Send Orders for Reprints to reprints@benthamscience.net

Mini-Reviews in Organic Chemistry, XXXX, *XX*, 1-14

MINI-REVIEW ARTICLE

Electrosynthesis of Sugar Derivatives

Cintia C. Santiago[1,*], Natividad Bejarano Rengel[1], Pablo S. Fernandez[2] and Agustín Ponzinibbio[1]

[1]*Departamento de Química Universidad Nacional de La Plata, CEDECOR, UNLP, calle 115 y 47, s/n, 54 - 221-4226977 / 6979 / 6981, Argentina;* [2]*Department of Chemistry, State University of Campinas, Brazil*

ARTICLE HISTORY

Received: October 19, 2023
Revised: November 21, 2023
Accepted: November 29, 2023

DOI:
10.2174/0118756298267514240104101246

Abstract: The last decades have witnessed significant advances in the synthesis of bioactive carbohydrates. As in all fields of organic synthesis, the search for more environmentally friendly alternative synthetic methods is a current and expanding concern. Consequently, electrochemical organic synthesis has emerged as an efficient and sustainable methodology. Herein, we present recent developments in the synthesis of glycosides and other carbohydrate derivatives using electrochemical methods. Diverse natural and synthetic *O*-, *S*-, and *C*-glycosides were obtained using new approaches for the electrochemical activation of sugar precursors. The reported derivatives exhibited wide structural diversity on both the sugar moiety and the aglycone, revealing the great potential of the electrochemical methods.

Keywords: Carbohydrates, oligosaccharides, glycoconjugates, electrochemical glycosylation, anodic oxidation, electrochemistry, green chemistry.

1. INTRODUCTION

Along with proteins and nucleic acids, carbohydrates are one of the three main families of bioactive natural products, undoubtedly the most structurally diverse and complex [1-3]. To mention just a few attributes in living systems, sugars act as the primary source and storage of energy, intervene in many signaling and trafficking processes, integrate structural components, such as the cell wall and the extracellular matrix, and modify protein properties [4-7].

In nature, carbohydrates are rarely found in a free state. They assemble oligo- or polysaccharides or are attached to other macromolecules, commonly proteins or lipids, forming glycoconjugates. Through a glycosylation reaction, the sugar is effectively linked through its anomeric carbon to the rest of the biomolecule. Hence, mastering glycosylation is mandatory to elucidate the sugar code as well as to synthesize the more stable and potentially bioactive glycomimetics [8-11].

Nonetheless, the chemistry that governs the glycosidic linkage formation is not simple. The main challenges regarding this matter include selectively controlling the configuration of the glycosidic bond (α or β), effectively blocking other potentially reactive groups of the sugar (regioselectivity), avoiding degradation under some reaction conditions (normally acidic), and the appropriate employment of hydroxyl protecting groups [3,12-14].

In recent decades, electrochemistry has been slowly but steadily moved from physical-chemical laboratories, where the research is primarily focused on the optimization of energy storage in batteries, to organic synthesis laboratories, where the electrochemical setup is used to generate relevant molecules [15]. This migration is sustained in a few simple changes that must be implemented to incorporate electrochemistry into the synthetic chemist workspace.

In a typical electrosynthesis experiment, a conventional round bottom flask (an undivided cell) or an H-shape cell (a divided cell) holds inside the electrodes (anode and cathode, sometimes a reference electrode) connected to a power supply and a voltmeter to control either current or potential. This electrochemical reactor, commonly known as "cell", contains substrates, reagents, and organic solvent/s mixed with soluble electrolytes, typically salts with inorganic anions, and for some transformations, suitable additives. Within this closed electric circuit, Single Electron Transfer (SET) occurs, generating radicals, usually from the electrode to the substrate, in 3 different ways: direct electrolysis (inert electrode), indirect electrolysis (active electrode), or mediated electrolysis (using additives). Further considerations on technical features and mechanisms exceed the aims of this mini-review. Nonetheless, there are excellent works that cover these topics [16-19].

Multiple facts support the renaissance of the application of electrochemistry to organic synthesis [20-22]. Electrochemical processes fulfill most of the principles of green chemistry [23-25]. They are normally performed at low or room temperatures and use green or non-volatile solvents and mediators instead of metal-based catalysts, strong acids, or bases. In an electrolytic cell, it is feasible to accurately tune the potential and current. Thus, toxic or highly reactive reagents may be generated *in situ*, avoiding their unsafe ma-

*Address correspondence to this author at the Departamento de Química Universidad Nacional de La Plata, CEDECOR, UNLP, calle 115 y 47, s/n, 54 - 221-4226977 / 6979 / 6981, Argentina;
E-mail: csantiago@quimica.unlp.edu.ar

1570-193X/XX $65.00+.00

nipulation. This monitoring also prevents side reactions and ends all the transformations instantly, without any chemical quenching, by simply turning the power off [20]. In addition, the procedure could run on renewable energy sources, making it entirely sustainable.

Among all these features, mild reaction conditions and efficient reaction control specifically circumvent many historically major problems attributed to the synthesis of glycosides. Consequently, the potentially significant benefits from the implementation of electrochemical methods in the synthesis of glycosides are evident and promising [26-29].

Herein, we present recent advances in the synthesis of glycosides and other sugar derivatives using electrochemical methods. As synthetic chemists, we will focus on the molecules that can be obtained inside an electrolytic cell, their structure, reaction conditions, and reaction selectivity. Our main purpose in this mini-review is to update the reports presented by Marra and Scherrmann [26], Manmode *et al.* [27], and Nokami *et al.* [28, 29] since significant progress in the above-mentioned topic has been accomplished in recent years. Additionally, a few contributions not covered in the previously cited works are also included.

2. ELECTROSYNTHESIS OF *O*-GLYCOSIDES AND OTHER O-LINKED SUGAR DERIVATIVES

O-glycosides are the most common target molecules in the growing field of carbohydrate electrosynthesis. The ubiquity of these bioactive molecules in nature and their consequent relevance to medicine and microbiology [5],[7] are the basis of the ever-growing interest in reliable methods to synthesize them. Consequently, several groups have contributed to the search for novel preparations of *O*-glycosides and other O-linked sugar derivatives using electrochemical tools.

Extensive studies on the selective electrochemical building of cholesterol anomeric and non-anomeric glycosides, as well as other sterols, have been conducted by Morzycki *et al.* In 2010, after developing conditions for the electrochemical activation of only one of the four cholesterol oxidation sites, the hydroxyl group at C3 (Fig. **1**), Morzycki *et al.* [30] investigated whether carbohydrates could work as suitable nucleophiles in these transformations.

The general method uses an H-cell system (a divided cell), DCM, cholesterol, and an excess of sugar bearing a free hydroxyl group either at the C1 or C6 position (Fig. **1**). It must be said that the use of DCM as a solvent instead of the more conventional polar solvents is unusual but effective. Tetrabutylammonium tetrafluoroborate ($TBABF_4$) or tetrabutylammonium hexafluorophosphate ($TBAPF_6$) are used as electrolytes, and to complete the cell setting, platinum or glassy carbon electrodes are chosen.

Three sugars were tested as nucleophiles (Fig. **1**): 2,3,4,6-Tetra-O-acetyl-D-glucopyranose (**1**), 2,3,4,6-Tetra-O-benzyl-D-glucopyranose (**2**), and 1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose (**3**). From the first two molecules, products **5** and **6** were obtained in 28% and 21% yields, respectively, as a mixture of anomers 1:1 (α/β =1). Even though these reactions showed no anomeric stereoselectivity regarding the sterol, both glycosides bear β configuration on C3. Protected D-Galactose, which links to the sterol through its OH at C6, afforded product **7** in 20% yield with 3β configuration. Several byproducts were detected, and a portion of intact cholesterol could be recovered from reaction media.

As the authors stated, the significance of the method relies on the synthesis of glycoconjugates derived from sterols using non-activated sugars rather than on the synthesis of glycosides and other conjugates because of the lack of anomeric stereoselectivity.

Encouraged by this promising result, Morzicki *et al.* continued their research to optimize this outcome. Hence, three years later, Tomkiel *et al.* [31] proposed using aryl thioether derivatives of cholesterol and other sterols (activated glycosyl acceptors) instead of the 3β-hydroxy-Δ5-steroids (non-activated glycosyl acceptors) that were used in the previous work to activate the steroidal skeleton.

Using similar electrolytic settings to the earlier study, several tests were performed utilizing four sterol thioethers (C-3 toluyl and phenyl sulfides, **8**, **9**, and isomeric 3a,5a-cyclosteroid-6β-yl toluyl and phenyl sulfides **10**, **11**) and

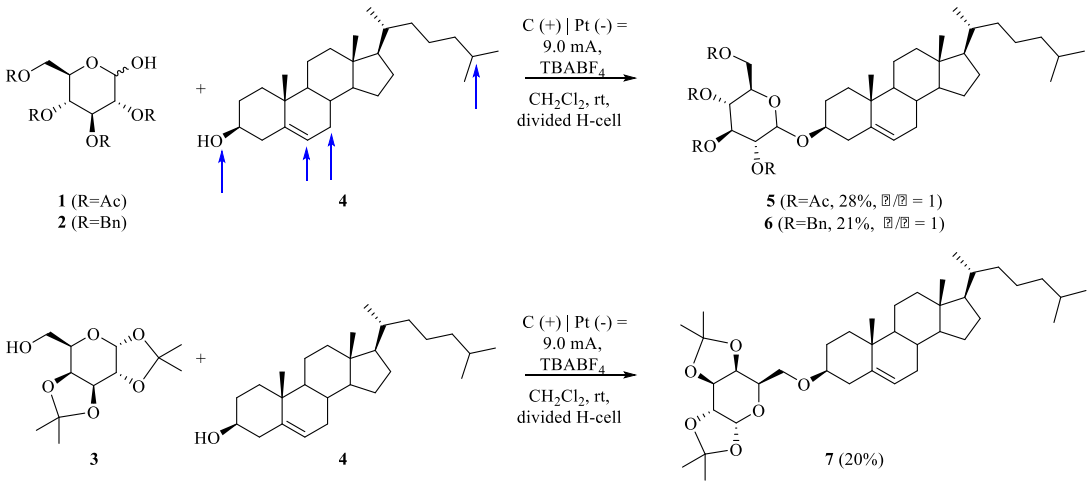

Fig. (1). Electrosynthesis of glycoconjugates by Morzycki *et al.* [30]. Blue arrows indicate the 4 potential electrooxidation sites of cholesterol.

1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose (**3**) as nucleophile (Fig. **2**). The O-linked glycoconjugate **7** was obtained in 12-52% yield, but steroidal by-products and, in some cases, reagent isomerization were detected. 6β-p-Tolylsulfanyl-3α,5α-steroids (**11**) proved to give better conversions than their analogs, 6β-phenylsulfanyl-3α,5α-cyclosteroids.

Under optimized conditions, expected glycoconjugates were prepared with 1,2:5,6-di-O-cyclohexylidene-D-glucofuranose only in a 12% yield, whereas in the case of 2,3,4,6-Tetra-O-benzyl-D-glucopyranose, a 20% yield was reported, reaching anomeric selectivity with an α/β ratio=1:4.

