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Achmatowicz Reaction and its Application in the Syntheses of Bioactive Molecules

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Abstract

Substituted pyranones and tetrahydropyrans are structural subunits of many bioactive natural products. Considerable efforts are devoted toward the chemical synthesis of these natural products due to their therapeutic potential as well as low natural abundance. These embedded pyranones and tetrahydropyran structural motifs have been the subject of synthetic interest over the years. While there are methods available for the syntheses of these subunits, there are issues related to regio and stereochemical outcomes, as well as versatility and compatibility of reaction conditions and functional group tolerance. The Achmatowicz reaction, an oxidative ring enlargement of furyl alcohol, was developed in the 1970s. The reaction provides a unique entry to a variety of pyranone derivatives from functionalized furanyl alcohols. These pyranones provide convenient access to substituted tetrahydropyran derivatives. This review outlines general approaches to the synthesis of tetrahydropyrans, covering general mechanistic aspects of the Achmatowicz reaction or rearrangement with an overview of the reagents utilized for the Achmatowicz reaction. The review then focuses on the synthesis of functionalized tetrahydropyrans and pyranones and their applications in the synthesis of natural products and medicinal agents.

Introduction

Functionalized tetrahydropyrans are subunits of numerous biologically active natural products and medicinal agents.[1-5] Over the years, numerous methods have been developed to efficiently construct these heterocyclic templates. To date, general approaches for the synthesis of substituted tetrahydropyrans include the Prins and related cyclizations, the hetero-Diels-Alder reaction, ring-closing olefin metathesis, oxa-Michael reaction, and radical cyclization. Despite the availability of a wide range of methods for the synthesis of substituted tetrahydropyran derivatives, there are limitations with respect to substrate scope, reliability and availability of starting materials. Furfural and furan derivatives are readily available from agricultural byproducts, mainly corncobs, wheat bran, and oats. Furan derivatives can also be prepared from mono- and polysaccharides as well. Therefore, transformation of furan derivatives into functionalized pyranones and tetrahydropyrans holds great promise in organic synthesis.

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The Achmatowicz reaction converts furfuryl alcohols into substituted dihydropyranone acetals (also identified as pyranuloses), which are otherwise poorly accessible, through an oxidative rearrangement process.[6] This reaction exploits furan-2-yl carbinols as substrates, which undergo oxidative ring expansion to smoothly provide 6-hydroxy-2*H*-pyran-2(3*H*)-ones (Figure 1).[7] The reaction was initially employed in the conversion of dihydropyranones to methylglycosides and carbohydrates. Subsequently, this oxidative ring expansion strategy was further developed into a synthetically valuable transformation, particularly for the preparation of functionalized pyranones and substituted tetrahydropyrans. The Achmatowicz reaction can incorporate two chiral centers. Many asymmetric Achmatowicz reaction variants have also been developed. This has provided access to pyranones and tetrahydropyrans diastereoselectively and in optically active form. These heterocyclic templates have been extensively utilized in the synthesis of bioactive natural products, carbohydrates, and medicinal agents. Also, the Achmatowicz variant for the construction of piperidone derivatives starting from furan-2-yl amines, namely, the aza- Achmatowicz reaction (Figure 1) was accomplished. The potential of Achmatowicz-type reactions, however, has not been fully exploited in synthesis. A recent review by Deska and co-workers outlines various chemical methodologies for oxidative ring expansion.[7] Another review by Rutjes and co-workers details an aza-Achmatowicz reaction leading to the synthesis of functionalized piperidones.[8]

In this review, we briefly highlight the key methods available for tetrahydropyran synthesis. We will then provide various effective strategies including asymmetric technologies to construct pyranone and tetrahydropyran templates and their further elaboration to the synthesis of bioactive natural products. In this context, the key Achmatowicz reaction is highlighted in the retrosynthetic analysis of the target molecules. The review provides a broad picture of principles, strategies and useful applications of functionalized pryanones and tetrahydropyran derivatives prepared from readily available furans and furfurals.

1. General approaches to the synthesis of substituted pyranones and functionalized tetrahydropyrans

Frequent occurrence of tetrahydropyran structural features prompted the development of a variety of stereoselective methodologies over the years.[9] The scope and limitation of these methods vary widely. In this section, we briefly outline general methods for the synthesis of these substructures. These selected methodologies are relevant to the construction of tetrahydropyran ring in the context of Achmatowicz reaction. For convenience, as shown in Figure 2, these methods are categorized according to the retrosynthetic disconnection of the pyran ring. There are namely, (a) C2-C3 disconnections; (b) O1-C2 disconnections; (c) C3-C4 disconnections; and (d) O1-C6 and C2-C3 disconnections.

1.1 Tetrahydropyran ring through C2-C3 disconnection—Among various strategies for the construction of tetrahydropyran rings, C2-C3 bond formation is common, efficient, and provides the THP ring in a stereopredictable manner. This particular strategy covers three well known reactions, Prins Reaction/Cyclization (Scheme 1), Petasis-Ferrier rearrangements (Scheme 2), and Panek annulation (Scheme 3). In general, all the three strategies presented involve the generation of an oxo-carbenium ion followed by an attack by

a C3 nucleophile in an intramolecular fashion. In particular, in Prins cyclizations and Panek annulations, the C2-C3 disconnection is based on the Lewis acid-mediated oxocarbenium ion formation (Schemes 1 and 3). In the Petasis–Ferrier rearrangements, the oxygen linked to C4 coordinates to the Lewis acid to open the acetal, thus simultaneously generating an oxocarbenium ion and an enolate (Scheme 2).

The Prins cyclization is used in the generation of 2,6-*cis* tetrahydropyran systems. Similarly, Petasis–Ferrier rearrangement offers access to 2,6-*cis* tetrahydropyran rings, with the further benefit of the C4 ketone functionality to be exploited for additional structural modification. Panek annulation nicely complements these two methods allowing access to either 2,6-*cis* or 2,6-*trans* dihydropyran rings based upon the choice of appropriate substrate. The resulting dihydropyran products could be then converted to functionalized tetrahydropyran derivatives through simple reduction or through further manipulation of the alkene functionality.

1.1.1 Prins Reaction: The Prins Reaction is a Lewis acid-promoted condensation between an aldehyde (**1**) and a homoallyl alcohol (Scheme 1). This reaction has emerged as a reliable method for the synthesis of substituted tetrahydropyran derivatives.[10] The reaction proceeds through the key oxocarbenium intermediate **5**, which is generated from hemiacetals (**3**, **4**). Subsequently, a 6-endocyclization provides a secondary carbocation (**6**), which is trapped by a nucleophile to form substituted tetrahydropyran **7**. In this case, ring closure proceeds through a chair transition state and the stereochemical outcome at C4 is driven by the nature of the nucleophilic trapping agent, which is generally a Lewis acid counterion. This reaction holds great potential for the construction of substituted tetrahydropyrans with the introduction of a number of new stereocenters in optically active form. However, the major drawback has been racemization attributed to the two competing oxonia-Cope rearrangements of the oxocarbenium ion intermediate. To overcome these issues and preserve optical purity of Prins products, a series of modified conditions were developed. Rychnovosky and co-workers demonstrated that the use of $SnBr_4$ greatly suppresses the competing oxonia-Cope pathways, as cyclizations prompted by $SnBr_4$ are considerably faster than BF_3-OEt_2/AcOH-promoted reaction.[11] The Prins cyclization has been employed as a key reaction in the syntheses of numerous biologically active natural products.[12-17]

1.1.2 Petasis-Ferrier rearrangement: Petasis-Ferrier union/rearrangement was developed for the synthesis of 2,6-*cis*-tetrahydropyran-4-ones. The synthesis involves two independent methods, Ferrier-rearrangement[18, 19] and Petasis-type reactions.[20] The reaction encompasses the condensation[21] of a chiral bis-silylated β-hydroxy acid (Scheme 2) with an aldehyde (**9**) to provide a dioxanone (**10**). Carbonyl olefination employing Cp_2TiMe_2[22, 23] followed by Lewis-acid (LA) promoted rearrangement of the resulting enol acetal (**11**) provides the 2,6-*cis*-disubstituted tetrahydropyran-4-one (**13**). As shown, the reaction proceeds through an endo attack onto the oxocarbenium intermediate (**12**). The use of iBu$_3$Al leads to reduction to the alcohol, whereas Me_2AlCl affords the ketone.

Smith and co-workers demonstrated the utility of this reaction in the total syntheses of natural product, such as (+)-Phorboxazole A,[24, 25] (+)-Zampanolide,[26-28] and (+)-Spongistatin.[29] However, the effectiveness of this tetrahydropyran synthesis is limited due to

incompatibility of the reaction conditions with acid-sensitive functionalities present on the substrate molecule.

1.1.3. Panek [4+2] annulation: Panek annulation is mediated by a Brønsted or a Lewis acid of an aldehyde (Scheme 3) with a *syn*-allylsilane (**14**) leading to the formation of a dihydropyran ring (**16**).[30, 31] The reaction displays high diastereoselectivity showing the relative configuration (2,6-*cis* or 2,6-*trans*), strongly dependent on the nature of the R_2 substituent. Panek and collaborators also proposed a stereoselective annulation employing *anti*-allylsilanes to provide *cis*-dihydropyran rings.[32]

1.2 Synthesis of tetrahydropyran rings through O1-C2 disconnection

1.2.1. Nucleophilic substitution cyclizations: The simplest strategy leading to tetrahydropyrans by O1-C2 bond formation is represented by cyclization based on nucleophilic substitution.[9] A variety of methods for the stereoselective formation of secondary alcohols allows effective preparation of the appropriate hydroxyl nucleophile and also of the leaving groups (LG), which often derive from chiral alcohols. The general strategies are shown in Scheme 4. The 6-*exo*-*tet* cyclization proceeds with inversion at the electrophilic carbon center according to Williamson reaction mechanism.[33] Therefore, both the *2,6-trans* (**18**) or the *2,6-cis* (**20**) stereochemical outcome for the reaction is manageable taking into account the configuration of the reactive center (Scheme 4, top). The rate of reactivity towards nucleophilic substitution is primary > secondary > tertiary. Contrary to SN2, the SN1 processes encompass the formation of stabilized allylic or benzylic carbocations (**22**) for nucleophilic trapping center (Scheme 4, bottom). Therefore, the stereochemical outcome of the reaction depends upon the nature of the stereogenic centers on the substrate and the experimental conditions employed.[9]

1.2.2 Nucleophilic substitution cyclizations by epoxide ring opening: A regio- and stereoselective synthesis of six-membered oxygenated heterocycles was reported by Nicolaou and co-workers using a Brønsted or Lewis acid-catalyzed cyclization of hydroxy epoxides.[34, 35] This methodology has been utilized for stereoselective formation of tetrahydropyrans especially in the context of natural product synthesis.[36, 37] As shown in Scheme 5, trans-γ-hydroxy epoxides bearing an alkene (**24**) affords the corresponding tetrahydropyran (**26**). The reaction favors *6-endo* over *5-exo*-cyclization with high selectivity.[31] The main advantage of the epoxide ring opening reaction is the predictable stereochemical outcome. Since the reaction mechanism involves an SN2 displacement, either 2,6-*cis* or 2,6-*trans*-tetrahydropyrans can be selectively obtained. Several stereoselective epoxidation methods provide versatility of this method. Furthermore, there are possibilities to form polycyclic chemical templates by an iterative process using this method.[9] The methodology, however, usually requires a high level of substrate design and takes a variety of steps within the synthetic path toward complex natural products.

1.2.3 Conjugate addition: Conjugate addition has been extensively utilized in the construction of tetrahydropyran rings.[38] The methodology involves an intramolecular nucleophilic attack by a hydroxyl group on the electron-deficient β-carbon of an α,β-unsaturated carbonyl system (**27**) through an *exo* (or *endo*) ring closure, leading to the

formation of the corresponding tetrahydropyran (Scheme 6). Cyclization can be performed under Brønsted basic or acidic conditions. The formation of a 2,6-*trans* tetrahydropyran (**29**) is kinetically favoured under basic conditions (low temperatures and short reaction times), while the 2,6-*cis*-product (**28**) is thermodynamically favored (higher temperatures and longer reaction times). Under acidic conditions, the transition state leads to the thermodynamic 2,6-*cis*-disubstituted tetrahydropyran derivative instead of the kinetically favoured *trans*-product based on a frontier molecular orbital (FMO) prediction.[9]

1.2.4 Alkene-mediated cyclizations: Transition metal-mediated strategies for electrophile-activated alkene additions have received considerable attention over years for tetrahydropyran synthesis.[39-41] Typically, tetrahydropyran rings are formed by a *6-exo-trig* cyclization of δ-hydroxy alkenes (**30**) in the presence of an appropriate metal salt (ML_n),[9] providing the corresponding tetrahydropyrans with high stereoselectivity (Scheme 7). A general mechanism of the reaction involves the intramolecular attack of an oxygen nucleophile on an activated olefin catalyzed by a metal.

The stereochemical outcome of the cyclization is driven by the nucleophilic attack occurring on the face opposite to the electrophilic π-complexation (Scheme 7). Therefore, the facial selection of the alkene can be controlled through appropriate coordination of the chiral directing group or by a chiral metal reagent/catalyst. Both stoichiometric and catalytic methods for metal-based alkene additions leading to tetrahydropyrans have been developed. Stoichiometric processes commonly include the employment of mercury(II) salts. Iodo and seleno salts have also been used for the synthesis of tetrahydropyran derivatives. The extent of an intramolecular oxymercuration reaction is driven by the stability of the cationic intermediates. The stereochemical outcome is controlled by the substrate usually leading to the thermodynamically more stable tetrahydropyran product. Among the many mercury reagents employed, mercury acetate is most frequently used. However, lack of a high level of diastereoselectivity is a common issue.[42, 43] Catalytic processes generally involve palladium complexes,[44] although other transition metals, such as Pt,[39] Ag,[41] Sn,[40] and Ce, are increasingly gaining importance.[45] The oxidation state of Pd drives the catalyst reactivity. Accordingly, Pd(0) complexes are nucleophilic and participate in the reaction through π-allyl cation intermediates. On the other hand, Pd(II) complexes display an electrophilic tendency and lead to the formation of reversible π-complexes.[9]

1.3 Methodologies encompassing C3–C4 disconnection

1.3.1 Class 1 and Class 2 ring-closing metathesis: Ring-closing metathesis (RCM) represents a powerful method for carbon–carbon bond formation often employed in organic synthesis.[46, 47] Numerous substituted tetrahydropyran rings have been constructed using this methodology.[48] In particular, syntheses through C3–C4 ring closure are more common than through C2–C3 bond ring closure.[49] RCM processes have several advantages for the synthesis of tetrahydrofuran substructures. The reactions are done under mild conditions, show good functional group compatibility, and maintain full stereochemical integrity. RCM reactions can be subdivided in two main classes, namely Class 1 and Class 2 (Scheme 8). Class 1 involves the ring closure of an ether bearing allylic and homoallylic functionalities (**35**) to provide 3,4-dihydropyrans (**36**), followed by reduction to the corresponding

tetrahydropyrans (**37**). Class 2 reactions involve the cyclization of homoallylic acrylate substrates (**38**) to furnish unsaturated lactones (**39**), which by a successive reductive acetylation/alkylation protocol can be effectively functionalized to tetrahydropyrans (**37**).[9, 50, 51] Either the first-generation Grubbs catalyst (G-I) or the second-generation Grubbs catalyst (G-II) have been employed for these reactions.

In Class 1 RCM, the acyclic stereochemistry of the R_1 and R_2 substituents determines the formation of either 2,6-*cis*- or 2,6-*trans*-dihydropyran derivatives.[52] In Class 2 RCM, the dihydropyranone is converted to either 2,6-*cis*- or 2,6-*trans*-derivatives by stereoselective processes.

1.4 Methodologies encompassing O1–C6 and C2–C3 disconnection

1.4.1. Hetero-Diels–Alder reaction: The Diels–Alder (DA) reaction represents a valuable method for the stereoselective formation of highly functionalized six-membered rings. This reaction has been widely employed for the synthesis of six-membered nitrogen and oxygen heterocycles. The hetero- Diels–Alder (HDA) reaction usually proceeds with high regio- and diastereoselectivity and with good yields.[53] The tetrahydropyran ring can be assembled by bond formation at O1–C6 and C2–C3 followed by reduction of the resulting double bond. This reaction proceeds with the formation of two σ bonds and could potentially generate up to three new chiral centers in a single step with a high degree of stereochemical control.

There are two main approaches for stereocontrolled HDA applied to tetrahydropyran synthesis. The first approach involves the use of a chiral auxiliary to direct π-facial selectivity. This reaction generally proceeds through an endo transition state to give 2,6-*cis*-cycloadducts. The second approach exploits the coordination of a chiral Lewis acid to activate the aldehyde or ketone carbonyl while directing the approach of the diene to one face of the carbonyl dienophile.

In particular, Danishefsky and collaborators used unactivated aldehyde heterodienophiles in the presence of Lewis acid catalysts.[54] The mechanism of the initial Lewis acid catalyzed coupling of aldehyde (**41**) with activated diene (**40**) would lead to the formation of dihydropyran ring (**42**) through either the Mukaiyama–aldol pathway or the Diels-Alder pathway (Scheme 9).[55] Several chiral catalysts have been developed for the asymmetric HDA reaction with chiral Cr(III) complexes.[56] The HDA reactions with less nucleophilic dienes also provide good enantioselectivity.[57]

2. The Achmatowicz reaction

2.1 Mechanistic insights and evolution of Achmatowicz reaction—Historically, Clauson-Kaas and co-workers converted furan derivatives to 2,5-dialkoxy-2,5-dihydrofurans in the presence of bromine and methanol as a solvent (Figure 3).[58-60] Conversion of these 2,5-dihydrofurans to substituted pyranones was reported in the late 1960s and early 1970s independently by Cavill and co-workers and Achmatowicz and co-workers in the context of the synthesis of juvenile hormones and synthesis of carbohydrates.[6, 60-62] For the synthesis of their dihydropyranone intermediates, Cavill and co-workers employed an oxidative condition utilizing bromine followed by exposure to dilute hydrochloric acid (Figure 3).

Achmatowicz and co-workers converted furans to dihydropyranones by similar oxidative and hydrolytic conditions (Figure 3).[62, 63] The Achmatowicz reaction essentially represents an oxidative cleavage of a furan ring followed by an intramolecular cyclization, providing 6-hydroxy-2*H*-pyran-2(3*H*)-ones in mild conditions (Figure 1).[64] Oxidative ring expansion of furfuryl amines is known as the aza-Achmatowicz reaction (Figure 1), and provides substituted dihydropyridinones. This process can afford functionalized piperidines and their derivatives.[65-67]

Due to numerous applications, the potential of the Achmatowicz reaction was recognized and subsequently many variants of the original procedure were developed. These include broadening of substrate scope and expanded use of oxidizing agents to improve the overall efficiency of the reaction.[65, 68-75] Several reagents are widely used for the oxidative step. The most usual oxidants employed have been Br_2/MeOH[76, 77] and NBS/water.[78-82] The reaction pathway is shown in Scheme 10. When furfuryl alcohol derivatives (**43**) are reacted with methanolic bromine or NBS, bromonium ion (**44**) forms and the cyclic intermediate is subsequently opened by methanol to provide a *cis/trans*-mixture of the relatively stable and isolable acetals (**46**) through the intermediate of bromoacetal (**45**). Their subsequent acidic hydrolysis provides the *cis*-dicarbonyl alcohols (**47**), which immediately rearranges/cyclizes into the corresponding hydroxy pyranones **48** upon ring-closure.[8]

In addition to the classical methodologies, a series of variations of the Achmatowicz reaction have been developed that employ photochemical approaches as well as protocols involving metal- and biocatalysis. Moreover, the scope and diversity of the Achmatowicz reaction products have been broadened, particularly substituents on the furan-2-yl carbinols or their derivatives.[83-85] The asymmetric Achmatowicz reaction is achieved in a number of ways: (i) formation of the starting material via enantioselective hydrogenation or alkylation of the parent carbonyl substituted furan; (ii) chiral resolution of the starting material; or (iii) application of enantioselective oxidation conditions such as the Sharpless epoxidation or dihydroxylation.[79, 86-90] The most common and recently developed methodologies for Achmatowicz-like reactions are outlined in Scheme 11. Weeks and co-workers reported a variant of the Achmatowicz reaction employing one equivalent of bromine in a water–tetrahydrofuran mixture as the solvent. This condition oxidized 1-furylethanol and provided the Achmatowicz reaction product in 17% yield. Interestingly, an excess of halogenating agent gave maltol at elevated temperature.[91] Jurczak and co-workers developed a variation of this protocol utilizing acetonitrile or aqueous acetone as the reaction medium.[92] Martin and co-workers later exploited this procedure for the stereoselective construction of linear polyketide fragments.[93, 94] Georgiadis and co-workers reported a user-friendly procedure using *N*-bromosuccinimide (NBS) in aqueous tetrahydrofuran at 0 °C.[95]

Honda and co-workers adapted the NBS protocol in the synthesis of steroid natural products and their analogues.[96-98] This protocol was also further utilized in stereoselective construction of highly substituted acyclic side-chains in castasterone.[99] The combination of NBS in aqueous THF with inorganic bases such as sodium acetate or sodium bicarbonate was used in order to buffer hydrogen bromide formed during the reaction.[100-103] This protocol was employed in the synthesis of pyranone substructures[69] and in the total synthesis of natural products.[104-107] The issues related to the use of bromine and poor water

solubility of pyran-3-ones, prompted the development of new non-bromine-based oxidizing agents such as *m*-CPBA in a variety of solvents.[108-113] This alternative furylcarbinol ring expansion was nicely employed in natural product total syntheses.[114-117]

The Lefebvre protocol with *m*-CPBA involves epoxidation on furfuryl alcohol derivatives (**43**) rather than bromination. The resulting epoxyalcohol intermediate **49** opens to provide the keto aldehyde intermediate **47** which then converted to pyranones **48** similar to the reaction with bromine (Scheme 12).[8] In this context, dimethyldioxirane was also used as a useful alternative to *m*-CPBA for Achmatowicz reaction.[118]

Beyond bromination and epoxidation, other alternative procedures employing inorganic oxidizing agents have been described. Piancatelli and co-workers developed chromium(VI)-based reagents for Achmatowicz reaction-based ring expansion. Treatment of 5-methylfurfuryl alcohol with pyridinium chlorochromate (PCC) provided desired pyranones in high yield (Scheme 11).[119] Sodium chlorite was employed as an oxidant for Achmatowicz reaction.[120] In particular, Oishi and co-workers reported a combination of sodium chlorite and 2-methylbut-2-ene in the synthesis of fragments of the polyether toxin yessotoxin.[121] Hypervalent iodine was also developed as a useful alternative for the radical-based methodologies. Piancatelli and co-workers reported the use of iodobenzenediacetate (IBDA) in aqueous media, which led to the formation of unstable hemiacetals and resulted in ring expansion in the presence of neighboring nucleophilic groups.[122-126] In particular, treatment of furfuryl alcohols with IBDA and magnesium perchlorate in aqueous acetonitrile resulted in smooth oxidative ring expansion (Scheme 11).[127]

2.2 Metal-catalysed, photolytic and eco-friendly Achmatowicz reaction variants—The metal-catalysed Achmatowicz reaction represents an important variant of the original procedure. The Sharpless epoxidation protocols were utilized for the transformation of the α-furylcarbinols. Ho and co-workers employed a combination of *tert*-butyl hydroperoxide (*t*-BuOOH) with vanadyl acetylacetonate $VO(acac)_2$ for the synthesis of 6-hydroxypyranones (Scheme 13).[128] This methodology has been successfully exploited for the total synthesis of highly complex compounds.[89, 129-131]

The use of tartrate-modified titanium alkoxides instead of $VO(acac)_2$ in the presence of *t*-BuOOH led to enantioselective oxidative furan cleavage, and this protocol was utilized in the synthesis of pyranicin.[90] The employment of heterogeneous catalysis for Achmatowicz-like reactions was developed by Jacobs and co-workers. In particular, hydrogen peroxide activation was achieved by means of the titanium silicalite 1 (TS-1).[132] The photolytic oxygenations have been employed for the Achmatowicz reaction. In particular, visible-light irradiation in the presence of organic dyes led to the [4+2] cycloaddition of singlet oxygen with the formation of secondary ozonide intermediates.[133] Pyranone compounds were obtained under reductive quenching with dimethyl sulfide or triphenylphosphine.[134, 135] The singlet-oxygen induced Achmatowicz reaction was further developed and exploited as a versatile synthetic protocol.[136, 137] The oxidative furan cleavages are characteristic in the biosynthesis of many natural compounds. In particular, the heme-dependent cytochrome P450 proteins are involved in epoxidation reactions.[138-141] Recently, Deska and co-workers reported the use of a chloroperoxidase in combination with glucose oxidase, providing

hydrogen peroxide from atmospheric oxygen, towards the oxidative rearrangement of a variety of furfuryl alcohols.[142] Also, the first enzymatic Achmatowicz reaction using laccase and aerial oxygen was published as an eco-friendly alternative.[75]

Recently, Tong and co-workers developed an interesting procedure.[143] To overcome the generation of side products, such as succinimide (in the case of using NBS) and *m*-chlorobenzoic acid (in the case of using *m*-CPBA), these authors exploited the inexpensive, non-toxic, stable and environmentally friendly Oxone with an inorganic halide salt (such as KBr) to work as the catalyst (Scheme 13). It was hypothesized that the oxidation of the inorganic halide salt by Oxone would lead to the formation of a transient brominating agent which can induce the Achmatowicz reaction in the same way of bromine and NBS. This methodology allows the access to highly functionalized dihydropyranones without organic waste and chromatographic purification.

2.3 Overview of the general application of Achmatowicz reaction products— The Achmatowicz reaction has found wide application, particularly in the Targeted Oriented Synthesis (TOS) of natural products, where the pyranone acetals derived from the Achmatowicz reaction have been utilized as building blocks to build substituted tetrahydropyrans, spiroketals, and oxa-bridged bicycles (Scheme 14). In particular, the development of highly effective methods for transforming the Achmatowicz reaction products, namely the resulting functionalized dihydropyranone acetals, has provided the possibility of accessing a wide variety of key pyran-based substructures. These include Kishi reduction,[144] Feringa-O'Doherty O-glycosylation,[81, 145, 146] [5+2] cycloaddition,[147, 148] and more recently, spyroketalization,[114] reductive ring expansion,[149] and *trans*-selective arylation.[150] These are among the most common transformations applied to the Achmatowicz reaction products. The Achmatowicz reaction coupled with these reactions provides convenient routes for the preparation of complex molecular architectures of several natural products and their unnatural congeners, oligosaccharides and for the synthesis of skeletally diverse compounds for medicinal chemistry applications. Nevertheless, the potential synthetic utility of the Achmatowicz reaction and its densely functionalized dihydropyranone products appear to remain underdeveloped and underestimated. In the next paragraphs, a detailed overview of the application of the Achmatowicz reaction in the field of the total synthesis of naturally occurring compounds and for the preparation of pyran-based chemical templates will be provided.

3. Achmatowicz reaction in the synthesis of natural compounds

3.1 Synthesis of (+)-Herboxidiene/GEX1A and Spliceostatin A—Herboxidiene (**50**, Scheme 15) was isolated from *Streptomyces chromofuscus* in 1992. It displayed potent and selective phytotoxicity against a myriad of broad leaf weeds over coplanted wheat.[151] In 2002, Yoshida isolated six structurally related compounds, among them GEX1A.[152, 153] GEX1A was identified as herboxidiene (**50**). It showed reduction of plasma cholesterol levels by up-regulating the gene expression of low-density lipoprotein receptors.[154] Furthermore, it promoted G1 and G2/M cell cycle arrest in a human normal fibroblast cell line, WI-38. A total synthesis of (+)-herboxidiene employing the Achmatowicz reaction was reported by Ghosh and Li.[118] The retrosynthesis of (+)-herboxidiene (**50**) is shown in

Scheme 15.[155] A Suzuki cross-coupling was envisioned to link the vinyl iodide **51** and boronate **52** at a late stage of the synthetic path. The functionalized tetrahydropyran fragment **51** was planned from furfural derivative **53** via an Achmatowicz reaction followed by reduction of the resulting hemiketal.

As shown, aldehyde **53** was treated with allylmagnesium bromide and then subjected to lipase resolution to provide optically active alcohol **54** (Scheme 16). Achmatowicz reaction of alcohol **54** with *t*-BuOOH in the presence of a catalytic amount of $VO(acac)_2$ afforded the rearranged hemiketal. Kishi reduction of the resulting hemiketal with trifluoroacetic acid and triethylsilane provided enone **55**. Enone **55** was further functionalized to a suitable tetrahydrofuran derivative. Selective ozonolysis of the terminal olefin of **55** and oxidation of the resulting aldehyde with $NaClO_2$ led to the corresponding acid which was then converted into its methyl ester **56**. Reduction of **56** with $NaBH_4$ in the presence of $CeCl_3{\cdot}7H_2O$ followed by cyclopropanation furnished cyclopropane derivative **57** as a single diastereomer.[156] Compound **57** was then subjected to Barton's deoxygenation reaction to open the cyclopropane ring and provide the corresponding methyl group (**58**).[157] It was then converted to vinyl iodide **51**.

Achmatowicz reaction was also employed by Ghosh and Chen in the synthesis of FR901464 (**59**) and Spliceostatin A (**60**, Scheme 17).[130] Both natural products are very potent inhibitors of spliceosome. FR901464 was isolated from the fermentation broth of *Pseudomonas sp*. No. 2663 and exhibited remarkable antitumor activity.[158] A more stable methylated derivative of FR901464, named spliceostatin A (**60**), retained similar potent antitumor activity as FR901464.[159-162] Both FR901464 and spliceostatin A effectively inhibited *in vitro* splicing and promoted pre-mRNA accumulation by binding to SF3b, a ribonuclear protein in the spliceosome.[160] The retrosynthetic analysis shows the use of cross-metathesis to couple the epoxy alcohol segment **61** and the amide segment **62** at a late stage of the synthesis (Scheme 17). The functionalized pyranone ring (synthon **63**) could be obtained from furan derivative **64** using an Achmatowicz reaction as the key step.

Synthesis of the key dihydropyranone ring fragment **63** is shown in Scheme 18. Enantioselective reduction of commercially available acetyl furan **65** with (*S*)-2-Me-CBS and borane dimethylsulfide led to enantiomerically pure alcohol **64**. The key Achmatowicz reaction was then performed with *t*-BuOOH in the presence of a catalytic amount of $VO(acac)_2$ to provide the intermediate hemiketal. This was reduced to enone **66** by employing Kishi's protocol.[144] In order to install the (*S*)-methyl-bearing stereocenter, enone **66** was treated with MeLi/CuBr to provide ketone **63** diastereoselectively. The synthesis highlights the use of an Achmatowicz reaction in the preparation of optically active and highly functionalized tetrahydropyran subunits.

3.2 Synthesis of (+)-Monanchorin—Monanchorin (**67**, Scheme 19) was first isolated in 2004 from the sponge *Monanchora ungiculata*.[163] There is a significant synthetic interest in these guanidinium natural products due to the fact that these cationic natural compounds can mimic cellular ions and inhibit ion pumps (e.g., Na^+/K^+-ATPase or Ca^{2+}-ATPase).[164] O'Doherty and co-workers devised an asymmetric approach,[165] to access both Monanchorin enantiomers.[166] The retrosynthetic analysis is shown in Scheme 19. The monanchorin

synthesis was planned by an acid-catalyzed deprotection/cyclization of the bis-Boc-protected guanidine **68**. The guanidine derivative was prepared from the corresponding amino amicetose. The synthesis of dihydropyranone **69** was planned from acylfuran **70** using an Achmatowicz reaction as the key step.

The synthesis started with the addition of excess 2-lithiofuran (**71**) to caproic acid (**72**) to form key acylfuran intermediate **73** (Scheme 20). Transfer hydrogenation of this ketone using Noyori's (*S,S*)-catalyst[167] led to the enantiomerically pure furan alcohol **74**. An Achmatowicz reaction with NBS in buffered THF/H_2O provided pyranone **69** in excellent yield. A two-step acylation/Pd-catalyzed glycosylation was then performed to form a *p*-methoxybenzyl ether at the anomeric position diastereoselectively, leading to pyranone **75** as the key intermediate.

3.3 Synthesis of Musellarins A–C

3.3.1 Total syntheses of (±)-Musellarins A–C: Musellarins A–C attracted much attention due to their uncommon bicyclic tetrahydropyran motif.[168] Also, these diarylheptanoids show a wide variety of medicinal properties as antioxidant, anticancer, antibacterial, antifungal, antiosteoporosis, and antihepatotoxic agents. They also display melanogenic inhibitory properties.[169]

Tong and co-workers reported the first total syntheses of racemic Musellarins A–C (**76a-c**, Scheme 21), employing an Achmatowicz reaction as the key step.[109] The retrosynthetic analysis involved a stereoselective Heck coupling of enol ether **77** with a suitable aryl diazonium salt.[170] The synthesis of enol ether was planned from ketone **78** via Pd-catalyzed reduction of its enol triflate derivative. Lactone **78** was derived from intramolecular Friedel–Crafts cyclization[171] of γ-aryl enone **79**. This derivative was envisioned through an Achmatowicz reaction of furfuryl alcohol **81** followed by Kishi reduction. The required furan derivative could be generated by Wittig olefination of aldehyde **82** followed by reduction.

