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ACHMATOWICZ REARRANGEMENT – 50 YEARS OF APPLICATION

PÓŁ WIEKU ZASTOSOWAŃ PRZEGRUPOWANIA ACHMATOWICZA

MOTTO: TANTUM SCIMUS, QUANTUM MEMORIA TENEMUS.

Summary: *Chemical sciences proved instrumental in formulating theories and in providing materials which are crucial for development of contemporary technical civilization. Methods of chemical synthesis, necessary for supply of materials designed for specific technical needs have attained efficiency, which allows preparation of even most complicated molecules encountered in Nature. Academic stereo- and enantioselective total syntheses of natural products (such as: alkaloids, peptides, isoprenoids, lipids, carbohydrates and phenolics) are generally regarded as the top achievements of XX century organic chemistry. Along the line, this paper recalls ingenious project of total synthesis from simple furan derivatives, of pyranes and pyranosides, basic stuff of natural carbohydrates, suitably functionalized for a stepwise conversion into variety of sugar structures. The project designed in the Institute of Organic Chemistry, Polish Academy of Sciences in Warsaw, began its proof of principle experimental validation in 1970. Its success led to a widespread application of what is presently known as the Achmatowicz reaction/Achmatowicz rearrangement for syntheses of simple and complex, oxygen and nitrogen heterocyclic systems, including great variety of natural products.*

Keywords: *Furylcarbinols, pyrans, pyranoses, monosaccharides, total syntheses of natural and modified sugars, unsaturated sugars, Achmatowicz rearrangement*

Streszczenie: *Nauki chemiczne odegrały kluczową rolę w kształtowaniu zarówno podstaw teoretycznych jak i zaplecza materialnego współczesnej cywilizacji przemysłowej. Metody syntezy chemicznej, niezbędne do wytwarzania materiałów technicznych o pożądanych właściwościach, osiągnęły sprawność pozwalającą na otrzymanie związków odpowiadających cząsteczkom organicznym pochodzenia biologicznego, o najwyższym stopniu złożoności. Syntezy totalne, stereo- i enancjoselektywne, związków naturalnych (alkaloidów, peptydów, izoprenoidów, lipidów, węglowodanów i związków fenolowych) uznano za najważniejsze osiągnięcia klasycznej chemii organicznej. Poniżej przedstawiamy genezę i rozwój projektu totalnej syntezy z prostych pochodnych furanu, wielofunkcyjnych piranów i piranoz – zasadniczej heterocyklicznej sześcioczłonowej struktury pierścieniowej naturalnych cukrów, glikozydów i ich oligomerycznych pochodnych, opracowanego w Instytucie Chemii Organicznej PAN w Warszawie, który w 1970-tym roku osiągnął zrealizowaną z powodzeniem fazę weryfikacji doświadczalnej. Osiągnięcie, które zyskało nazwę reakcji (przegrupowania) Achmatowicza, stanowi obecnie jedno z popularniejszych narzędzi stereokontrolowanej syntezy tlenowych i azotowych związków heterocyklicznych.*

Słowa kluczowe: *furylokarbinole, pirany, piranozy, monosacharydy, totalne syntezy cukrów prostych, nienasycone piranozy, przegrupowanie Achmatowicza*

Introduction

There is a relatively well established opinion in academia, shared by larger learned circles, that chemical sciences in Poland are well developed and scientific achievements of contemporary Polish scientists are properly recognized in the global scientific literature [1]. From the organic chemistry standpoint, the perception of towering achievements in the last century have been focused on total organic syntheses of natural products (NP), particularly secondary metabolites (SM), in their versions allowing for the efficient control of the target's chirality. Secondary metabolites, which exhibit a wide diversity of selective biological activities, became indispensable as lead compounds and therapeutic agents for contemporary medicine and pharmaceutical industry. They are very seldom available from natural sources in quantities required for industrial manufacturing of pharmaceutical active substances and their preparations, hence the continuous interest in their alternative resources. Chemical synthesis, which started in XIXth century from targeting as simple chemical molecules as urea (F. Wöhler, 1828) and acetic acid (H. Kolbe, 1845), quickly expanded its scope to thousands of reactions and millions of various products of increased complexity. It has become a new reliable source of useful natural products and their analogs and mimics for structure – activity relationship studies. Total syntheses of complex, multifunctional, polycyclic and loaded with chiral centers natural products, such as: alkaloids, antibiotics, vitamins, isoprenoids and acetogenins, has throughout the last century served as the ultimate test of chemists ingenuity in planning and craft in executing of multistep sequences of

Osman Achmatowicz (Born Dec. 20 1931, Vilnius) – Professor of organic chemistry in research and education institutions in Warsaw since 1975, active researcher and educator in natural products chemistry, structure elucidation, stereoselective synthesis, and organic stereochemistry. Member of the IUPAC committees (1978-2017), Polish Chemical Society (Deputy President [1982-1986], awarded Kostanecki Medal 1983), Society for Advancement and Propagation of Science, Societas Scientiarum Varsoviensis and other. Fellow of the World Innovation Foundation since 2002. Son of Professor Osman Achmatowicz (1899-1988), also distinguished organic chemist.
O. Achmatowicz graduated from Chemistry Department Warsaw Technical University in 1955. Obtained his Ph. D. (1961) and D. Sc. (1967) from University of Warsaw. Visiting Scientist of: National Research Council of Canada (1961-1963), University of California San Francisco (1963-1964), Queens University, Kingston, Ont., Canada (1973-1974) and Wisconsin University, Madison, WI, USA (1986-1987).

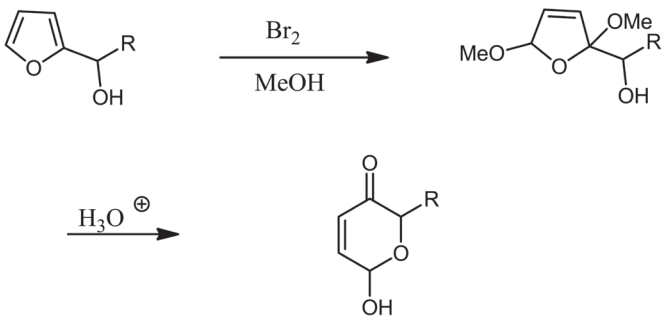
Osman Achmatowicz (ur. 20 grudnia 1931 w Wilnie) – Profesor chemii organicznej, kolejno w IChO PAN (1975-1977), SGGW (1977-1991) i w Instytucie Farmaceutycznym (1991-2012). Specjalizował się w chemii związków naturalnych (alkaloidy, antybiotyki, węglowodany), stereochemii, organicznej syntezie enancjoselektywnej; jest ekspertem w dziedzinie nomenklatury chemicznej. Syn Osmana Achmatowicza (1899-1988) także chemika organika. Autor reakcji imiennej o szerokim zastosowaniu w syntezie i chemii związków naturalnych. Absolwent Wydziału Chemicznego Politechniki Warszawskiej (1955), stopień naukowy doktora uzyskał w 1961 roku a habilitację w 1967 roku na Wydziale Chemii Uniwersytetu Warszawskiego. Tytuł naukowy profesora otrzymał w 1975 roku. Wiceprezes ZG PTChem (1982-1986) i Towarzystwa Naukowego Warszawskiego (2001-2004), członek Komisji Nomenklatury Organicznej IUPAC (1978-2011). Działa w Towarzystwie Krzewienia i Popierania Nauk oraz Komisji do spraw Etyki w Nauce PAN. Odbywał staże stypendialne w: National Research Council of Canada w Ottawie (1961–1963), Uniwersytecie Kalifornijskim w San Francisco (1963–1964), Queen's University w Kanadzie (1973–1974). Zajmował także stanowisko profesora wizytującego na Uniwersytecie Wisconsin-Madison w latach 1986–1987. W latach 1991-2011 był sekretarzem Centralnej Komisji do Spraw Stopni i Tytułów Naukowych.