Changing the steroid for thioethers derived from diosgenin and methyl 3β-hydroxy-5-cholen-24-oate, using 1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose, glycoconjugates were prepared in 30% and 17% yields, respectively.

As in the first study from this group, several byproducts were detected in all the reaction tests and reagent isomerization in some cases. Consequently, the authors hypothesized that this phenomenon is probably linked to the C-3 aryl thioether group present in the steroidal molecule, so secondary reactions that originate these adducts cannot be avoided using this thioether-activated system.

The previous supposition encouraged the group to explore more efficient glycosyl acceptors that reduce both the number and proportion of by-products. In the next two subsequent studies, other activated steroids were tested. Suitable alternatives for the synthesis of glycoconjugates were the readily accessible diphenylphosphate derivative **12** [32], 3α,5α-Cyclocholestan-6β-ol (i-cholesterol) 1**3,** and its tert-butyldimethylsilyl (TBDMS) ether **14**, [33] since they displayed moderate yields and produced only low proportion of isomerization and secondary products (Fig. **3**).

Interestingly, the authors clearly exposed the value of their synthetic method by performing a conventional chemical-promoted preparation of a steroid-derived glycoconjugate [33]. No coupling between the steroid and the carbohydrate was detected, stressing the importance of the proposed electrochemical setting (steroidal ethers electrochemical activation) as a relevant and unique method to achieve glycoconjugates of steroids.

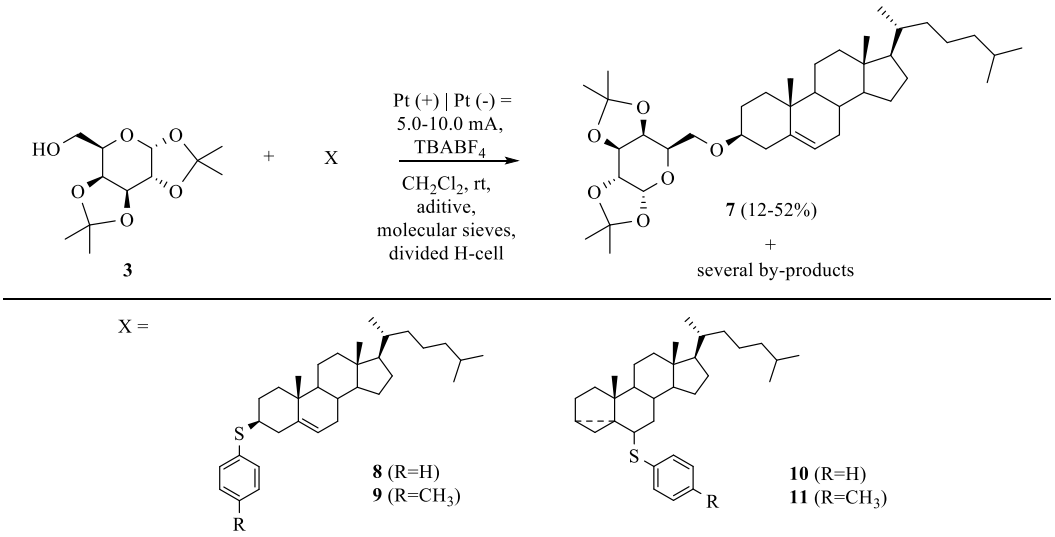

Fig. (2). Optimization tests by Tomkiel *et al.* [31].

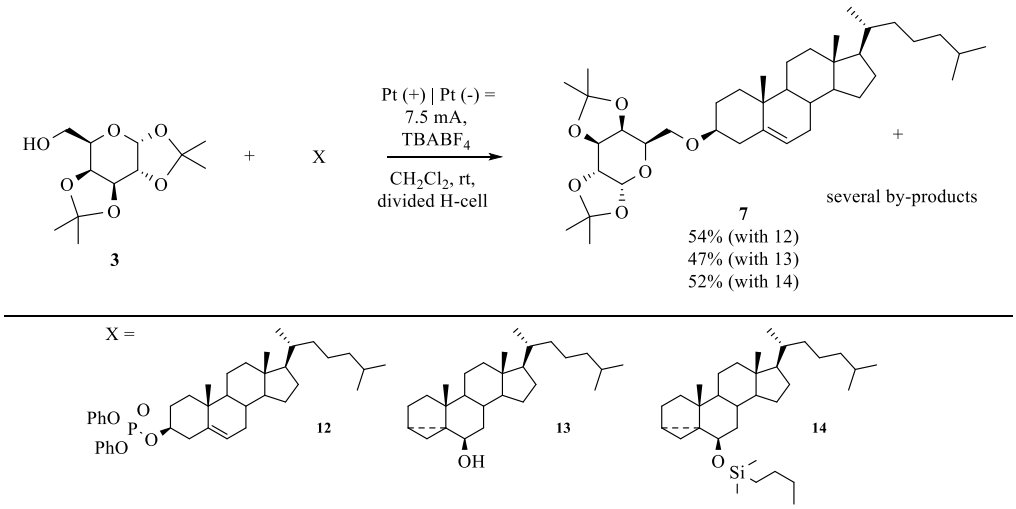

Fig. (3). Alternatives for the synthesis of glycoconjugates by Tomkiel *et al.* [32, 33].

After examining the structural diversity and activation of steroids, the next focus of this group was on how differences in the carbohydrate counterpart affect the electrochemical system outcome. Tomkiel *et al.* [34] examined the coupling of cholesteryl diphenylphosphate (the best steroid glycosyl acceptor tested previously) with several fully and partially protected sugars.

In this reaction, the real electrophile is the carbocation derived from cholesteryl diphenylphosphate, which has two resonance structures bearing the positive charge at positions C3 or C6 (Fig. **4**). Under the reaction conditions, the most stable steroidal carbocation is the one charged on C3 and originates the thermodynamic reaction product. Conversely, the one that holds a greater positive charge on C6 produces the kinetic reaction product. Most of the sugars tested by the group in the present and previous works originated glycoconjugates from the steroidal carbocation charged on C3 **17** (the most stable carbocation, thermodynamic product). However, interestingly, with an S-glycoside, 1-thio-β-D-glucose tetraacetate, the major product was the 3α,5 α-cyclobcholestan-6β-yl-thio-β-D-glucoside tetraacetate **18** (6-β-substituted, major product 40% yield), a 6-substituted glycoconjugate, which is the kinetic product. Since the electrochemical system is the same, this effect is clearly due to the glycoside. The authors claimed that sulfur attacks the carbocation faster than oxygen because the latter shows more tendency to be protonated than sulfur and, in consequence, moves towards the carbocation slower.

As aforementioned, all the oxygen nucleophiles gave only 3β-substitution products showing regioselectivity regarding the steroid. Several simple alcohols were tested, showing 10-67% yields according to the complexity of the alcohol 19a-d (alcohols with higher steric effects exhibit lower yields). Partially protected carbohydrates were also tested, reaching yields of 40% and 46% in the case of glucofuranose and 2,3,4,6-tetrabenzyl-glucopyranose, respectively, with no anomeric selectivity in the latter (Fig. **4**).

Finally, experiments on the preparation of polycholesterylated products were conducted using sugars with 3-4 free OH and reaction ratios of 1:3/4 cholesteryl diphenylphosphate/free OH on the carbohydrate. Electrochemical reactions of 1,6-anhydro-β-D-glucopyranose and O-methyl-α-D-glucopyranoside afforded mixtures of products. In the first case, the major product was the tricholesterylated adduct (21% yield), which could be easily isolated from the mixture by column chromatography due to being the less polar compound. This also applies to the O-methyl-α-D-glucopyranoside case, although the tetracholesterylated product (6% yield) was not the major product. On the attempt of a coupling reaction with cholesteryl diphenylphosphate and a disaccharide, 2,3,4,3',4'-penta-O-benzylsucrose, only cleavage of the glycosidic bond was found.

So far, this is the only method reported that introduces several cholesteryl groups through a single-step reaction to assemble polycholesterylated compounds. These are relevant to creating materials that might be used as biocompatible nanocarriers [34]. Although several adducts are produced in the process, the polycholesterylated products are easily separated by column chromatography.

The group of Itoh has been largely involved with electroglycosylation towards the obtention of O-glycosides. Their research has been particularly centered on the automated assembly of oligosaccharides. Manmode *et al.* thoroughly reviewed the methods used in Itoh's laboratory and close collaborators over several years of work until 2018 [27]. Therefore, only the most recent discoveries will be discussed here: two works from Manmode *et al.* [35,36], Isoda *et al.* [37], Yano *et al.* [38], Liu *et al.* [39], and Shibuya *et al.* [40].

Manmode *et al.* [35] studied an efficient way to control the stereoselectivity of the glycosidic bond to develop the automated electrochemical assembly of β-Glucans. To this end, the authors first designed and optimized the selective electrochemical preparation of both β-(1,3) and β-(1,6)-disaccharides (69-86% yield). Their strategy consisted of pre-activating β-thioglycosides by turning them into α-glucosyl triflates *in situ* and then coupling them to a methyl glucoside acceptor (Fig. **5**). Through this technique, a variety

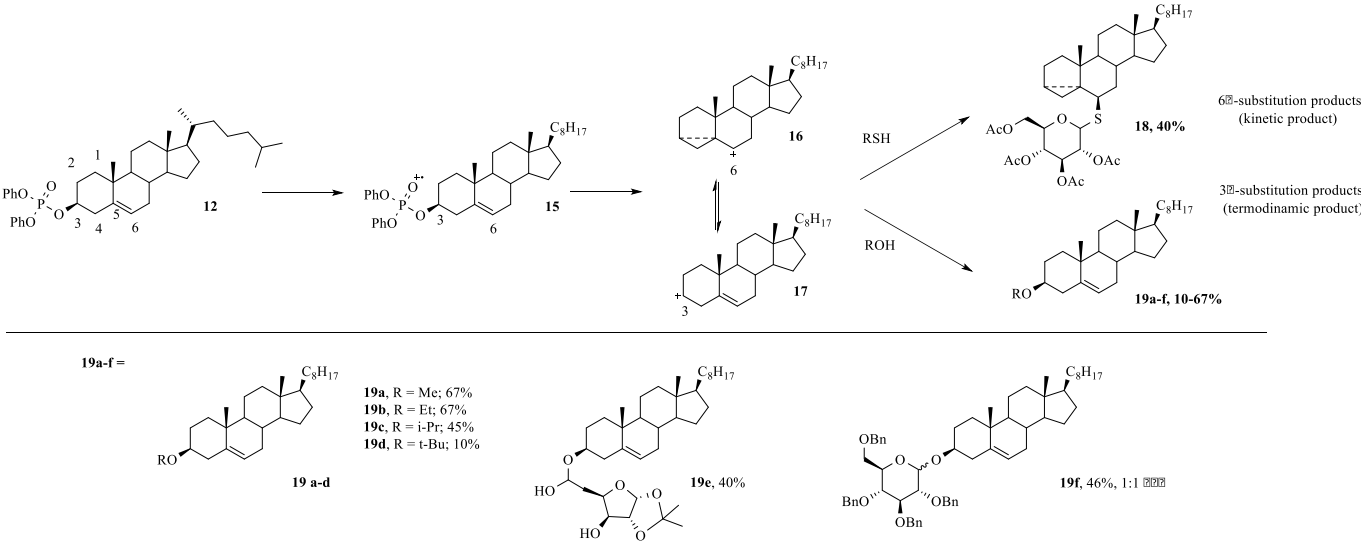

Fig. (4). Electrochemical reactions by Tomkiel *et al.* [34].

of β-(1,3) and β-(1,6)-disaccharides were obtained in good yields (45-83% and 69-86%, respectively). Next, an automated electrochemical assembly protocol with temperature control was used to synthesize a β-(1,6)-trisaccharide in 61% yield (Fig. **6**).

