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Review

Synthesis and Applications of Periodate for Fine Chemicals and Important Pharmaceuticals

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ABSTRACT: An emerging interest for the application of periodate in the synthesis of active pharmaceutical ingredients (APIs) and for the valorization of renewable feedstock is eminent. However, periodate exhibits a high molecular mass, is expensive compared to other common bulk-oxidizers and is used only reluctantly in technical applications. Recently, a new and green electrochemical synthesis was established. The preparation and regeneration method for periodate lowers costs and enables the use of periodate in the synthesis of regulated products. This review will briefly introduce the key innovations in the electrochemical synthesis of periodate and will survey the most important applications of periodate in the production of fine chemicals.

KEYWORDS: *periodate, electrolysis, Malaprade oxidation, Lemieux−Johnson oxidation, active pharmaceutical ingredients*

1. INTRODUCTION

Despite its importance, the production of fine chemicals is one of the most waste and energy intensive operations in the chemical industry. The extensive use of chemical reagents causes the consumption of fossil and natural resources and generates large amounts of chemical waste and greenhouse gas emissions.[1−5] Thus, the development of new, "green" methods is crucial to successfully avert climate change. However, the costs of these novel approaches must be competitive with conventional processes. Active pharmaceutical ingredients (APIs) need to become more affordable to third-world countries,[6] and fossil resources need be substituted by renewable feedstocks.[7] These requirements constitute the perhaps the most demanding yet most urgent challenge of the 21st century.

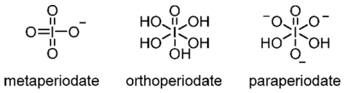

Figure 1. Valence structural formulas of metaperiodate, orthoperiodate, and paraperiodate.

Periodate is a high-performance oxidizer which is already used in fine chemicals industry. It has a unique reactivity and selectivity toward 1,2-diols, while presenting a superior tolerance for many common functional groups at suitable pH and temperature.[8,9] It is stable, safe, and easy to handle and store. In addition, its reduction is kinetically favored in comparison to perchlorate and perbromate.[10] It has thus become an invaluable synthetic tool in the total synthesis of complex organic molecules but is often avoided due to limited commercial availability, contaminations with toxic heavy metal impurities,[11−13] and difficult waste management. However, this situation is changing substantially. Recently, a clean electrochemical synthesis and recycling protocol for periodate was developed by our group.[14,15] The method is in line with the principles of green chemistry[16,17] and offers a more cost-efficient access to this oxidizer. Electrosynthesis is highly compatible and attractive with the expansion of renewable energies and is among the hottest topics in contemporary chemistry.[18−21] It allows a superior waste management and the development of sustainable as well as efficient chemical processes. The combination of a high-performance oxidizer generated by electrochemistry constitutes a perfect match.[22] Electrical current is a low-cost oxidizer and is environmentally benign if produced from renewable energy sources.[23] Conventional oxidants in turn extend the scope of reactivity and often provide higher selectivity.[24] The use of electricity could allow the reduction of power peaks or the storage of overcapacities in the electric grid, respectively. Advantageously, the anodic production (oxidation at electrode) of periodate may be paired with already existing bulk electrolysis, e.g., the electrochemical water-splitting reaction. Thus, periodate would be produced instead of less valuable dioxygen. Market data reveal that ∼37 000 t of iodine and iodine derivatives are distributed worldwide per year, which are supplied by less than ten key-producers predominantly located in China (William Blythe, Jinan FuFang Chemical, Qingdao Tocean Iodine Products, Henan Wanxiang Chemical, Shandong Boyuan Pharmaceutical & Chemical, Jiangxi Shengdian S&T, Zhejiang Hichi Chemical, Zibo Wankang Pharmaceutical Chemical, Jiodine Chemical (Qingdao), Jindian Chemical, Shanghai Zechong, GHW International, and Zhengzhou Meifu Chemical).[25] Of

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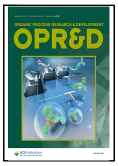


course, the use of periodate suffers from low atom economy[4,26] due to the high molecular weight, but may be neglible if sufficient recycling methods are established.

Periodate comes in a variety of compounds of which metaperiodate (IO_4^-) is the most commonly known and used. Other forms are the para- ($H_2IO_6^{3-}$) and the orthoperiodate (H_5IO_6) (Figure 1). According to our recent market investigations, the cost for sodium metaperiodate is around 29 $/kg for orders from 25 to 100 kg. Price comparison between sodium and potassium metaperiodate ($NaIO_4$, KIO_4) revealed that potassium metaperiodate is roughly three times as expensive (97 $/kg) as the respective sodium salt. Since 2019, we noticed varying compound availability and price implying high market fluctuations.[14] Sodium paraperiodate ($Na_3H_2IO_6$) is presumably the most cost-efficient source of periodate, as metaperiodate is usually obtained in about 70% yield from recrystallization from paraperiodate. However, the high price (101 $/kg) and the preliminary REACH registration underline its less common usage compared to metaperiodate. It is thusly assumed that the annual tonnage imported and manufactured is below 1000 kg.

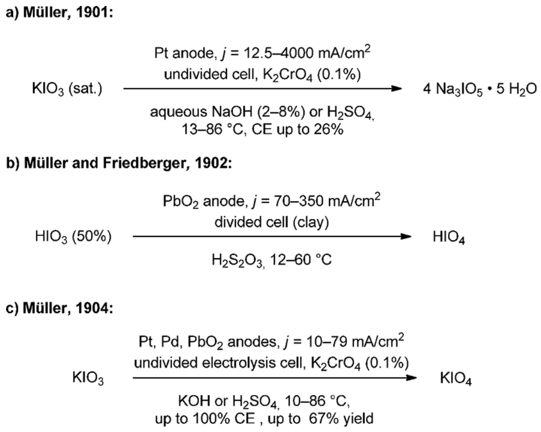
The scope of periodate-based applications in organic synthesis has been previously reviewed by Fatiadi[27] and Sudalai,[28] while mechanisms were surveyed by Buist,[9] Dryhurst,[29] and Sklarz.[30] Stark summarized the application of the Malaprade oxidation in the synthesis of natural products.[8] In contrast, we focus on active pharmaceutical ingredients (APIs), as the contamination-free synthesis of periodate affects this area majorly. A particular focus will be directed toward commercial APIs listed on the world health organization's (WHO) list of essential medicines, which encloses the safest and most effective medicines available.[31] These molecules will be highlighted accordingly in the respective figures and schemes. This review is meant to give a general overview about the commercial use of periodate and the most interesting synthetic strategies therein. Furthermore, we wish to provide inspiration for researchers that periodate is an attractive alternative in novel synthetic routes for "greener" chemistry. The first part of this review is dedicated to methods for periodate synthesis, as the literature is scattered and often difficult to access due to publishing date and language. We also want to eliminate some confusion about the various forms and equillibira of periodate among chemists which likely originates from said obstacles. In the second part, we will demonstrate synthetic applications of periodate for fine chemicals and APIs (active pharmaceutical ingredients). A strong focus will be directed toward commercial products and promising targets. Our aim is to give chemists inspiration for the possible implementation of periodate-based reactions into synthetic routes by outlining trial and tested synthetic strategies. We hope to convince our readership of the advantages of periodate over other comparable bulk oxidizers due to its accessibility via electrochemical means.

2. PERIODATE

2.1. Preparation. The synthetic methods and pathways for periodate have not been reviewed to date. Thermochemical methods were developed as early as the 19th century and have been thoroughly studied. Please note that to date, the various structures of periodate were not investigated and that those were not exactly specified within many publications in this chapter. The very first synthesis of periodate was achieved by Ammermüller et al. in 1833 by purging an iodine solution with chlorine gas (Cl_2).[32−35] The following methods used hypochlorite (OCl^-),[36,37] chlorate (ClO_3^-), peroxodisulfate ($S_2O_8^{2-}$),[38] persulfate (SO_5^{2-}),[39] permanganate (MnO_4^-),[40] ozone (O_3),[41−43] hydrogen peroxide (H_2O_2),[44] or even hypervalent Xe compounds[45] to oxidize iodide, iodine, or iodate to periodate. Nitric acid (HNO_3)[46] or oxygen (O_2)[47] may also be utilized at elevated temperatures. However, the use of oxidants is wasteful, cumbersome, and even dangerous. Oxidants must be synthesized as well, the separation of the product from byproducts is tedious, and the use of high temperatures is in general energy consuming.

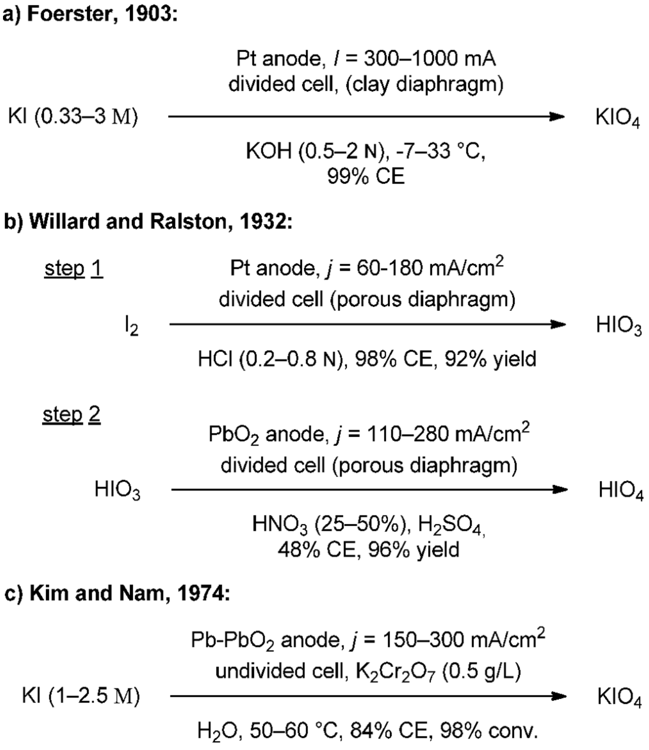
Electrochemical methods are superior to conventional methods due to a more direct application of energy, a readily

Scheme 1. Initial Studies by Erich Müller for the Electrochemical Synthesis of Periodate[a]



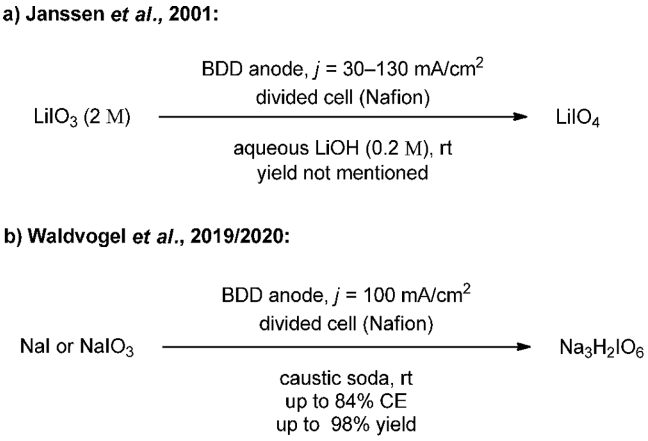
[a] The nature of periodate was not further specified; see section 2.2.

Scheme 2. Subsequent Studies by Foerster, Willard, and Nam[a]



[a] The exact nature of periodate was not specified; see section 2.2.

Scheme 3. Anodic Generation of Periodate at Boron-Doped Diamond (BDD)[a]



[a] The nature of periodate was not further specified; see section 2.2.

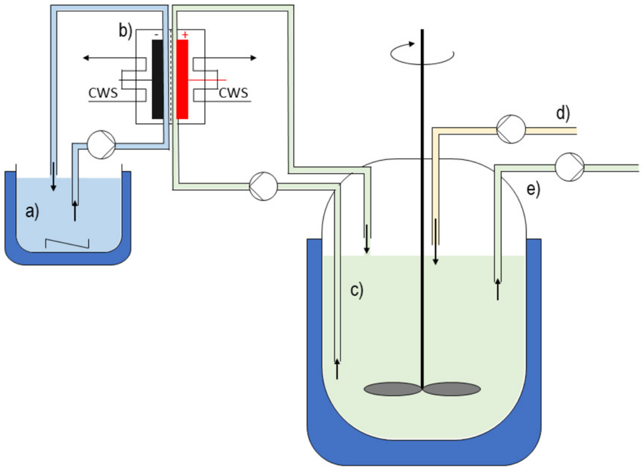
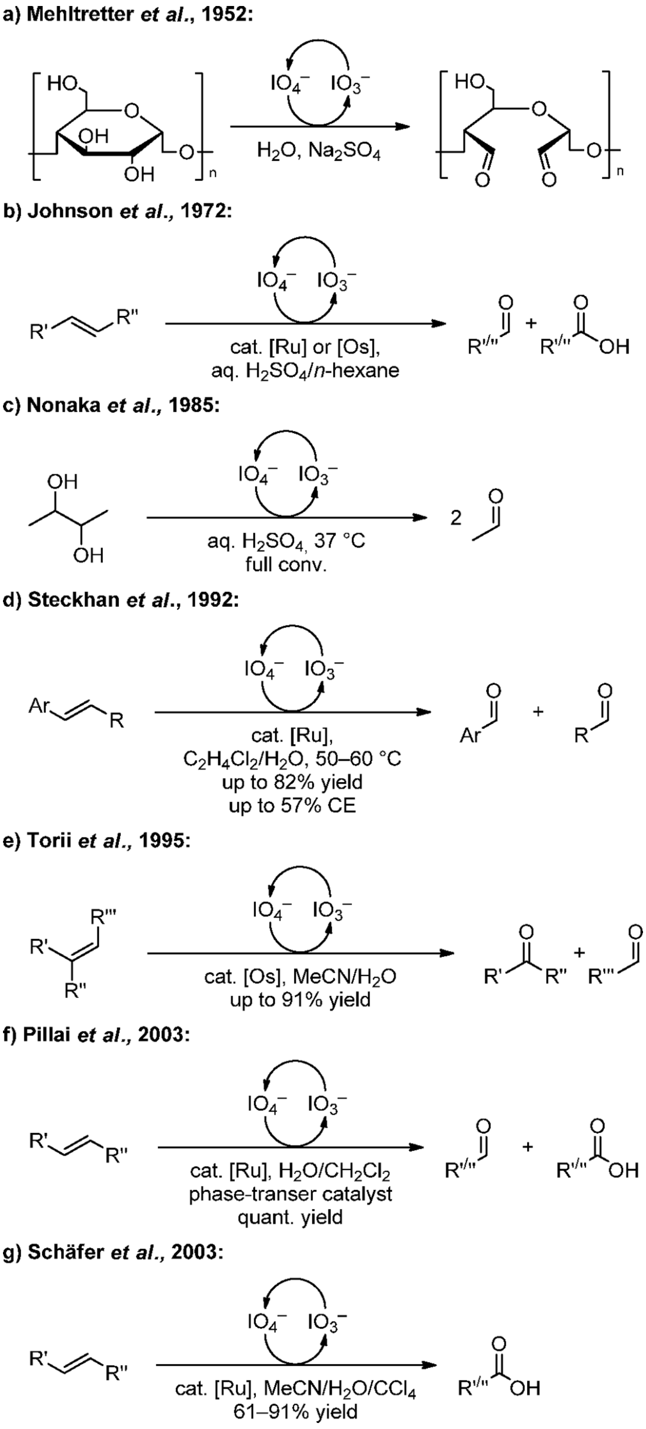


Figure 2. Schematic representation of a continuously stirred tank reactor (CSTR) coupled with electrolysis, (a) catholyte, (b), divided electrolysis cell, (c) anolyte, (d) feeding of starting material, (e) product collection for filtration, CWS = cooling water system.

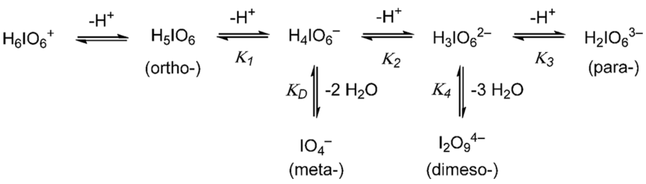
availability of electric current, and intrinsic safety.[48] Pioneering work was done by Erich Müller, who investigated the electrochemical synthesis of periodate in a series of studies between 1901 and 1904. In his first study, the electrolysis of aqueous iodate solutions was investigated in relation to pH, current density, temperature, and additives at platinum electrodes (Scheme 1a). The best performance was observed at alkaline pH, low current density, and low temperatures. Competing reduction processes in the undivided cell setup were an omnipresent challenge. However, potassium chromate (K_2CrO_4) was discovered to be an efficient antireducing agent, which prevents the reduction of iodate to iodide by forming a chromium-oxide diaphragm on the cathode.[49] Alternatively, a divided cell setup was also found to be effective. The investigation of the electrosynthesis of periodate was next deepened in the study by Müller and Friedberger (Scheme 1b). Prompted by the peculiarity at that time that periodate is formed in alkaline but not in acidic media, various anode materials were tested and lead dioxide was discovered to be excellent and suitable for the electrolysis in acidic media.[50] Today, we know that the standard redox potentials between iodate and periodate is higher in acidic than in alkaline

Scheme 4. Electro-mediatory Systems for the Malaprade, Lemieux−Johnson, and Ruthenium-Catalyzed Oxidations[a]



[a] Regeneration of periodate was afforded at PbO_2 anodes.

Scheme 5. Equilibria of Periodate in Aqueous Solution



media.[51] Lead dioxide is effective in acidic media due to a high overpotential versus the formation of oxygen, which reduces water-splitting as a side reaction.[52,53] The subsequent study extended the electrolytic conditions as well as various anode materials (Pt, PbO_2, Pd) and confirmed previous findings, including the mechanism proposed for lead dioxide anodes (Scheme 1c). The experiments suggested that lead dioxide intrinsically oxidizes iodate and, thus, acts catalytically during electrolysis. In addition, the positive effect of mediators (Cl^-, SO_4^{2-}) was assigned to the electrolytic formation of the corresponding oxidized species hypochlorite (ClO^-) and persulfate (SO_5^-). The effect of chlorate (ClO_3^-) was attributed to oxidize iodate directly.[54] More recent data for the standard redox potentials suggest that this is not the case.[51] Müller's studies were the most fundamental for following research regarding the electrochemical periodate synthesis. Subsequent studies focused on starting materials, pH, precipitation issues as well as on additives, process development, and cell design.

The use of iodide or iodine as starting material was the subject of many the following investigations.[55] Iodate is expensive compared to iodide or iodine. Hence, the multistep electrolysis is preferred, although not trivial.[14] A general problem for a multistep electrolysis is the divergent solubility of iodic species. Müller reported the precipitation of periodate in alkaline media, while Foerster and co-workers reported the thick precipitation of iodine under acidic conditions (Scheme 2a). The precipitation of either of those species is problematic, as the coating of electrodes decreases the current efficiency and iodine is eliminated from the electrolyte.[56−60] Foerster recognized the disproportion of iodine and of hypoiodite to iodate in alkaline media (eqs 1−4).

$$I_2 + OH^- \rightleftharpoons I^- + HIO \tag{1}$$

$$HIO + OH^- \rightleftharpoons IO^- + H_2O \tag{2}$$

$$3IO^- \rightleftharpoons IO_3^- + 2I^- \tag{3}$$

$$\text{overall: } 3I_2 + 6OH^- \rightleftharpoons IO_3^- + 5I^- + 3H_2O \tag{4}$$

In conclusion, the electrolytic steps from iodide to iodate are favored in alkaline media, whereas the anodic step from iodate to periodate is favored at acidic conditions in terms of precipitation. Useful strategies have been developed to obviate the issue of precipitation. Mehltretter and co-workers were the first to conduct a sequence of electrolysis at different pH. The first part was carried out under alkaline conditions, and the second, under acidic conditions.[12,61,62] Hirakata and co-workers pursued a similar approach for the electrolysis of iodate to periodate, but instead of changing the pH intermittently, the electrolysis was started at a defined pH. It decreased during electrolysis, and the solution turned acidic over time.[63] In Willard's and Ralston's report, periodic acid was produced from iodine in a two-step electrolysis (Scheme 2, b). The first step was performed at platinum anodes in diluted hydrochloric acid. The chloride was claimed to catalyze the formation of iodic acid (eqs 5 and 6). Noteworthily, platinum anodes are usually not stable in the presence of chloride.[64]

$$2HCl + I_2 \rightleftharpoons 2ICl + 2H^+ + 2e^- \tag{5}$$

$$ICl + 3H_2O \rightleftharpoons HIO_3 + HCl + 4H^+ + 4e^- \tag{6}$$

The chloride was removed as chlorine gas at the end of electrolysis. However, the precipitation of iodine was not successfully prevented.[65] The resulting iodic acid was then electrolyzed at lead dioxide anodes in diluted nitric acid. Kim and Nam were the first to electrolyze iodide to periodate by an eight-electron oxidation, but their observations are contradictory (Scheme 2c).[66] Precipitation issues with iodine were even reported during electrolysis of iodide to iodate despite working in alkaline media. In the final step, no precipitation was reported despite performing the electrolysis in neutral media.[67,68] The efficiency of the electrolysis was best at low and inferior at high hydroxide concentration, whereas Hickling and Richards reported differently.[69] This demonstrates the complexity of the electrolysis, which shows high dependency on both materials and conditions. Waldvogel and co-workers recently developed an electrochemical continuous flow process to produce paraperiodate at boron-doped diamond (BDD) anodes in a divided cell. The electrolysis conditions were strongly alkaline, and precipitation could not be prevented. Instead, clogging of the flow system was avoided by keeping the electrolysis at steady state, in which the suspension had favorable properties.[70] This facilitates downstream processing, which is recognized as a key costdriver in electrosynthesis.[71] A schematic representation of this setup is described later in this chapter.

Another challenge is the reduction of periodate at the cathode. In an undivided cell, reduction could be prevented using either potassium chromate (K_2CrO_4) or dichromate ($K_2Cr_2O_7$) as additives. The chromates form a chromium-oxide layer on the cathode surface, which acts as a protective diaphragm.[49] However, chromium(VI) contaminations are highly toxic. For this reason, a divided cell setup is preferred using a cation-exchange membrane (e.g., Nafion).[72]

The anode materials for the electrochemical synthesis of periodate have been extensively studied. Lead dioxide was the anode material of choice for more than a century since Müller's exploration of its high performance within the periodate electrosynthesis.[50,73] A catalytic effect was proposed by Müller, which was confirmed by Willard[65] and Nam.[66] Powdered lead dioxide was found to oxidize both iodide and iodate (eqs 7 and 8).

$$PbO_2 + 3IO_3^- + 2H^+ \rightleftharpoons Pb(IO_3)_2 + IO_4^- + H_2O \tag{7}$$

$$PbO_2 + 2I^- + 2H^+ \rightleftharpoons Pb + I_2 + H_2O \tag{8}$$

However, lead dioxide is labile and disintegrates under anodic conditions thus contaminating the electrolyte. Lead contaminations are highly toxic and difficult to remove. They appear in forms of sheds, "mud" and salts,[74−78] and were merely removed by filtration in early production methods.[12,61,62] Alternatively, it may be removed by recrystallization, which comes along with substantial loss of product. Subsequent research focused on the development of more durable PbO_2 anodes (Nam,[79−81] Rhes,[82] Shirai[13]), but still the contamination is not precluded. Less toxic and more stable electrode materials were tested, such as nickel (NiOOH), graphite, carborundum, magnetite, iridium oxide, or ruthenium oxide.[69,83−85] However, all materials showed only limited durability and/or formed toxic contaminations that are strictly regulated e.g. for pharmaceutical products. According to ICH guideline Q3D (R1) on elemental impurities, Pb is a class I element and the permitted daily exposure (PDE) is limited to not more than (NMT) 5 μg/day resulting in NMT 0.5 ppm in the drug preparation. "The elements As, Cd, Hg, and Pb are human toxicants that have limited or no use in the manufacture of pharmaceuticals for every route of administration".[86,87] For this reason, the use of metal-based electrodes imposes a major obstacle for a broad application of periodate in the pharmaceutical industry. High costs for purification and quality assurance emerge that prohibit the use of periodate economically. On the other hand, the source of metal contamination was (entirely) eliminated using boron-doped diamond (BDD) anodes instead of PbO_2. BDD is equally efficient as lead dioxide but is more durable and can be manufactured from renewable resources.[88−91] BDD electrodes are commercially available and frequently used in electrosynthesis.[92−94] In a study by Janssen and co-workers, BDD anodes were employed to electrolyze lithium iodate (Scheme 3a). However, lithium salts are expensive and are expected to stay expensive due to their extensive use in batteries ($LiIO_3$: 369 \$/kg; LiI: 231 \$/kg). The study was focused on electrode processes and sufficient solubility rather than synthetic aspects.[95,96] Lehmann and co-workers published the anodic oxidation of chloride to perchlorate at BDD anodes, but the conditions used were highly unfavorable (not depicted).[97] High current densities, an undivided cell setup, as well as a low pH and temperature resulted in a low current efficiency of 65%. The electrolysis of iodide to periodate at BDD was claimed but was not performed. Müller noted earlier that the oxidation of iodide is unequally more difficult.[49,54] In a recent study by our group, the electrolysis of iodide to periodate at a BDD anode was developed (Scheme 3b). From the perspective of costs, we determined sodium iodide to be the most cost-efficient starting material (NaI: 26 \$/kg), and from standard redox potentials, we concluded that the oxidation would be favored under basic conditions.[51] Our findings resulted in a scalable and highly efficient flow-electrolysis with yields of up to 86%.[14] The method was further extended to the electrolysis of iodate and is augmented by an efficient recycling method.[15] The iodate was recovered up to 96% by precipitation with 2-propanol, and the (re)subjection to electrolysis yielded up to 83% of periodate. It thus becomes more affordable and interesting, not only for the use in API production but also for the valorization of renewable resources.[10,98−100] A schematic representation of the flow-electrolysis setup is included in Figure 2 and described later in this chapter.

The recycling of iodate to periodate is of industrial interest and has been established by chemical and electrochemical means.[43] Mehltretter and co-workers were the first to publish the *ex-cell* electrochemical regeneration of periodate from oxidant liquors in the production of oxystarch (Scheme 4a).[11,101] Periodic acid was recovered in 94% yield in average, and the oxidant could be reused with an average loss of 16% per run. A similar process was developed by Pfeifer et al.[102] Johnson and co-workers published the electrochemical regeneration of periodate in a double-mediatory process (*in-cell*, Scheme 4b).[103] The periodate was generated in the aqueous phase in the anodic compartment, and subsequently osmium or ruthenium precursors were transformed into the respective peroxo-species. Those are soluble in organic solvents and mediated the oxidative cleavage of C−C double bonds. The process constitutes the electrochemical Lemieux−Johnson or the oxidation by ruthenium tetroxide. A metal-free mediatory process was developed by Nonaka and co-workers, corresponding to the electrochemical analogue of the Malaprade oxidation (Scheme 4c).[104,105] Yields and conditions were improved by Steckhan[106] and by Torii (Scheme 4d−e).[107] Pillai used a phase-transfer catalyst (Scheme 4f),[108] whereas Schäfer designed a flow apparatus wherein the generation of periodate and the oxidation of the organic target were separated (Scheme 4g).[109] In all cases, iodate was converted at lead dioxide anodes. The examples demonstrate that the combination of electrochemistry and a high-performance oxidizer is not only orthogonal but also efficient.

In conclusion, the electrolysis to periodate has been thoroughly investigated over the past century. Conditions must be chosen carefully, but the most favorable found so far are an alkaline pH, a divided cell setup, and BDD anodes. Lower current densities are more efficient, but space-time yields are then also lower. Currently, the issue of precipitation and coating was solved by Waldvogel et al. by simulating a late stage of the electrolysis in a continuously stirred tank reactor (CSTR). A schematic representation of such is given in Figure 2.

