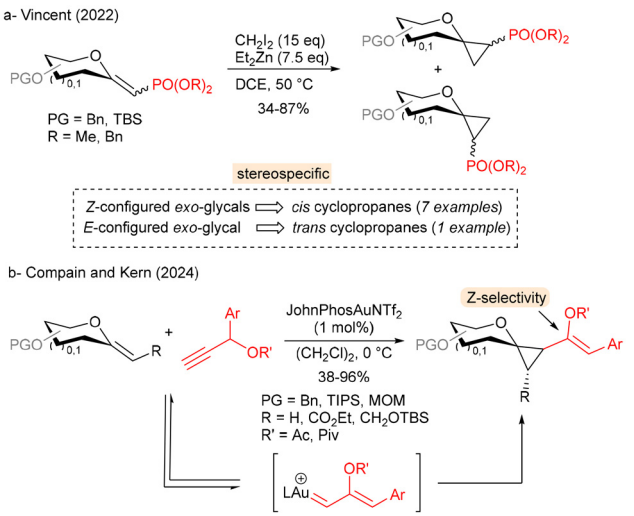
Since these initial reports, the two strategies for synthesizing anomeric spirocyclopropyl-*C*-glycosides have been reviewed and analyzed in depth by S. Vincent's group in 2022, following their work on the development of the first controlled and selective synthesis of spirocyclic cyclopropyl glycosyl-1-phosphate analogues *via* a Simmons–Smith reaction (Scheme 32a).[34,135] Consequently, only the latest advances and contributions in this field are discussed here. In 2023, Cossy's group post-functionalized 5-membered *exo*-glycals, also *via* a Simmons–Smith cyclopropanation, to obtain spirocyclopropyl-*C*-glycosides in good yields.[136] More recently in 2024, our group described the first alkenyl cyclopropanation of *exo*-glycals,[137] taking advantage of the gold(I)-catalyzed 1,2-ester migration of propargyl acetates. The reaction proceeded with high yields and excellent chemoselectivity, as well as moderate to high diastereomeric control, typically towards β-*cis* products in the pyranoside series, along with complete (*Z*)-selectivity regarding the alkene moiety. The preferential activation of the propargyl fragments



Scheme 30 General strategies for the synthesis of spirocyclopropyl-*C*-glycosides.



Scheme 31 Early examples of the synthesis of spiro-*C*-glycosides *via* the two main pathways.

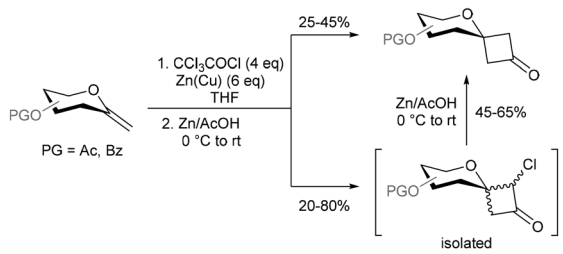


Scheme 32 Gold(I)-catalyzed reactions of *exo*-glycals with propargyl esters.

and the concerted [2 + 1] insertion are both facilitated by the selection of ligands and electron-enrichment of the arene in the propargyl esters (Scheme 32b). Of note, Nagib's group has very recently reported the synthesis of two spirocyclopropyl-*C*-glycosides from the corresponding *exo*-glycals *via* innovative Fe-catalyzed cyclopropanation reactions involving *in situ* generated iron carbenes.[138]

Spirocyclobutyl-*C*-glycoside analogues remain largely underrepresented in the literature, with only one recent example of their synthesis since Suárez's 2008 work on photo-induced Norrish type II–Yang cyclization.[125b,139] Recently, in 2023, L. Juhász and his colleagues studied the previously unexplored [2 + 2] cycloaddition reactions of several methylene *exo*-glycals with dichloroketene.[140] The reaction conditions led to excellent regioselectivity, but the *in situ* dehalogenation of some cycloadducts failed. The diastereomeric mixtures obtained from monohalogenated spiro-cyclobutanones could be dehalogenated in an additional step (Scheme 33).

Notably, spirocyclopropyl-*C*-glycosides have also been described within the iminosugar series, further expanding the structural diversity of this class of glycomimetics.[110b]



Scheme 33 Synthesis of cyclobutanones by [2 + 2] cycloadditions of *exo*-glycals.

9. Conclusion

Gem-C,*C*-glycosides represent a uniquely challenging and underexplored subclass of glycomimetics that offer compelling structural and functional diversity for chemical biology and drug discovery. Their presence in complex natural products and bioactive compounds underscores their biological relevance, yet their synthesis continues to pose significant hurdles, particularly in the formation of quaternary pseudo-anomeric centers with defined stereochemistry. Recent advances—including catalytic approaches such as metal-hydride hydrogen atom transfer (MHAT), C–H activation, and metal-catalyzed cyclopropanation — have successfully addressed key challenges in the construction of *gem-C*,*C*-glycosyl frameworks. These innovative methodologies enable more direct and modular access to these densely functionalized motifs, substantially expanding the synthetic toolbox. Beyond enhancing synthetic efficiency, they also open new avenues for the design of structurally novel glycomimetics of therapeutic interest. As the field continues to mature, the integration of advanced stereoselective strategies, mechanistic insight, and biologically driven design will be critical to fully realizing the synthetic and biomedical potential of *gem-C*,*C*-glycosides.

Author contributions

Conceptualization, P. C.; methodology, P. C. and D. H.; literature review, D. H., P. C., N. K., M. P. and D. T.; writing – original draft preparation, P. C., D. H. and M. P.; writing – review and editing, P. C., D. H., N. K., M. P. and D. T. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included, and no new data were generated or analysed as part of this review.

Acknowledgements

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4 The term "*C*-glycoside", widely cited in the literature, is however inexact from a strict chemical perspective because these compounds are not acetals. IUPAC suggests using terms like "*C*-glycosyl compounds" or their analogs for greater accuracy (see also ref. 6*a*). The primary advantage of this common term lies in its conciseness, effectively emphasizing the structural differences from the parent glycoside.

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7 The term "quaternary center" is frequently misused in the literature. According to the IUPAC definition, a quaternary carbon is one that is specifically bonded to four other carbon atoms. However, this term is often incorrectly applied, for example, to tertiary alcohols and tertiary centers bonded to heteroatoms. For the sake of conciseness, the term "quaternary" will be used in this article to refer to the pseudoanomeric carbon in *gem*-*C*,*C*-glycosyl compounds.

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