reactions. Simply forming final products was not sufficient; the synthetic steps should be regio- and stereoselective offering as high efficiency of the final outcome as possible [2–6]. Chemistry has attained almost magical power in assembling complex molecules (also with designable functionality), through accumulated knowledge created by generations of exceptionally gifted individual scientists. Sometimes, the accomplishments have been honored by associating the name with a particular molecular transformation or chemical process [7]. Among the recent achievements developed in local academic environment, which enjoy very wide international recognition, we have chosen to single out the Achmatowicz rearrangement (Scheme 1). It is mainly for sentimental reasons, since we were members of the research group which contributed to the general method of total synthesis of carbohydrates, heralded by a seminal publication which appeared in *Tetrahedron* nearly 50 years ago [8]. In the late 1960-ties Aleksander Zamojski and Osman Achmatowicz, the scientists employed by the Institute of Organic Chemistry, Polish Academy of Sciences (IChO, PAS) in Warsaw, conceived a project, aimed at total synthesis of monosaccharides. The two scientists proposed parallel lines of research:

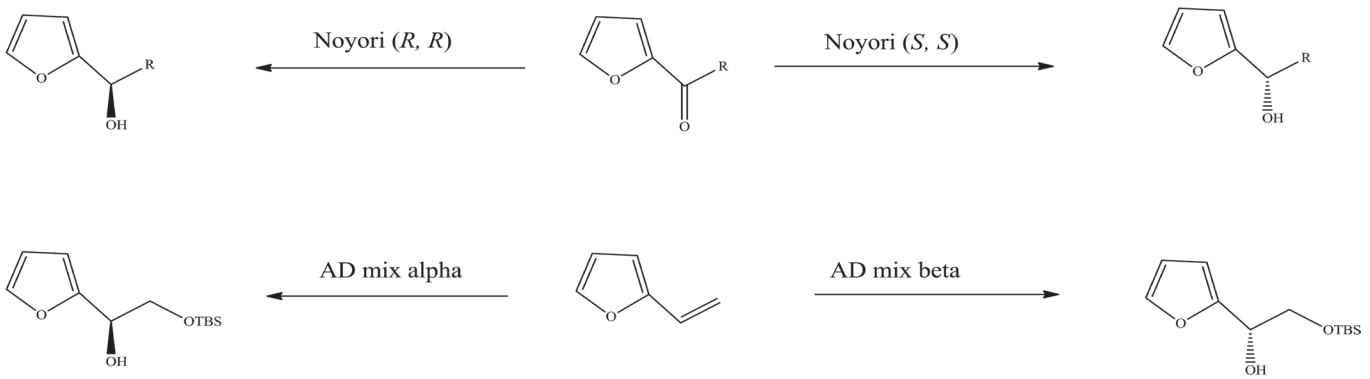
a) an assembly of pyran compounds (monosaccharides) starting from key substrates deriving from the hetero- Diels-Alder reaction;
b) an assembly of pyran compounds starting from the key substrates, relatively easily available methoxylated furan derivatives (formal 1,4-dicarbonyl synthons).

Both total syntheses allowed for an introduction of all functionalities needed to produce a variety of natural pyranosides in a diastereoselective manner. Ultimately, both approaches manned by gifted Ph. D. students proved successful and attracted attention of wide circles of natural product chemistry researchers. This paper is devoted to some reminiscences of the Achmatowicz rearrangement (ARE) (Scheme 1) [7, 8], origins and its extraordinary dynamic development as the furan pathway to carbohydrates, and its follow up applications in wider perspective of natural product synthesis. Scheme of canonical version of the transformation reported in 1971 as the general approach to monosaccharides is presented below. (R = H, CH_3, CH_2OH).

Scheme 1. A stepwise transformation of furyl carbinols into pyranose enuloses, versatile synthons for natural products, known as Achmatowicz reaction (or Achmatowicz rearrangement)

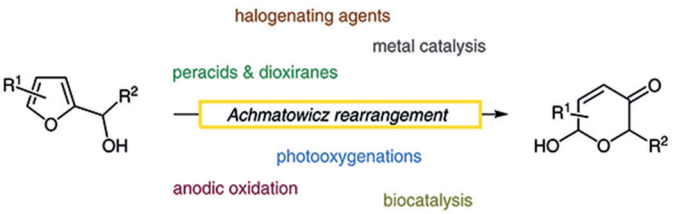


Scheme 2. Access to furylcarbinols of defined chirality from 2-alkylfurylketones and 2-vinylfuran by catalytic reduction (Noyori) and dihydroxylation (Sharpless) procedures



Most 2-furyl alcohols applicable as reactants are chiral. Thus, since the original invention much effort has been invested in securing access to required 2-furyl alcohols of suitable enantiomeric purity (Scheme 2) [9, 10] and developing more efficient transformations. It resulted in a gradual improvements in the stereoselectivity control, atom economy, chemical waste reduction [11–14], switch from stoichiometric to catalytic reagents [15, 16], as well as experimental application and practical deployment of biocatalysis [17, 18] in selective one step reaction depicted on Scheme 2 and 3 below.