Mediatory systems were proven successful, but the scope is usually quite limited. Racemization or degradation may occur if the organic molecule gets in contact with the anode, which would be the case for water-soluble compounds. Future challenges to solve are, e.g., the wasteful recrystallization of para- to metaperiodate.

2.2. Various Periodate-Specific Features, Equilibria, and Their Analysis.

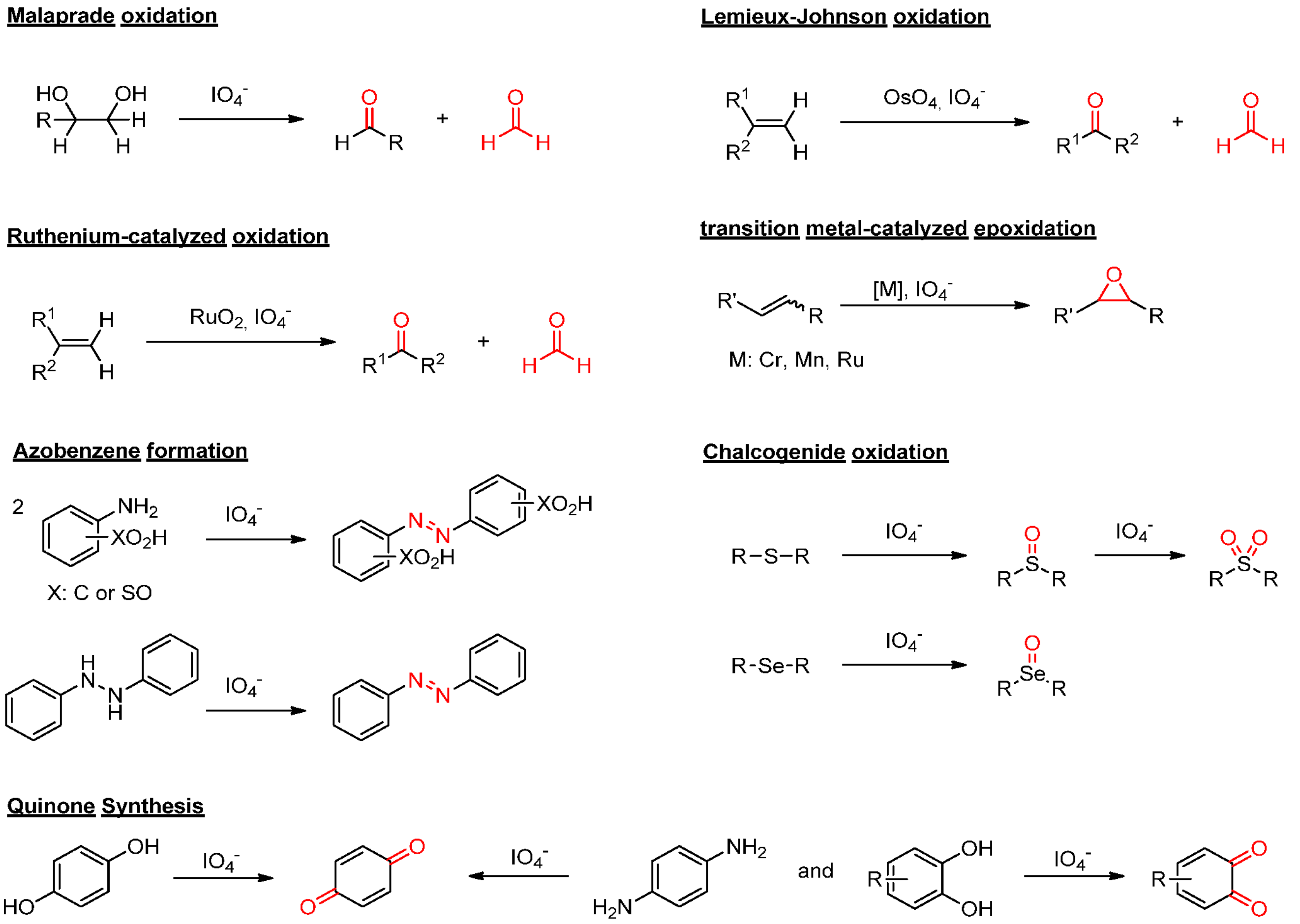
Before continuing with its application in organic synthesis, we want to give some clarification about the nature and major forms of periodate in equilibrium. In many publications, structures have not been assigned correctly, which may be reasoned in the manifold of structures of periodate and contradicting the literature. In addition, our impression is that there is still much confusion about the nomenclature, which is probably a result of the rather imprecise definition. Suitable analytical methods will also be introduced herein.

According to IUPAC, the hexavalent oxo-species of iodine is commonly named "orthoperiodic acid" (H_5IO_6, systematic name: pentahydroxidooxidoiodine) and its corresponding anion "orthoperiodate" (IO_6^{5-}, systematic name: hexaoxidoiodate). The tetravalent oxo species is commonly named "periodic acid" (HIO_4, systematic name: hydroxidotrioxidoiodine) and its corresponding anion "periodate" (IO_4^-, systematic name: tetraoxidoiodate).[110] In practice, however, the term "periodate" is used superordinate for all iodine species in a formal oxidation state of +7, such as for *ortho*-periodic acid (H_5IO_6), *meta*- (MIO_4), *para*- ($M_3H_2IO_6$), *meso*- (M_3IO_5), or *dimeso*-periodate ($M_4I_2O_9$).[35] In addition to those main species, a myriad of dimers, oligomers, and polymers of periodate exist, but the coverage of those would be beyond the scope of this review and has been reviewed elsewhere.[51,111−114]

Iodine in periodate can assume the coordination numbers four and six, such as in meta- or orthoperiodic acid.[115] In solid state, the ortho-acid is transformed into the meta-acid by sublimation under loss of two molecules of water ($H_5IO_6 \rightarrow HIO_4 + 2\ H_2O$).[116] Alternatively, it is obtained by acidic recrystallization from hot solution.[12,61,62] Orthoperiodic acid is obtained by hydration of metaperiodic acid, thus being the predominant form in aqueous solutions. The true octahedral geometry of orthoperiodic acid was confirmed by Raman and infrared spectroscopy,[117] and later by single-crystal X-ray diffraction.[118−122]

The first evidence for the acidic nature of orthoperiodic acid was found by the formation of paraperiodate under alkaline conditions.[32] Paraperiodate has a very low solubility in water

Scheme 6. Relevant Scope of Periodate-Mediated Oxidations Used in Pharmaceutical or Other Organic Syntheses



and, thus, was determined by simple gravimetry.[35,123,124] The molecular formular was confirmed by atomic absorption spectroscopy.[125] Several studies focused on the basicity of orthoperiodic acid after the polybasic behavior had been predicted by conductivity measurements.[126] The dissociation constants of three replaceable protons were estimated consecutively[127−129] and were then complemented and refined by Crouthamel[130] and Horvath.[125] Current readings range at $pK_1 = 0.98$, $pK_2 = 7.42−7.55$, and $pK_3 = 10.99−11.25$ in dependence of the background electrolyte. In extreme cases, orthoperiodic acid can accept a proton from very strong acids, such as perchloric acid, to form $H_6IO_6^+$ [$pK(H_6IO_6^+) = −0.8$].[131] The dissociation of protons 4 and 5 is not observed in aqueous solution, although Li_5IO_6 may be obtained by thermolysis (Scheme 5).[132,133]

Subsequent research focused on the dehydration of orthoperiodic acid (K_D) and the condensation reaction to dimesoperiodate (K_4). The equilibria were investigated by ultraviolet−visible light (UV−vis) spectroscopy at various temperatures and pH ranges. Accordingly, the formation of metaperiodate was favored at acidic pH and at elevated temperatures, whereas the dimerization was neglectable.[130,134] The *ortho*−*meta* equilibrium was further supported by the presence of both species in both Raman and infrared spectroscopy.[117,135,136] Additionally, contraction/dilatation experiments with aqueous periodate solutions during neutralization were revealing. A very strong dilatation was observed from orthoperiodic acid up to the first equivalent point followed by a volume contraction up to the second. The dilatation was explained by the superimposition of the reactions in eqs 9 and 10

$$H_5IO_6 + OH^- \rightleftharpoons H_4IO_6^- + H_2O \tag{9}$$

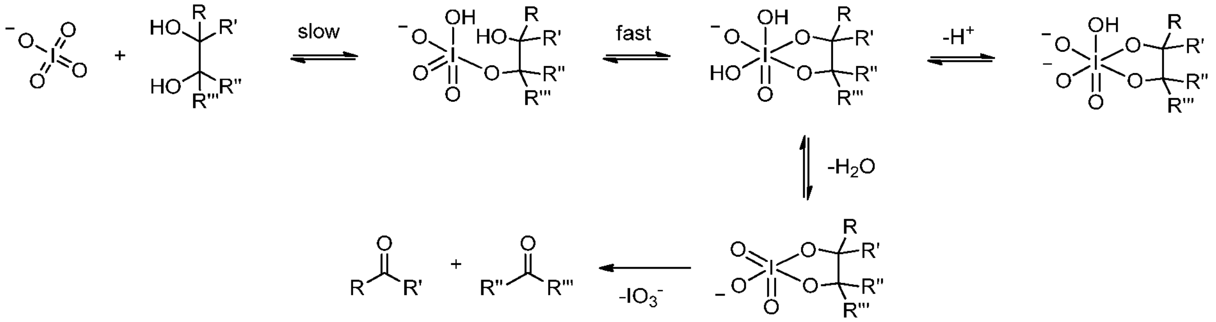
$$H_4IO_6^- \rightleftharpoons IO_4^- + 2H_2O \tag{10}$$

while the subsequent contraction was reasoned by the reaction in eq 11.[137]

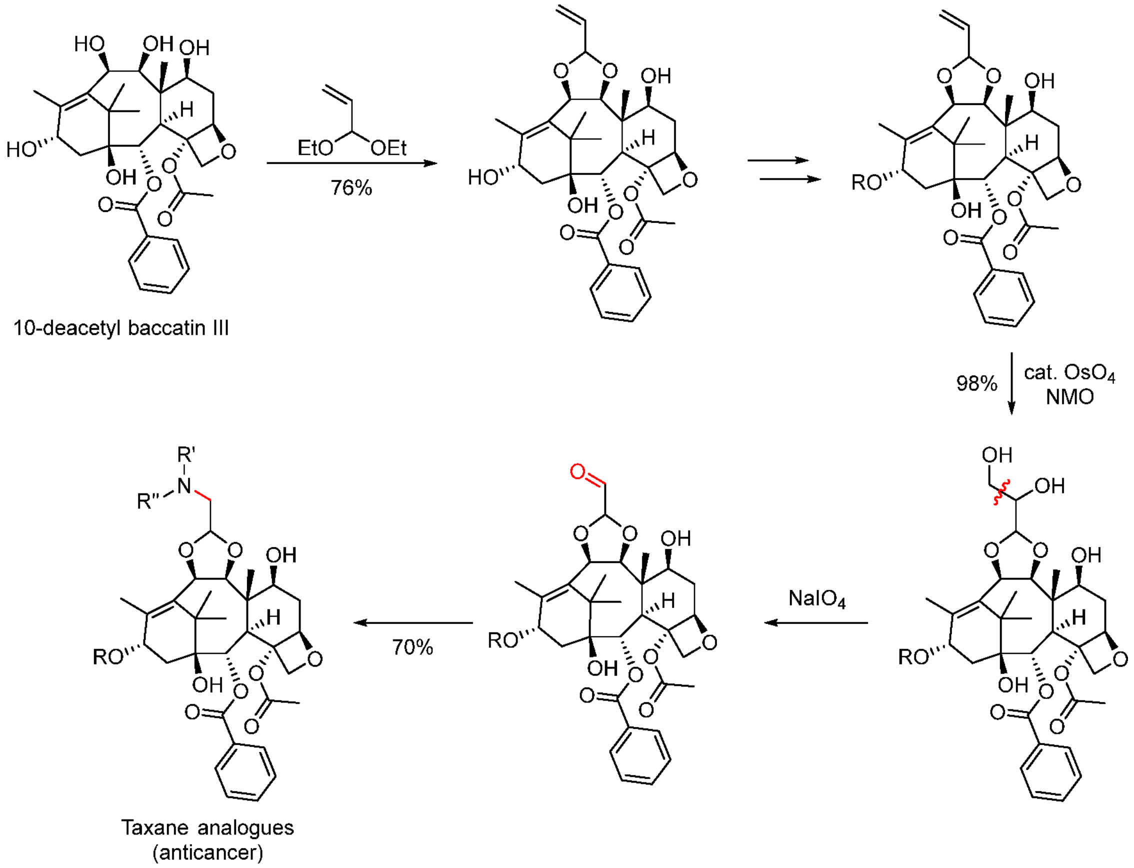
$$IO_4^- + H_2O + OH^- \rightleftharpoons H_3IO_6^{2-} \tag{11}$$

The equilibrium between $H_4IO_6^-$ and IO_4^- was further investigated by ^{127}I NMR spectroscopy, wherein one major resonance was observed. IO_4^- was concluded to be the most abundant species in solution first, but after re-evaluation of data an equilibrium under rapid water exchange was assumed.[138−140] The validity of the previous photospectroscopic study was doubted by Kerezsi; the assumption of markedly different absorption maxima of $H_4IO_6^-$ and IO_4^- had been invalid. A recent study by Horvath and co-workers supported this theory and could assign all absorption maxima to similar values. Raman spectroscopy at higher concentrated solutions indicated no evidence for the existence of metaperiodate. Thus, it was concluded that the equilibrium shifted toward orthoperiodic acid. Condensation, as predicted in several studies by Buist[141−143] and Kustin,[144] was disproven following the arguments of Horvath, and the equilibrium between ortho- and dimesoperiodate was hence considered

Scheme 7. Mechanism for Cleavage of Glycols



Scheme 8. Synthetic Route to Taxane Analogues



neglectable.[125] In conclusion, the equilibria of periodate in aqueous solution are still not entirely understood. Contradictions arise from Horvath's results and dilatation experiments, among others. However, the form of periodate in solution may be best described by three-basic orthoperiodate, as in accordance with our research.

Finally, the commonly used analytic methods shall be briefly introduced: Quantification of periodate species was achieved by volumetry, gravimetry, and/or UV−vis spectroscopy. Volumetry is based on the comproportionation reaction of periodate and iodide to iodate (eq 12).

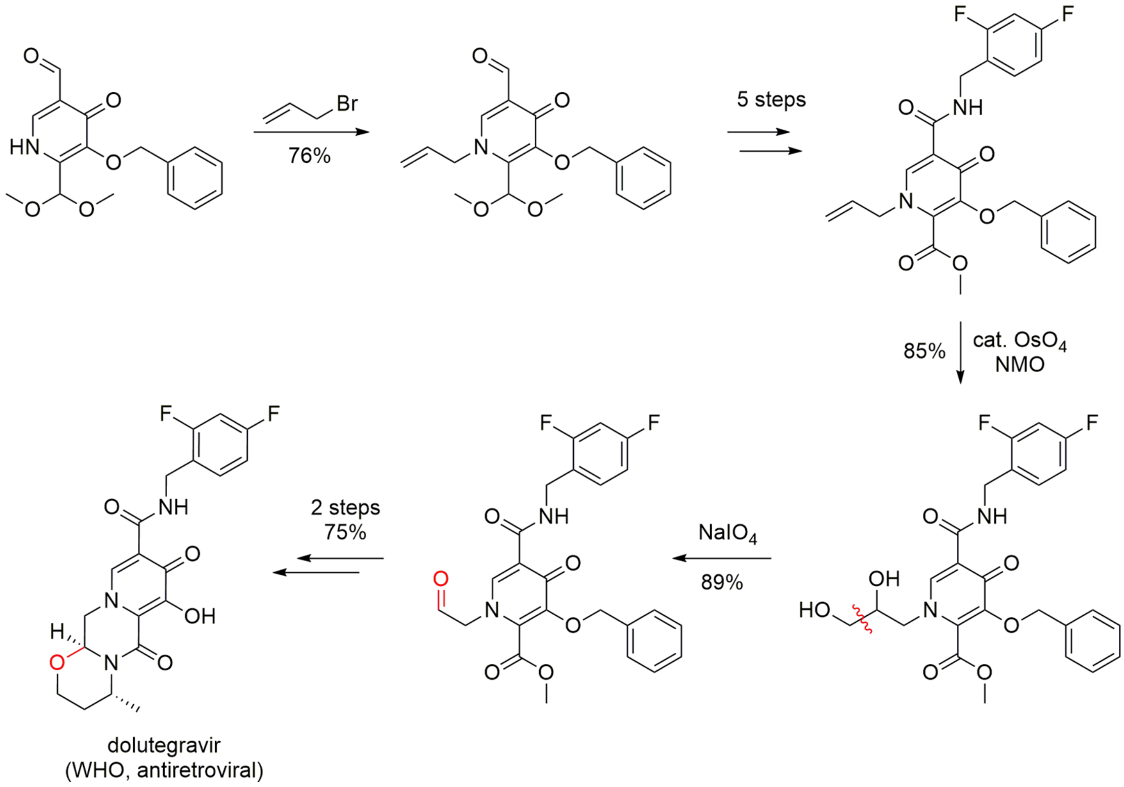
$$IO_4^- + 2I^- \rightleftharpoons IO_3^- + I_2 \qquad (12)$$

Gravimetry is usually based on the formation of less soluble salts, such as barium periodate or paraperiodate.[145−147] Photospectroscopy relies on photoactivity, which was first reported by MacDonald and co-workers,[148] and which was utilized by Crouthamel to confirm the dissociation constants.[134] Further analysis methods are conductometry and potentiometry.[126,149] Structural assignments were achieved by Raman or infrared spectroscopy, and by single-crystal X-ray diffraction.[117−122] Modern analytical protocols were developed by Potthast and Waldvogel using high performance liquid chromatography coupled to a photodiode array (LC-PDA). The iodine species (I^-, IO_3^-, periodate) could be separated on an inverse column within 2 min.[14,43] ^{127}I NMR spectroscopy may also be used, but signals are very broad due to the quadrupole moment of the iodine nucleus. This renders the interpretation of complex mixtures difficult, and nonsymmetrical structures may remain unnoticed.[150]

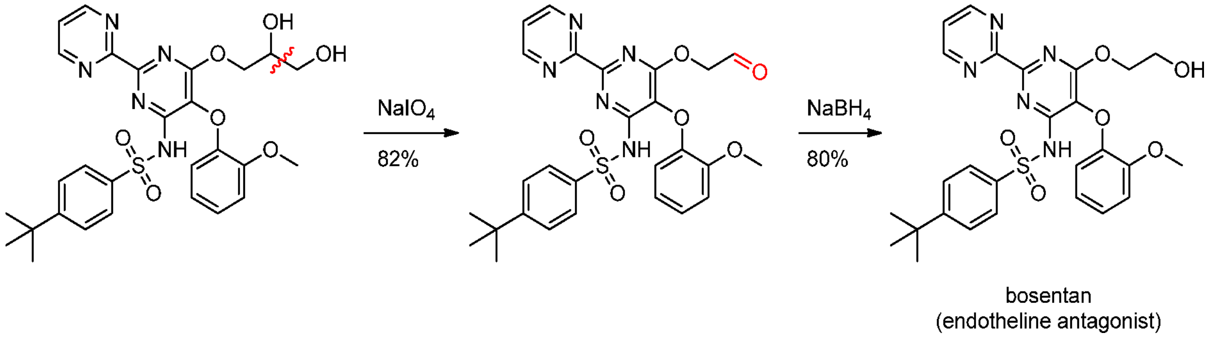
3. MALAPRADE OXIDATIONS

Metaperiodate is most widely used for the C−C cleavage of 1,2-diols according to the Malaprade oxidation whereby two

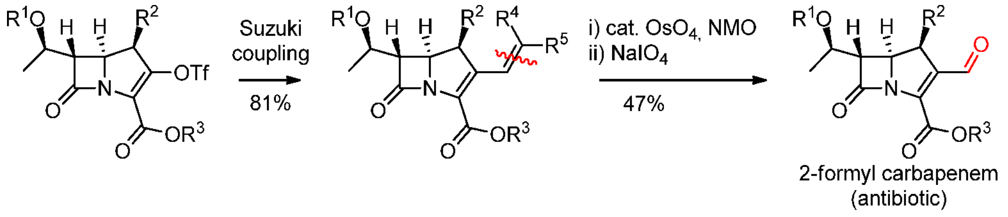
Scheme 9. Synthetic Route of Dolutegravir



Scheme 10. Key-Synthetic Steps for Bosentan



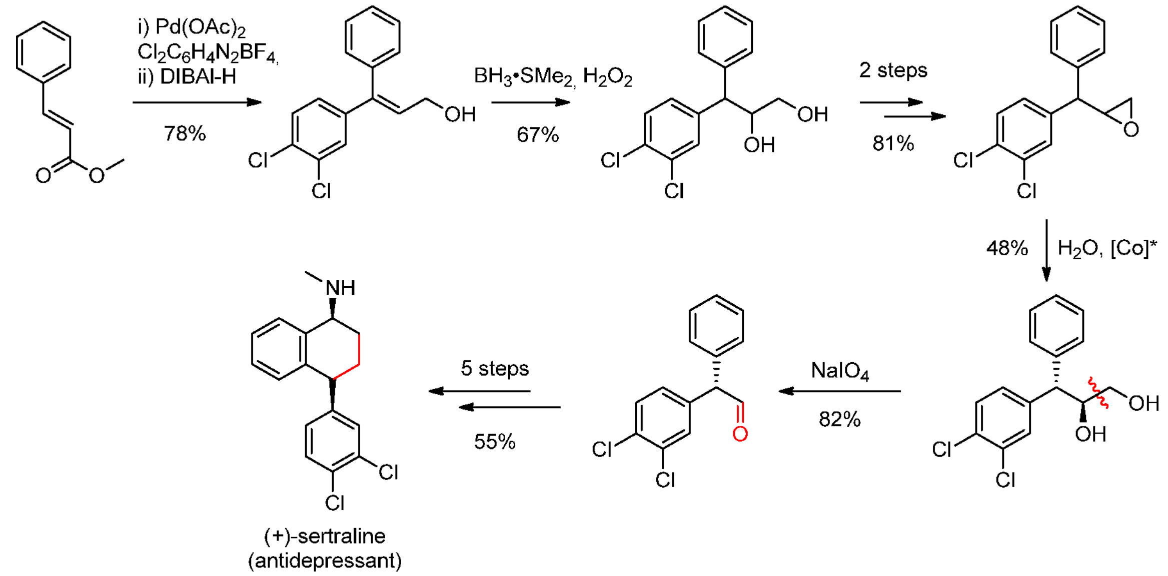
Scheme 11. Key-Synthetic Steps for Carbapenem



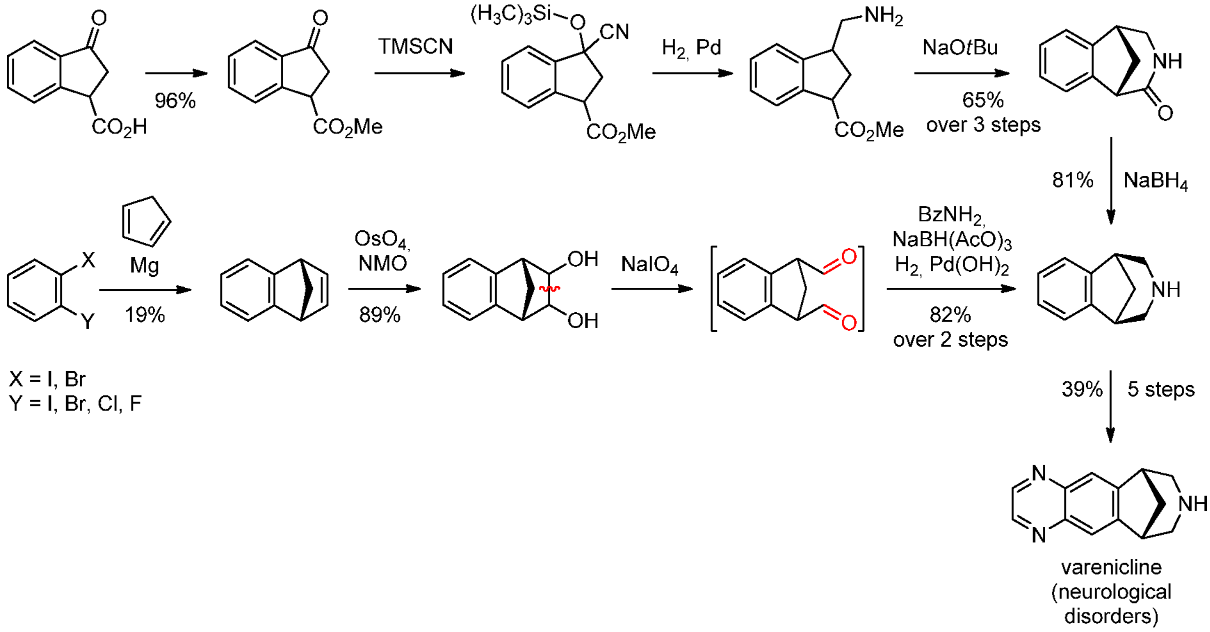
carbonyls are formed. Related oxidations utilize periodate for the cleavage of C−C double bonds in conjunction with a catalyst—formally a sequence of a dihydroxylation followed by the Malaprade oxidation. Typical catalysts are osmium tetroxide (Lemieux−Johnson), ruthenium tetroxide (formed *in situ* from suitable salts such as $RuCl_3$ or RuO_2), or permanganate (Lemieux−von Rudloff).[151−153] Other uses of periodate are the oxidation of chalcogenides—especially sulfur compounds,[154,155] the epoxidation of alkenes,[156−161] formation of azobenzene derivatives,[162−165] and various quinone syntheses[162,166,167]—and will be outlined in the later chapters of this review (Scheme 6).

The Malaprade oxidation is usually performed in aqueous solvent mixtures with slightly acidic to neutral pH. This transformation is very selective and quickly proceeds at room temperature. Beside α-diols, the fission works for α-ketols, α-diketones, or α-amino-alcohols, or related structures, albeit slower.[30] The mechanism proceeds through formation of the cyclic diol-periodate diester followed by dehydration and internal rearrangement to the fission products (Scheme 7).