With these promising results in hand, the authors decided to focus on building biologically important oligosaccharides that contain these bonds: a cyclic β-dodecaglucan bearing both β-(1,3)- and β-(1,6)-linkages present in the fungal cell wall. Trisaccharide **22** obtained with their automated electrochemical assembly protocol was used as a substrate, and they initially proposed two strategies to build a hexasaccharide unit **23**: a [3+1+2] strategy and a [3+2+1] (Fig. **6**). Unfortunately, the [3+1+2] strategy generates only a tetrasaccharide (the second step failed), whereas the [3+2+1] one generates only traces of the hexasaccharide **23**. Therefore, a third plan was implemented, the [3+3], a coupling of two different trisaccharides. This approach led to the desired hexasaccharide **23** with an 18% yield.

Recently, Shibuya *et al.* [40] modified the preparation of a precursor β-1,6-glucan trisaccharide **24** and improved the same automated production of electrochemical hexasaccharide **23**. The researchers were able to modify the reaction conditions for the trisaccharide **24** through a mechanistic study of the trisaccharide synthesis reaction using low-temperature NMR and variable-temperature NMR experiments (VT-NMR), increasing the hexasaccharide **23** yield to 46% (1.5 times higher than that obtained using the original methodology).

The automated electrochemical assembly technique developed by Manmode *et al.* in 2018 [35] was used again in 2019 [36] for the stereoselective synthesis of cyclic oligo-

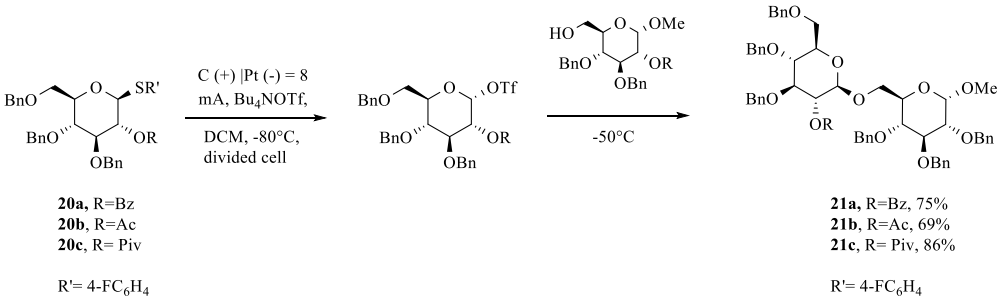

Fig. (5). Electrochemical synthesis of β-(1,6)-disaccharides by Manmode *et al.* [35].

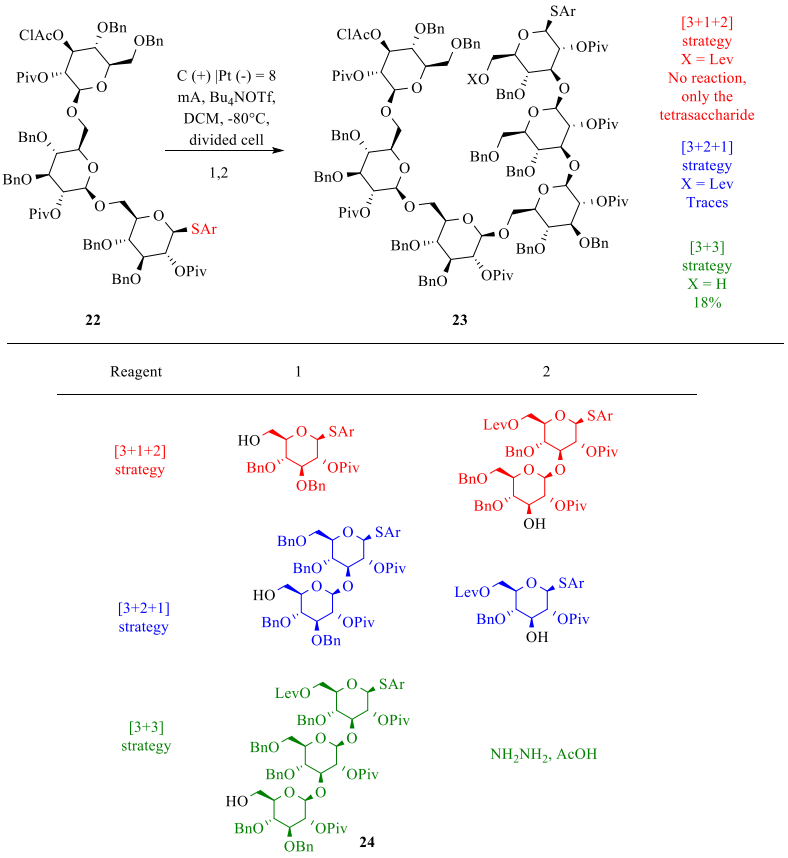

Fig. (6). Manmode *et al.*'s strategies for the hexasaccharide scaffold [35]. Conditions: C (+) |Pt (-) = 8 mA, Bu_4NOTf, DCM, -80°C, divided cell.

saccharides. After careful electrolyte selection, glucosamine-containing cyclic tetra-, penta-, and hexa-saccharides were selectively produced (only β-(1,6) glycosidic bonds between monosaccharides) in very good yields (81%, 93%, and 78%, respectively, as can be seen in Fig. **7**). Additionally, the authors successfully synthesized a cyclic tetrasaccharide from a tetrasaccharide containing primary and secondary unprotected OH in 84% yield. Considering that this process uses more straightforward linear structures for being cyclized, this alternative would represent an initial step in the large-scale synthesis of cyclic oligosaccharides. In this way, it was demonstrated that in addition to electrochemical glycosylation, the automated technique is also effective for intramolecular glycosylation, enabling the preparation of cyclic products (Fig. **7**).

In order to expand the scope of a system proposed by Manmode *et al.* [35], Isoda *et al.* [37] proposed the utilization of two mixed electrolytes: tetrabutylammonium triflate (Bu_4NOTf) and tetrabutylammonium bis(trifluoromethanesulfonyl-amide) (Bu_4NNTf_2), instead of using only the former as in the original technique. This change in the reaction medium allows a highly selective preparation (ratio α/β=6:94) of β-(1-6) disaccharides from β-thioglucosides lacking a stereocontrolling group linked to C2 with 69% yield. It is worth noting that this is the first example of an organic electrochemical reaction, where the stereoselectivity is enhanced by the use of mixed electrolytes and not by substrate modification. Regarding the cause of this phenomenon, the researchers theorized that Bu_4NOTf is essential to form *in situ* a more reactive reaction intermediate, which probably governs the selectivity of the glycosidic bond. In contrast, the Bu_4NNTf_2 contributes only as a supporting electrolyte.

Taking advantage of this improvement done by Isoda on Manmode's procedure, Yano *et al.* [38] performed the total synthesis of a natural glycolipid, Myc-IV (C16:0, S) **31**, in a 33% yield. Myc-IV (C16:0, S) is a Myc-lipochitooligosaccharide (LCO), a plant glycolipid identified as a signal molecule from *Arbuscular Mycorrhiza*, an organism product of a symbiotic relationship between a fungus and a plant. Myc-IV (C16:0, S) is made of a β-(1,4)- tetrasaccharide **30** attached to a fatty acid tail of 16 carbons. The sugar unit of β-(1,4)-tetrasaccharide **30** was obtained through a [2+1+1] automated electrochemical assembly (AEA) with high β selectivity in 47% yield (Fig. **8**) and using the mixture of electrolytes Bu_4NOTf/Bu_4NNTf_2. This total synthesis was rapid and stereoselective, thus proving the potential of the system AEA for the preparation of biologically active molecules.

Itoh *et al.* recently started to work on glycals [39], which are unsaturated glycosyl donors. These compounds are suitable for accessing 2-deoxysugars, a common synthetic target, since these are often found in many biologically active natural products and drugs [41-43]. However, a significant chal-

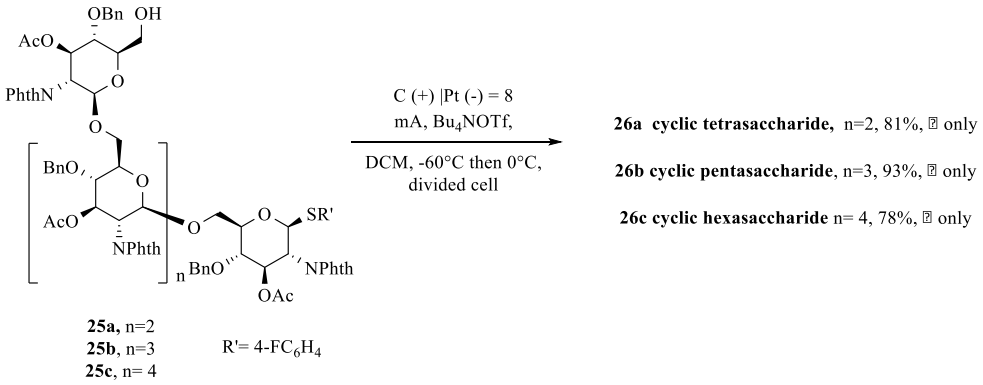

Fig. (7). Glucosamine-containing cyclic tetra-, penta-, and hexa-saccharides by Manmode *et al.* [36].