The synthetic path (Scheme 22) began from phosphonium salt **83**. Wittig olefination of aldehyde **82** followed by reduction provided the desired furfuryl alcohol **81** in good yield. An Achmatowicz reaction of alcohol **81** using *m*-CPBA at 0 °C provided dihydropyranone hemiacetal **80** in excellent yield. Subsequent Kishi reduction of **80** with trifluoroacetic acid and triethylsilane led to a mixture of dihydropyranone **79** and the Friedel–Crafts cyclization adduct **78**.

3.3.2 Total synthesis of (-)-Musellarins A–C: Tong and co-workers also explored the possibility of accessing *trans*-2,6-dihydropyranones for the synthesis of (-)-musellarins A–C (**76a-c**).[150] Kishi reduction has been widely recognized as a useful method for the construction of functionalized *cis*-2,6-dihydropyranones. However, access to their *trans* counterparts starting from Achmatowicz products has not been explored. Tong and co-workers developed an efficient procedure which provided excellent *2,6-trans* diastereoselectivity. The strategy involved a regioselective reductive γ-deoxygenation and a Heck–Matsuda coupling. This led to the first asymmetric total synthesis of the cytotoxic (-)-

musellarins A–C. A number of structural variants of musellarins have also been synthesized. Synthesis of the key *trans*-2,6-dihydropyranone **89** (Scheme 23) started from enantiomerically, pure furfuryl alcohol **86**, which was obtained from aldehyde **85** using Noyori asymmetric reduction as the key step. An Achmatowicz reaction of furanyl alcohol **86** using NBS followed by acetylation of the resulting ketal provided **87** in high yield. Reduction of acetate **87** with Zn in acetic acid provided δ-deoxygenation product **88**. Subsequent Heck–Matsuda coupling of **88** with the suitable aryl diazonium salts catalyzed by $Pd(OAc)_2$, occurred in excellent yield, leading to the key intermediate **89** for the synthesis of (-)-musellarins A–C.

3.4 Synthesis of (+)-Attenol B—Attenol A and Attenol B (**90**, Scheme 24) were isolated from the Chinese bivalve *Pinna attenuate* and represent structurally novel bicyclic ethereal derivatives which display potent cytotoxicity.[172] The minor metabolite Attenol B bears a unique 6,8-dioxabicyclo-[3.2.1]octane (6,8-DOBCO) system. Tong and co-workers have utilized an Achmatowicz reaction for synthesis of the target tetrahydropyran-based natural compounds.[173] In a recent article, they reported synthesis of the 6,8-DOBCO core of Attenol B by a sequential Achmatowicz reaction and bicycloketalization of furfuryl diol **92**, a process formerly developed for diastereoselective synthesis of hexoses[107, 174] and Papulacandins.[175-177] Diol **92** was readily obtained from Julia–Kocienski olefination[178] of furan aldehyde **93** followed by Sharpless asymmetric dihydroxylation.[179]

Synthesis of the key intermediate **91** (Scheme 25) started from a Julia–Kocienski olefination between the 2-formylfuran derivative **93** with the 1-phenyl-1H-tetrazol-5-yl (PT) sulfone **94**. This provided enyne derivative **95** with excellent *E/Z* (10:1) selectivity. Sharpless asymmetric dihydroxylation of olefin **95** employing AD-mix β led to the vicinal diol **92**. An Achmatowicz reaction of **92** by treatment with *m*-CPBA and CSA-promoted bicycloketalization in one pot affording the 6,8-DOBCO intermediate **91** in excellent yield on a gram scale.

3.5 Synthesis of (+)-Didemniserinolipid B—Didemniserinolipids A–C are novel serinolipids isolated from the methanolic extract of marine tunicate *Didemnum sp* by Jiménez and co-workers in 1999.[180] Tong and co-workers utilized an Achmatowicz reaction in the total synthesis of (+)-didemniserinolipid B (**96**, Scheme 26) in 19 steps from commercially available materials.[108] In particular, the target compound was assembled from the 6,8-DOBCO system (**97**).[181-183] The key 6,8-DOBCO fragment **97** was envisioned from hydrogenation and diastereoselective ketone reduction of the bicyclic acetal **98**. The synthesis of this acetal was planned from Achmatowicz reaction of a suitable enantiopure furfuryl diol **99** followed by dehydrative ketalization.

Synthesis of bicyclic derivative **98** (Scheme 27) started with Vilsmeier-Haack formylation of the commercial furan **100**. Julia-Kocienski olefination followed by Sharpless asymmetric dihydroxylation of the resulting olefin with AD mix-β provided the vicinal diol **99** in high yield. The sequential Achmatowicz reaction and bicycloketalization steps were carried out with *m*-CPBA and CSA, respectively, furnishing the desired bicyclic acetal **98** as a single diastereomer in excellent yield.

3.6 Synthesis of (+)-Psoracorylifol B and (+)-*ent*-Psoracorylifol C—

Psoracorylifols A–C were isolated from the seeds of *Psoralea corylifolia* L. in 2006.[184] These compounds demonstrated significant antimicrobial activity *in vitro* by inhibiting *Helicobacter pylori*. These derivatives contain a common all-carbon quaternary stereocenter on the tetrahydropyran ring in addition to a phenolic moiety. Interestingly, psoracorylifol B (PsB, **101**, Scheme 28) and psoracorylifol C (PsC) also possess a 6,8-DOBCO framework. Tong and co-workers reported asymmetric total syntheses of PsB (**101**) and PsC exploiting an Achmatowicz reaction on the furan intermediate **105** followed by bicycloketalization for construction of the 6,8-DOBCO substructure in 104.[114]

The key Achmatowicz transformation is shown in Scheme 29. The synthesis of furan diol **105** was achieved in an enantioselective manner. Treatment of the diol **105** with *m*-CPBA provided the Achmatowicz reaction product pyranone acetal. Treatment of the resulting acetal with CSA afforded the key 6,8-DOBCO framework **103** in high yield.

3.7 Synthesis of (±)-6-*epi*-cleistenolide and chemoenzymatic synthesis of (–)-6-epi-cleistenolide—

Cleistenolide [(-)-**109**, Scheme 30] was isolated from *Cleistochlamys kirkii* Olive, a plant of *Annonaceae* species.[185] Extracts of this plant are employed in traditional medicine for treatment of wound infections, rheumatism, and tuberculosis.[186] Cleistenolide displays *in vitro* antibacterial activity against *Staphylococcus aureus* and *Bacillus anthracis*, and antifungal activity against *Candida albicans.*[185] In several earlier synthetic approaches to phomopsolides, Achmatowicz products were converted in γ-hydroxy-δ-lactones,[187-189] Mhaske and collaborators recently reported a protecting-group-free total synthesis of (±)-6-*epi*-cleistenolide and (–)-6-*epi*-cleistenolide employing an Achmatowicz reaction as the key step.[190] Accordingly, furylallyl alcohol **106** was benzoylated and subsequently subjected to dihydroxylation with OsO_4 and NMO to give furan diol (±)-**107** in high yields. In a subsequent Achmatowicz reaction step, it was reacted with NBS to provide the dihydropyranone (±)-**108** in 60% yield. The reaction yield was greatly improved to 95% when NaOAc and $NaHCO_3$ were added as buffer. Oxidation of lactol **108** using CrO_3 in AcOH followed by treatment with $NaBH_4$ in 2-propanol and final acetylation led to the desired (±)-**109**.

3.8 Synthesis of the C1–C14 fragment of marinolic acids, mupirocins, pseudomonic acids and thiomarinols and total synthesis of pseudomonic acid methyl monate C—

Pseudomonic acids (Pseudomonic acid methyl monate, **110**, Scheme 31) were isolated from the bacterium *Pseudomonas fluorescens* NCIB 10586 species. They are potent inhibitors of Gram-positive pathogens.[191, 192] Mupirocin W and H belong to another class of antibiotics isolated from *Pseudomonas fluorescens* which display similar bioactivity to pseudomonic acids.[193, 194] Thiomarinols were recently isolated from marine bacterium *Pseudoalteromonas* sp. SANK 733903 and display activity towards methicillin-resistant *S. aureus* (MRSA). Another class of thiomarinols, namely marinolic acids, were found active against *Bacillus subtilis* and MRSA.[195] All of these compounds share a similar C1–C14 carbon sequence.

Srihari and co-workers reported the synthesis of common intermediate **111** (Scheme 31) involving an Achmatowicz reaction as the key step.[100] The synthesis of tetrahydropyran

derivative **111** was planned by Julia-Kocienski olefination of aldehyde **112** and an appropriately functionalized sulfone. Compound **112** was envisioned from allyl alcohol **113** utilizing a Johnson–Claisen rearrangement and *syn*-dihydroxylation. The preparation of allyl alcohol **113** involved Achmatowicz reaction on the chiral mono-protected furyl alcohol **114**.

Synthesis of intermediate **112** is outlined in Scheme 32. Alcohol **114** underwent an Achmatowicz reaction using NBS, $NaHCO_3$ and NaOAc and the acetal **115** formed smoothly in 95% yield. It was then converted to the corresponding acetate. Treatment of the resulting acetate with $BF_3{\bullet}OEt_2$ in the presence of triethylsilane yielded enone **116**. DIBAL-H reduction of enone **116** provided allyl alcohol **113** in high yield with good diastereoselectivity (5:1 dr). Johnson–Claisen rearrangement of allylic alcohol **113** with trimethyl orthoacetate provided ester **117**. Substrate controlled dihydroxylation of dihydropyran **117** with OsO_4 followed by reduction with $LiAlH_4$ and oxidation with Dess–Martin periodinane afforded the key aldehyde **112** in good yield.

3.9 Synthesis of the south eastern segment (C1–C16) of (+)-sorangicin A—

(+)-Sorangicin A (**118**, Scheme 33) was isolated from *Sorangium cellulosum* by Höfle and Reichenbach.[196] This compound exhibited potent antibacterial activity against both gram-positive and gram-negative bacteria through the inhibition of DNA-dependent RNA polymerase.[197]

Srihari and co-workers reported a stereoselective synthesis of the C1–C16 fragment of **118** utilizing Achmatowicz reaction as the key step.[101] The retrosynthetic analysis shows that acetal **120** was planned from furfuryl alcohol **121** using an Achmatowicz reaction.

The synthesis of dihydrofuran **119** is shown in Scheme 34. Furfuryl alcohol **121** was obtained in an enantiopure form. Selective reduction of α,β-unsaturated ester **121** with a $NiCl_2$–$NaBH_4$ system provided furfuryl alcohol **122**. An Achmatowicz reaction with NBS furnished the pyranone lactol **123** along with its diastereomer (4:1 ratio), which were separated by chromatography. Compound **123** was converted to its acetate and treatment of this acetate with allyl trimethylsilane and $BF_3{\bullet}OEt_2$ provided allylated product **124**, which was subsequently converted into **119**.

3.10 Diastereoselective synthesis of the BCD tricyclic core of Brownin F—

Brownins A–H were isolated from the bark of *Harrisonia brownii*. These compounds are believed to be responsible for their bioactivity in the treatment of dysentery and cholera.[198, 199] Brownin F (**125**, Scheme 35) displays a complex structure featuring a pentacyclic core. Commeiras and co-workers reported a diastereoselective synthesis of the spirocycle **126**.[200] The retrosynthetic analysis involves the trapping of carbonyl ylide **127** (Scheme 35) with an appropriate dipolarophile to generate the seven-membered ring. Carbonyl ylide generation was planned *in situ* through either the metal-catalysed decomposition of α-diazoketones or thermal exposure of acetoxypyranones **128**. The preparation of enone **128** involved the crucial Achmatowicz reaction of furan derivative **129**.

Furan derivative **130** (Scheme 36) was planned from commercially available furfuryl alcohol,[201] which underwent a Pd-free Sonogashira coupling reaction with iodide **131**.[202]

Removal of silyl ether with HF•py afforded the desired lactone derivative **132**. This derivative was subjected to an Achmatowicz reaction employing *m*-CPBA to give hemiacetal **133** in good yield. This was subsequently protected to provide the key acetoxypyranone intermediate **134**.

3.11 Synthesis of the oxa-pinnaic acid core—Pinnaic acid (**135**, Scheme 37) was isolated in 1996 from the mollusc *Pinna muricata*.[203] This alkaloid was able to inhibit the cytosolic phospholipase A2, displaying interesting anti-inflammatory properties.[204] Marquez and co-workers reported the synthesis of a derivative of this natural product by replacing the spirocyclic piperidine framework with a spirocyclic pyran unit (oxa-pinnaic, **136**).[205] Oxa-pinnaic acid could be derived from the spirocyclic pyran **137** by olefin extension. This would be accessible from spirocyclic lactol **138**. A crucial Achmatowicz reaction of cyclic tertiary furfuryl alcohol **139** was envisioned for this synthesis. Intermediate **139** was generated from the reaction of lithiofuran with cyclopentanone **140**.

The synthesis of compound **142** (Scheme 38), which is a fully functionalized core of **136**, utilized Roche ester **141** as the chiral starting material. Other stereocenters were introduced through asymmetric synthesis. The addition of lithiofuran (**71**) to cyclopentanone **140**[206] afforded furfuryl alcohol **139** as a single diastereomer with the depicted stereochemistry. An Achmatowicz reaction in the presence of NBS provided the corresponding lactol. Sakurai allylation of the resulting lactol furnished allylspiropyranone **142** as a single diastereoisomer.

3.12 Synthesis of the Polymaxenolide and Pinnaic acid cores—Polymaxenolide (**143**, Scheme 39) was isolated in 2004 from the hybrid soft coral *Sinularia maxima* × *Sinularia polydactyla*. It represents the first example of a hybrid metabolite from marine origin. It contains a spirocyclic pyran core. [203] The spirocyclic core of polymaxenolide is common to other natural products such as pinnaic acid, tauropinnaic acid[207] and halichlorine.[208] Marquez and co-workers carried out a divergent synthetic approach starting from a common synthetic intermediate to be quickly and efficiently converted to the spirocyclic piperidine and spirocyclic pyran cores of the desired natural products.[206] A cyclic tertiary carbinol (**145**, Scheme 39) was recognized as the suitable common precursor. Accordingly, cyclopentanone **144** was treated with 2-lithiofuran (**71**) to provide furfuryl alcohol **145**. Treatment of this alcohol with *m*-CPBA under classical Achmatowicz reaction conditions followed by boron trifluoride-promoted allylation of the lactol intermediate in the presence of allyltrimethylsilane afforded pyranone derivative **146**.

For the generation of the spirocyclic piperidine core, the authors treated the key furfuryl alcohol **145** (Scheme 40) with hydrazoic acid to provide the corresponding azide. It was then reduced under hydrogenation condition to the corresponding amine. Tosylation of the amine afforded compound **147**, which was the substrate for the subsequent key Achmatowicz reaction. Treatment of sulfonamide **147** with *m*-CPBA afforded the hemi-aminal. Allylation of the resulting hemiacetal under a Lewis-acid promoted reaction provided enone **148**. Selective 1,4-reduction using Stryker's reagent ($[(PPh_3)CuH]_6$) afforded piperidone **149**. Deoxygenation of this ketone produced the desired spirocyclic piperidine **150**.

3.13 Synthesis of Halichondrins

3.13.1 Synthesis of Norhalichondrin B: Halichondrins are naturally occurring polyether macrolides originally isolated from the marine sponge *Halichondria okadai*. Halichondrins are anti-mitotic agents and display distinct antitumor activity profiles in human tumor models.[209] The structures of the Halichondrins (e.g. Norhalichondrin B, **151**, Scheme 41) show a 53–55 carbon backbone which can be divided in two domains: the spiroketal containing the C31–C53/55 region and a C1–C30 macrolactone characterized by a 2,6,9-trioxatricyclo[3.3.2.0]decane substructure.[210, 211] Phillips and co-workers described a total synthesis of **151** utilizing an Achmatowicz reaction and ionic hydrogenation for the generation of pyrans and pyranopyrans structural segment.[212]

The syntheses of both key synthons **152** and **155** involved a key Achmatowicz reaction (Schemes 42 and 43). For intermediate **152** (Scheme 42), furfural **157** underwent Brown crotylation using (-)-Ipc_2-(*E*)-crotylborane to give **153**. The Achmatowicz reaction was carried out with *t*-BuOOH and $VO(acac)_2$ to provide the pyranone hemiacetal which was immediately subjected to trifluoroacetic acid-mediated ionic hydrogenation in the presence of Et_3SiH, to yield the desired pyranone **158** as a single diastereomer (d.r.>20:1). This was converted to aldehyde **159** in seven steps and was finally converted to the functionalized tetrahydropyran derivative **152** as reported.[131, 213] For intermediate **155**, furfural **157** served as the starting material (Scheme 43). Brown crotylation with (-)-$(Ipc)_2$-(*Z*)-crotylborane afforded compound **160**. Achmatowicz reaction with *t*-BuOOH, $VO(acac)_2$, followed by reaction with trifluoroacetic acid and Et_3SiH, furnished pyranone **161** in high yield as a single diastereomer (d.r.>20:1). A three-step sequence including (i) removal of the TBS, (ii) tandem Jones oxidation and (iii) $NaBH_4$ reduction led to **162**. Sequentially, reduction of the lactone with $LiBH_4$, formation of the seven-membered ketal, protection of the secondary alcohol functionality as TES ether and ozonolysis provided aldehyde **163**, which was finally converted to pyranopyran derivative **155**.

3.13.2 Synthesis of the C1–C15 domain of Halichondrins: Synthesis of the C1–C15 domain of the halichondrins was carried out in a slightly different pathway (**164**, Scheme 44).[214] The retrosynthetic analysis shows the key Achmatowicz reaction for the conversion of a furfuryl alcohol (**167**) to a pyranone scaffold.

Accordingly, furfuryl alcohol **167**, was subjected to an Achmatowicz reaction with *t*-BuOOH as the oxidant and $VO(acac)_2$ as the catalyst (Scheme 45). The resulting pyranone hemiacetal was immediately subjected to benzoylation conditions using O'Doherty's protocol to provide ketone **169**. $NaBH_4$ reduction of ketone followed by cross metathesis with methyl acrylate provided the corresponding α,β-unsaturated ester. The resulting ester was converted to pyranopyran **170** upon treatment with TBAF. Grieco oxidation[215] performed on **170** with *m*-CPBA in the presence of BF_3•OEt_2 produced lactone **171**. The synthesis of the C27-C38 and C44-C53 subunits of Norhalichondrin B also involved an Achmatowicz reaction.[131]

3.14 Synthesis of (-)-Rasfonin—Rasfonin (**172**, Scheme 46), was isolated in 2000 from the fermented mycelium of *Talaromyces* species 3656-A1.[216] It induces apoptosis in *ras*-

dependent Ba/F3-V12 cells. Nanda and co-workers reported the synthesis of rasfonin **172**.[217] The retrosynthetic analysis of the target molecule **172** shows a functionalized acid (**173**) and an alcohol fragment (**174**). The alcohol fragment was constructed using an Achmatowicz reaction.

The synthesis utilized optically active aldehyde **176** (Scheme 47), which was prepared by an enzymatic desymmetrization step. Addition of 2-lithiofuran (**71**) to aldehyde **176** gave alcohol **177**. It was oxidized to the corresponding ketone. Reduction of this ketone with *L*-Selectride provided alcohol **175** stereoselectively. An Achmatowicz reaction with $NaHCO_3$, NaOAc, and NBS afforded lactol **178** as a mixture of diastereomers in excellent yield. Oxidation of the lactol functionality and Luche reduction[218]provided the key functionalized tetrahydropyran **174** stereoselectively.

3.15 Synthesis of Aspergillides A-C

3.15.1 Synthesis of Aspergillide C: Aspergillides A, B, and C (**179-181**, Scheme 48) are 14-membered bicyclic macrolides bearing 2,6-*cis*- and 2,6-*trans*-fused dihydro- or tetrahydropyan rings. They were isolated from the marine-derived fungus *Aspergillus ostianus* strain 01F313.[219] These naturally occurring molecules displayed potent cytotoxicity against mouse lymphatic leukaemia cells and toward a number of human cancer cell lines, including HL-60 (promyelocytic leukaemia), MDA-MB-231 (breast carcinoma), and HT1080 (fibrosarcoma) cell lines.[220] Srihari and co-workers described the total syntheses of Aspergillide C.[221] The retrosynthetic strategy shows the key Achmatowicz reaction to construct pyranone derivative **182**.

The synthesis of dihydropyran synthon **187** (Scheme 49) was carried out from furfural **185**. Reaction of this latter with alcohol enolate of ethyl acetate (**186**) furnished alcohol **184**. The racemic mixture was resolved by Sharpless-type kinetic resolution,[222] providing pyranone lactal **187** and the stereochemically-defined furfuryl alcohol (*R*)-**184**. Lactal **187** was directly used for the synthesis of (+)-aspergillide C, while intermediate (*R*)-**184** was further subjected to an Achmatowicz reaction to afford lactal *ent*-**187**, which was used instead for the synthesis of (–)-aspergillide C.

3.15.2 Synthesis of (+)-Aspergillide B and (+)-7-*epi*-Aspergillide A: Srihari and co-workers also described the syntheses of (+)-7-*epi*-aspergillide A and (+)-aspergillide B (**179** and **180**, Scheme 48).[223] In this case, the acid **188** could be derived from dihydropyranone, *ent*-**183** and trimethylsilylacetylene derivative **189** (Scheme 50). Acetal *ent*-**183** was obtained from the chiral furfuryl alcohol (*R*)-**184** using an Achmatowicz reaction

Addition of an enolate derived from ethyl acetate to 2-furoyl chloride (**190**) provided the β-keto ester (Scheme 51). Enantioselective reduction of this keto-ester with Noyori's Ru[(1*R*, 2*R*)-*p*-TsNCH(Ph)CH(Ph)NH](η^6-*p*-cymene) catalyst in the presence of a catalytic amount of *t*BuOK provided (*R*)-**184**. The subsequent Achmatowicz reaction proceeded smoothly under standard conditions. Acylation of the resulting lactol gave enone *ent*-**183**.

3.16 Synthesis of the C94–C104 fragment of Symbiodinolide—Symbiodinolide (**191**, Scheme 52), a marine natural product was isolated from dinoflagellate *Symbiodinium*

sp. Symbiodinolide has a molecular weight of 2860 and contains 61 chiral centers. Stereochemistry and absolute configuration of many chiral centers have not yet been determined.[224] This molecule displays voltage-dependent N-type Ca^{2+} channel-opening activity in the nanomolar range. It also shows COX-1 inhibition activity in the low micromolar range. Takamura and collaborators proposed a stereoselective route to the C94–C104 fragment involving a key Achmatowicz reaction.[225] The authors envisaged that fragment **192** could be assembled via coupling between dithiane **193** and aldehyde **194**. The vicinal diol functionality at the C101 and C102 positions could be stereoselectively introduced by dihydroxylation of enone **195**, which could be derived by an Achmatowicz reaction on the enantiomerically pure alcohol **196**, which is easily accessible from furfuryl alcohol **197**.

Furfuryl alcohol **197** was converted to optically active alcohol **196** by TBS protection, regioselective lithiation followed by the addition of 2-benzyloxy acetaldehyde, Albright–Goldman oxidation[226] and asymmetric Noyori transfer hydrogenation (Scheme 53). An Achmatowicz reaction in the presence of NBS and subsequent treatment of the lactol with $(MeO)_3CH$ provided acetal enone **195**. Oxidation of **195** with $RuCl_3/NaIO_4$ in the presence of $ZnCl_2$ followed by protection of the resulting diol functionality and reduction with $NaBH_4$ afforded functionalized tetrahydropyran derivative **198**. This was then converted to the key aldehyde synthon **194**.

3.17 Synthesis of (+)-Peloruside A—Peloruside A (**199**, Scheme 54) is a 16-membered macrolide which was isolated from the marine sponge *Mycale hentscheli*.[227] This naturally occurring molecule shows antimitotic activity (G2-M arrest) in the low nanomolar range against a variety of cancer cell lines.[228-231]

Gazaille and co-workers carried out the synthesis of peloruside A (**199**) by employing an intramolecuar vinylogous aldol reaction for the cyclization as an alternative to macrolactonization. Their synthetic strategy involved an Achmatowicz reaction as the key step (Scheme 54).[110] An Achmatowicz reaction of furan derivative **201** was planned to provide enone **200**. This pyranone intermediate contains all the functionalities for elaboration to peloruside A.

Accordingly, macrolactone **203** was prepared for the key Achmatowicz reaction. Reaction of furan **203** with *m*-CPBA in the presence of trichloroacetic acid afforded the desired pyranone intermediate **204** in good yield (Scheme 55).

3.18 Synthesis of (+)-Brevisamide—Brevisamide (**205**, Scheme 56) is a marine monocyclic ether amide derivative isolated from the dinoflagellate *Karenia brevis*. This natural product contains a functionalized tetrahydropyran core featuring a conjugated 3,4-dimethylhepta-2,4-dienal and an acetylated terminal amine framework.[232] Zakarian and collaborators reported a protecting-group-free total synthesis of brevisamide.[104] Their retrosynthetic approach involved a key Achmatowicz reaction for construction of the tetrahydropyran-containing synthon **206**. A catalytic asymmetric Henry reaction on aldehyde **208** was planned to provide the required furan derivative **207**. A Stille cross-coupling was designed to install the conjugated dienal sub-structure of brevisamide, **205**.

The synthesis of pyran derivative **206** (Scheme 57) started from the reduction of the nitro group of furanyl intermediate **207** followed by chemoselective acetylation to give carbonate **209**. An Achmatowicz reaction of **209** in the presence of NBS led to the cyclic hemiketal intermediate, which was immediately treated with BF_3•OEt_2 and Et_3SiH to provide enone **210**. The methyl group was installed by conjugate addition of lithium dimethylcuprate[94] and was followed by reduction of ketone with $NaBH_4$. Formation of the key (*E*)-iodoalkene **206** proceeded smoothly employing a silylcupration-iododesylilation protocol.[233, 234]

3.19 Synthesis of the C6-C18 fragment of the Lituarines—The marine metabolites, okadaic acid, and lituarines possess an unusual spiro[furan-2,2′-pyrano[3,2-*b*] pyran] framework (**211-213**, Scheme 58).[235, 236] Lituarines are a group of three macrolactones isolated from the New Caledonian sea pen *Lituaria australasiae*. They display potent cytotoxicity towards KB cells and show inhibitory effects on the growth of a variety of fungi species. Robertson and co-workers reported a synthesis of the C6-C18 tricyclic spiroacetal core of the lituarines. The synthesis highlights one of the first cases of a chemoselective Achmatowicz reaction in the presence of a second furan ring lacking an α-hydroxyl group.[237] The retrosynthetic analysis of lituarine tricyclic spiroacetal (**214**) involved introduction of the methyl substituent by kinetic 1,4-addition to butenolide spiroacetal **215**. This was generated through a key Achmatowicz reaction starting from the tetrahydropyran derivative **216** deriving from oxy-Michael cyclization of enoate **217**.

In particular, compound **216** underwent furan oxidation under typical Achmatowicz reaction conditions in an excellent yield as shown in Scheme 59. Further oxidation with TPAP provided butenolide **215**.[238]

3.20 Synthesis of the Maitotoxin key fragments

3.20.1 Synthesis of the ABCDEFG ring system of Maitotoxin: Maitotoxin is the largest and most toxic secondary metabolite ever isolated and characterized.[239-242] It is one of the causative agents of the ciguatera fish poisoning infecting consumers of contaminated seafood, representing a major environmental and health hazard. It interferes with cell membrane ion channels and Ca^{2+} ion influx, thus causing neurotoxicity.[241, 243-245] Nicolaou and collaborators described the synthesis of the ABCDEFG polycyclic system of Maitotoxin (**220**, Scheme 60).[246] The synthesis highlights the versatility of the furan-based Noyori reduction and Achmatowicz reaction sequence for accessing the tetrahydropyran framework present in Maitotoxin and other marine neurotoxins.[247-249] The retrosynthetic analysis outlines a convergent path to fragment **220** employing three key Achmatowicz reaction steps. Synthesis of the G-ring was planned from furfuryl alcohol **197**.[250] The ABCDE pentacyclic system was disconnected into smaller fragments which were designed from appropriate furan precursors. Accordingly, the ABCDE ring system could be built upon C ring disconnection through a β-alkyl Suzuki coupling and an acetal formation/methylation of the AB endocyclic ketene acetal phosphate **221** with vinyl ether **222** as the required synthons. Both fragments could be linked to furan-containing precursors, namely furfural (**185**) and furfuryl alcohol (**197**).

The synthesis of ring A (Scheme 61) started from furfural-derived ethylene ketal **224**, which was submitted to lithiation followed by addition of γ-lactone. Subsequent reaction with pivaloyl chloride provided ketone **225**. Noyori asymmetric reduction of **225** provided enantiomerically pure alcohol which was then protected as its benzyl ether. Ketal cleavage with aqueous HCl led to aldehyde derivative **226**. Aldol reaction of aldehyde **226** with Evans chiral auxiliary (**227**) provided the enantiomerically pure alcohol **228**. The Achmatowicz reaction in the presence of *m*-CPBA gave a lactol which was reduced with Et_3SiH and BF_3•OEt_2 to provide enone **229** in good yield.

Synthesis of ring D (Scheme 62) started from protected furfuryl alcohol **230** which in four steps gave furanyl alcohol **232**. An Achmatowicz reaction of **232** followed by reduction with BF_3•OEt_2 and Et_3SiH afforded ketone **233**. Stereoselective introduction of the methyl group was achieved with MeMgBr and the resulting tertiary alcohol was protected as the TMS ether. Subsequent regio- and stereoselective addition of diisoamylborane across the double bond afforded, upon oxidative workup and PMB ether formation, the fully protected D ring. The pivalaate ester was then reduced with DIBAL-H to afford alcohol **234**.

3.20.2 Synthesis of the WXYZA′ domain of Maitotoxin: Nicolaou and co-workers also reported the synthesis of the WXYZA′ domain of maitotoxin (**235**, Scheme 63).[251] Tricyclic ester **236** was identified as a key precursor originating from the secondary alcohol **237**. Synthesis of the pyranopyran subunit **237** was planned from pyran fragment **238** in turn deriving from furfuryl alcohol (**197**) using an Achmatowicz reaction as the key step. [246] More recently, Onoue and co-workers reported the synthesis of the QRS ring system of Maitotoxin employing an Achmatowicz reaction as a key step.[252]

3.21 Synthesis of Pyranicin—Pyranicin (**239**, Scheme 64) was isolated from the stem bark of *Goniothalamus giganteus* tree (native to Thailand) and prototypical of acetogenins which contain a single tetrahydropyran ring.[253] This class of natural compounds can interrupt the final electron transfer from NADH to ubiquinone, thus decreasing cellular ATP production and leading to cell death by apoptosis. Pyranicin displays exceptional activity against various cancer cell lines. Phillips and co-workers devised a synthesis of pyranicin involving retrosynthetic disconnection in three key synthons; tetrahydropyran derivative **240**, alkynyl olefin **241**, and butenolide **242**.[90] This work highlights the utility of the Achmatowicz reaction and Kishi reduction sequence for assembly of the tetrahydropyran ring.

The subunit coupling involved the use of Carreira's asymmetric alkynylation[254] and Fu's alkyl-alkyl Suzuki coupling.[255] Synthesis of the tetrahydropyran ring was designed from furan derivative **243** using an Achmatowicz reaction followed by Kishi reduction.

As shown in Scheme 65, addition of dodecylmagnesium bromide to furan **244** produced furfuryl alcohol **243**. Sharpless asymmetric kinetic resolution conditions, as well as the Achmatowicz reaction provided the corresponding hemiacetal. Reduction of this resulting acetal with *i*-Pr_3SiH in the presence of BF_3·OEt_2 afforded enone **245**. Hydrogenation of **245**, followed by ketone reduction with *L*-Selectride, protection of the resulting secondary

alcohol, removal of the benzyl ether, and oxidation with Dess-Martin periodinane, provided key aldehyde **240**.

3.22 Synthesis of D- and L-Swainsonine—Swainsonine (*D*-Swainsonine, **246**, Scheme 66) belongs to indolizidine natural products. They show potent glycosidase inhibitory activity.[256] Over the years, many of these mannosidase inhibitors have received much synthetic attention.[257-261] O'Doherty and co-workers[80] reported a synthesis (-)-D-swainsonine starting with furfuryl alcohol **249**. As shown, synthetic strategy involved an Achmatowicz reaction as the key step to provide substituted pyranone **248**. This pyranone was converted to swainsonine **246** via bicyclic derivative **247**.

As reported in Scheme 67, reaction of 2-lithiofuran (**71**) with γ-butyrolactone and subsequent TBS protection led to furyl ketone **250**. This was subjected to Noyori's reduction protocol to afford furfuryl alcohol *ent*-**249**. Achmatowicz reaction of ent-**249** with NBS in THF and H_2O furnished the desired pyranone *ent*-**248** in high yield.