Scheme 12. Synthetic Route of Sertraline



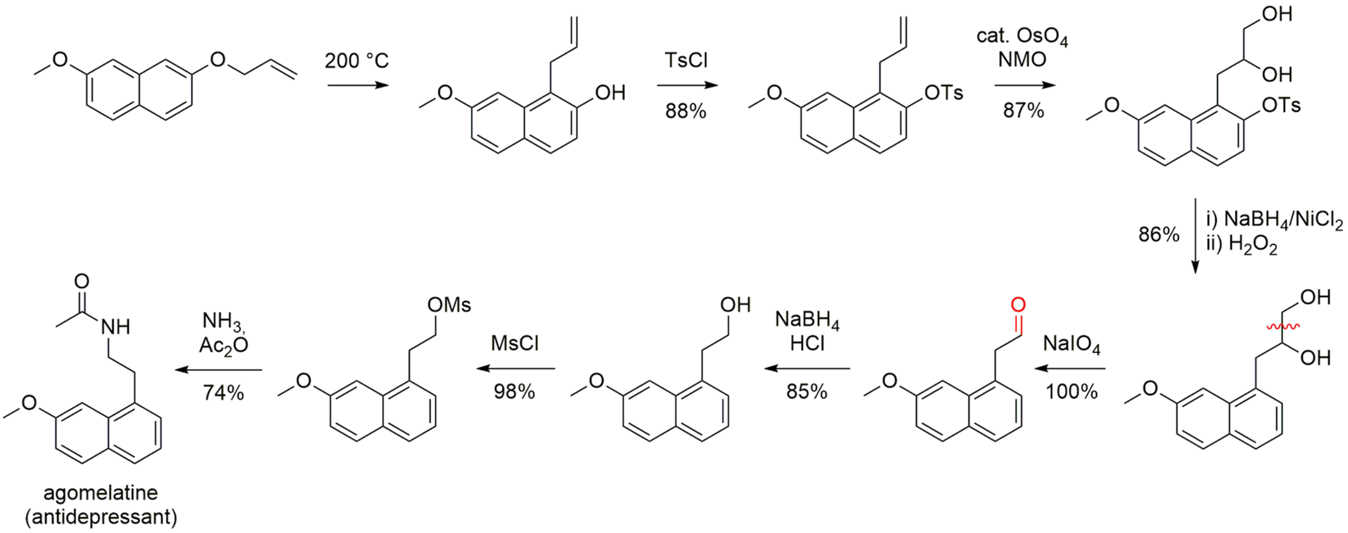
Scheme 13. Synthetic Routes of Varenicline



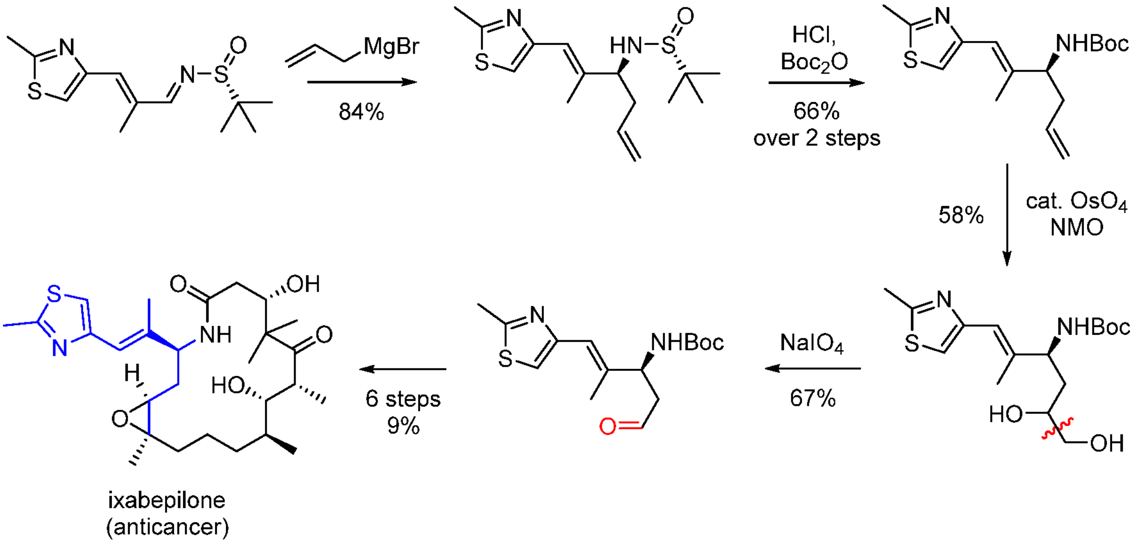
The oxidation does not perform if the formation of the cyclic diester is impossible, e.g., for constrained *trans*-diols.[8,9,168,169] It was proposed that only the dehydrated form of the diester is capable of decomposition to the products. This is favored at acidic conditions, while higher pH gives the inactive hydrated dianion. Notably, the hexavalent diester is more acidic than periodate itself, which in the case of acid-sensitive substrates requires buffering.[8,9] In the context of the Malaprade oxidation, its implementation into any synthetic route is interesting, i.e., the formation of the diol and the successive use of the carbonyl. The most common and simplest strategy for the generation of a 1,2-diol is by dihydroxylation of a double bond, which can be installed by various methods. The most common approach is the oxidation using OsO_4. The reaction can be carried out catalytically when a co-oxidant such as *N*-methylmorpholine *N*-oxide (NMO) is used. This reaction is referred to as "Upjohn dihydroxylation" and selectively forms *syn*-diols.[170] Due to steric hindrance of the intermediate ester, trans-diols are kinetically disfavored thus resulting in the syn-selectivity of the reaction. These methods will be part of the discussion in the following examples.

3.1. Alkene Oxidation. The excellent selectivity and reliability of the Malaprade oxidation allow for safe and well-controlled late-stage functionalization of complex organic molecules, as exemplified by the synthesis of taxane analogues. Those are useful in the treatment cancer and neurodegenerative disorder, and are closely related with cabazitaxel and docetaxel (*Jevtana, Taxotere, Sanofi*),[171] and paclitaxel (*Abraxane, Bristol Myers Squibb*).[172] The analogues were prepared in a semisynthetic route from 10-deacetyl baccatin III, which can be isolated from the yew tree (Scheme 8).[173,174] After installation of the double bond by ketalization, the preparation was followed by an Upjohn dihydroxylation to afford the diol in excellent yield (98%). The diol was cleaved

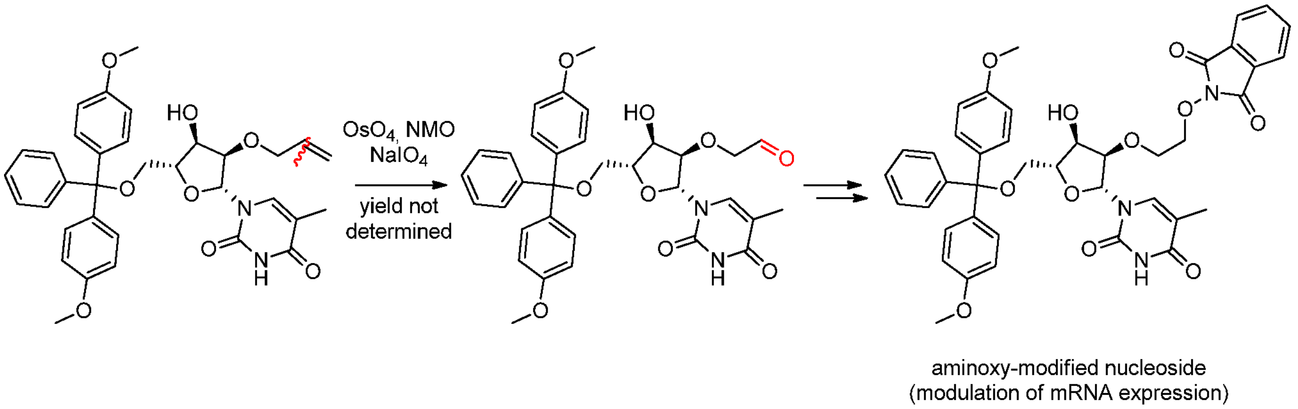
Scheme 14. Synthetic Route of Agomelatine



Scheme 15. Synthetic Route of Ixabepilone



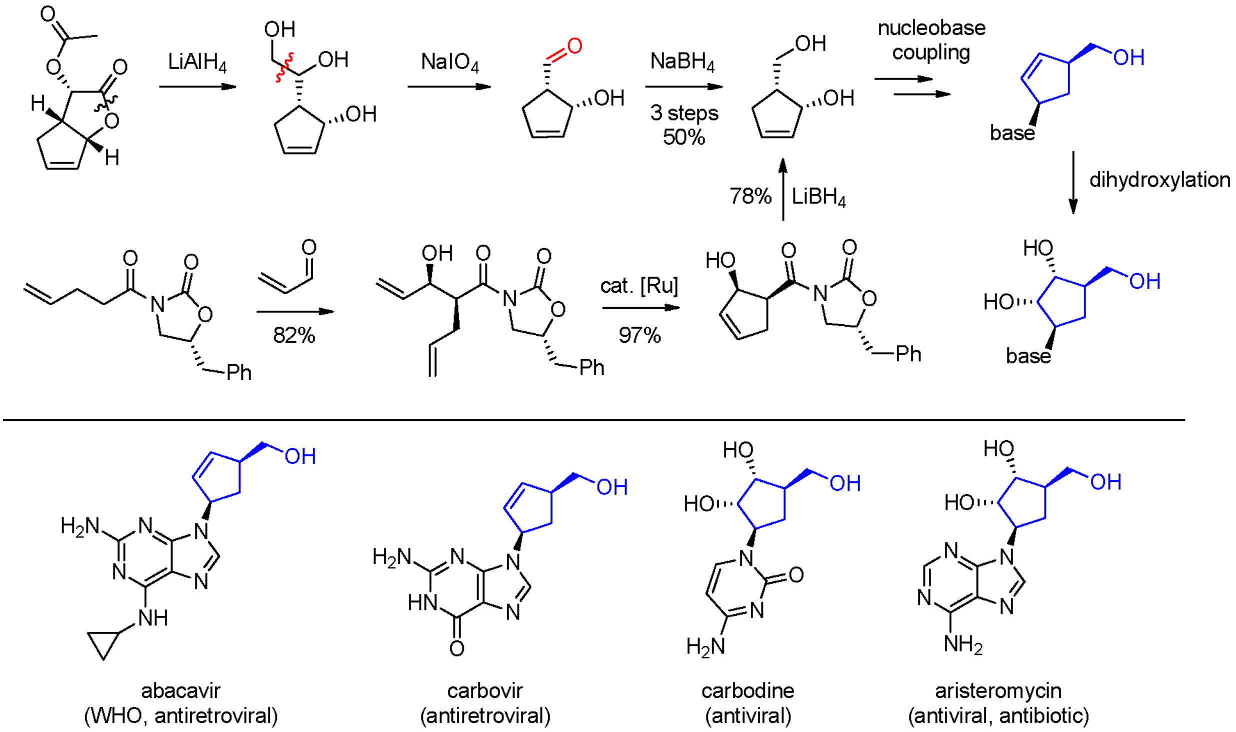
Scheme 16. Synthetic Route of Aminoxy-Modified Nucleosides



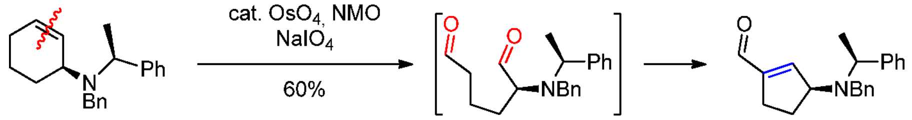
with periodate, and the product was used after extraction without further purification. The sequence of Upjohn dihydroxylation and Malaprade oxidation is common and should not be confused with the Lemieux–Johnson oxidation.

The HIV1 integrase inhibitor dolutegravir was developed by *ViiV Healthcare* and is licensed and sold by *GlaxoSmithkline* (*GSK*) as *Tivicay* and in combination therapies as *Triumeq*, *Dovato*, and *Juluca*. The dolutegravir franchise contributed £4.7 B revenue in 2020.[175] It proved to be particularly effective in

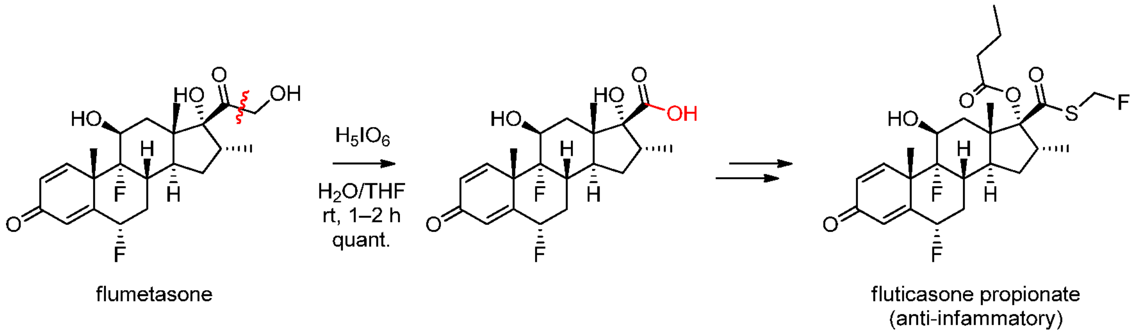
Scheme 17. Synthetic Route of Carbocyclic Nucleosides



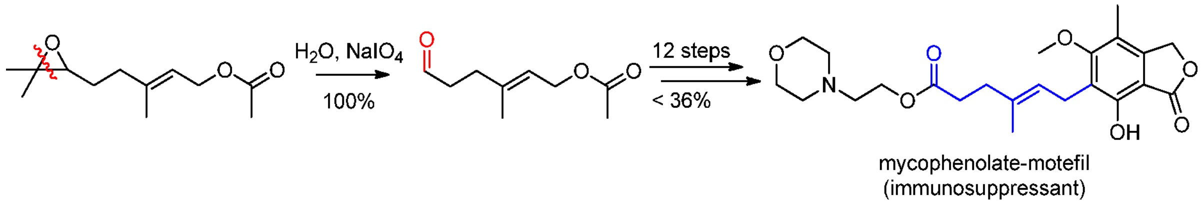
Scheme 18. Alternative Pathway for the Synthesis of Precursors for Carbocyclic Nucleosides



Scheme 19. Key Synthetic Steps for Fluticasone

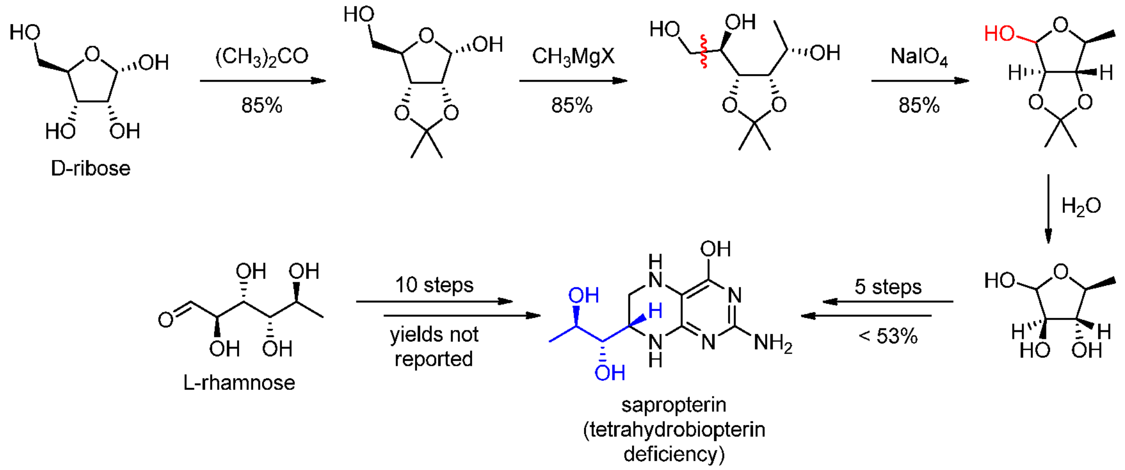


Scheme 20. Key Synthetic Steps for Mycophenolate-motefil

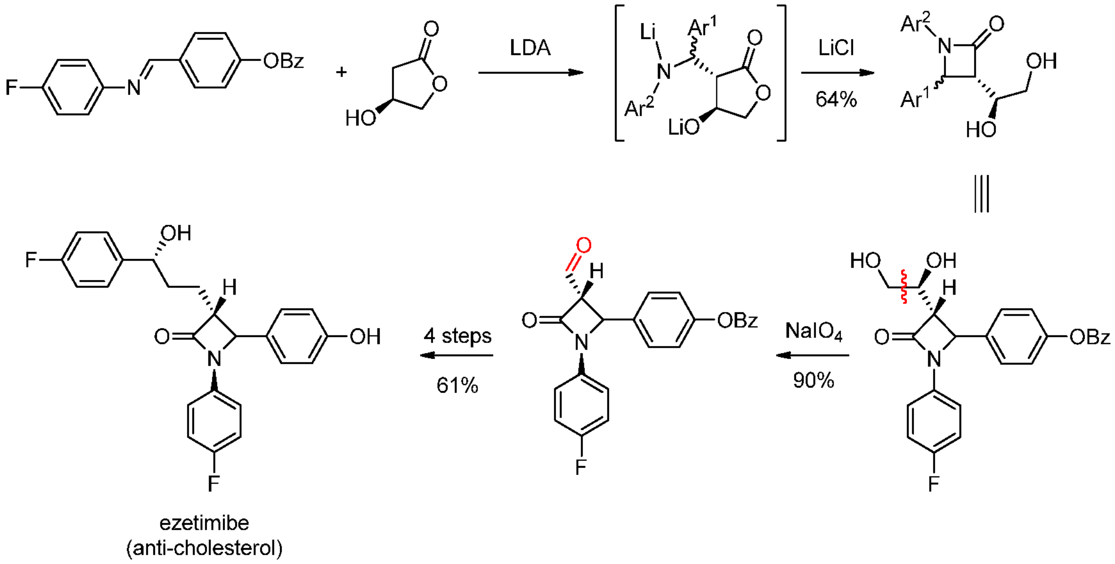


the treatment of HIV and is an important preventive treatment after potential exposure to the virus (PEP - Post Exposure Prevention).[176] Furthermore, dolutegravir is listed on the WHO's model list of essential medicines, as is connotated in Scheme 9.[31] Periodate was used in *GSK*'s synthesis of dolutegravir. The Malaprade oxidation was integrated into the route via allyl functionalization and Upjohn dihydroxylation (Scheme 9).[177−181] Alternative routes employ the Lemieux−Johnson or ruthenium-catalyzed oxidation.[178,182,183] The use of metal catalysts for such transformations was

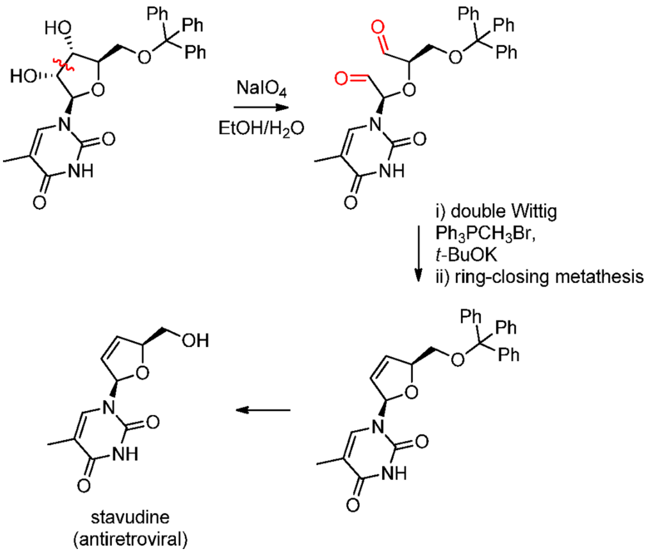
Scheme 21. Synthetic Route of Sapropterin



Scheme 22. Synthetic Route of Ezetimibe



Scheme 23. Key Synthetic Steps for Stavudine



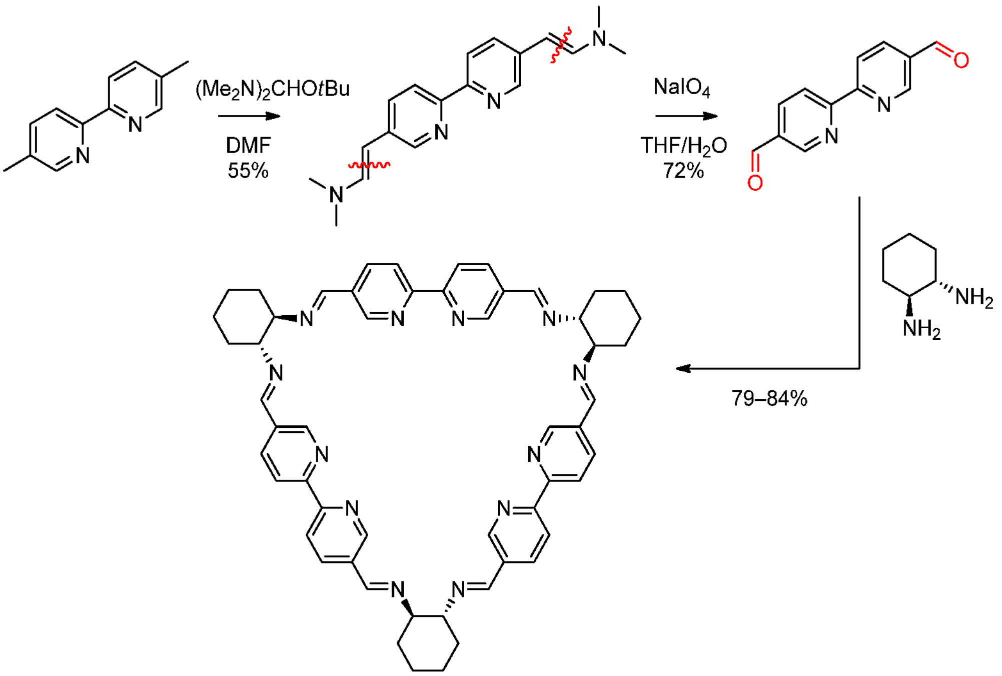
avoided in a recent report by Aoyama and co-workers by direct installation of 1,2-propanediol (not depicted).[184] Another efficient route was recently published by Opatz et al.[185]

A similar strategy was reported for the synthesis of bosentan, among other APIs. An allylic double bond was installed by nucleophilic substitution and was subjected to dihydroxylation with catalytic amounts OsO_4. The diol was subsequently cleaved by periodate on late stage (Scheme 10).[186] Alternative pathways progress via addition of isopropylidene glycerol or utilizes bidirectional approaches as is described later in this review. Bosentan, sold as *Tracleer* by *Johnson & Johnson*, is an endotheline receptor antagonist and is used for the treatment of class III pulmonary artery hypertension.[187]

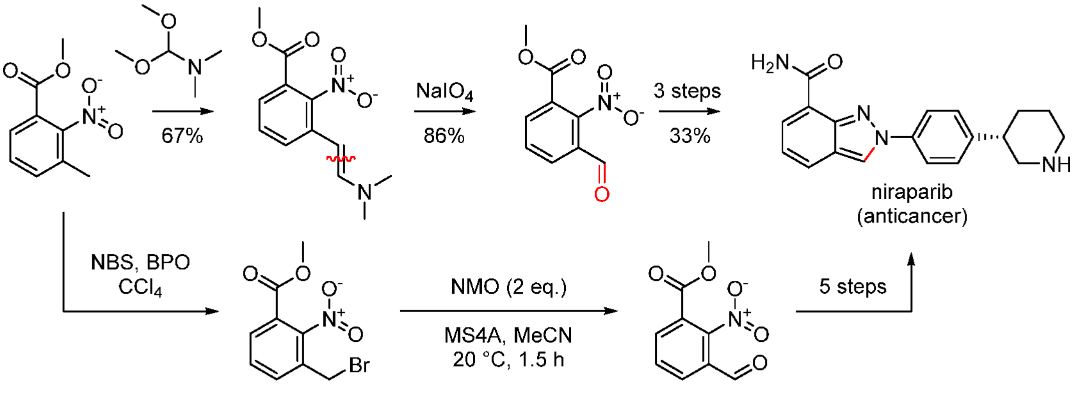
A synthesis for novel carbapenem scaffolds was developed by *Merck & Co. (MSD)*. Carbapenem compounds provide antibiotic activity and may be useful against Gram-positive microorganisms, such as methicillin resistant *Staphylococcus aureus* or *Staphylococcus epidermidis*. The C−C double bond was installed via Suzuki−Miyaura cross-coupling reaction, which was then dihydroxylated by OsO_4/NMO and cleaved by periodate in a one-pot protocol (Scheme 11).[188]

Sertraline is sold under the brand name *Zoloft* as an antidepressant that belongs to the class of selective serotonin

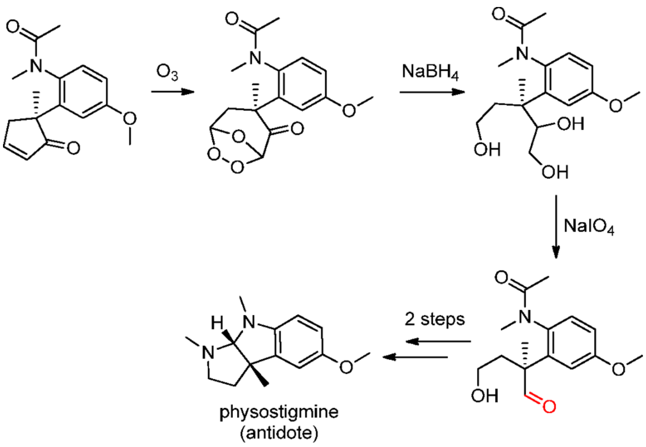
Scheme 24. Direct Enamine Cleavage by Periodate



Scheme 25. Key Synthetic Steps for Niraparib



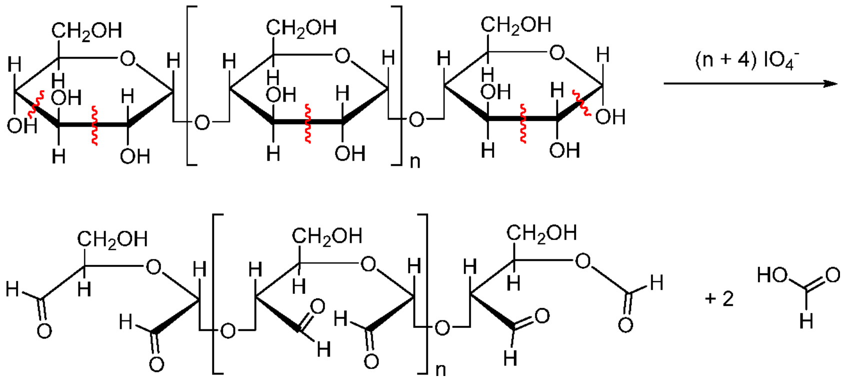
Scheme 26. Key Synthetic Steps for Physostigmine



reuptake inhibitors. It was discovered in 1970 by *Pfizer*[189] and is one of the most prescribed antidepressants ever.[190] The Malaprade oxidation was used for its enantiopure synthesis according to Sudalai and co-workers.[191] A sequence of Heck–Matsuda coupling, reduction, and hydroboration of the allyl alcohol introduced the 1,2-diol (Scheme 12). The Malaprade oxidation gave the corresponding aldehyde in 82% yield. Again, the aldehyde was used after extraction without further purification. As an advantage to previous syntheses,[192,193] the chiral selectivity was achieved by a catalytic sequence of epoxidation and hydrolysis.