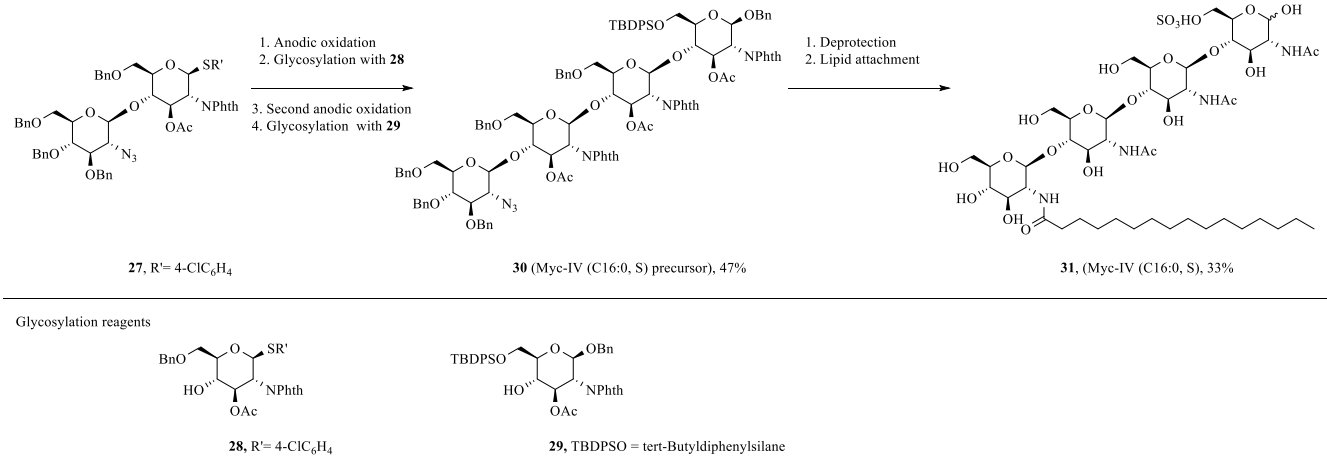

Fig. (8). Synthesis of Myc-IV (C16:0, S) by Yano *et al.* [38]. Anodic oxidation conditions: C (+) |Pt (-) = 8 mA, Bu_4NOTf, TfOH, DCM, -80°C, divided cell.

lenge in working with glycals is effectively controlling the selectivity of the newly formed glycosidic bond since they lack a directing group on C2.

To prepare 2-deoxysugars, Liu *et al.* [39] developed a highly stereoselective and broad functional group tolerant system that uses an undivided cell and 2-bromoacetonitrile ($BrCH_2CH_2CN$) as an additive (Fig. **9**). An interesting library of more than a dozen 2-deoxyglycosides and their glycoconjugates, mainly D-galactal derivatives, has been obtained in short times (1-2 h) and good yields (75-92%).

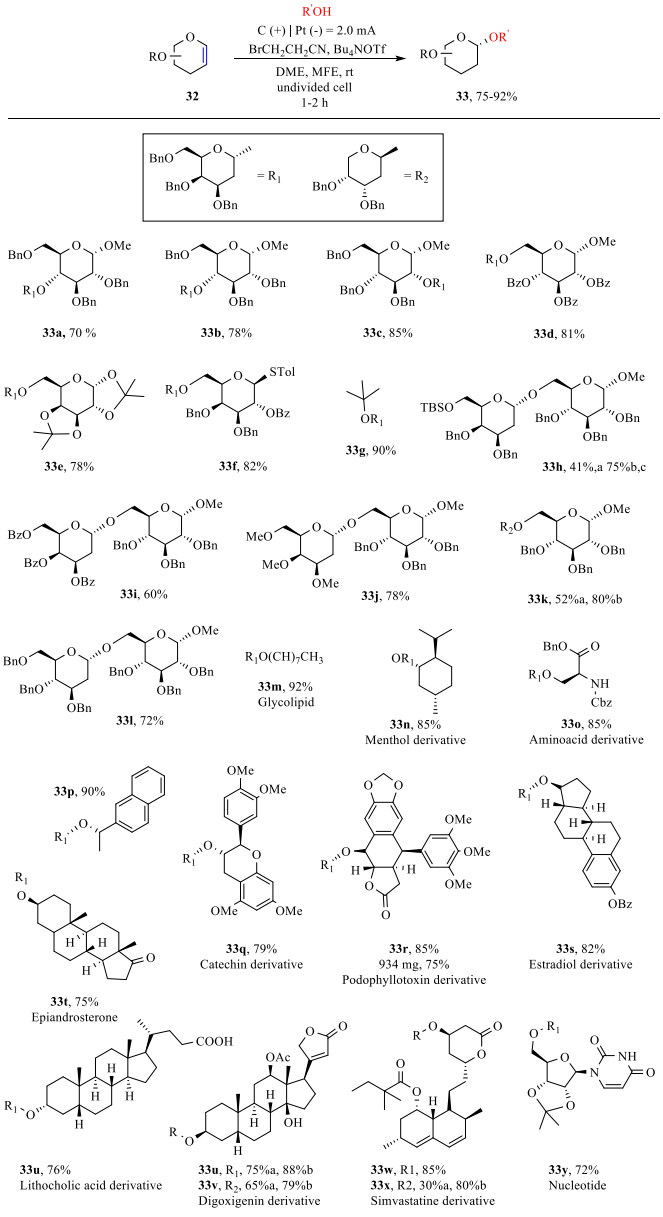

Fig. (9). Liu's system and scope [39] a. Standard reaction conditions, b. DCM solvent., c. With pinene as an additive.

Moreover, an iterative electroglycosylation of a trisaccharide and a scalable production were achieved. Under similar reaction conditions, the trisaccharide was synthesized in an isolated yield of 75% by iterative electroglycosylation. Considering several mechanistic experiments conducted to study this transformation, the authors proposed a plausible mechanism, in which the involvement of bromine derivatives is crucial. Whereas, the scalable preparation of podophyllotoxin-derivative, a leading antiviral, was performed at a 1 g-scale with a yield of 75% approximately.

A study by Liu *et al.* [39] is the first to describe an electrochemical method for producing valuable 2-deoxy sugars. With further glycal transformations (refer to the Miscellaneous section), the authors continue to investigate the scope of this technique.

3. ELECTROSYNTHESIS OF *C*-GLYCOSIDES

The structural similarity between *O*- and *C*-glycosides is a well-known fact that explains the ever-increasing interest in the latter as *O*-glycoside mimetics [44]. The presence of the C-C bond instead of the highly labile O-C bond makes these compounds more resistant to both chemical and enzymatic degradation and more suitable for their use as pharmaceutics [45]. Moreover, many inhibitors and antibiotics are based on *C*-glycosides, such as dapagliflozin, the inhibitor against type II diabetes [46, 47]. Additionally, many natural products containing C-branched sugars have been described, such as Altromycin B, *C*-glucosylxanthones, and the well-studied laxative Aloin.

Several groups have recently contributed to exploring the scope of electrochemical methods applied to the research on innovative preparations of these bioactive carbohydrates. In 2010, innovating a well-known *C*-glycosylation approach *via* olefination–cyclization, Xu and Moeller [48] developed a convenient Wittig reaction-anodic oxidation synthetic sequence. The authors aimed to produce aldehyde-containing C-glycosides (see **34** and **35**, Fig. **10**) suitable for further modifications and applications.

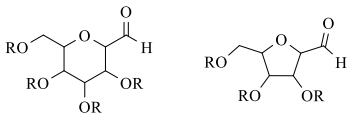

Fig. (10). Xu and Moeller's target scaffolds [48].

The presented two-step procedure (Fig. **11**) starts with a conventional double bond-building reaction that opens the sugar ring, adding through the phosphonium ylide a new carbon moiety containing a good leaving group X **11** (-OMe, -SMe). The strategic incorporation of the X group would be critical in the final deprotection of the carbonyl group towards the obtention of the C-glycoside targets. As expected, this traditional Wittig olefination works well for both pyranose and furanose carbohydrates demi-protected with Bn or Me as protecting groups. An important finding is that during the cyclization step, along with the leaving group X, a methyl ether (OMe) moiety is added to the aglycone. This is probably due to a radical mechanism reaction in which the OMe group is incorporated from one of the reaction solvents, as explained in the group's subsequent work [49].

More considerable challenges were faced in the second step, the innovative one: anodic oxidation. Several reaction conditions were tested, including various solvents (MeOH and MeOH/THF mixtures), electrolytes, and different applied currents. An open-cell equipped with reticulated vitreous carbon (RVC) anode and a platinum wire cathode, anhy-

drous MeOH as the solvent, LiClO4 as the electrolyte, a constant current of 8.0 mA, and the additive 2,6-lutidine were selected as optimal settings.

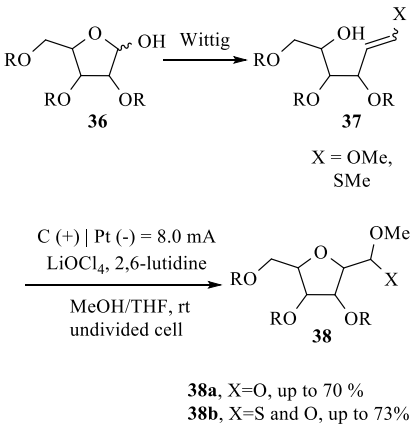

Fig. (11). Xu and Moeller´s method for synthesis of target furanoses and pyranoses derivatives [48].

The described electrochemical procedure worked smoothly to produce furanose-derived *C*-glycosides **38**. However, the technique encountered some difficulties when pyranose substrates were used. Several fragments of the products were found, probably because of pyranoses' slower rates of cyclization. After trying a few unsuccessful changes to the cyclization procedure, the researchers finally succeeded in producing the pyranose product in good yields (71%) by employing pyranose substrates with X=SMe instead of those with X=OMe. It should be noted that even though a mixture of acetal products is created (X=SMe/OMe=4), both compounds would lead to the same aldehyde-containing final product since the next reaction step requires the hydrolysis of these acetals.

Also, from Moeller's group, Smith [49] continued expanding the *C*-glycosides synthetic strategy introduced by Xu and Moeller [48] but varying the targeted *C*-glycosides for analogs of inhibitors of type 1 fimbrial adhesin FimH (Fig. **12**, **39**), an adhesive protein of *Escherichia coli*. This is a mannose-binding adhesin that facilitates the bacteria installation along the whole urinary tract, actively contributing to the development of urinary tract infections (UTIs) [50].

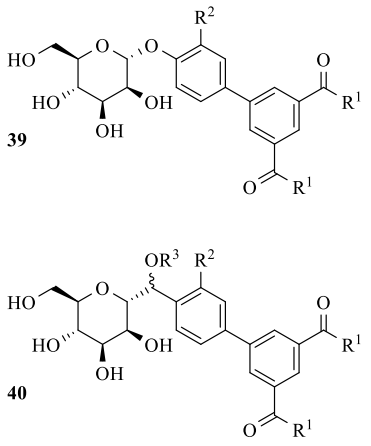

Fig. (12). Potential FimH inhibitors (R^1, R^2 alkyl and phenyl groups).

The initial synthetic approach for the construction of this family of *C*-glycosides **40** consisted of replacing the X group with a biaryl structure on the *C*-glycoside precursor that was prepared in the previous work from the group [48]. Unfortunately, this strategy was unsuccessful. The authors next suggested an approach that resembled the one in the former paper: a two-step Wittig olefination-anodic oxidation from a reducing sugar, followed by biaryl system synthesis. In this modification, an aromatic ring-containing aglycone bearing an OMe/SMe group is attached to the sugar during the Wittig reaction step, and then this aglycone is modified to form the desired biphenyl structure (a similar reaction path in Fig. **13**). These oxidation studies were conducted testing different potentials (1,17-1,34 V), using several substituted aryl rings at different positions (aryl positions 4, 3, and 2), and replacing the additive 2,6-lutidine for LiOMe.