Scheme 3. Scope of reagents and conditions driving Achmatowicz rearrangement as a selective single step reaction

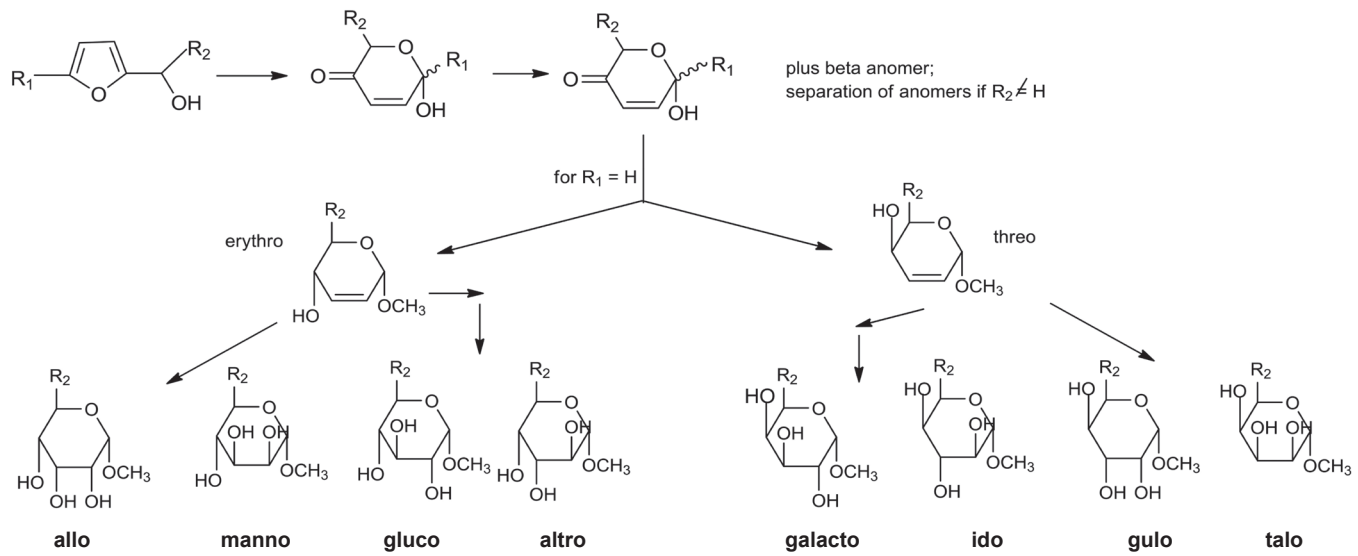


Total syntheses of carbohydrates

Sugars are essential components of a primary as well as secondary metabolism. Generated by carbon dioxide fixation in a multistep electron transfer process summarized as photosynthesis, carried out by green plants equipped with chlorophyll as the catalyst, carbohydrate materials (cellulose, lignans, starch and other polysaccharides) are amassed in agrotechnical crops and natural biomass in quantities exceeding 350 gigatons of carbon dioxide turnover per annum globally. Yet, apart from a few common sugars qualifying as commodity chemicals (cellulose, glucose, sucrose, lactose, etc.), many mono- and oligosaccharides are in short supply as raw materials for particular purposes such as pharmaceutical manufacturing, biotechnology, bioengineering and synthetic biology [19,20]. Glycans, glycoproteins, glycolipids and other glycoconjugates are of utmost importance to most biological functions and processes registered as normal physiology or markers of pathology. Consequently, various sugar molecules, from monosaccharide analogs and simple glycosides to complex branched chain oligosaccharides, are employed as therapeutics with functions spanning from enzyme inhibitors to vaccines [21, 22]. Early knowledge of carbohydrate structure frequently represented by molecular formula $C_n(H_2O)_n$ inspired attempts like formaldehyde condensation under moderate basic conditions (Butlerov reaction), which indeed has produced a sweet tasting mixture of sugar like substances, called formose. Remarkably, Emil Fischer managed to prove unanimously around 1900 that formose contains grape sugar – glucose, albeit in racemic form. Fischer's studies on sugars and their synthetic derivatives culminated in the first total synthesis of D-glucose, during which configuration of four consecutive chiral centers was properly assembled [23]. Throughout XX century, the numerous attempts were made to design and develop various practical approaches to syntheses of carbohydrates from non-sugar substrates, and vast literature of these efforts is discussed in comprehensive reviews [24–28]. The approach conceived by O. Achmatowicz around 1970 was based on a well-established conversion of furan compounds into 2,5-dialkoxy-2,5-dihydro derivatives, electrochemically, or under bromine catalysis; such compounds were by then already used as 1,4-dicarbonyl synthon precursors for assembly of various heterocyclic systems [11, 15, 16].

Ingenious plan of the stepwise conversion of suitably functionalized furan derivatives into naturally occurring pyranoses begins with alfa 2-furylcarbinols. They were to be exposed to dialkoxylation followed by a mild acidic hydrolysis. This treatment should bring about a spontaneous rearrangement into 2,3-unsaturated-pyranose-4-ulose, a pyran derivative (Scheme 1) suitably functionalized for subsequent stepwise transformations into regular or structurally modified monosaccharides [8]. Thus, 2-furylcarbinol was considered a suitable precursor of

Scheme 4. General scheme illustrating the Achmatowicz approach to monosaccharides (R = H for aldopentoses, R = CH_3 for 6-deoxyaldohexoses, and R = CH_2OH for aldohexoses