Varenicline (*Chantix/Champix*) was developed by *Pfizer* and had revenue of $919 M in 2020.[194] It is used to aid with smoking cessation and treat neurological disorders. The synthesis includes an interesting example of the Malaprade oxidation.[195−197] The initial synthetic route started from 3-oxoindane-1-carboxylic acid, which was esterified, and was then transformed into the cyanohydrin trimethylsilyl ester at the keto group (Scheme 13). Subsequent reduction, formation of the cyclic lactam, and further reduction yielded the target molecule. In total, the benzazepine was established in 51% overall yield in 5 steps; however, no periodate was used in this specific synthesis route.[198] An alternative to this, in which a 1,2-dihalogenated formed an aryne and underwent Diels—Alder reaction with cyclopentadiene, was also etstablished.[199] In this example, the isolated double bond within the obtained

Scheme 27. Periodate Oxidation of Amylose, Haworth Projection[258]



Scheme 28. Synthetic Route of Rivaroxaban

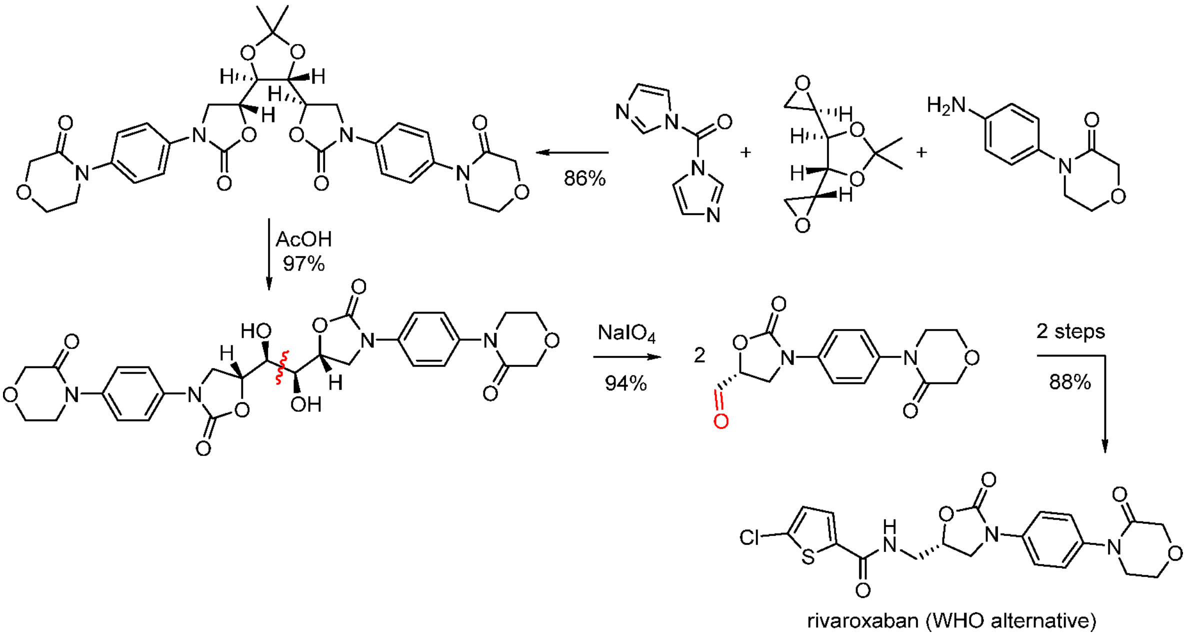
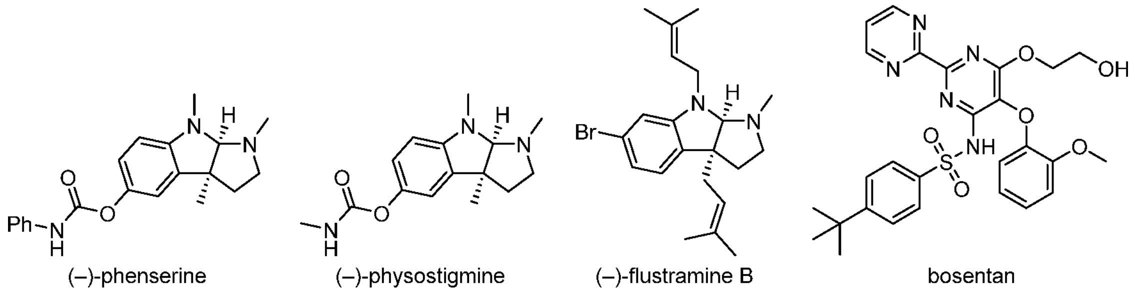


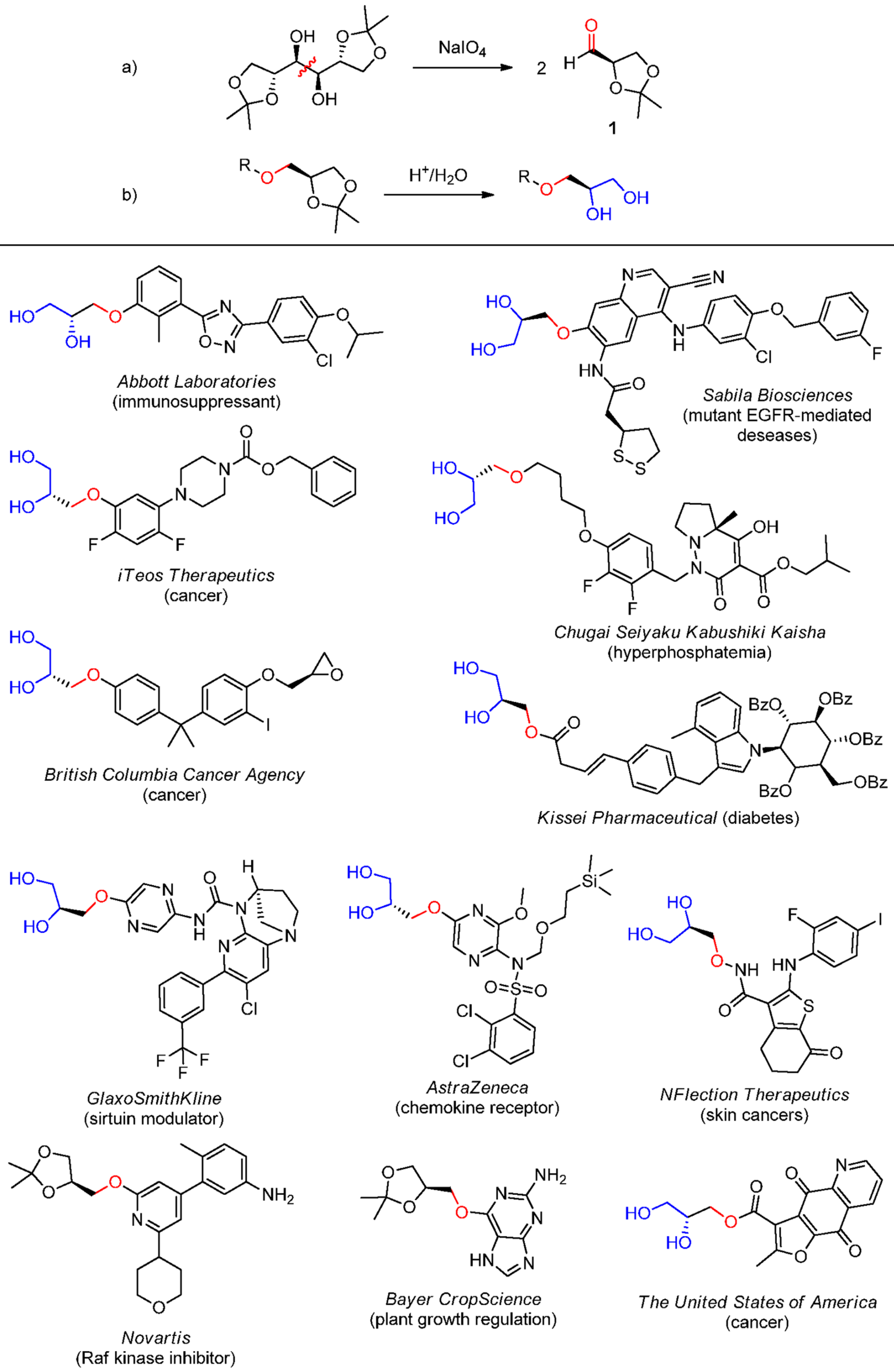
Chart 1. Further APIs with Bidirectional Synthetic Approach Reported



dihydronaphthalene was subjected to Upjohn dihydroxylation and consequently oxidized via the Malaprade reaction. Here, periodate was effectively used to generate two aldehyde moieties in a single step. The Malaprade oxidation was telescoped by a twofold reductive amination with benzyl amine and subsequent hydrogenative deprotection to yield the desired benzazepine core.[200] Despite only obtaining a 14% yield over 4 steps, the dihalogenobenzene is commercially more readily available than the oxoindane (1-bromo-2-fluorobenzene: 128 $/kg). Notably, a tandem ozonolysis was developed to replace the Malaprade oxidation, but this pathway involves the use of platinum and palladium catalysts in high loading and gives significantly lower yields (not depicted).[200] The ozonolysis will be briefly compared with the Lemieux–Johnson oxidation in the next section. The final synthesis of varenicline was accomplished in 39% yield over 5 steps.[201−205]

Another efficient way of installing a double bond for this type of reaction is the Claisen rearrangement, which was used in the synthesis of the antidepressant agomelatine (Scheme 14). Agomelatine was developed by *Servier* under the brand name *Valdoxan*.[206] After tosylation and following dihydrox-

Chart 2. Synthesis of (*R*)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde and the Application of Such To Form a Side Chain[a]



Abbott Laboratories
(immunosuppressant)

Sabila Biosciences
(mutant EGFR-mediated deseases)

iTeos Therapeutics
(cancer)

Chugai Seiyaku Kabushiki Kaisha
(hyperphosphatemia)

British Columbia Cancer Agency
(cancer)

Kissei Pharmaceutical (diabetes)

GlaxoSmithKline
(sirtuin modulator)

AstraZeneca
(chemokine receptor)

NFlection Therapeutics
(skin cancers)

Novartis
(Raf kinase inhibitor)

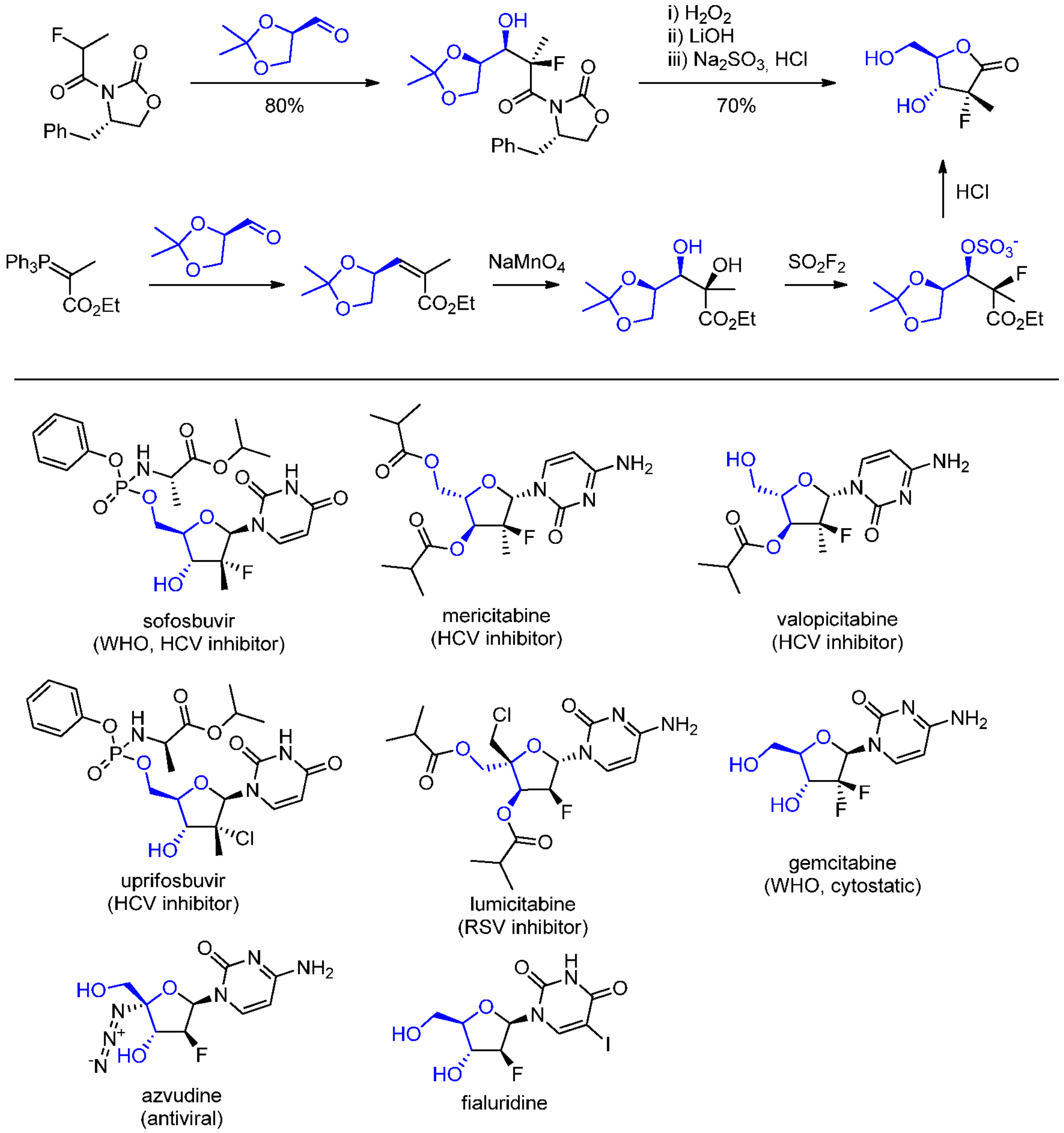
Bayer CropScience
(plant growth regulation)

The United States of America
(cancer)

[a] Structures from left to right and top to bottom: Oxadiazole,[271] dithiolane,[272] 2-oxo-thiazole,[273] dihydropyridazine-3,5-dione,[274] halogenated compound,[275] 1-(-D-glycopyranosyl)-3-substituted nitrogenous heterocyclic compound,[276] urea analogs,[277] sulphonamide,[278] heteroarylaniline,[279] compound as Raf kinase inhibitor,[280] 2-amino-6-oxypurine,[281] and furoquinolinediones.[282]

ylation, the resulting diol was cleaved by periodate. The obtained aldehyde was used without further purification for subsequent transformations.[207] However, handling $NaBH_4$/HCl on a larger scale is hazardous as it forms the gaseous, flammable, and highly poisonous diborane (B_2H_6).[208,209]

A comprehensible example for the diol cleavage is the synthesis of ixabepilone, which was originally developed by *R-Pharm US Operating, LCC* for *Bristol Myers Squibb* and now is sold as *Ixempra* for the treatment of breast cancer.[210] Preparation of the required 1,2-diol moiety proceeded via a Grignard addition of allyl bromide to an Ellman's auxiliary, Scheme 29. Synthetic Routes of Fluorolactones and Related Structures

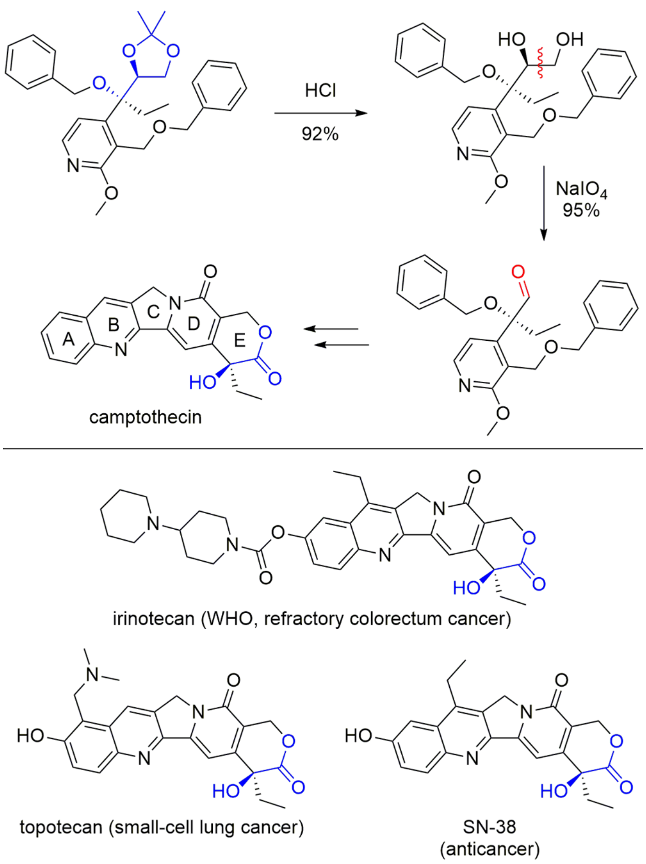


followed by an Upjohn dihydroxylation with OsO_4/NMO (Scheme 15). Subsequently, the diol was cleaved in the Malaprade oxidation. The yields of both oxidations were comparatively low, which might be due to the presence of the thiazole substructure and the internal alkene possibly poisoning the catalyst. The overall yield was only about 1% but seems competitive compared to other total syntheses by step count.[210,211]

A library of aminoxy-modified oligonucleotides was synthesized by *ISIS Pharmaceuticals*, which were reported to modulate mRNA expression. The synthesis of the linker was performed via Upjohn dihydroxylation and Malaprade cleavage, among others (Scheme 16).[212] Alternative routes to prepare the glycol linker followed nucleophilic substitution with ethyl 2-bromoacetate and reduction.

Carbocyclic nucleosides are potent reverse transcriptase inhibitors and are used for the treatment of HIV and HBV or as a cytostatic agent.[213,214] The ribose-mimicking carbocycles in abacavir, carbovir, and 1592U89 were synthesized by means of the Malaprade oxidation in publications by Olivio et al.[215,216] Abacavir is listed on the WHO list of essential medicines and has an excellent clinical profile for the treatment of HIV in combination with dolutegravir (*Triumeq*, *GSK*).[175,217] The starting material for abacavir was an *endo*-hydroxy lactone that is accessible by the hetero Diels–Alder reaction of cyclopentadiene with glyoxalic acid.[218] The enantiomerically pure form was obtained via enzymatic acetylation. The endohydroxy lactone ester was then reduced to the corresponding triol, was cleaved by periodate, and reduced with sodium borohydride in good yield and without the need for intermediate isolation (Scheme 17).[215,216] Competing pathways employ Evan's or Oppolzer's auxiliary and enclose asymmetric Aldol reaction and ring-closing metathesis.[219−221] Even though those routes gave higher yields, the cleavage of auxiliaries and the more intensive use of reagents are less atom efficient.[4] Aristeromycin[222−224] and carbodine[222,225] were synthesized accordingly.

Scheme 30. Key Synthetic Steps for Camptothecin



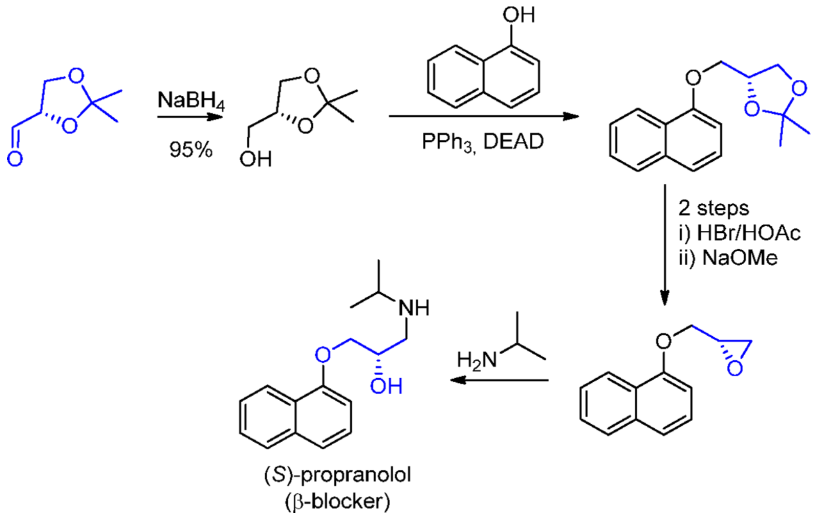
Alternatively, precursors for carbocyclic nucleosides can be obtained by ring contraction. The synthesis follows a stereoretentive aziridine ring opening via Upjohn dihydroxylation−Malaprade cleavage and a subsequent intramolecular aldol closure (Scheme 18).[226]

3.2. Ketol/Diol Cleavage. The fission of α-ketols and α-hydroxy acids is a common transformation with periodate, which is achieved under mild reaction conditions in high yields.[9,30,169] The *Glaxo* research group reported the synthesis of fluticasone propionate or furoate, which are used as anti-inflammatory corticosteroids with approved indications for topical or inhaled treatments (asthma/COPD).[175] The fluticasone is obtained from flumetasone by the fission of the α-hydroxy ketone using periodic acid (Scheme 19).[227] The use of periodic acid instead of sodium periodate may be based on the better solubility in organic solvents.[228] However, as we elucidated in the previous section, the equilibria of periodate in solution let us assume that the reactive species are identical (three-basic orthoperiodate; see section 2.2). Notably, the fission of the α-ketol was preferred over the oxidation of the secondary alcohol, which is known to be less accessible.[229] Likewise, the cleavage of the external α-ketol was preferred over the internal α-ketol. The cleavage of α-hydroxy acids by periodate was demonstrated in the synthesis of (−)-goniomitine (not depicted).[230]

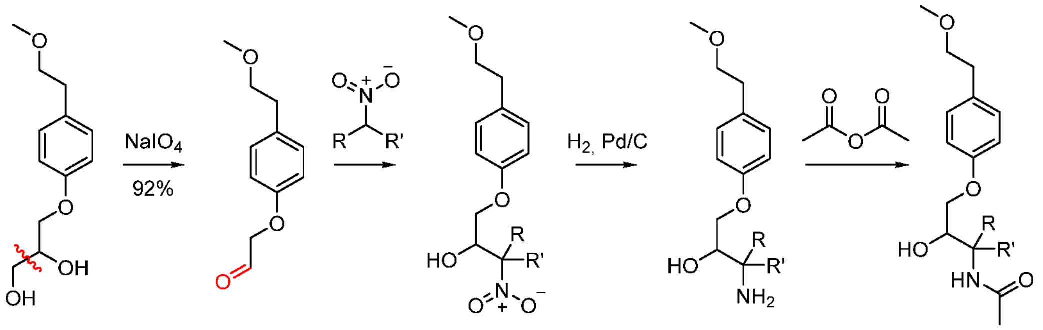
Another example is the combination of the Malaprade with the Prileschajew reaction. *m*-CPBA (*meta*-chloro perbenzoic acid) effects the transformation of the double bond to the epoxide, which is subsequently cleaved by periodate (Scheme 20). This combination was used for the synthesis of the (*E*)-methyl 6-acetoxy-4-methylhex-4-enoate fragment in mycophenolate-mofetil.[231−233] Mycophenolate-mofetil is sold under the brand name *Cellcept* by *Roche* and is used as a highly potent immunosuppressant. It reached a net sale of CHF 700 M. in 2017/2018.[234] Macrolides were synthesized accordingly (not depicted).[235]

The Malaprade oxidation is particularly useful for the processing of simple sugars, which naturally provide 1,2-diol moieties. Carbohydrates are typically obtained from natural resources and are cost-efficient chiral synthons. Costs range up to 53.30 $/kg depending on their natural abundance (D-ribose 10.75$/kg, L-rhamnose 53.30 $/kg, D-galactose 28.50 $/kg, D-glucose 4.60 $/kg, D-sorbitol $9.70/kg, D-fructose $0.97/kg). Sapropterin (*Kuvan*, *Biopten*) is used for treatment of tetrahydrobiopterin deficiency, its natural analog, and had a revenue of $457 M in 2020 by *BioMarin Pharmaceutical*.[236] Sapropterin was synthesized in 9 steps by *Natco Pharma* with D-ribose as starting material. Ketalization, methylation, and the Malaprade oxidation gave rise to the stereogenic part in the final structure (Scheme 21).[237] In the original route by *BioMarin*, sapropterin was synthesized in 10 steps from the more expensive L-rhamnose,[238] among others.[239]

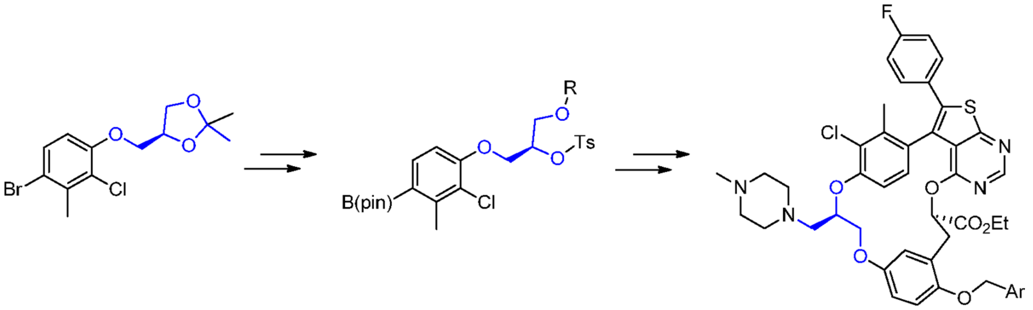
Scheme 31. Synthetic Route of Enantioenriched Propranolol



Scheme 32. Synthetic Route of for Dialkyl-Substituted *β*-Blockers



Scheme 33. Key Synthetic Steps for Macrocyclic MCL-1 Inhibitors[a]



[a]Pin = pinacolato, Ts = tosyl, R = bis(4-methoxyphenyl)phenylmethyl or allyl.

Ezetimibe belongs to the class of acetidinones and is used for the treatment of cardiovascular diseases in the brands *Zetia* and *Atozet*, which together netted a revenue of $881 M. in 2020.[240] Wu et al. developed an efficient method for the synthesis of ezetimibe with the Malaprade oxidation as a key transformation. The 1,2-diol moiety and the *β*-lactam system were constructed in a single step by reacting (*S*)-3-hydroxy-*γ*-lactone with an imine. The stereoconfiguration was induced intrinsically.[241] The (*S*)-3-hydroxy-*γ*-lactone is produced from D-maltose (8.10 $/kg).[242] The Malaprade oxidation gave the aldehyde intermediate in 90% yield without further purification (Scheme 22). Notably, the aldehyde was labile and required quick isolation. Patented routes used chiral auxiliaries for the synthesis, which may seem economically prohibitive.[243,244]

The Malaprade oxidation was also used for the synthesis of stavudine, which is an unsaturated nucleoside derivative. The C−C double bond in the 2,5-dihydrofurane substructure was established via cleavage of the ribose diol followed by twofold Wittig olefination and ring closing metathesis (Scheme 23).[245,246] Noteworthily, a McMurry reaction with $TiCl_3$ might be more efficient here. An alternative synthesis incorporates selenoxide elimination, which is often induced using periodate (for more detail on chalcogenide oxidations, see section 5). However, stavudine was removed from the US market in 2020 due to its potential severe toxicity.[247]

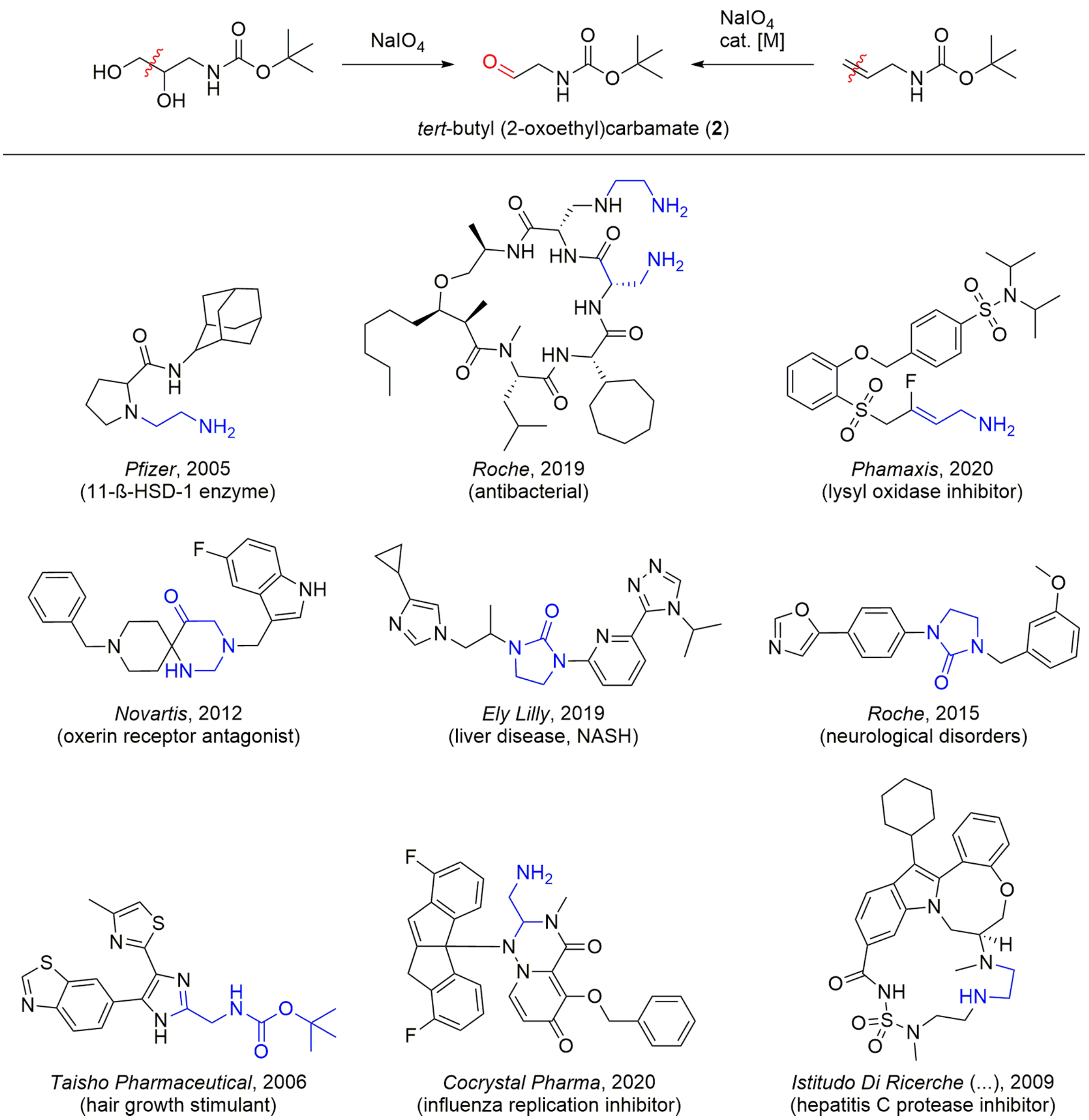
A remarkable strategy for the synthesis of the double bond and fission was reported by Budesinski and Hodacova.[248,249] In a bidirectional approach, a relatively acidic methyl group was transformed by Mannich reaction into an enamine using Bredereck's reagent. The enamine can be cleaved by periodate without the use of metal catalysts, although the use of this reagent decreases the atom economy (Scheme 24).