3.23 Synthesis of (+)-Uprolide G Acetate—Cembranolides are marine natural products isolated from marine soft corals and gorgonians and show a wide range of biological activities.[262-265] In particular, cembranolides bearing the α-methylene-γ-lactone substructure such as sinularolides,[266] crassocolides,[267, 268] michaolides,[269, 270] eupalmerins,[271] and uprolides[272-274] display potent cytotoxicity against various cancer cell lines. This may be due to their excellent Michael acceptor properties for biological nucleophiles.

Recently Tong and co-workers reported the synthesis of uprolide G acetate (**251**, Scheme 68).[275] Their synthetic plans involved a key Achmatowicz reaction step of furfuryl alcohol **254** with a subsequent reduction to form the functionalized tetrahydropyran core **253**. This will be further elaborated to the key intermediate (**252**).

The synthesis of key intermediate **258** (Scheme 69) started with the preparation of the enantiomerically pure alcohol **256** from aldehyde **255** in a five-step sequence. The key Achmatowicz reaction was performed by treatment with NBS to provide the dihydropyranone acetal **257**. This lactol was subjected to Kishi reduction, palladium-catalyzed chemoselective hydrogenation and final $CeCl_3$-mediated MeLi addition to provide a mixture of diastereomers from which the desired isomer **258** was isolated by flash chromatography.

4. Synthesis of Bioactive Carbohydrates

Carbohydrates are the most abundant biomolecules in nature and play key roles in all living organisms, including energy production, and maintenance of structural and functional features of the cell. They also play critical roles in many biological processes including immunological responses, infections, and cancers. The carbohydrate structural features in natural products play important roles on the mechanism of action, especially in terms of target binding, solubility and transport across membranes.[276-278]

The development of effective stereoselective synthetic methodologies that do not rely on naturally occurring mono- or polysaccharides is important. This may greatly expedite the investigation of the biological functions of carbohydrates as well as the development of carbohydrate-based therapeutic agents. Over the years, there has been a significant effort toward the synthesis of monosaccharides from achiral starting materials.[279, 280] The pioneering work by Sharpless and Masamune on the *de novo* stereoselective synthesis of hexopyranoses,[279] was followed by a number of new strategies.[86, 280-286] These approaches, however, did not fully address the key issues of the stereochemistry at the anomeric position and stereoselective glycosidation.[287] Accordingly, a variety of *O*-glycosidation methods,[288, 289] using the Pd-catalyzed Tsuji-Trost allylic alkylation were developed to link monosaccharides.[290-294] These methods involved the work of Lee,[295, 296] Feringa,[146] O'Doherty,[81, 145] Liu,[297-299] and Rhee.[300]

The *de novo* synthesis of carbohydrates developed by Feringa[146] and O'Doherty[81] is based on the Achmatowicz reaction and stereoselective Pd-catalyzed glycosidation. As shown, furan **43** was converted to dihydropyranone **48** (Scheme 70). Lipase-mediated enzymatic resolution of **48** provided acetate derivative **259**. Feringa and co-workers focused on the glycosidation of ester **259** using a palladium-catalyzed acetal bond formation, leading to disaccharide **260** in a highly stereoselective manner. Subsequent stereoselective reduction led to alcohol intermediate **261**. This alcohol was then converted to carbohydrate derivative **262**. This iterative catalytic asymmetric synthetic protocol thereby provides access to the preparation of polysaccharide intermediates.[146]

O'Doherty and co-workers synthesized a variety of carbohydrate derivatives using the Achmatowicz reaction in conjunction with the asymmetric synthesis of furan alcohols.[81] As shown, Noyori reduction of furyl ketone **263** (Scheme 71) provided optically active alcohol (*S*)-**43**. Achmatowicz reaction followed by Boc-protection provided **264**. A Pd-catalyzed glycosylation of Boc-derivative **264** led to the pyranose intermediates **265**. This intermediate was converted to a variety of carbohydrates. For example, stereoselective reduction of the keto group provided intermediate **266**. Osmium-catalyzed dihydroxylation resulted in the *syn*-diol derivative **267**. The combination of reduction and dihydroxylation reactions allowed the installation of six stereocenters stereoselectively.

O'Doherty and co-workers applied this method in the synthesis of a number of naturally occurring carbohydrate structural motifs (Figure 4). In particular, achiral 2-acetylfuran **268** was converted to anthrax tetrasaccharide **269**, useful for anthrax detection and vaccine development.[301] Cleistetroside-2 (**270**) and their derivatives were also synthesized. These compounds displayed antimicrobial activity against several methicillin-resistant *Staphylococcus aureus*.[302] Mezzettiaside-2 (**271**) and congeners were synthesized as anticancer/antibiotic oligosaccharides.[88] Merremoside D **272**[299] and carbohydrates including digitoxin (**273**, anticancer properties),[303] vineomycinone B2 (**274**),[304] vineomycin B2 trisaccharide (**276**)[305] (antitumor and antibacterial activities), methymycin analogues such as **275** (antibiotic activity),[306] and landomycins A and E (**277a,b**, antitumor activity)[307] were also synthesized using these protocols.

Tang and collaborators reported a series of studies involving dynamic kinetic diastereoselective transformations of lactol **278** (Scheme 72) which was derived from an Achmatowicz reaction. In particular, these authors speculated that chiral catalysts could improve diastereoselectivity for the acylation of **278**. Chiral catalyst-directed dynamic kinetic diastereoselective acylation (DKDA) would then provide a useful route for the synthesis of either *trans*- or *cis*-280.[308] Accordingly, the authors found that both α- and β-isomeric products **280** could be prepared in high diastereoselectivity using catalyst **279** or *ent*-**279**. This demonstrates that the combination of chiral organocatalyst directed DKDA and Pd-catalyzed glycosidation would allow complete stereochemical control of the anomeric center for the stereoselective synthesis of natural and non-natural carbohydrate substructures.

A stereoselective iridium-catalyzed dynamic kinetic internal transfer hydrogenation reaction was developed by Tang and co-workers.[309] As shown, an Achmatowicz reaction on **43** provided pyranones **48**. An internal redox isomerization methodology provided easy access to key intermediates for the synthesis of a series of naturally occurring sugars. The authors screened several Brønsted acids to accelerate the rate of equilibrium between *cis* and *trans*-epimers. It was found that the *cis* isomer **281** (Scheme 73) could be obtained almost exclusively in nearly quantitative yield when 2,6-dichlorobenzoic acid was used as the co-catalyst. Mitsunobu inversion of the allylic alcohol could be employed to provide the *trans* isomer. [309]

The combination of the Achmatowicz reaction and the iridium-catalyzed isomerization also provided an effective path for the synthesis of noviose (Scheme 74). Intermediate **282** was prepared in two steps involving Grignard addition and an Achmatowicz reaction of acetylfuran (**268**). The isomerized product **283** was converted to noviose (**284**) by sequential methylation, reduction, and dihydroxylation reactions.[309]

A chiral catalyst-controlled divergent synthesis was exploited to provide access to all possible stereoisomers of naturally occurring rhodinopyranosides and amicetopyranosides.[310] The compounds were prepared by a sequence of an Achmatowicz reaction, Pd-catalysed glycosidation, and chiral catalyst-controlled tandem reductions. Naturally occurring antimalarial disaccharide β-narbosine B, **289**, (Scheme 75) was synthesized from both *cis*- and *trans*-**285**, both deriving from the Achmatowicz reaction. Natural product α-narbosine B6 was prepared in a similar fashion.[310]

Conclusion

The Achmatowicz rearrangement/reaction is an oxidative ring expansion of a functionalized furfuryl alcohol to a dihypyranone acetal. These dihydropyranones can be converted to functionalized tetrahydropyrans, dihydropyranones, δ-lactones, carbohydrates, and related derivatives. Since furfural and furans are readily available, there is a growing interest in Achmatowicz reaction in organic synthesis. Over the years, numerous oxidative processes have been developed, including metal catalyzed, enzymatic, photolytic and electrochemical procedures. More recently the KBr/Oxone protocol appeared efficient and environmentally-friendly as the reaction produced no organic waste. The versatility of the Achmatowicz

reaction has been demonstrated in the synthesis of a wide variety of biologically active natural products and bioactive carbohydrates. In this review, we have highlighted the Achmatowicz reaction, the development of various oxidative protocols, and the application in synthesis of functionalized tetrahydropyrans and their conversion to natural products and various carbohydrates. The review provides a broad picture of the Achmatowicz reaction and we hope that it will stimulate further development particularly in the areas of asymmetric synthesis and process development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AIBN Azobisisobutyronitrile

***t*-BuOOH** *tert*-Butyl hydroperoxide

CBS	Corey-Bakshi-Shibata catalyst
COX-1	Cyclooxygenase-1
***m*-CPBA**	*meta*-Chloroperoxybenzoic acid
CSA	Camphorsulfonic acid
DA	Diels–Alder
DIBAL-H	Diisobutylaluminium hydride
DIPT	Diisopropyl *D*-tartrate
DKDA	Dynamic kinetic diastereoselective acylation
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
2,2-DMP	2,2-Dimethoxypropane
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DOBCO	dioxabicyclo-[3.2.1]octane
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
FMO	Frontier molecular orbital
G-I	First-generation Grubbs catalyst
G-II	Second-generation Grubbs catalyst
HDA	Hetero- Diels–Alder
HFIP	Hexafluoroisopropanol
IBDA	Iodobenzenediacetate
Ipc	Isopinocampheyl
LA	Lewis-acid
LDA	Lithium diisopropylamide
LG	Leaving group
MRSA	Methicillin-resistant *S. aureus*
NAD	Nicotinamide adenine dinucleotide
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide

NMO	*N*-Methylmorpholine *N*-oxide
PCC	Pyridinium chlorochromate
Piv	Pivaloyl
PMB	*para*-Methoxy benzyl
PsB	Psoracorylifol B
PsC	Psoracorylifol C
PPTS	Pyridinium *p*-toluenesulfonate
PT	Phenyltetrazole
RCM	Ring-closing metathesis
RNA	Ribonucleic acid
TBAF	Tetra-*n*-butylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TCDI	1,1′-Thiocarbonyldiimidazole
TEA	Triethylamine
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TES	Triethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TPAP	Tetrapropylammonium perruthenate
TOS	Targeted Oriented Synthesis
TS-1	Titanium silicalite 1
VO(acac)$_2$	Vanadyl acetylacetonate

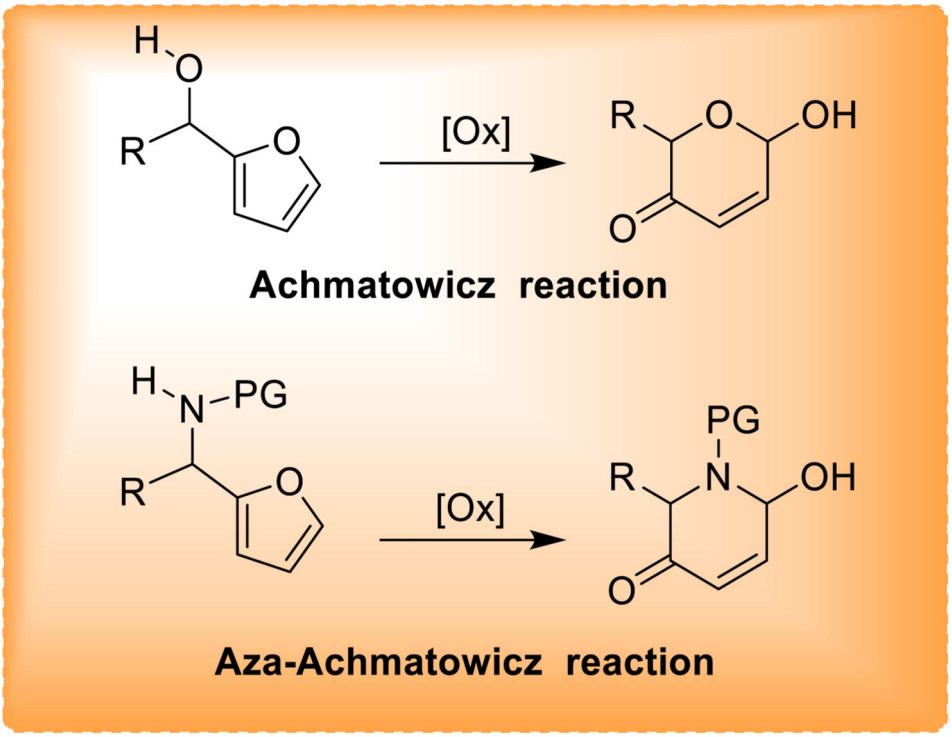


Figure 1.
General outline of Achmatowicz and aza-Achmatowicz reactions.

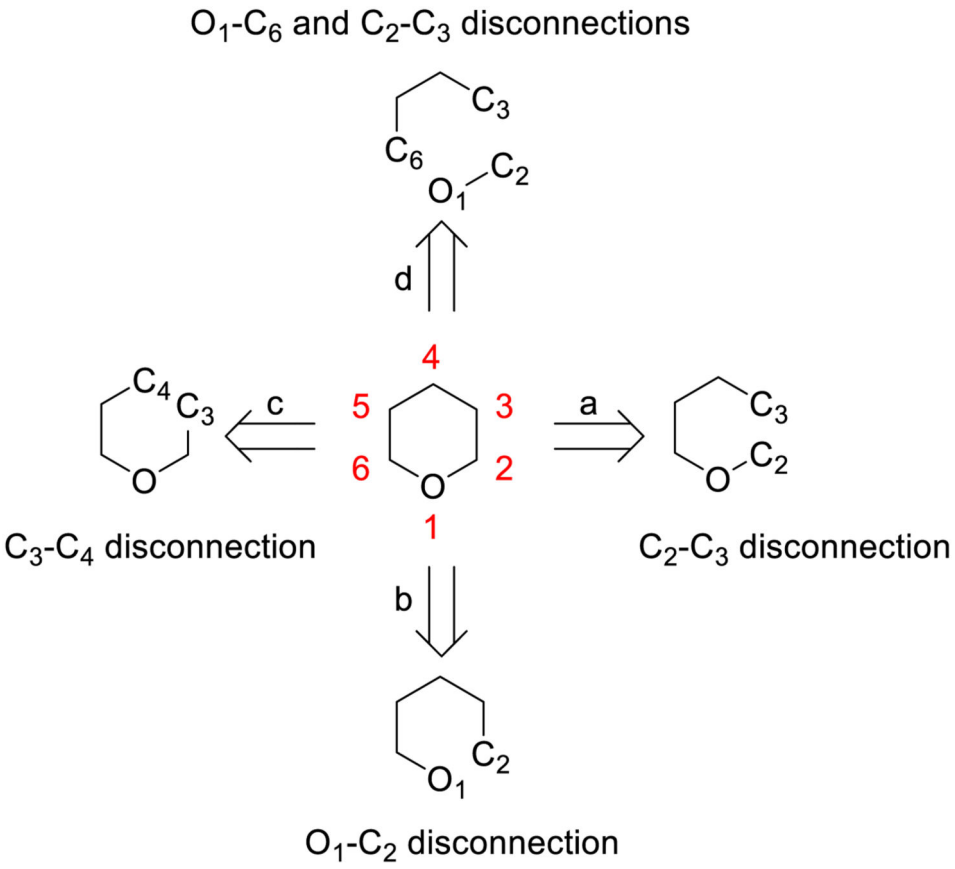


Figure 2.
Key retrosynthetic disconnections of the pyran ring.

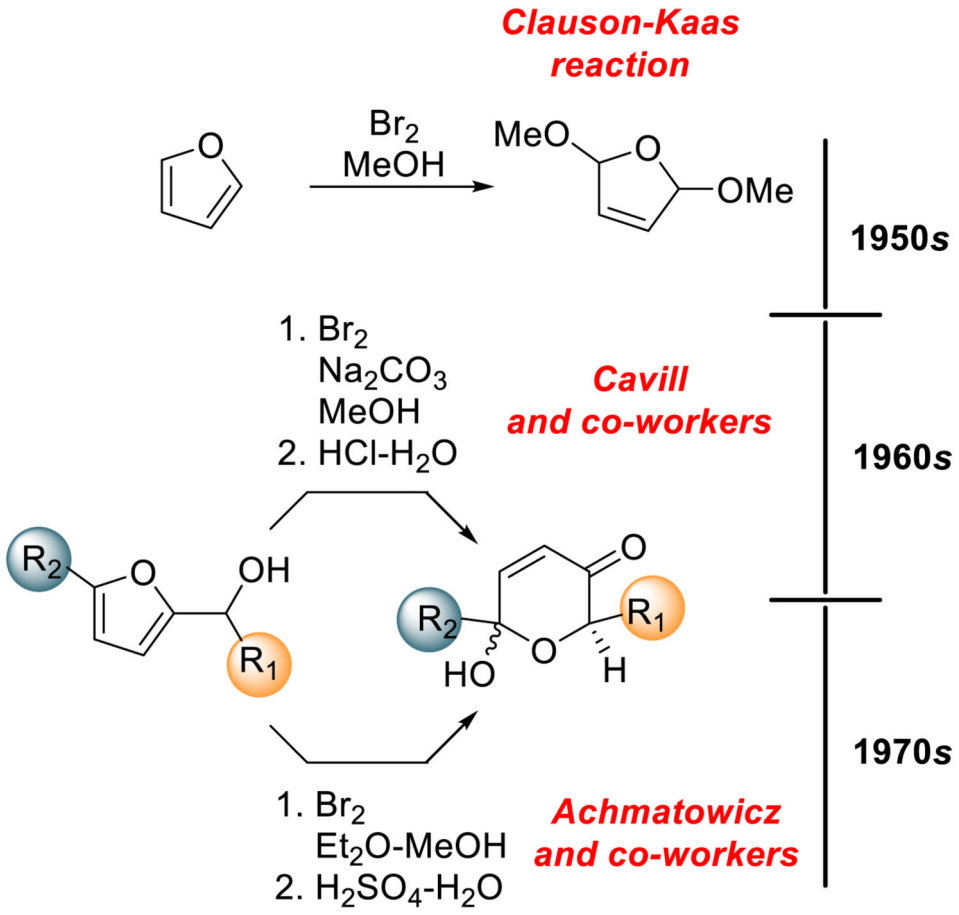


Figure 3.
The timeline and historical overview of furan oxidative ring expansion.

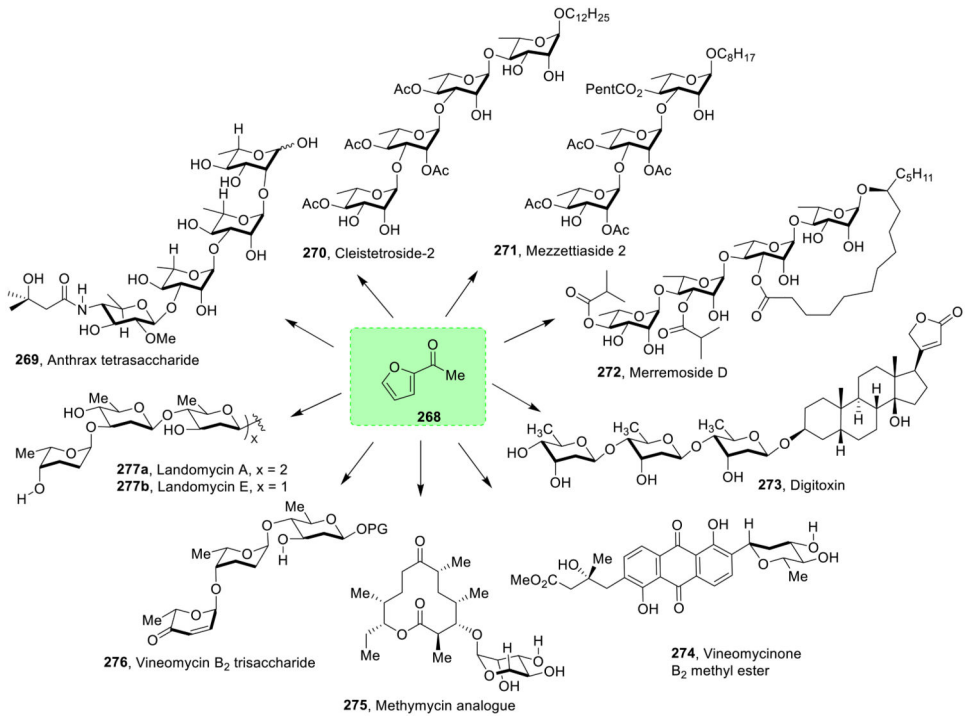
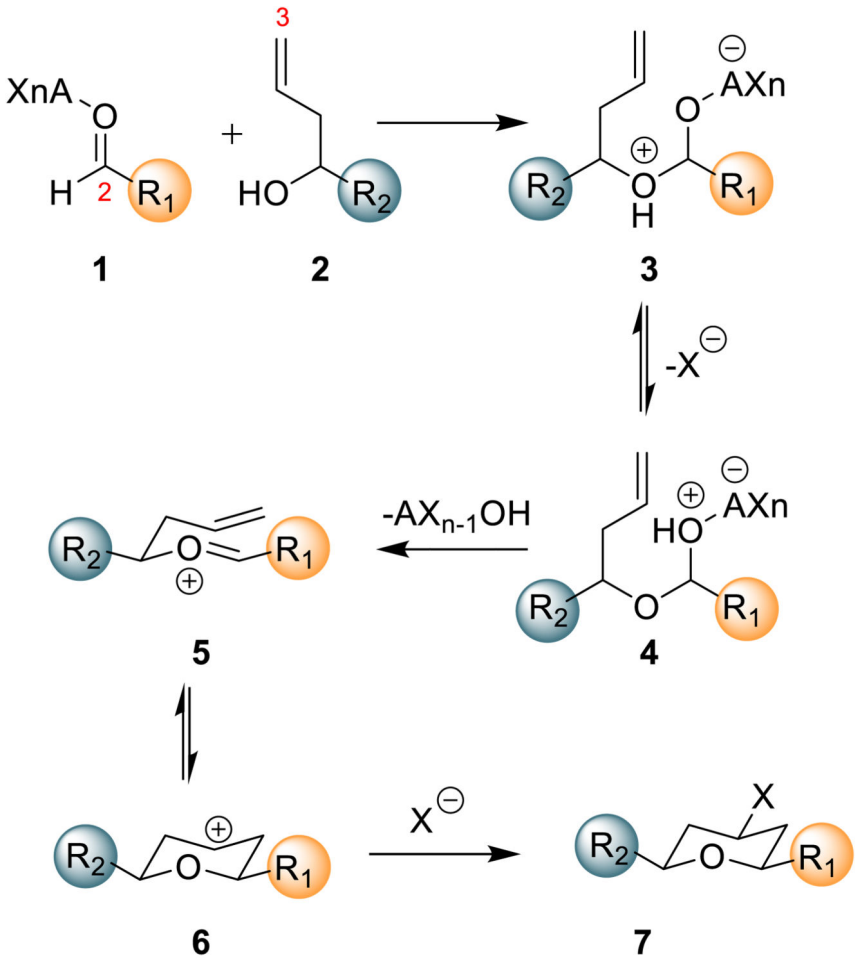
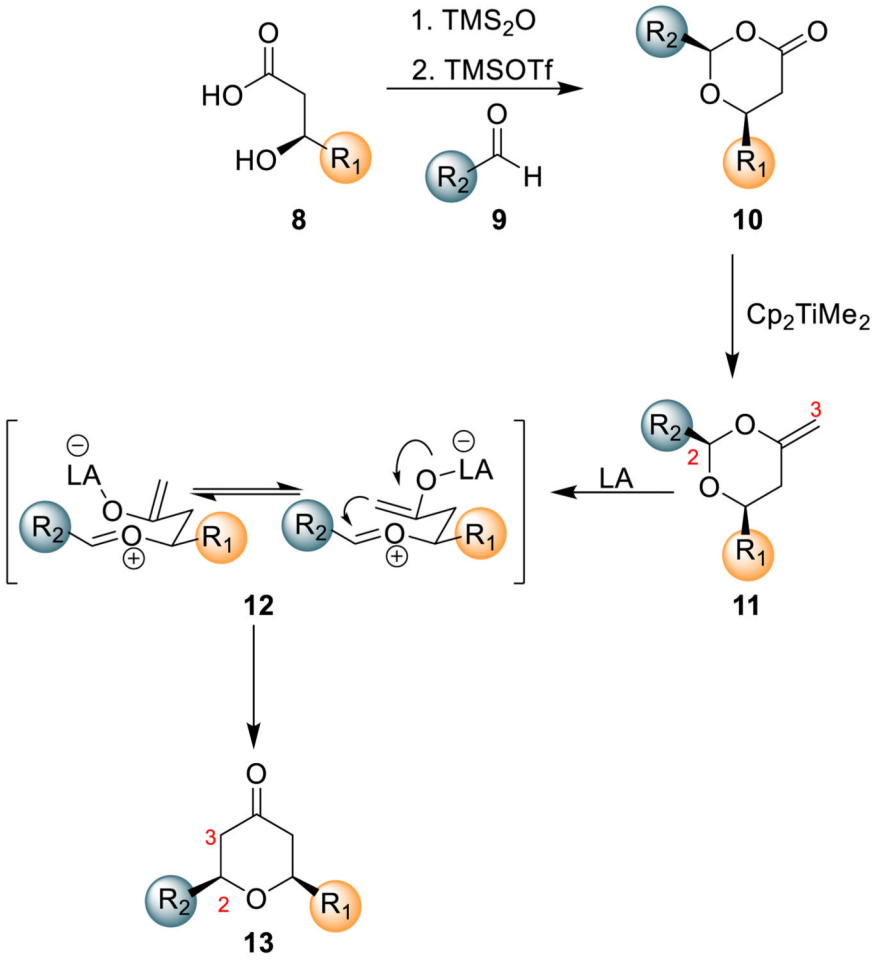


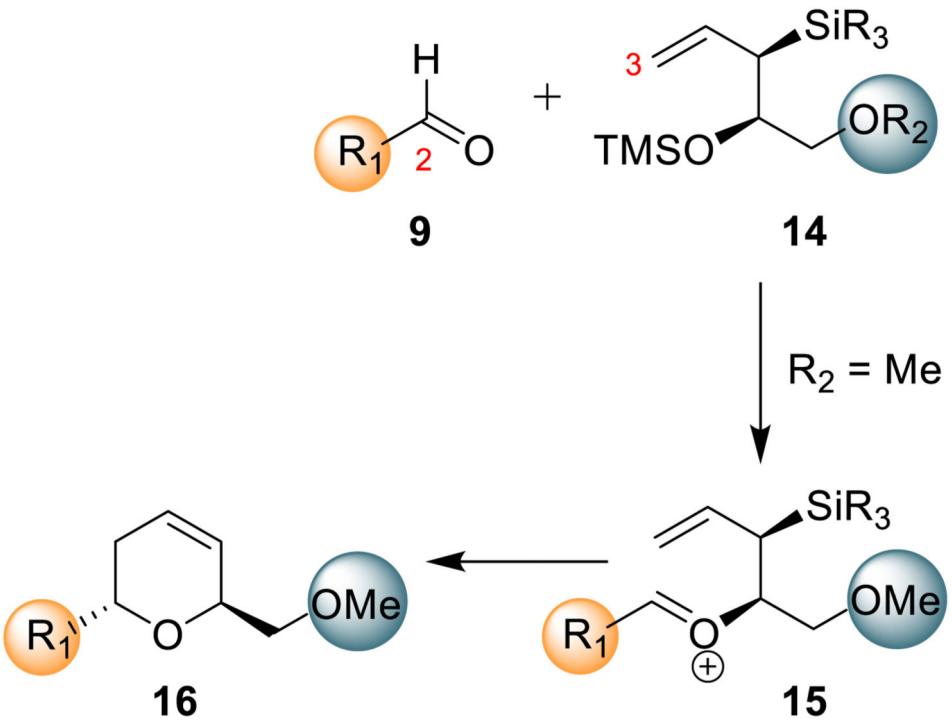
Figure 4.
Naturally occurring carbohydrate structural motifs originating from 2-acetylfuran.



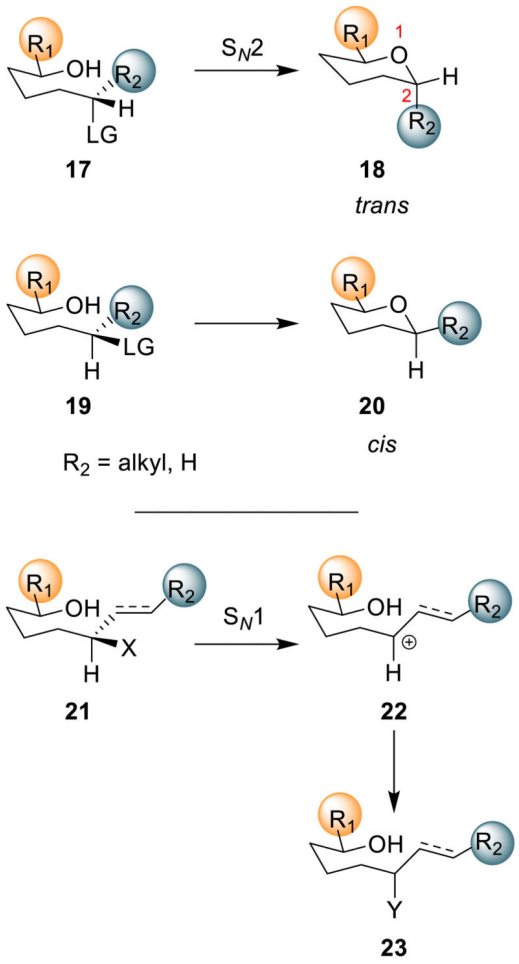
Scheme 1.
General scheme for Prins cyclization.



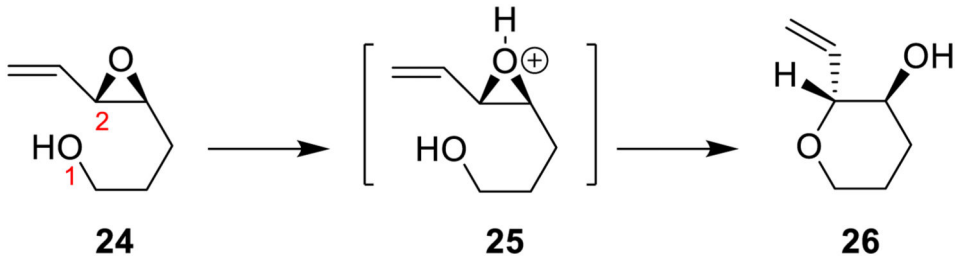
Scheme 2.
General scheme for Petasis–Ferrier rearrangement mechanism.



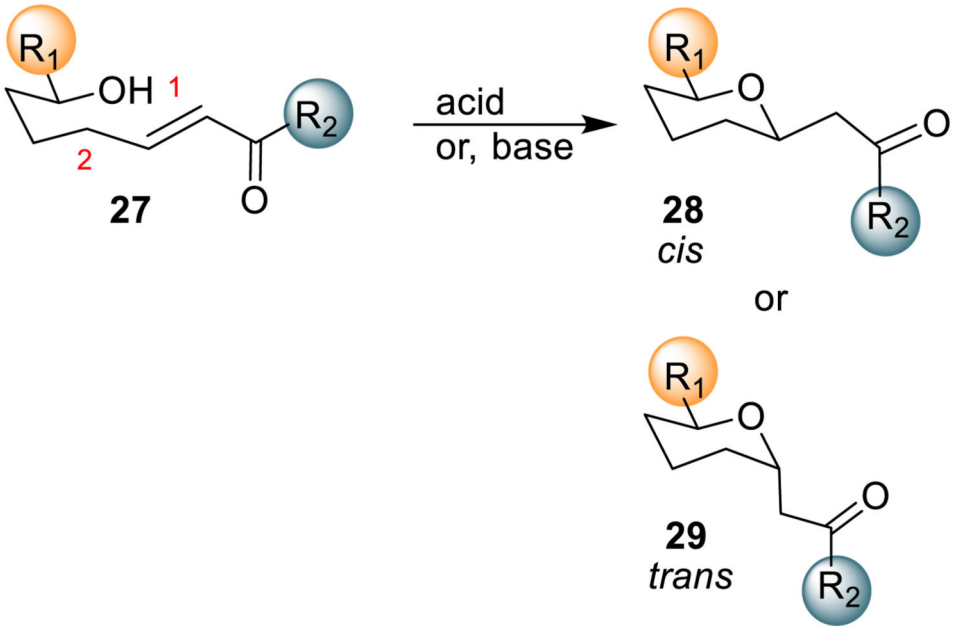
Scheme 3.
General scheme for Panek annulation.