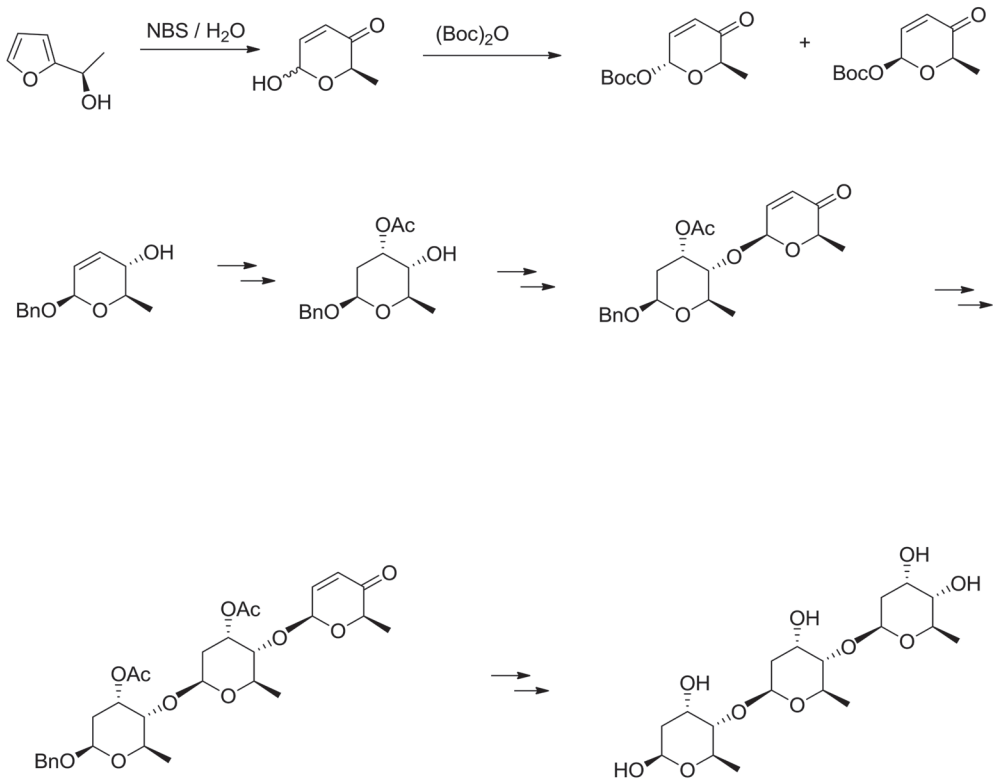


pentopyranoses, while 2-furylethanol should provide precursor for 6-deoxyhexoses, and 2-furylethanediol, for natural hexoses. The power of the outlined concept resides in multifunctionality of the key enulose intermediate and a possibility of an excellent diastereoselectivity control in a sequence of planned reactions, like carbonyl group reduction, followed by the double bond conversion into a *cis*- or *trans*- vicinal diols, through dihydroxylation or epoxidation followed by hydrolysis. The plan of synthesis is presented in a following scheme which shows the robustness of the methodology allowing synthesizing practically any monosaccharide [8]

It should be stressed, that although above scheme represent syntheses of pentoses or hexoses as racemic mixtures, it was realized from the beginning that the alfa-furyl carbinol carbon atom, if chirally substituted, should preserve its configuration throughout the rearrangement, and therefore the method should be applicable to synthesis of monosaccharides of either D- or L-series (subject to availability of furylcarbinols of suitable absolute configuration). That working hypothesis was successfully verified by synthesis of methyl glycosides of selected D- and L-aldohexoses [29, 30] after meticulous preparations of (S-)- and (R+)- furylcarbinols by classic separation of their diastereomeric derivatives. The main part of the project was concluded in approximately four years with completing of five Ph. D. Theses, defended in the IChO, PAS in Warsaw, by P. Bukowski, B. Szechner, R. Bielski, Z. Zwierzchowska and H.M. Burzyńska, under the supervision of Professor O. Achmatowicz. In summary, the following classes of monosaccharides have been obtained as methyl glycosides: aldopentopyranoses [31, 32], deoxyhexoses of antibiotic origin (aculose, amicetose, cinerulose and 6-deoxyaldohexoses; [33–35]), regular aldohexoses [36] and ketopentopyranoses and ketohexopyranoseses [37–38]. Some additional syntheses were completed within Achmatowicz's group, apart from the ongoing Ph. D. program. These included: ribose derivatives [39], noviose [40], 6-deoxy-6-nitro-mannose [41], antibiotic aminohexose glycosides – kanosaminide [30] and aminooctose - lincosaminide [42]. Racemic pentenulose was also tested, in form of anomeric esters, as glycosylation synthon for preparation of O- and C- glycosides under Lewis acid catalysis [43, 44]. Finally, the same racemic synthon was used for syntheses of disaccharide precursors from suitably protected D-monosaccharides, demonstrating facile chromatographic separation of obtained diastereoisomeric mixtures [45, 46]. The results summarized in referenced publications and the recent book chapters [47, 48] have proven the soundness of the initial concept, and have demonstrated its practical experimental viability; in principle, all exercised chemical transformations secured facile every step diastereoisomer resolution, for both operational purposes - analytical control (TLC; HPLC) and preparative separation (SiO_2 column chromatography).

When many years later O'Doherty published an extensive review on asymmetric synthesis of sugars in Advances in Carbohydrate Chemistry and Biochemistry [28] substantial portion of the chapter was devoted to application of the Achmatowicz rearrangement. In retrospect, it can be concluded that the appreciation of the rearrangement applicability was rather slow at first, but exploded when availability of chiral furyl carbinols was secured by facile asymmetric hydrogenation of 2-furyl ketones with use of Noyori catalysts or via Sharpless dihydroxylation of 2-vinylfuran (Scheme 2) [9, 10]. Vinylfuran,

Scheme 5. The key steps of digitoxose synthesis, trisaccharide sugar moiety which constitutes a glucon part of cardiotonic Digitalis glycosides [49, 50]



which can be easily generated from furfural, by using methylenating or hydroxymethylenating C1 synthons like Wittig or Grignard reagents, can also be converted to useful vicinal hydroxyaminated synthons. It is worth adding that synthetic, enantiomerically pure enuloses, like D-aculose, have gained great popularity as O- and C- glycosylating synthons in Pd catalyzed preparative protocols, particularly useful for glycodiversification, in oligosaccharide synthesis [49–51], and preparation of natural glycosides and glycoconjugates [28, 52, 53]. They have been also applied in syntheses of other natural products, including acetogenin antibiotics, terpenoid saponins, and alkaloids [28, 54-57].

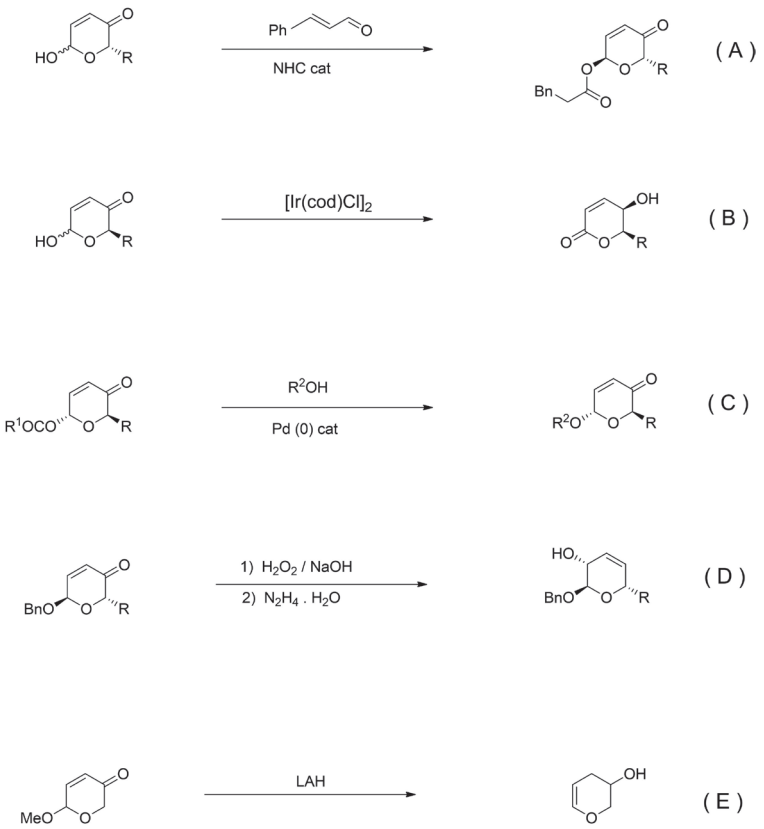
Short outline of pyranosuloses chemistry