The latter approach was used for the synthesis of Niraparib (*Zejula*), which was developed in collaborative research by *Merck & Co.* and *GSK*. The medicine is registered by *GSK* as a PARP (poly ADP ribose polymerase) inhibitor for the treatment of ovarian and lung cancer.[175] The acidic methyl group was subjected to Mannich conditions using Bredereck's reagent and was subsequently cleaved by the Malaprade oxidation (Scheme 25). The original synthetic route was developed by *Merck & Co.*, which included a bromination using *N*-bromosuccinimide (NBS) and dibenzoylperoxide (BPO) in CCl_4 and oxidation by *N*-methyl-2-pyrrolidone (NMP).[250] However, CCl_4 is a class I solvent according to ICH Q3C ("to be avoided") and the process was improved by using periodate.[251,252] The current manufacturer of niraparib is *Tesaro Inc.*[253]

The Malaprade oxidation may be combined with other oxidants to circumvent the use of toxic and/or expensive metal catalysts (Os, Ru). The ozonolysis and Malaprade oxidation were used in the synthesis of physostigmine, which is used as an antidote for anticholinergic poisoning. The medicine is marketed by *Dr. Franz Köhler GmbH* as *Anticholium*.[254] The ozonolysis and reduction at an *α*,*β*-unsaturated cyclopentenone yielded a diol that was subsequently cleaved by periodate (Scheme 26).[255]

Finally, periodate is commercially used for the modification of carbohydrates or polyols.[256,257] The modification amylose (1,4-*α*-linked glucose units), for instance, relies upon the fission of the 2,3 diol in the D-glucopyranose (Scheme 27). One formic acid is released per end unit, which allows structural investigations.[258] The degradation of the carbohydrates continues further to alkoxymalonaldehydes, and finally to monocarbonoxides species if an excess of periodate is used.[30,258] Selectivity is achieved by geometrical constraints and different oxidation kinetics. However, the field is saturated in literature and has been reviewed extensively.[168,259] Worth mentioning are the recent synthesis of cellulose or chitin

Chart 3. Synthesis of *tert*-Butyl (2-Oxoethyl) Carbamate and Its Application[a]



Pfizer, 2005
(11-ß-HSD-1 enzyme)

Roche, 2019
(antibacterial)

Phamaxis, 2020
(lysyl oxidase inhibitor)

Novartis, 2012
(oxerin receptor antagonist)

Ely Lilly, 2019
(liver disease, NASH)

Roche, 2015
(neurological disorders)

Taisho Pharmaceutical, 2006
(hair growth stimulant)

Cocrystal Pharma, 2020
(influenza replication inhibitor)

Istitudo Di Ricerche (...), 2009
(hepatitis C protease inhibitor)

[a] Structures from left to right and top to bottom: proline,[322] cyclic peptide antibiotics,[323] haloallylamine sulfone,[318] triazaspiroalkanes,[324] imidazolidine,[325] *N*-phenyl lactame,[326] thiazolylimidazole,[327] pyridopyrazine,[328] macrocyclic indole.[329]

nanocrystals,[99,100] the multiple functionalization of cellulose microfibrils,[260,261] and cellulose-based wastewater treatment.[262,263] Commercial applications are in anticancer drug carriers[264] and in water-stable implantable tissues.[265,266] Notably, an electrochemical, periodate-based process for the synthesis of dialdehyde cellulose (DAC) was reported (using lead dioxide anodes).[102]

Bidirectional approaches adduce for the most atom efficient examples among the syntheses. Rivaroxaban, sold under the brand name *Xarelto*, is a factor Xa inhibitor used as an anticoagulation treatment and is the best-seller of the *Bayer AG* and *Johnson* & *Johnson* with a total revenue of $6.8 B in 2020.[267] A very efficient alternative synthesis route was patented by *Changzhou Yabang Pharmaceutical*, who developed a late-stage symmetrical fission of a diol.[268] The dimer was constructed from D-mannitol (D-mannitol: 2.97 $/kg; Scheme 28). The exclusive distribution rights expire in 2022 (depending on the country), which renders the alternative route advantageous. A similar bidirectional strategy was used for the (academic) synthesis of several pyrrolidinoindoline derivatives [(−)-phenserine, (−)-physostigmine, (−)-flustramine B], which show activity against glaucoma and Alzheimer's disease (Chart 1)[269] and for the synthesis of bosentan monohydrate.[270]

In addition to its importance in total syntheses of pharmaceuticals, many other important building blocks and chiral auxiliaries can be generated by the Malaprade oxidation. Their synthesis and application for fine chemicals will be introduced in the following part. Well-known is (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (**1**), which is used for a myriad of syntheses. Due to the uneconomic removal of auxiliaries, it is rather used as a building block in pharmaceutical syntheses.[268,270] It can be obtained from D-(+)-mannose after twofold ketal formation and the Malaprade

Scheme 34. *tert*-Butyl (2-Oxoethyl)carbamate as a Key Fragment in Several Pharmaceuticals

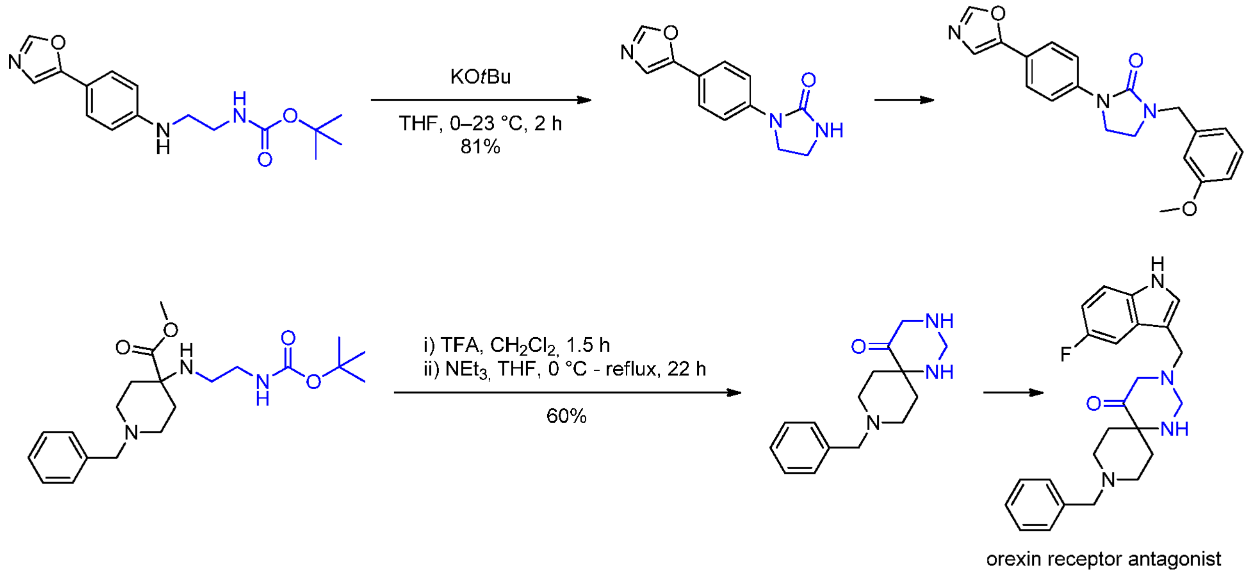
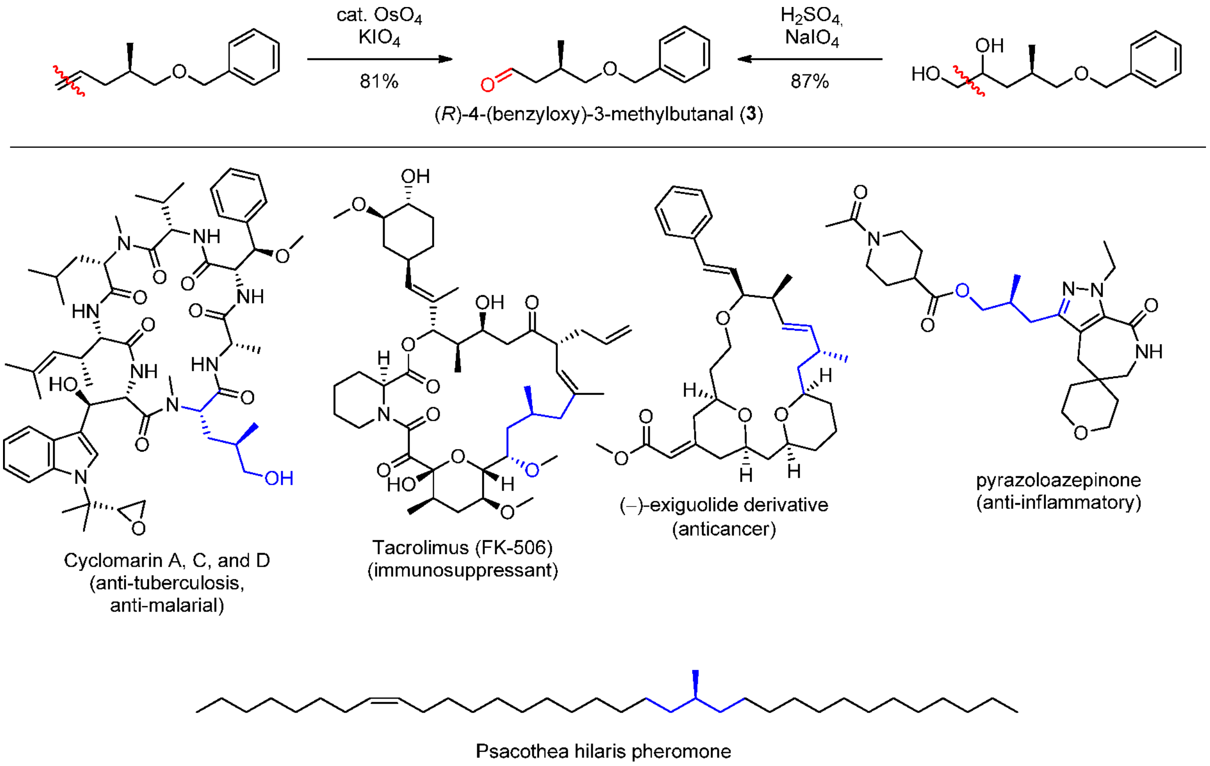


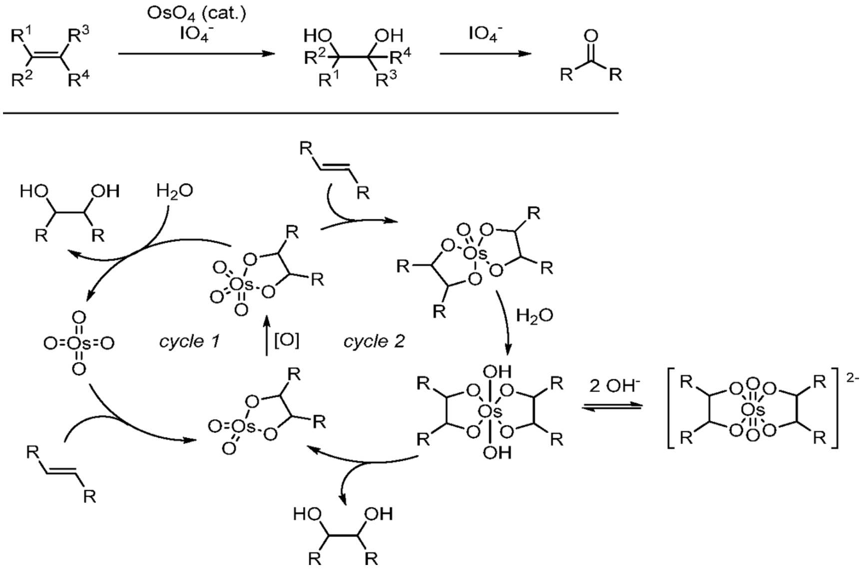
Chart 4. (*R*)-4-(Benzyloxy)-3-methylbutanal as a Key Fragment



oxidation (D-(+)-mannose: 27.70 \$/kg). Notably, 2 equiv of the product are formed in this process, therefore counting as both a bidirectional approach and highly atom efficient. **1** often forms a side chain in the final structure as is exemplified in Chart 2, but it is also used to form core structures in several transformations.

Building block **1** is also used for the synthesis of fluorolactones, which itself is a key building block for nucleoside mimetics. These have antiviral and/or cytotoxic activities/properties and are most important in the treatment of hepatitis C virus infection or cancer:[283,284] Gemcitabine and the groundbreaking Sofosbuvir (*Sovaldi*, *Vosevi*, among others), as representatives of such, are listed in the WHO list of essential medicines.[285,286] Synthetic routes were innovated by *Hoffman La Roche* and Pharmasset (now *Gilead*).[287,288] In the most advanced synthetic route, the molecule was built up in using a stereoselective aldol reaction. The stereoselectivity was induced by a chiral oxazolidinone auxiliary (Scheme 29).[289] An alternative and technically more viable route proceeded *via* Wittig reaction. The formed double bond was stereoselectively dihydroxylated using sodium permanganate. The diol was then sulfurylated and ring-opened by nucleophilic attack of the fluoride in the one-pot protocol.[290−293] Strategies *via* epoxidation have been reported as well.[294]

Scheme 35. Proposed Mechanism for the Lemieux–Johnson Oxidation



Camptothecin alkaloids, such as irinotecan originally developed by *Yakult Honsha Ltd.* (*Camptosar*, *Pfizer*)[206] or topotecan (among others *Hycamtin*, *Novartis*), are potent anticancer agents.[295] They bind topoisomerase I and the DNA complex, effectively preventing religation and in consequence causing DNA damage and apoptosis. Lu, Luo, and co-workers developed a method for the synthesis of the ring E using **1** as a key fragment (Scheme 30).[296] Here, the Malaprade oxidation was applied even twice, once for the synthesis of **1** that is installed into the camptothecin precursor and again for the Malaprade oxidation of the deprotected 1,2-diol. Overall, a 14% yield was isolated in high purity without the use of chromatography. An alternative pathway proceeded through Sharpless asymmetric dihydroxylation and oxidation of a 3,4-dihydro-2*H*-pyran in ring **E** along with photoredox or other catalytic approaches.[297−301] Further applications of periodate in the synthesis of camptothecin derivatives are in the formation of boronic acids (not depicted).[302,303]

β-Blockers antagonize *β*-adrenoceptors and are particularly useful in cardiovascular therapies.[304] As a racemate, they are most efficiently synthesized by nucleophilic ring opening of an epoxide as a central key step.[305−307] However, for enantioselective routes building block **1** was first reduced to (*S*)-2,2-dimethyl-4-hydroymethyl-1,3-dioxolane using sodium borohydride.[308] Alternative syntheses of **1** from glycerol and subsequent resolution seem laborious and are therefore less investigated.[309,310] The alcohol was then coupled to 1-naphthol under Mitsunobu conditions, and the 1,3-dioxolane was transformed to the oxirane in a sequence of acidic/basic treatments (Scheme 31). The oxirane was ring-opened by nucleophilic attack of isopropylamine, which is a perfectly atom-efficient substitution method. An alternative route employing the Malaprade oxidation was reported by Shibasaki et al. for the synthesis of racemic pindolol.[311,312] Later, *Beiersdorf* used this method for the synthesis of dialkyl-substituted *β*-blockers (Scheme 32).[313]

Building block **1** was also used in *Abbvie*'s synthesis of macrocyclic MCL-1 inhibitors, which may be used for the treatment of cancer.[314] Notably, 860 substances and 5727 reactions were reported in the patent according to Reaxys, with the actual synthesis being well encrypted. The building block played a key role in the ring closure of the macrocycle, which was achieved by nucleophilic substitution of the tosyl group by a nearby phenolate (Scheme 33).

Another attractive synthon is *tert*-butyl (2-oxoethyl) carbamate (**2**), which is synthesized via either Malaprade or Lemieux–Johnson oxidation (Chart 3).[315−318] It is part of the structure of many recent API candidates, as it provides a versatile reactivity for follow-up modifications.[319−321] Recent examples are also summarized in Chart 3. Modifications enclose the formation of an alkyl urea moiety or spirocyclic substructures, which again allow for further functionalization (Scheme 34).

(*R*)-4-(Benzyloxy)-3-methylbutanal (**3**) is another interesting fragment, which is synthesized via Malaprade[330] or Lemieux–Johnson oxidation (Chart 4).[331] It is a component of various cyclomarins[332,333] and gives access to tacrolimus,[334] (−)-exiguolide derivatives,[335] substituted pyrazoloazepin-8-ones,[336] and the sacothea hilaris pheromones.[337] Cyclomarins have antituberculosis and antimalarial effects and are important in the background of resistances. Alternative syntheses were developed by Kazmaier and co-workers,[338,339] and others.[340,341] Tacrolimus is a strong immunosuppressant (even stronger than ciclosporin)[342] and already has commercial importance together with related substances. The given route was developed by *Merck & Co. (MSD)*. Exiguolide derivates provide anticancer activity and are simpler analogs of pharmacologically active bryostatins.[343] Pyrazoloazepinone derivatives are agents with an anti-inflammatory effect and are important in the treatment of inflammatory diseases, such as asthma or chronical obstructive pulmonary disease (OPCD). Other pyrazoloazepinones were developed by *AstraZeneca* and others.[344−347]

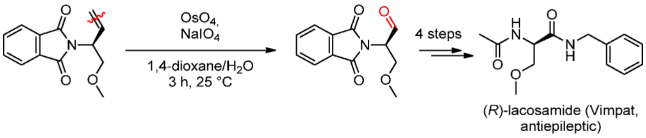
In conclusion, the Malaprade oxidation has many commercial applications for either the direct synthesis of APIs or as building block. It was often implemented in the synthetic route by introduction of a C−C double bond and successive dihydroxylation by osmium tetroxide. The double bond has been installed by various high-yielding and orthogonal standard methods, such as Diels−Alder cyclization, Aldol condensation, nucleophilic substitution, or cross-coupling reaction. A broad spectrum of methods is available.

A future application of periodate could be the synthesis of building blocks for pharmacologically active *N*-heterocyclic diols.[348]

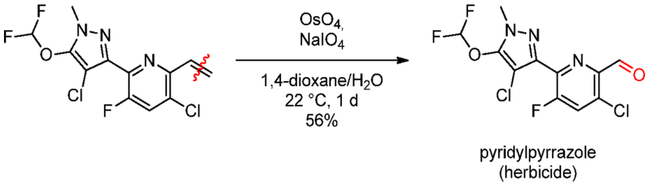
4. TRANSITION-METAL-CATALYZED OXIDATIONS WITH PERIODATE

Periodate represents a valuable oxidant in combination with transition metal catalysts, such as osmium, manganese, or ruthenium. It is often employed as a terminal oxidant in the Lemieux–Johnson, the Lemieux–von Rudloff, and ruthenium tetroxide catalyzed C═C fissions, which will be the subject of the following section.

Scheme 36. Key Synthetic Steps for Lacosamide



Scheme 37. Key Synthetic Step for Pyridylpyrrazole



4.1. Lemieux–Johnson Oxidation. The Lemieux–Johnson oxidation represents the second major type of oxidations that involve periodate in conjunction with osmium tetroxide. It is part of a common strategy to form valuable carbonyl functions by the cleavage of vinylic, allylic, or even aromatic double bonds.[349] Advantages of the Lemieux–Johnson oxidation are the "one-pot-two-step" protocol of the dihydroxylation and the diol cleavage and the extraordinarily high selectivity toward alkenes and diols. Formally, it is a sequence of the osmium tetroxide catalyzed dihydroxylation and the Malaprade oxidation, wherein the metal catalyst is regenerated by periodate (Scheme 35). It works in aqueous solvent mixtures, at ambient conditions for a broad scope of substrates.[152,350−352] The mechanism of dihydroxylation was proposed to follow the formation of the cyclic osmate diester by a concerted [3 + 2] cycloaddition,[170] oxidation of the osmate, and elimination of the diol in a primary cycle. In a secondary cycle, the osmate diester adds another alkene forming a bicycle and liberates the diol upon hydration.[353,354] A low pH was suggested as otherwise a stable dioxo-osmate complex is formed, which constitutes a resting state.[355−358] Sterically less hindered alkenes and alkenes with higher electron densities are favored.[349,359] For tetrasubstituted olefins, low hydrolysis rates were assumed leading again to inhibition of the catalysis.[360,361] In contrast, the addition of tertiary amines, such as pyridine, 1,4-diazabicyclo[2.2.2]octane (DABCO), or 2,6-lutidine, enhanced the reaction rate and improved the yields in osmium-catalyzed oxidations due to ligating effects.[360,362−364] The use of the sequential Upjohn dihydroxylation and Malaprade cleavage was often preferred over the combined Lemieux–Johnson process, albeit having a higher step count. We assume lower costs for the primary oxidant [*N*-methylmorpholine *N*-oxide 50 wt % in H_2O, \$3.64/kg (on volume of 2 to 20 t)], better availability of research data, and slightly better yields.[365] A further disadvantage might be the oxidation of alcohols as side reactions. However, some studies show a noninnocent behavior of the oxidant.[349] In some cases, the use of periodate was explicitly required,[366] whereas in others it was not necessary.[367] Even so, the process intensification is favorable from an economic and sustainable perspective.[368]

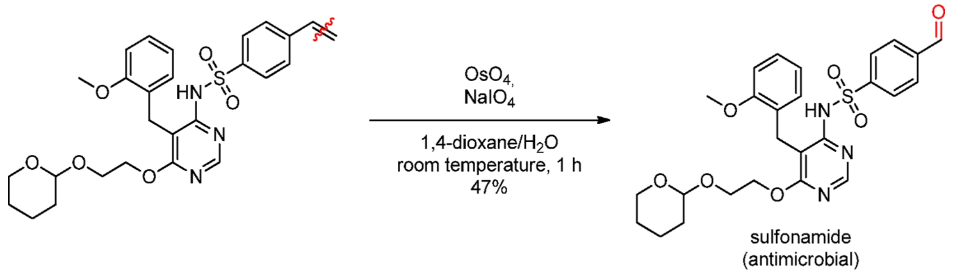
Despite the high price and toxicity, osmium tetroxide is still utilized for the double-bond cleavage, as reliable alternatives are sparse. Ozonolysis has a high-energy demand for generation, cooling, and drying of the air, and the equipment is expensive. The method gives significantly lower yields and poses serious safety hazards.[369,370] In contrast, the costs and safety for the use of osmium was largely improved by microencapsulation of the metal.[371] The metal is immobilized on a polyurea matrix, which is marketed as *EnCat* technology by *Reaxa*. It reduces metal contaminations of the product and improves the recyclability of the catalyst.

(*R*)-Lacosamide is sold under the brand name *Vimpat* and is used for the treatment of pain and epilepsy. The drug is distributed by *UCB Pharma* and is expected to reach a peak sale of € 1.5 B by 2022.[372] Innovated by Kohn in 1996,[373] the synthesis was improved extensively between 2011 and 2014. Problems were the use of the unnatural and expensive D-serine,[374−378] resolutions with 50% loss of substance,[379] high step counts,[380,381] and low atom economy.[382−384] In recent methods, the Lemieux–Johnson oxidation was used for the synthesis of the D-serine substructure in (*R*)-lacosamide (Scheme 36).[385] Problems were claimed to be solved by a short asymmetric synthesis with 2-vinyloxirane as starting material.[386] The oxidation by $RuCl_3/NaIO_4$ was used alternatively.