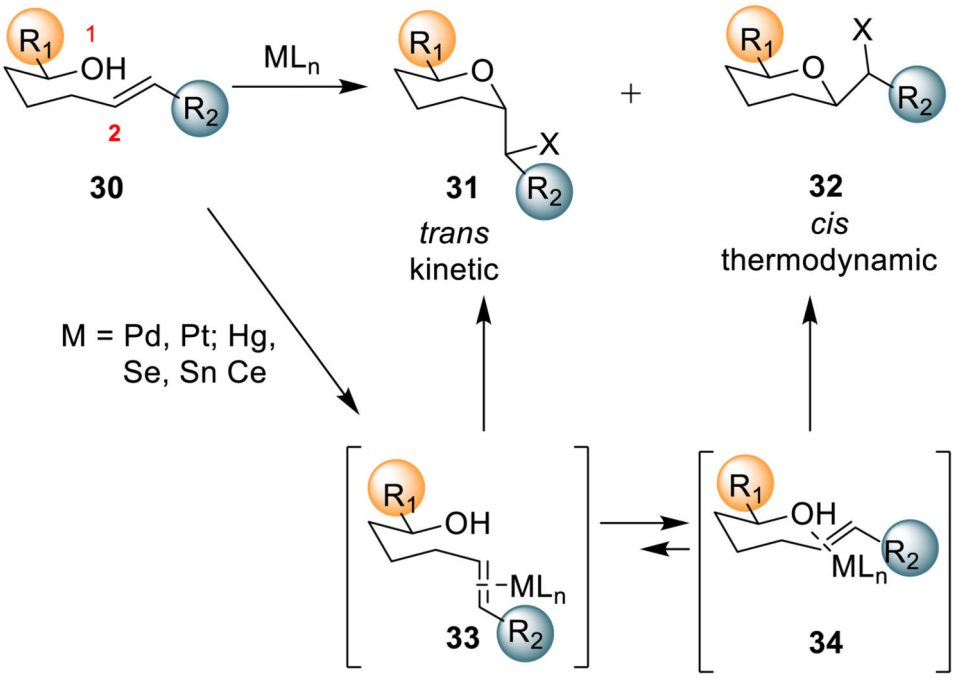
Scheme 4.
General outline for nucleophilic substitution strategies.



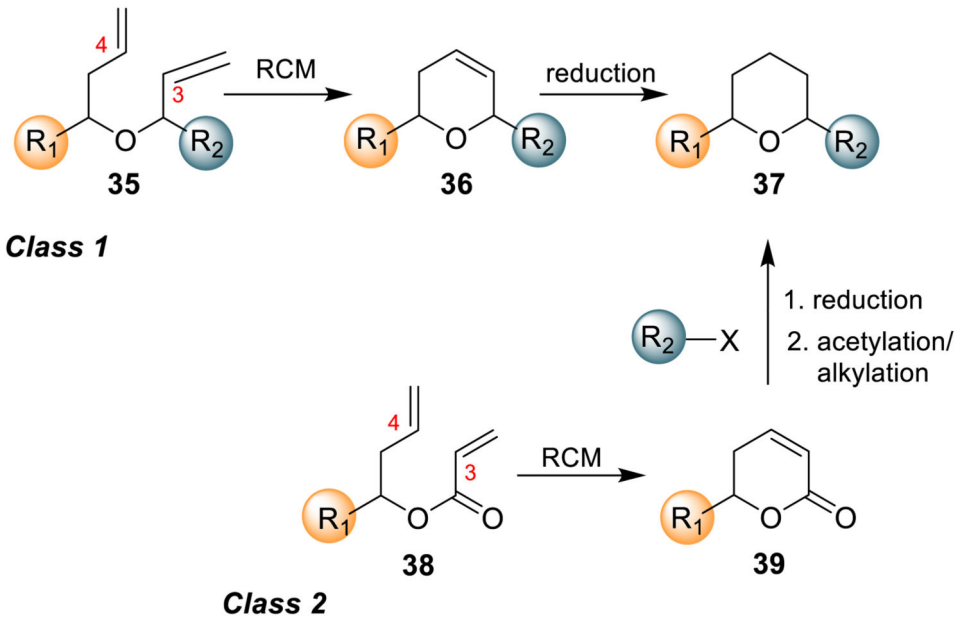
Scheme 5.
Intramolecular selective 6-*endo* epoxide opening by Nicolaou.



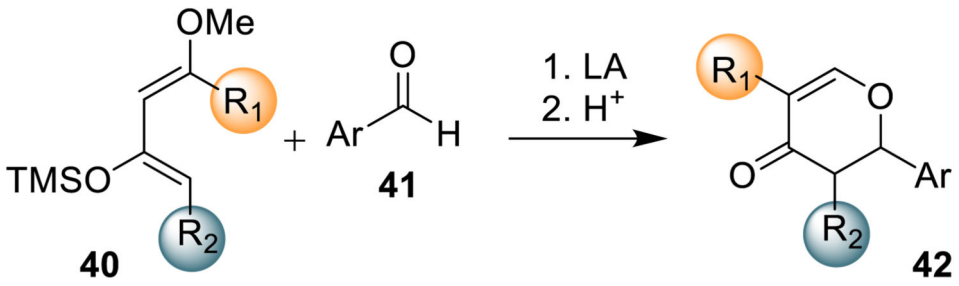
Scheme 6.
General scheme for conjugate addition.



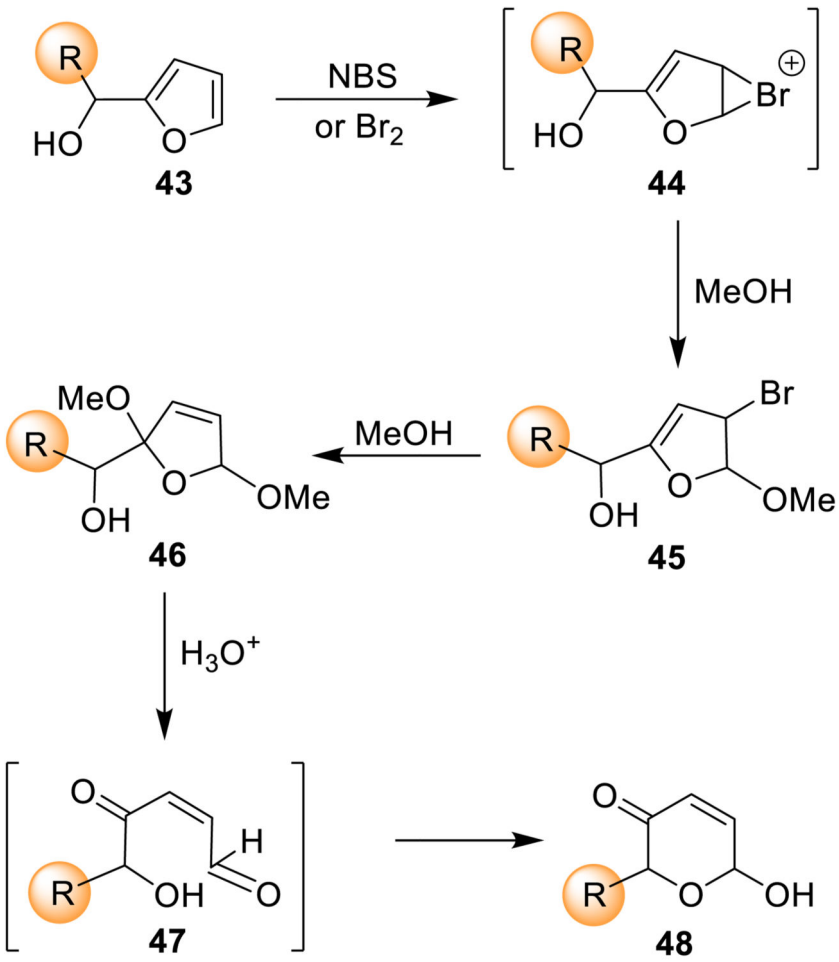
Scheme 7.
General scheme for metal-mediated alkene cyclization.



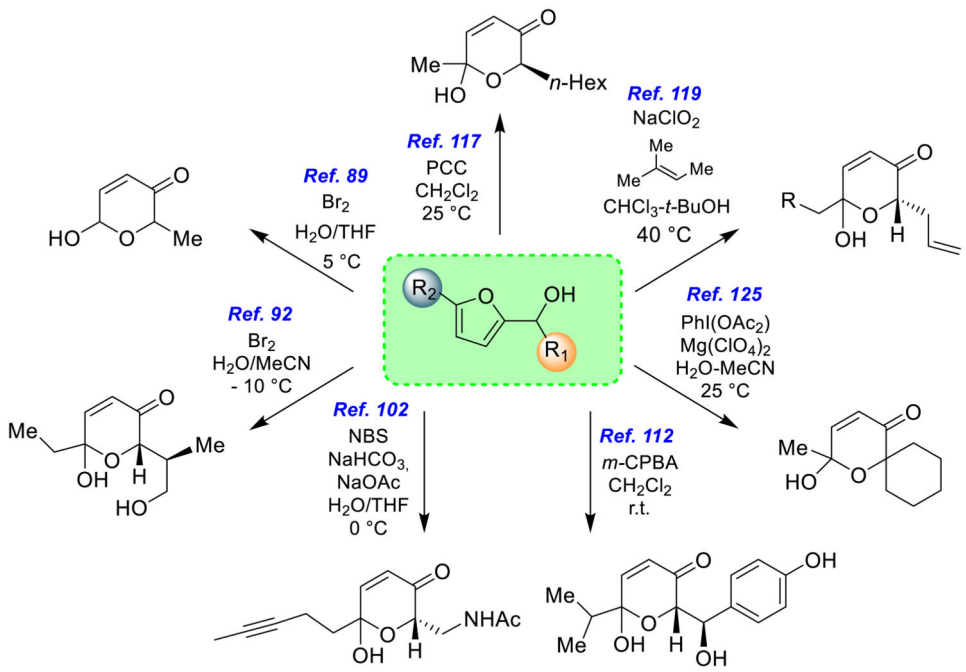
Scheme 8.
General scheme of Class 1 and Class 2 ring-closing metathesis.



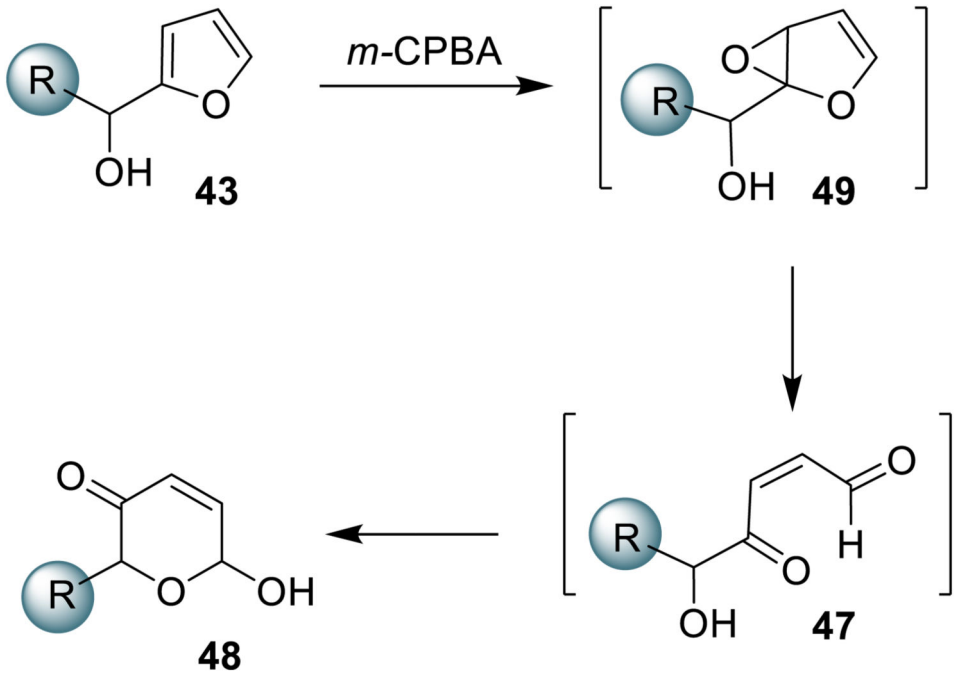
Scheme 9.
Hetero-Diels–Alder reaction between Danishefsky's type diene and an arylaldehyde.



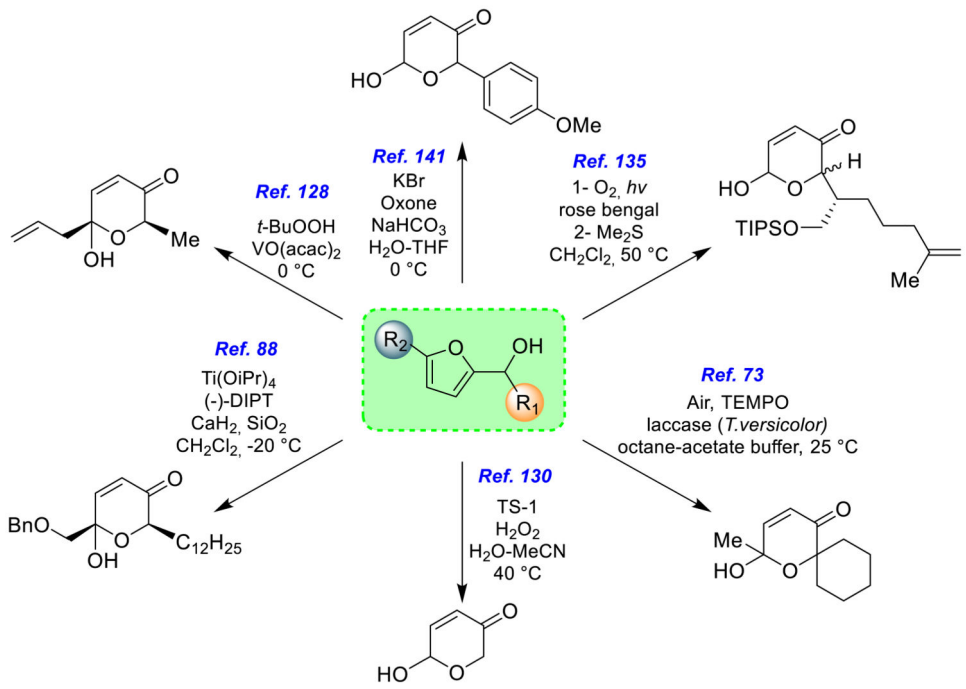
Scheme 10.
Achmatowicz reaction in the presence of Br_2/MeOH or NBS/MeOH systems.



Scheme 11.
Synthetic protocols for the Achmatowicz reaction.

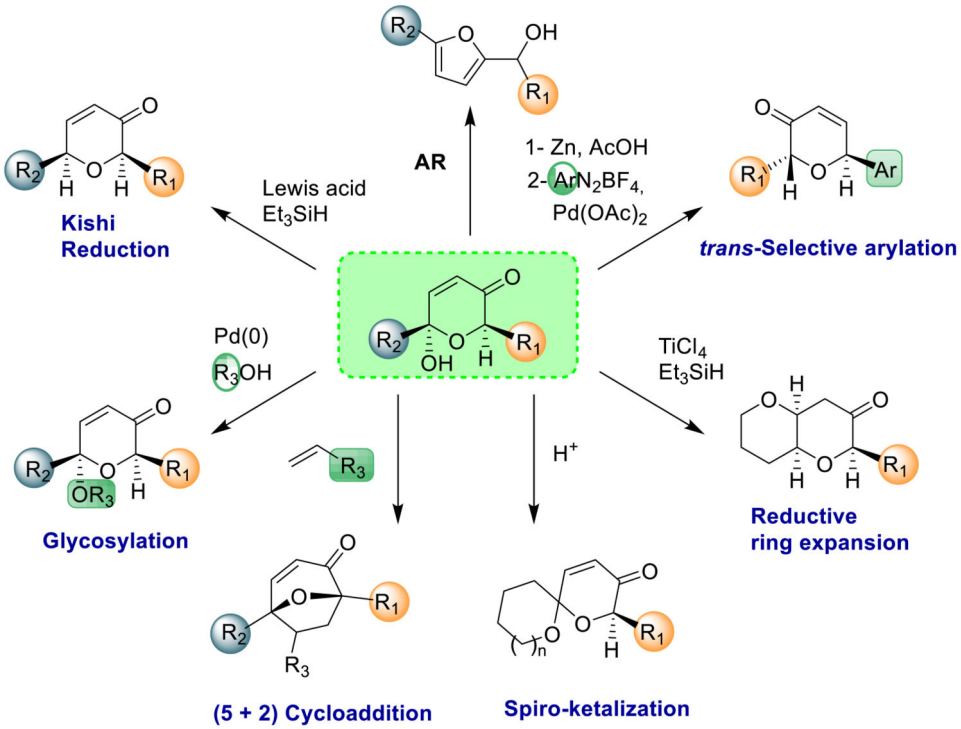


Scheme 12.
Achmatowicz reaction in the presence of *m*-CPBA.



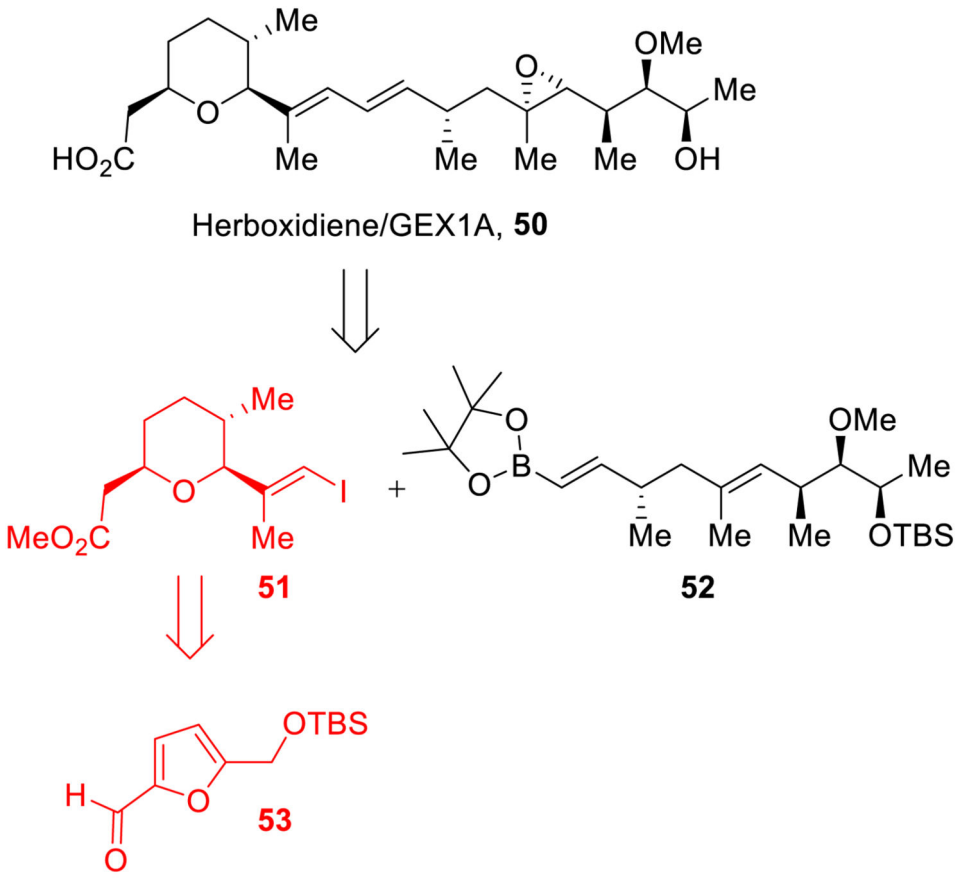
Scheme 13.

Metal-catalysed, photolytic and eco-friendly synthetic variants for Achmatowicz reaction.



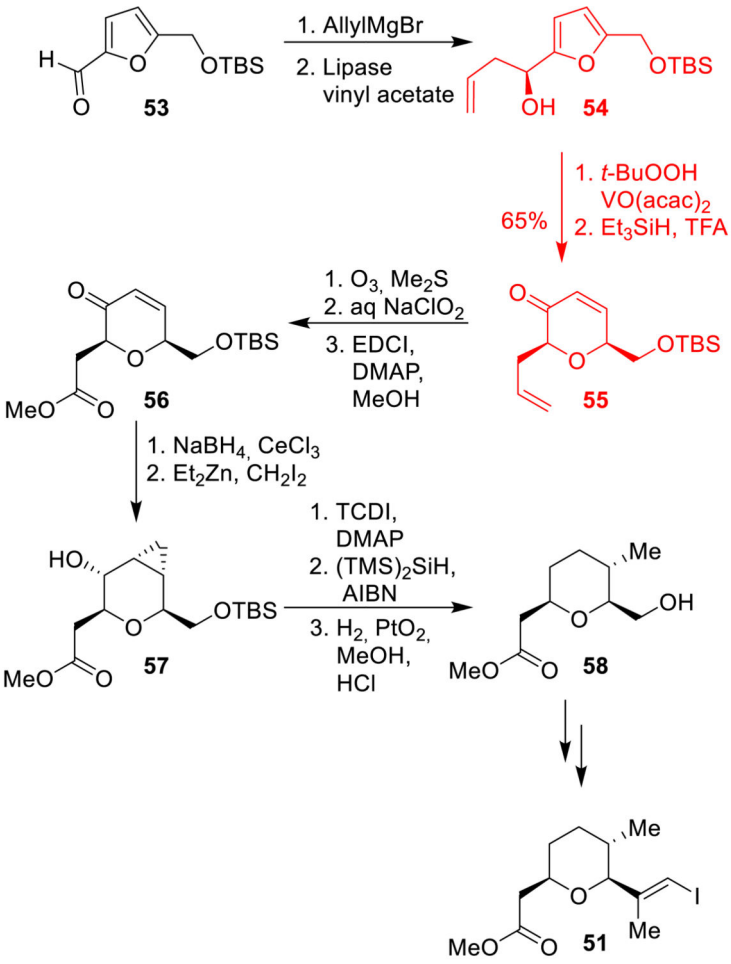
Scheme 14.

Representative transformations and applications of Achmatowicz reaction adducts.



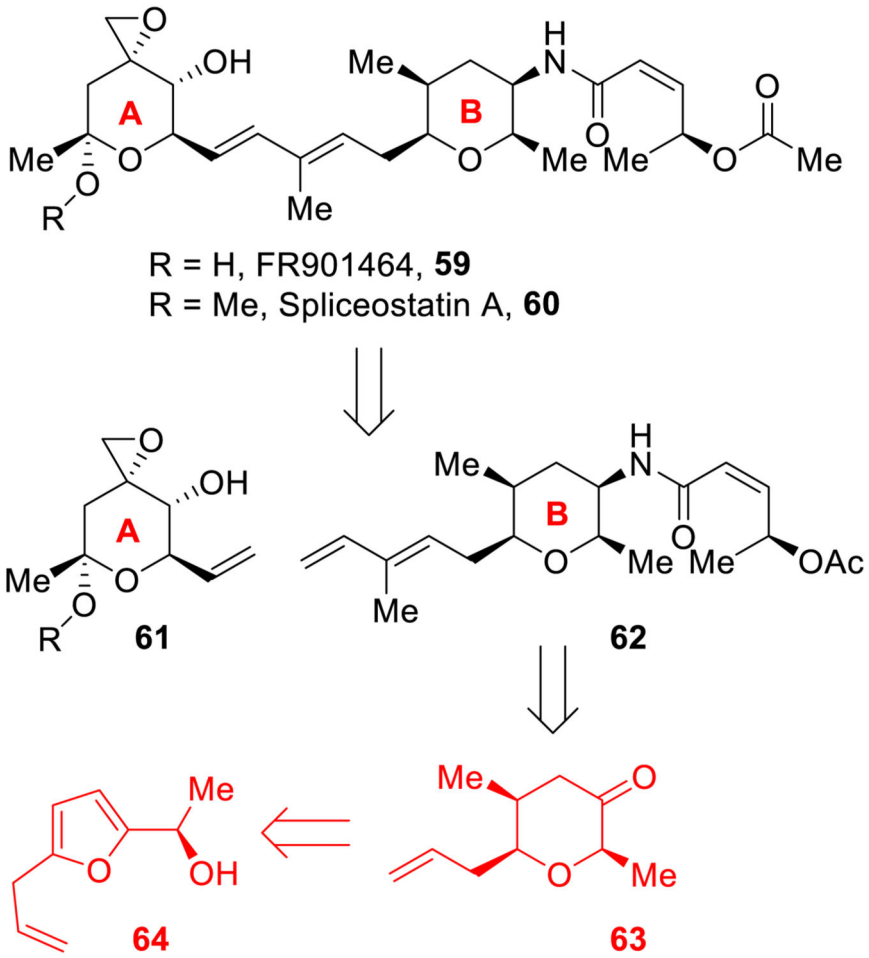
Scheme 15.

Retrosynthetic analysis for the synthesis of Herboxidiene (**50**). A key Achmatowicz reaction step is highlighted in red.



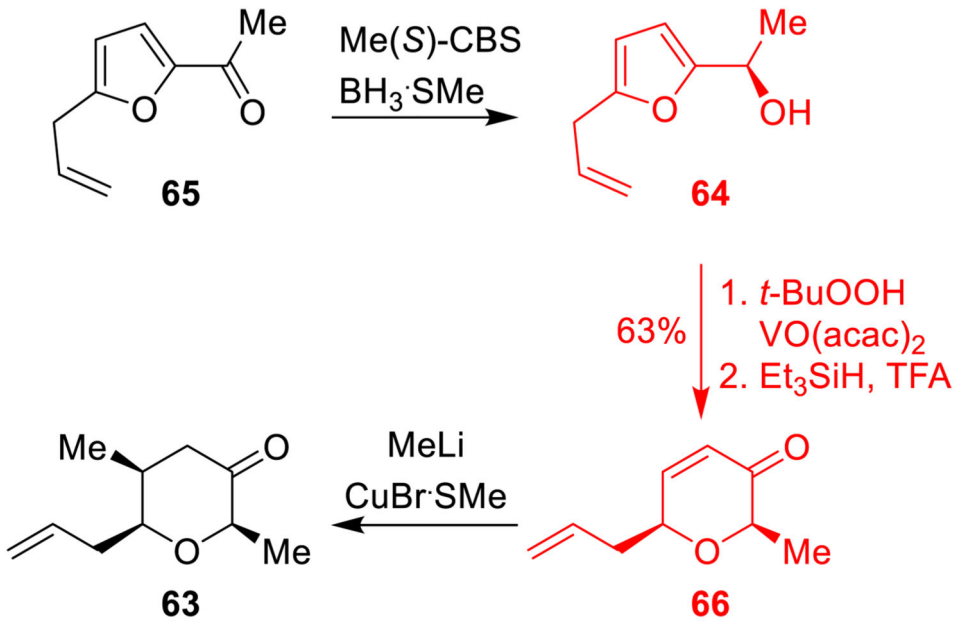
Scheme 16.

Synthesis of the key vinyl iodide **51** involving an Achmatowicz reaction (highlighted in red).



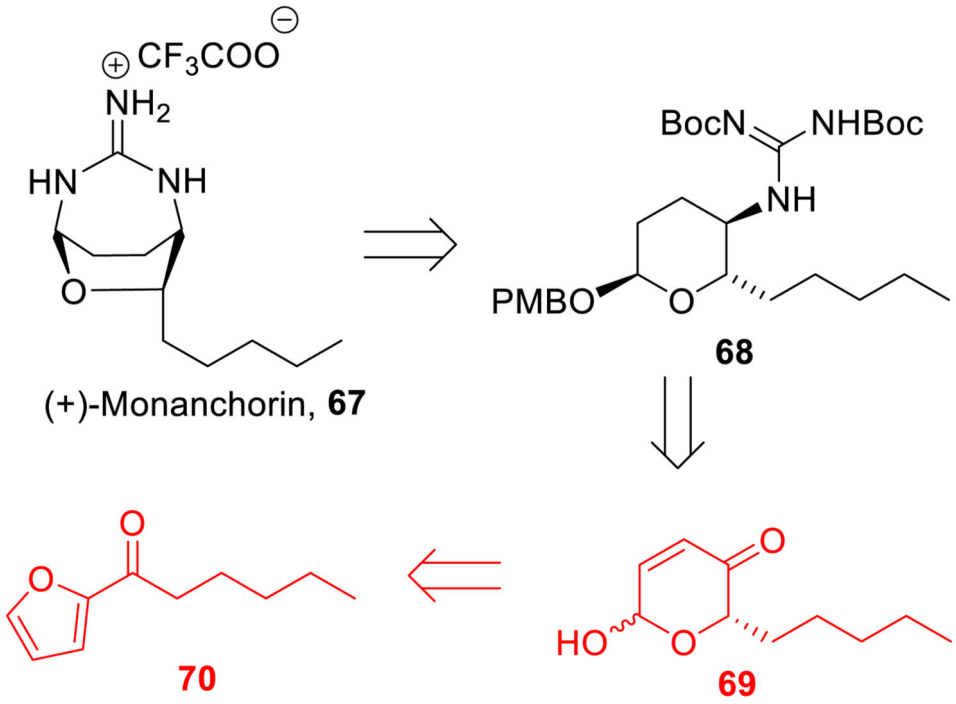
Scheme 17.

Retrosynthetic analysis for the synthesis of FR901464 (**59**) and Spliceostatin A (**60**). A key Achmatowicz reaction is highlighted in red.



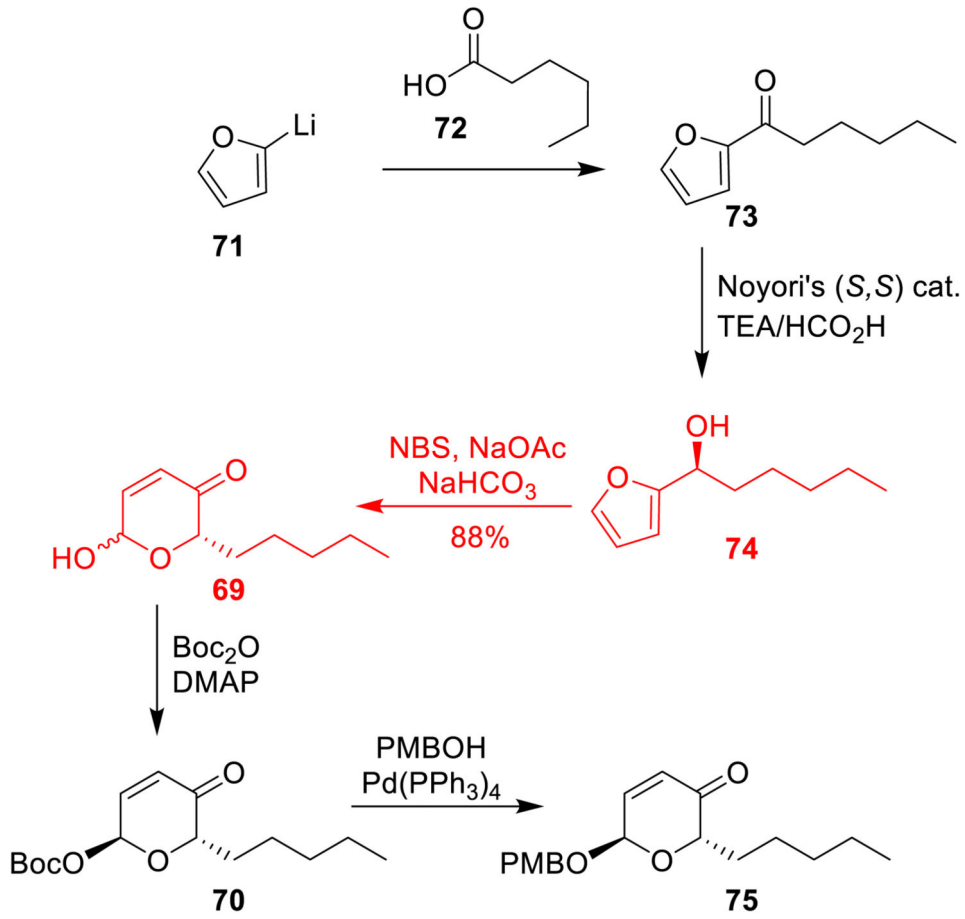
Scheme 18.

Synthesis of the key retrosynthetic fragment **63** using an Achmatowicz reaction as a key step (highlighted in red).



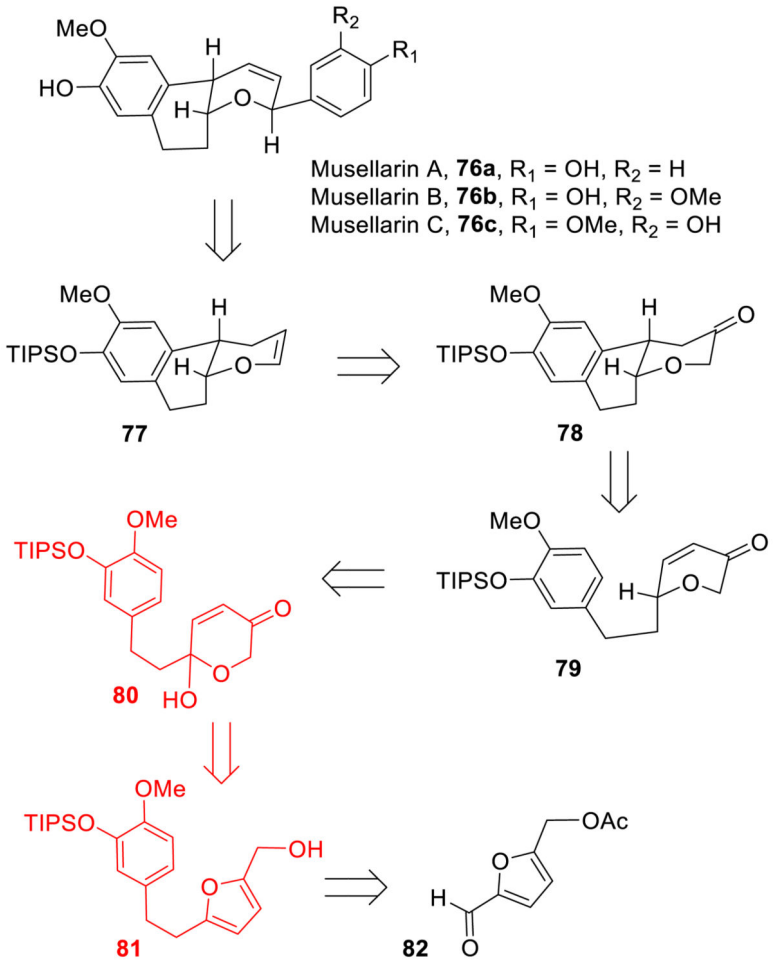
Scheme 19.