Primary ARE products (Scheme 1) were named pyran-2-en-4-osuloses by the rearrangement originators, who preferred sugar nomenclature, and/or 6-hydroxy-2H-pyran-2(3H)-ones by some other authors. They were also referred to as „enuloses" or „lactols" in short, to stress the presence of a hemiacetal center, essential for further transformations. These small molecules, already resembling some natural pyranoses, are heavily loaded in functionality. In a conjugated double bond containing pyrane ring every carbon atom represents some diverse but selective reactivity, which can be applied for chemical derivatization and/or introduction of additional functional groups [8] as illustrated on Schemes 6 and 7. Evidently, the most important issue in a pyranosulose further functionalization, is stereoselectivity. It has been repeatedly demonstrated that the substrate furylcarbinol carbon atom preserves its configuration throughout the rearrangement but to enforce further chirality control and integrity additional means have to be devised. Anomeric mixture formation can easily be avoided in case of hexoses or higher sugars by constructing 1,6-anhydro bicyclic ring system, which ensures an excellent diastereoselection [58, 59]. Pentenuloses or 6-deoxyhexenuloses can be conveniently transformed into optically active compounds by constructing chiral molybdenum and iridium complexes, which can be separated by column chromatography into air-stable pro-D and pro-L monosaccharide precursors [60–62]. Additionally, iridium catalyzed dynamic kinetic isomerization can convert 2,3-en-4-uloses into regioisomeric unsaturated lactones with excellent control of newly created C-4 chiral center. (Scheme 6 B)

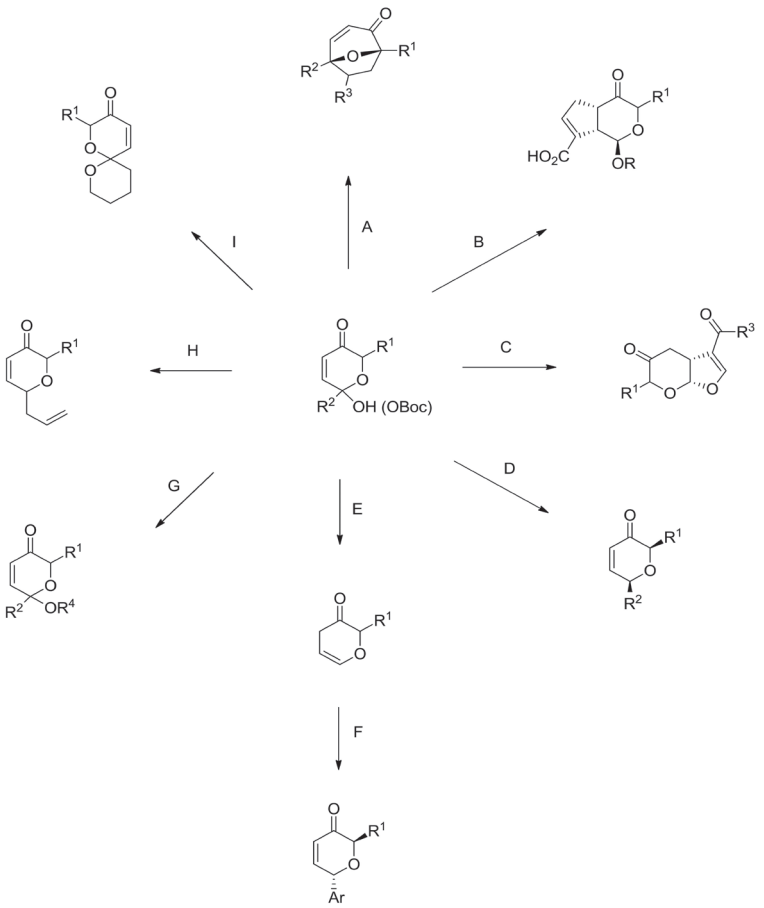
Double bond reactivity is rather typical, featuring formation of Michael products on exposition to carbanion precursors [63–65] (but also known in aza- and oxa-Michael versions), photochemically activated C-C bond formation in reaction with isopropanol, and Diels-Alder cycloadditions even with non-activated substrates like butadiene. Enulose esters can be selectively acylated under kinetically or thermodynamically controlled conditions. It can be also accomplished by N-heterocyclic carbene catalyzed dynamic kinetic resolution or organometallic enantiomeric scaffolds, which afford very efficient glycosyl donors for Pd (0) catalyzed reactions with alcohol, saccharide, or phenol acceptors [66–69]. It has been established that anomeric Boc (*t*-butylcarboxy) substituent is particularly useful for such glycosylations, in which configuration of the anomeric center is retained [52, 53]. With such a wide array of stereocontrolled glycosylation methods (occasionally called etherification) ARE synthons become easily manageable and competitive sugar precursors, applicable in syntheses of complex targets, instead of natural sugars pool, which involves inevitable multistep protection-deprotection sequences and typical difficulties at the glycosylation step. Use of enuloses as glycosyl donors offers wide opportunities for glycodiversification in medicinal chemistry, as demonstrated in preparation of new analogs of cardiac glycosides and antibiotic sugars [50, 51]. Potential of enuloses anomeric exchange is undoubtedly more extensive than O-glycosylation, as exemplified by facile C-arylation carried out on ARE product esters, with arylboronic acids [76]. Obviously, enuloses and their glycosides can undergo plethora of known 1,2- , 1,4- and 3,4 addition reactions, typical for conjugated enone sytems, like double bond saturation, ketone reduction, Michael addition, etc. [56, 65, 70]. In particular, attaining some feasibility of the 2,3-double bond relocation, via Wharton rearrangement or reductive transformation of 2,3-enulosides [70–72] makes more room for stereocontrolled anomeric center chemistry focusing on O- and C- glycosylations [73-78]. (Scheme 7) On the less obvious side of enulose reactivity array are dipolar cycloadditions, made useful through detailed insight in their mechanism and stereoselectivity. ARE products can be made into reagents for a variety of dipolar cycloadditions, facilitating formation of condensed ring systems. These include oxa-[3 + 2] and [5 + 2] cycloadditions [79–81], which pave way to condensed (fused) ring O-heterocyclic products. Transition from carbohydrate-related pyranoses to a large group of naturally occurring pyrans which are typically 2,6-alkylated, is now possible by application of Kishi reductive procedure [82], which applies hydrosilanes in the presence of Lewis acids for stereoselective removal of a hemiacetal hydrogen atom. (Scheme 7) Interestingly, pyranosenuloses can also undergo ring contraction under basic and thermal activation conditions, providing substituted cyclopentenes by a rearrangement resembling Piancatelli reaction of furylcarbinols. That ring contraction reaction found application in the synthesis of some simple antibiotic molecules, like terrein or pentenomycin [99, 100] and remains of potential interest for prostaglandin syntheses. Finally, ARE can be applied as a step in biomass conversion into platform commodity chemicals (like 5 or 6 carbon chain aliphatic alcohols, diols or triols) from furfural or 5-hydroxymethyl furfural – typical sugar dehydration products. In order to illustrate better the potential of ARE, we decided to supplement its short schematic characteristic of Schemes 6 and 7 by a selection of natural product targets, chosen from hundreds of recently published syntheses [83 – 100], (Scheme 8).