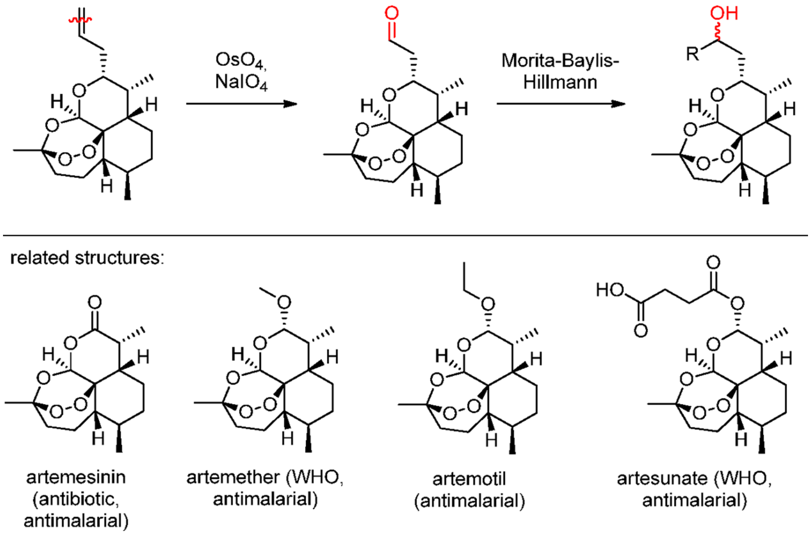
Syngenta used the Lemieux–Johnson oxidation for the synthesis of pyridylpyrrazole herbicides. The double bond was installed by Stille coupling (Scheme 37).[387]

Sulfonamides constitute an important class of pharmaceutically active compounds, which often provide antimicrobial

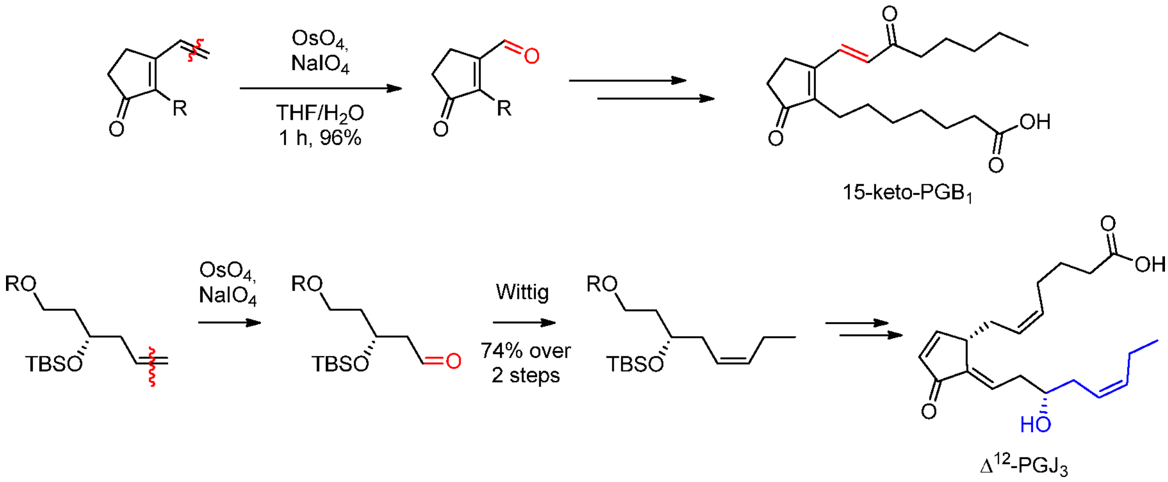
Scheme 38. Key Synthetic Step for Sulfonamide



Scheme 39. Key Synthetic Steps for Artemisinin and Derivatives



Scheme 40. Key Synthetic Steps for Prostaglandin Derivatives



activity. The first developed, but still important, antibiotics are prontosil, sulfanilamide, and sulfamethoxazole. *Hoffmann-La Roche* developed a library of sulfonamide substances, wherein the *p*-vinylbenzenesulfonamide moiety was modified by the Lemieux–Johnson oxidation (Scheme 38). The compounds were suggested for the treatment of circulatory disorders, in particular hypertension, ischemia, vasospasms, and angina pectoris.[388]

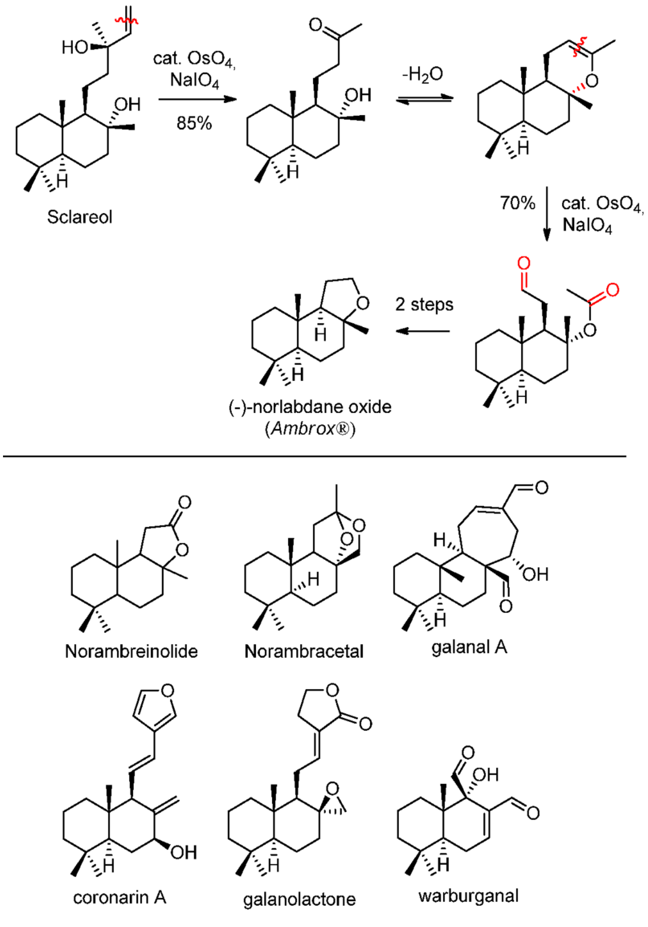
The Lemieux–Johnson oxidation was used for the synthesis of a series of new artemisinin derivatives, which showed high activity against cancer according to the authors.[389] It was used for the modification of the side chain of 10-deoxoallylartemesinin followed by Morita–Baylis–Hillmann reaction (Scheme 39). Artemisinin and derivatives (artemether, artemotil, artesunate) are used generally for the treatment of malaria, and some are listed in the WHO model list of essential medicines. Artemisinin is obtained semisynthetically, whereby the scaffold is obtained biologically from the plant *Artemisia annua*. The modification of artemisin and its derivatives via the Lemieux–Johnson oxidation could help to fight spreading resistances, poor oral uptake, and short plasmatic lifetimes.[389]

Prostaglandins are an important class of bioactive molecules that provide a broad spectrum of activity. The Lemieux–Johnson oxidation was used in the synthesis of prostaglandins Δ^{12}-PGJ$_3$[390] and 15-keto-PGB$_1$ (Scheme 40).[391]

(−)-Norlabdane oxide (*Ambrox*) is one of the most important perfume components beside muscone and civetone. The price reaches about 1000 \$/kg and the yearly production accounts to ∼30 t worldwide. The main producers are *Firmenich*, *BASF*, and *Henkel*. Before 1950 however, (−)-norlabdane was obtained from ambrein, the chief constituent of ambergris, a rare metabolic product of sperm whales that floats chunkily in the water after secretion.[392] Fishermen recently found ambergris in worth of \$1.5 M (127 kg · 12,000 \$) in a dead sperm whale.[393] In a semisynthetic approach, (−)-norlabdane is obtained from naturally more abundant sclareol by twofold double-bond cleavage (Scheme 41).[394,395] Further labdane derivatives synthesized accordingly are norambreinolide (from (+)-*cis*-abienol),[396] norambracetal,[397] galanal A, warburganal, galanolactone, and coronarin A.[398,399]

Arylacetyl amino thiazoles were identified as potent inhibitors for cyclin dependent kinases and thought to be useful in the therapy of proliferative diseases.[400] The Lemieux–Johnson oxidation was used for the synthesis of 2-(4-formylphenyl)acetic acid from 4-(2-(ethoxycarbonyl)vinyl)-

Scheme 41. Key Synthetic Steps for Norlabdane Oxide



phenylacetic acid (Scheme 42).[401,402] But apparently, the target and congeners SN-032 (formerly BMS-387032) did not pass phase 2 studies.[403]

Benzimidazoles provide pharmacological activity and are represented in many APIs, such as dabigatran, telmisartan, thiazolones, pyridyl pyrazoles, and imidazolidinones. Their widespread use as pharmacologically active substances originates in the broad applicability of such derivatives as antimicrobial, anticancer, antiprotozoal, anti-inflammatory, antitubercular, anti-HIV, antiviral, among others.[404] According to a survey done by Taylor et al. in 2014, the benzimidazole scaffold appears among the top 30 of most frequently used ring systems in small molecule drugs as described in the FDA orange book.[405] Synthetic routes were developed by *Smith-Kline Beecham Corporation* between 2004 and 2007 (now *GSK*) and two pathways were elaborated (Scheme 43a, c).[406−409] The Lemieux–Johnson oxidation was applied in pathway (c) after the double bond had been installed by Stille coupling. Compared to pathway (a), it needs more synthetic steps and uses toxic metal reagents, but the starting material is more readily available, and the harmful reagents could be replaced by less harmful ones. However, we suggest pathway (b), wherein 3,4-dinitrobenzoic acid is obtained from inexpensive toluene in high yield. Alternatively, acylated toluidines could be envisioned as precursors for the benzimidazole scaffold.[410] Subsequent reduction and imidazole formation should then yield the desired structure.[411−413] Similar approaches are employed during the syntheses of telmisartan and dabigatran.[414−417]

Strychnos indole alkaloids provide valuable biological activity and are structurally related to morphine. An efficient and facile synthesis route was published recently, in which the core structure was modified by Lemieux–Johnson oxidation (Scheme 44). The synthesis of stychnopivotine, malagashanol, stychnosplendine, and isosplendine was reported by Maertens et al.[418]

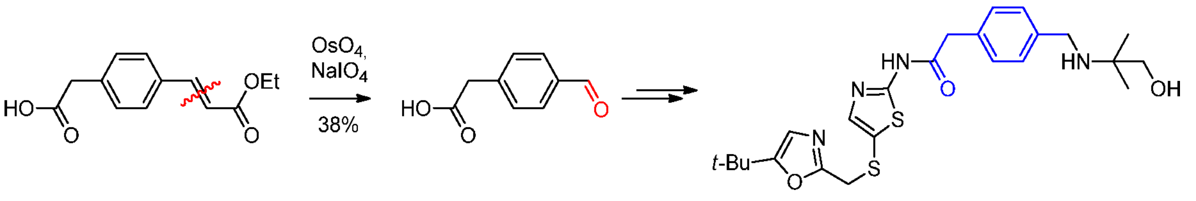
The total synthesis of (−)-exiguolide was developed by Ishihara et al. using the Lemieux–Johnson oxidation (Scheme 45).[419] The delivered aldehyde formed a pyran substructure, which is a common motif in many macrolides, such as bryostatin 1, rhizoxin D, peloruside A, and leucascandrolide A (Chart 5). Another part of the exiguolide cycle was synthesized using the Malaprade oxidation as described earlier (see Chart 4 in previous section).

Platanic acid has cytotoxic activity, among others, and is synthesized by C–C double bond cleavage from natural occurring betulinic acid. The best yields are obtained with the Lemieux–Johnson oxidation (81%),[420,421] while alternative ozonolysis gave significantly lower yields and required unfavorable reaction conditions (−78 °C, dichloromethane, chloroform, up to 44% yield) (Scheme 46).[422−425] The RuO_4/$NaIO_4$ cleavage gave up to a 60% yield at ambient temperature in environmental benign solvents (H_2O/ethyl acetate).[426,427]

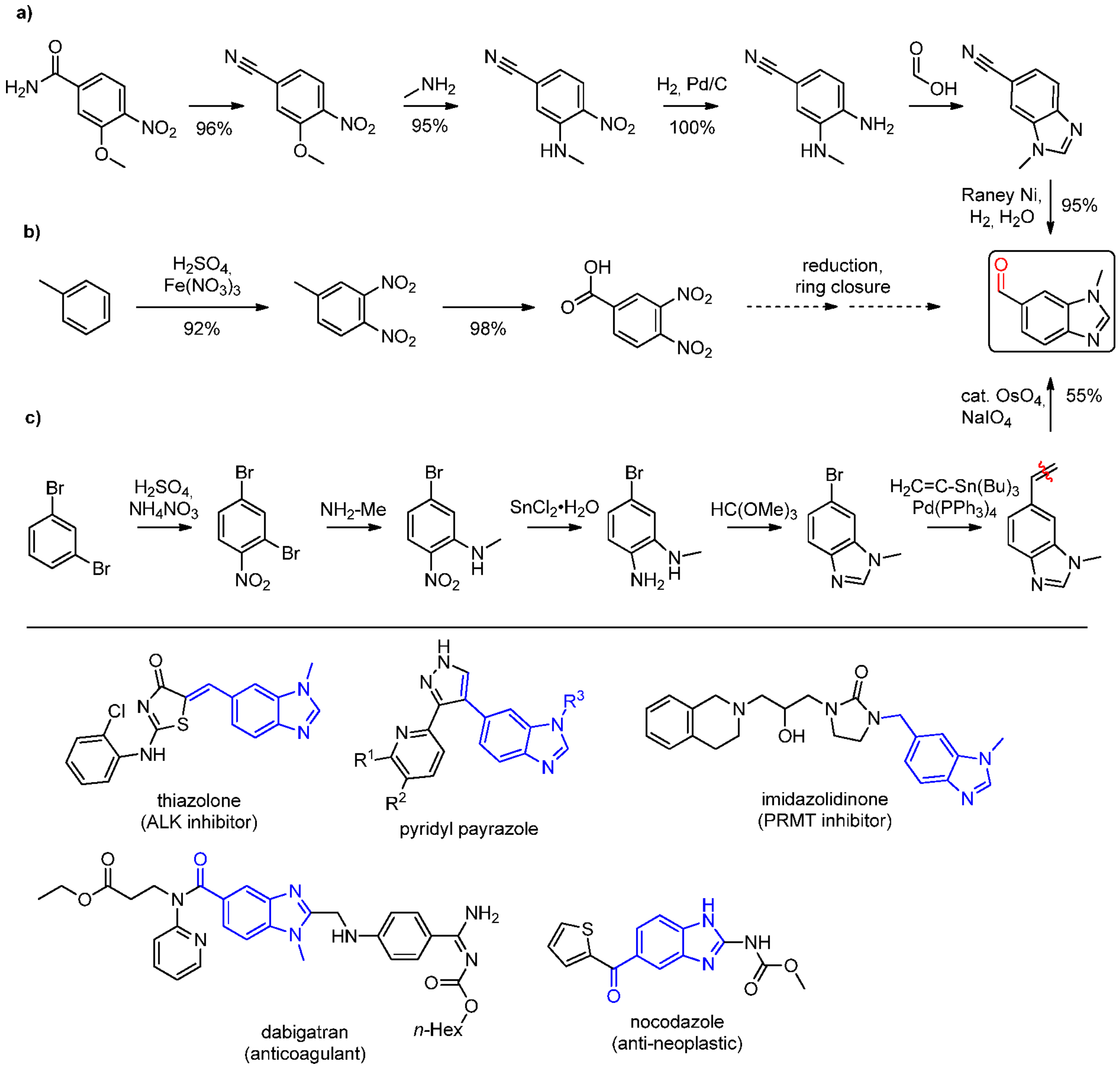
In conclusion, the Lemieux–Johnson oxidation is a valuable tool for the synthesis of APIs and natural products. Advantages are the high selectivity for alkenes over other functional groups and the efficient one-pot procedure. Problems derive from the high toxicity and volatility of OsO_4, but efficient immobilization techniques reduce the risks and metal contaminations of the product stream. An osmium-free alternative is the Prévost–Woodward reaction, which was shown to work with substoichiometric amounts of periodate by Sudalai and coworkers.[428] A future application of the Lemieux–Johnson oxidation could be in the renewable energy sector for the catalytic oxidation of methane to methanol.[429,430]

4.2. Ruthenium-Catalyzed Oxidations. Periodate is often used as a terminal oxidant in ruthenium-catalyzed oxidations, in which ruthenium tetroxide is formed from $RuCl_3$ or RuO_2 precursors. It represents a strong and versatile oxidant in organic chemistry and readily oxidizes hydrocarbons, alcohols, aldehydes, sulfides, and sulfoxides.[431,432] Ethers or amines are oxidized to esters or amides, respectively,[433] aryls

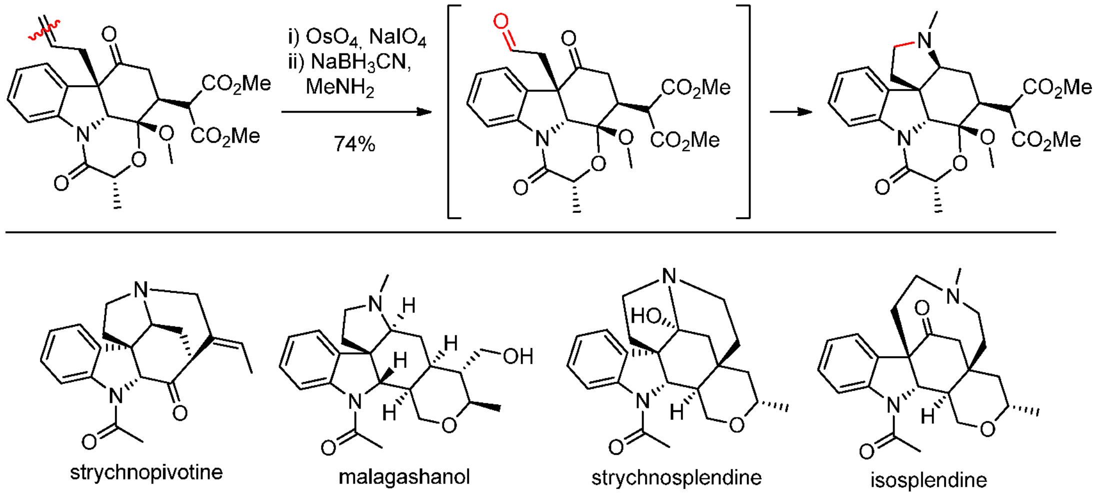
Scheme 42. Key Synthetic Step for Arylacetyl Amino Thiazoles



Scheme 43. Synthetic Routes (a)−(c) for Benzimidazole Derivatives and Examples



Scheme 44. Key Synthetic Steps for Indole Alkaloids



Scheme 45. Key Synthetic Steps for Exiguolide

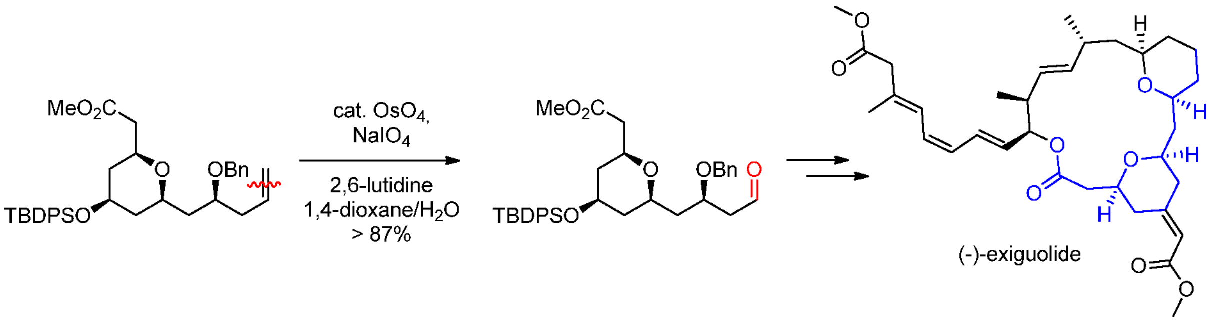
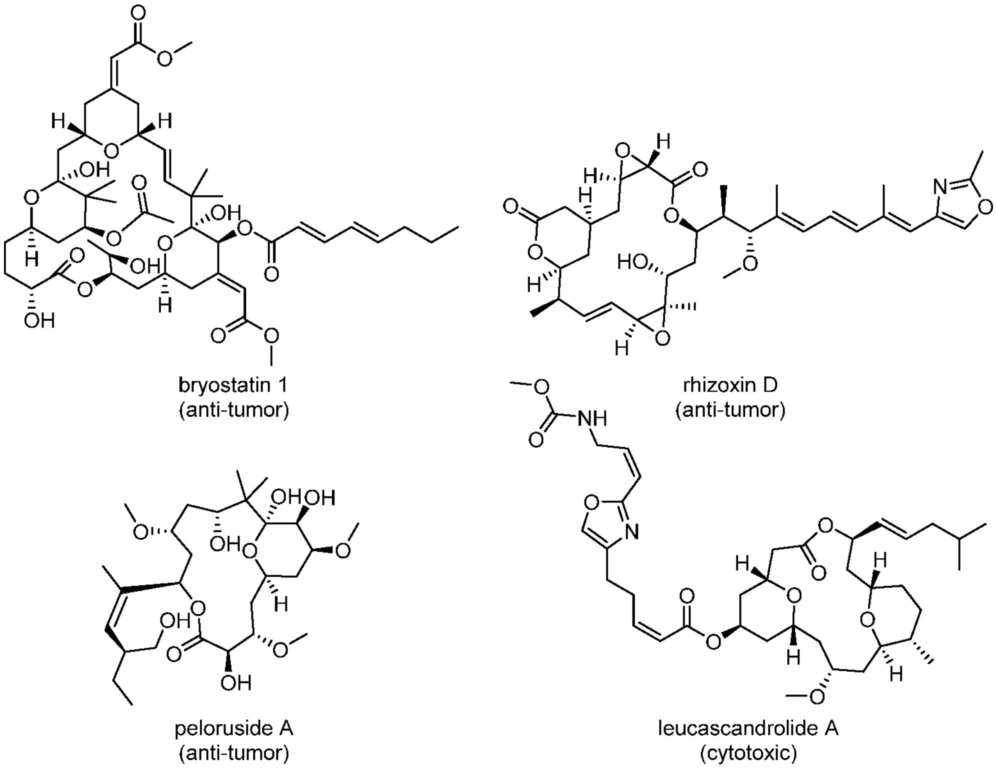
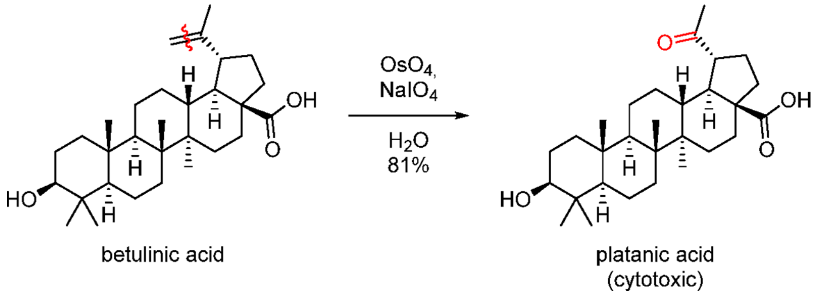


Chart 5. Macrolides Comprising Pyran Substructures



Scheme 46. Key Synthetic Step for Platanic Acid



are degraded into carboxylic acids,[434−436] alkenes are cleaved to carboxylic acids,[437] and alkynes are oxidized to diketones (Figure 3).[438,439] The reactions are highly dependent on pH value and solvent system. Favorable conditions were found for acidic, aqueous mixtures with acetonitrile and tetrachloromethane as cosolvents.[440] Combinations of acetone/MeCN/CCl_4, ethyl acetate/MeCN/CCl_4, or dimethyl carbonate/H_2O are also advantageous.[441] Methane sulfonamide may be a suitable replacement for MeCN,[442] whereas ethers, benzene, and pyridine are unsuitable solvents due to vigorous decomposition.[443]

Ruthenium tetroxide may be applied as a substitute for OsO_4, i.e., in the cleavage of alkenes to carbonyls. Perruthenates are less toxic and less volatile and provide higher reactivity than the corresponding osmium oxides but are more expensive (RuO_2: 16800 \$/kg; OsO_4: 11873 \$/kg).

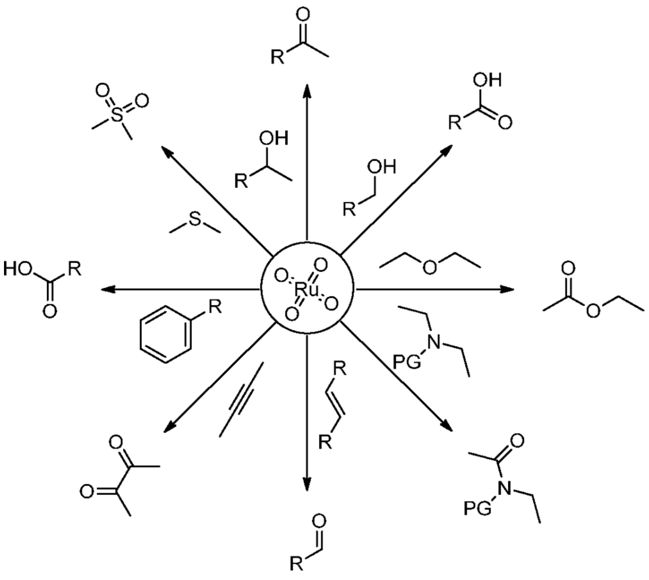
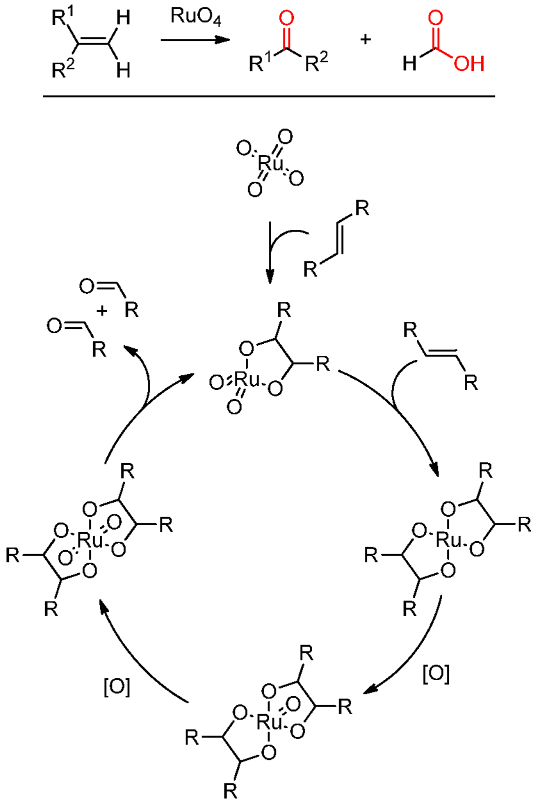


Figure 3. Scope of reactivity of ruthenium tetroxide (selection). PG = protecting group.