Although yields (up to 86%) of several conditions studied were favorable, some substituted phenyl and aryl systems were problematic to prepare. The authors theorized that this is due to a decomposition reaction pathway after the cyclization step that sensibly lowers reaction yields. After rationalizing the proposed reaction mechanism and further assays, the authors concluded that altering the chosen aryl structure in the aglycone would enable a more efficient biaryl system building. Accordingly, a bromostyrene derivative ylide is used in the Wittig olefination to assemble a mannose-based biaryl system (Fig. **13**).

Three years later, Smith *et al.* used their expertise in preparing *C*-glycoside derivatives to synthesize a *C*-glycoside functionalized microelectrode array [51]. Microelectrode arrays are important tools to monitor the interactions that take place when a biological receptor, normally a protein, binds to a carbohydrate substrate. The arrangement typically consists of many components, including a functionalized microelectrode coated in a porous polymer with easily modifiable functional groups that serve as handles for a spacer linker, which is then attached to the ligand. This ligand shares structural similarities with a natural protein-ligand (an *O*-glycoside) and generally has an extra functional group that enables monitoring of the binding by an optical method.

By changing the final step of the previously optimized method, Smith *et al.* assembled a novel pair of potential FimH *C*-glycoside antagonists (Fig. **14**). The former bromostyrene *C*-glycoside precursor was modified by adding a pyrene-derived (**47**) chain instead of an additional aromatic ring in the original procedure. This highly conjugated hydrocarbon chain serves two purposes. One is facilitating the complete glycoside's attachment to the electrode surface by straightforward reactions between its final OH group and the polymer functional handling that has been previously applied to the electrode's surface. The other function is to allow optical measurements to confirm the occurrence of electrode-glycoside bonds.

4. ELECTROSYNTHESIS OF *S*-GLYCOSIDES

Thioglycosides are not common in nature [52] and structurally differ from native *O*-glycosides [53, 54]. Nonetheless, thioglycosides have emerged as the most widely used starting material in electrochemical glycosidation reactions. Specifically, aryl thiols have been the most commonly used sub-

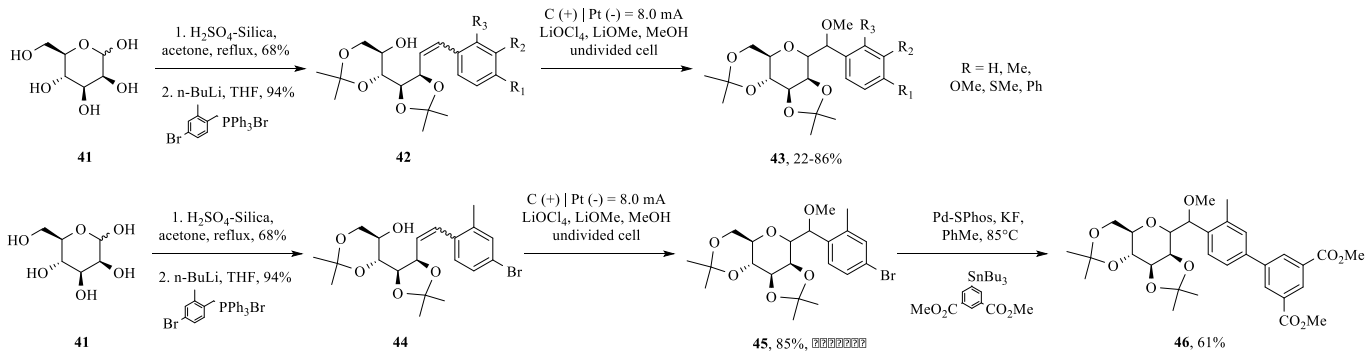

Fig. (13). Preparation of biaryl-containing C-glycosides by Smith [49].

strates in the last few decades due to their significantly lower oxidation potentials than other glycoside types, as reported by most of the works reviewed here. This broad preference for *S*-glycosides as glycosylation donors is supported by several factors, such as their enzymatic and chemical resistance compared to *O*-glycosides [45] and facile attainability since they can be stereoselectively prepared from free sugars through various known methods [1,55,56].

As opposed to their popularity as substrates and intermediates, the electrochemical synthesis of this type of chalcogenglycosides has not drawn significant attention. To the best of our knowledge, in the last decade, only one group has reported these compounds as synthetic targets of its electrochemical method. Zhu *et al.* [57] prepared several *S*-glycosides through an electrochemical nickel-catalyzed Migita cross-coupling (Fig. **15**).

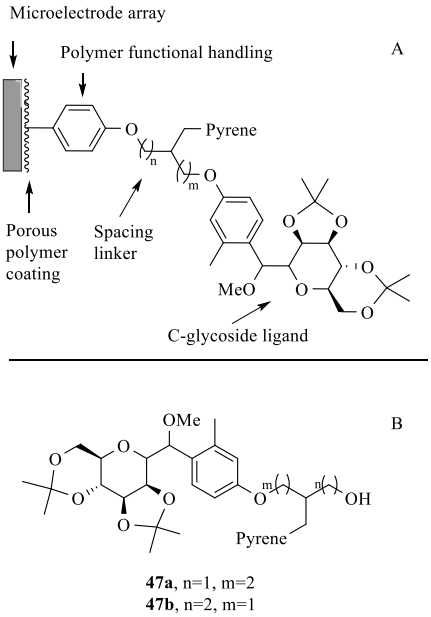

Fig. (14). Parts of a *C*-glycoside functionalized electrode array (**A**) and C-glycoside ligands (**B**) prepared by Smith *et al.* [51].

This mild procedure generates a selective S–C glycosidic bond from protected and even unprotected glycosyl thiols, as well as functionalized aryl bromides and iodides. It is conducted at room temperature for only 3 hrs and gives yields up to 95%. The chosen halides bring variety to the resulting S-glycosides since their groups include many different moieties, such as aryls with electron-withdrawing and electron-donating groups, heterocycles like quinoline and pyridine, and even unsaturated groups, such as alkenyl and alkynyl (Fig. **15**). Also, for the glycoside part diversity, other monosaccharides and oligosaccharides are used, and high anomeric selectivity is achieved in all cases. Finally, extending the scope of the method, unprotected glycosyl thiols and protected cysteine (amino acid) are successfully used in arylation assays. To date, the presented strategy is the only Pd-free and electrochemical alternative to the arylation of cysteine that can develop a new route to the bioconjugation of peptides.

5. MISCELLANEOUS

N-glycosides are also an important family of glycosides to review. Nonetheless, there is not much information regarding the synthesis of glycosylamines by electrochemical methods. Similar cases found were directly orientated to the building of nucleosides that bear a furanose unit, which is clearly a nucleotide precursor [58-60].

Regarding other types of carbohydrate derivatives (pseudoglycosides or non-anomeric glycosides), it is worth mentioning the advances achieved with glycals, a topic that Itoh's group has also contributed to. In 2021, Liu *et al.* [61] synthesized regioselectively trifluoromethylated glycals **71**. The developed electrolytic system works well with a variety of protecting groups, utilizes an undivided cell using CF_3SO_2Na as the trifluoromethyl source and $MnBr_2$ as the redox mediator, and gives up to 90% yield (Fig. **16**). Moreover, the authors discussed a hypothesis that proposes a radical mechanism for this reaction.

The versatility of the former procedure was demonstrated by Luo *et al.* [62], who used this method to afford a series of 2-bromoglycals **72** from different carbohydrate scaffolds with several protective groups (up to 96% yield, Fig. **16**). The quaternary ammonium salt Bu_4NBr (tetrabutylammonium bromide, TBAB), which is convenient, cheap, nontoxic, and easily handleable, acts as the source of bromine in metal-catalyst-free and oxidant-free reaction conditions. The authors also suspected that the nature of the transformation is radical, as reported in the research by Liu *et al.* [61], due to analysis with cyclic voltammetry and radical trapping. To demonstrate the potential for the bromo-enol bond, several reactions were tested on one of the compounds obtained under the technique, the tri-O-benzyl-2-bromogalactal. So-

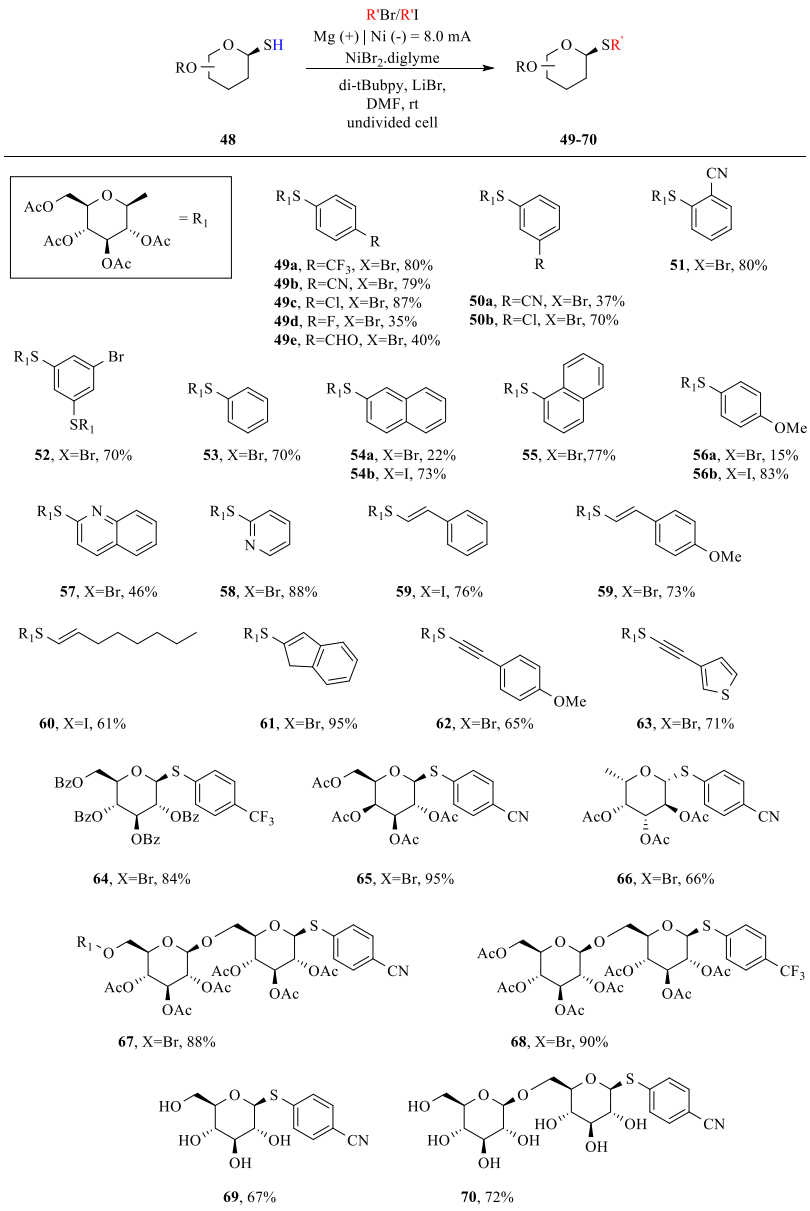

Fig. (15). Electrochemical nickel-catalyzed Migita cross-coupling by Zhu *et al.* [57] (R^1=aryl, alkenyl, alkynyl, heterocycles).

nogashira coupling (with phenylacetylene), Suzuki coupling (with potassium phenyltrifluoroborate), and a Ferrier rearrangement reaction were also performed efficiently.