Retrosynthetic analysis for the synthesis of (+)-Monanchorin (**67**). A key Achmatowicz reaction step is highlighted in red.



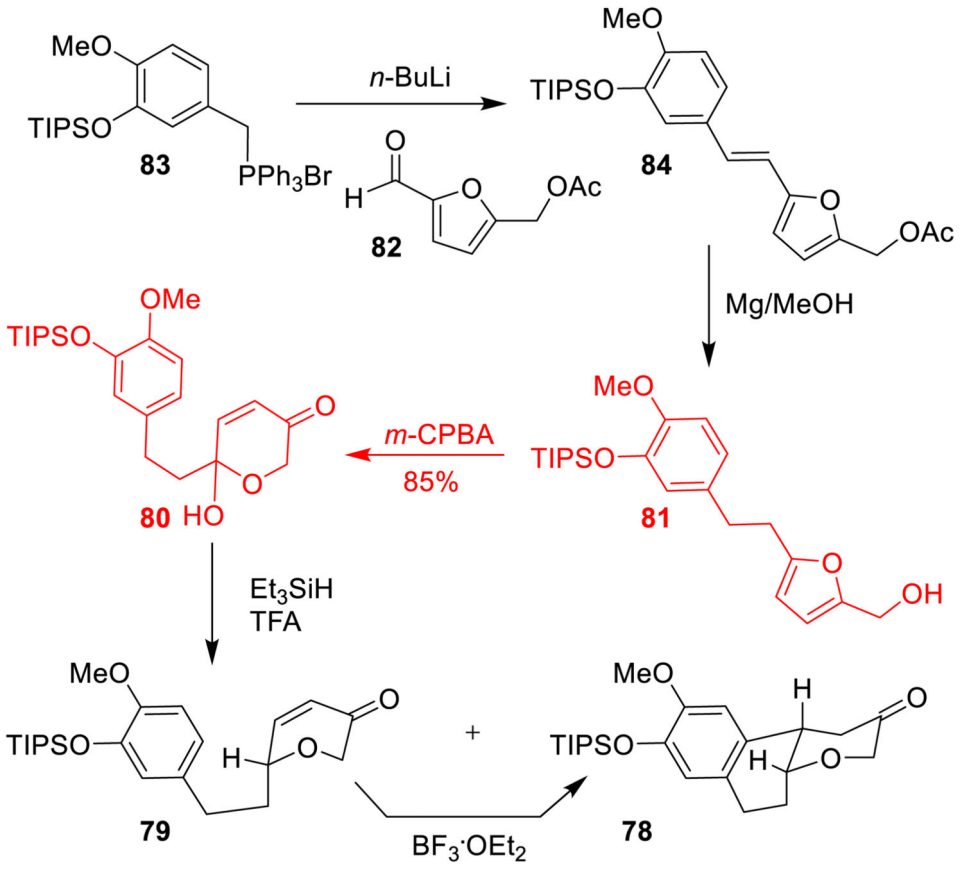
Scheme 20.

Synthesis of the key enone fragment **75** using Achmatowicz reaction (highlighted in red).



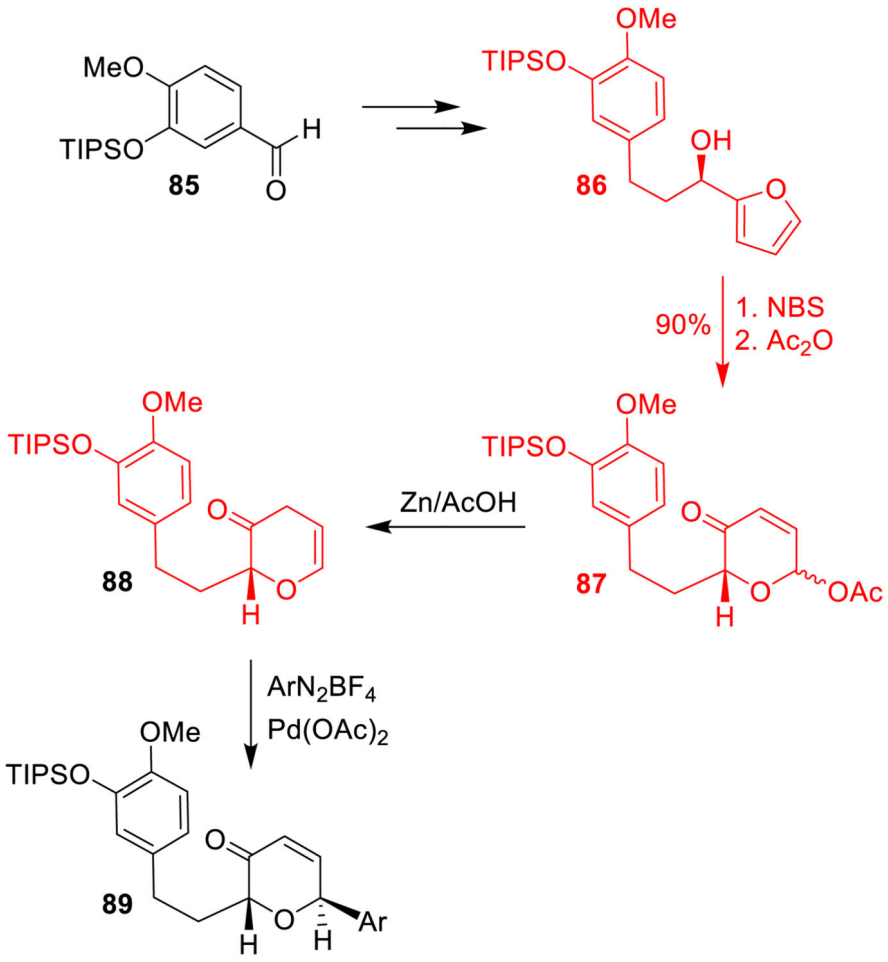
Scheme 21.

Retrosynthetic analysis for the synthesis of (±)-Musellarins A–C (**76a-c**). A key Achmatowicz reaction step is highlighted in red.



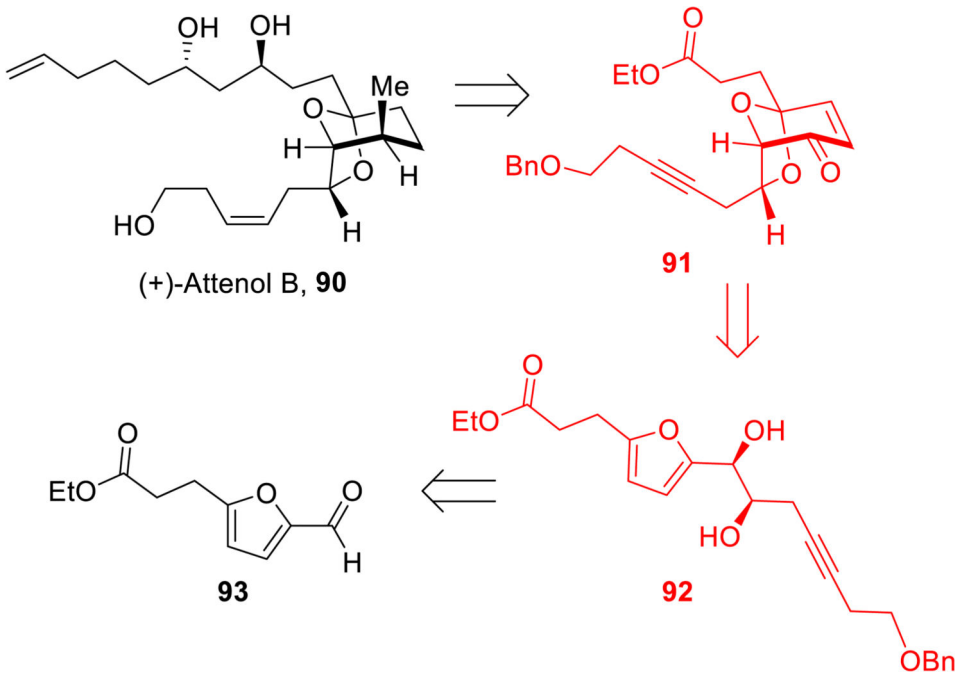
Scheme 22.

Synthesis of the key lactone fragment **78** by an Achmatowicz reaction (highlighted in red).



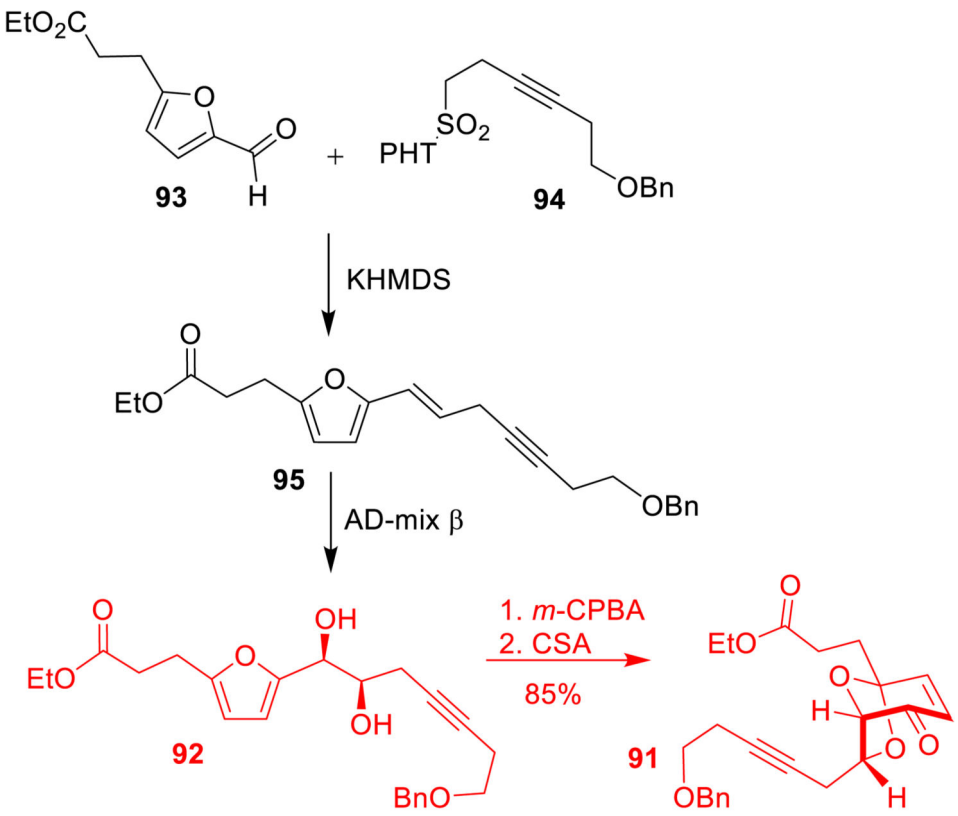
Scheme 23.

Synthesis of key intermediate **89** for the synthesis of (-)-musellarins A–C involving an Achmatowicz reaction (highlighted in red).



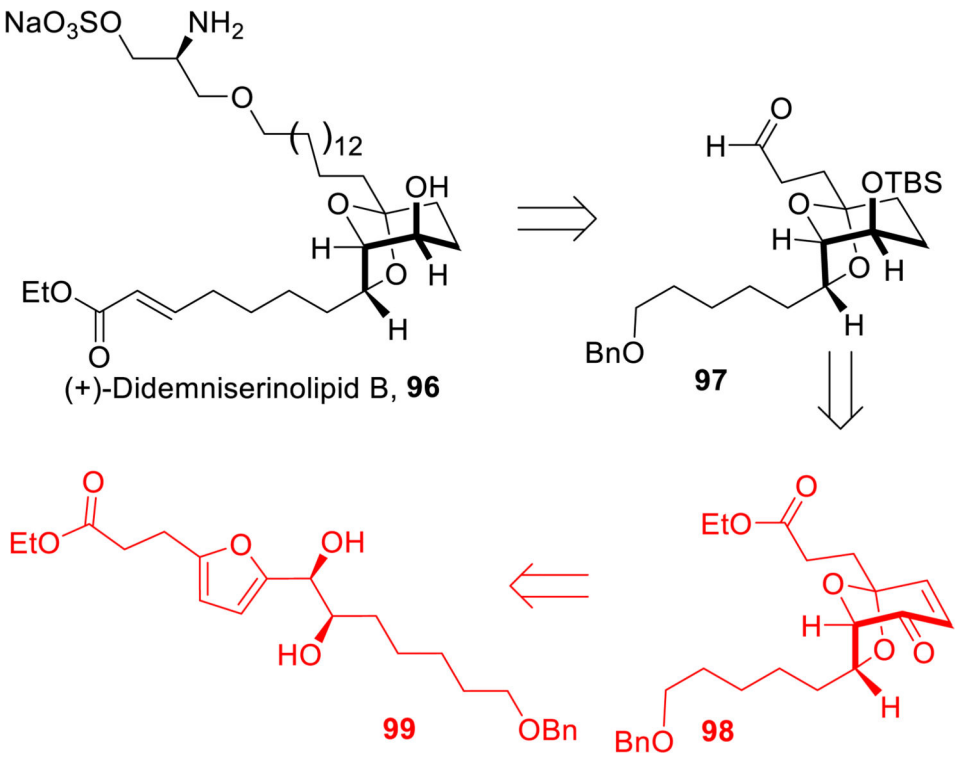
Scheme 24.

Retrosynthetic analysis for the synthesis of (+)-Attenol B (**90**). A key Achmatowicz reaction step is highlighted in red.



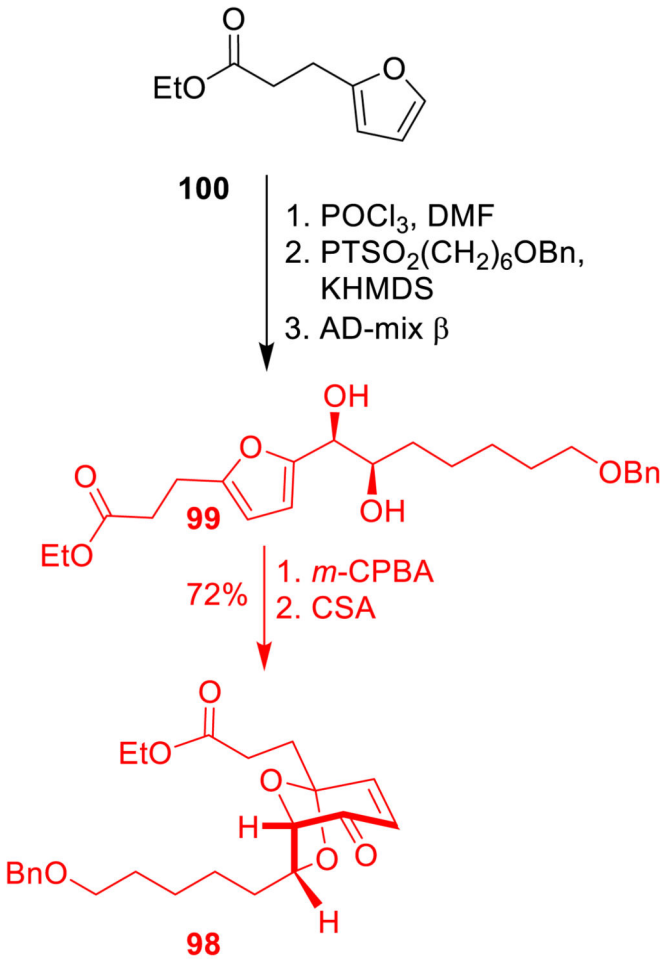
Scheme 25.

Synthesis of the key retrosynthetic fragment **91** involving an Achmatowicz reaction (highlighted in red).



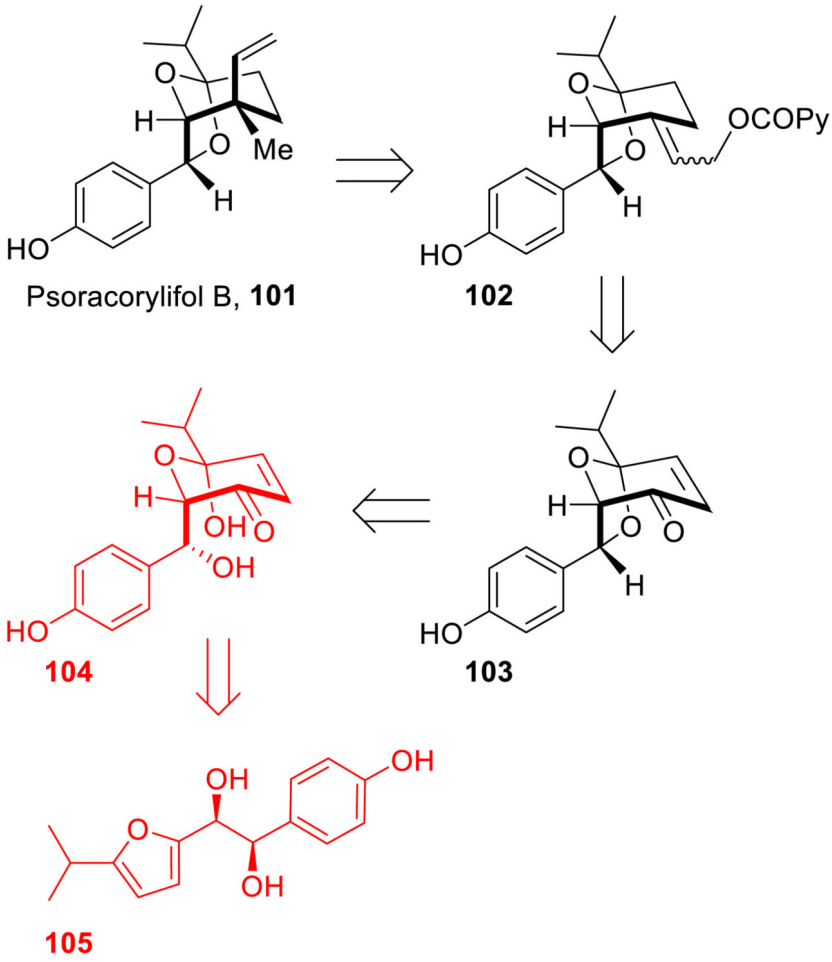
Scheme 26.

Retrosynthetic analysis for the synthesis of (+)-Didemniserinolipid B (**96**). A key Achmatowicz reaction is highlighted in red.



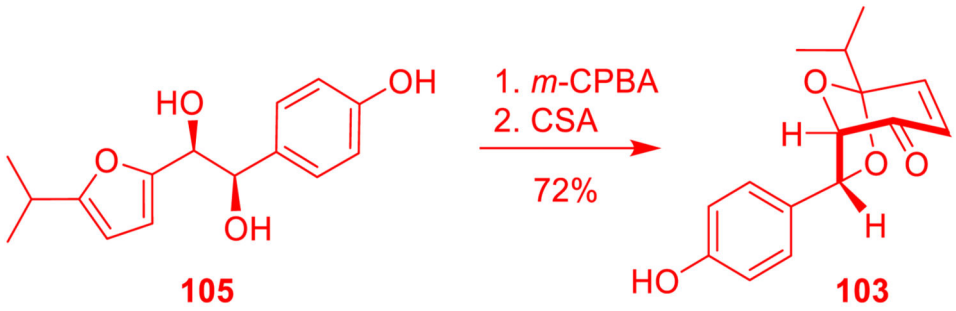
Scheme 27.

Synthesis of the key retrosynthetic fragment **98** involving an Achmatowicz reaction (highlighted in red).



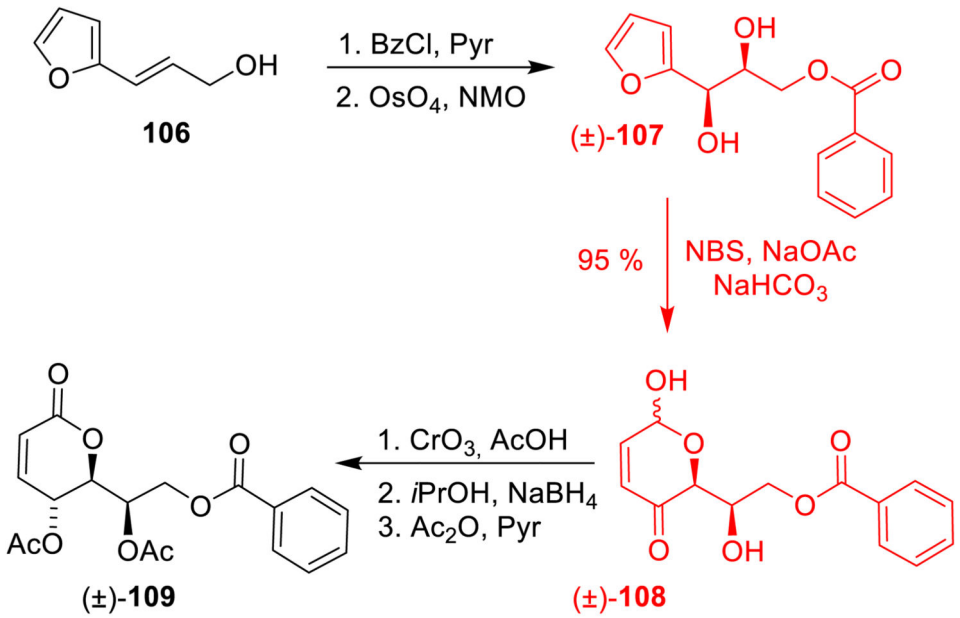
Scheme 28.

Retrosynthetic analysis for the synthesis of (+)-psoracorylifol B (**101**). A key Achmatowicz reaction is highlighted in red.



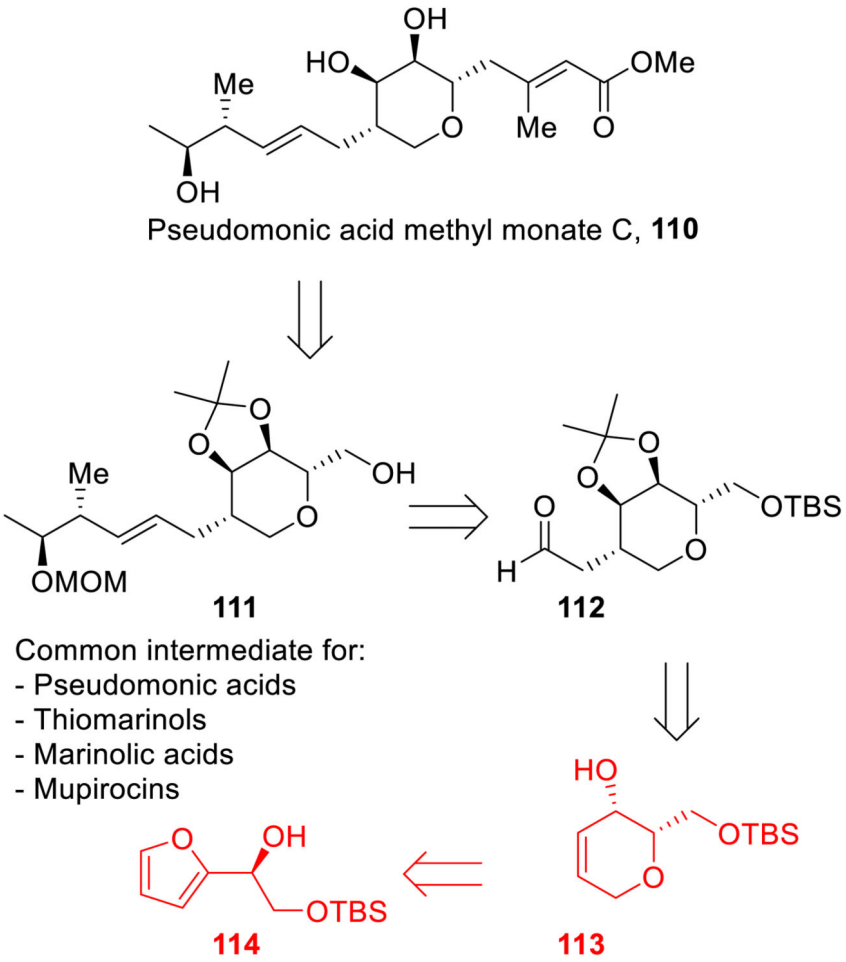
Scheme 29.

Synthesis of the key retrosynthetic fragment **103** involving an Achmatowicz reaction (highlighted in red).



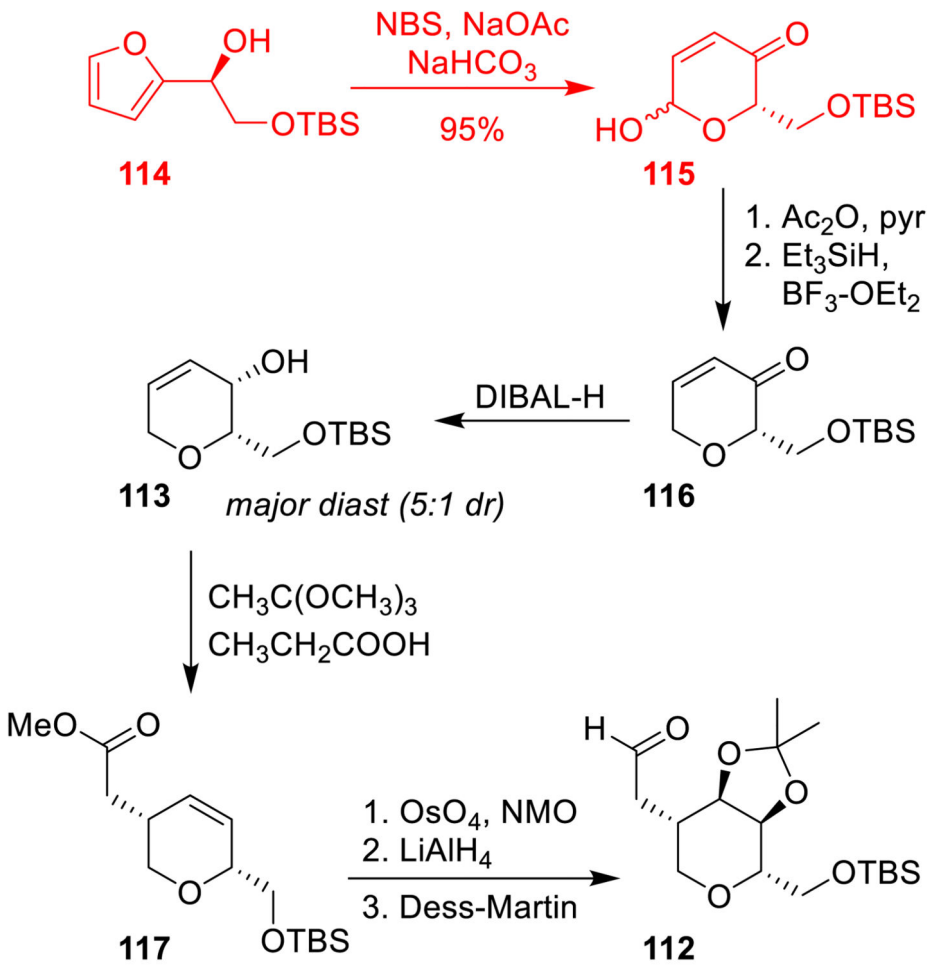
Scheme 30.

Synthesis of (±)-6-*epi*-cleistenolide (±)-**109** involving an Achmatowicz reaction (highlighted in red).



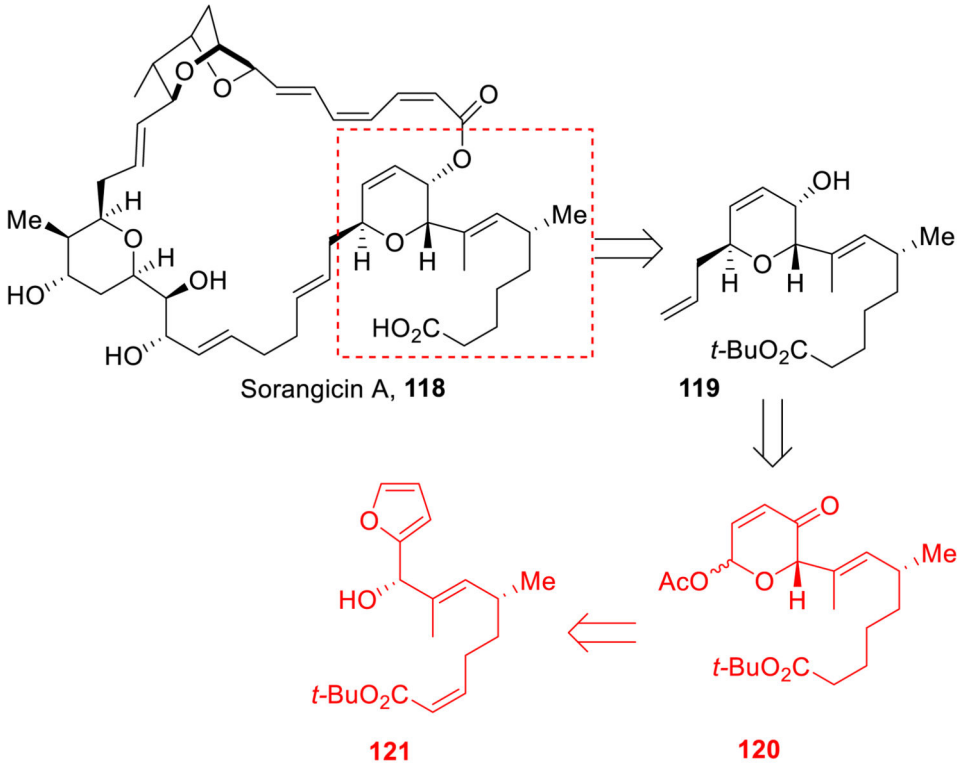
Scheme 31.

Retrosynthetic analysis for pseudomonic acids, thiomarinols and mupirocins. A key Achmatowicz reaction is highlighted in red.



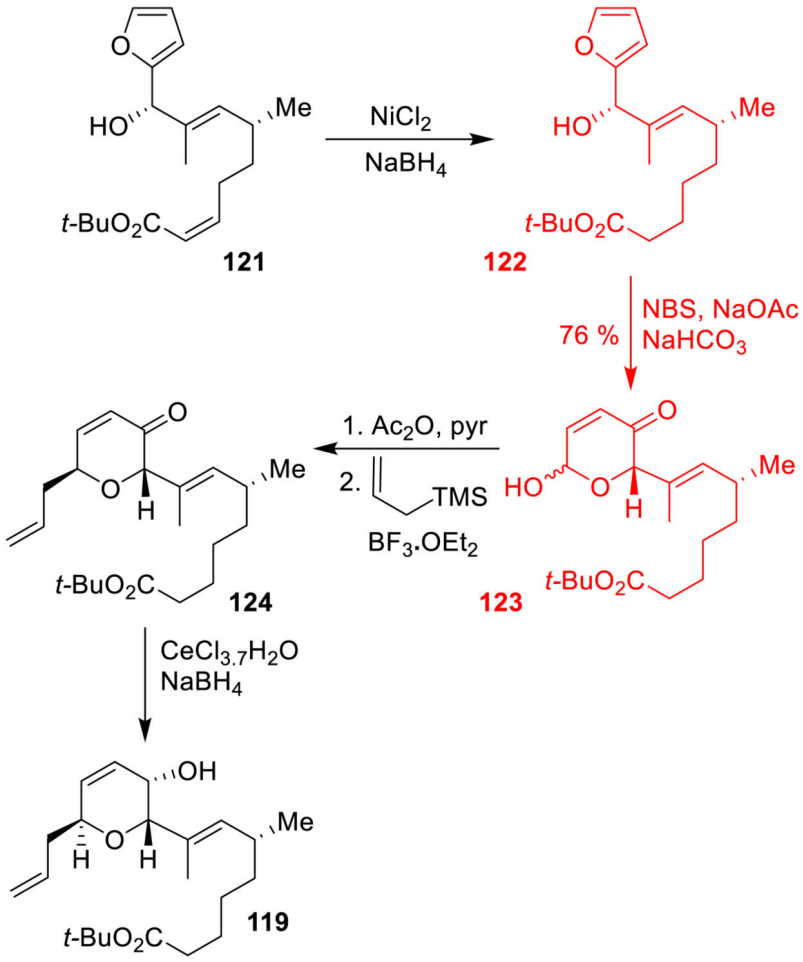
Scheme 32.