Scheme 47. Presumed Mechanism for the Ruthenium-Catalyzed Oxidative Alkene Fission



Quantum chemical investigations of the mechanism suggest that the olefinic fission proceeds through the Ru(VIII)-dioxo-bis(2,5-dioxolane), which is formed after twofold concerted [3 + 2] cycloaddition and twofold oxidation by the primary oxidant (Scheme 47). The Ru(VIII) bisglycolate can readily cleave the C−C bond due to a lower stability compared to Os(VIII) species.[444] Recent computational studies indicate a noninnocent role of periodate in the oxidative cyclization of 1,5-dienes,[445] which too could affect other reactions.[446] The emerging aldehydes are usually oxidized to carboxylic acids, but recent developments enable the halt of the oxidation at this[351] or the diol stage.[447−452] The cleavage of alkynes to aldehydes,[437,453] and the oxidative cyclization of dienes are further important innovations,[454,455] as well as the immobilization of the ruthenium on composite materials,[352] or on silica.[456,457] The application of ruthenium catalysts in natural product synthesis has been reviewed thoroughly.[458−460]

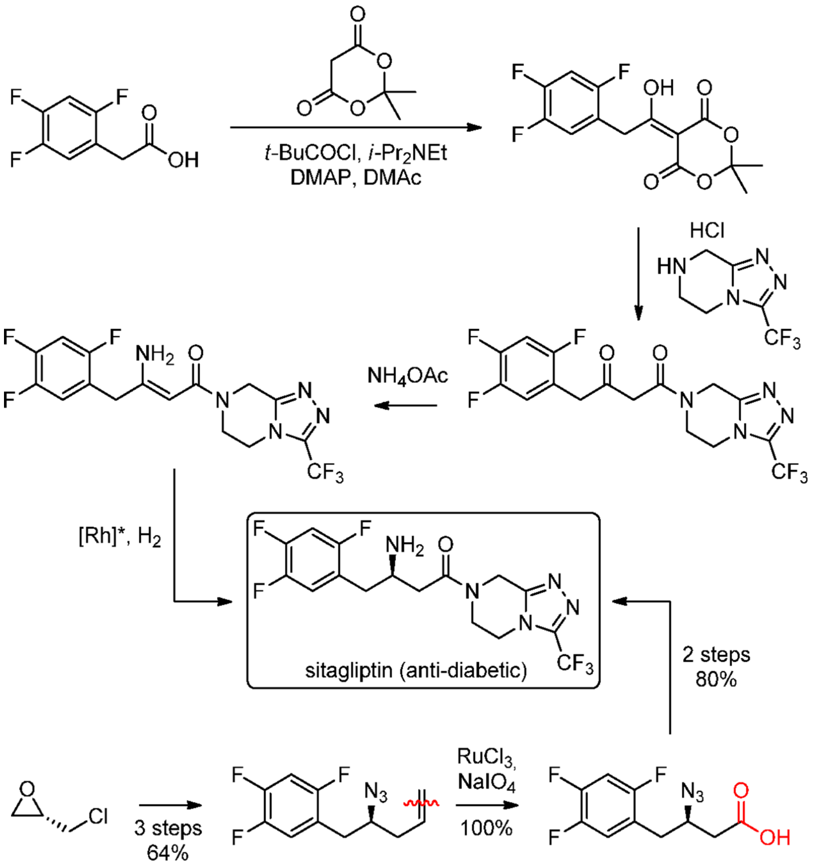
Sitagliptin was innovated by *MSD* and is used as medication for diabetes mellitus type 2. Sold as the single component, *Januvia*, it had a revenue of \$3.3 B, while the combination product with metformin *Janumet* had a revenue of \$2.0 B in 2020.[240] An improved synthesis of sitagliptin was awarded with the 2006 Greener Synthetic Pathways Award by the US Environmental Protection Agency.[461] The critical step in the synthetic route is the formation of the enantiomer, which has been established by rhodium-catalyzed enantioselective hydration of the unprotected enamine (Scheme 48). Notably, the hydrogenation was performed in the final step to maximize the yield with respect to the expensive catalyst.[462,463] In an alternative synthesis, the title compound was obtained from commercially available (*S*)-epichlorohydrin and by several telescoped Grignard reactions. The double bond was cleaved by ruthenium catalysis, and the furnished carboxylic acid was used for the formation of the respective amide.[464] Remarkably, the adjacent azide moiety remained untouched by the oxidation.

Contemporary industrial processes for carboxylic acid congeners start with castor oil. An alternative, future pathway based on natural feedstock might be from oleic or aleuritic acid, which are components of vegetable oils and shellac (35%).[465−467] Those can be used for the synthesis of value-added products azelaic acid, pelargonic acid, and methyl 9-hydroxynonanoate. Azelaic acid is used for the treatment of acne,[468] and pelargonic acid, as herbicide.[469] Methyl 9-hydroxynonanoate is part of mupirocin and used as an antibiotic drug.[470] The cleavage is established by RuO_4/periodate oxidation where dihydroxylation forms aleuritic acid as an intermediate (Scheme 49).[465,471] Competing routes occur via ozonolysis and oxidation with $KMnO_4$.[472]

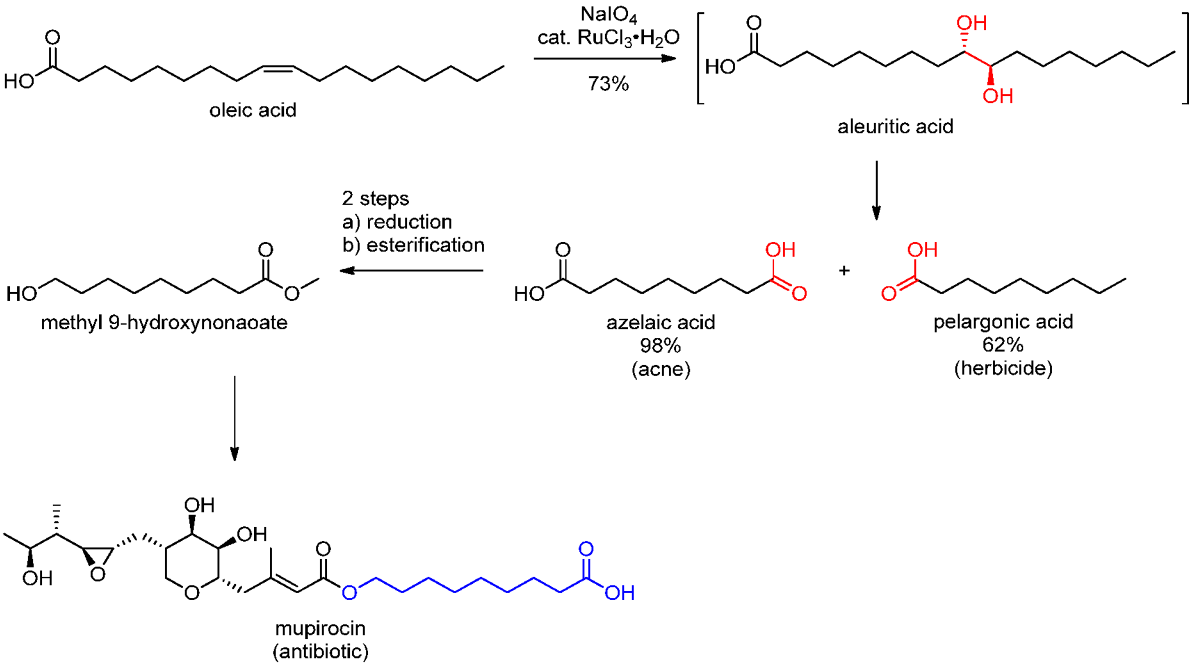
Alprazolam is sold under the brand name *Tafil*, or *Xanax*, among others, and is used as a tranquilizer in the short term management of anxiety disorders.[473] The synthesis was developed by *The Upjohn Company* (now *Pfizer*), where ruthenium catalysis was used to cleave a conjugated C−C double bond followed by ring expansion (Scheme 50).[474] Further developments featured ruthenium-free synthesis.[475] Commercially relevant congeners that might be synthesized accordingly are lormetazepam (*Dr. F. Köhler GmbH, Sedalam*), triazolam (*Halcion*), lorazepam (*Ativan*), midazolam (*Versed*), oxazepam (*Adumbran*), diazepam (*Valium*), among others.

Besides olefin cleavage, the Ru/IO_4^- system is used for the formation of diones from vicinal dihaloalkenes.[476] Gribble and co-workers synthesized isatins (indole-2,3-diones) from indoles using catalytic $RuCl_3{\cdot}3H_2O$ in combination with $NaIO_4$ (Scheme 51). After iodination of the indole, the oxidation gave the *N*-methylisatin in high overall yield (79%),[477] while osmium tetroxide or permanganate was reported to fail for this type of oxidation. The method may be applied for the synthesis of metisazone, which is obtained in the condensation of *N*-methylisatin with thiosemicarbazide. Metisazone is an antiviral agent that is used for prophylaxis

Scheme 48. Synthetic Routes of Sitagliptin



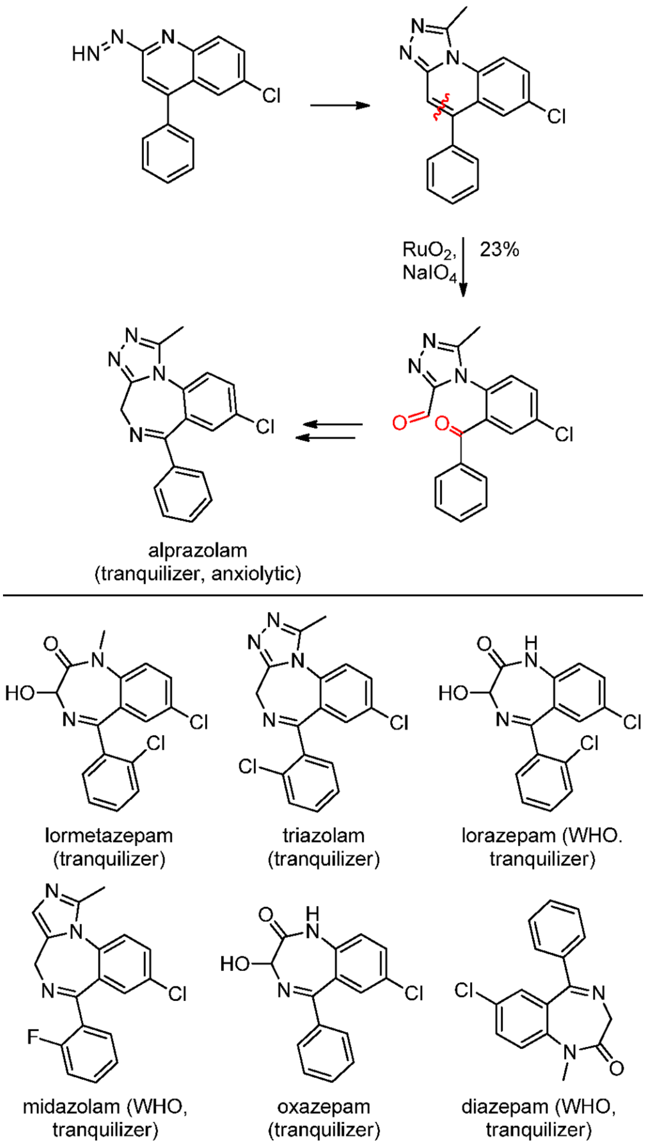
Scheme 49. Fission Products of Oleic Acid



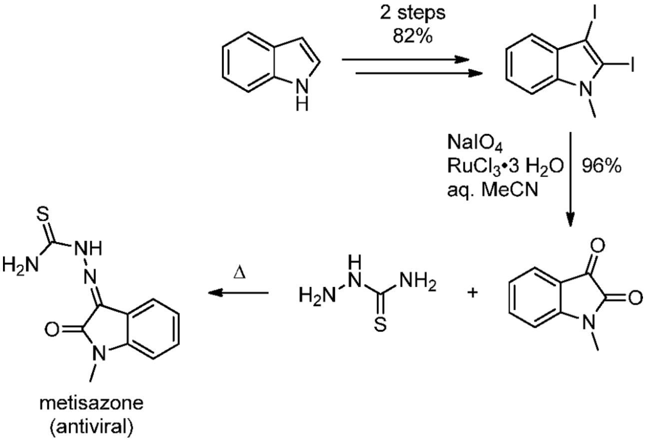
against smallpox.[478] A competing route is with TBHP and copper acetate.[479]

Quinine is a potent antimalarial drug that also shows activity against resistant plasmodial strains. It was listed in the WHO model list of essential medicines until 2006 and had a revenue of $800 M in 2018.[480] Besides for pharmaceuticals, it is used in organo-catalysis and is an ingredient of tonic water. The vast interest in quinine led to the extensive investigation of its total synthesis by many renowned chemists (Woodward/Doering, Jacobsen, Kobayashi, Aggarwal, Stork).[481,482] In 2018, Maulide

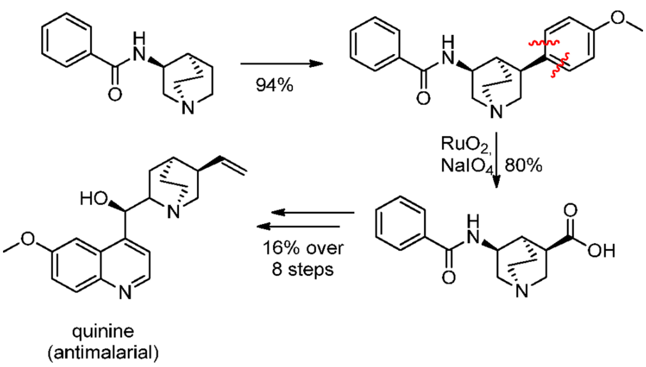
Scheme 50. Key Synthetic Steps for Alprazolam and Derivatives



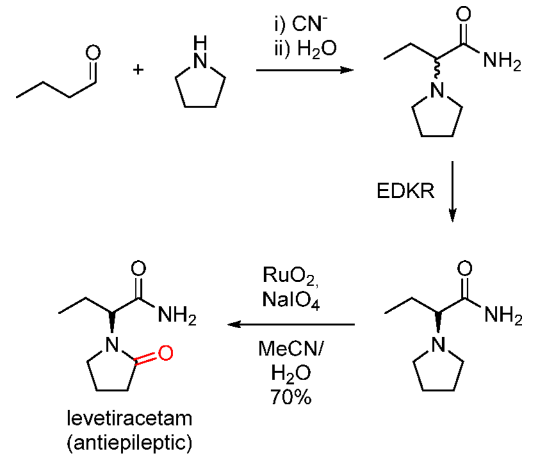
Scheme 51. Synthetic Route of Metisazone



Scheme 52. Key Synthetic Steps for Quinine



Scheme 53. Synthetic Route of Levetiracetam



and co-workers published a flexible synthetic route aided by the ruthenium-catalyzed oxidative degradation of aryl moieties (Scheme 52). The anisole moeity was decomposed cleanly to the carboxylic acid in 80% yield under retention of configuration,[483] while the benzamide remained untouched.

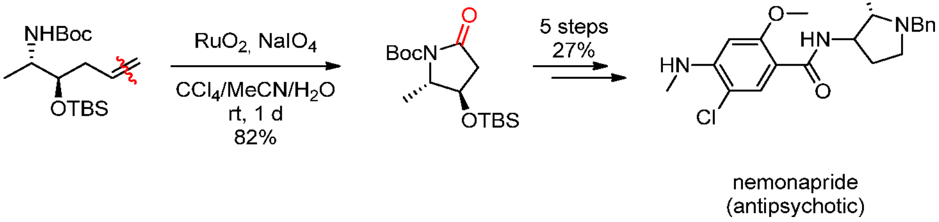
Levetiracetam is an anticonvulsant, which had a revenue of \$788 M in 2020 and sold more than 1000 t. The innovator and market leader is *UCB Pharma*, which markets levetiracetam under the brand name *Keppra*.[484] Our group investigated a ruthenium(VIII)-catalyzed oxidation for the regioselective and stereoretentive synthesis of levetiracetam using periodate as the terminal oxidant (Scheme 53).[15] The development features a short, competitive route comprising Strecker synthesis, enzymatic dynamic kinetic resolution (EDKR), and RuO$_2$/periodate oxidation. The starting materials are inexpensive, the resolution is atom efficient, and the final oxidation has a low ecological impact due to electrochemical recycling of the terminal oxidant. Remarkably, the oxidation did not affect the newly formed stereocenter. An alternative pathway using ruthenium catalysis was reported by Stoltz and co-workers (not depicted).[485]

A similar core structure was synthesized for nemonapride, which provides antipsychotic activity. Instead of pyrrolidine oxidation, a linear alkene precursor was cleaved to the corresponding acid using RuO$_2$/NaIO$_4$. The pyrrolidone was established by intramolecular amidation (Scheme 54).[486]

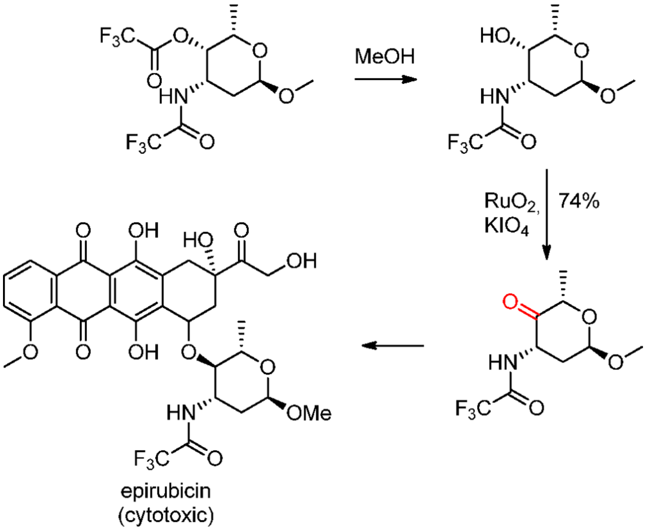
A simple ruthenium-catalyzed alcohol oxidation was used for the synthesis of epirubicin. Epirubicin is sold by *Pfizer* and is used as a cytotoxic agent (Scheme 55).[487] Notably, the less commonly used potassium periodate was used in this reaction.

Cyclic sulfones behave like epoxides and may be formed to make *cis* diols susceptible to nucleophilic substitutions, which typically proceed under inversion of configuration. Sharpless

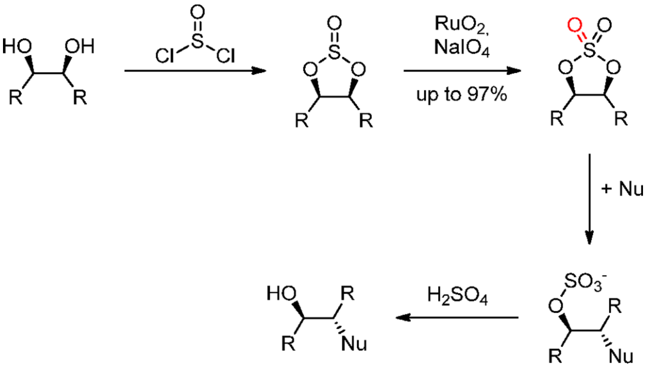
Scheme 54. Key Synthetic Steps for Nemonapride



Scheme 55. Key Synthetic Steps for Epirubicin



Scheme 56. Ruthenium-Catalyzed Oxidation of Cyclic Sulfones



and co-workers reported the clean and high-yielding synthesis of cyclic sulfones using catalytic RuO_4 in combination with periodate (Scheme 56).[488]

This strategy was used by *Johnsen Matthey* to improve the synthesis of piperazine drugs (Chart 6).[489] The most relevant target structures are lurasidone (*Latuda*), tiospirone, revospirone, aripiprazole (*Lauroxil*), buspirone, gepirone, ipsapirone, and eptapirone. Notably, the oxidation is not feasible with OsO_4.[443]

Similarly, a medicinal chemistry project from *Roche* used the oxidation and subsequent cleavage of the cyclic sulfone to synthesize the bicyclic amino-acid HYDIA (Scheme 57).[490] HYDIA antagonizes group II metabotropic glutamate receptors (mGluR2/3) and may be used to treat neuropsychiatric disorders.[491]

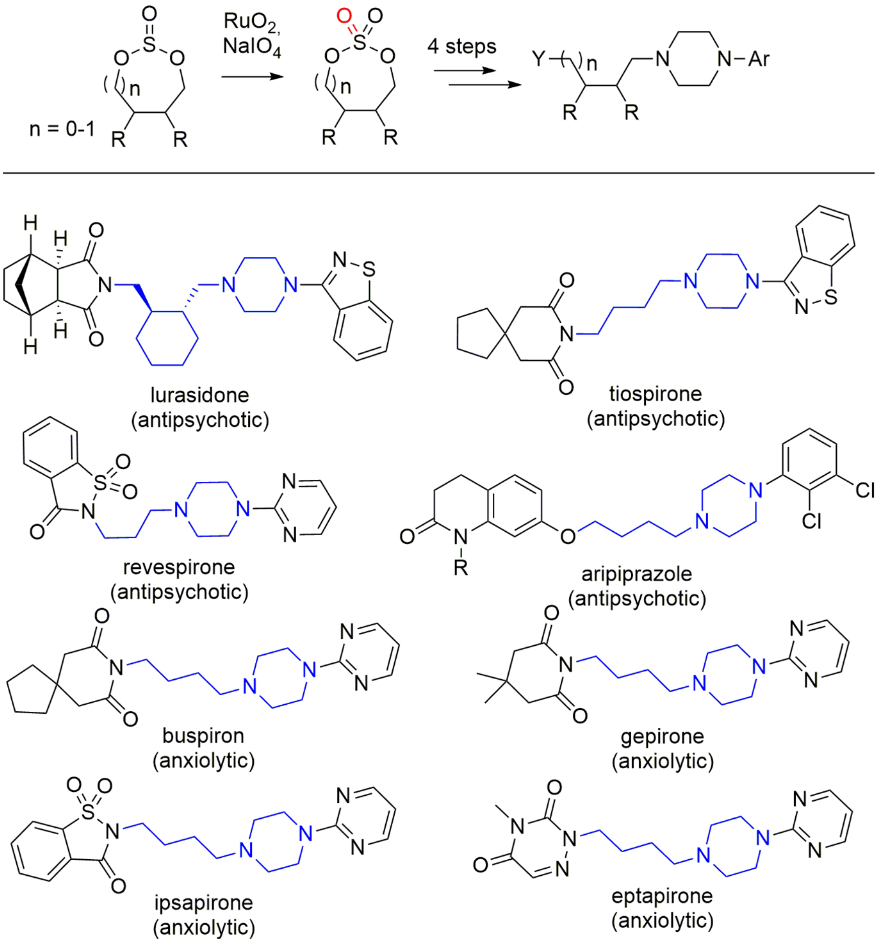
Eli Lilly and Company developed a ruthenium tetroxide-catalyzed method for the oxidation of penicillin or cephalosporin sulfides to the corresponding sulfone (Scheme 58). Without the metal catalyst the reaction was incomplete and afforded low yields. Other methods required elevated temperatures.[492] Related important compounds are sultamicillin (*Unacid*, *Pfizer*) and sulbactam. A ruthenium/periodate-catalyzed sulfide oxidation was demonstrated to work with immobilized ruthenium on carbon nanorods.[493]

Finally, we want to focus on biologically active *N*-cyanosulfoximines, which represent a hot topic currently.[494−497] Very recently, an electrochemical method was developed by our group and the efficient synthesis of sulfoxaflor (*Isoclast*), a commercial insecticide, was showcased (Scheme 59).[498] The two-step sequence followed an electrochemical oxidation to the *N*-cyanosulfilimine and a ruthenium-catalyzed oxidation with periodate to the corresponding sulfoximine, whereby electrochemically produced periodate was used.

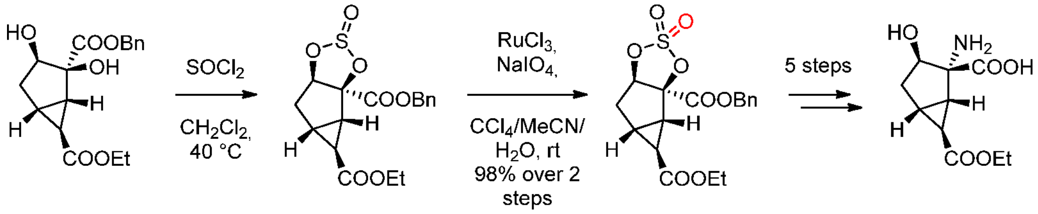
4.3. Lemieux−von Rudloff Oxidations. The combination of catalytic amounts of permanganate and stoichiometric amounts of periodate (Lemieux−von Rudloff oxidation) features a less expensive and less toxic alternative to ruthenium or osmium oxidations and can be performed in several mixed solvent systems such as butanol/water, dioxane/water, or acetone/water.[151] Notably, C−C double bonds are first dihydroxylated permanganate and subsequently cleaved by periodate, which also serves as the terminal oxidizer. However, the carboxylic acid is often obtained due to overoxidation of the carbonyl group, if the reaction is too hot, too basic, or too acidic or if the amount of permanganate is too concentrated.[151,153,499] A proposed (simplified) catalytic cycle is given in Scheme 60. According to literature, the initial step features addition of the permanganate to the double bond followed by a rearrangement to a 5-membered ring.[500] Subsequent hydrolysis gives the reduced manganese species and the diol, which is subsequently cleaved by periodate to the dialdehyde. It has to be noted that the exact mechanism is more complex, as the disproportion of the manganate species under different conditions may follow different routes. Also, the reoxidation to the permanganate using periodate may occur with other manganese species, not just MnO_2. For more specific information we would like to refer the reader to the review by Mishra et al., which provides detailed insight into the mechanisms involving permanganate ions.[500] The formed carbonyls from this catalysis cycle are very susceptible to overoxidation with MnO_4^-, yielding the respective carboxylic acids.[151,499]

The Lemieux−von Rudloff oxidation was used for the synthesis of dutasteride and finasteride, as both are a selective inhibitor of the 5*α*-reductase and used in the therapy of BPH (benign prostatic hyperplasia). The synthesis starts with the

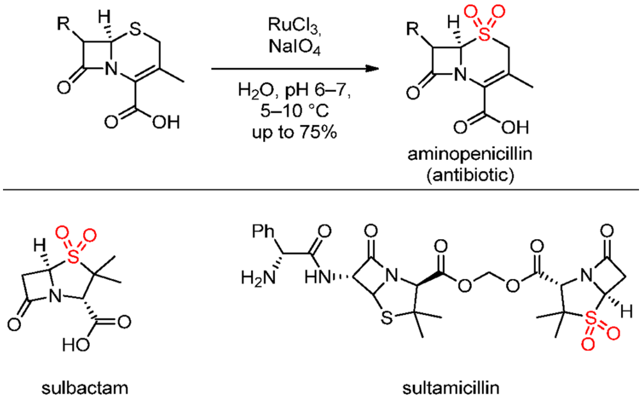
Chart 6. Key Synthetic Step for Lurasidone and Congeners



Scheme 57. Key Synthetic Steps for HYDIA



Scheme 58. Key Synthetic Step for Aminopenicillin

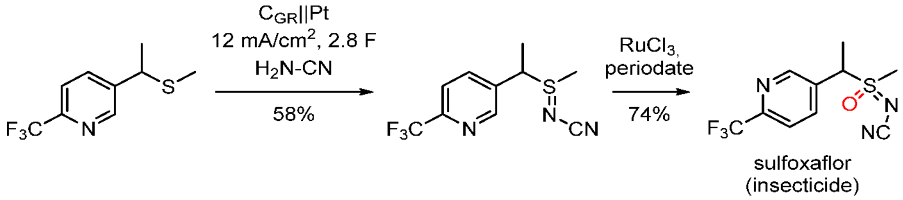


oxidation of 3-oxo-4-androstene-17β-carboxylic acid (etienic acid), wherein the double bond is cleaved and modified to the corresponding amide (Scheme 61).[501−504] The yield was not given, but the product was directly used for further synthesis. Notably, the modified double bond is in place of the target double bond in testosterone. The synthesis was shortened and scaled-up by Reddy and co-workers.[505] The 5,6-dehydropyridinone substructure is established again by periodate, which will be discussed in the next section about sulfide oxidations.

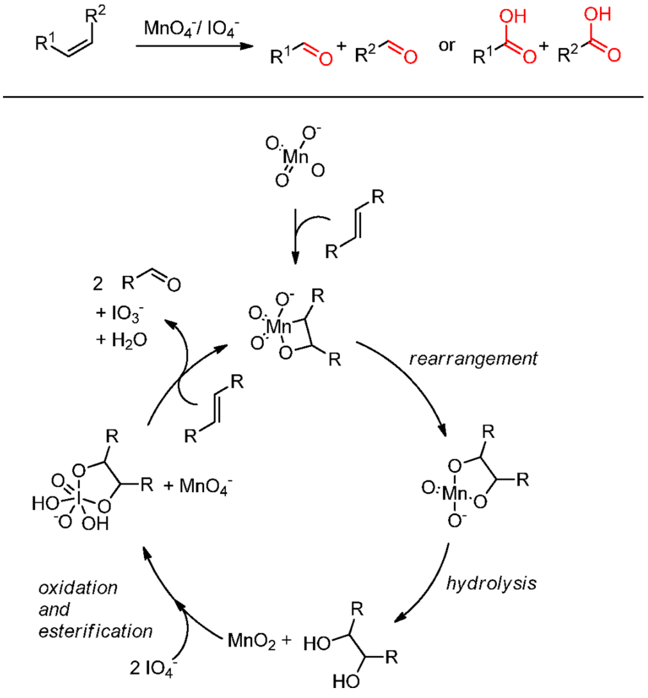
The Lemieux−von Rudloff oxidation was reported by Pan et al. for the synthesis of progesterone (often prescribed against, e.g., endometriosis and/or as a hormonal contraceptive),[506−508] which is sold by various providers, e.g. by *Merck KGaA* as *Crinone*. In this example the required double bond was established by an elimination reaction with sulfuric acid (Scheme 62). Other synthesis routes employ 16-Dehydropregnenolone (16-DP) as readily available starting material from bioavailable diosgenin.[509−512]

In conclusion, metal-catalyzed oxidations with periodate are an important field in medicinal chemistry providing many

Scheme 59. Key Synthetic Steps for Sulfoxaflor



Scheme 60. Presumed Mechanism for the Manganese-Catalyzed Oxidative Alkene Fission Using Periodate as Terminal Oxidizer (Lemiuex−von Rudloff Oxidation)



important APIs. Periodate has proven to be suitable as a secondary oxidant in osmium- and ruthenium-catalyzed oxidations. By tuning the reaction conditions, a broad but selective scope of reactivity is made accessible.