So far, this review has covered several methods for the electrosynthesis of complex carbohydrate targets. Herein, we have discussed these procedures for preparing extremely specific carbohydrate-based structures on a laboratory scale. However, one interesting aspect of electrosynthesis is to produce sugar commodities in large quantities.

Mass, clean, and efficient production of commodity chemicals from biomass is a promising area in green chemistry. As electrochemical techniques have several inherent benefits for sustainable processes, including moderate operating conditions and customizable selectivity, several research groups are currently working on this aspect. Considering that there are excellent works that cover this topic [63], it is worth briefly mentioning some representative articles.

Glucaric acid is one of the most valuable compounds that can be obtained from this renewable natural resource [64]. This carboxylic diacid is commonly used as an additive on food and drugs [65] and serves as a building block in the synthesis of polymers, detergents, and chelating agents [66, 67], among other uses. Chemical and biological oxidation are the two main methods used in industry to prepare D-glucaric acid. Both methods have drawbacks, including toxic oxidation reagents, low selectivity, secondary products and high working pressures for the former method, large reaction times, lower yields, and difficult purification procedures for the latter.

Liu *et al.* [68] developed an efficient method to produce D-glucaric acid *via* the electrolysis of glucose from biomass. Using NiFe-layered double hydroxide (LDH) nanosheet arrays as precursor material, their method introduced two novel nanostructured electrodes: a NiFeNx nickel foam cathode

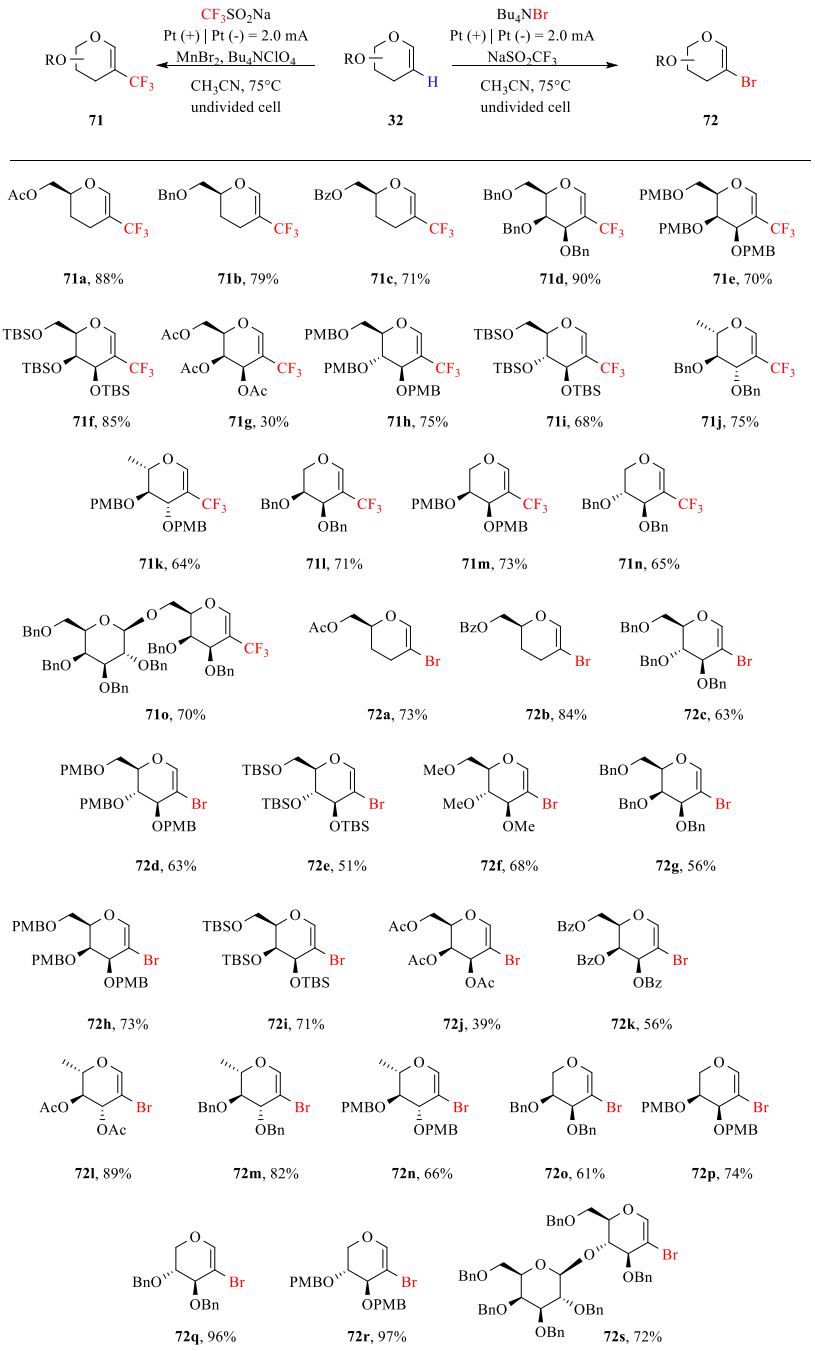

Fig. (16). Electrochemical transformations on glycals by Itoh *et al.* [61, 62]

and a NiFeOx nickel foam anode, both in KOH solution. At a potential of 1.39 V, an 83% yield was achieved. Moreover, as the oxidation of glucose to glucaric acid progresses in the anode, hydrogen is produced in the cathode. Thus, by producing two value-added compounds, glucaric acid and H_2, this electrochemical system highly valorizes biomass feedstock.

One of the main difficulties in glucose electrooxidation from biomass is reaction selectivity towards a particular product. Numerous works have studied the electrooxidation and degradation mechanism of glucose and other compounds normally found in biomass [69, 70, 71, 72, 73]. Finding optimal electrolysis conditions is crucial for achieving the desired transformation, but it is also important to prevent compound degradation, which is generally promoted by the pH medium and temperature.

Regarding this, the production of high-added-value compounds with aldehyde and ketone groups, which are vulnerable under basic conditions, is challenging. Zhou *et al.* [74] tried to tune the extent of biomass oxidation towards aldehyde and ketone groups-containing valuable chemicals, such as formate (potassium formate is a common additive for animal feed) and 2,5-furandicarboxylic acid (FDCA, a relevant building block for polymers). Through an extensive study on the degradation pathway, the authors developed a scalable single-pass continuous flow reactor (SPCFR) system to en-

hance the electrooxidation selectivity of formate (81.8% yield, 76.5% selectivity), particularly for large concentrations and volumes.

CONCLUSION

Organic electrosynthesis is a promising and growing field. Nowadays, it is not unusual to find at least one publication presenting novel electrochemical methods in every issue of traditional organic chemistry journals. Nonetheless, evidently, most of the electrosynthesis applied to the preparation of glycosides is still unexplored. A large number of carbohydrate transformations are waiting for alternative electrochemical methods to make the synthetic process greener.

In this mini-review, we have discussed that although there are already a reasonable number of electrochemical techniques enabling the building of *O*-glycosides, the construction of glycomimetics (*C*-, *N*-, *S*-glycosides, and others) and more complex structures, such as oligosaccharides, remains mostly undeveloped.

Despite the long way ahead towards a more extended methodology for carbohydrate electrosynthesis, encouraging advances have undoubtedly been achieved, such as automated oligosaccharide electrosynthesis, utilization of the sunlight directly as a power source for the cells, exploration of other glycosyl donors as starting material (glycals), successful preparation of steroids-derived *O*-glycosides, and the targeting of *S*-glycosides, among others.

On the other hand, as some authors [75] suggest, it is necessary to include descriptions of the product/s isolation and purification steps in the discussion section of the paper. With a few exceptions, these parts are normally relegated to the Supporting Information, and there is not a single mention or comment related to them in the discussion part of the papers. As organic chemists, we always expect some details related to the experimental issues to be faced in these stages. We strongly believe that this small change would encourage more chemists to incorporate electrochemical tools in their laboratories.

Finally, we are aware that the development of a universal electrochemical technique to obtain different classes of glycosides using the same system is an ambitious and naive expectation. However, the prospects for the next decade are encouraging, and undoubtedly, there will be many interesting contributions to the rising field of carbohydrate electrosynthesis.

LIST OF ABBREVIATIONS

?? = ????????????????

?? = ????????????????

?? = ????????????????

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors wish to thank UNLP, CICPBA, and CONICET of Argentina for financial support. A. P. is a research fellow at CONICET.

REFERENCES

[1] Miljkovic, M. *Carbohydrates: Synthesis, Mechanisms, and Stereoelectronic Effects,* 1st ed; Springer-Verlag: New York, NY, USA, **2009**. http://dx.doi.org/10.1007/978-0-387-92265-2

[2] Lindhorst, T.K. *Essentials of Carbohydrate Chemistry and Biochemistry,* 3rd ed; Wiley-VCH: Weinheim, Germany, **2007**.

[3] Rüdiger, H.; Gabius, H-J. The biochemical basis and coding capacity of the sugar code. In: *The Sugar Code: Fundamentals of Glycosciences*; Gabius, H-J., Ed.; Wiley-VCH: Weinheim, Germany, **2009**; pp. 3-14.

[4] Varki, A. Biological roles of glycans. *Glycobiology,* **2017**, *27*(1), 3-49. http://dx.doi.org/10.1093/glycob/cww086 PMID: 27558841

[5] Galan, M.C.; Jones, R.A.; Tran, A.T. Recent developments of ionic liquids in oligosaccharide synthesis: the sweet side of ionic liquids. *Carbohydr. Res.,* **2013**, *375*, 35-46. http://dx.doi.org/10.1016/j.carres.2013.04.011 PMID: 23685038

[6] Bertozzi, C.R.; Kiessling, L.L. Chemical glycobiology. *Science,* **2001**, *291*(5512), 2357-2364. http://dx.doi.org/10.1126/science.1059820 PMID: 11269316

[7] Mishra, N.; Tiwari, V.K.; Schmidt, R.R. Recent trends and challenges on carbohydrate-based molecular scaffolding: General consideration toward impact of carbohydrates in drug discovery and development. In: *Carbohydrates in drug discovery and development: Synthesis and application*; Tiwari, V.K., Ed.; Elsevier: Cambridge, MA, US, **2020**; pp. 1-69. http://dx.doi.org/10.1016/B978-0-12-816675-8.00001-4

[8] Koester, D.C.; Holkenbrink, A.; Werz, D.B. Recent advances in the synthesis of carbohydrate mimetics. *Synthesis,* **2010**, *19*, 3217-3242.