If only a single example of the ARE synthetic significance could be selected for presentation out of the large collection amassed in recent decades, a polycyclic marine toxin would

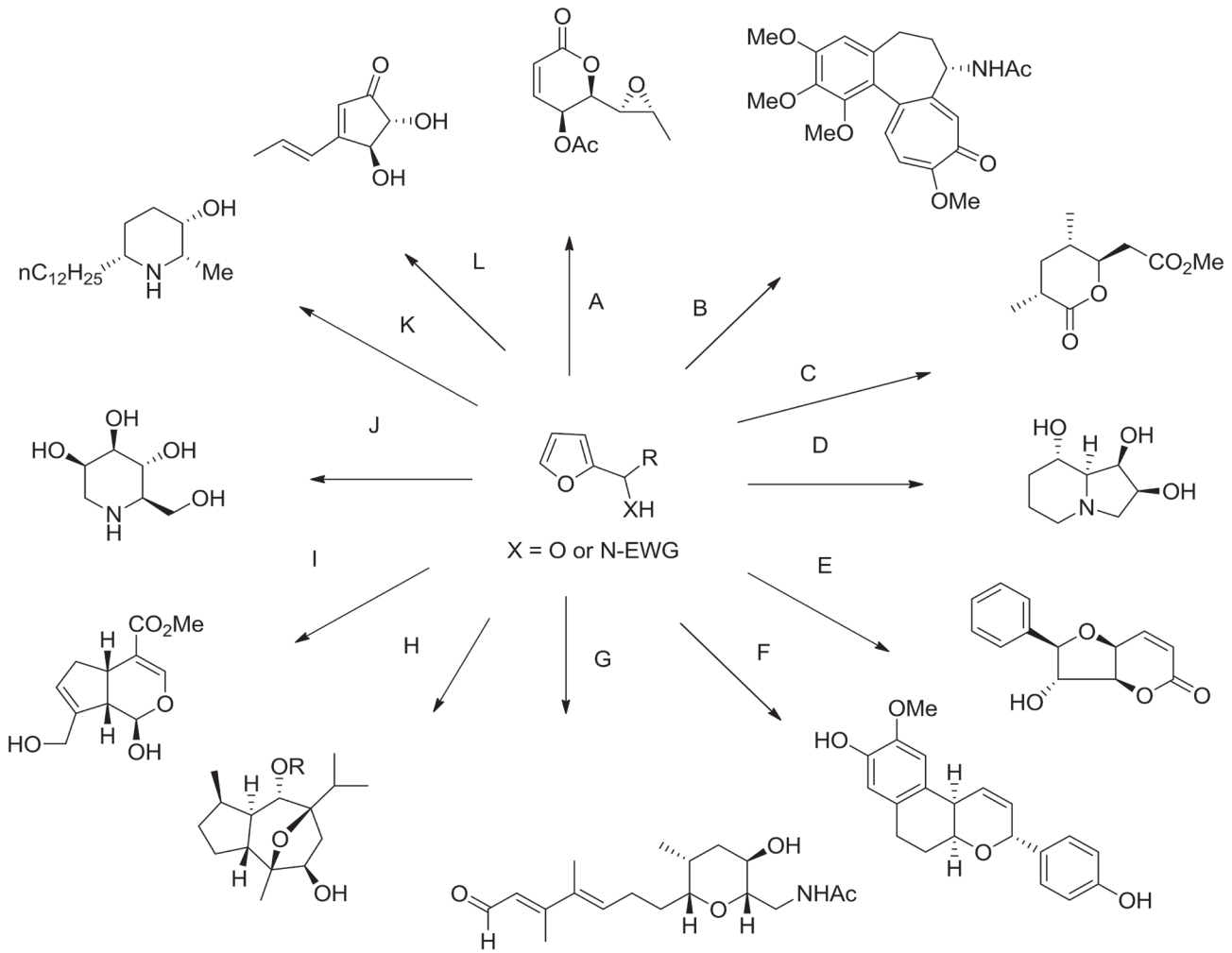
Scheme 6. Examples of the regio- and stereo- selective transformations of ARE hemiacetals, anomeric esters, and glycosides which add versatility to their synthetic potential (Refs. 60-78)



Scheme 7. Selected enulose transformations: A) 5 + 2 cycloaddition; B) 3 + 2 cycloaddition; C) oxa- 3 + 2 cycloaddition; D) Kishi reduction; E,F) for R^2 = H reductive elimination followed by Matsuda-Heck arylation; G) Pd catalyzed glycosylation; H) anomeric C-allylation; I) intramolecular bicycloketalization for R^2 = ω-hydroxybutyl. (Refs.: 65 and 73 – 82)



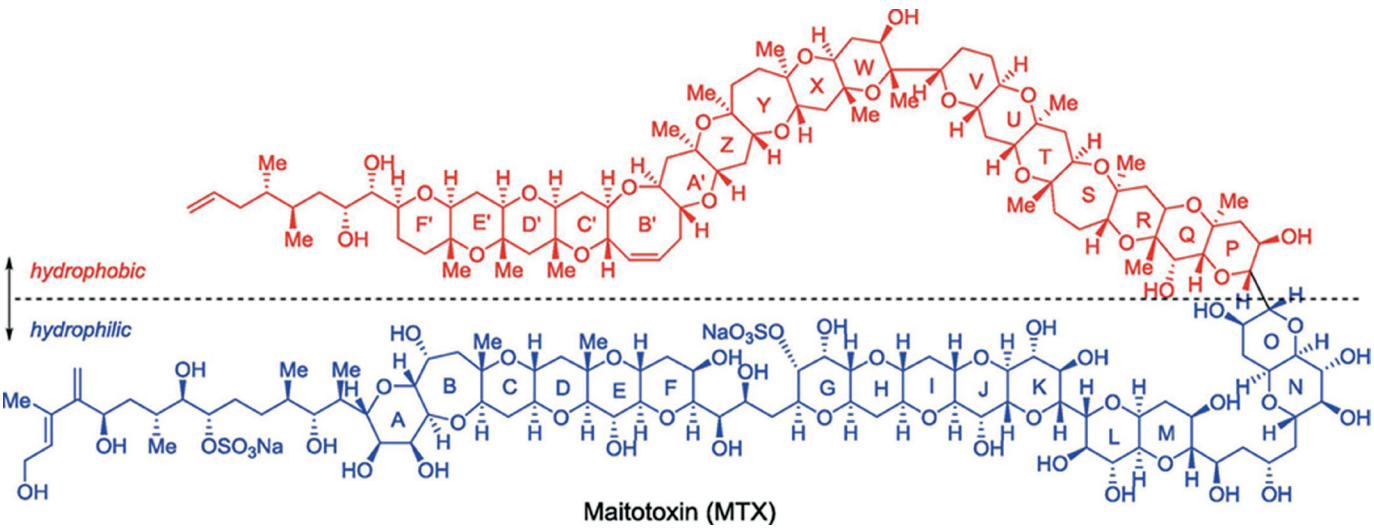
Scheme 8. Examples of the ARE synthetic targets prepared from furylcarbinols or corresponding amine derivatives. The 12 examples shown were selected from hundreds of ARE syntheses described in literature in the last few decades. A) asperlin [83,84]; B) colchicine [85]; C) Prelog-Djerassi lactone [86,87]; D) L-swainsonine [88]; E) isoaltholactone [89]; F) musellarin [90,91]; G) breviccamide [92]; H) engelrin [93,94]; I) genipin [95]; J) nojirimycin [96]; K) deoxycassine [97,98]; L) terrein [99,100].