5. CHALCOGENIDE OXIDATIONS

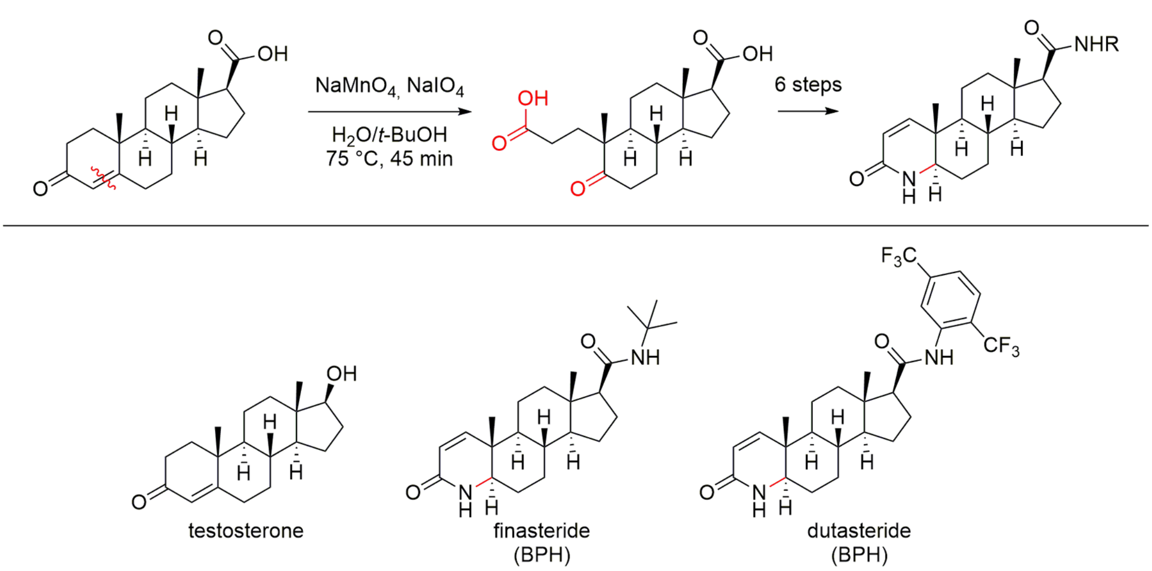
Chalcogenide oxidations constitute the third major type of periodate oxidations, which will be the focus of the following section.

5.1. Sulfide Oxidations. Sulfoxides and sulfones are common structural motifs in APIs and compounds for crop protection.[513−515] An important API comprising a sulfoxide is omeprazole (*Losec*/*Prilosec*), which was the highest selling drug in 2000 and had a revenue of $6 B by *AstraZeneca*.[516] Further representatives are rabeprazole, lansoprazole, pantoprazole, and (*rac*)-modafinil (Figure 4).

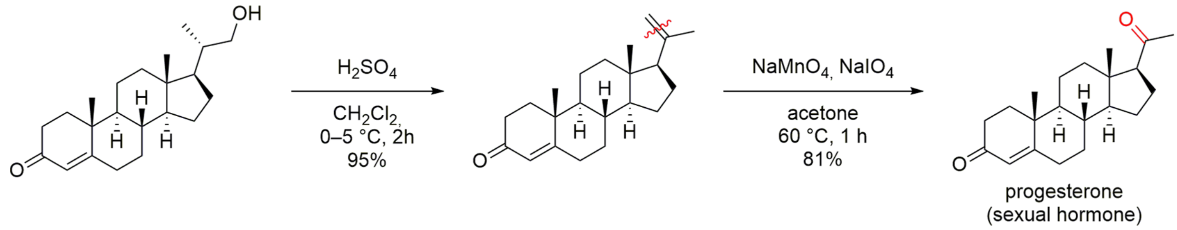
The oxidation of sulfides can be facilitated by periodate.[155,517] Common conditions are a neutral to acidic pH and moderate temperatures in aqueous solvents. Higher temperatures and excess periodate favor the formation of the sulfone.[154] Thus, the oxidation by periodate is advantageous, allowing precise control of the reaction progress and excellent yields, whereas other oxidants may fail and give mixtures.[518] The mechanism was investigated by Ruff and co-workers in kinetic and quantum-chemical studies. Proposed was a single-step oxygen transfer for each oxidation step to sulfoxide and to the sulfone (Scheme 63).[519,520]

Periodate was applied to establish the sulfoxide moiety in imidazolidine,[521] diphenyl ether,[522] isoxazoline, and phenyloxazolidinone derivatives (Chart 7).[523−525] The oxidations were performed conveniently in a late stage using mild reaction conditions. A commercial substance of the phenyloxazolidinone class, but without sulfoxide, is linezolid (*Zyvoxid*, Pfizer),

Scheme 61. Key Synthetic Steps for Finasteride and Dutasteride Steroids



Scheme 62. Key Synthetic Steps for Progesterone



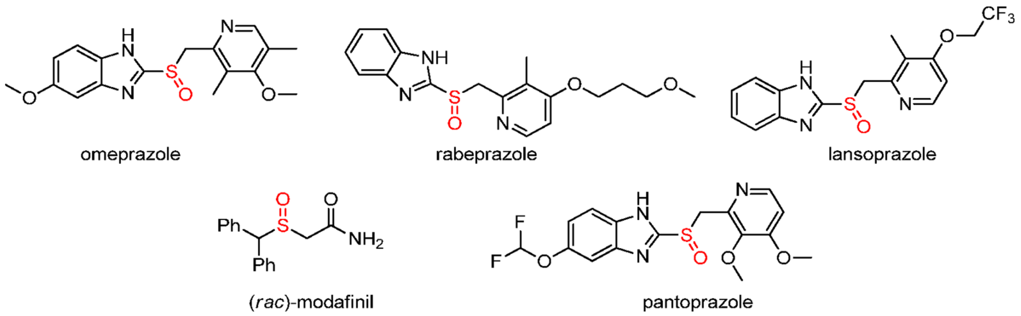
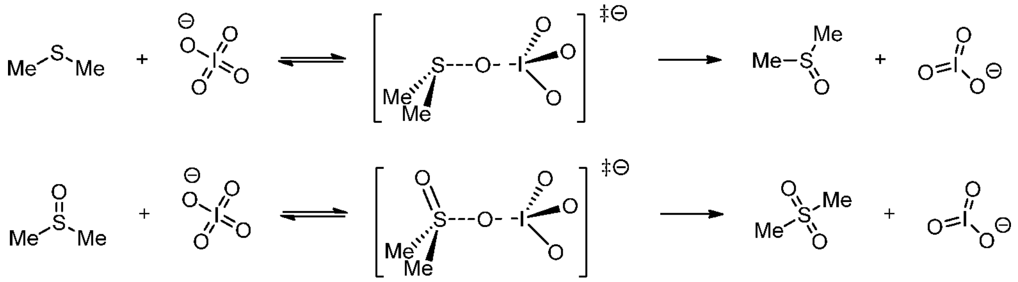


Figure 4. Important APIs containing a sulfoxide moiety.

Scheme 63. Presumed Mechanism for Sulfide and Sulfoxide Oxidation



which is listed on the WHO list of essential medicines for the treatment of tuberculosis. Periodate was also used for the synthesis of sulindac, which provides anti-inflammatory activity. The API was developed by *Merck & Co.* and is sold under the brand name *Clinoril* (Chart 7).[526−529]

Fulvestrant is an antiestrogen and is used in the treatment of breast cancer. It is marketed under the brand name *Faslodex* by *AstraZeneca* and had a revenue of $580 M in 2020.[530] The process was developed by MacDonald et al. and Liu et al., who both used periodate for the final sulfide oxidation to sulfoxide.[531,532] The synthesis of benzimidazole sulfoxides, which are related to the antiparasitic drugs fenbendazole and albendazole, was facilitated by periodate.[533] Furthermore, periodate was used for the synthesis of pesticides, such as cyano-dialkylphenyl sulfoxide[534] and dioxolanes (Chart 7).[535]

The oxidation of sulfide also enables the generation of C−C double bonds by elimination of sulfinic acid.[536] This transformation was used in the synthesis of finasteride and dutasteride as an alternative to poisonous 2,3-dichloro-5,6-dicyano-1,4-benzochinone (DDQ) and expensive bis-(trimethylsilyl)-trifluoroacetamide (Scheme 64).[537]

5.2. Selenide Oxidations. An analogous transformation with selenide was found useful for the synthesis of *α*,*β*-unsaturated alcohols in (−)-morphine,[538] (−)-codeine, and (−)-galanthamine,[539,540] which are all listed in the WHO model list of essential medicines (Scheme 65). In different routes, those structures were also synthesized by the Lemieux–Johnson and the Malaprade oxidation.[541,542]

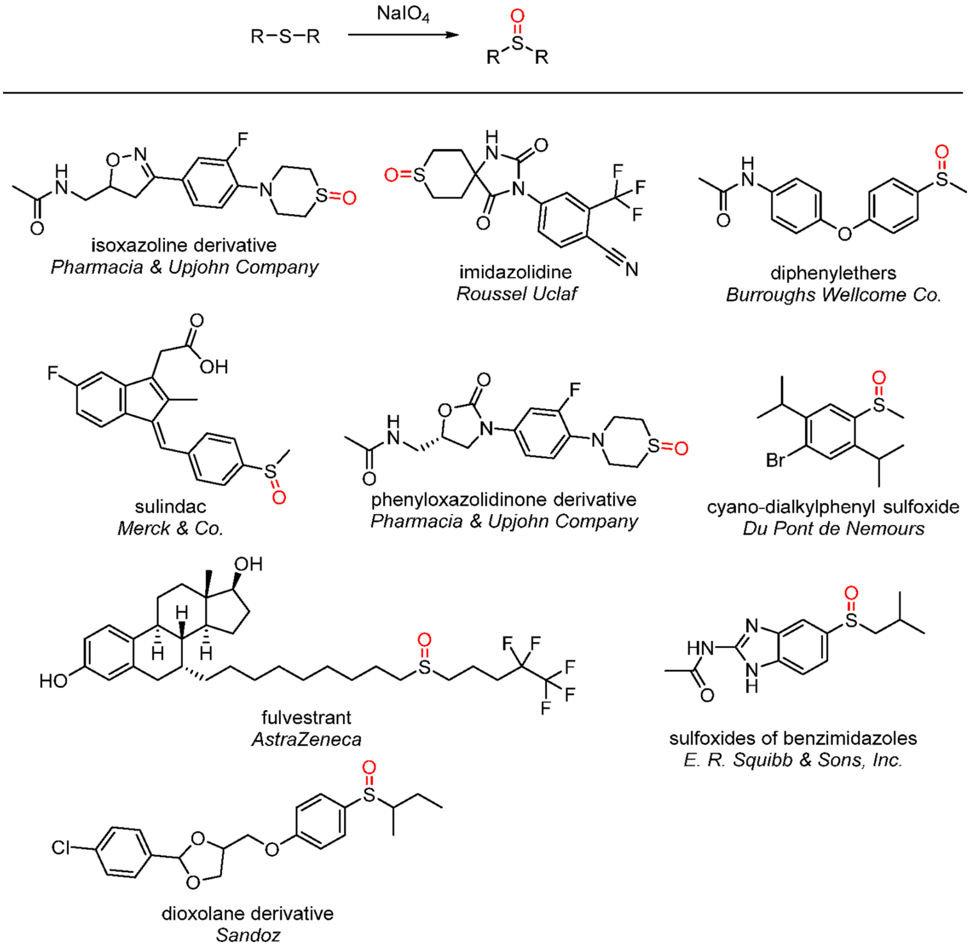
Stavudine is a carbocyclic nucleoside and a useful antiviral agent for the treatment of HIV. It is sold under the brand name *Zerit* by *Bristol-Myers Squibb* (patent expired). The synthesis of the C−C double bond in the 2,5-dihydrofurane was established by either selenoxide or sulfoxide elimination by periodate (Scheme 66).[536,543] An alternative synthesis of stavudine was already outlined in the Malaprade section of this review.

In conclusion, chalcogenide oxidation of sulfur or selen may be facilitated by various oxidizing agents, but periodate is used if high selectivity and precision are needed. Important applications are in the double bond generation in opioids and cholesterols, and in the synthesis of sulfoxides, such as fulvestrant and sulindac. A future application might be the synthesis of sulfoximines, which are generally of great interest as pharmaceutical targets.[496,544,545]

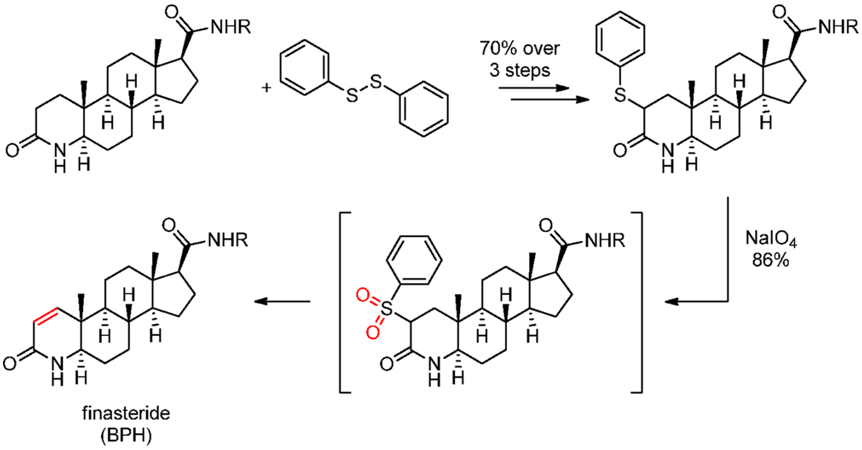
6. CONVERSION OF RENEWABLES AND MISCELLANEOUS APPLICATIONS

Periodate can also be used as an oxidizer to produce fine chemicals from renewable feedstocks. Recently, the synthesis of either 5-iodovanillin or vanillin from various lignins was reported.[98] Selectivity was achieved through simple adjustment of the pH giving either product in up to 15.8 wt % (Scheme 67). Both products constitute a valuable building block for

Chart 7. Summary of Sulfoxide-Comprising APIs



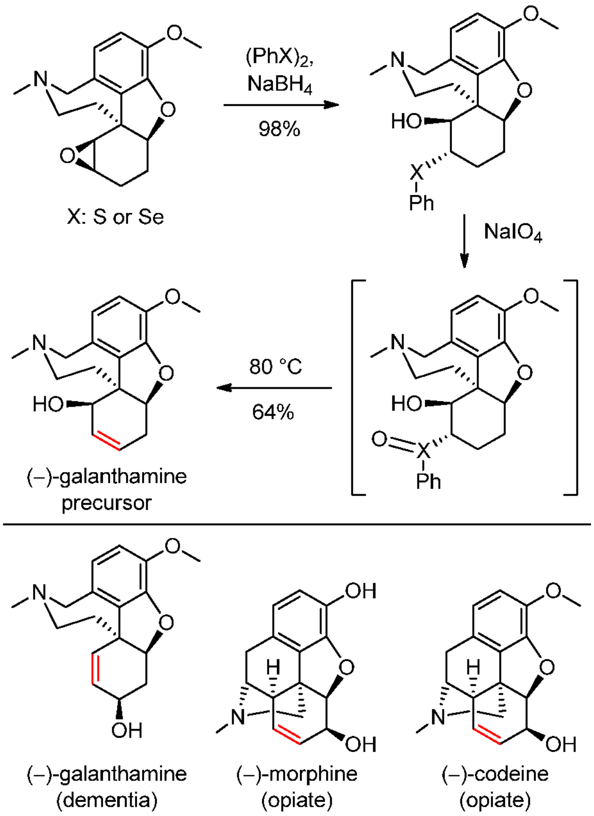
Scheme 64. Key Synthetic Steps for Finasteride



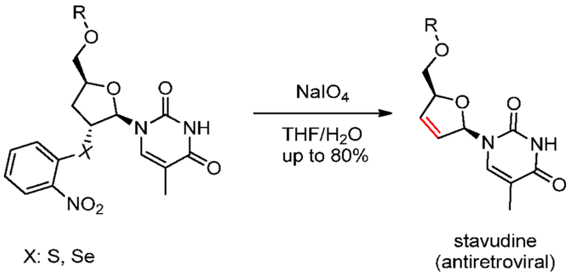
further chemical transformations such as cross-coupling and annulation reactions.[546−553] Vanillin may also be utilized for the synthesis of curcumin and its derivatives, which may be used for the treatment of Alzheimer's disease.[554,555] Furthermore, the unique selectivity periodate can be exploited for the functionalization of cellulose and chitin (via vicinal diol cleavage) as was described earlier in this review.[99,100]

Periodate also finds niche uses in the synthesis of benzoquinones, an important and versatile structural motif with manifold applications. Other suitable oxidizers include cerium reagents, Fremy's salt, hypervalent organic iodine species, and direct anodic oxidation of hydroquinones.[556−559] Patented application also include the synthesis of 2-thio-substituted 1,4-benzoquinones for use as antioxidants in rubber manufacturing. Notably, the synthesis could also be carried out using catalytic amounts of periodate in the presence of hydrogen peroxide.[560] The synthesis of 1,4-benzoquinones was also reported, with several examples isolated in excellent yields starting from 1,4-diamines. The same authors also used periodate for the synthesis of dinitriles from 1,2-diamines

Scheme 65. Key Synthetic Steps for Opiate Derivatives



Scheme 66. Key Synthetic Step for Stavudine Using Organo-Seleno Compounds



using periodate in either water or aqueous organic solvents.[167] However, there are no other publications to our knowledge exploiting this unique feature of periodate. A periodate-loaded ultraresin (polyethylene imine, $M_n = 10\,000$) was reported for the synthesis of 1,2-benzoquinones by Barth et al.[162] The aforementioned reactions are depicted in Scheme 68.

Periodate was also used as the terminal oxidant for the epoxidation of alkenes using transition metal catalysts based on chromium,[158] manganese,[156,157,160,161] or ruthenium.[159] However, there appear to be no patented procedures for industrial applications of these reactions (not depicted).

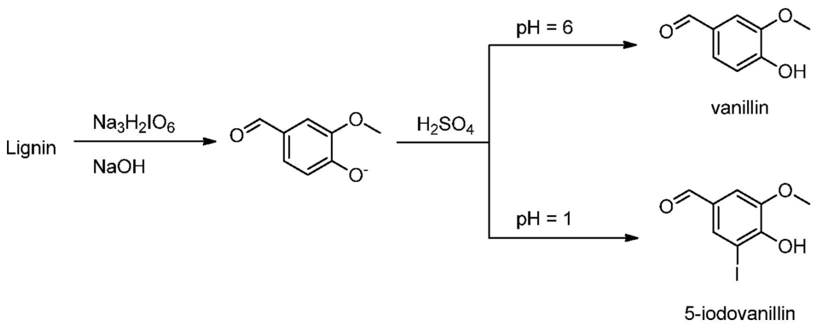
In the synthesis of rosuvastatin, periodate was used to form aldehydes from either alkyl halides or alcohols (Scheme 69).[561] Rosuvastatin has a cholesterol-lowering effect and is used for the medication cardiovascular diseases. It is sold as *Crestor* (*AstraZeneca*), *Lipocomb*, or *Triveram* (*Servier*) and had a revenue of $1.4 B in 2020 only by *AstraZeneca*.[530] The starting material was made by an enzyme-catalyzed tandem aldol reaction with DERA (deoxyribose-5-phosphate aldolase), and the oxidation with periodate was performed after alcohols were protected as cyclic carbonate, and, thus, was fully orthogonal with the halide functional group. The corresponding aldehyde was further reacted in a Wittig olefination.[561]

Periodate was applied in the synthesis of eliglustat, which is used for the oral treatment of Gaucher's disease. Eliglustat is sold under the brand name *Cerdelga* by *Sanofi* and had global sales of €234 M in 2020.[171] The synthesis followed a hydroxybromination of alkenes using substoichiometric amounts of periodate. The reaction relates to the Prévost–Woodward reaction mentioned earlier in this review (Scheme 70).[562]

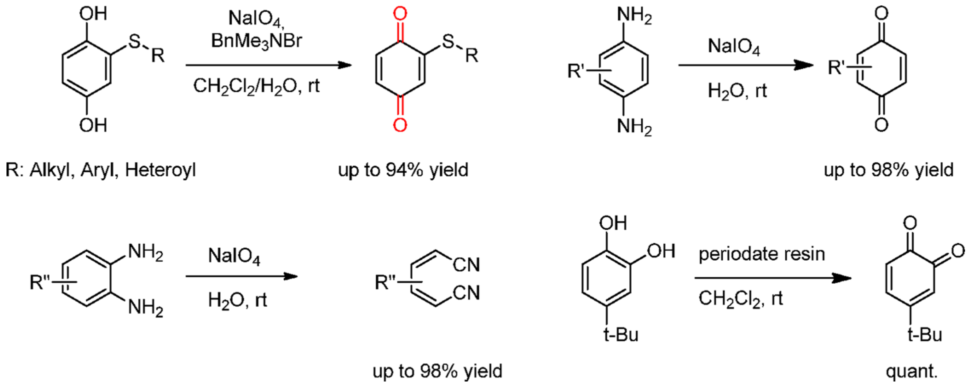
7. SUMMARY

In summary, periodate is an essential oxidizer for glycolic cleavages, for the oxidation of sulfides or selenides, and as a terminal oxidant in metal catalysis. Recent developments in its electrochemical synthesis provide significant improvements, i.e., a contamination-free synthesis, simple recycling, and convenient process management. The Malaprade oxidation is the major application of periodate, where diols are cleaved into invaluable carbonyl moieties. It is useful not only in the synthesis of common (chiral) building blocks, fragments, and auxiliaries but also for late-stage transformations of highly complex chemical structures. Clearly, the strength of periodate lies in the stereoretentive nature, the extraordinary selectivity toward diols, and the safe handling compared to other oxidants. Periodate is furthermore used in combination with transition metal catalysts that extend the substrate scope to readily available alkenes. The combination with the osmium-catalyzed dihydroxylation allows the efficient fission of alkenes into carbonyls. In ruthenium tetroxide catalyzed oxidations,

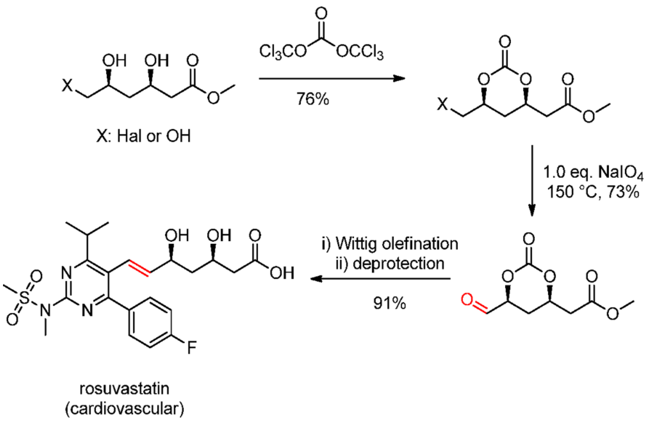
Scheme 67. Conversion of Lignin to Either Vanillin or 5-Iodovanillin Using pH Control



Scheme 68. Synthesis of Quinones and Dinitriles Using Periodate as Oxidizer



Scheme 69. Key Synthetic Steps for Rosuvastatin (X = Cl, Br, I)



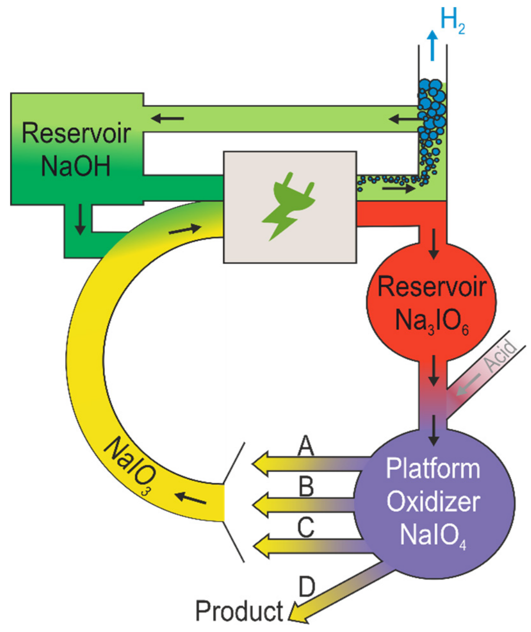


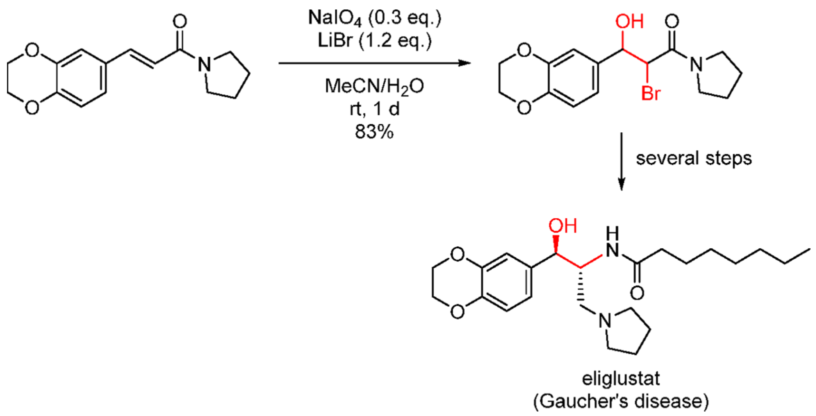
Figure 5. Anodic generation of periodate as "platform oxidizer" for use in organic synthesis during water splitting electrolysis.

periodate is used as a primary oxidant, which enables further a versatile chemistry.

8. OUTLOOK

Because of the achievements in the periodate synthesis, periodate-based transformations might be increasingly considered in future processes making pharmaceuticals more available and decreasing barriers to access. Periodate might be used as a replacement for competing oxidants or in the development of alternative synthetic routes that allows the creation or bypass of intellectual property space. We hope to inspire medicinal and process chemists with possible synthetic strategies and to encourage the application of periodate in future technical synthesis. In addition to API synthesis, periodate is extremely useful in the modification of carbohydrates, fatty acids, and other natural feedstocks. Considering the future transition from fossil to natural

Scheme 70. Key Synthetic Steps for Eliglustat



feedstocks, the synthesis and recycling of periodate could become increasingly important. The current development of generating high performance oxidizers in the water splitting instead of oxygen will propel periodates into a versatile reagent (Figure 5). However, efficient recovering and recycling strategies for closing the iodate/periodates loops represent the next challenges to be addressed.

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Notes

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