Synthesis of the key retrosynthetic fragment **112** involving an Achmatowicz reaction (highlighted in red).



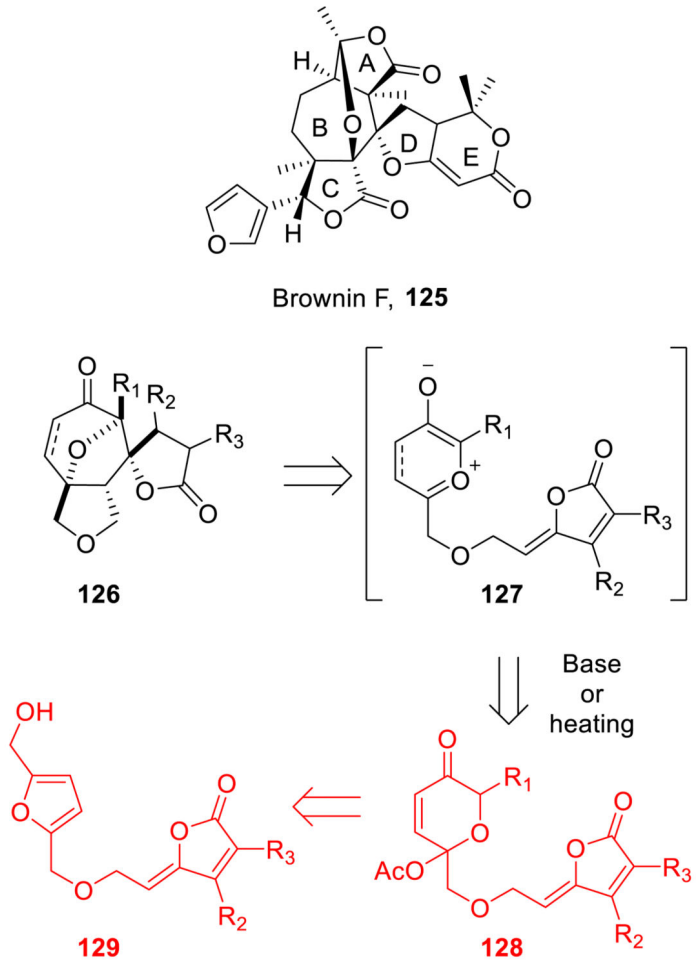
Scheme 33.

Retrosynthetic analysis for synthesis of the south eastern segment (C1–C16) of (+)-Sorangicin A (**118**). A key Achmatowicz reaction step is highlighted in red.



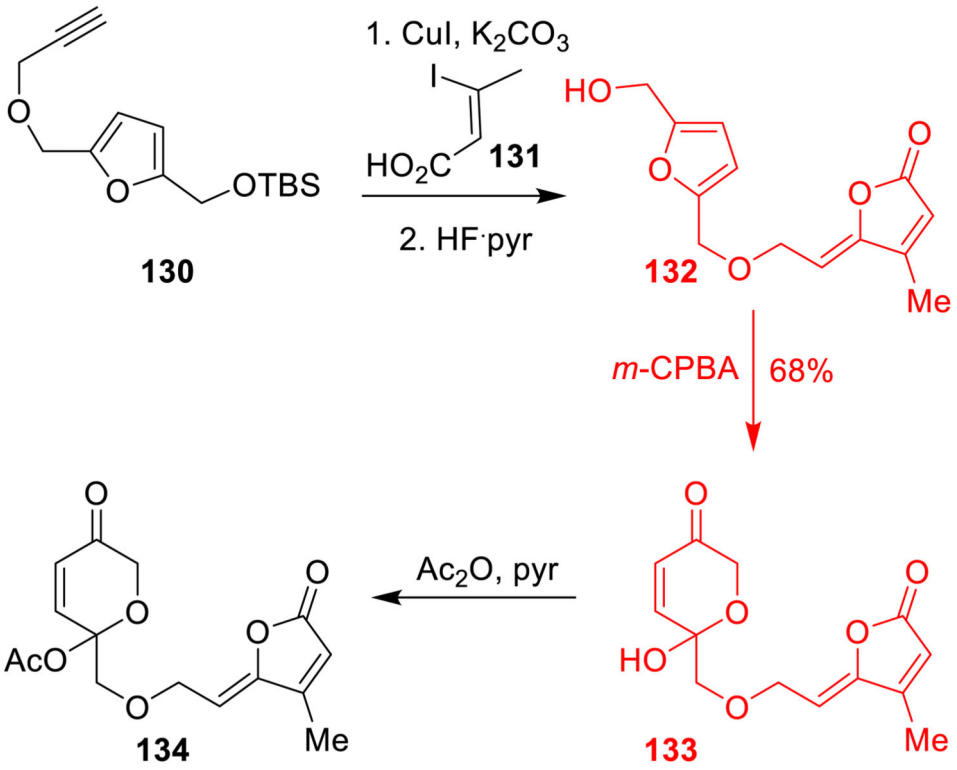
Scheme 34.

Synthesis of the key retrosynthetic fragment **119** involving an Achmatowicz reaction (highlighted in red).



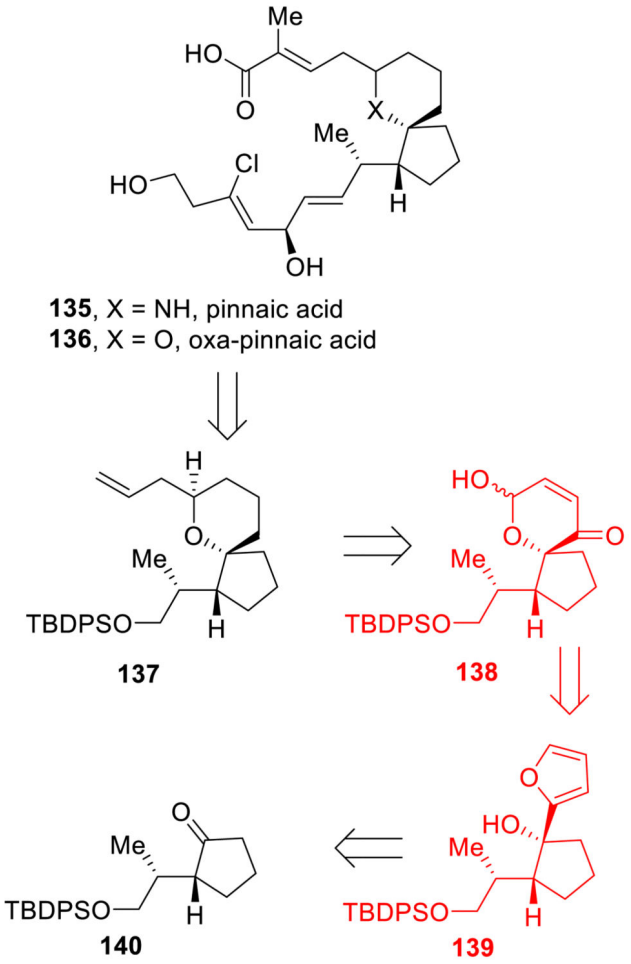
Scheme 35.

Retrosynthetic analysis for the synthesis of the BCD tricyclic core (**126**) of Brownin F (**125**). A key Achmatowicz reaction is highlighted in red.



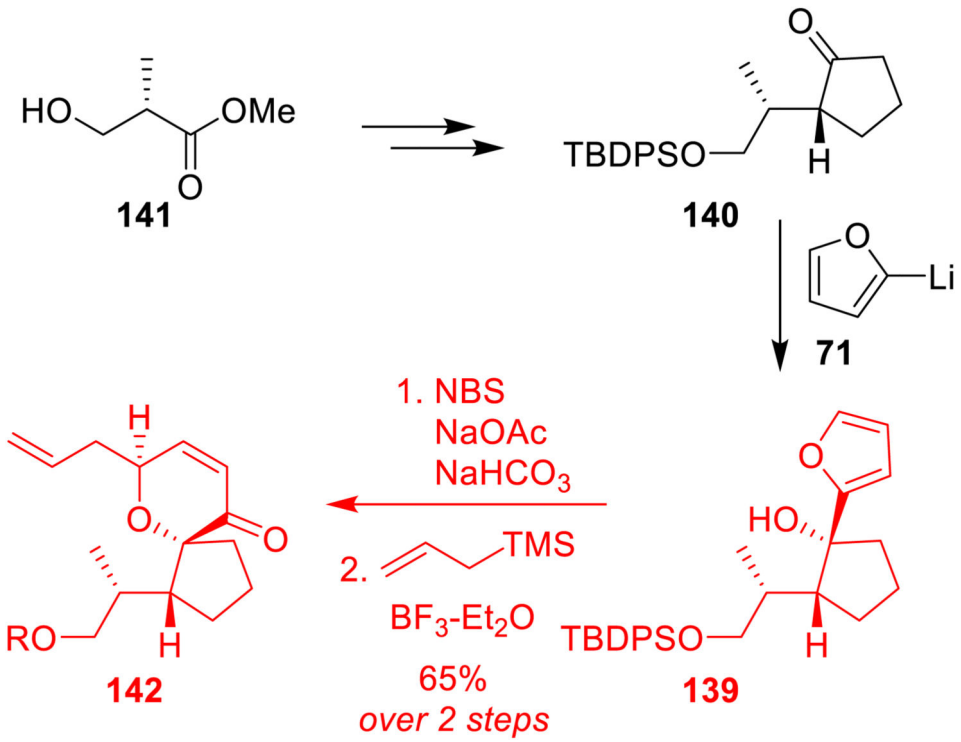
Scheme 36.

Synthesis of the representative intermediate **134** involving an Achmatowicz reaction (highlighted in red).

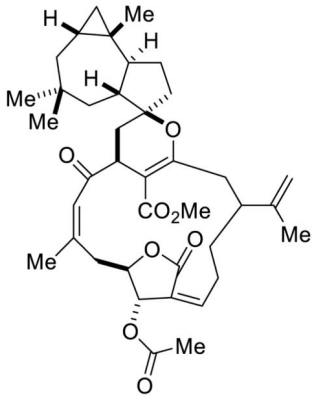


Scheme 37.

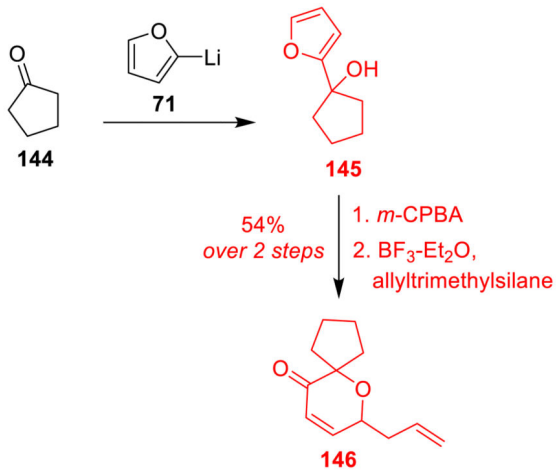
Retrosynthetic analysis for the synthesis of oxa-pinnaic acid (**136**). A key Achmatowicz reaction is highlighted in red.



Scheme 38.
Synthesis of the key fragment **142** involving an Achmatowicz reaction (highlighted in red).

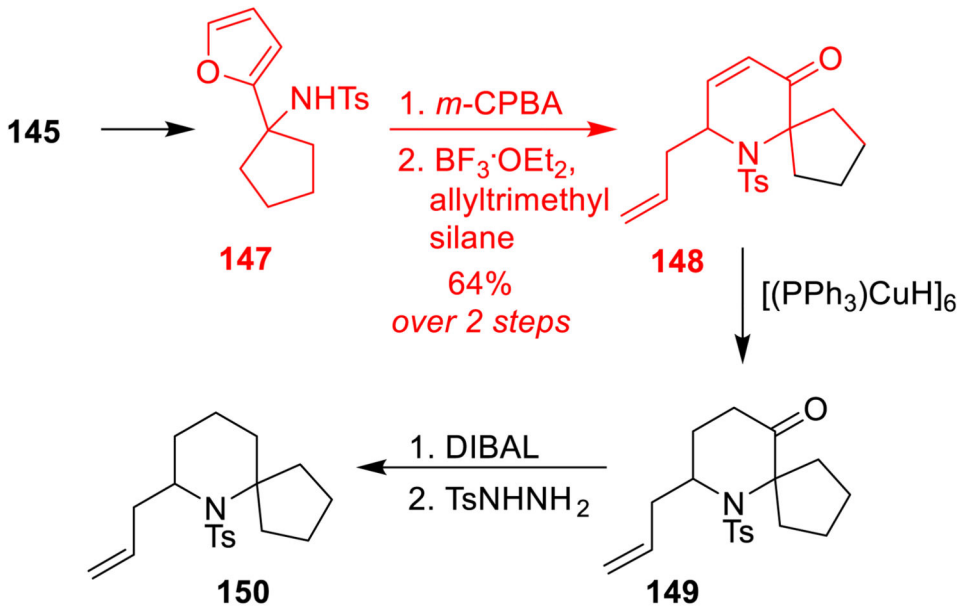


Polymaxenolide, **143**



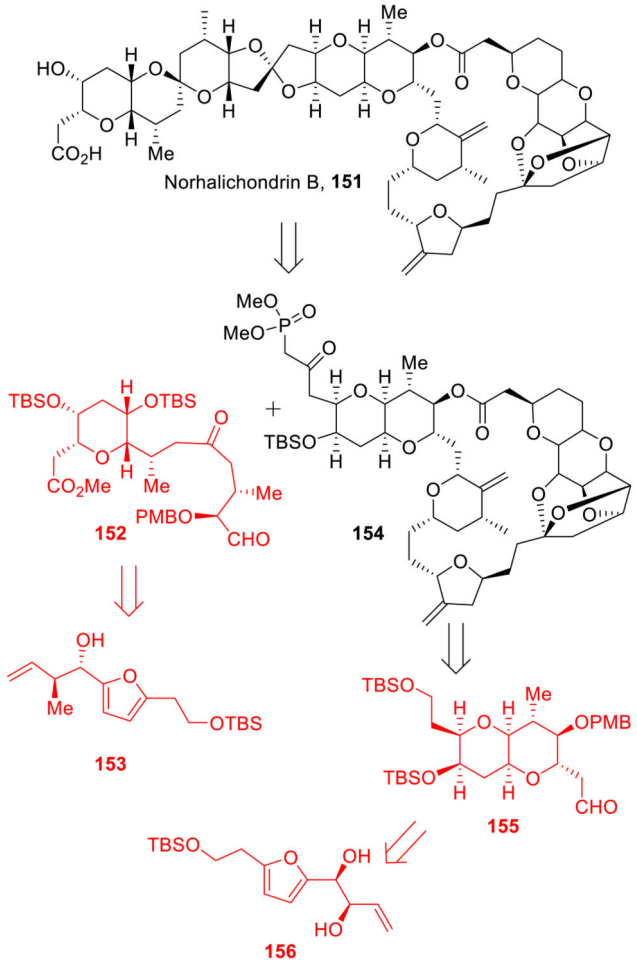
Scheme 39.

Synthesis of the of the spirocyclic pyranone core (**146**) involving an Achmatowicz reaction (highlighted in red).



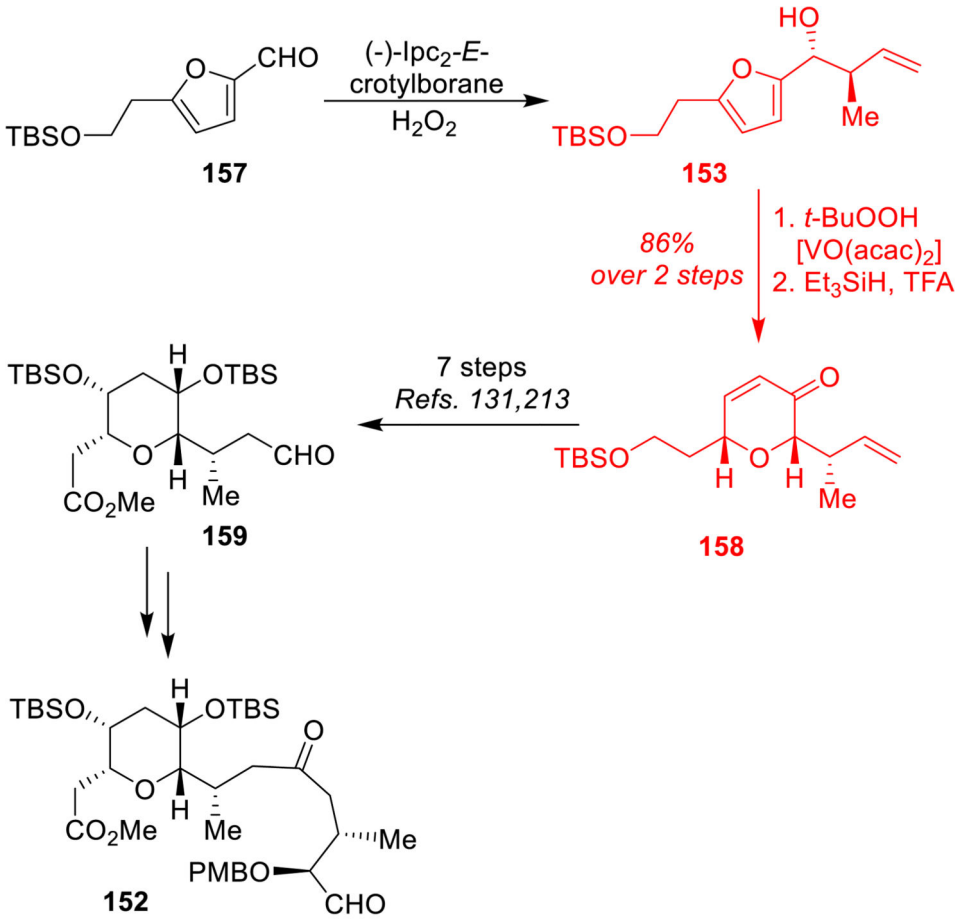
Scheme 40.

Synthesis of the spirocyclic piperidine core **150** involving an Achmatowicz reaction (highlighted in red).



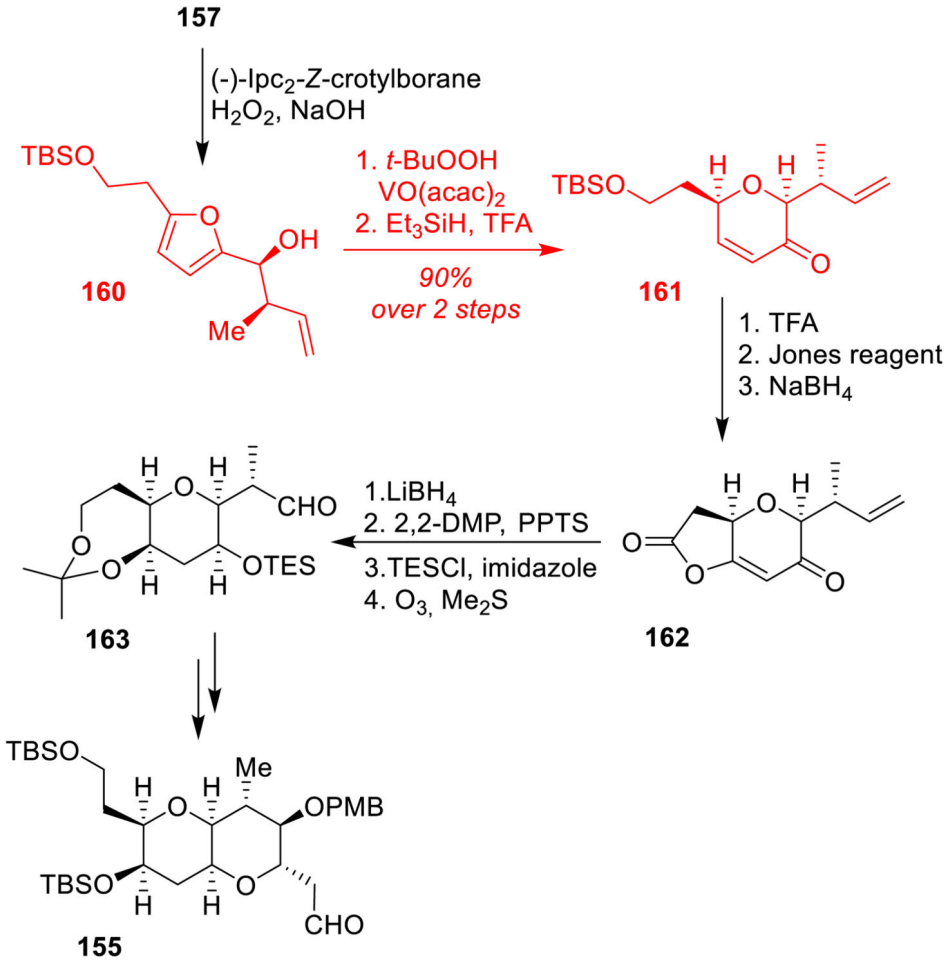
Scheme 41.

Retrosynthetic analysis for the synthesis of Norhalichondrin B (**151**). Key Achmatowicz reactions are highlighted in red.



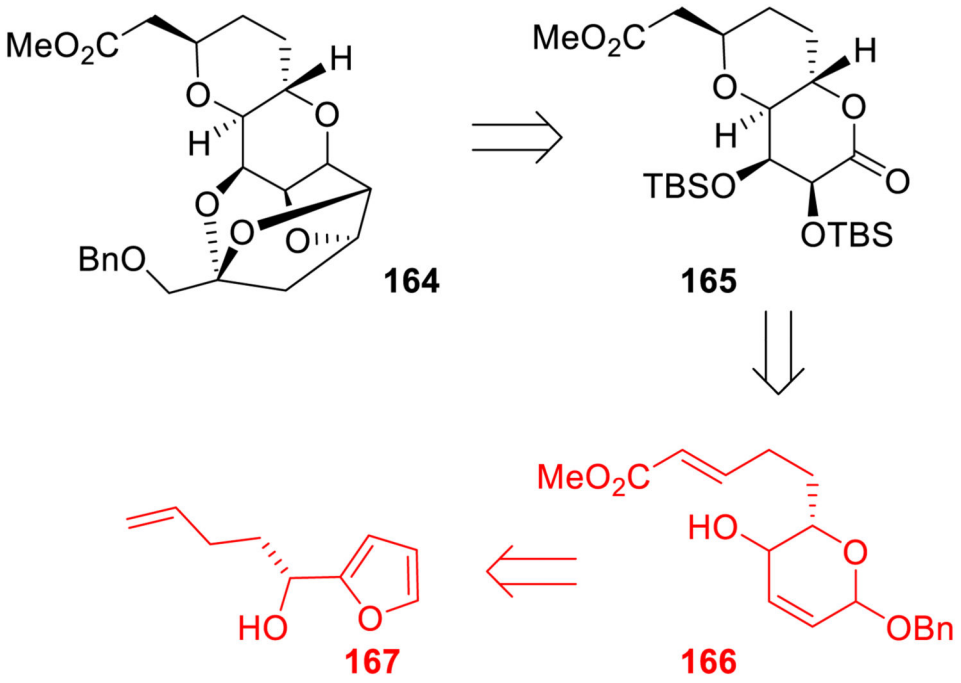
Scheme 42.

Synthesis of the of key retrosynthetic fragment **152** involved an Achmatowicz reaction step (highlighted in red).



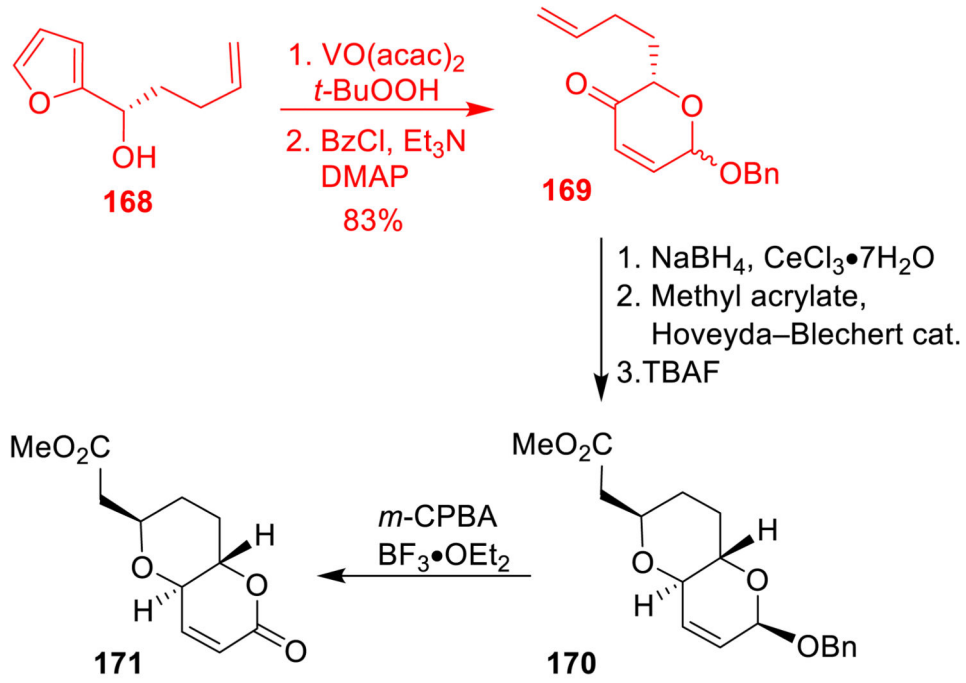
Scheme 43.

Synthesis of the key retrosynthetic fragment **155** encompassing an Achmatowicz reaction (highlighted in red).



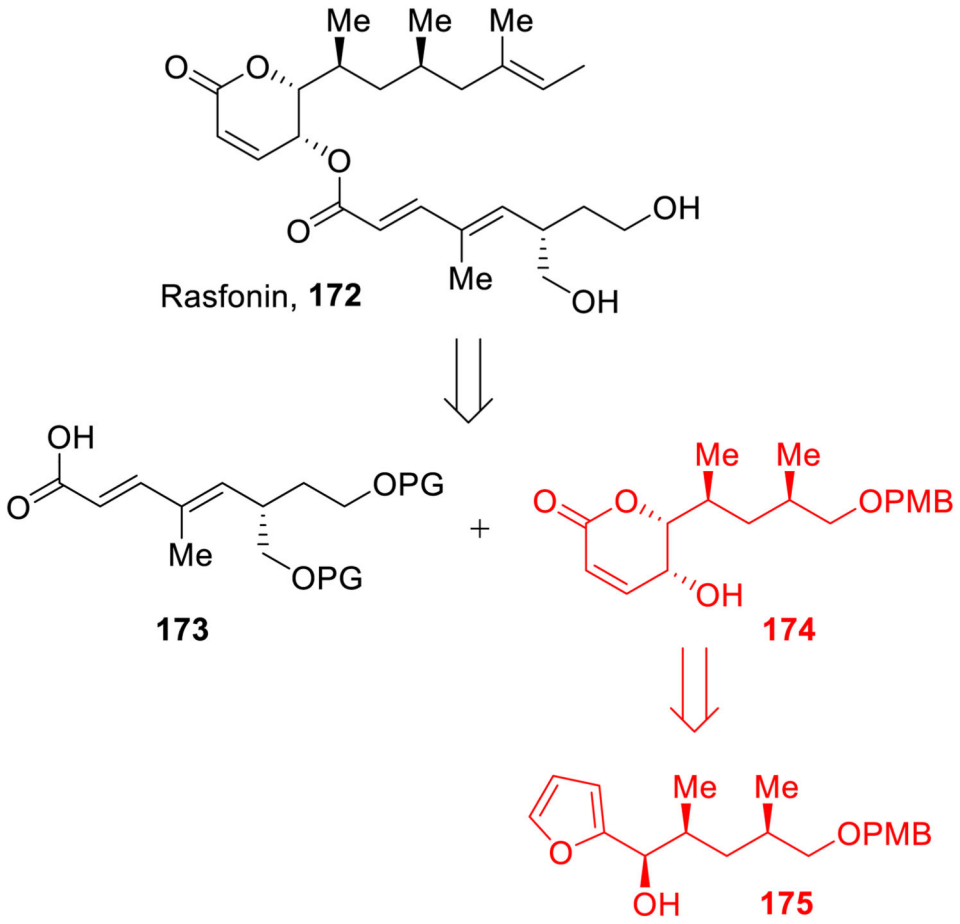
Scheme 44.

Retrosynthetic analysis for synthesis of the C1-C15 domain of the halichondrins (**164**). The key Achmatowicz reaction is highlighted in red.



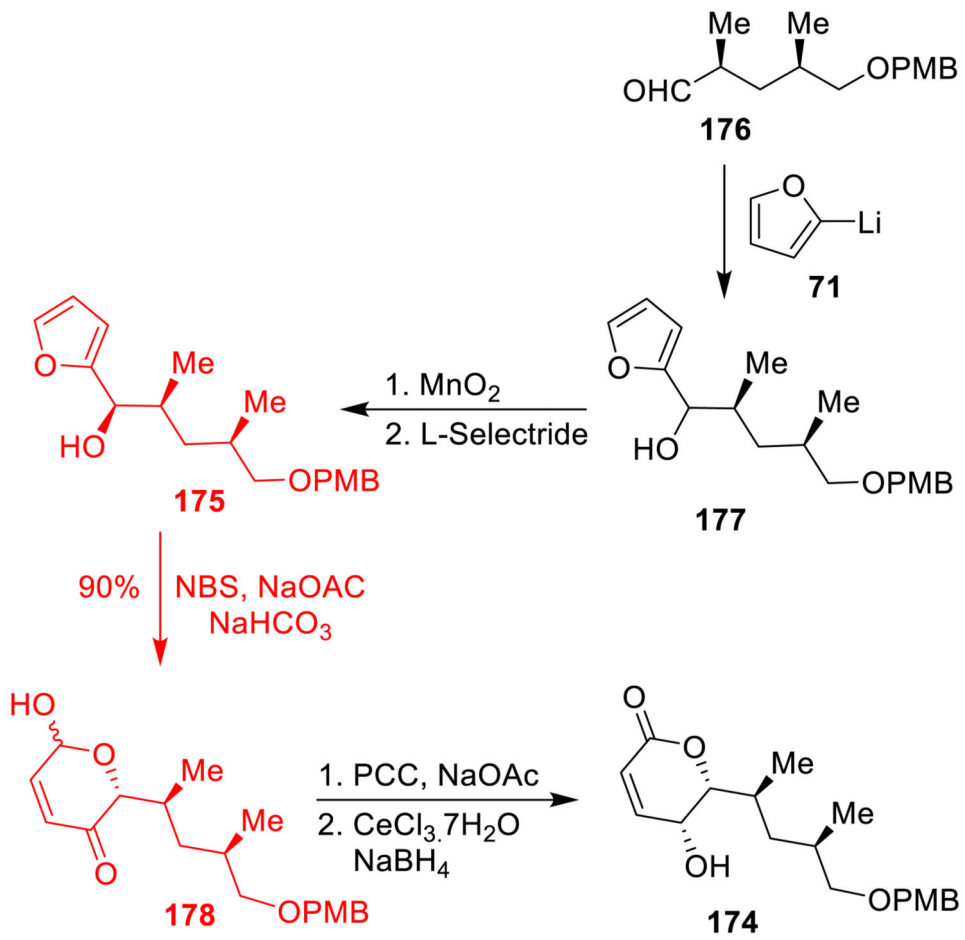
Scheme 45.

Synthesis of the key pyranopyran fragment **171** involving an Achmatowicz reaction (highlighted in red).



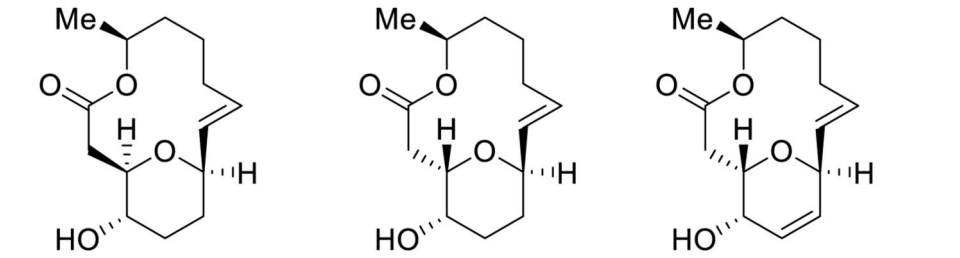
Scheme 46.

Retrosynthetic analysis for the synthesis of Rasfonin (**172**). A key Achmatowicz reaction is highlighted in red.

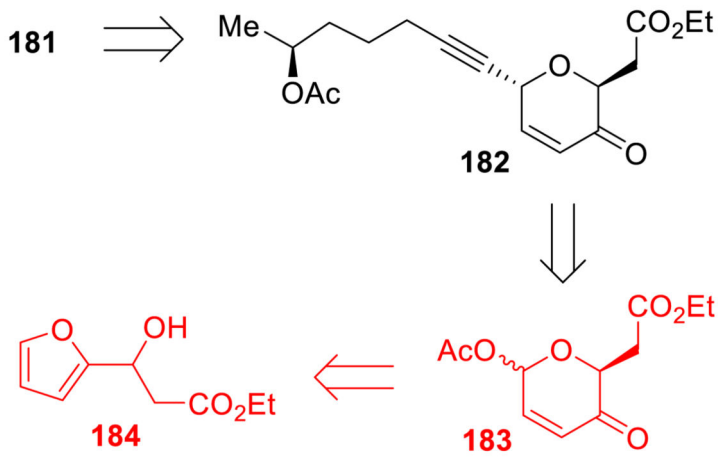


Scheme 47.