[9] Bernardi, A.; Sattin, S. Interfering with the sugar code: Ten years later. *Eur. J. Org. Chem.,* **2020**, *2020*(30), 4652-4663. http://dx.doi.org/10.1002/ejoc.202000155

[10] Gabius, H.J.; Cudic, M.; Diercks, T.; Kaltner, H.; Kopitz, J.; Mayo, K.H.; Murphy, P.V.; Oscarson, S.; Roy, R.; Schedlbauer, A.; Toegel, S.; Romero, A. What is the sugar code? *ChemBioChem,* **2022**, *23*(13), e202100327-e202100351. http://dx.doi.org/10.1002/cbic.202100327 PMID: 34496130

[11] Ernst, B.; Hart, G.W.; Sinaý, P. *Carbohydrates in Chemistry and Biology*; WILEY-VCH Verlag GmbH, **2000**. http://dx.doi.org/10.1002/9783527618255

[12] Karak, M.; Haldar, A.; Torikai, K. Current tools for chemical glycosylation: Where are we now? *Trends Glycosci. Glycotechnol.,* **2021**, *33*(195), 2014.7E. http://dx.doi.org/10.4052/tigg.2014.7E

[13] Andreana, P.R.; Crich, D. Guidelines for O-Glycoside formation from first principles. *ACS Cent. Sci.,* **2021**, *7*(9), 1454-1462. http://dx.doi.org/10.1021/acscentsci.1c00594 PMID: 34584944

[14] Streety, X.S.; Obike, J.C.; Townsend, S.D. A Hitchhiker's guide to problem selection in carbohydrate synthesis. *ACS Cent. Sci.,* **2023**, *9*(7), 1285-1296. http://dx.doi.org/10.1021/acscentsci.3c00507 PMID: 37521800

[15] Wiebe, A.; Gieshoff, T.; Möhle, S.; Rodrigo, E.; Zirbes, M.; Waldvogel, S.R. Electrifying organic synthesis. *Angew. Chem. Int. Ed.,* **2018**, *57*(20), 5594-5619. http://dx.doi.org/10.1002/anie.201711060 PMID: 29292849

[16] Schotten, C.; Nicholls, T.P.; Bourne, R.A.; Kapur, N.; Nguyen, B.N.; Willans, C.E. Making electrochemistry easily accessible to the synthetic chemist. *Green Chem.,* **2020**, *22*(11), 3358-3375. http://dx.doi.org/10.1039/D0GC01247E

[17] Kingston, C.; Palkowitz, M.D.; Takahira, Y.; Vantourout, J.C.; Peters, B.K.; Kawamata, Y.; Baran, P.S. A survival guide for the "Electro-curious". *Acc. Chem. Res.,* **2020**, *53*(1), 72-83. http://dx.doi.org/10.1021/acs.accounts.9b00539 PMID: 31823612

[18] Jörissen, J.; Speiser, B. Preparative electrolysis on the laboratory scale. In: *Organic electrosynthesis*; Hammerich, O.; Speiser, B., Eds.; CRC Press: Boca Raton, US, **2016**; pp. 265-329.

[19] Möhle, S.; Zirbes, M.; Rodrigo, E.; Gieshoff, T.; Wiebe, A.; Waldvogel, S.R. Modern electrochemical aspects for the synthesis of value-added organic products. *Angew. Chem. Int. Ed.,* **2018**, *57*(21), 6018-6041. http://dx.doi.org/10.1002/anie.201712732 PMID: 29359378

[20] Shatskiy, A.; Lundberg, H.; Kärkäs, M.D. Organic electrosynthesis: Applications in complex molecule synthesis. *ChemElectroChem,* **2019**, *6*(16), 4067-4092. http://dx.doi.org/10.1002/celc.201900435

[21] Yan, M.; Kawamata, Y.; Baran, P.S. Synthetic organic electrochemistry: Calling all engineers. *Angew. Chem. Int. Ed.,* **2018**, *57*(16), 4149-4155. http://dx.doi.org/10.1002/anie.201707584 PMID: 28834012

[22] Garg, S.; Sohal, H.S.; Malhi, D.S.; Kaur, M.; Singh, K.; Sharma, A.; Mutreja, V.; Thakur, D.; Kaur, L. Electrochemical method: A green approach for the synthesis of organic compounds. *Curr. Org. Chem.,* **2022**, *26*(10), 899-919. http://dx.doi.org/10.2174/1385272826666220516113152

[23] Frontana-Uribe, B.A.; Little, R.D.; Ibanez, J.G.; Palma, A.; Vasquez-Medrano, R. Organic electrosynthesis: A promising green methodology in organic chemistry. *Green Chem.,* **2010**, *12*(12), 2099-2119. http://dx.doi.org/10.1039/c0gc00382d

[24] Beil, S.B.; Pollok, D.; Waldvogel, S.R. Reproducibility in electroorganic synthesis—myths and misunderstandings. *Angew. Chem. Int. Ed.,* **2021**, *60*(27), 14750-14759. http://dx.doi.org/10.1002/anie.202014544 PMID: 33428811

[25] Yao, N.; Wang, H.B.; Hu, Y.L. Recent progress on electrochemical application of room-temperature ionic liquids. *Mini Rev. Org. Chem.,* **2017**, *14*(3), 237-254. http://dx.doi.org/10.2174/1570193X14666170420115644

[26] Marra, A.; Scherrmann, M-C. Electrochemical glycosylation. In: *Carbohydrate Chemistry Chemical and biological approaches*; Rauter, A.P.; Lindhorst, T.K.; Queneau, Y., Eds.; The Royal Society of Chemistry: London, UK, **2014**; Vol. 40, pp. 160-177. http://dx.doi.org/10.1039/9781849739986-00160

[27] Manmode, S.; Matsumoto, K.; Nokami, T.; Itoh, T. Electrochemical methods as enabling tools for glycosylation. *Asian J. Org. Chem.,* **2018**, *7*(9), 1719-1729. http://dx.doi.org/10.1002/ajoc.201800302

[28] Nokami, T.; Saito, K.; Yoshida, J. Synthetic carbohydrate research based on organic electrochemistry. *Carbohydr. Res.,* **2012**, *363*, 1-6. http://dx.doi.org/10.1016/j.carres.2012.09.023 PMID: 23089173

[29] Nokami, T. Electrochemical glycosylation. *Glycoforum,* **2022**, *25*(3), A8.

[30] Morzycki, J.W.; Łotowski, Z.; Siergiejczyk, L.; Wałejko, P.; Witkowski, S.; Kowalski, J.; Płoszyńska, J.; Sobkowiak, A. A selective electrochemical method of glycosylation of 3β-hydroxy-Δ^5-steroids. *Carbohydr. Res.,* **2010**, *345*(8), 1051-1055. http://dx.doi.org/10.1016/j.carres.2010.03.018 PMID: 20371036

[31] Tomkiel, A.M.; Brzezinski, K.; Łotowski, Z.; Siergiejczyk, L.; Wałejko, P.; Witkowski, S.; Kowalski, J.; Płoszyńska, J.; Sobkowiak, A.; Morzycki, J.W. Electrochemical synthesis of glycoconjugates of 3β-hydroxy-Δ^5-steroids by using non-activated sugars and steroidal thioethers. *Tetrahedron,* **2013**, *69*(42), 8904-8913. http://dx.doi.org/10.1016/j.tet.2013.07.106

[32] Tomkiel, A.M.; Kowalski, J.; Płoszyńska, J.; Siergiejczyk, L.; Łotowski, Z.; Sobkowiak, A.; Morzycki, J.W. Electrochemical synthesis of glycoconjugates from activated sterol derivatives. *Steroids,* **2014**, *82*, 60-67. http://dx.doi.org/10.1016/j.steroids.2014.01.007 PMID: 24486463

[33] Tomkiel, A.M.; Biedrzycki, A.; Płoszyńska, J.; Naróg, D.; Sobkowiak, A.; Morzycki, J.W. 3α,5α-Cyclocholestan-6β-yl ethers as donors of the cholesterol moiety for the electrochemical synthesis of cholesterol glycoconjugates. *Beilstein J. Org. Chem.,* **2015**, *11*, 162-168. http://dx.doi.org/10.3762/bjoc.11.16 PMID: 25815065

[34] Tomkiel, A.M.; Siergiejczyk, L.; Naróg, D.; Płoszyńska, J.; Sobkowiak, A.; Morzycki, J.W. Electrochemical cholesterylation of sugars with cholesteryl diphenylphosphate. *Steroids,* **2017**, *117*, 44-51. http://dx.doi.org/10.1016/j.steroids.2016.05.011 PMID: 27263439

[35] Manmode, S.; Kato, M.; Ichiyanagi, T.; Nokami, T.; Itoh, T. Automated electrochemical assembly of the β-(1,3)-β-(1,6)-glucan hexasaccharide using thioglucoside building blocks. *Asian J. Org. Chem.,* **2018**, *7*(9), 1802-1805. http://dx.doi.org/10.1002/ajoc.201800345

[36] Manmode, S.; Tanabe, S.; Yamamoto, T.; Sasaki, N.; Nokami, T.; Itoh, T. Electrochemical glycosylation as an enabling tool for the stereoselective synthesis of cyclic oligosaccharides. *ChemistryOpen,* **2019**, *8*(7), 869-872. http://dx.doi.org/10.1002/open.201900185 PMID: 31309034

[37] Isoda, Y.; Kitamura, K.; Takahashi, S.; Nokami, T.; Itoh, T. Electrochemical glycosylation as an enabling tool for the stereoselective synthesis of cyclic oligosaccharides. *ChemElectroChem,* **2019**, *6*, 4149-4152. http://dx.doi.org/10.1002/celc.201900215

[38] Yano, K.; Itoh, T.; Nokami, T. Total synthesis of Myc-IV(C16:0, S) *via* automated electrochemical assembly. *Carbohydr. Res.,* **2020**, *492*, 108018-108023. http://dx.doi.org/10.1016/j.carres.2020.108018 PMID: 32339812

[39] Liu, M.; Liu, K.M.; Xiong, D.C.; Zhang, H.; Li, T.; Li, B.; Qin, X.; Bai, J.; Ye, X.S. Stereoselective electro-2-deoxyglycosylation from glycals. *Angew. Chem. Int. Ed.,* **2020**, *59*(35), 15204-15208. http://dx.doi.org/10.1002/anie.202006115 PMID: 32394599

[40] Shibuya, A.; Kato, M.; Saito, A.; Manmode, S.; Nishikori, N.; Itoh, T.; Nagaki, A.; Nokami, T. Stereoselective electro-2-deoxyglycosylation from glycals. *Eur. J. Org. Chem.,* **2022**, e202200135. http://dx.doi.org/10.1002/ejoc.202200135

[41] Bennett, C.S.; Galan, M.C. Methods for 2-deoxyglycoside synthesis. *Chem. Rev.,* **2018**, *118*(17), 7931-7985. http://dx.doi.org/10.1021/acs.chemrev.7b00731 PMID: 29953219

[42] De Lederkremer, R.M.; Marino, C. Deoxy sugars: Occurrence and synthesis. In: *Advances in Carbohydrate Chemistry and Biochemistry*; Horton, D., Ed.; Academic Press: New York, US, **2007**; Vol. 61, pp. 143-215.