have been a likely choice. It is because of their utmost structural and stereochemical complication, but also due to their value for medicinal chemistry and clinical pharmacology [101–102].

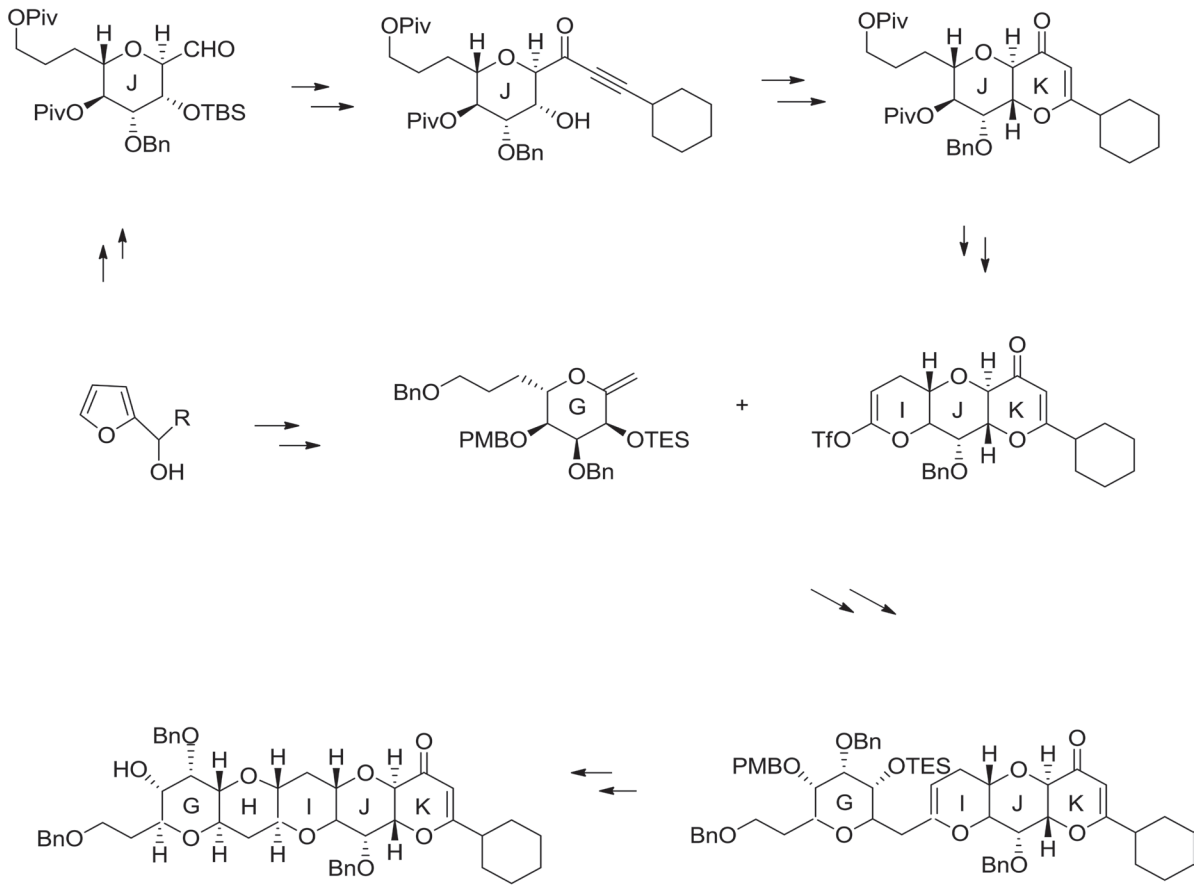
Maitotoxin (MTX), the most complex and the largest non-polymeric secondary metabolite compound ever isolated, is presented in form of 2D formula with graphical indicators of chiral

Scheme 9. Structural formula of maitotoxin



centers configuration. The toxin, isolated in minute amounts from dinoflagellate organism *Gambierdiscus toxicus*, has molecular formula $C_{164}H_{256}O_{68}S_2Na_2$, corresponding to the molecular weight of 3422 Daltons; its molecule is assembled in 32 rings system, which contains 98 chiral centers. Its toxicity against small rodents is phenomenal – LD_{50} ca. 50 ng/kg upon intraperitoneal injection and its connection with calcium channels conductivity is now well established. Availability of MTX and similar marine neurotoxins, responsible for occasional massive poisoning following sea food consumption is extremely low and the substance supply for necessary research depends critically on synthetic capability. It became apparent that elaboration of synthetic methods for preparation of polycyclic ethers of such complexity will involve new methodologies based on stepwise assembly of subunits, based on chiral pyran synthons. Modular approach to MTX polycyclic scaffolds, studied in leading academic organic synthetic centers met with spectacular success relatively recently [103]. Remarkably, an extensive application of ARE chemistry took place in early synthetic stages of several multicyclic MTX domains [104, 105]. An example of GHIJK domain was selected for presenting the key intermediate structures of the multistep synthesis (Scheme 10).