Synthesis of the key retrosynthetic fragment **174** involving an Achmatowicz reaction (highlighted in red).

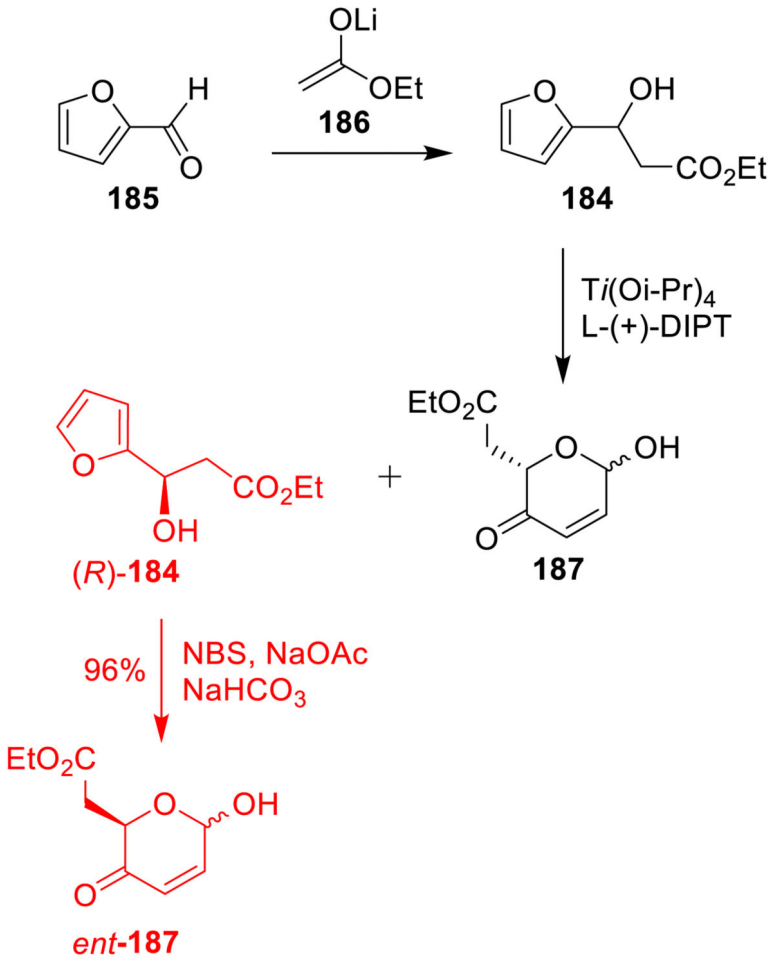


(-)-Aspergillide A,**179** (-)-Aspergillide B, **180** (+)-Aspergillide C, **181**



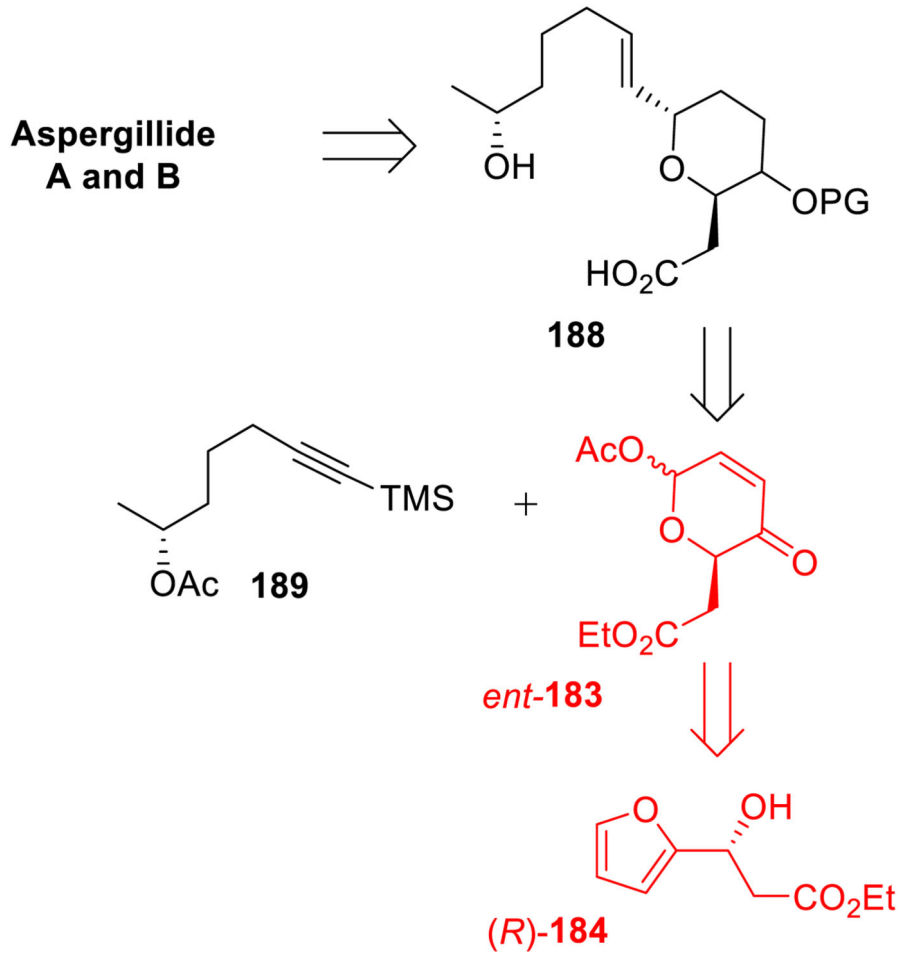
Scheme 48.

Retrosynthetic analysis of Aspergillide C (**181**). A key Achmatowicz reaction is highlighted in red.



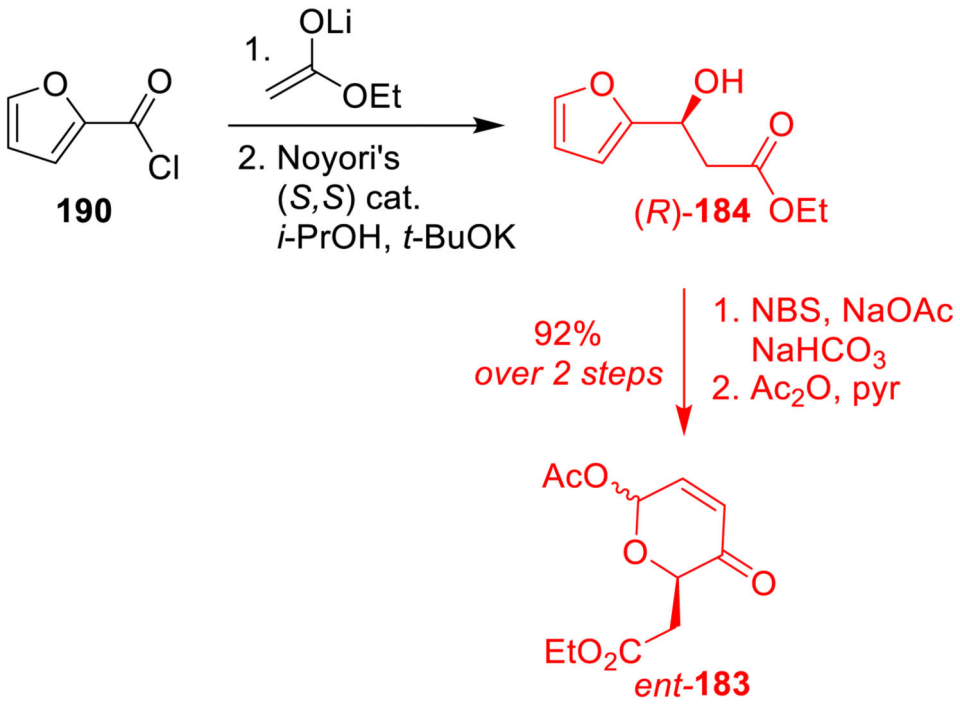
Scheme 49.

Synthesis of the key retrosynthetic fragment **187** involving an Achmatowicz reaction (highlighted in red).



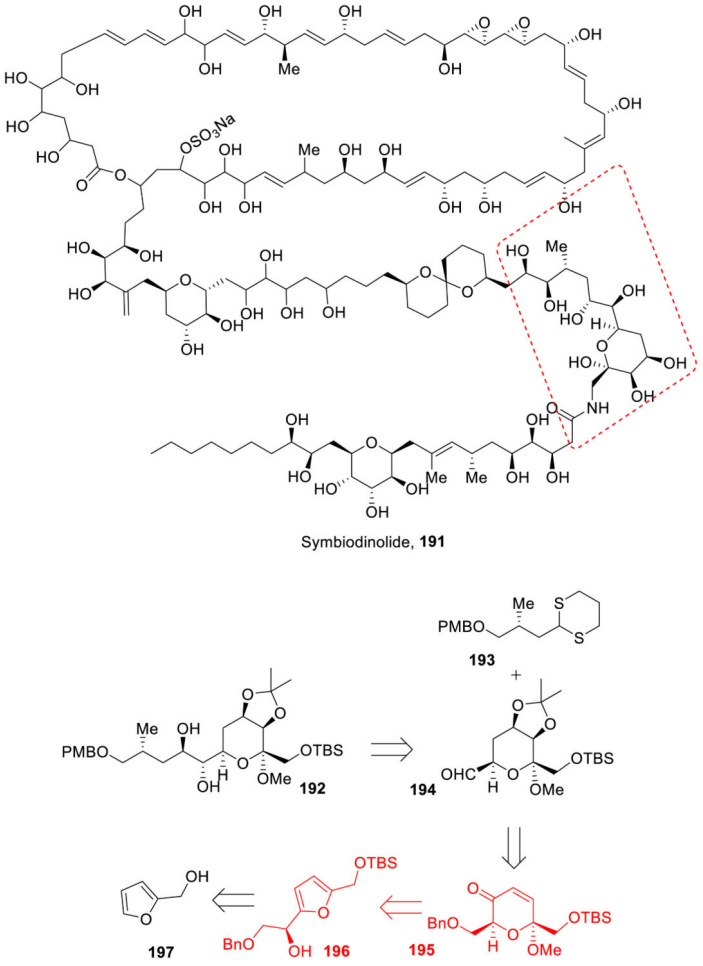
Scheme 50.

Retrosynthetic analysis for the synthesis of Aspergillides A and B (**179** and **180**). A key Achmatowicz reaction is highlighted in red.



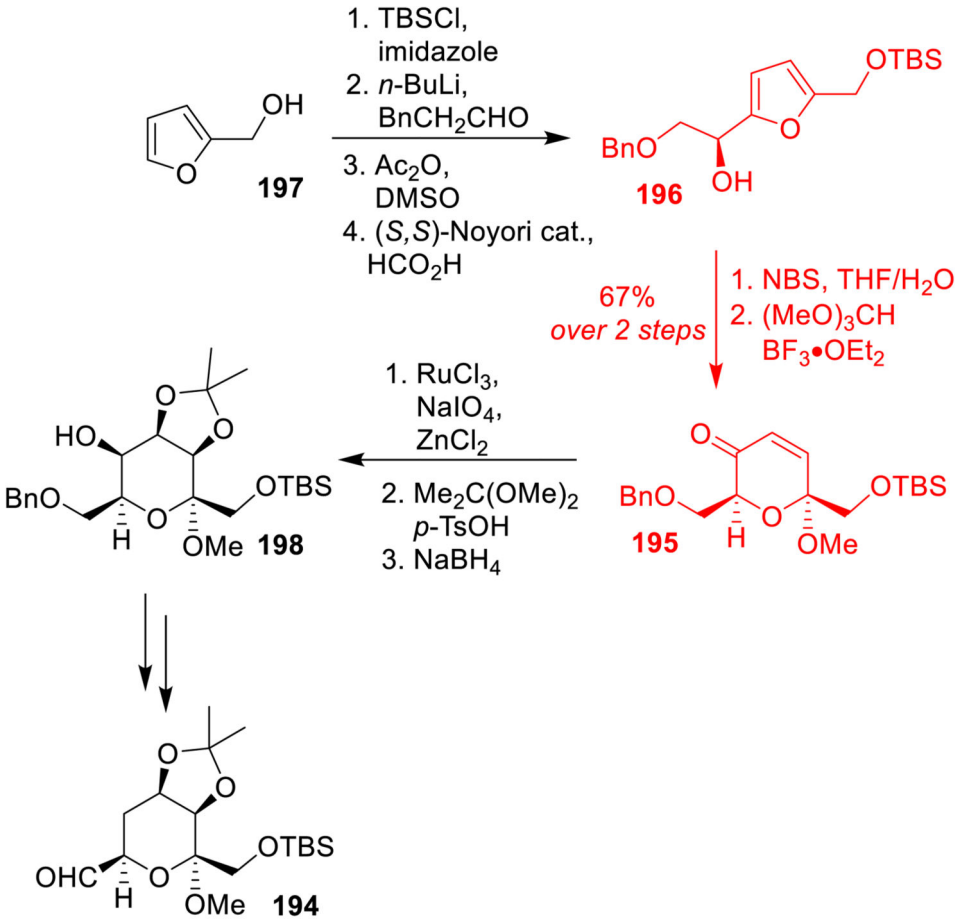
Scheme 51.

Synthesis of the key retrosynthetic fragment *ent*-**183** involving an Achmatowicz reaction (highlighted in red).



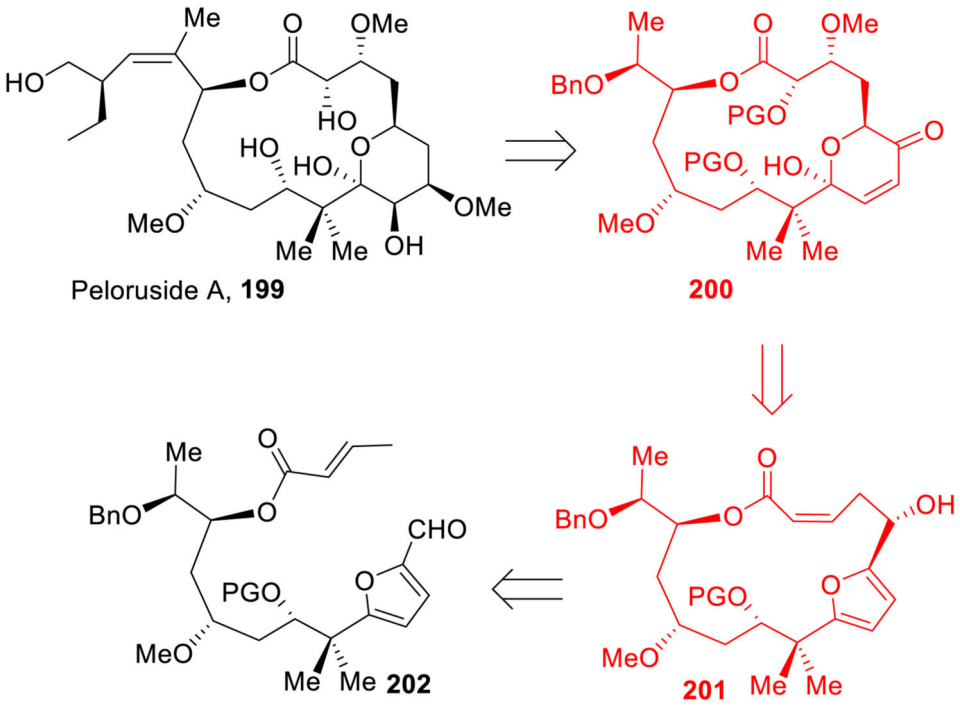
Scheme 52.

Retrosynthetic analysis for synthesis of the C94–C104 fragment of Symbiodinolide (**192**). A key Achmatowicz reaction is highlighted in red.



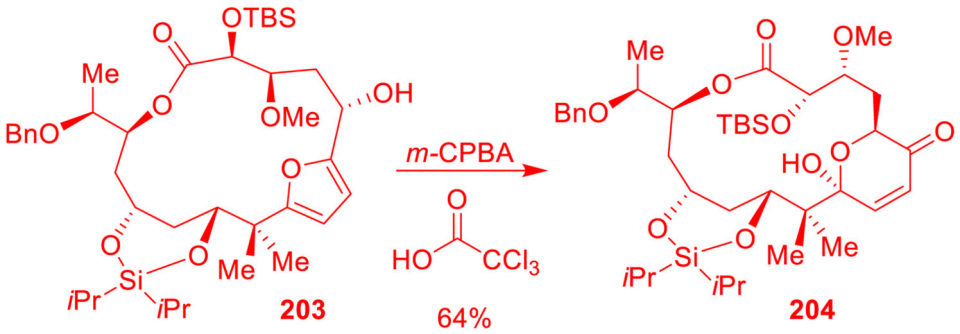
Scheme 53.

Synthesis of the key retrosynthetic fragment **194** involving an Achmatowicz reaction (highlighted in red).



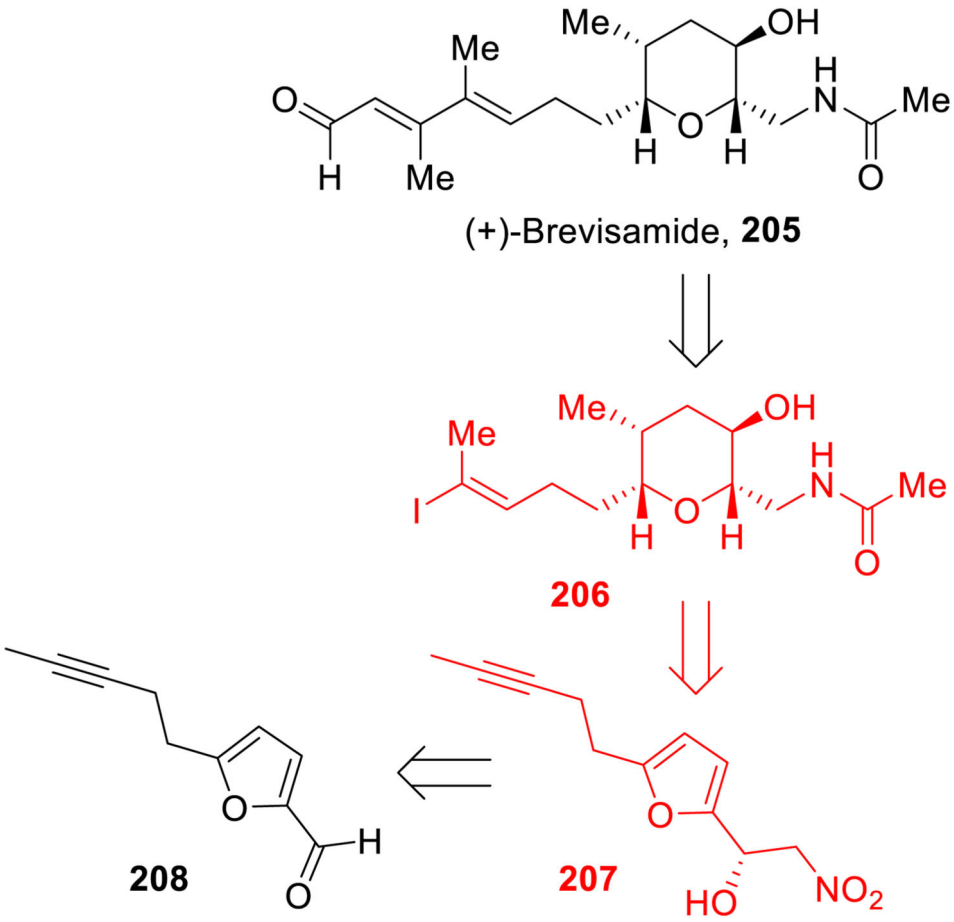
Scheme 54.

Retrosynthetic analysis for the synthesis of Peloruside A (**199**). A key Achmatowicz reaction is highlighted in red.



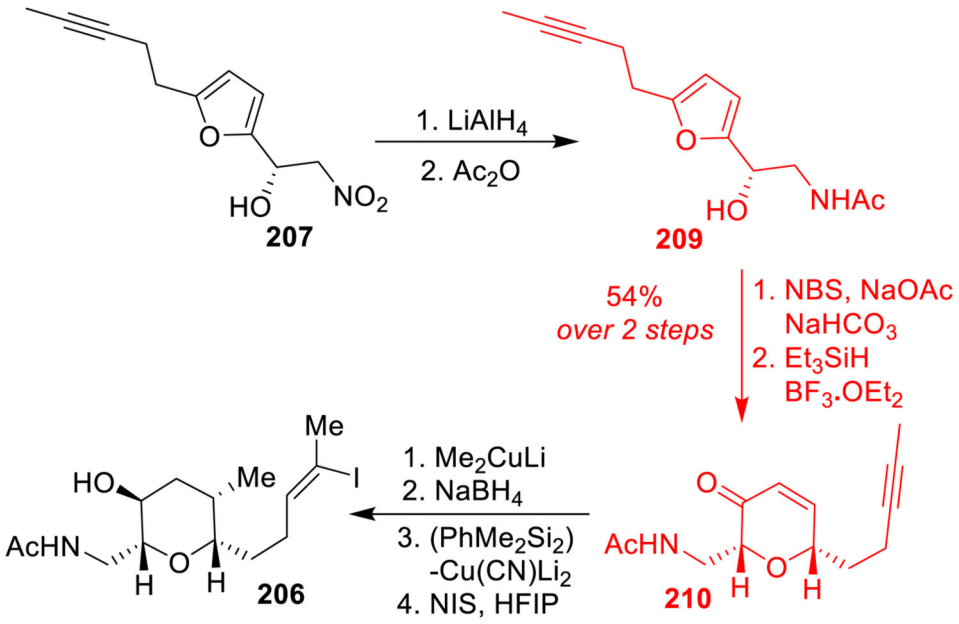
Scheme 55.

Synthesis of the key retrosynthetic fragment **204** involving an Achmatowicz reaction (highlighted in red).



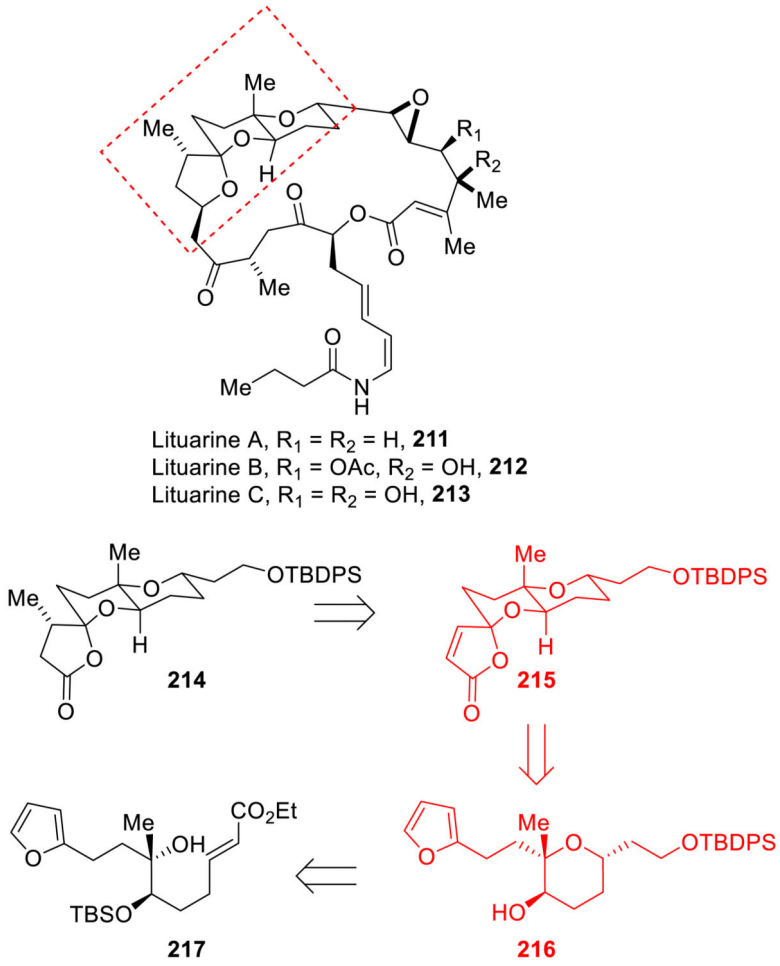
Scheme 56.

Retrosynthetic analysis of (+)-Brevisamide (**205**). A key Achmatowicz reaction step is highlighted in red.



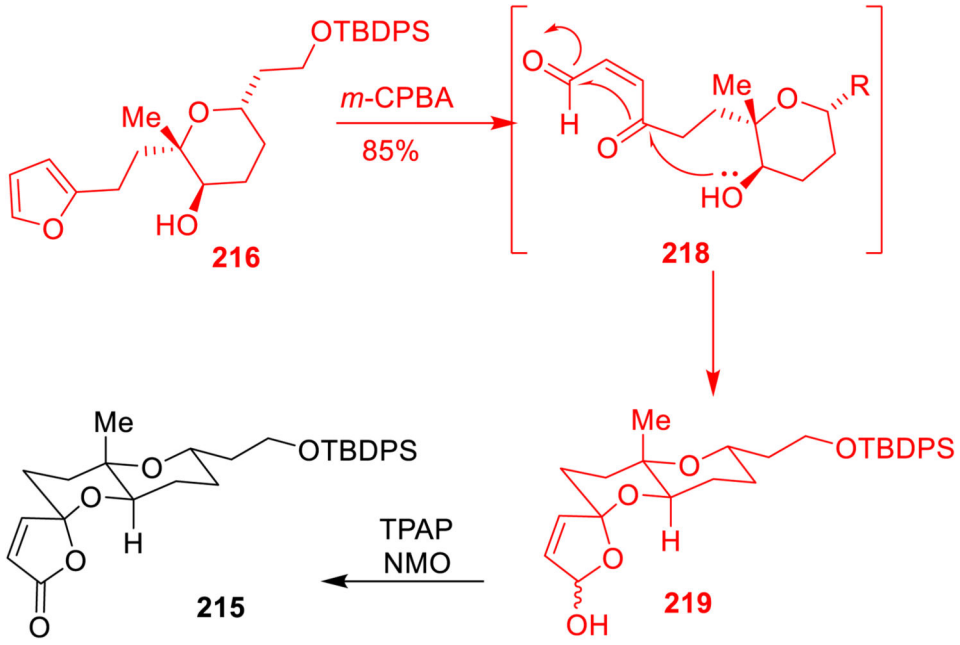
Scheme 57.

Synthesis of the key retrosynthetic fragment **206** involving an Achmatowicz reaction (highlighted in red).



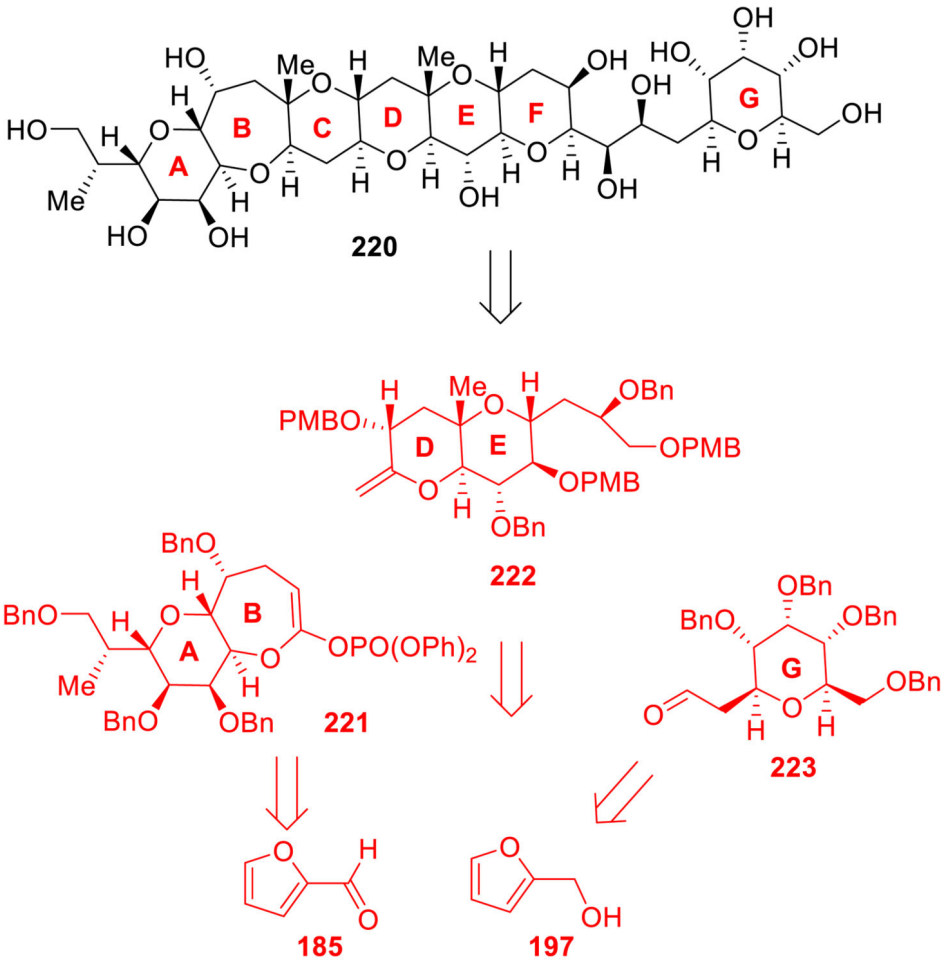
Scheme 58.

Retrosynthetic analysis of the C6-C18 fragment (**214**) of the Lituarines A-C (**211-213**). A key Achmatowicz reaction is highlighted in red.



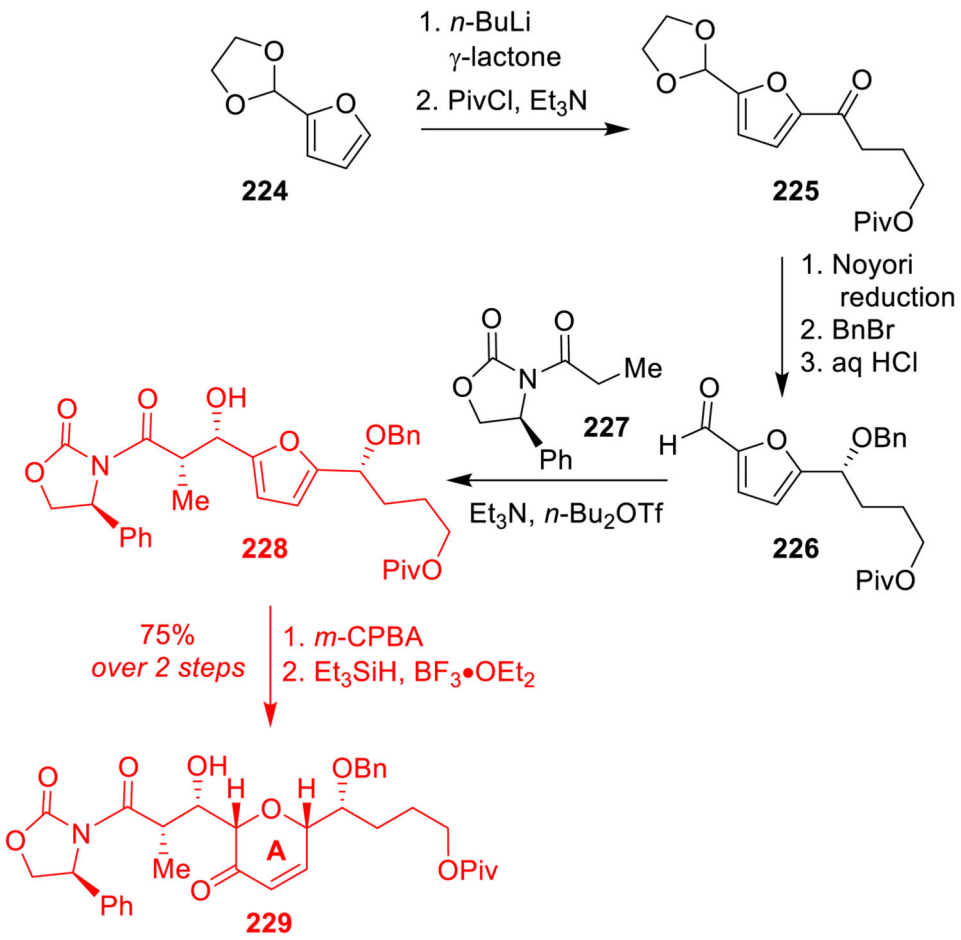
Scheme 59.

Synthesis of the key retrosynthetic fragment **215** involving an Achmatowicz reaction (highlighted in red).