[43] Meng, S.; Li, X.; Zhu, J. Recent advances in direct synthesis of 2-deoxy glycosides and thioglycosides. *Tetrahedron,* **2021**, *88*, 132140-132182. http://dx.doi.org/10.1016/j.tet.2021.132140

[44] Levy, D.E. Strategies towards C-Glycosides. In: *The Organic Chemistry of Sugars*; Levy, D.E.; Fugedi, P., Eds.; CRC Press: Boca Raton, FL, US, **2005**. http://dx.doi.org/10.1201/9781420027952.ch7

[45] Brito-Arias, M. *Synthesis and Characterization of Glycosides*; Springer: New York, NY, USA, **2007**.

[46] Hussain, N.; Hussain, A. Advances in Pd-catalyzed C–C bond formation in carbohydrates and their applications in the synthesis of natural products and medicinally relevant molecules. *RSC Adv.,* **2021**, *11*(54), 34369-34391. http://dx.doi.org/10.1039/D1RA06351K PMID: 35497292

[47] Yang, Y.; Yu, B. Recent advances in the chemical synthesis of *C* -glycosides. *Chem. Rev.,* **2017**, *117*(19), 12281-12356. http://dx.doi.org/10.1021/acs.chemrev.7b00234 PMID: 28915018

[48] Xu, G.; Moeller, K.D. Anodic coupling reactions and the synthesis of *C*-glycosides. *Org. Lett.,* **2010**, *12*(11), 2590-2593. http://dx.doi.org/10.1021/ol100800u PMID: 20462275

[49] Smith, J.A.; Moeller, K.D. Oxidative cyclizations, the synthesis of aryl-substituted C-glycosides, and the role of the second electron transfer step. *Org. Lett.,* **2013**, *15*(22), 5818-5821. http://dx.doi.org/10.1021/ol402826z PMID: 24199843

[50] Sarshar, M.; Behzadi, P.; Ambrosi, C.; Zagaglia, C.; Palamara, A.T.; Scribano, D. FimH and anti-adhesive therapeutics: A disarming strategy against uropathogens. *Antibiotics,* **2020**, *9*(7), 397-413. http://dx.doi.org/10.3390/antibiotics9070397 PMID: 32664222

[51] Smith, J.A.; Xu, G.; Feng, R.; Janetka, J.W.; Moeller, K.D. *C*-glycosides, array-based addressable libraries, and the versatility of

constant current electrochemistry. *Electroanalysis,* **2016**, *28*(11), 2808-2817.
http://dx.doi.org/10.1002/elan.201600200

[52] Lian, G.; Zhang, X.; Yu, B. Thioglycosides in carbohydrate research. *Carbohydr. Res.,* **2015**, *403*, 13-22.
http://dx.doi.org/10.1016/j.carres.2014.06.009 PMID: 25015586

[53] Aguilera, B.; Jiménez-Barbero, J.; Fernández-Mayoralas, A. Conformational differences between Fuc(α1–3)GlcNAc and its thioglycoside analogue. *Carbohydr. Res.,* **1998**, *308*(1-2), 19-27.
http://dx.doi.org/10.1016/S0008-6215(98)00066-4 PMID: 9675354

[54] Buckingham, J.; Brazier, J.A.; Fisher, J.; Cosstick, R. Incorporation of a S-glycosidic linkage into a glyconucleoside changes the conformational preference of both furanose sugars. *Carbohydr. Res.,* **2007**, *342*(1), 16-22.
http://dx.doi.org/10.1016/j.carres.2006.11.007 PMID: 17145047

[55] Driguez, H. Thiooligosaccharides in glycobiology. *Top. Curr. Chem.,* **1997**, *187*, 85-116.
http://dx.doi.org/10.1007/BFb0119254

[56] Qiao, M.; Zhang, L.; Jiao, R.; Zhang, S.; Li, B.; Zhang, X. Chemical and enzymatic synthesis of S-linked sugars and glycoconjugates. *Tetrahedron,* **2021**, *81*, 131920.
http://dx.doi.org/10.1016/j.tet.2020.131920

[57] Zhu, M.; Alami, M.; Messaoudi, S. Electrochemical nickel-catalyzed Migita cross-coupling of 1-thiosugars with aryl, alkenyl and alkynyl bromides. *Chem. Commun.,* **2020**, *56*(32), 4464-4467.
http://dx.doi.org/10.1039/D0CC01126F PMID: 32196023

[58] Okamoto, K.; Shoji, T.; Tsutsui, M.; Shida, N.; Chiba, K. Electrochemical nickel-catalyzed Migita cross-coupling of 1-thiosugars with aryl, alkenyl and alkynyl bromides. *Chemistry,* **2018**, *24*, 17902-17905.
http://dx.doi.org/10.1002/chem.201804285 PMID: 30216580

[59] Okamoto, K.; Tsutsui, M.; Morizumi, H.; Kitano, Y.; Chiba, K. Electrochemical synthesis of imino- *C* -nucleosides by "reactivity switching" methodology for *in situ* generated glycoside donors. *Eur. J. Org. Chem.,* **2021**, *2021*(17), 2479-2484.
http://dx.doi.org/10.1002/ejoc.202100106

[60] Shoji, T.; Kim, S.; Chiba, K. Synthesis of azanucleosides by anodic oxidation in a lithium perchlorate–nitroalkane medium and diversification at the 4′-nitrogen position. *Angew. Chem. Int. Ed.,* **2017**, *56*(14), 4011-4014.
http://dx.doi.org/10.1002/anie.201700547 PMID: 28266101

[61] Liu, M.; Luo, Z.X.; Li, T.; Xiong, D.C.; Ye, X.S. Electrochemical trifluoromethylation of glycals. *J. Org. Chem.,* **2021**, *86*(22), 16187-16194.
http://dx.doi.org/10.1021/acs.joc.1c01318 PMID: 34435785

[62] Luo, Z.X.; Liu, M.; Li, T.; Xiong, D.C.; Ye, X.S. Electrochemical bromination of glycals. *Front Chem.,* **2021**, *9*, 796690.
http://dx.doi.org/10.3389/fchem.2021.796690 PMID: 35004613

[63] Vedovato, V.; Vanbroekhoven, K.; Pant, D.; Helsen, J. Electrosynthesis of biobased chemicals using carbohydrates as a feedstock. *Molecules,* **2020**, *25*(16), 3712-3749.
http://dx.doi.org/10.3390/molecules25163712 PMID: 32823995

[64] Ragauskas, A.J.; Williams, C.K.; Davison, B.H.; Britovsek, G.; Cairney, J.; Eckert, C.A.; Frederick, W.J., Jr; Hallett, J.P.; Leak, D.J.; Liotta, C.L.; Mielenz, J.R.; Murphy, R.; Templer, R.; Tschaplinski, T. The path forward for biofuels and biomaterials. *Science,* **2006**, *311*(5760), 484-489.
http://dx.doi.org/10.1126/science.1114736 PMID: 16439654

[65] Zhang, Q.; Wan, Z.; Yu, I.K.M.; Tsang, D.C.W. Sustainable production of high-value gluconic acid and glucaric acid through oxidation of biomass-derived glucose: A critical review. *J. Clean. Prod.,* **2021**, *312*, 127745.
http://dx.doi.org/10.1016/j.jclepro.2021.127745

[66] Mehtiö, T.; Toivari, M.; Wiebe, M.G.; Harlin, A.; Penttilä, M.; Koivula, A. Production and applications of carbohydrate-derived sugar acids as generic biobased chemicals. *Crit. Rev. Biotechnol.,* **2016**, *36*(5), 904-916.
http://dx.doi.org/10.3109/07388551.2015.1060189 PMID: 26177333

[67] Mangiameli, M.F.; González, J.C.; Bellú, S.; Bertoni, F.; Sala, L.F. Redox and complexation chemistry of the Cr^{VI}/Cr^{V}-d-glucaric acid system. *Dalton Trans.,* **2014**, *43*(24), 9242-9254.
http://dx.doi.org/10.1039/c4dt00717d PMID: 24816781

[68] Liu, W.J.; Xu, Z.; Zhao, D.; Pan, X.Q.; Li, H.C.; Hu, X.; Fan, Z.Y.; Wang, W.K.; Zhao, G.H.; Jin, S.; Huber, G.W.; Yu, H.Q. Efficient electrochemical production of glucaric acid and H_2*via* glucose electrolysis. *Nat. Commun.,* **2020**, *11*(1), 265.
http://dx.doi.org/10.1038/s41467-019-14157-3 PMID: 31937783

[69] Barragan, J.T.C.; Kogikoski, S., Jr; da Silva, E.T.S.G.; Kubota, L.T. Insight into the electro-oxidation mechanism of glucose and other carbohydrates by CuO-based electrodes. *Anal. Chem.,* **2018**, *90*(5), 3357-3365.
http://dx.doi.org/10.1021/acs.analchem.7b04963 PMID: 29424228

[70] Handa, Y.; Watanabe, K.; Chihara, K.; Katsuno, E.; Horiba, T.; Inoue, M.; Komaba, S. The mechanism of electro-catalytic oxidation of glucose on manganese dioxide electrode used for amperometric glucose detection. *J. Electrochem. Soc.,* **2018**, *165*(11), H742-H749.
http://dx.doi.org/10.1149/2.0781811jes

[71] Kapetanović, E.; Beil, S.B. Site-Selective electrochemical oxidation of carbohydrates. *ChemElectroChem,* **2023**, *10*(22), e202300411.
http://dx.doi.org/10.1002/celc.202300411

[72] Holade, Y.; Guesmi, H.; Filhol, J.S.; Wang, Q.; Pham, T.; Rabah, J.; Maisonhaute, E.; Bonniol, V.; Servat, K.; Tingry, S.; Cornu, D.; Kokoh, K.B.; Napporn, T.W.; Minteer, S.D. Deciphering the electrocatalytic reactivity of glucose anomers at bare gold electrocatalysts for biomass-fueled electrosynthesis. *ACS Catal.,* **2022**, *12*(20), 12563-12571.
http://dx.doi.org/10.1021/acscatal.2c03399

[73] Opallo, M.; Dolinska, J. Glucose electrooxidation. In: *Reference Module in Chemistry, Molecular Sciences and Chemical Engineering*; Wandelt, K., Ed.; Elsevier: Amsterdam, **2018**; pp. 633-642.

[74] Zhou, H.; Ren, Y.; Yao, B.; Li, Z.; Xu, M.; Ma, L.; Kong, X.; Zheng, L.; Shao, M.; Duan, H. Scalable electrosynthesis of commodity chemicals from biomass by suppressing non-Faradaic transformations. *Nat. Commun.,* **2023**, *14*(1), 5621.
http://dx.doi.org/10.1038/s41467-023-41497-y PMID: 37699949

[75] Listratova, A.V.; Sbei, N.; Voskressensky, L.G. Catalytic electrosynthesis of *N*, *O* -heterocycles – recent advances. *Eur. J. Org. Chem.,* **2020**, *2020*(14), 2012-2027.
http://dx.doi.org/10.1002/ejoc.201901635