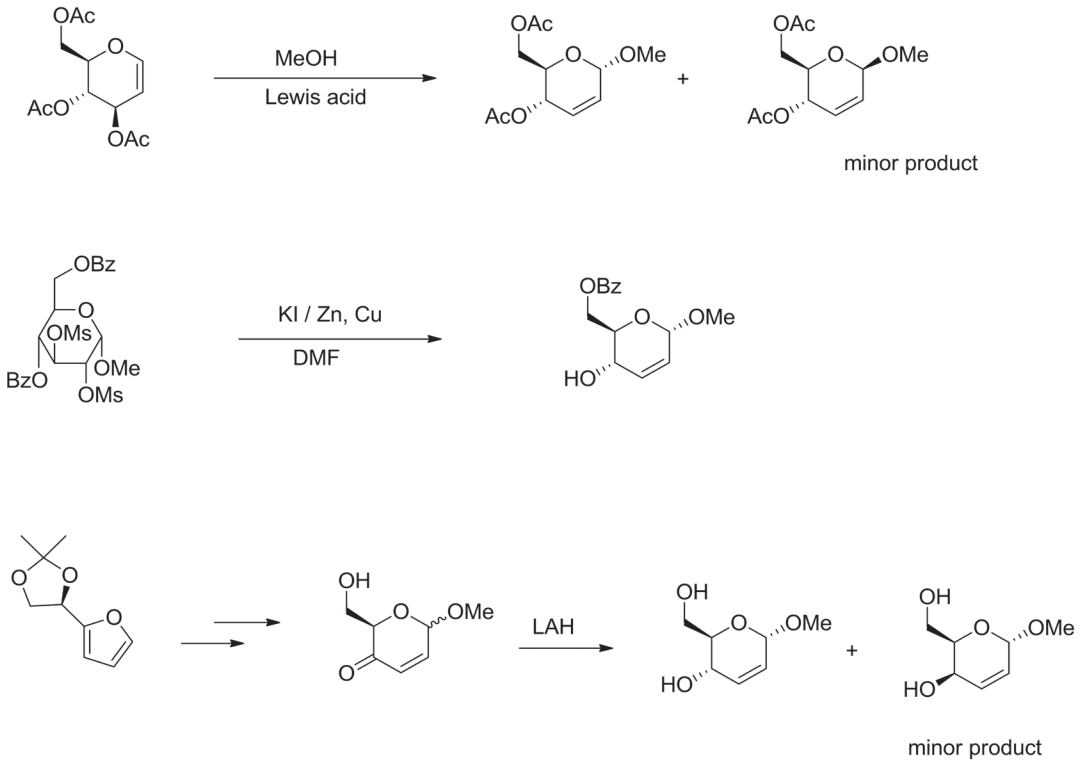
Scheme 10. The key steps in the assembly of GHIJK domain of maitotoxin with deployment of ARE.



Unsaturated sugars between chemistry and biology

Unprecedented advances in general chemical synthesis took place during 20th century. It is despite traditional divisions between relatively narrowly specialized and fragmented fields of interest, e.g. carbohydrate chemists exercised their craft a way apart from chemists interested in oxygen heterocyclic chemistry. The present common perception of organic chemistry as a toolbox for bioinformatics and systems biology, concentrates on effectiveness of synthesis as the way to deliver required compounds, with no reflection on historical distinctions, for which ARE can serve as an illustrious example. While recognized as an efficient method for preparation of multifunctional pyrans and pyranoses during 1970-ties, the rearrangement procedures have been constantly improved. Parallel to significant advancement in research on furan oxidation methods [11, 106], even **well established** ARE procedures [9, 16] are further modified in search for more green and user friendly conditions. Presently, even one pot sequential realization of the ARE initiated reactions under practically anhydrous conditions are achievable [107, 108]. In face of current availability of the ARE synthons and widespread knowledge of their versatility (Schemes 6, 7) it can be concluded that the rearrangement has already merged the mainstream unsaturated carbohydrate chemistry [109-116], once divided between "glycal chemistry" (two upper rows) and "furan chemistry" (lower row) as depicted on Scheme 11.

Scheme 11. Access to 2,3-unsaturated pyranosides from D-glucal triacetate, D-glucoside 2,3-methanosulphonyl-4,6-dibenzoate, and 2-furylethandiol-1,2 derivative. [110,111]



Currently, there is a rich selection of commercially available synthons and efficient methods for their desymmetrization and/or functionalization. Therefore, a judicious choice of planned synthetic pathway should be based on search of the literature of the subject, since even very similar (isomeric) starting materials may require radically different approach. For example, a useful bicyclic synthon, levoglucosenone, is easily obtainable by a single step pyrolysis of cellulose, 1–6 linked D-glucose polymer. The transformation of levoglucosenone to its regioisomer, isolevoglucosenone, requires several steps. However, isolevoglucosenone can be easily prepared from 2-furylethanediol with use of ARE, in two steps [58, 59, 117]. It has been demonstrated on numerous examples, that hex-2,3-enopyranoses obtained by ARE total synthetic procedures from furan substrates can serve as very convenient glycosylation reagents for preparation of oligosaccharides, such as glycons in cardiac glycosides [28,50,51], anthrax toxins [118] and antibiotic sugar moieties [119]. It is very important because corresponding native deoxy-pyranoses are practically unavailable from natural sources. There is already a trend to use these glycosylating synthons for medicinal compounds derivatization and glycodiversification, which is likely to spread to other groups of biologically active compounds [119]. Such translation is feasible because basic synthetic technologies such as enantioselective functionalization of olefins [120], dynamic kinetic transformation of lactols [67, 121] and assorted methods of stereoselective catalytic glycosylations [77, 78] are already in place, and ready to be supported by complementary biocatalytic methods [15–18].

Conclusion

Achmatowicz (and aza-Achmatowicz) rearrangement (ARE) [7], which functions in chemical literature as a name reaction since 1986 [122], was originally described as a general approach to the selective, stepwise synthesis of monosaccharides from simple furan derivatives [8]. Its initial application to preparation of rare sugars, like deoxy and unsaturated pyranoses, as well as racemic and/or D- and L-sugars and their derivatives, were gradually extended to wide selection of pyran and piperidine based natural products and their mimics [47, 56, 57]. The key issue of the total synthetic approach to natural products – chirality control – has been in case of ARE successfully addressed either by an enantioselective chemical catalysis, or biocatalysis [18, 57]. This methodological versatility proven on hundreds of experimental examples, installed ARE as a reliable, validated tool for accessing a variety of oxygen and nitrogen heterocyclic synthetic targets. Particularly strong connection of ARE derived 2, 3-unsaturated pyranoses to biologically active natural products and medicinal chemistry of carbohydrate conjugates has been well documented [47, 57]. Remarkably, ARE which has been continuously improved as far as oxygen delivery and energy transfer for its basic molecular transformation is concerned, fits well into the current trend of postulated transition in synthesis towards green circular chemistry. Thus, after half a century from its commencement, ARE appears to be an active methodological set of validated utility. Evidently, ARE appears to be more than a historical episode since the methodology

goes beyond successful application to challenges of recent decades, and can be easily accommodated to the industry 4.0requirements. In particular, the idea of bio-feedstock as a raw material for furan derived platform chemicals, can adapt ARE as one of the key selective process operations.

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