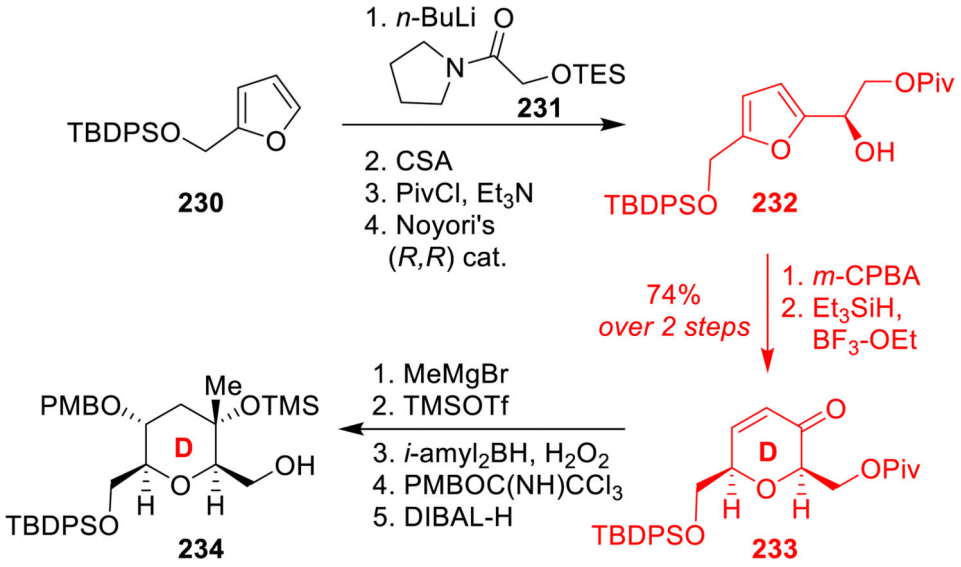
Scheme 60.

Retrosynthetic analysis of the ABCDEFG ring system of Maitotoxin (**220**). Key Achmatowicz reaction is highlighted in red.



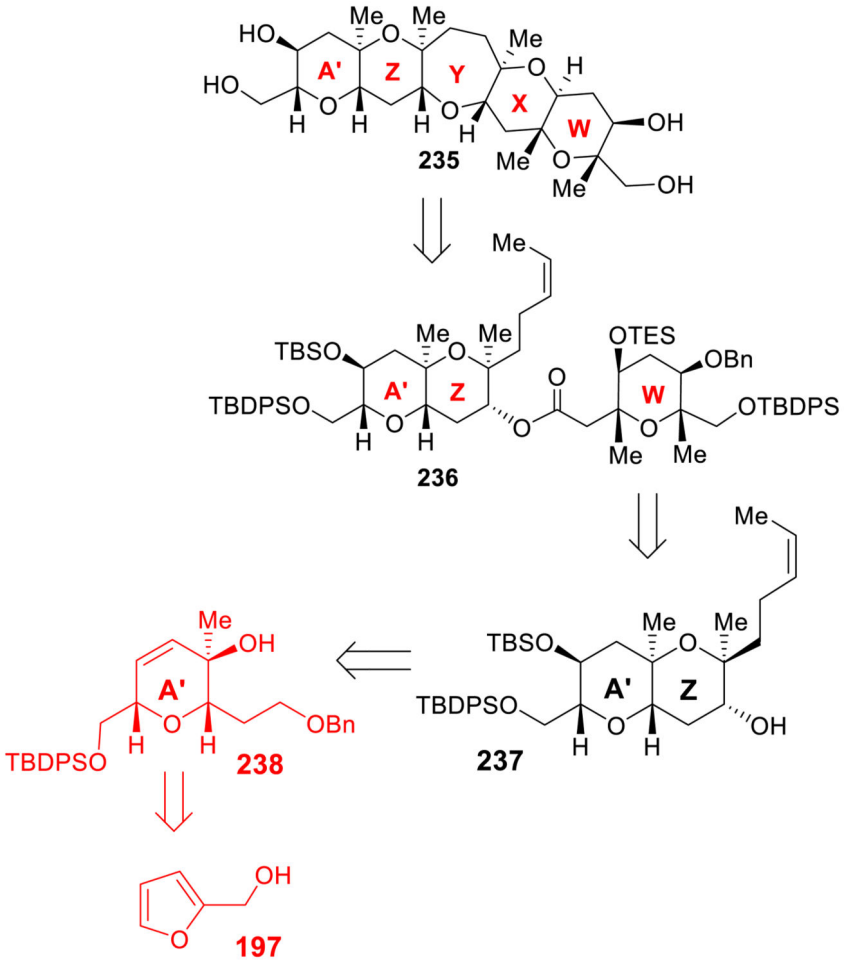
Scheme 61.

Synthesis of the key intermediate **229** involving an Achmatowicz reaction (highlighted in red).



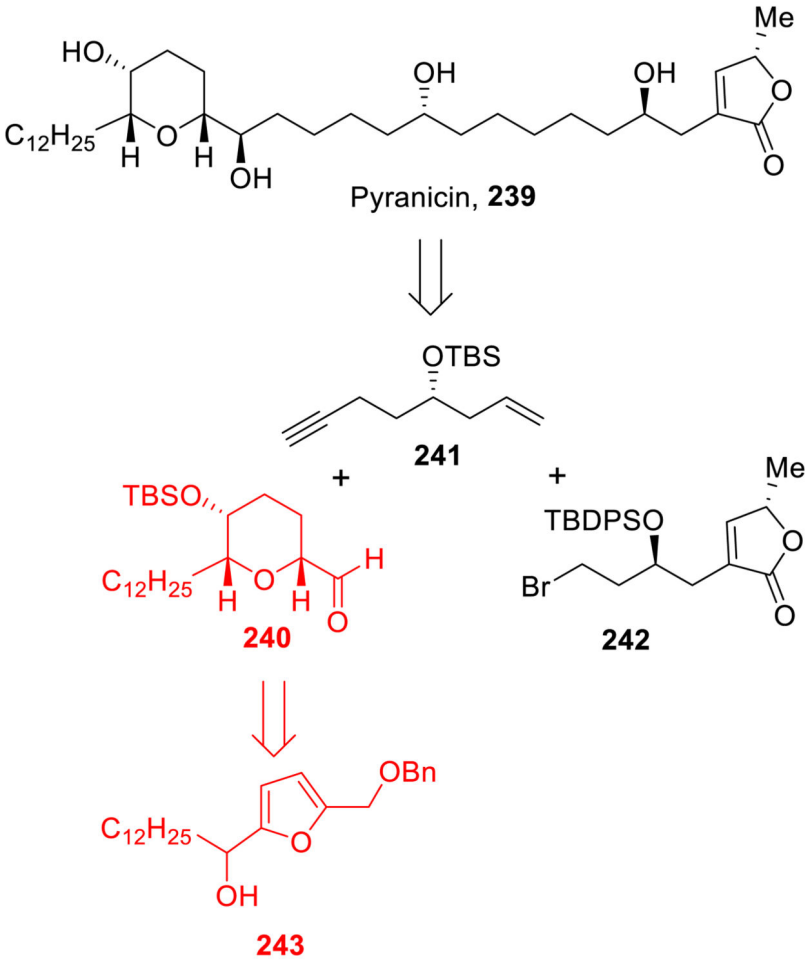
Scheme 62.

Synthesis of the key intermediate **234** involving an Achmatowicz reaction (highlighted in red).



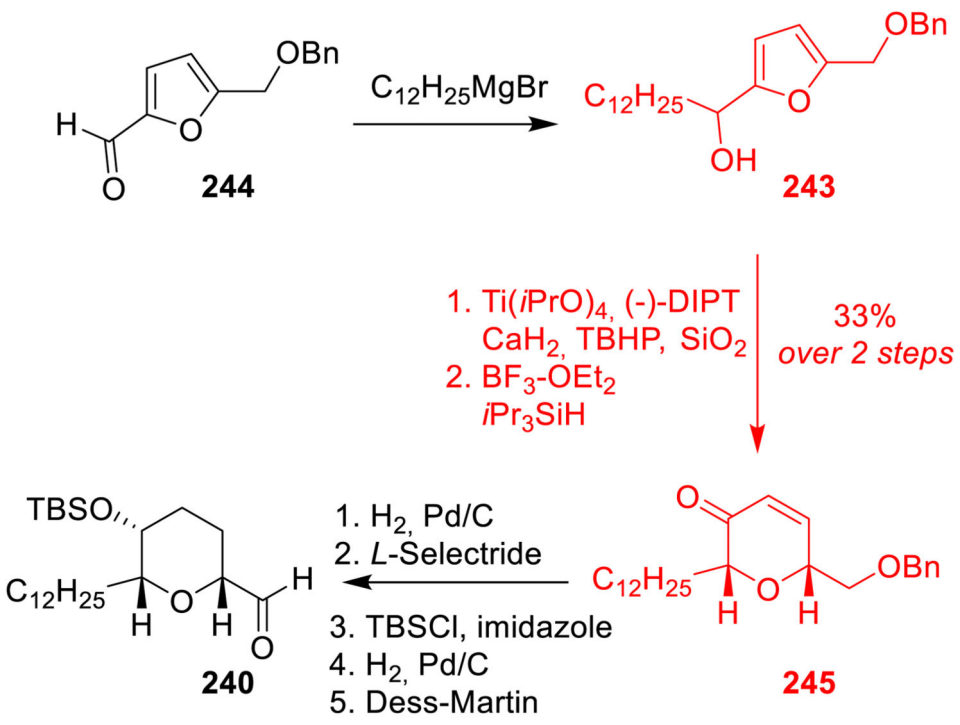
Scheme 63.

Retrosynthetic analysis of the WXYZA′ domain of Maitotoxin (**235**). A key Achmatowicz reaction is highlighted in red.



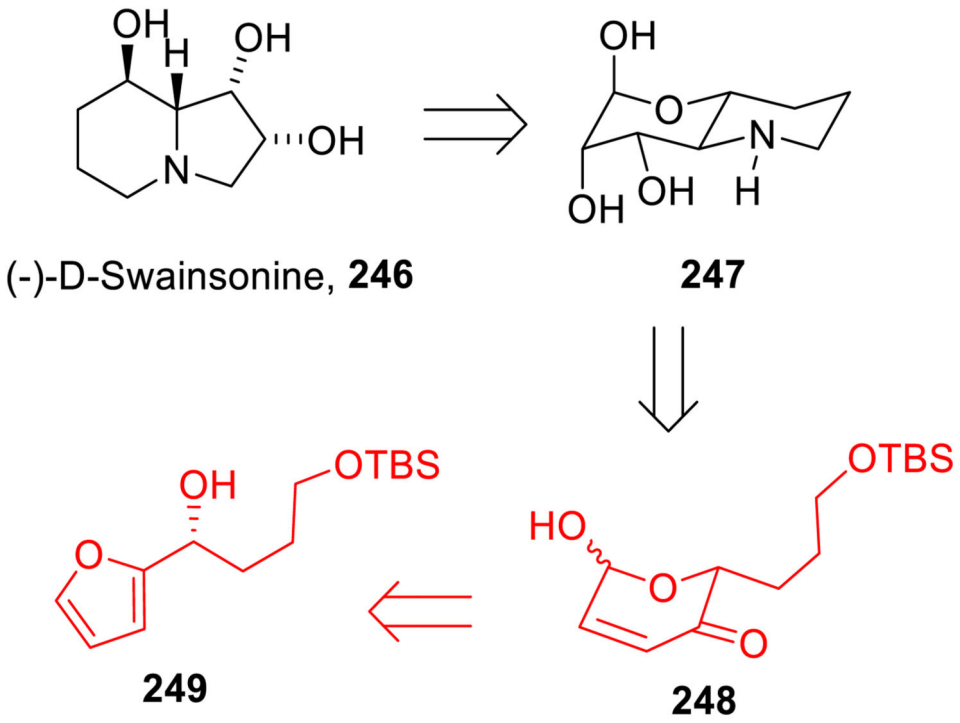
Scheme 64.

Retrosynthetic analysis of Pyranicin (**239**). A key Achmatowicz reaction is highlighted in red.

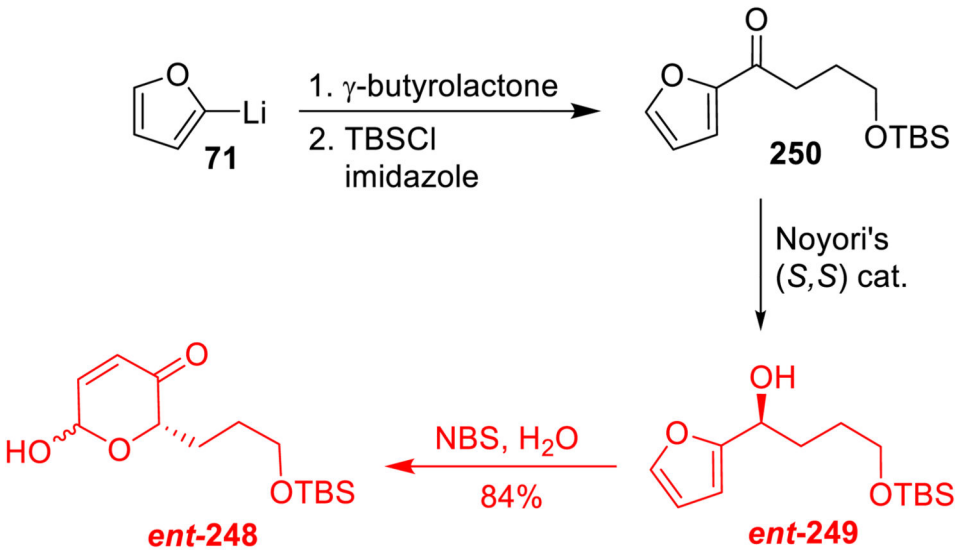


Scheme 65.

Synthesis of the key retrosynthetic fragment **240** involving an Achmatowicz reaction (highlighted in red).

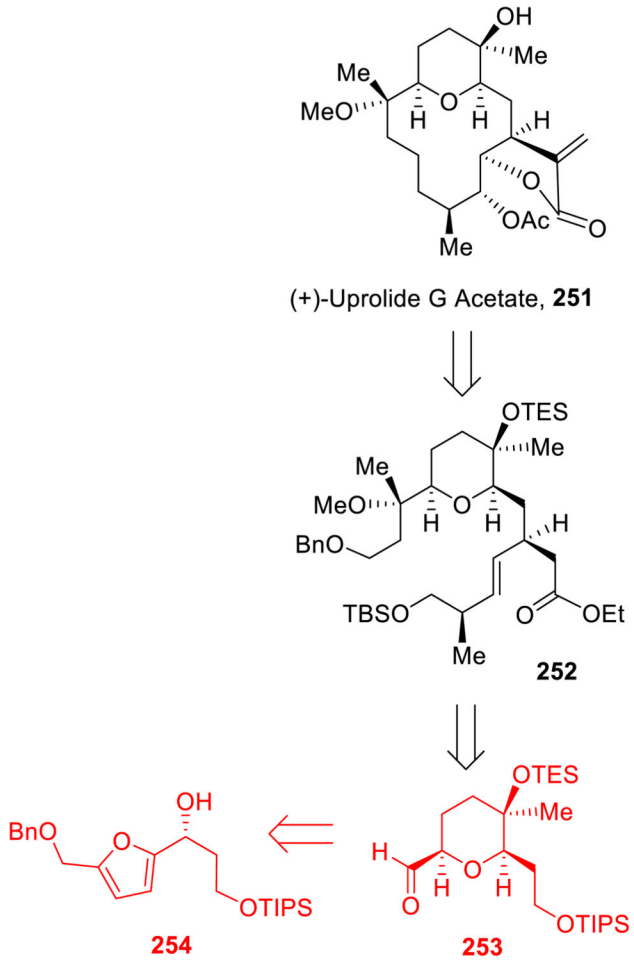


Scheme 66.
Retrosynthetic analysis of (-)-D-Swainsonine (**246**). A key Achmatowicz reaction is highlighted in red.



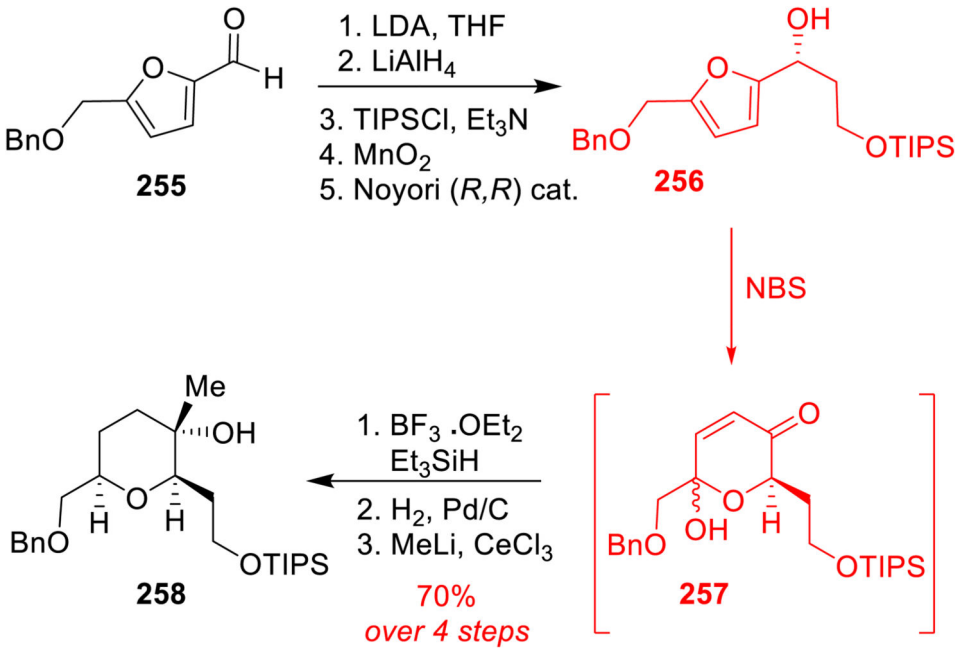
Scheme 67.

Synthesis of the key retrosynthetic fragment *ent*-**248** involving an Achmatowicz reaction (highlighted in red).



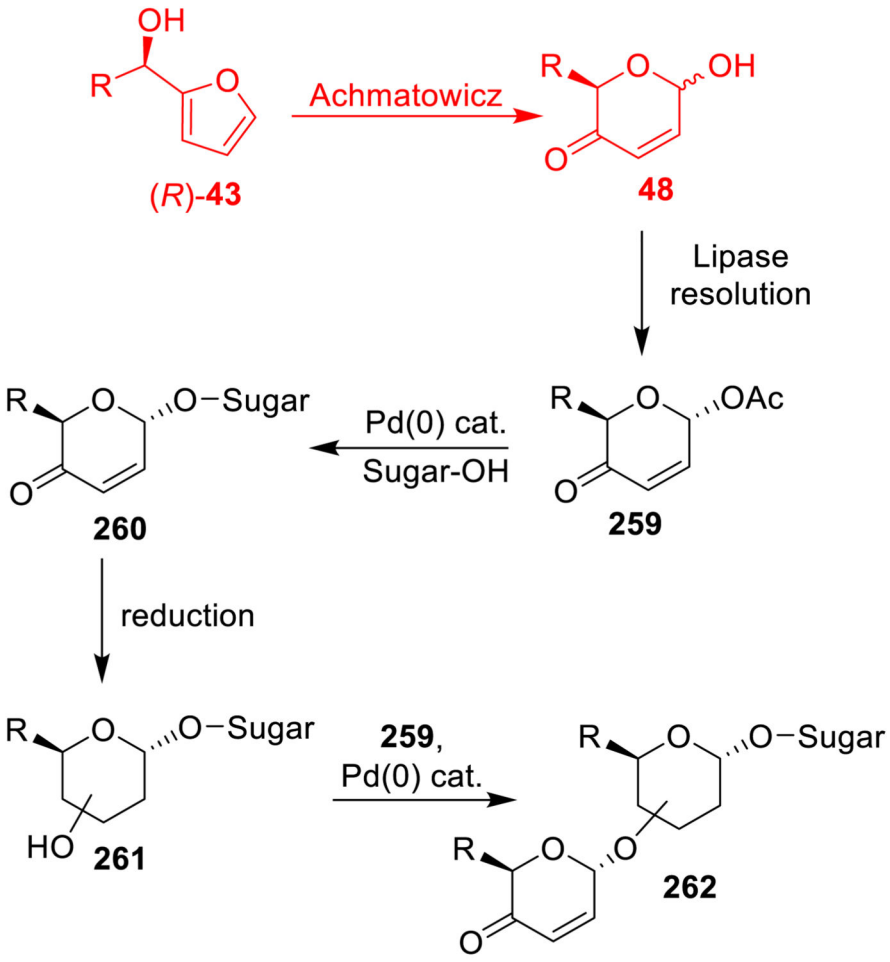
Scheme 68.

Retrosynthetic analysis of (+)-Uprolide G acetate (**251**). A key Achmatowicz reaction is highlighted in red.

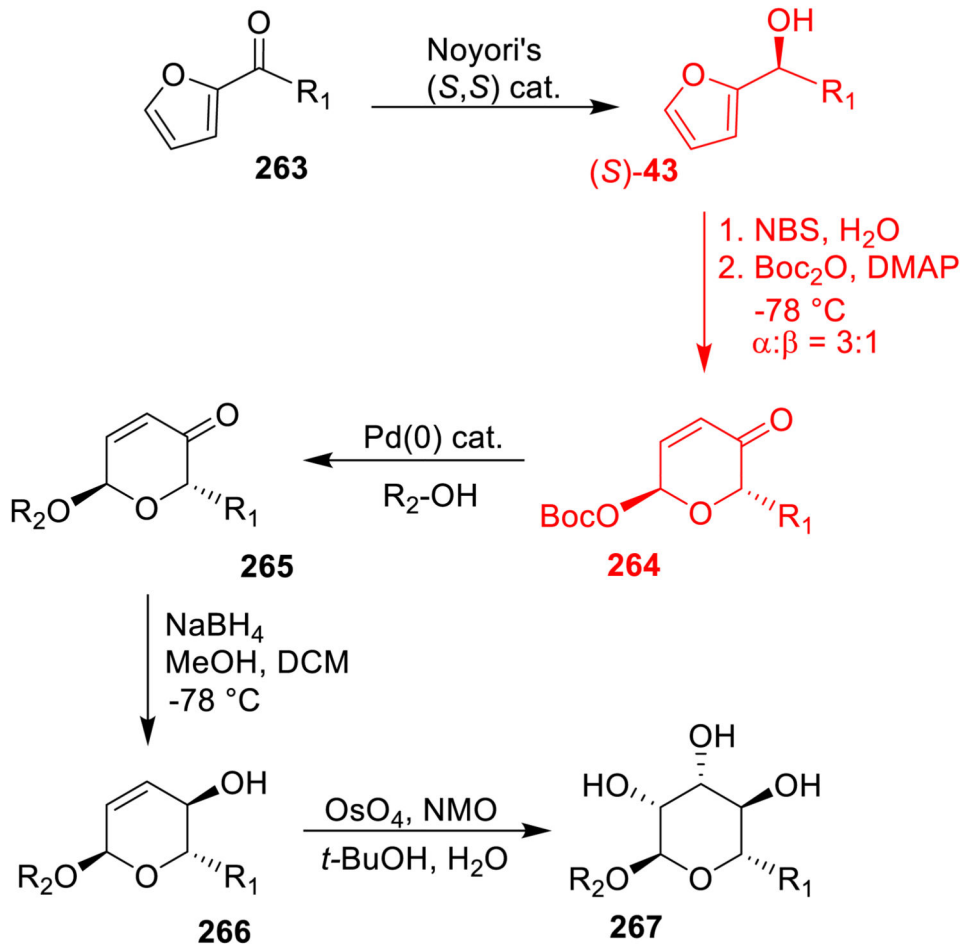


Scheme 69.

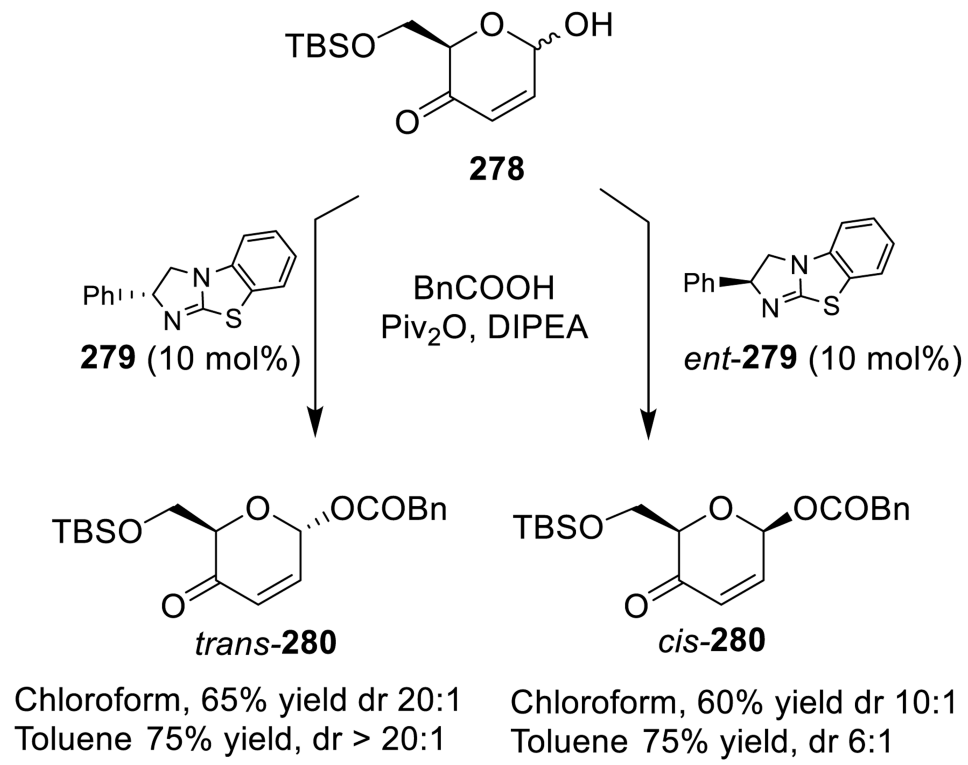
Synthesis of the key intermediate **258** involving an Achmatowicz reaction step (highlighted in red).



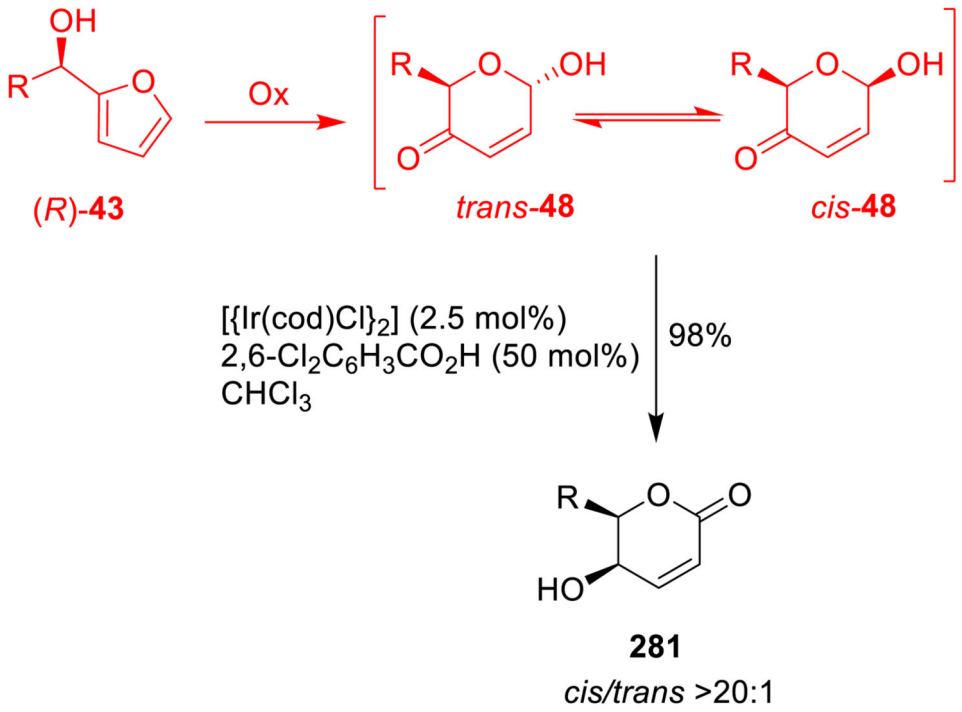
Scheme 70.
Feringa's approach to carbohydrate synthesis.



Scheme 71.
O'Doherty approach to *de novo* carbohydrate synthesis.

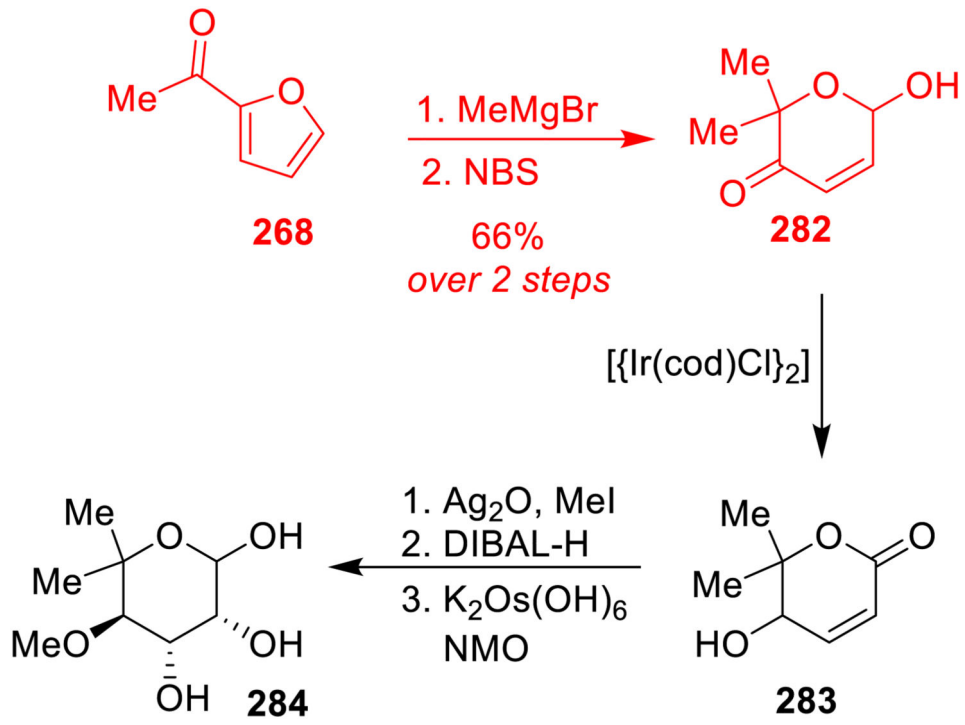


Scheme 72.
Catalyst directed DKDA for lactol **278**.

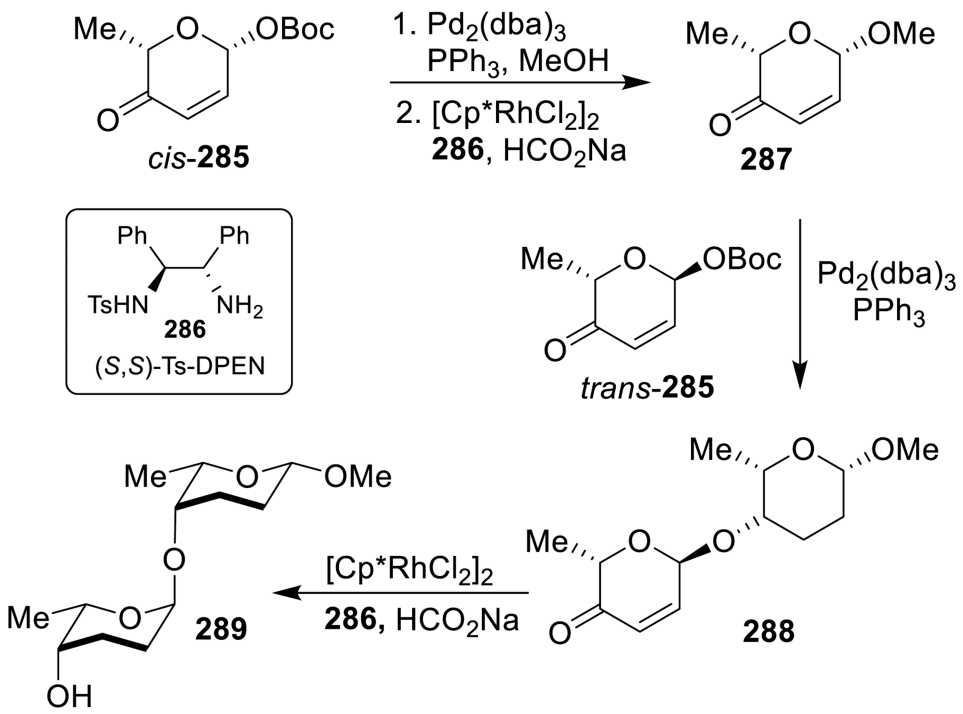


Scheme 73.

Achmatowicz rearrangement and stereoselective iridium-catalyzed dynamic kinetic internal transfer hydrogenation reaction.



Scheme 74.
De novo synthesis of noviose **284**.



Scheme 75.
Synthesis of disaccharide β-narbosine B **289**.